Lumping, Transformation of Variables, and Invariant Manifolds

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Parameterization of reduced models

- It is not unusual for scientists to be interested in "derived" quantities rather than in the "natural" variables of a model.

  Examples:

  - Active fraction of an enzyme $= \dfrac{[\mathrm{E}_{\mathrm{active}}]}{\sum_i \mathrm{E}_i}$
  - Energy charge $= \dfrac{[\mathrm{ATP}] + \frac{1}{2}[\mathrm{ADP}]}{[\mathrm{ATP}] + [\mathrm{ADP}] + [\mathrm{AMP}]}$

- The goal of model reduction is to obtain a model expressed in terms of a few variables.

  But which variables?

- Can we kill two birds with one stone?

Motivational example: linear metabolic pathway

$$S_{i-1} \underset{v_{i-}}{\overset{v_{i+}}{\rightleftharpoons}} S_i, \qquad i = 1, 2, \ldots, N$$

- Reversible Michaelis-Menten kinetics (rescaled):

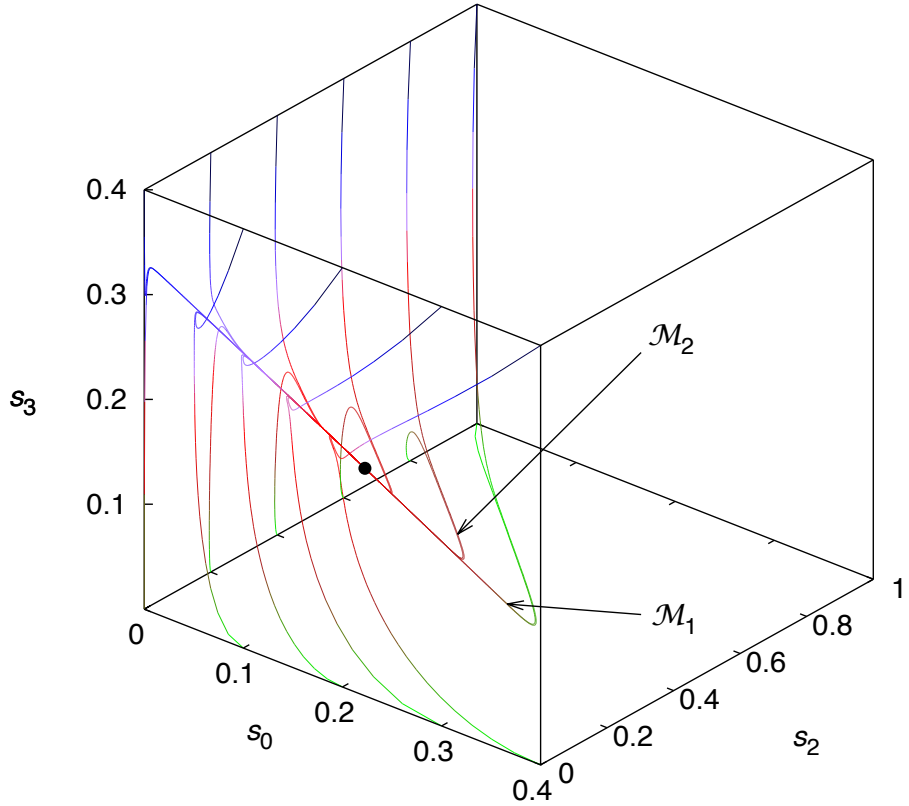
$$v_{i+} = \frac{\gamma_i s_{i-1}}{1 + s_{i-1}/\alpha_i + s_i/\beta_i}$$

$$v_{i-} = \frac{\eta_i s_i}{1 + s_{i-1}/\alpha_i + s_i/\beta_i}$$

$$\sum_{i=0}^{N} s_i = 1$$

Ref: Roussel and Fraser, *Chaos* **11**, 196 (2001).

Slow invariant manifolds



$$\mathsf{S}_0 \rightleftharpoons \mathsf{S}_1 \overset{\text{slow}}{\rightleftharpoons} \mathsf{S}_2 \overset{\text{slower}}{\rightleftharpoons} \mathsf{S}_3 \rightleftharpoons \mathsf{S}_4 \rightleftharpoons \mathsf{S}_5$$

$$\alpha_i = \beta_i = 1,\ \gamma_1 = \eta_1 = 1\,\mathrm{s}^{-1},\ \gamma_2 = \eta_2 = 0.1\,\mathrm{s}^{-1},\ \gamma_3 = \eta_3 = 0.01\,\mathrm{s}^{-1},$$
$$\gamma_4 = \eta_4 = \gamma_5 = \eta_5 = 1\,\mathrm{s}^{-1}$$

Parameterization of invariant manifolds

- A d-dimensional differentiable manifold can be parameterized (at least locally) by a set of d coordinates z_i such that

$$\mathbf{s} = \mathbf{s}(\mathbf{z})$$

- In standard approaches to the computation of slow invariant manifolds, $\mathbf{z}$ is a subset of the $\mathbf{s}$ variables.
- Instead, take

$$\mathbf{z} = \boldsymbol{\zeta}(\mathbf{s})$$

where $\boldsymbol{\zeta}$ is a known function of $\mathbf{s}$.

Special case: In linear aggregation or lumping,

$$\boldsymbol{\zeta}(\mathbf{s}) = \mathbf{L}\mathbf{s}$$

where $\mathbf{L}$ is a constant matrix.

Evolution equation for $\mathbf{z}$

- Given $\mathbf{z} = \boldsymbol{\zeta}(\mathbf{s})$, differentiation with respect to time gives

$$\dot{\mathbf{z}} = \boldsymbol{\zeta}_{\mathbf{s}} \dot{\mathbf{s}}$$

  where

$$\boldsymbol{\zeta}_{\mathbf{s}(ij)} = \frac{\partial \zeta_i}{\partial s_j}$$

- If we have computed the manifold in this parameterization, viz. $\mathbf{s} = \mathbf{s}(\mathbf{z})$, then we have the evolution equation for the reduced model

$$\dot{\mathbf{z}} = \boldsymbol{\zeta}_{\mathbf{s}} \dot{\mathbf{s}}|_{\mathbf{s}=\mathbf{s}(\mathbf{z})}$$

Invariance equation

- For a manifold parameterized by $\mathbf{s} = \mathbf{s}(\mathbf{z})$, differentiation with respect to time gives

$$\dot{\mathbf{s}} = \mathbf{s}_\mathbf{z}\dot{\mathbf{z}}$$

where

$$\mathbf{s}_\mathbf{z}(ij) = \frac{\partial s_i}{\partial z_j}$$

are a priori unknown partial derivatives of the manifold.

- Combining this equation with the evolution equation, we get

$$\dot{\mathbf{s}} = \mathbf{s}_\mathbf{z}\boldsymbol{\zeta}_\mathbf{s}\dot{\mathbf{s}}$$

or

$$\left(\mathbf{I} - \mathbf{s}_\mathbf{z}\boldsymbol{\zeta}_\mathbf{s}\right)\dot{\mathbf{s}} = \mathbf{0}$$

This is the invariance equation.

Nature of the problem

- We have the invariance equation, which has N components:

$$(\mathbf{I} - \mathbf{s}_\mathbf{z}\boldsymbol{\zeta}_\mathbf{s})\,\dot{\mathbf{s}} = \mathbf{0} \qquad (\mathrm{I})$$

- We also have the d-component constitutive equation

$$\mathbf{z} = \boldsymbol{\zeta}(\mathbf{s}) \qquad (C)$$

- We are only interested in solutions of (I) that are consistent with (C).
- We need to solve (C) along with $N - d$ components of (I) for the N unknown functions $s_i(\mathbf{z})$.

Iterative solution

1. Start with some physically reasonable ansatz for $\mathbf{s}(\mathbf{z})$, say $\mathbf{s}^{(0)}(\mathbf{z})$, e.g. a partial equilibrium approximation; set $k = 0$.

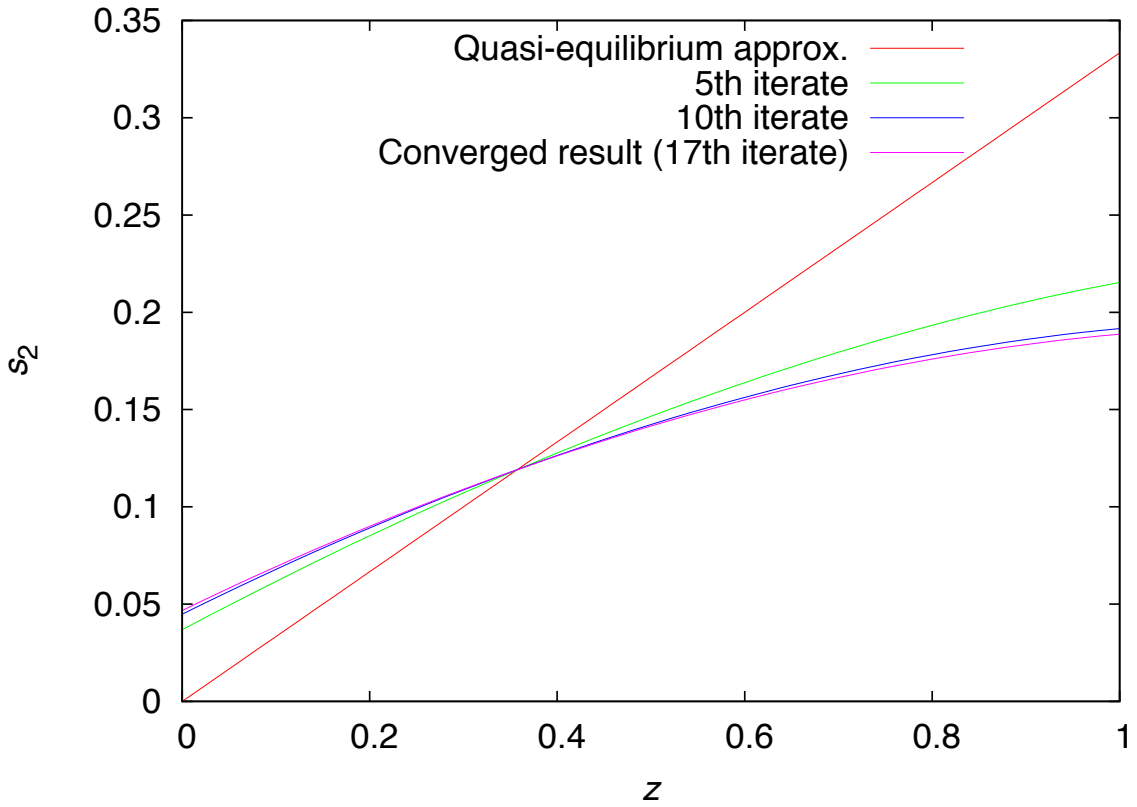
2. Calculate the partial derivatives $\mathbf{s}_{\mathbf{z}}^{(k)}$.

3. Solve each of the $N - d$ components of $\left(\mathbf{I} - \mathbf{s}_{\mathbf{z}}^{(k)} \boldsymbol{\zeta}_{\mathbf{s}}\right) \dot{\mathbf{s}} = \mathbf{0}$ in turn for $s_i^{(k+1)}$ subject to (C) for fixed $\mathbf{s}_{\mathbf{z}}^{(k)}$. (Chained iteration)

   Both $\boldsymbol{\zeta}_{\mathbf{s}}$ and $\dot{\mathbf{s}}$ may depend on $\mathbf{s}$.

4. If the calculation has not converged, set $k \leftarrow k + 1$ and go back to step 2.

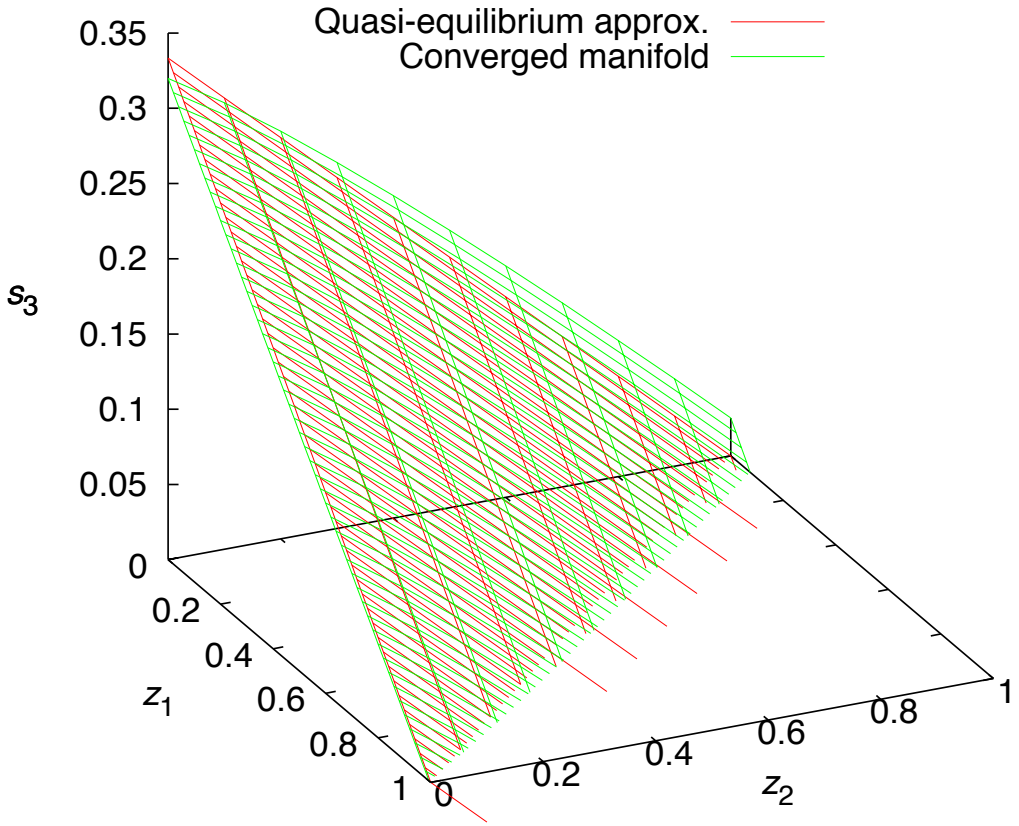
One-dimensional slow manifold: convergence



$$\zeta(\mathbf{s}) = s_0 + s_1 + s_2$$

$$\alpha_i = \beta_i = 1,\ \gamma_1 = \eta_1 = 1\,\mathrm{s}^{-1},\ \gamma_2 = \eta_2 = 0.1\,\mathrm{s}^{-1},\ \gamma_3 = 0.09\,\mathrm{s}^{-1},\ \eta_3 = 0.05\,\mathrm{s}^{-1},$$
$$\gamma_4 = \eta_4 = \gamma_5 = \eta_5 = 1\,\mathrm{s}^{-1}$$

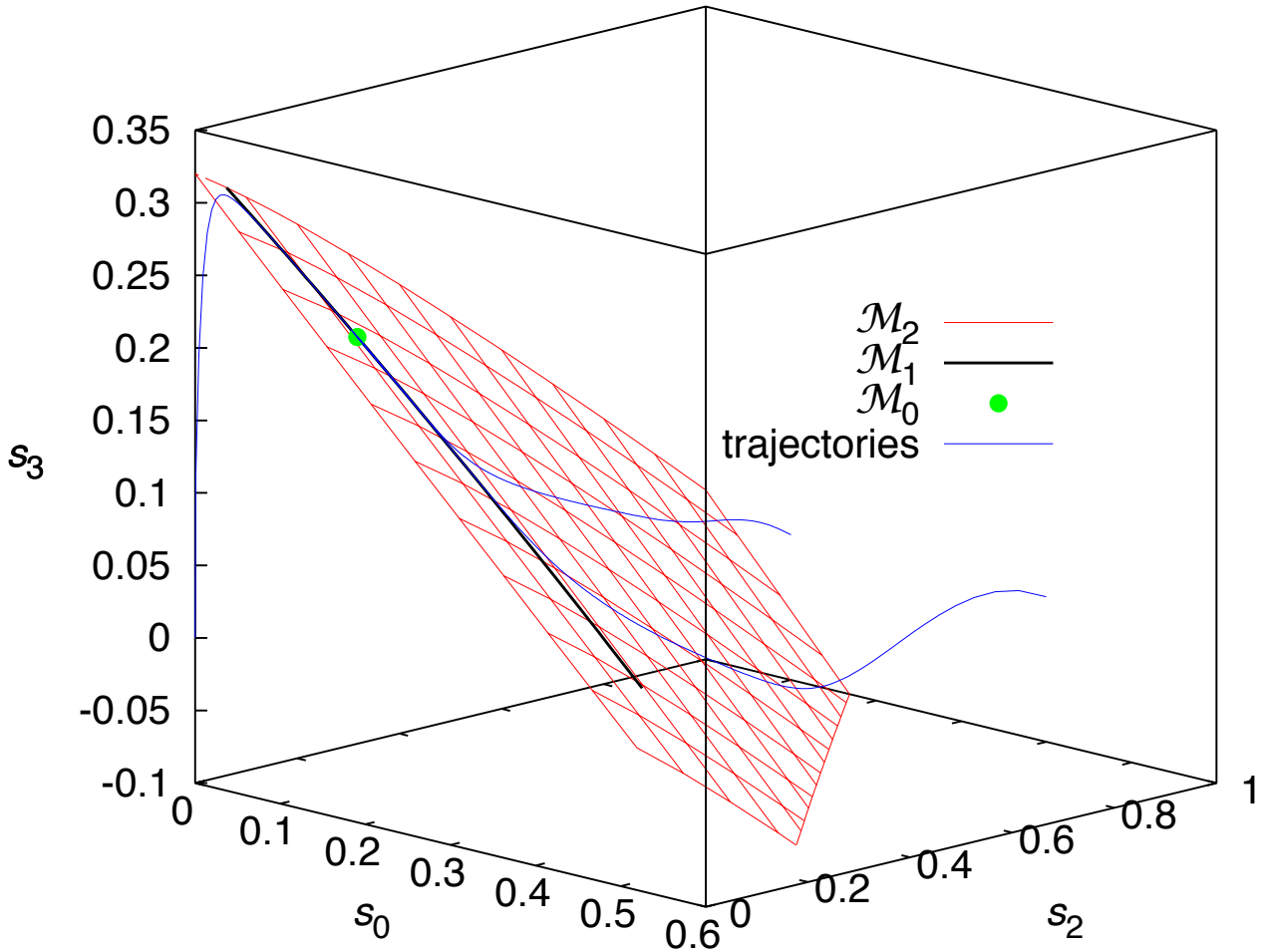
Two-dimensional slow manifold: convergence



$$\zeta(\mathbf{s}) = \begin{bmatrix} s_0 + s_1 \\ s_2 \end{bmatrix}$$

Converged after ~ 6 iterates

Converged results



A small hydrogen combustion model

$$\mathrm{H_2} \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} 2\mathrm{H} \qquad \mathrm{O_2} \underset{k_2^-}{\overset{k_2^+}{\rightleftharpoons}} 2\mathrm{O}$$

$$\mathrm{H_2O} \underset{k_3^-}{\overset{k_3^+}{\rightleftharpoons}} \mathrm{H} + \mathrm{OH} \qquad \mathrm{H_2} + \mathrm{O} \underset{k_4^-}{\overset{k_4^+}{\rightleftharpoons}} \mathrm{H} + \mathrm{OH}$$

$$\mathrm{O_2} + \mathrm{H} \underset{k_5^-}{\overset{k_5^+}{\rightleftharpoons}} \mathrm{O} + \mathrm{OH} \qquad \mathrm{H_2} + \mathrm{O} \underset{k_6^-}{\overset{k_6^+}{\rightleftharpoons}} \mathrm{H_2O}$$

- Conservation relations:
$$m_{\mathrm{H}} = 2[\mathrm{H_2}] + 2[\mathrm{H_2O}] + [\mathrm{H}] + [\mathrm{OH}]$$
$$m_{\mathrm{O}} = 2[\mathrm{O_2}] + [\mathrm{H_2O}] + [\mathrm{O}] + [\mathrm{OH}]$$
- Four independent concentrations

Ref.: Gorban, Karlin and Zinovyev, *Physica A* **333**, 106 (2004).

A physically motivated nonlinear lumping function

- Take the "partial" Lyapunov function

$$G' = \sum_{\text{stable species}} s_i \left[\ln\left(\frac{s_i}{s_i^*}\right) - 1 \right]$$

- The computation of the one-dimensional slow manifold is similar to that described above, with two wrinkles:
  - The functional equation and lumping relation are solved as a system rather than using chained iteration.
  - It is necessary to stabilize the calculation.
    (This is sometimes also the case with the linear pathway model.)

A simple stabilization method

- The functional equation implicitly defines a relation

$$\mathbf{s} = \mathcal{F}(\mathbf{S_z})$$

- Add $w\mathbf{s}$ to both sides, where w is an arbitrary weight, and rearrange:

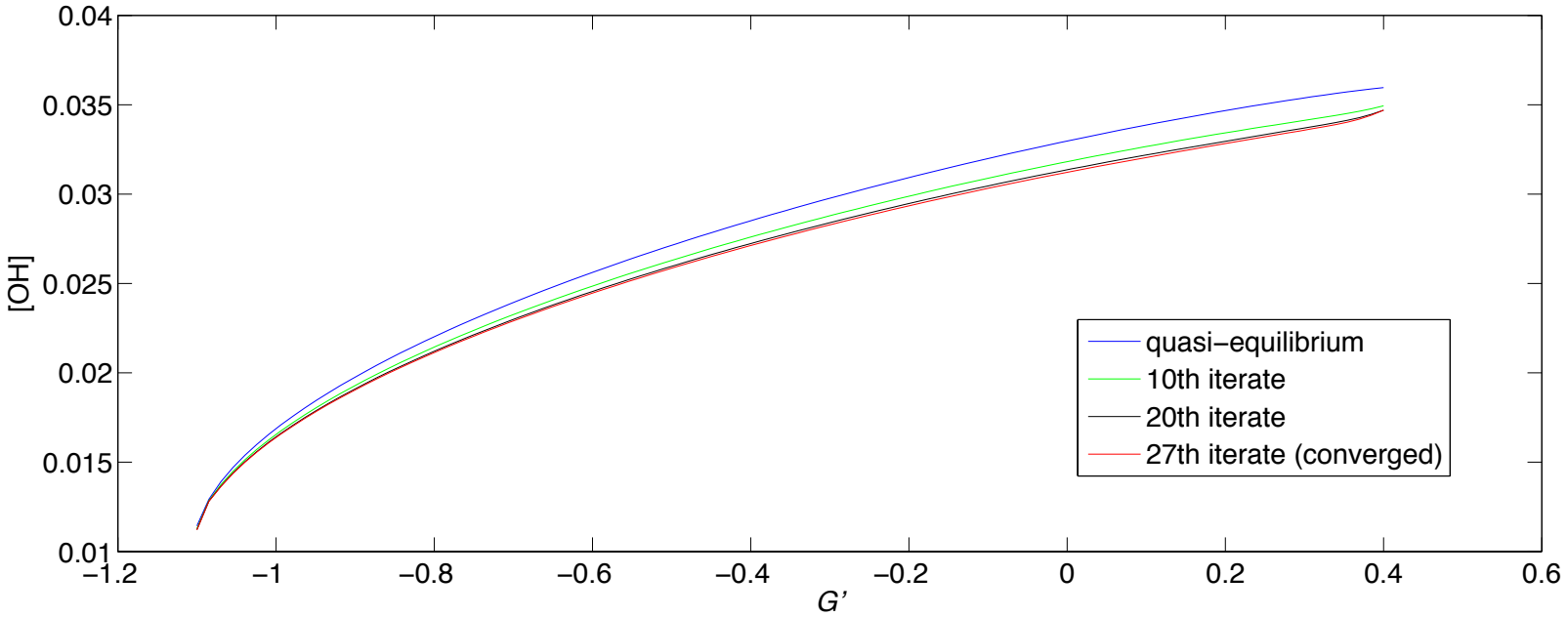
$$\mathbf{s} = \frac{\mathcal{F}(\mathbf{S_z}) + w\mathbf{s}}{1 + w}$$

- We can solve this by iteration:

$$\mathbf{s}_{i+1} = \frac{\mathcal{F}(\mathbf{S}_{\mathbf{z},i}) + w\mathbf{s}_i}{1 + w}$$

- Using $w > 0$ slows convergence, but increases stability.
  Roussel, *J. Math. Chem.* **21**, 385 (1997); Davis and Skodje, *J. Chem. Phys.* **111**, 859 (1999).

Results hot off the presses!

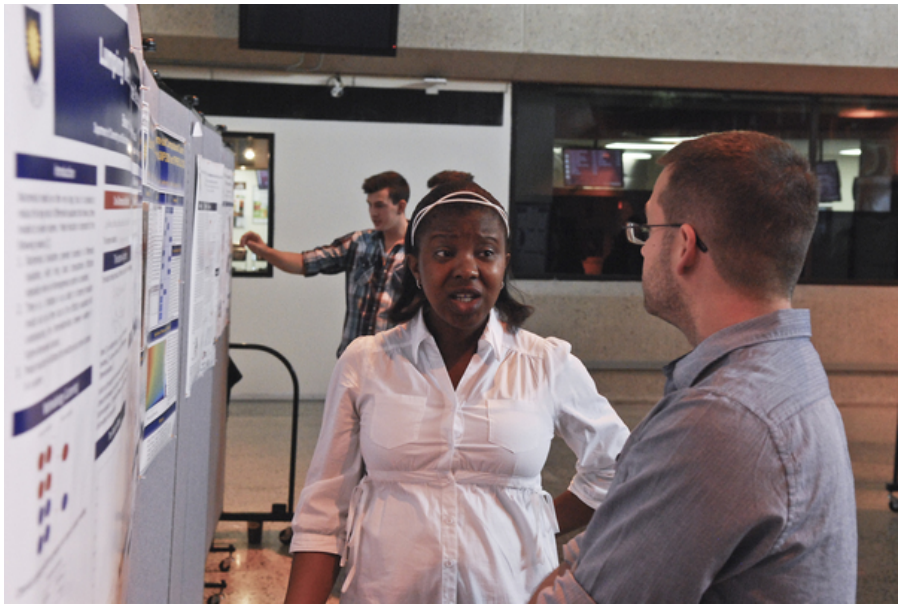


$w = 10$

Future perspectives

- Ongoing work:
  - Reduction of chemical master equation
- Potential future avenues of investigation:
  - Study stability of alternative computational sequences for solving the functional equation
  - Exploit modularity of biochemical networks
  - Nonlinear transformations
  - Exact slow time scale coarse graining of spatial models

Acknowledgments



Blessing Okeke

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