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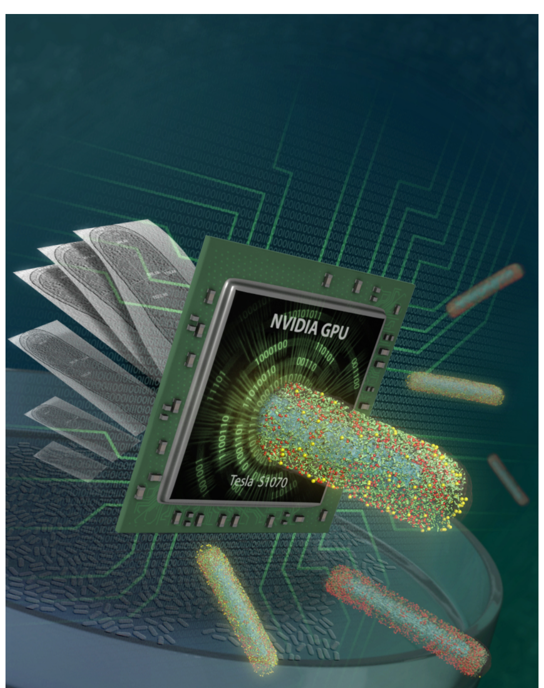
Part 3: Introduction to Master Equation and Complex Initial Conditions in Lattice Microbes

Joseph R. Peterson and Michael J. Hallock
Luthey-Schulten Laboratory
University of Illinois at Urbana-Champaign



NIH Workshop on Computational Biophysics
November 17th, 2016
George Institute of Technology
Atlanta, GA, USA

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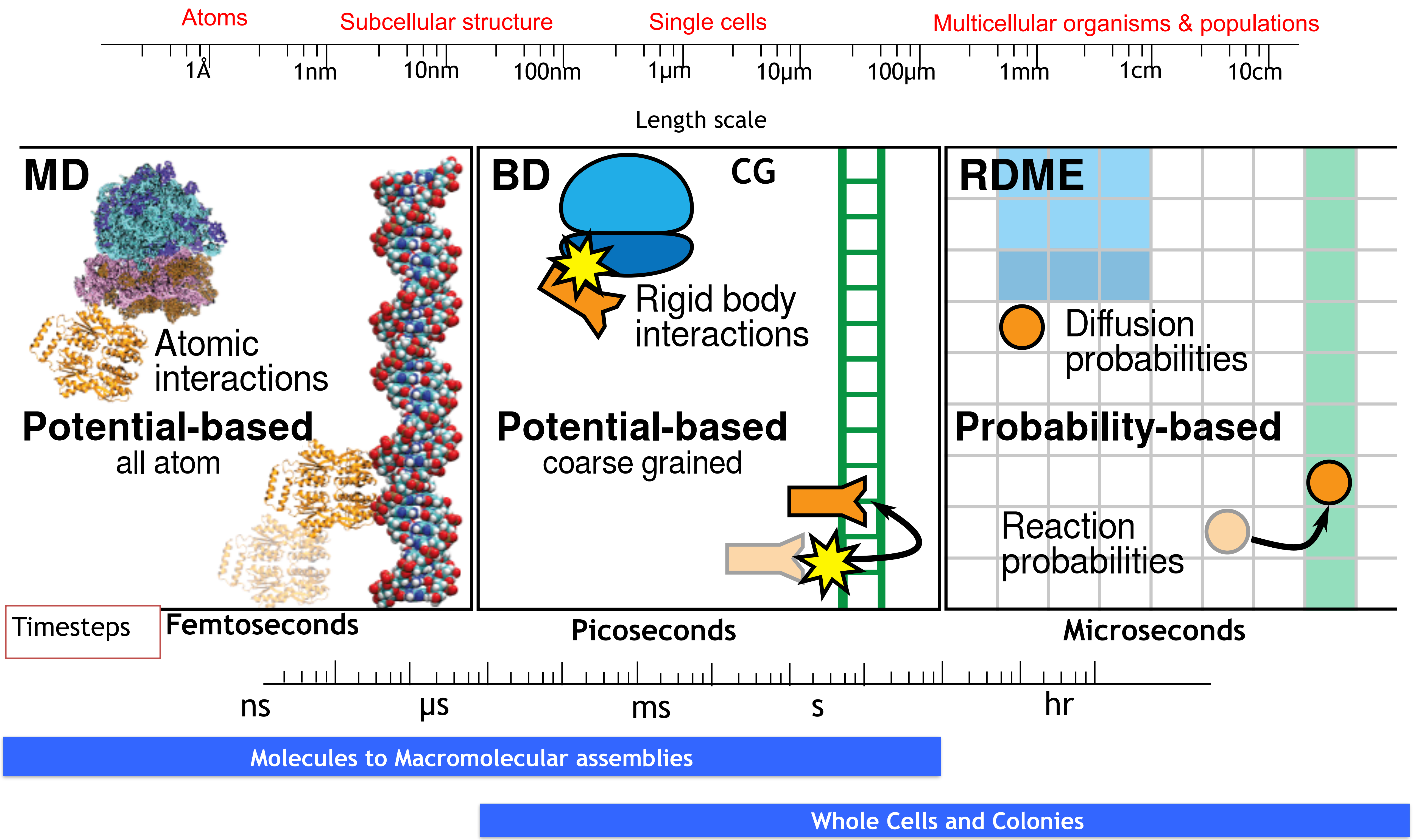
Introduction to Master Equation and LM Simulations

- Theory
  - Master Equation
  - Chemical Master Equation
    - Stochastic Gene Expression
    - Predator-Prey Model
    - Effect of DNA Replication
  - Reaction-Diffusion Master Equation
    - “Min” System
- Creating Complex Geometries in Lattice Microbes

Biological Modeling at Different Scales



Master Equation

Deterministic ODE

$$\frac{d\vec{x}}{dt} = \mathbf{A}\vec{x}$$

Probabilistic ODE

$$\frac{dP(\vec{s},t)}{dt} = \mathbf{A}P(\vec{s},t)$$

State Vector

$$\vec{s} = \begin{pmatrix} s_1 \\ s_2 \\ \ldots \\ s_N \end{pmatrix}$$

Transition Matrix
(Probability of Birth/Death)

$$\mathbf{A}(t) = \mathbf{A}(0)$$

Chemical Master Equation

$$\frac{dP(\vec{s},t)}{dt} = \mathbf{A}P(\vec{s},t) \qquad \mathbf{A} = \mathbf{R} \cdot \mathbf{S}$$

Transition Matrix Represents Chemical Reactions by:

Rate Matrix

$$\mathbf{R} = \begin{pmatrix} \alpha_1 \\ \alpha_2 \\ \cdots \\ \alpha_M \end{pmatrix}^{\mathsf{T}}$$

Stoichiometric Matrix

$$\mathbf{S} = \begin{pmatrix} s_{1,1} & s_{1,2} & \cdots & s_{,M} \\ \vdots & \vdots & \ddots & \vdots \\ s_{1,M} & \cdots & \cdots & s_{N,M} \end{pmatrix}$$

where: α_i are propensities for a reaction to occur

and: $s_{i,j}$ are the counts of each reactant

Chemical Master Equation

$$\frac{dP(\vec{s,t})}{dt} = \sum_{\mu=1}^{N} \alpha_\mu(\vec{s} - s_\mu)P(\vec{s} - s_\mu, t) - \alpha_\mu(\vec{s})P(\vec{s}, t)$$

Transition propensities are related to macroscopic rate constants:

First order: $s_i \xrightarrow{k} p_i$ $\alpha(\vec{s}) = ks_i$

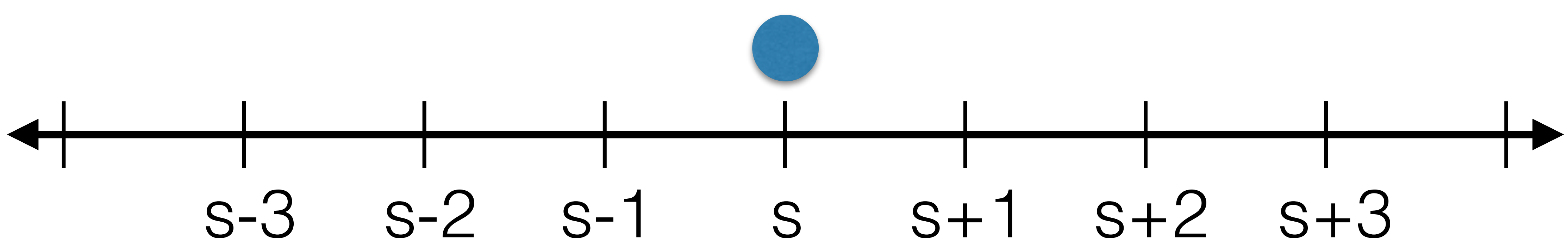
Second order: $s_i + s_j \xrightarrow{k} p_i$ $\alpha(\vec{s}) = \frac{k}{V}s_i s_j$

Probability of reaction μ occurring in some time is:

$$\alpha_\mu(\vec{s})dt$$

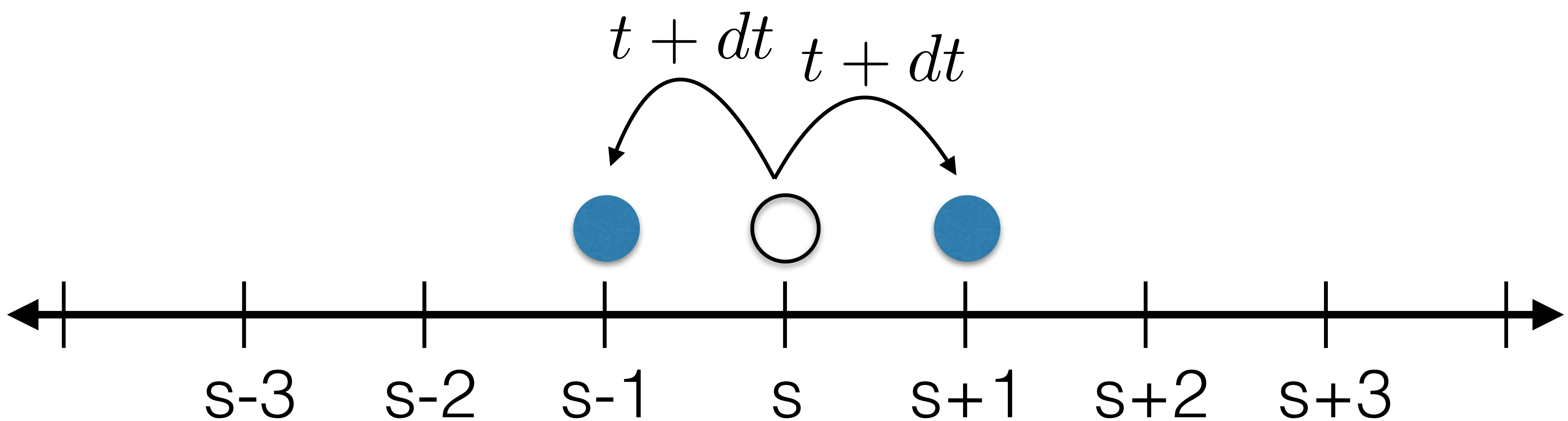
Chemical Master Equation

$$\frac{dP(\vec{s},t)}{dt} = \sum_{\mu=1}^{N} \alpha_\mu(\vec{s} - s_\mu)P(\vec{s} - s_\mu, t) - \alpha_\mu(\vec{s})P(\vec{s}, t)$$



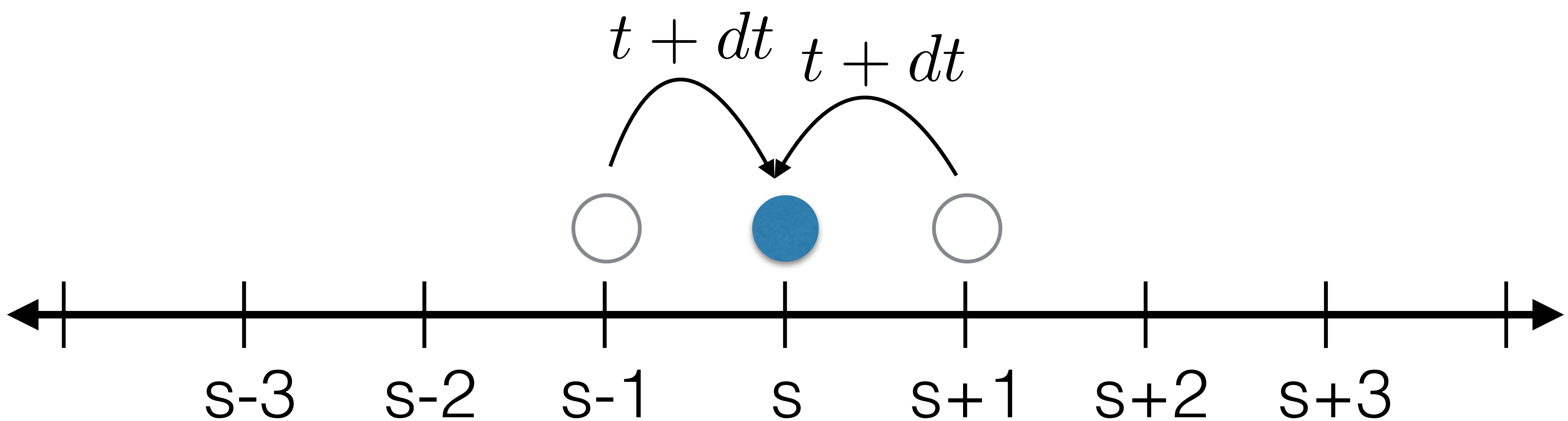
Chemical Master Equation

$$\frac{dP(\vec{s,t})}{dt} = \sum_{\mu=1}^{N} \alpha_\mu(\vec{s} - s_\mu)P(\vec{s} - s_\mu, t) - \alpha_\mu(\vec{s})P(\vec{s}, t)$$



Chemical Master Equation

$$\frac{dP(\vec{s,t})}{dt} = \sum_{\mu=1}^{N} \boxed{\alpha_\mu(\vec{s} - s_\mu)P(\vec{s} - s_\mu, t)} - \alpha_\mu(\vec{s})P(\vec{s}, t)$$



Stochastic Gene Expression

Reaction Scheme

$$D \xrightarrow{k_t} D + m$$

$$M \xrightarrow{k_d} \emptyset$$

Constitutive
Gene Expression

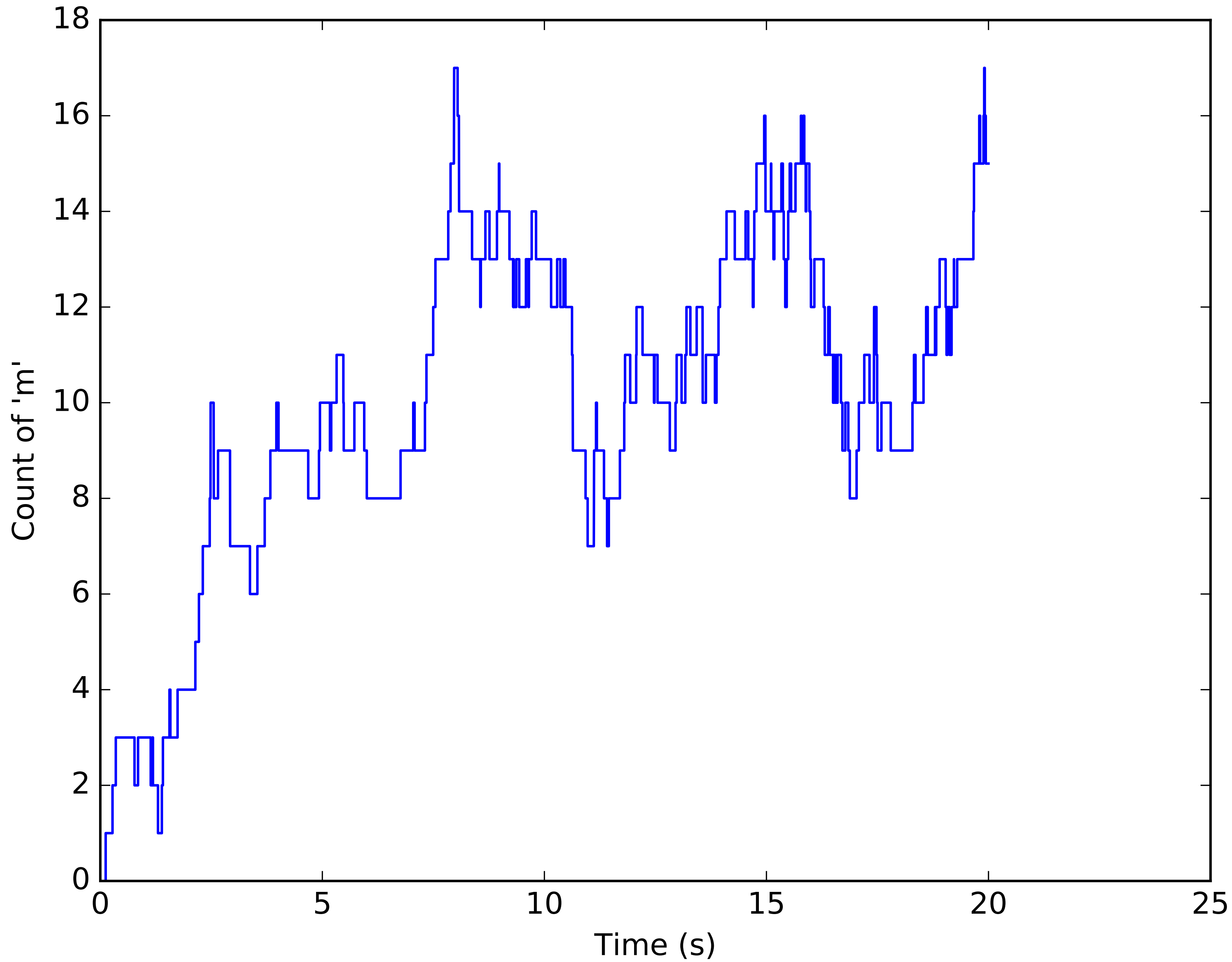
ODE

$$\frac{dm}{dt} = k_t - k_d m$$

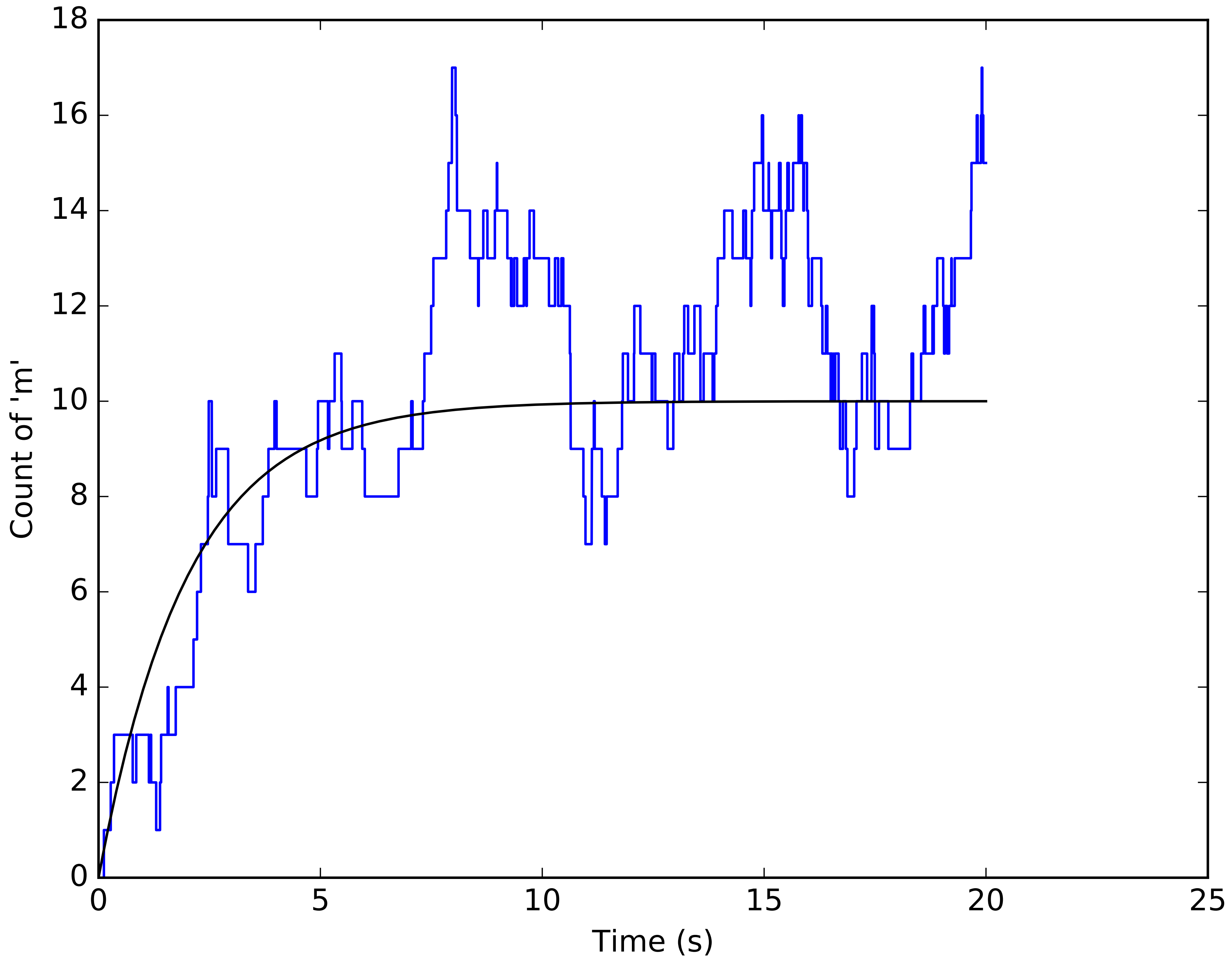
Chemical Master Equation

$$\frac{dP(m,t)}{dt} = - k_t P(m,t) - k_d m P(m,t) + k_t P(m-1,t) + k_d (m+1) P(m+1,t)$$

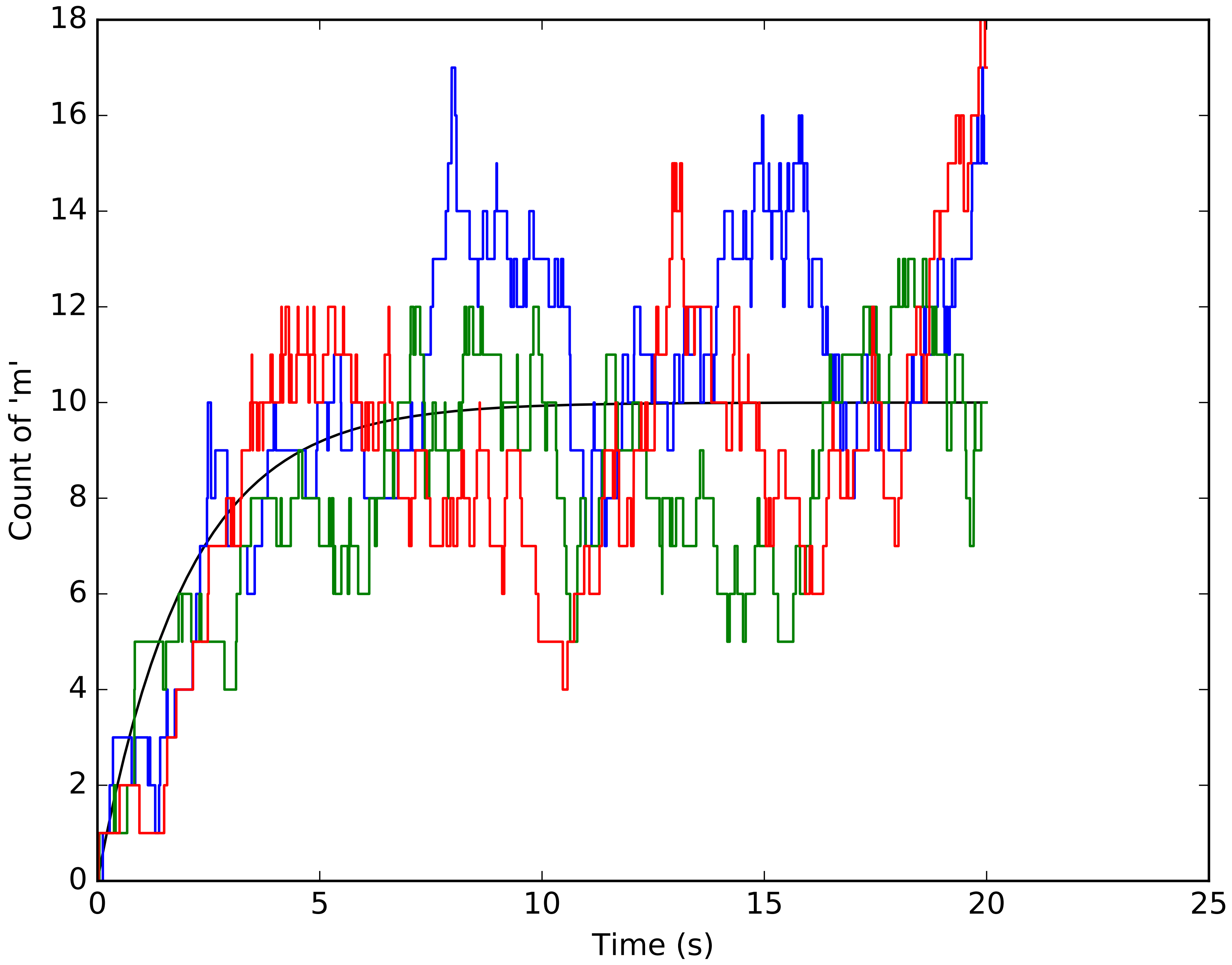
Stochastic Gene Expression



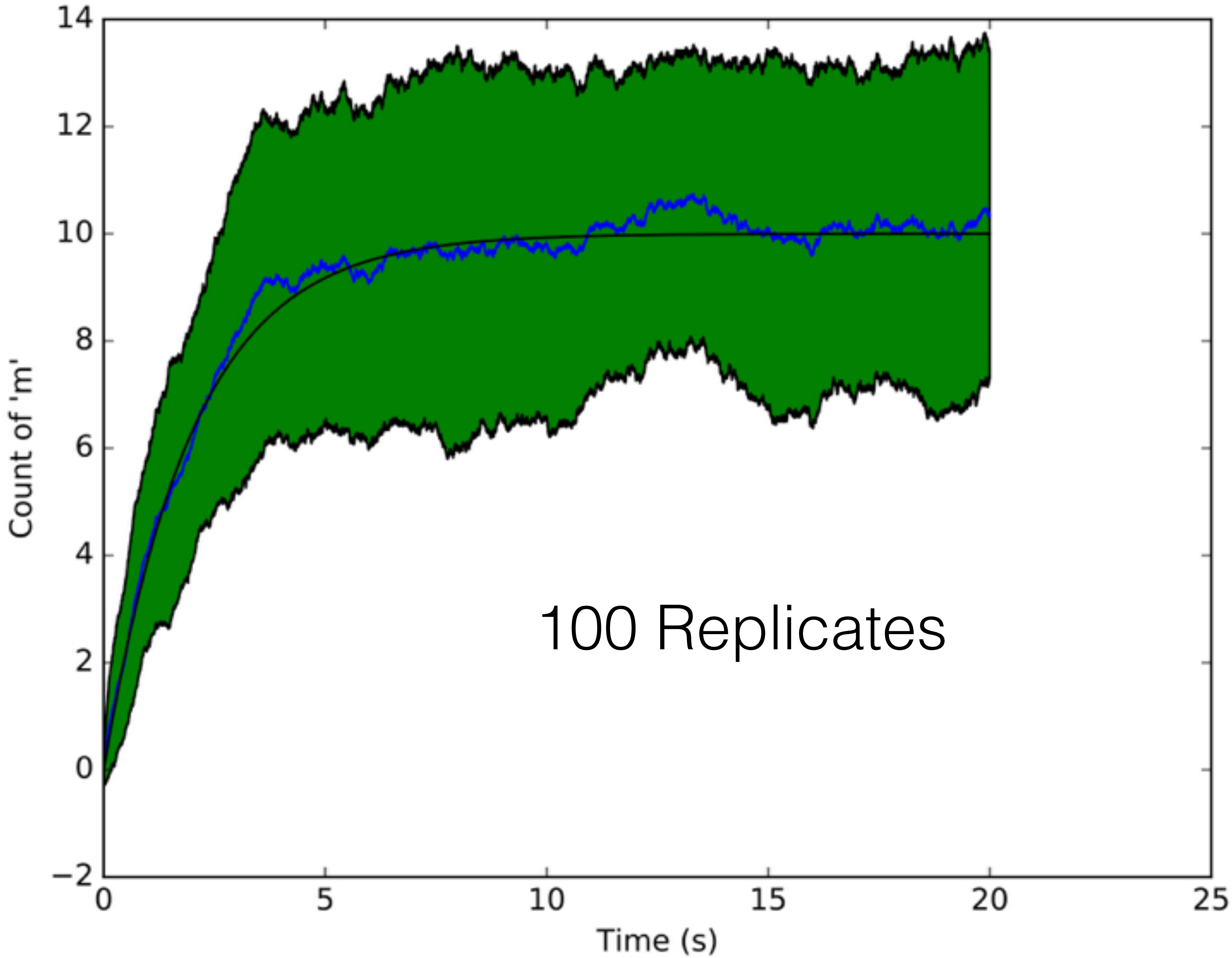
Stochastic Gene Expression



Stochastic Gene Expression



Stochastic Gene Expression



Exact Solution to Constitutive Gene Expression

Moment Generating Function

$$F(z,t) = \sum_{m=0}^{\infty} z^m P(m,t)$$

$$\frac{\partial F(z,t)}{\partial t} = \sum_{m=0}^{\infty} m z^{m-1} P(m,t)$$

CME

$$\frac{dP(m,t)}{dt} = -k_t P(m,t) - k_d m P(m,t) + k_t P(m-1,t) + k_d (m+1) P(m+1,t)$$

Multiply by z^m and sum over m

$$\frac{\partial F(z,t)}{\partial t} = -k_t \sum_{m=0}^{\infty} z^m P(m,t) - k_d \sum_{m=0}^{\infty} m z^m P(m,t) + k_t \sum_{m=0}^{\infty} z^m P(m-1,t) + k_d \sum_{m=0}^{\infty} z^m (m+1) P(m+1,t)$$

Factor out z and Compute Moments

$$\frac{\partial F(z,t)}{\partial t} = -k_t F(z,t) - k_d z F(z,t) + k_t z F(z,t) + k_d \frac{\partial F(z,t)}{\partial t}$$

Exact Solution to Constitutive Gene Expression

$$\frac{\partial F(z,t)}{\partial t} = -k_t F(z,t) - k_d z F(z,t) + k_t z F(z,t) + k_d \frac{\partial F(z,t)}{\partial t}$$

Assume Steady-State and Solve

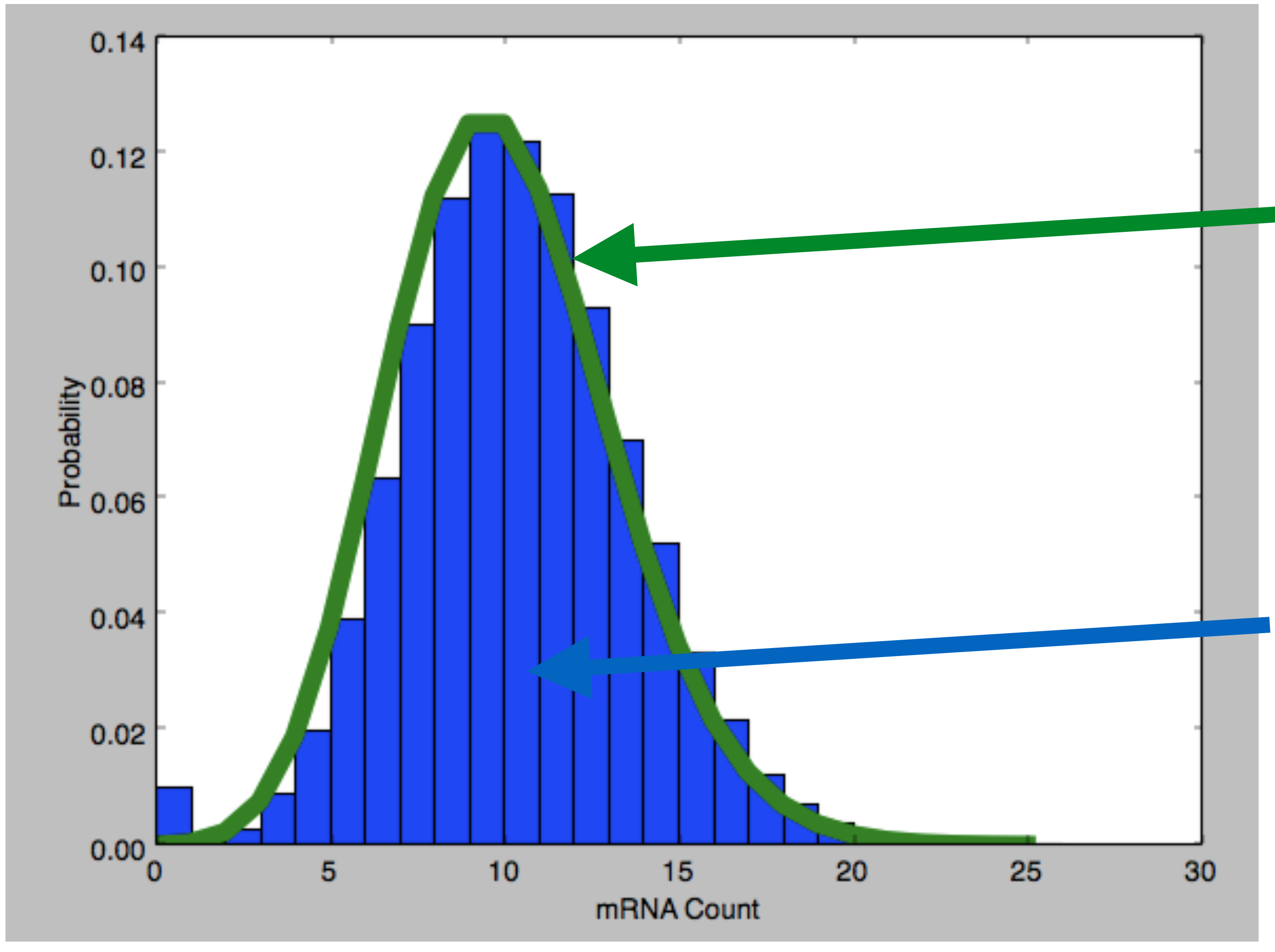
$$F(z,t) = Ce^{\frac{k_t}{k_d} z}$$

Taylor Expand and Group Terms

$$F(z) = e^{-\frac{k_t}{k_d}} \sum_{m=0}^{\infty} \frac{\left(\frac{k_t}{k_d}\right)^m}{m!} z^m \longrightarrow P(m) = \frac{e^{-\frac{k_t}{k_d}} \left(\frac{k_t}{k_d}\right)^m}{m!}$$

Exact Solution to Constitutive Gene Expression

$$P(m) = \frac{e^{-\frac{k_t}{k_d}} \left(\frac{k_t}{k_d}\right)^m}{m!} \longrightarrow \quad \langle m \rangle = \frac{k_t}{k_d} \qquad Var[m] = \frac{k_t}{k_d}$$



Exact Distribution

Simulated Distribution

Lotka-Volterra (Predator-Prey)

Model

Prey

Predator

$$\varnothing \xrightarrow{k_a} X$$

$$X + Y \xrightarrow{k_p} 2Y$$

$$Y \xrightarrow{k_d} \varnothing$$

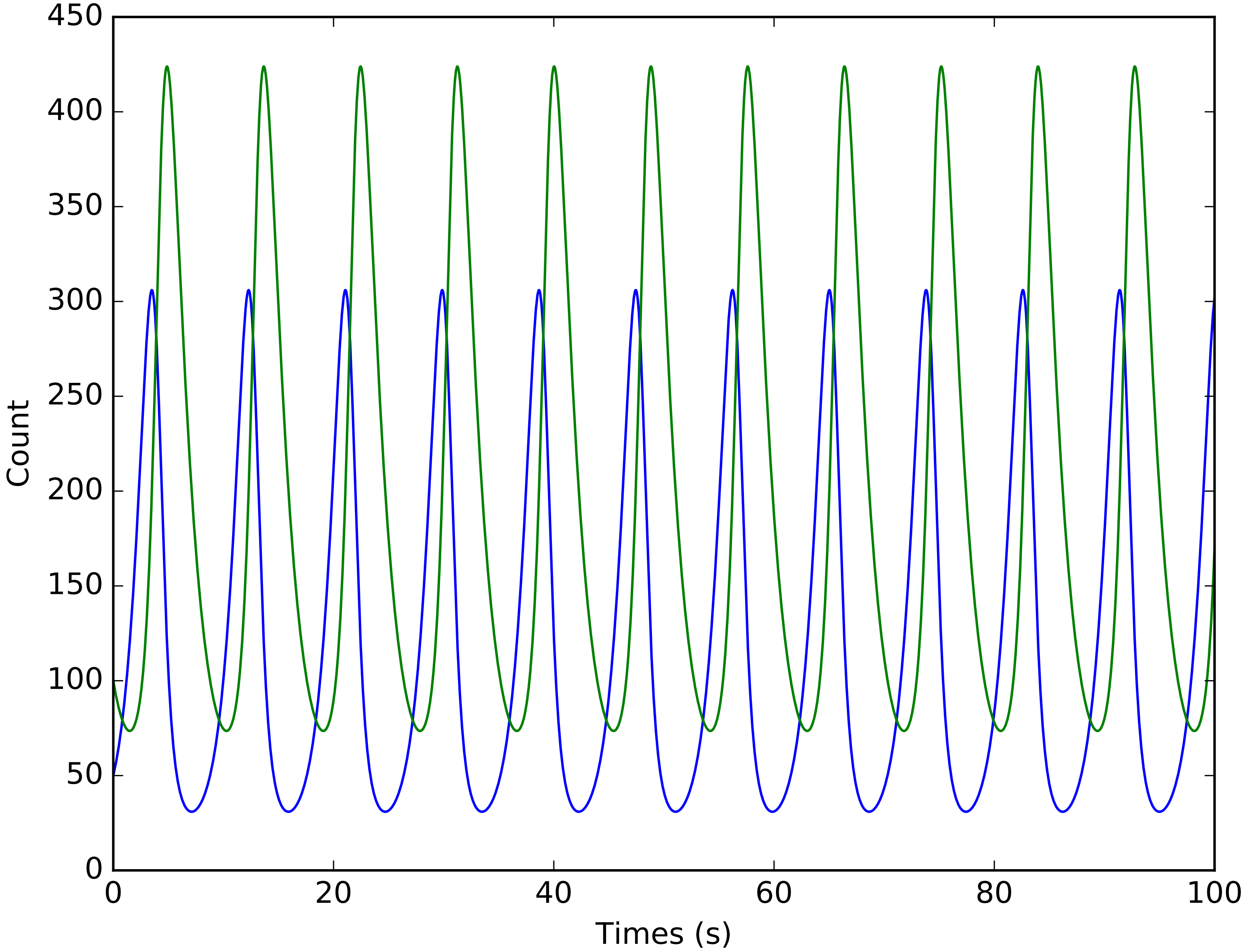
ODEs

$$\frac{dX}{dt} = k_a - k_p XY$$

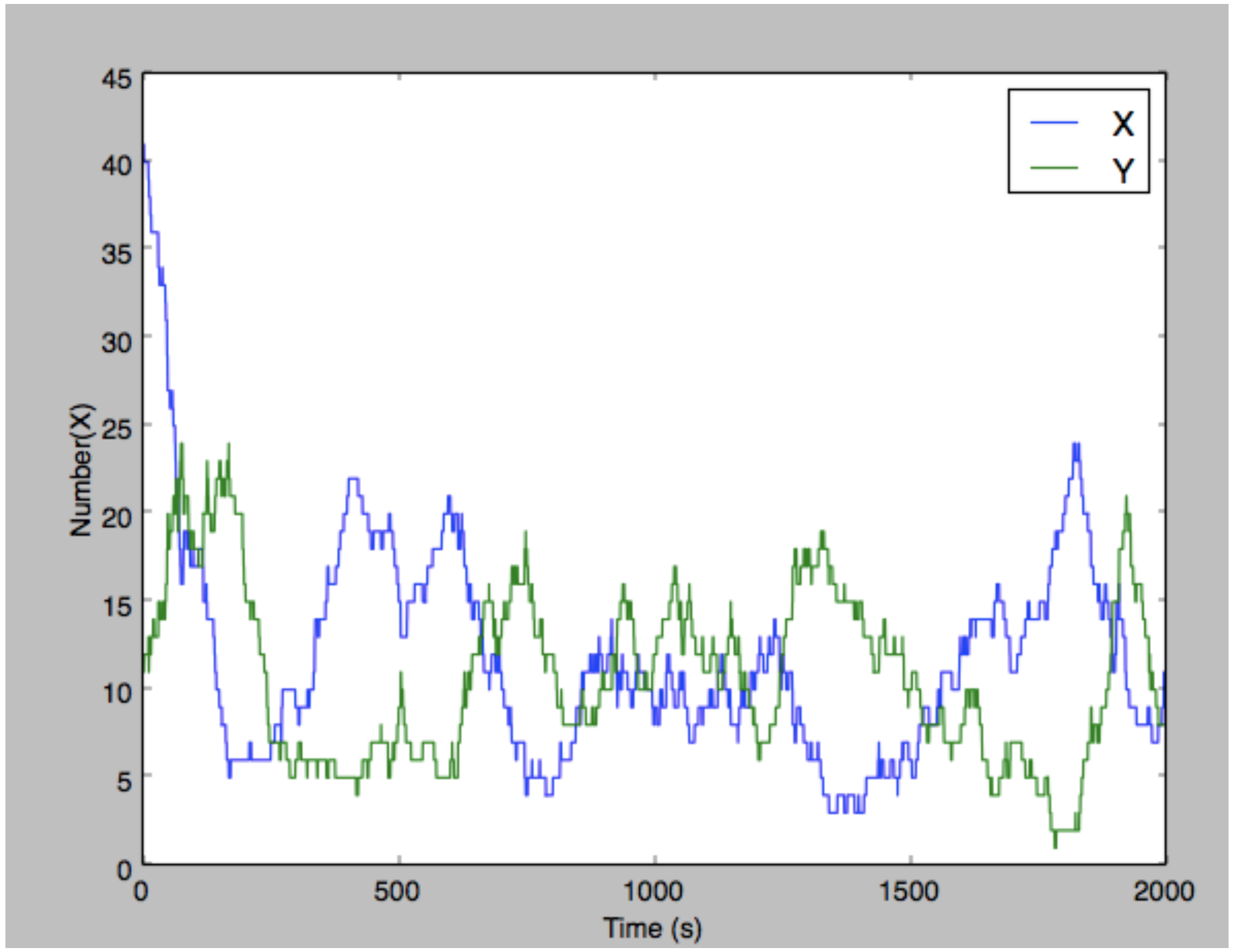
$$\frac{dY}{dt} = k_p XY - k_d Y$$

Lotka-Volterra (Predator-Prey)

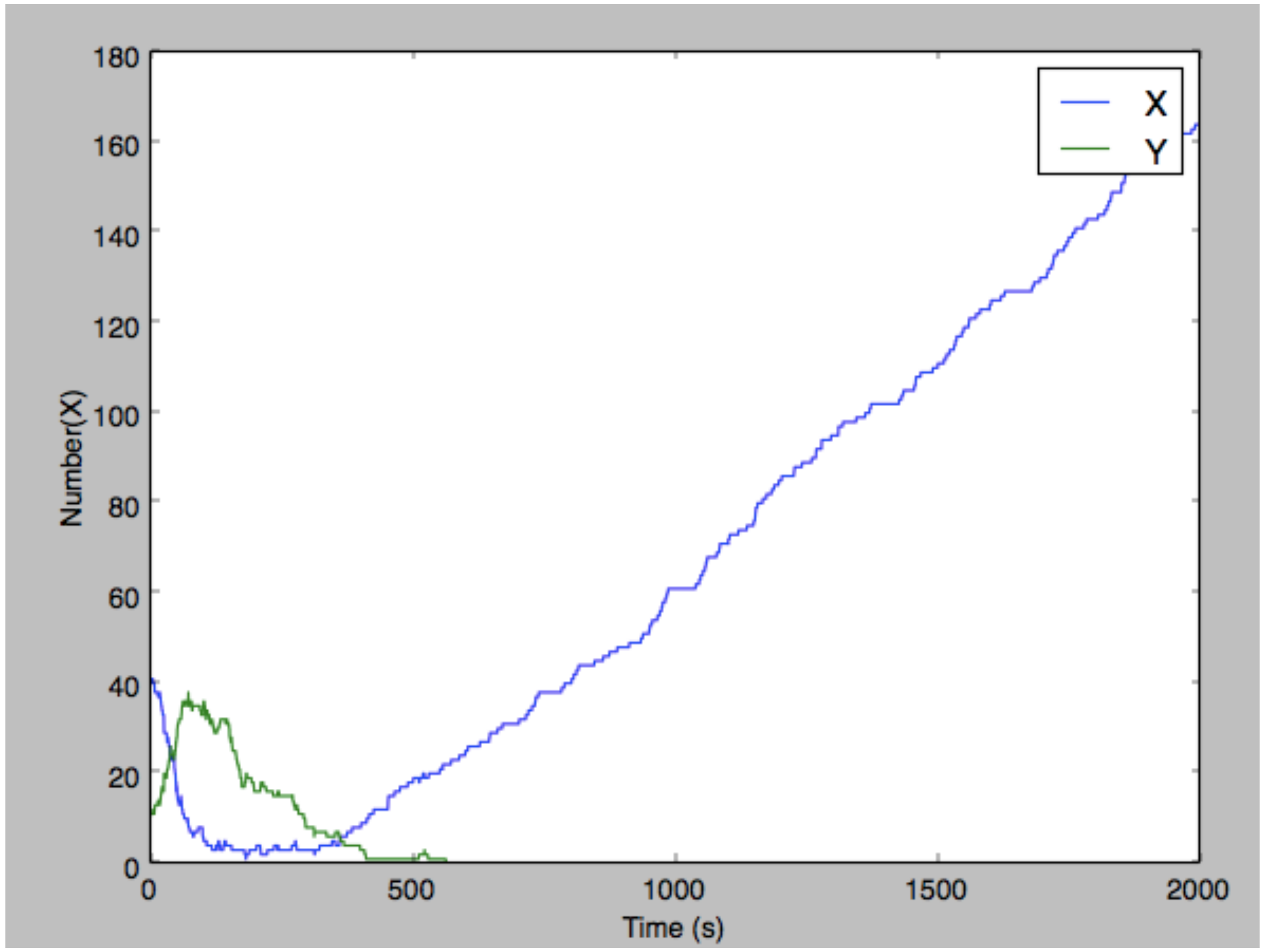
Deterministic Solution



Lotka-Volterra Simulations



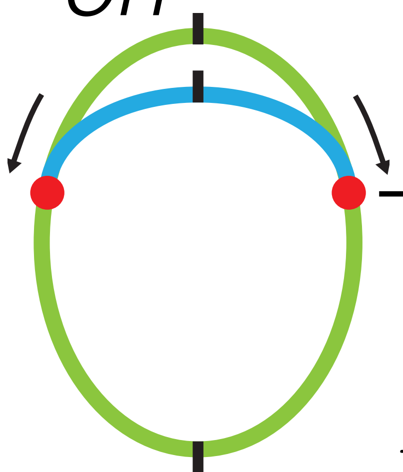
Stable Limit Cycle



Predator Extinction Event

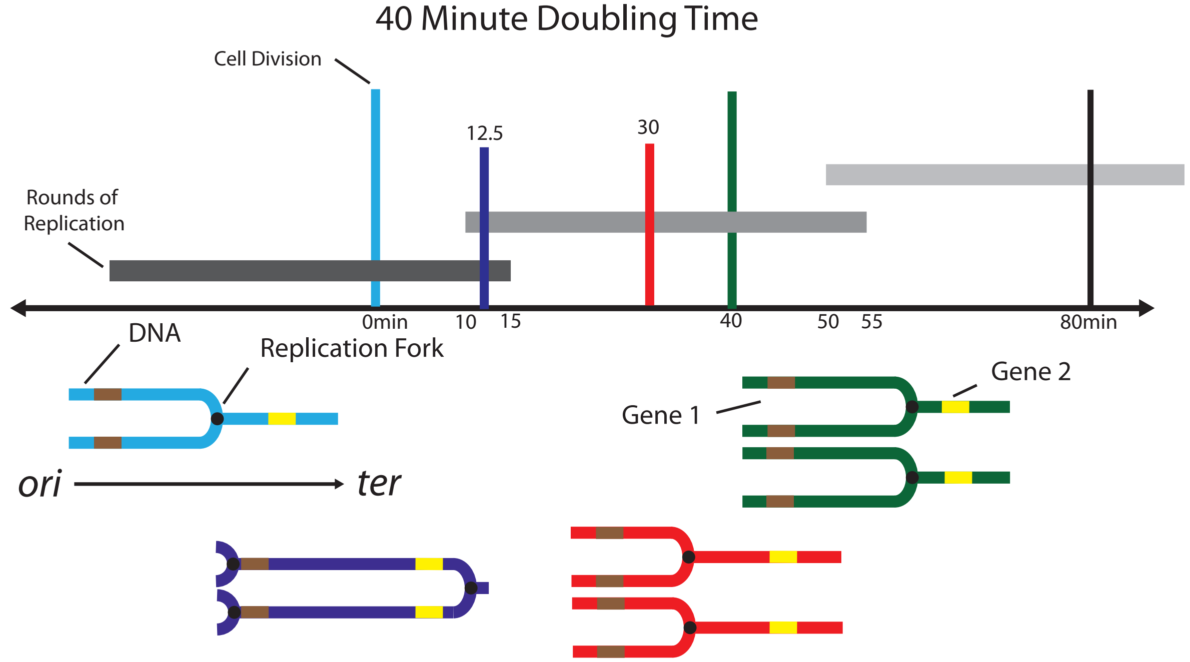
Effects of DNA Replication on mRNA Noise [2]

Replication Schematically



$t_D \approx 45min$

Replication Model [1]

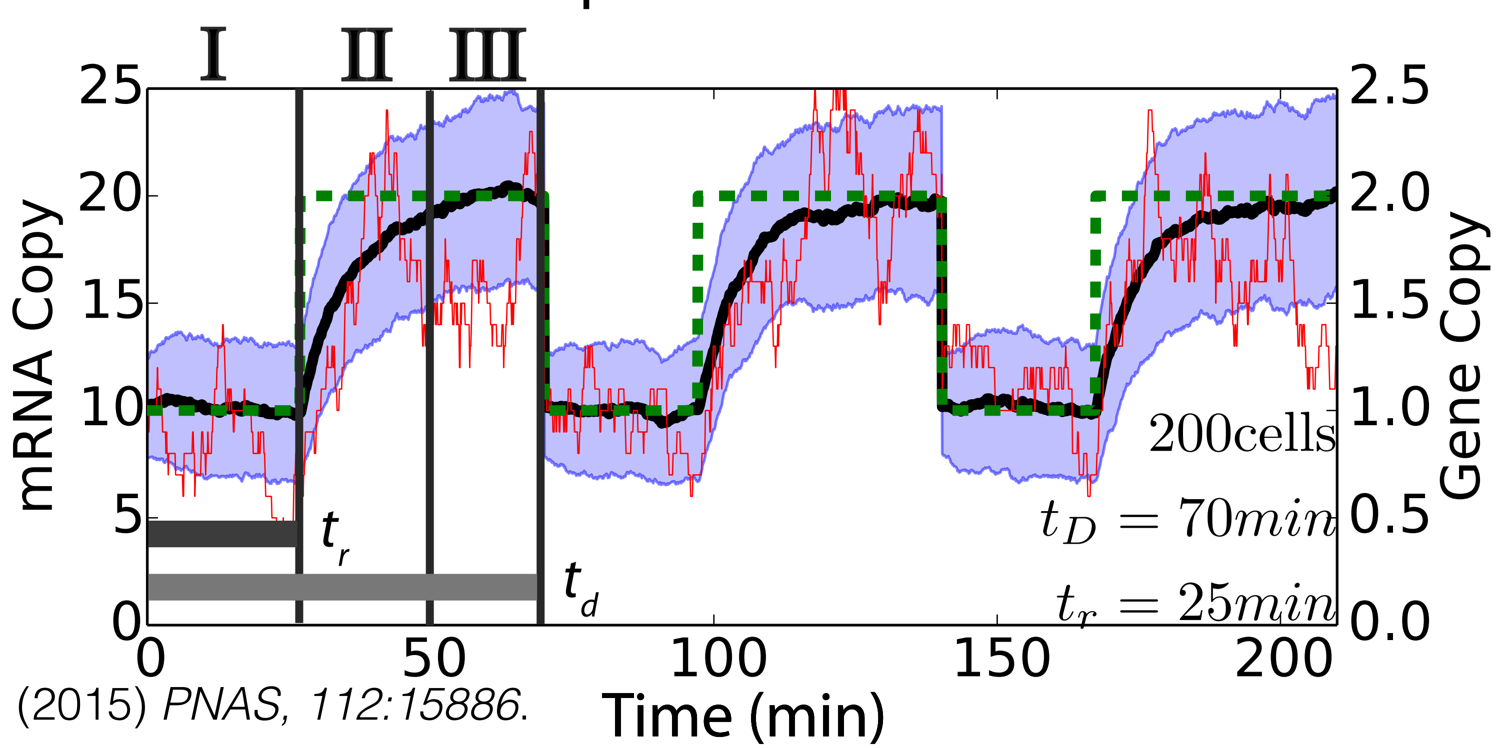


Reaction System

$$D(t) \xrightarrow{k_t} D(t) + m$$

$$m \xrightarrow{k_d} \varnothing$$

Example Simulation



1) Cooper and Helmstetter, (1968) *J. Mol. Biol.* 31:519.
2) J.R. Peterson, J.A. Cole, J. Fei, T. Ha, Z. Luthey-Schulten, (2015) *PNAS, 112:15886.*

Exact Solution

Constitutively Expressed Genes are
Poisson-Distributed throughout the cell cycle

$$\sigma_m^2(t) = \bar{m}(t) = \begin{cases} \frac{k_t}{k_d} & 0 < t < t_r \\ \frac{k_t}{k_d}\left(2 - e^{-k_d(t-t_r)}\right) & t_r < t < t_D \end{cases}$$

Time-averaging CME yields moments of $P(\vec{s})$

$$\langle m \rangle = \langle m \rangle_1 \left[1 + f + \frac{e^{-fk_d t_D} - 1}{k_d t_D}\right]$$

$$f = \frac{t_D - t_r}{t_D}$$

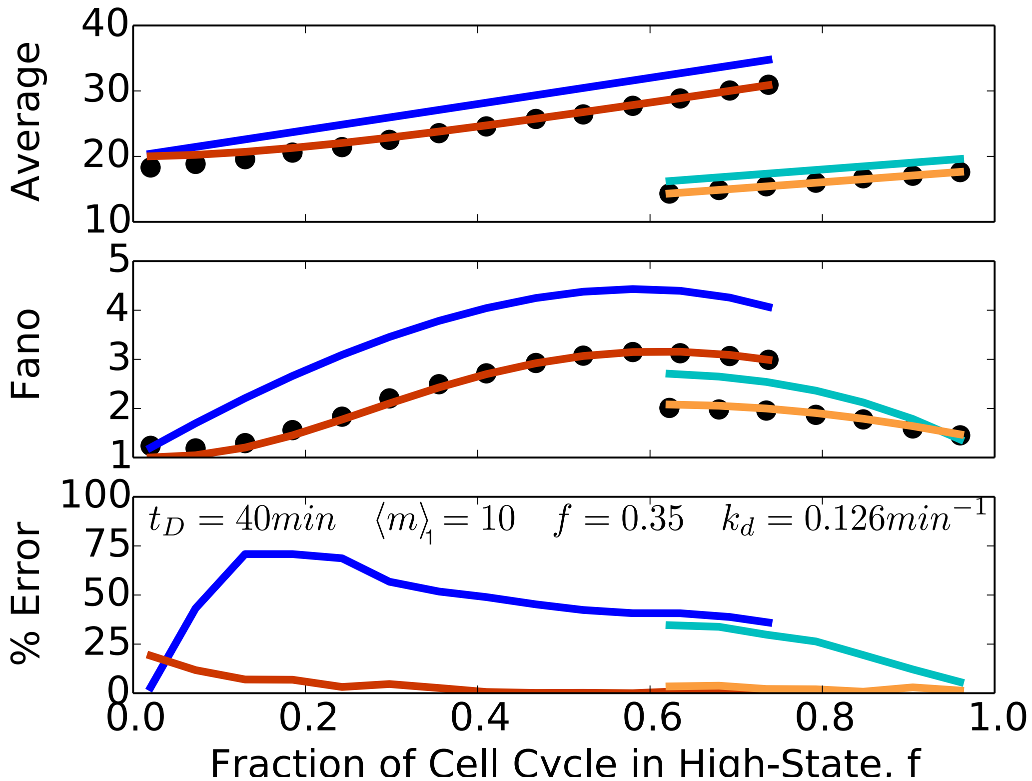
$$\mathrm{Var}[m] = \langle m \rangle - \langle m \rangle^2 + \langle m \rangle_1^2 \left[1 + 3f + \frac{8e^{-fk_d t_D} - e^{-2fk_d t_D} - 7}{2k_d t_D}\right]$$

$$\mathrm{Fano}[m] = 1 - \langle m \rangle + \frac{\langle m \rangle_1^2}{\langle m \rangle} \left[1 + 3f + \frac{8e^{-fk_d t_D} - e^{-2fk_d t_D} - 7}{2k_d t_D}\right]$$

Only mean, degradation rate and doubling time are needed

Model Validation

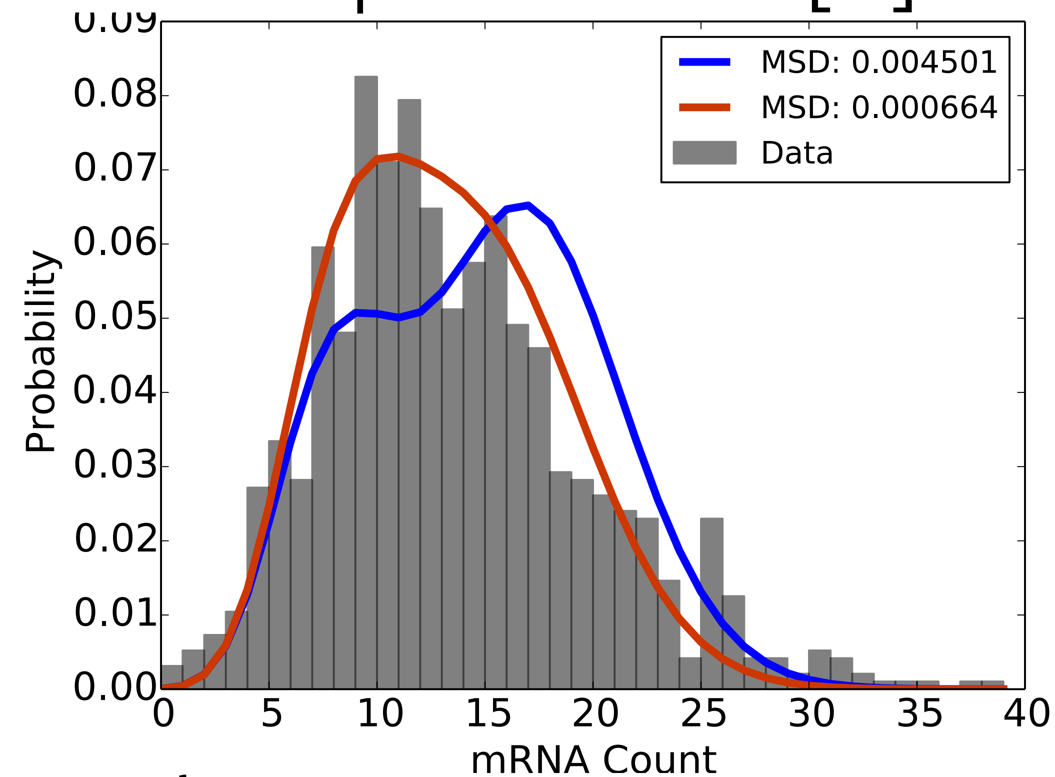
Simulations

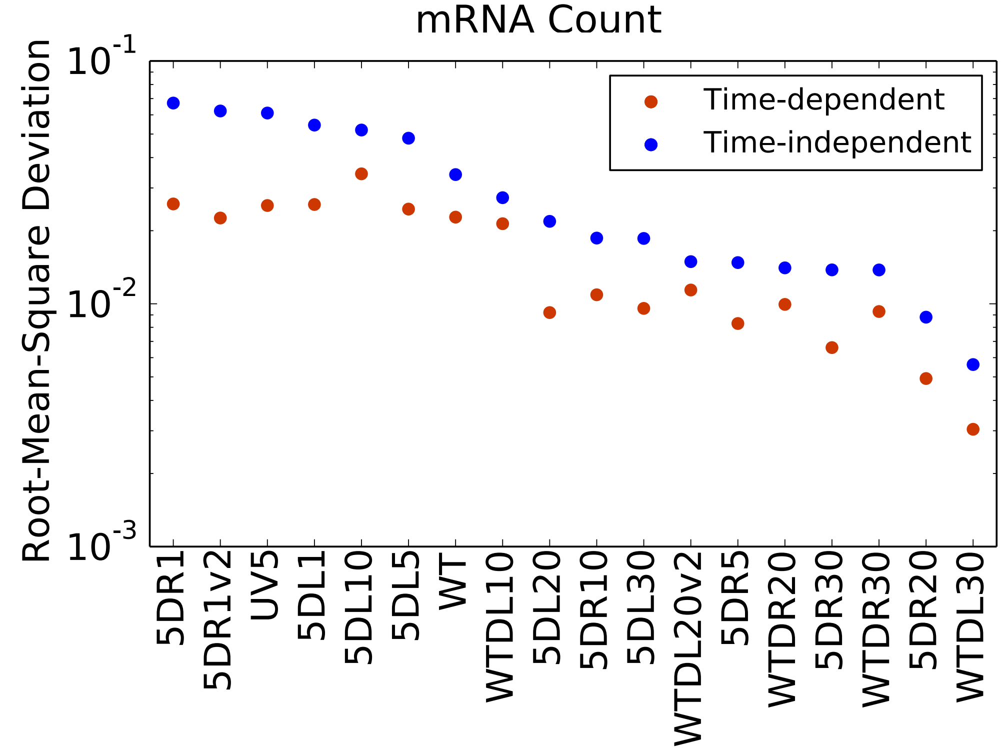


Ignoring mRNA dynamics gives large errors

Analytical theory **nearly exact**

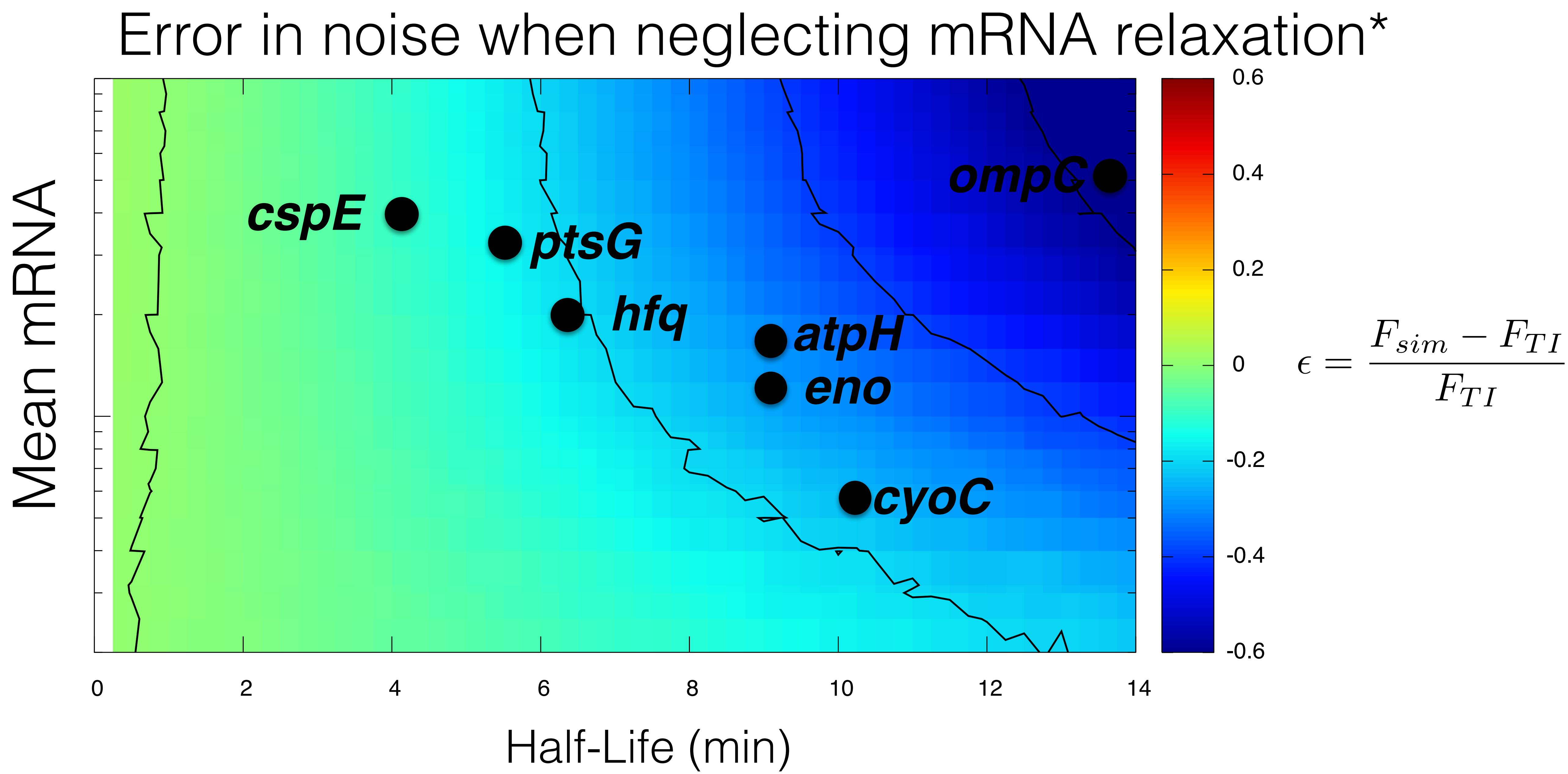
Experiments [1]





1) Jones et al, (2014) *Science*, 346:1533.

Region of importance



Effect is large when:

- mRNA half-life is large
- mean mRNA count is high

* 70 min doubling time

Other Noise Sources

- Regulated Gene expression

$$\bar{m}(t) = \begin{cases} \frac{k_t}{k_d}\frac{k_{\text{on}}}{k_{\text{on}}+k_{\text{off}}} & 0 < t < t_r \\ \frac{k_t}{k_d}\frac{k_{\text{on}}}{k_{\text{on}}+k_{\text{off}}}\left(2 - e^{k_d(t_r - t)}\right) & t_r < t < t_D \end{cases}$$

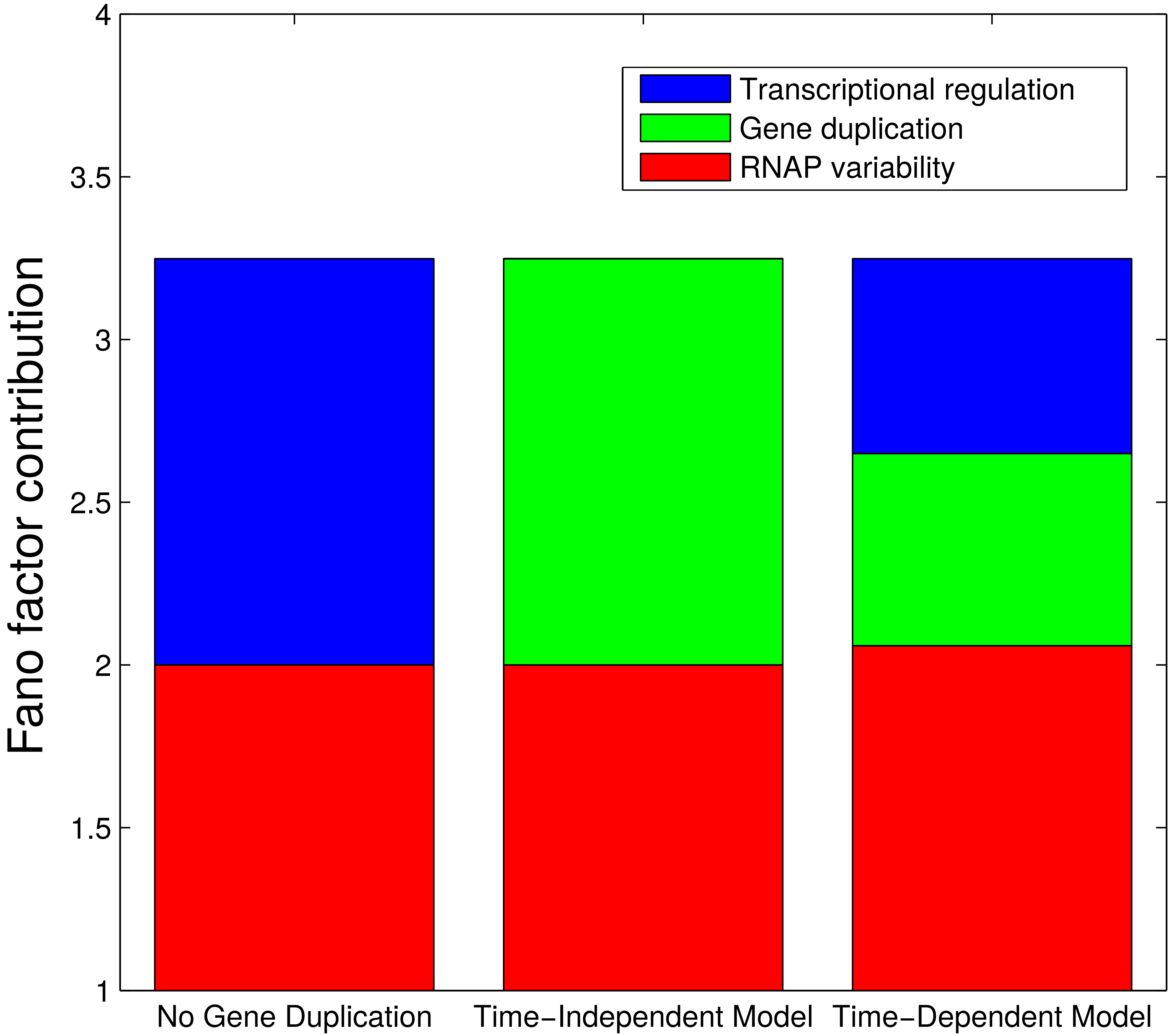
$$\sigma_m^2(t) \approx \bar{m}(t)\left(1 + \frac{k_t k_{\text{off}}}{(k_{\text{on}}+k_{\text{off}})(k_{\text{on}}+k_{\text{off}}+k_d)}\right)$$

- RNA polymerase variability (<m>/10 Fano units)

$$\text{Fano}[m] \approx \text{Fano}[m|\bar{k_t}] + \frac{\nu \text{Var}[k_t]}{E[m]k_d^2}$$

- Relaxing assumption that mRNA relaxes before cell division

Conflicting Interpretation of Experiments



Potential Misinterpretation of Experimental Data

<u>Parameters</u>

$t_D = 40min$

$\langle m \rangle_1 = 10$

$f = 0.35$

$k_d = 0.126min^{-1}$

Reaction-Diffusion Master Equation

$$\frac{dP(\vec{s},t)}{dt} = \mathbf{A}P(\vec{s},t)$$

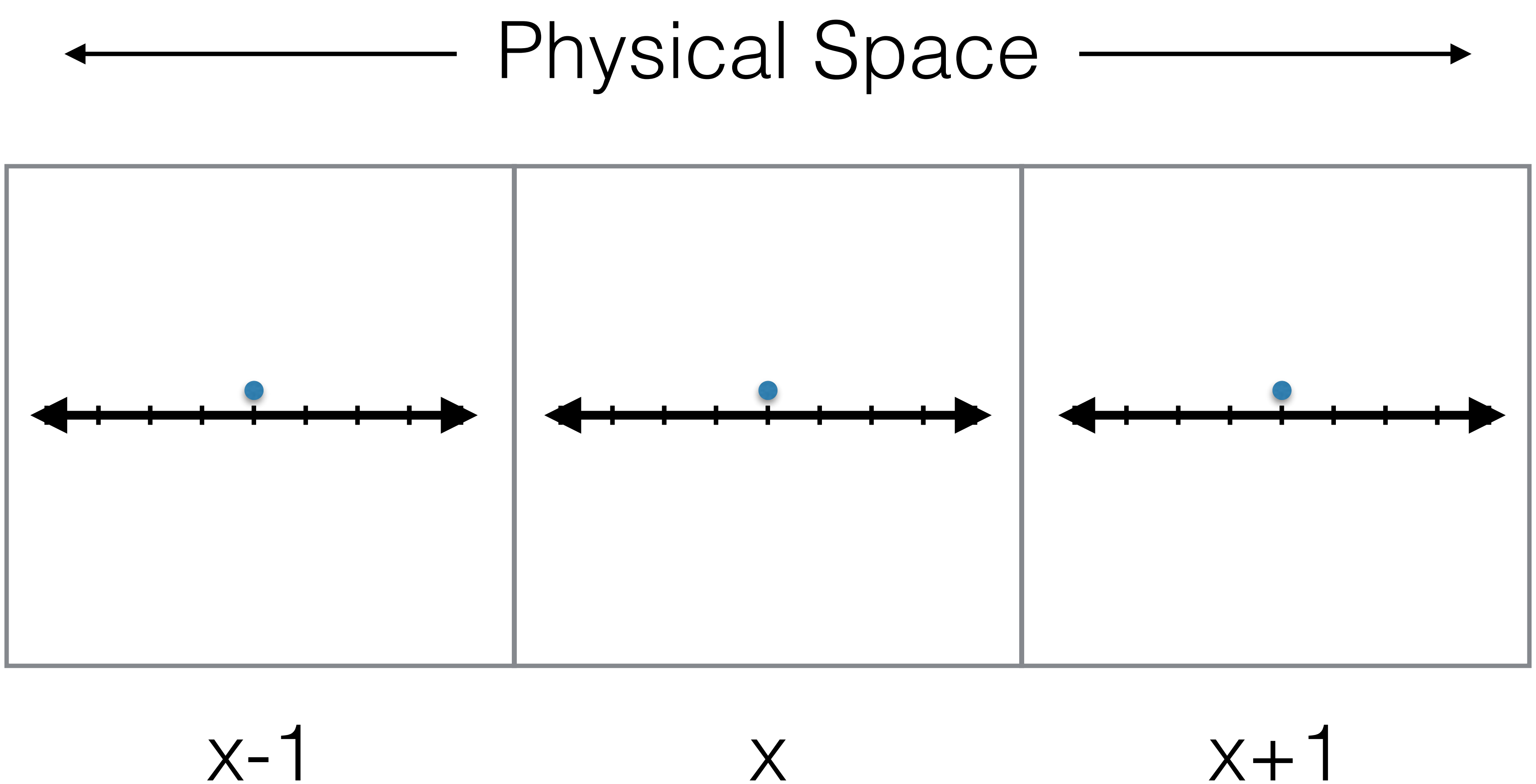
$$\mathbf{A} = \mathbf{R}\cdot\mathbf{S} + \mathbf{D}$$

$$\frac{dP(\mathbf{x},t)}{dt} = \sum_{\nu}^{V}\sum_{r}^{R}[-a_r(\mathbf{x}_\nu)P(\mathbf{x}_\nu,t) + a_r(\mathbf{x}_\nu - \mathbf{S}_\mathbf{r})P(\mathbf{x}_\nu - \mathbf{S}_\mathbf{r},t)]$$
$$+\sum_{\nu}^{V}\sum_{\xi}^{\pm\hat{i},\hat{j},\hat{k}}\sum_{\alpha}^{N}[-d^\alpha x_\nu^\alpha P(\mathbf{x},t) + d^\alpha(x_{\nu+\xi}^\alpha + 1_\nu^\alpha)P(\mathbf{x} + 1_{\nu+\xi}^\alpha - 1_\nu^\alpha,t)]$$

Reaction-Diffusion Master Equation

$$\frac{dP(\vec{s},t)}{dt} = \mathbf{A}P(\vec{s},t)$$

$$\mathbf{A} = \mathbf{R}\cdot\mathbf{S} + \mathbf{D}$$



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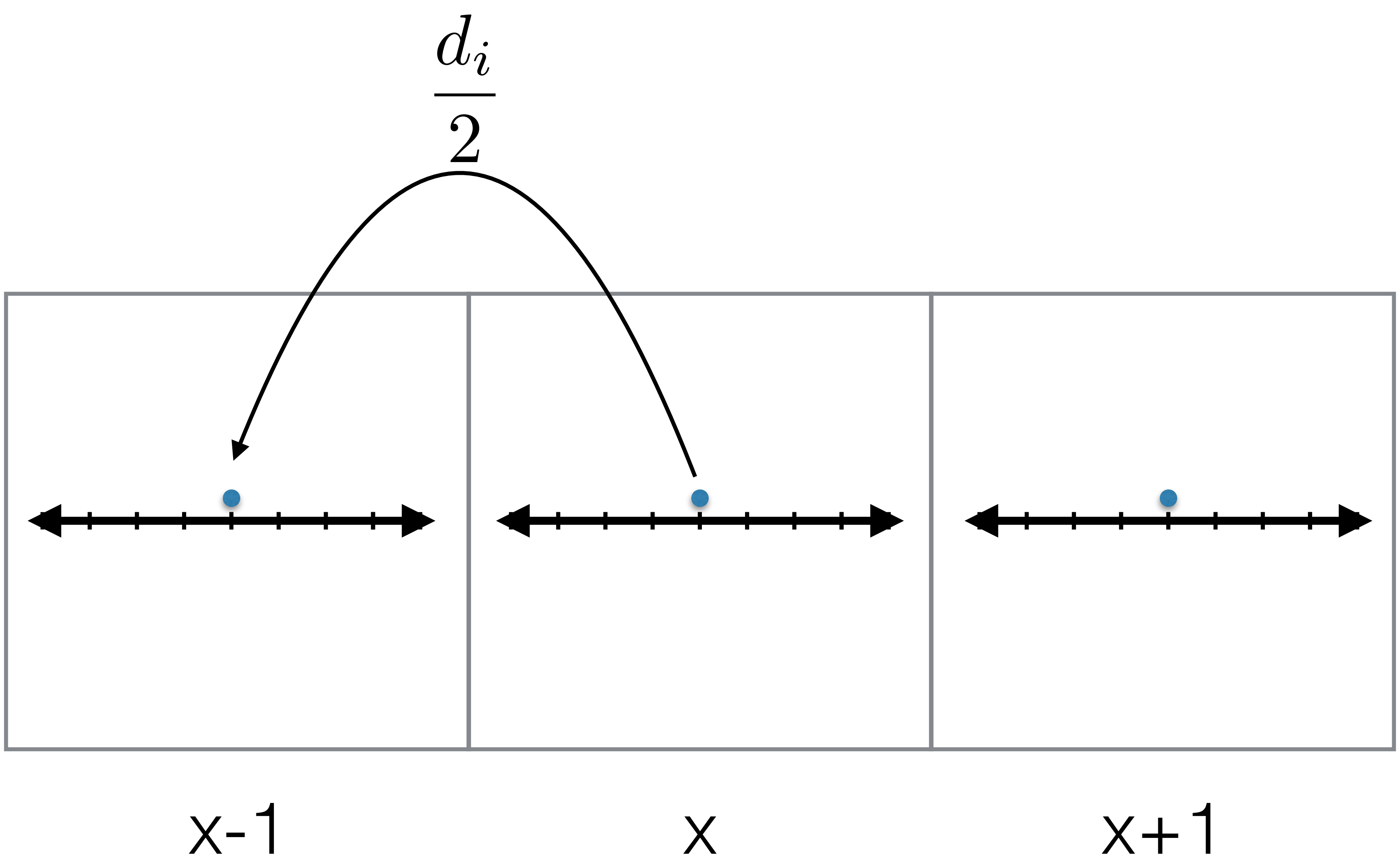

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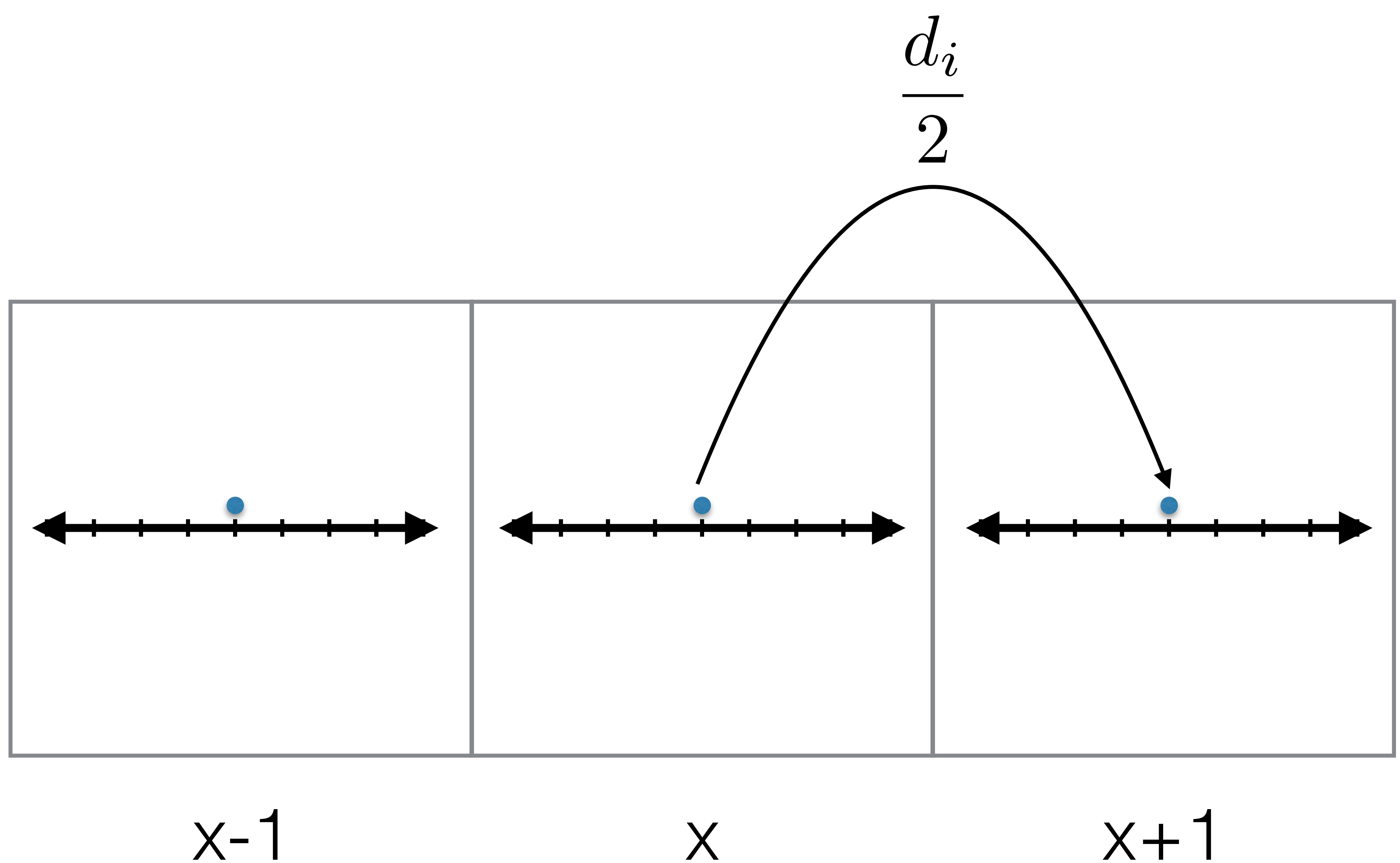
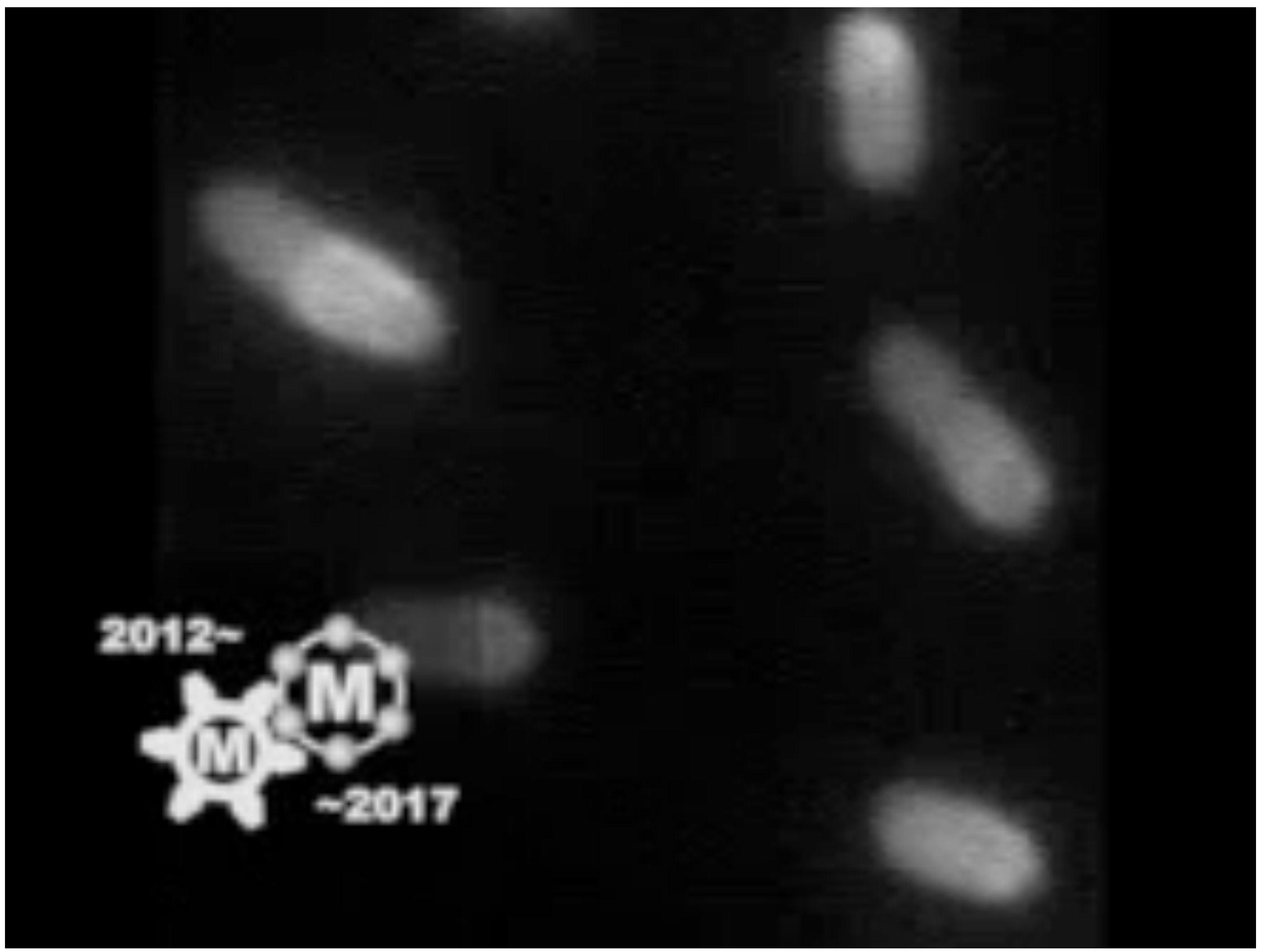
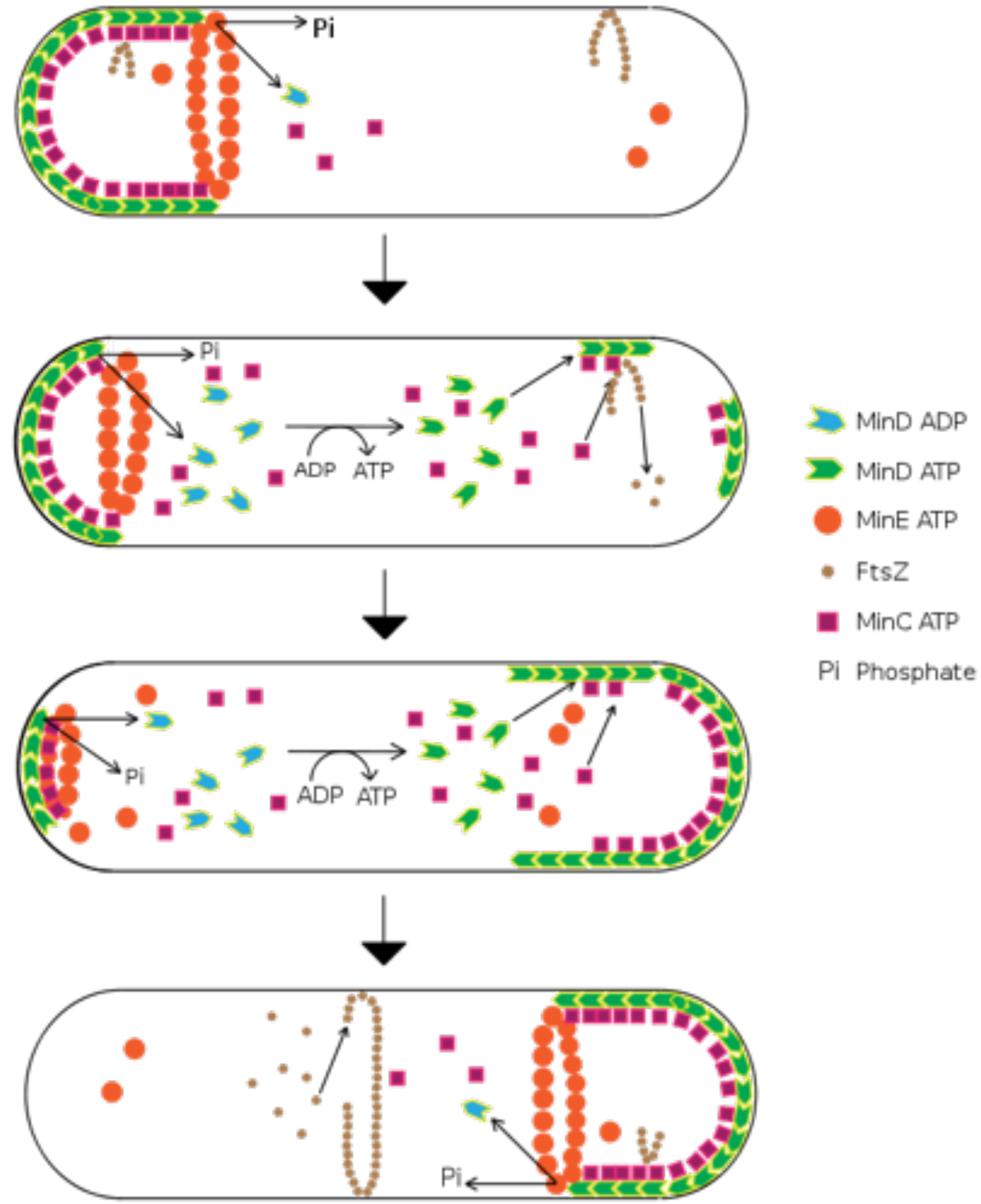


Min System Example

Sets up the "center plane"
for cell division

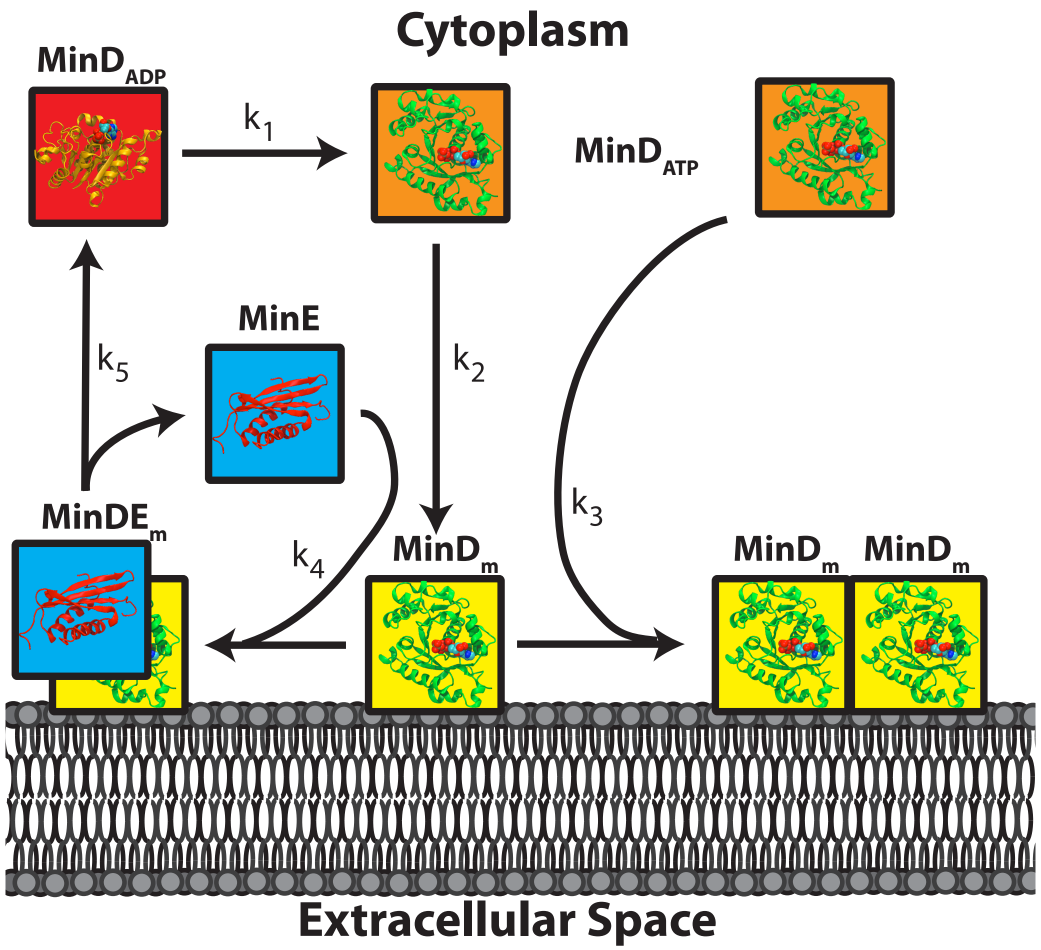


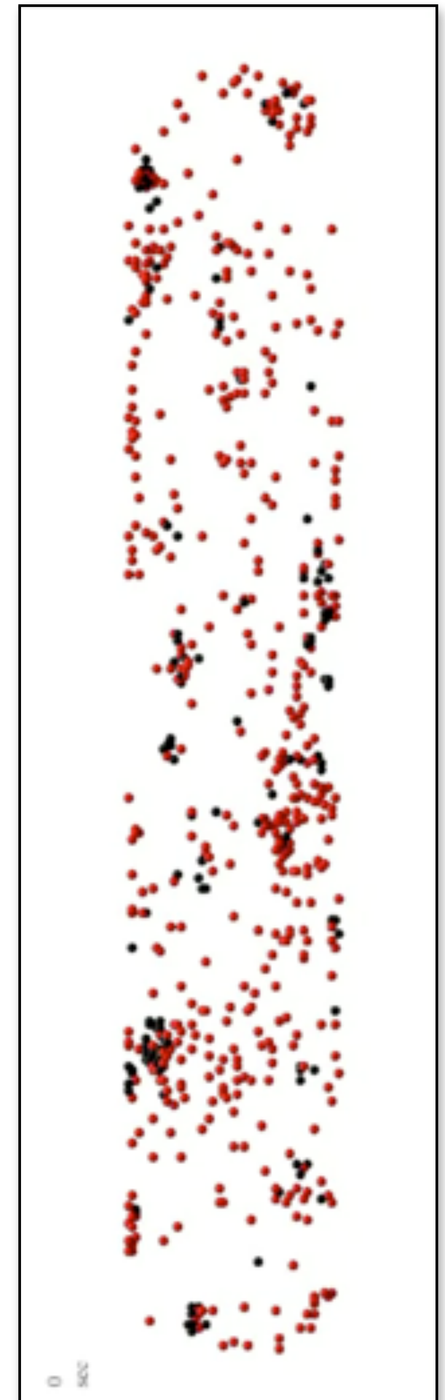


https://www.youtube.com/watch?v=6bnB9Oeh3TA
https://en.wikipedia.org/wiki/Min_System#/media/File:MinCDE_System2.svg

Min System Example

Schematic
Reaction System

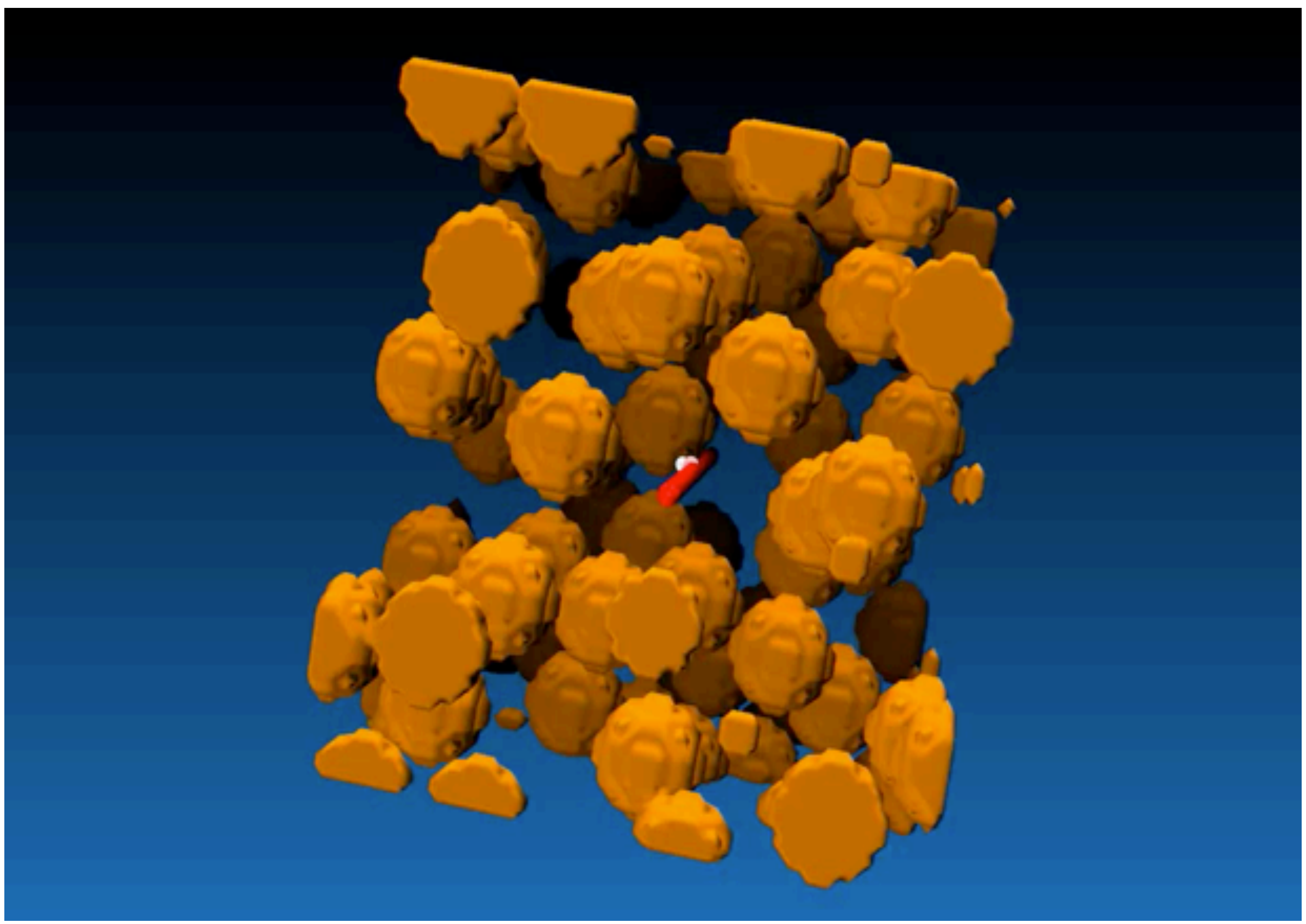


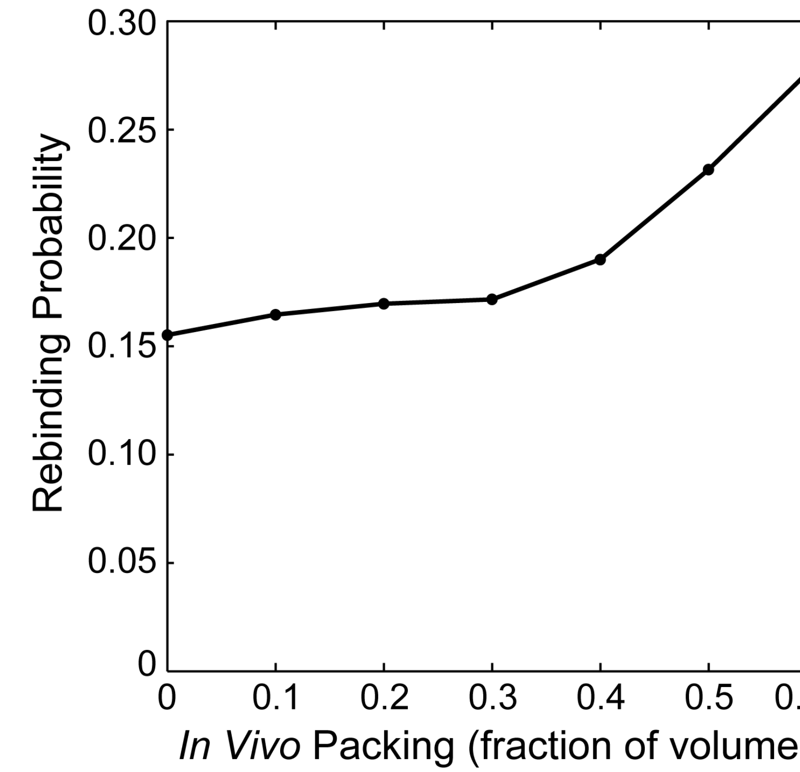


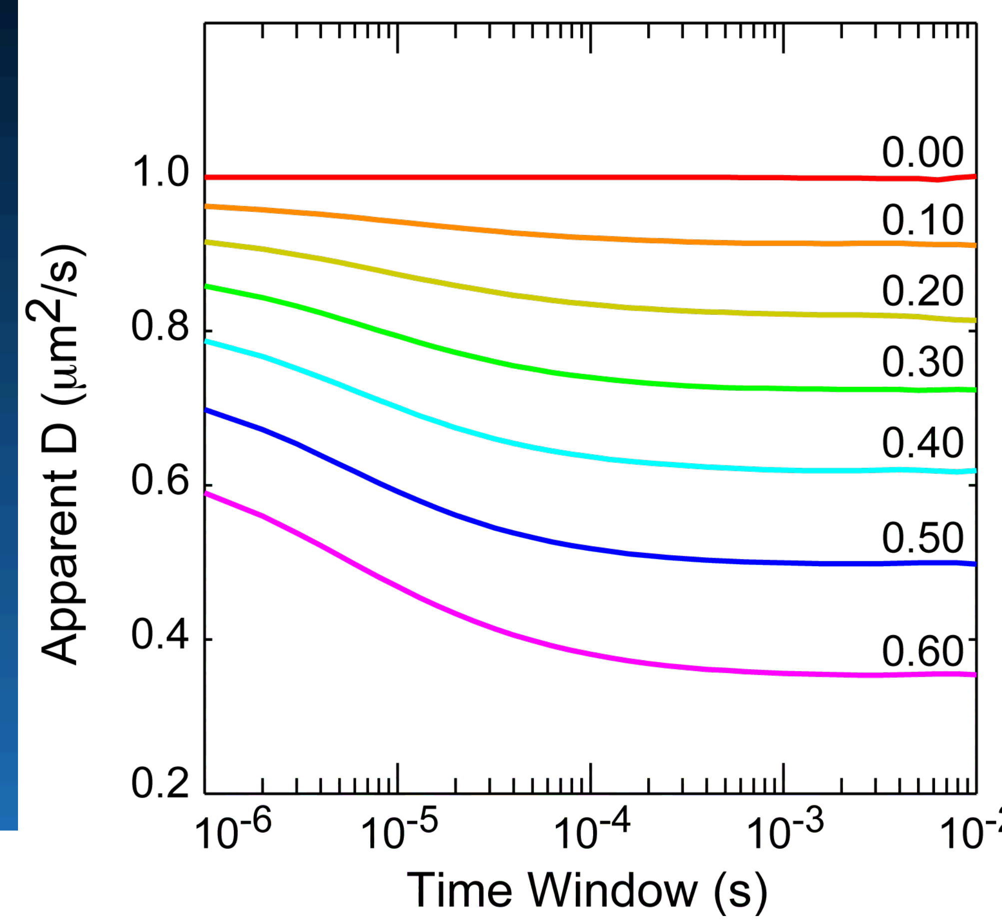
J.R. Peterson, M.J. Hallock, J.A. Cole, Z. Luthey-Schulten, (2013) *PyHPC '13: Proceedings of the 3rd Workshop on Python for High-Performance and Scientific Computing.*

Complex Geometries in Lattice Microbes

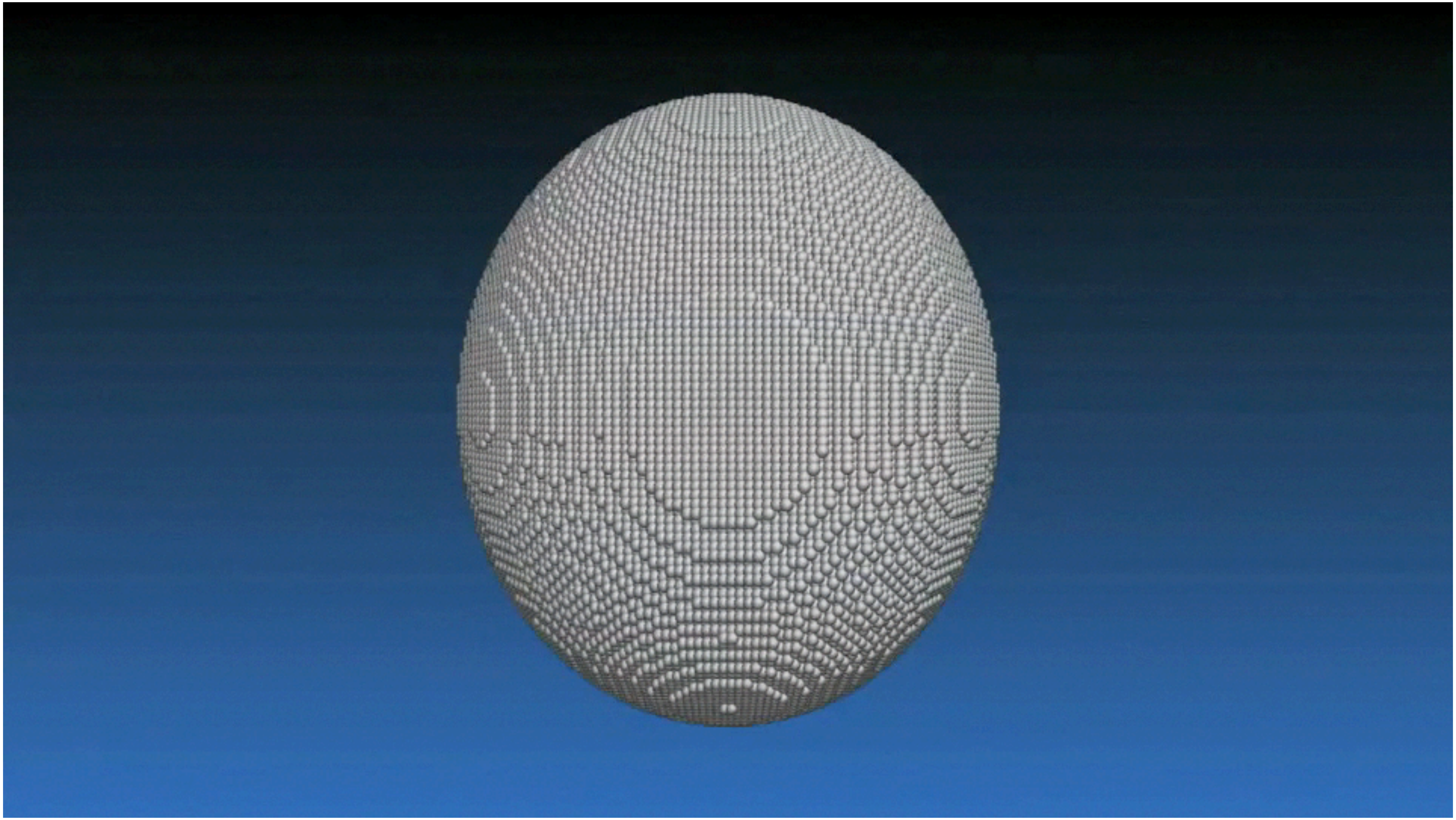
Examining Propensity for a Transcription Factor to Rebind to DNA after Unbinding as a Function of Packing Fraction



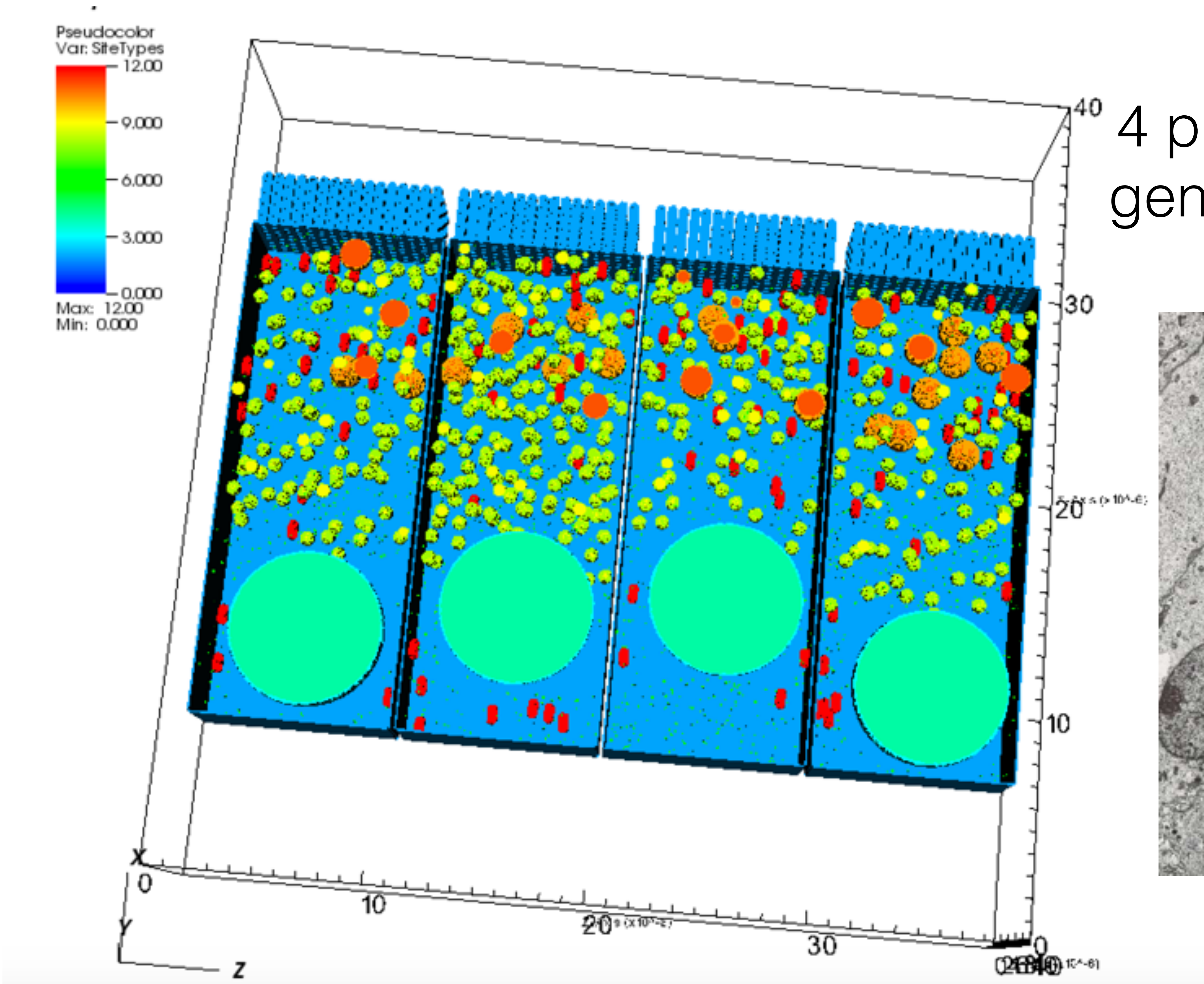




Complex Geometries in Lattice Microbes



Complex Geometries in Lattice Microbes

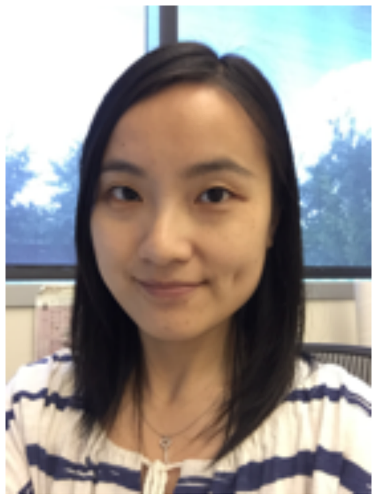


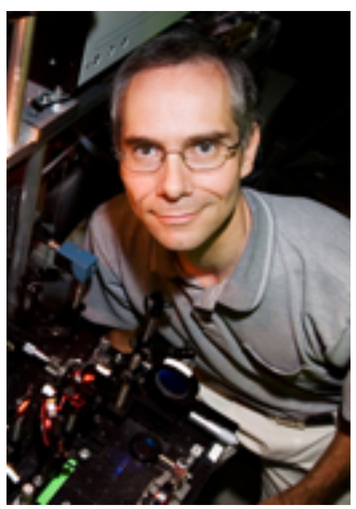
4 programmatically generated epithelial cells

https://s-media-cache-ak0.pinimg.com/originals/7f/c4/ed/7fc4ed17cfa66eb820a99d6fbf3055fc.jpg

Acknowledgements

Collaborators



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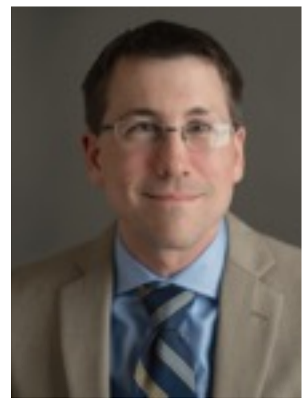


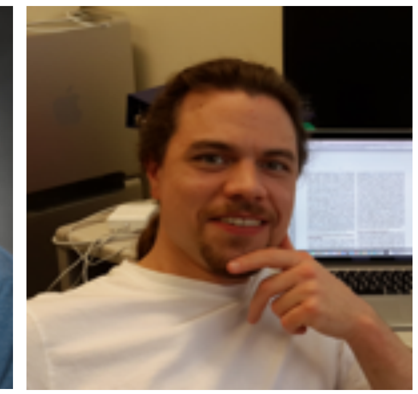



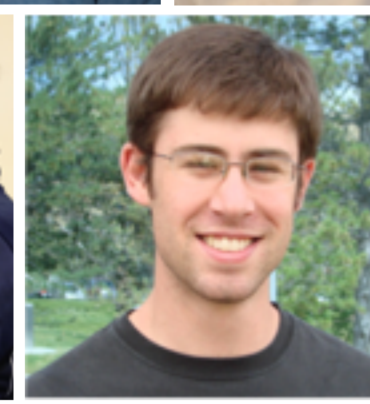

Funding and Computer Time

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XSEDE
NCSA