Stochastic multi-scale models of biomolecular networks

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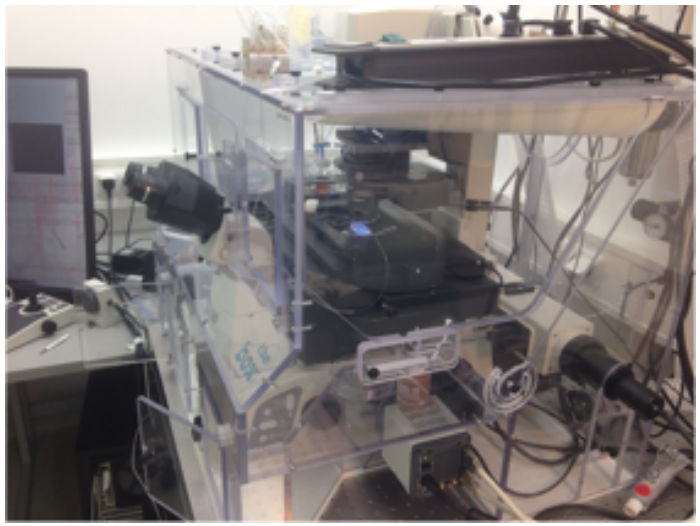
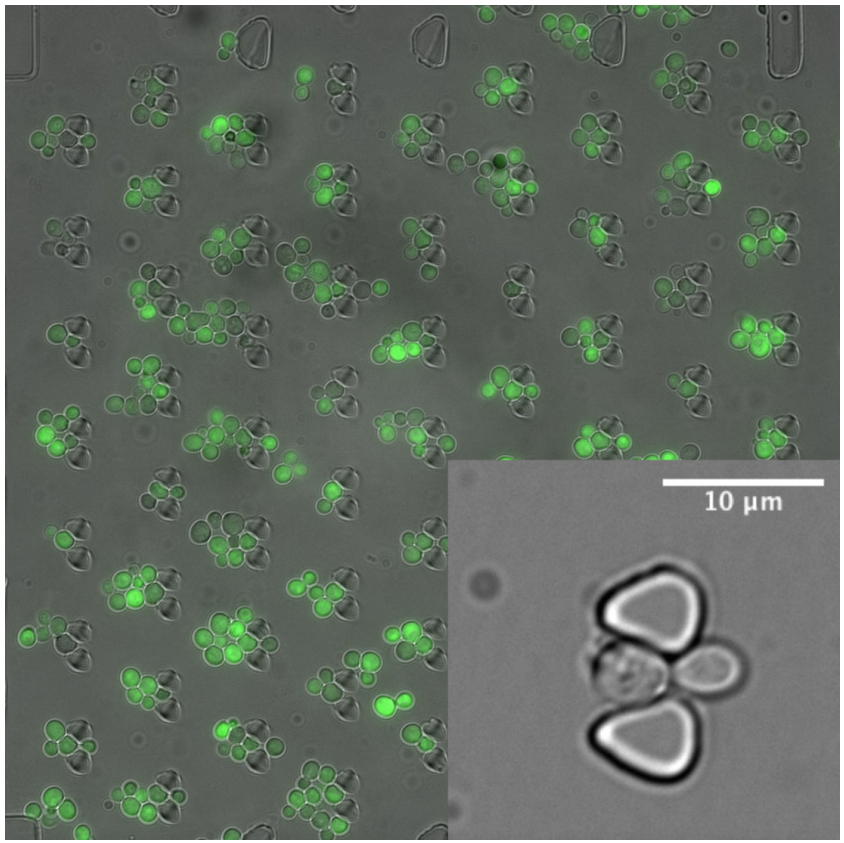
...joint work with A. Ganguly and D. Altintan
(SIAM Multiscale Modeling and Simulation, in press, 2015/arxiv)

Outline

Our research

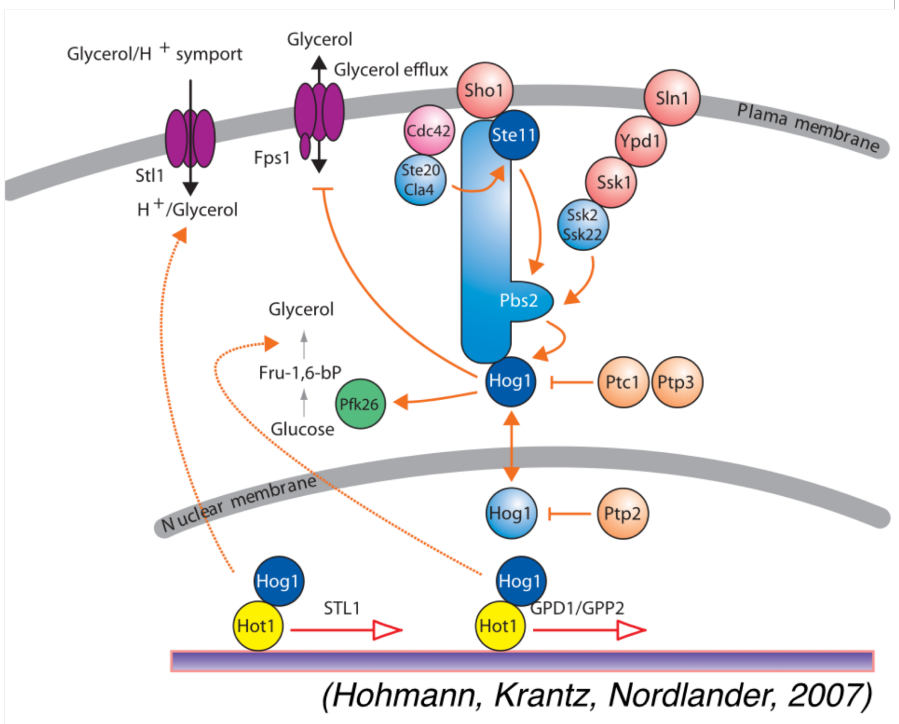
- Statistical inference (ML) methods
- Stochastic analysis of systems
- Single-cell experiments
- Microfluidic chips

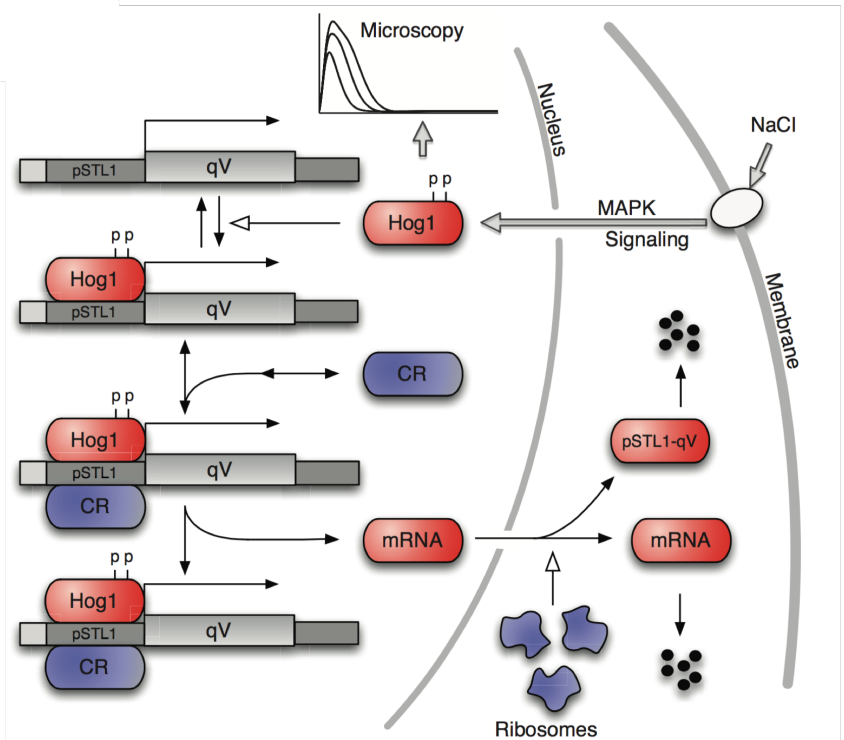




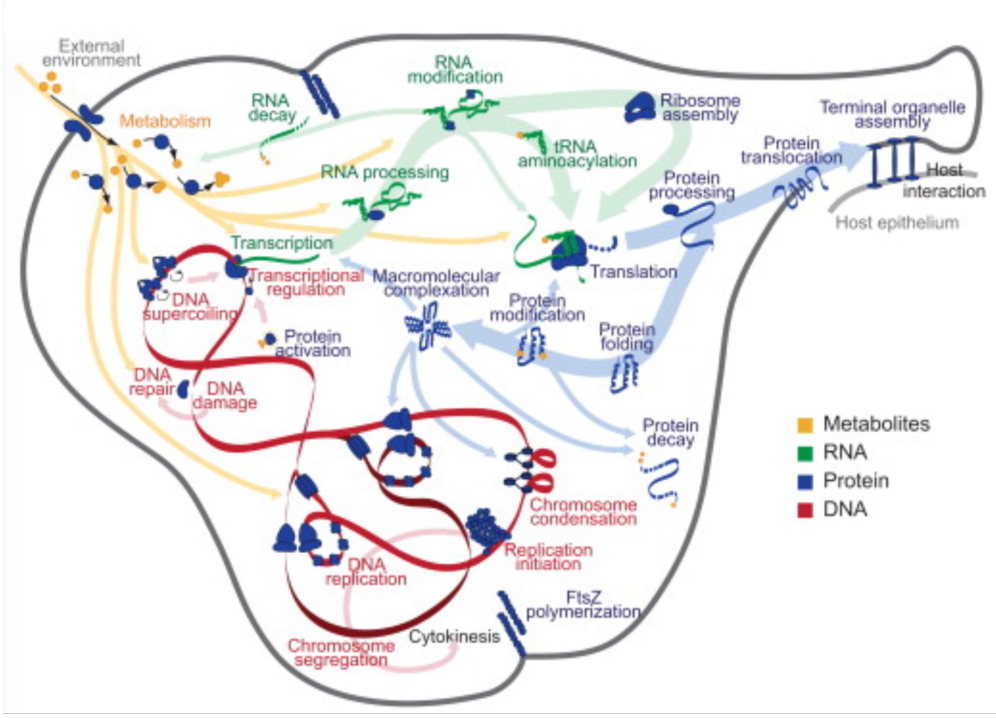
Example: osmotic stress response

- High-osmolarity induced gene expression in yeast *(PNAS'12)*





Motivation: Cell biology is multi-scale (...and multi-level)



Karr et al, Cell'12

- System-level understanding requires coupling of cellular processes.
- Cross-regulation between signaling, gene expression metabolism.
- Different time-scales results in computational bottleneck.
- On top of that: spatial effects (e.g. membrane trafficking) often significant - additional scale of resolution.

Population models (aka Petri nets)

$$R_k : \nu_{k1}^- S_1 + \nu_{k2}^- S_2 + \ldots + \nu_{km}^- S_m \xrightarrow{c_k} \nu_{k1}^+ S_1 + \nu_{k2}^+ S_2 + \ldots + \nu_{km}^+ S_m$$

$\nu_k = (\nu_{k1}^+ - \nu_{k1}^-, \nu_{k2}^+ - \nu_{k2}^-, \ldots, \nu_{km}^+ - \nu_{km}^-)^T$ Stoichiometric change vector

$X(t) = (X_1(t), X_2(t), \ldots, X_m(t))^T$ State vector , $c_k \in \mathbb{R}_+$: Rate constant

$X(t) = X(t-) + \nu_k$ occurrence of R_k updates the state vector

- Jump process formulation (CTMC)
  Continuous time, countable states - stochastic simulation or chemical master equation.
- Diffusion approximation
  Continuous time, continuous state - stochastic differential equation, Fokker-Planck equation.
- Mean-field approximation - thermodynamic limit
  Continuous time, continuous state - ordinary differential equation (RRE).

Multi-scale models

Combine different model description to exploit multi-scale nature.
Addressed questions:

1. *How do we partition a given CTMC model into discrete and approximate, continuous parts?*
2. *How can we bound the error for a certain partition?*
3. *How can we simulate such a multi-scale model?*

Research agenda

- Propose partitioning according to Poisson approximation.
- Perform path-wise, strong error analysis.
- Design dynamic partitioning algorithm to simulate multi-scale systems efficiently.

Random time-change representation

$$R_k : \nu_{k1}^- S_1 + \nu_{k2}^- S_2 + \ldots + \nu_{km}^- S_m \xrightarrow{c_k} \nu_{k1}^+ S_1 + \nu_{k2}^+ S_2 + \ldots + \nu_{km}^+ S_m$$

Propensity function example: $a_k(x) = c_k \prod_{i=1}^{m} \binom{x_i}{\nu_{ki}^-}, \quad k = 1, \ldots, r$

e.g. $R_k : S_1 + S_2 \xrightarrow{c_k} *$, $a_k(X) = c_k X_1 X_2$ or $S_1 \xrightarrow{c_k} *$, $a_k(X) = c_k\, X_1$
With $a_k(x)dt \equiv$ the probability of reaction R_k to occur in time interval $(t, t + dt]$.
A path-wise representation of the CTMC is as follows

$$X(t) = X(0) + \sum_{k=1}^{r} \xi_k \left(\int_0^t a_k(X(s))\mathrm{d}s \right) \nu_k,$$

where ξ_k's are independent Poisson processes.

Scaling

The abundance of species and time-scales of reactions can vary over different orders of magnitude. We introduce additional scaling variables to make that explicit (other variables are $O(1)$).

$$
\begin{array}{rrcl}
 & \bar{X}_i^N & = & X_i/N^{\alpha_i}, \quad \bar{X}_i^N = O(1), \\
 & d_k & = & c_k/N^{\beta_k}, \quad d_k = O(1), \\
\text{Example} & a_k(X) & = & c_k X_i = N^{\beta_k} d_k N^{\alpha_i} \bar{X}_i^N \equiv N^{\beta_k+\alpha_i} \lambda(\bar{X}_i^N) \\
 & a_k(X) & = & N^{\beta_k+\nu_k^- \cdot \alpha} \lambda_k(\bar{X}^N), \quad \Longrightarrow \ \lambda_k(\cdot) = O(1), \\
 & t & \to & t\, N^\gamma, \\
 & X^N(t) & = & \bar{X}^N(t\, N^\gamma).
\end{array}
$$

We obtain random time-change model for normalized variables

$$
X^N(t) = X^N(0) + \sum_{k=1}^{R} \xi_k \left(N^{\rho_k} \int_0^t \lambda_k(X^N(s))\mathrm{d}s \right) \nu_k^N,
$$

where we define $\rho_k = \gamma + \beta_k + \nu_k^- \cdot \alpha$ and $\nu_{ki}^N = \nu_{ki}/N^{\alpha_i}$.

Idea

- High intensity Poisson process can well be approximated by Brownian motion (plus dift), i.e. $\xi(t) \approx t + W(t)$.

Theorem (Kolmos, Major, Tusnady)

There exists a Brownian motion $W(t)$ on the same probability space as $\xi(t)$ such that

$$\Gamma = \sup_t \frac{\tilde{\xi}(t) - W(t)}{\log(2 \vee t)} < \infty \quad (a.s.),$$

where $\tilde{\xi}(t) = \xi(t) - t$ is the centered Poisson process.

- That is

$$\left[\frac{1}{\sqrt{n}} \tilde{\xi}(nt) - \frac{1}{\sqrt{n}} W(nt) \right] \leq \frac{\log(2 \vee nt)}{\sqrt{n}} \Gamma,$$

  where $\frac{1}{\sqrt{n}} W(nt)$ is a standard Brownian motion $W(t)$.
- Strategy: Replace reaction count process of high scaling factor N^{ρ_k} by an diffusion approximation.

Multi-scale approximation

- Jump-Diffusion Approximating process (first reaction replaced)

$$Y^N(t) = X^N(0) + N^{\rho_1} \int_0^t \lambda_1(Y^N(s))\mathrm{d}s\, \nu_1^N + W_1\left(N^{\rho_1} \int_0^t \lambda_1(Y^N(s))\mathrm{d}s\right) \nu_1^N + \sum_{k>1} \xi_k \left(N^{\rho_k} \int_0^t \lambda_k(Y^N(s))\mathrm{d}s\right)\ \nu_k^N$$

- Piece-wise deterministic Markov process (Jump-ODE)

$$Y^N(t) = X^N(0) + N^{\rho_1} \int_0^t \lambda_1(Y^N(s))\mathrm{d}s\, \nu_1^N + \sum_{k>1} \xi_k \left(N^{\rho_k} \int_0^t \lambda_k(Y^N(s))\mathrm{d}s\right)\ \nu_k^N$$

- Between two jumps overall system state $Y^N(t)$ evolves deterministically.

Bounding the error

- Compute bound on path-wise error for some $T \geq 0$

$$\sup_{t \leq T} \mathrm{E}|X^N(t) - Y^N(t)| = \sup_{t \leq T} \sum_{i=1}^{m} \mathrm{E}|X_i^N(t) - Y_i^N(t)|$$

for different reactions replaced by an approximation.

Theorem

Let $X^N(t)$ be the exact jump process and $Y^N(t)$ its jump-diffusion approximation with reaction $k = 1$ replaced then for $T \geq 0$

$$\sup_{t \leq T} \mathrm{E}|X^N(t) - Y^N(t)| \leq C_T(C' \log N^{\rho_1}/N^{m_1} + K''/N^{2\rho_1 + m_1})$$

where $|v_k^N| = O(N^{-m_k}) = O(\sum_{i \in R_k} N^{-\alpha_i})$ with $R_k = \{i \in \mathbb{N} \mid v_{ki} \neq 0\}$ and with the reaction non-specific constant $C_T = \exp\left(2 \sum_{k=1}^{r} N^{\rho_k} |\nu_k^N| L_k T\right)$

From a bound to an algorithm

- Convert reaction-specific error terms involving scaling variables back to states and propensities

$$\delta_k = \log N^{\rho_k}/N^{m_k} + 1/N^{2\rho_k + m_k}$$

- Fix time horizon $\Delta = O(N^{\gamma})$ and recall that $a_k(X)\Delta = O(N^{\rho_k})$ and $(N^{-m_k}) = O(\sum_{i \in R_k} N^{-\alpha_i}) = O(\sum_{i \in R_k} 1/X_i)$
- Then the jump-diffusion error criterion is

$$\delta_k(\Delta) = \sum_{i \in R_k} \frac{\log(a_k(X)\Delta)}{X_i} + \frac{1}{(a_k(X)\Delta)^2 X_i}$$

- Fix approximation accuracy ϵ and check at every Δ for each reaction k whether the incurred error of approximating it by diffusion is below ϵ.

Example: Bursty birth-death process

Consider the single species S

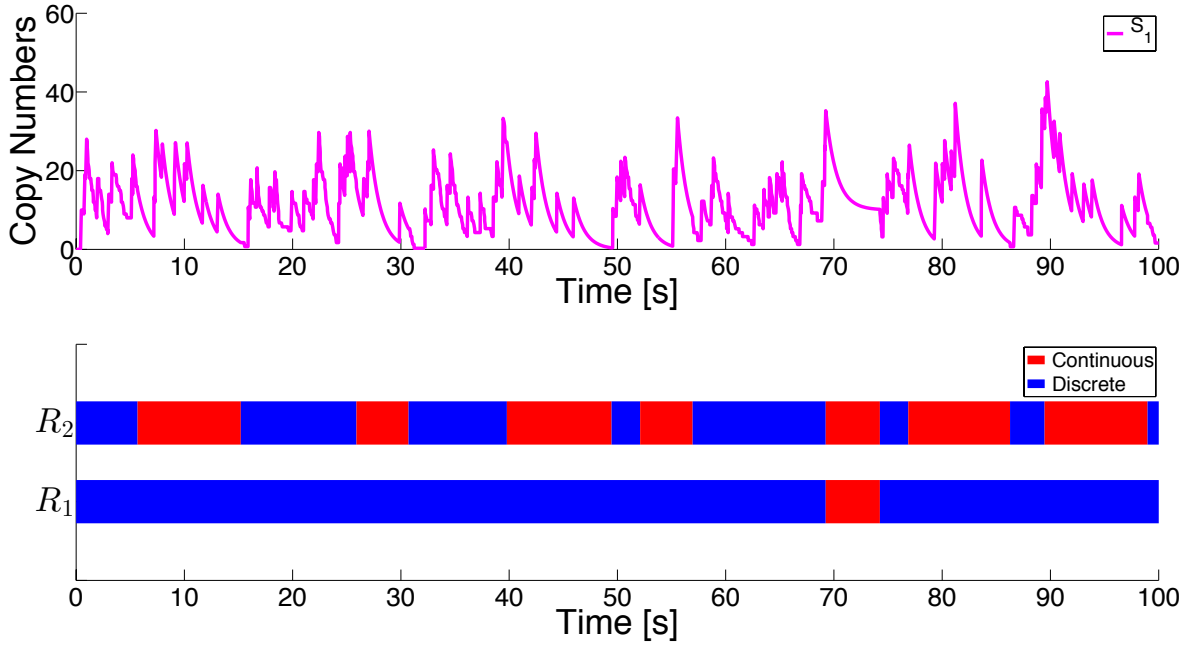
$$\emptyset \xrightarrow{c_1} 10S, \quad S \xrightarrow{c_2} \emptyset. \tag{1}$$

with the number of molecules of S at time t is denoted by $X(t)$. we use

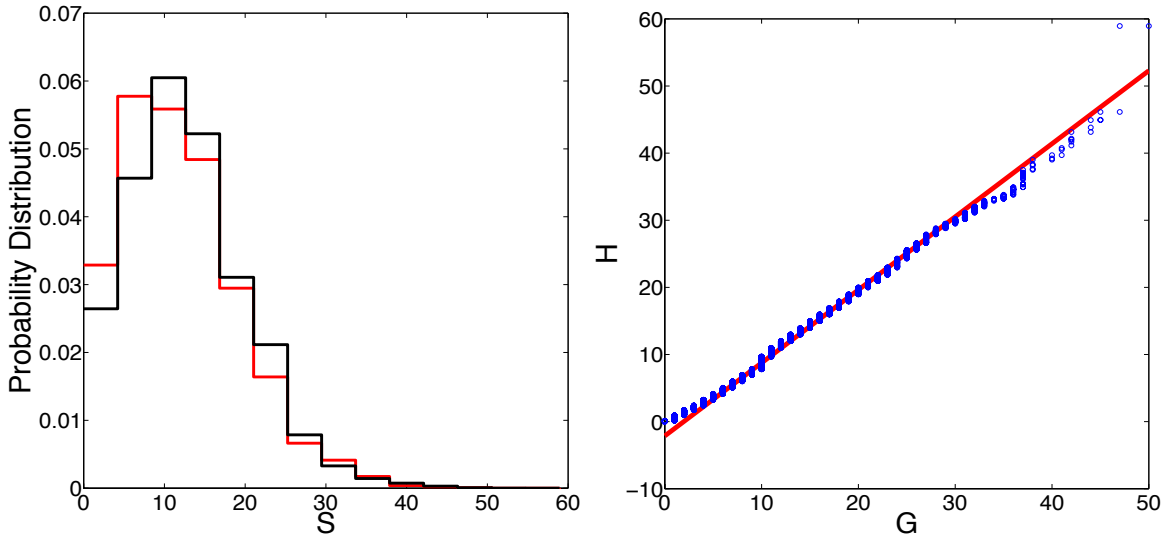
$$X(0) = 0, \quad \Delta = 0.1, \quad \varepsilon = 0.09, \quad P = 50.$$

Reaction constants of R_1, R_2 are given as $c_1 = 1\,\mathrm{molec\,s^{-1}}$, $c_2 = 1\mathrm{s}^{-1}$.
Death process is expected to be approximated by diffusion.

Dynamic partitioning



Weak error analysis by simulation



The Lotka-Volterra model

Let S_1 and S_2 denote the prey and the predator, respectively. The corresponding Lotka-Volterra prey-predator model can be depicted as

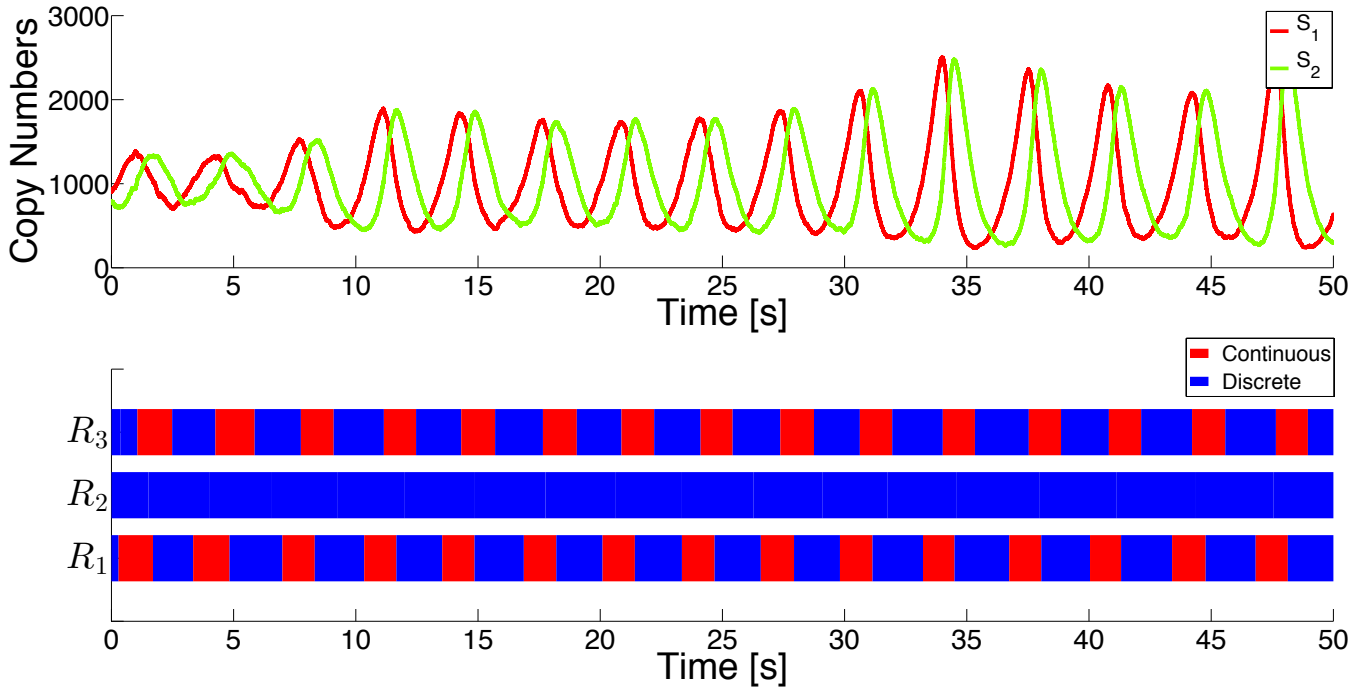
$$S_1 \xrightarrow{c_1} 2S_1, \quad S_1 + S_2 \xrightarrow{c_2} 2S_2 \quad S_2 \xrightarrow{c_3} \emptyset. \tag{2}$$

Let $X_1(t)$ and $X_2(t)$ denote the number of the prey and the predator at time $t > 0$, respectively, then, the state of the system is defined by $X(t) = (X_1(t), X_2(t))^T \in \mathbb{N}^2_{\geq 0}$. We use

$$X(0) = (900, 800)^T,\ c_1 = 2\mathrm{s}^{-1},\ c_2 = 0.002\mathrm{molec}^{-1}\mathrm{s}^{-1},\ c_3 = 2\mathrm{s}^{-1}.$$

$$\Delta = 0.5,\ \varepsilon = 0.03,\ P = 50,\ t \in (0, 50)$$

Dynamic partitioning



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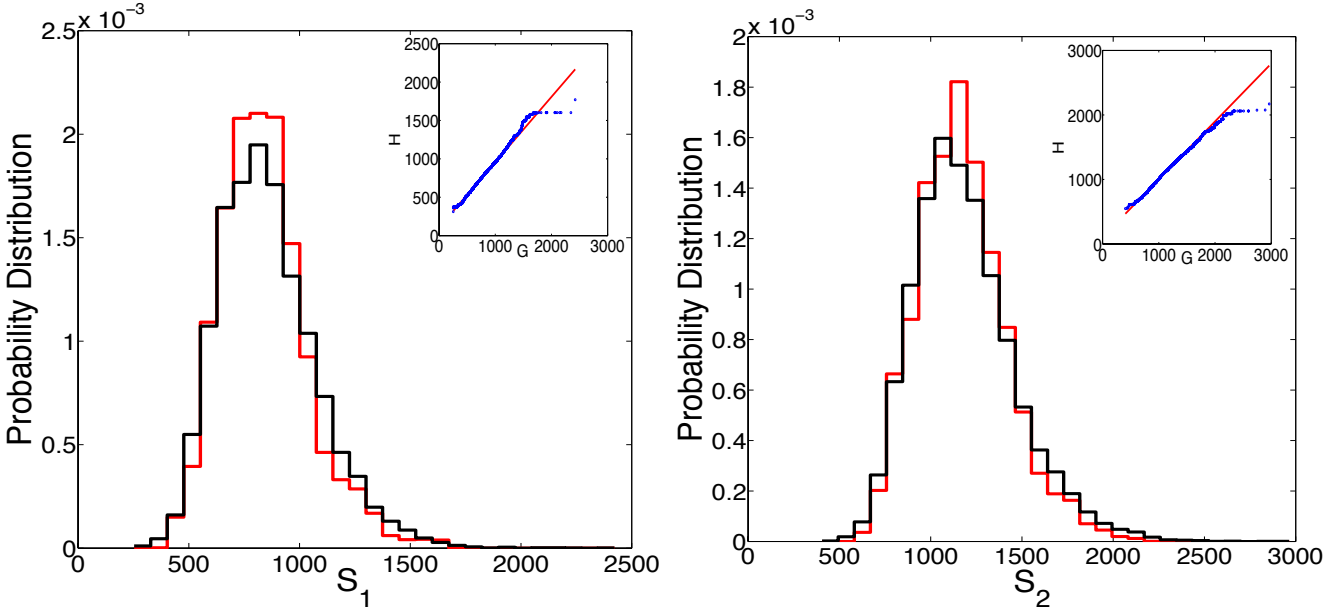
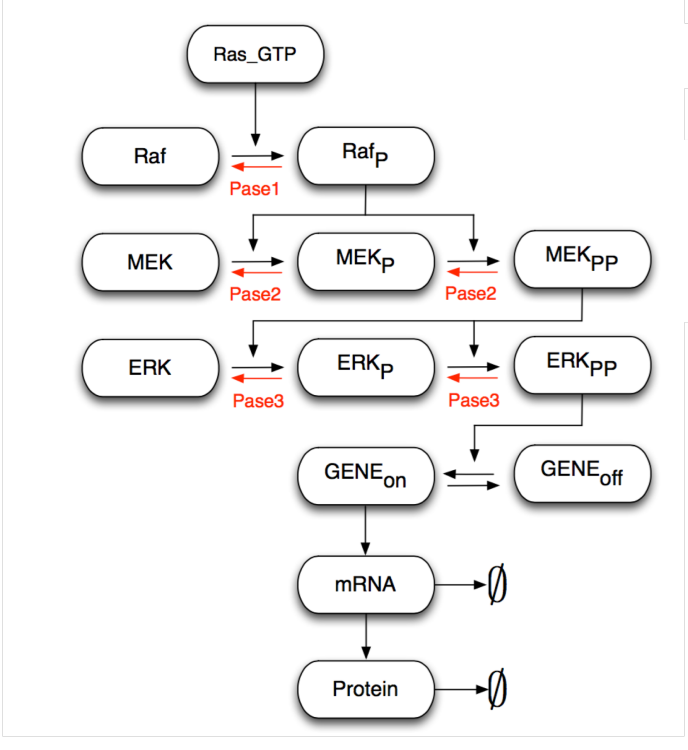
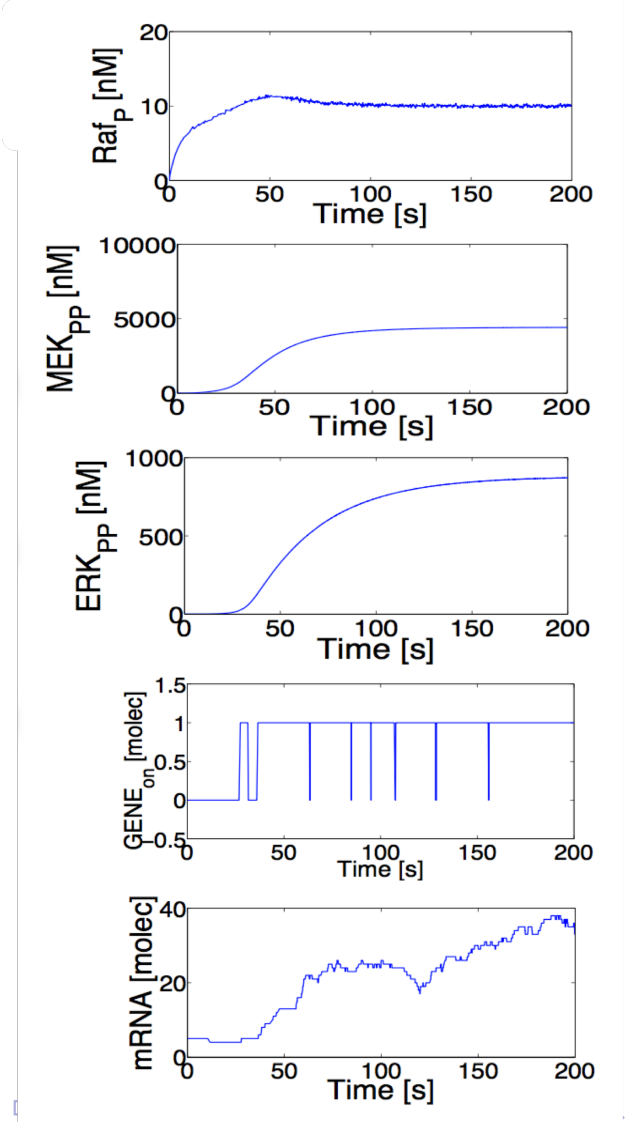


EGFR signaling and gene expression

- Rate constants and abundances based on *Schoeberl et al., Science Sci'09*
- 30 signaling reactions, 6 gene expression reactions
- Runge-Kutta strong order 2 SDE integrator





Conclusions

- Multi-scale models essential for systems biology.
- Traditional hybrid models often involve ad-hoc partitioning of species.
- Reaction partitioning leveraging existing approximation results for point processes.
- Generally, every state becomes a jump-diffusion process (i.e. no species partitioning).
- Explicit bound for finite-time error for approximating specific reaction channels.
- Real gain requires higher-order integration schemes for SDEs.
- Bounds for ODE-Jump and ODE-SDE-Jump.