Запорожский государственный медицинский университет
Кафедра медицинской и фармацевтической информатики

Computational biology

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Computational biology

Computational biology is an interdisciplinary field that applies the techniques of *computer science, applied mathematics* and *statistics* to address biological problems.

The main focus lies on *developing mathematical modeling* and *computational simulation techniques*. By these means it addresses scientific research topics with their theoretical and experimental questions without a laboratory.

It encompasses the fields of :

- **Computational biomodeling**, a field concerned with building computer models of biological systems.
- **Bioinformatics**, which applies algorithms and statistical techniques to the interpretation, classification and understanding of biological datasets. These typically consist of large numbers of DNA, RNA, or protein sequences. Sequence alignment is used to assemble the datasets for analysis. Comparisons of homologous sequences, gene finding, and prediction of gene expression are the most common techniques used on assembled datasets; however, analysis of such datasets have many applications throughout all fields of biology.

- **Mathematical biology** aims at the mathematical representation, treatment and modeling of biological processes, using a variety of applied mathematical techniques and tools.
- **Computational genomics**, a field within genomics which studies the genomes of cells and organisms. High-throughput genome sequencing produces lots of data, which requires extensive post-processing (genome assembly) and uses DNA microarray technologies to perform statistical analyses on the genes expressed in individual cell types. This can help find genes of interest for certain diseases or conditions. This field also studies the mathematical foundations of sequencing.

- ***Molecular modeling***, which consists of modelling the behaviour of molecules of biological importance.
- ***Protein structure prediction and structural genomics***, which attempt to systematically produce accurate structural models for three-dimensional protein structures that have not been determined experimentally.
- ***Computational biochemistry and biophysics***, which make extensive use of structural modeling and simulation methods such as molecular dynamics and Monte Carlo method-inspired Boltzmann sampling methods in an attempt to elucidate the kinetics and thermodynamics of protein functions.

IUPS Physiome Project

IUPS Physiome Project

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.

IUPS Physiome Project

http://www.physiome.org.nz/index_html

IUPS Physiome Project

About

- Overview
- Sponsors
- Roadmap
- Research Groups
- Publications
- Body Systems
- Events

Tools

- Tools
- CellML
- FieldML
- Databases
- Ontology Viewer

Projects

- Cardiovascular System
- Urinary System and Kidney
- Respiratory System
- Musculo-Skeletal System
- Integumentary System
- Digestive System
- Nervous System
- Endocrine System
- Immune System
- Female Reproductive System
- Male Reproductive System
- Special Sense Organs
- Related Projects

The IUPS Physiome Project

The Physiome Project is a worldwide public domain effort to provide a computational framework
human and other eukaryotic physiology. It aims to develop integrative models at all levels of bio
from genes to the whole organism via gene regulatory networks, protein pathways, integrative
tissue and whole organ structure/function relations. Current projects include the development o

- ontologies to organise biological knowledge and access to databases
- markup languages to encode models of biological structure and function in a standard format different application programs and for re-use as components of more comprehensive models
- databases of structure at the cell, tissue and organ levels
- software to render computational models of cell function such as ion channel electrophysiolog metabolic pathways, transport, motility, the cell cycle, etc. in 2 & 3D graphical form
- software for displaying and interacting with the organ models which will allow the user to mo scales

An important goal of the project is to develop applications for teaching physiology.

The following PDFs describe aspects of the project:
Nature Review,
European Journal of Physiology Review,
Experimental Physiology Review.
This is an electronic version of an article published in Experimental Physiology:
complete citation information for the final version of the paper, as published in
the print edition of Experimental Physiology, is available on the Blackwell Synergy
online delivery service, accessible via the journal's website at
http://www.blackwellpublishing.com/journals/EPH or http://www.blackwell-synergy.com

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Projects

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E-mail website feedback to webmaster@physiome.org.nz

Physiome Bioinformatics

Modeling Hierarchies

- Genes
- Proteins
- Biophysical models
- Constitutive laws
- Organ model
- Whole body model

Molecular Biology

Physiology

Bioengineering

Clinical medicine

Databases

- Genome
- Protein
- Physiology
- Structural
- Bioeng. Materials
- Clinical

Mathematical Models

Level 1 models: Molecular models

Level 2 models: Subcellular Markov models

Level 3 models: Subcellular ODE models

Level 4 models: Tissue and whole organ continuum models

Level 5 models: Whole body continuum models

Level 6 models: Whole body system models

Visualization Tools

- Interrogation of model parameters
- Animated visualization of computational output
- From molecular level through to the whole body
- Web based
- Coupled to the computational models in a user-friendly fashion.

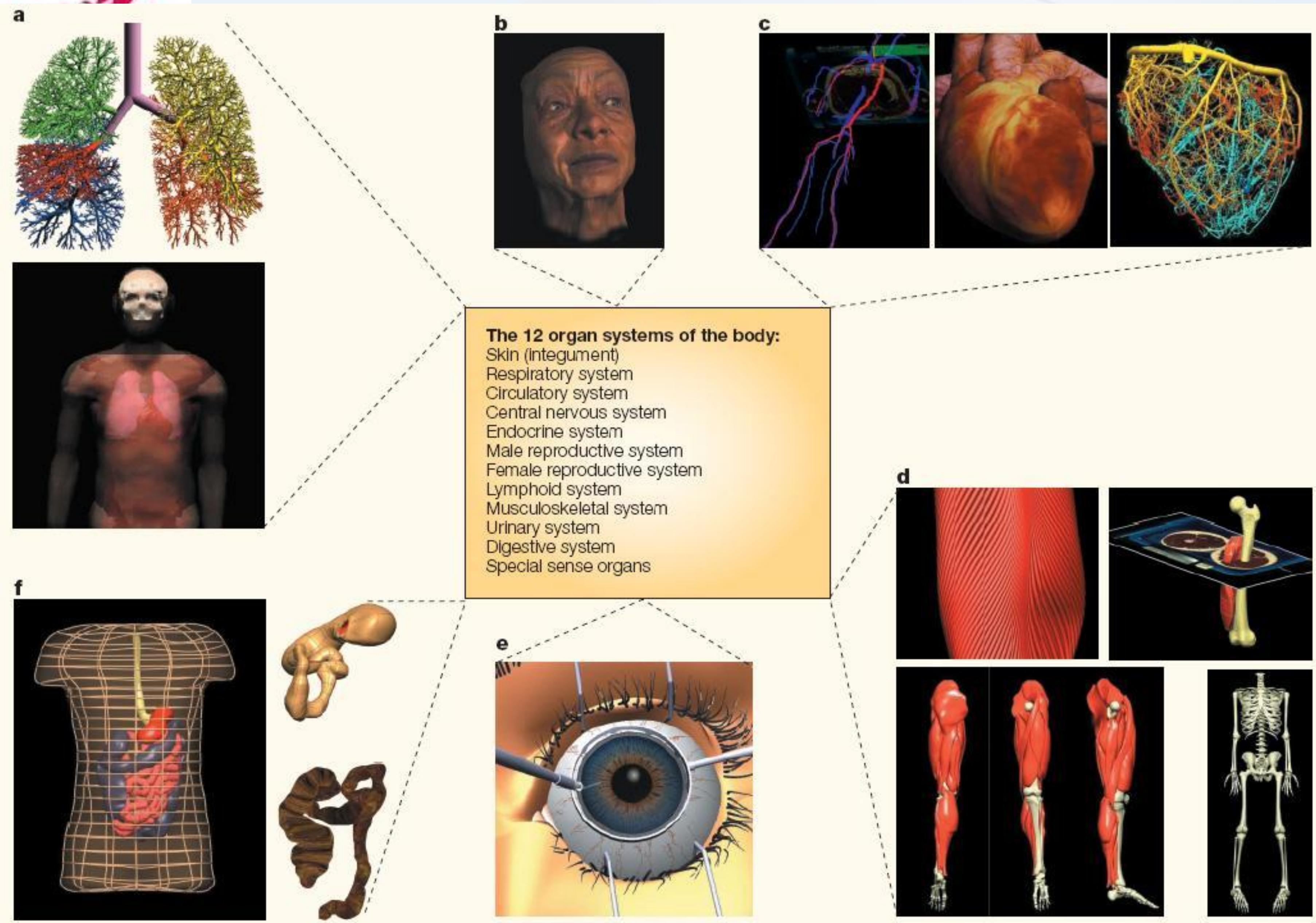
Instrumentation

- Structural measurements
  - geometry and tissue microstructure of organs
  - present methods too slow and tedious
- Material property measurements
  - mechanical, electrical, thermal, etc
  - variety of species
  - pathological conditions
  - nonlinear, coupled parameters

Physiome Groups

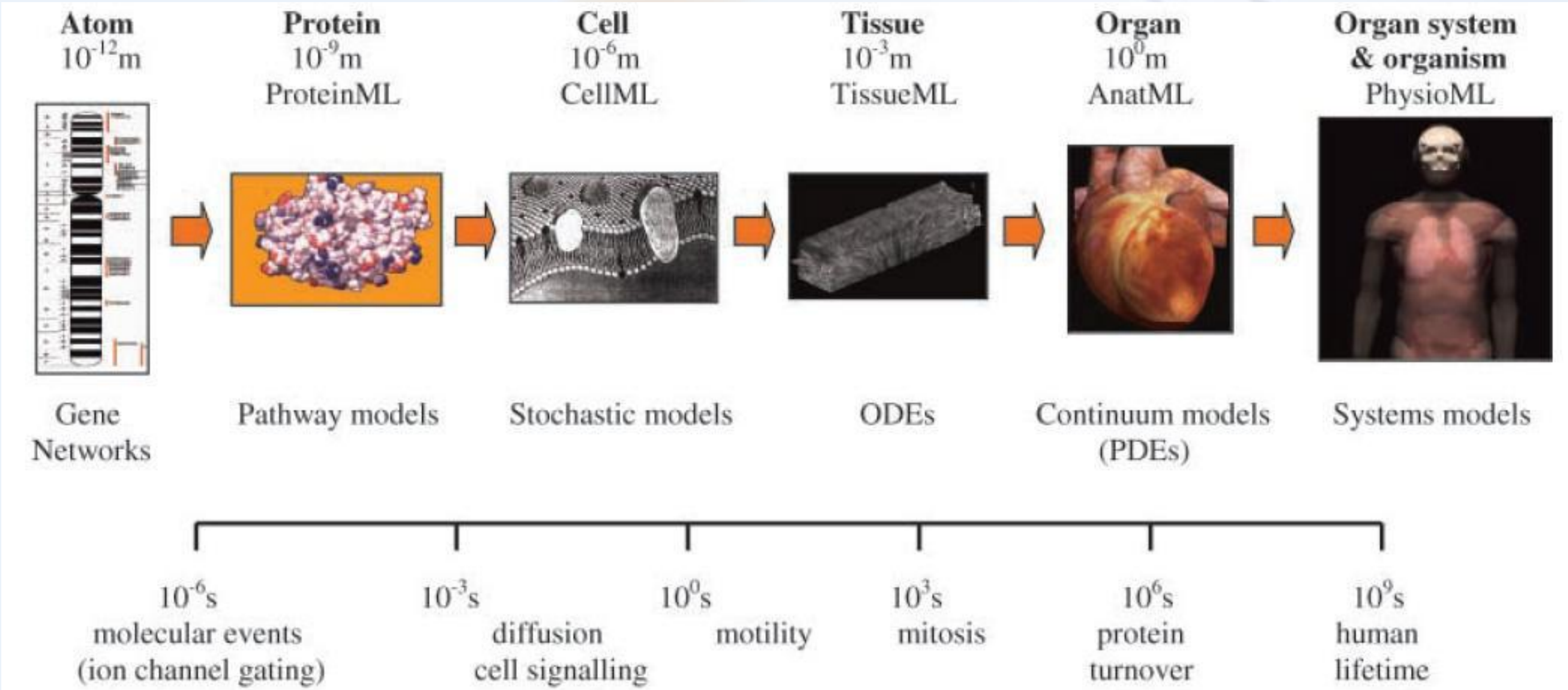
- BioNoME (UCSD)
  - Biology Network of Modeling Efforts;
- Cardiome Project
  - the model and most active group
- Microcirculatory Physiome Project
- Endotheliome Project
- Pulmonary Physiome

IUPS Physiome Project.PhysioML



IUPS Physiome Project

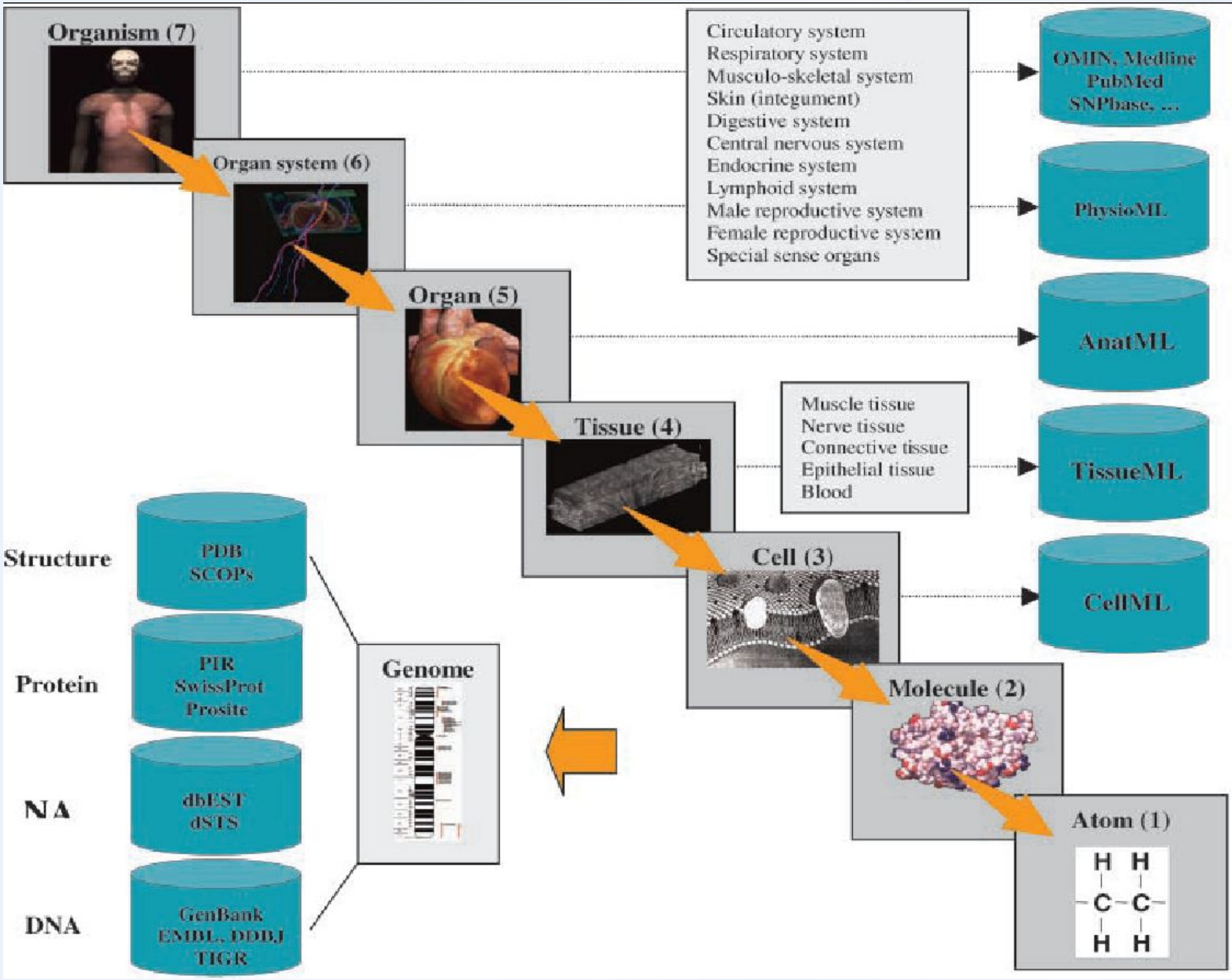
Spatial and temporal scales



The wide range of spatial and temporal scales encompassed by the Physiome Project are shown in slide. 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.

Markup languages (PhysioML, AnatML, TissueML, CellML) are defined for each spatial level as indicated here. The types of mathematical model appropriate to each spatial scale are also indicated.

IUPS Physiome Project



What is – ontology?

Ontology - the "science of being" - typically has different meanings in different contexts.

Webster's Dictionary defines ontology as:

- a branch of metaphysics relating to the nature and relations of being
- a particular theory about the nature of being and the kinds of existence

- **Several philosophers - from Aristoteles (4th Century BC) to Leibniz (1646-1716), and more recently the 19th Century major ontologists like Bolzano, Brentano, Husserl and Frege - have provided criteria for distinguishing between different kind of objects (a.g. concrete vs. abstract) and the relations between them.**

- **In the late 20th Century, Artificial Intelligence (AI) adopted the term and began using it in the sense of a "specification of a conceptualization" in the context of knowledge and data sharing (Gruber).**

- Sowa proposes the following: "The subject of ontology is the study of the categories of things that exist or may exist in some domain.
- The product of such a study, called an ontology, is a catalog of the types of things that are assumed to exist in a domain of interest D from the perspective of a person who uses a language L for the purpose of talking about D."

The use of ontologies in medicine is mainly focussed on the representation and (re-)organization of medical terminologies.

Physicians developed their own specialized languages and lexicons to help them store and communicate general medical knowledge and patient-related information efficiently.

Such terminologies, optimized for human processing, are characterized by a significant amount of implicit knowledge.

Medical information systems, on the other hand, need to be able to communicate complex and detailed medical concepts (possibly expressed in different languages) unambiguously. This is obviously a difficult task and requires a profound analysis of the structure and the concepts of medical terminologies. But it can be achieved by constructing medical domain ontologies for representing medical terminology systems.

Benefits

- Ontologies can help build more powerful and more interoperable information systems in healthcare.
- Ontologies can support the need of the healthcare process to transmit, re-use and share patient data.
- Ontologies can also provide semantic-based criteria to support different statistical aggregations for different purposes.
- Possibly the most significant benefit that ontologies may bring to healthcare systems is their ability to support the indispensible integration of knowledge and data.

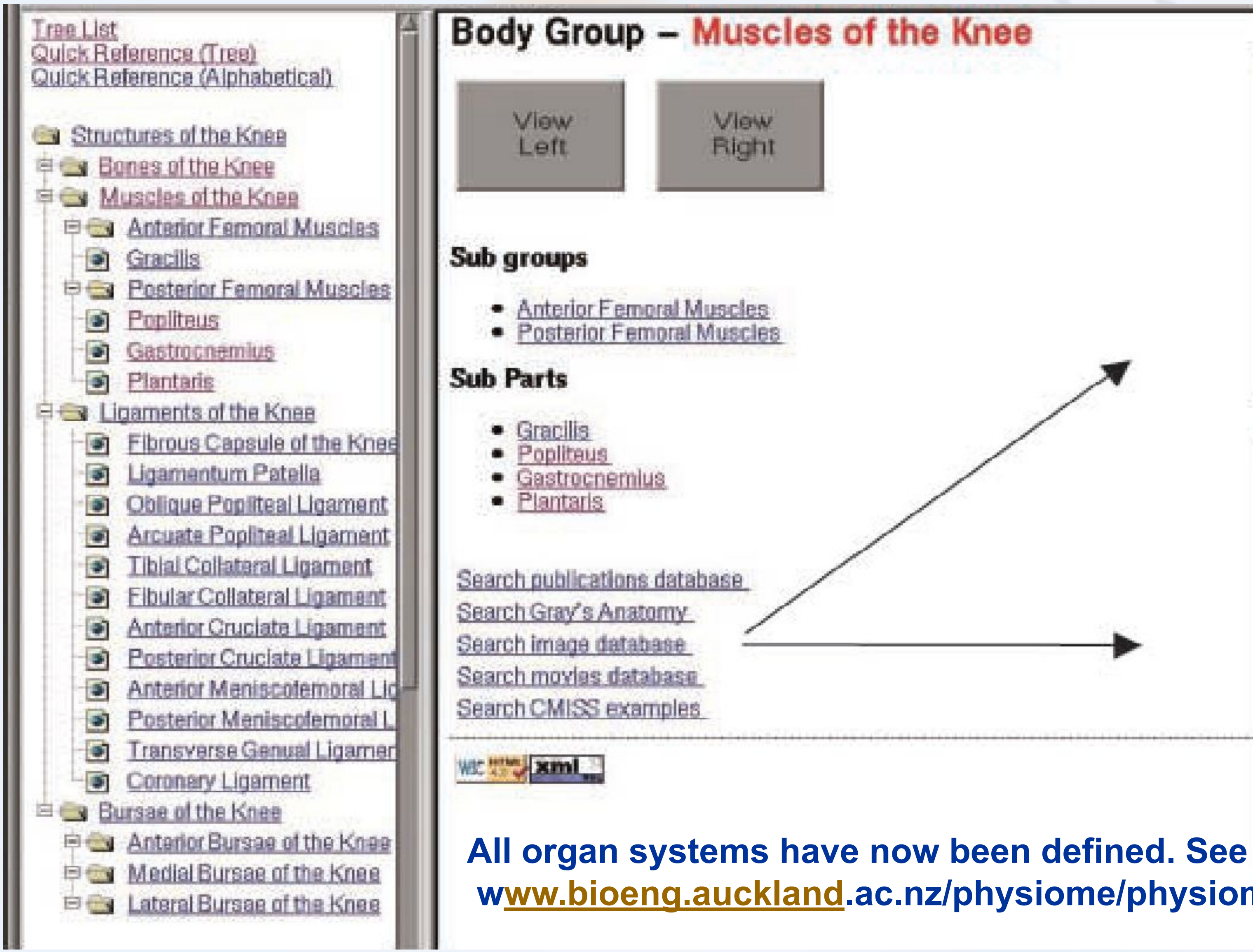
- On the negative side:

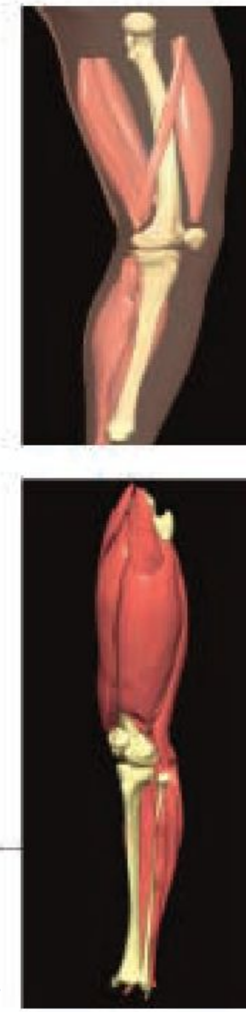
- Some remain sceptical about the impact that ontologies may have on the design and maintenance of real-world healthcare information systems.

IUPS Physiome Project

Model ontologies

The web pages setup to display an ontology tree for human anatomy.

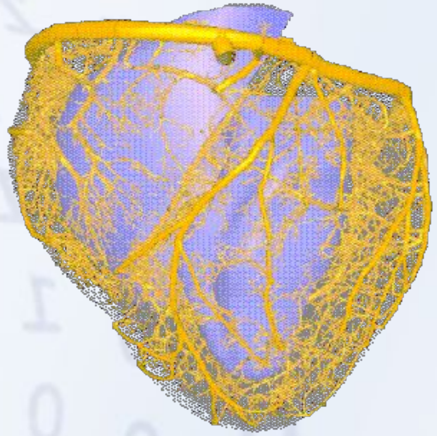


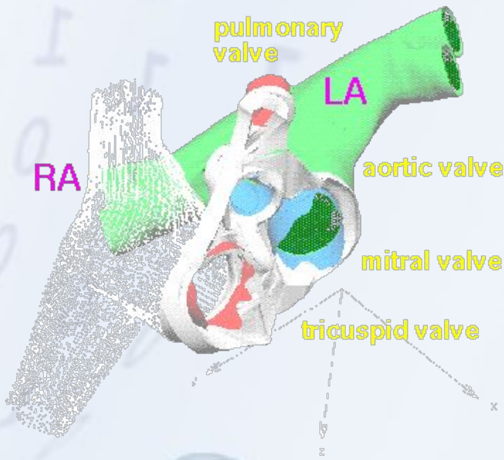


All organ systems have now been defined. See www.bioeng.auckland.ac.nz/physiome/physiome.php).

Anatomy

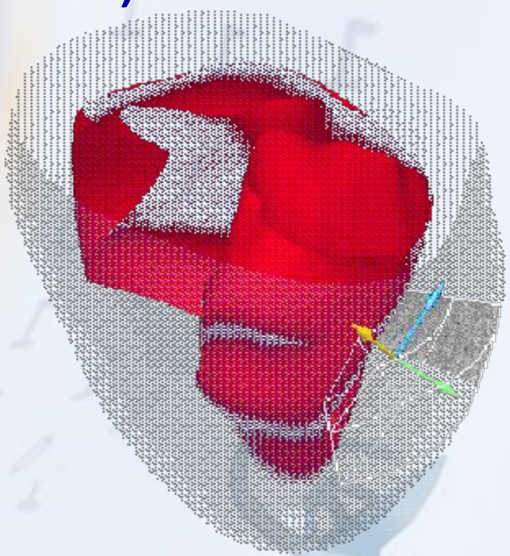
- Completed or underway:
  - Vent. geom. & fibre-sheet structure for dog
  - Vent. geom. & fibre-sheets for rabbit
  - Coronary anatomy for pig
  - Atrial geometry & structure for pig
  - Cardiac valve structure
  - Automated measurement rig
- Needed soon:
  - Geom. & fibre-sheet structure for pig, human
  - Geom. & fibre-sheet structure for hypertrophy etc





Mechanics

- Completed or underway:
  - Material properties -
    - biaxial tests on dog myocardium (AU)
    - shear testing of pig myocardium (AU)
    - torsion testing of rabbit pap. muscle (JHU)
  - ECM structure (UCSD, Columbia, AU, JHU)
  - Functional studies on gene targetted mice (UCSD)
  - Infarct modelling (UCSD, Columbia, AU)
  - Ventricular aneurysm (UCSF)
  - Acute ischaemia (UCSD, UWash)
- Needed soon:
  - Microstructure & mechanical properties of cytoskeleton & ECM



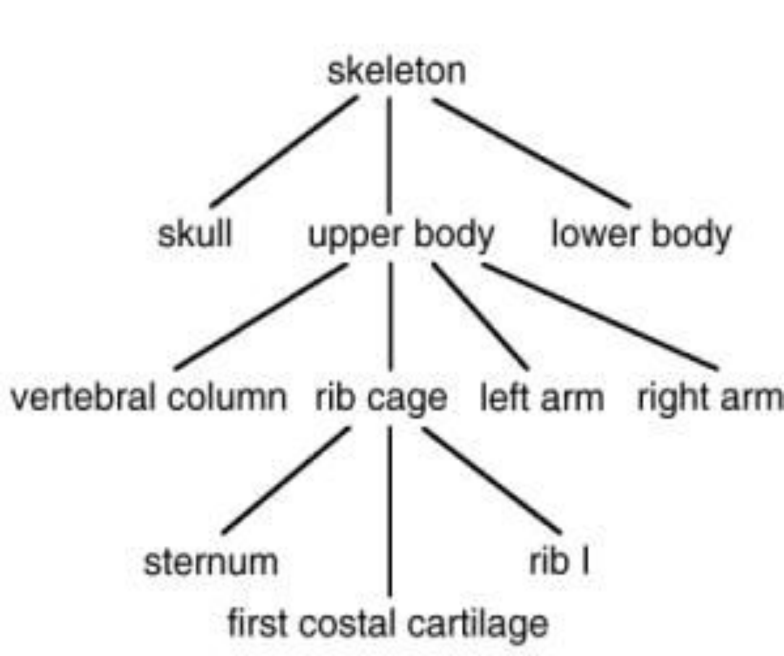
Activation

- Completed or underway:
  - Ionic current models
  - Spatial distribution of ion channels
  - SA, atrial, AV, HIS, Purkinje
  - Reentrant arrhythmias
  - Defibrillation studies
  - Heart failure
  - Mutations
  - EC coupling
  - CellML
- Needed soon:
  - Spatial distribution of gap junctions
  - Drugs -> models -> clinically observable effects
  - Mutations
  - Expression profiling in acquired heart disease

IUPS Physiome Project

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.

IUPS Physiome Project

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.

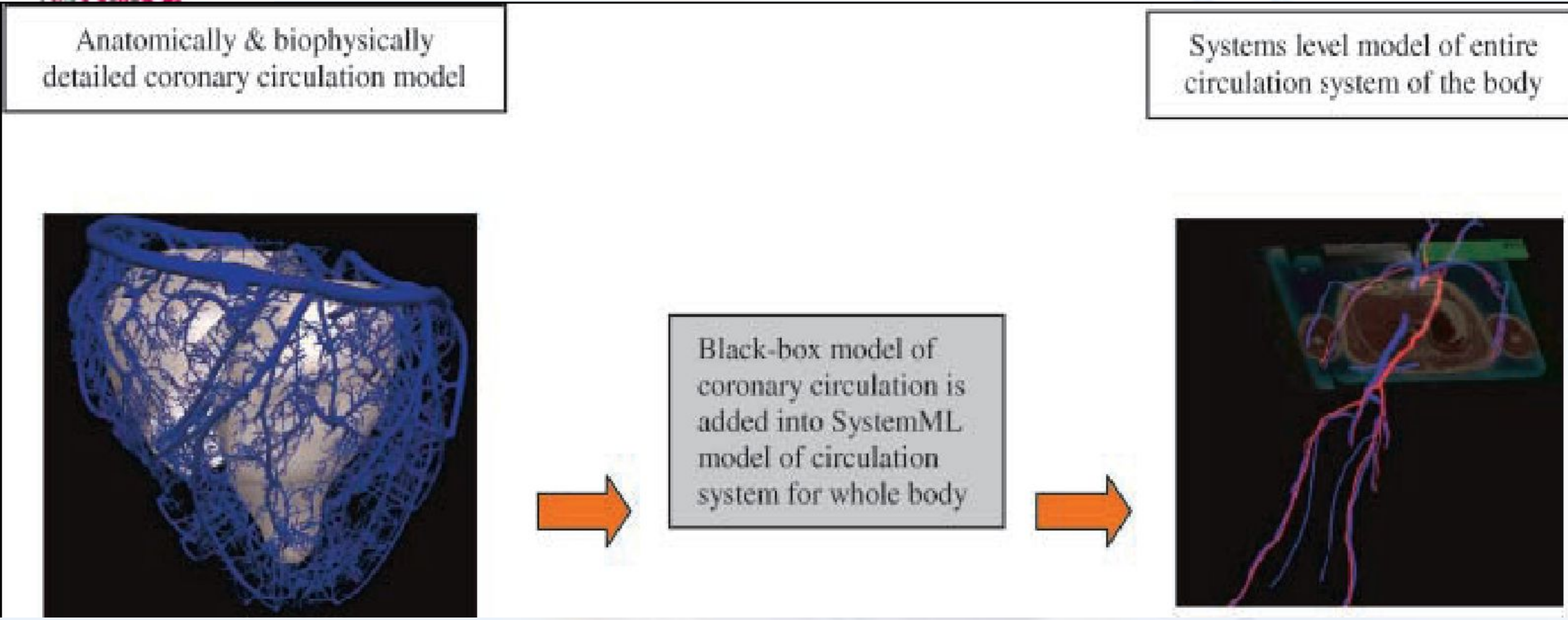
IUPS Physiome Project

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.

IUPS Physiome Project.PhysioML

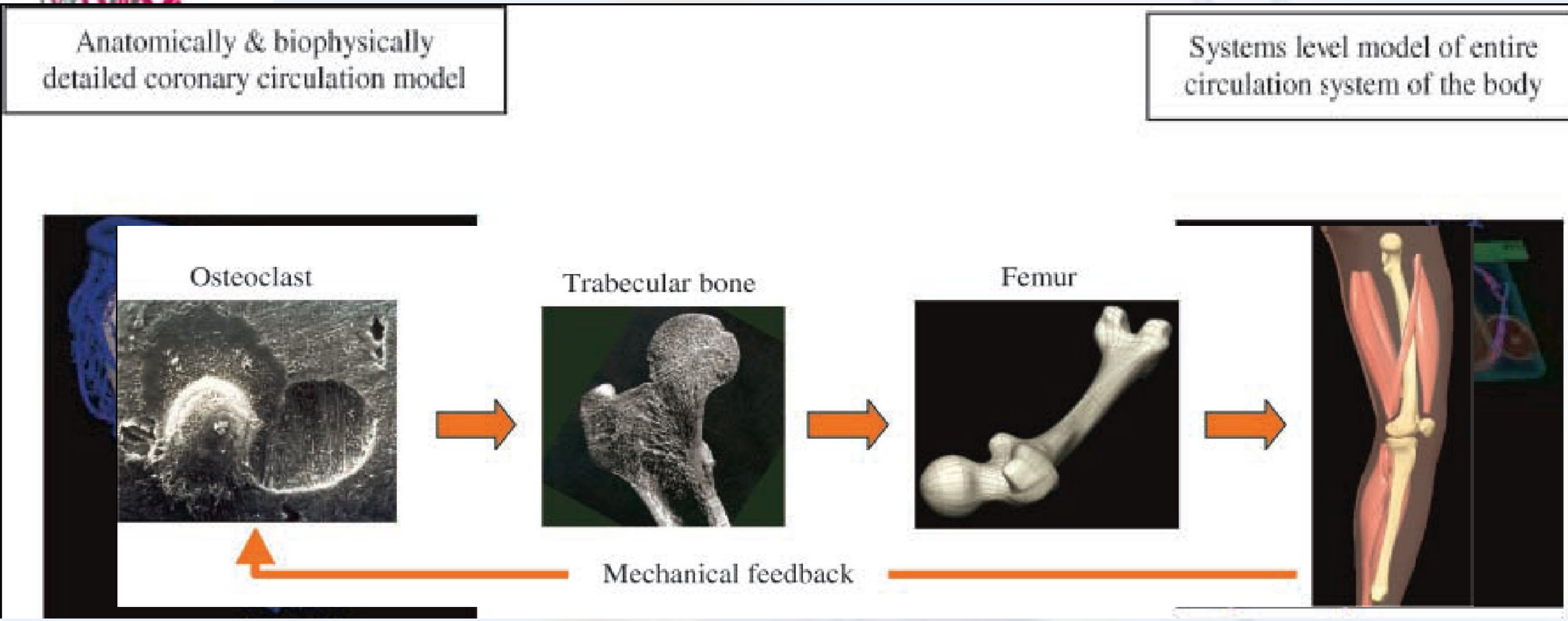
Computational models of organ systems



Computational models of organ systems, such as the circulatory system shown on the right, are defined with the markup language PhysioML such that parameters of a component (e.g. The coronary circulation) are linked to anatomically detailed models of the coronary circulation defined in AnatML.

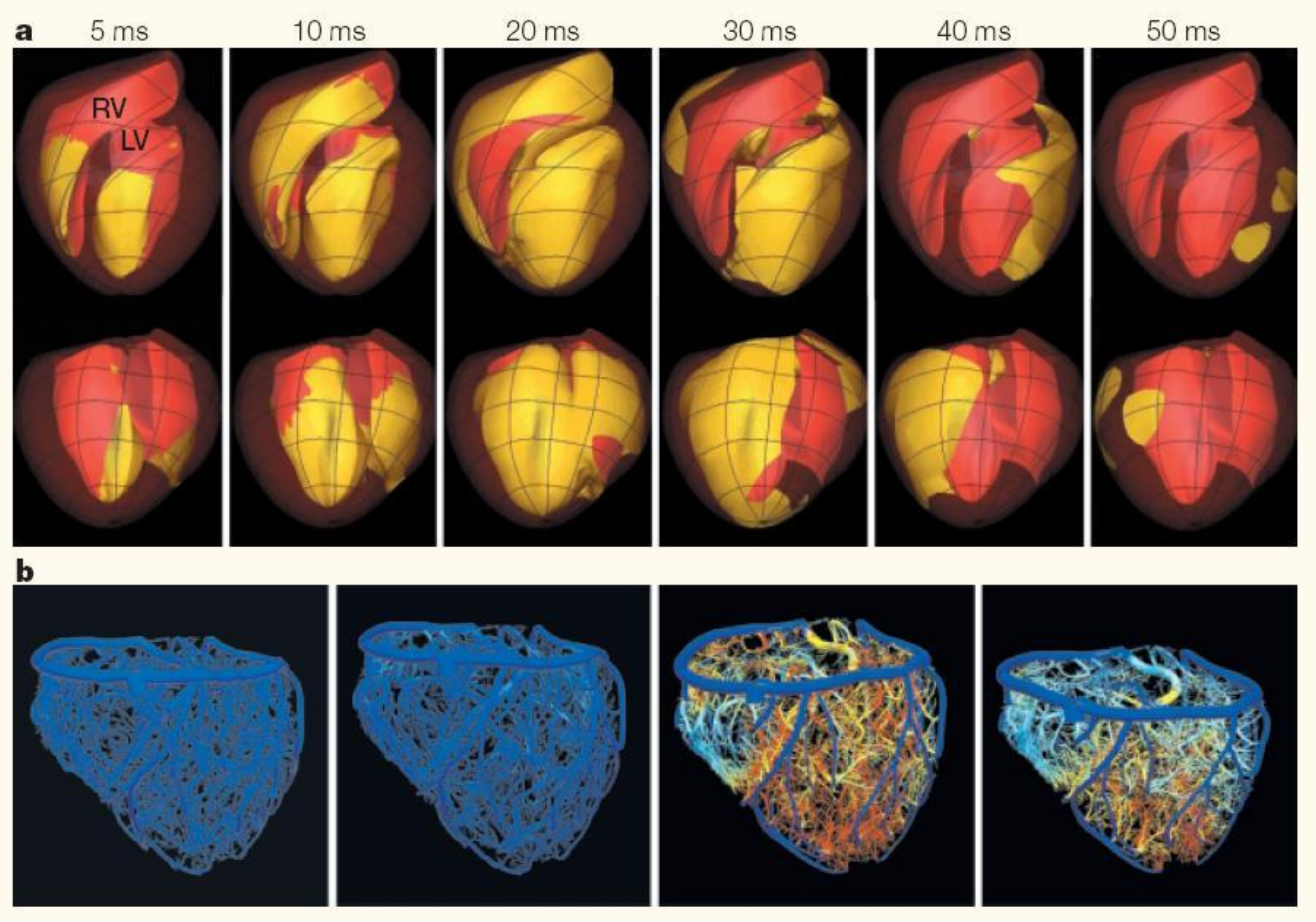
IUPS Physiome Project.PhysioML

Computational models of organ systems



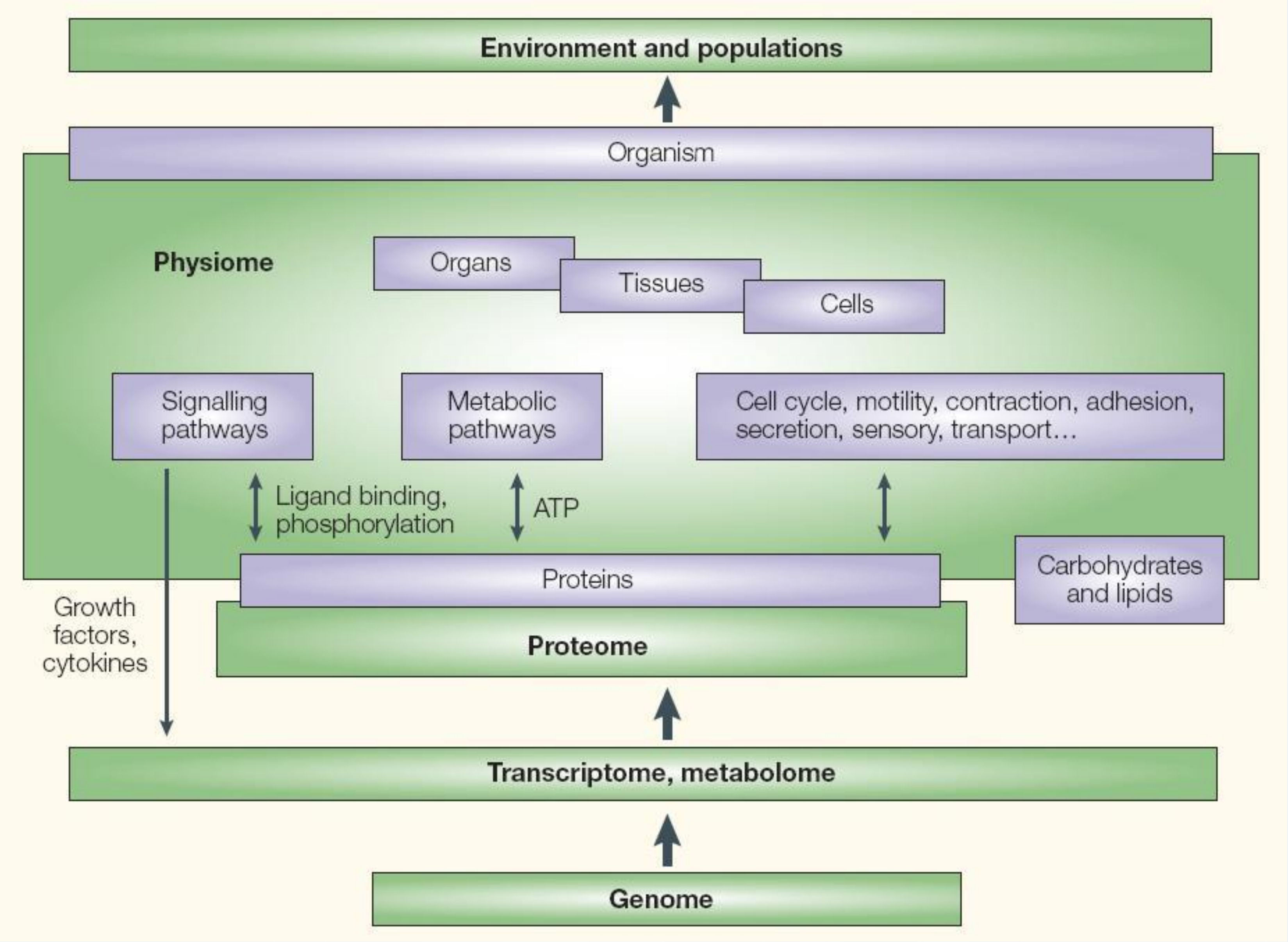
The process of integrating from cell (osteoclast) to tissue (trabecular bone) to organ (femur) to organ system (leg) is illustrated here. The mechanical stress computed at the organ system level can then be fed back to the cellular processes controlling the balance of osteoblasts and osteoclasts in the bone modelling unit.

IUPS Physiome Project.PhysioML
Cardiom Project



IUPS Physiome Project

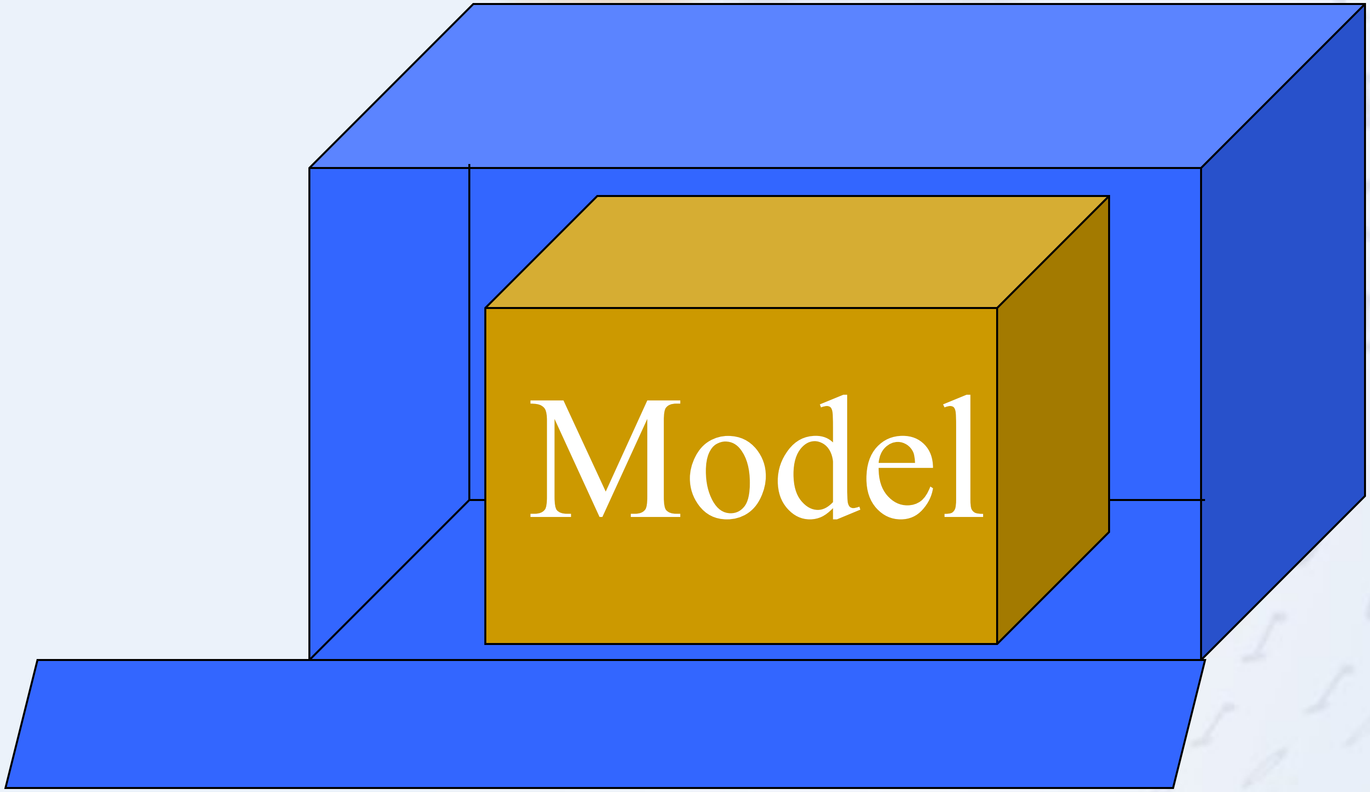
Relationship between the Physiome and other areas of biological organization



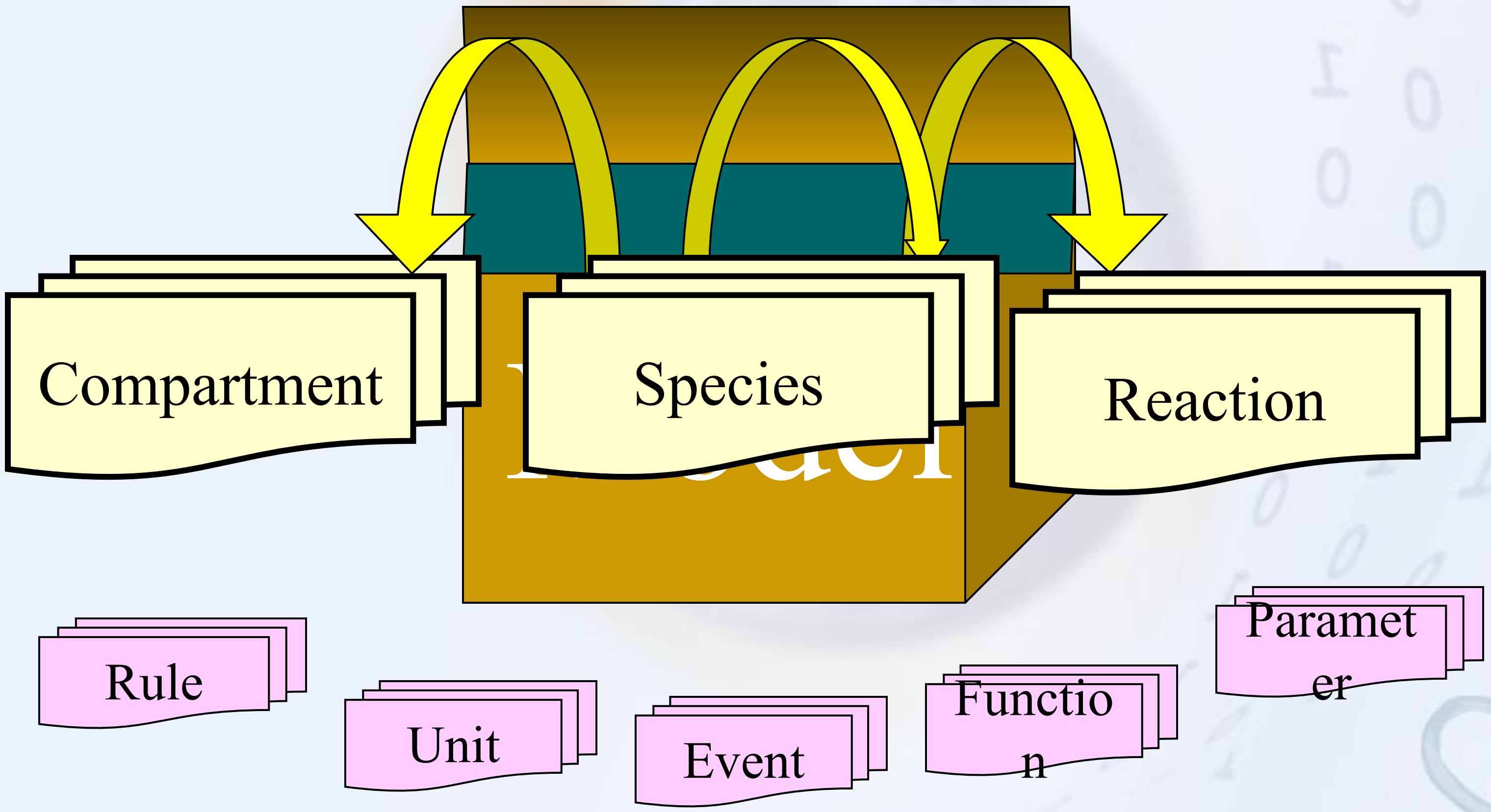
SBML

- SBML is a machine-readable format for representing models.
- It's oriented towards describing systems where biological entities are involved in, and modified by, processes that occur over time. An example of this is a network of biochemical reactions. SBML's framework is suitable for representing models commonly found in research on a number of topics, including cell signaling pathways, metabolic pathways, biochemical reactions, gene regulation, and many others.

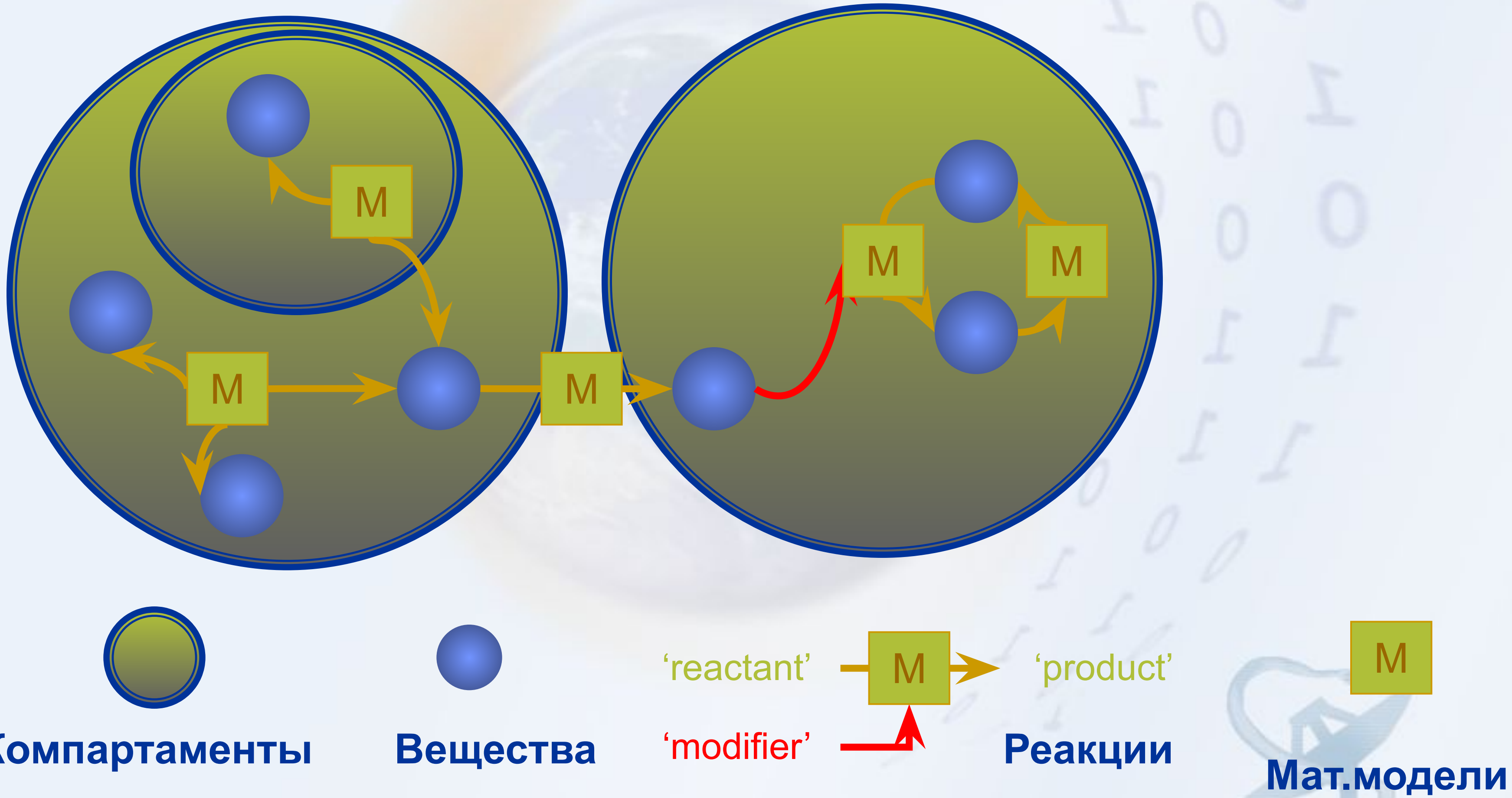
SBML Wrapper Contains One Model



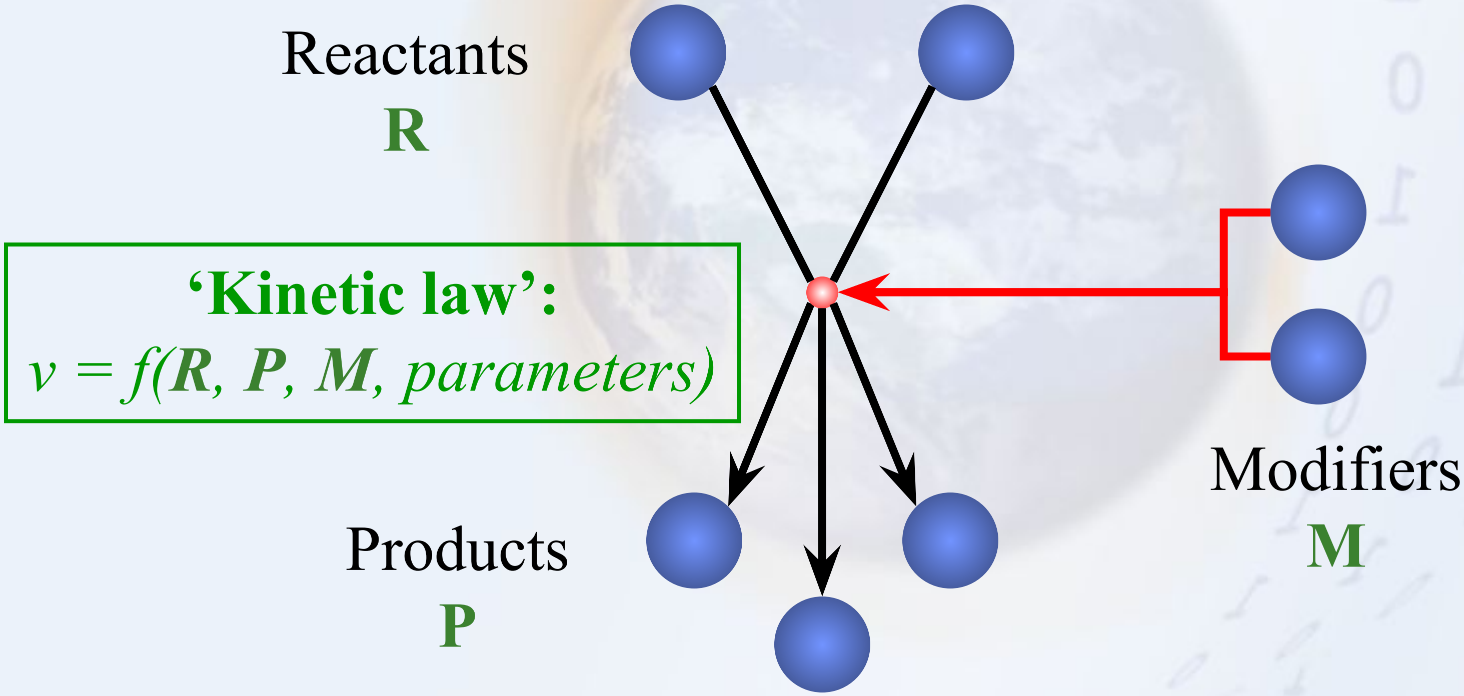
How Is an SBML Document Structured?



Основные функциональные единицы SBML



Reactions According to SBML



What Does SBML Look Like?

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns = "http://www.sbml.org/sbml/level1" level =
   "1" version = "1">
   <model name = "ATitle">
      <listOfCompartments>
      </listOfCompartments>
      <listOfSpecies>
      </listOfSpecies>
      <listOfReactions>
      </listOfReactions>
   </model>
</sbml>
```

XML info

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns = "http://www.sbml.org/sbml/level1" level =
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SBML Wrapper

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<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns = "http://www.sbml.org/sbml/level1" level =
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      </listOfReactions>
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```

Model

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns = "http://www.sbml.org/sbml/level1" level =
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    <model name = "ATitle">
       <listOfCompartments>
       </listOfCompartments>
       <listOfSpecies>
       </listOfSpecies>
       <listOfReactions>
       </listOfReactions>
    </model>
</sbml>
```

Compartment List

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns = "http://www.sbml.org/sbml/level1" level =
   "1" version = "1">
    <model name = "ATitle">
       <listOfCompartments>
       </listOfCompartments>
       <listOfSpecies>
       </listOfSpecies>
       <listOfReactions>
       </listOfReactions>
    </model>
</sbml>
```

СПАСИБО ЗА ВНИМАНИЕ