Spatial Gradients in Kinase Activity Regulation

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***Short abstract* — In living cells proteins motilities regulate the spatio-temporal dynamics of molecular pathways. We consider here a simple reaction–diffusion model of mutual kinase-receptor activation showing that the level of cell activation is controlled by kinase diffusion coefficient and distribution of membrane receptors.**

I. MODEL

We assume that membrane receptors bind extracellular ligands that leads to a cascade of processes and receptor activation, but the limiting step in this cascade is receptor phosphorylation by the intracellular kinase (as in the case of B-cells activation). In turn, active receptors may activate kinase molecules. This defines the positive feedback. The activated kinases may freely diffuse over the entire cell volume (which is supposed to be a ball of unit radius) where they are inactivated by uniformly distributed phosphatases.

We consider first the spherically and then the axially symmetric case. We will use the following notation:

$K(t, r, \theta)$ – the concentration of the active kinase

$R(t, \theta)$ – the surface concentration of the active receptors

$P(\theta)$ – the total surface concentration of receptors (active and inactive) – assumed to be fixed in time.

The above assumptions lead to a system of reaction-diffusion equations, which in appropriate non-dimensional units takes the form:

$$\frac{\partial K}{\partial t} = \alpha^{-2}\nabla^2 K - K, \quad \text{inside the ball (cell)}$$

$$\frac{dR}{dt} = qK_b(P-R) - bR, \quad \text{at the boundary of the ball,}$$

with the non-linear Robin-type boundary conditions for K:

$$aR(1-K) = \alpha^{-2}\vec{n}\cdot\vec{\nabla}K,$$

where $K_b(\theta)$ denotes kinase concentration at the boundary, $d = \alpha^{-2}$ is the kinase diffusion coefficient, whereas q, b and a are relevant kinetic coefficients.

II. RESULTS

In the ***spherically symmetric case*** the stable steady state solution reads:

$$K(r) = K_c \frac{e^{\alpha r} - e^{-\alpha r}}{2\alpha r}, \quad \text{where} \quad K_c = K(0) > 0 \quad \text{if}$$

$$be^{2\alpha}(1-\alpha) - b(\alpha+1) + qaP\alpha^2(e^{2\alpha}-1) \geq 0 \quad \text{and}$$

$$K_c = 0 \text{ otherwise.} \qquad (1)$$

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In the limit of infinite diffusion, $\alpha = 0$, the stable nonzero solution exists only for $b < 3qaP$. According to inequality (1), for $b > 3qaP$ the positive solution exists only for sufficiently small diffusion $d = \alpha^{-2}$; for larger diffusion kinases cannot be stably activated (Fig.1).

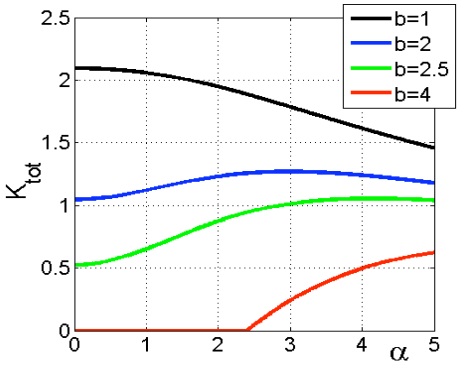

Fig. 1. Total amount of active kinase K_{tot} as a function of α for q=a=P=1

In the ***axially symmetric case*** we demonstrated that for the large range of parameters the concentration of receptors at one pole of the cell increases the total kinase activation level.

Particularly, for $q = a = 1, b = 4$, and the uniform receptor concentration $P(\theta) \equiv 1$, kinases may be activated only for $\alpha > 2.4$. When the uniform total receptor distribution is replaced by $P(\theta) = (3/4)(1+\cos\theta)^2$ (giving the same total amount of receptors), kinases may be activated for substantially smaller values of $\alpha > 1.04$, Fig. 2.

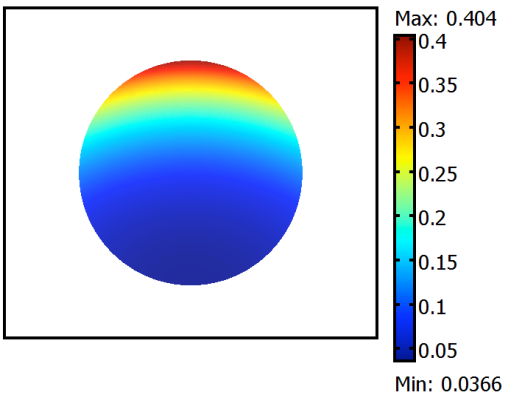

Fig. 2. Steady state spatial distribution of active kinase in axis-symmetric case for $q = a = 1, b = 4, \alpha = 2, P(\theta) = (3/4)(1+\cos\theta)^2$ calculated using COMSOL package. The same amount of receptors if distributed uniformly over the cell membrane does not lead to any kinase activity.

III. CONCLUSIONS

In systems with positive feedback, cell activation can result from the lowered motility of substrates leading to their co-localization. This effect could play a key role in B-cell activation, where B-cell receptors are co-localized by virus.