

Effect of the EGF binding cooperativity on EGFR activation on the cell surface

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Abstract

An reaction-diffusion model of EGFR signaling on the cell surface was constructed elucidating the differential spatio-temporal EGFR activation patterns due to the EGF binding cooperativity.

Keywords: EGFR, cell signaling, cooperativity, reaction-diffusion model

1 Introduction

Scatchard analysis of the binding of EGF to its receptor (EGFR) exhibits a concave-up plot indicating the negative cooperativity. A model for the aggregating system is proposed as one of the mechanisms to explain it, noticing the role of the cooperativity in lateral signal propagation on cell membrane [1].

In this study the model is extended as the reaction-diffusion model (RD model) to simulate the dynamic processes on the cell surface to investigate the relationship between the cooperativity and the lateral signal propagation.

2 Method and Results

The model for the aggregating system shown in Fig.1 is extended as an RD model to simulate the reaction-diffusion dynamics in the sphere surface space representing a cell membrane which is parameterized with a variable θ as in Fig.2. The set of reaction-diffusion equations and the parameter values are shown in Table 1 in which $\Delta(= \partial^2/\partial\theta^2 + \partial/\tan\theta\partial\theta)$ denotes the Laplacian in a sphere surface space. The parameters d , o and i represent the normalized diffusion coefficient, the EGF clearance rate constant, and the internalization rate constant of EGFR, respectively. The unit D stands for the density in the unit of mol/dm^2 . E , m_0 , m_1 , d_0 , d_1 , and d_2 are chemical species representing free EGF, free EGFR, EGF bound EGFR monomers, free receptor dimers, one EGF bound dimers, and two

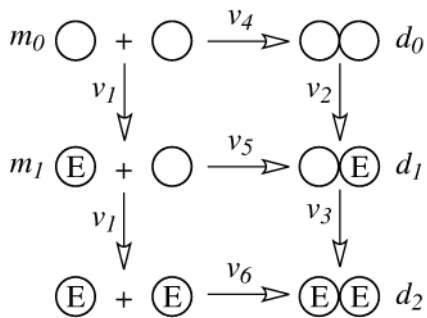


Figure 1: Reaction scheme

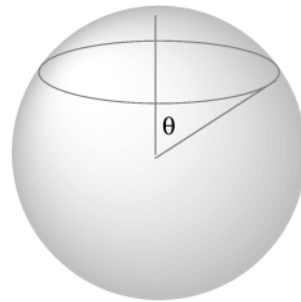


Figure 2: Sphere surface space

Table 1: Kinetic equations and parameter values of RD model

$\partial e_d/\partial t = v_0$	$v_0 = oe$	$k_a = 0.01 \text{ nM}^{-1} \text{ s}^{-1}$
$\partial e/\partial t = d\Delta e - v_0 - v_1 - v_2 - v_3$	$v_1 = k_a m_0 e - k_d m_1$	$k_d = 0.01 \text{ s}^{-1}$
$\partial m_0/\partial t = d\Delta m_0 - v_1 - 2v_4 - v_5$	$v_2 = 2k_a d_0 e - k_d d_1$	$l_a = 0.1 \text{ nD}^{-1} \text{ s}^{-1}$
$\partial m_1/\partial t = d\Delta m_1 + v_1 - v_5 - 2v_6$	$v_3 = ck_a d_1 e - 2k_d d_2$	$l_d = 0.1 \text{ s}^{-1}$
$\partial d_0/\partial t = d\Delta d_0 - v_2 + v_4$	$v_4 = l_a m_0^2 - l_d d_0$	$d = 0.01 \text{ s}^{-1}$
$\partial d_1/\partial t = d\Delta d_1 + v_2 - v_3 + v_5$	$v_5 = 2l_a m_0 m_1 - l_d d_1$	$o = 0.01 \text{ s}^{-1}$
$\partial d_2/\partial t = ad\Delta d_2 + v_3 + v_6 - v_7$	$v_6 = cl_a m_1^2 - l_d d_2$	$i = 0.001 \text{ s}^{-1}$
$\partial d_{2d}/\partial t = v_7$	$v_7 = id_2$	

EGF bound dimers, respectively. The system is characterized by system parameters, c and a . The factor c features the cooperativity and a describes the diffusion deceleration for the signaling molecule complex (d_2) that is reported with regard to the observations in the single molecule imaging [2].

The simulation analysis demonstrated that there exists the substantial effect of the cooperativity on EGFR activation patterns in time and space. The typical responses to the temporal stimuli of 1 nM EGF around the north pole ($\theta = 0$) are shown in Fig. 3 for which the simulations are performed with the strong positive cooperativity ($c = 1000$) under the condition of EGFR overexpression (EGFR density = 1 nD). The deceleration factors a are 1 and 0.1 in the cases (1) and (2), respectively. The signal elongation is observed to appear with respect to the deceleration of d_2 .

3 Discussions

The RD system could be differently characterized by the location in the parameter space due to the nonlinearity of the system. It is suggested that the over expression of EGFR could elongate the activation in a certain parameter subspace, demonstrating that the RD model could be useful to elucidate the system characteristics in the dynamics of EGFR signaling on cell surface.

References

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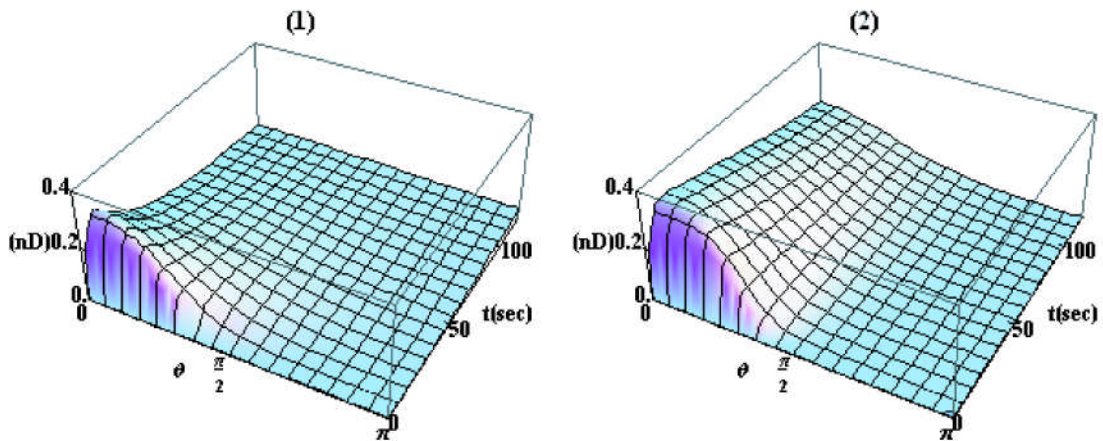


Figure 3: Typical dynamics of the EGFR activations