Strongly correlated phenomena in Quantum Field Theory, Nanophysics and Hydrodynamics

Trieste, 12-15 December 2005

Phase separation in eukaryotic chemotaxis

A. Gamba, A. de Candia, S. Di Talia, A. Coniglio,
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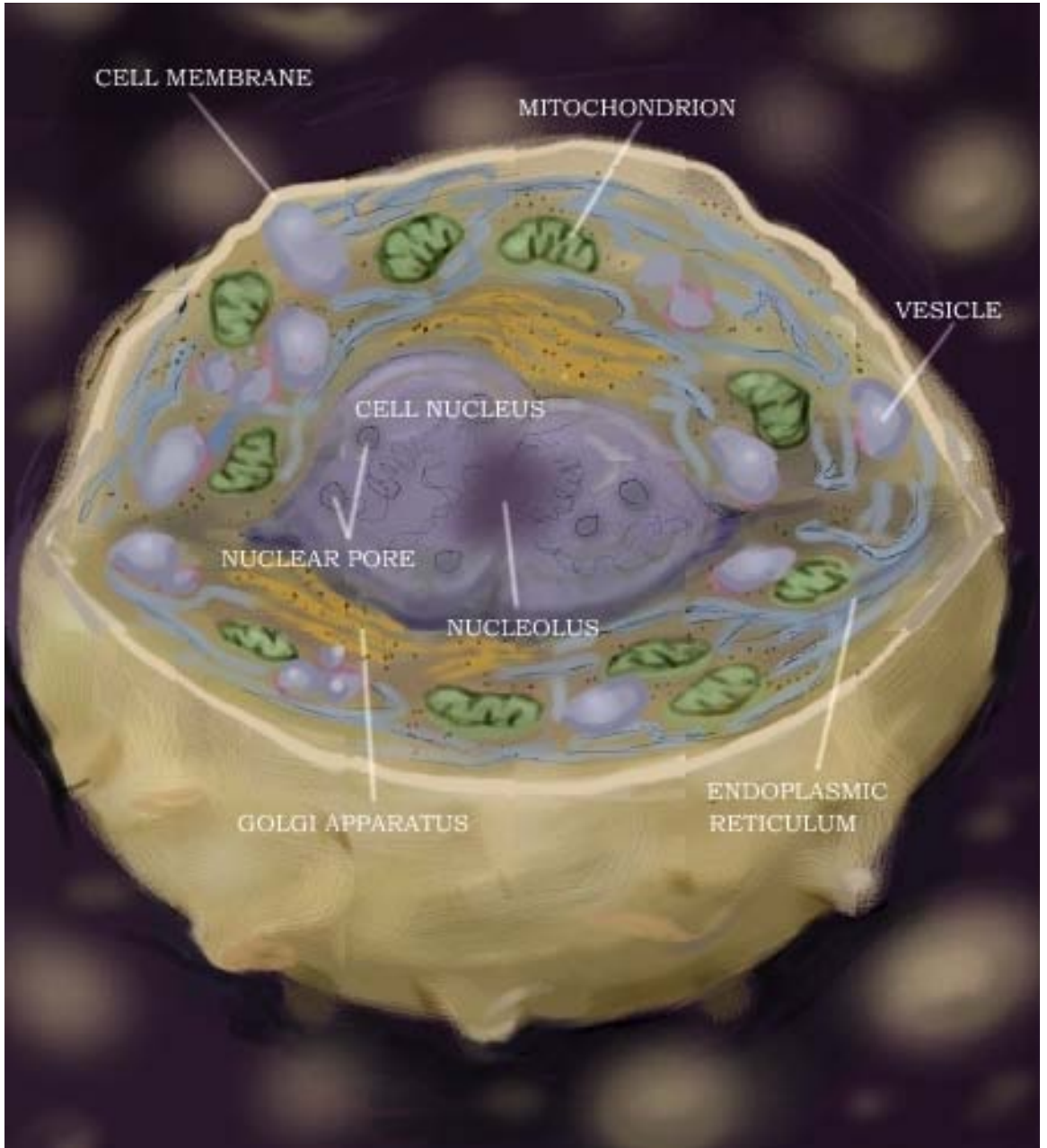
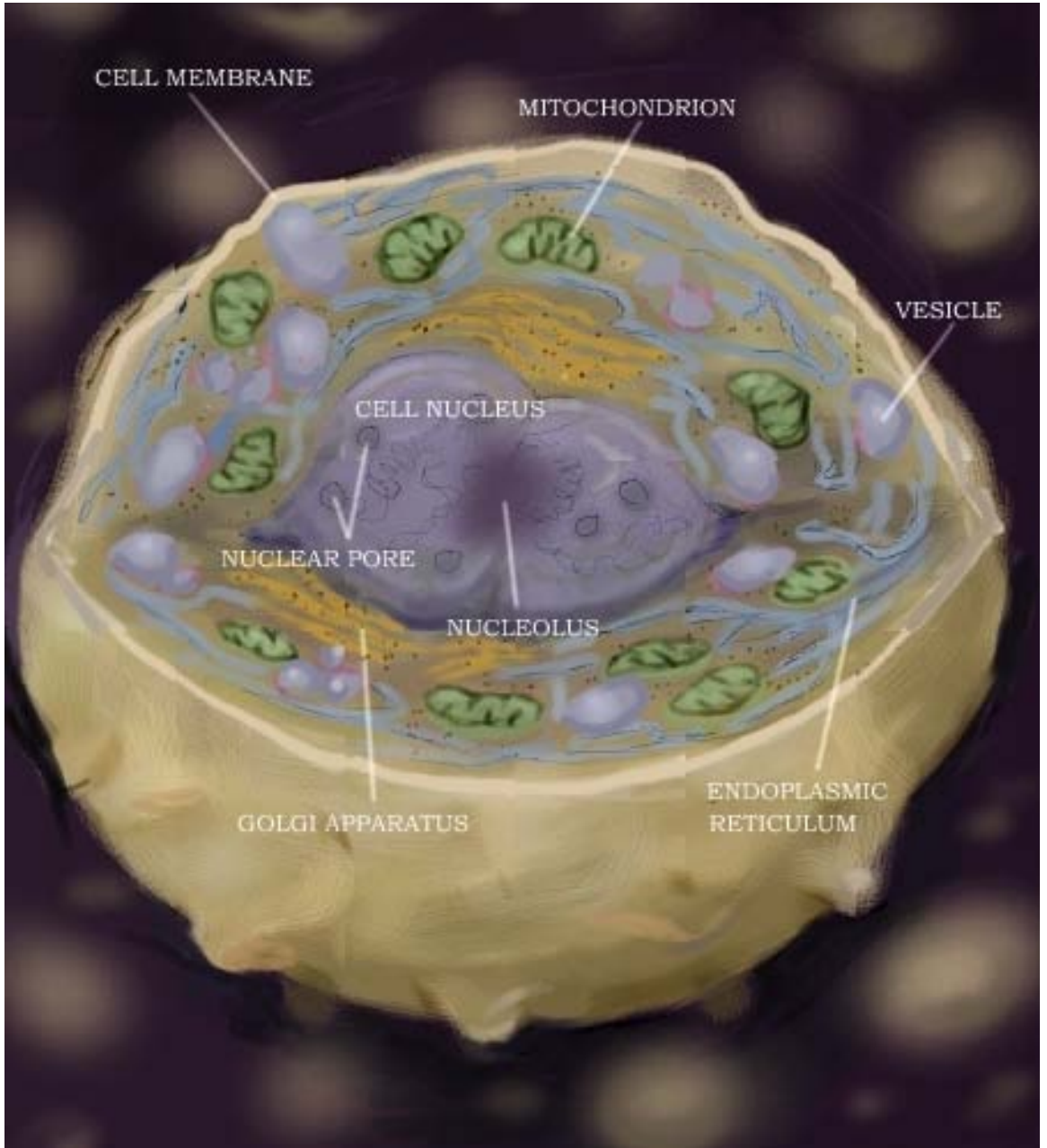
Outline

- Directional sensing and motility of eukaryotic cells
- Model reaction-diffusion system
- Phase separation instability
- Detection of slight anisotropic signals
- Monte Carlo results

Eukaryotic cells

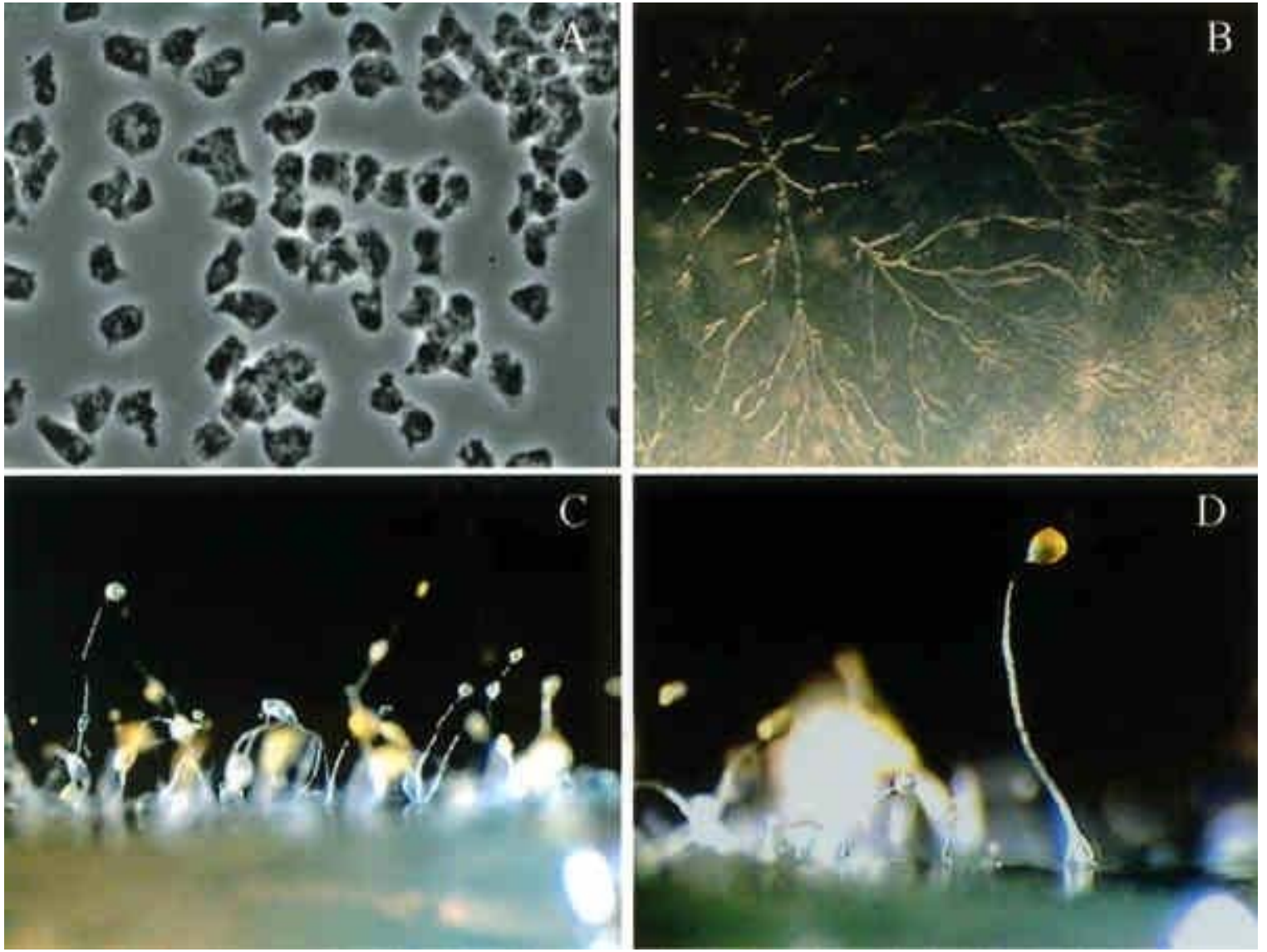


Eukaryotic cells

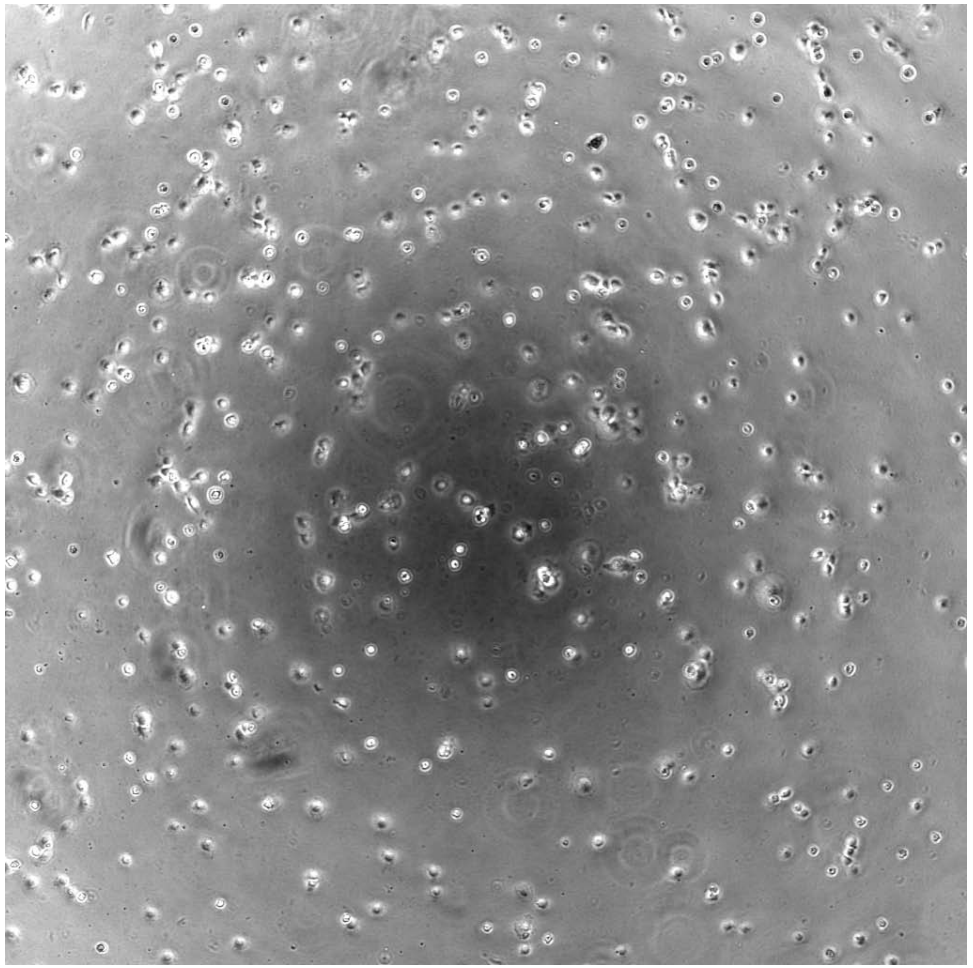


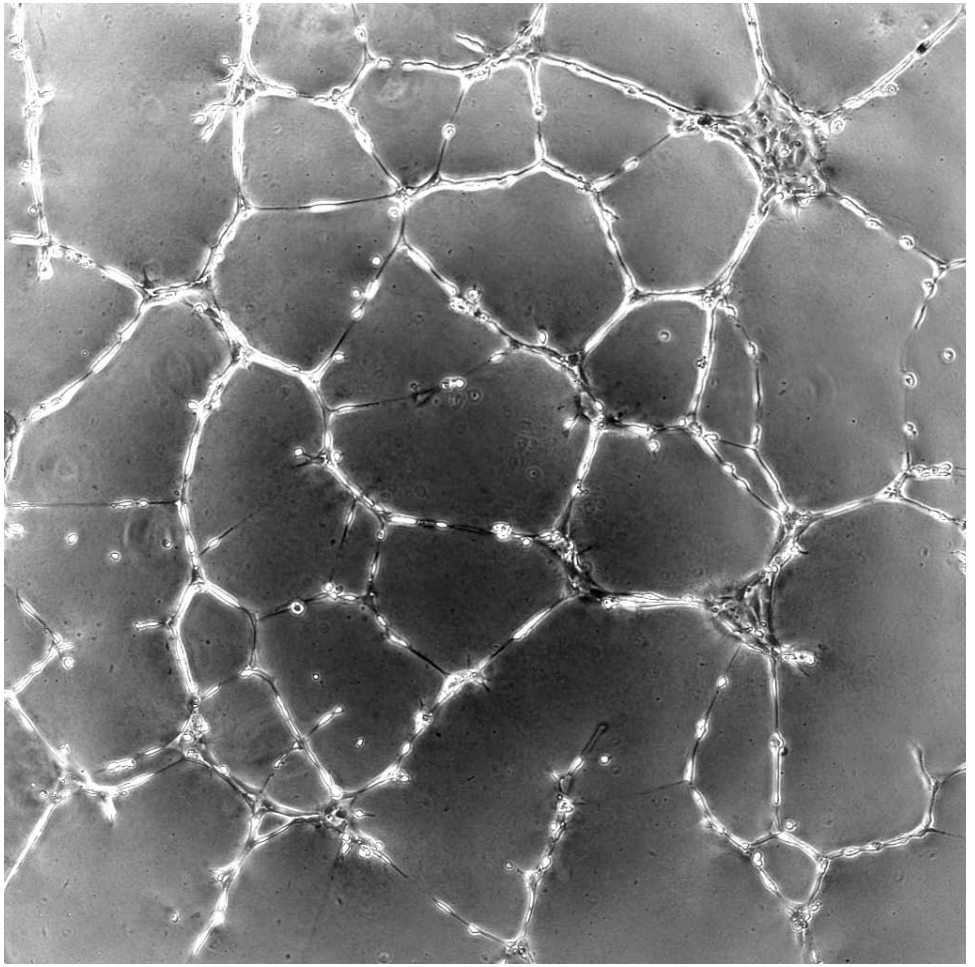
Many eukaryotic
cell types form
multicellular aggregates
by motion
directed by
chemical signals

Dictyostelium



Blood vessel formation





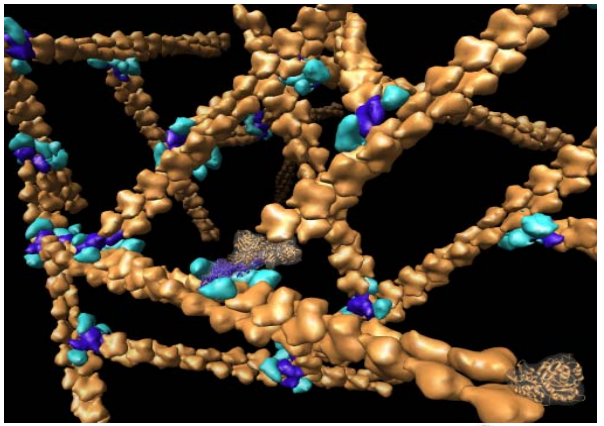
Aggregation guided by chemical signals

- Formation of tissues, in particular:
  - Blood vessels
  - Nervous system
- Healing of wounds
- Cells of the immune system navigating to sites of inflammation

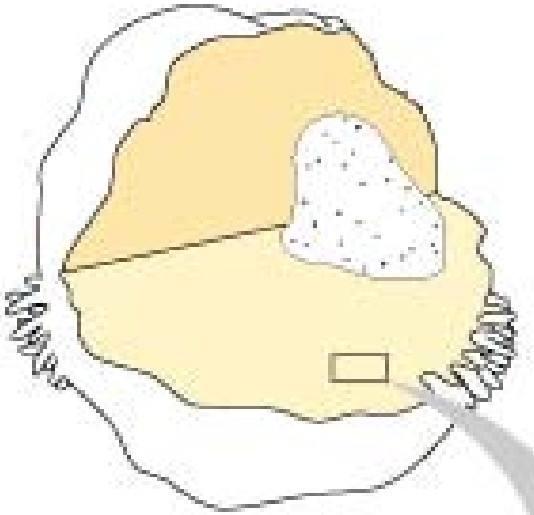
Aggregation is possible thanks to:

1. Motility
2. Sensing

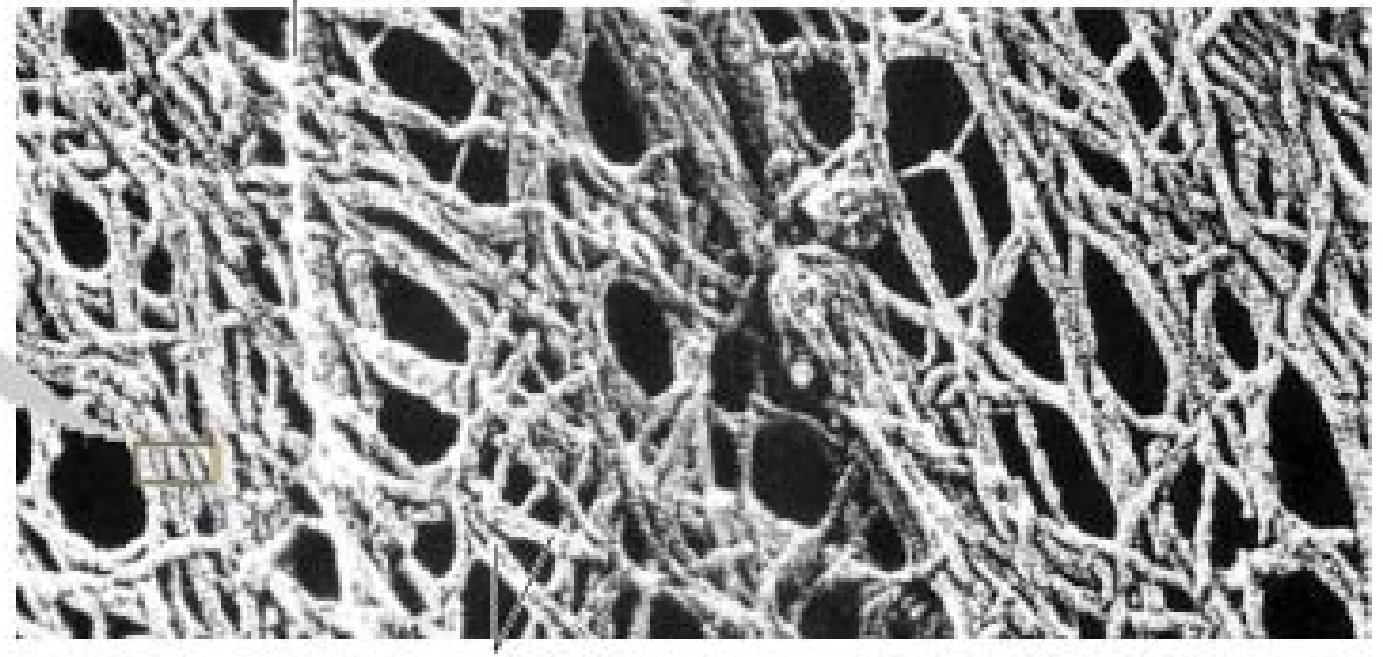
Motility



Actin filaments



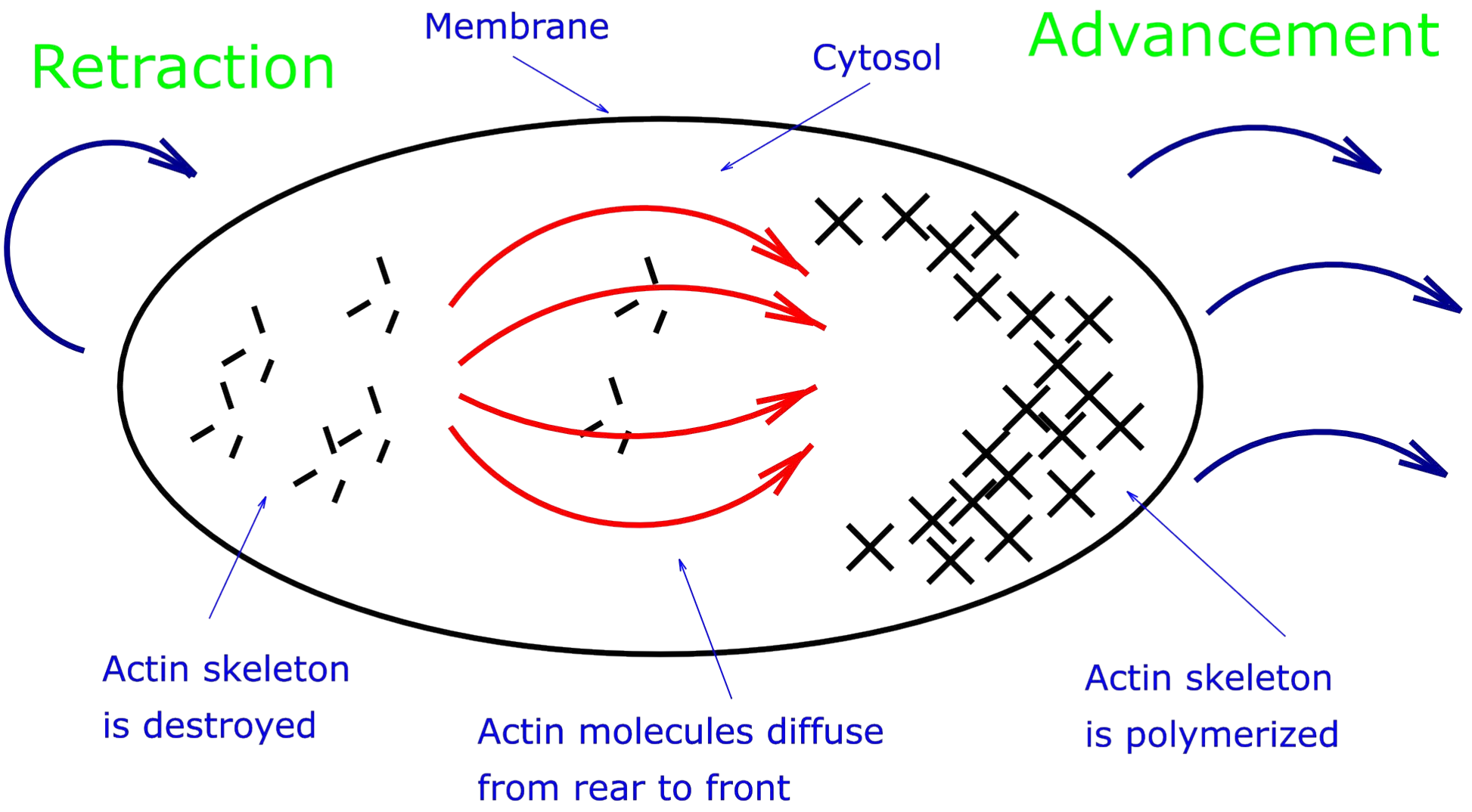
Microtubule



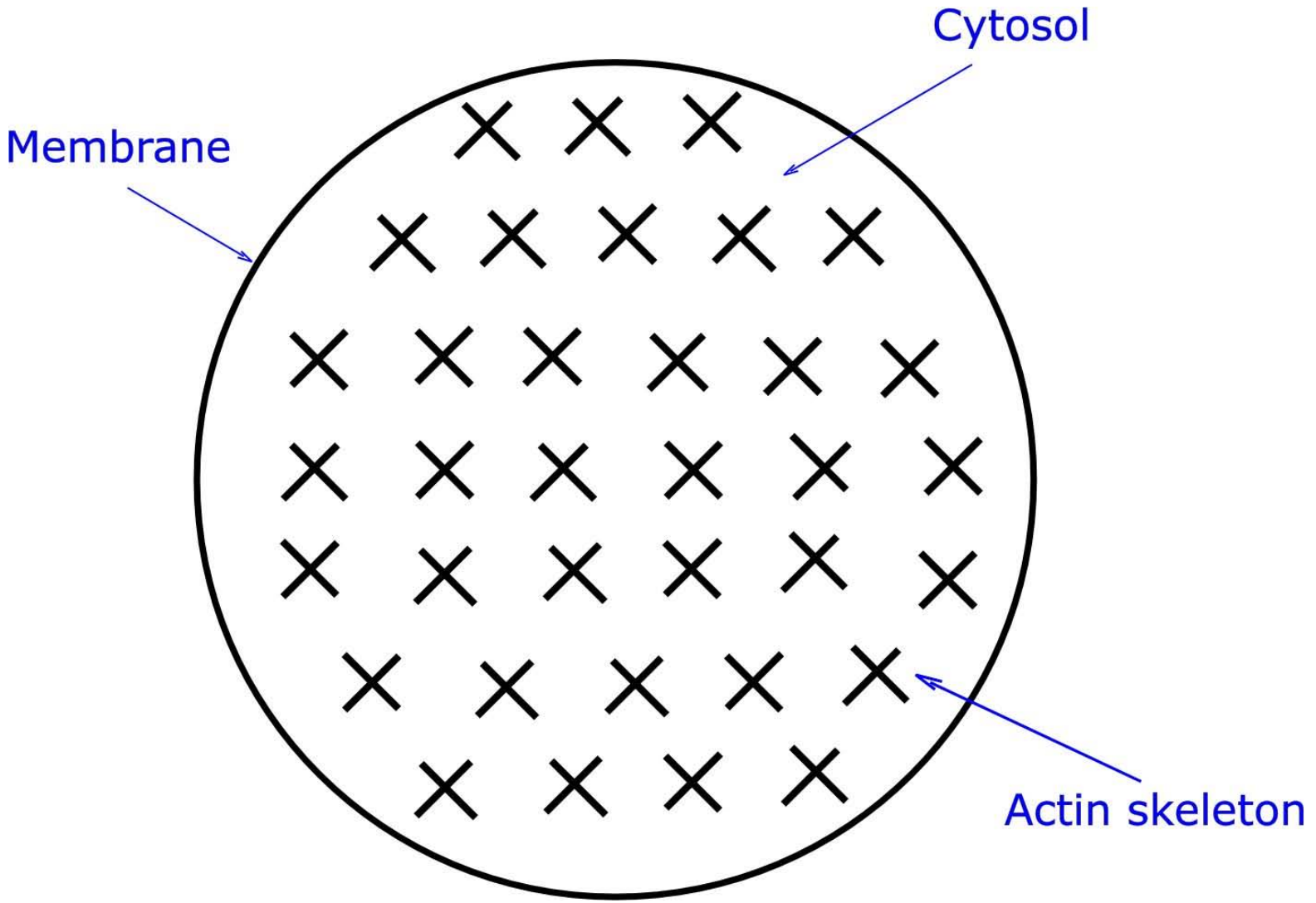
Microfilaments

0.25 µm

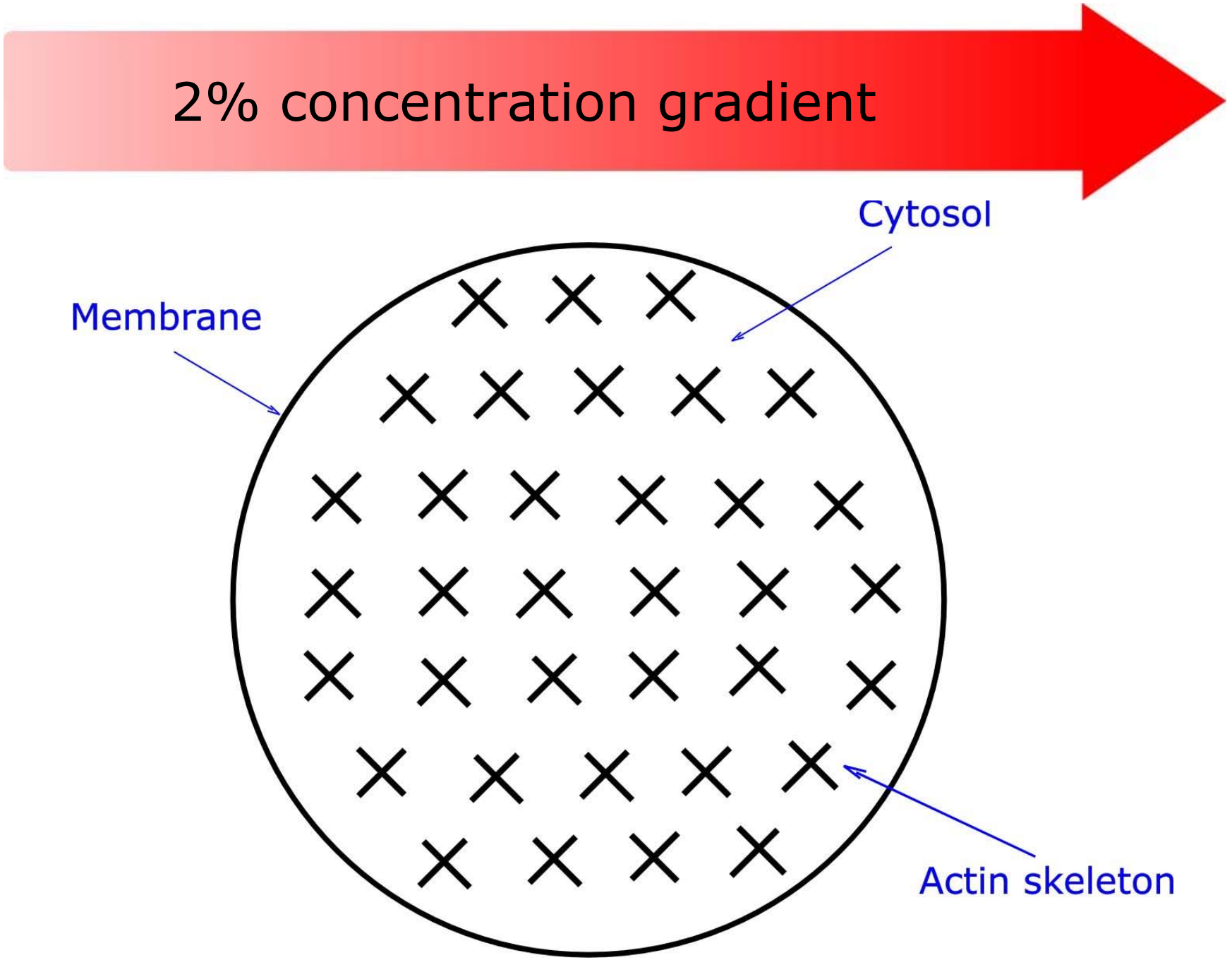
Motility


Retraction
Membrane
Cytosol
Advancement
Actin skeleton
is destroyed
Actin molecules diffuse
from rear to front
Actin skeleton
is polymerized

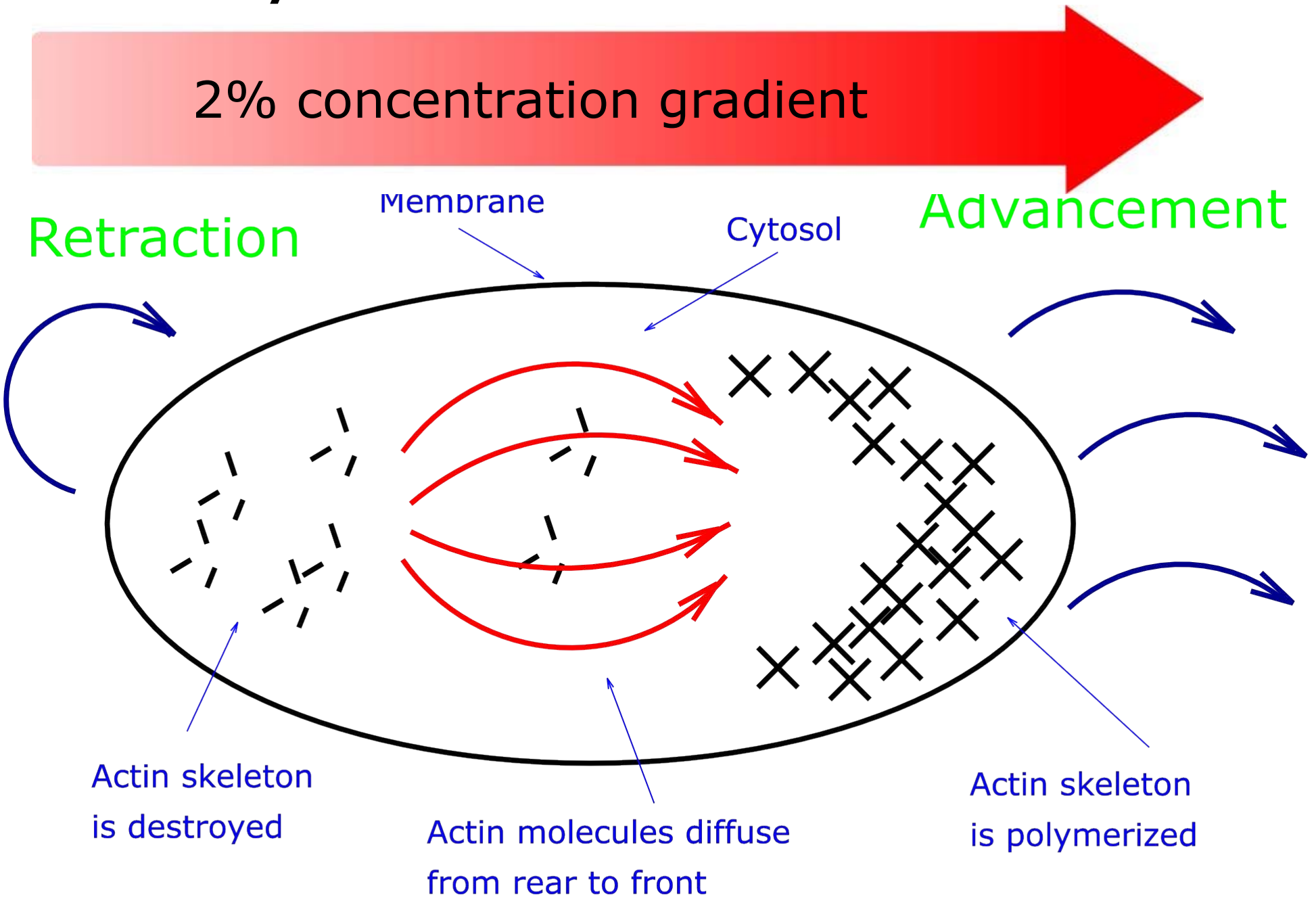
Quiescent cell



Sensing


2% concentration gradient
Cytosol
Membrane
Actin skeleton

Motility


2% concentration gradient
Retraction
Membrane
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Actin skeleton
is destroyed
Actin molecules diffuse
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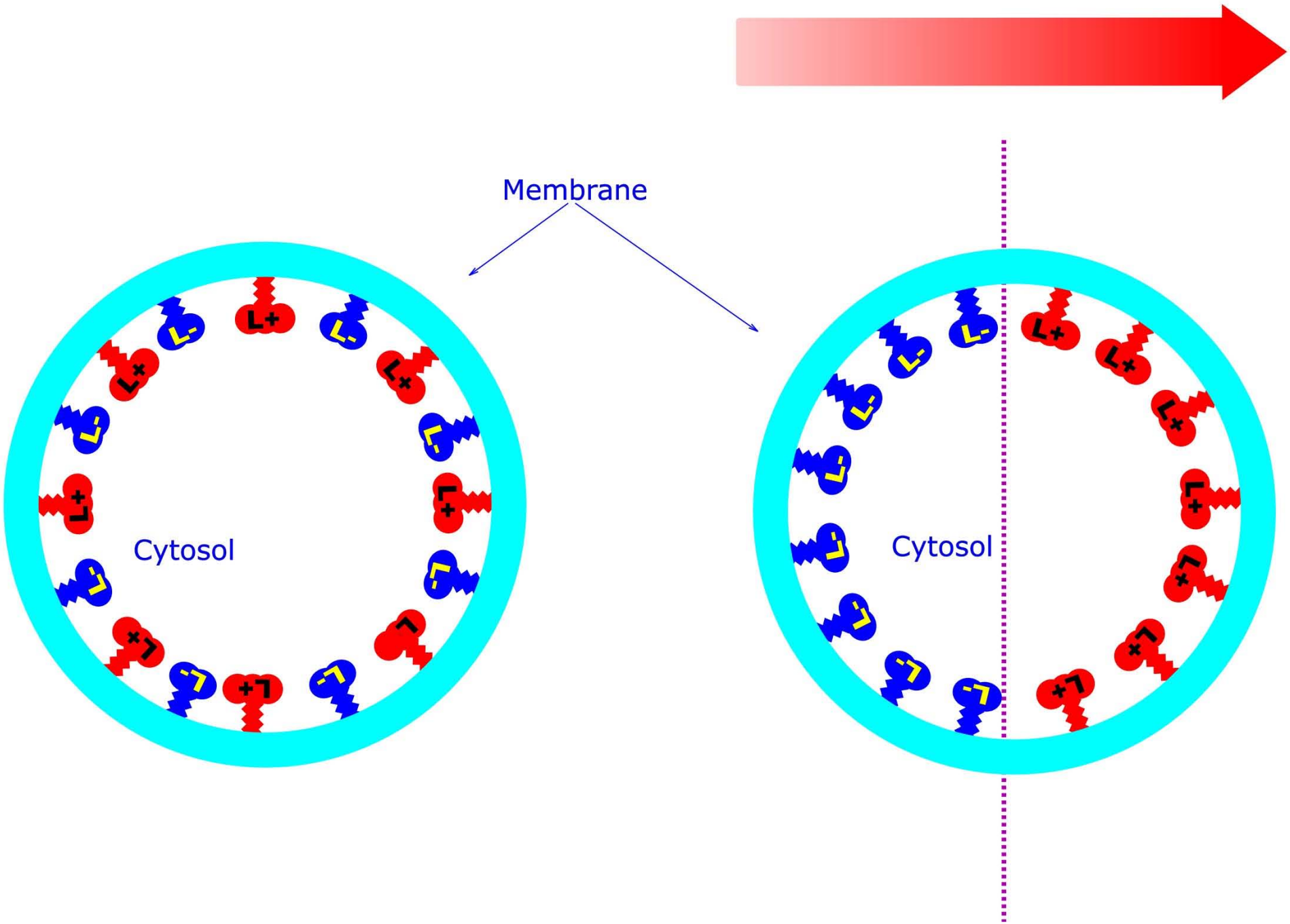
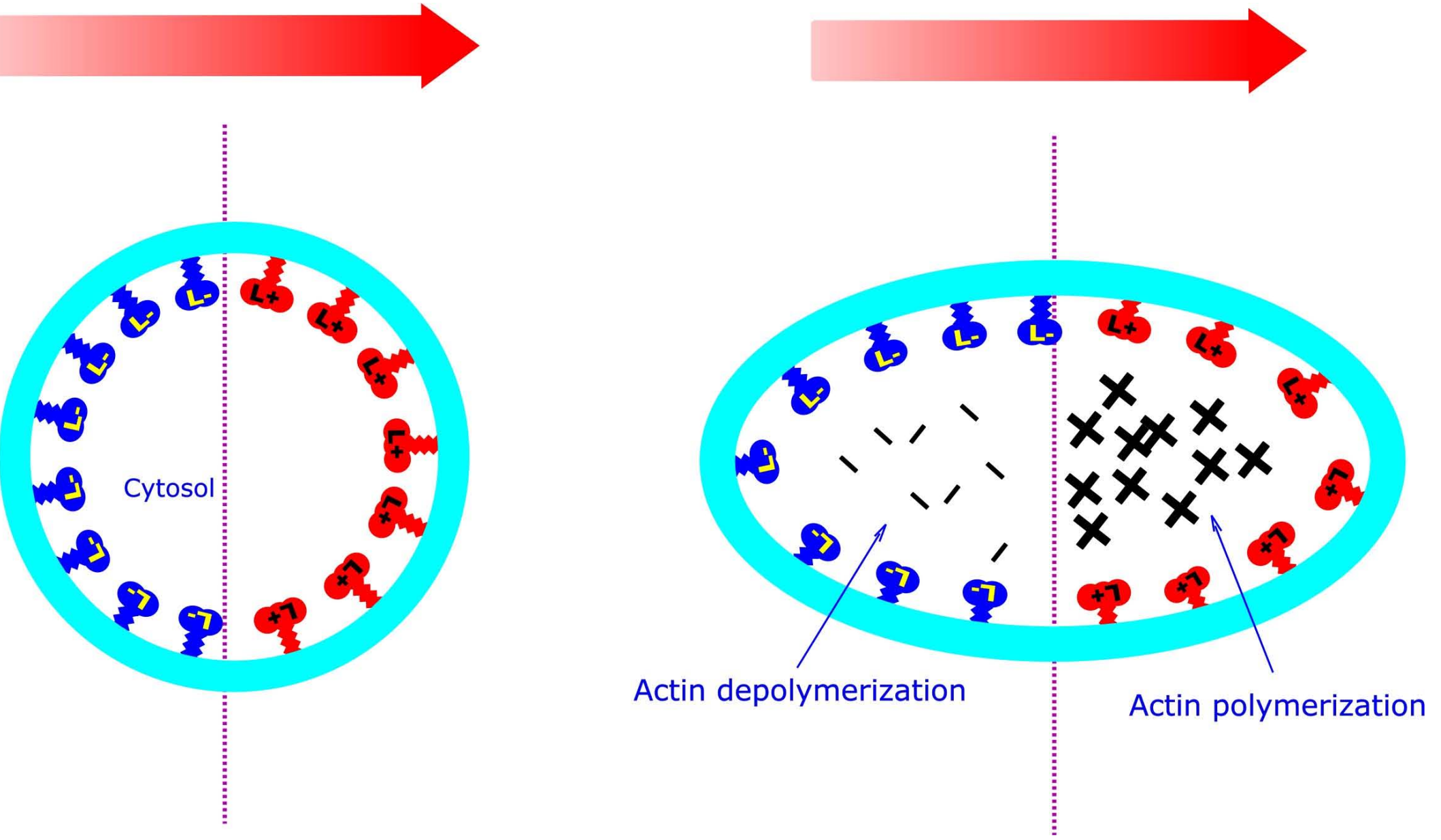
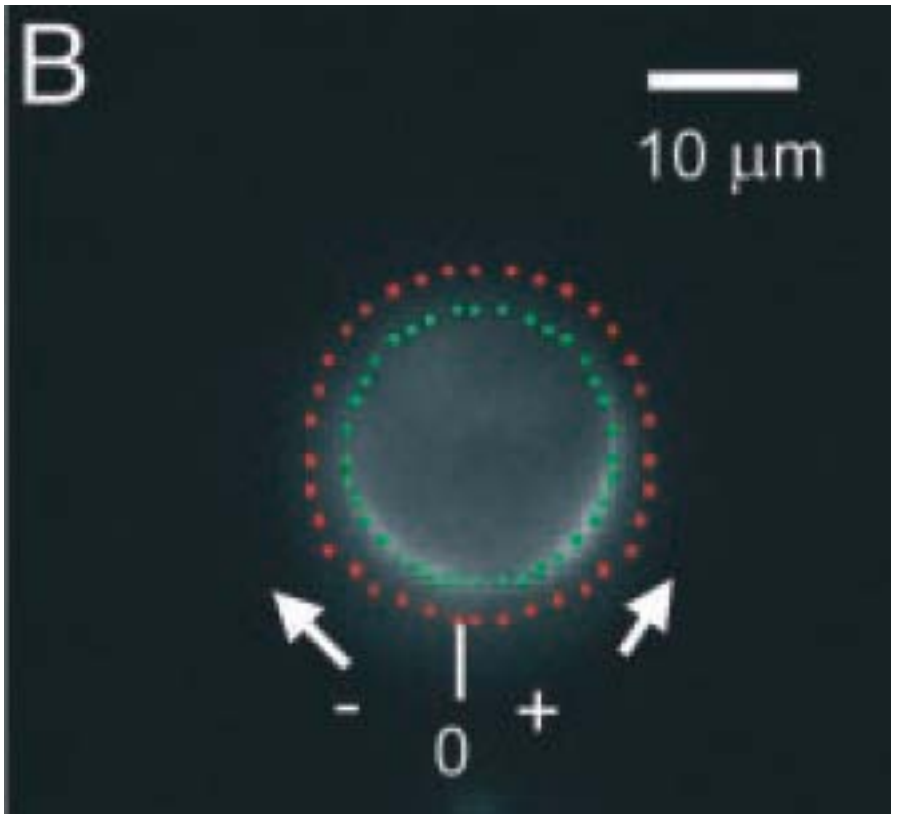


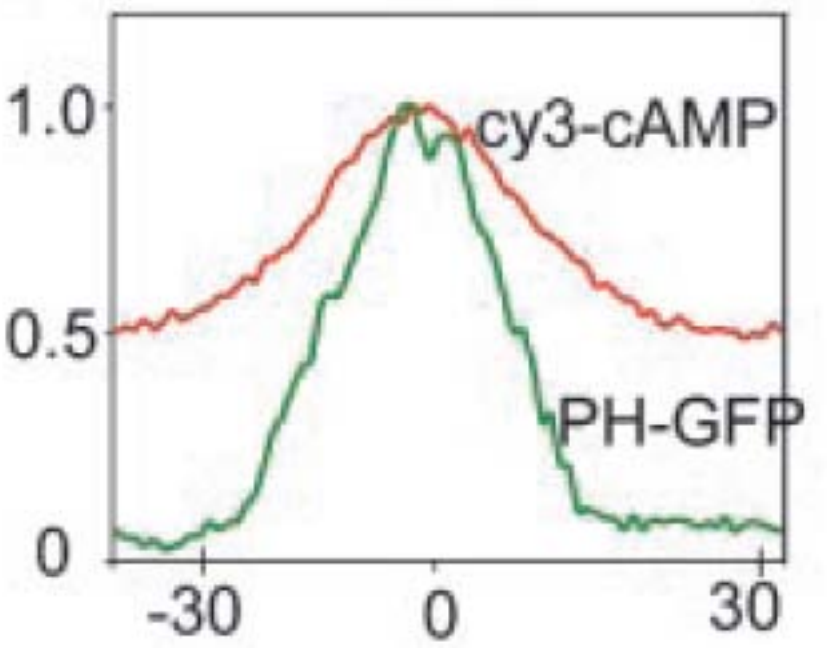
Uniform stimulation

(slightly) anisotropic stimulation

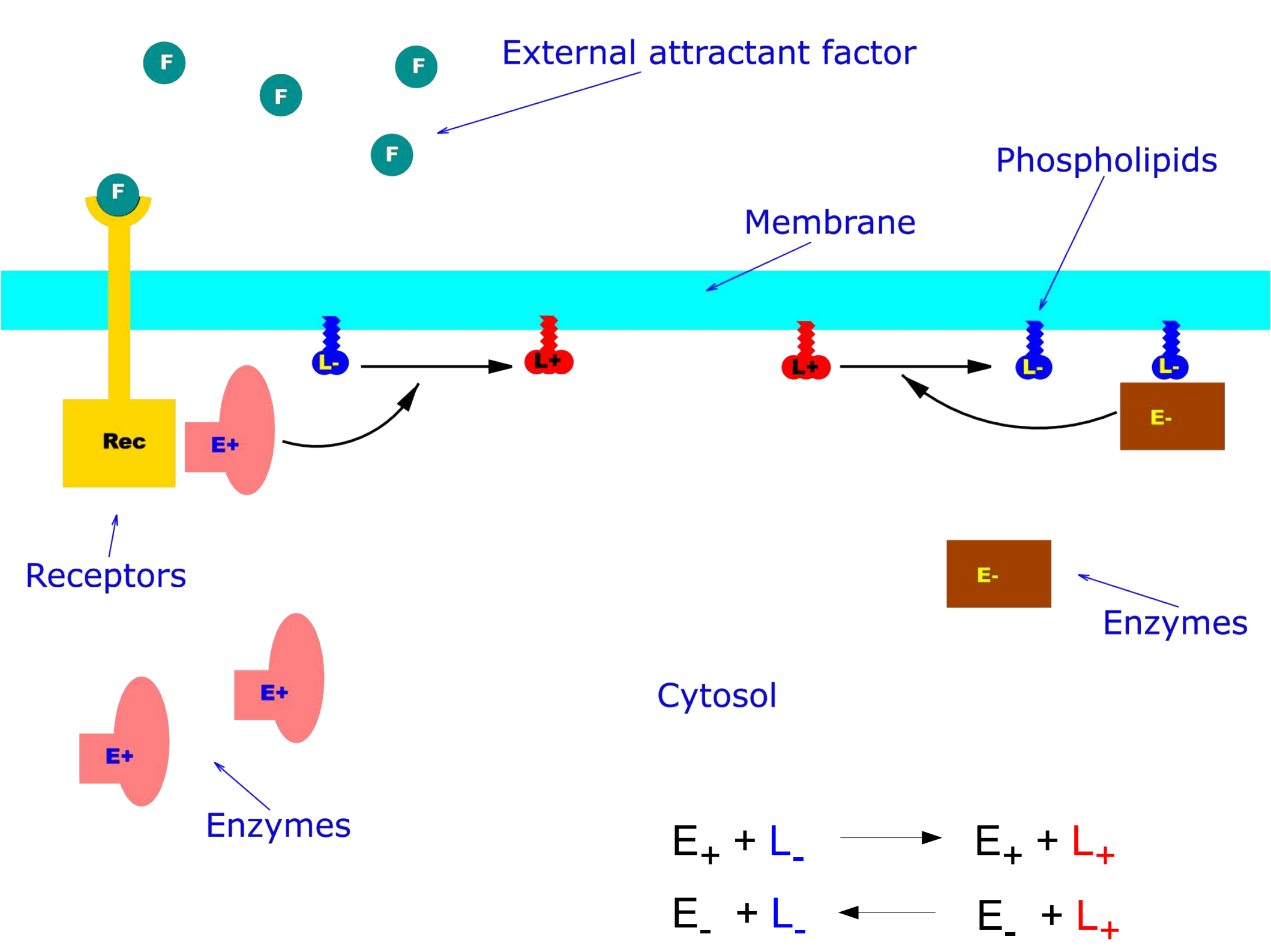

Cytosol
Actin depolymerization
Actin polymerization

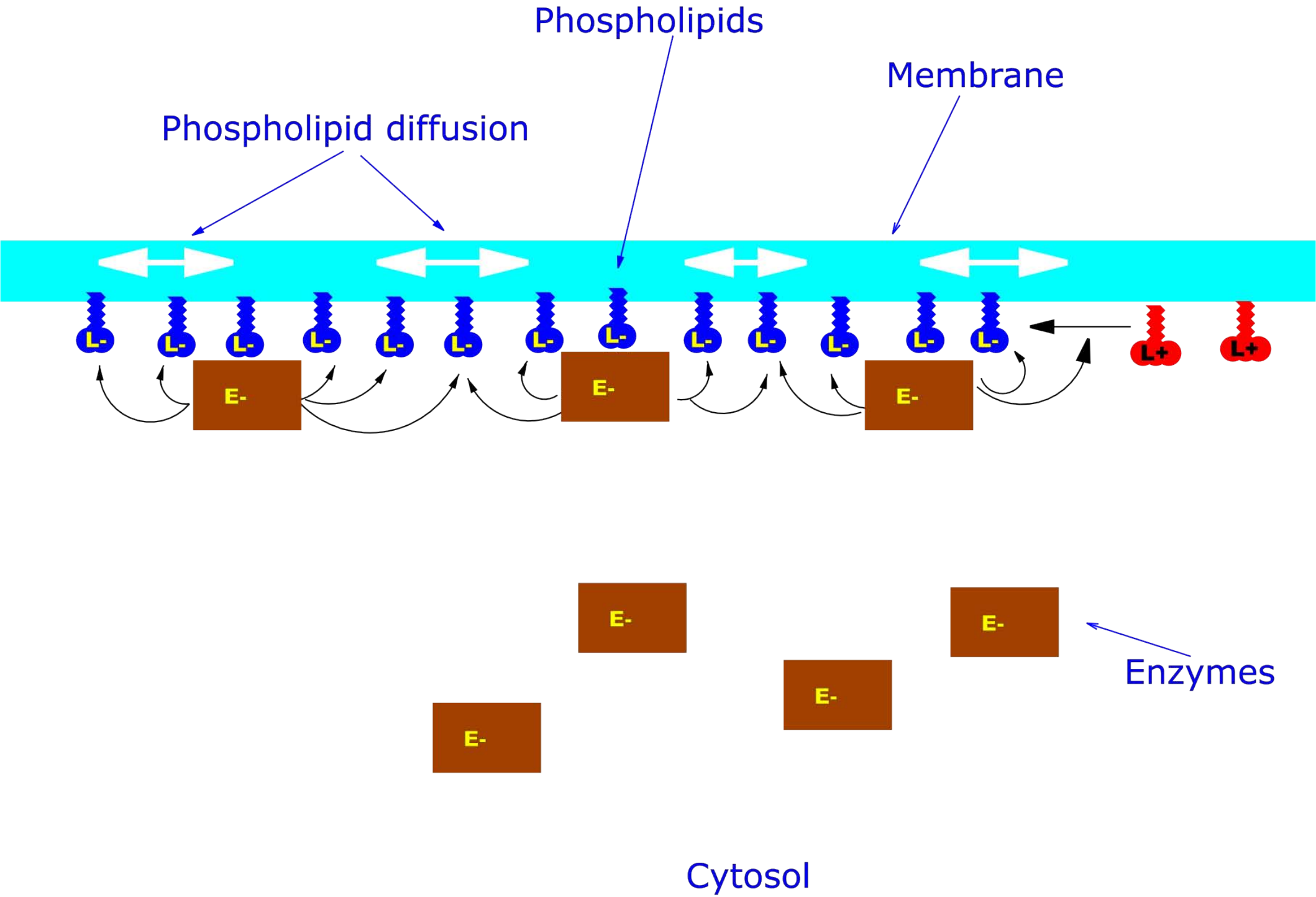
Devreotes, Janetopoulos. J. Biol. Chem. **278** (2003) 20445





Janetopoulos, Ma, Devreotes, Iglesias, PNAS **101** (2004) 8951


F
F
F
F
External attractant factor
F
Phospholipids
Membrane
L-
L+
L+
L-
L-
Rec
E+
E-
Receptors
E-
Enzymes
E+
E+
Cytosol
Enzymes
$E_+ + L_- \rightarrow E_+ + L_+$
$E_- + L_- \leftarrow E_- + L_+$


Phospholipids
Membrane
Phospholipid diffusion
L-
L+
E-
Enzymes
Cytosol

Association processes:

$$\mathrm{A} + \mathrm{B} \;\rightarrow\; \mathrm{A}\cdot\mathrm{B}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{A}\cdot\mathrm{B}] \;=\; k_{\mathrm{ass}}[\mathrm{A}][\mathrm{B}] - k_{\mathrm{diss}}[\mathrm{A}\cdot\mathrm{B}]$$

Product of constituent concentration

Association rate

Dissociation rate

Catalytic processes:

$$\mathrm{E} + \mathrm{A} \;\rightarrow\; \mathrm{E} + \mathrm{B}$$

(actually $\mathrm{E} + \mathrm{A} \;\rightarrow\; \mathrm{E}\cdot\mathrm{A} \;\rightarrow\; \mathrm{E} + \mathrm{B}$)

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{B}] \;=\; k_{\mathrm{cat}}\,\frac{[\mathrm{E}][\mathrm{A}]}{K + [\mathrm{A}]}$$

Michaelis-Menten constant

$$\varphi = [\mathrm{L}_+] - [\mathrm{L}_-]$$

$$c_0 = [\mathrm{L}_+] + [\mathrm{L}_-]$$

Activated receptors

Total number of E- enzymes bound to the membrane

$$\partial_t \varphi = D\nabla^2\varphi + \alpha \frac{c_0 - \varphi}{2K + (c_0 - \varphi)} - \beta \frac{c_0^2 - \varphi^2}{2K + (c_0 + \varphi)}$$

Total number of E- enzymes in the cell

$$\partial_t \beta = -\left(\frac{k_{\mathrm{ass}}}{2V}\int_S (c_0 - \varphi)\mathrm{d}\sigma + k_{\mathrm{diss}}\right)\beta + \frac{N k_{\mathrm{ass}}}{2V k_{\mathrm{cat}}}$$

Cell volume

Cell surface

$$\varphi = [\mathrm{L}_+] - [\mathrm{L}_-]$$

$$c_0 = [\mathrm{L}_+] + [\mathrm{L}_-]$$

Effective potential, depending on the number of activated receptors and the total number of available enzymes

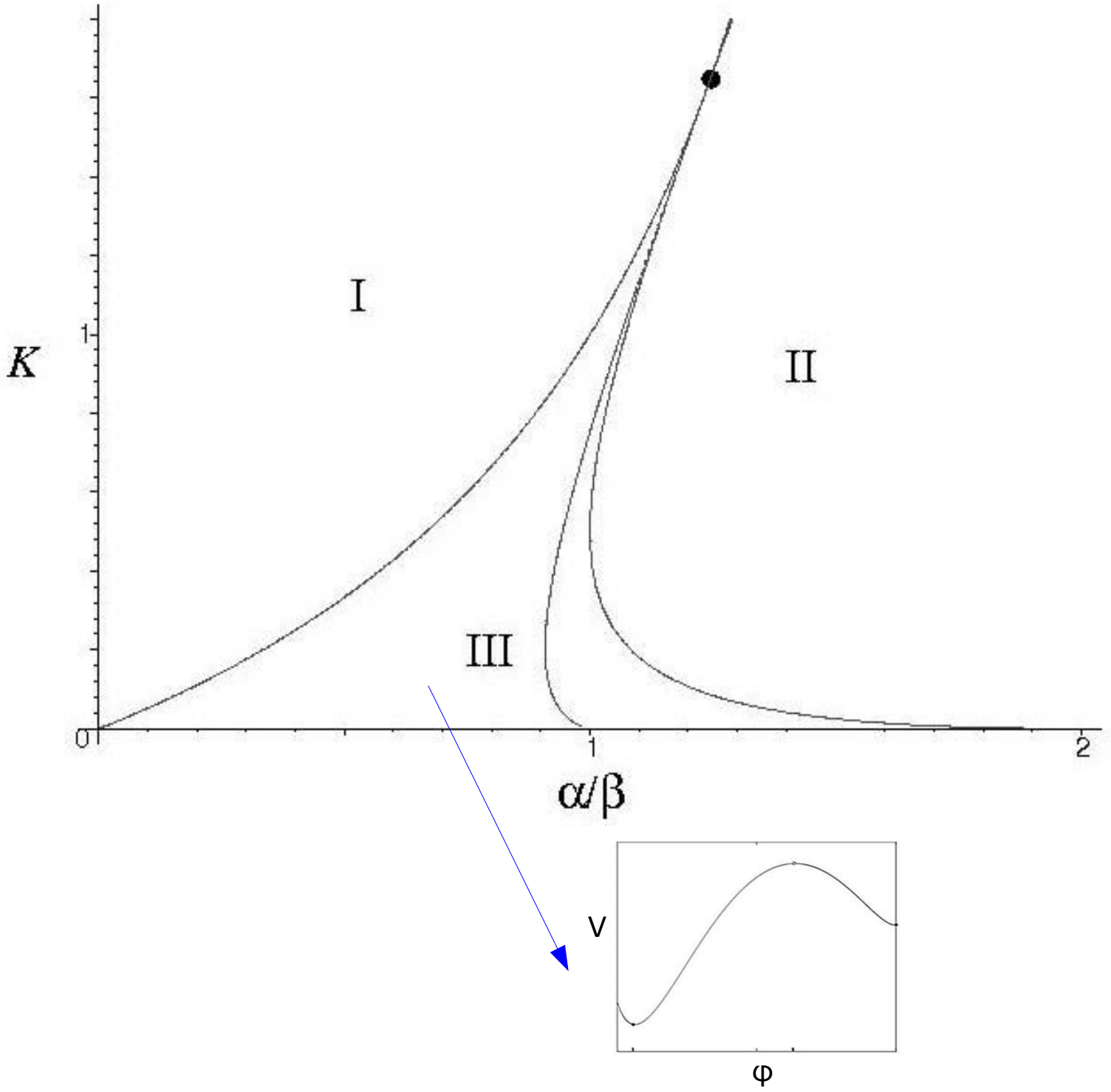
$$\partial_t \varphi = D_2 \nabla^2 \varphi - \frac{\partial V_{\alpha,\beta}}{\partial \varphi}(\varphi)$$

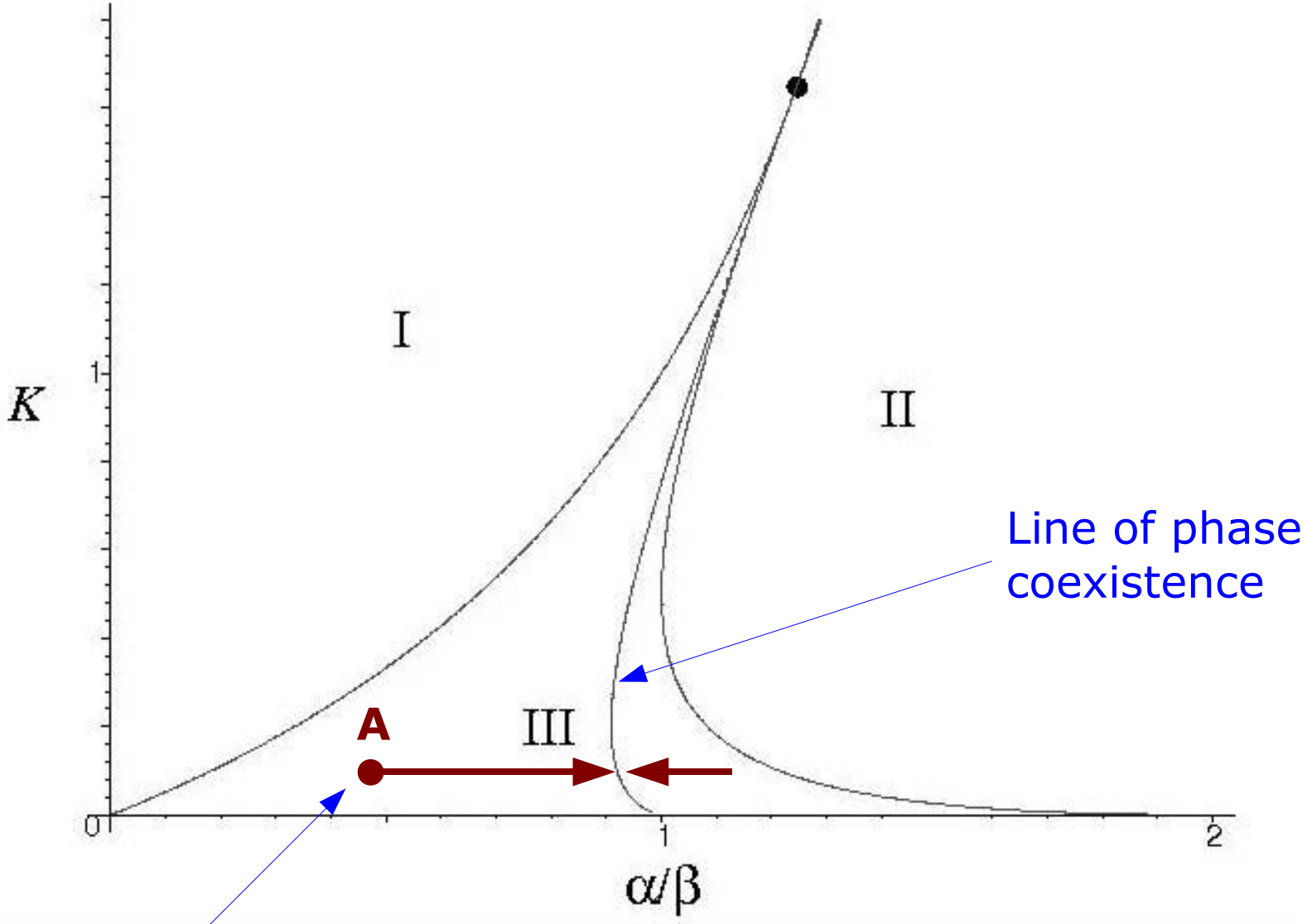
Total number of E- enzymes in the cell

$$\partial_t \beta = -\left(\frac{k_{\mathrm{ass}}}{2V} \int_S (c_0 - \varphi) \mathrm{d}\sigma + k_{\mathrm{diss}} \right) \beta + \frac{N k_{\mathrm{ass}}}{2V k_{\mathrm{cat}}}$$

Cell volume

Cell surface

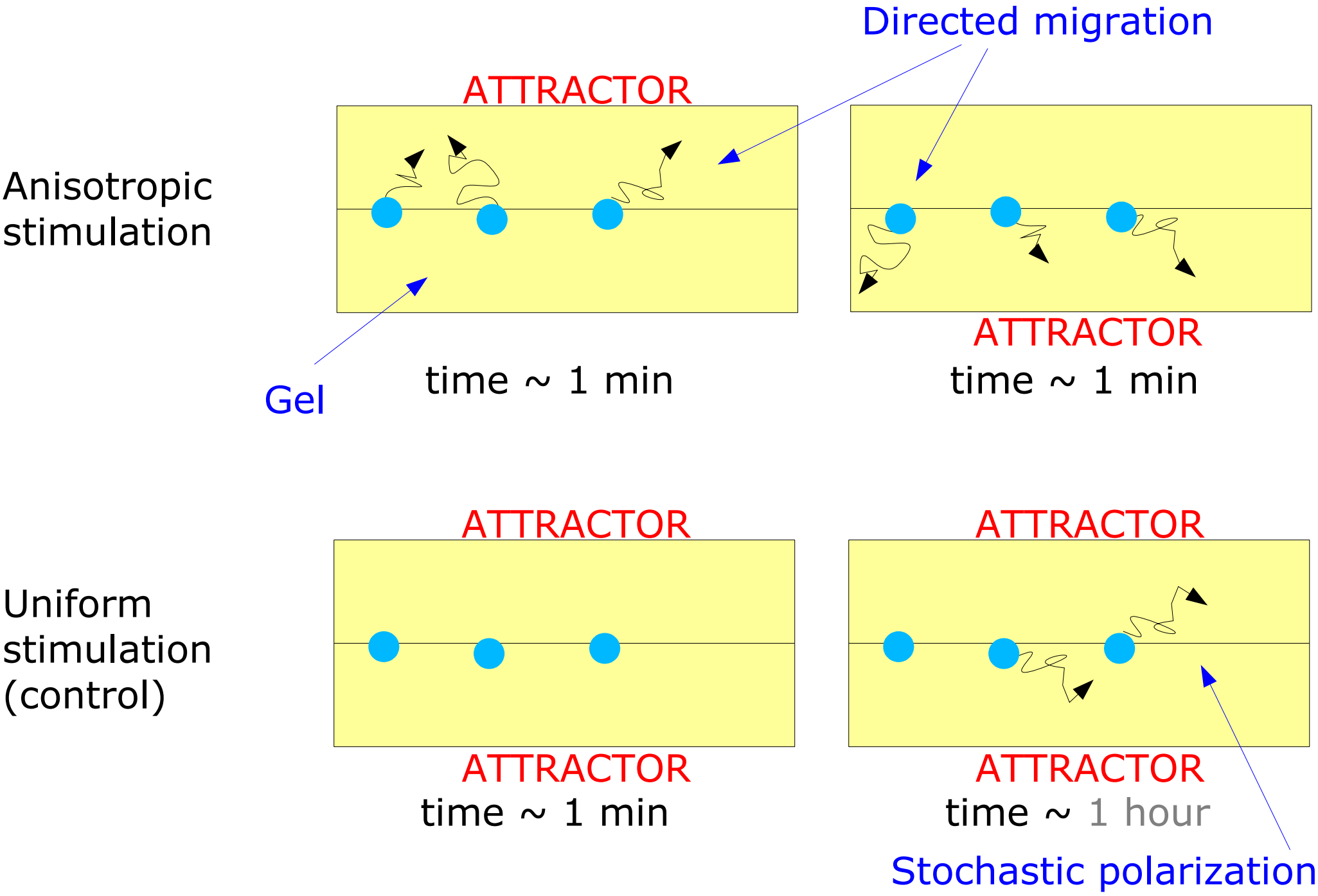

K
1
0
1
2
α/β
I
II
III
V
φ



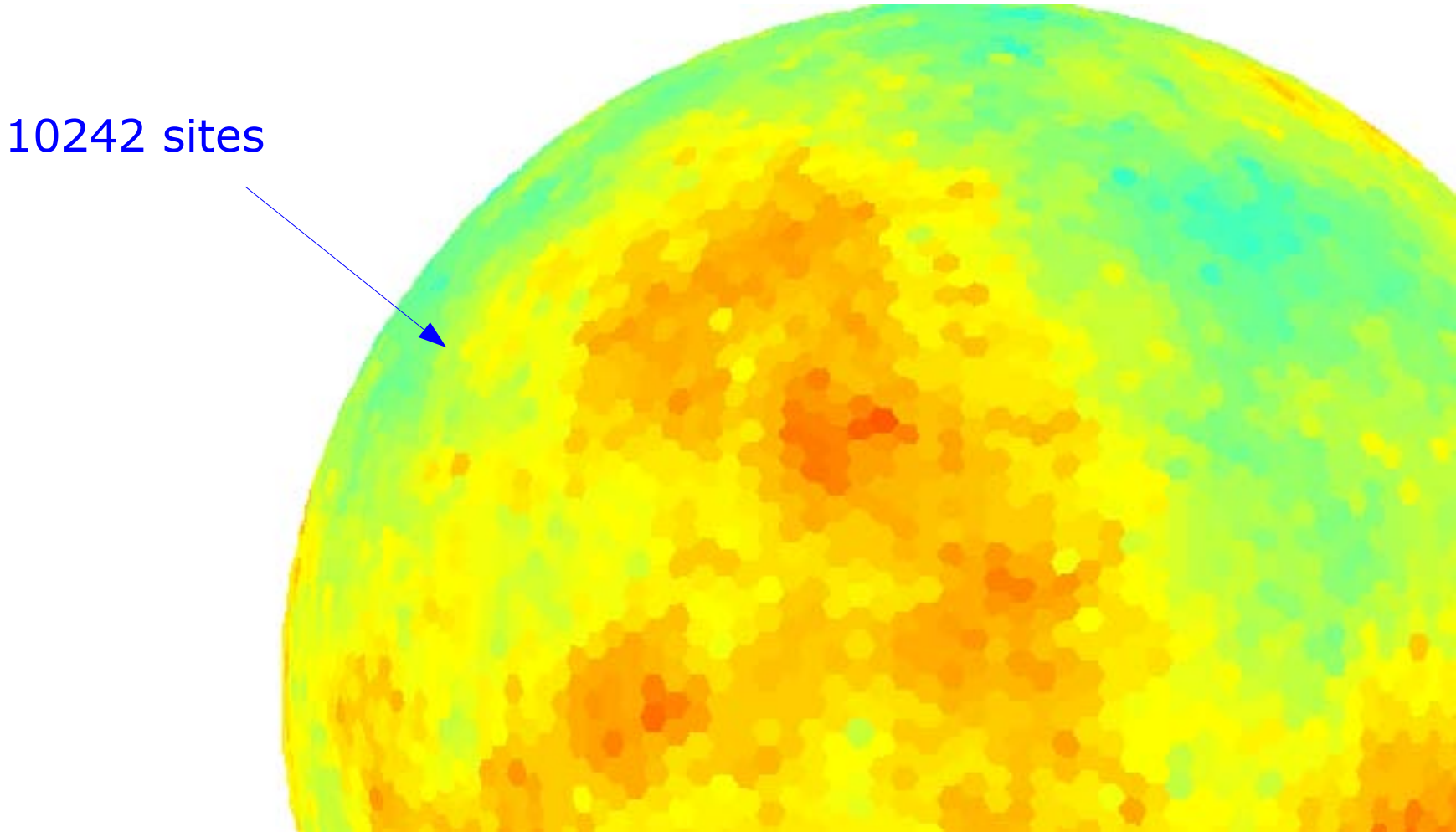
Line of phase coexistence

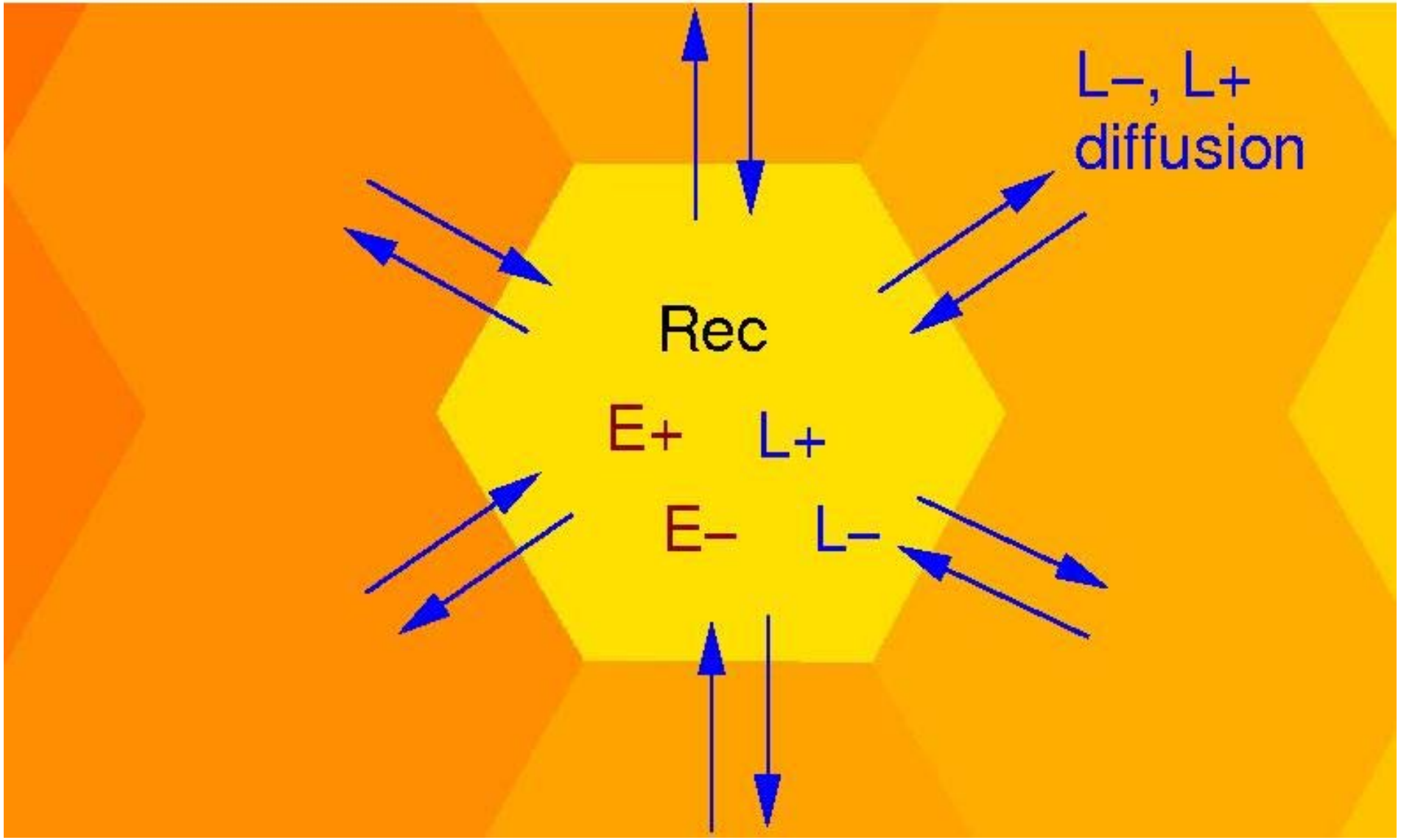
Parameter values at initial time

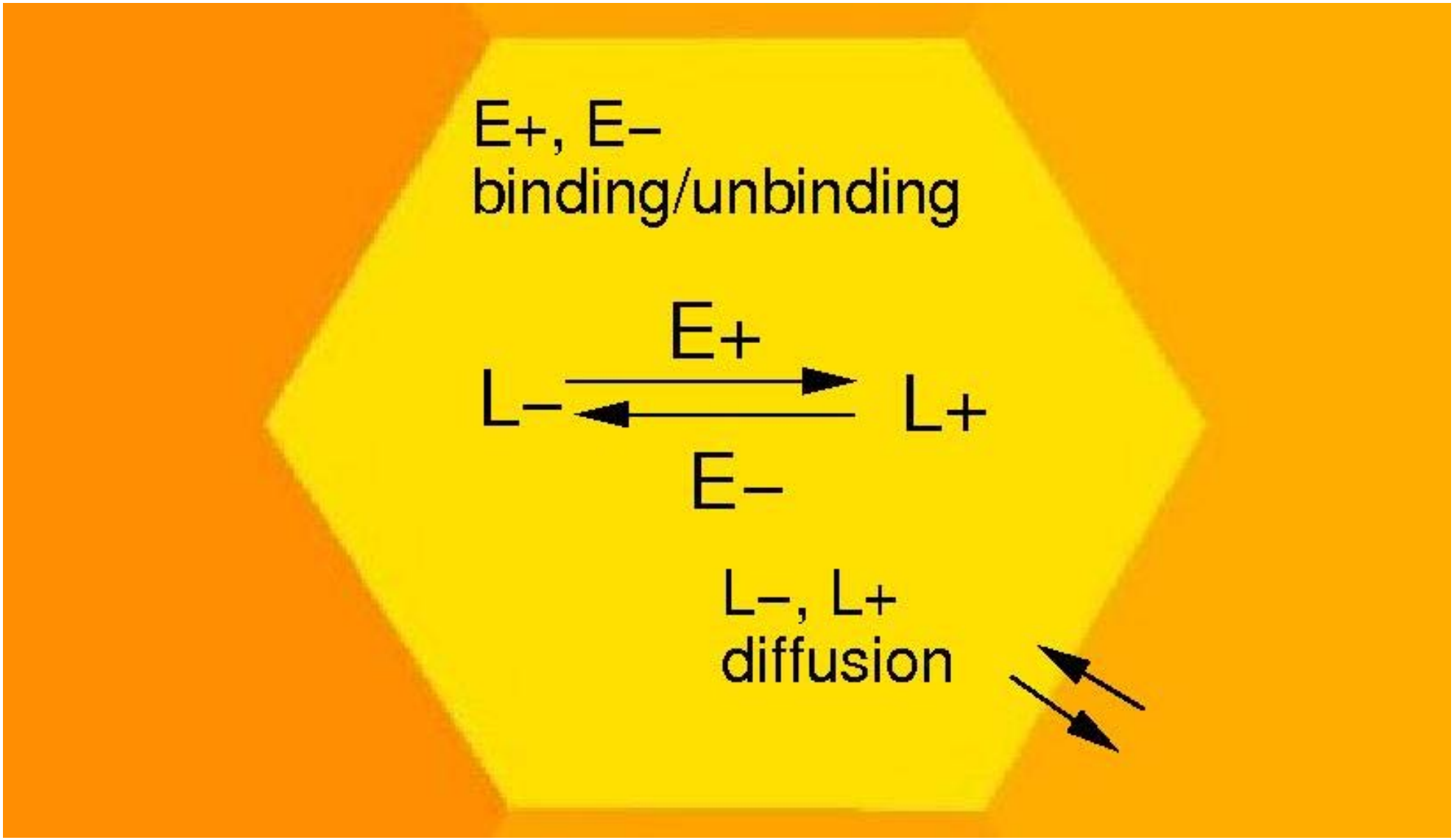
Boyden chamber

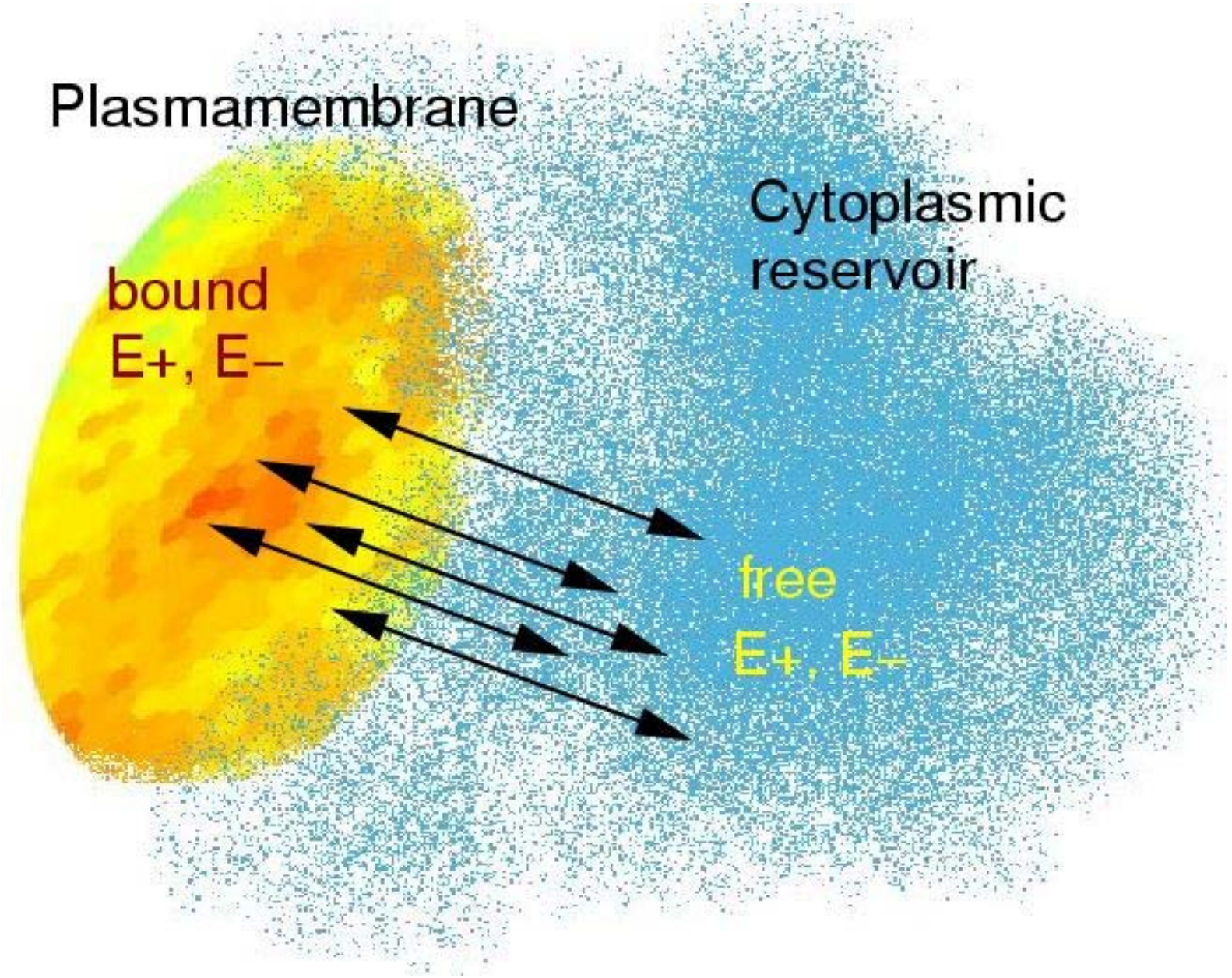


Monte Carlo simulation

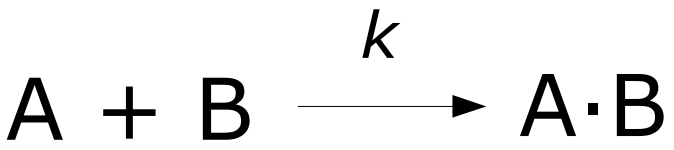



L–, L+
diffusion
Rec
E+
L+
E–
L–


E+, E–
binding/unbinding
E+
L–
L+
E–
L–, L+
diffusion


Plasmamembrane
Cytoplasmic
reservoir
bound
E+, E–
free
E+, E–

Association process:

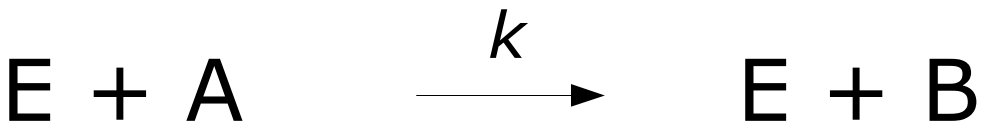


$$\text{rate} \propto k\,[A][B]$$

Kinetic rate constant

Local concentrations

Catalytic process:



Local concentrations

$$\text{rate} \propto k \frac{[E][A]}{K_{MM} + [A]}$$

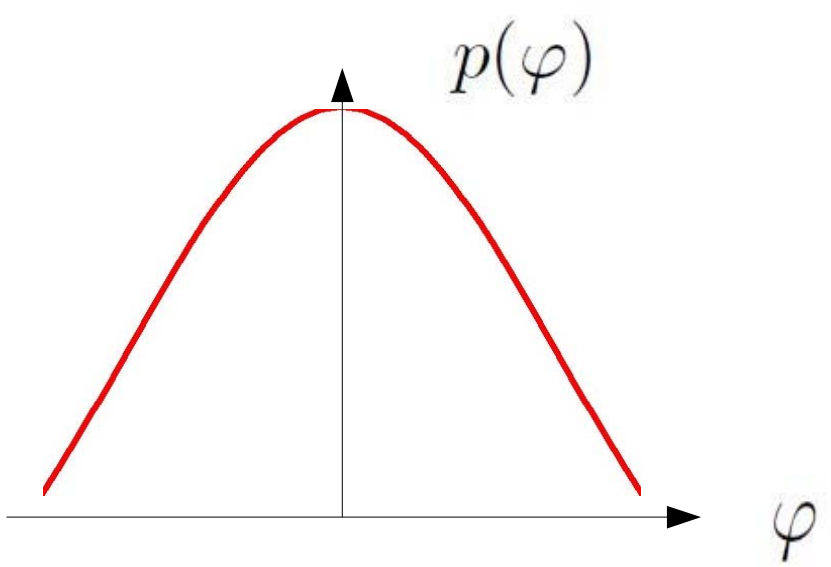
catalytic rate constant

Michaelis-Menten constant

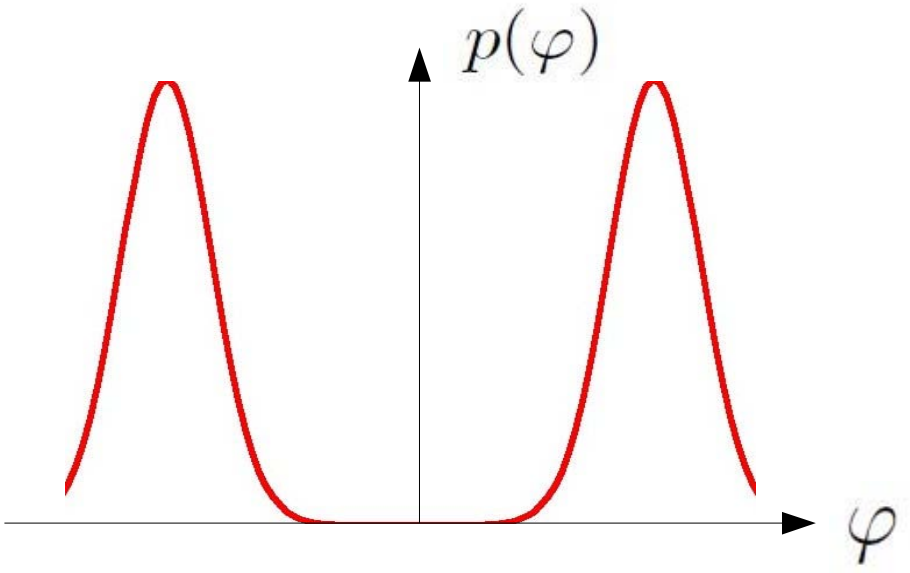
D	0.1 – 2 $\mu m^2/s$	
[Rec]	0 – 100 nM	~ 0 – 10^5 / cell
[L+], [L-]	500 nM	~ 10^6 / cell
[E+], [E-]	5 - 50 nM	~ 10^4 - 10^5 / cell
k_{cat}	1 s^{-1}	
k_{diss}	0.1 s^{-1}	
k_{ass}	50 s^{-1} μM^{-1}	

$$\varphi = [\mathbf{L}_+] - [\mathbf{L}_-]$$

$$g = \frac{1}{2}\left(3 - \langle \varphi - \langle\varphi\rangle\rangle^4 / \langle(\varphi - \langle\varphi\rangle)^2\rangle^2\right)$$



$g \sim 0$



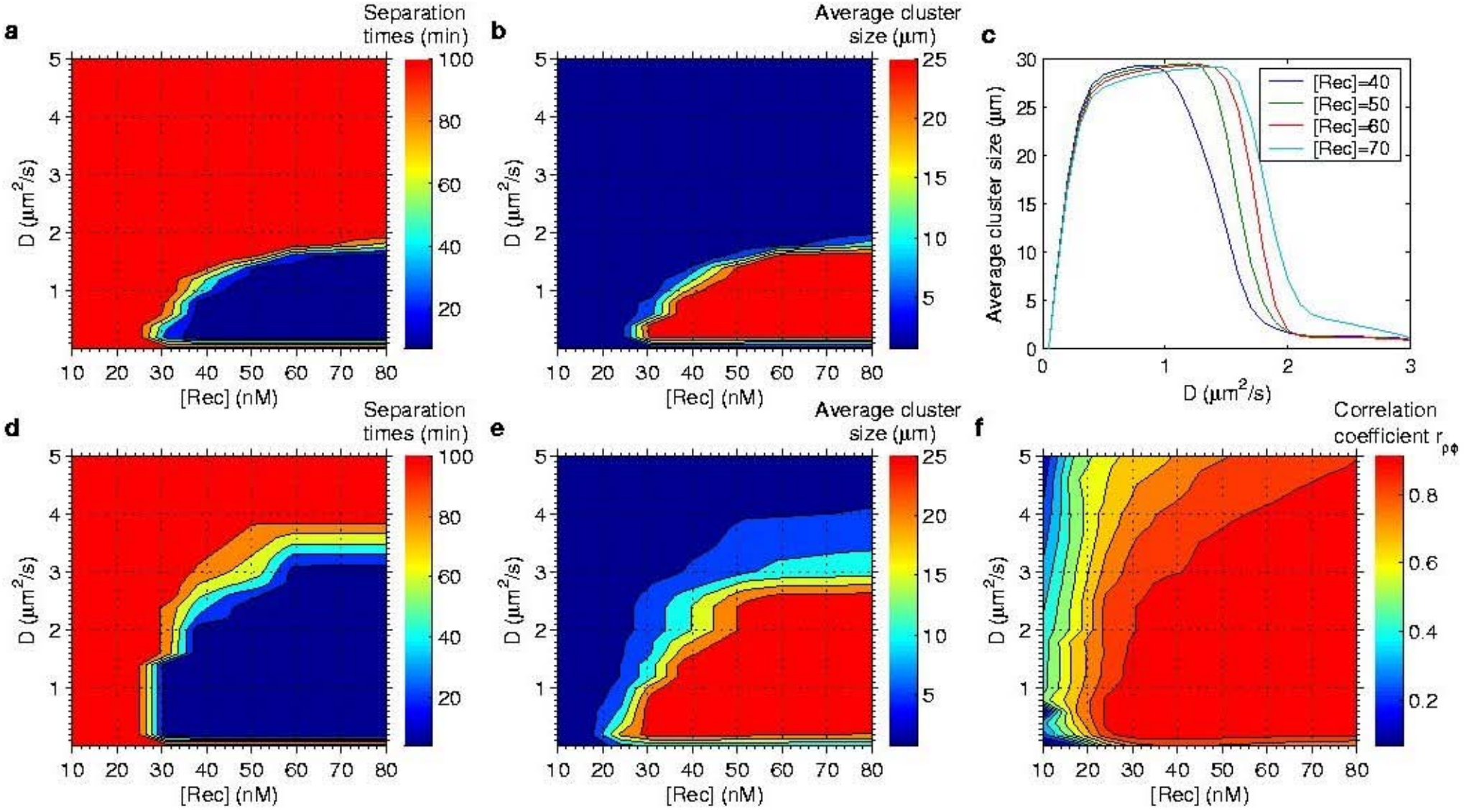
$g \sim 1$

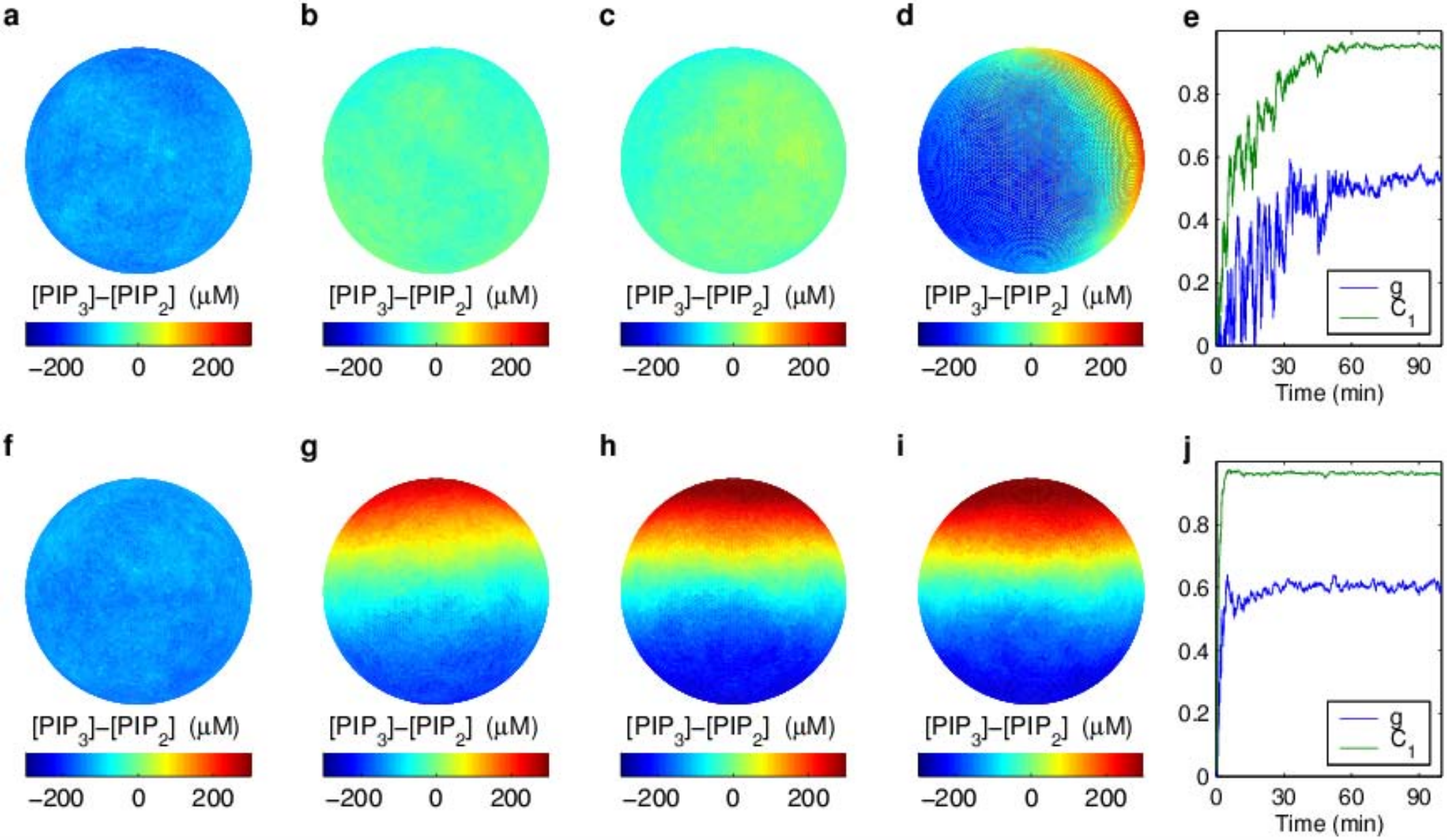
$$\varphi = [\mathbf{L}_+] - [\mathbf{L}_-]$$

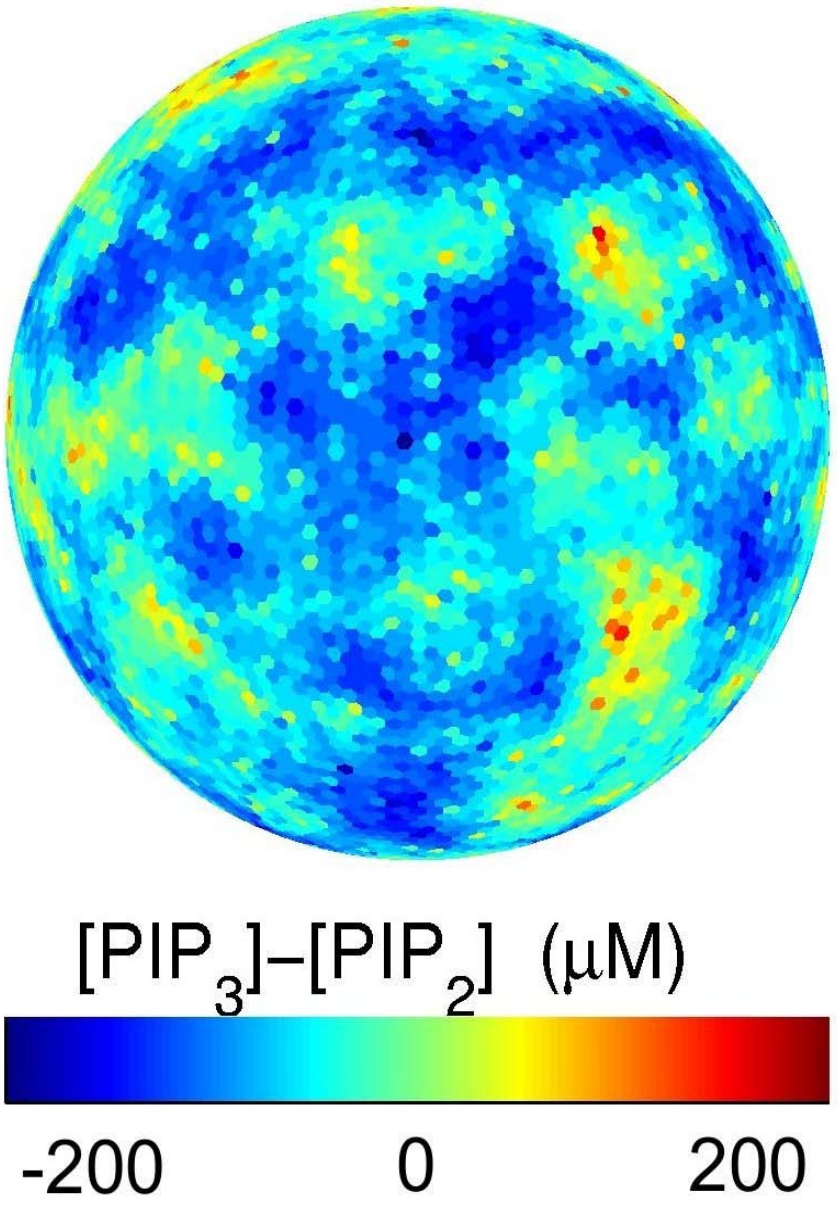
$$\delta\varphi = \varphi - \langle\varphi\rangle$$

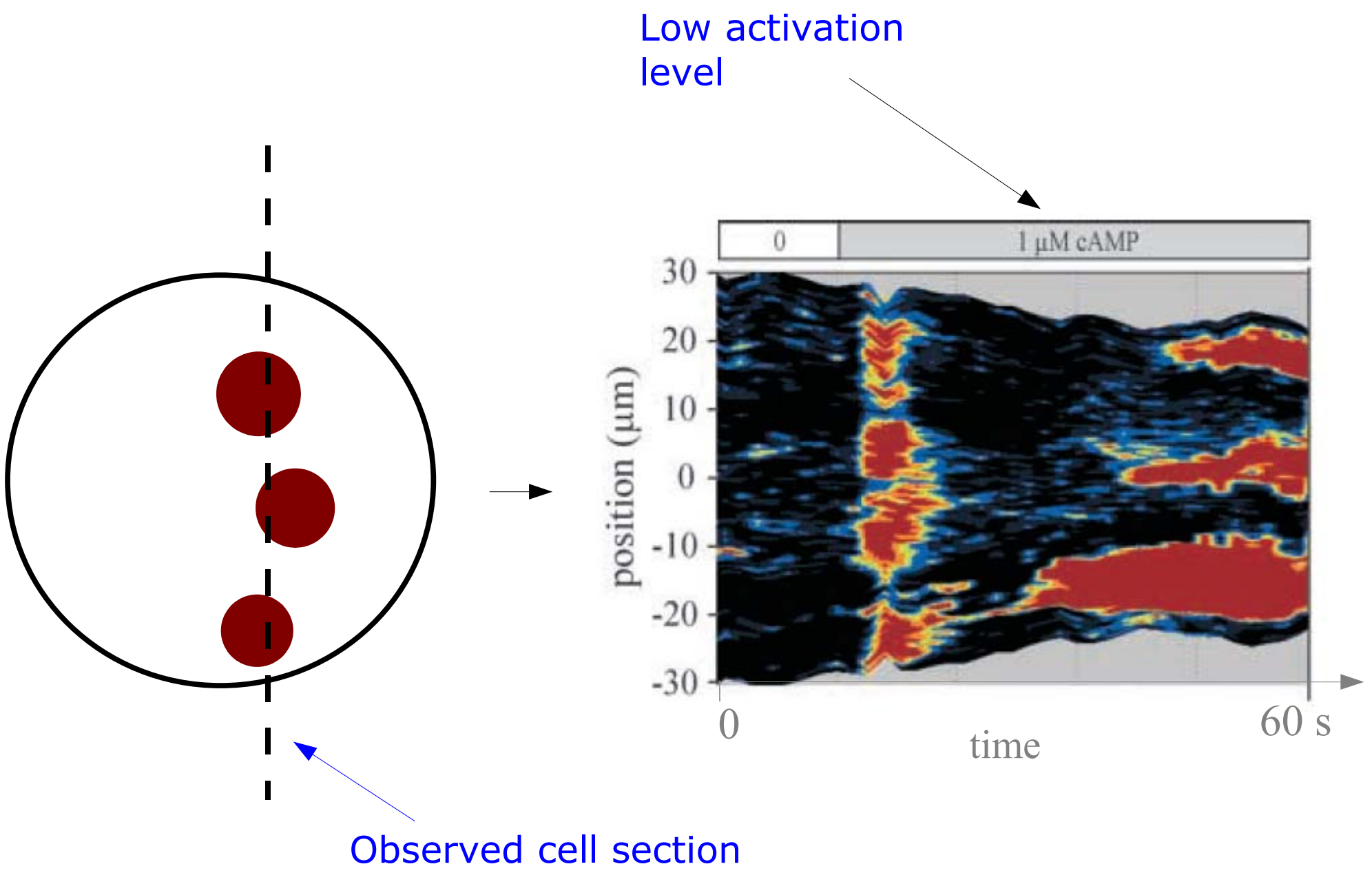
$$\langle\delta\varphi(\mathbf{u})\delta\varphi(\mathbf{u}')\rangle = \sum_{l=1}^{+\infty} C_l P_l(\mathbf{u}\cdot\mathbf{u}')$$

$$\text{cluster size} \sim \frac{\pi R}{2\sum_{l=1}^{\infty} C_l l}$$


a
Separation times (min)
100
80
60
40
20
D (μm²/s)
[Rec] (nM)
b
Average cluster size (μm)
25
20
15
10
5
c
Average cluster size (μm)
D (μm²/s)
[Rec]=40
[Rec]=50
[Rec]=60
[Rec]=70
d
e
f
Correlation coefficient r_ρφ
0.8
0.6
0.4
0.2


a
b
c
d
e
[PIP3]–[PIP2] (μM)
−200
0
200
0.8
0.6
0.4
0.2
0
0
30
60
90
Time (min)
gC1
f
g
h
i
j


[PIP3]–[PIP2] (μM)
-200
0
200



Postma et al., J. Cell Sci. **117** (2004) 2925

Conclusions

The phase separation scenario explains in simple terms:

- The large amplification of shallow chemotactic gradients
- The fact that cells do not respond to uniform stimulation
- Stochastic cell polarization
- The formation of small phosphoinositide clusters for low levels of stimulation

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Phase separation in eukaryotic chemotaxis
PNAS **102** (2005) 16927