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The IUPS human physiome project

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Abstract The Physiome Project of the International Union of Physiological Sciences (IUPS) is attempting to provide a comprehensive framework for modelling the human body using computational methods which can incorporate the biochemistry, biophysics and anatomy of cells, tissues and organs. A major goal of the project is to use computational modelling to analyse integrative biological function in terms of underlying structure and molecular mechanisms. To support that goal the project is establishing web-accessible physiological databases dealing with model-related data, including bibliographic information, at the cell, tissue, organ and organ system levels. Here we discuss the background and goals of the project, the problems of modelling across multiple spatial and temporal scales, and the development of model ontologies and markup languages at all levels of biological function.

Keywords Bioengineering · CellML · Computational Biology · Markup Languages · Ontologies · Physiome Project · Systems Biology

Introduction

The completion of the first draft of the human genome sequence [16, 33] is a remarkable achievement that demonstrates the power of international and interdisciplinary co-ordination in science. It represents an im-

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pressive collaboration between molecular biology, biotechnology, computer science and mathematics and has been the driving force behind major innovations in all of these disciplines. However, as the authors of the Human Genome Project's sequencing paper themselves conclude, "In principle, the string of genetic bits holds long-sought secrets of human development, physiology and medicine. In practice, our ability to transform such information into understanding remains woefully inadequate" [2]. This statement reflects the knowledge that the sequencing of the 3 billion base pairs in the human genome, and the discovery of 17,000 of the likely 35,000 genes is only the start. A more daunting challenge now lies before us: that of integrating this incredible wealth of information to allow the determination of structure and function at all levels of biological organisation.

Physiology has traditionally been concerned with the integrative function of cells, organs and whole organisms. However, as reductionist biomedical science succeeds in elucidating ever more detail at the molecular level, it is increasingly difficult for physiologists to relate integrated whole organ function to underlying biophysically detailed mechanisms that exploit this molecular knowledge. Organ and whole organism behaviour needs to be understood at both a systems level and in terms of subcellular function and tissue properties. Understanding a reentrant arrhythmia in the heart, for example, depends on knowledge of not only numerous cellular ionic current mechanisms and signal transduction pathways, but also larger scale myocardial tissue structure and the spatial distribution of ion channel and gap junction densities¹ [10, 20, 21]. The model encompasses the anatomy and cell and tissue properties of the heart and is capable of revealing the integrated physiological function of the electrical activation, mechanics and metabolism of the heart under a variety of normal and pathological conditions [29]. The computational techniques and software tools developed

¹ A computational model of the mammalian heart has been developed over the last 20 years as a collaborative effort by research groups at the University of Auckland (NZ), the University of Oxford (UK) and the University of California, San Diego (USA).

for this project are equally applicable to other organs and systems in the body. A model of the lungs, for example, encompassing gas transport and exchange, pulmonary blood flow and soft tissue mechanics is now well underway as a collaboration between a number of universities in the UK, the US and New Zealand [13, 31, 32]. A necessary means of coping with this explosion in complexity is mathematical and computational modelling – a situation very familiar to engineers and physicists who have long based their design and analysis of complex systems on computer models. Biological systems, however, are vastly more complex than human engineered systems and understanding them will require specially designed instrumentation, databases and software. It will also require an unprecedented degree of both international and interdisciplinary collaboration. Here we outline a proposal to establish a framework for handling the hierarchy of computational models, and associated experimental data and publications, which will help integrate knowledge at the genomic and proteomic levels into an understanding of physiological function for intact organisms. It is called the “IUPS Physiome Project” to emphasize the oversight role of the International Union of Physiological Sciences (IUPS) in the project.

The IUPS 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 in 1993. The name 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” [2, 3, 4]. A satellite workshop “On designing the Physiome Project”, organized and chaired by the Chair of the IUPS ‘Commission on Bioengineering in Physiology’ (Prof Jim Bassingthwaight), was held in Petrodvoretz, Russia, following the 33rd World Congress in St Petersburg in 1997. A symposium on the Physiome Project was held at the 34th World Congress of IUPS in Christchurch, New Zealand, in August 2001 and the Physiome Project was designated as a major focus for IUPS during the next decade.

The long-range goal of this project is to understand and describe the human organism, its physiology and pathophysiology, and to use this understanding to improve human health. A major aim is to develop computer models to integrate the observations from many laboratories into quantitative, self-consistent and comprehensive descriptions. As with the Human Genome Project, the vast expansion in the use of the internet has been instrumental in bringing together a growing number of Physiome Centres providing databases on the functional aspects of biological systems, covering the genome, molecular form and kinetics, cell biology, up to intact functioning organisms. These databases provide some of

the raw information to develop physiological systems models to simulate whole body organs. Data on cell and tissue structures and physiological functions are growing at similar rates, aided by technical advances such as improved biological imaging techniques. Similarly, modelling resources and software are developing fast enough to allow the development of realistic computer simulations of whole organs to commence. As well as striving for the long-term strategic goals, the project will facilitate biomedical research in the short term by increasingly making well-documented and refereed models available to a much wider range of non-mathematical users.

Meetings were held on the Physiome in 1997 in San Diego and on the “Endothelome” (Kurashika, Japan) and the “Microcirculation Physiome Project” (San Francisco, USA) in 1998. The year 2001 saw a remarkable burst of interest in biological simulation. The first “International Conference on Computational Biology” was held in the US (Carson et al. [7]). INSERM (France), MRC (UK) and NIH (USA) held strategy meetings on this emerging field, while the Novartis Foundation held a landmark symposium on “*In Silico* Simulation of Biological Processes” (Bock and Goode [6]). A very significant development over the last two years has the large investment by NIGMS in collaborative data collection and modelling projects through the “GLUE” grants (see www.nigms.nih.gov). Journals have started to include website references from which published models can be downloaded. Thus, some of the early aims of the Physiome Project in raising awareness and establishing links are already being achieved.

Spatial and temporal scales

The wide range of spatial and temporal scales encompassed by the Physiome Project are shown in Fig. 1. It should be emphasized that no one model would encompass the 10^9 dynamic range of spatial scales (from the 1-nm pore size of an ion channel to the 1-m scale of the human body) or 10^{15} dynamic range of temporal scales (from the 1 μ s typical of Brownian motion to the 70 years or 10^9 s typical of a human lifetime). Rather, it requires a hierarchy of models, such that the parameters of one model in the hierarchy can be understood in terms of the physics or chemistry of the model appropriate to the spatial or temporal scale at the level below [26]. This hierarchy of models must range from gene networks, signal transduction pathways and stochastic models of single channels at the fine scale, up to systems of ordinary differential equations, representing cell level function, and partial differential equations, representing the continuum properties of tissues and organs, at the coarse scale.

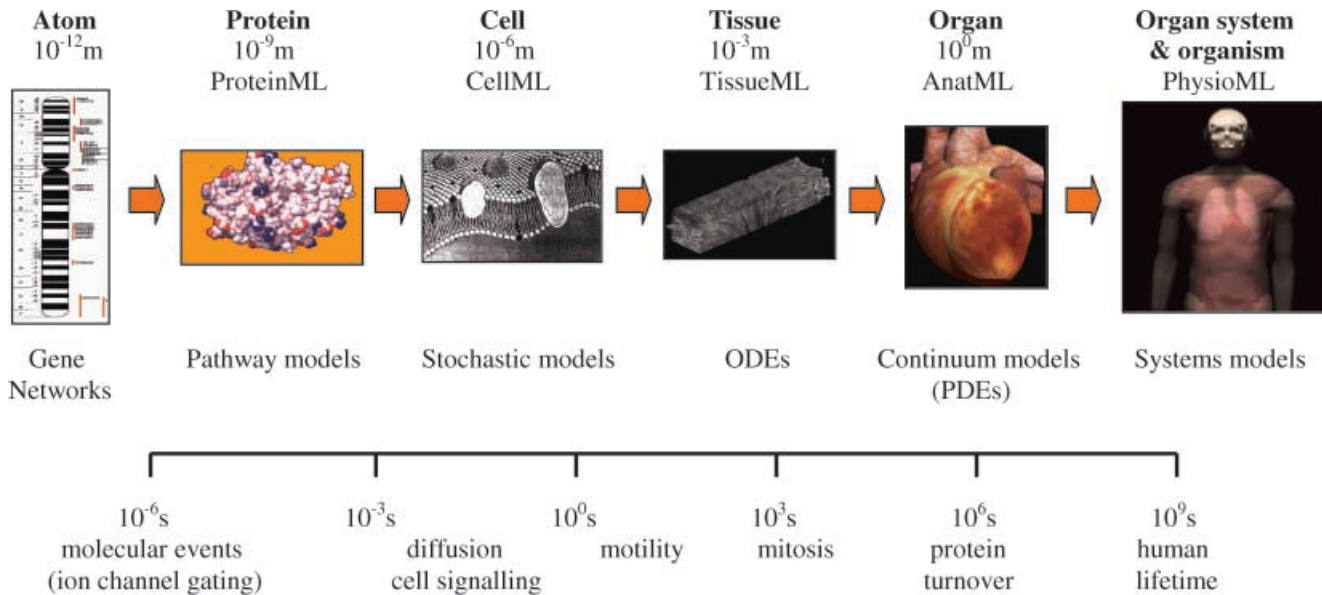
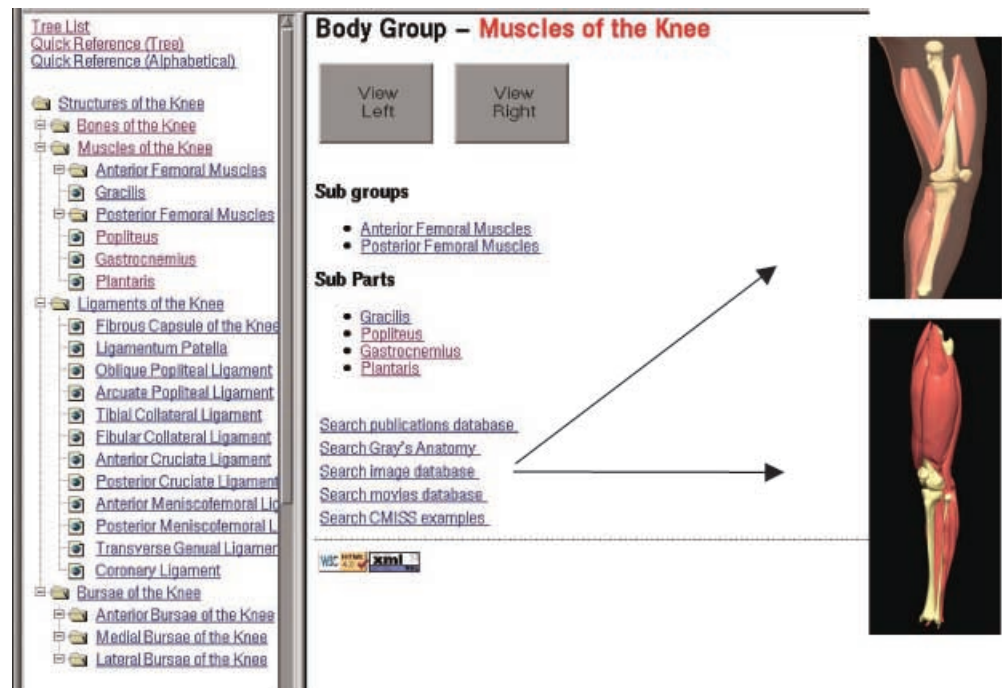


Fig. 1 Spatial (*top*) and temporal (*bottom*) scales encompassed by the Human Physiome Project. Markup languages (PhysioML, AnatML, TissueML, CellML) are defined for each spatial level as indicated here and discussed in the text. The types of mathematical model appropriate to each spatial scale are also indicated. The last

two images on the *right* in this figure, and all subsequent anatomical images, are from anatomically based models developed by the Auckland Bioengineering group. The tissue image is a 3-D confocal microscopy reconstruction of a transmural segment of rat heart by the Auckland group

Fig. 2 The web pages setup to display an ontology tree for human anatomy. All organ systems have now been defined (see www.bioeng.auckland.ac.nz/physiome/physiome.php). Shown here is the musculo-skeletal system for the knee. The leaves of the tree appear on the right and provide access to the databases of relevant information, such as journal publications, anatomical notes, images, movies and models, etc. Note the buttons *View Left* and *View Right* indicating that the models can be viewed with 3-D visualisation software (available as a plugin)



Model ontologies

Ontologies reflect the vernacular and rules that characterise a particular body of knowledge. It is important that the databases of information (publications, data, models, etc) can be accessed via a number of alternative ontologies. One obvious ontology is the organ system

ontology used in standard anatomy and physiology textbooks – and this is illustrated in Fig. 2. Another ontology needed is one based on the physical equations being solved in the integrated tissue and organ models. For example, in the heart there will be a hierarchy of models including myocardial mechanics, myocardial activation, ventricular fluid mechanics, and humoral/

neural control, etc. This is being defined in a model-based ontology that allows the hierarchy of models to be accessed and combined to form larger integrative models. Other ontologies will be based on classifications from histology, cell biology and molecular biology and a further one will be based on disease processes. It is essential for models developed in different ontologies to be able to interact and be readily combined to form compound models that unite disciplines. The Physiome markup languages described below as a means of achieving this are derived from a single base, thus ensuring that they all possess the fundamental mechanisms necessary for cross-disciplinary interaction.

Physiome markup languages

A major problem for modellers at present is the lack of standards for exchanging biological models. Frequently, models published in mathematical form in journals are incomplete or contain errors that can make it difficult for anyone else to code the model. There is an increasing availability of source code for models, but by distributing the computer code instead of the model itself, the recipient is restricted to a particular implementation and cannot easily combine models obtained from different sources. Over the last 3 years a collaboration between scientists at the University of Auckland, NZ, and Physiome Sciences in Princeton, NJ, USA, has developed a set of related public domain XML-based languages² that are suitable for describing biological models. The languages describe the mathematical concepts that make up these models, as well as provide facilities for metadata and documentation to give the model context. Models consist of a network of re-usable components, each with variables and equations manipulating those variables. The mathematics in a model are marked up using MathML, which is an XML vocabulary developed under the supervision of the World Wide Web Consortium. Information about the origins of the model uses the Resource Description Format (RDF), which is also a recommendation of the World Wide Web Consortium.

These markup languages, which are designed to encapsulate structure and function at the level of cells, tissues, organs and organ systems, are listed below.

CellML

This markup language is being developed to deal with models covering all aspects of cellular function. A number of electrophysiological, metabolic and signal transduction pathway models have already been developed in CellML format and are currently available from

the website www.cellml.org. This list will be extended to include many more models covering all cell types and all aspects of cell function as these models are published.

TissueML

This tissue level markup language is being developed to encapsulate the properties of all four tissue types: (1) muscle tissue (including skeletal, cardiac and smooth muscle); (2) nerve tissue; (3) connective tissue (including loose connective tissue, bone, cartilage and blood); and (4) epithelial tissue (characterized by the number of cell layers, the shape of component cells, and the surface specialisation).

AnatML

This markup language is being developed to describe anatomy. AnatML files have now been created for many organs and systems in the body and an ontology for this “top down” aspect of the Physiome is accessible via the web at www.bioeng.auckland.ac.nz/physiome/physiome.php.

PhysioML

The PhysioML markup language is being developed to describe systems level physiological models. Note that the organ models above are sometimes too complex to include in a simulation of an entire organ system and it is then necessary to find simpler models which can adequately represent their behaviour relevant to the questions asked of the systems model. The parameters of the simple model should be interpretable in terms of the anatomically and biophysically detailed organ model. An example is given in Fig. 3. This key concept of being able to relate models across multiple spatial scales will be vital to the success of the physiome project and is illustrated again in Fig. 4

Databases and software tools

A software user interface is being developed to provide a window with tools appropriate to each level, as depicted in Fig. 5. This open-source software will include visualisation tools to provide access to data and models at each level where these models are encapsulated in the Physiome markup languages described above. The information displayed at a particular level is relevant to the position within the window above at which this level window is opened. Solutions obtained by running a model at one level can be interpreted within the context of the more structurally detailed model at the level below or used to define a parameter of the lower spatial resolution model above.

² XML (eXtensible Markup Language) was developed by the W3C (World Wide Web Consortium) – see www.w3c.org. XML is a structured document format that is both human and machine readable.

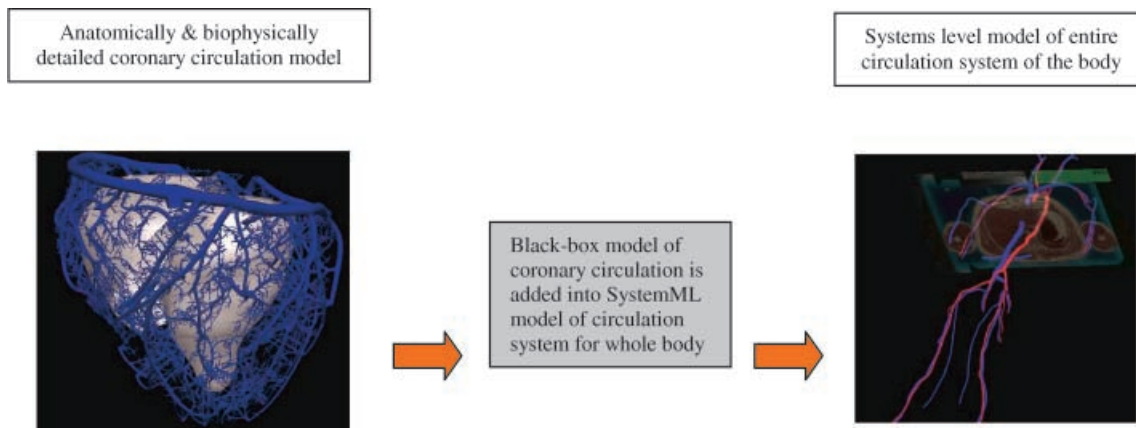


Fig. 3 Computational models of organ systems, such as the circulatory system shown on the *right*, are defined with the markup language PhysiML such that parameters of a component (e.g. the

coronary circulation) are linked to anatomically detailed models of the coronary circulation defined in AnatML, as shown on the *left*.

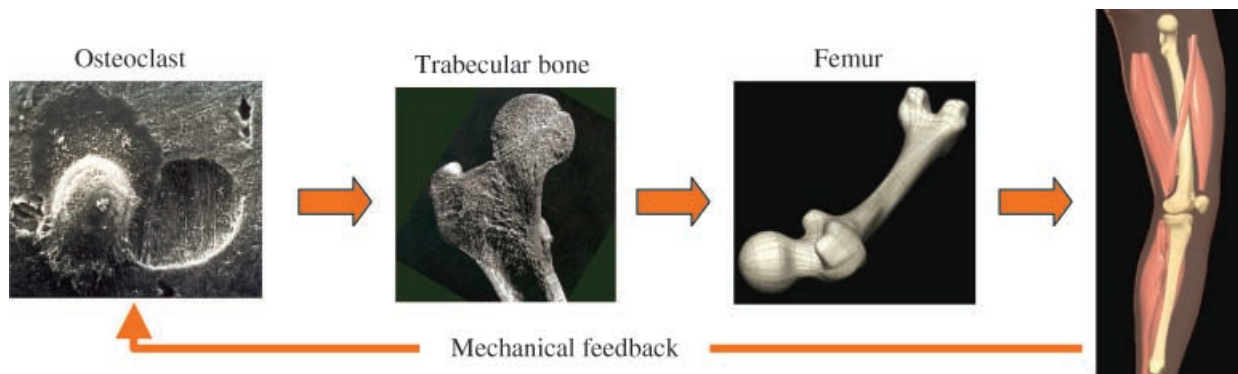


Fig. 4 The process of integrating from cell (*osteoclast*) to tissue (*trabecular bone*) to organ (*femur*) to organ system (leg) is illustrated here. The mechanical stress computed at the organ

system level can then be fed back to the cellular processes controlling the balance of osteoblasts and osteoclasts in the bone modelling unit

Key stages of model development

The development of databases and models will proceed through the following five stages: a *descriptive* stage, a *formulation* stage, an *implementation* stage, a *model validation* stage, and a *biomedical interpretation* stage [23].

Descriptive stage

Refereed journal publications are used to understand the basic biological processes and to source experimental data to develop the quantitative aspects of the models. A database with web interfaces for data entry and retrieval (see www.bioeng.auckland.ac.nz/publications/publications.php) has been created to contain bibliographic information. To facilitate this stage help is being solicited from researchers in numerous labs around the world who are willing to identify the key papers to enter into the database. The bibliographic information is placed in the web-accessible database by the groups responsible for

each area. For example, entering “lung” or “heart” in the keyword field retrieves a list of papers which have been used in the development of the lung and heart models, respectively. Implementing a review process at the descriptive stage will be considered. For example, review comments by an expert in the field could also be placed in the database. This would have two advantages. First, many with the biological expertise to perform the review process do not have the mathematical ability to do this well if the descriptive components have already been translated into model equations. Secondly, the ultimate aim of this programme is health-related and it is therefore important that the Human Physiome is documented at one level in a manner that is accessible to clinicians and biologists without particular mathematical expertise.

Formulation stage

This is the process of turning the biological data into a mathematical model comprising equation systems relating the variables and parameters of interest. The approach

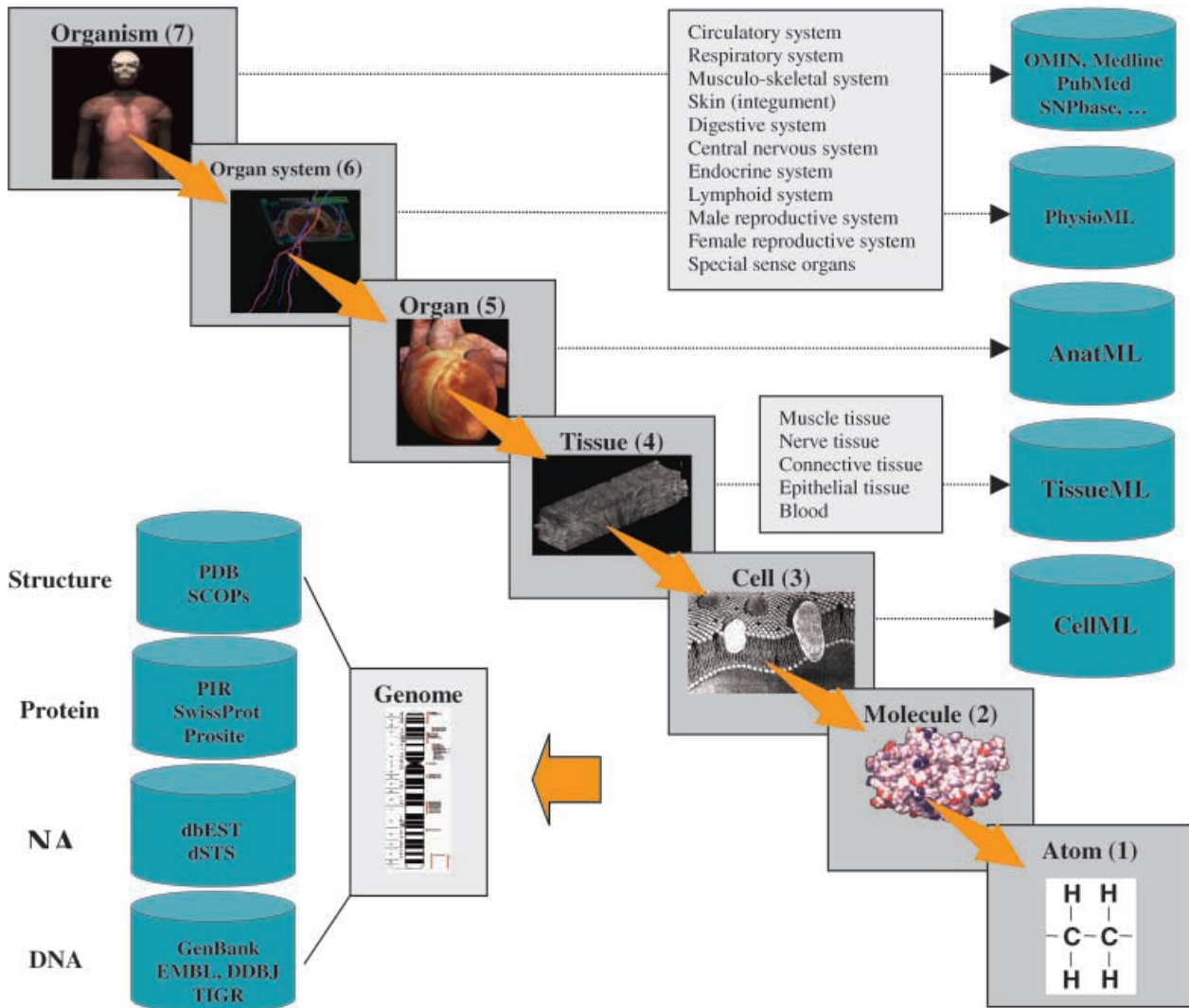


Fig. 5 Accessing information at the various spatial scales. Note the database of organ system models based on PhysioML files, the database of anatomical models based on AnatML files, the database of tissue structure and properties based on TissueML files, and the database of cell pathways and ion channel properties based on CellML files. The markup languages ensure that models are encoded in a consistent form and allows simulation packages to import the models in a standard format. Note that the CellML

language is already well developed and many cell models are available (see www.cellml.org). Databases of clinical information and databases of genomic and proteomic data are already well established, as indicated, but an important goal of the project is to ensure that information can be extracted from these top level and bottom level databases via the user interfaces in a form that is compatible with the Physiome Project

used to translate the descriptive model into a set of mathematical equations varies greatly depending on the problem type and spatial scale of interest. Some of the common approaches are listed below.

Tissue mechanics

The equations come from the physical laws of mass conservation and momentum conservation in three dimensions and require a knowledge of the tissue structure and material (constitutive) properties together with a mathematical characterization of the anatomy and fibrous structure of the organ (or bone, etc). Solution of the

equations gives the deformation, strain and stress distributions throughout the organ [10]. Examples are the large deformation soft tissue mechanics of the heart, lungs, skeletal muscles and cartilage and the small strain mechanics of bones [21]. The mathematical techniques required for these problems are now well established and the main challenge is to define the geometry of all body parts and the spatial variation of tissue structure and material properties. The most urgent requirements are to define the markup language (FieldML) which allows the anatomy and spatial property variations to be captured in a format for storage and exchange, and to develop the visualisation tools for viewing the 3-D anatomy and computed fields such as stress and strain. Another high

priority is to enhance the tools that allow a generic model to be customized to individual patient data from medical imaging devices such as MRI, CAT and ultrasound.

Fluid mechanics

The equations are also based on mass conservation and momentum or energy conservation and the requirement for a mathematical representation of anatomy is similar, but now the constitutive equations come from the rheology of a fluid (e.g. blood or air) and the solution of the equations yields a pressure field and a flow field. Examples are blood flow in arteries and veins and gas flow in the lungs [30, 31]. In some cases the equations can be integrated over a vessel or airway cross-section to reduce the problem to the solution of one-dimensional equations, while in others a full 3-D solution is required. The top priorities in this area are as above – the markup languages, visualization tools and patient customisation tools.

Reaction-diffusion systems

There are many issues of transport by diffusion and advection, coupled to biochemical reactions, in physiological systems [18, 22, 28]. The transport equations are based on well-established laws of flux conservation and the numerical solution strategies are also well developed. Examples are the electrical activation of the heart (equations based on conservation of current) and numerous problems in developmental biology. The need for good anatomical descriptions using FieldML is similar to the above two categories. The main challenges lie in developing good models of the biochemical reactions and capturing these in the CellML format for storage and exchange.

Electrophysiology

All cells make use of ion channels, pumps and exchangers. 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) [14, 17]. Examples are the Hodgkin-Huxley models of action potential propagation in nerve axons [12], the Noble and Rudy models for cardiac cell electrophysiology [8] and pancreatic β -cell models of the metabolic dependence of insulin release. The major challenge now is to relate the parameters of these models to our rapidly increasing knowledge of gene sequence and three-dimensional 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 FieldML

for handling the spatially varying parameters such as channel density. The most urgent requirements are authoring tools, application programming interfaces (APIs) and simulation tools.

Signal transduction pathways

The governing equations here are based on mass balance relations. The information content is often based on signal dynamics rather than steady-state properties, so a system dynamics and control theoretical framework is important. An example is the eukaryotic mitogen-activated protein kinase (MAPK) signalling pathway which culminates with activation of extracellular signal-regulated kinases (ERKs) [1]. The signal transduction pathway definitions can be encapsulated in CellML and a priority now is the development of tools which will allow the activity of the pathways to be modeled in the context of a three-dimensional cell and linked to ion channel and pumps (e.g. as sites of phosphorylation) and to tissue and organ level models.

Metabolic pathways

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 [28].

Cell homeostasis

Models of cellular metabolism, ion regulation, energetics and redox state, which maintain balances of mass, charge, energy, etc.

Gene networks

This relates to the study of gene regulation, where proteins often regulate their own production or that of other proteins in a complex web of interactions. The biochemistry of the feedback loops in protein-DNA interactions often leads to nonlinear equations. Techniques from nonlinear dynamics, control theory and molecular biology are used to develop dynamic models of gene regulatory networks [19].

Implementation stage

This is undertaking the numerical and mathematical analysis to solve the systems of equations via computer simulation. Note that an additional process of mathematical analysis is often used to understand the computational model and so further reduce it. This is often the goal of

mathematical biology and is important in forming links between the models at different levels (cell, tissue, organ, etc). It is worth noting here that the key to widespread use of biological simulation packages may well be grid computing, or “e-Science” as it is called in the UK. The simulation of whole organ function typically requires high performance computing on parallel supercomputers. Web interfaces designed to allow biologists to adjust relevant parameters, run models and visualise results are being established (see, for example, www.bioeng.auckland.ac.nz/physiome).

Model validation stage

Whilst there is a micro-process of validation within each of the descriptive, formulation and implementation stages, this is the process of using independent data, not used in model formulation, to validate the model. It is noteworthy that this aspect of the project is currently being considered by the Bioengineering community.

Biomedical interpretation stage

This is the end process of using the model to gain insight into biology and pathology, which is of course the major goal of the project. The Physiome Project will provide powerful tools for understanding data and guiding experimental hypothesis driven research.

Conclusions and prospects

Two major developments in current medicine are, on the one hand, the much publicised genomics (and soon proteomics) revolution and, on the other, the revolution in medical imaging in which the physiological function of the human body can be studied with a plethora of imaging devices such as MRI, CT, PET, ultrasound, electrical mapping, etc. The challenge for computational biology, and hence the Physiome Project, is to link these two developments for an individual – to use complementary genomic and medical imaging data, together with computational modelling tailored to the anatomy, physiology and genetics of that individual, for diagnosis or treatment of that individual. To achieve this requires the development of vast databases of information at all spatial and temporal scales, and the development of a hierarchy of models dealing with biophysics at various spatial scales but all linked so that parameters in one model are the output of models at a finer spatial or temporal scale. In this paper we have outlined the development of an infrastructure to support the Physiome Project. There is good reason to believe that we are on the brink of a major revolution in biology – one in which mathematical modelling of proteins, cells, tissues, organs and organ systems allow the linking of genomic and proteomic information to integrated whole-organism behaviour, and

the quantitative understanding of human pathologies in terms of the altered model parameters of normal physiology.

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