Computational models on the spatial temporal aspects of subcellular processes

Yinghao Wu
Department of Systems and Computational Biology
Albert Einstein College of Medicine
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Outline

- Background
- Theory of chemical kinetics
- Modeling temporal dynamics of subcellular processes
- Simulations of spatial organization of subcellular processes

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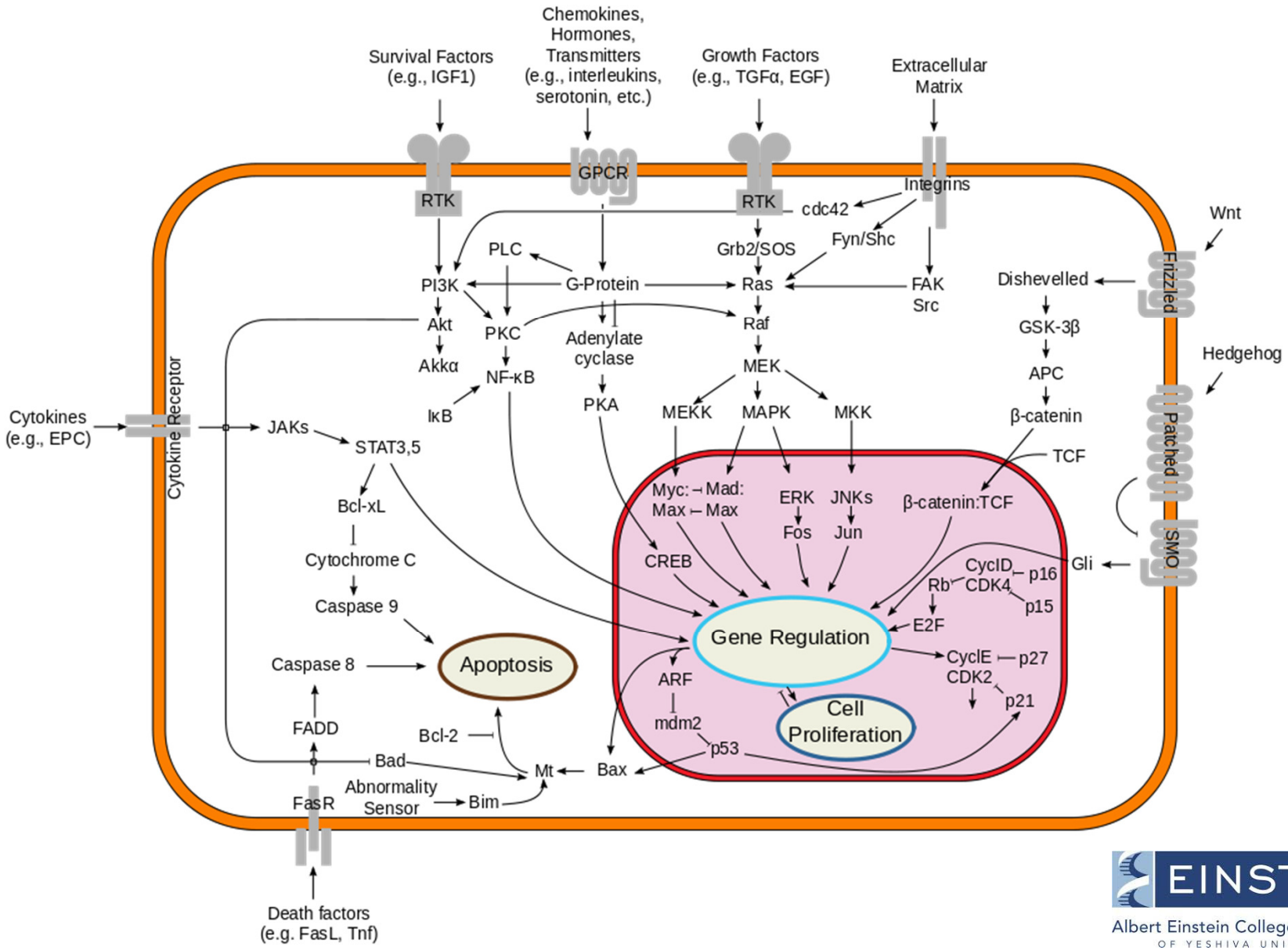

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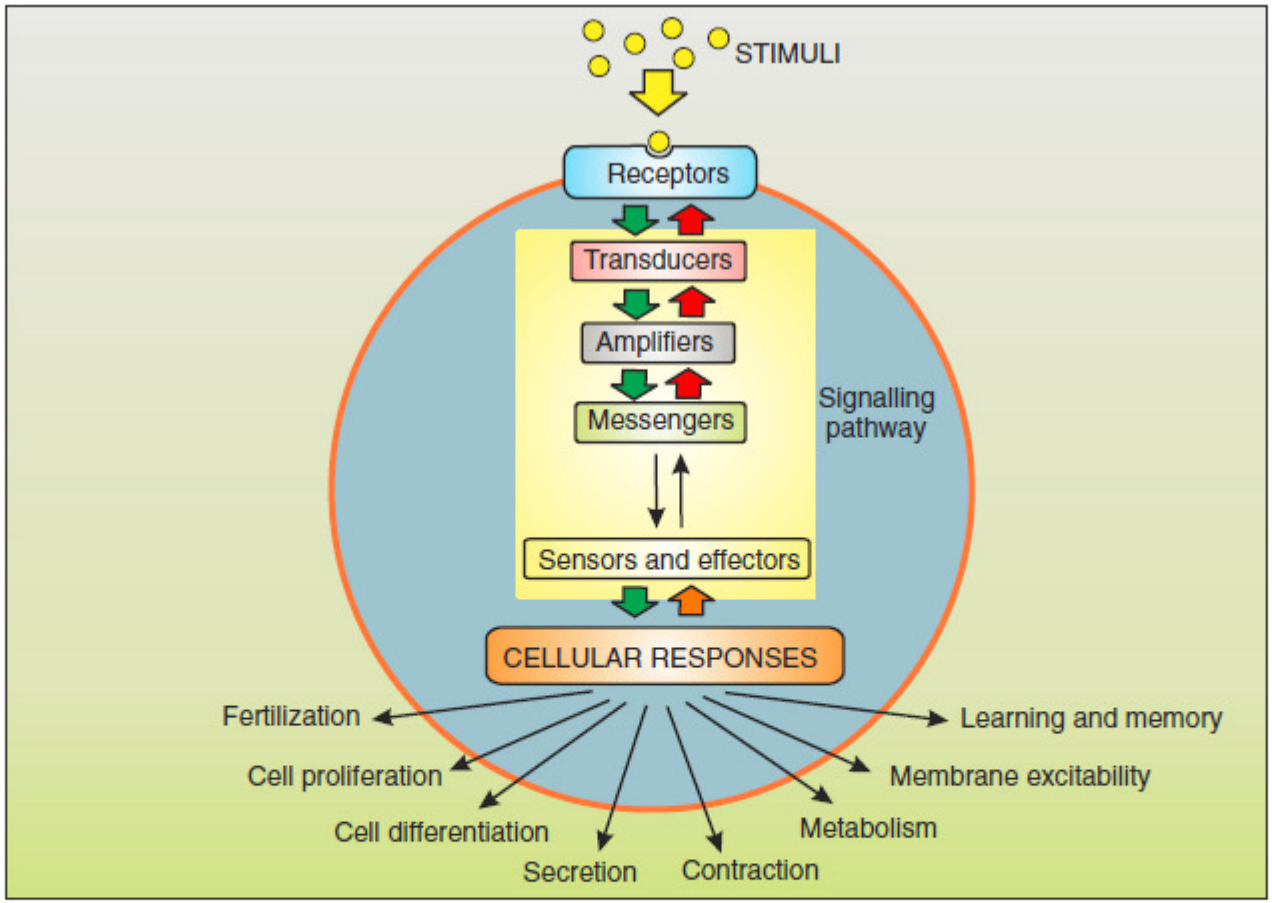
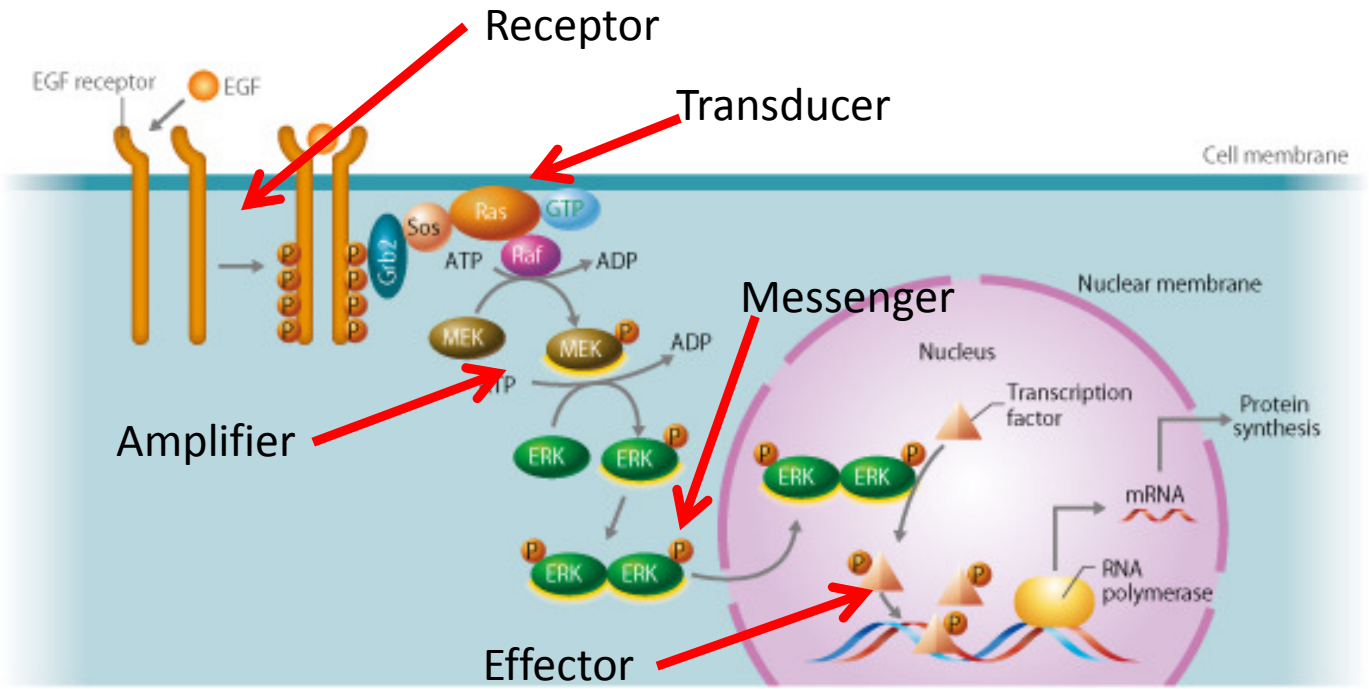


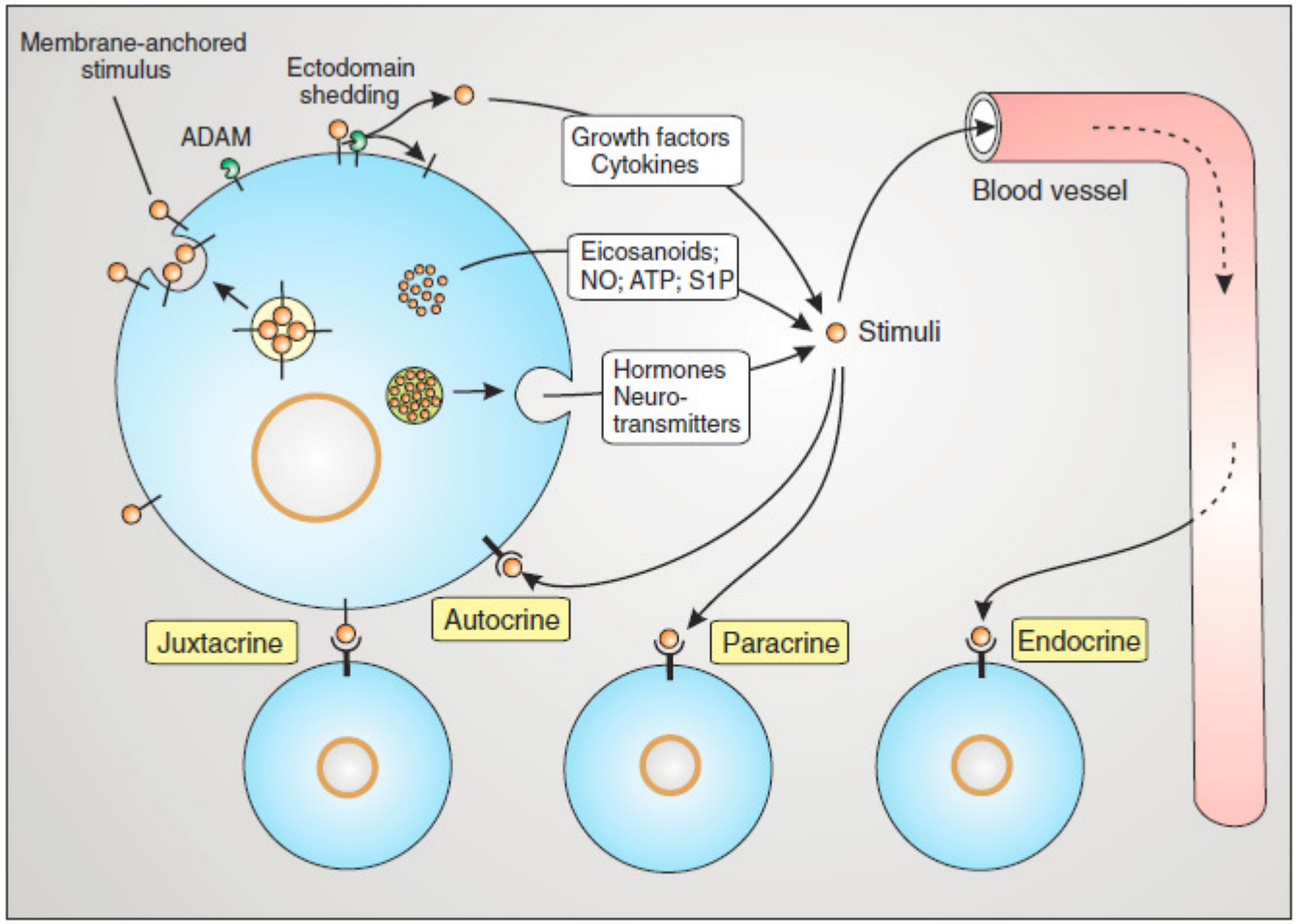
The basic principle of a cell signalling pathway.
Stimuli (e.g. hormones, neurotransmitters or growth factors) acting on cell-surface receptors relay information through intracellular signalling pathways that can have a number of components. They usually begin with the activation of transducers that use amplifiers to generate internal messengers that either act locally or can diffuse throughout the cell. These messengers then engage sensors that are coupled to the effectors that are responsible for activating cellular responses. The green and red arrows indicate that cell signalling is a dynamic process consisting of ON mechanisms (green arrows) during which information flows down the pathway, opposed by the OFF mechanisms (red arrows) that switch off the different steps of the signalling pathway.



Binding of the EGF ligand to **EGF receptors** encourages two EGF receptors to come closer to each other and dimerize. During this process, the three-dimensional conformation of the intracellular domain of the EGF receptor changes, thereby activating the tyrosine kinase in the domain, and inducing the two EGF receptors forming the dimers to mutually phosphorylate each other's tyrosine residues. **Adapter proteins and other mediators** in signal transduction bind to the activated EGF receptor dimers to form a receptor signal-transduction complex. Some of these adapter proteins have an SH2 (Src Homology 2) domain that recognizes the phosphorylated tyrosine on the receptor and specifically binds to activated proteins. Some activated complexes **activate a series of signal cascades** in which the Ras small G protein is involved. Then finally, the activated Ras regulates the expression of proteins through the mitogen-activated protein (MAP) kinase cascade. **Activated extracellular signal-regulated kinases (ERKs or MAP kinases) dimerize and enter the nucleus**. Within the nucleus, **ERKs phosphorylate transcription factors and promote the transcription of genes** su

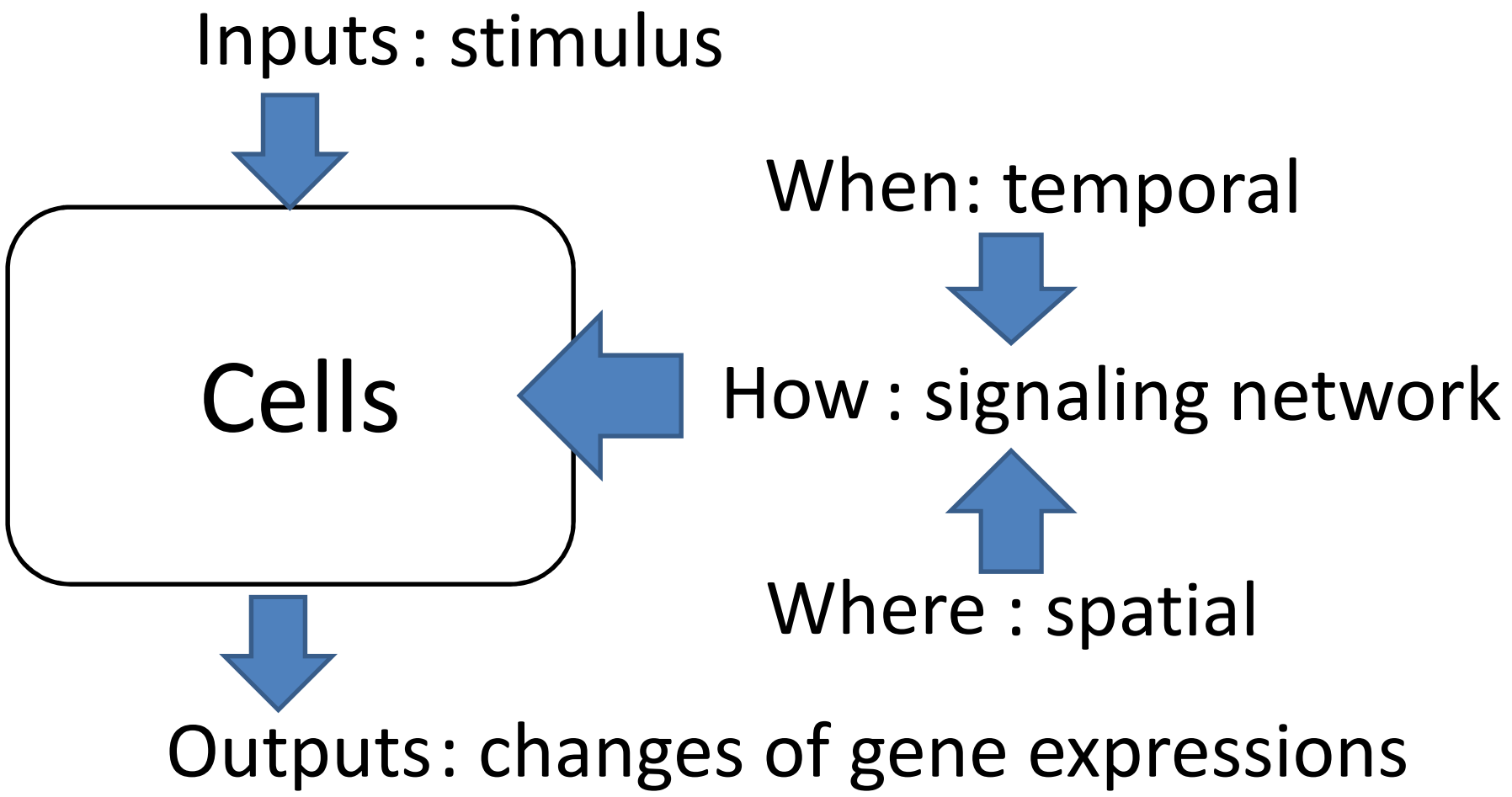
Extracellular Stimuli

- Not only chemical
- Electrical : Neural receptors
- Optical: Rhodopsin
- Mechanical: Integrin, Adhesive receptors
- Always mixed

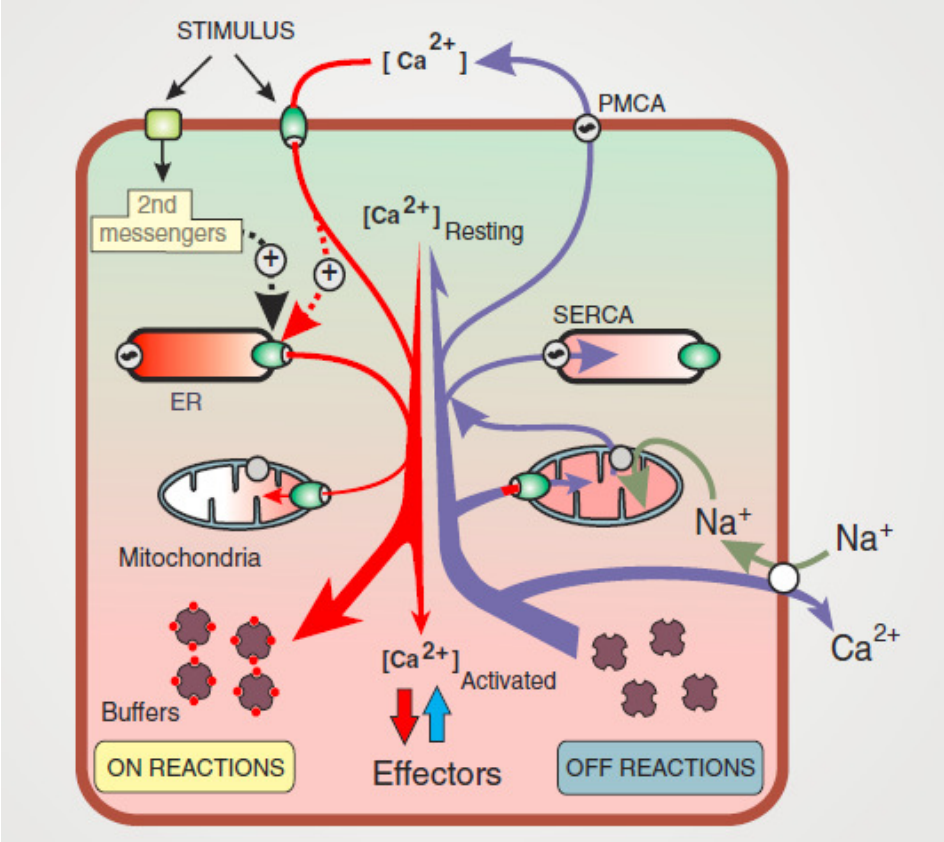


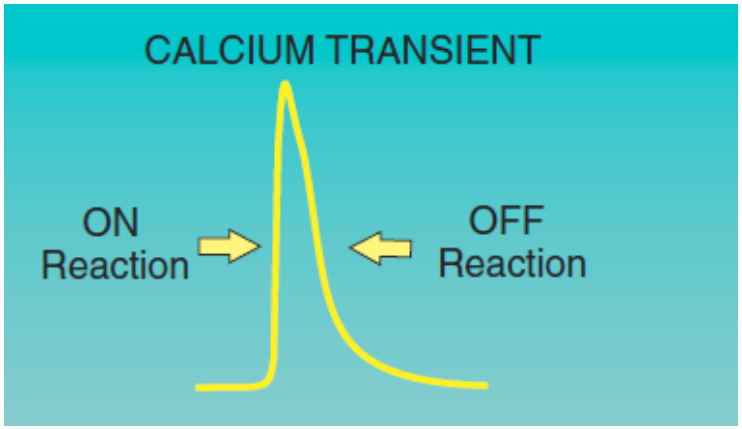
Formation and mode of action of cell stimuli.
Cell stimuli are released from cells through different mechanisms: membrane-anchored stimuli are released by ectoderm shedding; stimuli formed in the cytoplasm pass out across the plasma membrane; stimuli packaged into vesicles are released by exocytosis. Such stimuli have four main modes of action. Membrane-anchored stimuli on the surface can activate receptors on neighbouring cells directly (juxtacrine). Stimuli that are released from the cell can feed back to activate receptors on the same cell (autocrine); they can diffuse to neighbouring cells (paracrine); or they enter the blood stream to act on cells further a field (endocrine).

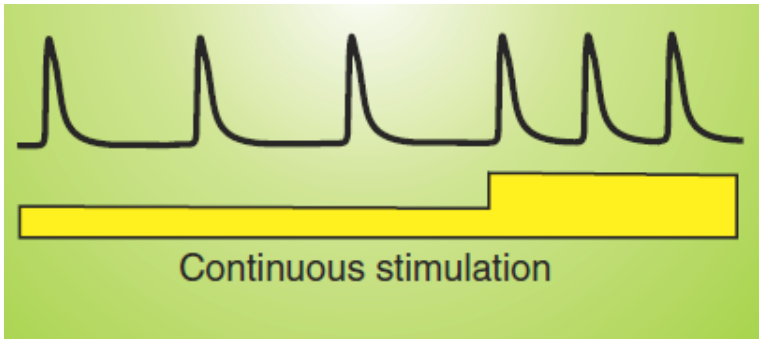
From the opinion of a physicist



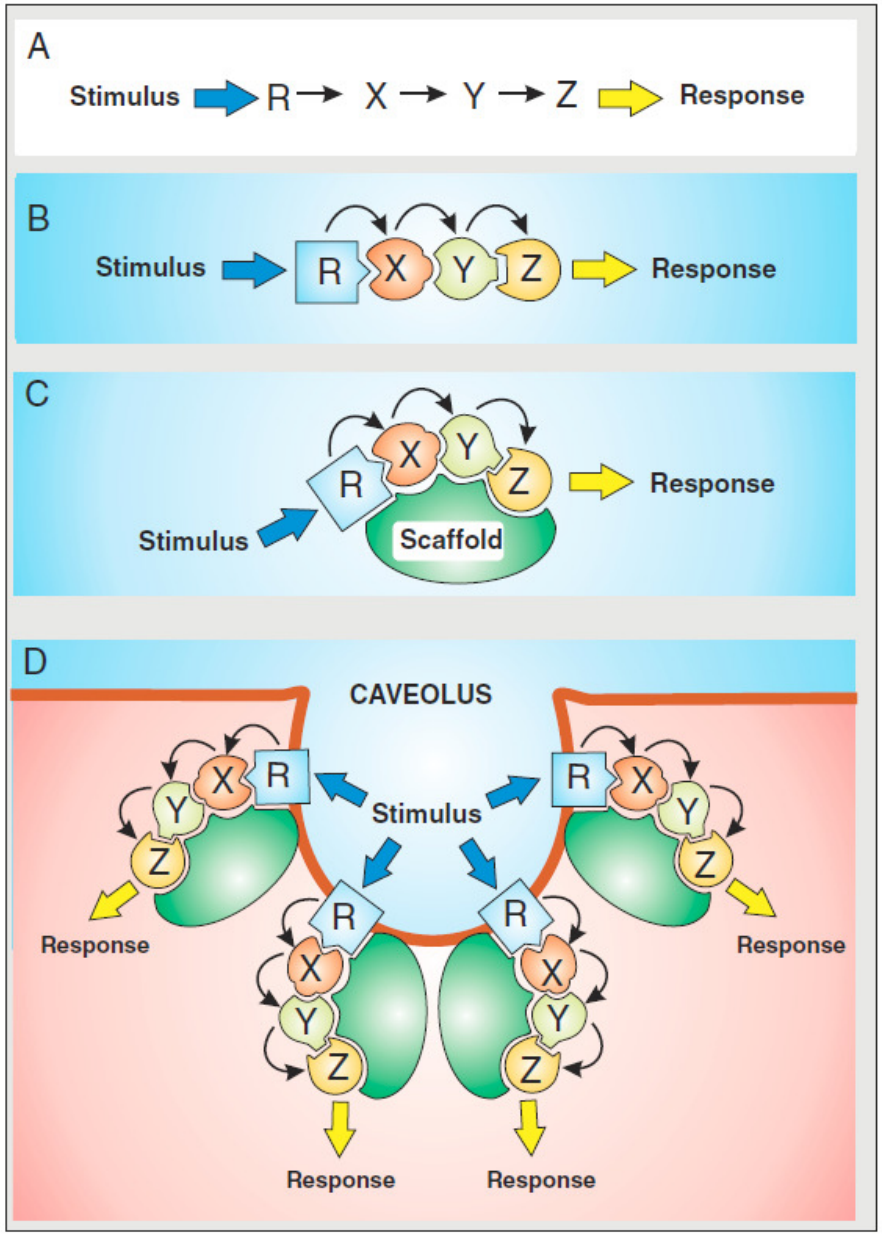
Temporal aspects of signalling







Spatial organization of cell signaling



A. The basic components of a typical signalling pathway, consisting of a receptor (R) and three signalling components (X, Y and Z).
B. In those cases where the signalling components are proteins, information is transmitted through protein–protein interactions using signal transduction domains. For example, a motif on protein X recognizes a specific binding site on protein Y and so on.
C. A variety of scaffolds function to hold together the individual components of signalling pathways to create macromolecular signalling complexes.
D. These macromolecular signalling complexes can be aggregated in specific locations within the cell, as occurs in lipid rafts and c

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Bimolecular interactions

Binding is not all-or-nothing:

$$A + B \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} AB$$

Portion of A and B will be bound, portion will be free

Equilibrium

Reaction is in equilibrium when concentrations do not change:

$$X \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} Y$$

$$\frac{d[Y]}{dt} = [X] \cdot k_{on} - [Y] \cdot k_{off} = 0 \qquad \text{(mass action law)}$$

(unimolecular reaction)

Equilibrium

Binding (bimolecular reaction):

$$A + B \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} AB$$

Reaction is in equilibrium when concentrations do not change:

$$\frac{d[AB]}{dt} = [A] \cdot [B] \cdot k_{on} - [AB] \cdot k_{off} = 0 \qquad \text{(mass action law)}$$

Equilibrium is reached when:

$$[A] \cdot [B] \cdot k_{on} = [AB] \cdot k_{off}$$

Equilibrium is still dynamic!!!

Equilibrium is reached when:

$$[A] \cdot [B] \cdot k_{on} = [AB] \cdot k_{off}$$

Rearrange to define **equilibrium dissociation constant K_D**:

$$K_D = \frac{k_{off}}{k_{on}} = \frac{[A] \cdot [B]}{[AB]}$$

Units:

$$K_D = \frac{[A] \cdot [B]}{[AB]} \qquad \{M\} = \frac{\{M\} \cdot \{M\}}{\{M\}}$$

Rate constants:

$$K_D = \frac{k_{off}}{k_{on}} = \frac{[A] \cdot [B]}{[AB]}$$

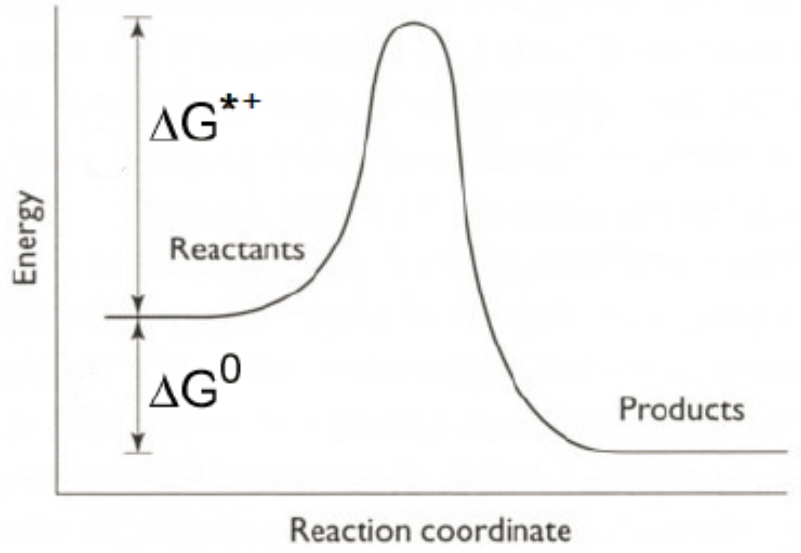
k_{off}: $\{s^{-1}\}$

k_{on}: $\{M^{-1} \cdot s^{-1}\}$

Reaction kinetics

Equilibrium thermodynamics does not provide any information on rates of chemical changes!

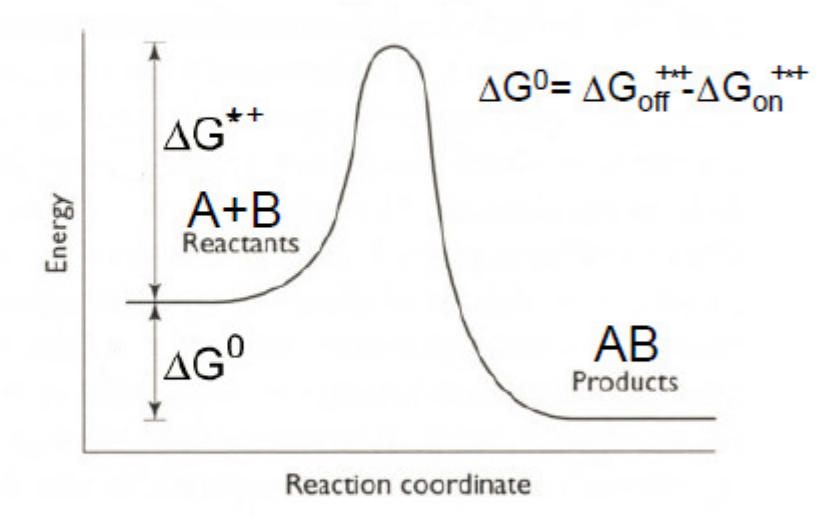
Energy profile for a generic chemical reaction:



Gibbs free energy (ΔG^0) determines ratio of reactants/products (thermodynamic properties), activation energy (ΔG^{++}) determines rates (kinetics)

Relation between K_D, $k_{on/off}$, and ΔG

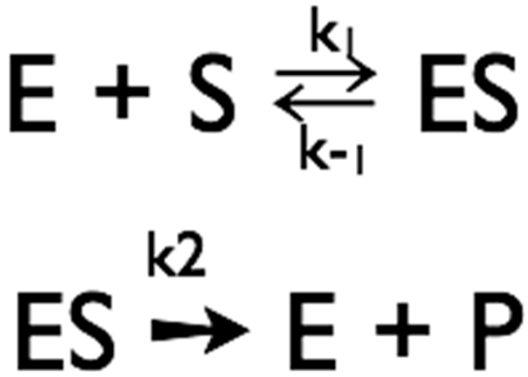
$$\frac{[A][B]}{[A \cdot B]} = \frac{k_{off}}{k_{on}} = K_D$$



In terms of free energies:

$$K_D = \frac{k_{off}}{k_{on}} = \frac{Ae^{(-\Delta G_{off}^{++}/RT)}}{Ae^{(-\Delta G_{on}^{++}/RT)}} = e^{(-(\Delta G_{off}^{++} - \Delta G_{on}^{++})/RT)} = e^{(-\Delta G^{0}/RT)}$$

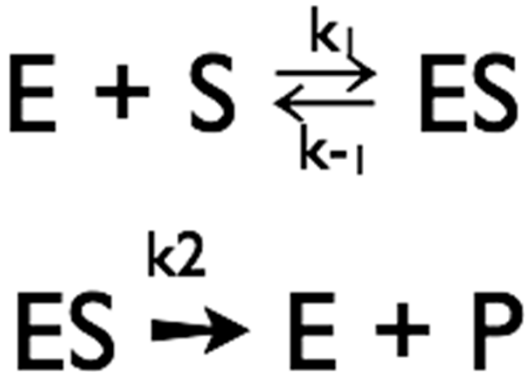
Michaelis-Menten Kinetics



Simplest enzyme mechanism

- One reactant (S)
- One intermediate (ES)
- One product (P)

Michaelis-Menten Kinetics



1. First step: The enzyme (E) and the substrate (S) reversibly and quickly form a non-covalent ES complex.
2. Second step: The ES complex undergoes a chemical transformation and dissociates to give product (P) and enzyme (E).
3. $v=k_2[ES]$
4. Many enzymatic reactions follow Michaelis–Menten kinetics, even though enzyme mechanisms are always more complicated than the Michaelis–Menten model.

Michaelis-Menten Kinetics

Now: we derive the Michaelis-Menten Equation

$d[ES]/dt = k_1[E][S] - k_{-1}[ES] - k_2[ES]$

$= 0$ (steady state assumption, see previous graph)

solve for [ES] (do the algebra)

$[ES] = [E][S]\, k_1/(k_{-1} + k_2)$

Define K_M (Michealis Constant)

$K_M = (k_{-1} + k_2)/k_1 \Rightarrow [ES] = [E][S]/K_M$

rearrange to give $K_M = [E][S]/[ES]$

Michaelis-Menten Kinetics

substitute $[E] = [E]_0 - [ES]$

$$\frac{([E]_0 - [ES])[S]}{[ES]} = K_M$$

multiply both sides by [ES]

$$K_M[ES] = ([E]_0 - [ES])[S]$$

solve for [ES]

$K_M = [E][S]/[ES]$

$$[ES] = \frac{[E]_0[S]}{K_m + [S]}$$

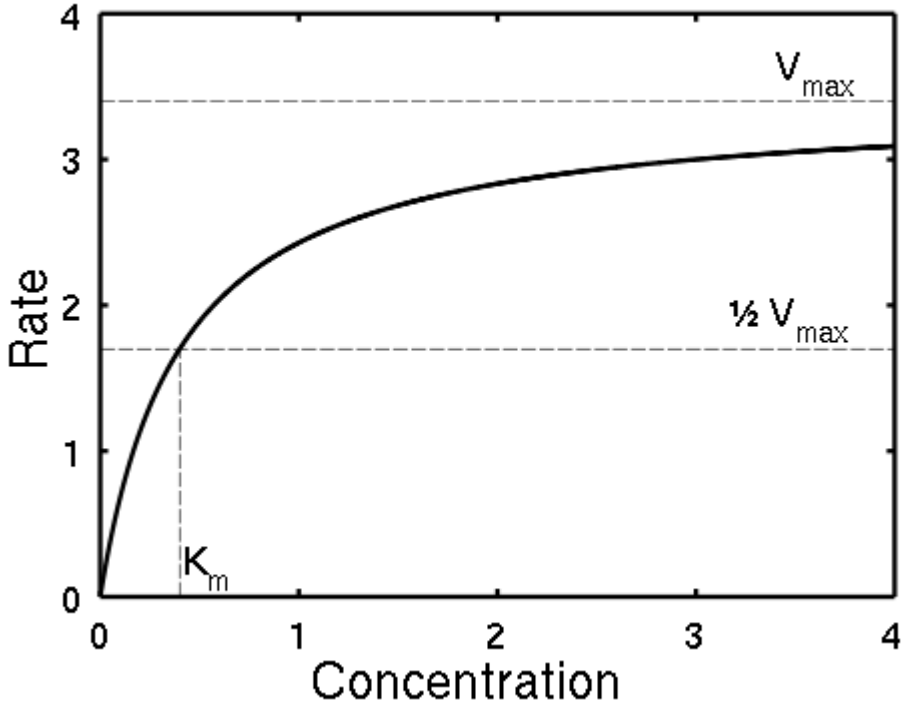
multiply both sides by k_2 (this gives get the velocity of the reaction)

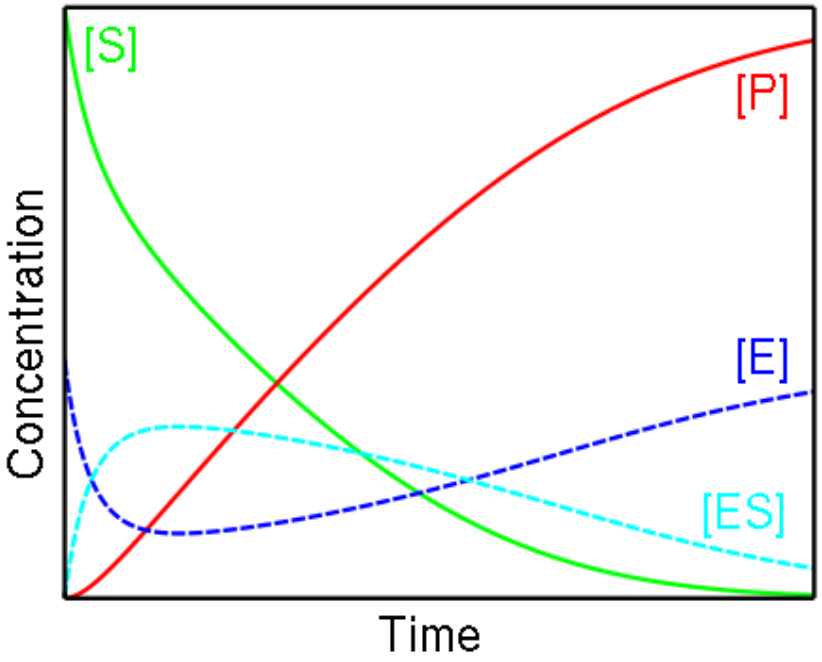
$$\frac{dP}{dt} = v = k_2[ES] = \frac{k_2[E]_0[S]}{K_M + [S]}$$

and remember that $k_2[E]_0 = v_{\max}$

$$v = \frac{v_{\max}[S]}{K_M + [S]}$$ Michaelis Menten Equation

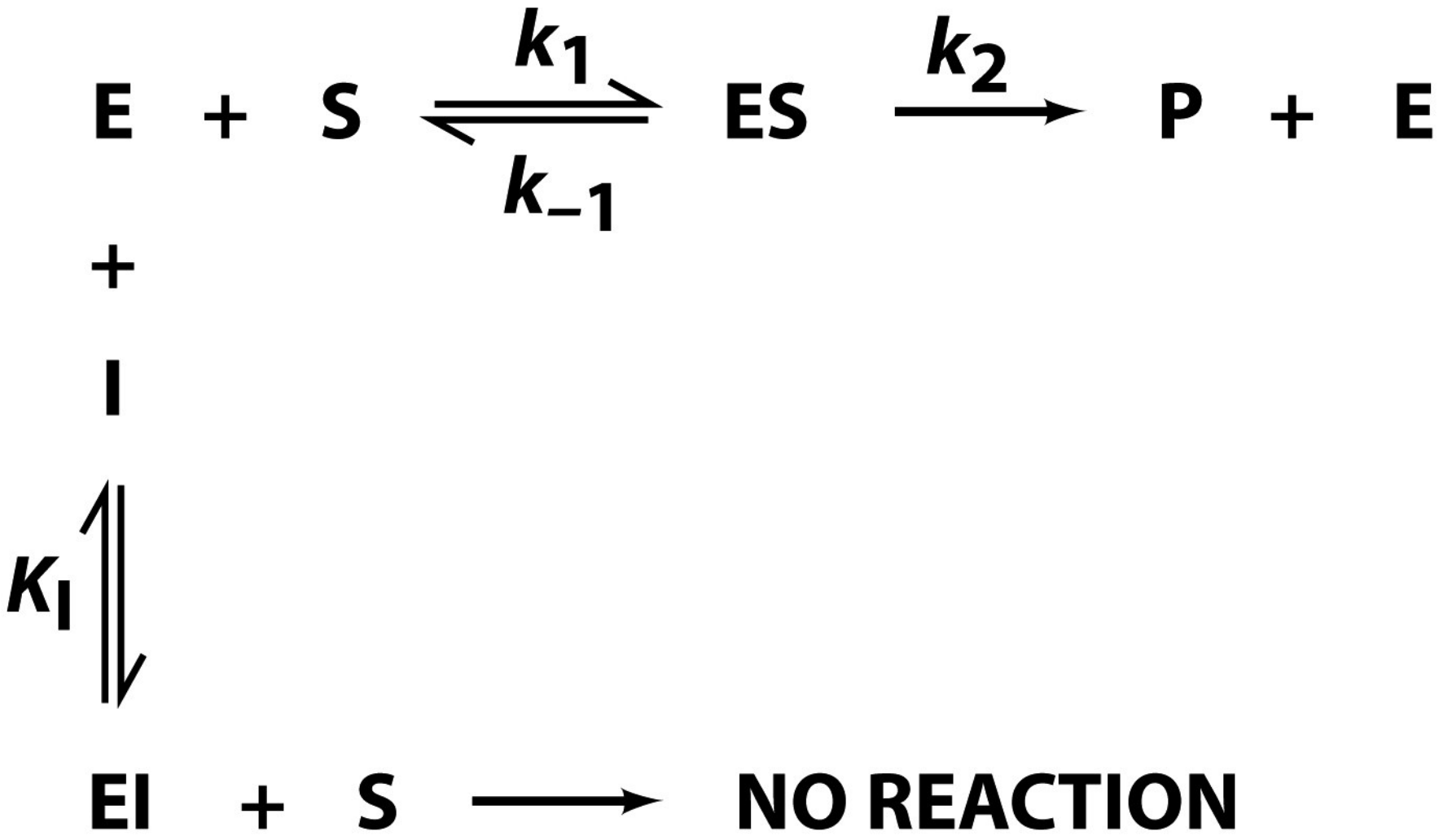
Michaelis-Menten Kinetics



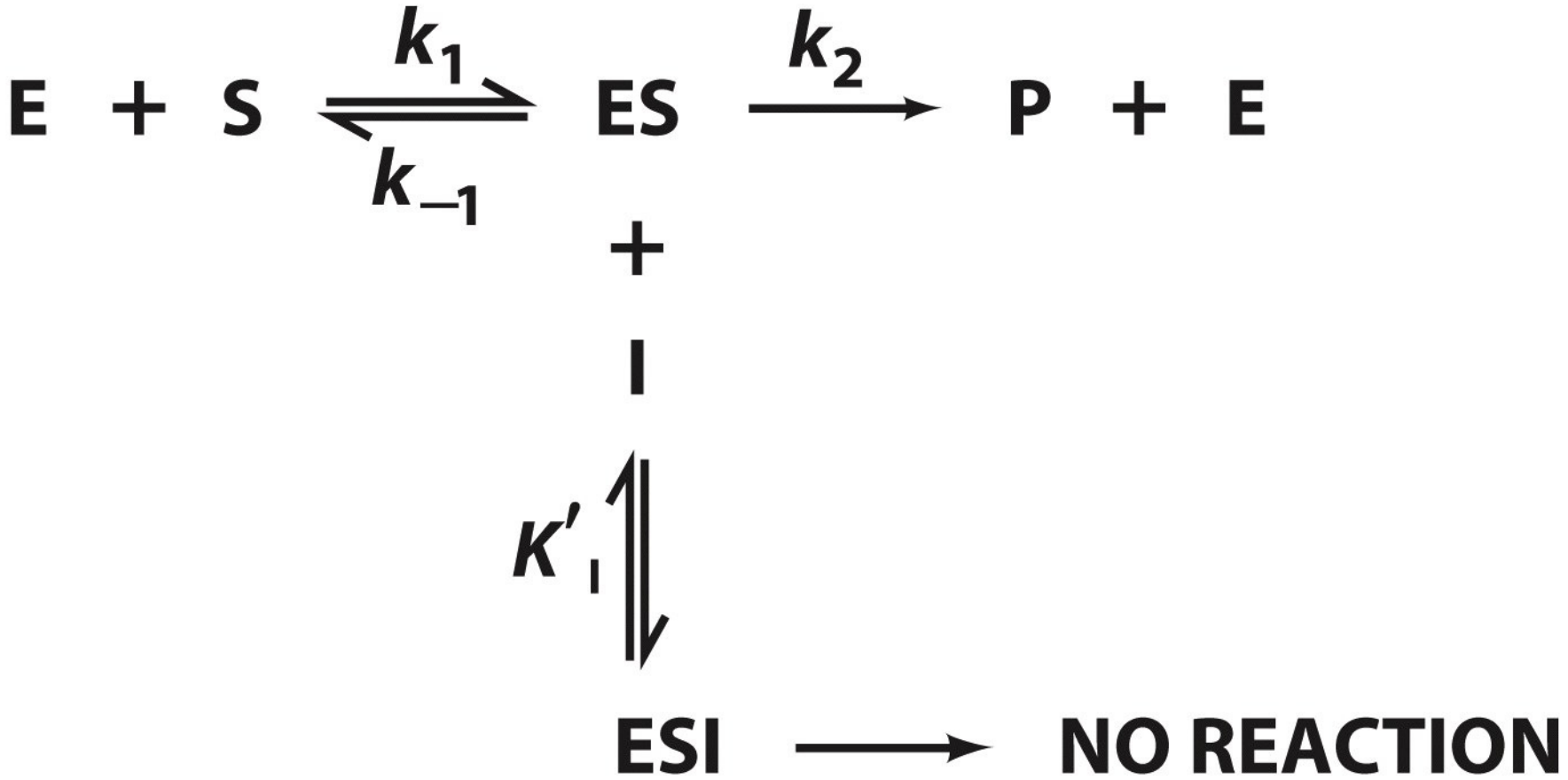


$$v = \frac{d[P]}{dt} = V_{\max}\frac{[S]}{K_m + [S]} = k_{\text{cat}}[E]_0\frac{[S]}{K_m + [S]}$$

Competitive Inhibition



Uncompetitive Inhibition



Mixed (competitive and uncompetitive) Inhibition

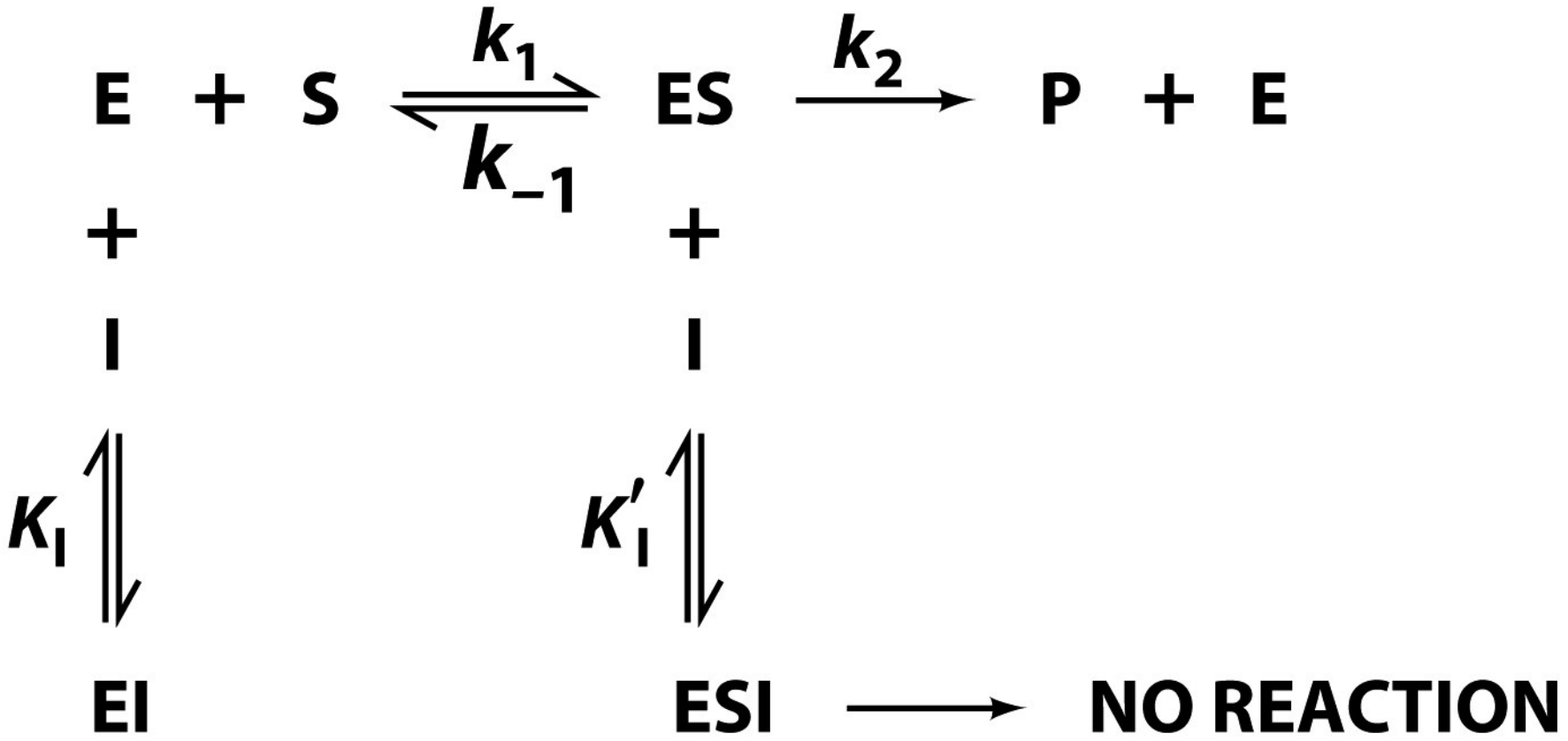
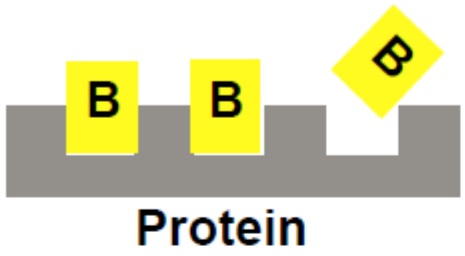


Table 12-2 Effects of Inhibitors on Michaelis–Menten Reactions[a]

Type of Inhibition	Michaelis–Menten Equation	Lineweaver–Burk Equation	Effect of Inhibitor
None	$v_o = \frac{V_{max}[S]}{K_M + [S]}$	$\frac{1}{v_o} = \frac{K_M}{V_{max}}\frac{1}{[S]} + \frac{1}{V_{max}}$	None
Competitive	$v_o = \frac{V_{max}[S]}{\alpha K_M + [S]}$	$\frac{1}{v_o} = \frac{\alpha K_M}{V_{max}}\frac{1}{[S]} + \frac{1}{V_{max}}$	Increases K_M^{app}
Uncompetitive	$v_o = \frac{V_{max}[S]}{K_M + \alpha'[S]} = \frac{(V_{max}/\alpha')[S]}{K_M/\alpha' + [S]}$	$\frac{1}{v_o} = \frac{K_M}{V_{max}}\frac{1}{[S]} + \frac{\alpha'}{V_{max}}$	Decreases K_M^{app} and V_{max}^{app}
Mixed (noncompetitive)	$v_o = \frac{V_{max}[S]}{\alpha K_M + \alpha'[S]} = \frac{(V_{max}/\alpha')[S]}{(\alpha/\alpha')K_M + [S]}$	$\frac{1}{v_o} = \frac{\alpha K_M}{V_{max}}\frac{1}{[S]} + \frac{\alpha'}{V_{max}}$	Decreases V_{max}^{app}; may increase or decrease K_M^{app}

[a] $\alpha = 1 + \frac{[I]}{K_I}$ and $\alpha' = 1 + \frac{[I]}{K_I'}$

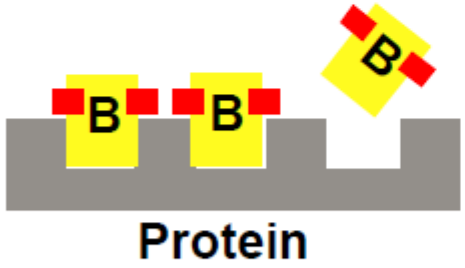
Non-cooperative versus cooperative



Not Cooperative

$$000 + B \underset{}{\overset{K}{\rightleftharpoons}} 00B$$

$$00B + B \overset{K}{\rightleftharpoons} 0BB$$



Cooperative

$$000 + B \overset{K}{\rightleftharpoons} 00B$$

$$00B + B \overset{\tau K}{\rightleftharpoons} 0BB$$

τ can be positive or negative (positive or negative cooperativity)

Hill Equation – Simplest Model

We assume that the ligands bind simultaneously (unrealistic!):

$$E + n\ S \longleftrightarrow ES$$

Assuming Rapid Equilibrium

$$K = \frac{ES}{E\ .\ S^n}$$

$$v = \frac{\mathrm{Vmax}\ S^n}{K + S^n}$$

← Hill Coefficient

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$$v = \frac{\mathrm{Vmax}\ S^{n}}{K + S^{n}}$$

← Hill Coefficient

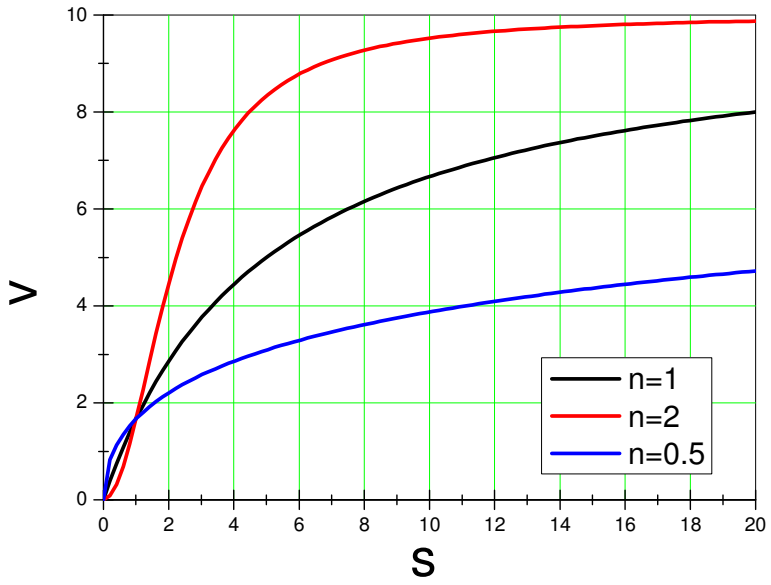
The Hill Coefficient, n, describes the degree of cooperativity.

If n = 1, the equation reverts to a simple hyperbolic response.

n > 1 : Positive Cooperativity

n = 1 : No Cooperativity

n < 1 : Negative Cooperativity



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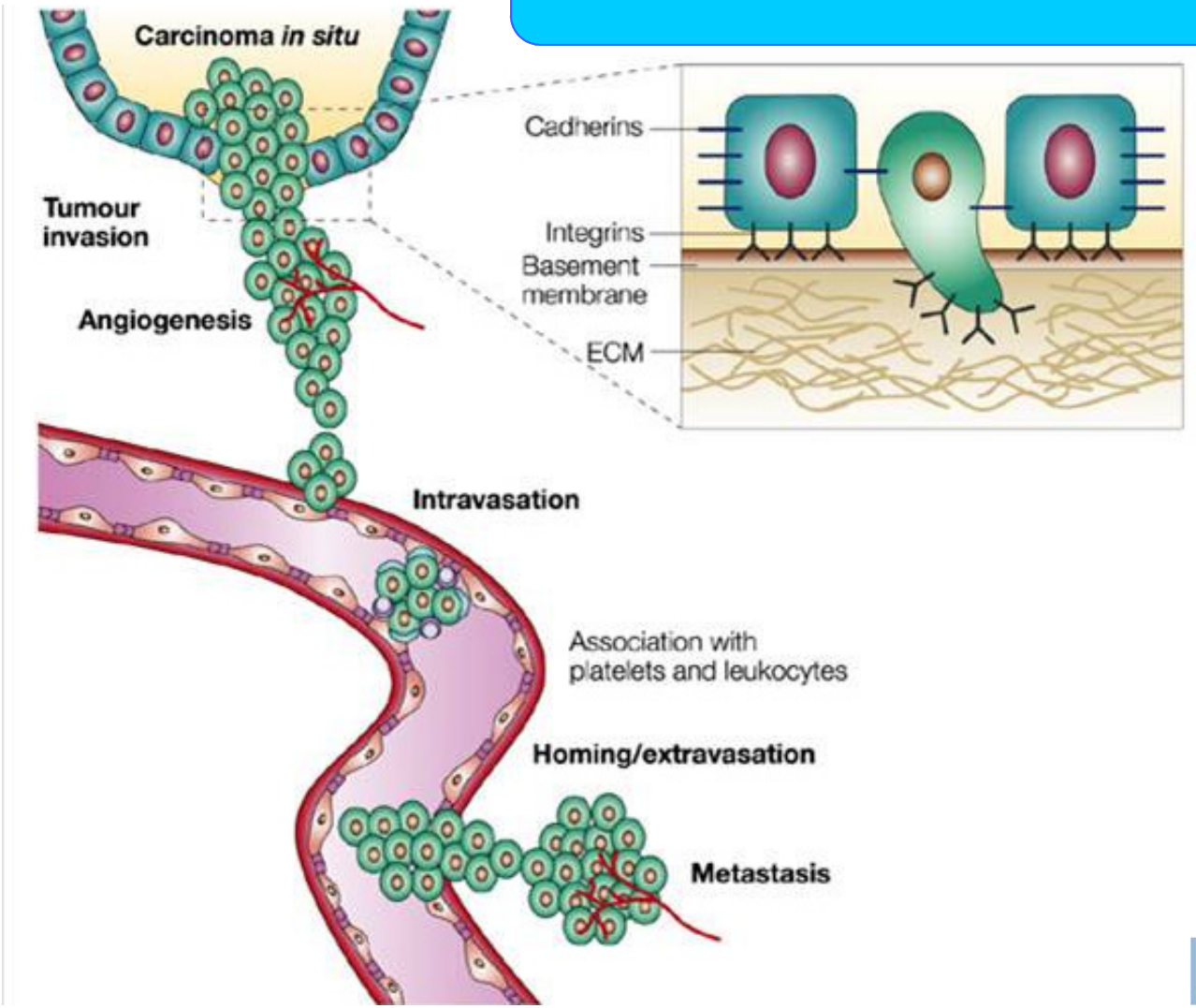
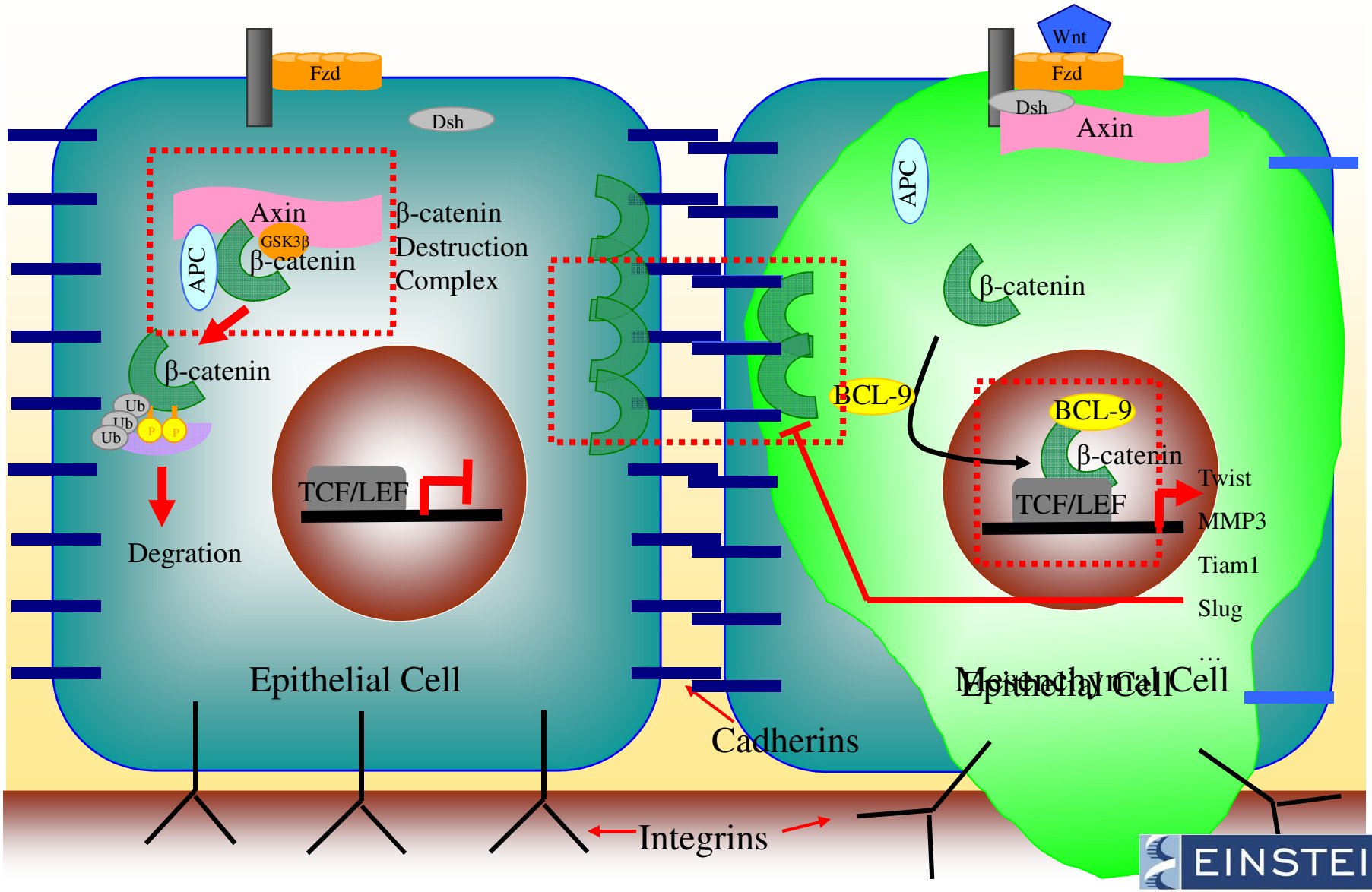
Wnt signaling pathway

Epithelial-mesenchymal Transition



Wnt signaling pathway



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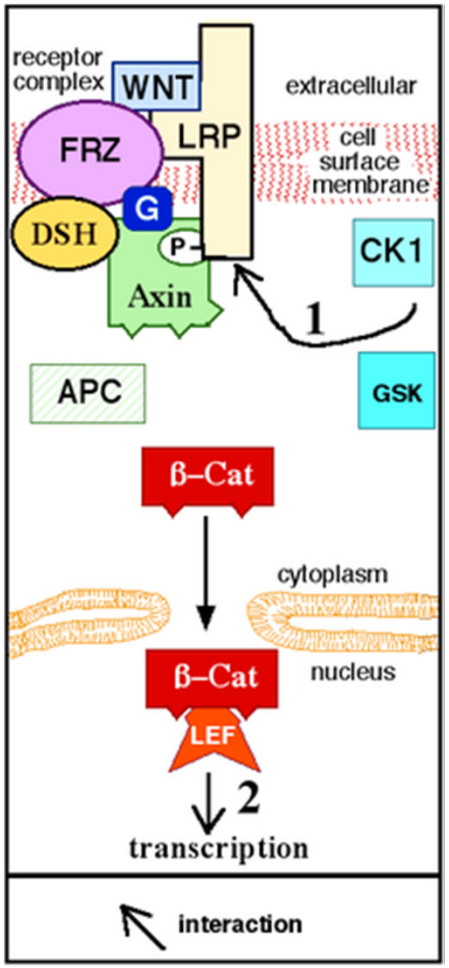
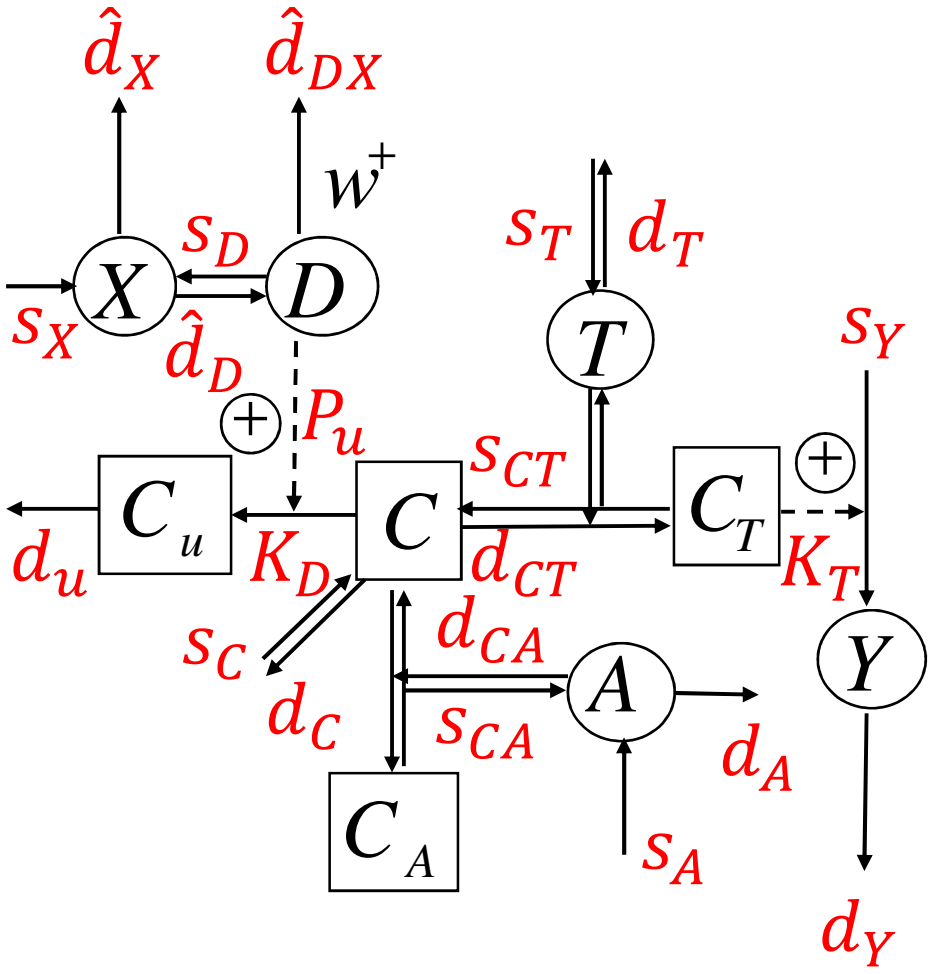
A simple model of Wnt signaling network





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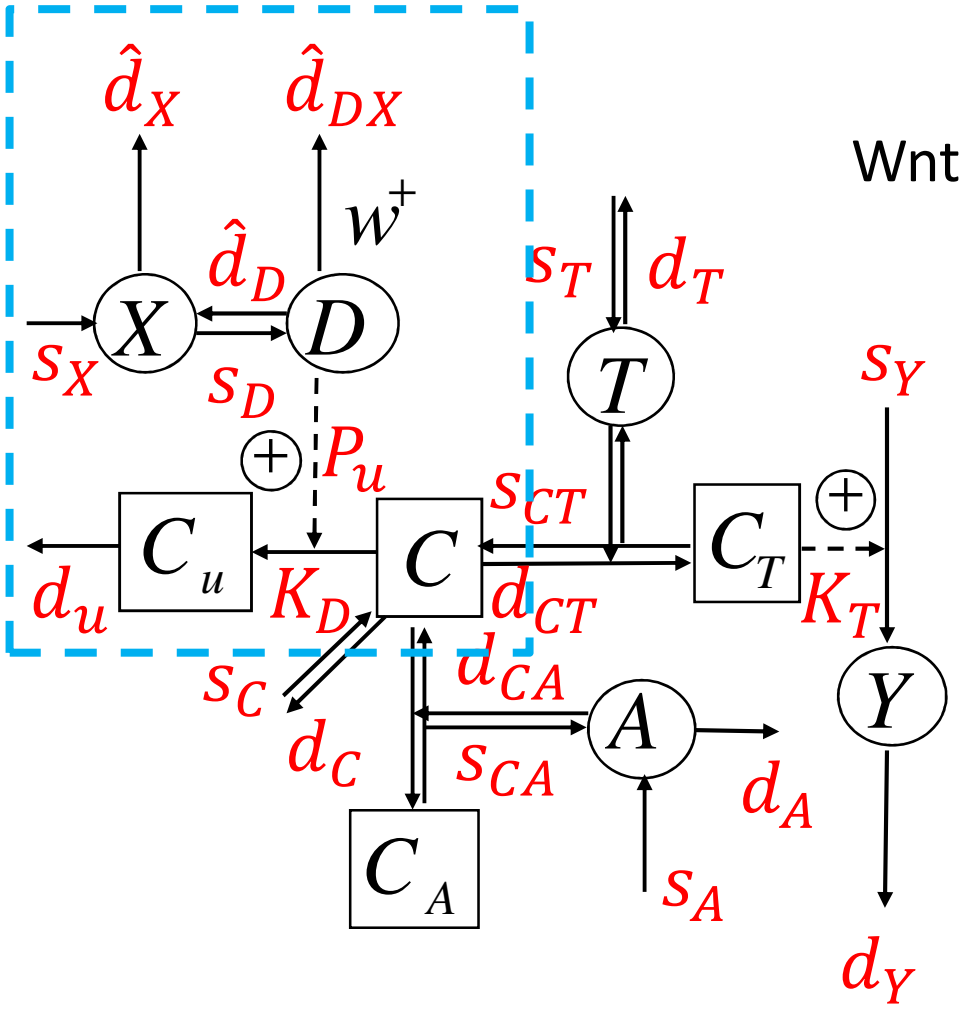
A simple model of Wnt signaling network



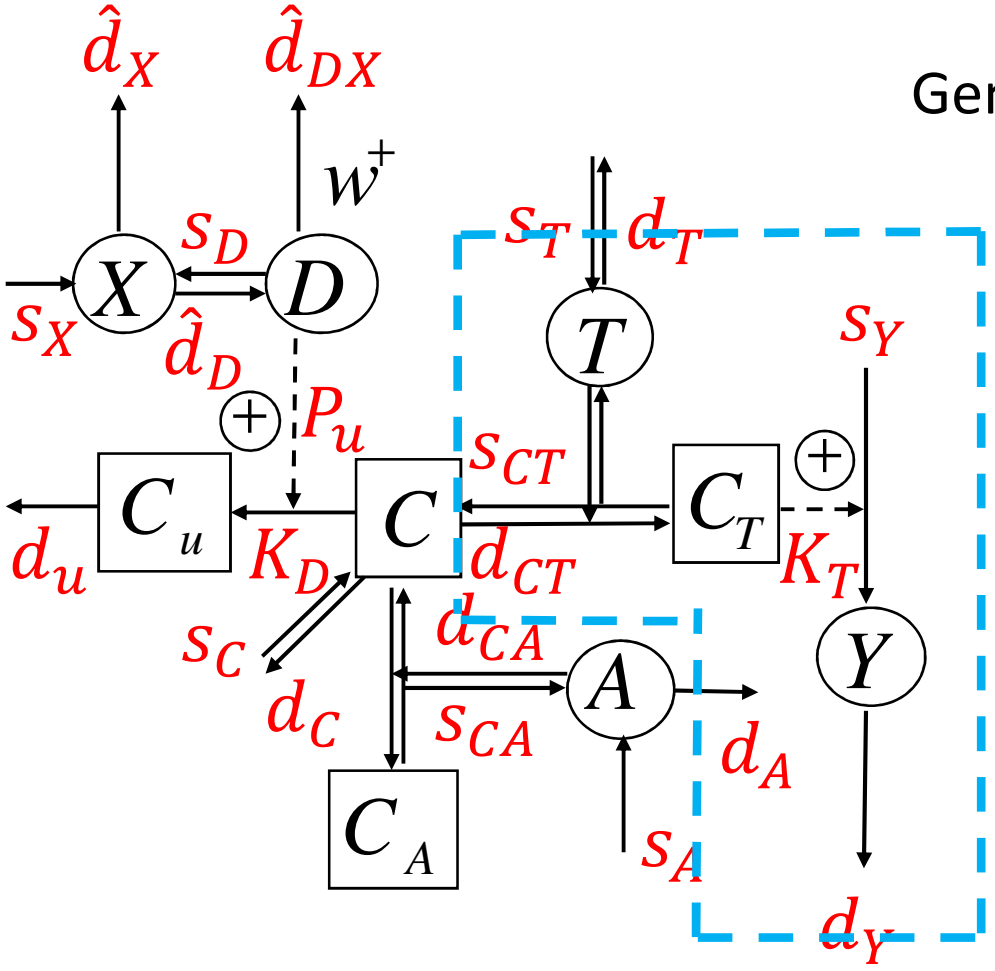
Wnt stimuli and destruction cycle

$$\frac{d[D]}{dt} = s_D[X] - (\hat{d}_D + \hat{d}_{DX}(s_\infty))[D]$$

$$\frac{d[X]}{dt} = s_X - s_D[X] - \hat{d}_X[X] + \hat{d}_D\,[D]$$

$$\frac{d[C_u]}{dt} = \frac{P_u[D][C]}{[C] + K_D} - d_u[C_u]$$

A simple model of Wnt signaling network



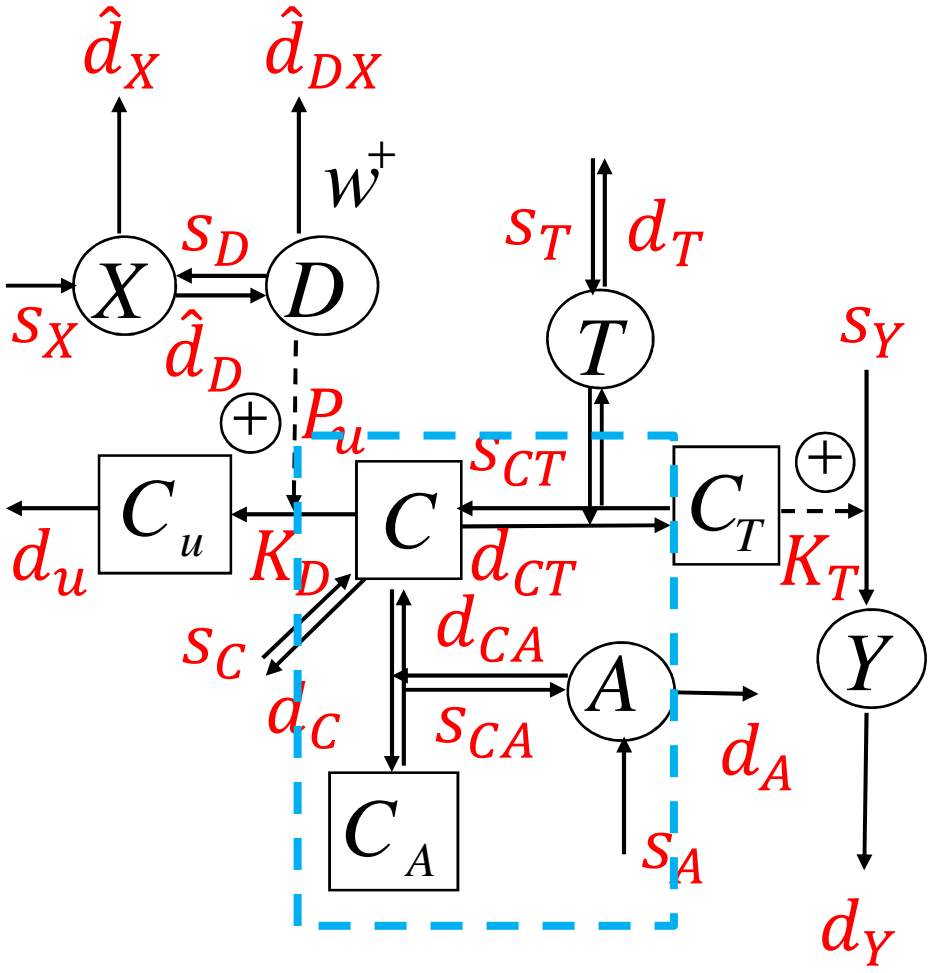
Gene regulation

$$\frac{d[T]}{dt} = s_T + d_{CT}[C_T] - (s_{CT}[C] + d_T)[T]$$

$$\frac{d[C_T]}{dt} = s_{CT}[C][T] - d_{CT}[C_T]$$

$$\frac{d[Y]}{dt} = \frac{s_Y[C_T]}{[C_T] + K_T} - d_Y[Y]$$

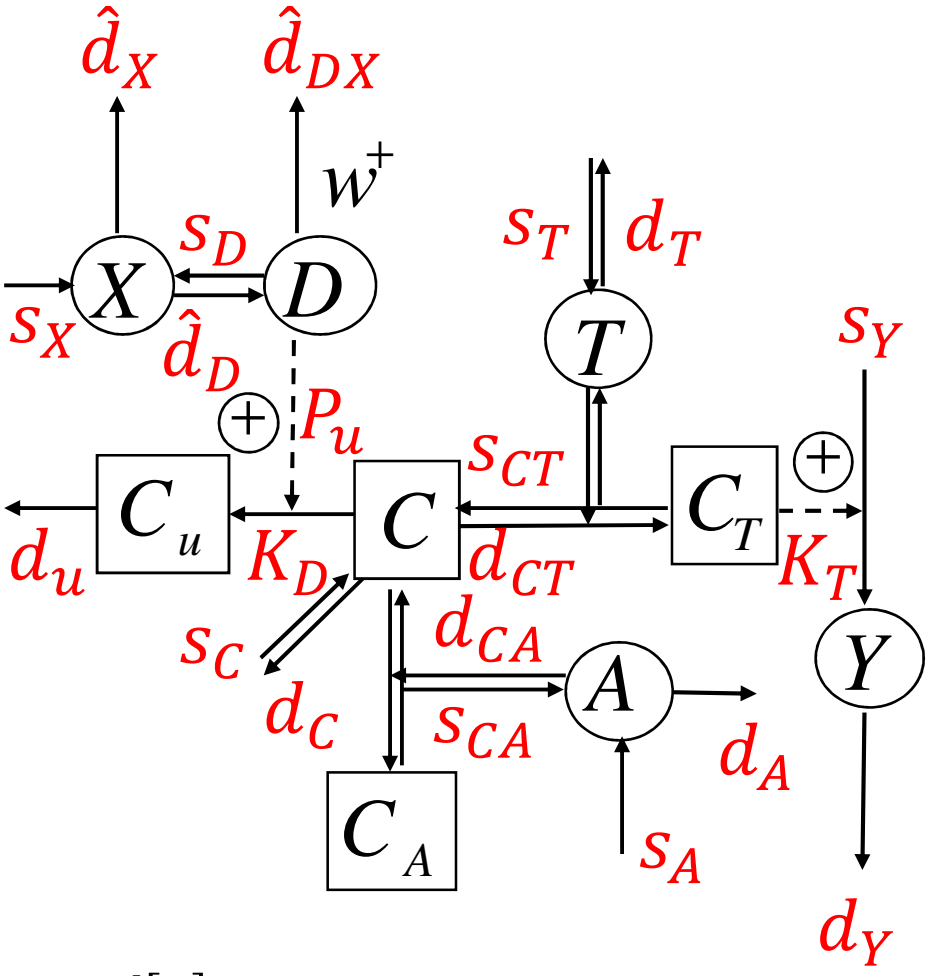
A simple model of Wnt signaling network



Cell adhesion

$$\begin{cases} \dfrac{d[A]}{dt} = s_A + d_{CA}[C_A] - (s_{CA}[C] + d_A)[A] \\ \dfrac{d[C_A]}{dt} = s_{CA}[C][A] - d_{CA}[C_A] \end{cases}$$

A simple model of Wnt signaling network



$$\frac{d[C]}{dt} = s_C + d_{CA}[C_A] + d_{CT}[C_T]$$

$$-(s_{CA}[A] + s_{CT}[T] + d_c)[C] - \frac{P_u[D][C]}{[C] + K_D}$$

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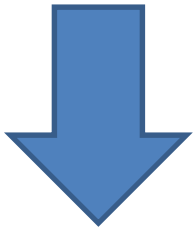
A simple model of Wnt signaling network

$$\begin{cases} \dfrac{d[D]}{dt} = s_D[X] - (\hat{d}_D(s_\infty) + \hat{d}_{DX}(s_\infty))[D] \\ \dfrac{d[X]}{dt} = s_X - s_D[X] - \hat{d}_X[X] + \hat{d}_{DX}(s_\infty)[D] \\ \dfrac{d[C_u]}{dt} = \dfrac{P_u[D][C]}{[C] + K_D} - d_u[C_u] \end{cases}$$

$$\begin{cases} \dfrac{d[T]}{dt} = s_T + d_{CT}[C_T] - (s_{CT}[C] + d_T)[T] \\ \dfrac{d[C_T]}{dt} = s_{CT}[C][T] - d_{CT}[C_T] \\ \dfrac{d[Y]}{dt} = \dfrac{s_Y[C_T]}{[C_T] + K_T} - d_Y[Y] \end{cases}$$

$$\begin{cases} \dfrac{d[A]}{dt} = s_A + d_{CA}[C_A] - (s_{CA}[C] + d_A)[A] \\ \dfrac{d[C_A]}{dt} = s_{CA}[C][A] - d_{CA}[C_A] \\ \dfrac{d[C]}{dt} = s_C + d_{CA}[C_A] + d_{CT}[C_T] \\ -(s_{CA}[A] + s_{CT}[T] + d_c)[C] - \dfrac{P_u[D][C]}{[C] + K_D} \end{cases}$$



Solve these ODEs by Mathematica

Dsolve and NDSolve

- For ODEs without initial conditions, use Dsolve

Type of Equation	Syntax	Example Equation(s)	Dsolve for Example
One ODE	Dsolve[eqn,y,x]	y''+16y=0	Dsolve[y''[x]+16y[x]==0,y,x]
Multiple ODEs	Dsolve[{eqn1,eqn2,…},{y1,y2,…},x]	y1'-y2-x=0 y2'-y1-1=0	Dsolve[{y1'[x]-y2[x]-x==0,y2'[x]-y1[x]-1==0},{y1,y2},x]

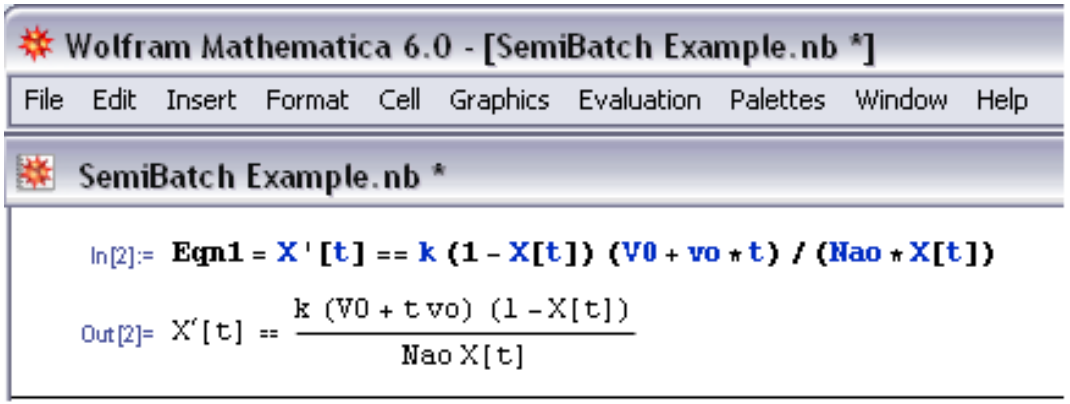
- For ODEs with initial conditions, use NDSolve

Type of Equation	Syntax	Example Equation(s)	Dsolve for Example
One ODE	NDSolve[{eqn,i1,i2…},y,{x,xmin,xmax}]	y''+16y=0,y(0)=1, y'(0)=0	NDSolve[{y''[x]+16y==0,y[0]==1,y'[0]==0},y,{x,0,30}]
Multiple ODEs	NDSolve[{eqn1, eqn2, ..., i1, i2, …},{y1,y2},{x,xmin,xmax}]	y1'-y2-x=0 y2'-y1-1=0 y1(0)=0,y2(0)=0	NDSolve[{y1'[x]-y2[x]-x==0,y2'[x]-y1[x]-1==0,y1[0]==y2[0]==0},{y1,y2},{x,0,20}]

Entering in Mathematica

- Open Mathematica (Version shown here is Mathematica 6)
- Use the following steps to solve the ODE in Mathematica:

1. Input ODE



2. Define given variables

```
In[4]:= k = 2.7;

In[5]:= V0 = 5;

In[9]:= vo = 0.05;

In[7]:= Nao = 2500;
```

Entering in Mathematica (cont.)

3. Define a variable to NDSolve and enter inputs

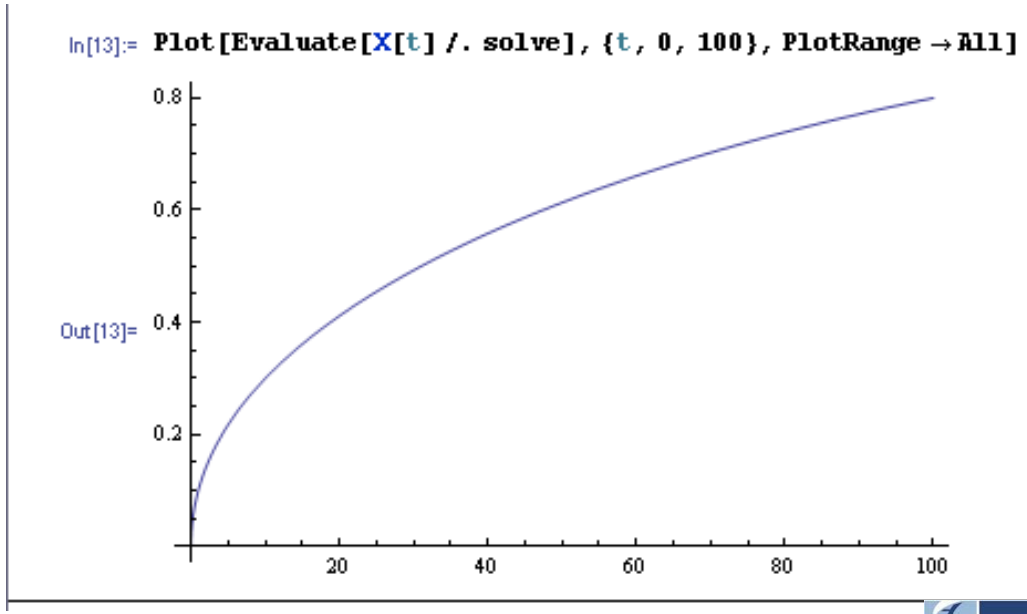
```
In[12]:= solve = NDSolve[{Eqn1, X[0] == 0.0001}, X, {t, 0, 100}];
```

X is conversion, and X[0] is entered as 0.0001 instead of 0 so that the ODE will not be undefined

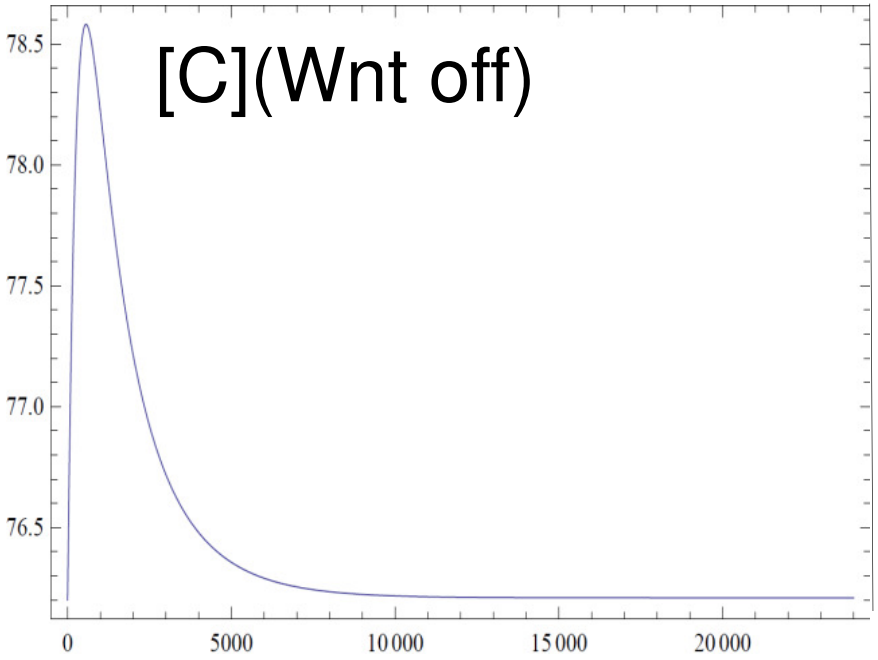
4. Plot the solution

```
In[13]:= Plot[Evaluate[X[t] /. solve], {t, 0, 100}, PlotRange → All]
```

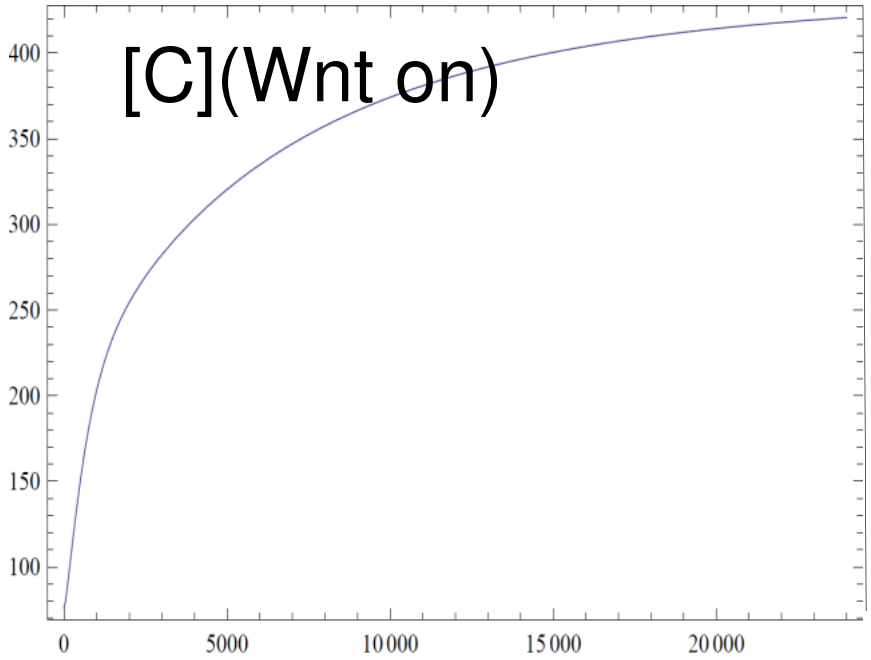
Out[13]=



A simple model of Wnt signaling network



time



time

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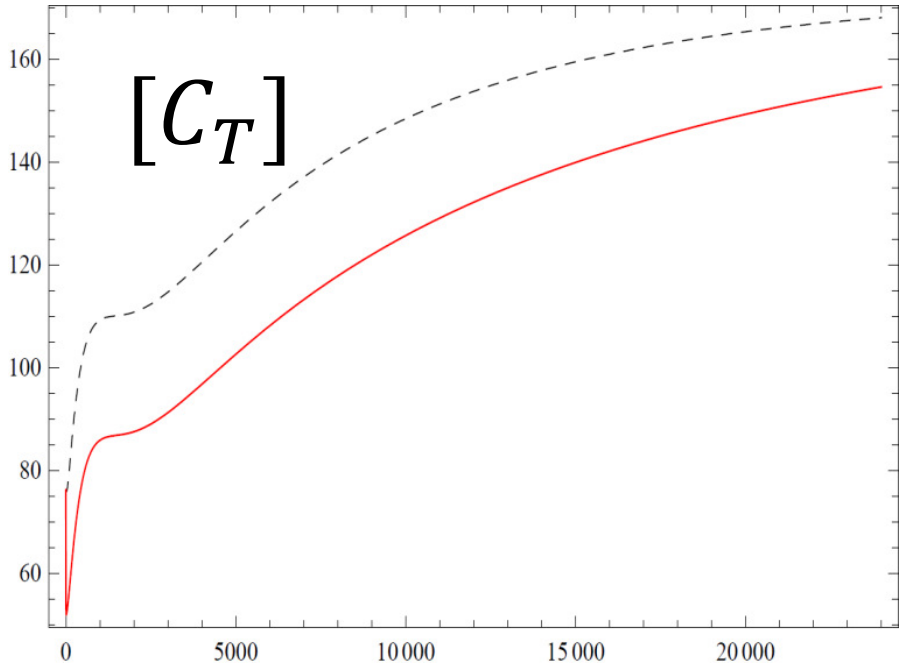
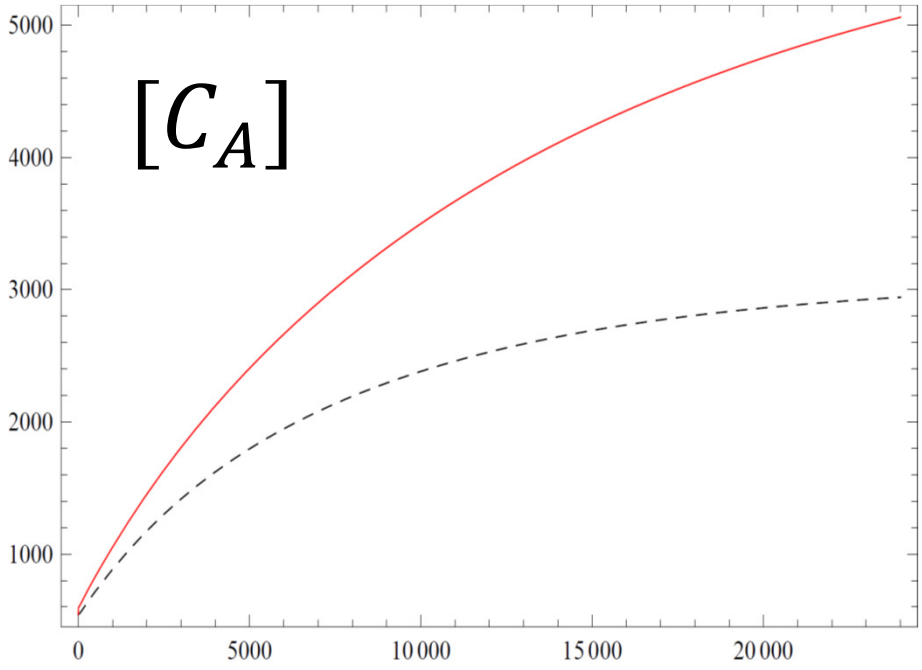


time

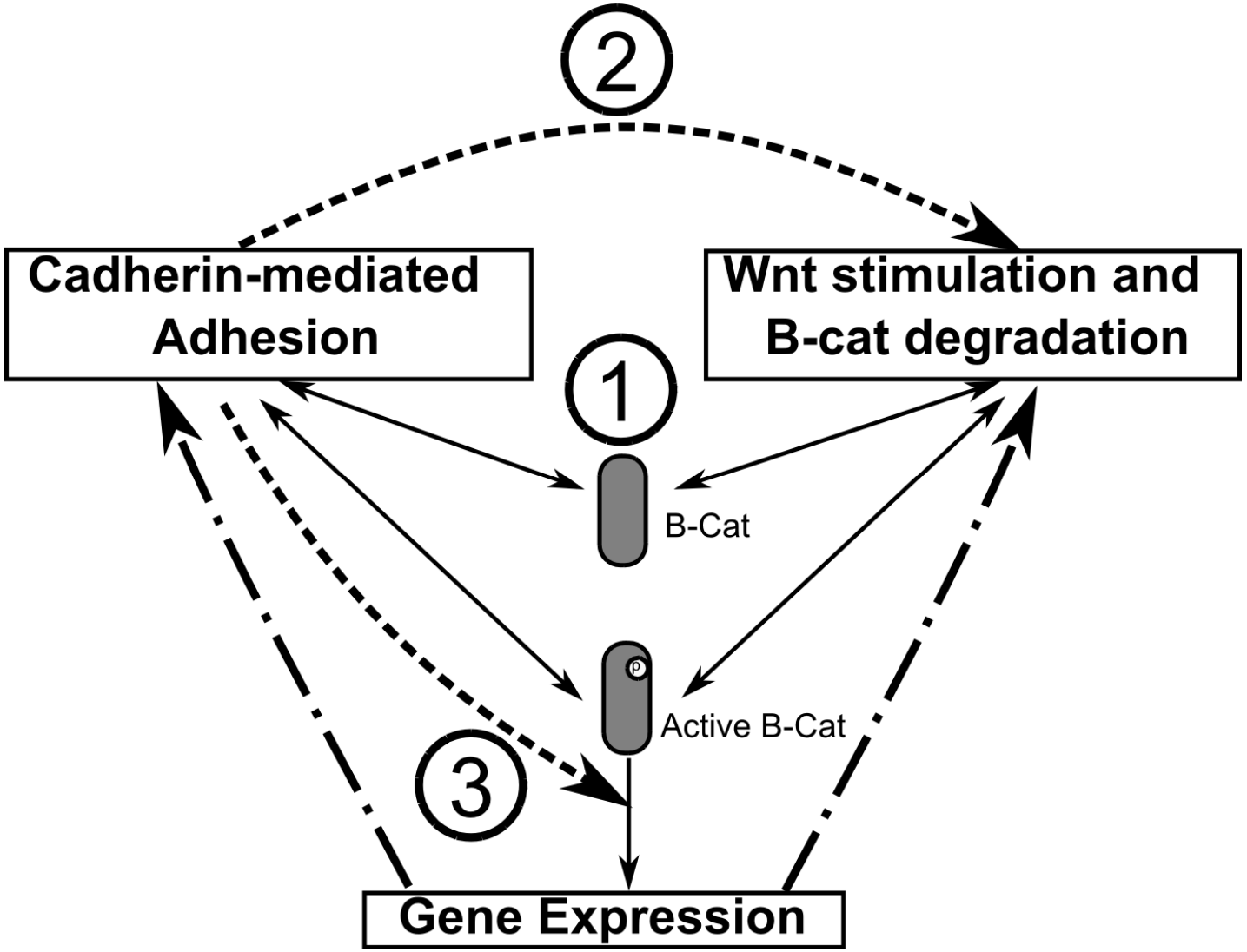


time

Outline

- Background
- Theory of chemical kinetics
- Modeling temporal dynamics of subcellular processes
    - A simple model of Wnt signaling network
    - A more complicated model of Wnt network
    - Network crosstalk
- Simulations of spatial organization of subcellular processes

A more complicated model of Wnt signaling network



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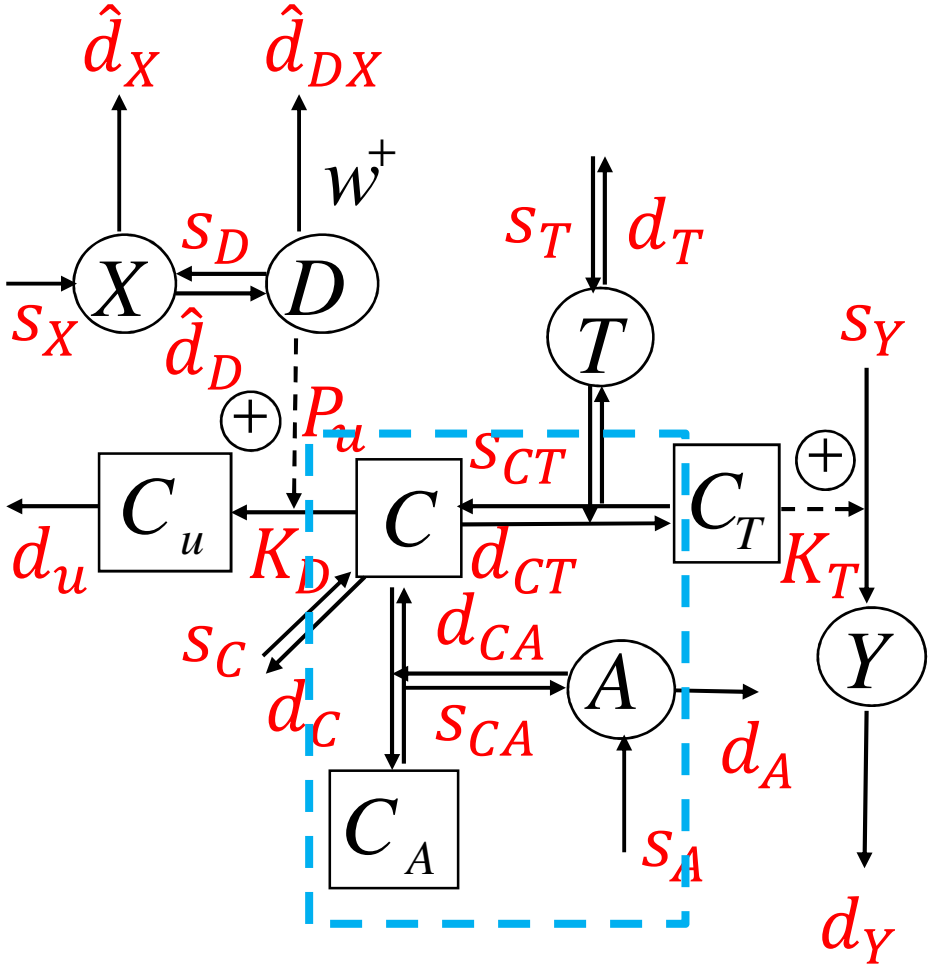
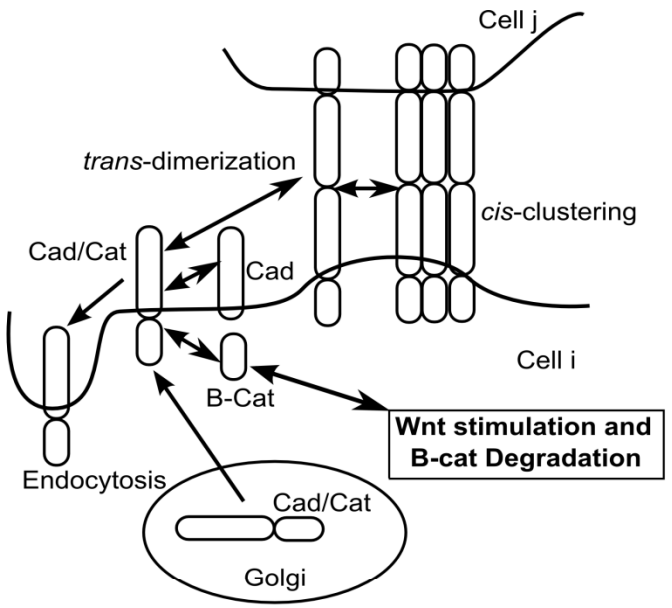
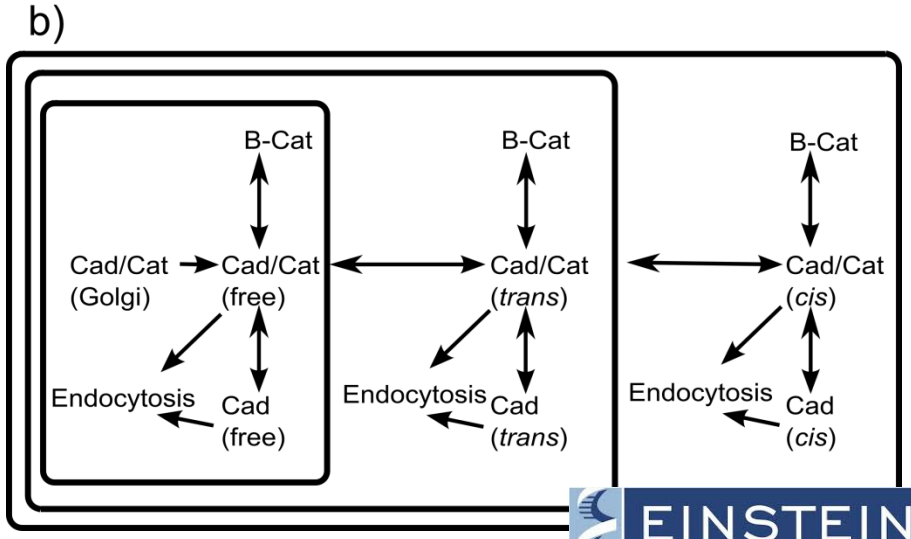
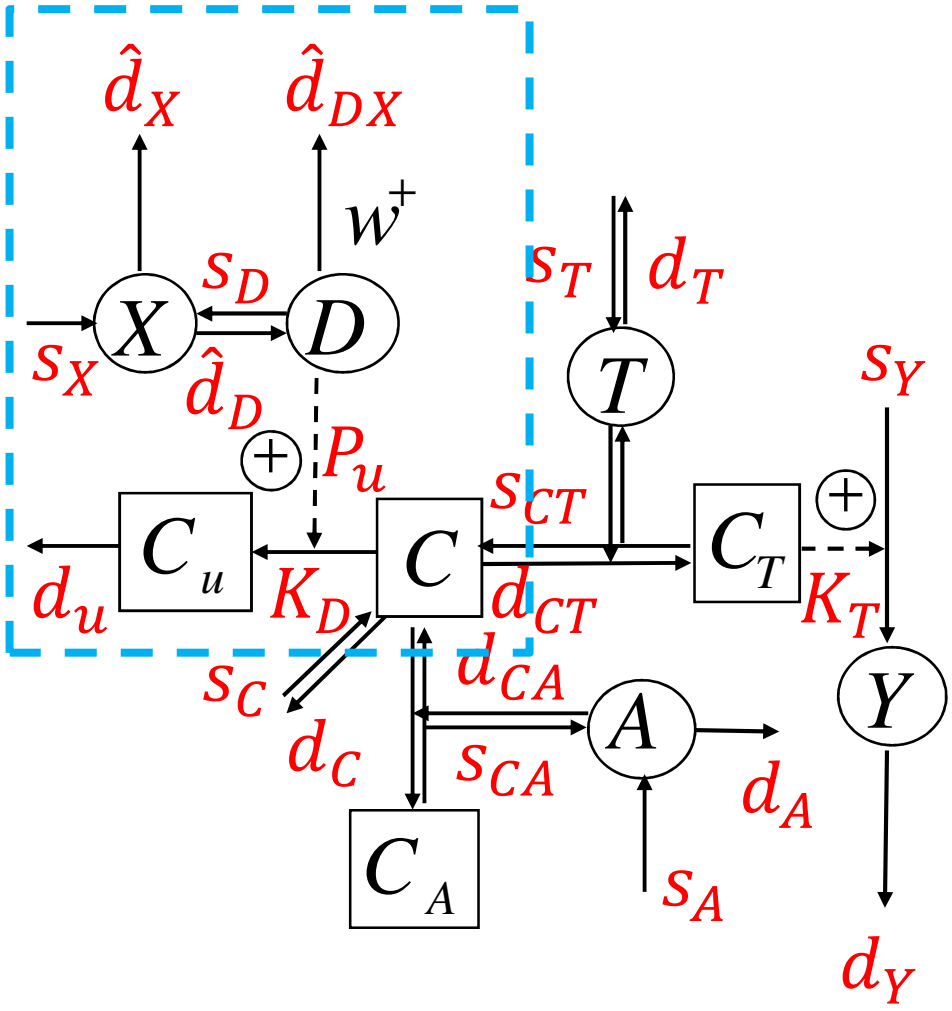
A more complicated model of Wnt signaling network

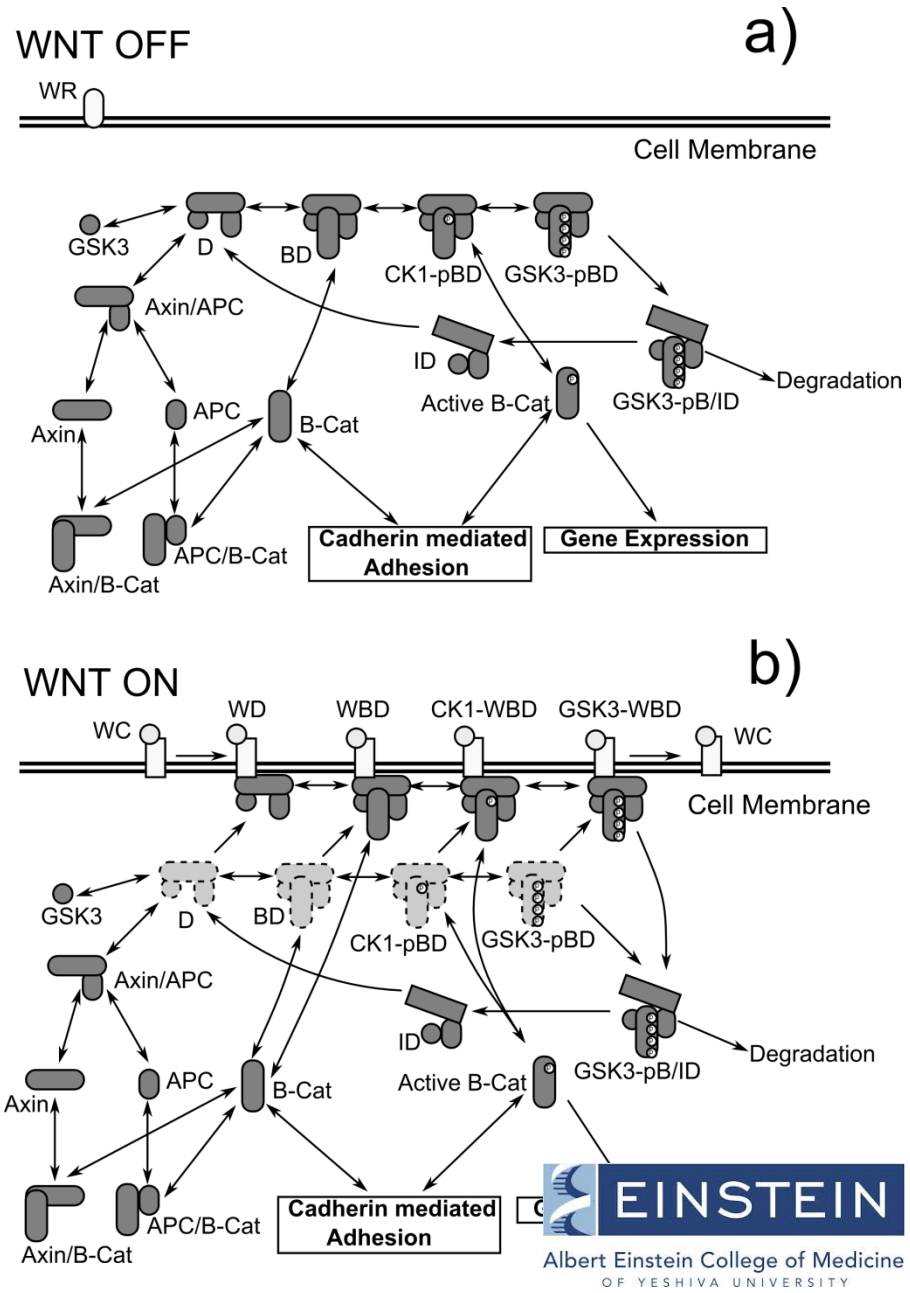




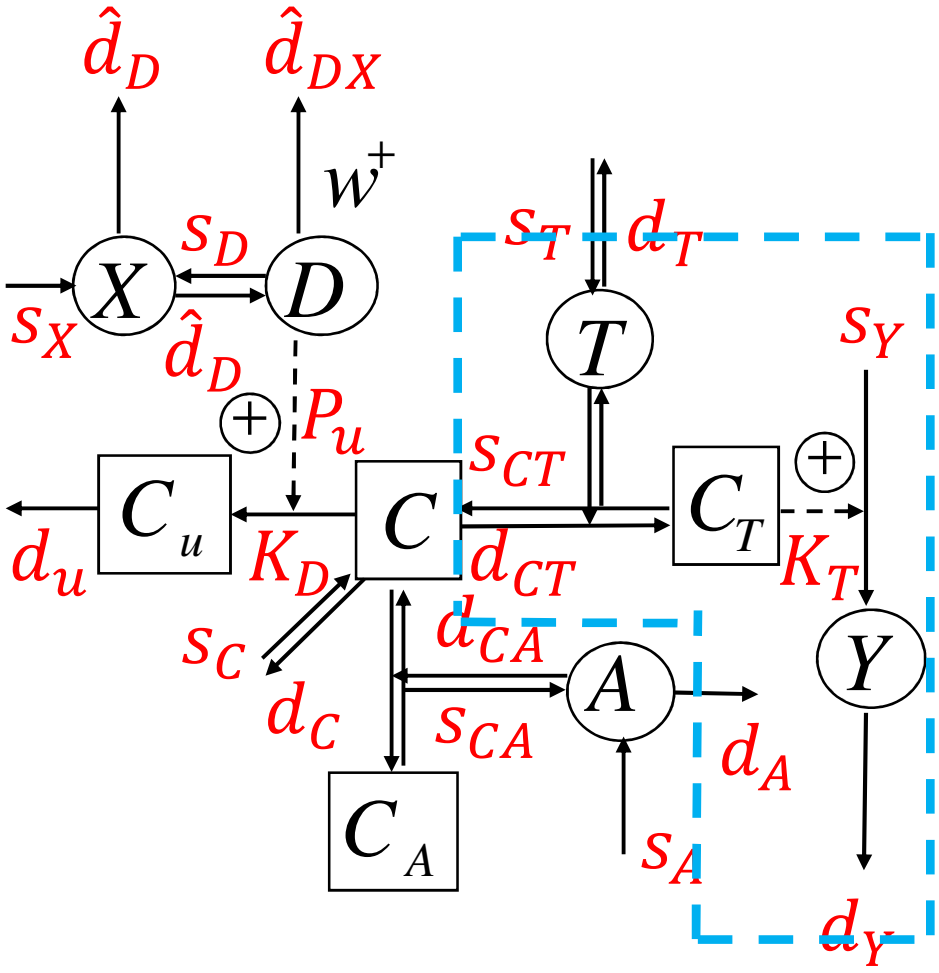


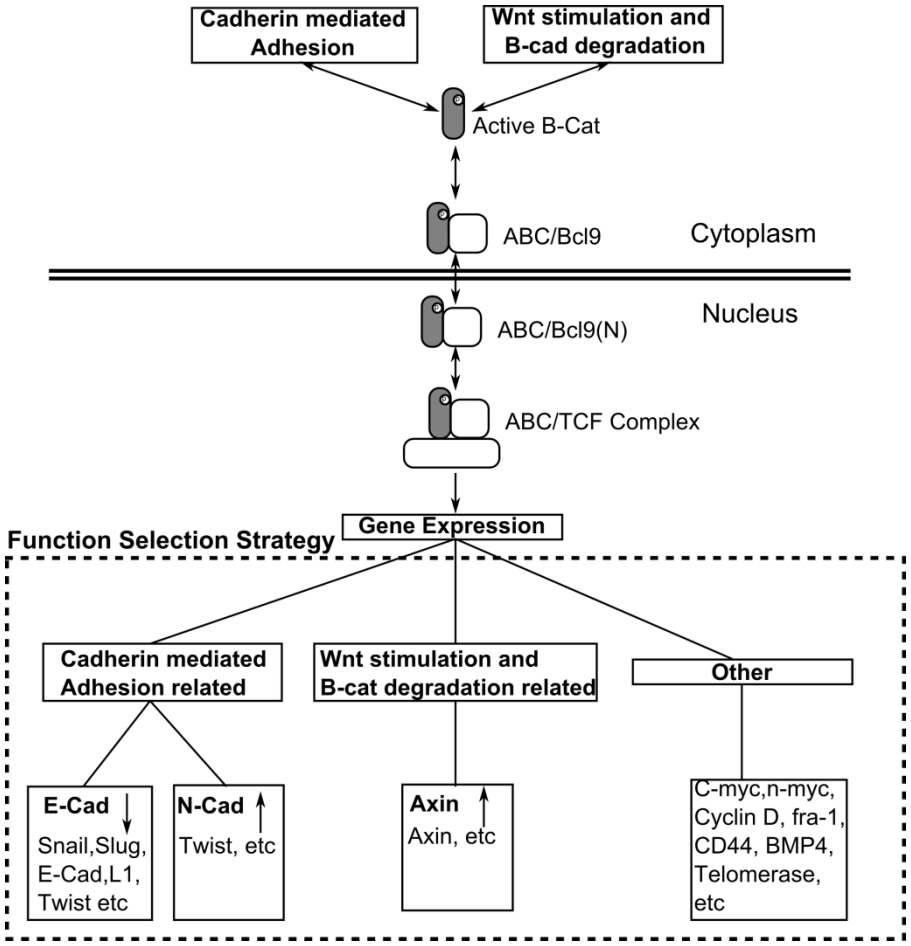
A more complicated model of Wnt signaling network





A more complicated model of Wnt signaling network





A more complicated model of Wnt signaling network

	Index	Chemical reactions	Descriptions	Parameters
	(1)	S_{Axin}	Synthesis of proteins	$S_{Axin} = 20nMh^{-1}$
	(2)	S_{APC}		$S_{APC} = 200nMh^{-1}$
	(3)	S_{B-cat}		$S_{B-cat} = 602nMh^{-1}$
	(4)	S_{WC}		$S_{WC} = 346nMh^{-1}$
	(5)	$d_{Axin}[Axin]$	Degradation of proteins	$d_{Axin} = 1h^{-1}$
	(6)	$d_{APC}[APC]$		$d_{APC} = 1h^{-1}$
	(7)	$d_{B-cat}[B-cat]$		$d_{B-cat} = 0.1h^{-1}$
	(8)	$k_{\deg}^{WC}[WC]$		$k_{\deg}^{WC} = 1h^{-1}$
	(9)	$d_{B-cat}[ABC]$		$d_{B-cat} = 0.1h^{-1}$
Adhesion Network	(10)	$S_{Cad/Cat}$	Synthesis of Cad/Cat complex in Golgi	$S_{Cad/Cat} = 206nMh^{-1}$
	(11)	$k_{\deg}^{BC}[Cad/Cat]_{golgi}$	Degradation of Cad/Cat complex in Golgi	$k_{\deg}^{BC} = 1h^{-1}$
	(12)	$k_{shuttle}[Cad/Cat]_{golgi}$	Shuttling Cad/Cat complex from Golgi to cell surfaces	$k_{shuttle} = 2.43h^{-1}$
	(13)	$k_{endo}^{free}[Cad/Cat]_{free}$	Endocytosis of Cad/Cat complex on cell surfaces	$k_{endo}^{free} = 1h^{-1}$
	(14)	$k_{endo}^{trans}[Cad/Cat]_{trans}$		$k_{endo}^{trans} = 0.5h^{-1}$
	(15)	$k_{endo}^{cis}[Cad/Cat]_{cis}$		$k_{endo}^{cis} = 0.3h^{-1}$
	(16)	$k_{endo}^{free}[Cad]_{free}$	Endocytosis of cadherin on cell surfaces	$k_{endo}^{free} = 1h^{-1}$
	(17)	$k_{endo}^{trans}[Cad]_{trans}$		$k_{endo}^{trans} = 0.5h^{-1}$
	(18)	$k_{endo}^{cis}[Cad]_{cis}$		$k_{endo}^{cis} = 0.3h^{-1}$
	(19)	$k_{BC,f}^{free}[B-Cat][Cad]_{free} - k_{BC,b}^{free}[Cad/Cat]_{free}$	Formation of Cad/Cat complex	$k_{BC,f}^{free} = 30nM^{-1}h^{-1}\, k_{BC,b}^{free} = 100h^{-1}$
	(20)	$k_{trans}^{f}[Cad/Cat]_{free} - k_{trans}^{b}[Cad/Cat]_{trans}$		$k_{trans}^{f} = 30nM^{-1}h^{-1}\, k_{trans}^{b} = 100h^{-1}$
	(21)	$k_{BC,f}^{cis}[B-Cat][Cad]_{cis} - k_{BC,b}^{cis}[Cad/Cat]_{cis}$		$k_{BC,f}^{cis}, k_{BC,b}^{cis}$ depends on membrane organization effects
	(22)	$k_{trans}^{f}[Cad/Cat]_{free} - k_{trans}^{b}[Cad/Cat]_{trans}$	Formation of trans-dimer	$k_{trans}^{f}, k_{trans}^{b}$ depends on adhesion condition
	(23)	$k_{cis}^{f}[Cad/Cat]_{trans} - k_{cis}^{b}[Cad/Cat]_{cis}$	Formation of cis-cluster	k_{cis}^{f}, k_{cis}^{b} depends on adhesion condition
Destruct Complex Cycle	(24)	$k_{AX/B,f}[Axin][B-Cat] - k_{AX/B,b}[Axin/B-Cat]$	B-cat retention caused by Axin.	$k_{AX/B,f} = 0.015nM^{-1}h^{-1}\; k_{AX/B,b} = 100h^{-1}$
	(25)	$k_{AP/B,f}[APC][B-Cat] - k_{AP/B,b}[APC/B-Cat]$	B-cat retention caused by APC.	$k_{AP/B,f} = 0.005nM^{-1}h^{-1}\; k_{AP/B,b} = 100h^{-1}$
	(26)	$k_{AP/AX,f}[Axin][APC] - k_{AP/AX,b}[Axin/APC]$	Formation of Axin/APC	$k_{AP/AX,f} = 0.1nM^{-1}h^{-1}\; k_{AP/AX,b} = 10h^{-1}$
	(27)	$k_{D,f}[Axin/APC][GSK3] - k_{D,b}[D]$	Formation of destruction complex	$k_{D,f} = 0.75nM^{-1}h^{-1}\; k_{D,b} = 100h^{-1}$
	(28)	$k_{BD,f}[D][B-Cat] - k_{BD,b}[BD]$	Binding B-cat by destruction Complex	$k_{BD,f} = 3.84nM^{-1}h^{-1}\; k_{BD,b} = 1000h^{-1}$
	(29)	$k_{p,WNT-OFF}^{CK1}[BD] - k_{dp,WNT-OFF}^{CK1}[CK1-pBD]$	Phosphorylation of B-cat by CK1	$k_{p,WNT-OFF}^{CK1} = 250h^{-1}\; k_{dp,WNT-OFF}^{CK1} = 200h^{-1}$
	(30)	$k_{p,WNT-OFF}^{GSK3}[CK1-pBD] - k_{dp,WNT-OFF}^{GSK3}[GSK3-pBD]$	Phosphorylation of B-cat by GSK3	$k_{p,WNT-OFF}^{GSK3} = 400h^{-1}\; k_{dp,WNT-OFF}^{GSK3} = 100h^{-1}$
	(31)	$k_{transform}[GSK3-pBD]$	Transformation of Destruction Complex	$k_{transform} = 300h^{-1}$
	(32)	$k_{\deg radation}[GSK3-pB/ID]$	Degradation of GSK3-pB	$k_{\deg radation} = 100h^{-1}$
	(33)	$k_{recov}[ID]$	Recovery of Destruction Complex	$k_{recov} = 10h^{-1}$
	(34)	$k_{release,WNT-OFF}^{ABC}[CK1-pBD] - k_{ass,WNT-OFF}^{ABC}[ABC][D]$	Release of ABC	$k_{release,WNT-OFF}^{ABC} = 32.4h^{-1}\; k_{ass,WNT-OFF}^{ABC} = 0.54nM^{-1}h^{-1}$
Wnt Activation	(35)	$k_{LD}^{f}[WC][D]$	Binding to Wnt/receptor complex	$k_{LD}^{f} = 2500nM^{-1}h^{-1}$
		$k_{LD}^{f}[WC][BD]$		
		$k_{LD}^{f}[WC][CK1-pBD]$		
		$k_{LD}^{f}[WC][GSK3-pBD]$		
	(36)	$k_{BD,f}[WD][B] - k_{BD,b}[WBD]$	Binding B-cat by destruction Complex	$k_{BD,f} = 3.84nM^{-1}h^{-1}\; k_{BD,b} = 1000h^{-1}$
	(37)	$k_{p,WNT-ON}^{CK1}[WBD] - k_{dp,WNT-ON}^{CK1}[CK1-WBD]$	Phosphorylation of B-cat by CK1	$k_{p,WNT-ON}^{CK1} = 250h^{-1}\; k_{dp,WNT-ON}^{CK1} = 4000h^{-1}$
	(38)	$k_{p,WNT-ON}^{GSK3}[CK1-WBD] - k_{dp,WNT-ON}^{GSK3}[GSK3-WBD]$	Phosphorylation of B-cat by GSK3	$k_{p,WNT-ON}^{GSK3} = 120h^{-1}\; k_{dp,WNT-ON}^{GSK3} = 60h^{-1}$
	(39)	$k_{transform}[GSK3-WBD]$	Transformation of destruction complex	$k_{transform} = 300h^{-1}$
	(40)	$k_{release,WNT-ON}^{ABC}[CK1-WBD] - k_{ass,WNT-ON}^{ABC}[ABC][WD]$	Release of ABC	$k_{release,WNT-ON}^{ABC} = 25920h^{-1}\; k_{ass,WNT-ON}^{ABC} = 54nM^{-1}h^{-1}$
Signaling transduction	(41)	$k_{p}^{Y142}[ABC] - k_{dp}^{Y142}[ABC/Bcl9]$	ABC binds to Bcl9	$k_{p}^{Y142} = 20h^{-1}\; k_{dp}^{Y142} = 20h^{-1}$
	(42)	$k_{NT}^{f}[ABC/Bcl9] - k_{NT}^{b}[ABC/Bcl9(N)]$	ABC/Bcl9 transports into Nuclear	$k_{NT}^{f} = 20h^{-1}\; k_{NT}^{b} = 20h^{-1}$
	(43)	$k_{BT}^{f}[ABC/Bcl9(N)] - k_{BT}^{b}[ABC/TCF]$	ABC binds to TCF	$k_{BT}^{f} = 20h^{-1}\; k_{BT}^{b} = 20h^{-1}$

doi:10.1371/journal.pone.0100702.t002

Stochastic simulation

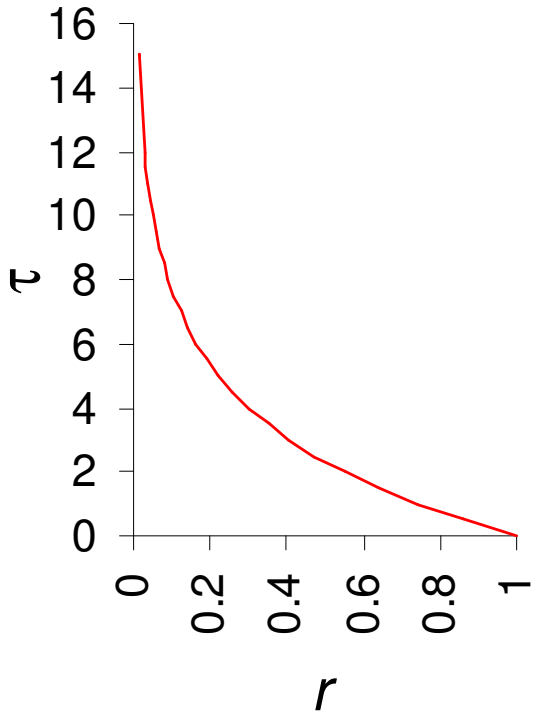
Step 1: Given the system state, determine the rate of each reaction, a_r.

- Reaction 1: $S_1 + S_2 \rightarrow S_3$, with rate constant k_1
  - X_1, X_2 are the numbers of the reactant molecules
  - Define the stoichiometry: $h_1 = X_1X_2$; this will give dependence on amounts of molecules.
  - Then $a_1 = h_1k_1 = k_1 X_1X_2$ = rate for this reaction.
- Reaction 2: $S_1 + S_1 \rightarrow S_2$,
  - $h_2 = X_1(X_1-1)/2$

- Finally, define: $a_0 = \Sigma a_r$ (r = 1 to R)
  - This is the combined rate of all possible reactions

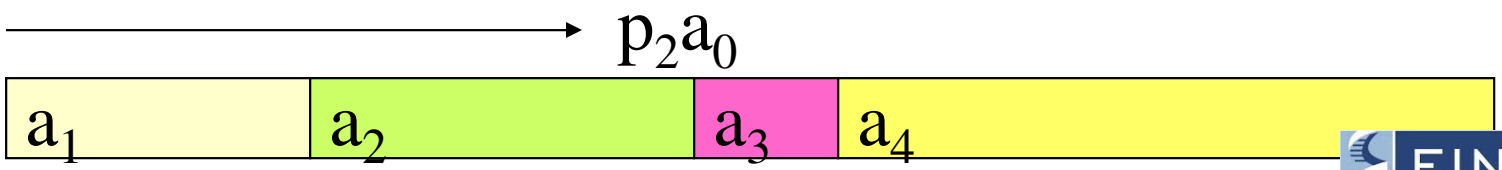
Step 2 When does the next reaction occur …

- Pick p, a uniform random number from 0 to 1
- Let $$\tau = \frac{1}{a_0} \ln\left(\frac{1}{p}\right)$$
- This is time of the next event.
- (Note that the time step doesn't have to be predetermined, and is exact.)



Step 2 …and which reaction is it?

- Determine which reaction occurs at time τ:
- Pick p_2, another uniform random number from 0 to 1
- Find r, such that: $\sum_{i=1}^{r-1} a_i < p_2 a_0 < \sum_{i=1}^{r} a_i$
- Think about dividing a_0 into R pieces of length a_r
- p_2 determines r based on weighting:



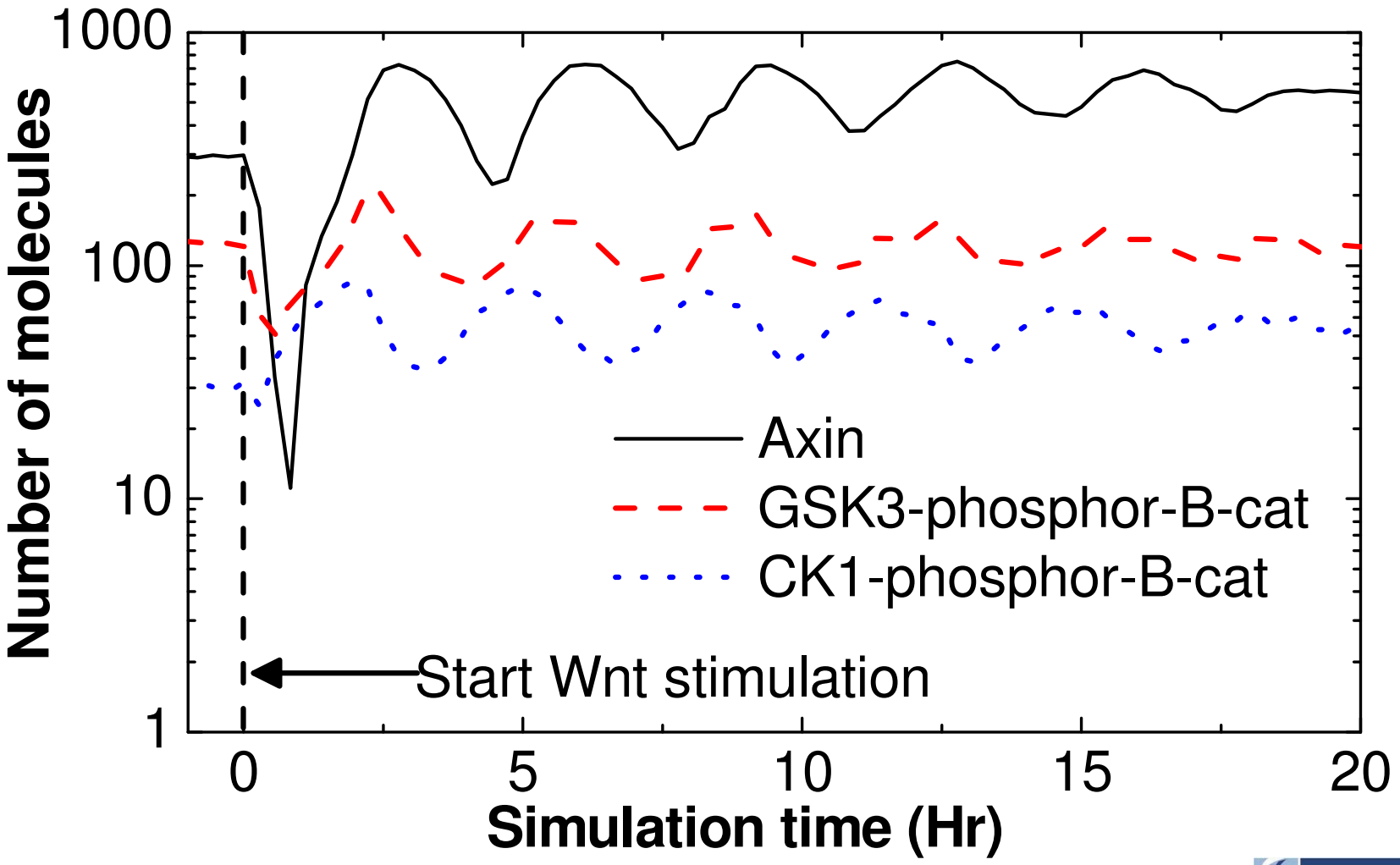
Step 3 Update the System State

- Update $t = t + \tau$
- Update $X = [X_1, X_2, \ldots X_C]$ according to the reaction stoichiometry
  - Subtract substrates and add products for the indicated rth reaction.
  - For each c, $X_c = X_c - S(r,c) + P(r,c)$
- In matrix format:
  - X(end+1,:) = X(end,:) – S(r,:) + P(r,:)
- Update reaction step counter (RC = RC+1).

Step 3 is to determine how each of C chemicals are affected

Do these three steps iteratively.

A more complicated model of Wnt signaling network



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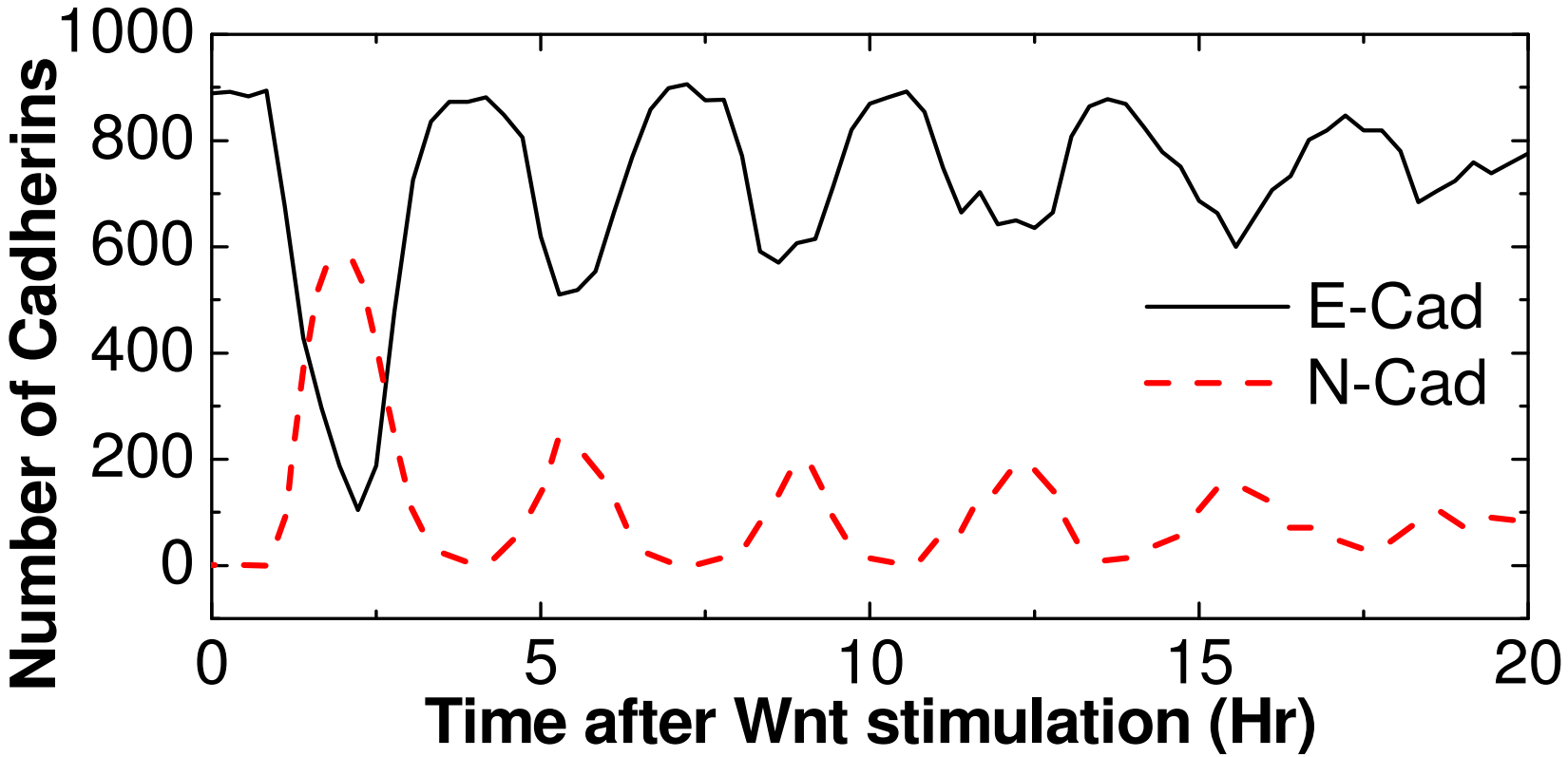

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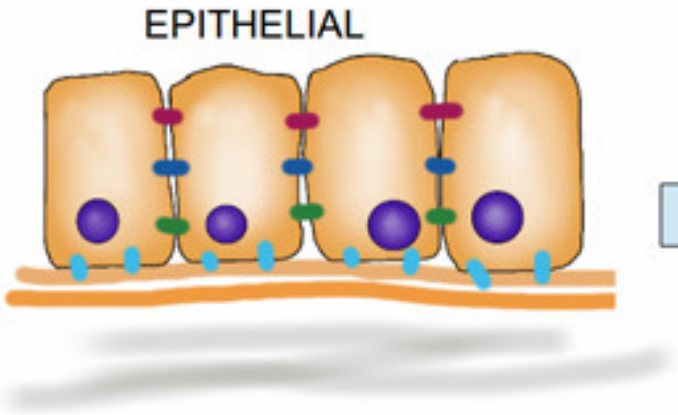
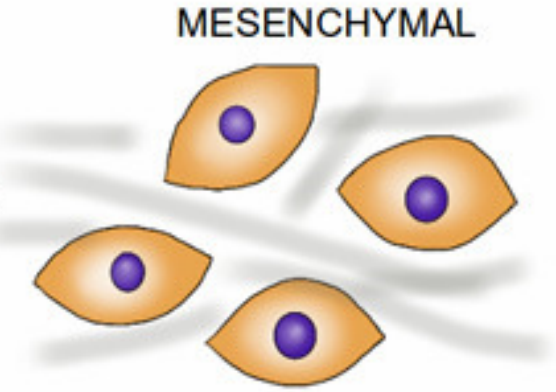


EMT



Cell polarity

Cell adhesion (to each other and to Extra Cellular Matrix

Stationary

High level of E-cadherin

Low level of N-cadherin

No cell polarity

Loss of cell adhesion

Ability to migrate and invade

Low level of E-cadherin

High level of N-cadherin

Buddhini Samarasinghe
EINSTEIN
Albert Einstein College of Medicine
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Outline

- Background
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- Modeling temporal dynamics of subcellular processes
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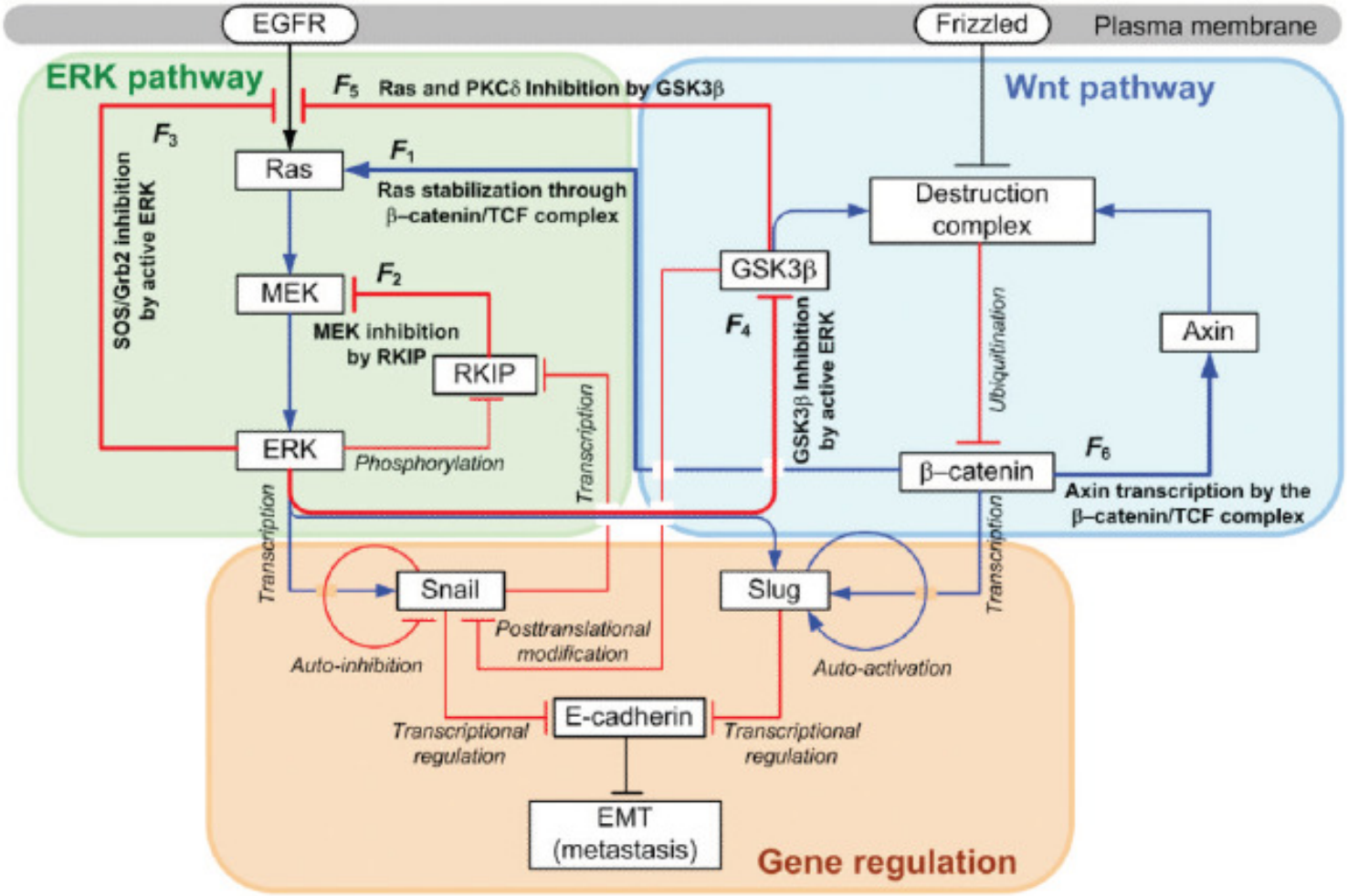
    - Network crosstalk
- Simulations of spatial organization of subcellular processes

Crosstalk between Wnt and EGF signaling networks



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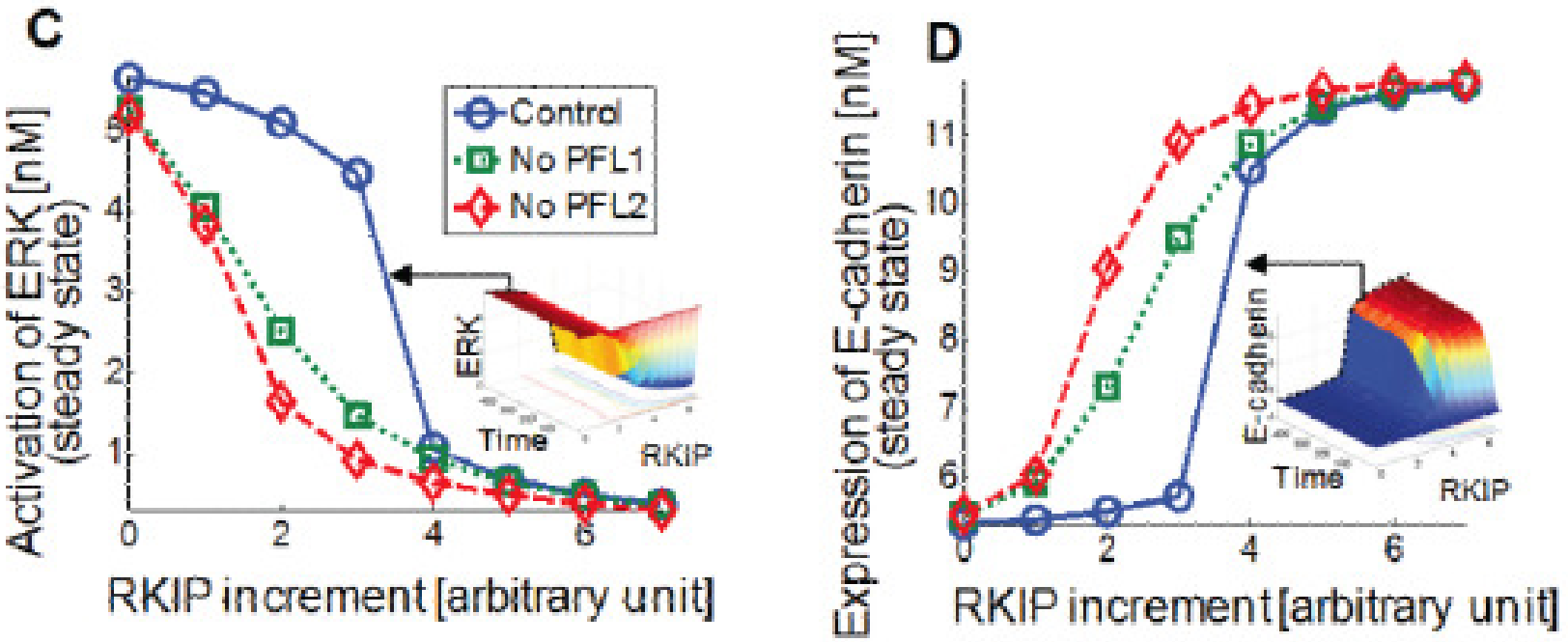

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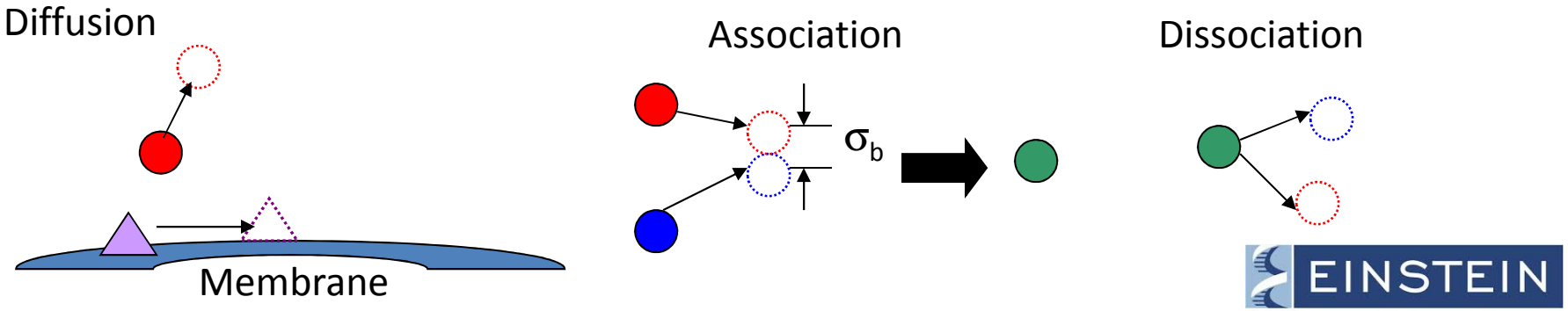
Spatial Stochastic Simulators

- Particle based
  - Individual molecules are represented as point-based particles, which diffuse random distance and random direction at each time step
  - If two reacting molecules pass near each other they may react
  - Computations increase with number of molecules
  - Smoldyn, MCell, CDS



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    - Receptor clustering
    - Complex assembly

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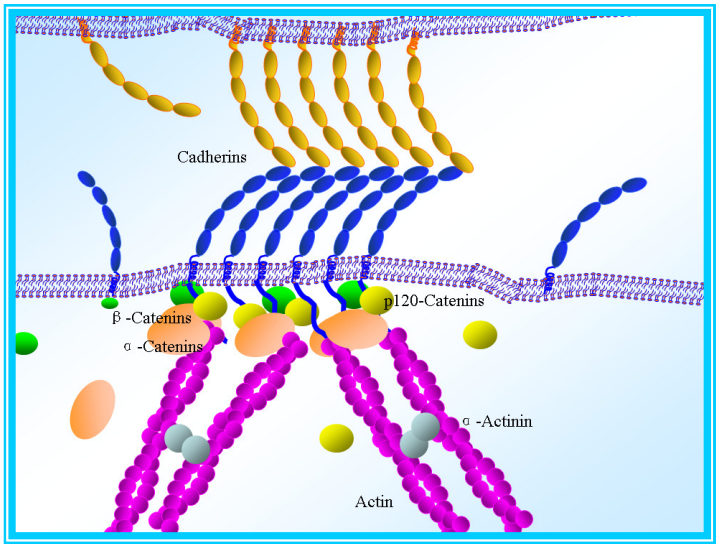
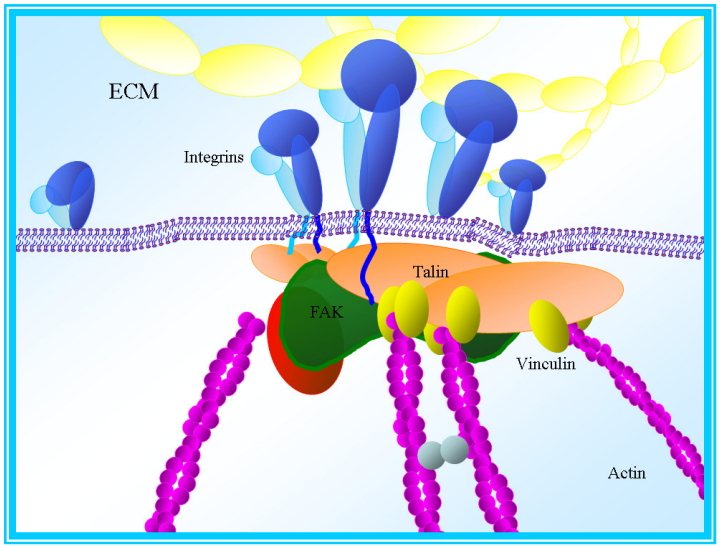
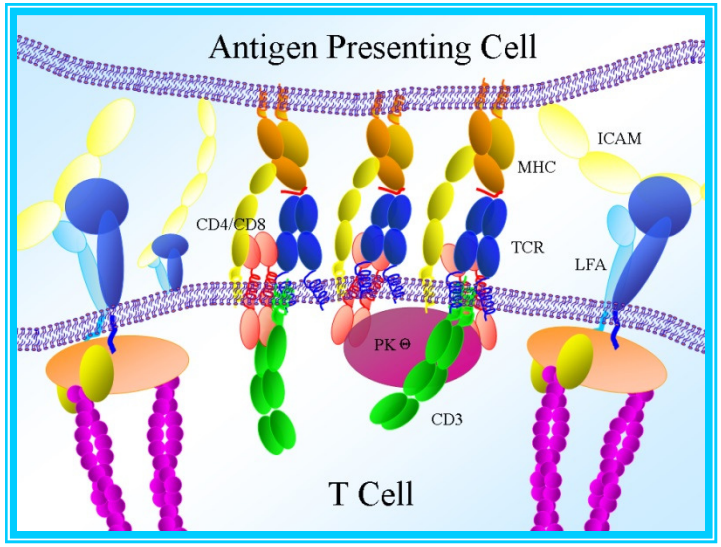
Receptor Clustering



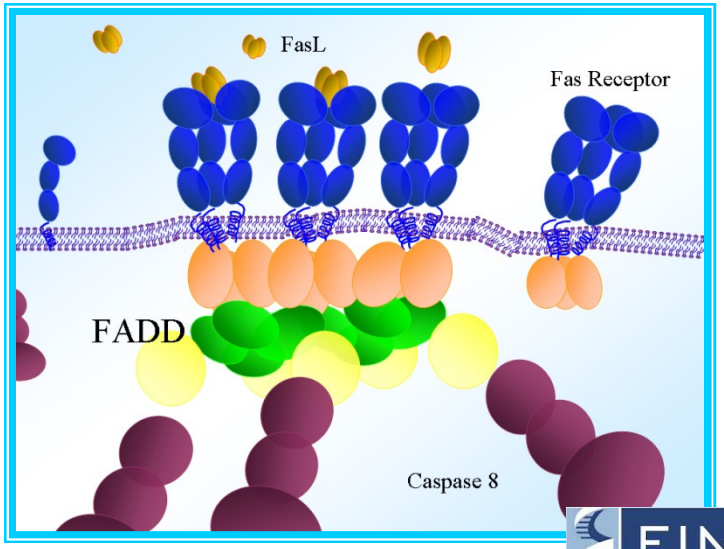
Adherens Junction



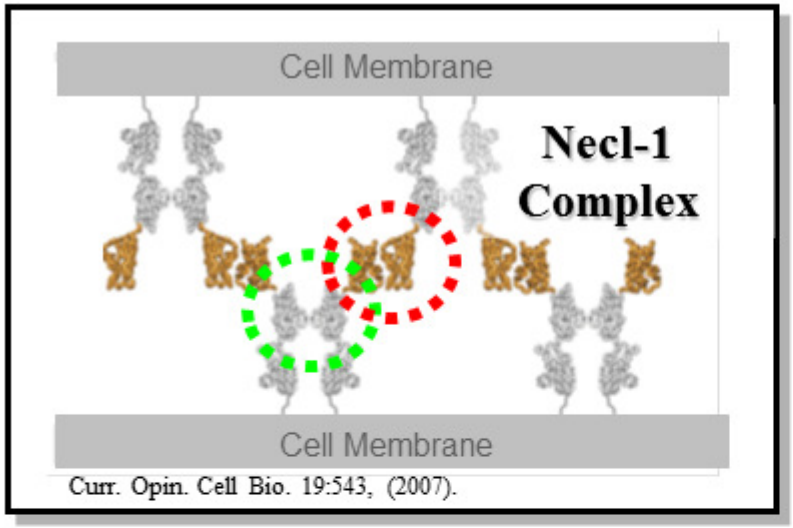
Focal Adhesion



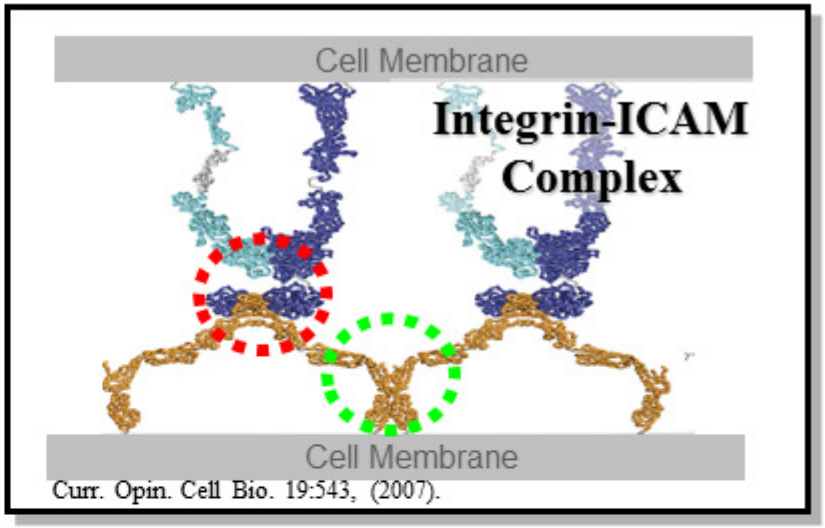
T Cell / Antigen Presenting Cell Interface



Fas Signaling Pathway



Curr. Opin. Cell Bio. 19:543, (2007).



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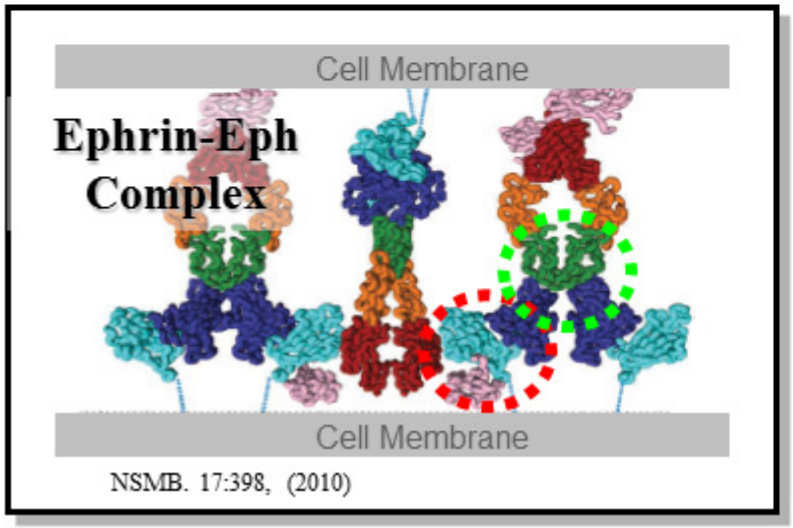
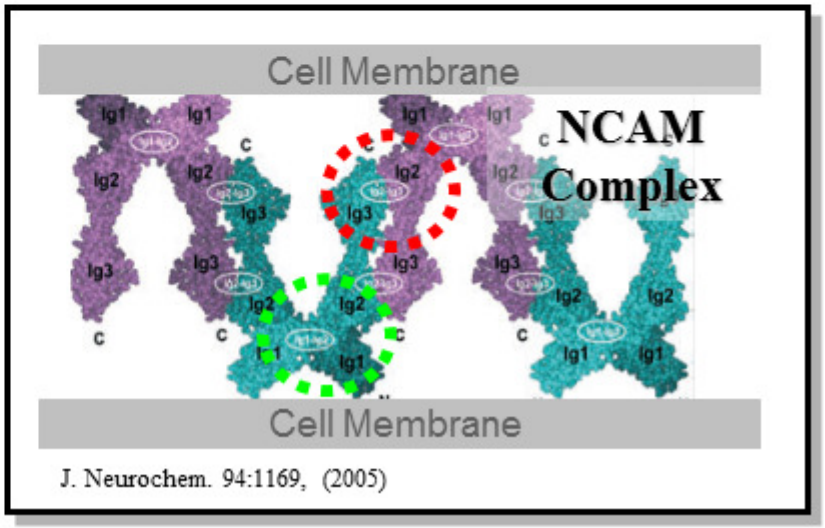
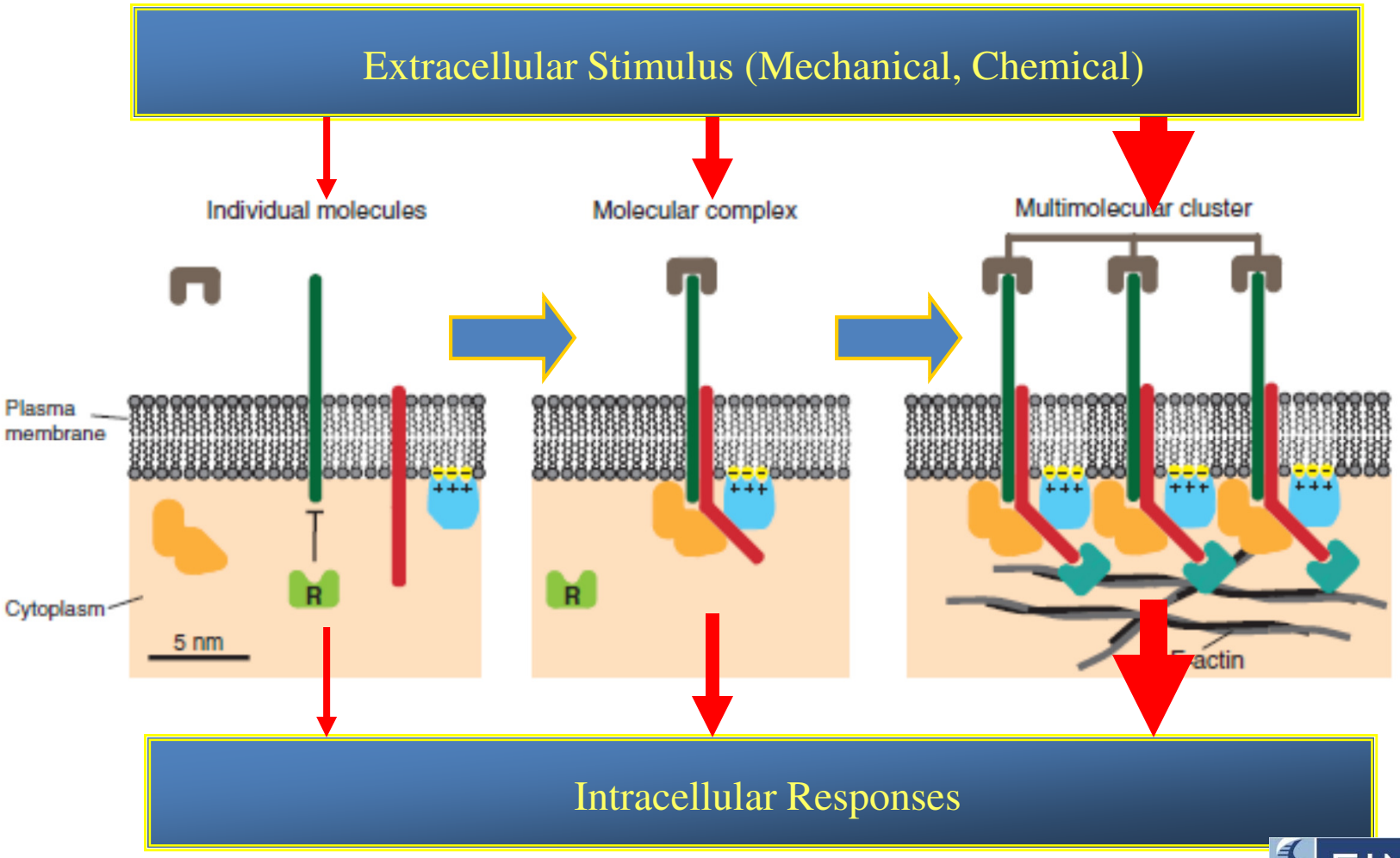
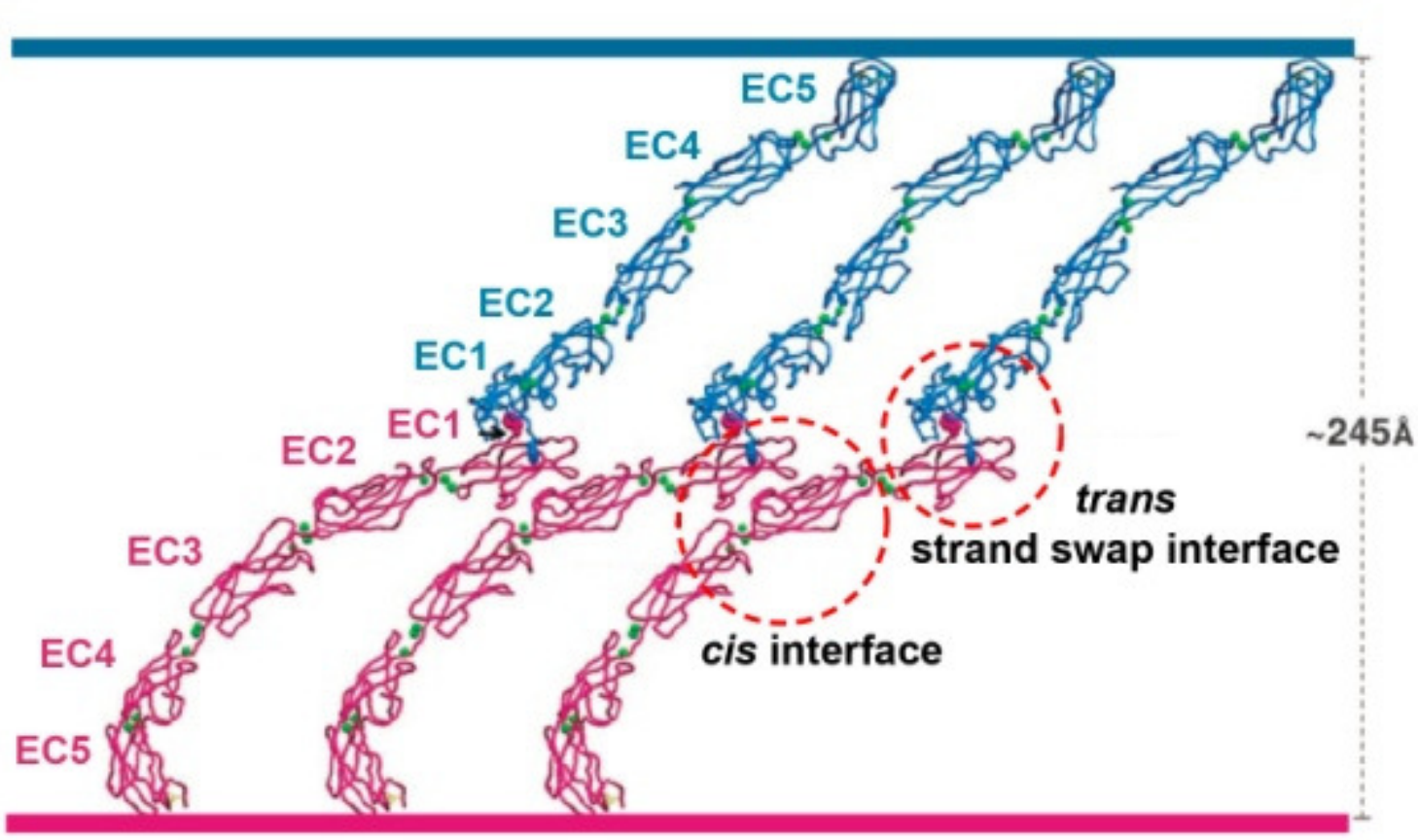


NSMB. 17:398, (2010)



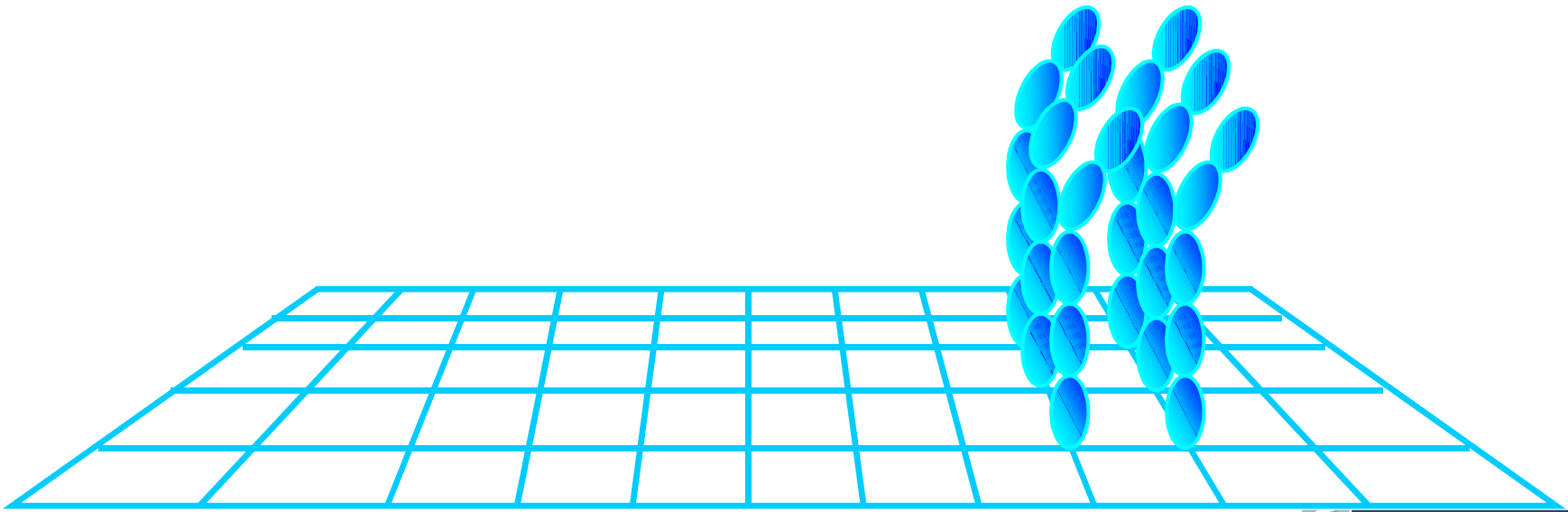
J. Neurochem. 94:1169, (2005)



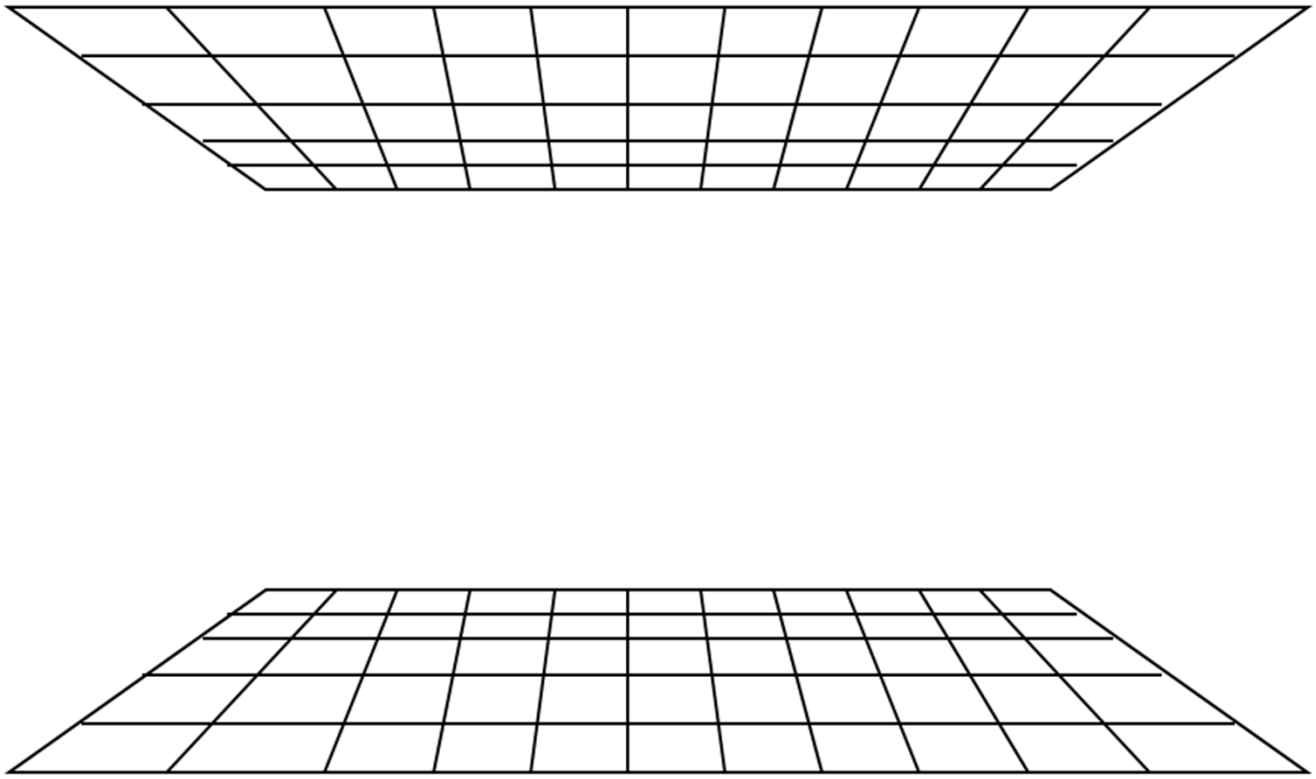


Simulation Strategy

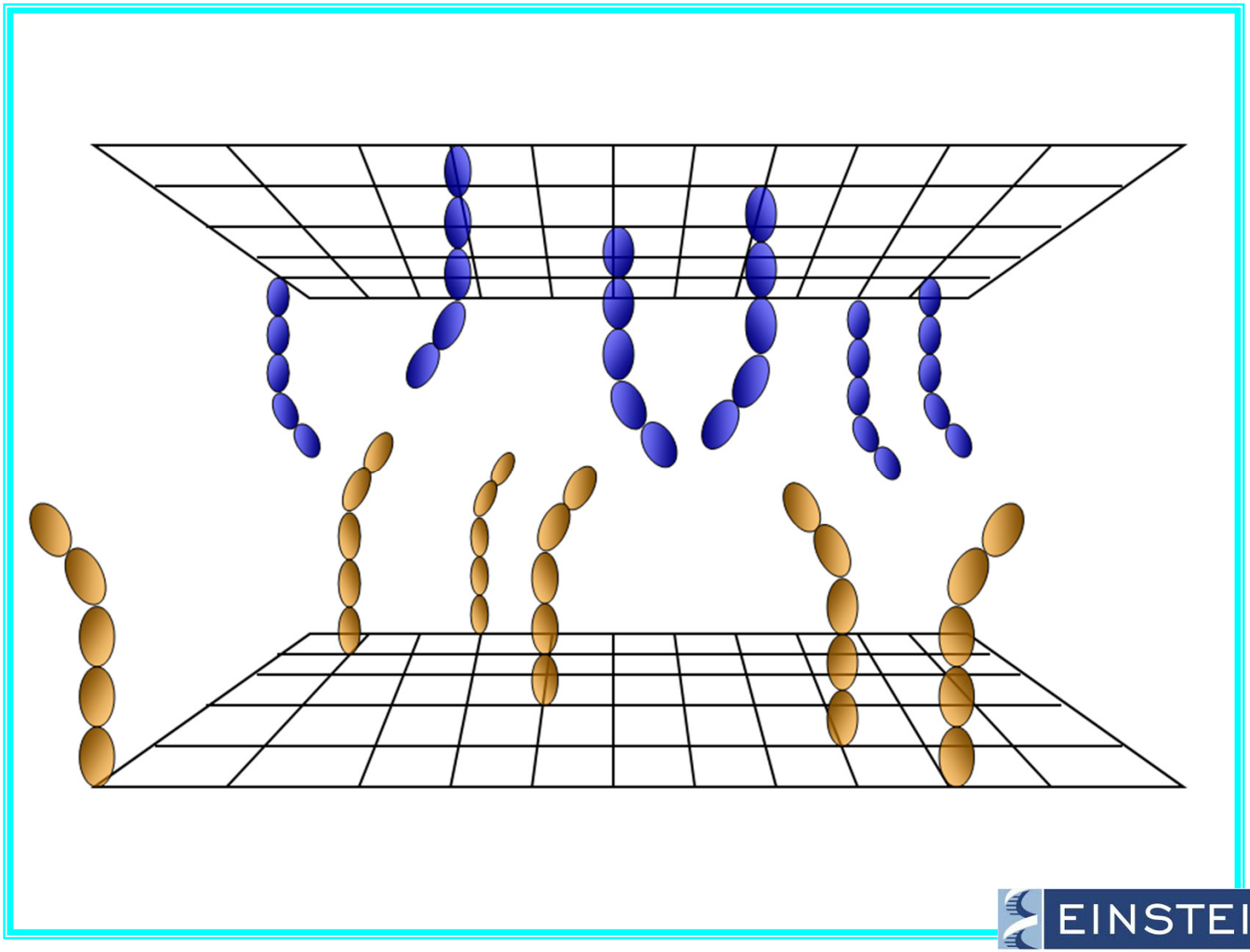
- In order to carry the membrane interface simulation, the cell membrane is first simplified as a two-dimensional lattice space.
- While the cadherin molecules can be randomly diffused on this space, by moving from one lattice point to one of its nearest neighbor point in each step.



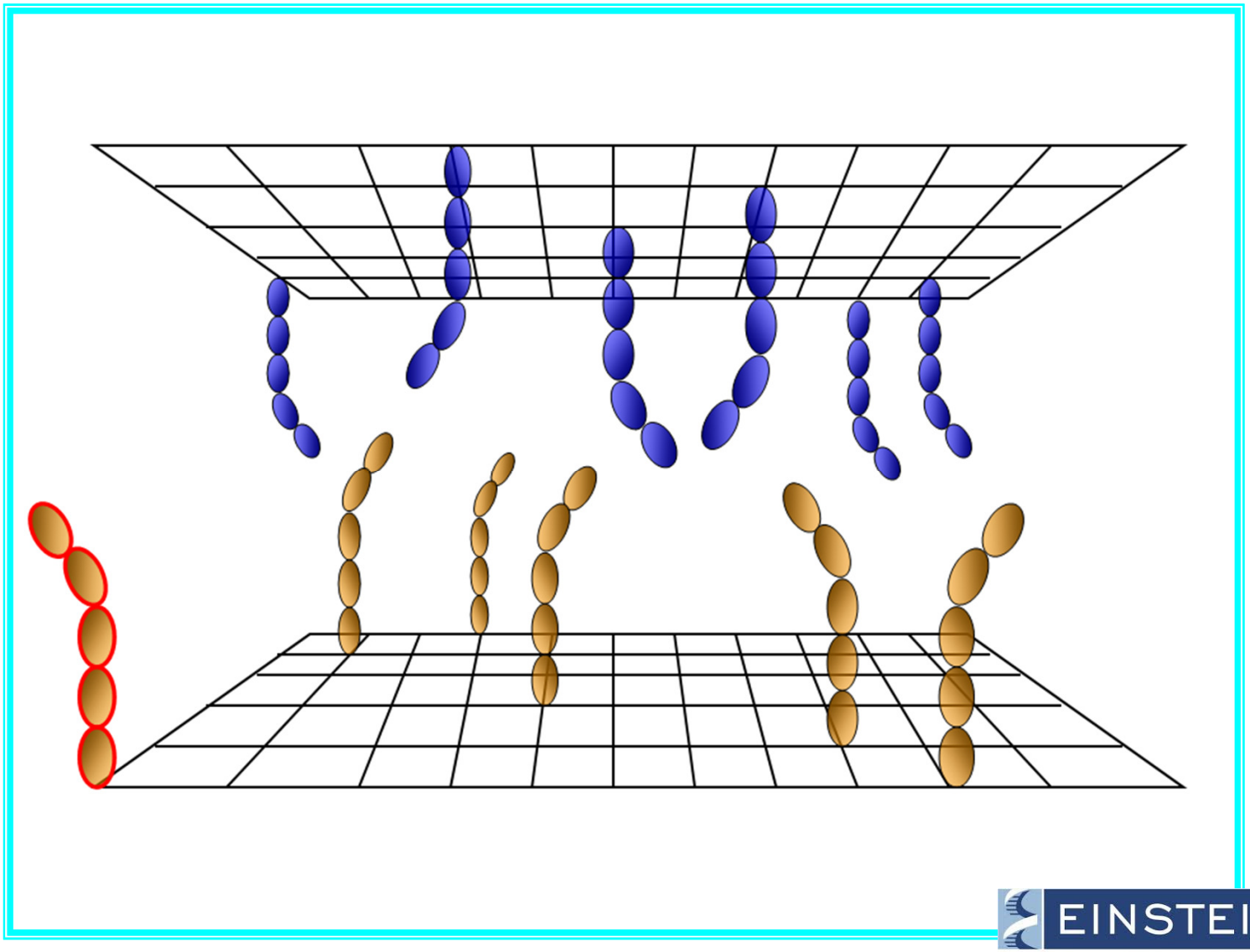
Simulation Strategy



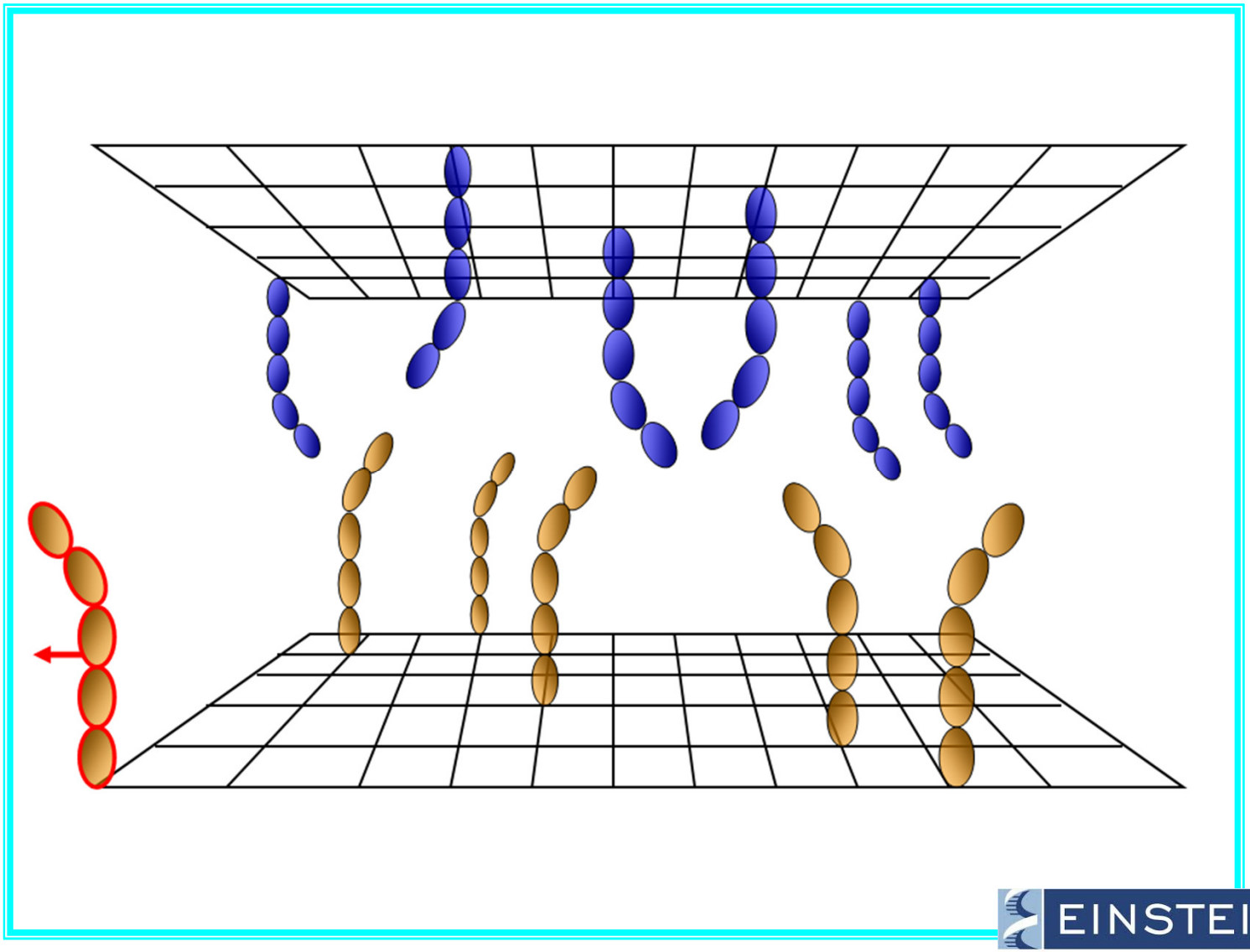
Simulation Strategy



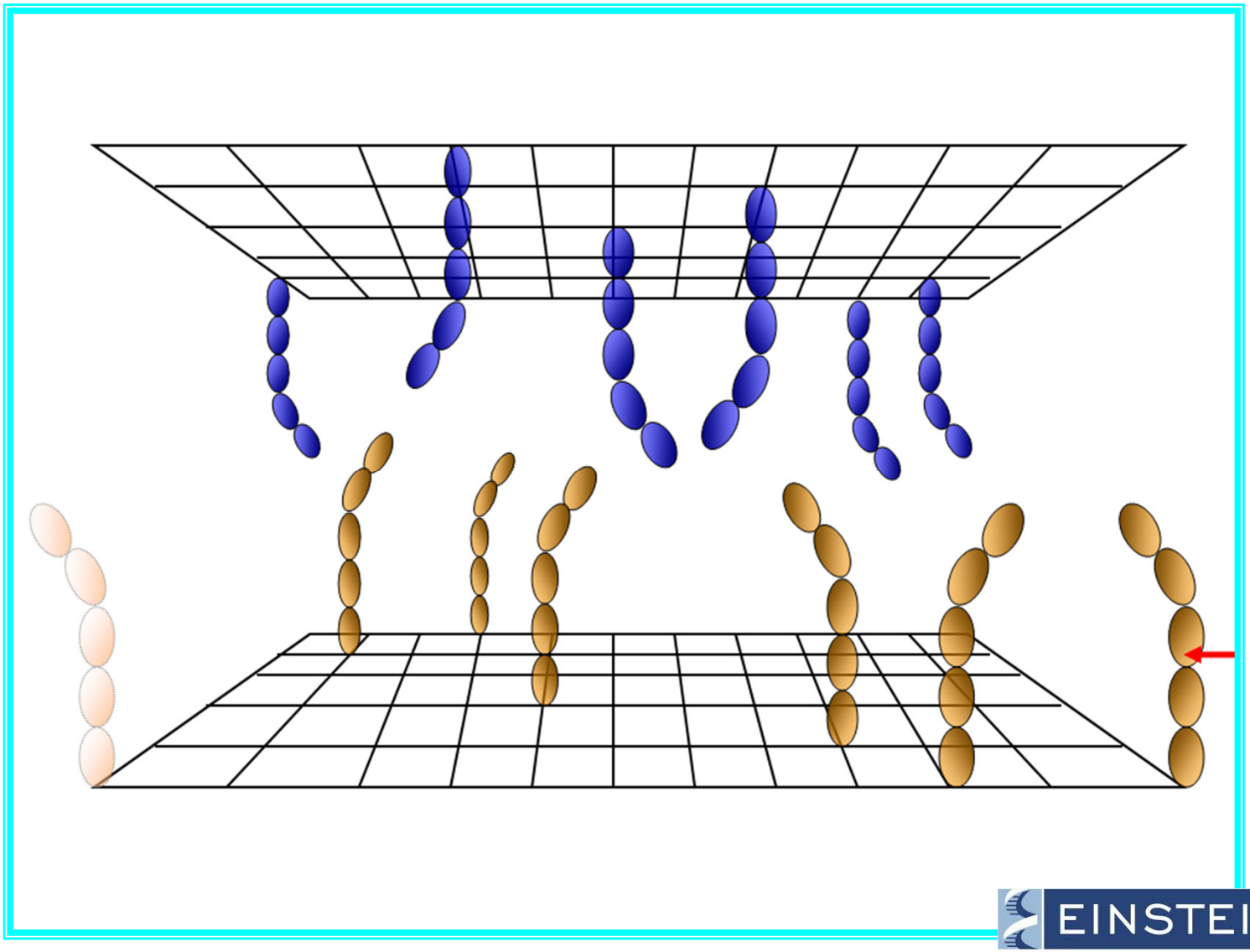
Simulation Strategy



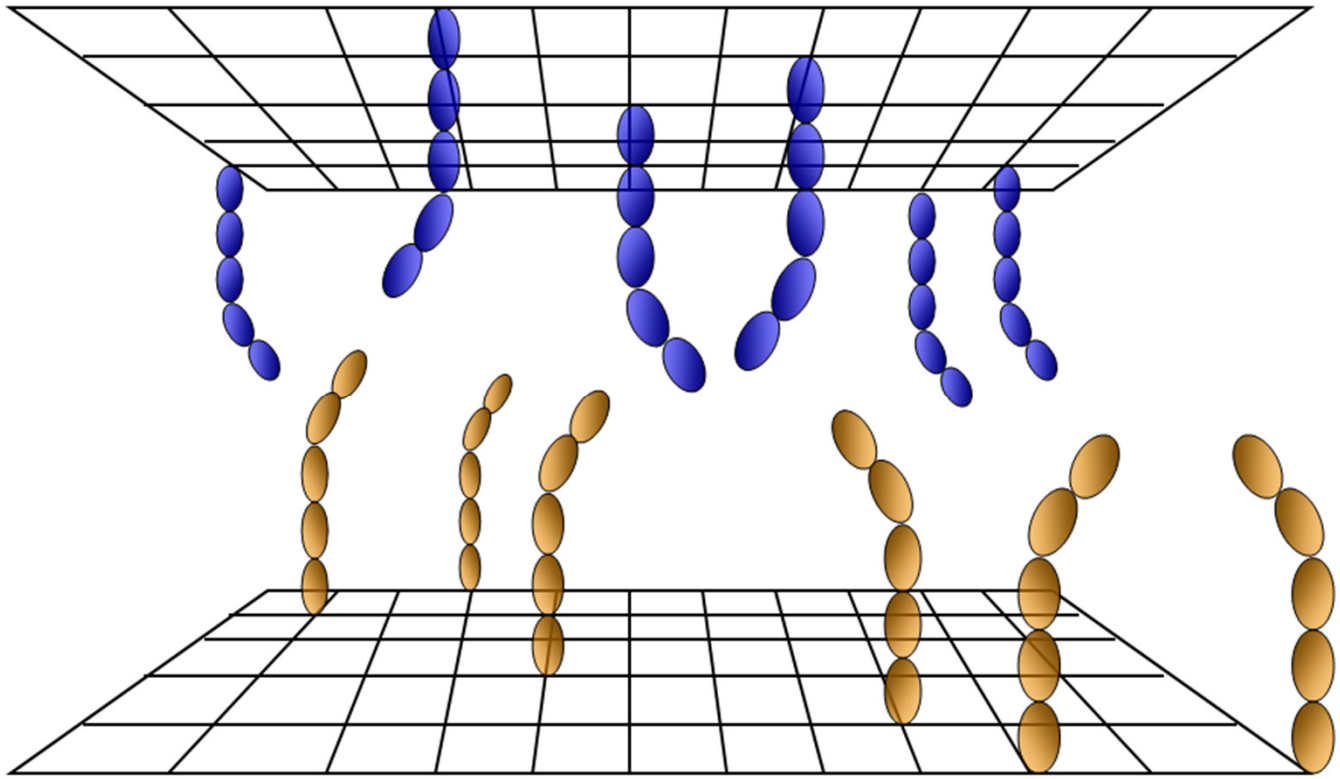
Simulation Strategy



Simulation Strategy



Simulation Strategy



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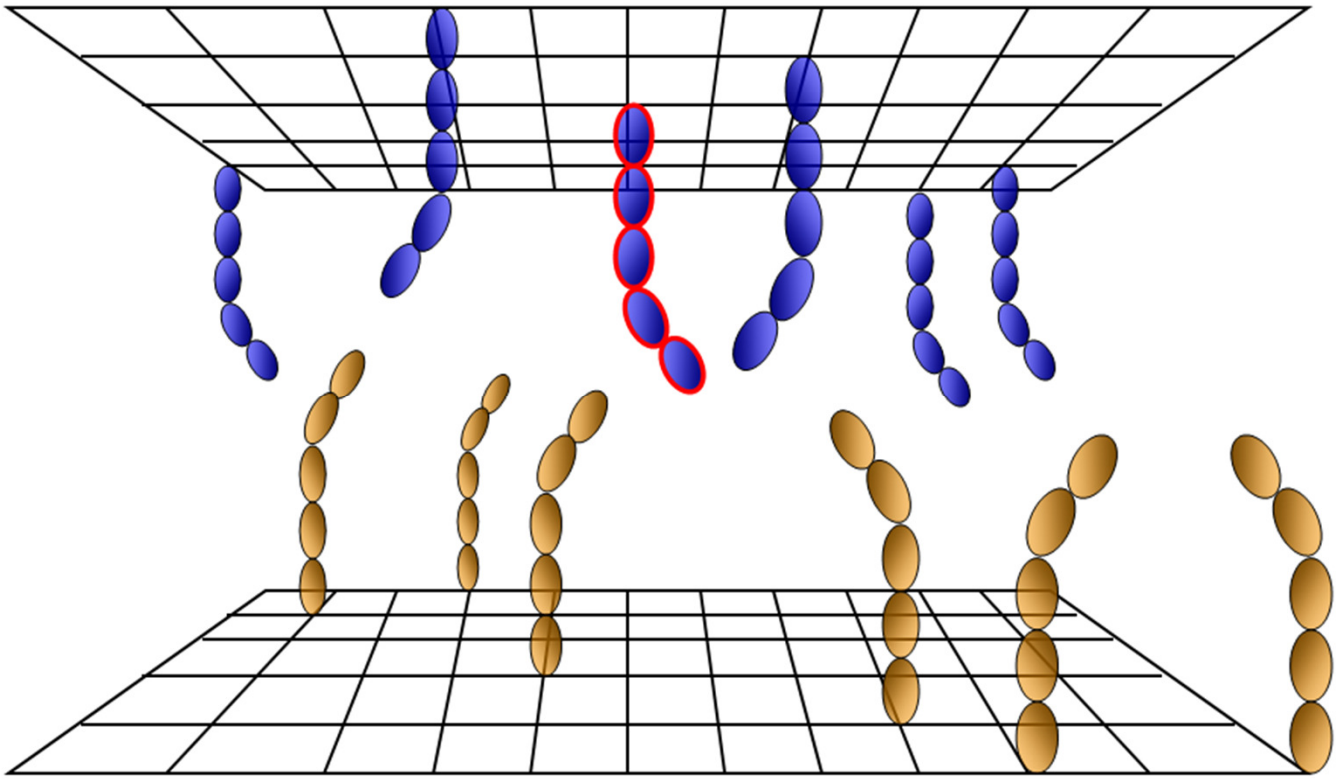

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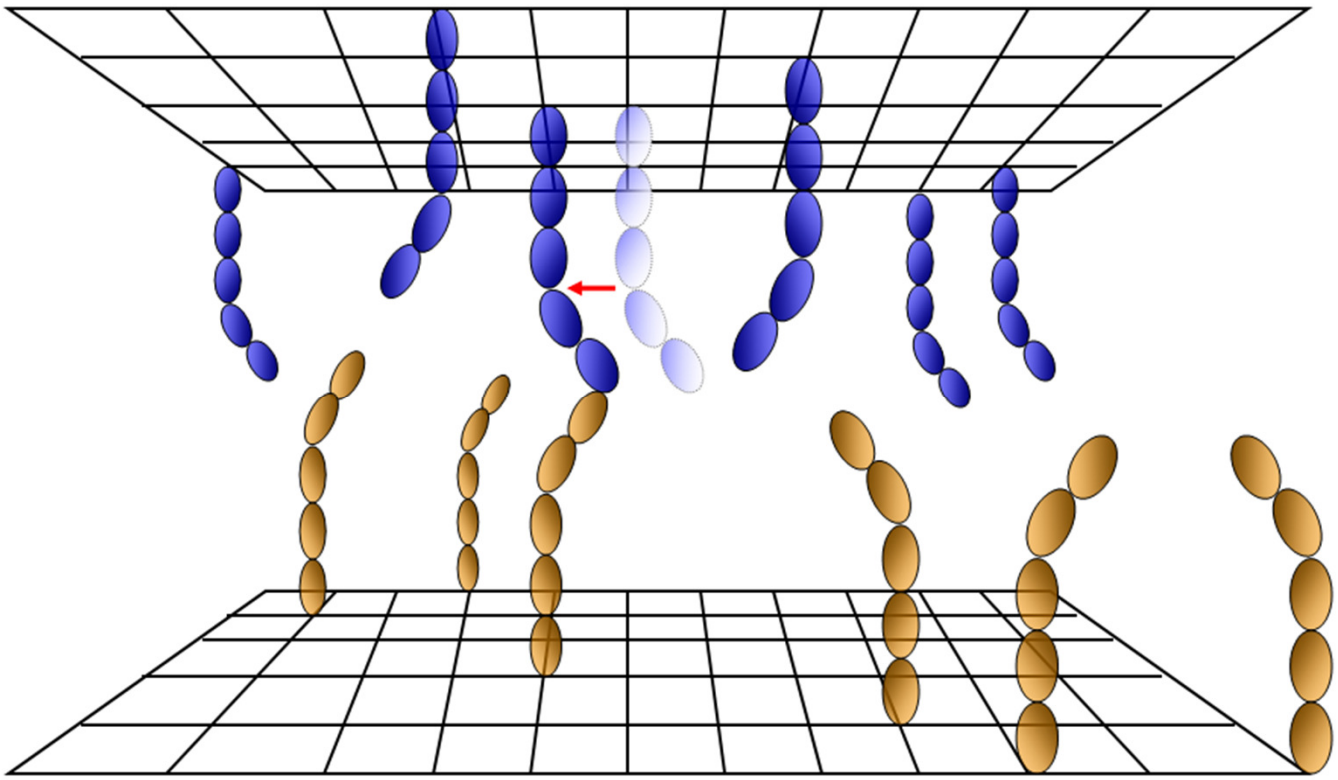

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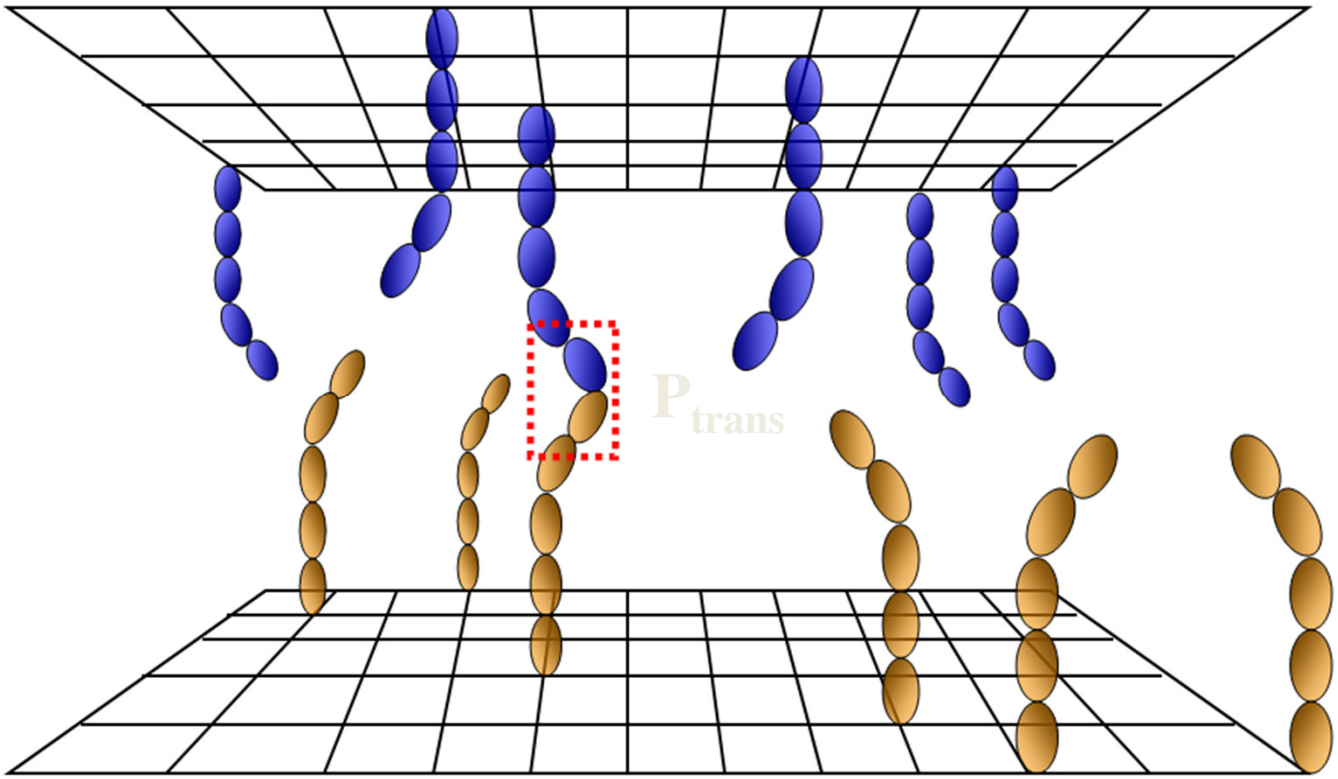

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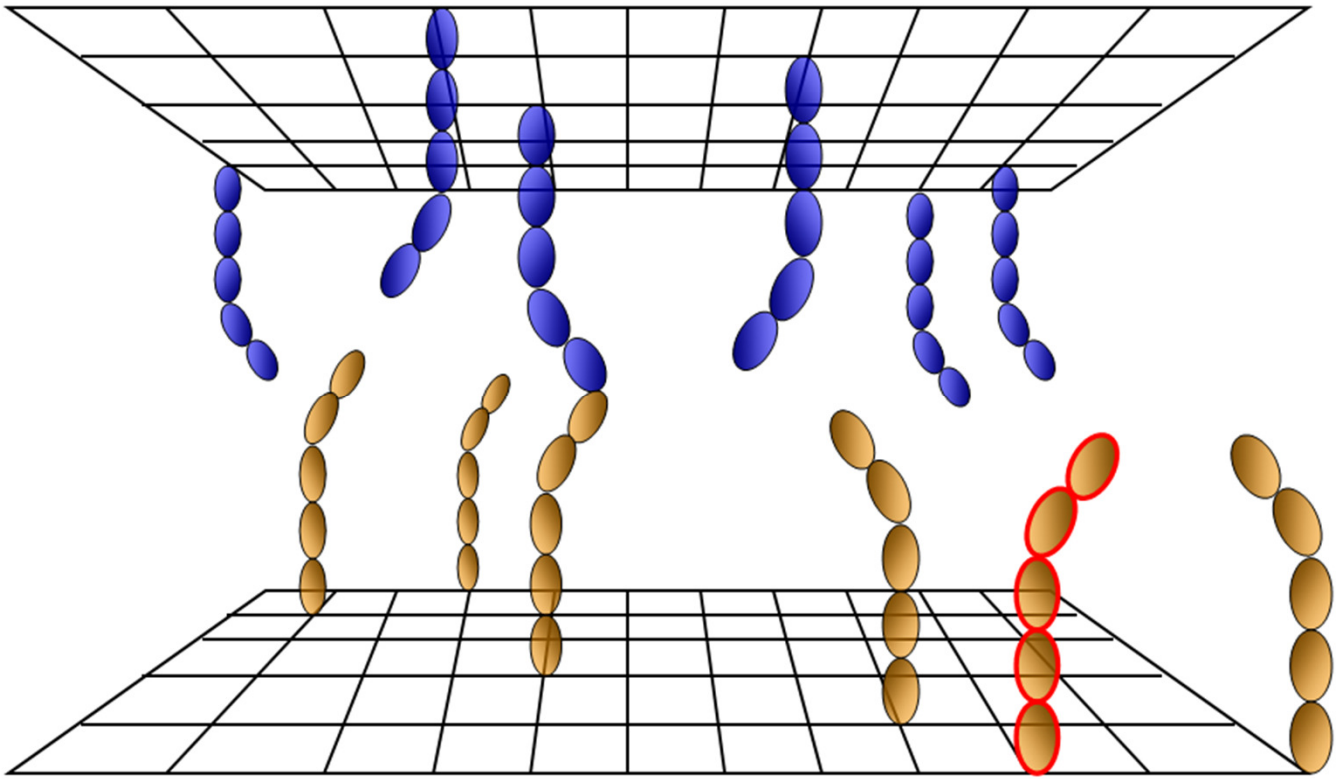

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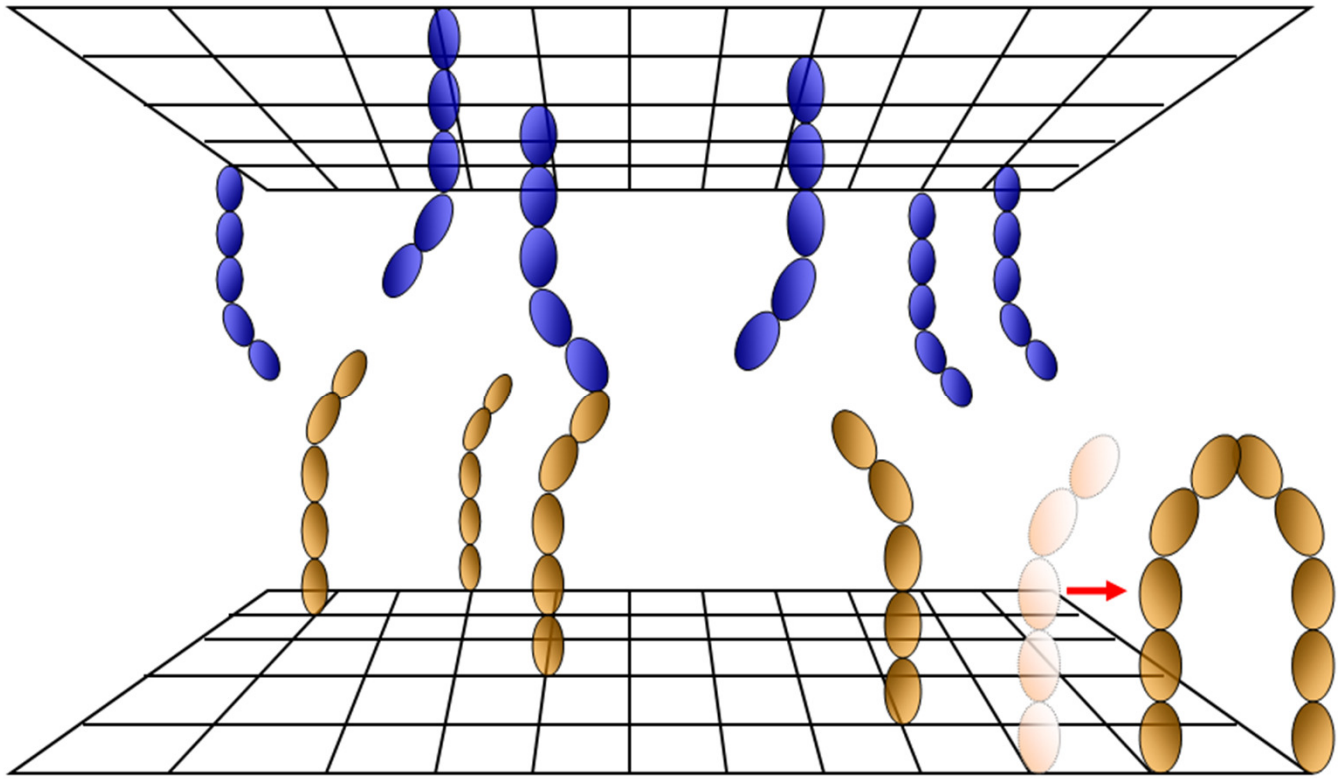
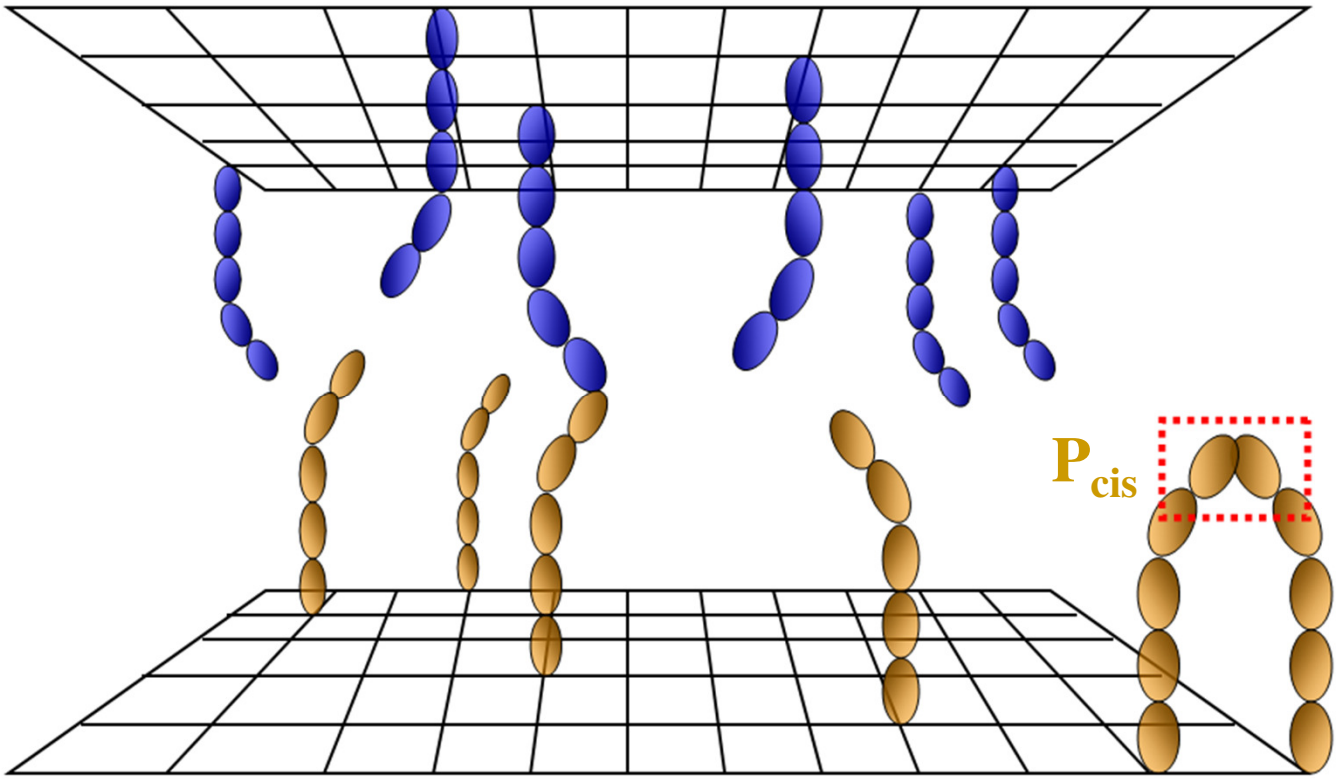
Simulation Strategy

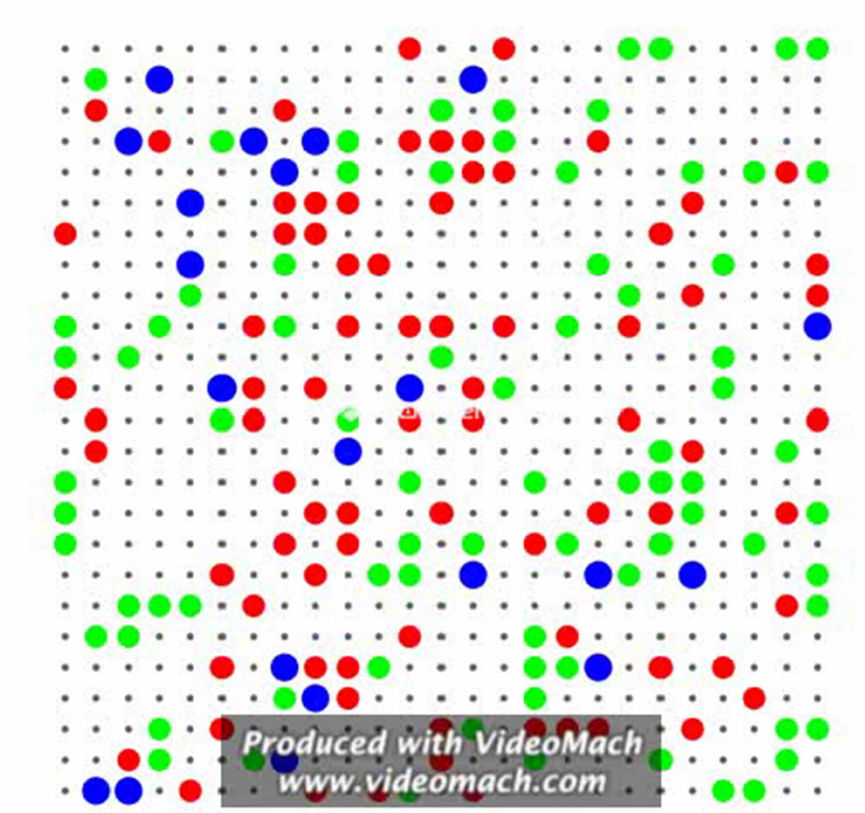


Simulation Strategy

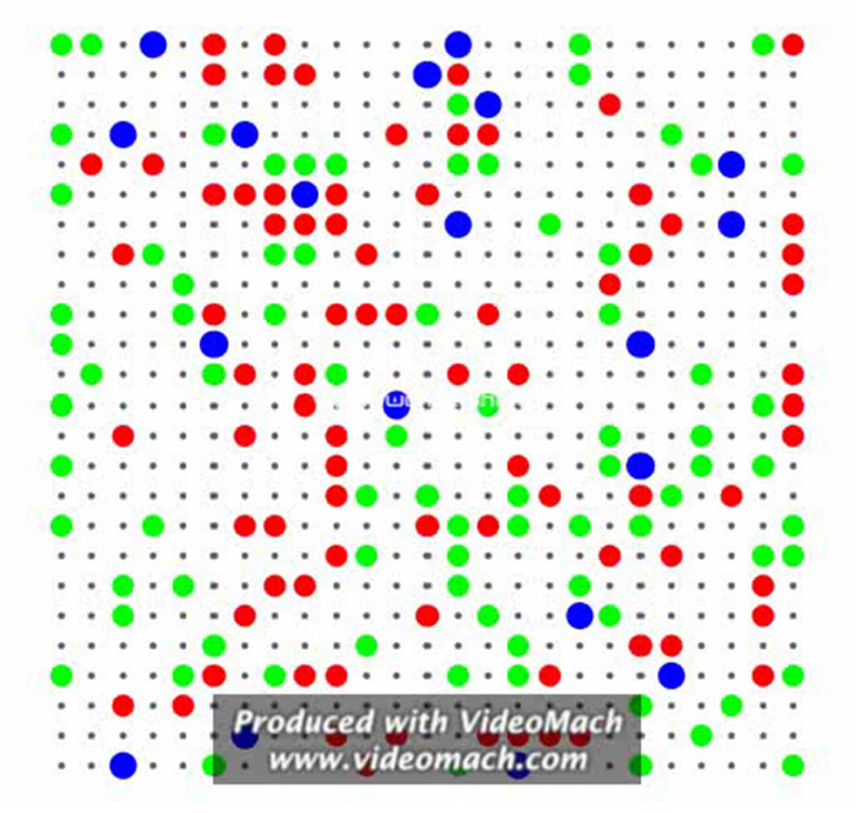


Simulation trajectory

Wild-type



Cis mutant



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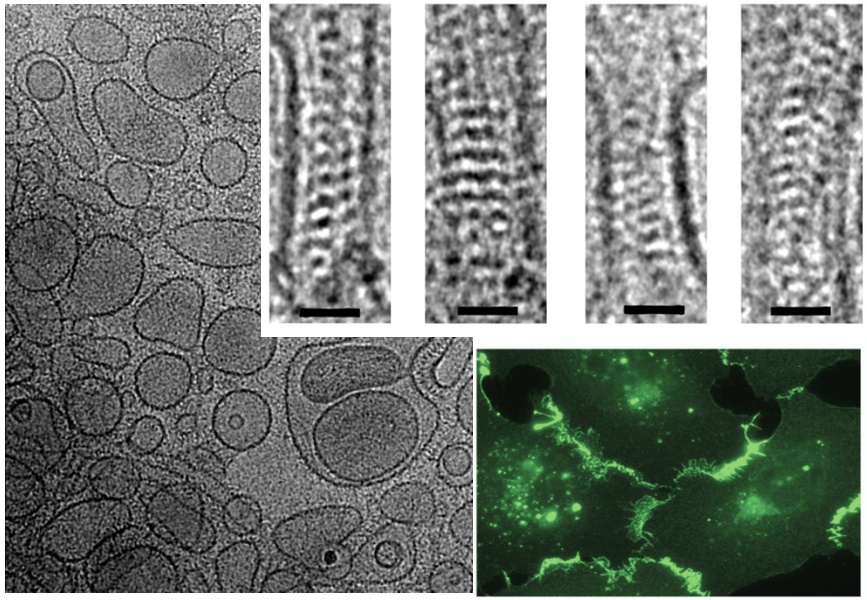
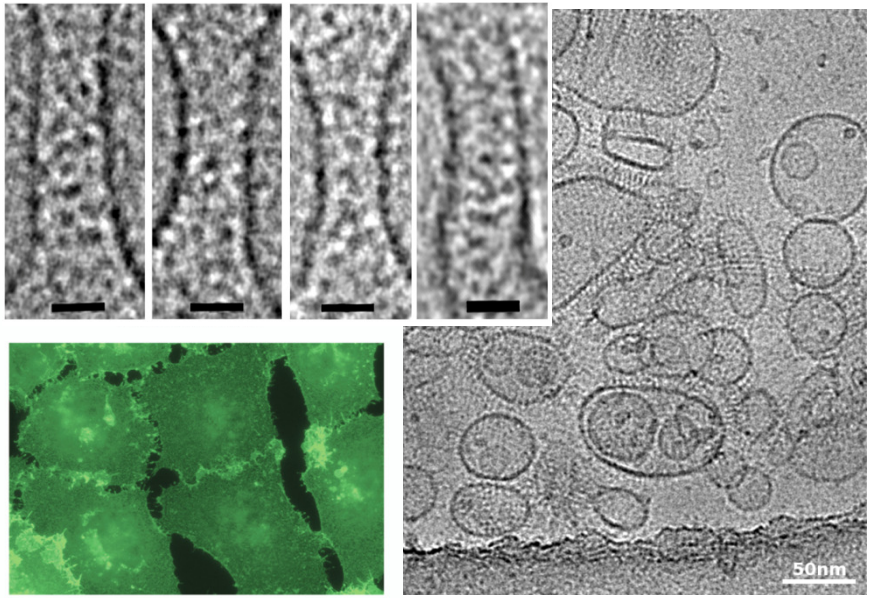
Experimental Validation

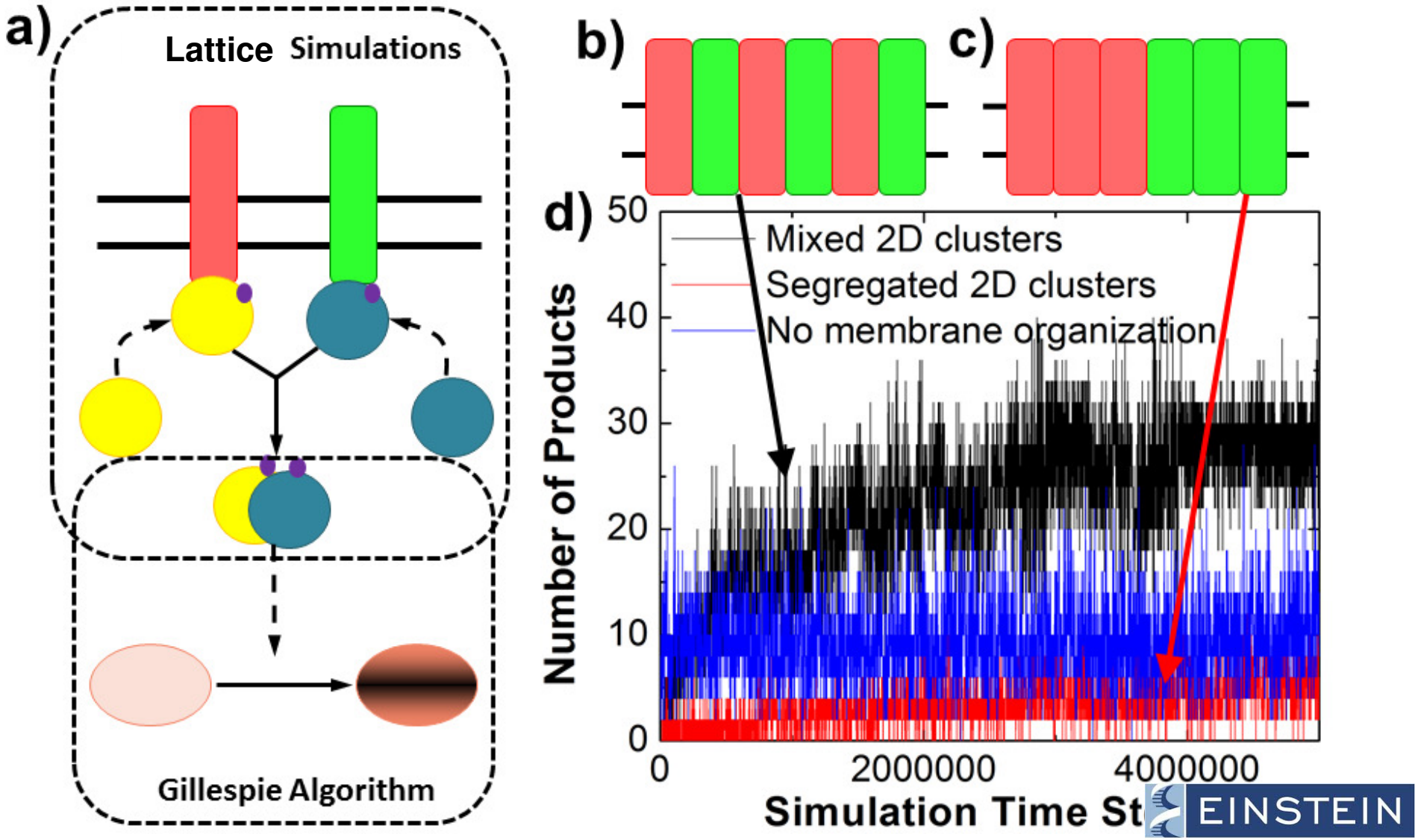
Wild-type



Cis mutant



Receptor clustering regulates cell signaling



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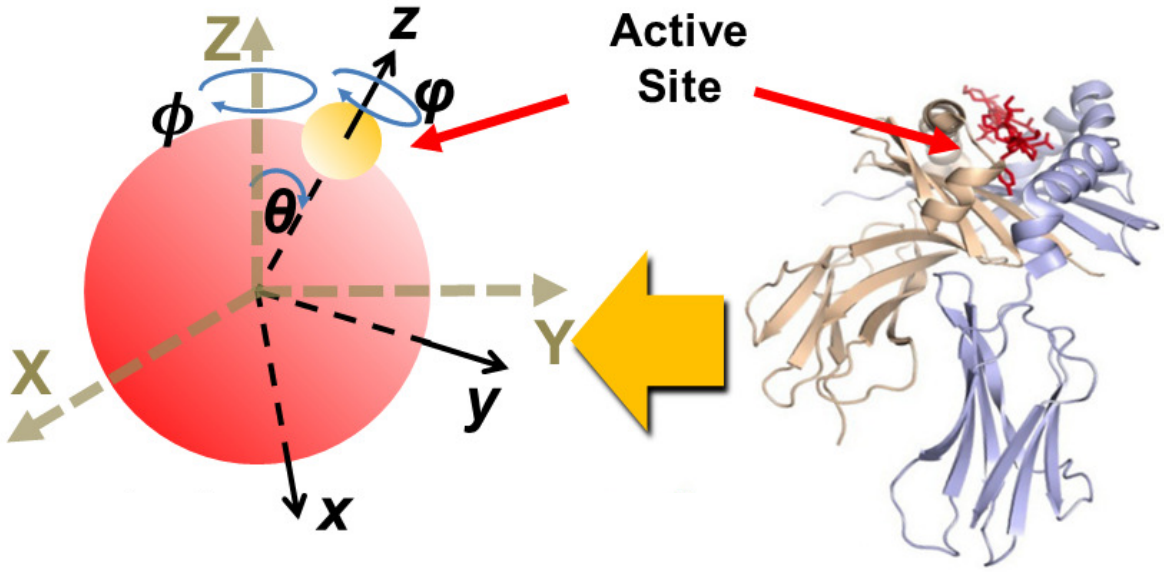
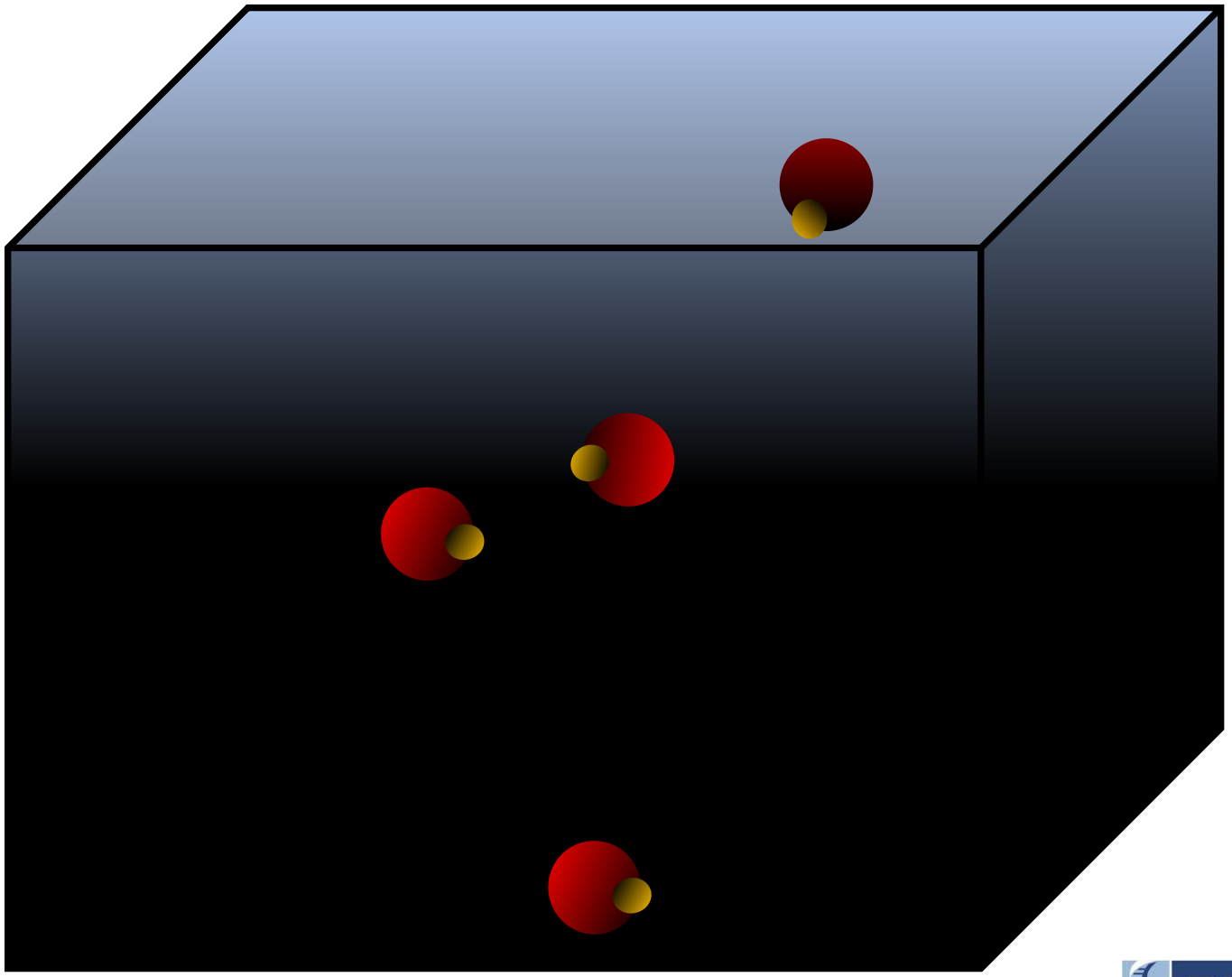
Outline

- Background
- Theory of chemical kinetics
- Modeling temporal dynamics of subcellular processes
- Simulations of spatial organization of subcellular processes
    - Receptor clustering
    - Complex assembly

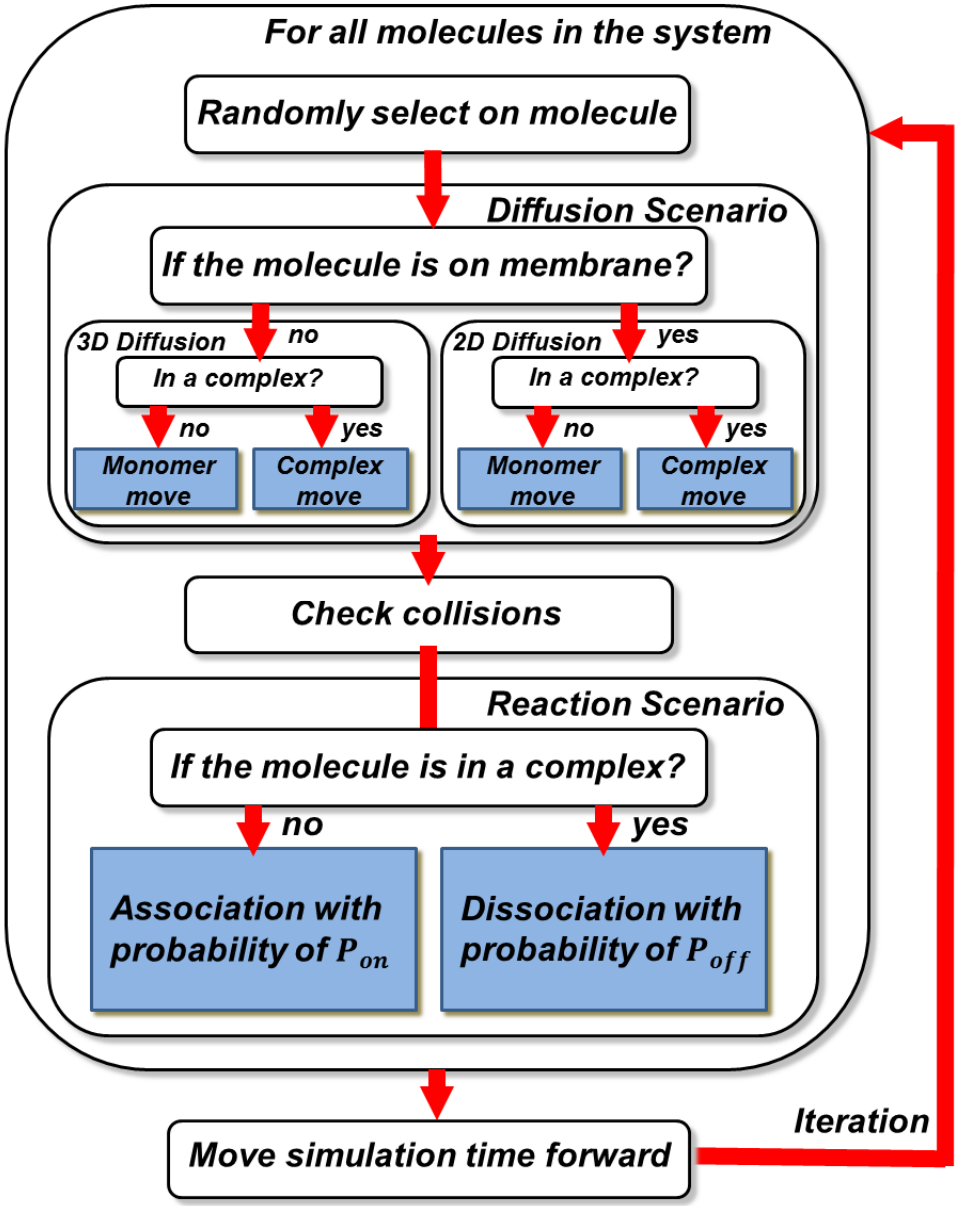
Modeling cellular heterogeneity: **rigid-body model**

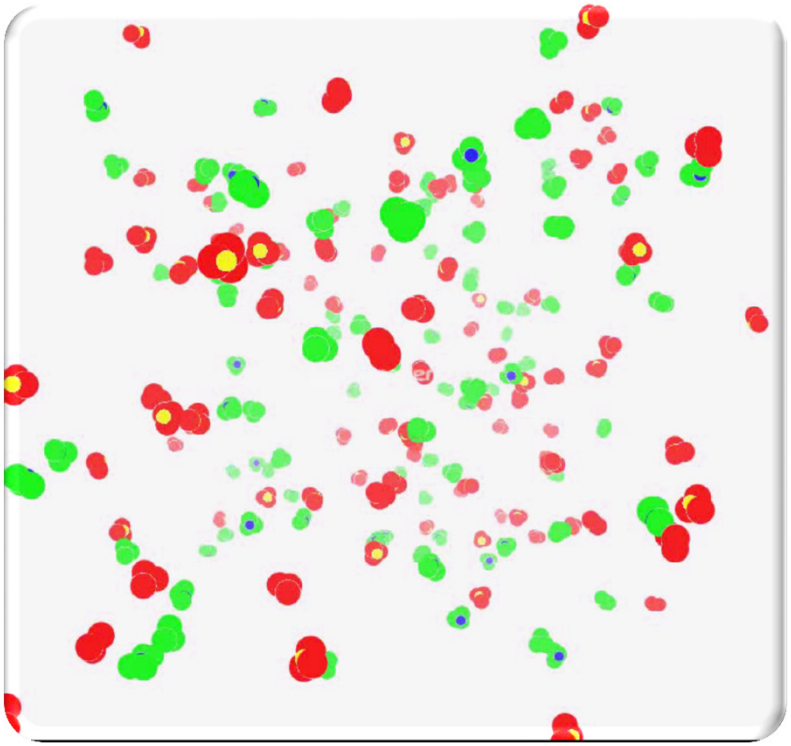


Modeling cellular heterogeneity: **rigid-body model**

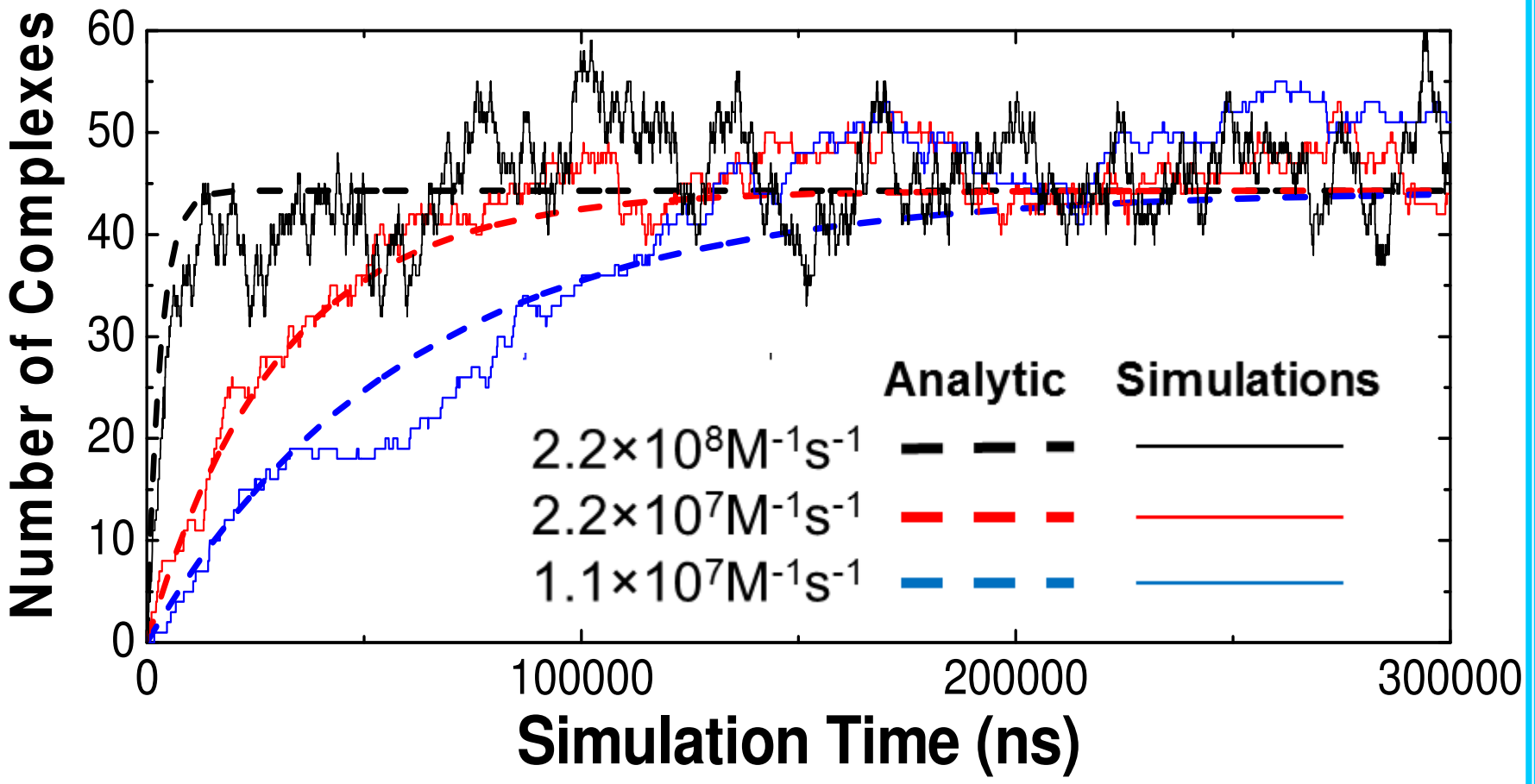


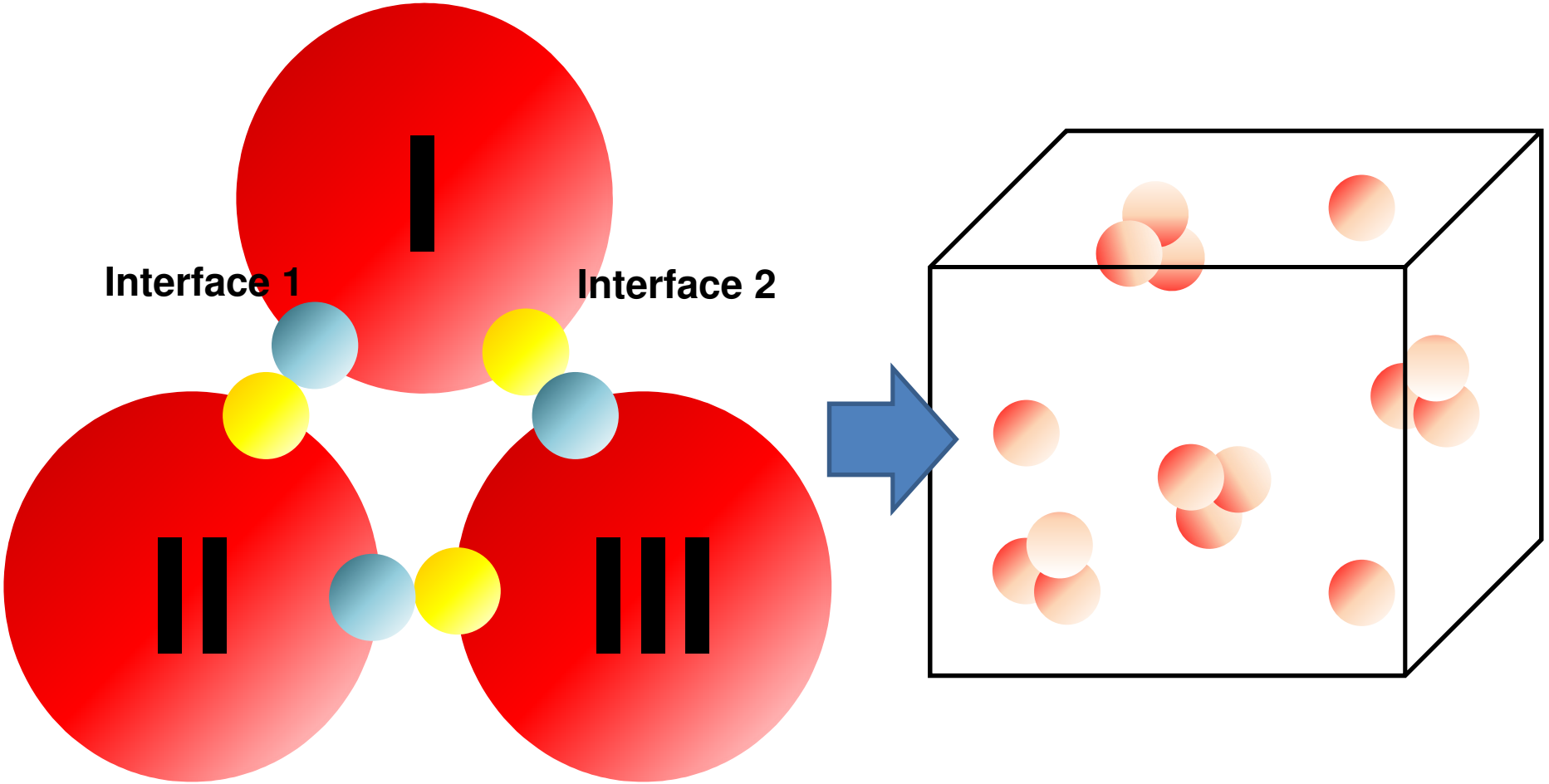
Modeling cellular heterogeneity: **simulation algorithm**

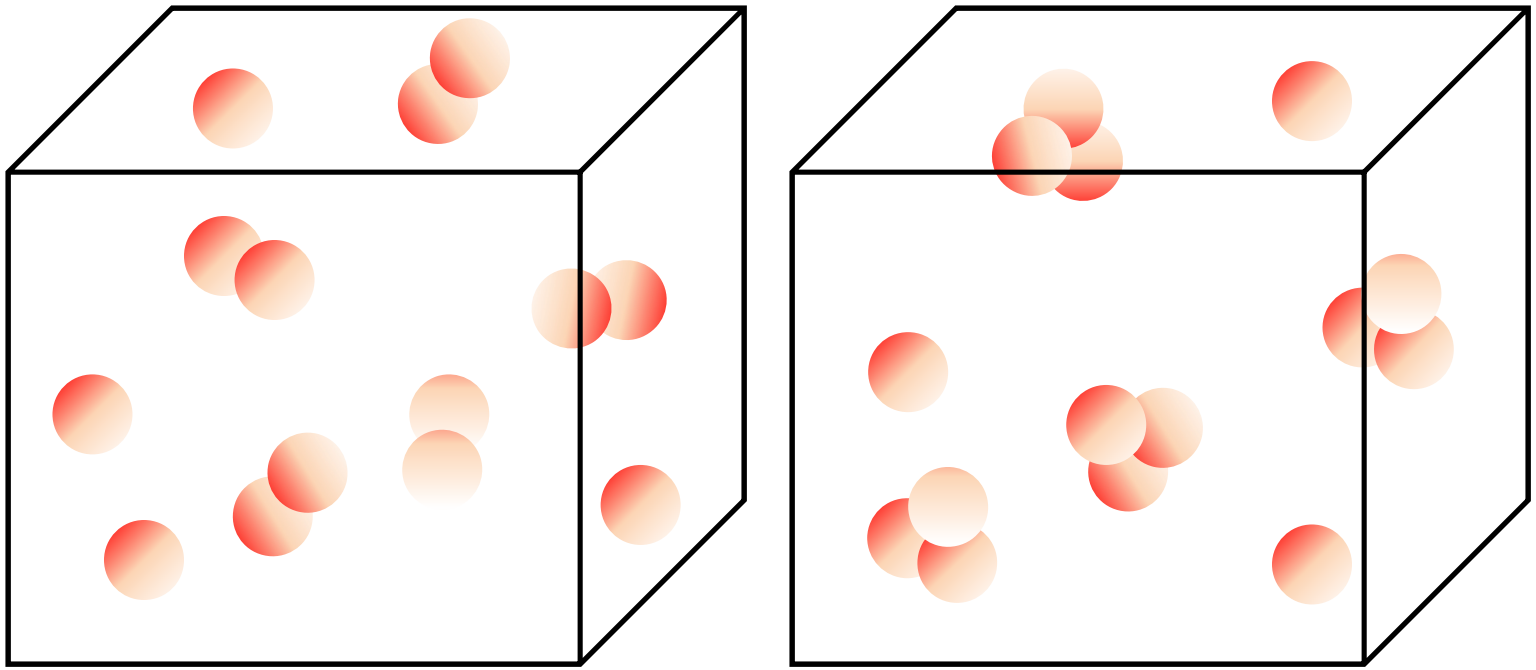


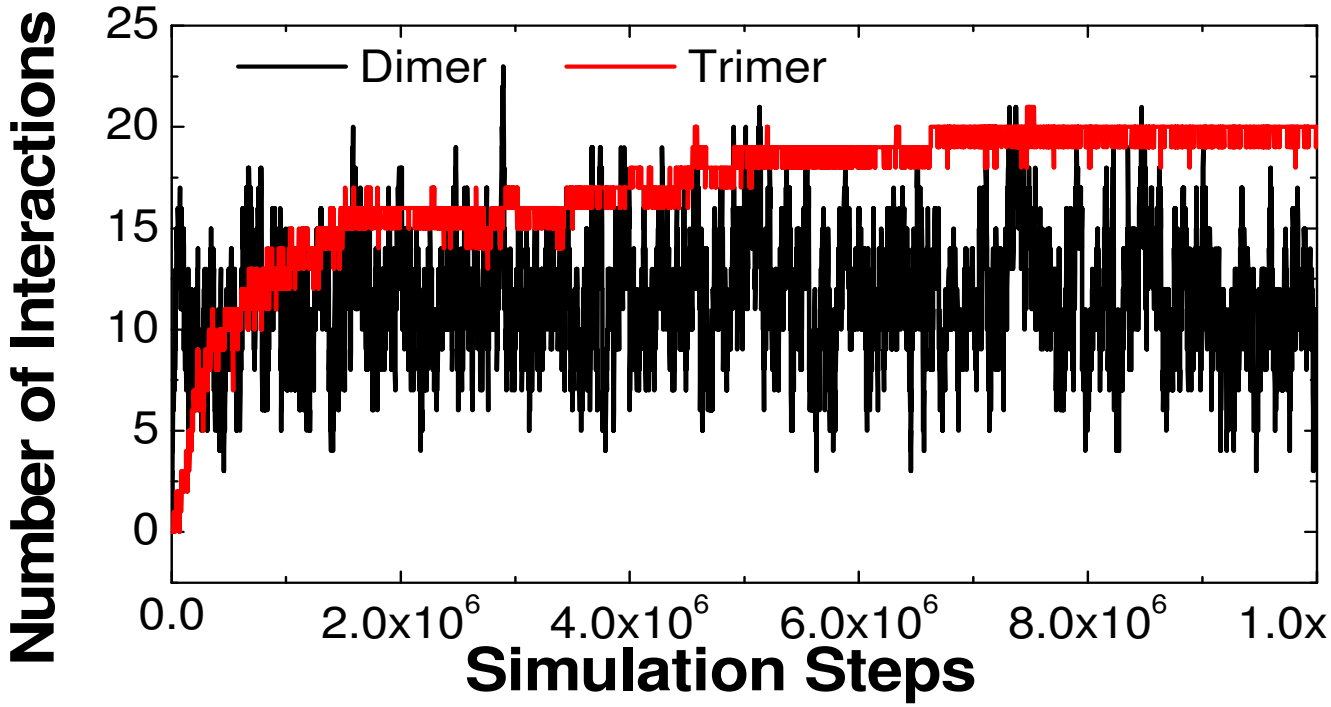


Modeling cellular heterogeneity: **model validation**









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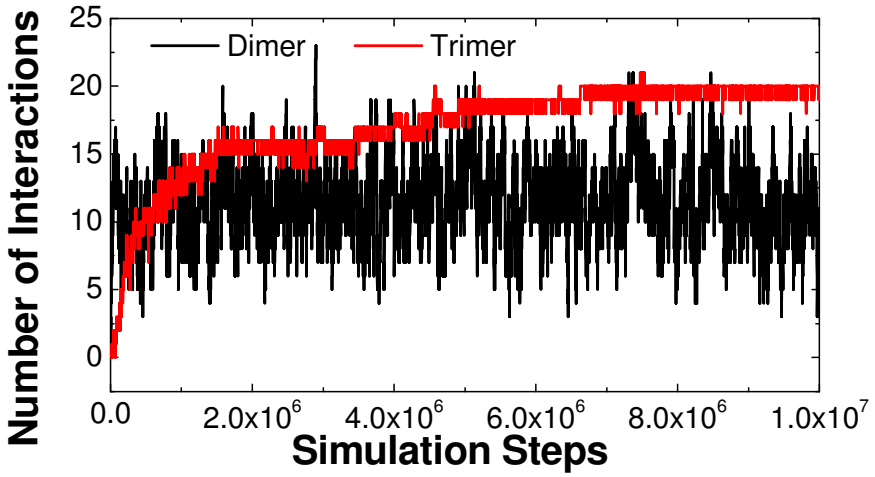
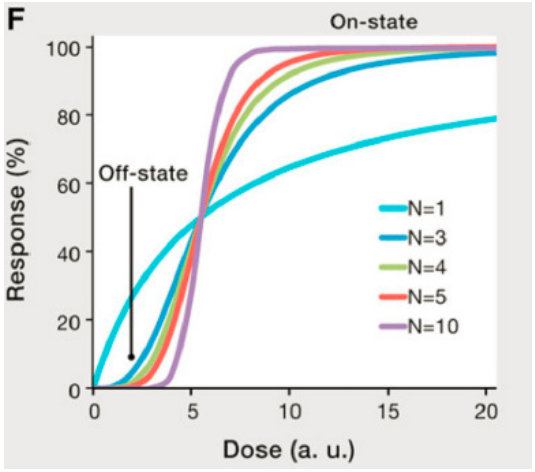
Functional significance of forming high-order complex





- The cooperativity exists when multimeric spatial organization requires the formation of initial seed complex. This intrinsic cooperation leads to slower kinetics during complex assembly, but it is significant to the functions of signal transduction. It leads to the fact that cells could exhibit an all-or-none transition only when there is a persistent and high dose of stimulation, which is called a threshold response.

- The biological noises due to conformational fluctuations of macromolecules or randomness in molecular diffusions can be reduced through the spatial formation of high-order molecular patterns.

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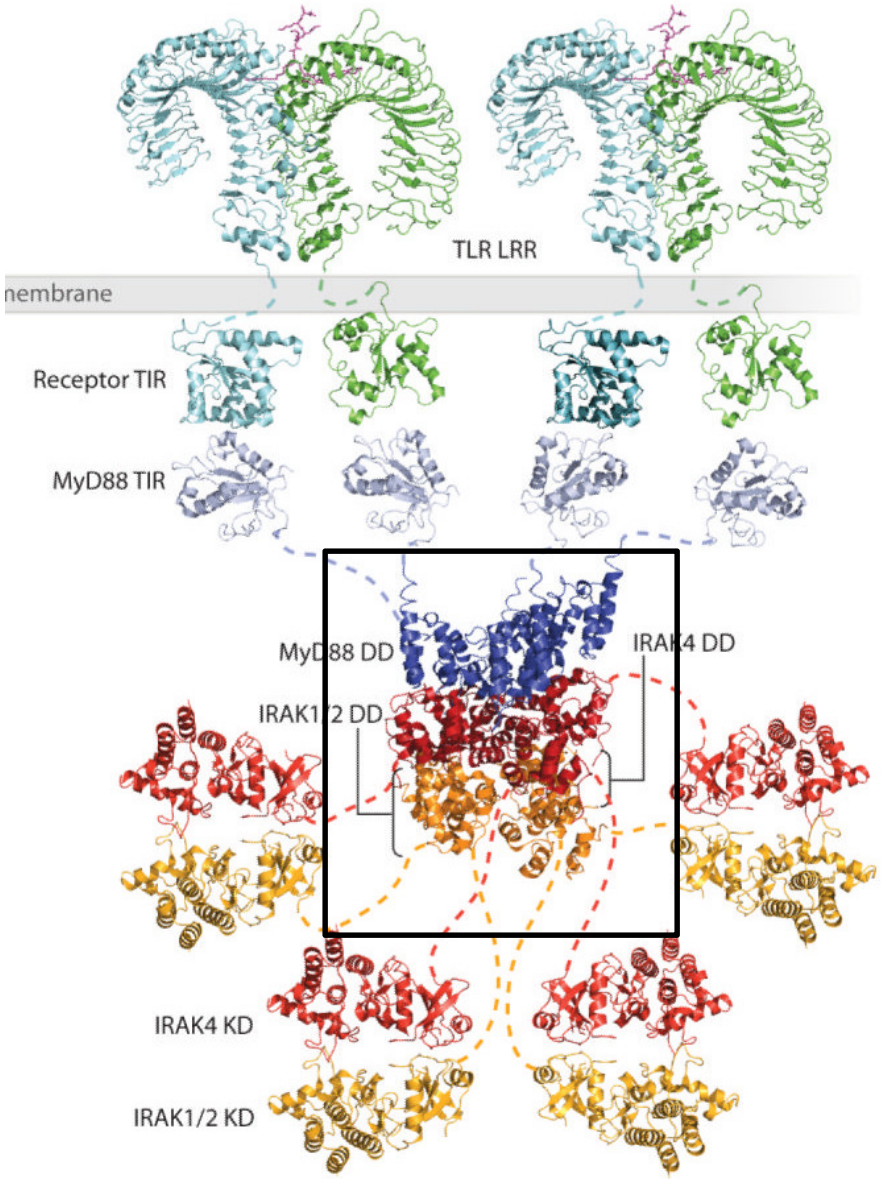
Assembly of signalosome: a real example



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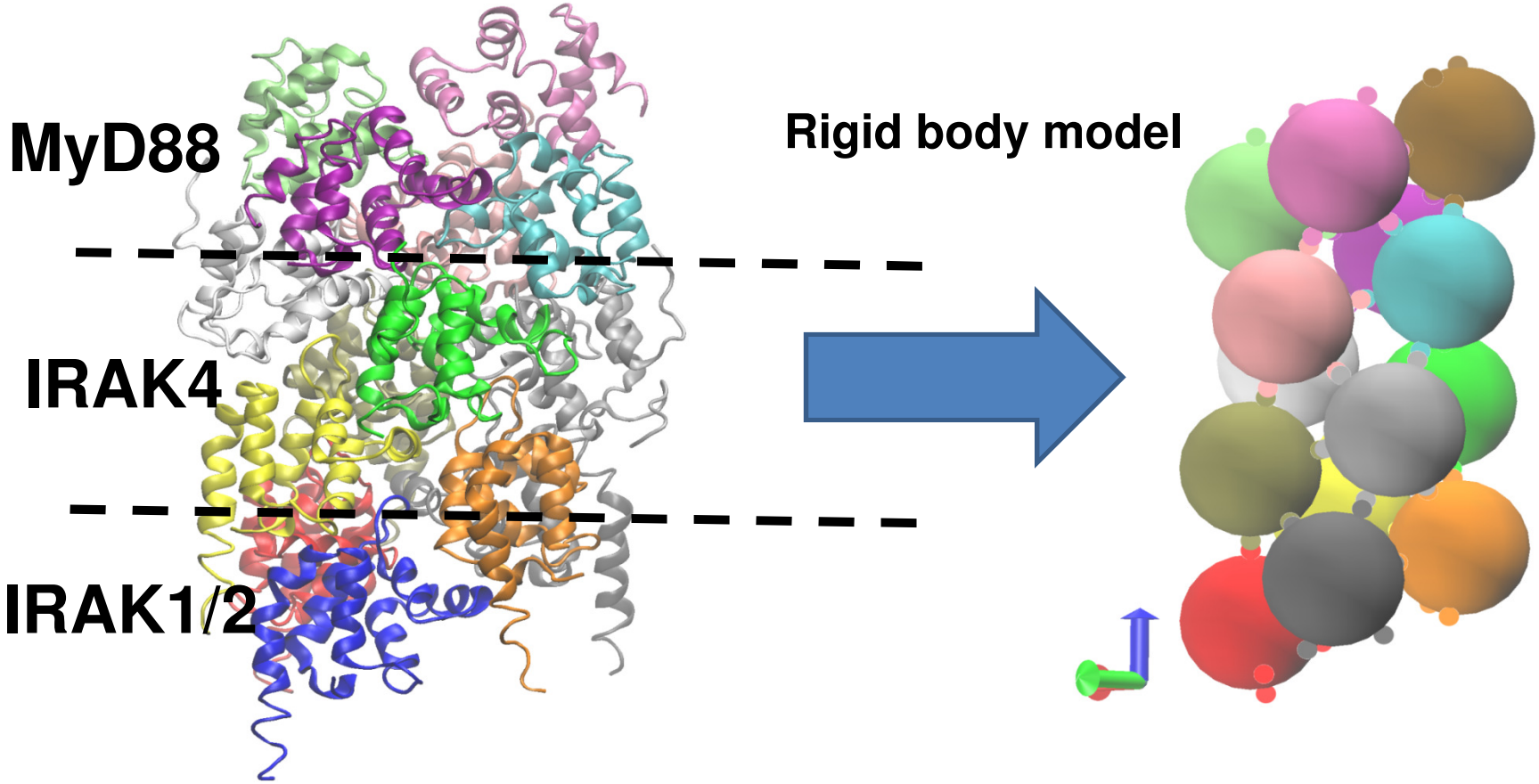

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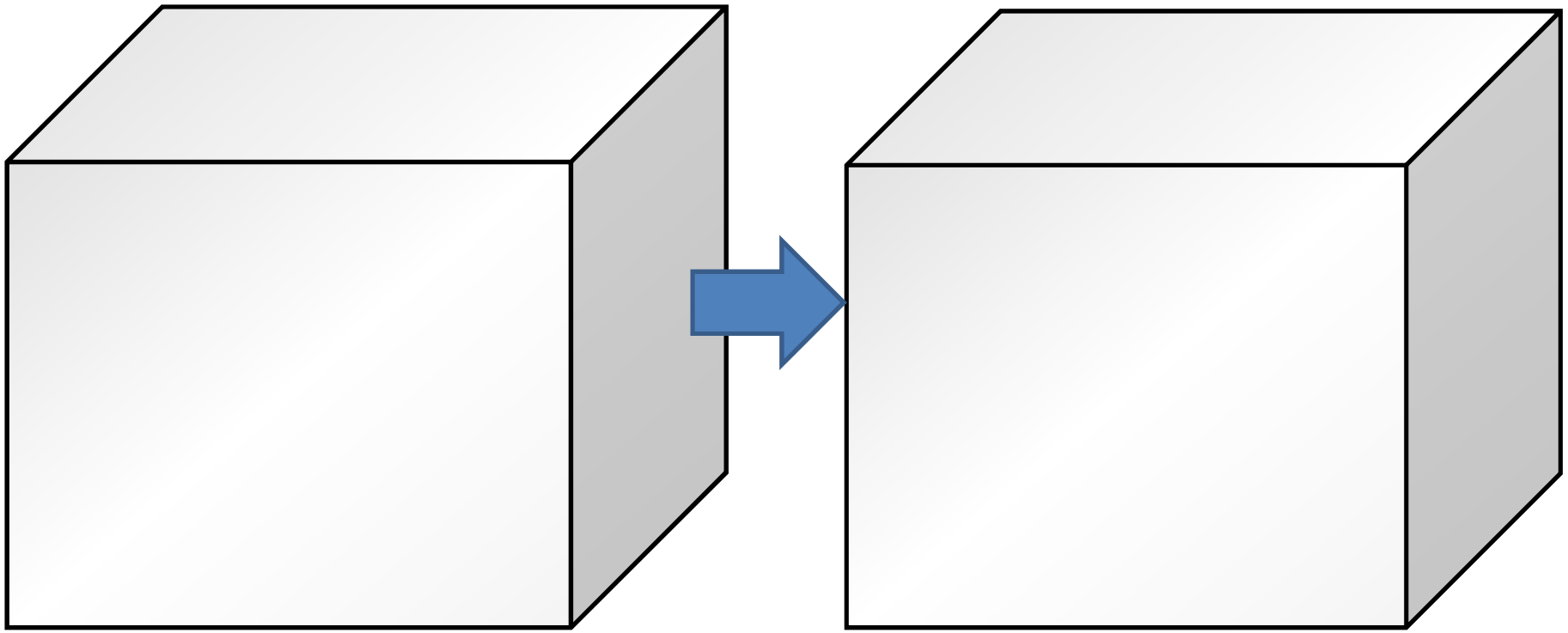

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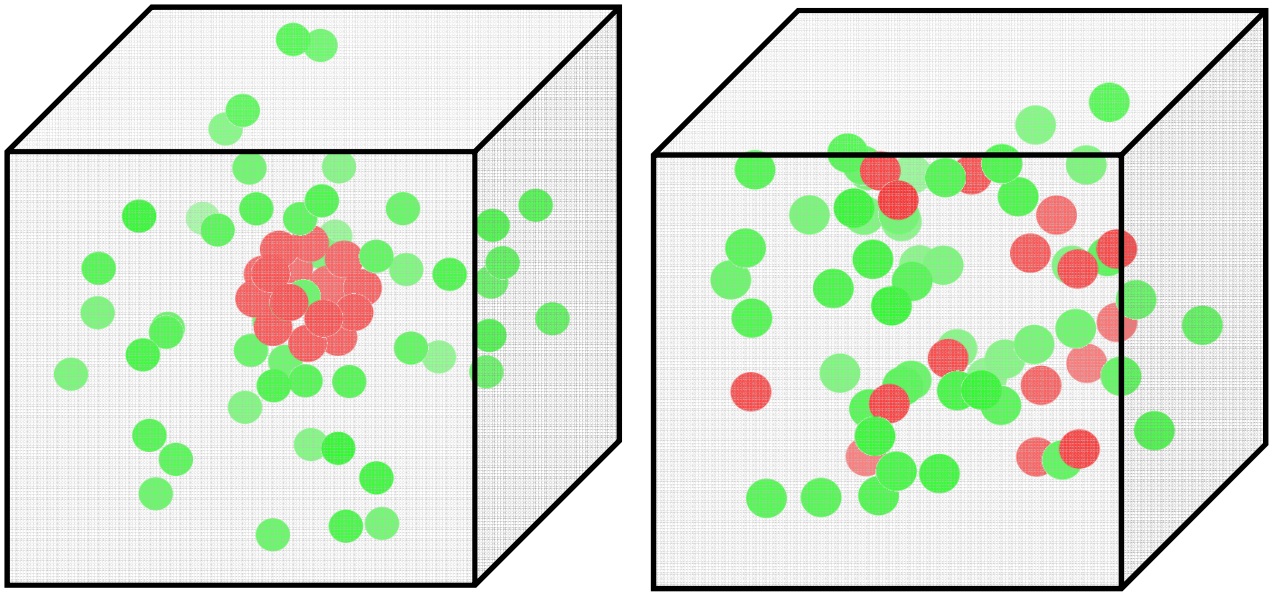
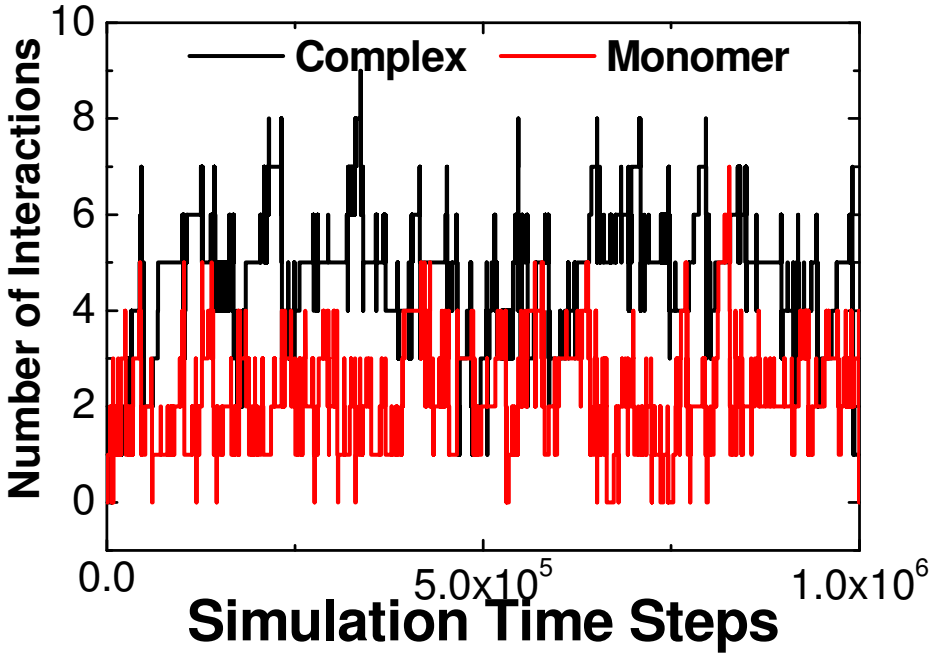
Functional significance of forming high-order complex





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Summary

- Background
- Theory of chemical kinetics
- Modeling temporal dynamics of subcellular processes
- Simulations of spatial organization of subcellular processes