Biochemical reaction networks: gene regulation, signaling, metabolism, ...
Processing information to coordinate activity

regulatory & signaling networks as information processing systems

coordinating the processing of matter and energy
Stochastic cells: simple dimerization reaction

- simple dimerization reaction
  - homodimerization: $M + M \rightleftharpoons D$
  - as distinct from heterodimerization: $A + B \rightleftharpoons AB$
- introduce Petri net representation
  - places (circles): molecular species
  - transitions (rectangles): chemical reactions, parameterized by rate constants
  - arcs (directed segments): stoichiometric weights
Stochastic cells: simple dimerization reaction

- compare stochastic and deterministic simulations
  - deterministic
    - \( \frac{dy}{dt} = f(y; k_b, k_u); y = (M, D) \)
  - stochastic
    - Gillespie algorithm

Petri net for \( M+M \leftrightarrow D \)

Stochastic vs. deterministic simulation
Chemical master equation

- differential equation describing the dynamics of the probabilities of all microstates in a system
- \( P(m,d) \) = probability of having \( m \) Monomers and \( d \) Dimers
- linear equation in a combinatorially large state space

\[
\frac{dP(m,d)}{dt} = [k_b(m)(m-1)]P(m+2,d-1) - [k_b(m)(m-1)]P(m,d) + [k_u(d+1)]P(m-2,d+1) - [k_u(d)]P(m,d)
\]
Gillespie algorithm

- Gillespie’s “Direct Method”, a.k.a. continuous time Monte Carlo
- a stochastic method for simulating reaction dynamics
  - exact sampling of distribution represented by master equation
  - pick at random a reaction to occur next, and a time at which it will occur (consistent with reaction rates)

\[ M + M \rightarrow D: k_b [M] ([M]-1) \]

\[ D \rightarrow M + M: k_u [D] \]

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

Next reaction drawn uniformly from weighted rates

Next reaction time \( t_{\text{wait}} \) drawn from probability distribution \( \rho(t) = \Gamma \exp(-\Gamma t) \)
The Repressilator

- Repressilator
- Repressor Oscillator
  - engineered synthetic system encoded on a plasmid (introduced into *E. coli*)
  - oscillatory mRNA/protein dynamics from mutually repressing proteins
  - TetR inhibits λ cl inhibits Lacl inhibits TetR (rock-paper-scissors)
- paper describes both experimental system and mathematical models
  - ODE-based model
  - stochastic, reaction-based model
A simple deterministic model

\[
\frac{dm_i}{dt} = -m_i + \frac{\alpha}{1 + \rho_j^n} + \alpha_0 \\
\frac{d\rho_i}{dt} = -\beta(\rho_i - m_i)
\]

- mRNA synthesized and degraded
  - synthesis has part that depends on relevant repressor concentration (Hill function), and part that represents “leaky” transcription
- protein synthesized and degraded
- time rescaled in units of mRNA lifetime; protein concentrations in units of $K_M$; mRNA concentrations in units of their translation efficiency
A more complex Repressilator reaction network

Hill function in limit that $P_1$ unbinding much faster than $P_2$ unbinding
Dynamics of the stochastic Repressilator

TetR repression by LacI: modeling via Petri nets

- TetR (mRNA)
- TetR (protein)
- LacI
- \( P_0^{tetR} \)
- \( P_1^{tetR} \)
- \( P_2^{tetR} \)

**Binding** (A, B, C, \( k_b \))
A + B \( \rightarrow \) C; rate = \( k_b \) [A][B]

**Unbinding** (C, A, B, \( k_u \))
C \( \rightarrow \) A + B; rate = \( k_u \) [C]

**CatalyzedSynthesis** (C, P, \( \gamma_m \))
C \( \rightarrow \) C + P; rate = \( \gamma_m \) [C]
(transcription)

**CatalyzedSynthesis** (C, P, \( \gamma_p \))
C \( \rightarrow \) C + P; rate = \( \gamma_p \) [C]
(translation)

**Degradation** (C, \( k_d \))
C \( \rightarrow \) \emptyset; rate = \( k_d \) [C]
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
Infectious Disease Models

- SIR model
  - Susceptible-Infectious-Recovered
  - infection: S+I → I+I
  - recovery: I → R