Computing structural and dynamic properties of biological systems at multiscale

3. Stochastic networks

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Outline

1. Chemical master equation and approximations

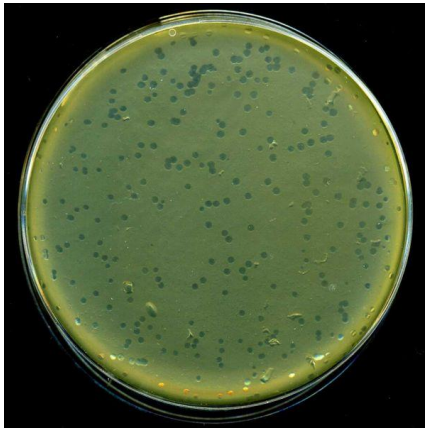
2. Finite buffer algorithm for optimal state enumeration

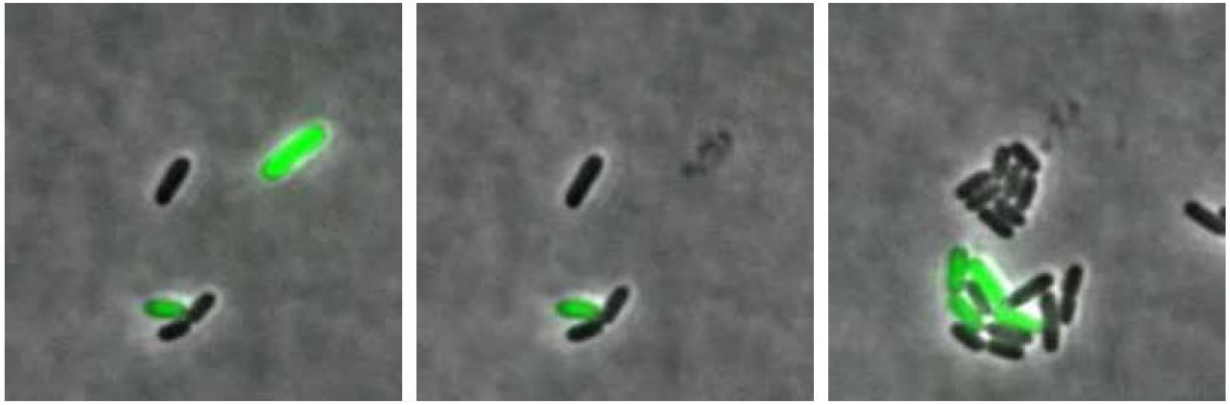
3. How do we know if results are correct and error estimation
   - Probability flux

4. Results of simple and complex stochastic networks
   - Comparison with other method

Stochastic Genetic circuits

- **How is cell fate determined?**





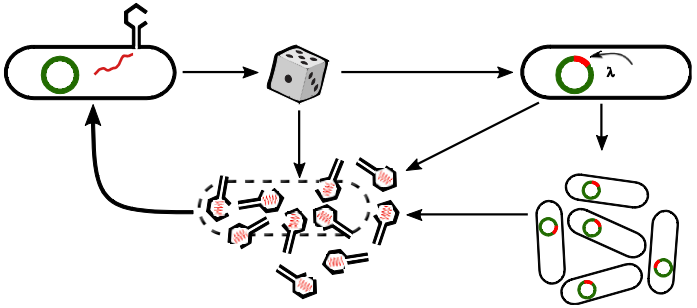
(St-Pierre and Endy, *PNAS*, 2008)

Implication for cancer biology

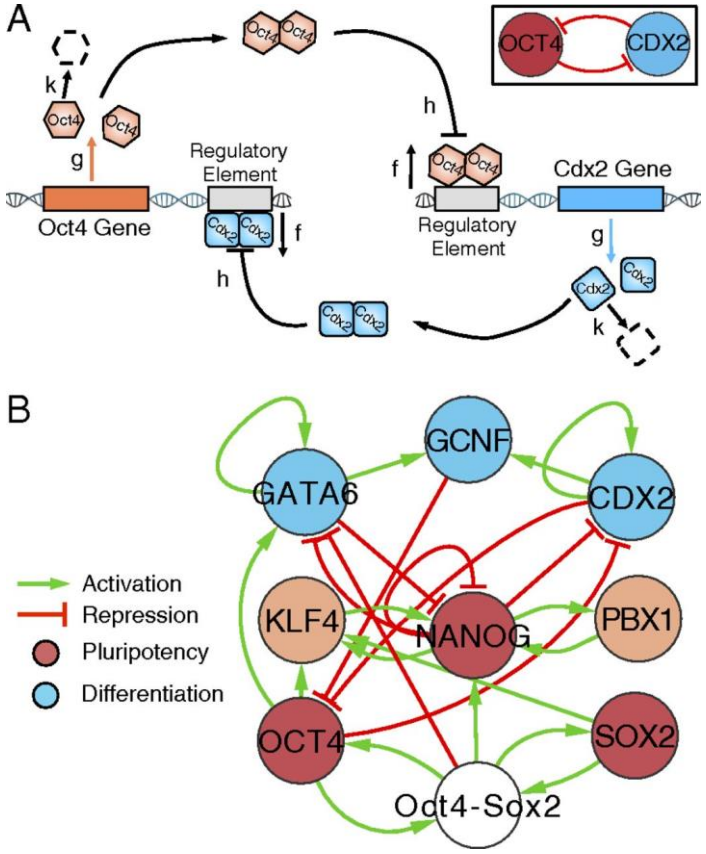
Stochastic network and cellular fate

- Origin of stochasticity:
  - Many molecular networks are of small copy numbers (eg. μM – nM) and are stochastic:
    - transcription regulation, protein synthesis, signal transduction.
  - Slow reactions: multistable systems
  - Burst in transcription and translation
  - Cell-cell variaton
  - External environment

- Epigenetic Landscape of stochastic networks: Broad applications
  - Phage lambda
  - Stem cell differentiation



(Phage work: McAdams and Arkin, 1997; Aurell and Sneppen, 2002; Zhu, Yin, Hood, and Ao, 2004)



(Zhang and Wolyness, 2014)

Chemical Master Equation

- A general framework for studying biological networks
  - Assumption: well-mixed system

Molecular reactions, state, and probability

- Molecular species and reactions:
  - *m* molecular species: $\{X_1, \ldots, X_m\}$
    - X_i: i-th molecular species
  - *n* chemical reactions: $\mathcal{R} = \{R_1, \ldots, R_n\}$

- Microstate:
  - combination of copy numbers at time t:

    $$\mathbf{x}(t) = (x_1(t), \ldots , x_m(t)) \in \mathbb{N}^m$$

  - probability of system in state $\mathbf{x}(t)$:

    $$p(\mathbf{x}(t))$$

State Space and Probability Landscape

- State space $\mathcal{X}$:
  - The set of all possible combination of copy numbers

    $$\mathcal{X} = \{ \mathbf{x}(t) \mid t \in (0, \infty)\},\ \text{discrete}$$
  - Size of state space: $|\mathcal{X}|$, countable

- Probability landscape at time t :

  $$\{p\ (\mathbf{x}(t) \mid (\mathbf{x}(t) \in \mathcal{X}\ \}$$

Chemical Reactions: Stoichiometry and Reaction Rate

- Chemical reaction r_k has the form:

$$c_1(k)\, X_1 + c_2(k)\, X_2 + \ldots + c_m(k)\, X_m \rightarrow c_1'(k)\, X_1 + c_2'(k)\, X_2 + \ldots + c_m'(k)\, X_m.$$

  - Brings system from state $\mathbf{x}_i$ to $\mathbf{x}_j$: A jump process

- Reaction rate: determined by intrinsic rate constant r_k and copy numbers of reactants, which are given by the state $\mathbf{x}_i$

$$A_k(\mathbf{x}_i, \mathbf{x}_j) = A_k(\mathbf{x}_i, \ldots) = A_k(\mathbf{x}_i) = r_k \prod_{l=1}^{m} \binom{x_l}{c_l}$$

  - If a reaction connects $\mathbf{x}_i$ and $\mathbf{x}_j$, $A_k(\mathbf{x}_i, \mathbf{x}_j) > 0$,
    - Else $A_k(\mathbf{x}_i, \mathbf{x}_j) = 0$
  - If more than one reaction connects $\mathbf{x}_i$ and $\mathbf{x}_j$,

$$A(\mathbf{x}_i, \mathbf{x}_j) = \sum A_k(\mathbf{x}_i, \mathbf{x}_j)$$

Discrete Chemical Master Equation

- A foundation framework for studying mesoscopic biological networks

$$d\,p(\mathbf{x}, t)/\,dt = \sum_{x'} [\, A(\mathbf{x}', \mathbf{x})\, p\,(\mathbf{x}', t) - A(\mathbf{x}, \mathbf{x}')\, p\,(\mathbf{x}, t)]$$

  - $p(\mathbf{x}(t))$ is of continuous time
  - **States are discrete**

- Matrix form: let $\mathbf{A} = \{\, \mathbf{A}(x_i, x_j)\}$, $\mathbf{A} \in \mathbb{R}^{|\mathcal{X}| \times |\mathcal{X}|}$

$$d\,p(\mathbf{x}, t)/\,dt = \mathbf{A}\, p(\mathbf{x}, t)$$

Discrete CME

- Full account of probabilities of jumps:
  - Regardless whether copy numbers are small or large, jumps are large or small
  - Full stochasticity
- Can generate trajectories with correct probabilities
  - Based on the network architecture and reaction rates with enumerated states
- Little applications
  - Not feasible beyond very simple systems

Challenge: Requires full description of the discrete state space!

The Holy Grail

- Time-evolving probability landscape p(**x**, t) over all possible states
  - Full stochasticity
  - Can account for nonlinearity in reactions

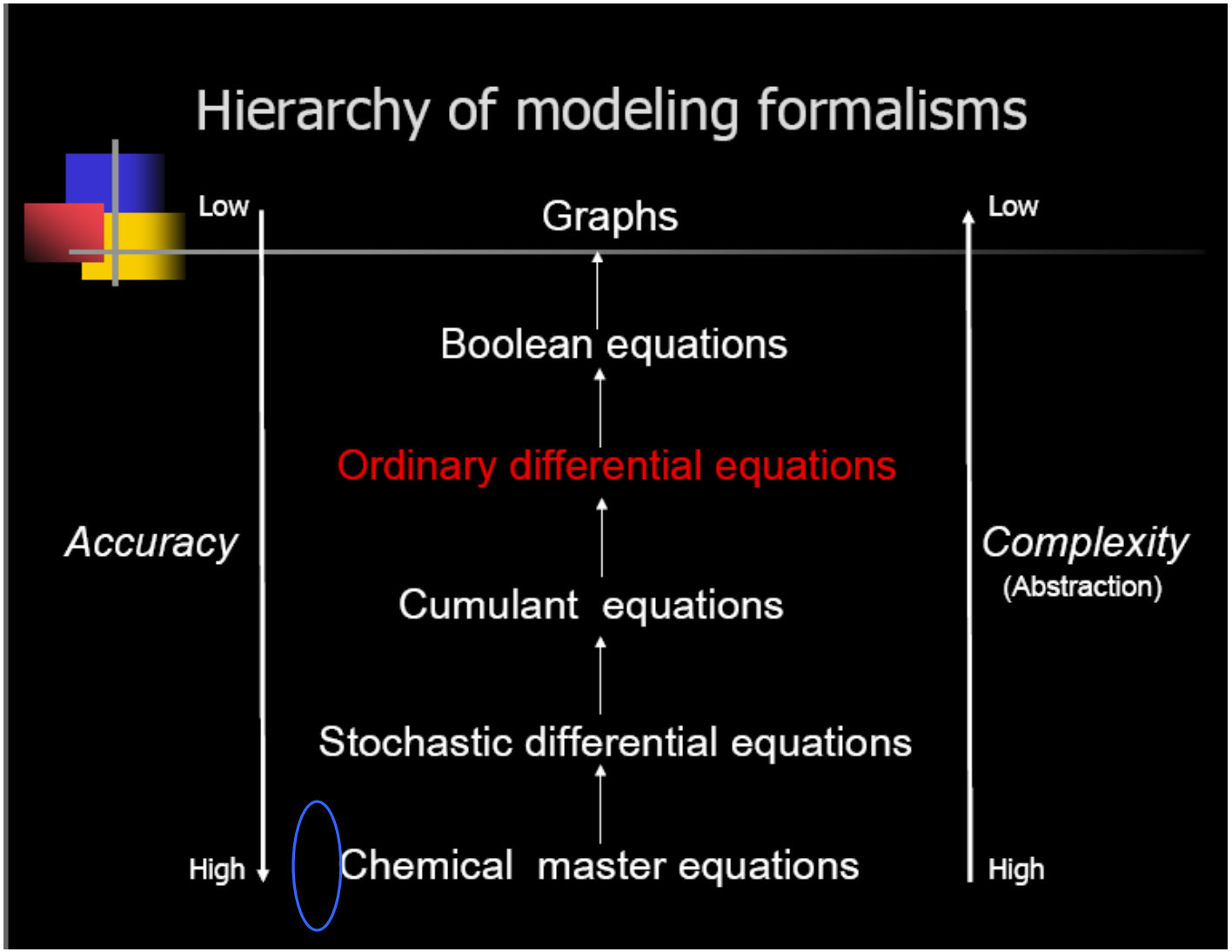
- Vector filed on the same state space
  - Discrete view: same *k*-pointed hats but of very different sizes
  - Continuous view: generic vector field and such structures may be lost.

An Analogy

(see Qian and Beard, 2008)

- Physics and chemistry:
  - Schrodinger Equation
  - Wave function or density function (or partition function in stat mech)
- Exact solution
  - Possible for systems with 100s of atoms
    - e.g. DFT.

- Systems biology:
  - Chemical Master Equation
  - Landscape probability distribution and dynamic changes
- Exact solution
  - Nothing is known about how far we can go!



(Courtesy: Prof Luonan Chen)

Solving Chemical Master Equation

- Analytical solution: not possible in general
  - Except for toy problems or with assumptions
    - e.g., scale separation, fast equilibrium for some reactions
- Direct numerical solution
  - Requires full description of the enormous discrete state space
    - Expecting explosive combinatorial size of space.
  - Not feasible beyond simple systems.

(van Kampen, 1992)

Approximating discrete chemical master equation

- Finite State Projection:
  - Truncating the full state space
  - With error estimation: accuracy certificate

    (Munsky and Khammash, *J Chem Phys*, 2006)
  - Difficulty in choosing specific subspace and limiting its size
  - Need absorption state
  - Cannot compute the steady state probability landscape
    - Leakage accumulates

Stochastic Simulation Algorithm

- Generating reaction trajectories through Monte Carlo
- But follows high probability events (Gillespie, 1977)
  - Very inefficient in sampling rare events.
- Difficult to assess convergency
- Recent work: biased Monte Carlo for rare events:
  - wSSA (Kuwahara & Mura, 2008), dwSSA (Daigle et al, 2011), swSSA (Roh et al, 2011)
  - Adaptively Biased Sequential Importance Sampling (ABSIS)

(Cao and Liang, J Chem Phys, 2013, 139(2):025101)

Approximating dCME with Continuous Chemical Master Equation

- Regarding **state space as continuous**,
- Assumption:
  - Difference in the amount of molecules in neighboring states are infinitesimally small:

$$\partial\, p(\mathbf{x}, t)/\partial\, t = \int_{\mathbf{x}'} [\, A(\mathbf{x}', \mathbf{x})\, p(\mathbf{x}', t) - A(\mathbf{x}, \mathbf{x}')\, p(\mathbf{x}, t)]\, d\,\mathbf{x}'$$

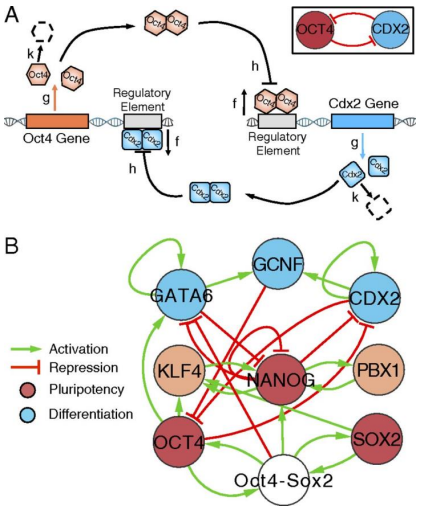
Not valid when only a handful of molecules !

Approximating continuous chemical master equation

- Fokker-Planck Equation: Approximating continuous CME
  - Neighboring states have small difference
  - Further assumptions: (Munsky and Khammash, *J Chem Phys*, 2006)
    - Jumps are small: $|x_i - x_j| < \varepsilon$
    - Transition probability vary slowly: $A(x, y) \approx A(x + \varepsilon_1, y + \varepsilon_2)$
    - Probability vary slowly: $p(\mathbf{x}, t) \approx p(\mathbf{x} + \varepsilon, t)$
  - Replace the jump operator A(x', x) from x' to x:
    - with a differential operator
    - 2nd order Taylor expansion of the differential operator with higher order truncation
- Other Approximation
  - Stochastic differential equation: Langevin equation

Errors due to these approximations are generally not known!

General Approach



- Identify a significant biological problem
- Construct a reasonable stochastic network

- Compute solutions
  - Simulation using Gillespie algorithm
  - Langevin/Fokker-Planck stochastic equation
  - Analysis with Gaussian assumptions
  - Techniques from other fields such as quantum field theory

- But is the network correct? Are we finding the right solutions?

- The truth is unknown except simple cases
  - Experimental results can provide answer but too much degeneracy
    - Not for theory and algorithm development

Can mathematics help?

How to describe the discrete state space for direct solution of dCME?

- Naïve approach (Method 1)
  - B^n, where:
    - B = the maximum possible copy number of each molecular species in the system = "buffer size"
    - n = number of species.
  - e.g. # of states exponentially large:
    - eg, 16 molecular types, 30 total copies: $(30+1)^{16}=7.27\text{x}10^{23}$
  - Many such states will never be visited

- Following trajectory of states from simulation
  - No guarantee all accessible states will be visited

Needs a method that can efficiently describe accessible states

Finite Buffer dCME Method

- Optimal enumeration algorithm of state space
  - Assumes finite number of net molecules synthesized
  - Starts with a given initial condition

- Optimal in memory requirement and time complexity
  - All states reachable from an initial condition will be accounted for
  - No irrelevant states are included
  - All possible transitions will be recorded
  - No infeasible transitions will be attempted

(Cao and Liang, *BMC Systems Biology*, 2008, 2:30;
Cao et al, *PNAS*, 2010, 107(43):18445-50
Cao and Liang, *J Chem Phys*, 2013, ,139(2):025101
Cao, Terebus, and Liang, 2014, manuscript)

Algorithm 1 State Enumerator($\boldsymbol{M}, \boldsymbol{R}, B$)

Network model: $\boldsymbol{N} \leftarrow \{\boldsymbol{M}, \boldsymbol{R}\}$;
Initial condition: $\boldsymbol{s}^{t=0} \leftarrow \{c_1^0, c_2^0, \ldots, c_m^0\}$; Set the value of buffer capacity: $c_{m+1}^0 \leftarrow B$;
Initialize the state space and the set of transitions: $\mathcal{X} \leftarrow \emptyset$; $\boldsymbol{T} \leftarrow \emptyset$;
Stack $ST \leftarrow \emptyset$; Push(ST, $\boldsymbol{s}^{t=0}$); *StateGenerated* ←FALSE
while $ST \neq \emptyset$ **do**
  $\boldsymbol{s}_j \leftarrow$ Pop (ST);
  for $k = 1$ to n **do**
    if reaction R_k occurs under condition $\boldsymbol{s}_j$ **then**
      if reaction R_k is a synthetic reaction and generates u_k new molecules **then**
        $c_{m+1} \leftarrow c_{m+1} - u_k$
        if $c_{m+1} \geq 0$ **then**
          Generate state $\boldsymbol{s}(j, R_k)$ that is reached by following reaction R_k from $\boldsymbol{s}_j$;
          StateGenerated ←TRUE
        end if
      else
        if reaction R_k is a degradation reaction and breaks down u_k molecules **then**
          $c_{m+1} \leftarrow c_{m+1} + u_k$
        end if
        Generate state $\boldsymbol{s}(j, R_k)$ that is reached by following reaction R_k from $\boldsymbol{s}_j$;
        StateGenerated ←TRUE
      end if
      if (*StateGenerated* = TRUE) and ($\boldsymbol{s}(j, R_k) \notin \mathcal{X}$) **then**
        $\mathcal{X} \leftarrow \mathcal{X} \cup \boldsymbol{s}(j, R_k)$;
        Push(ST, $\boldsymbol{s}(j, R_k)$);
        $\boldsymbol{T} \leftarrow \boldsymbol{T} \cup t_{\boldsymbol{s}(j,R_k),\boldsymbol{s}_j}$;
        $a_{i,j} \leftarrow$ Transition Coefficient($\boldsymbol{s}(j, R_k)$, $\boldsymbol{s}_j$, R_k)
      end if
    end if
  end for
end while
Output $\mathcal{X}$, $\boldsymbol{T}$ and $\boldsymbol{A} = \{a_{i,j}\}$.

(Cao and Liang, *BMC Systems Biology*, 2008, 2:30)

- Works for networks of reactions with arbitrary stoichiometry

- Optimal in memory requirement and time complexity
  - All states reachable from an initial condition will be accounted for
  - No irrelevant states are included
  - All possible transitions will be recorded
  - No infeasible transitions will be attempted

Computing Steady State Distribution

- Once states are defined, can compute steady state probability landscape with mild assumptions:

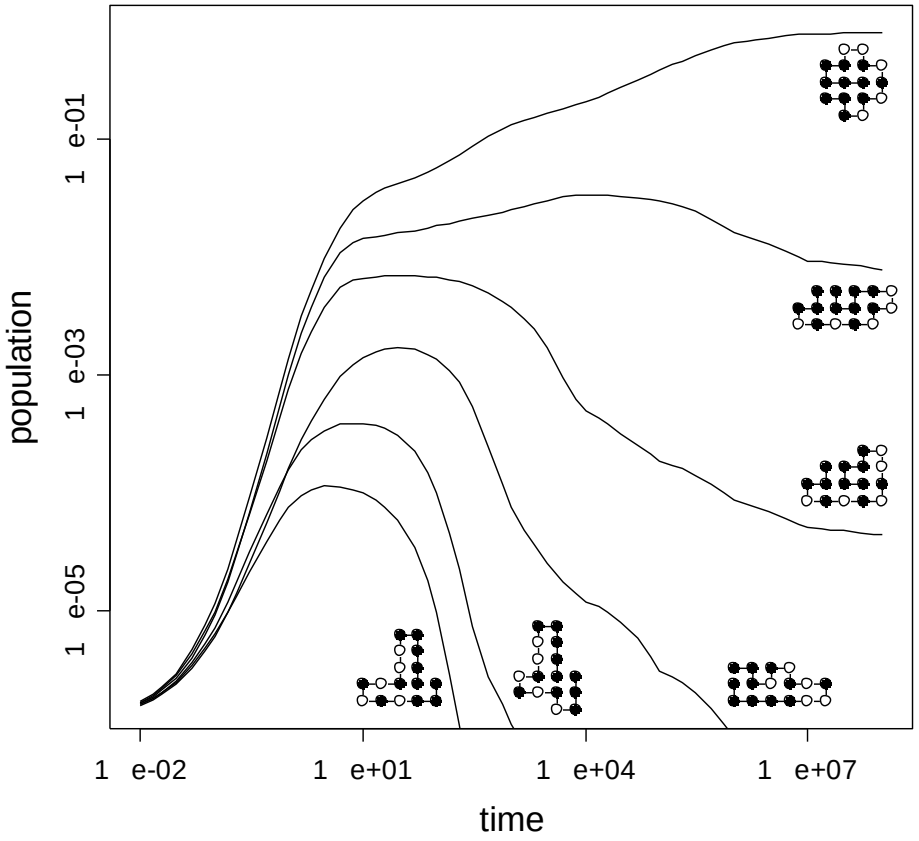
  Let $M = A + I\,\Delta t$, solve $p = M\,p$

  - Does not depend on initial condition
  - It is the eigenvector with eigenvalue = 1
  - e.g. Arnoldi method

(Cao and Liang, *BMC Systems Biology*, 2008, 2:30)

Computing Dynamics

$$d\,p(\mathbf{x}, t)/\,dt = \mathbf{A}\,p(\mathbf{x}, t), \qquad p(\mathbf{x}, t) = p(\mathbf{x}, 0)\,e^{\mathbf{A}t}$$



Can use Krylov subspace method

(Sidje, 2002)

Eg. In a study of model proteins, where time-dependent dynamics changes of probability /concentration of all states/conformations during folding process are computed.

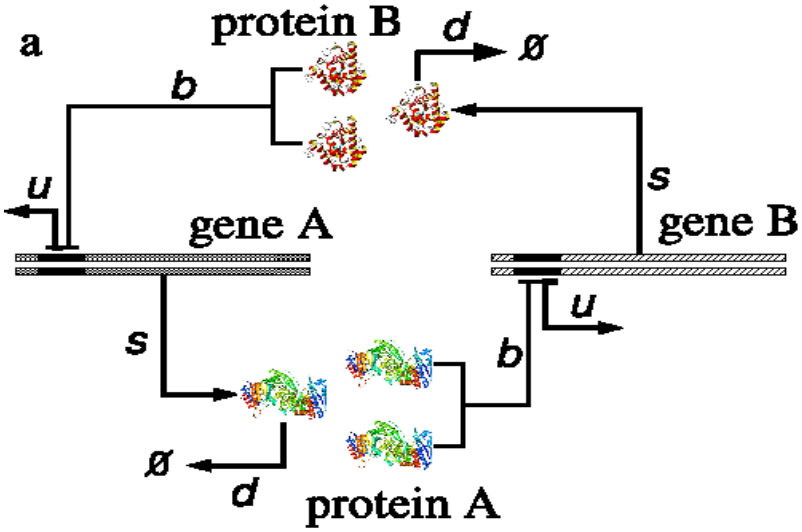
800,000 states

9-orders of magnitude

Kachalo, Lu, and Liang, *Phys Rev Lett*, 2006, 96:058105:1-4

Example: Toggle Switch

- Two genes, A and B.
  - Products repress each other.
  - One of the simplest networks with bistability
  - No general analytical solution.



b

$$Gene A \xrightarrow{s} Protein A$$

$$Gene B \xrightarrow{s} Protein B$$

$$Protein A \xrightarrow{d} \emptyset$$

$$Protein B \xrightarrow{d} \emptyset$$

$$2 \times Protein A + Gene B \xrightarrow{b} Bound Gene B$$

$$2 \times Protein B + Gene A \xrightarrow{b} Bound Gene A$$

$$Bound Gene A \xrightarrow{u} 2 \times Protein B + Gene A$$

$$Bound Gene B \xrightarrow{u} 2 \times Protein A + Gene B$$

J Collins et al, 2000, Nature

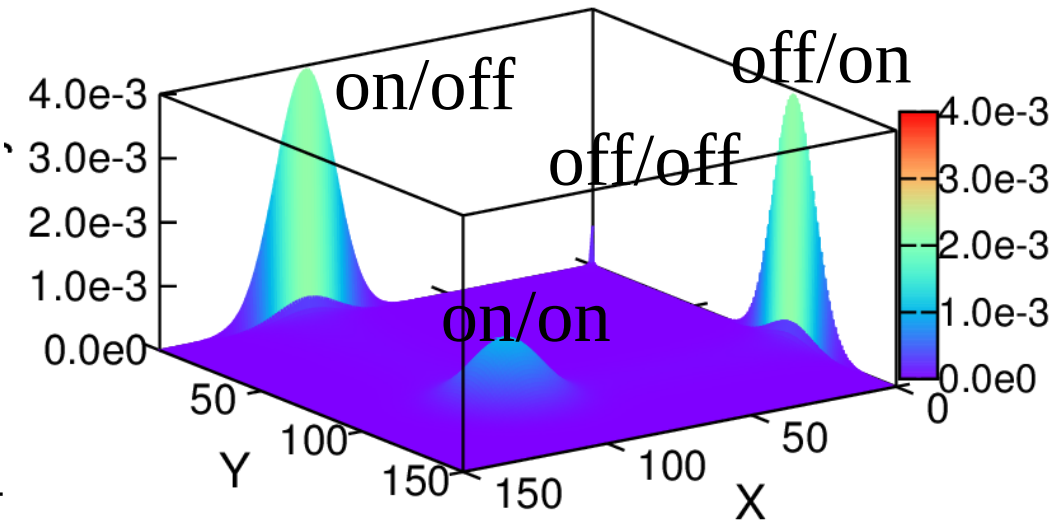
Recent approximation methods:
(Schultz, Onuchic, and Wolyness, 2007, JCP;
Kim and Wang, 2007,)

Toggle-Switch: Our results

- Size of state space:

# Prot A	# B	Size
10	10	764
50	50	19,804
100	100	79,604
150	150	179,404
200	200	319,204
250	250	499,004
300	300	718,804
350	350	978,604
400	400	1,278,404

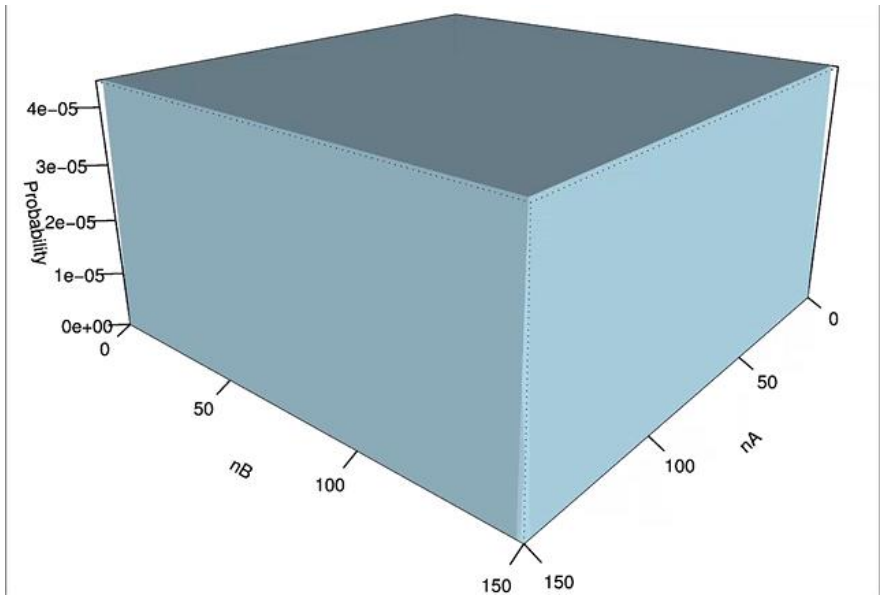
- Exact landscape of steady state probability:



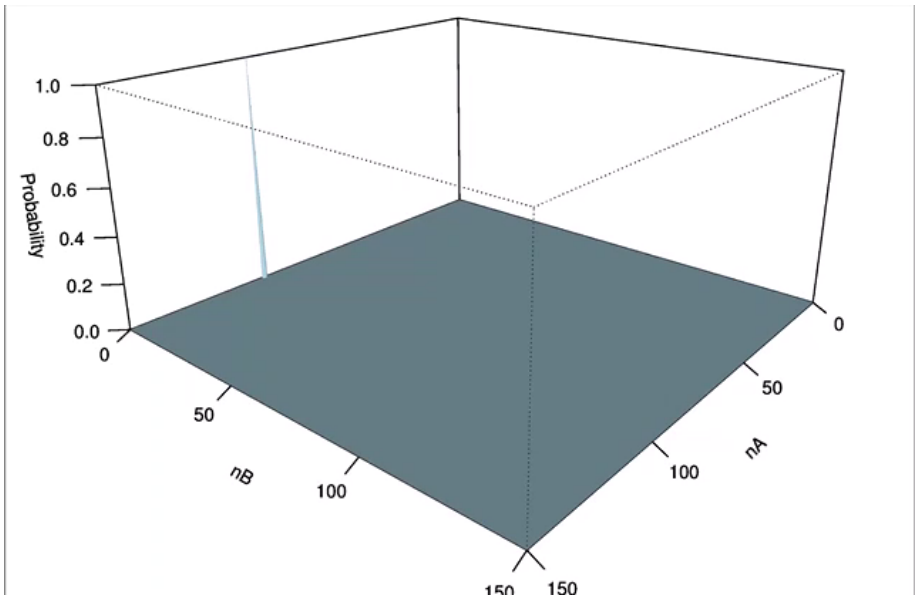
Clear bistability

Time evolving probability landscapes of toggle switch

Starting from uniform distribution



Starting from state (A=100, B=0)



How to go beyond simple motifs?

- Challenging task
  - Most studies have just a few nodes
  - Use approximations: *eg* Langevin, with unknown errors
  - Or run Gillespie algorithm, and hope for the best

Direction Solution: Multi-finite Buffer dCME Algorithm

- How do we know if computed attractive basins are real?
- How to be sure if the computed landscape is not erroneous?
  - How to quantify errors?
- What are the best accuracy we can achieve?

- Probability flux, boundaries, and truncation error of finite state space
  - Boundary probability and convergency theory
  - Can answer all above questions

- Mb-dCME algorithm and optimized finite state space
  - Decomposition of reaction graphs
  - Independent Birth-Death components
  - Multiple buffer queues to control truncation errors

(Cao, Terebus, and Liang, 2014, manuscript)

Independent Birth-Death Components of Reactions

- iBDs: Decompose reactions into independent components
- Each iBD is of infinite size, except *j*-th iBD
- Study the steady state distribution

$$\bar{\pi}_N^{(N)} \equiv \pi_{\partial,\, B_j}^{(\mathcal{I}_j)} = \sum_{\boldsymbol{x}\in\partial,\, B_j} \pi^{(\mathcal{I}_j)}(\boldsymbol{x}) = \sum_{\boldsymbol{x}\in\partial,\, B_j} p^{(\mathcal{I}_j)}(\boldsymbol{x},\, t=\infty)$$

Analysis of Truncation of Infinite Rate Matrix

- Truncation of infinite spaces, where

$$\mathcal{I} = (\infty, \cdots, \infty) \qquad \mathcal{I}_i = (\infty, \cdots, B_j, \cdots, \infty)$$
$$\mathcal{I}_{i,j} = (\infty, \cdots, B_i, \cdots, B_j, \cdots, \infty)$$

where $\Omega^{\mathcal{B}} \subseteq \Omega^{\mathcal{I}_{i,j}} \subseteq \Omega^{\mathcal{I}_j} \subseteq \Omega^{\mathcal{I}}$.

Lemma 5. *At steady state,* $\boldsymbol{\pi}^{\mathcal{I}_{i,j}}(\boldsymbol{x}) \geq \boldsymbol{\pi}^{\mathcal{I}_j}(\boldsymbol{x})$ *and* $\boldsymbol{\pi}^{\mathcal{I}_{i,j}}(\boldsymbol{x}) \to \boldsymbol{\pi}^{\mathcal{I}_j}(\boldsymbol{x})$ *componentwise for any* $\boldsymbol{x} \in \Omega^{\mathcal{I}_{i,j}}$ *when buffer capacity* $B_i \to \infty$.

- Can determine minimum buffer required for errors to be smaller than a pre-defined tolerance

- Optimal memory allocation so errors are minimized

Direction Solution: Multi-finite Buffer dCME Algorithm

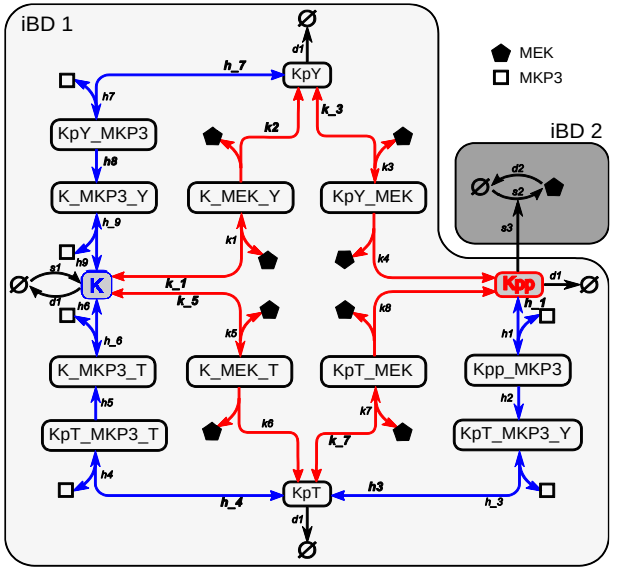
- How do we know if computed attractive basins are real?
- How to be sure if the computed landscape is not erroneous?
  - How to quantify errors?
- What are the best accuracy we can achieve?

- Yes to all with mf-dCME method!

(Cao, Terebus, and Liang, 2014, manuscript)

MAPK cascade

- Closed system, 16 molecular species (n=16), 35 reactions.
- Reduction factor of *ca*. 10^9



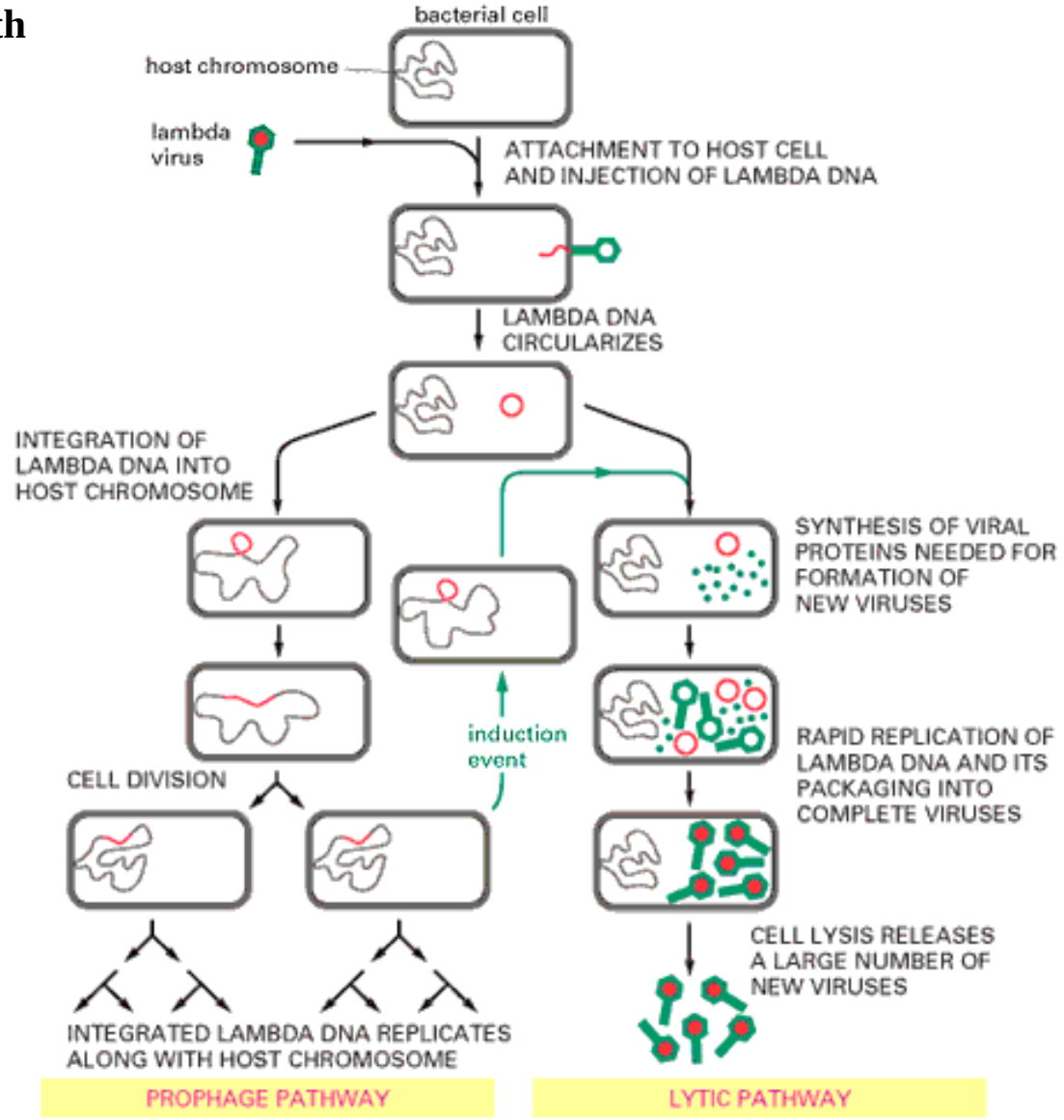
Sizes of Buffer Queues	Mb-dCME Finite Buffer	Hypercube Method	Reduction Factor
3, 3	2, 176	4.3×10^{9}	2.0×10^{6}
6, 6	209,304	3.3×10^{13}	1.6×10^{8}
9, 9	6,210,644	1.0×10^{16}	1.6×10^{9}
14, 6	2,706,935	1.1×10^{11}	4.1×10^{4}

- All with errors quantified and ensured that they are small (Cao, Terebus, and Liang, 2014, manuscript)

Example: Phage Lambda's Life Cycle:

A choice between lysogenic and lytic growth

- Two pathways:
  - Prophage/ Lysogenic pathway
    - Integrate into host genome
  - Lytic pathway:
    - genome replication, protein sysnthesis, assembly of viral particles, cell lysis, escape of mature phage
- Epigenetic memory
  - Passed along



(Arkin, Ross, McAdam, 1998)

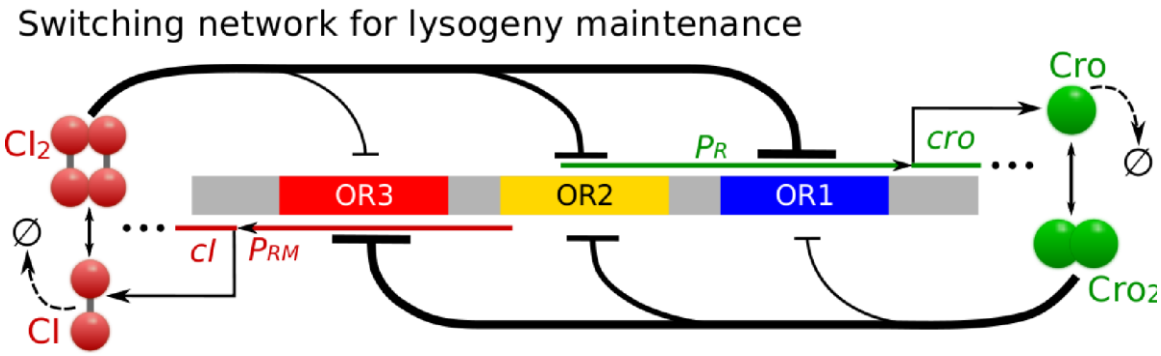
(Essential Cell Biology, Second Edition, Garland Science, 2004)

How does it work?

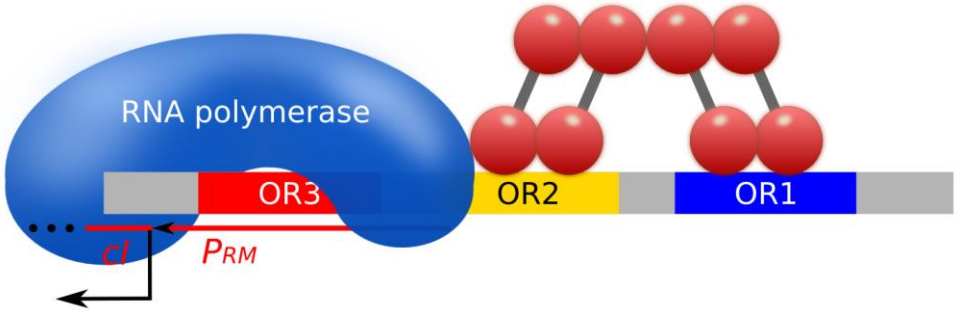
- Systems stability against perturbation
- Robustness against genetic mutation
- Regulation mechanism of the switch
- Heritable epigenetic state
  - DNA damage due to UV

Our model

- 13 molecular species
- 51 reactions
- 1.7M microstates



- Cooperativities
  - CI_2, Cro_2
  - Neighboring sites
- Implicit OR-OL looping effect
  - Stabilized CI_2 binding to OR_2, with 10 × higher CI synthesis rate with CI_2 bound OR_2
  - P_{RM} suppressed when CI_2 bound to OR_3
    - Only possible with looping

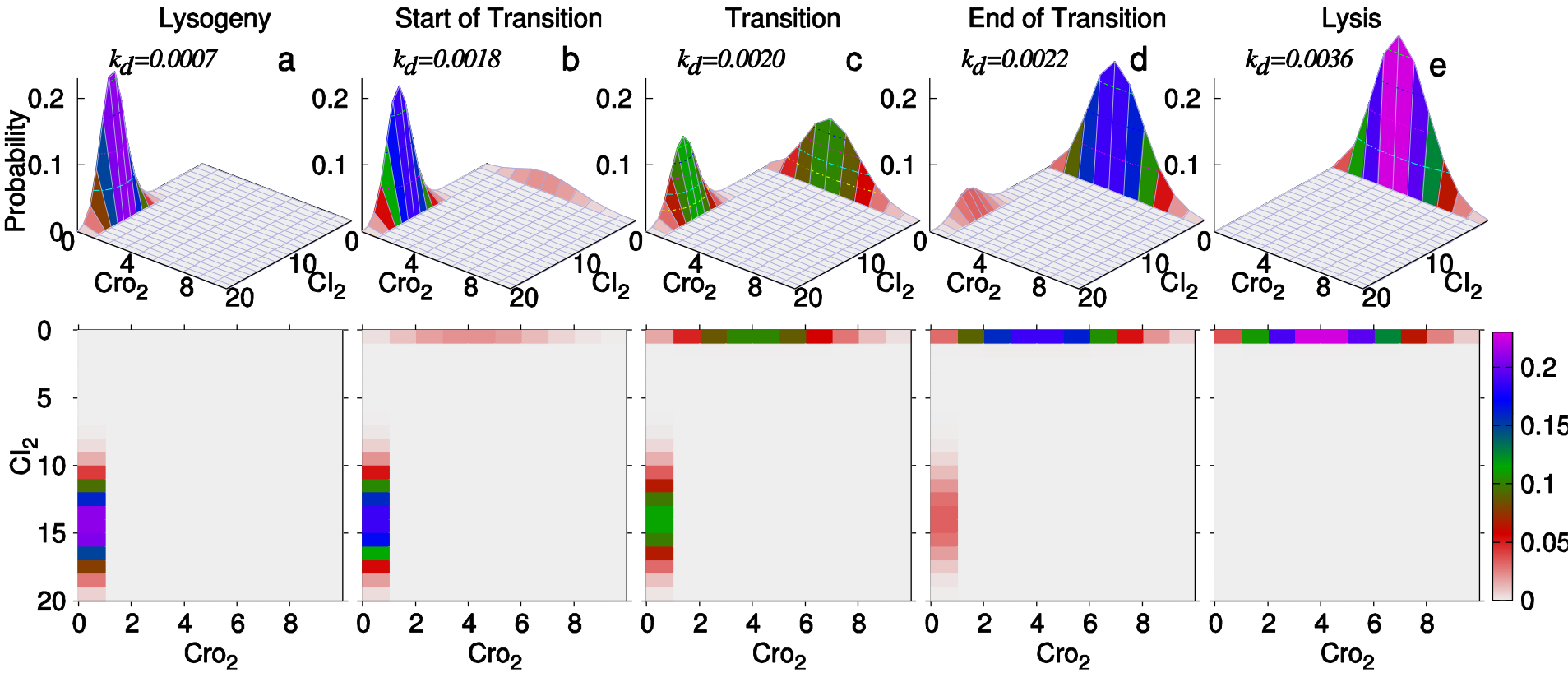


(Cao, Lu, and Liang, *Proc Natl Acad Sci USA*, 2010)

Steady State Probablistic Landscape

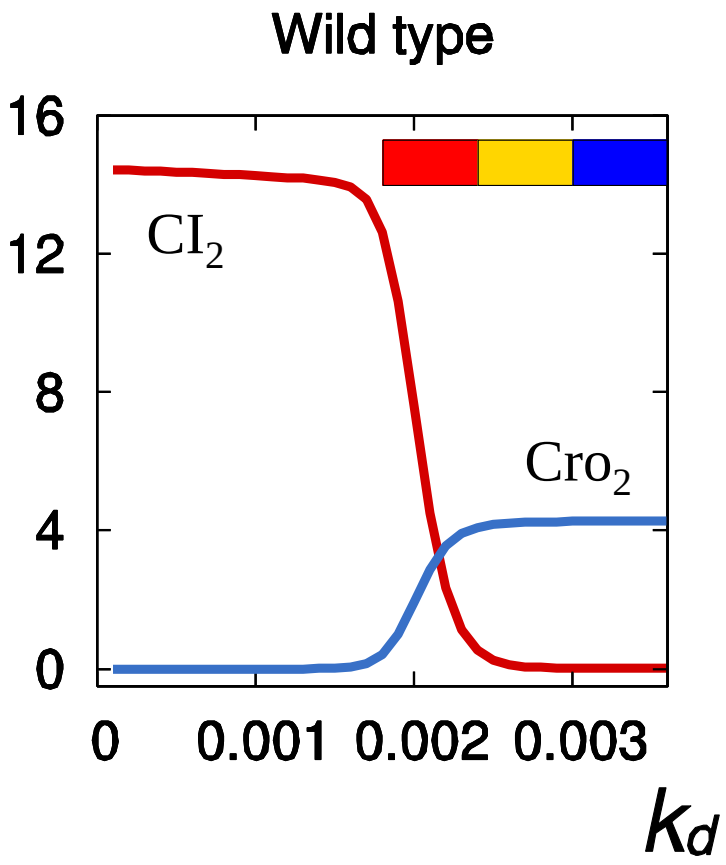
• Lysogenic induction (phage induction):
-- Switching from lysogeny to lytic development

- Different UV dosage: varying CI degradation rate
  - Projection of 13D landscape to CI_2-Cro_2 subspace



Titration Curve: A Mechanistic Picture

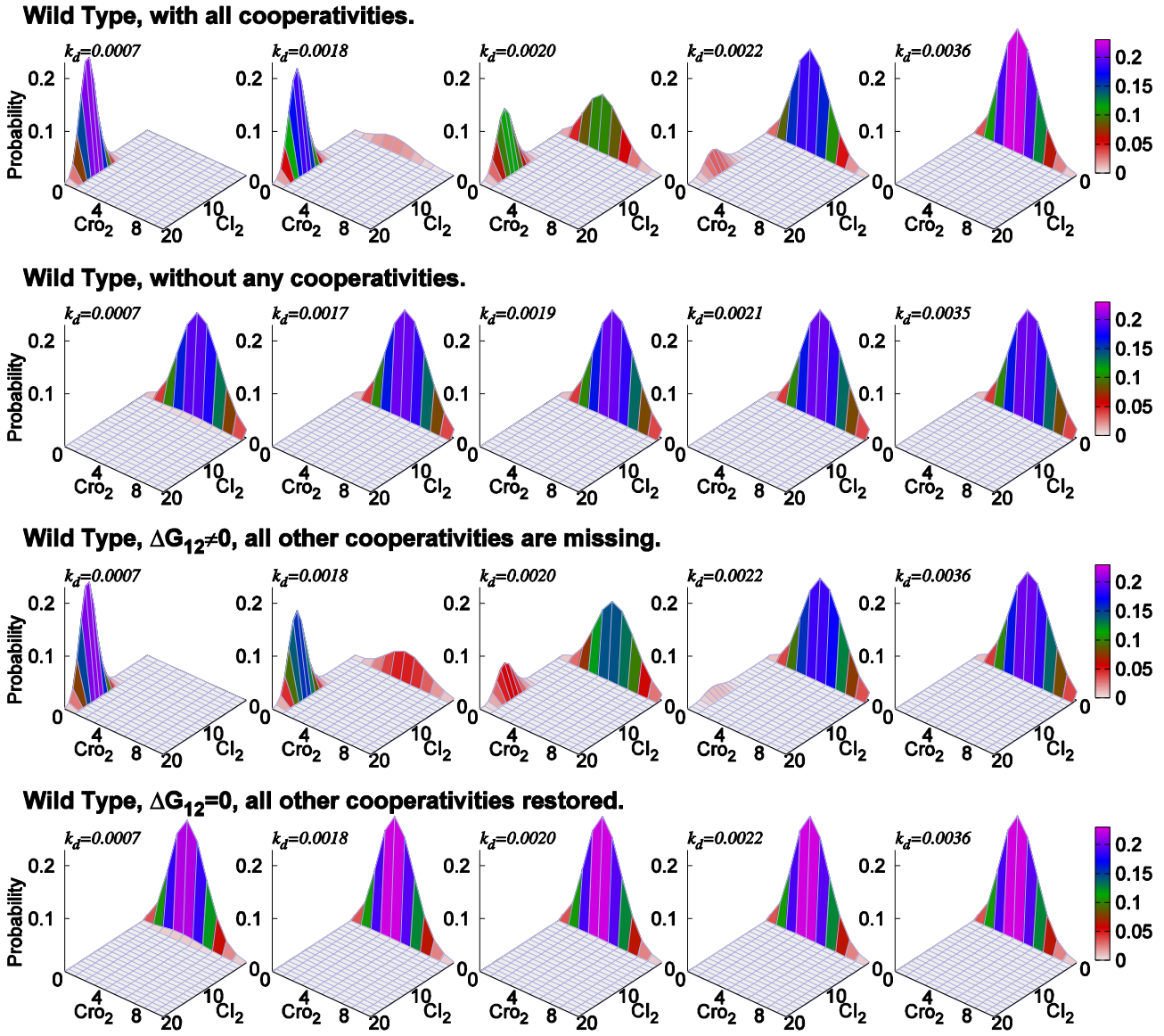
- **CI_2 and Cro_2 level:**
  - Integrate CI_2 and Cro_2 over landscape
- **Wild type: Deep Threshold**
  - Stable to UV irradiation
    - CI degradation rate can fluctuate over a wide region
    - CI level changes little and Cro suppressed
  - Efficient switch over a narrow region:
    - Ultransensitivity for true signal after set point



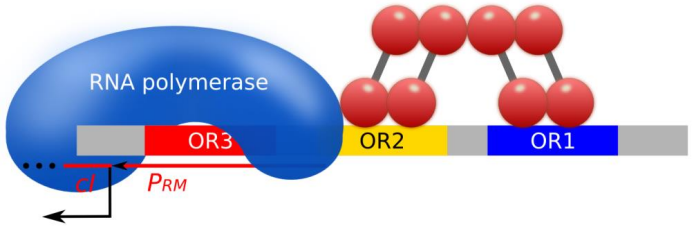
- Maintenance of epigenetic state
  - Same lysogeny upon cell growth and cell division

Mechanism:

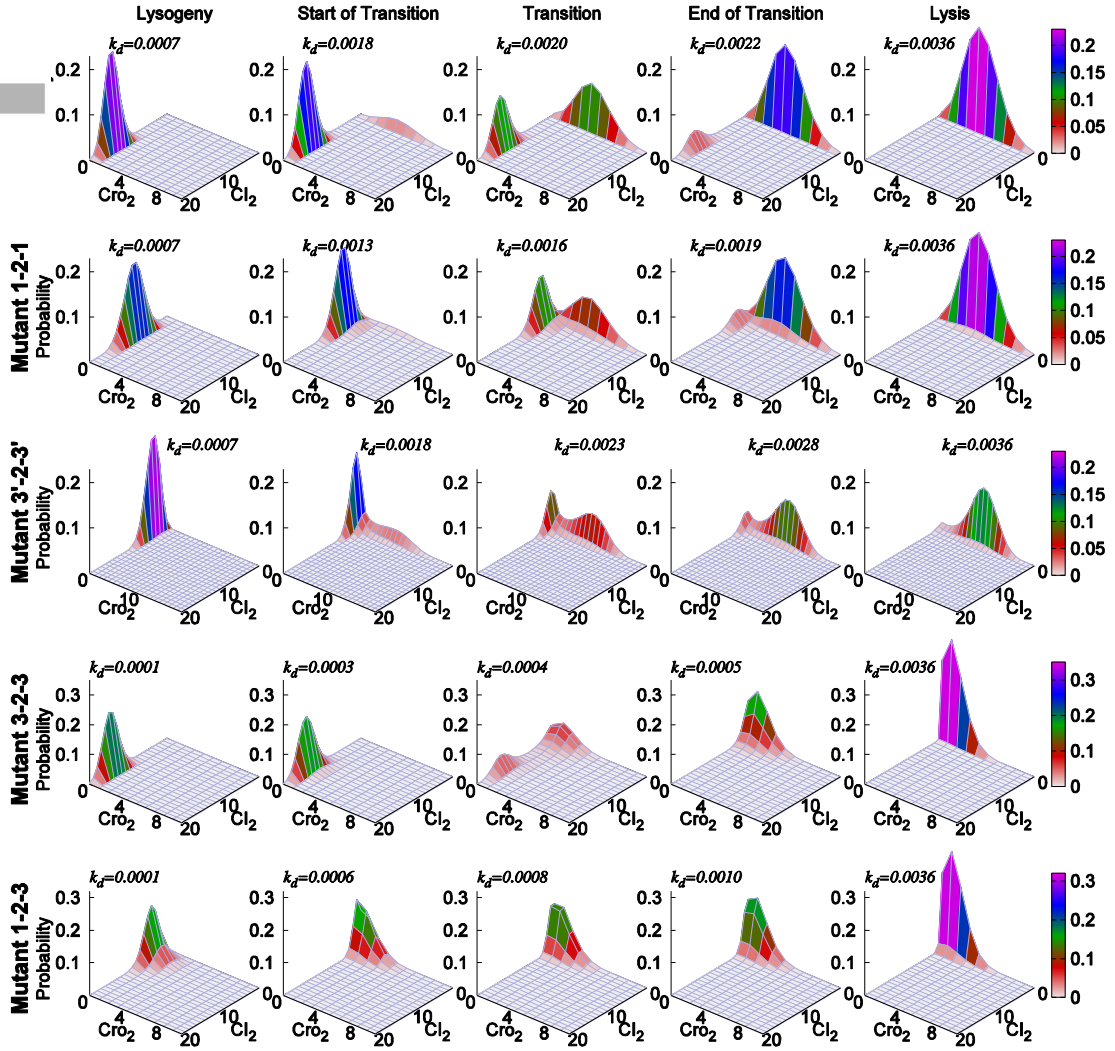
- Cooperativity is essential.
  - Otherwise, no lysogeny.



Effects of Altered Operators



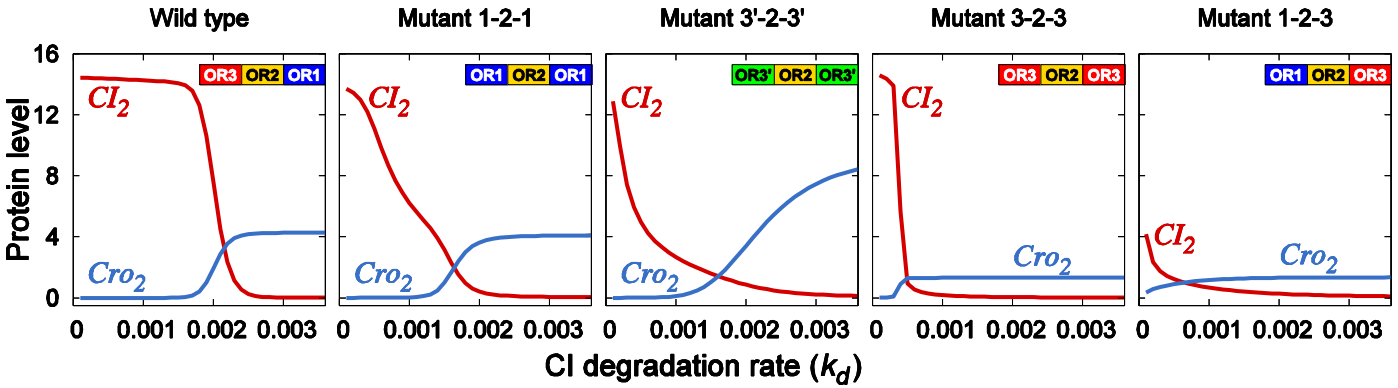
- Wild Type
- Mutants:
  - 1-2-1
  - 3'-2-3'
  - 3-2-3
  - 1-2-3



(Little et al, 2003, *EMBO J*)

Titration Curves: A Mechanistic Picture of Little Study

- All mutants have lower threshold in lysogenic-lytic state transition
  - And also leaky: switching not efficient
- Mutants can be induced to lytic state with lower UV dosage
  - Consistent with Little's "hair trigger" mechanism
- Some cannot lysogenize
  - 1-2-3



Comparison with Stochastic Simulation Algorithm

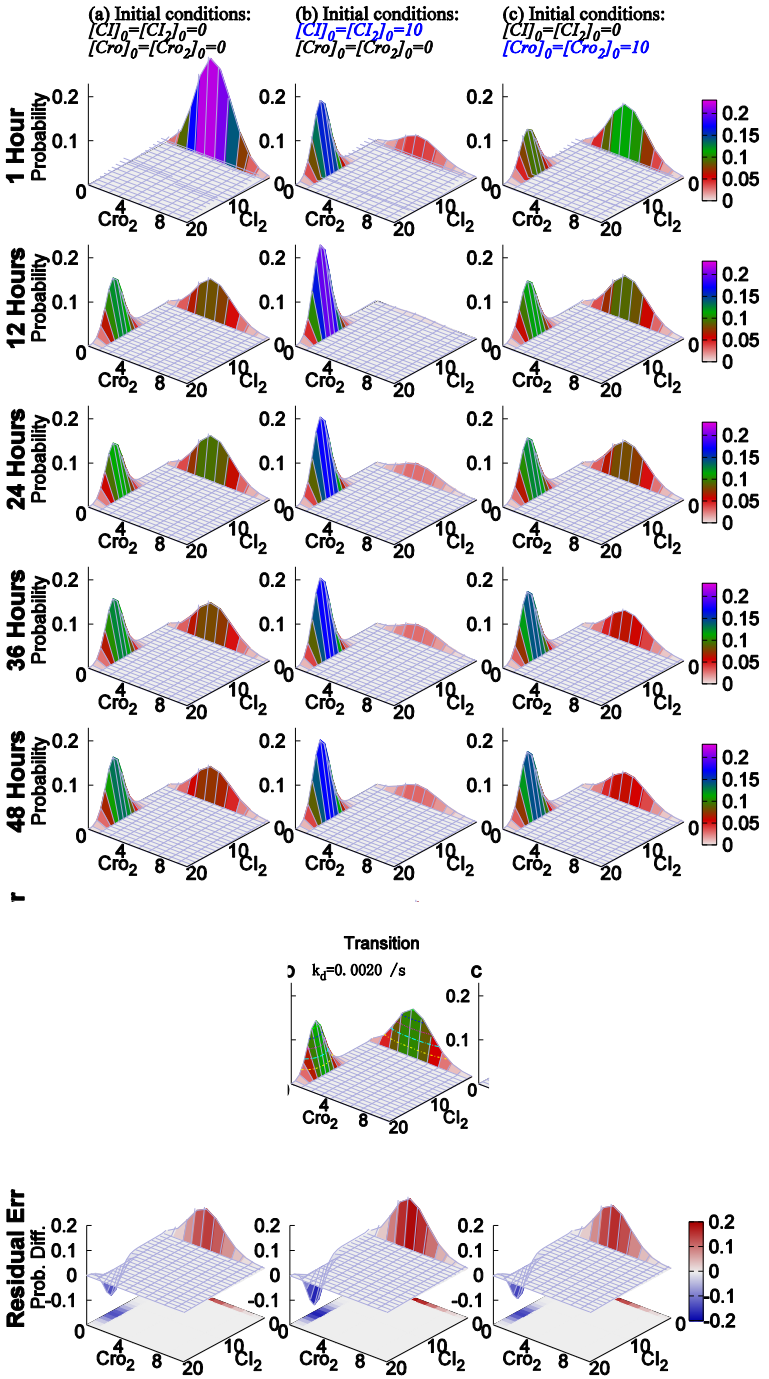
- Improved Gillespie algorithm: StochKit
  - Same model parameters, with CI k_d = 0.002/s
  - Three different initial conditions

(Li, Cao, Petzhold, and Gillespie, 2008)

- Time:
  - dCME: 8 hours, 2GHz quad core, AMD
  - SSA: not yet converged after 48 hours

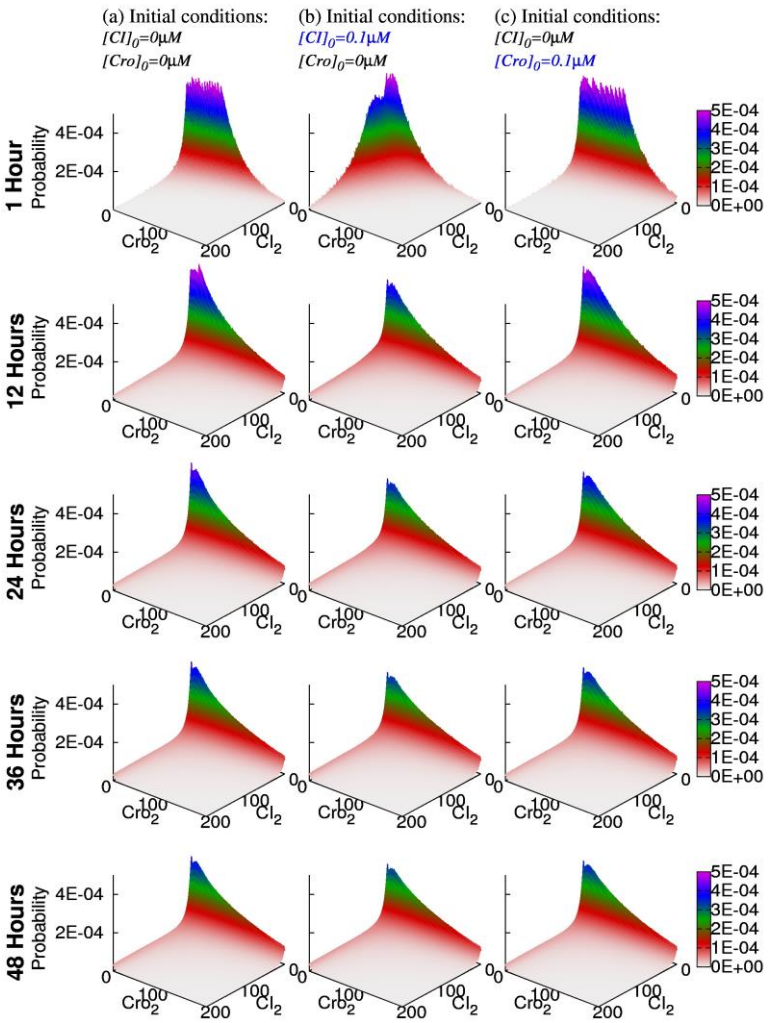
- Wrong conclusion

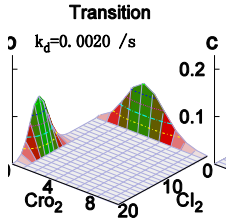
(Cao, Lu, and Liang, *Proc Natl Acad Sci USA*, 2010)



Comparison with Langevin SDE Method

- Langevin SDE
  - Same model parameters, with CI kd = 0.0021/s
  - Three different initial conditions
- Time:
  - dCME: 8 hours,
  - Langevin SDE: not yet converged after 48 hours
- Wrong conclusion
  - Transition phase vs lytic state
- It is unclear how much improvement can be achieved if different formulation of SDE and different stochastic parameters are chosen.





Remark

- dCME method can compute exact probabilit landscape of stochastic network
  - Can solve problems that Gillespie algorithm is challenged
- Study critical rare events
- Mechanistic understanding

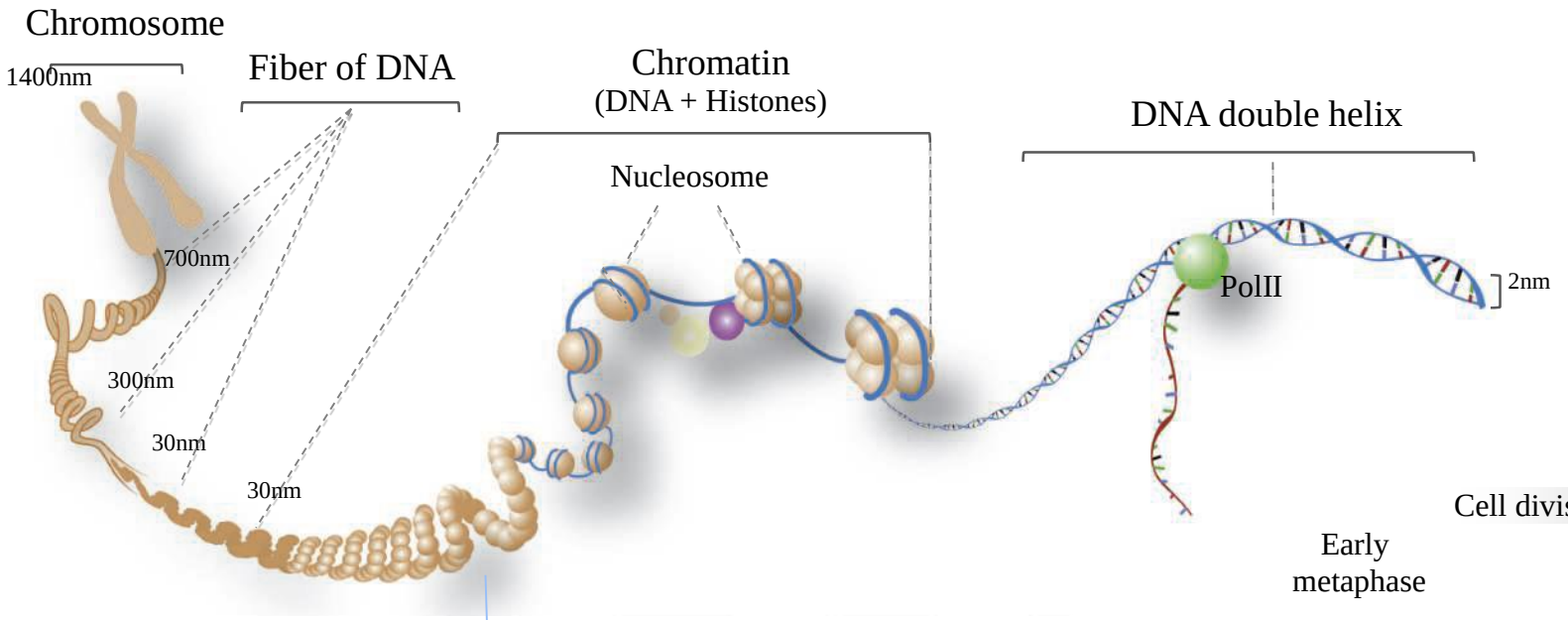
3. Chromosome Folding: Epigenetic States of Cell

- How do distant genetic elements cooperate dynamically?

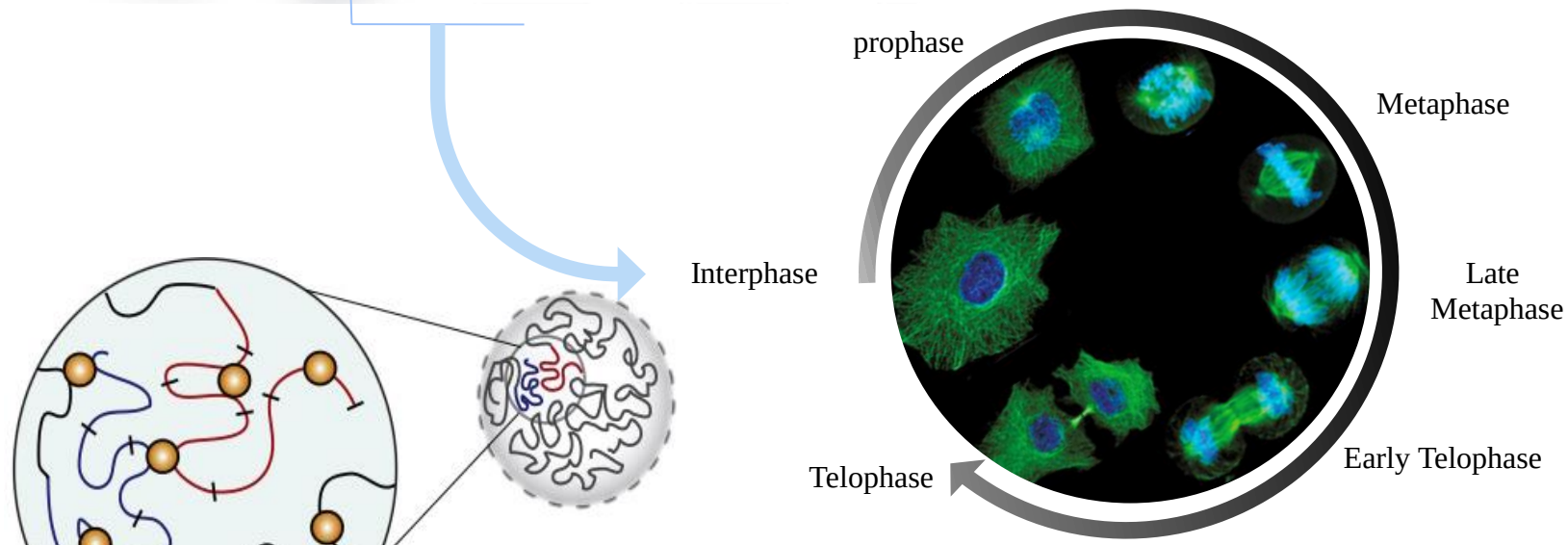
- Higher-order folding behavior of chromosome

- **Noise removal: exclude nonspecific interactions**
- Reconstructing 3D structures of chromosome

(with Gamze Gürsoy, Yun Xu, and Prof. Amy Kenter, manuscript)

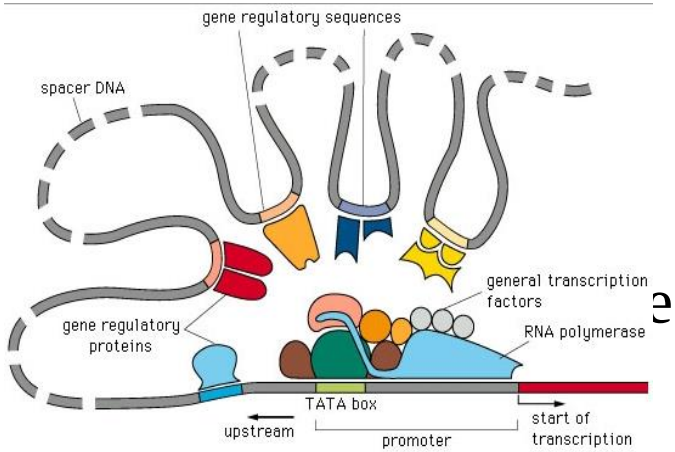


Cell division / cell cycle

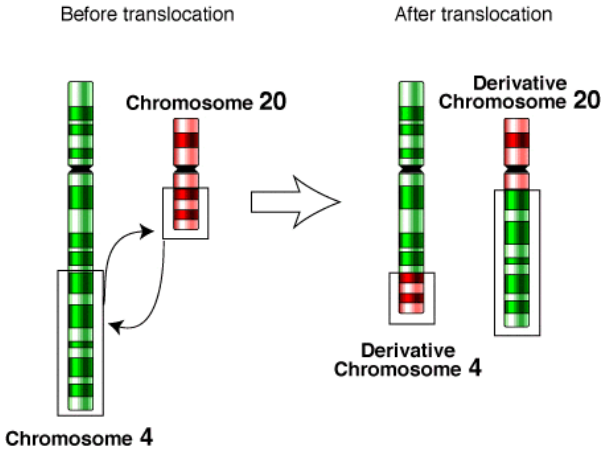


Modified from ELIZABETH PENNISI. **SCIENCE** VOL 337 7 SEPTEMBER 2012

- Chromatin looping and organization: key to cell functions
  - Gene regulation
  - Translocation

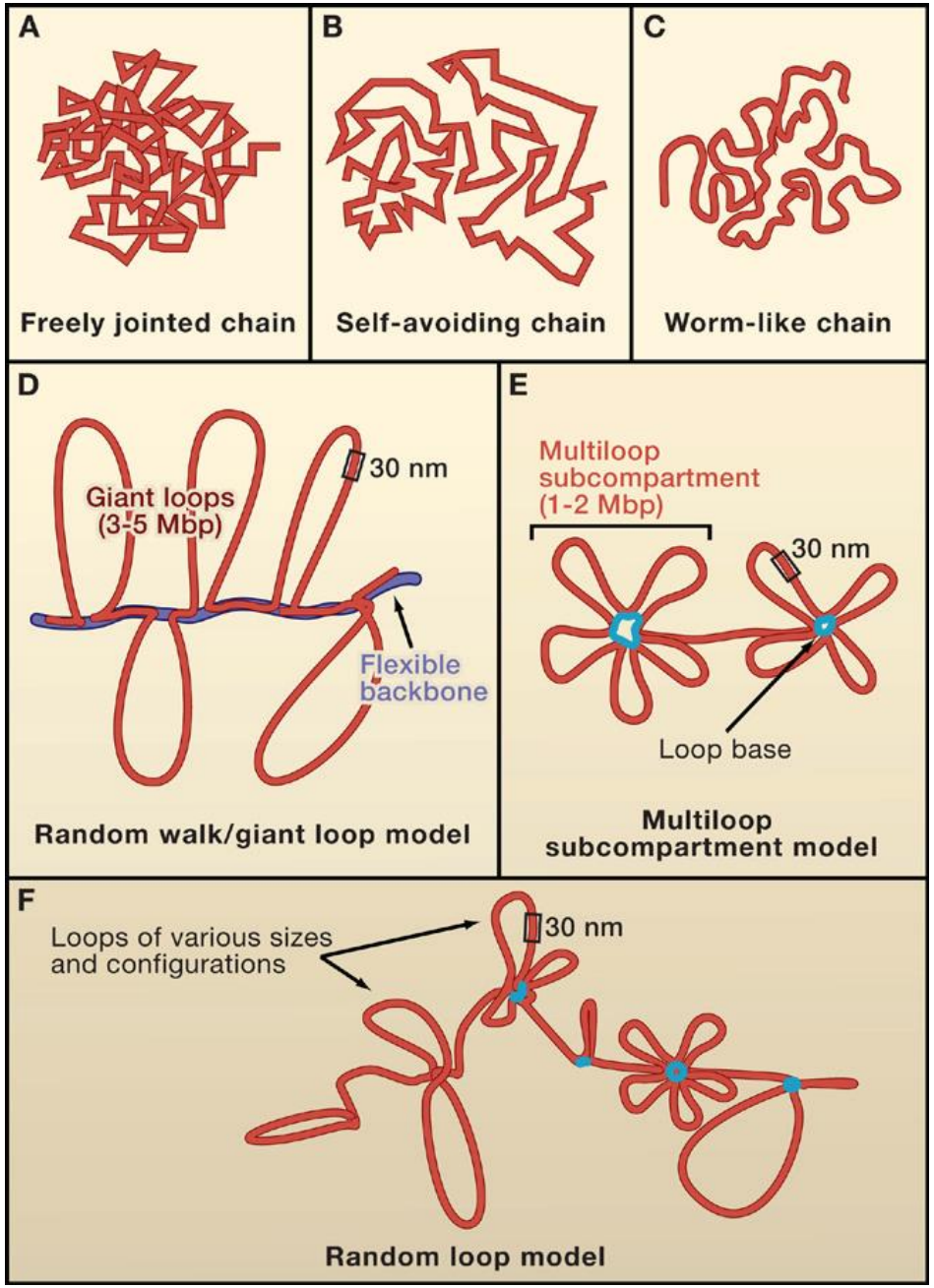


es?



http://pbil.univ-lyon1.fr/baobab/article.php3?id_article=278
http://upload.wikimedia.org/wikipedia/commons/c/cb/Translocation-4-20.png

(Work of Kuhn, Flory, de Gennes, Heerman, Langowski)



- Chain polymer models: very useful
- Challenging
  - Excluded volume
  - Physical properties
    - 30 nm fibre
    - Persistence length
  - Extremely challenging in sampling:
    - **Severe nuclear confinement**

      \+

      Experimental constraints

(from Jhunjhunwala, et al, *Cell*, 2009)

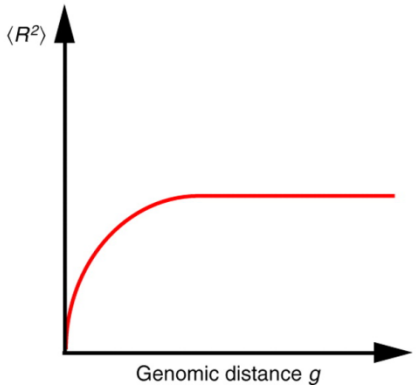
Higher Order Architecture of Chromatin Folding

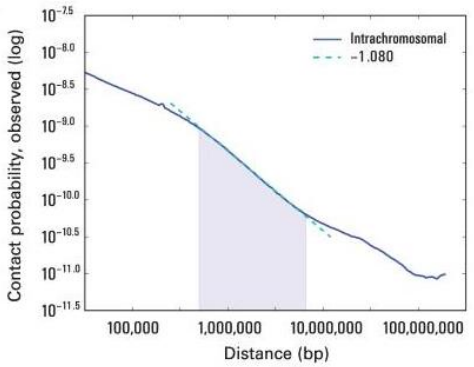
$R^2(g)$ scaling: Spatial vs genomic distances
(FISH studies)

- Short genomic distances

$$R^2(g) \sim g^{2\nu}, \text{with } \nu \sim 0.3$$

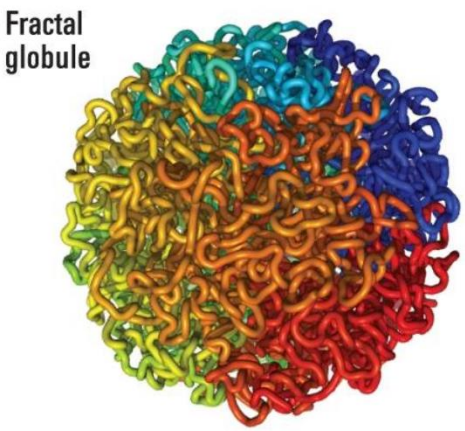
- Longer genomic distances: levels off

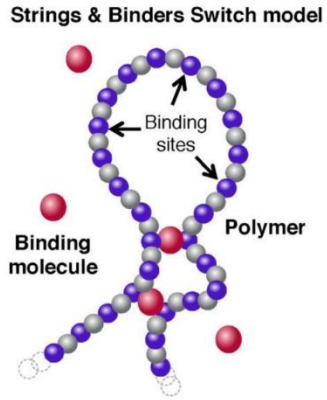




$P_c(g)$ scaling: Looping probability vs genomic distances
(HiC studies) $P_c(g) \sim g^{-\alpha}$

- Diverse, but on average: $\alpha \sim 1.08$





Fractal Globule (FG) model:

- Explains α and ν at short genomic distance
- Not: leveling-off effects and the diverse α exponents

Strings and Binders Switch (SBS) model:

- Average scaling of α and ν
- But, significant parameter tuning
- Results are mutually exclusive

(Lieberman-Eiden et al, 2010, *Science*,)

(Barbieri et al, 2012, *PNAS*)

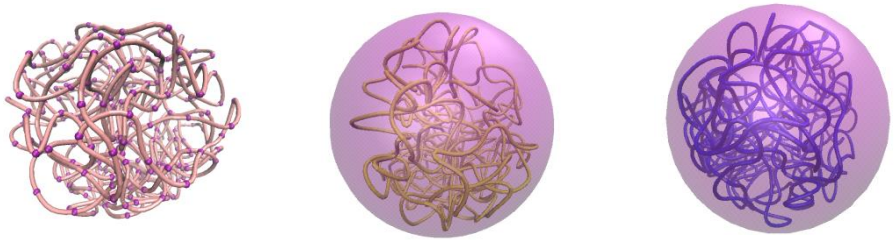
Our Approach: C-SAC Model

Constrained Self-Avoiding Chromatin model

- Physical model of chromatin: with appropriate properties
  - Polymer beads
  - *D*: 30 nm chromatin fiber
  - Bond length: persistence length L_p =150 nm
  - Self-avoiding with excluded volume
  - 1,000 units ~ 5,000 beads ~ 15 Mbp long chain

- **Spatial confinement explicitly modeled !**
  - Not possible with MD or Metropolis Monte Carlo

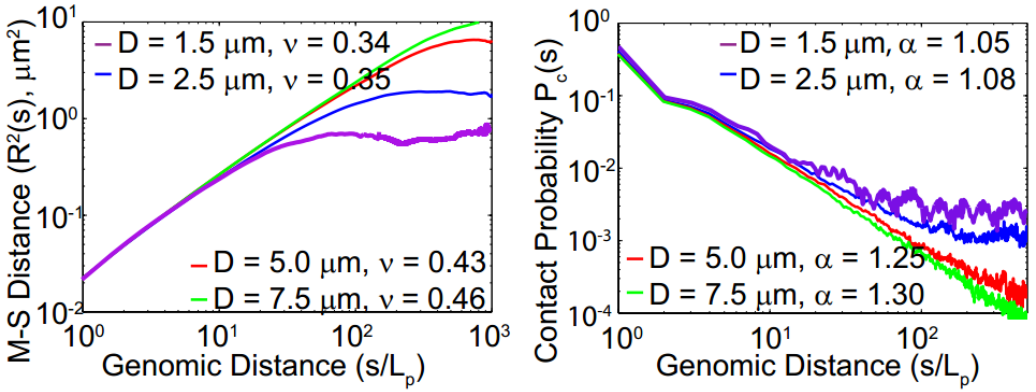
- 10,000 C-SAC chains
  - Properly weighted!



(Gürsoy, Xu, Kenter, and Liang, *Nucleic Acid Res*, 2014)

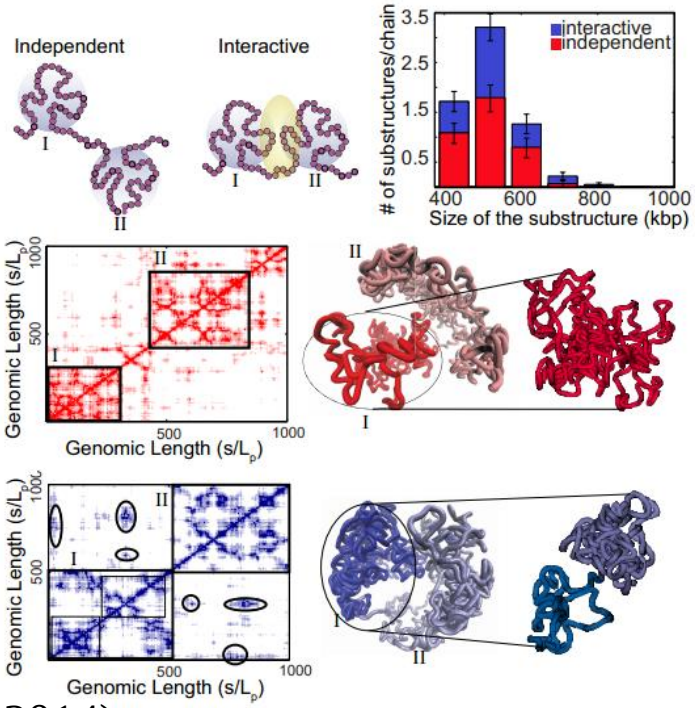
Spatial Confinement Important for Chromosome Folding

- Reproduces $R^2(g)$ and $P_c(g)$ scaling
  - Currently the only polymer model account for all facts
  - Without tuning parameter



- Drives formations of topological domains

- **Nucleus size regulates chromosome structure**
  - induces different folding landscapes
    - e.g., Stem cell with nucleus occupying 95% of volume



(Gürsoy, Xu, Kenter, and Liang, *Nucleic Acid Res*, 2014)

Remark

- Chromatin Chain Polymer Model and Sampling Techniques
  - In confinement and with experimental constraints
- **Removal of noise due to non-specific interactions**

Summary

- Stochastic genetic circuits and cellular state
  - Foundational principles and algorithms
  - Cellular fate

- Chromosome folding and nuclear confinement: 3D structure predictions
  - Removal of noise due to non-specific interactions.
  - 3D physical basis of gene activation and cellular programming

→ Acknowledgement!

Collaborators

- **Youfang Cao (**UIC)
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- **Anna Terebus** (UIC)
- Wei Tian (UIC)
- **Yun Xu** (UIC)
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- **Luisa Di Pietro (UIC)**
- **Linda Kenney (UIC)**
- **Amy Kenter (UIC)**
- John Marko (NWU)
- Lisa Xu (SJTU)

Papers: http://gila.bioe.uic.edu/lab/ (left column)

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