Clinical applications of Physiome Project models

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Abstract

The Physiome Project is contributing to the bioengineering analysis of human physiology and associated clinical applications by developing models of structure–function relations that incorporate accurate models of human anatomy. Biophysically based equations are solved, subject to measured boundary conditions, on these anatomical geometries. The primary goal is to include all relevant physical processes together with a multi-scale modelling approach that attempts to link protein level function in ion channel or signal transduction pathways, for example, to tissue structure and the integrative function of whole organs or organ systems. We give four examples of the physiome modelling approach, all motivated by clinically important problems: reflux of stomach contents through the gastro-oesophageal junction, aspects of the musculo-skeletal function of the knee and leg, tracking the spread of melanoma in lymphatic ducts and analyzing ultrasound measurements of cardiac mechanical function.

1 Introduction

The Physiome Project represents an engineering approach to computational physiology [1–3]. It includes the development of XML-based mark-up languages such as CellML (www.cellml.org) for encoding models of cellular function (and, in fact, any time-dependent but non spatially varying process) and FieldML for encoding parameterisations of spatially varying fields. The project is also committed to the development of tools for creating models, editing and visualising them, and computational code for solving the equations. It is based on open source software (see, e.g., www.cmiss.org), and is committed to providing bioengineers, physiologists and, in some cases, clinicians with user-friendly tools for understanding physiological processes or interpreting clinical data.

The main features of the physiome approach to modelling are (i) the accurate mathematical representation of the anatomy; (ii) the use of biophysically governing equations (i.e. based on physical conservation laws); (iii) the coupling of multiple systems of biophysically based equations, such as in cardiac electro-mechanics which couples large deformation mechanics with the solution of reaction-diffusion equations for wavefront propagation; and (iv) the use of multi-scale modelling – linking ion channel conduction in cardiac cells, for example, to tissue-level diffusive processes. Developing models of physiological processes that encompass both multiple physics (tissue mechanics, fluid mechanics, electrical current flow, etc.) and multi-scale aspects is very difficult and has been achieved in few cases (the heart is one
of them). However, the framework is being developed. There are now over 300 models of cellular function in the CellML database (see www.cellml.org/models); much progress has been made on at least 4 of the body’s 12 organ systems (cardiovascular [4], respiratory [5], musculo-skeletal [6] and digestive [7]) and the work is well underway on several others. The return on this effort is partly an enhanced understanding of physiological structure–function relations and partly the use of physiome models in numerous clinical applications in education and training, clinical diagnostics, surgical planning, design of medical devices and drug discovery.

We illustrate some of these clinical applications in this chapter with models of the gastro-oesophageal junction (Section 2), musculo-skeletal system (Section 3), the lymphatic system and melanoma (Section 4), and ventricular mechanics (Section 5). In all the cases, the applications are at an early stage of development and all have the close involvement of medical specialists to ensure that the models are clinically useful.

2 Modelling the gastro-oesophageal junction

The gastro-oesophageal junction (GOJ) has two main functions: it relaxes with swallowing to allow free passage of food from the oesophagus to the stomach and at the same time it maintains a pressure barrier between positive intra-abdominal pressure and negative intra-thoracic pressure to prevent reflux of gastric contents into the oesophagus between swallows [8, 9].

There are a number of factors which help the GOJ in maintaining its closure. For instance, the arms of the crura (a muscle thickening of the diaphragm) are wrapped around the junction to help it close, and the phreno-oesophageal ligament (a ligament extending from the crura towards the GOJ) maintains the axial position of the GOJ during swallowing. These factors add to the complexity of the role the GOJ plays during swallowing.

If the GOJ fails to prevent the reflux of the gastric contents back into the oesophagus during swallowing, the *gastro-oesophageal reflux disease* (GORD) may occur. Long-term complications of GORD might result in inflammation of the oesophagus, caused by acids reflected from the stomach or cells in the oesophageal wall developing an abnormal shape and colour, leading to cancer. New Zealand has the largest mortality rate per capita in the world followed by the United States [10], with a total number of 3381 patients hospitalised in New Zealand with GORD in the years 2001 and 2002 [11]. This disease also affects an estimated 5–7% of the global population [12] with direct and indirect costs of US$10 billion per year [13].

Since the structure and position of the GOJ is different at rest compared to when it is distended during swallowing, it is difficult to image radiographically [14]. The most common diagnostic tools used to detect swallowing difficulties include manometric measurements and barium swallows. While the manometric readings can detect abnormalities in the peristaltic wave from pressure measurements, the barium swallow can detect peristaltic abnormalities visually. Each method has its limitations including cost and exposure to x-rays. However, a cost-effective tool which allows the clinicians and patients to view the anatomy of the oesophagus and the GOJ and at the same time observe the peristaltic wave in three dimensions is currently not available.

To obtain a better understanding of the causes of GORD, more information about the detailed microstructure of the GOJ and its effect on the functional behaviour of the GOJ and the oesophagus is required. To help facilitate this, three-dimensional (3D) anatomical geometries of the oesophagus and GOJ are being constructed [15]. The model combines the detailed microstructural anatomy and physiology of the GOJ in a way not attempted previously.
The model will not replace current diagnostic tools, but it is envisaged that it will be used alongside the current techniques to provide better understandings of how the anatomy and physiology of the GOJ are integrated both in health and disease states and allow the determination of the contributions of different elements of anti-reflux surgery. Information from this study will also be useful for designing clinical treatments, and in education of health professionals and patients.

2.1 Model construction

To obtain accurate geometry of the oesophagus and the GOJ, the boundaries of the specified structures were manually traced on a set of cross-sectional photographic images obtained from the Visible Human Project [16], as shown in Figure 1(a). A small number of points were selected from the traced data set to construct 3D elements. To obtain a smoother and more accurate model, the oesophagus was fitted using an iterative linear fitting process with tricubic Hermite basis functions. The fitting procedure consisted of calculating the orthogonal (or closest distance) projections of the ‘data points’ onto a point on the face of the mesh. The objective of the iterative linear fitting is to minimise the root mean square (RMS) error by minimising the distances between the data points and the model. Figure 1(b and c) illustrates the effect of fitting on the 3D model. The final oesophageal mesh is shown in Figure 2 in relation to other structures in the region.

2.2 Microstructural information

Before mathematically incorporating the patterns of muscle activity (e.g. swallowing) derived from pressure studies, detailed information about muscle fibre type, size and orientation is

Figure 1: (a) The boundaries of the oesophagus were manually traced on a set of cross-sectional photographic images (2 mm apart) obtained from the Visible Human Project. (b) A small number of points were selected from the traced data points to construct 3D oesophageal model. The initial model of the oesophagus is crude with sharp edges. (c) To increase the accuracy of the model and to achieve smooth surfaces, the model undergoes an iterative linear fitting procedure.
needed. For this reason, the oesophageal wall was initially divided into three layers representing the outer longitudinal muscle (LM) layer, followed by the circular muscle (CM) layer and, finally, the innermost sub-mucosal (SubM) layer in accordance with Ref. [17]. The general fibre orientations were then added to the LM and the CM layers in a form of vectors corresponding to the muscle fibre directions, as shown in Figure 3.

Microstructural information is currently being obtained from a cadaver tissue. The GOJ tissue was surgically excised, immersed in a fixative solution to preserve its anatomical features and embedded in wax. The sample was then taken to a extended-volume imaging system [18] to obtain the microstructural information. The device consists of a three-axis translation stage where a tissue sample embedded in wax can be sequentially imaged and milled. At each step, the top surface is stained for fibre type and connective tissue and imaged using a high-resolution (8.2 megapixel) digital camera. The imaged surface is removed by the mill and the process is repeated throughout the tissue block. To provide proof of principle, the process has been applied to an en bloc harvest of the GOJ from a sheep with a sample image shown in Figure 4.

2.3 Functional simulations

Once the anatomical model with detailed microstructural information is obtained, the mechanical activity of the oesophagus and the GOJ will be simulated using the same technique that has been used to model the heart [19]. The governing equations of mechanics are currently used.

Figure 2: Three-dimensional anatomical geometries of the oesophagus, diaphragm, crura, inferior vena cava, stomach and aorta.
Figure 3: Vectors (represented by short grey lines) were added to represent the general fibre orientation as shown on the arms of the crura.

Figure 4: Image of stained GOJ from sheep specimen showing the muscle layers and connective tissue. Image outlines the transition in the muscle layer between the oesophagus to the GOJ and down to the stomach. Note that the central tendon of the diagram has arched downwards as part of the wax-embedding process.

to represent the movement of the oesophagus and GOJ under the influence of applied forces. The results obtained from the model will be evaluated qualitatively using pressure measurements obtained from manometric readings of a person of similar age and gender to the cadaver that was used to obtain the microstructural information. Once the model is appropriately validated, further simulations will be performed to improve our understanding of the roles of the various components in disease states such as GORD.
3 Modelling musculo-skeletal system mechanics

The modelling of musculo-skeletal system (MSS) mechanics can be organised into a hierarchical order covering a wide range of analyses from simple rigid-body mechanics of skeletal bones to complex continuum mechanics problems with active muscle contraction. One clinical application of rigid-body mechanics of skeletal bones is to determine the joint angles from motion capture data (kinematics) of a patient with walking abnormalities (e.g. cerebral palsy) during gait. This helps clinicians to make decisions associated with surgical procedures that alter muscle length to rectify the patient’s walking pattern. In cases where it is not feasible to identify the spastic muscles in a pathological gait accurately using joint angles alone, it is necessary to consider muscle deformation during gait. This can be achieved by the inclusion of muscle models and morphing them to maintain attachment points or solving passive finite elasticity problems together with a suitable constitutive model subject to displacement boundary conditions. The addition of cell models for activation of neuromuscular junctions provides the ability to characterise additional function. An example where this type of modelling approach can be utilised is to study the forces generated in the muscles associated with mastication (chewing). The following sections outline the frameworks involved in different modelling approaches including the creation of anatomically based MSS structures with some examples.

3.1 Anatomically based geometries

To use any musculo-skeletal model for clinical or any other industrial applications, one needs anatomically based structures of the MSS. The creation of subject-specific anatomically accurate geometry of structures therefore plays a vital role in the modelling process. The methods outlined below briefly describe how to create such structures.

3.1.1 The MSS database (generic models)
Currently, we have a database consisting of finite-element (FE) volume geometries of most of the muscles and bones of the human body. These structures have been created by fitting [20] linear FE volume meshes to the data derived from two sources. For muscles, the Visible Human [16] images have been digitised to create the data points using the software CMISS (www.cmiss.org). The data for bones were created by the scanning of full-scale plastic skeleton model SOMSO (www.somso.de) using a hand-held Polhemus Fastscan laser scanner. Figure 5 depicts the steps involved in creating an anatomically based structure.

![Figure 5: Fitting procedure for creating anatomically based structures of MSS. (a) Digitisation of VH images using CMISS. (b) Initial linear mesh of rectus femoris created using some of the digitised data. (c) The fitted tri-cubic Hermite FE model of the muscle.](image-url)
The models created via the process outlined above are used as the reference or generic FE meshes. To use these structures for subject-specific analyses, it is necessary to customise them to match with the musculo-skeletal structures of the subject.

3.2 Customisation of generic models

We use a method known as ‘host mesh fitting’ [21] to customise the generic models available in our database to create subject-specific structures. This technique will be used again in later examples in this chapter. In this case, two sets of fiducial markers (data points) are required which are chosen as anatomical landmarks of the structures. For example, some of the fiducial markers used in femur customisation are centre of femoral head, greater trochanter and lateral and medial epicondyles. These control points on generic structures are readily available, and the equivalent points pertinent to the subject (known as target points) are derived from a series of the subject’s magnetic resonance images (MRI) or computed tomography (CT) scan images. The generic structure is then embedded in a geometrically simpler mesh called a host mesh, which is then deformed to minimise the total error between the landmark and target points. Since the generic mesh is completely embedded in the host mesh, the former also undergoes a similar degree of deformation with the latter. As the information of the generic mesh with respect to the host mesh is known at the undeformed state, the customised geometry is obtained by updating this information with respect to the deformed host mesh. The steps involved in the customisation process are shown in Figure 6.

3.3 Gait analysis

Gait analysis is the systematic study of human walking. It involves measuring several variables and determining important parameters that can be used to interpret or compare one’s walking pattern. The key parameters that are either directly measured or derived from measured data are...
joint angles, ground reaction forces and muscle activity. Of these parameters, the one frequently used by surgeons is joint angles (from kinematics) during the gait cycle.

### 3.3.1 Kinematics

To determine the joint angles during walking, markers are placed on the subject’s/patient’s body; by using high-speed video cameras the coordinates of the markers are recorded. These coordinates are then used to compute joint (hip, knee, elbow, etc.) angles and they are then plotted against the gait cycle. The artworks of Figure 7(a) and 7(b) show screen shots from an animation created from gait and sagittal plane hip-angle (flexion/extension) data during one complete gait cycle, respectively.

Although surgeons use the joint angles to make decisions on muscle length-correction procedures, as was discussed above, these angles do not provide any information about muscle lengths during walking. Some studies have suggested that knowledge of muscle (and tendon) lengths during walking is useful for deciding if a particular muscle should be surgically lengthened. Unnecessary lengthening of these muscles may result in weak and dysfunctional legs. Inclusion of muscles into the rigid-body skeletal model will be discussed in the next section.

### 3.4 Muscle deformation during gait

#### 3.4.1 Host mesh technique (geometric approach)

The skeletal muscles have at least one origin and one insertion. These are the locations where the muscles are attached to the bones via tendons. The principal assumption in the host mesh technique is that these attachment locations with respect to the bones and muscles remain unchanged during walking.

First, the 'local coordinates' of the muscle attachments with respect to both the muscle and bones are determined. This enables the computation of the global coordinates of muscle attachments at any muscle/bones configuration. The motion capture data are then used to
update the positions of the bones. Finally, the new configuration of the deforming muscle is determined using a two-step procedure. Initially, the muscle is subject to the same rigid-body transformation that a bone has undergone. This bone is chosen to be the one that stays usually parallel or nearly parallel to the muscle for all configurations. For instance, the tibial transformation is used to determine the preliminary transformation of gastrocnemius muscle, although it is attached to the femur and calcaneus. After the preliminary transformation, the global coordinates of the attachment locations on both the muscle and the bones are determined. In the second step, the muscle is embedded in a host mesh, and all the nodal information of the muscle mesh is recorded with respect to the host mesh. This configuration of the host mesh is known as the undeformed state. The host mesh is then deformed to minimise the error between the attachment points on the muscle and their corresponding points on the bones. Since the muscle mesh is completely embedded in the host mesh, the former undergoes the same degree of deformation with the latter. As the nodal information of the muscle mesh with respect to the host mesh (undeformed) is already available, the current or deformed muscle geometry is obtained by updating the nodal information with respect to the deformed host mesh.

It is thus possible to determine muscle lengths during gait and compare them with the normal muscle lengths. It must be noted that the deformation of the muscle using this approach is independent of the constitutive properties of the muscle. However, the deformation of the host mesh can be controlled by subjecting it to additional constraints such as change in elemental arc lengths, arc curvatures and surface curvatures. Figure 8 depicts the steps involved in determining the gastrocnemius length during the full gait cycle.

Figure 8: Simulation of gait cycle with muscles using the host mesh technique. Anterior and lateral views of lower limb structures with muscle host meshes (left); muscle length (normalised with respect to neutral position) changes during gait cycle (right).
3.4.2 Passive deformation of muscles

As outlined above, the muscle deformation using the host mesh technique does not consider any constitutive properties of the muscle. In reality, the arrangement of fibres within a muscle and constitutive parameters dictate how it deforms. A constitutive model based on the muscle’s fibre structure is therefore needed to formulate the finite elasticity problem. Thus, by solving the finite elasticity problem with a suitable constitutive model and subject to displacement boundary conditions (attachments), one can obtain the deformed muscle configuration. This method is, however, computationally expensive; if several muscles are involved, time taken for a complete gait cycle simulation would prohibit the use of this method as a practical tool. Moreover, the success of the method heavily depends on the accuracy of the constitutive model (i.e. form of the model and the model parameters).

3.5 Contact mechanics and passive deformation

3.5.1 Patello-femoral articulation

Patello-femoral articulation is of special interest to clinicians, as the knee joint is one of the most frequently injured joints in the human body. Two surgical procedures that are performed to relieve anterior patella pain are Maquet and medial transfer procedures [23]. These procedures help to reduce the peak stresses and to distribute the surface pressure evenly in the patella. Thus, strain and stress distribution patterns in the patella during flexion/extension are useful for surgeons to plan these surgical procedures. To obtain the stress and strain distribution of the patella, it is necessary to formulate a finite elasticity problem with contact forces between the patella and femur. Contact forces are calculated as a function of the gap between the contact points on the adjacent bodies. With a suitable constitutive model, the finite elasticity problem can be solved to obtain stress distribution in the patella during knee flexion/extension. Figure 9 depicts the continuum contact mechanics model of the knee.

3.5.2 Constitutive models

In the simulation of patello-femoral articulation above, it is necessary to have three constitutive models for the muscle (rectus femoris), bones (femur and patella) and ligament (anterior cruciate).

Figure 9: Simulation of patello-femoral articulation in knee flexion [5]. (a) Knee flexion at 60°. (b) The stress distribution of the patella at 60° flexion. The displacement boundary conditions to the model are the tibial movement with respect to the femur (fixed) [23].
Since the muscles have a fibrous structure arranged in sheets, a non-linear model based on fibre and sheet axes can be used (e.g. the pole-zero constitutive model). These types of models have been extensively used for cardiac muscles [24]. Because both skeletal and cardiac muscles are striated and possess anisotropic properties, these types of models are suitable for skeletal muscles as well. The bones are considered to possess linear isotropic constitutive properties. As such, the strain energy is defined as a function of the first and second invariants of the deformation tensor with two model parameters: the Poisson’s ratio and Young’s modulus. The constitutive properties of cartilage are modelled in a similar fashion to bone with an additional constraint in the strain-energy function to account for incompressibility. The incompressibility of the material is introduced to the strain-energy function using the third invariant of the strain tensor.

4 Modelling the lymphatic system and melanoma

Melanoma is a serious form of skin cancer. If melanoma is not detected and removed in its earliest stages, it can quickly spread throughout the body. Like other cancers, it can spread to lymph glands – more properly termed lymph nodes. These are usually about the size of a pea, and fluid from the skin drains into them through a fine network of tubes. Melanoma cells can travel through these tubes to the lymph nodes, and the detection of melanoma cells in the lymph nodes is one of the earliest signs of the cancer spread.

A sentinel lymph node biopsy (SLNB) is a technique used to determine whether melanoma has spread to lymph nodes. This method detects the first lymph nodes that cancer cells will reach if it has spread. These nodes are called sentinel nodes (SNs) because they normally act as ‘sentinels’ monitoring infection in that part of the skin. In hospitals that have the necessary technology, the SN is located using lymphoscintigraphy (LSG) imaging, which is shown in Figure 10. A radioactive tracer is injected into the skin site where the primary melanoma was found, and this tracer is then tracked as it drains into the SNs. These nodes are then surgically removed and examined for any sign of tumour cells. The histological results of the biopsy highly influence a patient’s prognosis.

Figure 10: LSG images of a patient with primary melanoma on their forearm [26]. (a) Early imaging (10 min post-injection) tracks the lymph vessel draining the skin site. (b) Late imaging (2½ h post-injection) shows two SNs located in the axilla.
The ability to locate SNs quickly and efficiently is clearly important in enabling the critical early detection for melanoma spread. The Sydney Melanoma Unit (SMU) helped pioneer the SLNB technique and has the world’s largest database of over 5000 treated patients. Currently, there is no good way to visualise melanoma SLNB data in three dimensions for clinical use. In this study, we have developed an anatomically based technique to visualise this clinical data that relates primary melanoma sites to sentinel lymph nodes. This provides important clinical information when full LSG mapping is not available or impractical.

4.1 Methods

High-resolution images from the Visible Human dataset [16] provided the required 3D anatomical data used to generate a model of the human skin. From this data digitisation, FE mesh construction and fitting techniques were applied as follows:

1. **Data Digitisation**: The skin surface was located visually on each image and digitised to create a 3D data cloud from stacked 2D slices (Figure 11a).
2. **Initial Linear Mesh**: The initial linear mesh creation involved a process of selecting data points from the digitised data cloud at regular intervals. These selected data points were used as nodes to create linear FEs in rectangular cartesian coordinates to approximate the skin surface.

![Figure 11: Construction of the FE skin mesh. (a) Stacked 2D Visible Human images used to digitise the skin. (b) Fitted skin mesh.](Image)
3. **Fitting**: A bi-cubic-slope continuous FE mesh was created from the initial linear mesh by fitting the data points via the application of the same non-linear fitting process outlined above [20].

The skin model (Figure 11b) has been constructed using 842 nodes and 886 elements to give an RMS error of 2.3 mm.

LSG data from the SMU has been recorded in two dimensions; therefore to visualise this data in three dimensions, it has been mapped onto the skin model. The melanoma site on each patient has been recorded as an \((x, y)\) coordinate on body outline maps. These body outlines have been morphed using the ‘free-form’ deformation technique called ‘host mesh’ fitting [20, 21] referred to in the previous section to align with the skin model (Figure 12a). Melanoma points from the torso and legs have then been projected into the page in the \(y\) direction onto the skin model.

The arms and feet required special consideration, since the orientation of the skin model was not the same as the body outlines. The arms have been moved laterally, via host mesh fitting relative to a rigid-body translation of bones at the elbow joint. Melanoma points on the arms have been projected by separating the skin mesh into anterior and posterior arm segments, and then projecting orthogonally onto them. The feet and hand melanoma points have been placed onto the model manually.

4.2 **Results**

Spatial statistical analysis of the data has been conducted, investigating melanoma sites based on sentinel lymph node locations and vice versa. Analysis has shown that lymphatic drainage of the skin is highly variable; however, consistent patterns do appear. For example, regions of skin on the torso and upper limbs that can potentially spread to more than three

![Figure 12: Projecting melanoma points from body outlines onto the skin mesh. (a) Host mesh fitting the anterior torso body outline to the skin mesh, note the arms are treated separately. (b) Projected melanoma points on the left arm.](image-url)
lymph node fields (Figure 13). This highlights and quantifies the need for awareness in the clinic that melanoma can spread to multiple sites when patients have a primary lesion in these areas.

Figure 14 demonstrates the utility of a clinical and educational tool developed as part of this study. It provides the ability to select regions of skin and display the potential draining lymph node fields. This is based on all previous cases, and also displays the percentage likelihood of melanoma spread for each node field.

Figure 13: Heat map showing the likelihood that the skin will drain to four or more lymph node fields.

Figure 14: Potential SN sites based on a region of skin on the torso in the highlighted element. From previous patient data, 75% have had drainage to the right axilla, 50% to the left axilla and 25% to the left groin.
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These detailed spatial maps provide the first anatomically accurate link between the skin and lymphatic drainage. The extension and ongoing application of this work in the clinic is a novel method to capture data for both improving melanoma diagnosis and providing a better understanding of lymphatic drainage in the body. The novel displays of SLNB data will be incorporated into a software tool that will be made available to clinicians to improve the diagnosis and treatment of melanoma.

5 Interpretation of cardiac ultrasound measurements with physiome models

During the mid-1990s, tissue Doppler imaging (TDI) was introduced as a standard feature on the cardiac ultrasound imaging scanners. TDI is used to measure the contraction and relaxation velocities of the heart wall during the cardiac cycle. For example, to examine the base-apex velocity of the left ventricular (LV) myocardium, the ultrasound probe is placed close to the apex of the heart, which remains approximately stationary through the cardiac cycle. Thus, the recorded velocity trace from the basal region reflects the motion of the base towards and away from the apex in this imaging projection. A base-apex velocity trace from a normal subject is shown in Figure 15. Motion towards the probe is defined as a positive velocity and vice versa. The typical velocity trace consists of three major components: the positive ejection wave during systole (S-wave) when the base moves towards the apex/probe, and two negative waves during diastole (when base moves away from the apex/probe) – first the early filling wave (E’-wave) and then the late filling wave during atrial contraction (A’-wave). In addition, a spike can be seen in the velocity trace on each side of the ejection wave: the pre-ejection and post-ejection velocity spikes. Considerable research effort has been invested in studying these spikes, but still their causes have yet to be determined.

![Figure 15: Recording of longitudinal wall velocities of the left ventricular base in a normal individual. There are several waves in the velocity trace, including the ejection wave (S) and the two velocity waves in diastole during early filling (E’) and late filling (A’). Furthermore, there are two velocity spikes: one before and one after the ejection phase, which are encircled in the figure.](image-url)
5.1 Finite-element simulations of the cardiac cycle

By using an FE model of the ventricular myocardium to simulate the cardiac cycle, we have investigated possible mechanisms of the pre-ejection and post-ejection velocity spikes. The geometry of the FE model was fitted to geometric measurements of the endocardial and epicardial surfaces of an isolated dog heart. A description of the myocardial microstructure, which consists of myofibres organised in layers or sheets, where both the fibres and the sheets change their orientation throughout the heart wall, was included in the model. Figure 16 shows the FE mesh of the ventricular walls including the fibre-sheet orientations. The passive elastic properties of the myocardium were modelled as a non-linear, orthotropic, hyperelastic material in the form of the pole-zero law. In addition, the myocardial tissue was constrained to be incompressible, which introduced a hydrostatic pressure term into the passive constitutive relation [27]. During systole, an active stress component was added along the local myofibre direction. The active fibre stress component was a function of fibre stretch and an activation parameter [25]. To simulate the cardiac cycle, a time-varying pressure was applied to the endocardial surfaces of the ventricular elements. At each time step, the activation parameter (and thus active fibre stress) was regulated to obtain a physiological pressure–volume relationship during the various phases of the cardiac cycle [28].

Two different possible mechanisms causing the pre-ejection and post-ejection velocity spikes were investigated. We first hypothesised that the pre-ejection velocity spike was due to propagation of activation from inner layers with dominantly longitudinal fibres to outer layers with...
dominantly circumferential fibres. Due to isovolumic conditions, we predicted that activation of longitudinal fibres would decrease long-axis diameter and increase short-axis diameter, and subsequent activation of circumferential fibres would have opposite effect. These deflections in axis diameters may account for the pre-ejection velocity spike. During relaxation, we proposed that propagation of relaxation from the outer layers to inner layers would cause an opposite deflection pattern in the diameters and hence cause the post-ejection velocity spike.

The second mechanism was based on the hypothesis that if activation and mechanical shortening started prior to mitral valve closure (MVC), this initial shortening would be interrupted at the time of MVC due to the isovolumic cavity constraint imposed by the valve closure. At the time of aortic valve opening (AVO), shortening would resume. This changing deformation pattern would show up as a wave or spike in the velocity trace prior to ejection. Similarly, if relaxation and lengthening start prior to aortic valve closure (AVC), the lengthening would stop at the time of AVO when the cavity is isovolumic and resume at the time of mitral valve opening (MVO). Thus, a wave or spike would be seen in the velocity trace just after ejection.

The effect of heterogeneous activation (propagating from endocardium to epicardium) and relaxation (propagating from epicardium to endocardium) on the pre-ejection and post-ejection velocity spikes, respectively, was incorporated and tested in the model simulations. The results were compared with a simulation with homogeneous activation and relaxation, that is the activation parameter was simultaneously and equally increased in all regions. The results showed that there were no pre-ejection or post-ejection velocity spikes in the velocity trace in the homogeneous case. In the heterogeneous case, a changing deformation pattern occurred just before and after ejection that gave rise to the two spikes. Figure 17 shows the velocity traces from the homogeneous and heterogeneous cases.

Introducing a brief phase of active contraction in the simulation paradigm before introducing the isovolumic contraction occurring between MVC and AVO caused an initial shortening that was interrupted at MVC and re-occurred during AVO, and hence produced a pre-ejection spike in the velocity trace. Similarly, introduction of relaxation prior to AVC caused a lengthening that was interrupted at AVO and resumed during MVO, and thus produced the post-ejection velocity spike. These simulations were carried out under both homogeneous and heterogeneous activation and relaxation. The velocity spikes were present in both cases, but were slightly increased in the heterogeneous case.

According to both hypotheses, the isovolumic cavity constraint is a prerequisite for the generation of the velocity spikes. We tested this by removing this constraint. In the pre-ejection case, we allowed ejection to occur directly after filling (during the normal isovolumic contraction phase), thus simulating complete mitral regurgitation where blood is pumped back into the left atrium from the LV. In the post-ejection case, filling was allowed to occur directly after the ejection had stopped (during the normal isovolumic relaxation period), thus simulating complete aortic regurgitation where blood is flowing back from the aorta into the LV. In both of these simulations, there was a smooth transition from filling to ejection or from ejection to filling, respectively, and the respective velocity spike was not present during both homogeneous or heterogeneous activation and relaxation. Figure 18 shows the traces from the aortic regurgitation simulations.

We are currently performing clinical measurements to test out hypotheses further. The preliminary results show that both longitudinal and circumferential shortening precede MVC and that both longitudinal and circumferential lengthening precede AVC. Thus, the clinical results support our second hypothesis as the main cause of the pre-ejection and post-ejection velocity spikes. We have also carried out pilot studies where the mitral or aortic valve was prevented from closing by inflating a stent over the valve leaflets. The preliminary results from those experiments confirmed the simulation results and produced a smooth transition from filling to
Figure 17: Traces from the simulations using homogeneous activation and relaxation in the top panel and heterogeneous in the lower panel. Applied pressure–volume loops are shown on the left (a,d); shortening of the base-apex dimension in the middle (b,e); base-apex shortening velocity trace on the right (c,f). The velocity waves are labelled as in Figure 15. In the homogeneous case, there is a smooth transition from filling to ejection and from ejection to filling as seen in (b), and virtually no velocity spikes are present in (c). In the heterogeneous case, there is a change in the deformation pattern before and after ejection (e), which causes a velocity spike on both sides of the S-wave (f). Due to the ultrasound velocity sign convention, where shortening velocity is positive and lengthening velocity is negative, the velocity traces in (b) and (f) are the derivative of the negative (b) and (e) traces, respectively.

Figure 18: Aortic regurgitation simulation: (a) applied pressure–volume loop; (b) shortening of the base-apex dimension; (c) base-apex shortening velocity trace. The velocity waves are labelled as in Figure 15. There is a smooth transition from shortening to lengthening in (b) as the volume was allowed to increase during early relaxation, and the post-ejection velocity spike have disappeared in (c).
ejection in the case of mitral valve stenting and a smooth transition from ejection to filling in the case of aortic valve stenting, which essentially removed the respective velocity spike.

The simulation model we used in this study was capable of reproducing the typical deformation and velocity patterns that are measured by ultrasound imaging of the LV myocardium. Furthermore, the model was also used to test proposed mechanisms behind certain components of the velocity trace. Thus, this type of modelling seems useful to improve our insights of cardiac mechanics, to test hypotheses, and to support experimental and clinical studies.

6 Summary

We have presented four examples of current applications of Physiome Project models. In all the four cases, the models are based on an accurate representation of the anatomy of the relevant organ or organ system; in most cases, there is an attempt to use multi-scale modelling (either currently or planned) to link cell-level function into tissue and organ level analysis. All the four examples, reflux of stomach contents through the gastro-oesophageal junction, aspects of the musculo-skeletal function of the knee and leg, tracking the spread of melanoma in lymphatic ducts and analysing ultrasound measurements of cardiac mechanical function, were motivated by clinically important problems, and the applications have been developed in a close collaboration between bioengineers and clinicians. These examples are at a fairly early stage of development, but all are contributing to and making use of the growing database of models and tools developed for the Physiome Project.

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References


