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Review
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Current progress of computational modeling for guiding clinical atrial fibrillation ablation

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Abstract: Atrial fibrillation (AF) is one of the most common arrhythmias, associated with high morbidity, mortality, and healthcare costs, and it places a significant burden on both individuals and society. Anti-arrhythmic drugs are the most commonly used strategy for treating AF. However, drug therapy faces challenges because of its limited efficacy and potential side effects. Catheter ablation is widely used as an alternative treatment for AF. Nevertheless, because the mechanism of AF is not fully understood, the recurrence rate after ablation remains high. In addition, the outcomes of ablation can vary significantly between medical institutions and patients, especially for persistent AF. Therefore, the issue of which ablation strategy is optimal is still far from settled. Computational modeling has the advantages of repeatable operation, low cost, freedom from risk, and complete control, and is a useful tool for not only predicting the results of different ablation strategies on the same model but also finding optimal personalized ablation targets for clinical reference and even guidance. This review summarizes three-dimensional computational modeling simulations of catheter ablation for AF, from the early-stage attempts such as Maze III or circumferential pulmonary vein isolation to the latest advances based on personalized substrate-guided ablation. Finally, we summarize current developments and challenges and provide our perspectives and suggestions for future directions.

Key words: Atrial fibrillation; Catheter ablation; Computational modeling; Atrial fibrosis

1 Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias worldwide (Rahman et al., 2014; Patel et al., 2018), characterized by very chaotic and irregular propagation throughout the atria, leading to cardiac acceleration and the loss of mechanical contraction (Heijman et al., 2016; Nattel et al., 2020). Approximately 1%–2% of the world's population suffers from AF, a percentage which is expected to double by 2050 (Nishida and Nattel, 2014). In China, the prevalence of AF is 0.77%–1.03%, and there were 5.26 million patients over the age of 18 years in 2013; the prevalence also is increasing year by year (Li et al., 2013). Even more worrying, AF increases the risks of other serious diseases, mainly stroke and heart failure, which are associated with high morbidity and mortality (Benjamin et al., 2017; Ahmed et al., 2019), high treatment costs (Ha et al., 2017), and reduced quality of life (Sławuta et al., 2020). Thus, the management of AF is critical and urgent for individuals and society. In general, treatment of AF is often attempted with anti-arrhythmic agents, electrical cardioversion, and maze/catheter ablation strategies. Because of limited efficacy and significant side effects in some cases (Miller et al., 2019), treating AF with anti-arrhythmic agents is not the optimal choice.

Ablation therapy (catheter ablation) is an alternative option, especially for AF patients who do not tolerate anti-arrhythmic agents (Bhatti et al., 2019), and in terms of therapeutic effect, it seems to be more effective than anti-arrhythmic agents as well (Hakalahti et al., 2015). The principle of catheter ablation therapy is creating lesions with a catheter using radiofrequency energy or cryoenergy. The lesion forms a barrier to prevent the conduction of electrical activity, halting fibrillation (Verma et al., 2015). Aggressive ablation pattern such as Cox's Maze III procedure

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(Cox et al., 1991) has been found to have a high success rate in treating AF. This approach involves a complicated set of incisions made in a maze-like pattern on the left and right atria to block the abnormal impulses that cause AF. However, ablation requires open-heart surgery, which is time-consuming and may cause complications (Weimar et al., 2012). Pulmonary vein isolation (PVI) (Haïssaguerre et al., 1998) represents the cornerstone of current catheter ablation approaches for the treatment of AF. This approach achieves the goal of electrically isolating AF triggers in pulmonary veins (PVs) through circumferential ablation lesions in the PVs, thus successfully terminating AF, especially in patients with paroxysmal AF. However, the success rate of this strategy in patients with persistent AF (PeAF) remains limited as the triggers for PeAF may originate outside of PVs (Dewire and Calkins, 2013; Conti et al., 2018; Pallisgaard et al., 2018). Although several different extra-PVI ablation approaches have been developed and attempted to increase the success rate of clinical procedures, whether patients with AF can benefit from these additional ablation strategies remains uncertain (Latchamsetty and Morady, 2018). There is no one-size-fits-all ablation approach. Hence, the most efficient and personalized ablation strategies with the fewest ablation lesions need to be pursued.

Virtual ablation with computational modeling has some unique advantages in comparison with clinical catheter ablation. For example, (1) different ablation strategies can be tested in the same biophysical model; (2) the effectiveness of any ablation strategies can be tested; (3) modeling parameters are flexibly controlled; (4) computational modeling costs less; and (5) lastly and most importantly, there is no risk to human life. Based on these advantages, computational modeling can provide additional information about the mechanisms of AF initiation and maintenance, and help to determine a personalized optimal ablation strategy. Over the past several decades, research groups worldwide have made many attempts with significant progress. This review provides a detailed description of virtual ablation for AF, from the initial attempt to the latest development.

2 Development of the computational modeling for atrial fibrillation ablation

2.1 Early development

Early-stage three-dimensional (3D) computational modeling for AF ablation is briefly summarized in Table 1. Dang et al. (2005) created the first life-size 3D biophysical model for evaluating ablation patterns and comparing ablation outcomes in silico with clinical data. They integrated a magnetic resonance imaging (MRI)-derived monolayer bi-atrial model with the homogeneous modified Luo-Rudy ionic model (Luo and Rudy, 1991). The monodomain reaction-diffusion function was solved by the finite volume approach to simulate wave propagation in cardiac tissue (Virag et al., 2002). The gold standard Cox's Maze III and 12 other less invasive ablation patterns were simulated in this biophysical AF model. The results confirmed an excellent success rate for Maze III and illustrated that both right and left atrial ablation lesions should be included in less invasive ablation patterns. The work in this paper indicated that computational modeling could be useful for the development of new ablation patterns.

Table 1 3D geometrical atrial models

Reference	Image source	Geometry	Atrial myocyte model	Fiber orientation	Numerical solution	Ablation pattern
Dang et al., 2005	MRI	Monolayer, bi-atrial	Modified Luo-Rudy model	No	FVM	Maze, modified maze
Ruchat et al., 2007a, 2007b, 2007c	MRI	Monolayer, bi-atrial	Modified Luo-Rudy model	No	FVM	Maze, modified maze
Rotter et al., 2007	MRI	Monolayer, dilated, bi-atrial	Modified Luo-Rudy model	No	FVM	PVI, linear ablation
Reumann et al., 2008	Visible female	Multilayer, bi-atrial	Cellular automaton	Visible female data	FEM	PVI, linear ablation maze
Gong et al., 2015	Heart specimen	Bilayer, bi-atrial	Modified Courtemanche model	Image-based	FDM	Maze, modified maze

3D: three-dimensional; MRI: magnetic resonance imaging; FVM: finite volume method; FEM: finite element method; FDM: finite difference method; PVI: pulmonary vein isolation.

Ruchat et al. (2007a, 2007b, 2007c) used one MRI-derived atrial model to test the effectiveness of different AF ablation line patterns and defined more efficient ablation patterns for the modified maze. The results suggested that Maze III was the most efficient ablation pattern and that the mini-maze ablation pattern was an effective strategy for converting fibrillation to sinus rhythm. The authors also found that the more ablation lines there were, the more effectively AF was terminated, and a combination of ablation lines in the left and right atria enhanced the success rate. Notably, potential complications after AF ablation often led to atrial flutter (Steinbeck et al., 2018). Rotter et al. (2007) used one MRI-derived atrial model to simulate five different ablation strategies and investigated their effects in AF termination and their propensity to form atrial flutter substrates. Furthermore, they expanded the same atrial geometry by 1.26 times to mimic the AF-introduced characteristic of dilated atria (Nattel and Harada, 2014). They demonstrated that PVI in combination with extra linear lesions had a higher success rate than PVI alone. There were a higher atrial flutter incidence and a decreased incidence of AF termination in the dilated atrial model compared with the nondilated model with four of the five ablation patterns.

Another computational model for AF ablation was published by Reumann et al. (2008). They constructed a realistic multilayered bi-atrial anatomical model, including atrial thickness and detailed anatomical structures, based on the visible female dataset (Seemann et al., 2006) and combined it with an advanced cellular automaton model (Reumann et al., 2007) and isotropic conduction. AF was induced at 35 different locations on the left atrial surface via an s1/s2 stimulus induce-protocol (Haïssaguerre et al., 1998). Ten different ablation patterns were simulated to test the optimal patterns to terminate AF. The results of the simulation found that the ablation pattern with a single circumferential lesion surrounding all PVs displayed a lower success rate in all simulation tests (Reumann et al., 2008). By contrast, the success rate reached its maximum with the combination of a circumferential ablation pattern and at least two additional linear ablation lesions. However, it may be worthwhile to note that one circumferential lesion line around all PVs, rather than lines around each individual PV, is used in current clinical practice at most institutions to avoid complications and thus achieve a higher success rate of PVI (Woods and Olgin, 2014).

In 2015, Xia's group used one detailed 3D AF model to study the efficacies of different ablation patterns (Gong et al., 2015). The cardiac anatomical model was reconstructed from a healthy adult heart with a detailed conduction system and realistic fiber orientation (Deng et al., 2012). The focus pacing protocol was used to initiate AF (Gong et al., 2007). Eight different ablation patterns based on the standard Maze III were simulated and evaluated in terms of the time required for AF termination. The authors discovered that the ablation lines on the right atrium were connected to the superior and inferior vena cava, and one modified Maze III pattern with fewer ablation lines was as effective as the standard Maze III pattern.

In general, because of the development of more realistic atrial models, these early studies mentioned above used a computational simulation model of the human atria to evaluate different ablation patterns and compared the results with both the standard Maze III procedure (as a reference) and clinical outcomes. These computational models demonstrated that modeling could effectively address specific clinical questions regarding the efficacies of AF ablation strategies. It should be noted that in the early work, most ablation strategies were non-personalized, and were basically developed by making small changes from Maze III or circum-PVI. At this point, more accurate heterogeneous electrical properties and atrial structural remodeling representation, especially fibrosis, have not been integrated with computational modeling. At the same time, most of the clinical questions that need to be addressed involved patient-specific ablation targets for patient treatment. Hence, non-personalized models and ablation strategies do not meet the essential requirements for clinical practice.

2.2 Connection between atrial fibrillation and fibrosis

In recent years, patient-specific AF models have been developed by more realistic representations of the atrial substrate, mainly because electroanatomic remodeling of the atria has been shown to be conducive to the progressive nature of the generation and maintenance of AF (Nattel and Harada, 2014). Moreover, structural remodeling, especially atrial fibrosis, plays a crucial role in this process and has been clinically demonstrated to be associated with AF (Seitz et al., 2011; Morgan et al., 2016). Specifically, the interaction between fibroblasts and myocytes changes the conduction velocity (CV) and action potential duration (APD), both of which slow localized regional conduction, increase conduction heterogeneity, and provide an AF substrate, thus promoting the formation of reentry (Nguyen et al., 2014; Cochet et al., 2018). Hence, information on the degree and extent of fibrosis in patients with AF is extremely useful in obtaining the personalized atrial arrhythmogenic substrate to guide clinical catheter ablation. Voltage mapping during catheter ablation for AF is commonly used in clinical practice for the assessment of atrial fibrosis (Rolf et al., 2014). However, it has a number of drawbacks, such as weak correlation with the fibrotic substrate, lack of standardized and reproducible protocols, and the invasive nature. In contrast, advanced late gadolinium-enhancement-MRI (LGE-MRI) is a novel tool, which has been shown recently to be less invasive and more reproducible for assessing fibrotic substrate. The approach is to localize and quantify the substrate by providing 3D visualization of the remodeled atria (Pontecorboli et al., 2017; Fochler et al., 2019; Mărgulescu et al., 2019; Sim et al., 2019). These developments in image processing and electrical signal processing techniques contribute to mapping the patient-specific arrhythmogenic substrate of AF and identifying optimal ablation targets (Nademanee et al., 2004; Sanders et al., 2005; Takahashi et al., 2008; Ganesan et al., 2013; Seitz et al., 2017), permitting developments of custom-tailored ablation strategies. A workflow for a patient-specific model to predict the optimal AF ablation strategy is shown (Fig. 1). Table 2 provides an overview of the published patient-specific models of AF and their properties. The details of the progress in this area are discussed in the following sections.

2.3 Optimal atrial fibrillation ablation strategies using personalized computational models

PaK's group used virtual in silico modeling to study the efficacy of different ablation methods and to guide catheter ablation in the last decade. Specifically, Hwang et al. (2014) used the computational platform devolved by their group to perform patient-specific virtual AF ablation and validate the outcomes of in silico AF ablation with the empirically chosen clinical ablations. In their study, 20 left atrial models were created from 20 patients' clinical spiral computed tomography (CT) merged with 3D electroanatomical map data. Five different virtual ablation protocols (using PVI, PVI with three different additional ablation lines, and complex fraction atrial electrogram (CFAE)) were applied to the models to test their efficacies. They found that circumferential pulmonary vein isolation (CPVI) with additional ablation lines was the most effective ablation pattern to terminate AF in the left atrium. Moreover, the CFAE-guided approach did not yield better success rates, which was

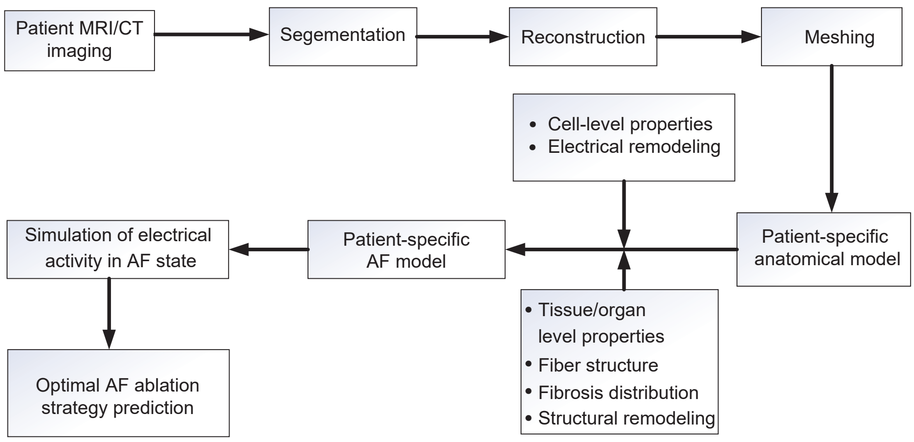

Fig. 1 Workflow for a patient-specific model to predict the optimal AF ablation strategy. LGE-MRI or CT images from individual patients with AF are processed to segment, reconstruct, and mesh a patient-specific anatomical model. Next, cell/tissue/organ-level properties are assigned to the anatomical model to create a patient-specific AF model and personalized simulations are conducted to determine the optimal ablation strategy. AF: atrial fibrillation; MRI: magnetic resonance imaging; LGE-MRI: late gadolinium-enhancement-MRI; CT: computed tomography.

Table 2 Patient-specific models of AF and their properties

Reference	n	Image source	Geometry	Cell model	Fibrosis distribution	Fiber orientation	NS	Ablation pattern	Guide for clinical practice
Hwang et al., 2014	20	CT	Monolayer, left atrial	Modified, CRN model	No	No	FEM	PVI, linear ablation, CFAE	No
Hwang et al., 2016	1	CT	Monolayer, left atrial	Modified, CRN model	No	No	FEM	PS-based, ShEn-base, DF-based, CFAE	No
Lim et al., 2017	10	CT	Monolayer, left atrial	Modified CRN model	No	No	FEM	DF-based, PS-based	No
Shim et al., 2017	108	CT	Monolayer, left atrial	Modified CRN model	No	No	FEM	PVI, linear ablation, CFAE	Yes
Kim et al., 2019	118	CT	Monolayer, left atrial	Modified CRN model	No	No	FDM	PVI, linear ablation, CFAE	Yes
Lim et al., 2020b	27	CT	Monolayer, left atrial	Modified CRN model	Clinical voltage map-based	Atlas-based	FDM	PS-based, DF-based	Yes
Lim et al., 2020a	10	CT	Monolayer, bi-atrial	Modified CRN model	Clinical voltage map-based	Atlas-based	FDM	PVI, IAC-based	No
McDowell et al., 2015	4	MRI	Bilayer, left atrial	Krummen model+ fibroblasts	Thresold-based	Atlas-based	FEM	PS-based	No
Zahid et al., 2016	10	MRI	Bilayer, bi-atrial	Modified CRN model	Thresold-based	Atlas-based	FEM	Graph-based	No
Deng et al., 2017	12	MRI	Bilayer, bi-atrial	Modified CRN model	Thresold-based	Atlas-based	FEM	RD-based	No
Hakim et al., 2018	12	MRI	Bilayer, bi-atrial	Modified CRN model	Thresold-based	Atlas-based	FEM	RD-based	No
Boyle et al., 2018b	11	MRI	Bilayer, bi-atrial	Modified CRN model	Thresold-based	Atlas-based	FEM	RD-based	No
Boyle et al., 2018a	12	MRI	Bilayer, bi-atrial	Modified CRN model	Thresold-based	Atlas-based	FEM	RD-based	No
Boyle et al., 2019	10	MRI	Bilayer, bi-atrial	Modified CRN model	Thresold-based	Atlas-based	FEM	RD-based	Yes
Ali et al., 2019	12	MRI	Bilayer, bi-atrial	Modified CRN model	Thresold-based	Atlas-based	FEM	PVI, RD-based	No
Shade et al., 2020	32	MRI	Bilayer, bi-atrial	Modified CRN model	Thresold-based	Atlas-based	FEM	RD-based	No
Bayer et al., 2016	1	CT	Bilayer, bi-atrial	Modified CRN model	Possibility method	Rule-based	FEM	PVI, linear ablation, AS-based, PS-based	No
Roney et al., 2018	12	MRI	Bilayer, bi-atrial	Modified CRN model	Possibility method, thresold-based	Atlas-based	FEM	PVI, IAC-based	No
Roney et al., 2020	50	MRI	Bilayer, left atrial	Modified CRN model	Thresold-based	DTMRI-based	FEM	PVI, linear ablation, PS-based	No
Alessandrini et al., 2018	1	MRI	Bilayer, left atrial	Modified CRN model	No	Rule-based	FEM	Basket Cathter-based	No
Roy et al., 2020	6	MRI	Bilayer, left atrial	Modified FK model	Thresold-based	No	FDM	PVI, linear ablation, RD-based	No
Gharaviri et al., 2021	1	MRI	Bilayer, bi-atrial	Modified CRN model	Possibility method	DTMRI-based	FDM	PVI, linear ablation, LAAI	No

AF: atrial fibrillation; n: number of patients; NS: numerical solution; CT: computed tomography; MRI: magnetic resonance imaging; CRN: Courtemanche-Ramirez-Nattel; FK: Fenton-Karma; DTMRI: diffusion tensor magnetic resonance imaging; FEM: finite element method; FDM: finite difference method; PVI: pulmonary vein isolation; CFAE: complex fractionated atrial electrogram; PS: phase singularity; ShEn: Shannon entropy; DF: dominant frequency; IAC: interatrial connection; RD: reentrant driver; AS: activation sequence; LAAI: left atrial appendage isolation.

in agreement with the clinical findings (Kim et al., 2017).

Hwang et al. (2016) tested the efficacies of four different rotor ablation methods, including phase singularity (PS), dominant frequency (DF), Shannon entropy, and CFAE-cycle length (CFAE-CL). The results showed that virtual ablation of the DF area terminated AF, but not ablation of the areas detected by the PS, Shannon entropy, or CFAE-CL method. Another study by Lim et al. (2017) demonstrated that the outcomes of the DF-based ablation strategy were affected by CV, and the DF ablation pattern could not terminate AF under persistent AF conditions.

Shim et al. (2017) conducted a randomized prospective study to evaluate the feasibility of computational modeling-guided ablation. In their study, 108 patients with PeAF were randomly assigned to the in silico (n=53) and empirical ablation groups (n=55). In the in silico ablation group, five different ablation patterns (using PVI, three additional linear ablations, and CPVI+CFAE ablation) were tested in each CT-derived left atrial model, and the most rapid pattern for terminating AF was achieved in clinical practice. They concluded that in silico ablation was feasible under clinical time constraints. Meanwhile, comparing recurrence rates for patients after follow-up, the outcome of the computational simulation ablation was not inferior to that of real clinical ablation procedures.

Kim et al. (2019) updated the outcome of the clinical feasibility study on computational modeling-guided AF ablation. During the mean 31.5 months follow-up, the clinical recurrence rate after computational modeling-guided ablation was significantly lower than that after empirical ablation (20.8% vs. 40.0%). Meanwhile, there was a better long-term rhythm outcome of PeAF ablation in modeling-guided ablation. However, we would like to note that CPVI was much more commonly chosen in the empirical group (30.9%) than in the modeling-guided ablation group (1.0%). In contrast, extensive ablation strategies were used more widely in the modeling-guided ablation group, which may partially explain the better long-term outcomes.

Lim et al. (2020b) developed an improved simulation platform reflecting anatomy, fibrosis, fiber orientation, and electrophysiology using personal map data obtained during AF ablation procedures. They tested the accuracy of the improved simulation platform retrospectively in 17 patients and also tested its feasibility prospectively in ten patients during clinical procedures. The authors found that their improved platform could be applied in clinical AF ablation procedures after further validation. Based on this improved platform, Lim et al. (2020a) reporting their tests of the impact of ablating interatrial connections (IACs) after CPVI. They discovered that the extra interatrial ablation improved the success rate in terminating AF, which was especially apparent with a cavotricuspid isthmus ablation.

Trayanova's group performed the most comprehensive computational modeling-guided AF ablation. McDowell et al. (2015) were the first to combine patient-specific atrial structure and fibrosis distribution as quantified from clinical LGE-MRI in a proof-of-concept study that addressed the following challenges: (1) the association between fibrosis distribution and AF and (2) the detection of optimal ablation targets. The authors demonstrated that AF could not be induced when the ablation area encompassed a meander of persistent reentrant drivers (RDs) and that patient-specific fibrosis distribution was crucial in initiating and maintaining AF and detecting the optimal ablation targets. Based on the methodology described by McDowell et al. (2015), Zahid et al. (2016) developed an automatic approach using the principles of graph theory to predict optimal left atrial flutter ablation targets. The novel algorithm was named the "minimal cut algorithm," and was designed to locate the smallest amount of tissue separating the left atrium in two disconnected components.

Boyle et al. (2018a, 2018b) published two articles to validate the accuracies of RDs predicted from computational modeling and those observed by electrocardiographic imaging (ECGI) (Haissaguerre et al., 2016) and focal impulse and rotor mapping (FIRM) (Narayan et al., 2012), respectively. They found that simulations revealed additional areas harboring RDs that can never be identified with FIRM (termed "latent RDs"). Long-term outcomes were better in patients in which there were fewer latent RD sites, suggesting that latent RD sites may be a potential explanation for failed FIRM-guided ablation. Furthermore, more exhaustive PeAF substrate ablation targets should be identified based on computational modeling compared with FIRM-guided ablation. ECGI-guided ablation of targets in regions harboring RDs in both ECGI and simulations may lead to much better results when compared with ablation of non-overlapping RDs from ECGI targets. Thus, a combination of modeling and ECGI may improve the success rate in terminating AF.

As discussed above, fibrotic remodeling has a more vital link with the location of RDs. Hence, electrophysiological properties such as APD and CV in the patient-specific computational model may affect optimal ablation targets. Deng et al. (2017) conducted a sensitivity study to investigate the influence of 10% variation of atrial APD or CV on exact locations of RDs in 12 patient-specific computational AF models. They discovered that changes in electrophysiological properties led to variation in the likelihood that RDs would be anchored to a specific site, meaning that RD trajectories based on personalized ablation strategy alone may not produce a satisfactory effect. A further study based on these results was published by Hakim et al. (2018). They found that a total of 21 emergent RDs were observed in the 9/12 atrial models by reapplying the same AF-induced protocol to the post-ablation model under average electrophysiology conditions. A total of 71% of emergent RD locations were close to sites in pre-ablation simulation with ±10% variation in APD or CV conditions. Hence, repeating simulation and ablation of emergent RDs could alleviate the uncertainty caused by electrophysiology parameters.

In 2019, Trayanova's group used an innovative approach termed OPTIMA (optimal target identification via modeling of arrhythmogenesis) to predict the optimal ablation target and steer patients' ablation procedures (Boyle et al., 2019). They constructed ten patient-specific PeAF bi-atrial models integrating realistic atlas-based fiber orientation and fibrosis distribution. Then, they performed a set of custom-tailored ablation lesions by connecting RDs to the nearest anatomic barriers. AF induction pacing protocol was repeated to observe new emergent RDs until each of the 40 pacing sites failed to induce arrhythmias. The OPTIMA personalized ablation targets were imported into the clinical electroanatomic navigation (CARTO) maps by a series of co-registered steps and used to steer the patients' clinical ablation procedures. During follow-up, none of the patients in this study had a recurrence of PeAF, and only one patient was required to repeat the ablation due to paroxysmal AF and atrial flutter.

Ali et al. (2019) developed 24 models based on pre- and post-PVI LGE-MRI from 12 AF patients to investigate the association between apparently successful PVI and AF recurrence post-PVI. The results indicated that both preserved RDs missed during PVI and the emergence of new RDs post-ablation contributed to post-PVI AF recurrence.

In the latest article on AF ablation published by Trayanova's group, Shade et al. (2020) developed a personalized approach to predict the recurrence rate post-PVI via machine learning (ML) and their previous MRI-derived AF computational model simulation. The ML classifier used deductive and inductive features extracted from LGE-MRI-based AF results and raw pre-procedure LGE-MRI images as the input features. Ten-fold nested cross-validation was used to train, validate, and test the classifier. Feature selection was unbiased via random forests. A quadratic discriminant analysis classifier was used to predict the probable AF recurrence rate post-PVI. Ultimately, their ML algorithm predicted AF recurrence post-PVI with an average validation sensitivity of 82%.

Several European groups have also made significant improvements in the virtual simulation of AF ablation. Bayer et al. (2016) tested new radiofrequency ablation strategies for AF termination. One realistic CT-derived bilayer bi-atrial model integrated with rule-based fiber orientation and statistically distributed fibrosis was constructed in this study. Three ablation strategies were used for the AF termination test: (1) PVI+addition lines; (2) detection of ablation areas near the RDs by phase mapping; and (3) lines streaming the sequence of electrical activation during sinus rhythm. The third ablation strategy was found to be the most effective ablation pattern to terminate AF, and it was not inferior to the personalized substrate-guided ablation patterns.

Roney et al. (2018) used patient-specific simulation to predict the efficacy of ablation of IACs for the treatment of PeAF. In their study, 12 LGE-MRI-derived bi-atrial bilayer models were created. The models were integrated with electrophysiological heterogeneity, fiber orientation, and IACs. Two different approaches (a probabilistic approach and fibrotic remodeling, including conductivity and ionic conductance changes) were used to model atrial fibrosis. All three IACs and PVI can either be ablated or not. The outcome of the ablation showed that 75% ablation patterns in combination with IACs were useful in all 12 computational models and the extent of fibrosis in the right atria had an inverse correlation with the success rate of terminating AF when combining fibrotic remodeling. Roney et al. (2020) compared left atrial ablation techniques, in which they constructed 20 paroxysmal AF and 30 PeAF left atrial bilayer models integrated with diffusion tensor MRI atlas-based fiber orientation and fibrosis distribution. Six different ablation approaches were used on reconstruction models to identify the optimal ablation approach for every patient. Subsequently, they used three sets of metrics as the input variables of the ML random forest classifier to predict the binary ablation response. They discovered that the optimal ablation strategies varied between individuals. Both the properties of patient-specific fibrosis and driver locations played crucial roles in determining the optimal ablation approach. Meanwhile, the distribution of ablation lesions also should be considered.

Alessandrini et al. (2018) implemented a computational framework to benchmark basket catheter-guided ablation in silico. They created one magnetic resonance angiography-derived left atrium integrated with rule-based fiber orientation and a uniform wall thickness of 3 mm. The trajectory density of the induced reentries in their model was treated as a rotor-ablation target. The simulation results revealed that the phase maps derived from intracardiac electrograms could be a powerful tool to map atrial activation patterns. Yet, they may mislead physicians due to inaccurate localization of the rotor tip depending on electrode resolution and distance to the wall.

Roy et al. (2020) applied five different ablation strategies on six left atrial models with patient-specific geometry and fibrosis distribution to explore the association between the location of RDs and fibrosis distribution and to identify potential target areas for ablation procedures. They found that ablating the target areas and connecting them to the nearest boundary with linear lesions was superior compared with strategies such as ablating the target areas alone or clinically accepted PVI.

Recently, the left atrial appendage (LAA) has received increasing attention for its role in the recurrence of AF. Gharaviri et al. (2021) developed a model with wall thickness heterogeneities and realistic fiber orientations, performed LAA isolation, and investigated its impact on AF recurrence in three different degrees of fibrosis. The authors suggested that LAA isolation was an effective way to reduce recurrence, especially in those with high levels of fibrosis.

3 Challenges and future directions

Over the past two decades, significant progress has been made in the computational modeling of AF. However, there remain some challenges to be tackled. There is no direct evidence to prove the feasibility of using the LGE-MRI methodology to obtain the distribution of the fibrosis in remodeling atria (Chrispin et al., 2016; Haissaguerre et al., 2016; Schade et al., 2016; Sohns et al., 2017). More studies are needed to validate and ascertain connected findings. Personalized high-density electroanatomical substrate mapping data can play a supporting role in identifying fibrosis. Another important aspect is that the spatial resolution of most clinical images is not good enough to detect the microscopic structural changes that conducted microanatomic reentry as a substrate for AF initiation, maintenance, and ablation (Zhao et al., 2017); therefore, higher-resolution spatial images will be required to improve the accuracy of computational models.

Furthermore, the representation of patient-specific fiber orientation is complex and yet critical for simulated atrial arrhythmia (Ho and Sánchez-Quintana, 2009). The methods of measuring fiber orientation and the incorporation of fiber orientation into computational models should be pursued (Pashakhanloo et al., 2016; Roney et al., 2021). Future atrial models for AF ablation could incorporate ganglionated plexi, which play an essential role in the pathophysiology of AF (Bayer et al., 2019).

Moreover, since the patient-specific electrophysiological data can only be acquired in an invasive and time-consuming way, most computational models of AF ablation use the "uniform atrial cells model" (Courtemanche et al., 1998) and non-specific representation of fibrotic remodeling in fibrotic regions (Pedrotty et al., 2009). However, changing the electrophysiological parameters has been proved to significantly influence the simulation results of AF (Saha et al., 2018). Thus, novel approaches such as noninvasive body surface potential map recordings (Giffard-Roisin et al., 2017) that can measure personalized electrophysiological information should be introduced for computational modeling of AF ablation.

ML techniques, including recent deep-learning approaches, have the potential to give new insights into AF that are difficult to observe and analyze with existing methods; they could also enable further automation of the entire process of computational simulation to eliminate manual choosing bias (Cantwell et al., 2019; Trayanova et al., 2021). In virtual ablation studies, ablation lesions are performed simultaneously, whereas in clinical ablation procedures, lesions are performed sequentially. This difference leads to deviations between the results which should be addressed in the future. In addition to the sequential characteristics of ablation, the automatic identification of ablation targets is also essential. Therefore, more accurate and time-saving algorithms, such as those based on directed networks (Vandersickel et al., 2019), need to be further designed and innovated to minimize human operations and the time required for ablation.

Additionally, the ultimate purpose of computational simulations is to guide clinical AF ablation. Therefore, the results of computational simulations must be tested against the most stringent clinical and experimental criteria so that they can be safely applied to the actual clinical procedure.

Finally, in order to guide rather than merely predict clinical ablation, computational simulations need to be carried out in real time alongside clinical ablation procedures. Computational modeling must be simple enough for cardiologists to manipulate the entire simulation process. The duration of simulation should also meet the essential clinical requirements, all of which demand tremendous advances in hardware or software to improve computing power and computational algorithms (Kaboudian et al., 2019).

4 Conclusions

In summary, although virtual ablation of AF by personalized computational modeling has been developed rapidly during the last decade, it has not become a routine clinical tool. The long simulation time does not meet the requirements of actual clinical practice, and the computational modeling approach is not simple enough for cardiologists to manipulate the entire simulation process. Furthermore, computational modeling is mainly used to predict short-term rather than long-term clinical outcomes, and long-term outcomes are of most concern to cardiologists. Nonetheless, there is great potential for personalized computational modeling to become an alternative approach to drive new developments in AF treatment.

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Author contributions

Zhenghong WU and Yunlong LIU wrote the manuscript. Zhenghong WU created the figure and tables. Zhenghong WU, Lv TONG, and Diandian DONG edited the manuscript. Dongdong DENG and Ling XIA contributed the framework of the manuscript. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Zhenghong WU, Yunlong LIU, Lv TONG, Diandian DONG, Dongdong DENG, and Ling XIA declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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