Pacemaker rhythm by cellular automata

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How can sinus node – the heart natural pacemaker, deliver more than 90 thousand beats per day, 365 days a year for more (hopefully many more) than 70 years straight?

Shift from the component level to the system level perspective appreciates the cellular automata approach.
How does the nature calculate?

**Reaction-diffusion modeling:**

- Simulate the flow of ionic currents through the ion channels and the associated membrane potential (e.g., celebrated Luo-Rudy model)
- The connection between the cells is modeled by electrical resistors
- Propagation of the impulse is calculated by solving equations used to describe electrical circuits.

**Cellular automata modeling:**

- The cardiac tissue is a set of discrete elements connected in a regular way
- Each element, automaton, can have a finite number of allowed states
- An automaton state varies as a function of its last state and the states of neighboring automata, namely according to a set of predefined rules.

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Functional structure of the sinus node by leading pacemaker site.

Observed locations of the leading pacemaker site (the source of the excitation signal within SAN) in a rabbit.
Conclusions: integrative modeling of pacemaker via cellular automata

An oscillatory timed automaton will be proposed that maps time changes of the membrane potential of a nodal cell to automata states.

Automata will be coupled according to heterogeneous network of intercellular connections.

Although the model is based on simple rules, it is able to reproduce:
- emergence of the leading pacemaker site in the result of self-organization process for which the structure of intercellular connections is crucial.
- effects of aging on SAN, such as:
  - structural changes in cell-to-cell interactions due to collagen deposition
  - impairment of the expression of genes responsible for gap junctions
- Since the model is based on macroscopic properties of activation, so it cannot refer directly to cellular ion channels and currents (as reaction-diffusion approaches). However, this limitation, could be partially overcome by introducing parameters that indirectly reflect the most relevant aspects of channel dynamics.

All these phenomena can be efficiently simulated on commercial computers since cellular automata approach reduces the computational burden.
Let \( \varphi(t) : L \times L \rightarrow \{0, 1, 2, \ldots, T-1\} \)

evolves according to the rules

(I) If \( \varphi(t, I) = \sigma \geq 1 \) then \( \varphi(t+1, I) = (\sigma + 1) \mod T \)

(II) If \( \varphi(t, I) = 0 \) then

\( \varphi(t+1, I) = 1 \) if more than \( F \) neighbors are 1

\( \varphi(t+1, I) = 0 \) otherwise

Patterns achieved after long time evolution on a square lattice with Moore neighborhood:

- Pattern of stable periodic object (SPO)
- Pattern of fixation

*Patterns that live independently of other sites and subordinate all other sites*
The unique ability of a pacemaker cell is to generate action potential that is distinct from the surrounding atrial myocardium. Critical to pacemaker activity is the gradual depolarization of the cellular membrane until the threshold for the next action potential is reached.
Synchronization: the main collective phenomenon in biological systems

Concept of phase oscillator

By synchronization we mean adjustment of rhythms of oscillating objects due to their coupling.

sustained oscillating units:
  - active systems containing intrinsic sources of energy enabling oscillatory dependences
  - oscillations are stable to small perturbation

rhythms of oscillations are described by period $T$ or frequency $\omega = 2\pi / T$

adjustment of rhythms of interacting oscillators:
  - frequency entrainment
    $$K_f(t) = \frac{M}{N}$$
  - phase entrainment
    $$K_\Phi(t) = \left| \frac{1}{N} \sum_{l=1}^{N} e^{i\Phi_l(t)} \right|$$

By synchronization we mean adjustment of rhythms of oscillating objects due to their coupling.
Pulse coupled phase oscillators.

Peskin model of pulse coupled phase oscillators:

- free evolution
  Linear growth until the threshold then fire and reset

- interaction
  When fire then distribute $\varepsilon$ "energy" to all neighbors

Result: all oscillators fire at the same moment
Oscillatory timed automata

Automata states and clocks

A guard on an edge of an automaton is a constraint which restricts the transition represented by the edge.

Result: 3 oscillatory timed automata, interacting as in Peskin model, achieve the synchronization in a fixed number of time steps for a given $\varepsilon$. 
The pacemaker cellular automaton will be called stochastic if its clock $x$ jumps into the threshold value $\Theta(\sigma)$ with probability:

$$s = \left( \frac{x}{\Theta(\sigma)} \right)^{\xi}$$

for $\xi >> 1$.
Lesson 2 from physiology: pulse couplings between nodal cells

* moment when the impulse arrives

3-state oscillatory timed automaton $\sigma = 0, 1, 2$ with transitions:
- **firing**, **refractory**, **activity** guarded by clock $x$, $\Theta(\sigma)$

- if $x < a$ then $x := x + 1$
- if $x < a$ and impulse then $x := a$
- if $x < r$ then $x := x + 1$
- if $x < r$ and impulse then $x := \left\lceil \frac{x}{2} \right\rceil + 1$
## 3- state timed automaton:

\( \varphi(t, I) = (\sigma, x) \) with \( \sigma = 0,1,2 \) and \( x = 1,...,\theta(\sigma) \)

### Free

\[
\begin{align*}
\text{if } \varphi(t, I) &= (\sigma, x < \theta(\sigma)) \text{ then } \varphi(t + 1, I) = (\sigma, x + 1) \\
\text{if } \varphi(t, I) &= (\sigma, \theta(\sigma)) \text{ then } \varphi(t + 1, I) = (\sigma + 1,1)
\end{align*}
\]

### Coupling

\[
\begin{align*}
\text{if } [\varphi(t, I) &= (2, x) \land |\{\varphi(t, I') = (0, x), I' \in N(I)\}| > F] \\
\text{then } \varphi(t + 1, I) &= (0,1) \\
\text{if } [\varphi(t, I) &= (1, x) \land |\{\varphi(t, I') = (0, x), I' \in N(I)\}| > R] \\
\text{then } \varphi(t + 1, I) &= (1,\left\lfloor \frac{x}{2} \right\rfloor + 1)
\end{align*}
\]

Let the phase of PCA be

\[
\Phi(t, I, x) = x \delta_{0,\varphi(t,I,x)} + [x + \theta(0)] \delta_{1,\varphi(t,I,x)} + [x + \theta(0) + \theta(1)] \delta_{2,\varphi(t,I,x)}
\]

Thus, each time an automaton attains state 0 its phase is set to 1
Notice that for 2 interacting PCA with

\[ \theta(0) = 2, \quad \theta(1) = 4, \quad \theta(2) = 5 \]

We can expect that PCA will synchronize to the marching cells pattern.

Synchronization to marching cells.
Sinus node cells were sparsely interconnected compared to the extent of interconnections observed in other tissues.

A typical sinus node cell was connected to only 4.8 +/- 0.7 neighbors compared with 11.3 +/- 2.2 cells in the left ventricle.

The aggregate gap junction profile length per unit myocyte area was 26.5 times greater in the left ventricle than in the sinus node.
Starting from a square lattice an edge between neighboring cells (Moore neighborhood) is created with probability \( d \) so \( \langle n \rangle = 8d \)

\[
p_{\text{break}}(I, I') = \frac{p}{\text{deg}(I')}
\]

\[
p_{\text{connect}}(I, I'') = \frac{1}{\text{deg}(I') - 1}
\]

1 MC step means application of rewiring to each edge twice. Free boundary conditions are assumed.
Example of the network structure if the rewiring algorithm is applied 100 times to each connection. The red edges describe actual neighbors of the exemplary cell of densely connected cells (vertex degree is 12). Connections of other cells - neighbors from the Moore neighborhood are shown also.
Enhanced heterogeneity of intercellular connections

Preferential wrinkled 2D square stochastic network

![Graph showing vertex degree distribution: \( <d> = 4.5 \)](image)

- **no rewirings**
- **\( p=0.01 \) (100)**
- **\( p=0.01 \) (500)**

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Impulse coupled PCA network:

*in critical regime:*

\[ <n> = 4.8 \] mean number of neighbors

*Excitable medium couplings:*

- \( F > 0 \), i.e., a neighbor in 0 switches the clock of PCA in 2.
- \( R > 1 \), i.e., more than one neighbor in 0 switches the clock of PCA in 1.

*Deterministic evolution on a homogeneous network*

*Stochastic evolution on a heterogeneous network*
Impulse coupled PCA network:

in critical regime:

\[ <n> = 4.8 \] mean number of neighbors

Pacemaker couplings:

- \( F > 1 \), i.e., more than a neighbor in 0 switches the clock of PCA in 2.
- \( R > 2 \), i.e., more than two neighbors in 0 switches the clock of PCA in 1.

Deterministic evolution on a homogeneous network

Stochastic evolution on a heterogeneous network
When susceptibility of a cell for couplings in *refractory* state is less than susceptibility of the cell in *activity* state then expanding periodic patterns occur.

When susceptibility of a cell in *refractory* state is greater than susceptibility of the cell in *activity* state then collapsing periodic patterns can emerge.
Limit states for pulse coupled PCA: deterministic & homo case

- **collaps**
- **expand**
- **march & collaps**
- **march & expand**
- **march**

### Graphs

- **F > 0, R > 0**
- **F > 0, R > 1**
- **F > 1, R > 0**
- **F > 1, R > 2**

**Mean number of neighbors**

- **2, 3, 4, 5, 6, 7, 8**

**Probability to occur**

- **0.0, 0.2, 0.4, 0.6, 0.8, 1.0**

- **pulsing state**
- **random clusters**
Case:

low density of intercellular connections and $F >> R$:

homogeneous lattice

network after 100 MC
Results: dominating period and size of synchronized cells cluster

Deterministic PCA Homogeneous network

Stochastic PCA Heterogeneous network

Sensitivity for shortening period

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Results: dominating period and size of synchronized cells cluster

\[ \kappa_f(t) = \frac{M}{N} \]
Results: distribution of oscillations

Case:
- Lattice 100x100
- of stochastic PCA (f=9, r=11, a=19) with $\xi=10$
- free boundary conditions.
- $<n>$ neighbors of the Moore neighborhood
- rewired 50MC with $p=0.01$
Results: patterns of synchronization by Kuramoto order parameter

- Deterministic rule on homogeneous network
- Stochastic rule on wrinkled network (p=0.01, J=50)
- Stochastic rule on wrinkled network (p=0.01, J=100)
- Stochastic rule (ξ=10) on homogeneous network

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Makowiec, in G. Mauri et al. (Eds.): UCNC 2013, LNCS 7956, 138 (2013)
Thank you