Computational Molecular Biology

ReaDDy

Reaction-diffusion simulations for signal transduction cascades

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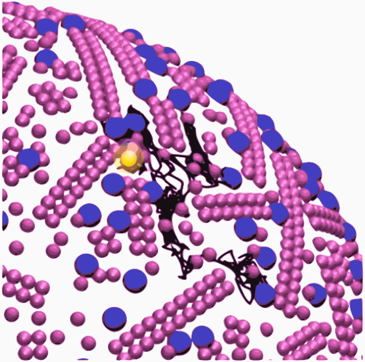
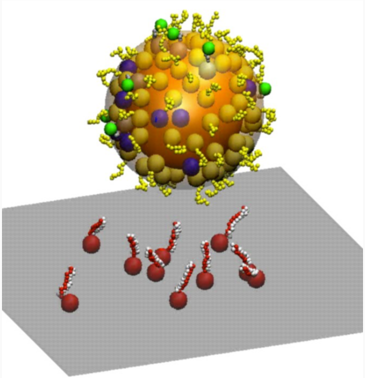
Reaction-diffusion simulations





ReaDDy software package

Content and goals

Content

- Motivation from biology
- Physics
- Molecular simulation
- Reaction-diffusion models $\rightarrow$ ReaDDy model
- ReaDDy implementation and neighborlists
- Membrane mechanics
- Lotka-Volterra models

Goal

- **why, where** reaction-diffusion methods are applied
- **how** to perform reaction-diffusion simulations

Organizational details

- everyone subscribed to participants list?
- bookmark this
  `https://readdy.github.io/readdy_documentation/workshop_info`
- Linux, Bash, Python?

Biology by the numbers

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How many proteins are in a cell?

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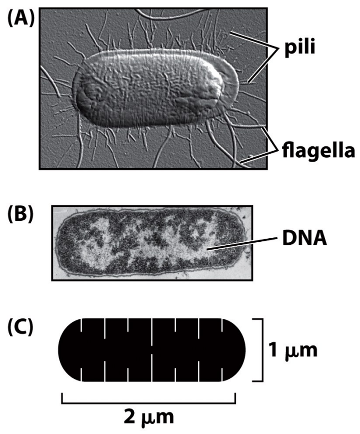


Figure 2.1 Physical Biology of the Cell (© Garland Science 2009)

Number of proteins in E.coli

- 1 ?
- 1,000 ?
- 1,000,000 ?
- 1,000,000,000 ?
- 1,000,000,000,000 ?

Some numbers for E.coli

Table 1.1 Rules of thumb for biological estimates

	Quantity of interest	Symbol	Rule of thumb
E. coli	Cell volume	$V_{E.\ coli}$	$\approx 1\ \mu m^3$
	Cell mass	$m_{E.\ coli}$	≈ 1 pg
	Cell cycle time	$t_{E.\ coli}$	≈ 3000 s
	Cell surface area	$A_{E.\ coli}$	$\approx 6\ \mu m^2$
	Genome length	$N_{bp}^{E.\ coli}$	$\approx 5 \times 10^6$ bp
	Swimming speed	$v_{E.\ coli}$	$\approx 20\ \mu m/s$
Yeast	Volume of cell	V_{yeast}	$\approx 60\ \mu m^3$
	Mass of cell	m_{yeast}	≈ 60 pg
	Diameter of cell	d_{yeast}	$\approx 5\ \mu m$
	Cell cycle time	t_{yeast}	≈ 200 min
	Genome length	N_{bp}^{yeast}	$\approx 10^7$ bp
Organelles	Diameter of nucleus	$d_{nucleus}$	$\approx 5\ \mu m$
	Length of mitochondrion	l_{mito}	$\approx 2\ \mu m$
	Diameter of transport vesicles	$d_{vesicle}$	≈ 50 nm
Water	Volume of molecule	V_{H_2O}	$\approx 10^{-2}$ nm^3
	Density of water	ρ	1 g/cm^3
	Viscosity of water	η	≈ 1 centipoise (10^{-2} g/(cm s))
	Hydrophobic embedding energy	$\approx E_{hydr}$	25 cal/(mol Å^2)
DNA	Length per base pair	l_{bp}	$\approx 1/3$ nm
	Volume per base pair	V_{bp}	≈ 1 nm^3
	Charge density	λ_{DNA}	2 e/0.34 nm
	Persistence length	ξ_P	50 nm
Amino acids and proteins	Radius of "average" protein	$r_{protein}$	≈ 2 nm
	Volume of "average" protein	$V_{protein}$	≈ 25 nm^3
	Mass of "average" amino acid	M_{aa}	≈ 100 Da
	Mass of "average" protein	$M_{protein}$	$\approx 30{,}000$ Da
	Protein concentration in cytoplasm	$c_{protein}$	≈ 300 mg/mL
	Characteristic force of protein motor	F_{motor}	≈ 5 pN
	Characteristic speed of protein motor	v_{motor}	≈ 200 nm/s
	Diffusion constant of "average" protein	$D_{protein}$	$\approx 100\ \mu m^2/s$
Lipid bilayers	Thickness of lipid bilayer	d	≈ 5 nm
	Area per molecule	A_{lipid}	$\approx \frac{1}{2}$ nm^2
	Mass of lipid molecule	m_{lipid}	≈ 800 Da

Table 1.1 Physical Biology of the Cell (© Garland Science 2009)

Number of proteins in E.coli

Typical Actin concentration

$$c = 0.5\mathrm{mM} = \frac{n}{V}$$

leads to

$$n \approx 300,000$$

Number of proteins between 10^3 and 10^6

Relative numbers

Relative **weight** of macromolecules

Substance	% of total dry weight	Number of molecules
Macromolecule		
Protein	55.0	2.4×10^6
RNA	20.4	
23S RNA	10.6	19,000
16S RNA	5.5	19,000
5S RNA	0.4	19,000
Transfer RNA (4S)	2.9	200,000
Messenger RNA	0.8	1,400
Phospholipid	9.1	22×10^6
Lipopolysaccharide	3.4	1.2×10^6
DNA	3.1	2
Murein	2.5	1
Glycogen	2.5	4,360
Total macromolecules	**96.1**	
Small molecules		
Metabolites, building blocks, etc.	2.9	
Inorganic ions	1.0	
Total small molecules	**3.9**	

Table 2.1 Observed macromolecular census of an *E. coli* cell. (Data from F. C. Neidhardt et al., Physiology of the Bacterial Cell, Sunderland, Sinauer Associates Inc., 1990 and M. Schaechter et al., Microbe, Washington DC, ASM Press, 2006.)

Table 2.1 Physical Biology of the Cell (© Garland Science 2009)

Relative **volume** of macromolecules
(proteins + other) $\approx 60\%$
Dense packing of spheres $\approx 70\%$

Overview of E.coli

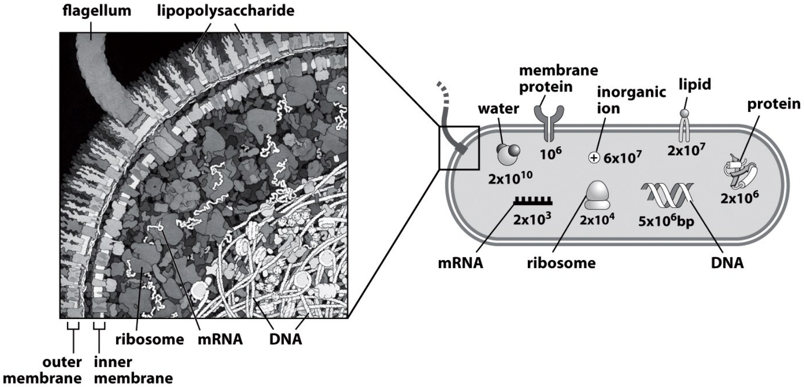
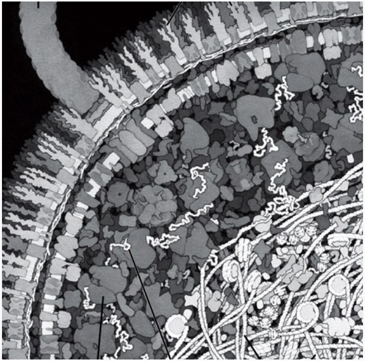
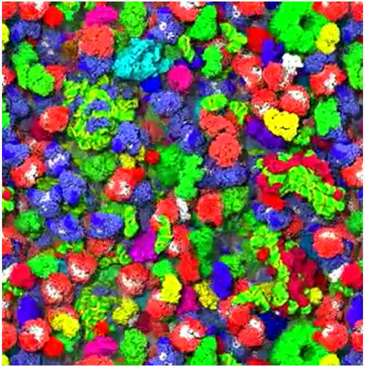


Figure 2.2 Physical Biology of the Cell (© Garland Science 2009)

Reaction-diffusion

Cell is crowded





Transport via diffusion

Diffusion = dominant form of transport

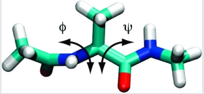
Diffusion

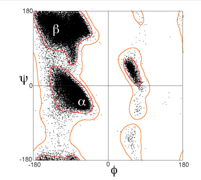
- stochastic/probabilistic motion
- systems at finite temperature
- ignore solvent - implicit solvent

Macro-molecules interact = Reactions

Conformational change

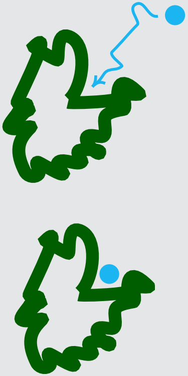
$$A \rightleftharpoons B$$





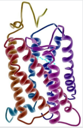
Protein-ligand interaction

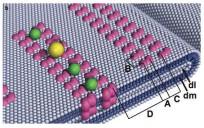
$$A + B \rightleftharpoons C$$

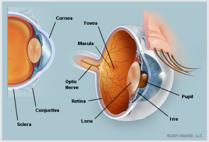


Reaction diffusion simulations generate realisations of **mesoscopic** systems

Different scales of visual signaling

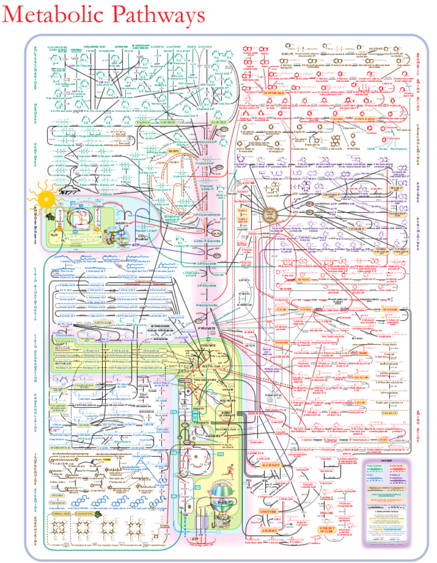


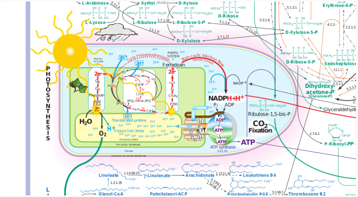




Why is RD useful?

Metabolic processes





www.sigmaaldrich.com/technical-documents/articles/biology/interactive-metabolic-pathways-map.html

Experiments

- New techniques enable detailed images
- Proteins can be made flourescent
- Reach sub-μm scale