

# Noise in Gene Regulatory Networks

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# Summary

## Models for Chemical Reactions

Macroscopic Model

Microscopic Model

Mesoscopic Model

## Chemical Reactions as Markov Processes

The Chemical Master Equation

A result for linear/affine transitions

An equivalence property

## Comments

# Stochastic and Deterministic Models

Chemical reactions can be modeled by

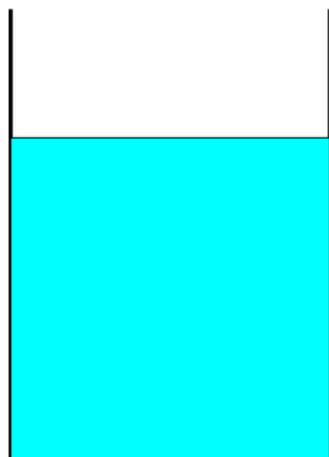
- ▶ Deterministic ordinary differential equations involving the species concentrations (macroscopic model)
- ▶ Many spatial agents each one describing a single molecule (microscopic model)

Both the approaches present advantages and drawbacks

- ▶ When there are few molecules of a species the concentration description is meaningless, mass action kinetics are not valid, and discrete models are necessary.
- ▶ Multi-agent models require a huge computational effort to be simulated

# Macroscopic model

The system state is given by the concentration of the species and ODEs can be easily written.



Consider the reversible reactions



leading to the ODEs

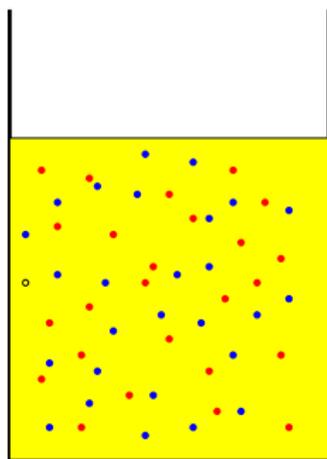
$$\dot{x}_1 = -K_{21}x_1 + K_{12}x_2 \quad (3)$$

$$\dot{x}_2 = K_{21}x_1 - K_{12}x_2 \quad (4)$$

where  $x_i$  is the concentration of the species  $S_i$ .

# Microscopic model

Every single particle is modeled as a distinct agent with a specific position and velocity.



- ▶ Monomolecular reactions occur according to the given rate.
- ▶ Dimolecular reactions occur when two particles are in the same spot and the absolute value of their relative velocity is large enough.

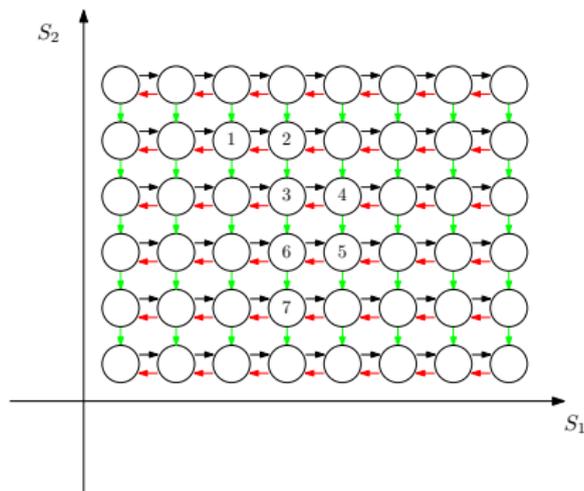
# The Chemical Master Equation (Mesoscopic model)

The mesoscopic model tries to combine both the approaches.

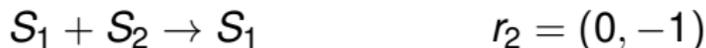
- ▶ The system is described in terms of the  $n$  reactants and/or products  $\{S_1, S_2, \dots, S_n\}$
- ▶ The state of the system is given by the integer vector  $\{x_1, x_2, \dots, x_n\}$  representing the number of molecules for every species
- ▶ The system is considered a time-continuous Markov model
- ▶ The  $M$  chemical reactions represent the Markov transitions which can be described by the stoichiometric vectors  $(r_1, \dots, r_M)$
- ▶ The probabilities of every state configuration are described by a vector  $\mathcal{P}(t) = [\mathcal{P}_1(t), \mathcal{P}_2(t), \dots]$  which evolves according to

$$\dot{\mathcal{P}}(t) = A \mathcal{P}(t) \quad (5)$$

# A graphical representation clarifies the meaning of the Mesoscopic Model



The reactions with the relative stoichiometric vectors are



# Transition Probabilities

The probability that the reaction  $R_\mu$  will be the next reaction and that will occur within the next time  $dt$  is given by  $a_\mu(x)dt$ .

- ▶ If  $R_\mu$  represents a supply ( $\emptyset \rightarrow \text{'Products'}$ ), then

$$a_\mu(x) = c_\mu \quad (6)$$

- ▶ If  $R_\mu$  is a monomolecular reaction ( $S_i \rightarrow \text{'Products'}$ ), then

$$a_\mu(x) = c_\mu x_i \quad (7)$$

- ▶ If  $R_\mu$  is a dimolecular reaction ( $S_i + S_j \rightarrow \text{'Products'}$ ), then

$$a_\mu(x) = c_\mu x_i x_j \quad (8)$$

# Chemical Reactions and Markov Processes

Let us consider a chemical system with  $n$  molecular species and  $m$  elementary reactions and its related mesoscopic model.



where  $x(t) \in \mathbb{N}^n$  is the vector of molecule numbers at time  $t$ ;  $r_i \in \mathbb{N}^n$  is the stoichiometric vector of the  $i$ -th reaction and  $W_i \in \mathfrak{R}^+$  is the transition rate.

The transitions described by (9) can be naturally modeled by a jump Markov system (markovian Petri net).

# The Chemical Master Equation

Let us consider how the probability  $p$  of the configuration  $x$  at time  $t$  evolves. It satisfies the ODE

$$\dot{p}(t)(x, t) = \sum_i W_i(x - r_i) p(x - r_i, t) - \sum_i W_i(x) p(x, t) \quad (10)$$

which is known as the Chemical Master Equation.

Defining  $\mathcal{P}(t)$  as the vector containing the probabilities of all the possible configurations  $x$ , we have that

$$\dot{\mathcal{P}}(t) = \mathcal{A} \mathcal{P} \quad (11)$$

where the entries in  $\mathcal{A}$  depend on the terms  $W_i(x)$ . This means that the evolution of the PDF follows a linear dynamics, even though the transition rates are not linear.

# Notation

- ▶ I shall use capital letters to denote random variables/random processes and lower case letter to denote their realizations
- ▶  $E[X]$  is the mean of the stochastic variable  $X$
- ▶  $E_X(t) := E[X(t)]$  is the mean of the stochastic process  $X(t)$  at time  $t$
- ▶  $V_{XY}(t_1, t_2) := E[X(t_1)X(t_2)^T]$  is the second moment
- ▶  $R_{XY}(t_1, t_2) := E[X(t_1)X(t_2)^T] - E[X(t_1)]E[X(t_2)]$  is the second central moment
- ▶  $R_X(t_1, t_2) := R_{XX}(t_1, t_2)$  and  $V_X(t_1, t_2) := V_{XX}(t_1, t_2)$

# Notation

A process  $X$  is stationary (wide sense) if and only if, for all  $t, t_1, t_2, \tau$ ,

$$E_X(t) = E_X; \quad R_X(t_1, t_2) = R_X(t_1 + \tau, t_2 + \tau) \quad (12)$$

Two stationary processes  $X$  and  $Y$  are mutually stationary (wide sense) if and only if

$$R_{XY}(t_1, t_2) = R_{XY}(t_1 + \tau, t_2 + \tau) \quad (13)$$

In such a context, the following definitions make sense

- ▶  $R_{XY}(t) := R_{XY}(t, 0)$  (abusing the notation!)
- ▶  $\Phi_{XY}(i\omega) := \mathcal{F}(R_{XY}(t, 0))(i\omega)$

## A result for linear/affine transitions

In many applicative cases, the transition rate functions  $W_i(\cdot)$  can be considered linear. In the case of linear/affine transition rates some analytical results can be proved.

### Theorem

*If  $W_i(x) = c_1^{(i)}x + c_0^{(i)}$  then, there exist matrices  $A, D(t) = D(E_X(t)) \in \mathfrak{R}^{n \times n}$ ,  $D(t)$  semi-positive defined and a vector  $C_0 \in \mathfrak{R}^n$  such that*

$$\frac{d}{dt}E_X(t) = AE_X(t) + C_0 \quad (14)$$

$$\frac{d}{dt}R_X(t, t) = A\frac{d}{dt}R_X(t, t) + \frac{d}{dt}R_X(t, t)^T A^T + D(E_X(t)) \quad (15)$$

$$\frac{d}{dt_1}R_X(t_1, t_2) = AR_X(t_1, t_2) \quad (16)$$

# Proof

Let us evaluate  $\frac{d}{dt} E_X(t)$

$$\begin{aligned}\frac{d}{dt} E_X(t) &= \sum_x x \frac{dp(x, t)}{dt} = \\ &= \sum_{i, x} x W_i(x - r_i) p(x - r_i, t) - \sum_{i, x} x W_i(x) p(x, t) = \\ &= \sum_{i, x} (x + r_i) W_i(x) p(x, t) - \sum_{i, x} x W_i(x) p(x, t) = \\ &= \sum_{i, x} r_i W_i(x) p(x, t).\end{aligned}$$

Define  $f(x) := \sum_i r_i W_i(x)$  and we have

$$\frac{d}{dt} E_X(t) = E[f(x(t))]$$

# Proof

In the linear/affine case  $W_i(x) = c_1^{(i)}x + c_0^{(i)}$ , thus

$$f(x(t)) = \sum_i r_i W_i(x(t)) = \sum_i r_i [c_1^{(i)}x(t) + c_0^{(i)}] = \quad (17)$$

$$= \sum_i r_i c_1^{(i)}x + \sum_i r_i c_0^{(i)} = Ax(t) + C_0 \quad (18)$$

That leads to

$$\begin{aligned} \frac{d}{dt} E_X(t) &= E[f(x(t))] = E[Ax(t) + C_0] \\ &= AE_X(t) + C_0 \end{aligned}$$

# Proof

Let us evaluate the dynamics of  $R_{XX}(t, t)$

$$\begin{aligned}\frac{d}{dt} V_X(t, t) &= \sum_x x x^T \frac{dp(x, t)}{dt} = \\ &= \sum_{x,i} x x^T [W_i(x - r_i) p(x - r_i, t) - W_i(x) p(x, t)] = \\ &= \sum_{x,i} (x + r_i)(x + r_i)^T W_i(x) p(x, t) - \sum_{x,i} x x^T W_i(x) p(x, t) = \\ &= E\left[\sum_i x r_i^T W_i(x)\right] + E\left[\sum_i r_i x^T W_i(x)\right] + E\left[\sum_i r_i r_i^T W_i(x)\right] = \\ &= E[x f^T(x)] + E[f(x) x^T] + E\left[\sum_i r_i r_i^T W_i(x)\right]\end{aligned}$$

# Proof

$$\begin{aligned}\frac{d}{dt}R_X(t, t) &= \frac{d}{dt}V_X(t, t) - \frac{d}{dt}(E_X(t)E_X(t)^T) = \\ &= E[x(t)f^T(x(t))] + E[f(x(t))x(t)^T] + E\left[\sum_i r_i r_i^T W_i(x(t))\right] + \\ &\quad - E_X(t)E[f(x(t))^T] - E[f(x)]E_X(t)^T = \\ &= E[(x(t) - E_X(t))(f(x(t)) - E[f(x(t))])^T] + \\ &\quad + E[(f(x(t)) - E[f(x(t))])(x(t) - E_X(t))^T] + \\ &\quad + E\left[\sum_i r_i r_i^T W_i(x(t))\right]\end{aligned}$$

# Proof

In the linear case  $f(x(t)) - E[f(x(t))] = A(x(t) - E_X(t))$ , thus

$$\frac{d}{dt}R_X(t, t) = AR_X(t) + R_X(t)A + E\left[\sum_i r_i r_i^T W_i(x(t))\right] \quad (19)$$

Define  $D(t)$  and consider its Choleski factorization in terms of  $B(t)$ , as follows

$$D(t) = D(E[W(x(t))]) := E\left[\sum_i r_i r_i^T W_i(x(t))\right] \quad (20)$$

$$D(t) = B(t)B(t)^T. \quad (21)$$

We can write that

$$\frac{d}{dt}R_X(t, t) = AR_X(t) + R_X(t)A + D(t) \quad (22)$$

# Proof

Let  $p(x_1, t_1, x_2, t_2)$  be the joint probability of the random variables  $X(t_1)$  and  $X(t_2)$ . Let us evaluate the dynamics of  $R_{XX}(t_1, t_2)$ , observing that the Chemical Master Equation holds also for the joint probability.

$$\begin{aligned}\frac{d}{dt_1} V_X(t_1, t_2) &= \sum_{i,x,y} xy^T \frac{d}{dt_1} p(x_1, t_1, x_2, t_2) = \\ &= \sum_{x,y} xy^T [W_i(x - r_i)p(x - r_i, t_1, y, t_2) - W_i(x)p(x, t_1, y, t_2)] \\ &= \sum_{i,x,y} (x + r_i)y^T W_i(x)p(x, t_1, y, t_2) - \sum_{i,x,y} xy^T W_i(x)p(x, t_1, y, t_2) \\ &= \sum_{i,x,y} r_i W_i(x)p(x, t_1, y, t_2)\end{aligned}$$

# Comments

In the non-stationary case we have

$$\frac{d}{dt}E_X(t) = AE_X(t) + C_0 \quad (23)$$

$$\frac{d}{dt}R_X(t, t) = AR_X(t, t) + R_X(t, t)A^T + D(E_X(t)) \quad (24)$$

$$\frac{d}{dt_1}R_X(t_1, t_2) = AR_X(t_1, t_2) \quad (25)$$

The evolution of the mean of the molecule numbers follows a standard linear/affine dynamics.

The autocovariance of the molecule numbers evolves according to the second equation which is a Differential Riccati Equation.

The cross-covariance follows a purely linear dynamics.

# The stationary scenario

We have that the signal  $E_X$  does not depend on  $t$ , therefore it satisfies the relation

$$AE_X + C_0 = 0 \quad (26)$$

This implies that  $D(t) = D(E_X(t))$  does not depend on  $t$ , either. Moreover,  $R_X(t_2 + \tau, t_2)$  depends upon  $\tau$  only. Hence we have

$$AR_X(t, t) + R_X(t, t)A^T + D = 0 \quad (27)$$

$$\frac{d}{d\tau} R_X(t + \tau, t) = AR_X(t + \tau, t). \quad (28)$$

That Lyapunov Equation is known in physics as the fluctuation-dissipation problem, since it is very often related to a balance between phenomena of expansion and dissipation.

# An equivalence property

## Theorem

Assume that the Markov process described by the reactions  $x(t) \xrightarrow{W_i(x(t))} x(t) + r_i$  with affine transition rates reaches the steady state. Consider

$$AR_X(t, t) + R_X(t, t)A^T + D = 0 \quad (29)$$

$$\frac{d}{d\tau} R_X(t + \tau, t) = AR_X(t + \tau, t). \quad (30)$$

Factorize  $D$  as  $D = BB^T$ . The power spectrum of  $x$  is given by

$$\Phi_X(\omega) = G(i\omega)G(i\omega)^* \quad (31)$$

where  $G(s) = (sI - A)^{-1}B$