# DISCRETE STOCHASTIC SIMULATION OF SPATIALLY INHOMOGENEOUS BIOCHEMICAL SYSTEMS

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# Systems Biology In the News

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By SHARON BEGLEY

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FROM THE ARCHIVES: February 21, 2003

## Biologists' New Approach: Do Not Shoot the Radio

How would a team of biologists fix a radio? First, they'd secure a large grant to purchase hundreds of identical working radios. After describing and classifying scores of components (metal squares, shiny circles with three legs, etc.), they'd shoot the radios with .22s.

Examining the corpses, the biologists would pick out those that no longer work. They'd find one radio in which a .22 knocked out a wire and triumphantly declare they had discovered the Key Component (KC) whose presence is required for normal operation.

But a rival lab would discover a radio in which the .22 left the Key Component intact but demolished a completely different Crucial Part (CP), silencing the radio. Moreover, the rivals would demonstrate that the KC isn't so "key" after all; radios can work fine without it.

Finally, a brilliant post-doc would discover a switch whose position determines whether KC or CP is required for normal operation. But the biologists still can't fix the blasted radios.

For those of you who haven't looked inside a radio lately, the Key Component is the wire connecting the external (FM) antenna to the innards of the radio, the Crucial Part is the internal (AM) antenna and the switch is the AM/FM switch.

Biologists can't repair radios because their part-by-part approach fails to describe the radio as a system -- what's connected to what and how one part affects another.

Biologists' affinity for the one-part-at-a-time approach, argues biologist Yuri Lazebnik of Cold Spring Harbor Laboratory on New York's Long Island, who dreamed up the radio analogy, is "a flaw of biological research today."

For that, thank the events of 50 years ago.

On Feb. 28, 1953, a Saturday, James Watson spent the morning at his Cambridge, England, lab piecing together cardboard representations of the "base pairs" in the DNA molecule. With that, he and Francis Crick realized that the master molecule of heredity is shaped like a spiral staircase, or double helix.

This discovery ushered in the era of the gene and gave birth to a new field: molecular biology. The study of living things became a science in which progress meant describing the smallest bits possible, usually one at a time -- one stretch of DNA, one RNA, one protein. The double helix, Harvard University naturalist E.O. Wilson once said, "injected into all of biology a new faith in reductionism" -- a "shoot the radio" approach.

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**Harvard Medical School Launches New Department to Study Human Biology at the Level of Whole Systems**

***The Department of Systems Biology will seek to understand the causes of diseases at the level of cells and organ systems, and identify new approaches for treatment***

BOSTON-September 23, 2003-Harvard Medical School today makes a significant commitment to the emerging field of systems biology in announcing the creation of the Department of Systems Biology (DSB), one of the first department-level systems biology programs in the nation. Systems Biology seeks to build from our current knowledge of genetic and molecular function to an understanding of how a whole cell works as a system and from there to multi-cellular systems such as organs and whole animals. The Department of Systems Biology will be Harvard Medical School's first completely new department in more than two decades

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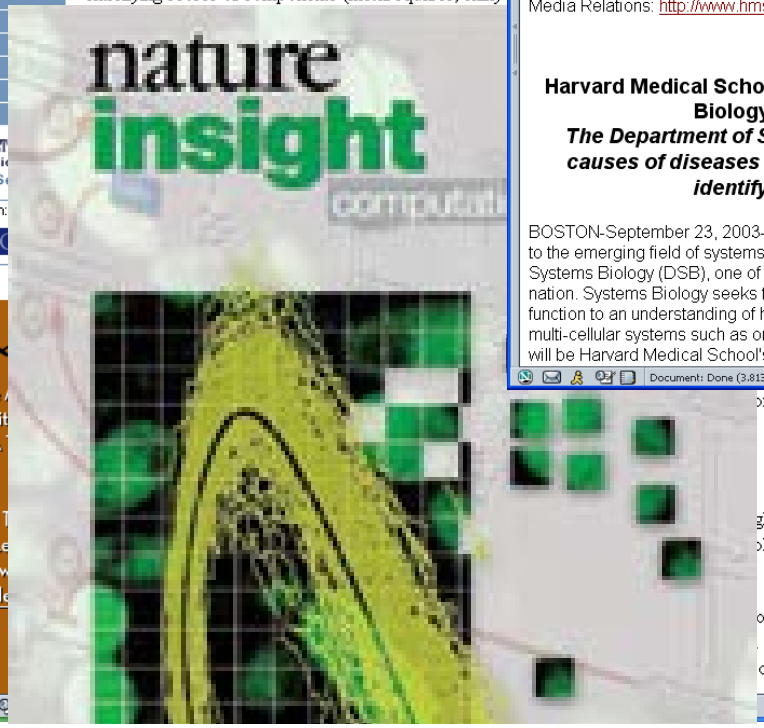



# What is "Systems Biology"?

**[WTEC Benchmark Study (2005): M. Cassman, A. Arkin, F. Doyle, F. Katagiri, D. Lauffenburger, C. Stokes]**

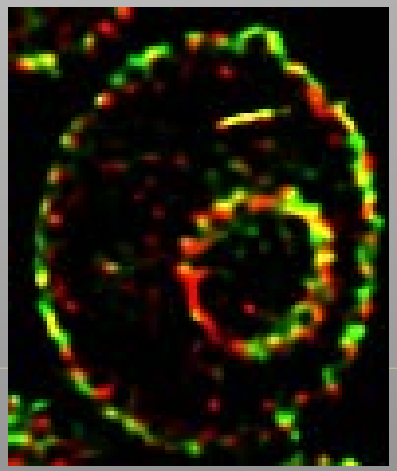
Definition: The understanding of biological network behavior through the application of modeling and simulation, tightly linked to experiment

# Why Discrete Stochastic Simulation?

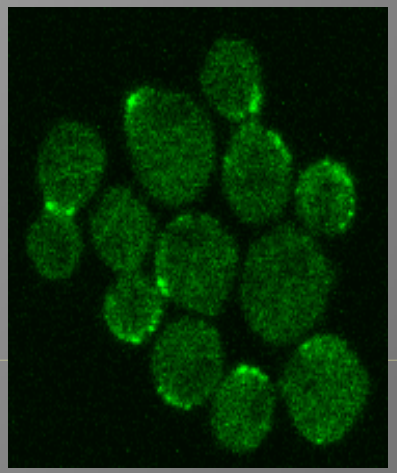
- An ODE model cannot capture effects due to small numbers of key chemical species
- A molecular dynamics model is too slow given the model complexities and time scales of interest

# Why Spatially Inhomogeneous?

*Unfolded protein response in the endoplasmic reticulum – C. Young, A. Robinson, U. Delaware*



*Polarization in yeast mating – T. M. Yi, UC Irvine*



# Outline

## Discrete stochastic simulation for well-mixed systems

- Chemical master equation
- Stochastic simulation algorithm (SSA)
- Accelerated methods
  - Tau-leaping
  - Hybrid
  - Slow-scale SSA
  - Finite state projection (FSP)

## Discrete stochastic simulation for spatially inhomogeneous systems

- Inhomogeneous SSA (ISSA)
- Fundamental issues
- Accelerated methods
- Complicated geometries

# Discrete Stochastic Simulation

- Well-stirred mixture
- N molecular species $S_1,\ldots S_N$
- Constant temperature, fixed volume $\Omega$
- M reaction channels $R_1,\ldots R_M$
- Dynamical state $X(t) = (X_1(t),\ldots,X_N(t))$ where $X_i(t)$ is the number of $S_i$ molecules in the system

# Stochastic Simulation Algorithm

*Gillespie, 1976*

- Propensity function $a_j(x)dt =$ the probability, given $X(t) = X$ that one $R_j$ reaction will occur somewhere inside $\Omega$ in the next infinitesimal time interval $[t, t + dt]$
- When that reaction occurs, it changes the state. The amount by which $X_i$ changes is given by $\upsilon_{ij} =$ the change in the number of $S_i$ molecules produced by one $R_j$ reaction
- $X(t)$ is a jump Markov process

# Stochastic Simulation Algorithm

- Draw two independent samples $r_1$ and $r_2$ from $U(0,1)$

  and take $\tau = \frac{1}{a_0(X)} ln\left(\frac{1}{r_1}\right)$

  $j =$ the smallest integer satisfying $\sum_{j'=1}^{j} a_{j'}(x) > r_2 a_0(x)$

- Update X $X \leftarrow X + \upsilon_j$

Fast Formulations of SSA: Next Reaction method (Gibson & Bruck, 2000), Optimized Direct Method (Li & Petzold, 2004), Sorting Direct Method (McCollumna et al., 2004), Logarithmic Direct Method (Li & Petzold, 2006), Constant Time Method (Slepoy et al., 2008), SSA on GPU (Li & Petzold, 2009), Next Subvolume Method for ISSA (Elf & Ehrenberg, 2004)

# Tau-leaping

*Gillespie, 2001*

- Given a subinterval of length $\tau$, if we could determine how many times each reaction channel fired in each subinterval, we could forego knowing the precise instants at which the firings took place. Thus we could leap from one subinterval to the next.
- How long can that subinterval be? Tau-leaping is exact for constant propensity functions, thus $\tau$ is selected so that no propensity function changes 'appreciably.'
- Current implementations:
  - Adaptive stepsize
  - Non-negativity preserving
  - Reverts to SSA when necessary

$$x_{n+1} = x_n + \nu P(a(x), \tau)$$

where

$P(a,\tau)$ Poisson variable with parameters $a$ and $\tau$

# Hybrid Methods and Slow-Scale SSA

**Hybrid methods** *Haseltine & Rawlings, 2002; Mattheyses, Kiehl & Simmons, 2002; Puchalka & Kierzek, 2004; Salis & Kaznessis, 2005; Rossinelli, Bayati & Koumatsakos, 2008 (ISSA)*

- Slow reactions involving species present in small numbers are simulated by SSA
- Reactions where all constituents present with large populations are simulated by reaction-rate equations

Cannot efficiently handle fast reactions involving species present in small numbers

**Slow-Scale SSA (ssSSA)** *Cao, Petzold & Gillespie, 2004*

- Fast reactions, even those involving species present in very small numbers, can be treated with the stochastic partial equilibrium approximation (slow-scale SSA)

# Chemical Master Equation

- The CME describes the evolution of the probability density vector (PDV) for the system:

$$\frac{\partial P\left(x,t|x_0,t_0\right)}{\partial t} = \sum_{j=1}^{M} \left[a_j(x-\nu_j)P(x-\nu_j,t|x_0,t_0) - a_j(x)P(x,t|x_0,t_0)\right]$$

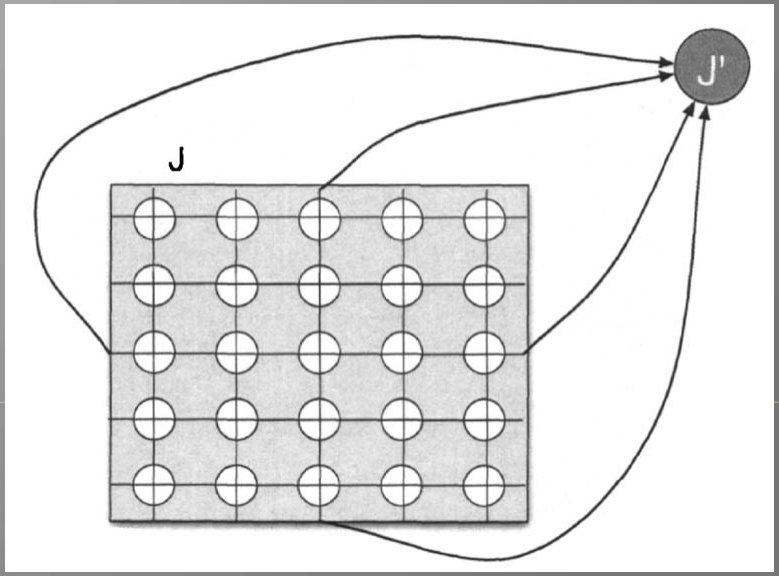
# Finite State Projection Method

*Khammash & Munsky, 2006*

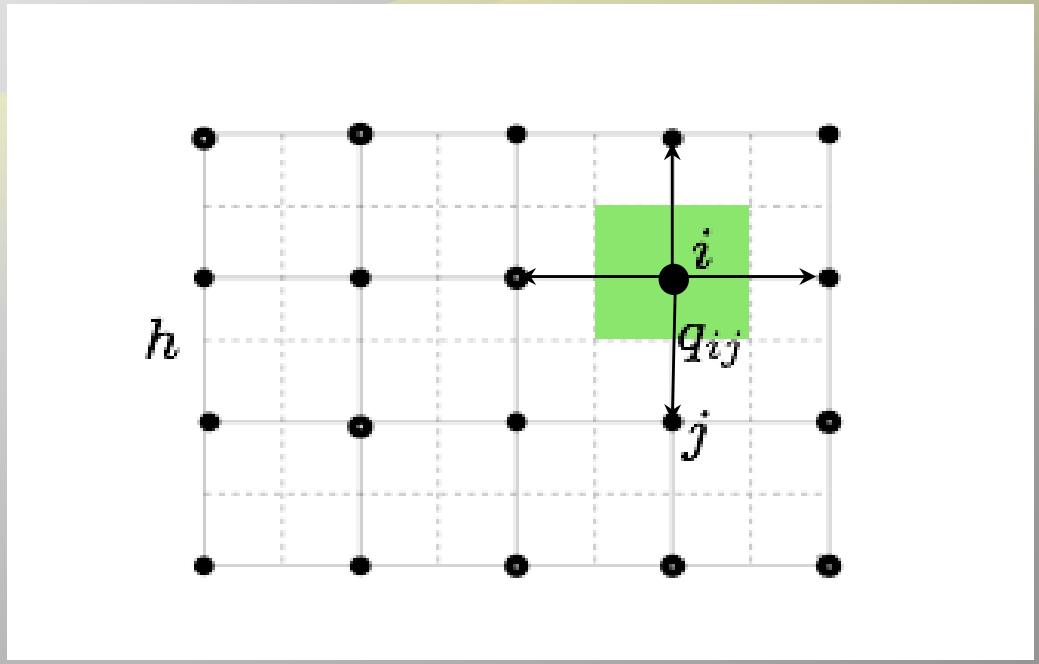
- The CME is a large (possibly infinite) linear ODE.

$$\dot{P} = A\,P(t) \Rightarrow P(t) = \exp(At)P(0)$$

- Use a truncated state space with an absorbing state.
- Solve directly.
- Absorbing state provides bound on the error.



# Inhomogeneous SSA (ISSA)




- Introduce a discretization of the domain into subvolumes (voxels) and assume that the well-stirred assumption is fulfilled within each subvolume (green). Diffusion is introduced as jumps from one subvolume to adjacent subvolumes.
- Cartesian, uniform mesh: $q_{ij} = \frac{\gamma}{h^2}$ $\qquad X_i \xrightarrow{q_{ij}} X_j$

# Reaction-Diffusion Master Equation (RDME)

$$\frac{\partial p(\mathbf{x},t)}{\partial t} = (\mathcal{M} + \mathcal{D})p(\mathbf{x},t)$$

- Reaction part and diffusion part. The diffusion operator is given by influx and outflux of probability for each subvolume in the mesh (just as in the case for reactions).

- With q as on the previous slide and a uniform Cartesian mesh, we get convergence in mean to the solution of the macroscopic diffusion equation in the limit h -> 0. (Compare the 5-point stencil, finite difference method).

# Fundamental Issues and Complications

- The limit h -> 0 is not attainable for physical reasons. Condition on the mesh parameter h:

$$\rho_R << h^2 << \alpha\gamma\tau_{min}$$

Elf & Ehrenberg, 2004

For reaction-diffusion systems, for small enough h, molecules never react!

Isaacson, 2009

Theory and proposed improvement on algorithm

Erban & Chapman, 2009

- Propensities vary with molecular crowding, roughly as a function of the size of the molecules

Lampoudi, Gillespie, Petzold, 2007, 2009

Ellis, 2001; Despa, 2009

# Simulation of Diffusion

**Huge computational complexity necessitates consideration of high performance computer architectures. However, large numbers of fast diffusive transfers puts severe limitation on speedup.**

- Multinomial Simulation Algorithm (MSA) *(Lampoudi, Gillespie, Petzold, 2008)*
  - Tau-leaping specifically adapted to diffusion: the propensities for diffusive transfers are conditional -> conservative

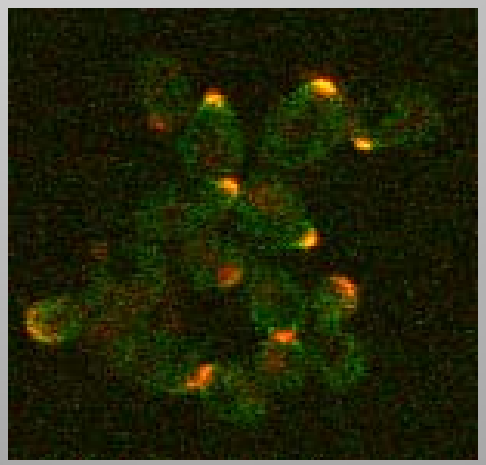
- Diffusion FSP (DFSP) *(Drawert, Lawson, Khammash, Petzold, 2009)*
  - Diffusion of molecules originating in one voxel is independent of diffusion of molecules originating in all other voxels

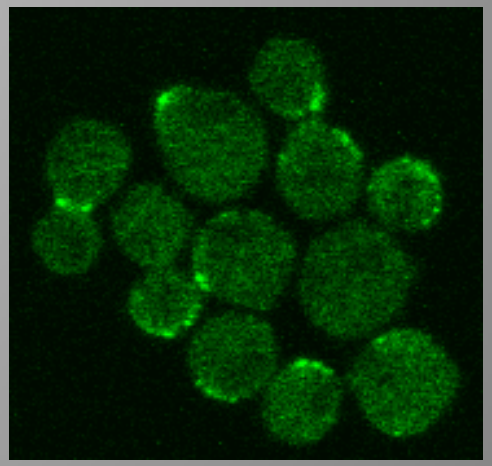
# Diffusion FSP Algorithm

- Use truncated state space ( $A_j$ )
- Solve: $\dot{P}_j = A_j P_j(t) \Rightarrow P_j(t) = \exp(A_j t) P_j(0)$
- Note: $P_j(0) = [1, 0, 0...]^T \Rightarrow P_j(t) = \text{First column of } \{\exp(A_j t)\}$
- Pick a random number against the PDV
- Distribute molecules according to the selected state

# Cell Polarization in Yeast Mating

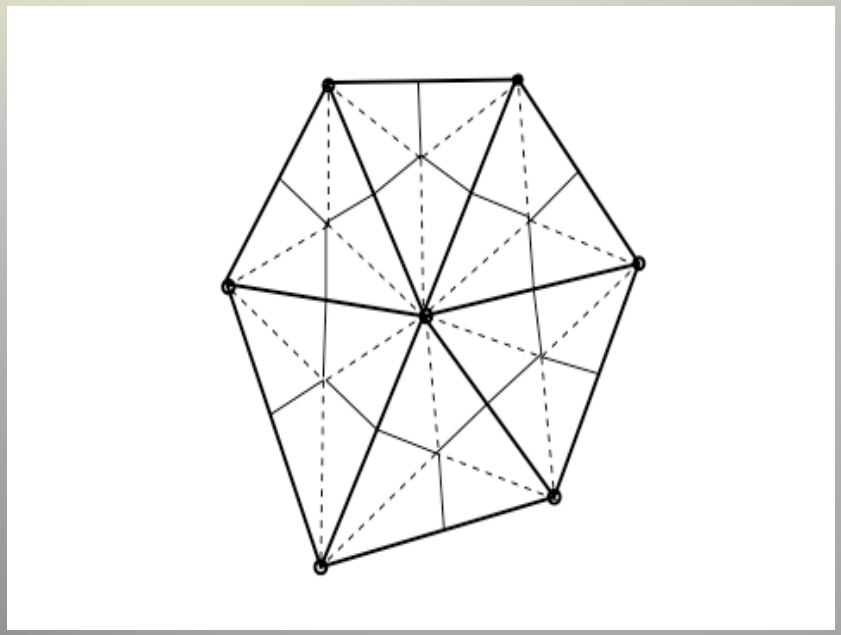
- Well mixed assumption is violated by definition!





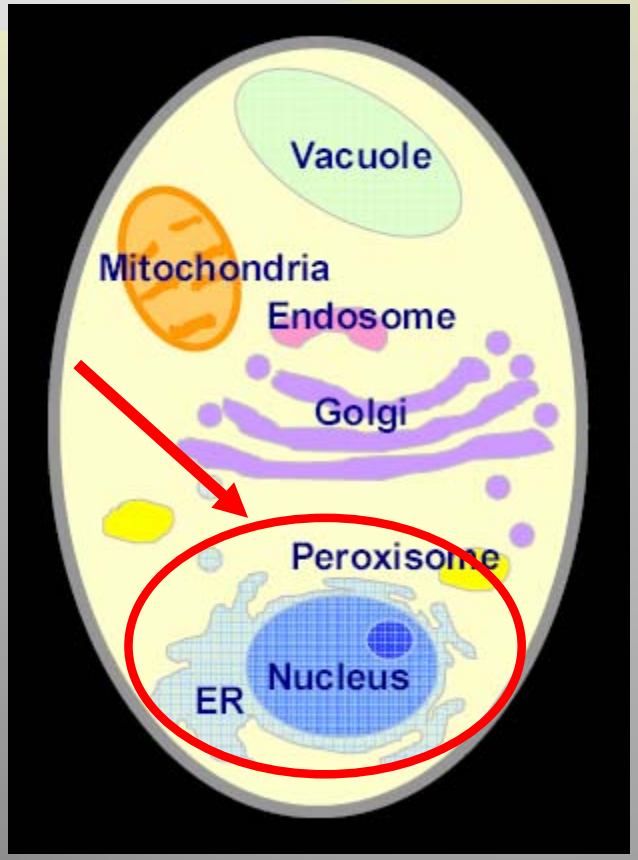
•Tau-Mu Yi, UC Irvine

# Complicated Geometries and Unstructured Meshes

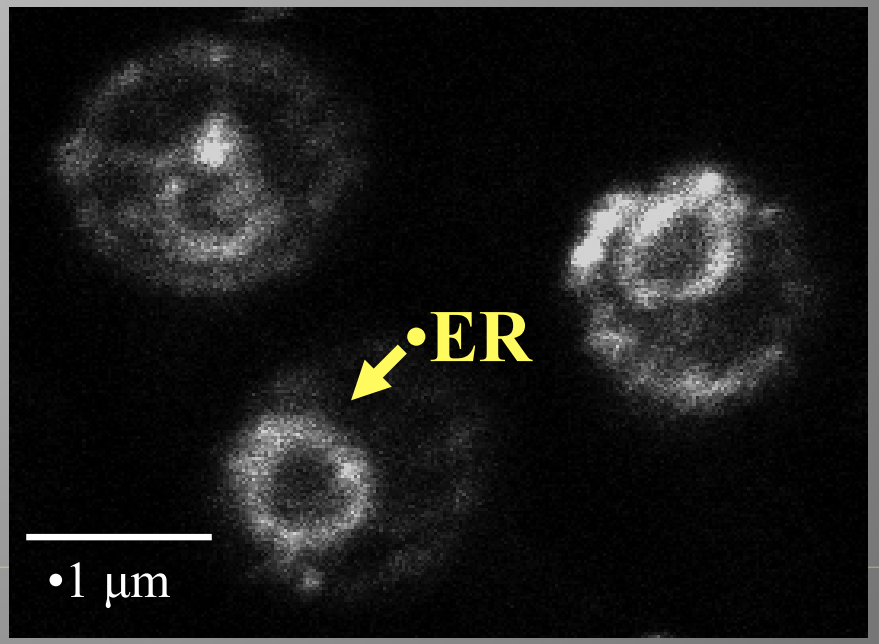


- Early work on complicated geometries (Isaacson & Peskin, 2006)
- Unstructured meshes and complicated geometries (Engblom, Ferm, Hellander, Lotstedt, 2009
  - Well-stirred assumption in the subvolumes is determined by the dual of the Delauny triangulation (Voronoi cells)
  - Adaptive hybrid method, reactions by operator splitting (Ferm, Hellander, Lotstedt, 2009)
  - URDME software built on top of COMSOL Multiphysics
  - Currently limited in ability to handle stochastic stiffness

# Protein Interactions in the Endoplasmic Reticulum (ER)



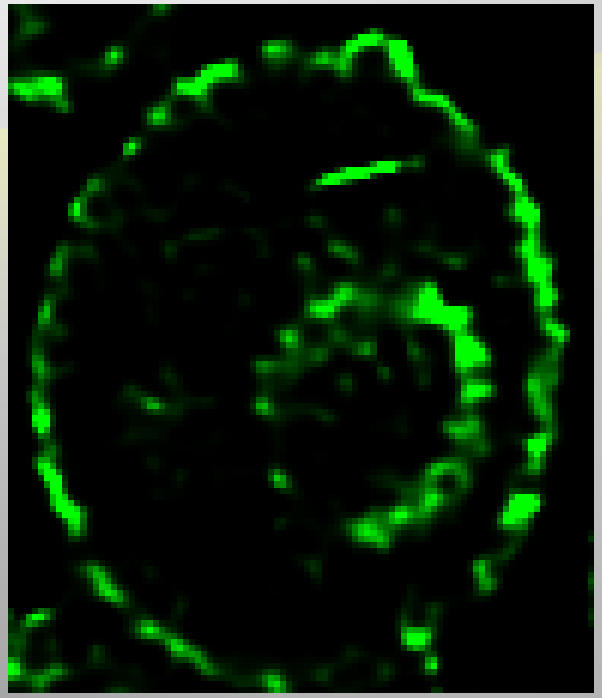

- Organelle surrounding nucleus
  - -Lumen (interior) and
  - -Large irregular membrane surface



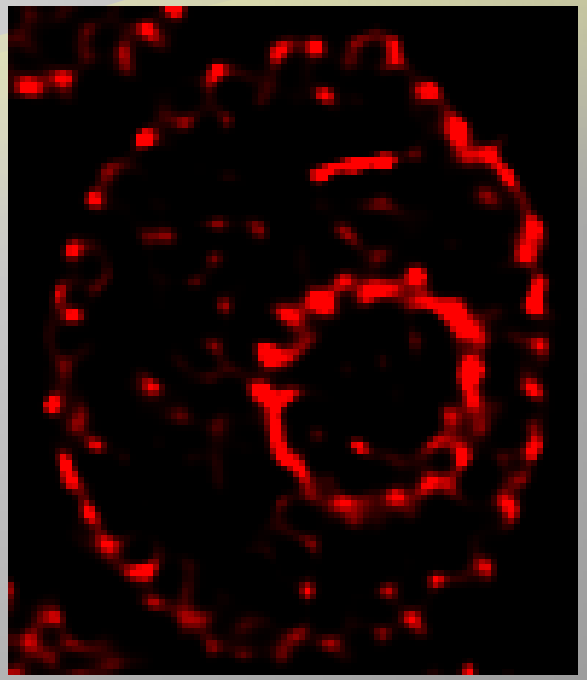

- "Gatekeeper" for proteins

Carissa Young, University of Delaware

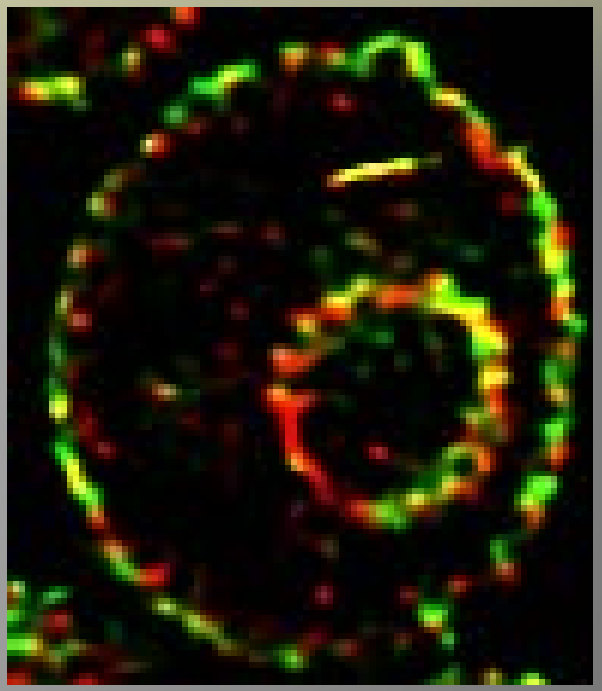
# Experimental Evidence for Spatial Localization



•BiP-Venus



•Sec63-Cerulean

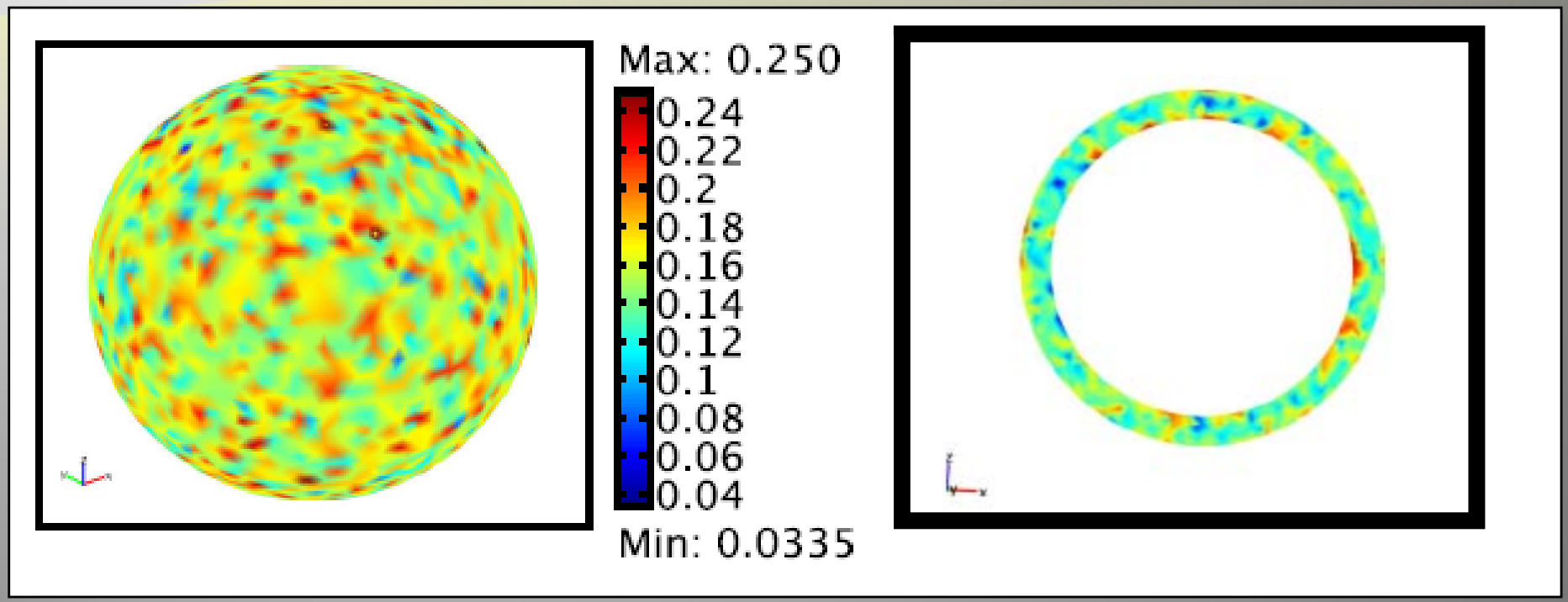


•Merged Image

*S. cerevisiae* BJ5464 cells expressing fusion proteins BiP and Sec63 with various GFP variants. Images captured on Zeiss 5LIVE confocal microscope, Plan Apochromat 63x/ NA 1.40.

Carissa Young, University of Delaware

**Initial simulations of the spatial stochastic model produced variation in spatial concentrations due to stochastic fluctuations on both the membrane and the lumen, even though initial conditions were homogeneous.**




**Concentration profile of total BiP on the ER membrane (left) and lumen (right) at simulation time t=5s**

**Currently investigating effects of highly irregular ER geometry**

Collaborators: Dan Gillespie, Frank Doyle, Anne Robinson, Mustafa Khammash, Tau-Mu Yi, Per Lotstedt, Andreas Hellander

Students: Min Roh, Marc Griesemer, Kevin Sanft, Brian Drawert, Michael Lawson

Former Students and Postdocs: Yang Cao, Muruhan Rathinam, Hong Li, Teri Lampoudi

Thanks!

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