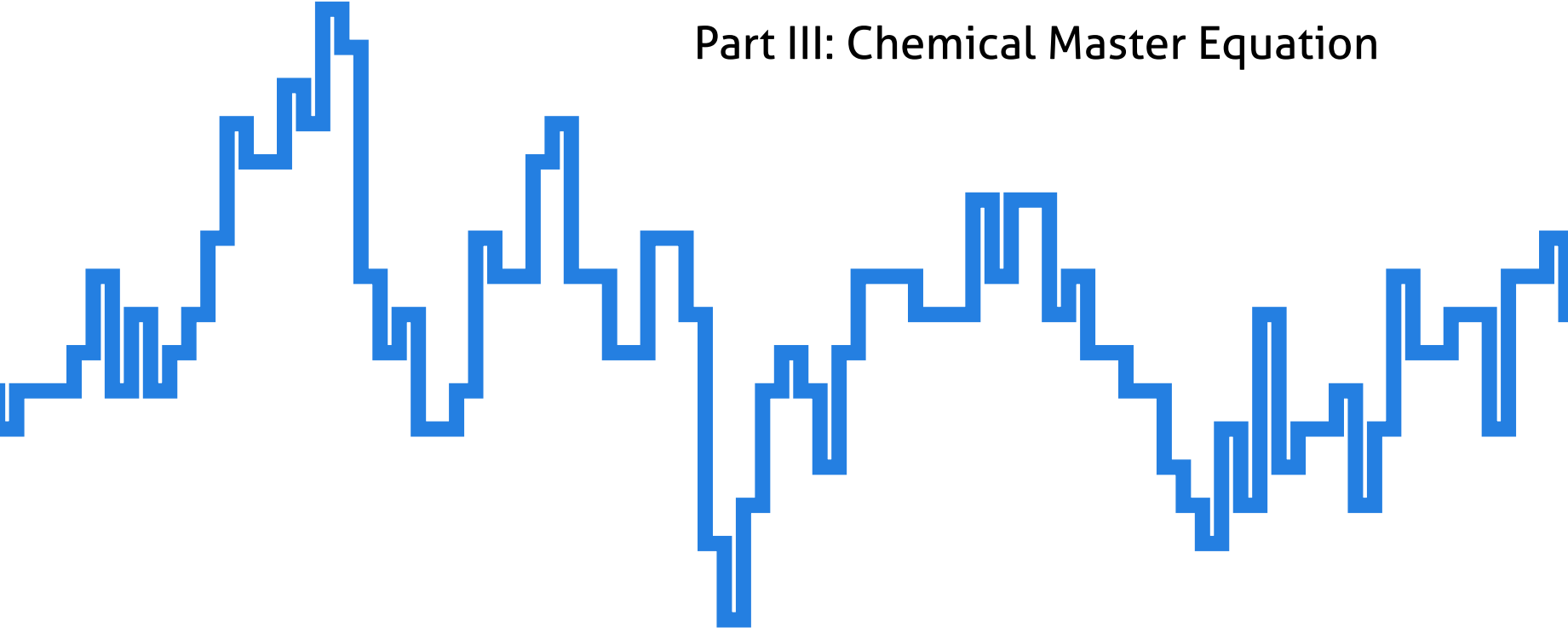
Stochastic Modelling in Systems Biology

Part III: Chemical Master Equation



Chemical Master Equation

Time-evolution equation for the
probability distribution of the stochastic process.

History

1940 Delbrueck used it early to study autocatalytic reactions.

1967 McQuarrie generalised it to chemical reaction networks.

1976 Gillespie illustrated connection to stochastic simulation algorithm.

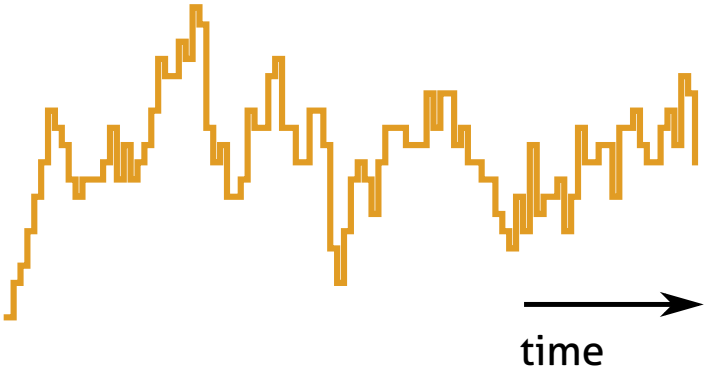
1992 Gillespie derived it from kinetic theory.

1997 Arkin popularised Gillespie's work to study stochastic gene expression.

Chemical Master Equation

Exact description of the stochastic process sampled by the Gillespie algorithm.

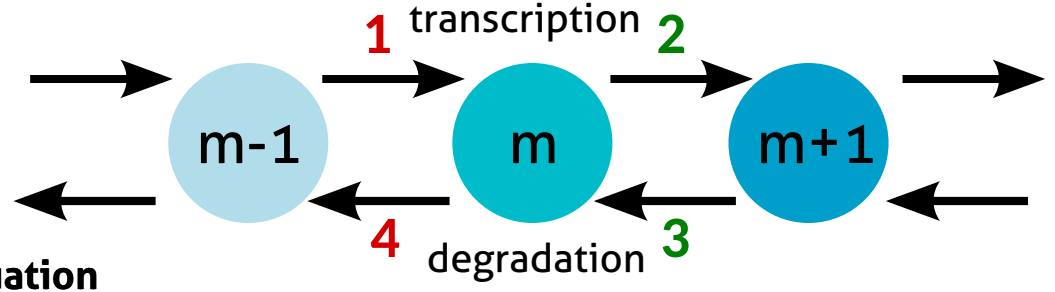
Stochastic simulation in time



Master equation picture

We exchange random numbers by their probability distribution.

Solving the master equation



Master Equation

$$0 = \frac{\mathrm{d}}{\mathrm{d}t}P(m) = a_0(m-1)P(m-1) - a_0(m)P(m) + a_1(m+1)P(m+1) - a_1(m)P(m)$$

Balance between transitions 1&4

$$0 = a_0(m-1)P(m-1) - a_1(m)P(m)$$

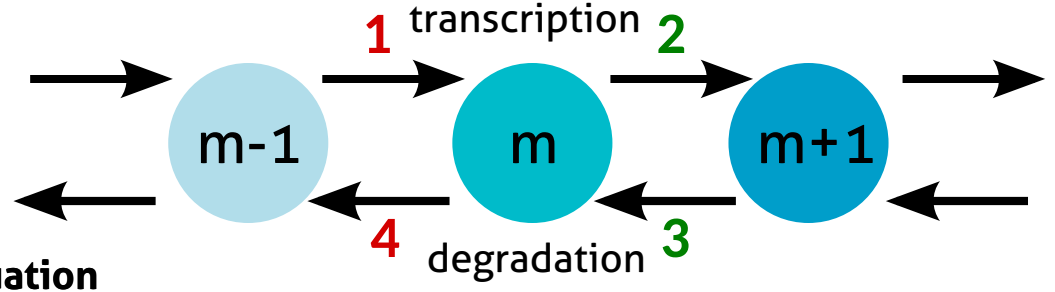
Balance between transitions 2&3

$$0 = a_1(m+1)P(m+1) - a_0(m)P(m)$$

$$P(m) = \frac{a_0(m-1)}{a_1(m)}P(m-1) = \frac{k_0}{k_1 m}P(m-1)$$

Both relations are equivalent: **detailed balance**

Solving the master equation



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Both relations are equivalent: **detailed balance**

Implications for gene expression noise

$$P(m) = \frac{\mu^m}{m!} e^{-\mu}$$ This is the **Poisson distribution**

Properties [wikipedia: Poisson distribution]

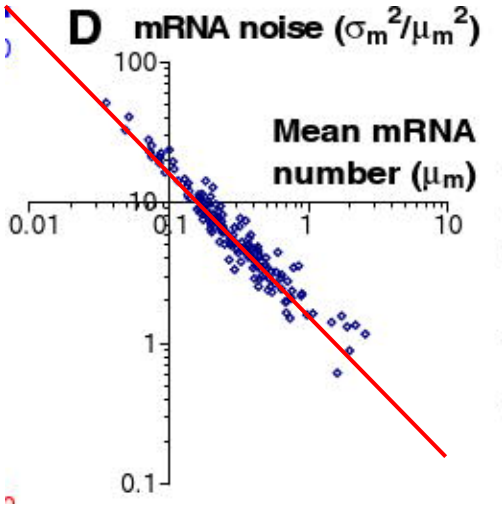
1) mean $\bar{m} = \mu$ 2) standard deviation $\sigma_m = \sqrt{\mu}$

Conclusions

1) stochastic model agrees on average with the deterministic result

2) size of noise (CV) decreases with the square-root of the mean

$$\mathrm{CV} = \frac{\sigma_m}{\bar{m}} = \frac{1}{\sqrt{\mu}} \iff \log \frac{\sigma_m^2}{\bar{m}^2} = -\log \mu$$



Solving the master equation

The constant P(0) is determined from

$$\sum_{m=0}^{\infty} P(m) = 1 \quad \text{with} \quad P(m) = \frac{\mu^m}{m!} P(0) \quad \text{and} \quad \mu = \frac{k_0}{k_1}$$

is the deterministic result

which gives

$$P(0) \sum_{m=0}^{\infty} \left(\frac{k_0}{k_1}\right)^m \frac{1}{m!} = P(0) e^{\mu} = 1 \iff P(0) = e^{-\mu}$$

$$P(m) = \frac{\mu^m}{m!} e^{-\mu}$$ This is the **Poisson distribution**

Solving the master equation

So we have

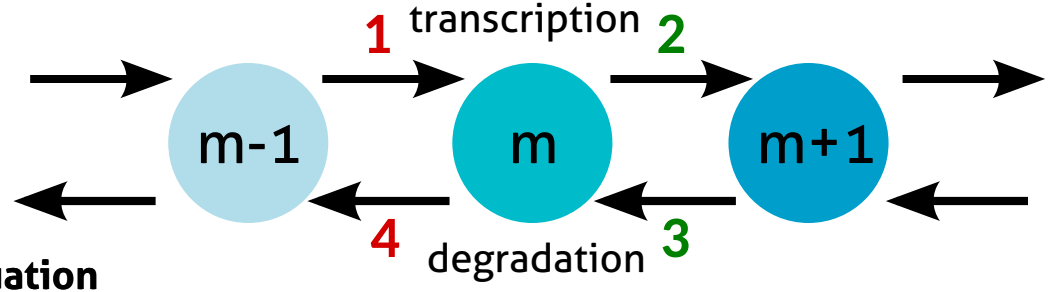
$$P(m) = \frac{k_0}{k_1 m} P(m-1)$$

$$P(m-1) = \frac{k_0}{k_1 (m-1)} P(m-2) \qquad P(m-2) = \frac{k_0}{k_1 (m-2)} P(m-3)$$

Which means

$$\begin{aligned} P(m) &= \frac{k_0}{k_1 m} \times \left[\frac{k_0}{k_1 (m-1)} P(m-2) \right] \\ &= \frac{k_0}{k_1 m} \times \left[\frac{k_0}{k_1 (m-1)} \times \left[\frac{k_0}{k_1 (m-2)} \times \left[\ldots \times \left[\frac{k_0}{k_1} P(0) \right] \right] \right] \right] \\ &= \left(\frac{k_0}{k_1} \right)^m \frac{1}{m!} P(0) \end{aligned}$$

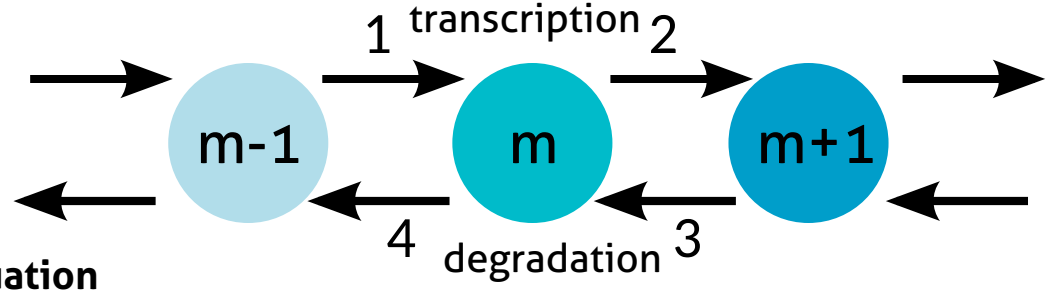
Solving the master equation



Master Equation

$$0 = \frac{\mathrm{d}}{\mathrm{d}t}P(m) = a_0(m-1)P(m-1) - a_0(m)P(m) + a_1(m+1)P(m+1) - a_1(m)P(m)$$

Solving the master equation



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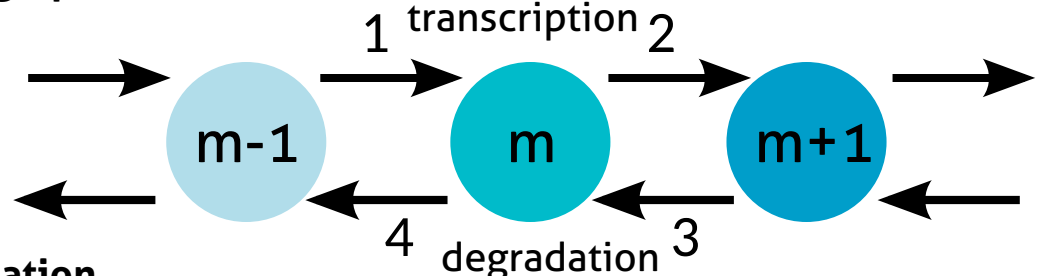
Master equation for the transcription model

Model

	propensity	stoichiometry
transcription	$a_0(m) = k_0$	$m \to m+1$
degradation	$a_1(m) = k_1 m$	$m \to m-1$

Transition graph

assume $\Omega = 1$!



Master Equation

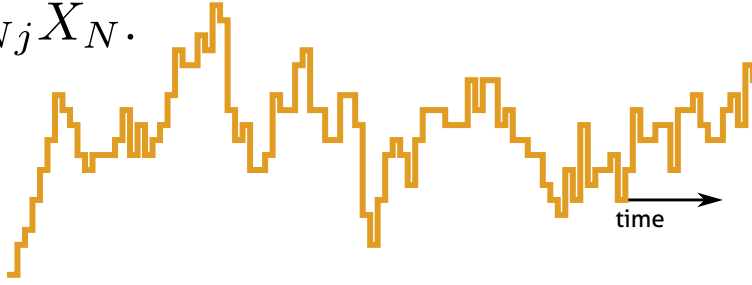
$$\frac{\mathrm{d}}{\mathrm{d}t}P(m) = \underbrace{a_0(m-1)P(m-1)}_{1} - \underbrace{a_0(m)P(m)}_{2} + \underbrace{a_1(m+1)P(m+1)}_{3} - \underbrace{a_1(m)P(m)}_{4}$$

This is an ODE for the probabilities.

General form of the Chemical Master Equation

General formulation: *R* reactions of the form

$$s_{1j}X_1 + \ldots + s_{Nj}X_N \rightarrow \; r_{1j}X_1 + \ldots + r_{Nj}X_N.$$



Time-evolution equation for the
probability distribution of the stochastic process.

$$\frac{\mathrm{d}}{\mathrm{d}t}P(\boldsymbol{n}) = \sum_{r=1}^{R} \left(w_r(\boldsymbol{n} - \boldsymbol{S}_r, \Omega)P(\boldsymbol{n} - \boldsymbol{S}_r) - w_r(\boldsymbol{n}, \Omega)P(\boldsymbol{n})\right)$$

state vector $\vec{n} = (n_1, n_2, ..., n_N)$

where $n_j \in \{0, 1, 2, \ldots\}$

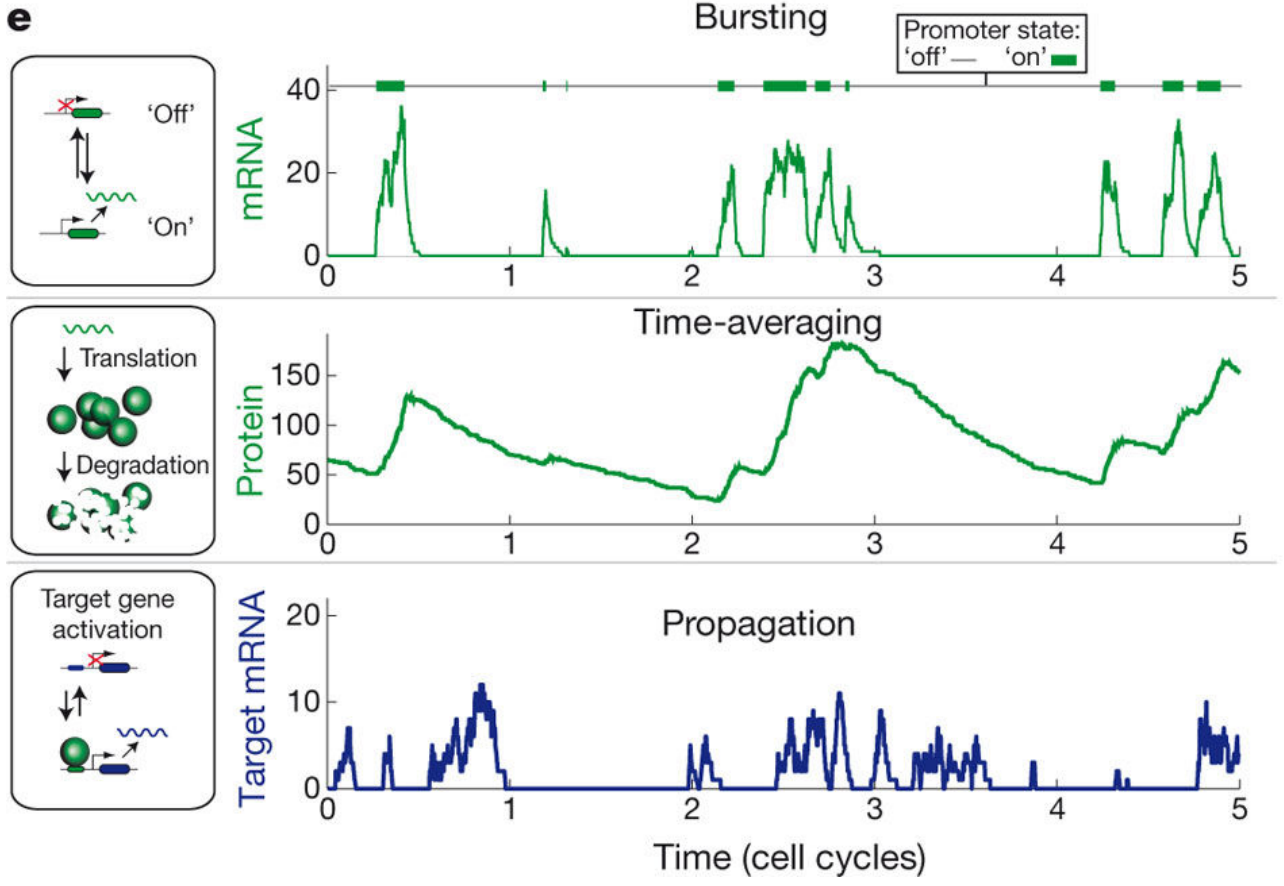
$P(\boldsymbol{n})$	probability
$\boldsymbol{S}_j$	stoichiometries
$w_j(\boldsymbol{n}, \Omega)$	propensity
Ω	reaction volume

This is called the **curse of dimensionality:**
the number of states is typically $\mathbb{N}^N$

Analytical solutions exist only in very simple cases.

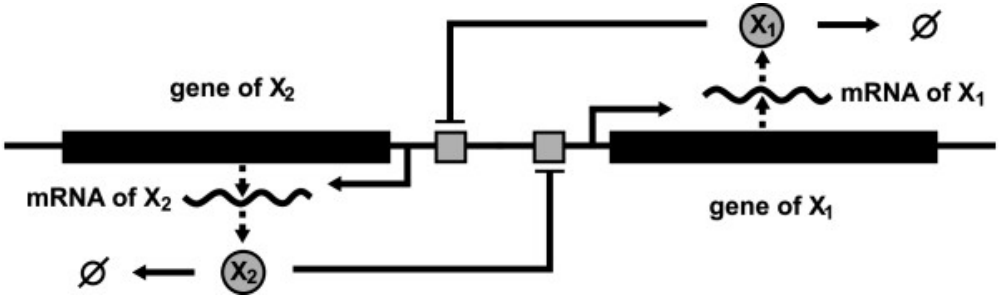
.... has to be solved using approximations or stochastic simulation algorithm.

Consequences of noise: bursting gene expression



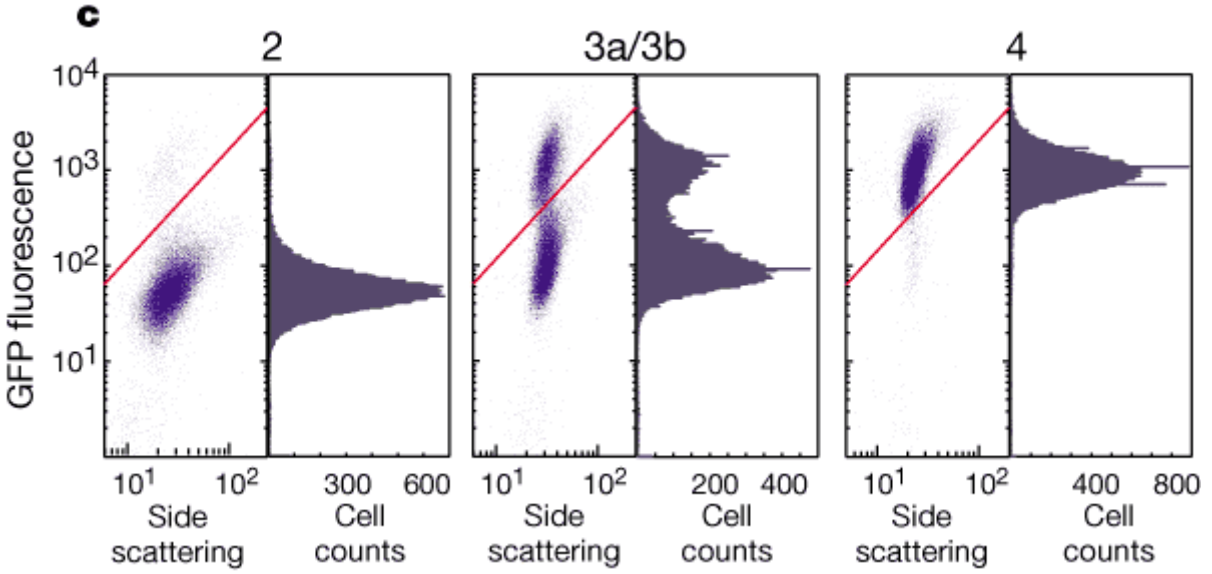
Eldar, Elowitz (2010) Nature 467, 167-173

Consequences of noise: genetic toogle switch



Synthetic gene circuit expressed on plasmids

Similar circuits are believed to operate in cells to control cell fate decision and differentation



Gardner, Cantor, Collins (2000) Nature 403, 339-342

Conclusions

1) Gene expression noise decreases
   with the mean number of lowly abundant molecule

2) Noise can dramatically change biological circuit behaviour

3) Chemical Master Equation can be solved only in simple cases,

4) We require stochastic simulation methods & approximations
   to understand gene regulatory networks

→ *Q&A Session*: Implementation of Stochastic Simulation Algorithm