Published in final edited form as:

Methods Mol Biol. 2009 ; 571: 489–505. doi:10.1007/978-1-60761-198-1_32.

Modeling spatial and temporal dynamics of chemotactic networks

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Abstract

When stimulated by chemoattractants, eukaryotic cells respond through a combination of temporal and spatial dynamics. These responses come about because of the interaction of a large number of signaling components. The complexity of these systems makes it hard to understand without a means of systematically generating and testing hypotheses. Computer simulations have proved to be useful in testing conceptual models. Here we outline the steps required to develop these models.

Keywords

Mathematical model; chemotaxis; reaction-diffusion; systems biology; virtual cell

1. Introduction

What does a mathematical model tell me that I didn't know before? This is a common question posed by experimenters, suspicious that models merely package already-known information and provide few new insights. Models can do two things. First, they can “verify that known interactions in some system can produce the observed qualitative behavior.” (1). When employed this way, models act mostly as tools providing a form of consistency check, ensuring that the posited conceptual models behave as they are supposed to. However, the real benefit of models is a predictive tool. In this case, models usually precede complete knowledge of the system but serve to channel experimental investigations.

It is usually thought that the introduction of mathematical and computational techniques in the study of signaling pathways is a relatively new phenomenon – an offshoot of the advent of Systems Biology. And, while it is true that recent years have seen a veritable blossoming in the use of computational models in cell biology, it is also worth remembering that mathematical models have a long history of making significant contributions to the understanding of biological systems. The best such example is the use of models by Hodgkin and Huxley to understand electrophysiology.

Mathematical models of bacterial chemotaxis (reviewed in (2)) have a strong record of successfully leading to predictions that were later confirmed experimentation. Macnab and

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Koshland (3) were the first to use theoretical means to postulate a signaling mechanism that accounted for the adaptive behavior observed in the run/tumble behavior of bacteria (Fig. 1). Their “temporal gradient apparatus” consists of two enzymes catalyzing the synthesis (enzyme 1) or degradation (enzyme 2) of a compound. Both enzymes are activated chemoattractant receptor modification, albeit at different rates: fast for enzyme 1, slow for enzyme 2. In a time-varying gradient of increasing chemoattractant concentration, the net result is an increase in the concentration of the compound. Though presented as a conceptual model, it later led Koshland to posit that the enzymes could be regulated through methylation – a prediction that later proved to be true (4). Another example of theory leading experimentation is the proposal by Barkai and Leibler (5) that the bacterial signaling mechanism is robust (verified later (6)) or that of Bray and Morton-Firth (7) that the sensing capabilities could be increased if receptors worked cooperatively, in such a way that ligand-mediated changes in the activity of a receptor would propagate to neighboring receptors in a cluster – a model for which there is now experimental evidence (8).

It is perhaps not surprising, owing to the successful marriage between models and experiments in bacterial chemotaxis, that mathematical modeling has quickly become an accepted tool for studying eukaryotic chemotactic networks (reviewed in (9)). In this chapter we outline the steps necessary for developing these models. We begin by presenting some necessary theoretical background.

1.1 Modeling temporal dynamics

When developing a model describing the temporal dynamics of a biochemical network we use ordinary differential equations (ODEs). For a network with n interacting species, labeled $C_1, \dots, C_n$, we describe temporal changes in the concentration of species i , denoted by C_i through the differential equation:

$$\frac{dC_i(t)}{dt} = f(C_1, \dots, C_n). \quad (1)$$

The function f specifies the interconnections that affect the concentration of C_i . The specific form of this function depends on the assumptions made about the biochemical interaction. We consider two types of reactions: Binding reactions and enzymatic reactions.

1.1.1 Binding reaction $(C_1 + C_2 \xrightleftharpoons[k_r]{k_f} C_3)$ —

Each time the forward reaction occurs, molecules of species C_1 and C_2 bind together to create one molecule of C_3 . With the reaction affinity of k_f we can use a flux term $J_f = k_f \times C_1 \times C_2$ to represent the rate of consumption of C_1 and C_2 , which is also the rate of production of C_3 . The reverse reaction occurs with affinity k_r with one unit of C_3 decomposing into one unit of C_1 and one unit of C_2 . The flux $J_r = k_r \times C_3$ represents the rate the reverse reaction. The whole reaction therefore occurs at the combined rate of:

$$\frac{dC_3}{dt} = -\frac{dC_1}{dt} = -\frac{dC_2}{dt} = J_f - J_r = k_f C_1 \times C_2 - k_r C_3.$$

1.1.2 Enzymatic reaction using Michaelis-Menten dynamics

$(S + E \xrightleftharpoons[k_{-1}]{k_1} SE \xrightarrow{k_2} P + E)$ —In enzymatic reactions, the enzyme E catalyzes the conversion of the substrate S into product P . The substrate S and enzyme E reversibly form an intermediate SE that is converted to product P with affinity $k_2 \times E$. The standard assumption is that the enzyme turnover is so fast that the concentration of enzyme-substrate intermediate does not change during the reaction: $dSE/dt=0$. This reaction occurs at the rate of:

$$\frac{dP}{dt} = \frac{V_{\max} \times S}{K_m + S}.$$

where $V_{\max}=k_2 E_{\text{Tot}}$ and $K_m=(k_{-1}+k_2)/k_1$.

1.2 Modeling spatial dynamics

The most significant difference between the observed chemoattractant-induced behavior of bacterial and eukaryotic cells is that the latter can interpret gradients spatially. This is observed experimentally in that gradients elicit spatially segregated distributions of intracellular markers when exposed to chemoattractant gradients (10). Modeling the concentration of a biochemical species C_i that depends on time, t and spatial dimension, x , requires the use of partial differential equations (PDE). In particular, biochemical models using reaction-diffusion equations are needed:

$$\frac{\partial C_i(x, t)}{\partial t} = f(C_1, \dots, C_n) + D \frac{\partial^2 C_i(x, t)}{\partial x^2} \quad (2)$$

As before, the function f specifies the interconnections that affect the concentration of C_i . The right-hand most term in the PDE specifies the diffusion of the species. The variable D is the diffusion coefficient. Its value can range around $10 \mu\text{m}^2/\text{s}$ for proteins in the cytosol, $1 \mu\text{m}^2/\text{s}$ for lipids in the membrane, and $0.1 \mu\text{m}^2/\text{s}$ for proteins in the membrane (11).

To solve for $C_i(x, t)$ requires that an initial distribution, $C_i(x, 0)$, be known. It is also necessary to have boundary conditions. For PDEs, there are several available choices. The most common form of boundary condition is to specify the flux of the species at the boundary.

In modeling spatial dynamics, it is sometimes necessary to consider situations where the interacting species reside on different compartments. For example: binding can occur when one reactant resides on the cell membrane (a binding site) and the other in an extra- or intracellular volume (e.g. the cytosol). In this case, the product is on the membrane.

1.3 LEGI model of gradient sensing

As an example of how to create a computational model of a chemosensory system we use a simplified model of gradient sensing, referred to as the LEGI (local excitation, global inhibition) model (9). This model can be viewed as an extension of the Macnab and Koshland model (3) in that receptor occupancy triggers two types of signals: a fast excitation and a slow inhibition that together regulate and observable response. Where the model differs is that it assume different spatial localizations: the excitation is local; the inhibition, global. When the spatial location is not an issue, for example, when the cell is stimulated by a homogeneous chemoattractant stimulus, the response is, as in the bacterial case, adaptive. However, in the presence of a chemoattractant gradient, the LEGI model leads to a spatial response. In this chapter we assume that this response regulates binding sites for phosphoinositide 3-kinase (PI3K). This is part of a model that combines parallel LEGI mechanisms to regulate the phospholipid signaling observed in *Dictyostelium* cells (12).

2. Materials

2.1 Compartmental models

In general, the right-hand side of Equations (1) and (2) are nonlinear functions of the species' concentrations. As such, analytic solutions are rarely available. It is thus necessary to solve this equation numerically, requiring a numerical simulation package. The most popular, general-purpose packages are Matlab (Mathworks, Natick, MA), Mathematica (Wolfram, Champaign, IL) and Maple (Maplesoft, Waterloo, Canada). All are relatively easy to use and provide great functionality. Alternatively, a number of simulation packages specifically tailored to the biological signaling community have appeared (reviewed in (13)). In most of these, a graphical user interface allows the user to specify a biochemical interaction by selecting the type of reaction and the kinetic coefficients. The package then automatically generates and solves the necessary ODEs.

2.2 Spatial models

For spatially-varying models, the list of available simulation packages is considerably smaller. Comsol Multiphysics (Comsol, Burlington, MA), a general-purpose simulation package originally designed to work with Matlab but now independent, allows the user to specify general PDEs, or to select from one of several pre-defined forms, including reaction-diffusion equations such as Equation (2). The solution is obtained using finite-element methods (14).

The Virtual Cell is one of the few simulation packages specially tailored to cell biology that can deal with spatially varying simulations. Unlike most other software packages that reside and carry out the simulations in the user's computer, the Virtual Cell software is maintained at a central server within the National Resource for Cell Analysis and Modeling (NRCAM) at the University of Connecticut Health Center (15). Using the Virtual Cell is done through a Java application over the internet. Use of the Virtual Cell requires an account, available at www.nrcam.uchc.edu/login/login.html. Funded through the National Center for Research Resources, a component of the National Institutes of Health, the Virtual Cell is free for users in an academic environment. General purpose tutorials are available (16).

3. Methods

In this chapter, we use the LEGI model of gradient sensing as an example to demonstrate how these processes can be modeled mathematically, and connected together in simulation to produce gradient sensing. We use the Virtual Cell as our modeling environment (*see Note 1*). The reactions modeled in the LEGI model are listed in Table 1; the molecules involved, as well as their spatial distribution in the cell geometry are specified in Table 2.

A complete model in Virtual Cell consists of three components:

- A Biomodel component where we specify: the molecular species involved in the biological model, the physiological compartments in which they reside, and their interactions;
- A Geometry component that allows for specifying the shapes and dimensions of each compartment; and
- A Mathematical component based on the Virtual Cell Math Description Language (VCMDL) that allows for access of mathematical formulae behind the biological model.

To create a biological model in Virtual Cell, it is necessary to define both the Biomodel component and the Geometry component. Equations in the Mathematical component are generated automatically but are also available for manual editing.

3.1. Specifying the components

1. When Virtual Cell is started, a new instance of Biomodel opens, allowing the creation of a new model (Fig. 1).
2. We start by double clicking on the unnamed compartment, and naming it “EC” (for extracellular).
3. To add a cellular compartment, use the Feature Tool by clicking the icon, then click the EC compartment. You now specify the name of the cell’s intra-cellular (IC) and cell membrane (CM) (Fig. 1A). We will only need this one cellular compartment to create the LEGI gradient sensing model.
4. Next, add all the molecular species to the model by using the Species Tool (Fig. 1B). To start, click the icon followed by the EC compartment, and name the new species “L” (for Ligand). Click Add. Similarly, click on the Membrane and Cytosol compartments to add in molecular species that belong in each. Table 2 lists the necessary molecular species and their respective compartments.
5. When all the molecular species are added (Fig 1C), we can proceed to define interactions between them. Each reaction is defined in a specific compartment. Reactions in a volume can only involve molecules from the same volume, but reactions on the membrane can involve molecules from the membrane and neighboring compartments.

3.2. Specifying the reactions

1. We start by defining the membrane binding reaction between the extra-cellular ligand (L) and the receptors (R) on the cell membrane. As this reaction includes molecules in both the membrane and extra-cellular compartments, it takes place in the membrane compartment. Right click on the cell membrane compartment, and choose the “Reactions...” option. This will open a new window (Fig. 2A) where all membrane reactions can be defined. This window is divided into three sections, representing the EC (extra-cellular compartment), CM (cell membrane), and IC (intra-cellular compartment). All available molecules are displayed in the appropriate compartments.
2. To add a new reaction, click the reaction icon, and click in the middle region representing the Membrane compartment. Click the connection icon to link the molecular players to this reaction. Draw lines from the species to the reaction. As the line is drawn and the mouse hovers on the reaction site, three possible names: “reactant,” “product” and “catalyst” can appear. Choose the proper category to end the line.
3. Double click on the reaction to open the “Reaction Kinetics Editor” (Fig. 2B). Choose the kinetic type as “General [molecules/($\mu\text{m}^2\text{s}$)]” for the purpose of this example (see **Note 2**). Type in the expression for the reaction rate J (see **Note 3**). For the ligand membrane binding reaction, this expression is:

$$J = k_f * R_CM * L_EC - k_r * C_CM.$$

When this expression is defined, the software automatically recognizes previously undefined variables, namely the kinetic rate constants in this case. We can now specify the rate constants “ k_f ” and “ k_r ” of this reaction. As we are not modeling any membrane currents, the variable “ I ” can be ignored.

4. To define a catalytic reaction, simply adjust the reaction rate expression “J” to include the catalytic activities of the enzymes involved. We proceed to define all reactions listed in Table 2 Fig. 2C shows a graphical representation of all reactions in the CM compartment.
5. Save this model as “LEGI.”

3.3. Specifying the geometry

1. To define the simulation system completely, we need to describe the geometry of the simulation: how large the cell is, where it resides in space, etc. In this example, we assume that the cell is a two-dimensional circle of radius 5 μm , and the chemoattractant source is positioned approximately 13 μm away from the cell center (see **Note 4**).
2. To define this geometry, we go to the menu tab in the Biomodel window: File → New → Geometry → Analytic → 2-D. This will open up a “Geometry Editor” (Fig. 3A).

3. We want an extra-cellular space large enough to fit the cell and leave room for the chemoattractant source. Click on “Change domain,” and specify the domain size to be a square 15 μm by 15 μm with origin at (0, 0) (Fig. 3B).
4. Rename sub-volume name to “EC,” and leave its value at “1” to represent the EC compartment.
5. Click “Add” to add the IC compartment. Name the sub-volume “IC,” and change its value expression to:

$$(x - 6)^2 + (y - 6)^2 < 25,$$

which is the formula for a circle of with radius 5 μm and centered at (6,6).

6. Save this geometry as “2DLEGI.”

3.4. Linking the physiological and geometrical models

1. So far we have created a physiological model and a geometrical model. Now we link them to form a complete application in the Virtual Cell. Go to the “Applications” panel on the right side of the physiological model, right click on “LEGI” (Fig. 4A), select “Create Deterministic Application,” and enter the name (e.g. “Needle”) of this new application. Double clicking on “LEGI” to expand it, you see the list of applications associated with this physiological model.
2. We must now link this application to its geometry. Double click on the “Needle” application to open the “Application Editor” (Fig. 4B).
3. Click on “View / Change Geometry” under the “StructureMapping” tab. In the new window, click on the “Change Geometry” button, and select the “2DLEGI” geometry you have created. This “Info for Geometry” window now displays the 2DLEGI geometry (Fig. 4C). Close this window.
4. Back in the “Application” window, we can link the physiology structures to their appropriate geometries. Click the icon; link “IC” to “IC” and “EC” to “EC” (Fig. 4D).

3.5. Specifying initial conditions

1. We must specify initial conditions and diffusive properties of each molecular variable in the physiological model. These properties are designed to be part of each application. For each physiological model, many applications can be created, thus many initial conditions, etc, can be tested (*see Note 5*).
2. In this application, we assume that molecules in the IC and EC are able to diffuse, while molecules in CM are not diffusible. Diffusion coefficients are found in Table 2 under the “Diffusion” column. Initial concentrations for molecules in all compartments are also found in Table 2.

3. Go to the “Initial Conditions” tab in the “Application” window. Click on each molecular species name, and modify the information on the bottom half of the panel to match the information in Table 2.
4. The ligand source “L_source” is represented by a fixed concentration (1 μM) at a fixed location (a quarter circle of radius 1 at the bottom right corner of the simulation domain). To define the fixed concentration, check the box under the “Clamped” column (Fig. 5). To define the fixed location, use the following expression for the initial concentration:

$$(x - 15)^2 + (y - 15)^2 < 1$$

5. Save this application.

3.6. Running a spatial simulation

1. Click the “Simulation” tab in the “Application” window, and click “New” to define a new simulation. You can change the name of this simulation by double clicking on the simulation name.
2. Select this simulation, and click “Edit.” A new window will open, where you can change the simulation specifications.
3. We can start the simulation at parameters different than those previously defined, or give the simulation a finer spatial resolution by modifying the “Mesh” properties to contain more X and Y elements. For the purpose of this example, we only need to modify information under the “Task” tab. Click the “Task” tab, set “Time Step” to 0.1 seconds, “End Time” to 500 seconds, and keep every 10 time samples (Fig. 6A). Click OK.
4. Back in the “Application” window, select this simulation and click “Run.” The simulation request will be sent to the Virtual Cell server to compute, and “Running status” will indicate “completed” when the simulation is successful (Fig 6B).
5. Click the “Results” button to view simulation results. A new window will open (Fig 6C).
6. In this simulation, we are interested in the spatial distribution of the cell’s response (PI3KA) on the cell membrane. Select “PI3KA_CM” from the variable list. Click on the icon to draw a line around the cell’s circumference. Start at the back of the cell.
7. When the line is drawn, the “Show Spatial Plot” button will become active. Click on it, and a spatial plot of PI3KA will appear (Fig. 6D).

3.7. Running a temporal simulation

1. We can also simulate the cell’s response to a uniform step function as the chemoattractant stimulus.

2. In the “Applications” panel to the right side of the “Model” window, right click on the application “Needle.” Select “Copy As,” then “Deterministic Application.” Name this new application “Uniform,” and open this application to modify.
3. Under the “Initial Conditions” tab, check the “Clamped” box corresponding to “L_EC” and change the “Initial Condition” to $0.001 + 0.999 \cdot (t > 200)$.
4. Under the “Reaction Mapping” tab, uncheck the “Enabled” box corresponding to Rx. These last two steps set up the extra-cellular ligand concentration as a step function going from 0.001 μM to 1 μM at $t = 200$ seconds.
5. Repeat Steps 1 to 5 in Section 3.5 to set up a simulation. In this simulation, we are interested in the temporal response of the cell’s response (e.g. PI3KA). We can also check that the cell’s receptor occupancy variable C behaves like the input ligand signal. Select “C_CM” from the variable list. Click on the icon, and place a point anywhere along the cell membrane.
6. When the point is placed, the “Show Time Plot” button will become active. Click on it, and a time plot of C will appear. Also plot the time profile for PI3KA. We can confirm that, while the cell’s receptor occupancy displays a step like time profile, the cell’s membrane-bound PI3K (PI3KA) levels display a transient peak before settling back to its pre-stimulus level (Fig. 6E).

4. Notes

1. The complete Virtual Cell implementation of the complementary LEGI model (12) is freely available in the Virtual Cell. To access this model, go to the menu options in the main model window. Click File $\rightarrow$ Open $\rightarrow$ Biomodel. Under “Shared Models,” choose “LiuYang” and open the “LEGI” model.
2. In the Virtual Cell, the default units are μM for volumetric concentrations, and molecules/ μm^2 for membrane-bound species. The spatial dimension is in μm^2 .
3. When specifying reactions, make sure to use the variable names used in the Stoichiometry diagram on the top of the “Reaction Kinetics Editor” form.
4. Boundary conditions for this simulation assume that there is no flux of protein across the cellular membrane. In situations where the cell and stimulus is symmetric, zero flux boundary conditions can also be used to take advantage of this symmetry. For example, in (17) a three-dimensional model of the cell used symmetry in the x, y and z directions was developed. This allowed simulations to run on only one eighth of the cell, saving both computer time and memory.
5. In setting the initial conditions, one would like to recreate the cell’s basal levels. However, as the correct values are rarely known, it is more customary to run the simulation for some time with no (or small) stimulus, and to let the cell equilibrate at this value. In this model we did so by specifying that the stimulus was 0.001 μM and letting the cell reach steady-state in 200 seconds, at which point the concentration is increased to 1 μM .

6. This reaction (#1) is not a true reaction, but rather one way of setting up diffusion of “L” from source “L_source.” We can interpret it as the source releasing the chemoattractant (L) at rate k_r with the chemoattractant diffusing through the rest of the extra-cellular space, and degrading at a rate of k_r .

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Figure 1. Specifying the components.

A. Adding a new feature inside the EC (Extra-Cellular) compartment, with feature name IC (Intra-Cellular), and membrane name CM (Cell Membrane). B. Adding a new molecular species to the structure EC, with name L (ligand). C. All the molecular species are added to associated compartments.

Figure 2. Specifying the reactions.

A. Molecular species are divided into three adjacent regions, EC (extra-cellular), CM (cell membrane), and IC (intra-cellular). Reactions can be specified in any of these three compartments. B. In the “Reaction Kinetic Editor,” we specify the reaction rate expression, as well as the kinetic reaction rates associated with the expression. C. In this model, the reactions are defined in CM. Solid lines going from molecular species to reaction sites connect reactants; solid lines going from reaction sites to molecular species connect products; and dotted lines connect enzymes to reaction sites.

Figure 3. Specifying the geometry.

A. In the “Geometry Editor,” we define the intra-cellular (IC) and extra-cellular (EC) geometries. B. The domain size of the geometry was set in this example to be a square $15 \times 15 \mu\text{m}$ with origin at (0,0).

Figure 4. Linking the physiological and geometrical models.

A. The application panel. B. When a new application is created, all structures are linked to the same compartment. C. Specify the geometry to be used for the application. D. Link physiological structures to geometric compartments.

Figure 5. Specifying initial conditions.

The initial conditions are specified in this application. Note that, by clicking on the “Clamped” box, the concentration can be fixed throughout the simulation.

Figure 6. Running simulations.

A. The parameters for the simulation are specified in the “Simulation” tab in the “Application” window. The “Mesh” properties specify spatial parameters. The temporal parameters specifying the simulation are set under the “Task” tab. B. Once it begins (at the NRCAM servers) the “Running status” indicates the state of the simulation. C. Clicking on the “Results” tab (in panel B) leads to a spatial representation of the simulation output. All species can be plotted at different saved times by selecting the correct variable and time step. D. A spatial plot can be selected. In this case, this is the bound PI3K along the perimeter of the cell. E. Similarly, time profiles can be obtained at any point. In this case we see the

bound chemoattractant (C_{CM}) and bound PI3K ($PI3K_{CM}$) on the cell membrane as a function of time for a spatially homogeneous dose of chemoattractant.

Table 1.

List of reactions.

Reaction	Description	Reaction type	Reaction rate (#/($\mu\text{m}^2\text{s}$))	k_f (units)	k_r (units)
1 $L_{\text{source}} \leftrightarrow L$	Diffusion of cAMP from source	(see Note 6)	$k_f \times L_{\text{source}} - k_r \times L$	1 (#/($\mu\text{m}^2\text{s}$))	1 (#/($\mu\text{m}^2\text{s}$))
2 $L+R \leftrightarrow C$	cAMP binding to CAR1	Binding	$k_f \times L \times R - k_r \times C$	1.66 ($\mu\text{M}\text{s}$) ⁻¹	0.39 (s^{-1})
3 $E+C \rightarrow EA+C$	Receptor-mediated local excitation	Enzymatic	$k_f \times E \times C - k_r \times EA$	0.001 ($\mu\text{m}^2/(\#\text{s})$)	0.1 (s^{-1})
4 $I+C \rightarrow IA+C$	Receptor-mediated global inhibition	Enzymatic	$k_f \times I \times C - k_r \times IA$	0.01 ($\mu\text{M}\text{s}$) ⁻¹	10 (#/($\mu\text{m}^2\text{s}$))
5 $BS+EA \rightarrow BSA, BSA+IA \rightarrow BS$	LEGI-mediated activation of binding site for PI3K	Enzymatic	$k_f \times BS \times EA - k_r \times BSA \times IA$	0.01 ($\mu\text{m}^2/(\#\text{s})$)	1000 ($\mu\text{M}\text{s}$) ⁻¹
6 $PI3K+BSA \leftrightarrow PI3KA$	PI3K binding to binding sites	Binding	$k_f \times PI3K \times BSA - k_r \times PI3KA$	2 ($\mu\text{m}^2/(\#\text{s})$)	1 (s^{-1})

Table 2.

List of species.

Molecule	Description	Compartment	Initial Condition	(units)	Diffusion ($\mu\text{m}^2/\text{s}$)
L_source	Chemoattractant concentration at the source	EC	Variable		300
L	Chemoattractant concentration	EC	Variable		300
R	Unoccupied receptor	CM	100	$\#/\mu\text{m}^2$	
C	Occupied receptor	CM	0	$\#/\mu\text{m}^2$	
E	Excitation substrate	CM	100	$\#/\mu\text{m}^2$	
EA	Local excitation signal	CM	0	$\#/\mu\text{m}^2$	
I	Inhibition substrate	IC	0.1	μM	13
IA	Global inhibition signal	IC	0.1	μM	13
BS	Inactive PI3K binding site	CM	100	$\#/\mu\text{m}^2$	
BSA	Activated PI3K binding site	CM	0	$\#/\mu\text{m}^2$	
PI3K	Free, cytosolic PI3K	IC	0.1	μM	10
PI3KA	Bound, activated PI3K	CM	0	$\#/\mu\text{m}^2$	