Activation of B-cells by spatial reorganization

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Short abstract **– We propose a reaction-diffusion model of kinase-receptors mutual activation to show that clusterization of a tiny fraction of B-cell receptors can lead to its activation. Likewise, the displacement of the B-cell nucleus toward the cell membrane can also induce its activation. Kinases are first activated locally then the activation propagates as a travelling wave.**

I. MODEL

We assume a mutual interaction of membrane receptors with cytosolic kinases, in which after binding extracellular ligands, membrane receptors are phosphorylated by the kinases. In turn, active receptors activate kinase molecules. This positive feedback leads to bistability and allows for 'yes' or 'no' responses to signal. The kinases, activated at the membrane, are dephosphorylated in the cytoplasm by limited number phosphatases, what creates a gradient of their activity. The kinase inactivation is described by a Michaelis-Menten type of kinetics. The cytoplasm occupies the region between two spheres of radii $R_1 < R_2$. B-cells, when inactive have very thin cytoplasm and thus we consider the ratios $R_1/R_2 \geq 0.9$. Let $K(t, r, \theta)$ and $Q(t, \theta)$ denote, respectively, the concentrations of the active kinases and the surface concentration of the active receptors, $P(\theta)$ is the total surface concentration of receptors. In appropriate non-dimensional units, the considered model takes form:

$$\frac{\partial K}{\partial t} = \alpha^{-2}\nabla^2 K - bK\frac{H}{H+K} \qquad \textit{inside cytoplasm}$$

$$\frac{dQ}{dt} = (c_0 + K_b^2)(P-Q) - bQ \qquad \textit{at cell membrane}$$

Here $K_b(t,\theta) = K_b(t,\theta,R_2)$; $\mapsto^{\square\sim} \ll d$ is the kinase diffusion, b is the phosphatase activity, whereas c_0 and H are kinetic coefficients. The system is supplemented by the Robin boundary conditions for K: $aQ(1-K_b) = \alpha^{-2}\vec{n}\cdot\vec{\nabla}K$ at the cell membrane, reflecting activation of kinases by receptors, and $\vec{n}\cdot\vec{\nabla}K = 0$ at the nuclear membrane.

II. RESULTS

In the case of uniform receptor distribution $P(\theta) = P$, for broad range of parameters the system exhibits bistability. For $P \in (P_{\min}, P_{\max})$ and the other parameters fixed, the cell achieves the state of low or high activity according to the initial condition. Both $P_{\min}$ and $P_{\max}$ are the growing functions of the kinase diffusion coefficient d, i.e. the limited diffusion enables activation at lower receptor concentration. Moreover $P_{\min}$ and $P_{\max}$ are decreasing functions of cytoplasm thickness R_2-R_1. As a result activation of the cell can be induced by a concentration of a small fraction of receptors on a sufficiently small fraction of the cell membrane, i.e. by increasing P locally, Fig. 1. The minimal size of activating cluster increases with kinase diffusion and thickness of cytoplasm. Alternatively, cell can be activated by a displacement of the nucleus, what locally makes the cytoplasm thinner, Fig. 2. In both cases receptors and kinases are first activated locally, than the activation spreads as a travelling wave due to the system bistability.

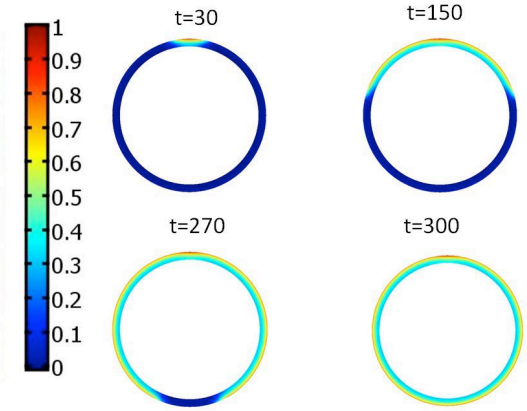

Fig. 1. The kinase activation induced by concentration of 1/100 of the receptors on the 1/300 fraction of the cell membrane. Remaining parameters are $\mapsto$ =10, b=12, H=0.1, c_0=0.01. The calculations were done using the COMSOL package.

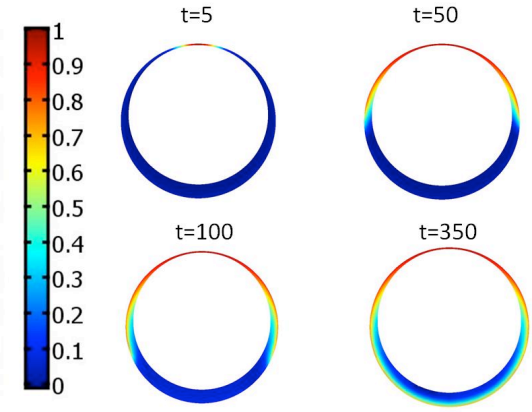

Fig. 2. The kinase activation induced by displacement of the nucleus; here the centre of the nucleus is at r=0.08, whereas R_1/R_2=0.9. Remaining parameters are as in Fig. 1.

III. CONCLUSIONS

The spatial reorganization of the B-cell components can lead to its activation. The B-cell can be activated by formation of a small cluster of membrane receptors (e.g. co-localized by a virus) or by displacement of the B-cell

Acknowledgments: This work was founded by Polish Committee for Scientific Research grant N N501 132936 and Foundation for Polish Science grant TEAM/2009-3/6.

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