Literature Review: Complexity science approach to Atrial Fibrillation

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Abstract

In this literature review, the electrophysiology of heart cells, specifically heart muscle cells (myocytes) and sinoatrial node cells, are elucidated and their relation to action potential propagation to contract the heart is described. Methods to simulate the action potentials of these cells are mentioned and are seen to be a computationally costly way of modelling large scale heart tissue. Studied models of electrical wavefront propagation that could cause AF, such as the ring model, leading circle model and spiral wave model are described; spiral wave reentry has been observed to be an underlying mechanism. Cellular automata—where cells' states change based on the states of their nearest neighbours—are viable models that reduce the amount of computation by not considering differential equations relating to the action potentials. Therefore, reentry can be modelled on a large scale more easily. Moore neighbourhoods used with a Markus model can achieve smooth spiral waveforms that are isotropic and therefore model spiral wave reentry in a cellular automata models effectively. New directions of research can be taken to more accurately model AF such as: the morphology of the heart, modelling 3D scroll wave dynamics and using hybrid I/O automata.

1 Introduction

Medical science and the study of disease has been a crucial marker of society's success and development through the ages. Understanding disease gives insights into how to treat and diagnose serious conditions, of which can be fatal. One such condition that has eluded explanation and effective treatment is Atrial Fibrillation (AF), which is the leading cause of Ischaemic stroke in people over 75—seemingly due to incomplete contraction which leads to the formation of blood clots that can travel to the brain [1]. It has been known that there are cardiovascular diseases that are predisposed to initiate AF, such as Congestive Heart Failure, Pericarditis, Coronary Heart Disease and Hypertension through a combination of atrial pressure and dilation, but the precise mechanics are unknown. AF and VF (ventricular fibrillation) are thought to be caused by the breakup of waves of electrical impulses, that induce contraction, into interfering wavelets that produce chaotic behaviour.

Healthy hearts have a regular, sinus rhythm which is moderated by the sinoatrial node located in the right atrium of the heart. Fibrillatory activity in the atrium is characterised by a hastened activation of cells: atrial cells activate 300-600 times a minute in contrast to the expected sinus rhythm of 60 to 100 beats per minute.

Current treatment involves introducing antiarrhythmic drugs of which side effects include proarrhythmia, a form of cardiac arrhythmia, which can cause sudden death [2]. Surgical methods primarily involves the Maze procedure, by which a children's maze-like pattern is cut into the atria such that there is only one path that the electrical impulse can take from the sinoatrial node to the atrioventricular node. The treatment is usually successful but still may lead to fibrillation [3]. The ablation of cells in has been shown to treat AF therapeutically. Catheter ablation has had suboptimal success rates. Electrogram-guided ablation is a burgeoning area of research: complex fractionated atrial electrograms are proposed as sites for ablation; they seem to be critical for AF [4].

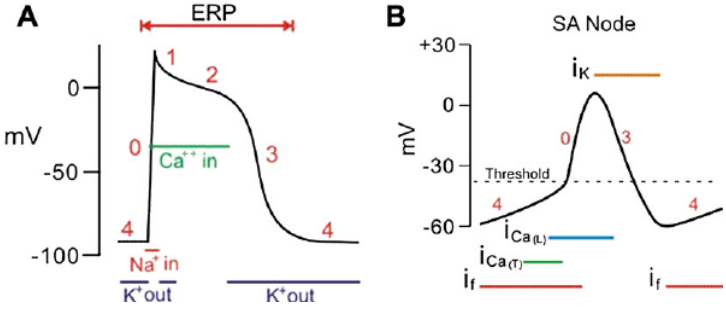
Electrograms are used for non-contact mapping and can be used to elucidate areas of fibrillatory activity. The most popular types are unipolar and bipolar. Unipolar electrograms have problems subtracting far-field signal and the wavefront direction affects the amplitude of the wave recorded—in contrast to bipolar electrograms—but the morphology of the surface can indicate the direction of the wavefront. Bipolar electrodes offer the advantage of a superior signal-to-noise ratio but with markedly less amplitude in sensing depolarization [5].

2 Electrophysiology of the heart

Signals propagate through the heart by an action potential arising due to the interplay of ions with pacemaker cells, in the sinoatrial and atrioventricular nodes, and myocardial cells in cardiac muscle [6]. See figure 1 for a diagram of the action potentials involved.

Myocardial cells in the heart have a potential difference and concentration gradient intrinsic to their structure: Na^+ and Cl^- ions are higher in concentration outside of the cell, while K^+ and organic anions (A^-) are more concentrated on the inside. Ca^{2+} ions are higher in concentration extracellularly but they are bound, mainly in the sarcoplasmic reticulum. This gives a resting membrane potential of -75mV, when no action potential is propagating, as the only ion that is allowed free movement is K^+ of which the concentration gradient and potential difference balance out the efflux (due to the concentration gradient) and influx (due to the negative resultant potential difference). This is phase 4 of the action potential. There are gates through which specific ions can flow into or out of the cell when a threshold voltage has been reached. After a sufficient stimulation, positive ions (mainly Na^+) flood into the myocardial cell which causes rapid depolarisation (phase 0). Once depolarised enough, after a small efflux of K^+ and Cl^- ions (phase 1), Ca^{2+} ion voltage-gated

Figure 1: Diagram of the action potential in a myocardial cell (A) and in sinoatrial cell (B). Numbers on the diagram indicate phases of the action potential. ERP = Effective refractory period [8]



channels open, which induces Ca^{2+} release from intracellular stores. This gives a plateau of potential difference (phase 2) where an influx of K^+ ions sustains the voltage plateau against the efflux of Ca^{2+} ions. The free calcium ions cause myocardial contraction. After a this long plateau phase, K^+ ion channels reopen to repolarise the cell (phase 3) to get ready for another contraction, reverting to phase 4. The period where a cell cannot contract and undergoes repolarisation ready for contraction is the refractory period.

In the sinoatrial node, the depolarising current is primarily fulfilled by Ca^{2+} ion movement, which is slow in comparison to the fast Na^+ currents of the myocardial cells. SA node action potentials have only three of the phases found in the myocardial action potential. Phase 4 is the spontaneous depolarization (pacemaker potential) that triggers the action potential. Phase 0 is the depolarization phase of the action potential. This is followed by phase 3, repolarization. Once the cell is completely repolarized at about -60 mV, the cycle is spontaneously repeated.

Ectopic firing—from a focus, not located at the Sinoatrial node, at which action potentials are initiated—can arise from 'afterdepolarisations': the free intracellular Ca^{2+} concentration rises sharply during the depolarised phase of the action potential; when relaxation occurs, the concentration of Ca^{2+} is reduced by uptake into the sarcoplasmic reticulum via Na^+/ Ca^{2+} exchange. This is an electrogenic process: three Na^+ ions are exchanged for a single Ca^{2+}, thus making the potential difference more positive. This induces an inward current that can depolarise the cell which can lead to spontaneous action potentials firing [9].

Atrial cell fibrosis causes cells to be unresponsive. Current research suggests that this is due to excessive Ca^{2+} loading, which occurs with tachycardia as many action potentials are enacted. Furthermore, this leads to electrical remodelling of the heart, making AF the more probable pathway of activation regardless of the mechanism for tachycardia [9]. Due to fibrillation, the concentration of the intracellular Ca^{2+} is altered, thus impairing effective contraction which may give rise to blood clots that can cause strokes.

3 Types of Models

Mechanisms thought to be responsible for active cardia arrhythmias are either enhanced/abnormal pulse formation or re-entry. For the former, simulations have included modelling the ionic currents to propagate action potentials such as the Fenton-Karma model [10] [11] and modelling the impulse of an action potential using generic reaction-diffusion equations, such as the FitzHugh-Nagumo Model [12]. Most of these models are based on the pioneering work of Hodgkin and Huxley who described the action potential of the giant squid axon, which bears similarities to cardiac cells [13]. For all of these models bidomain or monodomain approaches can be used to model the electrical propagation in myocardial tissue. The bidomain model takes into account the anisotropy of intracellular and extracellular spaces. The monodomain model is a reduction of the bidomain model by assuming anisotropy ratios of intracellular and extracellular domains are equal—this is the most commonly used model.

Re-entry—the mechanism by which a propagating impulse fails to die out after normal activation of the heart—has been studied in depth via various circus reentry formulations: the Ring Model, the Leading circle model, the Figure-of-Eight model and the Spiral Wave model [14] [15]. The Ring model models a wave of propagation that moves along one, unidirectional pathway of heart tissue and returns to the origin of excitation, thus simulating a central anatomical obstacle (inexcitable tissue) in the centre. This implies that the conduction velocity and the refractory period are both factors: the length of the circuit (pathlength) must be greater or equal to the wavelength (the distance travelled by an impulse during the refractory period—the product of conduction velocity and refractory period). The smaller the wavelength, the greater the number of reentry circuits that can be accommodated during the refractory period to promote fibrillatory behaviour. See figure 2(c).

The leading circle model found that there need not be a block of inexcitable tissue at the centre of circus movement for a reentry circuit to occur, using properly timed stimuli (see figure 2a). [16]. To rectify this reentry, it would be thought that the refractory period must increase to limit number of accommodated circuits, but incompatible observations have been found in antiarrhythmic drugs that block Na^+ channels, thus slowing down depolarisation. Such agents are effective in terminating AF, but according to leading circle theory should promote AF because they decrease conduction velocity and thereby decrease the wavelength. See figure 2(a) for diagram.

The Figure of Eight model has a centre where two concurrently propagating waves circulate in opposite directions that merge into a common, central pathway.

The Spiral wave model—which consists of a single rotating wavefront around a core, simulating tachycardia—has been observed in systems that have sites that have excited, refractory and resting states in both homogeneous and heterogeneous media [17] [18]. See figure 2(b) and and figure 3. Experimental demonstration of spiral waves has been achieved by in research by Davidenko et al and the concept is now seen to be an underlying driver of fibrillation; the paradigm appears to more closely correspond with many clinical and experimental observations than other models [19] [20]. The curvature of the wave is related to the speed of the wave, the more curvature the slower the speed of propagation. High curvature, and far-field instability, leads to spiral wave breakage into daughter wavelets. This agrees with popular classical modes of thought regarding the initiation of fibrillatory con-

Figure 2: Diagram showing the leading circle and spiral wave models of reentry. PL = pathlength, RP = refractory period, CV = conduction velocity, WL = wavelength [7]

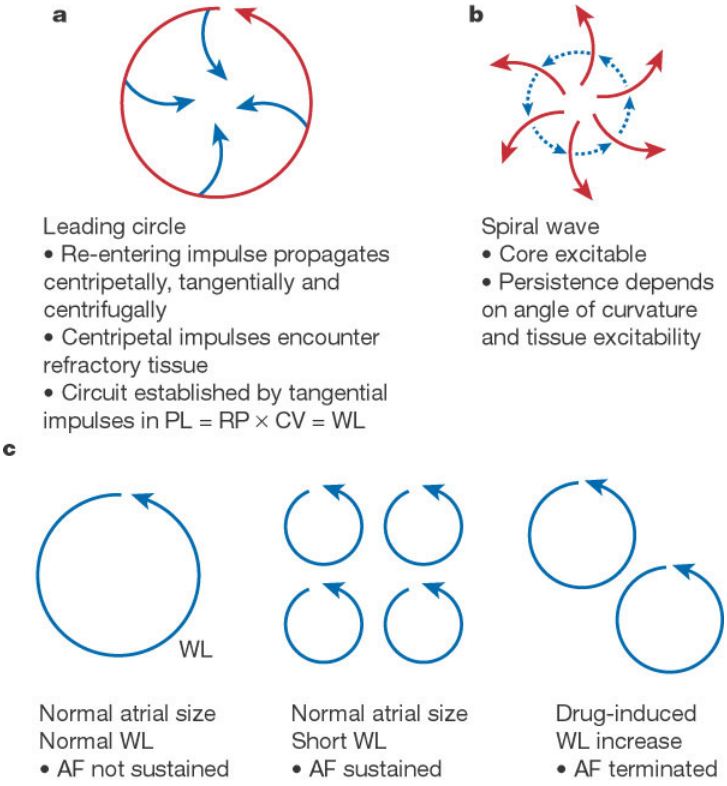
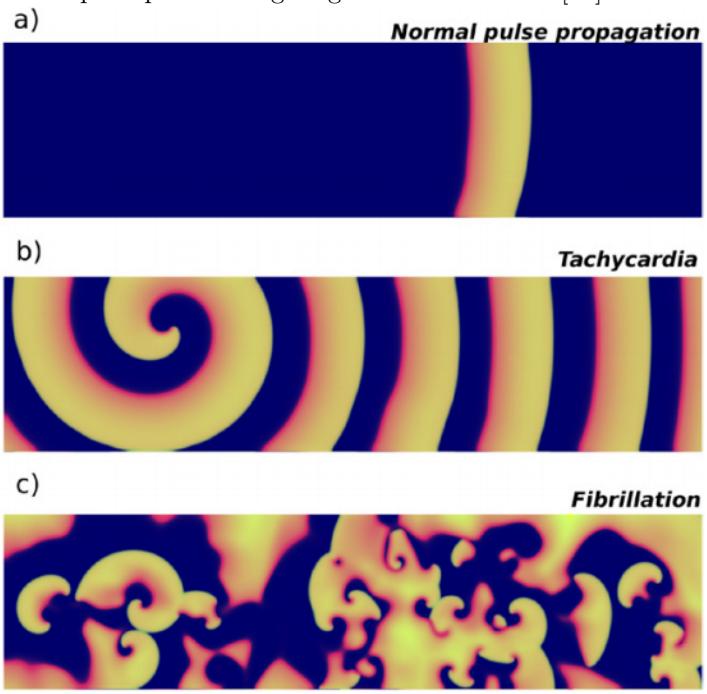


Figure 3: Diagram showing a spiral wave reentry circuit. (a), a normal wavefront in the heart. (b) spiral wave, which simulates tachycardia, as can be seen by multiple propagating wavefronts in a small area. (c), turbulent activity due to break up of spiral wave giving rise to fibrillation [23]



traction, multiple circuit reentry, and recent opinions where single, small reentry circuits or local generators have been found to promote fibrillatory activity—the core of the spiral [22] [9]. The tip of the spiral wave has been seen to drift around the core, thus moving the whole spiral wave. This mechanic can be a factor in promoting fibrillatory activity. Extending the spiral wave model to 3D gives rise to scroll waves which propagate through multiple layers of cells and give rise to more complex dynamics and is therefore hard to implement computationally.

4 Cellular Automata Models

Recent research has shown that rotating wavefronts can be initiated in regions where the proportion of transverse coupling between strands of tissue is reduced, leading to fibrillatory activity, in contrast to normal 'linear' wavefronts. This can be seen in the cellular automata model developed by Christensen et al. and reflects current opinion: the fibrosis of cells, which reduces the coupling of electrical signals to other cells, leads to AF [21]. Other studies suggest that the coupling of fibroblasts to atrial myocytes heterogeneously gives rise to spiral wave breakups [24].

Cellular automaton models have been formulated as there is no need to simulate the exact shape of the action potential, based on differential equations, and it is high speed in large scale simulations [25]. Only relative properties such as the excitation wavefront, refractory period and the morphology of the heart need be considered. Cells' states depend only on the states of their neighbours: they are either at rest, become excited, or are refractory. This is seen in research by Fedotov, using a cellular automaton model on the surface of a triangulated sphere to model spiral rotor waves on a closed, heterogeneous surface [27]. It was shown that both a decrease in refractory period and conduction velocity from a "healthy" myocardium state, where no irregular excitation waves above 300bpm are observed, resulted in an area where spiral waves were formed. In addition, a multi-electrode system was created to study the localization of AF sources.

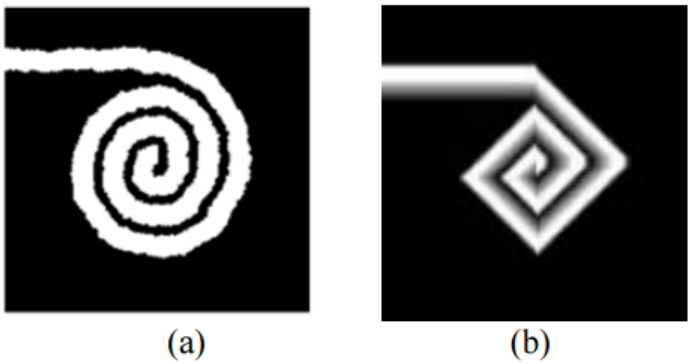
Mainly square lattices have been used for such cellular automata models. One problem is isotropy, especially when spiral waves are simulated. As seen in research by Pourhasanzande et al, Moore, rather than Von Neumann, neighbourhoods can be used with a Markus model reducing the square shape of the spiral wave by choosing an appropriate threshold value of neighbours [26]. See figure 4.

More cellular automata models have been researched by Siregar et al, where a 3D model of the heart, with simplified morphology is simulated and, in addition, a 2D CA model is compared qualitative model [28] [29]. A hybrid I/O cellular automata approach has also been studied in research by Bartocci et al to describe cardiac tissue and improve the efficiency of the simulation process [30].

5 Conclusion

Modelling Atrial Fibrillation (AF) to ascertain its causes accurately, allowing for effective treatment, has been extensively studied over the past few decades. It is the largest cause of strokes linked with cardiac arrhythmia in aging populations; is due to impaired contractility of the atria in the heart, leading to blood clot formation. Irregular action potentials, mediated by ionic species, observed in AF causes some atrial heart

Figure 4: Diagram showing spiral wave generated by using (a)—a Moore neighborhood—and (b)—a Von Neumann neighborhood showing the reduction of flat edges using the Moore model with the Markus method [26]



muscle cells, myocytes, to contract at 300+ times per minute, much faster than healthy hearts which contract at 60 to 100 times per minute. This beating is regulated by the sinoatrial node which propagates periodic signals through myocytes, causing contractions. Altered refractory period and conduction speed of signals has been seen to promote AF in various models and is caused physically by the fibrosis of cells, reducing the coupling of electrical signals to some myocytes; giving rise to reentry circuits. The most prominent reentry model, the spiral wave model, has been seen to more closely follow clinical and experimental observations than other models of wavefront action. Cellular automata modelling paves the way for large scale simulations of tissue in the heart without the need to solve differential equations, that govern the action potentials, which can be computationally costly. Moore neighbourhoods are seen to be more effective at producing isotropy of spiral waves, reducing flat edges, in rectilinear cellular automata models. Modelling scroll waves, using hybrid cellular automata models and replicating the morphology of the heart more closely seem to be viable directions for further research.

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