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Computer Modeling of Atrial Fibrillation

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Introduction

The recent development of models of atrial cellular dynamics and of realistic atrial anatomic structures has enabled modeling and computer simulation to become important investigative tools in the analysis of atrial arrhythmias. The *cell model* includes membrane potential, transmembrane ionic currents and ion concentrations. The *tissue model* describes the overall geometric structure of the tissue as well as how cells are interconnected. For these studies, the mechanical properties of the heart are decoupled and only the electrical properties are considered.

The most important use of computer simulation is in enabling "clean" experiments, in which exactly one parameter of interest is varied. This may be difficult or impossible to do in tissue experiments. Modeling provides other advantages when used to complement traditional experiments and clinical work. Computer simulations can guide experiments by providing hypotheses to test *in vivo* that have been verified already *in silico*. In addition, simulations can be used to investigate and to explain experimental and clinical observations. This continual feedback between simulation and experiment can reduce time and money spent on animal experiments and can generate valuable information about human arrhythmias while avoiding issues of patient safety.

Modeling Requirements

Cell models

The shape of the atrial cellular action potential (AP) is essentially different from that of the ventricular cell. The main features which distinguish atrial from ventricular cells are the contributions of the outward potassium currents I_{to}, I_{kur}, and I_{sus}, which create a variety of atrial AP morphologies, from triangular APs with no sustained plateaus to long APs with spike-and-dome shapes. Two mathematical models of human atrial cells based on data recorded from human atrial myocytes have been published. The model developed by Nygren et al. [1] uses 30 variables to model the cellular dynamics, while the model developed by Courtemanche, et al. [2], consists of 21 variables (Figure 1).

Both models include the Na^+, K^+, and Ca^{2+} currents; pumps; exchangers; sarcoplasmic reticulum (SR) calcium storage-and-release processes, involving intracellular Ca^{2+} uptake into the network SR (NSR); Ca^{2+} leak in the NSR back into the cytosol; Ca^{2+} release from the junctional SR (JSR) into the cytosol; calcium transfer from the NSR to the JSR; and calcium buffering. These models can reproduce a variety of observed AP behaviors, such as rate-dependence, a variety of AP shapes, and cellular remodeling during atrial fibrillation. The advantage of the Nygren model is the inclusion of the sustained outward K^+ current I_{sus}, which primarily determines the action potential shape during the peak and plateau. The Courtemanche model includes another current, the delayed rectifier current I_{kur}, which also plays an important role during the plateau phase. With these models, the contribution of various currents to atrial fibrillation (AF) can be explored separately. Therefore, blocking different ionic currents in these models can serve as preliminary studies to identify ionic targets for drug therapy in AF.

Tissue models

Anatomically, the atria are complex structures, containing nonconductive regions like blood vessels and valves as well as slow-conducting (interatrial connection at the fossa ovalis, isthmus of the right atrial floor) and anisotropic fast-conducting (Bachmann's bundle, pectinate muscles, crista terminalis) regions. Fiber orientation information, an important component of the anatomy in determining conduction, is essentially unknown beyond the general concept of fast conduction along certain structures such as the crista terminalis and the pectinate muscles.

Of necessity, simplified structures were used in early studies of atrial tissue dynamics, due both to limited computer resources and to a limited

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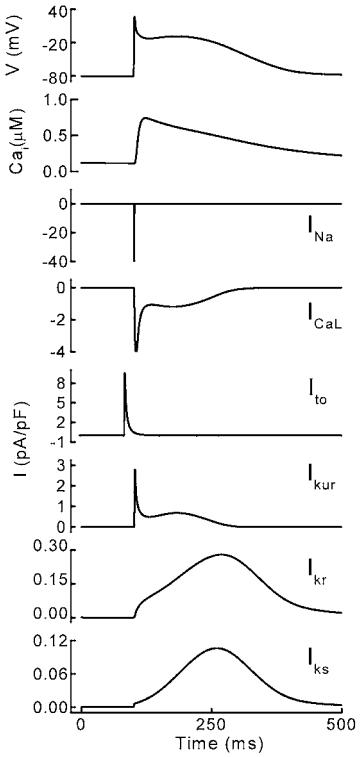

Fig. 1. *Simulation (by the authors) of the model of Courtemanche et al. [2]. Important currents are shown, together with transmembrane potential (top) and intracellular* Ca^{2+}.

understanding of atrial cellular processes and anatomy. But even simple models, such as a long one-dimensional strip or a small rectangular two-dimensional piece of tissue, provided important information about the dynamics of cell models when groups of cells were considered, rather than a single cell. These caricatures of the full anatomical structure have been necessary not only as first steps toward building a more representative atrial structure, but also as background work in understanding a wide range of healthy and diseased tissue dynamics.

Along these lines, small models focusing on a single complex structure within the atria have provided valuable information about that structure's contributions during arrhythmia initiation and maintenance. For example, several studies [3–5] have explored the anatomy of the pectinate muscle structure, which adds complexity to the atrial structure in two ways. First, pectinate muscles introduce relatively large local variations in tissue thickness. Second, they provide alternate pathways to distant sites through "bridge"-like structures. Both of these factors affect conduction patterns and therefore can affect the inducibility and the evolution of arrhythmias.

Building on insights gleaned from small and simple models, highly realistic models now are being produced and used. Harrild and Henriquez [6] produced a model of atrial anatomy that included many of the key structures and was designed to match published human atrial values (Figure 2). Although fiber information was not yet available and could not be included, conductivities were varied locally to model fast-conducting bundles and slow-conducting regions. The resulting anatomical tissue model, combined with the Nygren cell model [1], produced activation patterns that were consistent with published mapping studies of normal activation in human atria.

In the presence of disease, the already complex geometry of the atria often is quite different from structures considered normal, and different diseases may cause different changes. Congestive heart failure, mitral valve disease, and senescence can cause increased interstitial fibrosis within the atria [7]. In turn, this fibrosis can cause local conduction abnormalities that may lead to atrial arrhythmias. It is important to be able to add fibrosis to the tissue model to represent the diseased atria more realistically. In practice, as tissue modeling advances, it likely will be necessary to use several different models of diseased atria to ensure that results obtained for one tissue model can be applied more broadly.

What Modeling Can Teach About Fibrillation

Even without the full machinery of realistic cell and tissue models, some valuable information already has been gained from simpler simulations targeted at understanding the roles of particular structures in atrial conduction and arrhythmias. In particular, the pectinate muscles and the crista terminalis have been investigated. Also, a model recently has been produced that represents atrial anatomy realistically and is able to reproduce observed activation timing during sinus rhythm.

First steps: roles of structures and establishing activation patterns

Early steps toward modeling fibrillation included understanding the roles of specialized atrial structures during arrhythmic states. The role of the pectinate muscles in atrial fibrillation was investigated in Refs. [3] and [4]. They found that the presence of local thickenings of the tissue ("ridges") sustained reentry by anchoring the reentrant wave. Including a single bridge, a long-range connection, with a slightly faster conduction velocity gave rise to epicardial breakthrough patterns typical of fibrillation, and destabilized reentrant waves that were stable in the absence

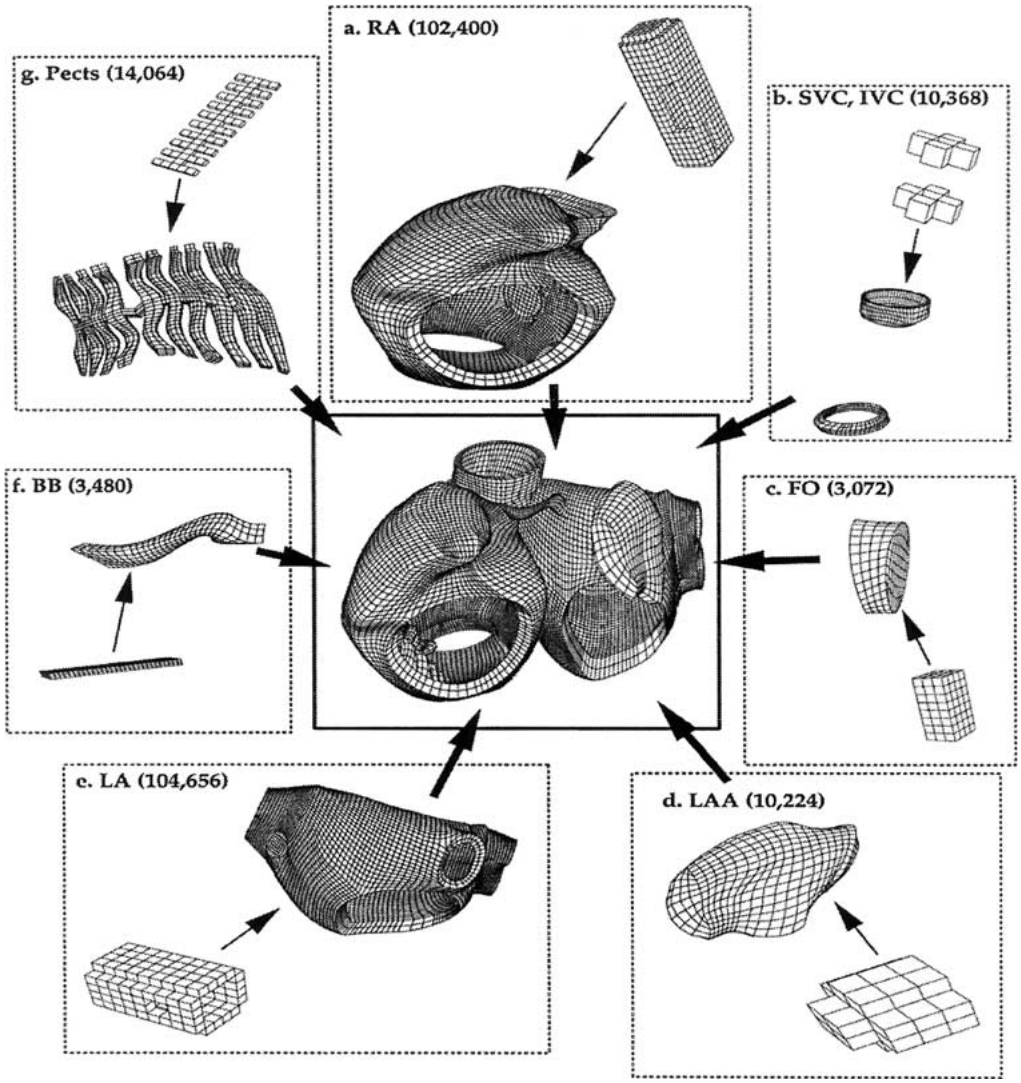

Fig. 2. *Block structure and low-density mesh views of each of the 7 parts (a through g) (periphery) and the fully assembled mesh (center). The number of elements used for each of the parts is indicated. The complete mesh includes 248 264 hexahedral elements. RA indicates right atrium; SVC/IVC, superior/inferior vena cava; FO, interatrial connection at the fossa ovalis; LAA, left atrial appendage; LA, left atrium; BB, Bachmann's bundle; and Pects, pectinate muscles. Reprinted from [6], by permission.*

of the bridge. With the presence of both ridges and bridges, additional patterns of activity could be seen, such as the anchoring of a reentrant wave to a bridge junction. One limitation of the studies was the use of a simplified cell model, adapted from the FitzHugh-Nagumo equations [8] used to represent a wide variety of excitable systems. Also, only a small piece of tissue was considered.

Wu et al. [5] also analyzed the role of pectinate muscles in fibrillation and found similar results. Ridges could serve as an anchor for a reentrant wave if the ridges were sufficiently thick. While the wave was anchored to the ridge, the activity pattern was more regular and resembled flutter. If the wave detached from the ridge, the activity in the tissue transitioned to a more irregular pattern characteristic of fibrillation. The ridges also formed a region where wave break was likely to occur and thus facilitated reentry initiation. The addition of a bridge facilitated the initiation of reentry by providing an alternate conduction pathway that was used in the reentrant circuit. Limitations of this study included the use of a ventricular cell model [9] and the simulation of only a small piece of tissue.

Ellis et al. [10] investigated a larger structure representing a simplified right atrium and including a fast conduction path representing the crista

terminalis. The gross features of key right atrial structures were included by using nonconducting regions to represent the superior and inferior venes cavae, the tricuspid annulus, the coronary sinus os, and the subeustachian ridge. Their study suggested that low transverse conduction along the crista terminalis may keep reentrant circuits larger and less likely to be induced. They also found that the dispersion of refractoriness produced by varying effective refractory period and junctional resistances spatially was proarrhythmic, leading more often to fibrillation than to the more organized reentrant pattern of flutter.

One limitation of this study was the use of the Van Capelle cell model, similar to the FitzHugh-Nagumo equations [8] of excitable media and, like the FHN model, not representing any ionic currents or processes. Another limitation was the use of a greatly simplified anatomical structure made up of a 20-sided geometrical figure that approximated the two-dimensional surface of a sphere (no tissue thickness). In addition, the more intricate structures of the pectinate muscles and thickening effects like the ridges described in earlier studies were not considered. Only the right atrium was considered.

Harrild and Henriquez [6] developed a realistic human tissue model and combined it with the Nygren cell model. They demonstrated how the fast-conducting bundle tissues, including the pectinate muscles, Bachmann's bundle, the crista terminalis, and the limbus of the fossa ovalis, contributed to the experimentally observed normal atrial activation sequence. By the nature of computer simulations, they were able to explore the activation sequence in detail and to verify their results with a number of published studies. Similarly, they simulated paced activity from the left and right atrial appendages and again compared the simulated activation sequences with experimental observations. This systematic validation of the tissue model left it ready for use in arrhythmia studies. There are some minor limitations of their model: exclusion of an electrical connection at the coronary sinus and simplified pectinate muscle structures (although more elaborate than previous pectinate muscle studies [3–5]); however, these deficiencies can be remedied fairly easily in the future.

Future projects

With realistic atrial cell and tissue models now available, hypotheses to investigate abound. Some of the important questions to address are discussed below.

Viability of cell models and tissue models in AF. Simulating atrial fibrillation can shed new light on the utility of particular cell and tissue models. If key currents are missing or inaccurate in a cell model, AF may become too difficult or too easy to induce in the model compared with experiment. Such discrepancies will identify improvements to be made in the cell models. Moreover, as human cell models are expanded to include regional variations in action potentials (now included in canine cell models [11]), these heterogeneities can be combined with realistic tissue models to understand their impact on arrhythmogenesis.

As with cell models, if certain anatomic structures critical to AF are missing from the tissue model, the simulation results will deviate from experimental observations. Further studies then can be performed to improve understanding of atrial anatomy. Already, simulations are helping to elucidate the roles of bundle tissues and other structures in inducing and maintaining AF, although a greater understanding of the contributions of these structures is necessary.

Relative roles of cell models and tissue models in atrial fibrillation. A fundamental understanding of the relative roles of cellular and tissue behavior during atrial arrhythmias may lead to improved therapies for treating AF. For instance, if it is found using a realistic cell model that simulated fibrillation occurs with equal likelihood in an anatomically accurate model of the atria as in a greatly simplified spherically based structure, drug-based therapies may take on a greater importance. Likewise, if simplified and realistic cell models produce similar AF results in an anatomically accurate atrial tissue model, surgical interventions such as catheter ablation may become the preferred treatment. In reality, we suspect that both cellular dynamics and anatomy affect AF inducibility and maintenance. However, it is possible that one component may become more important in the presence of certain diseases.

Modeling diseased states. As model sophistication and knowledge of changes that occur from diseases continue to increase, cell models will be developed to portray diseased conditions realistically. Interstitial fibrosis, which increases substantially during congestive heart failure, can be modeled to understand more fully its proarrhythmic properties and to design interventions to treat such diseases. Other conditions such as ischemia already are being incorporated into existing cell models [12] through variation of model parameters.

Computer simulations also can address how known predisposing factors contribute to AF. For instance, atrial enlargement is often associated with AF, presumably by increasing the atrial mass

[13]. However, this can be narrowed down and tested explicitly through modeling. Increased surface area, tissue thickening, and increased variability in tissue thickness can be investigated independently to show their effects on inducibility of AF.

Arrhythmia initiation. Simulations can help answer the question of what initiates atrial fibrillation. Experiments suggest that AF can be induced by several different mechanisms, including rapid pacing, heart failure, and rapidly discharging atrial foci [13]. However, it is unknown whether fibrillation induced by different mechanisms may itself be different. If it turns out that fibrillation initiated in different ways is fundamentally dissimilar, it may become important to identify how an arrhythmia was initiated and to provide treatment based on its mechanism of induction.

Remodeling during atrial fibrillation. In recent years, it has been established that "atrial fibrillation begets atrial fibrillation" [14] by inducing electrophysiological changes in the atrial myocardium. Important changes include decreased Effective Refractory Period (ERP), slowed conduction, reduction in rate adaptation of ERP, and increased spatial heterogeneity of ERP (see reviews of remodeling in Refs. [7], [13], and [15]). Cellular mechanisms responsible for these changes are being identified. For instance, a reduction in the L-type Ca^{2+} current is believed to be responsible for most of the alterations in APD while a reduction in the sodium current is believed to explain the slowed conduction. Almost certainly, additional electrophysiological changes occur during AF and may contribute to its perpetuation.

Some of the known changes induced during prolonged AF were incorporated into the Courtemanche atrial model [2] by altering currents to match experimentally measured values [16]. The resulting model produces action potentials typical of AF. Incorporating these remodeling changes into models will be critical for some applications, such as investigating means of terminating prolonged AF. Computer simulations of AF can be expanded to include other changes as they are discovered and, as computer resources increase, can introduce them by varying parameters over long time intervals in accordance with experimentally observed alterations during the progression of AF.

Clinical relevance. Most importantly, the improved understanding of arrhythmia generation and maintenance gained from computer simulations will lead to improved therapies for treating atrial fibrillation. Many conditions, including congestive heart failure, coronary artery disease, and hypertension, are known to promote the occurrence of AF [13,15]; however, the mechanisms by which they do so are not well understood. As modeling continues to advance, the effects of diseases like these on cardiac function can be simulated and their proarrhythmic properties identified.

The effects of antiarrhythmic drugs can be modeled by simulating their effects on ionic currents and concentrations. For instance, since AF recurrence occurs most often within the first few days of conversion to sinus rhythm while remodeling is being reversed, drug therapies can be designed to focus on that critical time period by increasing the intensity of the therapy or even using different drugs than used in later stages of recovery [13]. Remodeling also may present different ionic currents to target in antiarrhythmic drug development [16–18].

Therapeutic techniques such as catheter ablation may also be improved. Simulations may reveal ideal locations at which to introduce lines of block to prevent a reentrant circuit causing an arrhythmia.

Other types of interventions can be studied in simulations as well, such as direct current cardioversion. Changes in gene expression take place during prolonged AF [13,19] and simulation may point the way to useful gene-based therapies in the future [7].

Conclusions

The use of modeling and simulation is a highly promising tool for studying atrial arrhythmias. Most studies done to date have introduced a number of simplifications. However, within the last several years both cell models and tissue models have become increasingly sophisticated and now are capable of representing many of the complexities of atrial fibrillation.

The limitations of computer modeling of atrial arrhythmias primarily are related to the choices of cell and tissue models. Any cell model represents an *informed guess* of the cell-level dynamics and is most likely incomplete in as yet unidentified ways. Most models have known limitations; for instance, a model designed for use at a certain cycle length may not accurately represent the dynamics at different cycle lengths. Simulations using any given cell model inherit that model's known and unknown problems. Moreover, the variety of conditions under which cell models are developed may mean different models generate different results. As modeling of the underlying processes improves, improved cell models will become available and will converge to a standard model.

In tissue models, as in cell models, the main limitation is the unknown: some crucial element may be missing because it has not yet been identified. Tissue models are constrained to include effects of only those features that are included explicitly. If an important electrical connection is missing from the model, for example, results obtained from the model may be incorrect under some conditions. Ongoing feedback between tissue models and experiments will ensure continuing improvements of tissue models to include all known important anatomical features and commonly observed variations.

The final limitation of simulations is the inadequacy of available computer resources to handle all the details. Currently this can force researchers to choose carefully what questions to ask and which models to use to answer them. However, this selection often is beneficial, as it encourages studies to focus on more specific questions and to analyze phenomena in greater depth. As the understanding of cellular processes, mathematical sophistication, and computer resources increase, the contribution from modeling will become increasingly valuable.

References

1. Nygren A, Fiset C, Firek L, Clark JW, Lindblad DS, Clark RB, Giles WR. Mathematical model of an adult human atrial cell: The role of K^+ currents in repolarization. *Circ Res* 1998;82(1):63–81.
2. Courtemanche M, Ramirez RJ, Nattel S. Ionic mechanisms underlying human atrial action potential properties: Insights from a mathematical model. *Am J Physiol* 1998;275(44):H301–H321.
3. Gray RA, Pertsov AM, Jalife J. Incomplete reentry and epicardial breakthrough patterns during atrial fibrillation in the sheep heart. *Circulation* 1996;94:2649–2661.
4. Foster E, Gray RA, Jalife J. Role of the pectinate muscle structure in atrial fibrillation: A Computer Study. *Pacing Clin Electrophysiol* 1997;20: 1134.
5. Wu T-J, Yashima M, Xie F, Athill CA, Kim Y-H, Fishbein MC, Qu Z, Garfinkel A, Weiss JN, Karagueuzian HS, Chen P-S. Role of pectinate muscle bundles in the generation and maintenance of intra-atrial reentry: Potential implications for the mechanism of conversion between atrial fibrillation and atrial flutter. *Circ Res* 1998;83:448–462.
6. Harrild DM, Henriquez CS. A computer model of normal conduction in the human atria. *Circ Res* 2000;87(7):e25–e36.
7. Nattel S, Li D, Yue L. Basic mechanisms of atrial fibrillation—Very new insights into very old ideas. *Ann Rev Physiol* 2000;62:51–77.
8. FitzHugh RA. Impulses and physiological states in theoretical models of nerve membrane. *Biophysic J* 1961;1:445–466.
9. Luo C-H, Rudy Y. A model of the ventricular cardiac action potential: Depolarization, repolarization, and their interaction. *Circ Res* 1991;68(6):1501–1526.
10. Ellis WS, SippensGroenewegen A, Auslander DM, Lesh MD. The role of the crista terminalis in atrial flutter and fibrillation: A Computer Modeling Study. *Annals Biomed Engineer* 2000;28:742–754.
11. Ramirez RJ, Nattel S, Courtemanche M. Mathematical analysis of canine atrial action potentials: Rate, regional factors, and electrical remodeling. *Am J Physiol* 2000;279:H1767–H1785.
12. Nygren A, Giles WR. Mathematical simulation of slowing in cardiac conduction velocity by elevated extracellular $[K^+]$ in a human atrial strand. *Annals Biomed Engineer* 2000;28:951–957.
13. Nattel S. Atrial electrophysiological remodeling caused by rapid atrial activation: Underlying mechanisms and clinical relevance to atrial fibrillation. *Cardiovasc Research* 1999;42:298–308.
14. Wijffels MCEF, Kirchhof CJHJ, Dorland R, Allessi MA. Atrial fibrillation begets atrial fibrillation. *Circulation* 1995;92:1054–1068.
15. Nattel S, Li D. Ionic remodeling in the heart: Pathophysiological significance and new therapeutic opportunities for atrial fibrillation. *Circ Res* 2000;87:440–447.
16. Courtemanche M, Ramirez RJ, Nattel S. Ionic targets for drug therapy and atrial fibrillation-induced electrical remodeling: Insights from a mathematical model. *Cardiovasc Res* 1999;42:477–489.
17. Van Wagoner DR, Pond AL, Lamorgese M, Rossie SS, McCarthy PM, Nerbonne JM. Atrial L-type Ca^{2+} currents and human atrial fibrillation. *Circ Res* 1999;85:428–436.
18. Bosch RF, Zeng X, Grammer JB, Popovic K, Mcwis C, Kühlkamp V. Ionic mechanisms of electrical remodeling in human atrial fibrillation. *Cardiovasc Res* 1999;44:121–131.
19. van der Helden HMW, van der Zee L, Wijffels MCEF, van Leuven C, Dorland R, Vos MA, Jongsma HJ, Allessie MA. Atrial fibrillation in the goat induces changes in monophasic action potential and mRNA expression of ion channels involved in repolarization. *J Cardiovasc Electrophysiol* 2000;11(11):1262–1269.