

# Computational models of atrial fibrillation: achievements, challenges, and perspectives for improving clinical care

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## Abstract

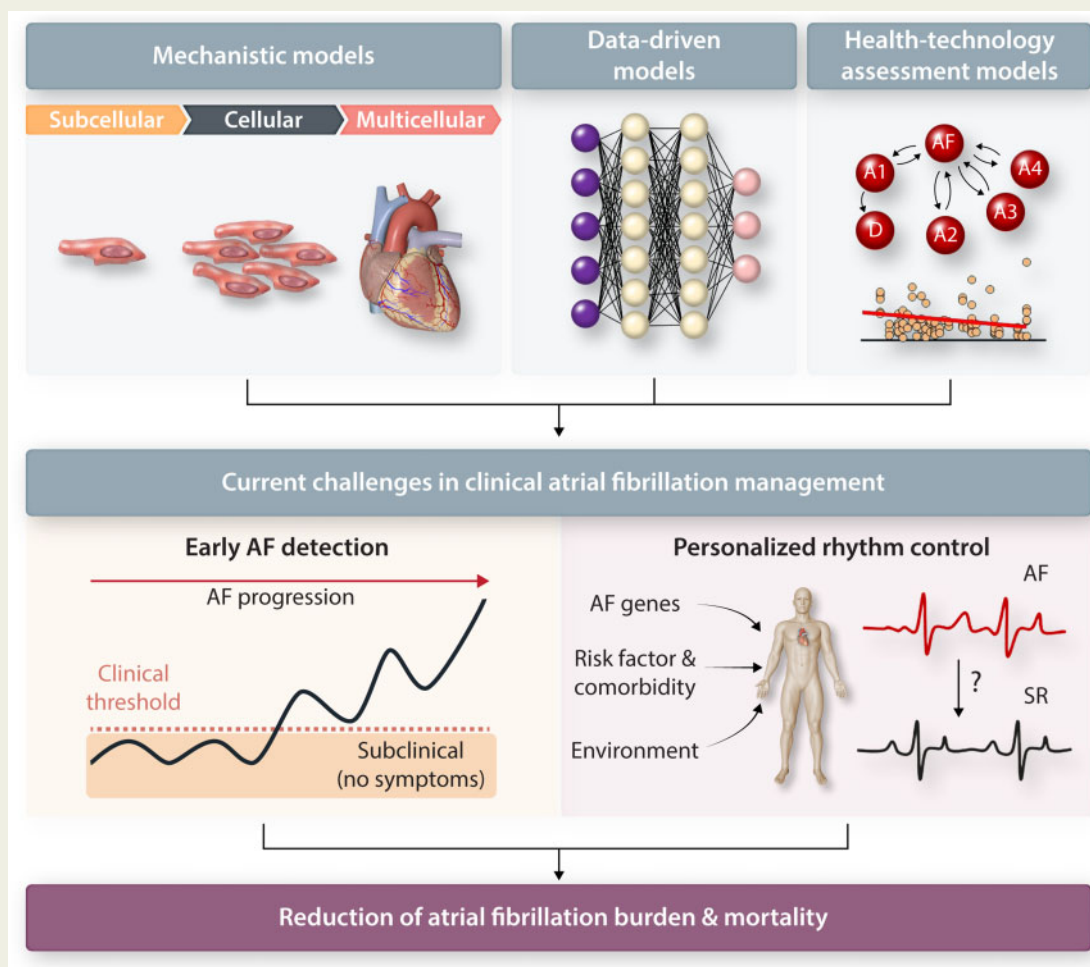
Despite significant advances in its detection, understanding and management, atrial fibrillation (AF) remains a highly prevalent cardiac arrhythmia with a major impact on morbidity and mortality of millions of patients. AF results from complex, dynamic interactions between risk factors and comorbidities that induce diverse atrial remodelling processes. Atrial remodelling increases AF vulnerability and persistence, while promoting disease progression. The variability in presentation and wide range of mechanisms involved in initiation, maintenance and progression of AF, as well as its associated adverse outcomes, make the early identification of causal factors modifiable with therapeutic interventions challenging, likely contributing to suboptimal efficacy of current AF management. Computational modelling facilitates the multilevel integration of multiple datasets and offers new opportunities for mechanistic understanding, risk prediction and personalized therapy. Mathematical simulations of cardiac electrophysiology have been around for 60 years and are being increasingly used to improve our understanding of AF mechanisms and guide AF therapy. This narrative review focuses on the emerging and future applications of computational modelling in AF management. We summarize clinical challenges that may benefit from computational modelling, provide an overview of the different *in silico* approaches that are available together with their notable achievements, and discuss the major limitations that hinder the routine clinical application of these approaches. Finally, future perspectives are addressed. With the rapid progress in electronic technologies including computing, clinical applications of computational modelling are advancing rapidly. We expect that their application will progressively increase in prominence, especially if their added value can be demonstrated in clinical trials.

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## Graphical Abstract



## Keywords

• Atrial fibrillation • Computer modelling • Electrophysiology • *In silico* • Personalized therapy

This article is part of the Spotlight Issue on Atrial Fibrillation.

## 1. Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia, affecting >43 million individuals globally.<sup>1</sup> In the European Union, AF currently affects >10 million adults, half of whom are  $\geq 75$  years old.<sup>2</sup> These numbers are projected to double by 2060.<sup>1, 2</sup> Current European guidelines recommend a holistic AF Better Care (ABC) pathway, involving anticoagulation to avoid stroke, better symptom management through rate- and rhythm control, and cardiovascular and comorbidity optimization.<sup>1</sup> AF management according to the ABC pathway improves outcomes and reduces healthcare costs in retrospective cohort studies,<sup>3, 4</sup> with limited data available from randomized clinical trials on the ABC pathway,<sup>5</sup> or related components such as comprehensive nurse-led care.<sup>6</sup> Recent data indicate that the adherence and persistence of AF patients during long-term use of mHealth-supported care based on the ABC pathway was good and was associated with a reduction in adverse clinical outcomes.<sup>7</sup> However, despite significant advances in its detection, mechanistic understanding and management, AF continues to have a major

impact on morbidity and mortality of millions of patients,<sup>1</sup> partly because of unresolved knowledge gaps in AF pathophysiology, screening, and therapeutic strategies, including rate/rhythm control and stroke prevention.<sup>8</sup> The development of actionable personalized approaches, which take into account patient-specific profiles and arrhythmia mechanisms, will likely be essential to overcome current challenges in AF management.<sup>9</sup> Over the last decades, multiscale computational modelling of cardiac electrophysiology has emerged as a modality to better understand complex arrhythmia mechanisms and the multifaceted interactions between arrhythmia substrates, drivers and triggers.<sup>10–14</sup> Employing the full control over parameters and complete observability inherent to computational models (e.g. enabling simultaneous evaluation of multiple readouts under precisely defined conditions), the key contributors to cardiac arrhythmias in various experimental settings and pathologies have been identified in realistic simulated contexts. In this narrative review, we highlight the emerging and future applications of computational modelling in AF management, providing a conceptual overview of the different *in silico* approaches that are available together with their notable achievements.

We also discuss challenges to the routine clinical application of these approaches. For more methodological details on model development, the interested reader is referred to other reviews.<sup>13, 15–17</sup>

## 2. AF pathophysiology

AF is a complex multifactorial disease promoted by several dynamic predisposing factors, including genetics, age-/disease-associated remodelling, and AF-related remodelling. The occurrence of AF is modulated by several systemic regulators such as the autonomic nervous system, haemodynamic changes and inflammation.<sup>18–20</sup> Strong interactions between AF determinants, including autonomic remodelling, calcium-handling abnormalities, ion-channel alterations, and structural remodelling are evident and have been described in detail in recent reviews.<sup>21–23</sup> In brief, the incidence of diastolic spontaneous calcium release events (SCaEs) is increased in paroxysmal, persistent and post-operative AF (POAF).<sup>18, 24</sup> Together with AF-associated ion-channel remodelling, SCaEs can lead to early and delayed afterdepolarizations (EADs and DADs, respectively). At the tissue and organ levels, afterdepolarizations can induce focal ectopic firing, often arising from myocardial sleeves around the pulmonary veins. Re-entrant activity initiated by ectopic activity acting on a vulnerable substrate (characterized by short effective refractory periods and slow, heterogeneous conduction) is considered a primary AF-maintaining mechanism and becomes more complex with advancing atrial remodelling.<sup>18, 21</sup> Atrial structural remodelling is a major cause of AF-promoting conduction abnormalities. AF is generally a progressive condition, moving from paroxysmal (resolving in <7 days) to persistent (remaining for >7 days) and, if not adequately managed, may become resistant to pharmacological and interventional therapies (permanent AF). AF progression is in part due to advancing age, the effects of underlying risk factors and AF-related atrial remodelling, and is independently associated with worse outcomes.<sup>18</sup> Of note, most patients have multiple AF-promoting factors and their interaction can produce distinct atrial remodelling patterns. For example, AF-related remodelling is distinct in dogs with and without ventricular tachycardiomyopathy (due to the absence or presence of atrioventricular block), as well as in persistent AF patients with and without left ventricular (LV) dysfunction.<sup>25, 26</sup> Although a major part of the AF-promoting substrate develops secondary to advancing age and acquired risk factors, AF also has an important genetic component. Common and rare genetic variants in numerous genes have been associated with AF, although for many variants, including the most common ones at 4q25 near *PITX2*, the exact pathophysiological mechanisms remain unknown.<sup>27</sup> Despite the growing knowledge of the arrhythmia substrates and triggers in AF, the contribution of each component in specific patient subgroups and individuals remains incompletely understood.<sup>21</sup>

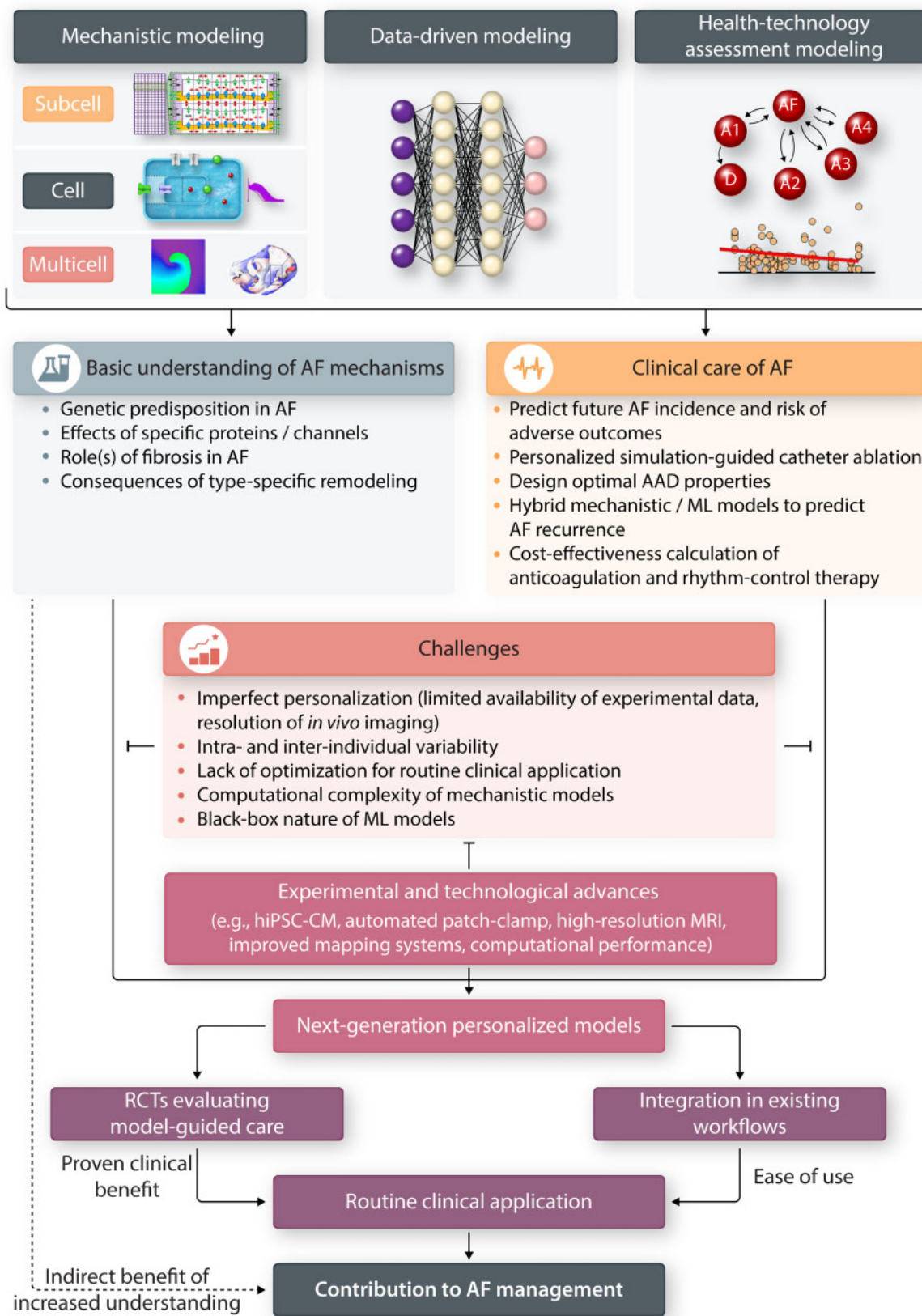
## 3. Clinical challenges in AF management potentially benefiting from computational modelling

Important knowledge gaps and challenges in AF management have recently been summarized.<sup>8, 9</sup> Two challenges in particular have received significant attention in computational modelling studies: identification of asymptomatic AF to enable early therapy and personalized rhythm-

control therapy, including prediction of AF recurrences. This section summarizes the clinical motivation for addressing these challenges. The contributions of computational modelling are detailed in the next section.

It is estimated that 10–40% of AF patients are asymptomatic.<sup>28, 29</sup> These patients often remain undiagnosed and therefore do not receive appropriate treatment, including early anticoagulation therapy, increasing their risk of thromboembolic strokes that may even be the first recognizable manifestation of the arrhythmia.<sup>28–30</sup> Undetected asymptomatic AF also delays initiation of rhythm-control therapy, allowing irreversible structural remodelling to develop, reducing therapeutic efficacy. Earlier AF-detection may enable prompt treatment, preventing disease progression and AF-related complications. In agreement, the EAST-AFNET4 trial demonstrated the benefit of early rhythm-control therapy in reducing the risk of adverse cardiovascular outcomes.<sup>31</sup> Although opportunistic screening is recommended and new technologies for recording heart rhythm might greatly facilitate AF-screening, the optimal approach for systematic screening and its potential benefit remain uncertain.<sup>29, 30</sup> By analysing large amounts of data and quantitatively projecting the effects of different screening strategies, computational approaches may facilitate AF-risk prediction and enable more reliable, cost-effective identification of asymptomatic AF.

Rate and rhythm control strategies using antiarrhythmic drugs (AADs) and catheter ablation are the cornerstones of symptomatic AF management. Historically, rate control was shown to be equally effective as rhythm control for the prevention of mortality and morbidity from cardiovascular causes in several studies.<sup>32–35</sup> The lack of benefit of rhythm control in earlier trials has largely been attributed to the limited efficacy and proarrhythmic side-effects of AADs.<sup>36</sup> Pulmonary vein isolation (PVI) through catheter ablation improves sinus rhythm maintenance compared to AADs and is devoid of ventricular proarrhythmia, potentially enabling better rhythm control. Indeed, a number of recent clinical trials have suggested that modern rhythm-control strategies may improve outcomes, at least in certain subpopulations of AF patients.<sup>31, 37, 38</sup> Nonetheless, the efficacy of catheter ablation remains suboptimal,<sup>39, 40</sup> largely due to a one-size-fits-most approach. For example, in patients with persistent AF,<sup>41</sup> arrhythmia-free survival rates after a single procedure were  $35.3 \pm 3.9\%$ ,  $28.0 \pm 3.7\%$ , and  $16.8 \pm 3.2\%$  at 1, 2, and 5 years, respectively.<sup>42</sup> Time to AF recurrence is a major determinant of AF outcome, where patients with later recurrences were more likely to have sporadic episodes and respond better to AADs and repeat ablation.<sup>43</sup> Despite the increasing prominence of catheter ablation,<sup>44–46</sup> AADs remain a major component of AF management, because of the large number of affected individuals, as well as the costs and risks of the invasive procedure required for ablation.<sup>1, 47–50</sup> However, drug-induced proarrhythmia and long-term toxicity often limit the choice of AADs.<sup>36, 51</sup> It is likely that specific rate- or rhythm-control strategies respond differently to distinct fundamental molecular and cellular determinants of AF, modulating the outcome of specific treatments. The underlying molecular and cellular determinants of AF might also be associated with the likelihood and time to AF recurrence.<sup>52</sup> Nevertheless, predicting which patients are likely to recur and may therefore require additional follow-up or more aggressive therapy is challenging. As such, a more personalized approach is needed to better stratify the benefit and risk of each treatment strategy, and select the optimal (combination of) AF therapies. Using personalized multiscale computational modelling, the outcome of both pharmacological and interventional rhythm-control strategies in an



**Figure 1** Overview of existing computational approaches, achievements, challenges, and their potential future directions in AF management. Both mechanistic and data-driven models are available and currently being used to study the AF pathophysiology (blue box) and improve AF clinical care (yellow box). However, several limitations exist (red box) that need to be resolved, e.g. through experimental and technological advances. By overcoming these limitations, demonstrating clinical benefit in randomized clinical trials (RCTs) and improving ease of use, computational modelling can improve AF management.

**Table 1** The current contributions of computational modelling of atrial electrophysiology on AF pathophysiology and clinical care

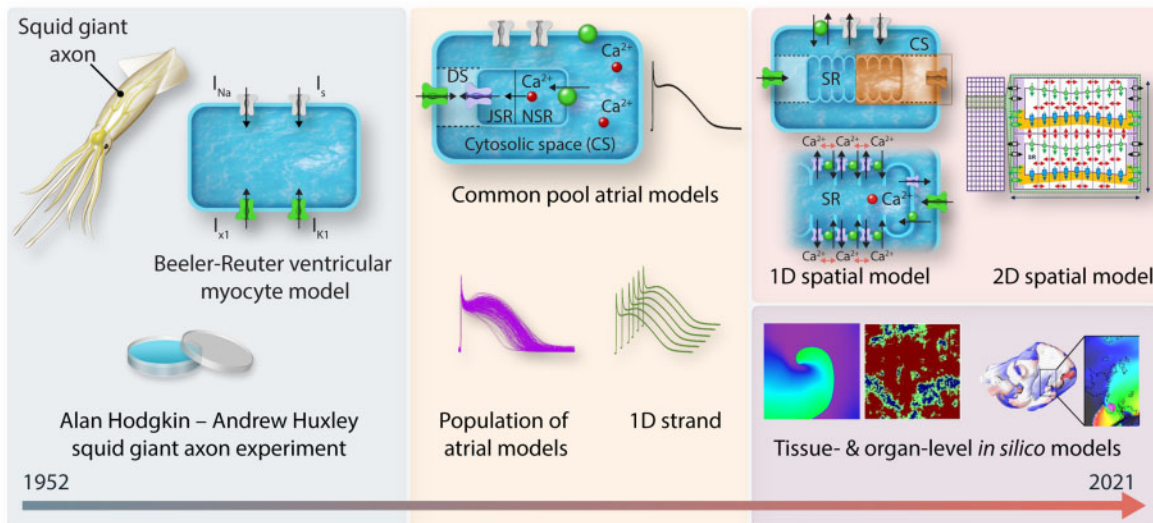
Clinical challenge	Model scale/type	Contribution	Example
Mechanistic models			
Early AF detection	Cellular and organ	Insights on proarrhythmic electrical and structural remodelling associated with AF risk factors	57–66
Personalized rhythm-control therapy	Subcellular and cellular	Identification of the ionic mechanisms underlying atrial arrhythmias and consequences of AF-related remodelling	12, 24, 67–74
	Cellular and tissue	Evaluation of potential novel AAD targets, notably Kv1.5 and K <sub>2P</sub> 3.1	75, 76
	Cellular and tissue	Identification of optimal pharmacodynamic characteristics of new AADs, including state-dependent and multi-channel inhibition properties	77–79
	Cellular	Evaluation of drug safety as part of the comprehensive <i>in vitro</i> proarrhythmia assay (CiPA) initiative	80
	Organ	Evaluating the outcome of different catheter ablation strategies in patient-specific models	81–84
	Organ	Simulation driven-targeting of AF (emergent) re-entrant drivers	85–87
	Organ	Prediction and prevention of post-ablation atrial arrhythmia and AF recurrences	88, 89
Data-driven models			
Early AF detection	Statistical	Prediction of AF risk based on clinical and genetic information	90–94
	ML	Prediction of AF based on sinus rhythm ECGs	95–97
	ML	Detection of AF based on facial pulsatile photoplethysmographic signals	98
	Statistical	Estimation of patient-specific atrial electrical remodelling patterns based on remote-monitoring technology	99
Personalized therapy	Statistical	Predicting spontaneous conversion to sinus rhythm in symptomatic atrial fibrillation	100
	Statistical	Predicting the likelihood of AF recurrence	101
	ML	Prediction of AF recurrence after the first catheter ablation procedure	102–104
	ML	Classification of intracardiac activation patterns during AF to detect regional rotational activity	105, 106
	ML	Identification of patients who may benefit from AF cardioversion	107
Health-technology assessment models			
Early AF detection	Population	Cost-effectiveness analyses of AF screening	56, 108
Personalized therapy	Population	Cost-effectiveness analyses of AF therapies (e.g. AADs, anticoagulants and ablation)	55, 109–111

individual patient might be predicted, facilitating the identification of the best patient-specific treatment strategy for AF.

## 4. Key achievements of computational modelling in AF

Conceptually, most of the computational models employed for studying AF can be divided into mechanistic and data-driven models (Figure 1, top). Mechanistic models integrate fundamental biophysical laws and concepts with experimental data to simulate cardiac electrophysiology. These models are usually dynamic, simulating changes in quantities of interest (membrane potential, intracellular concentrations, etc.) over time, and are therefore typically represented by systems of non-linear ordinary or partial differential equations. Their dynamic nature also means that they are inherently causal, e.g. reflecting how electrical activity spreads from a stimulus site by successively activating neighbouring cells. As such, these models are frequently employed to investigate the underlying pathophysiology of cardiac arrhythmia and to unravel the complex dynamic interactions among variables of interest, from atomic to organ

levels.<sup>53</sup> Meanwhile, data-driven models employ statistical or machine learning (ML) approaches to establish associations between predefined inputs and outputs. These models require fewer *a priori* assumptions than mechanistic models and can suggest hitherto unknown factors contributing to AF. Inputs of data-driven models are typically clinical data, including (semi-)quantitative clinical characteristics, as well as raw signals [e.g. electrocardiogram (ECG) or telemetry data] and imaging data. Their outputs are most often clinical outcomes or diagnoses, making their clinical application more direct than that of mechanistic models. Classically, data-driven models have employed multivariable regression to link inputs and outputs, but recent advances in ML and artificial intelligence have significantly expanded their abilities and range of applications.<sup>54</sup> Finally, some approaches fall somewhere in between mechanistic and data-driven models. For example, health-technology assessment models used in cost-effectiveness assessment of medical therapies,<sup>55, 56</sup> are dynamic and causal, but do not include fundamental biophysical laws and are primarily based on data from clinical trials. The following three subsections provide key examples of these computational approaches that are relevant for AF management (as summarized in Table 1 and Figure 1, blue and yellow boxes).



1952 ▶ Hodgkin – Huxley pioneered research on voltage-gated ion channels & propagating action potentials	Vigmond morphologically realistic atrial model incorporating the major structural features of atria ◀ 2001
1962 ▶ Noble modification of Hodgkin-Huxley equation to describe action & pacemaker potentials of Purkinje fibers of the heart	Maleckar human atrial cardiomyocyte model ◀ 2008
1964 ▶ Moe model of impulse propagation in a nonuniform two-dimensional system to study AF mechanisms	Grandi human atrial cardiomyocyte model with(out) AF-induced electrical remodeling ◀ 2011
1977 ▶ Beeler – Reuter model of mammalian ventricular myocyte with 4 ionic currents	Koivumaki human atrial model with 1D spatial calcium dynamics ◀ 2011
1985 ▶ Di Francesco – Noble model of cardiac action potentials & pacemaker activity	Krogh – Madsen anatomically realistic 3D structure model of human atria ◀ 2012
1987 ▶ Hilgemann – Noble rabbit atrial cardiomyocyte model	Voigt – Heijman human atrial model with 2D spatial calcium dynamics ◀ 2014
1990 ▶ Earm – Noble single-cell rabbit atrial model	Sanchez populations of human atrial models with SR & cAF variability ◀ 2014
1990 ▶ Rasmuson bullfrog atrial cardiomyocyte model	McDowell MRI-based patient-specific model of fibrotic left atria – 4 patients ◀ 2015
1996 ▶ Lindblad rabbit atrial cardiomyocyte model	Zahid patient-specific model of fibrotic atria with realistic EP – 20 persistent AF patients ◀ 2016
1998 ▶ Nygren adult human atrial cardiomyocyte model	Sutanto – van Sloun human atrial myocyte model with RyR heterogeneity & LTCC distribution (axial tubules) ◀ 2018
1998 ▶ Courtemanche human atrial cardiomyocyte model	Boyle patient-specific atrial models for targeted ablation – 10 persistent AF patients with atrial fibrosis (OPTIMA approach) ◀ 2019
1999 ▶ Courtemanche human atrial cardiomyocyte model with AF-induced electrical remodeling	Hansen <i>in silico</i> / <i>ex vivo</i> / <i>in vivo</i> human study on the effects of transient refractoriness modulation during AF mapping ◀ 2020

**Figure 2** Timeline of milestones in multiscale mechanistic modelling of atrial electrophysiology. The subcellular spatial models of human atria are depicted in yellow, the cellular models in blue/grey, and the tissue/organ-level (whole atria) models in red. Two of the earliest electrophysiological models are shown in grey. As displayed in the figure, the model complexity and prominence has increased over the year, from covering only four ionic currents in 1977 to advanced patient-specific whole-atria models and detailed models of subcellular calcium handling in 2020.

## 5. The role of mechanistic models to improve understanding and management of AF

### 5.1 Brief overview of the historical evolution of mechanistic models of AF

Computational modelling of electrophysiology began following the famous experimental work on cellular electrical activity in the squid giant

axon by Hodgkin and Huxley in 1952 (Figure 2).<sup>112</sup> Subsequently, various mathematical models of both neural and cardiac electrophysiology have been developed to address specific research questions and bridge knowledge gaps identified during laboratory experiments.<sup>13</sup> In 1962, Denis Noble for the first time utilized the Hodgkin-Huxley equations to explain the action potential of cardiac Purkinje fibres.<sup>113</sup> A similar approach was employed by Beeler and Reuter to develop the first ventricular cardiomyocyte model in 1977.<sup>114</sup> Inspired by the detailed ionic model of cardiac electrical activity by DiFrancesco and Noble,<sup>115</sup> the 1987

mathematical model by Hilgemann and Noble<sup>116</sup> was among the first to explore the electrophysiological properties of mammalian atrial cardiomyocytes. In 1998, the first human atrial *in silico* models were formulated by Nygren et al.<sup>117</sup> and Courtemanche et al.<sup>118</sup> These models were employed to study the consequences of experimentally characterized AF-induced electrical remodelling.<sup>75</sup> Subsequently, computational models of atrial cellular electrophysiology were refined to study atrial cell-cell interactions<sup>119</sup> and calcium-handling abnormalities.<sup>120</sup> Advances in experimental modalities such as (super-resolution) confocal microscopy revealed important differences in subcellular structure between atrial and ventricular cardiomyocytes, which motivated atrial cardiomyocyte-specific model structures. For example, atrial cardiomyocytes have a limited transverse-tubule network, which causes centripetal calcium wave propagation from the cell periphery towards the centre of the cell.<sup>13, 121</sup> This phenomenon can only be captured by models with spatial calcium handling.<sup>67, 122</sup> In 2014, a population modelling approach in which a large population of models is generated by varying individual parameters was first applied to atrial cardiomyocyte models to capture interindividual and intercellular variability.<sup>123</sup>

Already in 1964, Moe et al.<sup>124</sup> described a mathematical model of impulse propagation in a non-uniform two-dimensional system exhibiting self-sustained turbulent activity resembling AF. This seminal work has provided insights into the determinants of AF maintenance and revealed potential therapeutic interventions to control multiple wavelets in atrial tissue, which subsequently gave rise to the Cox maze procedure. Since the early 2000s, morphologically realistic organ-level atrial models, incorporating the major atrial structures, have also been developed<sup>125</sup> and advances in clinical imaging and computational resources have enabled the development of patient-specific models. For example, in 2015 McDowell et al.<sup>57</sup> provided the first proof-of-concept that a modelling approach with patient-specific fibrosis patterns could non-invasively identify AF ablation targets prior to the clinical procedure. This approach was subsequently expanded to better predict, diagnose or treat atrial arrhythmias.<sup>57, 58, 85, 126, 127</sup> Taken together, during the past 35 years, numerous atrial models ranging from subcellular to organ levels have been developed to examine atrial electrophysiology under both physiological and disease conditions.<sup>120–123, 125</sup> The milestones that have been briefly mentioned in this section are summarized in Figure 2, and those relevant for clinical AF management are discussed in detail below.

## 5.2 Cellular electrophysiology modelling

(Sub)cellular and multicellular computational models of cardiac electrophysiology (Figure 3A) can help to overcome experimental limitations by providing full control over parameters of interest. Among other things, (sub)cellular *in silico* modelling of atrial electrophysiology has contributed to the identification of the ionic mechanisms underlying atrial arrhythmias, including the determinants of alternans, as well as DADs and associated triggered activities in different forms of AF (Figure 3B). For example, a two-dimensional spatial calcium-handling model indicated that both ryanodine receptor (RyR) dysregulation and enhanced SERCA2a activity promoted increased sarcoplasmic reticulum calcium leak and SCAEs, causing DADs/triggered activity in paroxysmal AF.<sup>67</sup> Meanwhile, interleukin-1 $\beta$ -induced RyR dysfunction exacerbated the pre-existing calcium-handling abnormalities, leading to DADs in models of POAF.<sup>24</sup> *In silico* studies also demonstrated that AF-promoting atrial repolarization alternans might occur due to decreased RyR inactivation, and that calcium-driven repolarization alternans due to AF-associated electrical remodelling increased the vulnerability to ectopy-induced arrhythmia.<sup>12, 68, 69</sup> Finally, *in silico* models of human atrial

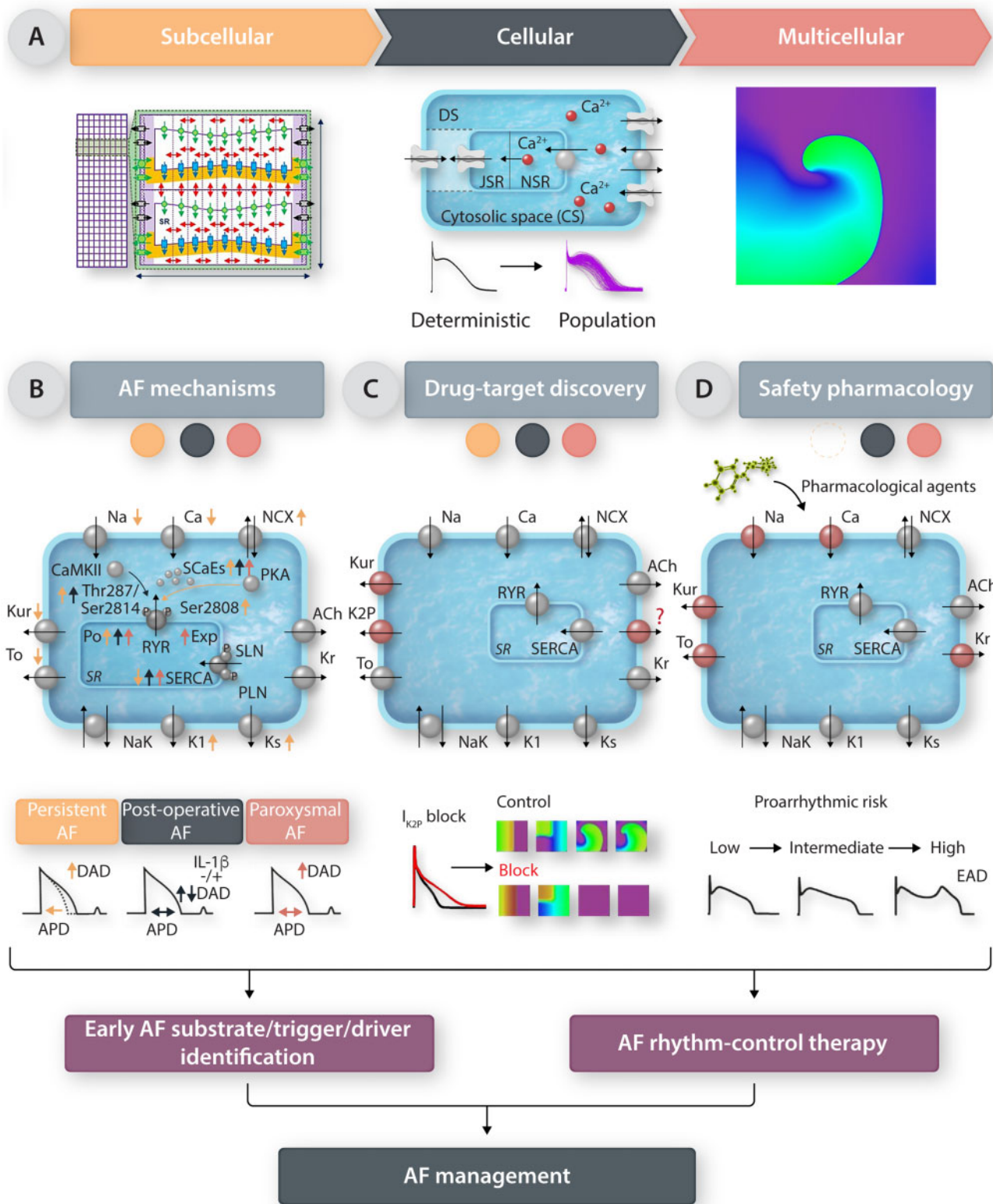
cardiomyocytes<sup>75, 118, 120</sup> have been used to study the impact of AF-related ion-channel remodelling<sup>70–74</sup> and remodelling associated with AF risk factors.<sup>59</sup> Until recently, most computational studies employed a single deterministic model, reflecting a representative atrial cardiomyocyte, thereby disregarding experimentally observed variability. However, with growing awareness on the importance of such variability, several modelling studies have started incorporating intra- and inter-individual variability of cellular parameters. The most common method involves stochastic scaling of the cellular parameters, typically the maximal ionic conductances, reflecting variability in ion-channel expression, resulting in a population of models.<sup>123, 128, 129</sup> Subsequently, models within this population that are too far outside of the experimental range are removed. The resulting calibrated populations reflect the natural heterogeneity within a population, encompass a wide range of cellular phenotypes and are therefore expected to yield more representative results.

Together, these cellular studies suggest a potential for model-based identification of therapeutic targets (Figure 3C). Moreover, by integrating experimental data on disease- and AF-associated remodelling, these computer models may provide insight into therapeutic effectiveness under different clinical conditions. For example, the atrial-selective expression of Kv1.5 ion-channels suggested that they may constitute an interesting atrial-selective ionic target for AAD therapy, but simulation of their role in atrial repolarization raised concerns<sup>75</sup> that were subsequently confirmed in clinical trials.<sup>130</sup> Simulations indicated that remodelling of K<sub>2P</sub>3.1 plays a major role in APD-shortening in long-standing persistent AF, but that down-regulation of K<sub>2P</sub>3.1 with LV dysfunction reduced antiarrhythmic efficacy of K<sub>2P</sub>3.1 current inhibition.<sup>76</sup> The perfect control offered by computer models in combination with the increasing availability of detailed Markov models of cardiac ion channels may also help to identify the optimal pharmacodynamic characteristics of new AADs, including state-dependent and multi-channel inhibition properties.<sup>77–79</sup> Thus, detailed cellular models provide information that might be relevant for future tailored rhythm-control therapy of AF.

In addition to their potential for AF drug development, computational cardiomyocyte models play an increasingly important role in cardiac safety pharmacology as part of the comprehensive *in vitro* proarrhythmia assay (CiPA) initiative (Figure 3D).<sup>80</sup> Although the main focus of CiPA is predicting the risk of potentially life-threatening ventricular arrhythmias, the initiative has shown, using stringent predefined validation criteria, that a population of ventricular cell models can reliably predict the risk of drug-induced proarrhythmia. This gives credibility to the use of computational models for guiding (regulatory) decisions with major financial and healthcare implications. Furthermore, in the future the CiPA initiative may indirectly affect AF management by influencing the regulatory approval of drugs involved in risk-factor management.

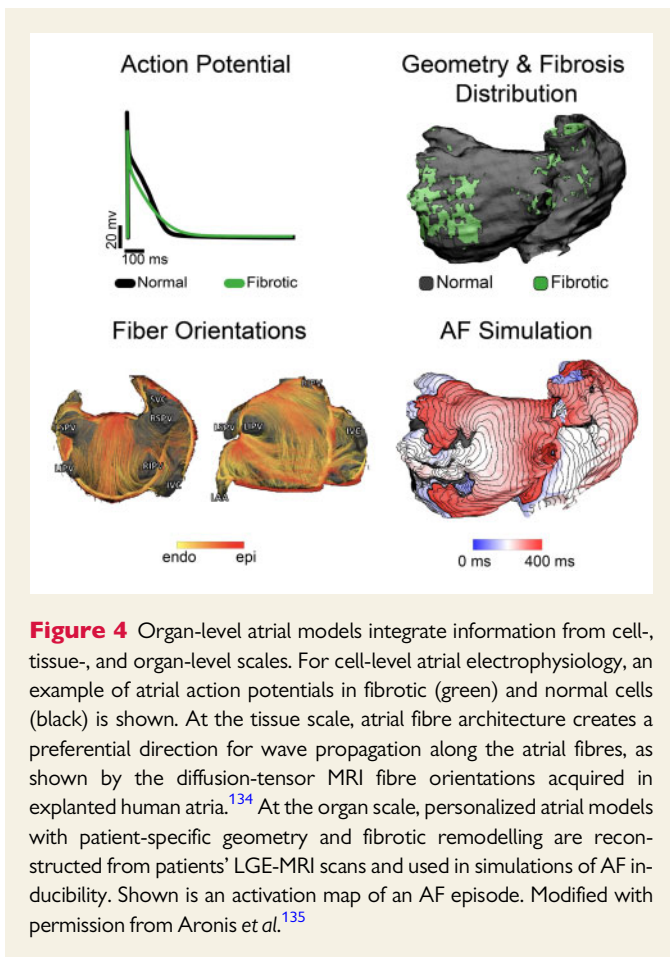
## 5.3 Organ-level modelling

The majority of contemporary simulation research in organ-level electrophysiology of the atria and AF accurately captures the complex 3-dimensional human atrial geometry acquired from computed tomography<sup>81, 131</sup> and magnetic resonance imaging (MRI),<sup>57, 60, 61, 132</sup> or employs surface models reconstructed from invasively-acquired electro-anatomic maps.<sup>133</sup> Such atrial models incorporate multi-scale representations of cell and tissue properties (Figure 4). Several of the aforementioned cellular ionic models have been used to capture atrial cell electrophysiology, including AF-promoting electrical remodelling, while properties at the tissue level account for the orthotropic conduction of electrical waves governed by atrial fibre orientation, which is commonly retrieved from atlases as atrial fibre orientation currently cannot be



**Figure 3** (Multi)cellular models of atrial electrophysiology and their roles in AF management. (A) Illustrations of currently available subcellular, cellular, and multicellular atrial electrophysiology models. (B–D) The role of cellular modelling to improve the understanding of basic AF mechanisms and determinants (B), in drug-target discovery, exemplified by  $I_{Kur}$  and  $I_{K2P}$  block, resulting in prolongation of APD and destabilization of reentrant waves (C), and in safety pharmacology (i.e. the CiPA initiative; D).





acquired *in vivo*.<sup>134, 136</sup> Studies have modelled atrial fibrosis detected on late gadolinium enhancement (LGE) MRI by changes in cellular electrophysiology and tissue conductivities, by stochastic removal of mesh elements in fibrotic areas, or by introducing patchy areas of electrical isolation.<sup>58, 62, 137</sup> Fibrotic remodelling has also been represented by explicitly modelling fibroblasts, which affect the electrophysiological properties of neighbouring cardiomyocytes via direct electrical coupling or paracrine mechanisms.<sup>10</sup> The multi-scale personalized atrial models simulate, following electrical stimulation, the propagation of electrical waves, as well as emergent phenomena such as the generation and maintenance of AF. The incorporation of structural and electrical remodelling in these models has enabled investigating the links between the altered electro-anatomical substrate and the dynamics of AF re-entrant drivers, as well as to propose options for simulation-guided AF treatment.

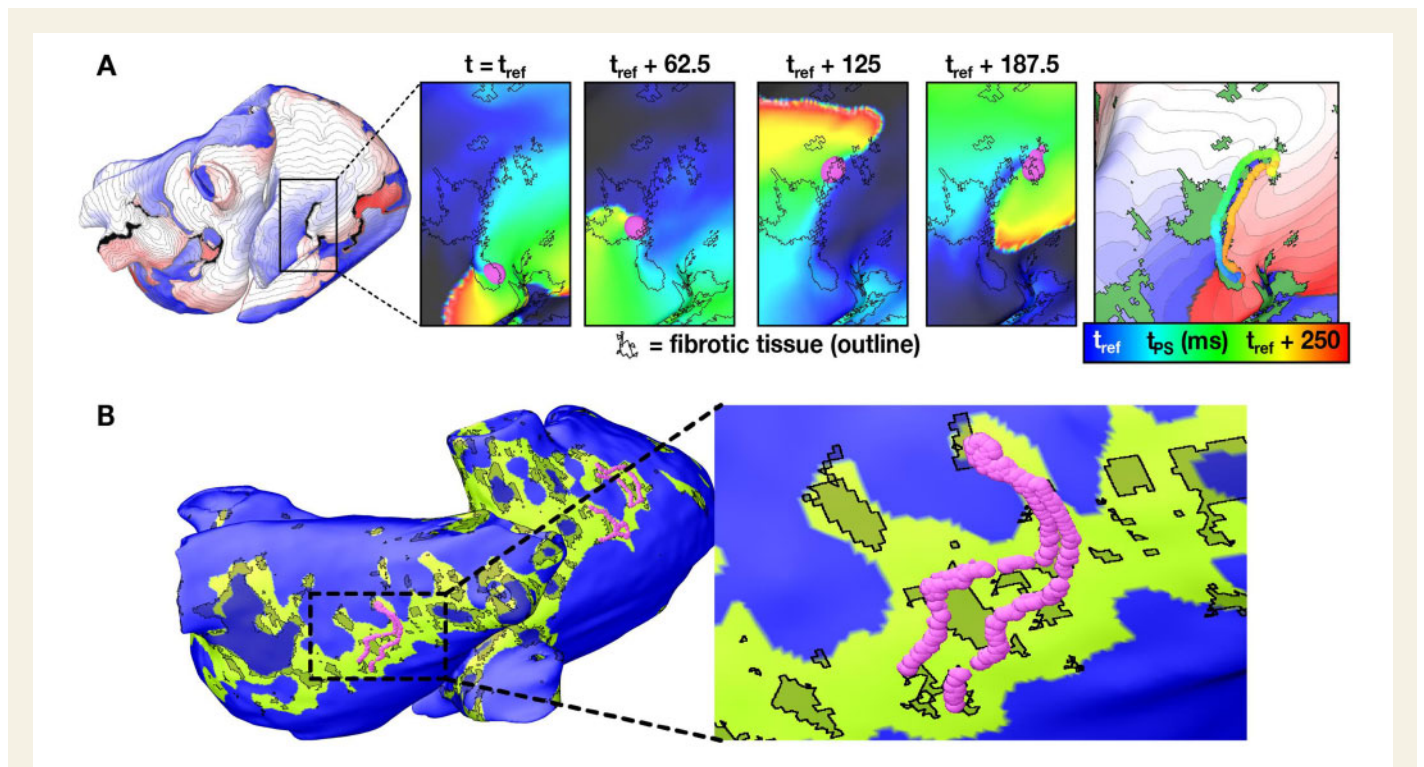
Organ-scale atrial computational modelling has provided insights into the fundamental mechanisms that govern propensity to AF. Notably, the extent and distribution of atrial fibrosis have been identified as critical determinants of atrial arrhythmogenicity and propagation dynamics during AF. The patient-specific distribution of fibrosis significantly affects AF dynamics in personalized atrial models. A number of studies have provided evidence that re-entrant drivers within regions of structural inhomogeneities and fibrotic remodelling have a significant role in maintenance of persistent AF.<sup>57, 58, 62–65</sup> Re-entrant drivers persisted in fibrosis boundary zones characterized by high fibrosis density and fibrosis entropy (Figure 5), corresponding to atrial regions with a high degree of intermingling between fibrotic and non-fibrotic tissue. Patient-specific

simulation studies have also explored the role of fibrosis in atrial arrhythmogenic propensity in relation to other atrial parameters. In atrial models reconstructed from LGE-MRI and histological data, re-entrant drivers persist in atrial areas of distinct structural 'fingerprints',<sup>66</sup> i.e. a combination of intermediate wall thickness, intermediate fibrosis, and twisted myofibre orientation. However, removal of fibrosis rendered the atrial model non-inducible for AF, reinforcing the primary role of fibrosis.<sup>66</sup> Furthermore, changes in action potential duration or conduction velocity changed the likelihood of a re-entrant driver being anchored in a specific fibrosis location.<sup>60</sup> Atrial wall thickness was also found to be an important determinant of re-entrant driver behaviour but only in the right atrium, while in the left atrium AF dynamics were primarily determined by fibrosis distribution.<sup>61</sup>

One of the most impactful applications of organ-level atrial modelling is the potential for developing personalized AF ablation strategies, tailored to target each patient's unique atrial AF substrate. A number of simulation studies presented personalized AF ablation strategies adjuvant to standard-of-care PVI.<sup>81–84</sup> Atrial models reconstructed from cardiac computed tomography scans of AF patients have been used to compare the outcome of different ablation strategies,<sup>81</sup> identifying PVI with posterior box isolation and anterior line ablation as the most effective strategy. The efficacy of these ablation strategies was subsequently evaluated in a prospective clinical trial of 108 patients with persistent AF, randomized to receive either standard-of-care ablation or ablation guided by the patient-specific models.<sup>82</sup> The study demonstrated that simulation-guided selection of the adjuvant lesion geometry is non-inferior to empirical AF ablation, but generally resulted in more extensive lesion sets.<sup>82</sup> This groundbreaking work showed the feasibility of applying simulation-guided AF-ablation therapy, but showed that further work is needed before any added-value can be confirmed. The atrial models used in these studies were homogeneous atrial models and did not incorporate patient-specific fibrosis or fibre orientations, possibly explaining failure to show improvement.

Similar ablation approaches were tested using bilayer atrial models but incorporating patient-specific fibrosis derived from LGE-MRI<sup>83</sup>; lesions used in clinical practice such as PVI, roof, and mitral lines were compared to circle lesions, perforated circles, lines, and crosses, as well as to lines streamlining the sequence of electrical activation during sinus rhythm, with the latter found to be most effective. Using the same modelling approach, Roney et al.<sup>84</sup> recently demonstrated that model ablation approaches based on clinical standards had limited success. To develop an optimal AF ablation approach for each patient, a random forest algorithm was trained to predict simulated ablation outcome for several input variables, including imaging metrics and simulated electrophysiological and lesion metrics. The results indicate that achieving optimal outcomes may require different AF ablation strategies in different patients.

Targeting AF-sustaining re-entrant drivers is a natural ablation strategy. However, as these drivers are difficult to localize during the procedure, simulations with personalized atrial models have offered an alternative strategy—determining the re-entrant driver locations in the models prior to the procedure. McDowell et al.<sup>57, 86</sup> were the first to demonstrate, in a four-patient proof-of-concept study, that ablation of atrial regions encompassing the meander of persistent re-entrant drivers rendered the model non-inducible for AF. The current methods for clinical intra-procedure localization of AF re-entrant drivers include focal impulse and rotor mapping (FIRM),<sup>138</sup> local electrogram-based parameters such as spatiotemporal electrogram dispersion<sup>139</sup> and instantaneous frequency modulation of single atrial signals,<sup>140</sup> as well as non-invasive



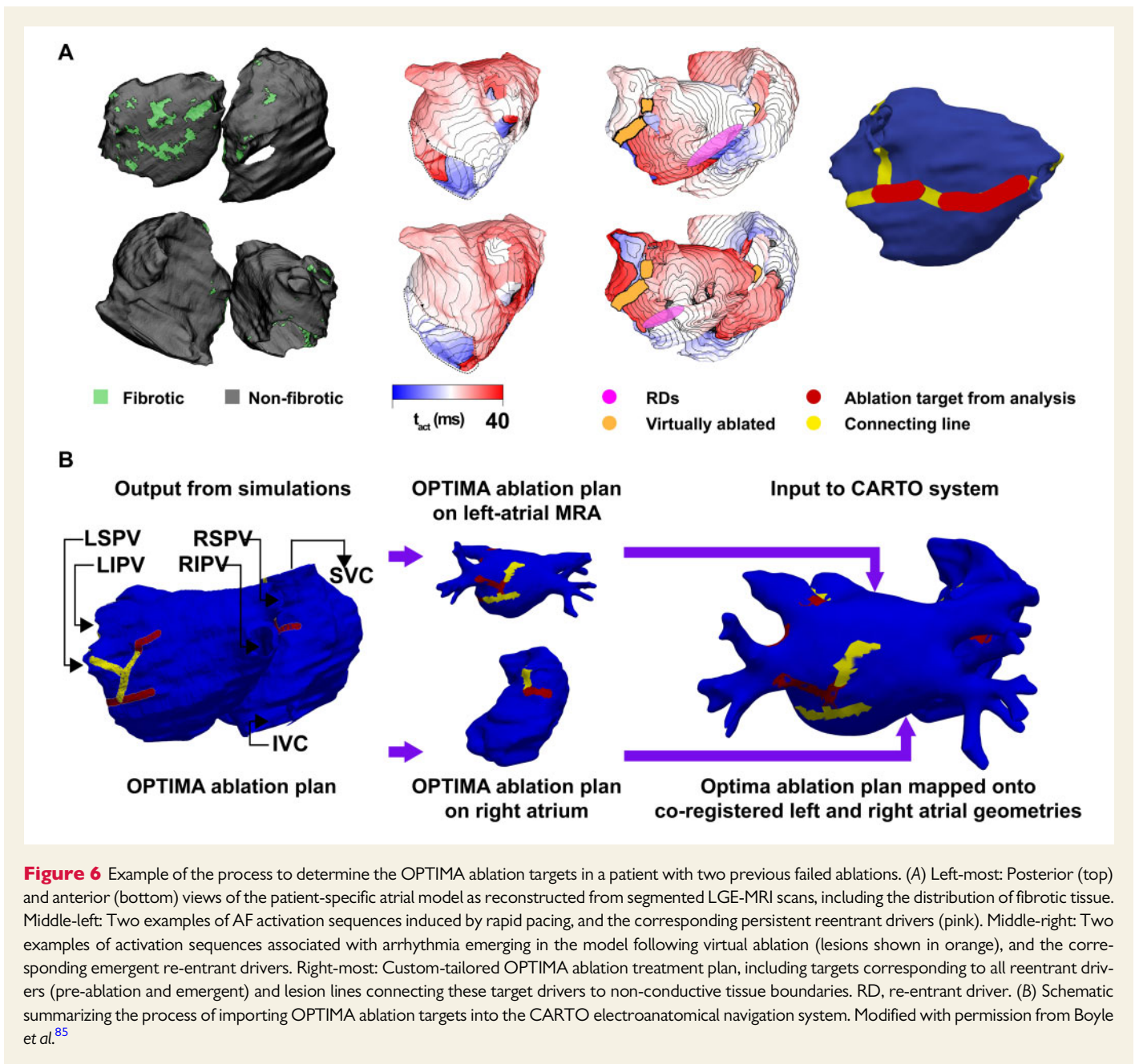
**Figure 5** Re-entrant drivers sustain AF in persistent AF patients. (A) Dynamic (i.e. time-varying) locations of the re-entrant driver organizing centre during an AF episode in a patient. An activation map (left) shows a re-entrant driver near the inferior vena cava. Inset panels show a zoomed-in view of the organizing centre (purple) at four timepoints. The fibrotic tissue boundaries are indicated by black outlines. Right-most panel shows the trajectory of the organizing centre over time superimposed on the activation map of the reentry and the fibrosis spatial pattern (green regions). (B) Location of the re-entrant driver organizing centre over time overlaid on the regions of the atria with characteristic fibrosis density and fibrosis entropy values predicted to be most likely to harbour re-entrant drivers (green). Modified with permission from Zahid *et al.*<sup>58</sup>

electrocardiographic imaging (ECGI).<sup>141</sup> AF patients that underwent FIRM-guided (11 patients)<sup>126</sup> or ECGI-guided (12 patients)<sup>142</sup> re-entrant driver ablation, in addition to PVI, had a significantly higher risk for AF recurrence if the clinical ablation sites were different from those found in the atrial models, suggesting that simulation driven-targeting of re-entrant drivers for AF can play a role in the clinical procedure. However, as personalized atrial models are reconstructed from cardiac images, and cannot prospectively incorporate invasively-acquired personalized electrophysiological information, so that predictions are rendered pre-procedurally, there is uncertainty in the predicted location of re-entrant drivers. Hakim *et al.*<sup>87</sup> demonstrated that this uncertainty can be substantially mitigated by repeating the AF inducibility simulations post-simulation of the initial ablation to capture and ablate emergent re-entrant drivers. Nonetheless, because of the reliance on non-invasive pre-procedural information, simulation-guided identification of AF ablation targets can at present not be applied to patients with a primarily functional substrate.

The first prospective entirely simulation-driven ablation study<sup>85</sup> enrolled 10 patients with persistent AF, for whom personalized atrial model with fibrosis distribution were reconstructed from LGE-MRI scans. Optimal ablation targets were determined pre-procedure non-invasively via computational modelling and utilized to steer patient treatment in an approach termed optimal target identification via modelling of arrhythmogenesis (OPTIMA). The approach was designed to completely eliminate the ability of the patient's fibrotic substrate to sustain AF: not only the clinically manifested AF but also emergent atrial

arrhythmias that could arise from the fibrotic substrate, e.g. following initial ablation. OPTIMA was thus designed not only to make ablation efficacious in patients with persistent AF but also to potentially eliminate the need for repeat ablations. An example of the OPTIMA ablation target set in one patient is shown in Figure 6A, together with the procedure to import the predicted ablation targets in the electro-anatomical mapping system (Figure 6B), so that the ablation catheter can be directly navigated to the targets. The initial feasibility study evaluating the OPTIMA approach included a limited number of patients and ablation times were not evaluated. Of the 10 patients enrolled, only one returned for re-ablation during the follow-up period, with atrial flutter rather than AF. For clinical acceptance, OPTIMA's efficacy will need to be evaluated in larger studies. A 160-patient randomized clinical study based on the OPTIMA approach has been approved (ClinicalTrials.gov identifier NCT04101539) and will establish the potential of computer modelling for the personalized management of AF.

Atrial macro-reentrant tachycardias or left-atrial flutters frequently occur after AF ablation due to modifications of the substrate introduced by the ablation lesions. Patient-specific atrial modelling has been employed to determine what lesion would render atrial flutter no longer inducible in a study of patients who were successfully treated for AF via catheter ablation, but experienced post-procedure left atrial flutter.<sup>88</sup> In a longitudinal study of 12 paroxysmal or persistent AF patients, Ali *et al.*<sup>89</sup> applied LGE-MRI-based atrial computational modelling to understand the differences in AF propensity of atrial fibrotic substrates pre- and post-ablation. The study demonstrated that AF recurrence



**Figure 6** Example of the process to determine the OPTIMA ablation targets in a patient with two previous failed ablations. (A) Left-most: Posterior (top) and anterior (bottom) views of the patient-specific atrial model as reconstructed from segmented LGE-MRI scans, including the distribution of fibrotic tissue. Middle-left: Two examples of AF activation sequences induced by rapid pacing, and the corresponding persistent reentrant drivers (pink). Middle-right: Two examples of activation sequences associated with arrhythmia emerging in the model following virtual ablation (lesions shown in orange), and the corresponding emergent re-entrant drivers. Right-most: Custom-tailored OPTIMA ablation treatment plan, including targets corresponding to all reentrant drivers (pre-ablation and emergent) and lesion lines connecting these target drivers to non-conductive tissue boundaries. RD, re-entrant driver. (B) Schematic summarizing the process of importing OPTIMA ablation targets into the CARTO electroanatomical navigation system. Modified with permission from Boyle et al.<sup>85</sup>

correlated with the presence of re-entrant drivers, which were either drivers unaffected by ablation, or new ones emerging post-ablation. Taken together, atrial organ-level modelling constitutes a unique tool for designing ablation strategies that optimize efficacy and minimize ablation-induced atrial pro-arrhythmia, thus providing new opportunities for improved rhythm control, as well as prediction and prevention of post-ablation recurrences.

## 6. Data-driven models for AF management

Traditional statistical models have significantly contributed to contemporary clinical AF management, e.g. in the prediction of stroke and bleeding risks<sup>143, 144</sup> and are typically derived from large-scale registries and trials

that investigated the relevant clinical outcomes. Statistical models have also been applied to several of the current challenges in AF management, including early AF detection,<sup>90, 91</sup> rhythm-control management,<sup>100</sup> and AF recurrence prediction.<sup>101</sup> Several statistical models have combined conventional risk scores based on clinical characteristics with biomarkers to increase their predictive performance.<sup>145</sup> Advanced statistical models have also been applied to large-scale genetic analyses, e.g. genome-wide association studies, to derive polygenic risk scores for the development of AF.<sup>92–94</sup> Nonetheless, statistical approaches are limited in their ability to identify relevant, potentially non-linear, interactions between numerous parameters that may be required for optimal prediction of the outcome of interest in today's large data sets. Artificial intelligence and ML may overcome this limitation.

Applications of artificial intelligence and ML in cardiac electrophysiology are emerging<sup>54, 146, 147</sup> and are discussed in more detail in a separate

review of this spotlight issue.<sup>148</sup> In brief, the ability of ML and ‘big data’ to identify complex associations between numerous variables of interest in a data-driven, hypothesis-free approach make them attractive for identifying occult AF determinants and establishing clinical decision support systems.<sup>146</sup> ML has been employed to predict the future AF incidence from electronic health records<sup>95, 96</sup> and sinus rhythm ECGs,<sup>97</sup> predict stroke risk from a daily AF burden signature,<sup>149</sup> define AF clinical classifications based on different risks for adverse clinical outcomes,<sup>150</sup> classify intracardiac activation patterns during AF to detect regional rotational activity,<sup>105, 106</sup> identify patients who may benefit from AF cardioversion,<sup>107</sup> and predict AF recurrence after the first catheter ablation procedure.<sup>102–104</sup> These ML approaches exploited diverse pre-procedural patient characteristics as inputs, including laboratory and clinical parameters,<sup>102, 103</sup> atrial geometry,<sup>151</sup> and imaging data.<sup>104</sup> Recent work has also demonstrated the feasibility of contact-free AF detection by ML-supported classification of facial pulsatile photoplethysmographic signals,<sup>98</sup> as well as data-driven estimation of patient-specific atrial electrical remodelling patterns based on remote-monitoring technology.<sup>99</sup> Such approaches may expand the opportunities for AF screening and subsequent monitoring in the future.

There is a growing interest in combining mechanistic and data-driven models to leverage the advantages of both approaches. In theory, data-driven approaches could directly predict the functional consequences of point mutations in ion-channel genes, which could then automatically be integrated in mechanistic models to study their impact on cardiac electrophysiology and arrhythmogenic risk. However, current experimental data sets are heavily skewed towards disease-causing variants, which limited the predictive accuracy of various ML approaches.<sup>152</sup> Alternatively, ML may support molecular dynamics simulations to study ion-channel gating in health and disease over physiological time scales,<sup>153</sup> thereby indirectly supporting mechanistic simulations of cardiac electrophysiology. At the organ-level, the perfect observability provided by mechanistic computer models creates unique opportunities for analysing and validating data-driven approaches to the detection of AF drivers, as has already been done for several electrogram-based biomarkers.<sup>139, 140</sup> Such approaches may help to evaluate and optimize the specificity of driver-detection algorithms (ML-based or otherwise), potentially reducing the number of unnecessary lesions. The recurrence of AF post-PVI could be predicted pre-procedurally by conducting mechanistic simulations of AF induction in atrial models reconstructed from paroxysmal AF patients with fibrosis on LGE-MRI, and training an ML classifier on simulated AF episodes and imaging features.<sup>104</sup> If this approach is confirmed to predict failure of PVI pre-procedurally, the patient’s ablation plan could then potentially be adjusted to include targeting of patient-specific extra-PVI areas of arrhythmogenic driver propensity using the simulation-driven OPTIMA ablation approach,<sup>85</sup> highlighting the potential of hybrid mechanistic- and ML-based modelling approaches.

## 7. Health-technology assessment models

Besides mechanistic and data-driven modelling, health-technology assessment models also play an important role in AF management, particularly for cost-effectiveness analyses of AF screening<sup>56, 108</sup> and AF therapies (e.g., AADs, anticoagulants and ablation).<sup>55, 109–111</sup> Health-technology assessment models are typically implemented using Markov models that simulate the transition of virtual populations between different clinical states, each of which have a specific value (e.g. quality-of-life)

and are associated with certain costs. The probability of individual transitions may differ for specific conditions, enabling the comparison of different therapies. For example, using a lifelong decision-analytic Markov model, cost-effectiveness of screening for asymptomatic AF was analysed and shown to be of clinical interest beyond the age of 75 years.<sup>108</sup> Meanwhile, a Markov model to calculate the total costs and quality-adjusted life-years associated with cryoablation and AAD therapy in paroxysmal AF patients demonstrated the superiority of cryoablation over AADs.<sup>111</sup> Some of these models have been combined with conventional statistical models (e.g., to detect asymptomatic AF<sup>154</sup>) or ML approaches. For example, a cost-effectiveness analysis of targeted screening for AF identification utilized a hybrid screening decision tree and Markov disease progression model.<sup>56</sup> Finally, patient-level Markov models can also be used to simulate AF progression patterns in an individual patient.<sup>155</sup>

## 8. Major limitations hindering application of computational modelling in clinical AF management

Despite the significant contributions of multiscale computational modelling of cardiac electrophysiology in improving the understanding of basic AF mechanisms, several challenges remain (summarized in *Table 2* and in the red box in *Figure 1*) and their routine clinical application remains limited.

Cellular electrophysiology models have proven useful for elucidating fundamental arrhythmia mechanisms. However, for tailoring AF therapy more detailed personalization of these models is needed. For example, accumulating evidence suggests that the antiarrhythmic efficacy of AADs is modulated by genetic and acquired risk factors.<sup>156</sup> Although cardiomyocyte models for a few subgroups of AF patients, including paroxysmal/long-standing persistent AF and absence or presence of left-ventricular dysfunction have been developed,<sup>67, 76</sup> more detailed personalization of cellular electrophysiology is hindered by the numerous interactions between individual risk factors producing complex atrial remodelling and the limited availability of experimental data. Cellular electrophysiological data are only available from patients undergoing open heart surgery (who may have a different risk-factor profile than typical AF patients) and are mostly restricted to the right-atrial appendage (which may not always be representative for other regions of the atria). Moreover, most experimental data were not obtained from studies with a predefined prospective design, potentially introducing a bias when *post hoc* defined subpopulations are used for model personalization. Due to the limited availability of human atrial samples and the challenging nature of cellular electrophysiology experiments, most currently available models still contain numerous components that have been parametrized based on data from various non-human species, which could also affect their ability to accurately reproduce arrhythmogenic mechanisms observed in patients. These and other challenges involved in translating mechanistic discoveries into clinically applicable therapies are discussed in more detail in another review in this spotlight issue.<sup>157</sup>

Similarly, although anatomical differences and patient-specific fibrosis patterns can be personalized in organ-level models based on LGE-MRI, the pre-procedural availability of electrophysiological information, which can affect model behaviour,<sup>60</sup> is limited. As such, currently available organ-level models are also not able to predict AF ablation targets in

**Table 2** Current challenges and future perspectives of computational modelling in AF management

No.	Challenge
1	Lack of personalization details (e.g. incorporation of genetic and acquired risk factors)
2	Limited availability of experimental data used to validate computational models (e.g. limited access to atrial tissues other than atrial appendage and to patient cohorts without an indication for cardiac surgery)
3	Limited pre-procedural availability of patient-specific electrophysiological information
4	Inability to image patient-specific fibre orientations
5	Limited spatial resolution of traditional MRI makes resolving the complex fibrosis patterns in the thin atrial walls challenging
6	Intra-individual heterogeneities are not fully characterized
7	Lack of cellular details in organ-level models that may be required to simulate realistic AAD effects due to high computational cost
8	Issues regarding simulation of intervening gaps, PV reconnection, focal ectopic firing and progression of the underlying substrates due to continued atrial remodelling remain unresolved
9	Complex integration with existing workflows and systems (e.g. requirement for LGE-MRI and its time-consuming segmentation, integration with electro-anatomical mapping systems)
10	'Black box' characteristic of deep-learning based machine learning models
No.	Future perspective
1	Advances in experimental methodologies as well as clinical imaging modalities may provide new opportunities for model development and personalization
2	Technological innovations in combination with new approaches for model simplification are expected to provide additional computational performance, enabling simulation of more detailed mechanistic-models
3	Increased standardization and improved attention to re-usability will likely facilitate the exchange of modelling approaches and their integration into existing workflows
4	An increasing availability of large data sets and modern (explainable) machine learning models
5	Hard evidence for the clinical benefit of using computational models (e.g. RCT) will be needed to motivate their routine use

patients with a primarily functional substrate. Furthermore, it is at present not possible to model patient-specific fibre orientations and the limited spatial resolution of traditional MRI makes resolving the complex atrial fibrosis patterns, including thin endomyocardial fibrosis and patches of surviving cardiomyocytes, difficult. Thus, model personalization at all spatial scales remains challenging.

Even when models can be personalized, it might be necessary to address intra-individual heterogeneities to capture uncertainty and temporal variation of electrophysiological properties. Although recent studies have integrated variability by applying population-modelling approaches, this is typically done by varying the maximum conductance of atrial ionic currents, based on *in vitro* experiments.<sup>128, 129</sup> However, at present, the extent of the variability of each cellular component is unknown and co-

expression of some channels, which has been recently observed,<sup>158</sup> is not considered. Furthermore, the electrotonic coupling influencing this intrinsic variability might vary across regions of the atria (affected by cell types, number of (myo)fibroblasts and neighbouring structures). At present, it is unknown to what extent variability in atrial anatomical, structural and functional properties would influence the overall behaviour of proarrhythmic substrates, drivers and triggers.

The computational requirements associated with multiscale mechanistic modelling represent another challenge potentially hindering clinical application, particularly when variability needs to be assessed in large-scale populations of models. While early *in silico* models were able to simulate the cellular behaviour of cardiomyocytes by only using a limited number of parameters and state variables, these are insufficient to capture all relevant properties of cardiomyocytes. Although detailed cell models have been developed, their computational complexity precludes their incorporation in organ-level models. Recent work has proposed innovative approaches to phenomenologically reproduce the electrophysiological consequences of subcellular calcium-handling abnormalities in multiscale models, enabling investigation of the interactions between ectopic activity and re-entry.<sup>159</sup> Nonetheless, some elements from detailed cell models may have to be sacrificed in organ-level models to retain a reasonable computational cost, which may limit their applications. For example, although simplified ionic models might be sufficient for tailored ablation therapy, evaluation of concomitant AAD effects will likely require more detailed ion-channel models that can capture state-dependent drug effects. Similarly, although organ-level computational investigations of AF recurrence following ablation therapy have provided important insight into the role of untreated and emergent re-entrant drivers,<sup>89</sup> issues related to the simulation of potential intervening gaps, pulmonary vein reconnection, focal ectopic firing and progression of the underlying substrates due to continued atrial remodelling remain unresolved.<sup>160</sup> Thus, more accurate representations of currently available therapies may be needed for model-guided selection of AF therapy in clinical practice.

Finally, the clinical application of personalized organ-level models requires significant multidisciplinary expertise and integration with complex existing workflows and systems, including availability of (high-resolution) LGE-MRI and integration in electro-anatomical mapping systems employed during ablation procedures. Moreover, processing of clinical data for model personalization (e.g. segmentation of atrial structures on LGE-MRI) is time consuming. Together, these challenges make routine application in the large population of AF patients across the globe challenging.

After data-driven models have been derived, their computational costs are significantly lower than those of mechanistic models and their integration in clinical workflows is more readily achieved, e.g. as clinical decision-support systems accessible through websites, apps or other digital systems. One weakness of deep learning-based ML approaches is their 'black box' characteristic, in which the intermediate process cannot be scrutinized. This property has traditionally hindered application of these models for clinical decision with potentially severe consequences, despite their popularity in research settings.<sup>161</sup> However, as ML predictions are being more extensively validated in multiple independent data sets, the confidence in their clinical applicability is expected to increase.

## 9. Future perspectives

As summarized in the lower part of *Table 2*, continuing advances in experimental methodologies (e.g. induced pluripotent stem cell-derived

cardiomyocytes,<sup>80</sup> medium/high-throughput automated patch-clamping),<sup>162</sup> as well as clinical imaging modalities (high-resolution MRI and contrast-enhanced computed tomography, advanced mapping systems)<sup>163</sup> may provide new opportunities for model development and personalization. At the same time, technological innovations in combination with new approaches for model simplification are expected to provide additional computational performance, enabling simulation of more detailed mechanistic models.<sup>159</sup> Increased standardization and improved attention to re-usability will likely facilitate the exchange of modelling approaches and their integration into existing workflows, in preparation for routine clinical care. The integration of ML and mechanistic modelling is expected to continue, e.g. through ML-based automated segmentation of LGE-MRI data to generate personalized models and to integrate simulation data and clinical characteristics.<sup>104</sup> For data-driven models used directly in clinical decision-making, there is an increasing emphasis on explainable ML models.<sup>164</sup> Explainable models may help to overcome some of the reservations towards black-box models, but, may also give a false sense of security, and inaccurate (low-fidelity) explanation models may limit trust in the explanation, and by extension, trust in the black box that it is trying to explain.<sup>165</sup>

Given the promise of recent proof-of-concept studies, but also in light of the aforementioned challenges, hard evidence for the clinical benefit of using computational models will be needed to motivate their routine use. Ideally, this evidence will come in the form of randomized controlled trials comparing model-guided care with routine clinical care. Since there are no commercial incentives to improve the use of currently available pharmacological AF therapies, and given the developmental challenges, as well as the size and costs of clinical trials required for approval of new AADs (reviewed in detail elsewhere in this spotlight issue<sup>157</sup>) it is likely that such trials will initially focus on optimizing AF ablation. In addition, AF ablation can be simulated with simpler cellular models, reducing the computational burden. Nonetheless, such trials will require personalized simulations for hundreds of patients, requiring significantly more resources than existing proof-of-concept studies. For example, assuming an AF recurrence rate of 25% with model-guided therapy instead of 35% with an alpha of 0.05 and 80% power would require a trial with  $2 \times 328$  AF patients. As such, these studies can only be initiated after the methodological and logistical challenges have been solved. However, if such studies confirm that simulation-guided AF ablation improves sinus rhythm maintenance, this may help to establish the clinical value of AF ablation in subsequent large outcome studies.

## 10. Conclusions

AF remains a major healthcare burden in need of better management approaches. Several challenges in AF management might benefit from computational modelling, including the detection of asymptomatic AF, improved rhythm-control management and prediction of AF recurrence. Computational modelling of atrial electrophysiology and arrhythmogenesis has advanced significantly over the last decades and initial regulatory and clinical applications are emerging (Figure 1). Nonetheless, several limitations remain, including the extent of personalization, incorporation of intra- and inter-individual variability, computational requirements, and model integration into clinical tools. These limitations have to be overcome to enable the randomized controlled trials required for routine clinical adoption of model-guided AF management (Figure 1). Finally, computational modelling has also provided important insight into AF

mechanisms. The indirect contribution of this mechanistic understanding is hard to quantify, but will also facilitate improved AF management.

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This review article does not contain new original data.

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