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Systems Biology and Multiscale Modeling

1.1 Introduction

The biological systems are characterized by a significant complexity ideally described using networks and pathways as well as their potential interconnections between their parts or with other external systems. They present temporal and spatial dimensions, which enable the definition of the system's evolution, growth, and development. Furthermore, the biological systems consist of several scales of representation starting from the cell level (e.g. gene pathways, molecular pathways, protein translation, and function) to higher levels such as tissue or organ level. The modeling of such systems is based on the proper definition of the outcomes and goals and according to them on the selection of the necessary subsets of features, which consist of the specific component parts which are necessary for the modeling goals' achievement. Then, the model of the system comprises the set of features and processes requiring some inputs and providing some outputs. First, the inputs are possible external "forces" which affect our set of features or even noise, which does not affect it. Outputs are the responses of the set of features and processes to the input stimuli, as this is observed from outside of the system.

The usual representation of a system model is provided by a mathematical model, which is defined by one or more mathematical equations and the necessary operations among them. The major advantage of using mathematical formulation for the representation of a biological system is that it is based on mathematical theorems and laws, which enable the implementation of simple as well as highly complex models empowering the proper evaluation of our hypothesis. Usually, differential equations are used for the development of biological mathematical models, but in other cases, simpler ones based on algebra or

Multiscale Modelling in Biomedical Engineering, First Edition. Dimitrios I. Fotiadis,
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Published 2023 by John Wiley & Sons, Inc.

geometry models can be employed. After the definition of a mathematical model, which describes a biological system, it is possible to perform the computational simulation. This means that the computational model simulates the biological system and its functions as those have been defined by the mathematical equations. Besides the computational models, other approaches in biological systems are: the stochastic models, which employ probabilistic mathematical laws and deterministic models whose components, mathematical variables, and parameters are represented by symbols with unique and not random values. The deterministic models are used to present the relationships between large numbers of entities, such as the molecules. Finally, the compartment models are distinguished by discrete boundaries between components called compartments.

1.2 Systems Biology

Systems biology is an evolving research field with many definitions, though all of them encompass a biological system, which describes some conditions, pathways, or mechanisms studied at one or more scales. The scales may have two orientations: (i) the first one is the categorization according to the organism (from molecular to organismic scale), and (ii) the second is the temporal scale (e.g. from nanoseconds to years) meaning the time scale under which the process is performed. Additionally, all definitions of systems biology conclude with the same aim: a better description and understanding of the biological system as a whole. Although the trend in computational biology is to employ systems biology for the description of a biological system, the concept is not new. On the other hand, it is being used and implemented for over a century. Schmitt and Schmitt [1] and Rashevsky [2] attempted to describe biological systems using mathematics and physics. Initially, the concepts were applied to neurophysiological systems [3]. The developed models were at organ-system level and they were considered as systems physiology models, while independent studies presenting systems pharmacology models were also reported. Pharmacokinetics and pharmacodynamics were modeled at all levels from cells to tissues and organs in order to describe the interaction of the body with the drug as well as its consequent effect on the body.

After the 1990s, an acceleration of big data collection has been observed meaning that omics types of data are collected. Such data include transcriptomics, lipidomics, proteomics, and metabolomics and they provide the opportunity to develop systems biology models at the microscopic level usually called molecular systems biology. In that case, the interaction between different components and molecules is usually described by creating dynamical networks and pathways. The pathways and networks provide an overall perspective of the mechanism and can describe all the interactions between these molecules as well as the consequences in the case of external factors and forces such as a mutation of a gene and the infection from a pathogenic organism. The first studies, which were based on omics data used available algorithms and methodologies for the development of systems biology models. In most cases, these approaches were adequate, especially in the case of simple systems or in the case of modeling one level or at least for the interaction between two scales.

The collection of big data leads to the development of models in the field of genetics. Computational models not only support the implementation of gene networks but they are also used for the understanding of their functionality [4–7]. In a similar manner, systems biology is used to understand the mechanisms of absorption, distribution, excretion, and toxicity of substances and/or molecules in order to prevent their potential negative effects before their use in clinical practice [8–10]. For that purpose, many algorithms and techniques have been employed such as Pathway Assist™ (http://www.ariadnegenomics.com/), PathArt™ (http://jubilantbiosys.com/), MetaCore™ (http://www.genego.com), and Pathways Analysis™ (http://www.ingenuity.com/). Other methodologies include clustering of gene-expression data and generation of interaction networks [11], superparamagnetic clustering [12], simulated annealing [13], probabilistic graphical models [14], and Monte Carlo optimization [15].

1.3 Systems Biology Modeling Goals

One of the main goals of systems biology modeling is to develop models of biological systems described mechanistically and/or mathematically to understand the biological details and interactions. Such models target usually at simulating the biological experiment by predicting its outcome, and in the case of accurate predictions, an important step is the understanding of the biological system's mechanisms [16–19]. As it is expected, the goals of systems biology range from the scale or level of the models. Thus, it is possible to identify very complex aims in the case of microscale modeling, where interactions between molecular components exist and their expressions and concentrations are required as boundary and initial conditions in order to describe adequately the biosystem in the specific scale or in the interaction with other scales. Similarly, simpler aims can be defined for: (i) macroscale models, where the biosystem can be described by simple mathematical equations, differential, or even algebraic and (ii) microscale models, where a simple chemical reaction is enough to describe the dynamics of the system. Ideally, the modeling goals are satisfied when a multidisciplinary approach is adapted which integrates the base theory with the basic experiment and the corresponding mathematical representation. All together support each other in a circular way: theory is necessary to define the experiment, which provides data for

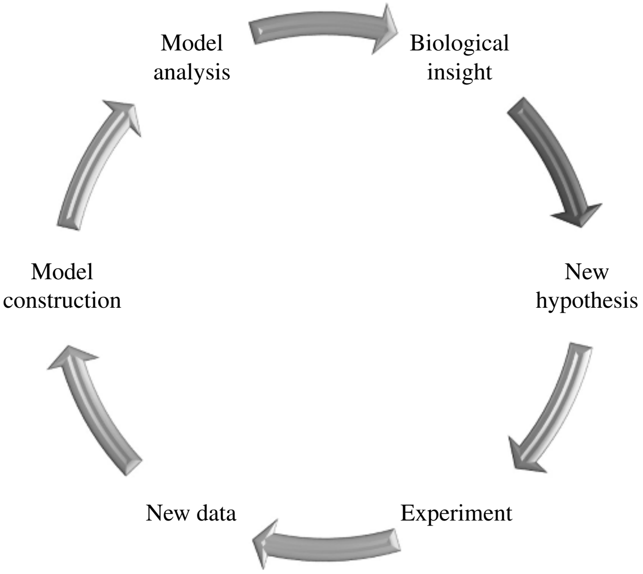

Figure 1.1 The iterative cycle of wet and dry laboratory research.

the development of the mathematical model but the mathematical model is validated by the experiment, which refines the current theory and determines new. Integrative systems biology involves the iterative cycle of wet and dry laboratory research (Figure 1.1).

Other systems biology modeling goals are a better understanding of the interaction between various systems inside an organization. Such interactions include signaling pathways, biochemical pathways, and gene networks. The homeostatic interactions define the functional states between the systems and may be responsible for pathologic conditions. Thus, the developed models aim to identify the role of each component or feature inside the network or pathway and the degree to which it may affect the organization. These models can describe the cell cycle from the division to its apoptosis or differentiation. Other models focus on the description of the transcription of genes and translation of proteins under specific regulatory pathways, e.g. under the regulation by an enzyme and under specific conditions such as increased body temperature. More complex biosystems include energy generation and intercellular communication which is very common in neurological applications and models.

Another major goal of systems biology modeling is to test a specific biological hypothesis about a biological function. Such models usually attempt to identify the behavior or response of the system to stimuli even internal or external. Moreover, they aim to predict the interaction between other organisms or to identify the effect of pathologic and abnormal conditions in the system. Such models are usual in pharmacodynamics and contribute to the development of new treatment approaches for pathologic conditions and diseases [20, 21]. Traditionally, drug development is based on the identification of the substance, which interacts with the compounds; their experimental and using animal testing; and, finally, their testing in patients in clinical studies. Unfortunately, potential side effects are discovered at a late stage, e.g. after their use in patients. On the other hand, using systems biology models in pharmacology or even in toxicology provides the in silico clinical trials and obviously benefits the proper identification of side effects at earlier stages and, in many cases, even before the animal testing. In this way, the benefit is considered huge not only in terms of socioeconomic factors by reducing the costs of clinical trials and experiments in animals but also socially by improving the healthcare of patients by reducing the potential side effects. Furthermore, a reduction in the population participating in the clinical trials is achieved.

1.4 Systems Biology Modeling Approach

Modeling biological processes often requires accounting for action and feedback involving a wide range of spatial and temporal scales. Biological systems are organized at scales of many orders of magnitude in space and time. Space spanning ranges from the molecular scale (10^{-10} m) to the living organism scale (1 m), and time ranges from nanoseconds (10^{-9} s) to years (10^8 s) (Figure 1.2).

Besides the multidisciplinary character of a systems biology model, the scales of the biosystem also define the type of approach which will be employed. For example, the typical modeling approaches for microscale biosystem modeling are the reaction kinetics using ordinary differential equations (ODEs), the lattice reaction-annihilation processes, and others. These approaches can be used for the modeling of molecular and subcellular processes such as mutations, gene alterations, signaling, metabolic pathways, and parts of the cell cycle. At the mesoscopic scale, the approaches include cell-level ODEs, cellular

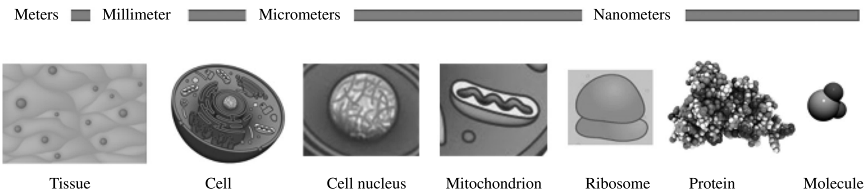

Figure 1.2 The space scales in biological systems.

automata, and evolution rules in order to model cell–cell interactions and cell–matrix interactions such as the phenomena of angiogenesis, the immune response, the local remodeling of the Extracellular matrix (ECM), etc. Finally, at the macroscopic scale, the typical approaches are usually based on the solution of partial differential equations (PDEs) such as the reaction-diffusion, the continuous mechanics, and the convection equations. These models are used for the simulation not only of processes at the tissue level, e.g. diffusion of nutrients, cell migration, and invasion, but also of the blood flow dynamics, plaque growth modeling, and bone dynamics, which will be described in detail in the next chapters (Chapters 3–9). Table 1.1 presents the modeling approaches for each scale and potential applications in systems biology. It is worth noting that interactions between these scales and approaches can be defined.

From the aforementioned, it is clear that there is a strong relation of the biological scale with the chosen experimental approach and the corresponding modeling approach. Figure 1.3 presents the relation of the modeling and experimental approach in correspondence to the biological scale. However, this scheme lacks one major characteristic of systems biology modeling concerning the interaction between the different scales (spatial and temporal) providing the ability to develop multiscale models able to simulate and describe complex phenomena in the biological systems.

To this end, Figure 1.4 presents a schematic illustration of the biological scales of significant relevance for cancer modeling including atomic, molecular, microscopic (tissue/multicellular), and macroscopic (organ) scales [22–24]. Compared to Figure 1.2, different scales represent both different spatial and temporal ranges. Multiscale cancer modeling requires the establishment of the linking between those scales.

Table 1.1 Modeling approaches and typical examples per scale in systems biology modeling.

Scale	Typical modeling approaches	Examples
Microscopic scale	Reaction kinetics using ODEs, the lattice reaction-annihilation processes	Mutations, gene alterations, signaling, metabolic pathways and parts of the cell cycle, mitosis, apoptosis, etc.
Mesoscopic scale	Cell level ODEs, cellular automata, and evolution rules	Angiogenesis, the immune response, the local remodeling of the ECM, etc.
Macroscopic scale	Reaction-diffusion, continuous mechanics, convection equations	Diffusion of nutrients, cell migration and invasion, cardiovascular dynamics, bone dynamics, etc.

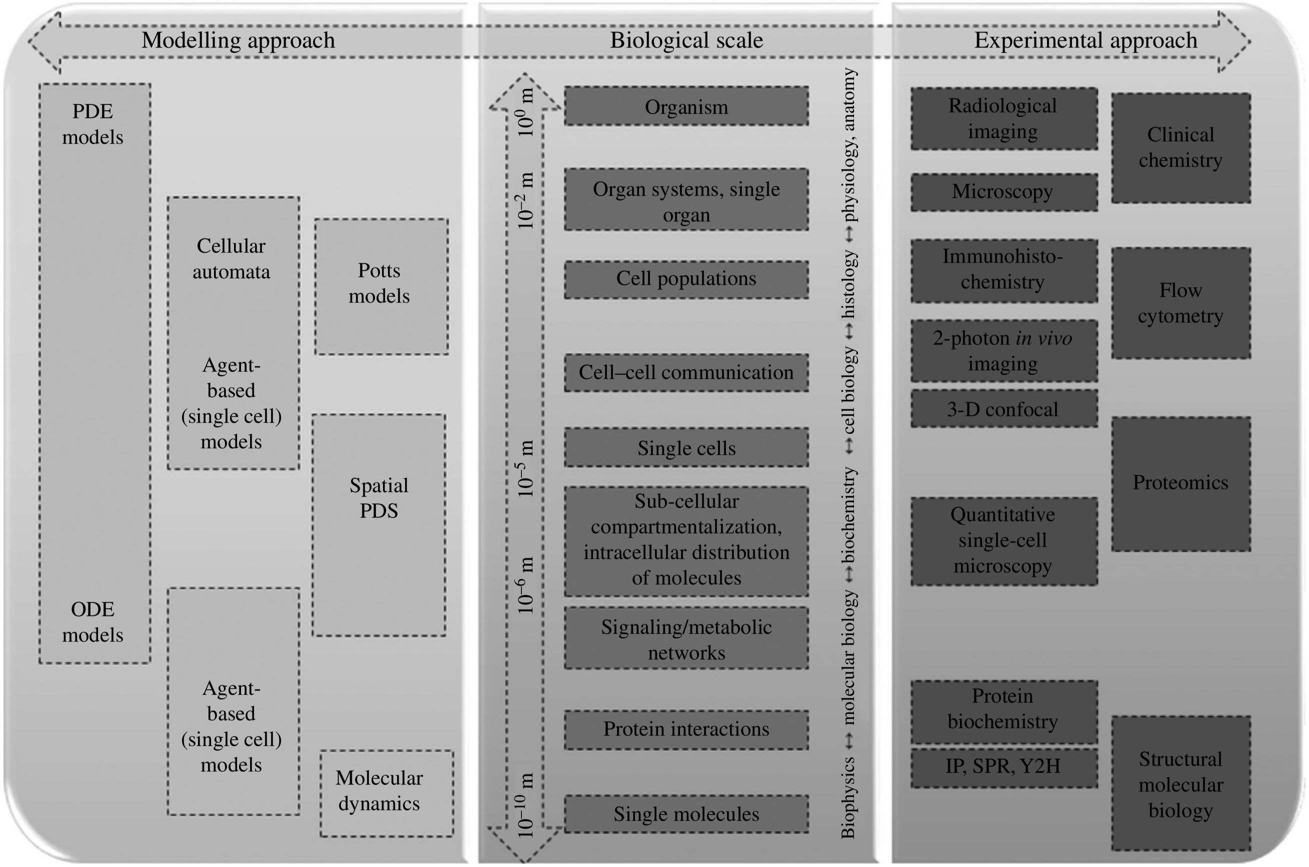

Figure 1.3 The relation of the modeling and experimental approach according to the biological scale.

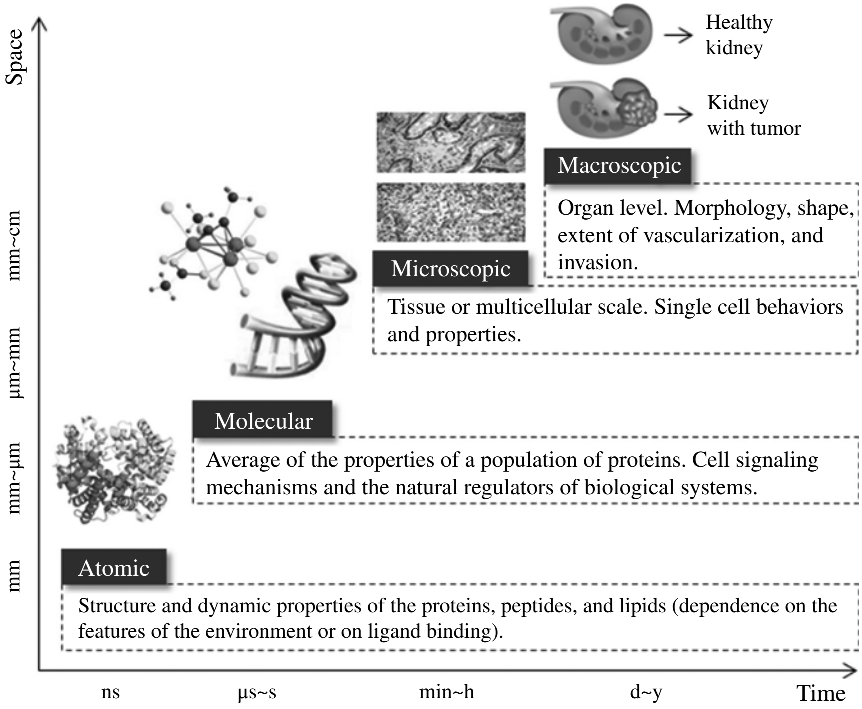

Figure 1.4 Schematic illustration of the biological levels of significant relevance for kidney cancer modeling.

Fundamentally, a multiscale model must explicitly account for more than one level of resolution across measurable domains of time, space, and/or function. To clarify, many models of physical systems implicitly account for multiple spatial scales by simplifying their boundary conditions into "black boxes" where assumptions about other spatial or temporal domains are summarized by governing equations. Further, explicitly modeled tiers of resolution must also provide additional information that could not be obtained by independently exploring a single scale in isolation.

1.5 Application of Multiscale Methods in Systems Biology

1.5.1 Introduction

Multiscale modeling is applied in various research areas ranging from the study of protein conformational dynamics to multiphase processes in granular media or hemodynamics, and from nuclear reactor physics to astrophysics [25]. Although a significant diversity is observed in research applications, there are many common principles and challenges such as the need for the development of advanced tools for programming and executing multiscale simulations, the validation of the numerical methods and results using experimental procedures, the selection of the proper numerical method according to the computational cost, and the biological substance or mathematical and physical aspects of the examined problem. In addition, despite the area of application, it is widely accepted that computer simulations are usually more cost-effective, efficient, and time-consuming compared to laboratory experiments and clinical studies.

According to Hoekstra et al. [26], a major question which arises is the determination of the concepts which orchestrate the multiscale modeling approaches which are inherent in multiscale systems. Traditional modeling approaches are focused on one scale. Considering the example of solid media, engineers may be interested in the macro-scale behavior of solids using continuum models and represent the atomistic effects by constitutive relations, while physicists may be more interested in the behavior of solids at the atomic or electronic level, often working under the assumption that the relevant processes are homogeneous at the macroscopic scale [27]. Under this assumption, civil engineers are able to design structures (buildings, bridges, etc.), without the need to deepen the origin of the interactions between the atoms in the materials. On the other hand, physicists can give insight on the evolution of phenomena at a fundamental level, but they may face several difficulties when dealing with an engineering problem at the macroscale level.

The common aim of mathematics, engineering, and systems biology is to achieve a thorough understanding of biological systems at different hierarchical levels. The Interagency Modelling and Analysis Group (IMAG) has suggested the following definition for the term "multiscale modeling" [28–32]:

"Multiscale, biomedical modeling uses mathematics and computations to represent and simulate a physiological system at more than one biological scale. Biological scales include atomic, molecular, molecular complexes, subcellular, cellular, multicell systems, tissue, organ, multiorgan systems, organism, population, and behavior. These multiscale biomedical models may also include dynamical processes which span multiple time and length scales."

A holistic understanding of many biological processes requires multiscale models which capture the relevant properties on all these scales [28–32]. It can be questioned whether the identification of general laws is relevant as a research aim for biology, but universal design principles, without doubt, play a critical role in engineering approaches that inspire a large part of systems biology [33].

For example, cancer is considered a complex, heterogeneous disease, characterized by many interaction processes evolving in multiple scales in time and space that act in parallel to drive cancer formation, progression, invasion, and metastasis [34]. These processes range from molecular reactions to cell–cell interactions, to tumor growth and invasion on the tissue scale, and even to larger scales, such as the physiology, pathophysiology, and population scales. In addition, many cancer properties (e.g. size, cell density, extracellular ligands, cellular receptors, mutation type(s), phenotypic distribution, vasculature status, blood vessel permeability, and treatment prognosis) are dynamic and patient-dependent, changing and evolving with both time and treatments (e.g. cell death rate may vary over time when the patient is subjected to chemotherapy). All these dynamically changing cancer properties make the development of effective cancer therapies extremely difficult. Computational models which include patient-specific parameters could be a supplementary tool to current statistical approaches to enhance personalized medicine and prediction of complex behaviors of cancer.

1.6 The Use of Systems Biology and Multiscale Modeling in Biomedical and Medical Science

At the organism level, an “infinite” number of processes is happening throughout its life. Moreover, these processes may be complex and define the interactions between pathways of the same level or multilevel interactions. The basic research in biomedical and medical science aims to identify the role of each process in order to clarify the causative mechanisms and pathways, which promote disease evolution. The overall target of such research is to provide the knowledge for the diagnosis, prognosis, and prediction of events related to the disease.

Computational modeling has an incremental role in understating the mechanisms, which underlie the disease in order to provide predictors potentially used for the diagnosis, prognosis, and prediction. For example, machine learning techniques and systems biology models are being implemented nowadays for risk stratification in cardiovascular disease [35]. In the same field, computational modeling is used for the estimation of hemodynamics and the calculation of variables such as endothelial shear stress or lipid accumulation for the prediction of regions, which are prone to atherosclerotic plaque growth [36–38]. Such models are implemented in many other diseases such as in cancer and oncology research [39], in arthritis [40], brain [41], etc. [42, 43].

1.7 Application of Computational Methods in Biomedical Engineering

A biological system is a set of self-organized, differentiated components (elements) that interact pair-wise among themselves through various networks and media, isolated from other sets by boundaries called teguments and whose relation to other systems can be described as a closed loop in a steady state [44].

Advanced computational modeling is essential to understand the complex mechanisms that couple material, structural, and topological hierarchy, merging phenomena of different nature, size, and time scales in hierarchical materials. Numerical modeling also allows extensive parametric studies for the optimization of material properties and arrangement, avoiding time-consuming and complex experimental trials, and providing guidance in the fabrication of novel advanced materials [45].

The terms "top-down" and "bottom-up" are used often in computational modeling, referring to the relative degree of detail in the model. More specifically, the term "top-down" is used to describe numerical approaches at the macroscopic level and "bottom-up" at the microscopic level. Both, however, are usually involved in the modeling process, and deciding on a level of complexity is ultimately dependent on modeling goals and data availability. Top-down modeling approaches capture the overall dynamical features of the system, expressed as a collection of interacting subsystems, and then modeling the subsystems. Bottom-up modeling focuses initially on each subsystem and then the overall system is modeled through their interconnection [46].

This section mainly presents the finite element method (FEM), the finite difference method (FDM), and the boundary element method (BEM), which are the most popular computational methods to carry out numerical simulations in a wide variety of engineering applications [47–52]. Initially, this section presents the fundamental principles, key terms, and nomenclature for the application of computational modeling in biomedical engineering. Then, a description of the main features of FEM, BEM, and FDM is presented.

1.7.1 Fundamental Principles

Two of the most basic and frequently used terms in computational studies are "model" and "system." A **model** is a hypothetical description or representation of a complex entity or process [46]. A **system** is a collection of objects, usually interconnected or interacting in a coordinated way. Thus, a **system model** is a collection of objects, or component parts, normally interconnected in some way.

Models of systems, or **system models**, also known as structured models or structural models, are usually based on physical (e.g. biophysical or biochemical) principles and hypotheses, descriptive information about how a system is structured and how it functions. For our purposes, this includes models based on physical laws and their consequences (e.g. law of mass action, mass-balance relationships, cell transduction processes, and Newton's second law). Systems have inputs and outputs, as illustrated in Figure 1.5. They represent essential features, satisfy goals, include simplifications, and usually have inputs (stimuli) and outputs (responses). Inputs are stimuli generated externally to the system which enter into the system and influence it. Outputs are system responses to input

Figure 1.5 Characteristics of system models.

stimuli. As systems can generally have more than one output, modeled outputs of interest are typically selected according to the aims of the modeling process. Therefore, system models can be defined by the relationships describing object connections and interactions of the inputs and outputs with system features.

Simulation means representation of the features of an object or a system using numerical methods. Each modeling process is a type of simulation. Mathematical modeling refers to the implementation of the equations of the system model on a computer aiming to: (i) obtain a solution to the examined problem and (ii) evaluate the model and study its properties or its predictive value. Simulation models are also called *in numero* models or *in silico* models or computational models.

Computational continuum mechanics deals with media at the macroscopic scale. Continuum models are established in which the microstructure of a medium is homogenized by phenomenological averaging. **Solid and fluid mechanics** are two of the most traditional areas of application.

Structural mechanics is considered a branch of solid mechanics due to the fact that structures are fabricated with solid media. The difference between these two terms can be explained as follows: computational solid mechanics refers to an applied-sciences approach, while computational structural mechanics focuses on the implementation of technological means to the analysis and design of structures.

Computational fluid mechanics is a branch of fluid mechanics that uses numerical analysis and data structures to solve and analyze problems that involve fluid flows. These problems deal with the equilibrium and motion of fluids – liquids and gases. Hydrodynamics, aerodynamics, and atmospheric physics are considered traditional subareas of application.

Explicit and implicit methods are different approaches applied in computer simulations of physical processes to obtain numerical approximations for the solution of time-dependent ordinary and PDEs. More specifically, explicit methods describe the state of a system at a later time from the state of the system at the current time. On the other hand, implicit methods lead to a solution by solving an equation involving both the current state of the system and the latter one. The engineering problem of heat transfer through an insulated rod is an indicative case study in implicit multiscale modeling. Whether solved using continuous PDEs or a discrete finite element approach, all solutions to this problem rely on carefully defining spatial boundary conditions, the fundamental laws of thermodynamics of a closed system, and material properties such as a thermal conductivity coefficient. Implicit methods require extra computational time and can be much harder to implement. Implicit methods are preferred in many problems which may arise in practice when the use of an explicit method requires impractically small time steps to control the error in the final result. In these cases, to ensure the required accuracy, an implicit method with larger time steps is used as it needs much less computation time. This implies that the selection of an explicit or implicit method depends on the problem to be solved.

Continuum mechanics problems may be subdivided into **statics** and **dynamics** according to whether inertial effects are taken into account or not. In **statics**, inertial forces are ignored or neglected. A **dynamic system (DS) model** is a model of a system, with inputs, outputs, and equations describing system motion in space and time. In other words, in order to know the motion of a DS in the "future," it is a prerequisite to know the status of the system "now." In physics and engineering, this distinction translates into a DS having the property that it can store energy in some form [46]. These problems may be subclassified into time invariant and quasi-static. **Time invariant** problems do not need to be considered explicitly (any time-like response-ordering parameter will do). In **quasi-static** problems (e.g. creep flow, fatigue cycling), a more realistic estimation of time is required but inertial forces are ignored as long as motions remain slow. In dynamics, the time dependence is explicitly considered because the calculation of inertial (and/or damping) forces requires derivatives with respect to the actual time to be taken.

Static problems can be classified into **linear and nonlinear statics**. Linear static analysis deals with static problems in which the response is linear in the cause-and-effect sense (e.g. if the applied forces on an object are doubled, the displacements and internal stresses are also doubled). Problems outside this domain are classified as nonlinear.

A final classification of computational solid and structural mechanics for static analysis is based on the **discretization method** by which the continuum mathematical model is discretized in space, i.e. converted to a discrete model of a finite number of degrees of freedom and may include the FEM, BEM, FDM, finite volume method (FVM), spectral method, and mesh-free method. For linear problems, FEMs currently dominate the scene, while BEMs are also widely used. For nonlinear problems, the use of FEM is dominant.

Figure 1.6 presents the solution to problems in biomedical engineering using computational means. **Differential equation models** model systems over continuous-time domains. Differential equations are algebraic or transcendental (sine, cosine, etc.) equalities which include terms with either differentials (e.g. $\mathrm{d}x$) or derivatives (e.g. $\mathrm{d}x/\mathrm{d}t$), defined continuously over one or more independent

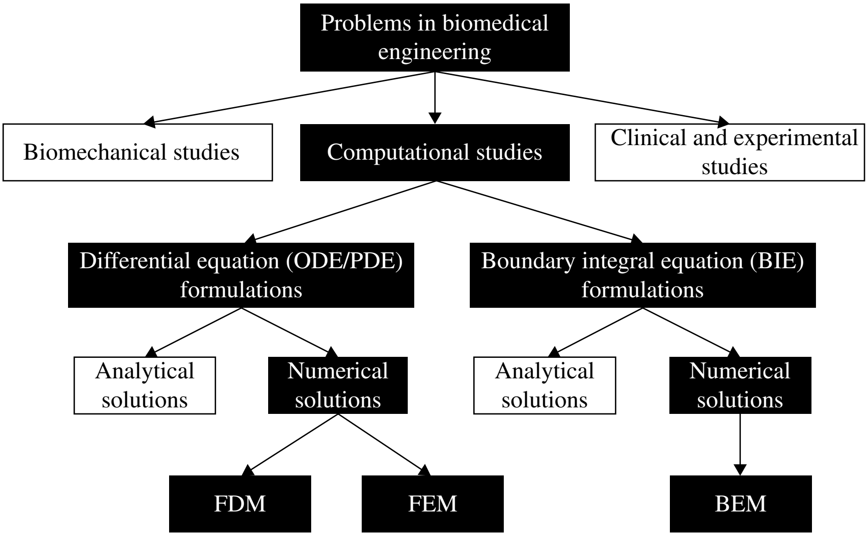

Figure 1.6 The solution of problems in biomedical engineering using FDM, FEM, and BEM.

variables (e.g. *t*, in which *t* denotes time). **Difference equations** (DE) are algebraic or transcendental equalities involving discrete sequences of values of the dependent variable(s) of the model, corresponding to discrete sequences of values of one or more of the independent variable(s) of the model. The description of the laws of physics for space- and time-dependent problems is usually expressed in terms of PDEs. Linear systems can often be represented by linear differential (ODE) or DE models, but these are not the only equations representing linear systems. For example, algebraic equations, like Newton's second law, and integral equations can also be linear. There is a close connection between differential and integral equations, and some problems may be formulated either way (e.g. Green's function, Fredholm theory, and Maxwell's equations).

FEM is a popular computational method for the solution of various problems in the domains of mathematics, physics, and engineering. It is widely applied to several areas including structural analysis, fluid flow, heat transfer, and mass transport. For the analytical solution of these problems, the solution of boundary value problems for PDEs is usually a prerequisite. The formulation of the problem results in a system of algebraic equations. The method leads to approximate values of the unknowns at discrete number of points over the domain. In order to solve a large problem, the problem is subdivided into smaller, simpler parts that are called **finite elements (FE).** The simple equations which model these FE are then integrated into a larger system of equations which models the problem as a whole. Section 2.3.2 provides a more detailed description on the analysis with FEM, which is often referred to as finite element analysis (FEA).

FDMs are numerical methods for solving differential equations by approximating them with DE, in which finite differences approximate the derivatives. FDMs are thus discretization methods. Nowadays, FDMs are the dominant approach to numerical solutions of PDEs. **FDMs**, which focus on the direct discretization of conservation laws, are favored in highly nonlinear problems of fluid mechanics. Spectral methods are based on global transformations, based on eigen decomposition of the governing equations, that map the physical computational domain to transform spaces where the problem can be efficiently solved. A recent newcomer to the scene of biomedical engineering are the mesh-free methods. These are FDMs on arbitrary grids constructed using a subset of FE techniques.

BEMs are computational methods of solving linear PDEs which have been formulated as integral equations (i.e. in boundary integral form). BEM applications cover fluid mechanics, acoustics, electromagnetics, fracture mechanics, and contact mechanics. BEM is often more efficient than other methods, including finite elements, in terms of computational resources for problems where there is a small surface/volume ratio. Conceptually, it works by constructing a "mesh" over the modeled surface. BEM is one of the most effective methods for numerical simulation of contact problems, in particular for simulation of adhesive contacts. However, for many problems the BEM is significantly less efficient than volume-discretisation methods (FEM, FDM, FVM).

Figure 1.7 presents the main stages of computer-based simulations showing the interaction between the physical system, the mathematical model, the discrete model, and discrete solution. Figure 1.7 introduces the terms "discrete" and

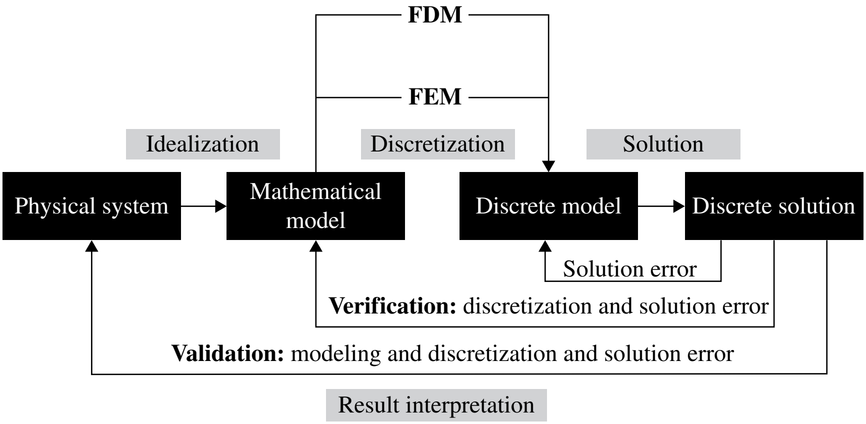

Figure 1.7 The main stages of computer-based simulations.

"continuous." The term **continuous system** refers to a system in which the state variable(s) change continuously over time (e.g. the amount of water flow over a dam). Continuous systems are also known as analog systems. In a **discrete system**, the state variable(s) change only at a discrete set of points in time (e.g. customers arrive at 3 : 15, 3 : 23, 4 : 01, etc). Because discrete systems have a countable number of states, they may be described with precise mathematical models. As computers are often used to model discrete systems and continuous systems as well, several methods have been developed to represent real-world continuous systems as discrete systems (e.g. sampling a continuous signal at discrete time intervals). A combination of multiple computational techniques, including both continuous and discrete systems, is optimal for efficiently capturing information across biological scales.

Additional classification **into deterministic and stochastic models** divides systems based on whether they contain a degree of "randomness" that allows for multiple solutions to the same initial conditions. System dynamics usually are represented with **deterministic** (not random) variables, typically as differential or DEs. States and outputs of **stochastic DS models** are stochastic processes (also called random processes) evolving in time and governed by probability distributions, as well as by the basic system dynamics equations depicting biosystem structure. They are especially useful for describing the evolution of biosystem dynamics when the number of objects represented by state variables is very small (e.g. for intracellular processes where a number of molecules interact with a similar number of others).

Each spatial scale can be summarized by the biological functions occupying that tier of resolution, allowing for modeling techniques to be implemented based on how well they represent these functions [53]. Figure 1.8 presents a conceptual map of modeling techniques divided into continuous and discrete categories across spatial scales for which they are most appropriate.

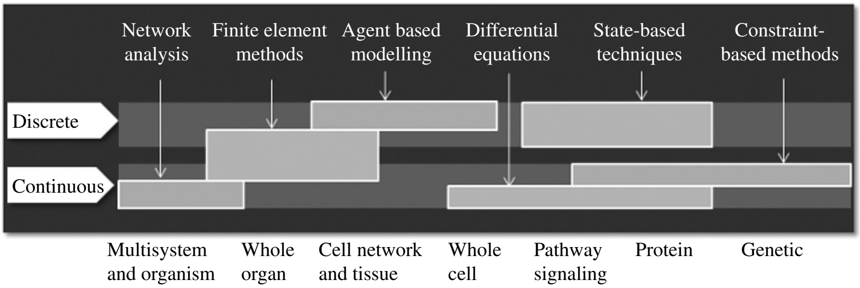

Figure 1.8 Conceptual map of modeling techniques divided into continuous and discrete categories across spatial scales for which they are most appropriate. *Source:* Adapted from Walpole et al. [53].

Network analyses include discrete state-based techniques (e.g. Markov chains and Boolean networks) as well as continuous systems biology approaches. These methods are well suited to modeling the smallest tiers of resolution (genomics, proteomics, and metabolomics) [53].

Agent-based modeling has become a very popular and powerful tool for representing discrete stochastic biological processes as either compartmentalized or spatially defined models. These models include geometries in one-, two-, and three-dimensional configurations and may be scaled such that each fundamental agent is as large (groups of organisms) or as small (subcellular membrane components) as it is desired.

Constraint-based modeling aims to reduce the number of possible flux profiles and identify one that best predicts the metabolic phenotype of the organism under specified genetic and environmental conditions. Constraints limit the number of possible flux profiles for a given organism to some finite number and additional constraints further reduce the flux space and allow us to make even more accurate *in silico* predictions of metabolic phenotype. Potential constraints are generally assigned to the following four categories: physico-chemical constraints (e.g. mass and energy balance), environmental constraints (e.g. temperature, pH, substrate availability), spatial/topological constraints (e.g. organelle compartmentalization), and self-regulatory constraints [54, 55].

1.7.2 Finite Element Method

The FEM is an analytical engineering tool originated in the 1960s by the aerospace and nuclear power industries to find usable, approximate solutions to problems with many complex variables [47]. FEM employs piecewise approximation in which the continuum (domain) of interest is divided into several subregions called finite elements. Initially, the solution of each FE is obtained independently and at the next stage, the overall solution for the continuum is derived through the combination of these individual FE results. The basic procedure in the isoparametric finite element formulation is to express the element coordinates and element displacements in the form of interpolations using the natural coordinate system of the element [56]. Figure 1.9 presents an indicative scheme of the application of FEM in biomedical engineering (e.g. for the modeling of long bones), including indicative input data, system features, and output data as described in Figure 1.4.

The accuracy of FEM depends on the element's geometry, geometry distortion, shape function, laws used in developing the governing equation, and materials to be analyzed. Basically, there are three groups of elements and those are: (i) line elements (for one-dimensional analysis), (ii) planar elements (also known as membrane elements, for two-dimensional analyses), and (iii) solid elements (for

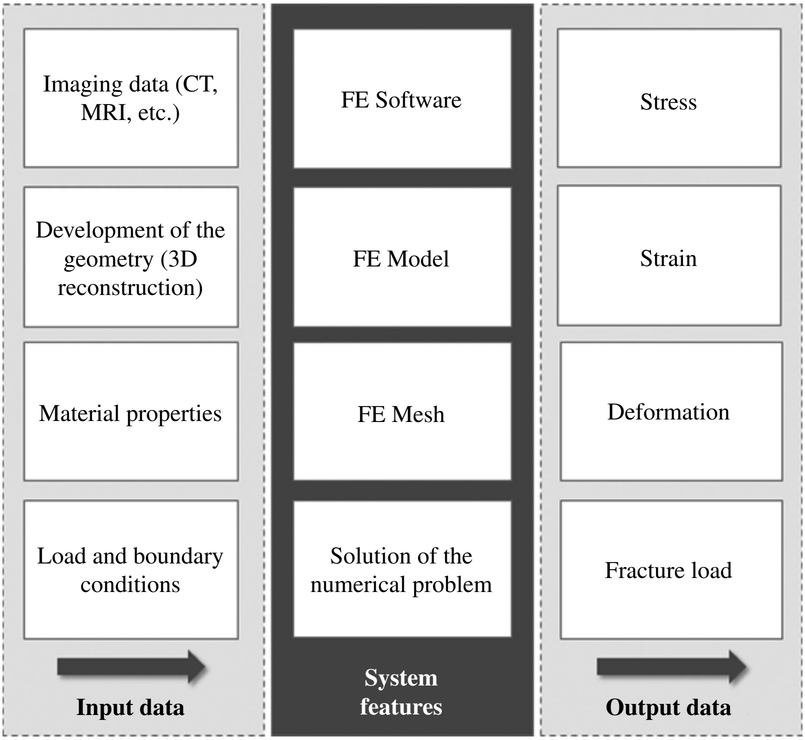

Figure 1.9 Indicative scheme of the application of the Finite Element Method.

three-dimensional analyses). There are various types of elements formulated under each group as depicted in Figure 1.10. For example, spring, bar, and flexure elements are element types which can be categorized under line elements. Another category is general planar elements including triangular and rectangular elements. Tetrahedron, hexahedron (also known as brick), and pentahedron elements (also known as triangular prism or wedge) are examples of general solid elements.

For two-dimensional analysis, bilinear quadrilateral elements are superior compared to simple linear triangular elements in terms of meshing and accuracy. Accuracy of simple linear triangular elements can be improved by using higher-order elements, but it leads to a problem known as mesh locking, which is the main drawback of triangular elements when the analysis is done for incompressible materials [57]. It has been found that quadrilateral elements provide better accuracy compared to triangular elements [58]. As for the three-dimensional analysis, hexahedron elements may give more accurate results compared to tetrahedron elements.

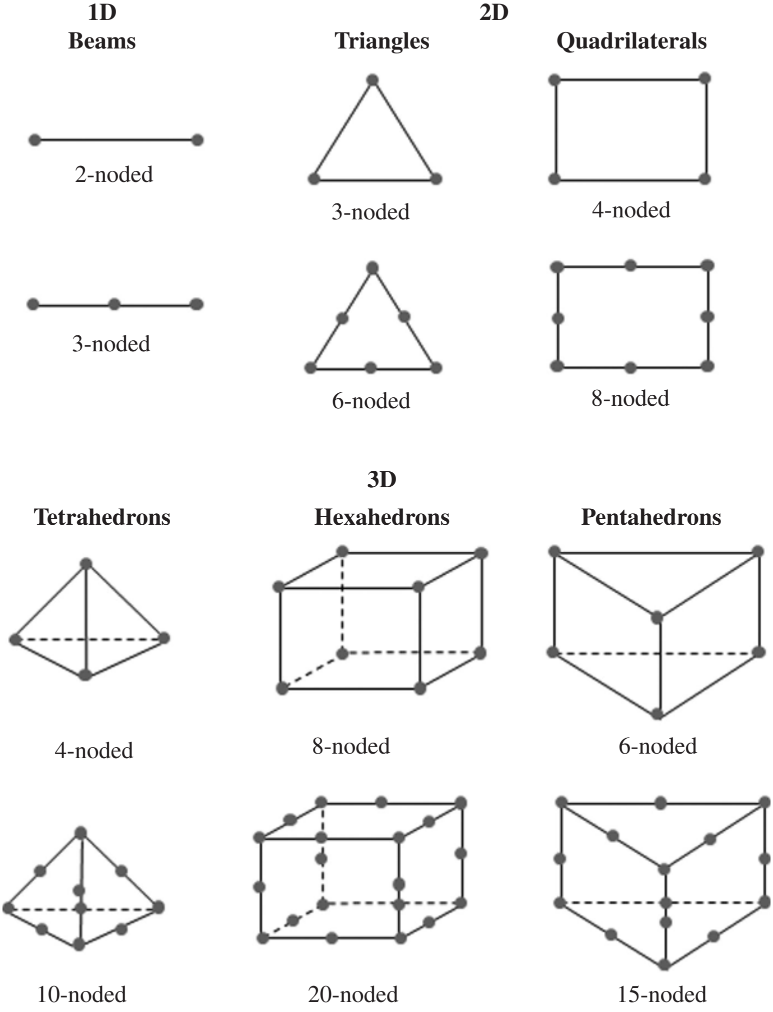

Figure 1.10 Different types of elements for discretization using the Finite Element Method.

In biomedical applications, the first step for the development of a computational model is to acquire the necessary imaging data in order to provide an accurate visualization and representation of the studied system. According to [59–62], excellent isotropic unstructured tetrahedral grid generation algorithms exist for creating finite element or finite volume grids from imaging-derived closed triangulated manifolds. The aim of isotropic algorithms is to create tetrahedral elements with nearly equal internal angles and approximately equal edge lengths. Nevertheless, with medical imaging data, the lengths of these edges are typically more related to the resolution of the image than they are to the physical problem to be solved and do not consider the geometrical scale. Moreover, the tessellation of the volume is typically disordered. Structured grids, typically structured hexahedral grids, are computationally efficient and can be made to fit the physics of the problem, but structured grids can be laborious to construct if they can be constructed at all.

The behavior of a phenomenon can be represented using mathematical models (approximate models), which are derived based on principles and laws. There are several principles which are used to formulate FE. The principle of static equilibrium (also known as direct method) is used for phenomena which can be represented by simple governing equations. In addition, the theorem of Castigliano as well as the principle of minimum potential energy can be applied to complicated elastic structural systems. Higher mathematical principles, known as variational methods, are used to formulate FEA for phenomena governed by complex mathematical models, involving derivative terms.

Once the approximate model has been developed using principles and laws as described earlier, shape functions are then applied according to the element geometry to complete the finite element formulation. A general equation for a single finite element is represented in the following form:

$$\left[\mathrm{k}\right]\left\{\mathrm{q}\right\}=\left\{\mathrm{Q}\right\}, \tag{1.1}$$

where [k] is the matrix representing characteristics of the continuum, {q} is the column matrix representing nodal values (output variable of interest), and {Q} represents the input to the continuum. For the case of stress analysis, [k] represents stiffness matrix, {q} represents vector of nodal displacements, and {Q} represents vector of nodal forces. Once individual FE are formulated, these would then be assembled to form global/assemblage equations which are represented as:

$$\left[\mathrm{K}\right]\left\{\mathrm{r}\right\}=\left\{\mathrm{R}\right\}, \tag{1.2}$$

in which [K] represents assemblage property matrix, $\{r\}$ represents assemblage vector of nodal unknowns, and $\{R\}$ represents assemblage vector of nodal forcing parameters.

1.7.3 Boundary Element Method

Engineers who are familiar with the FEM very often ask why it is necessary to develop yet another computational technique. The answer is that FEs have been proven to be inadequate or inefficient in many engineering applications and in some cases cumbersome to use and hence difficult to implement in computer-aided engineering systems. FE analysis is still a comparatively slow process due to the need to define and redefine meshes in the piece or domain under study.

The idea of BEMs is that we can approximate the solution to a PDE by looking at the solution to the PDE on the boundary and then use that information to find the solution inside the domain. Although this idea may sound strange, it is a very powerful tool for finding solutions. BEM is used for the solution of problems for which Green's functions can be calculated. These usually involve fields in linear homogeneous media. More specifically, BEM is preferred when very large domains are simulated as in these cases, an FEM approximation would have too many elements to be practical. A typical application of BEM is presented in Figure 1.11.

Therefore, BEM has emerged as a powerful alternative to FEM, particularly especially when better accuracy is required due to problems such as stress concentration or where the domain extends to infinity. The most important feature of BEs, however, is that different to the FEM and FDM, the methodology of formulating boundary value problems as boundary integral equations describes problems only by equations with known and unknown boundary states. This implies that only the discretization of the surface is required rather than the volume, i.e. the dimension of problems is reduced by one. Consequently, the necessary discretization effort is mostly much smaller and, moreover, meshes can easily be generated and design changes do not require a complete remeshing.

BE formulations typically give rise to fully populated matrices. As a consequence, the storage requirements and computation time will tend to grow according to the square of the problem size. By contrast, FE matrices are typically banded (elements are only locally connected) and the storage requirements for the system matrices typically grow quite linearly with the problem size. Compression techniques such as adaptive cross approximation/hierarchical matrices or multipole expansions can be used to improve these problems considering the cost of added

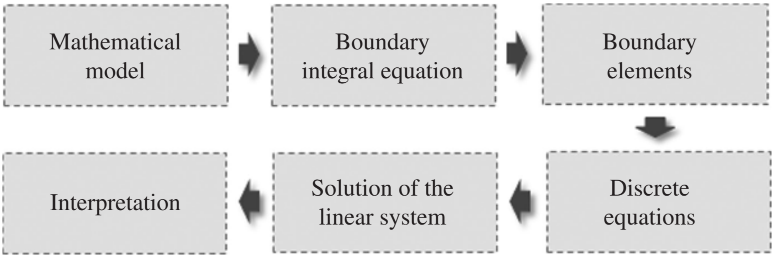

Figure 1.11 Typical application of the Boundary Element Method.

complexity and with a success rate that depends significantly on the nature of the problem being solved and the geometry involved.

Thus, modeling an entire three-dimensional body with FE and calculating stress (or other states) at every nodal point is very inefficient because only a few of these values will be incorporated into the design analysis. Therefore, using BEs is a very effective choice of computing resources, and, furthermore, since internal points in BE solutions are optional, the user can focus on a particular interior region rather than the whole interior.

1.7.4 Finite Differences Method

PDEs describe many of the fundamental laws (e.g. conservation of mass), covering thus a wide range of physical phenomena [63]. Examples include Laplace's equation for steady-state heat conduction, Maxwell's equations for electromagnetic waves, Navier–Stokes equations for fluid flow, etc. Most PDEs of interest do not have analytical solutions. So, a numerical solution must be used to find an approximate solution. The necessary approximation is executed at discrete values of the independent variables and the approximation scheme is implemented via a computational tool. The use of FDM leads to the replacement of all partial derivatives and other terms in the PDE by approximations. After some manipulation, a finite difference scheme is created from which the approximate solution is obtained. More specifically, the FDM works by replacing the region over which the independent variables in the PDE are defined by a finite grid (also called a mesh) of points at which the dependent variable is approximated. The partial derivatives in the PDE at each grid point are approximated from neighboring values by using Taylor's theorem.

If we consider that the function whose derivatives are to be approximated is properly behaved, by Taylor's theorem, we can create a Taylor series expansion. Let $U(x)$ have n continuous derivatives over the interval (a, i). Then for $a < x_o$, $x_o + h < b$:

$$\begin{aligned} U\left(x_o + h\right) = U\left(x_o\right) + hU_x\left(x_o\right) + h^2 \frac{U_{xx}\left(x_o\right)}{2!} + \ldots \\ + h^{n-1} \frac{U\left(n-1\right)\left(x_o\right)}{\left(n-1\right)!} + O\left(h^n\right), \end{aligned} \tag{1.3}$$

where:

- $U_x = \dfrac{\mathrm{d}U}{\mathrm{d}x}, U_{xx} = \dfrac{\mathrm{d}^2U}{\mathrm{d}x^2}, \ldots, U\left(n-1\right) = \dfrac{\mathrm{d}^{n-1}U}{\mathrm{d}x^{n-1}},$

- $U_x(x_o)$ is the derivative of U with respect to x evaluated at $x = x_o$,
- $O(h^n)$ is an unknown error term.

The usual interpretation of Taylor's theorem indicates that if we know the value of U and the values of its derivatives at point x_o, then we can write down Eq. (1.3) for its value at the (nearby) point $x_o + h$. This expression contains an unknown quantity which is written as $O(h^n)$. If we discard the term $O(h^n)$ in Eq. (1.3), we get an approximation to $U(x_o + h)$. The error in this approximation is $O(h^n)$.

1.8 Challenges

The use of computer models for the simulation of biological phenomena, regardless of spatial and temporal scales, involves the associated costs in labor and computation power and storage (Figure 1.12). Initially, any modeling and simulation tool relies on well-developed means that facilitate defining models and allow simulations to be conducted in reasonable time frames. Developing robust computational tools is labor-intensive and requires significant expertise in informatics, engineering, and mathematics.

The next step refers to the development of a model, which is directly related to the research discipline. Compiling adequate model input parameters and

Figure 1.12 Challenges in multiscale methods in systems biology. *Source:* 3DMan.eu/ Adobe Stock.

representing anatomical structures (e.g. generating meshes of complex geometry) are all parts of this process. This is usually a hidden cost, not necessarily reported with the results of a study.

After the establishment of the computational model, the next step is to use the model to simulate the physical conditions of a clinical or research problem. Simulations, particularly in multiscale modeling where coupling between physical domains and scales is necessary, are computationally intensive. Solutions may be obtained, but their interpretation may also be challenging, relying on an expert (e.g. clinician and physicist), possibly spending hours to confirm the validity of results and then extracting useful information applicable to the research area.

All these general challenges can be addressed in a research setting, implying that the development cost of tools and models can be afforded. Availability of suitable modeling frameworks and simulation environments will likely be the most important factor in the wider adoption of multiscale modeling in systems biology. Most of the present modeling and simulation tools are developed for single-scale modeling and alone are not sufficient for multiscale modeling. Some will however play major roles in the new emerging frameworks, as simulation of multiscale models will probably involve assembly of many of these simulators in an integrative manner, each individual being used in its own area of specialization [64].

The aim of this book is to provide answers to questions and challenges in multiscale methods in biomedical engineering such as:

- Which tier of resolution is the most appropriate and can provide information on the underlying mechanisms of a specific, complex disease (e.g. cancer, carotid artery disease, and osteoporosis)? Is there a tier of resolution that offers the least understanding of the disease?
- Which computational method is most accurate and less time-consuming for the examined tier of resolution?
- What kind of data/input are necessary for a specific application in biomedical engineering?
- How much time is required for the preparation and interpretation of the data?

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