OPTIMAL CONTROL BASED ON NONLINEAR CONJUGATE GRADIENT METHOD IN CARDIAC ELECTROPHYSIOLOGY

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requirements for the award of the degree of
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Specially dedicated to

my beloved father, Ng Kwai Weng and my beloved mother, Tai Hee.

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ABSTRACT

Sudden cardiac death is often attributed to cardiac arrhythmia, the situation when normal heart rhythm is disordered. In the context of optimal control of cardiac arrhythmia, it is essential to determine the optimal current required to be injected to the patient for dampening the excitation wavefront propagation resulting from cardiac arrhythmia, in which this process is known as defibrillation. Consequently, this leads to an optimization problem arising from cardiac electrophysiology, namely Optimal Control Problem of Monodomain Model (OCPMM). The OCPMM is a nonlinear programming problem that is constrained by parabolic partial differential equation coupled to a system of nonlinear ordinary differential equations, which turned out to be computationally demanding. The main aim of this research is on discovering more efficient optimization methods for solving OCPMM. First, the original complex problem is decomposed into sub-problems through the operator splitting technique for reducing the complexity of OCPMM. Next, the classical, modified and hybrid nonlinear conjugate gradient methods are employed to solve the split and discretized OCPMM. Numerical results prove that the modified method, namely the variant of the Dai-Yuan (VDY) method as well as the new developed hybrid method, namely the hybrid Ng-Rohanin (hNR) method are very efficient in solving OCPMM. Besides that, this research also studies the effects of control domain on OCPMM using two recognized factors, which are the position and the size. Numerical findings indicate that the control domains should consist of small size domains and located near to the excitation domain, for achieving better defibrillation performance. Lastly, based on the observed effects, an ideal control domain is proposed. Numerical results show that lowest current as well as shortest time are required by the ideal control domain during the defibrillation process. As a conclusion, the ideal control domain is capable of ensuring an efficient and successful defibrillation process.

ABSTRAK

Kematian kardium mengejut sering dikaitkan dengan aritmia jantung, keadaan apabila rentak jantung yang normal bercelaru. Dalam konteks kawalan optimum aritmia jantung, ia adalah penting untuk menentukan arus elektrik optimum yang diperlukan untuk disuntik kepada pesakit untuk melembabkan penyebaran muka gelombang terangsang yang disebabkan oleh aritmia jantung, di mana proses ini dikenali sebagai defibrilasi. Oleh yang demikian, ini membawa kepada masalah pengoptimuman yang timbul daripada elektrofisiologi jantung, iaitu Masalah Kawalan Optimum Model Monodomain (OCPMM). OCPMM adalah masalah pengaturcaraan tak linear yang dikekang oleh persamaan terbitan separa parabola yang ditambah kepada sistem persamaan terbitan biasa tak linear, ternyata menjadi cabaran dalam pengiraan. Tujuan utama penyelidikan ini adalah dalam pencarian kaedah pengoptimuman yang lebih cekap untuk menyelesaikan OCPMM. Pertama sekali, masalah kompleks asal dipecahkan kepada sub masalah dengan menggunakan teknik pemisahan operator untuk mengurangkan kekompleksan OCPMM. Kemudian, kaedah kecerunan konjugat klasik, terubahsuai dan hibrid digunakan untuk menyelesaikan OCPMM yang telah dipecah dan didiskret. Keputusan berangka membuktikan bahawa kaedah terubahsuai, iaitu kaedah varian Dai-Yuan (VDY) serta kaedah hibrid yang baru dibina, iaitu kaedah hibrid Ng-Rohanin (hNR) adalah sangat cekap dalam menyelesaikan OCPMM. Selain itu, penyelidikan ini juga mengkaji kesan domain kawalan bagi OCPMM dengan menggunakan dua faktor yang dikenalpasti, iaitu kedudukan dan saiz. Keputusan berangka menunjukkan bahawa untuk mencapai prestasi defibrilasi yang baik, domain kawalan harus terdiri daripada saiz domain yang kecil dan terletak berhampiran dengan domain perangsangan. Akhirnya, berdasarkan kesan yang diperhatikan, satu domain kawalan unggul dicadangkan. Keputusan berangka menunjukkan arus elektrik yang terendah serta masa yang tersingkat diperlukan oleh domain kawalan unggul semasa proses defibrilasi. Sebagai kesimpulan, domain kawalan unggul mampu memastikan proses defibrilasi dijalankan dengan cekap dan berjaya.

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LIST OF ABBREVIATIONS

CD	-	Conjugate Descent
DY	-	Dai-Yuan
FR	-	Fletcher-Reeves
HS	-	Hestenes-Stiefel
hA	-	Hybrid Andrei
hDY	-	Hybrid Dai-Yuan
hDYz	-	Hybrid Dai-Yuan zero
hHS	-	Hybrid Hu-Storey
hNR	-	Hybrid Ng-Rohanin
hZ	-	Hybrid Zhou
ICD	-	Implantable cardioverter defibrillator
LS	-	Liu-Storey
MBFGS	-	Modified Broyden-Fletcher-Goldfarb-Shanno
MDY	-	Modified Dai-Yuan
MFR	-	Modified Fletcher-Reeves
OCPMM	-	Optimal control problem of monodomain model
ODE	-	Ordinary differential equation
PDE	-	Partial differential equation
PRP	-	Polak-Ribière-Polyak
VDY	-	Variant of the Dai-Yuan
VPRP	-	Variant of the Polak-Ribière-Polyak

LIST OF SYMBOLS

D	-	Conductivity of the medium
E	-	Electrical field
F	-	Positive parameter
$\hat{F}$	-	Faraday's constant
$f(x)$	-	Objective function
$f(V, w)$	-	Vector-value functions
$f(y, u)$	-	Cost functional
G	-	Total number of global nodal points
$g(x)$	-	Function for equality constraint
$g(y(t), u(t), t)$	-	Continuously differentiable function
$h(x)$	-	Function for inequality constraint
$I(y(t), u(t), t)$	-	Continuously differentiable function
J	-	Current
$J(V, I_e)$	-	Cost functional
$\hat{J}(I_e)$	-	Reduced cost functional
$\mathbf{K}$	-	Stiffness matrix
k	-	Optimization iteration
L	-	Positive parameter
$\mathbf{M}$	-	Mass matrix
N	-	Neighborhoods of level set S
n	-	Index of the time-step
$p(x, t)$	-	Adjoint variable
Q	-	Charge across the capacitor
$q(x, t)$	-	Adjoint variable

$\hat{R}$	-	Universal gas constant
S	-	Level set
T	-	Final simulation time
$\hat{T}$	-	Absolute temperature
t	-	Time
$u(t)$	-	Control variable
V	-	Transmembrane potential
w	-	Ionic current variables
x	-	Decision variable
$y(t)$	-	State variable
$\dot{y}$	-	State equations
α	-	Regularization parameter
β	-	Surface-to-volume ratio of the cellular membrane
γ	-	Positive parameter
ε	-	Positive parameter
η	-	Vector normal to the boundary
θ	-	Scalar parameter
λ	-	Constant scalar
μ	-	Scalar parameter
τ	-	Positive parameter
ϕ	-	Scalar potential
$\varphi(\delta)$	-	Univariate function
ψ	-	Scalar parameter
Ω	-	Computational domain
ω	-	Nonnegative parameter
ϖ	-	Nonnegative parameter
$\mathcal{L}$	-	Lagrange functional
Ca^{2+}	-	Calcium
$D_{i,e}^{l}$	-	Conductivity in the fiber direction
$D_{i,e}^{n}$	-	Conductivity in the cross-sheet direction
$D_{i,e}^{t}$	-	Conductivity in the sheet direction

$\mathbf{d}^k$	-	Search direction
K^+	-	Potassium
Na^+	-	Sodium
δ^k	-	Step-length
θ^k	-	Conjugate gradient update parameter
ζ^k	-	Hybridization parameter
A_1	-	Operator
A_2	-	Operator
C_m	-	Membrane capacitance per unit area
c_1	-	Positive parameter
c_2	-	Positive parameter
c_3	-	Positive parameter
c_4	-	Positive parameter
D_e	-	Extracellular conductivity tensor
D_i	-	Intracellular conductivity tensor
E_x	-	Nernst potential for ion x
I_C	-	Capacitive current
I_e	-	Extracellular current
I_{ion}	-	Total ionic currents
I_m	-	Transmembrane current per unit area
I_x	-	Ionic current for ion x
J_e	-	Extracellular current
J_i	-	Intracellular current
N_j	-	Interpolation functions
r_x	-	Channel resistance for ion x
V_j	-	Time dependent nodal variables
$V\|_o$	-	Transmembrane potential in the observation domain
V_p	-	Plateau potential
V_{th}	-	Threshold potential

z_x	-	Valence of the ion x
ϕ_e	-	Extracellular potential
ϕ_i	-	Intracellular potential
Ω_c	-	Control domain
Ω_{c1}	-	First control domain
Ω_{c2}	-	Second control domain
$\tilde{\Omega}_{c1}$	-	Neighborhoods of first control domain
$\tilde{\Omega}_{c2}$	-	Neighborhoods of second control domain
Ω_{exi}	-	Excitation domain
Ω_o	-	Observation domain
$\partial\Omega$	-	Lipschitz boundary
$[x]_e$	-	Extracellular concentration of the ion x
$[x]_i$	-	Intracellular concentration of the ion x
$\|\cdot\|$	-	Euclidean norm of vectors
Δt_1	-	Local time-step for the linear PDE
Δt_2	-	Local time-step for the nonlinear ODEs
$\nabla\hat{J}(I_e)$	-	Reduced gradient

CHAPTER 1

INTRODUCTION

1.1 Optimization

Optimization is an essential tool in the analysis of physical systems, and may be defined as the science of determining the best solution among all feasible solutions for a certain mathematical problem. In general, an optimization problem consists of three basic elements; the objective function, the decision variables and the constraints. The objective function is a mathematical expression in terms of decision variables that can be used for determining the total cost or profit for a given solution. The decision variables represent the quantities of either inputs or outputs that the decision maker can control. Sometimes, the decision maker is restricted only to certain available choices, that is, the situation when the decision variables are constrained. The constraints can be classified as equality constraints $(=)$ or inequality constraints $(\leq \text{ or } \geq)$, depending on the signs used in the equations. Mathematically, a general optimization problem is given by

$$\begin{aligned} &\text{Optimize } f(x) \\ &\text{s.t.} \quad g(x) = 0 \\ &\qquad\; h(x) \leq 0 \end{aligned} \tag{1.1}$$

where $f(x)$ denotes the objective function, x denotes the decision variable, $g(x)=0$ denotes the equality constraint and $h(x)\leq 0$ denotes the inequality constraint.

Optimization problems can be divided naturally into discrete and continuous optimization problems depending on the types of the decision variables. In discrete optimization problems, the decision variables are only allowed for discrete values such as the integers. The discrete optimization problems can be further divided into two branches, namely combinatorial optimization and integer programming. As opposed to the discrete optimization problems, the decision variables for the continuous optimization problems are allowed to take on real values. If constraints are involved in the continuous optimization problem, the problem is said to be a constrained optimization problem. Otherwise, it is said to be an unconstrained optimization problem, which is generally easy to solve.

In general, constrained problem can be divided into linear and nonlinear. Linear programming problem refers to the optimization problem with all the elements are linear. However, if only the objective function is quadratic, then it turned out to be a quadratic programming problem, which is a special case of the linear programming problem with quadratic objective function (Floudas and Visweswaran, 1995). Lastly, if some of the elements of the optimization problem are nonlinear, consequently, it falls into the class of nonlinear programming problem.

Nonlinear programming problem has attracted the attention of science because most of real life problems are nonlinear in nature. This nonlinear programming problem is hard to solve than the linear programming problem because the feasible regions for the nonlinear constraints are hard to find, and at the same time the nonlinear objective may contains many local optima (Shang, 1997). Recently, the nonlinear programming problem that is constrained by partial differential equations (PDEs) has gained considerable amount of attention. This problem, now called PDE-constrained optimization problem, arises widely in many science and engineering applications. In fact, the main aim of this research is on discovering more efficient optimization methods for solving the PDE-constrained optimization problem arising from cardiac electrophysiology.

Figure 1.1 displays a graphical representation of the classification of optimization problems with particular focus on PDE-constrained optimization.

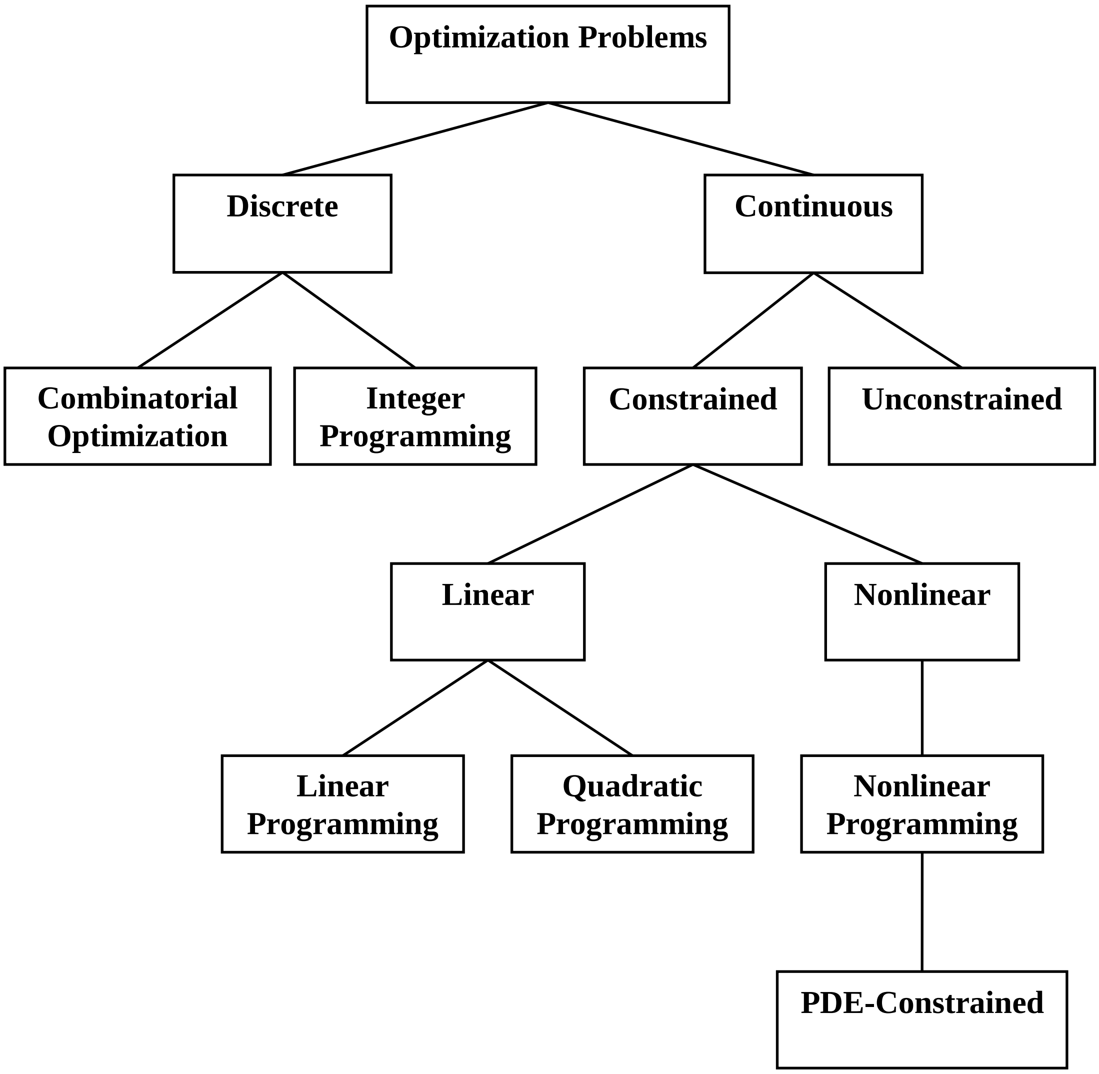

Figure 1.1 A classification of optimization problems

1.1.1 PDE-Constrained Optimization

Optimization of the systems governed by PDEs gives rise to a category of optimization problems called PDE-constrained optimization. The PDEs mathematically represent a multitude of natural phenomena, for example, heat flow, fluid flow and wave propagation. Consequently, it gives rise to various applications in science as well as engineering (Haber and Hanson, 2007). For instances, it arises in environmental engineering (Akcelik *et al.*, 2002; Laird *et al.*, 2005), mathematical finance (Bouchouev and Isakov, 1999; Egger and Engl, 2005), atmospheric science (Fisher *et al*., 2009), aerodynamics (Orozco and Ghattas, 1992; Hazra and Schulz, 2006) and biomedical engineering (Schenk *et al*., 2009; Arridge, 1999). However, this type of optimization problems is difficult to solve owing to the PDE constraints. Consequently, different approaches such as Tikhonov regularization (Egger and Engl, 2005), parallel computing (Biros and Ghattas, 2005) and preconditioning (Benzi *et al.*, 2011; Haber and Ascher, 2001; Rees and Stoll, 2010) have been proposed by researchers to cope with this numerical challenge.

Recall that the general optimization problem is defined in Equation (1.1). If the equality constraint $g(x)=0$ involves a PDE or a system of coupled PDEs, then Equation (1.1) is called the PDE-constrained optimization problem. Now, the decision variable x can be partitioned into two parts, i.e. $x=(y,u)$, where y and u denote the state and control variables. Thus, the PDE-constrained optimization problem now is given as

$$\begin{aligned} &\text{Optimize} \ \ f(y,u) \\ &\text{s.t.} \qquad\ \ g(y,u)=0 \\ &\qquad\qquad\ \ h(y,u)\le 0 \end{aligned} \tag{1.2}$$

where the PDE-constrained optimization problem with structure in Equation (1.2) is generally known as the optimal control problem.

1.1.2 Optimal Control

Optimal control theory is a modern approach to dynamic optimization. Specifically, it is an extension of calculus of variations (Sargent, 2000). This modern approach differs from the calculus of variations in that it introduces a new variable called control variable $u(t)$ that serves as an instrument of optimization (Rakamarić-Šegić, 2003). Once the optimal value for the control variable $u(t)$ is obtained, it follows that the solution to the state variable $y(t)$ can be determined.

In optimal control problem, the evolution of system from one stage to the next is governed by $u(t)$, while the behavior of system at any stage is described by $y(t)$ (Rao, 1984). In addition, $y(t)$ are governed by the following first-order differential equation, namely the state equations

$$\dot{y} = g(y(t), u(t), t) \tag{1.3}$$

where $g : \Re^n \times \Re^m \times \Re \to \Re^n$ is continuously differentiable and $t \in \Re$ as the time. Moreover, the state equations in Equation (1.3) are completed with initial and terminal conditions as follows

$$y(0) = y_0, \qquad y(T) = y_T \tag{1.4}$$

where $[0, T]$ is the time interval. Furthermore, a cost functional is required for measuring how good a given control $u(t)$ is. Thus, let the cost functional be given as

$$f(y, u) = \int_0^T I(y(t), u(t), t)dt \tag{1.5}$$

where $I : \Re^n \times \Re^m \times \Re \to \Re$ is continuously differentiable function defined on the time interval $[0, T]$. The optimal control problem can be stated as follows: Find the control input $u^*(t) \in \Re^m$ on the time interval $[0, T]$ that drives the system in

Equation (1.3) along a trajectory $y^*(t) \in \Re^n$ such that the cost functional in Equation (1.5) is minimized, given the initial and terminal conditions in Equation (1.4). Mathematically, the above optimal control problem is given by

$$\begin{array}{ll} \min & f(y,u) = \int_0^T I(y(t),u(t),t)dt \\ \text{s.t.} & \dot{y} = g(y(t),u(t),t) \\ & y(0) = y_0, \qquad y(T) = y_T \end{array}.$$

Optimal control problems with various physical backgrounds arise widely in many engineering and scientific areas. In this research, the focus is on the optimal control problem arising from cardiac electrophysiology.

1.2 Background of the Problem

Sudden cardiac death refers to an unexpected death of a person in a short time period, which is a common cause of death among adults. In China, sudden cardiac death episodes affect 544,000 people each year (Zhang, 2009). In the United States, sudden cardiac death takes the lives of over 450,000 people annually (Zheng *et al.*, 2001). Also, a recent study by Ong (2011) indicates that about 23% of approximately 16,000 deaths (per year) in Singapore are reported as cardiac death.

Sudden cardiac death is often attributed to cardiac arrhythmias, the situation when normal heart rhythm is disordered. As a consequence of the cardiac arrhythmia, the heart beats inconsistently and irregularly. It follows that death can occur within a short time period unless electrical defibrillation is given to the patient for restoring normal heart rhythm (Amann *et al.*, 2005; Dosdall *et al.*, 2010; Klein *et al.*, 2003).

The optimal control of cardiac arrhythmia was introduced by Nagaiah *et al*. (2011a), with attempt to determine the optimal current required during the defibrillation process. Specifically, the control objective was to utilize the optimal extracellular current for dampening the excitation wavefront propagation resulting from cardiac arrhythmia. Since Nagaiah *et al*. (2011a) employed the monodomain model to represent cardiac electrical behavior, thus, the above optimization problem is given the name Optimal Control Problem of Monodomain Model (OCPMM).

The monodomain model composed of a PDE coupled to a system of ordinary differential equations (ODEs) representing cell ionic activity, which is a simplified version of the bidomain model. The bidomain model is a powerful mathematical model for simulating cardiac electrical activity, however, the numerical solution for it is computationally demanding. Thus, the monodomain model is chosen by Nagaiah *et al*. (2011a) to form OCPMM, as this model can be solved at a less computationally demanding manner than the bidomain model. Since the monodomain model appears as constraints in OCPMM, it falls into the class of PDE-constrained optimization problem.

Two types of optimization methods have been applied for solving OCPMM, namely the nonlinear conjugate gradient methods (Nagaiah *et al*., 2011a) and the Newton method (Nagaiah and Kunisch, 2011). Nonlinear conjugate gradient method has computational advantage but usually requires many iterations to converge. In contrast, the Newton method is likely to converge with less iterations but requires higher memory storage.

Consequently, this leads to an idea of solving OCPMM using optimization methods which combine the merits of the above methods. This gives rise to two classes of optimization methods called modified and hybrid nonlinear conjugate gradient methods, which have low memory requirement and at the same time converge to the optimal solution with less iterations than the classical nonlinear conjugate gradient methods.

1.3 Statement of the Problem

For this research, the modified and hybrid nonlinear conjugate gradient methods are employed for solving OCPMM.

1.4 Objectives of the Study

Specifically, this research focuses on developing efficient numerical techniques for solving OCPMM as well as studying the effects of the control domain. In short, this research aims to achieve four objectives outlined in this section.

1. To apply the operator splitting technique to OCPMM. This technique is used to split the state and adjoint systems for OCPMM into sub-systems that are much easier to solve.

2. To solve OCPMM using classical, modified and hybrid nonlinear conjugate gradient methods. The performances of these three groups of optimization methods are then compared.

3. To observe the effects of control domain positioning as well as size on OCPMM. A number of test cases are considered in this research, which consist of different position and size of the control domain.

4. To propose an ideal control domain for OCPMM which is capable of ensuring an efficient and successful defibrillation process.

1.5 Scope of the Study

For this research, the mathematical modeling is based on the cardiac tissue rather than the whole heart. Moreover, the cardiac tissue is assumed to be located at either one of the chambers of the heart, depending on where the cardiac arrhythmia occurs. For example, if the cardiac arrhythmia is occurring in the left ventricle, then the cardiac tissue is assumed to be located in the left ventricle. In addition, the cardiac tissue is assumed to be insulated, i.e. surrounded by a non-conductive medium.

In the original OCPMM, Nagaiah *et al*. (2011a) ignored the constant scalar λ during the formulation of the optimal control problem. For this research, this constant scalar is included in the formulation of OCPMM for the purpose to improve the original OCPMM. As a consequence, the comparison of the results between Nagaiah *et al*. (2011a) and this research is unable to be performed due to the differences in the formulation of OCPMM.

For the numerical experiments, two-dimensional domain for the cardiac tissue is considered instead of three-dimensional. This is because the numerical solutions for the monodomain model are computationally demanding, especially in three-dimensional. Moreover, as shown in the literature, the OCPMM only solved on two-dimensional computational domain. Thus, two-dimensional computational domain is suitable and enough for this research.

Currently, there exist more than 40 nonlinear conjugate gradient methods which can be further categorized as classical, modified, hybrid, scaled, parameterized and accelerated. For this research, only the selected classical, modified and hybrid nonlinear conjugate gradient methods are chosen for solving OCPMM.

1.6 Contributions of the Study

There are three main contributions of this research, with each of them are listed in the following sub-sections.

1.6.1 Contribution to Development of Efficient Numerical Technique

This research is the first attempt to apply the operator splitting technique to OCPMM for the purpose of reducing the complexity of the problem. By utilizing the operator splitting technique, the nonlinear PDE in the state and adjoint systems is split into a linear PDE and a nonlinear ODE, which can be solved easily using different numerical schemes.

1.6.2 Contribution to Numerical Solutions for Optimal Control Problem

This research attempts to solve OCPMM using modified and hybrid nonlinear conjugate gradient methods. These two groups of optimization methods are proved to be superior to the classical methods in terms of optimization iterations. Moreover, a new hybrid nonlinear conjugate gradient method is developed in this research for solving OCPMM. This new developed method was proven to be performed better than other hybrid methods under the selected inexact line search in this research, that is, the Armijo line search.

1.6.3 Contribution to Defibrillation Process

The effects of control domain positioning as well as size on OCPMM are studied in this research. In the numerical experiments, the control domain corresponds to the electrodes of implantable cardioverter defibrillator (ICD) implanted in the chest of a patient. An ICD refers to a tiny device with the abilities of monitoring heart rhythm as well as delivering defibrillation shock to the patient when detecting an arrhythmia (Requena-Carrión *et al*., 2009).

Figure 1.2 shows ICD that implanted in the chest of a patient. As shown in the figure, ICD consists of two components; a pulse generator and two thin wires called electrodes. The pulse generator is a lightweight metal case that contains the battery and a tiny computer that continuously checks the heart rhythm. On the other hand, a set of electrodes are inserted into the heart through a vein in the upper chest, which function as an electrical shock sender when an arrhythmia is detected by ICD, in order to restore normal heart rhythm.

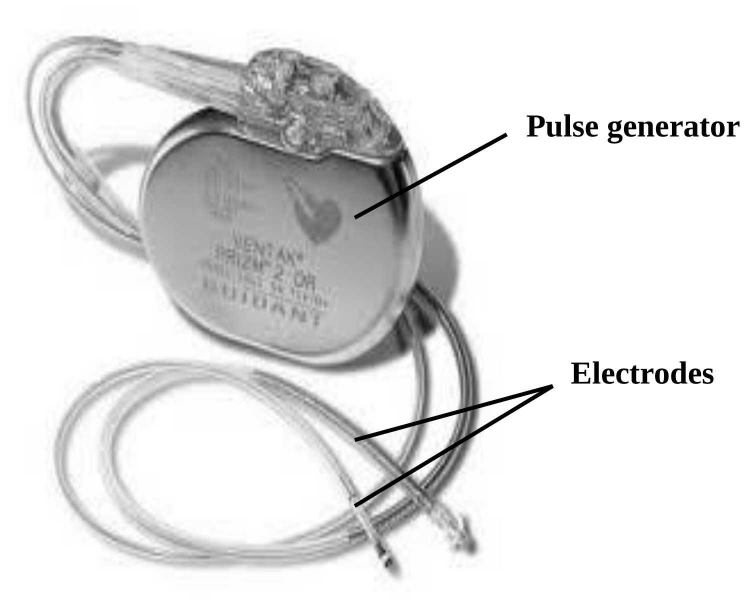

Figure 1.2 ICD that implanted in the chest of a patient (Taylor-Clarke, 2008)

Thus, from the numerical experiment results of this research, some interesting insights that can be applied to the science of cardiac electrophysiology were found. For example, the defibrillation performance can be improved by locating the electrodes nearer to the excitation region of the heart that is suffering from cardiac arrhythmia. Consequently, the observed effects from the numerical experiments can be contributed to the defibrillation process.

1.7 Organization of the Thesis

This thesis composed of six major parts. First, an introduction is given at the beginning of Chapter 1 to explain the research background and objectives. Next, the following sections identified the scope as well as the contributions of this study. In short, the main purpose of Chapter 1 is to show how this research is different from other previous works by describing its novelty.

Chapter 2 describes the literature review of the anatomy and physiology of the heart as well as the cardiac electrophysiology. Next, based on the literature review of cardiac electrophysiology, the bidomain and monodomain models used for simulating the cardiac electrical activity are then derived.

Next, Chapter 3 presents the formulation of OCPMM and the numerical approaches for solving it. The operator splitting technique for OCPMM is described first, followed by the numerical discretization of PDEs and ODEs. Besides that, this chapter also presents the strategy used for generating the computation mesh.

The numerical results for OCPMM using the classical, modified and hybrid nonlinear conjugate gradient methods are presented in Chapter 4. The numerical result for each method is analyzed and comparisons of results between these three groups of nonlinear conjugate gradient methods are reported as well.

Chapter 5 aims to observe the effects of control domain for OCPMM. The position and size effects are studied through some test cases and the observed effects are related to the science of cardiac electrophysiology, that is, the electrical defibrillation process.

Lastly, a conclusion of this research is provided in Chapter 6. This chapter also gives some recommendations for further improvement of the numerical solution technique for OCPMM.

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