Part III – Towards in silico Cells: Simulating processes in entire cells

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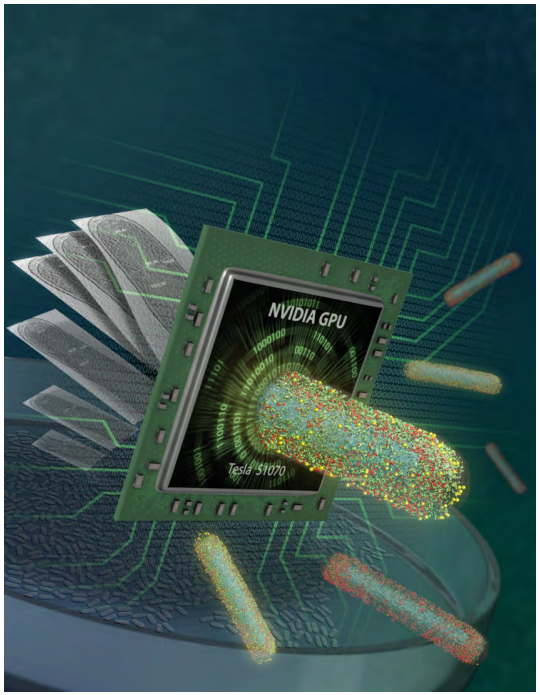
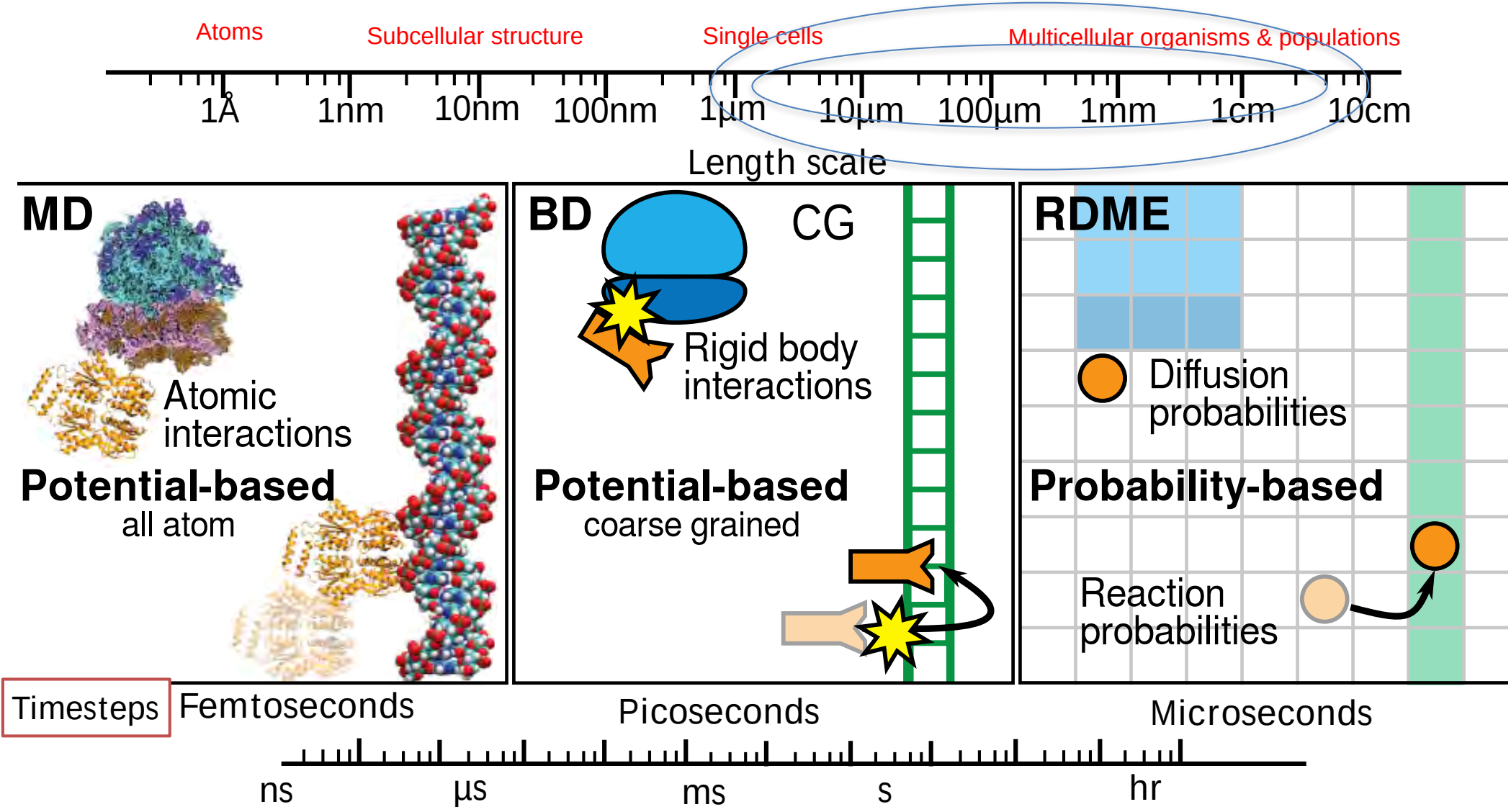
with **Mike Hallock and Joe Peterson**



Biological Modeling at Different Scales

Interactions span many orders of magnitude in space and time



Probability of Cellular State
Stochastic Dynamics

- Chemical Master Equation – Well-stirred reactions (Gillespie SSA)

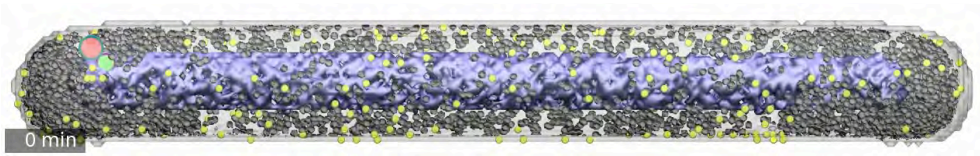
$$\frac{dP(\vec{x},t)}{dt} = \sum_{r}^{R} -a_r(\vec{x})P(\vec{x},t) + a_r(\vec{x}-\vec{s}_r)P(\vec{x}-\vec{s}_r,t)$$

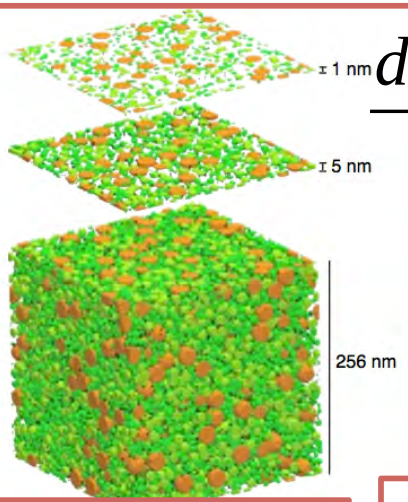
State x (# mRNA,O,I…)

- Reaction-Diffusion Master Equation (RDME)

Noisy cell in sea of IPTG

Exp. Baumeister, Ortiz, Xie, Elf, Moerner, Ha, Woodson, Williamson, Kuhlman





$$\frac{dP(\vec{x},t)}{dt} = \sum_{v\in V}\sum_{r=1}^{R} -a_r(\vec{x}_v)P(\vec{x},t) + a_r(\vec{x}_v-\vec{s}_r)P(\vec{x}-\vec{s}_r 1_v,t)$$

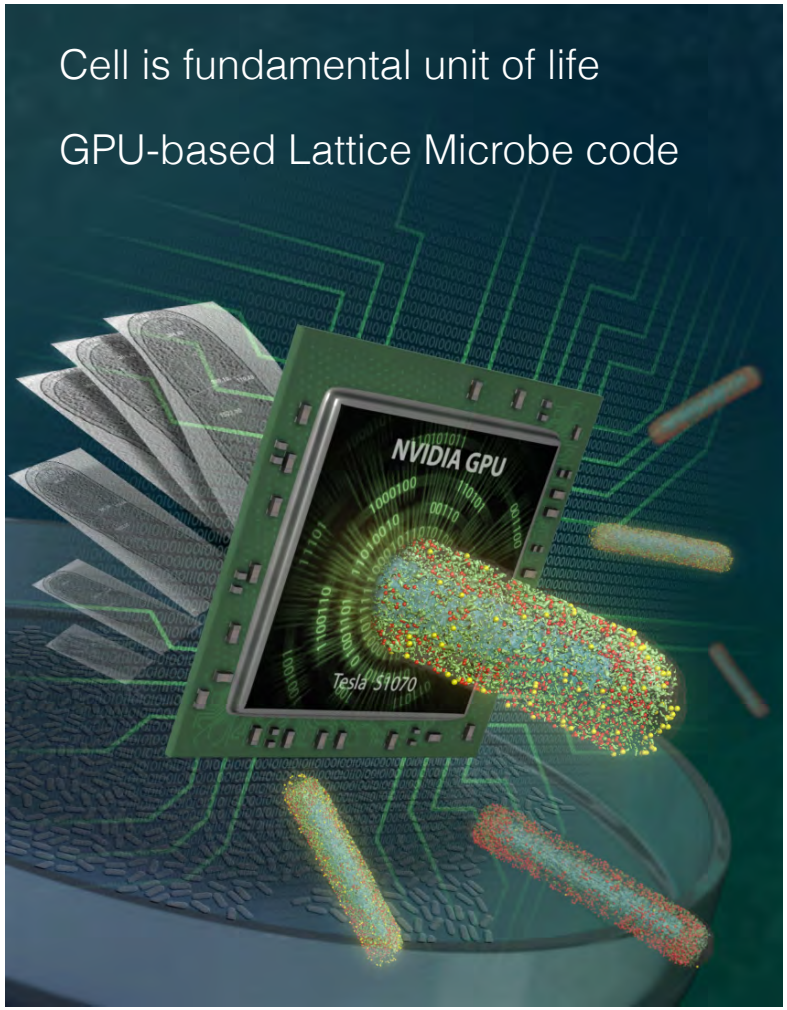
$$+ \sum_{i\in V}\sum_{j\in V}\sum_{\alpha=1}^{N} -d_{ij}^{\alpha}x_i^{\alpha}P(\vec{x},t) + d_{ji}^{\alpha}(x_j^{\alpha}+1_j^{\alpha})P(\vec{x}+1_j^{\alpha}-1_i^{\alpha},t)$$

Exp. proteomics

Heterogeneous cellular environment – 50% volume packed with macromolecules

Stochastic Cell Simulations

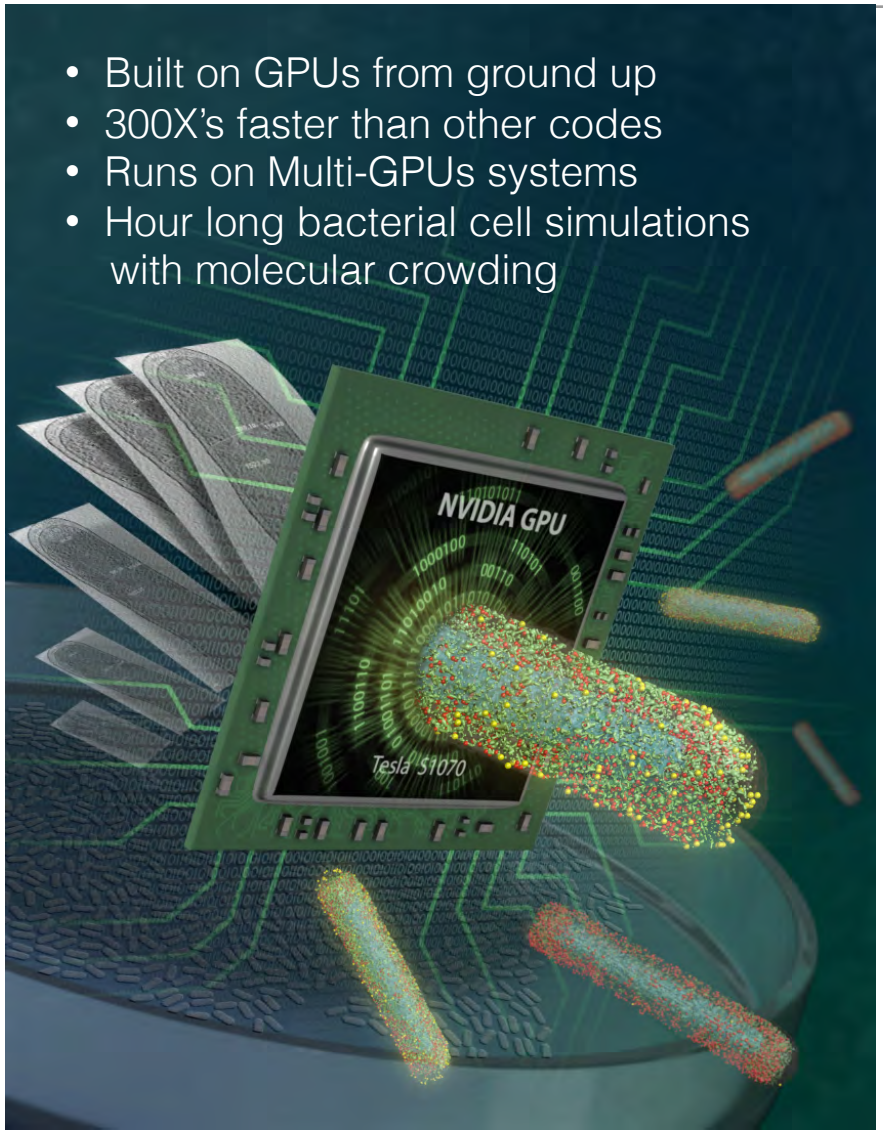
Promotes Integration of Theory and Experiments



- Packing & Diffusion Data < > SRI, CET, -omics
- Reactions & Parameters < > Biochem, SM, MD
- RDME Cell Model Simulations < > **Lattice Microbe** Multi-GPU Code over cell cycles
- Population (Constrained) FBA: Steady-state fluxes in cellular networks and growth rate distributions > *E. coli*, yeast, *M. mycoides*, stem cells, *M. acetivorans*
- Hybrid Reaction/Diffusion/FBA Models < > Cell Colonies

Software Released through http://www.scs.illinois.edu/schulten/lm/ and NIH Center for Macromolecular Modeling and Bioinformatics at Beckman Institute

2014-2016 Achievements with LM



Systems Biology Population FBA – 2013/2016

- P. Labhsetwar, J. Cole, Z. Luthey-Schulten, *PNAS 2013* (Ecoli)
- P. Labhsetwar, et al. (*2016* submitted) (Yeast/C13 Fluxes)

Time scale separations – 2014

- Cole, Luthey-Schulten, Whole Cell Modeling: From Single Cells to Colonies *Isr. J. Chem., 2014, (Nobel Prize Symposium Now&Then)*
- Cole, Hallock, Labhsetwar, Peterson, Stone, ZLS in *Computational Systems Biology: From Molecular Mechanisms to Disease,* Eds. Kriete and Eils, Elsevier, *2014*

Multi-GPU code for yeast & human cells- 2014/16

- Hallock, Stone, Roberts, Fry, ZLS, *Parallel Computing, 2014*
- Hallock & ZLS, Parallel & Distr. Comp. (*IEEE Workshop*), *2016*

Metabolic Reprogramming <-> Colony – 2015 …

- J. Cole et al., Spatially resolved metabolic co-operativitiy within dense bacterial colonies. *BMC Sys Bio. 2015*

Ribosome Biogenesis<-> Cell Division – 2014-16 …

- Kim, … ZLS, T. Ha, S. Woodson, *Nature, 2014* (MD/Exp)
- T. Earnest, .. J. Williamson, ZLS, *BPJ 2015* (LM/Exp)
- Earnest, … Kuhlman, ZLS (*2016 in revision*) (LM/Theory/Exp)

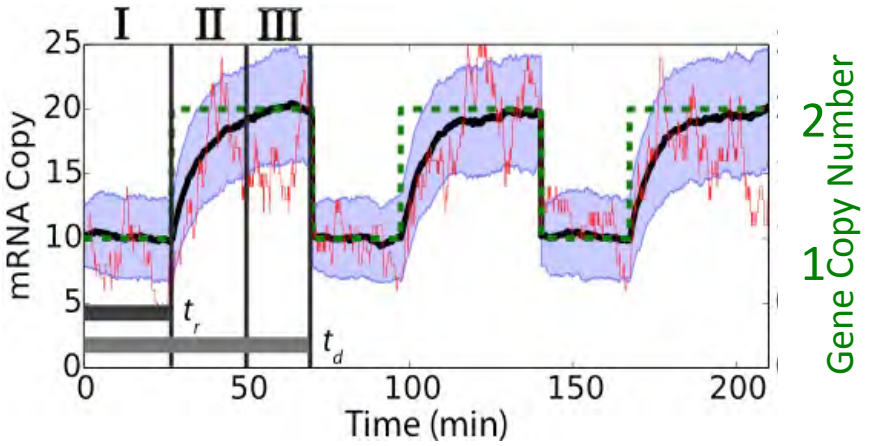
DNA Replication <-> mRNA and sRNA – 2015 …

- J. Peterson, J. Fei, Tj Ha, ZLS *PNAS 2015* (LM/Theory/Exp)

2015 Major Achievements

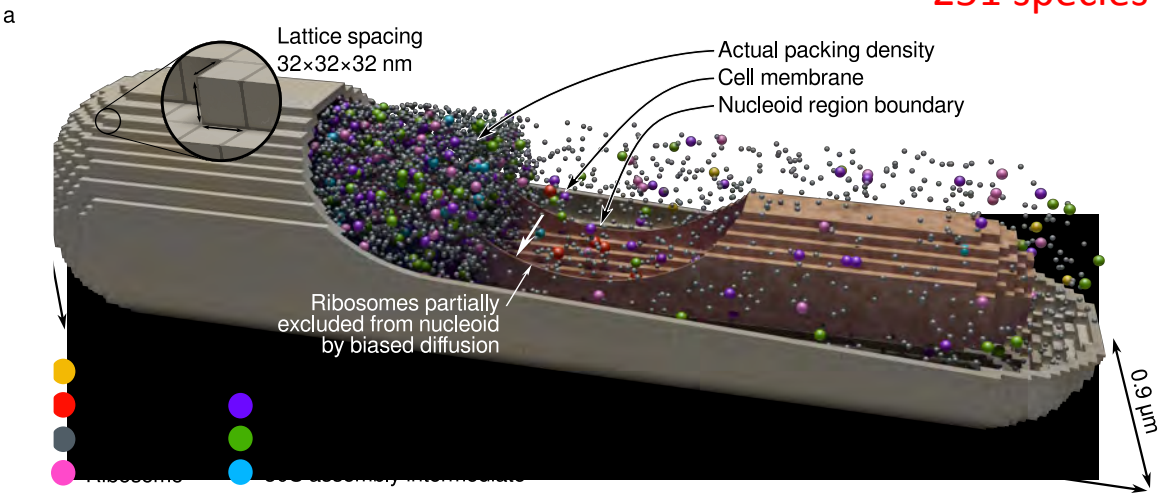
Combining experiments, theory, & simulations

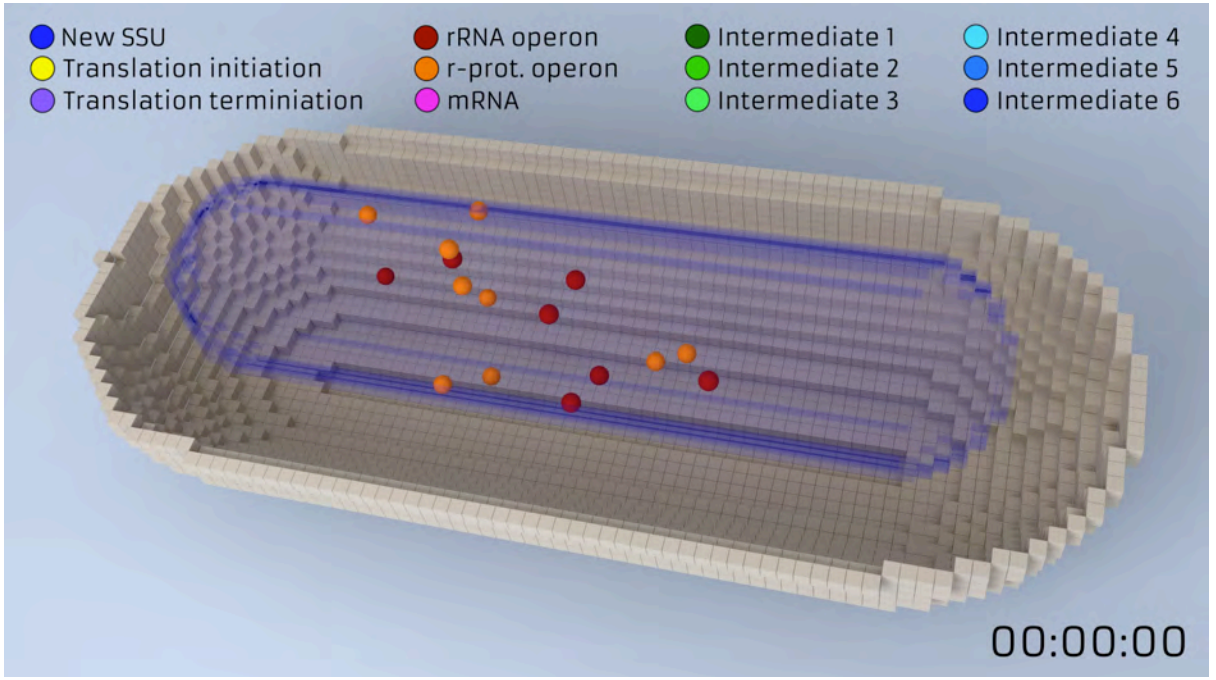
Effects of DNA Replication on mRNA Noise - CME



Ribosome Biogenesis - RDME

1300 rxns
251 species





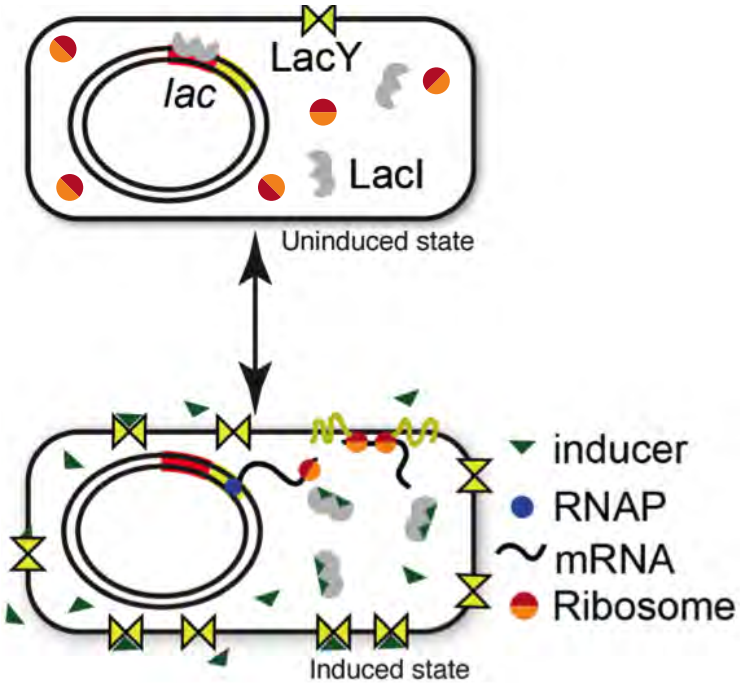
Kinetic Model of *lac* Genetic Switch

Reaction	Param	Stochastic Rate	Units	Source[a]
Lac operon regulation				
$R_2 + O \rightarrow R_2O$	k_{ron}	2.43e+06	$M^{-1}s^{-1}$	M
$IR_2 + O \rightarrow IR_2O$	k_{iron}	1.21e+06	$M^{-1}s^{-1}$	M
$I_2R_2 + O \rightarrow I_2R_2O$	k_{i2ron}	2.43e+04	$M^{-1}s^{-1}$	M
$R_2O \rightarrow R_2 + O$	k_{roff}	6.30e-04	s^{-1}	S
$IR_2O \rightarrow IR_2 + O$	k_{iroff}	6.30e-04	s^{-1}	S
$I_2R_2O \rightarrow I_2R_2 + O$	k_{i2roff}	3.15e-01	s^{-1}	M
Transcription, translation, and degredation				
$O \rightarrow O + mY$	k_{tr}	1.26e-01	s^{-1}	M
$mY \rightarrow mY + Y$	k_{tn}	4.44e-02	s^{-1}	S
$mY \rightarrow \varnothing$	k_{degm}	1.11e-02	s^{-1}	S
$Y \rightarrow \varnothing$	k_{degp}	2.10e-04	s^{-1}	M
Lac inducer–repressor interactions		TMG IPTG		TMG IPTG
$I + R_2 \rightarrow IR_2$	k_{ion}	2.27e+04 9.71e+04	$M^{-1}s^{-1}$	M K
$I + IR_2 \rightarrow I_2R_2$	k_{i2on}	1.14e+04 4.85e+04	$M^{-1}s^{-1}$	M K
$I + R_2O \rightarrow IR_2O$	k_{iopon}	6.67e+02 2.24e+04	$M^{-1}s^{-1}$	M K
$I + IR_2O \rightarrow I_2R_2O$	k_{i2opon}	3.33e+02 1.12e+04	$M^{-1}s^{-1}$	M K
$IR_2 \rightarrow I + R_2$	k_{ioff}	2.00e-01	s^{-1}	K
$I_2R_2 \rightarrow I + IR_2$	k_{i2off}	4.00e-01	s^{-1}	K
$IR_2O \rightarrow I + R_2O$	k_{iopoff}	1.00e+00	s^{-1}	K
$I_2R_2O \rightarrow I + IR_2O$	$k_{i2opoff}$	2.00e+00	s^{-1}	K
Inducer transport				
$I_{ex} \rightarrow I$	k_{id}	2.33e-03	s^{-1}	K
$I \rightarrow I_{ex}$	k_{id}	2.33e-03	s^{-1}	K
$Y + I_{ex} \rightarrow YI$	k_{yion}	3.03e+04	$M^{-1}s^{-1}$	K
$YI \rightarrow Y + I_{ex}$	k_{yioff}	1.20e-01	s^{-1}	K
$YI \rightarrow Y + I$	k_{it}	1.20e+01	s^{-1}	K

K – in vitro kinetic experiment

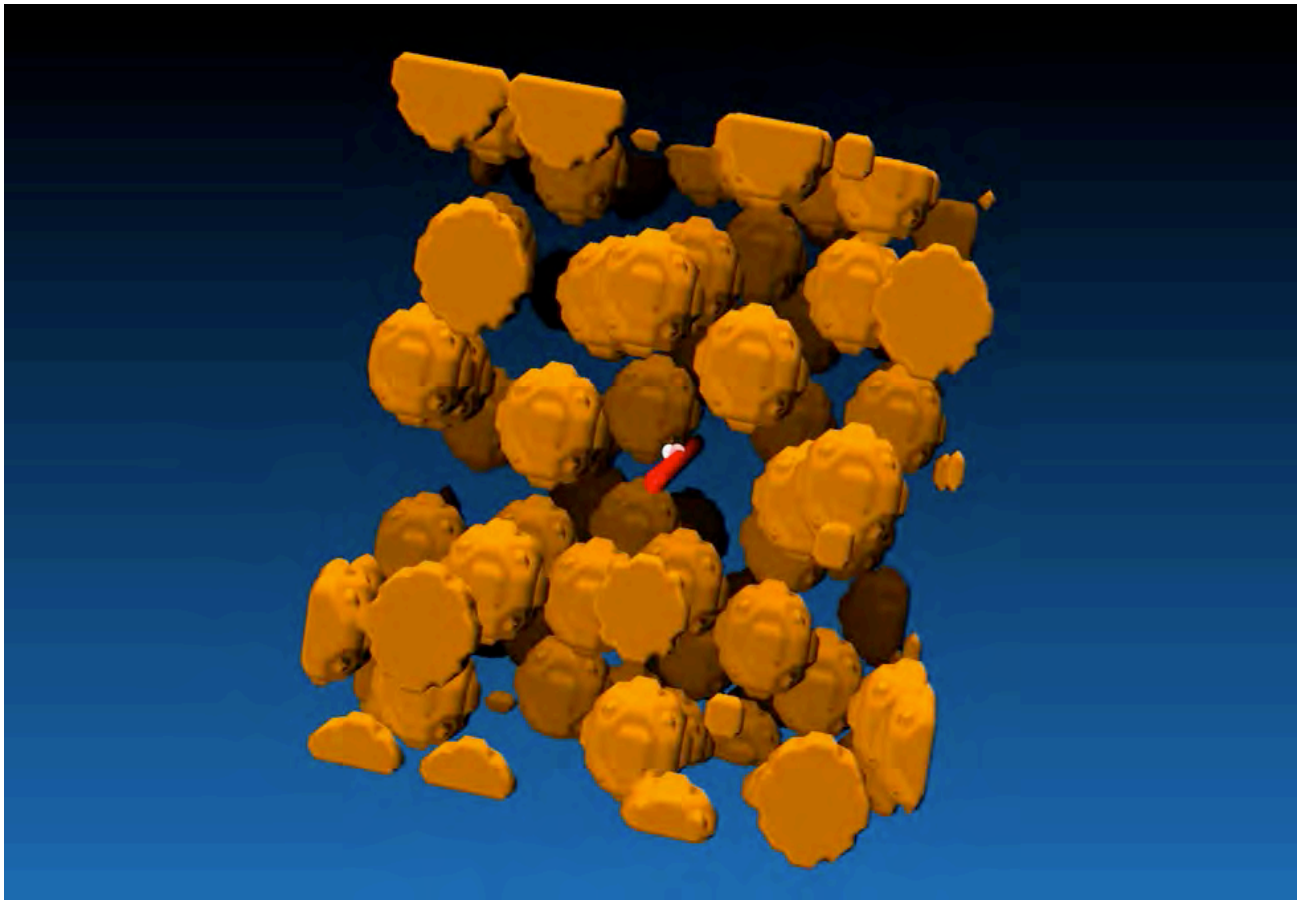
S – single molecule experiment

M – model parameter fit to single-molecule distributions

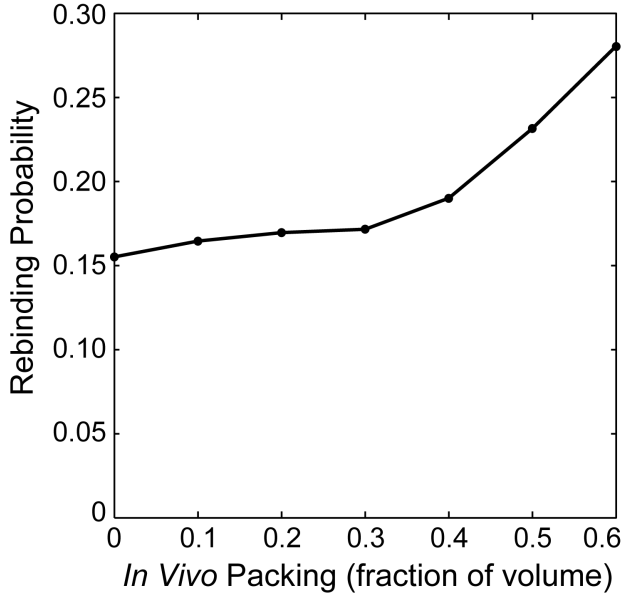


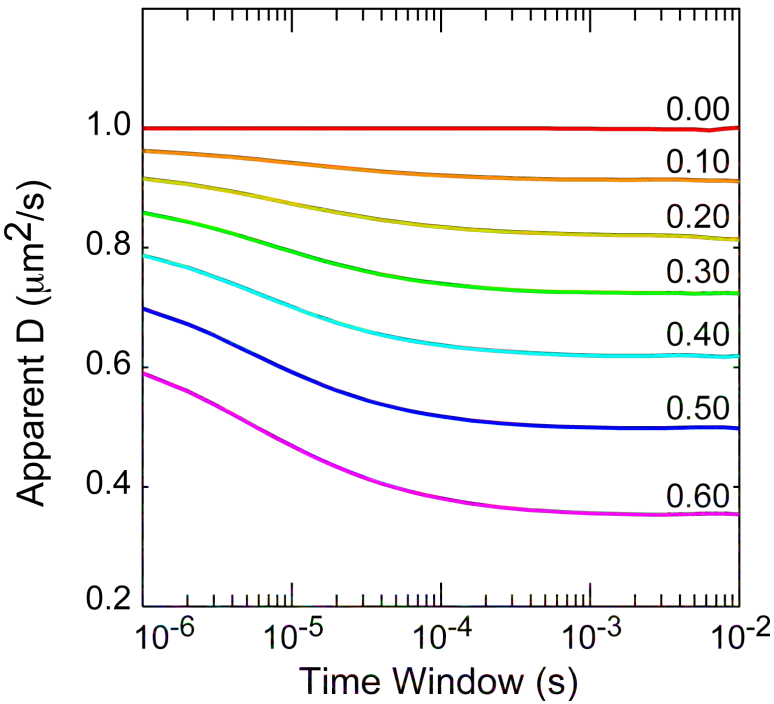
Roberts, …ZLS, PloS CompBio 2011

Effect of *in vivo* crowding on repressor re-binding



E. Roberts, J. Stone,L. Sepulveda, W.M. Hwu, ZLS, **IEEE**, 2009

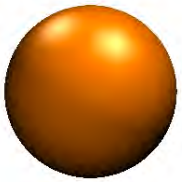




A Window into the Cell with VMD

John Stone

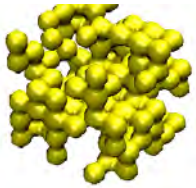
John Cole



Ribosome

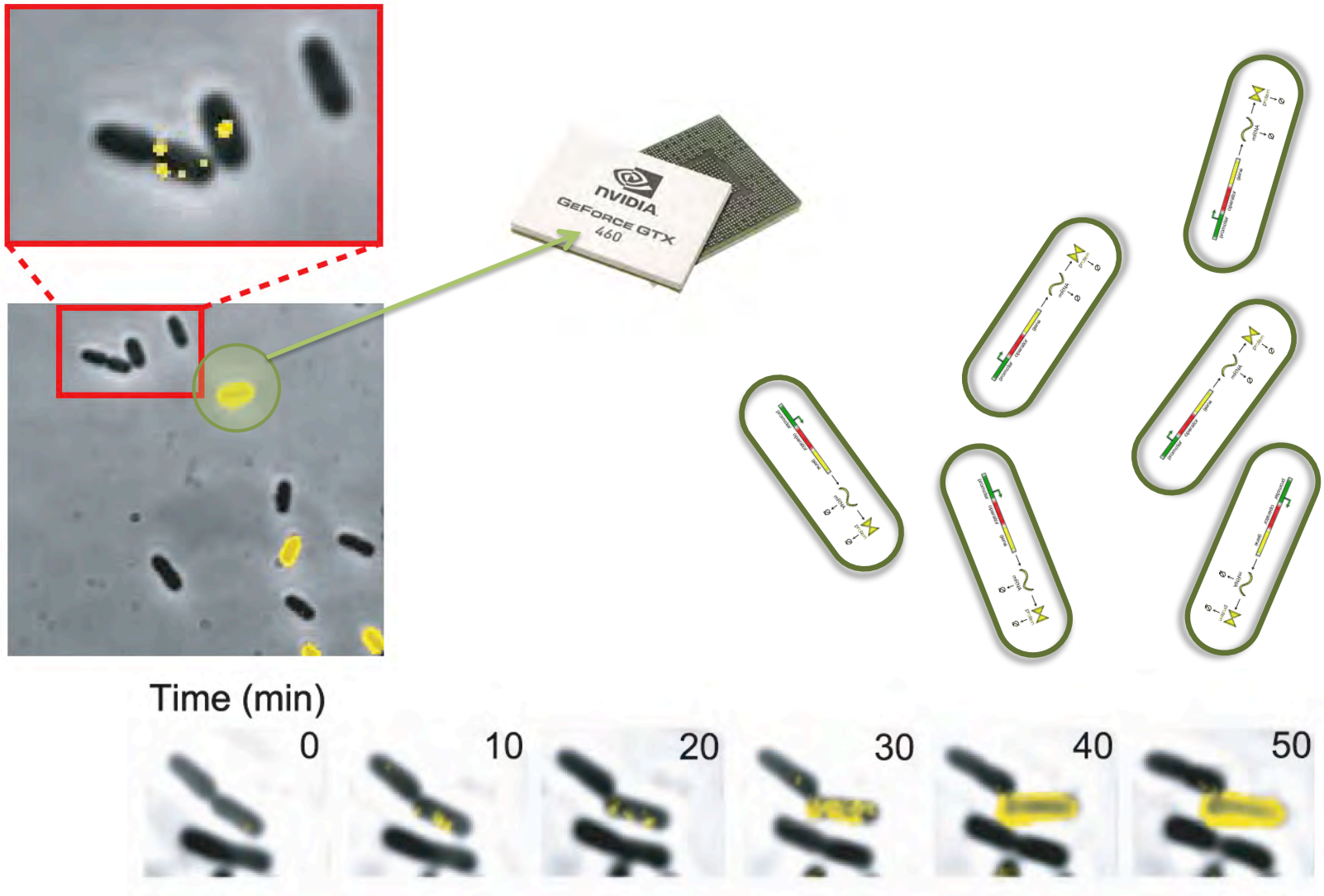
Polymerases/
Large Complexes

Small Complexes/
Proteins



Lattice sites

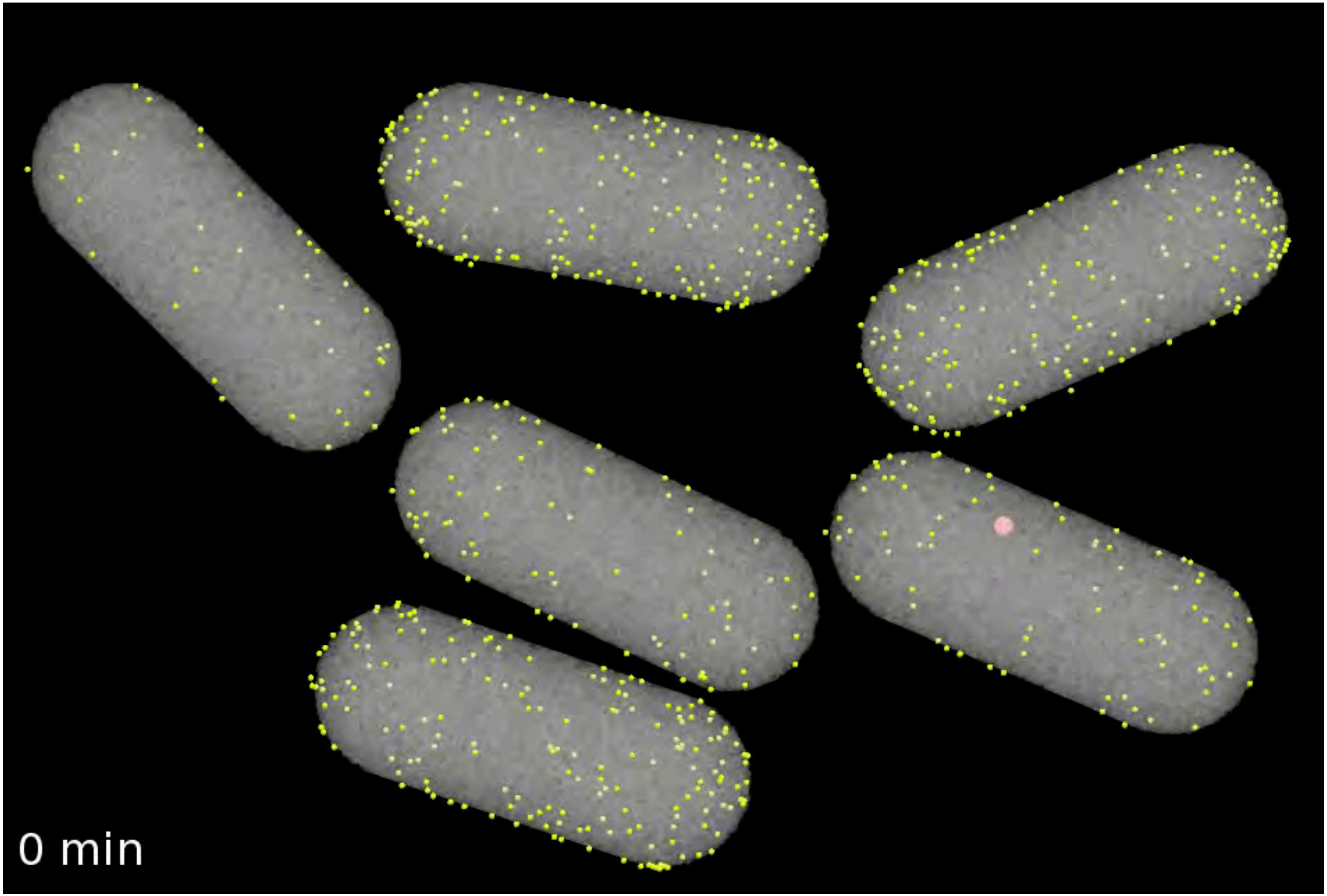
Motivation: Capture Timescale and Fraction of Cells Undergoing Phenotypic Switching



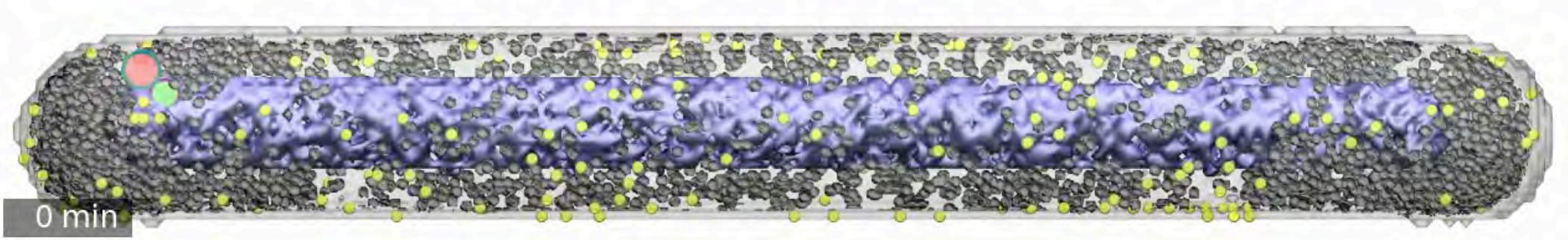
Experimental data from Choi, Cai, Frieda, Xie (2008) *Science*

Simulations from Roberts, Magis, Ortiz, Baumeister, ZLS *PloS Comp. Biol. 2011*

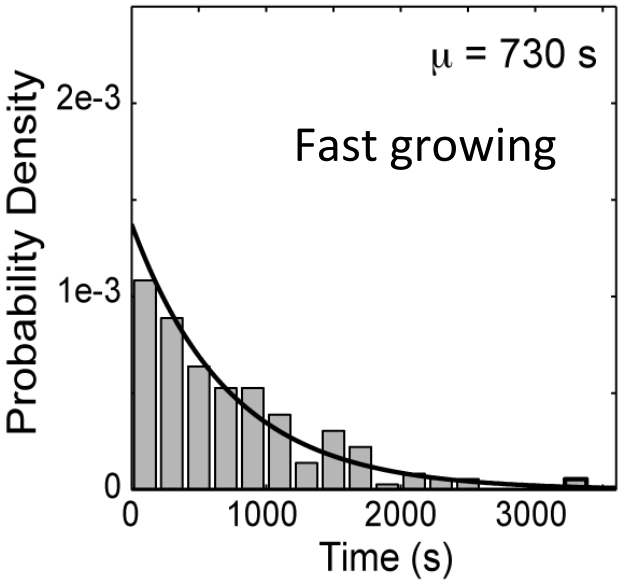
Switching in Fast Growing E. coli Cells – Bursting of mRNA

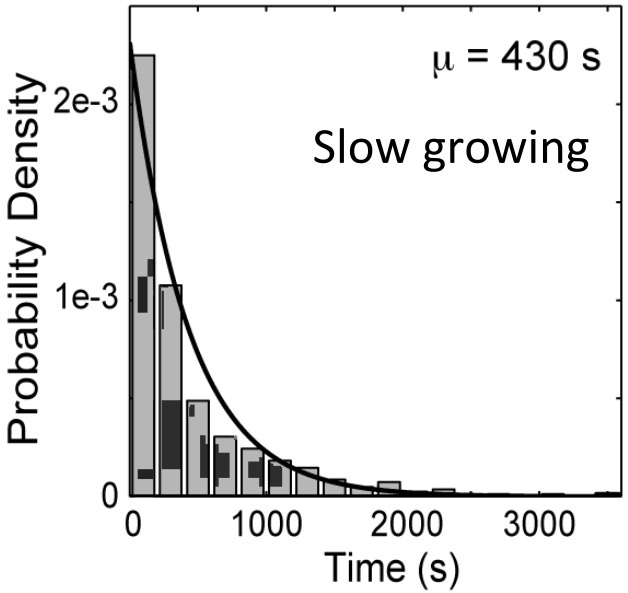


In vivo – Slow Growing *E. coli*

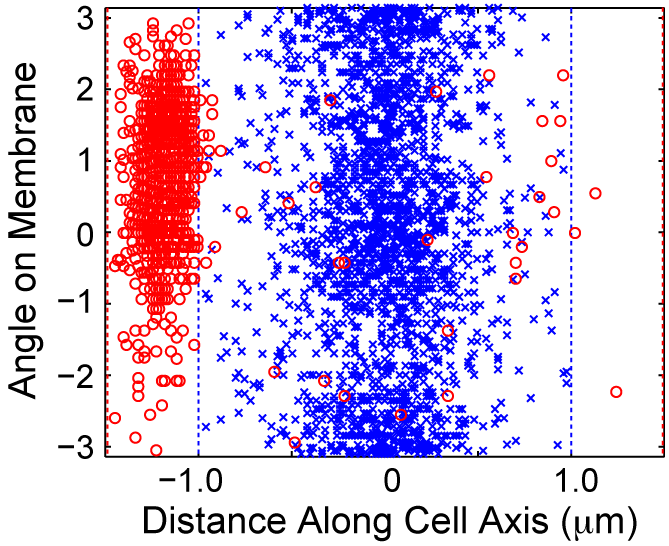


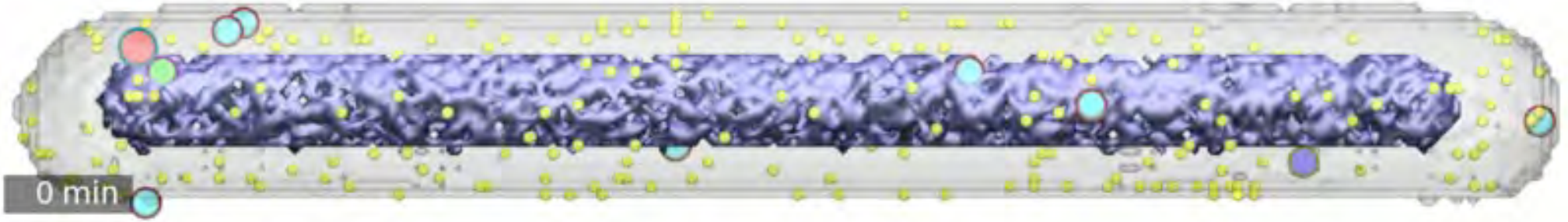
Lifetimes Repressor-Operator Complexes



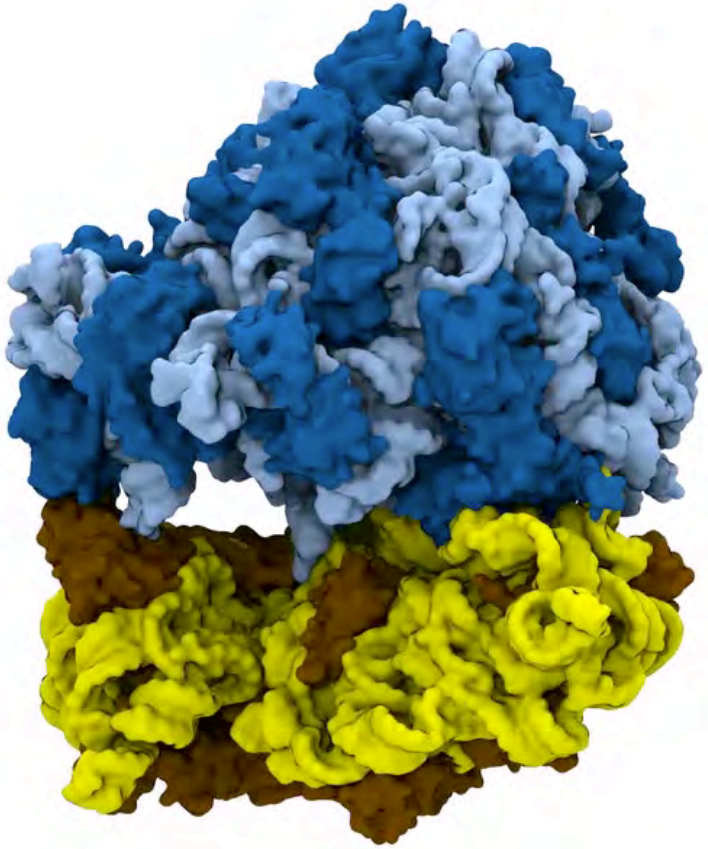


Localization of mRNA

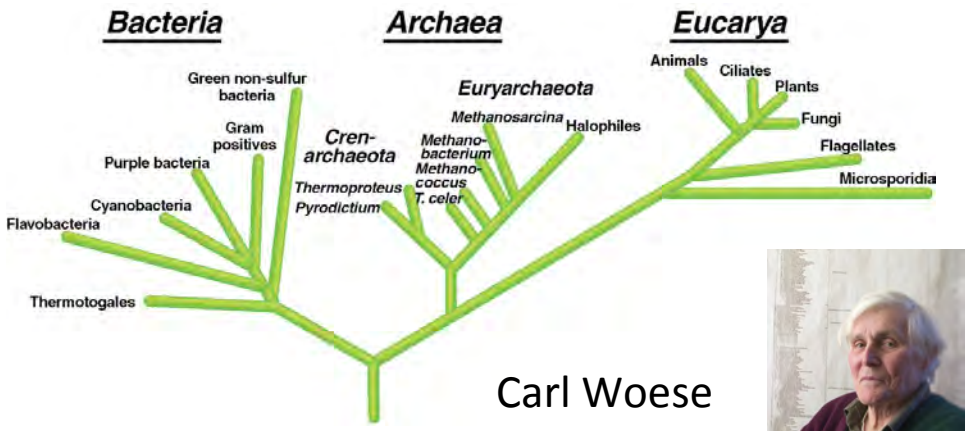




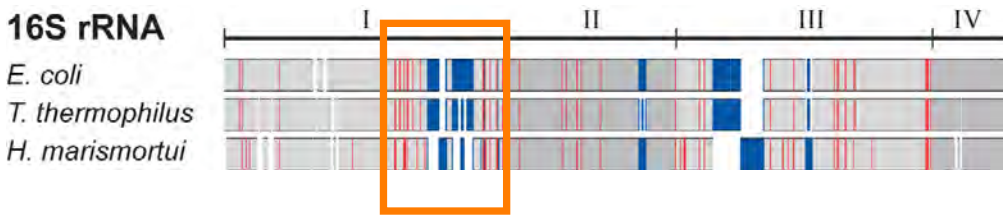
Molecular Signatures in Evolution of Translation ⟺ Kinetic Model Ribosome Biogenesis



Universal Phylogenetic Tree



Carl Woese

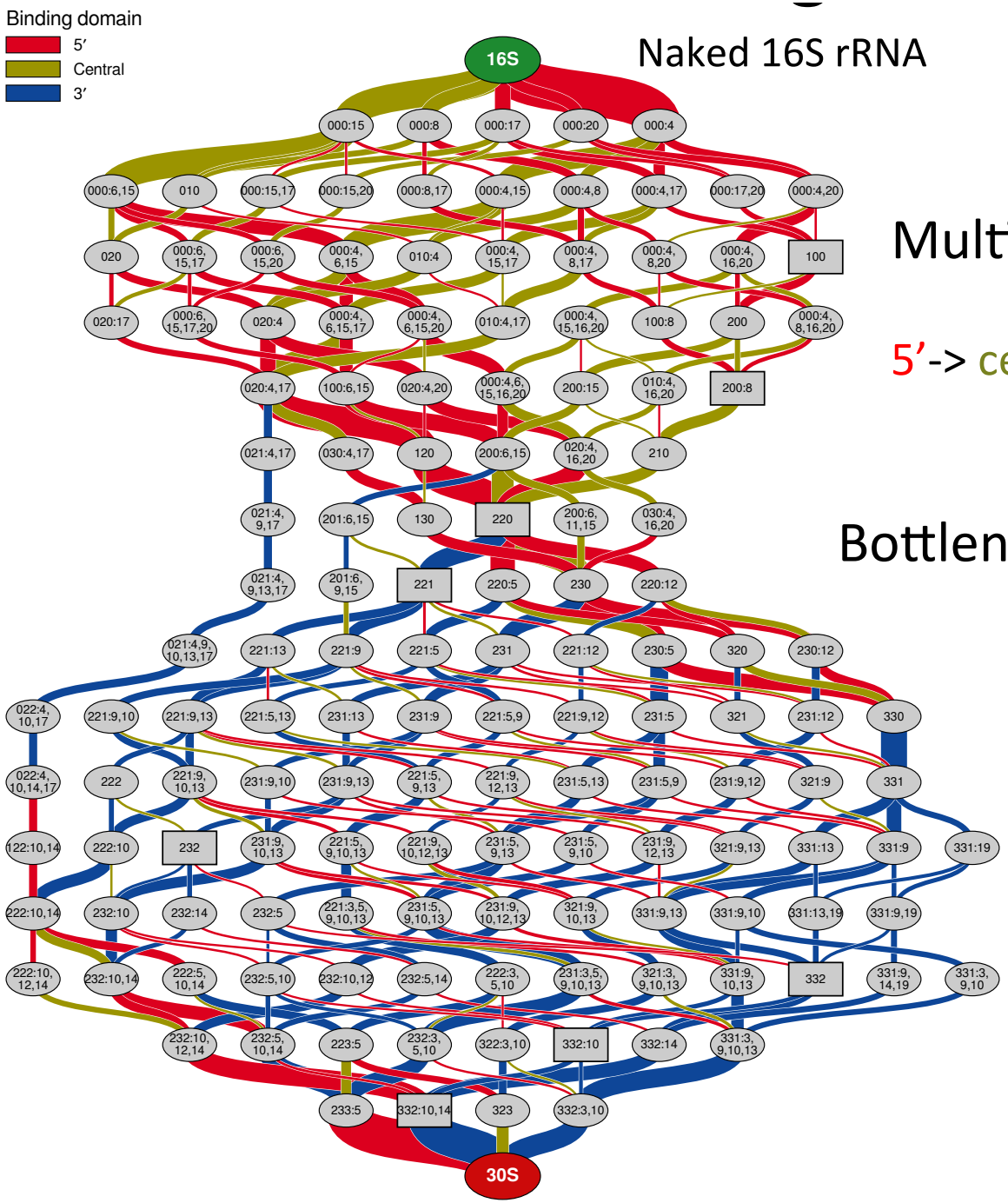


Dynamical function of ribosomal signatures: idiosyncrasies in ribosomal RNA and/or proteins characteristic of the domains of life

Roberts, … Woese, Luthey-Schulten (2008) ***PNAS,*** Kim,… Luthey-Schulten, Ha, and Woodson "Protein-guided RNA dynamics during early ribosome assembly" (2014) ***Nature***

Earnest, ….Williamson, ZLS "Whole Cell Model of Ribosome Biogenesis" (2015), **Biophys. J**.

In vitro kinetic model - 30S Assembly at 40 C



Multiple Paths

5’-> central -> 3’

Bottleneck S220

Tyler Earnest

J. Williamson

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	$X_i(\boldsymbol{x}) \longrightarrow X_i(\boldsymbol{x}+\boldsymbol{\delta}_i)$	Estimated or from SM