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Mathematical Approaches to Understanding and Imaging Atrial Fibrillation: Significance for Mechanisms and Management

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Compendium

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The Clinical Profile and Pathophysiology of Atrial Fibrillation: Relationships Among Clinical Features, Epidemiology, and Mechanisms

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Cellular and Molecular Electrophysiology of Atrial Fibrillation Initiation, Maintenance and Progression

Role of the Autonomic Nervous System in Atrial Fibrillation: Pathophysiology and Therapy

Mathematical Approaches to Understanding and Imaging Atrial Fibrillation: Significance for Mechanisms and Management

Atrial Fibrillation Therapy Now and in the Future: Drugs, Biologicals, and Ablation

Stanley Nattel, Guest Editor

Mathematical Approaches to Understanding and Imaging Atrial Fibrillation Significance for Mechanisms and Management

Natalia A. Trayanova

Abstract: Atrial fibrillation (AF) is the most common sustained arrhythmia in humans. The mechanisms that govern AF initiation and persistence are highly complex, of dynamic nature, and involve interactions across multiple temporal and spatial scales in the atria. This article aims to review the mathematical modeling and computer simulation approaches to understanding AF mechanisms and aiding in its management. Various atrial modeling approaches are presented, with descriptions of the methodological basis and advancements in both lower-dimensional and realistic geometry models. A review of the most significant mechanistic insights made by atrial simulations is provided. The article showcases the contributions that atrial modeling and simulation have made not only to our understanding of the pathophysiology of atrial arrhythmias, but also to the development of AF management approaches. A summary of the future developments envisioned for the field of atrial simulation and modeling is also presented. The review contends that computational models of the atria assembled with data from clinical imaging modalities that incorporate electrophysiological and structural remodeling could become a first line of screening for new AF therapies and approaches, new diagnostic developments, and new methods for arrhythmia prevention. (*Circ Res.* 2014;114:1516-1531.)

Key Words: arrhythmias, cardiac ■ atrial fibrillation ■ atrial remodeling ■ computer simulation

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia and an important contributor to population morbidity and mortality, affects >2 million people in the United States alone; data suggest that its prevalence will continue to increase as the population ages.^{1,2} The mechanisms that govern AF initiation and persistence are highly complex, of dynamic nature, and involve interactions across multiple temporal and spatial scales in the atria, often leading

to unpredictable outcomes and emergent phenomena at the organ level. Electrophysiological experimental investigations in cells, tissues and the whole animal, and the human patient³⁻⁸ have led to a rapid increase in the body of knowledge regarding the mechanisms underlying AF. In this quest, modeling and simulation of atrial electrophysiology and arrhythmias have played an important role not only in hypothesis-driven research at various levels of integration, but also in providing

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Nonstandard Abbreviations and Acronyms

2D	2-dimensional
3D	3-dimensional
AF	atrial fibrillation
AP	action potential
APD	action potential duration
cAF	chronic atrial fibrillation
LA	left atrium
LGE	late gadolinium enhancement
PM	pectinate muscle
PV	pulmonary vein
RA	right atrium
SR	sarcoplasmic reticulum

the framework for the unification of diverse experimental findings. With the increase in computer power during the past decades and the advancement in imaging technologies, multi-scale, biophysically detailed models of the atria have made the initial foray into clinical translation, as part of the emerging discipline of computational medicine,⁹ by evaluating therapeutic approaches and contributing to the patient-specific optimization of cardiac care.

The present review article, part of a thematic series in *Circulation Research* on AF, provides a broad overview of the plethora of approaches in modeling atrial arrhythmias. The article focuses on the important role mathematical approaches and computer simulations have played in our mechanistic understanding of AF and discusses the emerging role of image-based simulation and modeling in assisting the clinical diagnosis and treatment of atrial arrhythmias.

Modeling AF: Overview of Approaches

Modeling AF, even in its most simple mathematical representation, involves propagation of an electric impulse (atrial cell action potential [AP]) in a network of cells. In their vast majority, models of AF involve biophysically detailed atrial cell membrane kinetics, that is, ionic currents, pumps, and exchangers, the mathematical description of which is based on the formalism introduced by Hodgkin and Huxley.¹⁰ In the study of AF, cells either form a regular 2- or 3-dimensional (2D or 3D) network or are arranged in a volumetric representation of atrial geometry and structure. In addition, cellular automata models have been used in the study of atrial arrhythmias, most notably the first model of AF, by Moe et al¹¹ in 1964, which suggested that AF is maintained by multiple meandering wavelets; this study has had a profound effect on AF research for many years, as well as on the concepts of arrhythmia and its therapy. This section reviews briefly the methodological basis and advancements in both cell automata and biophysically based models of AF.

Cellular Automata Models

Cellular automata models involve regular grids of cells (typically 2D and of square or hexagonal structure), in which each cell is in one of a number of states. The behavior of a cell in the grid evolves at discrete time steps, following state update

functions. Cell state updates are obtained by taking into account cells' states in the local neighborhood only. In the classical article by Moe et al,¹¹ cells in the automaton existed in 1 of 5 states, an absolutely refractory state, 3 stages of partial refractoriness permitting firing after a delay of decreasing duration, and an excitable state. The duration of the absolute refractory period was varied and was distributed randomly within the sheet. Although simulation of AF using a cellular automaton is computationally inexpensive, its most significant drawbacks are lack of dynamic electrotonic interactions (because influences do not extend beyond a defined neighborhood) and inability to dynamically regulate ionic flows. Despite these significant limitations, cellular automata models have enjoyed resurgence in the past few years,^{12,13} driven by the need to use rapidly executable models in clinical applications and to provide a framework for quick interpretation of clinical observations.

Biophysically Detailed Cell Electrophysiology Models

Biophysically based cell models, typically following the Hodgkin-Huxley formulation, represent current flow through ion channels, pumps, and exchangers, as well as subcellular calcium (Ca) cycling, and are governed by a set of ordinary differential and algebraic equations; ionic models differ vastly in their level of complexity. For the atrial cell, several ionic models have been developed, as reviewed in recent articles.¹⁴⁻¹⁶ Here, we briefly summarize these developments and highlight the newest advancements in representing atrial cell electrophysiology not covered by these reviews.

The earliest atrial cell models were based on measurements in frog¹⁷ and rabbit.^{18,19} Two human atrial cell models were subsequently developed by Courtemanche et al²⁰ and Nygren et al²¹ and have been used widely in AF multiscale simulations. Although these models have been partially developed using the same human experimental measurements, the paucity of the latter had necessitated the use of additional experimental data obtained from mammalian hearts. Therefore, the 2 models differ by their AP shape and dynamics, and have different rate-dependent behavior and restitution, because of marked differences in Ca handling formulation (see reviews^{22,23}). The model by Courtemanche et al²⁰ has been further extended to reproduce regional heterogeneities and electrophysiological remodeling in the human atria,²⁴ account for acetylcholine-dependent influences,²⁵ and simulate effects of drug delivery^{26,27}; a canine atrial cell model²⁴ has also been developed based on it.

Because new human data have recently become available, both models have been modified to improve their physiological accuracy. Maleckar et al²⁸ reimplemented the model by Nygren et al,²¹ with improved description of repolarization and rate dependence. Koivumäki et al²⁹ further extended the models by Nygren et al²¹ and Maleckar et al²⁸ by accounting for atria-specific characteristics of sarcoplasmic reticulum (SR) Ca uptake and release and, specifically, the delay between peripheral and central SR Ca release, characteristic of cells lacking t-tubules. Krummen et al³⁰ modified the model by Courtemanche et al²⁰ to account for extracellular K accumulation during rapid pacing and to fit AP duration (APD) and its restitution to newly available clinical recordings.

A third lineage of human atrial cell models was commenced by Grandi et al.³¹ The model incorporated new Ca dynamics formulation based on data from atrial myocytes at physiological temperature obtained from patients and also represented the contribution of β -adrenergic and cholinergic stimulation. The model was recently modified³² to represent a mutation (E299V) in KCNJ2, the gene that encodes the inward rectifier K channel protein, and used to examine its effect on AP (it resulted in abbreviated APD).

All 3 distinct human atrial cell models were further augmented to represent APs under chronic AF conditions. This effort has been based on seminal studies by the Wijffels et al,³³ who proposed that "AF begets AF," emphasizing that persistence of AF leads, in itself, to electrophysiological alteration in AP properties (predominantly via the altered expression of different ion channels),^{34–36} which, in turn, increases the propensity to chronic AF (cAF). To represent remodeling under the conditions of cAF, human ionic channel measurements were used to construct the respective cAF versions of the 3 main human ionic models, as summarized in the review by Bers and Grandi.¹⁶ The study by Wilhelms et al³⁷ provided a systematic benchmarking of these 3 models, their corresponding augmented models, as described above, as well as their cAF versions. Figure 1 illustrates the benchmarked AP models (paced at a frequency of 1 Hz) as well as the differences between the ionic currents and Ca cycling in the models; the model by Krummen et al³⁰ was not included in this analysis because the benchmarking study preceded its publication. This benchmarking provided information that could be used to guide the selection of the cell model for a particular study. In terms of usefulness of the cell models in the study of AF, as tested by Wilhelms et al,³⁷ re-entrant arrhythmia was inducible with all cAF models; however, the resulting spiral wave dynamics were highly divergent, underscoring the fact that the choice of cell model should be tailored to the application. For instance, the model by Courtemanche et al²⁰ was found unique in its ability to consistently produce stable beat-to-beat APD alternans for tissue-level simulations (and so is the model by Krummen et al³⁰). The differences in ionic model properties may reflect inherent electrophysiological variations in human atrial myocytes behavior and regional electrophysiological differences in the human atria; dynamic parameter fitting and adjustments³⁸ might offer a standardized approach in model development.

Two recent developments in single atrial cell models left the realm of the Hodgkin–Huxley formalism. The goal of the modeling effort by Voigt et al³⁹ was to help ascertain the mechanisms of SR Ca release events in human paroxysmal AF (rather than cAF); experimental data from right atrial (RA) appendages from patients with sinus rhythm and patients with paroxysmal AF were used for model development. The model was based on that by Grandi et al,³¹ but included a spatial representation of Ca handling and stochastic gating of ryanodine receptors. Model results demonstrated that both ryanodine receptor dysregulation and enhanced SR Ca pump activity promote increased SR Ca leak and SR Ca release events, causing delayed afterdepolarizations in paroxysmal AF atrial cells.

The second model development⁴⁰ entailed a different mathematical modeling approach that allowed characterization of Ca movement within the (idealized) 3D volume of an atrial

myocyte. Novel model aspects included the geometrically realistic representation of Ca release sites within the cell, allowing for exploration of their interaction, as well as Ca wave initiation and propagation. The study explored the generation of centripetal Ca waves during excitation–contraction coupling and the effect of positive inotropic stimulation on the spatial profile of Ca signals. It remains unknown, however, whether such modeling approaches could be incorporated in tissue-level atrial models and used in the study of AF.

Multiscale Modeling of Propagation

In tissue, atrial myocytes are electrically connected via low-resistance gap junctions. Ionic current can flow from cell to cell via this pathway, in addition to the current exchange between intracellular and extracellular spaces through cell membrane proteins, as described above. Propagation in excitable media, such as atrial tissue, is typically modeled using spatially continuous models that are viewed as resulting from a local spatial homogenization of behavior in tissue compartments (membrane, intracellular, and extracellular spaces). Current flow in the tissue structure is typically governed by the monodomain reaction–diffusion partial differential equation over the tissue or organ volume, with the use of conductivity tensor fields. Simultaneous solution of the partial differential equation(s) with the set of ionic model equations represents simulation of electric wave propagation in the heart. The conductivity tensor fields used in these continuous models integrate all the information about the distribution of gap junctions over the cell membranes as well as the fiber, sheet, and other microstructure organization in the atria.

The methodology for modeling atrial propagation is the same as that for modeling wave propagation in the ventricles; thus, for detailed information on the various approaches, we direct the reader to comprehensive reviews on the subject.^{14,15,41,42}

Geometric and Image-Based Atrial Modeling

Cellular automata and biophysically detailed models have both been used with simple 2D geometries (sheets of atrial tissue).^{11,12,25,43–47} Because of the smaller atrial wall thickness as compared with the ventricles, 2D geometries rather than 3D slabs of tissue have been typically used in simplified AF simulations.

In contrast, geometric atrial models include those of high structural detail of an atrium part, such as RA appendage, pulmonary veins (PVs), crista terminalis, or pectinate muscles (PMs), of different animal species,^{48,49} or geometric models of at least one of the atria chamber. Development of high-resolution geometric models of isolated atrial structures has been motivated by the notion that specific atrial structural substrates are more likely to be involved in sustaining AF.⁵

Three-dimensional models of at least one of the atria have predominantly aimed to represent organ anatomy in the study of human AF. The exception is the high-resolution structural model of the sheep atria acquired by serial surface imaging^{50,51}; the complex structure of this model is shown in Figure 2A. The group of models based on geometric representations of at least one of the human atrial chambers can further be sub-classified into surface and volumetric models. Surface models represent atrial geometry in 3D but neglect wall thickness^{53–56}, the latter is not true for volumetric models.^{52,57–62} Furthermore,

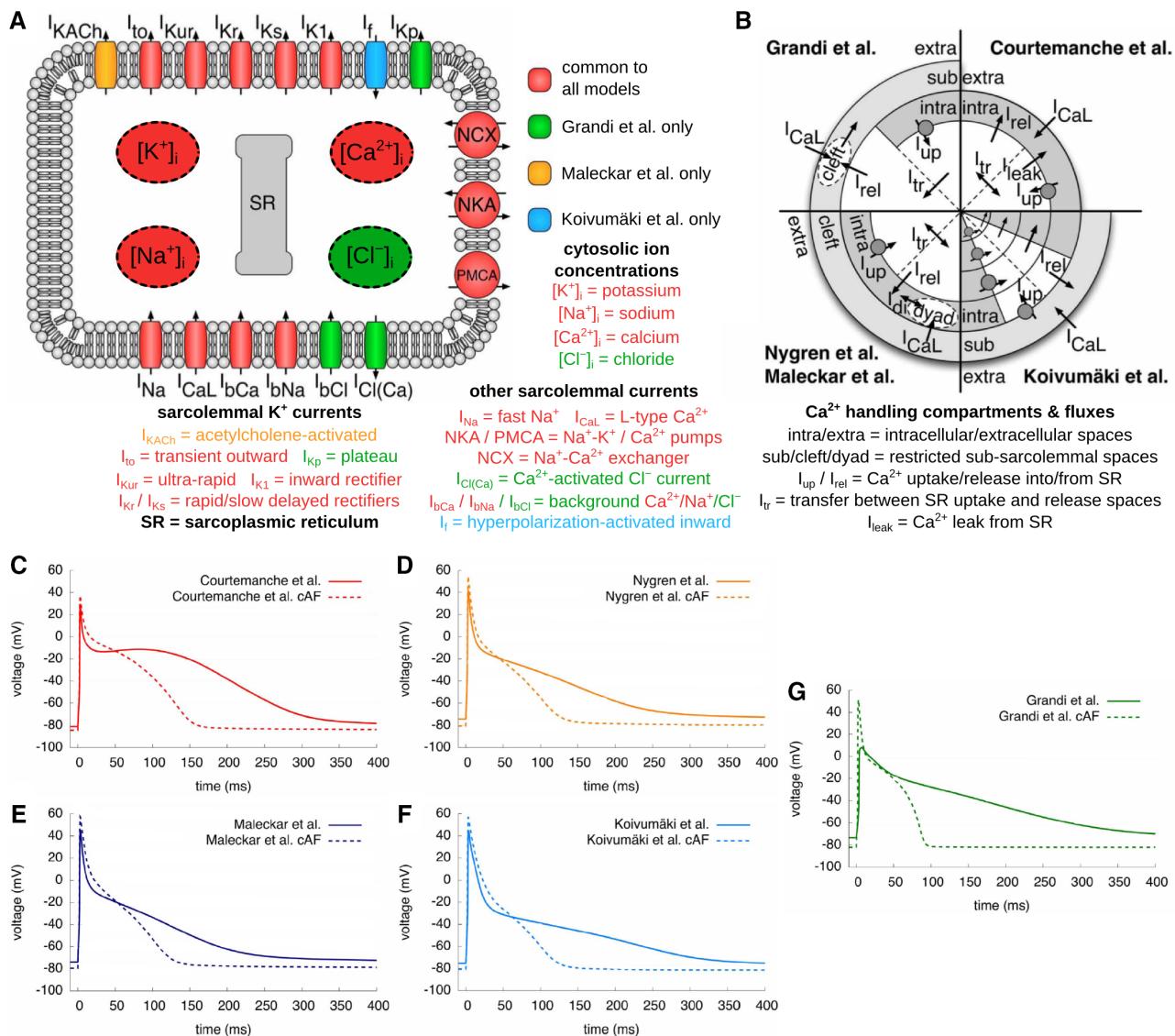


Figure 1. Human atrial cell ionic models. **A**, Schematic of the atrial cell, including representations of ionic channels and intracellular ion concentrations used in the various human atrial cell models. **B**, Schematic of Ca handling with different compartments and currents in the various atrial cell models. Each of the models' Ca handling is represented in one quarter of the schematic. White spaces in the central region denote the sarcoplasmic reticulum (SR), with straight broken lines representing the division between SR uptake and release regions. Gray spaces represent the other compartments within the cell and outside of SR, with the cleft and dyad subspaces shown in white. Arrows indicate directions of Ca flow between the different compartments. The SR Ca pump is indicated by circle and arrow. The model by Koivumäki et al.²⁹ also incorporates additional compartments representing peripheral and central SR regions and the current flow between these regions and the intracellular space. Additional detail regarding Ca handling in the models can be found in the original publications.^{20,21,28,29,31} **D** to **G**, Control and chronic atrial fibrillation (cAF) action potentials of 5 atrial cell models paced at a frequency of 1 Hz. Modified from the figure as originally published in Wilhelms M et al (2012) Benchmarking electrophysiological models of human atrial myocytes. *Front. Physiol.* 3:487. doi: 10.3389/fphys.2012.00487.³⁷

human atrial models incorporate either idealized atrial shapes representing closed-surface organ properties^{53,56,63} (spheroidal shape of the atrium), including the topology of the insertions of veins and valves, or atrial geometries based on image acquisition^{52,54,55,62} using a variety of imaging modalities.

Human image-based atrial model development commenced with the use of the atrial geometry data set^{57–59,64–67} (see also table of models in Dössel et al¹⁴) resulting from the Visible Human project.⁶⁸ Subsequently, atrial geometries used in electrophysiological simulations were acquired using MRI^{52,54,55,62,69} (Figure 2B) as well as computed tomography⁷⁰,

refer to Pennell⁷¹ for a review of image acquisition. An informative comparison between some of the different geometries used in human atrial modeling can be found in Figure 5 of the review by Jacquemet et al.¹⁵ In addition, a comprehensive listing of human atrial models is provided in Table 1 of Dössel et al¹⁴; models not represented in that table include those recently published by McDowell et al^{52,62} and Tobón et al.⁶⁷ Fiber structure has also been represented in these models either manually or using a semiautomatic rule-based approach¹⁴ because diffusion tensor imaging of the thin atrial walls does not provide reliable information about atrial fiber

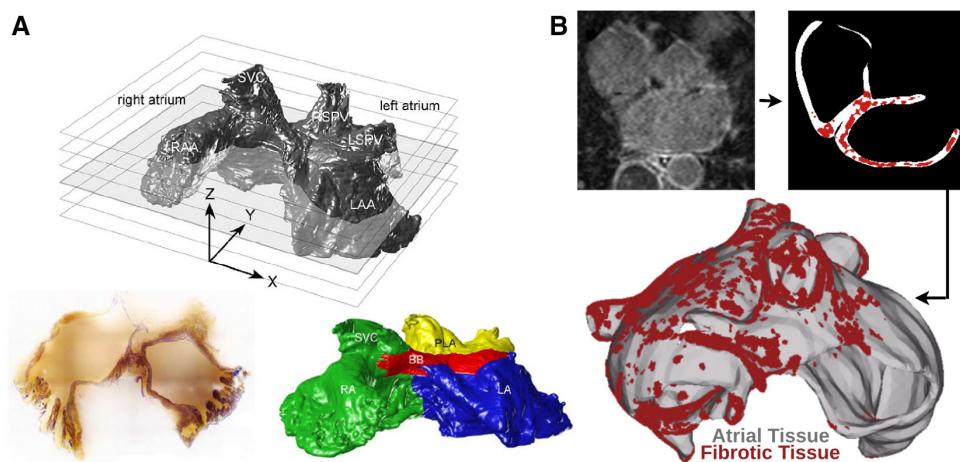


Figure 2. Geometric models of the atria. **A**, Volume image of the sheep atria acquired by serial surface imaging (resolution, 50 μm), with a representative slice. Subdivision of atria into different regions as represented by the different colors: right atrium (RA), green; left atrium (LA), blue; Bachman bundle (BB), red; and posterior LA (PLA), yellow. LAA indicates LA appendage; LSPV, left superior pulmonary vein; RAA, RA appendage; and RSPV, right superior pulmonary vein. Images reproduced from Zhao et al^{50,51} with permission of the publisher. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. **B**, A model of the fibrotic human atria generated from a patient late gadolinium enhancement (LGE) MRI scan (**top left**) after segmentation (**top right**) into normal and fibrotic tissue (fibrotic lesions in red). Reproduced with permission from McDowell et al.⁵²

architecture. Three-dimensional atrial models have often incorporated add-on representations of atrial structures such as the Bachman bundle, crista terminalis, PMs, and the coronary sinus sheath.

Recently, organ-level atrial models have begun to represent fibrotic structural remodeling associated with persistent AF. Atrial fibrosis is imaged using late gadolinium enhancement (LGE) MRI.⁷² McDowell et al^{52,62} created the first model of patient atria with fibrotic remodeling (Figure 2B) by segmenting out the enhanced regions in the LGE MRI scans; similar approaches followed.⁷³ McDowell et al^{52,62} used a sophisticated model of fibrotic remodeling in the LGE regions of the patient atria, accounting for (1) connexin downregulation/hypophosphorylation and lateralization, (2) collagen deposition, and (3) myofibroblast infiltration. Myofibroblasts in the fibrotic regions, represented by the ionic model of MacCannell et al,⁷⁴ were coupled to myocytes, as described in Maleckar et al.⁷⁵ The electrophysiological representation of fibrotic remodeling in the human atrial models remains, however, controversial because of the lack of experimental data. Similarly, the segmentation of the LGE MRI fibrotic regions and even the segmentation of the geometry of the thin atria from clinical MRI is fraught with uncertainty and is an area of intense image-processing research.

Exploring AF Mechanisms: Insights From Modeling

Mechanisms Landscape

Despite a significant body of basic and clinical research, the fundamental mechanisms governing AF initiation and maintenance are incompletely understood.⁷ As a result, treatment of AF remains ineffective, presenting a significant potential for improvement. Excellent recent reviews offer a detailed overview of the long history of exploration of AF mechanisms.^{3,6} It is now accepted conceptually that the clinical progression

of AF involves evolution from paroxysmal to persistent and permanent forms of the arrhythmia and that it reflects progressive electrophysiological and structural remodeling^{35,76,77} caused by the downward spiraling impact of the arrhythmia itself and the progression of the underlying heart disease.^{4,78} Note that the described progression is seen in only part of the patient population, with the issue of AF evolution remaining the subject of intense research.

Our understanding today is that paroxysmal AF is typically driven by rapid focal activity (either early or delayed afterdepolarizations) or local re-entry in the cardiac muscle sleeves around the PVs.^{79,80} Accordingly, PV isolation via radiofrequency ablation eliminates paroxysmal AF in 70% to 80% of the treated patient population.⁸¹ Persistent AF is thought to arise from electrophysiological remodeling of the atria resulting from altered protein expression and function of cardiac ion channels, often caused by AF itself.⁵ Its hallmark is the decrease in APD, often accompanied by increased delayed afterdepolarization risk attributable to Ca overload.^{5,82} The overarching persistent AF mechanism is currently thought to be functional re-entry: ≥ 1 rapidly rotating spirals, the emitted waves of which interact with anatomic and functional obstacles, leading to wavefront fragmentation and fibrillatory conduction.⁸³ Furthermore, autonomic neural remodeling contributes to AF recurrence and maintenance in both paroxysmal and persistent AF forms.^{84,85}

Electrophysiological remodeling itself accelerates the progression from paroxysmal to permanent AF^{4,78}; the latter is also associated with irreversible structural changes, particularly fibrosis,^{86,87} rendering the remodeled atria as a substrate for both functional and anatomic re-entry. Although the multiple-wavelet hypothesis,¹¹ according to which AF is the result of randomly propagating multiple electric wavelets changing in number and direction, has been a dominant mechanistic model of permanent AF (and even persistent

AF), recent clinical evidence⁸⁸ (albeit limited) has demonstrated that in humans permanent AF may also be the result of a small number of persistent rotors with fibrillatory conduction to the surrounding atrium.

Although not all atrial modeling efforts to uncover AF mechanisms are classifiable along the lines of AF progression as described above, they have nonetheless addressed mechanisms that could be pertinent to any form of AF. A review of the most significant mechanistic contributions made by atrial simulations is provided below.

Normal Atria: Intrinsic Atrial Structural and Electrophysiological Heterogeneities Predispose to Atrial Arrhythmias

Even in the structurally and electrophysiologically normal atria, the complex closed-surface geometry of the chambers,⁸⁹ with a set of distinct structural features such as orifices and discrete bundles, presents a substrate that predisposes to arrhythmia initiation under conditions of source–sink mismatch and also often determines the specific (anatomic) re-entrant pathways of the ensuing arrhythmia, as found by modeling studies.^{48,49,53,61,63,90–93} After the seminal experimental–simulation work by Spach et al,⁹⁴ atrial modeling results^{43,48,49,59,61,70} have similarly demonstrated that intrinsic differences in APD in the various atrial structures additionally predispose the atria to rhythm disorders. Local variation of wall thickness resulting from the presence of PMs has been shown^{90,93,95} to increase the downstream load on a propagating wavefront and result in wave breakup. Furthermore, PMs have been found to play a role in the conversion between AF and flutter by anchoring spiral waves.^{90,92} Modeling studies^{43,53,91,93} have implicated the highly anisotropic conduction and longer APD in the crista terminalis in setting up the conditions for re-entry generation. Using anatomic models of the rabbit RA and of the pig RA appendage, respectively, both based on histological reconstructions, studies by Aslanidi et al⁴⁹ and Zhao et al⁴⁸ demonstrated that because electrotonic coupling transverse to fibers in the crista terminalis is weak, high-frequency pacing at the border between the crista and PMs results in a reduced safety factor, leading to unidirectional block and subsequent generation of

re-entry. Based on results from a model of the human atria,⁶¹ Figure 3 shows the excitation wave on the epicardial surface of the atria during normal sinus rhythm as well as activation patterns in AF, the result of rapid pacing near the crista.

Other aspects of normal structure and electrophysiology have also been implicated, in simulation studies, in predisposing the atria to arrhythmias. Vigmond et al⁵³ showed that the muscular sheath of the coronary sinus could act as a pathway for re-entry and to also stabilize re-entrant circuits utilizing the isthmus near the inferior vena cava. Using a model of sheep atrial geometry and myofiber orientations also reconstructed from serial section images, Zhao et al⁵¹ demonstrated that the complex myocyte arrangement in the posterior left atrium (LA) contributes to dispersion in activation times in the region adjacent to the PVs and to increased vulnerability to arrhythmia following ectopic beats originating in PV sleeves; the arrhythmia vulnerability was exacerbated by spatial variation in APD across this region.⁵⁰ Another study⁷⁰ examined the effect of APD differences in the canine atria (LA versus RA as well as increased APD shortening with increased distance from the sinoatrial node) and found that the APD gradients increase the propensity of wavebreak, spiral wave core meander, and quasi-stable re-entry. Finally, the openings of the inferior and superior venae cavae⁵³ and that of the tricuspid valve⁶³ were shown to serve as anchors of re-entry (atrial flutter).

The parasympathetic nervous system also plays a role in creating a substrate for AF: through the release of acetylcholine, vagal stimulation causes a significant reduction in effective refractory period and rate adaptation loss.^{96,97} This effect creates APD nonuniformity over the atria attributable to the sparsely distributed vagal nerve endings (acetylcholine release sites). Using a new formulation of the acetylcholine-dependent K current, Kneller et al²⁵ demonstrated, in a 2D atrial model with periodic variations in acetylcholine concentrations, that sufficiently large vagally induced APD gradients may be established, causing a re-entrant wave to break up and the activity to transition into a cholinergic form of AF; the specific arrhythmia morphology was found to depend on substrate size.⁹⁸ The arrhythmogenic conditions associated

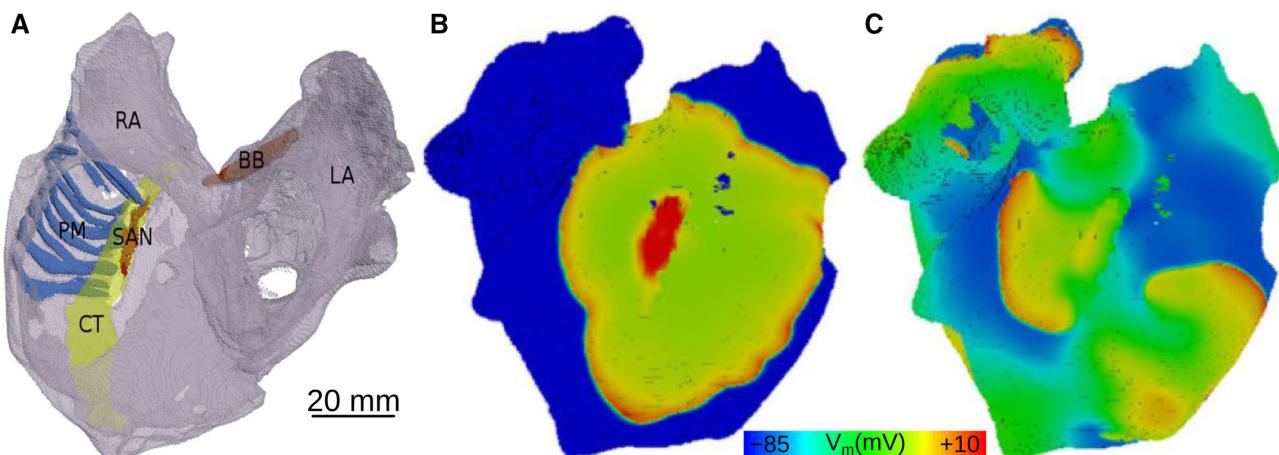


Figure 3. Membrane potential distribution on the epicardial surface of the human atria. A, Anatomical landmarks. B, Spontaneous normal rhythm. C, Pacing-induced atrial fibrillation resulting from different electrophysiological properties of the crista terminalis. With permission from Aslanidi et al.⁶¹ BB indicates Bachman bundle; CT, crista terminalis; LA, left atrium; PM, pectinate muscle; RA, right atrium; and SAN, sino-atrial node.

with nonuniform vagal stimulation were further explored,⁵⁶ providing a detailed analysis of vulnerability windows for ectopic beats under different levels and patterns of vagal activity. Finally, Atienza et al⁹⁹ simulated left-right differences in acetylcholine-dependent K current, finding that this difference resulted in faster rates of the LA rotor, driving RA activity.

Paroxysmal AF Initiation

The demonstration by Haïssaguerre et al⁷⁹ of the importance of PV foci in initiating arrhythmia constitutes an important advancement in our understanding of AF pathogenesis. Different cellular mechanisms have been proposed¹⁰⁰ for the generation of spontaneous activity in the cardiomyocyte sleeves of the PV, including automaticity and afterdepolarizations. In early simulations,¹⁰¹ PV automaticity has been represented by the addition of the hyperpolarization-activated inward current I_f to the human atrial AP; a PV cardiomyocyte-specific cell model was subsequently developed.¹⁰² The possibility of microreentry within PV sleeves of varying diameter and length was explored by the modeling study of Cherry et al¹⁰³; it demonstrated that the electric and microstructural characteristics of the PVs, distinct from those of the LA, result in heterogeneous and anisotropic conduction and PV re-entry. As presented in Figure 4A, a single premature LV activation invading the PV establishes PV re-entry, which in turn continuously re-excites the LA, presenting a focal source of LA activation.

Although simulation studies have not been conducted exploring how a biophysically and structurally detailed model of ectopy in the PV sleeves would drive the atria into paroxysmal

AF, the onset of paroxysmal AF has been explored by modeling the delivery of trains of pacing stimuli in the PV region. Gong et al⁶⁴ demonstrated that spontaneous firings of ectopic foci, coupled with sinus activity, produced dynamic spatial dispersions of repolarization, including discordant alternans, which caused conduction block and led to atrial flutter and AF (see Figure 4B as an example of the distribution of atrial transmembrane potential, including several distinct wavefronts). Although the likelihood of re-entry induction varied depending on ectopic foci locations and timing, ectopy from the PV region resulted in the largest vulnerable window.

A combined clinical–simulation study by Krummen et al³⁰ examined the mechanisms behind the clinical interventions that induce AF, namely the administration of isoproterenol or adenosine as well as rapid pacing. Isoproterenol and rapid pacing both steepened maximum APD restitution slope promoting AF initiation, although via distinct mechanisms, as demonstrated by the simulations. APD restitution steepening in the former intervention arose from the alteration of Ca dynamics, whereas restitution steepening in the latter stemmed from K accumulation. Adenosine did not steepen APD restitution, and AF propensity remained unchanged.

Finally, lone forms of paroxysmal AF have been found to be the result of inherited ion channel dysfunction. A missense gain-in-function *KCNQ1* S140G mutation has been implicated in a familial form of AF, with simulation research,¹⁰⁴ using a model of the human atrium, establishing the causal link between mutation and genesis of AF: increased I_{Ks} current arising from the mutation abbreviated APD, facilitated the conduction

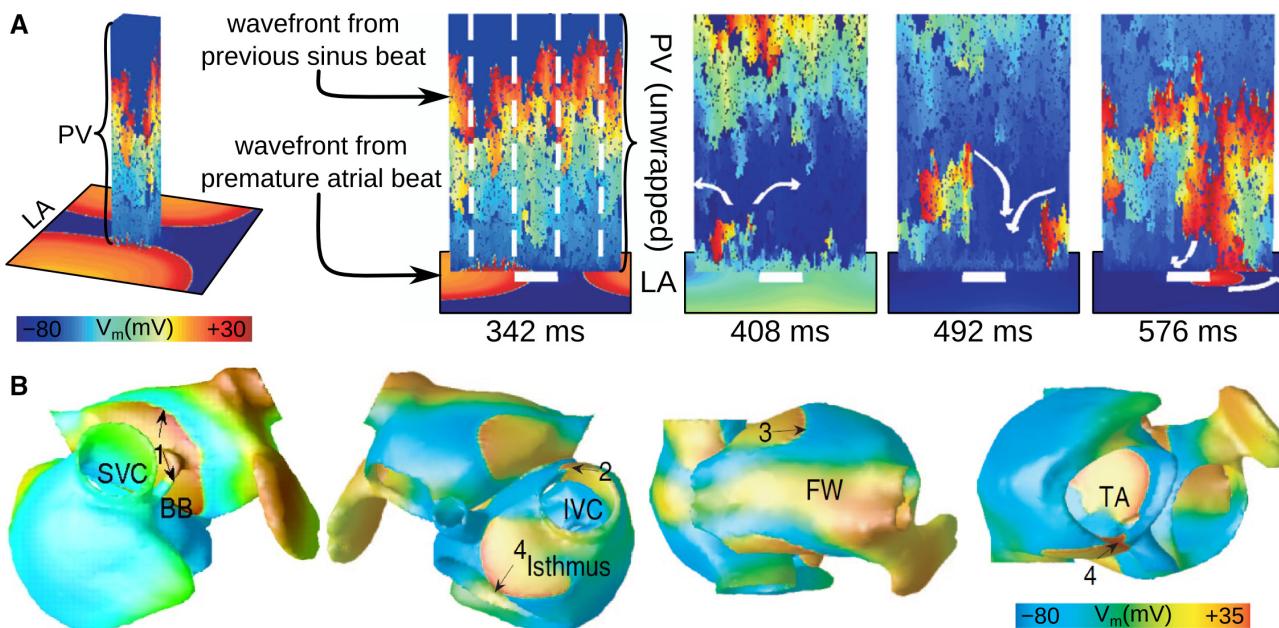


Figure 4. Initiation of paroxysmal AF. **A,** Continuous pulmonary vein (PV) reactivation of the left atrium (LA) attributable to heterogeneous venous conduction and re-entry following a single ectopic beat in the LA (with permission from Cherry et al¹⁰³). The sinus beat propagates heterogeneously along the vein (wrapped and unwrapped views, 342 ms). Vein length is 1 cm, and circumference is 2 cm, with 30% longitudinal and 65% transverse cellular disconnections. A single premature activation originating somewhere in LA invades PV following the sinus beat (342 and 408 ms), encountering block (408 ms) and establishing PV re-entry (492 ms). This re-entry continuously re-excites the LA, serving as focal source for LA activations (576 ms; propagation entering LA at bottom of image). **B,** A snapshot of membrane voltage in the human atria at a single time point during AF (different views of the atria are shown), in which numbered arrows (1–4) indicate multiple re-entrant wavelets. AF was induced by PV ectopic beats (with permission from Gong et al⁶⁴). BB indicates Bachman bundle; FW, free wall; IVC, inferior vena cava; SVC, superior vena cava; and TA, tricuspid annulus.

of high-rate atrial excitation waves, and stabilized re-entry. Similarly, numeric experiments³² have elucidated how a mutation (E299V) in *KCNJ2*, the gene that encodes the strong inward rectifier K channel protein (Kir2.1), results in AF.

AF begets AF³³: Electrophysiological Remodeling in Persistent AF

AF and very rapid tachyarrhythmias cause, over time, electric remodeling of the atria; the latter can also be induced by other conditions, most commonly congestive heart failure.¹⁰⁵ Electric remodeling is manifested as altered ion channel expression and function in a way that further promotes AF.^{4,106} The triggering mechanisms, chiefly among which is increased Ca load, lead to the onset of a chain of protective mechanisms resulting in electrophysiological remodeling of the tissue. Models of the atrial cell under the conditions of persistent AF have been developed, as described in the Biophysically Detailed Cell Electrophysiology Models section (termed cAF models, because they were used to represent electric remodeling in both persistent and permanent forms of AF; see next section for latter), and have made contributions to understanding the dynamic interplay between the various remodeled ionic channels/currents^{26,31} that give rise to diminished Ca transients and shorter APDs in persistent AF. A resulting characteristic of global atrial activity in persistent AF is rotor stabilization, which increases AF vulnerability and sustainability. This phenomenon has been investigated by modeling studies at the tissue level. Pandit et al⁴⁵ examined the behavior of a stable but meandering rotor and demonstrated

that increasing the magnitude of the inward rectifier current K current (I_{K1}) resulted in reduced meandering of the rotor (Figure 5). A recent modeling article⁴⁴ analyzed systematically the relative importance of ionic currents and transporters in modulating excitability, refractoriness, and rotor dynamics in human atrial tissue. Results underscored the important role of the Na/K pump in modulating APD, restitution, and dominant frequency of the re-entrant activity, providing comparisons between behavior in sinus rhythm and persistent AF; I_{K1} and I_{Na} were both found to strongly affect rotor stability.

Simulations of electrophysiological remodeling were also extended to 3D modeling of the human atria.¹⁰⁷ Colman et al,¹⁰⁷ incorporating heterogeneity in electric remodeling across the structures of the human atria, found that remodeling abbreviated atrial APD nonuniformly in the various atrial structures, resulting in relatively short APDs coexisting with marked regional differences in the APD at junctions of the crista terminalis/PMs and PVs/LA. The increased electrophysiological heterogeneity stabilized and accelerated re-entrant excitation waves, leading to rapid and sustained AF.

A different remodeling effect of AF has been hypothesized to stem from the fact that under AF conditions the atria become dilated. Atrial dilation exerts a mechanoelectric influence through stretch-activated ion channels; the effect is diastolic depolarization, abbreviated refractory periods, triggered activations, and increased dispersion in electrophysiological properties.^{108,109} Simulation studies in the human atria¹¹⁰ demonstrated that under dilation, focal sources near the PV initiated AF, resulting from electrophysiological

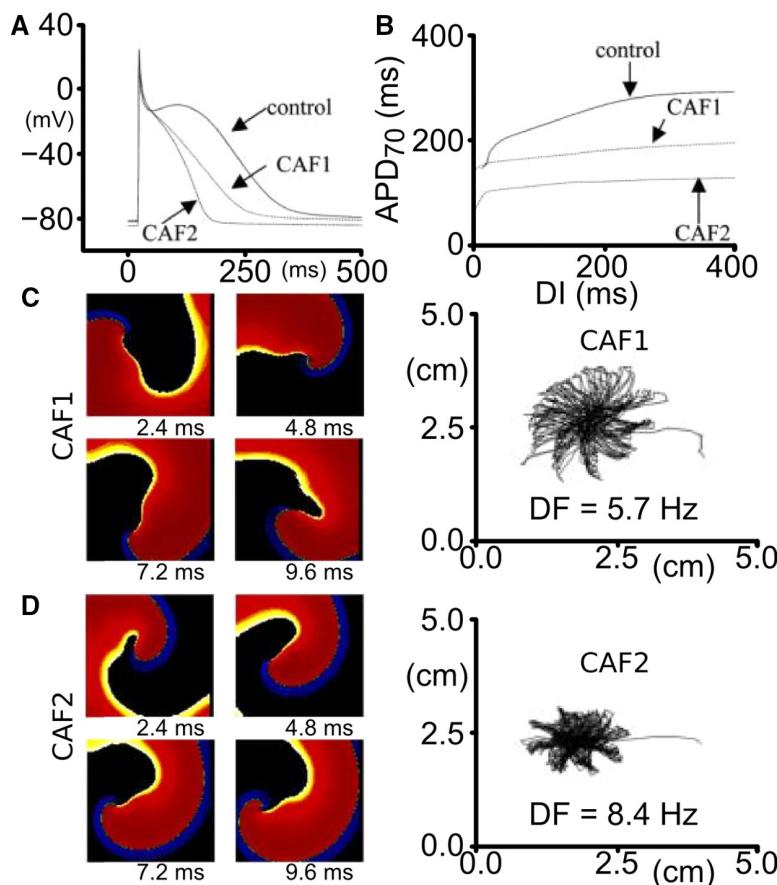


Figure 5. Rotor stabilization in persistent AF. **A,** Simulated action potentials (APs) in control and chronic atrial fibrillation (AF) conditions (CAF1, CAF2). CAF1 is an AF cell model with I_{to} and I_{Ca} reduced, without I_{K1} upregulation; CAF2 is the same model with I_{K1} increased. **B,** Electric restitution plotted as AP duration (APD) vs the diastolic interval (DI) in control and chronic AF cases. **C** and **D**, Spiral waves (phase movie snapshots) and tip meander in chronic AF conditions CAF1 and CAF2. Phase movies are shown at 4 distinct times. The figure demonstrates that I_{K1} stabilizes and accelerates re-entry, as manifested by the reduced tip meander. Modified with permission from Pandit et al.⁴⁵

alterations attributable to the heterogeneous stretch throughout the atria. Similarly, the experimental–modeling study by Yamazaki et al¹¹¹ highlighted the stabilization of meandering spiral wave filaments at locations with large gradients in myocardial thickness and thus stretch, leading to heterogeneous distribution of stretch-activated channels activation and their influence through mechanoelectric feedback.

Finally, a model of heterogeneous electric remodeling in the human atria was used⁶⁶ to assess the spatiotemporal organization of the activity in persistent AF using different signal analysis techniques, such as dominant frequency¹¹² and the organization index (ratio of signal spectral power to total power of the spectrum).¹¹³ The ability of dominant frequency and organization index maps to localize AF sources of high frequency was compared, with the results suggesting that a better localization might be obtained using organization index maps.

Fibrotic Remodeling and Permanent AF

Structural remodeling, and specifically fibrosis, is a hallmark of permanent AF.^{86,87} Fibrotic remodeling of atrial tissue involves processes that occur in parallel across multiple scales: at the membrane level, gap junction remodeling attributable to connexin 43/40 protein downregulation/hypophosphorylation and lateralization^{114,115}; at the cellular level, fibroblast proliferation and phenotype switching^{86,116}; and at the tissue level, the deposition of excess collagen,^{87,117} both from reactive interstitial fibrosis separating muscle bundles and from reparative fibrosis replacing dead cardiomyocytes, both interfering with electric continuity and slowing conduction.^{3,117} Thus, structural remodeling, combined with remodeling at the ion channel level as described above, gives rise to complex interactions at the organ level, setting the stage for AF initiation and maintenance in the fibrotic atria.

Models of the fibrotic atria have accounted for different aspects of fibrotic remodeling, in an attempt to elucidate the mechanisms leading to altered conduction and those responsible for the drivers and organization of permanent AF. The simplest model representation of atrial structural remodeling was based on the assumption that a component of structural remodeling, gap junction remodeling (connexin 43/40 downregulation/hypophosphorylation and lateralization), occurs throughout the atria in a uniform fashion. Two such studies have been conducted thus far: one⁶⁵ assumed that the coupling strength between computational cells was decreased (connexin 43/40 downregulation/hypophosphorylation only), whereas the other¹¹⁸ modeled increased anisotropy throughout the LA (representing both aspects of connexin 43/40 remodeling). The simulations showed⁶⁵ that decreasing the coupling between cells slowed conduction and decreased the wavelength, further perpetuating AF. Plank et al¹¹⁸ demonstrated that increased anisotropy throughout the fibrotic human LV was an additional mechanism for the breakup of PV ectopic waves into multiple re-entrant circuits; higher anisotropy ratios resulted in sustained re-entrant activity even though the ectopic focus was no longer present. Similar conclusions were obtained from a human atrial model⁷³ in which the locations of the fibrotic (ie, high anisotropy ratio) regions were implemented from patient MRI-LGE scans.

The next component of fibrosis, collagen deposition, has been represented in models as insulating barriers and in

several ways: (1) by removing randomly the electric connections between two 2D layers of atrial tissue, the endocardial and the epicardial, to model an increased level of dissociation between these 2 layers (a form of reactive interstitial fibrosis), mimicking experimental observations in goats¹¹⁹; (2) by introducing a set of random collagenous septa disconnecting cardiac fibers in the transverse direction¹²⁰ (reactive interstitial fibrosis again); and (3) by incorporating nonconductive or nonexcitable regions of various sizes throughout the tissue^{115,121,122} (reparative fibrosis), either randomly throughout the atria or based on imaging data. Endocardial–epicardial dissociation resulted¹¹⁹ in the number of AF re-entrant waves being significantly higher than that in the case without dissociation, exacerbating AF complexity. The increase in collagen content in the interstitial spaces between fibers was not found to affect longitudinal conduction,^{52,62,115} but caused slowed propagation in transverse direction, with the degree of slowing depending on the length of the collagenous septa.¹²⁰

Atrial models incorporating transverse collagen deposition^{115,121,122} (as in reparative fibrosis) have highlighted the significant interruption and disarray in atrial conduction patterns caused by it. Importantly, collagen deposition rather than connexin 43/40 remodeling was found to be the major factor in atrial conduction disturbances under heart failure conditions¹¹⁵ (Figure 6A). Furthermore, it was established that not only the total amount, but also the specific distribution of collagen deposition (as generated by a stochastic algorithm) governed the occurrences of conduction block.¹²¹ To evaluate the consequences of heart failure remodeling (ionic and structural) on AF dynamics, Tanaka et al¹²² used 2D models of transmural posterior LA sections generated from histological data; patchy distributions of collagen were also reconstructed from that data (Figure 6B, top). Simulations demonstrated that whether the mechanism sustaining AF was re-entrant or focal (generated by an S1–S2 protocol or pacing, Figure 6B), fibrous patches of large size were the major factor responsible for the different dynamics of AF waves in failing versus control hearts. The patches anchored re-entrant circuits (see white circles representing wavebreak, the locations of which, when associated with large collagen patches, remained the same regardless of AF induction protocol) and impaired wave propagation to generate delays and signal fractionation.

The third major component of fibrotic remodeling, fibroblast proliferation and phenotype switching, has also been represented in computational models of the atria, particularly in view of the fact that fibroblasts, in addition to being part of the structural remodeling of the atria, can also exert electrophysiological influences on neighboring myocytes, possibly either through electric coupling¹²³ or via paracrine effects.¹²⁴ The first study to explicitly incorporate fibroblast presence as a representation of fibrotic remodeling was the 2D atrial model by Ashihara et al.⁴⁶ Within the fibrotic region, coupling of fibroblasts (kinetics governed by a fibroblast ionic model) to atrial myocytes caused shorter APD, slower conduction, and lower excitability as well as spiral wave breakups, similar to experimental results¹²⁵ in neonatal rat monolayers. This effect was exacerbated when fibroblast density increased (Figure 7A). Interestingly, when fibroblasts were substituted by collagen in the model, wave

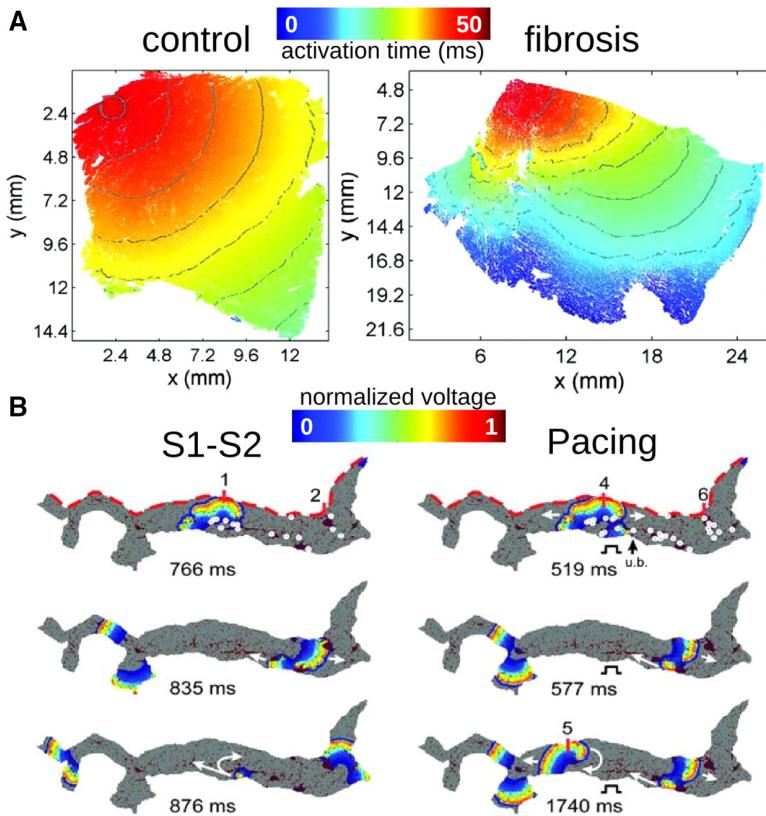


Figure 6. Modeling fibrosis as regions of collagen presence. Collagen is represented as an insulator. **A**, Simulations of propagation in 2-dimensional (2D) tissue sections (control, **left**; fibrosis, **right**). With permission from Burstein et al.¹¹⁵ **B**, Simulations in left atrial transmural slices for heart failure conditions. Snapshots at several time frames for cross-field stimulation (**left**) and pacing at a frequency of 6 Hz (**right**). Colors indicate transmembrane voltage from low (blue) to high (red). The site of unidirectional block (u.b.) is indicated by a black arrow. White circles on the upper voltage maps indicate sites of wavebreak. With permission from Tanaka et al.¹²²

breakups were not observed. Although this study presented intriguing mechanistic insight, it is important to acknowledge that myofibroblast–myocyte coupling needs additional evidence of its existence in the intact heart.

All 3 elements of fibrotic remodeling (gap junction remodeling, collagen deposition, and myofibroblast proliferation), in addition to cAF ionic remodeling, were combined together in the LA model generated from MRI-LGE data of a patient with permanent AF,^{52,62} capturing accurately both the atrial geometry and the distribution of fibrotic lesions. Here, fibroblast proliferation was represented in 2 ways: via fibroblast coupling to myocytes or via the paracrine effects on ionic channels, acknowledging the paucity of evidence regarding *in vivo* myocyte–fibroblast coupling in fibrotic regions. The model was used to examine the mechanisms for AF initiation by PV ectopic stimulation. The study found that for fibrotic lesions typical of human remodeled atria under the conditions of persistent AF, gap junction remodeling in the fibrotic lesions was a necessary but not sufficient condition for the development of AF following a PV ectopic beat. The sufficient condition was myofibroblast proliferation in these lesions, where myofibroblasts exerted either electrotonic or paracrine influences on myocytes within the lesions. Deposition of collagen in the lesions assisted the myofibroblasts’ paracrine or electrotonic effects by additionally shortening APD there (Figure 7B).

AF Management: Can We Learn From Atrial Models?

The ability to construct multiscale models of the electric functioning of the atria, representing integrative behavior from the

molecule to the entire organ, has paved the way for the use of these models in AF management. Specifically, modeling work has been conducted to determine molecular targets for pharmacological rate control and optimize antitachycardia pacing and AF ablation, as reviewed below.

Pharmacological Control of Atrial Rate

Antiarrhythmic drugs constitute the main treatment option for AF. However, atrial rhythm control pharmacotherapy has been limited because of its inadequate effectiveness and adverse side effects.³ In addition, such drugs are associated with risk of life-threatening ventricular proarrhythmia.¹²⁶ Accordingly, research on pharmacological control of atrial rate has been directed toward finding drug targets that are atria specific.¹²⁷ The role of atrial modeling in this field of research has been to uncover the mechanisms for drug action or the lack thereof. An experimental/simulation investigation of this type is represented by the study of Pandit et al.⁴⁷ The objective was to probe the effectiveness of block of the atria-specific current I_{Kur} and to exploit the inherent differences between atrial and ventricular Na-channel steady-state inactivation properties (by manipulating extracellular K concentration) in terminating cholinergic AF in pigs. Experimental results indicated that I_{Kur} was not a viable antiarrhythmic target, and simulations shed light on the mechanisms, showing that in cholinergic AF the contribution of I_{Kur} was dwarfed by the large magnitude of I_{KACH} . Furthermore, simulations determined that the lower availability of the atrial Na current at depolarized potentials could partly explain the earlier termination of AF compared with ventricular fibrillation during hyperkalemia. A recent attempt¹²⁸ to further explore the therapeutic strategy of blocking

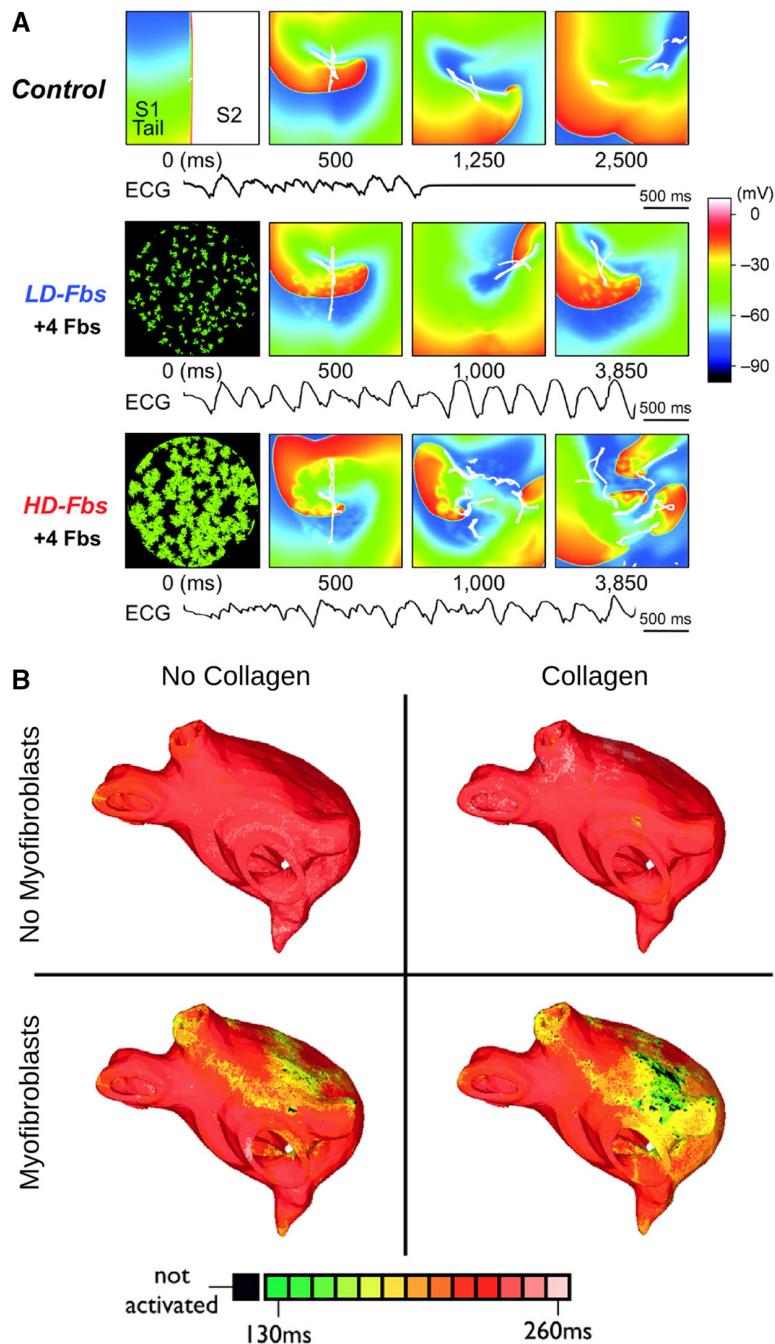


Figure 7. Modeling fibroblast proliferation in the regions of fibrosis. **A**, Effect of myocyte–fibroblast coupling on spiral wave behavior in a myocardial sheet of size 4.5×4.5 cm. **Top**, Control case without fibroblasts. **Middle** and **bottom**, Models of low-density and high-density fibroblast proliferation (LD-Fbs and HD-Fbs) in a central circular region of the sheet. In the LD-Fbs and HD-Fbs models, atrial myocytes (100 pF), each connecting to 4 fibroblasts (6.3 pF) within the Fb-Area, account for 12.5% and 50.0% of that area, respectively. The simulated ECG in each case is shown at the bottom. With permission from Ashihara et al.⁴⁶ **B**, Maps of action potential duration (APD) in 4 human atrial models (same atrial geometry). Fibrotic lesions are modeled with (**bottom row**) and without (**top row**) myofibroblast infiltration (exerting paracrine effects or coupling to myocytes), as well as with (**right column**) and without (**left column**) diffuse collagen deposition for both sets of maps. All models include gap junction remodeling in the fibrotic lesions. With permission from McDowell et al.⁶²

I_{Kur} demonstrated that the antiarrhythmic effects of I_{Kur} inhibitors are dependent on the kinetic properties of the blockade.

Block of Na-channel conductance by ranolazine displays marked atrial selectivity; Nesterenko et al¹²⁹ developed a Markovian model of Na-channel gating that elucidated the mechanisms underlying ranolazine's potent atrial selectivity. The possibility to develop Na channel blockers with maximal actions on fibrillating atrial tissue and minimal actions on ventricular tissue at resting heart rates was also probed.¹³⁰ A model of state-dependent Na-channel blocking (class I antiarrhythmic drug) action was used in simulations of AF and ventricular proarrhythmia. The study found that drugs that target inactivated channels are AF selective, whereas drugs that target activated channels are not. Such simulation methodology

has a strong potential to contribute to rational approaches to defining optimal Na-channel blocker properties.

Finally, simulation research⁴⁴ has provided mechanistic explanations regarding the lower efficacy of pharmacological treatment in patients with long-term versus short-term AF and of the antiarrhythmic properties of amiodarone and digitalis for AF treatment.

Antiarrhythmia Pacing for AF Termination

Pacemaker-based therapy for AF has been recognized as a possible alternative to drug therapy; today, many pacemakers and implantable defibrillators include pacing algorithms for AF prevention and termination.¹³¹ Most existing pacing algorithms deliver preventive therapies aimed to suppress AF triggers and

reduce dispersion in atrial refractoriness.¹³² Uldry et al¹³³ recognized that with the use of an atrial model, a better understanding of the degree of local capture by pacing can be achieved, which might have important implications for the development of pacing algorithms for AF termination. The authors used a 3D surface model of the human atria and rapidly paced it at a cycle length shorter than that of the detected arrhythmia, from a single site, in an attempt to terminate AF. Results demonstrated that the septum was the only pacing site that yielded AF capture in both atria. However, capture was sporadic, and overall, did not result in AF termination or permanent changes in AF pattern. A new pacing scheme, shown in Figure 8A, was subsequently devised,¹³⁴ in which the initial rapid septal pacing phase, this time from a large septal area (shown in red in septum, Figure 8A, left), was followed by a slow septal pacing phase from the same location (at a cycle length longer than that of the detected arrhythmia) aimed at lengthening the APD and thus eliminating any residual fibrillating wavelets that might have survived in areas distant from the septum during the rapid pacing phase. The new algorithm could suppress AF re-entries in a more robust way than single-site rapid pacing, with AF termination rate increasing from 10.2% to 20.2%. This simulation research provided a classical example of how realistic models of the atria can be used to generate new ideas and approaches to AF management optimization.

Optimizing Atrial Ablation

Catheter-based ablation, the delivery of heat to destroy the ability of cardiac tissue to generate and conduct electric signals locally, has emerged as a promising AF treatment option. The objective of AF ablation is to either abolish foci generating ectopic beats or to create zones of conduction block, eliminating re-entry. The procedure has successfully targeted AF triggers via PV electric isolation.¹³⁵ Aggressive ablation strategies, such as Maze III procedure,¹³⁶ were found to be the most effective when the underlying AF involved turbulent activity with multiple wavelets (presumably permanent AF). Human atrial models have been used to optimize AF ablation, suggesting strategies to minimize the size of ablation lesions, and to study the effect of gaps in ablation lines. An example⁶⁰ of simulated ablation lesions in a human atrial model is shown in Figure 8B. A set of studies^{55,137} explored the effectiveness of ablation line patterns that are less invasive than Maze III procedure and demonstrated that any such pattern needs to include ablation lines in both RA and LA so that a multiple-wavelet AF can be successfully terminated. Specifically, Maze III could be simplified while achieving the same success by diminishing RA ablation severity to a single line joining both vena cavae. In addition, simulations⁵⁵ showed that imperfect ablation lines in the Maze III procedure decreased success rate by ≤28%, with the rate depending on the location of lesion imperfection.

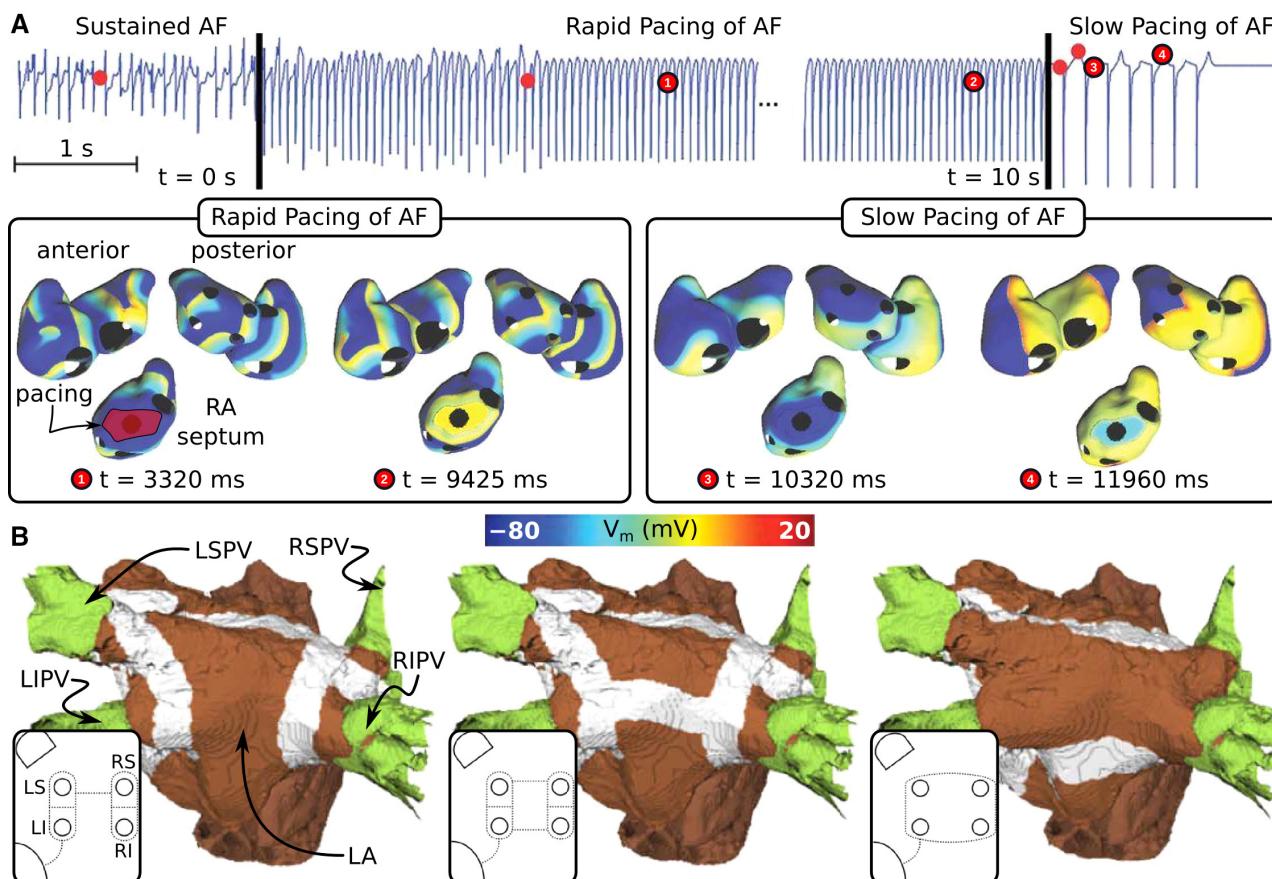


Figure 8. Simulations of atrial fibrillation (AF) management. **A,** Dual-stage septal pacing algorithm with successful AF termination in a 3-dimensional (3D) surface model of the human atria (with permission from Uldry et al¹³⁴). **B,** Modeling lines of ablation in the atria. Tissue targeted by ablation is shown in white. Modified with permission from Reumann et al.⁶⁰ LIPV (or LI) indicates left inferior pulmonary vein; LSPV (or LS), left superior pulmonary vein; RA, right atrium; RIPV (or RI), right inferior pulmonary vein; and RSPV (or RS), right superior pulmonary vein.

Recent ablation strategies have begun to target the LA wall in an attempt to alter the arrhythmogenic substrate.⁸⁸ Both 2D cellular automata models¹³ and biophysically detailed patient-specific models of fibrosis in the human atria¹³⁸ have shown preliminary success in providing guidance in AF substrate ablation. There is a high expectation that atrial models could be used to predict the optimal AF ablation strategies in a patient-specific manner.

Future of Simulation Research on AF Mechanisms and Atrial Arrhythmia Management

As this review demonstrates, mathematical modeling and computer simulations of atrial electrophysiology have made major contributions to the interpretation of an array of experimental data and to the dissection of the fundamental mechanisms and relationships underlying AF initiation and persistence. As this trend will continue in the future, atrial modeling as a tool will necessitate continuous adaptation and integration of new elements, including model redesign and evaluation, improvements in the execution time of biophysically detailed atrial models, implementation of consistent strategies for comparison with experimental measurements, and investing in efforts to ensure repeatability and consistency of modeling results. The advancement of atrial modeling will continue to be strongly dependent on developments in experimental methodologies, which provide data to constrain, enrich, and validate the models. Of particular importance will be the capability to better resolve the pathophysiological structure of the atria and to fully characterize the complex electrophysiological and fibrotic remodeling in disease. Major challenges that lie ahead for computer models of AF include, among others, elucidating the dynamics of human AF and detecting rotor locations, as well as understanding the multitude of factors that drive progression of AF in some, but not all, patients.

The use of atrial models in personalized diagnosis, treatment planning, and prevention of AF will also slowly become a reality; initial efforts in this direction are reviewed here. The feasibility of subject-specific AF modeling has been demonstrated through the use of atrial models reconstructed from clinical MRI scans. Biophysically detailed models of the atria assembled with data from clinical imaging modalities that incorporate electrophysiological and structural remodeling in cardiac disease are poised to become a first line of screening for new AF therapies and approaches, new diagnostic developments, and new methods for arrhythmia prevention. There are a number of important challenges that lie ahead: development and clinical translation of methodologies for personalized AF ablation planning, development of new and effective approaches for antiarrhythmia pacing, and devising improved methodologies for AF rate control. Finally, implementing patient-specific cardiac simulations at the patient bedside for AF therapy and management could become a thrilling example of computational approaches in translational medicine.

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