

INNOVATION

Integration from proteins to organs: the Physiome Project

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The Physiome Project will provide a framework for modelling the human body, using computational methods that incorporate biochemical, biophysical and anatomical information on cells, tissues and organs. The main project goals are to use computational modelling to analyse integrative biological function and to provide a system for hypothesis testing.

The revolution in molecular biology, which has dominated biological research for the past 20 years and will culminate this year in the completion of the final draft of the human genome, is a testament to the power of international and interdisciplinary science^{1,2}. The genome turned out to be relatively simple — there are about 40,000 protein-encoding genes in human DNA — but uncovering the full set of gene regulatory mechanisms and the full set of RNA transcripts (the ‘transcriptome’) is dauntingly complex, as one gene can apparently influence as many as 100 others through transcription-factor interactions. Similarly, discovering the full set of proteins that are produced by the genome (the ‘proteome’), as well as how these proteins are formed by both translation and post-translational modifications, is a huge task. It has, however, created an urgent need to integrate the vast amount of sequence, protein structure and signal-transduction-pathway data into a mathematical modelling framework that can deal with the complexity of cell, tissue and organ function.

Fortunately, there have been several important developments that will facilitate

this so-called ‘Physiome Project’ (BOX 1, FIG. 1). One is in medical physics, in which our ability to image structure and function in a clinical setting — with techniques such as NMR, magnetic resonance imaging, computer tomography and electrical imaging — is bringing great advances in diagnostic medicine. It is probable that within a few years whole-body scans that take less than one minute will be routine and cheap. Another development is in computational science. Advances in both computer hardware and computational algorithms have transformed many traditional areas of physics and engineering (for example, aircraft can be designed and tested *in silico* without the need for expensive wind-tunnel testing), and now these advances are expected to bring similar benefits to the understanding of biology and the practice

of medicine. When modern computational techniques are applied to anatomically and biophysically based models of human physiology, which are partly derived from the imaging techniques mentioned above, they provide the means to integrate the vast amount of data that are available from genomics, and also now from proteomics and glycomics (the corresponding attempt to describe all of the carbohydrates that are used by the body), into a framework that can be linked to whole-body physiology and clinical medicine.

Computational biology at the level of ion channels and biochemical pathways is usually referred to as ‘systems biology’, and progress in this field has been well documented in several recent reviews^{3–8}. Here, we describe the challenges and progress, at present, of incorporating these subcellular models into tissue- and organ-level models that are relevant to understanding human physiology, because this is the focus of the Physiome Project.

The modelling hierarchy

The need for mathematical modelling should hardly require justification — mathematics is the language for describing physical and chemical processes, and mathematical modelling is the only means of

Box 1 | A brief history of the Physiome Project

The concept of a ‘Physiome Project’ was presented in a report from the Commission on Bioengineering in Physiology to the International Union of Physiological Sciences (IUPS) Council at the 32nd World Congress in Glasgow, UK, in 1993. The term ‘physiome’ comes from ‘physio’ (life) and ‘ome’ (as a whole), and is intended to provide a ‘...quantitative description of physiological dynamics and functional behaviour of the intact organism’²⁶. A satellite workshop — On designing the Physiome Project — which was organized and chaired by the Chair of the IUPS Commission on Bioengineering in Physiology, Jim Bassingthwaite, was held in Petrodvorets, Russia, after the 33rd World Congress in St Petersburg in 1997. A meeting on the Physiome Project was held at the 34th World Congress of the IUPS in Christchurch, New Zealand, in August 2001, and the Physiome Project was designated, by the IUPS executive, as a major focus for the IUPS during the next decade. P.J.H. was appointed Chair of the newly created Physiome Commission of the IUPS in 2000, and is now co-chair, with Aleksander Popel, of the recently combined IUPS Physiome and Bioengineering Committee.

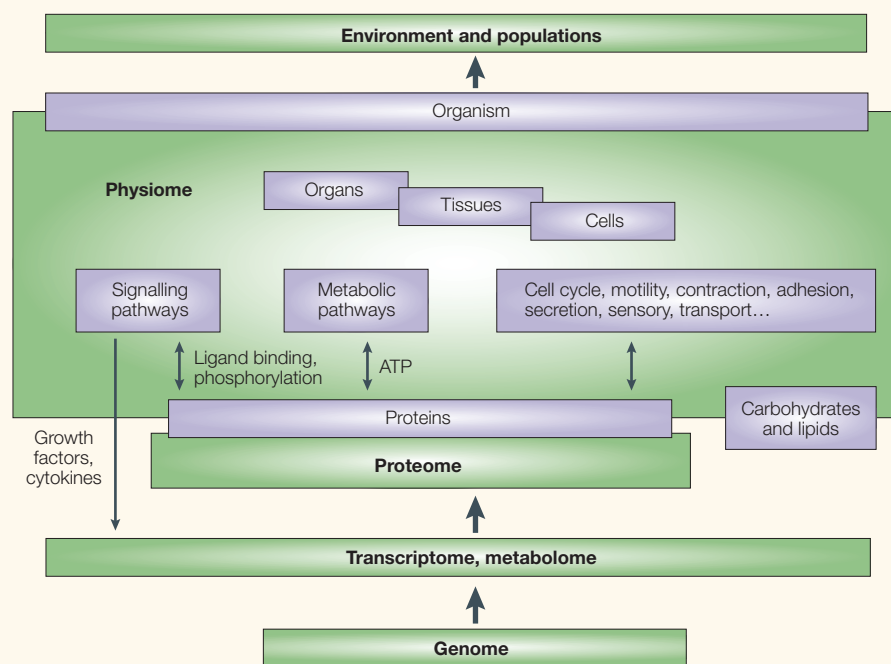


Figure 1 | Illustration of the relationship between the physiome and other areas of biological organization. The other areas of biological organization include the genome (the genes encoded in DNA), transcriptome (the messenger RNA produced by gene expression under particular conditions), metabolome (the metabolites that are present under particular conditions) and proteome (the proteins that are actually produced and where they reside — that is, the translation of the transcriptome together with post-translational modifications and protein trafficking). There is another level of organization above the physiome, which deals with populations and interactions with the environment. It should be noted that many other processes such as the assembly of carbohydrates and lipids are omitted.

providing a quantifiable framework for integrating numerous processes across many spatial and temporal scales. Any attempt to link molecular and cellular events with physiological function must deal with length scales that range from the 1 nm that is typical of a protein to the 1 m scale of an intact body (FIG. 2a). Similarly, the range of timescales must encompass the 1 μ s that is characteristic of Brownian motion to the 10⁹ s (70 years) that is characteristic of a human lifetime (FIG. 2b). It is clear that no single model can cover a factor of 10⁹ in a spatial scale and a factor of 10¹⁵ in a timescale. A more reasonable approach is therefore to develop models for a more limited range of spatial and temporal scales and to develop techniques to link the parameters of this hierarchy of models (see, for example, recent texts on computational biology^{9–12}). This means that, at any one level, there is a ‘black box’ that groups all of the detail at the level below (in either a spatial or temporal sense) into a mathematical expression. The parameters of this expression are determined directly from experiments, but can be related to another, more detailed, model at the finer spatial or temporal level. A familiar example of this is the

use of a coefficient of diffusion in the diffusion equation to represent the length scales that are associated with the Brownian motion of diffusing particles. The coefficient of diffusion is the black box that hides the detail at a more finely resolved spatial level behind an experimentally determined relationship between solute flux and concentration gradient.

An important question for mathematical modellers is how much detail to include in a model. If the added detail includes more free parameters (that is, model parameters that can be altered to force the model to match observed behaviour at the integrative level), the answer — in keeping with the principle of Occam’s Razor (‘entities must not be multiplied beyond what is necessary’) — has to be as little as possible. On the other hand, detail that is added in the form of anatomical structure and validated biophysical relationships can often constrain possible solutions and therefore enhance the physiological relevance of a model. It is surprisingly easy, for example, to create a model of ventricular fibrillation with over-simplified representations of cell electrophysiology. Adding more biophysical detail, however, in the form of membrane ion channels, allows

the arrhythmogenic vulnerability to be determined in terms of physiologically meaningful parameters, such as specific ion conductances.

In the next section, we discuss the ontologies (that is, taxonomies plus domain-specific concepts and relationships), databases and tools that are needed to create a modelling framework at the various levels of biological organization. In the following sections, we discuss the requirements for models at the organ, tissue and cell levels.

Ontologies and software tools

To access databases of information that are relevant to modelling, ontologies for structure (anatomy) and function are needed that, from the highest level of biological organization, begin with the organ systems and progressively access tissues, cells, cell organelles, proteins and protein domains (FIG. 3). There is reasonable agreement among anatomists on how to classify organ systems and among histologists on how to classify both the structure and function of tissues. An ontology for the functional and structural components of cells has been developed by the **Gene Ontology Consortium** (see Online links). A graphical tool for displaying models at all spatial scales, and interacting with their spatially varying material parameters, is being developed¹³. In addition, several software packages are being developed to carry out simulation studies with the models at the cell level (see Online link to **The National Resource for Cell Analysis and Modeling**) and at the tissue and organ levels (for example, the interactive computer program **CMISS** (continuum mechanics, image analysis, signal

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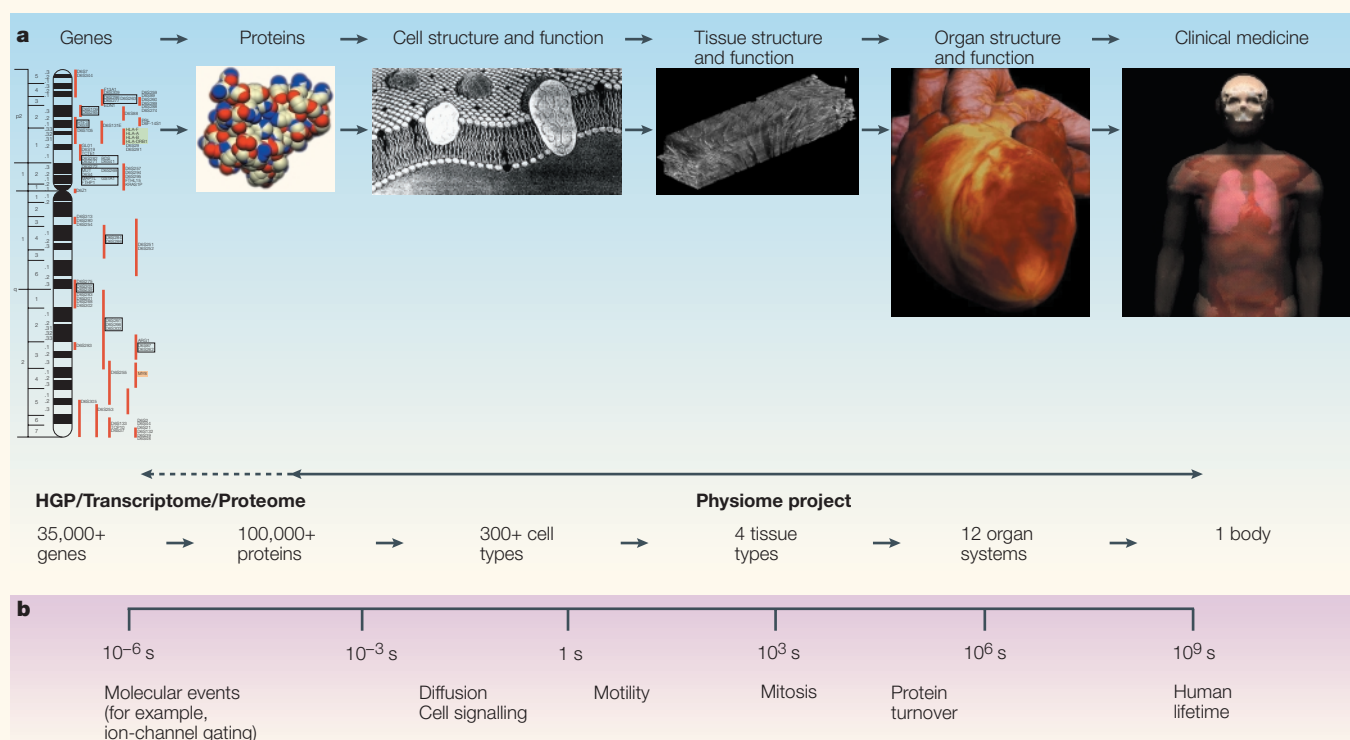


Figure 2 | Linking molecular and cellular events with physiological function must deal with wide ranges of length scales and timescales. a | Levels of biological organization from genes to proteins, cells, tissues, organs and finally the whole organism. The range of spatial scales — from ~1 nm for proteins to ~1 m for the whole body — requires a hierarchy of models. Different types of model are appropriate to each level, and relationships must be established between models at one level and the more detailed, but spatially or temporally limited, models at the level below. The organ-level and whole-body-level models shown are the Auckland heart and torso models, respectively^{32,38}. The tissue figure is a reconstructed three-dimensional confocal image of a transmural section of rat myocardium, which is also from the Auckland Bioengineering Institute, New Zealand²⁸. **b** | The range of temporal scales as shown here is even more daunting and again calls for a hierarchy of models. HGP, human genome project. Modified with permission from REF. 39 © Springer-Verlag (2002).

processing and system identification), **BioPSE** (Bioelectric Problem Solving Environment) and **Continuity**; see Online links). Typically, these latter models involve the solution of large numbers of partial differential equations and require high-performance computers.

Models at the organ level

The principles that govern the integrative behaviour of an organ or organ system derive from physical conservation laws such as the conservation of mass, momentum (linear and angular) and charge. Applying these conservation laws to an organ such as the heart, or to an organ system such as the blood-circulation system, requires either an extra relationship between stress and strain (for a deformable solid such as hard or soft tissue) or a strain rate (for a fluid such as blood or air). The ability to define such a relationship on the basis of experimental tests, without having to specify the detailed behaviour of all the components of the material, is the foundation of 'continuum models' and is the basis of modern engineering practice. For example, the stresses and strains that

are generated by bending a beam can be calculated from equations that are based on physical principles and that do not require knowledge of the detailed atomic structure of the material from which the beam is made. Similarly, conductivity coefficients that are used in the solution of a reaction-diffusion equation, such as the equation that governs electrical-current flow in excitable tissues, are based on a continuum representation of charge movement through the tissue. The key idea is to find relationships between stress and strain that are based on measuring the properties of the material experimentally, rather than on determining them from first principles. Finding such relationships is the 'art' of modelling.

An important point is that physical principles and global behaviour can give insights at a local level without the need to include every detail of the material in the model. For example, these principles have been used to understand the mechanics of the heart^{14–16}. When the heart dilates during diastole, the fibrous structure of the heart allows it to twist in a way that results in the sarcomere length of the muscle fibres being

quite uniform across the wall thickness. When the heart contracts in systole, the shearing action of the myocardial sheets results in a large degree of wall thickening (especially in the subendocardial region) to achieve a high ejection fraction. These insights into cardiac tissue have been gained using models of structure–function relations that are measured directly by experiment and are incorporated into the whole-heart continuum models. They do not require an understanding of the molecular detail. Understanding a disease process, however, such as the change in collagen and ion-channel expression that is associated with heart failure, often does require another model at a finer spatial scale to represent the signal-transduction pathways that couple mechanical events at the tissue level to gene expression at the subcellular level (BOX 2).

Another important aspect of the continuum modelling of an organ is the need to deal with many types of physical problem in the same spatial scale. In the heart, for example, myocardial contraction is governed by the laws of mechanics, but it is initiated by an electrical wave, the propagation

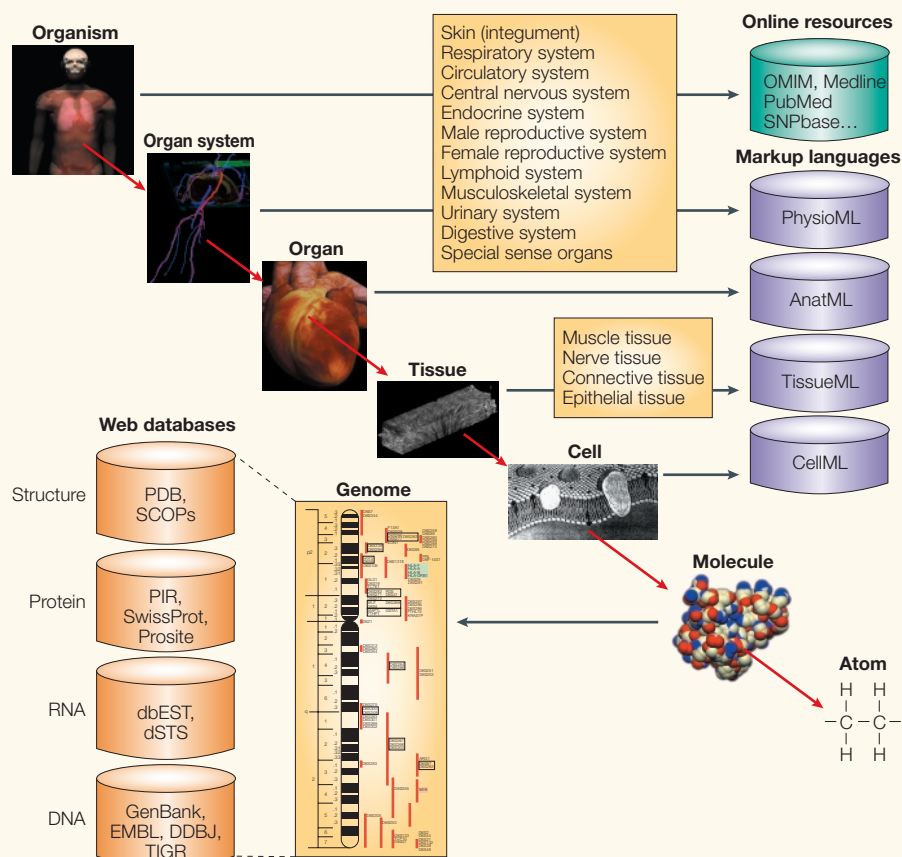


Figure 3 | Accessing information at the various spatial scales using ontologies and web databases that contain models encoded in markup languages. The markup languages ensure that models are encoded in a consistent form and allow simulation packages to import the models in a standard format (for information on CellML, see Online links). The Physiome Project database will allow models at, for example, the tissue level to be obtained from the TissueML database with parameters that are appropriate to the relevant organ (and to the spatial location in the organ). This is indicated here by the red arrow that illustrates the tissue structure at a particular location in the heart. dbEST, Expressed Sequence Tags database; dbSTS, Sequence Tagged Sites database; DDBJ, DNA Database of Japan; EMBL, European Molecular Biology Laboratory; OMIM, Online Mendelian Inheritance in Man; PIR, Protein Information Resource; SCOPs, Structural Classification of Proteins; SNPbase, Single Nucleotide Polymorphisms database; TIGR, The Institute for Genome Research. Modified with permission from REF. 39 © Springer-Verlag (2002).

of which is governed by the conservation of electrical current. Furthermore, the heart is supplied with energy by a bloodstream that also obeys the equations of mechanics, but with entirely different constitutive laws. Similarly, the function of the lungs is determined by three fundamental physical processes — gas flow in the airways, large-deformation tissue mechanics and blood flow in the pulmonary circulation. The coupling of these physical processes that occurs within an organ — electromechanics in the heart, or gas exchange between the airways and blood vessels in the lungs — is a key aspect of the organ models.

Parametric descriptions (which are usually based on finite-element or boundary-element computational methods) of all organs and organ systems can be established

using a markup language (for example, **AnatML**; see Online links), together with application programming interfaces that allow software developers to write code that reads the parameterized models into their simulation packages. Examples of such models are shown in FIG. 4.

Models at the tissue level

In many biological processes, the key to successful modelling is the ability to understand and represent structure–function relationships. This is true at the level of proteins, cells, tissues and whole organs and it is especially important for relating models across several spatial scales. For example, the load-bearing properties of a soft tissue, such as cartilage, can be modelled by a continuum mechanics constitutive law that

provides an average description of the mechanical properties that are relevant to the analysis of stresses and strains in the tissue. However, these load-bearing properties of cartilage can only be linked to the properties of the underlying collagen–proteoglycan matrix if the parameters of the ‘lumped-parameter’ constitutive law are derived from a tissue structural model that represents features such as the collagen types, their orientation, the degree of crosslinking and the state of proteases. This need to link models across different spatial scales is the greatest challenge for tissue-level modelling. For a recent summary of mathematical approaches to this problem in an engineering context, see REF. 17.

The spatial variation of material properties — such as the density of collagen, gap junctions or ion channels — is a key aspect of anatomically based models. For example, the variation across the heart wall in the density of the transient outward K^+ channel is probably responsible for the transmural repolarization gradient that gives rise to the dispersion of the T-wave of the electrocardiogram and, with certain familial mutations, provides the cellular basis for the Brugada and long-QT syndromes that can lead to potentially fatal reentrant arrhythmias^{18,19}. In addition, a physiome project on microcirculation is being undertaken as a collaboration between several groups (see Online link to **The Microcirculation Physiome Project**).

Models at the cell level

Two ontologies are required at the cell level — one that deals with cell structure, which includes the cytoskeleton and the three-dimensional (3D) configuration of organelles, and one that deals with cell function. A preliminary classification of most known cell types can be found under ‘Cells’ on **The IUPS Physiome Project** web site (see Online links) and a coordinated effort is underway to link to the Gene Ontology

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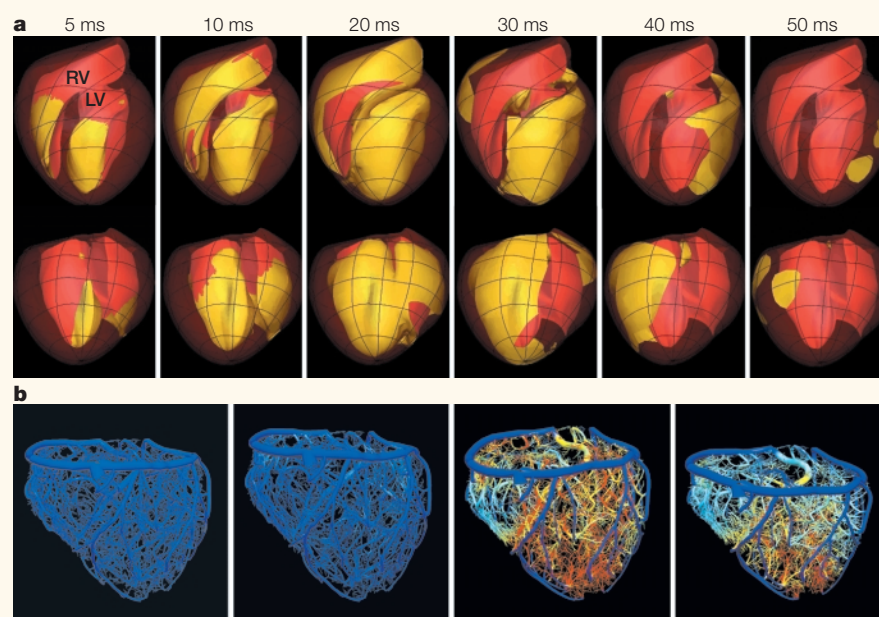
Consortium through the [global open biological ontologies \(GOBO\)](#) site (see Online links). It has become increasingly apparent that many aspects of cell function, as well as being confined to certain organelles, are also confined to microdomains in the organelles. 3D models of cell structure will therefore probably become increasingly important in modelling cell function, including signal-transduction pathways.

The primary functions of cells are transport, metabolism, signalling, motility, organizing the cytoskeletal structure and carrying out the cell cycle. In contrast to models at the organ and tissue levels, which are dominated by the physics of the governing continuum equations, models at this level are dominated by the complex biochemistry of cell proteins. Protein structure, however, does not need to be considered at this level, because models of protein–protein or protein–ligand interactions are based on experimentally measured kinetic parameters. However, at some stage, these parameters do need to be linked to models of the structure of a protein and, in particular, its protein-binding domains.

At present, the greatest challenge for computational cell biology is to develop standards for defining cell models so that they can, for example, communicate with one another in a consistent format, be analysed for consistency of units and constraint checking, and be read into simulation software in a standard format. As a first step towards this goal, a markup language ([CellML](#)²⁰; see Online links) has been developed to encapsulate models of cell function, and the database of CellML models now contains over 100 models, which include electrophysiological models, metabolic-pathway models and signal-transduction-pathway models. Mathematical equations are represented using MathML, and metadata, which includes bibliographic information, uses a syntax that is based on the Resource Description Format (see Online link to [The World Wide Web Consortium](#)). All CellML models are derived from peer-reviewed publications. The next goal is to develop open-source software tools for model simulation and graphical rendering of model components and simulation results.

Another notable markup-language development for biochemical networks is the systems biology markup language (SBML), which is a standard for exchanging information about pathway and reaction models between existing applications (for details, see Online link to the [Systems](#)

Box 2 | The Cardiome Project



An example of a Physiome Project organ model is the integrative model of the heart that was developed as a collaborative effort by groups at the University of Auckland, New Zealand, Oxford University, UK, and the University of California at San Diego, USA. The model (see FIG. 4c) is based on a finite-element model of the geometry and fibrous-sheet structure of myocardial tissue^{27,28}. Membrane currents through protein ion channels, pumps and exchangers are modelled at the subcellular level^{29–31} to reproduce the voltage changes (the ‘action potential’) in the cardiac muscle cell membrane, which support the propagation of the wave of electrical excitation in the myocardium that precedes each heart beat³² (see figure, part a). The reaction-diffusion equations that model current flow in the tissue are solved with an orthotropic diffusivity tensor, which is based on the fibrous-sheet structure of the tissue³³. The active properties of the muscle cells are based on models of troponin-C calcium binding, thin filament kinetics and myosin cross-bridge kinetics³⁴. Solving the equations of finite deformation elasticity provides the mechanical deformation in the myocardium throughout the cardiac cycle^{35,36}. The flow of blood and delivery of oxygen to the muscle cells is modelled by solving the equations of fluid flow in the coronary vessels and coupling the behaviour of the compliant vessel wall to the compressive stress that arises from the muscle contraction^{16,37} (see figure, part b).

Part a of the figure shows a model of myocardial activation. Wavefront locations are shown using an eikonal equation to simulate propagation from the distal ends of the Purkinje tree. For each sample time, anterior (top) and posterior (bottom) views are given. The endocardial surfaces of the left and right ventricles are coloured red. The regions of electrically activated myocardium at each time step are coloured yellow. Part b of the figure shows a model of cardiac mechanics, which includes the coronary arteries, at four stages in the cardiac cycle (from left to right: early in diastole, end-diastole, pre-ejection systole and end-systole). The colours (blue minimum to red maximum) indicate the flow reduction caused by compressive wall stresses acting on the coronary vessels. LV, left ventricle; RV, right ventricle. Part a is modified with permission from REF. 33 © Society for Industrial and Applied Mathematics (2002). Part b is reproduced with permission from REF. 16 © Society for Industrial and Applied Mathematics (2002).

[Biology Workbench](#)). Other projects for modelling subcellular processes are: the [E-Cell project](#) (see Online links), for modelling biochemical and genetic processes; the [Virtual Cell project](#) (see Online links), which provides a general framework for the spatial modelling and simulation of cellular physiology; and the [Gepasi](#) software package, for modelling biochemical systems (see Online links).

Conclusion and future directions

The complexity of biological systems, and the vast amount of information now available at the level of genes, proteins, cells, tissues and organs, requires the development of mathematical models that can define the relationship between structure and function at all levels of biological organization. The range of spatial scales (~1 nm for a protein to ~1 m for a person) and temporal

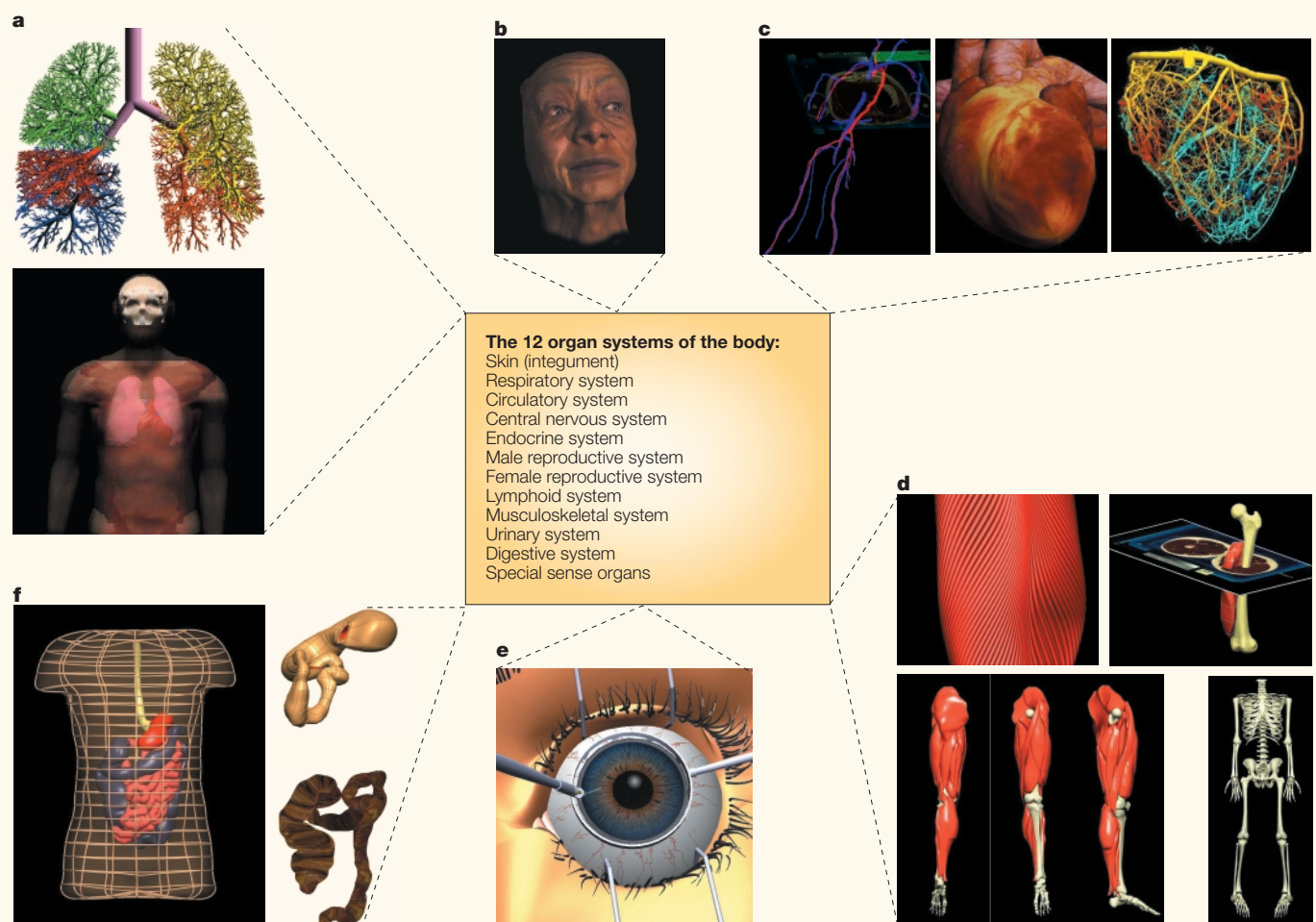


Figure 4 | The 12 organ systems of the body with illustrations of some of the anatomical models. The measurement and modelling of organ-system anatomy is well advanced and a database of finite-element models has been established (see Online link to The IUPS Physiome Project for further details, including the ontology of each organ system). It should be noted that in all cases, the models include a mathematical description of the anatomy and tissue structure (for example, the fibrous-sheet structure of the soft tissue in the heart). The organ models are as follows: **a** | the lungs, including the airways and soft parenchymal tissue, that are used for studying gas dynamics⁴⁰; **b** | a facial animation model; **c** | the circulation system and heart, including the coronary vasculature that is shown with the computed pressure distribution down the coronary arteries, which is used to study the regional distribution of blood flow and oxygen in the myocardium¹⁶; **d** | the musculoskeletal system, showing, in particular, the models of leg muscles that are used to study the biomechanics of gait; **e** | a model of the eye that is used to study stress distributions in the cornea during radial keratotomy (a surgical procedure that is used to eliminate myopia)⁴¹; and **f** | a model of the digestive system in the body that is used for transport studies in the small intestines and stomach and for applications in virtual surgery of the colon.

scales ($1\ \mu\text{s}$ for Brownian motion to 10^9s for a human lifetime) are clearly too great for a single all-encompassing model. Rather, the Physiome Project uses a hierarchy of models in which the (spatially or temporally) grouped parameters of a model component at one level can be interpreted in terms of the finer resolution of the models at the level below. This hierarchy of models must be linked to databases that hold parameters that are relevant to the cell and tissue types at the appropriate spatial location in an organ. XML (extensible markup language) standards must be developed to encapsulate the models (both structurally and functionally) at all levels. These model databases and the visualization

and simulation tools must be in the public domain and they must be accessible through the internet.

At the level of tissues, organs and organ systems, the equations that govern biological function are dominated by continuum physics, and the computational techniques that have been developed for solving engineering problems can be applied. However, it is very important that the anatomical and material complexity are not over-simplified, if the physiological function is to be understood in relation to the underlying structure and material properties. For the level below this, in which signalling pathways and other aspects of cellular function operate in the

highly complex 3D cell cytoskeletal and organelle structure, it is less clear how to apply continuum modelling. There are very significant mathematical challenges in building models that explain whole-cell function in terms of the kinetics of protein–ligand and protein–protein interactions and the spatial dimensions of subcellular microdomains. Recent symposia^{21–25} have begun to address these important issues. Progress here will link the organ, tissue and cell-level modelling that have been described in this article to the immense databases that are now emerging in this post-genomics era and will result in a more rational basis for medical diagnostics and drug discovery.

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doi:10.1038/nrm1054

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Acknowledgements

The authors gratefully acknowledge the contributions from members of the Bioengineering Institute at the University of Auckland, New Zealand. P.J.H. acknowledges the support of the New Zealand Foundation for Research, Science and Technology, the New Zealand Health Research Council and the Wellcome Trust. He is also grateful for the discussions on the Physiome Project, over many years, with D. Noble (Oxford University, UK), J. Bassingthwaite (University of Washington in Seattle, USA) and A. McCulloch (University of California at San Diego, USA).

Online links

FURTHER INFORMATION

AnatML: <http://www.physiome.org.nz/sites/physiome/anatml/pages/index.html>

BioPSE: <http://software.sci.utah.edu/biopse.html>

CellML: <http://www.cellml.org>

CMISS:

<http://www.bioeng.auckland.ac.nz/cmiss/cmiss.php>

Continuity: <http://cmrg.ucsd.edu/modelling/software>

E-Cell project: <http://www.e-cell.org>

Gene Ontology Consortium: <http://www.geneontology.org>

Gepasi: <http://www.gepasi.org>

Global open biological ontologies (GOBO):

<http://www.geneontology.org/doc/gobo.html>

The Bioengineering Institute:

<http://www.bioeng.auckland.ac.nz>

The IUPS Physiome Project:

<http://www.bioeng.auckland.ac.nz/physiome/physiome.php>

The Microcirculation Physiome Project:

<http://www.bme.jhu.edu/news/microphys>

The National Resource for Cell Analysis and Modeling:

<http://www.nrcam.uchc.edu>

The World Wide Web Consortium: <http://www.w3c.org>

Systems Biology Workbench: <http://www.sbw-sbml.org>

Virtual Cell:

http://www.nrcam.uchc.edu/vcell_development/vcell_dev.html

Access to this interactive links box is free online.

INNOVATION

Towards an e-biology of ageing: integrating theory and data

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Carole J. Proctor, Daryl P. Shanley and Darren J. Wilkinson

Ageing is a highly complex process; it involves interactions between numerous biochemical and cellular mechanisms that affect many tissues in an organism. Although work on the biology of ageing is now advancing quickly, this inherent complexity means that information remains highly fragmented. We describe how a new web-based modelling initiative is seeking to integrate data and hypotheses from diverse biological sources.

Recent years have seen rapid progress in understanding the science of ageing. A key factor has been the interaction between evolutionary (why?) and mechanistic (how?)

lines of research — this has helped to shape the probable genetic basis of ageing and the mechanisms that might be involved¹. It has also helped to overcome a situation in which the field was dominated by a plethora of rival theories with little effective dialogue between them. In particular, the ‘disposable soma theory’^{1,2} suggests that ageing is caused by evolved limitations in organisms’ investments in somatic maintenance and repair, rather than by active gene programming. This predicts that ageing is due to the gradual accumulation of unrepaired random molecular faults, which leads to an increased fraction of damaged cells and eventually to