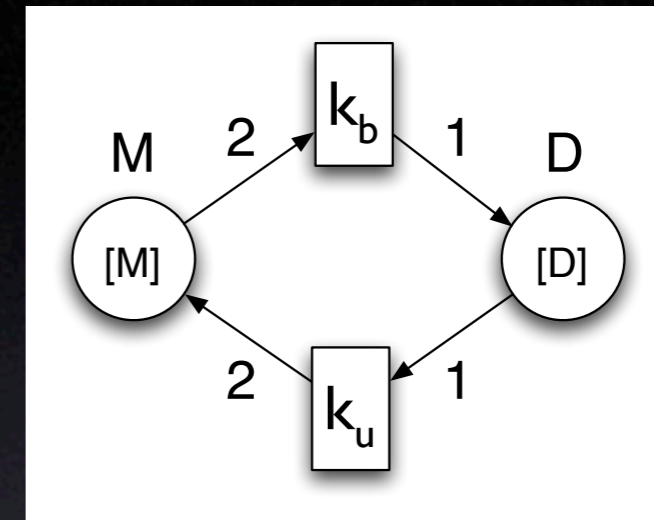
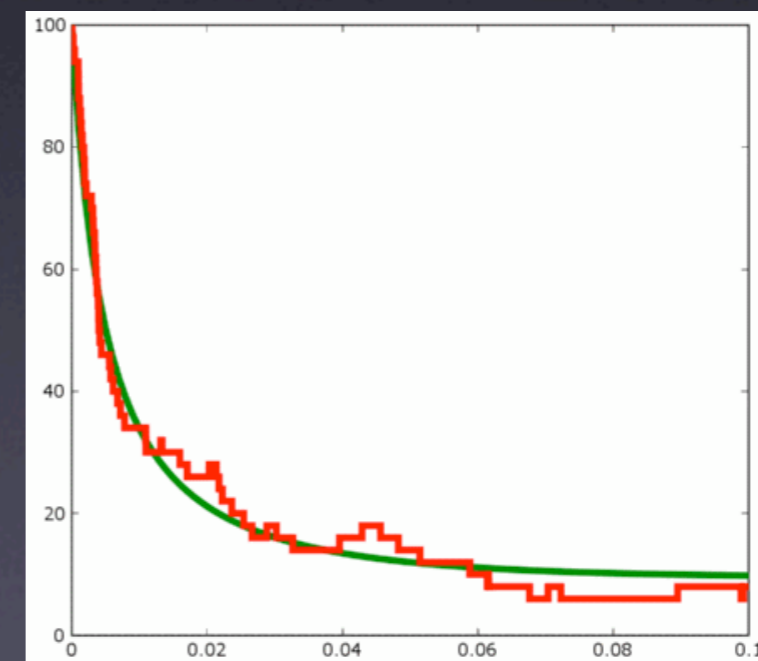


Stochastic cells: simple dimerization reaction

- simple dimerization reaction
 - homodimerization: $M+M \leftrightarrow D$
 - (as distinct from heterodimerization: $A+B \leftrightarrow AB$)
 - introduce Petri net representation
 - ▶ places (circles): molecular species
 - ▶ transitions (rectangles): chemical reactions, parameterized by rate constants
 - ▶ arcs (directed segments): stoichiometric weights
- compare stochastic and deterministic simulations
 - deterministic
 - ▶ $dy/dt = f(y; k_b, k_u); y = (M, D)$
 - stochastic
 - ▶ Gillespie algorithm



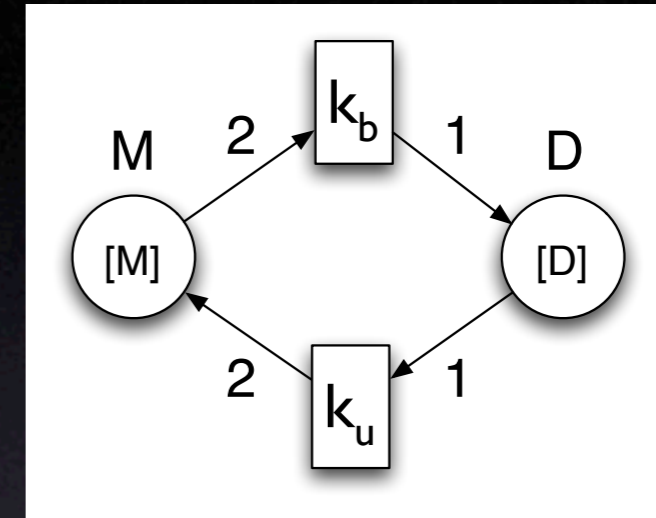
Petri net for $M+M \leftrightarrow D$



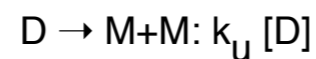
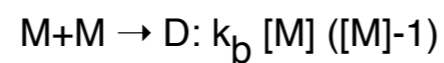
Stochastic vs. deterministic simulation

Gillespie algorithm

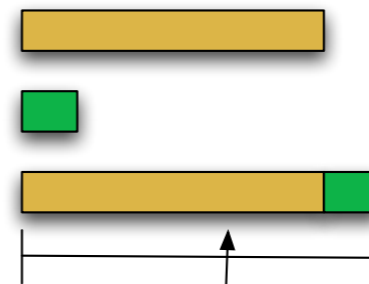
- Gillespie's "Direct Method", a.k.a. continuous time Monte Carlo, or the Bortz-Kalos-Lebowitz algorithm
- a stochastic method for simulating reaction dynamics
 - pick at random a reaction to occur next, and a time at which it will occur (consistent with reaction rates)



Petri net for $M+M \leftrightarrow D$



$$\text{Total rate} = \Gamma = k_b [M] ([M]-1) + k_u [D]$$



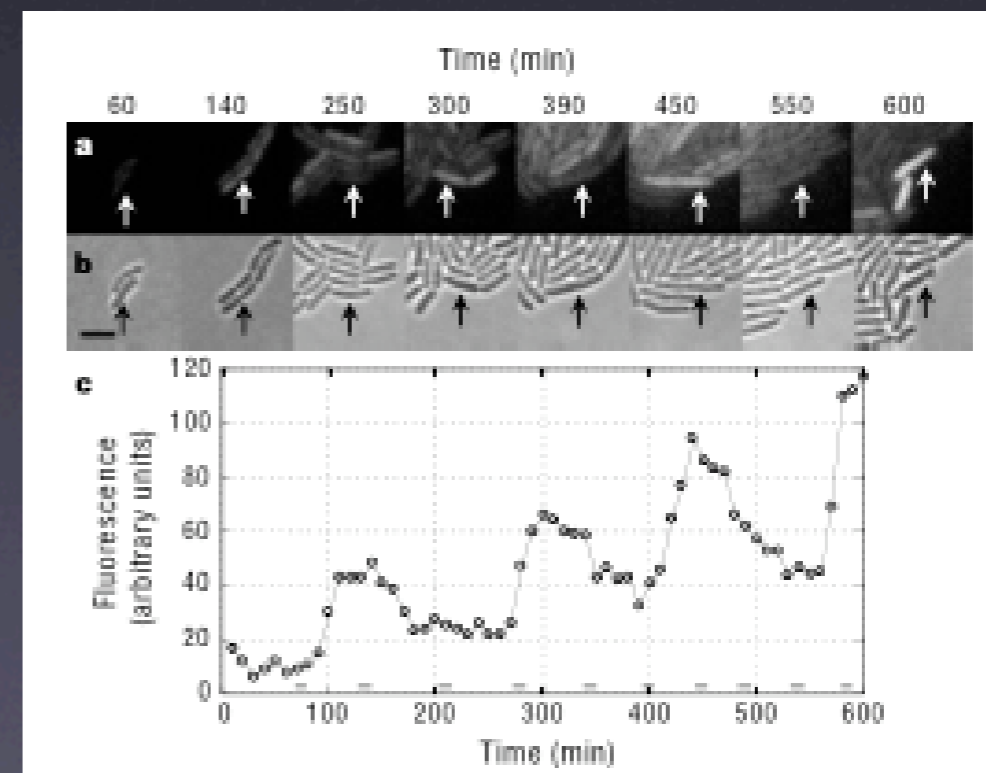
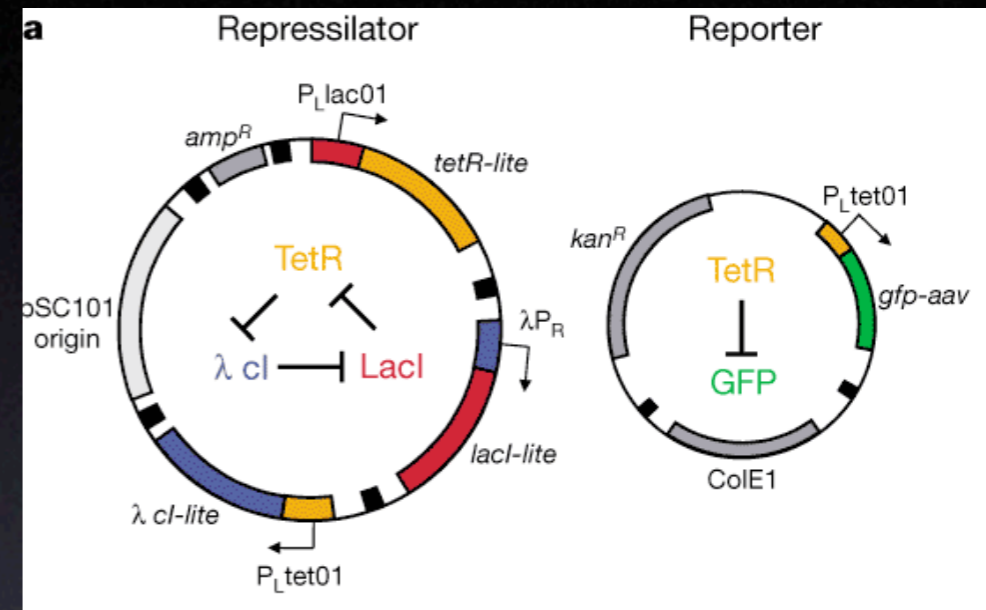
Next reaction drawn uniformly from weighted rates

Next reaction time t_{wait} drawn from probability distribution

$$\rho(t) = \Gamma \exp(-\Gamma t)$$

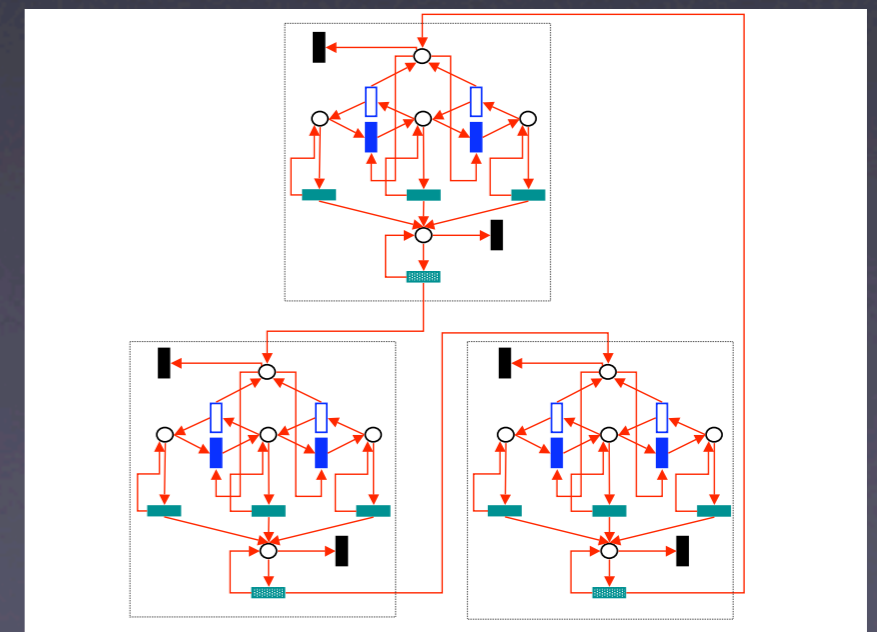
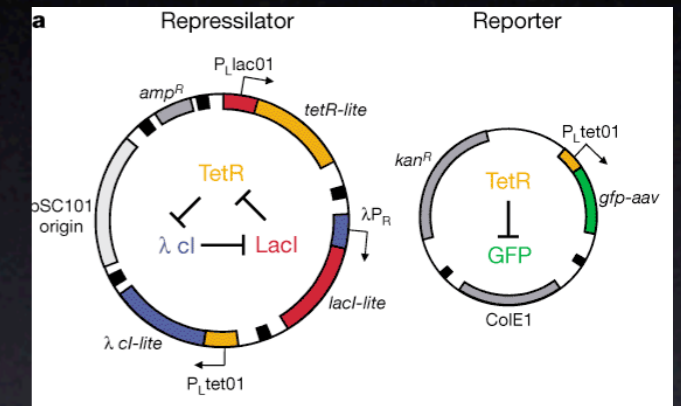
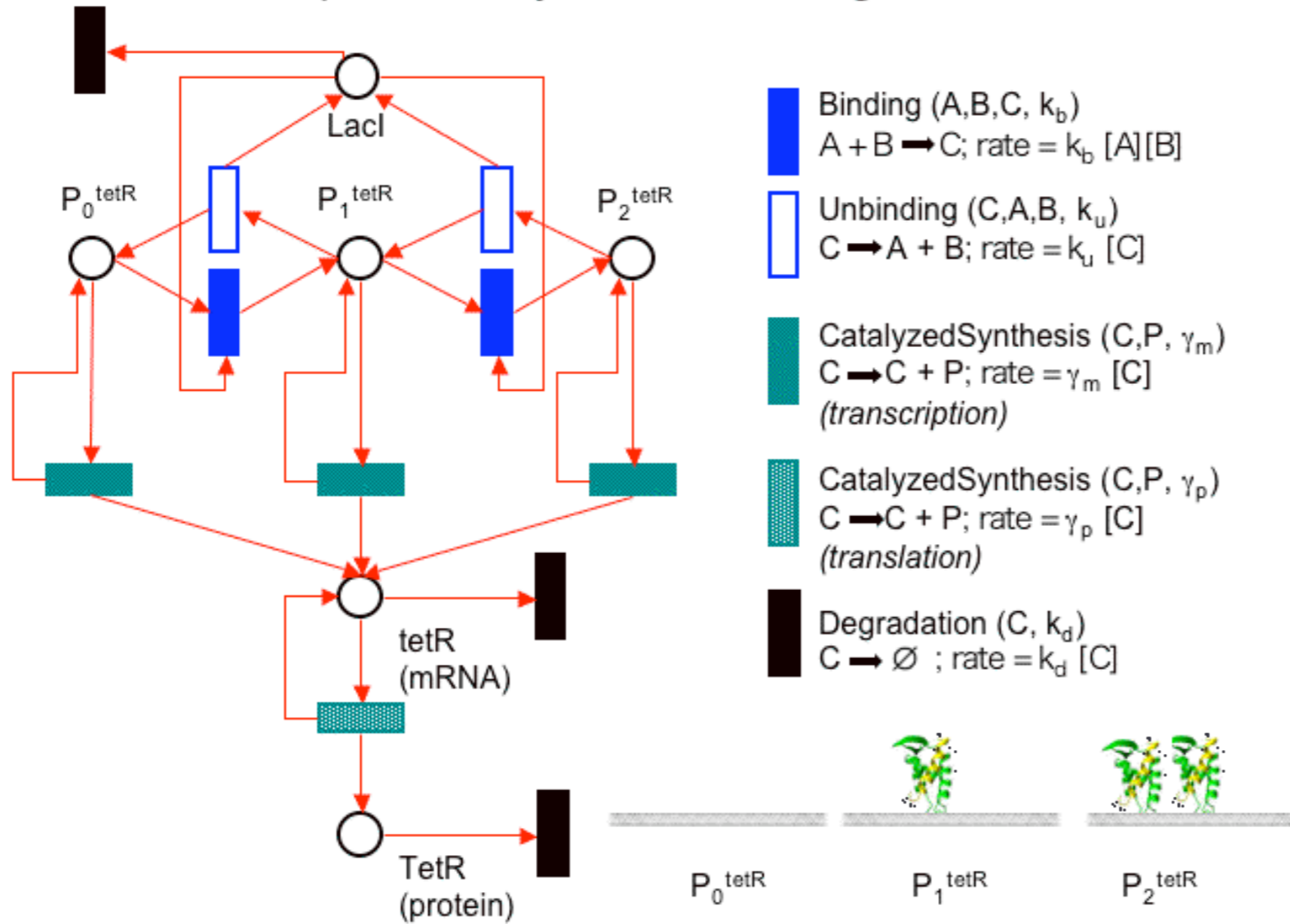
The Repressilator

- Repressilator
 - Elowitz & Leibler, Nature 403, 335-338 (2000)
 - Repressor Oscillator
 - ▶ engineered synthetic system encoded on a plasmid (introduced into *E. coli*)
 - ▶ oscillatory mRNA/protein dynamics from mutually repressing proteins
 - ▶ TetR inhibits λ cI inhibits LacI inhibits TetR (rock-paper-scissors)
 - paper describes both experimental system and mathematical models
 - ▶ ODE-based model
 - ▶ stochastic, reaction-based model



The Repressilator reaction network

TetR repression by LacI: modeling via Petri nets



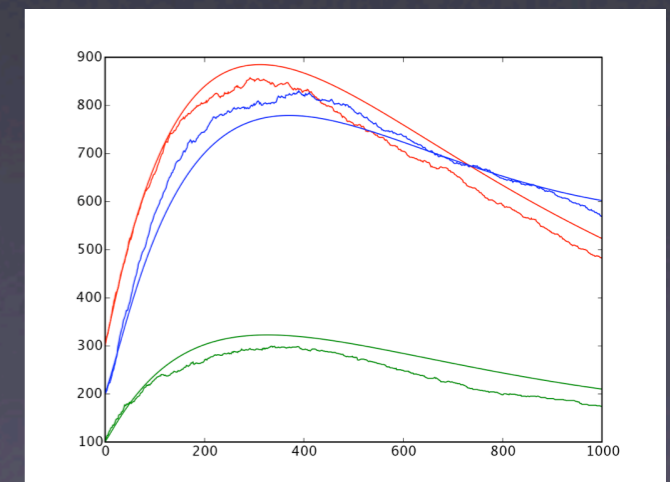
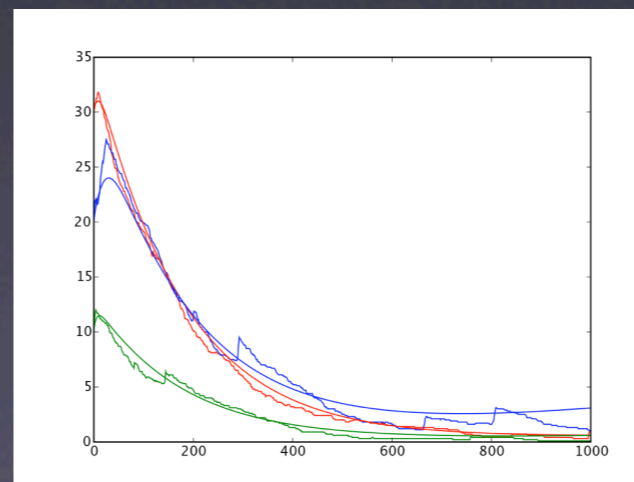
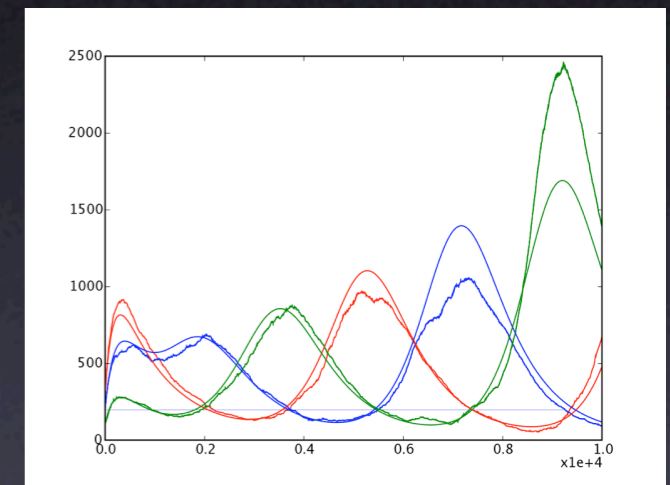
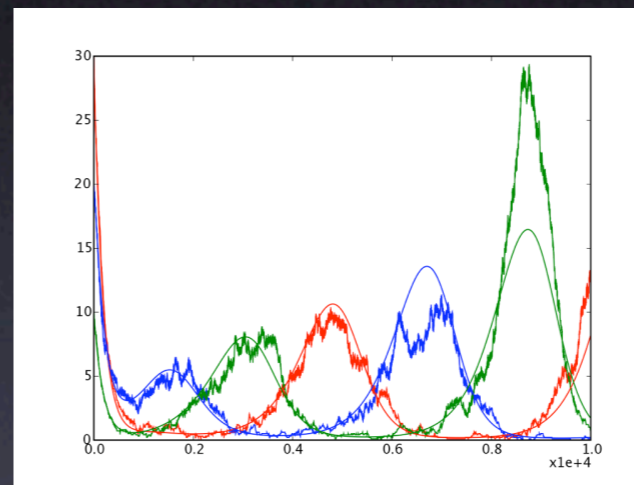
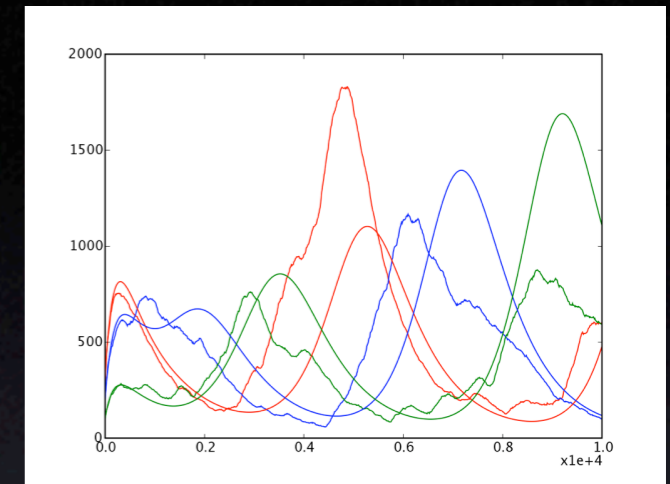
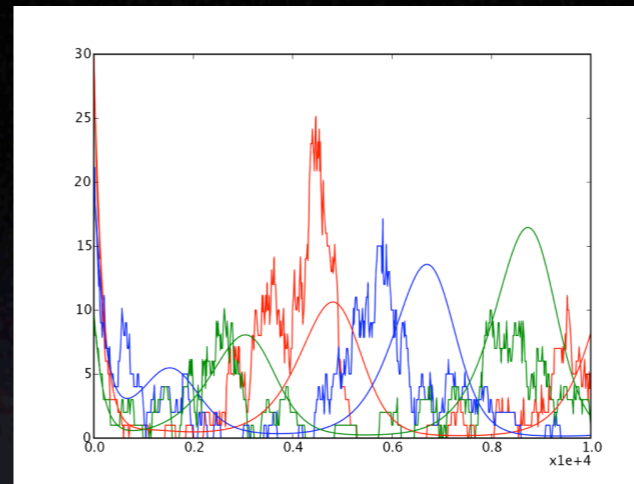
coarse-grained
continuum model

$$\frac{dm_i}{dt} = -m_i + \frac{\alpha}{(1 + \rho_i^n)} + \alpha_0 \quad \left(\begin{array}{l} i = lacI, tetR, cl \\ j = cl, lacI, tetR \end{array} \right)$$

$$\frac{d\rho_i}{dt} = -\beta(\rho_i - m_i)$$

Noise in the Repressilator

- *shot noise*
 - fluctuations due to fact that chemical numbers are discrete and potentially small
- *telegraph noise*
 - fluctuations due to fact that some states (e.g., promoter bound by protein) are either *on* or *off*
- can scale parameters in model to accentuate or diminish different types of noise



mRNA

protein