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# Percutaneous Transluminal Coronary Angioplasty as a <br> <br> Model of Cardiac Ischemia: <br> <br> Model of Cardiac Ischemia: Clinical and Modelling Studies 

by<br>Robert Scott MacLeod<br>Department of Physiology and Biophysics

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Subinitted in partial fulfillment of the requirements for the degree<br>Doctor of Philosophy<br>at<br>Dalhousie University<br>Halifax, Nova Scotia, Canada<br>May, 1990

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#### Abstract

Percutaneous transluminal coronary angioplasty (PTCA) is a palliative therapy for coronary artery disease in which a balloon-tipped catheter is inserted into a partially occluded coronary artery and inflated to pressures of 4-12 bar for durations of $10-300 \mathrm{~s}$. The resulting block of antegrade blood flow provides an experimental model of ischemia which has been studied in this dissertation. The technique of body surface potential mapping (BSPM) was used to continuously record 117-lead ECGs from patients undergoing PTCA; isointegral maps recorded before inflation of the balloon were subtracted from those recorded during inflation to produce isointegral difference maps. Based on these difference maps, the inflations could be separated into groups which corresponded to the coronary artery which had been dilated.

A mathematical solution to the inverse problem in electrocardiography was developed by which epicardial potential distributions could be calculated from body-surface distributions. This inverse solution was validated directly using simulated potentials from a single dipole source, and also indirectly by using the isointegral maps recorded during PTCA. From angiographic information of each patient's coronary circulation and the location of the PTCA balloon, it was possible to estimate the perfusion bed, and thus the : hemic region, for each inflation. While the angiographically determined location of the PTCA-induced ischemia agreed with a region predicted by the model, the inverse solution also yielded secondary regions predicted ischemia which could not be accounted for by clinical evidence. These results suggest that it is possible to construct a stable and useful inverse solution, which allows the recovery of the location of PTCA-induced ischemia in humans.


## Symbols and Abbreviations

A/D - Analog-to-Digital
$\mathrm{Ag} / \mathrm{AgCl}$ - silver-silver chloride
AP - Action Potential
BEM - Boundary Element Method
BSPM - Body Surface Potential Mapping
CAD - Coronary Artery Disease
CADD - Computer Aided Drafting and Design
CC - Correlation Coefficient
CPU - Central Processing Unit
CSA - Canadian Standards Association
CT -- Computer Tomography
DC - Direct Current
DSL - Dipole Source Location
ECG - Electrocardiogram
FEM - Finite Element Method
IC - Integrated Circuit
$\left[\mathrm{K}^{+}\right]_{0}$ - extracellular potassium concentration
LAD - Left Anterior Descending (artery)
LCx - Left Circumflex (artery)
LED - Light-Emitting Diode
MAP - Monophasic Action Potential
MRI - Magnetic Resonance Imaging
NMR - Nuclear Magnetic Resonance
PBRS - Pilkington-Barr-Ramsey-Spach method of forward solution
pH - Negative logarithm of the hydrogen-ion concentration
$\mathrm{pO}_{2}-\mathrm{Partial}$ pressure of oxygen
P,Q,R,S,T - Nomenclature of the waves of the electrocardiogram

## PTCA - Percutaneous Transluminal Coronary Angioplasty

RC - Right Coronary (artery)
RE - Relative Error
relres - Relative Residual error
RMC - Rudy-Messinger-Rapport-Cruse method of forward solution
rms - Koot Mean Square amplitude of a time-varying signal
ST - ST segment of the ECG
V - Variability
$\mathrm{V}_{1}--\mathrm{V}_{6}-$ Standard precordial electrode sites
VAC - Potential in Volts of an Alternating Current source
VCG - Vectorcardiogram
VGH - Victoria General Hospital
a - The scalar a
$\vec{a}$ - The vector $\vec{a}$
$A$ - The matrix $A$
$A^{-1}$ - Inverse of the matrix $A$
$A^{T}$ - Transpose of the matrix $A$
$d \vec{A}$ - Differential area directed along the outward unit normal
$C_{m}$ - Cruse weighting function for points in a triangle
$\vec{E}$ - Electric field [volt $\mathrm{m}^{-1}$ ]
$G$ - Gradient operator matrix
$I$ - Identity matrix
$\vec{n}$ - Outward unit normal of a surface
$\vec{J}$ - Gurrent density [amp $\mathrm{m}^{-2}$ ]
$L$ - Laplacian operator matrix
$N_{B}$ - Number of nodes on the torso surface
$N_{H}$ - Number of nodes on the heart surface
$N T_{B}$ - Number of triangles on the torso surface

$$
N T_{H} \text { - Number of triangles on the heart surface }
$$

## $p_{s}$ - Point at which a singularity exists

$S_{B}$ - Outer surface of the torso
$S_{H}$ - Epicardial surface of the heart
$t$ - Regularization parameter
$Z_{B H}$ - Forward transfer coefficient matrix
$Z_{H B}$ - Inverse transfer coefficient matrix
$\nabla$ - Gradient operator
$\nabla^{2}$ - Laplacian operator
$\Gamma$ - Vector of potential gradients
$\delta$ - Delta function
$\sigma-$ Conductivity $\left[\mathrm{S} \mathrm{cm}^{-1}\right]$
$\phi$ - Electrical potential [volt]
$\Phi$ - Vector of potential values
$d \Omega$ - Differential solid angle

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## Chapter 1

## Introduction

The aim of electrocardiography is to glean information about the electrical activityr of the heart from recordings of heart-produced potentials on the body surface; such recordings are called electrocardiograms (ECG). While the medical use of ECGs spans just over a century, the basis of a great deal of diagnostic electrocardiography has been of an empirical or statistical nature. This dissertation adopts a biophysical approach to electrocardiography basea on mathematical relationships between measurable biological quantities, derived from re laws of physics. The specific aim of this work was to develop a solution to the inverse problem of electrocardiography, with which epicardial potentials could be computed from ECGs recorded with multiple electrodes. In order to test the validity and clinical usefulness of this inverse solution, the method of body surface potential mapping (BSPM) was used to record high-resolution ECGs from patients undergoing percutaneous transluminal coronary angioplasty (PTCA). The unique possibilities of this controlled model of human ischemia include the ability to predict, from angiographic data, the approximate location of transient ischemia which is induced by inflation of a coronary balloon-catheter.

The development of this work followed two parallel tracks - a division which is reflected in the structure of the dissertation. Each chapter contains one section pertaining to the mathematical model, upon which the solution to the inverse problem was based, and a second section describing the experimental study of ischemia, which
was carried out using BSPM during PTCA. Chapter 2 contains a review of the relevant literature; Chapter 3 outlines the theoretical development of the inverse solution and describes the clinical studies of PTCA-induced ischemia; in Chapter 4, the results of both the mathematical modei id the clinical studies are presented. In this chapter also, the two streams of the dissertation join as the inverse solution is applied to experimental data obtained during PTCA. Chapter 5 contains discussion of these results and Chapter 6 summarizes the work. 'Two appendices are also included: the first describes the realistic human torso model used at Dalhousie University, and the modifications to it carried out in this study; the second appendix contains a technical description of the improvements to the BSPM system which were required to allow measurements during the PTCA procedure in the catheterization laboratory.

## Chapter 2

## A Review of the Literature

### 2.1 The Forward and Inverse Problems of Electrocardiography

### 2.1.1 Introduction

The forward problem of electrocardiography involves the calculation of body surface potentials from the electrical activity in the heart. Forward solutions are, in general, unique [1] (that is, there is no ambiguity regarding the body surface potentials produced by the cardiac sources) and they can be formulated in a number of different ways, each of which is based on a different conceptual model of the heart and the torso in which it is suspended. The inverse problem is the complement of the forward problem: given a distribution of body surface electrocardiograms (ECGs), predict the underlying cardiac electrical activity. Each different formulation of the forward problem has its inverse-problem counterpart and both are linked by a common concept of the electrical activity of the heart. Inverse solutions are generally not unique, that is, the same body surface potential distribution can be accounted for by many different patterns of cardiac activity. Only when meaningful electrophysiological constraints are placed upon the problem can unique inverse solutions be generated [2].

In this section, we will review briefly several approaches by which the forward and inverse problems have been solved. Special attention will be given to methods leading to solutions of the inverse problem in terms of epicardial potentials - which is
the topic of this dissertation. The reader is referred to recent comprehensive reviews by Gulrajani [ $3,4,5$ ] and Rudy and Messinger-Rapport [6, 7] for more extensive coverage.

### 2.1.2 Discrete versus distributed source models

The earliest theoretical approach to the inverse problem was based on a concept of the heart as a single current dipole at a fixed location [8] - a model which formed the basis of early electrocardiographic lead theory $[9,10,11,12,13,14,15,16]$ and which permeates a good part of the clinical electrocardiography as taught and prac-ticed today [9]. Indeed, to a reasonable approximation, the heart generates the same electrical potential distribution on the body surface as a dipole of appropriate size. orientation, and location. From this abstraction followed several forward and inverse solutions based on models of discrete sources, which include fixed multiple dipoles $[17,18]$, multipoles [19, 20], and single or double moving dipoles [21, 22, 23]. The biophysical framework for the application of electromagnetic theory and numerical mathematics required for the solution of the forward problem was developed by Gelerneter and Swihart [1, 24], Barr et al. [25] and Barnard, Duck, Lynn, and Timlake [26, 27].

An alternative family of forward and inverse solutions is based on the representation of the electrical activity of the heart as a distributed source in terms of epicardial surface potentials [28]. Inverse solutions conceived within this framework have numerous advantages over discrete-source models and much of the recent activity in cardiac modelling has focused on this area [ $7,29,30$ ].

The main advantage of the distributed equivalent source is that it can be interpreted with greater ease in physiological terms than dipolar/multipolar sources. For example, the changing amplitude, location, and orientation of a single dipole might represent the entire depolarization/repolarization cycle of the heart; however, there is no simple relationship between such a current source (which is not an entity which
can be determined experimentally) and the electrophysiology of the whole heart. In multiple-dipole models, it is possible to link the electrical activity of some part of the heart to the amplitude or orientation of the nearest dipole [17, 18], but the restricted number of dipoles in such a model (see below) requires that each represent a fairly large portion of the myocardium. There are, however, conditions in which activation of the heart is so localized that it can be adequately modelled as a single or double dipole [22]. Most often this approach is applied to the Wolff-Parkinson-White syndrome to locate an accessory conduction pathway between the atria and ventricles [31, 32].

The potentials on the epicardial surface, on the other hand, directly reflect underlying physiology (see section 2.2). The recording of epicardial maps has been performed in animal experiments for many years as a means of studying such phenomena as ischemia [33,34,35,36,37], arrhythmias [38,32], and the response of the heart to defibrillation [39, 40, 41]. In humans, epicardial potentials are recorded clinically to localize arrhythmias $[42,43,44,45]$, evaluate conduction abnormalities [46, 47, 48], or to follow recovery from bypass surgery [49]. While epicardial electrical activity is transferred uniquely to the body surface, body surface potential distributions are distorted by the effect of torso boundaries; epicardial potential distributions allow better examination of localized events such as ectopic foci [50,51] or the progression and extent of ischemia [34]. The presence of the torso volume conductor tends to distort and "smear" the epicardial distribution so that individual features are lost and large spatial gradients smoothed over when detected at the body surface [50]. Although it is obviously not possible to perform extensive recordings of epicardial potentials in clinical cardiology, there is growing interest in being able to predict epicardial potentials from noninvasive measurements on the body surface. Accurate rendition of epicardial potentials would allow preoperative screening of patients with arrhythmia, reducing the amount of time spent on cardiopulmonary bypass, or perhaps, in conjunction with techniques of catheter ablation, eliminating the need for
open-heart surgery altogether. Ischemia induced by exercise, coronary spasms or angioplasty could also be localized and monitored noninvasively.

The other main advantage of the distributed source model is that it can be used to derive unique, stable inverse solutions. In contrast, inverse solutions based on source models with larger numbers of dipoles than about 20 become unstable [28]. Furthermore, solutions using discrete source models are not unique without imposed constraints such as fixing the number, location, or orientation of the dipoles. Since the solution parameters are difficult to relate to measurable physical quantities, inverse solutions in terms of discrete sources cannot be directly validated in human or animal experiment. Solutions of the inverse problem in terms of epicardial distributions are unique [2]; the only requirement is knowledge of the geometry and conductivity of the volume conductor, which is also the only constraint applied. Inverse solutions in terms of epicardial potentials can also be made stable using the technique of regularization, as will be discussed in detail in section 3.1 .4 below. Validation of the results is possible, since the solution yields values of a measurable quantity (potential) which can be compared with recorded data. In general, inverse solutions in terms of epicardial potentials are, however, mathematically more complex than those employing simple source terms. This results in higher computation costs and a more extended development time for each solution. On the other hand, once a solution in terms of epicardial potentials has been calculated, the generation of multiple epicardial maps from body surface data is quite efficient since it requires only a multiplication of a vector of potentials by an inverse transfer matrix.

### 2.1.3 The solution in terms of epicardial potentials

### 2.1.3.1 The forward solution

A necessary prerequisite to most quantitative solutions to the inverse problem in electrocardiography is a forward solution, whose complement then becomes the inverse solution. The forward solution in terms of epicardial potentials can be derived using
one of two methods: the boundary element method (BEM) or the finite element method (FEM). The mathematical basis of the BEM is Green's Theorem [52, 53], which was applied first by Martin [54, 55], and later by Barr, Ramsey, and Spach [56] to a discretized description of the epicardial and torso surfaces. The resulting forward solution is a matrix of transfer coefficients which can be multiplied by a vector of epicardial potentials to generate an approximation of the body surface potentials. This can be expressed mathematically as

$$
\begin{equation*}
\Phi_{B}=Z_{B H} \Phi_{H}, \tag{2.1}
\end{equation*}
$$

where $\Phi_{B}$ and $\Phi_{H}$ are vectors of potential values on the body and heart surface, respectively, and $Z_{B H}$ is the forward transfer matrix. Solutions of this form have been developed by Barr, Ramsey and Spach [50, 56, 57], Horacek et al. [58], Cuppens and van Oosterom [59, 60], Rudy and Messinger-Rapport [6, 7], Meijs et al. (for the inverse solution of brain potential) [61, 62], Huiskamp and van Oosterom [30, 63, 64], and Walter and Kilpatrick [29]. The BEM, which has been adopted as the basis of the forward solution in th; dissertation, is described in detail in section 3.1.3.

The finite element method has also been used extensively to generate the transfer coefficient matrix of the forward solution. In the FEM, an energy function based on Laplace's equation is minimized over each volume element within the torso. The entire volume must first be discretized and a zero-, first-, or second-order polynomial basis function defined for each element. The potential function is then the sum of these piecewise continuous basis functions and can be evaluated anywhere within the volume. Since each element of the volume can be individually defined, local inhomogencities and anisotropic conductivity properties may be intreduced into the model. The FEM has been applied to numerous other problems in virtually all fields of engineering and tr : exists a rich selection of software for both the generation of the volume mesh elements and the solution of the resulting system of equations. Electrocardiographic forward solutions using the FEM have been developed by Yamashita [65], Colli Franzone [66, 67, 68, 69, 41] and Johnson [70]; Pilkington et al. have di-
rectly compared BEM to FEM [71, 72]. By first improving upon the BEM technique of Barr, Ramsey and Spach [56,57], Pilkington and co-workers demonstrated that both $\mathrm{BEN}_{\perp}$ and FEM produced forward and inverse solutions with virtually identical accuracy when applied to a simple geometry of concentric spheres.

### 2.1.3.2 The inverse solution

Once the matrix of forward transfer coefficients, $Z_{B H}$, has been generated by either BEM or FEM, the inverse solution can be obtained from the pseudo inverse of $Z_{B H}$. While the inverse solution formed in this way is unique, it is also highly unstable (see $[6,7,54,55]$ and section 3.1.4). To produce a useful and stable inverse solution, two forms of mathematical treatment have been applied: 1) statistical constraints, based on work by Foster [73] and Strand and Westwater [41], were used by Martin [50, 54] and Barr and Spach [55, 74]; 2) Tikhonov regulai ization techniques, which were first used in a cardiac inverse solution by Colli Franzone [66] and have since become the most commonly used metheds in inverse solutions [ $6,29,30,65,70$ ]. The specific types of Tikhonov regularization include zero-order, Laplacian, and gradientoperator smoothing (discussed in detail in section 3.1.4).

### 2.1.3.3 Validation

While direct validation of an inverse solution in terms of epicardial potentials is possible, there are a number of practical problems. For example, epicardial potentials and body surface ECGs should ideally be measured simultaneously with sufficient spat'al and temporal resolution to accurately reproduce the distributions over both surfaces. This requires not only that electrodes be affixed to the epicardium with the chest intact, but also that the measurement system be capable ot recording simultaneously the order of 200-300 individual leads at 500-1000 samples per second [75, 76]. For obvious ethical reasons, this is only feasible in animal experiments. Furthermore, the geometry of at least the body and heart surfaces must be known, if inhomogeneous
regions (eg., lungs) are to be included, each must also be defined geometrically and electrically through its conductivity properties. Barr and Spach validated both the electrical and geometrical integrity of their inverse solution by recording from chronically implanted epicardial electrodes and from body surface electrodes in a dog from which they subsequently obtained complete geometrical measurements [50, 74]. Cuppen and van Oosterom solved the inverse problem in humans in terms of activation times on the epicardium and endocardium (see below); they compared their results with data measured previously by Durrer et al. from a reperfused isolated human heart [59, 60]. Monro et al. [49], although not constructing an inverse solution per se, correlated epicardial electrograms from several implanted wire electrodes with simultaneously recorded ECGs in 21 coronary-bypass patients and mapped regions on the hody surface which showed a high correlation coefficient with electrograms. They found that in most cases in which ECGs were well correlated with epicardial electrograms, the body surface region from which the ECGs were obtained lay directly over the site of the epicardial electrogram; however, there was considerable overlap of correlated regions [49]. Acquisition of accurate geometrical information has become considerably less trnublesome with the availability of nuclear magnetic resonance imaging (MRI) systems with a spatial resolution of $2-3 \mathrm{~mm}[77,64,78]$.

Another method of direct validation is to suspend a source, be it an artificially constructed one (eg., a dipole) or an actual perfused heart, at a known location in a tank of known dimensions and measure potentials both on the wall the tank and near or on the surface of the source. This approach has been used extensively by Colli Franzone et al. [79, 66, 67, 68, 69] and Johnson [70]. While this method cannot completely replace experiments on the intact animal or human body, it does allow tight control over many parameters which affect the outcome of the model calculations:

1. The tank can be moulded to resemble a human shape and its geometry need only be measured once.
2. Conductivity inhomogeneities can be introduced one by one into the volume conductor to evaluate their effect on the accuracy of the solution.
3. The value of the potential can be measured anywhere in the tank and the number of locations sampled depends only on the technical limitations of the recording system.

It is also possible to validate a forward or inverse solution by means of data generated by computational means. Using realistic torso and heart geometry, the potential distribution on both the epicardial and torso surfaces can be calculated for some defined sources, such as a single dipole at a predetermined location. These data can then be quantitatively compared using the forward and inverse solutions. This approach was taken by Walker and Kilpatrick [29] and Yamashita and Takahashi [65]; it is also adopted in this dissertation (see section 3.1.4).

### 2.1.4 Some specific inverse solutions

Investigators at Duke University have published a long series of seminal articles and dissertations on the topic of inverse solutions. From the early work of Rogers [80], Barr [81] and Martin [54, 55] came the ideas and framework for subsequent studies of inverse electrocardiography in terms of epicardial potentials. Martin and Pilkington $[54,55]$ described the problem in terms of the potential distribution on a small sphere enclosing the heart. They used a Green's theorem approach to derive a matrix of forward transfer coefficients; to the irversion of this matrix, they applied both statistical constraints, based on work by Foster [73] and Strand and Westwater [82, 83], and a regularization technique described by Twomey [84]. In comparative studics, they concluded that the statistical methods were better suited to the regularization problem since no explicit a priori knowledge of the relationship between epicardial and body-surface potentials was required.

Barr, Ramsey and Spach subsequently devised a scheme, also using the Green's theorem approach, whereby the forward transfer coefficients could be derived in terms
of potentiais on the rea ${ }^{1 \times}$ ically-shaped epicardial surface $[56,57]$. The details of this method are described in section 3.1.3. For their inverse solution, Barr and Spach [50] selected the statistical methods described by Martin [54]. They were the first to compare measured with calculated values of epicardial potentials, and they found that the overall features of the true epicardial potential maps were reasonably well reproduced by their calculations.

Horacek et al. developed an inverse solution based on the method of Barr, Ramsey, and Spach, which they applied to a realistic human torso model [58]. To compute the inverse matrix from the (ill-conditioned) forward transfer matrix, they made use of a regularization method suggested by Hanson and Phillips [85] to generate a system which could be solved using singular value decomposition [86]. Horacek and co-workers applied their inverse solution to measured body surface maps of the QRS complex and interpreted the resulting epicardial maps in terms of the temporal development of the potential distribution, which allowed comparison with classical activation data gathered earlier by Durrer et al. [87].

Although the forward/inverse problem cannot in general be solved analytically, there are certain simplified geometries for which analytical solutions can be derived. Rudy and Plonsey [88] used an eccentric spheres model of the torso introduced by Bailey and Berry [89, 90, 91] to examine the effects of volume conductor properties and surface geometry on the forward/inverse problem [92]. In the eccentric spheres model, the torso is represented by the largest of several nested spheres, which contains spheres for the epicardial and endocardial surface of the heart, the lungs, and the subcutaneous muscle of the torso. The source of current in this model is a spherically shaped double-layer cap (with uniformly distributed dipole moment per unit area) located between the endocardial and epicardial spheres of the heart. By altering the size and location of the subvolumes of the model, and changing the conductivity of each, the effects of variations in geometry and electrical properties on the relationship between epicardial and torso potentials were evaluated. In more recent work, Rudy
and Messinger-Rapport [6, 7] developed a numerical solution to the inverse problem using the boundary element method and Tikhonov regularization, which they compared to the analytical solution derived from the concentric spheres geometry.

A slightly different approach to the inverse problem was taken by Cuppen and van Oosterom [59, 93]; instead of evaluating the inverse solution for epicardial potentials, they derived a solution in terms of ventricular activation times on the epicardial and endocardial surfaces of the heart. Geselowitz subsequently provided additional theoretical support for this technique by applying the formalism of the bidomain theory $[94,95,96]$ to the ECG. He showed that the area under the QRS complex of the ECG is related to the amplitude and activation time of the underlying myocardial action potentials; the area under the QRST, on the other hand, was shown to be a function of the area under the action potential and, thus, its amplitude and duration [97]. The basis of Cuppen and van Oosterom's approach was to treat the source of electrical activity as a uniform dipole layer moving like a wave through the myocardium. According to this model, activation of a cell drives it from its resting or "off" state, to its excited or "on" state, in which it remains until the whole heart is depolarized. The resulting system of equations is similar to that generated by inverse solutions based on epicardial potentials in that it is ill-conditioned and requires some form of regularization. In their initial work, Cuppen and van Oosterom used a truncated singular value decomposition to calculate a pseudo inverse matrix of transfer coefficients [59, 60].

More recently, Huiskamp and van Oosterom have refined both the on-off nature of the conceptual model and the numerical mathematics of the inverse solution $[30,63,64,98]$. The simple Heaviside step function, which had been used to describe the transition from "off" to "on" states in previous work, was replaced by a smooth sigmoidal function. Numerically, an iterative method of computing the inverse solution was implemented using the truncated pseudo inverse as the starting point; once an error estimate was iteratively minimized, regularization was applied
until physiologically acceptable activation times were obtained [30]. Validation consisted of: 1) qualitatively comparing inverse solutions from normal subjects [30] with activation data collected previously frem a perfused human heart by Durrer et al. [87]; 2) aligning one of the hearts used in Durrer's study in the computer model of the torso of a healthy subject and comparing computed activation maps with the Durrer data [87]; and 3) recording body surface maps from a patient before heart transplant, then recording epicardial electrograms from the excised heart using Langendorff perfusion [63]. Although in method 1) the body surface ECGs and epicardial electrograms came from two different individuals, the results of the inverse solution could be compared qualitatively with the measured activation maps. In 2) and 3) the calculated activation maps were considered physiologically reasonable, and forward solutions generated from them matched measured BSPM data quite well. However, direci comparisons of the calculated data with measured values in 2) and 3 ) were less then satisfactory. Especially in the case of the heart-transplant patient, the activation sequence of the excised heart indicated significant abnormalities, which the authors suggested might have resulted from the removal and handling of the discarded heart.

Walker and Kilpatrick devised a different conceptual model in which they represented the geometry of the torso as a nonuniform rectangular grid and the electrical interactions between the nodes by a resistor network [29]. By applying Ohm's and Kirchhoff's laws to each node point, they derived a sparse system of linear equations which could be solved numerically to produce a forward solution in terms of epicardial and body surface potentials. From clinical CT-scans, they produced a set of eight different human-torso geometries; lungs, spine, and sternum were routinely included in each, but were removed from one torso for the purpose of evaluating the influence of inhomogeneities on the calculations. For each of these geometries, a single dipole source was located in the heart and a forward calculation was performed for both epicardial and body surface potentials. These data provided the 'measured' potentials which were used either as input data for the inverse solution or as the epicardial data
against which the results of inverse solution were tested. Walker and Kilpatrick then evaluated the effects of errors attributable to incomplete or inaccurate geometrical information on the outcome of the forward solution. The results indicated that while the inclusion of inhomogeneities in the model reproduced more accurately the potential distributions, only the amplitudes were significantly altered. Far more important was the rendition of the subject's geometry. For the inverse calculation using actual measured body surface potentials, validation was carried out in an indirect manner; for each value of the regularization parameter a new inverse solution was derived, which provided, in turn, the input data for the forward solution. The output of the forward calculation was then compared with the measured potentials. Walker and Kilpatrick also computed a "noise amplification fantor", which they defined as the ratio of the average rms epicardial potential to the average rms ECG amplitude. The noise factor was interpreted as the value by which noise in a body-surface lead would be multiplied using the inverse matrix and was used as a measure of the stability of their solution. Values of the noise amplification factor of as high as 2000 were found to arise when no regularization was performed.

An even more fundamentally different approach to the inverse problem was taken by Nikias et al. [99, 100, 101, 102]. Instead of defining their model in terms of potentials which change with time, Nikias and co-workers transformed the problem from the time domain into the frequency domain and constructed inverse solutions in terms of the power spectrum of the epicardial potentials. In one case, the Minimai Relative Entropy principle was used to successively refine the approximation of the epicardial power spectrum from an initial (white noise) estimate [99, 102]. Early results indicate that this approach may prove less sensitive to measurement noise and require fewer torso elertrodes than "standard" inverse solutions [102]. While direct physiological interpretation of the results of such a frequency-domain model is difficult, these methods have been successfully used in canine preparations to localize and quantify the extent of ischemia $[100,101]$.

Most recently, the BEM has been used to compute epicardial potentials which arise from the application of a defibrillation pulse to the thorax [39, 40]. In a related study, Wolf et al. employed the BEM method to estimate endccardial potentials from those recorded on the epicardium [41]. The aim of these efforts was to generate a mathematical model of the effect of defibrillation on myocardial tissue so that the shape, width, and duration of the shock pulse and the site of its application could be optimized.

### 2.2 PTCA: A Model of Controlled Ischemia

### 2.2.1 Introduction

Coronary artery disease (CAD) remains the leading cause of death is the Western World, despite major advancements in understanding, prevention and treatment of this condition [103]. Underlying virtually all occurrences of myocardial ischemia in humans is a substrate of CAD, often a longstanding atherosclerotic narrowing of the coronary arteries [104]. There is as yet no treatment of CAD; palliative care ranges from reduction in stress on the heart or temporary dilatation of the coronary arteries with drugs, to invasive replacement of diseased portions of the coronary system ("bypass graft" surgery). Recently, a less invasive (nonsurgical) procedure has been introduced with which it is possible to mechanically restore adequate flow through a severely occluded coronary artery. In this procedure, called percutaneous transluminal coronary angioplasty (PTCA), a balloon-tipped catheter is inserted via an incision in the femoral artery into the occluded coronary and inflated to pressures of 4-12 bar for durations of $10-300 \mathrm{~s}$. Inflation of the balloon results in mechanical disruption of the plaque deposits and intimal linings of the vessel and, if successful, restores some degree of patency to the vessel. PTCA can be performed on any part of the coronary circulation, which consists of three main arteries: the left anterior descending (LAD), left circumflex (LCx), and right coronary (RC). Developed and first performed on a human in 1977 by Andreas Grüntzig, [105, 106, 107, 108, 109, 110, 111, 112], PTCA continues to undergo significant refinements and now enjoys worldwide acceptance as a viable alternative to coronary bypass graft surgery in as many as $20 \%$ of cases of severe coronary artery disease (see recent reviews [113, 114, 115]).

Balloon inflation during PTCA completely occludes the coronary artery under treatment and produces severe ischemia in tissues supplied by the vessel. Observing the course and consequences of this artificially induced ischemia remains a topic of considerable interest both in animal models [116, 117, 118, 119] and in humans under-
going clinical PTCA. Interest has focused specifically on changes in cardiac function [ 120,121$]$, haemodynamics of coronary perfusion $[122,123,124]$ and body-surface ECGs. The latter studies have dealt with changes in ST segments and T waves $[125,126,127]$, QRS complexes [128, 129], and with body surface potential distributions [130, 131, 132, 133, 134, 135]. The interest in PTCA goes beyond attempts to evaluate and improve the procedure itself; PTCA also provides an excellent model for reproducible, acute ischemia in humans. Much of the present knowledge of ischemia is based on invasive and destructive experiments in animal models and, therefore, can be applied only with caution to humans due to anatomical and physiological differences among species [136, 137]. Balloon angioplasty, on the other hand, has been shown to produce responses which mimic those seen in acute myocardial infarction and thus it provides a unique opportunity to follow such changes in vivo in humans $[126,138,139,121]$. Not only does PTCA generate ischemia which is controlled and reproducible; an accurate baseline is provided by the patient's own pre-inflation state. In addition, the location and to some degree the extent of the ischemia are also well documented by angiographic data which are routinely collected both before and during the procedure.

### 2.2.2 PTCA and functional changes

Inflation of the catheter balloon during PTCA stops antegrade perfusion of the artery under treatment, which induces a number of measurable responses. Specifically, such physiological parameters as left ventricular performance [140, 120, 141, 142], regional blood flow [140, 143, 144, 145, 146, 147], wall motion [140, 120, 121, 148, 149], lactate metabolism [140, 150], coronary potassium concentration [151, 152], and coronary pH [139] have been observed to change during the inflation/deflation cycle in PTCA in humans. Following inflation of the bailloon, physiological parameters normally follow a course of more or less gradual deviation from baseline, which sometimes reaches a peak after 10-40 s ; deflation usually results in a complete return to baseline values over a
somewhat more variable time period. Many haemodynamic parameters demonstrate a transient, post-deflation exacerbation in response to the release of ischemic stress [140, 143, 144].

Early studies of PTCA-induced ischemia concentrated on haemodynamic effects; Rothman et al. [143], for example, detected first a decrease and then, after deflation, a transient increase in venous flow rates with relatively short (10 s) inflations. Similar episodes of "reactive hyperaemia" after inflations of longer duration have since been reported in other studies [140]. Rothman et al. also demonstrated transient reductions in venous oxygen saturation, aortic pressure, and the first time-derivative of left ventricular pressure ( $d P / d t$ ) during balloon inflation [143].

A confounding factor in any examination of data obtained from patient undergoing PTCA is the role of collateral circulation, that is, perfusion of one and the same region of the coronary tree from two different sources. This can take the form of subepicardial and angiographically-visible connections called anastomoses, which link major portions of the coronary beds supplied by opposing main arteries. However, it is also possible, in humans but apparently not in dogs, for anastomoses to exist between narrower vessels further down the arterial tree and deeper within the myocardium [153]. Collaterals may link different coronary arteries, or different branches of the same artery, or even form around an existing stenosis [154]. Collaterals are generally thought to be latently present in human hearts, developing to any functional degree only in the presence of severe ( $>90 \%$ ) coronary artery disease $[154,104]$. The physiological significance of collaterals is still a matter of much debate.

Several groups have examined the effect of collaterals on a number of electrocardiographic and haemodynamic indices during PTCA [155, 123, 127]. Feldman and Pepine divided a small cohort (19 cases) of LAD-artery patients into two groups, depending on whether or not retrograde filling of the LAD could be observed. They found only statistically insignificant differences between the two groups in terms of ST-segment shifts, heart rate, aortic pressure and coronary pressure distal to the oc-
clusion. On the other hand, there were significant differences in ventricular filling pressure and a "coronary collateral resistance index", which they defined in terms of pressure- and flow-indices of collateral perfusion. A study of 118 patients by Bottner et al. revealed a significantly higher incidence of ECG response to PTCA (ST-segment shifts in Holter lead $V_{2}$ ) in a patient group with collaterals than in the group without [127]. Meier et al. conducted a study in which the presence of collaterals was correlated with the degree of stenosis, electrocardiographic changes (ST-segment shifts or altered $T$ waves) and coronary pressure proximal and distal to the occlusion, both before and during inflation of the catheter balloon [123]. In patients with visible collaterals, there was a higher degree of stenosis, fewer electrocardiographic changes, less occurrence of chest pain, and higher distal coronary pressures during the balloon inflation.

The PTCA procedure has provided an excellent model for the study of collateral flow itself, since the complete occlusion of one main coronary artery allows the contribution via collateral circulation of the other(s) to be studied [146, 147]. In a study by Cohen and Rentrop, patients undergoing PTCA of one artery had contrast medium injected and angiograms recorded from the contralateral one. In 15 of 17 patients, collateral channels were visible in the angiograms recorded during balloon inflation, while only 5 of 17 had collaterals detected before or after inflation [147].

In summary, there remains little doubt that patients in whom an angiographicallyvisible collateral system has developed, experience fewer and less intense ischemiarelated effects during PTCA balloon inflations. The functional significance of collaterals which are visible only during episodes of PTCA-induced ischemia, referred to as recruitible collaterals, remains unclear.

Two-dimensional echocardiography was first used by Hauser et al. to characterize transient wall motion abnormalities in humans during PTCA [121]. In a series of studies, Serruys et al. used echocardiography, radio-opaque epicardial wall markers and coronary angiography to monitor changes in ventricular wall motion, contraction,
and ventricular pressure brought about by 50 -second balloon occlusions in human subjects undergoing PTCA [120, 140]. Most notable of their results was a reversible response, which they described as the "W-phenomenon", characterized by late systolic lengthening and early diastolic shortening of ventricular wall segments located within the ischemic zone. First signs of the W-phenomenon were detected as early as on the fourth beat after occlusion; by 3 min post-deflation, it had disappeared. As an explanation for the W -phenomenon the auti ors suggested that the affected wall segments were rendered inactive, but slightly stiffened over resting conditions; they then responded essentially passively to the pressures within the chamber created by the remaining perfused and active myocardium.

Wohlgelernter et al. [156] reported a similar time-course of the measurable response to balloon inflation, beginning with wall motion abnormalities (at 10 s ), followed by electrocardiographic ST-segment changes (at approximately 22 s), and finally angina (after 30-40 s). In addition, they found no significant differences in several indices of ischemia, both echocardiographic (magnitude of peak dysfunction, time to onset of regional dysfunction, left ventricular ejection fraction) and electrocardiographic (magnitude and time to onset of ST-segment displacements), among groups of patients who demonstrated either no PTCA-induced angina ("silent ischemia"), angina at each inflation, or only occasional angina. Data were included in the study only from subjects in whom no angiographically-determined collaterals could be detected. The findings of Wohlgelernter et al. reinforce the opinion that chest pain is a poor indicator of both the extent and degree of ischemia.

Griffen et al. describe an analogous response to PTCA balloon inflation in patients without angiographically-observable collaterals [126]. The echocardiographic indicator detected in all patients studied was the appearance of a new wall motion abnormality, which occurred with a mean time delay after inflation of $13 \pm 5 \mathrm{~s}$. STsegment shifts appeared in nost (14 of 16) cases with a mean time delay of $19 \pm 12 \mathrm{~s}$ after inflation. These investigators also showed an inverse linear relationship be-
tween the time to onset of either echocardiographic or electrocardiographic changes and the rate-pressure product (heart rate $\times$ aortic systolic pressure). Reducing the rate--pressure product appeared to delay onset of ischemic symptoms, but cnly to a maximum of 30 s after inflation - not sufficient time to protect the myocardium from the ischemic stress of balloon inflation.

There is still a great deal of speculation regarding the physiological basis of the reduction in contractile activity observed in these PTCA studies. Of special note is certainly the rapid response (within 10 s of balloon inflation) of mechanical or contractile parameters to this acute and complete ischemia. Both the electrical events which precede and presumeably initiate this response, and their underlying cellular phenomena, will be discussed in the next sections.

### 2.2.3 PTCA and electrocardiographic changes

The ability to detect body-surface electrocardiographic changes from single ECG leads during balloon inflation varies greatly in the studies described in the literature. The use of both limb leads a - $n$ lected supplementary precordial leads (typically $\mathrm{V}_{2}$ and/or $\mathrm{V}_{5}$ ), yielded adequate sensitivity in some studies (Feldman et al. recorded STsegment shifts in 22 of 30 patients ( $73 \%$ ), 20 of whom had collaterals [128]) but not in others (Hauser et al. detected ischemic ECGs in only 8 of 19 patients (42\%) [121]). A full 12-lead precordial system using radiolucent electrodes detected significant changes in ST segments after 60 s of balloon inflation in $86 \%$ percent of one patient group screened for lack of collaterals [157]. Hoberg et al. described a Holter monitoring system using two bipolar chest leads, $\mathrm{CM}_{5}$ and $\mathrm{CC}_{5}$, with which they detected shifts in ST-segment trends in all 26 subjects of a study group [158].

The conclusion drawn by most investigators is that electrocardiographic effects do result from PTCA, except in cases in which a considerable degree of collateral flow is present. The ability to detect these changes is only a matter of adequate choice of both the lead system and the method of processing the recorded signals. This
conclusion is not surprising considering the consistent reports of severe changes in mechanical and haemodynamic parameters during angioplasty. The choice of ECG leads is often restricted by the radio-opacity of standard metallic ECG electrodes since precordial leads which obstruct the fluoroscopic image cannot be tolerated in the PTCA procedure.

Elucidation of the electrocardiographic effects of angioplasty on ST-segment changes was offered by Macdonald et al. in a study in which they differentiated between STsegment elevation and depression in standard leads $I, V_{2}$, and $V_{5}$ (and excluded patients with no ST-segment changes) within a cohort of patients undergoing PTCA of the LAD artery [159]. Of the concomitantly monitored haemodynamic parameters, which included great cardiac venous flow, aortic, left ventricular filling and distal coronary pressures, and collateral resistance, only distal coronary pressure, great cardiac vein flow, and collateral resistance were found to differ significantly between the two groups. All patients showed either ST elevation or depression, that is, never alternating directions, in repeated .nflations; the ST-depression? group displayed higher distal coronary pressure and great cardiac vein flow together with reduced collateral resistance. Macdonald et al. evaluated these findings in terms of the commonly-held, and theoretically supported (see section 2.2 .4 ) view that ST-segment elevation in a precordial surface lead reflects transmural ischemia, while the less severe subendocardial ischemia demonstrates itself by ST-segment depression. The haemodynamic differences between the two groups suggest a smaller reduction in perfusion in the ST-depression group than in the ST-elevation grorp, in accordance with the former's presumed lesser severity of ischemia. This interpretation of the results also implies an "all or nothing" model of ischemia, which assumes that each patient either has ST elevation or ST depression and never progresses from one state to the other over the duration of the balloon inflation [159].

The study by Bottner et al. would seem to substantiate the notion that STsegment elevation is linked to more severe ischemia [127]. ST-segment elevation in the

Holter ECG leads $V_{2}$ and $V_{5}$ occured in $75 \%$ of patients without collateral circulation but in only $13 \%$ of patients with documented collaterals. ST-segment depression was found with equal frequency ( $8 \%$ ) in both groups.

More recent studies have concentrated on varinus aspects of the morphology of the electrocardiogram recorded during balloon angioplasty, examining not only the ST segment but also the QRS complex and $T$ wave of the ECG, in both filtered [160] and unfiltered [121, 125, 128, 157] form; also investigated were effects of PTCA on vectorcardiograms [129, 161, 162, 163], intracoronary electrograms [164, 165] and even on the spatial distribution of "reciprocal" ECG changes [166].

Abboud et al. developed a computer-aided system of ECG processing for detecting QRS, ST-segment and T-wave morphological changes during PTCA [160]. Single-lead ECGs recorded during balloon inflation were either cross-correlated with a single beat from the pre-occlusion interval or digitally band-pass filtered between $150-250 \mathrm{~Hz}$. Changes in the cross-correlation coefficient of the QRS complexes or in the rms amplitude of the filtered QRS occurred in $80-90 \%$ of patients and could be detected sooner after inflation than changes in ST segments. These findings indicate that the high-frequency content of the QRS complex on the body-surface can serve as a sensitive and rapid indicator of ischemic changes brought about by balloon occlusion.

Abboud et al. also made use of a novel type of electrode which was constructed from the balloon catheter guide wire to monitor the intracoronary electrogram [160]. Notable in this study was that early indications of inflation-induced ischemia monitored as ST-segment shifts could be detected with the intracoronary lead typically within several seconds after balloon inflation, whereas standard surface leads $I, V_{2}$ and $V_{5}$ remained insensitive for up to 30 s . Similar results were reported earlier by Friedman et al. [164] in a more heterogeneous population of angioplasty patients, some of whom demonstrated angiographically-significant collaterals. Using an intracoronary electrode, they measured ST-segment shifts in 21 of 29 cases, while only 9
of 29 cases demonstrated similar shifts in a body-surface lead.
In a further study of QRS changes due to PTCA by Friedman et al., R-wave amplitude was examined, both with surface and intracoronary electrodes, before and during inflation of the angioplasty balloon [128]. Body-surface signals were averaged over a 10 -second period immediately before balloon deflation, while intracoronary electrograms were collected throughout the inflation. There was no increase in Rwave amplitude, but instead a small, statistically insignificant decrease during the balloon occlusion. Conversely, T-wave amplitude was found to increase during occlusion, both in surface leads and in the intracoronary electrode. This lack of increase in R-wave amplitude during occlusion appears to contradict the well-documented incidence of enlarged $R$ waves as a marker of myocardial ischemia [167, 168, 169, 170]. Feldman et al., however, point to considerable evidence in animal models that R-wave amplitude displays a biphasic response to ischemia - initially reduced, but subsequently enlarged over a time course which exceeds that typically seen in standard PTCA [171, 172, 173, 174].

### 2.2.4 Cellular mechanisms and the ECG in ischemia

The ECG recorded from the body surface is a consequence of the electrical activity of the cells of the heart. Hence, electrocardiographic changes due to PTCA must reflect altered myocardial electrical activity in response to the stress of acute ischemia. Experimental evaluation of the effect of myocardial ischemia has been based almost exclusively on data obtained from animal preparations and, thus, care must be taken when applying the results to humans. In the interests of brevity, for there exists a vast body of literature on this subject, the discussion will largely be restricted to those mechanisms pertaining to the "hyperacute" phase of ischemia spanning the first 1-3 min, as in PTCA inflation. The word 'acute' also implies ischemia of sudden onset, in contrast to 'chronic' ischemia which has existed for some time. Attention will be directed to the relationship between phenomena at the cellular level, and their
measurable manifestation on the epicardial and body surfaces (known as epicardial electrograms and body-surface electrocardiograms, respectively).

Studies from as early as 1903 have demonstrated the ability of the heart to resume regular activity after considerable periods of ischemia [175]. It was not until much later that development of intracellular recording techniques allowed direct access to the electrical activity of the individual cell [176]. In the 1950s these methods were successfully applied to cardiac tissue rendered either hypoxic (no oxygen but maintained perfusion) or ischemic (no perfusion) in either cardiac tissue preparations [177], or excised, perfused whole hearts [178]. In the intervening years, a great number of experiments have been performed on a variety of animal models of ischemia, and techniques have likewise progressed so that not only electrical activity, but also contractility, excitability, metabolism, and extra- and intracellular milieu can be measured.

The current state of thought is that myocardial cells go through three stages of response to acute ischemia. Beginning withar seconds of the occlusion is a modest (several mV ) but quick (within $10-30 \mathrm{~s}$ ) depolarization of the resting potential. This is followed over the next 5-20 min by a second stage of more gradual reduction in duration, amplitude, and rate of rise of the action potential, accompanied by a diminution of contractile force; the endpoint of this second stage is a steady state in which the cell is inactive with much reduced (more positive) resting potential. Reperfusion during either of these first two stages, collectively known as the "reversible" phase, will restore complete function of the cell, while a prolongation of ischemia beyond 15-20 min drives the tissue into a third and "irreversible" phase, which ends in cell destruction and death. Progression through these three stages varies, depending on the type of cardiac cells involved, the degree of ischemia and the local environment in which cells are situated (see $[104,171,179]$ for recent reviews).

### 2.2.4.1 TQ/ST-segment shifts

A great deal has been written about the mechanisms of the electrocardiographic indicators of ischemia, the best documented of which is the shift in potential during the TQ and ST segments of the ECG (see reviews [104, 171, 180] and [181, 182, 183]). Attempts to establish diagnostic criteria for the degree and extent of myocardial infarction in humans based on TQ/ST-segment shifts have generated a great deal of controversy [184, 185, 186, 187, 188].

The first reported observation of ST-segment shifts in a patient with coronary artery disease was by Pardee in 1920 [189]. Subsequent investigators proposed that these shifts were the reflection of a "current of injury", which was generated by differences in potential between ischemic and healthy tissue; these differences were believed to arise either during diastole, due to changes in resting potential [190], or during systole as a result of reduced plateau potentials of cells in the ischemic region [191]. In 1960, Samson and Scher reported results from simultaneous measurements of epicardial, intramyocardial, and intracellular potentials from ischemic canine hearts [192]. By using recordings from direct-coupled amplifiers, they showed that injury current flows during both diastole (because of a depolarized resting potential) and systole (due to the shortened AP-duration in ischemic cells).

These ideas remained unchallenged until the mid-1970s when precordial ST-segment mapping as a means of estimating extent and severity of ischemia was developed [184, 185, 186, 187, 188]. Conventional ECG amplifiers are AC-coupled and thus incapable of resolving injury currents into diastolic (TQ-segment) and systolic (STsegment) components. Since these two components are the results of fundamentally different conditions, it became crucial to evaluate the relative strength of each, as well as to advance understanding of the relationship between injury current and the spatial distribution of the underlying ischemia. Of the literature from this period, the review by Holland and Brooks [180] stands out as the most comprehensive. Employing both theoretical arguments and experimental data, the authors demonstrate the danger in
applying too simple a correlative model to the evaluation of TQ/ST-segment shifts and their diagnostic potential. Magnitude, polarity, and distribution of potentials produced by injury current are all complicated functions not only of the degree of ischemia, but also its location, spatial extent, and the amount of time elapsed since the onset of occlusion [180].

The complex time-dependence of the evolution of ST/TQ-segment shifts was demonstrated by Kléber et al., who recorded DC-coupled epicardial electrograms and transmembrane action potentials from adjacent regions in the ischemic porcine heart [37]. The first change they observed after occlusion was a loss of membrane resting potential and concomitant depression of the TQ-segment of the epicardial electrograms. The situation during systole was found to be somewhat more complicated. Kléber et al. reported that the loss of resting potential was followed within several minutes by a reduction in AP amplitude, with initially no appreciable delay in activation time of the cells in the ischemic region [37]. They postulated that during systole, the intracellular potential of the healthy tissue was slightly more positive than that of the ischemic region; the resulting current flowed from healthy to ischemic tissue, which they recorded as an elevation in the ST segment in epicardial electrograms. After several more minutes of ischemia, however, a sizeable delay in activation, together with a shortening of the ischemic AP, was observed. This was thought to generate an even greater potential gradient and a systolic intracellular current, which again flowed from the healthy to the ischemic tissue, producing ST-segment elevations in the epicardial electrograms. As a result of the changes in AP configuration and timing, the polarity and shape of the $T$ wave now became a function of the relative delay in excitation and duration of the AP in the ischemic cells compared with that in the healthy cells [37, 193].

This basic picture of the effects of ischemia on TQ/ST-segment shifts in the cardiac electrogram and body surface ECG, which has remained unchanged up to the present, is summarized in Figures 2.1-2.3. Figure 2.1 displays schematically the nor-


Figure 2.1: The relationship between the action potential shape and timing and the morphology of the normal ECG. The top row shows endocardial and epicardial action potentials while the bottom tracing is the unipolar ECG recorded by an electrode located on the body surface close to the heart. The duration of the epicardial AP is shorter than that of the endocardial, which produces a positive $T$ wave. During both the TQ and the ST segments, the tissue is isopotential and no ECG deflection is recorded.
mal situation. The endocardial and epicardial APs are very similar in shape but differ in the time of activation (endocardial first) and the duration (epicardial shorter). A unipolar electrode placed on the body surface over the epicardium senses an intracellular potential gradient directed towards it as a positive deflection. When both endocardial and epicardial regions are at rest (diastole), no potential gradient exists and the ECG shows no deflection. Similarly, when the entire heart is depolarized (ST segment), the ECG shows no deflection. The ECG shows deflection only while excitation is quickly spreading from endocardium to epicardium (QRS) and when repolarization returns the heart to the resting state ( $T$ wave). $R$ wave and $T$ wave are concordant since the complementary processes of excitation and repolarization proceed in opposite directions.

Figures 2.2 and 2.3 show the situation when a region of the heart first becomes ischemic. The AP from such a region displays a depolarized resting potential, reduced amplitude, and a slower rate of rise but initially unchanged duration. In both figures, panel A shows an ischemic region located in the subepicardium. During diastole, intracellular current flows from the depolarized ischemic zone into the surrounding healthy tissue, that is, away from the sensing electrode; this produces a negative deflection in the surface ECG. During systole, the direction of current flow is reversed due to the reduced amplitude and duration of the ischemic AP; current flows from healthy to ischemic regions, toward the sensing electrode and a positive deflection is detected. When the ischemic region is located in the subendocardial region, the situation is quite different, as shown in panel B of both Figures 2.2 and 2.3. In this case, the endocardial AP has reduced amplitude and duration. The resulting diastolic current again flows from ischemic to healthy tissue, but this current is now directed toward the epicardium; a surface ECG electrode senses this as a positive deflection. During systole, there is a reversal in the direction of current which results in ST-segment elevation.

In Figure 2.2 there is no delay in excitation of the ischemic tissue and the duration


Figure 2.2: The flow of injury current during both diastole (TQ) and systole (ST) arises from the potential gradient between healthy and ischemic tissue. Panel A shows the AP (top) and ECG (bottom) in the case of a region of epicardial ischemia, shown in the centre row as a hatched area; in panel $B$ the ischemic zone is located subendocardially.
of the AP is only slightly reduced; in panel B the endocardial AP still persists beyond the end of the epicardial AP. Therefore, the ST segment is negative and the T wave remains positive and concordant with the R wave. If, as shown in Figure 2.3, there is a delay in excitation and a further reduction in AP duration, the T-wave polarity will be reversed. These configurations were described by Kléber et al. [37], based on their simultaneous measurements of epicardial electrograms and intracellular potential.

With the more widespread use of multilead mapping systems, which allow the recording of electrograms or ECGs over a wider surface, has come the concept of "reciprocal" changes in TQ/ST segments; these are shifts of opposite polarity, which can be detected on the epicardium and bouy surface at locations spatially complementary to the sites of primary ST/TQ shifts $[182,183]$. These ant cenurd "secondary changes", since they do not represent a separate source of injury current but are the electrical reflection of the primary ischemia.


Figure 2.3: The additional effect of delayed activation and reduced duration of the AP in ischemic regions of the heart on the ECG.

### 2.2.4.2 Early stages of acute ischemia

There has been considerable investigation of the hyperacute stage of the myocardial response to ischemia that encompasses the 1-5 min immediately after cessation of perfusion, the period of time corresponding to the balloon occlusion of PTCA. One major reason for this intense scrutiny is the high incidence of spontaneous arrhythmias and ventricular fibrillation during the more advanced stages of this phase, as observed repeatedly in animal preparations $[194,195,196]$ and in humans (see reviews [171, 181]). Ever since Harris et al. first implicated a rise in extracellular potassium concentration $\left[\mathrm{K}^{+}\right]_{\mathrm{o}}$, in the occurrence of such acute ischemia-induced arrhythmias [196], the relationship between ischemia, potassium and electrical events in the heart has been extensively examined. Another conspicuous feature of the cardiac response to both hyperacute ischemia and increases in $\left[\mathrm{K}^{+}\right]_{\circ}$ is the occurrence of biphasic changes in conductivity and excitability (see reviews [181, 179, 104]).

In 1958, Swain et al. performed measurements of intramyocardial conduction time in a canine heart-lung preparation in which they stimulated at a single epicardial site
and monitored spread of activation with a row of epicardial clip electrodes [197]. A number of different substances were added to the blood perfusing the dog's heart to evaluate their effect on conduction time. The concentrations of the infusions were expressed in terms of the expected rise in plasma concentration, given a known volume of perfusate. During graded addition of potassium chloride, they observed a biphasic pattern in conduction time, consisting of slight decrease (at $2.5-3.0 \mathrm{mM}$ additional KCl ), followed by a large prolongation (at $6-7 \mathrm{mM}$ additional $\mathrm{KCl}_{1}$. Infusion of epinephrine resulted in no alteration in intramyocardial conduction times, even at doses which induced considerable shortening of AV-node delay.

Among the first to observe a temporary increase in excitability in hyperacute ischemia were C. Brooks et al., who found that the amplitude of the current pulse needed to stimulate regions of the ischemic left ventricle was reduced during the first several minutes after occlusion in 11 of 31 canine hearts [194]. Continued occlusion resulted in a gradual increase in threshold stimulation current. A similar biphasic response to acute ischemia was demonstrated in porcine hearts by Holland and H. Brooks [172]. From epicardial electrograms, they measured peak R-wave amplitude and ventricular activation time, defined as the time between base and peak of the $R$ wave, before and during occlusion of the LAD artery. Occlusion resulted almost immediately in a transient ( 20 s duration) $\mathrm{r} \quad$ action in both activation time and R -amplitude followed by a large increase in both parameters which peaked about 120 s after occlusion. Baseline levels were restored within several beats of relea, ng the occlusion. In another experiment, Holland and Brooks increased plasma $\left[\mathrm{K}^{+}\right]_{o}$ before each induced ischemic episode during which they measured the conduction time. At low to moderate $\left[\mathrm{K}^{+}\right]_{\circ}(3.4-8.8 \mathrm{mM})$, they found an inverse relationship between $\left[\mathrm{K}^{+}\right]_{\mathrm{o}}$ and initial conduction time, while at high $\left[\mathrm{K}^{+}\right]_{\mathrm{o}}(>8.8 \mathrm{mM})$ the initial conduction time was equal to or greater than preocclusion levels. Based on this evidence, they proposed that the electrical changes due to ischemia were driven by the leakage of intracellular potassium out of ischemic cells, a phenomenon previously
described in animal preparations [198]. The duration of the biphasic stage following occlusion was simply the time required before $\left[\mathrm{K}^{+}\right]_{\text {o reach }}$ a threshold value, which they proposed to be 8.8 mM ; any influence which prematurely boosted $\left[\mathrm{K}^{+}\right]_{o}$ reduced the duration of the biphasic period and, in the extreme, removed it completely.

Holland and Brooks also formulated a hypothesis for the mechanism of response of the heart to acute ischemia [172]. They examined the three essential components required for normal ventricular conduction: the Purkinje fibre network, the junctions between the Purkinje fibres and the myocardium, and the working myocardium itself. In experiments performed on isolated Purkinje fibres, Dominguez and Fozzard [199, 137] had found the same sort of biphasic response of conduction velocity to increased potassium concentration that had been observed by Holland and Brooks. Dominguez and Fozzard suggested that a slight increase in $\left[\mathrm{K}^{+}\right]_{\circ}$ (frcm 2.5 to 4.0 mM ) would drive the membrane potential marginally more positive and, hence, closer to threshold. Less current from neighbouring cells would then be necessary to elicit an action potential, which would, in turn, increase the speed with which excitation would proceed through the myocardium. A further rise in extracellular potassium, on the other hand, would drive the resting potential more positive and inactivate the fast sodium channels which are responsible for the rapid upstroke phase of the AP, reducing rate of rise, amplitude, and thus also conduction velocity.

Studies by Matsuda et al. [200] and Mendez et al. [201], cited by Holland and Brooks, documented a similar, biphasic response to slight elevations in $\left[K^{+}\right]_{0}$ at the junctions of the Purkinje fibre and myocardium; they observed a transient reduction in stimulation threshold followed by complete block at potassium levels $>11 \mathrm{mM}$ [201]. Direct evidence of the influence of changes in $\left[\mathrm{K}^{+}\right]_{\circ}$ on an intact heart was provided by Arnsdorf et al., who measured conduction times (intraatrial, intraventricular, atrioventricular and ventriculoatrial) with epicardial electrodes during gradually increasing hyperkalemia in dog hearts [202]. All conduction times decreased for slightly elevated values of $\left[\mathrm{K}^{+}\right]_{0}$ and rose beyond baseline for $\left[\mathrm{K}^{+}\right]_{0}>7-9 \mathrm{mM}$. The scenario
outlined by Dominguez and Fozzard has since become the most accepted hypothesis to explain the biphasic response of excitability and rate of excitation in the ischemic heart [174, 171].

Holland and Brooks further suggested that ischemia could bring about a change in the path of conduction, both because inactivated tissue would block spread of excitation, but also due to a more subtle diffraction of the excitation wave through regions with slightly altered conduction velocity. Thus, whether through changes in the Purkinje fibres, in their junctions with the working myocardium, or in the wo ${ }^{-}$king myocardium itself, the normal balance of multiple waves of excitation moving in different directions through the heart would be altered by ischemia and the QRS complex would be affected [172].

Several of these findings were corroborated by Elharrar et al. in a dog model, in which they activated the heart using an automatic threshold-following pacemaker which applied current pulses of minimal necessary duration [203]. In the first 3 min following occlusion, they detected a $17 \%$ decrease in the threshold stimulation pulse width, which was followed by a rapid and manifold increase in required stimulus width. They, too, found a marked dependence of the biphasic nature of the response on $\left[\mathrm{K}^{+}\right]_{o}$ and completely supressed transient reduction in threshold stimulus pulse width by pretreating the heart with a perfusate containing elevated $\left[K^{+}\right]_{o}(5 \mathrm{mM})$. When $\left[\mathrm{K}^{+}\right]_{0}$ was raised to $8-12 \mathrm{mM}$, threshold stimulus duration was reduced without occlusion, while at concentrations above this, the threshold stimulus pulse width was increased.

Further support for the occurrence of transient biphasic changes in excitation during acute ischemia was provided by David et al., who measured first R-wave amplitude [173], and later, intramyocardial conduction time (from endocardial to epicardial electrodes) [174], during acute ischemia in canine preparations. After 30 s of occlusion, they observed a $17 \%$ decrease in the sum of R-wave amplitudes from 5 surface-electrode leads which was concomitant with an $11 \%$ reduction in conduction
time. This finding was reversed at 180 s to a $53 \%$ increase in summed R amplitude associated with a $135 \%$ prolongation of conduction time. While electrical changes followed a biphasic pattern, haemodynamic parameters, such as end diastolic volume and cardiac output, changed monophasically. The authors interpreted this finding as proof that changes in the QRS amplitude represent a primary response to ischemia and do not simply reflect the changes in heart volumes via the Brody effect [204]. Data from a report by Barnhill et al. on coronary occlusion in a canine model show a similarly brief, transient increase in propagation velocity in both the longitudina. (along the fibre direction of the tissue) and transverse (across the fibre axis) directions, as well as a concomitant decrease in R-wave amplitude [118]. This initial phase is soon (within 1 min ) followed by an oppositely-directed progression to slower conduction and larger R waves. Employing both epicardial and endocardial electrograms, Kléber et al. recorded spread of excitation on the anterolateral wall of isolated pig hearts, using a matrix of 64 or 96 electrodes with DC-coupled amplifiers [38]. Their data also show a transient increase in both longitudinal and transverse conduction velocity, which occurred 1 min into the ischemic period.

Despite the evidence indicting extracellular potassium as the major, if not the only, contributing factor to the electrical response during acute ischemia, a study by Downar et al. provided findings which tempered this view [205]. By using blood draining from an ischemic porcine heart to perfuse another healthy heart, they elicited a full ischemic response, leading to eventual quiescence. While the $\left[\mathrm{K}^{+}\right]_{0}$ of this blood ranged from $7-9 \mathrm{mM}$, perfusion with blood containing artificially enhanced $\left[\mathrm{K}^{+}\right]_{\text {o }}$ to the same levels, even together with reduced pH and $\mathrm{pO}_{2}$, did not bring about the same effect. In fact, $12-16 \mathrm{mM}\left[\mathrm{K}^{+}\right]_{\text {o }}$ was required to induce the same response as the "ischemic blood". The authors were unable to determine what was present in the blood of their ischemic preparation, but altered potassium, pH and $\mathrm{pO}_{2}$ were not sufficient to mimic the effect.

Direct measurements of $\left[\mathrm{K}^{+}\right]_{0}$ in subendocardial, intramyocardial, and epicardial
regions by Hill and Gettes produced evidence of a heterogeneous distribution of potassium coucentration following acute occlusions in porcine hearts [206]. Levels of $\left[\mathrm{K}^{+}\right]_{0}$ were highest in the subendocardial region underlying the centre of the ischemic zone. Hirche et al. measured not only $\left[\mathrm{K}^{+}\right]_{0}$, but also pH and plasma norepinephrine following occlusion in pig hearts [195]. External pH dropped after occlusion, but with some delay ( 10 s ) and at a slower rate than $\left[\mathrm{K}^{+}\right]_{o}$; venous norepinephrine rose briefly during the first 5 min , but returned to baseline within 15 min . Occurrence of ventricular arrhythmias was also monitored during this time and followed a $\left[\mathrm{K}^{+}\right]_{\mathrm{o}}$-dependent time course, with an initial peak at about 3 min into occlusion, as $\left[\mathrm{K}^{+}\right]_{o}$ also reached its maximum value. The influence of catecholamines on the ischemic isolated rabbit heart has more recently been found to play a major role in the plateau phase of $\left[\mathrm{K}^{+}\right]_{0}$ changes, which occur some $7-10$ minutes after global occlusion [207], that is, not during the hyperacute phase we are concerned with.

In an attempt to further quantify the dependence of ischemic events directly on global perfusion rates, Watanabe et al. developed a unique preparation in which they shunted blood from the carotid artery to the cannulated LAD artery through a roller pump and were thus able to completely control perfusion in intact pig hearts [208, 209]. They applied a graded reduction in flow and recorded surface ECGs, epicardial monophasic action potentials (MAP) and electrograms, both on the epicardium and within the ventricular free wall. The appearance of TQ/ST-segment shifts, shortened MAP duration, and eventual inactivaivion, which mimic those changes associated with the acute phase of ischemia described earlier, could consistently be expressed as a function of perfusion rate, rather than as a function of time. One of their findings was that changes in electrograms recorded at sites within the myocardium occurred at higher global flow rates than changes at overlying electrodes on the epicardial surface. This result supports the present belief that perfusion during ischemia is most depleted in the subendocardial region, due to both its higher metabolic needs and the differential pressure within the myocardium which forces more blood to remain
in the epicardial layers [104]. Watanabe and co-workers also found that epicardial electrodes were relatively insensitive to significant levels of subendocardial ischemia in underlying regions, a phenomenon previously noted by Ross [210] and Flaherty [187].

Spatial mapping of $\left[\mathrm{K}^{+}\right]_{0}$ was performed by Coronel et al., who used an array of $10-48$ potassium-sensitive electrodes to measure distributions of both $\left[\mathrm{K}^{+}\right]_{0}$ and DC-potential over the epicardium of dog hearts during one- and two-stage occlusions [34, 211]. They observed considerable local spatial inhomogeneity in $\left[\mathrm{K}^{+}\right]_{o}$, both in the central, clearly ischemic, region and the border zone which divided it from healthy tissue. In general, afier 5 min of occlusion, the areas of high $\left[\mathrm{K}^{+}\right]_{0}$ corresponded quite well with those of depressed electrical activity. In some cases, however, regions were rendered inexcitable at lower levels of $\left[\mathrm{K}^{+}\right]_{\text {}}$ than expected. The authors suggested that the normal spread of excitation is inhibited by severely ischemic regions, which can surround and electrically isolate patches of otherwise still excitable tissue. Thus, not only local $\left[\mathrm{K}^{+}\right]_{o}$, but also the pattern of excitation, can affect the electrical response of the tissue. Coronel and co-workers also derived activation isochrone maps of the ischemic zone during sequences of normal, low-flow and no-flow conditions; they saw no significant change in spread of excitation during long periods of low-flow ischemia, when $\left[\mathrm{K}^{+}\right]_{\mathrm{o}}$ values had already risen by as much as 2 mM , until several minutes into the no-flow ischemic episode which followed. Thus, while no-flow ischemia always produced changes in spread of excitation, low-flow ischemia did not appear to alter its pattern. There were, on the other hand, shifts in TQ-segments during both low- and no-flow ischemia, whose distribution natched very closely that of the measured $\left[\mathrm{K}^{+}\right]_{0}$. Pooled TQ-segment shift data from all electrodes at any instant in time did not correlate well with the measured level of $\left[\mathrm{K}^{+}\right]_{0}$. However, the time course of changes in $\left[\mathrm{K}^{+}\right]_{o}$ and TQ-shift at each individual electrode was very similar and there was a highly correlated linear relationship between $\left[\mathrm{K}^{+}\right]_{\circ}$ and $T Q$-segment depression over the course of the occlusion. The slope of each TQ-change versus
$\left[\mathrm{K}^{+}\right]_{0}$ line differed from one electrode to the next, being smaller for electrodes located within the ischemic zone than for those outside or on the border between healthy and ischemic tissue.

A similar link between ischemia and potassium levels appears to exist in man. In 1954, Roesler and Dressler reported changes in ST segments and QRS morphology during spontaneous bouts of recurring, transient angina in two patients [212]. In another study, in which atrial pacing was used to induce transient ischemia, Parker et al. measured plasma potassium and lactate concentrations in the coronary sinus of a group of patients [213]. While in every case the response to pacing included increases in $\left[\mathrm{K}^{+}\right]_{o}$, those subjects who registered anginal pain during the test demonstrated larger increases in $\left[\mathrm{K}^{+}\right]_{0}$, significant lactate production, a drop in pH and larger STsegment depression than patients with no angina. Both lactate levels and pH were found to correlate well with $\left[\mathrm{K}^{+}\right]_{0}$. In several studies in which plasma potassium and pH were measured during PTCA, there was no change observed during balloon inflation, while each deflation was followed within 4-6 s by a transient decrease of pH and increase of $\left[\mathrm{K}^{+}\right]_{\circ}$ lasting approximately $1 \mathrm{~min}[139,151,152]$.

In human subjects, evidence of the regional differences in ischemia was provided by Donaldson et al., who recorded paced endocardial electrograms, monophasic action potentials (MAP) and surface ECGs in patients with reversible myocardial ischemia [214]. These investigators noted both a significant reduction in the time from pacing stimulus to the peak of the endocardial $T$ wave ("local repolarization time") and a concomitant delay in the time from stimulus to nadir of the QRS ("local activation time") within the ischemic region. By continuously augmenting the pacing frequency, Donaldson and co-workers could always detect the 'increased load' ischemia (versus the 'decreased supply' ischemia produced by PTCA balloon inflation) sooner, by a mean of 2.5 min , with the intracavitary electrodes than with a modified 12-lead surface ECG, demonstrating both the vulnerability of the subendocardial myocardium to acute ischemia and the relative insensitivity of body surface leads to ischemia in
the subendocardial region. Monophasic action potential (MAP) recordings showed reductions in amplitude and duration within the ischemic region during pacing.

At present, the question of what constitutes "ischemic blood" remains only partially answered; elevated potassium concentration and reduced pH are certainly part of the picture $[152,151,139,215,216]$ and catecholamines may play a role [195]. There remain, however, even more fundamental questions regarding the source of the extracellular potassium and its mode of appearance in the extracellular space $[34,217,218,219,220]$. The current consensus is that there exists a net efflux of potassium ions from the cell, although the route of exit is unclear [34, 219, 220]. A reduction in $\mathrm{Na}^{+} / \mathrm{K}^{+}$ATP-ase activity is one possibility, since it would account for a net loss of potassium from the cell, but this would also result in an increase in intracellular sodium, for which there appears to be no experimental proof [213, 220, 219]. On the contrary, during early ischemia, anaerobic glycolysis is activated and there is no drop in total cellular ATP [171]. The action of a potassium channel which opens in response to a drop in intracellular ATP has also been proposed. However, Elliott et al. have shown in ferret hearts that during hypoxia sufficient to reduce AP duration, there was no concurrent reduction in global ATP [218].

In summary, while the link between ischemia and potassium is established in animal models and it is strongly suspected in humans, there remain fundamental questions regarding the mechanisms which bring about changes in the electrical activity of the heart following acute occlusion. The biphasic response to ischemia, which has been established in numerous animal preparations, has yet to be found in humans. Although the underlying electrophysiology of ST/TQ-segment shifts is reasonably well understood, the effect of ischemia on the complex collection of events responsible for excitation of the ventricles is unresolved even in animal models. Ischemia is a strongly regional condition, with only cell-widths separating regions of healthy from inactivated myocardium; results from several investigators suggest that epicardial electrodes may be insensitive to underlying subendocardial ischemia. With
this background, we proceed now to examine the literature dealing with the use of body surface potential mapping to detect the effects of PTCA-induced ischemia in humans.

### 2.2.4.3 PTCA and body surface potential mapping

As described above, during the hyperacute phase of ischemia there are definite, if subtle, effects on the myocardium; these changes are often transient and show considerable regional heterogeneity. Since the ECG reflects underlying myocardial electrical activity, to examine the regional nature of changes arising in acute ischemia, one must record over as extended an area as possible. Of the noninvasive techniques, body surface potential mapping (BSPM) captures the most information and, hence, has found an ever-growing place in the examination of hyperacute ischemia during PTCA [129, 130, 131, 132, 134, 161, 162, 221], and [135, 222, 223, 224, 225, 226].

Selvester et al. have presented several reports of body surface electrical changes during PTCA as observed via a limited array of electrodes [129, 161, 162, 163]. From continuous recordings of precordial leads during numerous inflations, Selvester and his co-workers have monitored R- and S-wave amplitude and frontal plane axis shifts of the QRS vector-loop and documented significant changes in 11 of 19 patients during balloon occlusions, which could not be simply explained by shifts in ST' segment. They attribute these effects in rge part to conduction delays or complete blocks at one or more of five documel wd insertion sites of the Purkinje fibres into the working myocardium. A partial block of one or more of the subendocardial insertion sites is thought to alter the normal pattern of ventricular excitation and produce an asymmetry in depolarization. Through anatomical knowledge of these sites and the branches of the coronary circulation which supply them, it is then possible to speculate as to which of the insertion sites would most likely be affected by a specific occlusion [129].

In support of their hypothesis, Selvester et al. [161, 162] argue that the regional
differences in perfusion and metabolic need, even during global ischemia, must be taken into account, especially during the hyperecute phase. The subendocardial region, at the sites of interface between the Purkinje fibres and the myocardium, lies at the most distal portion of the coronary circulatory system, while its metabolic requirements are generally considered to be higher than those of the neighbouring mid-myocardial or epicardial regions. During coronary occlusion, the situation can be worsened due to the massive vasodilation which accompanies arterial hypotension; this creates an inverse pressure gradient from endo-to epicardial regions, which further shunts any available flow from collaterals away from the subendocardium [104]. Selvester et al. [161, 162] argue that these conditions can lead to a failure, or at least a delay, in conduction at the sites of insertion of the Purkinje system into the myocardium. The Purkinje fibres themselves are thought to be rather more robust in the face of ischemic challenge and would under such conditions conduct to other, healthy regions of the subendocardium [227, 104, 181].

Vondenbusch et al. were the first to employ an array of radiolucent epoxy/carbon electrodes, applied as a flexible mat of 63 electrodes to the precordial area ( 32 by 48 cm ), to monitor ST-segment changes during PTCA [222, 223, 228, 224, 229]. They observed reproducible ST-segment elevations which begin shortly after inflation of the angioplasty balloon and plateaued after about 20 s . Return to normal levels typically followed within 10 s of deflation of the balloon. By applying the Karhunen-Loéve (K-L) expansion technique to represent the isopotential map data as a weighted sum of basis orthonormal distributions, they were able to differentiate between occlusions of the three major coronary arteries. A plot of the value of the first K-L coefficient against the value of the second, for each of 15 cases of PTCA, revealed a clear separation in the location of the points representing occlusions of the LAD (second quadrant), LCx (fourth quadrant) and RC (first quadrant) occlusions [224].

Spekhorst et al. used a system of 64 epoxy/carbon radiolucent electrodes [230, 231] applied over the front and back of the torso to follow changes in both ST segment
[130], and QRS complex [131, 135] during balloon inflation in patients with LAD, LCx and RC artery stenosis. In the majority of cases they found distinctive patterns in body surface ST-segment isoarea difference maps (peak inflation minus pre-inflation) for angioplasty of each of the three arteries: for the LAD, positive values on the left anterior torso and negative on the lower right front and entire back; for the RC , positive on the lower anterior front and back with negative on the superior anterior front and superior back; for LCx, positive on the entire back and negative on the entire front [130]. A second set of distinctive distributions were found by subtracting QRS isointegral maps recorded during inflation from those before inflation: for the LAD, values were positive on the lower front; for the RC, positive on the lower back and negative on the front; for the LCx, pcsitive on the entire back and negative on the front [131]. Very similar potential distributions were reported by Hamel et al. for differences in ST-segment amplitude, measured 40 ms after the end of the S -wave [132, 134].

Early results using BSPM to evaluate long-term changes in patients undergoing PTCA in our laboratory indicate that there are, indeed, more lasting effects of the PTCA procedure. Comparison of body surface integral maps from recordings made several hours before, and 24 hours after successful PTCA, demonstrate significant reduction in T-wave integral values as a result of the PTCA procedure [133, 226]. This finding suggests that persistent changes in primary repolarization properties can occur in conjunction with PTCA.

## Chapter 3

## Theory and Methods

### 3.1 Solutions to the Forward and Inverse Problems of Electrocardiography

### 3.1.1 Introduction

In this dissertation the forward and inverse problems of electrocardiography (see section 2.1) have been solved in terms of epicardial and body surface potentials. The method of the forward solution is the boundary element method applied to a realistic homogeneous human torso (see appendix A) and the result is a forward transfer coefficient matrix $Z_{B H}$. Direct inversion of $Z_{B H}$ is not possible since the problem is ill-posed and any resulting inverse solution would be unstable. Therefore, we have applied the technique of regularization to compute a constrained inverse transfer coefficient matrix, $Z_{H B}$, with which epicardial potentials can be safely predicted from body surface potential maps. This section outlines the formulation of the problem and describes the steps involved in both the generation of the forward solution matrix and the regularization which produces a useful inverse solution.

### 3.1.2 Sources and the volume conductor

The sources of electrical activity in the heart are the membrane currents of the individual cardiac cells. Each one of these cells can be represented at some distance from the cell as a current dipole moment. The electrical activity of the whole heart can be
represented by a volunie distribution of dipole moments (primary sources), described by an impressed current density, $\vec{J}_{i}[25]$. Since these are the only electrical sources of appreciable magnitude in the torso, the resulting distribution of potential in the body volume surrounding the heart is determined by this source configuration; also contributing to the resulting potential distribution are the volume conductor properties, that is, the geometry and the electrical characteristics of the tissues in the torso (secondary sources). The fundamental problem of electrocardiology is to determine the relationships between the currents generated by the ceils of the heart and the potentials which can be measured on the surface of the torso.

Maxwell's equations describe the relationships between electric and magnetic fields in time and space. We can consider the volume between the heart and the body surface to be resistive and to respond in essentially a linear fashion, that is, the current density is everywhere proportional to electric field strength; the proportionality constant being the electrical condactivity, $\sigma$.

Although the different tissues making up the lungs, the bone and the skeletal muscle are known to have different values of conductivity, for our purposes we will assume that the effect of boundaries between regions of different conductivity on the potential distribution can be neglected. We thus assume a constant value for $\sigma$, that is, a homogeneous volume conductor. It can further be assumed that the volume conductor is electrically isotropic, that is the conductivity at any point is a scalar quantity.

Since the heart generates time-varying changes in impressed current density, the potential distribution in the volume conductor must also change with time. If the rate of change of the primary sources were high enough, the delay in response at the body surface would eventually become significant and for very high frequencies the effect of propagating electromagnetic waves would have to be considered. The magnitude of any delay is determined by the time constant of the tissues in the volume conductor. The time constant is in turn a function of the capacitive and inductive
properties of these tissues and for the human torso lies below $10 \mu \mathrm{~s}$. Conditions within the sources of the cardiac electric field change at a maximum frequency of 10 kHz , or equivalently, within at least $100 \mu \mathrm{~s}$; in fact, electrocardiographers rarely analyze ECG signals in the bandwidth above 1000 Hz . Thus, changes in the primary sources are reflected virtually instantaneously in the volume conductor and on the body surface [24]. Therefore we can, for all practical purposes, neglect any effects of time dependence and describe the system by a quasi-static formulation of Maxwell's field equations.

In summary, the electrocardiographic problem can be seen as a quasi-static formulation of time-varying current and potential distributions within a volume conductor which is to a good approximation linear piecewise homogeneous and isotropic.

The mathematical statement of the above can be phrased as follows: If we define a current density, $\vec{J}$, and electric field intensity, $\vec{E}$, in the linear, resistive, volume conductor $\mathrm{w}^{\circ}$ have the following general relationship:

$$
\begin{equation*}
\vec{J}=\sigma \vec{E} \tag{3.1}
\end{equation*}
$$

where $\sigma$ is the conductivity at any point outside the heart volume. This is a generalized vector form of Ohm's Law. Since we are assuming quasi-static conditions, we can define the electric field as the negative gradient of a scalar potential $\phi$ :

$$
\begin{equation*}
\vec{E}=-\nabla \phi . \tag{3.2}
\end{equation*}
$$

The total current density at any point in the volume conductor is equal to the sum of the impressed current density, $\vec{J}_{i}$, and ohmic component of current density, $\sigma \vec{E}$,

$$
\begin{equation*}
\vec{J}=\vec{J}_{i}+\sigma \vec{E} . \tag{3.3}
\end{equation*}
$$

In this expression, $\sigma \vec{E}$ is the passive response in the volume conductor to the primary sources which are represented by $\vec{J}_{i}\left(\vec{J}_{i}=0\right.$ outside the region of sources) Furthermore, since $\vec{J}$ is solenoidal, there is no net charge generated and the divergence of the
current density vanishes.

$$
\begin{equation*}
\nabla \cdot \vec{J}=\nabla \cdot \vec{J}_{i}+\nabla \cdot \sigma \vec{E}=0 \tag{3.4}
\end{equation*}
$$

By substituting equation 3.2 into 3.4 we get

$$
\begin{equation*}
\nabla^{2} \phi=\frac{1}{\sigma} \nabla \cdot \vec{J}_{i} \tag{3.5}
\end{equation*}
$$

which is the Poisson equation for the volume conductor. This reduces to the Laplace equation,

$$
\begin{equation*}
\nabla^{2} \phi=0 \tag{3.6}
\end{equation*}
$$

in the volume which contains no current sources $\left(\vec{J}_{i}=0\right)$.

### 3.1.3 Forward solution

The derivation which follows is based on Green's second identity and follows a rather well known course to a set of equations relating epicardial to body surface potentials $[6,56,53,52]$. Our discretization of these equations and the numerical form of the solution reflect the most recent ideas regarding the optimal means of producing an accurate solution to this problem $[6,7,61,62]$.

### 3.1.3.1 Analytical derivation

The starting point of the derivation is Green's second identity for two scalar, piecewise continuous functions, $f$ and $g$, which states that

$$
\begin{equation*}
\int_{S}(f \nabla g-g \nabla f) \cdot d \vec{A}=\int_{V}\left(f \nabla^{2} g-g \nabla^{2} f\right) d V \tag{3.7}
\end{equation*}
$$

where, the Green's volume $V$ is bounded by surface $S$ whose outward directed element is denoted $d \vec{A}$. We can define the function $f$ as $1 / r$, where $r$ is the distance from the source point $q$ to an arbitrary field point $p$, called the observation point, and the function $g$ as the scalar electric potential, $\phi$. The area element, $d \vec{A}$ is defined as $\vec{n} d A$,
where $\vec{n}$ is the outward normal to the surface and $d A$ is the scalar element of area of the integrating surface. With these substitutions, the Green's identity now reads

$$
\begin{equation*}
\int_{S}\left(\frac{1}{r} \nabla \phi-\phi \nabla \frac{1}{r}\right) \cdot d \vec{A}=\int_{V}\left(\frac{1}{r} \nabla^{2} \phi-\phi \nabla^{2} \frac{1}{r}\right) d V \tag{3.8}
\end{equation*}
$$

If there are no sources within the volume, $V$, the scalar potential $\phi$ satisfies the Laplace equation $\nabla^{2} \phi=0$ (equation 3.6), and the first term of the volume integral disappears. The second term of the volume integral includes the expression $\nabla^{2} r^{-1}$, which equals 0 for all $r \neq 0$. In the immediate vicinity of $r=0, \phi$ can be considered constant so that the volume integral becomes

$$
\begin{equation*}
-\int_{V} \phi \nabla^{2} \frac{1}{r} d V=\phi\left(p_{s}\right) C \tag{3.9}
\end{equation*}
$$

where $p_{s}$ represents the location of a singularity at which observation point and integration volume meet ( $r=0$ ) and

$$
\begin{equation*}
C=-\int_{V_{s}} \nabla^{2} \frac{1}{r} d V \tag{3.10}
\end{equation*}
$$

where $V_{s}$ is the reduced volume which just includes the singularity. It can be shown [93] that in general the integrand may be written as

$$
\begin{equation*}
\nabla^{2} \frac{1}{r} d V=-4 \pi \delta\left(\vec{r}-\overrightarrow{r^{\prime}}\right) \tag{3.11}
\end{equation*}
$$

where $\vec{r}$ and $\overrightarrow{r^{\prime}}$ are vectors from the origin to the observation point and any point $p$ within the volume of integration, respectively. The integral can now be evaluated as

$$
-\int_{V_{s}} \nabla^{2} \frac{1}{r} d V=\int_{V_{s}} 4 \pi \delta\left(\vec{r}-\overrightarrow{r^{\prime}}\right) d V=\left\{\begin{array}{cc}
0 & \left(p \text { outside } V_{s}\right)  \tag{3.12}\\
4 \pi & \left(p \text { inside } V_{s}\right)
\end{array}\right.
$$

It is possible to choose an observation point anywhere within the Green's volume to satisfy equation 3.8. The standard approach is to select the observation point very close to the boundary of, but still within, the Green's volume. Physically, we can assume that the potential at such a point is virtually identical to that on the real surface in question, while mathematically, the points remain inside the volume and the result $-4 \pi$ can be used for the integral in equation 3.12. This approach was taken
by both Barr et al. [56] and Messinger-Rapport and Rudy [6] and from equation 3.8 yields the following equation:

$$
\begin{equation*}
4 \pi \phi(p)=\int_{S}\left(\frac{1}{r} \nabla \phi-\phi \nabla \frac{1}{r}\right) \cdot d \vec{A} . \tag{3.13}
\end{equation*}
$$

A second strategy is possible, however, in which the observation point is located not just incide, but on the surface. It can be shown [26] that the integral in equation 3.9 can be evaluated at a point on the surface with the result $-2 \pi$. This results in a slightly different form of equation 3.8 than that given in equation 3.13 :

$$
\begin{equation*}
2 \pi \phi(p)=\int_{S^{-}}\left(\frac{1}{r} \nabla \phi-\phi \nabla \frac{1}{r}\right) \cdot \overrightarrow{d A} \tag{3.14}
\end{equation*}
$$

the obvious difference being an additive factor of $2 \pi \phi(p) . S^{-}$in this equation is the surface area excluding the singularity, that is, the integral is proper-valued and must be evaluated excluding the singularity at $r=0$. To maintain consistency between the two equations 3.14 and 3.13 , if the observation point is taken close to but still inaide the surface of integration, then the volume integral of $\nabla^{2}(1 / r) d V$ yields the result $-4 \pi$, as in equation 3.12 , and the surface integration is also performed over the entire surface; there is no singularity. If, on the other hand, the observation point is placed on the surface of integration, the olume integral yields the value $-2 \pi$ and the surface integral must be calculated by excluding the singularity, that is, as a proper-valued integral. Conceptually, placing the observation point on the surface is simpier and more accurate, and therefore, this approach is used in further discussion.

Figure 3.1 depicts the geometry to which we now apply Green's second identity. In this particular case, the Green's volume is the region enclosed by the epicardial and body surfaces, $S_{H}$ and $S_{B}$, which together comprise $S$. We proceed from equation 3.14 by separating the surface which bounds the Green's volume $V$ into the heart surface, $S_{H}$, and the body surface, $S_{B}$. The sense of the normal to the heart surface is redirected into the Green's volume so that by rearranging the integrals, we now have

$$
\begin{equation*}
2 \pi \phi(p)=\int_{S_{H}} \phi d \Omega-\int_{S_{B}} \phi d \Omega-\int_{S_{H}} \frac{\nabla \phi}{r} \cdot d \vec{A}+\int_{S_{B}} \frac{\nabla \phi}{r} \cdot d \vec{A} . \tag{3.15}
\end{equation*}
$$



Figure 3.1: The geometry of the forward/inverse problem. In panel $A$, the observation point $p$ is placed on the outer bounding body surface, $S_{B}$; in panel $\mathrm{B}, p$ lies on the inner bounding heart surface $S_{H}$. The $\Omega$ terms are the associated solid angles.

We have introduced $d \Omega$, the incremental solid angle, for the $\nabla(1 / r) \cdot d \vec{A}$ term and redirected the outward normal of the inner, epicardial surface to point into the Green's volume toward the body surface.

Equation 3.15 defines the potential at any point $p$ on either part of the surface $S$ (comprised of $S_{B}$ and $S_{H}$ ), as a function of 1) the potential and normal component of potential-gradient on surface $S_{H}$ and $S_{B}$, and 2) the location of the field point $p$ relative to $S_{H}$ and $S_{B}$. At the body-surface boundary $S_{B}$, the normal component of the potential gradient, $\nabla \phi_{n}=\nabla \phi \cdot d \vec{A}$, vanishes since the conductivity of the air is taken as zero, and hence the last term in equation 3.15 disappears. Since we are interested in deriving the relationship between potentials on $S_{H}$ and $S_{B}$, we will place $p$ first on one surface and then on the other and write equation 3.15 for each case. This situation is shown in Figure 3.1 for the case of an observation point on the body surface (panel A) and an observation point on the epicardial surface (panel B). The next section describes the development and solution of these equations.

### 3.1.3.2 Derivation of the coefficient matrices

The general approach to finding solutions to integral equations like equation 3.15 is to write one equation for each of a number of points on both of the surfaces and solve these equat.ins simultaneously. This is known as the collocation method in numerical mathematics and provides a means of reducing an integration over an arbitrary smooth surface to a sum of (somewhat simpler) integrals, each of which can be evaluated separately [232]. The particular application of the collocation method to this problem originates with work of Barr, Ramsey and Spach [56] and their notation will be used throughout.

We start by rewriting equation 315 for two observation points placed on the body and epicardial surface, respectively, as

$$
\begin{equation*}
\phi_{B}^{i}-\frac{1}{2 \pi} \int_{S_{H}} \phi_{H} d \Omega_{B H}^{i}+\frac{1}{2 \pi} \int_{S_{B}} \phi_{B} d \Omega_{B B}^{i}+\frac{1}{2 \pi} \int_{S_{H}} \frac{\nabla \phi_{H}}{r^{i}} \cdot d \vec{A}=0 \tag{3.16}
\end{equation*}
$$

and

$$
\begin{equation*}
\phi_{H}^{i}-\frac{1}{2 \pi} \int_{S_{H}} \phi_{H} d \Omega_{H H}^{i}+\frac{1}{2 \pi} \int_{S_{B}} \phi_{B} d \Omega_{H B}^{i}+\frac{1}{2 \pi} \int_{S_{H}} \frac{\nabla \phi_{H}}{r^{i}} \cdot d \vec{A}=0 . \tag{3.17}
\end{equation*}
$$

Here we have defined the differential solid angle $d \Omega_{P Q}^{i}$ as that subtended by an elemental area of the integration surface $Q$ at the $i^{\text {th }}$ observati ' 1 point on sur face $P$. Likewise, $\phi_{P}^{i}$ is the potential at the $i^{\text {th }}$ location on the surface $P$.

For $N_{B}$ points defined on the body surface and $N_{H}$ points on the epicardium, we can write equations 3.16 and $3.17, N_{B}$ and $N_{H}$ times, respectively (collocation method). Let us write discretized expressions for each of the resulting terms in equations 3.16 and 3.17 ; these expressions will be examined in detail below. From equation 3.16:

$$
\begin{align*}
\phi_{B}^{i}+\frac{1}{2 \pi} \int_{S_{B}} \phi_{B} d \Omega_{B B}^{i} & =\sum_{j=1}^{N_{B}} p_{B B}^{i j} \Phi_{B}^{j},  \tag{3.18}\\
-\frac{1}{2 \pi} \int_{S_{H}} \phi_{H} d \Omega_{B H}^{i} & =\sum_{j=1}^{N_{H}} p_{B H}^{i j} \Phi_{H}^{j} \tag{3.19}
\end{align*}
$$

$$
\begin{equation*}
\frac{1}{2 \pi} \int_{S_{H}} \frac{\nabla \phi_{H}}{r^{i}} \cdot d \vec{A}_{H}=\sum_{j=1}^{N_{K}} g_{B H}^{i j} \Gamma_{H}^{j}, \tag{3.20}
\end{equation*}
$$

and from equation 3.17:

$$
\begin{gather*}
\frac{1}{2 \pi} \int_{S_{B}} \phi_{B} a^{\prime} \Omega_{H R}^{i}=\sum_{j=1}^{N_{B}} p_{H S}^{i j} \Phi_{B}^{j},  \tag{3.21}\\
\phi_{H}^{i}-\frac{1}{2 \pi} \int_{S_{H}} \dot{\phi}_{H} d \Omega_{H H}^{i}=\sum_{j=1}^{N_{H}} p_{H H}^{i j} \Phi_{H}^{j}, \tag{3.22}
\end{gather*}
$$

and

$$
\begin{equation*}
\frac{1}{2 \pi} \int_{S_{H}} \frac{\nabla \phi_{H}}{r^{i}} \cdot d \overrightarrow{A_{H}}=\sum_{j=1}^{N_{H}} g_{H H}^{i j} \Gamma_{H}^{j} \tag{3.23}
\end{equation*}
$$

The argument of each of the summations can be separated into the product of a potential $\left(\Phi_{B}^{j}\right.$ or $\left.\Phi_{H}^{j}\right)$ or the gradient of a potential $\left(\Gamma_{H}^{j}\right)$ at a specific point $j$ on either one of the surfaces and a second fartor (the $p^{\prime} s$ and $g^{\prime} s$ ) based entirely on the geometry of the torso and the heart. $\Phi_{B}^{j}$ and $\Phi_{H}^{j}$ are the potentials at node $j$ on the body and heart surfaces, respectively; $\Gamma_{I}^{j}$ is the normal component of the potential gradient for point $j$ on the heart surface (the corresponding quantity is zero on the body surface). In reneral the $g_{P Q}^{i j}$ term links the value of the potential gradient ( $\Gamma^{j}$ ) at point $j$ on surface $P$ to the observation point $i$ on surface $Q$ while $p_{P Q}^{i j}$ is the geometrical coefficient which weights the contribution of the potential at node $j$ of surface $Q$ to the potential at observation point $i$ on surface $P$. The first subscript and superscript of each $p$ or $g$ term indicate the observation point, the second subscript and superscript, the element of the surface of integration; thus, for example, $p_{H B}^{i j}$ is the coefficient for the observation point $i$ on the epicardial surface and point $j$ on the surface of integration, the body surface.

Now by inserting the appropriate right-hand sides of equations 3.18-3.23, we get the discretized equivalent equations to 3.16 and 3.17 ,

$$
\begin{equation*}
p_{B B}^{i} \Phi_{B}+p_{-H}^{i} \Phi_{H}+g_{B H}^{i} \Gamma_{H}=0 \tag{3.24}
\end{equation*}
$$

and

$$
\begin{equation*}
p_{H B}^{i} \Phi_{B}+p_{H H}^{i} \Phi_{H}+g_{H H}^{i} \Gamma_{H}=0 \tag{3.25}
\end{equation*}
$$

where the summations over $j$ are implicit in each term and $i$ refers to a specific observation point on either the heart (equation 3.25) or the body (equation 3.24) surface. The $p$ and $g$ terms are the row vectors which express the geometrical contribution of each point on the surface of integration to the potential at the observation point $i$. If we write equation 3.24 for each point on the body surface and equation 3.25 for each point on the heart surface, two sets of equations result, which in matrix notation can be written as:

$$
\begin{equation*}
P_{B B} \Phi_{B}+P_{B H} \Phi_{H}+G_{B H} \Gamma_{H}=0 \tag{3.26}
\end{equation*}
$$

and

$$
\begin{equation*}
P_{H B} \Phi_{B}+P_{H H} \Phi_{H}+G_{H H} \Gamma_{H}=0 \tag{3.27}
\end{equation*}
$$

The $P^{\prime} s$ and $G^{\prime} s$ are the matrices formed by collocating all the elements of the associated $p^{i}$ and $g^{i}$ row vectors, one row for each observation point. For the $P_{H B}$ matrix, for example, each row contains $N_{H}$ elements from one $p_{H B}^{i}$ vector, and there are $N_{H}$ rows, each representing a different value of $i$. Here again, the first subscript represents the surface containing the observation points, the second subscript the surface of integration. $P_{H H}$ and $G_{H H}$ are square matrices of size $N_{H} \times N_{H}, P_{B H} \quad G_{B H}$ are sized $N_{B} \times N_{H}, P_{B B}$ is another square matrix of size $N_{B} \times N_{B}$, and $P_{H B}$ is sized $N_{H} \times N_{B}$.

By solving the equation 3.27 for $\Gamma_{H}$ and substituting the result into equation 3.26 we remove the need for explicit knowledge of the potential gradients. This leads, after sorting of variables, to

$$
\begin{equation*}
\left(P_{B B}-G_{B H} G_{H H}^{-1} P_{H B}\right) \Phi_{B}=\left(G_{B H} G_{H H}^{-1} P_{H H}-P_{B H}\right) \Phi_{H}, \tag{3.28}
\end{equation*}
$$

which can be rewritten as

$$
\begin{equation*}
\Phi_{B}=Z_{B H} \Phi_{H} \tag{3.29}
\end{equation*}
$$

with $Z_{B H}$ defined as

$$
\begin{equation*}
Z_{B H}=\left(P_{B B}-G_{B H} G_{H H}^{-1} P_{H B}\right)^{-1}\left(G_{B H} G_{H H}^{-1} P_{H H}-P_{B H}\right) \tag{3.30}
\end{equation*}
$$

Equations 3.29 and 3.30 define the solution to the forward problem in the desired form; $Z_{B H}$ is the transfer coefficient matrix which directly relates epicardial potentials to body surface potentials. It remains to examine each term of equation 3.28 and develop accurate computational methods for evaluating the elem nts of all the matrices involved. Once this has been achieved, we may convert epicardial potentials into body surface potentials and, thus, solve the forward problem.

### 3.1.3.3 Calculation of the geometrical coefficient matrices

In this section we develop strategies for the numerical evaluation of the individual elements of the six $G$ and $P$ coefficient matrices from which the final transfer matrix, $Z_{B H}$, can be calculated.

If one examines the equations for the geometrical coefficients, for example equation 3.18 , which reads

$$
\phi_{B}^{i}+\frac{1}{2 \pi} \int_{S_{B}} \phi_{B} d \Omega_{B B}^{i}=\sum_{j=1}^{N_{B}} p_{B B}^{i j} \Phi_{B}^{j},
$$

it is tempting to equate the individual $p_{B B}^{i j}$ terms of the right hand side to the associated solid angles $d \Omega_{B B}^{i j}$. This would, however, be equivalent to suggesting that the rotential over each triangular surface elements is constant, an approach used by some $[56,58]$ but more recently improved upon by others $[6,7,72]$. It is essential in any such approximation method that a separation of the potential values and the geometric coefficients be achieved. In this way we need calculate the geometric coefficients only once for each torso and epicardial surface configuration, and then apply these coefficients to obtain the forward solution for any set of epicardial potential values. This separation is intrinsic in the derivation of equations 3.26 through 3.28 and the $Z_{B H}$ matrix in equations 3.29 and 3.30 , which consists of coefficients which must be determined from geometrical data alone. The details of the various alternative schemes are given in the subsections below; the approximation employed in our work represents a synthesis of previously used methods. As a representative case, we will
first look in some detail at the $P_{B B}$ matrix and describe the calculations involved.
$P_{B B}$ matrix The $P_{E B}$ matrix contains the geometrical coefficients which arise from the integration of the potential multiplied by the solid angle over the area elements of the body-surface, as observed from the body surface itself (equation 3.18). The superscript $i$ represents the observation point, and the superscript $j$ a point on the surface of integration (body) for which the $\phi_{B} d \Omega_{B B}^{i}$ term is evaluated. For the discrete case, both body and epicardial surfaces are tessellated into triangles defined by vertices which are node points of the surface (see Appendix A). Potential values at the node points are either directly measured, or can be interpolated from neighbouring measurement points (see section 3.2). In evaluating the integrals in equations 3.18 3.23 , we are faced firstly with the roblem of estimating the value of $\phi$ over the surface of each triangle as a function of the known potential values at its vertices. Secondly, the integral of the product of the potential and a second function of distance must be approximated over the triangle in such a way as to maintain separation of the potential value from a purely geometric factor.

Barr et al. [56] used a simple, equally weighted average for the value of the potential which was considered constant over each triangle,

$$
\begin{equation*}
\phi_{T}^{k}=\frac{1}{3} \sum_{m=1}^{3} \phi_{k}^{m} \tag{3.31}
\end{equation*}
$$

where $\phi_{T}^{k}$ is the estimated value of the potential over the whole triangle $k$, and $\phi_{k}^{m}$ is the potential at vertex $m$ of triangle $k$. This estimation was later improved upon by Pilkington et al. [72]. For their calculations they divided each triangle into six subtriangles and took the value of the potential over each of these subtriangles as being constant and equal to that of the nearest vertex of the original triangle. This scheme is shown in panel A of Figure 3.2 for the case in which four triangles share the common vertex, $j$. For each of the four main triangles, there are two subtriangles which are given the potential value $\Phi^{j}$, for a total of eight triangles (triangles 1-8 in Figure 3.2). It is then possible to calculate the total solid angle subtended by each of


Figure 3.2: Triangle-division schemes. Four main triangles share a common vertex $j$ and are divided into subtriangles according to methods proposed by Pilkington et al. (Panel A) and Meijs et al. (Panel B).
these cight subtriangles at a given observation point $i$ and equate it with the element $p_{B B}^{i j}$ of the $P_{B B}$ matrix.

We can express this as the following approximation of the integral in equation 3.18:

$$
\begin{equation*}
\frac{1}{2 \pi} \int_{S_{B}} \phi_{B} d \Omega_{B B}^{i} \approx \sum_{\substack{j=1 \\ j \neq i}}^{N_{B}} \Phi_{B}^{j} \sum_{k=1}^{2 N T_{B}^{j}} \int_{T_{B}^{j k}} d \Omega_{B B}^{i j k}, \tag{3.32}
\end{equation*}
$$

where the first summation is over all points except the observation point itself $(i=j)$ and $N T_{B}^{j}$ is the number of triangles which share the vertex $j$. The surface area elements $T_{B}^{j k}$ are the $2 N T_{B}^{j}$ subtriangles associated with point $j$ on the body surface. For each of these subtriangles the integral can be evaluated exactly (analytically). The integral has thus been replaced by a summation over the discrete triangles which
define the surface. We may now approximate the entire equation 3.18 as follows:

$$
\begin{equation*}
\phi_{B}^{i}+\frac{1}{2 \pi} \int_{S_{B}} \phi_{B} d \Omega_{B B}^{i} \approx \Phi_{B}^{i}+\frac{1}{2 \pi} \sum_{\substack{j=1 \\ j \neq 1}}^{N_{B}} \Phi_{B}^{j} \Omega_{B B}^{i j} \tag{3.33}
\end{equation*}
$$

where we have defined the solid angle integral term as

$$
\begin{equation*}
\Omega_{B B}^{i j} \equiv \sum_{\cdot=1}^{2 N T_{B}^{j}} \int_{T_{B}^{j k}} d \Omega_{B B}^{i j k} \tag{3.34}
\end{equation*}
$$

From this it is easy to see the lin.: between the geometrical coefficients $p_{B B}^{i j}$ in equation 3.18 and the solid angle integrals in approximation 3.33.

A slightly different approach to this problem was proposed by Meijs et al. [61]; just as in the method by Pilkington et al., each original triangle is divided into four congruent subtriangles, formed by joining the midpoints of the three sides. The contribution of each of these subtriangles is evaluated and then combined in a weighted sum in such a way as to maintain the form outlined in equation 3.18. The resulting scheme is somewhat more complex than that described by Pilkington at al. [72] in several aspects.

The first difference involves the way each subtriangle contributes to the value of the geometric coefficient. In panel B of Figure 3.2, each of four main triangles is divided into four subtriangles, numbered 1-4. The total solid angle for the area associated with integration point $j$ subtended at the observation point $i$ is then evaluated as

$$
\begin{equation*}
\int_{j} d \Omega_{B B}^{i j}=\sum_{k=1}^{N T_{E}^{j}}\left(\frac{2}{3} \Omega_{B B}^{i k 1}+\frac{1}{6} \Omega_{B B}^{i k 2}+\frac{1}{6} \Omega_{B B}^{i k 3}+\frac{1}{3} \Omega_{B B}^{i k 4}\right) \tag{3.35}
\end{equation*}
$$

where $\int_{j}$ indicates an integration over the area associated with the vertex $j, N T_{B}^{\prime \prime}$ is the number of triangles which share $j$ as a common vertex, and $\Omega_{B B}^{i k 1}, \ldots, \Omega_{B B}^{i k 4}$ are the solid angles of the subtriangles $1, \ldots, 4$ of main triangle $k$ subtended at obscrvation point $i$. All of the four subtriangles from each main triangle are thus included in the sum, each with a weighting coefficient which reflects its position relative to the vertex $j$.

It is perhaps appropriate to note here the use of the phrase "associated with" to describe the contribution to the geometric coefficient of the area surrounding a node point. A point cannot produce a solid angle, but instead contributes the value of its potential to the integral while the subtriangles which lie close to it, that is, are associated with it, supply the geometric weighing values, based on the solid angle. In fact, the selection of the neighbouring triangles and the weighting given to their solid angles are key factors in deriving the numerical solution to the problem.

The scheme described by equation 3.35 reflects a difference in approach over that used by Pilkington et al. [72], for here it is assumed that each of the four subtriangles contributes some solid angle to the total assigned to each vertex of the original triangle, whereas the estimate suggested by Pilkington et al. included only the two closest subtriangles in the estimate for each vertex. The second difference in the approach taken by Meijs et al. [fi] lies in the way they approximated the potential of each of the subtriangles. Whereas Pilkington et al. [72] assigned a constant valie to each of the subtriangles, equal to the potential at the closest ver ex, Meijs et al. [61] estimated the potential for each of the subtriangles as a weighted sum of the potential values at each of the vertices of the main triangle, based on the assumption of a linear distribution of potential over the surface element. For each main triangle described by vertices $m, m+1$, and $m+2$, the values of the potential for the four subtriangles can be taken as

$$
\begin{align*}
& \bar{\Phi}_{1}^{k}=\frac{1}{6}\left(4 \Phi^{m}+\Phi^{m+1}+\Phi^{m+2}\right) \\
& \bar{\Phi}_{2}^{k}=\frac{1}{6}\left(\Phi^{m}+4 \Phi^{m+1}+\Phi^{m+2}\right)  \tag{3.36}\\
& \bar{\Phi}_{3}^{k}=\frac{1}{6}\left(\Phi^{m}+\Phi^{m+1}+4 \Phi^{m+2}\right) \\
& \bar{\Phi}_{4}^{k}=\frac{1}{3}\left(\Phi^{m}+\Phi^{m+1}+\Phi^{m+2}\right)
\end{align*}
$$

where $\bar{\Phi}_{n}^{k}$ is the mean value of the potential over subtriangle $n$ of the main triangle $k$ and $\Phi^{m}, \Phi^{m+1}$, and $\Phi^{m+2}$ are the potential values at the three vertices.

The two approximations in equations 3.35 and 3.36 must be considered together
in writing for the complete integral over the area associated with vertex $j$,

$$
\begin{equation*}
\int_{j} \phi_{B} d \Omega_{B B}^{i j} \approx \sum_{k=1}^{N T_{B}^{j}} \bar{\Phi}_{1}^{k} \frac{2}{3} \Omega_{B B}^{i k 1}+\bar{\Phi}_{2}^{k} \frac{1}{6} \Omega_{B B}^{i k 2}+\bar{\Phi}_{3}^{k} \frac{1}{6} \Omega_{B B}^{i k 3}+\bar{\Phi}_{4}^{k} \frac{1}{3} \Omega_{B B}^{i k 4} \tag{3.37}
\end{equation*}
$$

where $\bar{\Phi}_{1}^{k} \ldots \bar{\Phi}_{4}^{k}$ are the potentials values for the subtriangles as defined by equation 3.36.

The integral over the whole body surface can then be written as

$$
\begin{equation*}
\frac{1}{2 \pi} \int_{S_{B}} \phi_{B} d S \iota_{B B}^{i} \approx \frac{1}{2 \pi} \sum_{j=1}^{N_{B}} \int_{j} \phi_{B} d \Omega_{B B}^{i j} \tag{3.38}
\end{equation*}
$$

By inserting equations 3.36 and 3.37 , the right hand side of this equation can be further expanded to

$$
\begin{array}{r}
\frac{1}{2 \pi} \sum_{j=1}^{N_{B}} \sum_{k=1}^{N T_{B}^{j}}\left[\left(\frac{2}{3} \Phi_{B}^{m}+\frac{1}{6} \Phi_{B}^{m+1}+\frac{1}{6} \Phi_{B}^{m+2}\right) \frac{2}{3} \Omega_{B B}^{i k 1}\right. \\
+\left(\frac{1}{6} \Phi_{B}^{m}+\frac{2}{3} \Phi_{B}^{m+1}+\frac{1}{6} \Phi_{B}^{m+2}\right) \frac{1}{6} \Omega_{B B}^{i k 2} \\
+\left(\frac{1}{6} \Phi_{B}^{m}+\frac{1}{6} \Phi_{B}^{m+1}+\frac{2}{3} \Phi_{B}^{m+2}\right) \frac{1}{6} \Omega_{B B}^{i k 3}  \tag{3.39}\\
\left.+\left(\frac{1}{3} \Phi_{B}^{m}+\frac{1}{3} \Phi_{B}^{m+1}+\frac{1}{2} \Phi_{B}^{m+2}\right) \frac{1}{3} \Omega_{B B}^{i k 4}\right] .
\end{array}
$$

Gathering terms for $\Phi_{B}^{m}, \Phi_{B}^{m+1}$ and $\Phi_{B}^{m+2}$ yields

$$
\begin{align*}
\frac{1}{2 \pi} \sum_{j=1}^{N_{B}} & \sum_{k=1}^{N T_{B}^{\prime}}\left[\left(\frac{4}{9} \Omega_{B B}^{i k 1}+\frac{1}{36} \Omega_{B B}^{i k 2}+\frac{1}{36} \Omega_{B B}^{i k 3}+\frac{1}{9} \Omega_{B B}^{i k 4}\right) \Phi_{B}^{m}\right. \\
& +\left(\frac{1}{9} \Omega_{B B}^{i k 1}+\frac{1}{9} \Omega_{B B}^{i k 2}+\frac{1}{36} \Omega_{B B}^{i k 3}+\frac{1}{9} \Omega_{B B}^{i k 4}\right) \Phi_{B}^{m+1}  \tag{3.40}\\
& \left.+\left(\frac{1}{9} \Omega_{B B}^{i k 1}+\frac{1}{36} \Omega_{B B}^{i k 2}+\frac{1}{9} \Omega_{B B}^{i k 3}+\frac{1}{9} \Omega_{B B}^{i k 4}\right) \Phi_{B}^{m+2}\right]
\end{align*}
$$

It is not possible to transform this equation into the clearly separable form of equation 3.18 since the relationship between $m$ and $j$ is not fixed, but instead depends upon the triangularization of the surface. In equation $3.40, m$ is a specific vertex of one of the $N T_{B}^{j}$ triangles which surround the point $j$; the value of $m$ actually used in a calculation must be determined from a look-up table of triangle vertices, each
entry of which is pointed to by the value of $j$. Thus it is not possible to express $m$ as a fuaction of $j$ and simplify equation 3.40. However, it is possible to 'keep track' of all the geometry coefficients for any node by simply observing to which nodes $m, m+1$ and $m+2$ actualiy refer. Although the integral calculation proceeds over the body surface according to the summation over $j$ and $k$, as each coefficient of potential $\Phi_{B}^{m}, \Phi_{B}^{m+1}$ or $\Phi_{B}^{m+2}$ is evaluated, it is added to the value for that node to which $m, m+1$ or $m+2$ refers. Thus a true separation of potential $\Phi_{B}^{j}$ and its associated coefficient can be maintained and we can write

$$
\begin{equation*}
\frac{1}{2 \pi} \int_{S_{B}} \phi_{B} d \Omega_{B B}^{i} \approx \sum_{j=1}^{N_{B}} w_{i j} \Phi_{B}^{j} \tag{3.41}
\end{equation*}
$$

where $w_{i j}$ is the weighting factor applied to the value of the potential at node $j$, a value which, in turn, is the sum of all the weightings in equations 3.36 to 3.40 applied to this particular node. Again, while it is not possible to derive a closed analytical expression for $w_{i j}$, neither is it necessary; each $w_{i j}$ is a function of the specific geometry of the surface involved and is collated by keepirıg a running tally throughout the course of the calculation.

Since the same general situation of slightly indirect separation of potential and geometrir coefficieats arises in the development presented below, we will defer further discussion of this specific point to that section. The salient feature of this approach is that the entire calculation can eventually be reduced to calculating values for the solid angle over specific subtriangles. According to the reports of Meijs et al. [61, 62], the use of this type of triangle subdivision scheme was only necessary when the variation of the potential over the main triangle exceeded some predefined (small) value. Otherwise, a simple scheme assuming constant potential over the main triangles was employed. For their calculations of magnetic field, using a multi-sphere model of the head, they found optimal results when approximately $2 \%$ of the triangles were divided and recalculated. Far more crikical in reducing the error was the choice of original triangularization grid [61].

A second refinement outlined by Meijs et al., which brought about considerable
improvement to their results, is the numerical approximation of the $\Omega^{i i}$, or "autos solid angle" elements [61]. These are the integrals in which the observation point is one vertex of the triangle over which the integration is to be carried out. For each observation point, there is a set of triangles which share this same vertex, termed the "close region" by Barr et al. [56]. This is also the region which contains the singularity discussed earlier, the point at which $r \rightarrow 0$. In evaluating the integral expressions as proper value integrals, we should assume that the close region need not be included as it contains the singularity. However, this may not prove to be as accurate an estimation as one would like for a surface geometry which is defined by only a finite number of triangular surface elements; by excluding the triangles of the close region, we may be ignoring a relatively large portion of the surface, the size of which is determined by the number and size of the triangles. Ideally, one would like to shrink the boundaries of this close region down closer to the vertex and approximate the integral over the rest of this area by excluding just the actuai point of singularity.

The reason for the difficulty in performing numerical approximation is that any calculation of the auto solid angle, and the auto-integral to which it contributes, performed over a planar surface element from an observation point located anywhere on the same plane must by definition yield zero. This can be seen in the original expression for solid angle $\nabla(1 / r) \cdot d \vec{A}$, or its equivalent $(\vec{r} \cdot d \vec{A}) / r^{3}$, in which a dot product is formed from the vector $\vec{r}$, which lies in the plane of triangle, and the surface normal, which is perpendicular to the plane. Resolution of this problem is only possible if the observation point is somehow removed from the plane of integration, either by shifting the point or redefining the integration surface. Such a redefinition demands either a finer tessellation, which thereby reduces the size of the close region, or an approximation of the close region by another non-planar surface.

Meijs et al. [61] pursue the latter approach to evaluate the auto solid angle term by approximating the region around the observation point as a spherical section. Figure 3.3 shows the arrangement in which the basal vertices of the triangles which


Figure 3.3: The auto solid angle after Meijs et al. [61] is estimated by approximating the surface of all triangles sharing the same vertex $j$ as a spheroidal section. From the basal vertices a circular base is approximated while the common apex $j$ rests on the surface of the spheroid; $R$ is the projected distance from the apex of the spheroid to the centre of the circular base which has a radius $a$.
share point $j$ as their apical vertex are used to determine an estimate for the circular base of this section; the distance from the common vertex $j$ projected perpendicularly to a point in the plane of the circular base is $R$, while $a$ is the radius of the circle. The solid angle can then be calculated as

$$
\begin{equation*}
\Omega_{i i} \approx 2 \pi \frac{\cos (\alpha)-1}{\alpha} \tag{3.42}
\end{equation*}
$$

where

$$
\begin{equation*}
\alpha=\arccos (a / R) \tag{3.43}
\end{equation*}
$$

Using this estimate for the auto solid angle, it is then possible to determine the value of the complete auto-integral if one assumes constant potential $\Phi^{j}$ over the whole spherical section. Using this approximation technique, Meijs et al. achieved an improvement of $10 \%$ in the accuracy of computed ECGs in a concentric spheres model of the head over the case in which the close region contributed nothing to the integral [61].

To evaluate the auto solid angle for their model, Barr et al. used a more indirect approach [56]; they made use of t ) efact that the total solid angle about a single point subtended by a closed surface yields a known value, depending on whether the point is outside ( $\sum \Omega=0$ ), on ( $\sum \Omega=2 \pi$ ), or inside ( $\sum \Omega=4 \pi$ ) the surface. The value of $\Omega^{i i}$ can be estimated by the difference between this known value and the sum of all other solid angle terms. We used this approach in our calculations, both because of its elegant simplicity and the fact that it made use of a constraint which is ignored in the method proposed by Meijs et al..

Further general refinements to the methods for evaluating the integrals in equations 3.18 to 3.23 are contained in a more recent reports on inverse solutions by Messinger-Rapport and Rudy [6, 7], in which the authors describe a more elaborate function to characterize the variation of potential over the surface of a triangle. This function, first developed by Cruse [233], takes the form of a linear interpolating polynomial expansion which approximates the potential at any point $p$ within the triangle as a weighted sum of the values at each of the three vertices. This approach can be viewed as a more general form of that suggested by Meijs et al.; both of these schemes, in turn, can be interpreted as first-order approximations, while that of Barr et al. represents a zero-order approximation.

Using this general approximation we can write for the potential at any point $p$,

$$
\begin{equation*}
\phi(p) \approx \sum_{m=1}^{3} C_{m}(p) \Phi^{m}, \tag{3.44}
\end{equation*}
$$

where $\Phi^{m}$ is the value of the potential at vertex $m$ of the triangle. Likewise, for the potential gradient at any point $p$, using the same function $C_{m}(p)$,

$$
\begin{equation*}
\frac{\partial \phi}{\partial n}(p) \approx \sum_{m=1}^{3} C_{m}(p) \frac{\partial \Phi^{m}}{\partial n} . \tag{3.45}
\end{equation*}
$$

It is then possible to write for a triangle $k$ on the body surface,

$$
\begin{equation*}
\int_{T_{B}^{k}} \phi_{B} d \Omega_{B B}^{i} \approx \sum_{m=1}^{3} \Phi_{B}^{m} \int_{T_{B}^{k}} C_{m}(p) d \Omega_{B B}^{i}, \tag{3.46}
\end{equation*}
$$

where $p$ is any point in the triangle $k\left(T_{B}^{k}\right)$ over which the integration is to be performed. $\Phi_{B}^{m}$ is the potential at vertex $m$ of body triangle $k$. The interpolating polynomial can be written [233] as the sum of two functions - one dependent on the location of the midpoint of the triangle and the other on the position of the point in the triangle at which $C_{m}$ is evaluated:

$$
\begin{equation*}
C_{m}(p)=E_{m}\left(p_{c}\right)+A_{m}(p) \tag{3.47}
\end{equation*}
$$

where $p_{c}$ is the centroid of the triangle. We can further define $E_{m}$ and $A_{m}$ for a triangle in terms of a local, two-dimensional coordinate system $\left(x^{\prime}, y^{\prime}\right)$ in the plane of the triangle as

$$
\begin{align*}
E_{m}\left(p_{c}\right) & =1 / 3+\left(F_{m y} x_{c}^{\prime}-F_{m x} y_{c}^{\prime}\right) / 2 A  \tag{3.48}\\
A_{m}(p) & =\left(F_{m y} x_{p}^{\prime}-F_{m x} y_{p}^{\prime}\right) / 2 A, \tag{3.49}
\end{align*}
$$

where, as depicted in Figure 3.4, the centroid of the triangle in local coordinates is $p_{c}\left(x_{m}^{\prime}, y_{m}^{\prime}\right) ; F_{m x}$ and $F_{m y}$ are the $x^{\prime}$ and $y^{\prime}$ components of the vector which forms the side of the triangle opposite vertex $m$, and $x_{p}^{\prime}$ and $y_{p}^{\prime}$ are the coordinates of the point at which the function is to be evaluated, all in the local cartesian system.

With $C_{m}$ so defined, we can proceed to evaluate equation 3.46. Note that a subdivision of main triangles is no longer necessary since the integrand is the product of two functions $C_{m}(p)$ and $d \Omega_{B B}^{i}$, which are continuous functions of position. The integration itself, however, is slightly more complicated than for the methods described so far because the solid angle term cannot be separated from the Cruse weighting function. Instead of a solid angle calculation, evaluation of such an integral requires a method of numerical quadrature; for this we chose Radon's 7-point formula [234, 235], w._ich requires the calculation of both terms of the integrand at seven discrete points within the triangle to form a weighted sum estimate. The function $C_{m}(p)$ depends only on the coordinates of the triangle and can easily be evaluated at the seven Radon points determined in the local $x^{\prime}, y^{\prime}$ coordin system; $d \Omega_{B B}^{i}$ is a function of the distance


Figure 3.4: A local cartesian coordinate system is defined in the plane of the triangle over which the potential is to be estimated. $x^{\prime}$ and $y^{\prime}$ are the lo al coordinates, the triangle centroid is $p_{c}\left(x_{c}^{\prime}, y_{c}^{\prime}\right)$, and the vectors $\vec{F}_{1}, \vec{F}_{2}$ and $\vec{F}_{3}$ form the sides of the triangle opposite vertex 1,2 and 3 , respectively.
$r$ from the observation point $i$ and can also be determined at any point within the triangle in the global coordinate system.

The only remaining step now is to shape the expression in equation 3.46 into the appropriate final form described in equation 3.18 . We start by writing

$$
\begin{equation*}
\int_{S_{B}} \phi_{B} d \Omega_{B B}^{i} \approx \sum_{k=1}^{N T_{B}} \int_{T_{B}^{k}} \phi_{B} d \Omega_{B B}^{i} \tag{3.50}
\end{equation*}
$$

and proceed by inserting equation 3.46 to produce

$$
\begin{equation*}
\int_{S_{B}} \phi_{B} d \Omega_{B B}^{i} \approx \sum_{k=1}^{N T_{B}} \sum_{m=1}^{3} \Phi_{B}^{m} \int_{T_{B}^{k}} C_{m}(p) d \Omega_{B B}^{2}, \tag{3.51}
\end{equation*}
$$

where $N T_{B}$ is the number of triangles used to define the body surface and $m$ is the vertex number of each such triangle. Although equation 3.51 is not yet in the desired form, since the summation is over $N T_{B}$ triangles (each term of which includes a summation over each vertex of the triangle), it is possible to convert it into a summation over $N_{B}$ nodes (each term of which includes a second sum over the triangles which
share the common vertex). Hence, we write the right hand side of equation 3.51 as

$$
\begin{equation*}
\sum_{j=1}^{N_{B}} \sum_{n=1}^{N T_{B}^{j}} \sum_{m=1}^{3} \Phi_{B}^{m} \int_{T_{B}^{n}} C_{m}(p) d \Omega_{B B}^{i}=\sum_{j=1}^{N_{B}} w_{i j} \Phi_{B}^{j}, \tag{3.52}
\end{equation*}
$$

where $N T_{B}^{j}$ is the number of triangles which share the common vertex $j$ and $w_{i j}$ is an element of the weighting matrix $W$. The form of this equation is the same as that of equation 3.41 and again, although separation of geometrical coefficients from potential values is achieved, it is impossible to write an analytical expression for the weighting coefficients $w_{i j}$. The relationship between $j$ and $m$ is a function of how the surfare has been triangularized. Here also, however, it is possible to keep track of all sie coefficients which are applied to the potential at each node in a running sum to finally produce a $W$ matrix.

The actual calculation is more efficiently performed over each triangle of the surface, as suggested by equations 3.50 and 3.51 , than over each node, as described in equation 3.52. Using the former approach, the location of the points used in the approximation of the surface integral over each triangle (Radon's method) need only be calculated once for each triangle, while the latter approach requires the same calculation three separate times as each vertex of the same triangle is examined separately. Furthermore, the first methed promises a lower calculation cost than the second. From equations 3.51 and 3.52 we see that although $N T_{B}$ is larger than $N_{B}$, the product of $N_{B} \times N T_{j} \times 3$ is greater than $N T_{B} \because 3$, the result being the number of times the integral must be calculated. In our experience, $N T_{B}$ is typically twice as large as $N_{B}$, while $N T_{j}$ ranges from 4-7 in our model.

To complete the derivation, we rewrite equation 3.18 as

$$
\begin{equation*}
\phi_{B}^{i}+\frac{1}{2 \pi} \int_{S_{B}} \phi_{B} d \Omega_{B B}^{i}=\sum_{j=1}^{N_{B}} p_{B B}^{i j} \Phi_{B}^{j}, \tag{3.53}
\end{equation*}
$$

where

$$
p_{B B}^{i j}= \begin{cases}\frac{1}{2 \pi} w_{B B}^{i j} & \text { if } i \neq j  \tag{3.54}\\ \frac{1}{2 \pi} w_{B B}^{i i}+1 & \text { if } i=j\end{cases}
$$

The $w_{B B}^{i i}$ (auto-integral) term must be evaluated separately as described above.
$P_{B H}$ Matrix: The $P_{B H}$ matrix relates the contribution from the heart surface to the observation points on the body surface. It is a simplification of the previous case ( $P_{B B}$ ) in that no special consideration need be given the case of the observation point being on the surface of integration since two different surfaces are involveci. The result is thus identical to that for $P_{B B}$ but for the exclusion of the auto-integral term. We can derive an estimate from equation 3.19, repeated from above,

$$
-\frac{1}{2 \pi} \int_{S_{H}} \phi_{H} d \Omega_{B H}^{i}=\sum_{j=1}^{N_{H}} p_{B H}^{i j} \Phi_{H}^{j}
$$

by applying the same arguments as for the $P_{B B}$ matrix. Using the approach outlined by Pilkington et al., we can immediately write for the coefficient $p_{B H}^{i j}$,

$$
\begin{equation*}
p_{B H}^{i j}=-\frac{1}{2 \pi} \Omega_{B H}^{i j} \equiv-\frac{1}{2 \pi} \sum_{k=1}^{2 N T_{H}^{j}} \int_{T_{H}^{j k}} d \Omega_{B H}^{i j k} \tag{3.55}
\end{equation*}
$$

where $2 N T_{H}^{j}$ subtriangles, $T_{H}^{j k}$, surround each point on the heart surface and $d \Omega_{B H}^{i j k}$ is the solid angle subtended by each subtriangle about a point $i$ on the body surface. These solid angles can be evaluated analytically [27] to produce the $P_{B H}$ matrix.

Application of the method from Meijs et al. leads to an expression similar to the one derived above in equation 3.40 for the $P_{B B}$ case:

$$
\begin{align*}
-\frac{1}{2 \pi} \int_{S_{H}} \phi_{H} d \Omega_{B H}^{i} \approx & -\frac{1}{2 \pi} \sum_{j=1}^{N_{H}} \sum_{k=1}^{N T_{H}^{3}}\left[\left(\frac{4}{9} \Omega_{B H}^{i k 1}+\frac{1}{36} \Omega_{B H}^{i k 2}+\frac{1}{36} \Omega_{B H}^{i k 3}+\frac{1}{9} \Omega_{B H}^{i k 4}\right) \Phi_{H}^{m}\right. \\
& +\left(\frac{1}{9} \Omega_{B H}^{i k 1}+\frac{1}{9} \Omega_{B H}^{i k 2}+\frac{1}{36} \Omega_{B H}^{i k 3}+\frac{1}{9} \Omega_{B H}^{i k 4}\right) \Phi_{H}^{m+1}  \tag{3.56}\\
& \left.+\left(\frac{1}{9} \Omega_{B H}^{i k 1}+\frac{1}{36} \Omega_{B H}^{i k 2}+\frac{1}{9} \Omega_{B H}^{i k 3}+\frac{1}{9} \Omega_{B H}^{i k 4}\right) \Phi_{H}^{m+2}\right]
\end{align*}
$$

Here, $\Omega_{B H}^{i k 1}, \ldots, \Omega_{B H}^{i k 4}$ are the solid angles subtended by the four subtriangles of main (heart) triangle $k$ about the (body) point $i$. Each point $j$ on the heart surface is surrounded by $N T_{B}^{j}$ main triangles, each of which contributes to the value of the integral at that point.

The method of Rudy and Messinger-Rapport similarly yields an equivalent ex-
pression for the $P_{B H}$ integral:

$$
\begin{equation*}
-\frac{1}{2 \pi} \int_{S_{H}} \phi_{H} d \Omega_{B H}^{i} \approx-\frac{1}{2 \pi} \sum_{j=1}^{N_{H}} \sum_{n=1}^{N T_{H}^{j}} \sum_{m=1}^{3} \Phi_{H}^{m} \int_{T_{H}^{n}} C_{m}(p) d \Omega_{B H}^{i}=-\frac{1}{2 \pi} \sum_{j=1}^{N_{H}} w_{i j} \Phi_{H}^{j}, \tag{3.57}
\end{equation*}
$$

where $N T_{H}^{j}$ is the number of triangles which share the common vertex $j$ and $w_{i j}$ is an element of the weighting matrix $W . C(m)$ is Cruse's weighting factor for each vertex $m$ of the main triangle $n$, as described above.

The evaluation of these expressions involves the same computational tools as those used for $P_{B B}$ : evaluation of the integrals using either a closed analytical expression for the solid angle (methods of Pilkington or Meijs) or Radon's numerical quadrature (method of Rudy, Messinger-Rapport, and Cruse) summations, and the book-keeping of various weighting coefficients. The only difference is that no account need be taken of the case when $i=j$, since the observation point $i$ does not lie on the surface of integration.
$P_{H B}$ Matrix: This case is identical to the $P_{B H}$ matrix above, except that the surfaces are reversed: observation points lie on the heart surface and the body surface becomes the surface of integration. The equations 3.55-3.57 given above can be used directly for this case with the $H$ and $B$ reversed and the negative signs removed.
$P_{H H}$ Matrix: The diagonal elements of the $P_{H H}$ matrix contain auto-integral terms for the case when both the observation point and the triangle over which the integration takes place lie on the heart surface. Since the situation here is identical to that of $P_{B B}$ matrix, we can apply the same numerical techniques to the $P_{H H}$ matrix as were outlined in the equations above for the $P_{B B}$ matrix by replacing all the $B$-terms with their $H$ counterparts. Otherwise, equations 3.18 and 3.22 differ only in a negative sign before the integrai term.
$G_{H A}$ Matrix: The $G_{H H}$ matrix, which is derived from equation 3.23 above, is of a different form than the $P$ matrices evaluated so far. The integrand is the product of
the gradient of potential (instead of the potential itself) and the function $1 / r \cdot d \vec{A}$, not the solid angle. The manner in which the surface of integration is defined and discretized is, however, identical and many of the same methodological considerations apply to the formulation of the numerical solution. The goal is again to cnsure a separation of the geometrical factors from the physical quantity (potential gradient in this case) and produce an accurate estimate of the integral. In fact, the only difference in the final set of equations will lie in the manner in which the geometrical function is evaluated.

By first applying the method of Pilkington et al. to equation 3.23, we can write

$$
\begin{equation*}
\frac{1}{2 \pi} \int_{S_{H}} \frac{\nabla \phi_{H}}{r^{i}} \cdot d \vec{A}_{H} \approx \sum_{\substack{j=1 \\ j \neq i}}^{N_{H}} \Gamma_{H}^{j} \sum_{k=1}^{2 N T_{H}^{j}} \int_{T_{H}^{\prime k}} \frac{d A_{H}}{r^{i}}, \tag{3.58}
\end{equation*}
$$

where $T_{H}^{j k}$ is subtriangle $k$ of the $2 N T_{H}^{j}$ triangles which surround point $j$ on the heart surface. $\Gamma_{H}^{j}$ is the component of the potential gradient in the direction of the outward normal to the heart surface. To simplify the notation, let us define a symbol analogous to that used for the solid angle, $\Omega$, as

$$
\begin{equation*}
\Psi_{H H}^{i j}=\sum_{k=1}^{2 N T_{H}^{j}} \int_{T_{H}^{\prime j}} \frac{d A_{H}}{r^{i}} . \tag{3.59}
\end{equation*}
$$

With this, equation 3.58 becomes

$$
\begin{equation*}
\frac{1}{2 \pi} \int_{S_{H}} \frac{\nabla \phi_{H}}{r^{i}} \cdot d \vec{A}_{H} \approx \sum_{\substack{j=1 \\ j \neq i}}^{N_{H}} \Gamma_{H}^{j} \Psi_{H H}^{i j} . \tag{3.60}
\end{equation*}
$$

Using this definition for $\Psi$, we can again apply the methods of Meijs et al. and Rudy and Messinger-Rapport io the $G_{H F}$ matrix, which results in the following two expressions, first for the method by Meijs et al.:

$$
\begin{align*}
\frac{1}{2 \pi} \int_{S_{H}} \frac{\nabla \phi_{H}}{r^{i}} \cdot d \vec{A}_{H} \approx & \frac{1}{2 \pi} \sum_{j=1}^{N_{H}} \sum_{k=1}^{N T_{H}^{J}}\left[\left(\frac{4}{9} \Psi_{H H}^{i k 1}+\frac{1}{36} \Psi_{H H}^{i k 2}+\frac{1}{36} \Psi_{H H}^{i k 3}+\frac{1}{9} \Psi_{H H}^{i k 4}\right) \Gamma_{H}^{m}\right. \\
& +\left(\frac{1}{9} \Psi_{H H}^{i k 1}+\frac{1}{9} \Psi_{H H}^{i k 2}+\frac{1}{36} \Psi_{H H}^{i k 3}+\frac{1}{9} \Psi_{H H}^{i k 4}\right) \mathrm{I}_{H}^{m+1}  \tag{3.61}\\
& \left.+\left(\frac{1}{9} \Psi_{H H}^{i k 1}+\frac{1}{36} \Psi_{H H}^{i k 2}+\frac{1}{9} \Psi_{H H}^{i k 3}+\frac{1}{9} \Psi_{H H}^{i k 4}\right) \Gamma_{H}^{m+2}\right]
\end{align*}
$$

and also for that proposed by Rudy and Messinger- ${ }^{\top}$ pport:

$$
\begin{equation*}
\frac{1}{2 \pi} \int_{S_{H}} \frac{\nabla \phi_{H}}{r^{i}} \cdot d \vec{A}_{H} \approx \sum_{j=1}^{N} \sum_{n=1}^{N T_{j}} \sum_{m=1}^{3} \Gamma_{H}^{m} \int_{T_{H}^{n}} C_{m}(p) d \Psi_{H H}^{i} \tag{3.62}
\end{equation*}
$$

The missing step of the solution is to determine an estimate for the $\Psi$-term, as it appears in equations 3.60-3.62 above. Integration of the function $1 / r d A$ can be performed analytically only for simple geometries so that numerical quadrature is necessary; for this we chose Radon's 7-point method [234, 235] described in section 3.1.3.3. In equations 3.60 and 3.61 , the calculation is quite straightforward; for equaticn 3.62 the additional complication of the weighting function $C_{m}(p)$ can be taken into account by evaluating $C_{m}(p)$ at the same Radon points that are used for the calculation of the integral.

The case in which the observation point is a vertex of the integration triangle (auto-integral) must be dealt with differently for the $G_{H H}$ matrix than for the $P_{B B}$ or $P_{H H}$ matrices described above. As in the more general case of $G_{B H}$, we knc: of no analytical solution and therefore a numerical approach had to be adopted. A method was developed based on a solution first proposed by Barr et al. [56]. Barr and co-workers approximated each triangle by a sector of a circle. By then placing an observation point at a distance $d$ from the surface on a perpendicular line through the centre of the circle, as depicted in Figure 3.5, the following analytical solution to the integral can be formulated:

$$
\begin{equation*}
\int_{S} \frac{d A}{r}=\int_{0}^{\theta_{T}} \int_{0}^{u_{T}} \frac{u}{\sqrt{d^{2}+u^{2}}} d u d \theta=\sqrt{\theta_{T}^{2} d^{2}+r_{T}^{2} \theta_{T}^{2}}-0_{T} d, \tag{3.63}
\end{equation*}
$$

where $\theta_{T}$ is the angle subtended by the sector $S$ and $r_{T}$ is the radius of the sector.
Equation 3.63 holds only under the conditions specified and is, therefore, not as general a solution as one using numerical quadrature. However, this approach has the advantage, as pointed out by Barr et al. [56], of being correct when the observation point lies in the plane of the sector at the centre of the circle. In this case, with $d=0$, equation 3.63 simplifies to

$$
\begin{equation*}
\int_{S} \frac{d A}{r}=r_{T}^{2} \theta_{T}^{2} \tag{3.64}
\end{equation*}
$$



Figure 3.5: An analytical method for evaluating the $d A / r$ integral over the surface of a circular sector $S$. Each sector has constant radius, $r_{T}$, area $A$, and subtends an angle $\theta_{T}$; the observation point $p$ lies at distance $d$ on a line perpendicular to the surface through the centre of the circle.

It is possible to approximate a triangle by a circular sector and use this expression to derive an cstimate for the $\Psi_{i i}$ terms in equations $3.58-3.62$. The problem of determining an equivalent radius of the triangle can further be solved by noting that the area of a circular sector $A_{T}$ can be expressed as

$$
\begin{equation*}
A_{T}=\frac{\theta_{T} r_{T}^{2}}{2} \tag{3.65}
\end{equation*}
$$

from which we can write

$$
\begin{equation*}
r_{T} \theta_{T}=\sqrt{2 A_{T} \theta_{T}} \tag{3.66}
\end{equation*}
$$

which can be substituted into equatior 3.64 to yield for the triangle $T$,

$$
\begin{equation*}
\int_{T} \frac{d A}{r}=\sqrt{2 A_{T} \theta_{T}} \tag{3.67}
\end{equation*}
$$

We require only the value oi the area of the triangle and the angle subtended by the two sides which join at the observation point to estimate the value of the anto-integral case of the $G_{H H}$ matrix.

To improve the accuracy of this estimate the original triangle can be divided into subiriangles about the observation point $p$; the resulting subtriangles better approximate the circular sector which is still the basis of this solution. In computing the solution it is possible to successively bisect the base angle $\theta$ and recalculate the integrals for the resulting subtriangles. The sum of these values is the estimate of the total integral and is compared with that of the previous iteration until the difference drops below a predefined value. Through some geometrical manipulation it is possible to simplify this approach even further. In Figure 3.6 a vector $\vec{\rho}$ is anchored at the observation point (vertex 1) and sweeps through ine triangle from vertex 2 to vertex 3 in $N$ equiangular steps. The sides of the triangle are defined as vectors $\vec{a}, \vec{b}$, and $\vec{c}$, which lie opposite vertices 3,1 , and 2 , respectively. As $\vec{\rho}$ sweeps through the triangle, it ma es an angle $\delta_{j}$ with side $a$. Side $b$ can be viewed as the base of the triangle and the height relative to this base as $\dot{h}$. With $\alpha$ defined as the angle between $h$ and side $a, \vec{\rho}$ makes an angle $\alpha-\gamma_{j}$ with $h$ and we can write for the magnitude of $\vec{\rho}$,

$$
\begin{equation*}
\rho_{j}=\frac{h}{\cos \left(\alpha-\delta_{j}\right)} . \tag{3.68}
\end{equation*}
$$



Figure 3.6: A modified scheme for calculating the auto-integral terms for the $\mathcal{X}_{H M}$ matrix. The triangle in panel A is defined by vertices 1,2 , and 3 and the sides $\vec{a}, \vec{b}$, and $\vec{c}$. The vector $\vec{\rho}$ is anchored at the observacion point and sweeps in $N$ steps through the triangle from side $\vec{a}$ to $\vec{c}$. In panel B two successive vectors $\overrightarrow{\rho_{j}}$ and $\overrightarrow{\rho_{j-1}}$ define a subtriangle.

Each step made by $\vec{\rho}$ through the triangle defines another subtriangle made up of the vectors $\vec{\rho}_{j}$ and $\vec{\rho}_{j-1}$ (see Figure 3.6 , panel B). The area of this subtriangle is

$$
\begin{equation*}
A_{j}=\frac{\rho_{j} \rho_{j-1} \sin \delta}{2} \tag{3.69}
\end{equation*}
$$

where $\delta$ is the incremental angle subtended at each new step, that is, $\delta_{j}=\delta_{j-1}+\delta$ and $\delta=\theta / N$.

Equations 3.68 and 3.69 can be applied to each subtriangle and the sum for the whole triangle calculated. This yields for any triangle $T^{i i}$ in which one of the vertices is the observation point

$$
\begin{equation*}
\Psi^{i i}=\int_{T, י} \frac{d A}{r} \approx \sum_{j=1}^{N} \sqrt{2 \delta A_{j}}=\sqrt{2 \delta} \sum_{j=1}^{N} \sqrt{\frac{\rho_{j} \rho_{j-1} \sin \delta}{2}}=\sqrt{\delta \sin \delta} \sum_{j=1}^{N} \sqrt{\rho_{j} \rho_{j-1}}, \tag{3.70}
\end{equation*}
$$

where $N$ is the number of subtriangles into which the triangle $T^{i i}$ is divided.
Witu this, the $\Psi$ terms and thus the diagonal elements of matrix $G_{H H}$ can be estimated using equations $3.60-3.62$.
$G_{B H}$ Matrix: Computationally, the $G_{B H}$ represents a simplification of the $G_{H I H}$ matrix, since the observation points do not lie on the surface of integration. The
general methods described in equations 3.60-3.62 above can thus be used to solve for the matrix elements.
$Z_{B H}$ Matrix: The $\bar{Z}_{B H}$ matrix, as defined in equation 3.30, can be calculated from the submatrices $P_{B B}, P_{B H}, P_{H B}, P_{H H}, G_{H H}$, and $G_{B H}$. This requires the inversion of the $G_{H H}$ matrix and a con ${ }_{1}$ posite submatrix made up from $P_{B B}, G_{B H}, G_{H H}^{-1}$ and $P_{H B}$. This was performed using the numerical method of LU-decomposition, chosen for its high speed of computation and robust nature [236].

### 3.1.4 Inverse solution

The $Z_{B H}$ matrix defined in section 3.1.3 provides a means of estimating the potential distribution on the body surface from that on the epicardial surface. The purpose of the inverse solution is to do the reverse: from a known potential distribution on the body surface, to estimate the equivalent distribution on the epicardium. The forward solution can be stated mathematically as:

$$
\begin{equation*}
Z_{B H} \Phi_{H}=\Phi_{B}=\Phi_{B}^{M}+E_{B} \tag{3.71}
\end{equation*}
$$

where $\Phi_{B}$ are the calculated body surface potentials, which differ by an error term $E_{B}$ from the actual measured body surface potentials $\Phi_{B}^{M}$. When this equation is solved for the epicardial potentials, $\Phi_{H}$, the result is an inverse solution, whirh can be stated in a symmetrical form as

$$
\begin{equation*}
Z_{H B} \Phi_{B}=\Phi_{H}=\Phi_{H}^{M}+E_{H}, \tag{3.72}
\end{equation*}
$$

where $Z_{H B}$ is the transfer coefficient matrix used to estimate epicardial potentials $\Phi_{H}$ from the body surface potentials $\Phi_{B}$. The measured epicardial potentials $\Phi_{H}^{M}$ differ from the estimated values by an error function $E_{H}$.

The dimension of $Z_{B H}$ is $N_{B}$ by $N_{H}$, where $N_{B}$ is the number of nodes on the body surface and is typically larger than the number of nodes on the epicardial surface, $N_{I I}$. If we wish to solve such a set of equations for $\Phi_{H}$, the system is overdetermined, that
is, there are more equations than variables to solve for; in general, there is no unique solution. It is usually possible, however, to determine a solution of an overdetermined system which represents the "best compromise" and satisfies, or almost satisfics, as many of the imposed conditions as possible. If "best" is defined in the least squares sense, the sum of the squares of all the errors is minimized and for this type of problem a large number of numerical solution methods exist $[236,237,86]$.

In an overdetermined system there can be equations which are not linearly independent of all other equations in the system, a condition known as row degeneracy. Each linearly dependent equation reduces the number of equations which can contribute to the solution; the number of linearly independent equations is known as the rank of the matrix. When there is so much degeneracy that the rank of the matrix falls below the number of variables in the solution, the system is termed rank deficiert. Computationally, rank deficiency can arise because the finite accuracy of the processor no longer allows equations which are nearly linearly dependent to be differentiated. Likewise, errors in the real data used to generate such systems of equations can be large enough to generate functional linear dependence between equations. It is possible to compute the singular values of a matrix and use these to determine the condition number, which is the ratio of the largest to the smallest singular value. A matrix which is singular is one which has a condition number equal to infinity while an ill-conditioned matrix is one in which the inverse of the condition number approaches the round-off error of the cemputer. Ill-conditioned matrices result from the solution of ill-posed proùlems [236, 238].

The inversion of ill-conditioned matrices presents some difficulty because the result will be unstable if not handled properly. While it may be possible to numerically determine an inverse to such a matrix, even sra all fluctuations in the values of the matrix elements or the vectors by which the matrix is multiplied can produce disproportionately larger oscillations in the product. For a simple numeric I demonstration of this, see Rudy [7] or Gill et al. [238]. The inverse problems of electrocardiograph;
is ill-posed and the forward solution matrix, $Z_{B H}$, is ill-conditioned; application of standard numerical inversion techniques produces a $Z_{H B}$ matrix with a high degree of instability. The physical reason for instability in this problem lies in the fact that potential drops off quickly $\left(1 / r^{2}\right)$ with increasing distance from the source. Hence, epicardial potentials are much larger ( $\approx 20-25 \mathrm{mV}$ QRS amplitudes in intact human hearts [49]) than body surface ECGs (QRS amplitudes $\approx 2-2.5 \mathrm{mV}$ ). The transfer coefficients of $Z_{H B}$ must 'amplify' the body surface potentials and potentials from more distant surfaces, for example the back and lower torso, are weighted relatively more highly than those in the precordial area. Electrical noise, which inevitably as companies measured ECGs is, on the other hand, of approximately constant absolute amplitude all over the body surface; the higher weighting of more distant regions now applies to the noise and increases the overall error of the result. This problem does not arise in the forward solution since measurement noise in epicardial electrograms is relatively less than for ECG recordings. Furthermore, since the torso potentials are smaller in amplitude then epicardial electrograms, the transfer coefficients serve to attenuate the epicardial contributions and any noise they might possess. To reduce the effects of the ill-posed nature of the problem and generate a useful inverse to $Z_{B H}$, some means of constraining the solution is necessary.

### 3.1.4.1 Inverse solution constraints

As described in section 2.1 above, there are two families of constraining techniques which have been applied to the inverse problem in electrocardiography: statistical smoothing and regularization. Regularization techniques have been applied not only to problems in electrocardiographic modelling [ $6,7,5,79$ ], but also to those in many other fields, such as the study of weather layers near the eartn's surface [239].

The regularization techniques most often used to invert an ill-conditioned matrix are credited to Tikhonov [240]; they are also closely related to work by Twomey [84] and fall into the class of damped least-squares solutions. Characteristic of Tikhonov
regularization is the addition of a damping function to the matrix to be inverted producing a modified matrix equation which can be easily solved using standard inversion techniques. If we wish to apply regularization to the system $A x=b$, the modified equation can be written as

$$
\begin{equation*}
x=\left(A^{T} A+t M\right)^{-1} A^{T} b \tag{3.73}
\end{equation*}
$$

where $A^{T}$ is the transpose of $A$. The generalized inverse matrix is then

$$
\begin{equation*}
A^{+}=\left(A^{T} A+t M\right)^{-1} A^{T} \tag{3.74}
\end{equation*}
$$

The matrix $M$ is either the identity matrix $I$, or is derived from the gradient operator matrix $G$ or the Laplacian operator matrix $L$.

$$
M= \begin{cases}I & I \text { is the identity matrix } \\ G^{T} G & G \text { is the gradient operator } \\ L^{T} L & L \text { is the Laplacian operator }\end{cases}
$$

The discrete gradient- and Laplacian-operator matrices $G$ and $L$ are defined in terms of the first or second spatial derivatives, respectively. The gradient of a function $f$ can be estimated numerically as a weighted sum of the values of $f$ at all nodes on the surface. The structure of $G$ and $L$ can be best seen by writing for any point $i$ the gradient of the function $f$ as

$$
\begin{equation*}
\nabla f_{i}=\sum_{j=1}^{N} G_{i j} f_{j} \tag{3.75}
\end{equation*}
$$

Likewise the value of the Laplacian of $f$ at any point $i$ can be written as

$$
\begin{equation*}
\nabla^{2} f_{i}=\sum_{j=1}^{N} L_{i j} f_{j} \tag{3.76}
\end{equation*}
$$

where $\nabla$ is the gradient operator and $\nabla^{2}$ is the Laplacian operator. Typically, the points which contribute to the value of the gradient or Laplacian at point $i$ are those in the immediate neighbourhood of point $i$, so that the $G$ and $L$ matrices are sparse.

The factor $t$ in equation 3.73 is the damping coefficient and must be set beforehand in order for the regularization to be performed. The value of $t$ determines the degree
of damping or regularization applied to the solution. If $t$ is set to 0 , equation 3.73 reduces to the least-square approximation for the inverse, a form of the pseudo inverse:

$$
\begin{equation*}
x=\left(A^{T} A\right)^{-1} A^{T} b \tag{3.77}
\end{equation*}
$$

which for an ill-conditioned matrix yields an unstable solution. Mathematically, this instability can be seen to result from the small singular values of $A$, which are first squared ( $A^{T} A$ ) and then inverted. It can be shown [54] that regularization increases the value of small eigenvalues of $A^{T} A$ in a controlled way, while the larger eigenvalues remain unchanged. As the value of $t$ is increased, more and more damping is applied until the solution approaches zero. From this it is clear that the choice of a value for $t$ is of great importance in producing useful and stable solutions. Too little regularization and the solution will oscillate wildly; too much, and subtle spatial features of the distribution will be "smeared out" and resolution will be needlessly reduced. The value of $t$ must normally be set post priori, that is, a set of representative known solutions must be available and the inverse solution repeatedly applied with different values of $t$ until the best compromise is found. Only then can the regularized inatrix be applied to other problems in which unknown solutions are to be calculated.

### 3.1.4.2 Application of the regularization technique

In computing the inverse of the $Z_{B H}$ matrix, two methods of Tikhonov regularization were used in this study. In the first, termed zero-order, the identity matrix was used in equation 3.73 , while in the second, $M$ was calculated from the Laplacian operator. Physiologically, the application of regularization is equivalent to constraining some aspect of the epicardial potential distribution. For zero-order Tikhonov regularization, the amplitude is restrained to directly subdue wild oscillations in potential; the gradient and Laplacian operators restrict the first and second order spatial gradients, respectively, and thus limit how much the value of the potential can change from one node to neighbouring ones.

To calculate the Laplacian operator, the numerical method described by Huiskamp et al. [241] was applied to the geometry of the heart surface. The same method was used on the body surface to perform 3D interpolation of the body surface potential maps recorded during PTCA (see section 3.2). To determine optimal values of $t$, sets of epicardial and body surface potentials were calculated using a forward simulation based on a single dipole source. Models of this type have been used extensively in this laboratory and elsewhere to calculate body surface potentials [242, 5, 243, 23]. For a discrete source in a homogeneous torso, we can write [25] for any point $p$ on the surface of the volume conductor

$$
\begin{equation*}
\phi(p)=2 \phi_{\infty}(p)-\frac{1}{2 \pi \sigma} \int_{S_{B}} \phi_{B} d \Omega \ldots p \in S_{B} \tag{3.78}
\end{equation*}
$$

where the integral is taken over the bounding surface, in this case the body surface. $\phi_{\infty}(p)$ is the potential at point $p$ resulting from the source in the absence of any boundary, called the infinite medium potential. This terrn can further be written for a dipole as

$$
\begin{equation*}
\phi_{\infty}(p)=\frac{1}{4 \pi \sigma} \frac{\vec{r} \cdot \vec{p}}{r^{3}}, \tag{3.79}
\end{equation*}
$$

where $\vec{p}$ is the dipole moment of the single dipole and $\vec{r}$ is the radius vector from the dipole source location $q$ to the field point $p$. Equation 3.78 can be discretized and written once for $p$ at each of the $N_{B}$ node points on the body surface. The resulting set of linear equations can then be deflated [244, 245] and solved iteratively to generate a set of potentials on the body surface, $\Phi_{B}$ [23, 25, 242, 243].

To then calculate the potential values at the epicardial nodes, equation 3.78 can be written in discrete form for $p$ located at each of the epicardial node points. Using the previously calculated body surface potentials $\Phi_{B}$, the system can be easily solved for the node potentials $\Phi_{H}$. Sets of such simulated epicardial ( $\Phi_{H}^{S}$ ) and body surface ( $\Phi_{B}^{S}$ ) potentials were calculated for 3 dipoles located in the centre of the heart, ai the point $(25,300,-40)$ in the body co-ordinate system (see section A); these were then considered to be known values. They were used to both validate the forward solution
described in section 3.1.3 and to determine the optimal value of the regularization parameter $t$. For example, to test the accuracy of the forward solution matrix $Z_{B H}$, the product $Z_{B H} \Phi_{H}^{S}=\Phi_{B}^{G}$ was calculated and compared with the simulated body surface potentials $\Phi_{B}^{S}$.

The smparison of two sets of node potentials from the same surface can be carried out in a number of ways. Isopotential maps of both data sets may be calculated and compared visually (qualitative comparison) or a numerical index may be calculated which serves as a measure of the degree of difference or similarity between the two distributions (quantitative comparison). For quantitative comparison we chose four different numerical indices. The first is absolute maximum difference between the predicted and actual values. The second is the root-mean-square (rms) difference defined as

$$
\begin{equation*}
\sqrt{\frac{\sum_{i=1}^{N}\left(\Phi_{i}^{c}-\Phi_{i}^{s}\right)^{2}}{N}} \tag{3.80}
\end{equation*}
$$

and both are expressed in units of $\mu \mathrm{V}$. A third, related index may be calculated in which the rms difference is normalized by the rms value of the "known" distribution. This is termed the relaiive error [7] and is defined as

$$
\begin{equation*}
R E=\sqrt{\frac{\sum_{i=1}^{N}\left(\Phi_{i}^{C}-\Phi_{i}^{S}\right)^{2}}{\sum_{i=1}^{N} \Phi_{i}^{S}}} \tag{3.81}
\end{equation*}
$$

The smaller the value of either $R E$ or rms or maximum difference, the more similar are the two distributions. A third inder of the relationship between two distributions is the correlation coefficient. For this, each set of potentials is viewed as a vector in $N$-space and the "angle" between them is calculated as the dot-product of two vectors normalized by the product of the respective magnitudes, that is, for simulated and calculated potentials $\Phi^{C}$ and $\Phi^{S}$,

$$
\begin{equation*}
C C=\frac{\overrightarrow{\Phi^{C}} \cdot \overrightarrow{\Phi^{S}}}{\left|\overrightarrow{\Phi^{C}}\right|\left|\overrightarrow{\Phi^{S}}\right|} \tag{3.82}
\end{equation*}
$$

A value of $C C=1$ indicates that two vectors differ only by a constant factor, or equivalently, that the two distributions are identical but for a scaling factor.

To test the stability of the inverse solution, noise was added to the body surface potential distribution $\Phi_{B}^{S}$ before multiplication by $Z_{H B}$. We made use of an algorithm to compute random numbers with uniform density and amplitudes between 0 and 1 [236]. For applications such as ours, noise with a Gaussian or normal amplitude distribution is chosen because its amplitude distribution and frequency spectrum are most reminiscent of those produced by real electronic components [246]. To shape the uniform density random numbers into a Gaussian distribution, the $B C \cdot$ Muller method was used [236]. Parameters within the programs written accor ${ }^{\text {ing }}$ to this scheme determined the mean value and standard deviation of the random numbers generated.

For each individual trial of an inverse solution matrix, a set of $N_{B}$ noise values was computed from the same seed value; the mean value was always 0.0 and the standard deviation was set as a percentage of the rms amplitude of the torso potentials. The noise values were then added to the sinulated body surface potentials data and an inverse calculation was performed. The resulting epicardial distribution $\Phi_{H}^{C}$ was then compared with the simulated one $\Phi_{H}^{S}$ according to the methods described above. Trials were repeated 20 times for each of 1-5 different percentage values and the mean and standard deviation of the difference indices were calcuiated for each noise level. Thus, for each test of a specific inverse solution matrix, a table of 1-5 sets of three difference indices (variance, relative error and correlation coefficient), together with their standard deviations, was generated.

### 3.1.5 Summary

The Green's theorem has been applied to a homogeneous volume conductor bounded by the body and heart surfaces to derive a boundary element method (BEM) solution to the forward problem. The result is a forward transfer coefficient matrix $Z_{B H}$, constructed from 6 submatrices, which directly relates body surface to heart surface potentials. To generate the individual submatrices, the product of the potential or
potential gradient and a geometrical function of distance must be integrated over each triangular element of the tessellated surfaces. In this section, 4 different methods for computing these integrals have been compared and discrete equations for each approach have been developed.

In order to compute a stable inverse solution, regularization must be applied to the forward transfer matrix $Z_{B H}$. The method of Tikhonov was described in which either the identity matrix (Tikbonov zero-order) or a matrix based on either the first or second order gradient (Laplacian) served as a constraining function on the ill-condilioned $Z_{B H}$ matrix. The degree of regularization is determined by the $t$ parameter, a weighting factor applied to the constraining function; for small values of $t$ the solution reverts to the unconstrained least squares case ( $p s e u d o$ inverse) and is unstable, while large values of $t$ produce overdamped inverse solutions.

In section 4.1 the results of converting these equations into algorithms and computer programs will be presented.

### 3.2 Clinical Mapping Studies

Four clinical studies were carried out at the Victoria General (VG) Hospital in Halifax to examine the effect of PTCA on cardiac electrical activity:

1. PTCA \#1 A preliminary study to determine the feasibility of performing BSPM during the PTCA procedure.
2. DYE \#1 A preliminary study to examine the effects of contrast medium injection on the body surface potential distribution.
3. DYE \#2 A systematic evaluation of the effects of three different contrast media on a small set of patients using continuous BSPM recording throughout the injections.
4. PTCA \#2 A rigorously controlled study of selected PTCA patients, employing continuous BSPM recordings throughout the balloon inflation.

Many of the effects of balloon inflation during PTCA are not detectable using the standard limb leads (see section 2.2) and some remain invisible even with additional precordial leads. High resolution body surface potential mapping (BSPM) provides a tool with which a larger portion of the non-invasively measurable electrical information can be gathered. This technique has been used extensively in our laboratory to evaluate cardiac electrical activity in a number of diverse diagnostic groups $[247,248,249,250,251,252,253]$ and $[254,255,256,226,257,133]$.

### 3.2.1 Methodology common to all studies

### 3.2.1.1 Angioplasty proceảure

PTCA was performed in the usual manner. Briefly, a No. 8F guide catheter was positioned in the aucending aorta. An appropriately sized "steerable" balloon dilation catheter (USCI, 2.5 to 3.5 mm diameter, $20-25 \mathrm{~mm}$ length) was then positioned
through the guide catheter across the coronary artery stenosis so that when inflated, the balloon completely obstructed the coronary artery and eliminated antegrade blood flow. Inflations were performed as therapeutically appropriate, unless indicated otherwise.

## 

Coronary and left ventricular angiographic studies were performed before PTCA according to the standard method for the VG Hospital Catheterization Laboratory. Analysis of left ventricular wall motion and calculation of global and regional ejection fraction were carried out from the 30 degree right anterior oblique projection fluoroscope image. Coronary angiography was performed in multiple views with and without preadministration of nitroglycerin. During the PTCA procedure itself, digital subtraction angiograms [258] were recorded using the Digitron 2 system (Siemens Medical Systems, Chicago, IL). The images were displayed in the operating room throughout the PTCA procedure and stored as a hard-copy transparency.

### 3.2.1.3 BSPM recording and processing

To record in the catheterization laboratory, several technical changes were made to the BSPM recording system used in our laboratory. Firstly, the electrodes had to be made radiolucent so that fluoroscopic imaging would not be obstructed. In addition, the mapping electronics had to be isolated from the patient, since a cardiac catheter may provide a current path to the heart. See Appendix B for details of these developments.

The electrode configuration used in all mapping studies performed at Dalhousie is shown in Figure 3.7. Electrodes were applied by the same technician in every case to ensure consistent placement. To allow the free movement of the patient's arms during angiography and angioplasty, the limb leads (which are joined to form the Wilson Central Terminal for the BSPM system) were moved from the standard locations at the extremities to the pesitions suggested by Mason and Likar [259], on


## BSPM Electrode Placement

Figure 3.7: The electrode configuration used for body surface potential mapping. Leads 1-3 were placed on modified Mason \& Likar sites in PTCA studies; the row starting with lead 4 was aligned at the level of the fourth intercostal space at the sternum.
the torso. The right arm (RA) and left arm (I.A) equivalent electrodes were mounted slightly higher and more laterally than specified by Mason and Likar, at the acromial end of the clavicle, in order to make room for the standard ECG electrodes used in the catheterization laboratory. The inferior lead (LL) was affixed along the anterior axillary line on the iliac crest. A recent report by Papouchado et al. [260] suggests that this location, slightly lower than that prescribed by Mason and Likar, produces better agreement with the standard limb-lead positions.

Body surface potential maps were recorded at different times and for varying durations in these studies. The following nomenclature (see below for specific prutocol of each study) was devised to identify the recordings:

AB0: The initial baseline recording, of 15 s duration, taken at the start of every procedure.

AB1-n: Subsequent 15 -second baseline recordings collected with the balloon deflated, but normally in place in the lesion.

AI1-n: A secording of any duration which includes at least some part of a balloon infletion.

AD1-n: A recording of any duration performed during or after an injection of contrast med ${ }^{\circ} \mathrm{m}$.

AS1: A recording, typically of 15 s duration, of some spontancous event during the procedure, e.g., sudden onset of angina or obvious ischemic conditions.

ABF: A final 15 -second baseline recording made once the procedure was finished, but before the patient was removed from the catheterization laboratory.

All BSPM recordings could be divided into two groups based on their duration. Short recordings (15-20 s duration) were made to capture baseline conditions or any other stable state, for example, the last 15 s of a longer inflation. These records
were each treated as isolated episcdes and processed so as to yield a single averaged, representative ECG complex. To follow the transition from one physiological state to another, longer continuous recordings of up to 6 min were made, for example, before, during and after a complete inflation/deflation cycle, or for 2 min after injection of contrast medium. For analysis, these records were divided into shorter intervals or windows of $10-30 \mathrm{~s}$ duration, each of which was thought to cncompass a relatively stable period. As a basis for windowing, plots of selected leads of the unprocessed electrocardiograms were produced; windowing criteria included visible measures of ischemia (ST-segment shifts, T-wave peaking or inversion, QRS morphological variation), inflation timing (windows never crossed the commencement of balloon inflation or deflation) and data errors. To facilitate later examination of the processed maps, a supplementary nomenclature was devised for the results from these long inflation/deflation and dye recordings:

Ixa-z: Processis ; windows extracted from the long recording number ' $x$ ' made before or during inflation of the balloon, starting with labels $a, b, c \ldots$, etc. For example, 12a is the first window, which normally encompasses the 20 s just before balloon inflation, while I2c is the third window; both are from the second recorded inflation/defiation cycle.

Rxa-z: Processing windows extracted from a long recording of the inflation/deflation number ' $x$ ', but during the reperfusion phase, after deflation of the balloon. For example, R2c is the third window after deflation of the balloon in the second inflation/deflation cycle recorded, that is, not the same as I2c.

Processing of the BSPM data followed a pattern quite similar to that in other studies from our laboratory [ $249,252,253,254,255,256,261,226,133]$. All processing was carried out on either a VAX 8800, VAX 780 or VaxStation II computer (Digital Equipment Corp, Maynard, MA). From the windowed intervals of $10-30 \mathrm{~s}$ duration, individual complexes were separated and sorted into families based on signal mor-
phology; the beats in the largest family (majority cluster) were in turn averaged and the baseline was corrected to yield a single representative complex for each of the 120 leads. "Bad leads" were eliminated and "scalar plots" of these averaged complexes for the remaining leads plotted in a format which resembled the layout of the electrodes on the torso (see Figure 3.8). From the scalar plots, an initial visual evaluation of the resulis was performed. Programs were written to display and subtract avcraged complexes from one another to evaluate the changes occurring between the time of inflation and the time of the baseline recording which preceded it. Computed on- and offsets for the $\mathrm{P}, \mathrm{QRS}$ and T were corrected manually from plots of the three orthogonal vectocardiographic leads derived from the 117 body surface leads, and stored in the header of a standard map file [262] for use in subsequent map processing.

From the averaged complexes, iso-contour maps in a number of configurations could be computed. We calculated either isopotential maps from single instants or isointegra' maps from the QRS, QRST, ST and STT intervals. The ST segment was considred to extend from the J point (end of the QRS), $3 / 8$ of the way to the end of the $T$ wave. Production of isointegral maps also resulted in a substantial compression of data which made examination of a large number of patients feasible. For each single short recording, or each window from a longer sampling, a set of 4 contour maps (QRS, QRST, ST, STT) was produced.

To produce isointegral displays from the BSPM data, we used two different methods of interpolation and contouring. Both required that each electrode be assigned a position in three-dimensional space and that thic set of points be projected on a flat surface. For this, we used a realistic model of the human torso, which is described in Appendix A. In the first of the interpolation methods, a scheme developed previously in our laboratory was used to fit two-dimensional cubic spline functions to the data and estimate the value at each point in a $65 \times 37$ point " $Z$-array". More recently, we have implemented three-dimensional interpolation based on an algorithm described by Oostendorp et al. [241], with which values at the 352 node locations of the three-


Figure 3.8: A plot of the averaged ECG complexes for 120 body-surface leads. The location of each tracing reflects the location of the electrode on the torso; anterior leads are shown on the left, posterior leads on the right.
dimensional tors. ("node arrays") could be estimated from the body-surface data. Construction of contour lines was then performed using a method of two-dimensional bilinear interpolation described by Ideker et al. [263, 264, 265]. While the first interpolation and contouring method produced maps of higher spatial resolution, the second was much faster and could be used to generate interaciive displays.

Figure 3.9 contains a set of maps produced using the first interpolation method. The contour levels were chosen to span a decade in 7 logarithmic steps, based on a standard sequence of numbers commonly used in electronics: $1.0,1.5,2.2,3.3,4.7$, $6.8,10$. The data to be displayed are normalized by increasing multiples of 10 until the largest absolute value falls within the range of contour levels. For example, if the maximum were $750 \mu \mathrm{~V}$ and the minimum $-500 \mu \mathrm{~V}$, the nearest smaller value of the number sequence to the largest extreme (750) would be 6.8 ; thus, the largest contours would be $\pm 680 \mu \mathrm{~V}$, followed by $\pm 470, \pm 330 \ldots \pm 68 \mu \mathrm{~V}$ In all such maps of body-surface potentials the left half of the display represents the projection of the anterior surface of the torso and the right half, the posterior surface. The three "cut-outs" along the top toundary correspond to shoulder areas.

In order to emphasize the temporal changes in the body-surface potentials, maps, in the form of interpolated Z- or node-arrays were subtracted from each other. The most common example was the subtraction of a map recorded before inflation of the PTCA balloon from a second map recorded during the inflation. These "difference maps" were plotted in the same format as the original isointegral maps from which they were derived. The ranges of values in isointegral maps from different intervals vary a great deal. To make comparisons of the degree of change between maps possible, the difference maps were (optionally) normalized during the subtraction process. In subtracting map $M_{1}$ from $M_{2}$, the extrema of $M_{1}$, MAX $_{1}$ and MIN ${ }_{1}$ were first evaluated and then the normalized subtraction performed as foll ${ }^{1}$ ws:

$$
\begin{equation*}
V_{d i f f}=\frac{V_{2}-V_{1}}{M A X_{1} \cdots M I N_{1}} * 100 \tag{3.83}
\end{equation*}
$$

This allowed a difference map from one interval, for example, the QRST-integral, to


Figure 3.9: A sample plot of a set of body surface isointegral maps. The units are in $\mu \mathrm{Vs}$ and the contour levels are arranged in logarithmic steps taken from a fixed sequence of 7 numbers which span a decade (1.0, 1.5, 2.2, 3.3, 4.7, 6.8, 10.). Data values are normalized by factors of 10 until the largest absolute value falls within this range. The left side of each map represents the projection of the anterior torso surface, the right side, the posterior surface. The shaded circles mark the locations of the precordial electrodes $V_{1}-V_{6}$.
be compared with that from a QRS-integral, even though the absolute magnitudes of the maps would be much larger for the former than the latter.

A measure of the difference between two maps, the variability, $V$, was defined as

$$
\begin{equation*}
V=\sqrt{\frac{\sum_{i=1}^{N}\left(\Phi_{i}^{2}-\Phi_{i}^{1}\right)^{2}}{N}} * 10 \tag{3.84}
\end{equation*}
$$

where $\Phi_{1}^{2}$ are the data values from one $\mathrm{ma}_{\mathrm{F}}$ and. . the orresponding values from the other; $N$ is the number of nodes in the spatial disuibution (in the case of Z -arrays, which were the interpolated form used for this purpose, $N=65 * 37=2405$ ). $\quad v$ is simply the rms difference between the maps, multiplied by a factor of 10 .

### 3.2.2 Description of the individual studies

### 3.2.2.1 PTCA \#1

The primary purpose of this study was to determine the feasibility of recording high resolution body-surface ECGs in the catheterization laboratory during PTCA. To this end, a flexible patient-selection criteria and experimental protocol were devcloped; this experimental protocol had to be modified often, based on our experience with initial results.

Patient Selection: Patients were selected from the pool of those scheduled to undergo clinically indicated PTCA. There were no specific selection criteria other than a reiatively high expected probability of clinical success and the previous informed consent of the patient. Of the 17 patients within this group, PTCA was performed on the left anterior descending (LAD) artery of 6 , the left circumflex (LCx) artery of 3 , and the right coronary ( RC ) artery of 7 . In one case both the LCx and RC arteries were treated. One subject was later moved invo the DYE \#I study since only maps which followed contrast medium injection were of adequate quality.

Protocol: The experimental protocol allowed for the collection of BSPMs of 15 s duration at various times during the PTCA procedure. An initial baseline recording ( AB 0 ) was always acquired. BSPMs were collected during 1-4 of the inflations which
followed; recordings were made when indicated by the physician who performed the PTCA, largely on the basis of therapeutic criteria and the stability of the patient's condition. Each recording sequence normally consisted of a 15 -second baseline recording (AB1-n) made just before balloon inflation and a 15 -second sample recorded immediately before deflation (AI1-n). Often the initial insertion of the balloon catheter past the stenosis provided sufficient stimulus to incite a bout of ischemic activity; to monitor this "spontaneous" ischemia, recordings (AS1-n) were made whenever the operator observed any signs of ST-segment shift or altered T waves which occurred outside of a balloon inflation. Likewise, if obvious ECG changes after injection of angiographic contrast medium were detected, we performed 15 -second recordings, which were started coincidentally (within several seconds) with the injection (AD1-n).

Data Processing: Processing was performed as described in section 3.2.1. Duration of recording was uniformly 15 s and from the isointegral maps for QRS, ST, STT and QRST intervals, difference maps were produced by subtracting from the peak inflation map the baseline which preceded it (AIn - ABn).

### 3.2.2.2 DYE \#1

During the initial study PTCA \#1, it became clear that injections of angiographic contrast medium were often followed by severe distortion of the surface ECGs. Although these and other transient effects on coronary blood flow (increase), coronary resistance (decrease) and cardiac performance (decrease) have been reported in canine and human experiments $i$ the literature for over 30 years [ $125,266,267,268,269,270$ ], our understanding of tice physiological mechanisms involved is incomplete. Hypertonicity and the ionic nature of some radio-opaque dyes used in angiography have been indicated as exacerbating factors [125, 266, 268], while the Brody effect has been sugsested as the possible reason for changes in the ECG [270].

We observed that the effects of contrast medium on the body surface isointegral maps were severe enough to distort and perhaps even mask the changes brought
about by subsequent angioplasty balloon inflations. Hence, this effect represented a potential source of artifact which had to be minimized to ensure accurate and consistent results in our study of PTCA-induced ischemia. In order to characterize both the extent and tine course of changes induced by the contrast medium, we decided to conduct a concomitant pilot study on the effect of dye injection in patients on whom otherwise standard angiography was being performed.

Patient Selection: Subjects were selected from the group of patients undergoing standard cardiac angiographic evaluation in the VG Hospital. There were 7 patients in the study, 5 with angiography of the left coronary artery ( LC ) and 2 of the right coronary artery (RC); 2 patients whose conditicn upon angiography warranted immediate PTCA were included in the PTCA \#1 group as well.

Protocol: A series of eight recordings, each of 15 s duration, was performed on each patient. The contrast medium used in each case was Omnipaque 350 (Winthrop Pharmaceuticals, New York, N.Y.). The sequence for these recordings and their nomenclature were as follows:

1. Baseline recording (DB0) at the beginning of the procedure;
2. Second baseline recording (DB1) once the catheter was in place;
3. Peak injection recording (D0) commencing as the contrast medium was injectel;
4. Post 1 recording (D1), 1 min after the peak injection recording;
5. Post 2 recording (D2), 2 min after the peak injection recording;
6. Post 5 recording (D5), 5 min after the peak injection recording;
7. Post 10 recording (D10), 10 min after the peak injection recording;
8. Final baseline (DBF) at the end of the catheterization procedure.

To eliminate any lingering effects from previous injections, these recordings were collected during catheterization of only the first vessel for each patient.

Data Processing: Processing was carried out as described in section 3.2.1 to the point of the isointegral maps for the QRS, QRST, ST and STT intervals. Difference maps were caiculated, using the same baseline (DB0 or DB1) as the reference for each.

### 3.2.2.3 DYE \#2

A second dye study was derived from the first in a similar manner as the second PTCA study evolved from its predecessor. In order to more systematicaily evaluate different contrast media and the time course of their effects, we lengthened the recording time and included three of the standard dyes used in the VG Hospital for coronary angiography.

Patient Selection: As in the first dye study, subjects were chosen from the pool of patients undergoing routine angiographic evaluation in the catheterization laboratory of the VG Hospital. The DYE \#2 group comprised 10 patients: 3 subjects using Omnipaque 350 (Winthrop Pharmaceuticals, New York, N.Y.); 4 subjects using Hexabrix 320 (Mallinckrodt Canada, Pointe Claire, P.Q.); and 3 subjects using Isovue (Squit,b, Montreal, P.Q.).

Protocol: Electrocardiograms were recorded using the methods described in section 3.2.1. A. series of five recordings was performed for each patient. The procedure and nomenclature for these recordings were as follows:

1. Baseline recording (DB0) at the beginning of the procedure;
2. Left coronary injection recording (DL), which commenced 20 s before injection of the contrast medium and continued until 2 min beyond;
3. Post left coronary injection recording (DLP) of 15 s duration, recorded 5 min after injection of the conirast medium;
4. Right coronary injection recording (DR) commencing 20 s before and continuing unill 2 min after injection of contrast medium into the right coronary artery.
5. Post right coronary injection recording (DRP) of 15 s duration, recorded 5 min after injection.

These recordings were performed once per subject. In one patient belonging to the Hexabrix subgroup, only a right coronary injection was performed.

Data Processing: Data processing as described in section 3.2.1 was performed io window the long ( $120-140 \mathrm{~s}$ ) recordings and generate isointegral maps for the QRS, QRST, ST and STT intervals. Each long recording was divided into 6-7, 20second windows, yielding a set of maps (QRS, QRST, ST, STT) for each. Subtractive difference maps were calculated, using the baseline (DB0 or DB1) as a reference.

### 3.2.2.4 PTCA \#2

Based on the successful outcome of the preliminary study PTCA \#1, a more comprehensive protocol was developed for a second set of patients undergoing coronary angioplasty. To capture the transient nature of the electrocardiographic changes brought about by the inflation of the catheter balloon, we extended the continuous sampling duration to include the entre inflation and a two-minute post-deflation period. Fewer inflations per patient were recorded (typically 2). In order to glean some haemodynamic information on the effect of any collateral circulation, we monitored the mean pressure gradient across the untreated occlusion (transstenotic pressure) as well as that across the inflated balloon (transocclusion pressure) for as many patients as possible ( 13 of 16 ), even during inflations for which no ECGs were collected. Proximal pressure was sensed via the guide catheter located in the coronary ostium, while distal pressure could be measured through the lumen of the balloon catheter; mean values were generated electronically at the time of the procedure. In 3 cases, use of a "probe" catheter, which incorporates guide wire and balloon in the same narrow catheter, precluded measurement of distal pressures; in two other cases, mean pressures were calculated from recorded systolic and diastolic values after the procedure.

Patient selection: Patients who were scheduled to undergo clinically indicated

PTCA and met the following inclusion criteria were included in this study: first, severe stenosis ( $\geq 60 \%$ diameter reduction) of the proximal LAD, LCx or RC arteries; second, no clinical evidence of variant angina, and resting electrocardiogram which showed no diagnostic Q waves or ST elevation or depression of more than $100 \mu \mathrm{~V}$; third, normal global left ventricular wall motion (ejection fraction $\geq 45 \%$ ), and normal or only mildly hypokinetic eegional wall motion. Each patient was on antianginal therapy, including a. calcium antagonist, before PTCA.

Presence or absence of collateral filling of the artery undergoing dilation w'as determined in 6 patients (present in four, absent in two) from angiograms obtained before the PTCA procedure. Collaterals were considered present or ly when at least a portion of the main trunk of the artery was visualized by retrograde flow. No attempt was made to assess angiographic presence of collateral filling of the artery during occlusion at the time of PTCA (recruitable collaterals).

Protocol: Before beginning the PTCA procedure, several recordings of pressure in the artery under treatment were made to assess both initial haemodynamics and signal stability. All patients received 325 mg of aspirin orally before PTCA and $10,000 \mathrm{U}$ of heparin intra-arterially at the beginning of the procedure. Every reasonable effort was made to restrict administration of intracoronary nitroglycerin until after the research portion of the procedure had been completed. When initially positioned across the coronary artery stenosis, the balloon catheter occasionally obstructed coronary blood flow sufficiently to produce signs and symptoms of ischemia; if this occurred, several balloon inflations were performed to decrease the transstenotic pressure gradient and allow all evidence of acute ischemia to resolve. Otherwise, the early inflations were often chosen for BSPM study. To ensure that there were no confounding influences from injections of contrast medium, a waiting period of at least 2 min after the most recent injection was maintained. Patient position was kept constant to prevent artifactual changes in the ECGs or blood pressures.

The standard BSPM recording protocol was as follows:

1. Baseline recording ( AB 0 ) of 15 s duration before the PTCA procedure;
2. Inflation recording (AI1) commencing 20 s before inflation of the balloon and ending 2 min after deflation;
3. Second inflation recording (AI2) with a minimum of 5 min between inflations (same procedure as in 2.);
4. Final 15 -second baseline recording (ABF).

In some cases, short ( 15 s ) recordings were made to assess the reproducibility of peak-inflation effects.

Data Processing: Raw data were visually examined via plots of selected leads, typically lead 62 of the BSPM system, a precordial lead at the $\mathrm{V}_{4}$ location (see Figure 3.7. Based on the criteria outlined in section 3.2.1, the continuous recordings were divided into smaller sections (windows) for averaging and map construction. Each long-inflation record was thus separated into as many as 15 windows for each of which averaging was performed. Averaged complexes and isointegral maps were plotted and used to determine the best sé, of difference maps to construct. The criteria employed for this selection were signal quality, reproducibility of baseline recordings and temporal arrangement of the original recordings. Typically, the map from the first window of each long recording (I1a, I2a, etc.) served as the baseline or control recording for the entire inflation and was subtracted from all subsequently windowed records to produce a sequence of difference plots; from any short recordings were subtracted the temporally nearest previous baseline or initial window of a long recording. Maps from baselines and initial windows from long recordings were subtracted from each other to determine the stability of the control conditions.

## Chapter 4

## Results

### 4.1 The Forward and Inverse Solutions

### 4.1.1 Simulated potentials

Potential distributions for both the epicardial- and body-surfaces were calculated using a forward solution based on a single-dipole source and the realistic human torso model described in Appendix A. As outlined in aection 2.1.3, hree sets of potentials were calculated for $\mathrm{X}, \mathrm{Y}$, and Z dipoles at a fixed l •ation DSL \#18 ( $\mathrm{x}=25, \mathrm{y}=300$, $\mathrm{z}=-40 \mathrm{~mm}$, in body coordinates). The results, which will be referred to as simulated potentials, are shown in Figure 4.1 as 6 isopotential contour maps; che column on the left depicts the maps for the torso while the associated epicardial maps are displayed in the right hand column. (For a description of these displays, see Appendix A.)

On each map is indicated the location and magnitude of the maximum ( + ) and minimum ( - ) in units of $\mu \mathrm{V}$. The contours are drawn as solid and dashed lines for positive and negative potentials, respectively, while the contour levels are arranged in logarithmic steps based on the largest absolute extreme in each column (see section 3.2). The torso maps in Figure 4.1 are all scaled identically and the largest extreme, which has a value of -26.8 , is found in the Z-dipole distribution. Based on this value, the contour lines represent $\pm 22, \pm 15, \pm 10, \pm 6.8, \pm 4.7, \pm 3.3$ and $\pm 2.2 \mu \mathrm{~V}$. 'The epicardial maps have, in general, larger amplitudes and therefore are drawn with a different set of contours; based on the largest extreme in the epicardial maps in Figure 4.1 of


Figure 4.1: Simulated isopotential maps from a single dipole source.
$-65.40 \mu \mathrm{~V}$ (Y dipole), the chosen contour levels are: $\pm 47, \pm 33, \pm 22, \pm 15, \pm 10, \pm 6.8$ and $\pm 4.7 \mu \mathrm{~V}$.

### 4.1.2 Forward solution

Forward solution coefficient matrices ( $Z_{B H}$ ) were computed based on two of the methods described in section 3.1.3. The first of was developed following the original approach of Barr, Ramsey and Spach [56], with the improvements suggested by Pilkington et al. [72]; this will be referred to as the PBRS method. The second forward solution is also a derivative of that of Barr, Ramsey and Spach, but incorporates the refinements suggested by Rudy and Messinger-Rapport [6, 7] and Cruse [233]; this will be referred to as the $R M C$ method.

To evaluate the accuracy of a forward solution, sets of sinulated epicardial potentials computed from the dipole source were multiplied by the forward transfer matrix to produce calculated torso potentials, which were then compared to the simulated torso potentials arising from a dipole of the same location and orientation. The relative error, correlation coefficient, maximum absolute error and rms difference were then calculated in each case, and to allow qualitative comparison, torso isopotential may,s were plotted.

### 4.1.2.1 PBRS forward solution

Table 4.1 summarizes the results of the forward solution using both the PBRS and the RMC methods. The correlation coefficient for the PBRS forward solution ranges from 0.9890 to 0.9981 , while the relative error lies between 0.08573 and 0.20088 . These results indicate a good level of agreement; they were somewhat better for the X - and Y -dipole simulations than for those of the Z dipole, which is apparent in the torso maps in Figure 4.2.


Figure 4.2: Forwaid solution using the PBRS method. The left-hand culumn contains torso-potential maps simulated directly from a dipole source, while the right-hand column shows the corresponding torso maps calculated by multiplication of epicardial potentials by the forward transfer matrix. The letter in the right-hand cutout of cach map indicates the dipole orientation.

Table 4.1: Test of the forward solution for a single dipole source. Calculated torso potentials from both forward solutions were compared with simulated data. Units for ine rms error and maximum error are $\mu \mathrm{V}$, assuming unit values of torso conductivity and dipole moment.

| Test of Forward Solution Accuracy - Dipole Source |  |  |  |  |  |  |
| :---: | :---: | ---: | ---: | ---: | ---: | :---: |
| Model | Source | rms Error | Max. Error | Rel. Error | Corr. Coeff. |  |
| PBRS |  |  |  |  |  |  |
|  | X dipole | 0.5448 | 1.1175 | 0.08573 | 0.9966 |  |
|  | RMC dipole | 0.6853 | 1.5336 | 0.08901 | 0.9981 |  |
|  | Z dipole | 1.2722 | 4.7738 | 0.20088 | 0.9890 |  |
|  |  |  |  |  |  |  |
|  | X dipole | 0.3109 | 1.3480 | 0.04893 | 0.9988 |  |
|  | Y dipole | 0.4851 | 1.0770 | 0.06303 | 0.9996 |  |
|  | Z dipole | 1.2734 | 3.1222 | 0.20108 | 0.9798 |  |

### 4.1.2.2 RMC forward solution

The same comparison of simulated and calculated torso potentials was carried out for the RMC forward solution. As evidenced in Table 4.1, the match between simulated and calculated results was slightly better for the RMC than for the PBRS method; this is indicated by the higher correlation coefficient and lower relative error for the X and $Y$ dipoles. However, the differences were too small to warrant suggestion that one solution was better than the other. Comparison of the maps in Figures 4.2 and 4.3 also did not reveal any appreciable difference in the quality of the forward solutions.

### 4.1.3 Inverse Solution

Regularization, as described in section 3.1.4, was applied using two methods: the Tikhonov zero-order, and the Laplacian. The simulated potentials produced from the single-dipole source (the same set used in the previous section to evaluate the results of the forward calculations) were employed to derive an optimal value for the regularization parameter $t$ under ideal (no noise) conditions. For each regularization trial, a different value of $t$ was chosen, and an inverse transfer matrix $Z_{H B}$ was


Figure 4.3: Forward solution using the RMC method. The left-hand column contains torso-potential maps simulated directly from a dipole source, while the right hand column shows the corresponding torso maps calculated by multiplication of epicardial potentials by the forward transfer matrix. The letter in the right-hand cutont of coch map indicates the dipole orientation.
generated. This matrix was then multiplied by a vector of simulated torso potentials from either the $\mathrm{X}, \mathrm{Y}$, or Z dipole to produce a calculated epicardial distribution, which was, in turn, compared with the corresponding simulated epicardial distribution. Statistical comparison was carried out as for the forward solution, with relative error, correlation coefficient, maximum absolute error, and rms difference as error indicators. ${ }^{r}$ 'ımmaries of the regularization trials are presented in both tabular and graphical form - for each of the two regularization methods, each of the two forward solution methods, and for each of the $\mathrm{X}, \mathrm{Y}$, and Z dipoles. In every table, the optimal value (lowest error, highest correlation coefficient) for each of the four error indicators is underlined. In the ideal case, the optimal values should all be found at the same value of $t$; since this was not the case, an average was taken of the four optimal $t$-values obtained for each error indicator separately and the closest value of $t$ to the average one was underlined in the table. A $Z_{H B}$ matrix was computed with $t$ equal to the mean of the underlined values for "e associated regularization method. The results of these optimal inverse calculations are shown as epicardial maps in the following sections.

### 4.1.3.1 PBRS inverse solution

Tables 4.2 through 4.7 contain the results of the regularization trials based on the forward solution computed by the PBRS method. The first three tables contain the results for Tikhonov zero-order regularization, while the second set of three contains the corresponding data for Laplacian regularization. Figures $4.4-4.6$ show for eaci table the same data in graphical for' ${ }^{\prime}$ : maximum and rms error against $t$ in one plot, and relative error and correlatic cefficient against $t$ in the other. Each figure contains the results for both regularization methods (based on data from the same dipole).

Each of the statistical parameters in Figures 4.4-4.6 exhibited a slightly different response to changes in $t$. While the maximum error dropped sharply as $t$ approached

Table 4.2: Calculation of the inverse solution using Tikhonov zero-order regularization and the PBRS forward solution. Test potentials are from a single-dipole source at location 18 with X orientation.

| Calculation of Inverse Matrix: PBRS - Tikhonov - X dipole |  |  |  |  |
| ---: | ---: | ---: | ---: | ---: |
| Reg. Par. | rms Error | Max. Error | Rel. Error | Corr. Coeff. |
| 0.00001 | 36.3815 | 150.9173 | 1.81354 | 0.4800 |
| 0.00002 | 21.9538 | 126.5034 | 1.09435 | 0.6696 |
| 0.00005 | 8.2701 | 20.8769 | 0.41225 | 0.9225 |
| 0.00010 | 6.5261 | $\underline{16.0803}$ | 0.32531 | 0.9495 |
| 0.00020 | 5.3129 | 16.9577 | 0.26484 | 0.9655 |
| 0.00050 | 4.6926 | 18.0547 | 0.23392 | 0.9724 |
| 0.00075 | 4.6081 | 18.8663 | 0.22970 | 0.9733 |
| 0.00080 | 4.6071 | 19.0575 | $\underline{0.22965}$ | $\underline{0.9733}$ |
| 0.00085 | 4.6082 | 19.1801 | 0.22971 | 0.9733 |
| 0.00100 | 4.6248 | 19.6357 | 0.23053 | 0.9731 |
| 0.00200 | 4.9512 | 21.9627 | 0.24680 | 0.9694 |
| 0.00500 | 5.9390 | 26.0830 | 0.29605 | 0.9565 |
| 0.01000 | 6.9449 | 29.6298 | 0.34619 | 0.9408 |
| 0.02000 | 8.0476 | 33.3043 | 0.40116 | 0.9207 |
| 0.05000 | $\boxed{3} 5679$ | 38.1298 | 0.47694 | 0.8892 |
| 0.10000 | 10.7795 | 41.7626 | 0.53734 | 0.8635 |
| 0.20000 | 12.1192 | 45.4851 | 0.60412 | 0.8382 |
| 0.50000 | 14.2186 | 50.4787 | 0.70876 | 0.8102 |
| 1.00000 | 15.9521 | 53.8806 | 0.79518 | 0.7941 |
| 2.00000 | 17.4801 | 56.4882 | 0.87135 | 0.7796 |
| 5.00000 | 18.8402 | 58.7201 | 0.93914 | 0.7568 |
| 10.00000 | 19.4099 | 59.5897 | 0.96754 | 0.7365 |

Table 4.3: Calculation of the inverse solution using Tikhonov zero-order regularization and the PBRS forward solution. Test potentials are from a single-dipole source at location 18 with Y orientation.

| Calculation of Inverse Matrix: PBRS - Tikhonov - Y dipole |  |  |  |  |
| ---: | ---: | ---: | ---: | ---: |
| Reg. Par. | rms Error | Max. Error | Rel. Error | Corr. Coeff. |
| 0.00001 | 47.7548 | 235.5448 | 2.39865 | 0.3997 |
| 0.00002 | 42.4832 | 188.6037 | 2.13387 | 0.4431 |
| 0.00005 | 9.4210 | 20.5423 | 0.47320 | 0.9091 |
| 0.00010 | 6.9811 | 21.3408 | 0.35065 | 0.9468 |
| 0.00020 | 5.8247 | 15.9022 | 0.29257 | 0.9617 |
| 0.00050 | 5.1733 | 14.2193 | 0.25985 | 0.9686 |
| 0.00075 | 5.0218 | 14.9067 | 0.25224 | 0.9698 |
| 0.00080 | 5.0038 | 15.0530 | 0.25134 | 0.9700 |
| 0.00085 | 4.9819 | 15.2405 | 0.25023 | 0.9701 |
| 0.00090 | 4.9743 | 15.3288 | 0.24985 | 0.9701 |
| 0.00095 | 4.9636 | 15.5303 | 0.24932 | 0.9702 |
| 0.00100 | 4.9615 | 15.5996 | 0.24921 | 0.9702 |
| 0.00110 | 4.9474 | 15.9191 | 0.24850 | $\underline{0.9702}$ |
| 0.00120 | 4.9436 | 16.1718 | 0.24831 | 0.9701 |
| $0.0 \mathbf{u} 130$ | 4.9450 | 16.4541 | 0.24838 | 0.9700 |
| 0.00150 | 4.9513 | 16.9534 | 0.24870 | 0.9697 |
| 0.00200 | 5.0146 | 18.0377 | 0.25188 | 0.9686 |
| 0.00500 | 5.5345 | 22.3065 | 0.27799 | 0.9608 |
| 0.01000 | 6.1895 | 26.0946 | 0.31089 | 0.9504 |
| 0.02000 | 6.9977 | 30.2879 | 0.35148 | 0.9365 |
| 0.05000 | 8.2419 | 36.3634 | 0.41398 | 0.9129 |
| 0.10000 | 9.3310 | 41.2449 | 0.46868 | 0.8915 |
| 0.20000 | 10.5996 | 46.2138 | 0.53240 | 0.8686 |
| 0.50000 | 12.7050 | 52.5828 | 0.63815 | 0.8418 |
| 1.00000 | 14.6130 | 56.8248 | 0.73399 | 0.8270 |
| 2.00000 | 16.4507 | 60.1339 | 0.82630 | 0.8166 |
| 5.00000 | 18.2173 | 62.9056 | 0.91503 | 0.8068 |
| 10.00000 | 18.9950 | 64.0541 | 0.95409 | 0.8008 |

Table 4.4: Calculation of the inverse solution using Tikhonov zero-order regularization and the PBRS forward colution. Test potentials are from a single-dipole source at location 18 with Z-orientation.

| Calculation of Inverse Matrix: PBRS - Tikhonov - Z dipole |  |  |  |  |
| ---: | ---: | ---: | ---: | ---: |
| Reg. Par. | rms Error | Max. Error | Rel. Error | Corr. Coeff. |
| $0.0,0.001$ | 30.3528 | 133.1162 | 1.67716 | 0.57387 |
| 0.00002 | 19.2743 | 86.8627 | 1.06501 | 0.73690 |
| 0.00005 | 0.2983 | 26.3500 | 0.51378 | 0.91893 |
| 0.00010 | 7.1692 | 21.4041 | 0.39614 | 0.95112 |
| 0.00020 | 5.6135 | 16.2973 | 0.31018 | 0.97105 |
| 0.00050 | 4.8844 | 14.3065 | 0.26989 | 0.97803 |
| 0.00075 | 4.7255 | 13.3425 | 0.26111 | 0.97892 |
| 0.00080 | 4.7033 | 13.1849 | 0.25988 | 0.97901 |
| 0.00100 | 4.6438 | 12.6573 | 0.25660 | 0.97911 |
| 0.00150 | 4.5785 | 11.7345 | 0.25299 | 0.97868 |
| 0.00170 | 4.5648 | 11.4600 | 0.25223 | 0.97844 |
| 0.00200 | 4.5567 | 11.3618 | $\underline{0.25178}$ | 0.97799 |
| 0.00400 | 4.6081 | 11.2750 | 0.25462 | 0.97465 |
| 000500 | 4.6555 | 11.4317 | 0.25724 | 0.97305 |
| 0.01000 | 4.9365 | 14.2202 | 0.27277 | 0.96578 |
| 0.02000 | 5.4842 | 17.6773 | 0.30303 | 0.95397 |
| 0.05000 | 6.7555 | 23.1084 | 0.37328 | 0.92829 |
| 0.10000 | 8.1089 | 27.5537 | 0.44806 | 0.90069 |
| 0.20000 | 9.7058 | 31.9299 | 0.53630 | 0.86962 |
| 0.50000 | 12.1196 | 37.1253 | 0.66967 | 0.83313 |
| 1.00000 | 13.9912 | 40.2632 | 0.77309 | 0.81332 |
| 2.00000 | 15.5642 | 42.5043 | 0.86001 | 0.79945 |
| 5.00000 | 16.9156 | 44.2076 | 0.93468 | 0.78539 |
| 10.00000 | 17.4706 | 45.0691 | 0.96534 | 0.77561 |

Table 4.5: Calculation of the inverse solution using Laplacian regularization and the PBRS forward solution. Test potentials are from a single dipole source at location 18 with X orientation.

| Calculation of Inverse Matrix: PBRS - Laplacian - X dipole |  |  |  |  |
| ---: | ---: | ---: | ---: | ---: |
| Reg. Par. | rms Error | Max. Error | Rel. Error | Corr. Coeff. |
| 0.1 | 29.7936 | 93.5745 | 1.48514 | 0.56208 |
| 0.2 | 16.5840 | 74.4856 | 0.82667 | 0.77067 |
| 0.5 | 8.6209 | 23.8722 | 0.42973 | 0.91953 |
| 1.0 | 6.8126 | 18.4035 | 0.33959 | 0.94760 |
| 2.0 | 5.5852 | $\underline{12.4919}$ | 0.27841 | 0.96402 |
| 5.0 | 4.7620 | 13.4431 | 0.23738 | 0.97349 |
| 10.0 | 4.3657 | 13.8370 | 0.21762 | 0.97748 |
| 20.0 | 4.0580 | 14.3196 | 0.20228 | 0.98027 |
| 50.0 | 3.7742 | 15.5369 | 0.18814 | 0.98251 |
| 70.0 | 3.7317 | 16.1938 | 0.18602 | 0.98276 |
| 75.0 | $\underline{3.7208}$ | 16.3415 | $\underline{0.18577}$ | $\underline{0.98278}$ |
| 85.0 | 3.7280 | 16.6223 | 0.18583 | 0.98272 |
| 100.0 | 3.7400 | 17.0076 | 0.18643 | 0.98256 |
| 200.0 | 3.9391 | 18.8667 | 0.19635 | 0.98053 |
| 500.0 | 4.5018 | 21.6705 | 0.22440 | 0.97461 |
| 1000.0 | 5.0617 | 23.9185 | 0.25231 | 0.96798 |
| 2000.0 | 5.6610 | 26.1360 | 0.28219 | 0.95997 |
| 5000.0 | 6.3943 | 28.8304 | 0.31874 | 0.94894 |
| 10000.0 | 6.8855 | 30.7609 | 0.34323 | 0.94095 |
| 20000.0 | 7.3846 | 32.7458 | 0.36811 | 0.93237 |
| 50000.0 | 8.1296 | 35.4156 | 0.40524 | 0.91848 |
| 100000.0 | 8.7080 | 37.3347 | 0.43408 | 0.90723 |
| 200000.0 | 9.2638 | 39.2507 | 0.46178 | 0.89778 |
| 500000.0 | 10.1721 | 42.3400 | 0.50706 | 0.88958 |
| 1000000.0 | 11.3352 | 45.4857 | 0.56504 | 0.88555 |
| 2000000.0 | 13.0859 | 49.1996 | 0.65230 | 0.88185 |
| 5000000.0 | 15.7777 | 53.8765 | 0.78648 | 0.87656 |
| 10000000.0 | 17.4653 | 56.5894 | 0.87061 | 0.87301 |

Table 4.6: Calculation of the inverse solution using Laplacian regularization and the PBRS forward solution. Test potentials are from a single dipole source at location 18 with $Y$ orientation.

| Calculation of Inverse Matrix: PBRS - Laplacian - Y dipole |  |  |  |  |  |
| ---: | ---: | ---: | ---: | ---: | :---: |
| Reg. Par. | rms Error | Max. Error | Rel. Error | Corr. Coeff. |  |
| 0.1 | 44.3717 | 220.4412 | 2.22873 | 0.43086 |  |
| 0.2 | 25.0484 | 111.8355 | 1.25814 | 0.64109 |  |
| 0.5 | 11.1473 | 41.8595 | 0.55991 | 0.88242 |  |
| 1.0 | 8.2607 | 19.3505 | 0.41492 | 0.93041 |  |
| 2.0 | 6.4355 | 15.0533 | 0.32324 | 0.95636 |  |
| 5.0 | 5.1139 | $\underline{12.5474}$ | 0.25686 | 0.97207 |  |
| 10.0 | 4.5517 | 12.8285 | 0.22863 | 0.97768 |  |
| 20.0 | 4.1366 | 13.4184 | 0.20778 | 0.98129 |  |
| 40.0 | 3.9510 | 14.2812 | 0.19845 | 0.98247 |  |
| 50.0 | 3.9447 | 14.5856 | 0.19814 | 0.98234 |  |
| 60.0 | 3.9613 | 14.8480 | 0.19897 | 0.98203 |  |
| 75.0 | 4.0059 | 15.1646 | 0.20121 | 0.98142 |  |
| 100.0 | 4.1010 | 15.5897 | 0.20599 | 0.98026 |  |
| 200.0 | 4.4507 | 16.5957 | 0.22355 | 0.97607 |  |
| 500.0 | 5.0429 | 19.5807 | 0.25330 | 0.96841 |  |
| 1000.0 | 5.5389 | 21.9894 | 0.27821 | 0.96131 |  |
| 2000.0 | 6.0433 | 24.3105 | 0.30355 | 0.95343 |  |
| 5000.0 | 6.6088 | 27.2702 | 0.33195 | 0.94364 |  |
| 10000.0 | 6.9610 | 29.6746 | 0.34964 | 0.93699 |  |
| 20000.0 | 7.3604 | 32.3808 | 0.36970 | 0.92915 |  |
| 50000.0 | 8.0598 | 36.1305 | 0.40483 | 0.91458 |  |
| 100000.0 | 8.6212 | 38.7897 | 0.43303 | 0.90209 |  |
| $20 c 000.0$ | 9.1348 | 41.3925 | 0.45883 | 0.89116 |  |
| 500000.0 | 9.9501 | 45.4716 | 0.49978 | 0.88041 |  |
| 1000000.0 | 11.0762 | 45.4472 | 0.55634 | 0.87354 |  |
| 2000000.0 | 12.8559 | 53.8920 | 0.64573 | 0.86589 |  |
| 5000000.0 | 15.6087 | 59.0996 | 0.78400 | 0.85454 |  |
| 10000000.0 | 17.3165 | 61.8021 | 0.86978 | 0.84712 |  |

Table 4.7: Calculation of the inverse solution using Laplacian regularization and the PBRS forward solution. Test potentials are from a single dipole source at location 18 with Z orientation.

| Calculation of Inverse Matrix: PBRS - Laplacian - Z dipole |  |  |  |  |
| ---: | ---: | ---: | ---: | ---: |
| Reg. Par. | rms Error | Max. Error | Rel. Error | Corr. Coeff. |
| 0.1 | 23.9755 | 85.3665 | 1.32477 | 0.66560 |
| 0.2 | 20.6314 | 92.0795 | 1.14000 | 0.71776 |
| 0.5 | 10.1715 | 28.3969 | 0.56203 | 0.90721 |
| 1.0 | 7.6735 | 20.2917 | 0.42400 | 0.94679 |
| 2.0 | 6.3059 | 17.0654 | 0.34843 | 0.96543 |
| 5.0 | 5.1626 | 15.3525 | 0.28526 | 0.97884 |
| 10.0 | 4.7149 | 13.7449 | 0.26052 | 0.98324 |
| 20.0 | 4.5223 | $\underline{12.1631}$ | 0.24988 | $\underline{0.98459}$ |
| 40.0 | 4.4631 | 12.4088 | 0.24661 | 0.98435 |
| 50.0 | 4.4606 | 12.6107 | $\underline{0.24647}$ | 0.98405 |
| 60.0 | 4.4627 | 12.7668 | 0.24659 | 0.98375 |
| 100.0 | 4.4882 | 13.3633 | 0.24800 | 0.98260 |
| 200.0 | 4.5780 | 14.4762 | 0.25296 | 0.98023 |
| 500.0 | 4.8269 | 15.1699 | 0.26671 | 0.97517 |
| 1600.0 | 5.1389 | 14.9763 | 0.28395 | 0.96934 |
| 2000.0 | 5.5430 | 15.4080 | 0.30628 | 0.96162 |
| 5000.0 | 6.0864 | 16.0070 | 0.33631 | 0.94993 |
| 10000.0 | 6.4660 | 18.4468 | 0.35728 | 0.94043 |
| 20000.0 | 6.9227 | 21.1935 | 0.38252 | 0.92848 |
| 50000.0 | 7.7674 | 24.9787 | 0.42919 | 0.90568 |
| 100000.0 | 8.4358 | 27.5759 | 0.46612 | 0.88568 |
| 200000.0 | 8.9795 | 29.9139 | 0.49617 | 0.86826 |
| 500000.0 | 9.7639 | 33.0933 | 0.53951 | 0.85222 |
| 1000000.0 | 10.9072 | 35.8367 | 0.60268 | 0.84359 |
| 2000000.0 | 12.6419 | 38.6751 | 0.69853 | 0.83534 |
| 5000000.0 | 15.0142 | 41.8159 | 0.82962 | 0.82363 |
| 10000000.0 | 16.3181 | 43.4016 | 0.90166 | 0.81570 |

## Inverse Solution Regularization -.- PBRS

Tikhonov Zero-order: X dipole


* rms Error $\quad \boxplus-$ Max Error

Tikhonov Zero-order: X dipole
Relative Error

*-Rel. Error - G - Corr Coeff

Laplacian: X dipole


Laplacian: X dipole


Figure 4.4: Regularization of the inverse solution whose $Z_{B H}$ matrix was obtained by PBRS method: X dipole.

## Inverse Solution Regularization -- PBRS

Tikhonov Zero-order: Y dipole


Laplacian: Y dipole


Laplacian: Y dipole


Figure 4.5: Regularization of the inverse solution whose $Z_{B H}$ matrix was obtained by PBRS method: Y dipole.

## Inverse Solution Regularization -- PBRS

Tikhonov Zero-order: Z dipole

*- rms Error -E Max Error

Tikhonov Zero-order: Z dipole
Relative Error


Laplacian: Z dipole


Laplacian: Z dipole


Figure 4.6: Regularization of the inverse solution whose $Z_{B H}$ matrix was obtained by PBRS method: Z dipole.
its optimal value and rose again quickly beyond it, the rms error remained relatively stable over several decades of $t$-values. The curves of relative error and correlation coefficient, on the other hand, displayed symmetrical, complementary shapes. Neither the relative error nor the correlation coefficient changed as quickly with $t$ as the absolute error, nor as slowly as rms error. A general finding is that the dependence on $t$ is much more dramatic at the low end of its range. In fact, the curvas rose so sharply for small $t$ that these points were removed from the graph so that the more subtle fluctuations near the optimal values of $t$ could be observed.

Of the two regularization methods, the Laplacian regularization produced generally better (lower errors and higher correlation coefficients) values than the Tikhonov zero-order regularization. This can be seen from the tables and in the curves, which reveal that all parameters attained more optimal values for Laplacian regularization than for Tikhonov zero-order regularization. The error parameters were also not as sensitive to less-than-optimal values of $t$ when the inverse solution was regularized by the Laplacian method.

The tables reveal that the optimal value of the regularization parameter $t$ was not always the same for each of the error indicators. In Table 4.5, for example, the optimal value of $t$ would appear to be 75 , at least when based on all parameters but the maximum error, which reaches a minimum at $t=2$. The bottom, left-hand graph in Figure 4.4 shows this as a shift between the respective troughs of the two curves. This shift might appear to be something of a general finding for both regularization methods were it not for the data gathered from the Z-dipole trial, which is shown in Tables 4.4 and 4.7 and in Figure 4.6. In the Z-dipole case, there was general agreement on the optimal value of $t$ for all four error indicators.

Epicardial maps of the simulated dipole-source potentials, together with the calculated epicardial potentials at their respective optimal $t$-values, are presented in Figure 4.7. The left-hand column contains the maps plotted from the simulated epicardial data obtained by forward calculation for each of the three dipole orientations; the
maps in the middle column were produced by inverse calculations based on Tikhonov zero-order regularization, while those in the right-hand column were produced by inverse calculation based on Laplacian regularization. For all three dipoles, there were obvious errors in the Tikhonov-regularized maps, in which extrema were shifted and irregular notches appeared in the contours. The Laplacian-regularized maps, on the other hand, appeared to match their simulated counterparts more closely; the contours remained smooth and there were only slight shifts in location of the extrema.

### 4.1.3.2 RMC inverse solution

Equivalent computations to those described in the previous section were also performed based on coefficient matrices produced by the RMC method. Tables 4.8 through 4.13 contain the numerical results of the iegularization trials; these data are displayed graphically in Figures 4.8-4.10.

The error-indicator values resulting from a regularized inverse solution based on a $Z_{B H}$ matrix generated by the RMC method were virtually indistinguishable over broad ranges of $t$-values from those based on a $Z_{B H}$ matrix generated by the PBRS method. The RMC method seemed to produce an inverse solution which was, in general, more sensitive to values of $t$ which lay below the optimum; the error curves rose more sharply for small $t$ than did those for the PBRS solutions. Otherwise, inverse solutions produced from the RMC and PBRS methods appeared to be equivalent in their performance.

Examination of the epicardial maps modifies this evaluation only slightly. From Figures 4.11 and 4.7 , there were slight differences in epicardial potentials calculated by the PBRS and RMC methods, especially in the case when Tikhonov zero-order regularization was applied. The middle column of Figure 4.11 shows a downward shift in the minimum of the calculated X-dipole map and a less evident upward movement of the maximum for the Y dipole, relative to the simulated potentials in the left column of the same figure. In the corresponding Figure 4.7 for the PBRS


Figure 4.7: Epicardial maps from PBRS inverse solutions. Simulated potentials (lefthand column) are compared with calculated equivalents using Tikhonov zero-order (middle column) and Laplacian (right-hand column) regularization for all three dipole orientations.

Table 4.8: Calculation of the inverse solution using Tikhonov regula ization and the RMC forward solution. Test potentials are from a single-dipole source at location 18 with X orientation.

| Calculation of Inverse Matrix: RMC - Tikhonov - X dipole |  |  |  |  |
| ---: | ---: | ---: | ---: | ---: |
| Reg. Par. | rms Error | Max. Error | Rel. Error | Corr. Coeff. |
| 0.00001 | 89.6428 | 384.8418 | 4.46850 | 0.21202 |
| 0.00002 | 31.9298 | 176.4236 | 1.59163 | 0.53171 |
| 0.00005 | 14.6142 | 64.7550 | 0.72849 | 0.80537 |
| 0.00010 | 6.1801 | 16.7491 | 0.30807 | 0.95406 |
| 0.00020 | 5.0948 | $\underline{15.5096}$ | 0.25396 | 0.96789 |
| 0.00050 | 4.4878 | 16.9606 | 0.22371 | 0.97466 |
| 0.00070 | 4.4221 | 17.7877 | 0.22043 | 0.97544 |
| 0.00075 | 4.4124 | 17.9605 | $\underline{0.21995}$ | $\underline{0.97558}$ |
| 0.00080 | 4.4150 | 18.1742 | 0.22008 | 0.97558 |
| 0.00100 | 4.4495 | 18.8752 | 0.22180 | 0.97534 |
| 0.00200 | 4.9011 | 21.7719 | 0.24431 | 0.97073 |
| 0.00500 | 6.0614 | 26.5177 | 0.30215 | 0.95580 |
| 0.01000 | 7.1020 | 30.3522 | 0.35402 | 0.93939 |
| 0.02000 | 8.1841 | 34.1829 | 0.40796 | 0.91971 |
| 0.05000 | 9.6784 | 39.0834 | 0.48245 | 0.88932 |
| 0.10000 | 10.8860 | 42.6887 | 0.54264 | 0.86419 |
| 0.20000 | 12.2324 | 46.3182 | 0.60976 | 0.83846 |
| 0.50000 | 14.3060 | 51.0718 | 0.71312 | 0.80666 |
| 1.00000 | 15.9797 | 54.2520 | 0.79655 | 0.78668 |
| 2.00000 | 17.4628 | 56.7420 | 0.87048 | 0.76978 |
| 5.00000 | 18.8123 | 58.8464 | 0.93775 | 0.74779 |
| 10.00000 | 19.3899 | 59.6472 | 0.96655 | 0.73063 |

Table 4.9: Calculation of the inverse solution using Tikhonov regularization and the RMC forward solution. Test potentials are from a single-dipole source at location 18 with $Y$ orientation.

| Calculation of Inverse Matrix: RMC - Tikhonov - Y dipole |  |  |  |  |
| ---: | ---: | ---: | ---: | ---: |
| Reg. Par. | rms Error | Max. Error | Rel. Error | Corr. Coeff. |
| 0.00001 | 129.3884 | 577.9121 | 6.49900 | 0.15390 |
| 0.00002 | 61.2008 | 290.9860 | 3.07403 | 0.32343 |
| 0.00005 | 12.4882 | 45.5303 | 0.62726 | 0.85710 |
| 0.00010 | 7.0827 | 19.3962 | 0.35575 | 0.94659 |
| 0.00020 | 5.8386 | 15.0156 | 0.29326 | 0.96217 |
| 0.00050 | 4.9141 | 11.8190 | 0.24683 | 0.97167 |
| 0.00075 | 4.7170 | 12.8057 | 0 | 09693 |
| 0.00080 | 4.7054 | 12.8934 | 0.23634 | 0.97323 |
| 0.00090 | 4.6727 | 13.3927 | 0.23470 | $\underline{0.97326}$ |
| 0.00100 | $\underline{4.6616}$ | 13.7423 | $\underline{0.23414}$ | 0.97341 |
| 0.00200 | 4.7996 | 16.7513 | 0.24108 | 0.97092 |
| 0.00500 | 5.5271 | 21.8293 | 0.27762 | 0.96070 |
| 0.01000 | 6.3141 | 26.1558 | 0.31715 | 0.94848 |
| 0.02000 | 7.2165 | 30.7536 | 0.36247 | 0.93269 |
| 0.05000 | 8.5084 | 37.0463 | 0.42736 | 0.90737 |
| 0.10000 | 9.5733 | 41.8834 | 0.48085 | 0.88581 |
| 0.20000 | 10.7970 | 46.7114 | 0.54232 | 0.86320 |
| 0.50000 | 12.8254 | 52.8470 | 0.64420 | 0.83605 |
| 1.00000 | 14.6657 | 56.9482 | 0.73664 | 0.82041 |
| 2.00000 | 16.4573 | 60.1822 | 0.82663 | 0.80907 |
| 5.00000 | 18.2067 | 62.9228 | 0.91450 | 0.79866 |
| 10.00000 | 18.9862 | 64.0650 | 0.95365 | 0.79286 |

Table 4.10: Calculation of the inverse solution using Tikhonov regularization and the RMC forward solution. Test potentials are from a single-dipole source at location 18 with Z orientati n.

| Calculation of Inverse Matrix: RMC - Tikhonov - Z dipole |  |  |  |  |
| ---: | ---: | ---: | ---: | ---: |
| Reg. Par. | rms Er or | Max. Error | Rel. Error | Corr. Coeff. |
| 0.00001 | 165.4633 | 757.0747 | 9.14275 | 0.12572 |
| 0.00002 | 32.7125 | 176.7783 | 1.80754 | 0.51791 |
| 0.00005 | 12.1117 | 35.7666 | 0.66923 | 0.84797 |
| 0.00010 | 7.8814 | 31.8703 | 0.43549 | 0.92641 |
| 0.00020 | 5.2699 | 14.0746 | 0.2 .119 | 0.96511 |
| 0.00050 | 4.1786 | 12.2927 | 0.23089 | 0.97668 |
| 0.00075 | 3.9720 | 11.7498 | 0.21947 | 0.97829 |
| 0.00100 | 3.8795 | 11.3633 | 0.21436 | 0.97881 |
| 0.00150 | $\underline{3.8335}$ | 10.8920 | $\underline{0.21182}$ | $\underline{0.97866}$ |
| 0.00200 | 3.8625 | $\underline{10.8303}$ | 0.21342 | 0.97790 |
| 0.00500 | 4.3008 | 12.3646 | 0.23764 | 0.97148 |
| 0.01000 | 4.8813 | 15.5375 | 6.26972 | 0.96299 |
| 0.02000 | 5.6558 | 19.2217 | 0.31252 | 0.95099 |
| 0.05000 | 7.0838 | 24.7586 | 0.39142 | 0.92677 |
| 0.10000 | 8.5010 | 29.1834 | 0.46373 | 0.89956 |
| 0.20000 | 10.1178 | 33.4226 | 0.55906 | 0.86530 |
| 0.50000 | 12.3690 | 38.1949 | 0.68346 | 0.81890 |
| 1.00000 | 14.0382 | 40.9462 | 0.77569 | 0.79113 |
| 2.00000 | 15.4932 | 42.8864 | 0.85608 | 0.77190 |
| 5.00000 | 16.8321 | 44.3662 | 0.93006 | 0.75599 |
| 10.00000 | 17.4139 | 45.0858 | 0.96221 | 0.74790 |

Table 4.11: Calculation of the inverse solution using Laplacian regularization and the RMC forward solution. Test potentials are from a single-dipole source at location 18 with X orientation.

| Calculation of Inverse Matrix: RMC - Laplacian - X dipole |  |  |  |  |
| ---: | ---: | ---: | ---: | ---: |
| Reg. Par. | rms Error | Max. Error | Rel. Error | Corr. Coeff. |
| 0.1 | 50.0252 | 217.2312 | 2.49365 | 0.37553 |
| 0.2 | 27.7669 | 120.8695 | 1.38412 | 0.59205 |
| 0.5 | 11.5394 | 39.5259 | 0.57522 | 0.86815 |
| 1.0 | 7.3470 | 19.6469 | 0.36623 | 0.93956 |
| 2.0 | 5.8650 | 14.4016 | 0.29236 | 0.96017 |
| 5.0 | 5.0929 | $\underline{13.8647}$ | 0.25387 | 0.96938 |
| 10.0 | 4.6717 | 14.1762 | 0.23287 | 0.97387 |
| 20.0 | 4.2917 | 14.6048 | 0.21393 | 0.97757 |
| 50.0 | 3.8647 | 15.9226 | 0.19265 | 0.98138 |
| 75.0 | 3.7642 | 16.8187 | 0.18764 | 0.98225 |
| 90.0 | 3.7496 | 17.2770 | $\underline{0.18691}$ | $\underline{0.98238}$ |
| 100.0 | 3.7518 | 17.5568 | 0.18702 | 0.98236 |
| 200.0 | 3.9525 | 19.5719 | 0.19702 | 0.98057 |
| 500.0 | 4.5697 | 22.5021 | 0.22779 | 0.97434 |
| 1000.0 | 5.1507 | 24.8030 | 0.25675 | 0.96753 |
| 2000.0 | 5.7433 | 27.0600 | 0.28629 | 0.95969 |
| 5000.0 | 6.4513 | 29.7768 | 0.32158 | 0.94924 |
| 10000.0 | 6.9284 | 31.6622 | 0.34537 | 0.94173 |
| 20000.0 | 7.4117 | 33.5445 | 0.36946 | 0.93381 |
| 50000.0 | 8.1320 | 36.0952 | 0.40536 | 0.92119 |
| 100000.0 | 8.7189 | 37.9944 | 0.43462 | 0.91057 |
| 200000.0 | 9.3174 | 39.9071 | 0.46445 | 0.90093 |
| 500000.0 | 10.2825 | 42.8990 | 0.51256 | 0.89181 |
| 1000000.0 | 11.4352 | 45.8764 | 0.57002 | 0.88727 |
| 2000000.0 | 13.1266 | 49.4005 | 0.65433 | 0.88340 |
| 5000000.0 | 15.7489 | 53.9101 | 0.78505 | 0.87817 |
| 10000000.0 | 17.4261 | 56.5696 | 0.86865 | 0.87466 |

Table 4.12: Calculation of the inverse solution using Laplacian regularization and the RMC forward solution. Test potentials are from a single-dipole source at location 18 with Y orientation.

| Calculation of Inverse Matrix: RMC - Laplacian - Y dipole |  |  |  |  |
| ---: | ---: | ---: | ---: | ---: |
| Reg. Par. | rms Error | Max. Error | Rel. Error | Corr. Coeff. |
| 0.1 | 72.2160 | 367.1793 | 3.62731 | 0.27142 |
| 0.2 | 39.5294 | 174.4808 | 1.98551 | 0.46766 |
| 0.5 | 15.2419 | 52.0484 | 0.76558 | 0.80962 |
| 1.0 | 9.4056 | 24.7800 | 0.47243 | 0.91345 |
| 2.0 | 6.8745 | 17.6246 | 0.34530 | 0.95160 |
| 5.0 | 5.3388 | 12.0046 | 0.26816 | 0.97024 |
| 10.0 | 4.5603 | $\underline{9.6792}$ | 0.22906 | 0.97799 |
| 20.0 | 4.0839 | 10.6442 | 0.20513 | 0.98197 |
| 40.0 | 3.8625 | 12.1223 | 0.19401 | $\underline{0.98328}$ |
| 45.0 | $\underline{3.8574}$ | 12.3813 | $\underline{0.19375}$ | 0.98321 |
| 50.0 | 3.8579 | 12.5901 | 0.19378 | 0.98309 |
| 75.0 | 3.9326 | 13.4107 | 0.19753 | 0.98199 |
| 100.0 | 4.0450 | 14.0256 | 0.20318 | 0.98063 |
| 200.0 | 4.4340 | 15.9466 | 0.22271 | 0.97600 |
| 500.0 | 5.0242 | 19.3346 | 0.25236 | 0.96831 |
| 1000.0 | 5.4843 | 21.8576 | 0.27547 | 0.96170 |
| 2000.0 | 5.9594 | 24.2945 | 0.29933 | 0.95433 |
| 5000.0 | 6.5395 | 27.3451 | 0.32847 | 0.94454 |
| 10000.0 | 6.9250 | 29.7288 | 0.34784 | 0.93756 |
| 20000.0 | 7.3379 | 32.3794 | 0.36857 | 0.92976 |
| 50000.0 | 8.0184 | 36.1203 | 0.40275 | 0.91598 |
| 100000.0 | 8.5721 | 38.8282 | 0.43057 | 0.90405 |
| 200000.0 | 9.0998 | 41.4712 | 0.45707 | 0.89328 |
| 500000.0 | 9.9485 | 45.5342 | 0.49970 | 0.88236 |
| 1000000.0 | 11.0842 | 49.4593 | 0.55674 | 0.87531 |
| 2000000.0 | 12.8525 | 53.8612 | 0.64556 | 0.86735 |
| 5000000.0 | 15.5870 | 59.0561 | 0.78291 | 0.85513 |
| 10000000.0 | 17.2937 | 61.7676 | 0.86864 | 0.84692 |

Table 4.13: Calculation of the inverse solution using Laplacian regularization and the RMC forward solution. Test potentials are from a single-dipole source at location 18 with Z orientation.

| Calculation of Inverse Matrix: RMC - Laplacian - Z dipole |  |  |  |  |
| ---: | ---: | ---: | ---: | ---: |
| Reg. Par. | rms Error | Max. Error | Rel. Error | Corr. Coeff. |
| 0.1 | 123.6566 | 606.8671 | 6.83270 | 0.14884 |
| 0.2 | 29.0676 | 133.9580 | 1.60614 | 0.56434 |
| 0.5 | 11.9484 | 48.9674 | 0.66021 | 0.85519 |
| 1.0 | 7.8368 | 18.4844 | 0.43303 | 0.93012 |
| 2.0 | 6.0846 | 14.8516 | 0.33620 | 0.95654 |
| 5.0 | 4.8699 | 10.6322 | 0.26909 | 0.97174 |
| 10.0 | 4.4362 | 11.1569 | 0.24512 | 0.97621 |
| 20.0 | 4.1725 | 11.4977 | 0.23055 | 0.97846 |
| 50.0 | 3.9985 | 12.0764 | 0.22094 | $\underline{0.97929}$ |
| 75.0 | 3.9644 | 12.1732 | 0.21905 | 0.97915 |
| 80.0 | 3.9629 | 12.1896 | 0.21897 | 0.97908 |
| 90.0 | 3.9597 | 12.1828 | $\underline{0.21880}$ | 0.97896 |
| 100.0 | 3.9603 | 12.1628 | 0.21883 | 0.97882 |
| 200.0 | 4.0129 | 11.7481 | 0.22174 | 0.97732 |
| 500.0 | 4.2046 | 11.1391 | 0.23233 | 0.97387 |
| 1000.0 | 4.4716 | 12.3770 | 0.24703 | 0.96964 |
| 2000.0 | 4.8898 | 14.4395 | 0.27019 | 0.96308 |
| 5000.0 | 5.5769 | 17.3341 | 0.30816 | 0.95138 |
| 10000.0 | 6.0944 | 19.6846 | 0.33675 | 0.94160 |
| 20000.0 | 6.6431 | 22.2474 | 0.36706 | 0.93037 |
| 50000.0 | 7.5462 | 25.7745 | 0.41697 | 0.90974 |
| 100000.0 | 8.3039 | 28.2352 | 0.45883 | 0.89033 |
| 200000.0 | 9.0068 | 30.4317 | 0.49767 | 0.87190 |
| 500000.0 | 9.9545 | 33.3062 | 0.55004 | 0.85382 |
| 1000000.0 | 11.0162 | 35.7730 | 0.60870 | 0.84427 |
| 2000000.0 | 12.5508 | 38.4250 | 0.69350 | 0.83598 |
| 5000000.0 | 14.7988 | 41.5427 | 0.81772 | 0.82514 |
| 10000000.0 | 16.1382 | 43.2040 | 0.89172 | 0.81803 |

## Inverse Solution Regularization -- RMC

Tikhonov Zero-order: X dipole


Laplacian: X dipole


Tikhonov Zero-order: X dipole



- *- Rel. Error Corr Coef

Figure 4.8: Regularization of the inverse solution whose $Z_{B H}$ matrix was obtained by RMC method: X dipole.

Inverse Solution Regularization -- RMC
Tikhonov Zero-order: Y dipole


- rms Error Max Error

Tikhonov Zero-order: Y dipole


Laplacian: Y dipole
Laplacian: Y dipole



Figure 4.9: Regularization of the inverse solution whose $Z_{B H}$ matrix was obtained by RMC method: Y dipole.

## Inverse Solution Regularization -- RMC

Tikhonov Zero-order: Z dipole


Tikhonov Zero-order: Z dipole


* Rel. Error - Corr.Cusff

Laplacian: Z dipole


Laplacian: Z dipole


Figure 4.10: Regularization of the inverse solution whose $Z_{B H}$ matrix was obtained by RMC method: Z dipole.


Figure 4.11: Epicardial maps from RMC inverse solutions. Simulated potentials (left-hand column) are compared with calculated equivalents from Tikhonov zeroorder (middle column) and Laplacian (right-hand column) regularization for all three dipole orientations.
inverse solution, the X-dipole minimum was shifted only slightly downward, as was the maximum of the Y dipole. Just as in the PBRS epicardial maps, Laplacian regularization applied to the RMC solution produced smoother maps, which more closely resembled the simulated distributions in terms of both potential amplitudes and location of extrema, than did the Tikhonov zero-order regularization.

If one examines the actual data set for the simulated and calculated epicardial potentials, several features become clear. The largest percentage errors, for both Tikhonov and Laplacian regularization arose at nodes where the gradient of potential was large and the potential value small. For the X dipole, for example, this occurred along a circular arc running parallel to the contour lines near the transition from negative to positive values from about 7 o'clock to 1 o'clock in the top row of maps in Figure 4.11. The large potential gradient is evidenced by the high density of contour lines. The largest individual errors arising from the Laplacian regularization were considerably larger than the largest error for Tikhonov zero-order, for example at node 18 , where the error for the Laplacian inverse was $6.69 \mu \mathrm{~V}$, while in the Tikhonov inverse at the same node the error was $2.65 \mu \mathrm{~V}$. However, the Tikhonov inverse produced more nodes with large errors ( 7 with errors $>100 \%$ versus only 4 in the Laplacian). A reason for the difference in these two regularization techniques is that the Tikhonov zero-order regularization constrains the amplitude of the epicardial potentials without regard for the values at neighbouring points, while Laplacian regularization considers explicit input from other neighbours via the Laplacian operator. This leaves the Tikhonov solution better equipped to follow rapid changes in potential, while the amplitudes produced by the Laplacian inverse at any single node are bound to those of its neighbours and cannot follow steep gradients from node to node.

This fundamental distinction between the two regularization techniques also ex plains another anomaly in the epicardial maps in Figures 4.7 and 4.11. All three Tikhonov inverse solution maps exhibit localized errors in the vicinity of the apex,

Table 4.14: Summary of results of the inverse-solution tests for a single dipole source. Each inverse solution was calculated at the optimal $t$-value for that particular solution method, regularization method, and dipole orientation.

| Summary of inverse solution accuracy - dipole source |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Solution/Source | t-val | rms Error | Max. Error | Rel. Error | Corr. Coeff. |
| $\begin{aligned} & \text { PBRS } \\ & \text { X dipole } \end{aligned}$ |  |  |  |  |  |
|  |  |  |  |  |  |
| Tikhonov | 0.00050 | 4.6926 | 18.0547 | 0.23392 | 0.97242 |
| Laplace | 50.0 | 3.7742 | 15.5369 | 0.18814 | 0.98251 |
| Y dipole |  |  |  |  |  |
| Tikhonov | 0.00100 | 4.9615 | 15.5996 | 0.24921 | 0.97025 |
| Laplace | 40.0 | 3.9510 | 14.2812 | 0.19845 | 0.98247 |
| Z dipole |  |  |  |  |  |
| Tikhonov | 0.00200 | 4.5567 | 11.3618 | 0.25178 | 0.97799 |
| Laplace | 40.0 | 4.4631 | 12.4088 | 0.24661 | 0.98435 |
| RMC |  |  |  |  |  |
| X dipole |  |  |  |  |  |
| Tikhonov | 0.00070 | 4.4221 | 17.7877 | 0.22043 | 0.97544 |
| Laplace | 75.0 | 3.7642 | 16.8187 | 0.18764 | 0.98225 |
| Y dipole |  |  |  |  |  |
| Tikhonov | 0.00090 | 4.6727 | 13.3927 | 0.23470 | 0.97345 |
| Laplace | 40.0 | 3.8625 | 12.1223 | 0.19401 | 0.98328 |
| Z dipole |  |  |  |  |  |
| Tikhonov | 0.00150 | 3.8335 | 10.8920 | 0.21182 | 0.97866 |
| Laplace | 50.0 | 3.9985 | 12.0764 | 0.22094 | 0.97929 |

manifested as discontinuities in the contour lines. The apex is also the region of the epicardial surface with the highest spatial density of nodes; since Tikhonov regularization does not constrain the fluctuation in potential from node to node, the relatively small changes in calculated potential in this region escape sufficient damping. Due to the smuothness constraints applied in Laplacian regularization, on the other hand, the fluctuations in this area are well controlled, producing smooth contours which match those of the simulated epicardial potentials.

A final comparison of the PBRS and RMC inverse solutions is shown in Table 4.14,
in which the error indicators for each inverse solution at the optimal value of $t$ are gathered from Tables 4.2-4.13. Examination of this table indicates, for both methods of regularization, slightly more accurate results with the RMC method than with the PBRS.

In order to demonstrate the effect of changing the value of the regularization parameter $t$ on the epicardial maps which the inverse solutions produce, a set of $Z_{H B}$ matrices was computed for each of 8 different values of $t$ with Laplacian regularization. For each $Z_{H B}$ inatrix, epicardial maps were then computed from the simulated torso maps for the $\mathrm{X}, \mathrm{Y}$, and Z dipoles. The result was a set of 24 epicardial maps, which are shown in Figures 4.12 and 4.13. Each row of the figures includes the epicardial X-, Y-, and Z-dipole maps for a specific value of $t$ which is indicated at the bottom of each map. The $t$-values chosen were: $0.1,1.0,10 ., 100 ., 10^{3}, 10^{4}, 10^{5}$, and, $10^{6}$. Since the range of potential values which resulted was large, each map had to be scaled individually.

As anticipated, for values of $t$ well below the optimum, the inverse solution produced epicardial potentials which oscillated wildly and were poorly constrained (top row, Figure 4.12). The large areas in the maps with no contour lines indicate values which were below $10 \%$ of the maximum. At $t=1.0$, the basic shape and ucture of the maps were already obvious; this corresponds to the third point on the graphs in the lower rors of Figures 4.8-4.10. The maps were still quite coarse, however, with multiple islands of local maxima and minima. Not until $t=100$ did the maps become as smooth and continuous as the simulated maps which they were supposed to recover. As the value of $t$ was further increased, the potentials distributions became somewhat smoother, but did not change shape considerably; the amplitudes were further reduced with each increase in $t$.

This result agrees well with what would be expected from the Laplacian regularization technique. Too little regularization renders the inverse solution unconstrained and unpredictable; moderate application of Laplacian regularization smooths out the


Figure 4.12: The effect of changing the regularization parameter $t$ on epicardial maps. The value of $t$ ranges from 0.1 to 100 . and for each value, the calculated epicardial maps for the $\mathrm{X}, \mathrm{Y}$, and Z dipoles are shown.


Figure 4.13: The effect of changing the regularization parameter $t$ on epicardial maps. The value of $t$ ranges from $10^{3}$ to $10^{6}$ and for each value, the calculated epicardial maps for the $\mathrm{X}, \mathrm{Y}$, and Z dipoles are shown.
distribution and reduces the large fluctuations in amplitude. Too much regularization does little (if one ignores the reduced amplitudes and spatial gradients) to distort the topography of a distribution as simple as that from a single dipole; however, with more complex distributions containing multiple extrema, one can expect that overregularizing the inverse solution would compromise the spatial resolution of the map and would hinder the ability to discern local events on the epicardial surface.

### 4.1.4 Sensitivity of the inverse solution to noise

The analysis of the inverse solutions presented so far has assumed that the signals are free of noise, that is, they have been known with an accuracy limited only by the truncation error of the computer. As described in section 3.1.4, it is possible to generate random noise which can be added to potential distributions to which the inverse solution is applied. We performed tests in which the amplitude distribution of computer-generated random noise was shaped to produce Gaussian noise with a standard deviation equal to specified percentages of the rms amplitude of the simulated torso potential distributions produced by a dipole. This random noise was added to the torso potentials and the sum was multiplied by the inverse solution coefficient matrix $Z_{H B}$ to generate calculated epicardial potentials; these were then compared with the simulated epicardial distributions for the same dipole.

We chose the $Z_{H B}$ matrix which resulted from applying Laplacian regularization to a $Z_{B H}$ matrix generated by the RMC method to perform all noise calculations; the latter combination provided the best results in the comparisons described in the previous section and became the matrix with which epicardial maps were computed from clinical BSPM data (see section 4.3). We also wished to compare the sensitivity of the inverse solution to noise for several different values of the regularization parameter $t$. The results presented here were calculated with $t=75$ (a value equal to the optimum for the X dipole and very cloze to the optima for the Y and Z dipoles), $t=200$, and $t=500$.

Table 4.15: Noise sensitivity of the inverse solution. The inverse solution was calculated from the RMC forward solution with Laplacian regularization ( $\mathrm{t}=75$ ). To the torso data was added Gaussian noise with the standard deviation set as a percentage of rms potential. Error measures compare recovered epicardial potentials with simulated X-dipole data. All values are given as mean $\pm$ standard deviation for 20 trials.

| Inverse solution with Gaussian noise: RMC - Laplacian - t $=75-\mathrm{X}$ dipole |  |  |  |  |  |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Noise | rms Error |  |  | Max. Error |  |  | Rel. Error |  |  | Corr. Coeff. |  |  |
| 0.\% | 3.76 | $\pm$ | 0.00 | 16.82 | $\pm$ | 0.00 | 0.188 | $\pm$ | 0.000 | 0.982 | $\pm$ | 0.000 |
| 2.\% | 3.80 | $\pm$ | 0.02 | 16.96 | $\pm$ | 0.05 | 0.190 | $\pm$ | 0.001 | 0.982 | $\pm$ | 0.000 |
| 5.\% | 4.05 | $\pm$ | 0.06 | 17.18 | $\pm$ | 0.13 | 0.202 | $\pm$ | 0.003 | 0.979 | $\pm$ | 0.001 |
| 8.\% | 4.50 | $\pm$ | 0.12 | 17.40 | $\pm$ | 0.21 | 0.224 | $\pm$ | 0.006 | 0.975 | $\pm$ | 0.001 |
| 10.\% | 4.87 | $\pm$ | 0.17 | 17.64 | $\pm$ | 0.28 | 0.243 | $\pm$ | 0.008 | 0.970 | $\pm$ | 0.002 |
| 15.\% | 6.01 | $\pm$ | 0.28 | 19.85 | $\pm$ | 0.48 | 0.300 | $\pm$ | 0.014 | 0.955 | $\pm$ | 0.004 |
| 20.\% | 7.31 | $\pm$ | 0.38 | 22.68 | $\pm$ | 0.79 | 0.364 | $\pm$ | 0.019 | 0.934 | $\pm$ | 0.006 |
| 30.\% | 10.16 | $\pm$ | 0.58 | 30.03 | $\pm$ | 1.79 | 0.507 | $\pm$ | 0.029 | 0.881 | $\pm$ | 0.012 |
| 40.\% | 13.16 | $\pm$ | 0.77 | 38.08 | $\pm$ | 2.95 | 0.656 | $\pm$ | 0.039 | 0.819 | $\pm$ | 0.017 |
| 50.\% | 16.23 | $\pm$ | 0.96 | 46.43 | $\pm$ | 4.18 | 0.809 | $\pm$ | 0.048 | 0.755 | $\pm$ | 0.022 |
| 60.\% | 19.33 | $\pm$ | 1.14 | 55.04 | $\pm$ | 5.10 | 0.963 | $\pm$ | 0.057 | 0.693 | $\pm$ | 0.026 |
| 70.\% | 22.45 | $\pm$ | 1.32 | 63.95 | $\pm$ | 5.70 | 1.119 | $\pm$ | 0.066 | 0.635 | $\pm$ | 0.029 |
| 80.\% | 25.59 | $\pm$ | 1.50 | 72.87 | $\pm$ | 6.30 | 1.275 | $\pm$ | 0.075 | 0.583 | $\pm$ | 0.031 |
| 90.\% | 28.73 | $\pm$ | 1.68 | 81.89 | $\pm$ | 6.92 | 1.432 | $\pm$ | 0.084 | 0.536 | $\pm$ | 0.032 |
| 100.\% | 31.88 | $\pm$ | 1.86 | 90.91 | $\pm$ | 7.55 | 1.589 | $\pm$ | 0.093 | 0.495 | $\pm$ | 0.033 |

Table 4.16: Noise sensitivity of the inverse solution. The inverse solution was calculated from the RMC forward solution with Laplacian regularization ( $t=200$ ). To the torso data was added Gaussian noise with the standard deviation set as a percentage of rms potential. Error measures compare recovered epicardial potentials with simulated X-dipole data. All values are given as mean $\pm$ standard deviation for 20 trials.

| Inverse solution with Gaussian rene: $\mathrm{RMC}-$ Laplacian $-t=200-\mathrm{X}$ dipole |  |  |  |  |  |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Noise | rms Error |  |  | Max. Error |  |  | Rel. Error |  |  | Corr. Coeff. |  |  |
| 0\% | 3.95 | $\pm$ | 0.00 | 19.50 | $\pm$ | 0.00 | 0.20 | $\pm$ | 0.000 | 0.980 | $\pm$ | 0.000 |
| 2\% | 3.97 | $\pm$ | 0.01 | 19.59 | $\pm$ | 0.04 | 0.20 | $\pm$ | 0.001 | 0.980 | $\pm$ | 0.000 |
| 5\% | 4.09 | $\pm$ | 0.04 | 19.71 | $\pm$ | 0.10 | 0.20 | $\pm$ | 0.002 | 0.979 | $\pm$ | 0.000 |
| 8\% | 4.30 | $\pm$ | 0.07 | 19.83 | $\pm$ | 0.17 | 0.21 | $\pm$ | 0.004 | 0.977 | $\pm$ | 0.000 |
| 10\% | 4.48 | $\pm$ | 0.09 | 19.91 | $\pm$ | 0.21 | 0.22 | $\pm$ | 0.005 | 0.975 | $\pm$ | 0.001 |
| 15\% | 5.02 | $\pm$ | 0.06 | 20.20 | $\pm$ | 0.28 | 0.25 | $\pm$ | 0.003 | 0.968 | $\pm$ | 0.001 |
| 20\% | 5.73 | $\pm$ | 0.08 | 20.84 | $\pm$ | 0.29 | 0.29 | $\pm$ | 0.004 | 0.958 | $\pm$ | 0.001 |
| 30\% | 7.38 | $\pm$ | 0.12 | 23.62 | $\pm$ | 0.01 | 0.37 | $\pm$ | 0.006 | 0.931 | $\pm$ | 0.003 |
| 40\% | 9.21 | $\pm$ | 0.16 | 27.68 | $\pm$ | 0.53 | 0.46 | $\pm$ | 0.008 | 0.897 | $\pm$ | 0.005 |
| 50\% | 11.14 | $\pm$ | 0.20 | 32.42 | $\pm$ | 0.50 | 0.56 | $\pm$ | 0.010 | 0.857 | $\pm$ | 0.007 |
| 60\% | 13.18 | $\pm$ | 0.61 | 38.32 | $\pm$ | 2.33 | 0.66 | $\pm$ | 0.031 | 0.811 | $\pm$ | 0.015 |
| 70\% | 15.19 | $\pm$ | 0.70 | 43.52 | $\pm$ | 3.09 | 0.76 | $\pm$ | 0.035 | 0.767 | $\pm$ | 0.018 |
| 80\% | 17.22 | $\pm$ | 0.79 | 48.90 | $\pm$ | 3.89 | 0.86 | $\pm$ | 0.039 | 0.723 | $\pm$ | 0.020 |
| 90\% | 19.27 | $\pm$ | 0.88 | 54.54 | $\pm$ | 4.62 | 0.96 | $\pm$ | 0.044 | 0.682 | $\pm$ | 0.023 |
| 100\% | 21.32 | $\pm$ | 0.97 | 60.29 | $\pm$ | 5.03 | 1.07 | $\pm$ | 0.048 | 0.643 | $\pm$ | 0.024 |

Table 4.17: Noise sensitivity of the inverse solution. The inverse solution was calculated from the RMC forward solution with Laplacian regularization ( $t=500$ ). To the torso data was added Gaussian noise with the standard deviation set as a percentage of rms potential. Error measures compare recovered epicardial potentials with simulated X-dipole data. All values are given as mean $\pm$ standard deviation for 20 trials.

| Inverse solution with Gaussian noise: RMC - Laplacian - t=500-X dipole |  |  |  |  |  |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Noise | rms Error |  |  | Max. Error |  |  | Rel. Error |  |  | Corr. Coeff. |  |  |
| 0.\% | 4.57 | $\pm$ | 0.00 | 22.50 | $\pm$ | 0.00 | 0.228 | $\pm$ | 0.000 | 0.974 | $\pm$ | 0.000 |
| 2.\% | 4.58 | $\pm$ | 0.01 | 22.54 | $\pm$ | 0.02 | 0.228 | $\pm$ | 0.000 | 0.974 | $\pm$ | 0.000 |
| 5.\% | 4.63 | $\pm$ | 0.02 | 22.61 | $\pm$ | 0.06 | 0.231 | $\pm$ | 0.001 | 0.974 |  | 0.000 |
| 8.\% | 4.72 | $\pm$ | 0.04 | 22.67 | $\pm$ | 0.09 | 0.236 | $\pm$ | 0.002 | 0.972 | $\pm$ | 0.000 |
| 10.\% | 4.81 | $\pm$ | 0.05 | 22.71 | $\pm$ | 0.12 | 0.240 | $\pm$ | 0.002 | 0.971 | $\pm$ | 0.001 |
| 15.\% | 5.07 | 士 | 0.07 | 22.82 | $\pm$ | 0.15 | 0.253 | $\pm$ | 0.004 | 0.968 | $\pm$ | 0.001 |
| 20.\% | 5.42 | $\pm$ | 0.09 | 23.06 | $\pm$ | 0.04 | 0.270 | $\pm$ | 0.005 | 0.963 | $\pm$ | 0.001 |
| 30.\% | 6.30 | $\pm$ | 0.14 | 23.69 | $\pm$ | 0.14 | 0.314 | $\pm$ | 0.007 | 0.949 | $\pm$ | 0.002 |
| 40.\% | 7.35 | $\pm$ | 0.17 | 25.04 | $\pm$ | 0.16 | 0.367 | $\pm$ | 0.008 | 0.930 | $\pm$ | 0.003 |
| 50.\% | 8.51 | $\pm$ | 0.20 | 26.97 | $\pm$ | 0.04 | 0.424 | $\pm$ | 0.010 | 0.907 | $\pm$ | 0.005 |
| 60.\% | 9.74 | $\pm$ | 0.22 | 29.64 | $\pm$ | 0.25 | 0.486 | $\pm$ | 0.011 | 0.881 | $\pm$ | 0.006 |
| 70.\% | 11.01 | $\pm$ | 0.24 | 32.62 | $\pm$ | 0.61 | 0.549 | $\pm$ | 0.012 | 0.853 | $\pm$ | 0.007 |
| 80.\% | 12.32 | $\pm$ | 0.26 | 35.92 | $\pm$ | 1.04 | 0.614 | $\pm$ | 0.013 | 0.823 | $\pm$ | 0.008 |
| 90.\% | 13.65 | $\pm$ | 0.28 | 39.43 | $\pm$ | 1.51 | 0.681 | $\pm$ | 0.014 | 0.793 | $\pm$ | 0.009 |
| 100.\% | 15.00 | $\pm$ | 0.30 | 42.95 | $\pm$ | 2.00 | 0.748 | $\pm$ | 0.015 | 0.762 | $\pm$ | 0.010 |



Figure 4.14: Effect of Gaussian noise on the accuracy of the inverse solution.

The accuracy of the inverse solution in the face of applied Gaussian noise for $t=75$ (Table 4.15 and top row of Figure 4.14) was compared to that with $t=200$ (Table 4.16 and middle row of Figure 4.14) and $t=500$ (Table 4.17 and bottom row of Figure 4.14). At low noise levels ( $<5 \%$ ), the values of all four error indicators were closer to optimal values for $t=75$ than for either $t=200$ or $t=500$, but this situation reversed for noise at levels above $5-10 \%$ (depending on which error indicator is chosen). This is apparent in Figure 4.14 by the slopes of the curves, which are steepest in the plots in the upper row $(t=75)$ and become progressively flatter for the middle $(t=200)$ and bottom $(t=500)$ rows.

The effect of torso-potential noise on epicardial maps can be seen in Figures 4.15 4.17. The left column of each figure is made up of simulated torso isopotential maps from the X-dipole source with the addition of progressively larger amounts of Gaussian noise. The amount of noise, as a percent of rms amplitude of the noise-free map is indicated in the central "cutout" in the torso plot and again below each of the corresponding calculated epicardial maps, which form the centre and right-hand columns of each figure. The epicardial maps in the middle column were produced by a $Z_{B H}$ matrix computed with $t=75$; for those in the right-hand column, the value of $t$ was 500 .

The epicardial maps calculated with different $t$-values differed only slightly (maps were somewhat smoother in the case of $t=500$ ) with the noise levels up to $10 \%$. At $15 \%$ noise, the maps with $t=75$ showed infoldings in the contour lines and small positive and negative areas appeared as 'islands', isolated from the once-confluent 'mainland'. In the maps with $t=500$, the shape of the single central positive area was maintained and only small irregularities were present in the contour lines. Not until the noise level reached $50-60 \%$ did maps calculated with $t=500$ begin to break up and loose their smooth, confluent pattern. At the higher noise levels, the maps with $t=75$ showed numerous extrema, the largest of which had amplitudes well beyond their values without noise. These results indicate that the inverse solution with the


Figure 4.15: Simulated body surface and epicardial maps with added Gaussian noise. Noise levels $=0,2,5,8$, and $10 \%$.


Figure 4.16: Simulated torso maps and epicardial maps with added Gaussian noise. Noise levels $=15,20,30,40$, and $50 \%$.


Figure 4.17: Simulated torso maps and epicardial maps with added Gaussian noise. Noise levels $=60,70,80,90$, and $100 \%$.
optimal $t$-value under ideal conditions can be pushed towards serious instability when noise corrupts the input signal. Multiple extrema appear in both sets of maps as the noise level increases, but there are always more isolated extrema in the maps with $t=75$ than in the corresponding maps with $t=500$ maps.

The levels of noise in this experiment were considerably higher than would ever be expected in an actual BSPM recording, which in our recordings usually does not exceed $20 \mu \mathrm{~V}$ rms (before averaging). While a value of $t=500$ produced stable epicardial maps at noise levels up to about $50 \%$, under ideal (no noise) conditions it also increased the relative error from .188 to .228 and reduced the correlation coefficient from .982 to .974 , compared to values at the optimal value of $t=75$. With a relative error $=.202$ and correlation coefficient $=.980$ under ideal conditions, we felt that $t=200$ was a reasonable compromise between accuracy and stability and chose this value for the calculation of epicardial maps from clinical data.

### 4.1.5 Computation times

The computational cost of generating an inverse solution depends on the number of nodes in the torso model. Each node adds another equation to the system, increasing the time required to compute each part of the forward and inverse solution. This was the main motivation for reducing the number of nodes in the geometry, from the 1216 triangles/ 610 nodes of the original torso, to 700 triangles/352, of the new torso described in Appendix A. We did not, however, document the effect of this change on the accuracy of the inverse solution.

The forward solution requires much more computer time than the inverse solution itself since there are 6 individual submatrices to compute, which vary in size from $98 \times 98$ to $352 \times 352$. The required calculations for each of these are described in detail in section 3.1.3. Separate programs were written to produce each of these submatrices, and each program was validated by appropriate control computations. For example, in the computation of the $P$ :atrices according to the PBRS method, a
running total of the solid angles about each observation point was kept and compared to the theoretical values of 0 (observation point outside the surface of integration, as for $P_{B H}$ ), $2 \pi$ (observation point on the surface of integration, as for $P_{B B}$ and $P_{H H}$ ), and $4 \pi$ (observation point inside the integration surface, as for $P_{H B}$ ). Once the entire set of submatrices was evaluated, two separate programs computed two composite submatrices, the product of which was the $Z_{B H}$ matrix. This follows from equation 3.30 :

$$
Z_{B H}=\left(P_{B B}-G_{B H} G_{H H}^{-1} P_{H B}\right)^{-1}\left(G_{B H} G_{H H}^{-1} P_{H H}-P_{B H}\right)
$$

If we define two composite submatrices $Z_{p 1}$ and $Z_{p 2}$, such that

$$
\begin{equation*}
Z_{p 1}=\left(P_{B B}-G_{B H} G_{H H}^{-1} P_{H B}\right) \tag{4.1}
\end{equation*}
$$

and

$$
\begin{equation*}
Z_{p 2}=\left(G_{B H} G_{H H}^{-1} P_{H H}-P_{B H}\right), \tag{4.2}
\end{equation*}
$$

then

$$
\begin{equation*}
Z_{B H}=Z_{p 1}^{-1} Z_{p 2} . \tag{4.3}
\end{equation*}
$$

The total CPU time required to compute all the submatrices $\left(P_{B B}, P_{B H}, P_{H B}\right.$, $P_{H H}, G_{B F}$, and $G_{H H}$ ) on a VAX 8800 computer (Digital Equipment Corp, Maynard, MA) was for the PBRS solution, 26:33 min, and for the RMC solution, 6:10 min. Generation of the complete $Z_{B H}$ matrix from the submatrices, including validation of the two inversions and storage of both composite submatrices, required an additional 3:36 min, independent of the forward solution method. Each step could be performed either interactively or in a batch job. The time required to produce the inverse matrix was much shorter compared to the forward solution. The inverse solution was always performed interactively, to provide the user with full control over forward matrix, regularization method and $t$-parameter, as well as whether error calculations were to be performed. A single inverse solution required on the order of $5-10 \mathrm{~s}$ of execution time on a VAX 8800.

The large difference in CPU time between the PBRS and RMC forward solutions is striking The reason for this disparity lies in the greater efficiency of the Cruse algorithm paired with Radon quadrature to perform the integrations in the RMC forward solution, compared to the repeated solid angle computations required in the triangle-subdivision scheme of the PBRS solution. The cost of subdividing and recalculating was seen most clearly in the CPU time required to compute the $G_{B H}$ matrix: 46.1 s for the RMC method versus 11.22 min for the PBRS. The only difference in programming for the two forms of the calculation is in the repeated subdivision required in the PBRS solution versus the single execution of Radon's-quadrature algorithm in the RMC method. For its computational efficiency, the RMC method produced forward and inverse solutions which were just as accurate as those generated by the PBRS approach. The inverse solution employed for computing epicardial maps from clinical data (section 4.2) was based on the combination of RMC forward solution with Laplacian regularization.

### 4.2 Clinical Mapping Studies

### 4.2.1 Studies DYE\#1 and DYE\#2

The two DYE studies described in section 3.2 were undertaken to document the effects of injection of angiographic contrast media on body-surface potentials. Changes in the amplitude of QRS-, ST-, and T-isointegral maps followed injection of contrast medium in many cases. These changes were rapid in onset (within seconds of the injection), peaked within 20 s , and dissipated over the next $20-300 \mathrm{~s}$. There was also a transient rotation in the isointegral map distribution following injection. The body-surface maps from the study DYE \#2 were analyzed in terms of changes in the amplitude of extrema, and the rotation of the "zero-line". The zero-line was constructed (by hand) tangentially to the contour of zero potential where it intersected a second line joining the maximum and minimum. The time from injection of the contrast medium until complete resolution of these changes was also determined. Table 4.18 contains the values obtained for all 10 patients in the study DYE $\# 2$, grouped according to the contrast medium employed for each case. Rotations are denoted in degrees and values below $10^{\circ}$ were not recorded; the + and - signs before each value indicate the direction of rotation as counter-clockwise and clockwise, respectively. Fluctuations in amplitude of the maximum and minimum were expressed as a percent of the corresponding baseline value, a - sign indicating a reduction in amplitude. Parameters which varied less than $10 \%$ appear in the table as blank entries.

Changes occurred most frequently, with largest amplitude and duration, following injection of the contrast medium Hexabrix. The results for the other two contrast media were very similar, with changes slightly larger after injection of Omnipaque but more frequent after injection of Isovue. In ali but one case, the effects of either of these contrast media disappeared within 120 s after injection. On the basis of these results, for all cases in the study PTCA\#2, the dye Omnipaque was used and a

Table 4.18: Study DYE \#2. Vaiues are given as percent change in the maximum (Max Amp) and minimum (Min Amp), the amount of rotation in the zero-axis (Rot Amp), and the duration after injection of the contrast medium required to return to baseline (Max Dur, Min Dur, Rot Dur). LC=left coronary artery; RC=right coronary artery.

minimal waiting period of 120 s between injection of contrast medium and inflation of the PTCA balloon was maintained.

### 4.2.2 Study PTCA\#2

### 4.2.2.1 Isointegral maps

Figures 4.18-4.25 show a complete set of isointegral maps for a single inflation in a patient who underwent PTCA of the LAD artery. The centre column of each figure contains the map recorded just before balloon inflation, which serves as the baseline that was subtracted fiom maps recorded throughout the inflation (shown in the lefthand column) The resulting difference maps are shown in the right-hand column of each figure. There are two pages of isointegral maps for each of the QRS, QRST, ST, and ST-T intervals; the first page includes the maps recorded while the balloon was inflated, while on the second page are maps recorded after deflation of the balloon as the heart is reperfused. Each map represents the average of approximately 20 s of real time (see section 3.2). Contour lines are spaced in a logarithmic scale spanning one decade; the value of the maximum and minimum (in $\mu \mathrm{V}$ ) are included in each map and the variance index is written in the left-hand cutout of each difference map. Sets of maps like those in Figures 4.18-4.25 were produced for every inflation in every case in the study PTCA \#2.

In the case \#3229 shown in Figures 4.18-4.25, balloon inflation produced only a small change in the topology of the isointegral maps, but there were variations in amplitude, as can be observed in the difference maps. The first two difference maps for each integral, Ilb-I1a and I1c-I1a, which encompassed the first 40 s after inflation, showed the diffuse distribution characteristic of a lack of appreciable change. Only by the third map, I1d-Ila (40-60 s after inflation), did a stable maximum appear in the difference maps of the QRST-, ST-, and ST-T-integrals, collectively referred to as the repolarization integrals. The maximum grew in strength until it peaked in the first maps recorded after deflation (R1a), only to disperse relatively quickly after that.


Figure 4.18: QRS isointegral maps for an inflation in case \#3229. The map recorded before inflation (repeated in the middle column of each row) was subtracted from the maps recorded during the inflation (left column) to produce the isointegral difference maps (right column).


Figui. 4.19: QRS isointegral maps for reperfusion in case \#3229. The map recorded before inflation (repeated in the middle column of each row) was subtracted from the maps recorded following reperfusion (left column) to produce the isointegral difference maps (right column).


Figure 4.20: QRST isointegral maps for an inflation in case \#3229. The map recorded before inflation (repeated in the middle column of each row) was subtracted from the maps recorded during the inflation (left column) to produce the isointegral difference maps (right column).


Figure 4.21: QRST isointegral maps for reperfusion in case \#3229. The map recorded before inflation (repeated in the middle column of each row) was subtracted from the maps recorded following reperfusion (left column) to produce the isointegral difference maps (right column).


Figure 4.22: ST isointegral maps for an inflation in case \#3229. The map recorded before inflation (repeated in the middle column of each row) was subtracted from the maps recorded during the inflation (left column) to produce the isointegral difference maps (right column).


Figure 4.23: ST isointegral maps for reperfusion in case $\# 3229$. The map recorded before inflation (repeated in the middle column of each row) was subtracted from the maps recorded following reperfusion (left column) to produce the isointegral difference maps (right column).


Figure 4.24: ST-T isointegral maps for an inflation in case \#3229. The map recorded before inflation (repeated in the middle column of each row) was subtracted from the maps recorded during the inflation (left column) to produce the isointegral difference maps (right column).


Figure 4.25: ST-T isointegral maps for reperfusion in case \#3229. The map recorded before inflation (repeated in the middle column of each row) was subtracted from the maps recorded following reperfusion (left column) to produce the isointegral difference maps (right column).

In the second-last difference map of the series (R1d-Ila), a minimum appeared in the same location which the maximum had occupied in the repolarization maps, and disappeared again in the next, and last, difference map of the series. Stable patterns in the QRS difference maps did not develop until map Ile-Ila, in the form of a recordial maximum, which was similar to, and persisted as long after deflation as. those in the repolarization maps. The value of the variance index followed an analogous progression through the inflation for each type of integral, starting at a relatively small value, rising to a peak during the first map after deflation and relurning to preinflation values by the end of the recording.

Striking in these maps (and, in fact, in all maps we recorded) was the similarity among the difference maps for the QRST, ST, and ST-T integration intervals. The maps from which these difference maps were calculated, on the uther hand, were often quite dissimilar. While these mäps are all constructed from different intervals, they are all apparently affected in a dominant way by the changes in repolarization which occur during PTCA-induced ischemia. The QRS difference maps, although they resembled those from the repolarization integrals, differed more from inflation to inflation, had more diffuse extrema, and were less stable over the ourse of the inflation.

### 4.2.2.2 Peak difference maps

BSPM recordings were acquired during 34 inflations in the course of study PTCA \#2. Of these inflations, 18 occluded the LAD artery, 10 the RC artery, and 6 the LCx artery. For each inflation, peak difference maps were constructed by subtracting the preinflation map from one recorded either just before or just after release of the balloon occlusion. The peak difference maps for all inflations in PTCA \#2 are shown in Figures 4.26-4.31. Since the difference maps of the three repolarization integrals were so similar, peak difference maps from only the QRS, QRST, and ST integrals are shown. The codes in the centre 'cutout' at the top of each map denote the maps
used to form the difference; the intr ration interval and case number are placed in the right and left cutouts, respectively.

The difference maps within the same artery group shared some common features. In the group of LAD-artery cases (Figures 4.26-4.28), the most striking feature was the focused anterior positive area (cases \#3188, 3200, 3212, 3218, and 3229), which was spread around the right-shoulder area in one case ( $\# 3196$ ), and over the whole upper torso in two others (\#3192 and \#3236). In one case in the LAD-artery group, case \#3233, inflation of the PTCA balloon resulted in little change in the isointegral maps, as documented by the very diffuse pattern in the difference map.

The difference maps of the RC-artery patients in Figures 4.29-4.30 were also quite similar. In most cases, the reperfusion difference maps contained a V-shaped area of positive values, the maximum of which was usually located near the right mid-axillary line. Within the V-shaped positive area, there was a more focused minimum. In one patient in this group, case \#3220, there was little or no change in isointegral maps due to balloon inflation.

The results from the group of patients treated for stenosis of the LCx artery were relatively homogeneous across each integration interval and within the group, and the isointegral difference maps contained features also found in the RC-artery group (Figure 4.31). The maximum in these maps was normally found inferiorly (as in the RC-artery group), either on the left side or on the back. While a V-shaped line separating the positive from the negative areas was present in one case (\#3211), the V-line was not as symmetrical as in the RC-artery cases and the maximum was located at the left side and not the right. The clinical differentiation between cases of RC- and LCx-artery occlusions resulting in myocardial ischemia is a difficult one. The physiological reason for this is that, depending on which of the two arteries dominates the coronary circulation of the patient, the posterior region of the heart can be predominantly supplied be either the RC or LCx arteries. Examples of such difficult cases can be seen in the RC-artery case \#3230 in Figure 4.29 and the LCx-


Figure 4.26: Isointegral peak difference maps (peak minus pre inflation) for 6 inflations of the LAD areery in 3 patients from the study PTCA \#2.


Figure 4.27: Isointegral peak difference maps (peak minus pre inflation) for 6 inflations of the LAD artery in 3 patients from the study PTCA \#2.


Figure 4.28: Isointegral peak difference maps (peak minus pre inflation) for 6 inflations of the LAD artery in 3 patients from the study PTCA \#2.


Figure 4.29: Isointegral peak difference maps (peak minus pre inf son) for 6 inflations of the RCA artery in 3 patients from the study PTCA \#2.


Figure 4.30: Isointegral peak difference maps (peak minus pre inflation) for 4 inflations of the RCA artery in 2 patients from the study PTCA \#2.


Figure 4.31: Isointegral peak difference maps (peak minus pre inflation) for 6 inflations of the LCx artery in 3 patients from the study PTCA \#2.
artery case \#3228 in Figure 4.31. Both patients had PTCA performed on their respective dominant coronary arteries, and in both QRST and ST difference maps, there were broad areas of positive integral values located inferiorly, separated by a more or less horizontal band of contour lines from a rather diffuse, superior negative area. However, the m.xima in the repolarization maps (QRST, ST) in the LCx-artery case were more focused than those of the RC-artery maps, and lay in the middle of the map (left side of the torso). In the maps of the RC -artery case, the maxima were located on the right side or on the back and were not as clearly defined as in the LCx case. Thus, despite their physiological and electrophysiological similarities, these cases could be separated through the use of BSPM isointegral difference maps.

The maps in Figures 4.26-4.31 were then used to generate a set of average isointegral difference maps for each of the three coronary-artery groups, as shown in Figure 4.32. Each row of this figure contains the maps for one of the four different 1 gration intervals, while the maps in each column are from one of the three different patient groups (LAD, RC, and LCx). By calculating the means, the element. common to all maps in each group were enhanced, while the spurious differences were suppressed. Hence, the features in the average maps could be considered the most characteristic of ischemia resulting from the occlusion of the specific artery. For the LAD artery, the large confluent positive area over the left anterior surface was the unique feature found in the difference maps; the RC-atiery average maps contained a V-shaped band separating a superior minimum and a maximum on the inferior right side; the difference maps for the LCx-artery occlusion shared the precordial negative area found in the RC-artery maps, but were distinctive in that the maximum was located at waist level on the left side of the torso.

### 4.2.2.3 Jnstant maps

In several cases, difference maps were calculated not only from, integral maps but also on an instant-by-instant basis. Torso potential distributions during the QRS-complex


Figure 4.32: Peak difference maps. Average isointegral difference maps (QRS, QRST, ST, and ST-T) for each of the LAD-, RC-, and LCx-artery groups.
reflect the rapid activation of the ventricles and while an integral map over this period contains information about action potential amplitude and timing of activation in the myocardium [96], we wished to examine the effect of ischemia at a finer temporal resolution. We constructed series of instant maps from each sample during the QRS for 5 selected patients from the study PTCA \#2. This included two patients from the LAD-artery and one each from the RC- and LCx- artery subgroups, together with a fifth patient in whom both LAD and RC arteries were treated. For each inflation, the two averaged complexes which had been used to construct the peak difference map in Figures 4.26-4.31 were reprocessed to extract a series of Z-arrays for all the samples (every 2 ms ) in the QRS. This resulted in a series of 35-40 individual maps for the pre-inflation window, $\mathrm{W}_{\text {pre }}$, and the peak-inflation window, $\mathrm{W}_{\text {peak }}$, for each case.

Due to the rapid change in potential during the QRS, alignment of the two series of instant maps before subtraction is very critical - as has also been noted by others [271, 272]. QRS onset and J-point were determined first by computer algorithm and then adjusted manually. Each of the $N_{\text {pre }}$ instant maps from the preinflation window was then cross-correlated with each of the $N_{\text {peak }}$ instant maps of the peak inflation window, yielding an $N_{\text {pre }} \times N_{\text {peak }}$ array of correlation coefficients. We assumed that since the effects of PTCA-induced ischemia would not become apparent before the excitation reached regions which were directly affected, instant maps from the early part of the QRS would, in general, be very similar in both windows. Hence, the correlation coefficient would be expected to be very close to 1.0 in the first maps after QRS onset; maps were considered to be optimally aligned when the correlation was maximum for the first five maps in the QRS. This method was then used to align the onsets of QRS complexes in preinflation and peak inflation may, from which series of peak instant difference maps could be constructed.

The sensitivity of the difference-map technique to slight shifts in alignment is demonstrated in Figures 4.33 and 4.34. Each row in these figures contains peak inflation (left-hand column) and preinflation (middle column) maps and their difference
(right-hand column) for samples $6,18,30,42,54$, and 66 ms into the QRS. In Figure 4.33 , the alignment of the maps was carried out as just described. Depic ${ }^{\dagger}$. in Figure 4.34 are the equivalent maps produced from the same series of instant maps, but with the timing of the preinflation maps shifted by 1 sample, or 2 ms , back in time. As a result of such small shifts in alignment, the two sets of difference maps became quite dissimilar. For example, the difference map in the first row of Figure 4.33 was dominated by a focused precordial minimum within a V-shaped positive area below, while the corresponding map in Figure 4.34 showed a broad, superiorly located negative area and a precordial maximum. The difference maps in the two series only merged in the late stages of the QRS ( 66 ms ) with a stable pattern common to both, which continued to the end of the QRS. The same focused, dominating maximum of this common pattern could be seen in the QRS isointegral difference map for the same inflation, which is shown in the first map of the second row in Figure 4.28.

Instant difference maps constructed from two inflaticns in each of the five patients did not reveal any consistent change in the QRS due to PTCA-induced ischemia. In order to reduce the effect of misalignment of the instant maps, we divided the QRS into eighths and integrated the ECGs over these intervals. While this technique was somewhat more robust in the face of errors in the onset and duration of QRS, it too provided no useful data on changes in activation sequence due to ischemia. Differences between peak- and preinflation maps were very small and varied from one inflation to the next. Only the late stages of the QRS produced maps which demonsirated a consistent pattern across different inflations and different cases of the same artery; these maps were very similar to the isointegral maps for the entire QRS.


Figure 4.33: Peak-inflation (left-hand column), preinflation (middle column), and difference (right-hand column) isopotential maps from six different instants 1 the QRS.


Tigure 4.34: Peak-inflation (left-hand column), preinflation (middle column), and difference (right-hand column) isopotential maps from six different instants in the QRS. Alignment of the pre maps has been shifted by one sample ( 2 ms ) over the previous figure.

### 4.3 Application of the Inverse Solution to Clinical Data

From the 16 patients in
dy PTCA \#2, the data from a subset of 7 patients were selected ("NP7 subgroup") for tests of the inverse solution. The NP7 subgroup included two cases each of occlusions of the LAD, LCx, and RC arteries, along with a single case in which two different arteries (LAD and RC) were treated in the same patient. The input data for the inverse solution were sets of torso potentials which were interpolated to generate values at each of the 352 node points of the torso model (Appendix A), using the three-dimensional interpolation scheme described in section 3.2. Each $352 \times 1$ vector of torso potentials was then multiplied by the inverse transfer matrix $Z_{H B}$ to yield a $98 \times 1$ vector of epicardial potentials. Mathematically, this can be expressed as,

$$
\begin{equation*}
\Phi_{H}=Z_{H B} \Phi_{B}, \tag{4.4}
\end{equation*}
$$

where $\Phi_{H}$ contains torso potentials, $\Phi_{H}$ contains epicardial potentials, and the $Z_{B H}$ matrix is a function of the torso geometry and of the regularization parameter, $t$ (see section 3.1.4).

### 4.3.1 Difference Maps

As a test of the ability of the inverse solution to represent the spatial nature of ischemia, we applied $Z_{H B}$ to the isointegral difference maps produced from peak minus pre inflation BSPM recordings in each case of the NP7 subgroup. The resulting epicardial potential distributions were displayed as isointegral maps in the polar format described in Appendix A. Included in each map was an outline of each patient's particular coronary circulation.

The isointegral difference maps for five inflations in two cases of PTCA of the LAD artery (\#3196 and \#3229) are shown in Figures 4.35 and 4.39 as body-surface and epicardial distributions, respectively. The case number is provided above and to the left of each map and the integration interval is shown above and to the right. Below
each epicardial map is the code for the two inflations from which the difference was calculated; the same information is in the centre cutout of the body surface map. On the outline of each coronary circulation is marked the location of the PTCA balloon at the time of inflation. Figures 4.36-4.38 and 4.40-4.42 contain the torso and epicardial difference maps, respectively, for inflations in the RC artery, LCx artery, and both LAD (top two rows) and RC (bottom two rows) arteries, respectively.

Since transmural ischemia produces elevation of the ST segment in epicardial electrograms recorded from the affected area (see section 2.2), positive potentials in epicardial difference maps from the ST interval indicate underlying transmural ischemia. If the inverse solution has accurately estimated the potential distribution on the epicardial surface, areas of positive potential in the difference maps should identify those regions of the heart made ischemic by the loss of perfusion during the balloon inflation. Knowledge of the coronary anatomy of each patient and the location of the balloon during inflation provides another means of estimating the location of these underperfused regions. Agreement between these two methods was used as semi-quantitative validation of the inverse solution.

The epicardial difference maps from case $\# 3200$ in Figure 4.42 were recovered from a single patient who underwent serial PTCA of both the LAD and RC arteries. Occlusion of the LAD artery (arrow marks the location in the upper two rows of the f.gure) generated a focused positive area between the centre (apex of the heart) and the outer edge of the map, between 9 o'clock and 12 o'clock. This corresponded very well with the region which would normally be perfused by the LAD. A second, isolated positive area arose on the left atria, between 3 o'clock and 5 o'clock. In the lower two rows, occlusion of the RC artery produced a very different set of maps, again with positive potentials over the region of the heart which would be expected to be perfused by the occluded artery. Here also the model predicts a second region of postive difference which is located anterolaterally on the left atria, between 1 o'clock and 3 o'clock on the epicardial maps.


Figure 4.35: Isointegral peak difference maps (peak inflation minus preir flation) for 5 inflations of the LAD artery in 2 patients from the NP7 subgroup of the study PTCA \#2.


Figure 4.36: Isointegral peak difference maps (peak inflation minus preinflation) for 4 infiations of the RC artery in 2 patients from the NP7 subgroup of the study PTCA \#2.


Figure 4.37: Isointegral peak difference maps (peak inflation minus preinflation) for 4 inflations of the LCx artery in 2 patients from the NP7 subgroup of the study PTCA \#2.


Figure 4.38: Isointegral peak difference maps (peak inflation minus preinflation) for 4 inflations in a case (\#3200) from subgroup NP7, in which PTCA was applied to both the LAD (upper two rows) and RC (lower two rows) arteries in the same patient.


Figure 4.39: Calculated epicardial peak difference maps (peak inflation minus pre inflation! ior 4 inflations of the LAD artery in 2 patients in the NP7 subgroup of the study PTCA \#2.


Figure 4.40: Calculated epicardial difference maps (peak inflation minus preinflation) for 4 inflations of the RC artery in 2 patients from the NP7 subgroup of the study PTCA \#2.


Figure 4.41: Calculated epicardial difference maps (peak inflation minus preinflation) for 4 inflations of tne LCx artery in 2 patients from the NP'7 subgroup of the study PTCA \#2.


Figure 4.42: Calculated epicardial difference maps (peak inflation minus preinflation) for 4 inflations in a case (\#3200) from subgroup NP7, in which PTCA was applied to both the LAD (upper two rows) and RC (lower two rows) arteries in the same patient.

In the two LAD cases shown in Figure 4.39, positive potentials were spread over a larger area than in case $\# 3200$. In the maps shown in the upper three rows (case \#3196), there was also a focused negative area which was located near the centre of each map and which also overlarped the expected perfusion bed of the LAD artery. This suggested that perfusion of this region was being maintained, perhaps from one or both of the other two nonoccluded arteries. Angiograms of this patient revealed a larger than normal distal RC artery, which is indicative of extensive perfusion of the inferioposterior heart and possibly the apical regions by this artery. Another anomaly of this case was a second area of positive potential which extended down and almost encircled the central minimum. A possible explanation for part of this is that the single diagonal branch of the LAD artery in this patient contained a $90 \%$ stenosis and could have become partially occluded during inflation of the balloon which was located near the origin of the diagonal. The reason for the separate maxima on the left lateral and posterior heart in the maps in Figure 4.39 was not apparent.

In case \#3229, positive potentials covered the right heart, including the perfusion bed of the main branch of the LAD and the septal arteries which arise from it as well as the region perfused by the proximal RC artery. The region supplied by the diagonal branches of the LAD did not show any sign of ischemia. Analysis of the angiographic data from this patient showed that the second diagonal was, in fact, completely occluded, so that perfusion of this part of the heart had already been taken over by collaterals from the LCx artery. In this situation, occlusion of the LAD artery would not be expected to cause ischemia in the region perfused by these collaterals. As in previous cases, a smaller secondary maxima was observed on the left lateral atria, centred around 3 o'clock.

The RC-artery maps (Figure 4.40 and lower two rows of Figure 4.42) consistently contained a large area of positive potential encircling the lower part of each map which corresponded to the expected perfusion bed of the RC artery in these right-dominant patients. In case \#3230, there were also areas of positive potential which extended
up into the region of the heart normally perfused by the LAD and/or LCx arteries. There was angiographic evidence of collateral circulation present in this patient, the distal RC artery being supplied by the LAD and LCx arteries. The ischemia, which appeared in the differenc? maps when the RC artery was occluded, could then be explained by the "stealing" of blood from the distal left coronary arteries to supply the right. The case in the lower part of Figure 4.40 (case \#3235) revealed none of this stealing, although this patient did show some collateral flow in angiograms. This patient had a more extensive distal RC artery network than in case \#3230, hence the extension of the positive difference potentials up to the region also supplied by the LCx artery. Smail areas of positive potential, which were in some rases extensions of the primary maximum, alsu arose in the anterolateral region of the atria.

In epicardial maps of the LCx cases, shown in Figure 4.41, there were focussed areas of positive potentials found in a region to the left and posteriorly to the apex, encircled by the outline of the LCx artery. In the case shown in the upper two rows of maps (\#3211), the occlusion was locaied very proximally in the LCx artery. In the case shown in the lower two rows of the figure (\#3223) only the obtuse marginal of the LCx was dilated and the maximum was shifted slightly downwards, to a spot directly under the treated artery. As in the results for other patients, secondary maxima could be observed, in the LCx cases in the anterolateral regions of the atria, between 12 o'clock and 4 o'clock.

## Chapter 5

## Discussion

## 5.1 rorward and Inverse Solutions

### 5.1.1 Interpretation of transfer matrices

Forward matrix: the elements of each row $i$ of the forward transfer matrix $Z_{B H}$ can be viewed as the relative weights with which each epicardial region (represented by a node on the heart surface) contributes to the potential at a specific node $i$ on the body surface. For each node point on the body surface, there is a corresponding "contribution map" on the epicardial surface. Horacek [273] obtained similar results as "sensitivity maps" on the epicardial surface for selected body-surface leads; these maps were each obtained by simulated reciprocal energization of the leads in question. He suggested that the $Z_{B H}$ matrix from a forward solution provides the same information. Huiskamp and van Oosterom produced contribution maps of both epicardial and endocardial surfaces for some standard body-surface electrode locations from their forward solution [98].

Inverse matrix: similarly, each row $i$ of the $Z_{H B}$ matrix represents the relative sensitivity of each node on the body-surface to the epicardial potential at node $i$. This can be incerpreted in terms of electrocardiographic lead theory [274, 273, 275] to derive a lead system which is sensitive to any particular region of the epicardial surface. Such a lead system need not include electrodes corresponding to those nodes on the body surface for which the values in the row of the $Z_{H B}$ matrix are very
small; these leads would be insensitive to the epicardial potentials. In order to decide which of the remaining nodes should be included in a lead system, it is necessary to examine the information content of each lead and establish whether redundancies exists. Such considerations are often statistical in nature and are beyond the scope of this dissertation.

### 5.1.2 The homogeneity assumption

No effort was made in the forward and inverse solutions presented here to account for the inhomogeneous and anisotropic nature of the torso.

Van Oosterom and Huiskamp used their regularized inverse solution to compute ventricular activation maps of a subject, then multiplied the results by the forward transfer matrix for the inhomogeneous torso, $A$, to calculate the corresponding ECGs for the 12 standard leads. For their statistical analysis, they defined the RELative RESidual, RELRES, as the mean relative difference between the computed and actual ECGs calculated over N time instants. By selectively removing the sections of the $A$ matrix representing the contributions of the lungs and blood masses and recalculating the ECGs, they observed the effect of these inhomogeneous regions on the accuracy of the reconstructed ECGs. Over 100 ms of the QRS, the relres between the calculated and measured ECGs ir the complete inhomogeneous torso was 0.111 . Removing the lungs increased the relres to 0.144, while omitting the ventricular blood masses further increased relres to 0.518 . With both blood and lungs removed the relres was 0.544 , and with no boundaries (infinite medium assumption) the relres was 0.819.

There are two important differences between the van Oosterom and Huiskamp inverse solution and ours. The first is in the basic approach of the model: van Oosterom and Huiskamp generated activation sequences from their calculations, while our model produced potential distributions. A second, related difference is that they calculate activation sequences over both the epicardial and endocardial surfaces of
the ventricle, while our model generated epicardial potentials only. The most important consequence of this is that the blood masses fall within the Green's volume in the van Oosterom and Huiskamp model, and thus must be accommodated as an inhomogeneity in their calculations. With a model based on epicardial potentials, on the other hand, the blood masses lie external to the Green's volume and need not be explicitly included; the only substantial inhomogeneities within the Green's volume are the lungs, bone, and skeletal muscle mass. Moreover, Huiskamp and van Oosterom's inverse solution, requiring a very large number of nodes for the heart surface (consisting of both endocardial and epicardial surfaces), has a fundamental weakness: the system is underdetermined from the outset, that is, there is a larger number of elements on the heast surfaces than on the body surface.

Rudy and Messinger-Rapport [7, 276], using the idealized eccentric-spheres geometry, for which analytical solutions of the forward and inverse problems can be derived, showed that the effect of ignoring inhomogeneities was only a reduction in amplitude of the recovered 'epicardial' potentials, with nether a shift in the locations of extrema nor an appreciable loss of spatial resolution. The relative error was also markedly more sensitive to overestimation of the conductivity of skeletal muscle than to underestimation. Since the conductivity of muscle is higher than that of the remaining torso volume, Rudy and Messinger-Rapport's results suggest that it is better to err on the side of reducing, rather than enlarging, the inhomogeneity of the muscie mass. Similar results were obtained with regard to the 'lungs' in the eccentric spheres model: a reduction in the value of lung conductivity below the typical physiological value of $0.5 \mathrm{~m} 3 / \mathrm{cm}$ produced larger errors than an equivalent increase. Thus, it would seem that while inclusion of inhomogeneities improves the accuracy of the absolute values of the recovered potentials, the topology of the epicardial maps is not greatly affected.

Recent studies of the effect of inhomogeneity on the inverse solution using both realistic human geometry with measured body surface maps [29] as well as torso tank
simulations with dipole sources [70] have reported errors using the homogeneous torso assurnption. Walker and Kilpatrick observed changes in both amplitude and location of extrema in epicardial maps when the lungs were removed from their torso geometry [29]. The discrepancies between these results and those of Rudy and MessingerRapport may de due to the intrinsic symmetry and idealized containment (heart entirely enclosed by the lungs) of the eccentric spheres model.

A very comprehensive examination of the effect of thoracic inhomogeneities in a real torso was carried out by Stanley et al. [277]. In this study, inhomogeneous regions representing the lungs, sternum, spinal column and subcutaneous skeletal muscle from the same dog used in earlier work by Ramsey, Barr and Spach [56, 57] were included in the forward and inverse solutions and the results were compared to measured body surface and epicardial potentials. The investigators used a technique suggested by MicFee and Rush [278] and applied by Gulrajani and Miailioux [279], in which the effect $-f$ anisotropy of the skeletal muscle was approximated by expanding the torso dimensions to include a uniform 3 cm layer of isotropic muscie volume just under the new outer boundary. The findings of Stanley et al. suggest tinat it is this muscle layer which contributes more than any other inhomogeneity to the inverse solution.

While these studies indicate that the skeletal-muscle inhomogencity does affect the accuracy of the inverse solution, the very weight it appears to carry and the sensitivity of the results to its conductivity value demand great care in including it in any model. Application of a layer of uniform thickness, with or without anisotropy, would seem to be a rather oversimplified approach to the problem, especially given, as suggested by Rudy and Messinger-Rapport, that an overestimation has such detrimental effects on the results. Without individualized values for the location, thickness, anisotropy, and extent of the muscle layer, there is, in our opinion, a greater risk in including a crude estimate than in leaving it out of the geometrical model altogether. The lower conductivity of the lungs appears, from these studies, to exert a much smaller effect
or the accuracy of the inverse solution. While this would seem to indicate that exact placement and conductivity of lungs in a torso is not as critical as with the muscle layer, it also suggests that inclusion of the lungs may not be 'worth' the additional computation required by its presence.

### 5.1.3 Effect of geometry on the forward and inverse solutions

As early as in the first comparative study of calculated and measured epicardial potentials by Barr and Spach [50], the effects of errors in the geometrical model have been evaluated. Barr and Spach found that the inverse coefficient matrix calculated for one dog could be used for the body surface potentials recorded from a second dog with only a slight increase in the relative error. It should be noted, however, that these investigators observed only a moderately accurate statistical match between measured and computed epicardial maps, with a correlation coefficient seldom climbing above 0.8 , and the relative error frequently as high as 0.75 .

In the eccentric spheres model, the size and relative location of the heart and torso can be altered continuously and the inverse solution recalculated [276]. MessingerRapport and Rudy found that a shift in the heart position of .5 cm inside a spherical torso of 12.5 cm radius, which they estimated to be equivalent to the movement during normal respiration or posture changes, was sufficient to cause a $50 \%$ loss of spatial resolution in the epicardial distribution. Altered heart size also resulted in a substantial loss of resolution, especially on the posterior side of the epicardium. The authors concluded that an accurate rendition of torso geometry was more important than the inclusion of inhomogeneities in generating accurate inverse solutions.

Huiskamp and van Oosterom also examined the effect of errors in the geometry ois their inverse solution [64]. They generated forward and inverse transfer matrices for each of three normal subjects and used measured body-surface potentials from the same subjects to generate physiologically acceptable ventricular activation-time distributions; these they called the "real" inverse solutions. They then applied the
measured body surface potentials from each subject to the inverse transfer matrices of the other two and calculated another set of inverse solutions, which were referred to as "cross solutions". These results were compared in terms of relative and maximum errors. In a second step, both real and cross activation times were used, with the forward transfer matrix of each subject, to generate body surface maps. Real and cross maps were compared using the relres coefficient described in section 5.1.2. While Huiskamp and van Oosterom observed considerable diucrepancies in cross versus real inverse solutions with regard to the relative and maximum errors of the activation time distributions, the RELRES values for the associated forward calculations (BSPMs) were not as conclusive. In fact the Relres in one case was larger when the geometry and ECGs from the same subject were used than for cross solutions which utilized one subject's geometry and another's ECGs. However, the result these authors considered most significant in terms of the clinical usefulness of such an inverse solution, was the maximum error in the activation time. In the cases described by Huiskamp and van Oosterom, maximum error in activation time was highly sensitive to alterations in geometry - more so, in fact, than to the homogeneous torso assumption (described in section 5.1.2) and to either random or systematic electrode-placement errors [64].

In the studies conducted for this dissertation, a single, realistic human torso model, described in Appendix A, was used for all calculations. Without ready access to nuclear magnetic resonance equipment at the time of this study, we had no acceptable means of gathering customized geometrical data on the paiients whose epicardial maps were computed. From the reports of others, there is every reason to believe that the addition of such information would improve the quality of our results. The cost in terms of human effort and computing time of individualizing each inverse is very high at this time. Although semiautomatic systems of acquiring and triangularizing 3D surface data have been described [280, 63, 238], these emerging technologies were beyond our reach at the time of this study. Once the geometry information is represented in suitable form, the entire forward solution must be recalculated, which
required some minutes on our computer facilities (section 4.1). The computation of the inverse solution executes relatively quickly, provided that the regularization parameter has been established, and application of the inverse coefficient matrix to body surface map data takes only seconds for each map. If such en individualized inverse solution were to be applied to the clinical setting, the time to generate a patient-specific forward matrix would, given present technology, limit its diagnostic capabilities. One possible solution might be to generate a set of inverse solutions based on a number of basic body types and sizes. Input of some relatively simple measurements of the patient would then direct the program to the best-fit geometry.

### 5.2 Clinical Studies

### 5.2.1 Localization of ischemia

The usefulness of BSPM difference maps in the clinical evaluation of ischemia was demonstrated by the ability, on the basis of isointegral $r_{\text {:a }}$ rence maps, ic differentiate between PTCA occlusions in the LAD, RC, and : $P x$ : teries, as described in section 4.2. The inflations of the LAD artery produced very distinc ${ }^{+}$patterns in the difference maps; features in the difference maps from inflations in the RC and LCx arteries were more subtle, but still adequate to distinguish between the two arteries. Since there is a posterior region of the myocardium which can be supplied by either the RC or LCx arteries, depending on the structure of the patient's coronary tree, one would expect the maps from such cases to contain similarities. However, in an the cases in which significant changes followed inflation of the balloon, the BSPM difference maps contained sufficient detail to separate the RC- from the LCx-artery occlusions.

Within the set of peak isointegral difference maps from the same artery, we found certain features common to all integration intervals (each row of Figures 4.26-4.32 ard each column of Figure 4.32). The similarity between maps from the repolarization intervals (QRST, ST and ST-T) was most striking. Characteristics of the repolarization of the heart are considered primary when they are related to the shape, duration, or amplitude of the myocardial action potential, and secondary when they follow from the sequence of activation. The QRST integral reflects the primary repolarization properties of the heart [281, 282, 283]; it is a function of the area under the myocardial action potential [97] and is independent of the activation sequence. The ST and ST-T integral contains information about both the primary and the secondary repolarization charactoristics. The similarity in difference maps of all three repolarization integrals suggests that the changes which result from PTCA-induced ischemia are largely primary in nature. This agrees with the theory outlined in section 2.2.4.

Ischemia results in cells with depolarized resting potentials and APs of reduced duration, amplitude, and rate of rise, all of which would alter the area under the AP. The predominance of primary repolarization changes indicated by the isointegral maps also suggests that the effect of ischemia on secondary repolarization characteristics, that is, on the activation sequence of the heart, is minimal (see section 5.2.2).

The distribution of the isointegral maps from the repolarization integrals can also be interpreted in terms of the spatial extent of the PTCA-induced ischemia. Since the occlusion created by the PTCA balloon is complete, the resulting ischemia would be expected to be transmural in extent; during the ST segment, injury current would then flow into the ischemic zone from the surrounding healthy tissue causing a, shift in body-surface potentials. For an occlusion in the LAD artery, the ischemic region would be located anteriorly and the flow of current into this region would create a positive deflection in precordial ECG leads. The location of the maximum in the average difference maps in, for example, Figure 4.32, is experimental verification of this phenomenon. In occlusions of the RC artery, the right and posterior regions of the heart would be expected to become ischemic, since this is the region perfused by the RC artery. The systolic injury current would then flow inferiorly and produce a broader maximum on the right side of the body, a result confirmed in the average diffe.ance maps for the RC artery (Figure 4.32). The LCx artery supplies a region in the left lateral and posterior eart and the systolic difference maps produced by occlusion in this artery show a broad inferior left maximum. The systolic injury current flows inferiorly and to the left. In summary then, these results both support the physiological model of regional ischemia and agree with findings of other groups [130, 131, 132, 135].

The location and shape of the areas of negative potentials in the isointegral difference maps reflect the reciprocal changes referred to in section 2.2.4. Injury current flowing away from the sensing electrode is registered as a negative potential. The shape and location of the negative areas in the difference maps are anatomical com-
plements of the areas of positive potential.
There were 2 cases (\# 3233 and \# 3220), in which no meaningful change in the BSPM could be observed during PTCA. These were cases in which angiographically observable collaterals were present, hence it was assumed that sufficient retrograde perfusion of the region downstream from the occluded artery was provided by another vessel. These two cases illustrate one of the potential problems of PTCA as an experimental model of ischemia. Different patients, even those in whom the same artery is treated, demonstrate different patterns of 1 esponse, or even no response, to balloon occlusion, which can make interpretation of results somewhat more difficult. However, the ability to record data from the patient both at rest and during ischemia, along with the available angiographic information, allow at least qualitative analysis. As the studies reported here have shown, the electrocardiographic response to PTCA is reproducible within the same patient and, when illicited, contains featrres which reveal something of its physiological origins.

### 5.2.2 PTCA-induced changes in QRS

Despite applying several different methods of analysis (section 4.2), we were unable to show significant changes in the QRS-integral maps or instant maps during QRS which could be attributed to changes in activation sequence; instead, only effects due to injury currents or altered repolarization were observed. The fact that the instant difference maps from all but the last part of the QRS were so sensitive to even slight shifts in alignment suggested to us that the differences due to altered activation sequence were not significant. Even after alignment using the cross-correlation analysis method, we saw no consistent pattern in the difference maps across multiple inflations of the same artery. This surprised us since there is considerable evidence in the literature that spread of activation is altered by transient and brief periods of occlusion in animals [173, 174, 118, 172], as reviewed in section 2.2. Reports by two groups suggest that similar effects can be observed in the QRS complex of humans
during PTCA - a finding we were not able to substantiate.
Spekhorst et al. [130, 131, 135] utilized a BSPM technique very similar to ours, except that they applied an electrode array with 62 versus our 117 leads, and they did not perform any signal averaging. Instead, single beats were recorded at regular intervals throughout the inflation. Their results resemble ours, both in terms of instant maps during the QRS and in terms of mean peak difference maps. For example, the mean QRS difference maps shown by Spekhorst et al. as their Figure 6 [135] and our Figure 4.32 agree quite well in spatial distribution, especially with regard to the features which most clearly differentiate these maps from occlusions of the other coronary arteries (see section 4.2). Spekhorst and co-workers also devised a statistical classification test based on the mean QRS difference map to separate cases according to the artery under treatment and were able to identify all LAD cases; on the other hand, while they could identify a group which contained all RC- and LCx-artery cases (12), they could correctly separate only $71 \%$ (5 of 7) of the RC-artery cases and $60 \%$ ( 3 of 5 ) of the LCx-artery cases.

The difference between the report of Spekhorst et al. and our findings lies in the interpretation of the results. The changes in the QRS brought about by PTCA described by Spekhorst and co-workers occur late in ventricular activation; the question is whether these resulted from altered spread of activation or whether they are the first appearance of ST-segment shifts overlapping with the QRS. Arguments can be made for both interpretations. If ischemia were to bring about a reduction in the conduction velocity of the affected myocardium, the delay would perhaps not be large enough to become evident until the late stages of activation. Or the activation wavefront might not reach the ischemic zone until the latter portion of the QRS. On the other hand, the physiological mechanisms of ST-segment shifts are activated as soon as potential gradients arise between ischemic and healthy regions of myocardium. In the late stages of ventricular activation, a large portion of the ventricles has already been depolarized and can therefore begin generating injury current, which results in
the difference map patterns observed late in the QRS.
A strong piece of evidence for the argument that changes in the QRS-integral maps were largely a. result of injury-currents was the striking similarity between isointegral difference maps from the QRS and those from the three repolarization intervals (QRST, ST, and ST-T), both in individual cases and the average maps in Figure 4.32. Instant difference maps from late in the QRS also strongly resembled the repolarization isoiniegral difference maps, suggesting that the events which shape the QRS integral maps are only present late in the QRS interval and persist beyond it these are not depolarization, but repolarization events. This is shown in the series of instant maps in Figure 5.1, each column of which contains maps at specific instants in the QRS (first five maps) and the ST segment (last map in each column). The maps in the left-hand column were recorded just before a dilatation of the LAD artery in case \# 3200 (preinflation); those in the right-hand column are from corresponding instants in the ECGs recorded late in the same inflation (peak inflation). The time from QRS onset in milliseconds is indicated in the central cutout in each map. The pairs of maps in each row were quite similar until 68 ms (end of QRS), at which time a precordial maximum in the peak inflation map appeared and replaced the positive area $a^{t}$ the right shoulder as the dominant maximum. In trie next maps, recorded at 100 ms after onset of T RS or 30 ms beyond the J -point, the new maximum had spread downwards and to the right, and grown in amplitude (to $157.89 \mu \mathrm{~V}$ ) in the peak-inflation map, while the same location in the preinflation map was much less positive (about $50 \mu \mathrm{~V}$ ). The maximum in the last peak-inflation map was the dominant feature of the isointegral difference maps from this inflation and, although it began in the latter stages of the QRS, was a repolarization event.

While we were able to isolate an early phase of QRS, in which the repolarization difference pattern had not yet appeared, the findings in any one case did not correlate with others in which the same artery was treated and were also highly sensitive to the alignment of the instant maps from which the differences were calculated (see


Figure 5.1: Isopotential maps recorded before (le.t-hand column) and during (righthand column) inflation of the PTCA balloon. Time in the centre cutout is relative to the onset of QRS; the last row of maps is from 30 ms past the J-point.
section 4.2). For these reasons, we think it unlikely that the QRS difference maps attributed by Spekhorst et al. to altered spread of activation in the ventricles are, in fact, the result of changes in conduction velocity. Rather, they are the earliest stages of the intracellular injury current, which develops into the ST-segment shifts that dominate the difference maps of all the intervals.

Selvester and Wagner et al. have presented compelling evidence that PTCAinduced ischemia brings about drastic changes in the shape and amplitude of the QRS complex [161, 162, 163]. These investigators recorded only $\mathrm{V}_{2}, \mathrm{~V}_{5}$, and aVF leads using radiolucent carbon/epoxy electrodes and a Holter monitoring device, for 19 patients undergoing PTCA of the LAD artery. Although their analysis was confined to single beats of the $\mathrm{V}_{2}$ lead, the changes were dramatic: reduction in either R - or S-wave amplitudes of $50-100 \mu \mathrm{~V}$, depending on whether the PR or ST segment was chosen as the measurement baseline, and, in some cases, virtual disappearance of the QRS complex. We found no evidence of such changes in our results, either from the plots of single averaged beats, or in the QRS maps in instant or isointegral form.

There appear to be some differences in protocol between our studies and those of Selvester and Wagner et al. While inflation duration and patient population were analogous in both studies, Selvester and co-workers included data only from patients in whom no medication was administered during the procedure; in our studies, nitroglycerine was, on occasion, given from 1-28 min before the recording of a balloon inflation. The patient-selection procedure for our studies also included a thorough haemodjnamic evaluation (ejection fraction $>45 \%$ and no or only mild hypokinesia of the left ventricle). A curious finding which is not commented on by Selvester and Wagner et al., is that the marked changes in QRS morphology which occurred in $V_{2}$ appeared to be absent from ECGs recorded at $\mathrm{V}_{5}$ (see Figure 2 of [161]). The authors do remark [163] that the changes in QRS are poorly correlated with the degree of ST-segment shift and that this is a "labile relationship", even within inflations in the same patient. In some cases, substantial changes in QRS were present during one
inflation and missing in a later one, even though ST-segment elevations were similar in both. The authors do not mention whether there were beat-to-beat changes in QRS morphology within the same inflation.

We can only suggest that perhaps the less stringent patient selection criteria employed by Selvester and Wagner et al., combined with the lack of vasodilation therapy in their PTCA procedure might have produced a more severe ischemia in their studies. The changes they observed, only in lead $V_{2}$ and only in some inflations, could be but the first signs of altered spread of activation brought about by a degree of ischemia not induced in our studies.

### 5.3 Application of the Inverse Solution to BSPM Data

### 5.3.1 Validation

The methods of quantitative validation of the inverse calculations employed in this study were similar, in several aspects, with those used by other researchers. Like Walker and Kilpatrick [29], we calculated simulated potentials from a single dipole source to both set ihe regularization parameter, and quantitatively evaluate the accuracy of the forward and inverse solutions. Rudy and Miessinger-Rapport used a dipole layer source and an eccentric-sphere geometry in which analytical solutions were possible to validate their inverse solution [276, 7]. Like Huiskamp and van Oosterom [63, 30], we examined the epicardial distributions calculated with our model for physiological plausibility. While for the activation-time distributions com, , uted by Huiskamp and van Oosterom there exist at least limited measured data from humans [87], we know of no such complete epicardial potential maps from the in situ hum.n heart.

To overcome this problem and still provide some form of validation of our results, we took advantage of the controlled ischemia produced by PTCA (see sections 2.2 and 3.2). While it is not possible to know the epicardial potential pattern, eithei before or during PTCA, it is possible, based on the known location of the catheter balloon and the coronary circulation of the patient, to estimate where ischemia will occur while the balloon is inflated. By subtracting maps recorded just before inflation from those recorded during the late (peak) phase of the same inflation, we have generated body surface difference maps which reflect the effects of this ischemia. The body surface difference maps were then transformed, using the inverse solution, into equivalent epicardial difference maps. Since the presence of underlying ischemia is indicated by positive epicardial potentials, the location of maxima in the epicardial difference maps could be compared to the expected location of ischemia. As was shown in section
4.3 , the model produced maxima in the expected region in every case. Not only were there features in the epicardial difference maps which were common to all inflations of a particular artery, but within each group, subtle differences could be observed and explained on the basis of corroborative angiographic evidence. The model also generated secondary, spurious maxima which did not correspond to expected areas of ischemia. These were normally of smaller amplitude than the primary maximum and were found in regions overlying the atria. The lack of any obvious physiological reason for the occurence of ischemia in such areas suggests that this feature represents; an artifact of the inverse solution, perhaps related to the "crosstalk" phenomena of inverse solutions as described by Ideker et al. [284].

This method of validation is obviously rather indirect and qualitative rather than quantitative. Knowledge of the coronary circulation of a patient, even under the best angiographic visualization, is not sufficient to predict the physiological effect of an occlusion [136], even as compiete an occlusion as that produced by angioplasty. Many patients with coronary artery disease have developed an extensive, often angiographically undetectable, system of collaterals which can provide sufficient retrograde perfusion to reduce the ischemic load from the ioss of antegrade blood flow [127, 147]. In the RC-artery case \# 3230, it was possible to speculate on the role of the collaterals which had been angiographically observed; the area of ischemia predicted by the inverse solution which lay outside the perfusion bed of the occluded artery, suggested that "stealing" of blood from the LAD and/or LCx arteries was occurring via the collaterals which supply the RC artery. In the LAD-artery case \# 3229, the lack of predicted ischemia in the part of the heart supplied by the diagonals indicated that the angiographically observed stenosis of the second diagonal was probably complete and that collateral flow from the LCx artery had been established. We were unable, on the other hand, to explain why the area of positive potentials in the epicardial difference maps of the same patient extended so far into the region normally supplied by the RC artery. The spurious maxima which were observed are likewise without,
conclusive explanation and reveal a lack of uniqueness in ihe inverse solution. Hence, although this form of validation provides no quantitative proof of the degree of accuracy of the inverse solution, it suggests that the results are plausible, if not without artefact.

It should be emphasized that this form of validation is most fruitful when the coronary circulation of the patient is explicitly documented and taken into account. As can be seen from the 7 patients described in section 4.2 , there can be substantial differences in coronary trer between individuals, beyond the relatively broad classification of left, right or mixed dominance. Any evidence of collaterals, especially those that become functional only under ischemic stress (recruitable collaterals), is also of importance.

### 5.3.2 Clinical relevance

The primary goal of any inverse solution in clinical electrocardiography is to provide diagnostic information on the condition of a patient. While body surface potential maps contain the same information as in the corresponding epicardial maps, the presence of the body cavity distorts the potential distributions, adding implicit and irrelevant information about the patient's geometry to the electrical data of interest. By transforming the body-surface potentials to the epicardial surface, an inverse solution strips away the geometrical information and makes analysis and interpretation much more straightforward. Localization of ischemia to specific regions of the heart can assist in determining not only the presence, but also the physiological significance of occlusions of the coronary arteries. While an inverse solution like that developed by Huiskamp and van Oosterom et al. [30] has great potential to assist in the localization of arrhythmia and irregular conduction, a model such as ours is ideally suited to the study of ischemia.

In cases of multiple-vessel PTCA, the amount of heart tissue perfused by each artery is difficult to assess from angiographic data [285]. Collaterals may be visible,
but the degree of protection they provide is uncertain. During PTCA of such a case, an inverse solution could be applied to BSPM data collected during initial inflations of the occluded arteries to determine the extent and location of the resulting ischemia. Features in the epicardial maps might reveal the involvement of other vessels which are dependent on retrograde flow from the occluded artery; by monitoring changes from one inflation to the next, stability of the patient's condition could be assessed. Likewise, the response of patients to treatment with thrombolytic agents could be monitored by performing multiple recordings and using the difference map technique to follow changes in the extent of ischemia.

It would also be possible to collect BSPM data from patients undergoing exercise stress test or atrial pacing in order to establish the physiological significance of their stenosis. This type of screening is common in clinical electrocardiography, but at present yields less information than would be possible with an inverse solution. Atrial pacing has the significant advantages of being useable during such a procedure as PTCA, involving no motion of the patient, and yielding technically betrer BSPM recordings. Recent investigations suggest that atrial pacing is a good substitute to exercise testing in determining the functional success of PTCA [285].

## Chapter 6

## Conclusions and Summary

The aims of this dissertation - to explore the feasibility of using PTCA as an experimental model of ischemia and to develop a solution to the inverse problem of electrocardiography - have been achieved. The inverse solution takes the form of a matrix of transfer coefficients, with which it is possible to transform a body-surface potential distribution into a corresponding distribution on the epicardial surface. The boundary element method was used to generate a forward solution, from which an inverse solution was derived by applying Tikhonov regularization. The geometry used for the model was a realistic, homogeneous human torso consisting of 352 nodes and 700 triangles. From a single dipole source sets of epicardial and torso potentials were generated and then used to evaluate the accuracy of the forward solution; the optimal regularization parameter for the inverse solution was chosen experimentally as the value which produced the most acccurate epicardial potentials.

Several methods of computing the forward solution and performing the regularization of the inverse solution were compared, and the following conclusions reached:

- Forward calculations performed using the method of Barr, Ramsey and Spach, with improvements suggested by Pilkington (PBRS method) were compared to those according to the method of Rudy, Messinger-Rapport and the interpolation algorithm of Cruse (RMC method). Both methods produced almost identical forward-solution results.
- The inverse solution based on the forward solutions generated by the PBRS method reproduced simulated epicardial potentials as accurately as the inverse solution generated by the RMC method.
- Regularization using the Laplacian operator for the smoothing function performed sur stantially better than regularization with the identity matrix (Tikhonov zero-order).
- Inverse solutions regularized with the Laplacian smoothing operator showed better tolerance to input data contaminated with Gaussian noise when the regularization parameter was set at values larger than optimal under ideal conditions.
- Considerably less computer time was required to generate the forward solution using the RMC method than using the PBRS method.

Four studies of patients undergoing percutaneous transluminal coronary angioplasty were carried out: two in which the effect of the injection of contrast medium on body-surface potential distribution was examined, and two in which PTCA-induced ischemia was characterized. Data from the second study of PTCA-induced ischemia were analyzed and described in detail. The following results were obtained:

- In 14 of 16 patients, reproducible, transient ischemia was documented in the form of isointegral difference maps constructed by subtracting maps recorded before inflation of the PTCA ballo from those during inflation. In the two patients for whom no changes were ind, there was argiographic evidence of considerable collateral circulation.
- In each case in which ischemia was detected, there were features of the isointegral difference maps which were characteristic of the artery being treated. Even in the case of ischemia in the posterior region of the heart due to occlusion of


## the LCx and RC arteries, separation based on the location of the distributicn maximum was possible.

- We found no conclusive evidence, either in isointegral or instant maps of the QRS complex, of changes in the activation sequence of the heart due to PTCAinduced ischemia.

The inverse solution was applied to BSPM data of seven patients in the clinical study to examine whether the location of ischemia predicted by the model matched that suggested by angiographic examination of each patient. In every case, the model predicted an area of ischemia which was in agreement with that determined from the patient's coronary circulation and the location of the angioplasty balloon. In several cases, the epicardial potential distributions revealed subtle features of the area of ischemia which could be interpreted in terms of the unique coronary perfusion of each patient. The inverse solution also produced spurious areas of positive epicardial potential change for which there was no apparent explanation; this was presumably the result of model artefact.

Overall, the initial results described in this dissertation are very encouraging. They demonstrate the ability of the inverse solution to localize PTCA-induced ischemia on the epicardial surface, and on a more fundamental level, they confirm the utility of PTCA as a controlled model of ischemia in humans.

## Appendix A

## The Dalhousie Human Torso Model

## A. 1 General Description

For a specific solution to the forward or inverse problems of electrocardiography, a three-dimensional geometrical description of the volume conductor is required. This can take the form of an idealized geometry, for example the eccentric spheres used by Rudy and Plonsey [92, 88], or of a more realistic model of the body. Realistic models are constructed from measurements of a single person or animal and then applied to others with little or no modification; further improvement can be realized when measurements are taken from each subject in a study and a customized geometry is generated [29, 64]. Virtually all the reported geometrical models of forward/inverse solutions in electrocardiography employ a torso (body without extremities and head) as the outermost boundary; this truncation is justified because heart-produced potentials decay rapidly in the extremities.

The geometrical description of the volume conductor can take several forms, depending on the specific method of mathematical solution. For solutions based on the boundary element method (BEM), the surface bounding each region of the volume conductor must be defined by a set of node points which are linked to form simple polygons, most often triangles. If a homogeneous torso model is assumed for the solution in terms of epicardial potentials, only the outer body surface and the epicardial
surface of the heart need be defined. Each additional inhomogeneity requires its own surface and each subregion thus defined must be assigned a conductivity value. In the finite element method (FEM), the entire volume of the volume conductor must be tessellated into three-dimensional elements, typically tetrahedra. The conductivity of each finite element must be set, but can vary from element to element.

## A. 2 Coordinate System

There is no standard coordinate system for the human body. We have chosen a configuration similar to that described by Frank [286], which prescribes a right-handed Cartesian system with the y -axis formed by the cranio-caudal axis of the body, oriented towards the feet, the $x$-axis directed towards the left arm and the $z$-axis towards the back. The origin of our system is shifted from Frank's such that the top layer of the torso intersects the $y$-axis at 75 mm . Figure A. 1 shows a view of our torso model with this coordinate system.

## A. 3 Three-dimensional Torso Surface

A realistic human torso was determined in our laboratory from tomographic measurement of a single subject. The original version was developed by Horacek [243, 275, 58] and has since been used by others [23,279]. This model consists of 5 surfaces: the body, 2 lungs and 2 blood masses, which are defined by 952 points joined to form 1884 triangles. The body surface node points were determined from the outlines of 19 tomographic slices taken at regularly spaced (every 25 mm ) horizontal ( $\mathrm{x}-\mathrm{z}$ ) planes. For each slice, a set of 32 vectors radiating from the origin of the $x-z$ plane was constructed; the intersection of each vector with the body-surface outline formed a node point. The nodes ( 610 in all) were then joined with those from neighbouring layers to form 1216 triangles. This produced a fairly regular grid of nodes on the body surface.

To optimize the forward/inverse solutions, we decided to reduce the number of points in the torso model. First, each electrode location of the BSPM system was


Figure A.1: The body coordinate system. All elements of the torso and heart geometry are defined in the right-handed coordinate system shown here.
matched with a node point. A second set of nodes was then placed mid-way between rows of the electrode grid, resulting in a higher spatial density of nodes in the precordial area than on the anterior right side and back. From the point of view of the forward/inverse solution, this was an acceptable arrangement. Since the anterior surface of the torso is closer to the heart than the posterior surface, we decided on a system of 2 different node grids, a closely spaced ( 2.5 cm ) grid for the precordial area and a more loosely spaced $(5 \mathrm{~cm})$ grid over the inferior and right anterior and posterior regions. Node points in the shoulder and neck regions would be chosen so that an adequate and consistent spatial resolution, as judged qualitatively, would be maintained.

The initial step in defining the new torso nodes was to establish a regular grid on a two-dimensional representation of the torso surface. The grid size was determined by the $5-\mathrm{cm}$ electrode spacing of the mapping system, which is fixed in the vertical direction by the electrode strips (see section B ). The spacing around the circumference of the patient is not fixed, but is still quite regular in that strips are placed to best cover the surface between anatomical landmarks. Specific strips are placed, for example, on the spine (strip \#16), left (strip \#12) and right (strip \#1) mid-axillary lines, and the area between is covered by regularly spaced strips on each side. Based on the dimensions of the torso, this corresponds to a horizontal electrode spacing of approximately 2.5 cm in the precordial area and approximately 5 cm on the anterior right side and back. Hence a grid of node poin's was constructed which had 2.5 cm spacing in the precordial area and a 5 cm spacing elsewhere on the torso surface, and covered a rectangular area of $80 \times 40 \mathrm{~cm}$.

The next step was to fit this two-dimensional surface to the three-dimensional torso. An isometric-projection criterion was chosen to maintain as much of the spacing and regular nature of the grid as possible, as if an infinitely pliable but nonelastic sheet of fixed size and shape were wrapped around the torso. In the shoulder and midaxillary regions, extra nodes were added to better follow the curvature of the body.


Figure A.2: Torso nodes in two-dimensional display
The ends of the torso at the neck and lower trunk were capped by sets of horizontal triangles. Corresponding adjustments were made to the two-dimensional grid to produce the final version, shown in Figure A.2. Each node location is shown numbered and marked as either a simple node (filled square), a node/BSPM electrode (open hexagon), a node/precordial electrode (open diamond) or a node/BSPM/precordial electrode (square box with an ' $x$ ' inside). Note that the node points at the common edges of the torso have the same node number in this diagram.

The node points were then joined to form a closed surface of non-overlapping triangular surface elements. There are many ways of performing this triangularization and different criteria exist by which this process can be carried out [280, 264, 286, 287, $288,289]$, some of which can be performed automatically by computers [286, 290]. While the aim of many general triangularization schemes is to achieve equality of both the area of cach triangle in the surface as well as among the 3 angles of each triangle [ $287,288,289]$, other investigators have derived more specific criteria based on the intended application of the triangularization. Meijs et al., for example, defined not
only the triangularization but also the selection of nodes such that the solid angle of each triangle about the location of the source generator in their model of the human head was approximately equal [62]. A similar approach was taken by van Oosterom et al. to produce an equi-solid-angle torso surface [280]. One difficulty in determining equal solid angles is that a reference point about which the solid angle is calculated must be stiected; only if the modelling approach includes a single, fixed-dipole source (see section 2.1), is the choice of this point obvious.

We chose to perform a manual triangularization in order to generate triangles of consistent area, but also to maintain reasonably accurate representation of the surface with a minimal number of nodes. Since the node grid of the three-dimensional torso is, in general, quite regular with two different spacings for the precordial and posterior regions, a bimodal distribution of triangle areas shown in Figure A.3, was obtained. The larger-area triangles in the figure (area $>2100 \mathrm{~mm}^{2}$ ) are found, with the exception of 2 from the shoulder area, in the caps which close the body surface at neck and waist. Several views of the final version of the three-dimensional torso are depicted in Figure A.4.

## A. 4 Three-dimensional Epicardial Surface

For the calculation of the forward/inverse problem using the homogeneous torso (see section 3.1.3), the only additional geometrical information required is a description of the epicardial surface. The complete structure of a sliced post mortem human heart has been previously digitized in our laboratory [292, 293]. At the same time, the location and orientation of this heart within the Horacek torso was determined from radiographic views of the same subject from whom the torso geometry was constructed. The node points of the epicardial surface lie on the outlines of 6 of the slices through the heart, made perpendicular to an axis running from the apex of the heart, through the root of the aorta, which correspond to the sections of Durrer et al. [87]. The epicardial surface is represented by 98 nodes which form 192 triangles.

## Triangle Area Distribution

 File: NewTorso1.dat

Figare A.3: Distribution of triangle area $\left[\mathrm{mm}^{2}\right]$ in the three-dimensional torso model.


Figure A.4: The three-dimensional torso in several views.

In Figure A. 5 are two views of the three-dimensional epicardial surface. In the top panel is a frontal view ( $10^{\circ} \mathrm{left}, 10^{\circ}$ cranial) of the heart as it would be located in the body. The axis system is aligned with the body coordinate system, with the origin shifted to the centre of the heart for purposes of display. In the lower panel, the view has been shifted to $95^{\circ}$ to the left and $5^{\circ}$ caudally to provide an apical view of the heart. The nodes lie at the intersections of the 6 circumferences and the 16 meridians ( 96 nodes) and at the two end points of the surface.

## A. 5 Two-dimensional Projections of the Geometry

Any three-dimensional surface must be projected on a. plane if it is to be viewed on a display device or in hard-copy form. The need to show the distribution of some quantity, for example electric potential, over such a surface adds a further dimension to the problem and makes the need for an acceptable projection even more acute. Since our primary purpose is not to portray geometry but to document potential distributions over the torso and epicardial surfaces, we had to develop a standard projection for each surface which would be the basis for isocontour maps. The next two sections describe the approach we have taken in developing projections and the associated forms of display which allow comprehensive evaluation of the data with a minimum of geometrical distortion.

## A.5.1 The torso surface

Since the three-dimensional form of the torso surface was derived from a two-dimensional grid, there was no need to derive another means of projecting the torso onto a flat surface. BSPM recordings yield a maximum of 117 leads ("bad" leads reduce this number), from which a complete set of torso potentials at all node points had to be generated. This was both a necessary prerequisite for inverse solution calculations (see section 3.1.4) and a functional requirement for plotting reasonably


Figure A.5: The three-dimensional epicardial surface in frontal and apical views.
smooth iso-contour maps (see section 3.2). While values at 117 of the 352 node points could be determined directly from the measured data, potentials at the remaining node sites were estimated using a three-dimensional interpolation scheme proposed by Oostendorp and van Oosterom [241] and described in section 3.2. Figure A. 6 shows the two-dimensional torso surface, displayed as a set of numbered node points (upper panel), and in triangularized form (lower panel). Figure A. 6 differs from Figure A. 2 in that all nodes which form what is a common boundary in 3 dimensions have been given unique node numbers (those $>352$ ) in the latter figure; node 19 , for example, has become node 357 in the two-dimensional representation of Figure A.6. To produce contours according to the method of Ideker et al. [263, 264, 265] (see section 3.2), the line segments which make up the triangles, together with the node points on either side of each line, were gathered in an "edge table".

## A.5.2 The epicardial surface

To facilitate display of epicardial potential distributions, it was necessary to develop a new projection of the three-dimensional surface of the heart. The precedents in the literature for such a projection can be divided into two categories. In one group are those based on a realistic anterior/posterior view of the heart in which each display consists of two non-overlapping silhouettes of the heart as seen in standard anatomical views $[51,50]$. With the addition of some appropriate landmarks, these displays have the advantage of being almost instantly readable and allowing easy spatial association between epicardial potentials and underlying anatomy. The fact that two separate displays are presented does, however, require mental reconstruction. Distortions can arise at the edges of the display where the surface curves away from the view plane; the apparent area can be much smaller than the actual one and in the worst case, certain regions can disappear behind foreground surfaces.

To ensure that the entire heart is clearly revealed, various methods of "unwrapping" the surface have been described $[294,76]$; these form the second category of


Figure A.6: The two-dimensional torso geometry displayed in terms of node points (upper panel) and triangles (lower panel).


Figure A.7: The three-dimensional epicardial surface rotated so that the heart axis is aligned with the $y$-axis of the coordinate system.
projections. While the edge distortion is reduced by this type of projection, the problem of where to split the display remains. Mental reconstruction of the complete distribution and the spatial relationship between epicardial potential and anatomy is also more difficult than with realistic projections.

The method we have chosen is a hybrid of these two categories and has been used by several groups for displays of isochrone maps in clinical epicardial mapping $[46,45,294]$. It is semi-realistic in that the heart is viewed looking at the apex along the heart axis, but to ensure that the whole heart is represented, the surface is also partially unwrapped. This is perhaps best pictured with the heart mounted vertically on its axis with the apex at the bottom, as shown in Figure A.7. If one were to imagine the heart covered with a flexible material which is distensible only along
the horizontal direction, one could tear this covering along the top ring in Figure A.7. pull it away from the heart and stretch it so that it lay flat. Figure A. 8 viows this two dimensional projection of the epicardial surface, referred to as the polar display, as numbered node points; the same projection in triangularized form is in Figure A.9. At the centre of each polar display lirs the apex, surrounded by concentric rings which correspond to the ou' anes of the slices through the heart. Sixteen rays originating at the apex and arranged at a constant angular interval correspond to the vertical meridians in Figure A.7. The rings are not round, because the distance between nodes on the same ray and neighbouring rings has been maintained in the transformation from three to two dimensions.

The main adyantage of this form of display is that it contains all of the venticular surface and a portion of the atrial surface in a single diagrari, while still maintaining a semi-realistic view of the heart. The two significant disadvantages are that the atrial surface is greatly distorted, since it forms the outermost ring of the projection, and that only the ventricles are displayed in their entirety. As we are concerned primarily with the effect of PTCA-induced ischemia on ventricular activation and recovery properties, these limitations are of minor importance.

The remaining degree of freedom in the polar projection is the rotation of the display about the center (apex). The orientation was chosen in such a way that the course of the left anterior descending (LAD) artery would be directed approximately vertically from the top towards the centre; the posterior descending artery runs from the bottom upwards. This perspective resembles the way a surgeon would see the heart through an anverior incision and allows relatively easy orientation when viewing the epicardial maps. To assist in the interpretation of epicardial maps, the coronary circulation was also projected onto the epicardial polar display. Based on standard views from several textbooks of anatomy $[154,296,297]$ the coronary anatomy was traced over plots of the three-dimensional triangularized epicardial surface. The triangles in these plots provided a grid with which the location of each of the coronaries


Figure A.8: Polar display of the epicardial surface in node form. Node 1, which marks the atrial end of the heart surface, cannot be shown in this projection.


Figure A.9: Polar display of the epicardial surface in triangularized form. The first 16 triangles, which join the outermost right with node 1 , cannot be shown in this display.
could then be manually transposed to a separate polar plot. The result was entered into the computer using a commercial computer-aided drafting and design (CADD) program (Generic CADD, Generic Software, Inc., Bothell, WA). In consultation with a cardiac radiologist, the extent and location of the coronary tree was then adjusted to resemble that of a normal right-dominant human (see section 3.2). Figure A. 10 shows the final result with the coronaries labelled (top panel) and with all the triangles which are known to cover the right ventricle marked with an " $R$ " (lower panel). For a subset of patients from one of the PTCA studies described in section 3.2, the standard coronary diagram was altered, again in consultation with the same cardiac radiologist, to reflect the unique structure of each individual. Any epicardial maps from this subset of patients include their own coronary geometry.


Figure A.10: The epicardial projection with a labelled coronary-artery tree (top panel) and with the all right-ventricular triangles marked with an "R" (bottom panel).

## Appendix B

## Dalhousie Mapping System: Electrical Isolation Features

## B. 1 General Description

Patient safety standards are more stringent in the catheterization laboratory than elsewhere in the hospital, since the catheter(s) provide a conductive (fluid) path to the heart $[298,299,300]$. To ensure the safety of subjects during mapping studies under such conditions, several measures have been incorporated into the design of the bedside unit of our body surface potential mapping system. The aim of these measures was to reduce leakage currents below limits prescribed by the CSA and the Victoria General Hospital for patient monitoring devices. This was achieved through complete galvanic isolation of the input stage (patient-applied parts) from the control circuitry, which passes the signals to and from the computer. Batteries were used to supply power for the input stage; this guaranteed that no current path existed between the power mains and the electrodes attached to the patient. In addition, the bedside unit was physically divided into two separate subunits, namely the amplifier unit and the controller unit, which were on opposite sides of the isolation barrier. Figure B. 1 shows an overview of the entire mapping system. With this system, the most stringent Equipment Risk Class 3 requirements for leakage current of patientapplied parts specified by the Canadian Standards Association (CSA) were met.


Figure B.1: The BSPM system as it was used in the catheterization laboratory. Note optocoupler which galvanically separates the amplifier unit from the controller unit.

## B. 2 Electrodes

Electrodes used in the catheterization laboratory must either be located outside the field of view of the fluoroscope or be radiolucent, that is, constructed in a way that creates minimal distortion of the X-ray image. The electrodes used with our standard BSPM system were constructed from 8-mm diameter silver/silver chloride ( $\mathrm{Ag} / \mathrm{AgCl}$ ) pellets in cup-shaped epoxy housings. Linear arrays of 4-8 regularly spaced (5 cm centre-to-centre) electrodes were bonded together in flexible silicon strips and applied in vertical rows to the subject's torso. Since we wished to maintain this same lead configuration in the catheterization laboratory as well, a new set of radiolucent electrodes had to be constructed. By carefully drilling out portions of our standard electrodes, we determined that the contact surface area could be reduced to the order of $1 \mathrm{~mm}^{2}$ without detectable loss of signal quality. We then specified and had constructed (by In Vivo Metric Systems, Healdsburg, CA) electrodes which consisted of a 1 mm diameter $\mathrm{Ag} / \mathrm{AgCl}$ pellet in a bevelled epoxy housing. These electrod $\epsilon \mathrm{s}$ were housed in silicon-rubber strips, and connected within the strip by ultrathin unshielded wire. Lead wires running from the base of each strip to a 9 -pin connector were tefloncoated and individually shielded. Visual examination of test ECGs recorded with the radiolucent electrodes showed no loss of signal quality or stability over the standard electrodes. The radiographic performance in the catheterization laboratory was also excellent; each electrode was visible, but only as a barely discernible dot surrounded by a loop of the lead-wire connection.

## B. 3 The Mapping System

## B.3.1 Signal isolation

For each electrode in the BSPM system there is a single amplifier unit containing an input operational amplifier, programmable filter and sample-and-hold circuit. Sixteen such amplifier units share a single A/D converter, which passes a time-multiplexed
output signal, packed in 4-bit half-bytes (nibbles) through a 19 -channel "nibble bus" to the communications and control circuits. We chose to provide galvanic signal isolation at the nibble bus for several reasons: 1) the multiplexing and $A / D$ conversion reduces 128 analog channels down to 19 digital lines, only four of which are actually carrying data; 2) we considered it advantageous to handle digital rather than analog signals at the optocouplers since possible nonlinearities between input and output would have no effect on the discretized signal; 3) while the large data transfer rate ( $192 \mathrm{kB} / \mathrm{s}$ for 128 channels at 1000 samples/s) necessitated high-speed optocc ${ }_{\mathrm{p}}$ plers, this was a technical requirement easier to meet than that of stable linearity over an analog optocoupler.

Each of the 19 lines on the nibble bus passes through a digital optocoupler (HP 2630, Hewlett Packard, Palo Alto, CA) to the nonisolated side of the control circuitry. The maximum leakage current to ground of such an optocoupler is rated at $1 \mu \mathrm{~A}$ per channel ( $0.6 \mathrm{pF}, 1000 \mathrm{G} \Omega$ ). Figure B. 2 shows the circuit for a single HP 2630 IC containing two independent optocouplers. The anode of each light-emitting diode (LED) at the input of the optocoupler is connected to the +5 V supply via a currentlimiting resistor. Connected to the cathode of each diode is a single line of the nibble bus; when the line is pulled low, current flows through the LED and its emitted light is sensed by the photosensitive transistor in the receiver of the optocoupler, which directly drives the nonisolated controller end of the bus.

## B.3.2 Packaging of the mapping system

To ensure a complete and secure separation of the patient-appiied parts from the remainder of the mapping system, the bedside circuitry was divided into two physically separate units. Each unit was placed in its own hospital cart (Hewlett Packard Model 7810 C, Palo Alto, CA) and was thus fully mobile.


Figure B.2: The isolation circuit used in the BSPM system; each HP-2630 IC drives 2 lines of the 19 -bit "nibble bus".

## B.3.3 Controller unit

The unit which contains the AC-powered controller electronics, battery charger, oscilloscopes, heart rate meter and computer terminal, has been named the controller unit. It forms the interface between the battery-powered amplifier unit (see below) and the host computer; monitoring and control of the recording process by the operator is also carried out via the oscilloscopes, meter and terminal housed in the controller unit.

The controller unit is connected to the host computer via a 48-lead cable up to 200 m in lengtin, which carries all the data-communications and control lines. The 10 -meter long data cable which joins the amplifier unit to the controller unit also provides the +5 V power for the nonisolated side of the optocouplers located in the amplifier unit. The third cable (charge cable) runs from the battery-charging circuit of the controller unit to the amplifier unit, where it is connected via the main power switch directly to the three battery packs. The charge cable should be kept as short as
possible to ensure that the units be placed close together and away from the patient during battery recharge. During the recording session, the charge cable should never be connected to the amplifier unit as this would provide a potential path to ground via the chassis.

## B.3.4 Amplifier unit

Two dravers containing the 128 amplifiers for the mapping unit, the battery packs, power regulators, battery-level indicators and optocouplers are all housed in a separate hospital cart - the amplifier unit. This unit satisfies the leakage current requirements for patient-applied parts of the CSA and the VG Hospital, since it is galvanically decoupled from the rest of the mapping system and is kept free of any earth ground connections. Even the chassis is left floating from ground and should not be allowed to come in contact with other earth grounds in the room. The origiaal design of the individual amplifier, A/D converter and multiplexing circuits [301, 302] have proved dependable and were left essentially unchanged in this new design.

## B.3.5 Power supply

Power for the bedside unit is provided by two sources, one for the amplifier unit and a second for the cuntroller unit. On the patient-side, rechargeable, sealed lead/acid cells are grouped into $+18 \mathrm{~V},-18 \mathrm{~V}$, and +8 V supplies, regulated down to +15 V , -15 V and +5 V , respectively, each with 12.5 Ah capacities. The voltage levels of the battery supply are monitored by a set of three 10 -segment LEDs which linearly span the acceptable supply-voltage range under no-load conditions. The user selects via the main power switch between 'charge', 'charge state indicate', 'power on' and 'power off' settings. Only in the 'power on' state are the input amplifiers energized.

The power for the controller unit is derived from the secondary side of an isolation transformer (Hewlett Packard, Palo Alto, CA), mounted in the base of the controller unit cart. The 120 VAC is fed via a hospital-grade power strip to the oscilloscopes,


Figure B.3: A block diagram of the power connections for the battery supply of the BSPM system
heart-rate meter, computer terminal and a switched power supply, which provides the DC power for the controller unit ( $\pm 15 \mathrm{~V}$ and +5 V ) as well as for the controller side of the optocouplers in the amplifier unit $(+5 \mathrm{~V})$.

## B.3.5.1 Battery power supply

Figure B. 3 shows an overview of the battery-based power system used for the amplifier unit. A 6 -pole, 4 -way main power switch is mounted to the front panel of the battery drawer of the amplifier unit and used to select the power mode:

Off: The batteries are disconnected completely from any other part of the circuit.

Charge: The batteries are switched to the socket through which the battery charger is connected to the amplifier unit. In this mode no power is supplied to the amplifiers or battery indicators.

Indicate: A set of three 10 -segment bar-graph LED displays show the charge level of the batteries. The batteries are disconnected from the amplifiers and the charger in this mode so that their unloaded voltage is monitored. To activate the display of the charge level, the user must also hold down a toggle switch mounted near the main power switch.

Operate: In this setting the battery power is applied to the regulators and the amplifier circuitry. This is the normal operating mode for the bedside unit and the only one in which the amplifiers are energized.

## B.3.5.2 The batteries

The batteries themselves are of the sealed acid/lead, "Cyclon" type (Gates Energy Products, Denver, CO). They are custom units, but since the individual cells are constructed in a modular fashion, fabrication by the supplier (Prelco Electronics, Montreal, $\mathrm{P}^{\text {/ }} \quad$ required only modest extra cost and time. Two identical packs were each made ..um three $6 \mathrm{~V}, 12.5 \mathrm{Ah}$ "Monobloc" units, welded into an L-shaped configuration and connected in series, for a total capacity of 18 V at 12.5 Ah . The remaining $8 \mathrm{~V}, 12.5$ Ah pack was made from four individual, 2 V J -cells, encased in shrink-wrap plastic. The three packs were mounted in a drawer of the amplifier unit along with the regulators and charge state indicator circuits.

## B.3.5.3 Voltage regulator

The supply voltage from the batteries is regulated from 18 to 15 V and from 8 to 5 V using three separate regulator circuits. Figure B. 4 B shows a standard variable voltage regulator (LM338) arrangement. The "shutdown" lead provides the option of quickly regulating the output voltage to zero by connecting it to the "-sense" line, while R2 adjusts the output voltage. Figure B. 4 A shows the slightly more elaborate 18 V regulator circuit, as suggested by Sherwood [303]. Here a variable voltage regulator ( $\mathrm{MC1723}$ ) drives a separate transistor in order to provide the necessary


Figure B.4: The voltage- regulation circuit for: A) the 15 V power, derived from the 18 V battery and B ) the 5 V power, derived from the 8 V battery
current. Output voltage is controlled with the variable resistor R 2 ; by appropriately connecting one of the output lines to the common ground, identical circuits provide both +15 and -15 V regulation.

## B.3.5.4 Battery charger

Three separate chargers of identical basic design were constructed, one for each of the three battery packs. Figure B. 5 A ( 8 V charger) and B ( 18 V charger) depicts the circuit used for this constant-voltage, current-limited charger, based on a design by Ershler and Steadman [229, 303]. According to our planned pattern of use and after consultation with the manufacturer, we chose a value of 2.4 V per cell as an
optimal voltage for the charge circuit. As a result of this choice the charge cycle is relatively slow, which ensures that a depleted battery recharges fully overnight with only limited reduction in long-term battery life. The two circuits in Figure B. 5 differ only in their input transformers, 3-pin voltage regulators and the resistor, R9, with which output voltage is set.

## B.3.5.5 Charge indicators

To ensure as efficient a recharging schedule as possible and to provide early warning to the operator of any drop in battery voltage, a set of three battery-charge level indicators were constructed. The display for each of the three batteries is in the form of a 10 -segment LED bar graph, calibrated to linearly span the normal operating voltage. When all the LED segments are on, the battery is still within normal operating range but not necessarily fully charged; a drop below the middle LED segment indicates imminent loss of full power to the circuits. Continued operation beyond this point produces unpredictable oscillations in the input amplifiers. Figure B. 6 shows the charge indicator circuit used for the 8 V and 18 V batteries.

An integrated dot/bar display driver circuit (LM3914, National Semiconductor) contains a ladder network of resistors and comparators to drive the attached 10 segment LED bar graph. When the indicator switch, S1, is depressed, the unregulated battery voltage is applied to a fixed, 15 -volt regulator (7815) to generate the supply voltage for the IC . In the $\pm 18 \mathrm{~V}$ regulator, this same signal is applied to a $2: 3$ voltage divider whose tap provides the input signal for the display; for the 8 V indicator, the battery voltage is applied directly to the 'Sig In' pin (5). A 1.25 V reference voltage is generated between the 'Ref Out' (7) and 'Ref Adj' (8) pins of the LM3914 and the current drain to ground from 'Ref Out' determines the LED current of each segment. This reference voltage, together with resistors $\mathrm{R} 1-\mathrm{R} 4$, are used to adjust the voltage range over which the display should operate. The lower-limit voltage, set by R4, is applied to the $R_{\text {lo }} \operatorname{pin}(4)$, the upper limit, set by $R 2$, to the $R_{h i}$ (6) pin, the difference


Figure B.5: The battery-charging circuits for both $18 \mathrm{~V}(\mathrm{~A})$ and $8 \mathrm{~V}(\mathrm{~B})$ battery supplies.


Figure B.6: The battery-level indicator circuit for the $18 \mathrm{~V}(\mathrm{~A})$ and $8 \mathrm{~V}(\mathrm{~B})$ supplies
between the two, $\mathrm{V}_{\mathrm{d}}$, is linearly spanned by the 10 segments of the display.
For both charge indicators, the battery supply voltage covered by the indicator display was set at 200 mV , from 1.9-2.1 V per cell. The upper value indicates a still acceptable, although not fully charged, open-circuit voltage while the lower is characteristic of a cell in acute need of recharge. Thus, for the 8 V battery packs $\mathrm{V}_{\mathrm{d}}$ should be adjusted to $0.8 \mathrm{~V}, \mathrm{R}_{\mathrm{lo}}$ to 7.6 V and, therefore, $\mathrm{R}_{\mathrm{hi}}$ at 8.4 V . In the $\pm 18$ V indicator, the battery voltage spanned is $17.1-18.9 \mathrm{~V}, \mathrm{~V}_{\mathrm{d}}$ should be adjusted to 1.08 V , with $\mathrm{R}_{\mathrm{lo}}$ at 10.26 V and $\mathrm{R}_{\mathrm{hi}}$ at 11.34 V .

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