

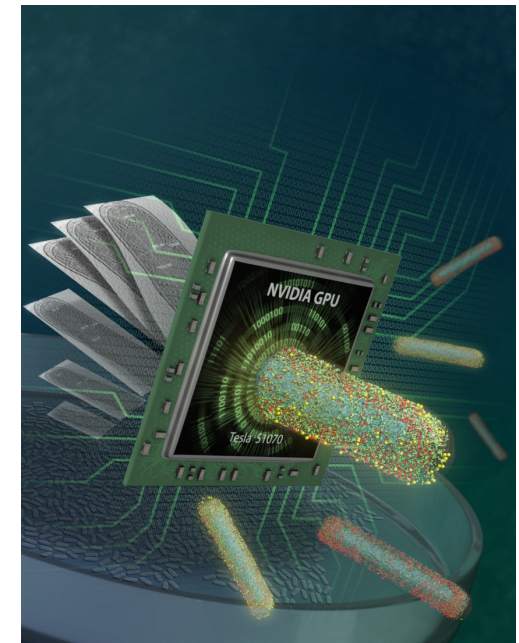
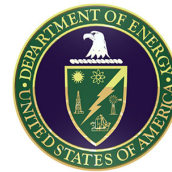
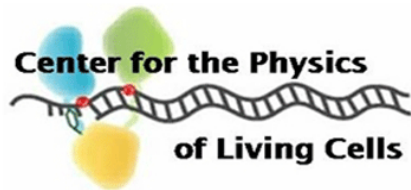
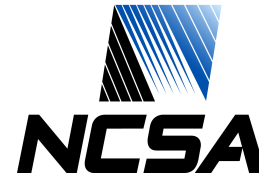
Simulations of Ribosome Biogenesis on the Whole Cell Level

Zaida (Zan) Luthey-Schulten

Dept. Chemistry, Physics, Beckman Institute, Center for Biophysics, and

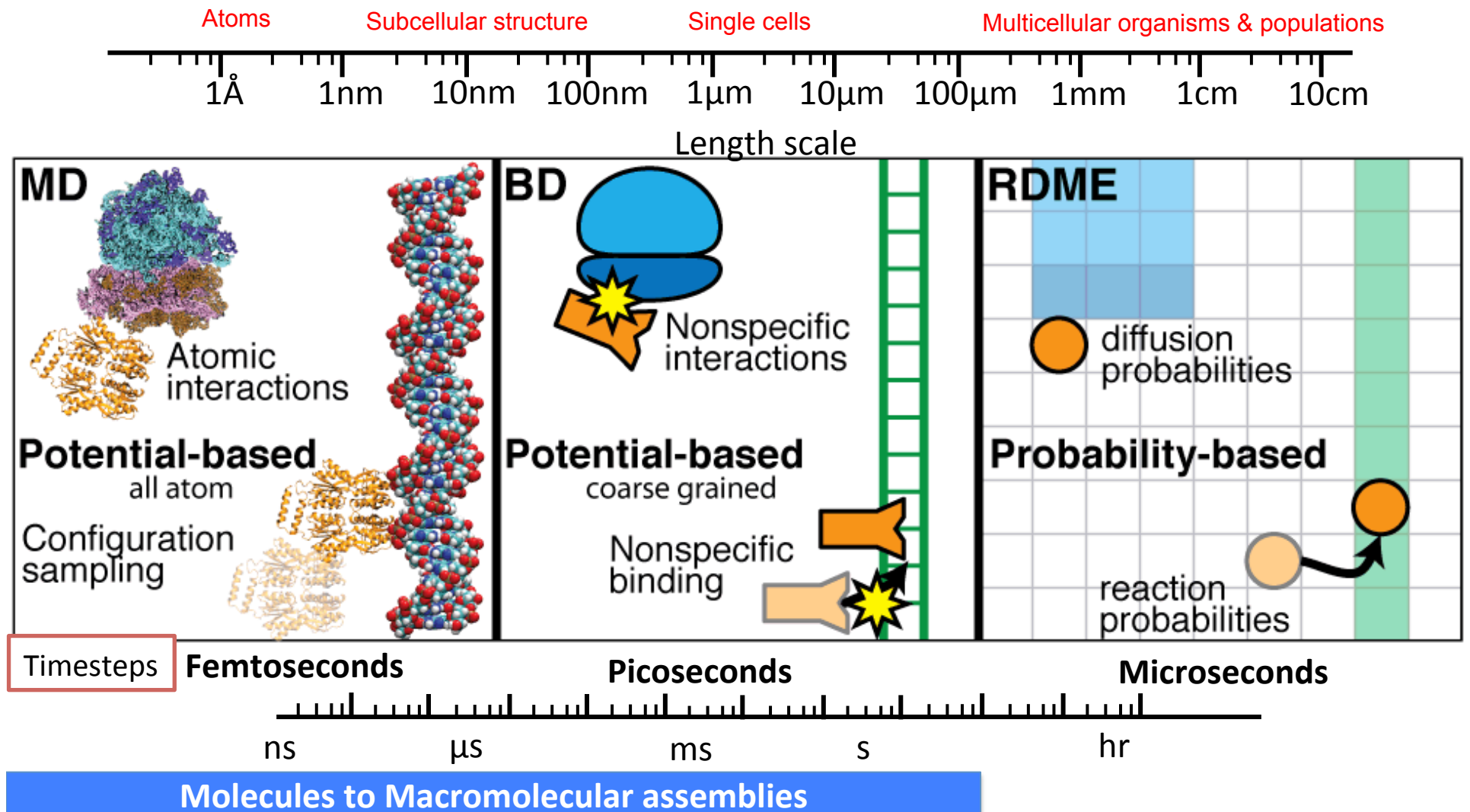
Carl Woese Institute of Genomic Biology, UIUC

2015 Blue Waters Symposium, SunRiver, Oregon



Biological Modeling at Different Scales

Biomolecular interactions span many orders of magnitude in space and time



Probability of Cellular State

Algorithms for Stochastic Dynamics

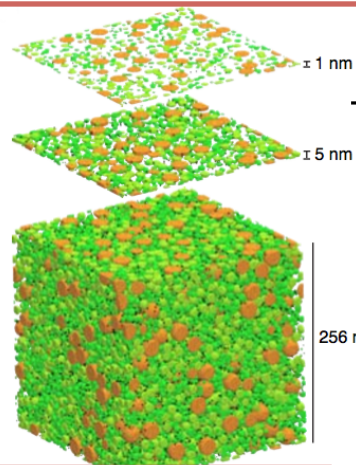
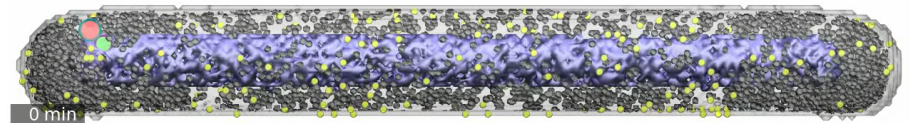
- Chemical Master Equation – Well-stirred system (Gillespie SSA)

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

- Reaction-Diffusion Master Equation (RDME)

Crowded noisy cell

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



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

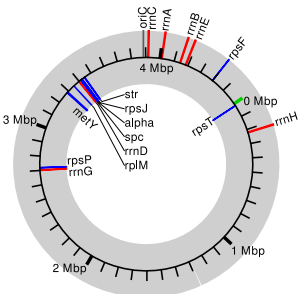
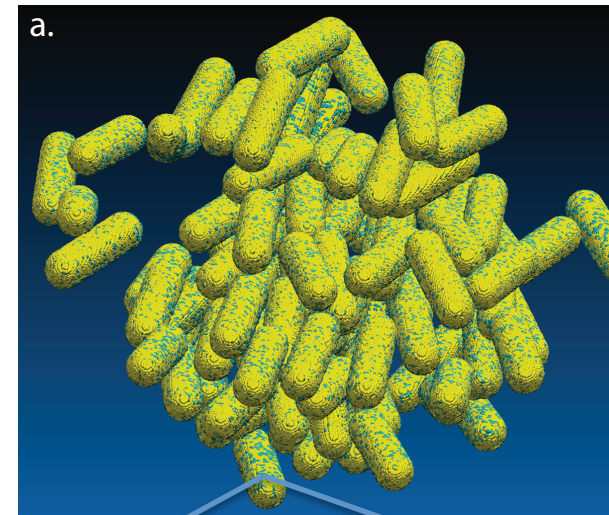
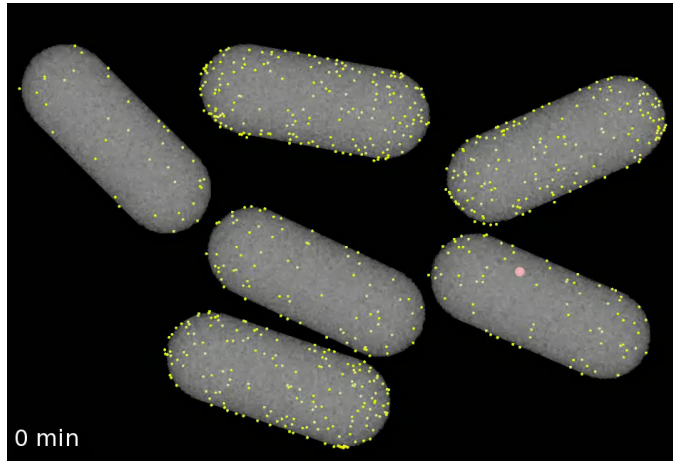
Exp. proteomics

Heterogeneous cellular environment – 50% volume packed with macromolecules

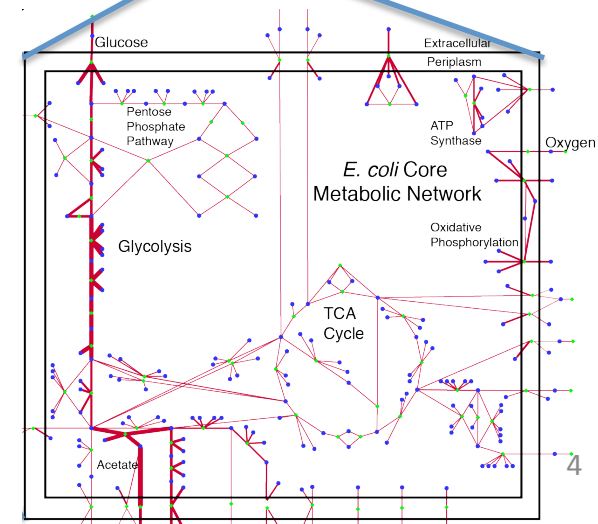
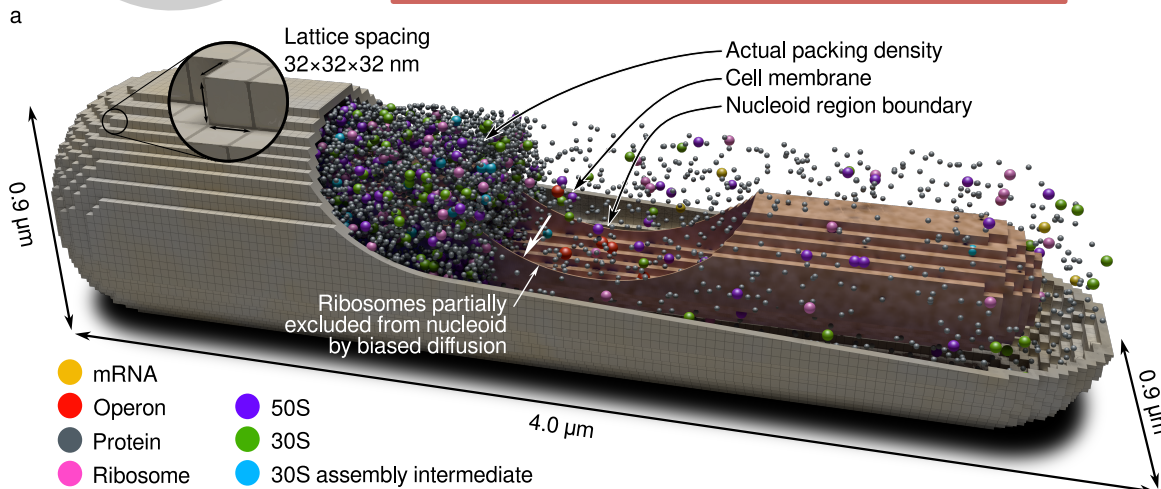
Challenging Cell Simulations & Experiments

Stochastic Gene Expression
Switching Cells

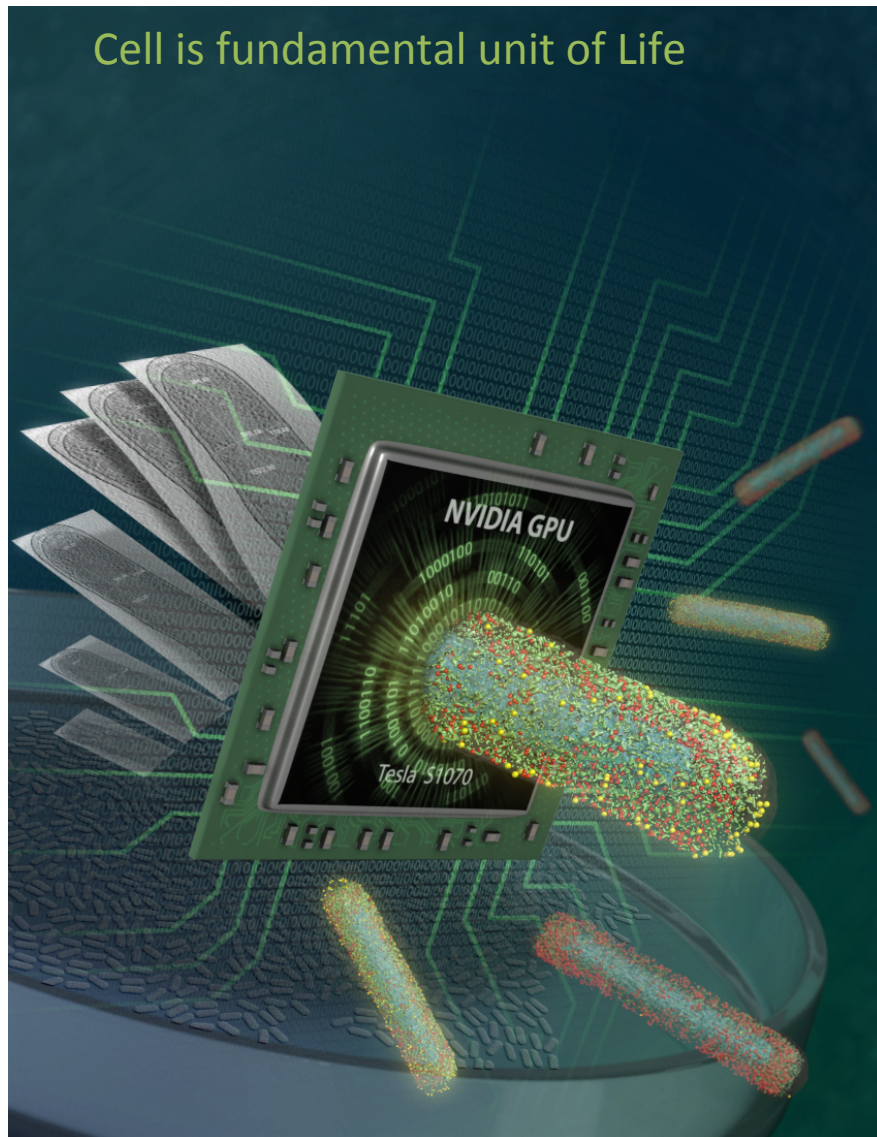
Metabolic Response in Colony of Cells
~2000 metabolic rxns



Ribosome Biogenesis - 1200rxns



Cell Simulations with Lattice Microbes



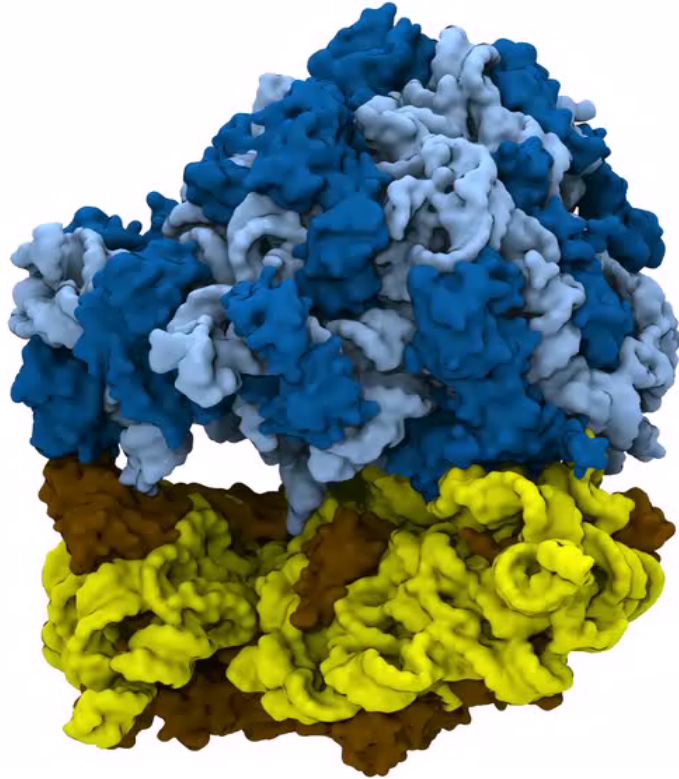
Cell is fundamental unit of Life

- Molecular crowding & protein/RNA distributions
- (CET, SM, RNA seq & proteomics data)
- Reactions as RDME solved on 3D lattice for cell cycle using Multi GPUs
- Kinetic parameters < biochem & SM experiments – e.g.sRNA, ribosome biogenesis
- Population FBA: Steady-state fluxes through thermodynamically balanced cellular networks and growth rate distributions – E. coli and Yeast
- Hybrid RD(ME)/FBA models – Cell Colonies

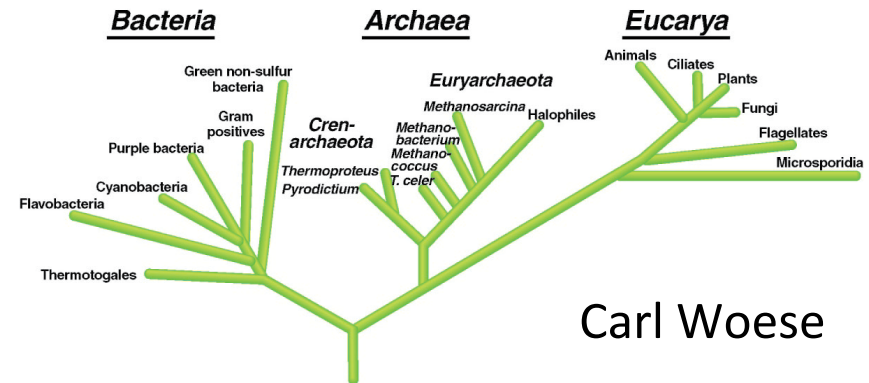
Roberts, ... ZLS (2009,2011,2013) *IEEE, PLoS CB, JCC*
Earnest, ...ZLS *Phys.Bio* (2012), Assaf,.. (2012,2013) *PRL*
*Labhsetwar, Cole, ...ZLS, (2013) *PNAS*
*Cole, ...ZLS,in *Comp. Sys. Bio.* (2014)
*Hallock,... *Par. Comp.* (2014), Peterson,...*PyHPC* 2013
* Cole,.. ZLS, *Israel J. Chem*, 2014, *BMC Sys. Bio.* (2015)
*Earnest,...Williamson, ZLS, *BPJ* (submitted 2015)

Molecular Signatures in Evolution of Translation

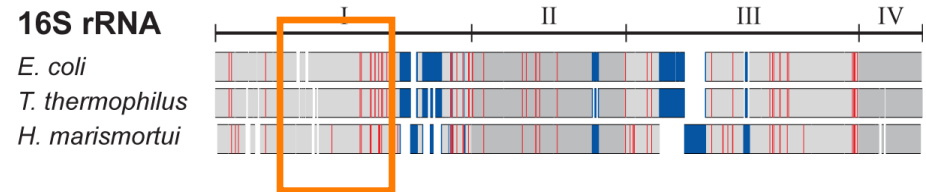
↔ Kinetic Model Ribosome Biogenesis



Universal Phylogenetic Tree



Carl Woese



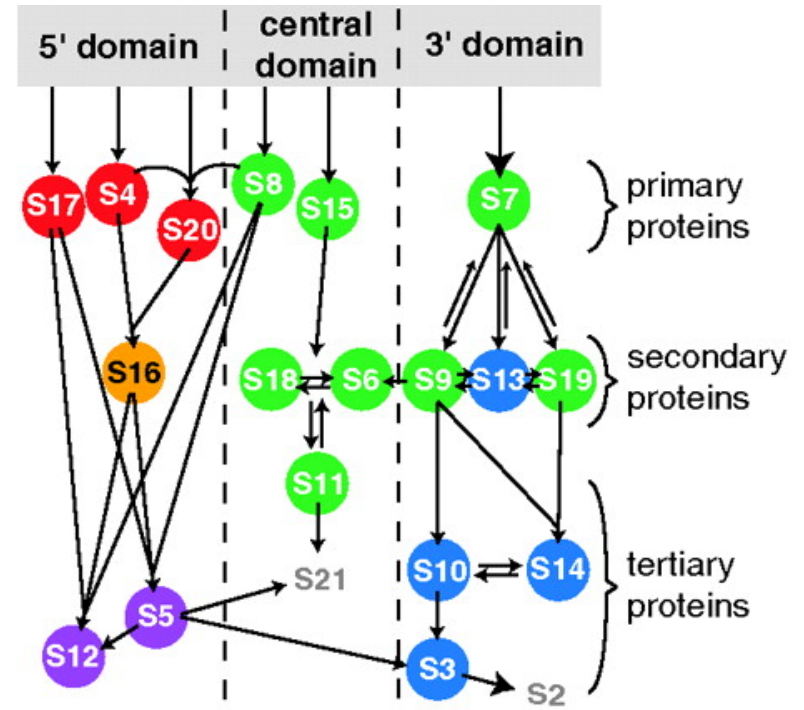
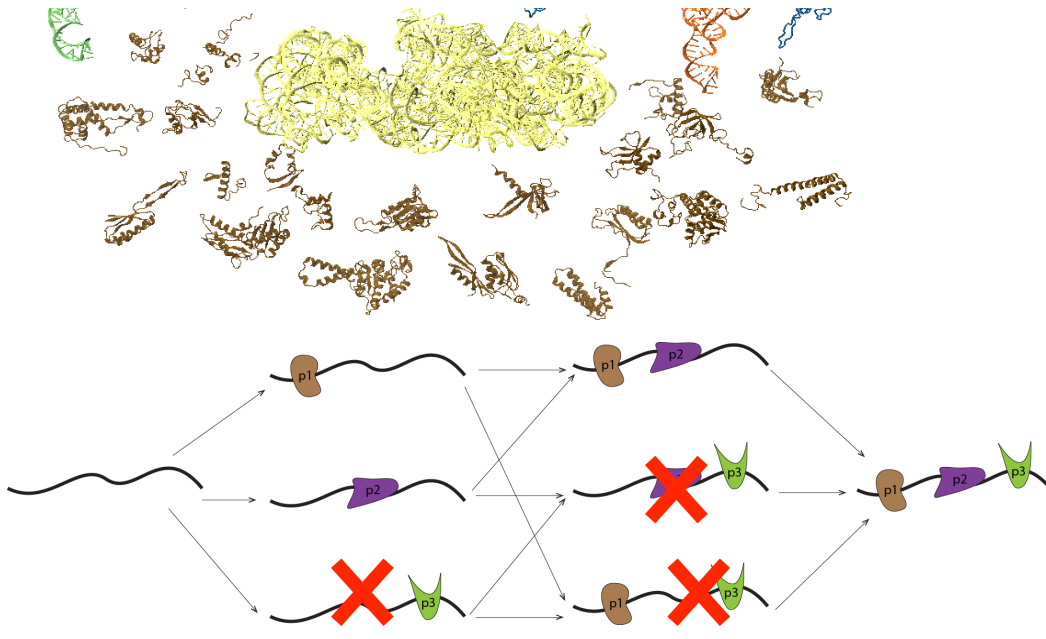
Dynamical function of ribosomal signatures: idiosyncrasies in ribosomal RNA and/or proteins characteristic of the domains of life

Roberts, ... Woese, Luthey-Schulten (2008) *PNAS*; Chen,.. Gruebele, Luthey-Schulten (2010) *BJ*
Chen, ... Ha, Woodson, Luthey-Schulten, (2012) *JPCB*; Lai, Chen, Luthey-Schulten (2013) *JPCB*
Kim,... Luthey-Schulten Z., Ha, and Woodson (2014) *Nature* "Protein-guided RNA dynamics during early ribosome assembly"

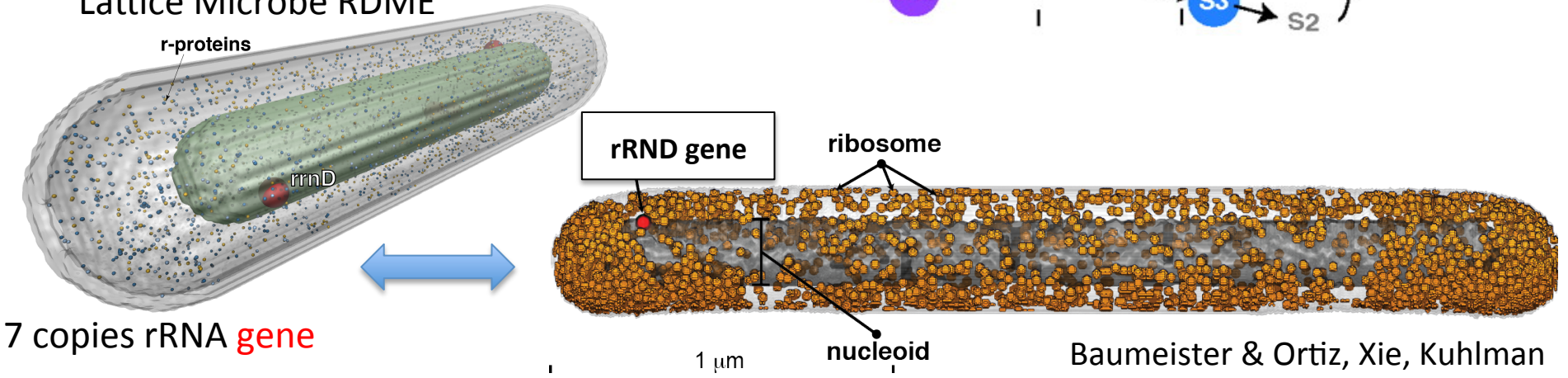
From *in vitro* Assembly Model to Biogenesis

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

Nomura Hierarchical Map >>> 1612 states



Lattice Microbe RDME

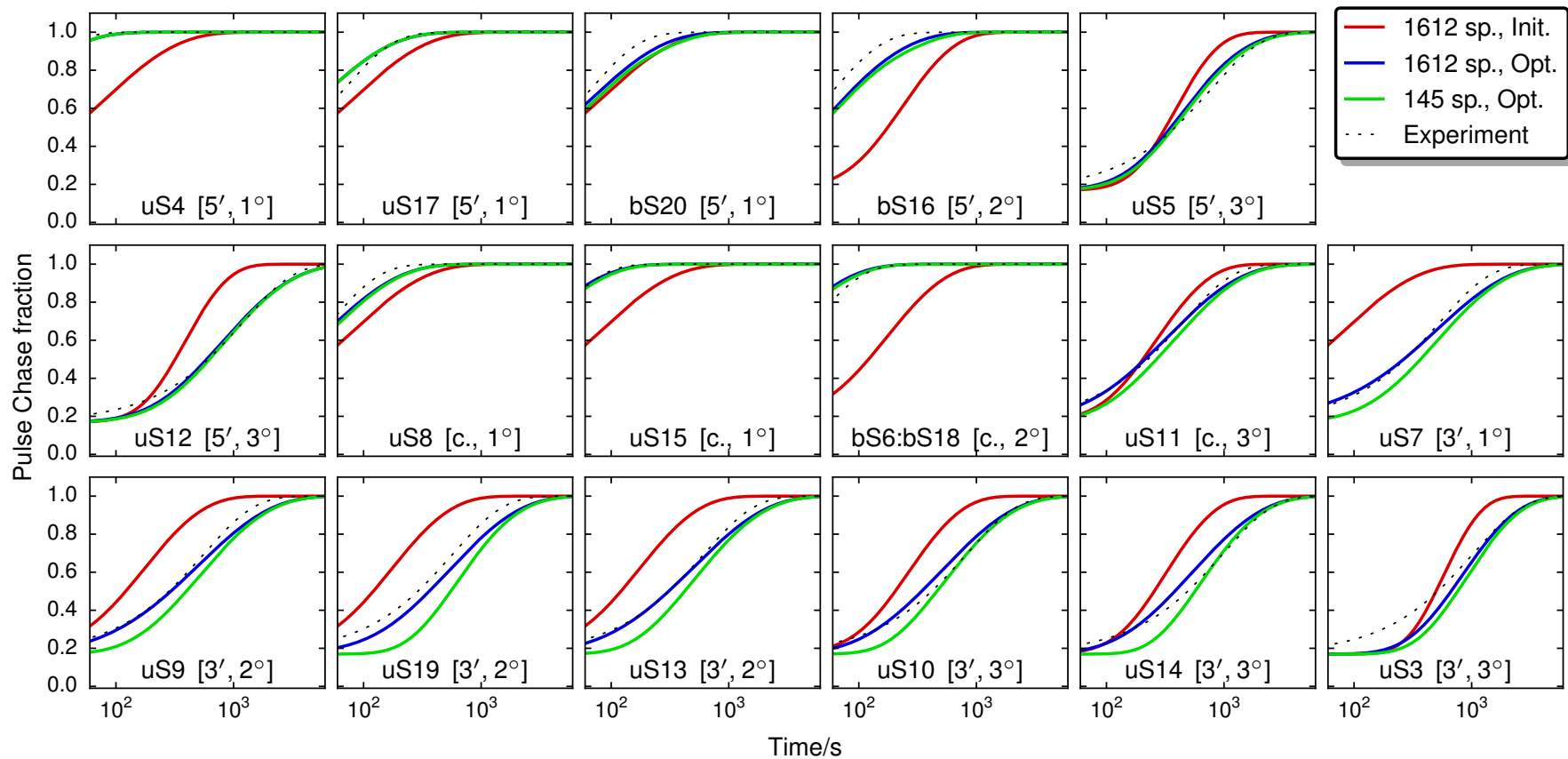


7 copies rRNA gene

Baumeister & Ortiz, Xie, Kuhlman

Comparison of full to reduced kinetic model – 40⁰ C

Pulse Chase experiments – Control Experiments – Williamson, Science 2010, Elife 2014

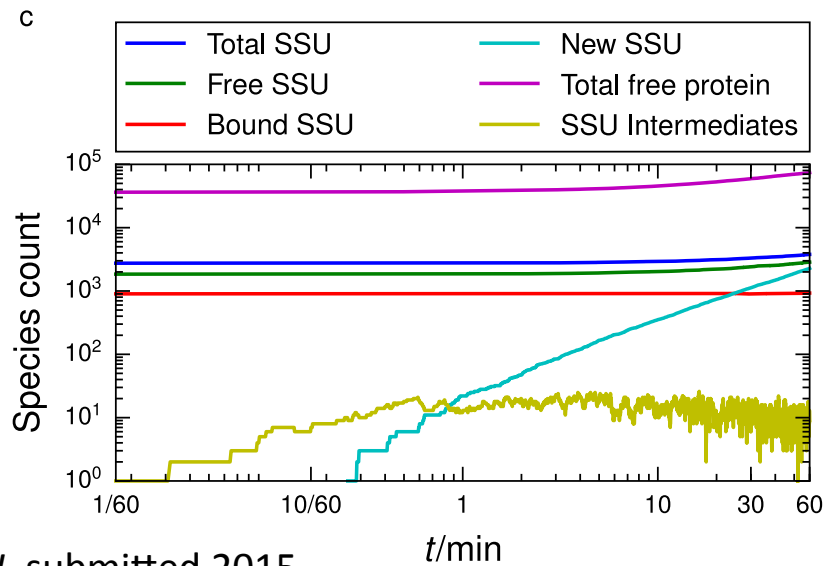
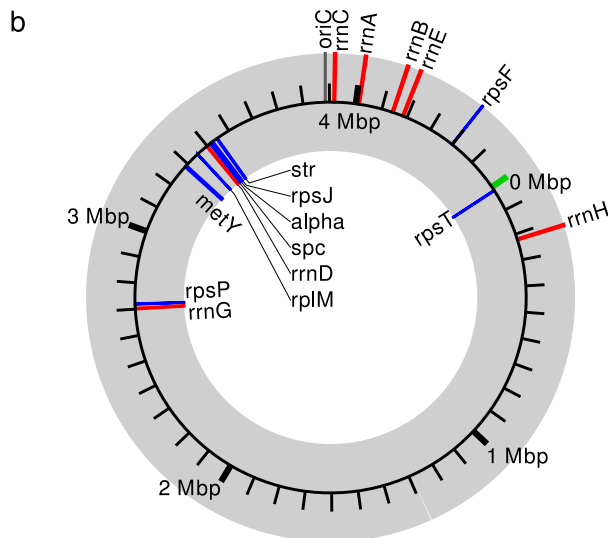
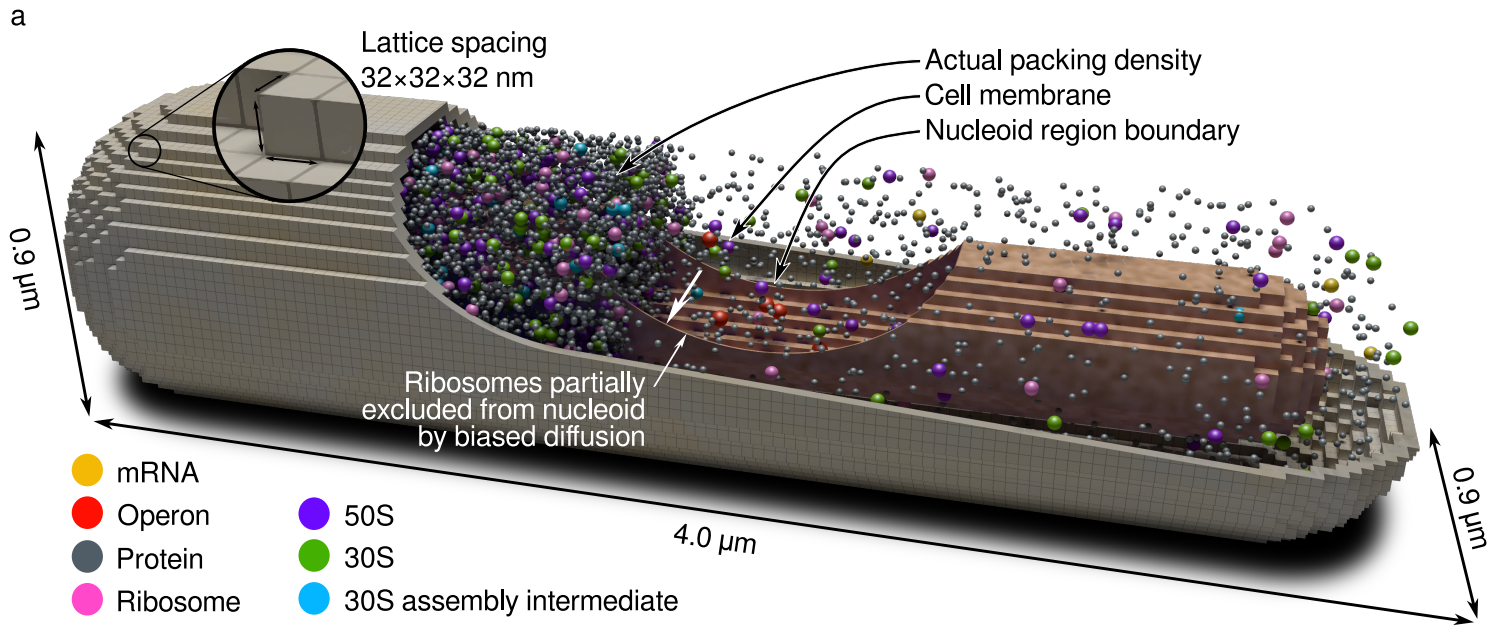


Earnest, Lai, Chen, Hallock, Williamson, Luthey-Schulten (submitted, 2015)

In vivo ribosome assembly on Blue Waters



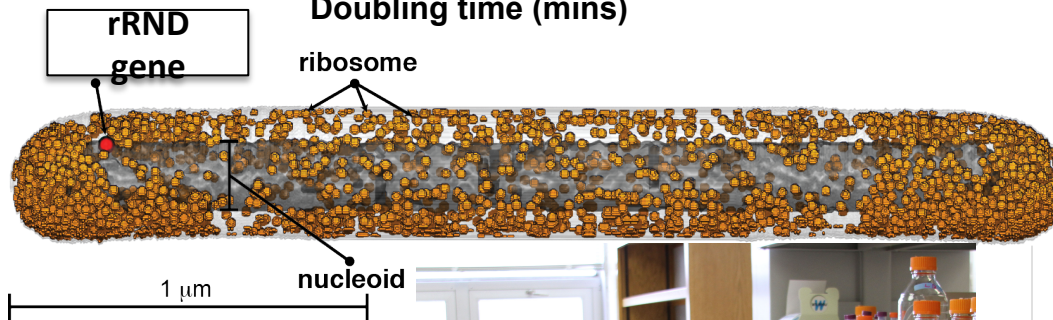
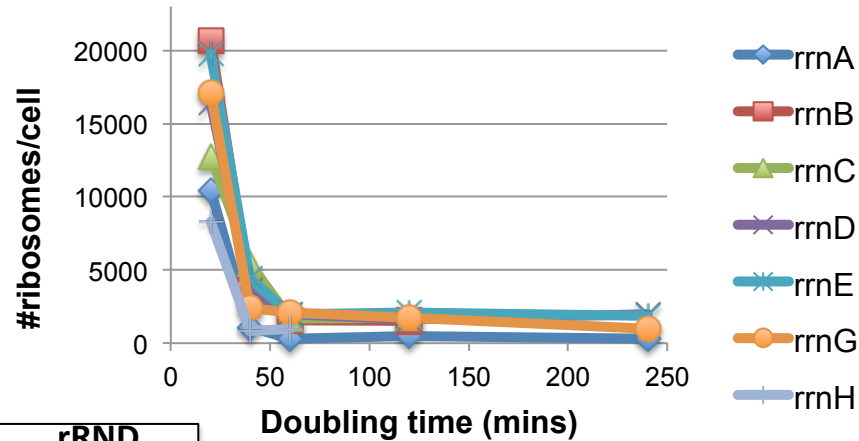
In silico Ribosome Biogenesis*



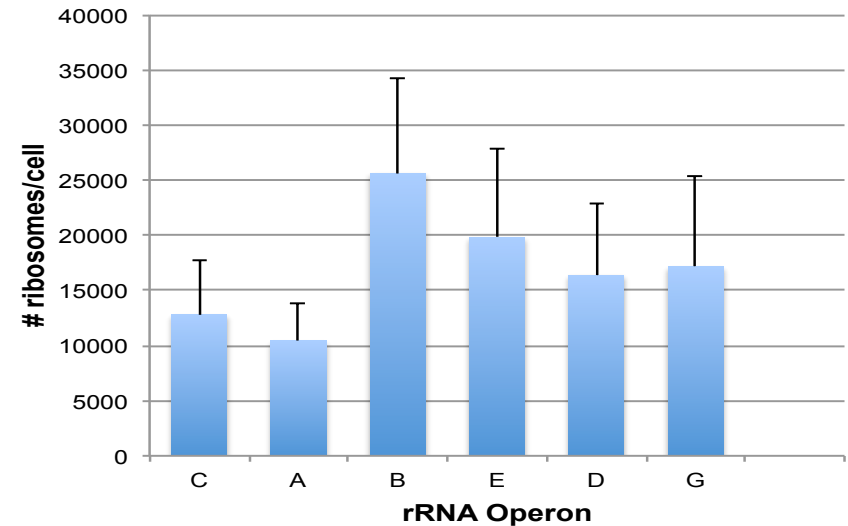
*Earnest, ..., Williamson, Luthey-Schulten. *Biophys. J.* submitted 2015

Experimental Data on Operon and Ribosome Distributions

Ribosome Distributions

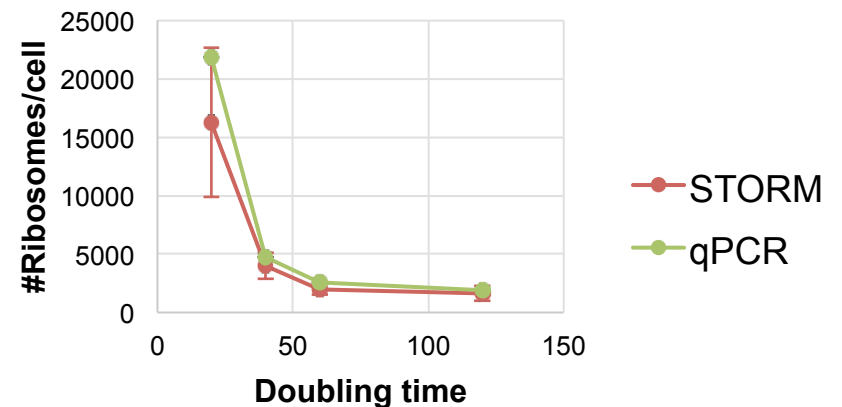


Expression levels in exp. growth

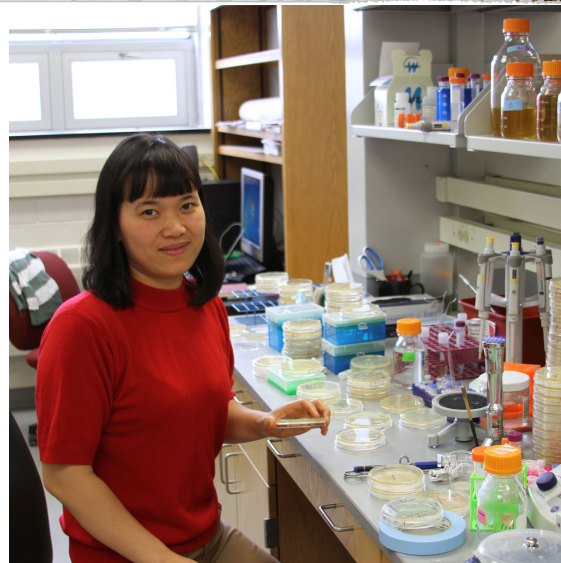


Distribution from CET in LM Simulations

Ribosomes from rrnD



Cac Nguyen
in
Kuhlman lab

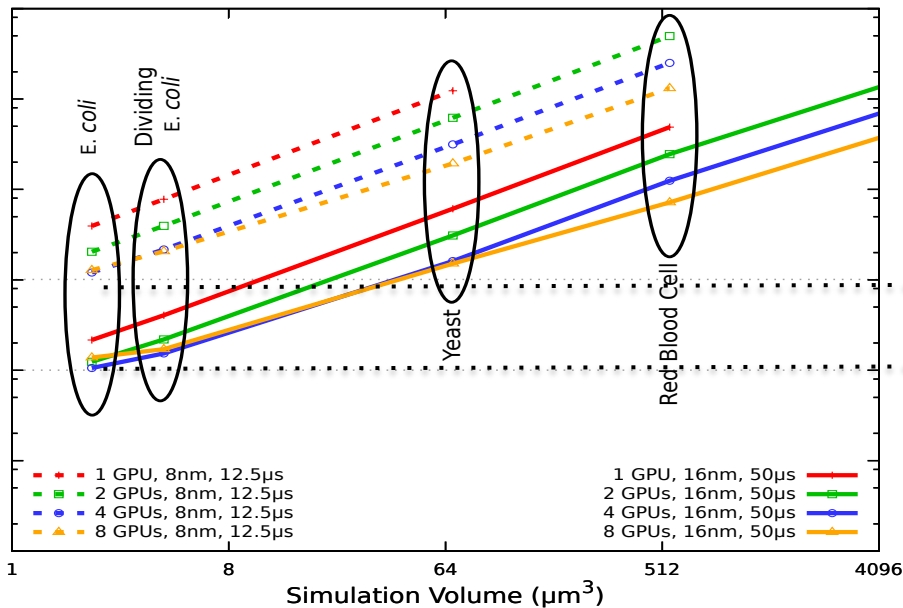


Improving Multi-GPU Performance

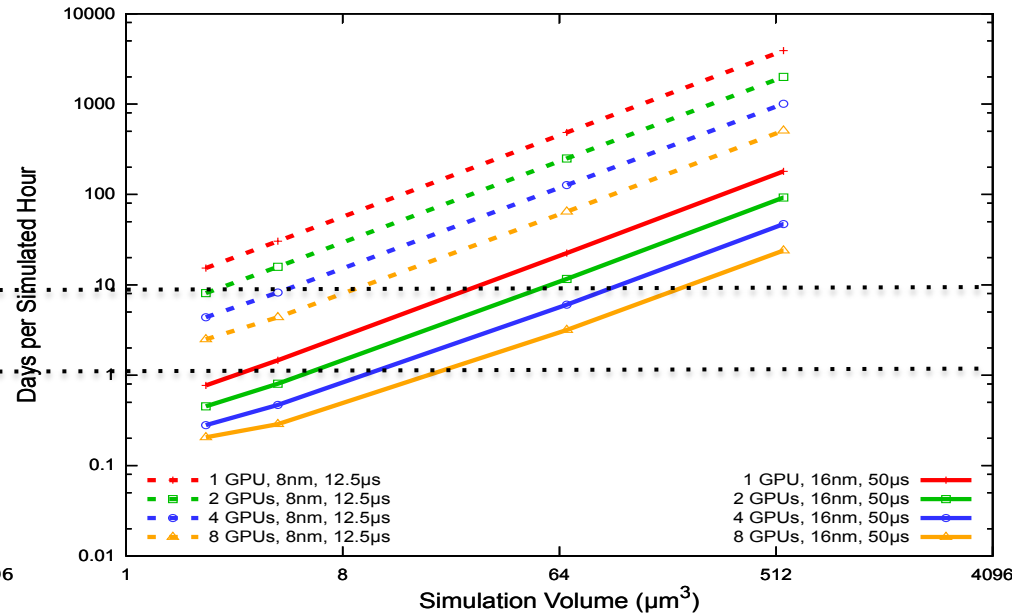
“Old” – January 2014 Hallock, et al. *Parallel Comp.*

New – Nov. 2014 *Supercomputing 2014*

Benchmark System Runtimes - NCSA Forge (Eight M2070s)

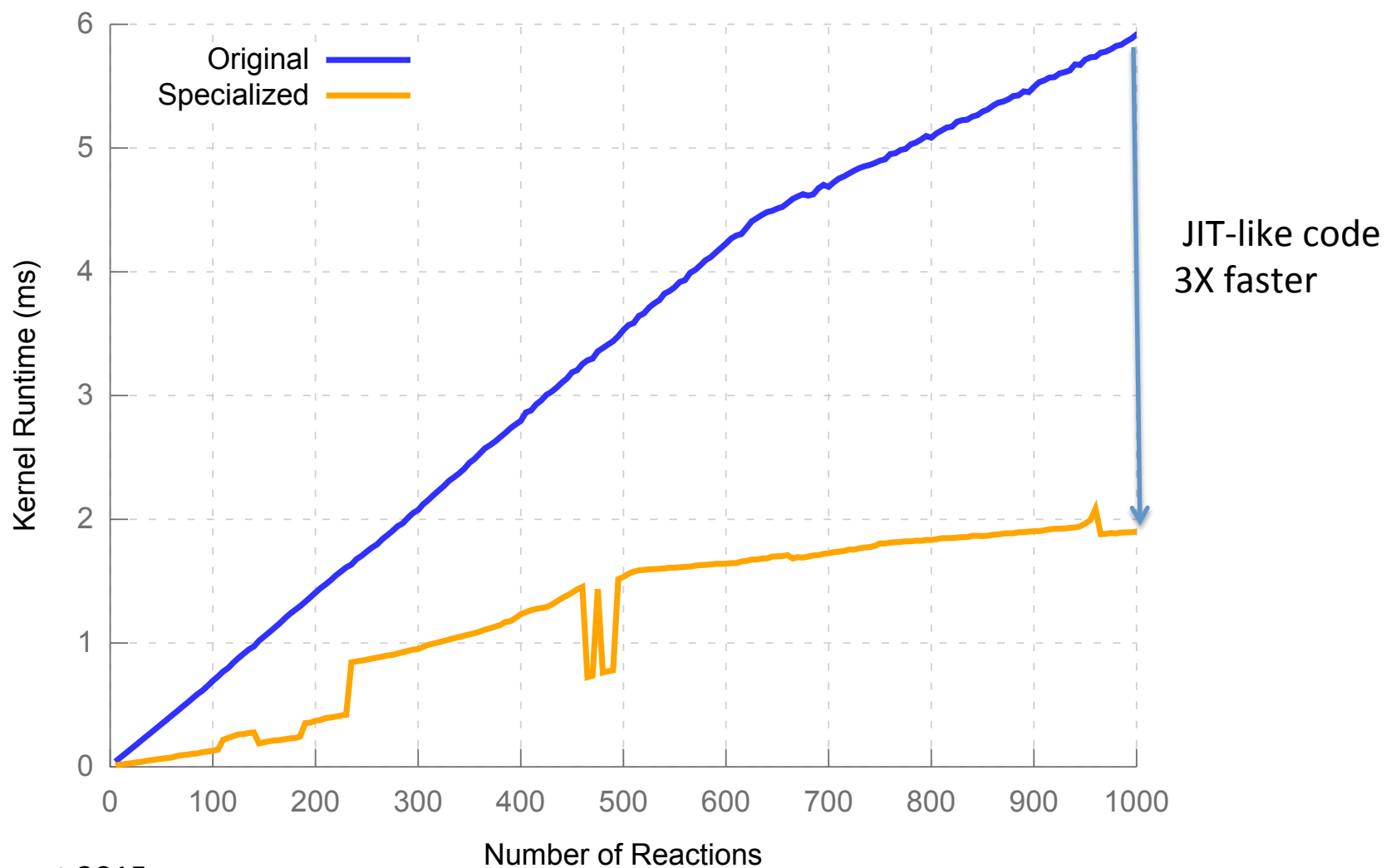


Benchmark System Runtimes - Cirrascale Eval (8x K40)



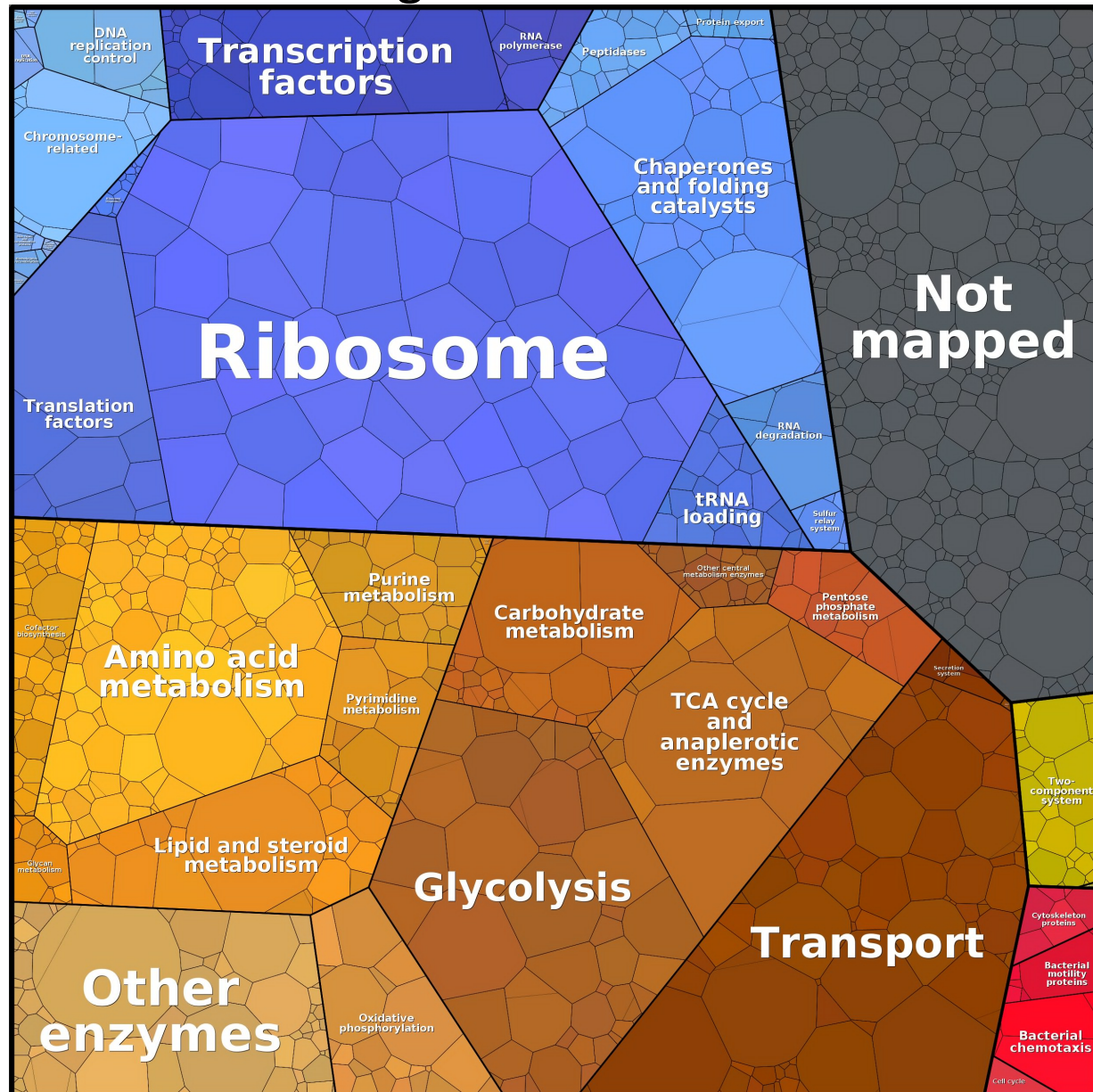
- Single GPU performance improved 2.5x – 3x from Fermi (2070) to Kepler (K40)
- Parallel efficiency improves for small simulations due to better host system topology and higher-performance inter-GPU communication
- Today -1 cell cycle simulation (~2 hours) of 1200 rxns, 255 species in ribosome biogenesis - 3 days with JIT code using GTX980 (Cuda 6.5) and 6 days (K20,Cuda 5x)

Reaction Kernel Code Generation Performance – 1200 Rxns, 255 species



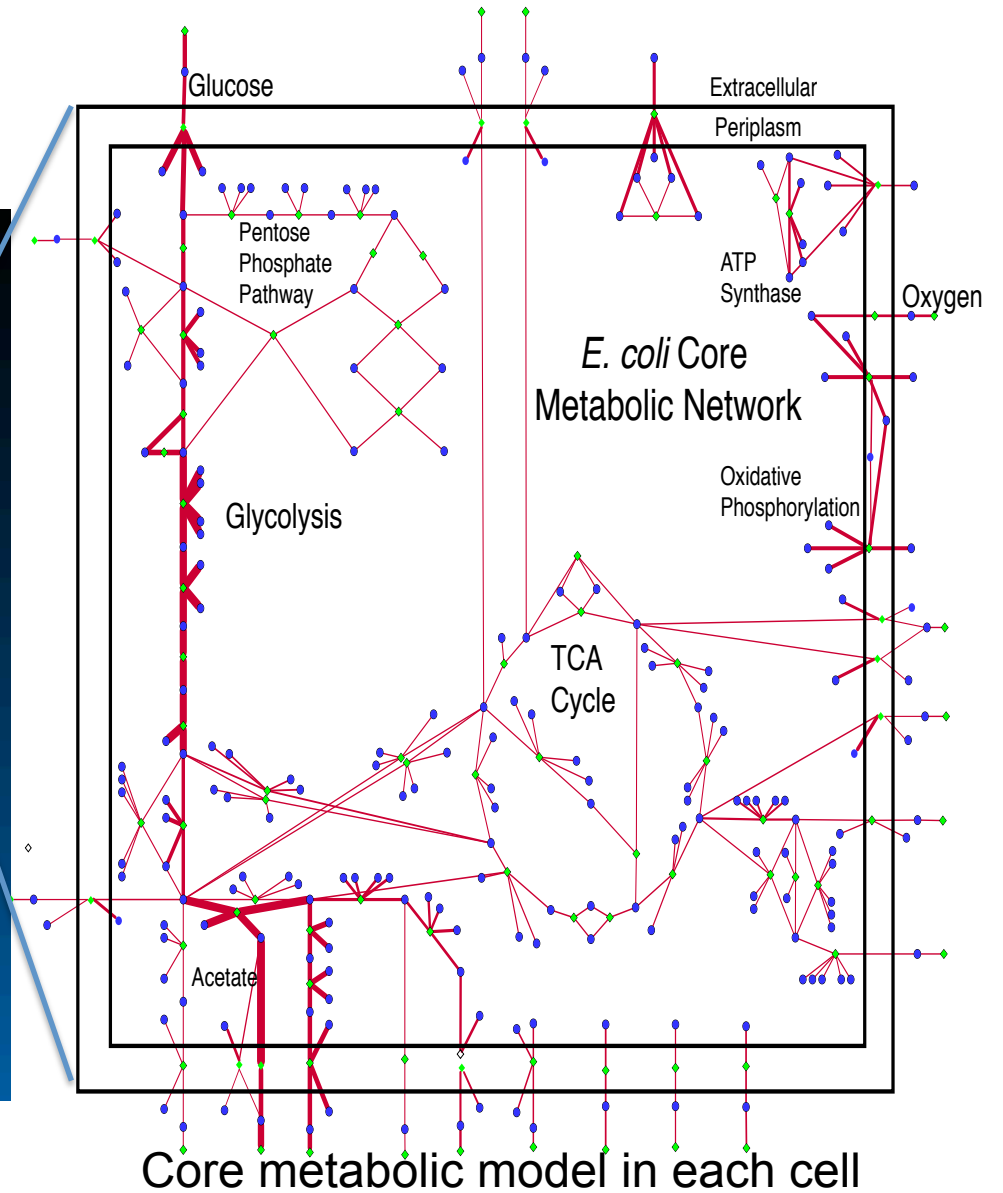
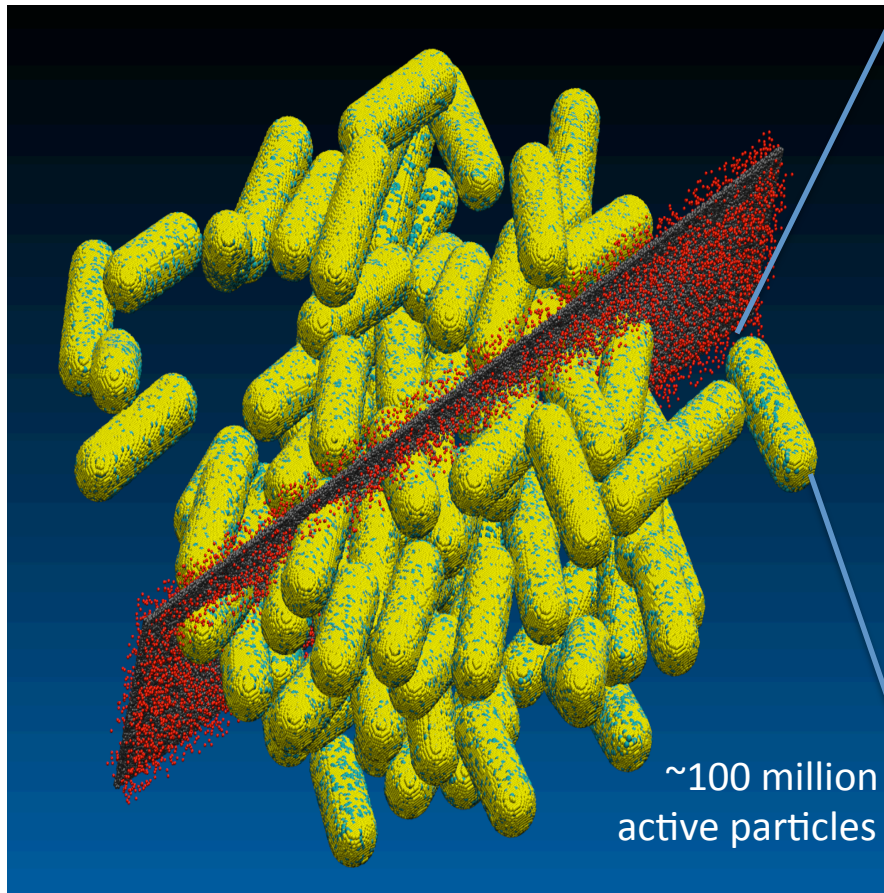
Future Goal: Reduced Models of All Cellular Networks

Big Data and HPC



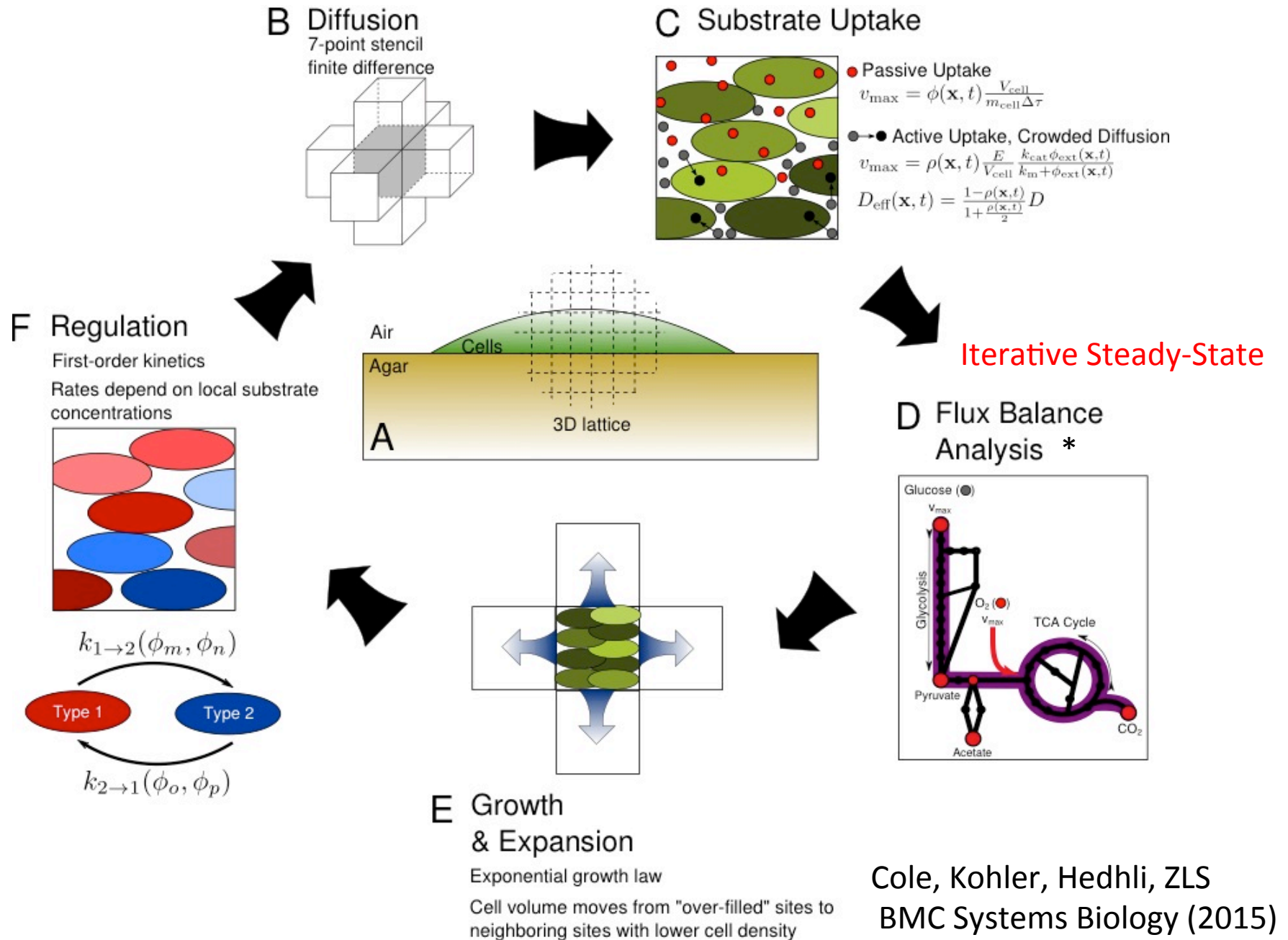
Competition for Resources in Bacterial Colonies

Hybrid RDME-Flux Balance Analysis
100 cells



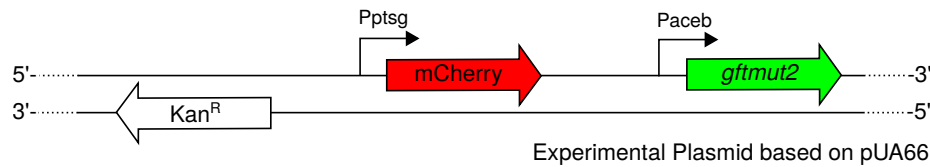
Cole,....., ZLS, in Computational Systems Biology,
2nd Edition (2014) - (Multi-GPU Keeneland)

3D Dynamical FBA Method (3DdFBA) for Cell Colonies

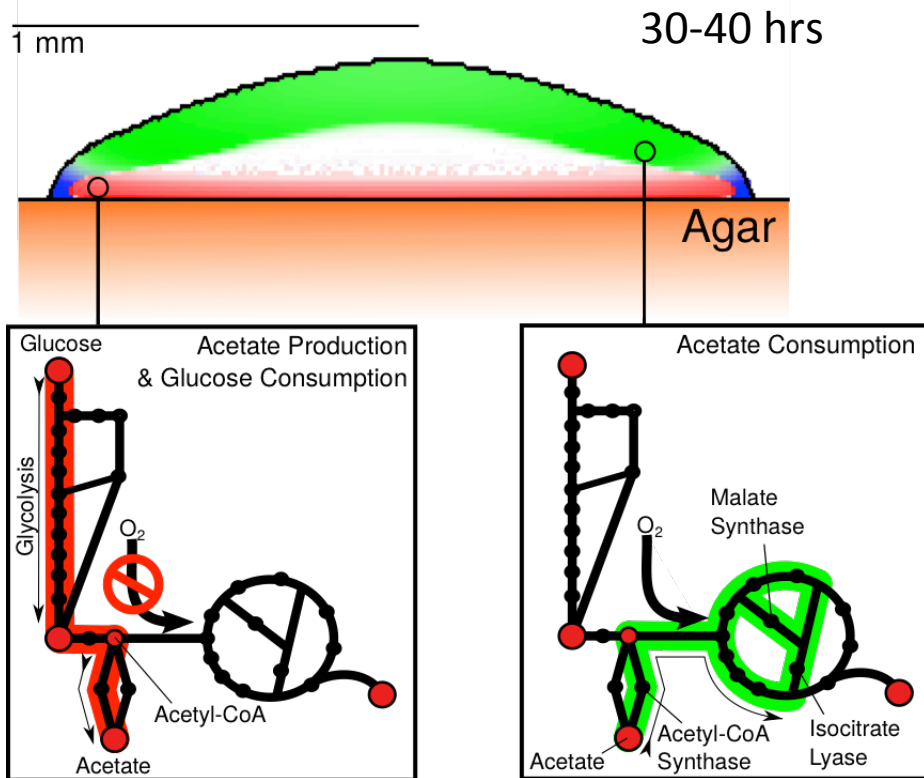


Cole, Kohler, Hedhli, ZLS
BMC Systems Biology (2015)

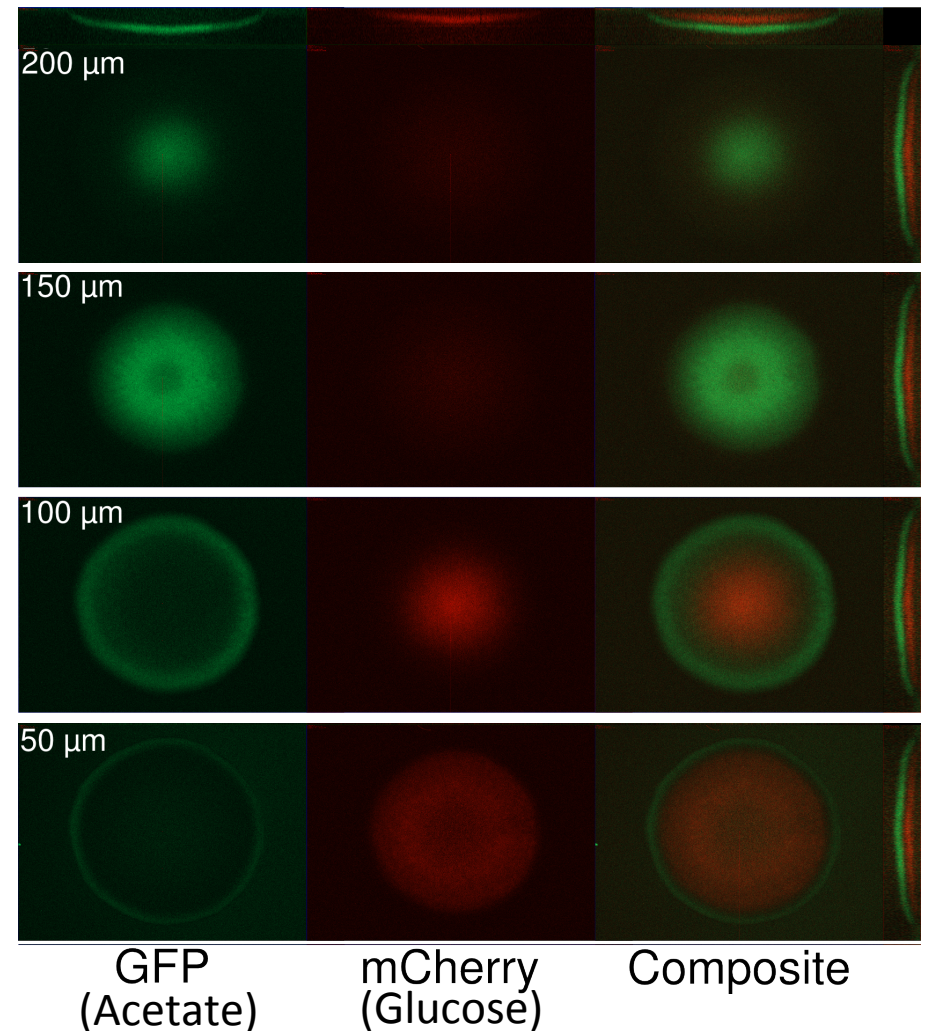
Substrate Gradients Drive Metabolic Differentiation



Predicted Metabolic Behavior



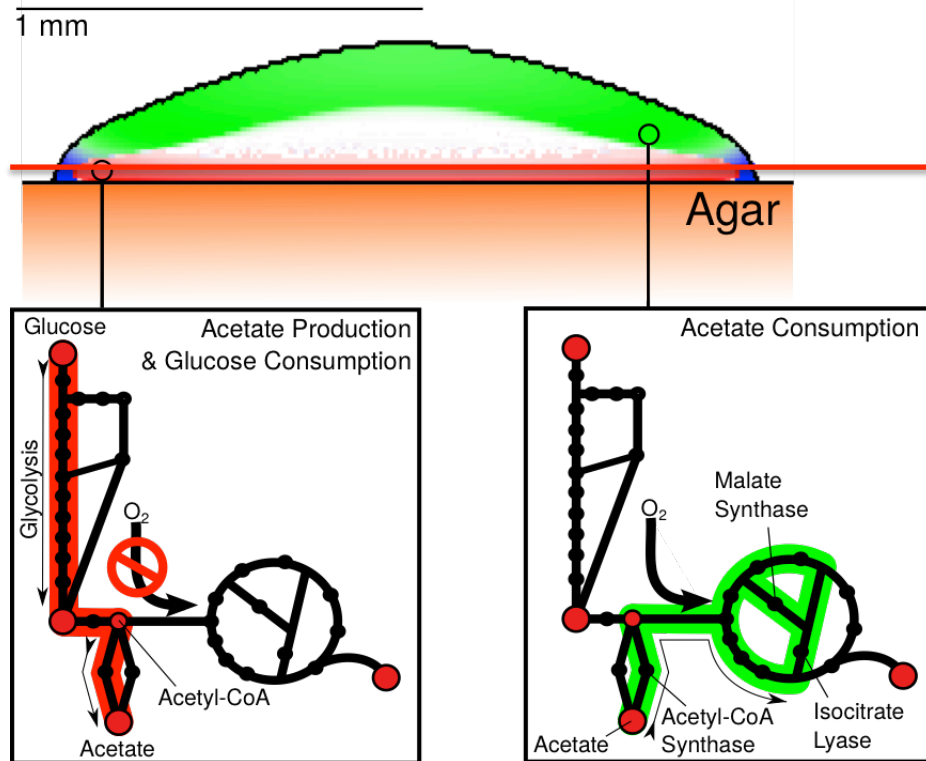
Experimental Metabolic Behavior



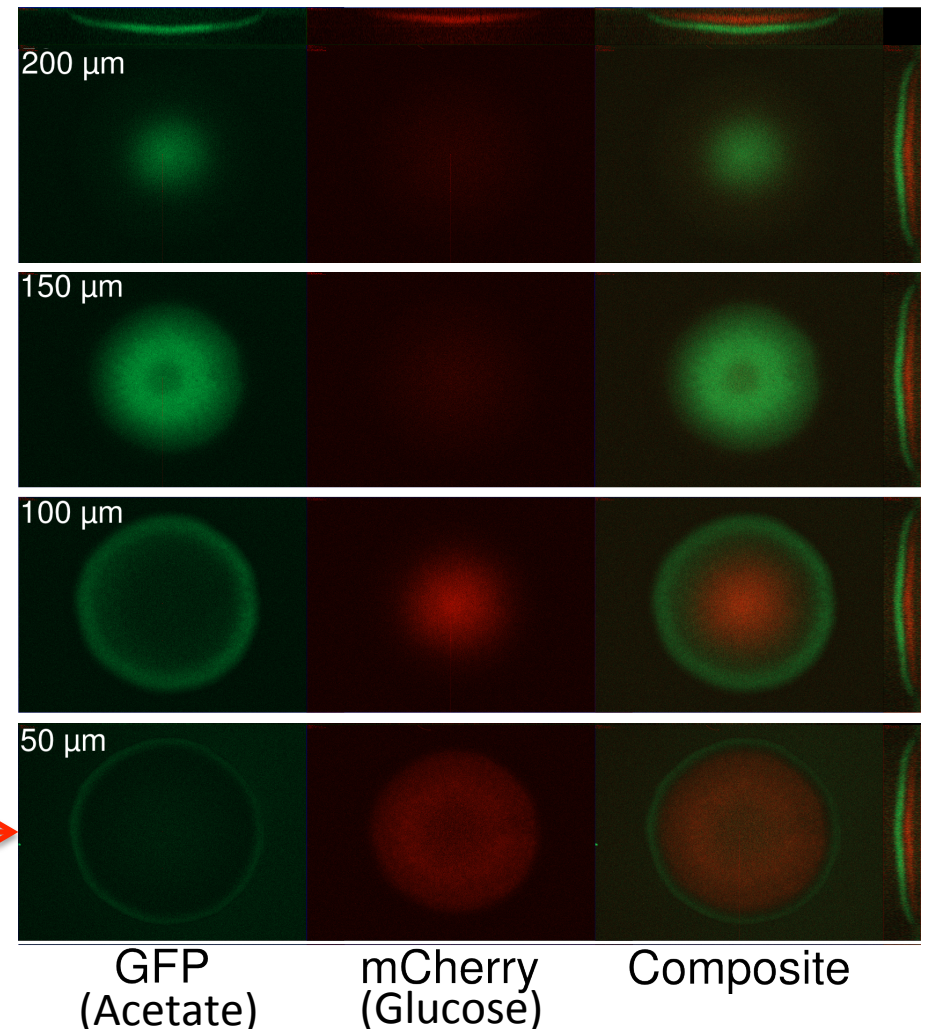
Substrate Gradients Drive Metabolic Differentiation

Optical Sectioning: Near base, oxygen-starved cells consume glucose and produce acetate

Predicted Metabolic Behavior



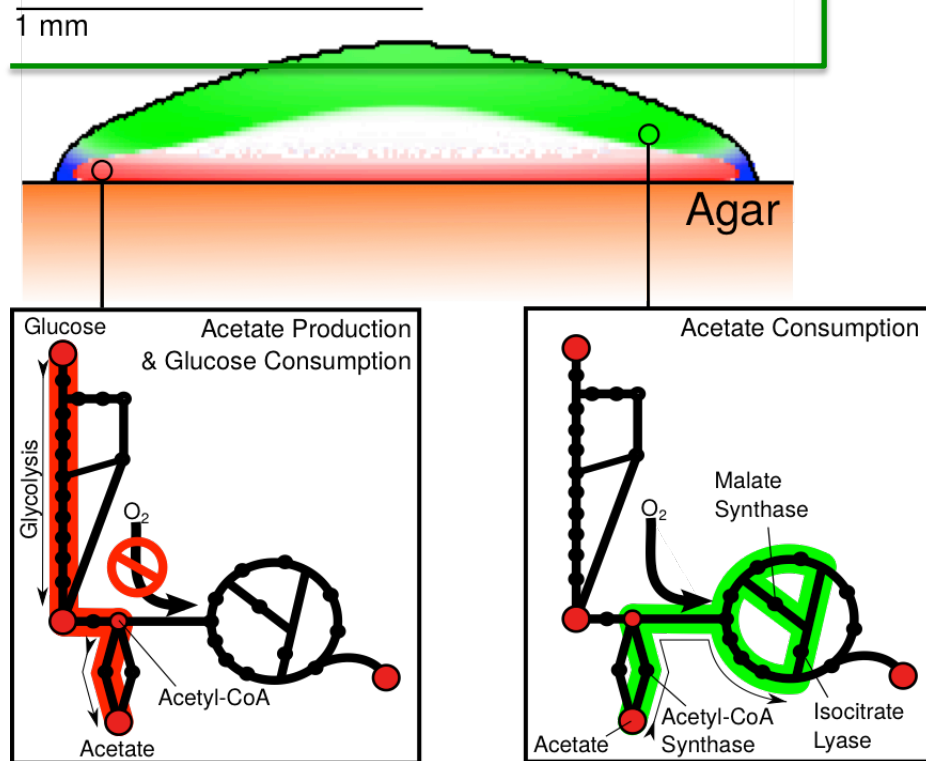
Experimental Metabolic Behavior



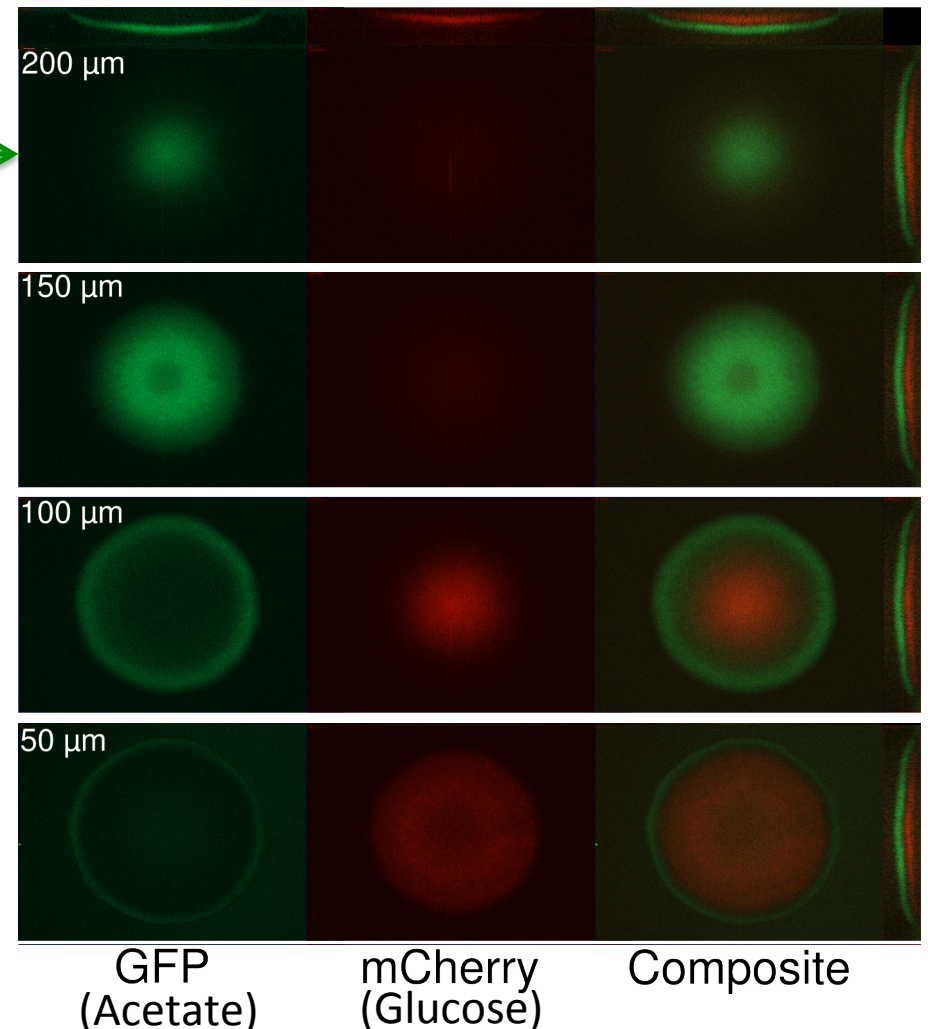
Substrate Gradients Drive Metabolic Differentiation

Near colony top, glucose-starved cells consume acetate. OS and side views confirm predictions.

Predicted Metabolic Behavior



Experimental Metabolic Behavior



Goal: RDME/FBA simulations of reduced networks for universal cellular processes

Variation Local Environment

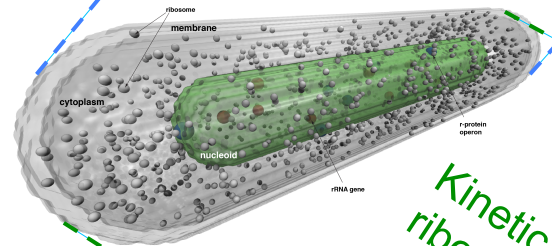


Networks: Signaling, Regulation, Metabolism, Translation



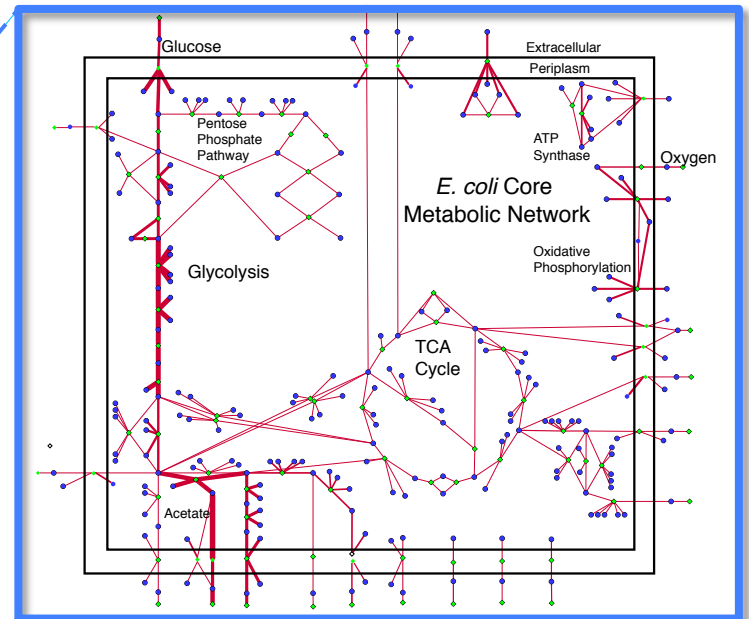
Cellular Responses

Growth? Secretion? Motility?



Kinetic ribosome biogenesis model

metabolic response calculated from FBA

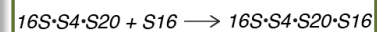
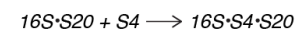
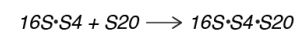
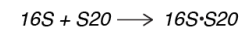
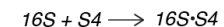


Other core cellular reactions

rRNA transcription

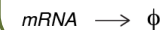
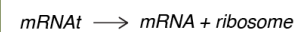
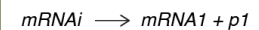
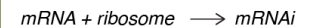


Ribosomal assembly

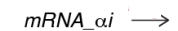
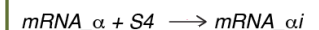


⋮

R-protein production



Regulation

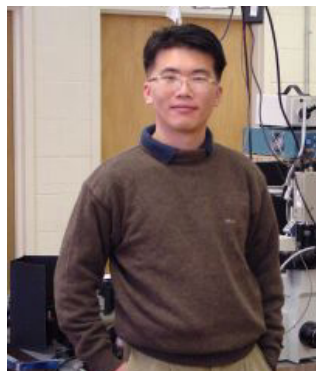


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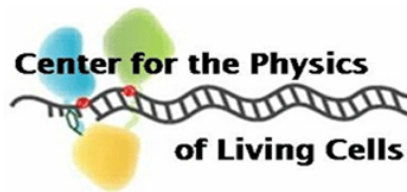
Tom Kuhlman,
M. Gruebele
Carl Woese 2012



Taekjip Ha, H. Kim
S. Woodson



Acknowledgments



NIH Center - Beckman Inst.
VMD, NAMD, LM

Max Planck Institute
FIB milling of cells

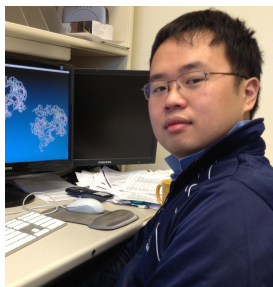
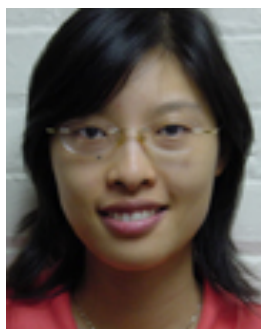


E. Villa UCSD

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Marcelo Melo

Joe Peterson,
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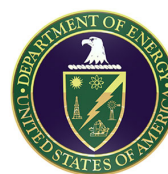
John Stone



P. Labhsetwar

John Cole

NCSA BW & XSEDE



Mike Hallock, Fry,