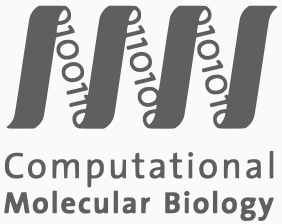

ReaDDy

Reaction diffusion simulations for cellular processes

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July 23, 2018

CMB Group, FU Berlin

ReaDDy

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Biological setting

Understand biological/soft-matter systems

- Biological function (life) = interaction of macromolecules
- Amount of proteins per cell: millions in total

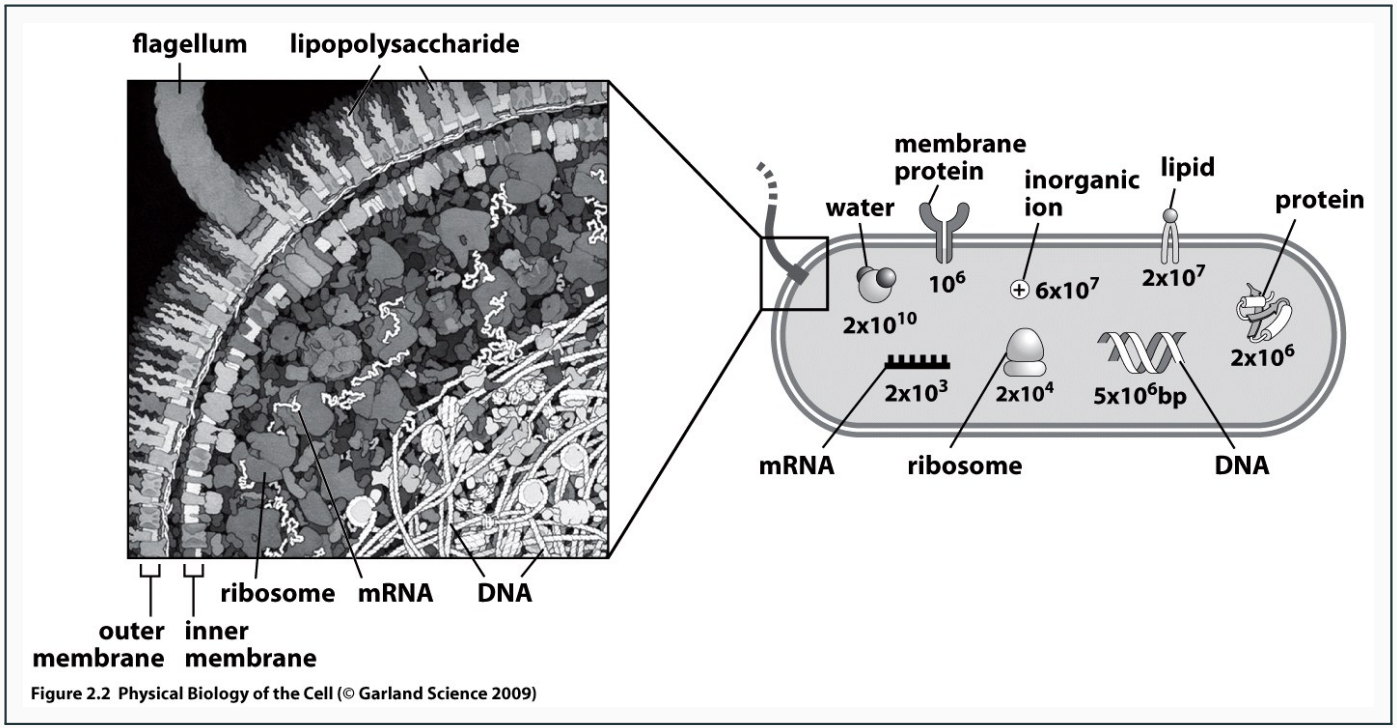
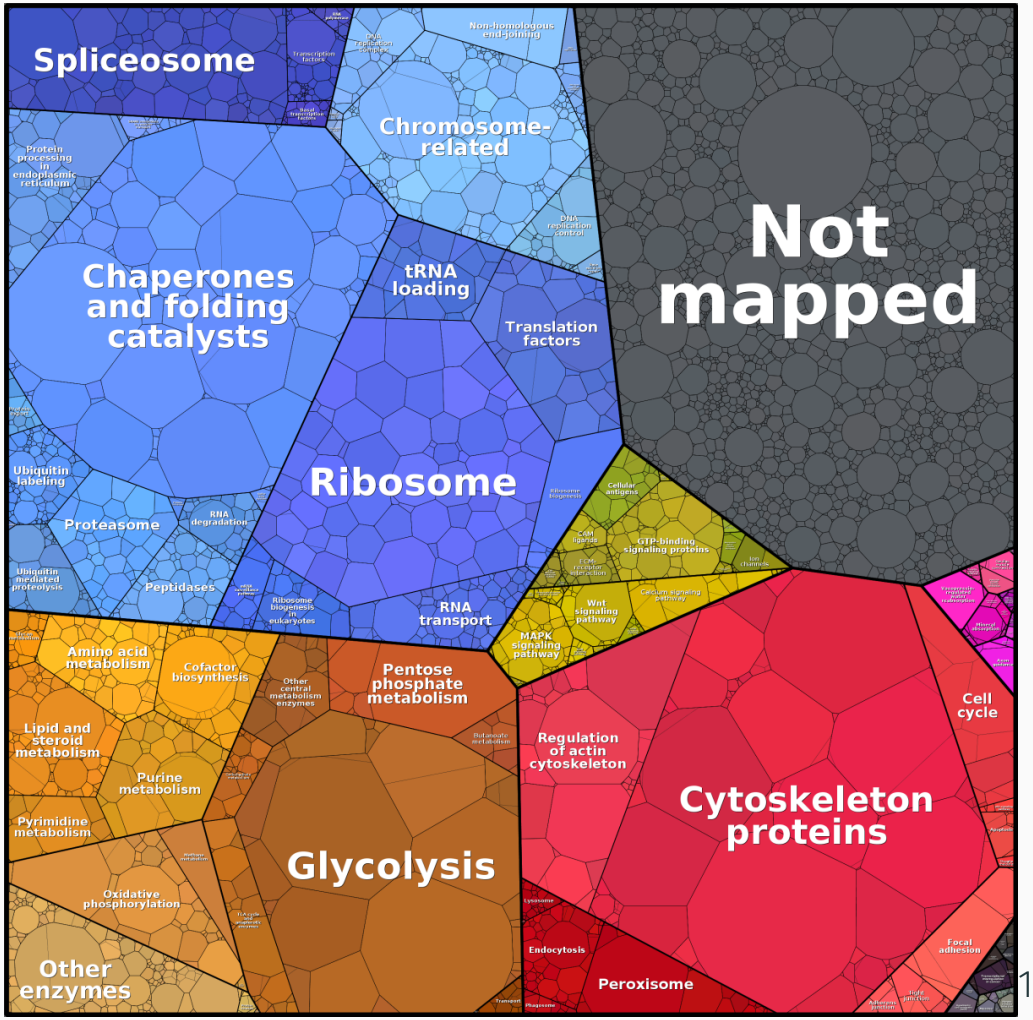


Figure 2.2 Physical Biology of the Cell (© Garland Science 2009)

How many different species of proteins are in a cell?

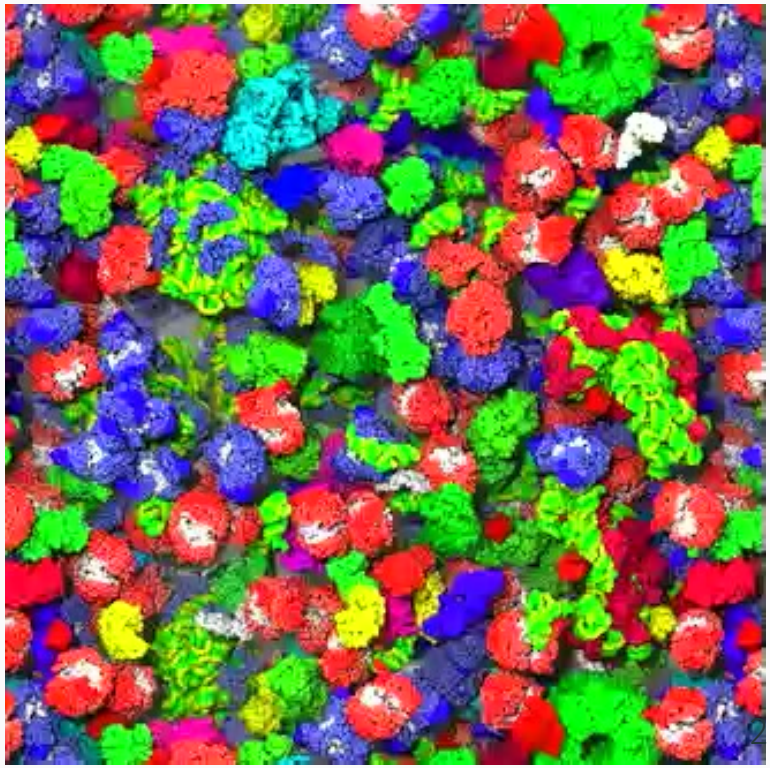


[1]

[1] Wolfram Liebermeister et al. (2014). "Visual account of protein investment in cellular functions". In: *Proceedings of the National Academy of Sciences*, p. 201314810.

Cells are crowded

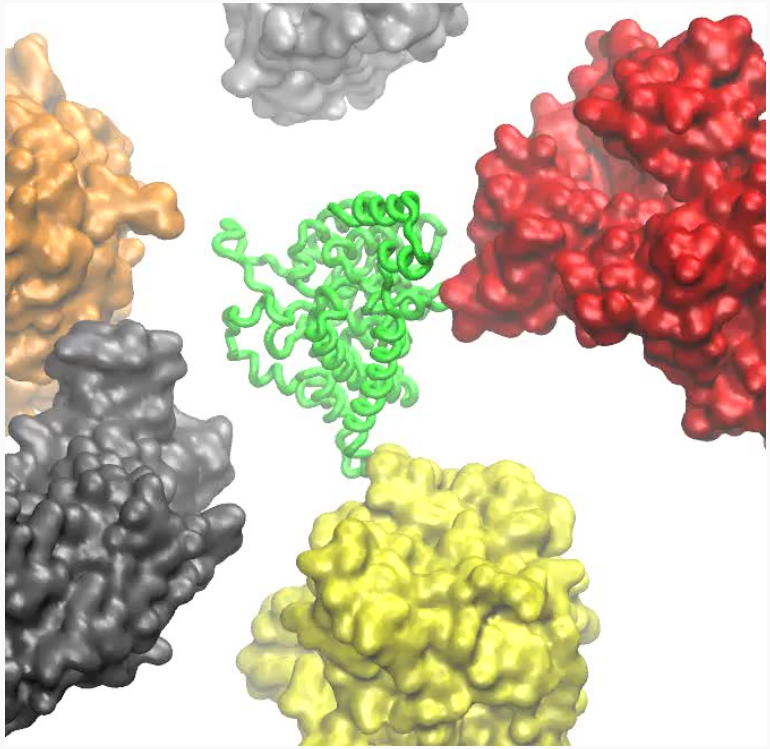
- Brownian dynamics simulation of cytoplasm
- Colored rigid bodies represent proteins



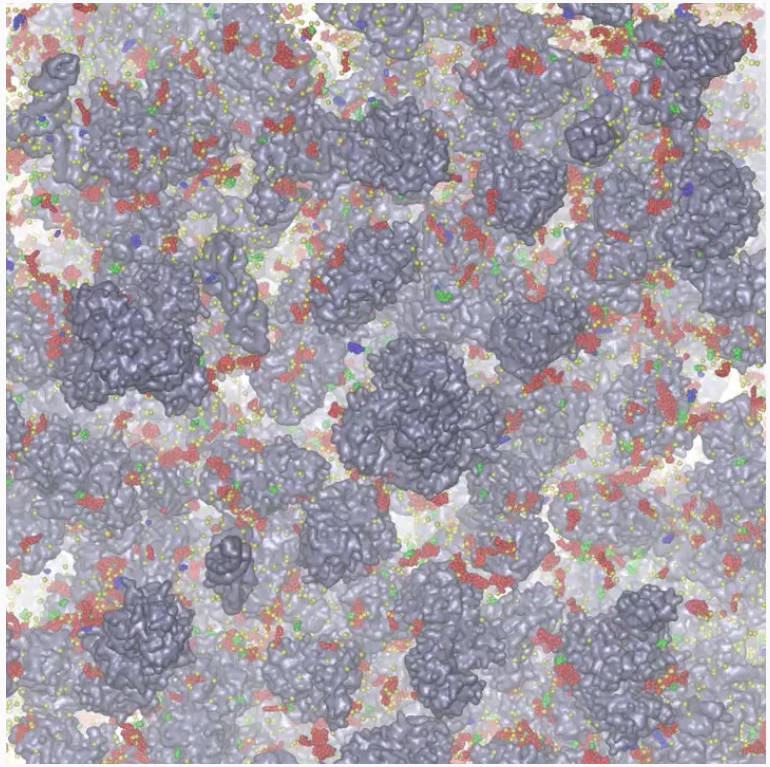
[2]Sean R McGuffee and Adrian H Elcock (2010). “Diffusion, crowding & protein stability in a dynamic molecular model of the bacterial cytoplasm”. In: *PLoS computational biology* 6.3, e1000694.

Protein interactions ...

...with each other



...with smaller molecules



3

[3] Isseki Yu et al. (2016). "Biomolecular interactions modulate macromolecular structure and dynamics in atomistic model of a bacterial cytoplasm". In: *eLife* 5.NOVEMBER2016, pp. 1–22.

Experiments achieve protein resolution

Experiments achieve protein resolution - Flourescence

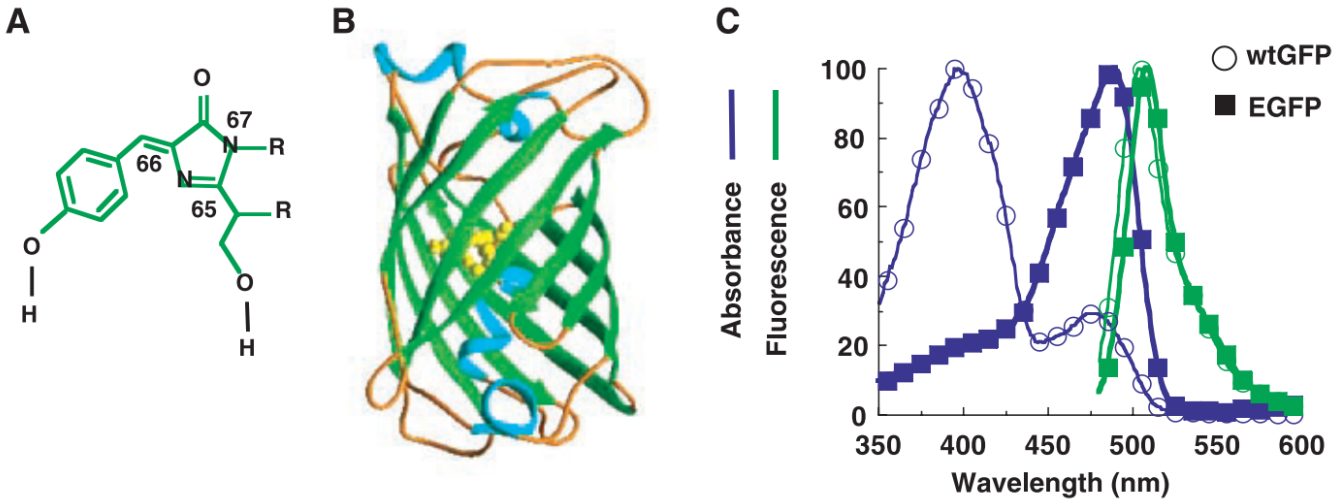
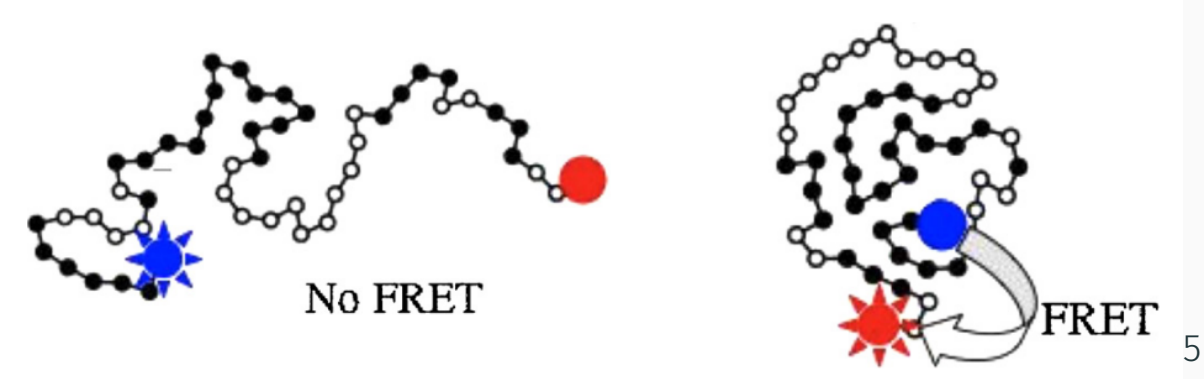


Fig. 1. (**A**) The wtGFP chromophore, consisting of a cyclized tripeptide made of Ser^{65}, Tyr^{66}, and Gly^{67}. (**B**) Chromophore location within an α helix inside the 11-strand β barrel of GFP [adapted from (*59*)]. (**C**) wtGFP's major and minor absorbance peaks (blue circles) and single fluorescence emission peak (green circles) compared with EGFP's single absorbance peak (blue squares) and single fluorescence emission peak (green squares). [4]

[4] J. Lippincott-Schwartz (Apr. 2003). "Development and Use of Fluorescent Protein Markers in Living Cells". In: *Science* 300.5616, pp. 87–91.

FRET



[5]

[5] Harekrushna Sahoo (2011). "Förster resonance energy transfer - A spectroscopic nanoruler: Principle and applications". In: *Journal of Photochemistry and Photobiology C: Photochemistry Reviews* 12.1, pp. 20–30.

FRAP,FLAP

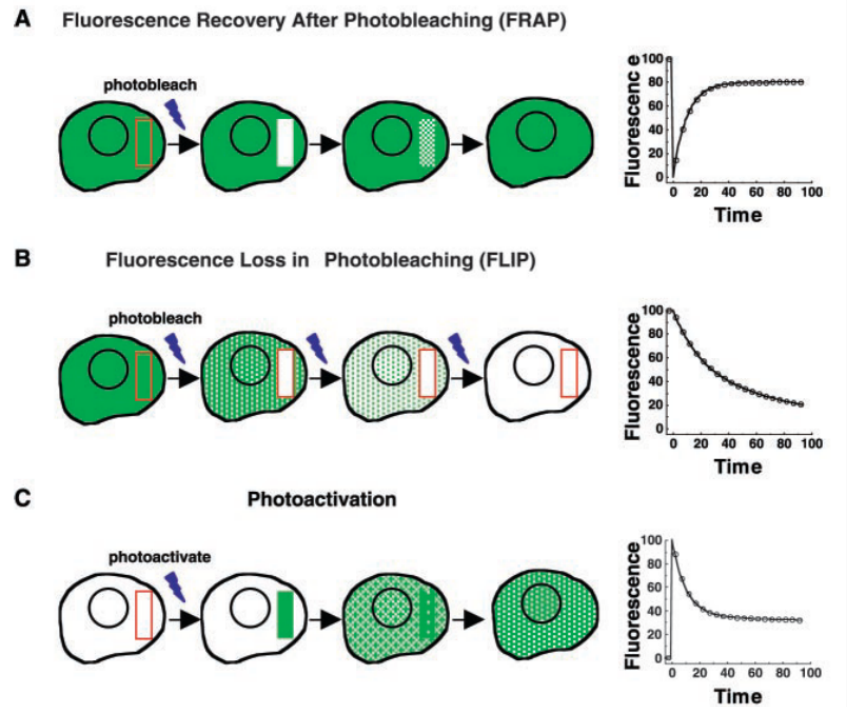


Fig. 3. Kinetic microscopy techniques. (**A**) In FRAP, a region of the cell (indicated in red) is selectively and intensely irradiated to photobleach fluorescent molecules. The recovery of fluorescent molecules into that region is assessed quantitatively to determine diffusion coefficients and mobile fractions. (**B**) In FLIP, a region of the cell (indicated in red) is repeatedly photobleached. Movement of fluorescent molecules into the region being photobleached results in loss of fluorescence from areas outside the box and can be used to access the boundaries for a protein's diffusional movement within a cell. (**C**) In photoactivation, selective irradiation of region (indicated in red) leads to the molecules in this region becoming fluorescent. These molecules can then be monitored as they move out of this region and throughout the cell.

6

[6] J. Lippincott-Schwartz (Apr. 2003). "Development and Use of Fluorescent Protein Markers in Living Cells". In: *Science* 300.5616, pp. 87–91.

measure diffusion of individual molecules

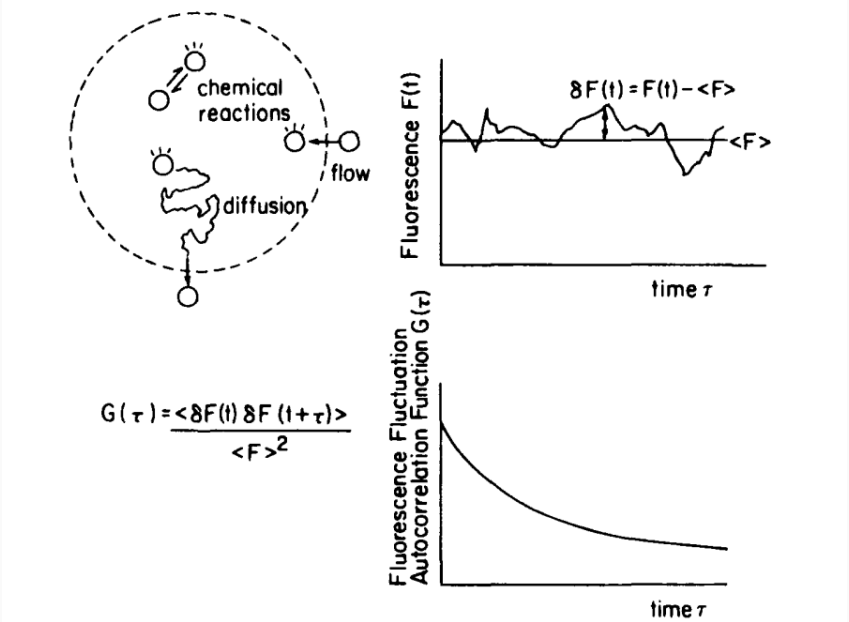


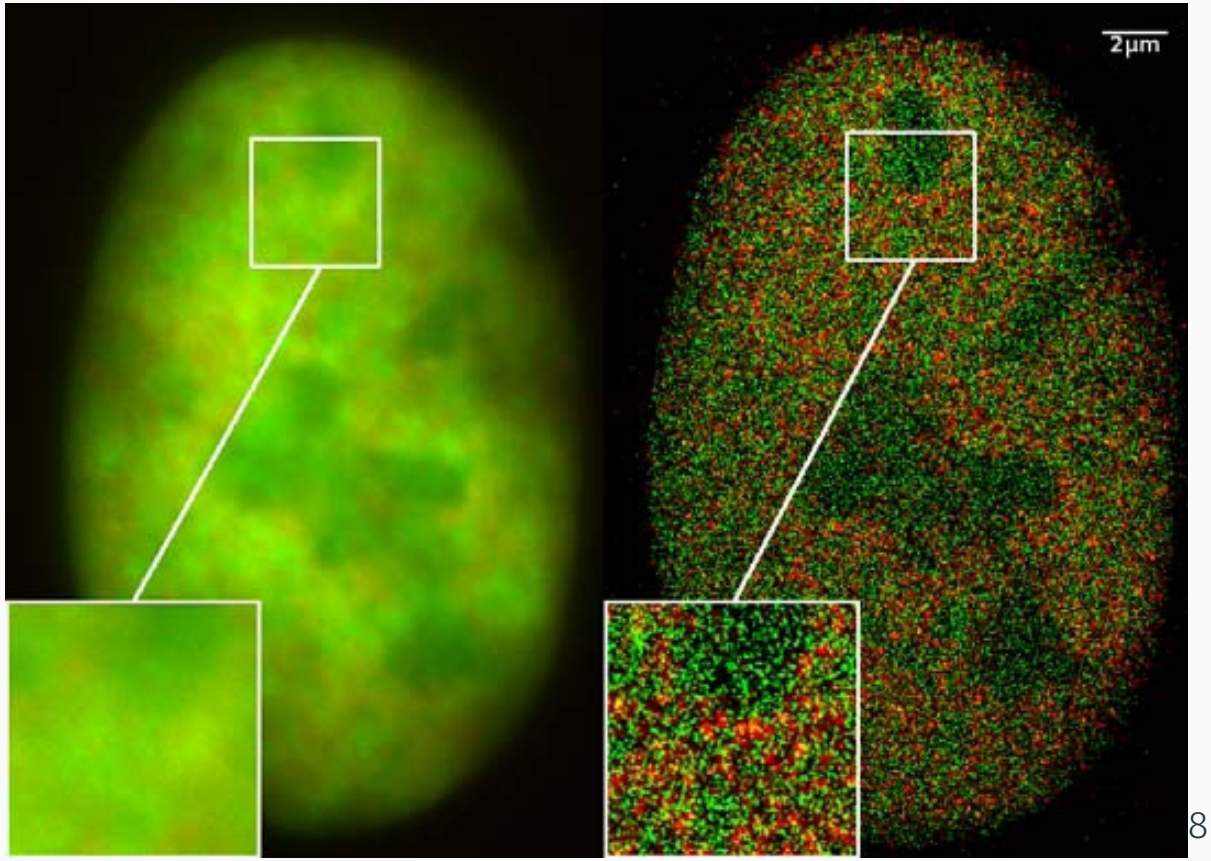
Figure 6.1. Conceptual basis of FCS. At equilibrium, fluorescent molecules are transported by diffusion or flow through an open illuminated and observed region or undergo transitions between states of different fluorescent yields, giving rise to fluctuations in the measured fluorescence. The fluctuations $\delta F(t)$ in the measured fluorescence $F(t)$ from the average fluorescence $\langle F \rangle$ are autocorrelated as $G(\tau)$. The autocorrelation function, which measures the average duration of a fluorescence fluctation, decays with time τ; the rate and shape of decay are related to the mechanisms and rates of the processes that give rise to the fluorescence fluctuations. The magnitude of $G(\tau)$ is related to the number densities and relative fluorescence yields of different chemical species in the sample region.

[7]

[7] Nancy L Thompson (2002). "Fluorescence correlation spectroscopy". In: *Topics in fluorescence spectroscopy*. Springer, pp. 337–378.

Superresolution - look at single proteins

sacrifice dynamics for resolution

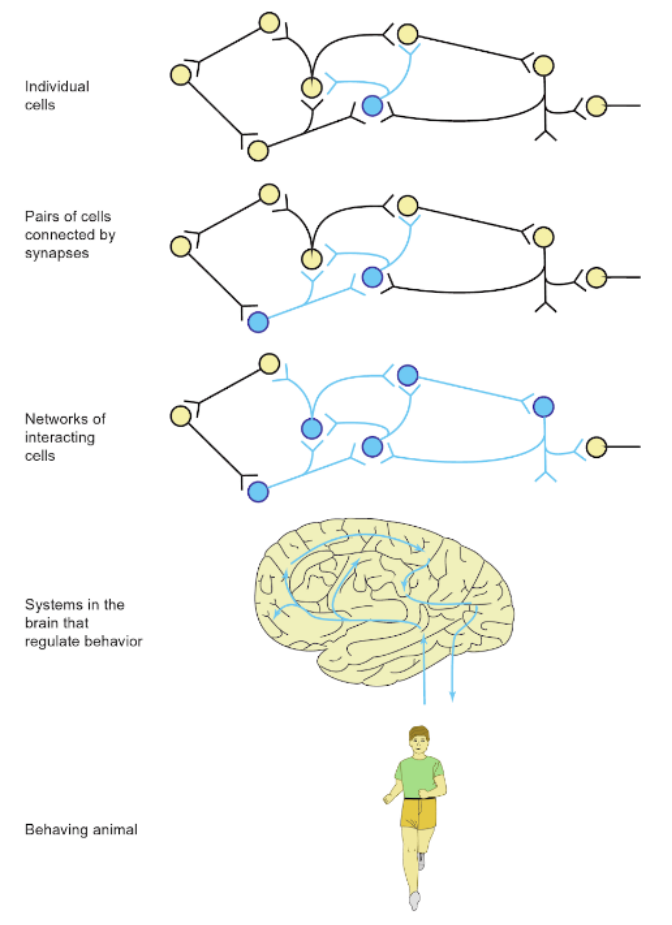


[8]

[8] Manuel Gunkel et al. (2009). “Dual color localization microscopy of cellular nanostructures”. In: *Biotechnology Journal* 4.6, pp. 927–938.

Example: Diffusion of single proteins in axons

Example: Axon segment diffusion



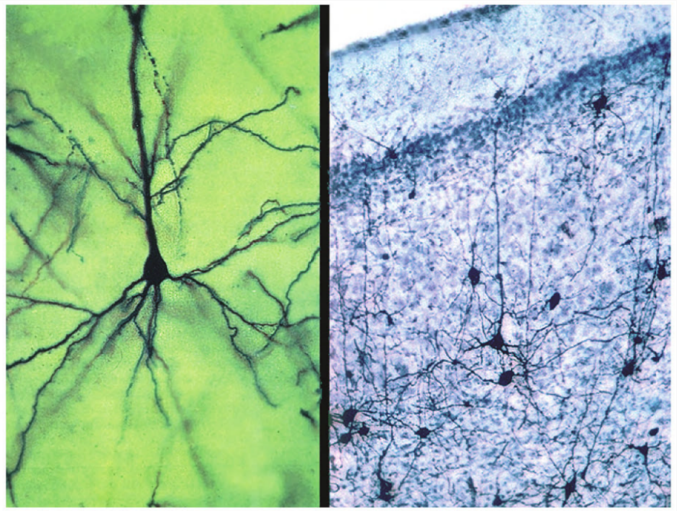


Figure 1–2. Golgi-stained cerebral pyramidal neurons are shown at two magnifications. Pyramidal neurons (and granule cells) are typical neurons of the cerebral cortex. Cell bodies of pyramidal neurons have a pyramid shape with a single apical dendrite and multiple basal dendrites. The axons are not visible in these images. (Micrographs courtesy of Thomas F. Fletcher—see http://vanat.cvm.umn.edu/neurHistAtls/pages/cns12.html.)

[9]

[9] Irwin B Levitan and Leonard K Kaczmarek (2015). *The neuron: cell and molecular biology*. Oxford University Press, USA.

Example: Axon segment diffusion

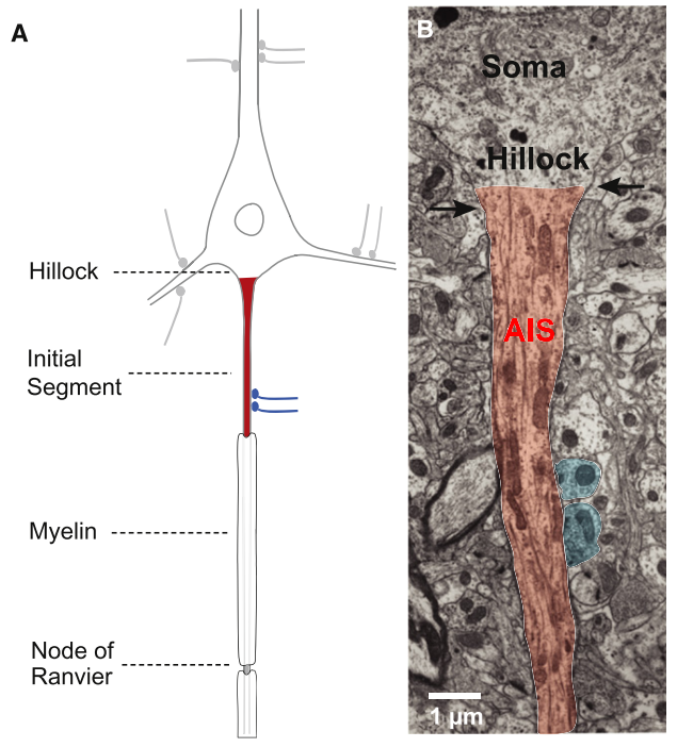
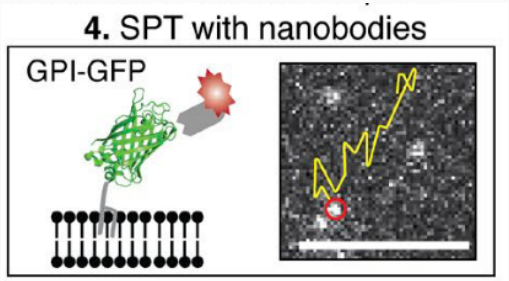


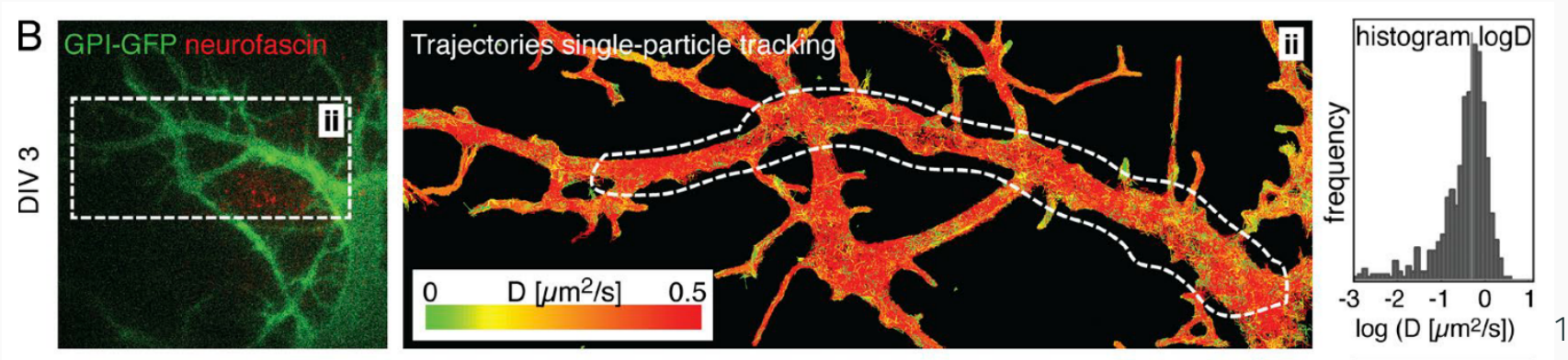
Figure 1. Anatomy of the Axon Initial Segment
(A) Schematic of a pyramidal neuron axon showing the location of the hillock, initial segment (AIS; red), and axon proper. Synaptic input onto the AIS is shown in blue.
(B) Electron micrograph of the AIS of a cortical pyramidal neuron. The soma, axon hillock, and AIS (red) are indicated. Blue areas indicate presynaptic terminals onto the AIS. Arrows (black) indicate the onset of the dense granular layer beneath the surface membrane indicating the start of the AIS. Adapted from Peters et al. (1968).

[10]

[10] Maarten H.P. Kole and Greg J. Stuart (Jan. 2012). "Signal Processing in the Axon Initial Segment". In: *Neuron* 73.2, pp. 235–247.

Example: Axon segment diffusion

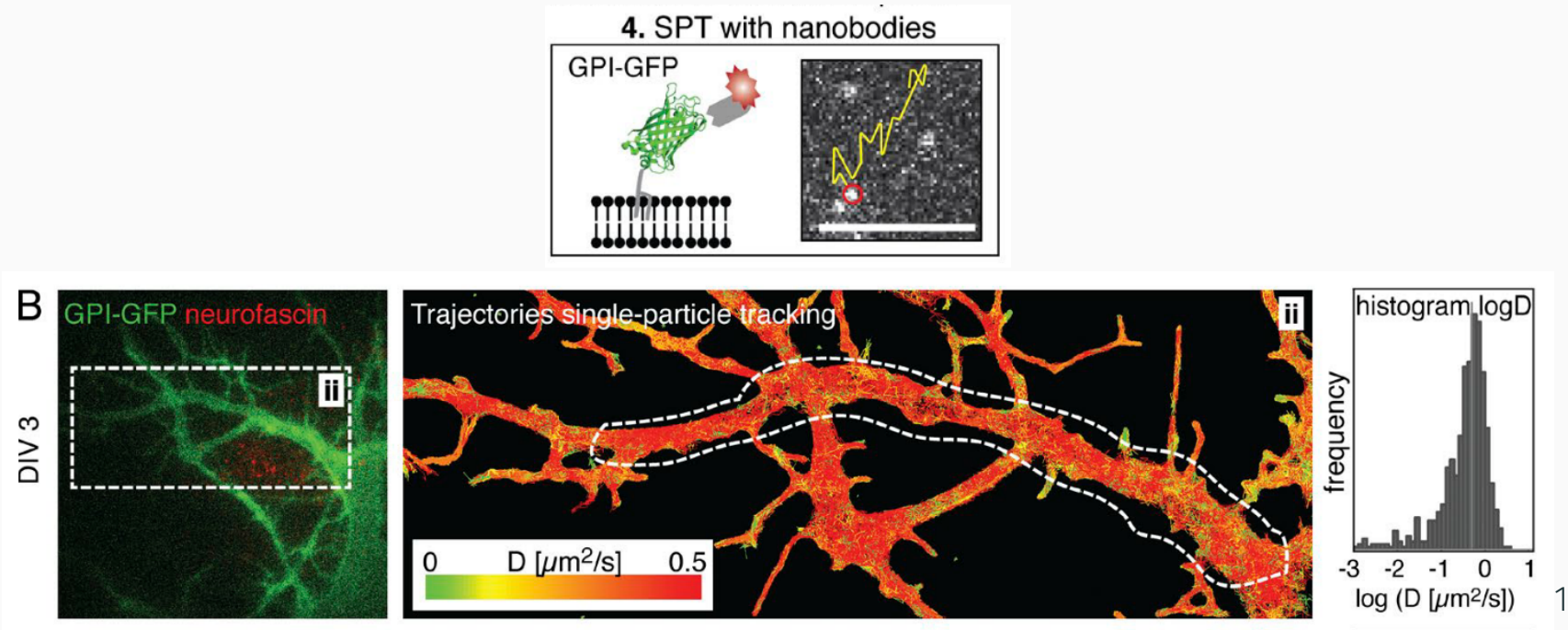




[11]

[11] David Albrecht et al. (Oct. 2016). "Nanoscopic compartmentalization of membrane protein motion at the axon initial segment". In: *The Journal of Cell Biology* 215.1, pp. 37–46.

Example: Axon segment diffusion



[11]

- Goal: explain such observations/measurements

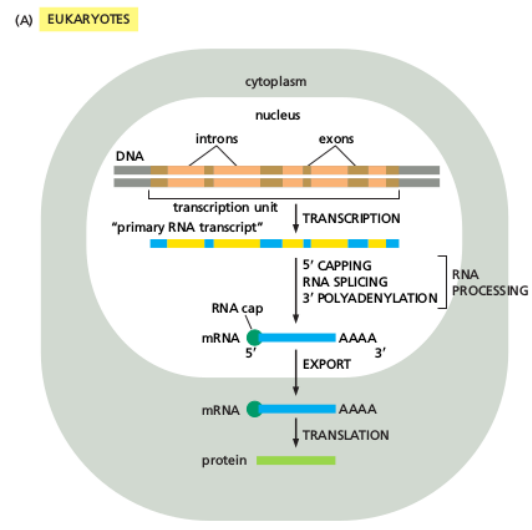
$\rightarrow$ need mathematical microscopic description

[11] David Albrecht et al. (Oct. 2016). "Nanoscopic compartmentalization of membrane protein motion at the axon initial segment". In: *The Journal of Cell Biology* 215.1, pp. 37–46.

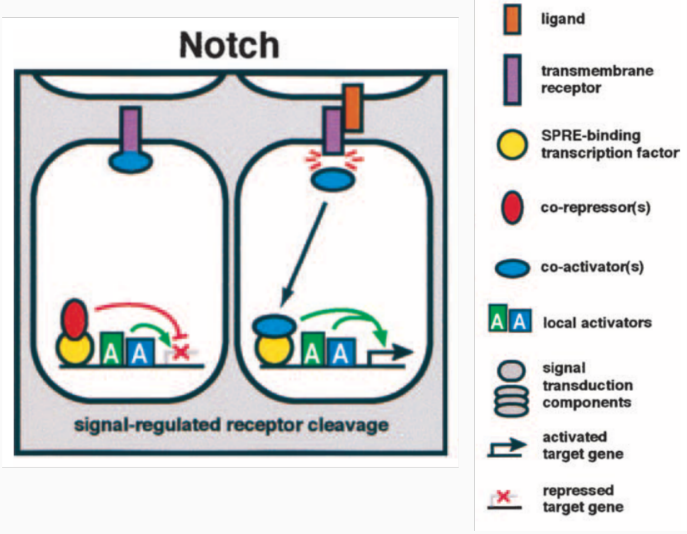
Microscopic models need to resolve space and time

Example: Gene regulation as signaling pathways

How do cells synthesize proteins?



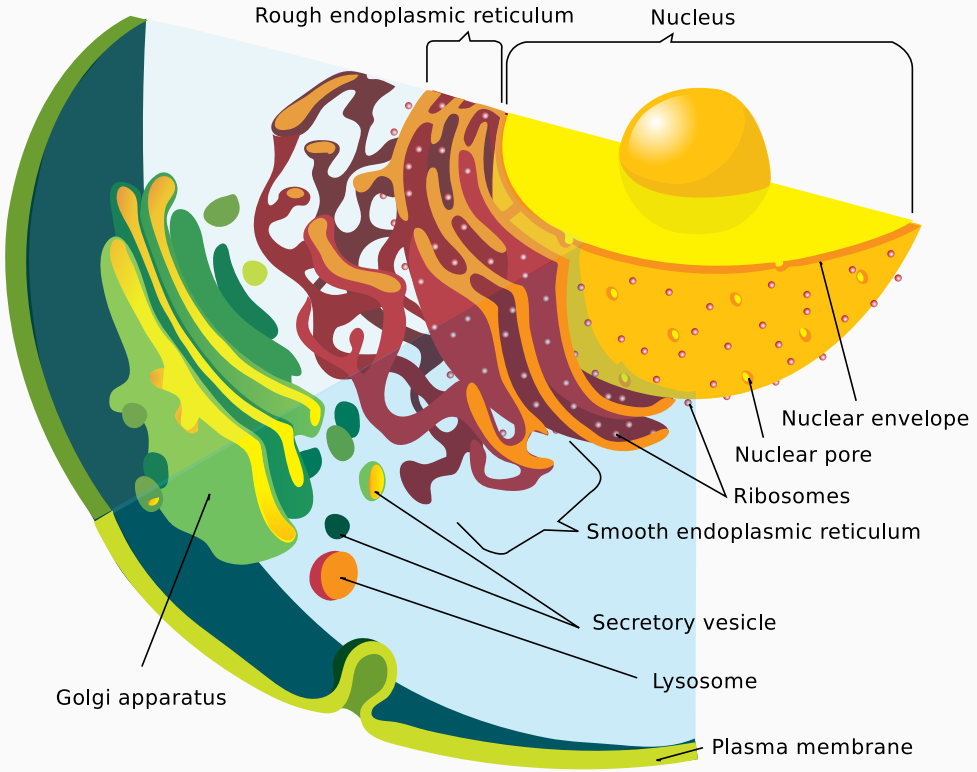
How can this be controlled?



12

[12] Bruce Alberts et al. (2008). *Molecular biology of the cell*. 5th ed. New York: Garland Science; S. Barolo (May 2002). "Three habits of highly effective signaling pathways: principles of transcriptional control by developmental cell signaling". In: *Genes & Development* 16.10, pp. 1167–1181.

Transport happens in confined geometries

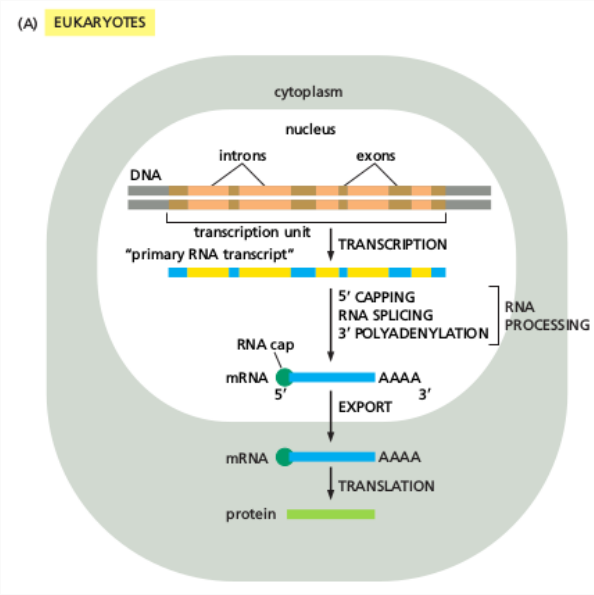


13

→ A microscopic model needs spatial and temporal resolution

[13] wikipedia

Some molecules appear in low copy numbers



- production of mRNAs → proteins occurs in pulses[14]
- stochasticity[15]
- mRNAs of particular species (coding a certain protein) may occur only 10-15 times in a cell[16]

→ A microscopic model needs to resolve single molecules

---

[14] Jonathan R. Chubb et al. (2006). "Transcriptional Pulsing of a Developmental Gene". In: *Current Biology* 16.10, pp. 1018–1025

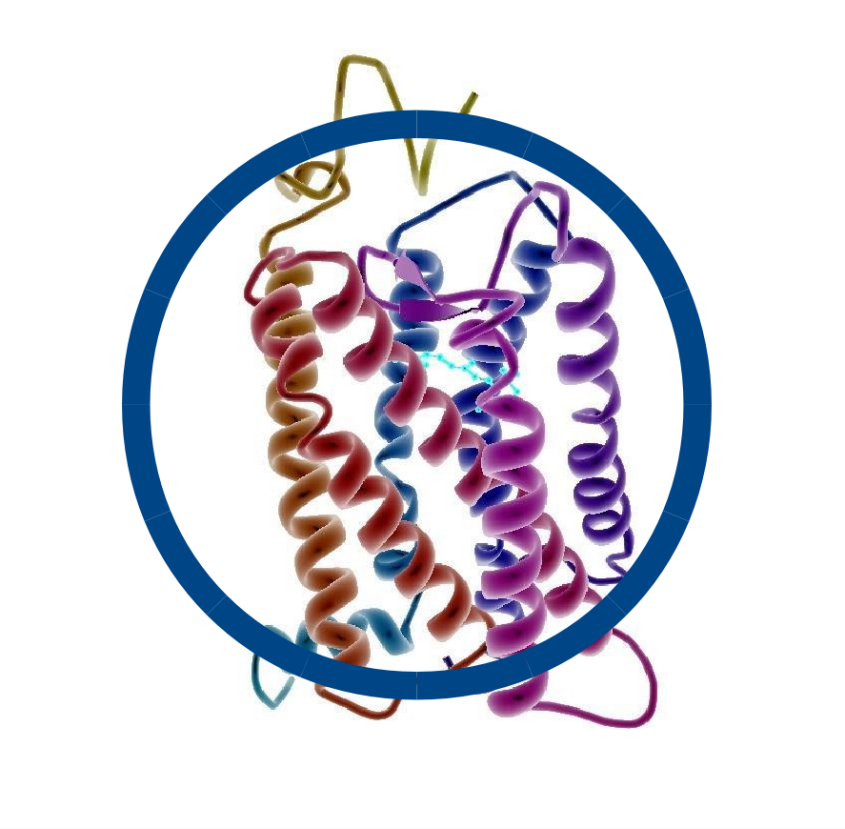
[15] M B Elowitz (Aug. 2002). "Stochastic Gene Expression in a Single Cell". In: *Science* 297.5584, pp. 1183–1186

[16] Bruce Alberts et al. (2008). *Molecular biology of the cell*. 5th ed. New York: Garland Science

Particle based reaction diffusion methods (PBRD and iPRD)

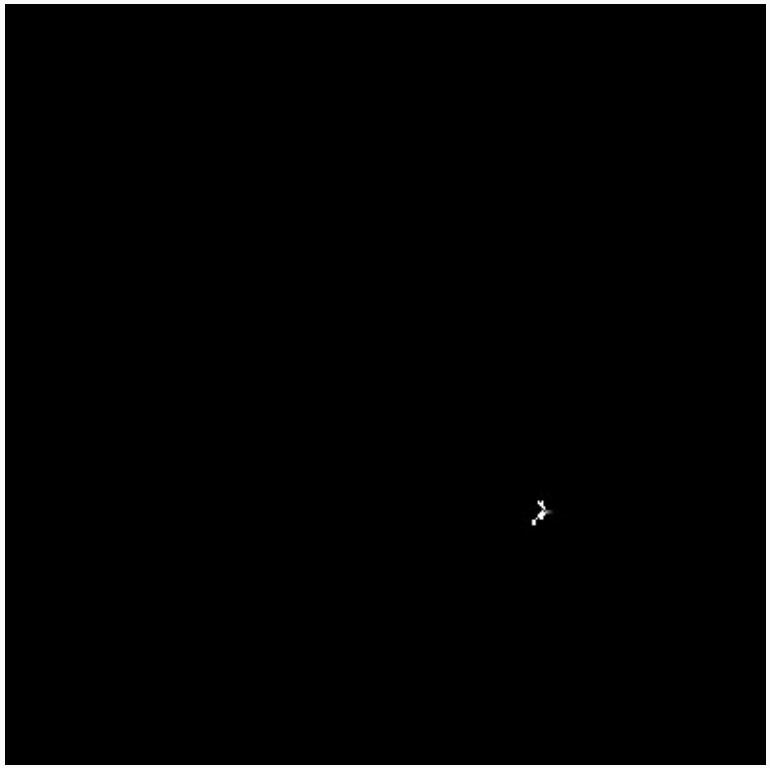
Particle based reaction diffusion methods

Molecules are represented as particles

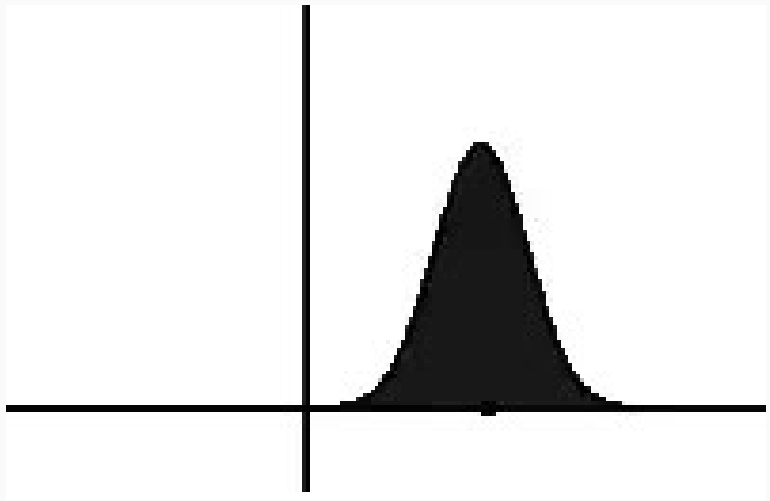


Diffusion

Brownian motion, formalized by Einstein, Smoluchowski ...

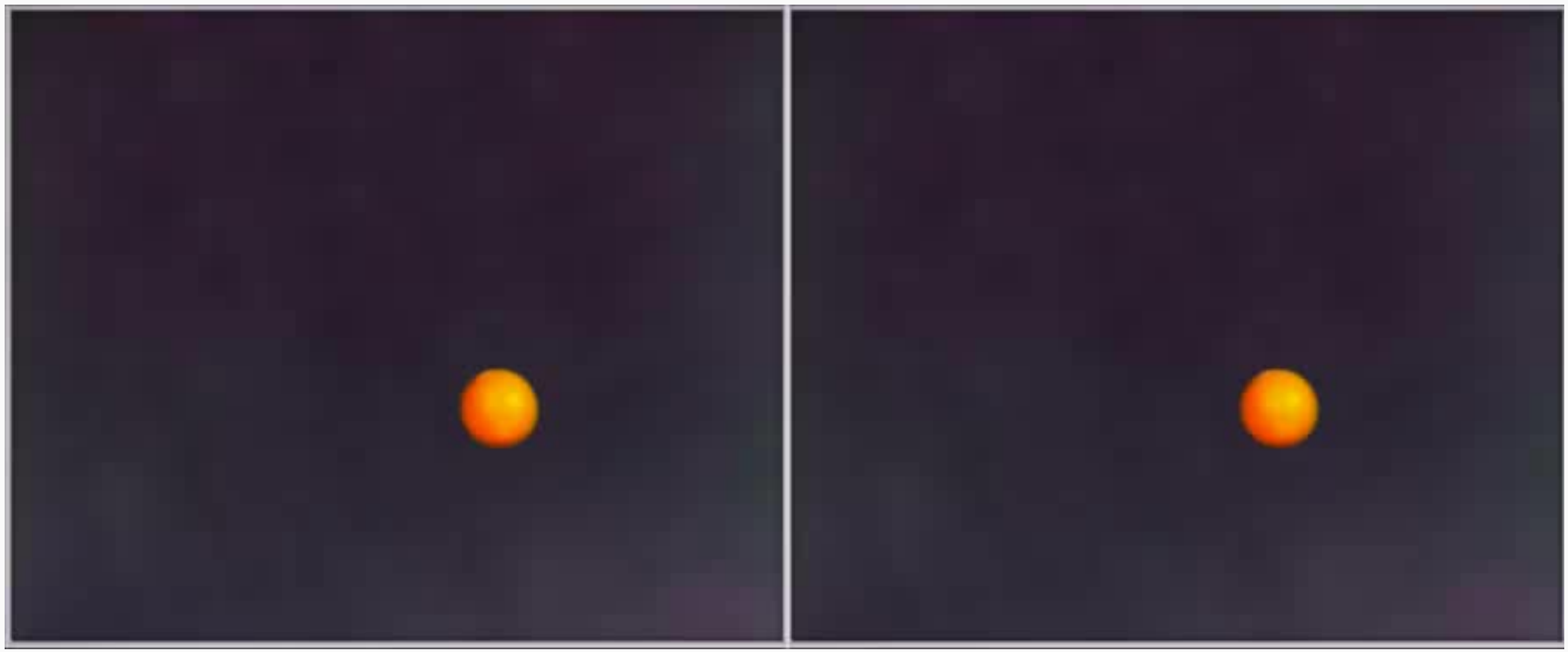


Stochastic



Probabilistic

Diffusion as a model for solvent



Langevin equation

$$m\frac{\mathrm{d}^2x}{\mathrm{d}t^2} = -\gamma\frac{\mathrm{d}x}{\mathrm{d}t} + F_{\mathrm{ext}}(x) + F_{\mathrm{random}}$$

Langevin equation

$$m\frac{\mathrm{d}^2x}{\mathrm{d}t^2} = -\gamma\frac{\mathrm{d}x}{\mathrm{d}t} + F_{\mathrm{ext}}(x) + F_{\mathrm{random}}$$

$$m\frac{\mathrm{d}^2x}{\mathrm{d}t^2} = -\gamma\frac{\mathrm{d}x}{\mathrm{d}t} - \nabla U(x) + F_{\mathrm{random}}$$

Langevin dynamics

Overdamped Langevin dynamics with *potentials*

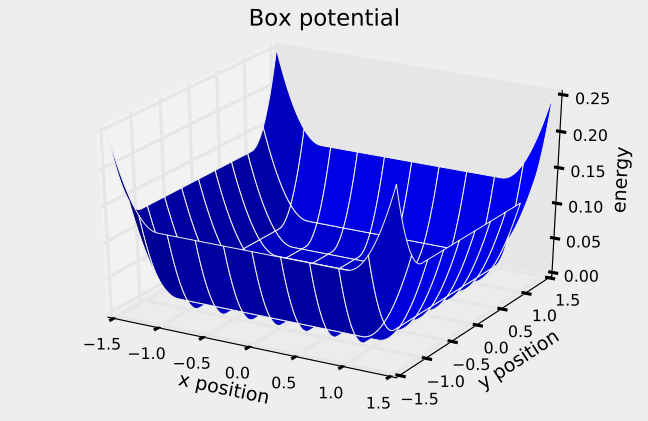
$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = -\beta D \nabla U(x(t)) + \xi(t), \quad \langle \xi(t)\xi(t') \rangle = 2D\delta(t - t')$$

Langevin dynamics

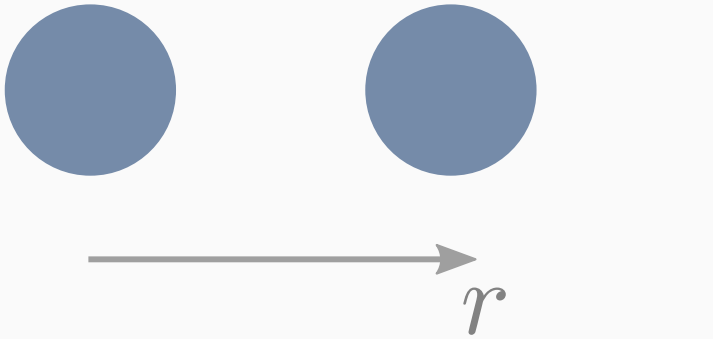
Overdamped Langevin dynamics with *potentials*

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = -\beta D \nabla U(x(t)) + \xi(t), \quad \langle \xi(t)\xi(t') \rangle = 2D\delta(t - t')$$

first order/external potentials

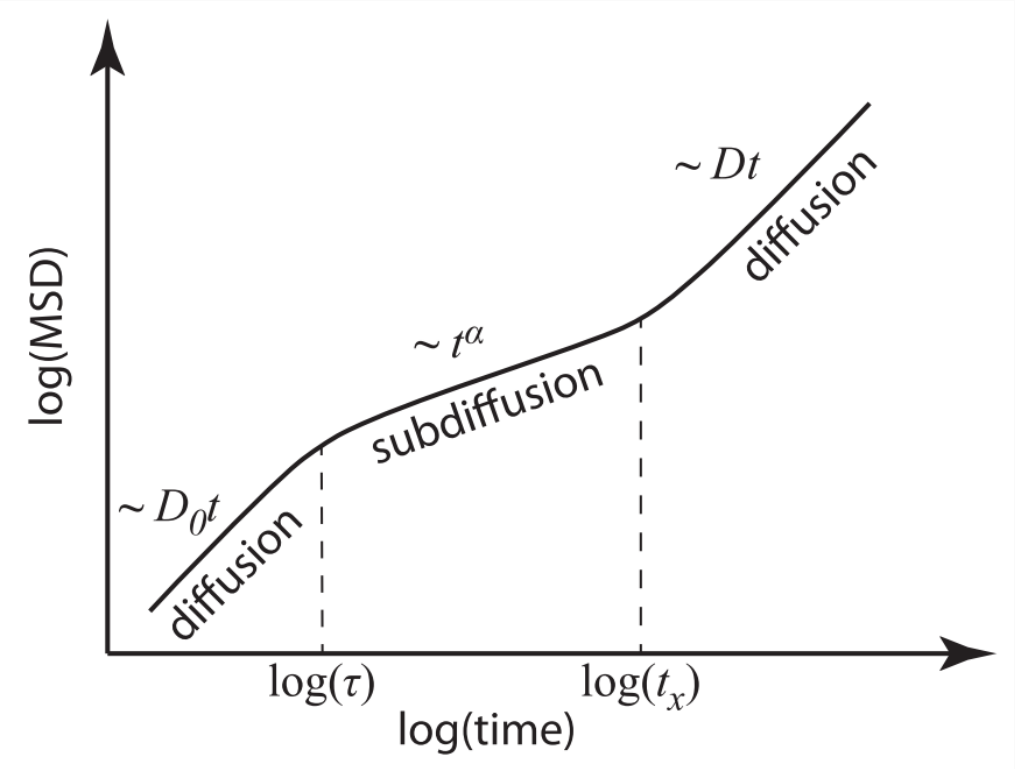


second order/pair potentials



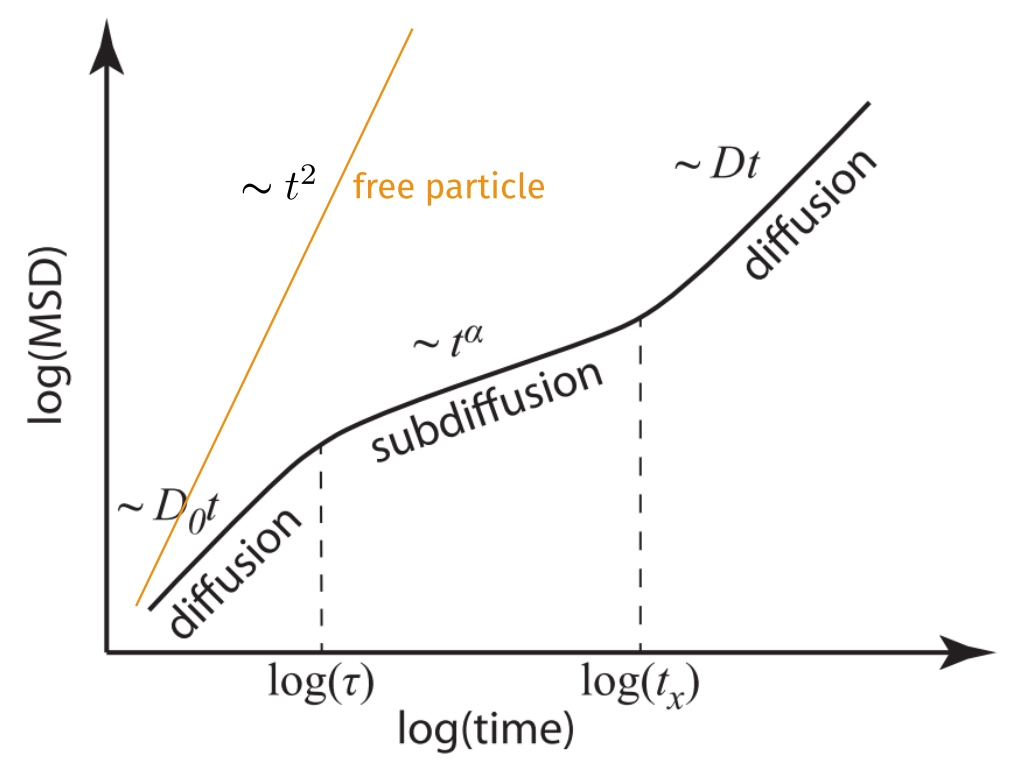
How to quantify diffusion? MSD

Mean Squared Displacement $= \langle (x_0 - x_t)^2 \rangle$



How to quantify diffusion? MSD

Mean Squared Displacement $= \langle (x_0 - x_t)^2 \rangle$

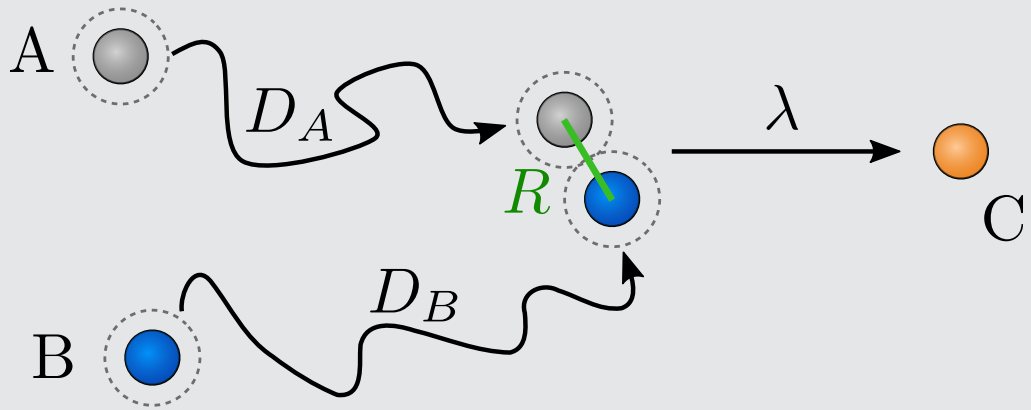


Reactions

Doi reaction model

Example:

$$\underset{\mathrm{R}}{\mathrm{A}+\mathrm{B}} \xrightarrow{\lambda_{\mathrm{on}}} \mathrm{C}$$

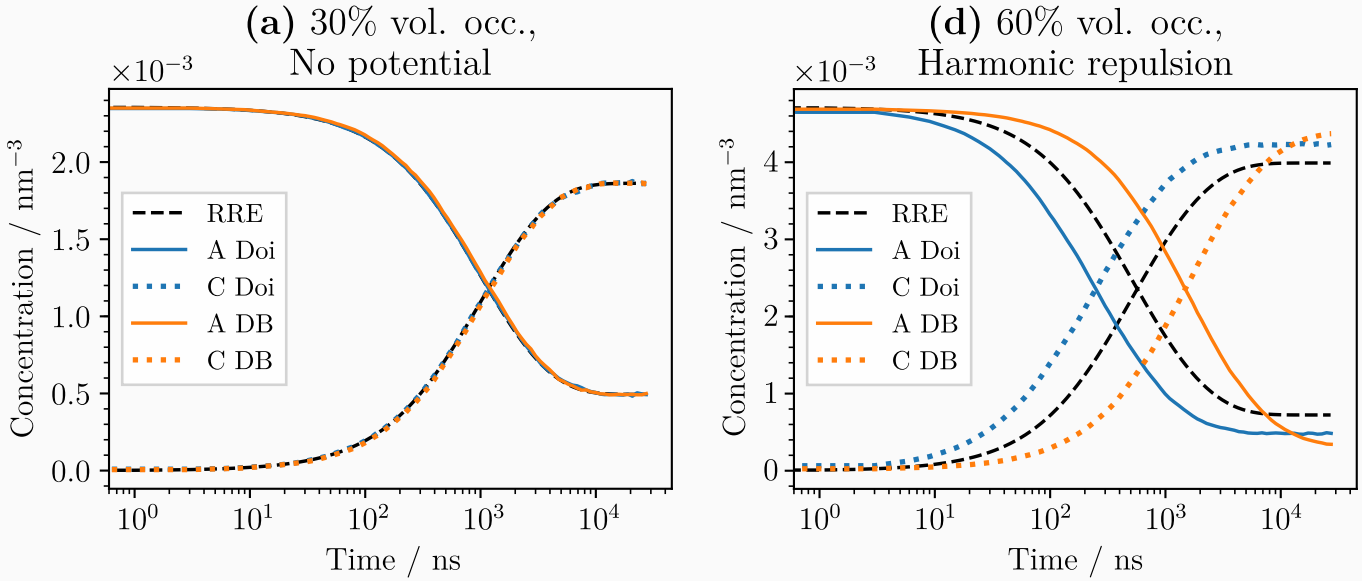


Reaction rates are microscopic → probability per unit time

How to quantify reactions? $n(t)$

Number of particles $n(t)$ will change over time

Consider A + B $\rightleftarrows$ C

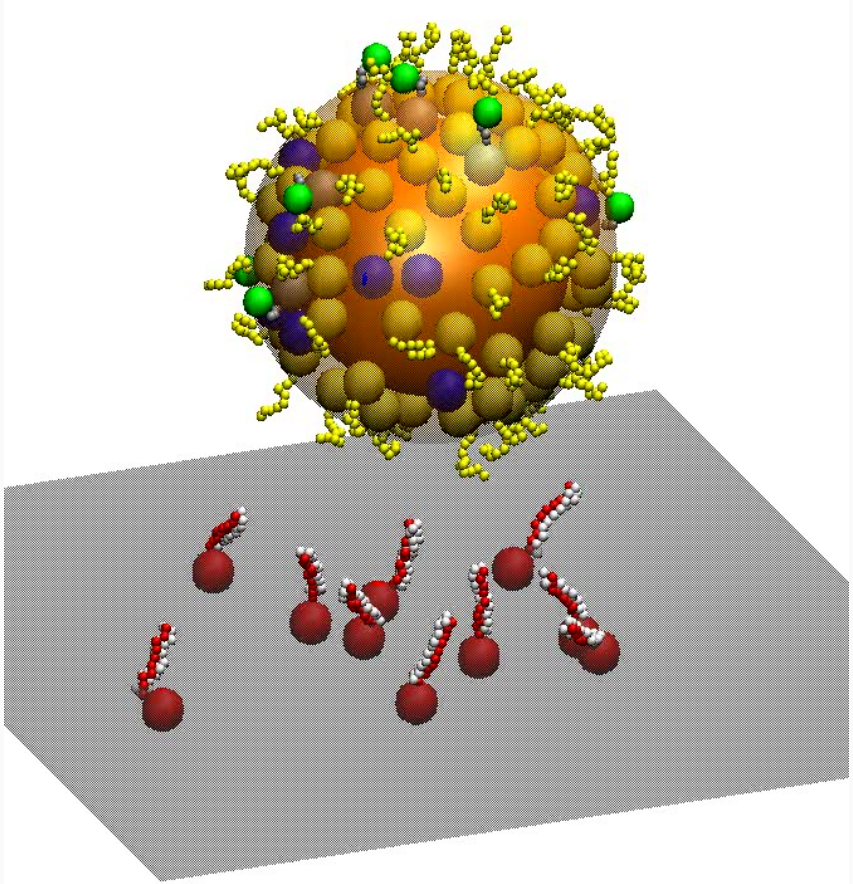


ReaDDy - an implementation of iPRD

ReaDDy

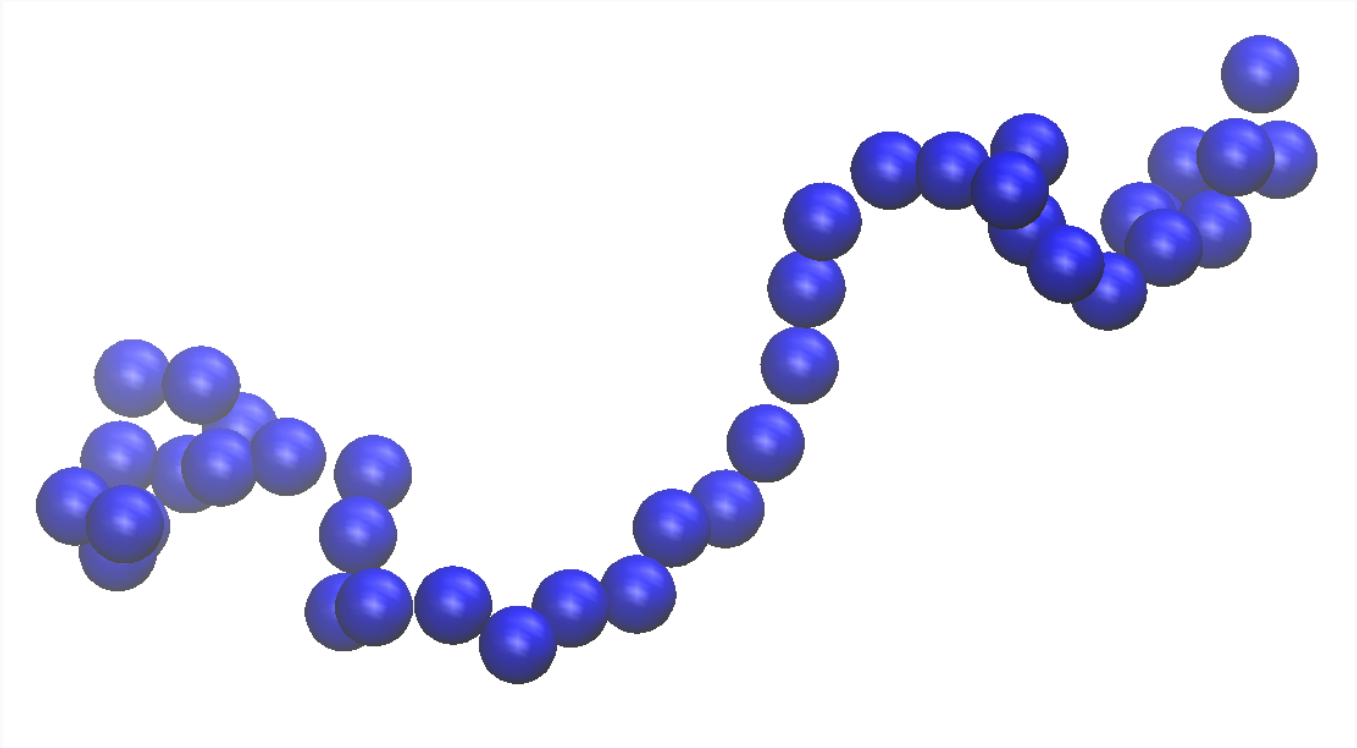
ReaDDy

ReaDDy

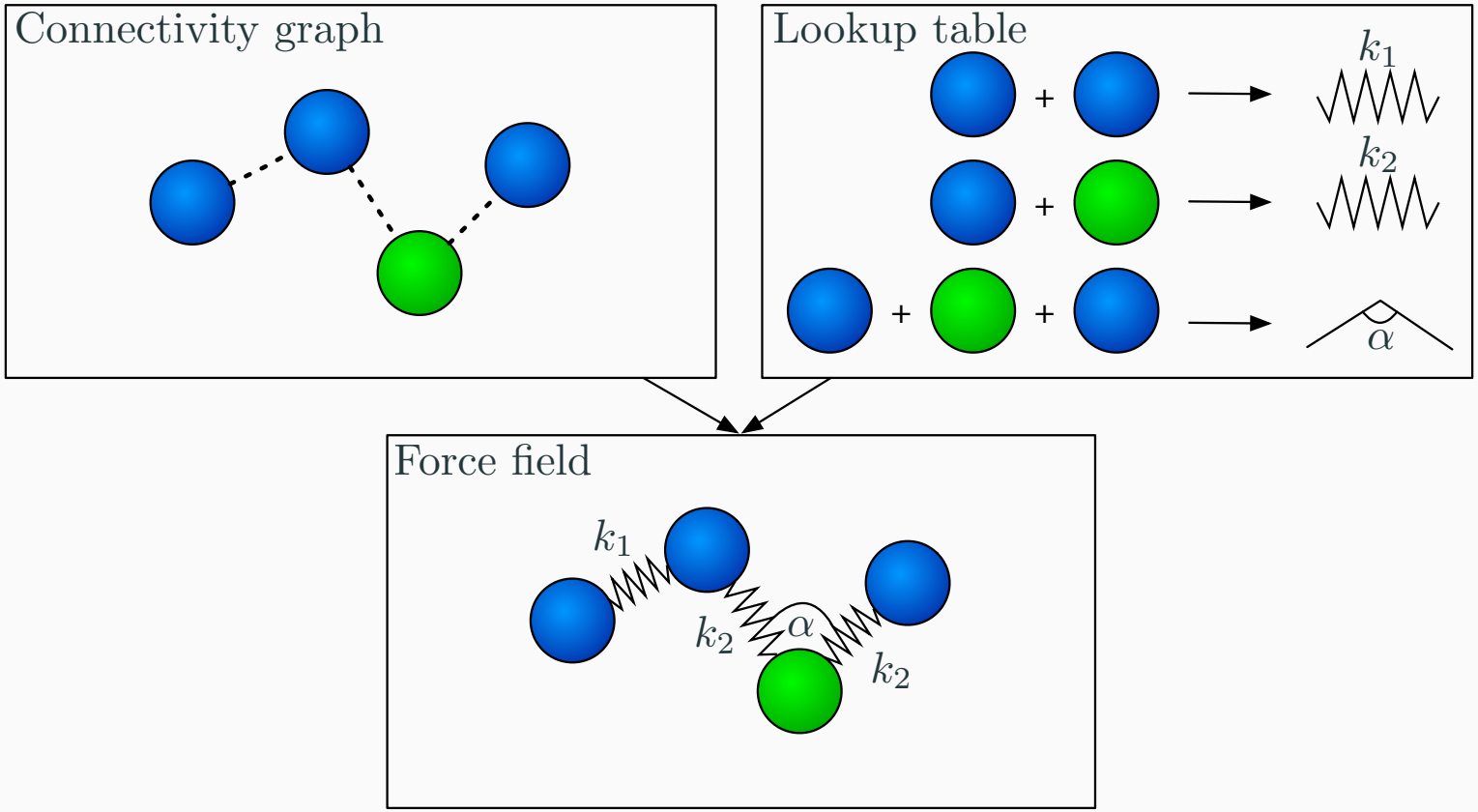


Topologies

- when structure of macromolecules is essential to the problem
- assembly of structures

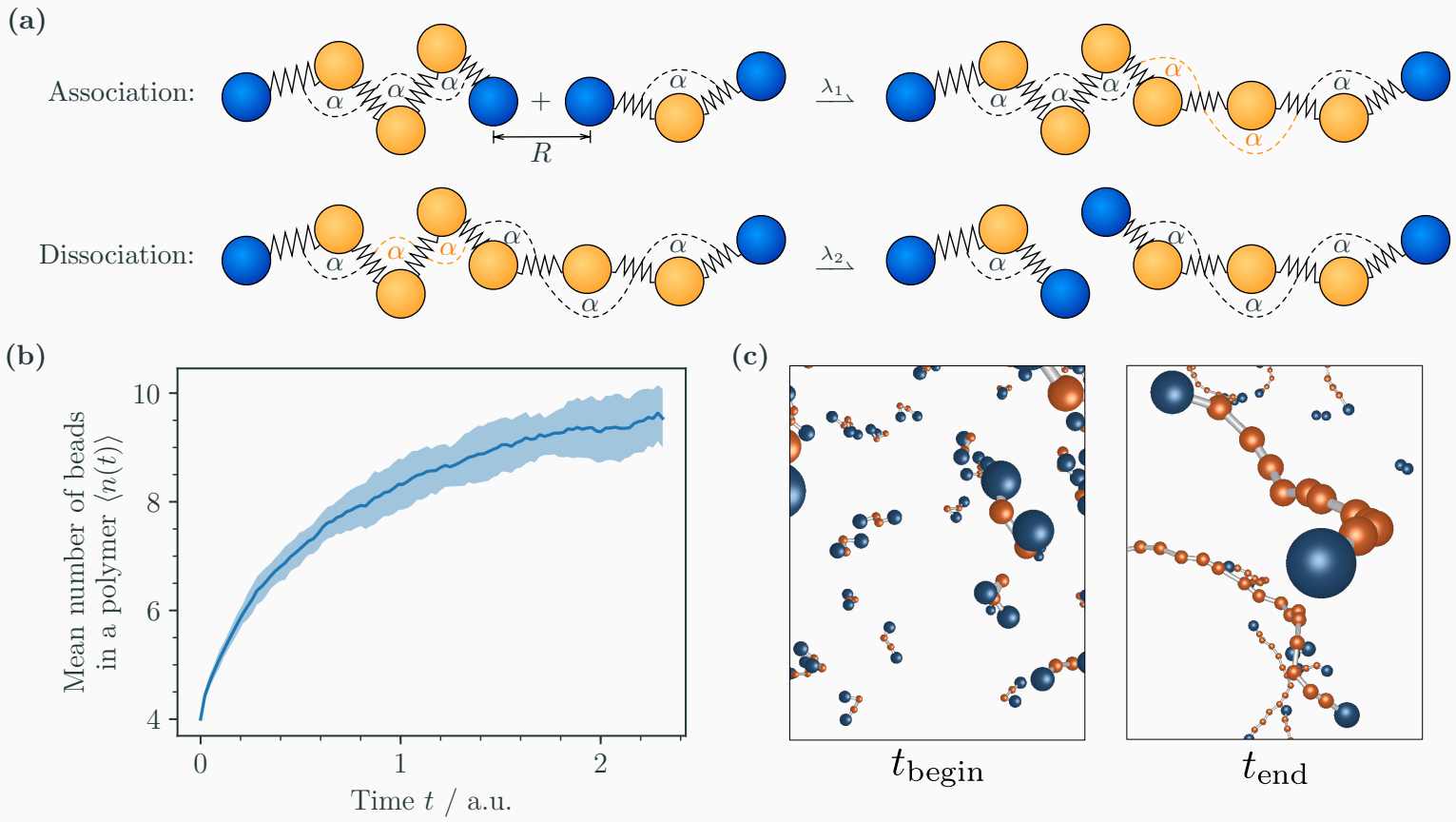


Force field

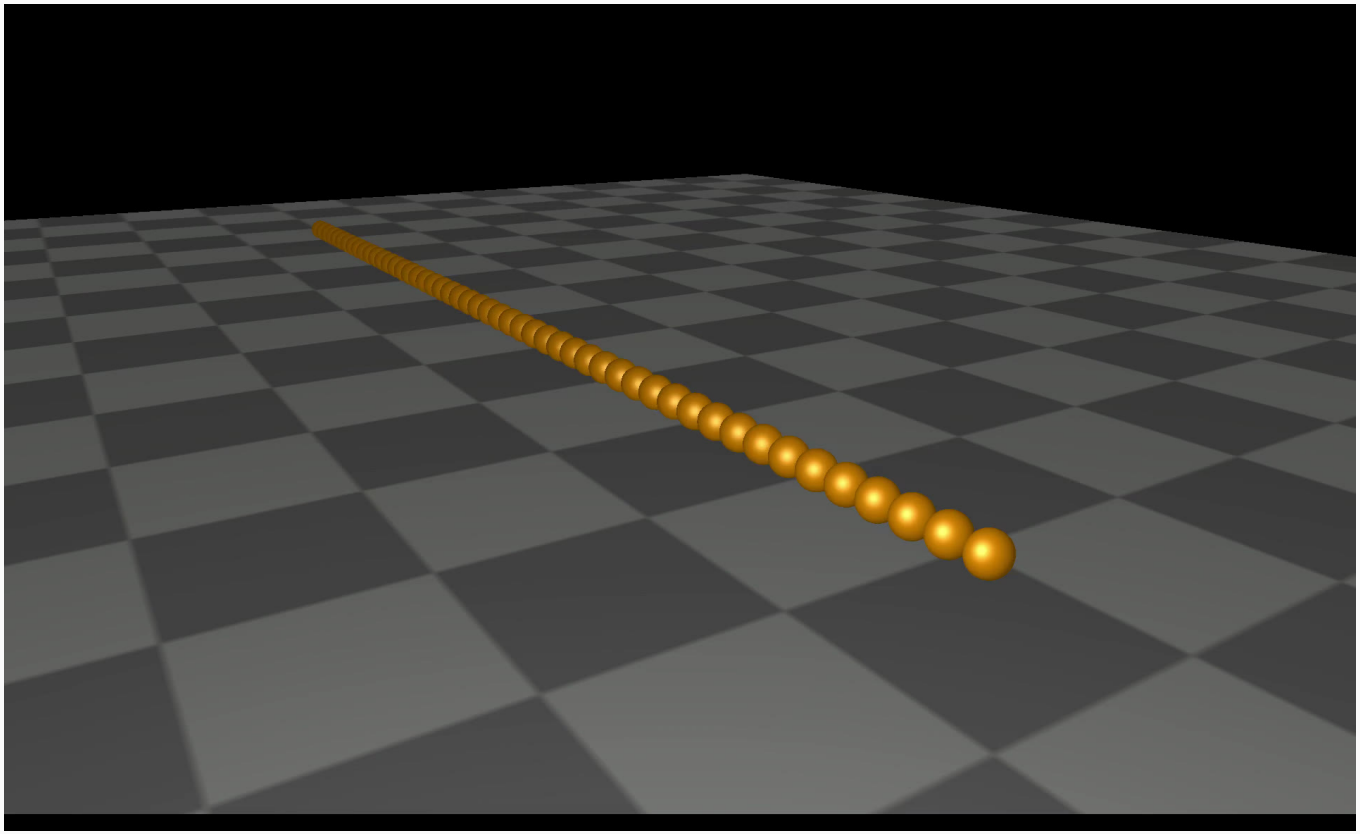

Connectivity graph
Lookup table
k_1
k_2
α
Force field
k_1
k_2
α
k_2

Topology reactions

Topology reactions allow changes to the graph



Topology reactions

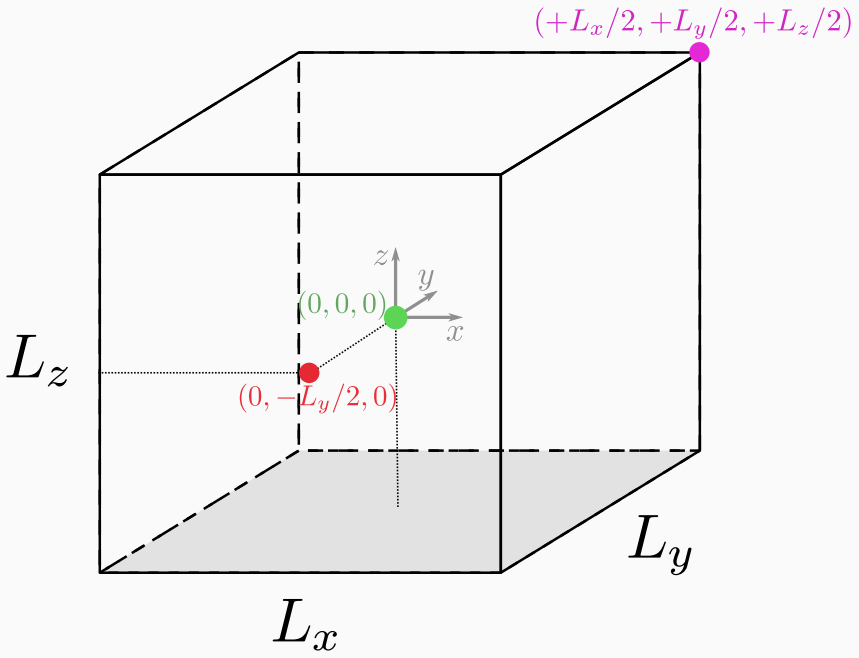


Simulation box

Particles are put in a (periodic) box

Simulation box

$\texttt{box_size} = (L_x, L_y, L_z)$



Simulation loop

Dynamics are propagated in time

```
begin
    initialize compute kernel;
    if has output file then
        write simulation setup;
    set up neighbor list;
    compute forces;
    evaluate observables;
    while continue simulating do
        call integrator;
        update neighbor list;
        perform reactions;
        perform topology reactions;
        update neighbor list;
        calculate forces;
        evaluate observables;
    tear down compute kernel;
```

Schedule

Monday	Introduction, installing ReaDDy, basic features of ReaDDy, observables and callbacks
Tuesday	Different reaction diffusion models, Lotka Volterra simulations, Reaction-limited vs. diffusion-limited
Wednesday	Macromolecules/coarse graining, Topology simulations, self assembly
Thursday	ReaDDy software structure, extend ReaDDy functionality, writing C++ potentials
Friday	Simulate your own system

References

References i

- Alberts, Bruce et al. (2008). *Molecular biology of the cell*. 5th ed. New York: Garland Science.
- Albrecht, David et al. (Oct. 2016). “Nanoscopic compartmentalization of membrane protein motion at the axon initial segment”. In: *The Journal of Cell Biology* 215.1, pp. 37–46.
- Barolo, S. (May 2002). “Three habits of highly effective signaling pathways: principles of transcriptional control by developmental cell signaling”. In: *Genes & Development* 16.10, pp. 1167–1181.
- Chubb, Jonathan R. et al. (2006). “Transcriptional Pulsing of a Developmental Gene”. In: *Current Biology* 16.10, pp. 1018–1025.
- Elowitz, M B (Aug. 2002). “Stochastic Gene Expression in a Single Cell”. In: *Science* 297.5584, pp. 1183–1186.

References ii

- Gunkel, Manuel et al. (2009). “Dual color localization microscopy of cellular nanostructures”. In: *Biotechnology Journal* 4.6, pp. 927–938.
- Kole, Maarten H.P. and Greg J. Stuart (Jan. 2012). “Signal Processing in the Axon Initial Segment”. In: *Neuron* 73.2, pp. 235–247.
- Levitan, Irwin B and Leonard K Kaczmarek (2015). *The neuron: cell and molecular biology*. Oxford University Press, USA.
- Liebermeister, Wolfram et al. (2014). “Visual account of protein investment in cellular functions”. In: *Proceedings of the National Academy of Sciences*, p. 201314810.
- Lippincott-Schwartz, J. (Apr. 2003). “Development and Use of Fluorescent Protein Markers in Living Cells”. In: *Science* 300.5616, pp. 87–91.

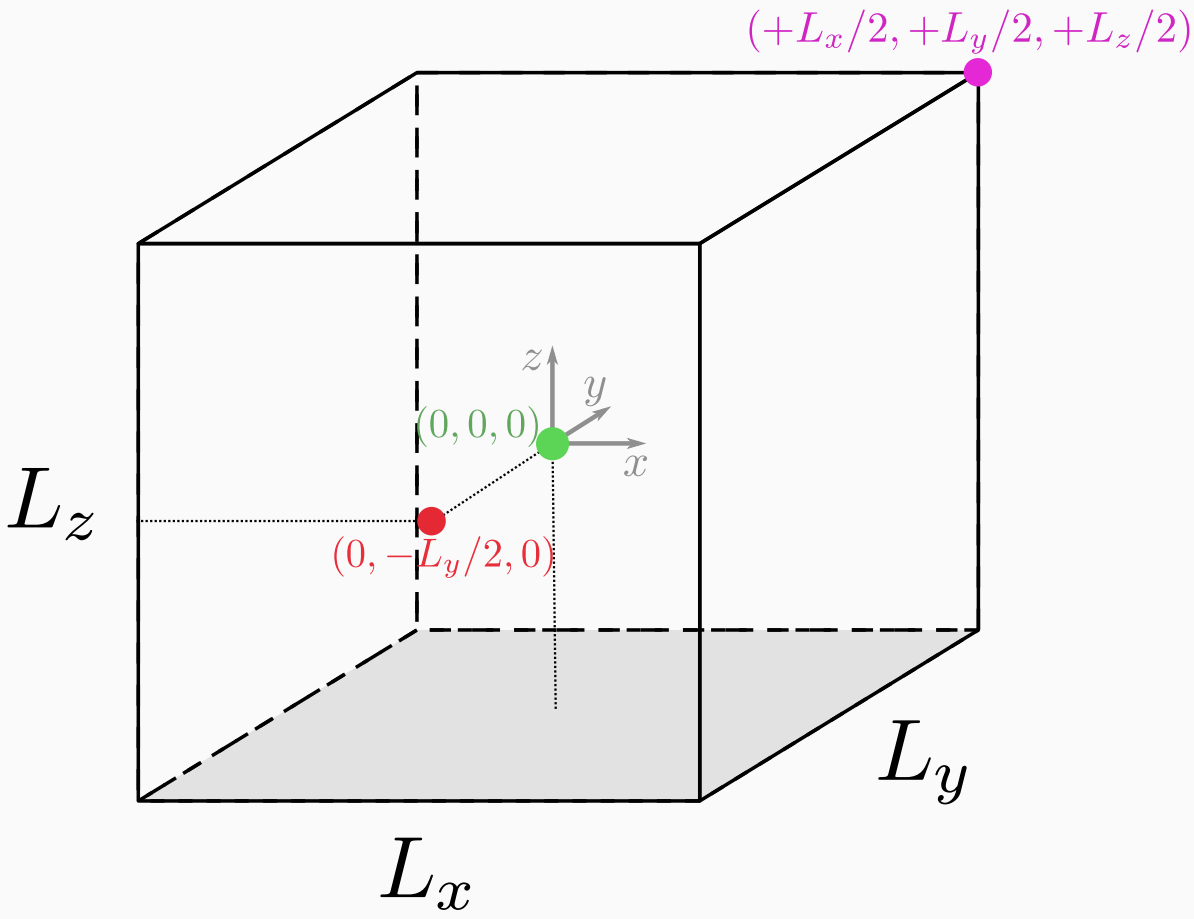
References iii

- McGuffee, Sean R and Adrian H Elcock (2010). “Diffusion, crowding & protein stability in a dynamic molecular model of the bacterial cytoplasm”. In: *PLoS computational biology* 6.3, e1000694.
- Sahoo, Harekrushna (2011). “Förster resonance energy transfer - A spectroscopic nanoruler: Principle and applications”. In: *Journal of Photochemistry and Photobiology C: Photochemistry Reviews* 12.1, pp. 20–30.
- Thompson, Nancy L (2002). “Fluorescence correlation spectroscopy”. In: *Topics in fluorescence spectroscopy*. Springer, pp. 337–378.
- Yu, Isseki et al. (2016). “Biomolecular interactions modulate macromolecular structure and dynamics in atomistic model of a bacterial cytoplasm”. In: *eLife* 5.NOVEMBER2016, pp. 1–22.

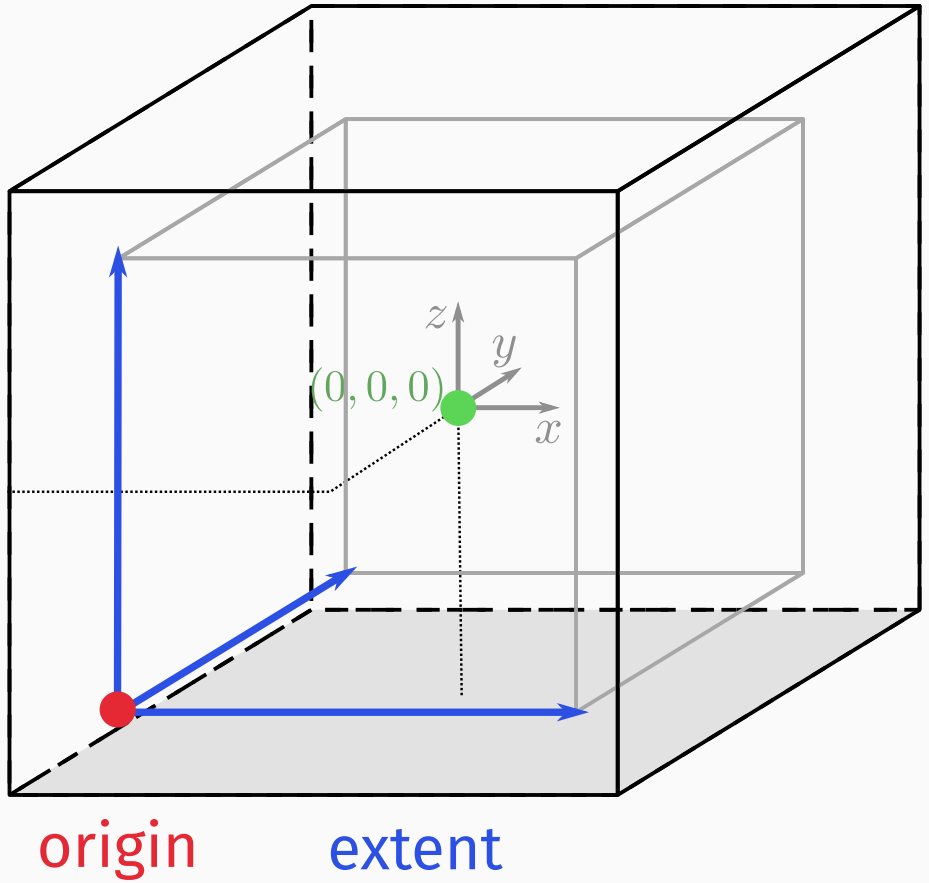
Simulation box coordinates

Simulation box

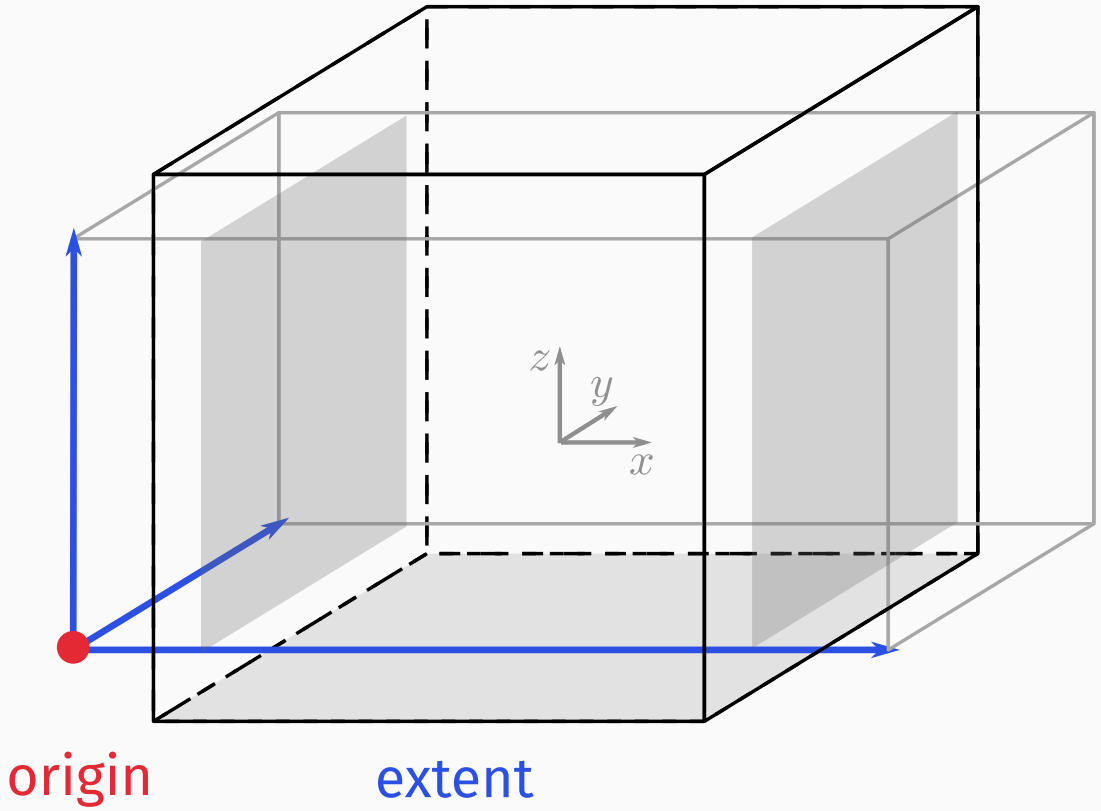
$$\texttt{box_size}= (L_x, L_y, L_z)$$



Box potential within simulation box



Box potential extending simulation box



simulation box must be periodic in x