MODELING THE SINOATRIAL NODE BY CELLULAR AUTOMATA WITH IRREGULAR TOPOLOGY

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The role of irregularity in intercellular connections is studied in the first natural human pacemaker called the sinoatrial node by modeling with the Greenberg–Hastings cellular automata. Facts from modern physiology about the sinoatrial node drive modeling. Heterogeneity between cell connections is reproduced by a rewiring procedure applied to a square lattice. The Greenberg–Hastings rule, representing the intrinsic cellular dynamics, is modified to imitate self-excitation of each pacemaker cell. Moreover, interactions with nearest neighbors are changed to heterogeneous ones by enhancing horizontal connections. Stationary states of the modeled system emerge as self-organized robust oscillatory states. Since the sinoatrial node role relies on a single cell cyclic activity, properties of single cells are studied. It appears that the strength and diversity of cellular oscillations depend directly on properties of intrinsic cellular dynamics. But these oscillations also depend on the underlying topology. Moderate nonuniformity of intercellular connections are found vital for proper function of the sinoatrial node, namely, for producing robust oscillatory states that are able to respond effectively to the autonomic system control.

Keywords: Cellular automata; sinoatrial node; Greenberg–Hastings model; Watts–Strogatz rewiring.

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1. Introduction

The regular pulses which result in rhythmic contractions of the heart begin in the area of the cardiac tissue called sinoatrial node. The activity of the sinoatrial node spreads throughout the atria causing atrial contraction. In parallel, activity is passed to the atroventricular node — the secondary cardiac pacemaker, and then the specialized conduction pathways — a His bundle and Purkinje fibers, conduct the impulse through the ventricles causing their contraction in unison. In the following we propose a cellular model for the sinoatrial node that produces robust oscillatory pulses.

Physiological properties of the heart are extensively studied. Reference 2 collects the widely accepted latest results. Some of the electrophysiological properties of the
The sinoatrial node consists of a relatively small number of cells: 70,000 in the case of humans. The electrophysiology of a single cell is reasonably well understood. But it is not yet clear how the pacemaker cells maintain the final function: successful pace making of the heart. The main difficulty concerns the arrangement of cells — how rather poorly connected cells can drive the heart contraction. There are two basic approaches to the organization of the sinoatrial node cells: the mosaic and gradient models. The first one considers coexistence of two types of cells: nodal and atrial. The second one assumes the gradual change of properties of individuals cells when moving from the central part of the sinoatrial node to its border. Our main objective is to find whether the observed gradual changes can result from heterogeneity of intercellular links and not from the differentiation of individual cells. We propose a simple model that arises from physiological facts related to the topology of cell connections.

Cellular automata have been used to model biological systems of different types. Excitable media such as the cardiac tissue have been modeled by cellular automata since the famous paper of Wiener and Rosenblueth. Reference 10 collects bibliography on the pacemaker modeling. On the other hand, there are papers describing the effect of perturbing topology (i.e. links between cells) on global properties of cellular automata. There are studies which consider adding an extra link, deleting links or links evolving together with automata. Their results indicate the strong qualitative changes of the system properties.

Our starting point is the Greenberg–Hastings model of excitable media. In the original Greenberg–Hastings model an excited cell is always refractory in the next timestep, and then it always becomes resting in the subsequent timestep. Finally, a resting cell becomes excited if and only if at least one of its 2D neighbors is excited. In the following, we propose two modifications to the Greenberg–Hastings model. The first one follows the ideas of Refs. 16 and 17. It corresponds to the self-excitation of a sinoatrial node cell: a cell does not stay in the resting state until the nearest neighbor excitation but eventually jumps in the excited state. The second modification concerns plain square lattice topology — it can be intuitively imagined as a considerable wrinkling of the initially flat structure.

The paper is organized as follows. In Sec. 2 we introduce the model and explain physiological motivation for the assigned assumptions. Section 3 contains results which were obtained by computer simulations. In the first subsection the dynamic properties of simple cellular automata with a regular line topology are discussed to explain the role of the parameters which drive the intrinsic cellular dynamics. Features of the cellular automata with inhomogeneous intercellular connections are presented in the next subsection. Specifically we investigate how the stationary evolution of a single cell relates to both the intrinsic cellular dynamics...
and heterogeneity of intercellular interactions. In the last section the perspective of further developments of the model is presented.

The paper considers some results presented in our previous papers just to clarify important aspects of the model. In the following, we propose a simplified algorithm of rewiring of intercellular connections. Then, since it is believed that the sinoatrial node activity relies on a single cell activity we concentrate on cyclic evolution of the three types of individual cells. The types are related to the role of a cell in the overall state. In particular, we investigate oscillations of cells that are most densely connected — called leaders, cells from the set of leftmost and rightmost columns — called output cells, and remaining typical cells.

2. Model Settings

2.1. *Elements of physiology of a sinoatrial nodal cell*

Each heart cell — myocyte, as any other cell of a body, is protected from the extracellular world by the plasma membrane, see Refs. 1 and 2 for details. The membrane is a lipid bilayer which excludes ions and complex molecules. In order to preserve the communication between a cell and the outside world, there are sinoatrial mechanisms of signal transduction. These mechanisms convert one kind of signal or stimulus into another. In the case of an excitable cell, like a myocyte or neuron, the ion channels — large proteins built in the cellular membrane, critically change their properties for the transduction of electrical signals. The critical changes are activated if the electrostatic potential of the membrane reaches a threshold value. Then, the potential changes are called the action potential. They start with depolarization of the membrane which is followed by the membrane repolarization.

The action potential in sinoatrial nodal cells, see Fig. 1, primarily depends on changes in the membrane conductance with respect to calcium ions \( \text{Ca}^{2+} \) for depolarization and potassium ions \( \text{K}^+ \) for repolarization. The duration of the action potential ranges from 200 to 400 ms. The intrinsic cyclic dynamics is traditionally represented by three phases:

- **firing** — fast depolarization of the membrane due to the \( \text{Ca}^{2+} \) inward currents.
- **refractory** — fast repolarization because of outward currents of \( \text{K}^+ \) which repolarize the cell membrane toward the equilibrium potential for \( \text{K}^+ \). The cell is refractory to the initiation of a new action potential. A cell recovers its resting potential.
- **activity** — spontaneous depolarization: there is no true resting state in the case of a nodal cell. Instead, many mechanisms (among which the basic one is the funny current \( i_f \)) slowly drive the membrane potential to the threshold value causing self-activation of a cell.
Fig. 1. Rapid changes in the electrical potential of the sinoatrial nodal cell membrane start from firing phase (F)-depolarization, primarily due to an increase in Ca$^{2+}$ conductance through calcium channels accompanied by a fall in K$^+$ conductance. It is followed by refractory phase (R)-repolarization which is due an increase in K$^+$ and a decrease in Ca$^{2+}$. Finally, activity phase (A) begins, i.e. a spontaneous slow depolarization starts that results from a pacemaker current $i_f$ carried in part by Na$^+$ and also by both decreased K$^+$ and increased Ca$^{2+}$. Letters A, F, and R correspond to the three phases of the electrical activity of a sinoatrial nodal cell.

The Greenberg–Hastings cellular automaton is a discrete dynamical system which can be related directly to the physiology of a sinoatrial nodal cell. A cell in the firing phase is always moved to the refractory phase. A cell in the refractory phase always becomes active. Finally, a cell from the activity phase switches to the firing phase. However, since durations of particular phases are different, the intrinsic cycle has to be modified. Bub et al.\textsuperscript{16,17} proposed to consider timesteps after which the jump to the next state had to be performed automatically. Moreover, when modeling the whole cardiac tissue of the embryo of a chicken, they also assumed that a cell can switch from activity to firing with a small probability without any external stimulus.

2.2. FRA cell

Let the state space of each cell be $\Sigma^* = \{\binom{n}{s}, s = 1, 2, \ldots, n\}$ where:

- $\Sigma = \{F, R, A\}$ is a discrete state set, $F$, $R$, $A$ denote the three main phases of the cellular membrane electrical properties: $F$ — firing $R$ — refractory and $A$ — activity phase;
- $n\sigma$ denotes the maximal time in which a cell can stay in a state $\sigma$. Correspondingly, we define $n_F$, $n_R$, and $n_A$;
- $s$ counts the timesteps spent by a cell in a state $\sigma$.

Let the function $\text{next} : \Sigma \rightarrow \Sigma$ be describing the only allowed sequence of states:

\[
\text{next}(F) = R \quad \text{next}(R) = A \quad \text{next}(A) = F
\]
Then, the modified Greenberg–Hastings rule reads as:

\[
\begin{pmatrix}
\text{next}(\sigma(t)) \\
1
\end{pmatrix}
\begin{cases}
\text{if } s(t) = n_\sigma \\
F \\
1
\end{cases}
\begin{pmatrix}
\sigma(t) \\
s(t) + 1
\end{pmatrix}
\begin{cases}
\text{if } \sigma(t) = A \text{ and a cell receives an external stimulus} \\
\sigma(t) \\
s(t) + 1
\end{cases}
\]

Hence, in the absence of an external stimulus each cell performs the intrinsic cyclic dynamics: \( F \rightarrow R \rightarrow A \rightarrow F \rightarrow \cdots \). This cycle has period \( T = n_F + n_R + n_A \). The durations of the firing, refractory and activity phases are steady according to physiological observations. However, sharp limits are usually physiologically unrealistic. Therefore, we propose to consider a possibility for an earlier jump to the next cellular state with a probability rapidly increasing to 1 when approaching the time limits \( n_F, n_R, \) or \( n_A \). The stochastic shortening of each cellular phase is proposed to be driven by the power function \( (s(t)/n_\sigma)^\xi \) with \( \xi > 1 \).

Formally, the deterministic rule (1) becomes the stochastic one as follows:

\[
\begin{pmatrix}
\text{next}(\sigma(t)) \\
1
\end{pmatrix}
\begin{cases}
\text{with probability } \left( \frac{s(t)}{n_\sigma} \right)^\xi \\
F \\
1
\end{cases}
\begin{pmatrix}
\sigma(t) \\
s(t) + 1
\end{pmatrix}
\begin{cases}
\text{if } \sigma(t) = A \text{ and a cell receives an external stimulus} \\
\sigma(t) \\
s(t) + 1
\end{cases}
\]

Note that if \( \xi \) is significantly greater than 1, then only a very few last steps of a given phase can be skipped. Therefore, the intrinsic cycle timings are still closely determined by values of \( n_F, n_R, \) and \( n_A \) and intrinsic oscillations have periods which are only slightly shorter than the deterministic cycle \( T \). If \( \xi \gg 1 \) then we restore the deterministic rule (1).

The just defined cell will be called the FRA cell.

2.3. Network of interaction

For a long time the heart tissue was considered as a syncytium — a multi-nucleated mass of cytoplasm which was not separated into individual cells. Development of the electron microscopy has proved that myocytes are individual, elongated units, bounded on their ends by intercalated discs — measurable gaps which separate the opposing cell membranes. These gaps are highly structured. Each gap junction allows many mechanisms which establish pathways for direct cell-to-cell communication. The largest gap junctions occur at the ends of a long cell which makes
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Fig. 2. A simplified picture of the ventricular tissue consists of branched chains of elongated cells with a strong cell-to-cell direct interaction due to gap junctions. The gap junction is a space between membranes of two neighboring cells. The membranes at the gap junctions are densely occupied by ion channels. The strongest gap junctions are at the ends of cylinder-shaped cells that effects in creation of a fiber. But gap junctions are also present between cells from different fibers. Because of these junctions a network of complex links between cells emerges. (The figures are produced using SERVIER Medical Art).

the transmission of signals highly effective in the end-to-end direction, see Fig. 2. The smaller (by the surface size) gap junctions are also found on other parts of the membrane that allows a cell to communicate directly with other neighboring cells.

Some statistical facts about the cardiac tissue connectivity are known. The crista terminalis tissue — the cardiac tissue which conducts signals from the sinoatrial node to the atrioventricular node, is characterized by a significant dominance of the end-to-end connections. But the distribution of connections in the sinoatrial node is quite different from the other parts of the heart. For example, it has been found for a canine sinoatrial node cell that at average from all nearest neighbors, namely from $4.8 \pm 0.7$ nearest neighbors, only $0.6 \pm 0.7$ are connected by the end-to-end gap junctions. Most of the connections, i.e. $3.5 \pm 1.9$, are lateral. The remaining connections $0.7 \pm 0.5$ are called side-to-side.

Because of the presence of the direct cell-to-cell connections, the heart tissue seems to be perfectly suited for network interaction modeling. Note that rare connections among the sinus node cells can be represented on a square lattice.

Let us start modeling intercellular connections by locating FRA cells in vertices of a square lattice. Interactions between FRA cells are established as links between vertices. The links are stochastically introduced depending on a parameter $d$, $0 < d < 1/2$ as follows, see Fig. 3 left:

**Rule I** for a given $d$, vertical and horizontal links are created with a probability $d/2$, while any diagonal link is added with a probability $2 \times d$.

Moreover, let us distinguish cells from the leftmost and rightmost columns assuming that they are input cells to the crista terminalis or equivalently, output cells of the sinoatrial node. Since connections to the crista terminalis cells should be
efficient, then each cell from these two columns is connected to the next one with probability 1. If \( d \) is small then some number of isolated cells can appear. In such a case, each isolated cell is linked to its nearest right neighbor. Thus, due to these two extra rules, some additional horizontal connections appear. The cells from top and bottom rows are also different from the other ones. They have less connections. This property imitates the connective tissue barrier which can be thought of as a shielding of the sinoatrial node border zone from surrounding atrium cells and protects the sinoatrial node from the atria hyperpolarizing influence.

Finally, we obtain a kind of stochastically diluted square lattice connections where diluting favors diagonal links. In the case of \( d = 0.45 \) the described construction leads to a network where on average about 10% of the connections are vertical, 11% horizontal and 79% diagonal, what reconstructs the statistics of connections in the sinus node described at the beginning of this subsection.

The resulting structure of interactions is flat because it relies on a square lattice connection. To make the surface uneven we propose the algorithm of rewiring links. The algorithm is based on the typical Watts–Strogatz\textsuperscript{24} rewiring rule of diffusive type but with two differences, see Fig. 3 right. The rule favors moving the links which connect to the cells with a small number of neighbors. The rule is local — it considers rewiring between nearest neighbors only.

Formally, the rewiring algorithm goes as follows:

**Rule II** for a given parameter \( p \in [0, 1] \) and a cell \( A \), the probability \( p_{\text{unlink}} \) to unlink a cell \( B \) from the cell \( A \) is

\[
p_{\text{unlink}} = \frac{p}{\text{deg}(B)} \tag{3}
\]

where \( \text{deg()} \) is the function calculating the vertex degree. A new cell \( B' \), which will be linked to the cell \( A \) in place of the connection to the cell \( B \), is
chosen from the set of actual nearest neighbors of the cell $B$. To preserve strong and stiff end-to-end connections, breaking a horizontal connection is not allowed. Unlinking from a leaf is forbidden also.

In practice, having $N$ cells arranged in vertices of square lattice we start a construction of intercellular connections by applying Rule I with $d = 0.45$. Then, we choose a cell at random and perform Rule II to all its non-horizontal links setting $p = 0.01$. The random choice of a cell is repeated $N$ times. Such execution of Rule II is referred as one Monte Carlo step (MCS). Thus in one MCS each connection has a chance to be rewired twice because unlinking with probability (3) considers each connection end separately. The table of vertex degrees is updated after each MCS. It is enough to fulfill demands of Rule II if $p$ value is so small.

In the following we study: $A$ — a network with no connection rewired, $B$ — a network obtained after 100 MCSs of rewiring, and $C$ — a network obtained after 500 MCSs. In Fig. 4 we show the properties of the three networks used in further investigations.

In Fig. 4 left, the distributions of the vertex degree are plotted for $A$, $B$ and $C$ networks. Note that the vertical axis is logarithmic. A normal distribution of the vertex degree occurs when the rewiring is not applied (it refers to the network $A$). After applying one hundred MCSs of rewirings (network $B$) the normal shape of the distribution is slightly modified. The mean value of vertex degree $\langle \nu \rangle = \sum_{i} i \text{Prob}(i)$ [where $\text{Prob}(i)$ means probability that a cell has the vertex degree equal to $i$] in the case of the networks $A$ and $B$ is about the same $\langle \nu \rangle = 4.45$. However, the network $B$ is heterogeneous — there exist few cells which are definitely more densely connected.

![Fig. 4. (Color online) Left — vertex degree distribution in the three networks considered: no rewired (black), rewired 100 MCSs (red), and rewired 500 MCSs (green), log-plots. The expected value of the vertex degree of a cell $\langle \nu \rangle$ is provided at the corresponding plot label. Right — example of the network structure if the rewiring algorithm is applied 100 times; a cell which is densely (its vertex degree is 12) connected to other cells — red (black) solid lines, point to all neighbors, and connections of other cells — green (gray) dashed lines, from the Moore neighborhood of the central cell, are shown.](image-url)
to other cells than a cell with the mean connectivity. When the process of rewiring
is continued then a network becomes of the exponential type — the distribution of
the vertex degree is given by an exponential decay (linear in the log-plot of Fig. 4
left). Note that if Rule II is performed for 500 MCSs then almost 32% of cells have
only one nearest neighbor. On the other hand some other cells have more than 30
neighbors.

In Fig. 4 right, a typical neighborhood of a densely connected cell from the
network \( B \) is presented together with new links of its traditional eight nearest neighbors
from the Moore neighborhood. The vertex degree of the central cell is 12. Due to
the locality of rewiring, the new connections spread a given FRA cell influence.
Although the radius of the influence is, in general, not larger than four lattice units
this heterogeneity makes the initially flat structure considerably wrinkled. In the
following we claim that the densely connected cells are essential for establishing
robust features of the whole system.

2.4. Intercellular interactions

Finally, we have to introduce the notion of the external stimulus which switches a
FRA cell from the state \( A \) to the state \( F \) independently of the intrinsic dynamics. Let us assume that at least \( T_F \) nearest neighbors in the state \( F \) produce a stimulus
strong enough to fire the FRA cell. Moreover, since not all intercellular connections
are equivalent — the end-to-end ones (horizontal in our description) are more effec-
tive than others, then influence of the left or right neighbor is twice stronger than
influence of any other neighboring cell. Namely, let each horizontal neighbor being
in the state \( F \) be counted as two other neighbors becomes heterogeneous.

Thus, if \( (i) \) is the state of a FRA cell located in the \( I \)th site of a network and
\( N_I \) is a set of its nearest neighbors where the horizontal neighbors are included
twice then

\[
\begin{align*}
\sigma(t) & = A \\
& \quad \text{and} \quad \left\{ \left( \sigma(t) \right)_{j \in N_I}, \left( \sigma(t) \right)_{j} = F \right\} \geq T_F \\
\text{then} \quad \left( \sigma(t + 1) \right)_{i} & = F \\
\left( s(t + 1) \right)_{i} & = 1.
\end{align*}
\]

(4)

The rule is applied synchronously, i.e. to each cell independently. The synchronous
updating nicely reproduces events that happen in parallel, i.e. at the same time.
One can have doubts if perfect synchronicity is physiologically reasonable. However
because each cell performs a stochastic intrinsic dynamics independently of other
cells the perfect synchronicity is limited.

2.5. Model summary

There is a tremendous physiological data available on cardiac modeling. The
just introduced model mimics only a few of them by considering: \( n_F, n_R, n_A, \)
\( \xi, T_F \) — quantities describing the dynamics of FRA cells, and \( d, p \) and number of MCSs — parameters related to the intercellular connections. The main purpose of our study is to find how simple three-state cells, rather poorly connected on average, self-organize themselves into a state which oscillates regularly.

The investigated systems consist of FRA cells arranged on networks, evolving according to either (1) or (2), and with the stimulus rule (4) applied synchronously. Such systems will be called FRA cellular automata and denoted FRA-CA. Thus, in the following, we simulate FRA-CA with different \( n_F, n_R, n_A \) values and FRA cells arranged in different manners. However, values of the following parameters are kept constant:

\[
\xi = 10, \quad T_F = 2, \quad d = 0.45, \quad p = 0.01.
\]

Setting the threshold \( T_F = 2 \) means that at least two neighbors in the firing state are necessary to switch a cell from the state \( A \) to \( F \). Notice that because we assume that the end-to-end connections are stronger than the others then only one horizontal neighbor (left or right) in \( F \) also switches a cell. Considering \( \xi = 10 \) the stochastic shortening of each cell state is a rare event but any of states: \( F, A, R \) can be shortened independently of the others. If \( p = 0.01 \) for a single Monte Carlo step then, after 100 MCSs of rewiring, each connection is rewired with probability close to 1.

The emerging oscillatory states should allow easy modulation to simulate the regulation that is present in the heart. In nature the modulation is achieved by the autonomic nervous system control which consists of the two parts: parasympathetic and sympathetic. Both parts influence the heart rate by sending bursts of impulses through the neuronal network. The network of myocytes is entangled with axons ends (communication between myocyte and neuron goes via synapses) of the autonomic network. The neural activity leads to the release of acetylcholine — the parasympathetic transmitter, or noradrenaline — the sympathetic transmitter, at the myocytes. In response, the myocyte self-activation time becomes longer (due to the parasympathetic activity) or shorter (due to the sympathetic activity). Note that such control can be directly implemented in the FRA cell dynamics by tuning of the activity time \( n_A \) in response to some external fields.

3. Simulation Results

Since the horizontal connections play a special role in the model, we start our discussion with FRA cells occupying vertices of a finite chain. A single chain can be considered as the zero-order approximation of a pacemaker.

3.1. FRA-CA with a chain topology

We performed simulations for \( N = 100 \) FRA cells arranged in a line, for all combinations of values of \( n_F, n_R, n_A \in \{2, 3, \ldots, 50\} \), starting from different random
Fig. 5. (Color online) The space-time patterns are shown with $n_F = 10$, $n_A = 20$, and $n_R = 15$ (left), $n_R = 5$ (right). The first step in firing is white, the other cells are gray. Cells in refractory state are light blue (gray), cells in activity state are dark blue (gray).

initial states. We assumed that FRA cells evolved deterministically following rules (1) and (4). In Fig. 5 space-time diagrams of typical evolutions are shown.

The intrinsic oscillatory behavior of each FRA cell moves a problem of the global stable dynamics of FRA-CA to the problem of synchronization of oscillators. We have found that stable systems are always periodic. Hence, due to the interactions the stable periodic evolution emerges. But only one of the two periods are present: either $T = n_F + n_R + n_A$, see Fig. 5 left, or $T^* = n_F + n_R + 1$, see Fig. 5 right. Note that $T^*$ is the shortest period possible — interactions between cells affect the activity phase and this phase is reduced to a single step after which each cell moves to the firing state.
It appears that, for a randomly initiated system, the probability of finding the final state as oscillating with periods $T$ or $T^*$ depends on the model parameters. In Fig. 6 we present these probabilities for the representative values of $n_F$ and $n_A$. The mirror symmetry between curves reflects the fact that no other periods are observed. A sharp transition is located where the refractory time $n_R$ crosses the firing time $n_F$. If $n_F \leq n_R$ then only the stabilization with period $T$ occurs. But if $n_F > n_R$ then the stabilization with period $T^*$ emerges with a rapidly growing probability. This transition takes place independently of $n_A$ but when $n_A$ is increasing then the time needed to obtain a stable solution becomes significantly shorter. Hence, the dynamical system studied has two types of attracting states. The basin of attraction of these two states is directly given by the relation between $n_F$ and $n_R$.

The oscillations of the whole system with period $T$ can be seen as an indicator of passive dynamics. It looks as if cells followed the intrinsic cellular dynamics independently of their neighbors. However, considering the oscillation phase of each FRA cell as the number of steps in its actual period, it appears that each cell evolves exactly one step behind its neighboring cell, see Fig. 5 left. The phase difference between the neighboring cells is equal to $\pm 1$ sometimes 0. Hence the stable solution means the synchronized evolution of all cells with the phase difference equal to $\pm 1$ sometimes to 0. In the case of $n_F = n_R = n_A$ this property of any stable solution can be rigorously shown. Hence, a very special adjustment of oscillatory phases of neighboring cells emerges due to interaction. This adjustment makes the system perfectly prepared to conduct external signals, such as for example, signals send by the autonomic nervous system to speed up or slow down the cellular intrinsic cycle.

The evolution with period $T^*$, see Fig. 5 right, can be interpreted as an indicator of active dynamics. Keeping periodicity $T^*$ requires permanent interactions between neighboring cells in order to reduce the intrinsic period $T$ to the shorter one. In the case of two FRA cells A and B, the stable evolution with period $T^*$ can be referred to as alternating impacts because within each period two stimuli take place. The
following evolution of cells $A$ and $B$ with $n_F > n_R$ and $n_A$ arbitrary explains the notion of alternating impacts:

$$
\begin{align*}
\text{time } t = 1 & \quad n_R + 1 & \quad n_R + n_F + 1 \\
A &: (F) \quad \ldots \quad (F) \quad (F) \quad (F) \quad (R) \quad (R) \quad (A) \\
B &: (R) \quad \ldots \quad (R) \quad (A) \quad (F) \quad \ldots \quad \ldots \quad (F)
\end{align*}
$$

(5)

Signs $\downarrow, \uparrow$ in (5) are used to depict (moments of time) when two cells interact — one cell fires the other one. Following the situation presented in (5), at first cell $A$ switches $B$ to firing state. The activity state of $B$ is reduced to one step. Then after next $n_F$ steps $A$ is switched to $F$ state by cell $B$. Hence $B$ cell stays in the activity state for one step only. These alternating impacts continue forever — a stable periodic evolution emerges, and the period length is $n_F + n_R + 1$.

A pair of FRA cells which performs the alternating impact evolution works as never-failing engine independently of other neighbors from a line. According to our simulations a presence of a single pair of FRA cells undergoing the alternating impacts is necessary and sufficient to establish the evolution with period $T^*$ in the whole line of FRA-CA. It is possible because the remaining pairs of a line have their oscillating phases adjusted. In Fig. 5 we see four pairs following impacts which are surrounded by cells having states with oscillating phases adjusted.

### 3.2. FRA-CA with irregular topology

Now let us move to a system consisting of $N = 100 \times 100$ FRA cells occupying vertices of the three networks described in Sec. 2.3. Let the dynamics be driven by the stochastic rule (2) and the synchronous update of cell states according to the external stimulus rule (4) be applied. We performed simulations with many random initial states and at different values of $n_F, n_R, n_A$. When analyzing the results of our experiments we ask whether the resulting stationary evolution is periodic and what is the period. Especially, we want to find if the transition between evolution with periods $T$ and $T^*$ is still present.

We describe our study in three steps. Firstly, we investigate properties of stationary patterns. Then, we propose a method to study periodicity of an individual cell. Finally, with an analysis based on statistical properties of oscillatory evolution of individual cells, we answer the problem of existence of critical changes in periodicity when FRA-CA is built on the three networks described in the previous section.

**Stationary state patterns:**

Let us start with considering configurations observed in stationary states. In general, all simulated systems exhibit the basic pacemaker properties, see Fig. 7:
Fig. 7. (Color online) Snapshots from the stationary states of FRA-CA with different irregular topologies: a network not rewired (left), rewired 100 MCSs (middle) and rewired 500 MCSs (right). \( n_F = 10 \), \( n_R = 20 \) and \( n_A = 50 \). The red (black) dots represent cells in the \( F \) state, the green (gray) dots represent cells in the \( A \) state and the white dots describe cells in the \( R \) state.

- The network states are robust, quickly achieved and they change rhythmically;
- Clusters, i.e. large structures consisting of neighboring cells being in the same state, emerge;
- Cells in the firing state form compact clusters but the spiral shapes appear only in the case of networks with rewired edges;
- Clusters made of cells in the firing state take the role of centers of a pacemaker’s activity; the oscillations from these centers propagate toward the borders.

Well-established spiral patterns made of cells in the firing state are claimed to be a sign of proper propagation of impulses in the cardiac tissue.\(^{28}\) Hence, we see that the heterogeneity in intercellular connections is crucial for restoring this pacemaker property.

**Oscillations of individual cells:**

Since the activity of a real pacemaker relies on a single cell activity, we should concentrate on features of an individual cell. Let us convert the state \( s \) of a single FRA cell into a value imitating the cellular electrical activity — Action Potential. Following Fig. 1, the action potential can be approximated by a piecewise function where each sinoatrial node phase is approximated by a different straight line in the following manner:

\[
\begin{align*}
\begin{pmatrix}
\sigma \\
\sigma
\end{pmatrix} & \rightarrow AP(s) = AP_0^\sigma + \frac{s}{n_\sigma}(AP_0^{\text{next}(\sigma)} - AP_0^\sigma) \\
\end{align*}
\]

where \( AP_0^\sigma = -65 \text{ mV} \), \( AP_0^F = -40 \text{ mV} \), and \( AP_0^R = 20 \text{ mV} \) are the AP values of the sinoatrial node cell at the beginning of the corresponding phases.\(^1\) The remaining notation is the same as in definition (1).

Using formula (6) we map the time series of a single cell into the Action Potential function. As the representative cells for the sinoatrial node activity we consider cells:

- (i) from the leftmost or rightmost column — output cells,
- (ii) any internal cell, and
- (iii) densely connected to a network.
We assume that a cell is densely connected if it has more than 12 nearest neighbors in the case of the rewired network and more than eight nearest neighbors in the case of the flat lattice (horizontal neighbors are counted twice). These cells will be called leader cells.

In the columns of plots in Figs. 8–10, we show $AP(t)$ signals obtained for two randomly selected cells of each type. The system evolves with $n_F = 10$ and $n_A = 20$ when $n_R = 5$ or $n_R = 20$ and the three different networks $A$, $B$, and $C$ are used to mimic intercellular connections. The time unit is chosen to be equal to $T^*$ to see clearly whether there are oscillations with the shortest period. Let us remind that because $T^* = n_F + n_R + 1$ then $T^*$ unit in the left column ($T^* = 16$ timesteps) is different from the right one ($T^* = 31$ timesteps), though timescales in both figures are the same — they cover a hundred timesteps. Note that cells of the same type evolve similarly in a given case. Both cells have similar periods and differences between the oscillating phases are nearly stable. This observation allows us to claim that we study properties of typical cells.

It occurs that if the refractory phase is short, namely for $n_R = 5$ (left columns in Figs. 8–10) then the activity phase is reduced to 1 timestep in all series discussed with one exception. Signals obtained for random cells from a network rewired 500 MCSs evolve with period $T$, see Fig. 10. This is due to the fact that network $C$ is strongly heterogeneous. Here it is highly probable that a randomly chosen cell is loosely linked to a network because it is a leaf. Such a cell evolves intrinsic cycle independently of the main dynamics driven by densely connected cells.

![Fig. 8. Action Potentials $AP(t)$ for randomly selected cells from network $A$. Few periods of stationary signals of two output cells, two typical cells, and two densely connected cells are plotted in the case $n_F = 10$, $n_A = 20$ and $n_R = 5$ (left) and $n_R = 20$ (right).]
Fig. 9. Action Potentials $AP(t)$ for randomly selected cells from network $B$. Few periods of stationary signals of two output cells, two typical cells, and two densely connected cells are plotted in the case $n_F = 10$, $n_A = 20$ and $n_R = 5$ (left) and $n_R = 20$ (right).

Fig. 10. Action Potentials $AP(t)$ for randomly selected cells from network $C$. Few periods of stationary signals of two output cells, two typical cells, and two densely connected cells are plotted in the case $n_F = 10$, $n_A = 20$ and $n_R = 5$ (left) and $n_R = 20$ (right).
If $n_R = 20$ and the network is not rewired, see Fig. 8 right column, then cells of all types oscillate with period $T$, which suggests that the whole system evolves with period $T$. When a network is strongly modified — as in the case of network $\mathcal{C}$, Fig. 10 right column, then the output and leader cells follow an evolution with period $T^*$. One can suppose that the period is $T^*$ even for $n_R > n_F$. According to the plots describing signals obtained from network $\mathcal{B}$, see Fig. 9, the duration of the activity phase can take any value.

**Statistical properties of oscillations of cells:**

The intrinsic stochasticity of rule (2) makes the identification of periods more difficult than in the deterministic case. Therefore, to extract basic oscillations we use Fourier analysis. We calculate the power spectrum $S(f)$ for stationary signals of 10,000 timesteps. Examples of spectra for selected series are given in Fig. 11. Notice that vertical axes use the logarithmic scale. The top plots show the power spectra of a total system signal which denotes the number of cells in the firing state. The rest of the plots present power spectra of the $AP(t)$ series of individual FRA cells. The lines corresponding to frequencies $1/T$ and $1/T^*$ are added to facilitate identification of spectra peaks.

All series provide the power spectra with evident maxima. All first maxima are wide and shifted to the right as compared to values $1/T$ or $1/T^*$. These effects are directly related to the stochasticity of the rule. It is easily noticeable that intensities of the maxima received from signals of individual output cells are found to be five orders stronger than maxima of the total output signals though both maxima are

![Fig. 11. Power spectra calculated from stationary signals presented in Figs. 7–9 right columns; log-plots. The limit frequencies $1/T$ and $1/T^*$ are given to help in determining what the driven oscillation is.](image-url)
located at the same frequency. Hence, communication with other parts of the heart
tissue, namely with the crista terminalis, via cell-to-cell connections would be much
stronger than communication driven by the mean oscillations of all output cells.

The power spectra exhibit well-localized peaks with the exception of spectra
obtained for the system considered on networks rewired 100 MCSs. In this case
maxima are wide — they look like as covering the whole interval between the
frequencies \(1/T, 1/T^*\). It is possible only if all durations of the activity phase are
simultaneously and equivalently present in a system.

To consider changes in the periodicity systematically, let us study oscillations
of FRA cells for \(n_F = 10\) and \(n_A = 20\) versus \(n_R = 2, 3, \ldots, 50\). Let us assume that
a given frequency \(f\) is dominating in FRA-CA if its power spectrum value \(S(f)\) is
greater than 1. In the case of log-plots presented on Fig. 11 our assumption implies
that we extract values which are non-negative. In Fig. 12 we show all frequencies
identified in this way for leader, output and typical cells. The results are collected
according to the three types of networks: no rewiring, 100 and 500 MCSs of rewiring.
Similar plots are found also for other values \(n_F\) and \(n_A\).

From first row of Fig. 12 we see that a flat network is a bi-stable system which
is similar to FRA-CA with a chain topology. There are two basic oscillations —
closely related to \(T^*\) and \(T\). If \(n_R\) is sufficiently short then the system oscillates
with period \(T^*\). Otherwise, the system evolves with period \(T\). Under conditions
presented in the figure, i.e. for \(n_F = 10\) and \(n_A = 20\), the transition appears at
\(n_R = 6\) or \(n_R = 7\).

![Fig. 12. Dominating frequencies in the power spectra of cellular signals: a leader, an output and a
cell (in columns), for different network models (in rows). \(n_F = 10, n_A = 20\) and \(n_R = 2, 3, \ldots, 50\).
The black points correspond to \(1/T\) and \(1/T^*\) frequencies.](image)
When the structure of a network is strongly modified — last row in Fig. 12, the switch in periodicity $T^*$ to $T$ disappears. The dominant frequency of leader cells is related to oscillations with period $T^*$ independently of $n_R$, though the oscillations with $T$ are also present. However, a randomly selected cell and an output cell can evolve with any of these two oscillations.

If the rewiring algorithm is applied for 100 MCSs then for small $n_R$ the dominant frequency corresponds to $T^*$ as in the case of the flat network. However, for larger $n_R$ all frequencies between $1/T$ and $1/T^*$ are present. Hence, the transition here means admitting evolution with the wide spectrum of possible oscillations. It is possible only if different lengths of the activity phase are permanently present in the system.

4. Conclusions and Hints for Further Model Development

The sinoatrial node is a complex and nonuniform tissue, and its complexity and nonuniformity are vital for its normal functioning. The observations made with our model support this belief.

Using the cellular automata approach we usually oversimplify modeled phenomena. However, we are still able to learn many interesting facts about emerging properties related to a modeled system and also can quickly gain insights into the role of the crucial ingredients of the phenomena. In the model proposed, thanks to the simplicity of a single cell dynamics, we could concentrate on the influence of topology.

The topology of intercellular connections qualitatively and quantitatively changes oscillatory properties of the FRA-CA system. The global state appears as self-organized to produce a robust oscillatory state. The strength and rate of oscillations depend on properties of intrinsic cellular dynamics and underlying topology. If the intercellular connections are simple — the FRA cells are arranged in a line or are placed in vertices of a flat square lattice, then a sharp transition between the two limit frequencies $1/T^*$ and $1/T$ occurs when $n_R$ changes. When this plain topology is slightly modified, for example by the considered rewiring procedure, we observe the presence of the wide interval $(1/T, 1/T^*)$ of possible oscillations. Moreover, few leading centers of pace making emerge. But if the connections are modified too strongly, then the overwhelming oscillations are reduced to ones with frequency $1/T^*$.

The further problem which can be easily investigated with FRA-CA is the problem of the control over heart rate driven by the autonomic nervous system. The aim of this control is to regulate the heart rate to actual needs of the organism. The autonomic control over the sinus node rhythm influences the speed of the slow depolarization phase of a cell only. It does not influence either the fast polarization phase or repolarization phase. Such modulation can be directly implemented into the FRA cell dynamics by elongating or shortening the activity time $n_A$ of each cell. But this modification would provide a qualitative difference to the resulting
oscillations, only if the intrinsic periodicity $T$ is present. The frequency $1/T$ is present in all systems investigated here, though its role is different in each topology. On the flat network the frequency $1/T$ is only possible if the refractory phase is appropriately long. On the most rewired network the frequency $1/T$ is almost absent. However, the system built on the slightly modified flat network not only admits a large variety of oscillations but also allows their fast and efficient modulation due to the existence of leading centers. Verification of this hypothesis is the aim of further developments of the model.

The autonomic system modulation is crucial for proper everyday life. However this modulation is also automatically switched on in the case of a disease. The permanent activity of the autonomous system (especially the sympathetic activity) leads to deleterious changes in the heart. Therefore understanding of the relation between the impulse formation in the sinoatrial node and the autonomic control is of special importance.  

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