Modeling Atrial Arrhythmias: Impact on Clinical Diagnosis and Therapies

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***Abstract*—Atrial arrhythmias are the most frequent sustained rhythm disorders in humans and often lead to severe complications such as heart failure and stroke. Despite the important insights provided by animal models into the mechanisms of atrial arrhythmias, direct translation of experimental findings to new therapies in patients has not been straightforward. With the advances in computer technology, large-scale electroanatomical computer models of the atria that integrate information from the molecular to organ scale have reached a level of sophistication that they can be used to interpret the outcome of experimental and clinical studies and aid in the rational design of therapies. This paper reviews the state-of-the-art computer models of the electrical dynamics of the atria and discusses the evolving role of simulation in assisting the clinical diagnosis and treatment of atrial arrhythmias.**

I. Introduction

Atrial arrhythmias are the most frequent sustained rhythm disorders in humans and often lead to severe complications such as heart failure and stroke. As is the case with most human arrhythmias, the mechanisms underlying atrial fibrillation (AF) are highly complex, dynamical and involve processes at multiple temporal and spatial scales. Atrial arrhythmias might originate from an alteration of the cellular membrane kinetics, gross anatomical abnormalities, perturbations of the neurovegetative balance, or a combination of all these cases. While experiments using animal models have provided significant information on the electrophysiological processes associated with AF, direct translation of the findings to new therapies in patients has not been straightforward. One reason is that the nature of AF induced in animal models is different than that seen in patients, due to differences in atrial geometry, ion channel distributions and the degree of tissue structure heterogeneity. As a result, the treatment of atrial arrhythmias has been developed largely from empirical findings in patients and has lacked a rational approach.

In parallel with the dramatic increase in computer power over the last few decades, computer models of cardiac electrophysiology have evolved from small strings of cells to detailed large-scale electroanatomical description of the whole organ. As a result, today's computer models can not only simulate arrhythmias and investigate mechanisms but also can evaluate therapeutic approaches. This evolution of computer models that can integrate information from the molecular to organ scales is opening a new avenues for in silico approaches for assessing the arrhythmogenic substrate, designing new clinical therapies and training physicians.

In this review, we present the state-of-the-art of computer models of the electrical dynamics of the heart and discuss the emerging role of simulation in assisting the clinical diagnosis and treatment of atrial arrhythmias.

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II. Atrial Arrhythmias

A. Current Management of Atrial Arrhythmias

AF has a heterogeneous clinical presentation, occurring in the presence or absence of detectable heart disease. Symptoms include extreme discomfort due to palpitation and rapid heart rate with dizziness and general weakness as signs of diminished cardiac output; however, AF can also be asymptomatic [1]. Acute symptoms do not influence the long-term effect of a non-functioning atrium, which will need to be hemodynamically compensated by increased ventricular activity and always harbors the risk of thrombus formation and systemic embolisation.

AF can result from many conditions including hyperthyreosis, myocarditis or heart failure; conversely, when no underlying abnormalty can be identified and the substrate remains unknown, AF is considered a primary arrhythmia (lone AF). The first step in clinical management is to estimate the patient's risk for systemic embolism and prevent this by anticoagulation, followed, if necessary, by pharmacological control of the rapid heart rate [2]. Electrical cardioversion to sinus rhythm is considered whenever symptoms adversely impact cardiac function [3]. When pharmacological control fails or the focal origin is evident, ablation (surgical or via radiofrequency catheters) is usually the next step to be considered. The creation of lesions on the atria acts either by altering the electric continuity of the atrium (the substrate) or by eliminating or isolating the initiating focus (the trigger) of the AF. A common procedure involves ablating specific areas near the openings of the pulmonary veins, as this region has been shown to contain the trigger for many patients with paroxysmal AF (AF characterized by brief episodes) [4].

While ablation has been successful therapy for many forms of AF, drawbacks remain, including complications inherent in any surgery, the potentially severe complications of lesions generated by radiofrequency energy to other cardiac structures or surrounding organs (e.g. perforation of the esophagus, phrenic nerve lesion, stenosis of the pulmonary veins) or the long-term consequences of prolonged X-ray exposure to the

clinicians performing the procedures. In addition, destruction of atrial tissue causes an irreversible loss of myocardial activity. Finally, ablation is not successful in all patients, particularly those with persistent AF. Therefore a better understanding of the triggers and various substrates of AF is needed to develop more effective cures, whether they be more specific drugs or an ablation strategy that is specific to an individual patient.

B. Bringing Computer Modeling into Clinical Research

An incomplete knowledge of human disease often requires the use of complex animal models to develop a mechanistic understanding of the pathophysiology and to design and test new therapies. Over time, this mechanistic approach has moved from the whole animal level to the molecular level. Despite significant breakthroughs, the reductionist approach to disease has made it difficult to translate a finding at the cellular and subcellular level to the care of a given patient. Approaches are needed that can integrate the myriad of data obtained from all levels to impact the practice of clinical medicine.

The most promising approach for integration across the wide temporal and spatial scales of the heart is the use of detailed, mathematical models, based on the biophysics of ion fluxes across membranes and from cell to cell, and computer simulations, in which parameters can be varied and the consequences quantified. These models, however, must constantly evolve, bringing in new knowledge and data as their predictive ability must get tested by performing careful experiments on hearts *in situ*. As long as a strong collaboration is maintained between clinicians, electrophysiologists and engineers, this approach opens the way for *in silico* experiments to aid in the understanding of pathophysiologic processes, the refinement of diagnostic methods, and the design of innovative therapies.

III. Modeling Atrial Electrophysiology

Cardiac electrophysiological modeling is usually performed by following a bottom-up approach. It starts by modeling channel gating kinetics (*molecular level*). Ionic currents, pumps and ion exchangers are then integrated into a membrane model (*membrane level*). The contribution of each ionic current is summed, and its effect on ionic concentration is taken into account (*cell level*). The cells are then coupled in order to form a tissue (*tissue level*). Tissue structure is constructed to reproduce cardiac anatomy (*organ level*). Finally, measurement devices (*e.g.* catheter electrodes or ECG leads) are simulated in the model (*clinician's level*).

A. Atrial Cell Models

The cell membrane, consisting of a dielectric lipid bilayer, acts as a capacitor. The electric charge (per unit area of membrane) $Q_m = C_m V_m$ accumulated at the membrane surface of an isolated cell is proportional to the membrane potential V_m, where C_m is the membrane capacitance per unit area of membrane. The total ionic current I_{ion} (per unit area of membrane) through the membrane channels, pumps and ion exchangers (by convention, positive currents are outward currents) is responsible for the variations of V_m according to the evolution equation

$$C_m \frac{\mathrm{d}V_m}{\mathrm{d}t} = -I_{\text{ion}}(V_m, \mathbf{s}) + I_{\text{stim}}(t) \quad (1)$$

$$\frac{\mathrm{d}\mathbf{s}}{\mathrm{d}t} = \mathbf{g}(V_m, \mathbf{s}) \quad (2)$$

where $\mathbf{s}$ summarizes all dynamical variables of the cell (*e.g.* intracellular ionic concentrations or the probability of an ion channel to be open) and the function $\mathbf{g}$ describes the dynamics of those variables. An external stimulus current I_{stim} is used to trigger an action potential.

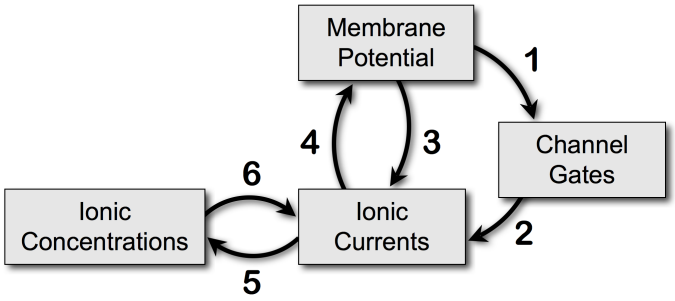

Fig. 1. Relations between the state variables of a cell: membrane potential, gating variables and ionic concentrations. The nature of the relation is explained in the text in the point corresponding to the number near the arrow on the figure.

The description of a cardiac cell model consists of specifying the variables ($\mathbf{s}$), their dynamics ($\mathbf{g}$), and their effect on the membrane potential (I_{ion}). The ion current I_{ion} is written as the sum of a number of ion channel currents, and pump or ion-exchanger currents. The state $\mathbf{s}$ of the cell is defined by the membrane potential, ionic concentrations and variables describing the state of the ion channel gates (*e.g.*, open, closed, or inactivated). These state variables are usually coupled as follows (see Fig. 1 and [5], [6]): (1) Channel gates are voltage-dependent; (2) Ionic currents are driven by channel gates and include ionic channels, pumps and ion exchangers; (3) Ion channels depend on the membrane potential through their intrinsic current-voltage relationship; (4) Variations in membrane potential are due to ionic currents; (5) Ionic currents produce changes in ionic concentration; (6) Ionic concentrations have an impact on ionic currents through the Nernst potentials as well as through ion channel inactivation.

Several models have been developed to specifically describe the atrial myocardial cell. Most of them extend, update or reformulate earlier models using the most recent experimental data available at that time, and rely heavily on the mathematical formulation introduced by Hodgkin and Huxley [7] for neuronal cells and its application to cardiac ventricular cells [8]–[10]. The first atrial myocardial cell models were based on measurements in rabbit atria [11]–[13]. Short thereafter, two human atrial cell models were published in Nygren *et al.* [14] and by Courtemanche *et al.* [15]. They differ by their action potential shape and by their dynamics [16]. More recently, a cell model was developed to reproduce the spontaneous activations observed in the pulmonary veins of rabbit atria [17]. The Courtemanche model has become more pop-

ular for the simulation of atrial arrhythmias, mainly because specific target parameters have been proposed to reproduce regional heterogeneity [18] and electrical remodeling [19], account for acetylcholine-dependent vagal stimulation [20], simulate the effect of drug delivery [19], [21] and create a canine atrial cell model [18]. To illustrate the level of electrophysiological details included in membrane models, a schematic representation of the Courtemanche *et al.* model is drawn in Fig. 2 and the time course of its membrane currents in Fig. 3.

B. Continuous Propagation Models

From the electrical viewpoint, cardiac tissue is a collection of excitable cells interconnected with their neighbors through gap junctions. Ionic current can flow from cell to cell by this pathway, or between the intracellular space and the extracellular/interstitial space through membrane channels, Propagation in excitable media has been described mostly by continuous models resulting from a local spatial homogenization. To formulate such model, the intracellular medium, the cell membranes and the extracellular medium are conceptually extracted from the cardiac excitable tissue and homogenized by mesoscopic averaging so that the three domains occupy the same continuous physical space, here denoted by Ω_{myo} (myocardium). The intracellular potential ϕ_i, the cell state $\mathbf{s}$ and the extracellular potential ϕ_e of the cells now become fields $\phi_i(\mathbf{x})$, $\mathbf{s}(\mathbf{x})$ and $\phi_e(\mathbf{x})$ defined on Ω_{myo}. The transmembrane potential is given by $V_m = \phi_i - \phi_e$. Current flow in the intra- and extracellular media is described in the continuous model by coarse-grained conductivity tensor fields $\boldsymbol{\sigma}_i(\mathbf{x})$ and $\boldsymbol{\sigma}_e(\mathbf{x})$ which integrate all the information about the microstructure and the distribution of gap junction over the cell membranes, including anisotropic properties of the tissue.

If the intracellular medium is considered to be continuous, the current flows are described by a continuity equation expressing the conservation of electric charge

$$\frac{\partial \rho_i}{\partial t} + \nabla \cdot \mathbf{j}_i = I_{\text{src},i} \tag{3}$$

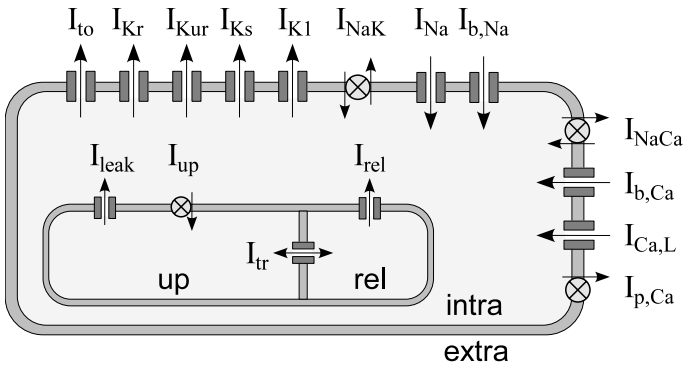

Fig. 2. Schematic view of the Courtemanche *et al.* human atrial cell model [15], illustrating its membrane currents, pumps and ion exchangers. The different compartments are indicated: the extracellular (extra) and intracellular (intra) media, and, in the sarcoplasmic reticulum, the uptake (up) and release (rel) compartment.

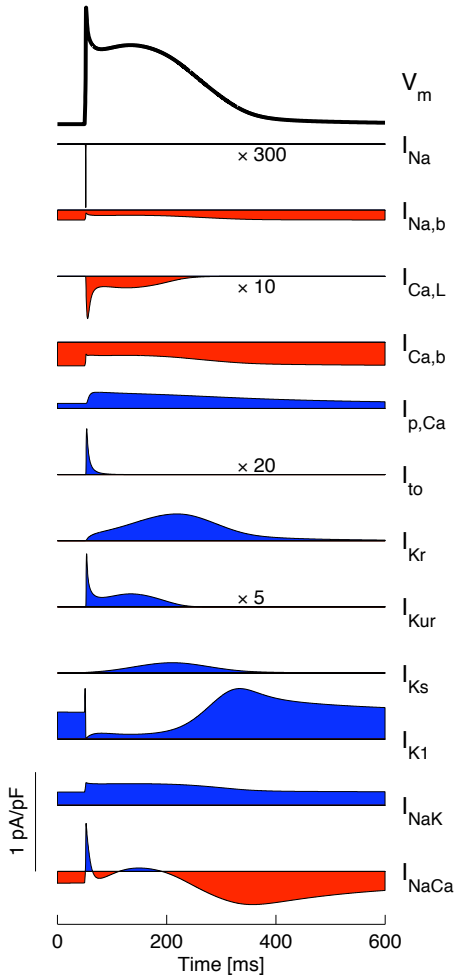

Fig. 3. Time course of the action potential and the 12 membrane currents (see Fig. 2) of the Courtemanche *et al.* model [15] during normal rhythm. Inward currents are shown in red and outward currents in blue. The currents I_{Na}, $I_{\text{Ca,L}}$, I_{to} and I_{Kur} were downscaled by a factor 300, 10, 20 and 5 respectively to be displayed on the same figure.

where ρ_i is the charge density, $\mathbf{j}_i$ is the current density in the intracellular medium and I_{src} is a current source term. A similar equation holds for the extracellular medium. The charge density is given by $\rho_i = V_m C_m S_v$, that is, charge density per unit volume = membrane potential × membrane capacitance per unit area of membrane × area of membrane per unit volume. The current density $\mathbf{j}_i$ is derived from the continuous equivalent of Ohm's law:

$$\mathbf{j}_i = -\,\boldsymbol{\sigma}_i\,\nabla\phi_i \quad , \tag{4}$$

where $\boldsymbol{\sigma}_i$ is the conductivity tensor. Finally, the source current (*inward* current) per unit volume $I_{\text{src},i}$ is given by $-I_{\text{ion}} S_v$, the ionic current through the membrane (by convention, *outward-oriented* if positive) per unit area of membrane × area of membrane per unit volume, leading to the equation

$$C_m\,\frac{\partial V_m}{\partial t} = S_v^{-1}\,\nabla\cdot\boldsymbol{\sigma}_i\,\nabla\phi_i - I_{\text{ion}} \quad . \tag{5}$$

Charges in the extracellular medium form the other side of the

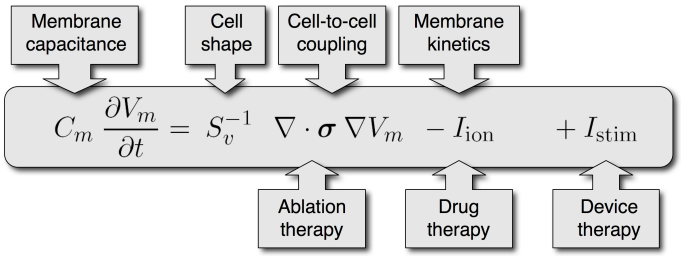

Fig. 4. The monodomain equation of electrical propagation. The physical properties incorporated into the equation are shown above and the terms affected by a therapy are shown below the equation.

capacitor, so $\rho_e + \rho_i = 0$ and $I_{\text{src},e} + I_{\text{src},i} = 0$. The current density is also supposed to satisfy Ohm's law $\mathbf{j}_e = -\boldsymbol{\sigma}_e \nabla \phi_e$, and the continuity equation becomes

$$-C_m \frac{\partial V_m}{\partial t} = S_v^{-1} \nabla \cdot \boldsymbol{\sigma}_e \nabla \phi_e + I_{\text{ion}} \quad . \tag{6}$$

The complete system is generally written as

$$S_v^{-1} \nabla \cdot \boldsymbol{\sigma}_i \nabla \phi_i = C_m \frac{\partial V_m}{\partial t} + I_{\text{ion}} \tag{7}$$

$$\nabla \cdot (\boldsymbol{\sigma}_i \nabla \phi_i + \boldsymbol{\sigma}_e \nabla \phi_e) = 0 \tag{8}$$

and is known as the *bidomain equations* [22], [23]. These equations have to be solved simultaneously in the domain Ω_{active} representing the active tissue. No current can flow out of the intracellular medium through gap junctions, that is, a von Neumann boundary condition is used for Eq. (7).

If the anisotropy ratios are equal, *i.e.* if $\boldsymbol{\sigma}_e(\mathbf{x}) = \kappa\, \boldsymbol{\sigma}_i(\mathbf{x})$ where κ is a constant, the bidomain equations (7) and (8) can be decoupled. The linear combination $(\kappa+1)^{-1}\kappa \times$ [Eq. (5)] $-\ (\kappa+1)^{-1} \times$ [Eq. (6)] gives the *monodomain equation*

$$C_m \frac{\partial V_m}{\partial t} = S_v^{-1} \nabla \cdot \boldsymbol{\sigma} \nabla V_m - I_{\text{ion}} + I_{\text{stim}} \tag{9}$$

where the effective conductivity tensor is defined as $\boldsymbol{\sigma}^{-1} = \boldsymbol{\sigma}_e^{-1} + \boldsymbol{\sigma}_i^{-1}$. An externally driven stimulation current $I_{\text{stim}}(t)$ is introduced to overcome the impossibility of applying stimulations from the extracellular space in this reduced formulation. No-flux boundary condition is used.

The monodomain propagation equation has been used widely when modeling an arrhythmia in the absence of external electric field (such as defibrillation). Its formulation is flexible enough to permit the incorporation of information about substrate properties and changes induced by a therapy (Fig. 4). Propagation patterns simulated by the monodomain model have been shown to match those obtained using the bidomain model [24].

C. Electrical Signals

Electrodes placed on the surface of the heart record the extracellular potential. This extracellular field is directly computed in the bidomain framework. In the monodomain case, Eq. (6) is solved using V_m and I_{ion} as obtained from the solution to the monodomain equation (9). Assuming an infinite uniform isotropic volume conductor, the signal of an electrode (unipolar electrogram) at location $\mathbf{x}$ close to the atrial surface is approximated by [25]:

$$\phi_e(\mathbf{x}, t) = \frac{1}{4\pi\sigma_e} \int_{\Omega_{\text{myo}}} \mathrm{d}\mathbf{y}\, \frac{\nabla \cdot \boldsymbol{\sigma}\, \nabla V_m(\mathbf{y}, t)}{\|\mathbf{x} - \mathbf{y}\|} \tag{10}$$

Extension of this formula to take into account the finite size of the torso as well as its inhomogeneity (lung, blood cavity) enables the computation of the atrial electrical activity as manifested on the torso (electrocardiograms) [26], [27].

D. Geometry and Structure

The construction of an anatomical model of the atria involves the following steps:

1) Geometry acquisition: The simplest method consists of creating a model reproducing approximately the morphology of the atria (two spheres) as well as its topology (holes corresponding to the insertion of veins and valves). The first models followed this approach [28]–[31]. Three-dimensional models designed for anatomy education also proved to be a useful source of geometrical data [32]. Medical imaging modalities made it possible to generate more realistic and possibly patient-specific geometries. Magnetic resonance imaging was used for that purpose [33], [34], as well as computer-aided tomography [35] and the dataset resulting from the Visible Human project [36]–[39]. Recent advances in high resolution imaging suggest that anatomical and histological data may be combined to create models of cardiac structure at the para-cellular scale [40], [41]. Table I lists the main published anatomical models of the atria. Some of them are illustrated in Fig. 5.

2) Comparison with normal atrial dimensions: Despite advances in segmentation techniques, determining whether a piece of tissue belongs to the working atrial myocardium based on image data is a difficult task, especially in the regions around the veins and valves, due in part to the thinness of the atria. It is therefore recommended to compare the dimensions of the model with reference anatomical data, such as the volume, extent and diameter of the left and right atria [45], [46], the size of the valves [45], [47], [48] and veins [45], [49]–[51], and if necessary correct the model to reflect as much as possible a given anatomical configuration.

3) Wall thickness: Reproducing realistic wall thickness can be challenging because anatomical information on the atrium remains scarce. To date, experiments, especially on atrial activation, have been bi-dimensional in nature. As a result, several studies neglect the three-dimensional effects and consider the atrial tissue as a 2D-surface embedded in a 3D space (denoted by Surf-2D in Table I). The atrial wall is parchment-like [52], with reported thickness around 0.2 mm [47], in the range 0.5–3.5 mm [53], and up to 3–5 mm in some part of the left atrium [54]. Disease, hypertrophy or structural remodeling may also affect wall thickness. For instance, patients with AF have been shown to have a thiner wall in the pulmonary veins region (2.2 ± 1.0 mm vs 2.6 ± 1.0 mm [55]).

4) Fast-conducting bundles and interatrial connections: The atria have a complex morphology due to the blood vessels and valves forming non-conducting regions. In addition, the structure contains a system of fast-conducting fiber

TABLE I
ATRIAL ANATOMICAL MODELS IN THE LITERATURE

Reference	Dataset	Domain	Mesh	Figure
Gray *et al.* [28]	two spheres	3D	cubic	
Ellis *et al.* [42]	icosahedron	Surf-2D	honeycomb	
Dokos *et al.* [30]	two spheres	Surf-2D	triangular	
Blanc *et al.* [29]	"peanut"	Surf-2D	structured	5A
Harrild *et al.* [32]	visualization model	3D	hexahedral	5D
Vigmond *et al.* [31]	computer generated	3D	interconnected cables	
Ridler *et al.* [35]	CT of canine atria	3D	interconnected cables	5C
Virag *et al.* [33]	MRI of human atria	Surf-2D	triangular	
Jacquemet *et al.* [26]	MRI of human atria	3D	cubic	5B
van Dam *et al.* [34]	MRI of human atria	Surf-2D	triangular	5E
Kuijpers *et al.* [43]	MRI of human atria	Surf-2D	triangular	5G
Wieser *et al.* [44]	MRI of human atria	Surf-2D	triangular	5H
Freudenberg *et al.* [37]	Visible Female	3D	cubic	
Seemann *et al.* [39]	Visible Female	3D	cubic	5F
Zemlin *et al.* [38]	Visible Female	Surf-2D	triangular	

MRI = magnetic resonance images; CT = computer-aided tomography;
3D = tridimensional domain; Surf-2D = 2D-surface embedded in a 3D space.

bundles to facilitate the conduction throughout the atria, and in particular between the right and the left atrium. These anatomical structures also affect the wall thickness. In the right atrium, the crista terminalis plays an important role in determining the circuit of atrial flutter [56]. The pectinate muscles, located in the epicardial side of the right atrium free wall, may provide a pathway for reentry through the bridges they create between distant regions [57]. Interatrial connections are crucial for both normal and abnormal rhythm. The Bachmann's bundle (anterior interatrial route) connects the region near the sinoatrial node to the anterior left atrial wall and is the natural pathway for normal activation. Conduction between the atria can also occur at the septum around the fossa ovalis, sometimes further subdivided into the antero-superior and postero-inferior septa [58]. Another route to the left atrium is through the muscular sheath of the coronary sinus (posterior interatrial route) [59], [60]. This connection can help forming macroreentrant circuits [31]. Note, however, that all these structures are patient-dependent (large inter-patient variability of their dimensions) and not ubiquitous [61].

5) Anisotropy of the working myocardium: The fast-conducting bundles are a source of anisotropic conduction. Electrophysiological studies have described anisotropic propagation in these bundles, for instance the crista terminalis [62], [63]. For the rest of the working myocardium, the fiber orientation is known only approximately, due to the difficulty of applying techniques such as diffusion tensor imaging (particularly in humans) to the thin atrial wall. Although sparse information from histological studies [52] was sufficient to introduce gross fiber structure in computer models [31], [38], [64], [65], accurately modeling the atrial fiber architecture over the whole atria is still a work in progress [66].

6) Meshing the computational domain: The last step is the generation of the computational mesh describing the atria geometry and structures. The type of mesh used (structured vs unstructured, for instance) is determined by the desired flexibility for describing the domain, especially in the presence of additional structures such as bundles. This choice is also influenced by the efficiency of available numerical methods for this type of mesh (node numbering, matrix bandwidth, number of nearest neighbors).

E. Specifying the Arrhythmogenic Substrate

In the framework of the monodomain approximation, once the computational domain is defined, two terms of Eq. (9) can be altered to make the substrate arrhythmogenic: the diffusion term ($\boldsymbol{\sigma}$) or the membrane kinetics (I_{ion}). Note that the geometry itself may also be an arrhythmogenic factor, as in the case of dilatation/hypertrophy.

1) Conduction Properties: In most models, conduction properties ($\boldsymbol{\sigma}$) are set to a uniform value in the working myocardium. An exception is within fiber bundles such as the Bachmann's bundle for which higher tissue conductivity should be used [32]. Another possibility is the incorporation of regions of slow conduction. The conductivity values are generally selected to reproduced conduction velocities measured *in vivo*.

2) Repolarization Dynamics: Changes in ionic currents can have a great macroscopic impact on the dynamics of depolarization waves and spirals, and on the occurrence of conduction blocks and reentry. The purpose of including these changes in a model is to reproduce diseased, remodeled or genetically modified cells, natural variability, or regional heterogeneities [18], [19], [39], [67], [68]. Such alterations of the membrane kinetics are typically studied systematically in a simplified geometry (1D or 2D) with uniform properties, and then integrated into a large scale model. The maximal conductances of selected ion channels are tuned to reproduce experimental data, notably action potential shape, duration, and dynamics (restitution). The identification and the range of changes in conductance of target currents is based on patch clamp data as far as possible. The optimization procedure can be performed manually, using a gradient descent-based [69] or genetic algorithm [70]. Reduced models are more flexible for such parameter estimation [68], [71].

F. Solving the Equations

In the monodomain case, the parabolic partial differential equation (9) has to be solved. Spatial discretization can

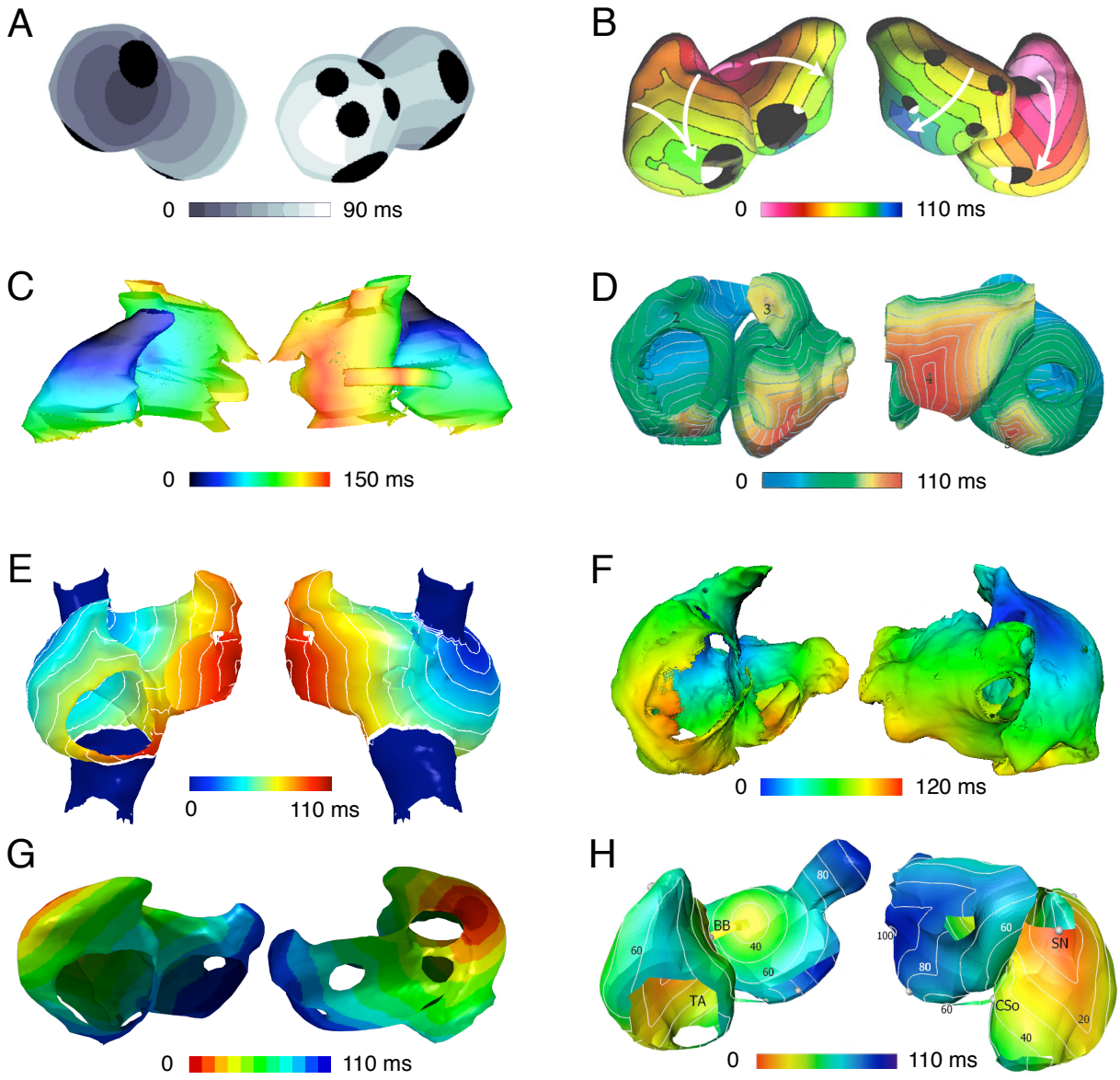

Fig. 5. Geometrical models of the human atria (except panel C which is canine). Anterior (left side of each panel) and posterior views (right side) are shown. Activation time during normal sinus rhythm is color coded. (A) Reproduced with permission from Blanc *et al.* [29]; (B) Reproduced with permission from Jacquemet *et al.* [26]; (C) Figure provided by E. J. Vigmond, based on Ridler *et al.* [35]; (D) Reproduced with permission from Harrild *et al.* [32]; (E) Figure provided by P. van Dam, based on van Dam *et al.* [34]; (F) Figure provided by F. M. Weber, based on Seemann *et al.* [39]; (G) Figure provided by N. H. L. Kuijpers, based on Kuijpers *et al.* [43]; (H) Reproduced with permission from Wieser *et al.* [44].

be performed through standard finite volume (difference) or finite element methods. Such methods have been described in the context of cardiac electrophysiology for cubic [71]–[73], triangular [74]–[78] and hexahedral meshes [79]–[81].

The number of computational nodes needed for a 3D atrial mesh with a resolution of about 300 μm is of the order of 1 million. An accurate description of microstructure would require many more nodes. Next, the time step is at most around 20 μs, which translates to 1 million steps to simulate 20 s of an arrhythmia, a duration required to assess the maintenance and stability of this arrhythmia, compute statistics describing cardiac dynamics (cycle lengths, lifespan of wavelets, etc.) and generate sufficiently long signals for applying the signal processing techniques used in experiments. With the use of Markov models becoming increasingly popular, even smaller time steps are often required to correctly handle the fast kinetics of their reactions. In total, the workload of one simulation includes about 10^{12} updates of the (20 or more) variables of a cell model.

As a result, simulating an atrial arrhythmia is computationally challenging. With today's computer power and parallel processing capabilities [82]–[84], however, the simulation is tractable. Good scalability properties have been recently demonstrated using up to 4096 processors [85] and up to 2 billion nodes [86].

G. An Example of Simulation of Atrial Fibrillation

To illustrate the development of a computer model of AF, this section provides an example of such a model based on the geometry presented in Virag *et al.* [33]. This geometry consists of a surface discretized by a triangular mesh comprising approximately 100,000 nodes. Propagation was described by the monodomain equation (9) along with the no flux boundary condition at the location of vein and valve openings. Membrane kinetics, that is, the term I_{ion} in (9), was based on the Courtemanche *et al.* model [15]. The conductivity tensor $\boldsymbol{\sigma}$ in (9) was uniform and isotropic, such that the conduction velocity was 70 cm/s during normal rhythm.

In order to create a substrate for AF, patchy heterogeneities (spatial scale: 2 cm [64]) in action potential duration (APD_{90}) were introduced by modifying the intrinsic local membrane properties. The channel conductances associated with the ionic currents I_{to} , I_{CaL}, I_{Kur}, and I_{Kr} (see Figs. 2 and 3) were altered by factors 0.2, 0.7, 0.1, and 1.5, respectively, in the patches and by factors 3, 0.5, 1, and 3 elsewhere. This resulted in an APD_{90} distribution of 195 ± 15 ms (range: 150–230 ms) during normal rhythm [87]. Sustained AF was induced by applying rapid pacing (cycle length: 150 ms) during 11 s to the appendage of the left atrium. The pacing site was located in a region with short APD_{90}, close to a large gradient in refractoriness, as inspired by the dog study by Fareh *et al.* [88].

Figure 6 shows the simulated AF initiation mechanism as well as the dynamics of self-perpetuating AF. The first wave break occurred after the fourth stimulation (Fig. 6A), where the gradient in refractoriness was sufficiently large to block propagation toward the region with longer APD (Fig. 6B), leading to a figure-of-eight reentry (Fig. 6C) interacting with further stimuli (Fig. 6D). Similar wave breaks generated through the same mechanism were observed several beats later in the right atrium (Fig. 6E–F). After the pacing protocol was stopped, simulated AF lasting for at least 20 s was observed as 3–6 wave fronts, propagating and interacting over the atria with a wavelength of 7.6 ± 1.2 cm and undergoing wave breaks at the location of large gradients in refractoriness [87].

This example illustrates how a mechanism suggested by an animal experiment (here the arrhythmogenic effect of gradient in refractoriness [88]) can be isolated and studied separately in a computer model. It also suggests further numerical experiments that could be performed (*e.g.*, changing the strength of the gradient in refractoriness, the conduction velocity, etc.) that could impact the characteristics of the simulated AF.

IV. Using Models to Study Different Mechanisms of Arrhythmia

As argued by Efimov *et al.* [89], after more than a century of research inspired by the concepts formulated by pioneers like Garrey [90], Mines [91], Lewis [92] and others [89], [93], the central questions about AF remain essentially the same: Is AF myogenic or neurogenic in nature? Is AF maintained by reentry or by focal activity? Is AF maintained by a single source, or are multiple sources required? Is there a critical mass of myocardium required to maintain AF? And how often is it a combination of all these conditions?

The application of computer modeling to these questions started in the 1960s, when Moe *et al.* proposed a cellular-automaton model of AF [94] that supported the multiple wavelet hypothesis, a conceptual description postulating that AF perpetuation relies on several independent wavelets randomly propagating in the atria [95]. Since then, different computer models ranging from a single cell to a full organ have been developed to investigate some of these questions. The structure of this section reviewing those models intentionally follows that of the review by Nattel *et al.* [93] that presented the clinically relevant mechanistic insights from animal models, to emphasize how computer models have played a complementary role in the study of AF.

A. Macroscopic Mechanisms

1) Stable circuits: To our knowledge, the first example of reentry in a 3D atrial geometry (two connected thin spherical hulls similar to Fig. 5A) was performed by Gray *et al.* [28]. An anatomical reentry was simulated, in which the reentrant wavefront was anchored at both the inferior vena cava and the tricuspid valve. This simple model illustrated the importance of anatomy (topology in particular) in determining the pathway of reentry.

Fiber bundles are another important element creating additional reentries pathways. For pectinate muscles, two roles have been identified through computer modeling: they may act as a ridge or as a bridge [57]. In the first case, local variations in wall thickness increase the load and facilitates wavebreaks, but also spiral anchoring around the ridge, which may be a possible explanation for conversion from AF to flutter-like activity [57]. A more recent simulation in a branching tissue confirmed the stabilization of rotors near the insertion of a bundle [96]. In the bridge case, two distant locations in the right atrium are connected by an alternative (usually faster) pathway. This bridge-like structure may form a reentrant circuit [57]. It could also destabilize the reentrant activity by acting as a delayed distant stimulation [28].

Other anatomical structures were identified as preferential pathways for reentry. Anisotropic conduction in the crista terminalis was a key element for the simulation of atrial flutter by Harrild *et al.* [82] (Fig. 5D), in agreement with noncontact mapping data in humans [56]. Ellis *et al.* reported occurrences of atrial flutter in a simplified computer model of the right atrium when transverse connections in the crista terminalis were uncoupled [42]. This observation was confirmed by Vigmond *et al.* in a more realistic canine atrial model with reduced transverse coupling in the crista terminalis [31]. In the same study, reentries were induced by an ectopic beat at several locations in the right and left atrium, leading to different reentrant circuits. Simulations revealed inter-atrial reentry pathways through the sheath of the coronary sinus, in addition to reentries around natural obstacles (vena cava, valves) and figure-of-eight functional reentry in the right atrium where a sufficiently large obstacle-free area is available. The importance of these bundles was assessed by analyzing how propagation was affected when removing them from the structure [31].

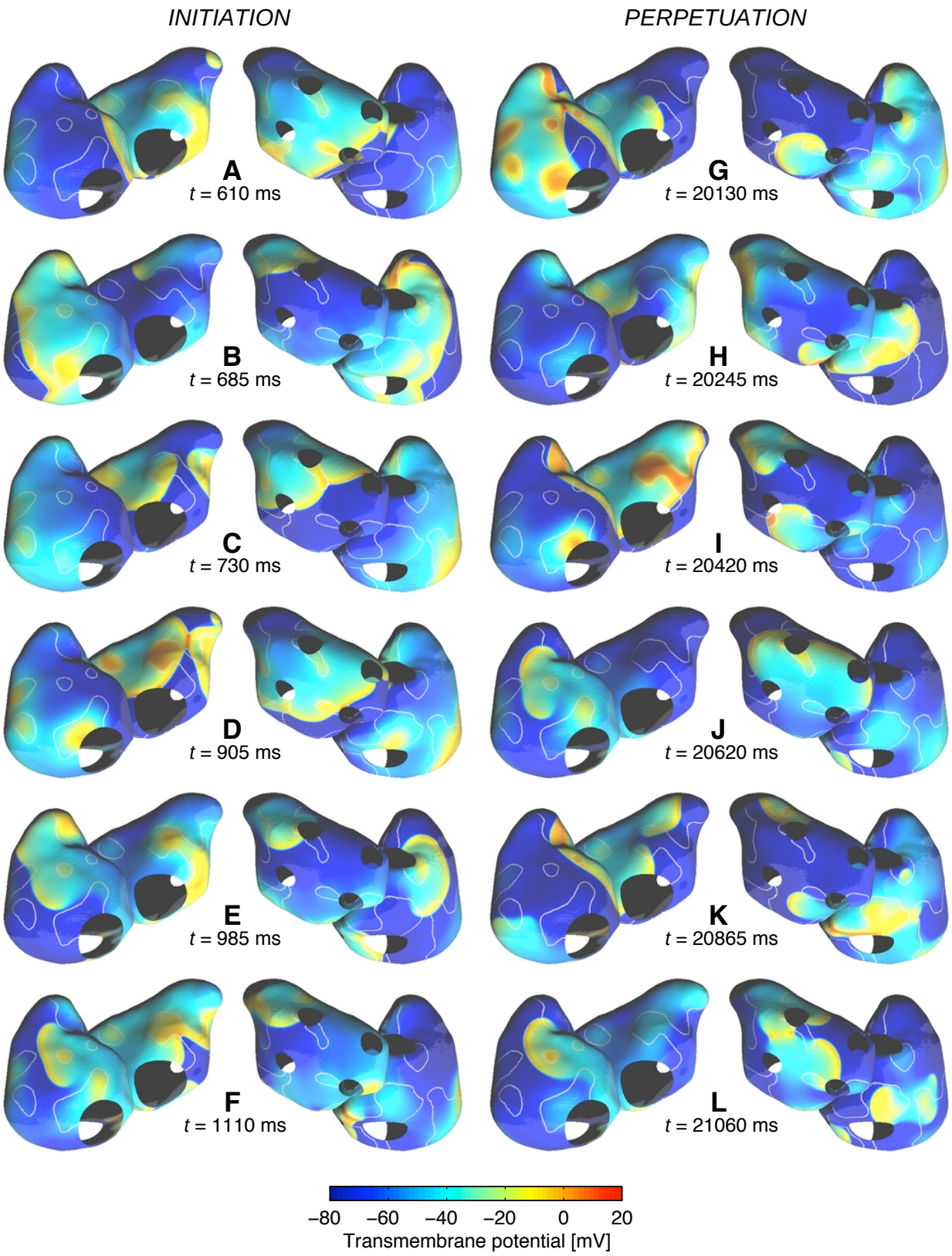

Fig. 6. Example of initiation and perpetuation of atrial fibrillation in a computer model. Membrane potential maps are color coded. White curves on the atrial surface mark the transition between regions of shorter and longer action potential durations (intrinsic ionic heterogeneity).

Identifying the reentrant pathways associated with anatomical structures is relevant because more complex rhythms like AF may combine several such reentries in addition to functional ones. Moreover, conversion or degeneration to AF may occur when a reentrant circuit becomes unstable.

2) Unstable Circuits and Atrial Fibrillation: A key requirement of an AF computer model is the capability of generating multiple wavefronts or wavelets that are self-sustaining. One possible source of instability and wavelet breakup is a steep restitution curve (this means significant beat-to-beat variations in Surf-2D at fast irregular rate) [97]. While spontaneous breakup has been associated with an increase in the slope of the restitution dependence, AF is usually associated with a loss of rate adaption and general flattening of the restitution dependence [19], [98]. There is also some theoretical evidences that restitution-based breakup may be transient, suggesting that other factors are needed to maintain the arrhythmia [99]. However, relatively steep restitutions (slope$>$1) have been measured in the human atria [100]. Its main consequence, repolarization alternans, has also been reported in rabbit pulmonary veins [101], in a sheep model of pace-induced AF [102], and in patients during the transition from flutter to AF [103].

Computer models have been developed to study the initiation and maintenance of AF in uniform, structurally healthy atria with different restitution properties. These models constitute a simple paradigm for investigating multiple-wavelet AF in an atrial geometry. In a peanut-shaped model (Fig. 5A), Blanc *et al.* [29] initiated a fibrillatory activity by applying 3 ectopic stimulations. Simulated AF was observed as 2 to 6 wavelets randomly propagating through the atrial surface. The presence of obstacles (veins and valves) affected the local activation rates were by promoting anatomical reentries, as shown by simply "filling the holes" (removing the obstacles) [104]. Qualitatively similar results were obtained by Virag *et al.* in a more realistic atrial surface (Fig. 5B) [33]. A steeper restitution was associated with a higher vulnerability to AF induced by burst-pacing. The initiation mechanism was identified as local repolarization alternans combined with non-uniform geometry [33]. Simulated AF, however, was usually not sustained in this structurally normal model, in agreement with Qu demonstrating that dynamical instability promotes wavebreaks but facilitates spontaneous termination of fibrillation [105]. Self-terminating simulated restitution-based AF episodes lasting for up to 5 minutes have been encountered [106]. This suggested that although some instability is needed to induce AF, a mechanism stabilizing the dynamics is necessary for permanent AF. Some stabilization can be achieved by abruptly remodeling the cells (flattening the restitution curve) [33], but other mechanisms (such as the effect of vagal action or structural remodeling) are expected to be involved. An important limitation of those models was the use of the modified Luo–Rudy model [10], [33] which overestimated beat-to-beat variations in action potential duration, resulting in a too broad histogram of local beat-to-beat intervals as compared to human mapping data [107].

More realistic histograms of local rates were obtained using a modified Courtemanche model in which the maximum restitution slope was made slightly $>$1 [64], [108]. By applying a ramp pacing protocol in the left atrium, Jacquemet *et al.* [64] initiated a fibrillatory activity consisting in 1 to 3 macroreentrant meandering wavelets with an average cycle length of 240 ms. Transient repolarization alternans was the main source of instability. Although episodes lasting $>$20 s were simulated, most of them self-terminated within 5–10 s [109]. Using similar membrane kinetics and the Harrild *et al.* atrial geometry [32] (Fig. 5D), Gong *et al.* applied a train of 10 ectopic stimuli after a normal activation and reported the vulnerability window for flutter and AF induction [108]. Ectopic foci created spatial dispersion in refractoriness, discordant alternans and eventually conduction block leading to reentry. Different macroreentrant circuits (typical and atypical flutter) were identified that depended on the location and the firing rate of the ectopic activity. In about one third of the cases, flutter spontaneously converted to AF; that is, to multiple wavelets simultaneously meandering in the atria [108]. These AF episodes tended to be unsustained as in Jacquemet *et al.* [64]. Similar unstable flutter circuits were encountered by Dang in another model also including fast conducting bundles (Fig. 5B) [106].

3) Multiple Wavelet Atrial Fibrillation: The multiple wavelet hypothesis of AF postulates that perpetuation of AF relies on several independent wavelets randomly propagating in the atria. Wavelet fractionation, collisions and coalescence would ensure the maintenance of a sufficient number of wavelets like a turbulence process [110]. Arrhythmogenic factors are expected increase the number of wavelets [107], [111] while therapeutic interventions should aim at reducing this number [112], [113]. The computer models of AF presented so far were based on anatomical data of young healthy subjects and involved only limited changes to the ionic channels. They do, however, provide an appropriate general framework to study multiple wavelet AF within a large continuous working myocardium including anatomical obstacles. In this context, wavelength (= conduction velocity $\times$ action potential duration) consistently played a major role in the inducibility and maintenance of AF. The design of a model of AF is constrained by the necessity to have a sufficiently short wavelength to enable the simultaneous coexistence of several wavelets. For a given geometry, there appear to be a critical wavelength above which no complex activity relying on multiple wavelets can be sustained for more than a couple of seconds [87], in agreement with experimental [114] and clinical data [115], [116].

Sustained AF in computer models is generally defined as $>$5–20 s. In contrast, the definition of persistent AF for clinicians is $>$7 days [2], a value far beyond the durations that can be simulated in today's computers. Even so, spontaneous termination appears to be a consistent feature of multiple wavelet AF observed in computer models with uniform properties and restitution-based mechanisms. Note that this conclusion is consistent with clinical experience in humans. Aggressive stimulation protocols in normal hearts initiate AF in most cases, but the episodes last just a few seconds before spontaneous conversion to sinus rhythm. The next subsections will investigate other possible mechanisms

that could stabilize or organize the complex dynamics in order to account for the long term maintenance of the arrhythmia.

B. Ionic Mechanisms

As the disease progresses from paroxysmal to persistent AF, atrial tachycardia induces ionic remodeling, a pathophysiological adaptation of the atrial cells to the fibrillatory rhythm, presumably due to intracellular calcium overload [117]. Other diseases, such as inflammatory conditions or congestive heart failure, can also lead to remodeling [118]. Electrophysiological remodeling typically involves changes in ion channel density. Computer models provide a tool for predicting the macroscopic effect of remodeling myocytes, for example down-regulation of specific ion channels as identified by patch-clamp recordings. None of the models developed so far actually simulates the remodeling process as a time dependent evolution. Rather, the arrhythmogenicity of the substrate is assessed before and after remodeling, or abrupt (instantaneous) remodeling is introduced [33].

Courtemanche *et al.* proposed a modification of their mathematical model to account for the reduction in action potential duration and rate adaptation observed in remodeled cells [19]. The effect of additional ion channel blockade was investigated. Subsequently, research groups explored different ways to remodel ion channels in order to reproduce in a model experimental data from various sources [64], [87], [108], [119]–[121]. The goals were always the same: (1) reducing the effective refractory period by modulating ion channels in order to shorten wavelength and therefore increase the likelihood of reentry; (2) stabilize reentries to promote sustained fibrillatory activity. For instance, Pandit *et al.* [120] studied functional reentry in a 2D model of atrial tissue remodeled by chronic AF. In this model, sustained rotors were observed and specific ionic targets for inducing rotor termination were identified (I_{Kur} and I_{to}). The model also showed that increasing the magnitude of the inward rectifier K^+ current (I_{K1}) resulted in a further stabilization of the rotor, as manifested by a reduced meandering.

Atrial dilation or stretch exerts a mechano-electric feedback on cardiomyocytes through stretch-activated ion channels. This interaction can aggravate AF vulnerability by inducing after-depolarizations, shortening refractory periods, slowing conduction velocity, or increasing their spatial dispersion [122]. Conversely, AF vulnerability may be reduced by stretch-activated channel blockers [123]. Kuijpers *et al.* [124] added a stretch-activated channel to the Courtemanche *et al.* model. For model parameters corresponding to acutely dilated atria, the resting potential was elevated and the upstroke velocity was reduced. Slower conduction velocity and conduction blocks caused by the mechano-electric feedback were observed in a 1D strand of cells [124]. An extension to a geometrical model of the atria confirmed these results [43]. Under stretch, a single focal source (cycle length: 600 ms) in the pulmonary veins initiated a reentrant wave after a few beats due to heterogeneity in tissue thickness that gave rise to spatial variations in stretch and effective refractory period [43].

C. Role of the Autonomic Nervous System

Even in the early analysis of the mechanisms of AF by Garrey [90], the parasympathetic nervous system was believed to play a role in creating a substrate for AF. The vagal form of AF was hypothesized to originate in the spatial heterogeneities in refractoriness resulting from the inhomogeneous effect of vagal stimulation [125], [126]. Through the release of acetylcholine, vagal stimulation causes a significant reduction of effective refractory period and a loss of rate adaptation [125], [127]. Indeed, several experimental models of AF involve direct exposition to acetylcholine [128].

Kneller *et al.* [20] proposed a mathematical formulation for an acetylcholine-driven potassium current $I_{\mathrm{K(ACh)}}$ in a canine atrial cell model based on the Courtemanche model [18]. In a 2D anisotropic sheet of atrial tissue, periodic variations of acetylcholine concentrations were introduced and the stability of reentry or the possible occurrence of fibrillatory activity was studied. Conditions were found for which inhomogeneous acetylcholine concentration induced sufficiently large gradients in refractoriness to break the initial spiral and lead to a cholinergic form of AF. When AF was sustained, fibrillatory activity was usually maintained by a mother rotor acting as a source of wavelets. The other wavelets were short-lived. Thus, despite the absence of beat-to-beat variations in refractoriness, AF could be initiated solely by spatial heterogeneity. A manifestation of the stable rate driven by the mother rotor was a clear dominant frequency in the electrograms.

In the absence of anatomical reentry, such as in a 2D sheet geometry, the substrate size has a major impact on the maintenance of fibrillatory activity [129]. The extension of the Kneller *et al.* model to an atrial geometry enabled the study of both functional and anatomical reentries in the presence of vagal action. A detailed analysis of the vulnerability window for ectopic beats in 3D canine atrial model by Vigmond *et al.* [130] (Fig. 5C) revealed that anatomical structures (veins and valves, coronary sinus sheath, and size of the tissue) constrained the pathways of reentries induced by zones of increased acetylcholine concentration. Different combination of anatomical and functional reentry (single rotor, figure-of-eight, purely anatomical reentry and sustained quasi-stable reentry) were observed.

Increasing the size of the tissue to that of the human atria leaves more space for functional reentries, as suggested by similar models of cholinergic AF implemented on a human atrial geometry [87], [109], [131]. In these simulations, a mother rotor in the left atrium appendage lasting for >10 s was the primary source of wavelets. This rotor was functionally anchored at a heterogeneity associated with longer refractory period. Spatio-temporal organization during sustained AF [87] was consistent with the experimental data from Berenfeld *et al.* [132]. However, since the majority of the data used in computer models come from canine experimental models, the relationship to human conditions needs to be determined.

D. Role of Regional Factors: Pulmonary Veins

Invasive electrophysiological studies have identified a subform of AF with focal origin located in the region around

the pulmonary veins (PVs) [4]. The electrophysiological properties of the cardiomyocyte sleeves of the PVs have been investigated and different mechanisms have been proposed to explain why PVs are an important source of ectopic foci [133]. Animal experiments suggest that spontaneous firing in PVs may be related to ion kinetics (automaticity, early/delayed afterdepolarization or Ca^{2+} release-related mechanisms, less negative resting potential), structure (abrupt variations in fiber orientation, fibrosis) and higher vulnerability to (micro-)reentry (shorter APDs, slow conduction) [93].

Computer models have been designed to test these mechanisms of ectopic activity. In order to induce automaticity, Kuijpers *et al.* [134] added an hyperpolarization-activated inward current (I_{f}) to the Courtemanche *et al.* model [15] to reproduce increased expression, which is possible under pathological conditions [135]. Fibrosis was incorporated as random uncoupling of transverse cell-to-cell connections. Reduced global conductivity, increased degree of fibrosis and higher I_{f} expression promoted automaticity with firing rates in the range 1300 to 1600 ms. More recently, Seol *et al.* developed a cell model exhibiting automaticity (cycle length: 535 ms) based on patch clamp measurement of isolated cardiomyocyte from rabbit PV sleeves [17]. Other simulations showed that spontaneous activations may arise due to differences in resting potential between left atrial myocytes and PV sleeve myocytes or coupled fibroblasts [136]–[138], at cycle lengths around 500 ms, down to 140–400 ms in extreme conditions.

In all but the extreme cases, the cycle length of spontaneous excitation was much longer than the effective refractory period of the atrial tissue. Typical cycle lengths of ectopic sources, as measured in patients undergoing catheter ablation, revealed significantly higher rates. In the simulation study of Gong *et al.*, no reentry could be initiated by repetitive excitations of the PVs when the cycle length was longer than 470 ms [108]. This suggests that other mechanisms are contributing to explain higher frequency sources, such as early/delayed afterdepolarization [139] or microreentry in the PV. While early afterdepolarization in atrial tissue has not been simulated yet to our knowledge, numerical experiments in a model of ventricular tissue shows that early afterdepolarizations can trigger or reinitiate reentrant wavefront [140]. The possibility of microreentry within the PV was explored by Cherry *et al.* [68]. In computer models of PV with varying diameter and sleeve length, longitudinal and transverse cell-to-cell connections were randomly removed to reproduce tissue structure observed histologically. Under appropriate conditions, premature atrial activation initiated unsustained (train of ectopic activations) or sustained ($>$2 s) microreentry. The prevalence of microreentry was higher for longer PV sleeve and depended critically on coupling properties. Microreentry cycle lengths were in the range 200 to 250 ms.

Another approach to study ectopic foci is to assume that a stable source of wavelets is present and to implement it by periodically injecting intracellular current at the presumed location of the focal source. Thus, the results becomes independent of the underlying mechanism triggering the focal activity. The relevance of this approach is supported by the absence of significant differences in cycle lengths between spontaneous and pacing-induced episodes of atrial tachyarrhythmias [108], [141]. Practically, sites of focal activity and their cycle lengths are selected based on clinical data. A train of stimuli is then applied to each site, simultaneously or not [108], [142], [143]. The success of arrhythmia initiation was found to depend on the location of the sites with respect to anatomical structures [108], [142] and repolarization heterogeneity [143]. When several ectopic foci are active at the same time, only a few apparent sources are present; the others are hidden because they fire during the refractory period of the surrounding tissue [143]. Simulated AF is clearly sustained at least as long as the focal activity is active [143] and enables fibrillatory dynamics with a longer wavelength than would be possible in a model purely based on multiple wavelet reentry, making it appropriate for modeling paroxysmal AF.

The complex fiber architecture in the PV region and the prevalence of fibrosis in the elderly support the hypothesis that microstructure plays a role in forming an arrhythmogenic substrate for AF. Simulations by Zemlin *et al.* showed that sharp transitions in conductivity generated by abrupt changes in fiber orientation may create a substrate for unilateral conduction block and reentry, even when the ectopic activity occurs at a slower rate than sinus rhythm [144]. Fibrosis also consists in abrupt changes in cell coupling, but at the microscale. Computer models have the ability to control fibrosis density and spatial distribution. Fibrosis is generally introduced as removal of cell-to-cell coupling or introduction of small inexcitable obstacles. Diffuse fibrosis was found to slow conduction, increase vulnerability to reentry, prolong the cycle length of reentry, and stabilize spiral wave [145], [146]. Another model showed the importance of spatial distribution of fibrosis. Tanaka *et al.* developed a 2D model representing a part of the posterior left atrium endocardium near the PVs, including structural and ionic remodeling as in AF associated with heart failure [147]. The dynamics and the cycle length of spiral wave reentry were governed by the interaction of wavelets with clusters of fibrotic patches of various sizes. Patchy fibrosis was more arrhythmogenic than diffuse fibrosis. While fibroblasts can couple to myocytes *in vitro* [148], the formation of fibroblast-myocyte gap junctions *in vivo*, either naturally or at some stage of structural remodeling, is still unclear [149]. Simulations suggest that when the two cell types couple, both impulse propagation velocity and repolarization can be modulated [150], [151]. In addition, excitability and spiral wave dynamics might be affected by this interaction [147].

E. Role of Left Atrium

The clinical outcome of catheter ablation therapy of AF suggests that the left atrium plays a particular role in AF. Experimental data support this hypothesis by demonstrating left-right differences in repolarization (shorter action potentials in the left atrium) [152] and in acetylcholine-dependent potassium current (larger channel density in the left atrium) [153]. Anatomical structure and bundles in the right atrium (crista terminalis, pectinate muscles, atrioventricular ring, appendage) were shown to have a different action potential morphology [18]. As a result of these left-right heterogeneities, a

gradient in atrial frequency was observed (faster rate in the left atrium) [154].

The most obvious difference between the left and the right atrium is the geometry and topology affecting the interplay between functional and anatomical reentries. In a simple geometry (Fig. 5A), it is possible to consider an identical left and right atrium in the absence of anatomical obstacles (which implies no anatomical reentry). In this case, cycle lengths are spatially homogeneous during AF, in contrast with the situation accounting for the vein and valve openings, in which obstacles tend to slow down the atrial rate while promoting reentry [104]. Based on the critical mass and multiple wavelet argument, the right atrium, which is larger in size, should have a more significant contribution to the maintenance of AF than the left atrium. Left-right ionic or structural differences need to be introduced in the computer model to reverse this effect.

The presence of a left-right gradient in action potential duration may help the left atrium drive the right atrium activity. Ridler *et al.* introduced smooth spatial variations in ion channel conductances to reproduce the prolongation in action potential duration along the pathway following normal activation [35]. This heterogeneity did not increase vulnerability to reentry induction, and even had some preventive effect. In a 2D rectangular tissue divided in two (right and left atrium), Atienza *et al.* simulated left-right differences in acetylcholine-dependent potassium current [155]. This resulted in faster rates in the left atrium, driven by a rotor, in agreement with their experimental data. The activity in the right atrium just followed that of the left whenever possible.

In the case of atrial hypertrophy or dilation [156], changes in volume may not be the same in the right and the left atrium, which may further strengthen left-right natural differences in intra-atrial pressure and wall stress (higher on the left). So far, dilation was implemented mainly as a scaling of the geometry [157]. In the future, geometrical models representing diseased atria need to be developed.

V. Using Models to Aid Diagnosis

Diagnosis of electrophysiological abnormalities is performed mainly through the analysis of electrical signals. The presence of an atrial arrhythmia is established by inspecting the standard electrocardiogram (ECG). Further classification is generally based on the duration of the arrhythmic event, previous history of arrhythmia, risk factors and response to therapy [2]. During catheter ablation procedures, endocardial electrograms are used to characterize the substrate, identify targets for ablation, monitor the progress and assess the success of the procedure.

The main objective of the application of computer modeling to diagnosis is to predict the changes in electrical potential time course caused by an alteration of the substrate, which enables a better interpretation of the signal waveforms. The signals generated by the models may also serve as benchmarks to evaluate the qualities and the weaknesses of biomedical signal processing techniques. Finally, computer models offer an easy way to explore new lead configurations that may help extract more information about the underlying fibrillatory dynamics. Along with the development of more detailed and patient-specific models, computer modeling is expected to play an increasing role in the interpretation of biomedical signals for diagnosis purposes.

A. Evaluation of Signal Processing Techniques

Signal processing tools have been developed to automatically analyze electrical signals (electrograms, ECGs) during an arrhythmia and extract some information about the progression of the disease [158]. Validating these techniques, however, requires some gold standard to compare with. Computer models provides such a standard since the substrate properties, wavelet dynamics and electrical signals can be all monitored.

Simulation studies, for instance, have demonstrated the correspondence between electrogram maximal derivative and local activation time, and have pointed out some limitations of this approach [159], [160]. In the case of more complex fractionated electrograms, double counting may arise, leading to an overestimation of the atrial rate [161], as confirmed by the comparison with monophasic action potentials in humans [162]. The increasing use of spectral analysis (dominant frequency in particular) to identify potential high frequency sources of AF [163] further illustrates the importance of signal processing for catheter ablation.

The models make it possible to simulate realistic atrial ECG signals as well as ventricular signals in the same model of the thorax, with the appropriate level of detail in volume conduction aspects [26]. Note that the atrial signals and the ventricular signals can be computed independently. The sum of these components may then be used to test procedures aiming at subtracting the ventricular involvement, with the simulated AF components serving as the gold standard [164]. Some recent developments in ECG processing techniques, such as cancellation of the ventricular activity [165], [166], vectorcardiogram analysis [167], estimation of the dominant frequency of the ECG [168] were validated in part by using signals originating from an atrial model combined with a torso geometry.

B. Interpretation of Signal Waveforms

During catheter ablation, electrograms form the working dataset for extracting information about the arrhythmogenic substrate that can be used to identify specific targets for ablation. Computer models can help in this procedure by giving some insights into the genesis of these signals and their link to local electrophysiological properties.

The origin of fractionated electrograms has been a topic of interest in computer modeling. In these models, electrogram fractionation was shown to arise due to discontinuity in conductivity or microfibrosis [64], [159], [169]–[172]. Electrogram morphology was also found to be affected by the underlying wavelet dynamics and tissue anisotropy [64], [109], and by zigzag conduction caused by fibrosis or patches of vagal stimulation [173].

Non-invasive assessment of atrial function through ECGs may also benefit from atrial model-based simulation of the P-wave [27]. For example, the elimination of the muscle

sleeves inside the pulmonary veins of a 3D atrial model was shown to result in a shortening of the P-wave [174]. Further model-based investigations of P-wave morphology may help determine the pathway of activation and the involvement of interatrial conduction bundles [175].

C. Optimization of Electrode Configurations

Because it is possible to compute electrograms or ECGs at any location in the computer model, simulations can be used to explore the effect of using different electrode configurations to facilitate diagnosis. There is growing evidence that the location of the nine electrodes of the standard 12-lead system is not optimal for studying AF [26]. Although using a vest with a large number of electrodes is feasible, it would be more convenient to move only some electrodes toward a more optimal position. Ihara *et al.* proposed a nine-electrode configuration dedicated to the analysis of AF that maximizes the information content extracted from the atria, while keeping five electrodes at their conventional position [176]. The optimization procedure used as a dataset the atrial component of body surface potential maps generated by a biophysical model of AF [26]. The same approach was followed to evaluate and design vectorcardiographic lead systems aimed at characterizing AF [177].

VI. Using Models to Design Effective Therapies

By using different simulated episodes of one or several mathematical models of atrial arrhythmias, established or novel therapeutic approaches can be tested. The main advantage is that the success of a therapy can be related to the substrate or to the mechanism maintaining the arrhythmia, simply because the underlying mechanisms are generally known and the electrical activity can be observed throughout the geometry.

Defining the success of a therapy using a computer model, however, is not straightforward. First, two different objectives should be attained: cardioversion (termination of the arrhythmia) and the absence of recurrence of the arrhythmia. In models, these two cases have to be tested separately. Second, clinical studies may consider the outcome as successful when the arrhythmia terminates within 48 hours. Such long simulations are definitely out of reach for today's supercomputers. Moreover, the mechanisms of this long-term process leading to termination after several days following the intervention remain unclear. In the modeling literature, a therapy is considered unsuccessful if a complex activity is still present 2 s (Reumann *et al.* [178]), ≈5 s (Kneller *et al.* [21]), up to 7.5 s (Reumann [179]), 8 s (Blanc *et al.* [180], [181]) or 30 s (Dang *et al.* [182], Rotter *et al.* [157], Ruchat *et al.* [183]–[185]) after its application. Another related limitation is the difficulty to demonstrate that the simulated arrhythmia was indeed sustained and would not have self-terminated after a few minutes or hours. Despite these limitations, the attempts at simulating therapies for atrial arrhythmias have demonstrated the potential of the *in silico* approach when combined to animal experiments and clinical trials. The simulation of three different therapeutic approaches will be discussed: pharmacological therapy, surgical/catheter ablations and electrical stimulations.

A. Pharmacological Approaches

In patients with AF, drugs are usually prescribed as the first step to control the ventricular rate (rate control). The action of these drugs is essentially on the atrio-ventricular node and has no direct interference with the fibrillatory process of the atria. Specific antiarrhythmic drugs are also used for pharmacological cardioversion (rhythm control). Additional drugs such as anticoagulants are often necessary to prevent severe side effects, notably thromboembolism and stroke. Antiarrhythmic drugs are effective in terminating AF in 47–84% of the patients with AF lasting less than 24h. For longer AF episodes, however, conversion to sinus rhythm is achieved only in 15–30% of the patients [2]. The electrophysiological mechanisms underlying the success or failure of these pharmacological therapies remain poorly understood [186]. As a result, new mechanistic insights may be used to improve AF management [186].

Antiarrhythmic drugs affect the dynamics of ionic channel gating. The simplest way to account for this effect in a model is to reduce the total ion channel conductance (constant channel blockade), exactly as if there were fewer ion channels [19]. This decrease in channel conductance can be quantified by a dose response curve expressed in the form of a Hill equation [20], [187]. The time constants of the channel may also be increased to slow down recovery from inactivation [187], [188]. Voltage-dependent blockades can be implemented using an additional gating variable [189], [190]. Finally, the most complete method is to develop a specific, drug concentration-dependent Markov model describing the interactions between the ion channel and the drug molecule [191].

Single cell models enable the ability to identify specific ionic target for drug therapy and determine the effect of a drug on the action potential morphology and dynamics [19]. However, predicting the efficacy of a drug on the heart based only on single channel or single cell data is often challenging. Certain drugs can give rise to unintended side effects [192]. For instance, while being effective at preventing recurrent AF, some drugs such as quinidine may promote ventricular arrhythmia [193].

It seems therefore desirable to study the effect of a drug in a piece of tissue sufficiently large to include the mechanism for triggering or maintaining the arrhythmia (inhomogeneity, structure, anatomical obstacles, focal source). This can be tested in both an animal model or a computer model. A key advantage of computer models in the drug discovery process, however, is their ability to test the efficacy of a drug that *would have* a given effect on a specific channel, even if no such drug is currently known. If convincing results follow, more effort could be invested in the search of a specific molecule before it is tested in animal experiments.

Simulations can provide insights into mechanisms that involve wavelet dynamics and thus could not be clearly deduced from single cell experiments, as illustrated by the case of Na^+ blockers (class I antiarrhythmic drug). Because the conduction velocity is slower after the delivery of the Na^+ blocker, the wavelength is shorter, creating free space for more wavelets, which is proarrhythmic. On the other hand, membrane ex-

citability is reduced in the reentrant circuits, resulting in a wider spiral core and more meandering wavelets [188]. The cycle length of reentry becomes longer, and eventually the number of wavelets tends to decrease [188], [194]. In a 2D mathematical model of cholinergic AF, Kneller *et al.* showed that AF termination could be achieved by pure sodium channel blockade [21]. In this model, the occurrence of fibrillatory conduction was closely related to the spatial length scale of the inhomogeneity in acetylcholine distribution [20]. The reduced excitability induced by the Na^+ blockade destabilized the mother rotor, which eventually drifted toward the boundary. Note that in these 2D models [21], [188], [194], anatomical reentry cannot occur. When propagating within the complex geometry of the atria, wavelets may anchor more easily to veins or valves due to their shorter wavelength, possibly leading to stable macroreentrant circuit reentry since no spiral core is anymore involved.

B. Surgical Maze and Catheter Ablation

To simulate both surgical and catheter ablation, lines are created at the anatomical locations suggested by an electrophysiologist (Fig. 7). In the model, tissue conductivity is then set to zero at the lines, forming barriers for impulse propagation [178], [182]. Imperfections in the ablation procedure can also be simulated by creating gaps in the line (incomplete lines [182]) or by limiting the depth of the lines (nontransmural lines [178]).

Early attempts by Blanc *et al.* to study ablation strategies in a computer model with a simplified geometry [29] revealed the importance of ablation lines in the right atrium [180], [181], [195]. Dang *et al.* [182] and Cherry *et al.* (personal communication, see also http://thevirtualheart.org) confirmed this outcome in more detailed 3D models with uniform properties. This result seems in contradiction with the everyday practice of electrophysiologists focusing on the left atrium as a target for ablation. However, a closer look at the simulated activity showed that the perpetuation mechanism relied on multiple randomly-propagating wavelets as well as short-lived reentries around the inferior vena cava [180]. This pathway was made ineffective by the right-atrium ablation lines. The lesson drawn from this first example is three-fold. First, there is an important difference between clinical and simulation studies: clinical studies usually treat a group of patients (this might mean different mechanisms) with the same therapy, while simulation studies test different approaches on the same type of fibrillation (this can be interpreted as trying all possible therapies on the same patient). Second, the model suggested that more effective therapies could be developed if the initiation or maintenance mechanism of the arrhythmia can be identified, as it actually happened for atrial flutter. Third, a better matching between the outcome of simulations and clinical statistics might be achieved by selecting an appropriate subgroup of patients whose disease would better correspond to the mechanism described by the models. For instance, in the Vincenti *et al.* study, although most episodes of paroxysmal AF found their origin in the left atrium, 15.3% were identified as originating from the right atrium based on the polarity of the ectopic P-wave recorded by Holter monitoring [196].

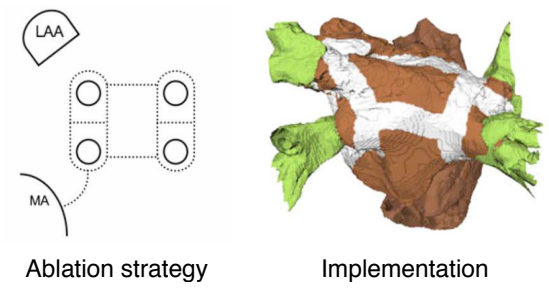

Fig. 7. *Left panel*: example of ablation strategy as seen by an electrophysiologist (LAA = left atrium appendage; MA = mitral valve annulus). *Right panel*: 3D representation of the implementation of the ablation strategy in a model of the atria (posterior view). Tissue targeted by catheter ablation is shown in white. Modified with permission from Reumann *et al.* [178].

Despite their limitations, computer models were still able to reproduce some results observed in clinical trials. Aggressive ablation strategies, such as the Maze III [197], were found to be the most effective when AF mechanism is based on a complex turbulent activity involving multiple wavelets, a situation presumably closer to chronic AF [182], [183]. Models have also proved useful to determine whether imperfections in an ablation line are sufficient to preclude the success of the therapy. Their advantage lies in the existence of a gold standard to compare with, namely ideal, perfectly transmural lines. In the Dang *et al.* [182] modeling study, imperfect ablation lines in the Maze III decreased the success rate by up to 28%, but this value depended critically on the anatomical location of this imperfection. Most failures were identified as atypical flutter around the mitral valve, a phenomenon also observed in the clinic [198].

Many of the recent efforts in RF ablation therapy target reentrant circuits or sources (ectopic foci) in the pulmonary veins, especially in patients with paroxysmal AF. Models have been developed, in which AF maintenance is ensured by several stable sources in the left atrium, implemented as groups of cells spontaneously firing in a predefined sequence [142], [199] or at a regular rate [143]. As expected, perfect isolation of these sources prevented AF reinitiation [178]. When some lesions were nontransmural (typically in the thicker areas of the left atrium) or when the ablation lines failed to circumscribe the sources, however, cases of AF recurrence were observed [178]. Therefore, the success rates in the model depended on how much information about the anatomy (such as tissue thickness) and the localization of the sources (of course, known by the model designers) were actually used in the planning of the ablation procedure [178]. In another study combining computer modeling and clinical data, Haissaguerre *et al.* analyzed the atrial fibrillatory cycle length (AFCL) in a model of AF driven by ectopic foci and in patients undergoing catheter ablation [143]. The progression of the atrial ablation therapy was monitored using the AFCL, a technique whose value has been demonstrated previously [200], [201]. In both the model and the patients, successive ablation of each active source tended to prolong AFCL until sinus rhythm was established, suggesting the hypothesis that AFCL is inversely associated with the number of active sources present within

the atria [143].

The ultimate goal would be to use computer models to systematically test new therapies before applying them in patients, similar to how simulation is used to design and test new products in the aeronautical or automotive industry. A step in this direction was made by Ruchat *et al.* after they developed a Minimaze, a simplified maze procedure for patients with permanent AF aiming at reproducing the excellent results of the Maze III operation with a lower risk [202]. A model was developed to retrospectively evaluate this idea [185]. When RF ablation was applied both to the endo- and epicardium, ablation lines were modeled as ideal lines. When only endocardial RF ablation was applied, a single 3-mm gap was introduced in the left isthmus line to mimic the effect of a nontransmural lesion. The conversion rates of permanent AF to sinus rhythm was similar in the model vs clinical data for both the nontransmural (65% vs 60%, $n = 20$) and the transmural Minimaze (88% vs 92%, $n = 26$) [185]. In both the model and the patients, occurrences of atypical flutter were observed in the case of imperfect ablation.

All these encouraging results motivate the future development of new patient- or disease-specific models of AF in order to more accurately predict the outcome of an ablation procedure. Models can not only give some idea about the success rate, but more importantly provide insights into the reason *why* it fails when it does, such as incomplete lines leading to atrial flutter.

C. Device Therapies: Atrial Pacing and Defibrillation

In patients with conventional indications for pacemaker implantation, atrial pacing has been shown to prevent AF [2], [203], [204]. Atrial flutter or single-circuit macro-reentries can be terminated by pacing, typically using an electrode in the right atrium appendage [205]. However, no pacing therapy has yet been shown effective in AF termination, probably due to its complex dynamics, the variable number of wavelets, and the shorter and variable excitable gap during AF. Computer models provide a tool to explore atrial therapies by electrical stimulations, to assess the feasibility of pace-termination of AF, and to help find the most appropriate electrode positions and pacing algorithms.

The basic mechanisms of flutter pace-termination have been studied in ring-shaped cable models in which a reentry was initiated [206]–[208]. The key was to stimulate in the excitable gap to elicit a unidirectional wave propagating in the opposite direction relative to the reentrant wave. When the pacing site is away from the reentrant circuit, inhomogeneities in conduction properties (presence of a zone of slow conduction) were shown to play a crucial role in determining the interval of pacing rates for which the pacing therapy succeeds [209], [210]. These observations were confirmed by Dang in a 3D atrial model [106]. With uniform and isotropic properties, (atypical) atrial flutter could not be pace-terminated, at least within the 20-s simulation time (note that therapy for atrial arrhythmias may accommodate for a much longer time if successful). In the same geometrical model, but including fast conduction in the crista terminalis and a zone of slow conduction in the cavo-tricuspid isthmus, typical atrial flutter was simulated and terminated by overdrive pacing either in the right atrium appendage or in the isthmus [106].

The possibility of local atrial capture during AF (see Fig. 8) has been demonstrated in animal and human experiments, although none of those experiments succeeded in terminating AF by pacing. Allessie *et al.* showed for electrically induced AF in dogs that it is possible to capture a region of atrial tissue with a diameter of about 6 cm by rapid pacing [211]. Daoud *et al.* was also able to capture a region of the human right atrium during electrically induced type I AF [212]. Pandozi *et al.* achieved local capture in patients with spontaneous chronic AF for 87.2% of the pacing sites, with a preference for the lateral wall over the atrial roof or the septum [213]. The phenomenon of local capture was reproduced in biophysical models of AF [106], as illustrated in Fig. 8. After 2–10 s seconds of pacing, the region under control reached a diameter of 4–6 cm for pacing sites in the right or left appendage, or in the right atrium free wall. In none of the models, however, could more than one atrium be controlled at a time for a single pacing site. The results depended on the type and complexity of AF. For organized forms of AF, results were similar to the flutter case. For complex forms involving mother rotors, pacing therapy was unsuccessful (the pacing site was distant from the rotor). In all the cases, decreasing pacing rate after reaching local control lead to a loss of control and eventually return to fibrillation [106]. In a preliminary study by Reumann in an anatomically-realistic sophisticated cellular automaton model of the atria [179], all attempts to prevent or suppress AF failed: 7.5 s after the pacing protocol started, the excitation patterns were still quasi-chaotic. Local control was only achieved when burst-pacing protocol (15-20 Hz in the right atrium free wall) was started before the premature beat triggering AF.

Since most techniques pace at a single site, it has been suggested that multi-site pacing could be more efficient in capturing both atria, and therefore leading to termination [214]. Preliminary tests in a computer model of AF featuring multiple wavelets reentries [106] suggest that controlling both atria is indeed possible by simultaneously pacing in the right and the left appendage. However, residual wavelets were generated at the collision interface between fronts coming from the two pacing sites, so that when the pacing rate was decreased or stopped, AF resumed [106].

Better control and higher adaptation capability are expected to be achieved by implementing closed-loop systems. In these devices, local information (*e.g.*, electrogram or monophasic action potential) could be used to decide when to trigger a stimulus [215]. This enables an automatic selection of the pacing rate based on the chaos control theory [216], whose application to reducing the complexity of cardiac fibrillation ("cardiac chaos") has been demonstrated [217], [218]. Computer models of the atria are ideal tools for assessing these new pacing algorithms for different forms of AF [106].

Another electrical therapy for the control or termination of AF is defibrillation. Atrial defibrillation can be performed in two different ways: at the hospital (electrical cardioversion) or using an implantable cardioverter-defibrillator device (ICD). For the latter option, the pain caused by the electrical shock is

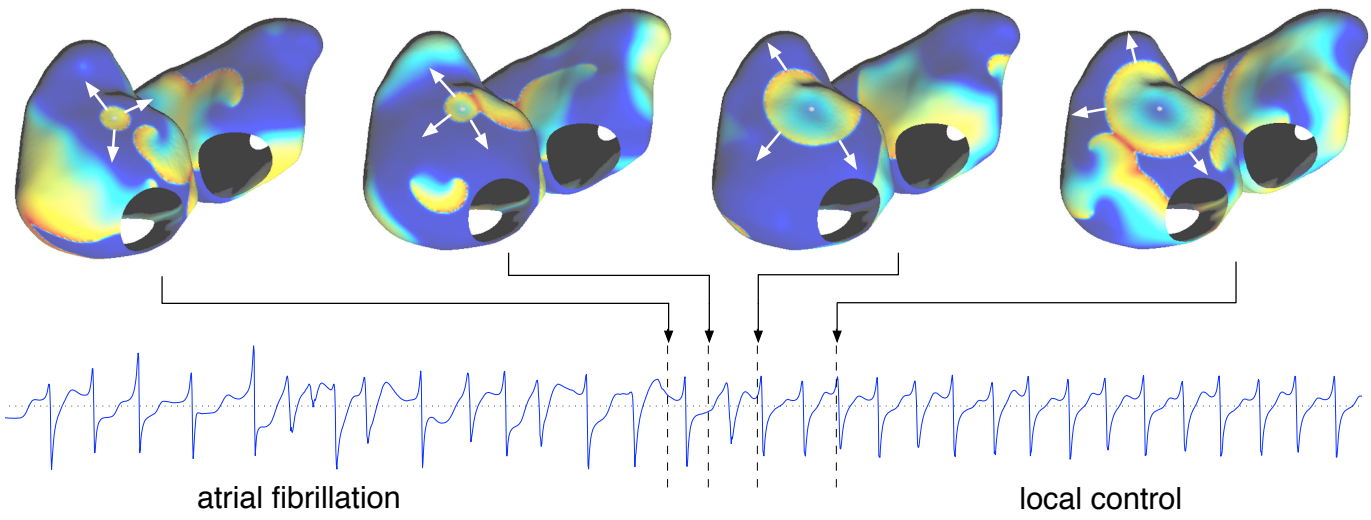

Fig. 8. Example of simulated antitachycardia pacing therapy. After 4 s of pacing in the right atrium free wall, local control is achieved. Membrane potential plots (anterior view) are displayed for different time instants. The electrogram shown is recorded in the right atrium appendage. Based on data provided by L. Dang [106].

an issue, but ICD-based electrical cardioversion of AF was shown to reduce the burden in patients having already an ICD for ventricular tachyarrhythmias [219]. Modeling atrial defibrillation is a very difficult task due to the effect of complex geometry with small wall thickness, fiber bundles [220] and the microstructure [221], [222]. Also, the use of the bidomain model (possibly surrounded by a conductive bath) is necessary to reproduce the effect of electrode stimulation. As a result, simulations of atrial defibrillation have been so far mostly limited to simple geometries. In a 2D model of atrial tissue, Kuijpers *et al.* showed how the loss of side-to-side coupling caused by fibrosis affects termination of reentry. A larger fibrosis density was associated with a higher success rate. Plank *et al.* further demonstrated in a thin 3D slab model of cholinergic AF that introducing fluctuations in conductivity (cell-to-cell coupling) decreased the defibrillation threshold [223]. In addition, more disorganized forms of AF involving a larger number of wavelets required a higher shock strength to defibrillate. In order to test defibrillation therapy in an anatomical model of the atria and accurately predict its outcome, it appears that many factors (geometry, macro- and microstructure, cell coupling, AF dynamics) would have to be carefully considered. The development of detailed models of ventricular defibrillation [224], a topic of more intense research, may provide useful insights into how to create models of atrial defibrillation.

VII. Future Trends and Challenges

Although most of the current models are based on data from a normal heart, one of the main trends in cardiac modeling over the past several years has been the incorporation of features of aging or structural heart disease. Advances in immunostaining and use of high-resolution microscopy methods have provided insights into changes in the cardiac microstructure underlying AF. Because changes in the microstructure, such as fibrosis, have been associated with a greater incidence of arrhythmia in patients [170], [225]–[227], models that account for the discrete nature of the impulse propagation may be more predictive than models that assume relatively uniform material properties. The incorporation of such discrete structure in large-scale models may require new methods such as multiscale finite elements. In this approach, an effective macroscale model is adaptively reconstructed when necessary from a microscale model via an numerical homogenization process [228], [229].

The development of more realistic models of the dynamics of ion channels [230] brings with it the ability to better model the electrical remodeling process accompanying AF as well as drug interactions. For arrhythmias in which changes in sympathetic and parasympathetic neural activity play a proarrhythmic role, some neural components may also need to be added to the models. These new cell models may help in refining molecular targets for drug action that can impact atrial cells with greater specificity.

Another trend has been the development of atrial models that are patient specific and permit inputs and generate outputs that can be directly related to clinical protocols and measurements. The ultimate goal is to combine in a real-time setting clinical data and model results for better classifying the different forms of arrhythmia and proposing more accurate diagnosis and more specific treatment. This environment would also be beneficial to physician training.

To fully realize these trends, however, several critical challenges must be overcome. The generation of a patient specific model requires building an appropriate computational mesh from image data. While significant progress has been made, generating a quality mesh is still a challenge. One approach is to develop several meshes of a reference human heart and then apply morphing techniques, with local corrections, to fit the mesh to new geometries. Numerical schemes such as phase-field methods can be used to facilitate the handling of boundary conditions in complex geometries [72]. Time and space adaptivity is another promising research direction that

could lead to a reduction in mesh size and computational load. Several promising algorithms such as adaptive mesh refinement [231], [232] have been proposed and applied to complex geometries [233].

The long computational time for simulating large-scale models remains a significant limitation in using the models to test therapies and in eventually bringing the models directly into the clinic as part of the diagnostic process. Within one day on a single processor of a current workstation (Dell Precision 490), about 24 s of arrhythmia can be simulated in the 3D atrial model from Jacquemet *et al.* [26] (800,000 Courtemanche units). This is still 3–4 orders of magnitude longer than real time. Scalability of cardiac propagation software has been established, which guarantees significant gain in computational performance with the use of parallel computers [82]–[86]. Some additional speedup could be obtained by developing more efficient parallel solvers with appropriate preconditioning [84]. While new computers will be faster, new models will require more computational power. More variables will be included, with time constants spreading over a wider range (due in part to Markov models), and microstructure may necessitate the use of smaller time steps. Nevertheless, even with significant speedup, simulating the effects of several days or months of AF for a given patient (to predict remodeling or simulate patient's followup) is still far beyond reach.

Available clinical signals typically include electrocardiograms, local endocardial electrograms, and possibly a map of the local rates or dominant frequency. Due to the large number of model parameters and their spatial variations, adapting a model to a patient (or equivalently solving the inverse problem) does not seem possible without *a priori* knowledge, such as which parameter is expected to vary from patient to patient and over what range. As a result, there may be a role for the creation of libraries of model results of different forms of AF with different statistical realizations of the parameter variations, along with the outcomes of simulated therapies. In combination with measured data and classification schemes, a clinician could use these libraries of simulated case studies to enhance his empirical knowledge and design a specific strategy for more effectively treating a patient.

Modeling as a tool necessitates continuous adaptation and integration of new elements, including a continuous interplay of electroanatomical study, model redesign and careful comparison of the model with *in situ* measurements to verify the consistency of the results. As computer models continue to evolve, *in silico* experiments are expected to play a more prominent role in both uncovering the mechanisms of cardiac disease and in developing more effective therapies that can be tailored to a given patient.

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