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The IUPS Physiome Project: a framework for computational physiology

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Abstract

The IUPS Physiome Project[1] is an internationally collaborative open-source project to provide a public domain framework for computational physiology, including the development of modelling standards, computational tools and web-accessible databases of models of structure and function at all spatial scales. A number of papers in this volume deal with the development of specific mathematical models of physiological processes. This paper stands back from the detail of individual models and reviews the current state of the IUPS Physiome Project including organ and organ system continuum models, the interpretation of constitutive law parameters in terms of micro-structural models, and markup languages for standardizing cellular processes. Some current practical applications of the physiome models are given and some of the challenges for the next 5 years of the Physiome Project at the level of organs, cells and proteins are proposed.

Keywords: Physiome; Computational physiology; Modelling

1. What is the Physiome Project?

The Physiome Project is a collaborative effort to develop an infrastructure for linking models of biological structure and function in human and other eukaryotic physiology across multiple levels of spatial organization and multiple time scales (Bassingthwaighte, 2000; Kohl et al., 2000; Hunter et al., 2002; Hunter and Borg, 2003). The levels of biological organization, from genes to the

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[1] IUPS is the International Union of Physiological Sciences (www.iups.org) and the IUPS Physiome Project is run under the auspices of the IUPS Physiome and Bioengineering Committee, co-chaired by the author and Prof Aleksander Popel.

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whole organism are: gene regulatory networks, protein–protein and protein–ligand interactions, protein pathways, integrative cell function, tissue and whole organ structure/function relations, and finally the integrative function of the whole organism. An overview of the Physiome Project is given in Fig. 1. The project requires the creation of web-accessible databases of mathematical models of structure and function at spatial scales which encompass nano-scale molecular events to metre-scale intact organ systems, a range of 10^9, and temporal scales from Brownian motion (microseconds) to a human lifetime (10^9 s), a range of 10^{15}. Clearly

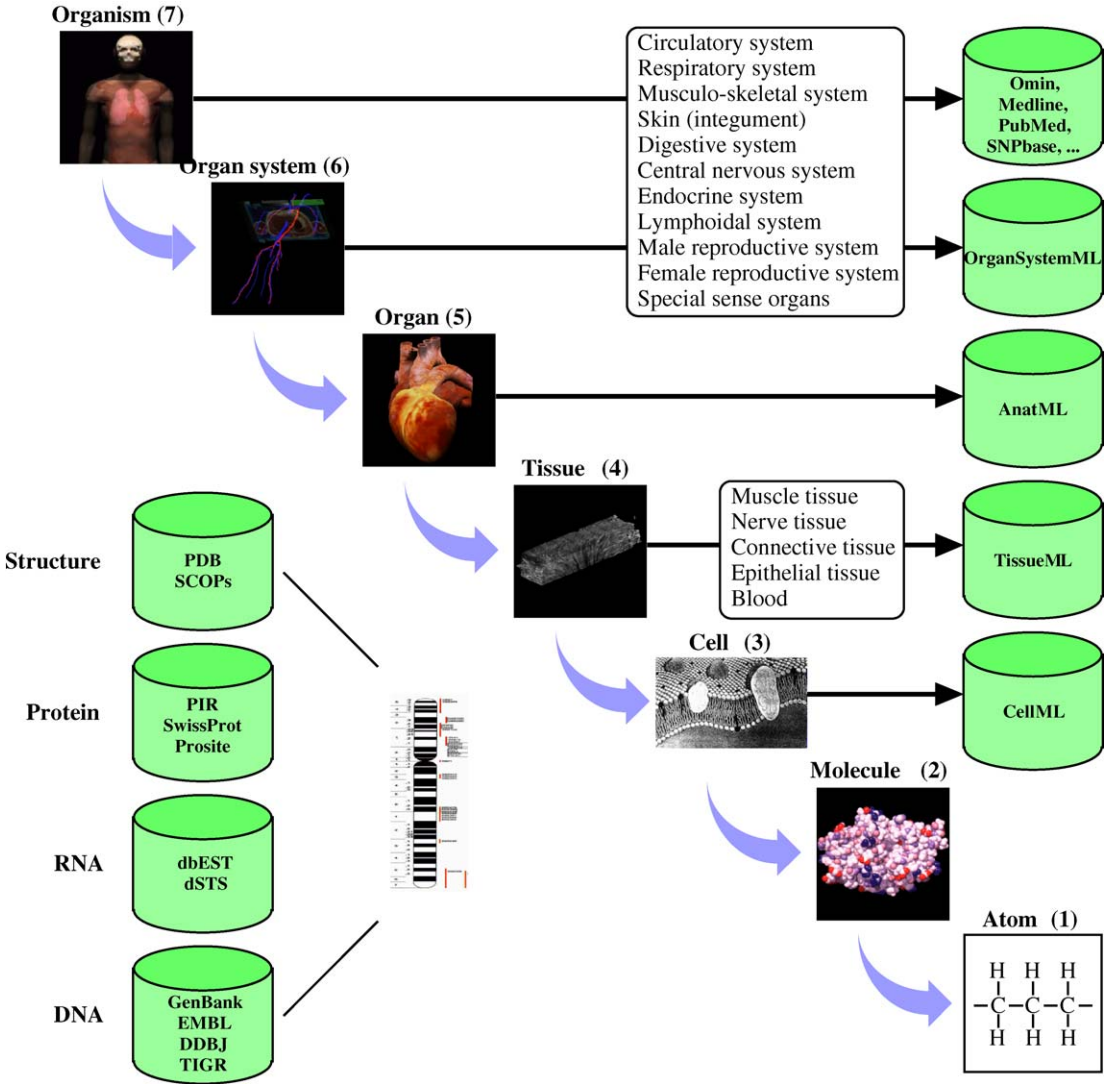

Fig. 1. Accessing information at the various spatial scales. The databases shown on the right hold model information encoded in markup languages such as CellML (see www.cellml.org) and AnatML. The markup languages ensure that models are encoded in a consistent form and allows simulation packages to import the models in a standard format. See www.bioeng.auckland.ac.nz/physiome/physiome_project.php.

this cannot be represented by one model but rather a hierarchy of models and modelling approaches such as stochastic models of ion channels and receptors for ligand binding calculations, ordinary differential equation lumped cell models, and partial differential equation continuum models at the tissue and organ levels. It also requires the model parameters at one scale to be linked to detailed models of structure and function at a smaller spatial scale—hence the need for "multi-scale modelling", as is discussed further below. Similarly in the time domain, a model dealing with the millisecond time scale of ion fluxes across the cell membrane during a cardiac action potential, for example, can be used to identify parameters in models dealing with the protein expression changes occurring over a period of weeks, months or years as occurs in heart failure.

The project is a worldwide public domain effort and a major current focus is the development of ontologies, markup languages and modelling standards (Crampin et al., 2004). Some of the groups actively involved in the Physiome Project are:

1. *Auckland*: Bioengineering Institute, University of Auckland, IUPS Physiome Project.
2. *Baltimore*: Physiological Mechanics and Transport Laboratory, John Hopkins University, Microcirculation Project.
3. *Boston*: Mechanical Engineering Department, MIT. International Consortium for Medical Imaging Technology (ICMIT).
4. *Haifa*: Department of Biomedical Engineering, Technion, Modelling standards.
5. *Kyoto*: Department of Physiology and Biophysics, Kyoto University, Heart Physiome Project.
6. *Okayama*: Department of Cardiovascular Physiology, Okayama University, Physiome Project.
7. *Oxford*: Oxford Cardiac Electrophysiology Group, University of Oxford, Heart Physiome Project.
8. *San Diego*: Cardiac Mechanics Research Group, Bioengineering Department, UCSD, Heart Physiome Project.
9. *Seattle*: Computational & Integrative Bioengineering, Bioengineering Department, University of Washington, Physiome Project.
10. *Sheffield*: Medical Physics and Clinical Engineering, Sheffield University, Tissue Physiome.
11. *Sydney*: Biomedical Engineering, University of New South Wales, Markup languages and software tools.

(see http://www.bioeng.auckland.ac.nz/physiome/physiome_project.php for web links).

The next section surveys current progress in using anatomically and biophysically based continuum models to analyse the function of organs and organ systems. The following two sections give first an example of how the constitutive law parameters of a continuum model can be calculated from a more detailed model of tissue microstructure, and then current progress in defining standards and markup languages for models of subcellular processes. Several practical applications of the continuum models are then described and the final section addresses some of the major challenges facing the Physiome Project over the next 5 years.

2. Continuum models of organ systems

Progress on developing physiome-style models of organ systems, in which physical conservation laws are solved on anatomically based models, is well underway for the heart, lungs, musculoskeletal system, digestive system and some sensory organs. In all of these projects the goal is to construct models that incorporate the detailed anatomy and tissue structure of the organs in a way that allows the inclusion of cell-based models and the spatial distribution of protein expression. The continuum models are briefly described here and in the next section we address the problem of how to link the constitutive law parameters of the continuum models to more detailed models of tissue microstructure.

2.1. The heart

The first and currently most advanced continuum model of an organ is the heart (Hunter and Smaill, 2000; Hunter et al., 2001; Kohl et al., 2001; Noble, 2002a; Smith et al., 2002). A computational framework has been developed for integrating the electrical, mechanical and biochemical functions of the heart (Hunter et al., 2003; Smith et al., 2004). The model uses finite element techniques with high-order basis functions (cubic Hermite) and therefore relatively few elements are required to provide an accurate description of ventricular anatomy (see Fig. 2). Galerkin finite element techniques are used to solve the large deformation soft-tissue mechanics using orthotropic constitutive laws based on the measured fibre-sheet structure of myocardial tissue (LeGrice et al., 1995, 1997, 2001; Nash and Hunter, 2001; Dokos et al., 2000, 2002).

The reaction–diffusion equations governing electrical current flow in the heart (and hence the activation wavefronts that spread around the heart and initiate contraction) are solved on a grid of deforming material points which access systems of ordinary differential equations representing the cellular processes underlying the cardiac action potential (Tomlinson et al., 2002; Nickerson et al., 2001; Buist et al., 2003). Navier–Stokes equations are solved for coronary blood flow in a system of branching blood vessels embedded in the deforming myocardium and the delivery of

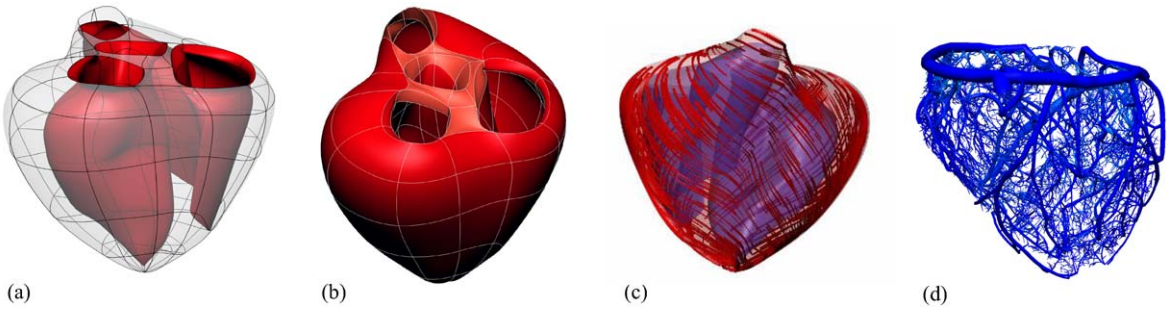

Fig. 2. Three-dimensional (3D) finite element model of the pig heart. (a) The left and right ventricular endocardial surfaces, shaded red, are seen through the translucent epicardial surface. (b) The epicardial surface of the model showing the heart valve orifices at the base of the heart. (c) Fibre orientation in the heart is described by a 3D finite element field, shown here on the epicardial surface. (d) The first six generations of the coronary arterial tree are shown in blue. (a)–(c) are from Stevens and Hunter (2003) and (d) is from Smith et al. (2002) by permission.

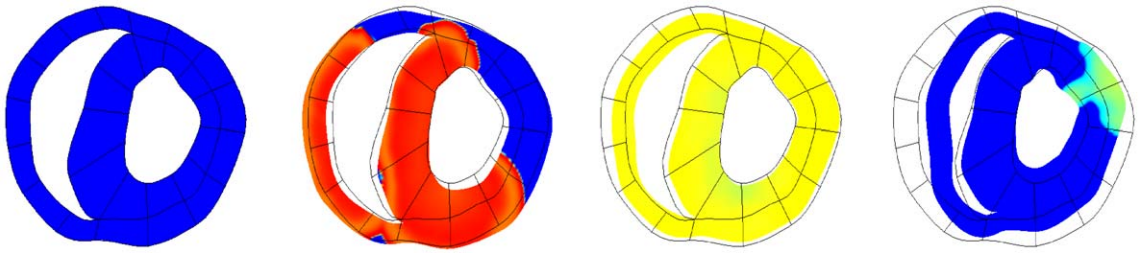

Fig. 3. An anatomically accurate 2D model of coupled excitation–contraction in the cardiac ventricles. The wave of cellular transmembrane voltage (scaled between −85 mV blue and +45 mV red) is shown on the deforming tissue model. The undeformed finite element mesh to shown to provide a reference for tissue deformation. From Smith et al. (2003), with permission.

oxygen and metabolites is coupled to the energy-dependent cellular processes (Smith et al., 2000). All of these equations have now been implemented with 'horizontal' integration of mechanics, electrical activation and metabolism (see Fig. 3), together with 'vertical' integration from cell to tissue to organ. For example, the transmembrane voltage change (cardiac action potential) found by solving reaction–diffusion equations at the tissue level, based on ion channel models at the cell level, triggers the release of calcium from intracellular stores that binds to troponin C and initiates actin–myosin protein interaction to generate force and drive muscle contraction (Hunter et al., 1998). The supply of blood through the coronary arteries and hence oxygen and metabolic substrates, is governed in part by the mechanical coupling between the coronary vessels and myocardial tissue (Smith et al., 2000, 2002). For a discussion of regional inhomogeneity in action potential shape and duration, see Clayton and Holden (2004), in this volume.

2.2. The lungs

A model of the lungs is also well advanced with integrative continuum models of the airways (Tawhai et al., 2000), pulmonary blood flow (Burrowes et al., 2004) and soft-tissue mechanics. The geometry of the five lobes of the human lung and the complex branching structure of the conducting airways have been modelled, along with models of the pulmonary blood vessels (see Fig. 4). The laws of conservation of mass and momentum are solved on the coupled air flow, blood flow and tissue mechanics systems (Tawhai and Hunter, 2001a,b) and linked to gas exchange in the alveoli. The challenge now is to develop tissue models that incorporate the structure and properties of the epithelial and connective tissue surrounding the airways and pulmonary blood vessels. The spatial distribution of cell types can then be included and the link made to diseases of the lungs such as asthma and chronic obstructive pulmonary disease (COPD).

2.3. The musculo-skeletal system

A model of the musculo-skeletal system has been developed (see Fig. 5a) that contains all the bones and muscles and for certain parts of the model (e.g. the leg) contains models of cartilage, tendons and ligaments.

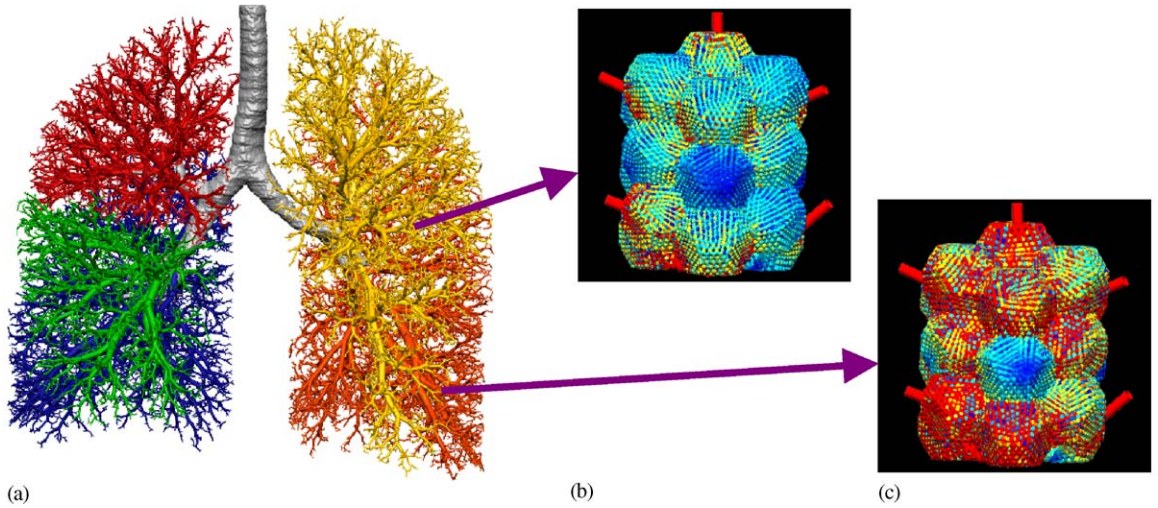

Fig. 4. (a) Airway model using computed tomography (CT) data to fit airways down to branch generations 6–9, and airway generation algorithm to fill a CT-based volume mesh from the CT airways out to the terminal bronchioles. The right upper lobe airways are green, right middle lobe are red, right lower lobe are blue, left upper lobe are yellow, and left lower lobe are orange. (b) and (c) A single alveolar sac comprising 19 alveoli clustered around a central duct, with a dense segmented capillary mesh wrapped over the alveoli. Only a single layer of capillaries passes between each pair of adjacent alveoli. The alveolar-capillary mesh has been used by Burrowes et al. (2004) to simulate blood cell transit through the pulmonary microcirculation under different pressure conditions typical of the vertical human lung. By altering the pleural, arteriolar, and venule pressures, transit in the different lung 'zones' can be simulated. (b) shows a flow solution for 'zone 3', where the arterial and venous pressure are greater than the alveolar pressure. (c) shows a flow solution in the same geometry for 'zone 2', where the alveolar pressure is less than arterial but greater than venous pressure. In these solutions red shows the greatest flow, and blue the least. From Crampin et al. (2004) with permission.

The models of bone use linear elasticity theory with inhomogeneous, orthotropic material properties based on trabecular density and structure. The models of muscle, tendons, ligaments and cartilage use finite deformation elasticity theory with nonlinear, inhomogeneous, orthotropic material properties based on material axes defined by the microstructure of the soft-tissue (Smith et al., 2004). Galerkin finite element methods are used to formulate the discrete equations. The solution of the finite elasticity equations for the muscles requires a sliding contact boundary condition to be imposed. Models of the neuro-muscular junctions are also under development to provide anatomically- and biophysically-based neural control of muscle activity.

2.4. The digestive system

A model of the gastro-intestinal (GI) system including the stomach, intestines and colon with mechanical and electrical tissue properties is also well advanced (Pullan et al., 2004, this volume). The anatomically based model is shown in Fig. 6.

The current purpose of the GI system simulations is to model the wave of electrical excitation and subsequent contraction passing down the stomach and intestines. The model is being used to aid in the interpretation of Superconducting Quantum Interference Device (SQUID) recordings of

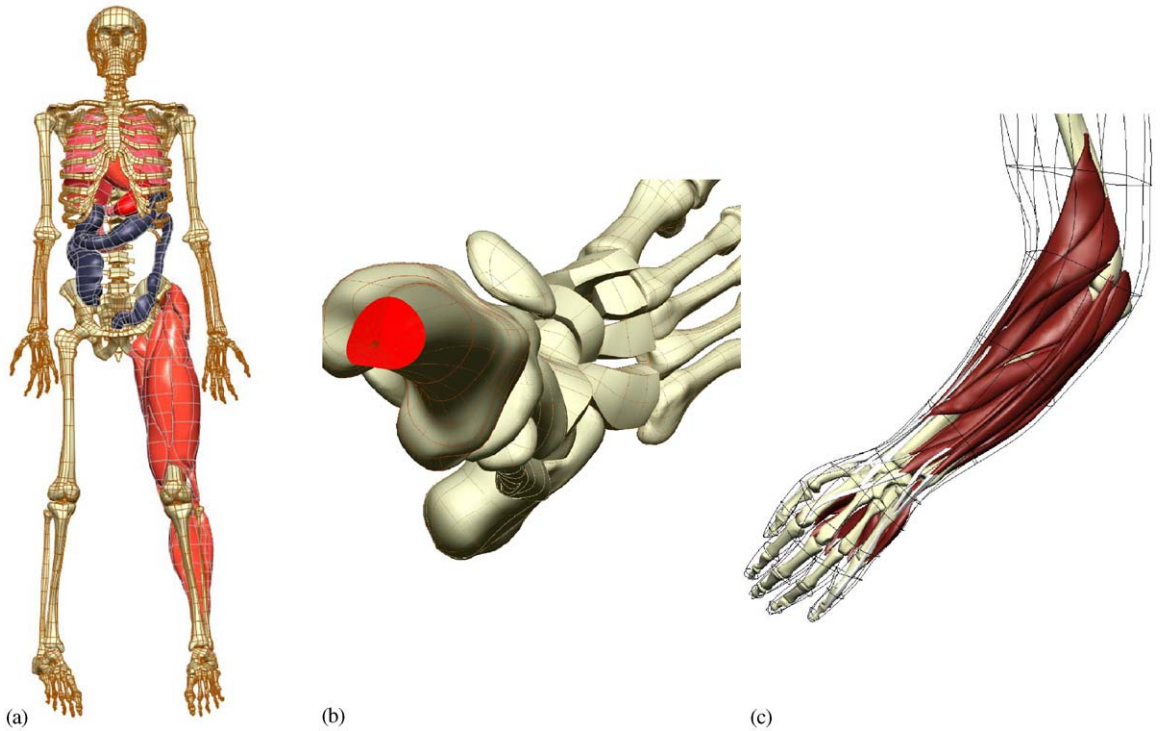

Fig. 5. Musculo-skeletal models. (a) The full human skeleton together with all leg muscles (and also including models of the lungs and digestive system within the thorax). (b) A model of the bones of the foot. (c) A model of the muscles, tendons and ligaments of the forearm (the lines are the edges of the finite element model of the skin).

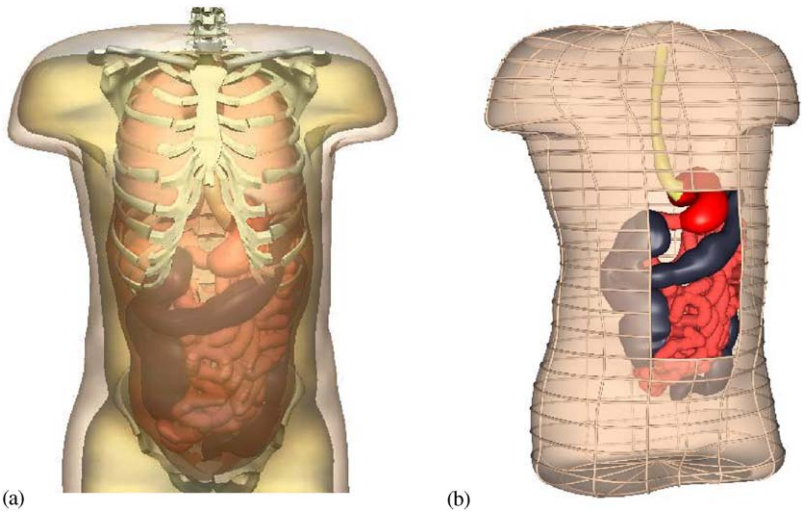

Fig. 6. (a, b) Anatomical models of the human torso and digestive system. The stomach, intestines and colon have been modelled for studying the electro-mechanics of the gastro-intestinal tract (Bradley et al., 1997; Pullan et al., 2004).

the magnetic field associated with electrical activity of the GI system, which have been shown to be able to discriminate disease states such as ischaemia (Pullan et al., 2004, this volume). The models are being developed to incorporate the smooth muscles and interstitial cells of Cajal using CellML-encoded models of the electromechanical properties of these cells.

In the above continuum organ models the tissue properties are defined by constitutive laws referred to material axes aligned with the tissue microstructure. It is sometimes possible to measure these properties directly with excised tissue samples, but usually it is more convenient (and instructive) to relate the constitutive law parameters to the observed structure and composition of the tissue via fine-scale models of the tissue. This is particularly the case when tissue composition and/or structure changes with spatial location in an organ—it may be difficult or impossible to obtain tissue samples suitable for functional tests, whereas microstructure can always be observed. In the next section we give an example of such a model.

3. Multi-scale modelling: linking tissue structure to continuum constitutive laws

There are four basic tissue types in the human body: muscle tissue, connective tissue, epithelial tissue and nerve tissue. Each of these is specialized to some extent to suit the functional requirements of particular organs. The challenge for the Physiome Project is to create anatomically detailed models of these tissue types—in order to link microstructural details at this level to the parameters of constitutive laws used in the continuum organ models—and to build up a database of the spatial variation of these material parameters both within an organ and across different organs.

The muscle tissue in the heart model, for example, contains an extra-cellular collagen matrix that has a large influence on the passive elastic properties of the tissue (Young et al., 1998). It is possible to obtain tissue samples suitable for mechanical testing from a few locations in the heart and to relate the measured mechanical properties to measurements of the underlying tissue structure (Malcolm et al., 2002; Nielsen et al., 2002). By observing the microstructure throughout the heart, it is then possible to infer the spatially varying material stress–strain parameters throughout the myocardium. Another example of multi-scale modelling is demonstrated in Fig. 7. Here a tissue level model is used to examine current flow through myocardial sheet structures and then the conductivity parameters of a continuum model are optimized to match the tissue model (Hooks et al., 2001, 2002).

For other examples of multi-scale approaches discussed in this volume see Burrage et al. (2004), Kuchel (2004), Smith and Crampin (2004), and Lovell et al. (2004).

4. Models of cellular processes

The primary processes operating within cells are transport, metabolism, signalling, motility, organizing the cytoskeletal structure, gene expression and carrying out the cell cycle. An XML-based standard for defining mathematical models of cellular function, called 'CellML'[2] has been

[2] See www.cellml.org

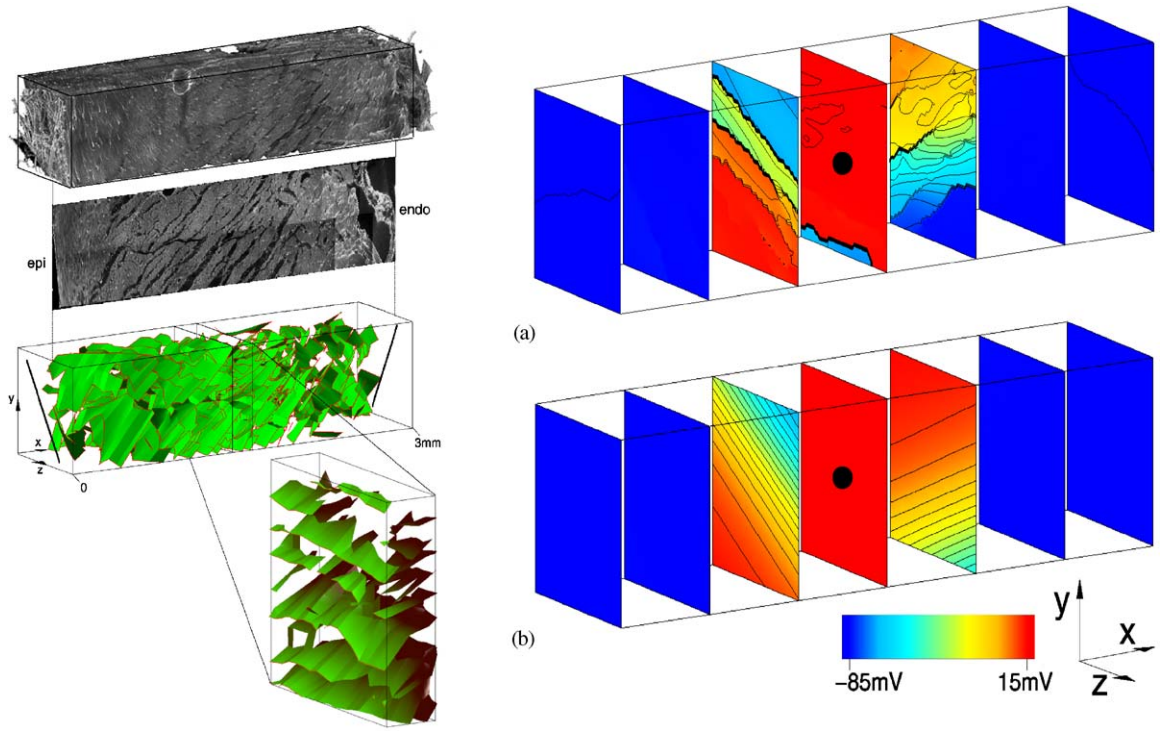

Fig. 7. Left upper: reconstructed volume of rat left ventricular free-wall myocardium. Left middle: transmural slice from the reconstructed volume showing a complex network of cleavage planes which course between myocyte laminae. Left lower: the bilinear finite element geometrical description of the cleavage planes through the entire rat tissue block, and a smaller midwall subsection. Myofibre orientation is shown on the epi- and endo-cardial surfaces. Right. Discontinuous model (a) and continuous model (b) potential maps. Transmembrane potentials are mapped on 7 equi-spaced surfaces through the reconstructed rat tissue volume, at 8 ms following midwall stimulation. Isopotential lines at 5 mV intervals are shown in black. Site of stimulation is shown with black dot at centre of volume. The cleavage plane obstacles in (A) lead to a highly discontinuous form of propagation, which is however well approximated by the continuous model. From Hooks et al. (2002) with permission.

developed in the Auckland Bioengineering Institute and is described in Lloyd et al. (2004) (this volume; see also Hedley et al., 2001). The web-accessible database of CellML models based on peer-reviewed journal publications currently contains about 180 models in the following categories: signal transduction pathway models (20 models), metabolic pathway models (28), cardiac physiological models (51), generic cell type electrophysiological models (4), skeletal muscle physiology models (2), genetic models (1), hair cycle model (1), kidney cell physiological models (4), gastrointestinal physiological models (1), neuron electrophysiological models (5), cell cycle models (8), immunology models (17), and calcium dynamics models (35).

Here we give examples of CellML-encoded models from two prominent cellular processes: ion channels and signal transduction pathways.

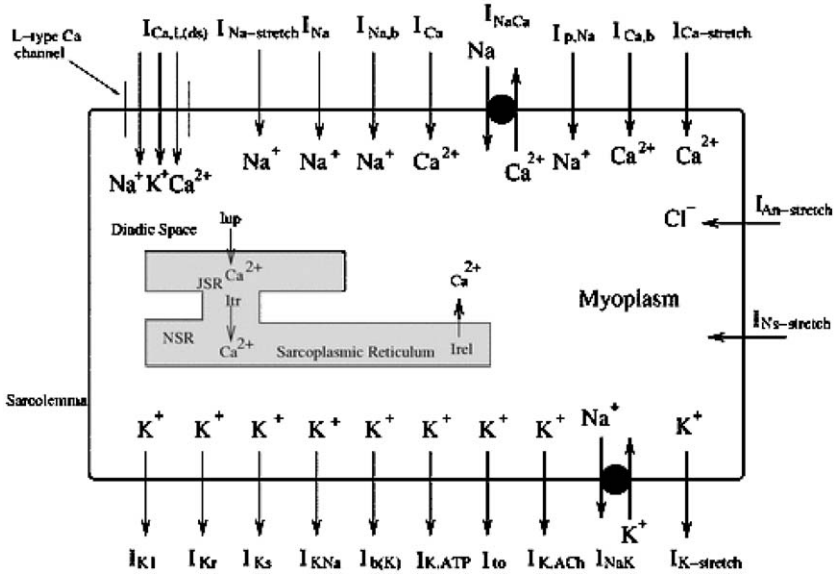

Fig. 8. The Noble ventricular cell model, incorporating ion channels, pumps and transporters linked to intracellular calcium transport mechanisms (Noble et al., 1998), available from the CellML website (www.cellml.org).

4.1. Ion channels and membrane receptors

Nearly all cells make use of ion channels, pumps and exchangers.[3] The mathematical description of the ion channel conductance and voltage (or ion)-dependent gating rate parameters is usually-based on the Hodgkin–Huxley formalism (typically using voltage clamp data) or more molecularly-based stochastic models (with patch clamp data). Examples are the Hodgkin–Huxley models of action potential propagation in nerve axons (Hodgkin and Huxley, 1952), the Noble and Rudy models for cardiac cell electrophysiology (summarized in Noble and Rudy, 2001) and pancreatic β-cell models of insulin release (Bertram et al., 2000). Fig. 8, which shows the Noble ventricular cell model (Noble et al., 1998) illustrates the nature of these models. A number of ion channels, pumps and transporters are modelled individually with Hodgkin–Huxley style kinetics and coupled to calcium transport processes within the cell.

The major challenge now is to relate the parameters of these models to our rapidly increasing knowledge of gene sequence and three-dimensional (3D) structure for these membrane bound proteins, together with tissue specific ion channel densities (and isoforms) and known mutations. The CellML markup language is currently being extended to link into another markup language called FieldML[4] for handling the spatially varying parameters such as channel density. The most urgent requirements are authoring tools, application programming interfaces (APIs) and simulation tools. See also Puglisi et al., 2004, and Bers (2004), in this volume.

[3] The main classes of membrane ion channels are: (i) voltage-gated Na^+ channels, (ii) voltage-gated K^+ channels, (iii) voltage-gated Cl^- channels, (iv) voltage-gated Ca^{2+} channels, (v) inwardly rectifying K^+ channels, (vi) Ca^{2+}-activated K^+ channels, (vii) cyclic nucleotide-gated channels, (viii) epithelial Na^+ channels, and (ix) ligand-gated Ca^{2+} channels.

[4] http://www.bioeng.auckland.ac.nz/physiome/physiome_project.php.

4.2. Signal transduction pathways and metabolic pathways

The governing equations for signal transduction pathways and metabolic pathways are usually based on mass balance relations. The pathway definitions can be encapsulated in CellML and a number of such models are available on the CellML site. An example of a signal transduction pathway is the model of β-adrenergic-cAMP-PKA pathway (Saucerman et al., 2003; Saucerman and McCulloch, 2004, in this volume). Metabolic pathways are used in synthesis, catalysis, mitosis, motility, signalling and apoptosis. Particular cases are carbohydrate metabolism, fatty acid and lipid metabolism, amino-acid metabolism, nucleotide metabolism and the electron transport chain (see the CellML website www.cellml.org for models dealing with many of these metabolic processes, and also Matsuoka et al., 2004, in this volume). A priority now is the development of tools which will allow the activity of the pathways to be modelled in the context of a 3D cell and linked to ion channels and pumps (e.g. as sites of phosphorylation) and to tissue and organ level models.

5. Physiome Project applications

Any application that requires a quantitative understanding of structure/function relationships in the human body will benefit from the Physiome Project. We give some specific examples here in educational and surgical training applications, clinical diagnostics and drug discovery.

5.1. Educational software

An important goal of the project is to develop applications for teaching physiology. An example of physiome models of the heart and torso being used in an educational application for teaching the principles of the ECG (EKG) to medical students is shown in Fig. 9. The top left panel shows the ion channel currents underlying the cardiac action potential. The top right panel shows the computed activation sequence on a whole heart ventricular model. The bottom left panel shows the corresponding computed body surface potentials and the bottom right panel shows the 3-lead ECG trace for a particular lead configuration. The top right panel and bottom left panel are 3D displays in which the heart or torso can be rotated and zoomed under user control as the time sequence plays. Since the whole heart and body surface calculations are computationally intensive, the sequences shown are pre-computed. The figures here are for a healthy heart but the effect of diseased states such as ion channel mutations or ischaemia can be displayed as models of these diseases are developed.

5.2. Virtual surgery and surgical training

An example of physiome models being used for training orthopaedic surgeons is shown in Fig. 10. The model used here includes the bones and muscles of the leg and is designed to allow the trainee surgeon to practice a femoral head screw placement operation. A model of the leg, containing the muscles and bones, is displayed in the context of an operating theatre. The trainee orthopaedic surgeon can practice the insertion of a femoral head screw and be assessed for

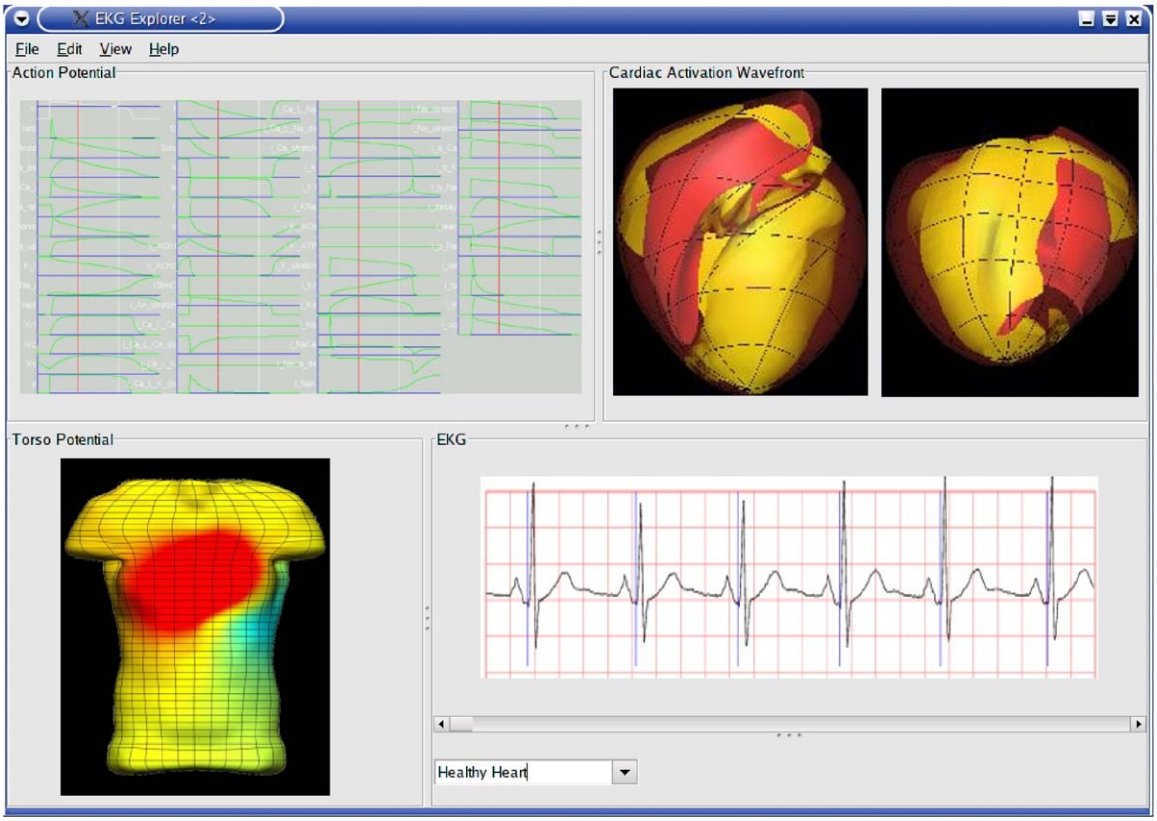

Fig. 9. An example of physiome models being used in an educational application. Models of cardiac ion channels (upper left) together with tissue conductivity yield myocardial deformation sequence (upper right). Current flow from the heart to the torso (bottom left) is used to compute the ECG traces (bottom right). Figure is courtesy of Dr. Carey Stevens of the Auckland Bioengineering Institute.

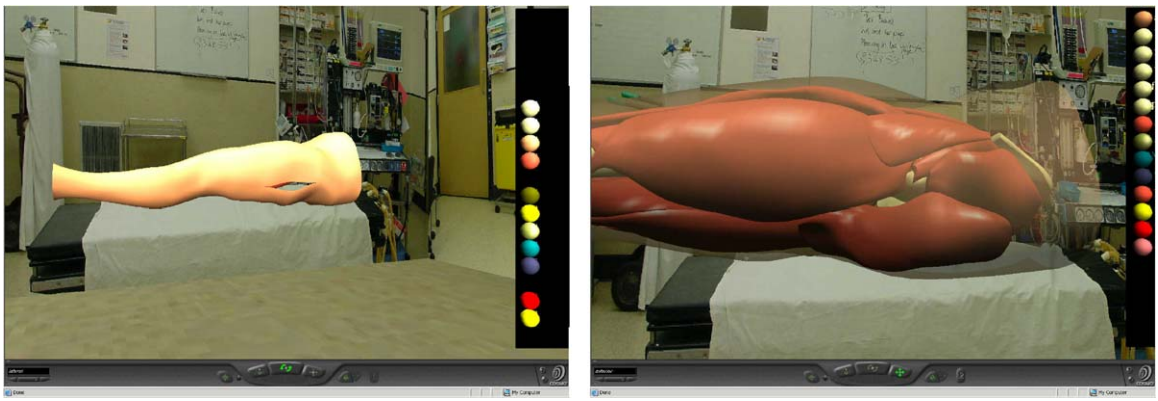

Fig. 10. An example of surgical training software based on physiome models. A model of the leg (bones and muscles) is placed in a virtual surgical environment where trainee surgeons can use various virtual tools to perform a femoral head repair operation and are scored on their performance. Figures courtesy of Dr. Phil Blyth of the Auckland Bioengineering Institute.

alignment accuracy. The software is currently being developed as a general purpose environment for surgical training and includes the use of haptic interfaces to provide, for example, force feedback.

5.3. Medical diagnostics

The physiome heart models are being used for clinical diagnosis of aberrant wall motion as illustrated in Fig. 11 (Young, 1999; Augenstein and Young, 2001). The background image is from a 1.5 T clinical MRI scanner. A finite element model of the left ventricle of the heart is shown superimposed on the image after fitting to the patient-specific data throughout the cardiac cycle. Distributions of strain in the left ventricular myocardium are then obtained and used for diagnosing aberrant wall motion. If ventricular pressure is also measured the models can be used, together with a knowledge of the material properties based on in vitro tissue testing, to predict the distribution of stress and hence regional work (Smith et al., 2001). The power of the physiome models in these applications is the ability to obtain important diagnostic information that cannot be directly observed, in this case the strain distributions in the myocardium from clinically observable MRI images.

5.4. Drug discovery

Pharmaceutical companies are increasingly aware (Noble, 2003) that mathematical modelling is likely to help reduce the enormous cost of drug discovery (currently USD1b and 15 years to develop a new drug), but the application of physiome models to drug discovery is in its infancy because there is still insufficient detail in the models at the protein level. However, a good

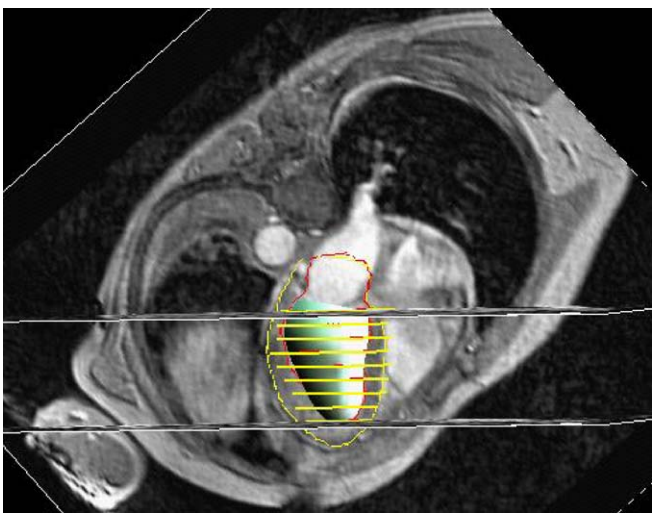

Fig. 11. An example of diagnostic software based on physiome models. A 3D heart model is shown superimposed on a clinical MRI image of the heart and torso (Young, 1999). Figure is courtesy of Dr. Alistair Young of the Auckland Bioengineering Institute.

illustration of the principle can be seen in the following example from the heart modelling work (Clancy and Rudy, 1999; Noble, 2002b,c). Most known mutations of the *SCN5A* gene on chromosome 3 that encodes the α-subunit of the sodium channel produce a small sustained inward current that prolongs the action potential plateau (i.e. delays repolarisation). Under certain conditions (see below) this can result in reactivation of the L-type calcium current and therefore early after depolarizations (EADs) which may generate re-entrant wave propagation seen clinically as torsade de Pointe and LQT3. For example, a mis-sense mutation on the outer surface of domain 4 alters the charge distribution on that domain and influences the voltage sensitivity of the inactivation gate formed by the intracellular loop between domains 3 and 4. By shifting the inactivation curve by $+10$–20 mV this increases the overlap between the m and h gate current–voltage relations and thereby increases the inward sodium 'window' current. Under conditions of low plasma potassium when the conductance of the repolarizing potassium channels is reduced, the long action potential plateau allows EADs to develop. Determining whether the EADs are capable of generating sufficient current in the tissue to give rise to re-entrant waves requires the cell models to be embedded in a whole heart organ model and such computations are currently underway.

6. Current challenges for the Physiome Project

In this final section some of the major challenges for the Physiome Project over the next 5 years at the levels of organs, cells and proteins are briefly discussed.

6.1. Organ systems

It is clear that the continuum modelling approach can be applied across all organ systems. The techniques and tools for modelling the continuum physics of organs are largely developed and it appears that current techniques of numerical analysis are capable of dealing with the anatomical complexity and highly nonlinear and inhomogeneous material properties. The anatomy and tissue structure of the heart, lungs, musculo-skeletal system and digestive system have been modelled and equations based on physical conservation laws such as those for mechanics, electrical activation and blood flow are being solved on the finite element or boundary element anatomically defined meshes. The constitutive laws defining the material properties such as stress–strain and current–voltage relations are formulated with respect to the material axes defined by the tissue structure in these organs. It will take several more years to complete this organ- and tissue-level framework for the human body but it is clearly achievable with the current measurement and modelling approach. Major organ systems not yet tackled with a physiome continuum modelling approach are the skin (integument), the central nervous system, the immune system, and the male and female reproductive systems.

What is less clear, however, is how to link down to the much greater complexity at the subcellular level. While this has been achieved in a few instances, such as the heart in which cardiac ion channel models are coupled to the whole organ, models of subcellular processes such as signal transduction pathways, metabolic pathways, motility and the cell cycle, for example, have seldom been coupled into tissue- and organ-level simulations.

Whole organ modelling of tumour growth is discussed in Alarcon et al. (2004), in this volume.

6.2. Three-dimensional cell models

Cells are the primary unit of biological function and there are only about 200 distinctive cell types in the human body.[5] They all share a few common organelles[6] although some contain occasional specialized organelles such as the sarcoplasmic reticulum in muscle cells. Furthermore, cellular processes such as metabolic pathways and signal transduction cascades[7] are common to nearly all cell types. The challenge therefore is to establish databases of models of these common elements including models for all the major organelles together with the specific parameters that make each cell type unique. The computational methods needed to define the 3D shape and internal structure of these cell types are exactly the same techniques as those which are used for defining the anatomy of organs.

As an example of why 3D cell models are needed, consider the cardiac myocyte. The pumping capacity of the heart is largely determined by the forces generated in cardiac myocytes by the molecular interaction of the myofilament proteins actin and myosin. These form a regular lattice parallel to the longitudinal axis of the cell. At one end of each 'sarcomere' (the contractile unit which repeats about 50 times along the length of the cell) the actin filaments bind, with the help of a protein called MLP (Muscle LIM Protein), to the Z-disc that helps maintain myocyte alignment across the cell. To transmit the molecularly developed stress to adjacent cells, and thence to myocardial tissue in order to generate ventricular pumping pressure, the cell maintains a 'cytoskeleton' of structural proteins. In particular, 'intermediate filaments' (IFs), made of the protein desmin, bind to the Z-disks and traverse the cell from the outer membrane to the nucleus orthogonal to the myofilaments. At the cell membrane the IFs bind to a cluster of proteins (costamere) that in turn connect, via transmembrane proteins (integrins), to the extra-cellular matrix. At the other end the IFs bind to proteins called lamins in the cell nucleus. Since it is not possible to measure forces within the cytoskeleton, there is currently little quantitative understanding of the role each component and how deletion or modification of a protein may lead to cell disruption and heart failure. Over the last 5 years transgenic mouse knockout experiments have shown that mutations in the genes that code for these structural proteins lead to various forms of heart failure. For example desmin knockouts give low force production and develop myocyte hypertrophy (Milner et al., 1999), and MLP knockouts develop dilated cardiomyopathies (Omens et al., 2002). A 3D model is needed to understand how the cytoskeleton maintains registration of the myofilaments and transmits forces to the surrounding tissue.

[5] usually divided into 17 major categories: blood, bone, cardiac, cartilage, CNS, epidermal, gastrointestinal, immune, neural, liver, pancreatic, respiratory, sensory system, skeletal muscle, generic, and male and female reproductive cells.

[6] such as the cell membrane, mitochondria, nucleus, endoplasmic reticulum, Golgi apparatus, centrioles, ribosomes, lysosomes and peroxisomes.

[7] The major signalling pathways are: (i) β_2-adrenergic/cAMP/PKA pathway, (ii) Cytokine JAK/STAT pathway, (iii) Integrin/FAK pathway, (iv) Ras/MAP kinase pathway, (v) Phosphatidylcholine pathways, (vi) Phosphatidylinositol 3-kinase pathway, (vii) Phosphoinositide pathways, (viii) Sphingomyelin/ceramide pathways, and (ix) TGF-β/SMAD pathway.

6.3. The link to proteins and genes

For the Physiome Project to make a real impact on drug discovery it must link the models of tissue and cell function described above to models of protein structure and function, since drugs work primarily at the level of proteins.[8] A number of web-accessible public domain databases are being developed that will greatly assist this effort. One is the Protein Data Bank (PDB)[9] that contains the 3D structure of around 20,000 proteins. Another is the 'Molecule Pages' database of around 3000 proteins involved in signal transduction pathways, created by the Alliance for Cellular Signalling (AfCS).[10] This latter has names, synonyms, sequence information, biophysical properties, domain and motif information, protein family details, structure and gene data, together with expert-authored information on protein states, transitions and functions. For a review of protein and gene databases relevant to the circulation system, see Winslow and Boguski (2003).

We now know that there are only about 30,000 genes in the human genome (Venter et al., 2001) and that this surprisingly low number is because genes are just the code for at least 100,000 proteins (splice variants and post-translational modifications account for the greater than three-fold difference). The greatest challenge is understanding how gene regulation works: the astonishing spatial and temporal control of protein expression that with almost the same genes (and therefore proteins) can produce a fruitfly, mouse or human being. A mathematical framework for handling the enormous complexity at this level is being developed by the systems biology community (see, for example, Kitano, 2002).

7. Conclusions

The long-term challenge for the Physiome Project is to build a modelling framework in which the effect of a gene mutation can be modelled all the way from its effect on protein structure and function to how the altered properties of the protein affect a cellular process such as signal transduction, and how the changed properties of that process alter the function of tissues and organs. There will be many other benefits from this integrative framework. Understanding how model parameters are affected by individual variation, by embryological growth, by aging and by disease, for example, will bring enormous benefits to the design of medical devices, the diagnosis and treatment of disease and the development of new drugs.

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[8] The major protein families are gene regulation proteins, structural proteins, receptor proteins, signalling proteins, transport proteins, motor proteins, enzymatic proteins, storage proteins and defensive proteins.

[9] See www.rcsb.org.

[10] See www.cellsignalling.org.

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