

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

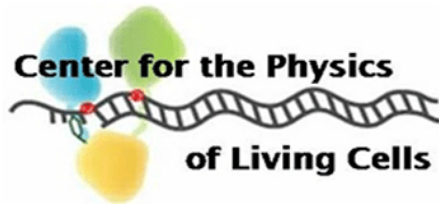
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Carl Woese Institute of Genomic Biology, UIUC

NIH Computational Biophysics Workshop, Pittsburgh, June 6-8, 2016

with **Mike Hallock and Joe Peterson**

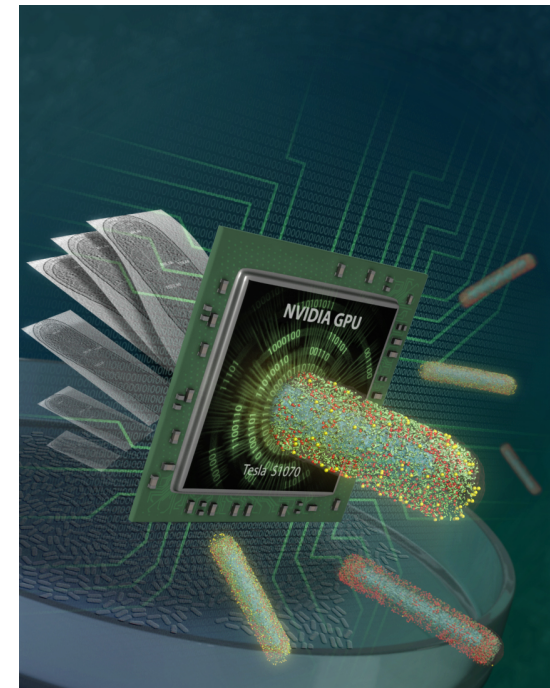


NCSA



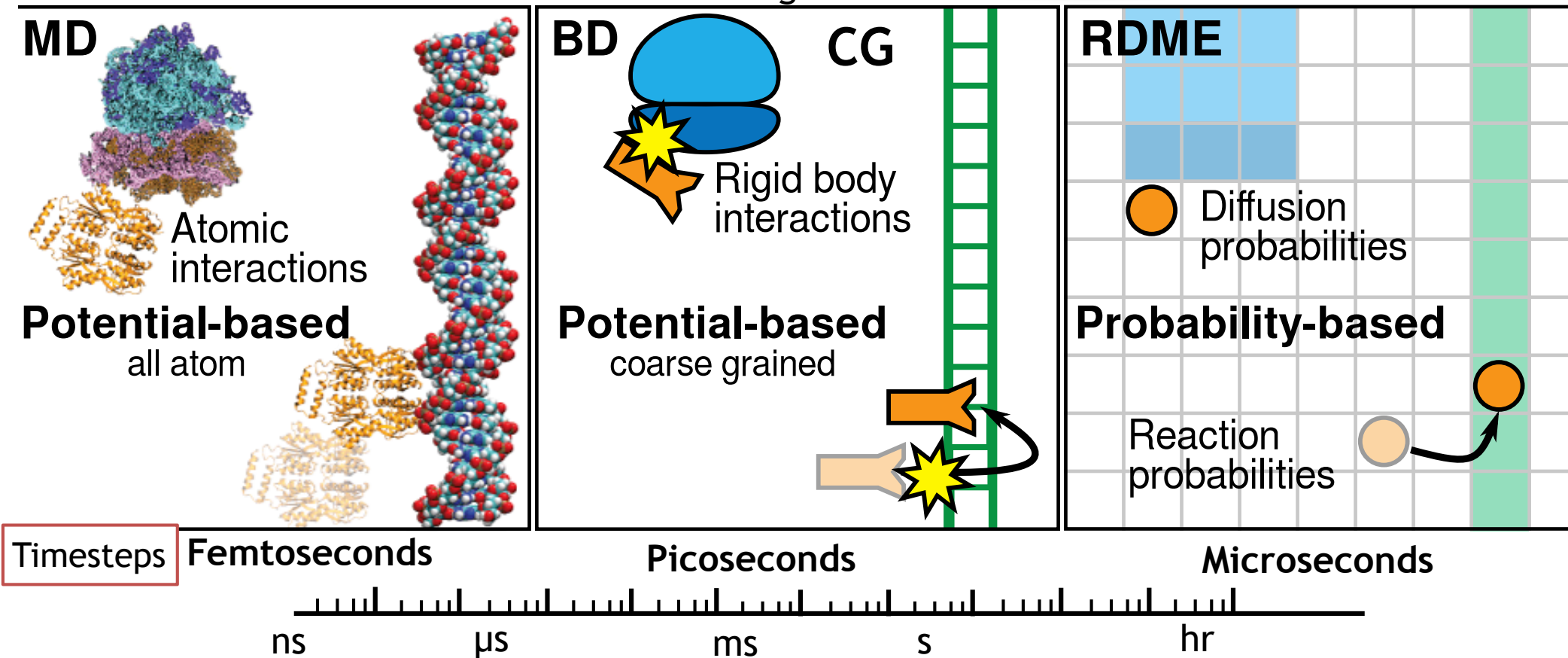
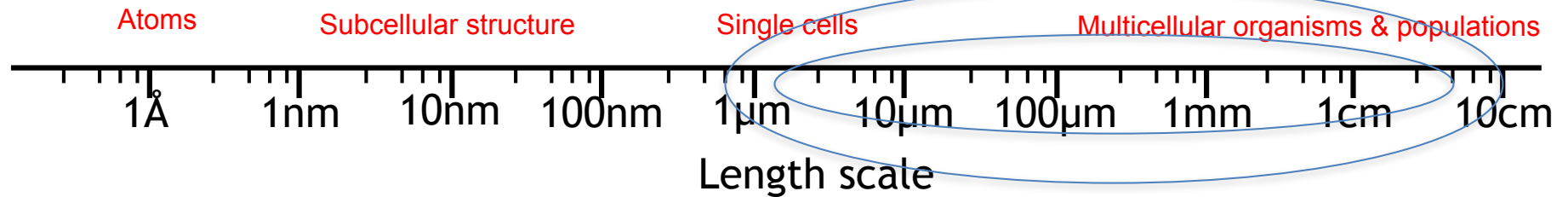
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Biological Modeling at Different Scales

Interactions span many orders of magnitude in space and time



Molecules to Macromolecular assemblies

Whole Cells and Colonies

Probability of Cellular State

Stochastic Dynamics

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

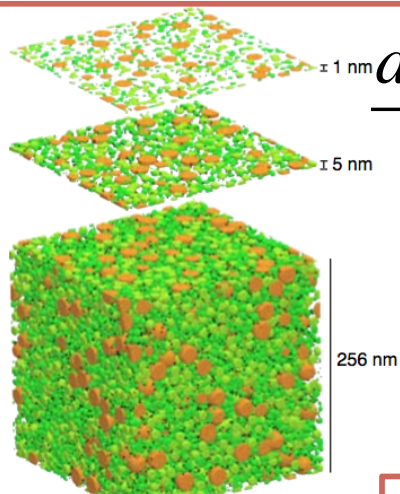
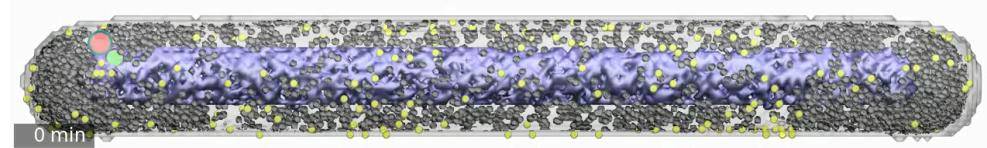
$$\frac{dP(\vec{x},t)}{dt} = \sum_r^R -a_r(\vec{x})P(\vec{x},t) + a_r(\vec{x} - \vec{s}_r)P(\vec{x} - \vec{s}_r,t)$$

State $\mathbf{x}$ (# mRNA, O, I...)

- Reaction-Diffusion Master Equation (RDME)

Noisy cell in sea of IPTG

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



$$\begin{aligned} \frac{dP(\vec{x},t)}{dt} = & \sum_{v \in V} \sum_{r=1}^R -a_r(\vec{x}_v)P(\vec{x},t) + a_r(\vec{x}_v - \vec{s}_r)P(\vec{x} - \vec{s}_r \mathbf{1}_v, t) \\ & + \sum_{i \in V} \sum_{j \in V} \sum_{\alpha=1}^N -d_{ij}^{\alpha} x_i^{\alpha} P(\vec{x},t) + d_{ji}^{\alpha} (x_j^{\alpha} + 1_j^{\alpha}) P(\vec{x} + \mathbf{1}_j^{\alpha} - \mathbf{1}_i^{\alpha}, t) \end{aligned}$$

Exp. proteomics

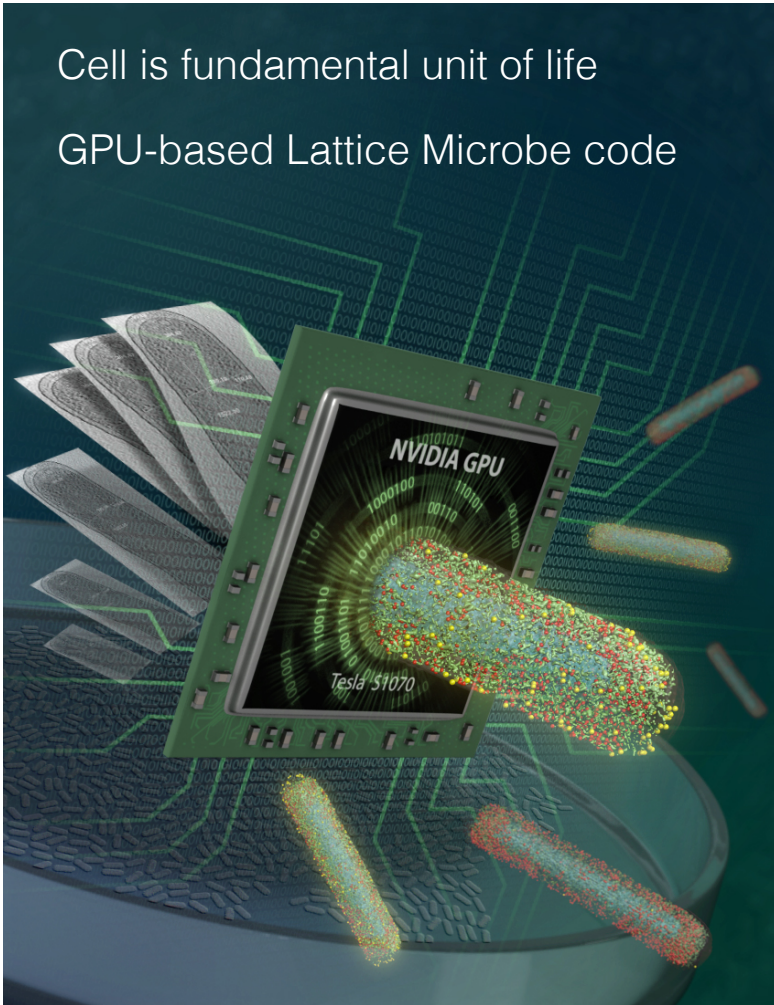
Heterogeneous cellular environment – 50% volume packed with macromolecules

Stochastic Cell Simulations

Promotes Integration of Theory and Experiments

Cell is fundamental unit of life

GPU-based Lattice Microbe code

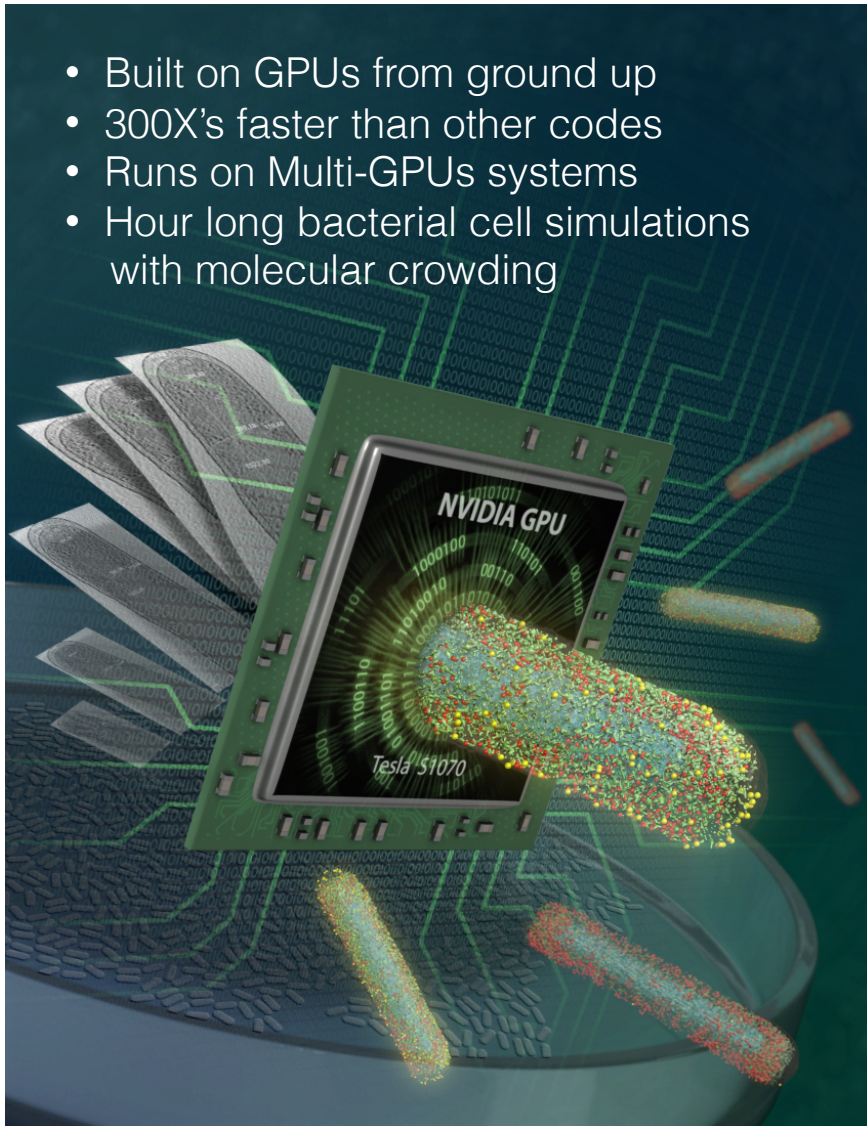


- Packing & Diffusion Data $\leftrightarrow$ SRI, CET, -omics
- Reactions & Parameters $\leftrightarrow$ Biochem, SM, MD
- RDME Cell Model Simulations $\leftrightarrow$ **Lattice Microbe** Multi-GPU Code over cell cycles
- Population (Constrained) FBA: Steady-state fluxes in cellular networks and growth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

- Built on GPUs from ground up
- 300X's faster than other codes
- Runs on Multi-GPUs systems
- Hour long bacterial cell simulations with molecular crowding



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-operativity 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)

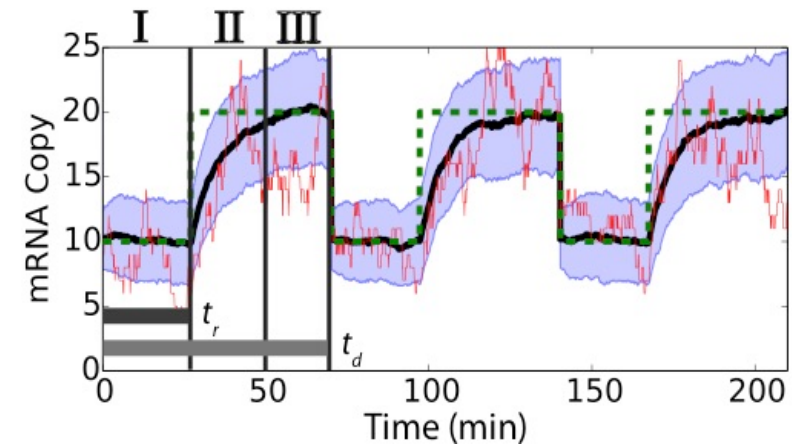
DNA Replication <-> mRNA and sRNA – 2015 ...

- 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



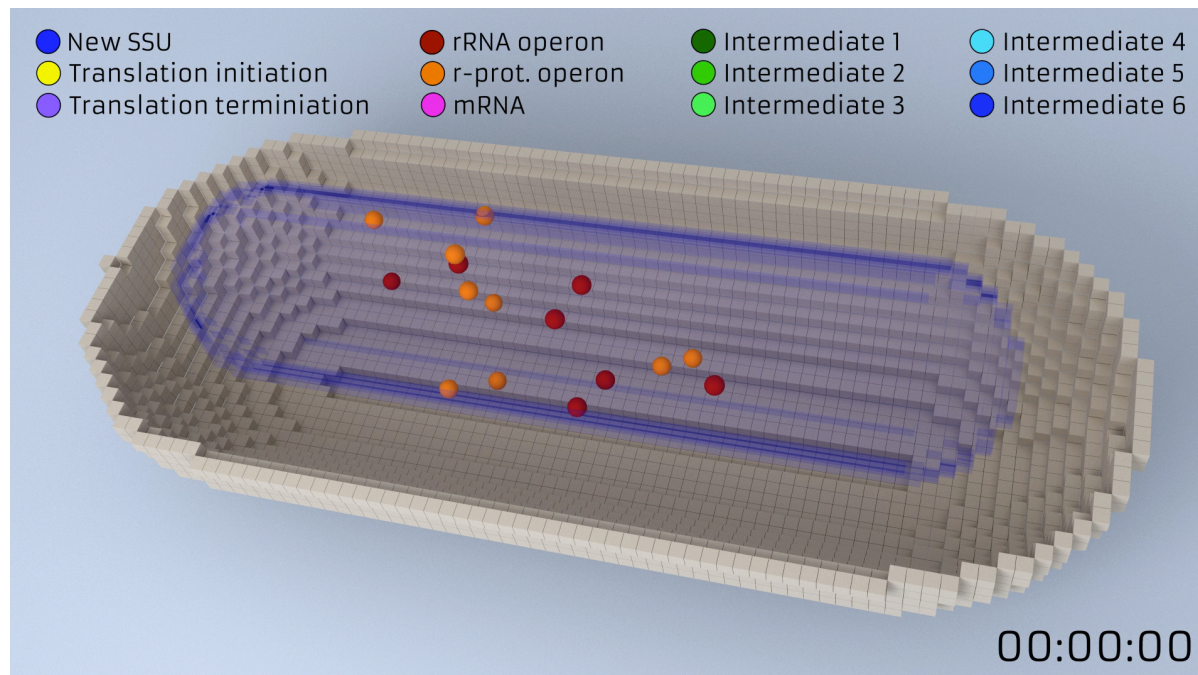
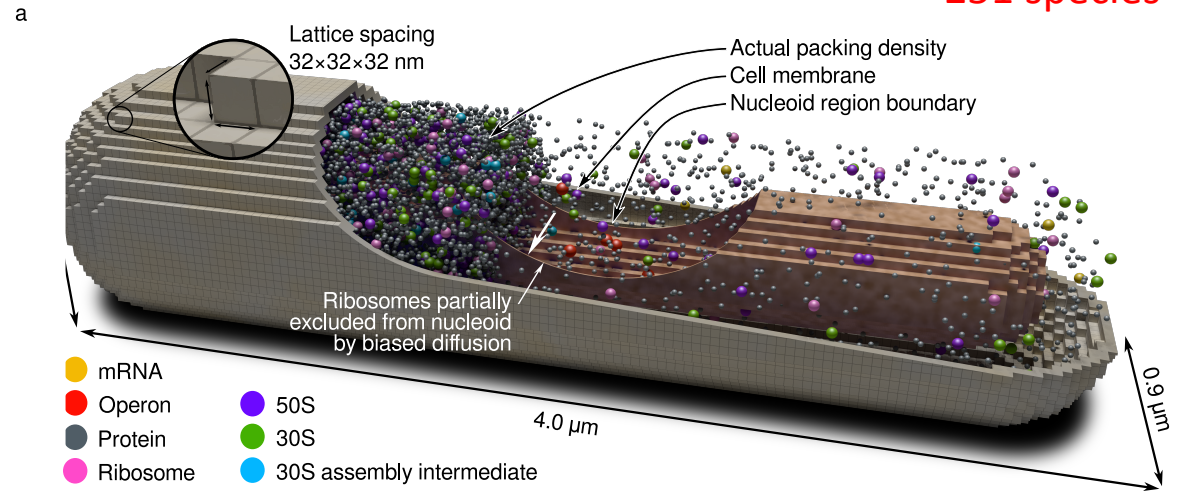
Gene Copy Number

2

1

Ribosome Biogenesis - RDME

1300 rxns
251 species



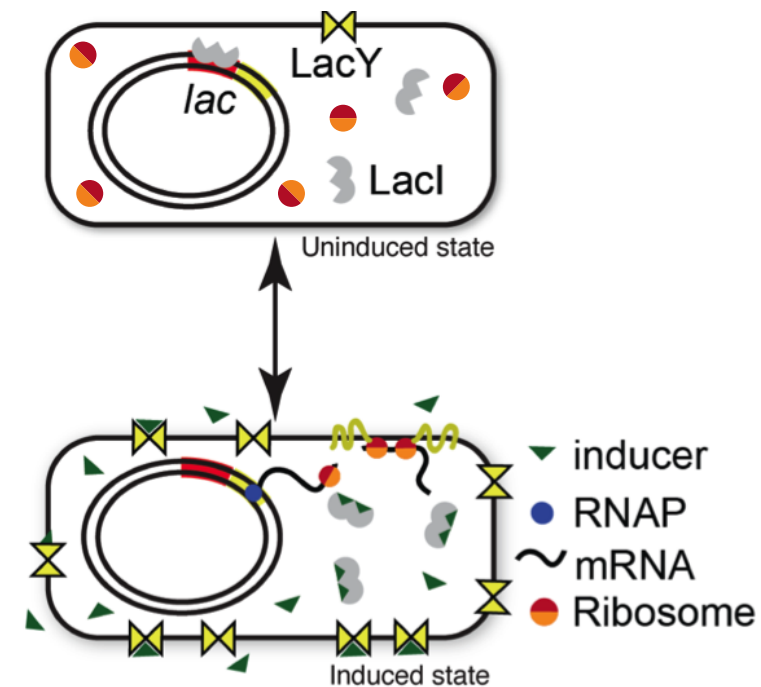
Kinetic Model of *lac* Genetic Switch

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 degradation						
$O \rightarrow O + mY$	k_{tr}	1.26e-01		s^{-1}	M	
$mY \rightarrow mY + Y$	k_{tn}	4.44e-02		s^{-1}	S	
$mY \rightarrow \emptyset$	k_{degm}	1.11e-02		s^{-1}	S	
$Y \rightarrow \emptyset$	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_{iopen}	6.67e+02	2.24e+04	$M^{-1}s^{-1}$	M	K
$I + IR_2O \rightarrow I_2R_2O$	k_{i2open}	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

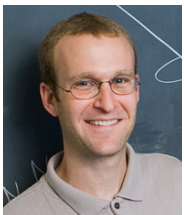
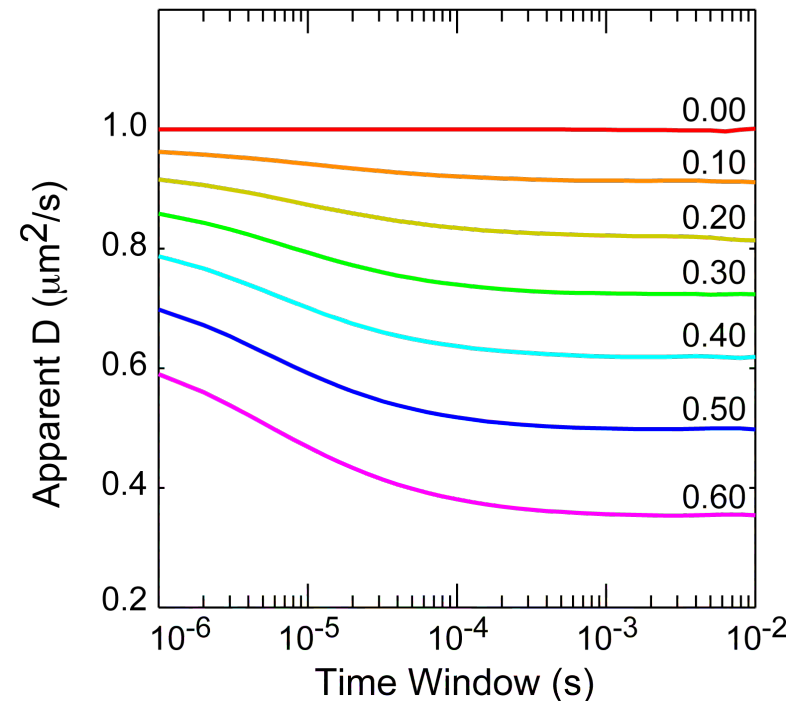
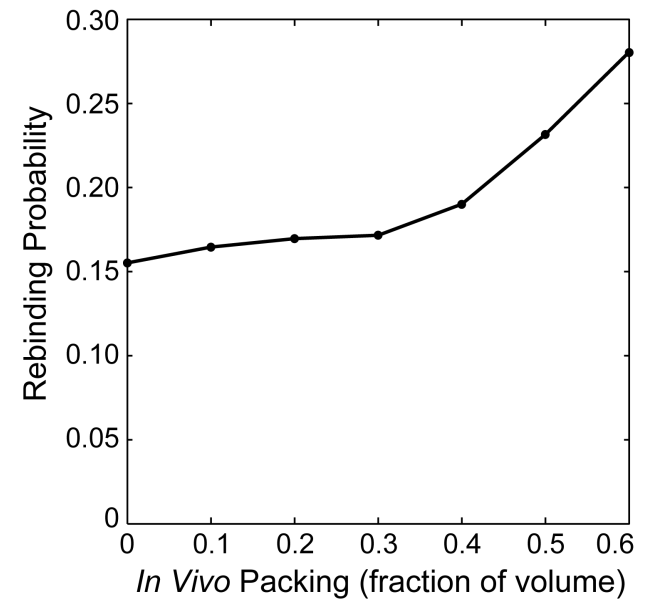
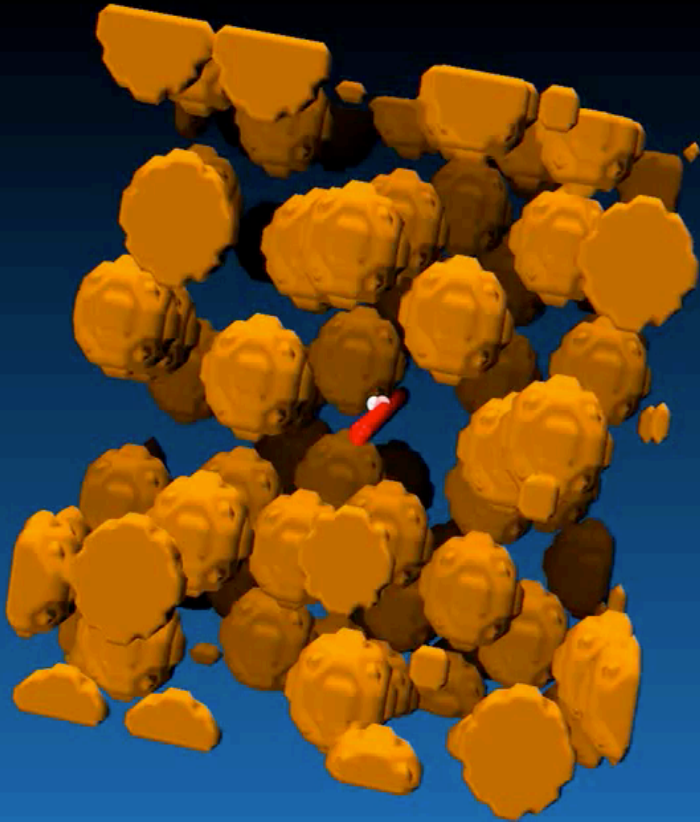
S – single molecule experiment

M – model parameter fit to single-molecule distributions



Roberts, ...ZLS, PloS CompBio 2011

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

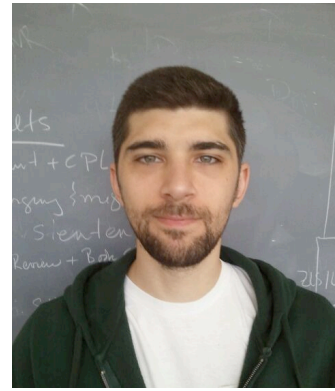


E. Roberts, J. Stone, L. Sepulveda, W.M. Hwu, ZLS, **IEEE**, 2009

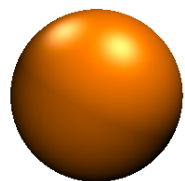
A Window into the Cell with VMD



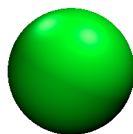
John Stone



John Cole



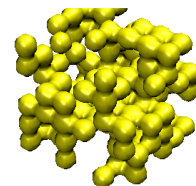
Ribosome



Polymerases/
Large Complexes

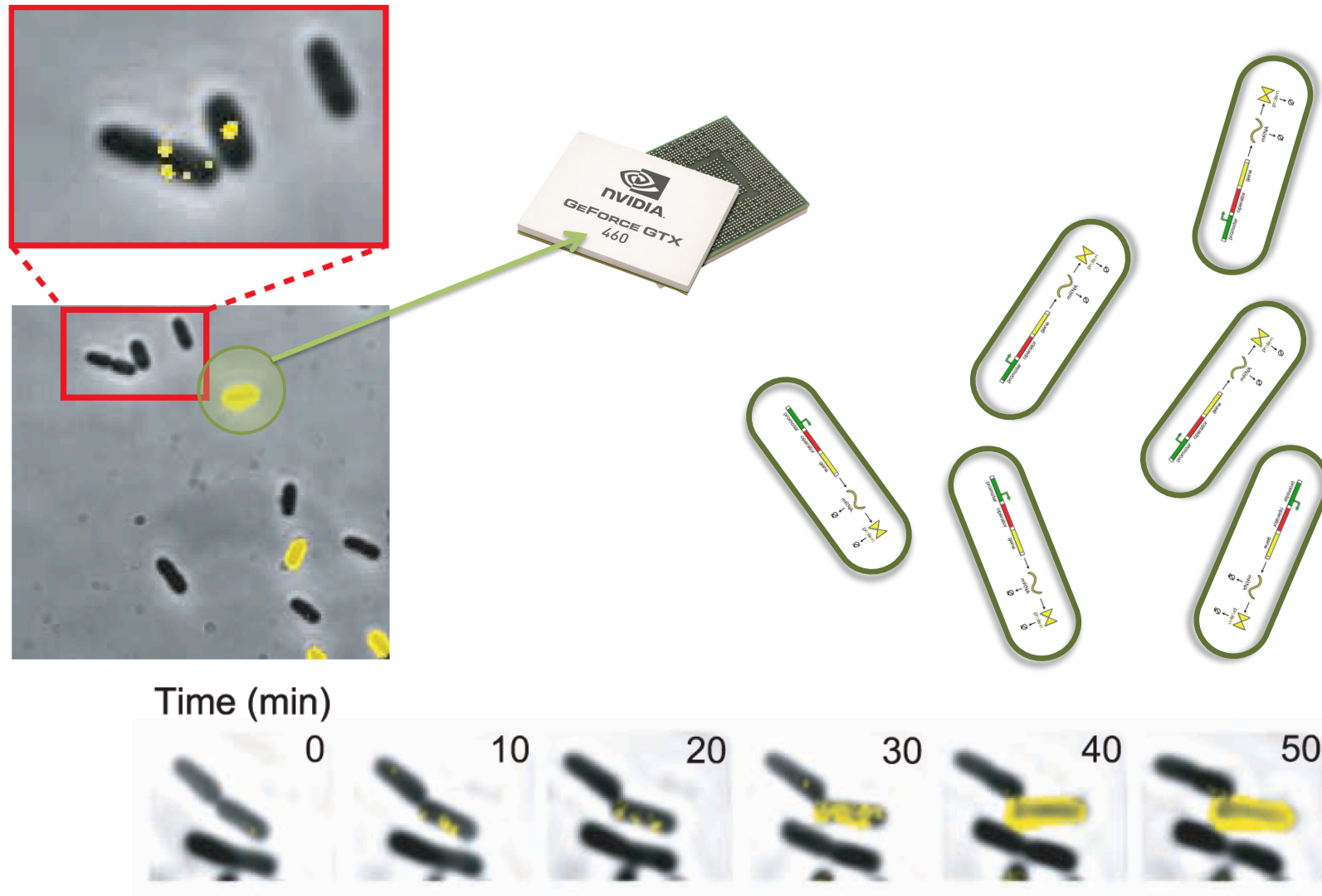


Small Complexes/
Proteins

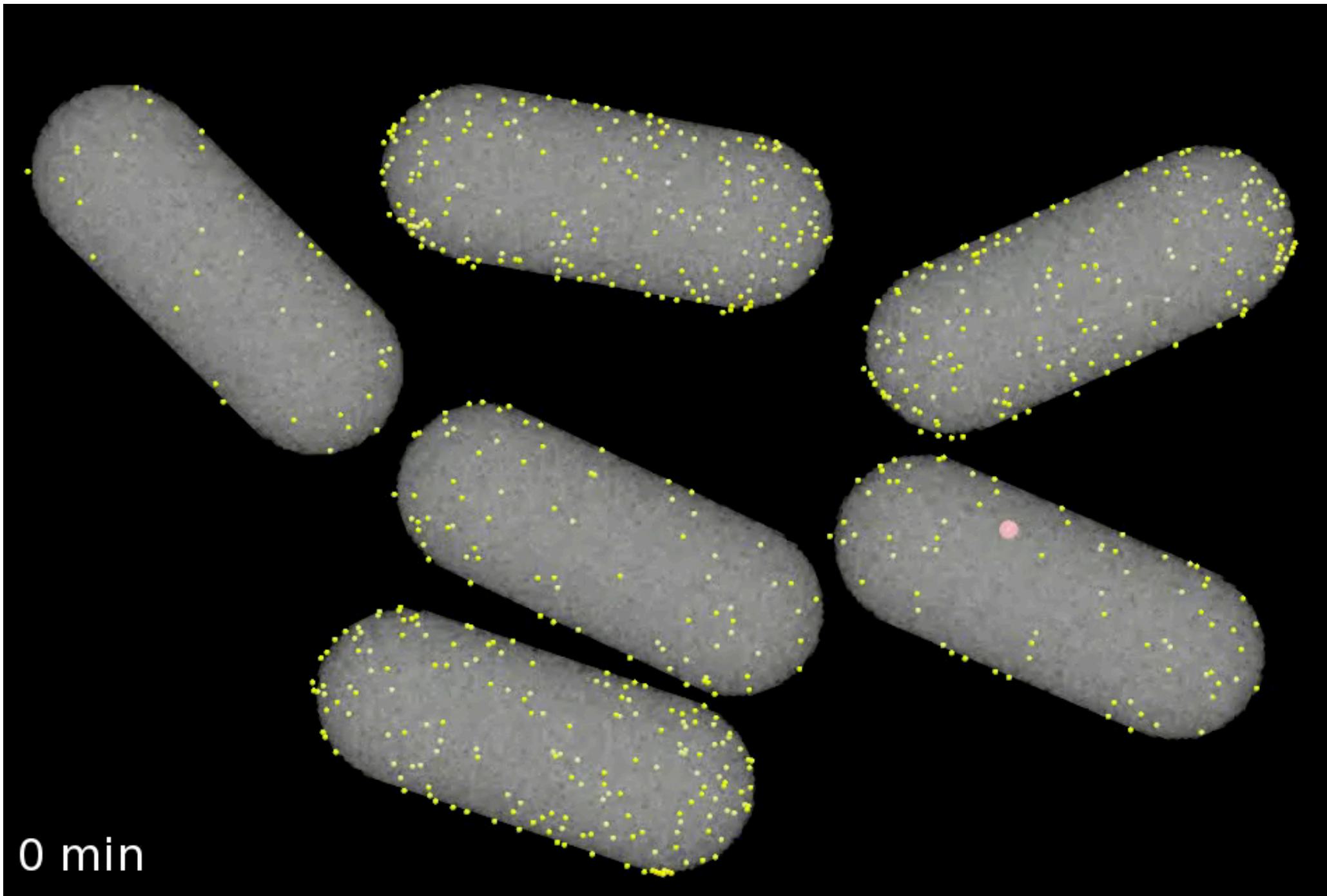


Lattice sites

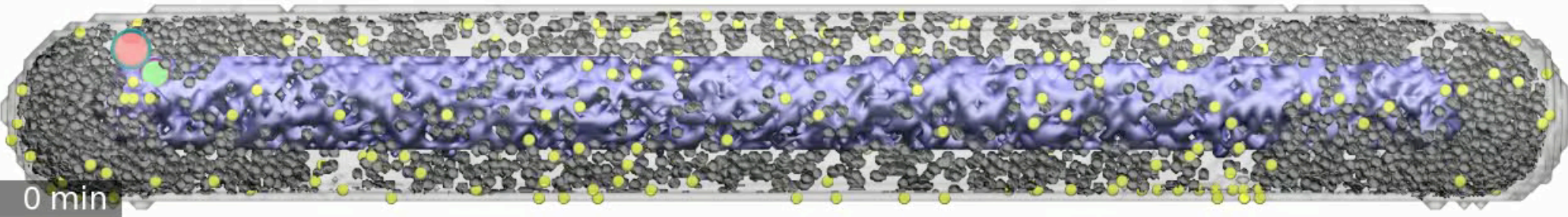
Motivation: Capture Timescale and Fraction of Cells Undergoing Phenotypic Switching



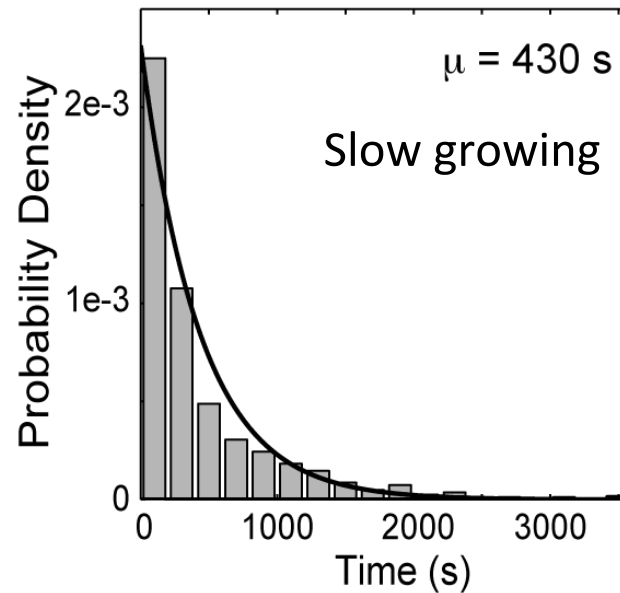
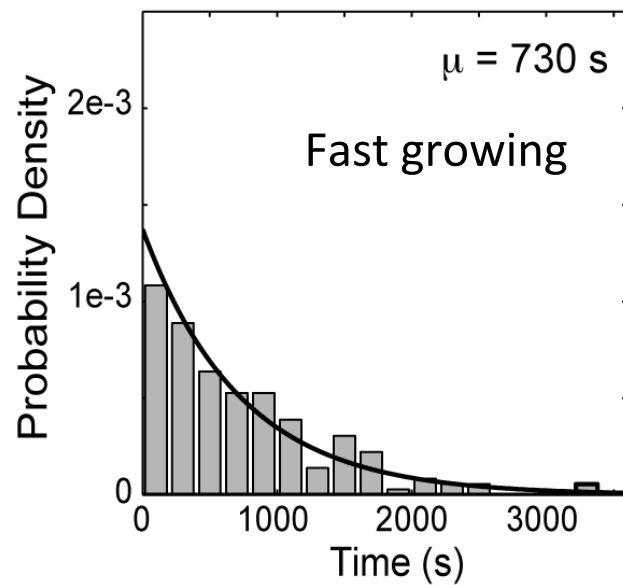
Switching in Fast Growing E. coli Cells – Bursting of mRNA



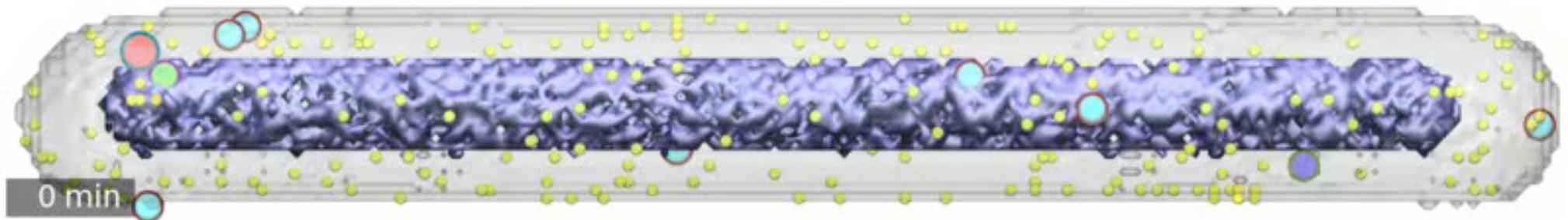
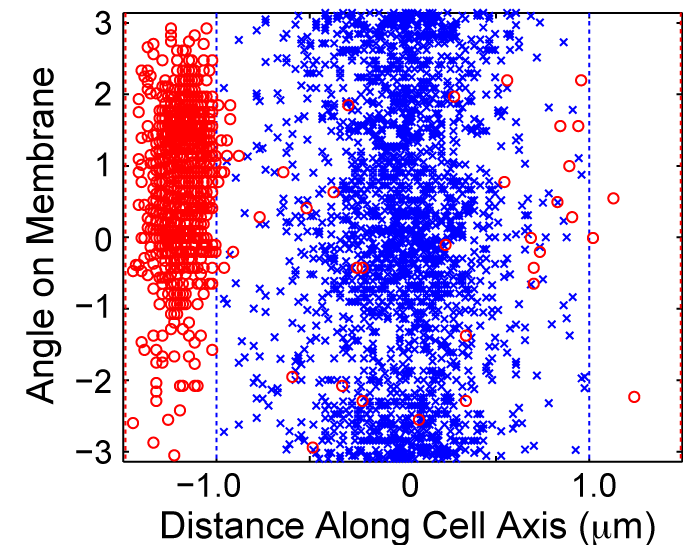
In vivo – Slow Growing *E. coli*



Lifetimes Repressor-Operator Complexes

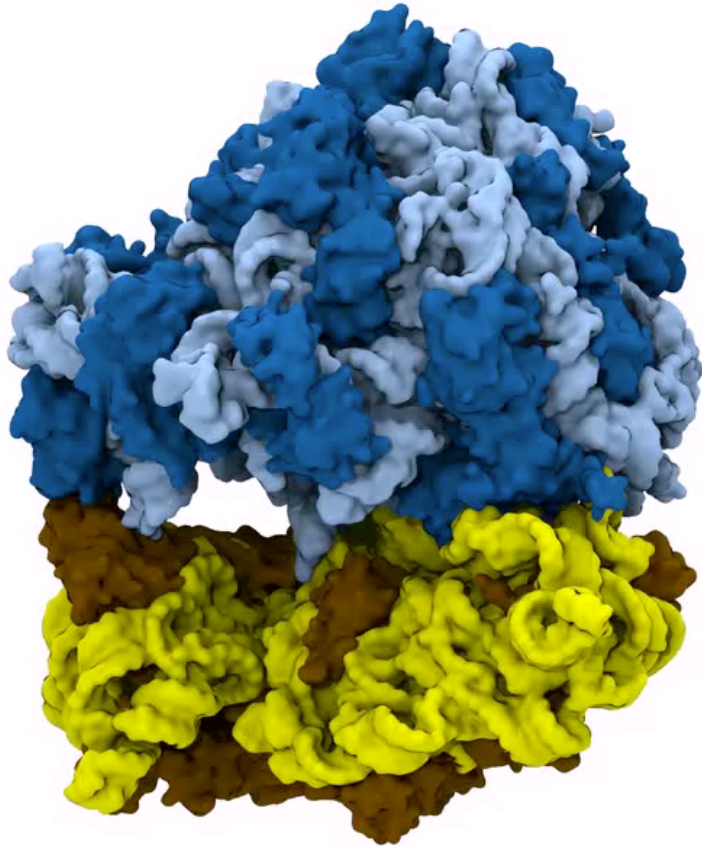


Localization of mRNA

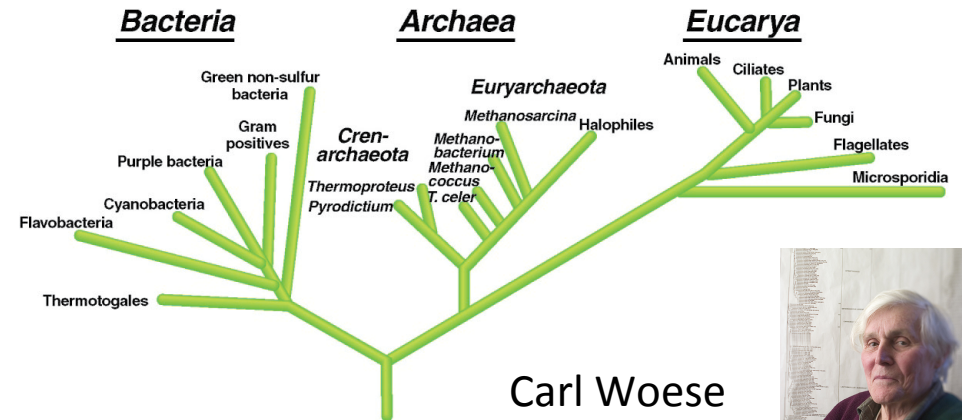


Molecular Signatures in Evolution of Translation

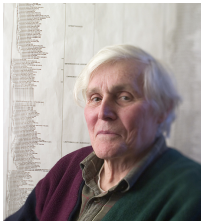
↔ Kinetic Model Ribosome Biogenesis



Universal Phylogenetic Tree

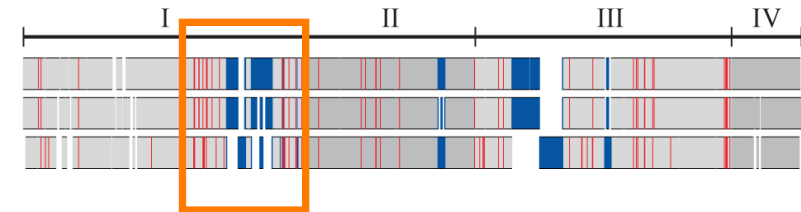


Carl Woese



16S rRNA

E. coli
T. thermophilus
H. marismortui

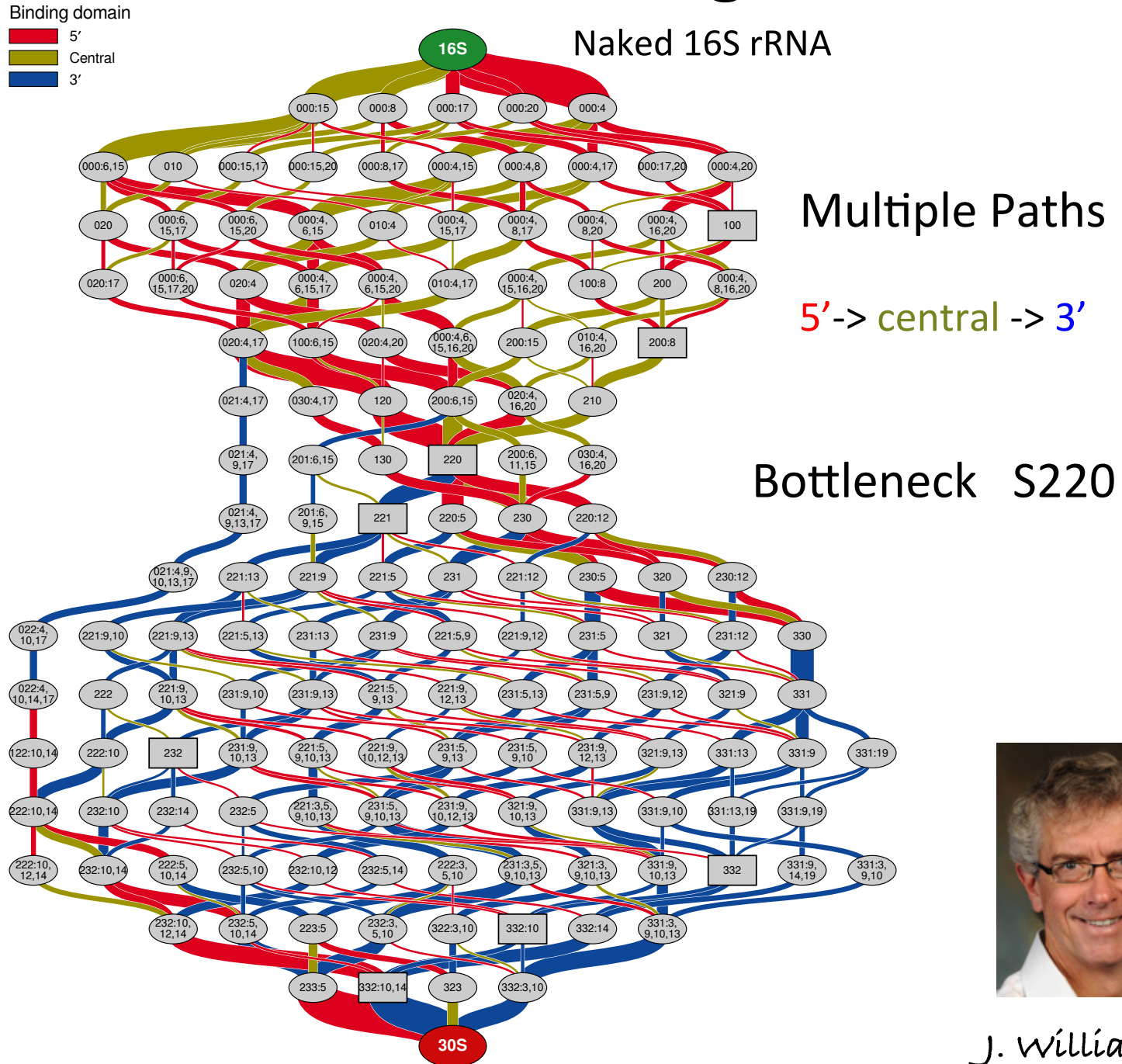


Dynamical function of ribosomal signatures: idiosyncrasies in ribosomal RNA and/or proteins characteristic of the domains of life

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



Tyler Earnest



J. Williamson

In vivo model - 1330 reactions, 251 species

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