# Competitive Interactions between Ectopic Foci and Reentry in Virtual Human Atrium

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## Abstract

*Atrial arrhythmias (flutter and fibrillation) are characterised by rapid and irregular activation of atrium. There are two possible mechanisms: abnormal spontaneous electrical activity of ectopic foci and multiple re-entrant wavelets. In this study, we developed a biophysically detailed computer model of virtual human atrium to study the interaction between the two major arrhythmic origins. Depending on their frequencies, phases and distance, the interaction is competitive with either ectopic focus or reentry dominating atrial electrical excitation. Collisions between the two lead to further wave-breaks and the formation of multiple re-entrant wavelets, providing a source for persistent atrial fibrillation. Focal activity acting as an organising centre, or mother motor which drives and controls the rhythm of reentry was observed.*

## 1. Introduction

Atrial arrhythmias (flutter and fibrillation) are the most common tachyarrhythmia that causes high morbidity and mortality [1-3]. Typically atrial arrhythmias are characterized by spatio-temporal irregular and high rate electrical activities (300-500 beats/min) [4] that represent abnormal atrial excitation and conduction pattern. There is considerable experimental evidence to support two putative mechanisms associated with atrial arrhythmias: abnormal spontaneous electrical activity from rapid ectopic focal origin [5] and multiple reentrant wavelets [6]. In some patients it is possible the two mechanisms co-exist or transfer from one type to the other.

Competitive interactions between these two arrhythmic origins have not been studied, and such interactions may generate complicated atrial conduction pattern facilitating the development and maintenance of persistent atrial fibrillation. Here we construct a biophysically detailed computer model of electrical activity for two-dimensional (2D) human atrial tissue. The model was used to investigate the interactions between ectopic focal activity and reentry. The effects of differences in their frequencies, phases and the distance between them were also studied.

## 2. Methods

A computer model of electrical activity of 2D virtual human atrial tissue was developed by incorporating a cellular model of action potential (AP) of the human atrial myocyte developed by Nygren *et al.* [7] into an isotropic and homogeneous partial differential equation (PDE), which takes the form:

$$\frac{dV(X,t)}{dt} = -\frac{1}{C_m}\sum_j i_j(X,V,t) + \nabla(D(X)\nabla V(X,t)) \quad (1).$$

$V$ is the membrane potential, $i_j$ the j-th gated membrane ionic channel current, $C_m$ the cell membrane capacitance. $X$ defines the physical space of the atrial tissue. $D$ is the diffusion coefficient that simulates gap junctional electrical coupling between atrial myocytes. $D$ is a scalar for tissue with homogeneous gap junction coupling or a spatial function for tissue with heterogeneous gap junction coupling.

In the model, the size of atrial tissue was 96x96 $mm^2$, which was discretized by a spatial resolution of 0.32 mm to form a 300x300 node discrete lattice. Each node of the lattice was modelled by the Nygren *et al.* model. The diffusion parameter $D$ was set to 0.3125 $cm^2\ s^{-1}$ that gives a conduction velocity of a planar wave of 0.3 m $s^{-1}$ in the tissue, which is consistent with experimental data [8].

In simulations, a re-entrant spiral wave was initiated by a standard s1 and s2 protocol. With an s1 stimulus, a conditioning planar wave was initiated and conducted in the tissue. After a time delay, an s2 stimulus was applied in the cross direction to the conduction of the conditioning wave. The wave initiated by the s2 propagates non-uniformly in the tissue. Closer to the refractory tail of the conditioning wave, the s2-evoked

excitation wave propagated slower as that part of tissue had recovered less. Further away from the refractory tail, the evoked excitation wave propagated faster as that part of tissue had recovered more. As a consequence, the wavefront of the excitation wave curved and formed a re-entrant spiral wave. Ectopic foci were modeled by a series of supra-threshold stimulus with amplitude of 6 nA and duration of 3 ms to a localized area (20x20 nodes) (the center position of focal region is variable). The period (or frequency) of ectopic focal activity was varied. The interaction between ectopic focal activity and reentry was studied for various relationships between the frequency of the ectopic focus ($f_e$), the frequency of reentry ($f_s$) and the critical frequency of the tissue ($f_c$, over which the ectopic stimuli failed to evoke one-to-one excitation wave in the medium). Effects of distance and phase differences between the two were also studied.

Numerically the 2D PDE model was solved by the explicit Euler method with a five-node approximation of Laplacian operator. With a space step of 0.32 mm, the time step was set to 0.01 ms, which are sufficiently small for stable numerical solutions [8]. The program was coded in $C^{++}$ and run on a SunBlade 2000 Solaris 5.8 Unix system.

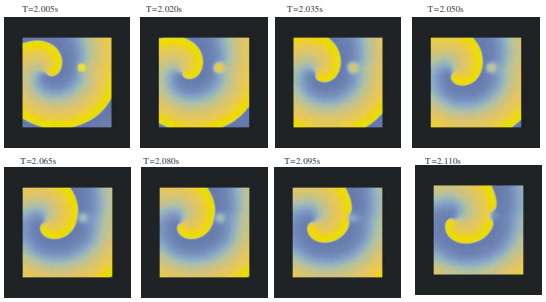


Figure 1. Snapshots (every 15 ms) of interaction between ectopic focus and reentry when $f_s > f_e$ in a 96 ×96 mm medium. Re-entry suppresses focal activity and dominates the rhythm of atrial excitation.

## 3. Results

When the frequency of reentry was higher than that of focal activity ($f_s > f_e$; Figure 1), the reentry suppressed the ectopic focus and dominated the activity of the whole medium. Depending on the initial distance between the core of the spiral wave and the position of ectopic region, the ectopic focus either had no effects on reentry if the distance was large (over half of the excitation wavelength), or perturbed the reentry to drift away from the auto-rhythmic region if the distance was small.

When the frequency of focal activity was close to that of reentry ($f_s \approx f_e$), the focal activity modulated the behaviors of the spiral wave. As a consequence, the tip of spiral wave drifted along the direction determined by the initial phase difference between the two. In a limited tissue size, the core of the spiral wave might be driven out of the medium and the spiral wave died. The focal activity would then dominate the atrial rhythm. However, if the site of the focal activity was far away from the core (over half excitation wavelength), then the modulation effect was negligible and the two sources co-existed in the medium.

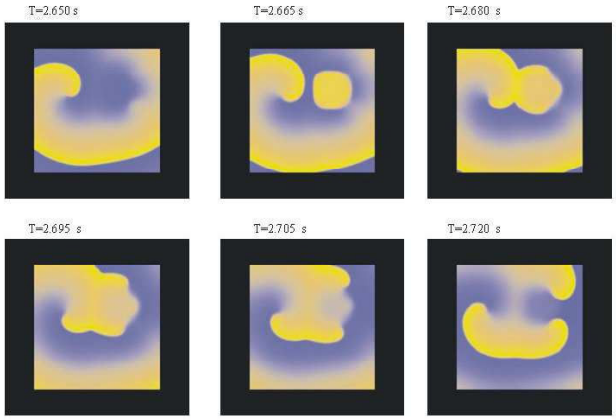


Figure 2. Snapshots of interaction between ectopic focus and reentrant spiral wave when $f_s < f_e < f_c$. Collisions between excitation waves break up the wavefront of spiral wave leading to formation of multiple reentrant wavelets.

When the frequency of ectopic focal activity was higher than that of the reentry, but lower than that of the critical frequency of the tissue (fs < fe < fc; Figure 2), the ectopic focal activity evoked excitation waves that only propagated in the retrograde direction, but not in the anterograde direction of a previous spiral wave. When the two waves met, they collided, which broke up the wavefront of reentry producing multiple wavelets. The generated wavelets had finite life time and died shortly. But new wavelets were continually being generated by collisions. This formed a stable source for producing persistent multiple re-entrant wavelets in a limited mass of atrial tissue.

When the frequency of focal activity was higher than both the reentry and the critical frequency of the tissue ($f_e > f_c > f_s$), the ectopic focal activity failed to evoke a 1 to1 excitation wave which propagated in the tissue, as the tissue was in the refractory period of a previous excitation. However, each of the stimuli evoked a small and incomplete membrane action potential in the vicinity

of the focal region, which was similar to the action potential generated by weakly excitable cardiac tissue. As a consequence, the focal region behaved functionally the same as a cardiac lesion with weak excitability and formed a conduction block to wavefronts as shown in Figure 3. When the wavefront of reentry reached the focal region, its wavefront was broken producing two new tips, each of which formed an independent re-entrant wavelet.

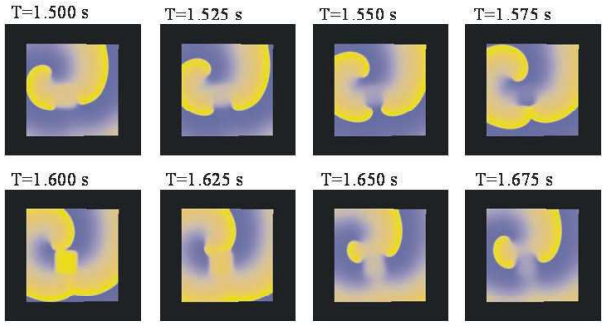


Figure 3. Snapshots of interaction between reentrant spiral wave and ectopic focal activity when ($f_e$>$f_c$>$f_s$). The focal region fails to evoke 1:1 excitation wave in the tissue, but forms conduction block to spiral wave.

The interaction was distance dependent. Figure 4 showed two different conditions. In panel A, the distance between the origin of the renetry and that of the focal activity was relatively large. In this case, the ectopic focal region acted as a lesion as discussed above. The lesion formed a conduction block to the re-entrant, which broke up the wavefront of spiral wave forming multiple reentry wavelets.

In case B, the distance was relatively small. In this case, by collision, the tip of the spiral wave moved to the focal region and was pinned to rotate around the border of the focal region. In responding to each beat of the focal activity, the original tip of reentry was destroyed by collision, but a new tip of reentry was born. The rhythm of the spiral wave was either determined by the size of the focal region or by the period of focal activity. In this way, a persistent re-entry was controlled by the focal activity, which acted as a mother motor or a driver for re-entry.

## 4. Discussion and conclusions

In this study, we developed a 2D biophysically detailed computer model of electrical activity of human atrium.

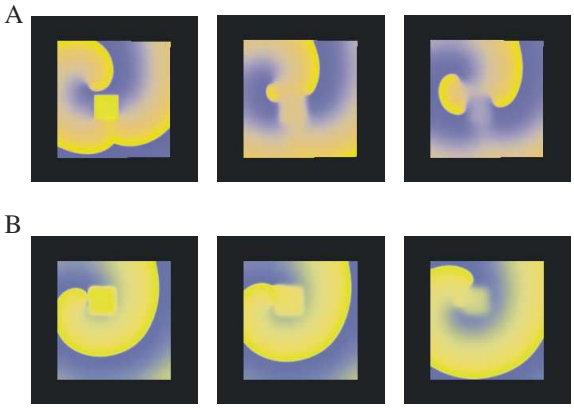


Figure 4. Snapshots of interaction between ectopic focal activity and reentry when $f_e > f_s > f_c$ with different distance between the tip of the spiral wave and the focal region. (A) The distance is large. Spiral wave breaks up forming multiple wavelets. (B) The distance is small. Spiral wave is trapped to rotate around the border of the focal region. The focal region serves as a driver for reentry controlling atrial excitation rhythm.

Using the model, we investigated the interactions between two major sources of human atrial arrhythmias: reentry and ectopic focal activities. The main finding of this study is that the interaction is competitive with either reentry or focal activity dominating atrial rhythm. It is possible for the two to co-exit. All of which is dependent on the differences between the frequencies, phases and distance between reentry and focal activity.

Focal activity may be suppressed if its frequency is lower than that of spiral wave. In this case, atrial excitation rhythm will be dominantly determined by spiral wave. Focal activity, though existing, does not contribute to atrial electrical excitation.

However, when the frequency of focal activity is close to that of re-entrant spiral wave, the focal activity may drive spiral wave out of medium and control atrial excitation. This is due to a periodic modulation to the excitability of cardiac tissue around the vicinity of the focal region produced by the focal activity. Such a periodic modulation in cardiac excitability disturbs the dynamical behaviours of spiral wave and introduces a series of regular displacements to the tip motion. If the period of the disturbance is close to the period of spiral wave, a “resonant drift” [9] occurs. As a result, the tip of the spiral wave drifts directly with the drift direction determined by the initial phase difference between the spiral wave and the ectopic focus. By varying the initial timing and location of focal activity, we have observed that the tip drifted in different directions with similar path pattern. In a limited atrial mass, such directed tip drift

may lead the spiral wave to move out of medium leaving the focal activity to dominate atrial excitation rhythm. However, when the distance between the two sources is large (over half of excitation wavelength), the modulation effect become negligible and both focal activity and reentry co-exist.

It has been unclear how multiple re-entrant wavelets can be sustained in a limited atrial mass [4] responsible for persistent atrial fibrillation. In our simulations we have found that by interaction, a stable source for generating multiple re-entrant wavelets can be formed by the interaction between focal activity and reentry. In the case when the frequency of focal activity is higher than that of spiral wave, but is slower than the critical frequency of the tissue, excitation waves of the two origins collide producing multiple wavelets of reentry. Though each of the generated wavelets has finite life time and dies shortly, new wavelets are always generated. This may be one of the possible mechanisms underlying the persistence of atrial fibrillation associated with multiple wavelets.

It has been conjectured that a mother rotor is necessary to drive and control the rhythm of atrial excitation during persistent atrial fibrillation. In our simulations focal activity serving as a mother motor has been illustrated. When the frequency of focal activity is high, the cardiac tissue fails to correspond beat by beat, the focal region can pin the tip of spiral wave to rotate around its border. In this case, the rhythm of the spiral wave will be determined by the size of the border and the rhythm of focal activity.

The interaction between focal activity and reentry is complicated. In this study we only classified some typical scenarios. In the model, we also ignored the complicated heterogeneities of electrophysiology, tissue structure and intercellular coupling in atrial tissue, all of which may have important roles in the initiation and conduction of atrial arrhythmias.

Acknowledgements

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