



Review

Computational modeling: What does it tell us about atrial fibrillation therapy?



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ABSTRACT

Atrial fibrillation (AF) is a complex cardiac arrhythmia with diverse etiology that negatively affects morbidity and mortality of millions of patients. Technological and experimental advances have provided a wealth of information on the pathogenesis of AF, highlighting a multitude of mechanisms involved in arrhythmia initiation and maintenance, and disease progression. However, it remains challenging to identify the predominant mechanisms for specific subgroups of AF patients, which, together with an incomplete understanding of the pleiotropic effects of antiarrhythmic therapies, likely contributes to the suboptimal efficacy of current antiarrhythmic approaches. Computer modeling of cardiac electrophysiology has advanced in parallel to experimental research and provides an integrative framework to attempt to overcome some of these challenges. Multi-scale cardiac modeling and simulation integrate structural and functional data from experimental and clinical work with knowledge of atrial electrophysiological mechanisms and dynamics, thereby improving our understanding of AF mechanisms and therapy. In this review, we describe recent advances in our quantitative understanding of AF through mathematical models. We discuss computational modeling of AF mechanisms and therapy using detailed, mechanistic cell/tissue-level models, including approaches to incorporate variability in patient populations. We also highlight efforts using whole-atria models to improve catheter ablation therapies. Finally, we describe recent efforts and suggest future extensions to model clinical concepts of AF using patient-level models.

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1. Introduction

The pathogenesis of atrial fibrillation (AF) involves a multitude of mechanisms that control its initiation, maintenance and progression, including alterations in electrical, structural, mechanical, neurohumoral, and metabolic properties [1]. The current management and treatment of AF remain unsatisfactory, likely due to incomplete understanding of the mechanisms underlying arrhythmogenesis and disease progression in an individual patient, and pleiotropic effects of current therapies.

Several factors have made it challenging to translate basic research findings into improved clinical management [2,3]. Simulation and modeling have proven tremendously valuable in physical sciences and engineering, and in the past five decades, computational approaches have also contributed to our understanding of cardiac physiology [4,5]. Multi-scale models of cardiac electrophysiology integrate structural

and functional data from experimental and clinical work with knowledge of atrial electrophysiological mechanisms and dynamics to improve our mechanistic understanding of this complex arrhythmia. Imaging-based whole-atria simulations have emerged as promising tools for AF management and treatment strategies tailored to each patient [6,7], contributing to the ongoing efforts towards precision medicine in cardiology.

Here, we review recent advances in our quantitative understanding of AF therapy with antiarrhythmic drugs (AADs) and catheter ablation through mechanism-based integrative mathematical models. We also discuss how approaches to incorporate variability might help to dissect mechanisms of disease and impact of treatment for specific patient populations. Finally, we describe recent efforts and suggest future extensions to model clinical AF concepts using patient-level models.

2. AF modeling approaches

Multi-scale mechanistic models are systems of differential equations in which dynamic quantities, so-called ‘state variables’ (e.g., ion channel states, membrane potential, intracellular ion concentrations), are iteratively updated depending on their current values. For example, the current membrane potential can determine

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the change in open probability of an ion channel. The most important modeling approaches at the level of the ion channel (Hodgkin-Huxley and Markov-type models), single cell (common pool and local control models) and tissue (mono- and bidomain approaches) are summarized in Fig. 1. Interested readers are referred to other reviews for methodological details [8–10]. In contrast to experimental work, simulation of mechanistic models provides perfect control over parameters, allowing observability of all model components, making them highly suitable to test for cause-effect relationships and explore AF mechanisms.

2.1. Cell models

The main characteristics and evolution of several commonly used human atrial cardiomyocyte models [11–15] have recently been reviewed [9,16]. The first human atrial cardiomyocyte models (Courtemanche et al. [11]; Nygren et al. [15]) focused on dynamic atrial electrophysiological properties and are still widely used for multi-scale simulations, along with their subsequent refinements and variants replicating regional atrial heterogeneity [14,17]. Subsequently, the Grandi and Koivumäki models have focused on the simulation of atrial Ca^{2+} -handling, emphasizing the importance of Ca^{2+} - and Na^+ -homeostasis in atrial electrophysiology [12,13]. The Grandi model also allows simulating the consequences of sympathetic and vagal stimulation (as in

the Maleckar model [14,18]). The Koivumäki model enables simulating centripetal Ca^{2+} diffusion, providing a first spatial representation of Ca^{2+} -cycling [13]. The Grandi model has also been merged with a spatial Ca^{2+} -handling model incorporating both transverse and longitudinal Ca^{2+} compartmentation [19], which has recently been employed to study the proarrhythmic effects of a heterogeneous distribution of Ca^{2+} -handling proteins [20]. Other extensions of the Grandi model include regulation of the basal and acetylcholine-activated inward-rectifier K^+ -currents I_{K1} and $I_{K,ACH}$, as well as atrial-specific two-pore-domain K^+ -channel (K_{2P}) models and their regulation in AF [21,22], and Markov-type Na^+ -channel and ultra-rapid delayed-rectifier K^+ -current (I_{Kur}) models [23–25]. Thus, contemporary cardiomyocyte models reproduce a wide range of experimental findings, but there is no single model that incorporates all key components. Each model has its own limitations, which should be taken into account when applying them to experimental findings.

2.2. Populations of models

Accounting for phenotypic diversity has become an important consideration when building models of cardiac electrophysiology and interpreting simulation results under (patho)physiological conditions. New tools, such as population-based approaches, have recently been developed to address some of the limitations of traditional modeling

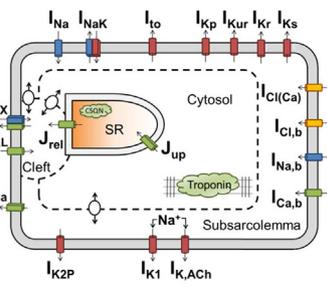
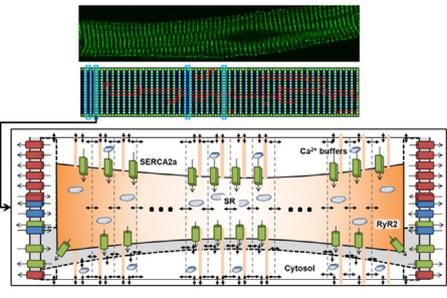
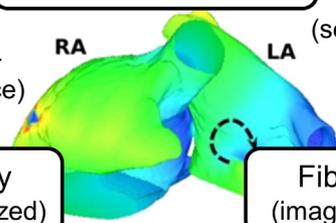
Computational modeling elements		Considerations for simulating AF therapy
Ion channel	<div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>Hodgkin-Huxley models (all gates function independently)</p> <p>$m \cdot h$</p> </div> <div style="text-align: center;">  </div> <div style="text-align: center;"> <p>Markov-type models (allow state-dependent transitions)</p>  </div> </div>	<p>Markov-type models are best suited to simulate state-dependence and kinetics of AAD binding</p>
Cardiomyocyte	<div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>Common-pool models (no spatial representation)</p>  </div> <div style="text-align: center;"> <p>Local control models (spatial representation)</p>  </div> </div>	<p>Local-control models enable Ca^{2+}-dependent ectopic activity (an accepted arrhythmia mechanism) and recently discovered effects of AADs (flecainide, ranolazine) on RyR2</p> <p>Computational complexity of local-control models presents a challenge for multicellular simulations</p>
Tissue	<div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>Monodomain (proportional conductivity of intra- and extracellular space)</p> </div> <div style="text-align: center;"> <p>Propagation</p> </div> <div style="text-align: center;"> <p>Bidomain (separate intracellular and extracellular space)</p> </div> </div>  <div style="display: flex; justify-content: space-around; margin-top: 10px;"> <div style="border: 1px solid black; padding: 5px;"> <p>2D/3D geometry (generic or personalized)</p> </div> <div style="border: 1px solid black; padding: 5px;"> <p>Fiber orientation (imaging or rule-based)</p> </div> </div>	<p>Tissue models can be computationally expensive but are essential to simulate reentrant activity</p> <p>Bidomain models are necessary when simulating external electrical stimulation (including cardioversion and defibrillation)</p>

Fig. 1. Schematic overview of the most important computational modeling approaches and elements at the ion channel, cardiomyocyte and tissue levels. The right column highlights a number of methodological considerations for simulating AF therapy. The whole-atria model figure was reproduced from [58].

approaches [26,27]. Populations of models are generally built from a baseline “average” model by varying sets of parameters within their experimental range or between theoretical upper/lower bounds. Statistical analyses of these populations have contributed to our understanding of the relative roles of the underlying parameters in modulating physiological properties of interest (i.e., sensitivity analysis), or revealing associations of certain parameter ranges or properties with specific physiological behaviors (e.g., repolarization abnormalities, ectopic activity, drug response) [28], as reviewed in [26]. Notably, although baseline variants of different atrial electrophysiological models exhibit important differences in action potential (AP) morphology and rate dependence [16,29], recent population-based simulations showed remarkable similarities in the ionic determinants of inter-subject variability in three different human atrial AP models [30]. Furthermore, populations of models with wide variations in ionic densities can yield APs consistent with experiments, even if baseline models are initially far away from the specific experimental cohort [31]. Although, there are requirements for the baseline model employed for population-based simulations, for example the ability to recapitulate the AF mechanisms being studied (e.g., not all models can simulate abnormal automaticity or ectopy), the population-based approach may 1) reflect natural cell-to-cell variability, even within a single right-atrial sample; 2) address uncertainty in measurements, whereby several expression patterns may produce the same AP under basal conditions but respond differently to challenges; and 3) reduce the impact of the selected parameters of the baseline model.

2.3. Tissue and organ (image-based) models

Atrial-tissue models can simulate the major arrhythmogenic mechanisms and such models have been used to investigate the ionic bases of clinically observed AF mechanisms involving steep APD gradients [32]. Given the small atrial-wall thickness, 2D geometries have been used extensively as approximations of atrial tissue for simplified AF simulations. Patient-specific anatomical models of the human atria have been constructed from diffusion tensor magnetic resonance imaging (MRI) reconstructions of tissue geometry. Recently, organ-level atrial models have also begun to represent fibrotic remodeling associated with AF. These geometries can be combined with heterogeneous AP models and recapitulate diverse forms of AF dynamics, including stable rotors, wavelets broken by repolarization heterogeneities, and multiple unstable meandering wavelets [17,33–37]. The 3D atria can also be incorporated into a torso model to simulate body-surface electrocardiogram (ECG) patterns [33] and have the potential to provide in-depth insights into AF mechanisms beyond current experimental or clinical technical capabilities. For example, integrating ex-vivo imaging and functional data in a 3D high-resolution whole-atria model has enabled the identification of specific structural properties (“fingerprints”) underlying localized AF drivers [38]. Image-based organ models and their applications have been reviewed recently [6,7] and are the focus of a separate review in this issue.

3. Anti-AF drug therapy: What can we learn from modeling?

3.1. Atrial efficacy and safety

The development of effective and safe AADs against AF remains an important unmet clinical need. Recently, both atrial-predominant and multi-channel block have emerged as promising strategies for AF therapy. Atrial-specific ion-channel block may enable antiarrhythmic effects while avoiding ventricular proarrhythmia. Combination therapy may allow synergistic antiarrhythmic drug responses and thus reduction of therapeutic doses, thereby minimizing deleterious side effects. Several modeling and simulation examples have highlighted their usefulness to predict safety and efficacy of anti-AF therapeutic strategies [39]. Many of these studies suggest that accurately accounting for drug-

channel interactions, instead of relying on steady-state concentration response curves or EC_{50} values, might be necessary to understand how AADs interact with a dynamically changing atrial (and ventricular) substrate [23,40–42]. These considerations might play an important role in the prospective design of novel AADs, whereby an optimal AF-selective pharmacological approach would aim at maximizing drug effects at fast atrial rates without impacting normal sinus rhythm.

One strategy to achieve atrial selectivity is to exploit differences in atrial vs. ventricular electrophysiology. Atrioventricular differences in AP- and I_{Na} -gating properties render certain Na^+ -channel blockers atrial-selective [40,43]. For example, ranolazine prolongs atrial AP duration (APD), slows conduction and suppresses AF, without affecting ventricular parameters [43]. Computational modeling has shown that ranolazine may also prevent proarrhythmic Ca^{2+} overload- and I_{Na} -mediated phase-3 afterdepolarizations in an atrial-selective manner [23]. Kinetics and state dependence of drug-channel interactions also modulate Na^+ -channel rate selectivity. In a combined experimental and computational study, anti-AF properties of Na^+ -channel blockers were potentiated by concomitant K^+ -channel blockade [40], prolonging the AP plateau and increasing APD. These effects led to a synergistic reduction of I_{Na} -dependent parameters (upstroke and conduction velocities), a more rapid termination of AF, and reduced AF inducibility [40]. Modeling has also demonstrated that AF-selectivity of I_{Na} inhibition is greatly augmented by blocking multiple atrial K^+ -currents (e.g., by acacetin) and translates into an enhanced termination of reentrant excitation waves. Importantly, virtual human ventricular cardiomyocytes and tissue were only modestly affected by acacetin and I_{Na} blockers [44].

Nevertheless, blocking K^+ channels that are also abundantly expressed in ventricular tissue might pose safety concerns due to the increased risk of torsade-des-pointes arrhythmias, making atrial-predominant ion-channels attractive anti-AF targets. The atrial-predominant small-conductance Ca^{2+} -activated K^+ -current (I_{KCa}) blocker ICAGEN indeed enhances the anti-arrhythmic properties of the I_{Na} inhibitors flecainide and ranolazine in guinea pig atria [45]. However, the role of I_{KCa} in either promoting or opposing AF is controversial, highlighting a role for modeling approaches to establish conditions in which I_{KCa} inhibition or stimulation might be anti-arrhythmic [46]. Atrial-predominant K_{2P} channels (e.g., $K_{2P3.1}$) are upregulated in AF and their inhibition reduces the stability of reentry in 2D-tissue simulations incorporating electrical remodeling observed in AF patients with preserved left-ventricular function, but not AF patients with left-ventricular dysfunction, where $K_{2P3.1}$ channels are downregulated [22]. These results demonstrate how combined experimental and computational studies can be used to predict therapeutic efficacy of new targets in specific patient populations. Numerous compounds targeting the atrial-predominant I_{Kur} have been screened in vitro and in AF animal models. However, evidence of antiarrhythmic efficacy in clinical trials is still lacking. A novel Markov-type model of I_{Kur} gating and drug-channel interaction revealed the ideal binding properties of I_{Kur} inhibitors that maximize AF-selectivity. The identified drug characteristics favor APD prolongation at fast atrial rates, while causing limited or no effect during normal heart rhythm. Despite being strongly downregulated in chronic AF (cAF) simulations, I_{Kur} contributes more prominently to APD in cAF than in sinus rhythm, and I_{Kur} inhibition in cAF displayed less cardiotoxic effects with increased efficacy [24,25]. Thus, these computational modeling results suggest that the lack of clinically effective I_{Kur} inhibitors might be partly explained by the fact that preclinical assessment of candidate drugs overly relies on steady-state drug concentration-response curves rather than accounting for channel-state specificity and kinetics of drug binding.

I_{K1} is upregulated in cAF, promoting reentry stabilization in experiments [47] and simulations [48,49]. Pentamidine analogue-6 (PA-6) inhibits I_{K1} , restores sinus rhythm in goats with persistent AF, and decreases AF complexity before cardioversion [50], without affecting QT interval or heart rate in dogs, thus representing a potential safe therapeutic candidate for AF [50].

3.2. Role of variability

Applying population-based approaches incorporating variability to study the effects of AADs substantially advances traditional approaches: it allows interpreting drug effects on electrophysiological properties at a population level and identifying the factors underlying the variability in drug-responses [26]. Indeed, a set of whole-atria models with identical structure (geometry and fiber orientation), but distinct electrophysiological properties selected from an experimentally calibrated population of AP models shows remarkable differences in AF properties [51]. Liberos et al. compared 3D-atrial tissue models with sustained versus self-terminating reentry circuits [52], showing that AF maintenance correlates with large L-type Ca^{2+} -current (I_{CaL}) and I_{Na} , and that I_{CaL} block could be an effective treatment depending on the basal availability of Na^+ and Ca^{2+} channels, with I_{Na} depression increasing overall efficacy. Thus, understanding the causes of variability in organ-level electrophysiological behavior and arrhythmia proclivity [28] may allow developing specific antiarrhythmic approaches for different arrhythmia phenotypes, potentially limiting the contribution of parameter- or model-dependent findings.

4. Computational modeling of AF ablation

Catheter ablation appears more effective than AAD therapy at maintaining sinus rhythm [53], and recent data suggest that AF ablation may even improve mortality in selected populations [54]. Overall, ablation results remain suboptimal, particularly in cAF patients [55,56]. Recently, several ablation strategies have been proposed with limited additional benefit compared to pulmonary vein isolation alone. Thus, the most effective ablation strategy remains unclear and is likely patient specific. Personalized computational models represent a promising tool to determine optimal ablation strategies in a given patient [7,10]. Simulation studies have provided information on the effectiveness of different surgical- or catheter-based ablation strategies to terminate AF in representative virtual atria [57,58]. Other studies have employed personalized computed-tomography [59] or MRI [37,60]-derived anatomies to retrospectively identify optimal patient-specific ablation strategies. The use of MRI also enables personalization of fibrosis patterns, which are a critical component of AF initiation and maintenance [37]. Recently, the practical feasibility of model-guided selection of predetermined AF ablation-lesion sets has been shown in a prospective randomized study, albeit only using personalization of computed-tomography-derived endocardial-wall anatomy [61].

These examples provide an important proof-of-concept and highlight the potential of image-based models for improving AF ablation, although it remains to be demonstrated whether they can improve patients' outcomes. Several other challenges remain. First, only a handful of labs worldwide have the available expertise, computing power and required collaboration between clinicians and engineers to perform these interdisciplinary studies. However, with technological advances, simulations will become faster and easier to use, with commercial applications facilitating a more wide-spread use. Second, the extent of personalization of whole-atria models remains limited. Although late-gadolinium-enhancement MRI can provide information on patient-specific structural abnormalities, its current spatial resolution is insufficient to detect microscopic structural abnormalities, which may alter atrial conduction, producing microreentry circuits maintaining AF [38]. Similarly, fiber orientation in whole-atria models is currently rule-based or adapted from an atlas of ex-vivo data. Finally, most whole-atria models employ a generic AP model (typically a version of the Courtemanche model [11]) to simulate electrophysiological properties [37,58,59]. Variability in electrophysiological parameters has a significant impact on reentrant driver localization, suggesting that simulation-predicted ablation strategies from patient-specific atrial models only incorporating individual fibrosis patterns alongside an average representation of AF-remodeled electrophysiology may not fully

reproduce the individual phenotype [62]. Patient-specific electrophysiological information can be obtained invasively using mapping systems, but integrating this information in whole-atria models within the time constraints of a single ablation procedure will remain challenging. Moreover, perhaps one of the most important future contributions of whole-atria models may be the identification of patients in whom ablation is unlikely to be successful, and therefore should not undergo invasive procedures in the first place. Besides population-based modeling approaches (discussed above), non-invasive electrocardiographic imaging [63] or information from patient-specific induced pluripotent stem-cell-derived cardiomyocytes [6] may be used in the future to constrain some electrophysiological properties, although both have their own limitations.

5. Modeling long-term outcomes of AF patients

Although cellular, tissue and whole-atria models have provided important information about AF mechanisms and the acute electrophysiological effects of antiarrhythmic therapies, they do not provide information on the long-term clinical outcomes of AF patients. Patient- or population-level models representing dynamic transitions between different clinical states over extended time-periods have been employed to study cost-effectiveness of treatment strategies. These patient/population-level models are often based on Markov-type decision models, methodologically similar to the ion-channel formulations employed in modern cardiomyocyte models [9,64], and can be employed to simulate the dynamic distribution of a large population over different states, or the stochastic transitions of a single virtual individual or ion channel [9,64].

Patient-level Markov models, typically covering a period from several years up to the lifetime of a virtual population with 1-month intervals, have been used to determine the cost-effectiveness of non-vitamin-K oral anticoagulants and warfarin (reviewed in [65]), more extensive ablation strategies [66] and screening for asymptomatic AF [67]. Patient-level models have also been used to design optimal screening strategies [67] and to identify the impact of differences in patient populations and the associated heterogeneity in treatment effects between different studies [68]. For example, in a patient-level model for anticoagulation of AF patients with dabigatran vs. warfarin, differences in patient characteristics between the RE-LY trial and subsequent observational studies in real-world populations could largely explain discrepancies in bleeding rates, but not the rates of ischemic stroke [68]. Most AF-related patient-level models simulate the clinical outcomes of patients with AF, rather than the arrhythmia itself. One notable exception studied AF progression at a much higher temporal resolution (minutes), simulating the stochastic transitions between sinus rhythm and AF during the lifetime of a virtual patient [69]. However, this model does not consider the proper epidemiology of AF, with every individual progressing to permanent AF by 80 years of age.

Thus, patient-level models enable simulations of clinically relevant time scales and outcomes. Current patient-level models predominantly focus on health-economics applications and are mainly based on statistical properties derived from clinical trials rather than fundamental mechanistic understanding. However, future 'hybrid' mechanistic cell/tissue/whole-atria and patient-level models may help to bridge the widely different time-scales relevant for linking AF pathophysiology, epidemiology and clinical management, thereby contributing to improved tailored AF therapy.

6. Computational modeling in the era of big data

Statistical models already play a central role in the clinical management of AF, for example to assess stroke/bleeding risks. Although there are certain commonalities between mechanistic and statistical models (e.g., their dependence on clinical/experimental data), a number of important differences should be considered. Most statistical models reflect

a static association between inputs and outputs, which are entirely derived from clinical or experimental data. The significant increase in data availability and advances in machine-learning techniques to derive models has promoted a strong interest in “big data”, which has been suggested to radically improve the diagnosis and treatment of cardiovascular diseases in the upcoming years [70]. Conversely, mechanistic models integrate information from clinical or experimental data (e.g., through parameter estimation procedures) with known biophysical laws to produce dynamic cause-effect simulations, and thus are essential to improve our understanding of the complex dynamics of AF, its underlying mechanisms and the effectiveness of specific therapeutic approaches. Ultimately, both strategies likely provide complimentary information and might even be integrated, whereby simulation output from a mechanistic model is combined with other clinical data in a statistical model to guide AF management in an individual patient.

7. Clinical relevance and conclusions

Computational modeling of AF has undergone substantial advances in the last 20 years. Although individual models are developed to address specific questions and usually operate on a limited subset of scales (e.g., addressing molecular and cellular AF mechanisms, whole-atria

electrophysiology, or different clinical states), together these models have covered AF pathophysiology from molecule to patient (Fig. 2). Statistical models (e.g., for stroke risk) already play a major role in clinical AF management and will be likely further refined with increasing data availability. At present, the relevance of mechanistic computational models is only indirect, serving as a plausibility check for mechanisms proposed based on experimental observations and helping to generate new hypotheses that can subsequently be tested experimentally. Their recent use in safety pharmacology may further affect clinical practice by guiding the preclinical development of novel AADs. Similarly, patient-level cost-effectiveness models may also affect clinical practice by influencing reimbursement policies. The direct clinical application of mechanistic models to guide AF therapy (notably ablation) is emerging, but is currently restricted to a few expert centers. Taken together, currently available models have provided insight into all major components of AF therapy, including AADs, ablation and anticoagulation, but their role in the disease management of AF patients is still in its infancy and there are numerous challenges that need to be overcome (Table 1). Nonetheless, technological advances and interconnection of different types of models are expected to further increase the relevance of computational modeling for clinical AF management in the years to come.

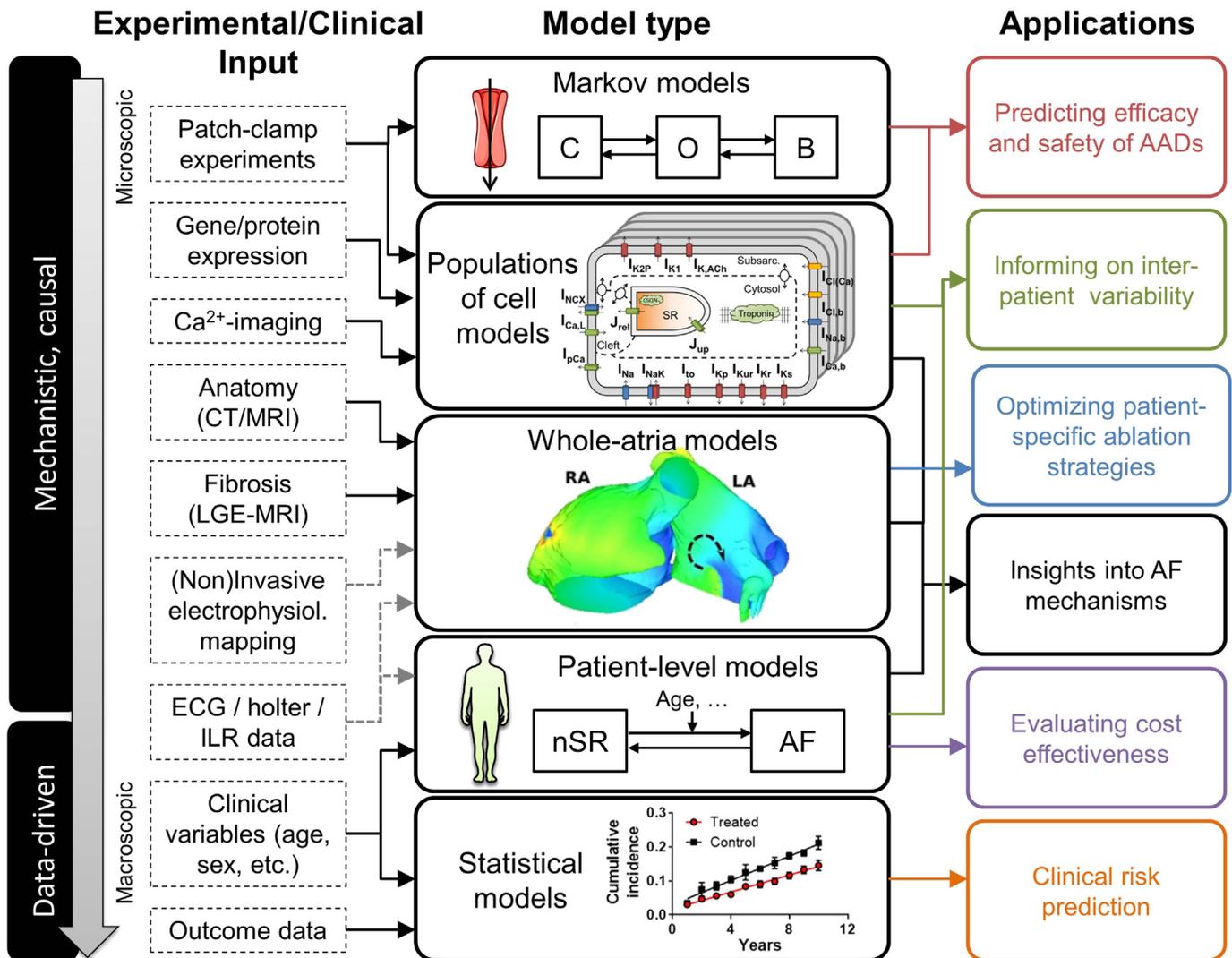


Fig. 2. Overview of types of models and their most important experimental/clinical inputs and applications. The whole-atria model figure was reproduced from [58].

Table 1
Summary of notable results and challenges for computational modeling of AF.

Notable results

1. A wide range of action potential models has been published, each reproducing numerous experimental observations.
2. Populations of models generated by varying model parameters can account for phenotypic diversity between patients and help to analyze differences between baseline models.
3. Combined experimental and computational studies can inform on the therapeutic efficacy against AF targets, including state-dependent drug-channel interactions and drug combinations, in specific subgroups of patients.
4. Whole-atria models have provided insight into the determinants of reentrant activity and drivers for AF.
5. Patient-specific anatomy and fibrosis patterns have been used to retrospectively identify optimal patient-specific ablation strategies, with initial prospective applications being explored.
6. Patient-level models can simulate the entire lifetime of a virtual cohort and inform on AF progression and cost-effectiveness of AF therapies.

Notable challenges

1. Each action potential model has different advantages and disadvantages, with numerous results being model specific.
2. The etiology of AF is diverse, but currently available cardiomyocyte models only have limited options for tailoring models to specific clinical conditions.
3. Only a handful of labs worldwide have the available expertise, computing power and required collaboration between clinicians, scientists and engineers to apply mechanistic whole-atria models in the clinical setting.
4. The extent of personalization of whole-atria models, particularly with regard to electrophysiological properties, remains very limited.
5. Current patient-level models do not incorporate fundamental mechanistic patterns of AF pathophysiology.
6. Integration of mechanistic modeling with “big data” approaches might help to improve AF diagnosis and management.

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