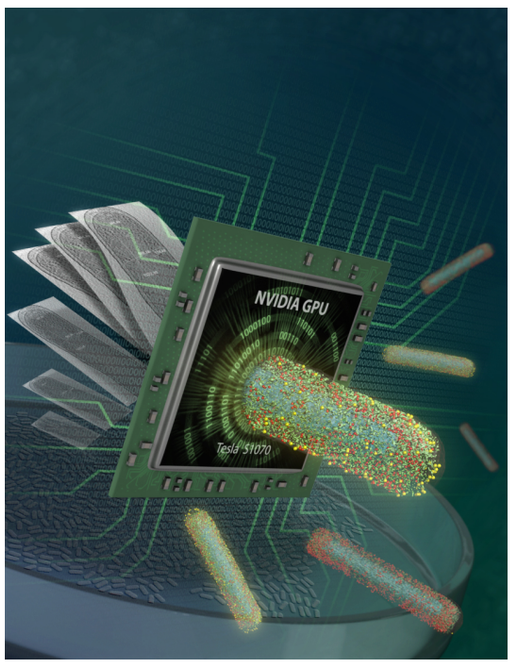
ILLINOIS
UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

Part 1: Introduction to Cell Simulations

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



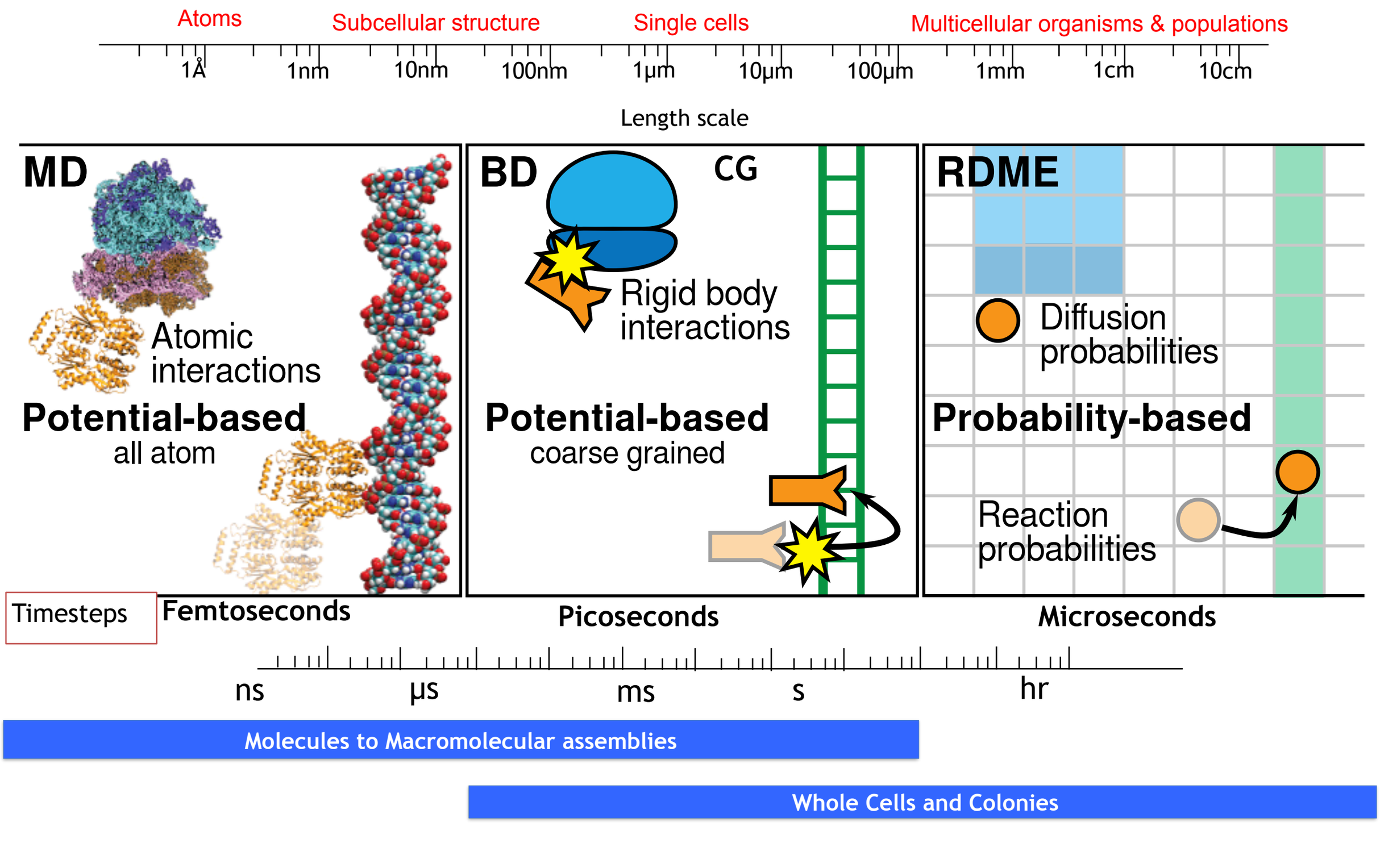
NIH Workshop on Computational Biophysics
November 17th, 2016
George Institute of Technology
Atlanta, GA, USA

NSF
Center for the Physics of Living Cells
NATIONAL INSTITUTES OF HEALTH
XSEDE
NCSA

Introduction to Cell Simulations

- Cell Simulation at Different Scales
- Stochastic Simulations
  - Theory
  - Lattice Microbes
- Probabilistic Simulations
  - *lac* Genetic Switch
  - Ribosome Biogenesis
- Continuum Simulations
  - *E. coli* Colony
  - Multi-species Communities
- On-going Research

Biological Modeling at Different Scales



Cell Simulation Techniques

- Particle Based
  - Molecular Dynamics
  - Brownian Dynamics
  - Green's Function Reaction Dynamics
  - Smoluchowski Dynamics
  - Dissipative Particle Dynamics
- Probability Based
  - Reaction-Diffusion Master Equation (RDME)
  - Chemical Master Equation (CME)
  - Cellular Potts Modeling
  - Lattice Gas
- Continuum Based
  - Advection-Reaction-Diffusion Equations
  - Flux-Balance Analysis

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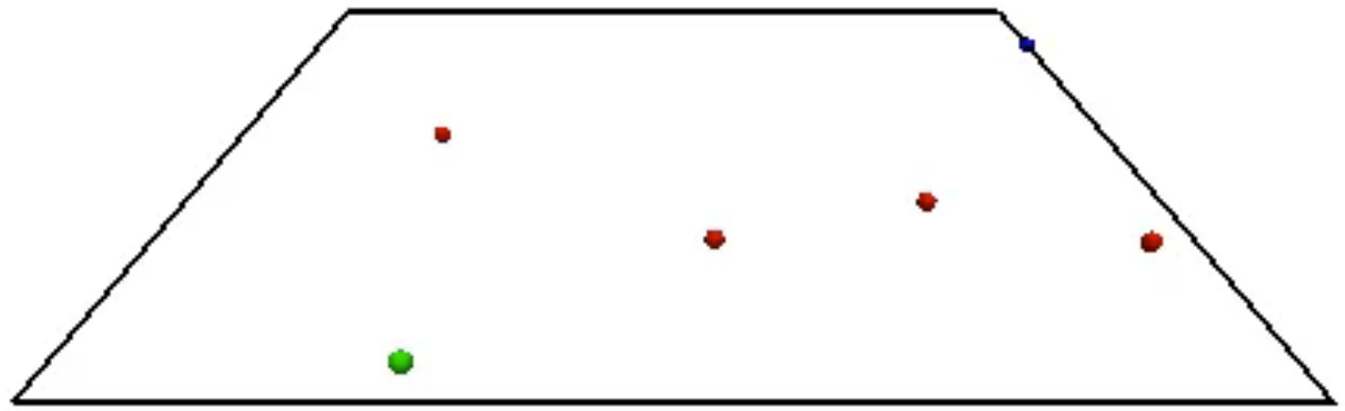
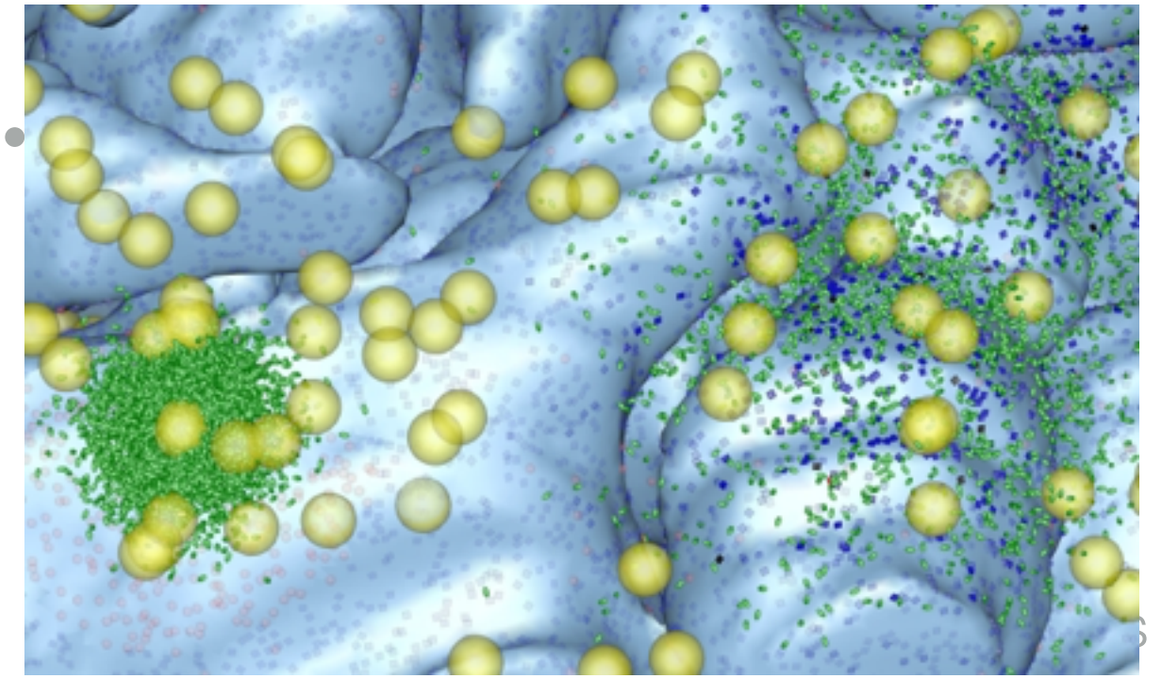


- Continuum Based
  - Advection-Reaction-Diffusion Equations
  - Flux-Balance Analysis

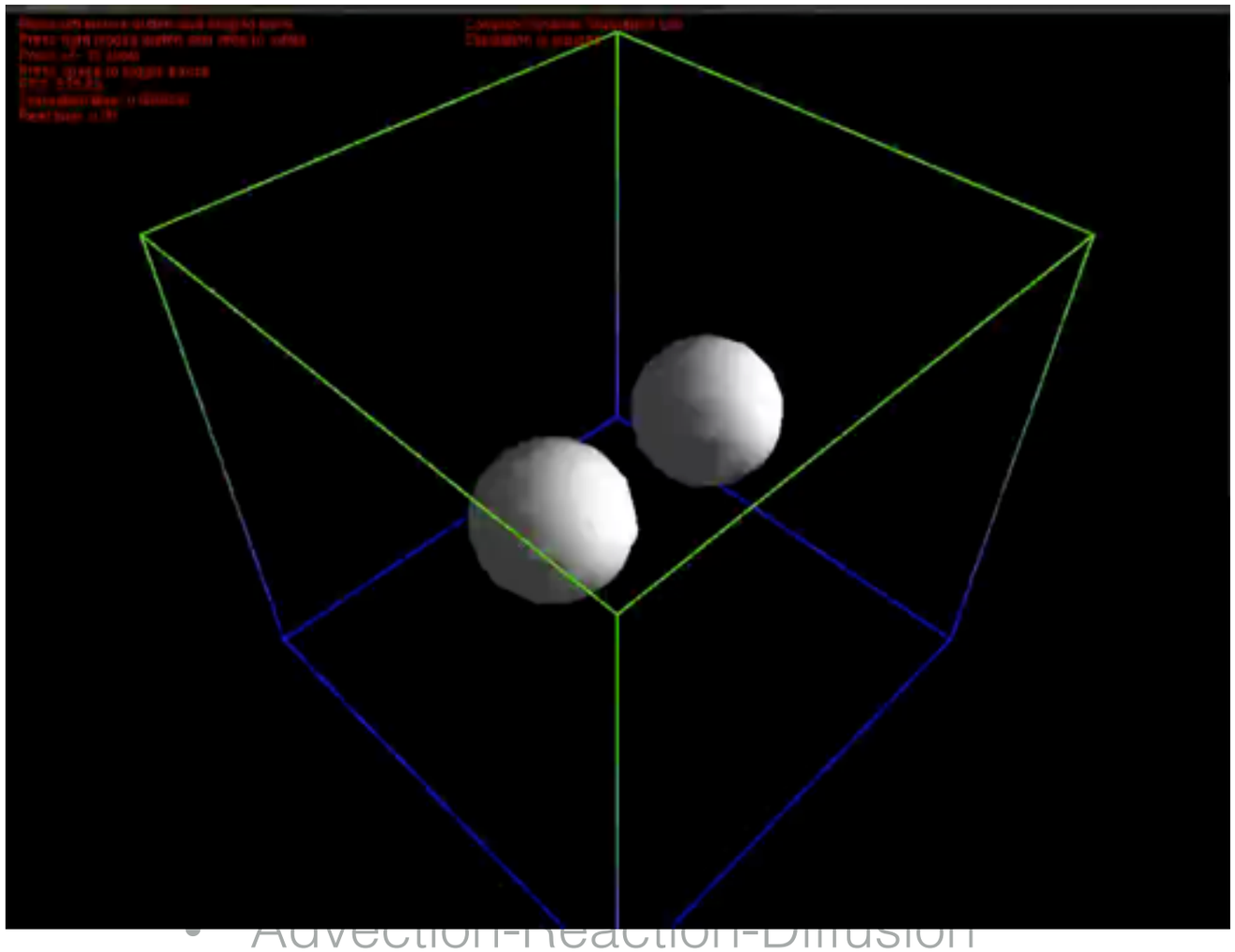
http://gfrd.org/algorithm

Cell Simulation Techniques



- Smoluchowski Dynamics
- Dissipative Particle Dynamics

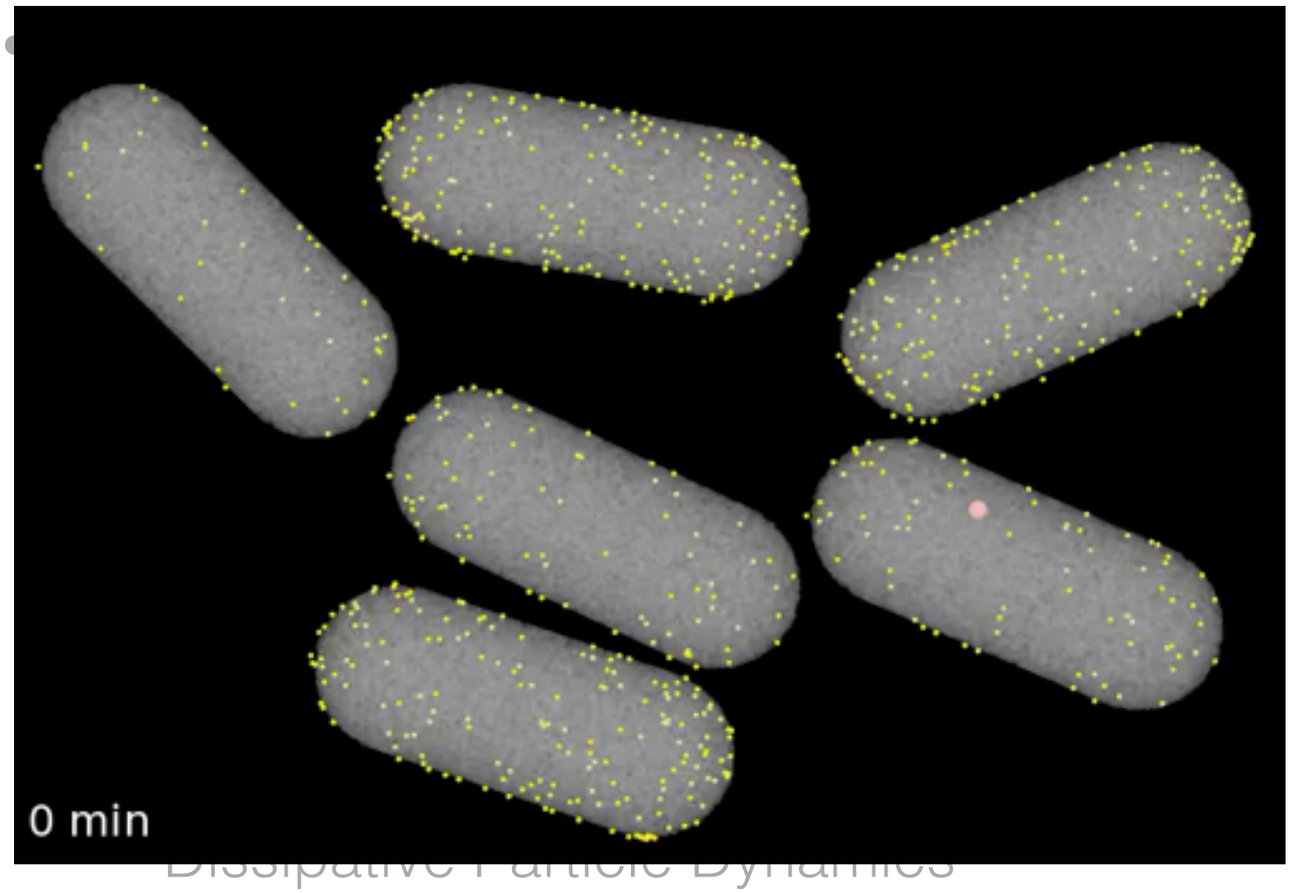
- Probability Based



- Advection-Reaction-Diffusion Equations
- Flux-Balance Analysis

https://www.youtube.com/watch?v=CvETkk1HRJ8

Cell Simulation Techniques



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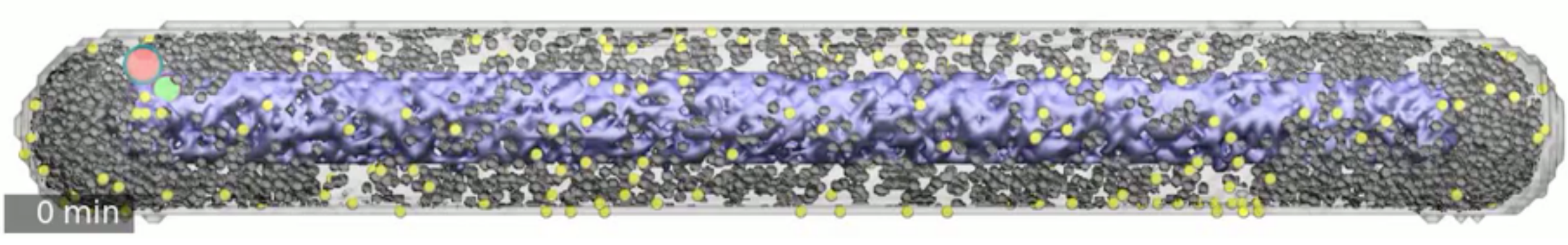
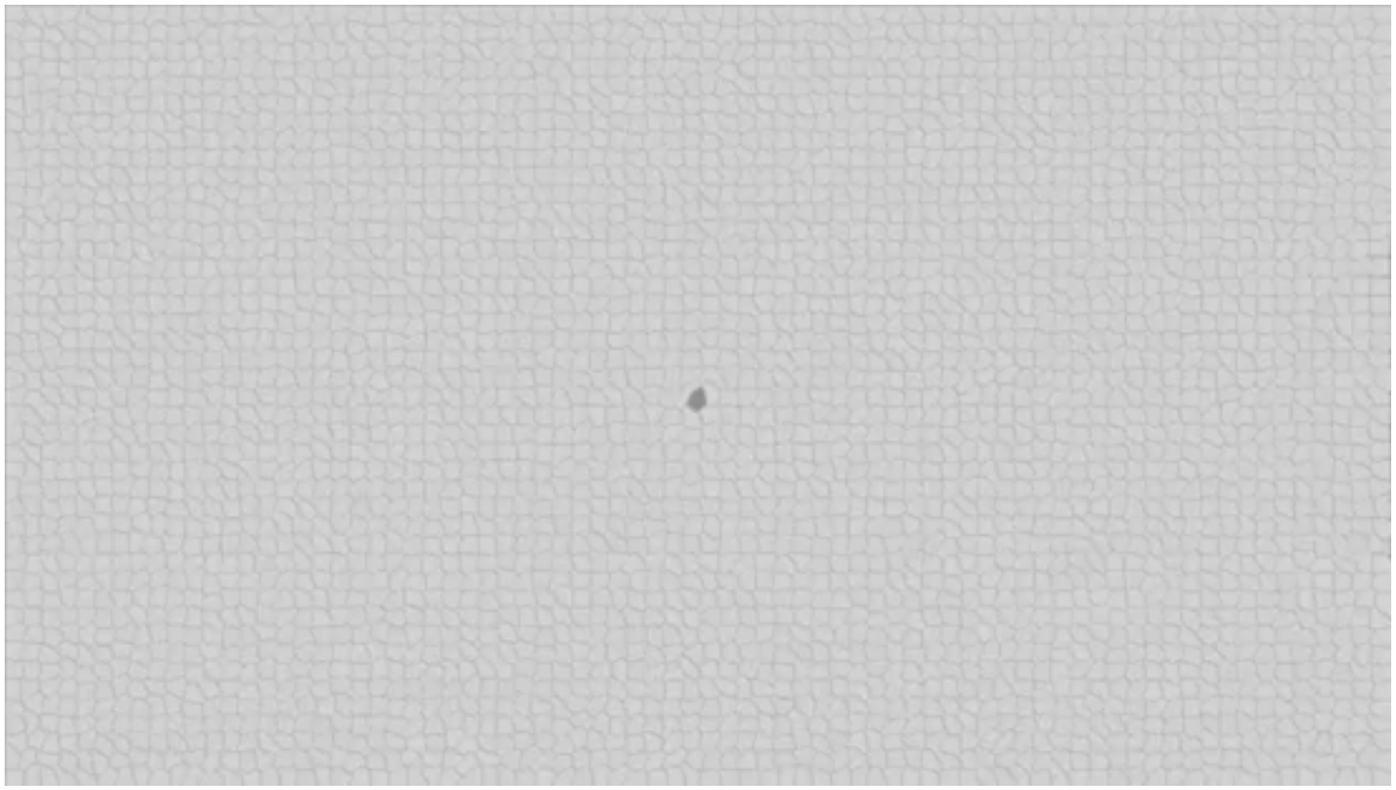
Dissipative Particle Dynamics



Cell Simulation Techniques

- Particle Based



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- Probability Based
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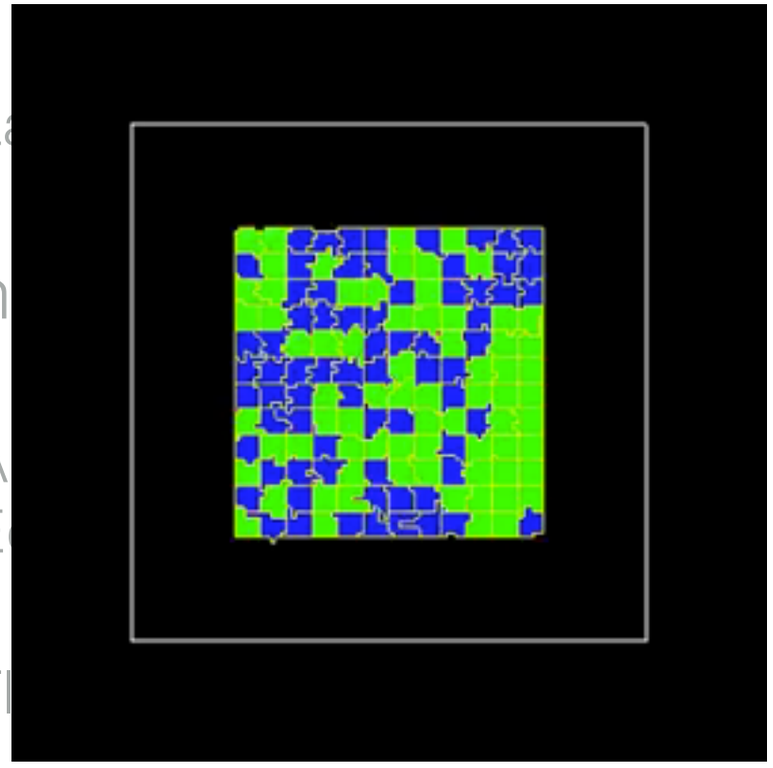

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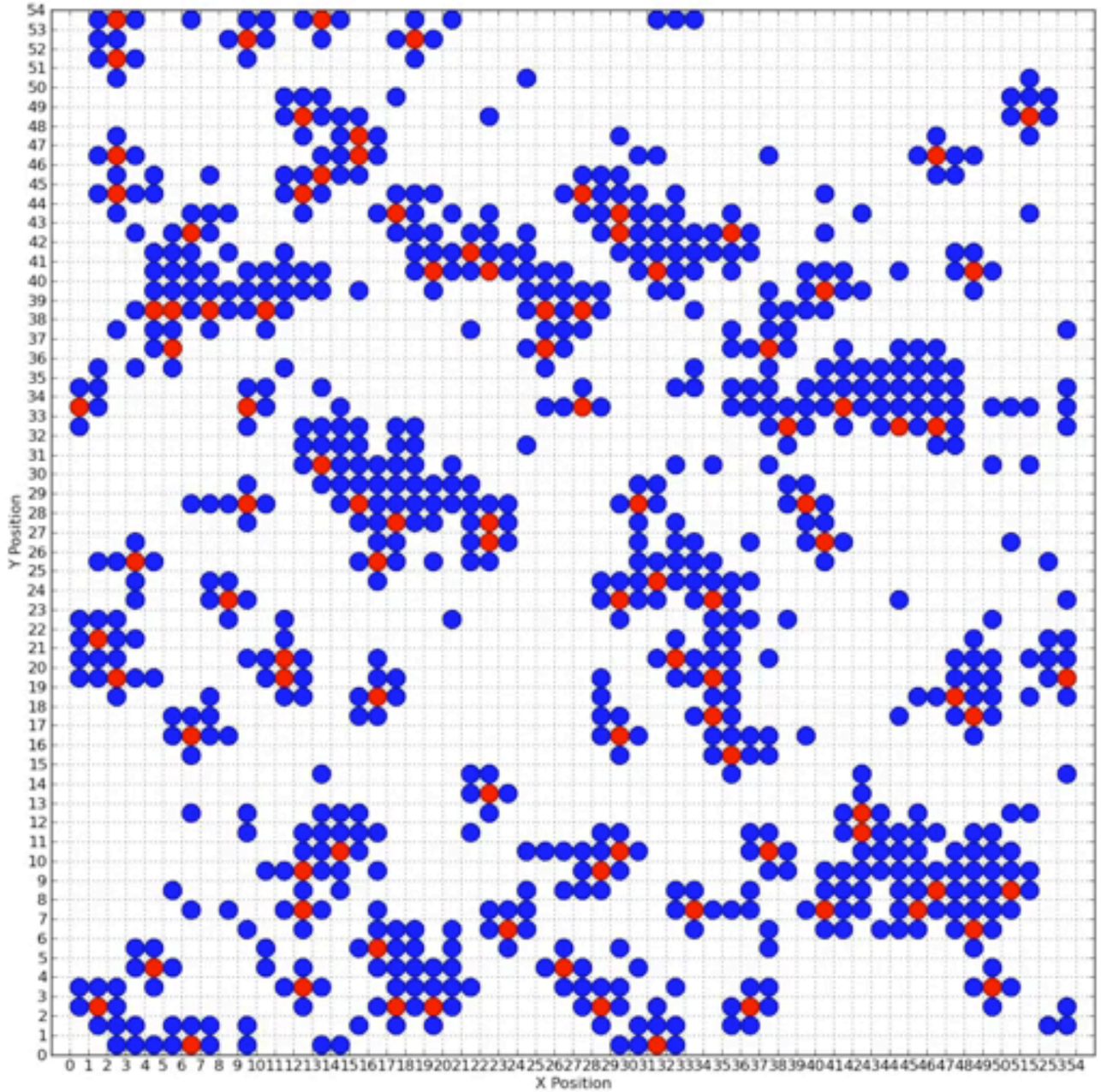
Cell Simulation Techniques

- Particle Based



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https://www.youtube.com/watch?v=1Wlh1zV4tqE

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https://www.youtube.com/watch?v=0hibGZi8TWs

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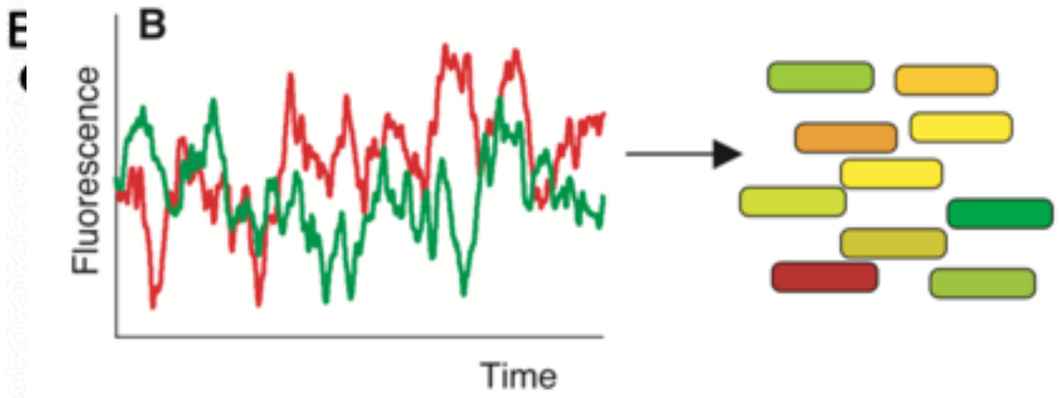
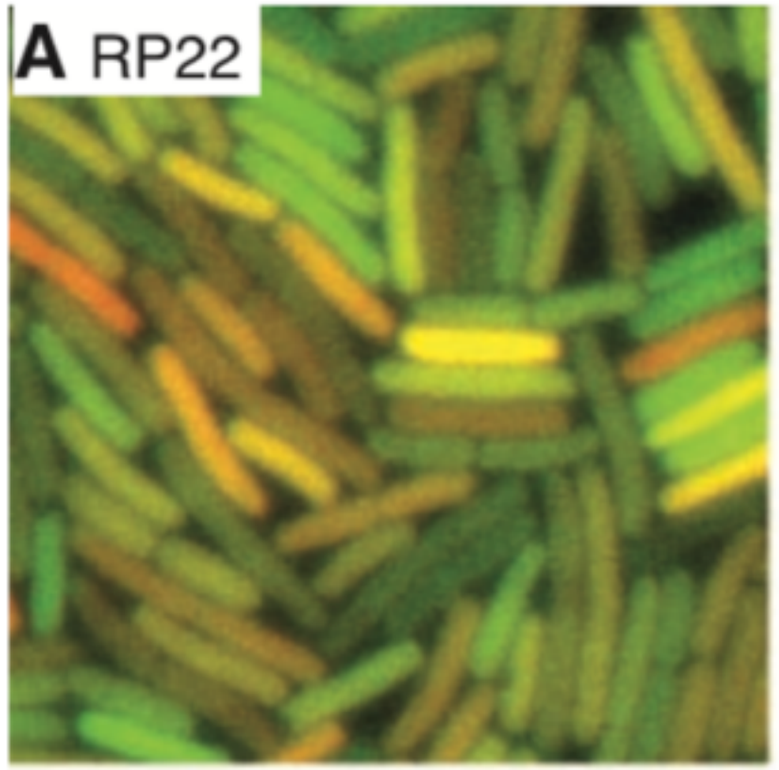
Probabilistic Simulations

Stochasticity in Biology

- Stochasticity (i.e. randomness)
  - Cellular events appear to be stochastic
  - Gives rise to ***Noise*** in populations
- Directly measurable
- Important at low copy numbers





Elowitz, Levine, Siggia, Swain. (2002) *Science*. 297(5584):1183-6.

Stochastic Simulations

Master Equation (ME)

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

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

Chemical Master Equation (CME)

$$\mathbf{A} = \mathbf{R}$$

$$\mathbf{R} = \begin{pmatrix} \alpha_{1,1} & \cdots & \alpha_{1,n} \\ \vdots & \ddots & \vdots \\ \alpha_{m,1} & \cdots & \alpha_{m,n} \end{pmatrix}$$

propensity

$\alpha_i \propto k_i$

rate constant

Reaction-Diffusion Master Equation (RDME)

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

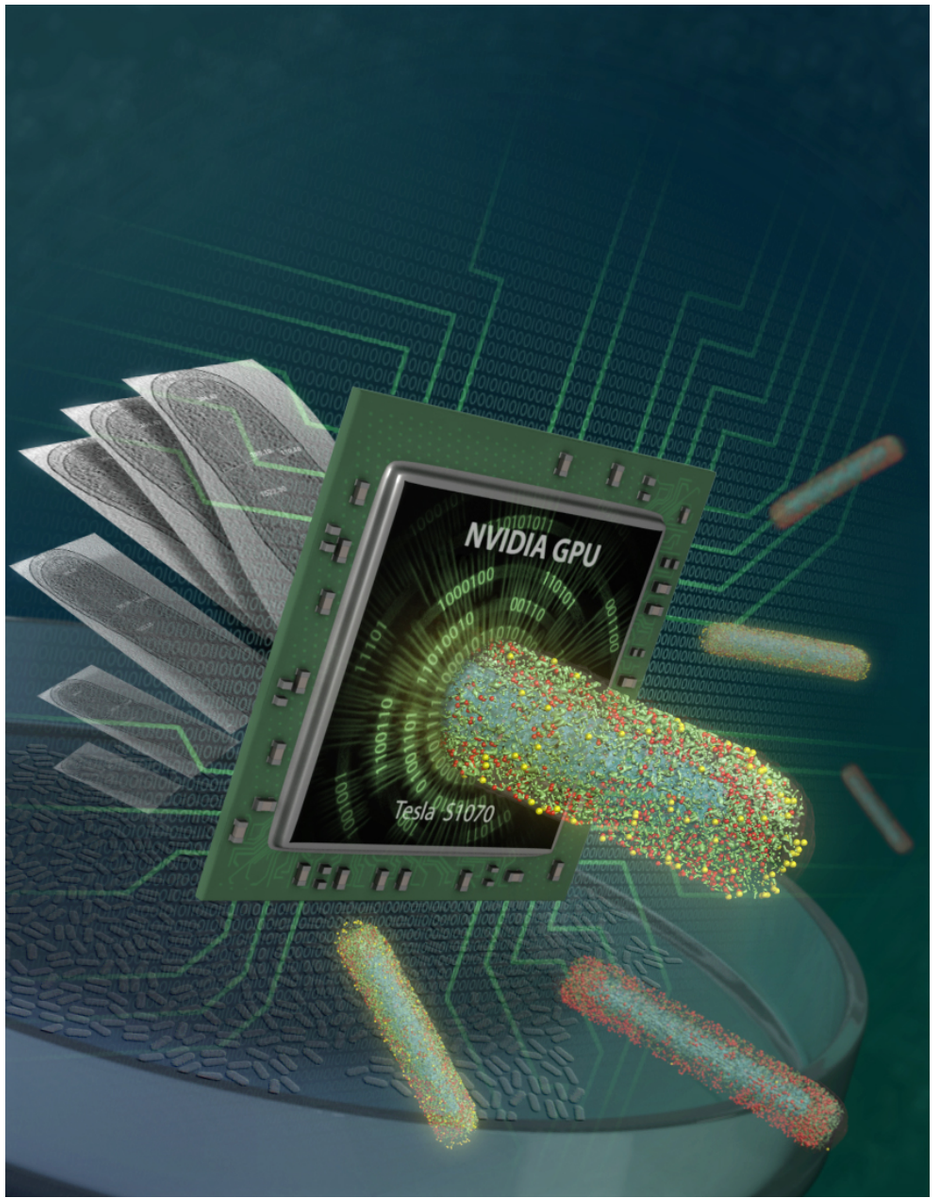
$$\mathbf{D} = \begin{pmatrix} d_{1,1} & \cdots & d_{1,n} \\ \vdots & \ddots & \vdots \\ d_{m,1} & \cdots & d_{m,n} \end{pmatrix}$$

propensity

$d_i \propto D_i$

diffusion constant

Lattice Microbes: A HPC Stochastic Simulator



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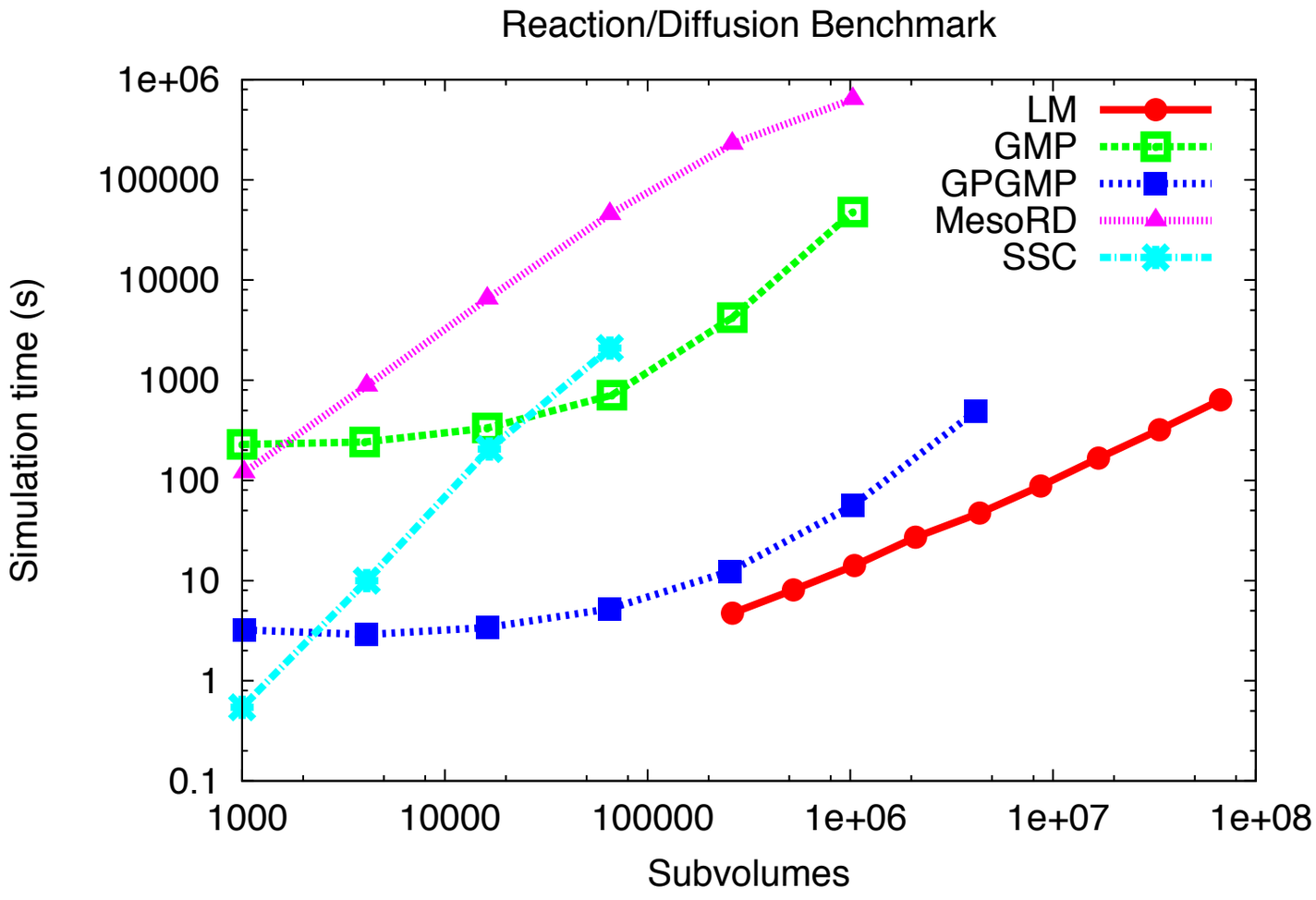
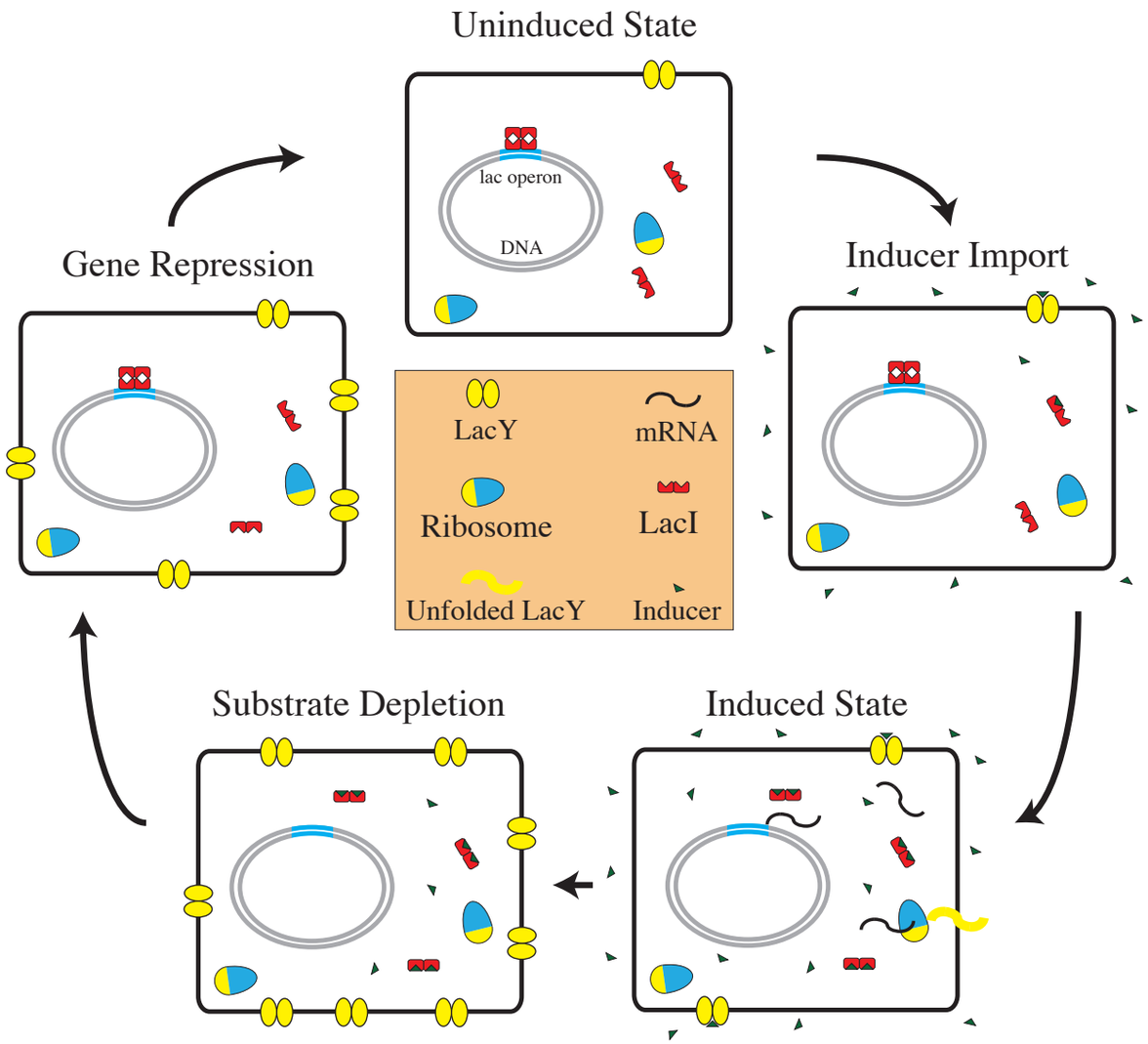


lac Genetic Switch

- An *inducible* genetic switch
- Presence of lactose "turns on" expression of its own transporter
- Gives rise to heterogeneity in populations

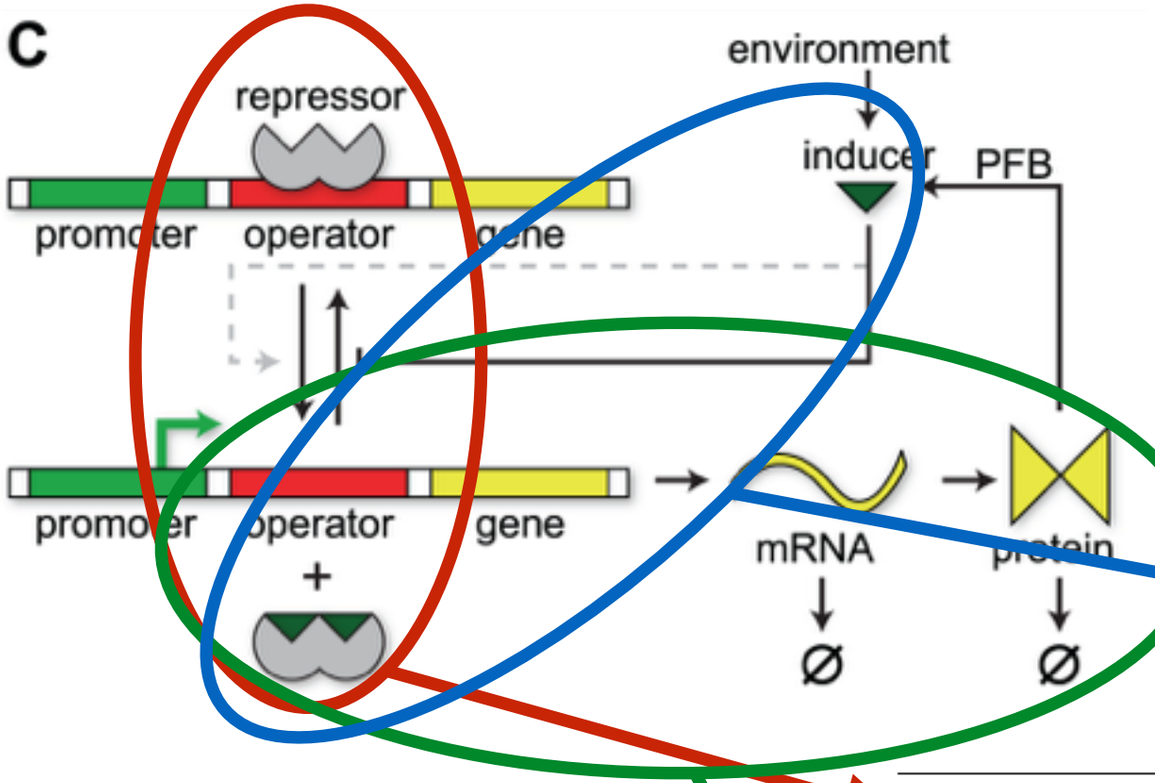


E. Roberts, A. Magis, J.O. Ortiz, W. Baumeister, and Z. Luthey-Schulten *PLoS. Comput. Biol.*, 7(3):e1002010, 2011

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.*

P. Choi, L. Cai, K. Frieda, X.S. Xie. (2008) *Science* 322:442-446.

lac Genetic Switch Reactions



Lac operon regulation	
$R_2 + O \rightarrow R_2O$	k_{ron}
$IR_2 + O \rightarrow IR_2O$	k_{iron}
$I_2R_2 + O \rightarrow I_2R_2O$	k_{i2ron}
$R_2O \rightarrow R_2 + O$	k_{roff}
$IR_2O \rightarrow IR_2 + O$	k_{iroff}
$I_2R_2O \rightarrow I_2R_2 + O$	k_{i2roff}
Transcription, translation, and degredation	
$O \rightarrow O + mY$	k_{tr}
$mY \rightarrow mY + Y$	k_{tn}
$mY \rightarrow \varnothing$	k_{degm}
$Y \rightarrow \varnothing$	k_{degp}

Lac inducer–repressor interactions	
$I + R_2 \rightarrow IR_2$	k_{ion}
$I + IR_2 \rightarrow I_2R_2$	k_{i2on}
$I + R_2O \rightarrow IR_2O$	k_{iopon}
$I + IR_2O \rightarrow I_2R_2O$	k_{i2opon}
$IR_2 \rightarrow I + R_2$	k_{ioff}
$I_2R_2 \rightarrow I + IR_2$	k_{i2off}
$IR_2O \rightarrow I + R_2O$	k_{iopoff}
$I_2R_2O \rightarrow I + IR_2O$	$k_{i2opoff}$
Inducer transport	
$I_{ex} \rightarrow I$	k_{id}
$I \rightarrow I_{ex}$	k_{id}
$Y + I_{ex} \rightarrow YI$	k_{yion}
$YI \rightarrow Y + I_{ex}$	k_{yioff}
$YI \rightarrow Y + I$	k_{it}

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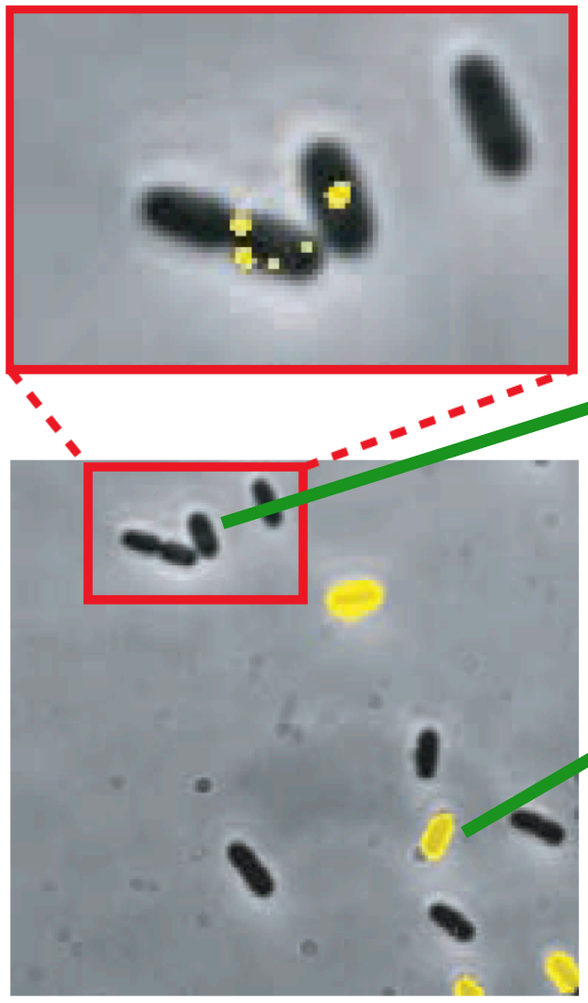
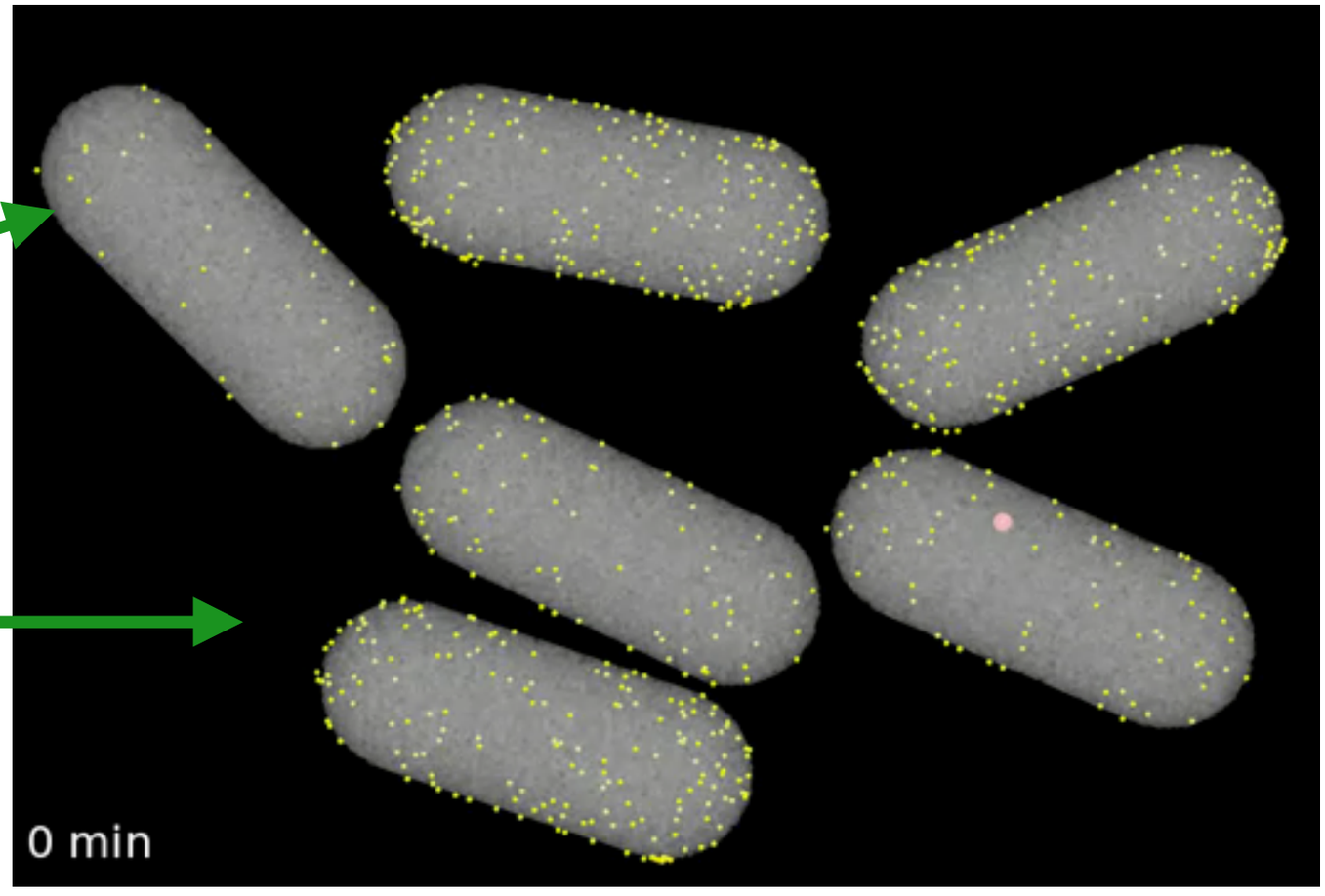
lac Genetic Switch

Simulate
on GPUs





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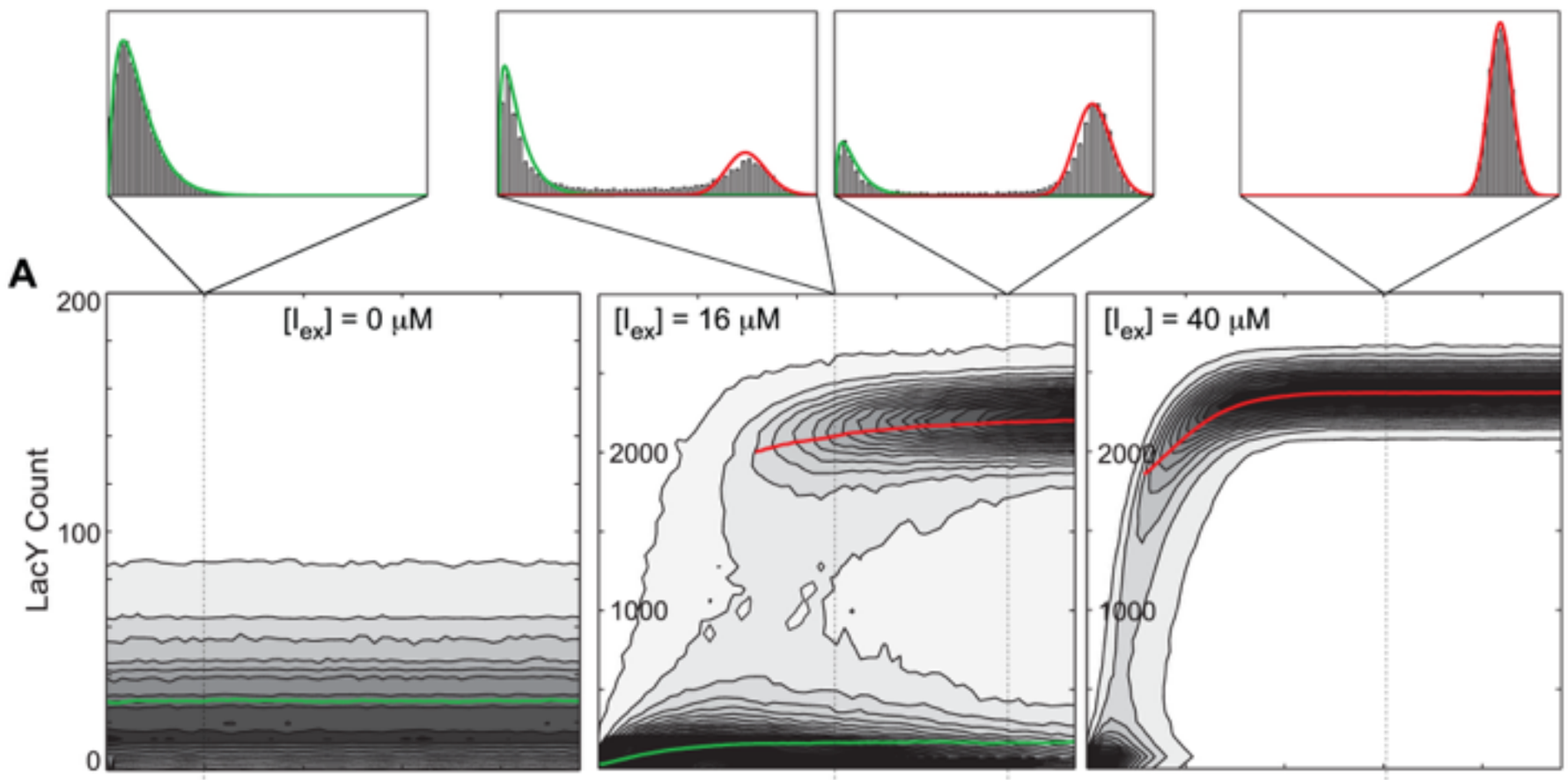
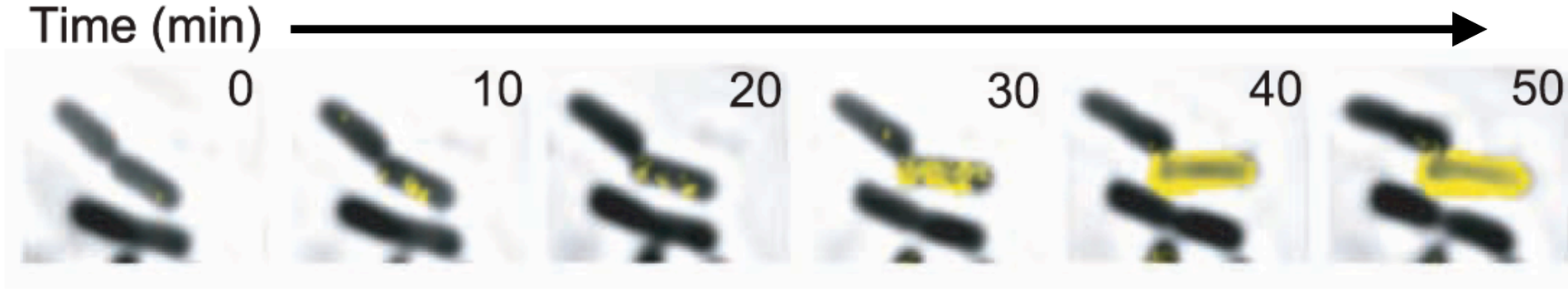
Switching Behavior Depends on Inducer Concentration



Induced State

Uninduced State



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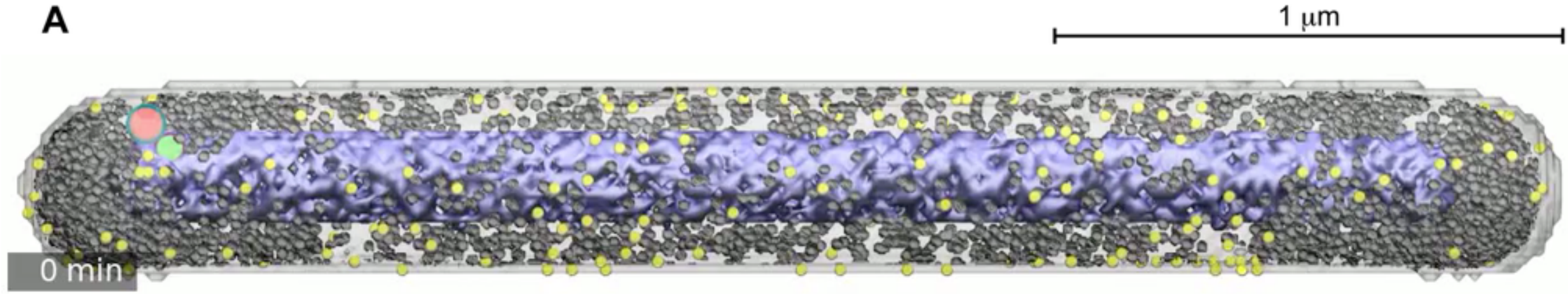
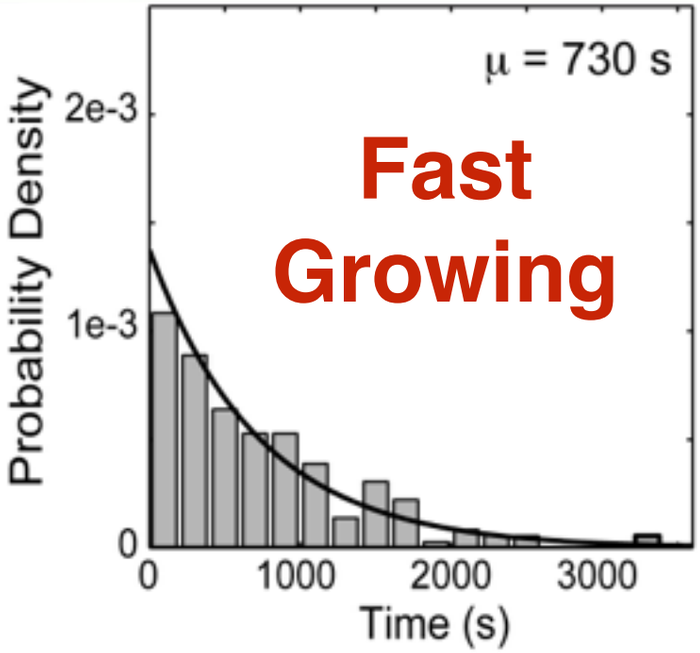
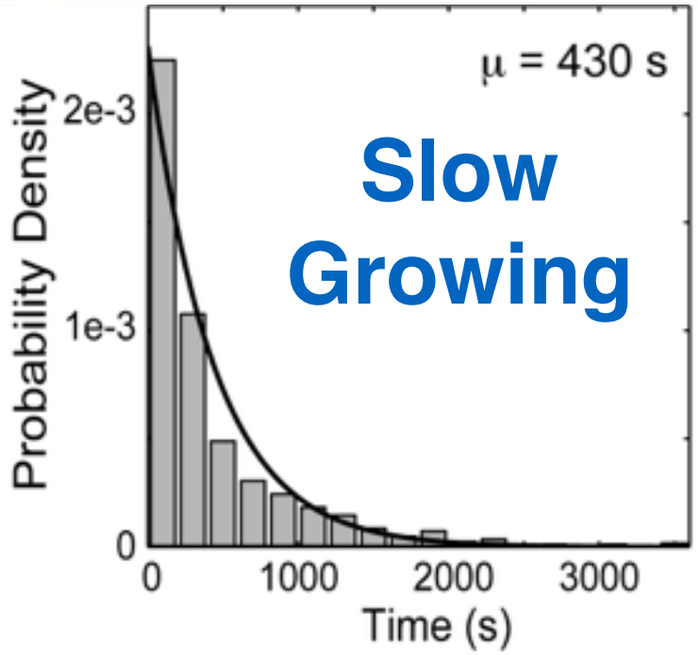
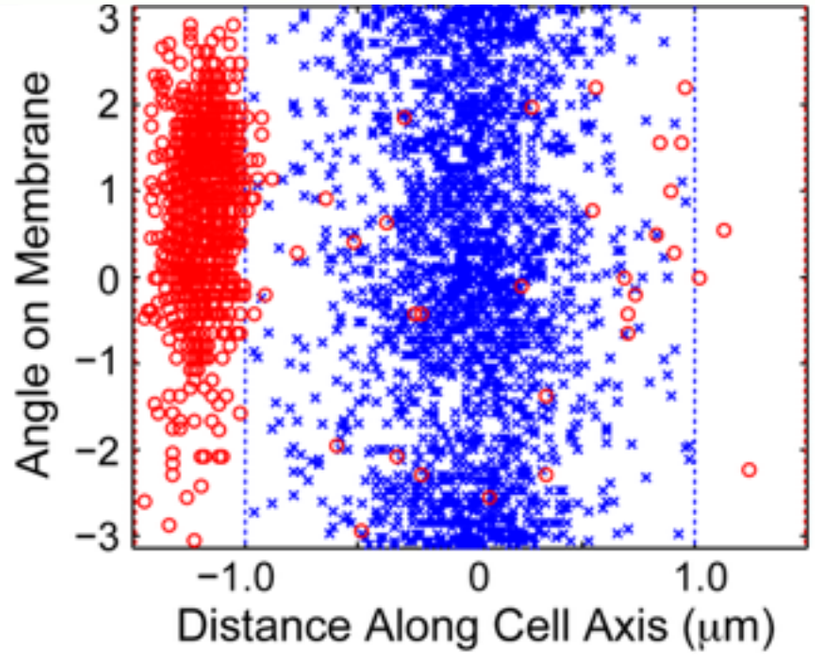
Switching Behavior Depends on Cell Structure









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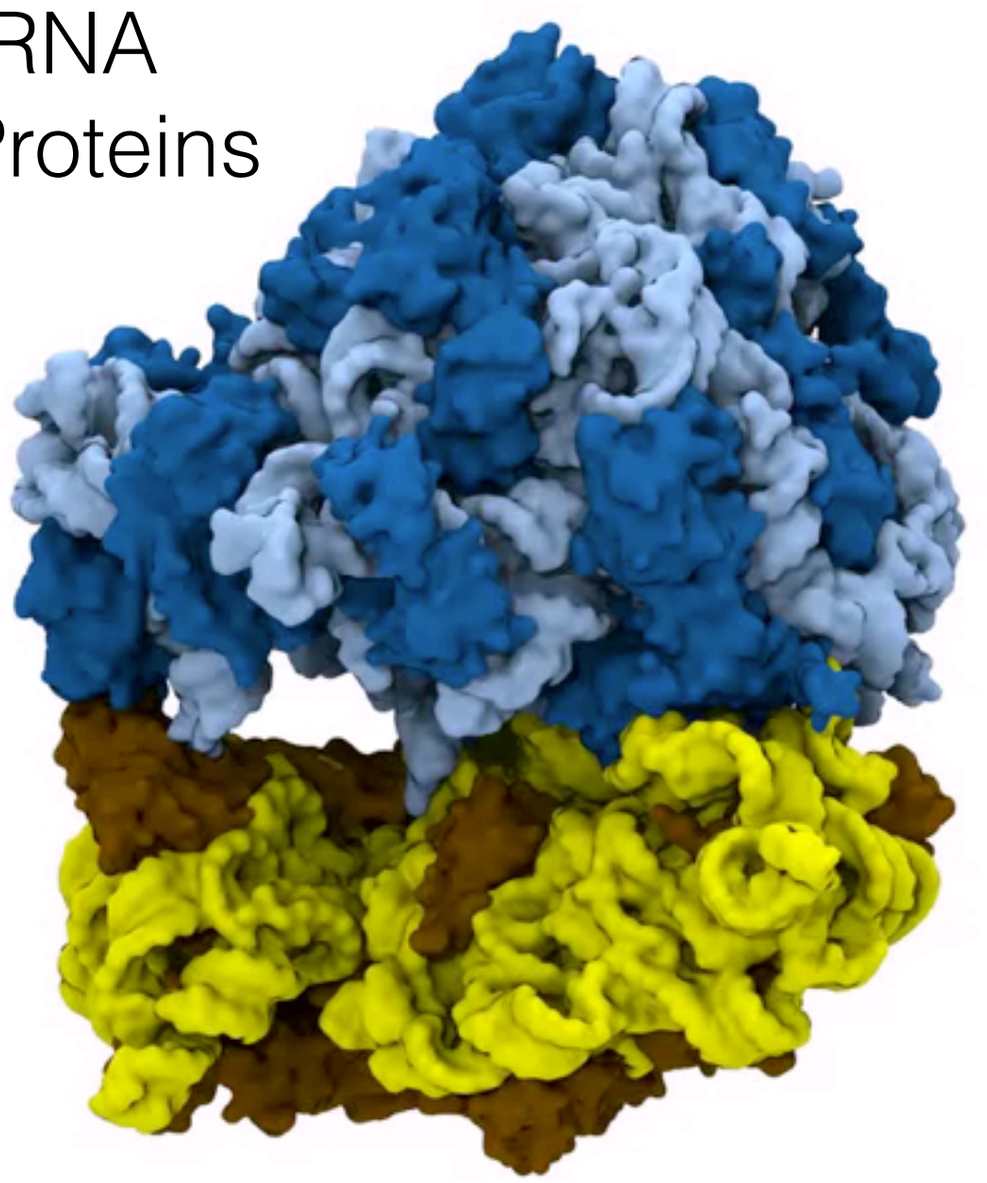
Ribosome Biogenesis

3 rRNA
~50 Proteins

LSU



SSU

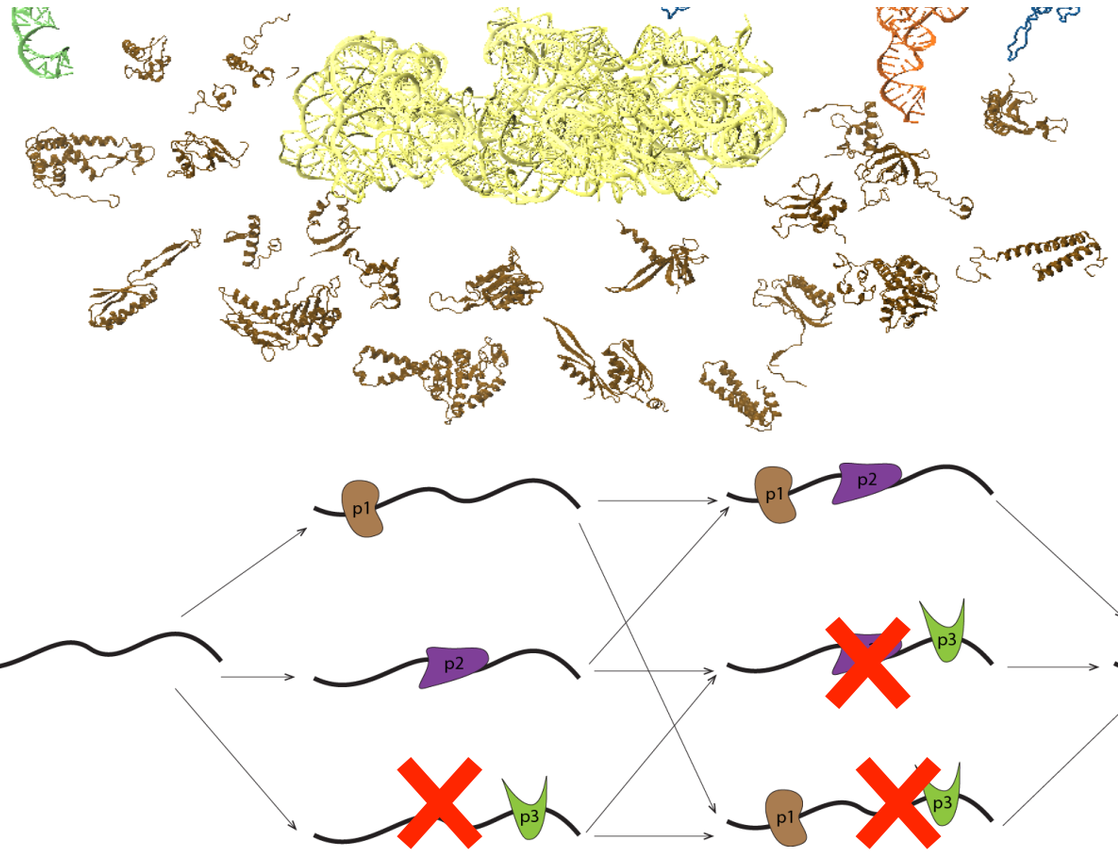
What are the timescales of assembly (of the SSU)?

How are assembly intermediates localized in cells?

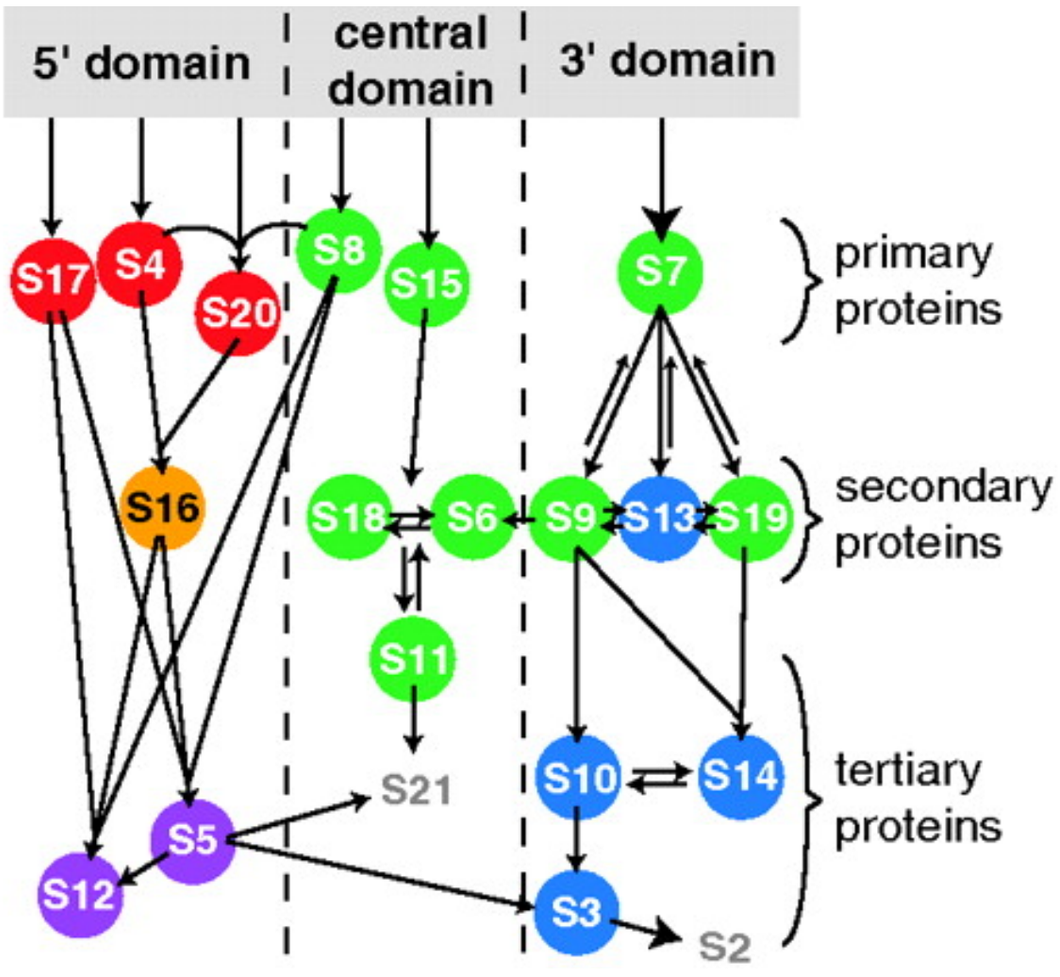
T.M. Earnest, J.A. Cole, J.R. Peterson, T.E. Kuhlman, Z. Luthey-Schulten. *Biopolymers*, 2016, Jul 22, 105(10): 735-751
T. M. Earnest, J. Lai, K. Chen, M. J. Hallock, J. R. Williamson, and Z. Luthey-Schulten. *Biophysical Journal*, 2015, Sep 15, 109(6): 1117-35

Ribosome Assembly Process

16S rRNA + 20 SSU proteins = 2^{20} states



Nomura Hierarchical Map >>> 1612 states



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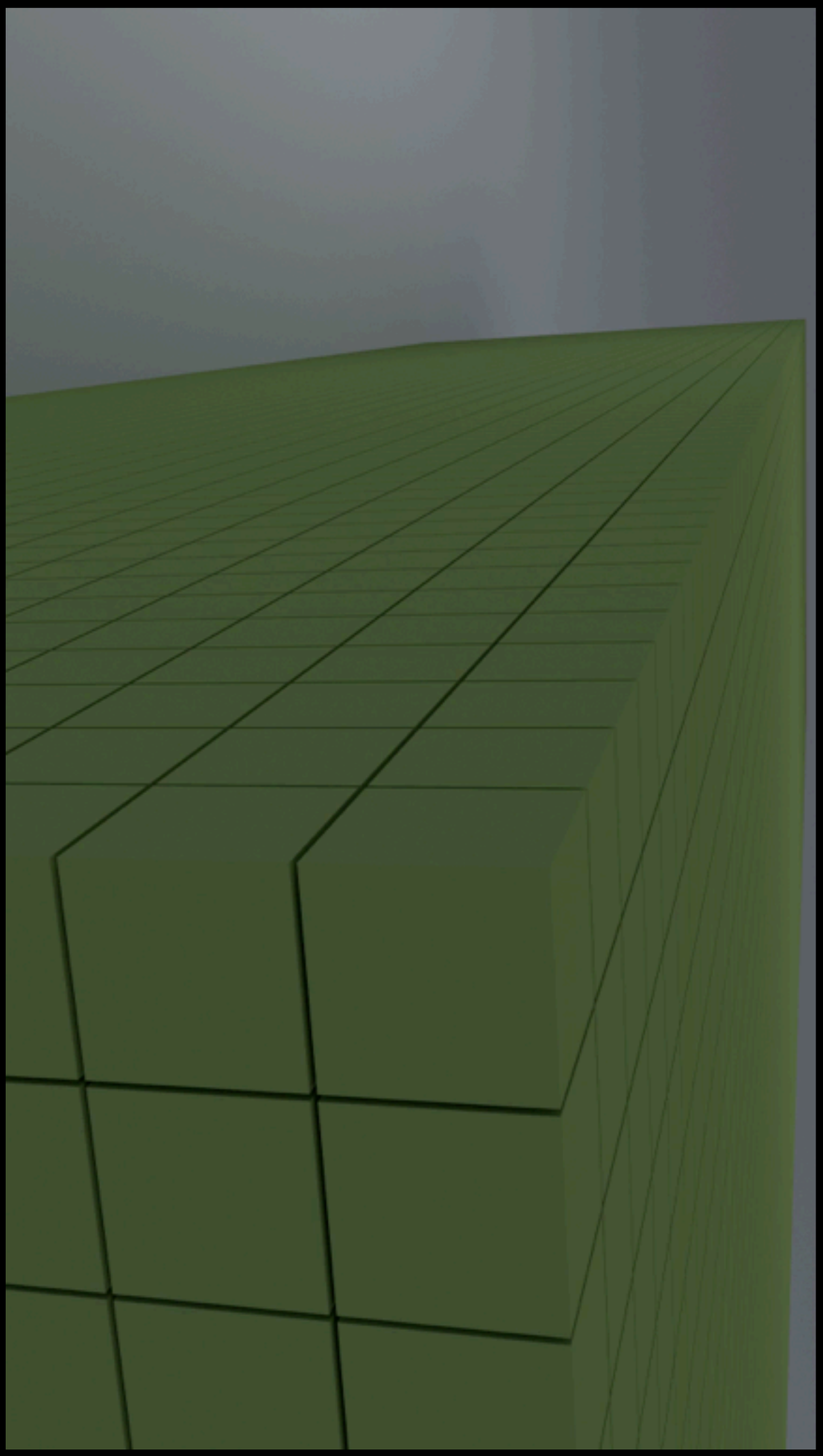
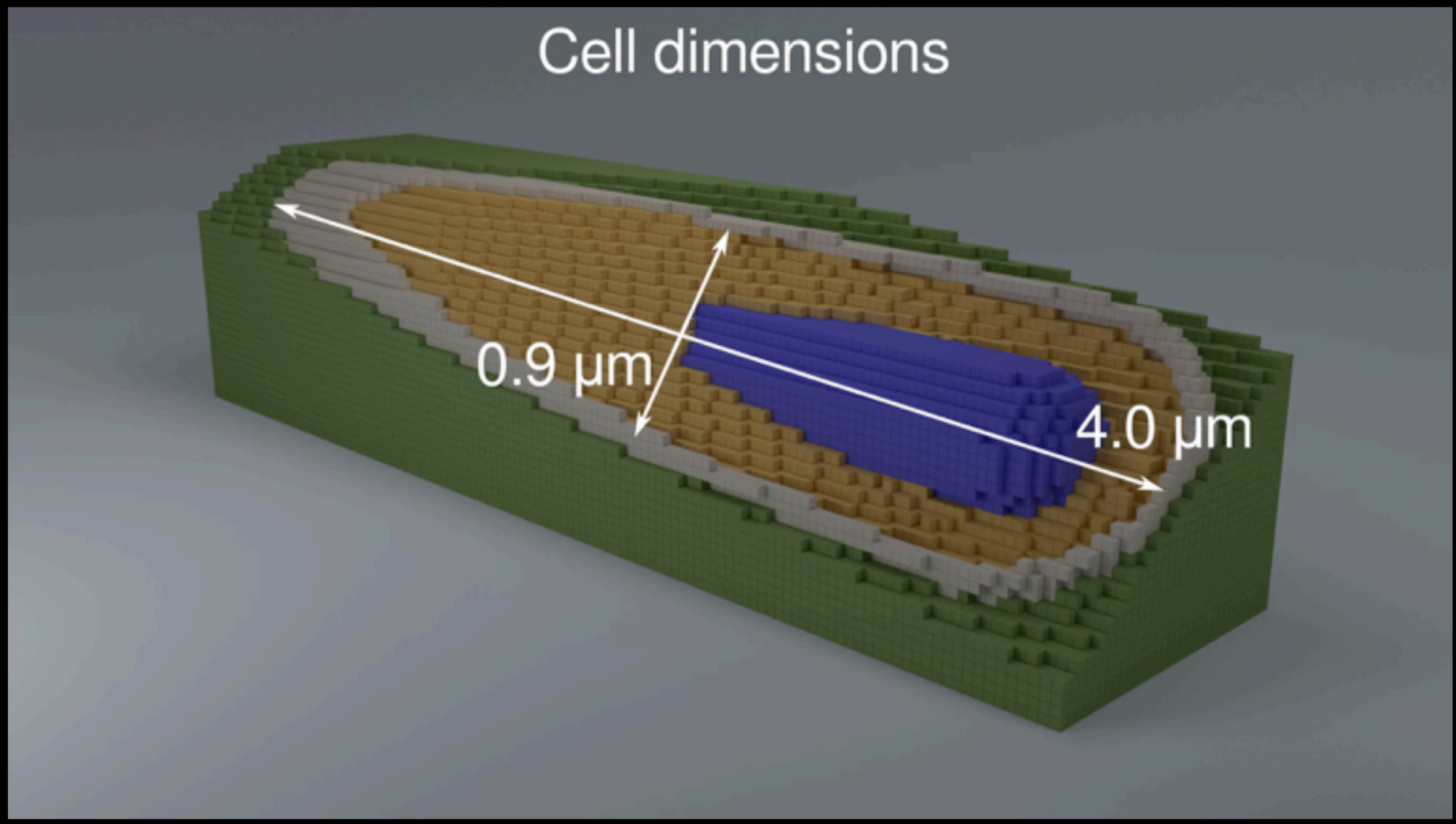
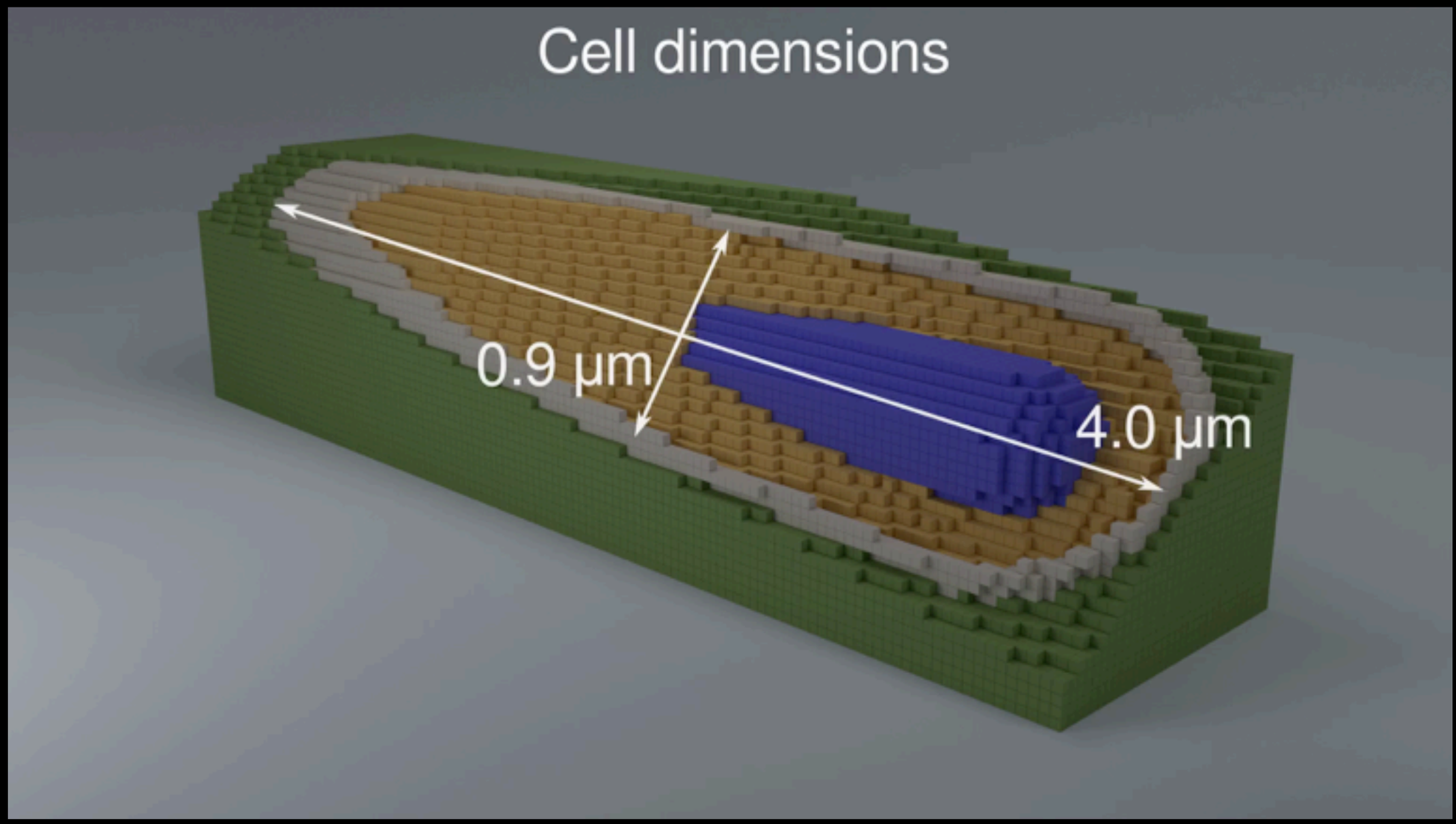
In vivo model - 1330 reactions, 251 species

	Reaction	Data source
Assembly	$Sx + I_i \longrightarrow I_{i+1}$	40ºC model, no modifications
Degradation	$mRNA \longrightarrow \varnothing$	From expt. half life
Transcription	$DNA \longrightarrow DNA + mRNA$ $DNA \longrightarrow DNA + rRNA$	Chosen to match relative protein abundance
Translation	$30S + mRNA + 50S \longrightarrow 30S + mRNA + 50S + n\ Protein$	From transcript lengths
Diffusion	$X_i(\boldsymbol{x}) \longrightarrow X_i(\boldsymbol{x}+\boldsymbol{\delta}_j)$	Estimated or from SM experiments (Elf)




Cell dimensions
0.9 µm
4.0 µm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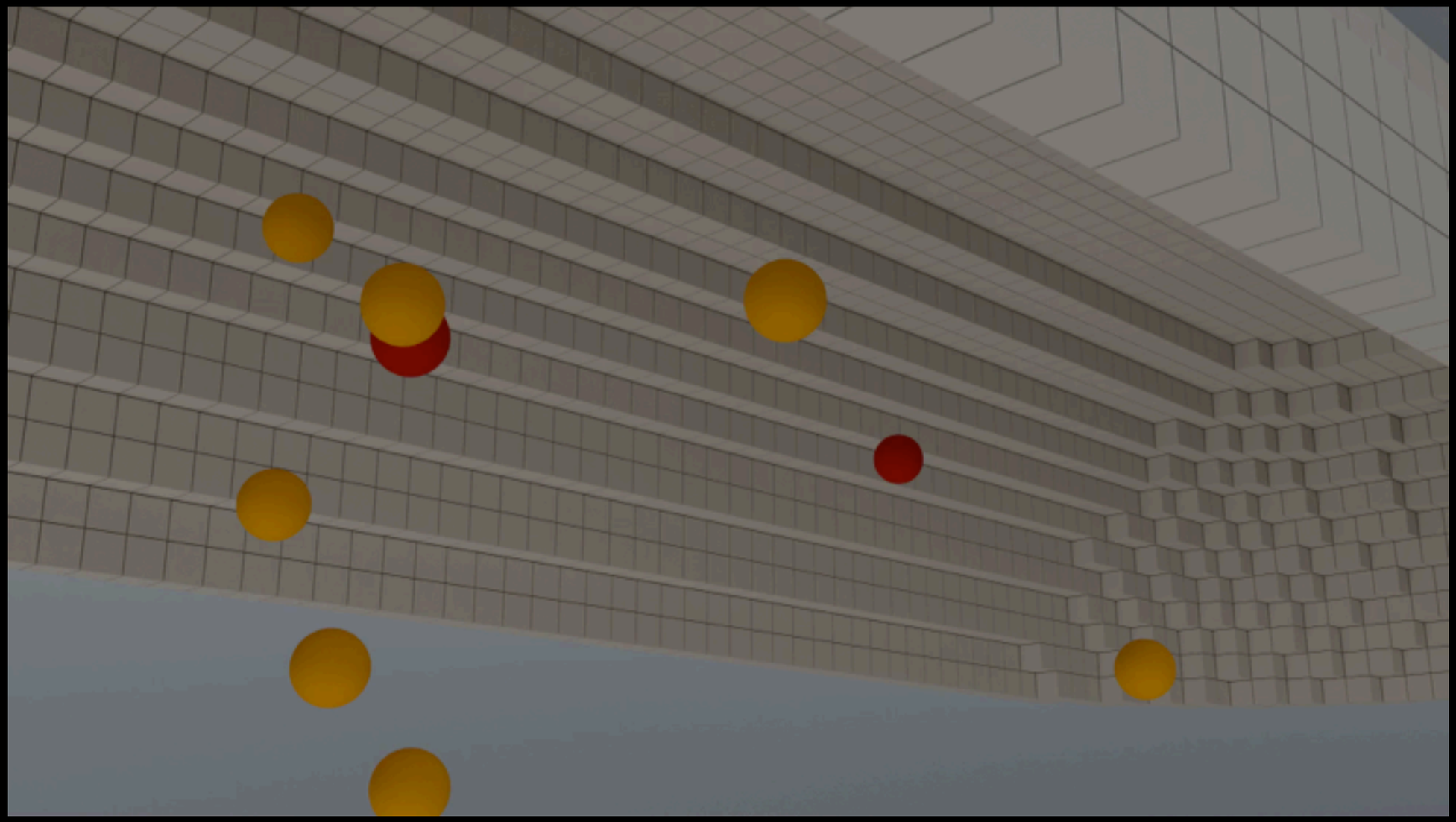
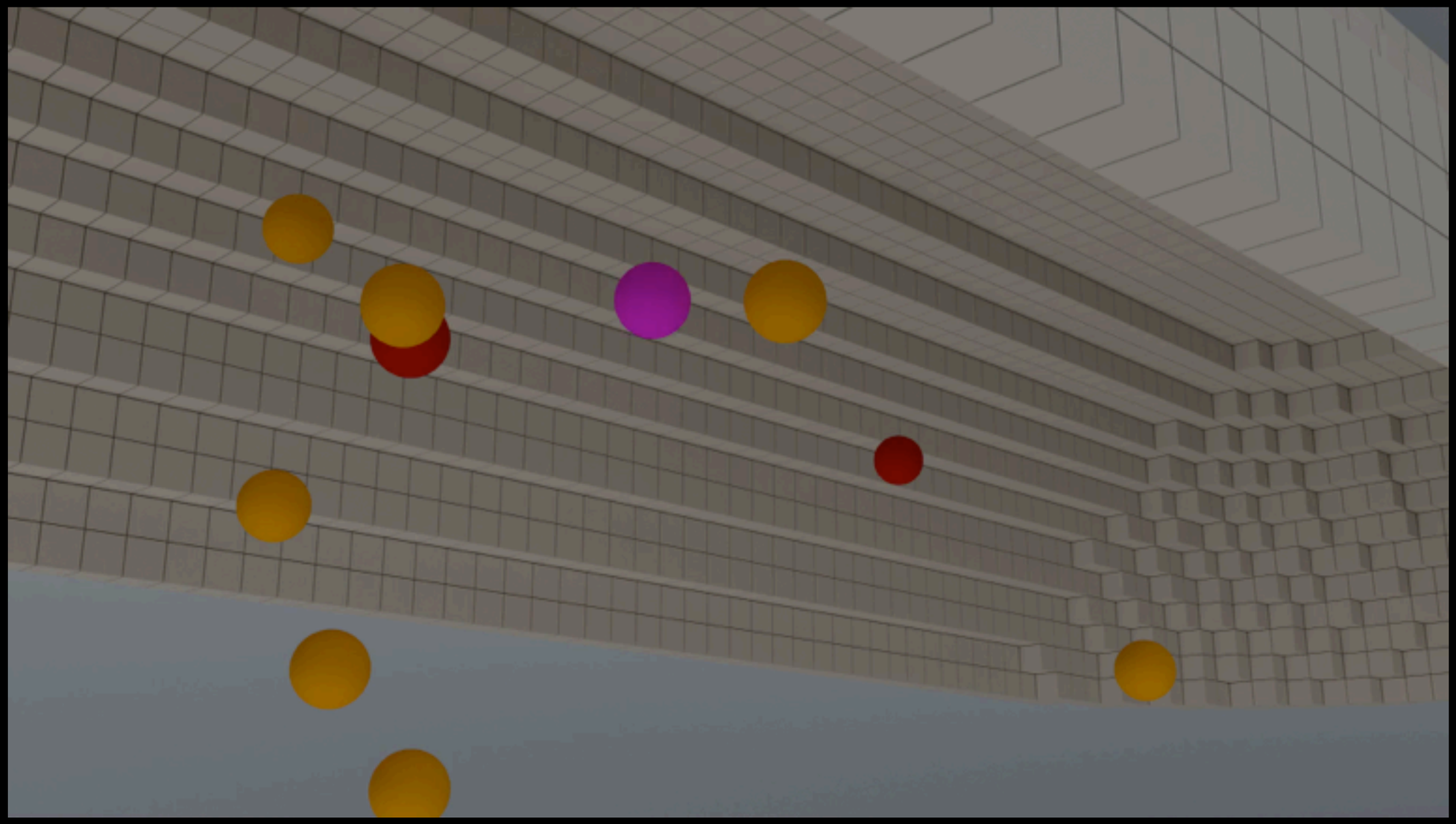
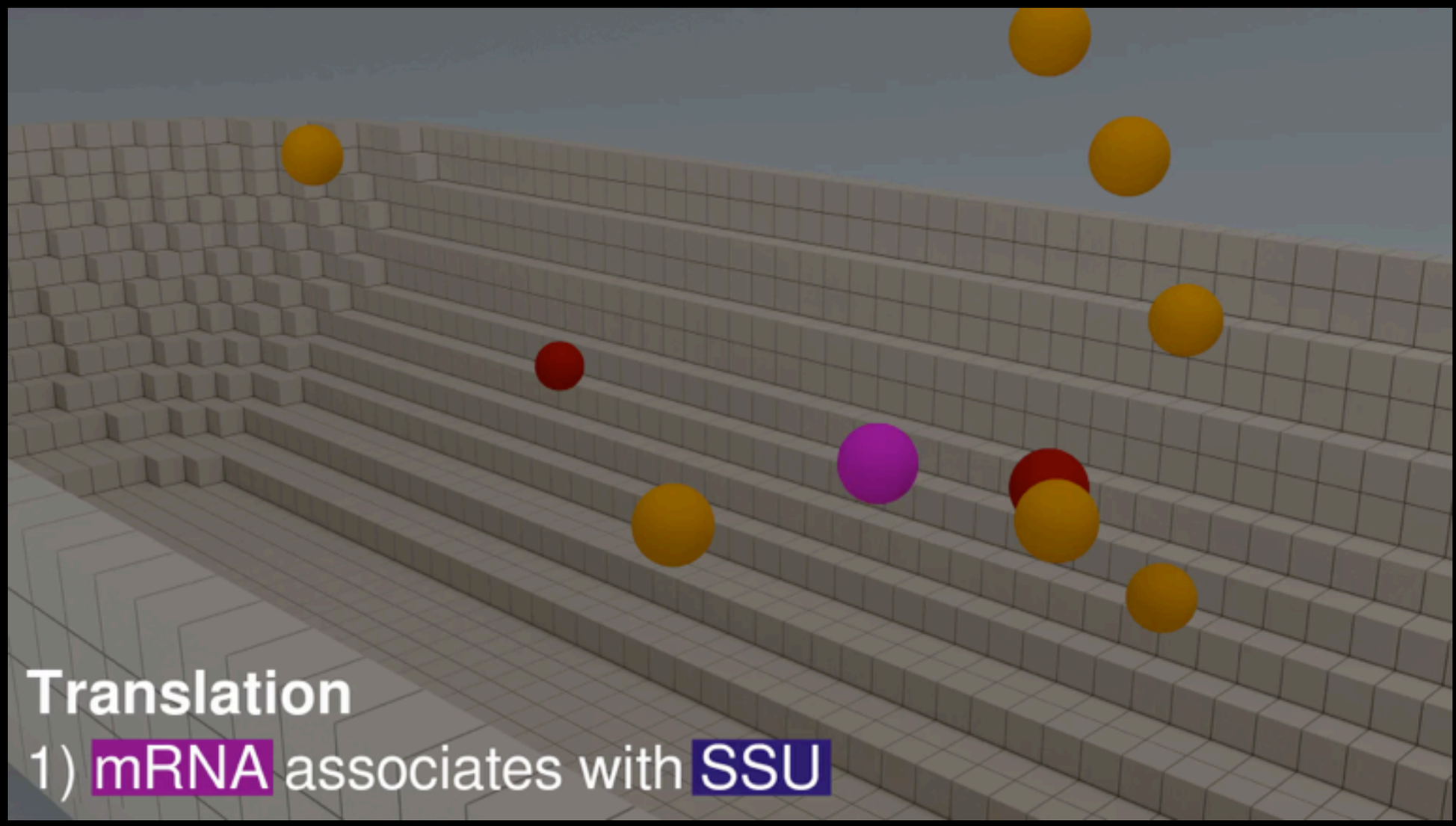
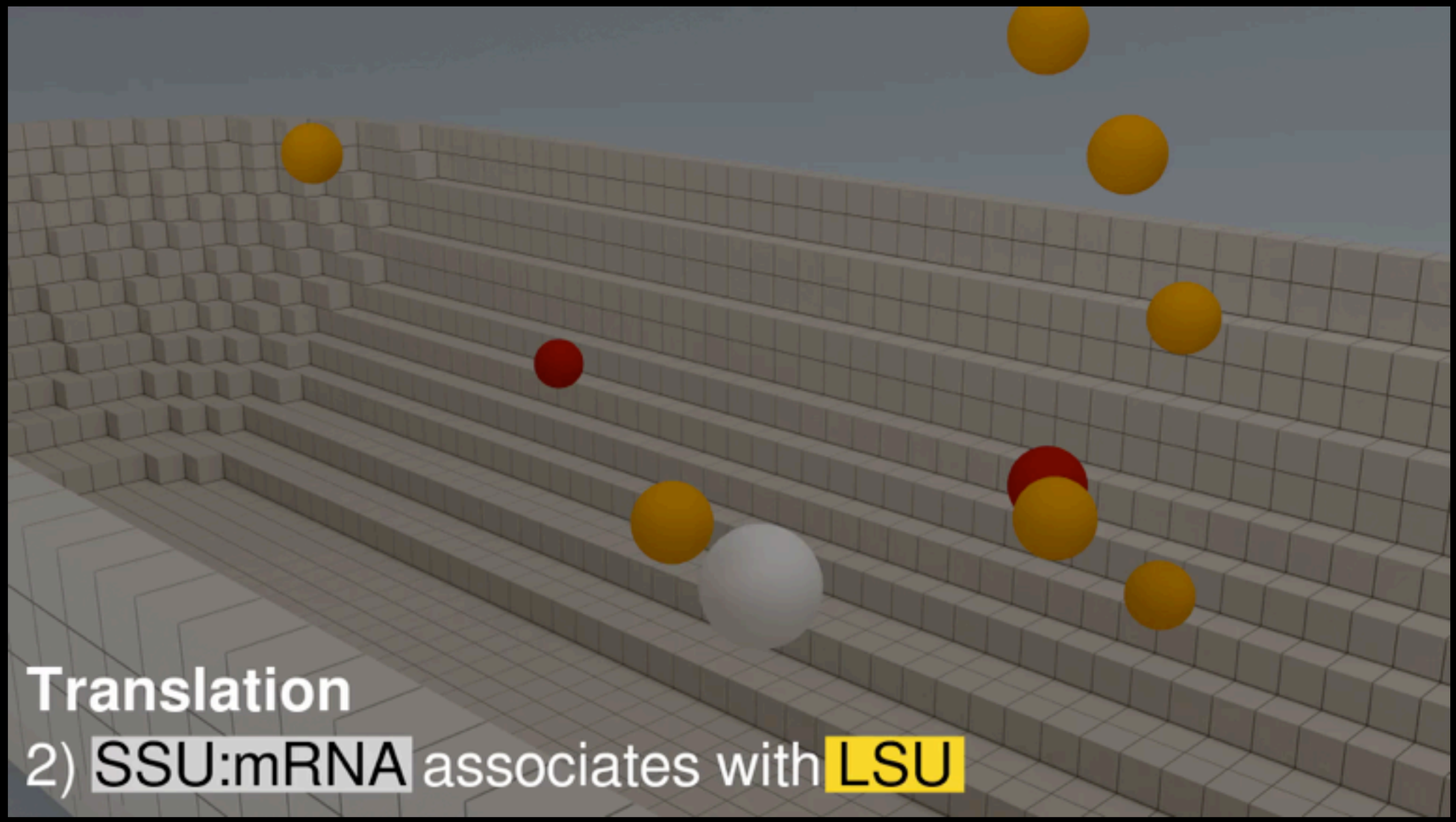
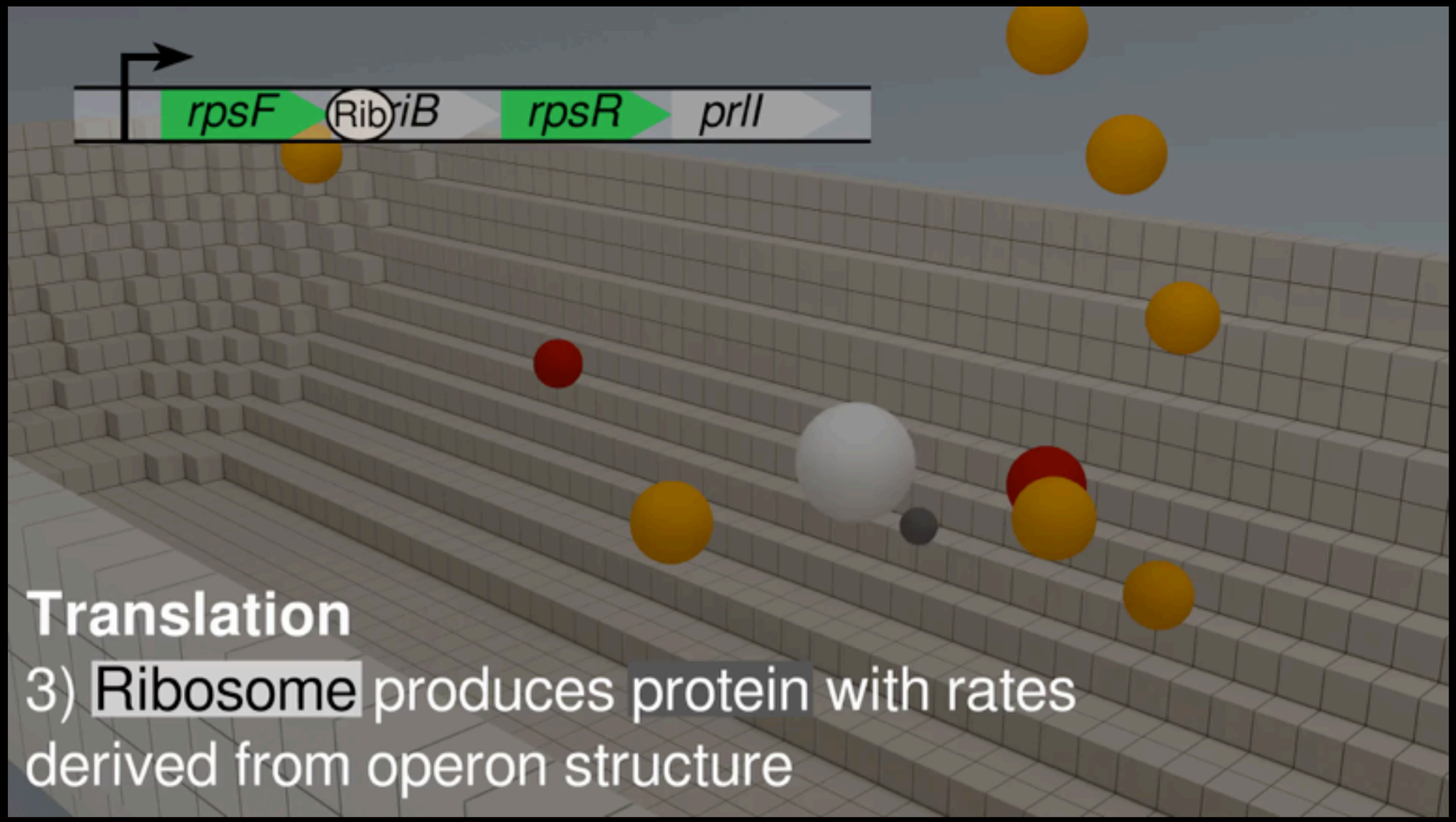
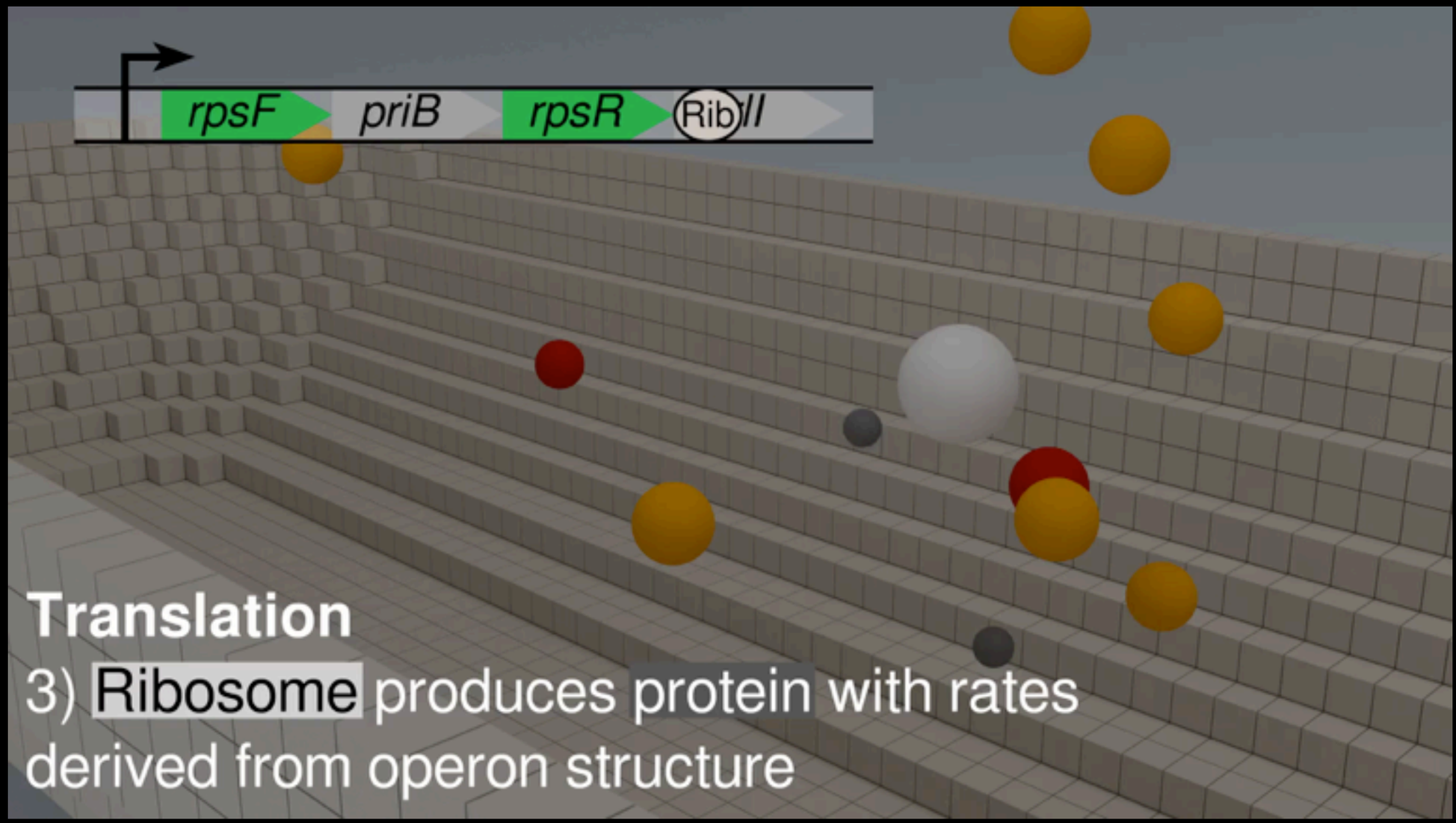


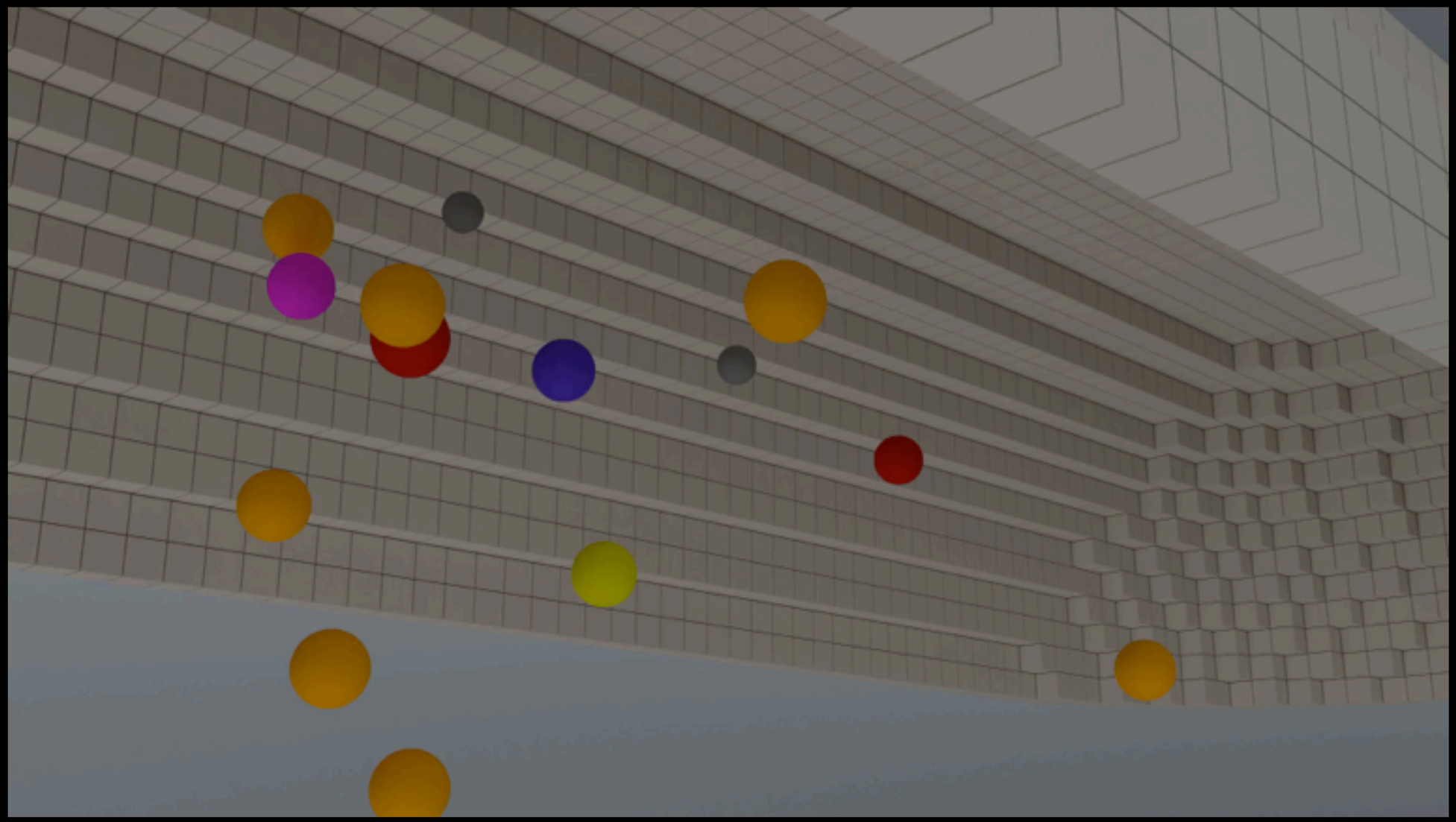



Translation
1) mRNA associates with SSU


Translation
2) SSU:mRNA associates with LSU


rpsF
RibiB
rpsR
prlI
Translation
3) Ribosome produces protein with rates
derived from operon structure

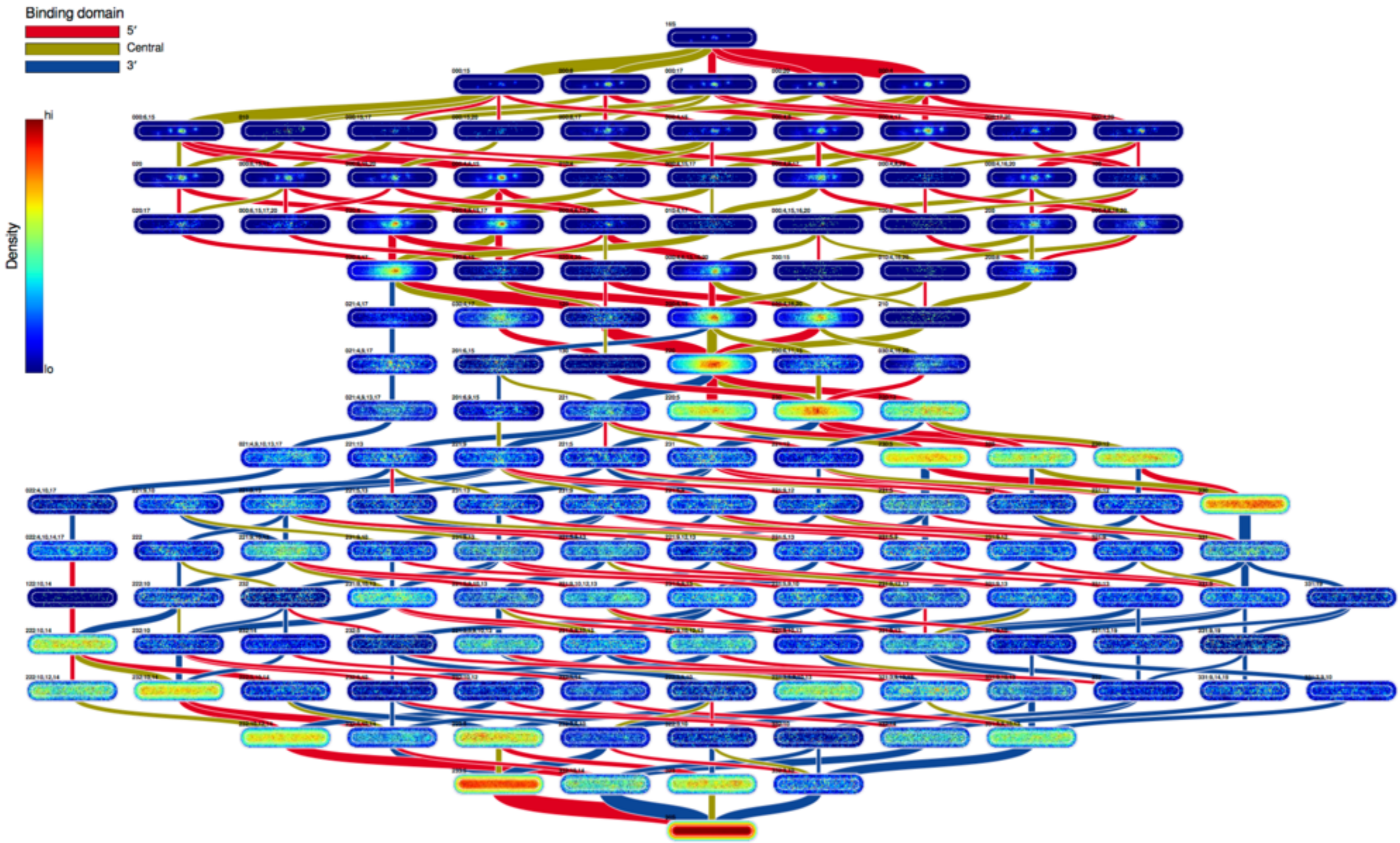

rpsF
priB
rpsR
Rib
II
Translation
3) Ribosome produces protein with rates
derived from operon structure




SSU Assembly
1) 16S rRNA is produced at the site of rrn operons

In silico Ribosome Biogenesis

a

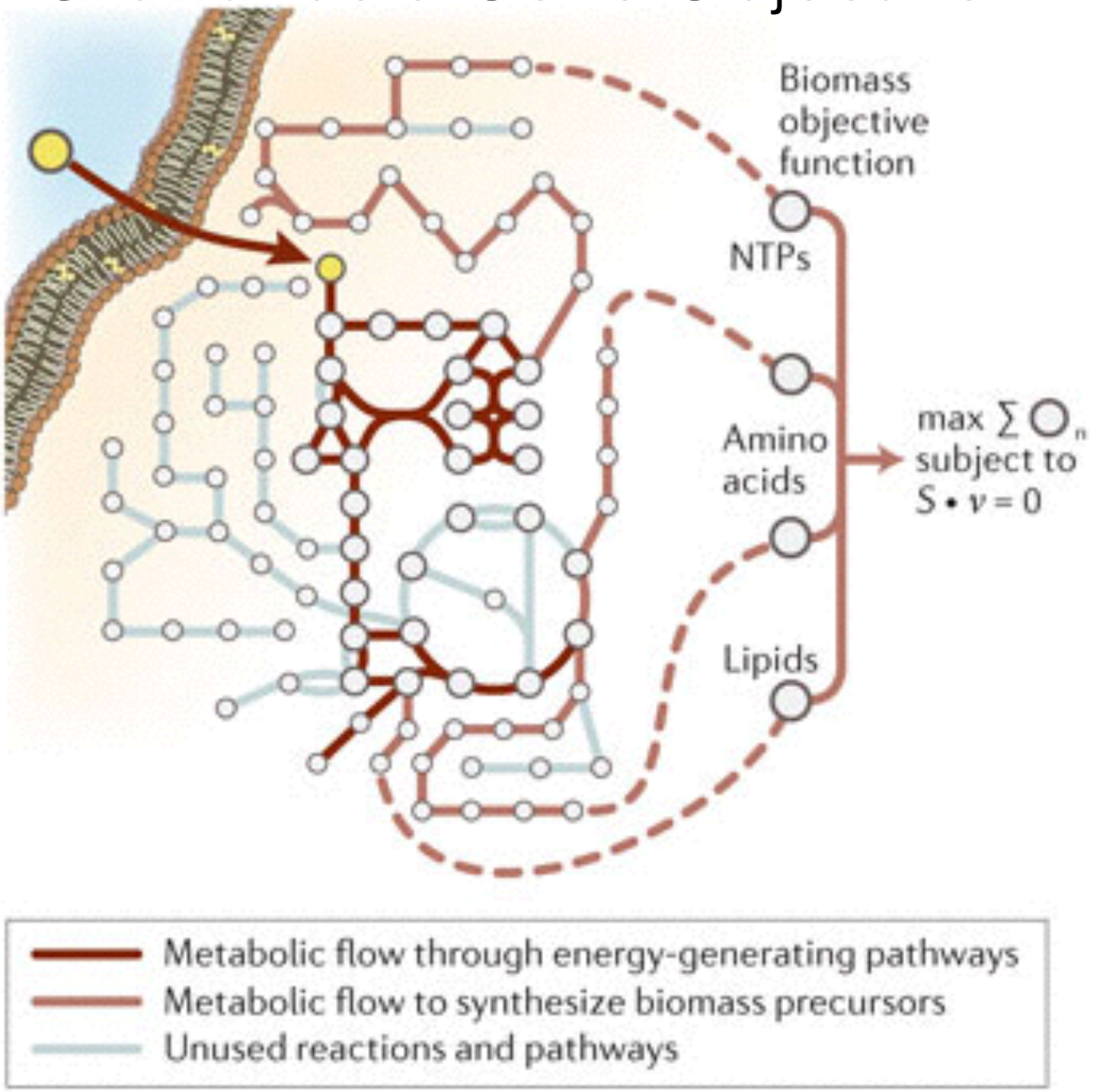


T.M. Earnest, J.A. Cole, J.R. Peterson, T.E. Kuhlman, Z. Luthey-Schulten. *Biopolymers*, 2016, Jul 22, 105(10): 735-751
T. M. Earnest, J. Lai, K. Chen, M. J. Hallock, J. R. Williamson, and Z. Luthey-Schulten. *Biophysical Journal*, 2015, Sep 15, 109(6): 1117-35

Continuum Simulations

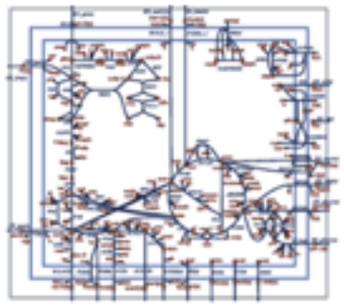
Flux Balance Analysis

Growth as a Cell's Objective



Method

1) Encode Metabolic Network as Matrix



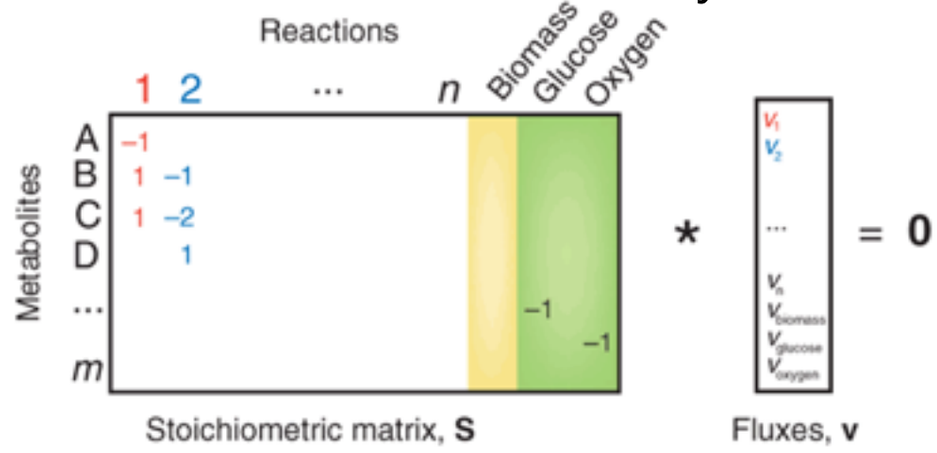
$A \leftrightarrow B + C$ Reaction 1

$B + 2C \rightarrow D$ Reaction 2

...

Reaction *n*

2) Assume Cell is at Steady State



3) Maximize Biomass Production

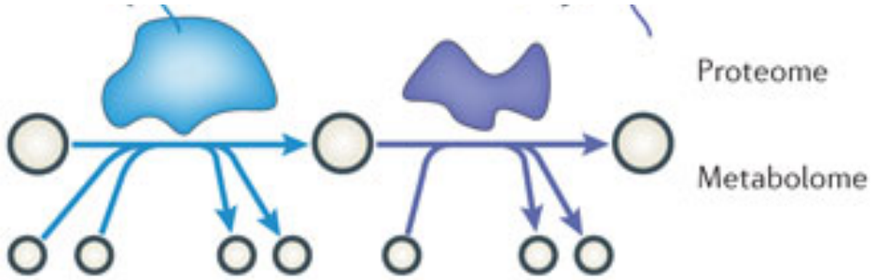
$$\mathbf{S} \cdot \vec{v} = 0$$

$$\text{maximize}\left(v_{biomass}\right)$$

J.D. Orth, I. Thiele, B.O. Palsson. *Nat. Biotech.* 2010 28:245-248.

Heterogeneity in *E. coli* Population

Enzyme Catalysis



$$V_{\max} = k_{cat}.[E]_{Total}$$

BRENDA database

Protein Copy number

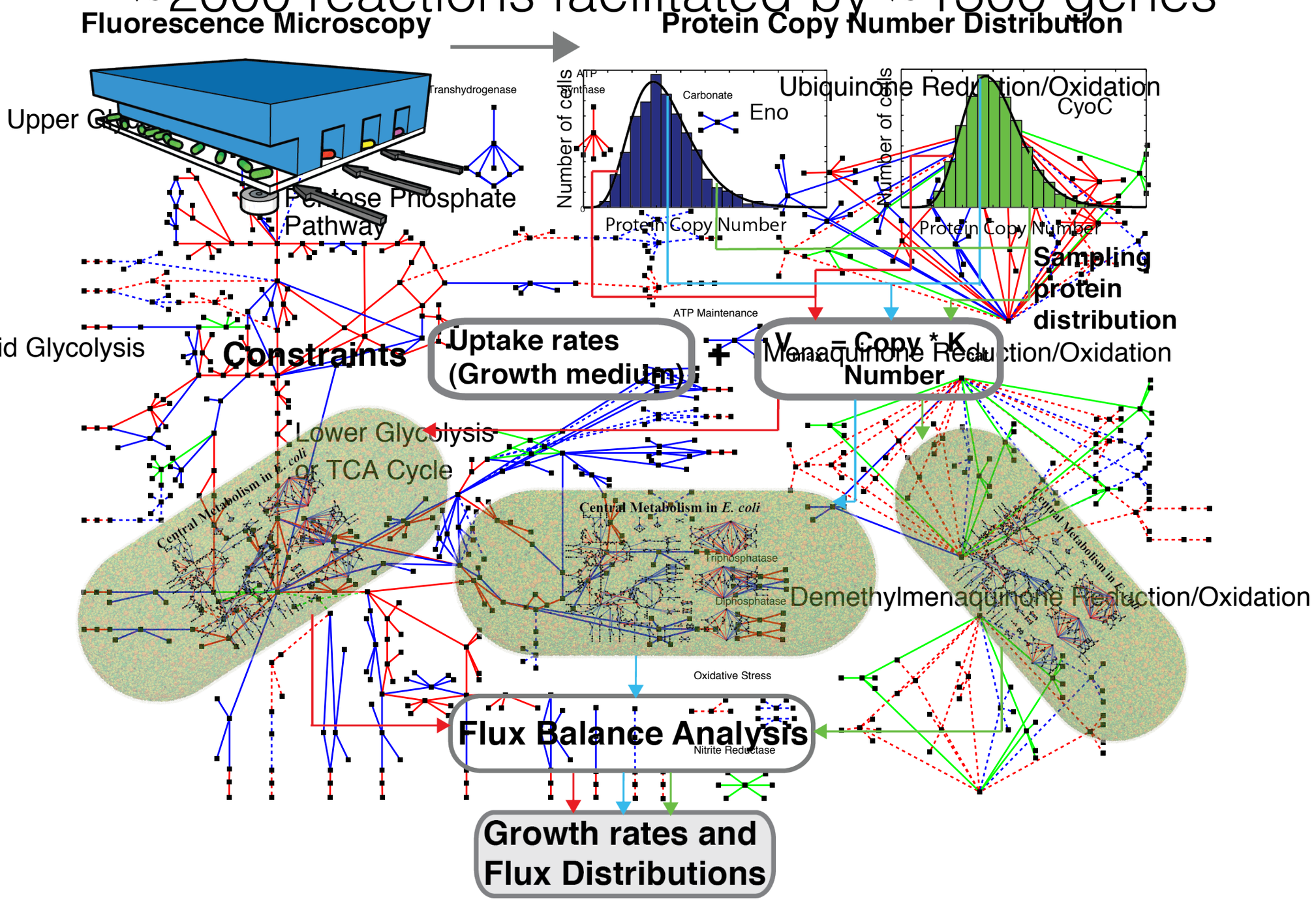
Gene expression is Noisy:

What population arises from difference in protein counts among cells?

P. Labhsetwar, J.A. Cole, E. Roberts, N.D. Price, Z. Luthey-Schulten. *Proc. Nat. Acad. Sci.*, 110(34):14006-11, 2013

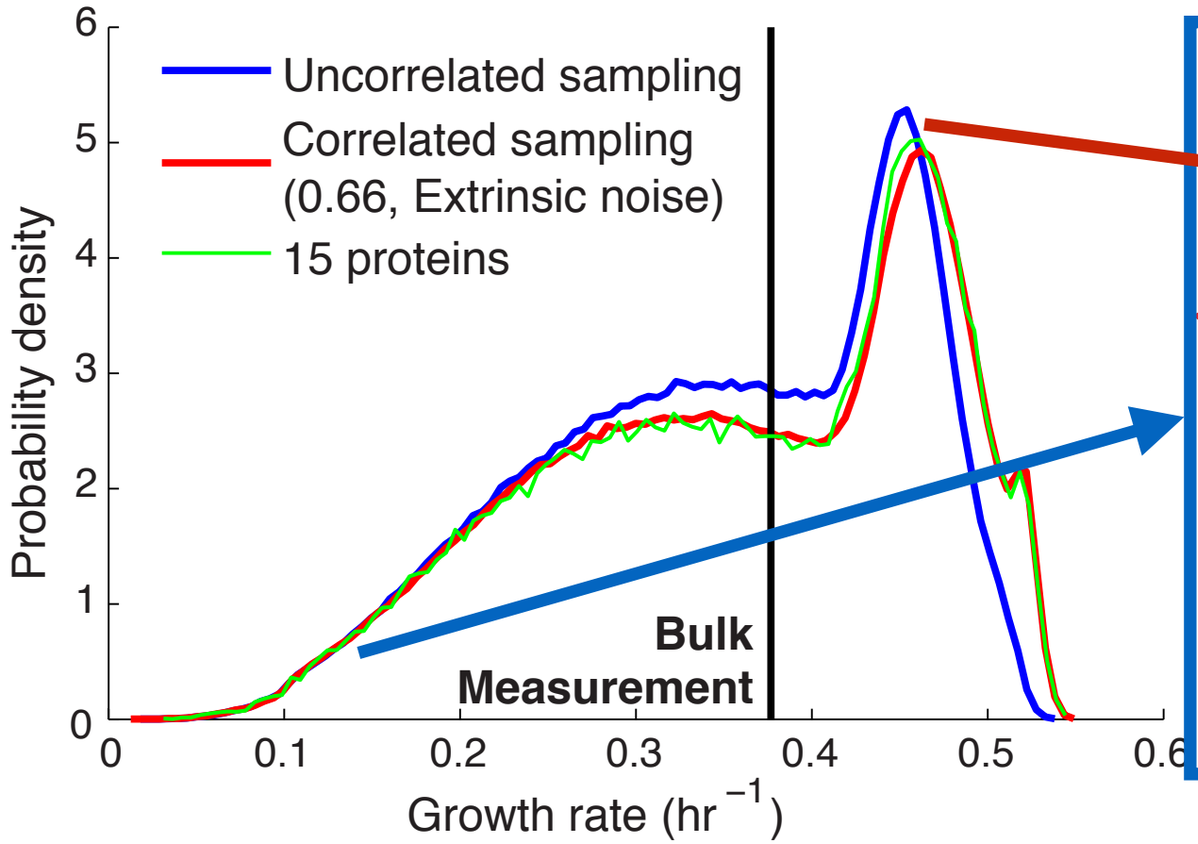
Sample Protein Counts

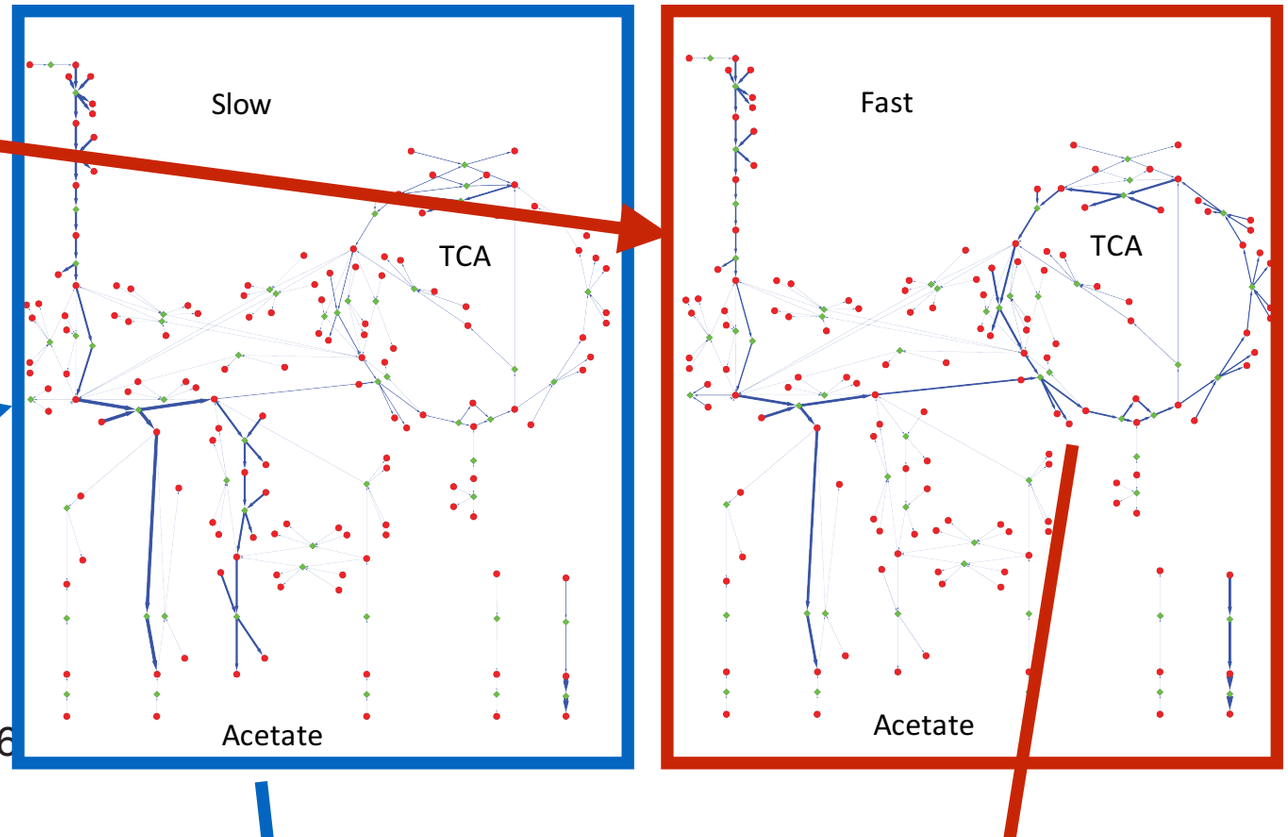
Start with a Metabolic Model for *E. coli* that has ~2000 reactions facilitated by ~1300 genes



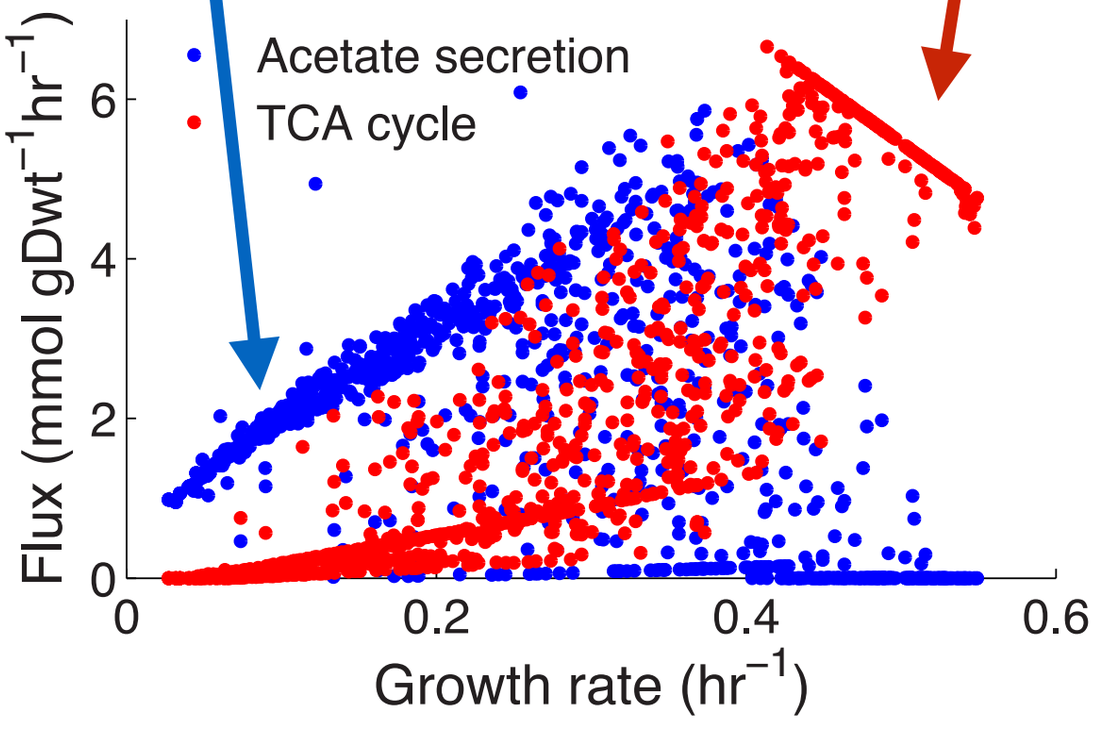
P. Labhsetwar, J.A. Cole, E. Roberts, N.D. Price, Z. Luthey-Schulten. *Proc. Nat. Acad. Sci.*, 110(34):14006-11, 2013

Growth Rates are Broadly Distributed





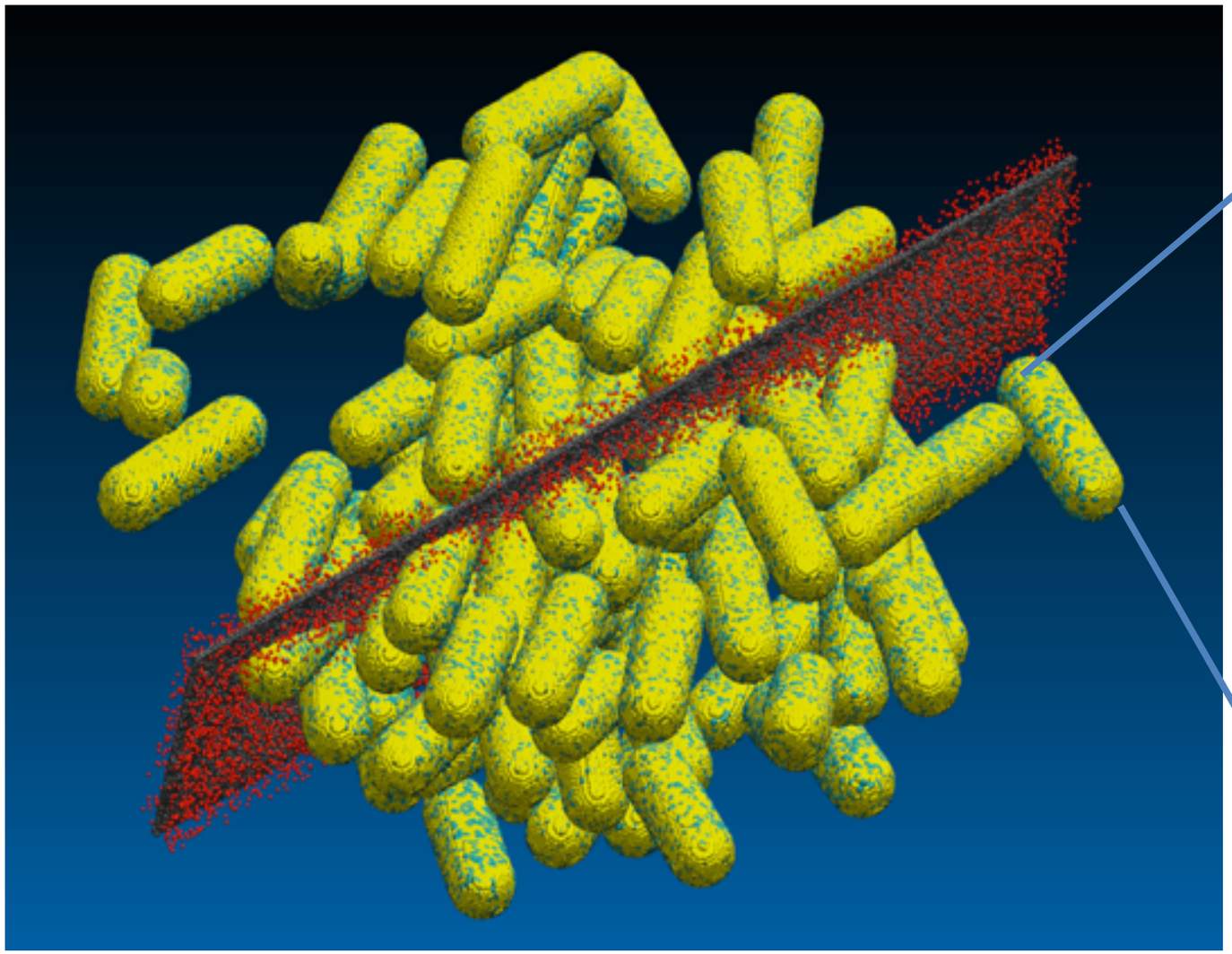
Isogenic cells have different growth phenotypes

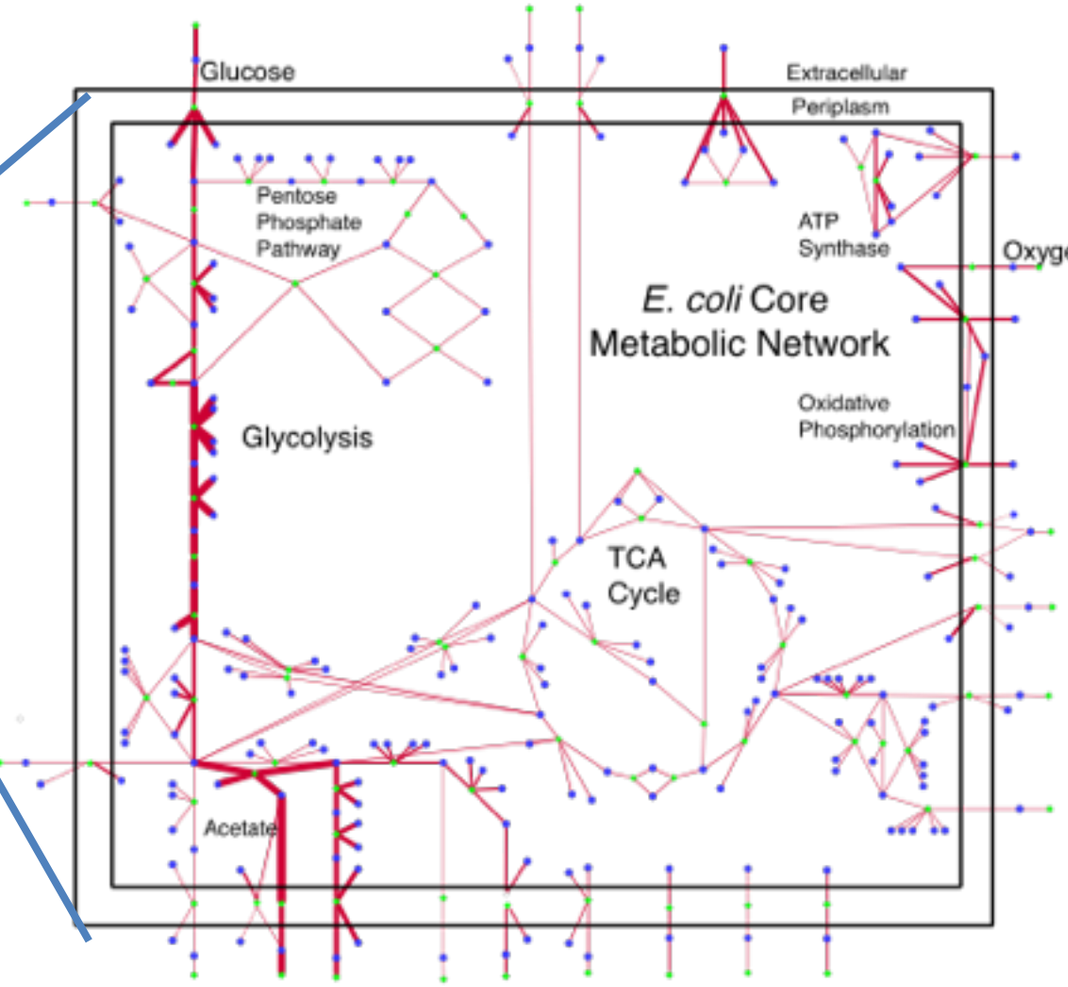


P. Labhsetwar, J.A. Cole, E. Roberts, N.D. Price, Z. Luthey-Schulten. *Proc. Nat. Acad. Sci.*, 110(34):14006-11, 2013

3D dynamic Flux Balance Analysis

Coupling Stochastic Modeling with Metabolic Modeling





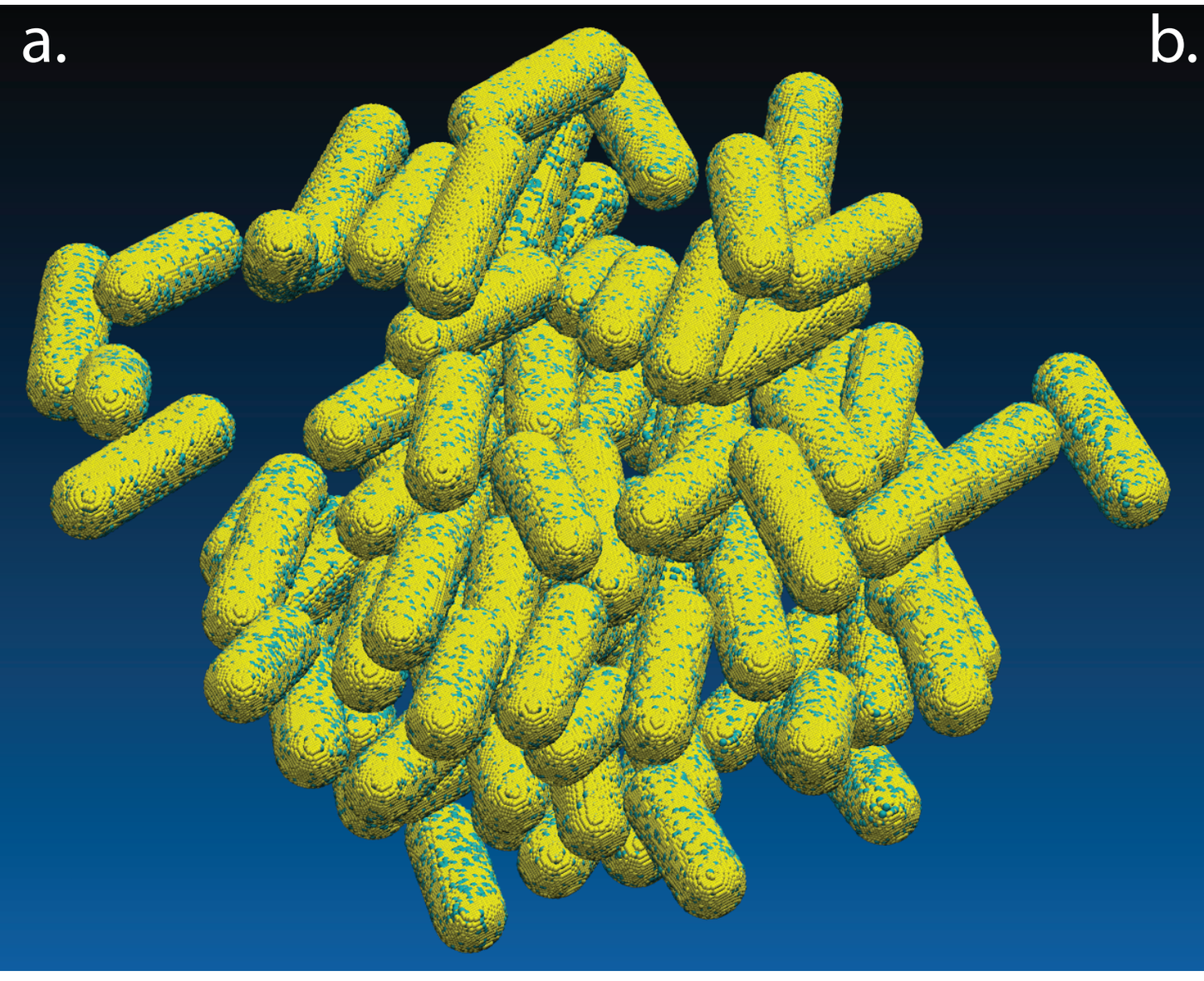
Oxygen

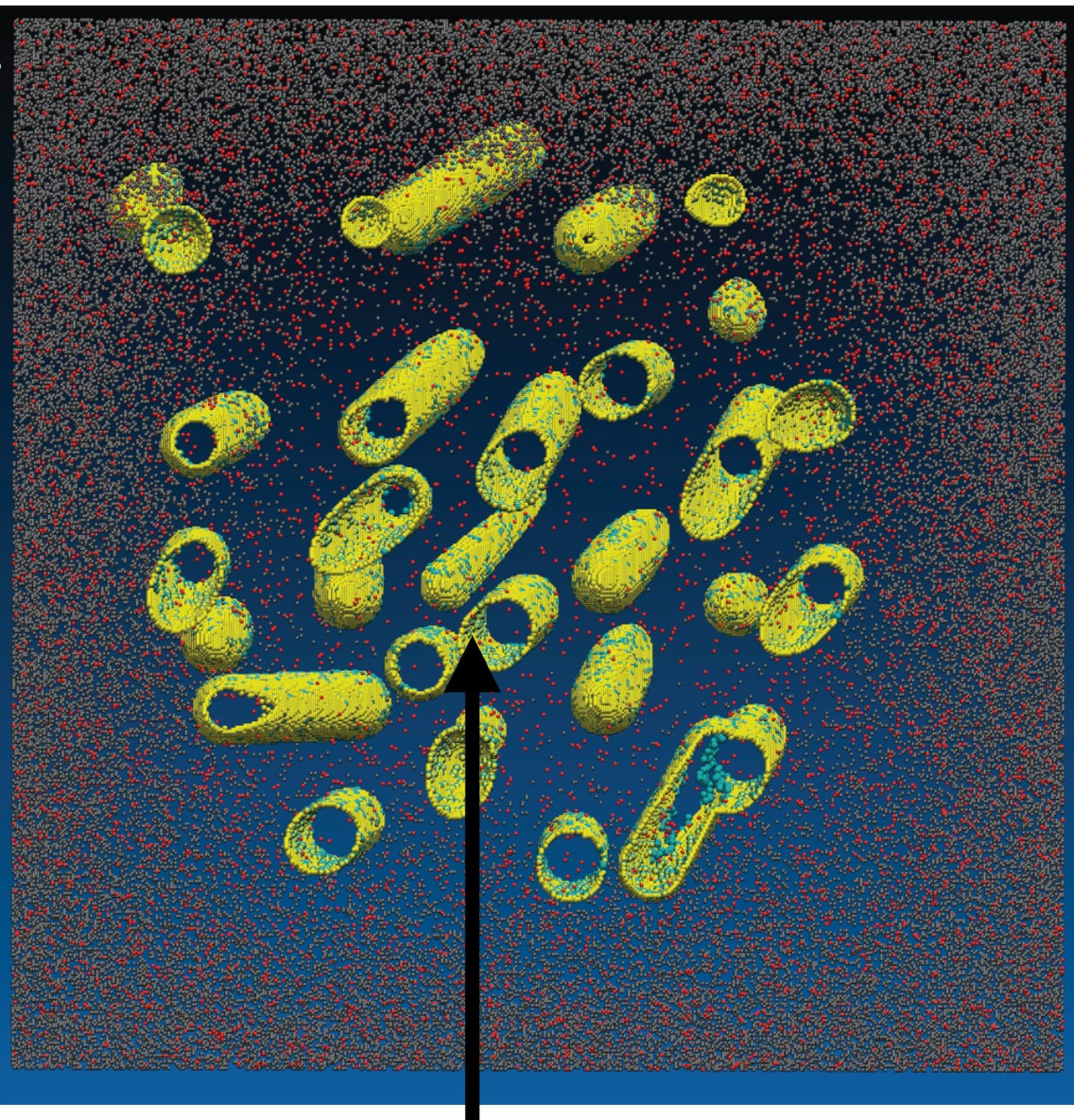
Glucose

Glucose Transporters

J. Cole, Z. Luthey-Schulten. *Isr. J. Chem.*, 2014, 54(8-9): 1219--1229

Heterogeneous Microenvironment in *E. coli*





Oxygen

Glucose

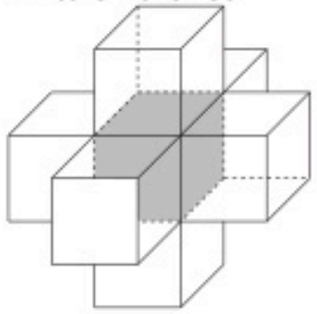
Glucose Transporters

Anoxic region arises inside colony

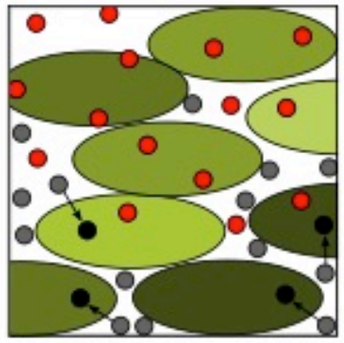
J. Cole, Z. Luthey-Schulten. *Isr. J. Chem.*, 2014, 54(8-9): 1219--1229

3D Hybrid RD - FBA Method for Cell Colonies*

B Diffusion
7-point stencil
finite difference



C Substrate Uptake



● Passive Uptake

$$v_{\max} = \phi(\mathbf{x},t)\frac{V_{\text{cell}}}{m_{\text{cell}}\Delta\tau}$$

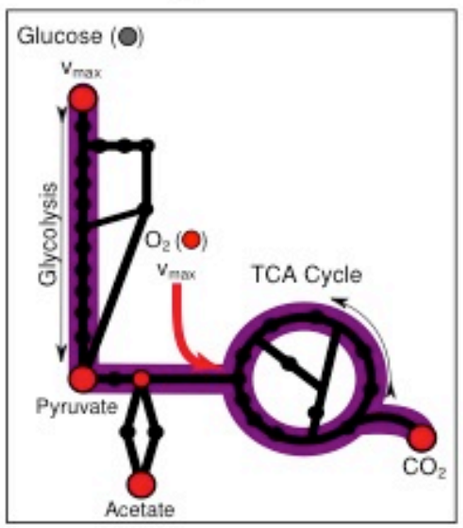
●→● Active Uptake, Crowded Diffusion

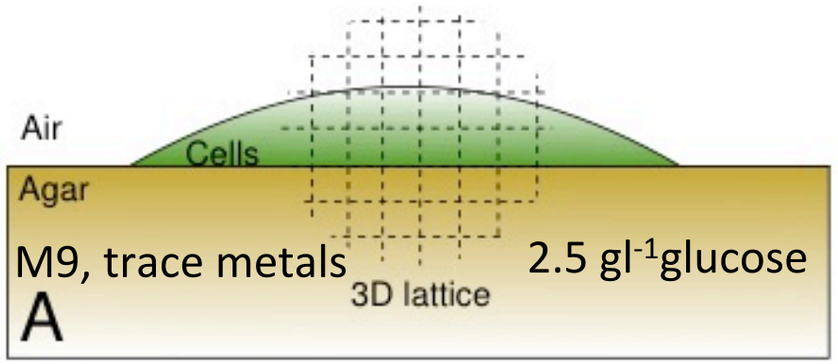
$$v_{\max} = \rho(\mathbf{x},t)\frac{E}{V_{\text{cell}}}\frac{k_{\text{cat}}\phi_{\text{ext}}(\mathbf{x},t)}{k_{\text{m}}+\phi_{\text{ext}}(\mathbf{x},t)}$$

$$D_{\text{eff}}(\mathbf{x},t) = \frac{1-\rho(\mathbf{x},t)}{1+\frac{\rho(\mathbf{x},t)}{2}}D$$

Iterative Steady-State Fluxes

D Flux Balance Analysis & Growth R

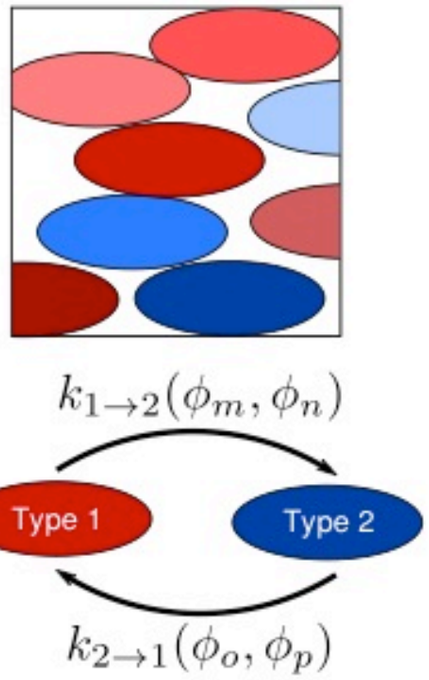


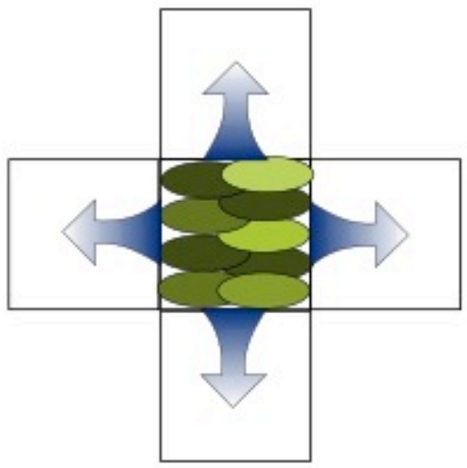


F Regulation

First-order kinetics

Rates depend on local substrate concentrations





E Growth & Expansion

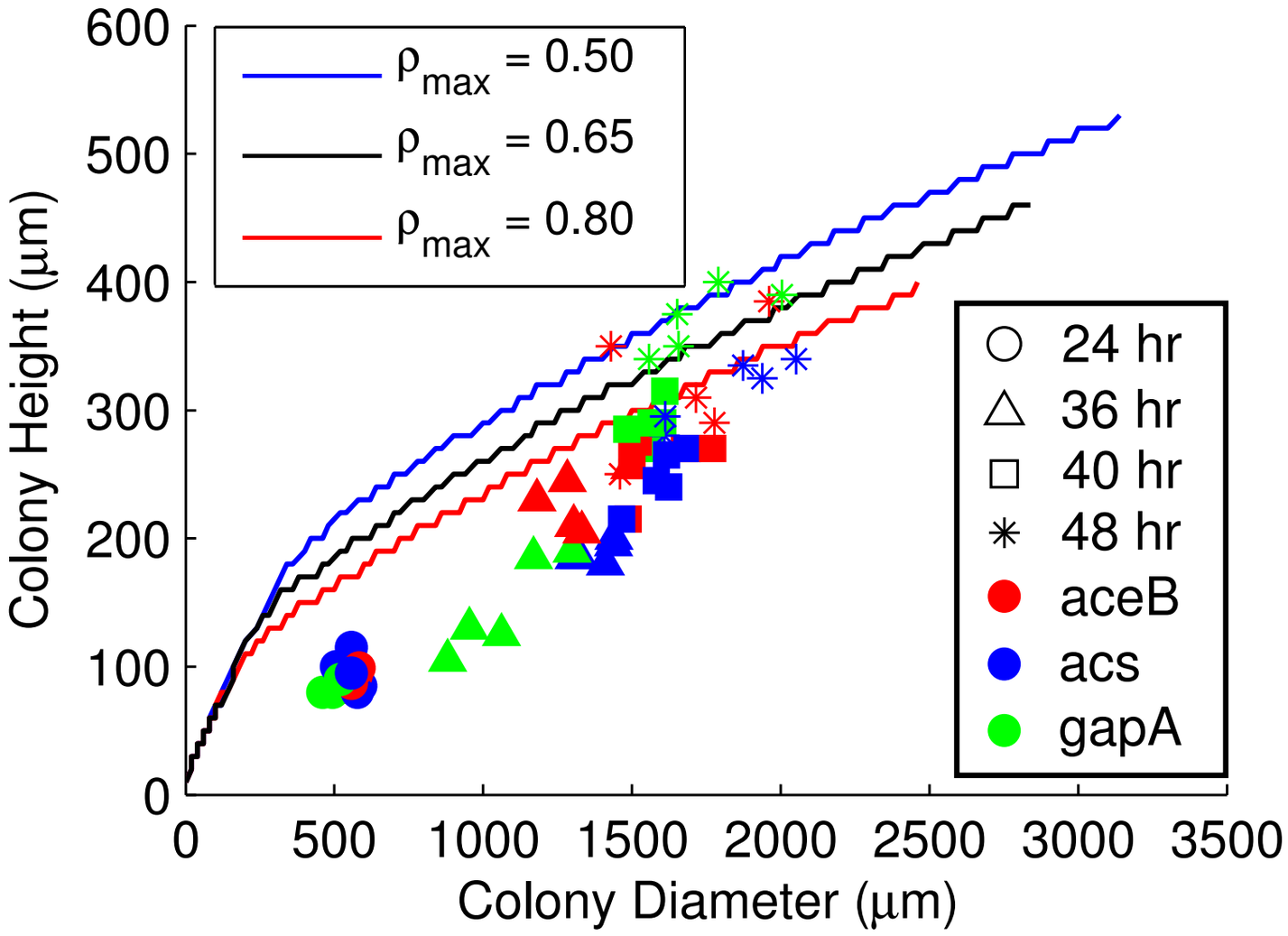
Exponential growth law

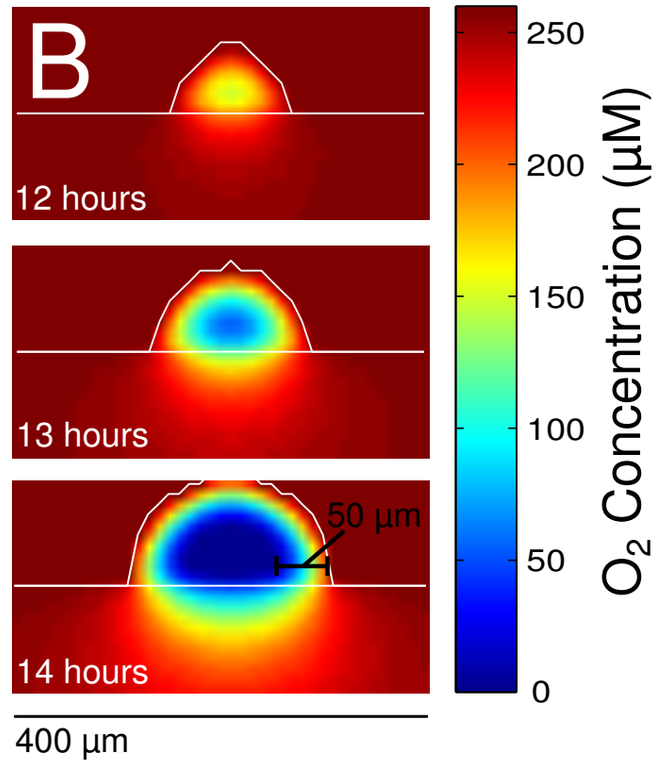
Cell volume moves from "over-filled" sites to neighboring sites with lower cell density

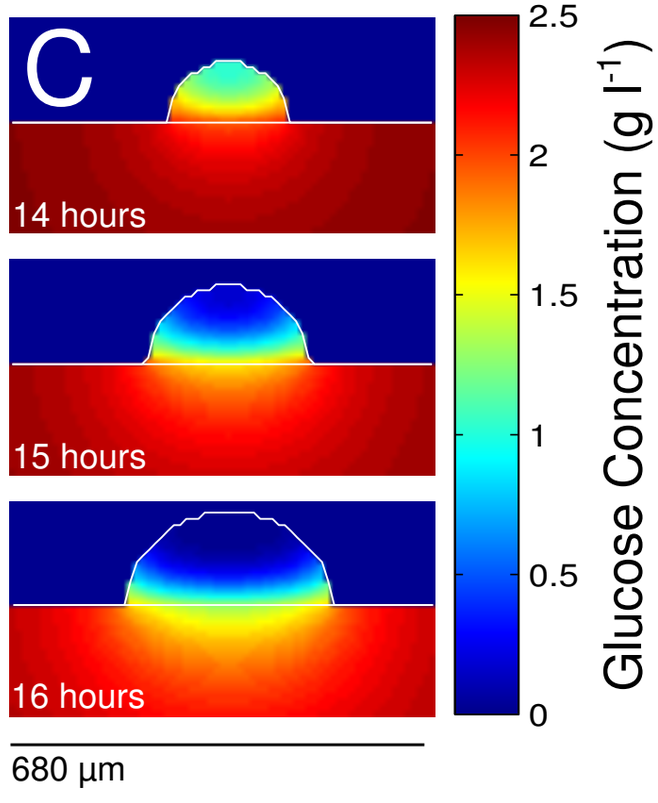
Time steps milliseconds for 30-40 hour growth

*Cole, et al. BMC Syst. Biol. (2015)

Colony Growth – Simulations & Experiments



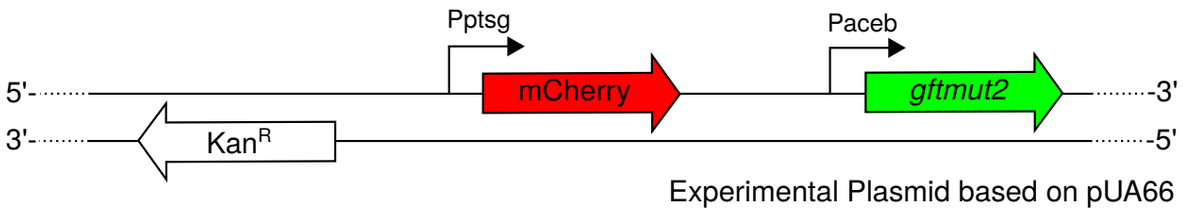




J. A. Cole, L. Kohler L, J. Hedhli, Z. Luthey-Schulten. *BMC Syst Biol*, 2015, 9(15)

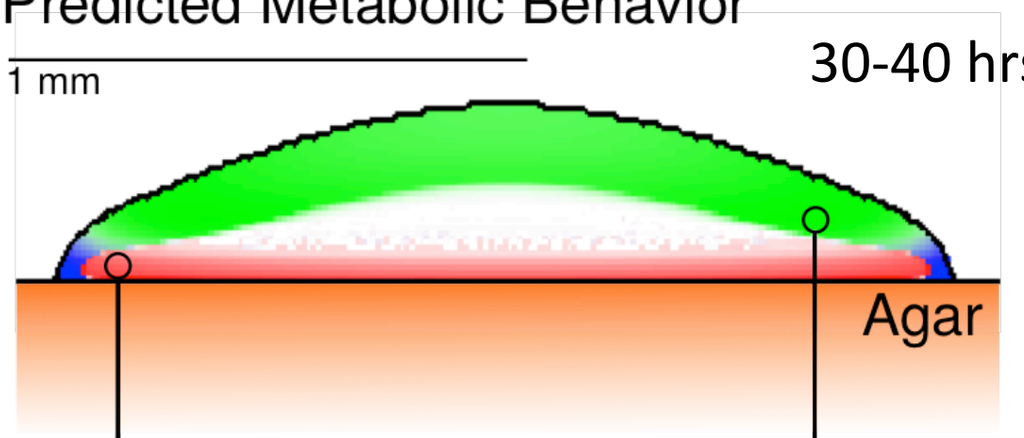
Substrate Gradients Drive Metabolic Differentiation

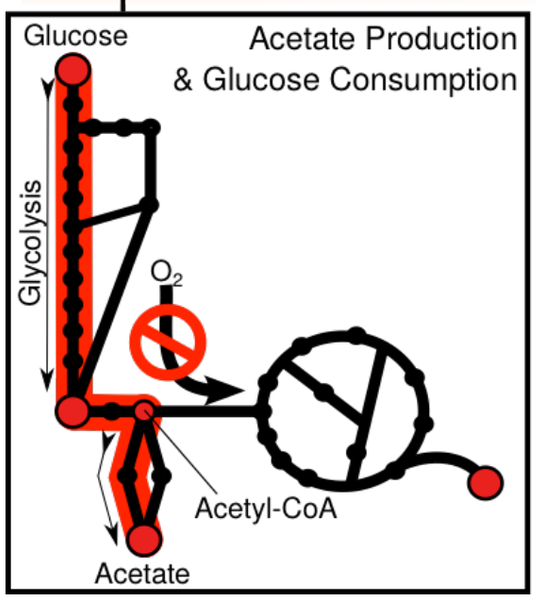
Prediction & Measurement of Acetate Cross Feeding

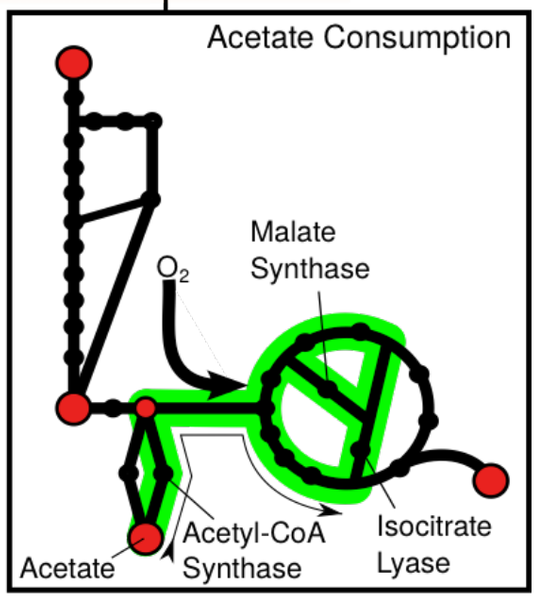


Experimental Plasmid based on pUA66

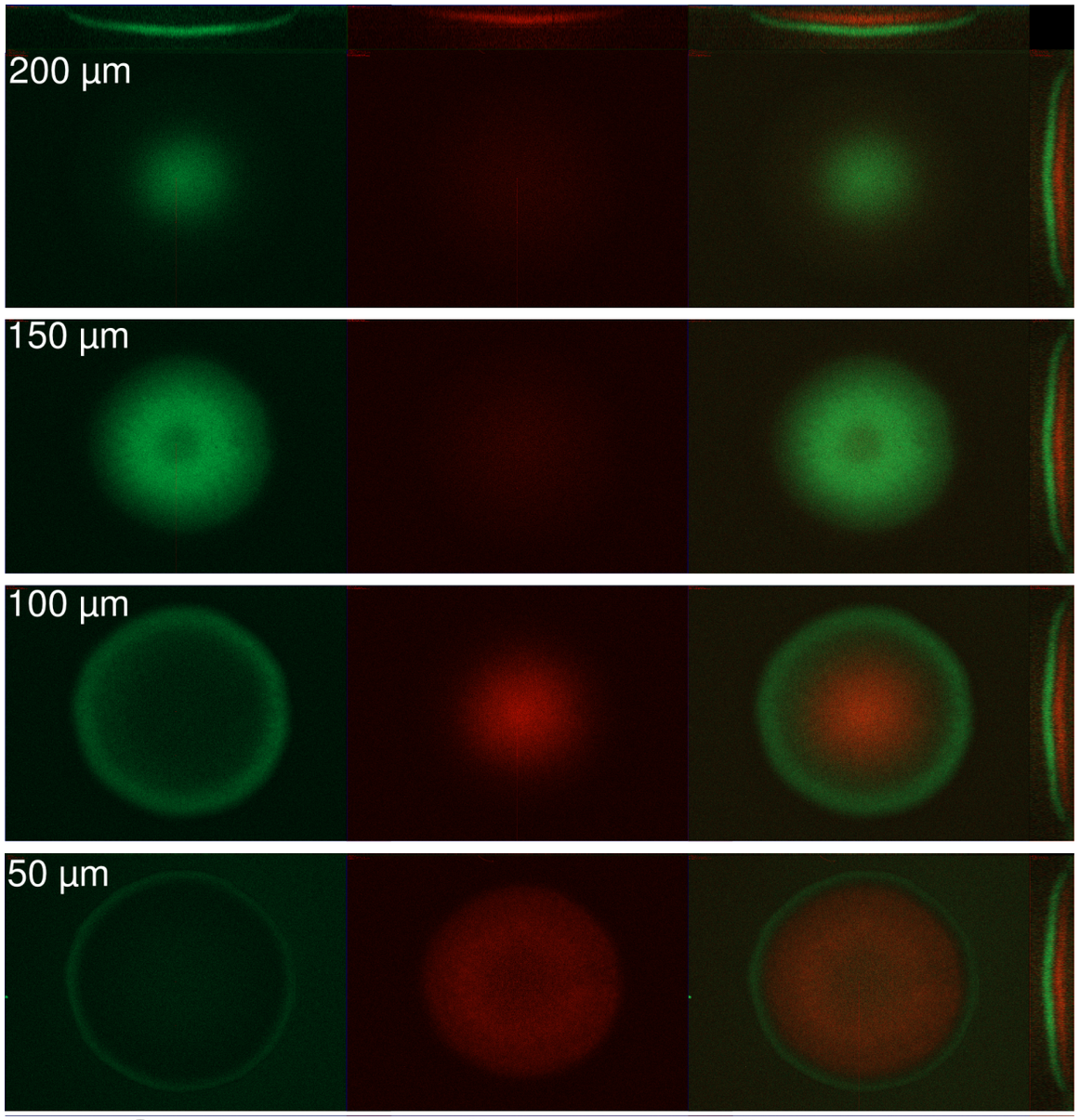
Predicted Metabolic Behavior







Experimental Metabolic Behavior

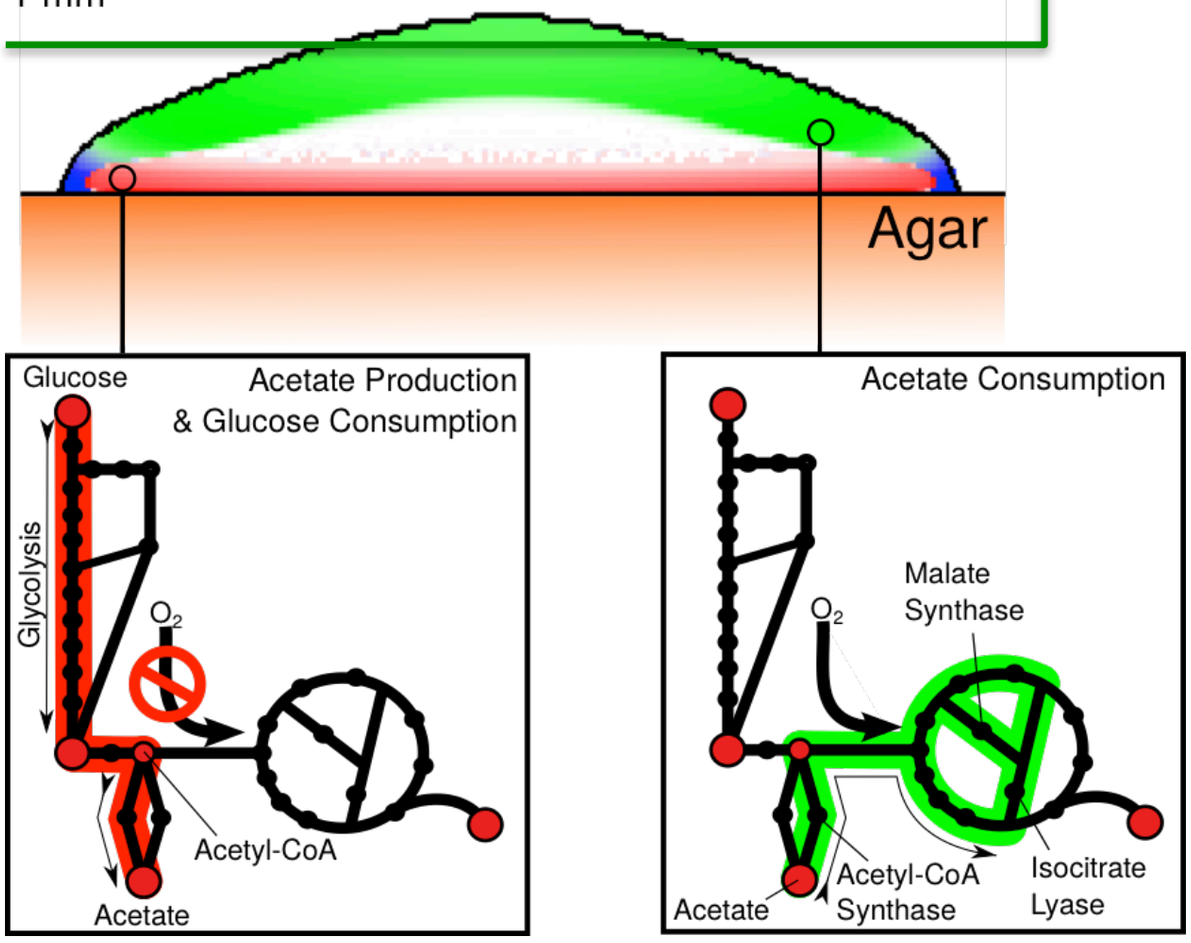


J. A. Cole, L. Kohler L, J. Hedhli, Z. Luthey-Schulten. *BMC Syst Biol*, 2015, 9(15)

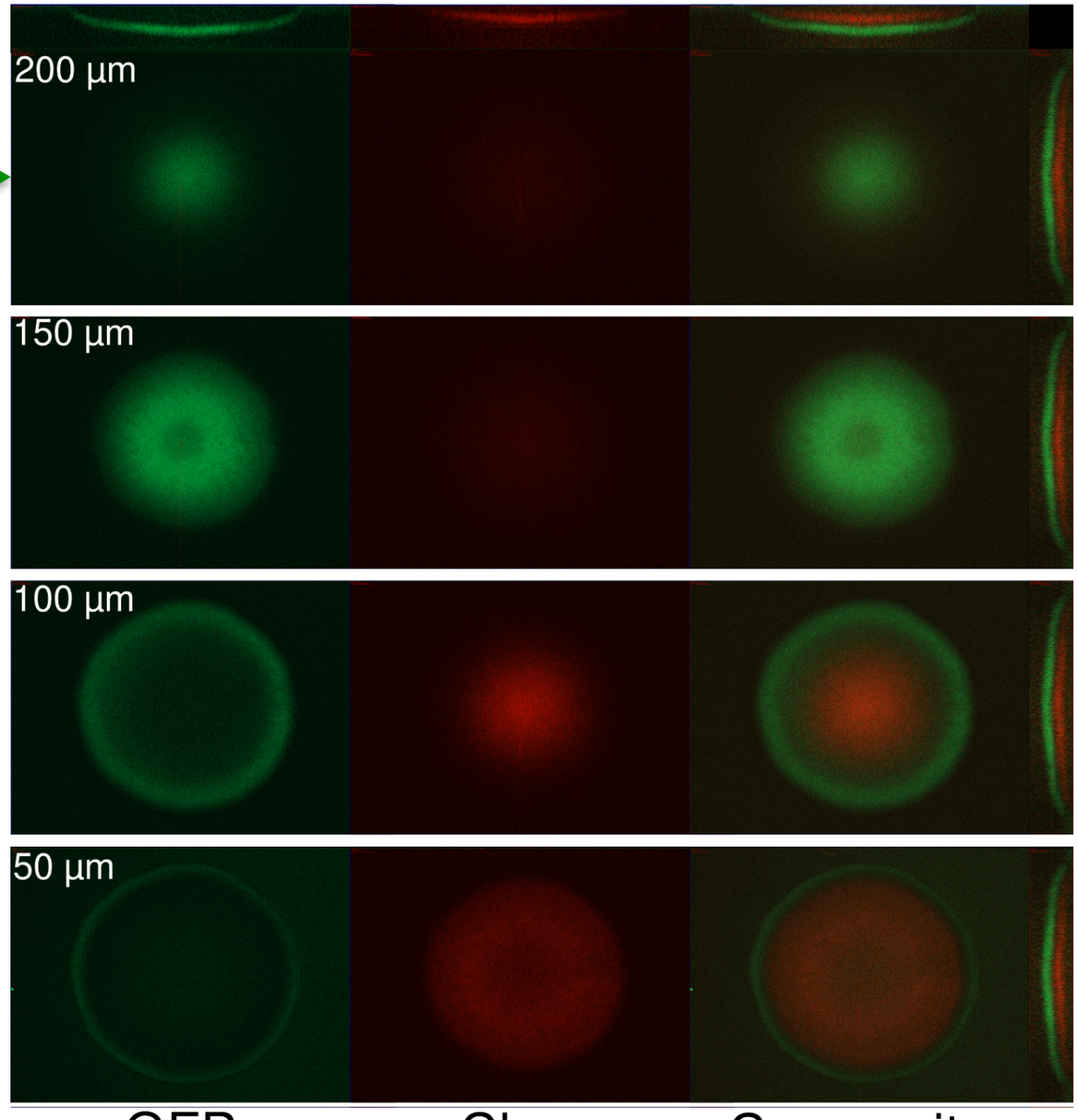
Substrate Gradients Drive Metabolic Differentiation

Optical Sectioning: Near colony top, glucose-starved cells consume acetate.

Predicted Metabolic Behavior



Experimental Metabolic Behavior



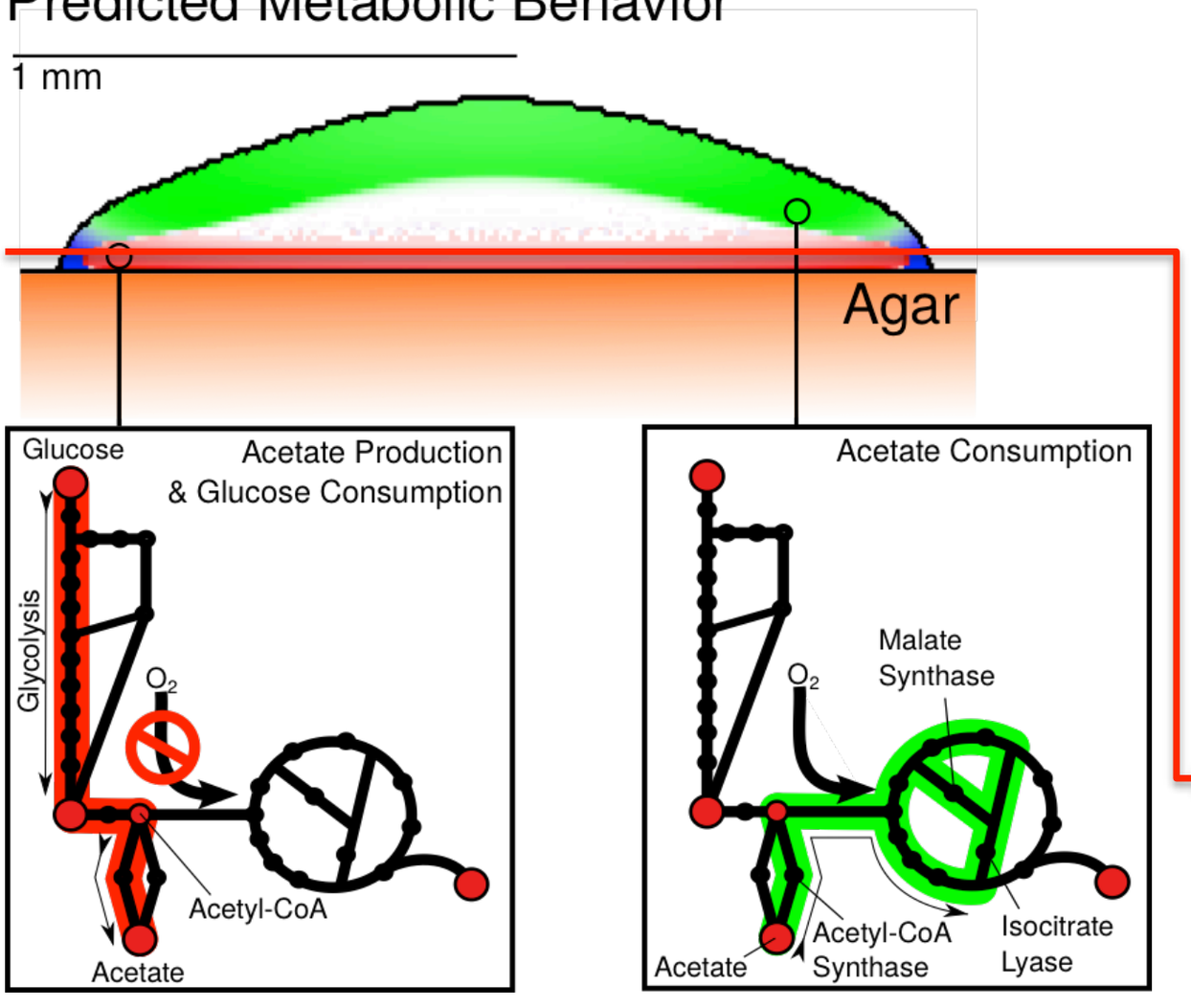
J. A. Cole, L. Kohler L, J. Hedhli, Z. Luthey-Schulten. *BMC Syst Biol*, 2015, 9(15)

Substrate Gradients Drive Metabolic Differentiation

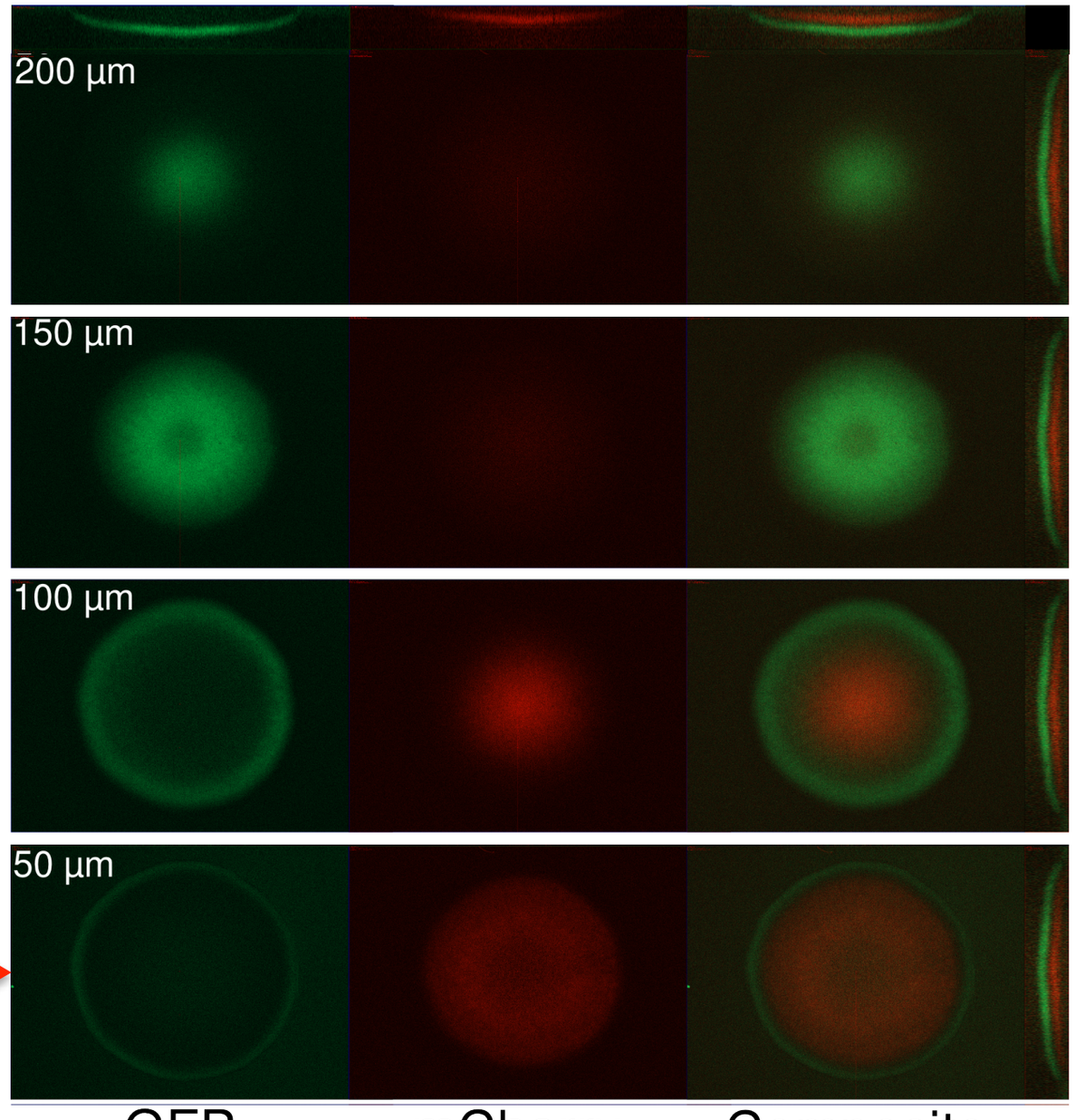
Fluorescence microscope with a structured illumination device- IGB Core Facilities

Near base, oxygen-starved cells consume glucose and produce acetate – See sideview!

Predicted Metabolic Behavior



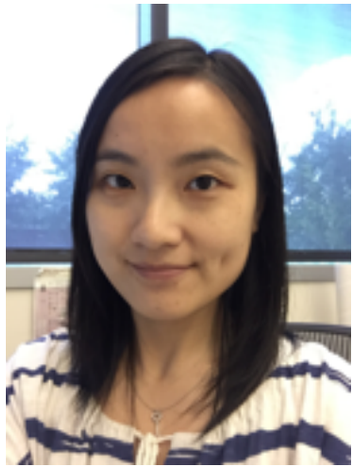
Experimental Metabolic Behavior



J. A. Cole, L. Kohler L, J. Hedhli, Z. Luthey-Schulten. *BMC Syst Biol*, 2015, 9(15)

Acknowledgements

Collaborators

Luthey-Schulten Laboratory










Funding and Computer Time

NSF

Center for the Physics of Living Cells

National Institutes of Health

XSEDE

NCSA