LOCATING ECTOPIC FOCI ON A CYLINDER*

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Arrhythmia is a condition in which an additional ectopic pacemaker is present in the tissue of the heart. Localization of ectopic foci is essential for successful radio-frequency ablation, an important surgical way of treating arrhythmia. In one of the possible mechanisms, arrhythmia induced by an ectopic foci located in one of the main blood vessels leading out or onto the heart. The therapeutic procedure in this case is usually ablation of the whole junction of the blood vessel with heart wall. In this way, whatever excitation occurs inside the vessel, it cannot penetrate the ventricles perturbing their contraction cycle. Such an ablation procedure is long and burdened with the risk of the perforation. A more safe method would involve the localization of the source of the excitation (*i.e.* the ectopic foci) and its ablation. The methods used in cardiology at present involve complicated localization systems and are time-consuming with the patient spending a long time on the operating table. Recently, Hall and Glass have developed numerical methods which allow to quickly to model the localization of the ectopic foci in a flat, square sample of an inhomogeneous medium. Here, we demonstrate an extension of this model for the case of a cylinder containing an ectopic foci, that can be a model of a blood vessel with the source of the ectopic beat inside it. Three methods of localization are implemented. Standard electrodes containing several active tips are used to stimulate the medium locally and locate the foci judging from the reaction of the system. The first one uses electrode activation times to compute the location of the ectopic site. The second one localizes it by measuring the resetting response of the foci, and the third one, uses wavefront curvature. Specifically for the cylindrical geometry of the blood vessel, we developed a localization procedure that allows to quickly localize the pacemaker.

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1. Introduction

Arrhythmia is a condition in which an additional ectopic pacemaker is present in the tissue of the heart. The localization of ectopic foci is essential for successful radio-frequency ablation, an important surgical way of treating arrhythmia in which the abnormal pacemaker is deactivated. In one of the possible mechanisms, arrhythmia is induced by an ectopic foci located in one of the main blood vessels leading out or onto the heart. The therapeutic procedure in this case is usually ablation of the whole junction of the blood vessel with heart wall. In this way, whatever excitation occurs inside the vessel, it cannot penetrate the ventricles perturbing their contraction cycle causing arrhythmia.

Such an ablation procedure is long and burdened with the risk of the perforation. A more safe method would involve the localization of the source of the excitation (*i.e.* the ectopic foci) and its ablation. The methods used in cardiology at present involve complicated localization systems and are time-consuming with the patient spending a long time on the operating table.

Recently, Hall and Glass [1] have developed geometrical methods which allow to quickly localize the ectopic foci using a triangular spacing of electrodes on a flat, square sample of an inhomogeneous medium described by modified FitzHugh-Nagumo equations with non-flux boundary conditions. In this paper, we discuss a modification of the algorithms proposed in [1] using a general placement of electrodes. In this way, we discuss the use and consequences of the methods proposed in Ref. [1] when the more usual in ablation practice linear electrodes are applied.

Next, we demonstrate an extension of this model for the case of a cylinder containing an ectopic foci, that can be a model of a blood vessel with the source of the ectopic beat inside it. Two methods of localization are implemented. In both, special but standard electrodes containing several active tips are used to stimulate the medium locally and locate the foci judging from the reaction of the system. The first one uses electrode activation times to compute the location of the ectopic site. The second one localizes it by measuring the resetting response of the foci. The anisotropy of the electrical conduction along the blood vessel and the characteristic way of the propagation of the excitation wave both methods can lead to a wrong interpretation and, consequently, to a localization which is false. Specifically for the cylindrical geometry of the blood vessel, we developed a localization procedure that allows to quickly localize the pacemaker and avoid confusion.

2. Numerical model

Simulations are performed in a model of cardiac tissue using simple FitzHugh-Nagumo reaction-diffusion equations [1]

$$\frac{\partial v}{\partial t} = \frac{1}{\mu}\left(v - \frac{1}{3}v^3 - \omega\right) + D_x\nabla^2 v + D_y\nabla^2 v + I_{\text{pace}} + I_{\text{stim}}(t)\,, \quad (1)$$

$$\frac{\partial \omega}{\partial t} = \mu(v + \beta - \gamma v)f(v)\,, \quad (2)$$

where v is the transmembrane voltage, ω is a slow current, and with a simplified with respect to Ref. [1] $f(v)$

$$f(v) = \begin{cases} \omega_{\text{L}} & v < -1 \\ \frac{\omega_{\text{H}}-\omega_{\text{L}}}{2}\,v + \frac{\omega_{\text{H}}+\omega_{\text{L}}}{2} & v \in <-1, 1> \\ \omega_{\text{H}} & v > 1 \end{cases}\,, \quad (3)$$

where $k = 4.0$, $\omega_{\text{H}} = 0.6$, $\omega_{\text{L}} = 0.4$ in the pacemaker area and 0.13 in the rest of the sample. The pacemaker is a circular area with a radius of 1.6 mm and with the ability to activate spontaneously every fixed time intervals. The parameter $\mu = 0.3$ controls the time scales of the action potential, the constant β is set to 0.7 and γ to 0.5. I_{pace} is a constant pacing current added to pacemaker area to make it oscillate. I_{stim} is a harmonically oscillating stimulation current used to excite cells. The stimulation current with amplitude 20 and frequency 10 rad/s is added to the ectopic foci area within a radius of 0.8 mm. The system of equations was integrated using the Euler scheme on a rectangular grid. The spatial grid spacing was set to 0.4 mm and the time step to 0.05 ms. The sample was a rectangular (100×100 grid elements), two-dimensional area with zero-flux boundary conditions on the edges. Applying periodic boundary conditions at the opposite edges of the sample simulated a cylinder. D is a diffusion coefficient responsible for the magnitude of the propagation velocity of the wave front. In homogeneous samples, it was fixed at 0.5. In anisotropic cases, $D_x = 0.1$ and $D_y = 0.6$ resulting in conduction velocity anisotropy in the x and y directions with the ratio of velocities equal to 1:3. Varying diffusive coefficients across the sample included the heterogeneity of the system. This was implemented by multiplying all diffusion coefficients at grid points by a random number of a uniform distribution from the range 0.5 to 1.0. This resulted in an average diffusion coefficient 0.375 in the isotropic case, and, in the anisotropic case, 0.075 in the x direction, and 0.45 in the y direction.

3. Localization methods

We needed to localize the pacemaker site with certain finite precision only. For catheter ablation, localization within a 3 mm distance from the true ectopic focus is sufficient, because the ablation area radius has a few millimeters in diameter. The important condition for the effective ectopic foci ablation is electrode positioning over the pacemaker. Glass and Hall in their work assumed that electrodes are 6 mm apart, arranged in a right-angled triangle. In our work, we assumed that electrodes positions can be varied independently. However, the localization procedures require the spatial positions of the electrodes to be known. To obtain them, we perform a respective electrodes localization procedure. In respective electrodes localization procedure every electrode is stimulated causing a circular activation pattern propagates through the sample, activating the rest of the electrodes. As activation time, we understand the moment when electrodes potential reaches maximum during the excitation of the local medium. After applying stimulation to all electrodes, for each pair of the electrodes we know the time which the wave front needs to propagate between them. If the propagation velocity is constant, the distances between every two electrodes can be computed. Next, two electrodes must be chosen, as the base for the respective localization reconstruction. The rest of the electrodes lie at the intersection points of the circles centered on the base electrodes and the radii from the distances calculated (Fig. 1).

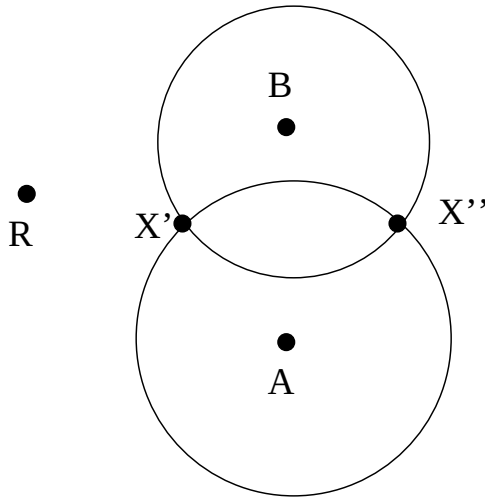

Fig. 1. Respective localization procedure. A and B are arbitrary chosen base electrodes. X' and X" are possible positions of reconstructed electrode position. The right one is chosen by using reference electrode R and reconstructing the proper activation sequence.

4. Hyperbolic and resetting localization

Both methods developed by Glass *et al.*, [1] were shown to be able to localize ectopic foci in a flat sample using three electrodes arranged in triangle. The hyperbolic method uses activation times of the electrodes due to a wave coming from the pacemaker. If the activation times difference between two of them is known, it means that the pacemaker lies on a hyperbola the foci of which are those electrodes (Fig. 2(a))

$$r_2 - r_1 = v\Delta t\,, \tag{4}$$

where r_1 and r_1 are distances from the ectopic foci to the electrodes, v is the mean conduction velocity, and Δt is the time difference between activations of the electrodes.

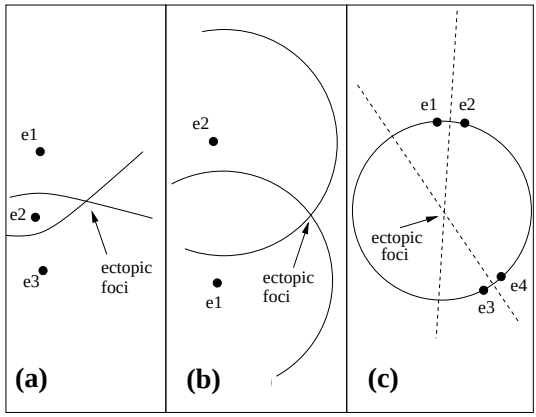

Fig. 2. Three ectopic foci localization methods. Hyperbola localization (a), resetting localization (b) and curvature localization (c).

In order to compute the pacemaker location, two pairs of electrodes are needed giving two hyperbole. Two hyperbolae can intersect maximally in four points. The valid one is chosen by computing activation sequence of circular wave coming out from each of suspected points.

In resetting localization, we assume that the ectopic foci beats with constant frequency (or that the frequency changes slowly). If an activation wave passes through the pacemaker area, it becomes depolarized and needs some time before the next spontaneous activation. This time, CL, is also the rate of pacemaker activity [1]. When an electrode is stimulated and the activation wave passes the ectopic foci, the time CL must pass until the next activation. The time when the response will arrive to the electrode

$$CI = 2\,\frac{r}{v} + CL\,, \tag{5}$$

where v is the propagation velocity and r is the distance between the pacemaker and the electrode. If this stimulation is done for two different electrodes, two distances are obtained. The ectopic foci lies on an intersection of two circles centered at the electrodes (Fig. 2(b)), with the radii equal to those distances. Again, the valid intersection point is distinguished from the activation sequence. If CI is equal $2CL$, it means that the stimulated wave annihilated with the one coming from the pacemaker.

5. Curvature localization

In this method, two pairs of the electrodes are positioned to be activated simultaneously. Assuming circular activation wave shape, the pacemaker will lie on the bisectrix to the electrodes in the pair. If two bisectrices are obtained, they will cross at the pacemaker area (Fig. 2(c)). This technique is quite difficult in clinical application because of a limited maneuverability of the electrodes.

6. Iteration of the procedures

The above localization methods are sensitive to position of the electrodes, the conduction velocity anisotropy, the heterogeneity of the sample and the pacemaker frequency. This sensitiveness results in erroneous ectopic foci location prediction. Hall and Glass [1] conducted numerical simulations which show that hyperbolic and resetting localization method predict pacemaker location which is closer to the true position. This gives the possibility to iterate the localization procedure and obtain converging distance to the pacemaker after each step. After each iteration, a localization procedure [1] should be performed in order to ascertain if the electrode is in the pacemaker area. The effectiveness of the curvature method is approximately the same as that of the other two methods proposed in [1].

7. The effect of the respective position of the electrodes on the methods

The predicted ectopic foci location is, in the best case, a linear function of the electrodes position. This can be modified by changing their localization with respect to ectopic foci. In Fig. 3 we show two extreme cases for each localization procedure.

The hyperbolic and the curvature localization methods give the best predictions if the electrodes are activated simultaneously (which means that during the activation, all electrodes lie on the wave front). Consequently, if the electrodes and the ectopic foci are co-linear, both methods fail.

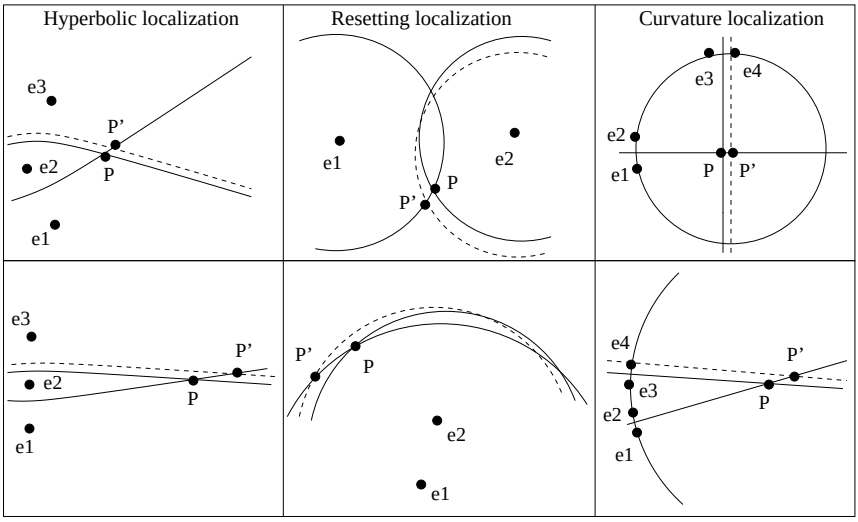

Fig. 3. Examples of electrodes and ectopic foci respective localization. In first row, cases with minimal influence of electrodes position on the pacemaker location prediction, in second, cases with maximal influence. e1, e2, e3, e4 are electrodes, P and P' are pacemaker positions before and after one of the electrodes movement, which influence on localization as dashed line.

The resetting method gives the best results if distance between electrodes is comparable with distance to the ectopic foci area. In the opposite case, when those distances are quite different (the electrodes are very close to each other and the pacemaker far away) during the pacemaker localization two similar circles are obtained. The intersection point of these circles is very sensitive both to the electrodes position (the circle center) and the pacemaker distance (the circle radius).

8. The effect of pacemaker frequency on the resetting method

The resetting localization method assumes constant the pacemaker activation frequency ($CL = \text{const.}$). This frequency stability depends on the nature ectopic focus. In the cardiac muscle, the source of the ectopic beat can be due to cells with an enhanced automaticity, due to re-entry (*i.e.* a closed path of the wave) caused by an anatomical obstacle or due to the functional block which can be described as a spiral wave. The uncertainty of the distance resulting from the variability of CL is derived from Eq. (5)

$$\Delta r \;=\; \frac{1}{2}\, v\, \Delta CL\,. \tag{6}$$

The effect of this uncertainty on the predicted pacemaker location depends on respective localization of the electrodes and is minimized when the distance between the electrodes and the pacemaker are equal (two base electrodes and pacemaker are form a right-angled triangle).

9. The effect of conduction anisotropy on the methods

Conduction anisotropy in excitable media results in an elliptical shape of the activation pattern coming out of the ectopic focus. This phenomena results from a preferential conduction direction. In the numerical model, anisotropy was modeled by different diffusion coefficients in two fixed perpendicular directions.

The hyperbolic and curvature methods, in fact, utilize the local geometry of the wave front, approximating it by a circle and locating the foci at its center. So the hyperbolic method predictions depends on the local curvature of wave front, which, in the case of an elliptical wave front varies. The resetting method, on the other hand, utilizes only the information about the time needed by the excitation wave to travel from the ectopic foci to the electrode, without any assumptions about the geometry of the wave front. The activation of the electrodes by the excitation wave coming out of the pacemaker is shown in Fig. 4. If the time intervals t_1, t_2 needed by the wave to travel from the pacemaker to the electrode e1 and e2, respectively, are known, the pacemaker location can be derived from

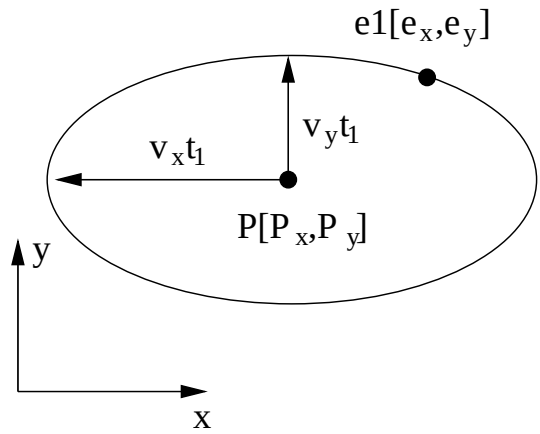

Fig. 4. Excitation wave coming out of ectopic foci area P and activating electrode e1. Elliptical wave front shape is caused by conduction velocity anisotropy.

$$\begin{cases} \dfrac{(\mathrm{e1}_x - P_x)^2}{(v_x t_1)^2} + \dfrac{(\mathrm{e1}_y - P_y)^2}{(v_y t_1)^2} = 1\,, \\ \dfrac{(\mathrm{e2}_x - P_x)^2}{(v_x t_2)^2} + \dfrac{(\mathrm{e2}_y - P_y)^2}{(v_y t_2)^2} = 1\,, \end{cases} \tag{7}$$

where P_x, P_y are the ectopic foci coordinates, $\mathrm{e1}_x$, $\mathrm{e1}_y$, $\mathrm{e2}_x$, $\mathrm{e2}_y$ are coordinates of the two base electrodes and v_x , v_y are conduction velocities in the x and y directions, respectively.

10. The effect of diffusion tensor heterogeneity on the methods

In our simulations, the heterogeneity of the excitable medium was created by varying the diffusion tensor coefficients, resulting in a conduction velocity heterogeneity. The hyperbolic and curvature localization methods were strongly affected by the distortion of the shape of wave front. If distortion exceeds a certain threshold (depending on the electrodes respective position), both methods can lose convergence. A possible solution in this case can be increasing spacing of the electrodes.

The resetting localization method is less affected by wave front distortion. All effects accumulate resulting in the computed pacemaker distance depending on the difference between the measured mean velocity and the velocity of the wave front propagating from pacemaker toward the base electrode.

11. Localization protocol on a cylinder

The dynamics of wave front propagation on a cylindrical two-dimensional excitable medium introduces new phenomena which must be taken into account in the localization of the ectopic foci. The most important phenomena is collision of the circular wave pattern on the opposite side of the cylinder resulting in two rings traveling along it. After the formation of the two rings, both the hyperbolic and the curvature methods became useless because the wave front curvature radius quickly increases to very large numbers. Only if the electrodes were activated before formation of the ring, the wave front curvature radius pointed to the ectopic foci location. This possibility can be used when electrodes are close to the pacemaker.

Due to these difficulties, we present a localization protocol on a cylinder based on the resetting method. We assume an anisotropic conduction velocity with a greater velocity along the cylinder. Also, we assume that electrodes are arranged along a straight line with a constant spacing (this type of the electrodes is usually used during catheter ablation).

The first step is the measurement of the conduction velocities along the axis and across the cylinder. This is done by stimulating one of the electrodes and measuring the activation time of the others. This time is then divided by the electrode spacing. To minimize the effect of the wave front velocity dispersion relation in excitable media, the electrodes spaced the most apart are chosen for this measurement.

The second step is the positioning of all electrodes along the cylinder and measuring the sequence of their activation by the excitation wave coming from ectopic focus. If one of the two most distant electrodes is activated, all electrodes are moved along cylinder until the electrode activated the first is one of the middle ones.

The third step is the use of the conducting resetting localization protocol according to Eqs. (7). (taking into account the anisotropy of the velocity) and positioning all electrodes in such a way that the middle electrode is over the predicted ectopic foci position.

The fourth step is the use of conducting confirmation protocol described by Hall and Glass [1] and repeating third step until the ectopic focus is founded.

This protocol can be more made more general by assuming a more general arrangement of the electrodes. But the respective localization protocol must be performed after each movement and there appears a possibility that the activation sequence can be perturbed by the activation of the electrodes from by a wave coming from both sides of cylinder.

12. Conclusions

This work is a response to the interest of cardiologists in ectopic foci localization in the veins and aortas of the heart. These vessels which may be approximated by cylinders. The ectopic foci localization and ablation should be performed as quickly as possible because of the high risk of perforation of the wall of the vessel. This motivated us to create a protocol allowing to localize the ectopic foci on a cylinder with conduction anisotropy and heterogeneity, and having a relatively small radius in comparison with the spacing of the electrodes — the conditions during catheter ablation in blood vessels. We started from the two methods developed by Hall and Glass [1] (hyperbolic and resetting) and from the curvature localization method. After analyzing the effect of the conditions which can occur in blood vessel on these methods, we chose the resetting method as the most suitable to this environment. The hyperbolic and the curvature methods also can be used during localization in blood vessel but only if the distance from the ectopic foci is less than the circumference of the vessel (then we can expect that wave front has still a circular shape, yielding information about pacemaker

location). Numerical simulations showed that the iteration of the resetting localization method converges to the true pacemaker location. The main weakness of our protocol is the assumption of the constant pacemaker frequency, required by the resetting method. Since the nature of the pacemaker mechanism in a blood vessel remains unclear, this reality of this assumption requires further investigation.

The ectopic localization protocol on a cylinder can be performed with standard catheter electrode configuration (several metal tips along catheter), without the need of an expensive mapping system. It is also important because of the very high risk of perforation during the mapping blood vessel with many electrode tips simultaneously.

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