Development of novel computational methods to simulate excitation waves in the whole rabbit heart

A thesis submitted to The University of Manchester for the degree of Doctor of Philosophy
in the Faculty of Engineering and Physical Sciences

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Jonathan Higham
School of Physics and Astronomy
Contents

Nomenclature ......................................................... 11
Abstract .............................................................. 14
Declaration ............................................................ 15
Copyright Statement ................................................... 16
Acknowledgements ..................................................... 17
The Author ............................................................. 18
Supporting Work ......................................................... 19

1 Introduction .......................................................... 20
  1.1 The structure and function of the heart ......................... 20
     1.1.1 The anatomical structure of the heart ..................... 20
     1.1.2 Cardiac myocytes ............................................. 21
     1.1.3 The mechanical function of the heart ...................... 22
  1.2 Electrophysiology of the heart ................................ 23
     1.2.1 Ionic channels and currents ................................. 23
     1.2.2 The action potential ......................................... 26
     1.2.3 Cardiac conduction pathway ................................ 28
     1.2.4 Fibrous structure of cardiac muscle ....................... 29
  1.3 Reasons for modelling cardiac systems ......................... 29
     1.3.1 Heart disease through history and today .................. 30
     1.3.2 Uses of animal models ....................................... 30
  1.4 Uses of cardiac models .......................................... 31
1.5 Thesis overview .......................................................... 32

2 Numerical methods and experimental techniques .................................. 36
  2.1 Single cell models ......................................................... 36
    2.1.1 The first model - Hodgkin and Huxley ......................... 36
    2.1.2 A brief history of cardiac modelling .......................... 39
  2.2 Numerical methods ..................................................... 40
    2.2.1 First order Euler method ...................................... 42
    2.2.2 The Monodomain equation .................................... 43
    2.2.3 Finite difference method ..................................... 44
  2.3 Experimental and clinical methods .................................. 45
    2.3.1 Diffusion tensor magnetic resonance imaging ............... 45
    2.3.2 The Electrocardiogram ........................................ 46
    2.3.3 Stimulation Procedures ....................................... 47
    2.3.4 Parameters of cellular action potentials ..................... 48
    2.3.5 Activation Sequence .......................................... 49

3 A review of rabbit single cellular models ........................................ 51
  3.1 Review of cellular models ........................................... 51
    3.1.1 Methods ......................................................... 52
    3.1.2 The Sino-atrial node .......................................... 52
    3.1.3 Atrial muscle ................................................. 54
    3.1.4 Atrio ventricular node and His bundle ....................... 54
    3.1.5 Ventricular muscle and Purkinje fibres ...................... 57
  3.2 A comparison between heterogeneous cell types .......................... 60
  3.3 Conclusions ............................................................ 63

4 Development of a two dimensional whole rabbit heart ........................ 66
  4.1 Creation of a two dimensional geometry ................................ 66
    4.1.1 Histological geometry and initial segmentation ............ 67
<table>
<thead>
<tr>
<th>CONTENTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1.2 Ventricular segmentation and the Purkinje network</td>
<td>67</td>
</tr>
<tr>
<td>4.1.3 Atrial tissue and the atrio-ventricular node</td>
<td>71</td>
</tr>
<tr>
<td>4.1.4 Development of the 2D framework</td>
<td>72</td>
</tr>
<tr>
<td>4.2 Results</td>
<td>77</td>
</tr>
<tr>
<td>4.2.1 Conduction velocities within the 2D model</td>
<td>77</td>
</tr>
<tr>
<td>4.2.2 Propagation through a 2D whole heart</td>
<td>78</td>
</tr>
<tr>
<td>4.2.3 Electrocardiogram recordings</td>
<td>79</td>
</tr>
<tr>
<td>4.2.4 Ventricular activation sequence</td>
<td>83</td>
</tr>
<tr>
<td>4.3 Adaptability of the 2D framework</td>
<td>86</td>
</tr>
<tr>
<td>4.4 Conclusions</td>
<td>86</td>
</tr>
<tr>
<td>5 Creation of a three dimensional whole rabbit heart</td>
<td>88</td>
</tr>
<tr>
<td>5.1 Creating the three dimensional geometry</td>
<td>88</td>
</tr>
<tr>
<td>5.1.1 Initial dataset</td>
<td>89</td>
</tr>
<tr>
<td>5.1.2 Noise removal</td>
<td>89</td>
</tr>
<tr>
<td>5.1.3 Ventricular segmentation</td>
<td>91</td>
</tr>
<tr>
<td>5.1.4 Mapping the Purkinje fibre network</td>
<td>94</td>
</tr>
<tr>
<td>5.1.5 Atrial segmentation and addition of the SAN</td>
<td>98</td>
</tr>
<tr>
<td>5.1.6 Addition of the AVN</td>
<td>99</td>
</tr>
<tr>
<td>5.2 Development of the full 3D model</td>
<td>99</td>
</tr>
<tr>
<td>5.3 Conclusions</td>
<td>109</td>
</tr>
<tr>
<td>6 Creation of ultra fast cellular modelling algorithms using</td>
<td>110</td>
</tr>
<tr>
<td>Graphical Processing Units</td>
<td></td>
</tr>
<tr>
<td>6.1 Motivation</td>
<td>111</td>
</tr>
<tr>
<td>6.2 Introduction to general purpose graphical processing</td>
<td>111</td>
</tr>
<tr>
<td>6.2.1 The graphics pipeline</td>
<td>112</td>
</tr>
<tr>
<td>6.2.2 GPU Architecture</td>
<td>113</td>
</tr>
<tr>
<td>6.2.3 Single instruction multiple data programming</td>
<td>115</td>
</tr>
<tr>
<td>6.2.4 Scientific uses of GPGPU</td>
<td>116</td>
</tr>
</tbody>
</table>
CONTENTS

6.3 Introduction to CUDA ........................................... 117
   6.3.1 What is CUDA ........................................... 117
   6.3.2 Comparison between C++ and CUDA .................. 118
   6.3.3 C++ and CUDA examples ............................... 119
6.4 Disadvantages of CUDA ....................................... 122
   6.4.1 Accuracy of computation ............................... 122
   6.4.2 Difficulties arising from SIMD ........................ 123
6.5 Differences in speed using CUDA ............................ 123
   6.5.1 CUDA speed increase in a dynamic homogeneous lattice 124
   6.5.2 CUDA speed increase in a heterogeneous ventricle .... 125
6.6 Conclusions .................................................... 126

7 Three dimensional whole rabbit heart - Case Studies ........... 129
   7.1 Propagation through the 3D whole heart .................. 129
      7.1.1 Internal view of AP propagation ..................... 130
      7.1.2 ECG recordings ....................................... 135
   7.2 Simulation of drug action .................................. 137
      7.2.1 Ivabradine ............................................ 137
      7.2.2 Tetrodotoxin ......................................... 141
   7.3 Simulation of atrial fibrillation ........................... 144
      7.3.1 Methods .............................................. 144
      7.3.2 Results .............................................. 144
   7.4 Conclusions ................................................ 145

8 Discussions and future work .................................... 149
   8.1 Summary ................................................... 149
   8.2 Discussions ............................................... 153
      8.2.1 The 2D Rabbit Heart .................................. 153
      8.2.2 The CUDA framework ................................ 153
      8.2.3 The 3D Rabbit Heart .................................. 155
8.3 Future work .......................................................... 156
  8.3.1 Anatomically detailed geometries ....................... 156
  8.3.2 Drug actions and atrial fibrillation within the 3D model . 158
  8.3.3 The 3D human heart ......................................... 159
  8.3.4 CUDA and GPU programming .............................. 159
  8.3.5 Additional effects and in depth models ................. 160
8.4 Closing words ..................................................... 160
List of Figures

1.1 Cross sectional view of the heart . . . . . . . . . . . . . . . . . . . . 21
1.2 Ionic current through a gated ion channel . . . . . . . . . . . . . . 24
1.3 Ionic current through an ion exchanger . . . . . . . . . . . . . . . 25
1.4 Morphology of an action potential . . . . . . . . . . . . . . . . . . 28

2.1 Schematic representation of a Hodgkin-Huxley type model . . . . . 37
2.2 Representation of a 1D finite difference stencil . . . . . . . . . . . 45
2.3 Morphology of a generic ECG recording . . . . . . . . . . . . . . . . 47
2.4 Schematic AP showing important parameters . . . . . . . . . . . . . . . . 50

3.1 Central sino atrial node action potential . . . . . . . . . . . . . . . 55
3.2 Peripheral sino atrial node action potential . . . . . . . . . . . . . . 55
3.3 Left atrial myocyte action potential . . . . . . . . . . . . . . . . . . . 56
3.4 AVN nodal cell action potential . . . . . . . . . . . . . . . . . . . . . 58
3.5 AVN atrial-nodal cell action potential . . . . . . . . . . . . . . . . . 58
3.6 AVN nodal-His cell action potential . . . . . . . . . . . . . . . . . . . 59
3.7 Purkinje fibre action potential . . . . . . . . . . . . . . . . . . . . . . 61
3.8 Ventricular action potentials . . . . . . . . . . . . . . . . . . . . . . 61
3.9 Review of AP parameters . . . . . . . . . . . . . . . . . . . . . . . . . 64

4.1 2D Mammalian cardiac histology . . . . . . . . . . . . . . . . . . . . . 68
4.2 2D histology after initial segmentation . . . . . . . . . . . . . . . . . 69
4.3 2D histology after manual cleaning . . . . . . . . . . . . . . . . . . . . 70
<table>
<thead>
<tr>
<th>Figure Reference</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4</td>
<td>2D ventricular segmentation</td>
<td>74</td>
</tr>
<tr>
<td>4.5</td>
<td>2D Atrio ventricular node</td>
<td>75</td>
</tr>
<tr>
<td>4.6</td>
<td>Completed 2D geometry</td>
<td>76</td>
</tr>
<tr>
<td>4.7</td>
<td>Conduction velocities in the 2D model</td>
<td>78</td>
</tr>
<tr>
<td>4.8</td>
<td>Simulated activation sequence from a 2D heart - 1</td>
<td>80</td>
</tr>
<tr>
<td>4.9</td>
<td>Simulated activation sequence from a 2D heart - 1</td>
<td>81</td>
</tr>
<tr>
<td>4.10</td>
<td>ECG calculated from a 2D heart</td>
<td>82</td>
</tr>
<tr>
<td>4.11</td>
<td>2D Ventricular activation sequence</td>
<td>85</td>
</tr>
<tr>
<td>4.12</td>
<td>Experimental ventricular activation sequence</td>
<td>85</td>
</tr>
<tr>
<td>5.1</td>
<td>3D DT-MRI rabbit heart geometry</td>
<td>90</td>
</tr>
<tr>
<td>5.2</td>
<td>Slices of digitally cleaned rabbit heart</td>
<td>92</td>
</tr>
<tr>
<td>5.3</td>
<td>3D digitally cleaned rabbit heart geometry</td>
<td>93</td>
</tr>
<tr>
<td>5.4</td>
<td>Fibre angles in ventricular tissue</td>
<td>95</td>
</tr>
<tr>
<td>5.5</td>
<td>3D reconstruction of the segmented rabbit ventricles</td>
<td>96</td>
</tr>
<tr>
<td>5.6</td>
<td>Iterative Purkinje fibre mapping</td>
<td>97</td>
</tr>
<tr>
<td>5.7</td>
<td>Final Purkinje fibre network</td>
<td>102</td>
</tr>
<tr>
<td>5.8</td>
<td>Atrial tissue slices</td>
<td>103</td>
</tr>
<tr>
<td>5.9</td>
<td>3D Atrial Geometry</td>
<td>104</td>
</tr>
<tr>
<td>5.10</td>
<td>Relative position of the SAN</td>
<td>105</td>
</tr>
<tr>
<td>5.11</td>
<td>Reconstructed SAN geometry</td>
<td>105</td>
</tr>
<tr>
<td>5.12</td>
<td>Implanted SAN Geometry</td>
<td>106</td>
</tr>
<tr>
<td>5.13</td>
<td>AVN Structure</td>
<td>107</td>
</tr>
<tr>
<td>5.14</td>
<td>External view of the segmented whole heart</td>
<td>108</td>
</tr>
<tr>
<td>6.1</td>
<td>Illustration of the graphics pipeline</td>
<td>112</td>
</tr>
<tr>
<td>6.2</td>
<td>Schematic GPU architecture</td>
<td>114</td>
</tr>
<tr>
<td>6.3</td>
<td>Schematic representation of CPU-GPU interaction</td>
<td>115</td>
</tr>
<tr>
<td>6.4</td>
<td>Speed increases in an ideal situation using GPGPU</td>
<td>124</td>
</tr>
<tr>
<td>6.5</td>
<td>Isosurface sequence of a stimulated ventricle</td>
<td>127</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td>6.6</td>
<td>Activation map of a stimulated ventricle</td>
<td>127</td>
</tr>
<tr>
<td>6.7</td>
<td>Realistic CUDA speed increase on a portable machine</td>
<td>128</td>
</tr>
<tr>
<td>7.1</td>
<td>Propagation through the 3D heart - 1</td>
<td>131</td>
</tr>
<tr>
<td>7.2</td>
<td>Propagation through the 3D heart - 2</td>
<td>132</td>
</tr>
<tr>
<td>7.3</td>
<td>Propagation through the 3D heart - 3</td>
<td>133</td>
</tr>
<tr>
<td>7.4</td>
<td>Propagation through the 3D heart - Isosurface representation</td>
<td>134</td>
</tr>
<tr>
<td>7.5</td>
<td>ECG calculated from a 3D heart</td>
<td>135</td>
</tr>
<tr>
<td>7.6</td>
<td>Action potentials during heart activity</td>
<td>138</td>
</tr>
<tr>
<td>7.7</td>
<td>Effects of Ivabradine on the rabbit ECG</td>
<td>139</td>
</tr>
<tr>
<td>7.8</td>
<td>Effects of Ivabradine on the rabbit ECG</td>
<td>140</td>
</tr>
<tr>
<td>7.9</td>
<td>Effects of Tetrodotoxin on the rabbit ECG</td>
<td>142</td>
</tr>
<tr>
<td>7.10</td>
<td>Effects of Tetrodotoxin on the rabbit ECG</td>
<td>143</td>
</tr>
<tr>
<td>7.11</td>
<td>Fibrillation in the 3D heart - 1</td>
<td>146</td>
</tr>
<tr>
<td>7.12</td>
<td>Fibrillation in the 3D heart - 2</td>
<td>147</td>
</tr>
<tr>
<td>7.13</td>
<td>Fibrillation in the 3D heart - 3</td>
<td>148</td>
</tr>
<tr>
<td>8.1</td>
<td>Overview of the major steps undertaken within this thesis</td>
<td>152</td>
</tr>
</tbody>
</table>
## List of Tables

2.1 Ionic currents in the Luo-Rudy model ............................ 41
3.1 Cell membrane capacitance ........................................ 53
4.1 Summary of cell models ............................................. 73
4.2 ECG parameters from the 2D rabbit heart ......................... 83
5.1 Summary of cell models ............................................. 101
6.1 Memory interface bandwidth ....................................... 114
7.1 ECG parameters from the 3D rabbit heart ......................... 136
8.1 Speed and price comparison between computational solutions .... 155
Nomenclature

$I_{Ca,b}$ .............................................. Background calcium leakage current
$I_{CaL}$ .............................................. Inward L-type Calcium current
$I_K$ ................................................... Time dependant potassium current
$I_{K1}$ ................................................. Time-independant potassium current
$I_{KP}$ ................................................. Plateau potassium current
$I_{KS}$ ................................................ Slow Potassium current
$I_{Kr}$ ................................................. Rapid Potassium current
$I_{leak}$ .............................................. Calcium leak to myoplasm from SR
$I_{Na}$ ................................................ Rapid inward sodium current
$I_{Na,b}$ ............................................. Background sodium leakage current
$I_{NaCa}$ ............................................. Sodium-calcium exchanger
$I_{NaK}$ .............................................. Sodium-potassium pump
$I_{nst(Ca)}$ ........................................ Non-specific calcium activated current
$I_{p(Ca)}$ ............................................ Sarcolemmal calcium pump
$I_{to}$ ............................................... Transient outward current
$I_{rel}$ ............................................... Calcium release to myoplasm from SR
$I_{up}$ ............................................... Calcium uptake from myoplasm to SR
$Ca^{2+}$ ............................................... Calcium ions
$K^+$ .................................................... Potassium ions
$Na^+$ ................................................ Sodium ions
$E_l$ ................................................... Leakage ion Nernst potential
$E_K$ ................................................... Potassium ion Nernst potential
$E_{Na}$ ................................................ Sodium ion Nernst potential
$g_l$ ................................................... Leakage ion Nernst potential
$g_K$ ................................................... Potassium ion Nernst potential
$g_{Na}$ ................................................ Sodium ion Nernst potential
V ......................................................... Membrane potential
\( \frac{dV}{dt}_{\text{max}} \) .................................. Maximum upstroke velocity of membrane potential
1D ...................................................... One Dimensional
2D ...................................................... One Dimensional
3D ...................................................... One Dimensional
AF ...................................................... Atrial Fibrillation
AM ...................................................... Atrial Muscle
AN ...................................................... Atrio-Nodal
AP ...................................................... Action Potential
APA ..................................................... Action Potential Amplitude
APD ..................................................... Action Potential Duration
ATP ..................................................... Adenosine Tri Phosphate
AVN ................................................... Atrio-Ventricular Node
BCL ..................................................... Basic Cycle Length
CPU ................................................... Central Processing Unit
CUDA ............................................... Compute Unified Device Architecture
CVD ................................................... Cardio Vascular Disease
CV ..................................................... Conduction Velocity
D ........................................................ Diffusion tensor coefficient
\( D_g \) ................................................ Diffusion tensor coefficient along fibre axis
\( D_{\perp 1} \) ........................................... Diffusion tensor coefficient normal to fibre axis
\( D_{\perp 2} \) ........................................... Diffusion tensor coefficient normal to sheet plane
DT-MRI .......................................... Diffusion Tensor Magnetic Resonance Image
ECG .................................................... Electro-Cardio Gram
ENDO ............................................... Endocardial
EPI ..................................................... Epicardial
GIMP ............................................... GNU Image Manipulation Program
GPU ................................................... Graphical Processing Unit
GPGP ................................................ General Purpose Graphical Processing
IVC ......................................................... Inferior Vena Cava
LA .......................................................... Left Atria
LV .......................................................... Left Ventricle
M ............................................................. Mid-myocardial
MDP ....................................................... Maximum Diastolic Potential
N ............................................................. Nodal
NH .......................................................... Nodal His
PCI ............................................................ Peripheral Component Interconnect
PCI-E ....................................................... Peripheral Component Interconnect Express
PF ............................................................. Purkinje Fibre
qPCR .......................................................... quantitative Polymerase Chain Reaction
RA ............................................................. Right Atria
RV ............................................................. Right Ventricle
SAN-C ..................................................... Sino Atrial Node Peripheral
SAN-P ..................................................... Sino Atrial Node Peripheral
SIMD ........................................................ Single Instruction Multiple Data
SVC ........................................................... Superior Vena Cava
TTX ............................................................ Tetrodotoxin
Abstract of thesis submitted by Jonathan Higham
for the Degree of Doctor of Philosophy and entitled
Development of novel computational methods to model the whole rabbit heart.
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Cardiovascular disease is a leading cause of death throughout the world. In order to understand
the mechanisms by which the heart functions, computational models of a variety of cardiac
myocytes have been developed. Although these models provide substantial information on the
activity of single heart cells, there is limited understanding of the interactions of these cells at
the tissue level. This thesis is concerned with the integration of such single cell models into
larger, more complex tissue structures. Firstly, this thesis introduces and reviews a number of
single cell models. These individual models were integrated into a structurally detailed 2D slice
of heart with a histological geometry. This model was used to investigate the cardiac sequence
of a rabbit heart, and a number of biophysical parameters were compared with, and found to
closely reproduce experimental data. To further investigate, a 3D rabbit heart geometry was
obtained and segmented into atrial, sino-atrial nodal, atrio-ventricular nodal, Purkinje fibre and
ventricular tissue, with each ventricle divided into endocardial, epicardial and mid-myocardial
regions, with an aim to investigate the effect of a number of pro- and anti-arrhythmic effects
on the rabbit heart. Analysis of the 3D model predicted huge computational load related to the
resolution of millions of cells. Currently, large scale computational simulations of cardiac ac-
tivity are carried out using dedicated supercomputing facilities, but such solutions can be costly
and unwieldy. To overcome this, investigation was carried out into the use of graphical pro-
gramming to decrease the computational time required to resolve such equations. Investigation
was carried out into the problem size at which graphical computation outperforms traditional
computation, and found to give up to a hundred-fold increase in computational speed at $10^6$
cells. These results pave the way for a new style of cardiac programming, allowing quick and
detailed investigation into a multitude of problems using cheap, easily available hardware.
Declaration

I declare that no portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

JONATHAN HIGHAM
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The Author

Jonathan Higham graduated from the University of Manchester with a Master of Physics (2:1) in 2007. In September that year, he joined the Biological Physics Department at the same University to begin work on his Doctor of Philosophy degree. This thesis represents his first major research project.
Supporting Work


Higham J., Aslanidi O., Zhang H., "Large Speed Increase Using Novel GPU Based Algorithms to Simulate Cardiac Excitation Waves in a Rabbit Ventricle", Computing in Cardiology, Hangzhou, China, 2011
1

Introduction

1.1 The structure and function of the heart

The heart is a complex muscular organ which forms the centre of the circulatory system in all vertebrate life. In mammals, the function of the heart is to allow the transport of blood throughout the body for a number of uses, including the supply of oxygen and the removal of waste products from numerous cells within the body. Beating around 2.5 billion times during a normal human lifespan [1], if the heart ceases to beat, a situation called cardiac arrest occurs, and death can occur within minutes [2].

1.1.1 The anatomical structure of the heart

The mammalian heart is split into two halves, left and right, with each half split further into two chambers, the atria and ventricle. The heart thus consists of four chambers: the left atrium, right atrium, left ventricle and right ventricle. The atria are much smaller than the ventricles, and are situated on top of the heart [3]. The left and right walls of the heart are separated from each other by a wall of muscle called the septum. The septum ensures that no blood can travel between the halves, a potentially dangerous effect [4].

On either side of the septum, the atria and ventricles are connected via two valves,
1.1: THE STRUCTURE AND FUNCTION OF THE HEART

Figure 1.1: Cross sectional heart schematic providing an internal view of many important heart structures. Adapted from [6].

the tricuspid valve between the right atrium and ventricle, and the mitral valve between the left atrium and ventricle. These valves only allow unidirectional flow, and ensure that blood can never travel from the ventricles back into the atria, which can interrupt healthy heart function [5]. A similar set of valves exists between the left ventricle and the aorta, and the right ventricle and the pulmonary artery. A labelled cross sectional schematic of a heart can be seen in Figure 1.1.

1.1.2 Cardiac myocytes

The vast majority of cardiac tissue is made up of myocytes, or muscle cells. Cardiac myocytes are typical, eukaryotic cells containing a number of different organelles bound by a cell membrane. Although differences in size exist, the average rodent ventricular myocyte is roughly 100-130\(\mu\)m in length, as measured across a number of different cell types and species, including rat, hamster, guinea pig [7]. Human cardiac
myocytes have been shown to be similar, averaging between 100-150\( \mu \)m in length [8], with rabbit ventricular cells having a length of around 100\( \mu \)m [9].

While the term myocyte also encompasses a number of specialised, non-contractile cells responsible for generating and conducting the electrical impulses that govern cardiac contraction, the majority of cardiac myocytes are devoted to contraction. Cardiac myocytes are the fundamental source of the contractile force in the heart [10, 11].

### 1.1.3 The mechanical function of the heart

The right atrium receives de-oxygenated blood from body tissue through the superior and inferior vena cava, and from the myocardium through the coronary sinus. Right atrial contraction forces blood through the tricuspid valve and into the right ventricle, shortly before right ventricular contraction forces the de-oxygenated blood through the pulmonary valve, into the pulmonary artery and on to the lungs. The left atrium receives oxygenated blood from the lungs through the pulmonary vein, and left atrial contraction forces blood through the mitral valve and into the left ventricle, which pumps oxygenated blood through the aortic valve, into the aorta, and on to the rest of the body.

The complex and specific timing of these rhythmic contractions is a consequence of the unique underlying electrophysiological properties of cardiac tissue [12], both the microscopic properties of individual cells, and the macroscopic properties of the structural geometry of the heart. An understanding of these mechanisms, along with the anomalies that can cause them to fail, is crucial to any understanding of cardiology, and the creation of computational models to further this understanding is the focus of this thesis.
1.2 Electrophysiology of the heart

In order to understand the macroscopic detail of the cardiac electrical excitation sequence, it is first necessary to underline the microscopic detail of the electrically active components that make up a mammalian heart. This section covers a multiscale view of heart physiology, from single cells to the complete conduction pathway.

1.2.1 Ionic channels and currents

The heart is composed of numerous different myocytes, all serving different functions, but all with a similar set of electrophysiological properties. The differences between myocytes serving these different functions are discussed in detail in Chapter 3. As previously discussed, each cell within the heart is bounded by a cell membrane, a phospholipid bilayer which separates the cell interior from the outside environment. The impermeable nature of this membrane to ions gives rise to the possibility of a difference in potential across the membrane, known as the membrane potential.

Though impermeable, a number of specialised protein structures span this membrane, functioning to regulate the transmission of charged ions both into and out of the cell. These protein structures include gated channels, as well as active ionic pumps and exchangers. Each of these channel types has a number of subtle differences in form and function. Gated channels passively allow ions to flow with the concentration gradient, while pumps use energy in the form of Adenosine Tri-Phosphate (ATP) to actively force ions across the membrane in a given direction, regardless of the concentration gradient. Exchangers are specialised pumps which move a specific ion across the membrane in one direction, while moving a different ion across the membrane in the opposite direction. The structure of both gated and exchanger ion channels are shown in Figure 1.2 and Figure 1.3.

Each of these channels is specific to a certain type of ion, and the cumulation of all channels governing a single ion gives rise to an ionic current. Currents which have the effect of a net increase in cell potential are termed inward currents, whether
Figure 1.2: A cell membrane shown bisected by a time dependent, gated ion channel for a specific positive ion, shown in grey circles. The tailed molecules arranged horizontally represent the phospholipid layer making up the cell membrane, while the vertical rectangles represent the ion channel. The bars at each end of the channel represent the gates responsible for opening and closing the channel. Panel (i) shows the gate in its initial state, with ion transfer blocked by the closed activation gate. In panel (ii), the activation gate opens and ions are free to transfer into the cell in the direction of the electrochemical gradient. In panel (iii), the inactivation gate closes and causes a cessation of ion flow.
Figure 1.3: A cell membrane shown bisected by an ion exchanger acting on two different types of ion. The cell membrane and ions are represented as in the previous figure, with the exchanger shown as the circle spanning the membrane layer. In panel (i) an ion of each type binds to the exchanger protein at a specific site. In panel (ii), the pump moves to exchange the ions. In panel (iii) the ions are released from their respective sites and the exchange is complete.
1.2: ELECTROPHYSIOLOGY OF THE HEART

this rise is due to a positive ion entering the cell or a negative ion leaving the cell. Conversely, currents which cause a net decrease in cell potential are termed outward currents. The magnitude of each of these currents may include potential, time and ion concentration dependence. This unique structure gives rise to the excitable nature of cardiac cells [13].

1.2.2 The action potential

For non-autoarrhythmic cells, an equilibrium potential exists known as the resting potential, usually at around -85mV [14]. At this potential, the net change in membrane potential due to the effects of all ionic currents through ion channels is zero. In addition to the connection to the extracellular space provided by these ion channels, each cell is also connected to its nearest neighbours via gap junctions. Electrical impulses from adjacent cells can cause the membrane potential of a myocyte to increase, changing the magnitude of a number of ionic currents. If the membrane potential is raised above the threshold level, these changes lead to the initiation of a cycle of rapid membrane depolarisation, followed by a slower repolarisation. This change in membrane potential is known as the action potential (AP). This cell will in turn pass an electrical impulse to the next adjacent cell, causing a propagation of AP known as an excitation wave to pass through the heart. This is the mechanism which governs the sequential contraction of heart muscle.

During the AP, a number of ionic currents come into play, as seen in Figure 1.4. While many areas of the heart contain unique cells with a wide variety in minor ion channels, giving rise to very different AP characteristics, the overall sequence of a single AP is governed by the same principal currents in almost all cardiac cells. The most important currents during the AP of a healthy cardiac myocyte are the inward sodium current ($I_{Na}$), the inward L-type calcium current ($I_{CaL}$), and the outward slow, rapid, and transient potassium currents ($I_{KS}$, $I_{Kr}$, $I_{to}$). The AP is divided up into four active phases (Phases 0-3), plus a resting state (Phase 4). These five phases are explained in
1.2: ELECTROPHYSIOLOGY OF THE HEART

detail below:

1. Phase 4 - During phase 4, the cell membrane potential is stable and polarised, usually at a potential of around -85mV. Cells which undergo muscular contraction are relaxed during this stage.

2. Phase 0 - Phase 0 is initiated by electrical impulses from adjacent cells, which cause sodium (Na+) channels to open, permitting a strong influx of sodium ions into the cell via the inward sodium current ($I_{Na}$), and causing rapid depolarisation of the cell membrane. This rapid depolarisation is sometimes referred to as the initial upstroke.

3. Phase 1 - Immediately following phase 0, phase 1 begins. This signifies the closing of the Na+ channels and opening of the potassium (K+) channels associated with the repolarising transient outward current, $I_{to}$. The efflux of potassium ions causes a sharp downward shift in membrane potential, and this phase is termed early repolarisation.

4. Phase 2 - After phase 1, a plateau in membrane potential is observed, due to the interaction of the depolarising influx of calcium (Ca^{2+}) ions corresponding to the L-type calcium current ($I_{CaL}$) and the repolarising efflux of K+ due to the slow and rapid potassium channels ($I_{Ks}$, $I_{Kr}$).

5. Phase 3 - During the repolarising phase, phase 3, the influx of Ca^{2+} ions slows while repolarisation is facilitated by an efflux of K+ ions due to the previously mentioned K+ currents, in addition to the rectifier current ($I_{K1}$).

The cumulative effect of all channels spanning the cell membrane gives rise to a specific AP curve. Though each individual type of cardiac cell has a variety of currents in addition to those described here, each cell follows a generalised AP shape as shown in Figure 1.4. Additional currents, and their effects upon the AP are discussed later in section 2.1.
1.2: ELECTROPHYSIOLOGY OF THE HEART

Figure 1.4: Generic action potential from an excitable cell. The labelled phases are phase 4, which corresponds to the cells resting at membrane potential, phase 0, the initial upstroke, phase 1, the early repolarisation phase, phase 2, the plateau phase, and finally phase 3, the repolarisation phase.

1.2.3 Cardiac conduction pathway

The initiator of electrical activity in the heart is the Sino-Atrial Node (SAN), located in the right atrium of the heart [15]. All myocytes within the heart have the ability to conduct a cardiac AP, but the SAN is one of the few regions of the heart capable of generating an AP [16]. While other areas of the heart do possess the ability to generate an independent, or auto-rhythmic AP, the SAN beats with the highest frequency and is usually the functional pacemaker in a healthy heart [17]. Once a signal is generated within the centre of the SAN, it passes to, and then through the peripheral SAN region via gap junctional coupling, before travelling into the right and left atrial cells. The signal then continues to propagate throughout the atria, causing atrial contraction.

Signals travelling through the atrial muscle eventually reach the Atrio-Ventricular Node (AVN). The AVN is located between the atria and the ventricles, and is the only
1.3: REASONS FOR MODELLING CARDIAC SYSTEMS

electrical connection between them [18]. The AVN serves to slow down the electrical signal, ensuring that atrial contraction is completed before the signal is passed to the ventricles, and therefore ensuring that there is a time delay between atrial and ventricular systole [19]. The AVN is connected to the bundle of His, which branches out into the Purkinje Fibre (PF) system, a network of fibres which lie along the internal ventricular walls. Signals travelling from the AVN into the PF are transmitted to the apex of the heart, where they propagate throughout the ventricles, causing ventricular contraction.

The geometric structure of this conduction pathway, along with the electrically active cells which make up cardiac muscle, govern contraction within the heart and are of prime importance to the understanding of many cardiac phenomena [20, 21].

1.2.4 Fibrous structure of cardiac muscle

In addition to the electrical heterogeneity encountered by the excitation wave propagating throughout the conduction pathway outlined above, cardiac muscle displays structural heterogeneity. Myocytes within the atria and ventricles are laid in a complex, layered, fibrous structure [22]. This structure has a large effect on the propagation of an excitation wave. In general, wave propagation is fastest along the direction of the fibre, and slower in directions perpendicular to the direction of the fibre. Fibre directions are essential to the specific sequence of heart excitation, and are of particular interest in large free space environments such as the thick ventricle walls.

1.3 Reasons for modelling cardiac systems

Since heart disease was first diagnosed, it has continued to claim lives globally, however, science has continued to advance and present new treatment options for cardiac disease. Computational cardiac modelling has grown alongside the advances in the field of medicine, and continues to fulfill a role in the present day.
1.3: REASONS FOR MODELLING CARDIAC SYSTEMS

1.3.1 Heart disease through history and today

The earliest documented case of human heart disease is dated over 3,500 years ago [23], however cardiac medicine as a field did not develop until much later, particularly during the renaissance with scholars such as Leonardo Da Vinci. Although Da Vinci did not greatly advance knowledge of the heart’s function, he described the anatomy in detail, and elaborated on the structure of the heart’s four chambers [24]. The initial developments into the function of the heart took place during the early 1600s, with the discoveries made by William Harvey [25, 26]. Developments continued to be made in the field, with the first medical textbook concerning heart disease published in 1749, various kinds of heart disease being identified and studied during the 1800s, and the eventual specialisation into diagnosis, prognosis and treatment during the early 1900s [27].

During 1900-1980, there was a steady climb in the number of deaths due to diseases of the heart in the United States [28]. Total mortality due to heart and related cardio-vascular disease (CVD) has plateaued in the past 30 years, with a slight downward trend in the last five [29]. While the past 20 years has seen a constant decline in deaths due to heart disease in the developed world, the opposite is occurring in less developed countries [30]. However as recently as 2007 it was reported that heart disease still accounted for a full 50% of all deaths in the developed world [31]. Heart disease remains the largest killer in the world today, as reported by the world health organisation [32].

1.3.2 Uses of animal models

While an ideal computational simulation would predict the electrophysiological behaviour inside a human heart, there are also advantages to modelling cardiac behaviour inside animals. Primarily, computational models rely on a large volume of clinical and experimental data, which is readily available for a variety of animals. The long history of scientific breeding of lab animals makes the acquisition of healthy animals straight-
forward. Animals can also be selected for a variety of characteristics, including age and gender.

The data necessary for the modelling of human cardiac behaviour is not so readily available. Data concerning human hearts may be collected during surgical procedure [33], but this carries the disadvantage that humans undergoing surgery are not fully healthy. Furthermore, the patients were under the effects of a number of drugs known to alter heart function [34]. For certain cell types, no experimental human data exists to date [35]. Therefore, until larger volumes of human cardiac data are obtained, it is sensible to look to animal models to further our understanding of the heart’s underlying mechanisms [36].

Due to a large volume of experimental data relating to the behaviour of a number of different cells within the rabbit, the rabbit heart was chosen as the focus for this thesis. While differences between the rabbit and human heart do exist, including differences in size, 300g in humans [37] versus 30g in rabbit [38], and resting heart rate, 70 beats per minute in humans [39] versus 260 beats per minute in the rabbit [40], rabbit hearts have been shown to be remarkably close to human hearts in terms of electrophysiological activity [41]. In particular, rabbits have been shown to match very closely with humans with respect to certain types of heart failure [42]. With these similarities in cardiac behaviour, coupled with a lack of electrophysiological data available for humans and an abundance for rabbits, creation of rabbit models to assess complex cardiac behaviour is a logical step forwards, and such models have been used to great success in recent years [43, 44].

1.4 Uses of cardiac models

Computational modelling provides a framework for integrating such small scale data into large, multi-scale simulations. This allows investigation into the electrical behaviour that arises as a result of complex interactions between individual cells in a multi-scale environment [45, 46].
The ultimate aim of computational cardiology is to provide a fast and accurate framework with which to investigate cardiac behaviour and further human understanding of the underlying mechanisms governing the heart. The insights into cardiac behaviour granted by such a framework could lead to new discoveries in the field of medicine, and improve the clinical treatment of patients suffering cardiac disease. Once developed, computational cardiology provides a non-invasive ability to investigate the effects of both pharmacological and surgical intervention on the dynamics of the heart [47].

1.5 Thesis overview

The rhythmic contractions of the heart are governed by the electrical activity of individual cells within the cardiac tissue, caused by the flow of charged particles through ionic channels. These ion movements can be experimentally investigated using isolated single cells, from which mathematical models may be established. Currently, there are a large number of these models of individual cardiac cells that have been developed by the scientific community. While they are scientifically interesting, they are far from representative of the biological situation of the whole heart. Though these models have succeeded in closely reproducing the ion channel kinetics of individual cells, as reviewed in detail in Chapter 3, as well as homogeneous sections of tissue and heterogeneous areas of the heart [48], there is currently no fully heterogeneous model of the complete conduction system of an entire rabbit heart in three dimensions [49].

In essence, the single cell models outlined within this thesis are all comprised of a number of differential equations, each one corresponding to the flow of ions through one of the ion channels described in Section 1.2. Depending on the current state of the ion channel, and the membrane potential of the cell, the change in current flowing through each channel is calculated, and applied to update the cell’s membrane potential. These currents within the model may be individually matched to their biological counterparts, as determined by experiment, and the sum total of all currents produces
an AP as seen in Section 1.2.2, which is again compared with experiment. The key features that these models attempt to reproduce are a number of AP parameters such as the width and magnitude of the AP, each dependent on a number of individual currents within the cell, as discussed in more detail in Section 3.2. The higher dimensional, 2D and 3D models used within this thesis are essentially groups of these single cells models laid out on an array, with each cell connected to adjacent cells via an additional equation to simulate the gap junctional coupling that exists between cells in cardiac tissue.

As outlined in the previous section, the ultimate aim of computational cardiology is a furthered understanding of the underlying mechanisms acting within the heart. To this end, this thesis is concerned with the creation and development of a number of computational methods focussed on the investigation of complex phenomena within the rabbit heart, with the final aims of creating a framework for large-scale, three dimensional simulation of the whole rabbit heart, the creation of techniques to generate a three dimensional anatomical structure for executing such a framework.

Finally, investigation was carried out into the effects of GPU based parallelisation on the computational time required for such simulations. Investigation into GPU based parallelisation acted primarily as a feasibility study to assess the possibility of further GPU based simulations throughout the field of heart modelling. In addition, this thesis aimed to collect relevant data for future experiments into GPU based parallelisation, such as expected speed increases and recommended problem sizes for maximum efficiency. A more detailed description of the individual chapters within this thesis is below.

The following chapter contains a mathematical discussion of the techniques used to solve the variety of ordinary and partial differential equations used to simulate cell behaviour on both single cell and tissue levels. A number of existing cellular models are examined, and the history of cardiac cellular modelling is discussed. The experimental techniques used to extract data used in the models are described, along with clinical apparatus used to diagnose a range of cardiac diseases.
In Chapter 3, individual cell models describing the variety of heterogeneous cells within the heart are introduced. Leading models for each cardiac cell type were chosen and the reasons for doing so justified. The difference in single cell behaviour within different areas of the heart is quantified and discussed, then correlated to the various functions of each area. The key cardiac cell types, in order of excitation during normal cardiac activity, are the SAN tissue, atrial muscle, AVN, Purkinje fibre and ventricle. While further subdivisions exist between these areas, each with their own important effects, these five areas represent the largest changes in function within the heart. The SAN is responsible for pacemaking, and as such produces autorhythmic, self induced APs. The atria is comprised of a medium length AP corresponding to short muscular contraction. The AVN produces a long, slowly travelling AP in order to prevent the ventricles contracting too soon after the atria. The Purkinje network expresses a very fast travelling AP with a steep upstroke, in order to depolarise areas of the ventricle simultaneously, and finally the ventricles produce a elongated AP, corresponding to the powerful ventricular contractions that force blood throughout the body.

In Chapter 4, a two dimensional model of the rabbit heart was developed, with a particular focus on structural heterogeneity. The individual cellular models outlined in Chapter 3 were placed within a two dimensional geometry taken from an experimentally obtained slice of heart, forming a complete heterogeneous model of the whole heart. Simulations are carried out to investigate the behaviour of the full heart. Activation sequence and timing are discussed, along with ECG data. The limitations and advantages of simulating cardiac excitation waves in two dimensions are discussed. Attention is paid to the intense computational load carried by large-scale detailed simulations, even in two dimensions. This chapter provides an important stepping-stone into the higher dimensional simulations carried out later within this thesis, and the reproduction of experimentally observed phenomena provides a proof of concept for the techniques used.

In Chapter 5, the creation of a new three dimensional geometry for the whole rabbit heart is discussed. The geometry contains atrial and ventricular tissue, which were
both computationally segmented into left and right halves. The ventricle was further segmented into endocardial, epicardial and myocardial cells, and heterogeneity from the apex to the base was added. A PF network was developed based on an existing study, and an AVN based on experimental data was added. The atrial tissue was segmented into the left and right atria, and a SAN based on experimental data was added. The geometry created by the techniques used within this chapter is the basis for all subsequent three dimensional models within this thesis.

Chapter 6 discusses new techniques for the computational analysis of cardiac behaviour. NVIDIA’s CUDA architecture is introduced and discussed from the point of view of biological simulations, including a study into obtainable speed increases and degree of parallelisation recommended for implementation. The basic attributes of highly parallel architectures such as CUDA are discussed, along with their relevant advantages and disadvantages, and the method by which models can be converted to run under the CUDA architecture is examined. This chapter introduces graphical processing as a viable alternative to conventional programming as a means for cardiac simulation.

In Chapter 7, initial simulations are run under healthy conditions to assess the validity of the 3D model, with respect to the activation sequence, and clinical parameters such as the ECG. The whole three dimensional model was used to carry out an investigation into the effects of channel blocking drugs on an ECG. A set of pharmacological compounds were applied to the model, including Ivabradine and Tetrodotoxin, and changes in whole heart parameters were compared and contrasted. Furthermore, atrial fibrillation was simulated, and the effects of the AVN as a filter for the transmission of high frequency atrial excitations to the ventricle were discussed. The results in this chapter reinforce the viability of the 3D model as an accurate representation of the macroscopic behaviour of the rabbit heart.

In Chapter 8, the results obtained in this thesis are discussed, with a focus on both the limitations and successes of the studies carried out within this thesis, and a discussion of possible future work in the area.
2

Numerical methods and experimental techniques

In chapter 1, many of the fundamental mechanisms behind electrical activity within the heart were introduced. However, in order to fully understand these mechanisms we require both experimental techniques for extracting useful data, and mathematical formulations to describe observed behaviour.

2.1 Single cell models

A number of these mathematical formulations have been developed over the course of the last century to computationally analyse the behaviour of excitable cardiac cells. This section contains a brief description of many of these models, and their part in furthering our understanding of the crucial mechanisms controlling the membrane potential within excitable cells.

2.1.1 The first model - Hodgkin and Huxley

The first model of ion channel behaviour leading to the creation of an Action Potential (AP) inside an electrically active cell was proposed by Alan Lloyd Hodgkin and
2.1: SINGLE CELL MODELS

Andrew Huxley in 1952 [50] - work for which they later received the 1963 Nobel Prize [51]. Although their experiments were carried out using the axons of a giant squid, their discoveries into the underlying equations governing the genesis of an AP form much of the basis for cardiac ion channel modelling today.

Hodgkin and Huxley represented the excitable cell as a collection of electrical components forming a physical system as seen in Figure 2.1. They divided the ionic current across the cell membrane into sodium and potassium currents \( I_{Na}, I_{K} \), as well as a small leakage current \( I_l \). They suggested that each current is determined by a driving force equal to a product of an electrical potential difference and a conductance, and produced the following equations to describe their three components of ionic current;

\[
I_{Na} = g_{Na}(V - E_{Na}) \tag{2.1}
\]

\[
I_{K} = g_{K}(V - E_{K}) \tag{2.2}
\]

\[
I_{l} = g_{l}(V - E_{l})
\]
2.1: SINGLE CELL MODELS

\[
I_l = g_l(V - E_l)
\]  (2.3)

where \(I_{Na}, I_K, I_l\) are the individual contributions to membrane current from the sodium, potassium and leakage currents, \(g_{Na}, g_k\) and \(g_l\) are the ionic conductances for sodium, potassium and all other ions respectively, \(E_{Na}\) and \(E_k\) are the equilibrium potentials for the sodium and potassium ions, and \(E_l\) is the potential at which the leakage current composed of all other ions is zero. The following equation governs the total change in membrane potential due to the total membrane current and the capacitance of the cell membrane, \(C_m\).

\[
\frac{dV}{dt} = \frac{-I_{ion}}{C_m}
\]  (2.4)

where,

\[
I_{ion} = I_{Na} + I_K + I_l
\]  (2.5)

Hodgkin and Huxley observed that the changes in membrane permeability appeared to depend on the membrane potential, and not on the membrane current. Their paper contains a detailed investigation into the nature of \(I_{Na}\), in which they concluded that the conductance, \(g_{Na}\) is a function of time and membrane potential. Using voltage clamp experiments to hold a cell at a single voltage, they observed that the conductance quickly increases before levelling off, and hypothesised that there were two mechanisms at work, an activation mechanism, and an inactivation mechanism, each with different time responses. Due to this complex nature of conductance, they proposed the following:

\[
g = m^a h^b g_{\text{max}}
\]  (2.6)

\[
\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m
\]  (2.7)

\[
\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h
\]  (2.8)

where \(g_{\text{max}}\) is a constant representing the maximal conductance, and \(\alpha\) and \(\beta\) are functions of membrane potential but not time. \(m\) represents an activation variable, and \(h\) represents an inactivation variable. These equations can also be written in the form;
2.1: SINGLE CELL MODELS

\[
\frac{dm}{dt} = \frac{1}{\tau_m} (m_\infty - m) \tag{2.9}
\]

\[
\frac{dh}{dt} = \frac{1}{\tau_h} (h_\infty - h) \tag{2.10}
\]

where;

\[
m_\infty = \frac{\alpha_m}{(\alpha_m + \beta_m)} \tag{2.11}
\]

\[
\tau_m = \frac{1}{(\alpha_m + \beta_m)} \tag{2.12}
\]

and;

\[
h_\infty = \frac{\alpha_h}{(\alpha_h + \beta_h)} \tag{2.13}
\]

\[
\tau_h = \frac{1}{(\alpha_h + \beta_h)} \tag{2.14}
\]

with all other variables as defined previously.

Later research into the formulation of the ion channels corresponding to each conductance has backed up this result, and these equations still form the basis for many electrical models used in the literature today [52–54].

2.1.2 A brief history of cardiac modelling

Following Hodgkin and Huxley’s influential work on the giant squid axon, the first step towards cardiac modelling was to apply these known equations to a cardiac cell as opposed to a nerve. This was first achieved by Dennis Noble in 1962 [55]. Numerous discoveries and refinements were published in response to an ever increasing depth of experimental data, including the discovery of calcium current in the heart [56], the discovery of additional components of the potassium currents [57] and the discovery of the sodium-calcium exchanger in cardiac muscle [58]. These discoveries were used to create the first working model of the action potential inside a ventricular cell by Beeler and Reuter in 1977 [58].
2.2: NUMERICAL METHODS

The Beeler-Reuter model was an important precursor to the Luo-Rudy model, first introduced in 1991, and subsequently revised in 1994 [59, 60]. The second iteration of the Luo-Rudy model was among the first models to include variations in all ionic concentrations, in addition to detailed calcium handling mechanics. At this point, the 3 currents proposed in the original Hodgkin-Huxley model had been extended to 15, and the revised formulation of $I_{ion}$ is given below, where Table 2.1 shows the given name of each channel current, along with corresponding ion or ions transferred.

$$I_{ion} = I_{Ca,b} + I_{CaL} + I_{p(Ca)} + I_{nat(Ca)} + I_{up} + I_{leak} + I_{rel}$$

$$+ I_{NaCa} + I_{Na} + I_{Na,b} + I_{NatK} + I_{Kp} + I_{K1} + I_{K}$$

Since these developments, a wide range of models for a variety of heterogeneous cells across the rabbit heart have been developed. The individual models used within this thesis are described in more detail in Section 3.1.

2.2 Numerical methods

Equations 2.9 and 2.10 deal with the rate of change of a single variable, with respect to the current value of that variable. They can therefore be represented as an Ordinary Differential Equation (ODE). Conversely, the approximation of tissue behaviour in higher dimensions involves the partial derivatives of several independent variables, and must be solved using a Partial Differential Equation (PDE).

In order to solve both the ODEs arising from the ion channel kinetics within the single cell models, and the Partial Differential Equations (PDEs) arising from the interactions of these cells on a larger scale, a number of mathematical techniques have been developed. While all techniques strive to attain the same explicit result, there are variations in complexity and accuracy between them. In general, more complex methods are more accurate, but require more time to computationally solve. Therefore, the correct choice of technique depends on the accuracy required for the problem, and is limited by the time available.
2.2: NUMERICAL METHODS

<table>
<thead>
<tr>
<th>Current</th>
<th>Ion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{Ca,b}$</td>
<td>$Ca^{2+}$</td>
<td>Background calcium leakage current</td>
</tr>
<tr>
<td>$I_{CaL}$</td>
<td>$Ca^{2+}$</td>
<td>L-type calcium current</td>
</tr>
<tr>
<td>$I_{p(Ca)}$</td>
<td>$Ca^{2+}$</td>
<td>Sarcolemmal calcium pump</td>
</tr>
<tr>
<td>$I_{nst(Ca)}$</td>
<td>$Na^+, K^+$</td>
<td>Non-specific calcium activated current</td>
</tr>
<tr>
<td>$I_{up}$</td>
<td>$Ca^{2+}$</td>
<td>Calcium uptake from myoplasm to SR</td>
</tr>
<tr>
<td>$I_{leak}$</td>
<td>$Ca^{2+}$</td>
<td>Calcium leak to myoplasm from SR</td>
</tr>
<tr>
<td>$I_{rel}$</td>
<td>$Ca^{2+}$</td>
<td>Calcium release to myoplasm from SR</td>
</tr>
<tr>
<td>$I_{NaCa}$</td>
<td>$Ca^{2+}, Na^+$</td>
<td>Sodium-calcium exchanger</td>
</tr>
<tr>
<td>$I_{Na}$</td>
<td>$Na^+$</td>
<td>Fast sodium current</td>
</tr>
<tr>
<td>$I_{Na,b}$</td>
<td>$Na^+$</td>
<td>Background sodium leakage current</td>
</tr>
<tr>
<td>$I_{NaK}$</td>
<td>$Na^+, K^+$</td>
<td>Sodium-potassium pump</td>
</tr>
<tr>
<td>$I_{Kp}$</td>
<td>$K^+$</td>
<td>Plateau potassium current</td>
</tr>
<tr>
<td>$I_{K1}$</td>
<td>$K^+$</td>
<td>Time-independent potassium current</td>
</tr>
<tr>
<td>$I_{K}$</td>
<td>$K^+$</td>
<td>Time dependent potassium current</td>
</tr>
</tbody>
</table>

Table 2.1: Shown are all currents used in the Luo-Rudy, and many subsequent models. This serves to illustrate the great complexity arising within the field of cardiac modelling, as opposed to the three currents used in the original Hodgkin-Huxley formulations, and provide an introduction to the majority of individual currents that make up the models used within this thesis.
2.2: NUMERICAL METHODS

2.2.1 First order Euler method

The forward Euler method is an approach used in numerical analysis to estimate the solution to an ordinary differential equation. As an explicit method, the Euler method calculates the state of the system at a future time given the state of the system at the current time. The state of the system can then be updated to equal the predicted state at time \((t + \Delta t)\), and the process can be computed continuously to find the evolution of the system over time. In general, then, for an explicit method, the state of a system at time \((t + \Delta t)\) is given as a function of the state of the system at the current time;

\[
S(t + \Delta t) = F(S(t))
\] (2.16)

The forward Euler method is an explicit method, and as such approximates the state of the system given only the previous system state. Given an initial time, \(t_0\), and an initial variable, \(y(t_0)\), the value of \(y(t_0 + h)\) can be approximated by the value of \(y(t_0)\) plus the slope of the function multiplied by the time-step, \(h\). Solving the first order Taylor expansion produces the following relationship, known as the first order forward Euler method;

\[
y_{t+h} = y_t + h \frac{dy}{dt}\bigg|_t
\] (2.17)

The first order Euler method is very simple and easy to compute, but requires a very small time step to approach a reasonable accuracy. Other numerical methods, such as higher order Euler methods, or the Runge-Kutta method provide higher accuracy solutions with a cost of increased computational time per timestep, however the almost instantaneous nature of certain cardiac channels enforces a need for small timesteps for any method. It has been shown that although small differences in accuracy between the different methods do exist, the errors are small enough to be inconsequential in the field of cardiac modelling with regards to action potential shape [61]. Due to its high speed, the Euler method therefore stands out as a suitable method to use for the calculation of the propagation of cardiac excitation.
2.2.2 The Monodomain equation

In addition to the ordinary differential equations that correspond to the ionic currents affecting membrane potential on a single cell level, the interaction of nearby cells through gap junctional coupling must be taken into account at a tissue level of simulation. These interactions can be described using the Bidomain equations [62], however, the solution of these equations is exceptionally computationally intensive, limiting the spatial and temporal resolutions at which they can be solved [63]. For this reason, a simple assumption may be applied to the Bidomain equations, that the anisotropy ratio between the intra- and extra-cellular spaces is equal. With this restriction, the Bidomain model reduces to the Monodomain model [64], where the change in membrane potential, $V$, with time, $t$, within a three dimensional anisotropic space is given by the following well known equation [65]

$$\frac{\partial V}{\partial t} = \nabla \cdot \left( D \nabla V \right) - \frac{I_{\text{ion}}}{C_m}$$  \hspace{1cm} (2.18)

where $I_{\text{ion}}$ is the total membrane current as described earlier, $C_m$ is the membrane capacitance, and $D$ is a tensor representing the diffusivity of electrical potential. This diffusion tensor can be represented as a 3x3 diagonal matrix with orthogonal values of diffusion along the leading diagonal. Given that diffusion has been shown to be dependent on cell orientation within tissue fibres [66], at each point within the tissue there maybe be constructed a local diffusion tensor, $D$. This may be written as

$$D = \begin{pmatrix} D_\parallel & 0 & 0 \\ 0 & D_{\perp 1} & 0 \\ 0 & 0 & D_{\perp 2} \end{pmatrix}$$  \hspace{1cm} (2.19)

where $D_\parallel$, $D_{\perp 1}$ and $D_{\perp 2}$ are the coefficients of diffusivity in directions parallel to the tissue fibres, perpendicular to the tissue fibres and parallel to the plane of a tissue fibre sheet, and perpendicular to both the tissue fibres and the plane of the tissue fibre sheet respectively, and may be determined experimentally from measurements of conduction velocity in each of the three directions relative to a fibre. In order to translate from these
local diffusion parameters to a globally defined diffusion tensor, $D$, it is necessary to know the eigenvectors corresponding to the direction of the tissue fibres at each point within the organ. These eigenvectors can be determined experimentally, as described in Section 2.3.1. To translate from the locally defined $D$ to a globally defined $D$, the following relationship is used

$$D = ADA^T$$

(2.20)

where $A$ is a matrix made up of the determined eigenvectors, given by

$$A = \begin{pmatrix} e_\parallel & 0 & 0 \\ 0 & e_{\perp 1} & 0 \\ 0 & 0 & e_{\perp 2} \end{pmatrix}$$

(2.21)

where $e_\parallel$, $e_{\perp 1}$ and $e_{\perp 2}$ are eigenvectors representing directions along the fibre axis, along the sheet plane but perpendicular to the tissue fibres, and perpendicular to both the tissue fibres and the plane of the tissue fibre sheet.

### 2.2.3 Finite difference method

A finite difference method is a type of numerical method to approximate the solution of a spatially dependent partial differential equation, such as Equation 2.18. In order to approximate a solution to such an equation over an $N$-dimensional space, the space must be divided into a number of discrete nodes. For simplicity, let us consider the 1D case with nodes separated by a spacing of $\Delta x$, as shown in Figure 2.2.

To approximate the evolution of the system through time, the first order forward Euler method was used. To approximate the solution in space, the centred second difference was used. The membrane potential of a cell, $x$, at a time $t + \Delta t$ is then given by

$$V_{x}^{t+\Delta t} = V_{x}^{t} + \Delta t \frac{D}{(\Delta x)^2} (V_{x-\Delta x}^{t} + V_{x+\Delta x}^{t} - 2V_{x}^{t})$$

(2.22)
2.3 Experimental and clinical methods

In order to both obtain data to accurately model properties of the heart, and validate the results of these models against observed results, a number of experimental and clinical methods are used. This section provides a brief description of the experimental techniques referred to throughout this thesis.

2.3.1 Diffusion tensor magnetic resonance imaging

As previously covered in Section 1.2, the orientation of myocyte fibres is important to the propagation of excitation waves within the heart. Diffusion Tensor Magnetic Resonance Imaging (DTMRI) allows us to quantitatively study the orientation of fibres within the heart [68]. DTMRI is a non-invasive medical technique for detailed, in vivo observations of internal structures and the associated local characteristics of water diffusion.

DTMRI segments a 3D image into small 3D elements known as voxels. Each voxel has a number of paired parameters, corresponding to a direction of diffusion and a rate of diffusion in that direction. In general, water diffuses more rapidly in a...
direction aligned with the internal structure, allowing DTMRI to predict detailed three-dimensional maps of fibre orientation within a given tissue.

Fibre orientation data from DTMRI has been found to accurately reproduce histologically obtained fibre orientations [69]. A quantitative comparison of DTMRI determined fibre architecture to that from histology can be found here [70]. However, as DTMRI is much more time-efficient and has no effect upon the tissue structure, it is an excellent method for reproducing the detailed fibre structures required for computational modelling [71].

2.3.2 The Electrocardiogram

While the differences in potential within each individual cell throughout the evolution of an AP are small, the heart is comprised of a huge number of such cells. In order to better understand the workings of the cardiac muscle, methods have been devised to record and interpret the overall changes in electrical activity within the heart. One of these methods is the Electrocardiogram, or ECG.

The ECG was originally developed in the early 1900s by Willem Einthoven, work for which he was awarded the 1924 Nobel Prize in Medicine [72]. Einthoven’s ECG used a string galvanometer of his own design to record the potential difference between a series of electrodes. These early electrodes took the form of baths of salt solution into which the patient’s limbs could be immersed. Three electrodes were used, one on each arm and one on the patient’s left leg. These electrodes record small electrical changes in the skin caused by excitation waves travelling across the heart [73]. The ECG output provides a non-invasive method to study the electrical activity occurring within a patient’s heart.

Figure 2.3 shows a schematic representation of a healthy mammalian ECG. The morphology of the ECG is dependent on the activation sequence of the heart. The P wave corresponds to the depolarisation, and consequently, contraction of the atria. The QRS complex represents the depolarisation and contraction of the ventricles. The
2.3: EXPERIMENTAL AND CLINICAL METHODS

Figure 2.3: Schematic representation of a healthy ECG, showing the P wave, QRS complex and T waves, corresponding to atrial depolarisation, ventricular depolarisation and ventricular repolarisation respectively.

PR interval therefore represents the time taken for impulses to travel from the SAN, through the atria, and on to the ventricles via the AVN and PF network. The duration of the QRS complex represents the time taken for the entire ventricle to activate after the impulse first leaves the PF. The T wave represents the repolarisation of the ventricles as they relax and return to their resting state. The QT interval therefore represents the total time between ventricular activation and subsequent relaxation. QT interval can be measured as the time between the Q wave and the peak of the T wave ($QT_p$), or as the time between the Q wave and the end of the T wave ($QT_E$). The PP interval is a measure of the distance between two successive P waves, and represents the heart rate. The RR interval is measured similarly, and under healthy conditions will be equal to the PP interval.

2.3.3 Stimulation Procedures

The majority of cardiac myocytes are non-autorhythmic cells that naturally rest at a membrane potential under which the total magnitude of all currents through the cel-
lular membrane is zero [12]. In order to investigate the AP characteristics of a single excitable cell, a stimulus must be applied to raise the membrane potential above the diastolic threshold [12, 74]. Single cell models were stimulated by applying a rectangular supra-threshold pulse to the cell for 2ms, at a frequency of 3Hz, following the protocol laid out by a number of experimental [75–79] and simulation studies [80].

2.3.4 Parameters of cellular action potentials

In order to quantify the electrical activity within single cardiac cells, a number of standard parameters based on AP morphology are used. The main parameters used to describe an AP within cardiac cells are described below.

**Maximum Diastolic Potential**

- The Maximum Diastolic Potential, or MDP of a cell is the most negative potential reached by the cell during phase 4 of an AP. In many cells, the MDP is roughly equivalent to the equilibrium potential at which there is no net change in membrane potential due to the effects of ionic currents [81]. For the majority of cardiac cells, MDP sits at around -80mV, although individual cell types express a range of different values.

**Maximum Upstroke Velocity**

- The maximum upstroke velocity, or \( \frac{dV}{dt}_{\text{max}} \), is simply the highest rate of change in membrane potential during the evolution of an AP. \( \frac{dV}{dt}_{\text{max}} \) greatly affects the conduction velocity in a given area, and tends to be largest in fast conductive tissues such as the PF network.

**Action Potential Amplitude**

- The Action Potential Amplitude, or APA is a measure of the magnitude of the upstroke during phase 0 of an AP. The APA is calculated as the maximal positive potential reached during the AP minus the MDP.
2.3: EXPERIMENTAL AND CLINICAL METHODS

Action Potential Duration

- The Action Potential Duration, or APD, is a measure of the time taken for a cell to repolarise during phase 3 of an AP. APD is the total time taken from the initial upstroke for the membrane potential to fall by a given percentage of the APA. This percentage is noted as a subscript, for example $APD_{90}$ is the time taken for the membrane potential to fall by 90%, to 10% of the difference between the maximal value and the $MDP$.

Basic Cycle Length

- The Basic Cycle Length, BCL, is a measure of the regularity of spontaneously generated APs within autorhythmic tissue. The BCL is simply measured as the time between spontaneously generated APs. When considering the heart as a whole through the analysis of an ECG, the BCL of the SAN is represented by the PP interval.

A summary of the above cellular parameters is shown in Figure 2.4. Together, these parameters allow analysis of the AP. Each of these parameters can greatly influence the macroscopic electrical properties of cellular tissue. The differences in cellular parameters within different cardiac tissues lead to the widely different excitable behaviour expressed within different regions of the heart, and are discussed in more detail in Section 3.2.

2.3.5 Activation Sequence

In addition to the ECG simulations described above, this thesis contains investigation into another whole-heart characteristic, termed the activation sequence. While ECG data provides a readily obtainable, non-invasive view of the electronic activity occurring within the heart, direct measurements of activation sequence provide a much clearer view into the progression of electrical waves throughout cardiac tissue. However, these measurements come at the expense of added complexity, taking as many as 200 electrodes to reconstruct a viable 3D activation sequence [82]. Throughout this
thesis, the time of activation at a given cell was given as the time (in ms), between the application of a stimulus, and the time at which the local current density within the given cell was at a maximum, following procedure laid out by experiment [83]. In the case of simulations with an endogenous self pacing structure, the time of application of a stimulus was replaced by the time at which activation of the first non-autorhythmic cell occurred. In the case of activation sequences related to a specific area, for example the ventricles, the time application of a stimulus was replaced by the time at which activation of the first non-autorhythmic cell within that area occurred.
3

A review of rabbit single cellular models

The mammalian heart is a largely heterogenous structure, on both a structural and functional level [84]. In order to accurately simulate the characteristics of the whole heart, the individual characteristics of each area of cardiac tissue must be studied. This section details the salient differences in channel kinetics and cellular parameters between the different cell types that make up the rabbit heart, along with an investigation into current models to describe this behaviour, and the effects of this ionic behaviour on the cellular parameters described in Section 2.3.4.

3.1 Review of cellular models

As outlined in Section 1.3.2, rabbit hearts provide a useful tool for the study of a number of life threatening cardiac conditions. As an animal for which there is a wealth of experimental data available on a variety of different cellular mechanisms, the rabbit has been a source of extensive study within the cardiac modelling community. This section outlines a number of well known models for numerous areas of the rabbit heart, introduces those used for the duration of this thesis, and justifies their choice by comparison to existing experimental data.
3.1: REVIEW OF CELLULAR MODELS

3.1.1 Methods

In all cases, the relevant models outlined for use within this thesis were re-written from a variety of different languages and styles into generic C++ header files. The advantage of this distributed style is that changes can be made to any individual cell type independent of a larger heterogeneous model. The kinetics describing a given cell can therefore be changed simply by picking and choosing the relevant header files from a repository of different cell types, even across different species (See Section 4.3). In addition, separating the component cellular kinetics into different files allowed their inclusion within later models of the whole heart, independent of the structure, geometry, heterogeneity and even dimensionality of later models (See Sections 4.1.4, 5.2.) All simulations were carried out at rabbit body temperature. Membrane capacitance differs greatly between different cell types, and is related to cell volume [85]. Experimentally reported values for the membrane capacitance were collected for each cell type, including areas of the SAN [86], AM [87], AVN [88, 89], PF [9], and Ventricular cells [90, 91]. These reported values are summarised in Table 3.1. APs in non-autorhythmic cells were elicited following the stimulation protocols laid out in Section 2.3.3, unless stated otherwise.

3.1.2 The Sino-atrial node

First discovered in 1907 [92], the SAN is one of the few autorhythmic areas of the heart [93]. As the area that generates action potentials with the shortest cycle length, it acts as the initiator of the heartbeat.

The inherent ability of the SAN to generate action potentials was described as early as the 1940s [94], and recognised to be due to an inward ionic flux that develops immediately post-repolarisation, leading to a slow diastolic depolarisation which triggers an action potential once a threshold potential is reached [95]. The contribution of relevant ion channels to the rise of diastolic depolarisation has been laid out as the absence or decay of a number of outward currents, alongside an increase in various inward
Table 3.1: Differences in cell membrane capacitance for a variety of cells throughout the rabbit heart.

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Membrane capacitance</th>
</tr>
</thead>
<tbody>
<tr>
<td>SANC</td>
<td>20(pF)</td>
</tr>
<tr>
<td>SANP</td>
<td>65(pF)</td>
</tr>
<tr>
<td>AM</td>
<td>50(pF)</td>
</tr>
<tr>
<td>AN</td>
<td>40(pF)</td>
</tr>
<tr>
<td>N</td>
<td>29(pF)</td>
</tr>
<tr>
<td>NH</td>
<td>29(pF)</td>
</tr>
<tr>
<td>PF</td>
<td>66(pF)</td>
</tr>
<tr>
<td>ENDO</td>
<td>88(pF)</td>
</tr>
<tr>
<td>M</td>
<td>88(pF)</td>
</tr>
<tr>
<td>EPI</td>
<td>88(pF)</td>
</tr>
</tbody>
</table>

A number of biophysically detailed models describing this behaviour, and thus the self pacemaking nature of the rabbit SAN have been developed, starting with the early Yanagihara et al. [97] model, followed by a number of other early models [98], and continuing with the Demir model in 1994 [99], Dokos model in 1996 [100].

While some earlier studies have modelled the SAN as a heterogeneous structure, a marked difference in a number of electrophysiological characteristics within the SAN has been reported, under both normal conditions [101–103] and after pharmacological intervention [104,105]. Recent studies have divided the SAN into two areas, the central SAN region (SAN-C), and the peripheral SAN region (SAN-P), beginning with the Zhang model in 2000 [86], followed by the Kurata models in 2002, 2008 [106, 107]. While the Kurata models are the most recent, they are based upon the Zhang models, and simulations within this thesis use the earlier Zhang models for SAN-C and SAN-P cells in all cases.
The Zhang model simulates SAN action potentials consistent with those recorded by experimental data. In addition, the model responds correctly under the influence of a number of channel blocking drugs [86]. Furthermore, the model correctly describes the functional heterogeneity arising from the centre to the peripheral regions of the SAN. The membrane potential of an isolated SAN-C cell as calculated by the Zhang model is shown in Figure 3.1, with the membrane potential of an isolated SAN-P cell shown in Figure 3.2, along with an experimentally recorded APs in both cases.

3.1.3 Atrial muscle

Situated at the top of the heart, the atrial muscle provides the contractile force necessary to pump blood into the ventricles. The atrial muscle is the first contractile tissue to depolarise following the initiation of the excitation sequence at the SAN [108].

From an electrophysiological stand point, atrial tissue is characterised by a moderately fast activation period with high $dV/dt_{\text{max}}$, corresponding to a moderate contribution to $I_{\text{ion}}$ from $I_{Na}$, and a short APD, corresponding to large repolarising potassium currents [109, 110].

Several cellular models of the rabbit atria have been developed, including the Hilgemann and Noble model in 1987 [111], and followed by the Lindblad model in 1996 [112]. All simulations of atrial activity within this thesis use the more recent Aslanidi models, themselves based on the earlier Lindblad formulations [113]. The membrane potential of a rabbit left atrial myocyte as calculated from the Aslanidi model is shown in Figure 3.3, along with an experimentally recorded AP.

3.1.4 Atrio ventricular node and His bundle

The AVN is a specialised area of conductive tissue, providing the only means through which electrical impulses can travel between the atria and ventricles, [115]. The AVN serves to slow the conduction of an AP between atrial and ventricular muscle, allowing the completion of atrial contraction prior to ventricular depolarisations, acting as a
3.1: REVIEW OF CELLULAR MODELS

Figure 3.1: Comparison of the evolution of a membrane potential within an autorhythmic central SAN cell in both experiment and model. (i) shows simulated membrane potential using the Zhang model. (ii) shows the membrane potential as recorded experimentally [102]. In both cases no stimulus was applied, but slow diastolic depolarisation leads to elevation of membrane potential above a threshold, causing subsequent depolarisation.

Figure 3.2: Comparison of the evolution of membrane potential within an autorhythmic peripheral SAN cell in both experiment and model. (i) shows simulated membrane potential using the Zhang model. (ii) shows the membrane potential as recorded experimentally [102]. As with the SAN-C cell, no stimulus was applied in either case.
3.1: REVIEW OF CELLULAR MODELS

Figure 3.3: Comparison of the evolution of membrane potential within an atrial myocyte in both experiment and model. (i) shows the membrane potential as simulated by the Aslanidi model, and (ii) shows an experimentally recorded AP [114]
defence against the propagation to the ventricles of dangerous arrhythmias arising in the atria, and preventing premature depolarisations of the ventricle tissue [116, 117].

AVN tissue is a complex combination of a number of electrophysiologically distinct tissues, including Nodal (N), Atrial-Nodal (AN), and Nodal-His (NH) tissues [118, 119]. The original segregation between these areas was not very strict, with N cells making up the zone with the slowest conduction velocity, the AN zone acting as a transitional region between the atrial muscle and the N zone, and the NH zone as a transitional region between the N cells and the His bundle [120].

The N cells that make up the so-called "slow pathway" of conduction throughout the AVN are particularly electrophysiologically interesting [121]. Much like the SAN, N Cells are capable of generating autorhythmic APs [122, 123]. These APs are generated with a much lower frequency than within the SAN, and are therefore overridden under normal conditions. This self pacing nature plays a large role under certain disease conditions, and the AVN is capable of pacing the ventricles in the absence of a SAN-generated AP [124, 125].

Only one comprehensive set of models has been developed to describe the action potential morphology within each distinct AVN region, by Inada et al. in 2009 [123]. The Inada models for AN, N and NH cells were used throughout this thesis. Membrane potentials for each of these cells, along with experimentally recorded APs are shown in Figures 3.4, 3.5 and 3.6.

### 3.1.5 Ventricular muscle and Purkinje fibres

The muscular component of the mammalian ventricular wall is a highly heterogeneous volume comprising of up to three cell types, Endocardial myocyte (Endo) cells, which make up the internal ventricular surface, Epicardial myocyte (Epi) cells, which make up the outer surface, with a layer of Midmyocardial (M) cells inbetween [127]. While M cells are not present in all species, there is evidence for the existence of M cells within the rabbit ventricle [76]. There are marked electrical differences between each
Figure 3.4: Comparison of the evolution of membrane potential within an autorhythmic AVN cell in both experiment and model. No stimulus was applied, but slow diastolic depolarisation leads to elevation of membrane potential above a threshold, causing subsequent depolarisation. (i) Single N cell AP as simulated by the Inada model, and (ii), as experimentally recorded AP from an N cell [122]

Figure 3.5: Comparison of the evolution of membrane potential within an AN cell in both simulation and model. (i) Single AN cell AP as simulated by the Inada model, and (ii), as experimentally recorded membrane potential from an AN cell [75]. In both cases, a stimulus was applied for 3ms to invoke an AP.
Figure 3.6: Comparison of the evolution of membrane potential within an NH cell in both simulation and model. (i) Single NH cell AP as simulated by the Inada model. (ii) Experimentally recorded membrane potential from an NH cell [126]. In both cases, a stimulus was applied for 3ms to invoke an AP.
of these three cell types [128, 129]. These differences lead to a unique action potential profile for each cell type, and can cause the tissue as a whole to be susceptible to a number of arrhythmogenic effects, as shown by Antzelevitch et al. [130].

The key features of ventricular action potentials are a fast activation corresponding to high $dV/dt_{max}$, and a lengthy APD. These characteristics allow the fast propagation of electrical impulses throughout the ventricular wall, while ensuring that the entire muscle is contracting at the same time. In addition, prolonged APD has been shown to lessen the risk of reentrant arrhythmias [131].

In addition to the three types of contractile cell present within the ventricle, there exists a specialised fibre network known as the Purkinje system. Made up of PF cells, the Purkinje system constitutes a key component of the cardiac conduction system, facilitating rapid, synchronised AP propagation throughout the entirety of the ventricular muscle [79].

Purkinje cells are characterised by an extremely high $dV/dt_{max}$ allowing very fast propagation of an AP throughout the entire PF network, which ensures that an AP arrives quickly at multiple Purkinje-ventricular junction sites [132].

There are numerous models available to describe the electrical activity within the rabbit ventricle, including the Puglisi models [133], Shannon models [134] and Aslanidi models [91]. The Aslanidi cellular models for the Endo, M, Epi and PF cells were used within this thesis. Figure 3.7 shows the AP for a PF cell, again comparing experiment to model, and Figure 3.8 shows APs for the Endo, M and Epi cell types from both experiment and model.

### 3.2 A comparison between heterogeneous cell types

The single cell results obtained, and articles reviewed during this section have shown incredible heterogeneity between the different cells that make up the cardiac conduction system within a rabbit. In addition to qualitatively studying the morphological differences in AP generation between different areas of the heart, there exist qualita-
3.2: A COMPARISON BETWEEN HETEROGENEOUS CELL TYPES

Figure 3.7: Evolution of membrane potential within a PF cell. (i) shows an AP as simulated by the Aslanidi model. (ii) shows an experimentally recorded AP from a rabbit PF cell [79]. In both cases, a stimulus was applied for 3ms to invoke an AP.

Figure 3.8: Evolution of membrane potential within a Epi, M and Endo cells. (i) shows a collection of APs as simulated by the Aslanidi model. (ii) shows experimentally recorded APs from corresponding rabbit ventricular muscle cells [76]. In all cases, a stimulus was applied for 3ms to invoke an AP.
3.2: A COMPARISON BETWEEN HETEROGENEOUS CELL TYPES

tive differences in a number of cellular parameters.

**Action Potential Duration**

Differences in APD are especially important when considering the generation of a number of cardiac phenomena, including the manifestation of dangerous arrhythmias [130, 135, 136]. In general the APD of cells within the heart shows a marked increase within ventricular and Purkinje cells. These results are summarised in Figure 3.9 (i), and can be seen to agree with those measured by experiment [75, 78, 122, 137–154].

**Maximum upstroke velocity**

Unlike APD, the differences in $dV/dt_{max}$ are large throughout the rabbit heart. Self pacemaking areas such as the SAN and N cells have a reduced $dV/dt_{max}$ due to a slow diastolic depolarisation, while areas requiring fast conduction of an AP have a substantially higher $dV/dt_{max}$. In general, SAN, N, AN and NH cells have a very small $dV/dt_{max}$, with muscular tissues such as the AM, Endo, Epi and M cells having large $dV/dt_{max}$, and fast conductive tissue such as the PF having the largest $dV/dt_{max}$. These results are summarised in Figure 3.9 (ii), and can be seen to agree with those measured by experiment [75, 76, 102, 122, 137, 138, 142–144, 146, 147, 149–161].

**Maximum diastolic potential**

The MDP for each single cell model was calculated. While most cells within the rabbit heart have an MDP of roughly $-85mV$, there is a variation from around $-60mV$ in the central SAN, to $-85mV$ in the Purkinje and ventricle cells. The calculated MDP for each cell type is summarised in Figure 3.9 (iii), and can be seen to agree with those measured by experiment [75, 76, 102, 122, 137–152, 154–161].
3.3: CONCLUSIONS

**Action potential amplitude**

As with the MDP, the APA for each single cell model was calculated. The calculated APA for each cell type is summarised in Figure 3.9 (iv), and can be seen to agree with those measured by experiment [76, 102, 122, 137, 138, 141–147, 149–152, 154–157].

**Basic cycle length of autorhythmic tissue**

In order to investigate the nature of the heart’s ability to generate APs with a lack of external stimuli, it is interesting to view the BCL of autorhythmic tissues. Figure 3.9 (v) shows a summary of the BCL from the three different autorhythmic cells in the rabbit heart. The BCL of the SAN is seen to be substantially lower than its counterparts, reinforcing its role as the leading pacemaker of the heart. All results shown agree with measured experimental data [88, 102, 122, 158, 159, 161].

3.3 Conclusions

This section provides a review of the wide range of models of single cell AP behaviour within a number of different rabbit cardiac myocytes. Section 3.2 clearly shows the electrophysiological differences between cells from different areas of the heart. The ability to generate APs within the SAN and AVN areas of the heart was compared, and the faster frequency of the SAN linked to its role as the leading pacemaker site. The differences in AP profile within the different muscular tissues were compared, with a focus on the heterogeneity found within the ventricular free wall. The unique electrophysiological properties of the Purkinje network were linked to its function as a conductive pathway, with high $dV/dt_{max}$ allowing fast transmission of impulses from the AVN throughout the entirety of the ventricular tissue. Importantly, all single cell models for further examination within this thesis are shown to closely reproduce experimentally obtained AP characteristics. Unfortunately, for a number of cells the experimental data did not take into account regional differences within similar tissue. These
Figure 3.9: A review of the differences in AP parameters between different cell types as simulated by the single cell models. (i) Shows $APD_{90}$ as calculated by the single cell models. (ii) Shows $dV/dt_{\text{max}}$. (iii) Shows the $MDP$. (iv) Shows the $APA$. (v) Shows the $BCL$ for auto-rhythmic cell types. In each case, the solid bars represent the simulated results with the small circles representing corresponding experimental data.
3.3: CONCLUSIONS

models can be expected to provide a good base from which to build higher dimension, heterogeneous models of the whole rabbit heart.
4

Development of a two dimensional whole rabbit heart

In this chapter, the creation of a 2D model to describe the whole rabbit heart is discussed. The model contains a number of cell types covering the initiation of the AP at the pacemaking site within the SAN, propagation through the atrial muscle, the conductive tissue made up of the AVN and PF, and finally the ventricular muscle. The model takes the form of a 2D lattice of individual points, each corresponding to a small area of equipotential tissue. Utilising the geometry created below, each area of tissue is set with electrophysiological properties described by one of the distinct cellular models introduced in Chapter 3.

In addition to reproducing accurate ECG data when compared to experiment, the model faithfully reproduces activation sequences recorded from healthy rabbit hearts. While limited in some ways by its 2D nature, it provides a fast and accurate method to investigate the nature of cardiac excitation.

4.1 Creation of a two dimensional geometry

The 2D model required an existing structural geometry to govern the relative positions of cells to each other. This section details the creation of such a geometry from an ex-
perimentially obtained slice of guinea pig cardiac tissue. Guinea pigs have been shown
to have morphologically similar hearts to rabbits [42, 162], and are thus a sensible
substitute in the absence of rabbit data.

4.1.1 Histological geometry and initial segmentation

A two dimensional slice of heart tissue was provided by Dr Halina Dobrzynski [163].
It was prepared using the following method. A heart was frozen and a tissue sec-
tion was cut through the long axis. This tissue section was then stained using Masson’s
trichrome, a commonly used three colour staining protocol [164, 165]. Masson’s
trichrome stains cardiac myocytes purple, while the connective tissue is stained blue.
This image was captured using a light microscope, and is shown in Figure 4.1.

Before the initial segmentation, the image was manually cleaned up using the GNU
Image Manipulation Program (GIMP) [166]. For simplicity, the papillary muscles
were removed, along with the aorta and any other satellite non-conducting tissue. Ar-
eas of tissue with similar colour principles (hue, shade, value) were selected and set
to blocks of single colour. In order to provide a pacemaking impulse, an area of right
atrial tissue was designated as SAN cells. Due to a lack of detailed SAN geometry
seen within the 2D slice, a gradient model was not used. This initial segmentation is
shown in Figure 4.2. As large variations in colour principle even within areas of the
same cell type cause a large volume of noise, this was cleaned up manually, leading to
an initial geometry shown in Figure 4.3. In all cases, GIMP was used to edit and clean
the geometry, and a built in GIMP function to threshold areas based on selected colour
principles was used to separate the tissues.

4.1.2 Ventricular segmentation and the Purkinje network

The ventricles were segmented into three different areas corresponding to Endo, Epi
and M cell types. A binary erosion algorithm was developed to calculate the distance
4.1: CREATION OF A TWO DIMENSIONAL GEOMETRY

Figure 4.1: 2D image of a heart stained with Masson’s trichrome and sliced through the long axis. Cardiac myocytes are stained purple, while the connective tissue is stained blue. [163]
Figure 4.2: 2D image of a heart after initial computational segmentation. Areas of the heart were selected and all connected regions with similar colour principles were set to a single colour. SAN tissue is coloured magenta, atrial muscle is coloured green, AVN tissue is shown in blue, and ventricular muscle is shown in red.
Figure 4.3: 2D image of a heart after manual segmentation. Areas of the heart were segmented automatically, then manually filled in. SAN tissue is coloured magenta, atrial muscle is coloured green, AVN tissue is shown in blue, and ventricular muscle is shown in red.
of each pixel within the ventricle from the ventricular wall. This algorithm iterates over
the dataset multiple times, and at each pass removes the outermost layer of ventricular
tissue, tagging each removed pixel with the index of the iteration during which it was
removed. The result is a 2D map with each pixel numbered by the distance in pixels
from that pixel to the outside of the ventricle. These distances were separated into
bands of pixels to give easily differentiated contours, and the resulting contour map is
shown in Figure 4.4 (i).

Given the distance in pixels between each cell to the edge of the ventricle, and the
thickness of the ventricular wall at each point, this observed erosion map was then
used to approximate a 2:2:1 ratio of Endo:Epi:M cells, similar to that reported by
experiment [167]. The resulting image was then cleaned up manually to give a smooth
division between the three cell types. The resulting ventricular segmentation is shown
in Figure 4.4 (ii).

A Purkinje network was added by assuming every cell on the internal ventricle
walls was a PF cell. In order to correctly simulate the realistic geometry of a 3D
Purkinje network, the fibres within the ventricular septum were double layered, causing
the impulse to travel down towards the apex before travelling back up and into the
ventricular tissue. While this is not a perfect replication of the action of a Purkinje
network within three dimensions, the distributed, 3D nature of the Purkinje network
makes a 2D approximation necessary. PF cells were electrically uncoupled from the
ventricles, and insertion points were added at equally spaced intervals along the fibre
to allow conduction.

4.1.3 Atrial tissue and the atrio-ventricular node

The AVN plays an important role in determining the activation time sequence of car-
diac excitation waves, in addition to being the one pathway facilitating the conduction
of an AP from the atria to the ventricles [115]. Therefore, an AVN structure was nec-
essary to reproduce correct electrical activation within the heart. However, as the AVN
in the sectioned heart lay perpendicular to the plane in which the slice was cut, no detailed AVN geometry could be seen. In order to replicate the effects of an AVN within the slice, an AVN structure complete with both a fast and slow pathway was created, measuring 1mm by 3mm as experimentally reported by Li et al [168].

The AVN node was inserted where the interatrial septum meets the ventricular tissue. The top of this AVN is electrically coupled to the bottom of the atrial muscle, and the bottom of the AVN pathway is electrically coupled to the top of the Purkinje network, as seen in Figure 4.5. To allow the full model to be visualised more easily, the AVN was moved to the side of the heart while the electrical coupling remained. The completed two dimensional geometry is shown in Figure 4.6.

4.1.4 Development of the 2D framework

A numerical algorithm was developed using the RMagick package to convert this image into a 2D lattice array containing the colour principles of each pixel. RMagick is an interface between Ruby, a high level, open source scripting language, and ImageMagick, an image editing software suite [169–171]. RMagick provides a number of simple functions to carry out tasks such as resizing an image, converting between different formats, and obtaining detailed information about an image [169]. In this case, the 2D bitmap image in Figure 4.6 was converted into a 2D integer array for use as the base geometry for 2D simulations.

The resolution of the final geometry was 0.03mm in both the x and y directions, with a total size of 600 by 590 pixels. Each pixel was assumed to be an area of equipotential cellular tissue. C++ was used to read in the 2D integer array and populate it with heterogeneous cellular tissue. The individual cell models used to simulate the ion channel kinetics within each region of the heart are summarised in Table 4.1.
### Table 4.1: Summary of the individual cell models used to simulate electrical activity in each area of the heart within the 2D model.

<table>
<thead>
<tr>
<th>Region of heart</th>
<th>Model name and reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SANC</td>
<td>Zhang SAN centre model [86]</td>
</tr>
<tr>
<td>AM</td>
<td>Aslanidi left atrial model [113]</td>
</tr>
<tr>
<td>AN</td>
<td>Inada atrial-nodal cell model [123]</td>
</tr>
<tr>
<td>N</td>
<td>Inada nodal cell model [123]</td>
</tr>
<tr>
<td>PF</td>
<td>Aslanidi Purkinje fibre model [91]</td>
</tr>
<tr>
<td>ENDO – Left</td>
<td>Aslanidi Endocardial cell model [91]</td>
</tr>
<tr>
<td>M – Left</td>
<td>Aslanidi Mid-myocardial cell model [91]</td>
</tr>
<tr>
<td>EPI – Left</td>
<td>Aslanidi Epicardial cell model [91]</td>
</tr>
</tbody>
</table>
Figure 4.4: (i) shows a contour map created by a binary erode algorithm applied to the ventricular tissue in the 2D geometry. Sections of tissue were removed from the dataset iteratively, creating a map with each pixel coloured by the distance from that pixel to the outside of the ventricular wall. (ii) shows the result of using this map to approximate a 2:1:2 ratio of Endo:M:Epi cells.
Figure 4.5: Creation of a schematic 2D atrio ventricular node based on experimentally obtained parameters. The AVN is shown connecting the atrial tissue to the PF network. All cell types are coloured accordingly.
Figure 4.6: 2D image of a heart after ventricle segmentation, PF addition and AVN addition. While the AVN remains electrically coupled as in Figure 4.5, it was moved to the right of the heart to facilitate visualisation. Different cell types are identified by the colours shown.
4.2 Results

Simulations were run using a single core of an AMD Athlon 64 X2 5000+ Processor. The 2D monodomain equation was solved with a time step of $t = 0.05 ms$. The atrial tissue at the base of the heart was modelled using the RA current kinetics described in Section 3.1.3. Due to the aforementioned lack of detail within the SAN, SAN tissue was modelled solely as SANC tissue, as described in Section 3.1.2. The AVN was split into a fast pathway described by the cell kinetics for AN cells, and a slow pathway described by the cell kinetics for N cells, both described in Section 3.1.4. The Purkinje network, along with all three ventricular cell types were described using the cellular kinetics described in Section 3.1.5. As propagation was initiated by the endogenous SAN, no applied stimulus was required. Values used for membrane capacitance, $C_m$, were identical to those described in Section 3.1.1.

4.2.1 Conduction velocities within the 2D model

In order to determine valid choices for the diffusion coefficients, $D$, within the 2D heart, it was necessary to reproduce experimentally observed conduction velocities (CVs) within the 2D sheet. Measuring accurate CVs within complex tissue is difficult without extensive investigation into the exact direction of conduction at each point [172]. Therefore, rectangular sheets of each non autorhythmic cell type were created, and a plane wave was initiated by the application of a supra-threshold pulse to one end of the sheet. Values for $D$ were chosen to reproduce experimentally observed CVs in each area of the heart. The computed CVs are shown in Figure 4.7, along with reported CVs from a variety of sources for cell types including the atria, [173–176], AVN, [123,175,177,178], Purkinje network [179,180] and ventricular tissue [176,180,181].

In all cases, the computed CVs are seen to closely reproduce the average reported result. The average CV from the collected atrial data was $60 cm/s$, with the simulated atrial CV within the 2D model at $55 cm/s$. Within the AVN, AN cells have a simulated CV of $16 cm/s$ as compared to an average CV from experiment of $11 cm/s$. Within the
4.2: RESULTS

Figure 4.7: Conduction velocities for a variety of cells as simulated within the 2D framework, along with relevant experimentally recorded data. All velocities are given in cm/s, and a close correlation between experiment and simulation can be seen.

PF network, the average experimentally recorded CV was $111\text{cm/s}$, with the simulated CV at $117\text{cm/s}$. Average CVs within the ventricular tissue as measured by experiment were $65\text{cm/s}$, with Endo, Epi and M cells having simulated CVs of $61\text{cm/s}$, $59\text{cm/s}$ and $60\text{cm/s}$ respectively.

4.2.2 Propagation through a 2D whole heart

Firstly, the simulation was allowed to settle to eliminate any transient effects caused by initial conditions, and the relevant parameters at rest were recorded. The simulation was then restarted and allowed to evolve, and the cellular potentials for full ten beats were recorded. The simulation continuously produced excitation patterns with a basic cycle length of $330\text{ms}$, within the range expected for a rabbit heart [182]. Snapshots of the evolution of the excitation waves leading to a single beat are shown in Figures 4.8 and 4.9.

The simulated evolution shows the qualitatively expected activation sequence for a rabbit heart. An AP is initiated within the SAN and travels out across the atrial mus-
cle. Upon entering the AVN, the conduction velocity is reduced, slowing the impulse such that the atria can complete excitation and contraction before the wavefront enters the ventricular muscle. Following transmission through the AVN, the excitation wave is quickly transmitted down the Purkinje network and into the ventricles, spreading throughout the ventricular muscle and completing the activation sequence.

4.2.3 Electrocardiogram recordings

The ECG is effectively a summation of the action potentials from each individual area of the heart [183]. It has been shown that a ‘pseudo-ECG’ corresponding to normal ECG parameters can be calculated by placing a hypothetical electrode at a point in space outside simulated cardiac tissue, and calculating the potential through it [184]. For a given electrode at a position \((x',y',z')\), the extracellular unipolar potential, \(\Phi_e\), is given by the membrane potentials, \(V\), using

\[
\Phi_e(x',y',z') = c \int (-\nabla V) \left( \frac{1}{r} \right) dx dy dz
\]

where \(\nabla V\) is the spatial gradient of \(V\), \(c\) is a constant dependent upon the radius of the fibre, and the intracellular and extracellular conductivities, and \(r\) is the distance from the source point \((x',y',z')\) to a field point, \((x,y,z)\), given by

\[
r = \sqrt{(x-x')^2 + (y-y')^2 + (z-z')^2}
\]

In order to calculate an ECG for the 2D model, a pseudo-electrode was placed at a point just below the ventricular apex. The potential through this electrode was recorded using Equation 4.1, and the results are plotted in Figure 4.10.

The ECG looks morphologically similar to the schematic given in Figure 2.3, in addition to body surface ECGs measured from healthy rabbits [185]. The relevant ECG time intervals were measured, and compared with experimental results [186]. The RR interval was measured as 330\(\text{ms}\), which compares favourably with the experimental recording of 350.8\(\text{ms} \pm 50.1\text{ms}\). The PR interval was measured as 75\(\text{ms}\), which again
4.2: RESULTS

Figure 4.8: Simulated activation sequence from the 2D virtual heart. Snapshots of the 2D heart coloured by membrane potential were taken at 25ms intervals. In sequence, the snap shots show the heart at diastolic rest, initiation of an AP from within the SAN, the conduction of an AP from the SAN and subsequent transmission throughout the atria, the transmission of the AP from the atria into the fast and slow pathways of the AVN, reentry and annihilation of the AP within the slow pathway of the AVN, and propagation of the AP throughout the Purkinje network.
Figure 4.9: Simulated activation sequence from the 2D virtual heart. Snapshots of the 2D heart coloured by membrane potential were taken at 25ms intervals throughout the activation sequence, and 50ms intervals throughout the inactivation sequence. In sequence, the snap shots show the transmission of an AP from the Purkinje network in the ventricles, the propagation of the excitation wave throughout the ventricles, complete ventricular activation and atrial inactivation, the beginnings of ventricular inactivation, the continuation of ventricular inactivation, and the initiation of a subsequent AP.
Figure 4.10: ECG computed from a pseudo-electrode placed just below the ventricular apex.
4.2: RESULTS

<table>
<thead>
<tr>
<th>Interval</th>
<th>Experimental Recording (ms)</th>
<th>Simulated Recording (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>350.8 ± 50.1</td>
<td>330</td>
</tr>
<tr>
<td>PR</td>
<td>72.5 ± 6.2</td>
<td>75</td>
</tr>
<tr>
<td>QRS</td>
<td>50.0 ± 4.3</td>
<td>40</td>
</tr>
<tr>
<td>QT P</td>
<td>147.7 ± 24.5</td>
<td>170</td>
</tr>
</tbody>
</table>

Table 4.2: Summary of the relevant ECG parameters as calculated from the 2D rabbit whole heart model, in addition to those from experimentally recorded rabbit ECGs [186].

corresponds closely to the experimentally recorded value of 72.5\(\text{ms}\) ± 6.2\(\text{ms}\). The value for the QRS complex is the only slightly aberrant result, with the value from the 2D model measured as 40\(\text{ms}\), slightly outside the measured experimental range 50.0\(\text{ms}\)±4.3\(\text{ms}\). Although the value for the QRS complex is outside of the experimental range as reported by Brunner et al., a wide variety in QRS lengths within rabbits has been reported, suggesting large individual variation in QRS length [186–189].

Additionally, the limitation of the model to 2D neglects the complex structure and anisotropic nature of the rabbit ventricles, a deciding factor in determining QRS length. The QT P length is once more in close correlation with experimental recordings, with an interval of 170\(\text{ms}\) measured via simulation, compared with 147.7\(\text{ms}\) ± 24.5\(\text{ms}\) via experiment. These results are summarised in Table 4.2.

4.2.4 Ventricular activation sequence

In order to validate this model against experimental recordings, the activation sequence of the ventricles was recorded as described in Section 2.3.5, with activation time given as the time since the activation of the first ventricular cell. While the ECG time intervals recorded in the previous section heavily suggest the correct overall activation sequence and timing throughout the heart, with the PP interval corresponding to SAN cycle length, PR interval corresponding to the conduction speed and sequence within
the AVN and atrial tissue, QRS duration corresponding to the ventricle depolarisation speed, and QT interval representing the ventricular repolarisation speed and sequence, it is useful to further investigate the activation sequence. The full activation sequence is shown in Figure 4.11.

Ventricular activation is shown to begin within the endocardial tissue and proceed towards the ventricular apex, before propagating upwards towards the base of the heart and transmurally towards the epicardium. The extreme base of the left and right ventricle are shown to take an extended period of time to activate, up to 58 ms in the case of the right ventricle. This is likely to be a limitation of the model due to its 2D nature, as only one Purkinje fibre is present, and it represents the longest transmission route from the AVN. However, the extreme basal tissue is small, with a minor contribution to the electric field of the whole heart, and the majority of the ventricle is activated more quickly, which leads to the reported QRS duration of 40 ms, in good agreement with experimental data.

This result was compared against that from a similar experiment [190]. While the available data is taken from human hearts, ventricular electrophysiology between human and rabbit hearts is similar [41, 42]. No comprehensive experimentally recorded activation data for a 2D plane of rabbit heart was available. In this experiment, the electrical activity of the heart was recorded by a number of electrodes positioned on the surface of the heart, as well as a number of multi-electrode needles that were introduced to the ventricular walls. The reported ventricular activation sequence is shown in Figure 4.11.

The simulated activation sequence is qualitatively similar to those reported by experiment. In particular, in all cases the initial ventricular activation surrounds the apex of the left ventricular cavity, shortly followed by activation at a similar position within the right ventricular cavity. In both simulation and experimental cases the excitation wave then propagates upwards and outwards through the ventricle, from apex to base and from the endocardium to the epicardium. In addition to the late activation of basal ventricular tissue discussed previously, experiments show the sequence of acti-
4.2: RESULTS

Figure 4.11: Ventricular activation sequence as simulated by the 2D whole heart model. Cells are coloured by activation time, given as the time between their activation and the activation of the first ventricular cell.

Figure 4.12: Ventricular activation sequences recorded by experiment [190]. Each panel shows the ventricular activation sequence as measured from a human heart. Activation within the ventricles to spread out more transmurally. This primarily suggests anisotropic conduction within the ventricular free wall, but also lends credence to the hypothesis that a single Purkinje fibre is not sufficient to provide a correct activation sequence. While other small discrepancies exist, they are also apparent between the two human hearts, suggesting individual differences play a large role.
4.3 Adaptability of the 2D framework

The 2D framework that allows creation of heterogeneous computational geometries based upon the colour principles of the pixels within an inputted bitmap, as well as the computational solvers for the ordinary and partial differential equations that arise from a given geometry are highly adaptable. In addition to the input of a bitmap created manually by the manipulation of an existing histological slice, as seen above, the framework is capable of creating or editing its own bitmaps with a variety of different shapes, both stochastic and deterministic. Furthermore, the framework is capable of accepting ion channel kinetics from a wide variety of existing channels, across a number of celltypes and a number of different species. While the details of cardiac simulations on species other than the rabbit are outside of the scope of this thesis, the framework has been used to provide simulation data for existing publications, and more details can be found in [191].

4.4 Conclusions

We can see from the activation map shown in Figure 4.11, and the ECG shown in Figure 4.10 that this 2D heart is a physiologically accurate approximation to data obtained experimentally from a real rabbit heart, however, the 2D nature of these simulations remains a barrier to full understanding. Many of the physiological phenomena that occur within the heart, such as the scroll waves associated with ventricular fibrillation, cannot occur within a 2D space. In addition, the lack of a comprehensive Purkinje network within a 2D space, and the absence of tissue anisotropy for a 2D heart prevent fully accurate reconstructions of experimentally observed data. It is therefore sensible to extend this work into 3D space, but the 2D simulations remain a useful proof of concept for the cellular models used. In addition, the extended complexity of the 2D heterogeneous geometry causes an intense computational load associated with simulation. A single heart beat of roughly 330ms in duration requires almost a full day of
4.4: CONCLUSIONS

computational time, suggesting that simulation of multi-scale cardiac modelling may provide additional difficulties, especially considering that the extension of a simulation of such size into 3D would increase the computational load by 100-fold.
Creation of a three dimensional whole rabbit heart

The previous chapter covered the use of electrically detailed single cell models within a larger geometry. However, limitations were seen to arise from the restriction of such a model into 2D space. It is therefore sensible to investigate the extension of the whole heart model into three dimensions.

There is currently no fully detailed three-dimensional model of the whole rabbit heart. In addition, even three dimensional models of individual cardiac areas are lacking in structural heterogeneity [167, 192], and lack the possible insights into complex cardiac behaviour offered by a comprehensive model of the whole heart. It has been shown that higher dimensionality models of the heart provide the closest approximation to reality, and form a good basis for the investigation of cardiac phenomena [193].

5.1 Creating the three dimensional geometry

In order to simulate the electrical activity of the whole rabbit heart, it is necessary to have a quantitative representation of the geometry of the heart, containing both structural and electrical heterogeneity.
5.1: CREATING THE THREE DIMENSIONAL GEOMETRY

5.1.1 Initial dataset

Cardiac geometry can be reconstructed and visualised from DT-MRI data sets [71]. DT-MRI datasets for whole rabbit hearts have been made available [194]. A complete dataset for a single heart was obtained and the geometry extracted. The full geometry is shown in Figure 5.1. The spatial resolution of this full 3D geometry was 200µm in each direction, with total dimensions of 128 x 120 x 190.

Using the techniques described in Section 2.3.1, DT-MRI also calculates 3 sets of corresponding eigenvalues and eigenvectors for the diffusion tensor at each point throughout a volume of 3D tissue. These values can be used as a measure of tissue anisotropy and sheet structure [71].

5.1.2 Noise removal

The DT-MRI dataset is visibly noisy, with large volumes of unconnected tissue generated on either side of the ventricular apex, in addition to smaller patches of random noise surrounding the atria. This dataset was cleaned up in two ways. Firstly, the large volumes of visible noise at the apex were removed manually. Then, smaller patches of random noise were removed by a combination of binary erode and dilate algorithms, a common methodology of noise reduction in binary datasets [195–197].

In addition to the noise within the geometry, the right ventricular, left atrial and right atrial cavities within the original heart undergoing the DT-MRI scan were not filled with liquid before scanning. This resulted in the collapse of these cavities, giving rise to connections between the cellular tissue of each chamber wall. This could lead to the conduction of an excitation wave between the right ventricle and the ventricular septum, bypassing the non-conducting volume offered physiologically by the ventricular cavity. Therefore, this tissue needed to be removed. Similarly to an existing study detailing rabbit ventricular segmentation, absent tissue was outlined manually on six planes, but these were spread throughout the entire ventricle, as opposed to only
5.1: CREATING THE THREE DIMENSIONAL GEOMETRY

Figure 5.1: 3D reconstruction of the rabbit heart based on a comprehensive DT-MRI dataset. (i) and (ii) show posterior and anterior views respectively. Note the visible noise on either side of the ventricular apex, in addition to the random noise around the atrial tissue.
the lower half used in the previous study [49]. The outlined absent tissue in each of these planes was then interpolated in 3D using MATLAB’s spline interpolation function [198] to generate a full right ventricular cavity. This cavity was then subtracted from the whole dataset to open up the right ventricle. The left and right atrial cavities were cleaned up manually. Finally, due to an excessive volume of noise in the basal atrial layers leading to a cloud of unconnected tissue, the top seven layers of atrial tissue were removed. Slices of tissue from the original and cleaned datasets are shown in Figure 5.2. There is a large volume of noise corresponding to both organised and random noise. In the slice at 5mm, a large amount of organised noise can be seen, likely the result of leftover unwanted tissue. In the slice at 12mm, the effects of opening up the right ventricular cavity can be clearly seen. At 20mm, there is a large volume of organised, repeating noise, likely caused by an artifact of the experimental protocol. At 32mm, only small patches of seemingly random noise are detected. A 3D view of the whole dataset after both manual and automatic cleanup is shown in Figure 5.3.

5.1.3 Ventricular segmentation

As discussed in Section 3.1.5, large regional differences in cellular heterogeneity can lead to the rise of a number of cardiac phenomena. Segmentation of the ventricles into different cell types is therefore important. It has been reported that the differences in fibre angle throughout the ventricular wall correspond to the different cell types present [66]. Furthermore, it has been shown that fibre orientation angles show a continuous progression across the ventricular surface, from roughly +70° at the endocardial surface, to −60° at the epicardial surface within the rabbit ventricle [199]. Cells pertaining to the midmyocardium have no inclination, lying roughly parallel to the transverse direction across the heart, and perpendicular to the transmural direction.

The fibre orientation angle is therefore a good basis for segmentation of the ventricle. Slices of ventricular tissue from the original geometry coloured by fibre angle were outputted as bitmap files using the algorithm developed in Section 4.1. The re-
Figure 5.2: Slices of rabbit ventricular tissue based on a comprehensive DT-MRI dataset. (i) shows the geometry as it appears within the initial dataset. (ii) shows the geometry after visible and random noise were removed by a combination of manual segmentation, and a binary erode/dilate algorithm.
Figure 5.3: 3D reconstruction of the rabbit heart based on a comprehensive DT-MRI dataset, after visible and random noise were removed by a combination of manual segmentation, and a binary erode/dilate algorithm. (i) and (ii) show posterior and anterior views respectively.
5.1: CREATING THE THREE DIMENSIONAL GEOMETRY

resulting slices of ventricular tissue can be seen in Figure 5.4 (i). These slices were then manually edited to provide a smooth, working geometry as seen in Figure 5.4. This procedure was carried out on every slice within the ventricular area, leading to a segmented, but noisy geometry. Finally, this segmented geometry was combined with the cleaned geometry shown in Figure 5.3 to give the segmented ventricular mass shown in Figure 5.5.

5.1.4 Mapping the Purkinje fibre network

The Purkinje network is a structure of utmost importance to the conduction system of the heart [16]. In addition, the sites at which the Purkinje system joins the ventricles are electrophysiologically important, and may lead to the development of arrhythmia [79]. In order to construct a PF cell geometry, a Purkinje network was obtained from existing literature [200]. While the available Purkinje network was from a canine, it has been shown that the general arrangement and appearance of Purkinje within rabbit and dog hearts are similar [201].

An algorithm consisting of a number of geometric transforms was developed to fit the Purkinje network to the ventricular cavities. These transforms included basic translations in the x, y and z directions, and the size of the Purkinje network could be stretched or compressed in any of these directions. Conversions of every individual cell from cartesian co-ordinates into both cylindrical and spherical polar co-ordinates, and back again were created, allowing the rotation of the entire geometry around any axis or point. A function was created to find the central voxel by averaging the total x, y and z co-ordinates of every cell, allowing rotation around the centre of the network.

These transforms were applied iteratively to reduce the distance between the fibres and the ventricular cavity, while stretching the network over the entire ventricle. After every few iterations, the network was examined using an automatic quantitative method which calculated and recorded the average distance between each voxel within the Purkinje network and the nearest voxel within the ventricle wall, as well as exam-
5.1: CREATING THE THREE DIMENSIONAL GEOMETRY

Figure 5.4: Slices taken through the rabbit ventricles at 5mm intervals. (i) shows the slices coloured by fibre angle. (ii) shows the slices after semi-automated segmentation into right and left ventricles, and Endo, Epi and M cell types, and after the simulated opening of the right ventricular cavity.
Figure 5.5: 3D reconstruction of the rabbit ventricles. Each panel represents the addition of an extra 5mm of tissue, coloured by cell type.
Figure 5.6: (i)-(vi) show the iterative geometric transforms applied to an existing Purkinje fibre network to fit to the left rabbit ventricle. The Purkinje network is shown in red, while the translucent blue surface represents the inner surface of the left ventricle.

Figure 5.6: (i)-(vi) show the iterative geometric transforms applied to an existing Purkinje fibre network to fit to the left rabbit ventricle. The Purkinje network is shown in red, while the translucent blue surface represents the inner surface of the left ventricle.

Snapshots throughout this sequence are shown for the left ventricle in Figure 5.6.

With these transforms completed, the final network was collapsed onto the ventricles by calculating the nearest inner ventricular cell at each point, before being manually cleaned up to avoid connections between individual fibres. The same procedure was then applied to the right ventricular cavity, following the same protocol outlined above. The Purkinje network within the right ventricle was also manually cleaned up, and insertion points were added to the ends of each fibre branch to allow conduction between the Purkinje fibres and the ventricles. The final completed network is shown in Figure 5.7.
5.1: CREATING THE THREE DIMENSIONAL GEOMETRY

5.1.5 Atrial segmentation and addition of the SAN

The atria were segmented into left and right manually in a similar manner to the ventricles. Slices of atrial tissue segmented into Left Atrium (LA) and Right Atrium (RA) are shown in Figure 5.8. In all cases, the LA is shown as red, with the RA shown as orange. The top of the right ventricle is also seen, in green and purple, due to the slightly tilted orientation of the initial dataset. A 3D view of the final segmented atria, without the connected ventricular tissue, is shown in Figure 5.9.

After the separation of atrial tissue into the left and right ventricles, a SAN was needed to provide endogenously generated pacing. A 3D, anatomically detailed SAN geometry has been developed previously [202]. This geometry was obtained by cutting groups of three neighbouring sections from the top to bottom of the SAN at roughly 200µm intervals. One slice from each group of three sections was stained with Masson’s trichrome in order to determine the outline of the geometry, myocytes and connective tissue. The other sections were immunoenzyme-labeled for either neurofilament-M or connexin-43, which have been shown to differ in expression for different cell types [203, 204]. Finally, the data from these sections was used by Dobrzynski et al. to separate the geometry into central and peripheral SAN cells, as well as atrial muscle. The initial dataset obtained is shown in Figure 5.10.

The SAN geometry was implanted into the right atrial wall using a method similar to the final step of the Purkinje network creation. After scaling the experimental data to an equal resolution, each cell within the geometry was collapsed onto the nearest cell within the atrial wall. The SAN cells were copied from the flattened experimental geometry and onto the atrial wall, retaining the shape and thickness of the experimental SAN. Care was taken to orient the SAN to span between the Inferior Vena Cava (IVC) and Superior Vena Cava (SVC) as reported in the initial geometry in Figure 5.10 (ii). The initial dataset after rescaling to the resolution of the whole heart geometry is shown in Figure 5.11 (i). The resulting SAN geometry, along with the remainder of the atria are shown in Figure 5.12 (ii).
5.1.6 Addition of the AVN

In order to provide a connection between the atria and the Purkinje network, in addition to slowing the conduction velocity of the AP before entering the ventricles, an AVN structure was necessary. A computational reconstruction of the rabbit AVN geometry has previously been created by Li et al [168]. In this study, AVN tissue was removed from a number of rabbit hearts before being fixed, sectioned into slices at varying intervals between $60\mu m$ and $360\mu m$, before each slice was either stained with Masson’s trichrome to identify histological differences, or immunoenzyme-labeled for either neurofilament-M or connexin-43 to identify electrophysiological differences, in a manner similar to that for the SAN geometry. The AVN was excised from the original dataset and inserted into the 3D geometry. Care was taken to line the penetrating bundle up with the primary branch of the PF network, ensuring correct conduction throughout the system. While the experimentally obtained geometry was flattened out, the border between atrial and ventricular tissue is not so straight in the 3D geometry. Thus, the remainder of the AVN was then wrapped around the atrial muscle using a similar method to that for the PF network; the AVN geometry was iteratively morphed by the arithmetic transforms described previously until it lay along the surface of the atria. The final AVN network is therefore a slightly different shape to that from the flat slice of tissue, but shares the same relation to the curved surfaces of the atrial and ventricular tissue within the model. The initial dataset, and the final AVN geometry used within the 3D model are shown in Figure 5.13, with left atrial and ventricular tissue included in both cases.

5.2 Development of the full 3D model

Each individual area of the three dimensional geometry was combined, producing the full geometry shown in Figure 5.14. The original DT-MRI dataset contains information relating to the tissue structure of the heart, in the form of eigenvectors at each
point. Therefore, the spatial orientation of each cell could be determined. This orientation was used to construct a detailed diffusion tensor for use throughout the muscular tissue of the heart as described in Chapter 2. Values for $D_{∥}$, $D_{⊥1}$ and $D_{⊥2}$ throughout anisotropic muscular regions were chosen as equal to those used in an existing study on the rabbit ventricle [49]. As the SAN, AVN and PF network that were added to the model were based on experimental data for which no detailed, anisotropic tissue structure involving cell orientation was determined, those regions were modelled isotropically. In all isotropic cases, values for $\mathbf{D}$ were chosen to reproduce experimentally observed conduction velocities, as in the Section 4.2.1 for the 2D model.

In addition to the anisotropy caused by the variation in cellular orientation throughout the ventricle, large differences in electrical activity between cells from different ventricular regions have been reported by a variety of sources [205–207]. There is sufficient difference in the AP morphology of cells from the left and right ventricle to warrant simulated heterogeneity between the halves, especially as these regional differences are believed to be a determining factor in the generation of numerous arrhythmias [208]. To this end, previously developed models of the right ventricles, based on the left ventricular model introduced in Section 3.1.5 were incorporated into the model. These new models take into account differences in left-right ventricle AP morphology via a number of changes to ionic currents, including a 10% reduction in $I_{CaL}$ channel conductance, a 30% increase in $I_{to}$ channel conductance, a shift in the time constants of the $I_{Kr}$ channel, a 30% increase in $I_{Ks}$ channel conductance, and finally a complete reformation of the $I_{K1}$ channel kinetics. More details can be found in [49]. A summary of each cell type used within the 3D model is shown in Table 5.1

It is generally accepted that the repolarisation sequence of the rabbit ventricle is in an inverse direction compared to the depolarisation sequence - from the base to the apex, as opposed to from the apex to the base [209,210]. This suggests that cells from the base of the ventricle have a much shorter APD than those at the top of the heart. In addition, a number of differences in individual ion channels have been reported throughout the heart. Specifically, $I_{Ks}$ has been reported as being roughly 3 times
## 5.2: Development of the Full 3D Model

### Table 5.1: Summary of the individual cell models used to simulate electrical activity in each area of the heart within the 3D model.

<table>
<thead>
<tr>
<th>Region of heart</th>
<th>Model name and reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SANC</td>
<td>Zhang SAN centre model [86]</td>
</tr>
<tr>
<td>SANP</td>
<td>Zhang SAN periphery model [86]</td>
</tr>
<tr>
<td>AM</td>
<td>Aslanidi left and right atrial models [113]</td>
</tr>
<tr>
<td>AN</td>
<td>Inada atrial-nodal cell model [123]</td>
</tr>
<tr>
<td>N</td>
<td>Inada nodal cell model [123]</td>
</tr>
<tr>
<td>NH</td>
<td>Inada nodal-His cell model [123]</td>
</tr>
<tr>
<td>PF</td>
<td>Aslanidi Purkinje fibre model [91]</td>
</tr>
<tr>
<td>ENDO – Left</td>
<td>Aslanidi Endocardial cell model [91]</td>
</tr>
<tr>
<td>M – Left</td>
<td>Aslanidi Mid-myocardial cell model [91]</td>
</tr>
<tr>
<td>EPI – Left</td>
<td>Aslanidi Epicardial cell model [91]</td>
</tr>
<tr>
<td>ENDO – Right</td>
<td>Modified Aslanidi Endocardial cell model [49]</td>
</tr>
<tr>
<td>M – Right</td>
<td>Modified Aslanidi Mid-myocardial cell model [49]</td>
</tr>
<tr>
<td>EPI – Right</td>
<td>Modified Aslanidi Epicardial cell model [49]</td>
</tr>
</tbody>
</table>

Table 5.1: Summary of the individual cell models used to simulate electrical activity in each area of the heart within the 3D model.
Figure 5.7: Purkinje fibre network after digital and manual cleaning, shown along with the left and right ventricular cavities. (i) and (ii) show posterior and anterior views respectively. (iii) shows the view looking upwards from the ventricular apex. In all three cases, ventricular tissue is shown in red and the ventricular cavities are shown in translucent blue.
Figure 5.8: Slices of atrial tissue at 1.25mm spacing, shown segmented into left and right atrial tissue. Different tissue types are coloured according to the key on the right.
5.2: DEVELOPMENT OF THE FULL 3D MODEL

Figure 5.9: Full geometry of the atria, segmented into left and right. (i) and (ii) show the atria from the horizontal long axis and short axis directions respectively, with (iii) providing an angled viewpoint.
5.2: DEVELOPMENT OF THE FULL 3D MODEL

Figure 5.10: Position of the SAN as predicted by computational reconstruction. (i) shows the position of the SAN within an obtained slice of atrial tissue. (ii) shows the relative position and orientation of the SAN as compared to the rest of the atria. Taken from [202]

Figure 5.11: Position of the SAN as predicted by histological data, showing the position of the SAN within an obtained slice of atrial tissue. (i), (ii) and (iii) show the SAN and atrial tissue as viewed from the x, y and z directions of the original dataset respectively. Different cell types are coloured according to the key below.
Figure 5.12: Position of the SAN after implantation within the right atrial wall. (i) and (ii) show the SAN and atrial tissue as viewed from the same angles provided in the original dataset in Figure 5.11. (iii) shows the LA and SAN tissue viewed from above. Different cell types are coloured according to the key below.
5.2: DEVELOPMENT OF THE FULL 3D MODEL

Figure 5.13: Structure of the AVN. (i) shows the position of the AVN as predicted by histological data within an obtained slice of tissue including both atrial and ventricular muscle. (ii) shows the position of the AVN within the 3D geometry, including both atrial and ventricular tissues.
Figure 5.14: External view of the fully segmented rabbit heart, showing left and right atria, ventricles, and the SAN.
larger in basal cells than in cells from the ventricular apex [211]. $I_{CaL}$ has been reported as roughly 1.3 times larger in apical cells compared to basal cells [212], and $I_{Kr}$ has been reported as being roughly 1.5 times larger in apical cells than in cells taken from the ventricular base [211]. These differences were incorporated into the left and right ventricular models, in a manner similar to an existing study [49]. However, unlike the previous study, the entire ventricle was used as opposed to only the lower section.

It has been shown that regional differences in AP morphology within the atria are a possible source of re-entrant arrhythmias [213, 214]. Differences in ionic currents between the LA and RA have been introduced to the atrial model based on detailed experimental data recorded from canine hearts in a previous study [113]. These modified Aslanidi models were used within the 3D model to provide sufficient differences between the left and right atrial cells.

5.3 Conclusions

With a completed 3D geometry available, in addition to comprehensive group of models detailing single cell action potential kinetics within rabbit cardiac tissue, the way was paved for computation of a full excitation sequence within a 3D rabbit heart. However an initial test run confirmed the massive computational load associated with such an extensive geometry as predicted in Section 4.4. Extrapolating from a few simulated milliseconds of simulated 3D heartbeat, the predicted simulation time to compute one full, 330ms beat of 3D rabbit heart activity was over two months. With simulations ideally comprising 4-5 beats for accuracy and the removal of transient effects caused by the initial conditions of the model, this was not a usable solution without access to high-end supercomputing facilities. Therefore, other avenues for the increase of computational efficiency were explored, as described in detail in Chapter 6.
6

Creation of ultra fast cellular modelling algorithms using Graphical Processing Units

Addendum The work in this section was submitted to Computers in Cardiology 2011, for which it was shortlisted as a contender for the Rosanna Degani young investigator of the year award. While that manuscript was written jointly by myself, Prof. Henggui Zhang and Dr Oleg Aslanidi, all model development and simulation was carried out by me, and all work here remains my own.

As mentioned previously in Section 1.3, a computational approach can be a useful tool for studying the cardiac excitation waves, however not without significant computational cost. Specifically, as detailed in Section 5.3, computing cardiac excitation waves within large, detailed 3D geometries can take months of computational time to obtain a useful result. In order to fully investigate the interactions of the 3D rabbit model within a number of different cases, it is therefore necessary to create a more efficient method of evaluating the relevant computational models.
6.1 Motivation

With the excessive computational time taken to compute even single cycles of excitation within the 3D model detailed, it was necessary to explore additional methods for simulation of complex, 3D geometries. Several parallel computing paradigms have been developed in order to implement complex cardiac models using up-to-date high-performance computing facilities [215–217]. However, the necessity of powerful supercomputing clusters for large scale cardiac simulations is costly and often inconvenient due to a limited number of such facilities. Therefore, there is a strong demand for more convenient, quick and cheap methods for resolving cardiac models that can also be implemented on commonly available hardware.

In this section, investigation is carried out into a novel method of parallelization using commercially available Graphical Processing Units (GPUs), with the aim of obtaining drastic speed increases over traditional methods. In particular, with a view to creating a fast and effective method to solve the huge number of computations arising from the execution of the full 3D rabbit heart model. It is shown that these widely available GPUs can offer such a cheap, convenient alternative to large numbers of Central Processing Units (CPUs), and allow a substantial increase of the computational speed in large-scale simulations of cardiac excitation waves.

6.2 Introduction to general purpose graphical processing

The GPU is a piece of specialized hardware resident within most personal computers for the purpose of graphical rendering. While originally only for the purpose of graphical rendering, the highly parallel nature of the GPU makes it an attractive target for more general computation, a field dubbed General Purpose on Graphical Processing Units (GPGPU) [218].
6.2: INTRODUCTION TO GENERAL PURPOSE GRAPHICAL PROCESSING

6.2.1 The graphics pipeline

In order to understand why GPUs are so well suited to parallel scientific computation, it is useful to briefly examine the original purpose of a GPU. GPUs were initially designed to carry out a number of simple operations in sequence, referred to as a graphics pipeline. The graphics pipeline consists of a number of simple operations carried out in sequence. A simplified graphics pipeline is shown in Figure 6.1.

The importance of the pipeline in illustrating the functionality of a GPU, is that unlike the majority of CPU-based operations necessary for the running of a home computer, each operation outlined in Figure 6.1 can be carried out completely independently. Each vertex is transformed independently of other vertices, each primitive is rasterised independently of other primitives, and each fragment is shaded independently of other fragments. In addition, all three operations can be carried out con-
secutively on one pixel, regardless of the relative position of other pixels within the pipeline. This unique structure has lead to the construction of a highly specialised parallel architecture for carrying out simplistic computations on numerous objects as quickly as possible.

### 6.2.2 GPU Architecture

In order to facilitate the processing of as much data through the graphics pipeline as possible, GPUs were originally split into a number of different processors, each with its own set of operations to carry out. Information in the form of vertex data arrives from the CPU, and is passed through vertex, fragment and texture processors where various transforms are carried out to convert the vertex input into usable data. While the intricacies of actual graphical programming are outside the scope of this thesis, they have been covered elsewhere [219].

However, as graphics hardware has become more advanced, the individual sets of processors within the GPU have become more versatile. In particular, both the vertex and fragment processors are highly computationally capable, with support for numerous floating point operations. The GPU as a whole can thus be viewed as a collection of independent programmable blocks [220]. A schematic diagram of the programmable hardware within a standard GPU is shown in Figure 6.2. Modern GPUs contain several hundreds of these programmable processors, leading to a huge increase in computational speed compared to a standard single core CPU, but there is an architectural disadvantage that comes along with the advantages gained by offloading computational power to the GPU. In general, a GPU will communicate with the rest of a computer system through a motherboard graphics connector such as a Peripheral Component Interconnect Express (PCI-E) slot. This connection, or bus, is responsible for transferring all data between the the north bridge and the GPU. A generic computer architecture is shown in Figure 6.3. It is important to note the differences in memory transfer speed between different areas of the computer, shown in Table 6.1.
Figure 6.2: Illustration of a schematic GPU architecture. Instructions are seen to arrive from the CPU, are processed through the sets of programmable vertex, texture and fragment processors, before the processed result is returned back to the CPU. Adapted from [220].

<table>
<thead>
<tr>
<th>Memory Interface</th>
<th>Bandwidth</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI-E x16 Bus</td>
<td>8GB/s</td>
</tr>
<tr>
<td>CPU Memory Interface</td>
<td>6.4 GB/s</td>
</tr>
<tr>
<td>GPU Memory Interface</td>
<td>35 GB/s</td>
</tr>
</tbody>
</table>

Table 6.1: Available memory bandwidth between different components within a standard desktop computer. The GPU memory interface is seen to be many times faster than the CPU memory interface, and this is one of the leading factors in the computational speed increases offered by GPGPU programming. Copying data from the CPU memory to the GPU memory is substantially slower, a leading cause of performance bottlenecks using GPGPU. All data was obtained from [220].
6.2: INTRODUCTION TO GENERAL PURPOSE GRAPHICAL PROCESSING

Figure 6.3: Schematic illustration of a simplified computer architecture. The north bridge is connected to the host memory via the CPU memory interface, and to the GPU via a motherboard graphics connector such as a PCI-E slot. The GPU is connected to the device memory via the GPU memory interface. Memory bandwidth across each individual connection is summarised in Table 6.1. Adapted from [220].

The large differences in memory transfer speed between different areas of a computer system gives insight into the possible problems faced when dealing with GPGPU programming. In general, while accessing and modifying data held within the GPU memory is exceptionally fast, transferring data from the CPU memory to the GPU memory causes a significant performance bottleneck.

6.2.3 Single instruction multiple data programming

Single Instruction Multiple Data (SIMD) is a programming ideal dealing with the enforced condition that a single operation is carried out to all input data. In essence, SIMD means that a single instruction from a processor can be carried out on numerous pieces of data, without waiting for further instructions from the host processor.

On a GPU, SIMD launches a series of operations called the kernel, which act on
6.2: INTRODUCTION TO GENERAL PURPOSE GRAPHICAL PROCESSING

thousands of threads with very little memory overhead. This allows near-simultaneous calculation of many independent floating point operations. However, this near simultaneous calculation, coupled with the fact that the same operation must be carried out on every kernel thread, means that this method of programming is suitable only for independent, data-parallel computations.

Activity of cardiac cells in the tissue can be separated into two components. The first is the generation of electrical membrane potential due to ion channels opening/closing, and the other is localized diffusion of membrane potential between cells due to inter-cellular electrical coupling between cells. The first of these is completely independent, with the current due to a single cells’ ion channels unrelated to the ionic current in neighbouring cells, and while the second of these is dependent on the potential within neighbouring cells, the contribution to this at each time step is calculated from the potential of the neighbouring cells at the previous time step, thus retaining data parallelism. The nature of these components of a cardiac model makes it an ideal candidate for an SIMD architecture such as a GPU.

6.2.4 Scientific uses of GPGPU

The power of GPUs has increased dramatically in recent years. Such an increase in power has made GPU programming an attractive solution to a number of scientific applications outside graphical rendering. The increase of computational speed produced by a highly parallel processor (such as GPU) depends on the degree of software parallelization. Speed increases in the range 10-120 times have been reported for a variety of scientific applications, including quantum chemistry [221], neural network computation [222], and electromagnetics [223].
6.3 Introduction to CUDA

In order to take advantage of the large speed increases possible using GPGPU, a number of new hardware and software architectures for General Purpose Graphical Processing (GPGP) have been created [224, 225]. Early attempts at GPGP met with little success, as independently developed methods of CPU-GPU interaction often lacked functionality, and were complex and difficult to use [226]. However, this has changed with the recent release of languages supported by leading GPU hardware developers, such as Nvidia’s CUDA.

6.3.1 What is CUDA

CUDA, standing for Compute Unified Device Architecture, is both Nvidia’s parallel computing architecture, and also the set of extensions to standard C/C++ to allow interaction between a computer’s CPU (termed the host), and a CUDA enabled GPU (termed the device). CUDA allows the user to allocate and access memory local to the device, copy data between the host and device, and offload parallel tasks to the GPU cores as a kernel [227].

CUDA kernels take the form of a C++ style function of type ’void’ and user specified input arguments. In addition, each kernel contains two additional inputs corresponding to the number of thread blocks, and the number of threads within each block. When a kernel is called, it is executed on all threads in parallel, and carries out the same operation on every thread in every block. Each thread is identified by a “thread ID” specifying its position within a thread block, and each block is identified by a “block ID”. This identifier can be used within the kernel to index array pointers, allowing each thread to act on, and modify a different memory address.
6.3.2 Comparison between C++ and CUDA

A standard piece of CPU pseudocode for cardiac simulations may have the following form, where serial computation refers to the set of ordinary/partial differential equations used to simulate cell/tissue behaviour, and the Euler method used to solve them.

1. Allocate memory on the host;
2. Initialize memory on the host;
3. Resolve serial computation on CPU;
4. Print results.

Steps 1 and 2 are carried out only once, at the outset of the code, and step 4 only once at the end, so for the purposes of computational efficiency only step 3 is important.

The same pseudocode rewritten in CUDA is similar, but with several important alterations:

1. Allocate memory on the host;
2. Allocate memory on the device;
3. Initialize memory on the host;
4. Copy data from host to device memory;
5. Resolve parallel kernel on GPU;
6. Copy data from device to host memory;
7. Resolve any serial computation on CPU;
8. Print results.
As with the C++ code, steps 1, 2, 3 and 8 are carried out only once, but steps 4-7 are all carried out with an equivalent time step to the time step of the numerical integration of Equation 2.22. Besides, any serial computation must be carried out on the CPU. As seen in Table 6.1, steps 4 and 6 are highly time consuming. Careful allocation of memory space to minimize the memory overhead caused by steps 4 and 6, and an emphasis on minimizing serial operations in step 7, are therefore key to achieving a maximal speed increase. Hence, the number of threads resolved within each kernel, and the computational load carried by each thread with comparison to that of the CPU are of primary importance.

6.3.3 C++ and CUDA examples

In addition to the different steps required to carry out computation in a serial or parallel manner, there are a number of subtle differences between standard C++ code and the code used to invoke a CUDA kernel. As an example, consider a function, myFunction to calculate a heavily simplified cellular equation where the membrane current is a function only of voltage;

\[ I_x = f(V) \] (6.1)

where \( V \) is the membrane voltage at the current time, and \( I_x \) is the contribution to membrane current from a single ion, \( x \). Applying this to a number of cells (N), using standard C++ syntax is straightforward using in-built loop functionality:

```c++
double myFunction(*Ix, *V){
    for(int i = 0; i < N; i ++){
        Ix[i] = f(V[i])
    }
}
```

which will iterate over the extent of N, calculating the result of the equation for each cell and storing the result in an array, Ix. Comparing this with code created to carry out
the same operation on CUDA highlights an important conceptual difference between CPU and GPU computation.

```c
__global__ myFunction(*Ix, *V){
    int i = threadIdx.x;
    Ix[i] = f(V[i])
}
```

It can be seen that the actual computation is identical within both the C++ and CUDA versions of the code, however the loop is completely absent within the CUDA formulation, replaced by the line `i = threadIdx.x`. This line sets the array subscript `i` equal to the thread id within CUDA. Therefore, for `N` threads with ids from 0 to `N`, the result will be identical for both computations, however while the C++ computation is carried out in serial order from 0 to `N`, CUDA carries out all operations simultaneously.

Problems can arise when using CUDA to resolve an equation in which a variable appears on both sides, for example when the state of a variable at a future time is dependent on the state of a variable at a current time, as in Equation 2.22. As each thread in the kernel executes concurrently, inconsistencies can arise if one thread attempts to access an area of memory while another thread attempts to write to it. Therefore, in order to create a CUDA implementation, the monodomain equation was spread across three kernels. The first calculates the total membrane current, `Iion`, for a given cell, and the second calculates the contribution of inter-cellular coupling (i.e., the spatial derivatives in Equation 2.18), and combines these into the rate of the voltage change, $\frac{dV}{dt}$. Finally, the third kernel takes place after a call to the function 'CudaThreadSynchronize’, and applies this change to the current membrane potential, `V`. 'CudaThreadSynchronize’ ensures that no further operations are carried out until all threads have reached this point, avoiding any inconsistencies. Simple CUDA code describing the execution of these kernels is shown below:

```c
calc_Iion<<<dimGrid, dimBlock>>>(args);
```
6.3: INTRODUCTION TO CUDA

calc_dDdV<<<dimGrid, dimBlock>>>(args);
cudaThreadSynchronize();
update_V<<<dimGrid, dimBlock>>>(args);

Here ‘dimBlock’ specifies the number of threads within a kernel block, 'dimGrid' specifies the number of blocks acted upon by the kernel, and in each case 'args' is a set of device memory pointers passed to the GPU. In order to minimize the effects of memory latency caused by steps 4 and 6 as described in the CUDA pseudocode above, as little information was retained within the host memory as possible. All differential variables were held within the device memory, and only the membrane potential, $V$, was copied to the host memory in order to visualize the output. Simple CUDA code to copy the potential from the device to the host memory at every millisecond of simulation time is follows:

```c
if(counter >= 1/dt){
    cudaMemcpy((void *)V,(void*)d_V,Fmemsize,
    cudaMemcpyDeviceToHost);
    counter = 0;
}
```

By comparison, similar sets of functions carried out using standard C++ would look like the following:

```c
calc_Iion(args);
calc_dDdV(args);
update_V(args);
```

and

```c
if(counter >= 1/dt){
    V = d_V;
    counter = 0;
}
```
The C++ version of the code is much simpler, essentially taking the form of the CUDA code with all synchronisation, memory copy and dimensional arguments removed. In order to obtain the best performance from a GPU, usage of memory allocation or copy functions to move data from the host to the device or vice-versa must be kept to a minimum. However, as many common C++ functions (such as file input/outputs) and command line arguments must be carried out on the host, such functions cannot be avoided completely.

6.4 Disadvantages of CUDA

While CUDA offers a vast speed increase over conventional serial programming, in addition to a large decrease in cost compared to a multiple CPU machine, it is not without its own disadvantages.

6.4.1 Accuracy of computation

While the most recent generation of CUDA capable GPUs carry up to 64-bit floating point precision, or double precision, as supported on a standard CPU, this precision is not universally supported across GPU hardware. While there have been attempts to support double precision calculations on earlier GPU models, the increased computational load outweighs a large proportion of the speed advantage obtained by using GPGPU [228].

While in general, for the purposes of computational modelling such accuracy is not required [229], there is a subtle problem that can arise from the truncation of data from single to double precision.

There are a number of ionic current equations which contain a variable which follows the form

$$\alpha_m = A \frac{V + E}{e^{b(V+E)} - 1}$$

(6.2)
where $\alpha_m$ is a gating variable used to calculate the density of a current, $V$ is the membrane potential, and $A, B$ and $E$ are current dependent constants. It can be seen that if $V = -E$ is true, the determinant reduces to zero, leading to the possibility of an error. Firstly, there are issues regarding finite precision arithmetic resulting in undefined behaviour at values close to zero. Using double precision arithmetic there is an extremely low chance that this will ever occur [230], but this is not the case when truncating to single precision accuracy. Secondly, the nature of the ionic channel models can lead to unphysical values of current at voltages approaching zero. Therefore, all currents with similar formulations must be re-written when using CUDA to take this into account. A simple threshold was applied to set the current at any value within a small margin of the anomaly causing values to a physically possible value outside of this range. This modification prevents both anomalous effects.

### 6.4.2 Difficulties arising from SIMD

SIMD enforces the condition that the operations carried out on each object within the stream must be the same. Although recent versions of CUDA provide support for more complex computational functions such as logical conditional operators, use of these reduces computational efficiency and should be kept to a minimum. When converting code from a serial language like C++ into CUDA, each line of operations must be carefully considered and parallelised efficiently, an exceptionally time consuming process.

### 6.5 Differences in speed using CUDA

The monodomain equation was solved using a finite difference method, with space steps equivalent to the resolution of the geometry at $\Delta x = 0.2\text{mm}$, $\Delta y = 0.2\text{mm}$, $\Delta z = 0.2\text{mm}$, and a time step of $\Delta t = 0.005\text{ms}$. Values for the diffusion tensor coefficients were chosen as $D_\parallel = 0.3\text{mm}^2/\text{ms}$, $D_{\perp 1} = 0.075\text{mm}^2/\text{ms}$ and $D_{\perp 2} = 0.0083\text{mm}^2/\text{ms}$
6.5: DIFFERENCES IN SPEED USING CUDA

Figure 6.4: Comparison of computational speed while running the idealised cardiac tissue model with a varying number of cells on a CPU and GPU. Speed is given as 1/time to compute $10^4$ kernel executions.

based upon those used in a similar study [49].

6.5.1 CUDA speed increase in a dynamic homogeneous lattice

In order to predict the maximum possible differences in speed between C++ and CUDA within the field of cardiac modelling, an idealised parallel environment was created. A lattice with a varying number of isolated homogeneous cells was created and populated with endocardial tissue. The number of cells was increased geometrically from $10^{1.5}$ to $10^{6.0}$ by factors of $10^{0.5}$, and the time taken to resolve $10^4$ kernel executions was recorded. Both the C++ CPU and CUDA GPU code were evaluated on the same machine, equipped with an Intel core i5 M450 CPU clocked at 2.40GHz, 4.00GB of host RAM, and a 48 core Nvidia GT 330M clocked at 1.2 GHz, 1GB of dedicated video memory and 2.7GB of total graphics memory. The results obtained are summarised in Figure 6.4.
Figure 6.4 shows that increasing the number of cells, and therefore the number of threads executed by a kernel, results in a dramatic increase in the speed of simulation on the GPU. While this speed comparison was carried out under idealised conditions, cardiac modelling is an intensely parallel process, and we can expect similar speed increases for a realistic heterogeneous geometry, as discussed in Section 6.5.2. However, it is worth noting that speed increases on a GPU are limited by the memory size of the problem. Due to the additional time required to move data from the host memory to the device memory, GPU speed starts to slow down at problem sizes larger than the device memory. Taking into account that the GT 330M used for the simulations within this thesis has around 3GB of total graphics memory, and that a cellular model of the complexity used within this thesis requires the storing of around 30 differential variables, an estimate for the largest possible problem size at which the given speed increase will continue to occur gives an expected maximum problem size of around $10^7$ - $10^8$ cells. It is possible to circumvent this limit however, both by buying more expensive GPU cards with a larger volume of memory, and using multiple GPU cards to resolve the parallel portions of a simulation.

### 6.5.2 CUDA speed increase in a heterogeneous ventricle

In order to test the obtainable speed increases using CUDA on a fully heterogeneous geometry, a section of the ventricular tissue was isolated from the whole heart. Single cell models as described in Chapter 3 were rewritten from C++ into CUDA, and incorporated into the three dimensional geometry. The monodomain equation was solved using a finite difference method, with space steps equivalent to the resolution of the geometry at $\Delta x = 0.2\text{mm}$, $\Delta y = 0.2\text{mm}$, $\Delta z = 0.2\text{mm}$, and a time step of $\Delta t = 0.005\text{ms}$. A small area of left ventricular tissue near the base of the ventricles was stimulated in the same manner as by experiment [231]. The results were compared between the C++ and CUDA variants of the code in order to check for accuracy. The potential at every cell was found to be identical between both the CUDA and C++ versions.
of the code. Time-stepped shots of an isosurface at 0mV showing the activation sequence of the stimulated heart as calculated by the CUDA code are shown in Figure 6.5. The simulated activation map is shown in Figure 6.6 (i), and Figure 6.6 (ii) shows the experimentally recorded activation map from a similar section of tissue.

The simulated ventricular activation sequence after stimulus application shows a good correlation with that experimentally recorded. Both the activation sequence and timing are similar between model and experiment. Furthermore, the 3D ventricle provides a heterogeneous collection of cell types within a realistic geometry in three dimensions, in contrast to the homogeneous geometry used at the inception of the CUDA framework in Section 6.5. The time taken to simulate the above activation sequence was compared using CUDA based code on the Nvidia GPU, and C++ based code on the Intel CPU. The results are shown in Figure 6.7.

The GPU based code is substantially faster, at 298 seconds, compared to 20375 seconds on the CPU, equating to a 68 fold increase in speed on a portable laptop GPU.

6.6 Conclusions

As expected from a serial processor, the CPU speed per cell stays consistent, at around $0.11 \times 10^4$ executions/second throughout. There was a much smaller difference in the time taken to resolve an increasing number of threads on the GPU, resulting in drastic speed increases as more threads are added. The GPU overtakes the CPU in speed when resolving geometries containing between $10^{3.5}$ and $10^4$ cells, and offers speed increases of up to two orders of magnitude on larger cell structures. While this only represents the extent of the possible speed increases under an ideal, homogeneous system of isolated cells, the computation of the underlying partial differential equations common to every cell is the largest computational bottleneck within cardiac modelling. We can therefore expect speed increases for realistic, heterogeneous systems to approach those recorded above. The GPU is therefore an ideal candidate for parallelising the computation of excitation waves within cardiac tissue.
Figure 6.5: Activation wave simulation inside a section of ventricular tissue. The simulated activation sequence is shown in (i), along with an experimentally recorded activation sequence in (ii). Both sequences are colour coded according to the panel on their right. Arrows show the site of application of the stimulus.

Figure 6.6: Isosurfaces at 0mV showing the propagation of an excitation wave throughout the simulated rabbit ventricle. Snapshots were taken every 5ms of simulation time.
Figure 6.7: Time taken to simulate a ventricular activation sequence on using both CUDA running on an Nvidia GT 330M, and C++ on an Intel core i5 M450. Time taken is given in minutes.
Three dimensional whole rabbit heart
- Case Studies

In this chapter, the results obtained through simulations using the 3D rabbit heart model are discussed. In every case, simulations were carried out using the CUDA programming architecture and models detailed in Chapter 6.

7.1 Propagation through the 3D whole heart

The monodomain equation was solved using a finite difference method, as in Section 6.5.2, with equivalent spatial and temporal steps. Single cell models for the remaining cells were rewritten from the C++ models detailed in Chapter 3 into CUDA, and incorporated into the 3D geometry. All computations were carried out on either an Nvidia GT 330M or an Nvidia GTX 480. As a test to ensure hardware consistency, the following simulation was carried out on both units, during which they produced identical outputs.

The system was allowed to evolve for the duration of three full beats, roughly 950ms, to remove any transient effects caused by the initial conditions. No stimulus was required due to the presence of a SAN. The membrane potentials for all cells were then recorded every millisecond for the duration of the heart beat. Figure 7.1 shows
the membrane potential throughout the 3D rabbit heart at every 15ms throughout the initiation of the heart beat at the SAN, and the following propagation of the heart beat throughout the AVN, PF network and into the ventricles. Figure 7.2 shows the membrane potential every 25ms throughout ventricular depolarisation, and subsequent repolarisation. Finally, Figure 7.3 shows the membrane potential throughout the 3D rabbit heart every 25ms throughout the final stages of ventricular repolarisation, and the initiation of a following heartbeat.

In every case, the model reproduces the expected electrical behaviour of a rabbit heart. Impulses are generated within the SAN, and propagate outwards and along the full conduction pathway made up of the atria, AVN, PF network and finally the ventricular muscle. Ventricular depolarisation begins at the apex, and then propagates upwards towards the base. It is interesting to note that the ventricles repolarise in the opposite direction, from base to apex, an effect observed experimentally [209, 210], caused by the apex to base heterogeneity incorporated within the model, and resulting in the upright T-wave seen on the ECG.

### 7.1.1 Internal view of AP propagation

In order to further investigate the activation pathway within the internal structure of the heart, an isosurface representation of the above activation sequence was produced, shown in Figure 7.4. The isosurface was set at a value of 0mV. Timesteps were chosen manually to show interesting features of the AP propagation, as discussed below.

Within Figure 7.4, (i) shows the initial spread of the AP into the atria from the SAN. (ii) shows the beginnings of AP propagation through the AVN. (iii) shows the continued AP propagation through the Purkinje network, as well as the repolarisation of the atria. (iv) shows the spread of the excitation wave upwards throughout the ventricle. (v) shows the fully depolarised ventricular tissue. (vi) shows the final stages of ventricular repolarisation, with the apical tissue returning to membrane potential much later than the basal tissue.
Figure 7.1: Snapshots of membrane potential throughout the 3D rabbit heart taken at 15ms intervals during the evolution of a heart beat. The excitation wave is shown to be generated within the SAN, before spreading out into the atrial tissue, through the AVN, and into the PF network, before spreading out through the ventricles after roughly 75ms of simulation time.
Figure 7.2: Snapshots of membrane potential throughout the 3D rabbit heart taken at 25ms intervals during the evolution of a heart beat. The excitation wave is shown having propagated upwards throughout the ventricles, causing full ventricular depolarisation. Repolarisation occurs in the reverse direction, with the base of the ventricle repolarising before the apex.
Figure 7.3: Snapshots of membrane potential throughout the 3D rabbit heart taken at 25ms intervals during the evolution of a heart beat. The final stage of ventricular repolarisation is shown, followed by the initiation of a subsequent beat travelling from the SAN through the atria, corresponding to a total basic cycle length of roughly 310ms.
7.1: PROPAGATION THROUGH THE 3D WHOLE HEART

Figure 7.4: This figure provides a detailed internal view of the important moments during the activation sequence on the rabbit heart. An isosurface was calculated at a value of 0mV. Individual panels were chosen as discussed within the main text.
7.1: PROPAGATION THROUGH THE 3D WHOLE HEART

Figure 7.5: ECG computed from a pseudo electrode placed just below the ventricular apex of the 3D rabbit heart. The P wave, QRS complex and T wave can be clearly seen.

7.1.2 ECG recordings

As shown in Section 4.2.3, it is possible to reproduce an ECG from a pseudo-electrode placed at a point in space outside a mass of simulated cardiac tissue. In order to reproduce ECGs from the 3D rabbit heart, an electrode was placed just below the ventricular apex. The computed ECG during the beat used to create Figures 7.1, 7.2 and 7.3 is shown in Figure 7.5.

The ECG can be seen to be qualitatively similar to that in Section 4.2.3, and that expected from experimental data [185]. The initial few milliseconds of the P wave are slightly noisy. This may be caused by the slight geometric irregularity due to the fact that the atria were not filled with blood prior to DT-MRI scan. In addition, both the S
7.1: PROPAGATION THROUGH THE 3D WHOLE HEART

<table>
<thead>
<tr>
<th>Interval</th>
<th>Experimental Recording</th>
<th>Simulated Recording</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>350.8 ± 50.1</td>
<td>298</td>
</tr>
<tr>
<td>PR</td>
<td>72.5 ± 6.2</td>
<td>65</td>
</tr>
<tr>
<td>QRS</td>
<td>50.0 ± 4.3</td>
<td>32</td>
</tr>
<tr>
<td>QT P</td>
<td>147.7 ± 24.5</td>
<td>158</td>
</tr>
</tbody>
</table>

Table 7.1: Summary of the relevant ECG parameters as calculated from the 3D rabbit whole heart model, in addition to those from experimentally recorded rabbit ECGs [186].

and T waves are substantially larger than their 2D counterparts, likely corresponding to the increased relative size of the ventricles in 3D.

Along with the qualitative analysis given by the measured ECG shown in Figure 7.5, a quantitative approach was necessary for full validation of the whole heart characteristics. To this end, common ECG intervals were measured and compared with experimental data.

The RR interval was measured as 298 ms, which again corresponds closely to the experimentally recorded value of 350.8 ms ± 50.1 ms. The PR interval was measured as 65 ms, which compares favourably with the experimental recording of 72.5 ms ± 6.2 ms. As with the 2D model, the value for the QRS complex length is outside of the experimental range reported, with the value from the 3D model measured as 32 ms, slightly outside the measured experimental range 50.0 ms ± 4.3 ms. Once again, it is useful to point out a wide range in QRS lengths within rabbits has been reported, and such a difference is likely down to individual variation in QRS length [186–189]. The QTP length is once again in close correlation with experimental recordings, with an interval of 158 ms measured via simulation, compared with 147.7 ms ± 24.5 ms via experiment. These results are summarised in Table 7.1.

As a further test of the individual single cell models, the ECG recorded from the whole heart, and the relationship between the two, APs from individual cells within
important areas of the heart were recorded from the 3D model, and plotted alongside the ECG recording. The resulting relationships are shown in Figure 7.6. As seen in the Figure, the AP generated within the AM closely corresponds to the P wave. The initiation of an AP within the apical atrial cell is close to the start of the QRS complex, with the initiation of a basal AP occurring towards the end of the QRS length. The basal ventricular cell repolarises before its apical counterpart, ending roughly at the peak of the T wave, while the apical ventricular cell is among the final cells to repolarise, corresponding with the end of the T wave.

7.2 Simulation of drug action

In order to both validate the behaviour of the complex 3D model, and to further investigate the complex activity within the rabbit heart, a number of case studies focusing on the effects of drugs were carried out.

7.2.1 Ivabradine

Ivabradine is a commonly used medication for the treatment of certain ischemic heart diseases in humans [232]. Application of Ivabradine selectively inhibits the $I_f$ current [233]. Highly expressed within the SAN and other autorhythmic tissues, $I_f$ is important in regulating the pacemaker activity leading to the generation of APs. Reduction of $I_f$ reduces pacemaking activity and decreases heart rate. Ivabradine is dose dependent, meaning a higher concentration or dose results in a larger effect.

As a selective drug, the effect of Ivabradine could be simulated by a reduction in the magnitude of the $I_f$ current within the single cell models of ion channel kinetics. Higher doses of Ivabradine were simulated by a progressively larger reduction. The effects of Ivabradine application, leading to a reduction in $I_f$, on the rabbit ECG are shown in Figure 7.7.
Figure 7.6: Action potential recordings at cells throughout the heart during the propagation of a normal heartbeat. (i) shows the AP recorded from an atrial cell. (ii) shows the AP recorded from a basal ventricular cell. (iii) shows the AP recorded from an apical ventricular cell. (iv) shows the ECG recorded during the same timescale.
Figure 7.7: ECGs recorded from a pseudo electrode placed just below the rabbit ventricle during the simulated application of Ivabradine via a successive block of the $I_f$ channel. The PP interval between the first and second beats is shown to be slightly extended from the subsequent beats due to the transient effects caused by the initial conditions. Successive reduction of $I_f$ channel conduction is shown to extend the PP interval while having no noticeable effects on the remaining ECG intervals. A summary of the relevant ECG time intervals can be seen in Figure 7.8.
Figure 7.8: ECG time intervals showing the simulated effect of Ivabradine upon the 3D whole rabbit heart model. Intervals were recorded from the ECGs shown in Figure 7.7.

The effect of Ivabradine on the majority of ECG parameters is small. The QRS and PR intervals are unchanged. Increased application of Ivabradine causes a successive increase in the PP interval, correlating with a slowing in pacemaker rate, as expected. Each 10% block of $I_f$ corresponded to roughly a 3ms increase in the PP interval. Also, although $I_f$ is not expressed within the ventricles, there are slight changes (1%) within the QT intervals. This is likely simply due to the reported ability of cardiac cells to vary APD at different pacing rates, known as restitution [234–236].

It is interesting to note that the initial simulated application of Ivabradine caused a slight decrease in PP interval, the opposite of expected behaviour. This decrease was complemented by a change in P wave morphology as seen by comparison between Figure 7.5 and Figure 7.7, however there was no further change between different levels of Ivabradine application. It is likely that this is caused by a shift in pacemaker
site, possibly from the slow pacing centre of the SAN to the faster pacing peripheral region. Although not usually associated with a decrease in PP interval, such a shift in the leading pacemaker site is a commonly seen feature of pharmacological applications to rabbit hearts [237]. In addition, differences in natural pacing rate between different areas of the SAN have been widely reported [86, 104, 106, 107]. All further simulated applications of Ivabradine closely correspond to experimentally reported effects [238, 239], as well as a similar study on a 1D whole rabbit heart [49].

7.2.2 Tetrodotoxin

Tetrodotoxin, or TTX, is a potent neurotoxin found in nature [240, 241]. Though highly poisonous, it has been found to have limited medical uses [242]. It acts to block the sites of the fast sodium channel, thereby reducing $I_{Na}$ [243]. As $I_{Na}$ is largely responsible for the upstroke during phase 0 of an AP, this has the effect of suppressing electrophysiological behaviour. As a selective inhibitor acting only upon the $I_{Na}$ current, the effects of TTX could be simulated by a reduction in the magnitude of the $I_{Na}$ current within all cell types. The effects of $I_{Na}$ reduction caused by the application of TTX are shown in Figure 7.9.
Figure 7.9: ECGs recorded from a pseudo electrode placed just below the rabbit ventricle during the simulated application of TTX via a successive block of the $I_{Na}$ channel. As with the $I_f$ block, PP interval between the first and second beats is shown to be slightly extended from the subsequent beats due to the transient effects caused by the initial conditions. Successive reduction of $I_{Na}$ channel conduction is shown to extend every ECG interval, until a 40% block where Purkinje-ventricular conduction is abolished, causing a lack of a QRS complex or T wave. A summary of the relevant ECG time intervals can be seen in Figure 7.10.
Figure 7.10: ECG time intervals showing the simulated effect of TTX upon the 3D whole rabbit heart model. Intervals were recorded from the ECGs shown in Figure 7.9.

The application of TTX has numerous effects on the behaviour of the 3D heart, as reflected in the following changes to ECG morphology. Firstly, the PP interval was increased, corresponding to a lack of $I_{Na}$ within the SAN causing a slightly delayed AP generation within the pacemaking tissue. Successive application of TTX reduces $dV/dt_{max}$ within cardiac cells, as the $I_{Na}$ current is largely responsible for the initial upstroke of the AP [12]. This causes a decrease in conduction velocity throughout the heart, with the slowing of impulses throughout the AVN and PF tissue increasing the PR interval, and the slowing of impulses throughout the ventricular tissue corresponding to an increase in QRS duration. At 40% $I_{Na}$ block, conduction across the Purkinje-ventricular junctions is terminated, due to the inability of the weakened Purkinje AP to generate a response in the substantially higher volume of ventricular tissue. As with the simulated application of Ivabradine, these results are all in line with ex-
pected results given the nature of TTX action on individual rabbit cardiac cells [244],
and the experimental reports of TTX application to cardiac tissue [245], and with a
similar study on a 1D whole rabbit heart [49].

7.3 Simulation of atrial fibrillation

As mentioned in Section 1.4, the ultimate goal of cardiac modelling is to provide a
fast and accurate framework with which to investigate cardiac behaviour, particularly
with a view to the development of medical treatments for various common cardiac
problems. To this end, accurate simulations of cardiac arrhythmias are necessary. This
section covers the generation of Atrial Fibrillation (AF) within the rabbit heart, and
a summary of the insights granted by such an experiment. AF is the most common
cardiac arrhythmia [246], affecting roughly 2.2 million people within the United States
[247]. The risk of AF increases with age, affecting from 0.5% at ages between 50 and
59 years, to almost 9% of adults between the ages of 80 and 89 years [248]. Therefore,
the generation and termination of AF is a sensible area for investigation.

7.3.1 Methods

As in Section 7.1, the monodomain equation was solved using a finite difference
method, with identical spatial and temporal steps, on an Nvidia GTX 480. Atrial fib-
riillation was induced by the cross field protocol. A square stimulus of duration $4ms$
was applied to the top half of the atria $38ms$ after the start of the simulation, resulting
in the generation of a spiralling wave within the atria.

7.3.2 Results

AF was initiated as described in the previous section. Figure 7.11 shows snapshots
of membrane potential throughout the whole 3D heart throughout the generation of
AF. While the leading AP propagates as normal through the AVN, Purkinje network
and throughout the ventricles, electrical activity is still seen in the atria long after the stage at which it would normally repolarise. In Figure 7.12, the spiral wave can be seen to continue to evolve throughout the atria, during the beginnings of ventricular depolarisation. Figure 7.13 shows the eventual self termination of AF within the atria, along with the final stages of ventricular repolarisation.

The rabbit atria is small and compact, and due to the relation between atrial size and AP wavelength it is difficult to generate sustained AF within a rabbit heart. Within the 3D model, the spiral wave corresponding to the generation of AF is seen to self terminate after only a few milliseconds. This is in good agreement with experimental results on Langendorff-perfused rabbit hearts, which have shown that artificially dilating the atria vastly increases the susceptibility of the rabbit heart to AF [249].

However, the generated AF remains for long enough for a number of conclusions to be drawn. It can be seen that an AP continues to propagate throughout the atria even after the beginnings of ventricular repolarisation. This suggests that the AVN and PF network are correctly acting in order to filter the transmission of high frequency signals towards the ventricles, allowing the ventricles to contract at a normal frequency despite the abnormal behaviour of the atria under AF conditions.

7.4 Conclusions

Throughout the various cases used to simulate a variety of cardiac responses to applied stimuli, the 3D model correctly reproduces expected experimental behaviour. Under normal physiological conditions, ECG morphology and time intervals, as well as activation sequence closely correspond to those recorded experimentally from rabbit hearts.

Upon the application of Ivabradine, the overall trend within ECG intervals matches those expected from experimental results. However, the initial application of ivabradine caused a slight decrease in overall P-P interval. However this decrease, along with the change in P wave morphology can be explained by a shift in leading pacemaker site.
Figure 7.11: Snapshots of membrane potential throughout the 3D rabbit heart taken at 15ms intervals during the initiation of AF. The excitation wave is shown to be generated within the SAN, before spreading out into the atrial tissue. After 38ms a stimulus was applied to the top half of the atria, and a spiral wave is seen to be generated.
Figure 7.12: Snapshots of membrane potential throughout the 3D rabbit heart taken at 15ms intervals during the evolution of atrial fibrillation. The spiral wave is seen to continue propagating.
Figure 7.13: Snapshots of membrane potential throughout the 3D rabbit heart taken at 15ms intervals during the self-termination of atrial fibrillation. After roughly 180 seconds, atrial fibrillation self terminates.

As with the application of drugs, the generation of AF within the model matches experimentally observed behaviour of AF within rabbit atrial tissue. Sustained re-entry was not possible within the 3D model due to the limited volume of atrial tissue, however it has been suggested that an increase in atrial volume corresponds to an increase susceptibility to AF [249]. Regardless, the self terminating AF generated within the 2D model provides an interesting look at the interactions within heterogeneous heart tissue, specifically the actions of the AVN and Purkinje network as a signal processor, protecting the ventricles from the harmful effects of high frequency stimulation.
Discussions and future work

This final chapter discusses and outlines the major conclusions and breakthroughs made throughout the creation of this thesis, along with their relevance in the wider world of cardiac modelling. The shortcomings and limitations of the models are discussed, with a view to possible future work and furthered understanding.

8.1 Summary

This thesis comprises a number of novel computational methods focussed on the investigation of complex phenomena within the rabbit heart. The focus of this thesis can be divided into three sections, all ultimately working towards the development of a comprehensive 3D rabbit heart model that can be used for the efficient simulation of the effects of drugs and arrhythmias; the development of a detailed 2D geometry with associated electrophysiology as a prototype and proof of concept for whole heart modelling, the development of a detailed 3D geometry for the purposes of rabbit whole heart modelling, and the use of GPGP to facilitate reasonable simulation timescales on large-scale, multidimensional cardiac models.

A number of single cell models to describe electrophysiologically different regions of the rabbit heart, including central and peripheral SAN tissue, three distinct and functionally different areas of AVN tissue, the Purkinje network and ventricular tissue,
were collected and re-written into a standard form. A 2D geometry was created, by computational and manual segmentation of a histological slice of rabbit heart, and populated with different cell types corresponding to SAN, AVN, PF and ventricular and connective tissue. The ventricular tissue was further classified by subdivision into Endo, Epi and M cells, based on an experimentally observed distribution. Finally, a 2D approximation of the Purkinje network and the AVN were added. This was then converted into a 2D lattice array, from which each cell type has been associated with their corresponding single cell electrophysiological model.

The 2D model was allowed to evolve over an extended period of time, producing a continuous heartbeat with no application of external stimuli. This heartbeat was shown to conform to existing experimental recordings of activation sequence, ECG morphology and ECG time intervals, indicating that the 2D model is a good representation of whole heart behaviour, and therefore provides a solid basis for the application of more detailed, higher dimensional whole heart models constructed in a similar fashion.

In order to extend the simulations into 3D, code was re-written into the CUDA language to take advantage of the highly parallel nature of graphical processing devices. A 68 fold increase has been observed when comparing GPU to CPU processing, given similarly dated and priced technology for both. In addition, the CUDA code is transferable across CUDA-enabled NVIDIA GPU processors, allowing portable distributions to be created for execution across a variety of hardware.

A 3D rabbit whole heart geometry was reconstructed from DT-MRI data set. The ventricles were segmented into left and right ventricular tissue, and then subdivided into Endo, Epi and M cell regions based on the observed fibre angles within the original data set. The atria were segmented into left and right using the same method, and a Purkinje network, as well as AVN and SAN regions were added based on computational reconstructions of histological data. Similar methods of lattice array conversion and single-cell model incorporation were employed in the 3D model as in the 2D model, and the simulation was allowed to beat without the application of an external stimulus. An ECG and activation sequence was recorded, and found to compare
favourably with experimental data. The applications of Ivabradine and Tetrodotoxin were simulated via blocking the $I_f$ and $I_{Na}$ channels respectively, and again whole heart characteristics were in good agreement with those recorded experimentally. Finally, AF was initiated via the cross field protocol, producing the expected behaviour, and further validating the 3D model as an accurate simulation of rabbit heart behaviour.
Figure 8.1: Overview of the major phases undertaken within this thesis. Red indicates the creation of single cell models, green and blue correspond to the important steps in the creation of the 2D and 3D models respectively. Finally, purple boxes correspond to the case studies carried out on the completed 3D model.
8.2 Discussions

In this section, the leading advances made during the course of this thesis are discussed, with a focus on both the positive improvements made, and negative aspects holding back progression.

8.2.1 The 2D Rabbit Heart

While several single cell models are available for the rabbit heart, there has currently been very little investigation into whole heart modelling. A comprehensive 1D model of the whole rabbit heart has been created [49], but to date there is no electrophysiological model that integrates a wide variety of different cell types describing the whole rabbit heart into an anatomically accurate geometry in higher dimensions.

The 2D model introduced here provides an insight into the whole heart dynamics caused by the interaction of different individual cells on a larger scale. CVs within each area of the model were chosen to reproduce those from experiment. The model correctly reproduces experimentally observed activation sequences and ECG parameters, and represents a solid proof of concept for multi-scale, higher dimensional whole heart models. As the model was limited by its 2D nature, no comprehensive case studies on pharmacological, surgical or pathological conditions were carried out. It is likely that the applications of this model with regards to further work have been largely superseded by the developments made into higher dimensions with the creation of the 3D model within this thesis, however its fast and efficient nature, coupled with its extreme portability allow it to be used in a variety of instances, across a wealth of different species, geometries and cell types.

8.2.2 The CUDA framework

In order to match the demand for increasing complexity, size, and dimensionality of biophysically detailed models of the heart, high performance computing is required
In order to match this demand, there has been a number of investigations into the relevance of a number of high-performance computer solutions within the realms of cardiac computation [215, 216], however there are advantages of GPU-based simulation over other solutions.

Possibly the most important factor as to the benefits of GPU-based modeling over multi-core CPU machines is one of cost. Reumann et al [216] showed a speed up of roughly 200x that presented here using a standard non-blocking Message Passing Interface (MPI) function. However, their simulations were carried out on 16384 of IBMs Blue Gene cores, valued at £ 13.3 million. By comparison, the GPU used to obtain the 68x speed up recorded in this thesis is an onboard mobile card included in the price of most laptops. Pitt-Francis et al also investigated the use of MPI in their paper [215], showing speed increases of roughly 10x that of a single CPU core using a 16 CPU core cluster. Once again, this speed increase is vastly lower, and less cost efficient than the speed increase reported here. The speed increase, estimated price and speed per price of each individual study are summarised in Table 8.1.

For the solutions by Pitt-Francis et al, CPU cost was estimated based on the current price of a standard Intel processor. The cost of the Reumann et al solution was based upon the current price of Blue-Gene hardware. While both cheaper and more expensive CPUs are available, it is a reasonable assumption to model differences based on a rough average cost. In addition to slight changes between CPU models, prices of computer hardware are naturally volatile. Regardless, the GPU is seen to vastly outperform both the high end and economy solution presented in terms of performance per price.

Outside of the realm of biological modelling, there have been numerous investigations into the uses of CUDA within other areas of science. Speed increases of a similar order to that presented here have been reported elsewhere [221–223], however the exceptionally highly parallel nature of detailed multi-scale cardiac modelling, with millions of individual cells modelled in a similar way, advances cardiac computation to the higher end of the speed up range expected by Nvidia [250].

The results outlined within Chapter 6 outline the GPU as a competent co-processor,
Table 8.1: Summary of the differences in speed, price and speed per price for a variety of HPC solutions. Speed increases were obtained from the respective published work [215,216]. For the solutions by Pitt-Francis et al, CPU cost was estimated based on the current price of a standard Intel processor. The cost of the Reumann et al solution was based upon the current price of Blue-Gene hardware. The GPU is seen to outperform both CPU based solutions.

8.2.3 The 3D Rabbit Heart

The creation of the 3D geometry is an important forward step into the modelling of a whole heart. It represents the culmination of a number of different studies into the detailed geometry of each individual area of the rabbit heart. From the individual studies used to create the 3D geometry, both the SAN and AVN were based upon rabbit data, providing a reliable source of relevant data for inclusion within the model. Due to the substantial difficulty in identifying the complex structure of the Purkinje network, there is a lack of data available for the rabbit. Thus, the only available reconstructed Purkinje network was based on data from a canine. While dog and rabbit hearts have been shown to be similar, homogeneity of species across the model would be ideal, as discussed in Section 8.3.1.

With the inclusion of the individual cell models introduced in Section 3, the model correctly predicts the evolution of membrane potential and activation sequence through-
out the whole heart. This activity is backed up by comparison to experiment of the ECG time intervals, and overall ECG morphology as discussed in Section 7.1.2.

In addition to a “wild-type” experimental run designed to simulate normal cardiac behaviour, simulations to assess the the effects of two channel blocking drugs were carried out on the 3D rabbit heart. The first simulation dealt with the application of increasing doses of Ivabradine via an increasing reduction in $I_f$ conductance. The second simulation dealt with the simulation of increasing doses of TTX via a similar conductance reduction, this time in $I_{Na}$. In general, every simulation closely followed experimental results reported by a variety of sources.

The final case study designed to test both the validity of the 3D model as a simulation tool, and the further use of the model to predict arrhythmic effects was a simulation of the effects of AF. AF was generated via a cross-field stimulus, and allowed to proceed until it self terminated a few hundred milliseconds later, as expected. While there was no time to carry out any detailed investigation into the effects of drug action upon the genesis and sustainability of AF, as discussed in the following section, the model provides a solid base from which to extend experimentation further.

## 8.3 Future work

In this section, possible future improvements to the techniques and experiments carried out within this thesis are introduced and discussed.

### 8.3.1 Anatomically detailed geometries

In this thesis, all available resources have been utilized in the creation of the 2D and 3D geometry of the rabbit heart. However, while all major features of the heart are present in the models, further work can be made if there are more available resources from biological data. In the 2D model, due to the absence of structural data for AVN, Purkinje fibre network and SAN within the given two dimensional geometry, a schematic
representation of the AVN was created based on experimentally obtained parameters, a Purkinje fibre network was added by assuming every cell in the internal ventricle wall was a PF cell, and an area of the right atrial tissue was designated as SAN cells. While using approximation for these structures is necessary, as the AVN and Purkinje network allow the conduction of an AP from the atria to the ventricles, and the SAN provides the pacemaking impulse that drives the entire heart, it would be ideal if there were available 2D geometries describing these areas within the rabbit heart.

With respect to the 3D model, a dog Purkinje network was applied to the rabbit ventricles in this study. While the Purkinje network within the dog was demonstrated to be similar to those in rabbits it would almost certainly be more accurate to use a rabbit Purkinje fibre network geometry instead. Advances into the generation and recording of rabbit Purkinje geometry have been made very recently by Akinson et al [251]. The authors have made numerous confirmations of the importance of a detailed Purkinje network within the rabbit, including detailed expression levels of major ion channels within the networks using quantitative Polymerase Chain Reaction (qPCR). In addition, the authors have noted a more developed His-Purkinje network in the left ventricle than the right ventricle, which may be of clinical relevance and should be taken into account of in future models. In conclusion, while necessary liberties were taken with the inclusion of some structures to both the 2D and 3D geometries, all models were created with a forward thinking approach, allowing the straightforward inclusion of more detailed geometric data if and when it becomes available.

As mentioned within Section 8.2.3, the SAN model produces slightly anomalous behaviour due to a slight possible shift in leading pacemaker site under the effects of $I_f$ blocking. To this end, the inclusion of more detailed heterogeneity within the SAN region is a possible source for further investigation. In particular, there is increasing evidence for a gradient model of SAN activity as opposed to the segmented central and peripheral regions presented here [86, 252, 253].
8.3: FUTURE WORK

8.3.2 Drug actions and atrial fibrillation within the 3D model

Even with the large increases in computational power offered by the GPU-based CUDA version of the 3D mode, computational timescales remain a leading factor in the limitation of obtainable results within this thesis. While timescales for a single beat of simulation time were reduced from a matter of years to a matter of days, multiple beats are generally desired to limit certain transient effects. Therefore, even utilising the increase in efficiency offered by GPU based code, simulation timescales for a single study can last 3-4 days. For comprehensive channel blocking studies such as those in Section 7.2, which require a simulation for each successive application of a drug, weeks of computational time must be set aside.

For this reason, it was not possible to carry out a full range of studies upon the 3D heart. Ideally, the effects of other drugs would be investigated. The code has been set up to allow the application of both E-4031, a selective potassium channel blocking drug, and Nifidepine, a selective calcium channel blocking drug, via modulation of the $I_{Kr}$ and $I_{CaL}$ channels respectively. In addition, an original aim was to verify the effects of each drug upon the generation and sustainability of AF under a number of conditions, however this was not possible due to the aforementioned time restraints.

In addition to the case studies carried out here, the highly dynamic and compliant nature of the 2D and 3D models makes additional investigation a simple task. The dependability of the models on either text based integer array inputs, or .bmp format images allows easy generation of heterogeneous areas within the model. For example, the generation of ischemic, fibrotic or other heterogeneous areas can be carried out simply by outlining the affected areas within any image editing software such as paint or photoshop, with any of the wide variety of tools provided by each program, or by computerised generation of a variety of shapes based on stochastic or deterministic variables. While not covered in this thesis specifically due to the focus on the rabbit, the generation of areas of increasing reduction in conductance within the mouse ventricle using various random protocols within this 2D model has been carried out elsewhere.
8.3: FUTURE WORK

8.3.3 The 3D human heart

It is commonly accepted that the final aim of computational modelling is the creation of detailed human models to investigate arrhythmias, propose solutions and test both surgical and pharmacological interventions and cures. To this end, the logical final step in this work would be the creation of a fully functioning human model to sit alongside the current 3D rabbit model.

The creation of computational algorithms using CUDA to resolve the multitude of partial and ordinary differential equations arising from multiscale cardiac modelling has the potential to be a huge step forwards towards the goal of a detailed, 3D human heart. Throughout the creation of the CUDA algorithms used within the 3D rabbit model, great care was taken to separate interdependence between the overall framework and individual cellular models. Therefore, cellular models for any species can be quickly switched in and out depending on the needs of the model.

A detailed 3D geometry of the human heart has currently not been constructed, and single cell data for each individual cell type within the human is sparse. However, with the constant progress being made into each of these areas, the creation of a 3D whole human model is a definite area for future advancement.

8.3.4 CUDA and GPU programming

The computational advantages of GPU based CUDA programming are outlined within this thesis. CUDA based code was found to run at roughly 68x faster than conventional C++ code, even on a comprehensive, detailed and heterogeneous 3D heart. However, it is worth noting that the specific speed increases obtained within this thesis are closely tied to the hardware upon which they were executed. As a prototype piece of work, the Nvidia 330M used to test the speed differences between the GPU based CUDA and CPU based C++ was a cheap, widely available, low specification card which is essen-
tially free with most laptops. The 330M contains 48 cores, each clocked at 1.2 GHz. Nvidia currently produces GPUs with even higher clock speed, and up to 512 cores. Although investigations have not been carried out into the scalability of cardiac modelling using these high-end cards, speed increases of up to 2000x have been reported in the fields of genetic algorithms, and fluid dynamics [250].

8.3.5 Additional effects and in depth models

Throughout this thesis, the focus has been squarely on the electrophysiological behaviour of the heart, using a static, immobile geometry unaffected by the electrical changes passing through it. In actuality, cardiac tissue is a complex system of muscle fibres, whose motion and contraction influence the underlying ionic mechanisms within single cells [254–256]. While these mechanisms are hugely complex and outside of the scope of this thesis, they must be included in any forward looking approach to the eventual creation of a fully detailed rabbit heart.

8.4 Closing words

This thesis represents the collection and review of a wide variety of single cell models, as well as the creation of two dynamic frameworks in two, and three dimensions respectively. Single cell models are introduced into these dynamic models, from which normal, drug-affected and arrhythmic electrophysiology of the rabbit heart can be simulated. While the models are limited in some ways by a lack of current experimental data, they represent a forward-thinking approach designed to incorporate any future discoveries into the geometry, structure and function of the heart on both a microscopic cellular, and macroscopic whole heart level.
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