Simulation of electrochemical processes in cardiac tissue based on cellular automata

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Abstract. A new class of cellular automata using special accumulative function for non-uniformity distribution is presented. Usage of this automata type for simulation of excitable media applied to electrochemical processes in human cardiac tissue is shown.

Keywords. cardiac tissue, cellular automata, computer simulation

1. Introduction
Currently the main method of diagnosis and analysis of cardiac arrhythmias is electrocardiography. Data analysis in electrocardiography is largely empirical. There is no complete understanding of relationship between graphical representation of electrocardiographic output and real processes occurring at the cellular level.

Some of the most common types of cardiovascular diseases are ventricular arrhythmias and fibrillation, the nature of which currently has not been completely studied. Electrochemical processes during arrhythmias are nonlinear and non-stationary, self-sustaining autonomous waves underlying these phenomena are called autowaves. Methods of the theory of cellular automata are used for simulation of autowaves [1 - 4]. Advantages of such models over the models based on differential equations [5 - 7] are simple adaptation to the problem and low computational cost, which allows carrying out real-time simulation. Adaptive non-uniform automata are used to analyze and model various processes in biology, logistics, energetics, pattern recognition, cryptography.

Existing methods based on cellular automata have disadvantages that do not allow them to be applied to the problem of action potential propagation in excitable media or impose restrictions on the simulation. It is, for example, leak of isotropy [1], impossibility of modelling specific non-uniformity configurations of media, impossibility of modelling non-conservative forces amplifying or damping depending on distance from source and traversed path [1 - 4].

Simulation of autowave electrochemical processes in human heart with additional possibility of obtaining results in the form of simulated electrocardiograms allows making more informative diagnostics of heart diseases by electrocardiograms and suggesting methods of preventing life-threatening arrhythmias.

Purpose of work. Creation of mathematical model and studying of electrochemical processes properties in human heart, leading to life-threatening autowave arrhythmias: premature ventricular contractions of different grade, sustained and non-sustained ventricular tachycardia.

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2. Model of electrochemical processes in cardiac tissue

In this work model, which allows taking in account different action potential duration in different cells, was created. One of the most known effects of action potential’s duration’s differences in different areas of cardiac tissue is partially reverse direction of action potential propagation during repolarization. Solution of this problem involves the use of different transition functions \( \delta \) in different cells of automaton.

The physical basis of the model is two types of electrochemical processes of intercellular interaction in cardiac tissue:

1. Amplification of \( K^+ \) ionic currents as a result of additional \( Ca^{2+} \) ions release from cellular depots.

   First factor that can reduce duration of repolarization phase is the active membrane transport, related to transformation of cells internal energy, in the form of adenosine triphosphate (ATP), into electromotive force of ionic currents. Increase in \( Ca^{2+} \) concentration at the phase of early repolarization leads to additional \( Ca^{2+} \) ions release from sarcoplasmic reticulum, this phenomenon is called calcium-induced calcium release (CICR) [8]. Increase in \( Ca^{2+} \) concentration within the membrane as a result of this process leads to weakening of \( Ca^{2+} \) ionic current into the cell and amplification of \( K^+ \) ionic current as a result of additional \( K^+ \) ionic channels opening by \( Ca^{2+} \) ions. Together, this results in a more rapid membrane repolarization. Part of the ions is transferred to the neighboring cells, it leads to even higher intensity of release, and thus, significance of this process increases with increasing distance from the source of depolarization.

2. Impact of neighboring cells membrane potential on the duration of \( Ca^{2+} \) ions channels activity during repolarization.

2.1. Second factor that can reduce duration of repolarization phase is the presence of other membranes in a later phase of repolarization near the membrane. Electrical charge on the outer surface of such membranes is lower, that’s why leaking current occurs between membranes through the gap junctions, and this current tends to equalize potential difference between them, as a result potential of membrane at earlier phase of repolarization decreases faster [9]. This in turn leads to faster closing of \( Ca^{2+} \) voltage dependent ionic channel in membrane, and as consequence, faster transition to rapid repolarization phase by \( K^+ \) ionic current, together this leads to shortening of repolarization duration in such cells.

2.2. Other version of this process is repolarization near the depolarizing area. During the autowave process, for example, ventricular tachycardia, two adjacent areas can be in the state of depolarization and repolarization respectively at the same moment. In this case high potential of depolarizing region over the repolarizing one causes electrical current through gap junctions that will maintain high potential of repolarizing membrane during some time. This will increase the duration of \( Ca^{2+} \) ionic channels activity, and so, duration of repolarization phase for cells near depolarizing area will also increase.

Models with non-uniform action potential duration were developed by authors [10 – 13]. Different action potential duration in different cells in these models was obtained by adding special component \( T \), which is function of action potential duration depending on cells location, to the cellular automaton, and using transition function that depends on \( T \).

Adaptive non-uniform cellular automaton is non-uniform cellular automaton, non-uniformity distribution of which depends on parameters that change as a result of its functioning.

In the models of processes, which result depends on traversed path, adaptive non-uniform cellular automaton with transition function that depends on additional variable of non-uniformity can be used; value of additional variable must be recalculated for each iteration by adaptation’s function depending on previous values of this variable for this cell.

Adaptive function of special form proposed, hereinafter referred to as accumulative function, it has next advantages over the memory functions of cellular automata [14, 15]:

1 – it introduces the ability to adaptively limit the upper limit of integration, depending on non-uniformity accumulative function value at the point \((x,y)\) using delta function \( \eta \);
2 – it takes in account not only the state of current cell, but also states of cells belonging to its neighborhood, also it uses memorizing with increment instead of simple memorizing. Properties 1, 2 together guarantee spatial increment of function with gradient directed from the source that defined by function \( g_0(x,y) \). Other important property of accumulative function is its above boundedness, which allows using its upper limit value, as variable \( t \) approaches infinity, in cellular automata as modelled values of forces, which are responsible for amplifying or damping. Examples of such forces are amplifying of Ca\textsuperscript{2+} ionic currents during mass repolarization and K\textsuperscript{+} during mass depolarization of cardiac tissue, their effect on action potential duration at the cell of cellular automaton can be determined numerically by accumulative function upper limit value.

Improved adaptive non-uniform cellular automaton with modified adaptation equations \( \gamma(\omega, g, q) \) and transition function \( \delta(\omega, q, g, r_g) \) proposed for excitable media simulation taking in account phenomena of repolarization’s duration variation, interaction of activation and repolarization and defined non-uniformity, related to structural damages of cardiac tissue:

\[
M \equiv (B, \Omega, Q, G, q, q_0, g, g_0, \delta, \gamma, r_g, \varphi),
\]

\[
\Omega \subset N, \ Q \subset \mathbb{N}^2, \ q, q_0 \in Q,
\]

\[
q \equiv (u, v, t, z) \in Q \subset \mathbb{N}^4,
\]

\[
\omega(q) : Q^{[\mathbb{N}]} \to \Omega \subset \mathbb{N}^2,
\]

\[
g \equiv (\Delta, a, p, h) \in G \subset \mathbb{Z}^4, \ g_0 \in G,
\]

\[
\delta(\omega, q, g, r_g) : \Omega \times Q \times G \times \mathbb{Z} \to Q,
\]

\[
\gamma(\omega, g, q) : \Omega \times G^{[\mathbb{N}]} \to G,
\]

\[
r_g(g) : G^{[\mathbb{N}]} \to \mathbb{Z},
\]

\( B \) – set of neighbors, simple rectangular grid and Moore neighborhood are used. Moore neighborhood is 8 cells having at least one adjacent point with the center cell and 16 cells having at least one adjacent point with one of these 8 cells.

\( \omega \) – function of input values, returns two values, \( \omega_a \) – average level of depolarization excitation in cells neighborhood \( B \) and \( \omega_b \) – average level of repolarization excitation, estimated by number of cells in depolarized and repolarized states respectively.

\( q \) – state vector, defined by four parameters \( u, v, t, z \):

\( u \) – level of excitation,

\( v \) – level of refraction, responsible for duration of excitable media refraction phase,

\( t \) – delay timer that defines increasing of action potential duration ( \( t > 0 \) ), takes in account potential difference between different areas of model, depends on non-uniformity parameter \( p \),

\( z \) – current state indicator that shows which process, depolarization or repolarization occurs at present time;

\( \varphi \) – additional function for converting states of cellular automaton \( q \) to action potential values, range of function \( \varphi \) belongs to the set of real numbers;

\( g \) – non-uniformity vector, which consist of four parameters \( \Delta, a, p, h \):

\( \Delta \) – parameter providing isotropy,
a – level of conduction abnormalities caused by structural damage expressed numerically, for example, delay of repolarization processes in this cell (abnormalities can be caused by various diseases, for example, myocardial infarction under conditions of ischemic heart disease); same as parameter \( \Delta \), this parameter does not changed by adaptive function between iterations, its value remains constant because processes of regeneration of damaged areas does not considered in this research.

\( p \) – parameter that models phenomena of repolarization’s duration decreasing depending on distance from the source of depolarization, taking in account traversed path; it reflects the processes of type 1, increase of Ca\(^{2+}\) ionic concentration as a result of ions release from cellular ionic depots; it is an example of «non-conservative» phenomenon, because amplification during depolarization wave propagation passes along a curved path: through the right ventricular, skirting interventricular septum to the left ventricular, that’s why it is necessary to use managed accumulative function for its adaptation.

\( h \) – parameter that models phenomena of repolarization’s duration decreasing depending on distance from repolarization source, which means area of excitable media that repolarized first; it reflects electrochemical processes of type 2.1, impact of neighboring repolarizing cells potential on the duration of repolarization in this cell; it is also an example of «non-conservative» phenomenon, because wave propagation during repolarization can pass along curved path in the presence of barriers, such as excited cells in refractory state or areas with conduction abnormalities, that’s why it is also necessary to use managed accumulative function for adaptation of this parameter.

\( \gamma(\omega, \{g_j\}, q) \) – function of adaptation for non-uniformity variable, accumulative functions do not used for parameters \( \Delta \) and \( a \), function just passes values of parameters \( \Delta \) and \( a \) to the next iteration:

\[
\gamma(\omega, \{g_j\}, (u, v, t, z)) = \gamma_\Delta(\{g_j\}), \gamma_a(\{g_j\}), \gamma_p(\omega, \{g_j\}, z), \gamma_h(\omega, \{g_j\}, z)
\]

\( \gamma_\Delta(\Delta_j) = \Delta_{x,y}, \gamma_a(a_j) = a_{x,y}, \)

parameter \( p \) is adapted at each iteration using accumulative function:

\[
\gamma_p(\omega, \{\Delta_j, p_j\}, z) = p_{x,y} + u_p(\omega, \Delta)(p_{x,y}), \left( \frac{\sum_j p_{x,j}(t)}{\sum_j \rho(p_{x,j}(t)) + \beta} \right) + \alpha_p \tag{2}
\]

function of adaptation for parameter \( h \) is constructed similarly to adaptation function for parameter \( p \), because phenomena modelled by them, weakening of Ca\(^{2+}\) ionic currents as a result of ions release from cellular depots and as a result of intercellular currents, both are «non-conservative» phenomena, whose intensity depends on traversed path from the source:

\[
\gamma_h(\omega, \{(\Delta, a, p, h)\}_j, z) = h_{x,y} + u_h(\omega, \Delta)(h_{x,y}), \left( \frac{\sum_j h_{x,j}(t)}{\sum_j \rho(h_{x,j}(t)) + \beta} \right) + \alpha_h \tag{3}
\]

cells, at which repolarization occurs first defined adaptively using managing function \( u_h \):

\[
u_{p,h}(\omega(t), \Delta) = \begin{cases} 1, & \omega_h(t) > \Delta \\ 0, & \omega_h(t) < \Delta \end{cases}
\tag{4}
\]

this condition is similar to the condition of excitation transfer between model cells, managing function of this type allows constructing accumulative function for adaptation of non-uniformity parameter \( h \) taking in account traversed path from the source of repolarization.
$\Delta_{x,y}, \alpha_{x,y}, p_{x,y}$ – values of non-uniformity parameters $\Delta$, $\alpha$, and $p$ in current cell, before the adaptation, this values are contained in the set $\{g_j\}$, which contains values of non-uniformity variables for all neighboring cells from the set $B$.

$a_p > 0$, $a_h > 0$ – accumulation increments, they define increasing of values $p$ and $h$, with increasing distance from the source of depolarization and repolarization respectively, different values of this parameters can be used for model calibration.

$r_{ji}(g)$ – interaction function that models phenomena of repolarization duration increasing depending on distance from simultaneously depolarizing area, related to increase of $Ca^{2+}$ ionic channels activity as a result of intercellular current between depolarizing and repolarizing area, this is electrochemical process of type 2.2.

$$r_{ji}(g) = p_i \sum_j \rho(p_{i,j}(t)), \quad (5)$$

$p_i > 0$ – coefficient of interaction, that reflects intensity of ionic currents between cells in depolarizing and repolarizing states,

$\rho(x)$ – non-zero indicator function.

3. Simulation of reentry type arrhythmia initiation without structural damages

Results of idiopathic tachycardia modelling, initiated in cardiac tissue without structural damages, presented at figure 1, figure 2.

Figure 1. Premature ventricular contraction after repolarization without gradient ring break:
1 – simulated electrocardiogram (II standard lead), premature ventricular contraction marked blue;
2 – cellular automaton state graphical representation after repolarization, darkest green areas are repolarized last.

Natural gradient of repolarization’s durations, marked green on figures 1.2, formed as a result of depolarization under conditions of $Ca^{2+}$ ionic currents damping with the increase of distance from atrioventricular node, can became the unidirectional block if its break occurs. Such unidirectional conduction area marked red on figures 2.2. Break can occur as a result of repolarization duration alterations in a small area near the gradient ring, this area marked blue at the figures 2.2.

So, T-wave alterations, widely used for prediction of idiopathic arrhythmias, associated with the actual electrochemical processes inducing arrhythmia, spontaneous formation of unidirectional conduction block.

Therefore, idiopathic arrhythmia can be prevented by decreasing of media automatism coefficient, by prevention of premature ventricular contractions or by prevention of repolarization’s duration gradient ring breaking.
Figure 2. Result of premature ventricular contraction after repolarization with gradient ring break:
1 – simulated electrocardiogram (II standard lead), reentry complex marked red, T-wave alteration marked purple;
2 – cellular automaton state graphical representation after repolarization, darkest green and red areas are repolarized last.

4. Conclusion
New class of non-uniform cellular automata using special accumulative functions for non-uniformity distribution presented. This type of automaton used for modelling of excitable media in application to electrochemical processes in human cardiac tissue.
Model allows estimating of life-threatening arrhythmia’s risks depending on the size of damaged area of heart tissue, formed, for example, as a result of myocardial infarction.
Obtained results allow making more informative diagnostics of idiopathic arrhythmias by T-wave alterations using electrochemical interpretation of underlying processes of these phenomena.
Developed mathematical method could be used for real time simulation of large processes variety in different excitable media, for example, simulation of atrial arrhythmias, by the construction of the appropriate models.

5. References
[1] Moe G K, Rheinboldt W C, Abildskov J A 1964 American Heart Journal 67 200
[2] Pourhasanzade F, Sabzpoushan S H 2010 World Academy of Science, Engineering and Technology 44 917
[3] Gerhardt M, Schuster H, Tyson J J 1990 Science 247 1563
[4] Markus M, Hess B 1990 Nature 347 56
[5] Weimar J R, Tyson J J, Watson L T 1991 Physica D 55 309
[6] FitzHug R 1955 Bull. Math. Biophysics 17 257
[7] Aliev R R, Panfilov A V 1996 Chaos, Solitons and Fractals 7(3) 293
[8] Venetucci L A, Trafford A W, O’Neill S C, Eisner D A 2008 Cardiovascular Research 77 285
[9] Stephan R 2004 Cardiovasc Res 62 309
[10] Tysler M, Turzova M, Svehlikova J 2003 Measurement science review 3 37
[11] Farina D, Dossel O 2007 Computers in cardiology 34 173
[12] Jiang Z, Mangharam R 2011 Conf Proc IEEE Med. Biol. Soc. 263
[13] Andreev S Yu et al 2010 Izvestiya of Tomsk Polytechnic University 317 189
[14] Alonso-Sanz R, Martin M 2003 Complex Systems 14 99
[15] Seck-Tuoh-Mora J C, Martinez G J, Alonso-Sanz R, Hernandz-Romero N 2012 Information Sciences 119 125