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Computational models of heart diseases

Recent progress in multi-scale models of the human atria

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Atrial fibrillation (AF) is the world's most common cardiac arrhythmia. Due to the complexity of the heart and highly irregular electrical activity during AF it is a grand challenge to underpin the mechanisms underlying the initiation and maintenance of AF. Complimentary to experimental physiology, biophysically detailed models of the heart provide a powerful platform for investigating the substrates that prompt and perpetuate AF. In the last decade, there has been significant progress in the development of atrial models at the cellular, tissue and whole organ levels. This article presents a review of recent advances in modelling of the human atria and their application to understanding AF.

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Introduction

Mathematical modelling has provided a powerful tool for the investigation of cardiac arrhythmias for over half a century [1]. Whereas many studies have focussed on the ventricles, the atria are associated with the most common arrhythmias [2]. Moreover, they are characterised by a large degree of complexity in electrical properties [3] and anatomical structure [4] and contain the primary and secondary cardiac pacemakers. Modelling the atria is therefore a challenging and scientifically attractive prospect.

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Biophysically detailed models of the human atria at single cell and tissue scale have existed for over a decade [5,6]. Recent advances in computational power and imaging technologies, combined with a greater availability of experimental data, have led to the development of highly sophisticated models capable of providing deeper insight into cardiac function. In this paper we present a brief review of such advances and their application to understanding human atrial function.

Models of the atrial action potential

The action potential (AP) is the temporal change in the transmembrane potential of cardiac myocytes. It governs cellular (and hence organ) contraction and is underlain by ionic currents, which transport charged particles across the cell membrane, and intracellular ion handling systems. In this section we describe available models of the human atrial AP.

Human atrial action potential models

The first biophysically detailed models of the human atrial AP were that of Courtemanche et al. [5] and Nygren et al. [7]. Both models have been used in numerous computational studies of the electrophysiological properties of the human

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atria (e.g. [8]), but display markedly different morphologies and rate dependent properties (for a detailed comparison see [9]). Both models shared the limitations of relatively simple intracellular calcium handling dynamics and some current formulations being based on animal data. Maleckar et al. [10] reformulated two of the potassium currents in the Nygren model based on recent human-specific data, improving its rate dependence. Koivumaki et al. [11] later updated the intracellular calcium handling model, representing diffusion of calcium through the cytosol with the assumption that T-tubules are not present in the atria. Despite this assumption not holding for healthy human atrial myocytes [12], the model did improve the dependence of the intracellular calcium transient on intracellular calcium release in accordance with experimental observations [13]. A new model was developed by Grandi et al. [14] which included a more sophisticated intracellular calcium handling model with detailed descriptions of calcium buffering, as well as models of atrial fibrillation (AF) induced electrical remodelling and beta-stimulation. In Colman et al. [15] a hybrid model was developed for use in three-dimensional simulations of the heterogeneous human atria during AF, incorporating the calcium dynamics of the Koivumaki et al. model and the potassium current reformulations of the Maleckar et al. model into the Courtemanche et al. model. This model also included the effects of AF-induced electrical remodelling (see 'Simulating atrial fibrillation induced electrical remodelling' section). Krummen et al. [16] expanded the Courtemanche et al. model by incorporating clinical data regarding remodelling, isoproterenol and adenosine to investigate ionic determinants of changes in AP-duration (APD) restitution and activation latency in single cell. Most recently, the Grandi et al. model was expanded in Voigt, Heijman et al. [17] to investigate arrhythmogenesis in paroxysmal AF. Stochastic channel gating was incorporated into the model which included an idealised two-dimensional spatial representation of calcium handling, allowing investigation of the behaviour of spontaneous calcium sparks.

Action potential model properties

The available models described above exhibit significantly different electrical properties, such as AP morphology, rate-dependence and calcium transient morphology (Fig. 1a–c), resulting from differing underlying current formulations and intracellular kinetics. These differences are in some respect

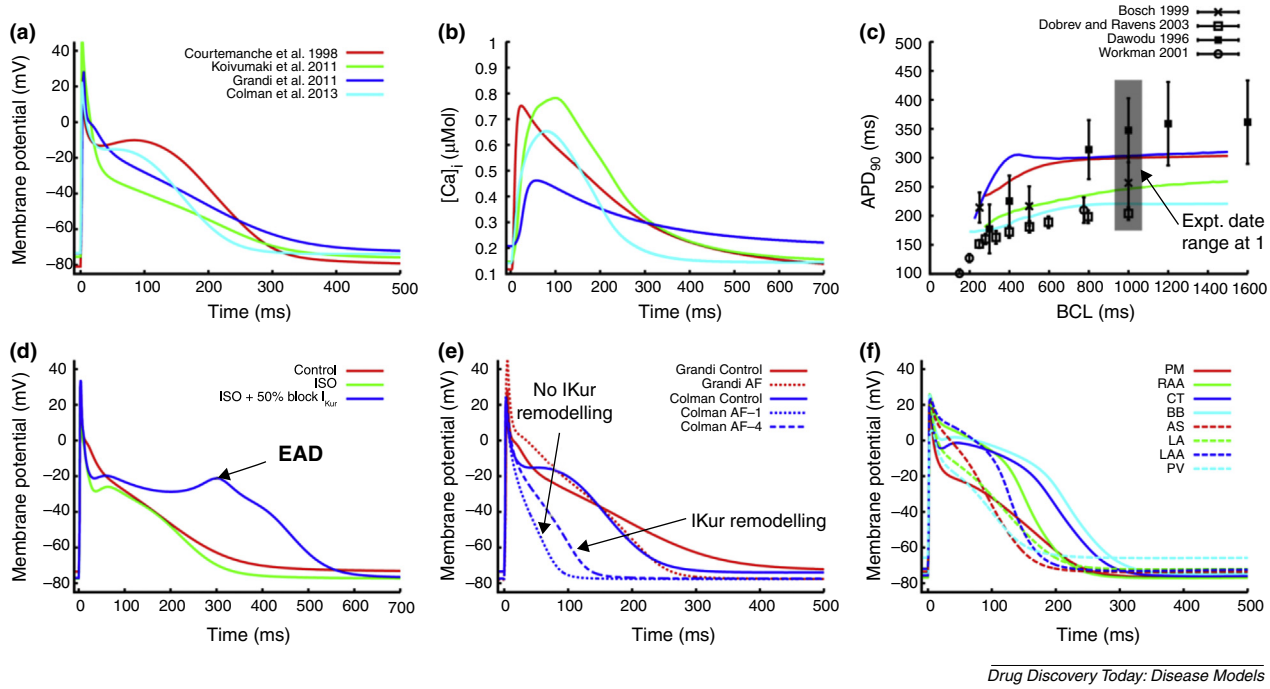

Figure 1. Single cell models of the human atrial action potential. (a–c) Simulated human atrial cellular activities from the four contemporary atrial cell models [5,11,14,15], demonstrating action potential morphology **(a)**, intracellular calcium transients **(b)** and action potential restitution **(c)**. Experimental data in (c) was from Bosch et al. [18], Dobrev and Ravens [21], Dawodu et al. [20] and Workman et al. [19]. The grey shaded area in (c) represents the range of experimental values of APD_{90} observed at 1 Hz across the literature. The colour key in a applies to all panels a–c. **(d)** The Grandi et al. model [14] is capable of reproducing early-after-depolarisations (EAD) under the effect of isoprenaline (ISO) and I_{Kur} block. **(e)** Models of AF-induced electrical remodelling, in the Grandi et al. [14] and Colman et al. [15] models. Note that remodelling of I_{Kur} prolonged the action potential compared to the case where it was not considered, but still the integral action of all remodelled ion channels resulted in significant action potential abbreviation compared to control. F: The family of regional cell models from Colman et al. [15]. PM = pectinate muscles, RAA = right atrial appendage, CT = crista terminalis, BB = Bachmann's bundle, AS = atrial septum, LA = left atrium, LAA = left atrial appendage, PV = pulmonary vein. Note the significant differences in morphology, duration and resting potential.