Action potential morphology heterogeneity in the atrium and its effect on atrial reentry: a two-dimensional and quasi-three-dimensional study

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Atrial fibrillation (AF) is believed to be perpetuated by recirculating spiral waves. Atrial structures are often characterized with action potentials of varying morphologies; however, the role of the structure-dependent atrial electrophysiological heterogeneity in spiral wave behaviour is not well understood. The purpose of this study is to determine the effect of action potential morphology heterogeneity associated with the major atrial structures in spiral wave maintenance. The present study also focuses on how this effect is further modulated by the presence of the inherent periodicity in atrial structure. The goals of the study are achieved through the simulation of electrical behaviour in a two-dimensional atrial tissue model that incorporates the representation of action potentials in various structurally distinct regions in the right atrium. Periodic boundary conditions are then imposed to form a cylinder (quasi three-dimensional), thus allowing exploration of the additional effect of structure periodicity on spiral wave behaviour. Transmembrane potential maps and phase singularity traces are analysed to determine effects on spiral wave behaviour. Results demonstrate that the prolonged refractoriness of the crista terminalis (CT) affects the pattern of spiral wave reentry, while the variation in action potential morphology of the other structures does not. The CT anchors the spiral waves, preventing them from drifting away. Spiral wave dynamics is altered when the ends of the sheet are spliced together to form a cylinder. The main effect of the continuous surface is the generation of secondary spiral waves which influences the primary rotors. The interaction of the primary and secondary spiral waves decreased as cylinder diameter increased.

Keywords: atrial fibrillation; action potential morphology; spiral wave; crista terminalis; computer simulations

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Although not fatal in itself, AF may lead to more serious conditions such as stroke, impaired cardiac output and ventricular tachycardia. The mechanisms underlying AF are not completely understood, although functional reentry has been implicated in

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its initiation and maintenance (Moe & Ablidskov 1959; Mandapati et al. 2000; Jalife et al. 2002). The dynamics of a functional reentrant wave is dependent on numerous factors, among which is the spatial heterogeneity of action potential morphology (Sampson & Henriquez 2002; Ten Tusscher & Panfilov 2003).

The atria are characterized with a significant variation in action potential morphology. The crista terminalis (CT), atrioventricular rings (AVR), atrial wall (AW) and the appendages (APG), have been found to have varying values for certain ionic conductances that create a distribution of action potential morphology (Spach et al. 1989a; Qi et al. 1994; Yamashita et al. 1995; Feng et al. 1998; Ramirez et al. 2000). Action potential variation has been demonstrated even within structures such as, for instance, the right atrial appendage (APG) (Boutjdir et al. 1986). Furthermore, a study by Spach et al. (1989b) documented an organized distribution of action potential morphology with the longest action potential duration near the SA node and decreasing duration in the tissue distal from it.

The dynamics of a functional reentrant circuit (spiral wave) in the atria is also dependent on the size of the tissue relative to the wavelength of the reentrant wave. Atrial reentry is initiated and maintained in a structure that is inherently periodic. Periodicity can strongly alter spiral wave stability, as demonstrated in the exhaustive survey of spiral wave breakup mechanisms by Fenton et al. (2002).

Factors that affect the dynamics of the AF wavefronts are difficult to dissect in an experimental setup; thus, a large body of research has focused on teasing out the various mechanistic influences on spiral wave sustenance by means of computer simulations (Pertsov et al. 1993; Karma 1994; Courtemanche 1996; Beaumont et al. 1998; Qu et al. 1999, 2000; Xie et al. 2001; Fenton et al. 2002). However, the majority of these simulation studies has focused on spiral wave breakup due to dynamic rather than naturally existing electrophysiological heterogeneities (Karma 1994; Qu et al. 1999; Xie et al. 2001). Structure-dependent heterogeneity in action potential morphology has rarely been included in these studies.

The purpose of the present study is to determine the effect of action potential morphology heterogeneity associated with the major atrial structures in spiral wave maintenance. The study also focuses on how this effect is further modulated by the presence of the inherent periodicity in atrial structure. The goals of the study are achieved through the simulation of electrical behaviour in a two-dimensional atrial tissue model that incorporates the representation of different action potentials in various structurally distinct regions in the right atrium. Periodic boundary conditions are then imposed on two parallel edges of the sheet to form a cylinder (quasi three-dimensional), thus allowing us to explore the additional effect of structure periodicity on spiral wave behaviour.

2. Methods

In this computational study, spiral wave behaviour was analysed in a finite difference grid that represented a sheet of atrial tissue. Simulations were performed to examine the effects of action potential morphology heterogeneity and surface periodicity for different sheet sizes and spiral wave initiation sites.
The electrical behaviour in the sheet was governed by the equation:

\[ \sigma \left( \frac{\partial^2 V_m}{\partial x^2} + \frac{\partial^2 V_m}{\partial y^2} \right) = \beta \left( C_m \frac{\partial V_m}{\partial t} + I_{\text{ion}} \right), \]

where \( \sigma \) is the intracellular conductivity, 1.74 mS cm\(^{-1} \), \( V_m \) is the transmembrane potential, \( C_m \) is the specific membrane capacitance, 100 pF cm\(^{-2} \), \( \beta \) is the surface-to-volume ratio of the membrane, 0.42 cm\(^{-1} \), and \( I_{\text{ion}} \) is the total ionic current density. The boundaries of the sheet were assumed to be insulated.

In the left panel of figure 1a, a sheet characterized with a uniform action potential corresponding to the atrial wall (AW) is shown; it measures 6×6 cm. The sheet on the right of figure 1a is modified to represent different action potential morphologies in the various atrial structures. Two vertical regions are defined, the CT, being 4.8×0.6 cm in the middle of the sheet, and the APG as a 2.4×0.3 cm region located 0.6 cm to the right of the CT. The AVR occupied the bottom of the sheet with dimensions of 0.24×6 cm. Size and position of structures in the sheet were based on human right atrium data (Cohen et al. 1995) and then scaled to the size of the atrial sheet. Since the CT predominantly runs from the superior to the inferior vena cava, it was placed vertically in the centre of the sheet with the other structures positioned with respect to it. The sheet incorporating variations in action potential morphology is termed ‘heterogeneous’ in the text below, while the sheet without such variations is referred to as ‘homogeneous’. The kinetics of the ionic currents and their regional variations were represented by the Ramirez–Nattel–Courtemanche canine atrial model (Ramirez et al. 2000); the latter is based on isolated cell recordings from the four distinct regions (AW, APG, CT and AVR) by Feng et al. (1998). Figure 2 shows the action potentials in the various regions of the sheet for a basic cycle length of 700 ms. Clearly, the CT has the slowest repolarization and the longest action potential duration (250 ms), while the AVR (186 ms) has the shortest duration. Although identical in action potential duration (228 ms), the AW has the characteristic spike-and-dome morphology, which is not present in the APG, giving it a slightly elevated plateau.

To examine reentry maintenance on a continuous surface, the no-flux boundary conditions on the vertical sides of the sheet were replaced with periodic boundary conditions to form a cylinder (figure 1b) of diameter 1.91 cm. The periodic boundary conditions were introduced shortly after the S2 stimulus. Additional simulations were performed using a sheet of increased size, 6×9 cm, which resulted in a corresponding increase in the cylinder diameter to 2.86 cm.

A single spiral wave was initiated by cross-field stimulation using two 4 ms stimuli. A 40 μA cm\(^{-1} \) S1 stimulus was applied to the left half of the sheet at the beginning of the simulation (figure 1c). At 235 ms, a S2 stimulus of 25 μA cm\(^{-1} \) was applied to the upper left quadrant of the sheet to initiate a spiral wave with its phase singularity, the organizing centre of the spiral wave, located over the CT; this was termed initiation site 1. An additional initiation site to the right of the CT, site 2, was also used, as shown in figure 1c.

The behaviour of the spiral wave was monitored over time. Transmembrane potential distributions as in figure 1d were converted to spatial maps of the phase variable using a time delay, \( \tau \), of 2 ms (Iyer & Gray 2001). Phase maps were then employed to calculate the position of phase singularities, the organizing centres.
Figure 1. (a) Geometry of the homogeneous and heterogeneous sheets. The homogeneous sheet is characterized with a uniform action potential corresponding to the atrial wall (AW). The heterogeneous sheet has regions of different action potential morphology corresponding to the crista terminalis (CT), atrioventricular ring (AVR) and appendage (APG). (b) The sheet is joined at the left and right boundaries to form a cylinder. (c) Spiral waves are initiated at two sites: initiation site 1 which is over the CT and initiation site 2, to the right of the CT. (d) Phase singularities, each representing the organizing centre of a spiral wave (left), are tracked over time and their consecutive locations are shown as phase singularity traces in the tissue (centre). Consecutive phase singularity locations are shown in progressively changing colours to mark time. Two different colour scales for time (right) are used for spiral waves of the two chiralities, counter-clockwise and clockwise (arrows above time scales), with pink and dark blue, respectively, indicating the most recent presence of a phase singularity.
of the spiral waves, using a threshold voltage of $-55 \text{ mV}$ (Larson et al. 2003). Phase singularity motion was tracked over time using phase singularity traces (figure 1d) where two different time scales, shown on the right, indicate the most recent position of a phase singularity, depending on the chirality of the spiral wave. A current location of a phase singularity is coloured pink for a counter-clockwise spiral wave and dark blue for a clockwise spiral wave, with the colour changing gradually to green for a location at which the phase singularity has not been present for 500 ms or more.

3. Results

Figure 3 illustrates the evolution of a spiral wave initiated at the CT (site 1), with columns a, b, c and d referring to the homogeneous sheet, heterogeneous sheet, homogeneous cylinder and heterogeneous cylinder, respectively. In each of columns a and b, a single spiral wave reentry is initiated by the cross-field stimulation protocol; the spiral rotates in a counter-clockwise direction. Both spiral waves meander while rotating, until $t=900 \text{ ms}$ where the spiral wave in the homogeneous sheet is terminated at the boundary. One observes that the spiral wave in the heterogeneous sheet propagates slower, with an average rotation period of 130 ms, compared to the 120 ms period in the homogeneous sheet. Of all heterogeneous structures, the CT has the largest impact on propagation due to it having the longest action potential duration. Its extended refractoriness is evident in the 540 and 660 ms panels of figure 3b. The short action potential of the AVR has no effect on overall electrical behaviour in the sheet due to the border location of the region. The difference in morphology between the action potentials in the APG and AW also has no observable effect on spiral wave behaviour.

Figure 4 shows phase singularity traces associated with the transmembrane potential maps in figure 3a,b. The influence of the prolonged refractoriness of the CT is manifested in figure 4b by the more complex path of the phase singularity
Figure 3. (Caption opposite.)
in and around the CT in the heterogeneous sheet. In contrast, in figure 4a, the phase singularity meanders in a quasi-periodic fashion, consistent with previous studies of spiral wave behaviour in homogeneous media (Xie et al. 2001).

To emphasize the role of the action potential morphology variation in the CT and the other structures in the electrical behaviour in the heterogeneous sheet, single action potential sequences taken from figure 3b from locations within the four different structures are presented in figure 5 (solid line traces). The figure demonstrates that the action potentials have shortened significantly due to the electrotonic interactions in the sheet during spiral wave reentry. In the same figure, we show, for comparison, action potential traces from the same locations in the heterogeneous sheet when it was paced at a basic cycle length of 120 ms (dashed traces), which corresponds to the average activation rate during reentry in the homogeneous sheet. Pacing the heterogeneous sheet at a rate of 120 ms
results in a conduction block at the CT for every other paced beat (2:2 activation rate), while the other structures remain activated at a rate 1:1. Clearly, block at the CT leads to the increased average spiral wave period of rotation in the heterogeneous sheet.

When periodic boundary conditions were applied (figure 3c,d), a clockwise secondary spiral wave appeared, resulting, together with the primary wave, in a figure-of-eight reentry. Spiral wave rotation period in the homogeneous cylinder remained nearly the same as in the sheet, 122 ms, while in the heterogeneous cylinder it decreased to 120 ms. This indicates that surface periodicity exerted an effect on the spiral wave rotation mostly in the heterogeneous sheet. Figure 4c,d demonstrates that the two phase singularities of opposite chirality (newest positions are pink and dark blue for the primary and secondary singularities, respectively) oscillate back and forth until they eventually annihilate each other at about 750 ms. Comparing the panels in figure 4, one notices that the phase singularity trace of the primary spiral wave is affected less by the presence of the CT in the heterogeneous cylinder, as compared to the heterogeneous sheet, indicating that surface periodicity is overriding the effect of the CT.

Simulation results obtained following spiral wave initiation outside the CT (site 2) are presented in figure 6 for the same four cases examined in figure 3. Comparison of columns a and b shows behaviour similar to the one observed for initiation site 1. The spiral wave in the homogeneous sheet rotates for two cycles before terminating at the bottom border of the tissue, at $t=660$ ms (see also

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**Figure 5.** Action potential traces from locations within the four different regions in the heterogeneous atrial sheet during the spiral wave reentry in figure 3b (solid lines) and when the sheet was paced at a rate of 120 ms (dashed lines).
Figure 6. (Caption overleaf.)
In contrast, in the heterogeneous sheet, the spiral wave survives for the entire simulation, 1 s. In panels $t=420$ and $660$ ms of figure 6b, long vertical regions of prolonged refractoriness associated with the CT are again observed. In figure 7b, the phase singularity meanders predominantly up and down the CT, showing a pronounced anchoring effect by the CT.

In figure 6c,d, application of periodic boundary conditions for initiation site 2 produces a more complex pattern of reentry than that observed for initiation site 1. Figure 7c,d illustrates this increase in complexity as judged by the presence of multiple secondary phase singularities, six and four for the homogeneous and heterogeneous cylinders, respectively, as compared to the single secondary singularity observed for initiation site 1, regardless of cylinder type. In the homogeneous cylinder (figure 7c), the phase singularity of the primary spiral wave quickly dies out as it does in the homogeneous sheet (figure 7a), but...
a secondary phase singularity survives, further spawning other secondary phase singularities and maintaining reentrant activity. In contrast, both phase singularities in the heterogeneous cylinder survive. The anchoring effect of the CT on the phase singularity movement in the heterogeneous sheet (figure 7b) was quickly overridden by the interaction with the secondary phase singularities (figure 7d).

The effect of the increase in horizontal tissue size (and thus in cylinder diameter) on spiral wave behaviour in the four cases is shown in figures 8 and 9, (initiation sites 1 and 2, respectively). In the homogeneous sheet, the increase in sheet size (figures 8 and 9a) has no effect on the behaviour of the phase singularity regardless of initiation site. However, increase in the homogeneous cylinder diameter clearly has an effect on reentrant behaviour: the movement of the secondary phase singularity, for both initiation sites, remains fairly independent of the primary singularity (figures 8 and 9c). Indeed, for initiation site 1, a figure-of-eight reentry is again observed in the homogeneous cylinder, but in contrast to the smaller cylinder (figure 4c), where the two-phase singularities annihilate each other very early, interaction here is minimal. For initiation site 2, there is a drastic change in secondary spiral wave behaviour (figure 9c). In contrast to the case of the smaller cylinder (figure 7c), where numerous relatively short-lived secondary singularities are observed, in figure 9c the only secondary phase singularity survives, establishing a single stable rotor. Therefore, in the large homogeneous cylinder, activity is maintained only if a secondary spiral wave is produced, regardless of initiation site.

Increase in sheet size for the heterogeneous case results in a change in the spiral wave behaviour. For both initiation sites, the phase singularity survives for the duration of the simulation, 1 s. For initiation site 2 (figure 9b), the phase singularity trace initially follows a path very similar to the smaller sheet, deviating only slightly near the end of the simulation. The phase singularity
trace for initiation site 1 (figure 8b) follows a different path than that observed in the smaller tissue.

The primary phase singularity traces in figures 8 and 9d are almost identical to those in figures 8 and 9b, respectively. The appearance of the secondary phase singularity in the heterogeneous cylinders has a minimal effect on the primary phase singularity, less than that seen in the homogeneous case. Unlike the homogeneous case, in the heterogeneous case the phase singularities are separated sufficiently so that their movement does not interfere with each other.

4. Discussion

The purpose of this simulation study was to determine the role of action potential morphology heterogeneity, associated with the major atrial structures, in spiral wave maintenance. In addition, we set to determine whether this spiral wave behaviour is further modulated by the presence of the inherent periodicity in atrial structure. To do so, we conducted simulations of spiral wave behaviour in two dimensions and quasi-three dimensions, by using an atrial sheet and subsequently forming a cylinder out of it. Transmembrane potential maps and spiral wave phase singularity traces were used to analyse how each of these factors contributed to spiral wave dynamics. Our results demonstrate that the prolonged refractoriness of the CT clearly affected the pattern of reentry while the variation in action potential morphology of the other structures did not. The spiral waves anchored to the CT in the sheet and were thus prevented from terminating at the boundary. The activation rate of the reentrant wave in the tissue with variations in action potential morphology was slower than in homogeneous tissue. Finally, the dynamics of the spiral wave was changed when the sheet was formed into a cylinder. The main effect of forming a continuous
surface was the appearance of secondary spiral waves influencing the primary spiral waves. The interaction between the primary and secondary spiral waves diminished as cylinder diameter increased.

(a) Heterogeneity in action potential morphology

Studies have demonstrated that several atrial structures play a role in maintaining reentry; however, the mechanisms underlying this behaviour have not been well clarified. The CT has been shown to be particularly important to reentry sustenance (Tai et al. 1998; Roithinger et al. 1999; Fenelon et al. 2003). Its anisotropic coupling has been found to contribute in longitudinal (Shoji et al. 2000; Kobayashi et al. 2003) and transverse (Ellis et al. 2000) conduction block. Research by Mizumaki et al. (2002) demonstrated that the thickness of the CT affects the degree of conduction block. Conduction block within the CT, however, appears to be functional in nature (Schumacher et al. 1999; Yamabe et al. 2002), suggesting that factors other than the CT structure must be considered, such as the different action potential morphology within the CT (Yamashita et al. 1995; Kalman et al. 1998). Our study documented a significant effect of the prolonged refractoriness exhibited by the CT on spiral wave behaviour. The design of our simulations allowed us to examine this effect separately from the structural features of the CT that might also affect reentry. The action potential morphology of the other structures included in the model had virtually no effect on reentry dynamics due to either the location of the structures off the pathway of the reentry, or the fact that local action potential duration and morphology in the structure was not significantly different from that in the AW.

This simulation study found that in a sheet where regions of different action potential morphologies are incorporated, the rotation of the spiral wave becomes slower, having a rotation period about 10 ms less than that in the homogeneous sheet. This is due to the prolonged refractoriness of the CT, which, at a pacing rate equal to the activation rate of the spiral wave reentry in the homogeneous sheet, conducts in a 2:2 fashion, while the other structures continue to activate at a rate of 1:1. The decrease in the rate at which the spiral wave rotates in the heterogeneous sheet indicates an enlargement of the spiral wave core, and increases in both critical wavefront curvature and trajectory of the spiral wave tip (Mandapati et al. 1998). The mechanism by which this occurs is the change in source-to-sink ratio (Pertsov et al. 1993; Cabo et al. 1994). Since the extended refractoriness of the CT decreases source current, the number of cells that can be activated (sinks) decreases, leading to a flattened reentrant wavefront curvature (Zykov 1987).

Our simulations also demonstrate that the spiral wave anchors to the CT. This occurs regardless of initiation site; when initiated on the CT, the spiral wave remains on the CT, and when initiated away from the CT, the spiral wave anchors when encountering the CT. This anchoring effect prevents the spiral wave from terminating at the boundaries of the sheet, as it occurs in a homogeneous sheet. Increase in sheet size could possibly improve the survival of the spiral wave in the homogeneous case; however, as demonstrated by our simulations, regardless of sheet size, the spiral wave survives in all four cases of heterogeneous sheets compared to none of the homogeneous cases. This finding clearly implicates the refractoriness of the CT as the factor responsible for
the difference in spiral wave behaviour. Even with the electrotonic interactions in the sheet playing a role, the different action potential morphology, and most importantly, duration, of the CT contributes significantly to reentry maintenance and therefore should be accounted for in the studies of AF. Most importantly, the spiral wave anchoring effect of the CT might have implications for the mechanisms by which AF is maintained. Anchored single-circuit reentrant activations could promote multiple-circuit reentrant AF via the mechanism of tachycardia-induced remodelling of atrial electrical properties (Wijffels et al. 1997; Allessie 1999). Class I anti-arrhythmic drugs, which have been found to result in decreased anchoring to functional obstacles (Kneller et al. 2005) are likely to also promote detachment of spiral waves from the CT.

(b) Periodicity of structure

The continuous surface topology of the atria can play a role in the maintenance of reentry through the interaction of spiral waves that travel around the thin atria and interact with each other and themselves. Approximating atrial geometry with a cylinder allows us to examine this effect on the behaviour of spiral waves. We found that in both the heterogeneous and the homogeneous cylinders of smaller size, secondary spiral waves are generated and their interaction with the primary spiral wave is the determining factor in reentry maintenance. For the heterogeneous cylinder, regardless of initiation site, the secondary spiral waves override the anchoring effect of the CT and reentrant activity is terminated. For both types of cylinders, initiation at site 1 results in a figure-of-eight reentry that eventually dies out due to mutual annihilation of the two-phase singularities of opposite chiralities. Initiation site 2 results in a more complex interaction between primary and secondary spiral waves in the cylinders. Multiple secondary phase singularities override the anchoring effect of the CT in the heterogeneous cylinders, while in the homogeneous cases, most of these secondary spiral waves eventually die out, leaving a single secondary spiral wave to maintain the activity.

In no instance of the heterogeneous case is the primary spiral wave terminated by encountering the boundaries. Termination of activity, as seen in the phase singularity traces, is solely due to interaction with a secondary phase singularity. Conversely, when activity is maintained in a homogeneous cylinder, it is because of a secondary phase singularity. In all cases of the homogeneous sheet, termination is due to the spiral wave encountering the boundary. For the cylinder simulations, in only a single case does termination occur and it is due to interaction of the primary and secondary phase singularities. Despite the joining of the left and right ends of the sheet, which in effect decreases the number of boundaries where the spiral wave can terminate, the survival of reentry is not enhanced, but rather hindered due to the effects of the secondary spiral waves.

(c) Tissue size

Increasing sheet/cylinder size further elucidated the effects of action potential morphology and periodicity of structure on spiral wave behaviour. No change in phase singularity traces occurred in any of the homogeneous sheets when tissue size was increased. For initiation site 2 in the heterogeneous sheet, there was similarly no change in phase singularity trace. For initiation site 1 in the
heterogeneous sheet, the phase singularity trace was affected upon increase in sheet size, but the anchoring effect of the CT remained. For all cylinders, the interaction between secondary and primary spiral waves diminished when the diameter was increased, with (primary) phase singularity traces in the large sheet and cylinder becoming more alike. This effect has been previously demonstrated in a homogeneous cylinder by Fenton et al. (2002). For both cylinder diameters, activity in the homogeneous case was maintained by the secondary spiral waves. In the heterogeneous cylinders, the primary and secondary spiral waves had little effect on each other.

From these observations, we suggest that in smaller animals species, secondary spiral waves in the atria are important since they override the anchoring effects of the CT or any other atrial structures. In larger animals, we expect that the anchoring effect will remain, since the primary spiral wave is affected to a much lesser degree by the secondary sources of activity. We view this as a possible reason for the differences in the mechanisms of reentry reported in different studies (Garrey 1914; Allessie et al. 1973; Vaidya et al. 1999; Chen et al. 2000). While multiple rotors may be sustained in larger atria, smaller species can sustain a single rotor that eventually extinguishes other secondary rotors.

5. Limitations

The atria are three-dimensional structurally complex organs. Our model is two-dimensional, and thus represents a gross simplification of the complex electrophysiological phenomena that take place in an organ of convoluted geometry. Furthermore, structures represented in our model, such as the CT, have anisotropic properties that are not accounted for in our simulations. Finally, propagation velocity in the atria could be affected in regions characterized with surfaces of nonzero Gaussian curvature (Rogers 2002). Our model does not intend to represent the complexity of AF but rather to address a very specific question. The intended geometrical simplicity of the model and the realistic representation of regional action potential morphology allows us to separate and dissect mechanisms in a way that would have been impossible to perform using a more anatomically realistic model of the atria, such as, for instance, the morphologically accurate atrial model developed previously by our group (Vigmond et al. 2001, 2004).

Editors’ note

Please see also related communications in this focussed issue by Bourn et al. (2006) and Solovyova et al. (2006).

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References


