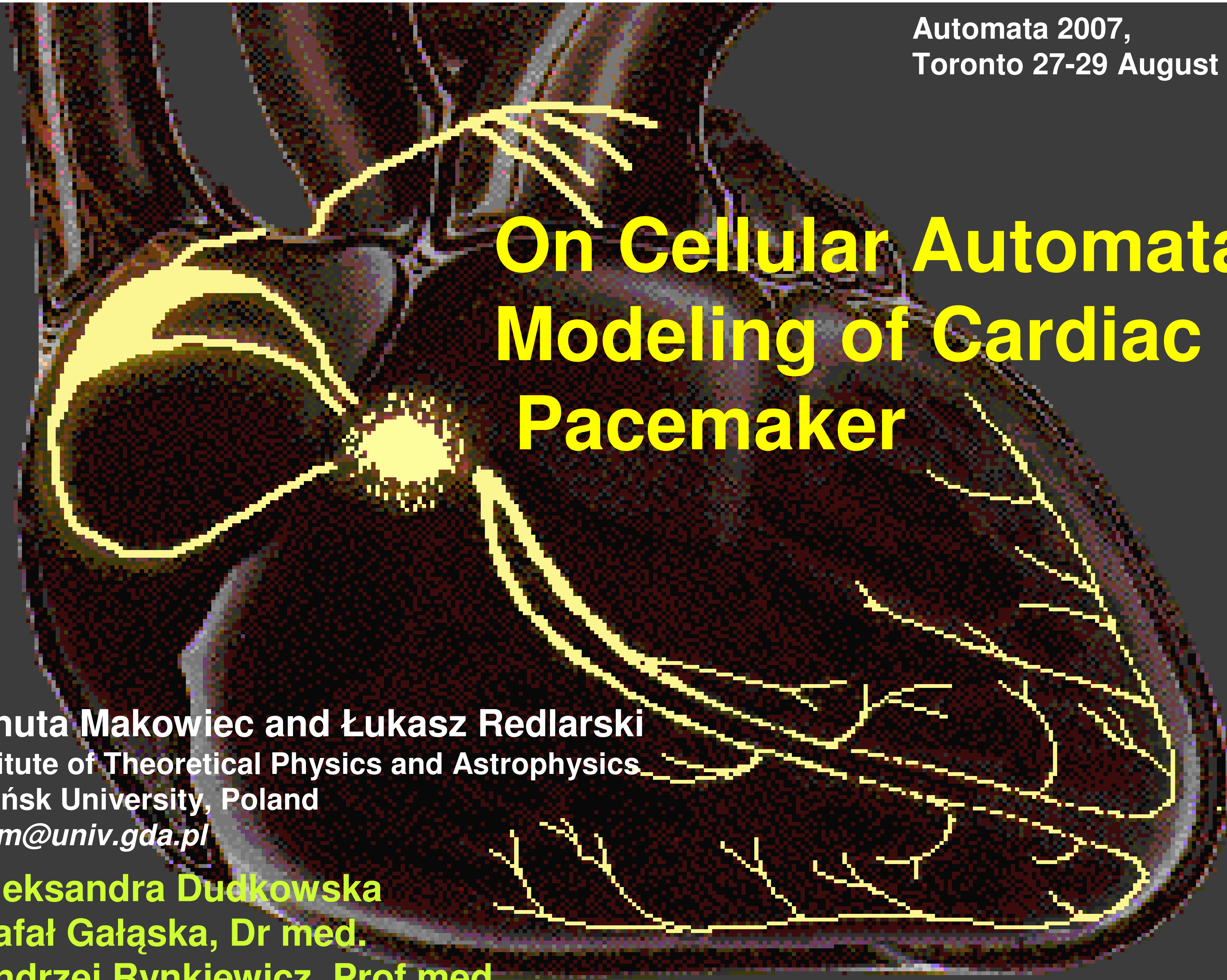
Automata 2007,
Toronto 27-29 August



On Cellular Automata Modeling of Cardiac Pacemaker

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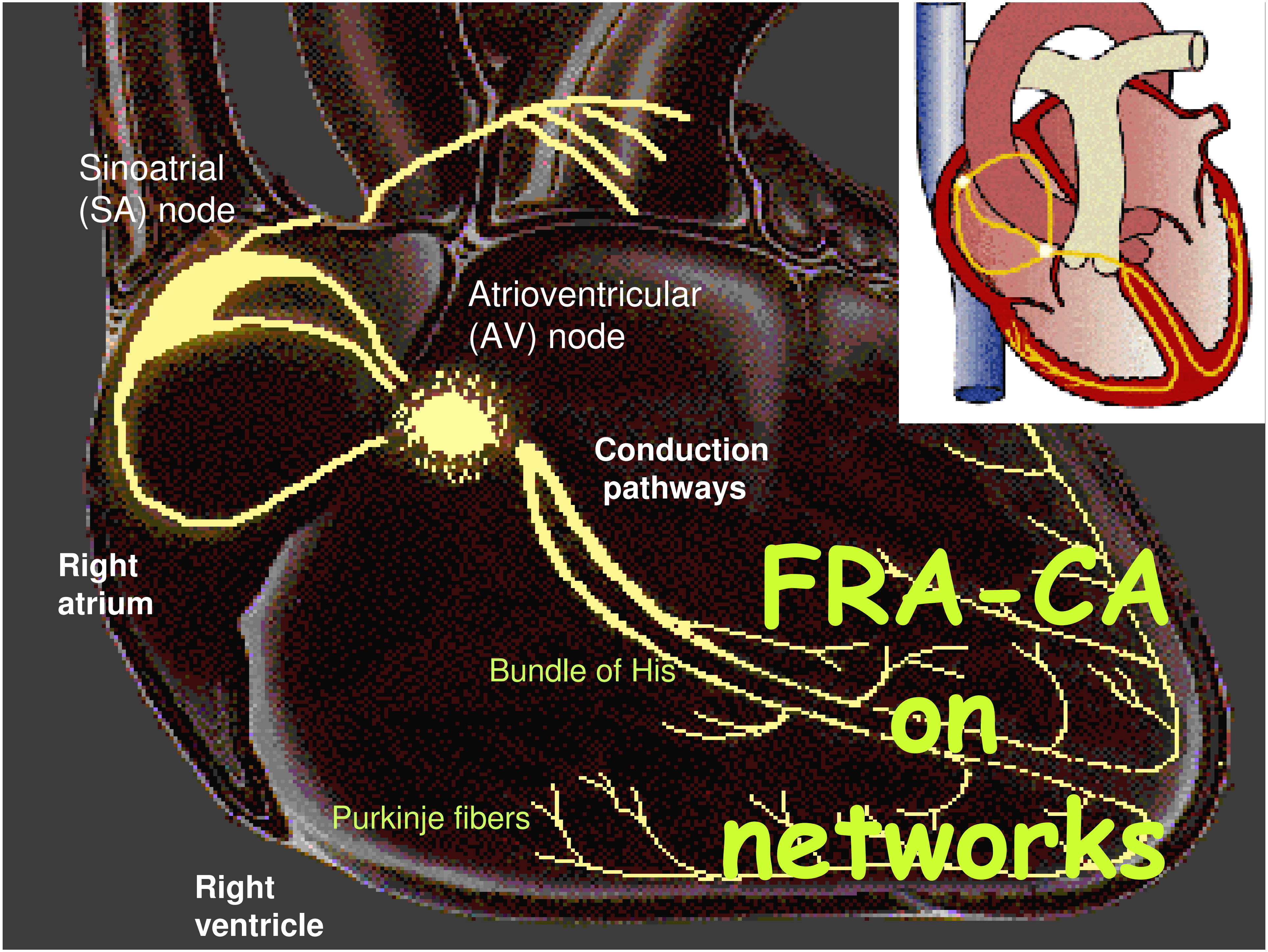
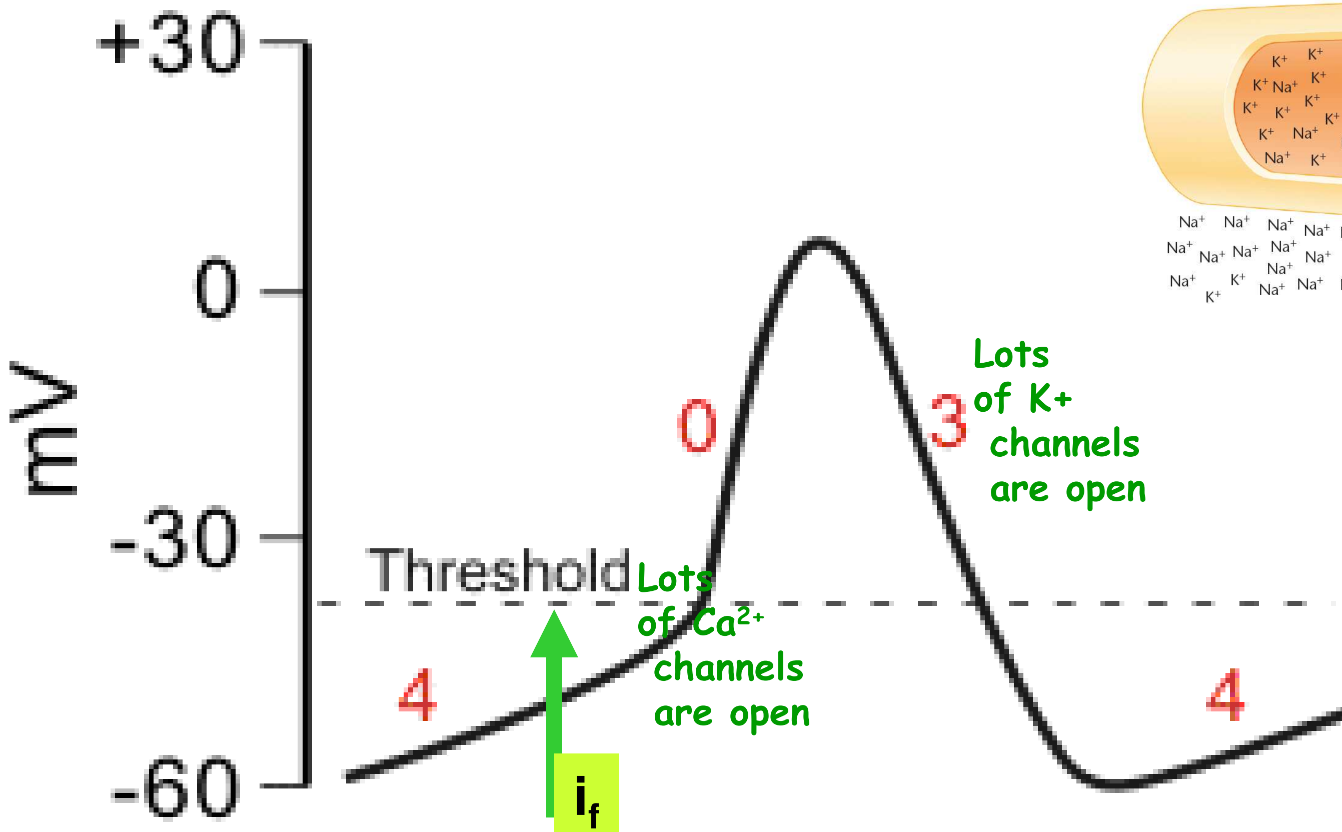
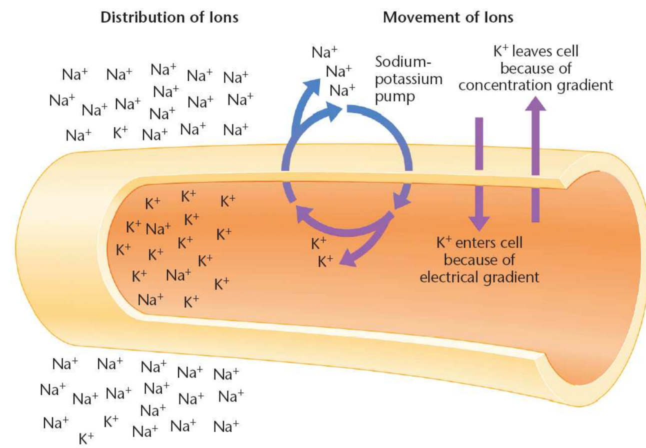


Sinoatrial
(SA) node
Atrioventricular
(AV) node
Conduction
pathways
Right
atrium
Bundle of His
Purkinje fibers
Right
ventricle
FRA-CA
on
networks

SA Node

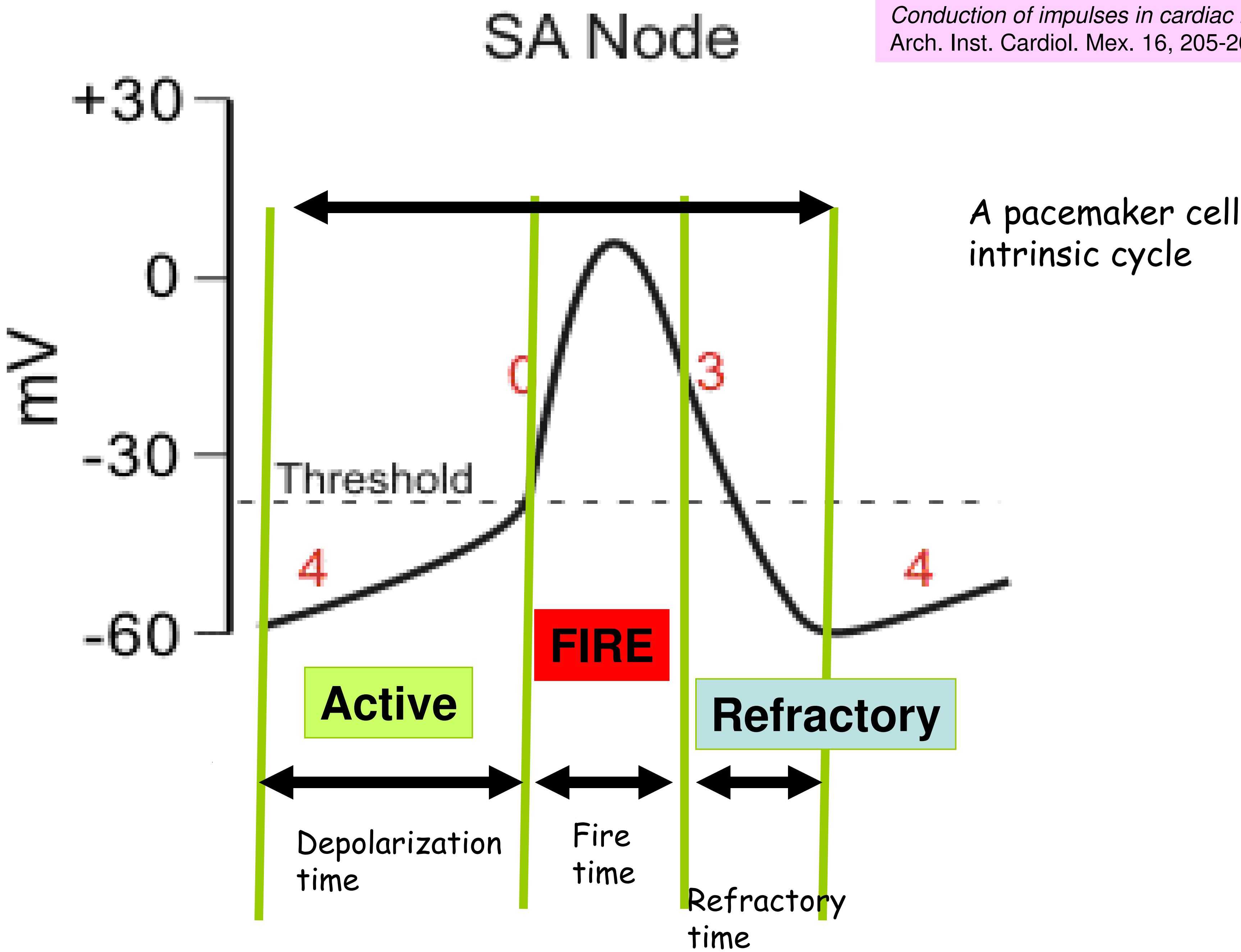


+30
0
-30
-60
mV
Threshold
4
0
3
4
Lots of Ca^{2+} channels are open
Lots of K+ channels are open
i_f



Distribution of Ions
Movement of Ions
Sodium-potassium pump
K^+ leaves cell because of concentration gradient
K^+ enters cell because of electrical gradient

WIENER, N., and ROSENBLUETH, A.
Conduction of impulses in cardiac muscle.
Arch. Inst. Cardiol. Mex. 16, 205-265(1946).



Assumptions:

Wiener Rosenblueth idea

A cell stays in one of the three states: F, R, A

Cellular automata with intrinsic transition rule

A cell remembers the unique sequence of states:

……… F ⟶ R ⟶ A ⟶ F…….

Greenberg-Hastings cellular automaton

cellular automata with memory

A cell remembers how long it stays in a present state

FRA - Cellular Automaton:

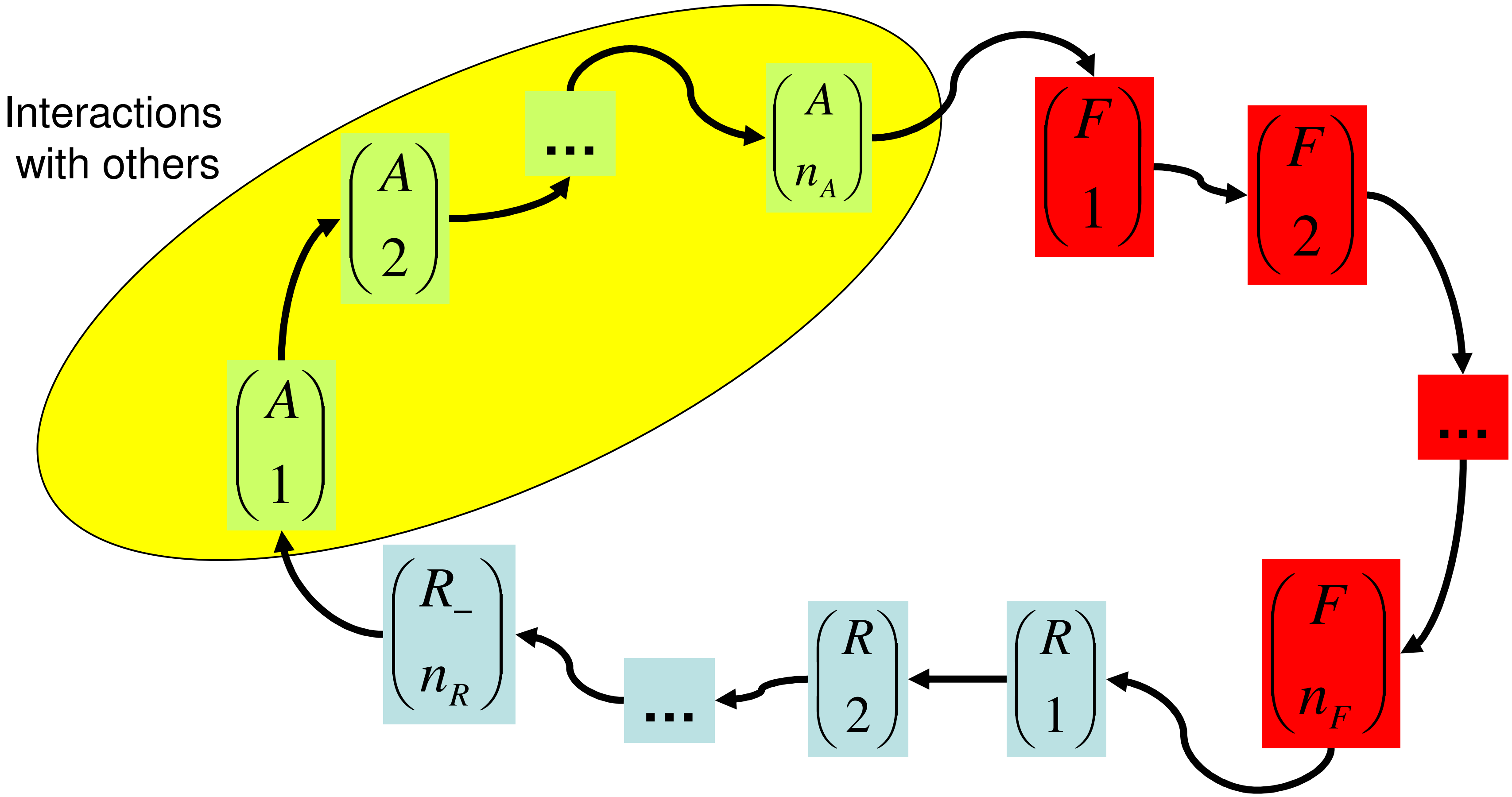
a cellular automaton state space:

$$\Sigma = \left\{ \left\{ \begin{pmatrix} F \\ f \end{pmatrix} \right\}_{f=1,2,\ldots,n_F} , \left\{ \begin{pmatrix} R \\ r \end{pmatrix} \right\}_{r=1,2,\ldots,n_R} , \left\{ \begin{pmatrix} A \\ a \end{pmatrix} \right\}_{a=1,2,\ldots,n_A} \right\}$$

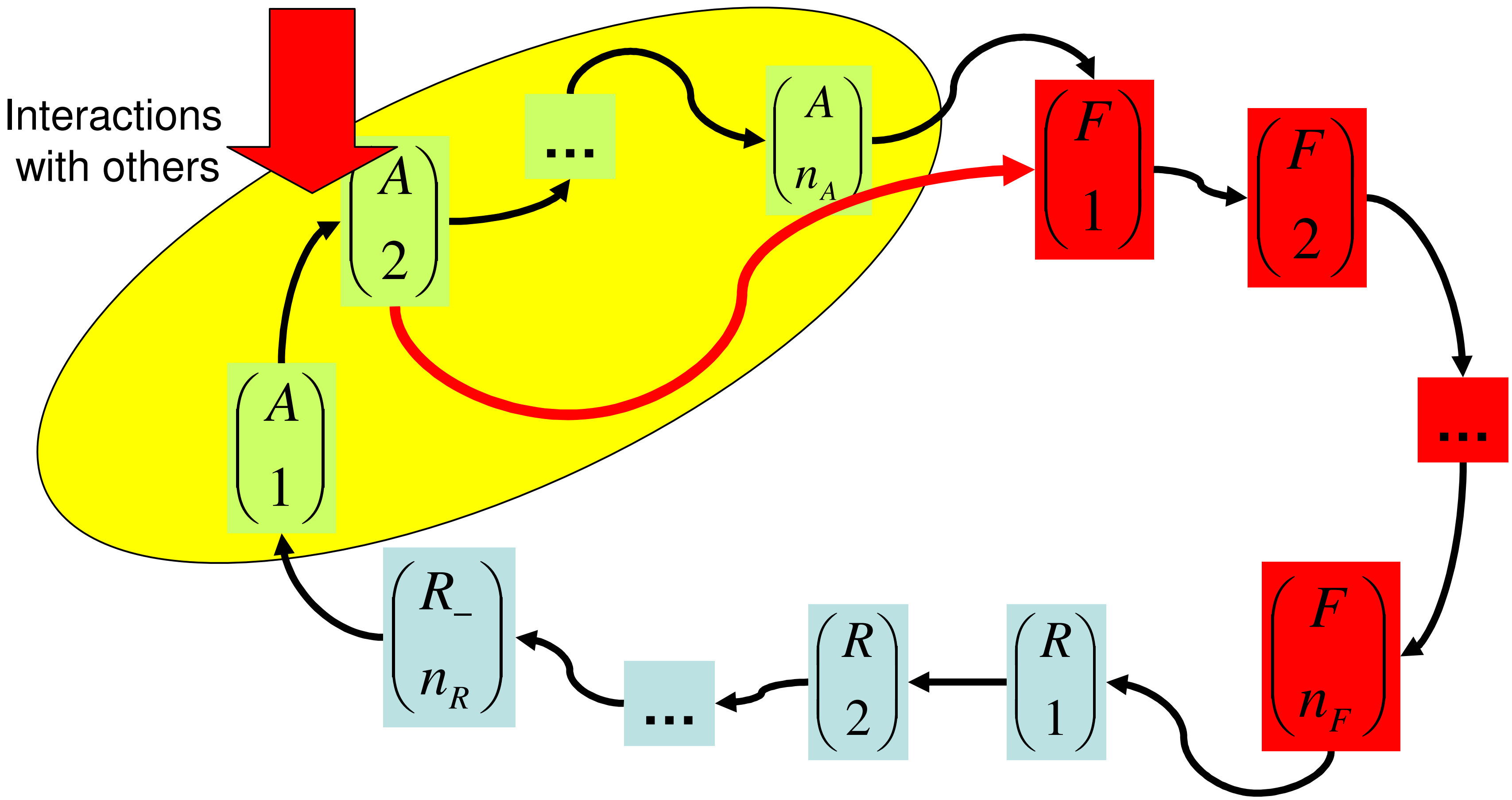
the intrinsic transition rule R :

$$\text{for} \quad S \in \{\mathrm{F}, \mathrm{R}, \mathrm{A}\} \text{ with a fixed order of states} : \mathrm{F} \rightarrow \mathrm{R} \rightarrow \mathrm{A}$$

$$\mathrm{R}\begin{pmatrix} S \\ k \end{pmatrix} = \begin{cases} \begin{pmatrix} \text{next } S \\ 1 \end{pmatrix} & \text{for} \quad k = n_S \\ \begin{pmatrix} S \\ k+1 \end{pmatrix} & \text{otherwise} \end{cases}$$



Interactions with others
$\binom{A}{1}$
$\binom{A}{2}$
...
$\binom{A}{n_A}$
$\binom{F}{1}$
$\binom{F}{2}$
...
$\binom{F}{n_F}$
$\binom{R}{1}$
$\binom{R}{2}$
...
$\binom{R\_}{n_R}$



Interactions with others
$\binom{A}{1}$
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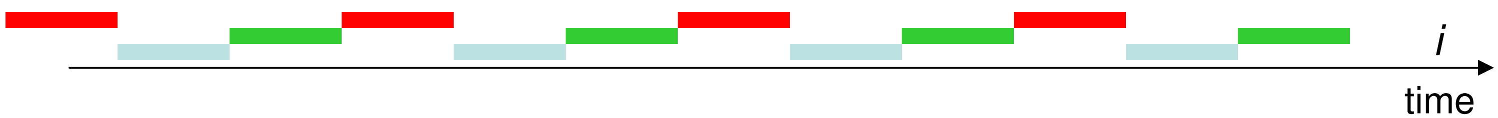
...
$\binom{A}{n_A}$
$\binom{F}{1}$
$\binom{F}{2}$
...
$\binom{F}{n_F}$
$\binom{R}{1}$
$\binom{R}{2}$
...
$\binom{R\_}{n_R}$

FRA cellular automaton
with $n_F=n_R=n_A=n$



Let $\varphi(i)$ - a ***phase*** follows the intrinsic cycle of a FRA -CA

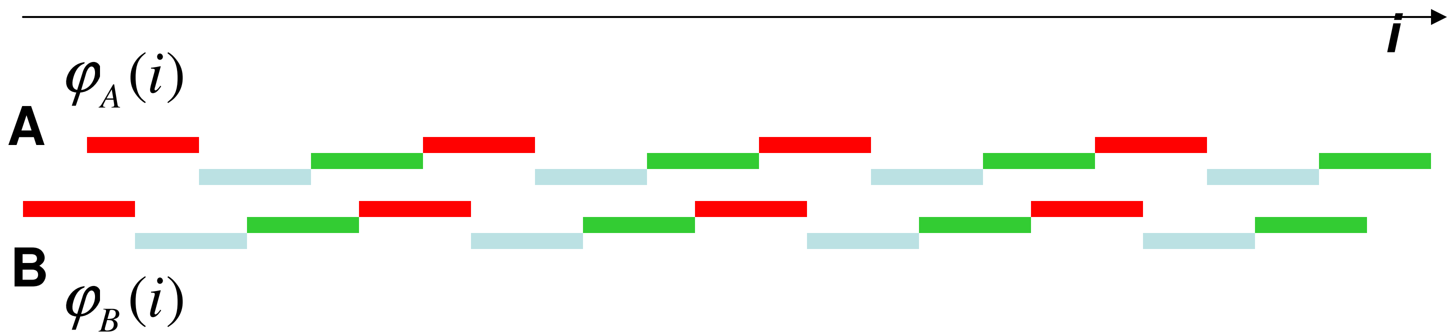
$$0 \le \varphi(i) < 3n \quad \text{for} \quad i = 0,1,2....$$

$$\varphi(i) = 0 \quad \text{for} \quad \begin{pmatrix} S \\ k \end{pmatrix}(i) = \begin{pmatrix} F \\ 1 \end{pmatrix}$$

$$\varphi(i+1) = \varphi(i) + 1 \quad \text{otherwise}$$

$\varphi(i)$ uniquely determines the FRA-CA state

Two FRA cellular automata with $n_F = n_R = n_A = n$



$$\Delta\varphi_{A,B}(i) = \varphi_B(i) - \varphi_A(i)$$

$$\varphi_B(0) > \varphi_A(0)$$

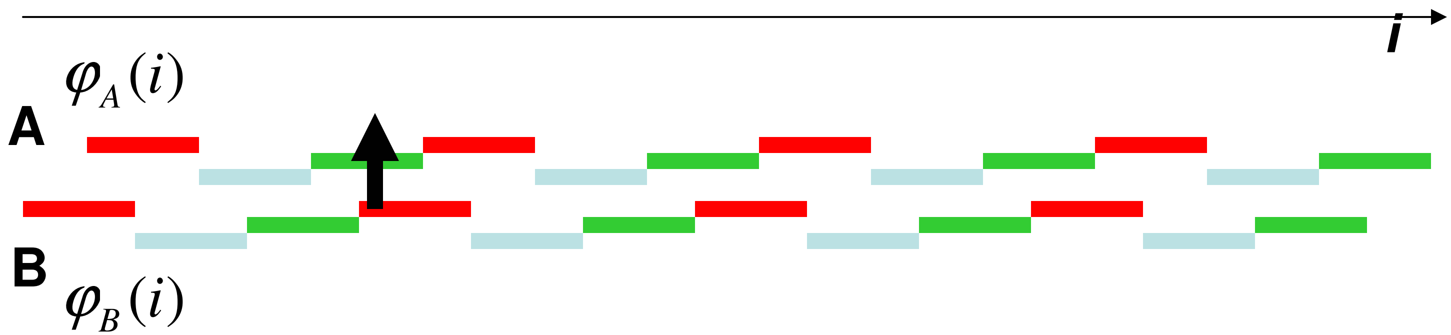
$$0 < \Delta\varphi_{A,B}(0) < n$$

$$n < \Delta\varphi_{A,B}(0) < 2n$$

$$2n < \Delta\varphi_{A,B}(0) < 3n$$

$$\Delta\varphi_{A,B}(0) = 0, n, 2n$$

Two FRA cellular automata with $n_F = n_R = n_A = n$



$$\Delta\varphi_{A,B}(i) = \varphi_B(i) - \varphi_A(i)$$

cases :

$$0 < \Delta\varphi_{A,B}(0) < n$$

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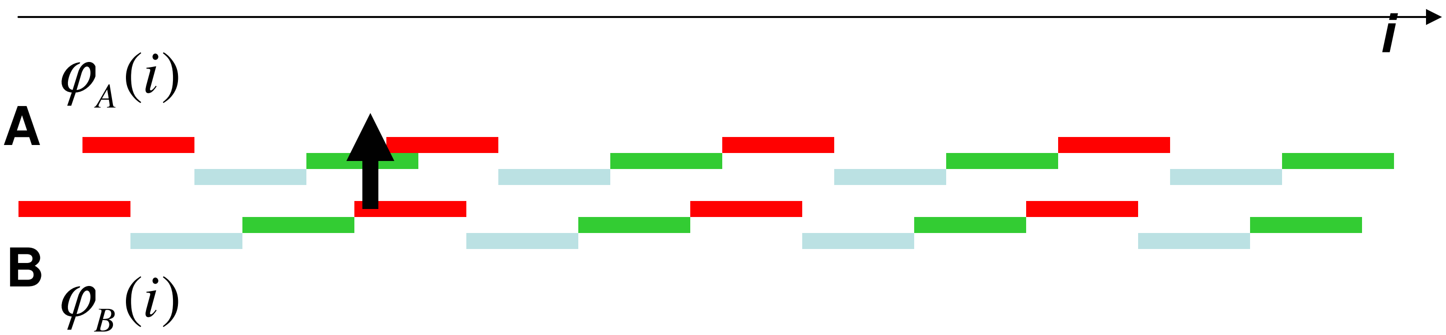

$$\Delta\varphi_{A,B}(i) = \varphi_B(i) - \varphi_A(i)$$

$cases:$

$$0 < \Delta\varphi_{A,B}(0) < n$$

$$|\Delta\varphi_{A,B}(i)| = 1$$

$$n < \Delta\varphi_{A,B}(0) < 2n$$

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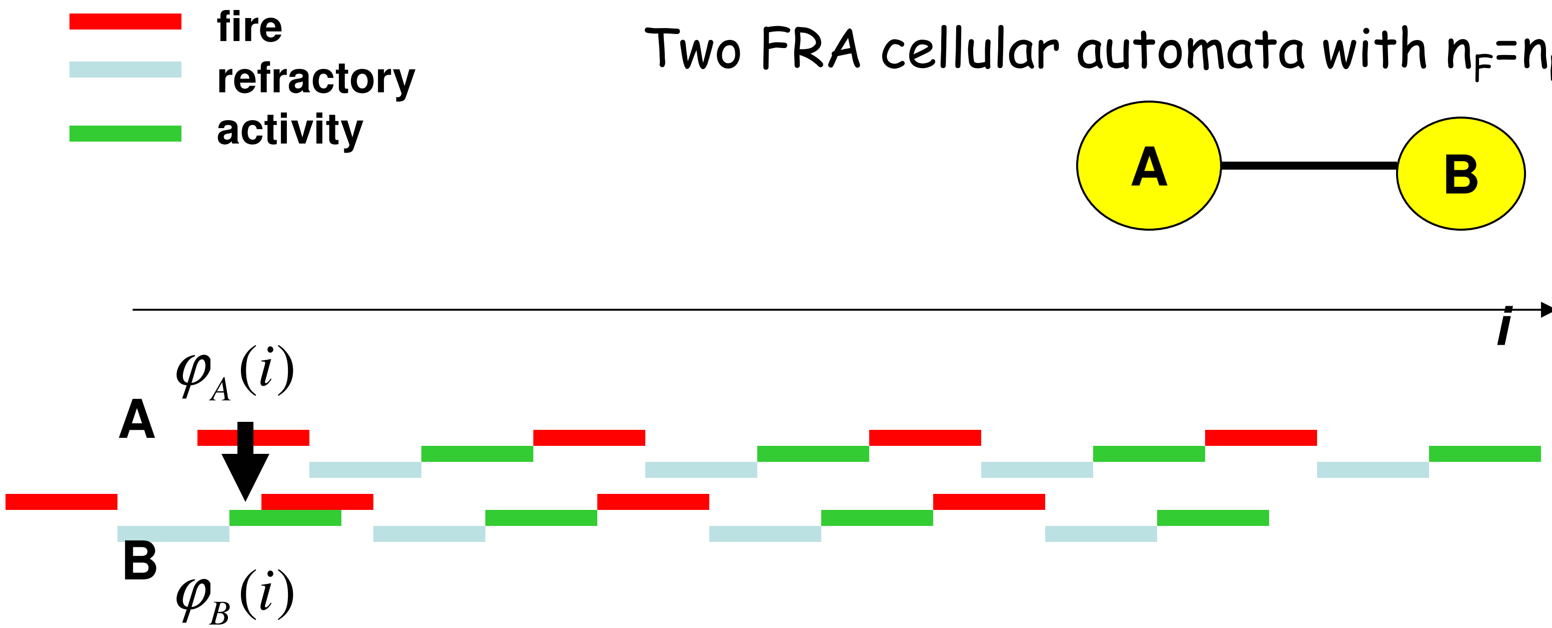

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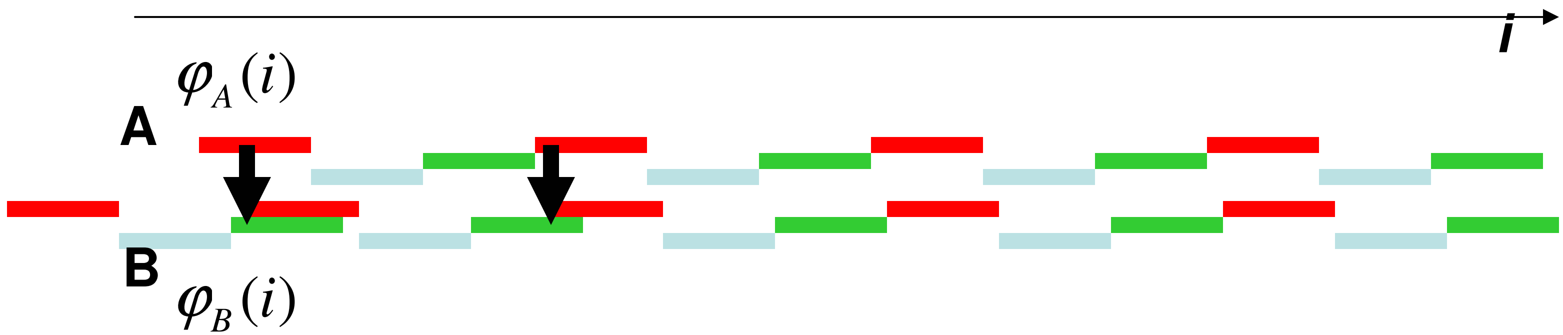

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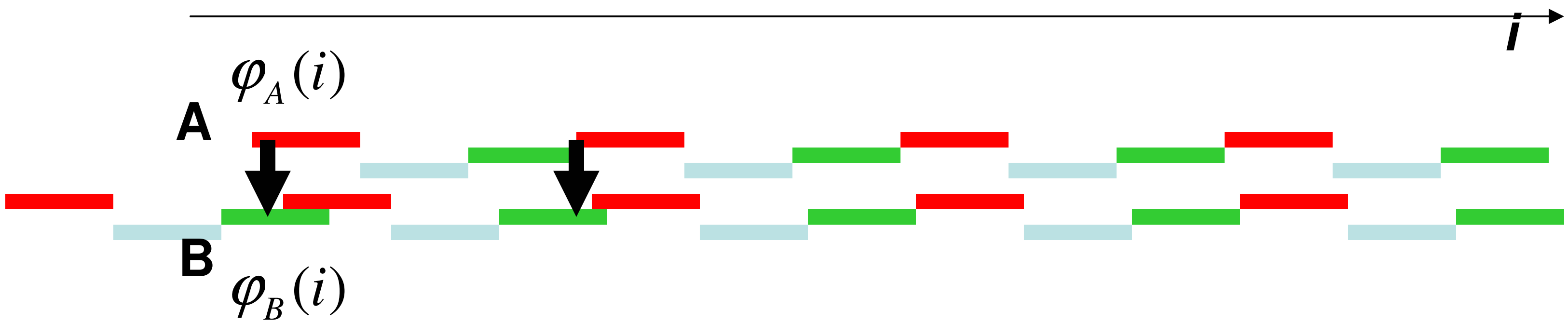

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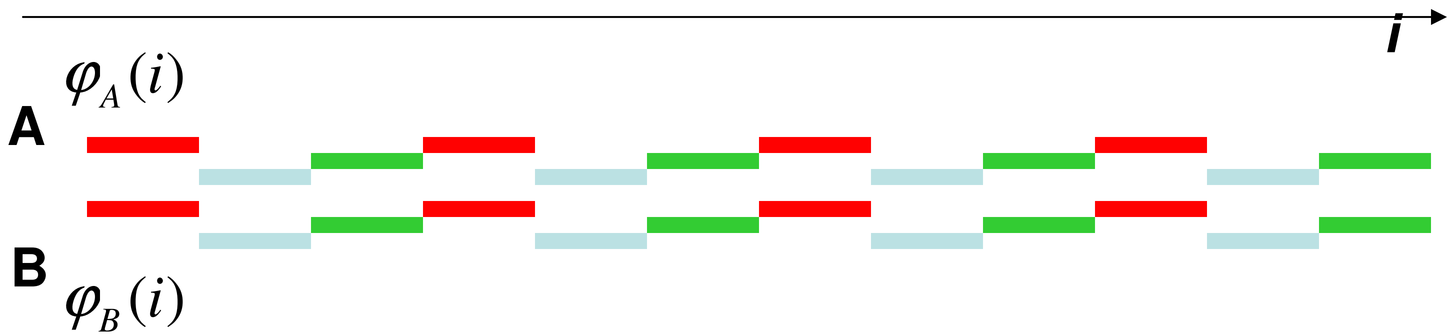
Two FRA cellular automata with $n_F = n_R = n_A = n$



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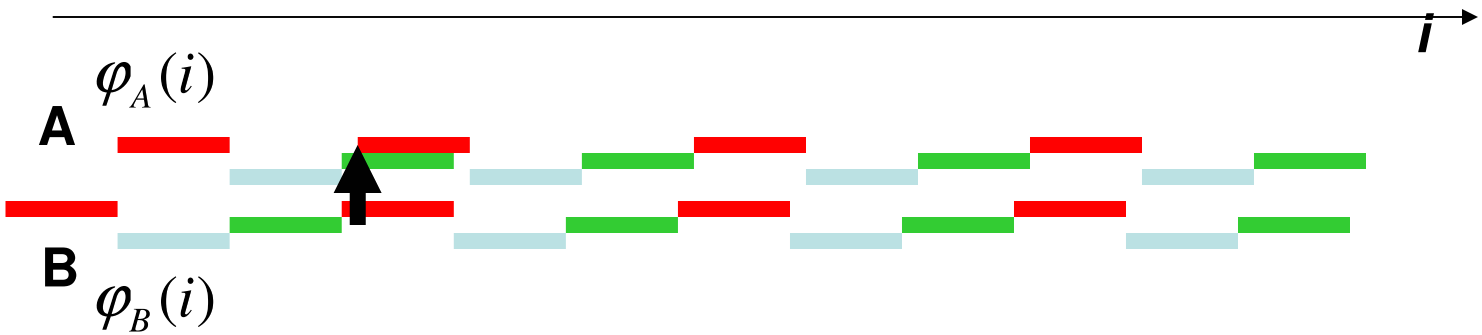
$$\Delta\varphi_{A,B}(0) = 0, n, 2n$$

$$\Delta\varphi_{A,B}(i) = 0$$

Two FRA cellular automata with $n_F=n_R=n_A=n$



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cases :

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$$2n < \Delta\varphi_{A,B}(0) < 3n$$

$$\Delta\varphi_{A,B}(0) = 0, n, 2n$$

$$|\Delta\varphi_{A,B}(i)| = 0,1$$

Fact:

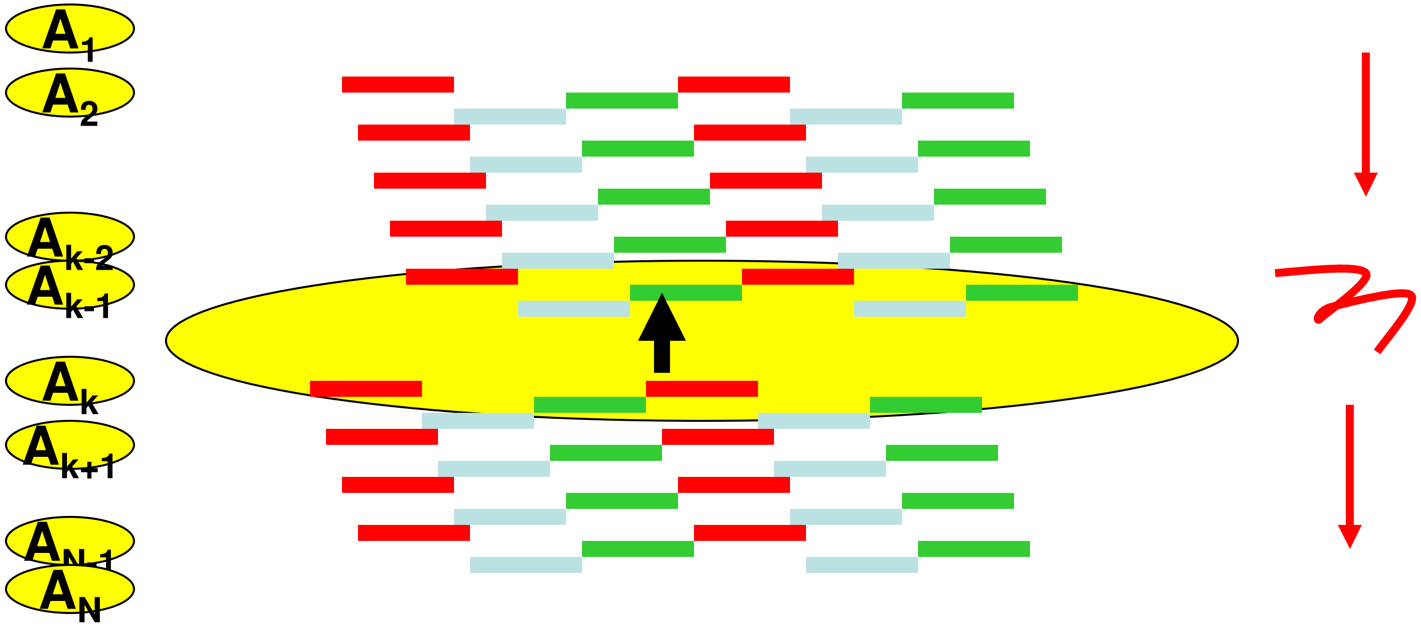
For the line of N FRA-CA : $(A_1, A_2, ..., A_N)$ with $n_F = n_R = n_A = n$ and open boundary condition, the only stable solution has the following property:

$$\Delta\varphi_{A_k, A_{k+1}}(i) = \pm 1, 0 \quad \text{for} \qquad k = 1, 2, ..., N-1$$

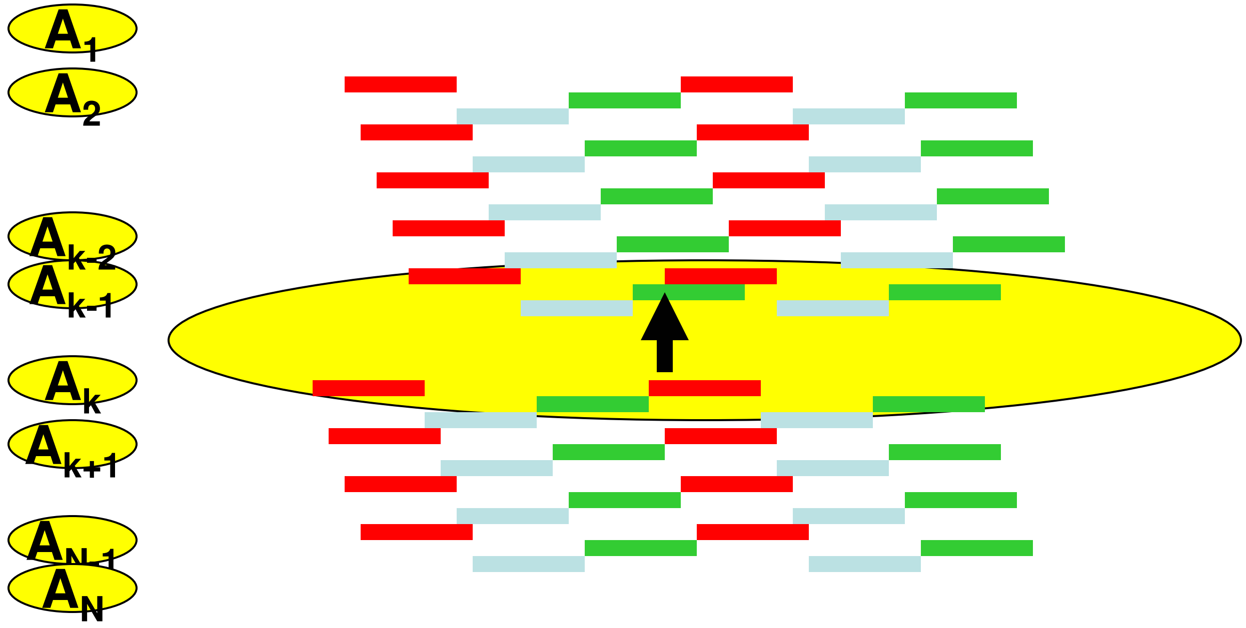
Corollary:

For the line of N FRA-CA : $(A_1, A_2, ..., A_N)$ with $n_F = n_R = n_A = n$ and open boundary condition, the only stable solution is periodic with the period length $T = n_F + n_R + n_A = 3n$

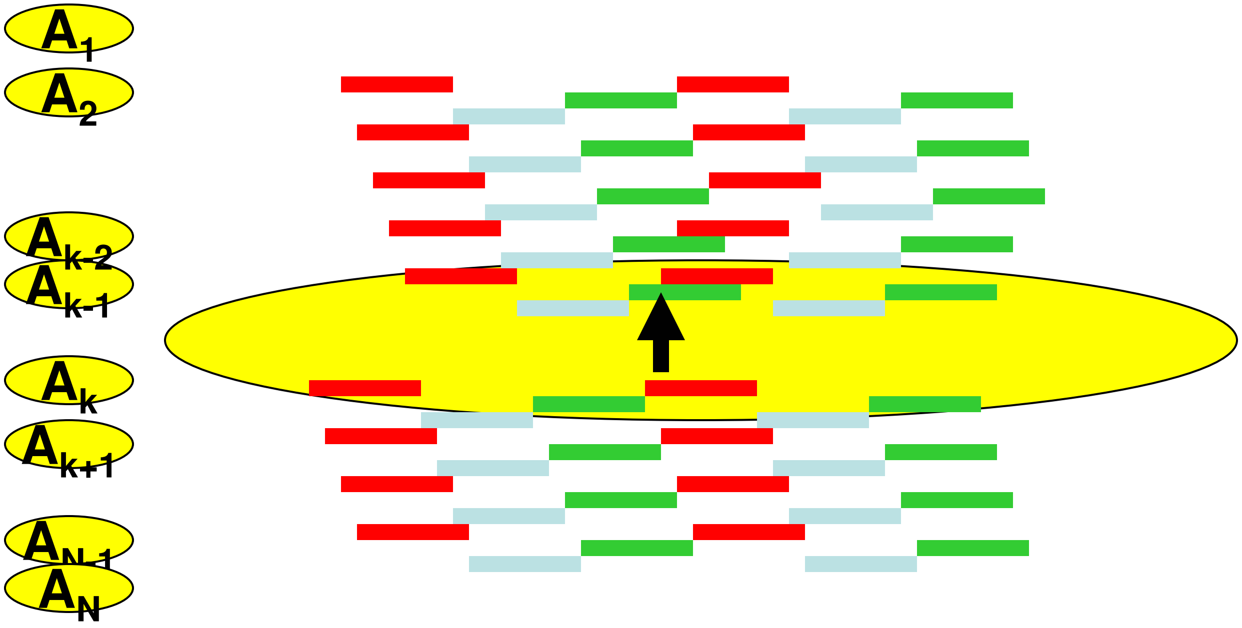
Draft of the proof:



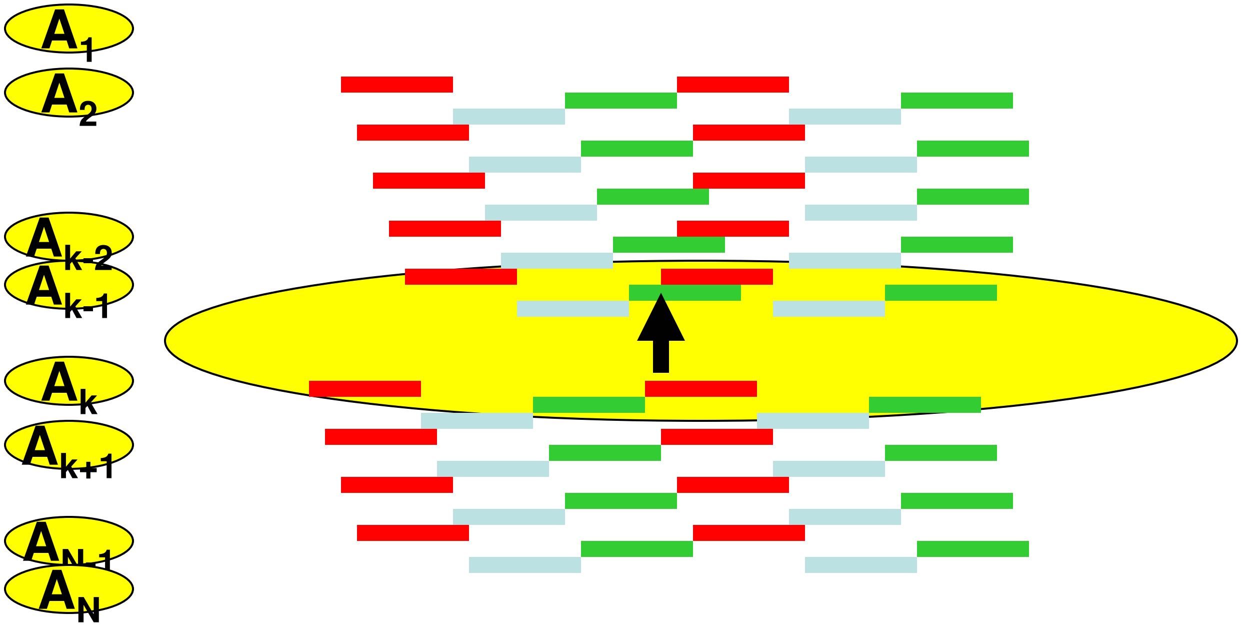
Draft of the proof:

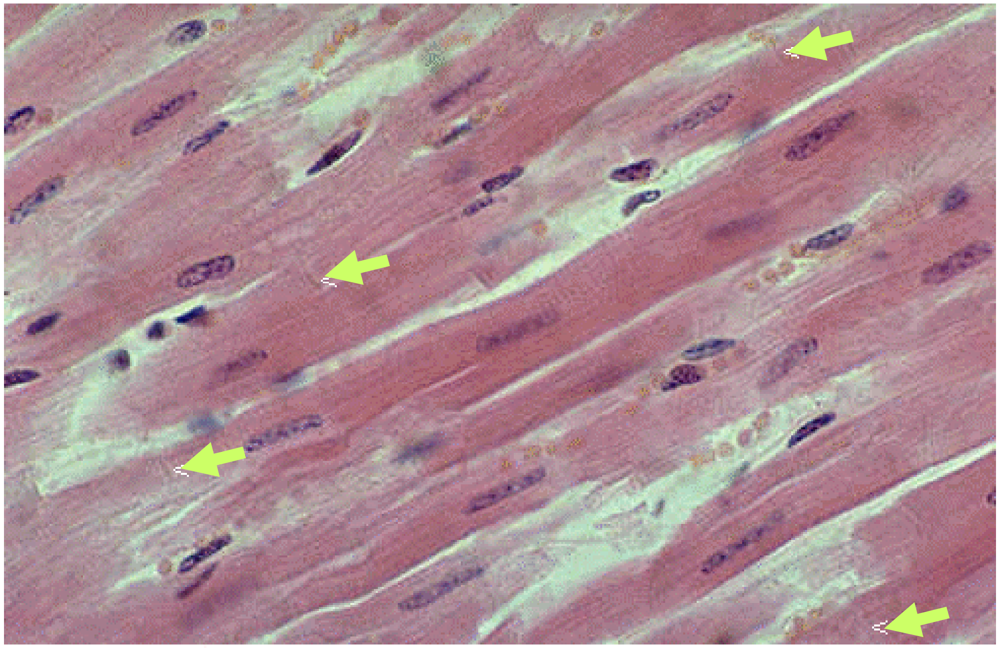


Draft of the proof:



Draft of the proof:

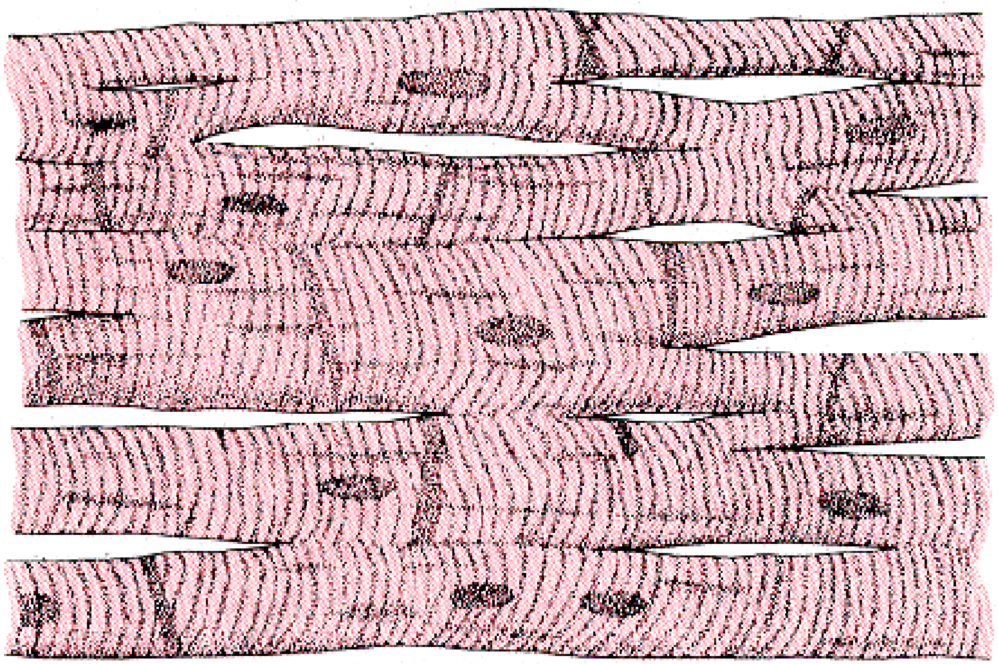




Cardiac muscle :

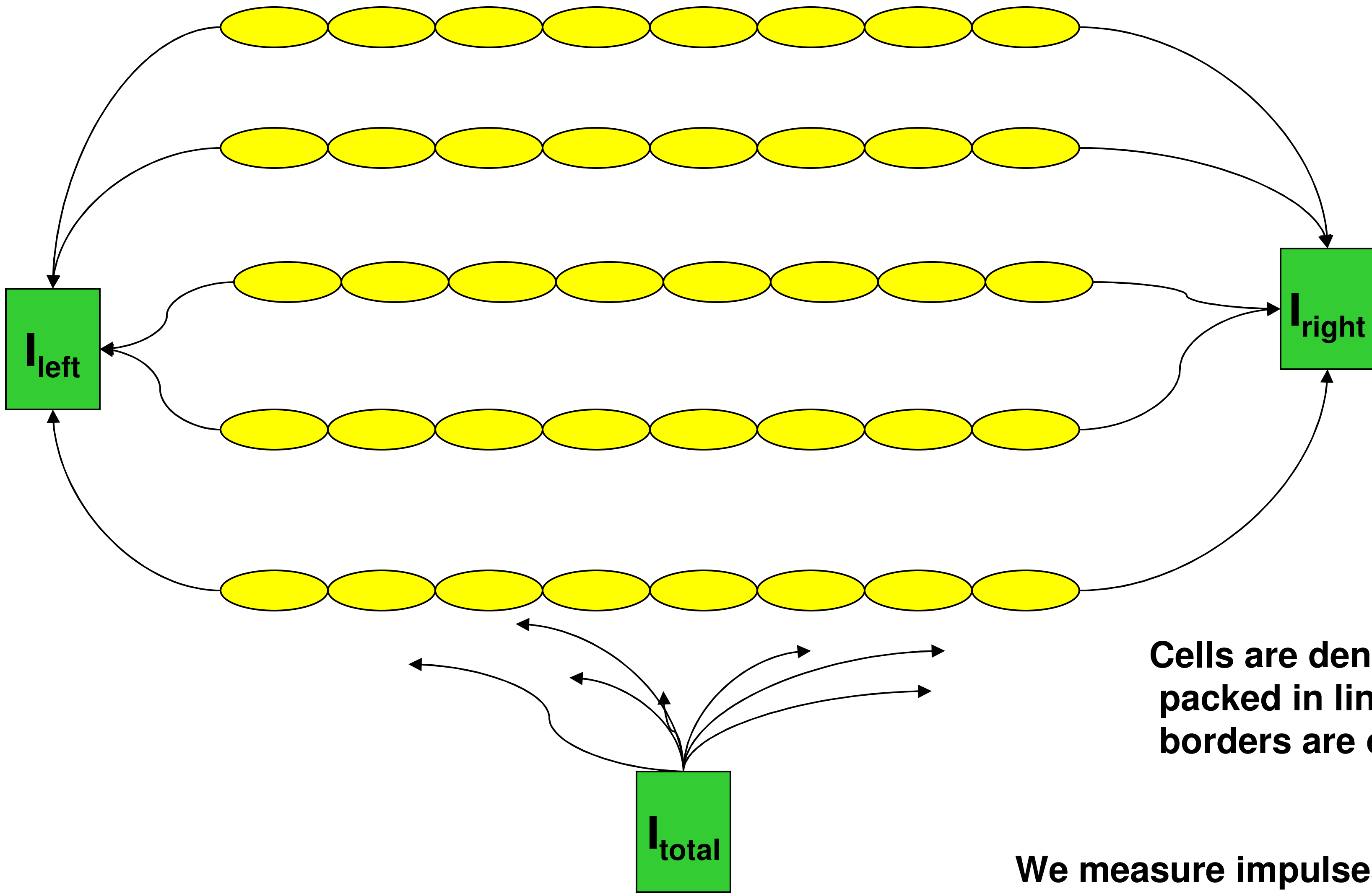
myocytes : 10-20 μm wide
50-100 μm long

Adapted from
http://www.vetmed.wsu.edu/VAn308/cardiac.htm



SA structure,
adapted from Guyton and Hall, 1996, Fig. 9-2,

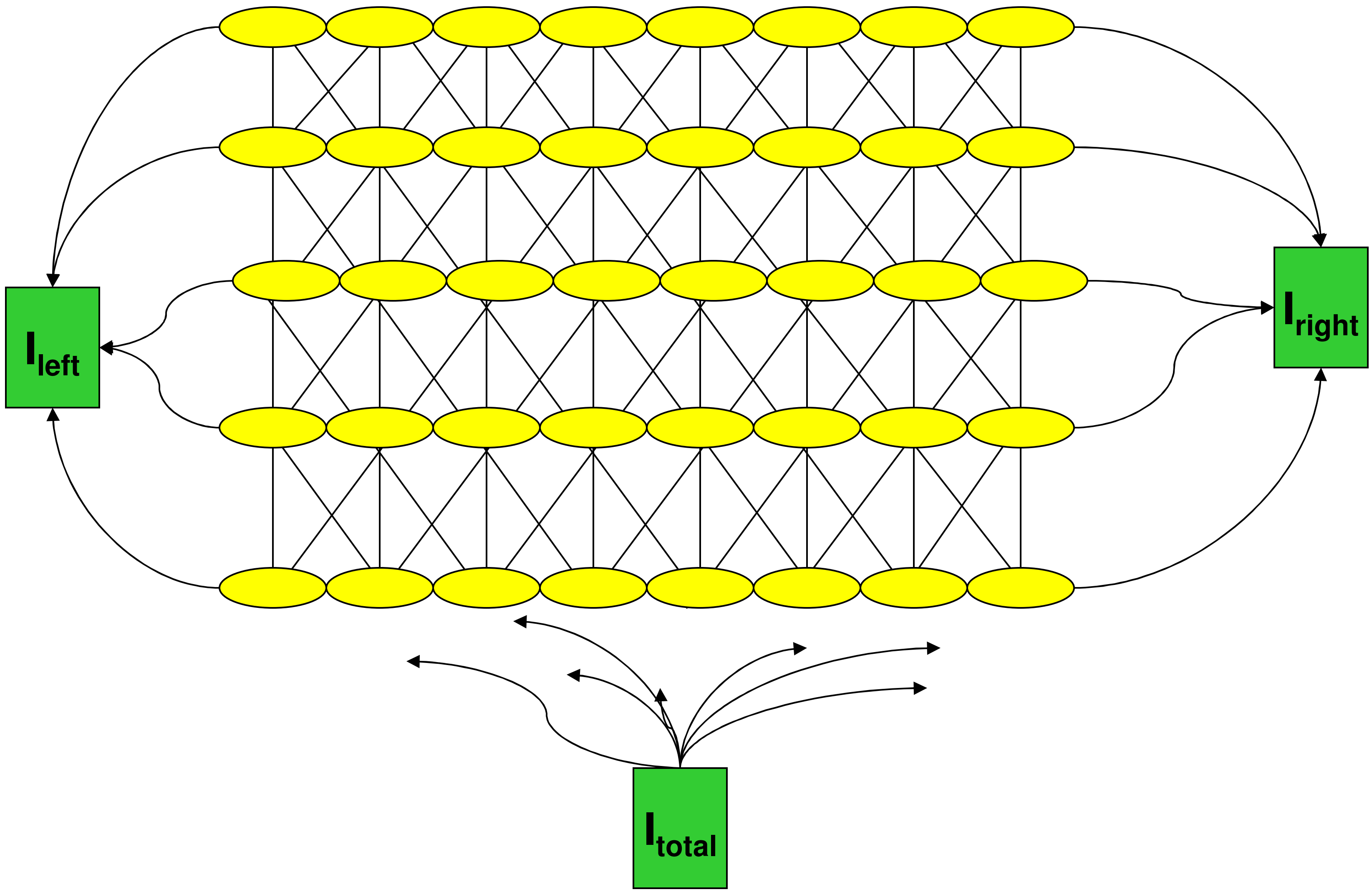
Network of FRA-CA



Cells are densely packed in lines, borders are open

We measure impulses of left, right, total

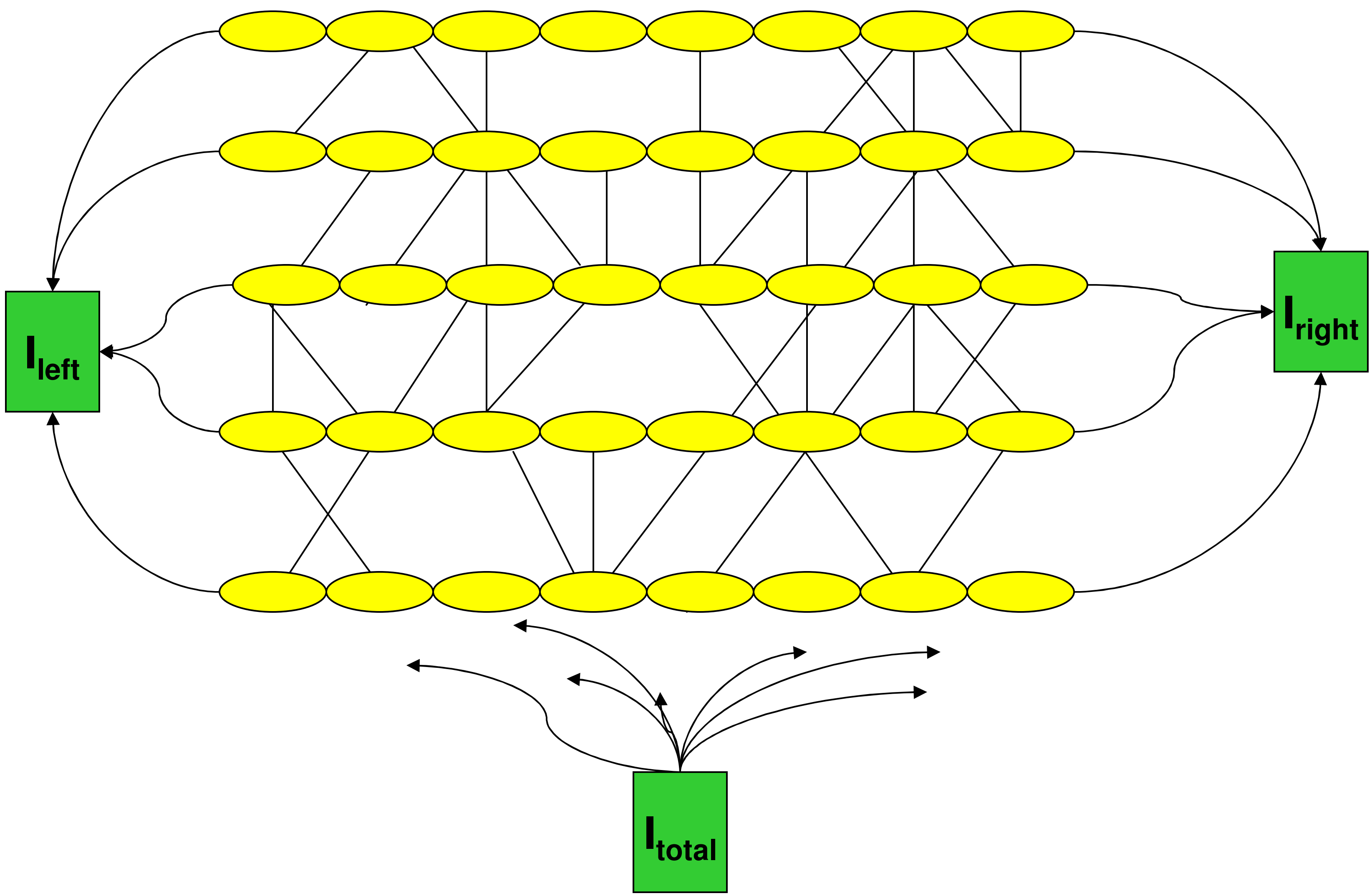
topology



topology

diluting= 0,…,1

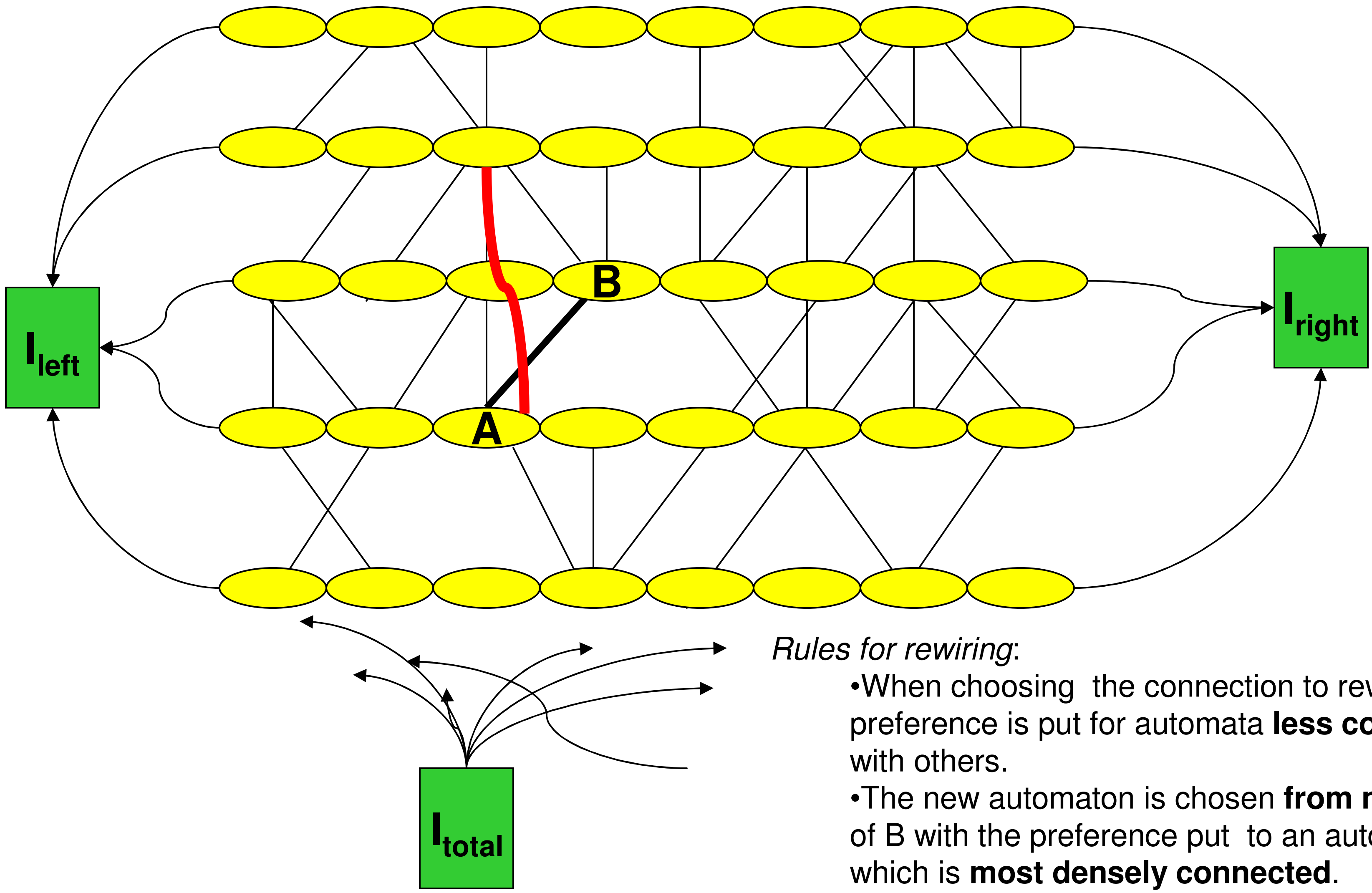
Edges are deleted with probability *diluting*



topology

diluting = 0,…,1 and rewiring = 0,…,1

Edges are deleted with probability *diluting*



Rules for rewiring:

- When choosing the connection to rewiring a preference is put for automata **less connected** with others.
- The new automaton is chosen **from neighbors** of B with the preference put to an automaton which is **most densely connected**.
- We **cannot rewire** the edge connecting to the left or right neighbor

FRA-CA **model parameters:**

n_F
n_R
n_A

FRA-CA intrinsic dynamics parameters

diluting
rewiring

topology parameters

T_F

interaction threshold

$$|\text{neighbors} \quad \text{in} \quad \textit{FIRE} \; \text{state}| > T_F$$

FRA-CA **model parameters:**

n_F
n_R
n_A

FRA-CA intrinsic dynamics parameters

diluting
rewiring

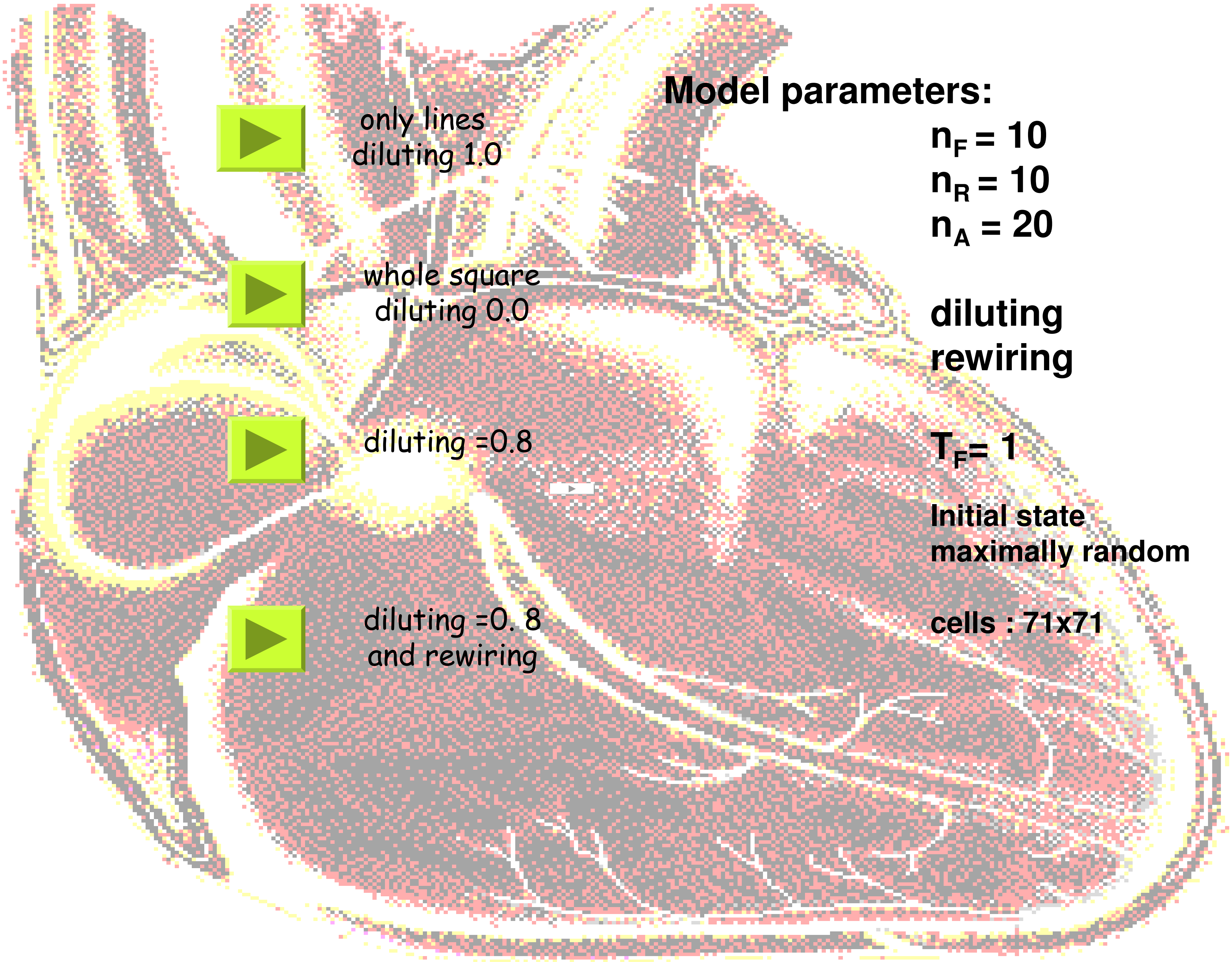
topology parameters

T_F

interaction threshold

$$| \text{neighbors} \quad \text{in} \quad FIRE \ \text{state} | > T_F$$

BUT NEIGHBORS FROM THE SAME LINE ARE DOUBLED



only lines
diluting 1.0

whole square
diluting 0.0

diluting =0.8

diluting =0. 8
and rewiring

Model parameters:

$n_F = 10$
$n_R = 10$
$n_A = 20$

diluting
rewiring

$T_F = 1$

Initial state maximally random

cells : 71x71

What is missed?

- Heterogeneity of cells

- Regulation by autonomous nervous system