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Computational Modeling for Bedside Application

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Abstract

With growing computer power, novel diagnostic and therapeutic medical technologies, coupled with an increasing knowledge of pathophysiology from gene to organ systems, it is increasingly feasible to apply multi-scale patient-specific modeling based on proven disease mechanisms to guide and predict the response to therapy in many aspects of medicine. This is an exciting and relatively new approach, for which efficient methods and computational tools are of the utmost importance. Already, investigators have designed patient-specific models in almost all areas of human physiology. Not only will these models be useful on a large scale in the clinic to predict and optimize the outcome from surgery and non-interventional therapy, but they will also provide pathophysiologic insights from cell to tissue to organ system, and therefore help to understand why specific interventions succeed or fail.

Keywords

patient-specific; prediction; computational modeling; CRT

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7. Disclosures

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2. Introduction

In the Physiome Project, integrative physiological function is described by computational modeling³⁵. The project was motivated by today's wealth of biological data – especially on the molecular and cellular levels, based in part on improved instrumentation such as nuclear magnetic resonance and confocal microscopy. Improved imaging modalities such as MRI and CT, along with other types of instrumentation, are also producing data at higher levels of biology.

A number of workshops and panel recommendations have recognized and addressed the importance in interpreting experimental multi-scale results. The multi-scale modeling consortium, along with the participation of the Interagency Modeling and Analysis Group of a number of federal agencies aims to promote the development and exchange of tools, models, data and standards for the Multi Scale Modeling community⁵². This is one of the major goals of the Physiome Project³⁵. Recently, the NSF blue ribbon panel recognized that Simulation Based Engineering Science⁵⁹ applied to the multi-scale study of simulation based medicine, may bring us closer to the realization of predictive, preventative, personalized, and participatory medicine⁵².

During the last few decades, there has been tremendous progress in computer power, diagnostic and therapeutic medical technologies, and knowledge of pathophysiology from gene to organ systems. Together with efforts to create online databases and tools to share this knowledge, it is increasingly feasible to apply multi-scale patient-specific modeling based on proven disease mechanisms to guide and predict the response to therapy in many aspects of medicine. This is an exciting and relatively new approach. These models will help us in a better understanding of human physiology and – most of all – will allow for predictive capabilities of surgery and therapy. In this paper a brief overview is given in recent accomplishments, and what the requirements are for accurate predictive patient-specific models in general. Finally, we'll discuss briefly what a patient-specific heart model could look like in cardiac resynchronization therapy.

3. Computational Modeling

A mathematical model is a description of a system in mathematical form and is used extensively in physics and biophysics. For many such models it is impossible to find an analytical mathematical solution. Computers can be used to obtain approximate solutions numerically and are therefore usually referred to as computational models.

Many computational models of physiology are written in terms of (coupled) ordinary and/or partial differential equations (ODEs and PDEs, respectively). An ordinary differential equation is an equation of an unknown function (the dependent variable) of an independent variable that relates the values of the function itself and of its derivatives of various orders. Differential equations are coupled when they share a common dependent variable. An example of a set of coupled ODEs is the description of the circulatory system, where changes in volumes and/or pressures in compartments of the circulatory system are described as a function of time⁵⁵. A partial differential equation is an equation where a function depends on more than one variable. An example of a set of coupled PDEs in solid mechanics is the equation of motion, where stress – force per unit area – depends on three spatial dimensions and time. An example of a set of coupled PDEs in electrophysiology is the bidomain model, where intra-cellular and extra-cellular voltages are solved for as a function of space and time. The equation of motion and the bidomain model are examples of so-called deterministic continuum models, where it is assumed that stochastic and discrete events are negligible¹⁷.

Typically, it takes more computational effort to solve a PDE than it does for an ODE, because of the diversity in possible solutions. Probably one of the best known computational tools to solve PDEs is the finite element method. This method was mainly developed in the 1950's, in order to address the needs for methods in designing complex structures in civil engineering. The method is suitable to solve PDEs on complex domains, like blood flow in the aorta, or deformation in the heart. In the finite element method, a continuous domain is discretized into elements and nodes and the solution is approximated on the domain by linear or higher order functions, which are defined in the elements. For a basic explanation of the finite element method and its application in surgery, see Hashim and Richens (2006)²⁸. For an in-depth explanation of the finite element method, see for example Bathe (1996)⁶.

Because computational models quantify physiology mathematically, they also define working hypotheses that are testable and reproducible and have already been used to improve our understanding of physiological systems and disease⁵. In the cardiovascular system, computational models have been used to develop subsequently-validated hypotheses on the role of repolarization dynamics in initiating life-threatening⁸¹ as well as benign⁸¹ rhythm disturbances. Furthermore, models have provided important insights into the electrophysiologic effects of defibrillation^{1,64,69}, and of the electrical and mechanical impact of pacing normal^{42,43,77} and failing^{44,46,76} hearts (figure 1). Because detailed information on the ion channel kinetics of individual myocytes is now available⁷⁵, computational models can also suggest cellular mechanisms underlying these disease states⁵⁴.

In the clinical arena, computational modeling has provided diagnostic indices^{29,36}, virtual surgery training platforms^{13,15,24,82} and to assess the effects of surgery^{19,26,27,80}.

4. Multi-scale modeling

The need to model at multiple levels – spatially and temporally – becomes clear by simply considering physiology: organisms consist of organs, which are made of different tissues; these tissues are made up of specialized connected cells and within these cells complex biochemical processes take place, which can only take place because of the underlying protein kinetics and gene expressions. This is, of course, a simplified view on scalar organization, since many more levels can be identified, ranging from nanometers at the molecule level to 1 m at the whole body level³⁵. Hence, a strong interconnection exists between all levels: normal function at a given level depends on the underlying synergy of sublevels – but also on higher levels, when considering feedback mechanisms. This also means that a significant disturbance at any given level will affect normal function on a higher level, exhibiting the need for *multi-scale patient-specific* models.

However, the design of a multi-scale model that encompasses all possible biophysical detail on all possible levels is an impossible task, because of the enormous man and computer power needed, even in the foreseeable future. Nonetheless, such a model would not be very useful, given that a model is a representation of reality to better understand that reality, and should be focused on solving a specific problem. Hence, for a patient-specific model, efforts should be aimed at the pathology in question. A highly detailed physiological model demands high computational effort. To reduce computational load, Crampin et al.¹⁶ and Bassingthwaite and Chizeck⁵ have acknowledged and addressed the need for simplified models at particular physiological levels. Taking into account the tradeoff between physiological – and thus computational – complexity of the model and accuracy of the results, Bassingthwaite and Chizeck proposed a strategy for the design of a multi-scale model of physiological systems⁵. This strategy involves a 6 step approach of design and validation of an initial high-resolution multi-scale model. Then, specific components will be simplified in order to gain computational speed, but still keeping these simplified components within a specific valid range. If necessary,

inadequate components will be replaced by more detailed ones. The resultant multi-scale model will then be validated again.

5. Mechanistic patient-specific modeling

5.1. Significance

Results of randomized clinical trials might not apply directly to individual patients, even to those who participated in the trial⁴¹. Important differences exist between individuals in respective treatment groups that can dramatically impact the likelihood of an individual benefiting from a therapy. Averaging effects across such different patients can give misleading results to the treatment of an individual whose characteristics likely differ from the mean of a population. This problem is especially highlighted in children, where variability in dimensions is much higher than in adults^{38,61}.

Secondly, patient-specific regression models have been successful in identifying patients that would most likely benefit from a certain therapy^{71,78}. However, one drawback of these types of models is that they may not provide much insight into pathophysiologic mechanisms in any specific individual. Modeling mechanistically from a biophysical base would not only provide predictions of certain therapies or surgical interventions, but also insight of success (or failure) of these therapies and interventions.

Thirdly, many important biophysical properties cannot be measured directly in patients although they can be quantitatively modeled. For example, stress – force per unit area – cannot be measured accurately without damaging tissue. Assuming that stress is a key factor for a specific pathology, information on the dynamics and distribution of biophysical stress may shed light on: a) cardiac mechanics, since stress is closely related to cardiac oxygen consumption³⁰; b) the mechanics and likelihood of tissue rupture in vascular aneurysms^{7,73,79}, if stress exceeds a certain threshold; c) potential stimuli for growth and remodeling in soft tissues^{25,50,65} and bone³².

5.2. Requirements

Initial considerations should be focused on clinically relevant parameter(s). There could be more than one: for example, in the heart, cardiac output is an important measured parameter, yet it may remain normal due to compensatory mechanisms that mask the disease state⁷⁴. In this way, cardiac output may be normal despite altered cardiac contractile function (reduced ejection fraction) with high end-diastolic pressures in heart failure, dyssynchronous regional wall function, that independently predicts remodeling^{37,86}, or valvular abnormalities. Computational modeling introduces the unique strength that it can be based on parameters that are not typically measurable (for example stress), yet are clinically important. An example is to know beforehand the distribution of stress in a residual limb that will be fitted with a prosthetic socket, so that stress distributions, that may cause pressure ulcers, can be prevented by optimizing the prosthesis⁶².

Operationally, the patient-specific model should generate parameter output that will aid clinicians in their decision making. This means that the model should contain most key factors (i.e. submodels at lower scales) that will influence this output parameter. But, in order to maintain decent computability, the model should not become over-intricate. For example, an important parameter in predicting the outcome of cardiac resynchronization therapy (CRT) in patients with heart failure and wide QRS (see section 5.5), is mechanical synchrony of contraction in the ventricular walls. A patient-specific model of cardiac electromechanics for this disease and therapy may thus include ventricular geometry, fiber architecture, an impulse conduction model, passive and dynamic active mechanical properties and a blood circulation model.

Naturally, a patient-specific model needs input from the patient. As tomographic imaging (e.g. CT, MRI) and image segmentation are important for obtaining information on geometric structures, obtaining material properties is equally important, preferably non-invasively. For patient-specific bone models, methods have been proposed and tested to obtain a linear stress-strain relation of bone – the Young's modulus – by converting Hounsfield units (a quantitative scale of radio-density) by CT imaging^{11,22}. For patient-specific cardiac models, methods have been proposed to estimate passive and contractile properties from tagged MR images^{53,72,79,80} and cavity pressure measurements. With regard to the latter, methods aimed at deriving end-diastolic and end-systolic pressure-volume relations from single beats^{12,48} can also be helpful in estimating material properties from these relations^{79,80}, but always in combination with data on regional shortening⁴⁷.

Because it is impossible to obtain all possible input parameters for each patient, existing data can be used for completion. For the patient-specific heart model, mentioned in section 5.5, cardiac fiber architecture will be obtained from the Johns Hopkins online datasets (<http://www.ccbm.jhu.edu/research/dSets.php>) and morphed into the patient-specific cardiac geometries, using the original data on a “host-mesh”²³. Efforts to create more online databases and tools on biological organization, one of the goals of the Physiome Project³⁴, will help in this matter. Another possibility is to estimate parameter values with adaptation algorithms, for example for bone density³², cardiac fiber architecture⁴, or circulation resistance⁵. A potential problem with these algorithms is that biological adaptation, on which the algorithms are based, might be part of the pathology: in case of cardiac fiber architecture, genetic defects can lead to fiber disarray⁴⁰. Such a fiber-related pathology may render the adaptation algorithm to fall outside the range of validity.

5.3. Prediction

The next logical step in using a patient-specific model is to predict – and if necessary, optimize – outcomes from therapy or surgical interventions by applying appropriate interventions. These model interventions can be exactly the same as the intervention to be performed in reality, or to apply the effects – when these are known – of a particular intervention in a model. In cardiac surgery, an example of the former is to remove tissue in a cardiac ventricular model, exactly as performed in ventricular reduction surgery (the Batista procedure)²⁶. To study prostate thermal therapy, one may model acoustic signals to assess pelvic bone heating in the thermal ablation of the prostate⁸⁵. An example of modeling intervention effects indirectly in cardiac surgery is constraining the motion of myocardium at two opposite regions in the left ventricle to investigate the influence of a myosplint on cardiac function and wall stress, without the need of having to model the physical contact between the myosplint and myocardium²⁷.

Predictions of the patient-specific models should be validated by comparison against clinical follow up whenever possible. If model predictions and clinical follow-up are not congruent, several possibilities must be considered. First, components of the patient-specific model may be oversimplified. If so, these inadequate components should be replaced with more detailed models⁵, that may require additional measurements. Second, the model may be based on an incomplete pathophysiologic understanding of the disease; additional theoretical and/or experimental studies may be needed to adequately revise the model.

For example, a model prediction may fail due to biological adaptation – especially in the long term. Most existing models of interventions to patient-specific models are used to study acute output parameters, and do not consider longer-term physiologic adaptation. Although acute parameters may accurately predict long-term outcome, when this is less clear then the implementation of adaptation algorithms is another useful application to enhance the predictive capabilities of patient-specific models after an intervention^{3,25,32,49,51,65} (recall our suggestion to use adaptation algorithms pre-interventional to complement missing input data).

5.4. Examples of patient-specific modeling

Investigators have been working on the design of patient-specific models in almost all areas of human physiology, at many spatial levels, which include bone structures^{2,23,51,57,60}, skeletal muscle⁶³, brain^{31,83}, eye⁶⁸, tongue⁹, teeth⁵⁶, lungs²⁰, heart^{38,53,67}, large arteries^{7,33,73,84}, and digestive system^{10,70}. Modeled physics include electrophysiology, solid mechanics, fluid dynamics (gas and fluid), chemistry, thermal dynamics, and combinations of these. Attempts are also being pursued to model specific pathologies like cancer on subcellular^{21,66} and tissue levels^{18,31}.

5.5. Patient-specific modeling of dilated cardiomyopathy and CRT

The most significant recent advance in management of heart failure (HF) with a conduction block has come from CRT^{8,14} and defibrillator³⁹ therapy. However, up to 30% of currently eligible patients fail to respond to CRT. Notably, exact estimation of the percentage of non-responders, or of factors predicting non-response, are difficult because of different criteria used to define 'response'. These criteria include improvements in the distance walked in 6 minutes, in the peak oxygen utilization (VO₂ max) during exercise, and a decrease in left ventricular end-systolic volume (indicating that cardiac dilatation is reversing). Although these factors make it difficult to select optimally select patients for CRT, this remains of paramount importance to reduce unnecessary implants, procedural risks and healthcare expenses.

Because computational models of cardiac electromechanics are currently able to predict the effects of ventricular pacing on regional wall mechanics and global function^{45,58,76}, we propose to develop new computational tools for optimally selecting patients for CRT, then for optimizing CRT to each individual patient. Having acquired IRB approval, two to five patients with NYHA Class III or IV will be recruited at the San Diego VA Medical Center.

Implementing the strategy outlined above, we will develop patient-specific computational models of the human heart from detailed mapping, and test their ability to predict observed short-term functional improvements after CRT. The clinical procedures that we will perform include: cardiac contrast CT to obtain ventricular geometry; electroanatomic mapping of both ventricles to obtain ventricular activation patterns during native (dyssynchronous) ventricular activation and during CRT; cardiac ultrasound to obtain dynamic ventricular (pseudo-) volumes and invasive dynamic pressure measurements during cardiac catheterization.

Pressure-volume loops will be obtained during maneuvers to alter preload and afterload. Three and six months follow ups will be performed to assess long-term outcomes, to determine the predictive accuracy of our models, and also to provide an opportunity for the patient-specific models to optimize CRT in a patient-tailored fashion.

6. Conclusions

Efforts are being put in place to develop efficient methods and computational tools for the design of mechanistic multi-scale patient-specific models on many levels of physiology. Together with the abundance of physiological data, these models will be useful on a large scale in the clinic to predict outcomes of surgeries and therapies.

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Figure 1.

Simulated isovolumic fiber strain (strain at opening of aortic valve with reference at end-diastole) in the ventricles for a failing canine heart, for left bundle branch block and pacing at the left ventricular free wall. Pacing sites are indicated by arrows. The black line in the ventricles indicates zero strain.