



PATIENT-SPECIFIC MODELING: NEED AND CURRENT APPROACHES

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Abstract : Recent developments in cardiac simulation have presented the heart as the most highly integrated example of a virtual organ. Computational modeling of tissue, organ, cells allow to link genomic and periodic information to the integrated organ behavior. This helps to better understand the functioning of heart in both diseased and healthy conditions. Patient-specific modeling (PSM) is the development of computational models of human pathophysiology that are individualized to patient-specific data. PSM has its potential to improve diagnosis, optimize clinical treatment by predicting outcomes of therapies and surgical interventions, and inform the design of surgical training platforms. The goal of this paper is to more broadly illuminate recent work in PSM by providing a survey of current publications in the field and also on computational optimization techniques used in the field of cardiac electrophysiology.

IndexTerms - Computational Modeling, Patient-Specific Modeling, Pathophysiology, Computational Optimization.

I. INTRODUCTION

Heart diseases are the leading cause of death world wide. In most cases sudden cardiac death is caused by cardiac arrhythmias [10]. Cardiac arrhythmias is a condition while, the heart can beat too fast, too slow, or with an irregular rhythm. However, the ionic mechanisms underlying many cardiac arrhythmias and genetic disorders are not completely understood, thus leading to a limited efficiency of the current available therapies. Because of the complex-nature of cardiac electrophysiology, computational model can act as a perfect tool to augment and fully analyze the experimental and clinical findings. Such approaches require deep perceptive of nature of multiple data sources from cellular ionic mechanisms and signaling pathways to electrical conduction at the tissue and whole organ level.

Over the last few decades, technological developments have made diagnostic information of the cardiovascular system far more detailed. This is particularly true in clinical cardiac electrophysiology (EP), which is focused on the diagnosis, prevention and treatment of heart rhythm abnormalities. Another reason is the availability of detailed anatomical and physiologic imaging data in cardiology, including: echocardiography, computed tomography (CT), magnetic resonance imaging (MRI), nuclear medicine, and positron emission tomography. Many physiological relationships related to cell, tissue, organ, or whole system can be approached by a mathematical relation.

The use of numerical methods in clinical medicine has grown exponentially over the past decade. Thus, patient characteristics may be simulated by a computer model, composed of a network of applied physiological relationships. Most current medical diagnostic practices lead to rough estimates of outcomes for a particular treatment plan [2], and treatments and their outcomes usually find their basis in the results of clinical trials. However, these results might not apply directly to individual patients [1] because they are based on averages. As an alternative, PSM can be used as a theranostic tool to tailor treatment and optimize an individual's therapy. Patientspecific modeling is intended to simulate the most likely status of a patient, given the available measurements. For patientspecific simulation, the same strategy may be used as for obtaining the basic simulation of the normal state. In contrast with average physiological behavior, for a specific patient, there is not as much quantitative information available. With less information, reliability of the estimate can be maintained only if the number of adjustable parameters is reduced to those parameters that describe patients pathology best.

In almost all applications in engineering and industry, we almost always try to optimize something - whether to minimize the cost and energy consumption, or to maximize the profit, output, performance and efficiency. Computational optimization is an important paradigm itself with a wide range of applications. The integrated components of an optimization process are the computational modeling and search algorithms. In essence, an optimization process consists of three components: model, optimizer and simulator.

Patient-specific computational models can promise to improve cardiac disease diagnosis and therapy planning. It helps in better understanding the electrical activity of heart. Rest of the paper is organized as follows section II describes the current approaches in Patient-Specific Modeling and section III on various optimization techniques.

II. PATIENT-SPECIFIC MODELING OF CARDIAC ELECTROPHYSIOLOGY

We briefly mention here some of the patient-specific modeling of cardiac electrophysiology (EP) that have been used in the past because of its potential to improve diagnosis, optimize clinical treatment by predicting outcomes of therapies and surgical interventions, and inform the design of surgical training platforms and also on computational models of human heart. Patient-specific modeling (PSM) is the development of computational models of human pathophysiology that are individualized to patient-specific data.

Kahlmann et al.[14] proposed a new method to automatically model and customize the Purkinje system based on the measured ECG of patient. Purkinje system was developed based on modified Prim algorithm concerning a set of predefined parameters (node density, conduction velocity, atrial distance, positions and time offsets of the root nodes). By using a fast marching simulation, the activation times of the ventricular myocardium was calculated. And finally, the forward calculation was solved using the lead field approach to obtain the simulated ECG effectively through matrix multiplication. Optimization of Purkinje parameters were done by taking the root mean square error between the simulated and measured QRS complexes of ECG as the cost function. A parameter transformation was applied, where all parameters could be transformed into the constraints with a closed interval [a,b] transformation. The measured ECG of patient was used to build the anatomical model. This approach helps to tailor the structure of Purkinje system through the measured ECG in a patient-specific manner. And also helped to study the effects of Purkinje parameters on the morphology of the ECG.

Potse et al.[9] has constructed computational models that mimic individual patients so that predicted signals could be directly compared with their measured equivalents. Here computational models were fitted to two heart-failure patients with ventricular conduction disturbances. The model were tuned to reproduce the measured electrocardiogram (ECG) and activation order on the left-ventricular (LV) endocardium. The results of tuning showed the absence of reentrant LV Purkinje activity, myocardial hypertrophy, reduced myocardial conductivity and a partially presented ventricular gradient. Two patients with HF who were eligible for CRT implantation were included. ECG were recorded using a novel ECG machine. The purpose of the study was to improve the understanding of the activation pattern in individual HF patients, the pathological mechanisms underlying this pattern and their relation to ECG. Using a computational model, the relation between hypothesized disease factors and the ECG can be investigated.

Vergara et al. [7] proposed a new method for the generation of Purkinje network using clinical measures of the activation time on the endocardium related to a normal electrical propagation leading to the generation of a patient-specific network. The Ensite NavX system allows to measure for each point of the ventricular endocardium the time at which the activation front that spreads through the ventricle has reached the subjacent muscle. The Ensite NavX system is able to accurately locate any electrode catheter within a 3D navigation field allowing the reconstruction geometry of any cardiac chamber and also it can accurately navigate to map the activation times. The method started with the use of fractal law to generate a tentative Purkinje network and such networks are corrected using the data of normal activation obtained from the Ensite NavX system, thus providing a patient-specific network. Eikonal equation is used for computing the activation time. Here the bundle of His and main bundle branches were manually designed. A fractal tree was generated as a tentative network. The growing process followed the $0Y^0$ production rule. In this method, each level of generation are identified as active branch and leaves. An active branch can generate other branches and leaves can terminate at their end points identified with the Purkinje muscle junction. The results showed that this method have reduced the absolute errors to some extent.

Villongco et al. [8] proposed a method to simulate left bundle branch block (LBBB) and RV placed ventricular activation pattern in 3D from non-invasive clinical measurements. Activation patterns were estimated in three patients using vectorcardiograms (VCG) derived from standard 12-lead ECG. Here a forward monodomain model of human ventricular action potential propagation in patient-specific anatomical models using high order 3D bi-ventricular geometry, human fiber architecture, and regions of heterogeneous conductivities due to the presence of myocardial infarction. From this proposed model, the total cardiac dipole at each time and this is compared with the VCG. From this it can be hypothesized that the optimal combination of excitation model parameters that minimizes a VCG objective function could predict activation patterns within the measurements.

Luo et al. [13] used a modified frequency slice wavelet transform that was employed to produce time-frequency image for heartbeat signal. The deep learning is performed for the heart beat classification. Features are extracted by the stacked denoising auto-encoder (SDA) from the transferred time-frequency image. Patient-specific heartbeat classification was achieved by fine-tuning on heartbeat samples. The model helps in automatic feature extraction, patient adaptive nature and low classification error.

III. COMPUTATIONAL OPTIMIZATION TECHNIQUES

Computational optimization is pervasive in a wide range of application. Optimization process is commonly performed by using optimization algorithms. The integrated components of such an optimization process are the computational modeling and search algorithms. Search algorithms are the tools and techniques of achieving optimality of the problem of interest. Simulation-driven design becomes a must for a growing number of areas, which creates a need for robust and efficient optimization methodologies. For any design and modeling purpose, the major objective is to gain sufficient insight into the system of interest so as to provide more accurate predictions and better designs. Therefore, computational optimization, modeling and simulation forms an integrated part of the modern design practice in engineering. There exist a wide range of algorithms for optimization, including gradient-based algorithms, derivative-free algorithms and meta-heuristics. Modern meta-heuristic algorithms are often nature-inspired, and they are suitable for global optimization. Some of the optimization algorithms are briefly described below.

A. Conjugate Gradient Method

The conjugate gradient method is one of most widely used algorithms and it belongs to a wider class of the so-called Krylov subspace iteration methods. In essence, the conjugate gradient method solves the following linear system

$$Au = b \quad (1)$$

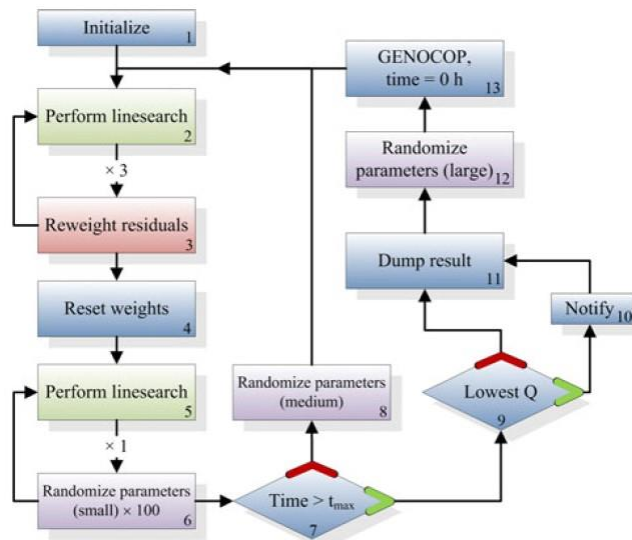


Fig. 1. Overview of the modified curvilinear gradient method.

where A is often a symmetric positive definite matrix. This system is equivalent to minimizing the following function $f(u)$.

$$f(u) = \frac{1}{2}u^T Au - b^T u + v \quad (2)$$

where v is a vector constant and can be taken to be zero.

Szekely et al. [9] proposed a series of modifications to the curvilinear gradient method for parameter optimization. They demonstrated the power and efficiency of the routine through fitting of a 22 parameter Markov state model to an electrophysiological recording of a cardiac ion channel. Here the implementation of the algorithm is demonstrated with an example of a Markov state model of ion channel gating to electrophysiological data from patch clamp recordings. Figure 1 outlines the overall workflow of the modified curvilinear gradient method. algorithm.

B. Trust-Region Method

In the trust-region algorithm, a fundamental step is to approximate the nonlinear objective function by using truncated Taylor expansions, often in a quadratic form in a so-called trust region which is the shape of the trust region is a hyperellipsoid. The approximation to the objective function in the trust region will make it simpler to find the next trial solution x_{k+1} from the current solution x_k . Then, we intend to find x_{k+1} with a sufficient decrease in the objective function. How good the approximation ϕ_k is to the actual objective $f(x)$ can be measured by the ratio of the achieved decrease to the predicted decrease.

$$\gamma_k = \frac{f(x_k) - f(x_{k+1})}{\phi_k(x_k) - \phi_k(x_{k+1})} \quad (3)$$

If this ratio is close to unity, we have a good approximation and then should move the trust region to x_{k+1} . The trust-region should move and update iteratively until the (global) optimality is found or until a fixed number of iterations is reached.

C. Particle Swarm Optimization

Particle swarm optimization (PSO) was developed by Kennedy and Eberhart in 1995, based on the swarm behaviour such as fish and bird schooling in nature. This algorithm searches the space of an objective function by adjusting the trajectories of individual agents, called particles, as the piecewise paths formed by positional vectors in a quasi-stochastic manner. The movement of a swarming particle consists of two major components: a stochastic component and a deterministic component. Each particle is attracted toward the position of the current global best g^* and its own best location x_i^* in history, while at the same time it has a tendency to move randomly. Let x_i and v_i be the position vector and velocity for particle i , respectively. The new velocity vector is determined by the following formula

$$v_i^{t+1} = v_i^t + \alpha \epsilon_1 \odot [g^* - x_i^t] + \beta \epsilon_2 \odot [x_i^* - x_i^t] \quad (4)$$

where ϵ_1 and ϵ_2 are two random vectors, and each entry taking the values between 0 and 1.

Loewe et al. [12] illustrated two classes of optimization approaches are evaluated: gradient-based trust region-reflective and derivative-free particle swarm algorithms. Using synthetic input data and different ion current formulations from the Courtemanche et al. electrophysiological model of human atrial myocytes, it is shown that neither of the two schemes alone

succeeds to meet all requirements. Sequential combination of the two algorithms did improve the performance to some extent but not satisfactorily. Thus, they proposed a novel hybrid approach coupling the two algorithms in each iteration. This hybrid approach yielded very accurate estimates with minimal dependency on the initial guess using synthetic input data for which a ground truth parameter set exists. To evaluate the accuracy and robustness of the proposed parameter estimation algorithms, both synthetic and measured current data were used.

D. Genetic Algorithm and Differential evolution

Genetic algorithms are a classic of algorithms based on the abstraction of Darwins evolution of biological systems, pioneered by J. Holland and his collaborators in the 1960s and 1970s. Genetic operators such as the crossover and recombination, mutation, and selection are used in the study of adaptive and artificial systems. Genetic algorithms have two main advantages over traditional algorithms: the ability of dealing with complex problems and parallelism. Whether the objective function is stationary or transient, linear or nonlinear, continuous or discontinuous, it can be dealt with by genetic algorithms. Multiple genes can be suitable for parallel implementation.

Differential evolution (DE) was developed by R. Storn and K. Price by their nominal papers in 1996 and 1997. It is a vector-based evolutionary algorithm, and can be considered as a further development to genetic algorithms. It is a stochastic search algorithm with self-organizing tendency and does not use the information of derivatives. Thus, it is a population based, derivative-free method.

As in genetic algorithms, design parameters in a ddimensional search space are represented as vectors, and various genetic operators are operated over their bits of strings.

However, unlikely genetic algorithms, differential evolution carries out operations over each component (or each dimension of the solution). Almost everything is done in terms of vectors. For example, in genetic algorithms, mutation is carried out at one site or multiple sites of a chromosome, while in differential evolution, a difference vector of two randomly chosen population vectors is used to perturb an existing vector. Such vectorized mutation can be viewed as a self-organizing search, directed towards an optimality.

Willemijn Groenendaal et.al [10] developed a new approach in which data are collected via a series of complex electrophysiology protocols from single cardiac myocytes and then used to tune model parameters via a parallel fitting method known as a genetic algorithm (GA). The dynamical complexity of the electrophysiological data, which can only be fit by an automated method such as a GA, leads to more accurately parameterized models that can simulate rich cardiac dynamics.

IV. CONCLUSION

This paper has surveyed a wide range of Patient-Specific Modeling of cardiac Electrophysiology which provide more insight on patient-specific data and also the importance of computational modeling in the field of cardiac electrophysiology. This knowledge can be applied to human heart physiology and the diagnosis and treatment of cardiac disease. The paper has briefly elaborated the techniques used in each PSM. Also reviewed various optimization algorithms, which helps to optimize the model parameters in computational models of cardiac electrophysiology.

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