Propagation of Electrical Excitation in a Ring of Cardiac Cells: A Computer Simulation Study

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1 Abstract

The propagation of electrical excitation in a ring of cells described by the Noble, Beeler-Reuter (BR), Luo-Rudy I (LR I), and third-order simplified (TOS) mathematical models is studied using computer simulation. For each of the models it is shown that after transition from steady-state circulation to quasi-periodicity achieved by shortening the ring length (RL), the action potential duration (APD) restitution curve becomes a double-valued function and is located below the original (that of an isolated cell) APD restitution curve. The distributions of APD and diastolic interval (DI) along a ring for the entire range of RL corresponding to quasi-periodic oscillations remain periodic with the period slightly different from two RLs. The "*S*" shape of the original APD restitution curve determines the appearance of the second steady-state circulation region for short RLs. For all the models and the wide variety of their original APD restitution curves, no transition from quasi-periodicity to chaos was observed.

2 Introduction

The propagation of an excitation wave in a ring of cardiac excitable cells is a subject of significant practical and theoretical importance [1, 2, 3]. The circulation of excitation in atrial tissue is observed during atrium flutter and in a ring-shaped preparation of atrial tissue [4]. A one-dimensional ring of excitable cells can be considered as a limiting case of a circle with a hole when the radius of the hole is commensurate with the radius of the circle.

Our previous qualitative knowledge [5] about excitation wave propagation along a ring can be summarized as follows:

1. The stationary propagation of action potential (AP) (with constant APD and DI) is possible when the maximum slope of the APD restitution curve is less than unity, and the length of the ring is greater than some critical value. When the RL reaches that critical value, further propagation becomes impossible.

2. The transition from stationary propagation to stationary quasi-periodic oscillations (of APD, DI and propagation velocity, Θ) is possible when the slope of the APD restitution curve is equal to or greater than 1 for some DIs. Further shortening of the RL leads to the breakup of propagation.

A recent analytical study [6] proved that a necessary and sufficient condition of wave propagation instability is the existence of the slope $\gamma \geq 1$ of the APD restitution curve of a cell in a ring. In this analytical study, an approximate expression was found for the physically possible period Λ_0 of spatial distribution of APD, DI and velocity, Θ, of the unstable wave front propagation in a ring of length L:

$$\Lambda_0 = 2L\left(1 - \frac{2\alpha L}{\pi^2}\right) \tag{1}$$

Here $\alpha = \Theta'(DI^*)/\Theta^2(DI^*)$, $\alpha L \ll 1$, and DI* is the diastolic interval at which $\gamma = 1$. The quasiperiodic oscillations of APD and DI in ring nodes appear, since Λ_0 is slightly smaller than $2L$ for $\alpha L \ll 1$.

These very important results are obtained by reducing the solution of the original PDE to a neutral-delay differential equation linearized in close vicinity of DI*. They are correct only under the assumption that APD restitution and dispersion curves are single-valued functions of previous DI and only when these functions are obtained in the course of unstable propagation. The latter requires the computer solution of the original PDE.

It remains unclear whether the above-mentioned assumption is valid for other existing cell models not considered in [6], how the parameters of quasiperiodic oscillation will change with progressive shortening of the RL, and how under these conditions the original APD restitution curve will be deformed. Therefore, to find the answers to these questions wave propagation is studied here in rings of cells each of which is described by different mathematical cell models. The results are prefaced by a short discussion of the APD restitution properties of a cell.

3 APD restitution of a cardiac cell

The restitution properties express an ability of a cardiac cell to recover after excitation. The recovery processes are difficult to observe in physiological experiments since they are determined by the temporal activity of membrane channels. That explains why physiologists prefer to measure the secondary effects of these processes on the duration of AP. The protocol of these measurements specifies that tissue is preconditioned by applying periodic stimulation with a period equal to the normal heart beat until steady-state condition is attained. Then, after comparatively short DI, a premature excitation is applied, and the resulting APD is measured. This process is repeated from the beginning with increased DI.

It was considered for a long time that the dependence of APD on DI (APD restitution curve) is single-valued. However, it was found [7] that the APD restitution curve changes when the frequency of the precondition stimulation is increased. Moreover, it was shown that different measurement protocols (e.g., S1, S2, S3 protocol) lead to the appearance of families of APD restitution curves. Thus, it is possible to hypothesize that the APD restitution curve is not a function only of the previous DI, but of the history of the preceding sequence of excitations. In order to justify this assumption, one can use the cell mathematical models based on clamp-experiment data, which reflect the dynamics of membrane channels during and after excitation.

The mathematical models describing the balance of membrane currents (ionic $\sum_{i=1}^{n} I_i$, capacitance $C_m \frac{dV}{dt}$ and stimulus I_{stim}) and the dependence of the gate and intermediate variables $y(y_1, y_2, \ldots, y_m)$ on membrane potential V and time t can be presented in the general form:

$$C_m \frac{dV}{dt} = -\sum_{i=1}^{n} I_i(V, y) - I_{stim} \tag{2}$$

$$\tau_y(V) \frac{dy}{dt} = y_\infty(V) - y \tag{3}$$

For our purposes we chose four mathematical models: Noble [8], Beeler-Reuter [9], Luo-Rudy [10], and the third-order simplified model [11]. They are distinguished by the number n and the character of the functions $I_i(V, y)$, and by the number m of gate variables y and expressions for time constant τ_y and y_∞. For example, the recovery processes in the Noble model are determined only by one gate variable whereas in the LR I model they are determined by three. The details can be found in the original publications cited above. For computer simulation we used Ashour-Hanna numerical algorithm [12] with $\alpha = 0.75$ and time step $0.02ms$. The APDs and DIs are measured at the 90% level of V_{max}.

In order to verify whether the APD after the next excitation depends only on the previous DI, a sequence of three excitation stimuli was applied

Model	Original AP		AP after first premature stimulus		AP after second premature stimulus	
	DI_0, ms	APD_0, ms	DI_1, ms	APD_1, ms	DI_2, ms	APD_2, ms
Noble	∞	380	38	151	38	151
BR	∞	291	20	117	20	146
LR I	∞	384	20	256	20	242
TOS	∞	384	20	256	20	148

Table 1: Results of consequtive stimulation with the equal DIs.

to the different single cell models so that the last two premature stimuli appear after equal DIs. The results, presented in Table 1, show that only for the Noble model after equal DIs the APs appear with equal durations. For the BR model, the APD after the second premature beat is longer than after the first, whereas for the LR I and TOS models in the same situation, the APD is shorter. In addition, the APD restitution curves are measured for the last three models, using computer simulations performed according to S1, S2, and S3 protocol. Under this pacing conditions, instead of one APD restitution curve we have a family of curves. Remarks that APD is not a function of only previous DI can be found in [7]. The pacing order of a cell placed in a ring will be different in comparison to these two protocols, especially during propagation with quasiperiodic oscillation. Therefore, one can expect the APD restitution curve of a cell in a ring to be significantly different from that of an isolated cell.

4 Computer simulation of wave propagation in a ring

For computer simulation, the ring is formed from a line of equidistant cells interconnected by diffusion. The corresponding mathematical model can be obtained by adding to the equation of cell model (2) the neighboring cell currents ($\alpha_x \frac{\partial^2 V}{\partial x^2}$, where α_x is a cell coupling conductance), and setting the initial ($V(0,x)$, $y(0,x)$) and boundary ($\frac{\partial V}{\partial x}|_\Gamma = 0$) conditions. After stimulation of one of the line ends and formation of a full propagating wave, both ends are connected numerically into a ring, so that the first and the last nodes of the ring become neighbors. To study the effect of a RL on excitation wave propagation, we started with the open ring at the initial RL and then decreased the RL by sequential elimination of nodes. The simulation is not interrupted, and the space step remains constant. The latter is chosen equal to $0.02cm$ for all models except the BR model where it was equal to $0.025cm$.

The computer simulation study is focused on the comparison of the wave propagation along rings described by different cell models, and the comparison of the APD restitution curves for an isolated cell and for a

Cell model	Propagation condition				
	Steady state	Start of quasi-periodic	Quasi-periodic (results for several RLs)	End of quasi-periodic	Breakup
Period of quasi-periodicity in a ring cell (*turns*) **/ RL** (*nodes*)					
Noble	–/115	174/113	70/110;40/103;19/75	–/70-68	–/35
BR	–/537	43/530	42/515;20/490	–/478	–/478-475
TOS	–/502	787/500	610/420;116/350	–/349	–/348
Period of APD distribution in space (*nodes*) **/ RL** (*nodes*)					
Noble	–/115	227/113	223/110;211/103; 142/75	–/70-68	–/35
BR	–/537	1034/530	1000/515;952/490	–/478	–/478-475
TOS	–/502	999/500	838/420;652/350	–/349	–/348
Range of APD oscillations in a ring cell (*ms*) **/ RL** (*nodes*)					
Noble	–/115	67.5/113	88/110;97/103;47/75	–/70-68	–/35
BR	–/537	190/530	213/515;231/490	–/478	–/478-475
TOS	–/502	10/500	134/420;150/350	–/349	–/348

Table 2: Summary of ring simulation results ("–" means no data).

cell in a ring (dynamic APD restitution). For the ring composed of LR I model cells, the quasiperiodic oscillations with small amplitude ($10ms$) were observed in the region of RLs from 514 to 510 nodes. Further decrease of the RL leads to the breakup of propagation. For other three models, the computer experiments were conducted for RLs corresponding to the beginning, the middle, and the end of the interval of unstable propagation. The results are summarized in Table 2.

The second region of steady-state propagation was found for the ring consisting of the Noble model cells. This region is located between the RL corresponding to the end of quasiperiodic oscillations and the breakup of propagation. The explanation of this is related to the "S" shape of the original APD restitution curve in the Noble model. This curve has two regions with a slope less than one. The same was observed in the TOS model synthesized for short APD [13].

Fig. 1 demonstrates the features of wave propagation along a ring of Noble model cells when the RL corresponds to the middle of quasiperiodic region. The APD restitution curve has a pronounced double-valuedness and is located below the original APD restitution curve. The range of APD oscillations in a ring cell (Table 2) and the range of APD distribution in space are increased with the shortening of the RL inside the region of quasiperiodic oscillations. In this region, the period of APD distribution Λ is slightly different from $2L$, and this difference increases with the decrease of RL. These properties are common for the rings described by other cell models.

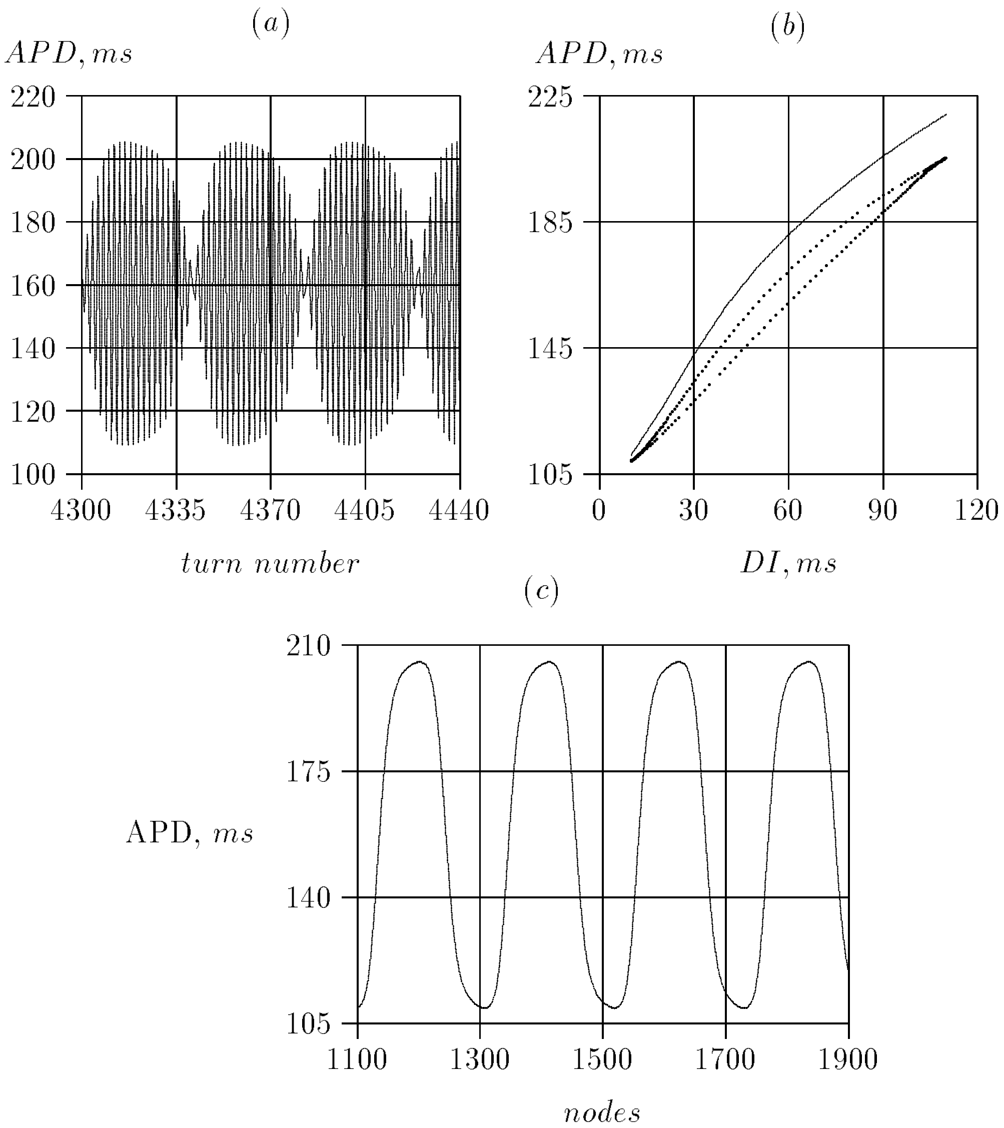

Figure 1: AP propagation in the 103 node ring simulated using the Noble model.
(a) APD in a point of a ring as a function of the number of turns; (b) APD restitution curves: original (solid line), in a cell of a ring (dotted line); (c) APD distribution along the ring for approximately 8 turns of the wave (x-axis shows the number of nodes traversed during circulation).

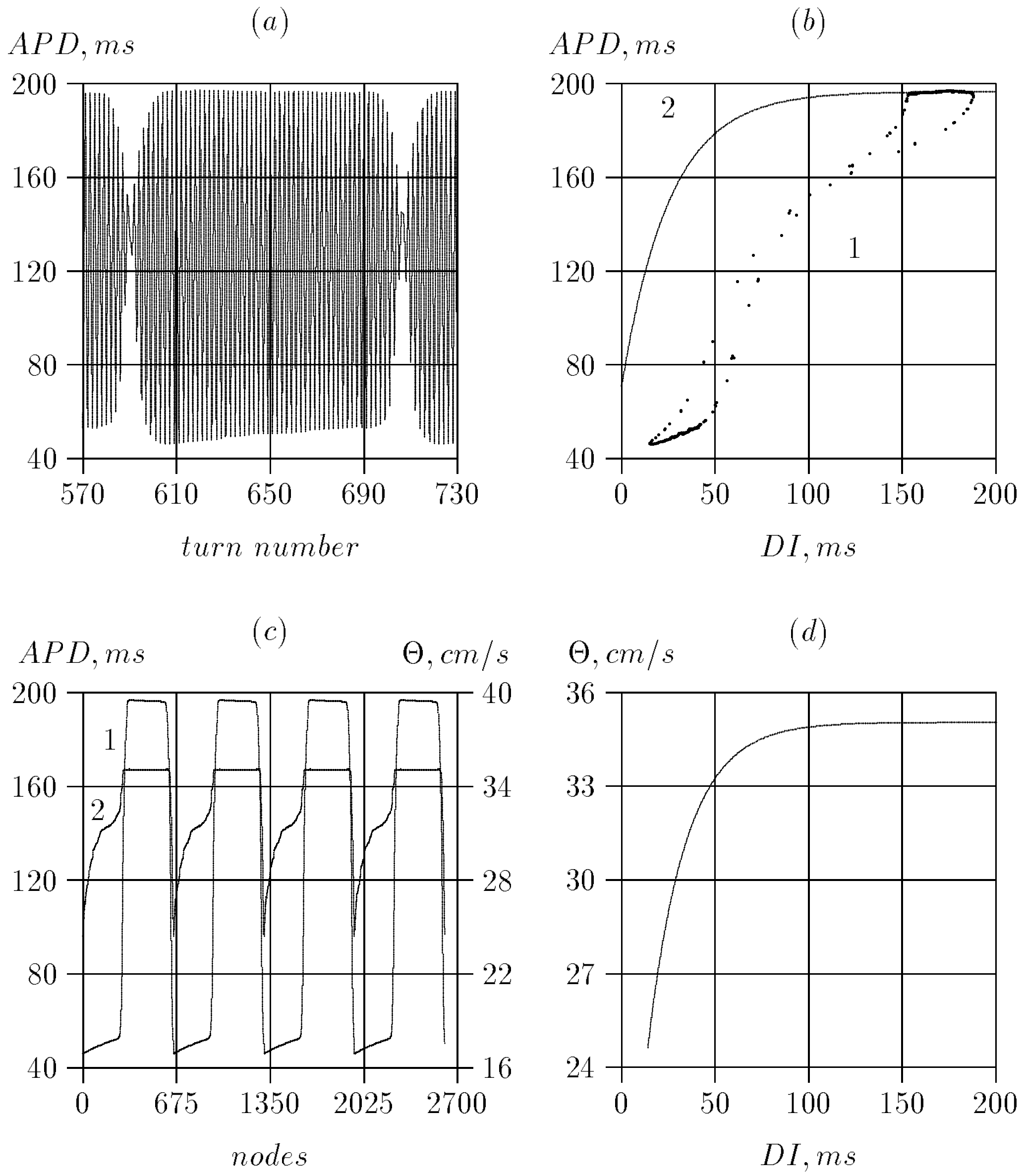

Figure 2: AP propagation in the 350 node ring simulated using TOS model. (a) APD in a point of a ring as a function of the number of turns; (b) APD restitution curves: original (solid line), in a cell of a ring (dotted line); (c) APD (1) and Θ (2) distributions along the ring for approximately 8 turns of the wave (x-axis shows the number of nodes traversed during circulation). (d) – dispersion curve.

Wave propagation in a ring of TOS model cells is illustrated in Fig. 2 for RL of 350 nodes, which is close to the end of the quasiperiodic region. This model is synthesized for $APD_{max} = 196ms$ with the APD restitution curve taken from [14]. The slope of this restitution curve is greater than unity for DIs less than $40ms$.

The experiments were conducted for three RLs: 500, 420, 350 nodes corresponding to the beginning, middle, and near the end of the quasiperiodic region. For RLs greater than 500 nodes, a steady-state condition was obtained. For RL = 500 nodes (see Table 2) the range of APD oscillations is small with a very large period of modulation. The APD is distributed periodically in space with the period of distribution slightly less then two RLs. After shortening RL to 420 nodes, the range of APD oscillations was $134ms$, and the period of slow modulation was about 610 turns. The range of the cycle-length variation was about $25ms$. The period of spatial distribution of APD was 838 nodes, which was smaller than two RLs by two nodes. The APD restitution curve obtained for this RL is no longer a single-valued function of DI. The difference between the upper and lower branches of this curve is between 5% and 10%, depending upon the value of DI. The multivaluedness of this curve is due to the fact that the APD restitution curve in a cell depends on the history of previous excitations.

In the case of a 350 node ring, the range of APD oscillations rose further (see Fig. 2a). The amplitude of oscillations is so large that the APD reaches its maximum value inside the slow modulation period. The range of cycle-length variation is about $35ms$. The difference between the upper and lower branches of the APD restitution curve (Fig. 2b) is between 3% and 25%, depending on the value of DI. The period of spatial distribution of APD (Fig. 2c) is about 652 nodes, which is smaller than two RLs by 48 nodes. The dependence of wave propagation velocity on DI (dispersion curve) is presented in Fig. 2d.

Due to the big variation in the cell model parameters, the comparison of wave propagation characteristics (see Table 2) is done after preliminary normalization. Ring length, L, and the period of APD distribution in space, Λ, are normalized to their respective critical values (L_{cr} and Λ_{cr}), which are defined as those occurring at the transition from steady state to quasiperiodic state. The APD range, ΔAPD, is normalized to APD_0, generated in a ring where the wave propagates without traces of recovery processes. Fig. 3a shows that in the region of RLs corresponding to the quasiperiodic oscillations, the ratio $\Delta APD/APD_0$ is monotonically increasing with the decrease of RL. The normalized Λ was decreasing linearly with shortening of the RL. In the latter case the curves for the BR and TOS models coincide.

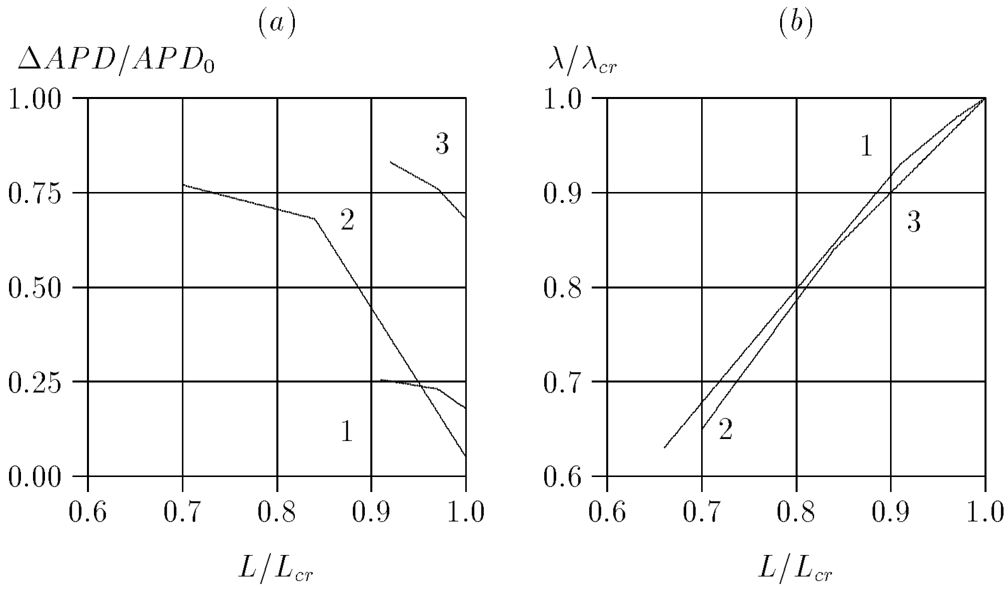

Figure 3: The normalized characteristics of wave propagation in a ring.
1 – Noble model; 2 – third-order model; 3 – Beeler-Reuter model.

5 Conclusion

1. The data presented confirm that the theoretical condition for transitioning from the steady-state to quasiperiodic oscillations holds for all cell models under consideration. The APD restitution curves measured for the critical RL lie below their original versions and manifest a splitting which is small enough to be neglected.

2. The APD restitution curves obtained for the range of RL corresponding to quasiperiodic oscillations have progressively increasing (as RL is shortened) downward shift and splitting. The splitting gets so large that the dynamic APD restitution can no longer be considered a single-valued function.

3. With progressive shortening of RL in the region of quasiperiodic oscillations, we observed: increase in oscillation amplitude; decrease in period of APD distribution, Λ, and period, T, of quasiperiodic oscillations; more pronounced increase in the fluctuation of the cell excitation cycle in a ring; transition to breakup, or for models with S-shaped APD restitution to the second steady-state region.

An open question of great interest is the relation between the restitution curve obtained for a cell placed in a ring and that for an isolated cell. Our experience shows that in models with the original APD restitution slope less than unity, quasi-periodicity is not observed; whereas a slope greater than unity in the APD restitution curve of an isolated cell always implies the greater than unity slope of the corresponding APD restitution in a ring and the ensuing quasi-periodicity.

6 Acknowledgments

We would like to thank Dr. James Weiss and Alan Garfinkel for their deep interest in this work and very helpful discussions.

Research in computer simulation of propagation of electrical simulation in a ring of cardiac cells at UCLA Computer Science Department is supported in part by the NIH Grant SCOR in Sudden Cardiac Death P50 HL52319, and by the NASA/Dryden Research Center Grant NCC 2-374.

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