Modeling of Atrial Fibrillation

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Summary

Computer modeling of atrial fibrillation (AF) is considered today as a potentially effective tool for better understanding AF mechanisms and for the development of therapeutic options. Computer models are based on an integrative approach, from the molecule to the patient, incorporating data about cell electrophysiology, cell-to-cell coupling and atrial anatomy. The link to clinical experiments is provided by the computation of endocardial electrograms or surface electrocardiograms (ECG). In this chapter we describe how modeling can be used to study different forms of AF and to evaluate therapies such as antiarrhythmic drugs, ablation and antitachycardia pacing. The ultimate goal is the development of patient-specific models in order to test AF therapies in the model before applying it to the patient.

Keywords

Atrial fibrillation, computer modeling, ionic currents, transmembrane potentials, antiarrhythmic drugs, ablation, pacing, patient-specific modeling, integrative research.

1 Introduction

Atrial fibrillation (AF) is the most common form of sustained cardiac arrhythmia [1]. Despite the importance of AF and the many years of research, the mechanisms of AF still remain unclear, and we do not fully understand how to treat it effectively [1]. In this context, the use of new tools such as numerical models of AF play an important role in generating new insights into AF mechanism and in the development of more successful therapies. Computer modeling of biophysical phenomena has gained increased importance with the recent improvement in computational speed. The use of such models may overcome the limitations encountered in experimental and clinical research, by providing access to all variables of interest at any time and any location and by allowing the possibility of performing and repeating experiments in controlled conditions.

Integrated functional computer modeling is considered today as a potentially effective solution for the development of therapeutic options [2]. However, in these models the translation of results to new clinically applicable AF therapies has been difficult because most computer models have not included the different cellular and structural aspects present in heart diseases [3]. Models are approximations of the biophysical systems and existing models differ in the tradeoff made between the amount of details included and the computational requirements. With given computing resources, the more detailed the model is, the heavier the computational complexity and the shorter the duration of the simulated arrhythmia and vice versa. The challenge in computer modeling is to choose the least possible number of relevant features that still accurately reproduce the biophysical phenomena [4]. The choice of a specific model depends on the question to be answered. A model should implement all features that are pertinent to the specific question or application considered.

After several years of controversy between theories of reentrant AF or focal AF, it has been demonstrated that several mechanisms can lead to disorganized, “chaotic” activation of the atrial tissue and short or prolonged episodes of AF. Moreover, multiple abnormalities of the atrial myocardium may result in abnormal atrial conduction. Therefore, AF may have different forms corresponding to different AF substrates. This polymorphic nature, rarely studied in biological experiments, severely hampers the development of a single therapy effective in all individual patients [5]. Computer models should aim at accurately reproducing the different AF types observed in humans and creating a basis for substrate-related diagnosis and therapy.

2 Modeling of Atrial Fibrillation

Despite their low acceptance into the clinical field, several computer models of human atria have been developed over the last decades. Already in 1964, Moe et al. created the first model of AF, a two-dimensional cellular automaton, in which sustained functional reentrant circuits were initiated [6]. About 40 years later, improvements in computational speed allowed the development of models incorporating a detailed description of atrial cellular membrane kinetics together with a realistic representation of atrial anatomy. In 2000, Harrild and Henriquez presented the first ionic-based model of 3D conduction in a realistically designed human atrial geometry [7]. At that time, the model's heavy computational demand limited its use to the simulation of a few seconds of activity. Simplification of the geometry and membrane model was necessary to enable the simulation of long episodes of atrial arrhythmias [8,9]. Today's computational power allows to run virtual experiments in complex biophysical models, including the simulation of different types of arrhythmias and AF therapies such as ablation [10,11,12], antiarrhythmic drugs [13] and rapid pacing of AF [14]. In this chapter, research in this field is illustrated by a biophysical model developed by the Lausanne Heart Group (http://www.lausanneheart.ch).

2.1 Integrative Approach: from the Single Cell to the Whole Atrium

The design of electroanatomical models follows an integrative bottom-up approach, from molecule to patient [3,15]. These computer models consist of several components: 1) a cell electrophysiology model describing the kinetics of ion channels through the cell membrane as well as variations in intracellular ionic concentrations, 2) a model of atrial tissue represented by a grid of atrial units, interconnected via resistors representing cell-to-cell coupling through gap junctions, 3) atrial geometry and anatomy. These components are assembled as shown in Figure 1 to create a computational framework for simulating the propagation of the electrical impulse in the atrial tissue.

Several atrial cell models have been proposed [15], the most commonly used being the Nygren *et al.* [16] and the Courtemanche *et al.* [17] models. These two human atrial cell models differ in their action potential shape (Figure 1) and dynamics. The Courtemanche model has become popular for the simulation of atrial arrhythmias because quantitative data are available to incorporate the effects of regional heterogeneities, AF-induced electrical remodeling or vagal stimulation through acetylcholine. It will be used in the simulations presented in this chapter.

The atrial cells are then coupled together with their neighbors in order to form a network of electrical resistors. Ionic current can flow from cell to cell via these pathways. The conductivity values associated with these resistors are generally selected to reproduce conduction velocities measured *in vivo*. In some models, conduction properties are set to a uniform value in the whole atrial tissue [9]. More sophisticated models include fiber orientation (anisotropy), conduction heterogeneities (e.g. slow conduction in the low right atrial isthmus) and fast conducting bundles such as the Bachmann's bundle, the crista terminalis and the pectinate muscles [7]. It should be noted, however, that there is a great interpatient variability in the presence and dimensions of these bundles or of the regions of enhanced conduction.

In existing models of atrial anatomy, the three-dimensional geometry is reconstructed from published or commercially available datasets [7,12], computer-aided tomography (CT) or magnetic resonance images (MRI) of patients [9,12]. Anatomy textbooks also provide information about atrial dimensions, atrial muscle bundles and propagation velocities [7,8], When using data obtained from medical imaging modalities, it is often needed to correct the reconstructed geometry by comparing it to reference anatomical data (e.g. difficulty to segment the valves). In the atrium, reproducing wall thickness can be challenging because of the lack of available information. As a result, several atrial models have been constructed as a monolayer tissue embedded in a three-dimensional structure, postulating that atrial activation can be described as a two-dimensional process [8,9]. Once the three-dimensional geometry is constructed, a computational mesh is generated (Figure 1). Each element of the mesh represents a group of atrial cells. This mesh forms the basis for the application of numerical methods to solve the monodomain propagation equation [15].

The atrial geometry used in the illustrations of this chapter is reconstructed from the CT scan of a patient in AF before an ablation procedure. This model includes atrial wall thickness, fast conducting bundles similar to the Harrild *et al.* model [7] and rule-based fiber orientation [8,18] (3:1 anisotropy ratio in conductivity for the baseline model). The volumetric mesh is composed of cubic elements with edge length of 330 μm, corresponding to 1.04 million computational nodes for the whole atria. The time step is 20 μs, which translates to 1 million steps for the simulation of 20 seconds of atrial activity.

2.2 Initiation, Perpetuation and Termination of Atrial Fibrillation

The propagation of a normal sinus beat was initiated by injecting an intracellular current into the cells of the sino-atrial region. The isochrones of a normal sinus beat are shown in Figure 1. Atrial activation propagates from the right to the left atrium through the Bachmann's bundle and the septum and terminates in the left lateral wall where three wavefronts converge.

In a computer model, atrial arrhythmias are typically initiated by applying programmed stimulation protocol or burst-pacing in a similar way to clinical experiments. Most attempts to initiate arrhythmias in a healthy substrate either failed or produced unstable reentrant waves that terminated after a few seconds. Models of pathological atrial tissue were needed to create conditions facilitating the perpetuation of AF. In all AF substrates of this chapter, conduction velocity was reduced to 60 cm/s in the longitudinal direction and 30 cm/s in the transverse direction. Different electrophysiological substrates (membrane properties) led to different AF types [19]. An example of AF initiation by burst pacing is presented in Figure 2. Ion channel conductances were modified to take into account AF-induced electrical remodeling [20]. AF was initiated by rapid pacing close to the left inferior pulmonary vein at a cycle length of 236 ms. After about 3 seconds of rapid pacing, conduction blocks were observed through dynamically-induced repolarization gradients, resulting in AF reentrant waves [21]. After 18 pacing stimuli, pacing was stopped and AF was sustained by multiple meandering functional and anatomical reentries (reentrant circuits).

Spontaneous termination of AF is frequently observed in patients as well as in computer models. In the example of Figure 2, spontaneous termination of AF occurred after about 12 seconds (8 seconds after burst pacing was stopped). The termination process involved reentrant waves simultaneously hitting lines of conduction block created by the refractory tail of wavefronts. With the help of computer modeling these spontaneous termination episodes can be studied in details. Identification of the spontaneous termination mechanisms could lead to a better understanding of AF and therefore to the development of more effective therapies.

2.3 Modeling Different Types of Atrial Fibrillation

In previous studies, different types of atrial arrhythmias have been simulated by adapting membrane kinetics to different arrhythmogenic conditions and by introducing heterogeneities in electrophysiological properties. For the sake of illustration, these AF dynamics obtained in different atrial geometries are reproduced in the model of Figure 1 using a modified Courtemanche *et al.*

model and the same conduction properties and similar initiation protocol to the previous paragraph. Transmembrane potential maps from six simulated AF episodes corresponding to different AF substrates and perpetuation mechanisms are presented in Figure 3:

• Macroreentrant circuit [8,21]: The current I_{CaL} is reduced by 63% to shorten action potentials and stabilize the reentry. The wavefront propagates from the right to the left through the septum and comes back to the right atrium using the connection between the left atrium and the coronary sinus musculature [8] (red star in Figure 3a).

• Cholinergic AF [22]: An acetylcholine-dependent K^+ current is added and I_{CaL} is reduced by 63%. This considerably decreases rate adaptation. Spatial variations in acetylcholine concentration are introduced to create repolarization gradients [22]. The resulting AF dynamics is maintained by stable rotors (the one shown as a red star in Figure 3c is stable for >5 seconds).

• Meandering wavelets [20,21] (the model of Figure 2): The current I_{CaL} is reduced by 30%, I_{to} by 80%, I_{Kur} by 90% and I_{Kr} is increased by 50% [20]. One to three wavelets meander throughout the atrial surface. The perpetuation mechanism involves beat-to-beat variations in action potential duration [21].

• Atrial dilation [11]: The meandering wavelet model is simulated in a patient-specific geometry featuring severe atrial dilation, the total atrial volume being 60% larger than the other model. Although wavelet dynamics is kept unchanged by the dilation, the increased tissue size provides space for more wavelets.

• Repolarization heterogeneities [19]: In addition to the modifications of the meandering wavelet model, patchy heterogeneities are created, in which I_{CaL} is decreased by 50% and I_{to} and I_{Kr} are increased by 200% relative to the original model. Wavebreaks are induced by repolarization gradients, which contribute to the maintenance of AF.

• Focal sources [23]: Using the substrate of the previous case, focal sources are modeled as spontaneous firing of groups of cells in the pulmonary veins at fixed cycle length (artificially induced by intracellular current injection). This focal activity enforces AF maintenance. The red stars in Figures 3k-l indicate the breakthrough patterns resulting from these sources.

3 Computer Modeling as a Tool to Develop New Therapeutical Strategies for Atrial Fibrillation

Strategies for AF therapy attempt to control ventricular rate and/or restore sinus rhythm. Antiarrhythmic drugs are often prescribed as a first therapeutical approach for AF. When pharmacological therapy fails or when AF is of focal origin, catheter ablation of AF has now become a standard intervention for patients with paroxysmal AF, especially for patients with focal triggers. Other ablation procedures such as the Maze procedure are currently performed in patients with permanent AF. In addition, recent pacemakers/defibrillators incorporate different features to prevent or terminate AF, such as overdrive pacing or antitachycardia pacing (ATP). Restoration of sinus rhythm can also be achieved by electrical cardioversion, delivering an intracardiac or external electrical shock.

Computer model of sustained AF open the way to *in silico* evaluation of AF therapies. Antiarrhythmic drugs can be simulated by modulating the ion kinetics of atrial cells (Figure 4a) [13]. Catheter or surgical ablation can be simulated by removing cell-to-cell coupling in the regions corresponding to the ablation lines (Figure 4b). Therapeutic pacing can be simulated by injecting intracellular current at the pacing sites (Figure 4c). Higher amplitude stimulation (e.g. electrical shock) would require more sophisticated models. Model-based studies of defibrillation have been mostly developed in ventricular models [24], but from this work one may learn how to apply very low energy shocks to find a way for pain free electrical therapies for AF.

To perform the *in silico* equivalent of animal or clinical experiments, multiple transmembrane potentials maps (from 20 to 50) are selected during one or several simulations of sustained AF. These maps correspond to different states of electrical activity in the atrial tissue. They serve as initial conditions for the repetitive application of the therapy [10,11,14], thus providing a tool to investigate the mechanisms underlying the success or failure of the therapy and estimate effectiveness in a statistical method.

3.1 Antiarrythmic Drugs

Antiarrythmic drugs are effective in terminating AF in 47%-84% of the patients with AF lasting less than 24 h. For longer episodes, conversion is achieved only for 15%-30% of patients [25]. Predicting the efficacy of a drug on the atrium based on single-cell data is indeed difficult due to

poorly understood mechanisms. Computer models offer a new tool in the drug discovery process by testing their effect at the organ level. Models can also target specific ionic currents of atrial cells even if no drug is currently able to induce these effects.

The mechanisms of termination of AF by class I antiarrhythmic drugs have been studied with help of computer simulations [13]. These drugs cause sodium channel blockade, slow down conduction velocity and create more space for reentrant wavelets, but also reduce membrane excitability and therefore produce wider reentrant wavefronts. It was shown by Kneller *et al*. in a two-dimensional tissue with cholinergic AF that AF termination could be achieved by pure sodium channel blockade [13]. This type of pharmacological study can be extended to any of the ion channel of interest.

3.2 Catheter or Surgical Ablation

Catheter and surgical ablation aim at creating lines of block to interrupt electrical conduction, thus preventing the AF reentrant process. Most of the recent catheter ablation strategies target ectopic foci in the pulmonary veins in patients with paroxysmal AF. This procedure has been modeled by including several stable sources in the left atrium. Perfect isolation of these sources prevented AF reinitiation [12]. In another modeling study, Haissaguerre *et al.* monitored the evolution of AF cycle length during catheter ablation in a model with several ectopic foci [23]. Successive ablation of the foci tended to prolong AF cycle length until sinus rhythm was established.

For permanent AF the gold standard is the Maze III procedure developed by Cox *et al.* [26]. This complex ablation procedure has proven to be effective in treating permanent AF, but it can be time-consuming and associated with a risk of serious complications. Less invasive radiofrequency catheter ablation procedures were developed and tested clinically. However, the ideal location and the number of ablation lines, their best connection and appropriate length still remain to be determined. Computer modeling permits a systematic assessment of existing ablation patterns. Simulation results confirmed that the most complex ablation patterns have higher success rate. Ablation patterns involving only the right or left atrium led to success rates in the range 20%-60% and 55%-80% respectively for permanent AF [0]. Ablation patterns combining lines in both atria showed an improved success rate of 80-100%, with the best results obtained with the Maze III pattern [26]. Simulation studies looked for ablation patterns reproducing the high conversion rate of the Maze III procedure with a minimum number of lesions. This optimum was reached by a pattern

combining an isolation of the pulmonary veins, the left isthmus line, and the line between the vena cavae in the right atrium [10]. A comparison between simulations and a clinical study supported the relevance of computer modeling for estimating conversion rates to sinus rhythm and residual atrial flutter [27]. Another model-based study evaluated the different patterns involved in pulmonary veins isolation for a normal and a dilated heart [11]. It showed that if AF persists in a normal heart after pulmonary veins isolation, a roof line offers fewer arrhythmogenic effects that other lines and may be the preferred additional lesion. However, in dilated atria both roof and mitral isthmus lines are required to reach satisfactory success rates in clinical practice.

In summary, computer modeling offers the possibility to test ablation line patterns in a reversible way in a human model, to test patterns generally not used in clinical experiments, to observe the AF termination process in detail and to study the impact of imperfections that may be present in the ablation lines.

3.3 Pacing of Atrial Fibrillation

Several pacing therapies such as burst or ramp pacing are currently used in implantable devices to terminate atrial tachycardia or atrial flutter. ATP algorithms designed to terminate atrial tachycardias deliver pacing bursts at a cycle length shorter than that of the detected arrhythmia. As compared to electrical cardioversion, pacing of AF has the advantage of being painless, safe and energy-efficient. While the possibility of local atrial capture by rapid pacing has been demonstrated in animals and humans [28,29], no pacing therapy has proved so far to be effective in terminating AF. This is probably due to the complex dynamics, the variable number of propagation wavefronts and the small and variable excitable gap observed during AF.

Computer modeling permitted a systematic study of ATP algorithms currently used in pacemakers such as burst pacing and a test of the optimal pacing sites and pacing cycle length leading to local capture of AF [14]. As a result, a higher ability to sustain capture was found in the right atrial free wall, the left atrial appendage, and the pulmonary veins where the wavefronts induced by pacing encompassed the major part of the paced atrium. This capture was accompanied by residual reentrant waves outside the area of capture and AF termination was not possible since with a stop of the pacing protocol reinitiation of AF is the rule. When pacing only in one atrium, control in both atria was not observed. Obtaining capture in both atria was found possible only when

pacing in the septum, although the ability to sustain capture was low. Modeling results confirmed that single site rapid pacing of AF cannot terminate acute nor permanent AF [28,29].

Cardioversion with a single high voltage shock can terminate AF reliably, with the major side effect being tissue damage and pain experienced by the patient. Based on this observation and using computer modeling, Fenton *et al.* developed a method to terminate AF called far-field antifibrillation pacing, delivering trains of rapid low-energy pacing from field electrodes [30]. The method was tested in isolated canine hearts, showing an AF termination success rate of 93% with only 13% of the energy needed for cardioversion applied in a single shock. Further studies are needed to assess clinical relevance, but these examples show that computer models contribute to the design of complex pacing schemes.

4 Link to Clinical Data and Patient-Specific Modeling

The link between computer simulations and clinical data is crucial for the validation of computer modeling experiments and for the translation of research results into clinically relevant applications. In computer models, direct access to transmembrane potentials is possible at any time and any location. In clinical experiments, invasive tools such as electrical mapping either by catheter-guided electrodes or by the electrode of an implantable device allow the recording of endocardial electrograms (Figure 5). These electrograms can also be generated in the computer model for a comparison with clinical data [20]. The standard 12 lead surface electrocardiogram (ECG) is the mostly used non-invasive tool for diagnosing cardiac arrhythmias. In a computer model this can simulated using a thorax model involving the geometries of the torso, lungs, heart and blood cavities (Figure 5). This results in signals that are in all aspects similar to those observed clinically. With this link to clinical data, computer models represent a complement to experimental and clinical studies.

It is recognized that computer modeling cannot go beyond the information that is integrated in it. A critical and continuous feedback from the physiological reality is therefore required. Modeling necessarily involves step-by-step integration of new elements from research in electrophysiology and anatomy. For example, the impact of mechanoelectrical coupling on AF perpetuation has been recently included and studied in models [31]. For arrhythmias, changes in neural influence could also be added and studied. With the development of new imaging techniques, new tools have been developed to better describe the patient's anatomy (predictive modeling). The ultimate goal is to use computer modeling to test a therapy before applying it to the patient, in a

similar way to simulations used to design and test new products in the aeronautical or automotive industry.

5 Conclusion

Computer modeling of AF is considered today as a potentially effective tool for a better understanding of AF mechanisms and for the development and testing of therapeutic approaches. By giving access to all variables of interest at any time and location, computer models provide access to data that cannot be obtained in biological experiments, and therefore represent a valuable complement to experimental and clinical studies. *In silico* experiments can be systematically and reproducibly carried out in controlled conditions, including setups that cannot be reproduced in the clinic for practical or ethical reasons. Computer models are based on an integrative approach, from molecules to the patient. They consist of a model of cellular electrophysiology describing ionic currents, a model of atrial tissue representing atrial cell interconnections via gap junctions and a model of atrial anatomy. The link to clinical experiments is provided by the computation of endocardial electrograms or surface electrocardiograms (ECG). Because of the polymorphic nature of AF, different computer models have been developed to reproduce specific pathological AF substrates observed in humans. This chapter describes different AF models whose perpetuation mechanisms are based on various pathologies resulting in different forms of chaotic atrial impulse propagation such as multiple wavelets reentry, meandering wavelets, repolarization heterogeneities, vagal stimulation, atrial dilation and focal sources. The methodology for the simulation of AF therapies such as antiarrhythmic drugs, ablation and antitachycardia pacing is explained. The ultimate goal is the development of patient-specific models based on each patient's anatomy and atrial substrate in order to test AF therapies in the model before applying it to the patient.

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Figures

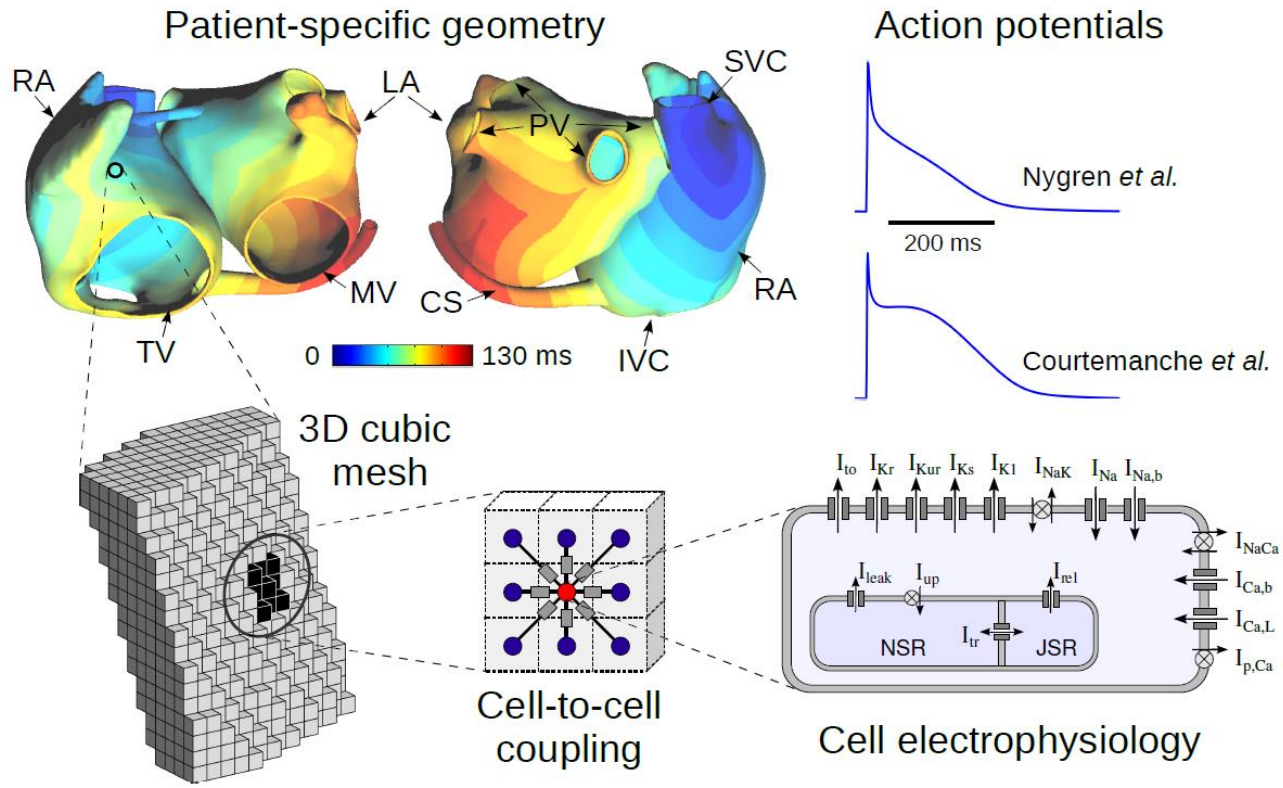

Figure 1. Integrative approach: from the single cell to the whole atrium. The cell electrophysiology is modeled using the Courtemanche *et al.* human atrial cell model, including several ionic currents flowing through the cell membrane, as well as ion pumps and exchangers [17]. Single cells are interconnected together via electric resistors representing the gap junctions to form an atrial tissue. The atrial tissue is finally reconstructed to reproduce an atrial geometry obtained from the CT scan of patient in AF before an ablation procedure. The major valves and vessels are represented: tricuspid valve (TV), mitral valve (MV), pulmonary veins (PV), superior and inferior vena cava (SVC and IVC) and coronary sinus (CS). To spatial discretization of the geometry is obtained using a mesh of 1.04 million cubes with sides of 330 µm. Iso-activation areas observed during normal sinus rhythm propagation are shown in color on the patient-specific geometry, from the earliest activation in dark blue in the right atrium (RA) to the latest in dark red in the left atrium (LA).

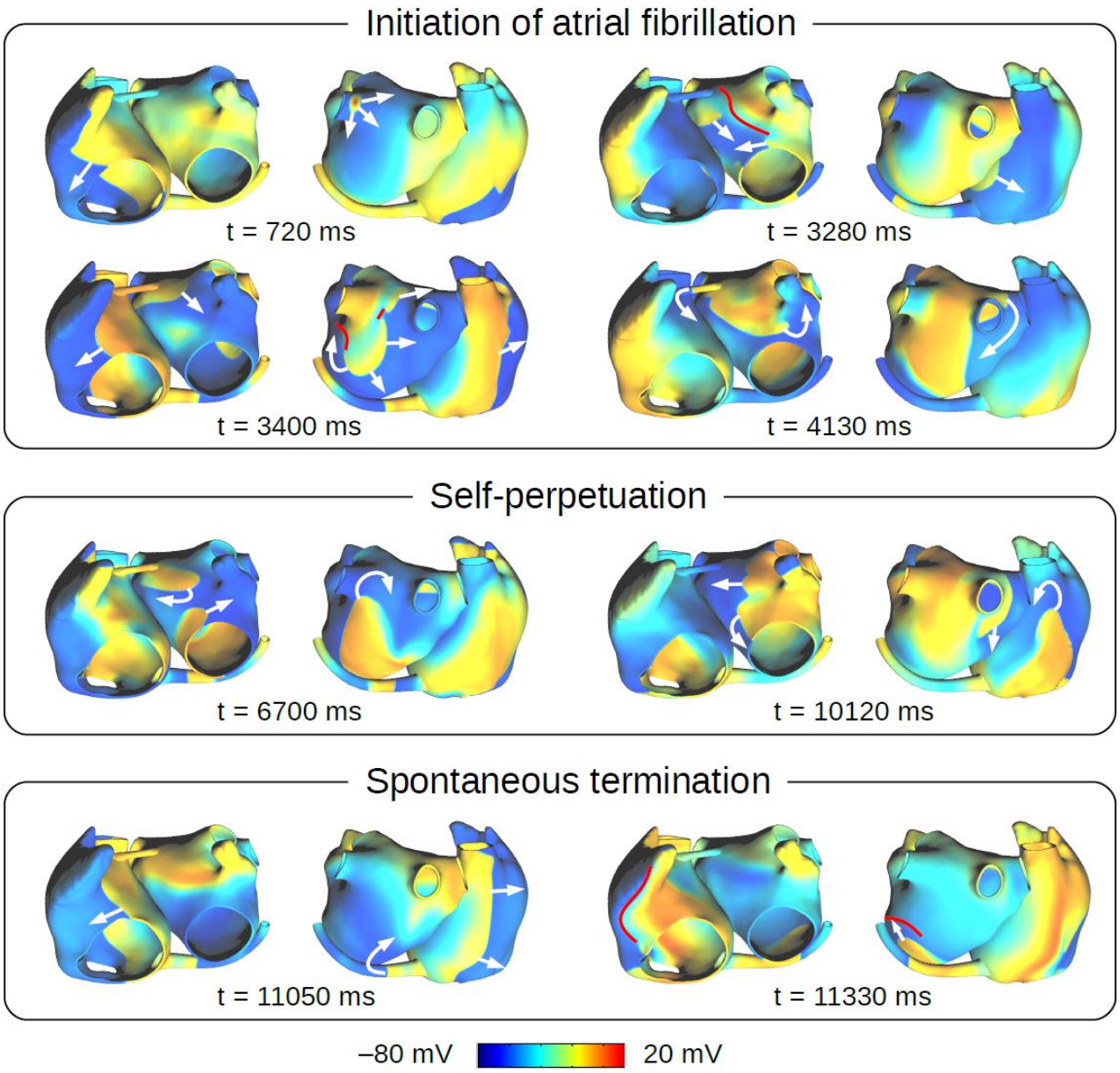

Figure 2. Example of initiation, perpetuation and spontaneous termination of AF. Instantaneous transmembrane potential maps are color-coded, blue representing the resting potential and red the depolarization potential. AF was initiated by rapid pacing close to the lower inferior pulmonary vein at a cycle length of 236 ms. After about 3000 ms of pacing AF reentrant waves can observed. After 4300 ms, pacing is stopped and the system is let to evolve freely. AF is sustained until spontaneous termination is observed after about 12000 ms. The white arrows represent the direction of propagation of the electrical activity. Lines of block to propagation due to refractory tissue are indicated as red lines. The model presented here corresponds to the meandering wavelets model of Figure 3.

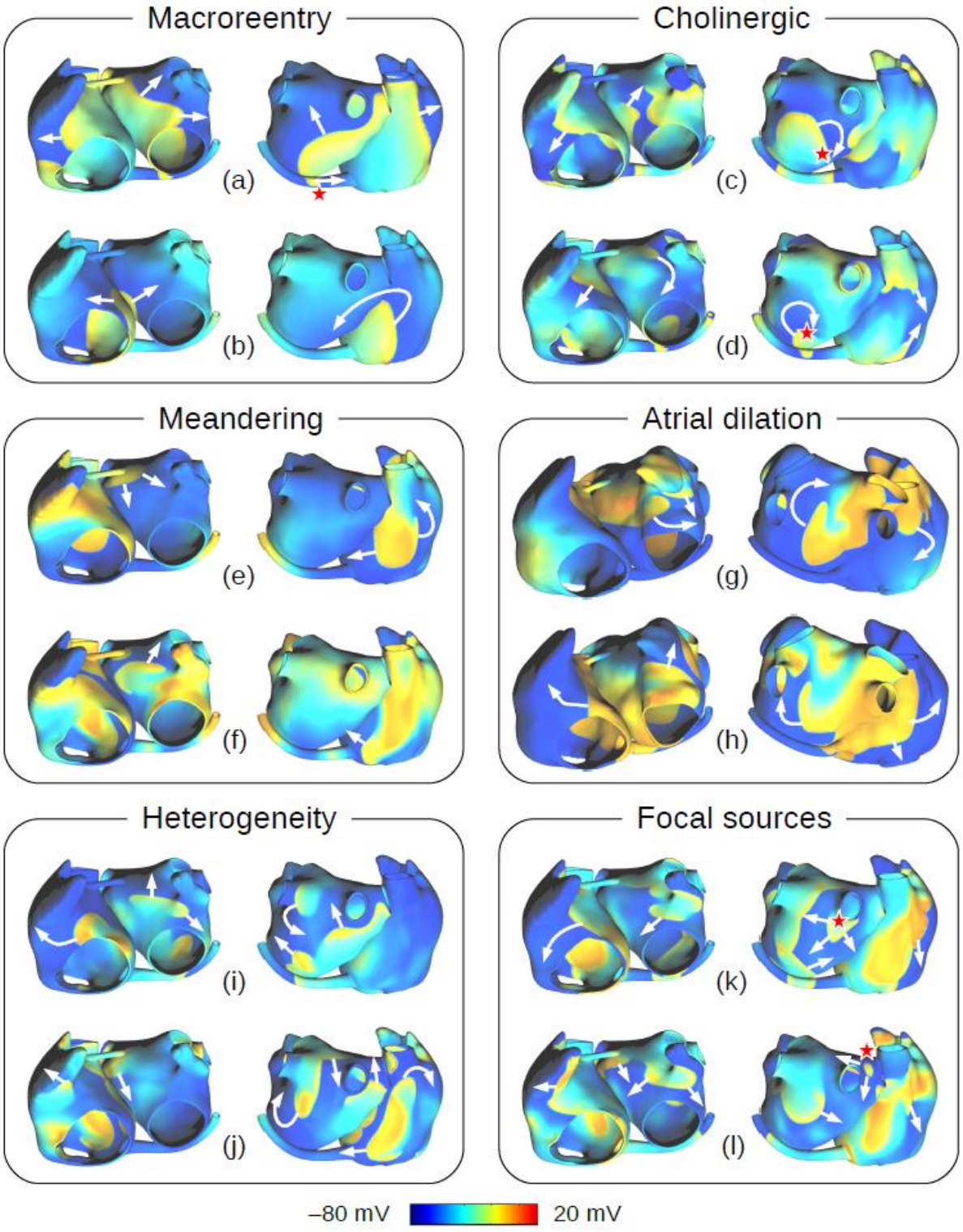

Figure 3. Six different forms of simulated AF resulting from different arrhythmogenic substrates. In each case, color-coded transmembrane potential maps are displayed. White arrows show the direction of wavefront propagation. Red stars indicate points of interest referred to in the text.

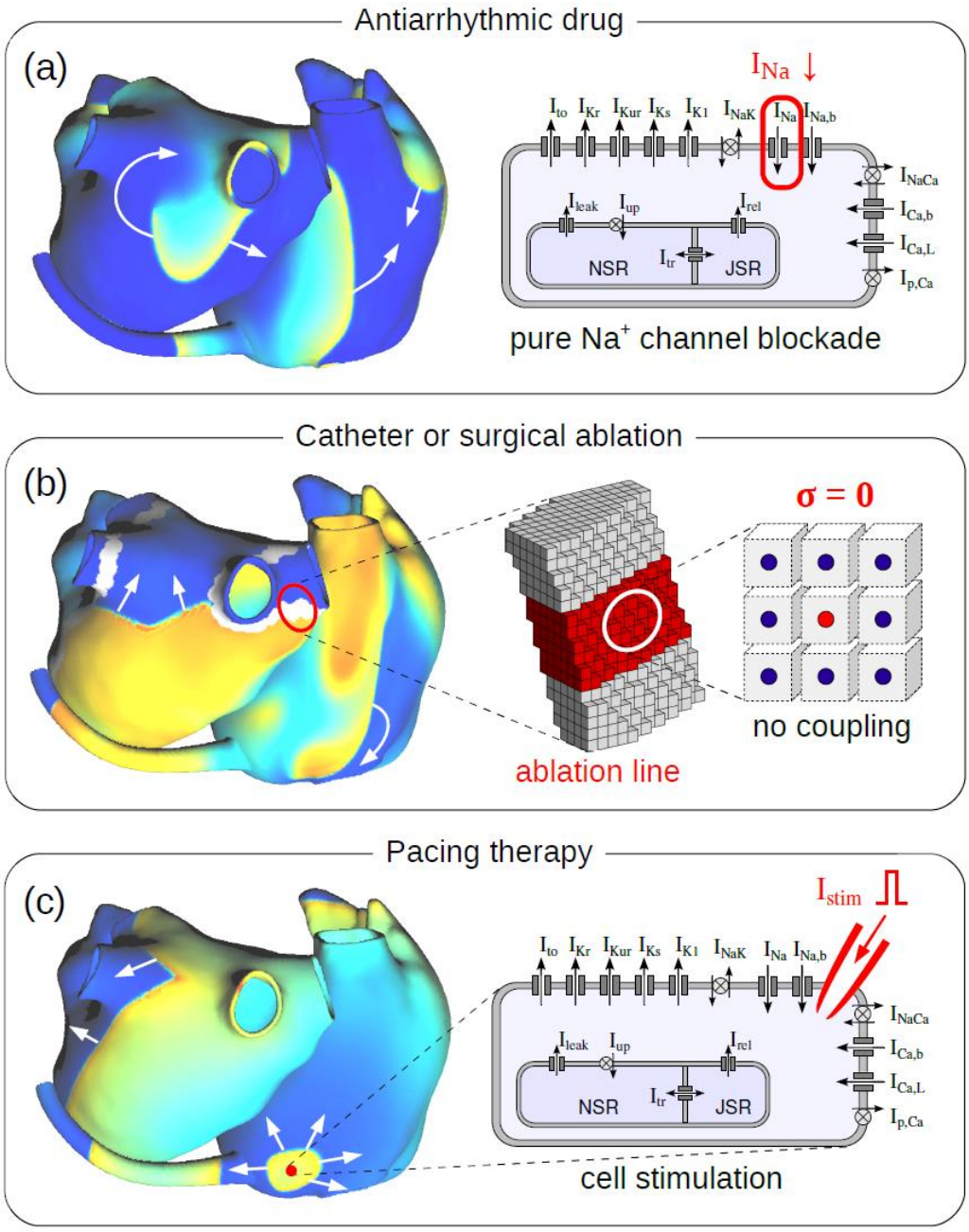

Figure 4. Computer modeling as a tool to develop new therapeutic strategies for atrial fibrillation. (a) Antiarrhythmic drugs can be simulated by modulating the ionic currents through the atrial cell membranes, in this example a class I antiarrhythmic drug leading to a sodium blockade as described by Kneller *et al* [13]. (b) Catheter or surgical ablation are simulated by setting the conductivity (σ) to zero for the cell located in the line, forming barriers to impulse propagation, in this example a two-by-two isolation of the pulmonary veins (in white) is simulated as described by Rotter *et al* [11]. (c) Pacing of AF is simulated by injecting a stimulus current (I_{stim}) inside the cells located at the pacing site. The white arrows represent the direction of propagation of the electrical activity.

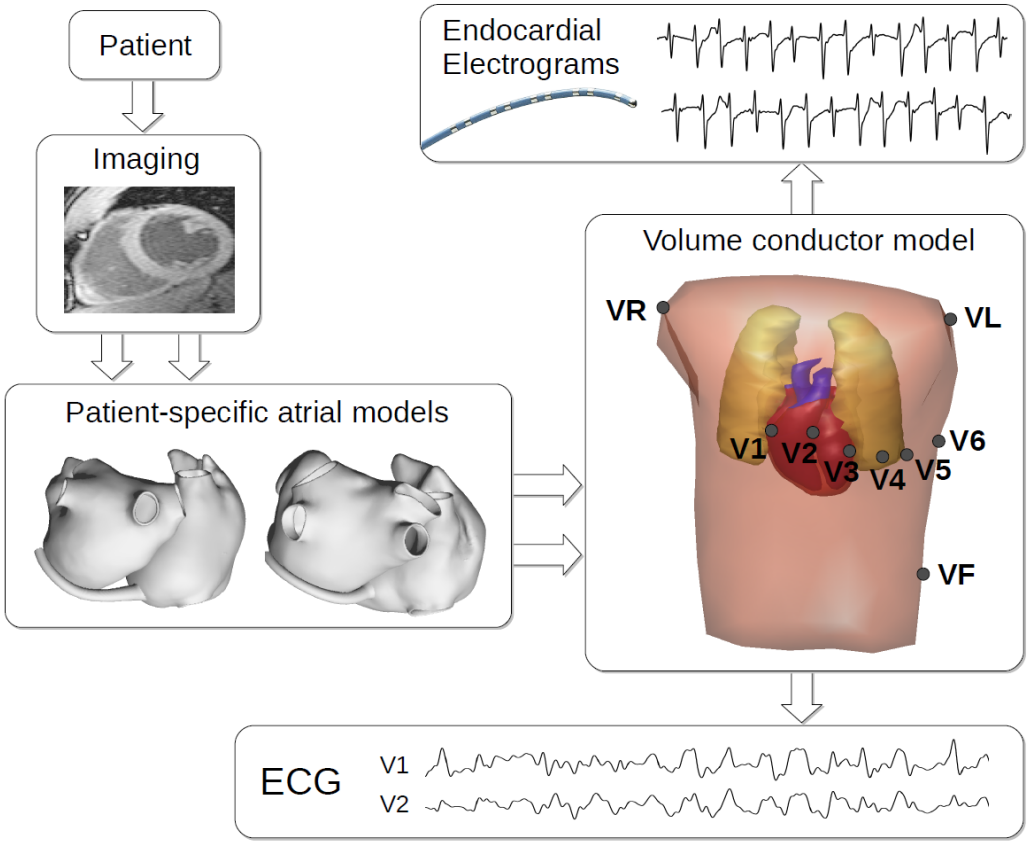

Figure 5. Illustration of patient-specific modeling and the link to clinical signals with the computation of endocardial electrograms and surface ECG.