

Modelling of Cell Motility and Angiogenesis

WPI, Vienna - Nov. 8-12, 2004

Directional sensing and phase separation in the eukaryotes

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Directional sensing

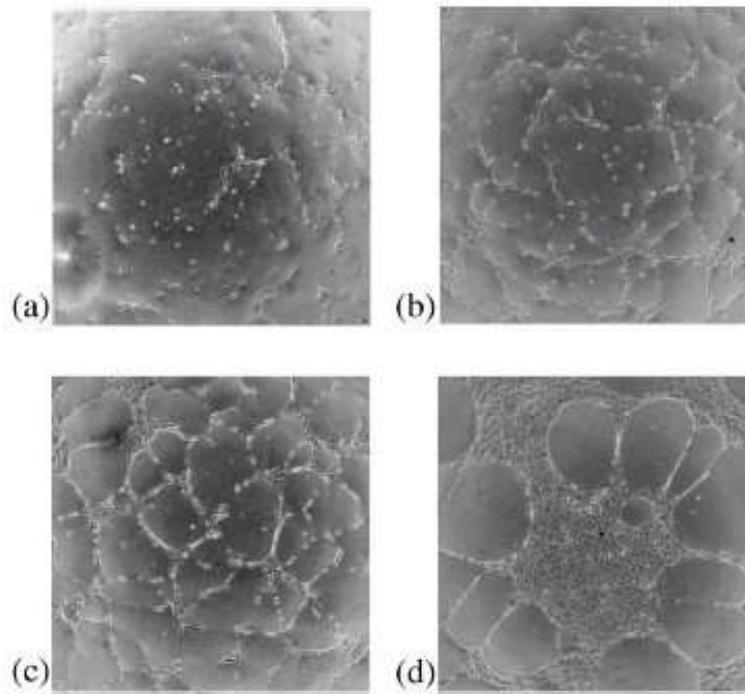
- The ability to sense extracellular directional cues and generate an internal amplified response
- It can induce changes in cell morphology and motility
- It plays a central role in development, immunity and tissue homeostasis

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Blood Vessel Networks

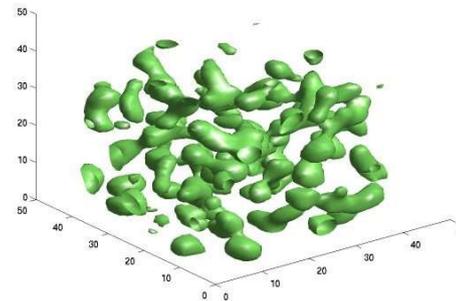


A new mathematical model accurately describes the formation of blood vessel networks, potentially providing a better understanding of vascular networks in living creatures as well as the pathological blood vessel formation that often accompanies certain cancers and other ailments. These images depict the structures that cells form on a growing medium for various initial cell densities, which are consistent with the new model's predictions. Image (a) shows the disconnected patterns that arise when the initial density is only 50 cells/square millimeter. The subsequent images show networks arise as the starting cell density is increased to (b) 100 cells/square millimeter, (c) 200 cells/square millimeter, and (d) 400 cells/square millimeter.

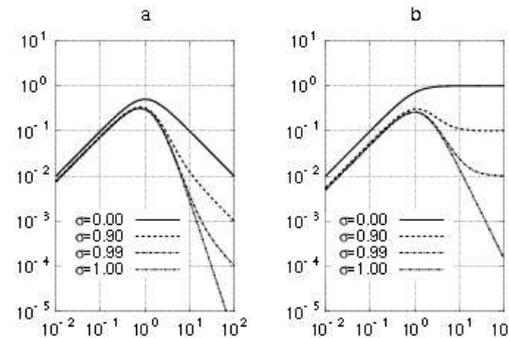
Source: A. Gamba *et al.*, *Physical Review Letters*, 21 March 2003

Additional information:
[Associated Physics News Update](#)

3D



role of inhibiting factors



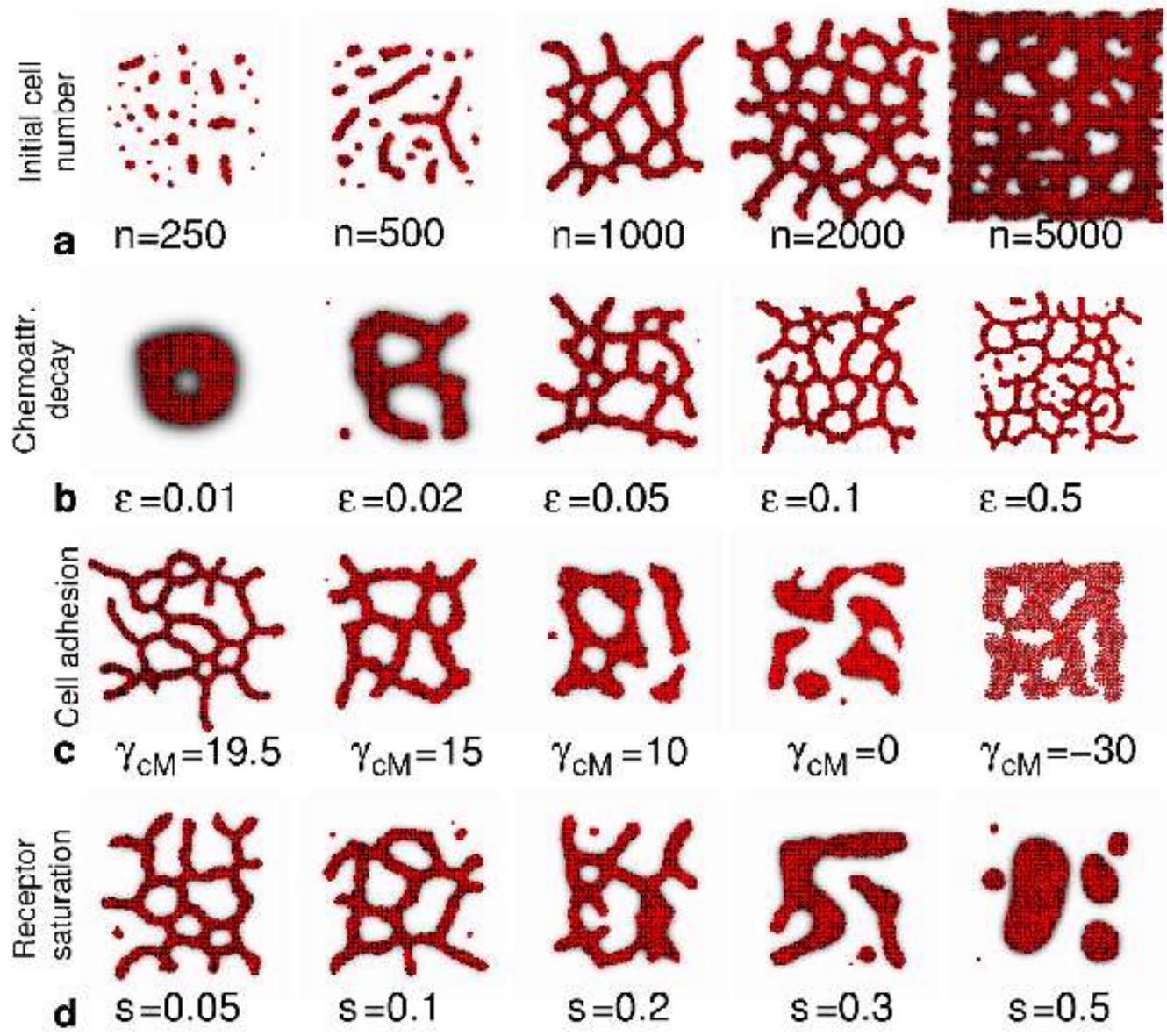
hydrodynamic limit of velocity-jump stochastic processes

$$\frac{\partial f}{\partial t} + v \cdot \nabla_x f = \mathcal{T}(S, f)$$

Cavalli, G., Naldi

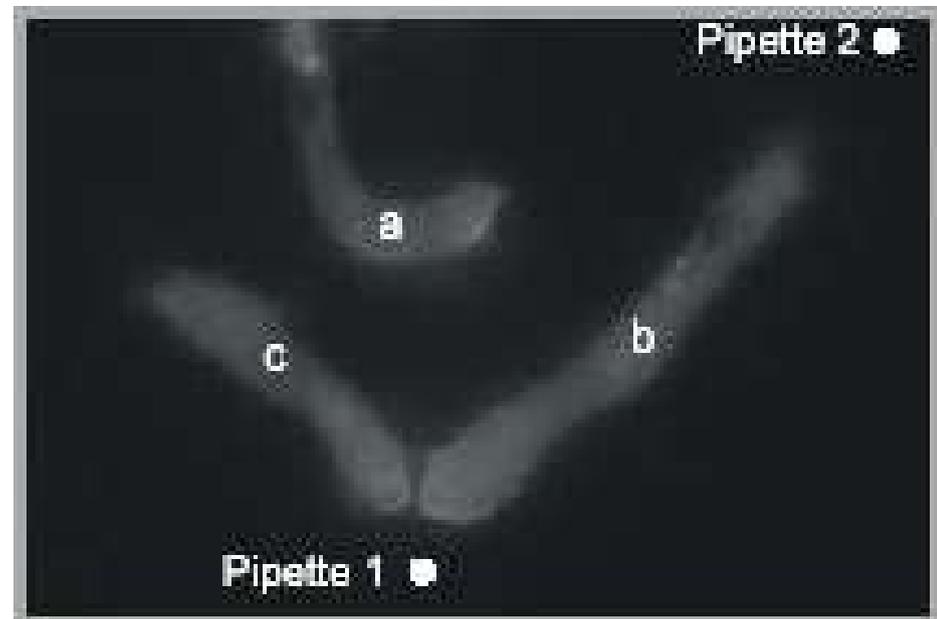
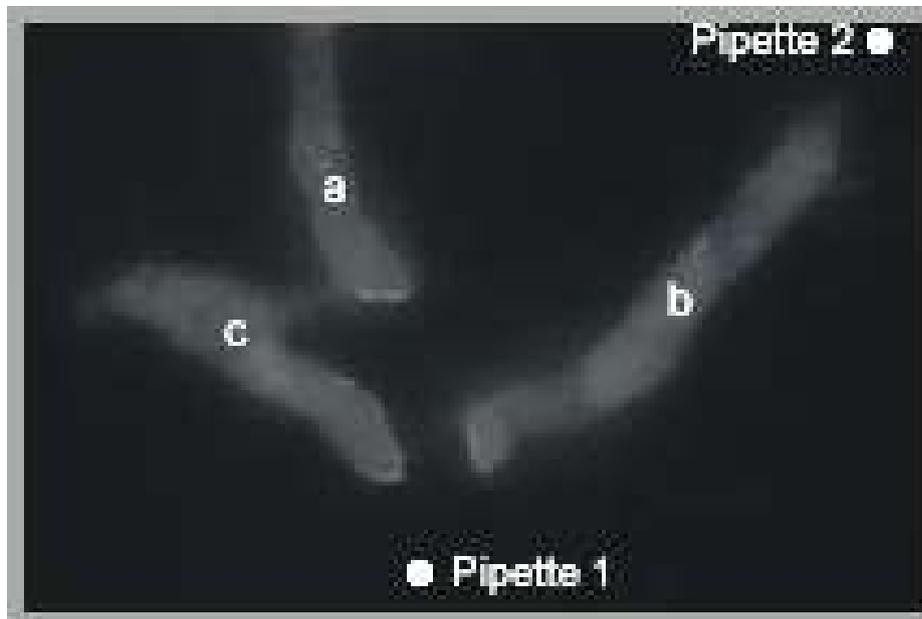
Di Talia, G.,
Lamberti, Serini

Filbet, Laurençot,
Perthame



Merks, Newman, Glazier

Directional sensing



Devreotes, Janetopoulos

Eukariotic chemotaxis

EXTERNAL
SIGNAL



DIRECTIONAL
SENSING



CELL POLARIZATION,
DIRECTED MOTION

shallow spatial gradients of extracellular
chemotactic factor (~5%)

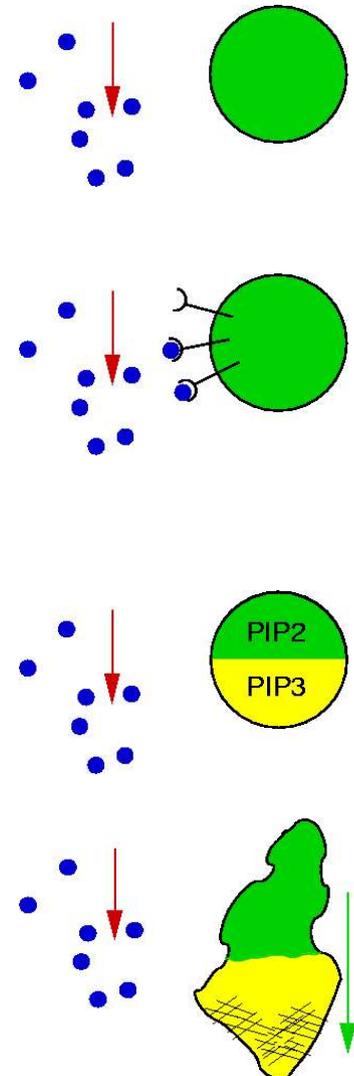
chemotactic factor binds to receptors

receptor activation mirrors shallow
chemotactic gradient



an “all or nothing” response is
somehow generated

localized PIP3 patches induce
actin polymerization

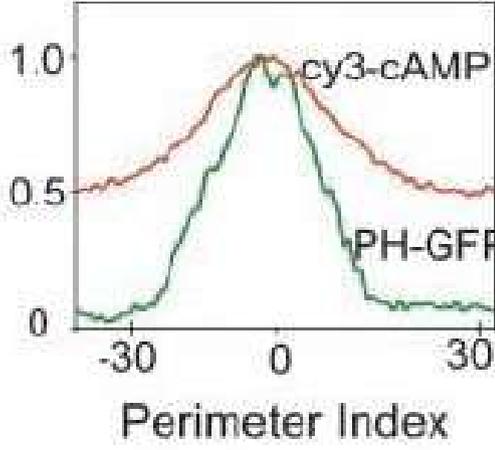
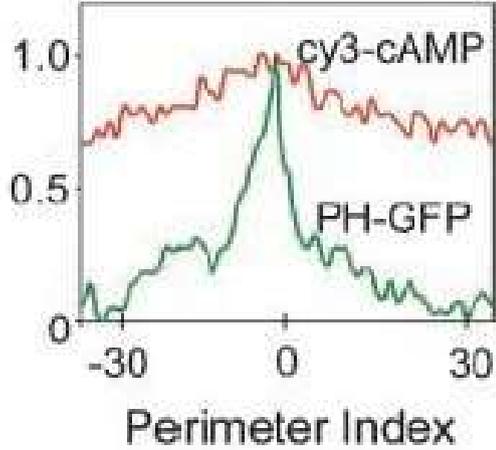
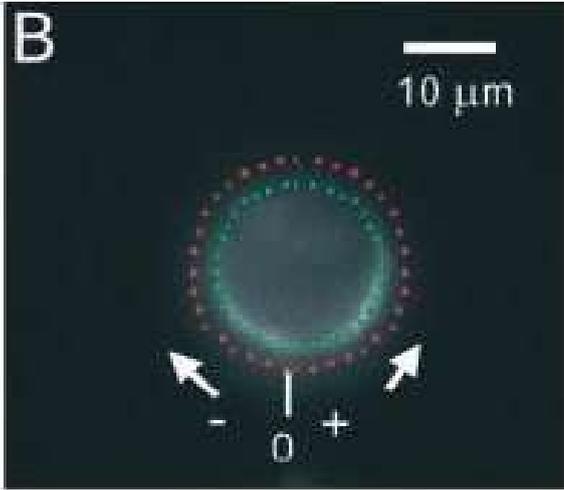
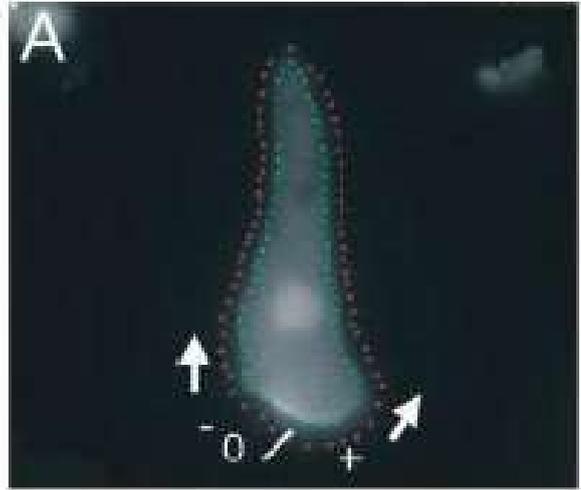


Immobilized cells

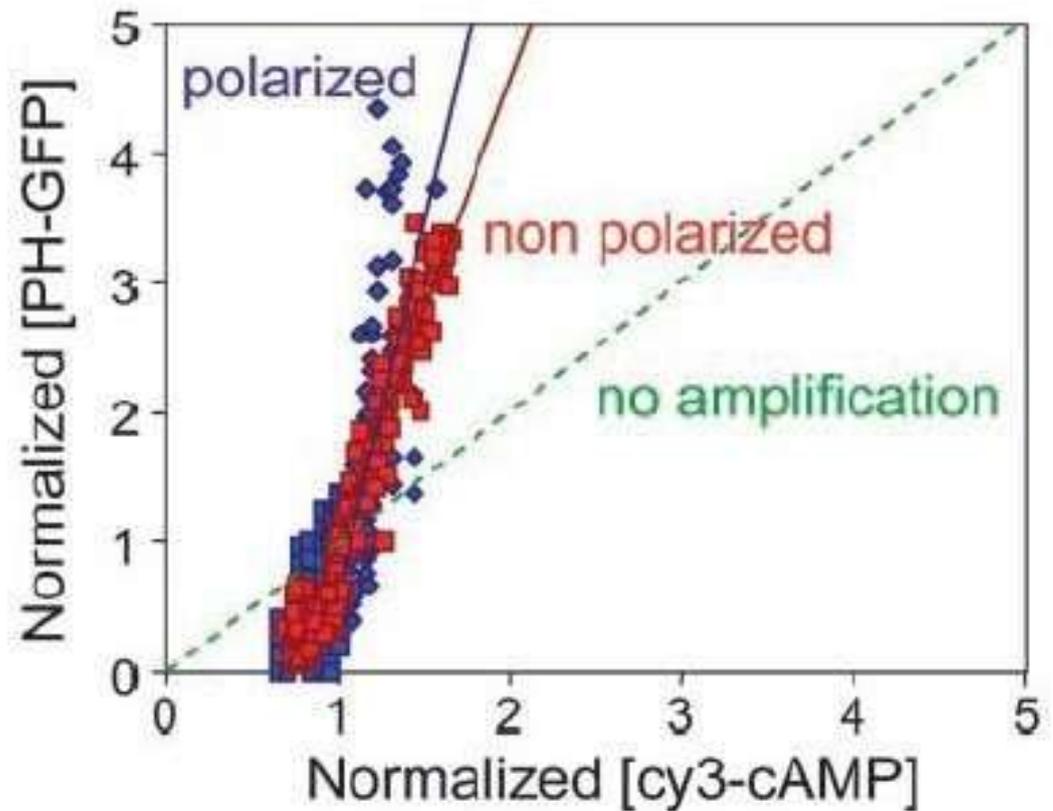
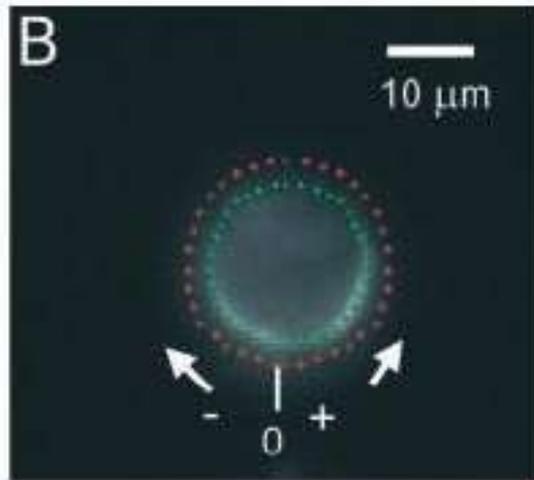


Devreotes, Janetopoulos

Directional sensing

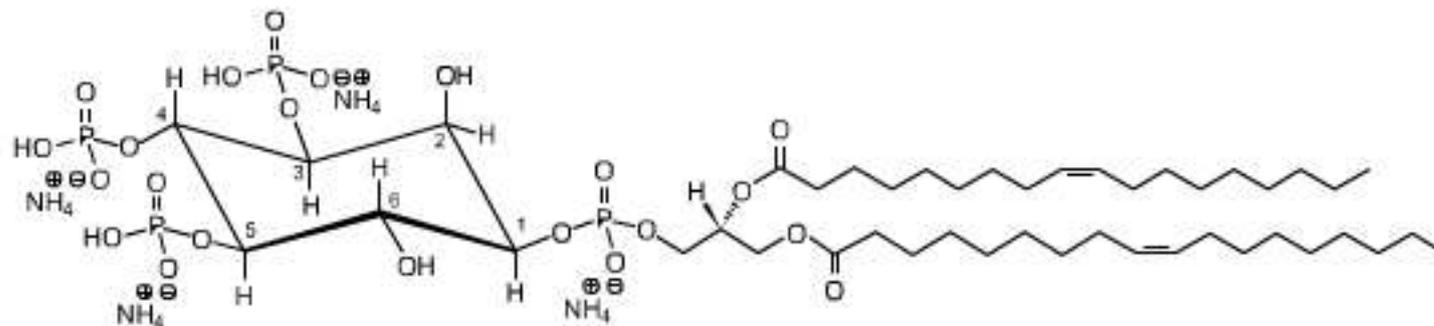
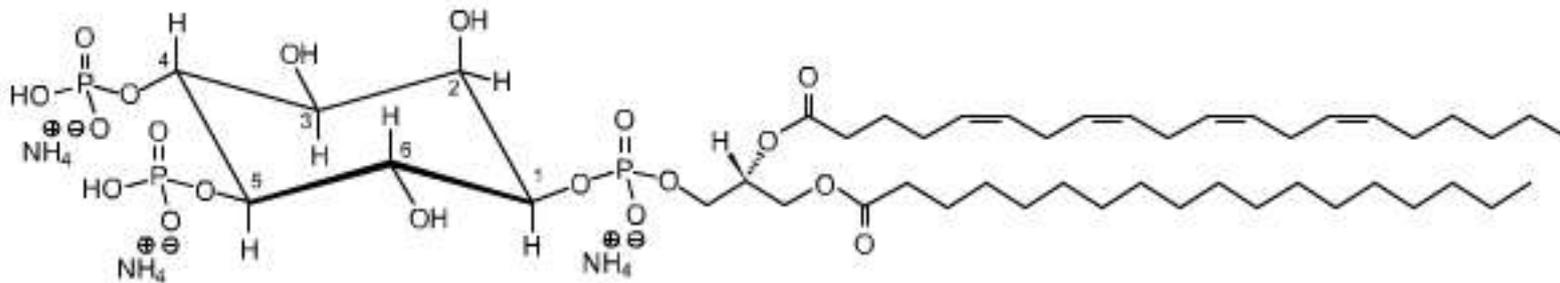


Signal amplification



PI(3,4,5)P₃ localization

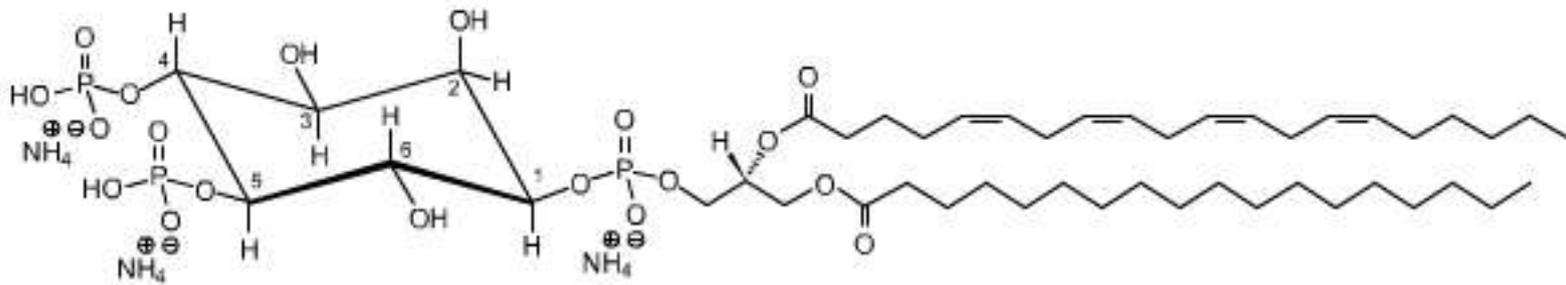
Phosphatidylinositol-4,5-bisphosphate [PI(4,5)P₂; PIP₂]



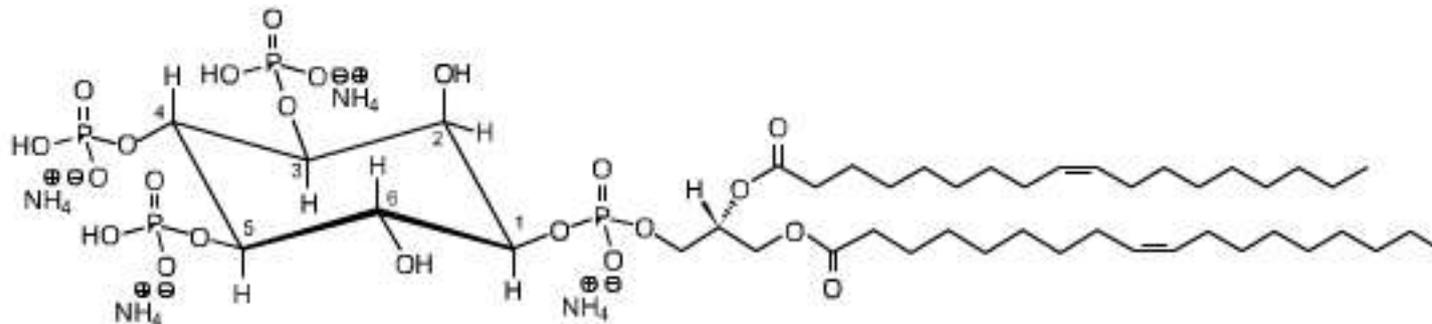
Phosphatidylinositol-3,4,5-triphosphate [PI(3,4,5)P₃; PIP₃]

PI(3,4,5)P₃ localization

Phosphatidylinositol-4,5-bisphosphate [PI(4,5)P₂; PIP₂]



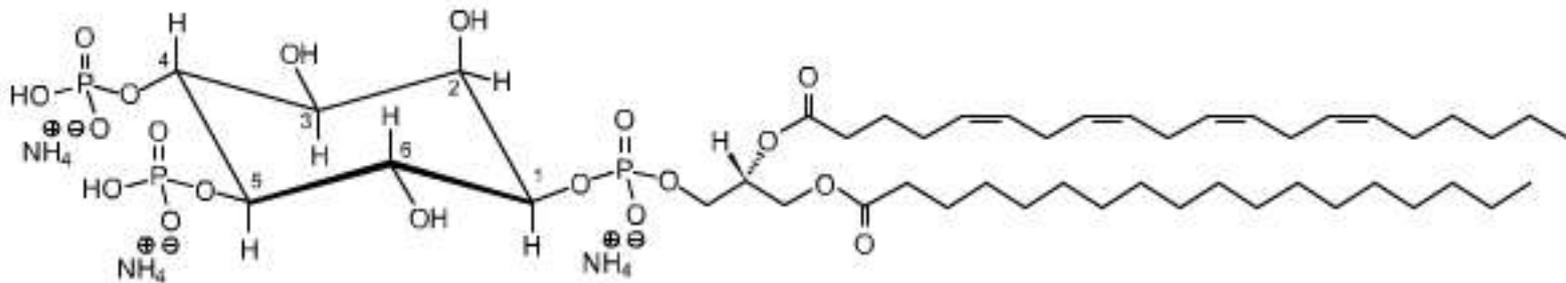
PI3K



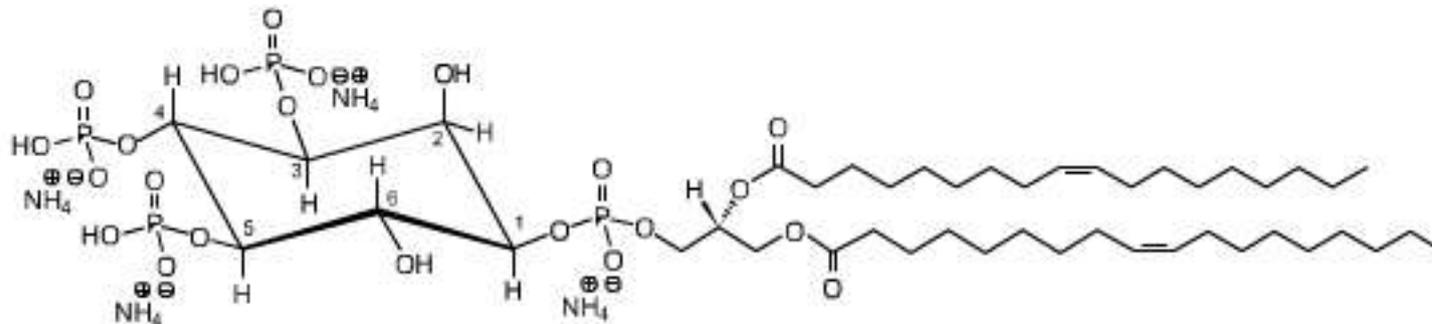
Phosphatidylinositol-3,4,5-triphosphate [PI(3,4,5)P₃; PIP₃]

PI(3,4,5)P₃ localization

Phosphatidylinositol-4,5-bisphosphate [PI(4,5)P₂; PIP₂]



PI3K ↓ ↑ PTEN

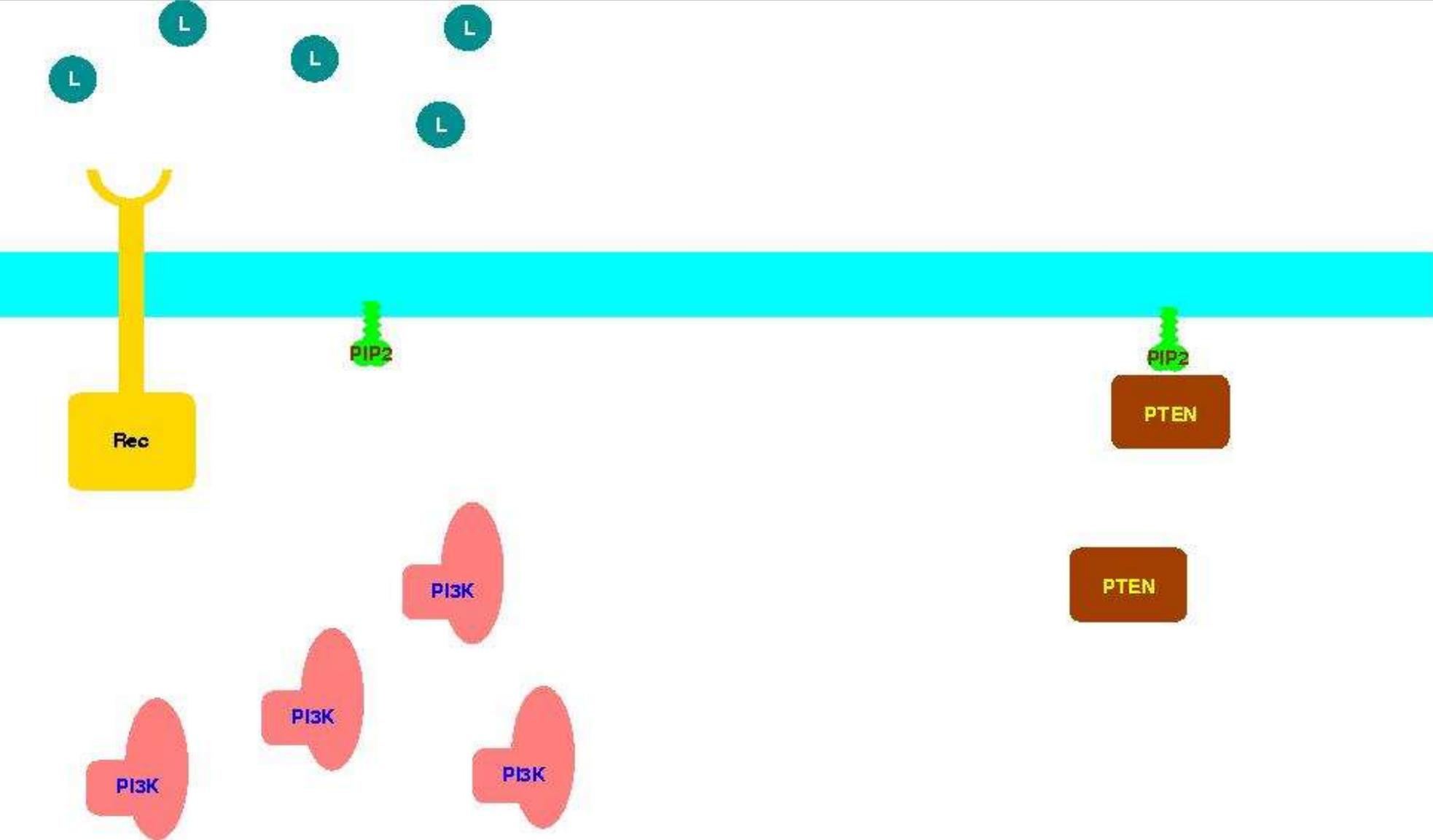


Phosphatidylinositol-3,4,5-triphosphate [PI(3,4,5)P₃; PIP₃]

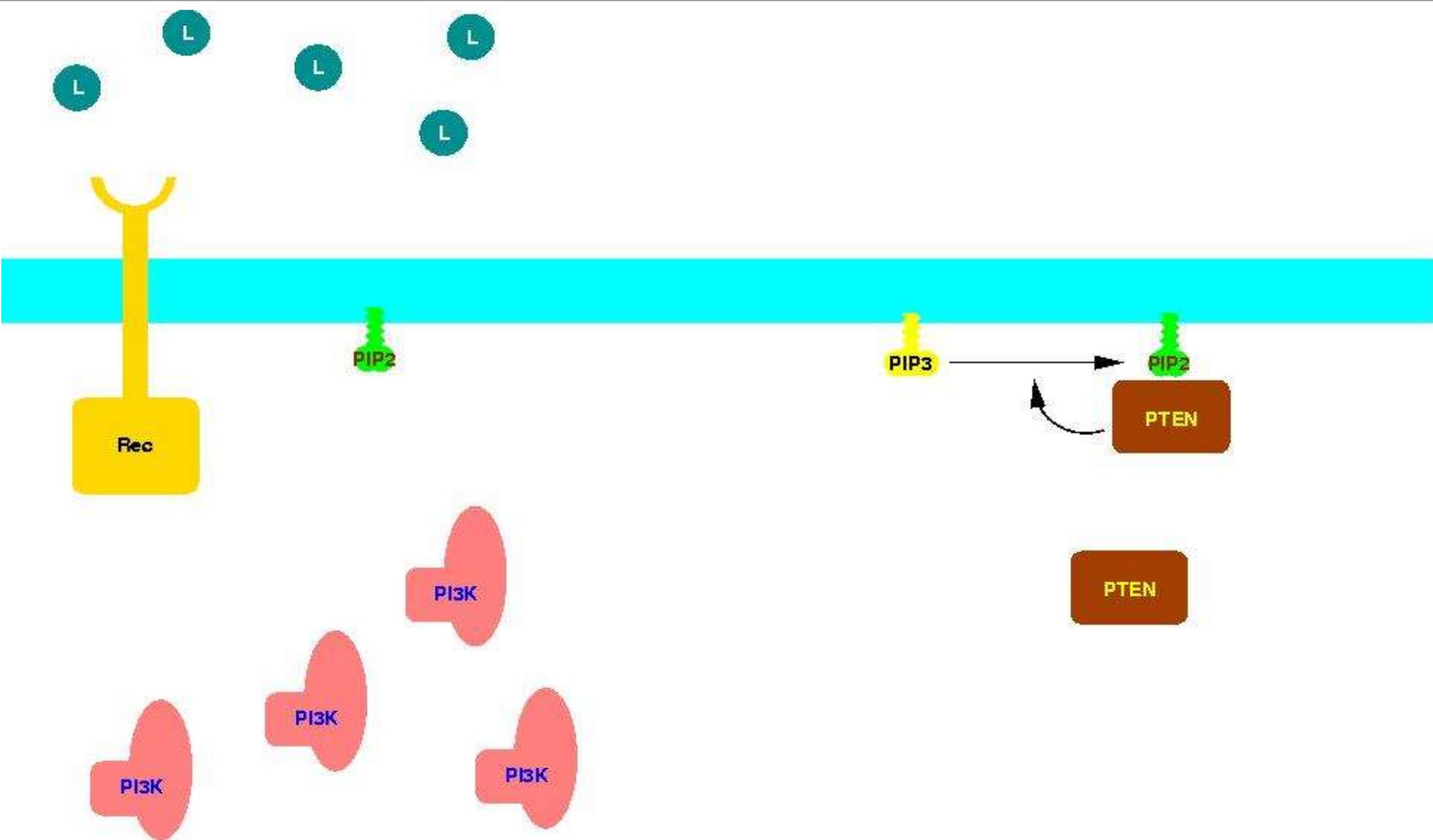
PI3K-PTEN localization

- In unstimulated cells the PI3Ks are cytosolic while a fraction of PTEN is bound to PIP2 on the plasmamembrane
- Chemoattractants bind to receptors, which recruit PI3Ks to the membrane, while PTEN rapidly dissociates

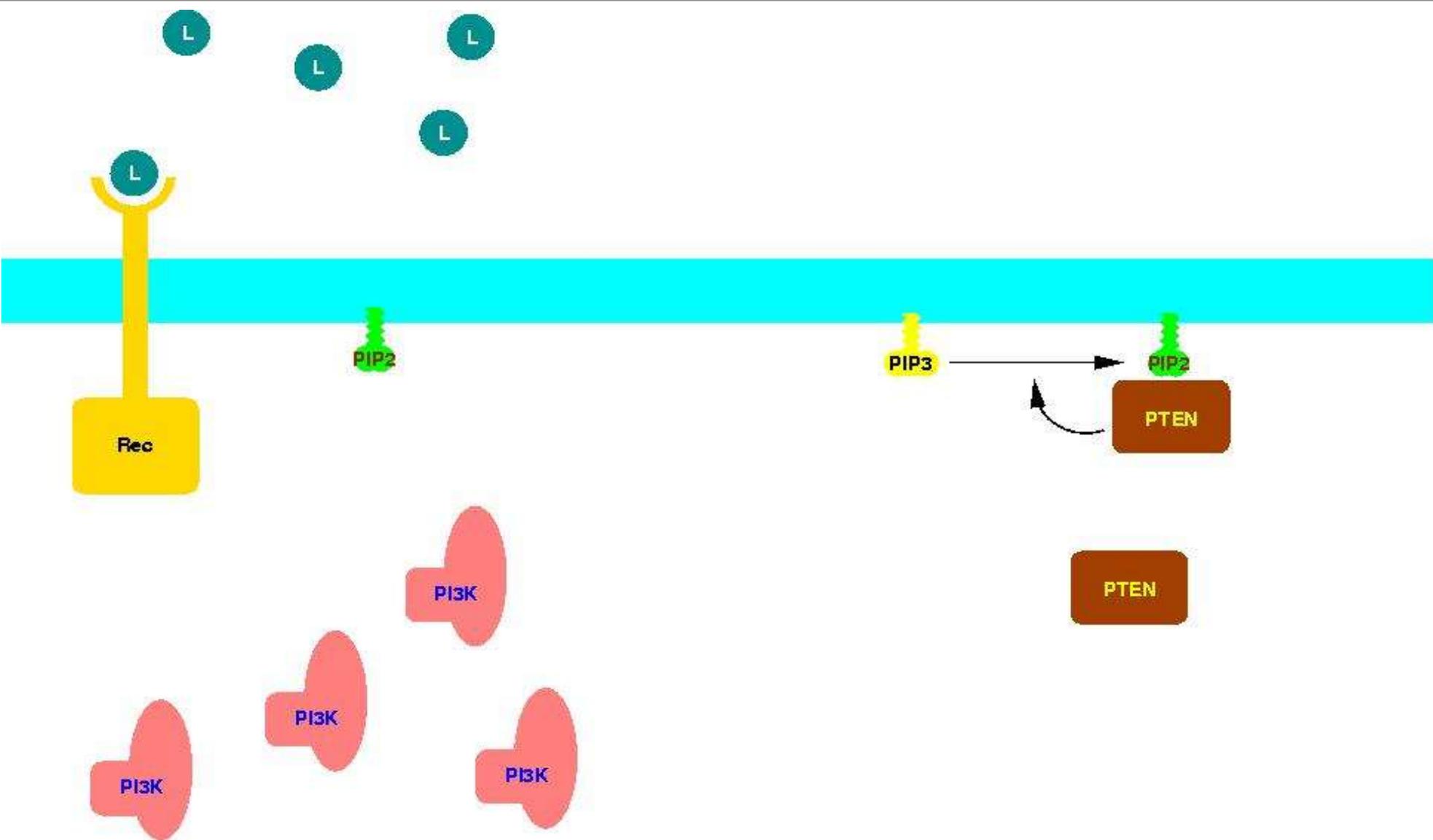
Biochemical scheme



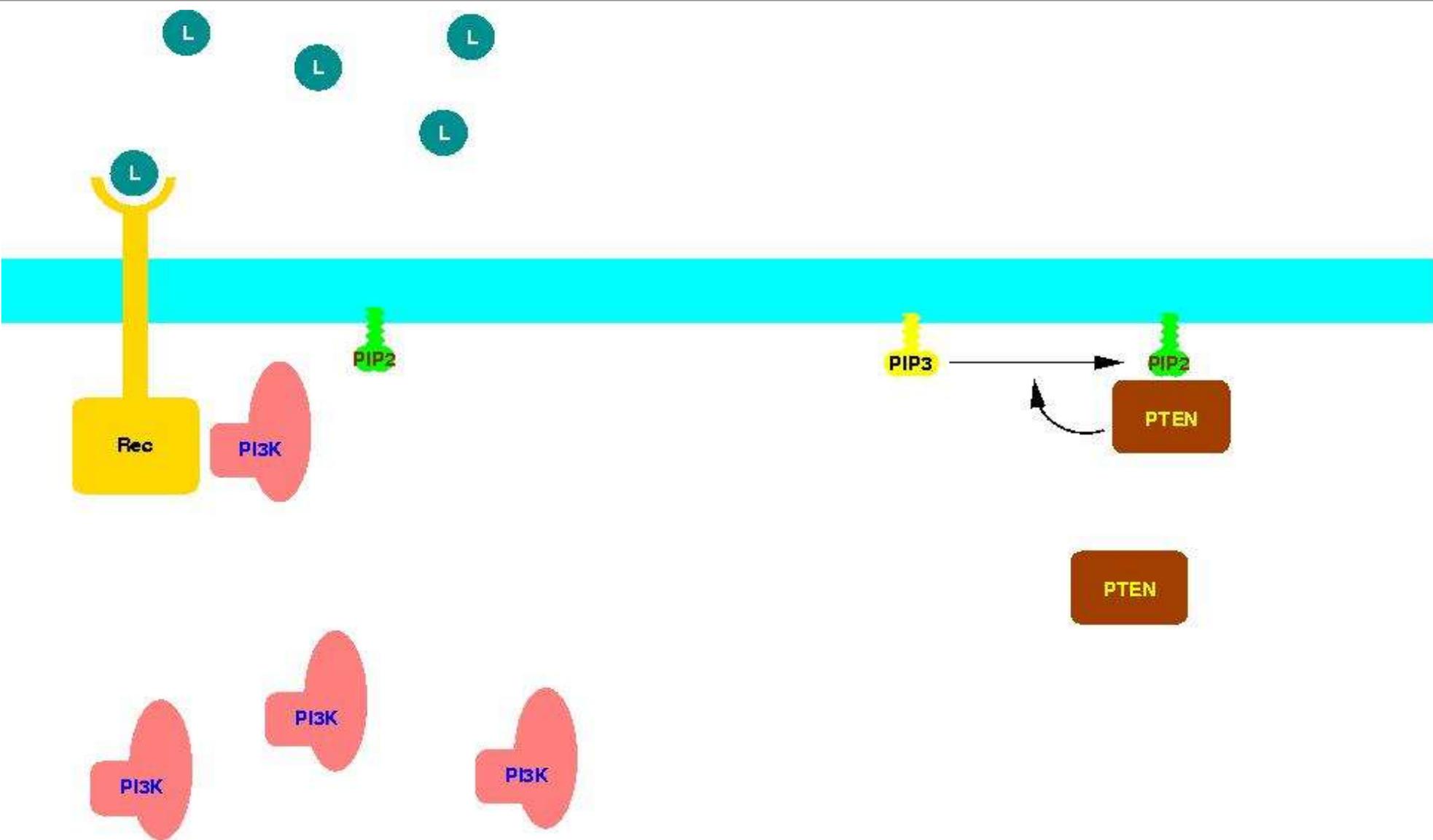
PIP3 dephosphorylation



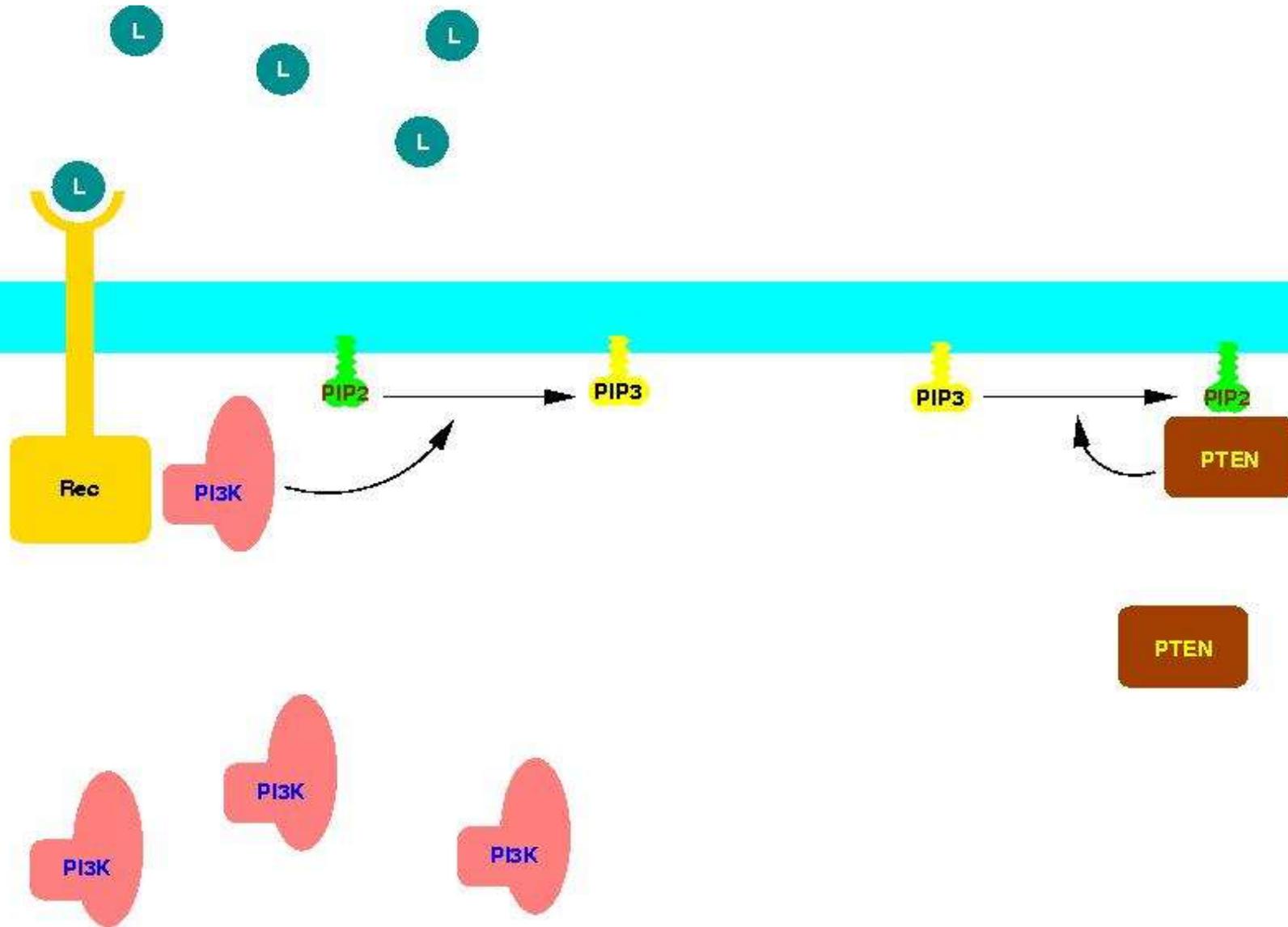
Receptor activation



PI3K recruiting



PIP2 phosphorylation



Different scales

Enzymes and phosphoinositides are quite different molecules:

- PI3K, PTEN are large (~ 200 kD), present in nM concentrations ($\sim 10^3$ /cell) slowly diffusing ($\sim 0.1 \mu\text{m}^2/\text{s}$)
- PIP2, PIP3 are smaller (~ 1 kD), present in μM concentrations ($\sim 10^6$ /cell) and have larger diffusivity ($\sim 1 \mu\text{m}^2/\text{s}$)

A phase separation scenario?

- PTEN binds to its own lipid product, PIP2
- PIP2 diffuses on the plasmamembrane
- Phosphoinositides mediate an effective attractive interaction among PTENs
- This effective interaction could induce spontaneous separation of the system in PIP2 and PIP3 rich phases
- Then, large amplification of small signal anisotropies would be a natural consequence

A phase separation scenario?

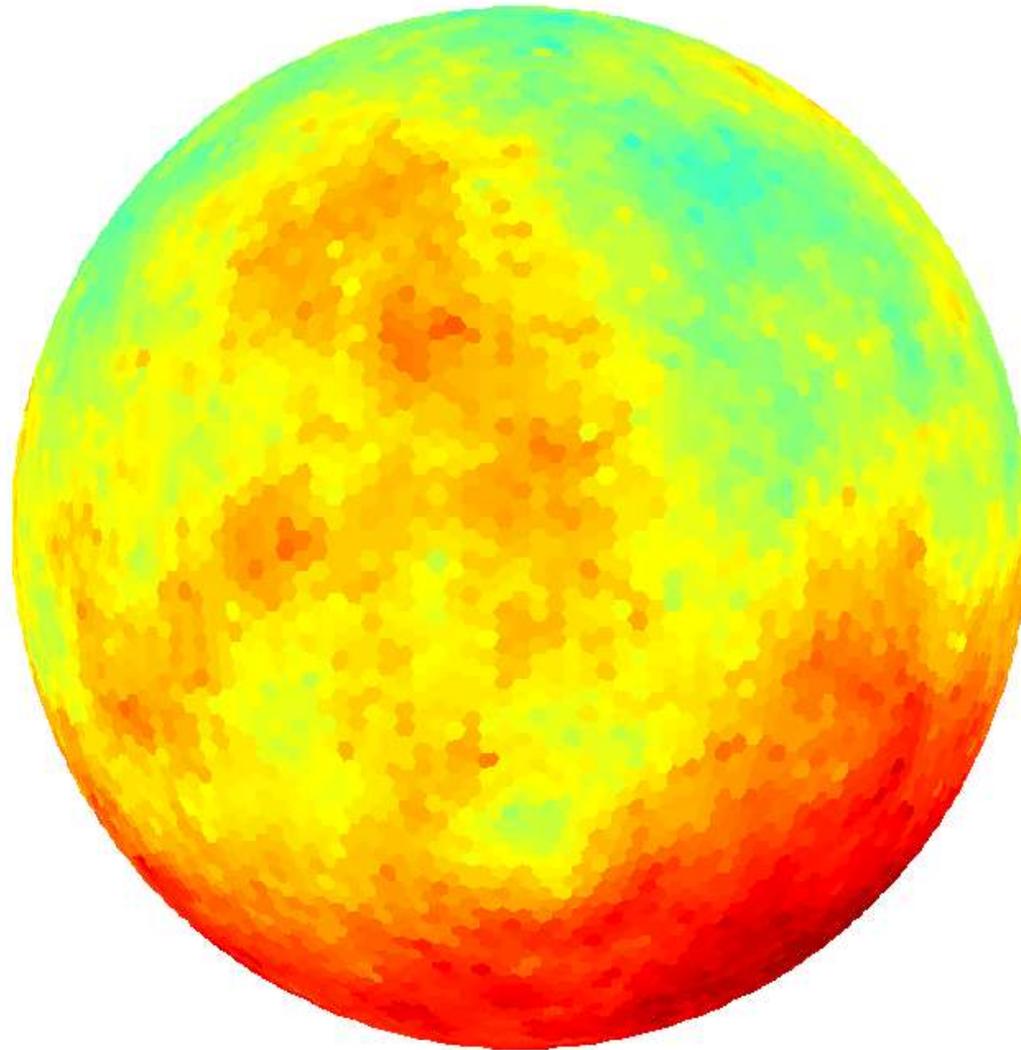
A detailed kinetic description is needed:

- to check that spontaneous phase separation can in principle be realized in this reaction-diffusion system
- to check that it can be realized using realistic values for reaction and diffusion rates

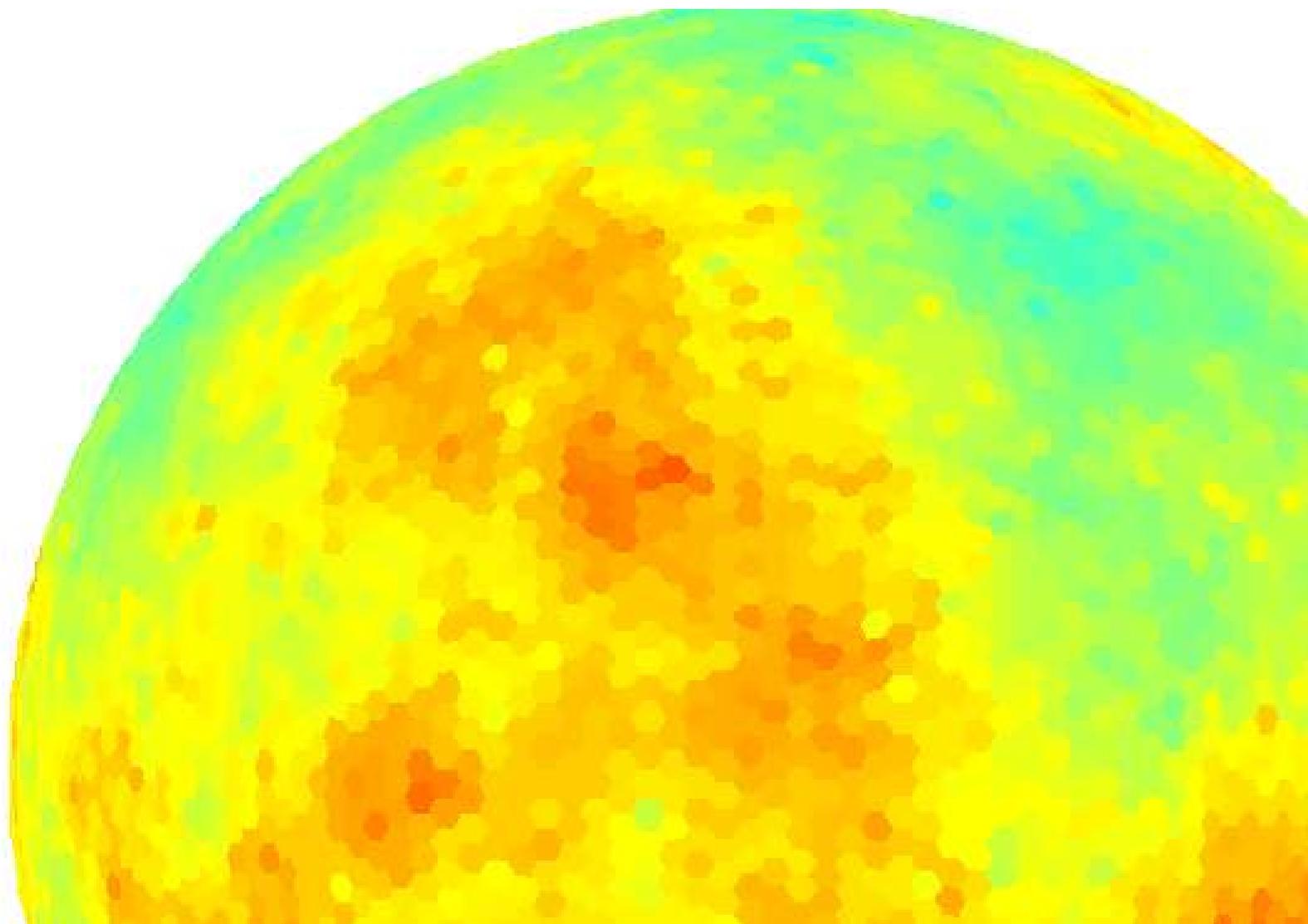
Stochastic dynamics

- Extremely low concentrations: fluctuations may be relevant
- Simulations can be performed using Gillespie's method, extended to the case of an inhomogeneous system

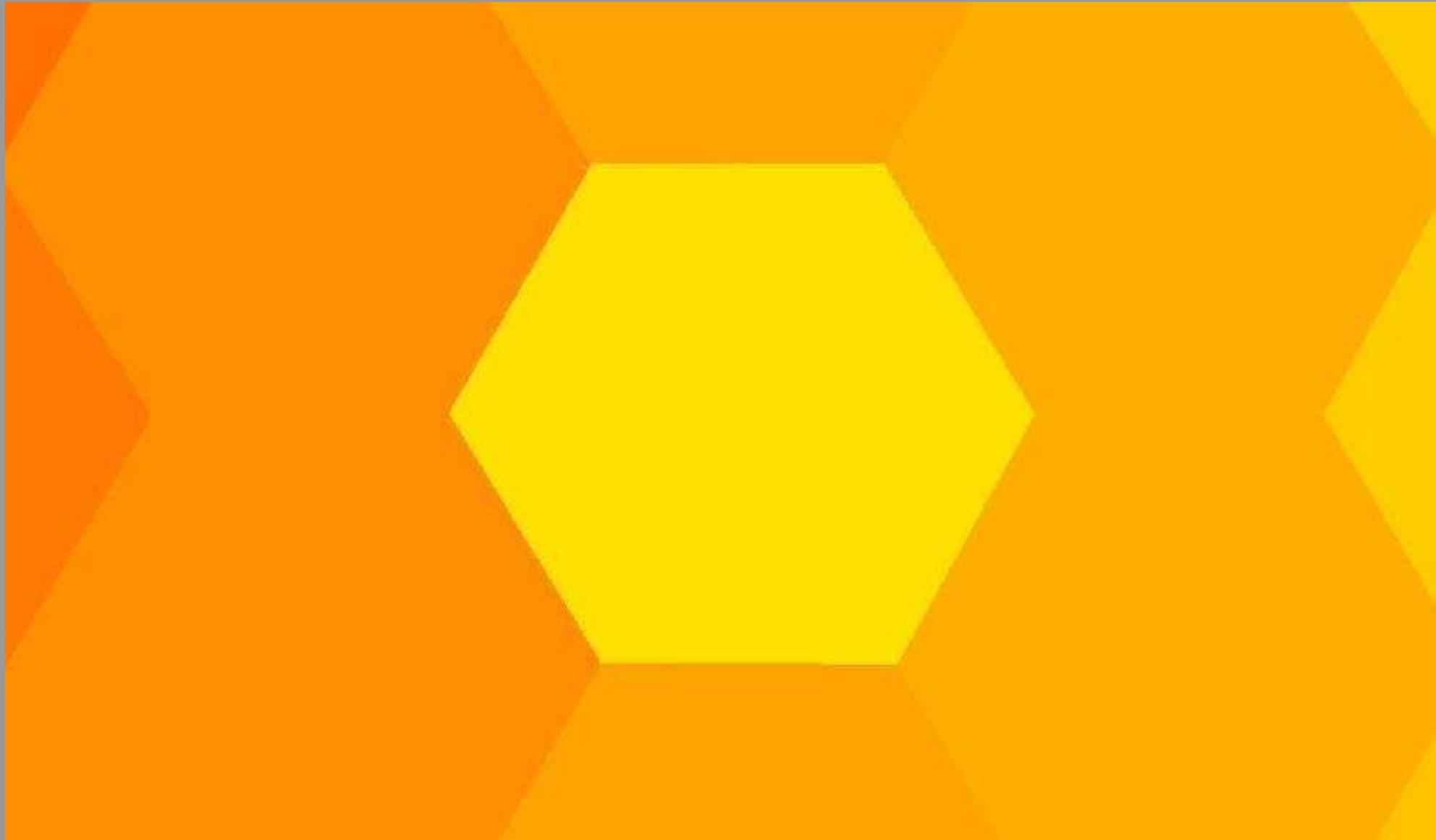
Computational lattice



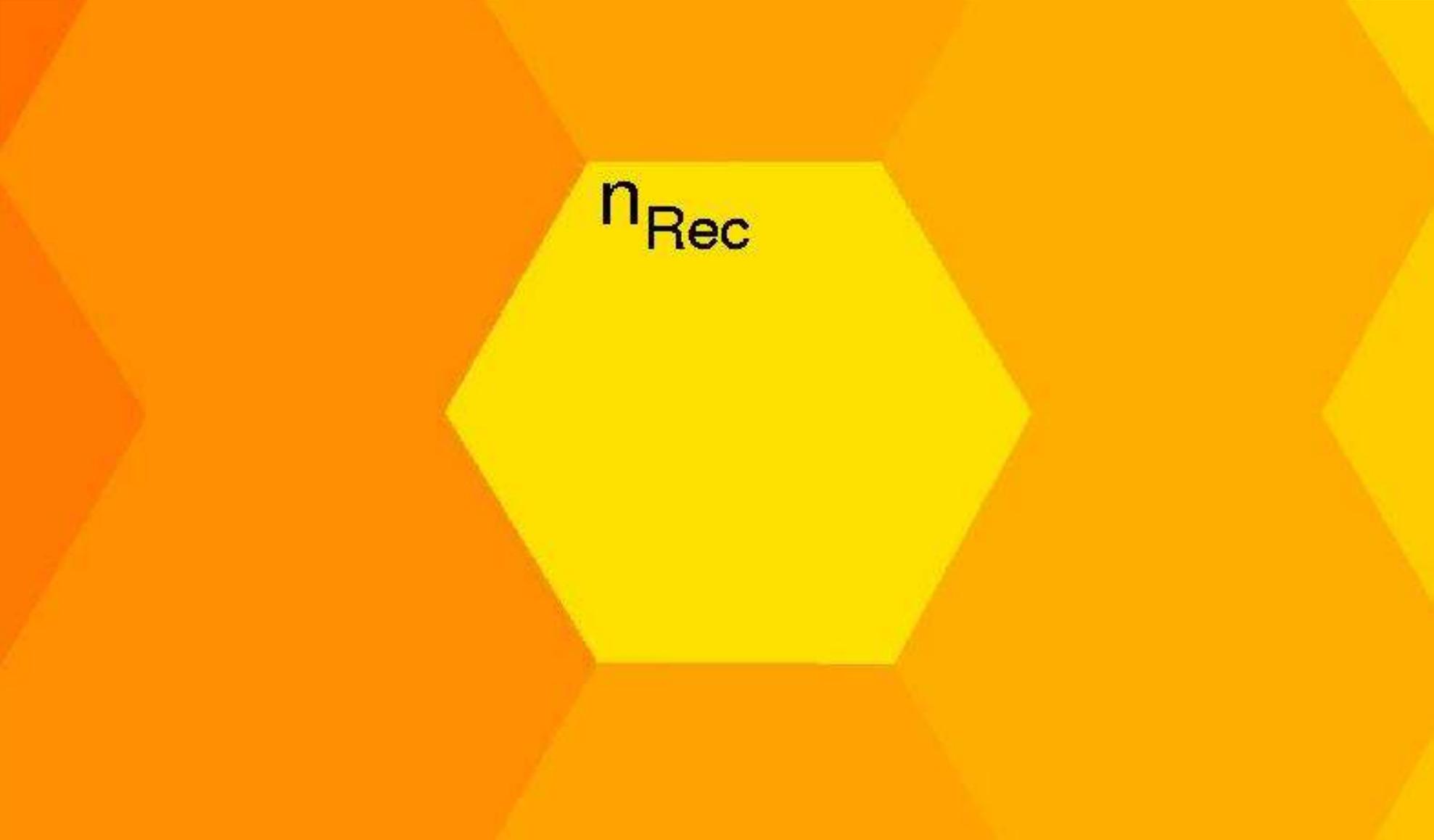
Computational lattice



Computational scheme



Computational scheme



n_{Rec}

Computational scheme



n_{Rec}
 n_{PI3K}

Computational scheme



n_{Rec}
 n_{PI3K}
 n_{PTEN}

Computational scheme

n_{Rec}
 n_{PI3K}
 n_{PTEN}
 n_{PIP2}

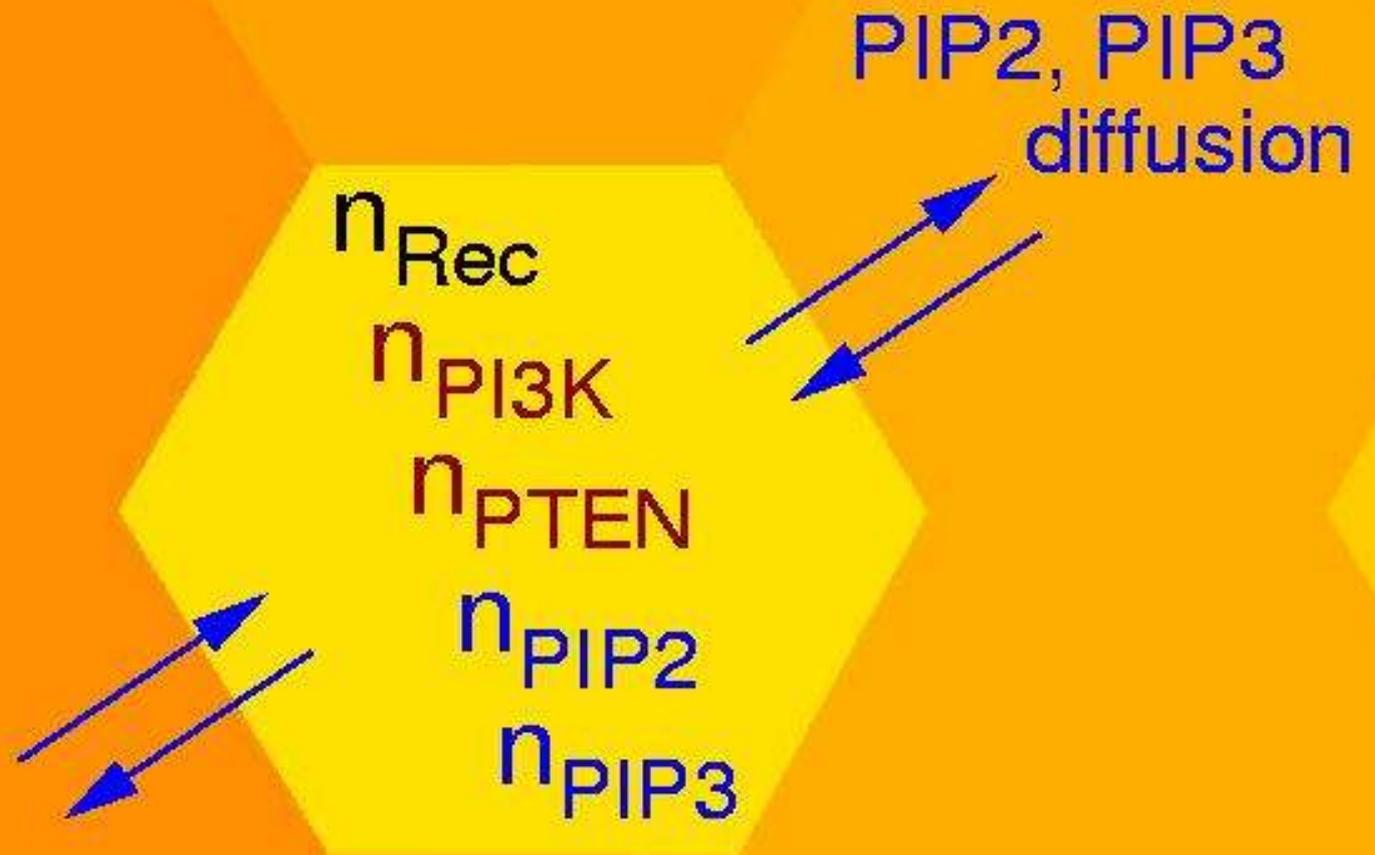
Computational scheme

n_{Rec}
 n_{PI3K}
 n_{PTEN}
 n_{PIP2}
 n_{PIP3}

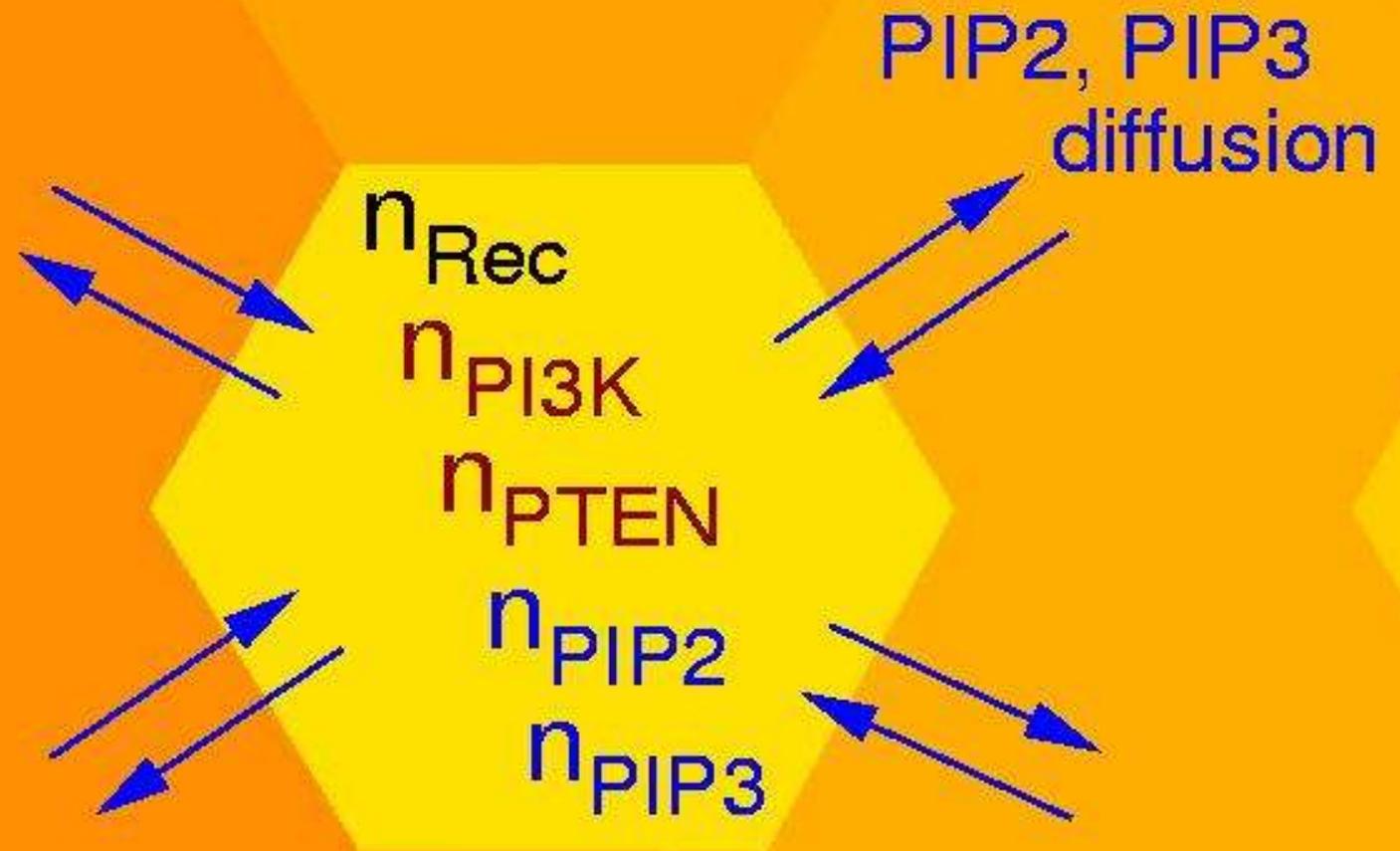
Computational scheme



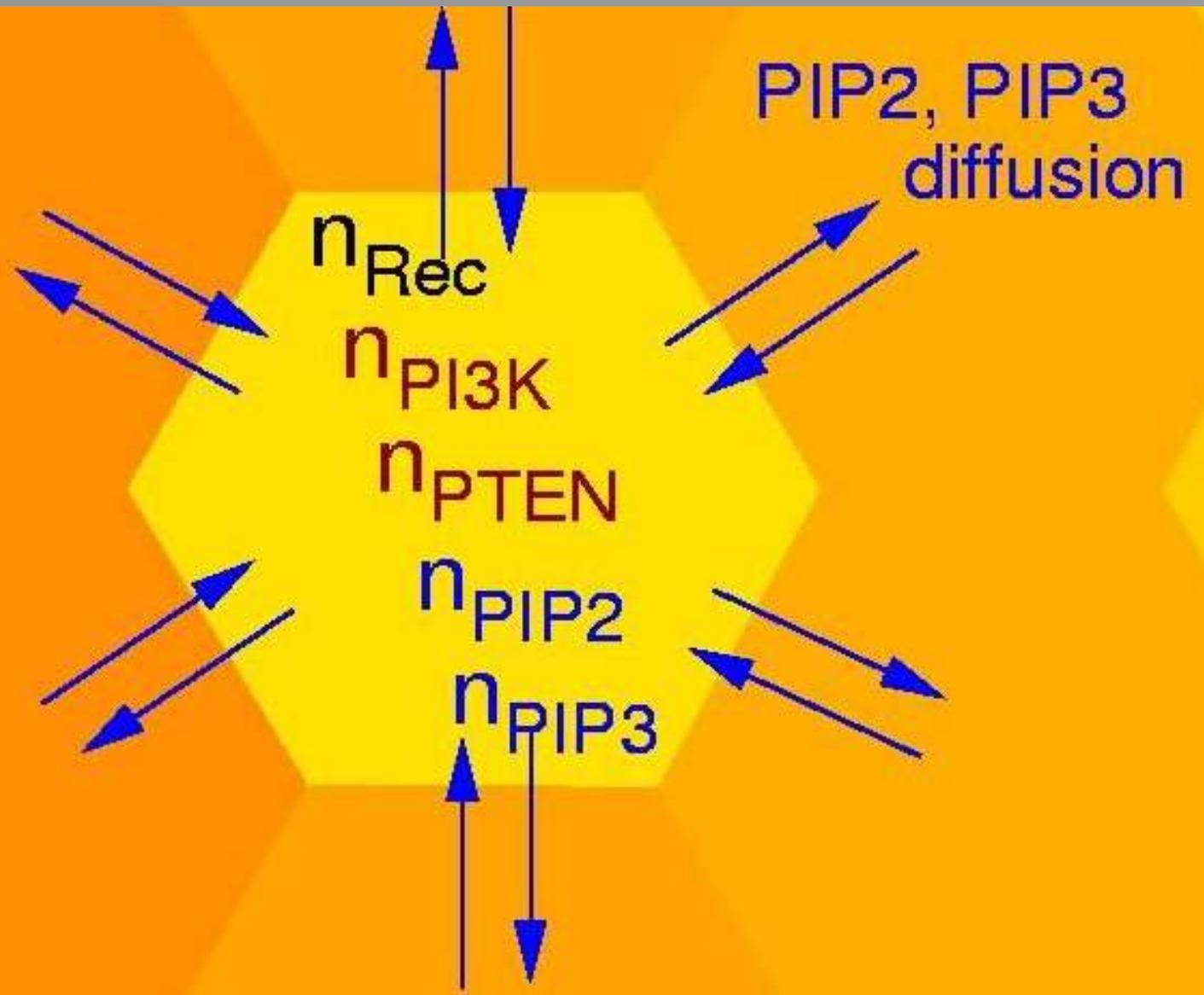
Computational scheme



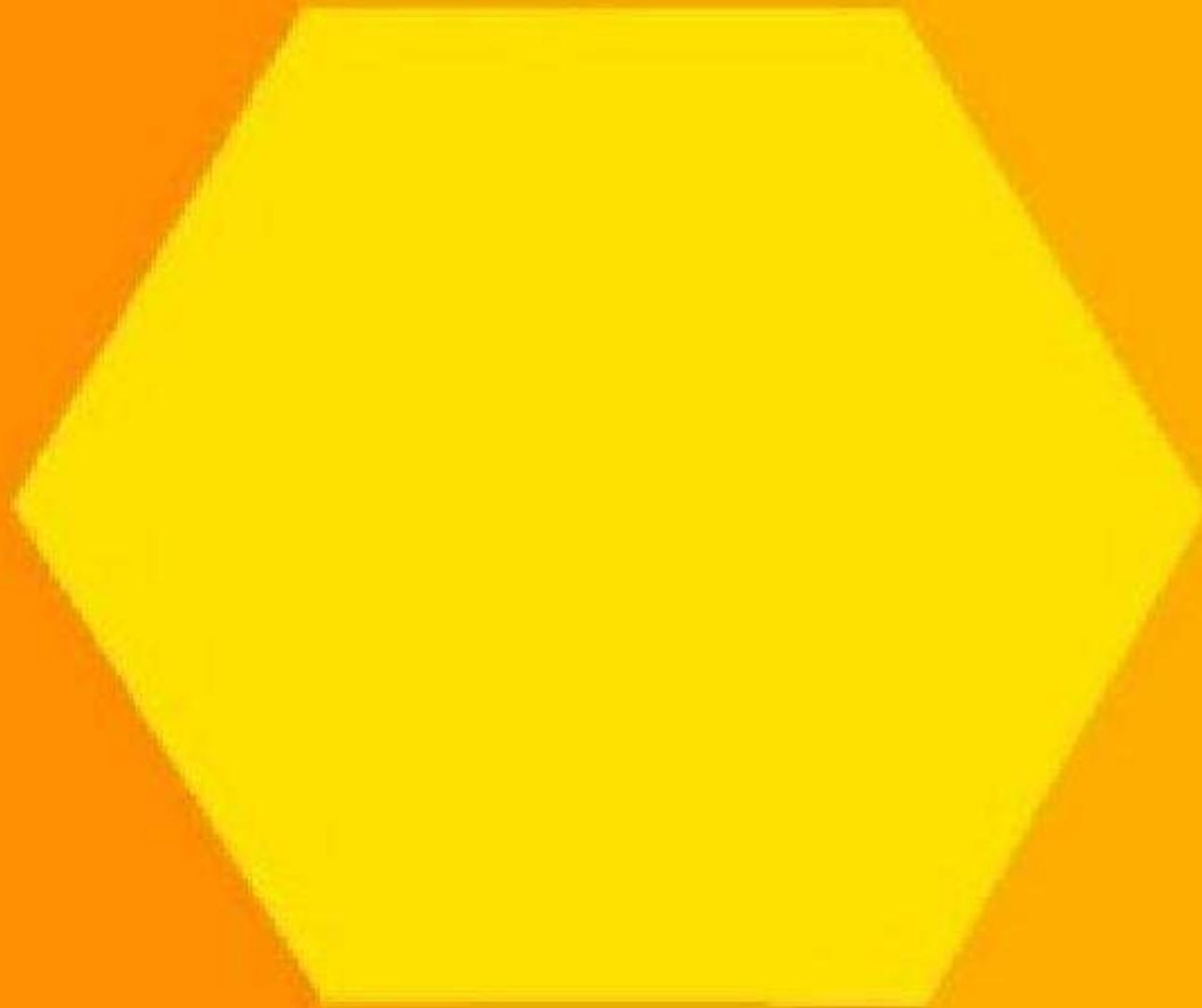
Computational scheme



Computational scheme



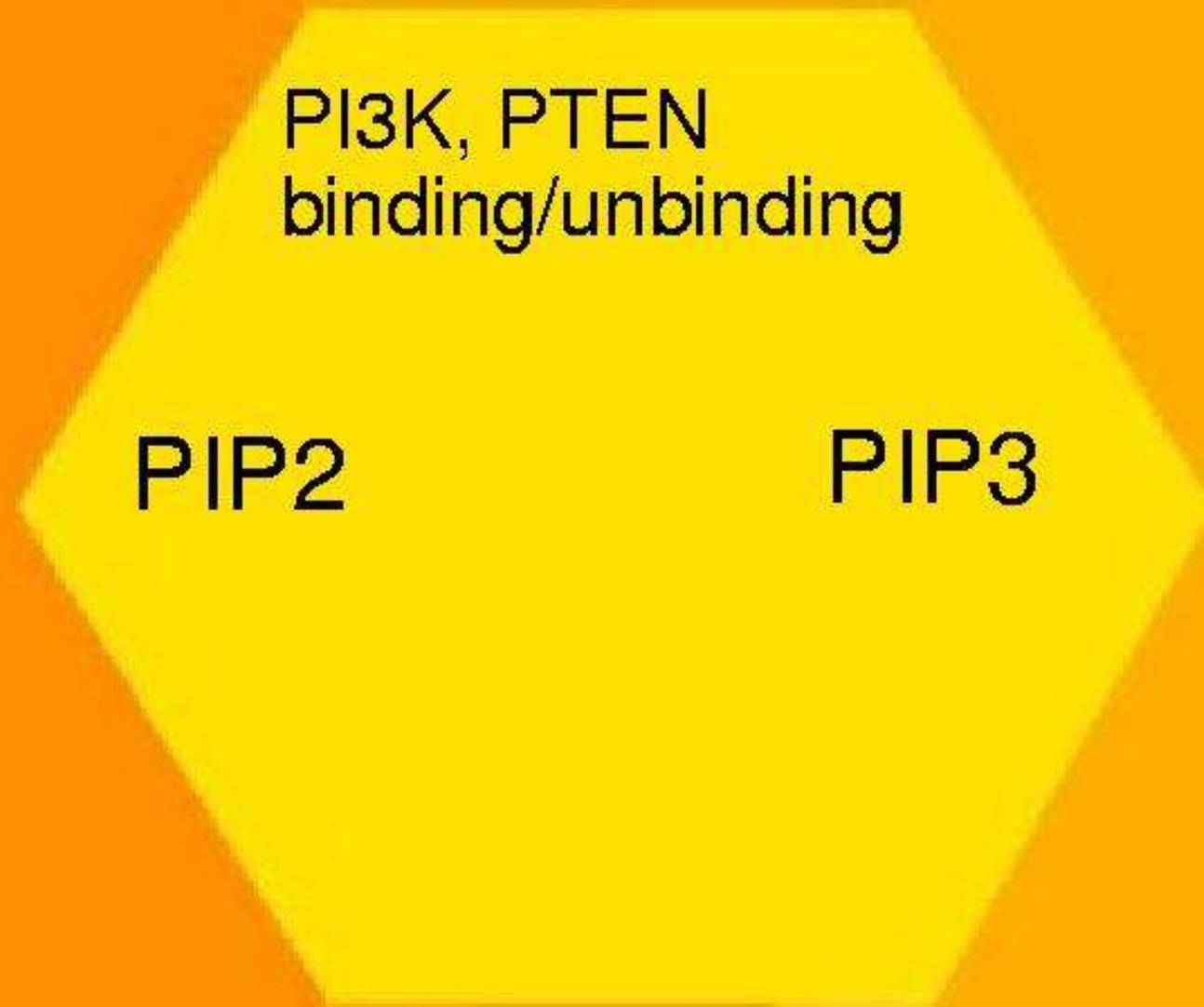
Computational scheme



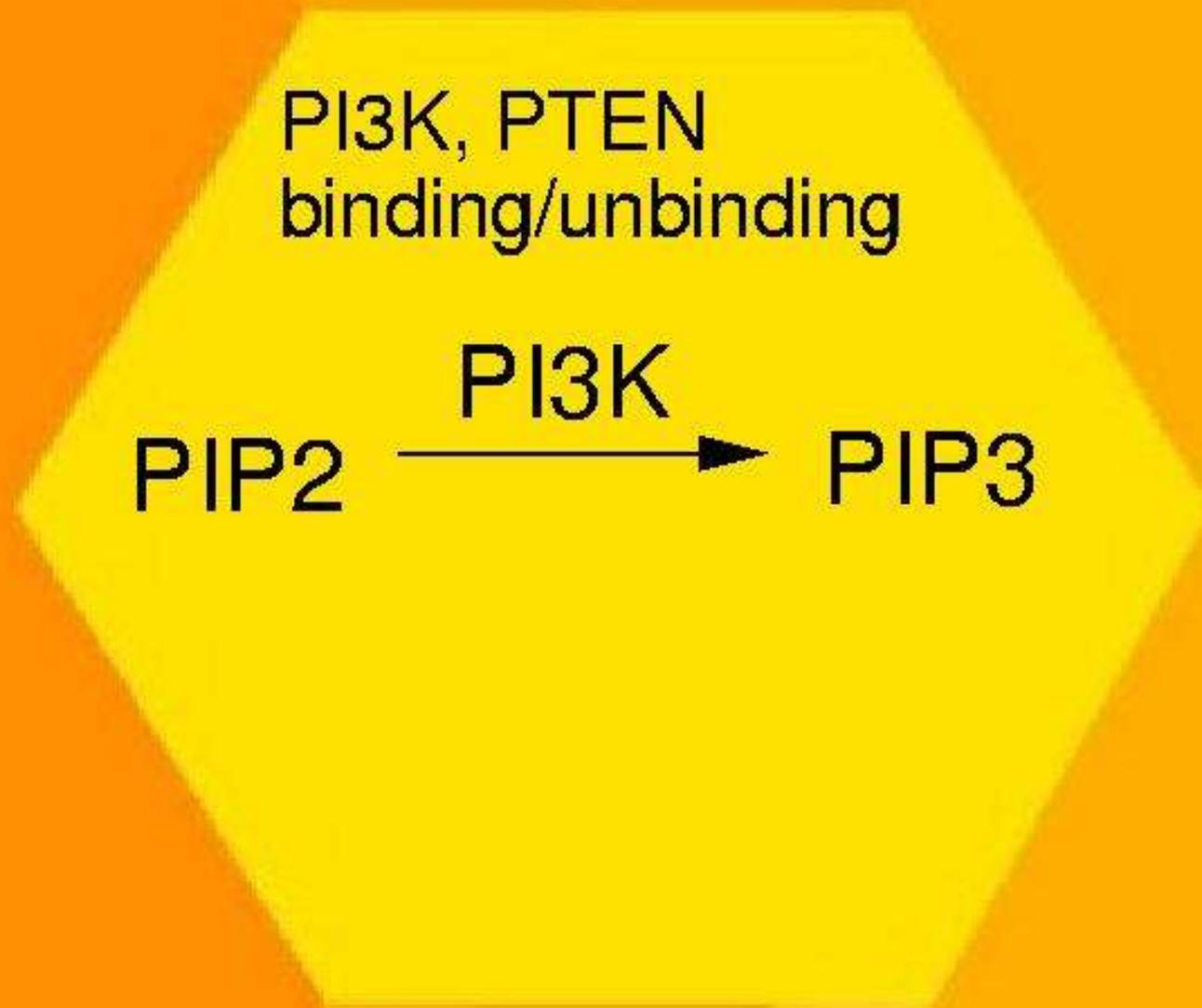
Computational scheme

PI3K, PTEN
binding/unbinding

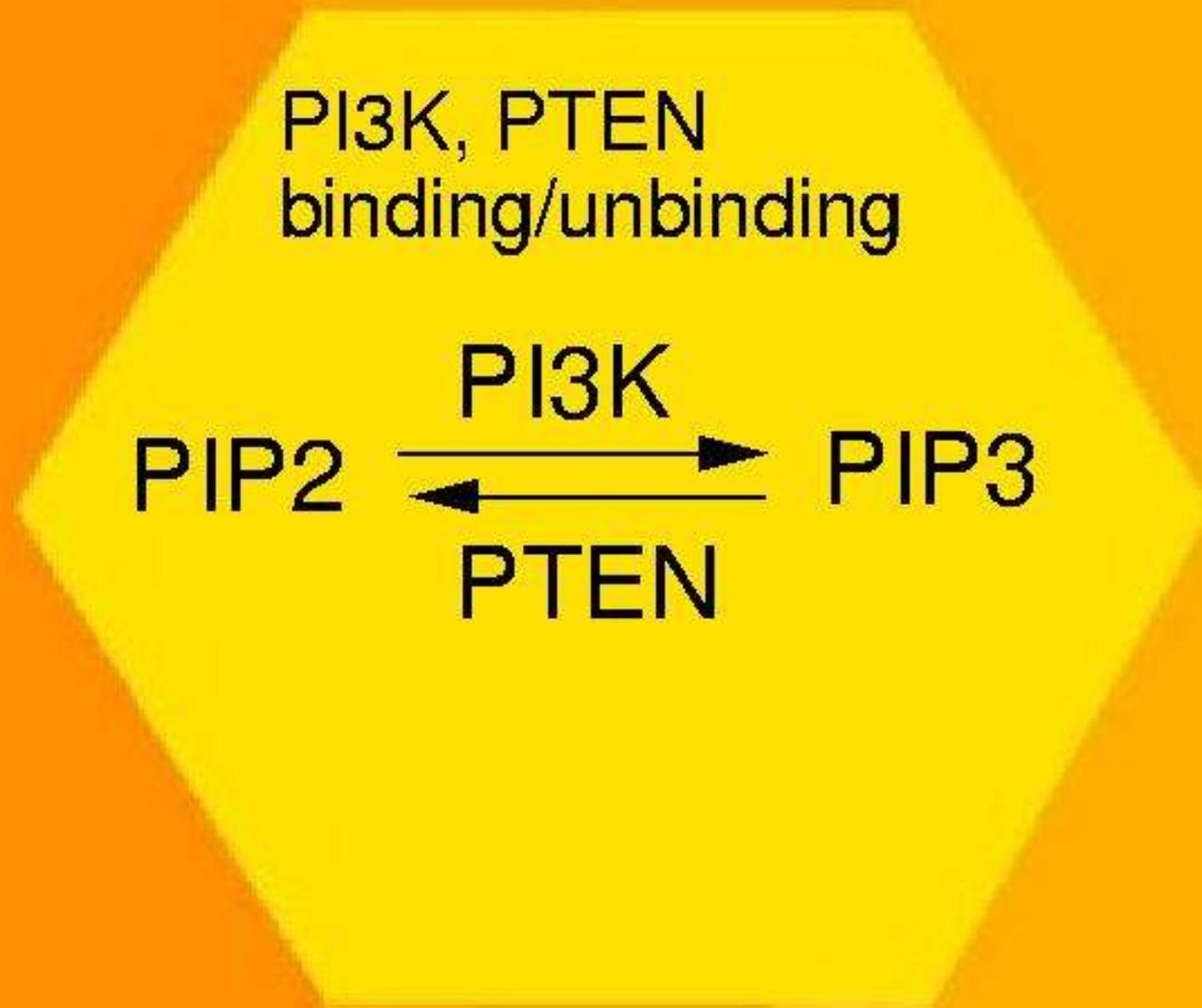
Computational scheme



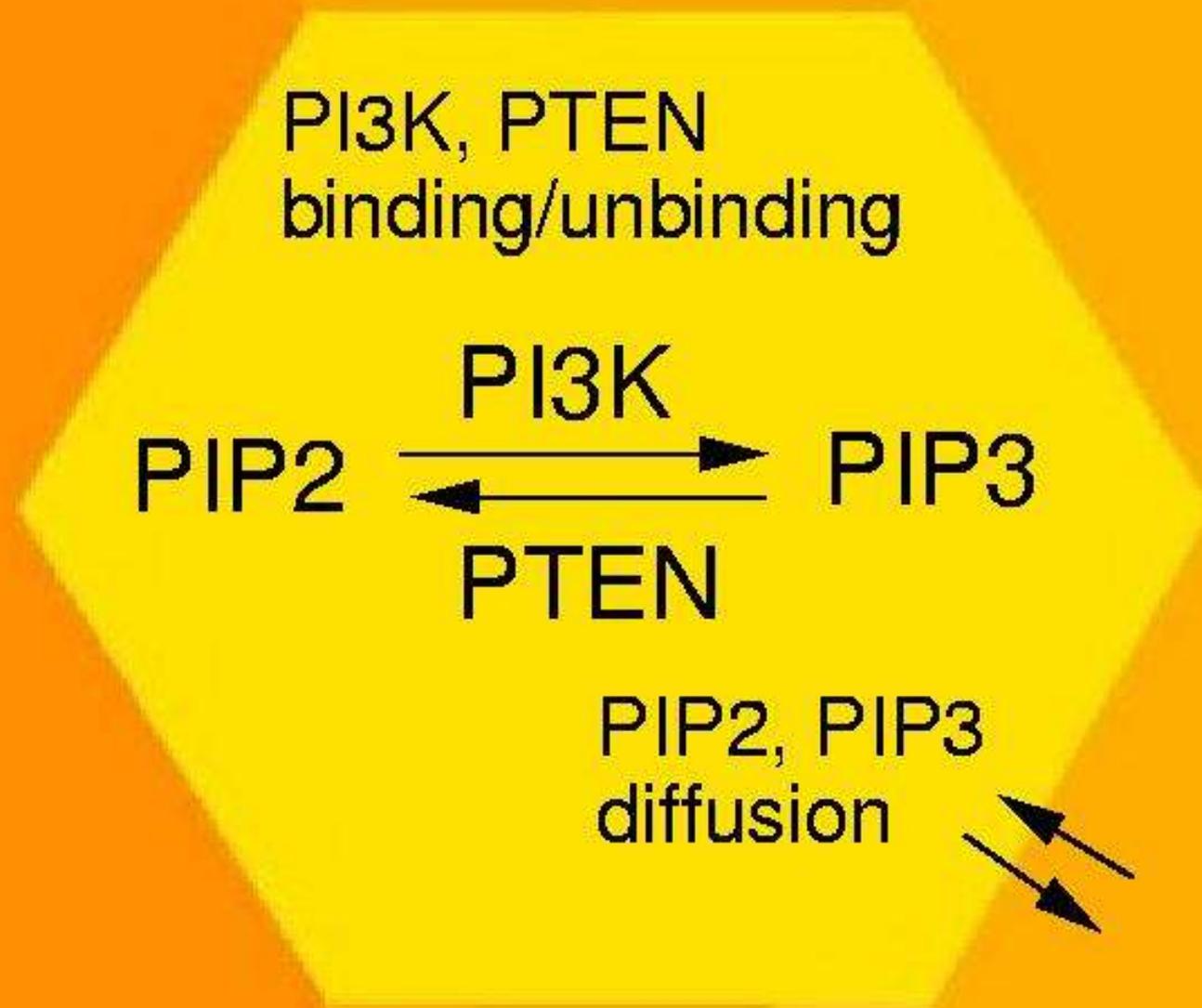
Computational scheme



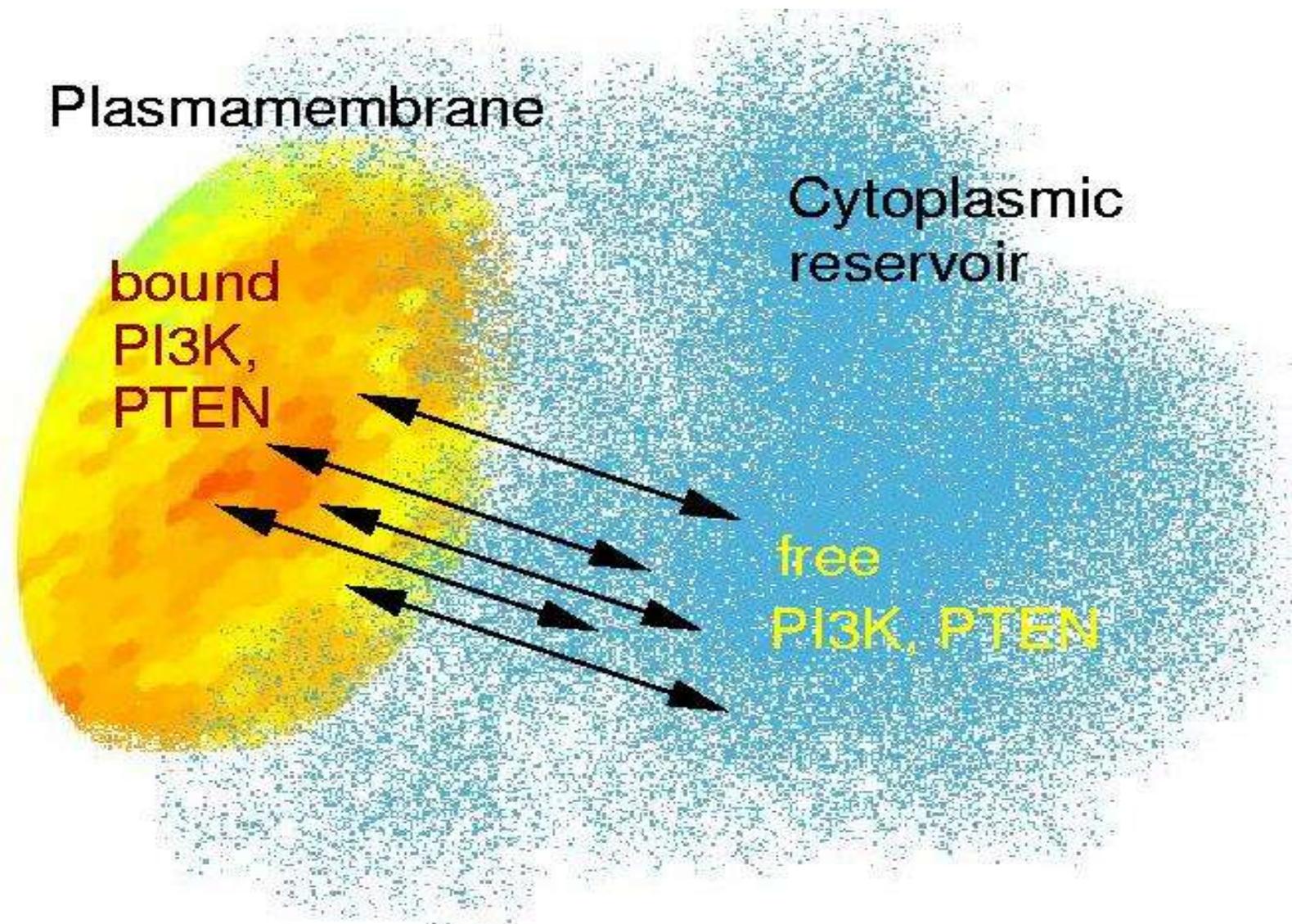
Computational scheme



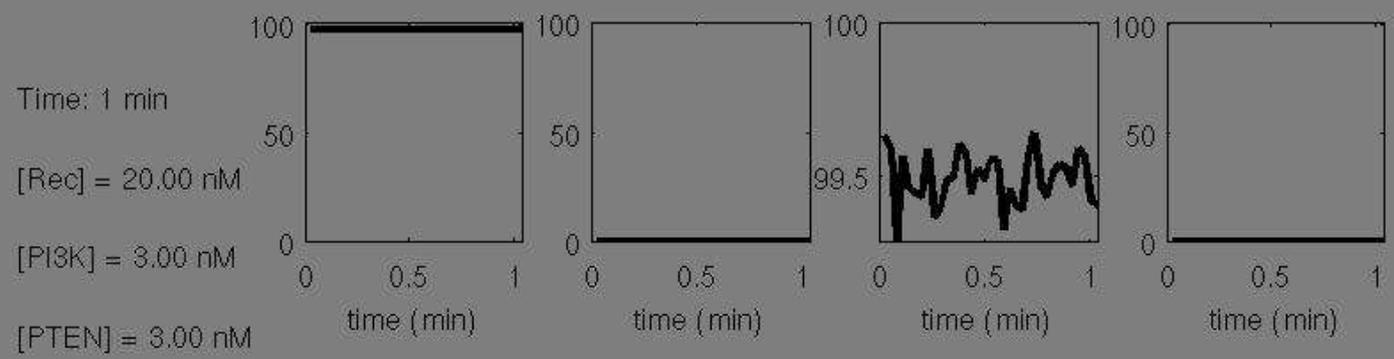
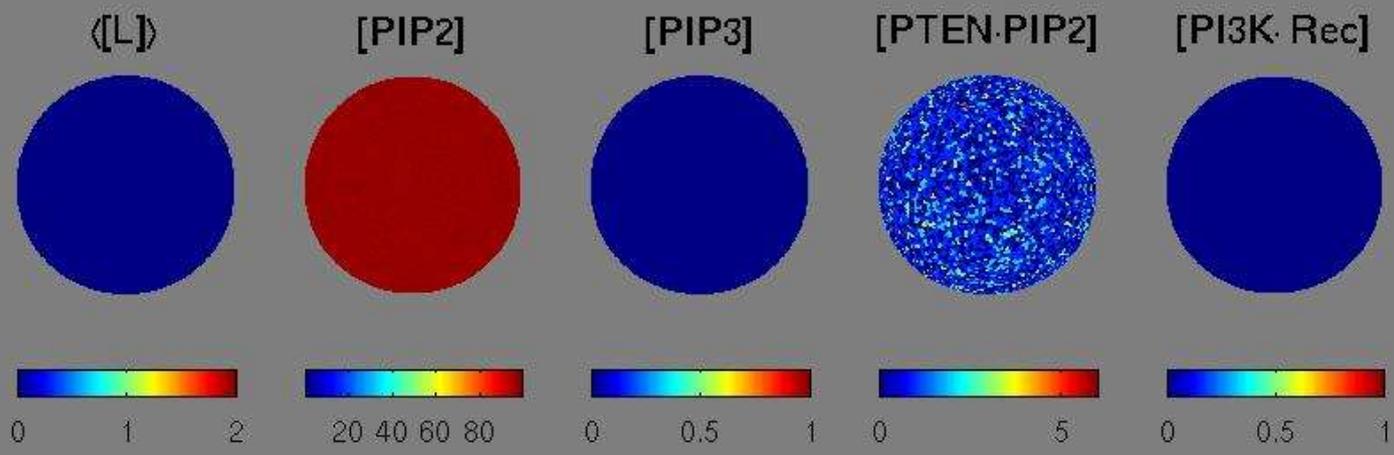
Computational scheme



Computational scheme



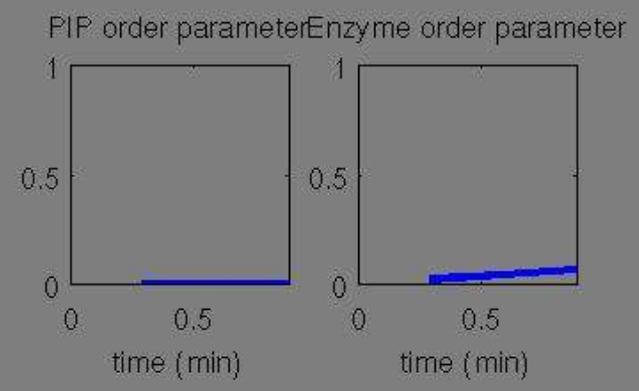
Isotropic receptor activation

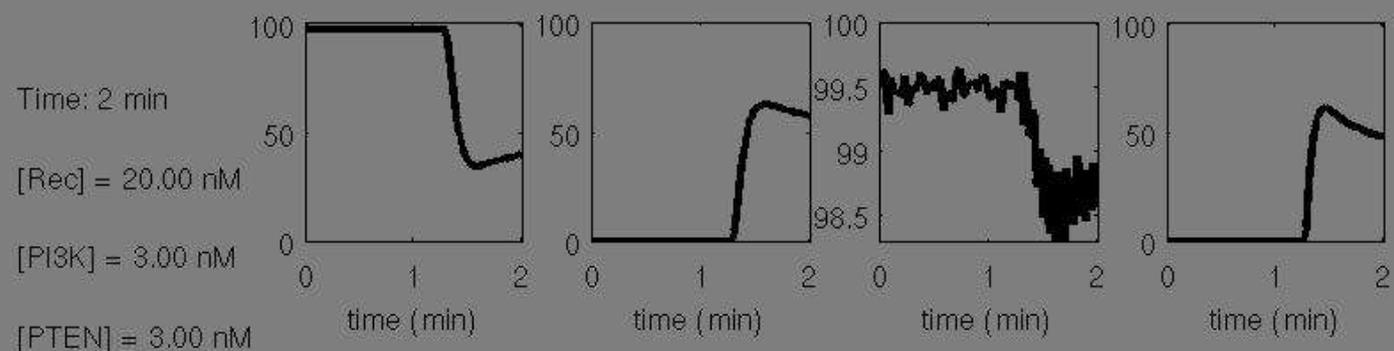
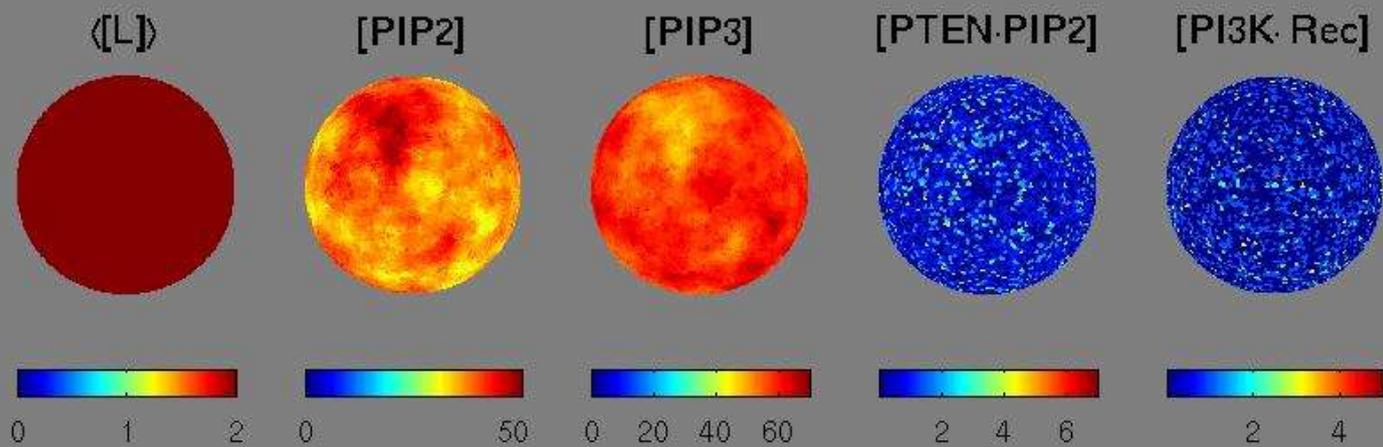


[PIP2] = 400 nM

$D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$

$\epsilon = 0.00\%$

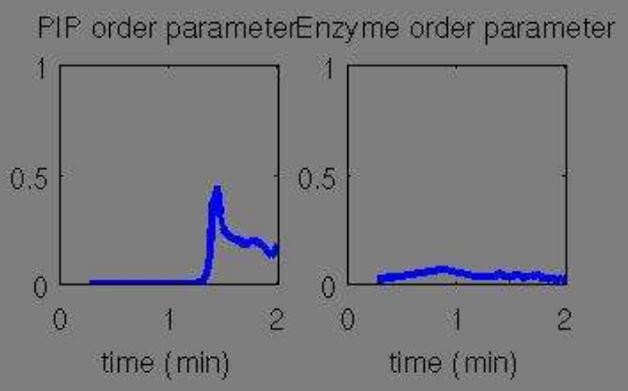


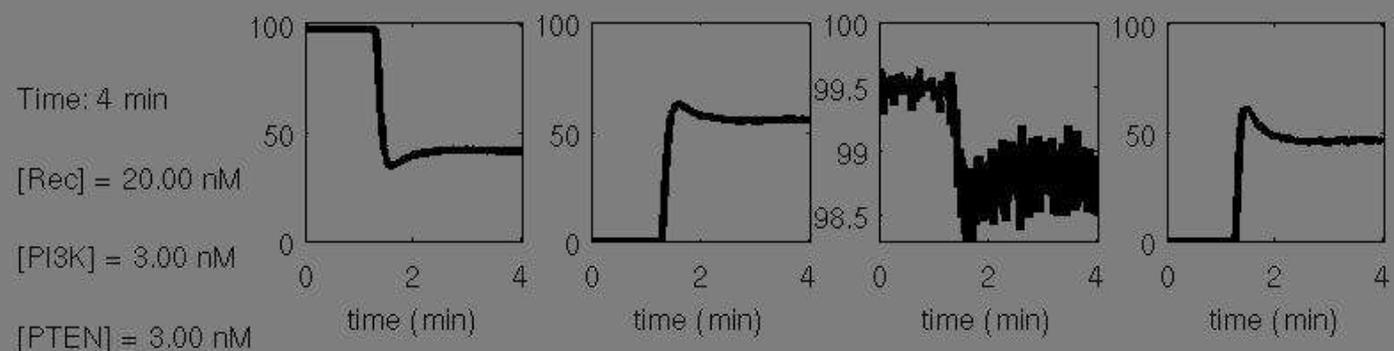
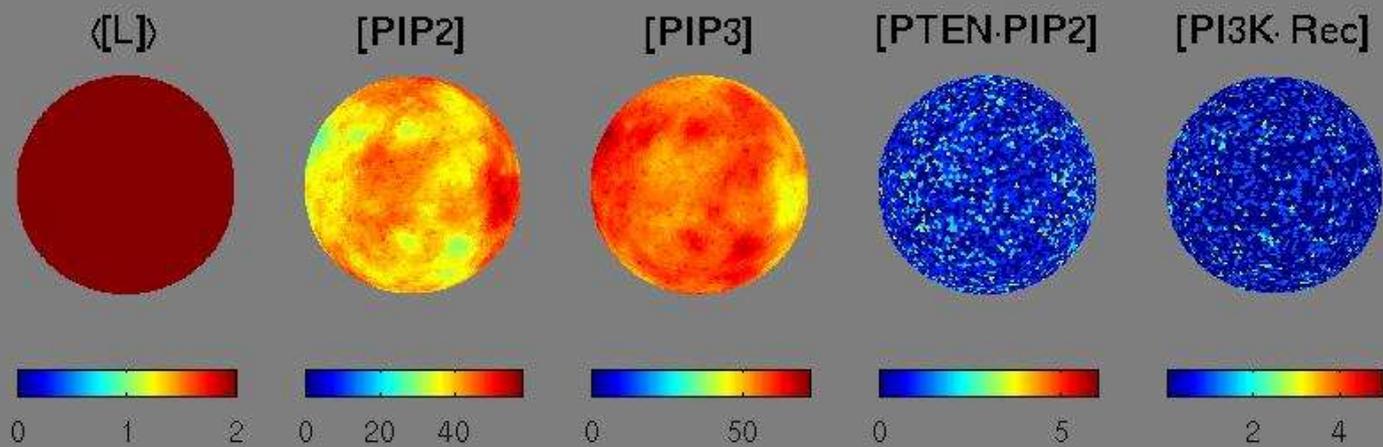


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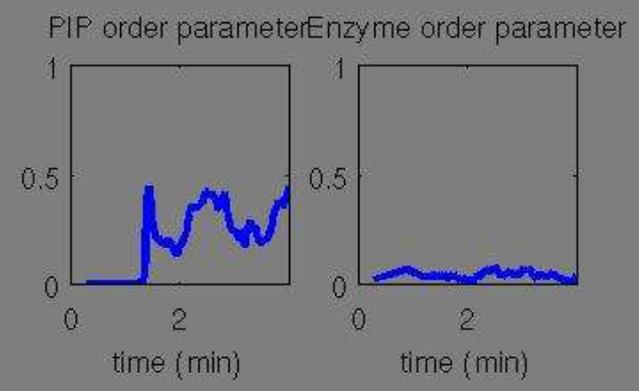


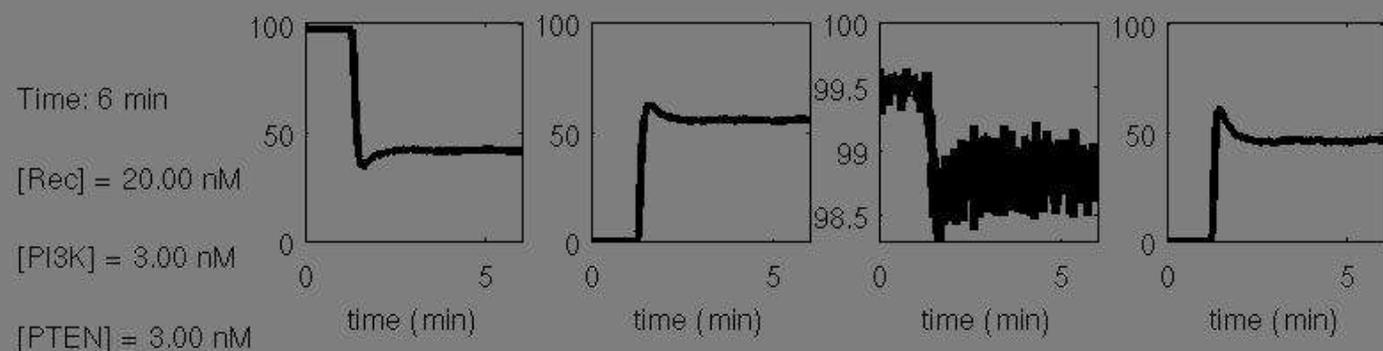
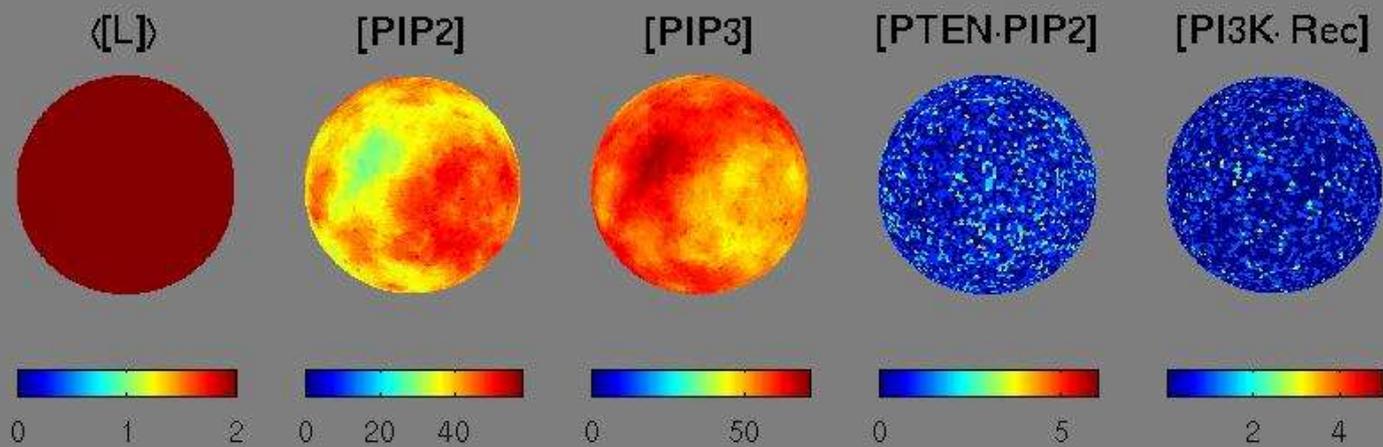


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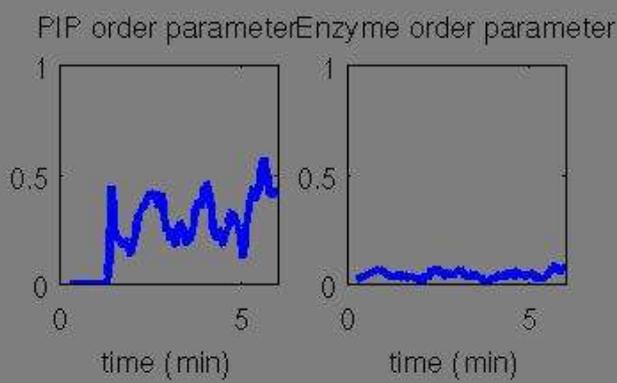


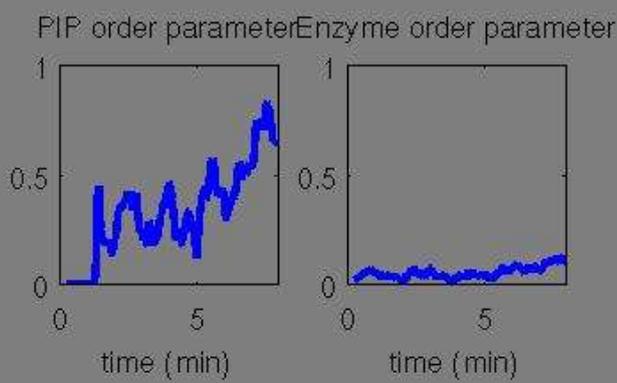
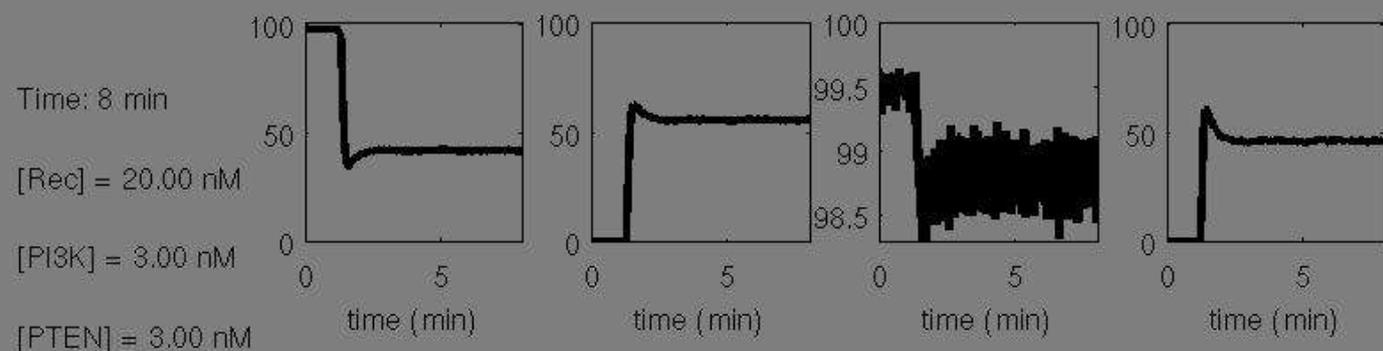
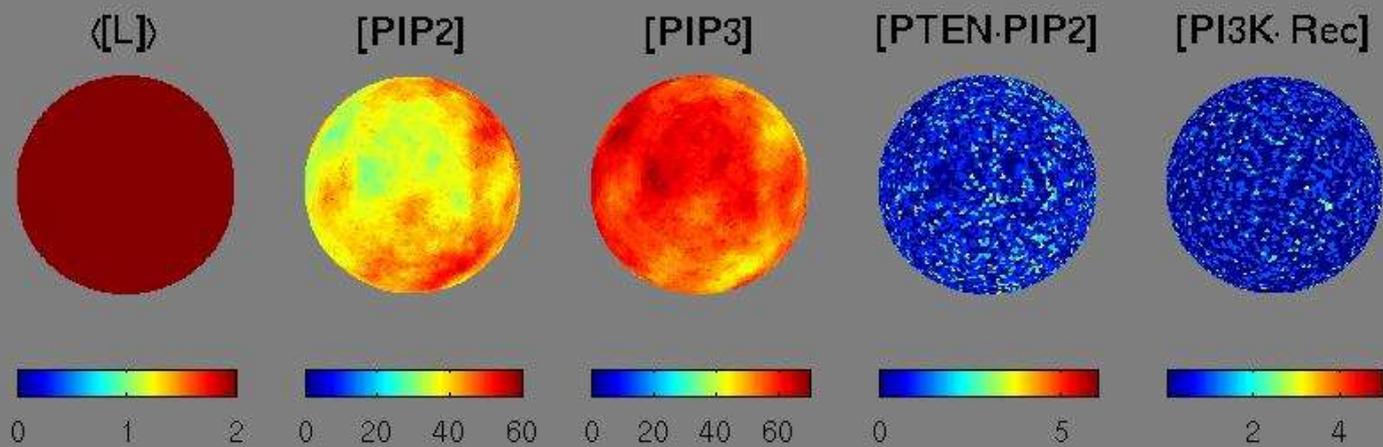


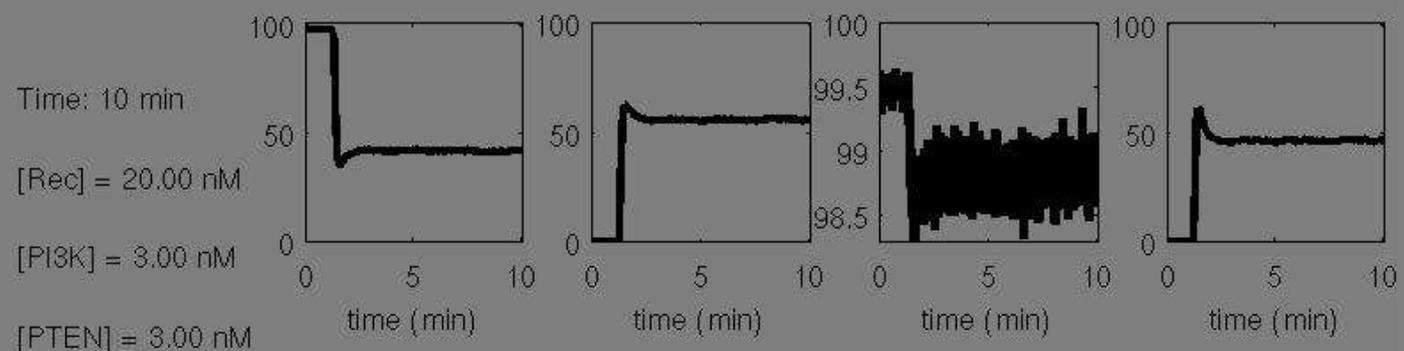
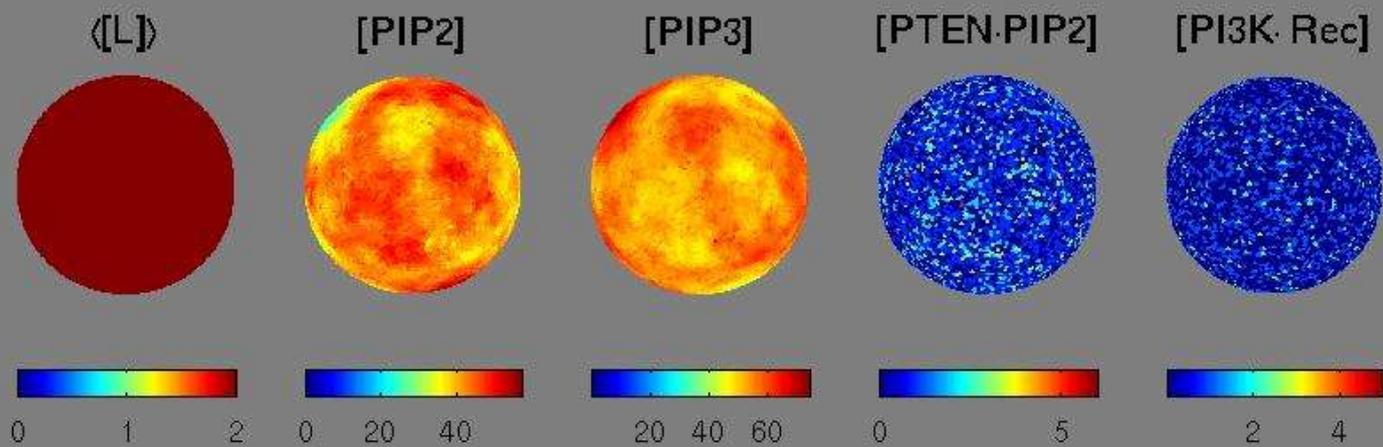
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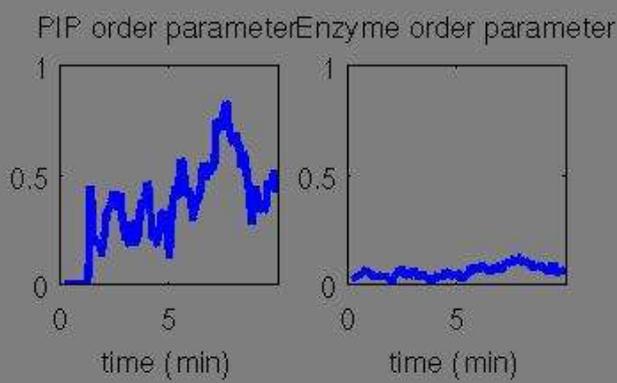


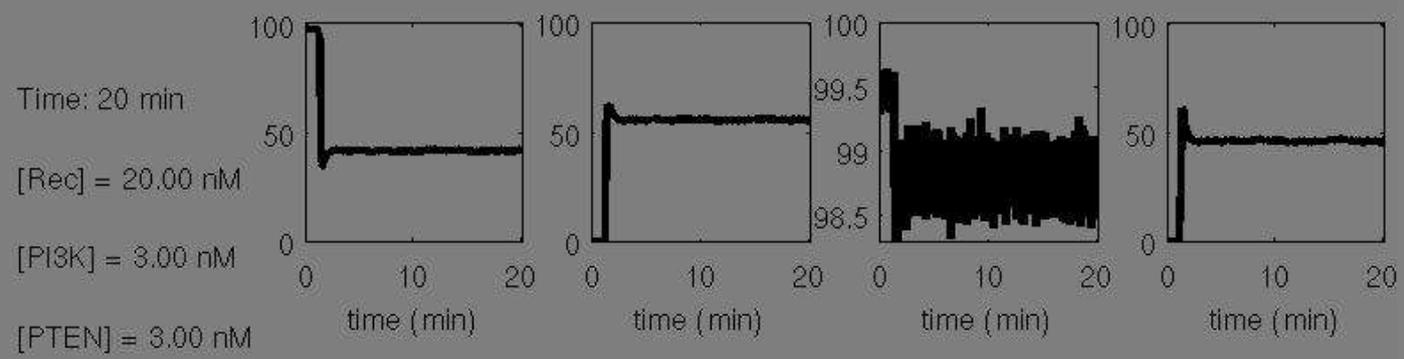
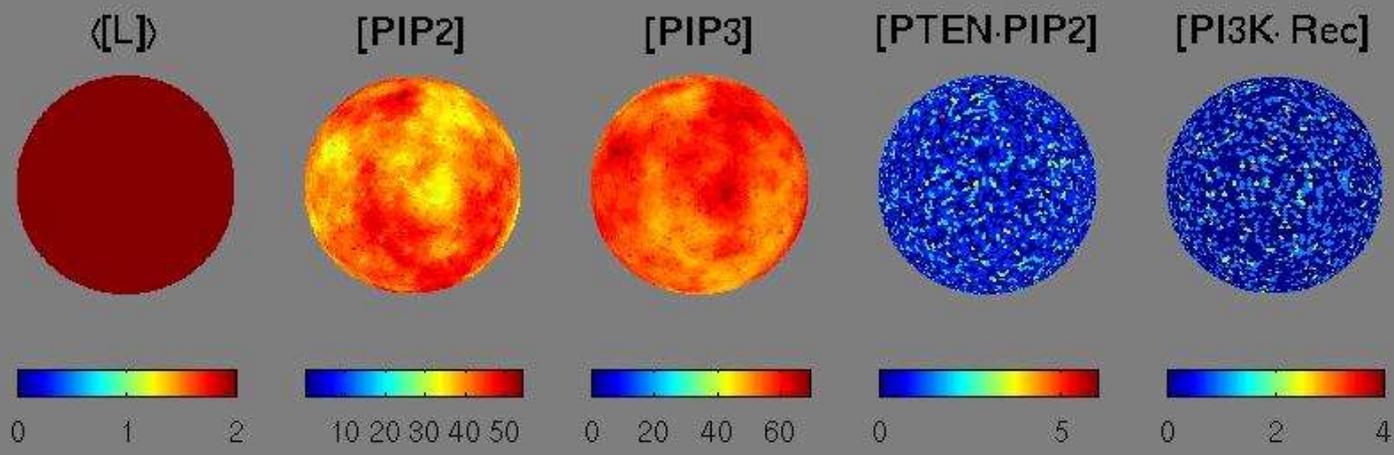


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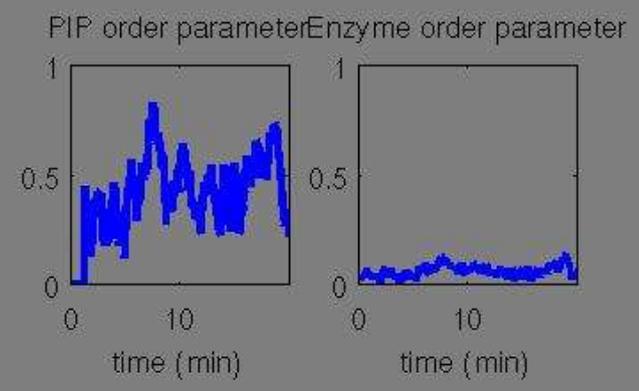


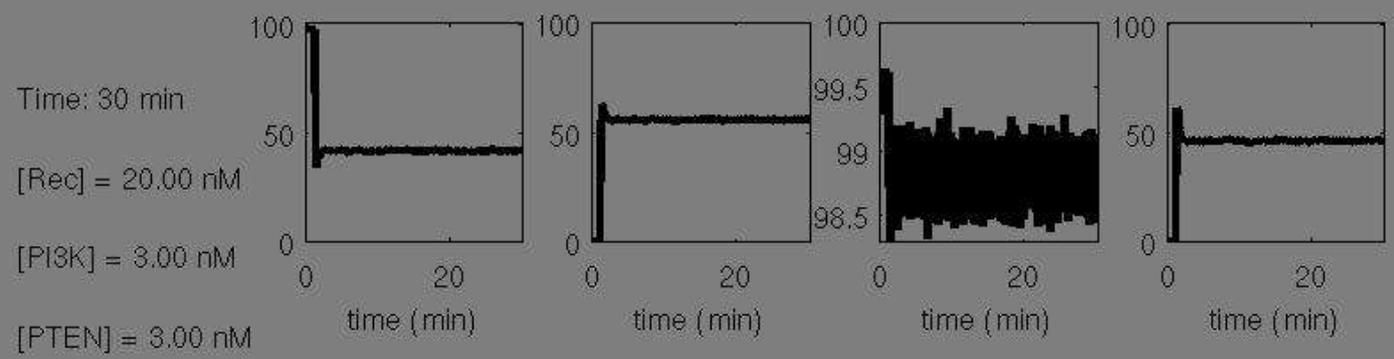
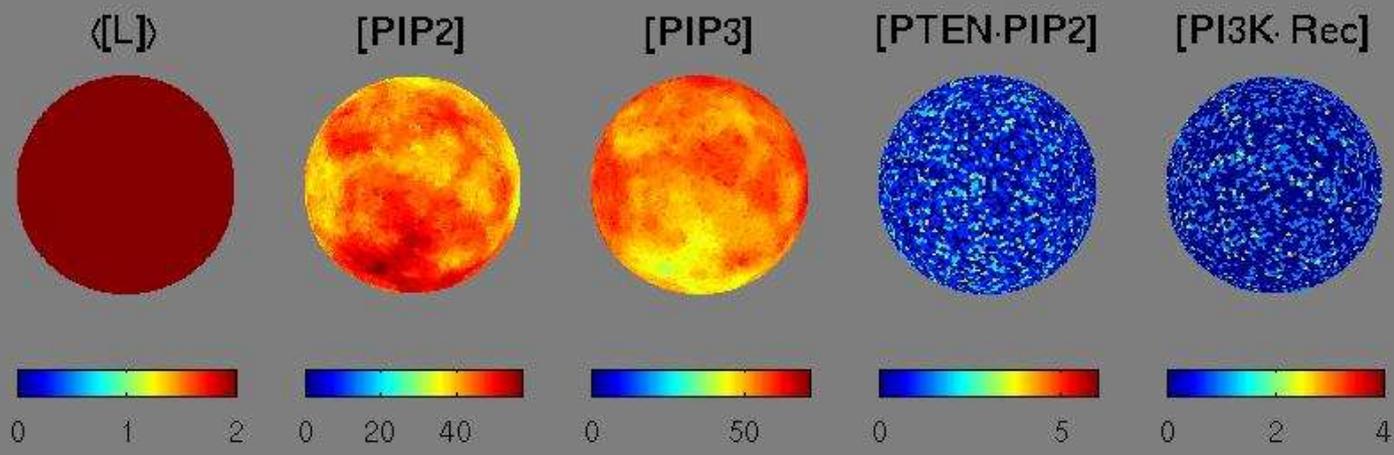


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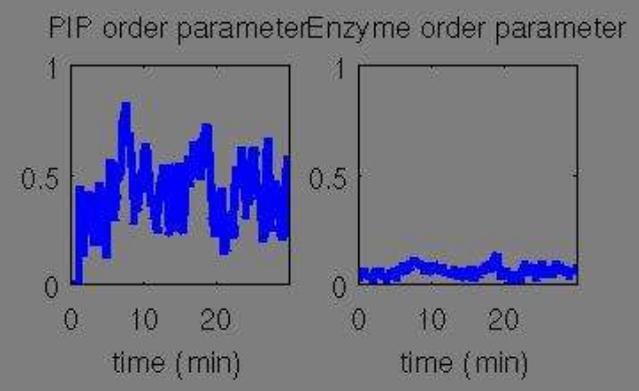


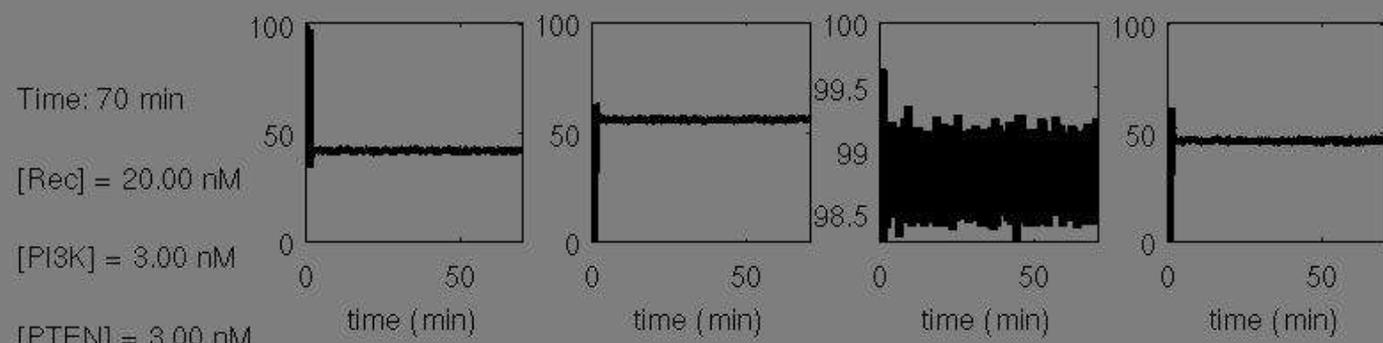
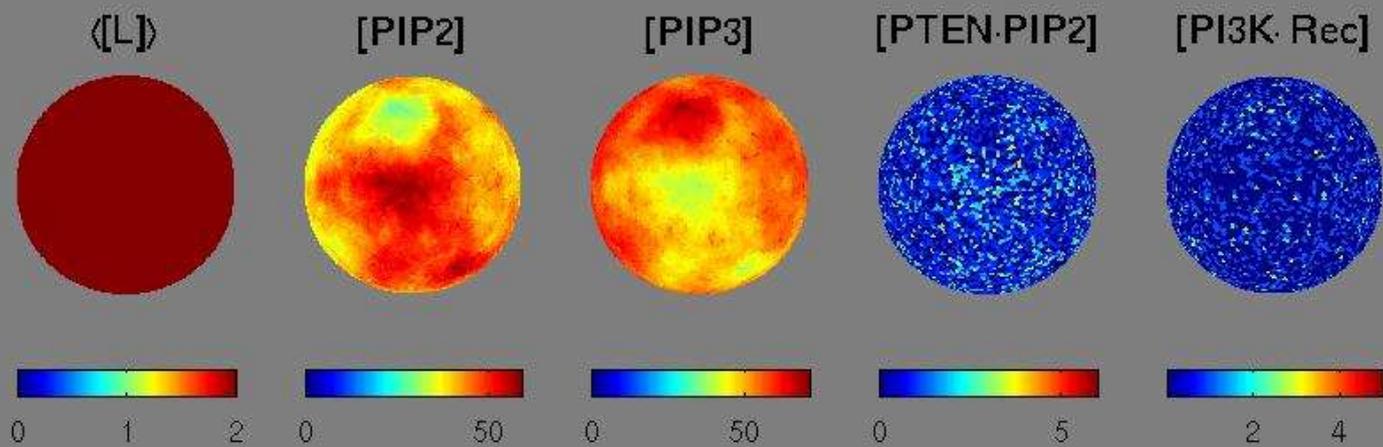


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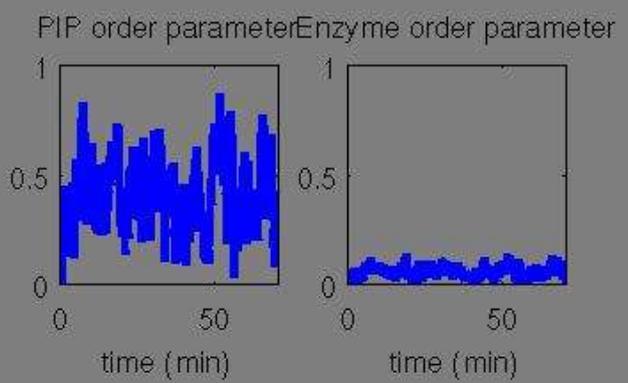
$D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$

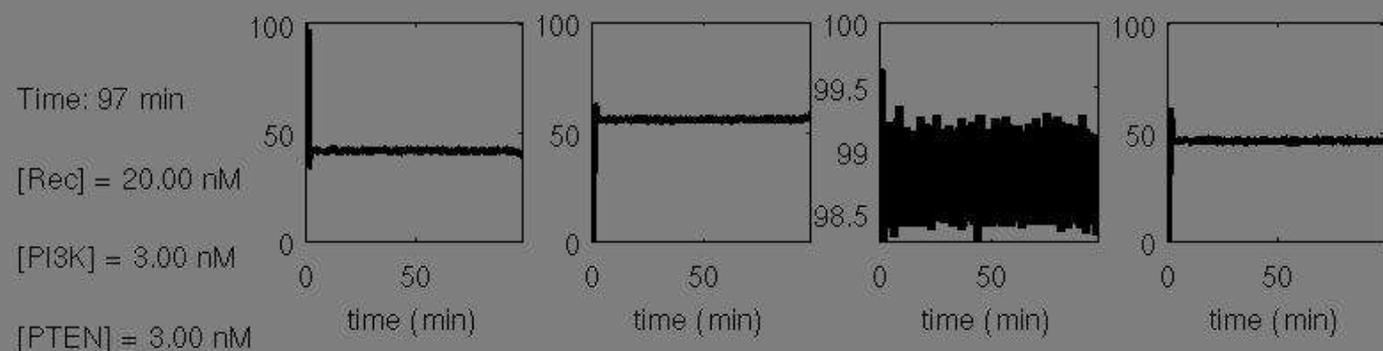
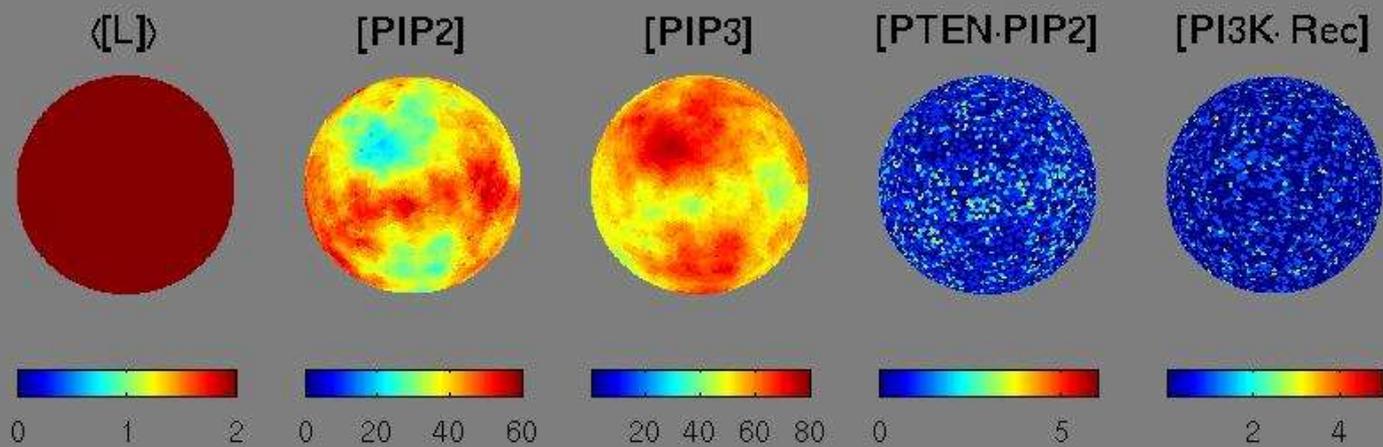
$\epsilon = 0.00\%$



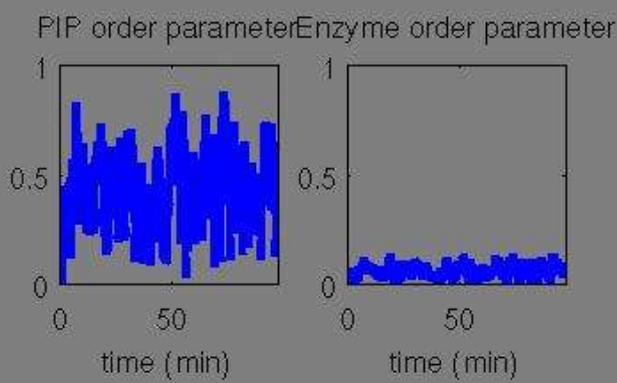


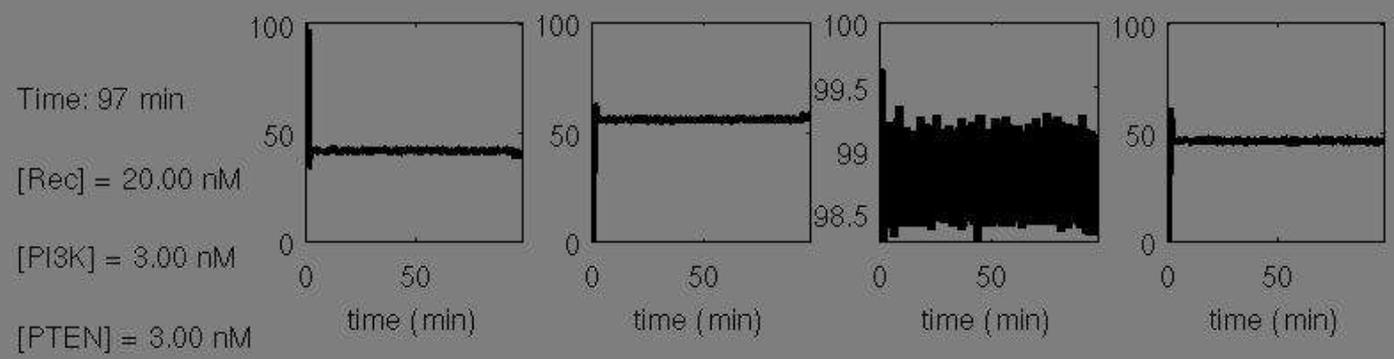
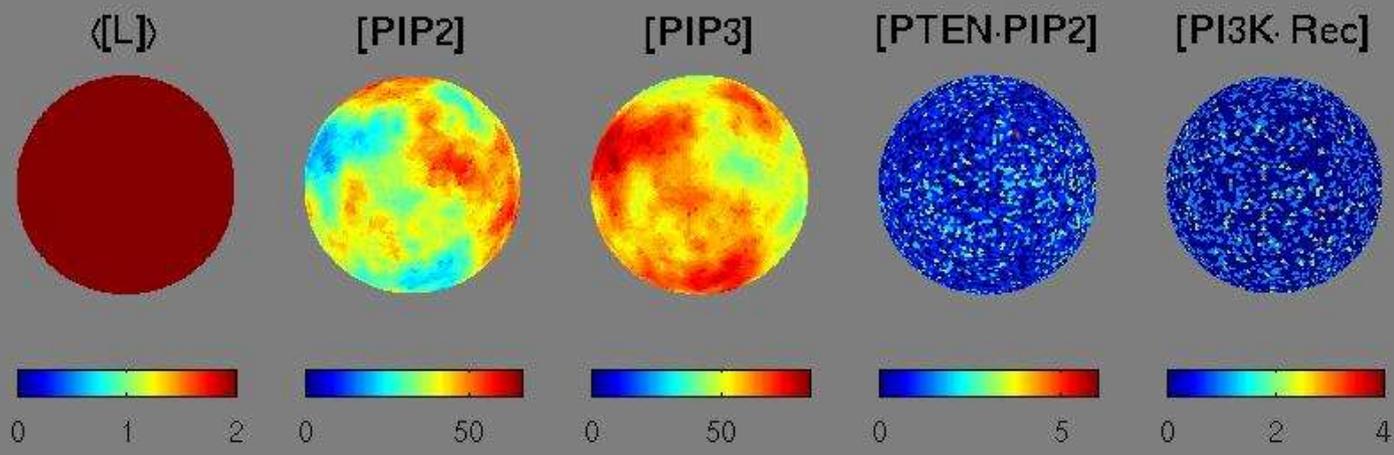
Time: 70 min
 [Rec] = 20.00 nM
 [PI3K] = 3.00 nM
 [PTEN] = 3.00 nM
 [PIP2] = 400 nM
 $D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$
 $\epsilon = 0.00\%$





[PIP2] = 400 nM
 $D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$
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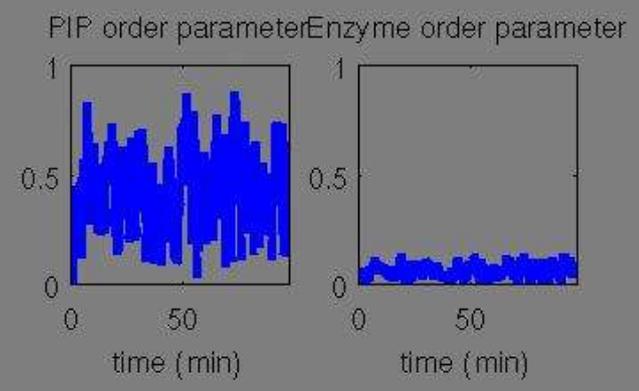


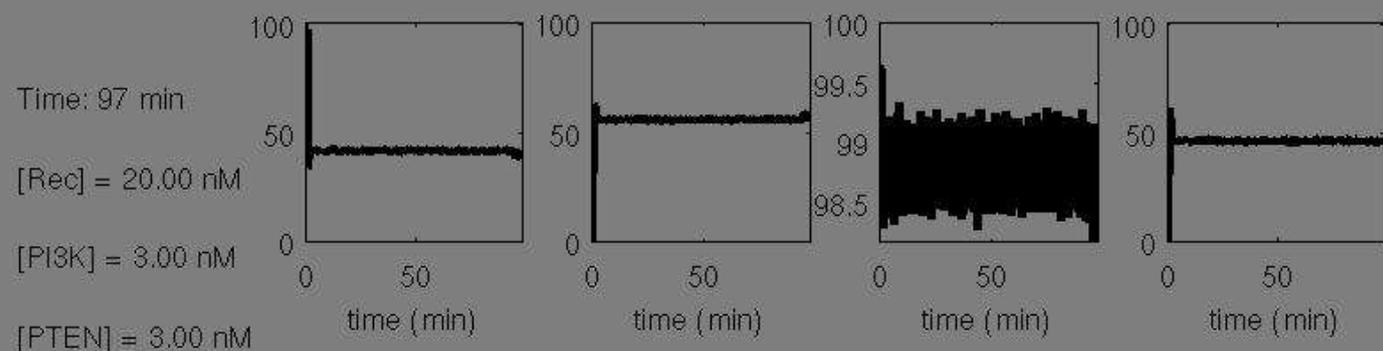
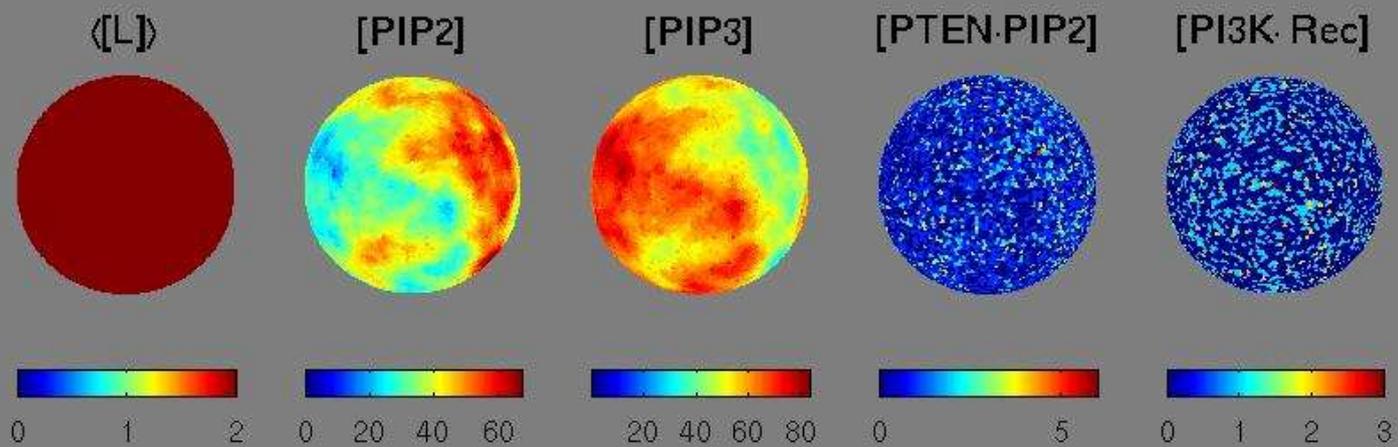


[PIP2] = 400 nM

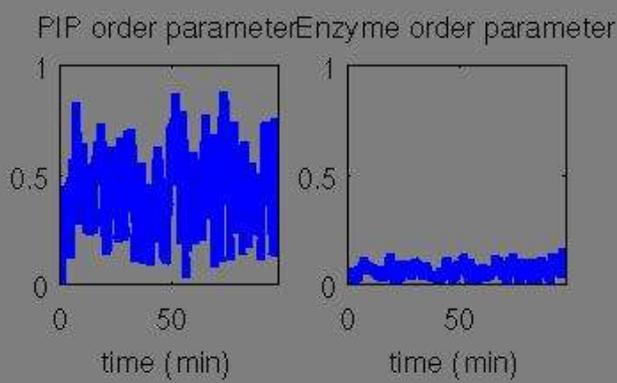
$D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$

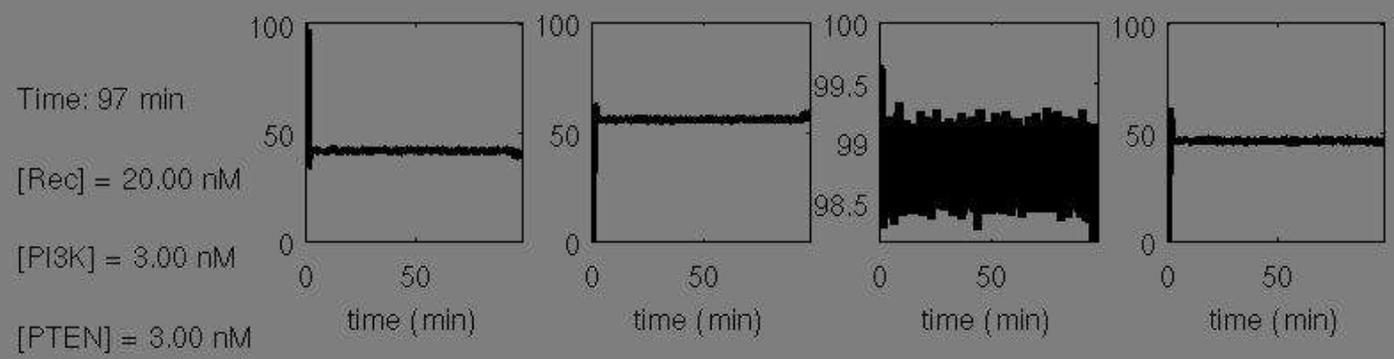
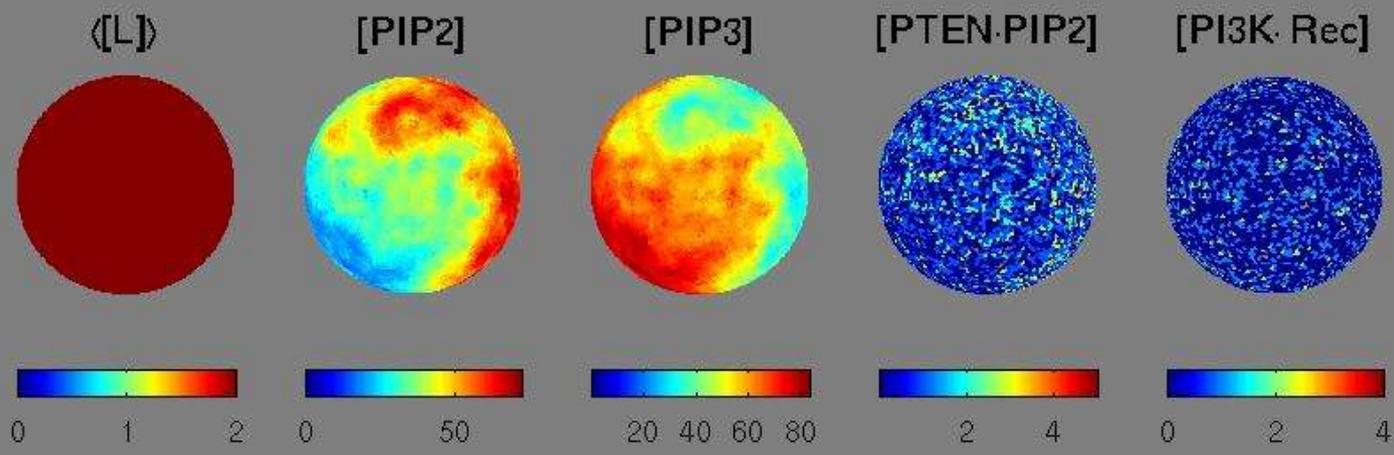
$\epsilon = 0.00\%$





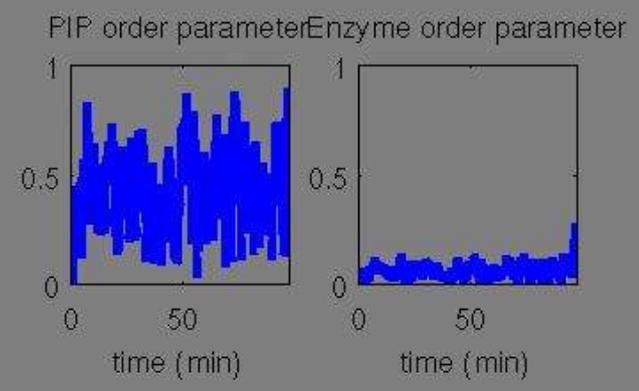
[PIP2] = 400 nM
 $D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$
 $\epsilon = 0.00\%$

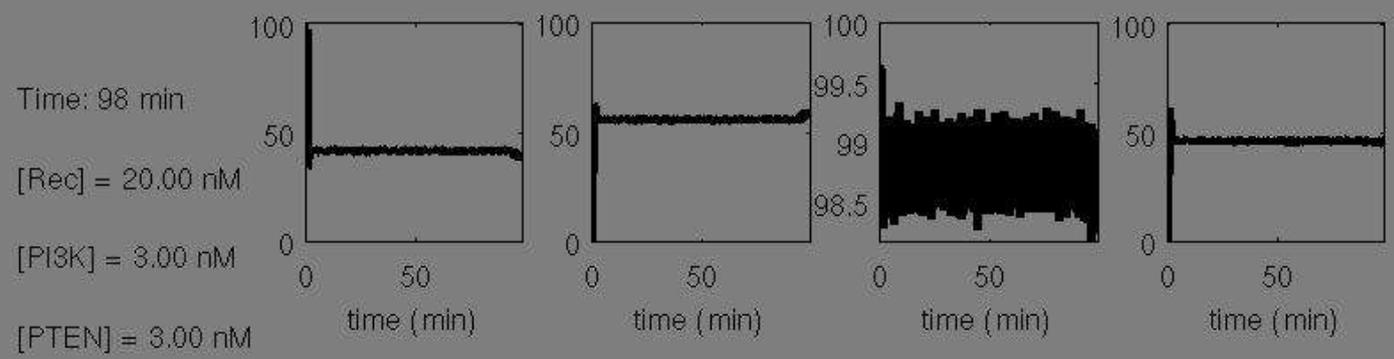
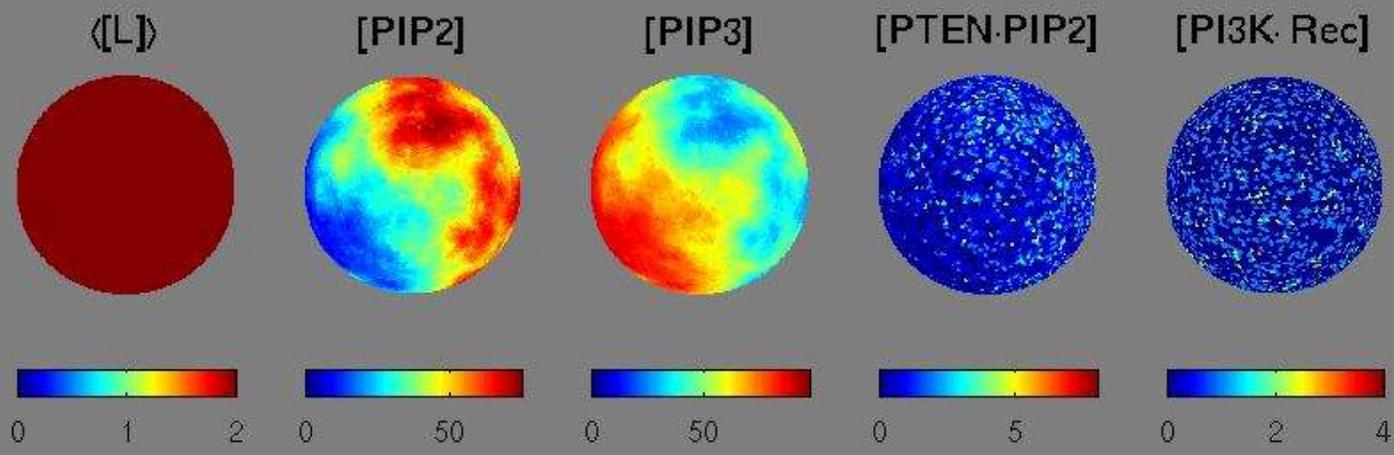




$D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$

$\epsilon = 0.00\%$

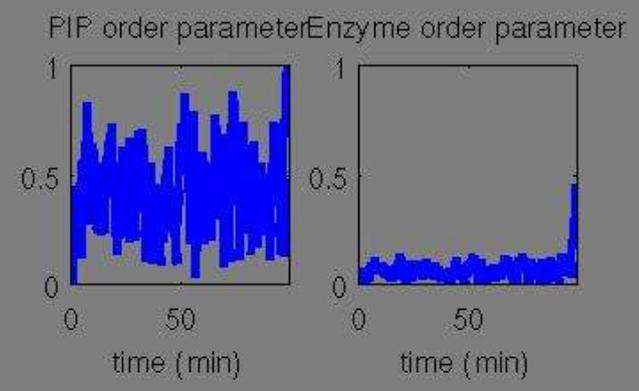


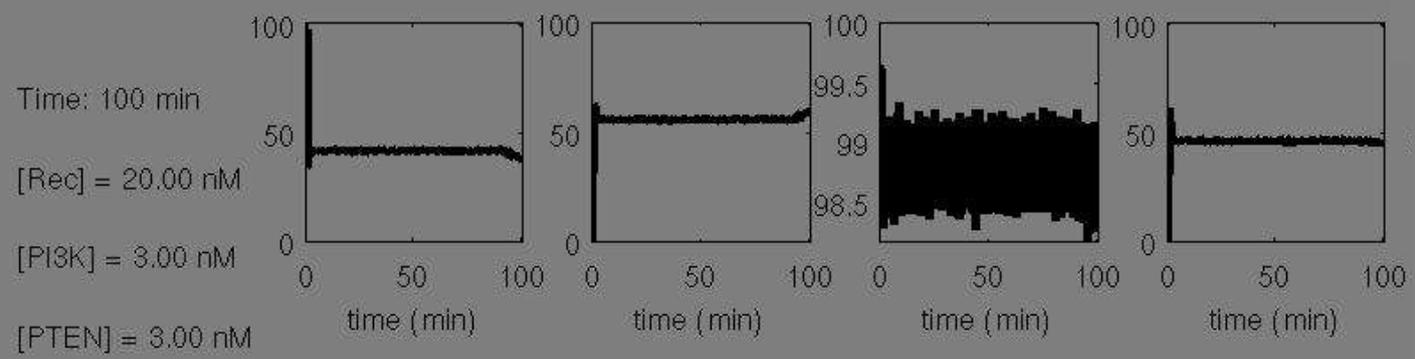
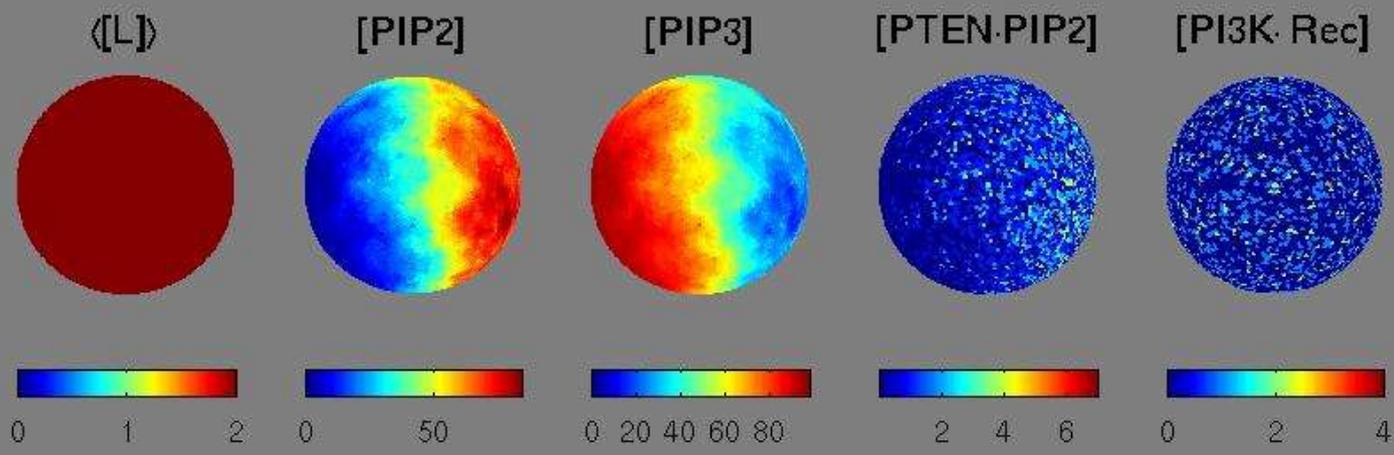


[PIP2] = 400 nM

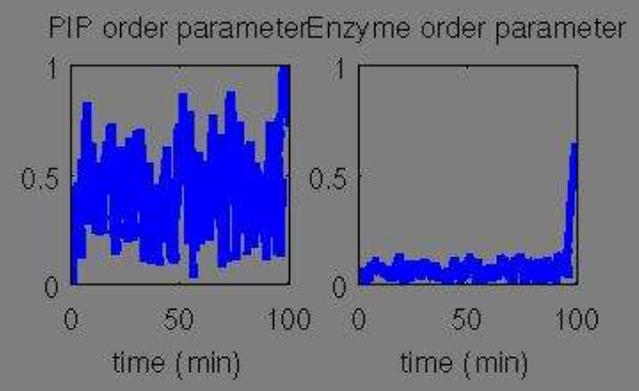
$D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$

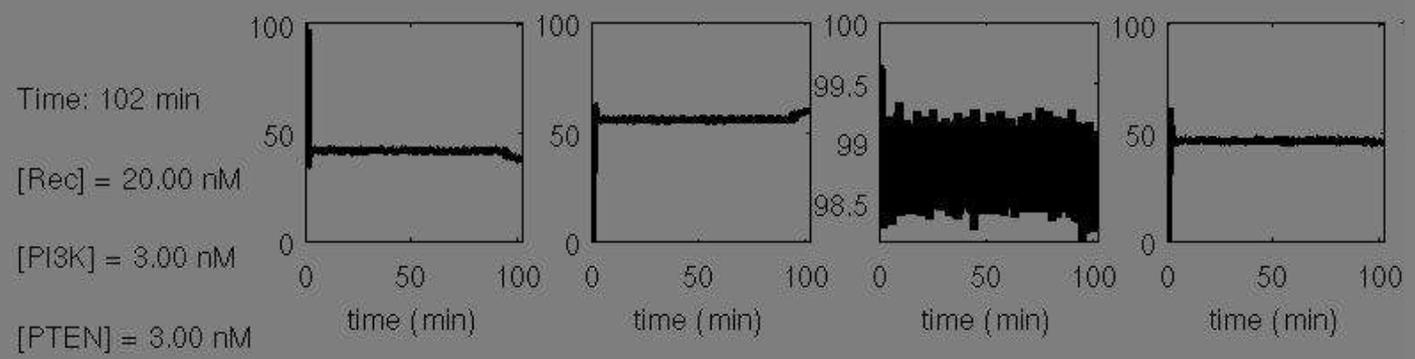
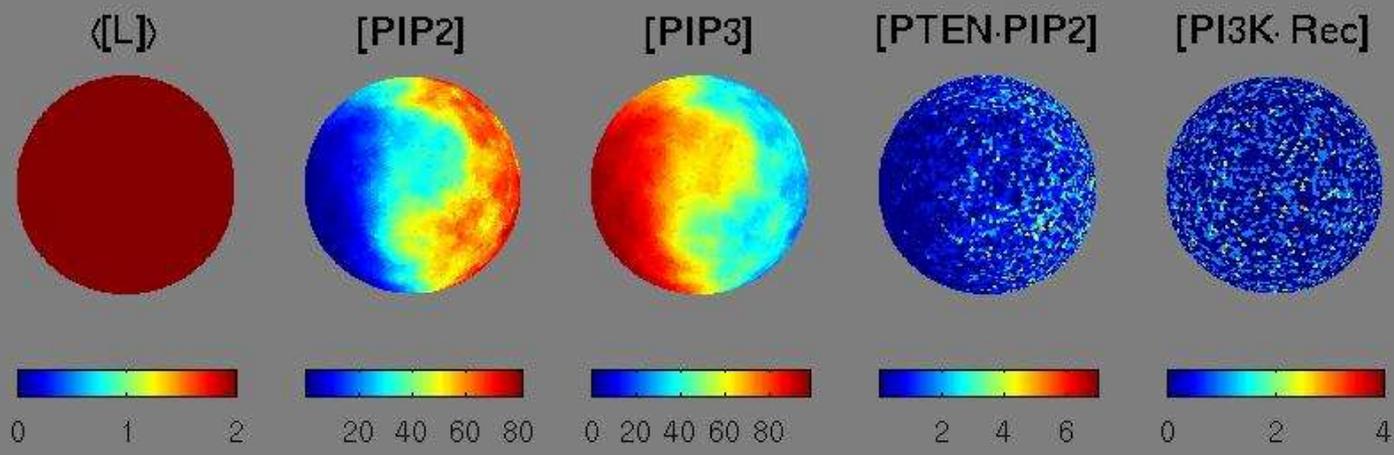
$\epsilon = 0.00\%$





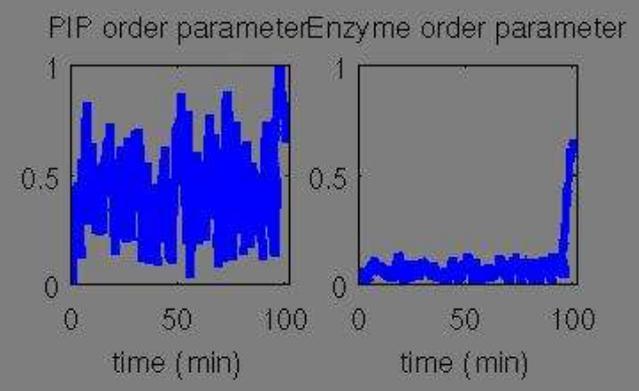
[PIP2] = 400 nM
 $D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$
 $\epsilon = 0.00\%$

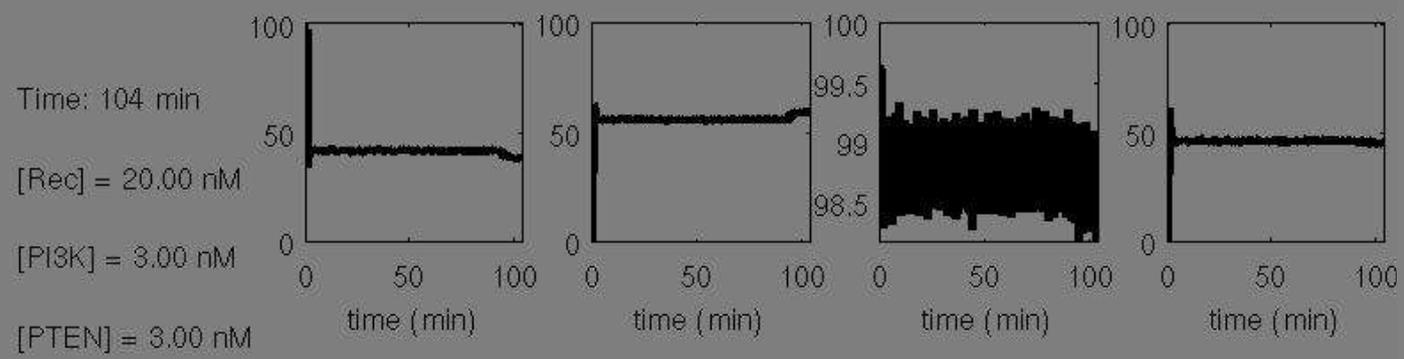
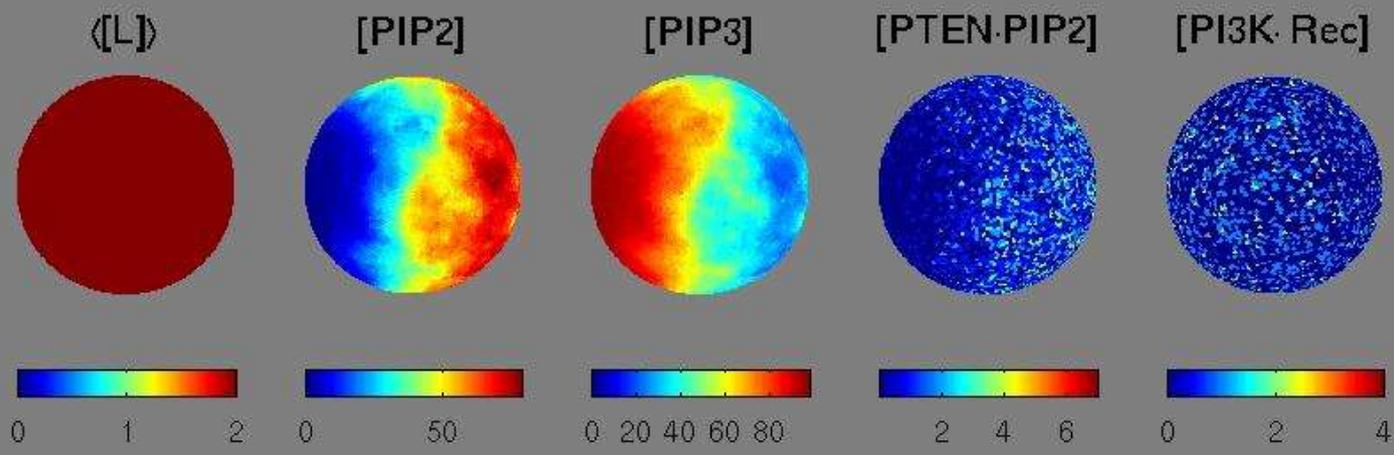




$D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$

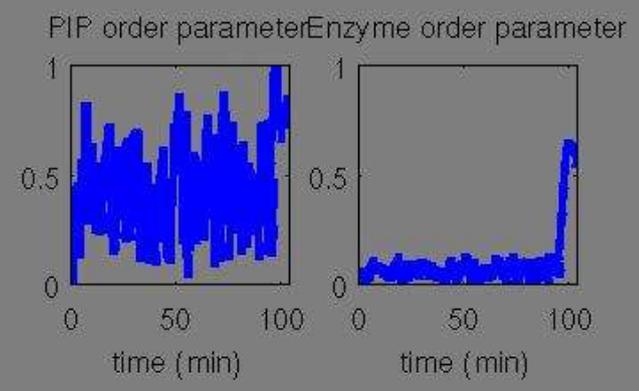
$\epsilon = 0.00\%$

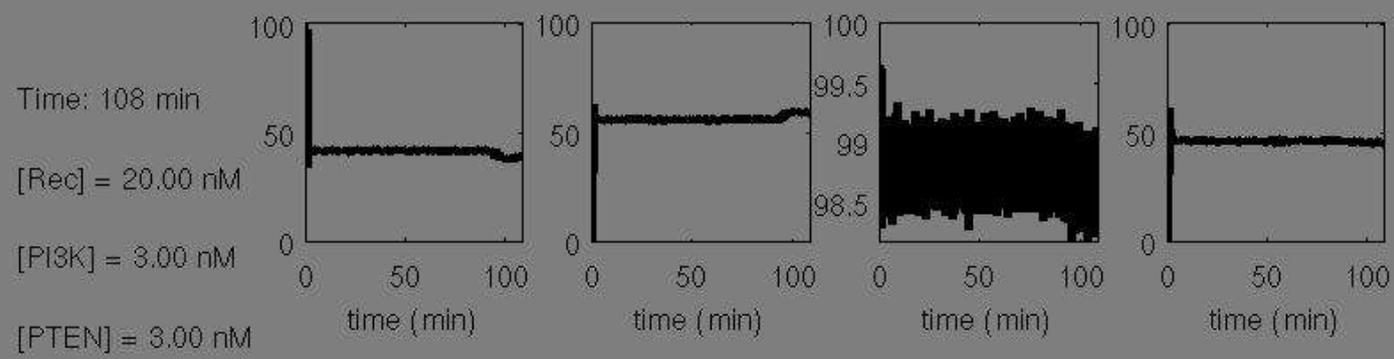
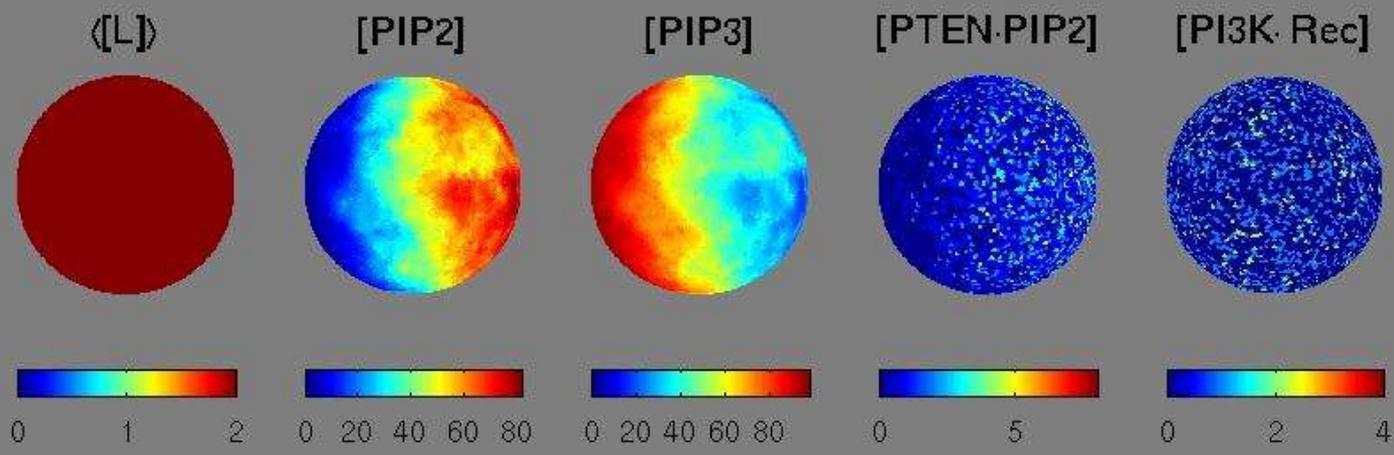




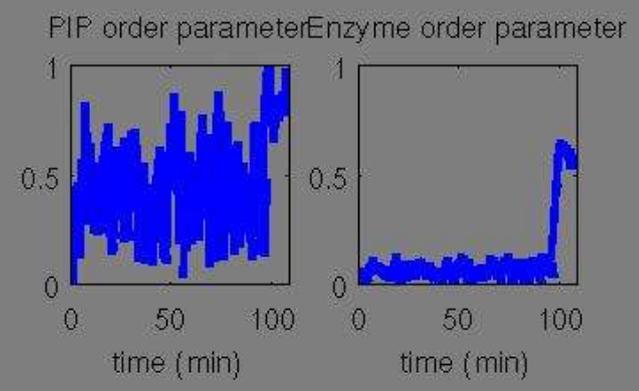
$D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$

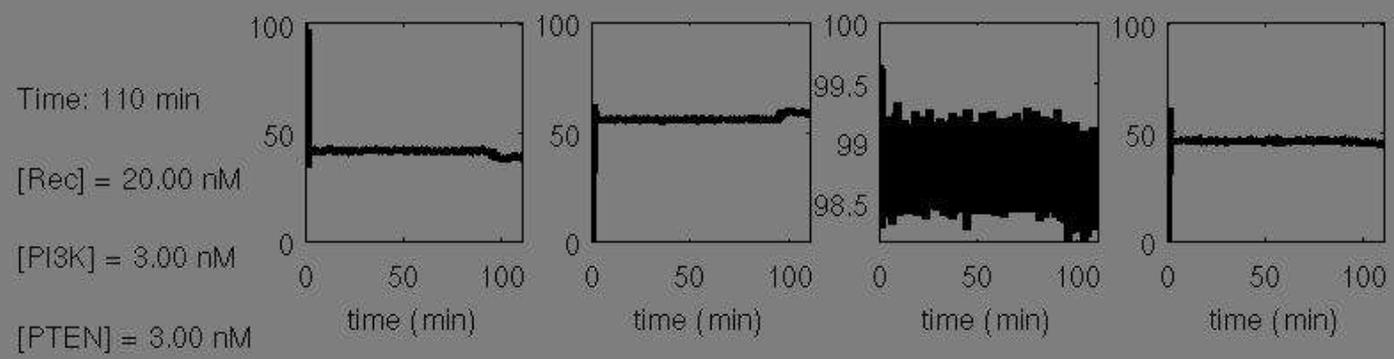
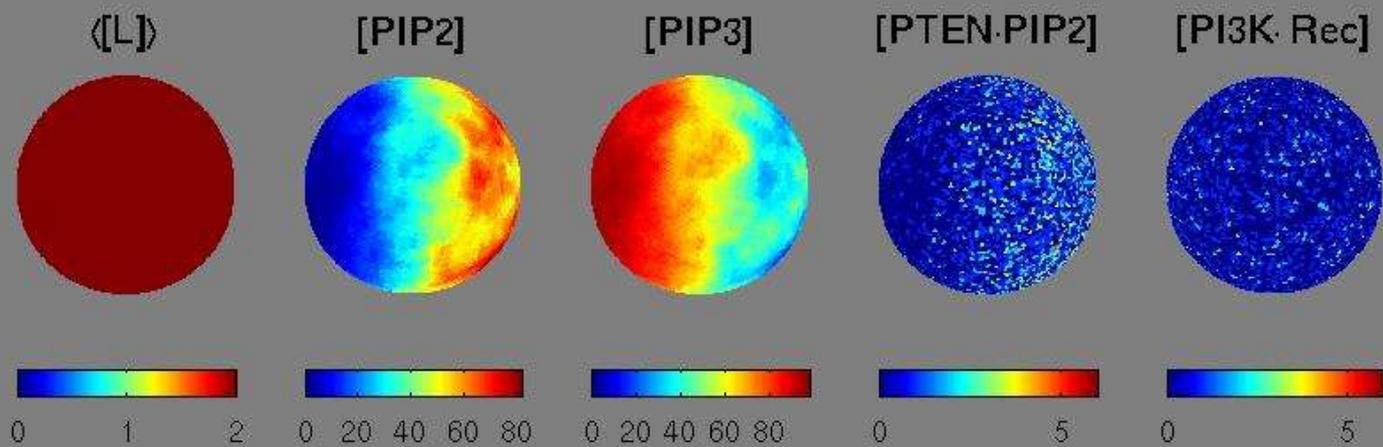
$\epsilon = 0.00\%$





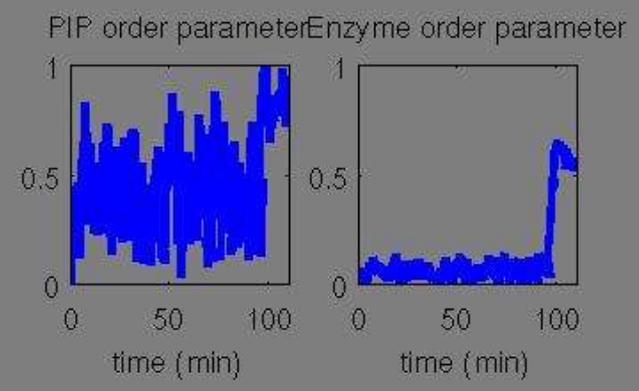
$D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$
 $\epsilon = 0.00\%$





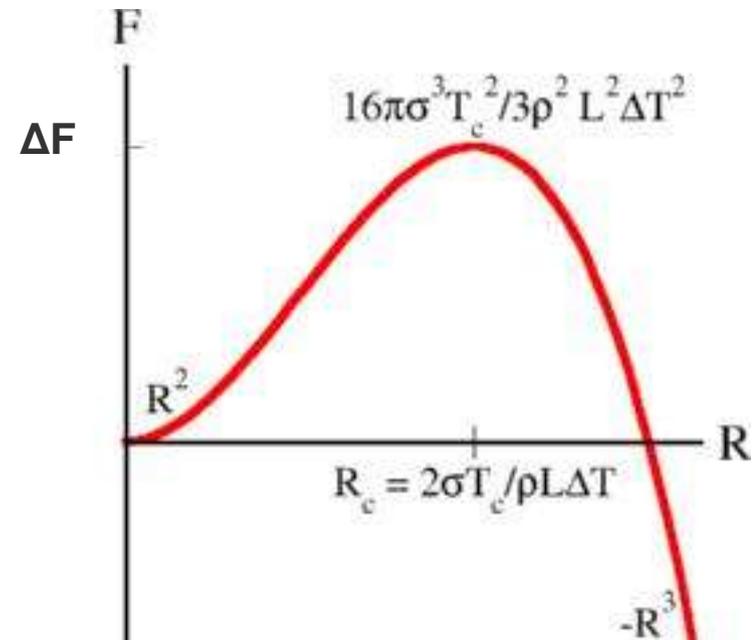
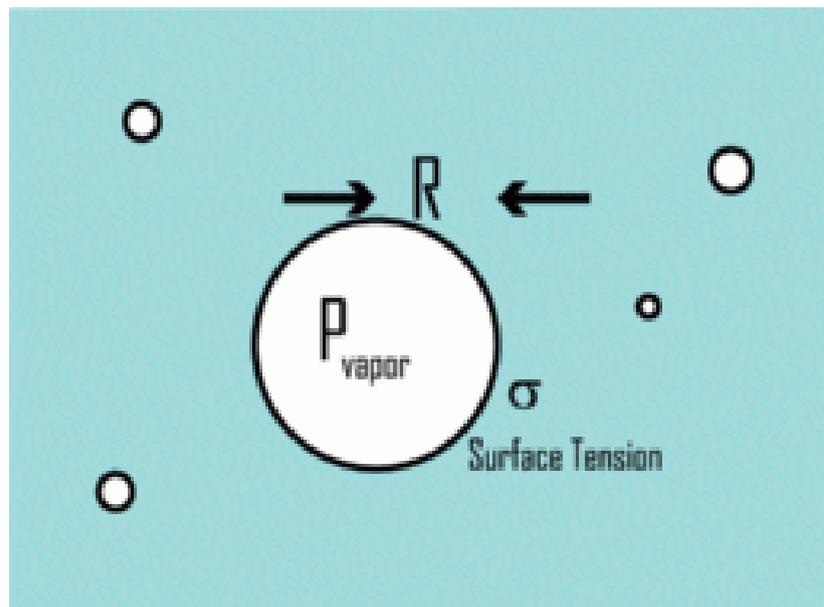
$D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$

$\epsilon = 0.00\%$

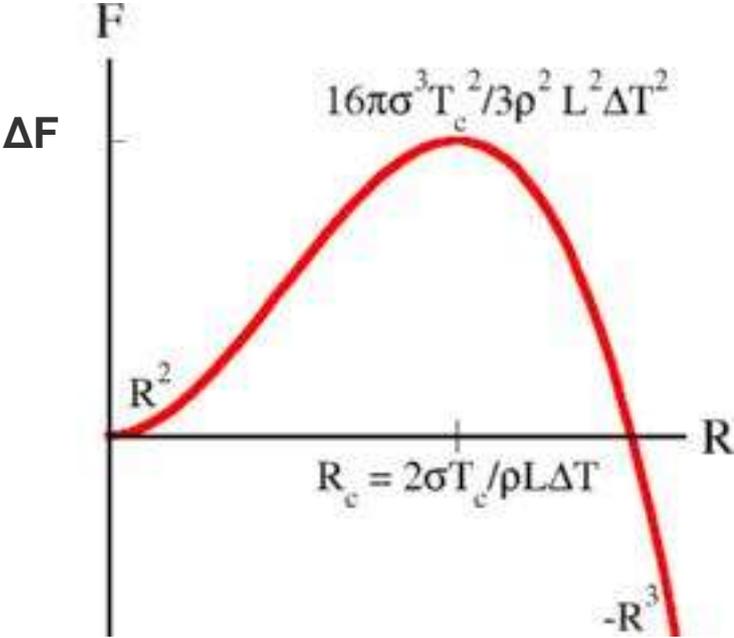
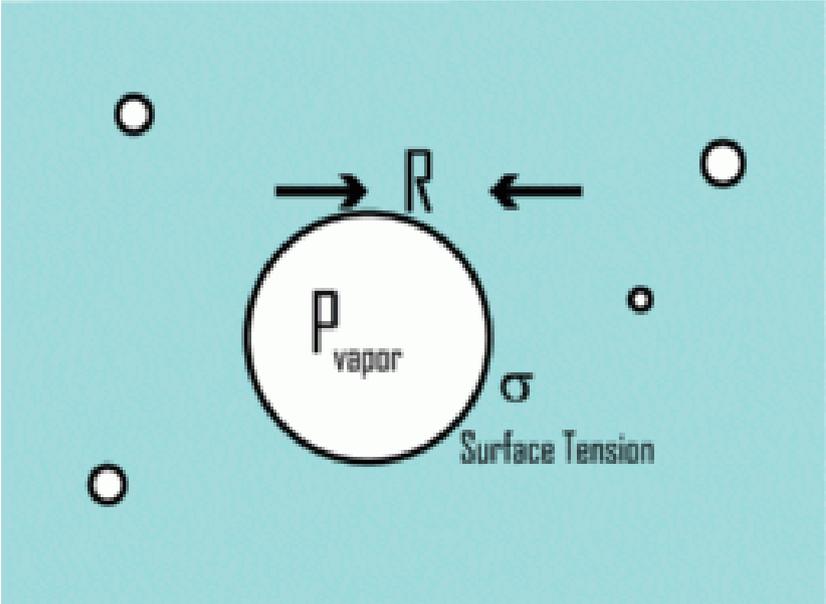


Nucleation

- Phase separation: the mixed state and the phase separated state are divided by a free energy barrier
- Phase separation starts when random fluctuations give rise to an homogeneous bubble of critical size
- Bubble formation is the result of the competition of two effects: surface tension tends to shrink the bubble, while the gain in bulk free energy favors its growth

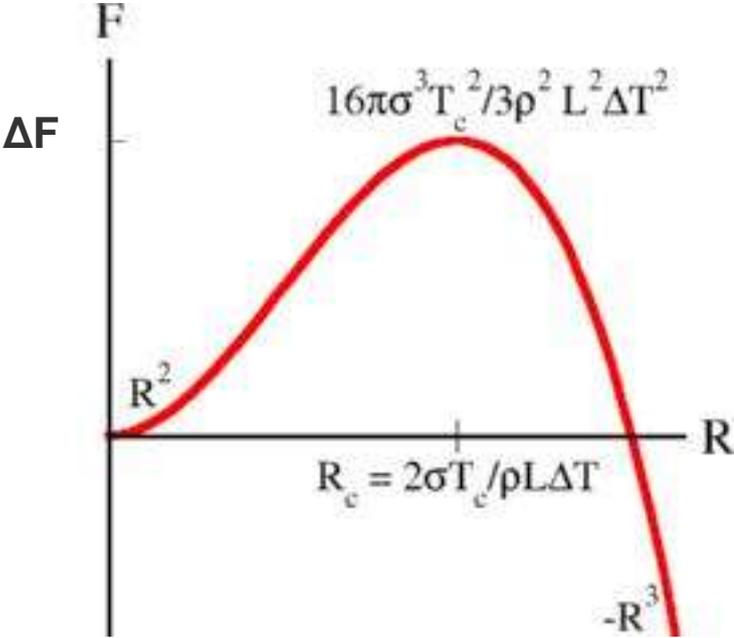
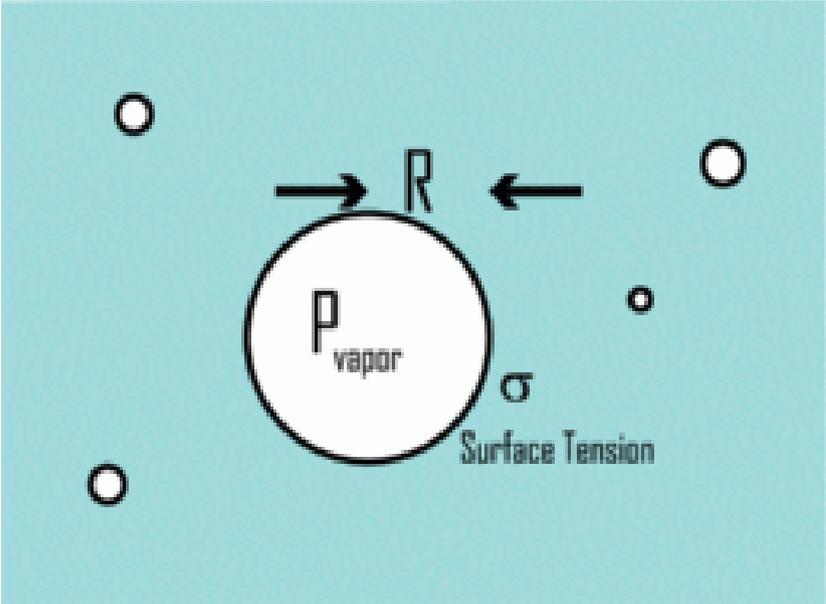


Nucleation



Nucleation

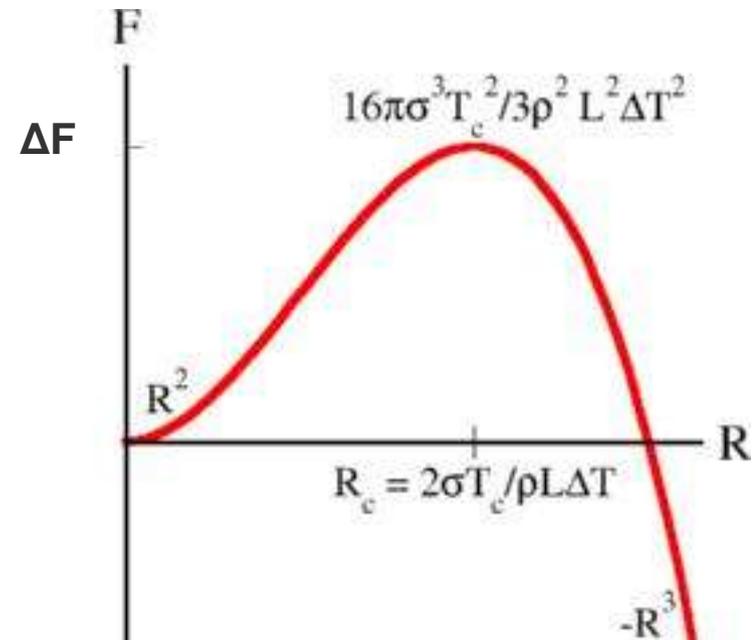
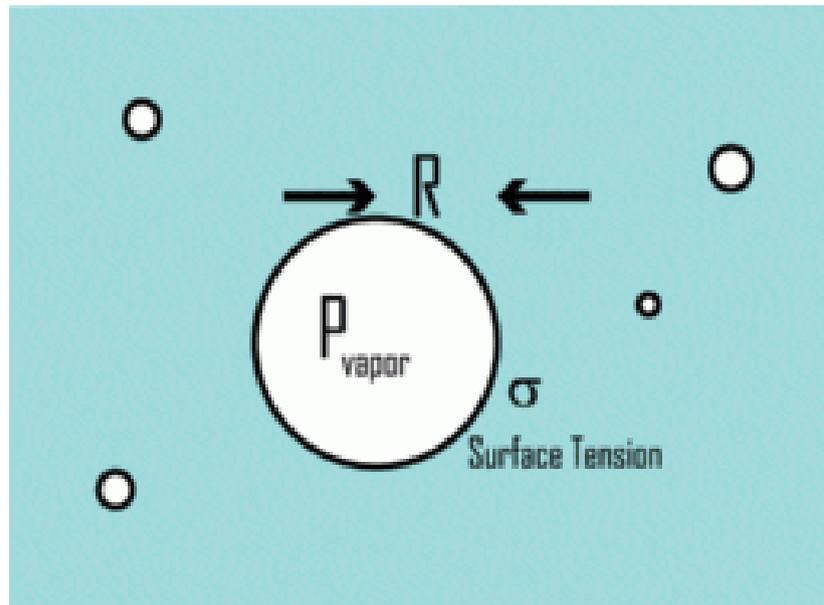
Prob $\propto e^{-\Delta F}$



Nucleation

- The probability that a random fluctuation gives rise to a homogeneous bubble of critical size is proportional to the Arrhenius-Boltzmann factor

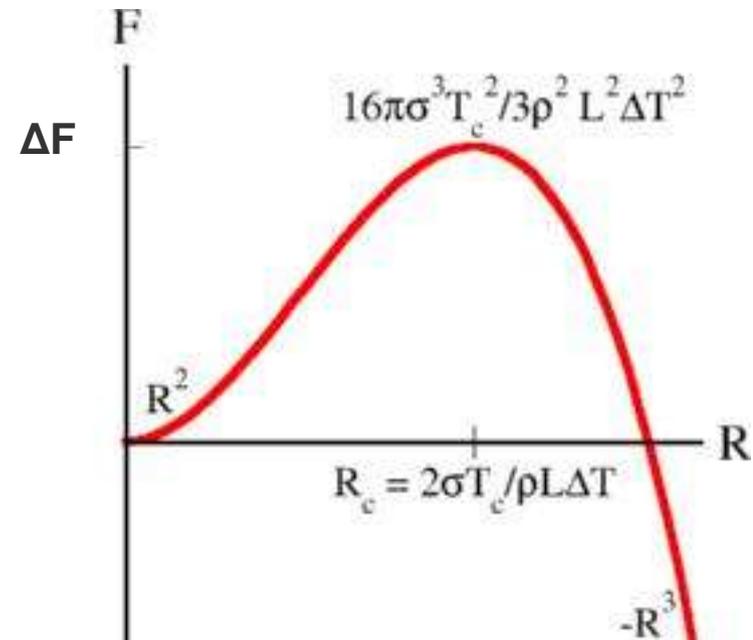
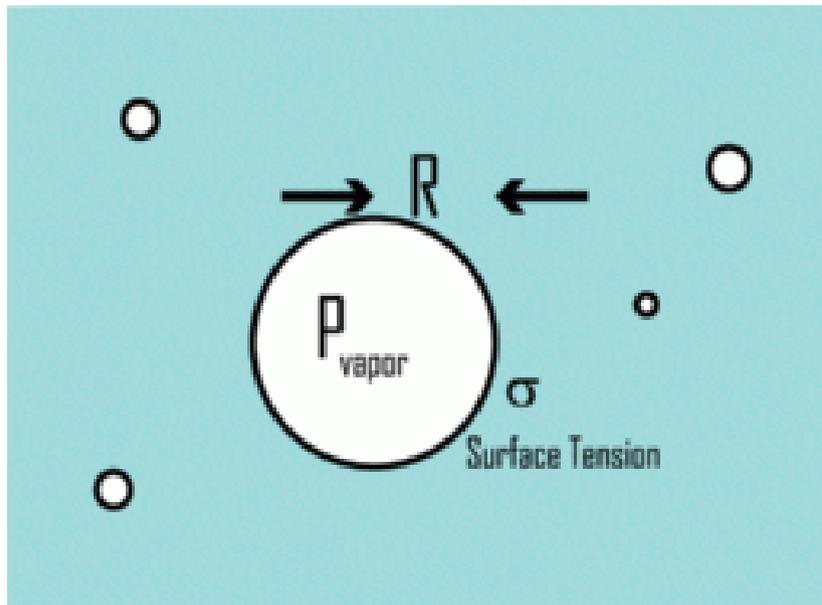
$$\text{Prob} \propto e^{-\Delta F}$$



Nucleation

- The probability that a random fluctuation gives rise to a homogeneous bubble of critical size is proportional to the Arrhenius-Boltzmann factor
- A small anisotropy in receptor activation can significantly increase the probability of the formation of a critical bubble in the regions with higher receptor activation

$$\text{Prob} \propto e^{-\Delta F}$$

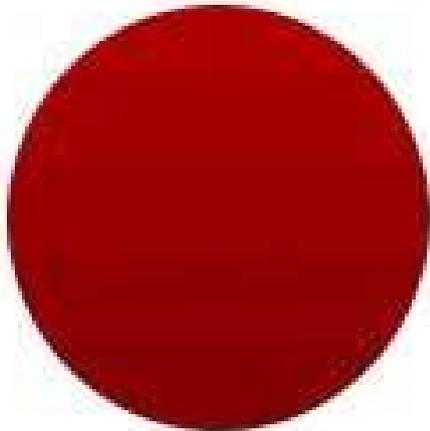


Nucleation

- The probability that a random fluctuation gives rise to a homogeneous bubble of critical size is proportional to the Arrhenius-Boltzmann factor
- A small anisotropy in receptor activation can significantly increase the probability of the formation of a critical bubble in the regions with higher receptor activation
- The anisotropy in receptor activation “helps” the system to find the direction of symmetry breaking. Therefore we expect symmetry breaking to take place in a shorter time. We also expect that the small anisotropy in receptor activation translates into a YES/NO response:

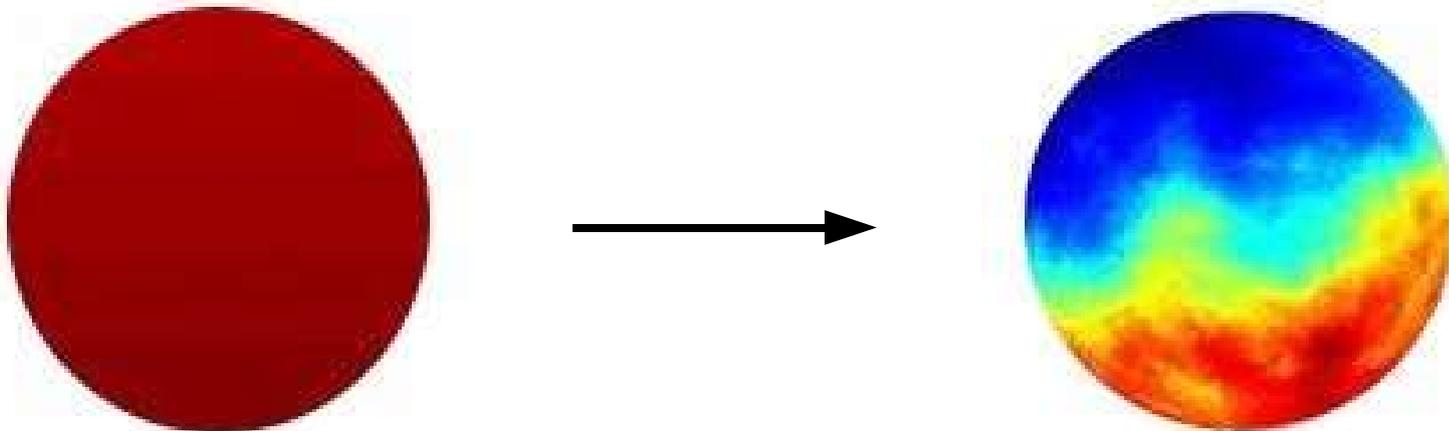
Nucleation

- The probability that a random fluctuation gives rise to a homogeneous bubble of critical size is proportional to the Arrhenius-Boltzmann factor
- A small anisotropy in receptor activation can significantly increase the probability of the formation of a critical bubble in the regions with higher receptor activation
- The anisotropy in receptor activation “helps” the system to find the direction of symmetry breaking. Therefore we expect symmetry breaking to take place in a shorter time. We also expect that the small anisotropy in receptor activation translates into a YES/NO response:

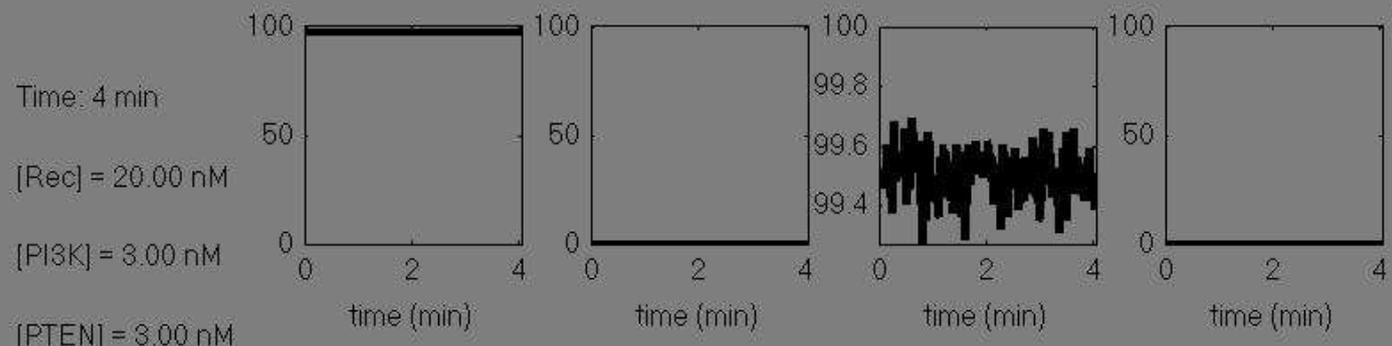
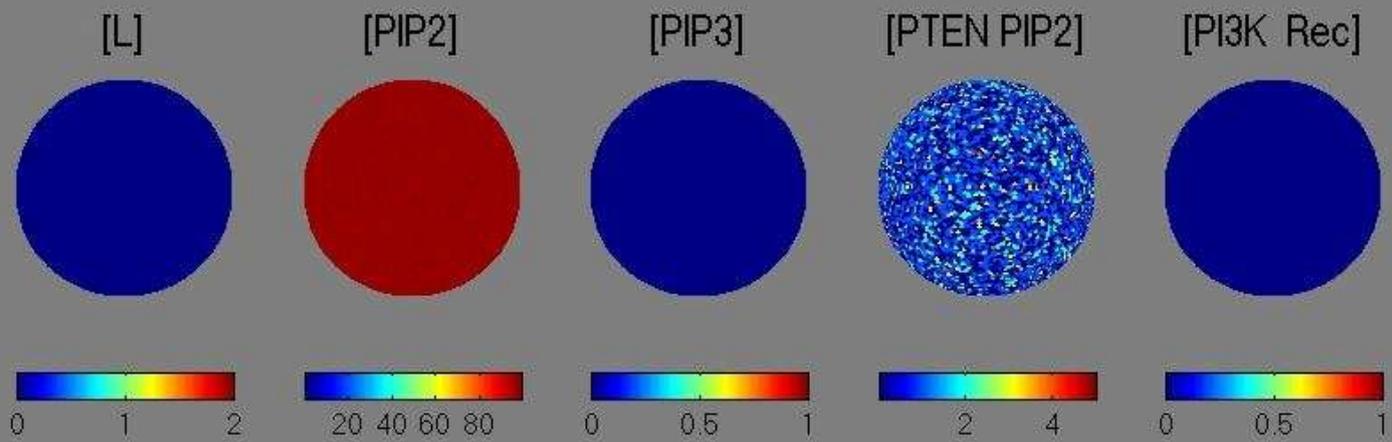


Nucleation

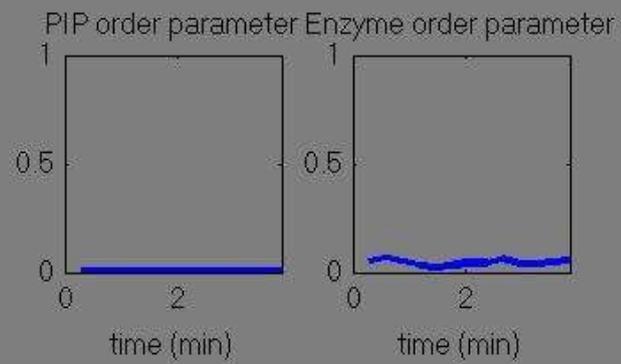
- The probability that a random fluctuation gives rise to a homogeneous bubble of critical size is proportional to the Arrhenius-Boltzmann factor
- A small anisotropy in receptor activation can significantly increase the probability of the formation of a critical bubble in the regions with higher receptor activation
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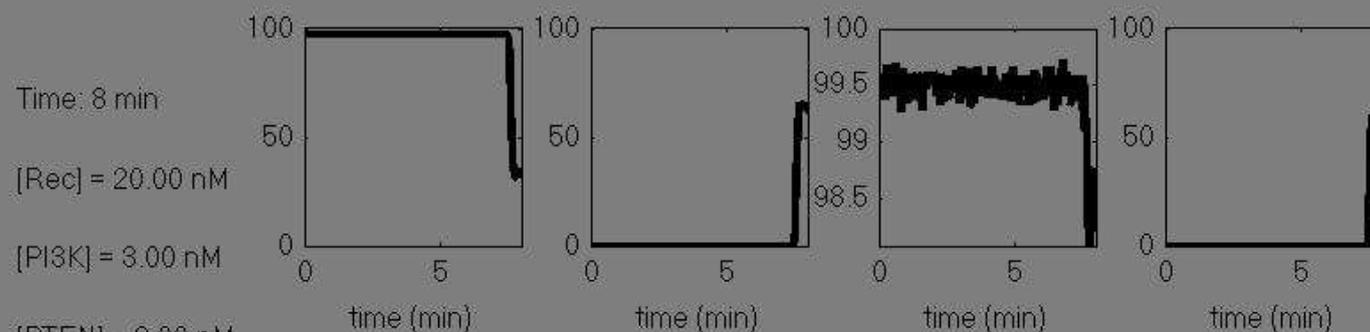
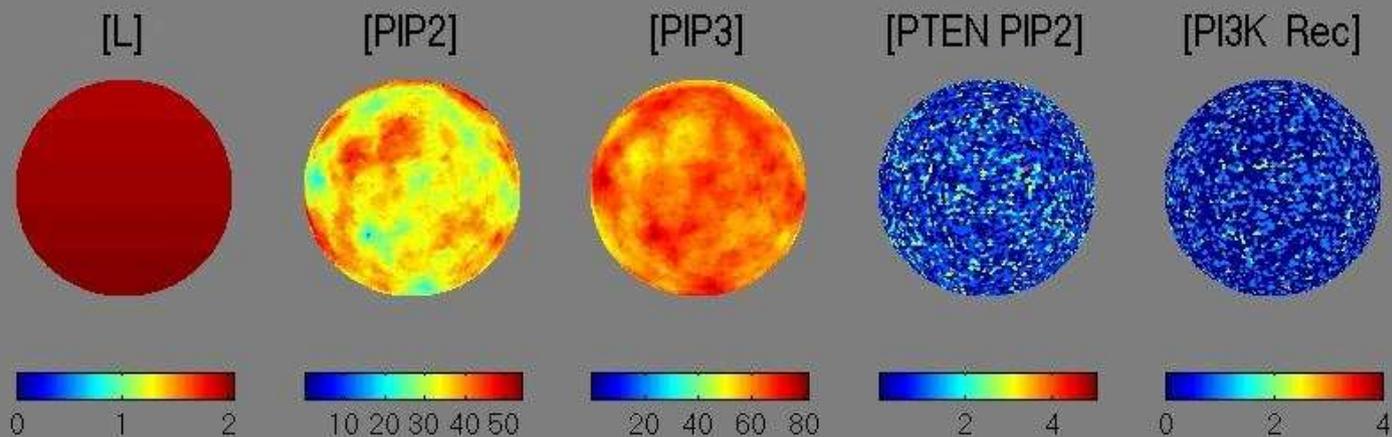


5% anisotropy in the chemotactic signal



Time: 4 min
 [Rec] = 20.00 nM
 [PI3K] = 3.00 nM
 [PTEN] = 3.00 nM
 [PIP2] = 400 nM
 $D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$
 $a = -5.00\%$





Time: 8 min

[Rec] = 20.00 nM

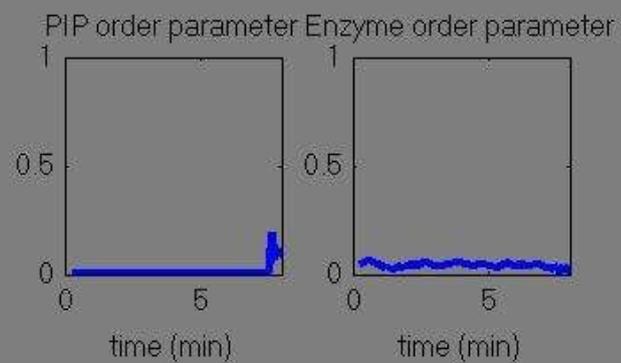
[PI3K] = 3.00 nM

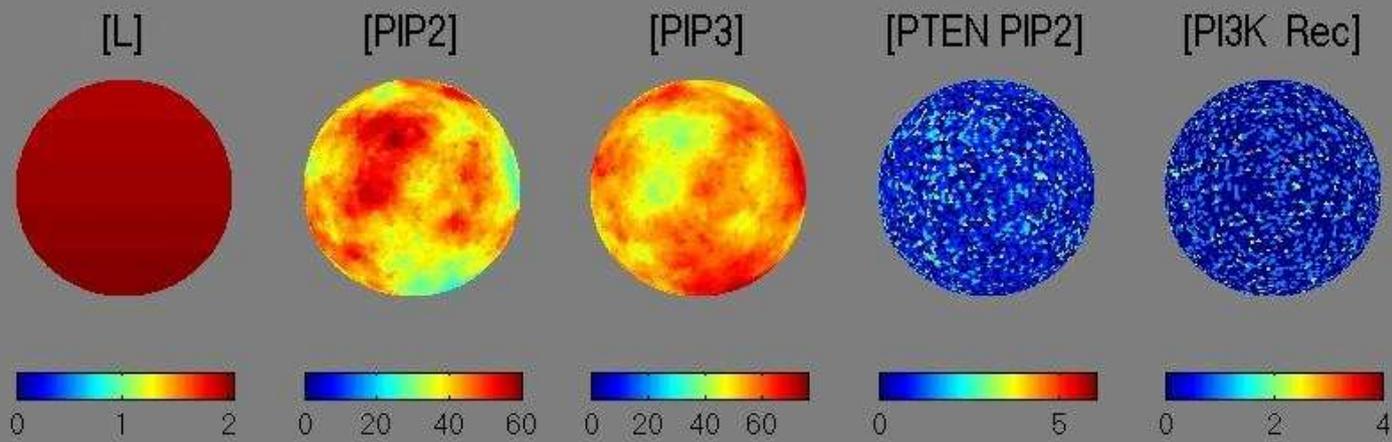
[PTEN] = 3.00 nM

[PIP2] = 400 nM

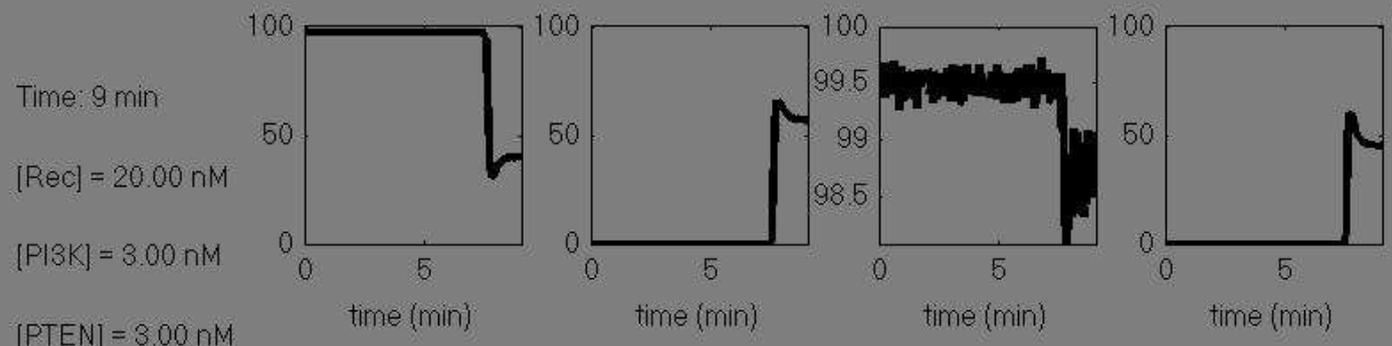
$D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$

$a = -5.00\%$

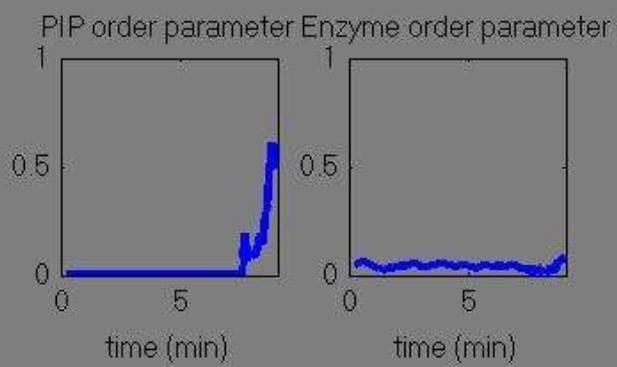


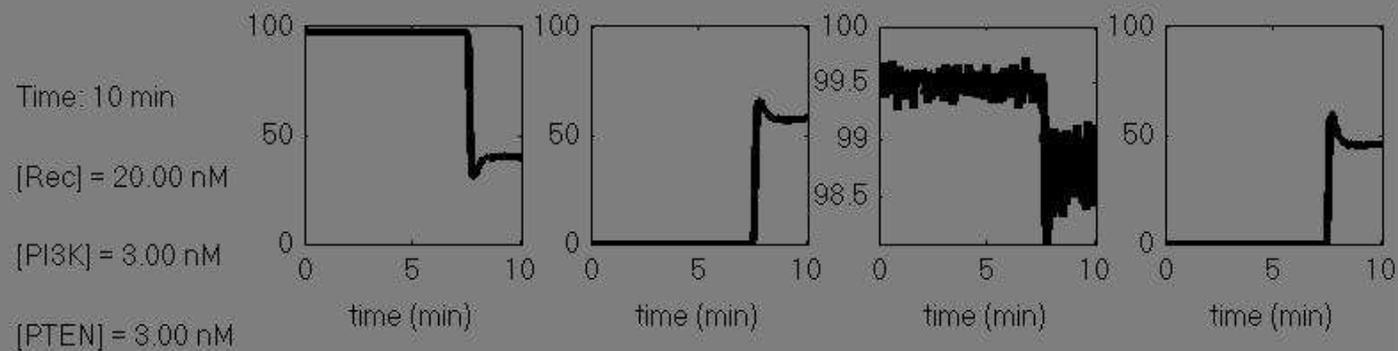
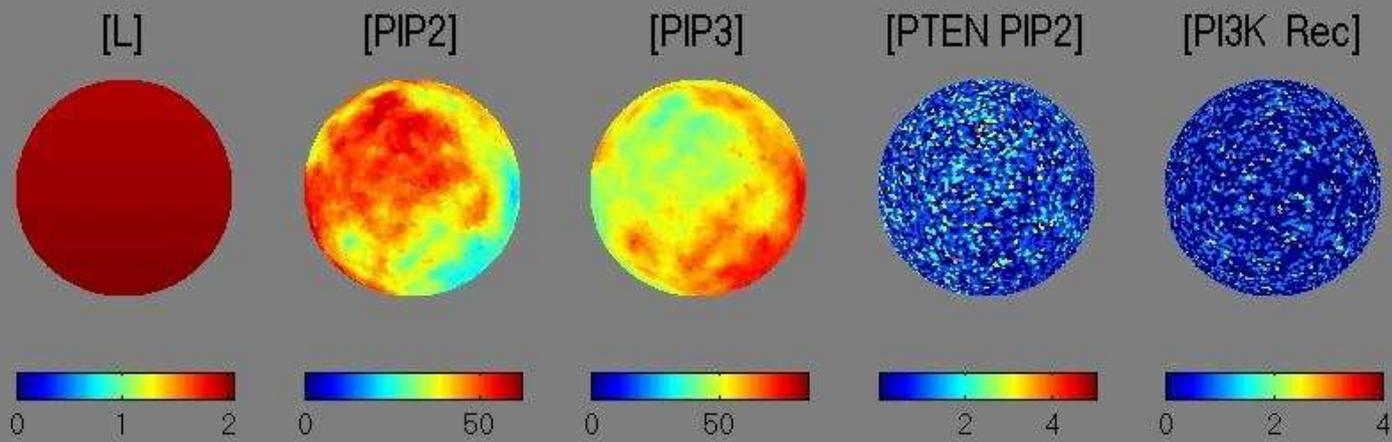


μ

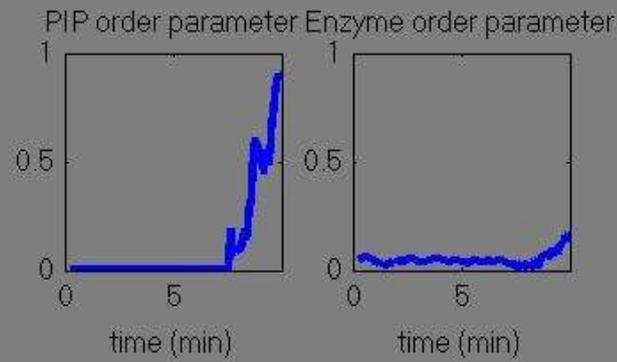


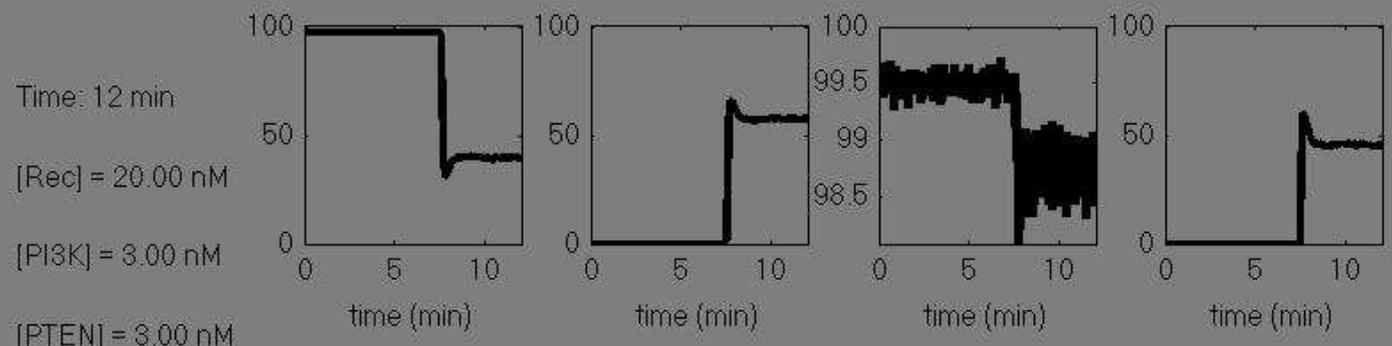
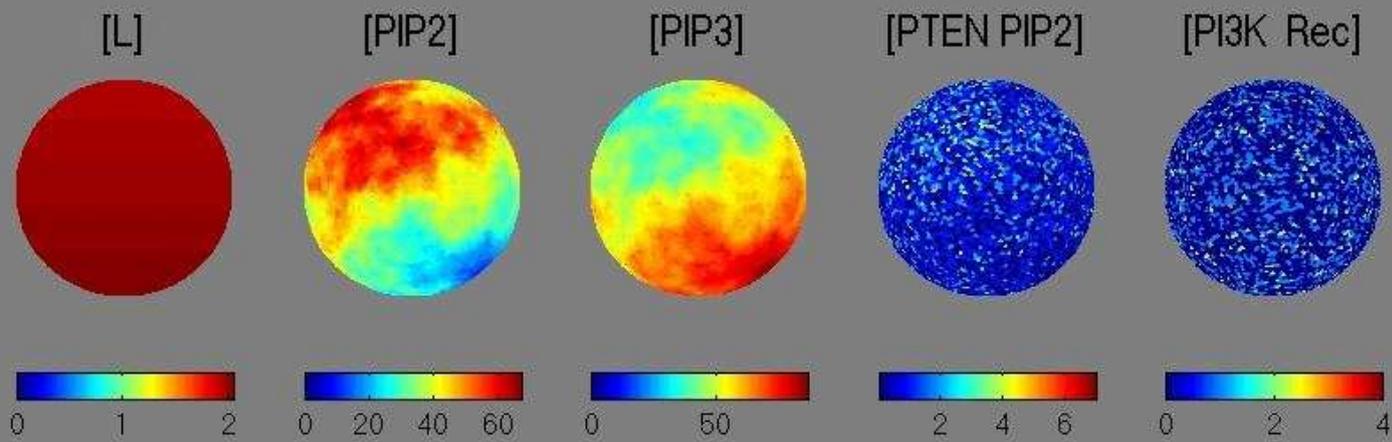
Time: 9 min
 [Rec] = 20.00 nM
 [PI3K] = 3.00 nM
 [PTEN] = 3.00 nM
 [PIP2] = 400 nM
 $D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$
 $a = -5.00\%$



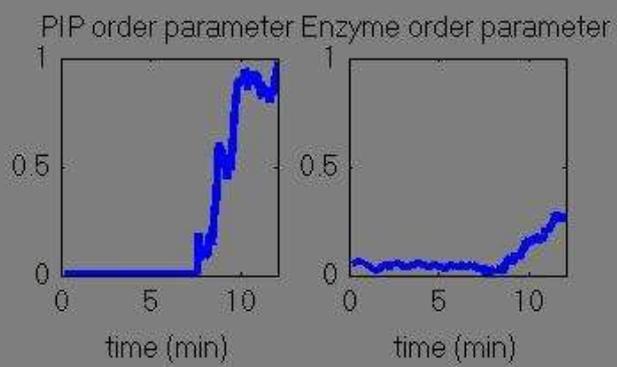


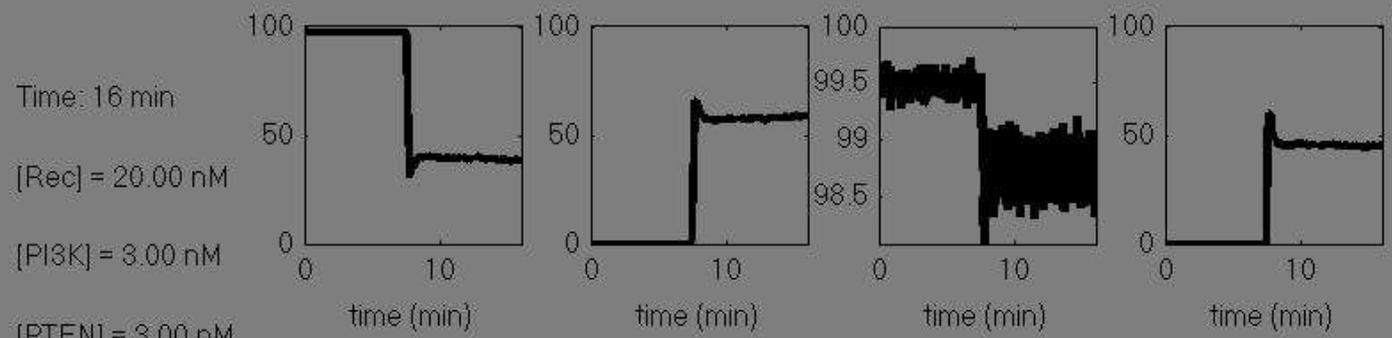
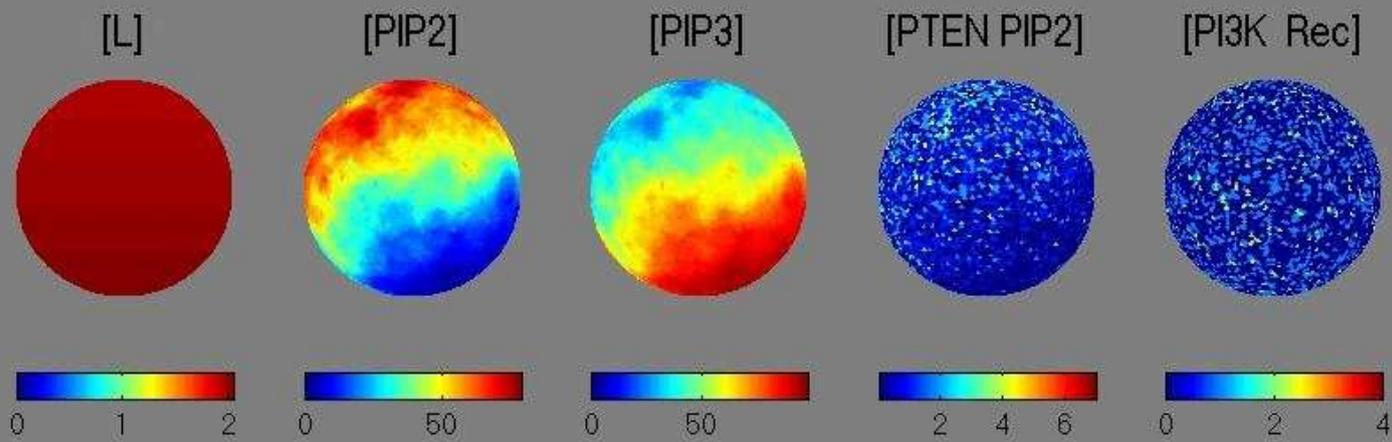
Time: 10 min
 [Rec] = 20.00 nM
 [PI3K] = 3.00 nM
 [PTEN] = 3.00 nM
 [PIP2] = 400 nM
 $D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$
 $a = -5.00\%$



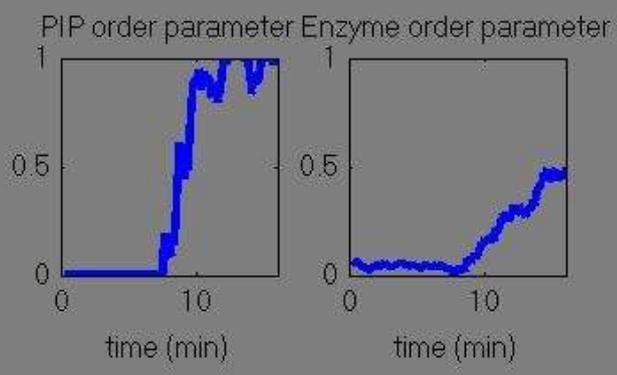


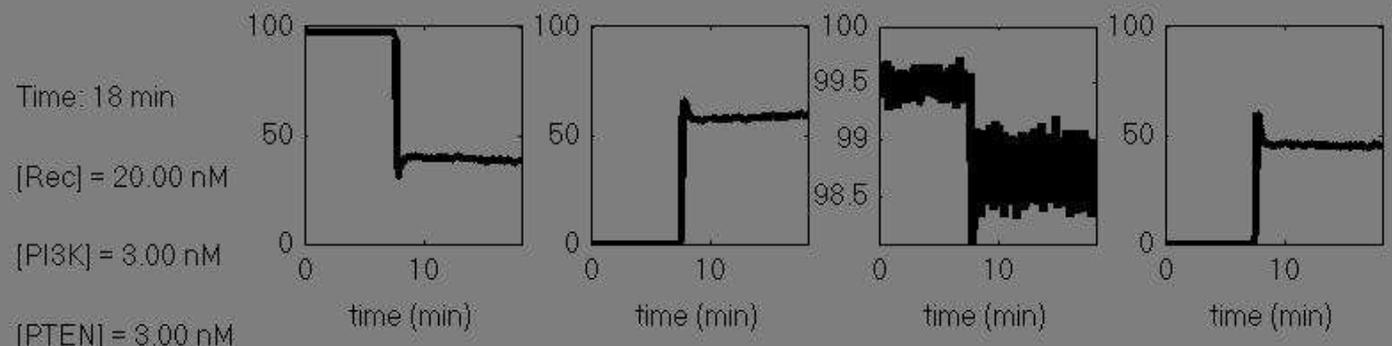
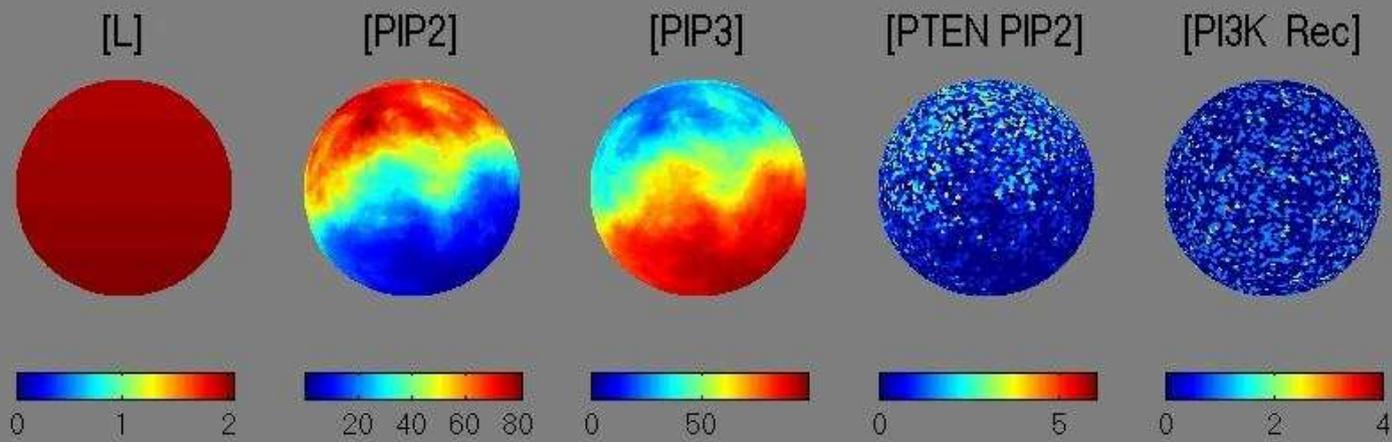
Time: 12 min
 [Rec] = 20.00 nM
 [PI3K] = 3.00 nM
 [PTEN] = 3.00 nM
 [PIP2] = 400 nM
 $D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$
 $a = -5.00\%$



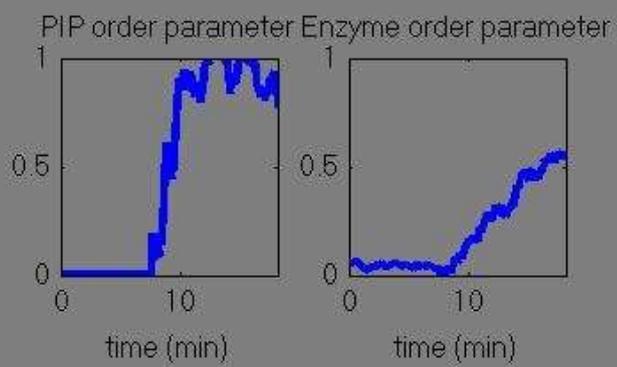


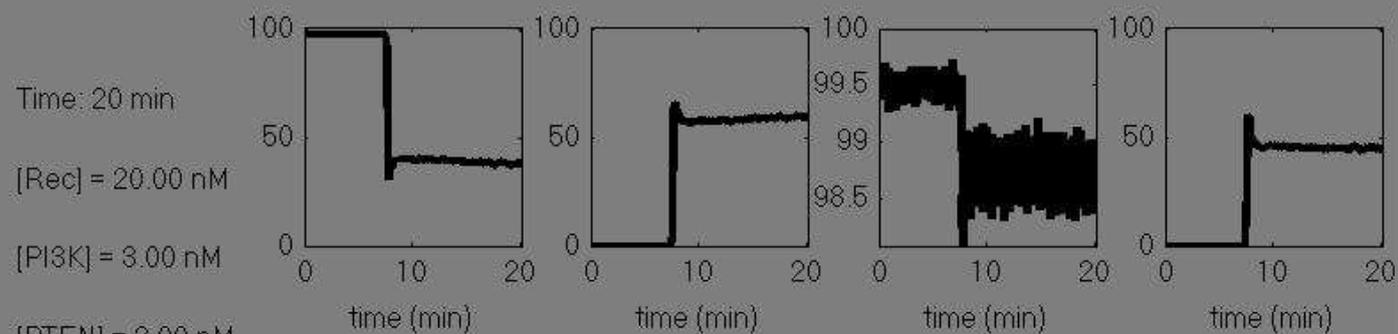
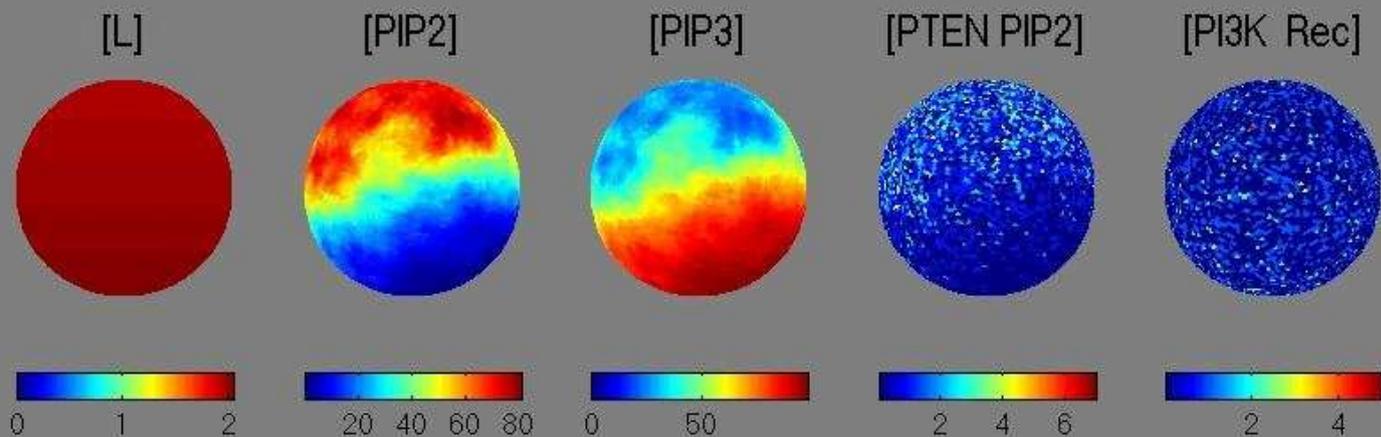
Time: 16 min
 [Rec] = 20.00 nM
 [PI3K] = 3.00 nM
 [PTEN] = 3.00 nM
 [PIP2] = 400 nM
 $D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$
 $a = -5.00\%$





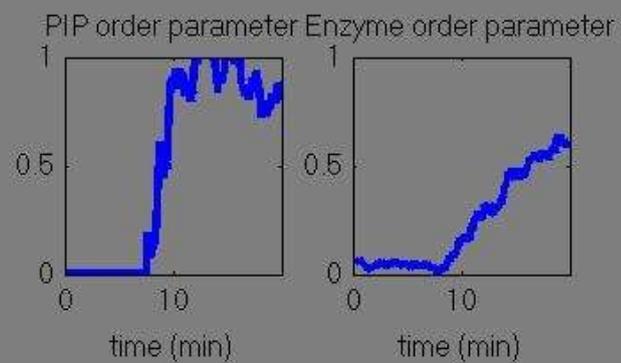
Time: 18 min
 [Rec] = 20.00 nM
 [PI3K] = 3.00 nM
 [PTEN] = 3.00 nM
 [PIP2] = 400 nM
 $D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$
 $a = -5.00\%$

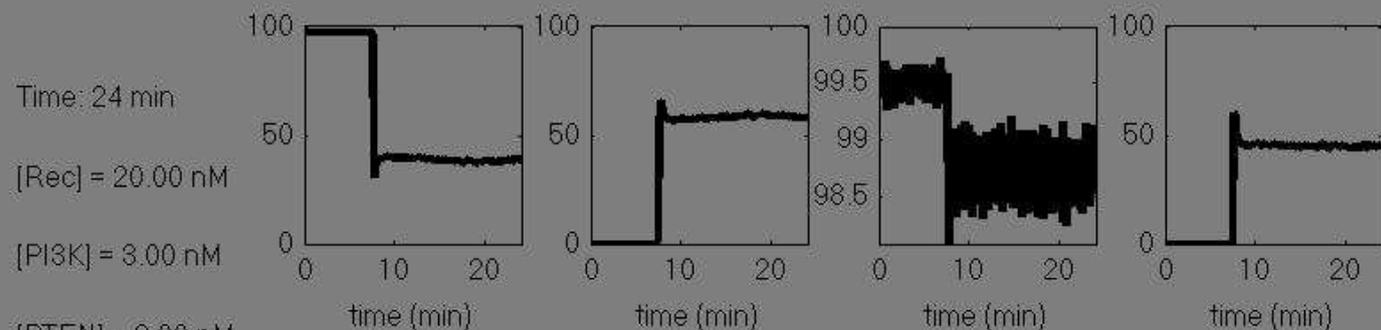
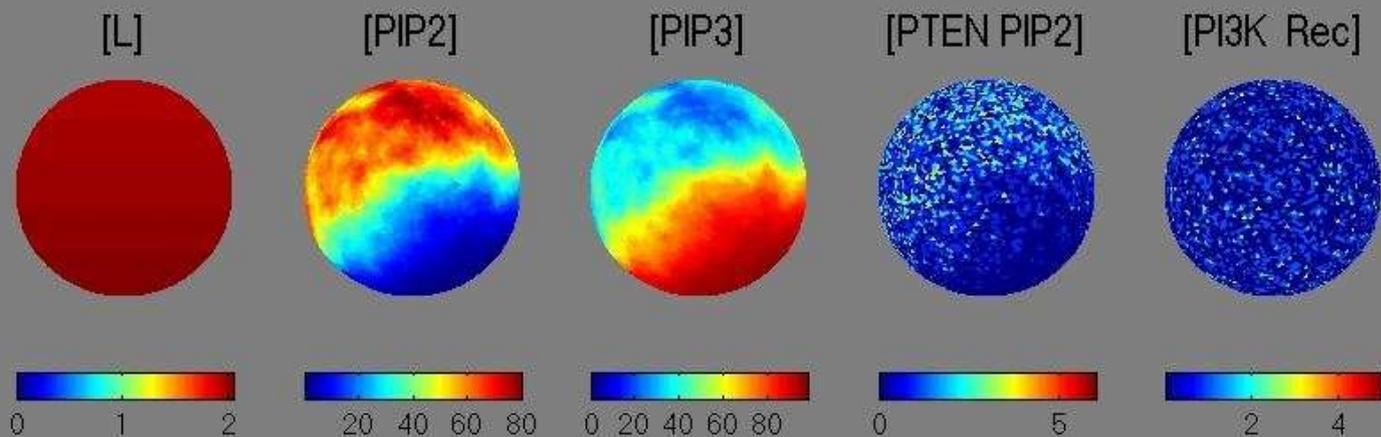




$D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$

$a = -5.00\%$





Time: 24 min

[Rec] = 20.00 nM

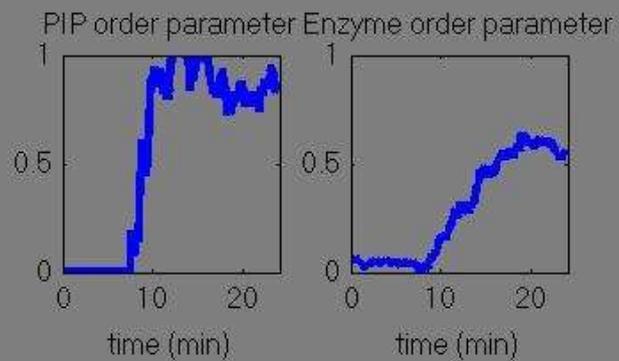
[PI3K] = 3.00 nM

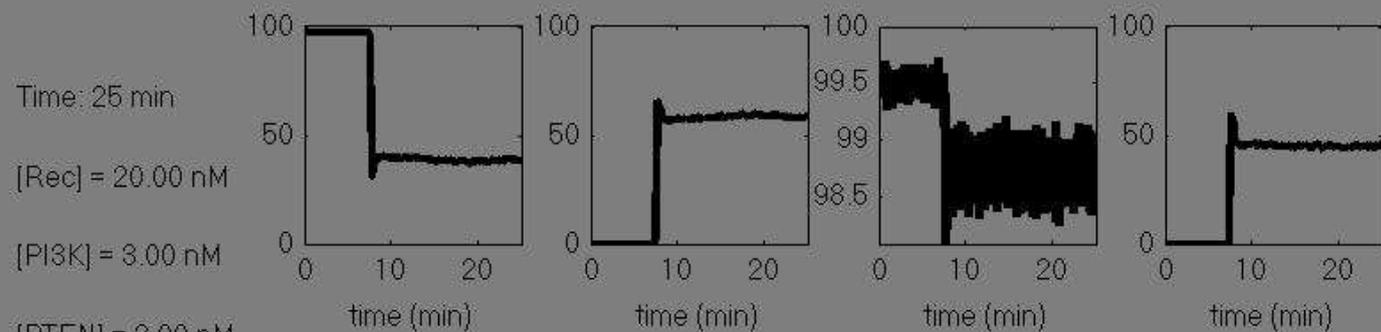
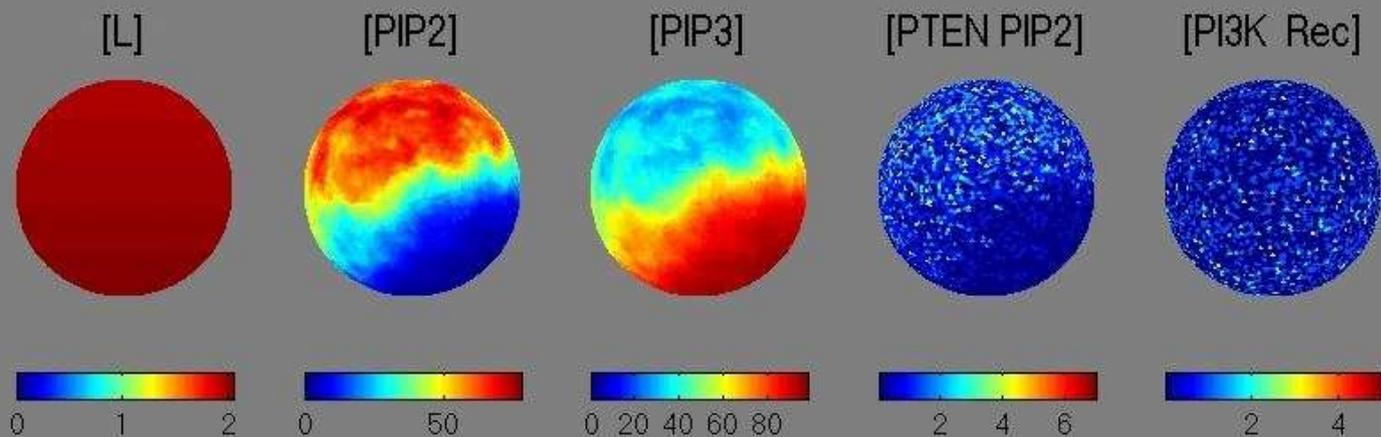
[PTEN] = 3.00 nM

[PIP2] = 400 nM

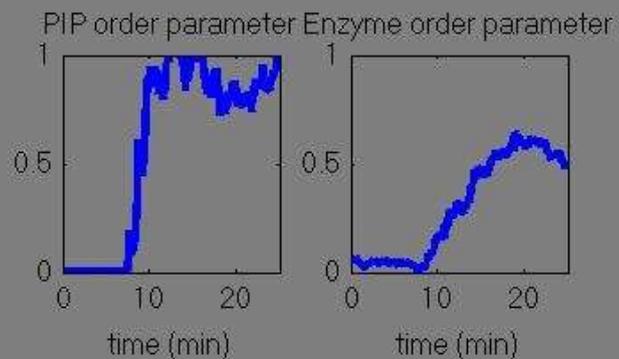
$D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$

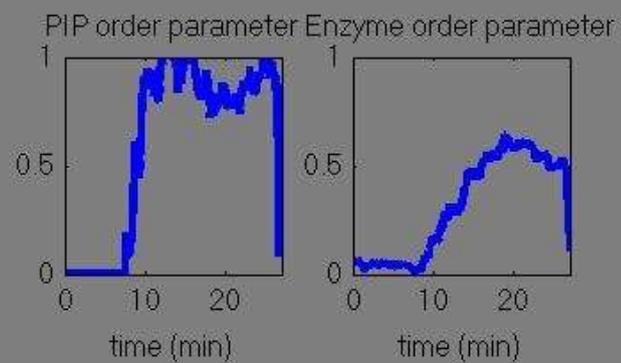
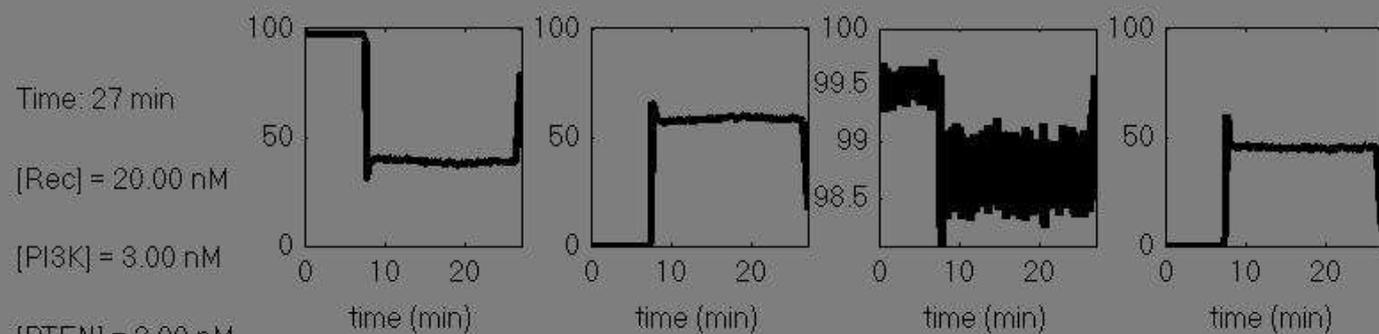
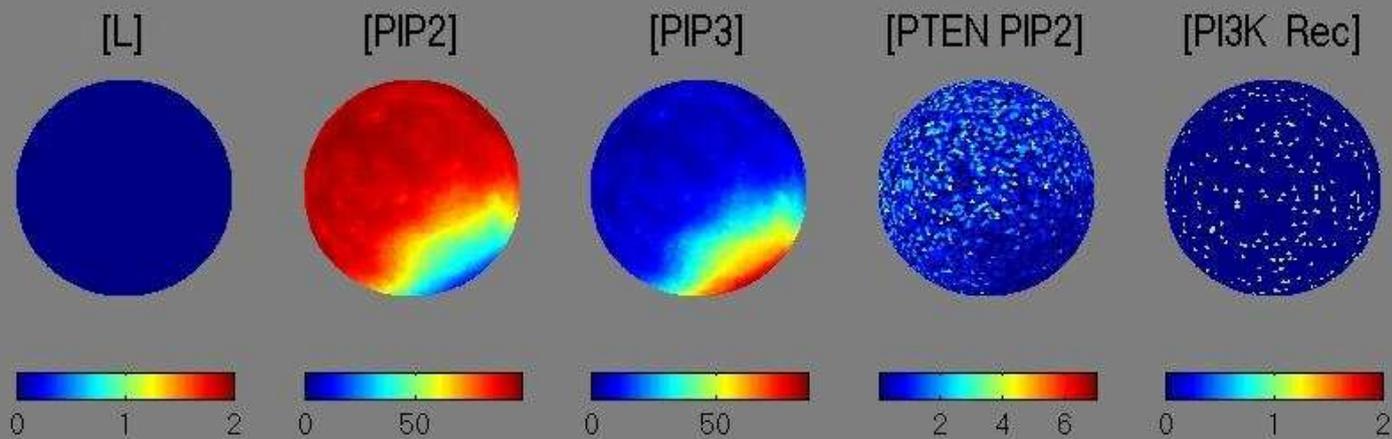
$a = -5.00\%$

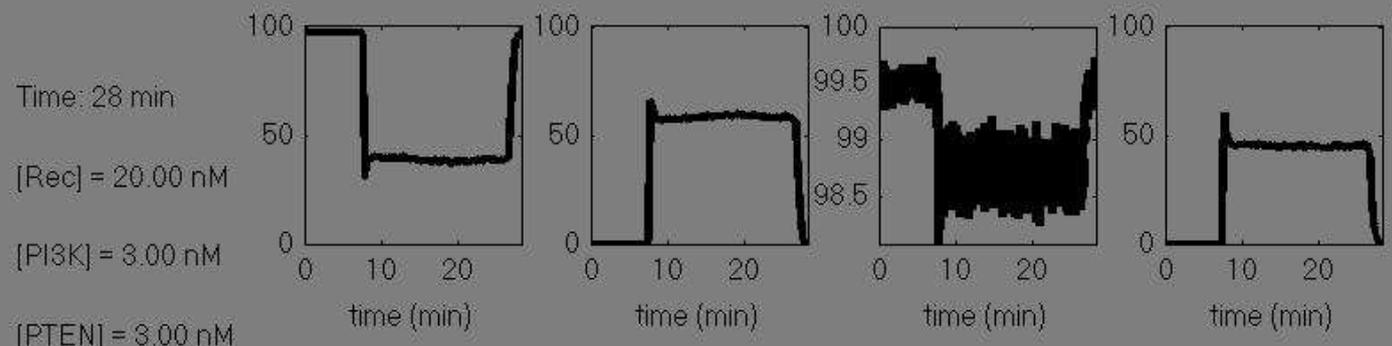
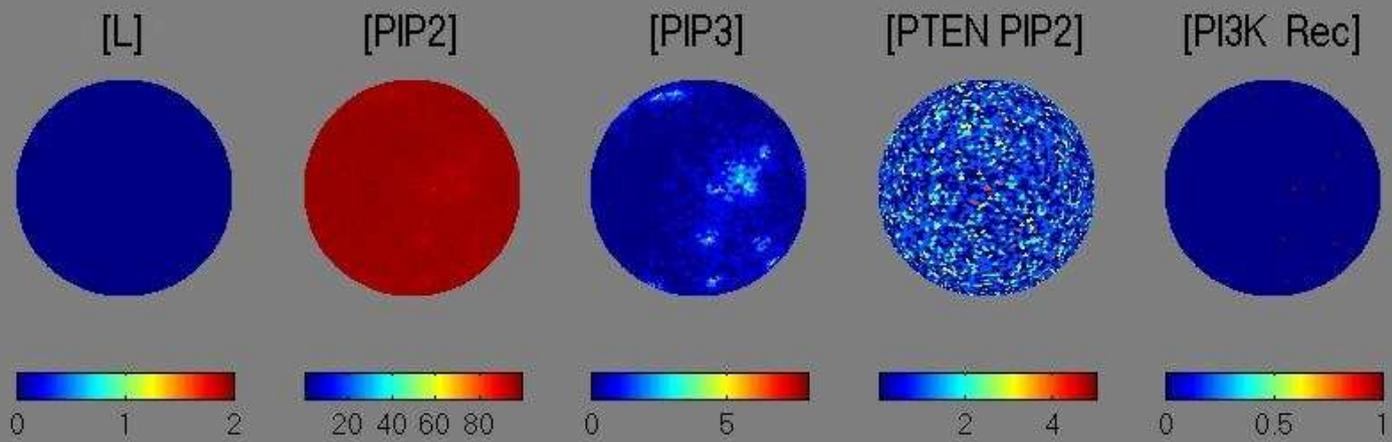




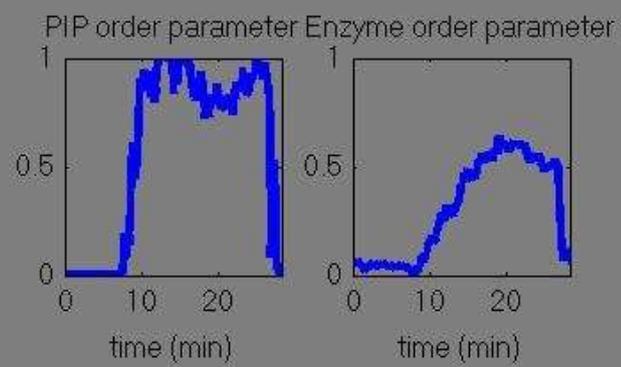
$D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$
 $a = -5.00\%$

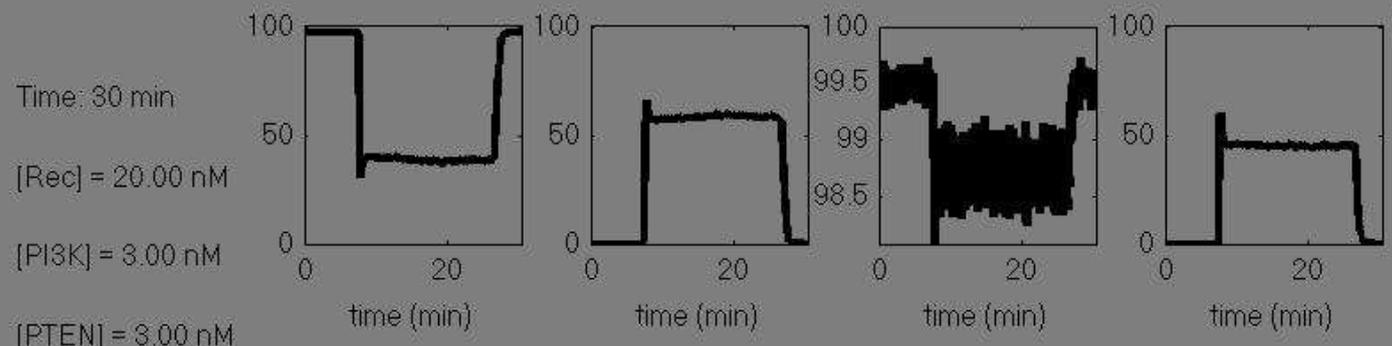
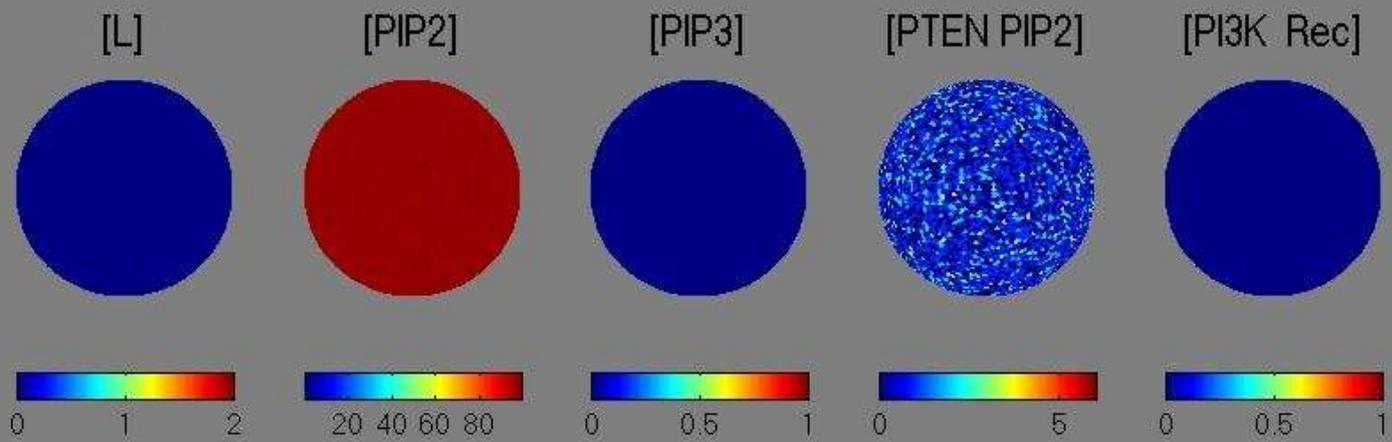




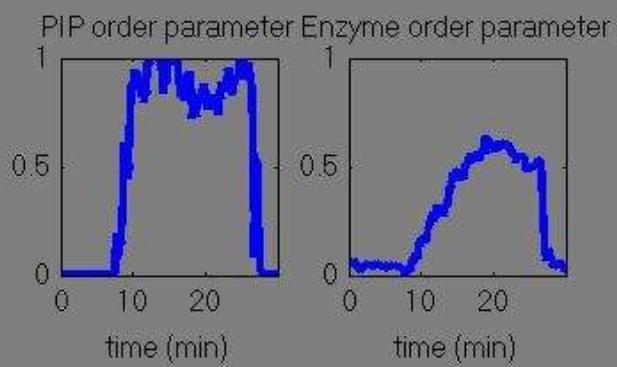


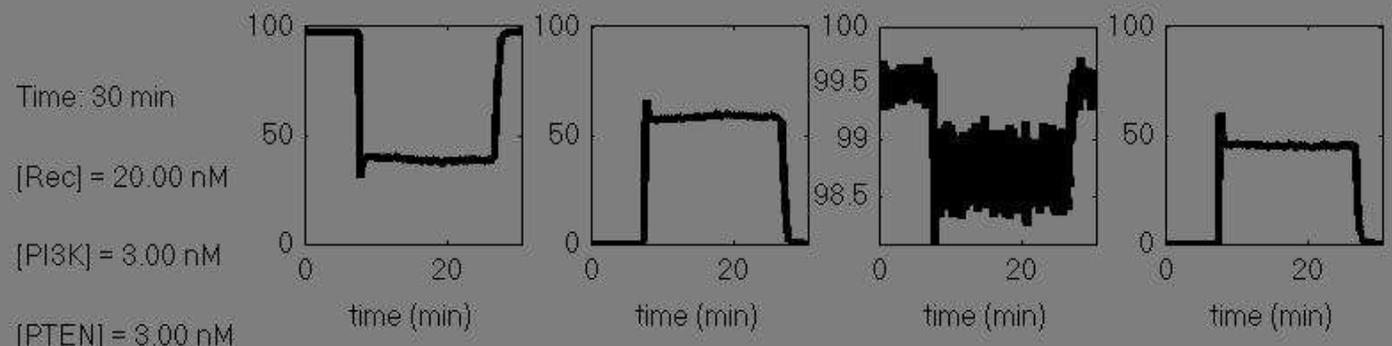
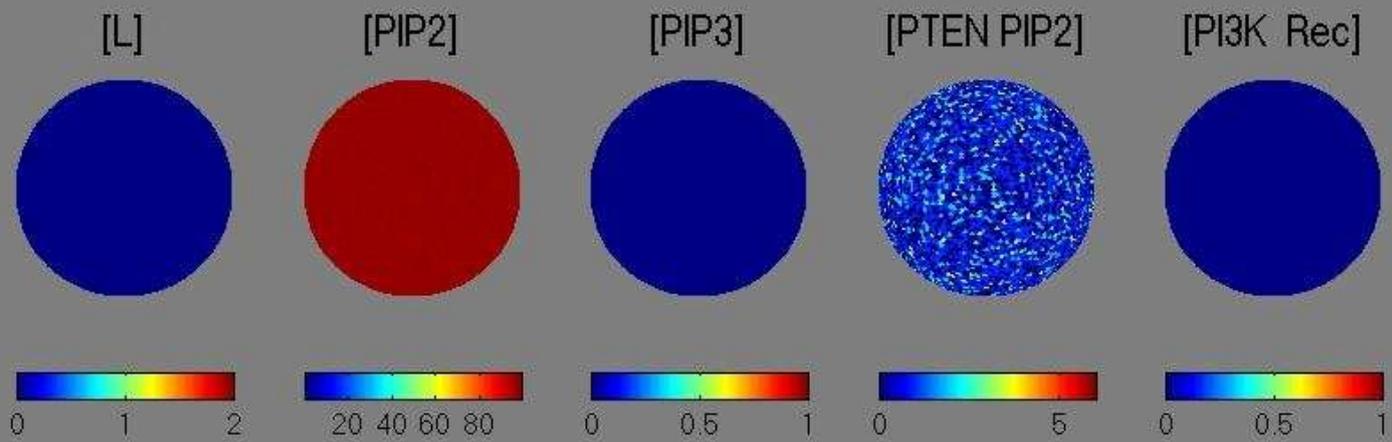
Time: 28 min
 [Rec] = 20.00 nM
 [PI3K] = 3.00 nM
 [PTEN] = 3.00 nM
 [PIP2] = 400 nM
 $D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$
 $a = -5.00\%$



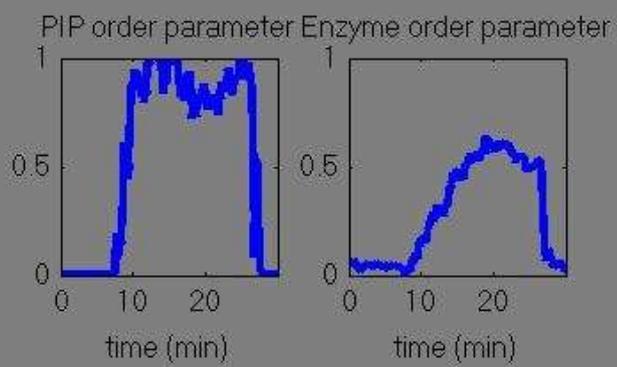


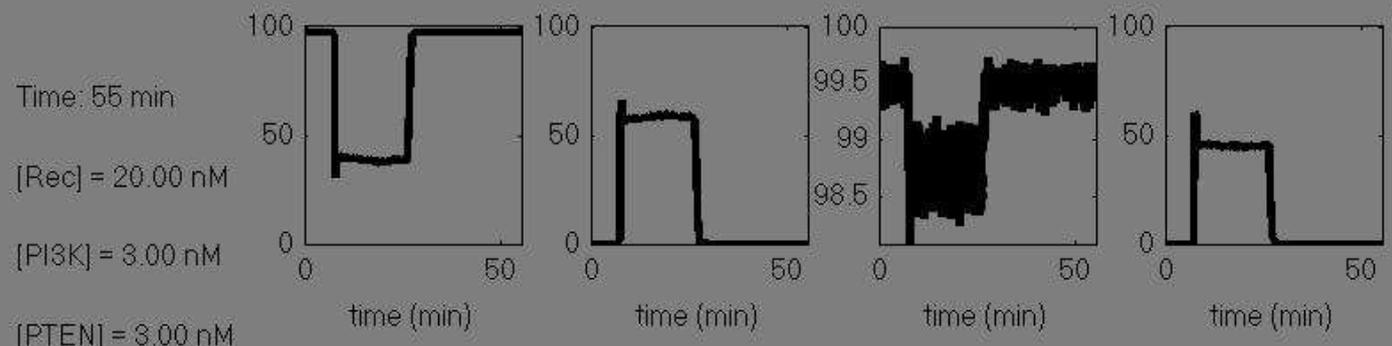
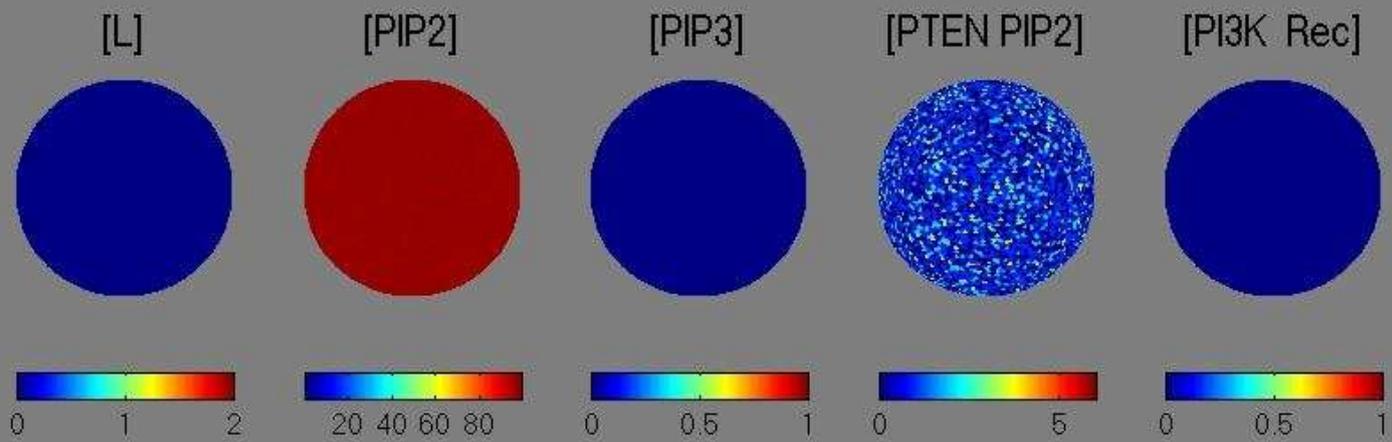
Time: 30 min
 [Rec] = 20.00 nM
 [PI3K] = 3.00 nM
 [PTEN] = 3.00 nM
 [PIP2] = 400 nM
 $D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$
 $a = -5.00\%$



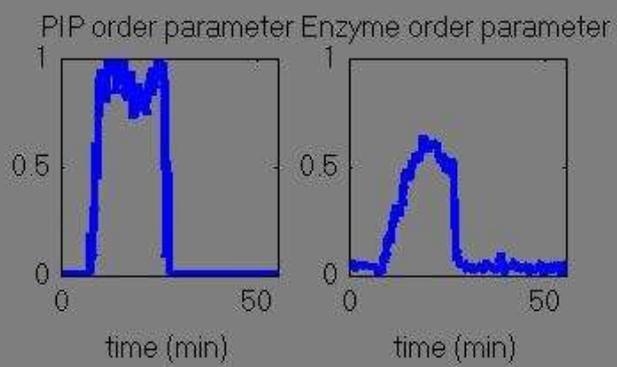


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 [Rec] = 20.00 nM
 [PI3K] = 3.00 nM
 [PTEN] = 3.00 nM
 [PIP2] = 400 nM
 $D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$
 $a = -5.00\%$

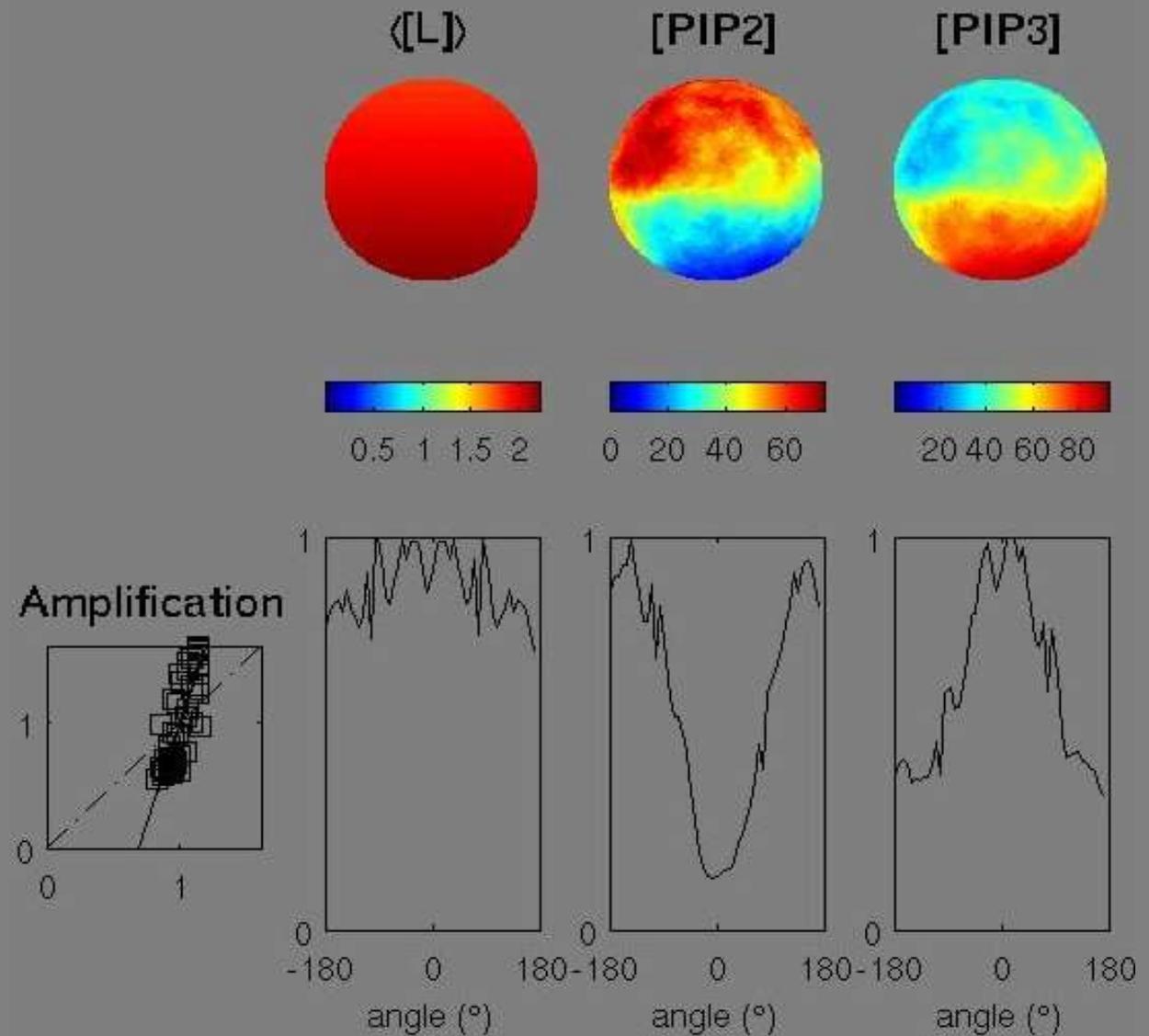




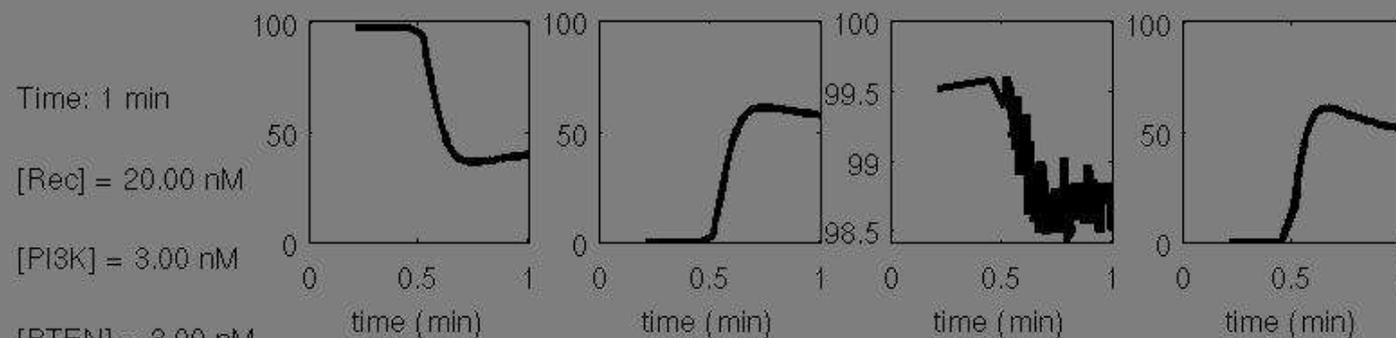
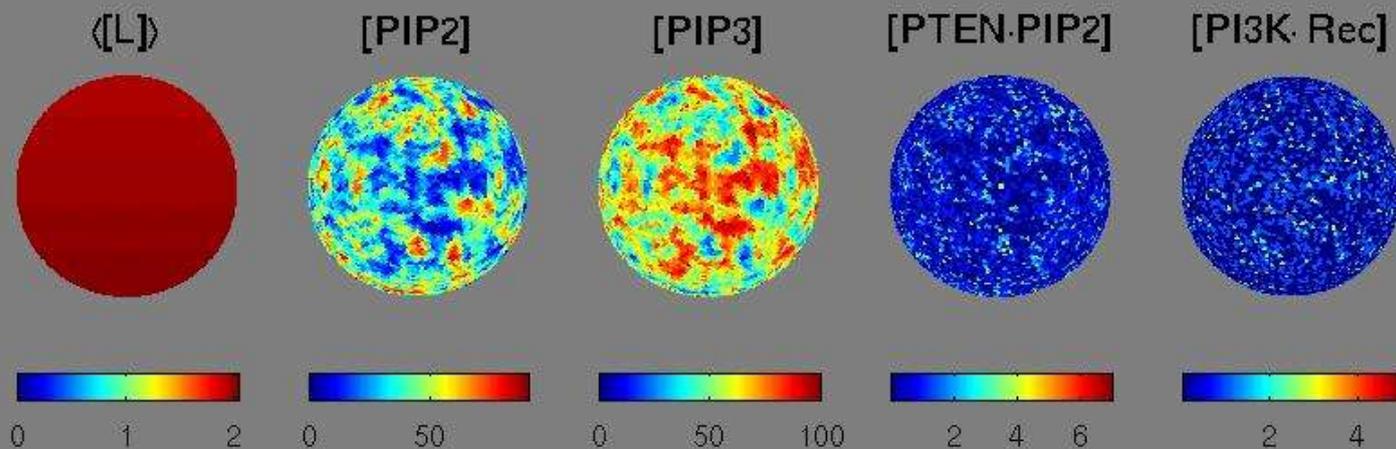
Time: 55 min
 [Rec] = 20.00 nM
 [PI3K] = 3.00 nM
 [PTEN] = 3.00 nM
 [PIP2] = 400 nM
 $D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$
 $a = -5.00\%$



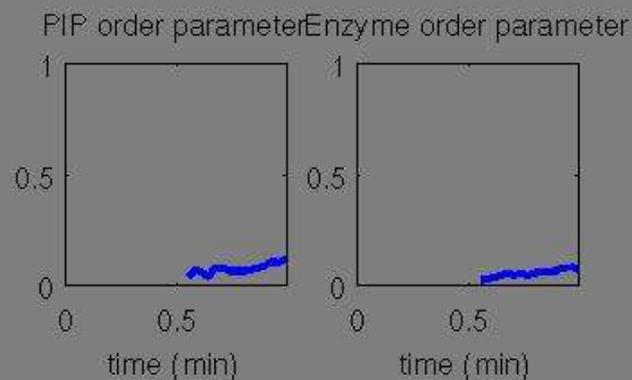
Signal amplification

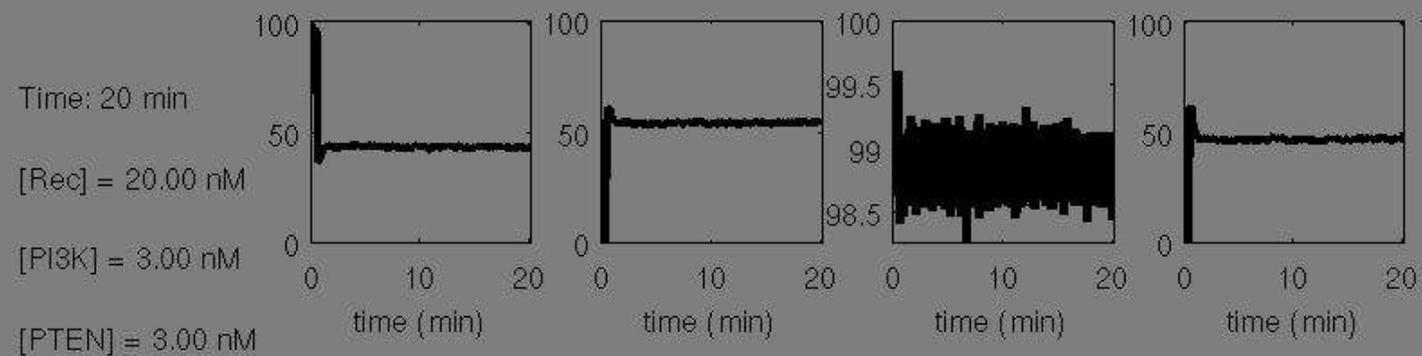
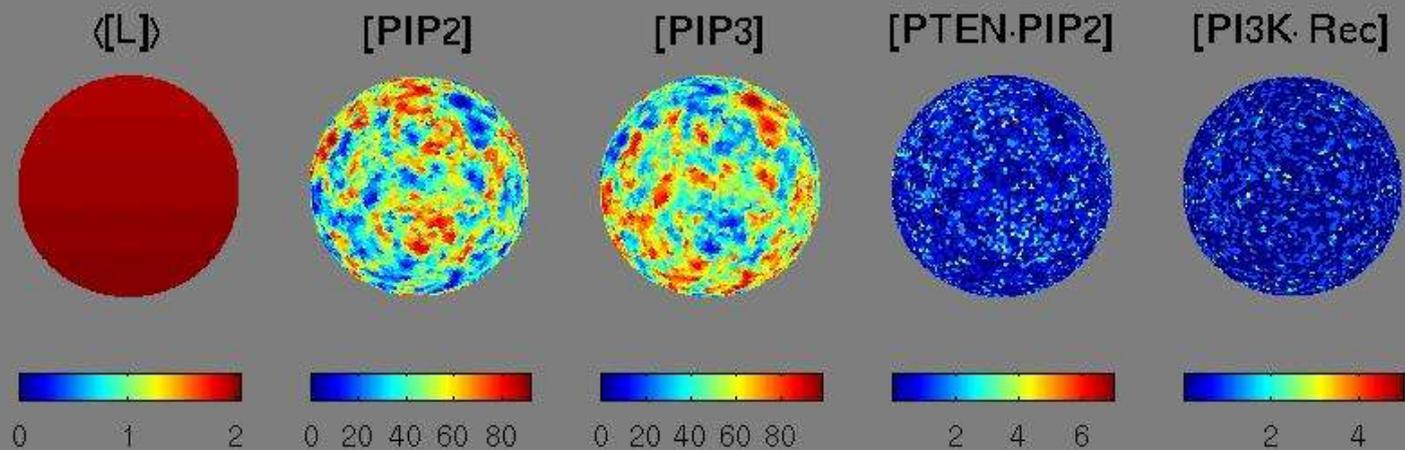


Role of diffusion

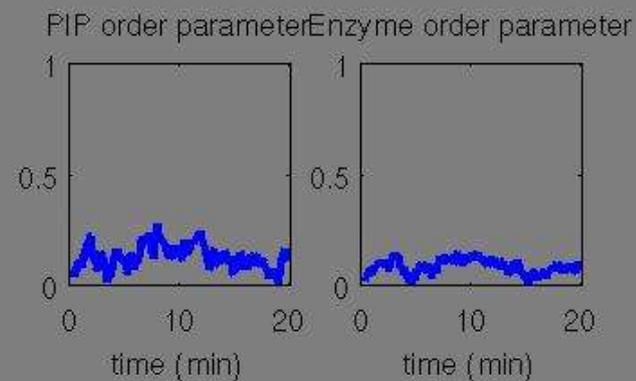


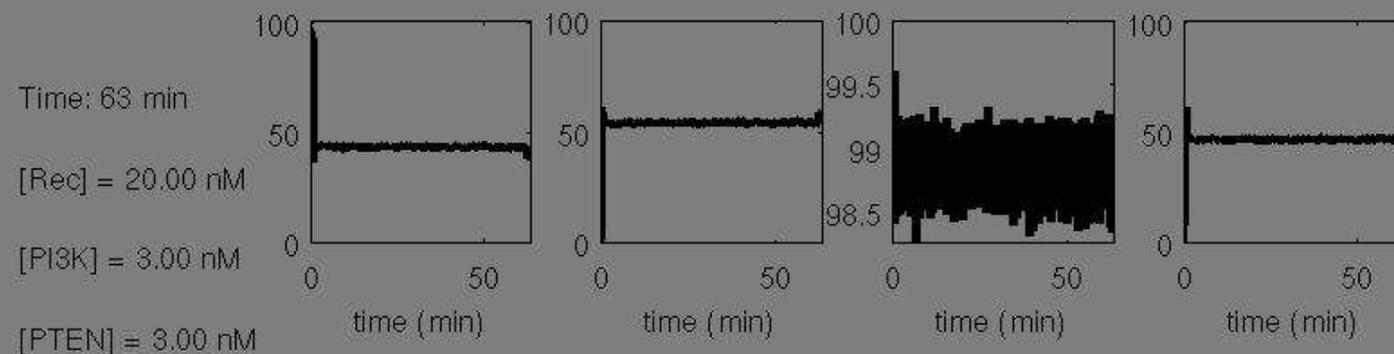
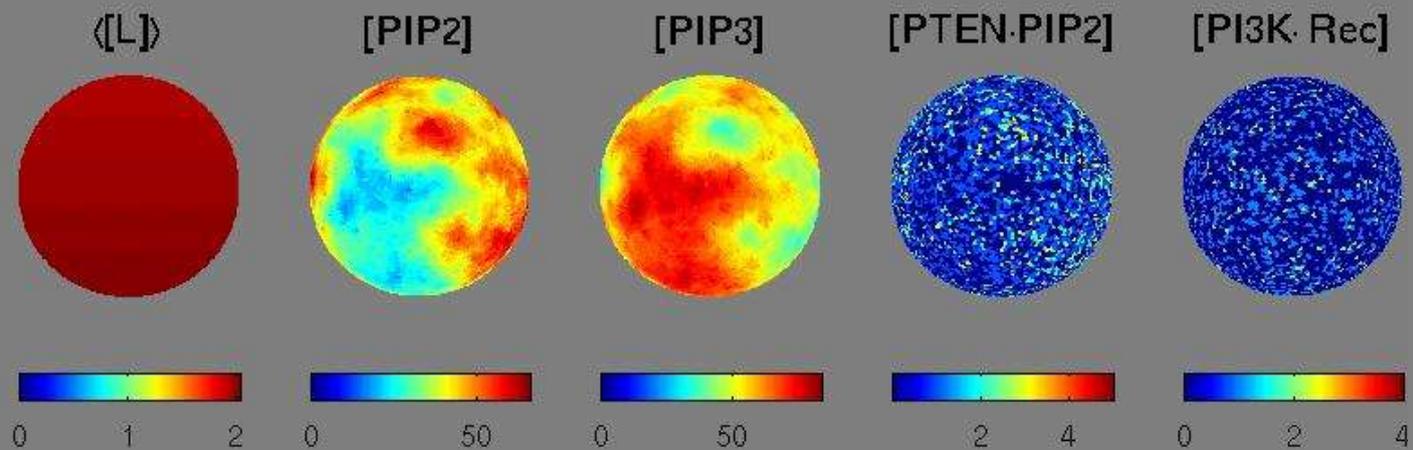
[PIP2] = 400 nM
 $D = 0.1000 \mu\text{m}^2 \text{s}^{-1}$
 $\epsilon = -5.00\%$





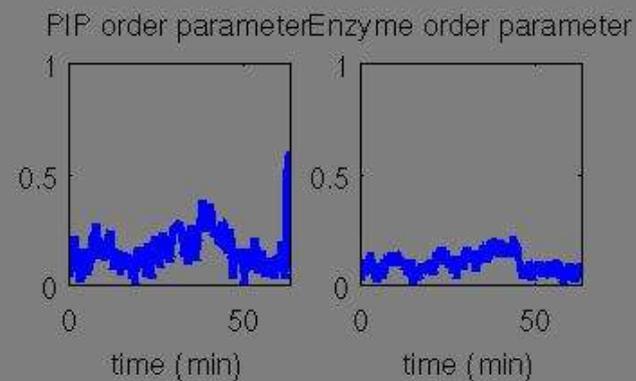
$D = 0.1000 \mu\text{m}^2 \text{s}^{-1}$
 $\epsilon = -5.00\%$

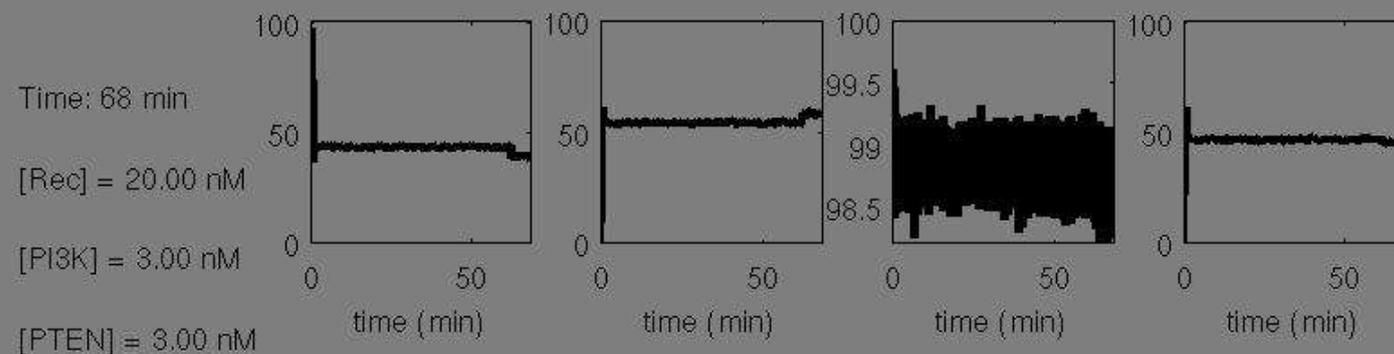
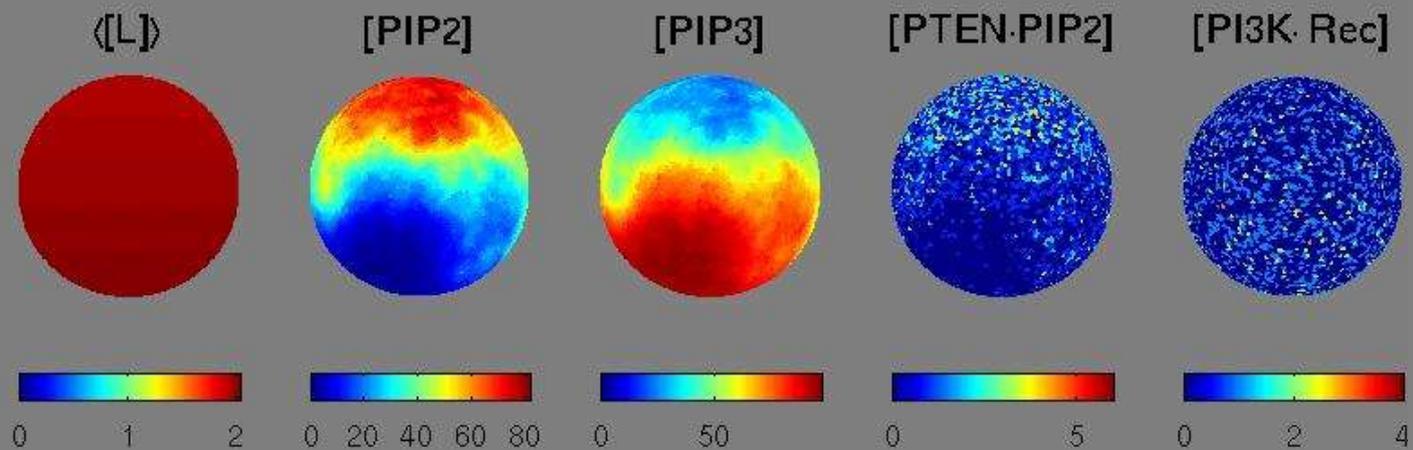




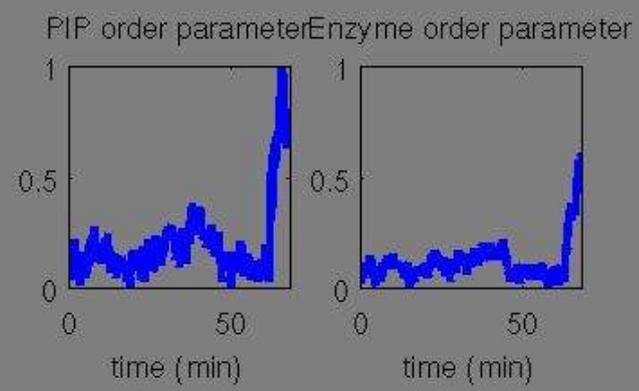
$D = 1.0000 \mu\text{m}^2 \text{s}^{-1}$

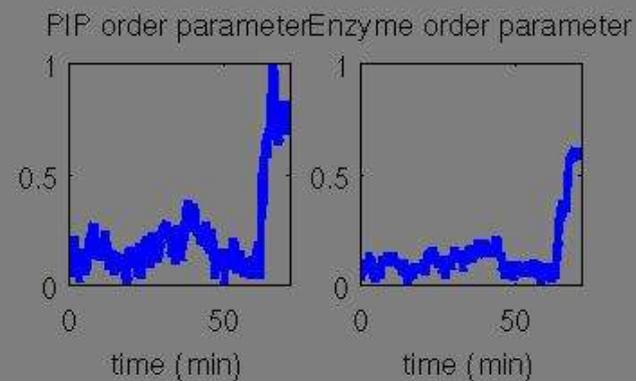
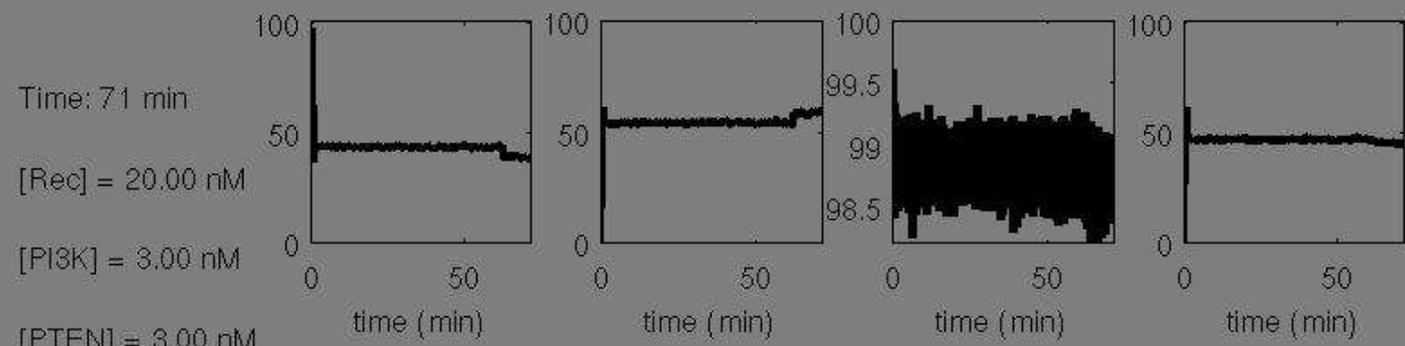
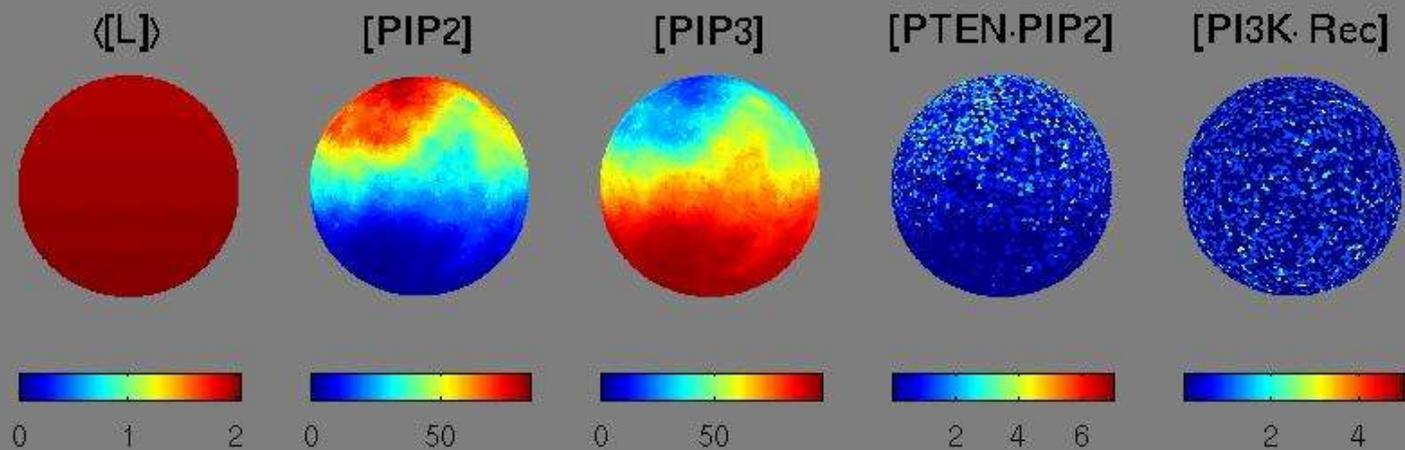
$\epsilon = -5.00\%$

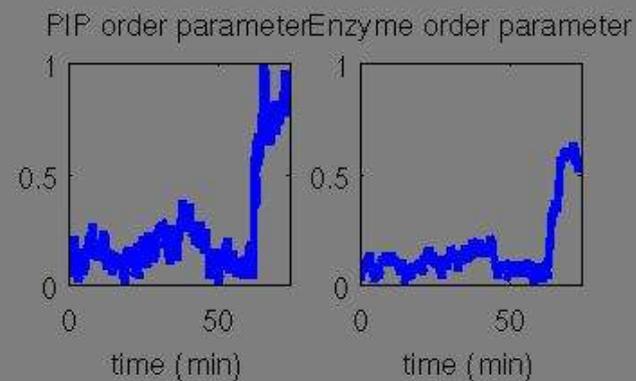
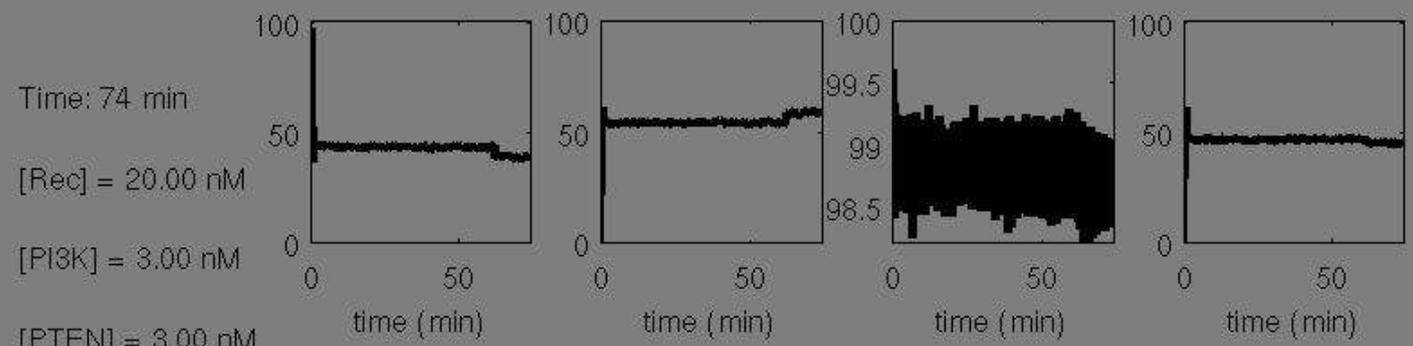
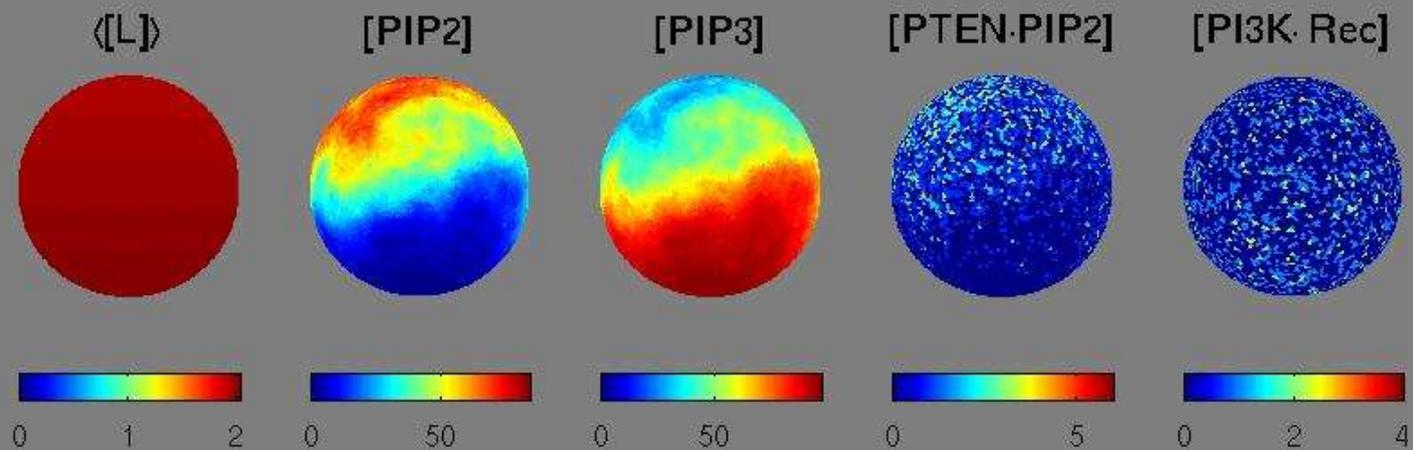


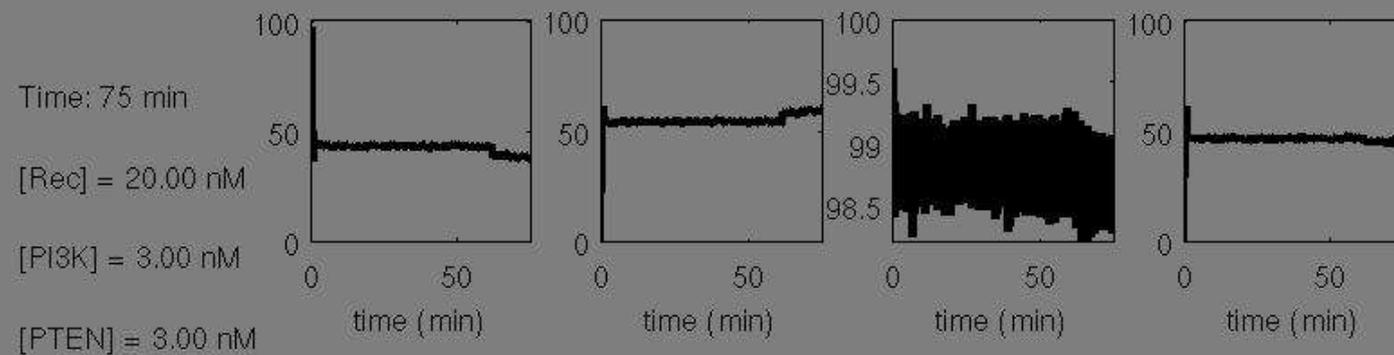
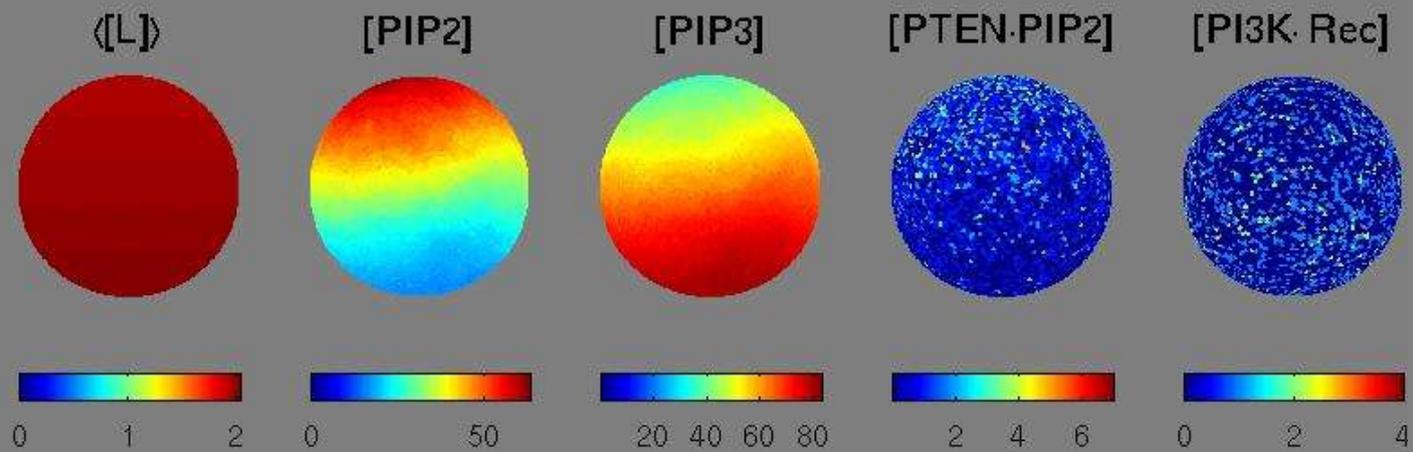


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 $\epsilon = -5.00\%$





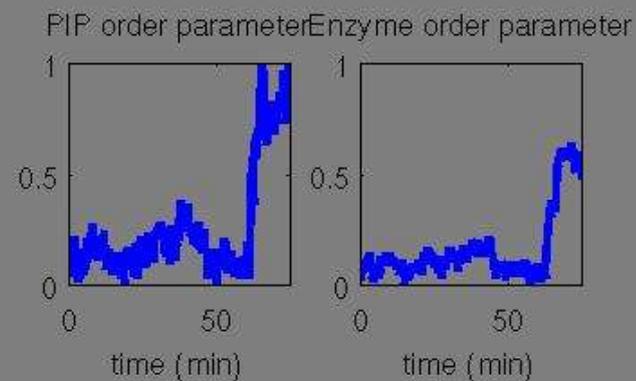


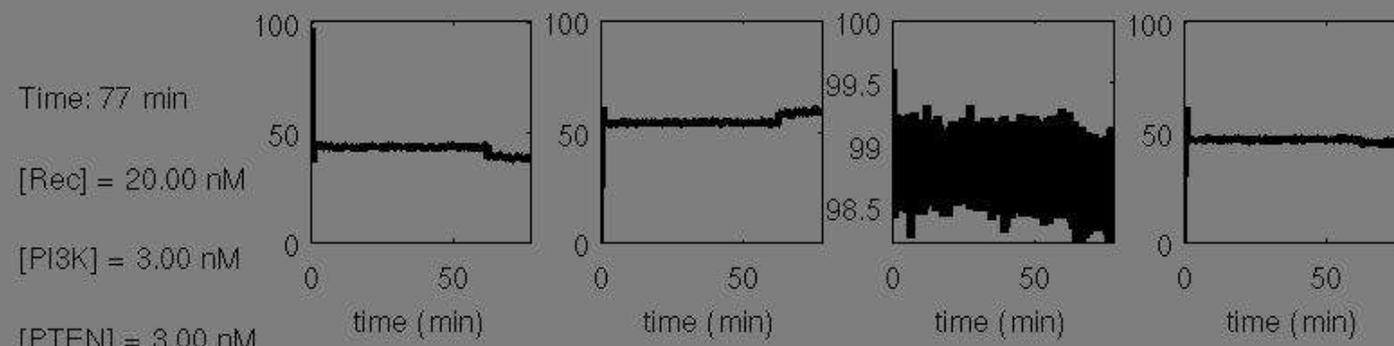
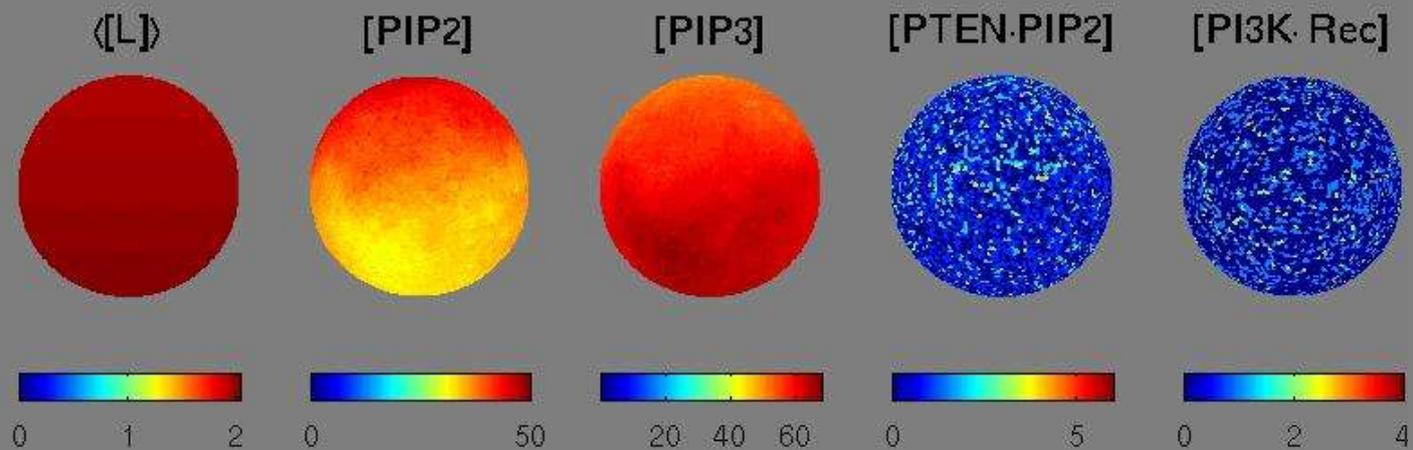


[PIP2] = 400 nM

$D = 10.0000 \mu\text{m}^2 \text{s}^{-1}$

$\epsilon = -5.00\%$

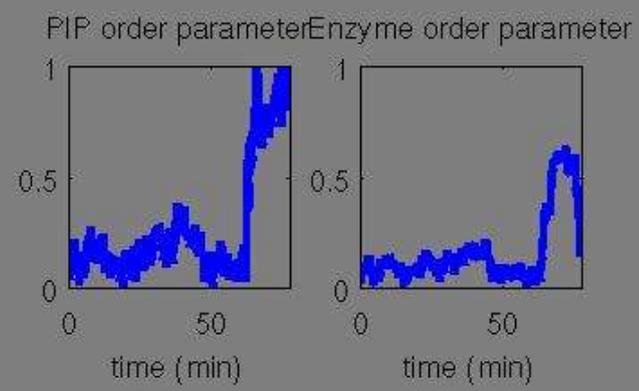


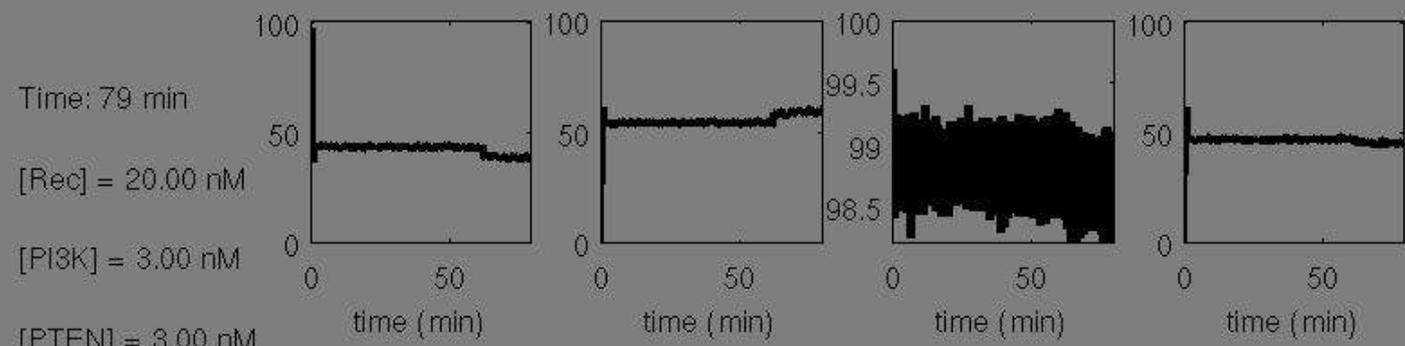
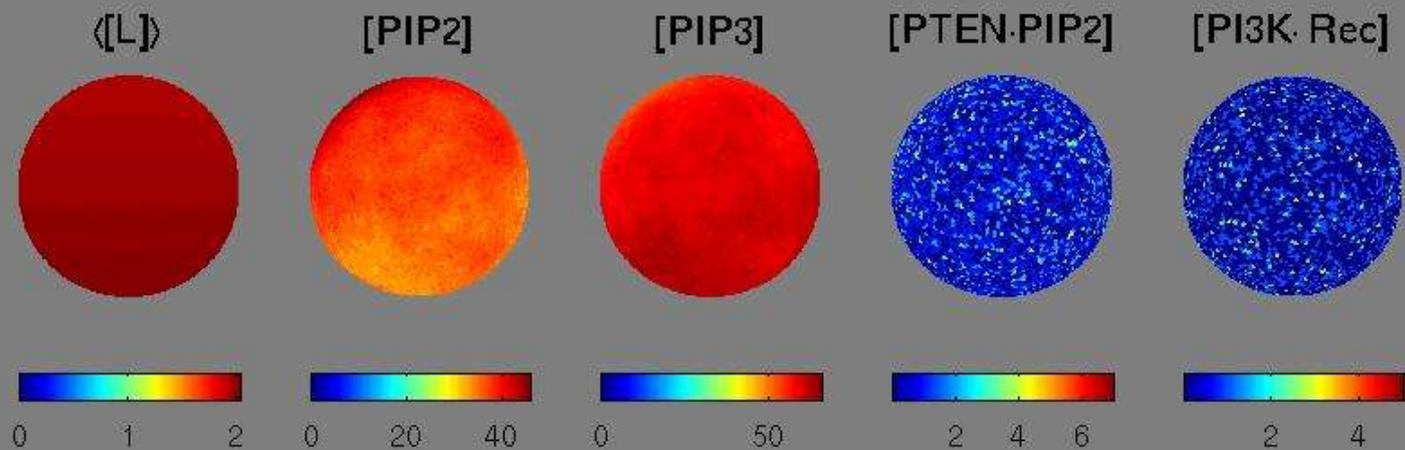


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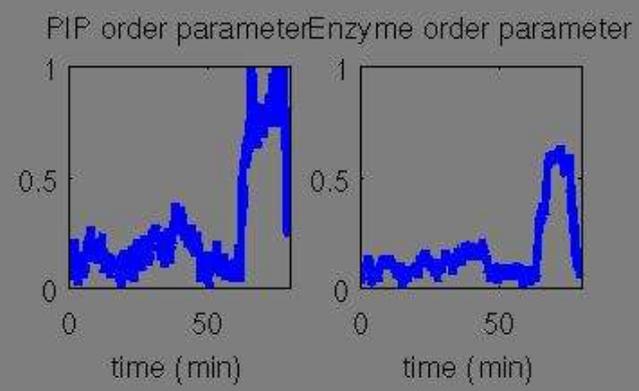
$\epsilon = -5.00\%$





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Conclusions

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It is interesting to observe that:

- The cell appears as a physical system whose behavior presents many analogies with critical phenomena taking place in the proximity of phase transitions.
- Rare, large fluctuations play a central role in the dynamics of this system
- Diffusion plays a role of mediator of an effective attractive interaction between similar enzymes

Directional sensing and phase separation in the eukaryotes

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