STOCHASTIC CHEMICAL KINETICS: Theory and Systems
Biological Applications

Péter Érdi
perdi@kzoo.edu

Henry R. Luce Professor
Center for Complex Systems Studies
Kalamazoo College

http://people.kzoo.edu/perdi/

and

Institute for Particle and Nuclear Physics, Wigner Research Centre,
Hungarian Academy of Sciences, Budapest

http://cneuro.rmki.kfki.hu/
STOCHASTIC CHEMICAL KINETICS: Theory and Systems Biological Applications

1973

1989

2014
I. Stochastic kinetics: why and how?
- Chemical kinetics: some basic concepts
- Fluctuations phenomena: introductory and historical remarks

II. Continuous time discrete state stochastic models
- Stochastic processes: some basic concepts
- Model frameworks, master equation
- Solutions of the master equation
- Stationary distributions
- Simulation methods
- Non-Markovian approaches

III. Systems Biological Applications
- Fluctuations near instabilities
- Enzyme kinetics
- Signal processing in biochemical networks
- The beneficial role of noise: fluctuation-dissipation theorem and stochastic resonance
- Stochastic models of gene expression
- Chiral symmetry
Stochastic kinetics: why and how?

Chemical kinetics: some basic concepts

**CHEMICAL REACTION**

\[ 0 = \sum_{i=1}^{n} v_{j,i} A_i \quad (j = 1, 2, \ldots, m) \quad (1) \]

\( m \): the number of different reactions; \( v_{j,i} \): stoichiometric coefficient of component \( A_i \) in reaction step \( j \), is positive for species that are produced, negative for species that are consumed in the reaction step \( j \).

**KINETIC EQUATION**

\[ \frac{dc(t)}{dt} = f(c(t); k); \quad c(0) = c_0 \quad (2) \]

where \( f \) is the function which governs the temporal evolution of the system, \( k \) is the vector of the parameters (rate constants or rate coefficients) and \( c_0 \) (with elements \( [A_1]_0, [A_2]_0, \ldots, [A_n]_0 \)) is the initial value vector of the component concentrations.

Continuous time Continuous state Deterministic (CCD model)

**MASS ACTION KINETICS**

\[ f_i(c) = \sum_{j=1}^{m} v_{j,i} v_j \quad (i = 1, 2, \ldots, n) \quad (3) \]

constituent functions of \( f \): the sum of the rates of the individual steps

Power law kinetics:

\[ v_j = k_j \prod_{k=1}^{n} [A_k]^{\alpha_{j,k}} \quad (4) \]

\[ f_i(c) = \sum_{j=1}^{m} v_{j,i} k_j \prod_{k=1}^{n} [A_k]^{\alpha_{j,k}} \quad (i = 1, 2, \ldots, n) \quad (5) \]

\( \alpha_{j,k} \): order of reaction
Einstein-Smoluchowski-Langevin theory of the Brownian motion I.

- gave a relationship for the time-dependence of the average of the square of the displacement $X(t)$ of the Brownian particle,

\[
< X(t)^2 > := < [x(t) - x(0)]^2 > = D t,
\]  

(6)

where $x(t)$ is the actual and $x(0)$ is the initial coordinate of the Brownian particle;

- found the connection between the mobility of the particle and the - macroscopic - diffusion constant

\[
D = \mu k_B T.
\]  

(7)

- considered the motion of the Brownian particles as \textit{memoryless} and non-differentiable trajectories, and helped prepared the pathway to the formulation of the theory of stochastic (actually Markov) processes.

- offered a new method to determine the Avogadro constant

\[\text{Figure 1:} \text{ there is a large discrepancy between the classical displacement and the Brownian motion displacement}\]

\[\text{FDT: the fluctuation of the particle at rest has the same origin as the dissipative frictional force}\]

\[\text{Figure 2:} \text{ non-differentiable trajectories}\]
Einstein-Smoluchowski-Langevin theory of the Brownian motion II.

Langevin equation: forcing function has a systematic and deterministic part, and a term due to the rapidly varying, highly irregular random effects:

$$\frac{dx}{dt} = a(x,t) + b(x,t)\xi(t)$$ (8)

The equation (8) is not precise, since \(\xi(t)\) is often non-differentiable, and therefore \(x(t)\) is also non-differentiable. (further studies: stochastic integrals: "Ito versus Stratonovich")

Retrospectively, Einstein’s theory: \(a(x,t) = 0\) and \(b(x,t) = \sqrt{2D}\xi(t)\) and assuming Gaussian white noise

$$\frac{dv}{dt} = -\gamma v + \sqrt{2D}dW(t).$$ (9)

White noise is considered as a stationary Gaussian process with \(E[\xi_t] = 0\) and \(E[\xi_t\xi_{t’}] = \delta_{t’,t-t}\), where \(\delta\) is the Dirac delta function.

Figure 3: white noise and its spectrum
Stochastic kinetics: why and how?

Fluctuations phenomena: introductory and historical remarks: Diffusion processes

\[ A = a \frac{\partial}{\partial x} + \frac{1}{2} b \frac{\partial^2}{\partial x^2} \]  (10)

- \( a(x,t) \): the velocity of the conditional expectation (called “drift”)
- \( b(x,t) \): the velocity of the conditional variance (called a “diffusion constant”).

The general form of the FP equation:

\[ \frac{dP}{dt} = AP \]  (11)

\[ b = 0: \text{Liouville process} \]

**Figure 4:** Temporal evolution of a Liouville process: drift of the PDF in time without changing its shape. Starting from a degenerate density function (i.e. when the initial PDF is concentrated to a point), the point will be drifted.
Ornstein-Uhlenbeck process (OU):

\[ a(x,t) = -kx, \quad b(x,t) = b, \quad (k > 0, D \geq 0). \]  

Figure 5: Temporal evolution of a special Wiener process: s a Gaussian process, but is not stationary. It is used in modeling the Brownian process. For finite \( t > t_0 \) the PDF is Gaussian, with mean \( x_0 + a(t - t_0) \), and the standard deviation \( |b(t - t_0)|^{1/2} \) is flattening out as time tends to infinite. For a special Wiener process the center of the spreading curve remains unchanged.

Figure 6: OU has a stationary PDF, and it is the normal density function. For any \( t > 0 \) the PDF is the normal density function with an exponentially moving mean. The temporal evolution of the standard deviation describes spreading out, but the width of the curve is finite even for infinite time. The OU process, defined by a linearly state-dependent drift and a constant diffusion term, proved to be a very good model of the velocity of a Brownian particle characterized by normal distribution.
Stochastic kinetics: why and how?

Fluctuation-dissipation theorem

- Noise in electric circuits being in thermal equilibrium by Nyquist (theory) and Johnson (experiments)
- Internal voltage fluctuation: proportional to the resistance $R$, temperature $T$ and the bandwidth of the measurement:
- Same forces that cause the fluctuations also result in their dissipation
- Chemical kinetics: estimation of individual rate constants from concentration fluctuations
- Chemical fluctuations measurements: electric conductance; fluorescence correlation spectroscopy
- Fluctuation or noise phenomena: representation in the time domain and the frequency domain

\[
<V^2> = 4RK_BT
\]  
(13)

\[
C(t) := E[\xi(t)\xi(t-\tau)]
\]  
(14)

\[
S(\omega) = \frac{1}{2\pi} \int_{-\infty}^{+\infty} C(t) \cos \omega \tau \, dt = \frac{1}{2\pi} <\xi^2>^{eq} \frac{\gamma(\omega)}{\gamma(\omega) + \omega^2}
\]  
(15)

$\gamma(\omega)$ is the Fourier transform of the dissipation constant, and $<\xi^2>^{eq}$ characterized the measure of the equilibrium fluctuations. The relationship is famously called the Wiener–Khinchine theorem.
Stochastic kinetics: why and how?

Model framework: preliminary remarks

\[ P_n(t) := P(\xi(t) = n) \quad (16) \]

\[ \frac{dP_n}{dt} = \mathbf{A}P_n(t). \quad (17) \]

\[ \frac{dP_n}{dt} = \sum n'[a_{nn'}P_n(t) - a_{n'n}P_n(t)]. \quad (18) \]

- chemical reaction is considered as a Markovian jump process
- Kolmogorov equation (master equation)
- \( a_{nn'} \): infinitesimal transition probability, which gives the probability (per unit time) of the jump from \( n' \) to \( n \)
- master equation: a gain-loss equation for the probability of each state \( n \)
**A model of genetic expression: first encounter**

inactive gene $\xrightarrow{\lambda_1^+} \text{active gene} \xleftarrow{\lambda_1^-} \text{mRNA} \xrightarrow{\lambda_2} \text{protein}$ \hspace{1cm} (19)

supplemented with two degradation steps (the second also called as proteolysis):

mRNA $\xrightarrow{\gamma_m} 0$ \hspace{0.5cm} protein $\xrightarrow{\gamma_p} 0$ \hspace{1cm} (20)

\[
\frac{dP(n_1,n_2,n_3)(t)}{dt} = \lambda_1^+(n_1^{\text{max}} - n_1 + 1)P(n_1 - 1, n_2, n_3) - \lambda_1^+(n_1^{\text{max}} - n_1)P(n_1, n_2, n_3) \\
+ \lambda_1^-(n_1 + 1)P(n_1 + 1, n_2, n_3) - \lambda_1^-(n_1)P(n_1, n_2, n_3) \\
+ \lambda_2 n_1 P(n_1, n_2 - 1, n_3) - \lambda_2 n_1 P(n_1, n_2, n_3) \\
+ \left(\frac{n_2 + 1}{\tau_2}\right) P(n_1, n_2 + 1, n_3) - \frac{n_2}{\tau_2} P(n_1, n_2, n_3) \\
+ \lambda_3 n_2 P(n_1, n_2, n_3 - 1) - \lambda_3 n_2 P(n_1, n_2, n_3) \\
+ \left(\frac{n_3 + 1}{\tau_3}\right) P(n_1, n_2, n_3 + 1) - \frac{n_3}{\tau_3} P(n_1, n_2, n_3),
\]

where $n_1^{\text{max}}$ denotes a constant number of switching genes \hspace{1cm} (21)
Continuous time discrete state stochastic models

Model frameworks, master equation

CDS model of chemical kinetics

- (a) takes into consideration
  - the discrete character of the quantity of components
  - the inherently random character of the phenomena
- (b) is in accordance (more or less)
  - with the theories of thermodynamics
  - with the theory of stochastic processes
- (c) is appropriate to describe
  - 'small systems'
  - instability phenomena

Figure 7: Renyi, A. (1953). Treating chemical reactions using the theory of stochastic processes. MT A Alk. Mat. Int. Kozl., 2, 83-101 (in Hungarian). The first complete treatment of a second-order reaction was given. This paper give evidence that the differential equation for the expectation of the stochastic model cannot be identified with the differential equation associated with the usual deterministic model.
Continuous time discrete state stochastic models

Model frameworks, master equation

Mathematical background

\( \{X(t)\}_{t \in \mathbb{R}} \) is a **continuous time Markov process** if the following equation holds for every \( t_1 < t_2 < \cdots < t_{n+1} \) (\( n \) is a positive integer):

\[
P(X(t_{n+1}) = j | X(t_1) = i_1, X(t_2) = i_2, \ldots X(t_n) = i_n) = \]

\[
P(X(t_{n+1}) = j | X(t_n) = i_n)
\]

(22)

The transition probability for a Markov process is defined as:

\[
p_{ij}(s,t) = P(X(t) = j | X(s) = i).
\]

(23)

Obviously, the following equation holds for the transition probabilities for all possible \( i \) values:

\[
\sum_{k \in S} p_{ik}(s,t) = 1
\]

(24)

Chapman–Kolmogorov equation:

\[
p_{ij}(s,t) = \sum_k p_{ik}(s,u)p_{kj}(u,t) \quad (i,j = 0,1,2, \ldots)
\]

(25)

The **transition probability matrix** \( P(s,t) \) can be constructed from the individual transition probabilities:

\[
P(s,t) = \begin{pmatrix}
p_{1,1}(s,t) & p_{1,2}(s,t) & \cdots \\
p_{2,1}(s,t) & p_{2,2}(s,t) & \cdots \\
& \vdots & \ddots
\end{pmatrix}
\]

(26)

The **absolute state probabilities** \( P_i(t) := P(X(t) = i) \) of a CDS Markov process, i. e. the probabilities for the system to be in the state \( i \), satisfy a relatively simple recursive equation with the transition probabilities:

\[
P_i(t) = \sum_j p_{ji}(s,t)P_j(s)
\]

(27)

\( P_i(t) \) functions are very often the most preferred characteristics of CDS Markov processes in physical and chemical applications.
Continuous time discrete state stochastic models

Master equation

\[
\frac{dP_i(t)}{dt} = \sum_j (q_{ji}P_j(t) - q_{ij}P_i(t)),
\]

(28)

The \( q_{ij} \) values: infinitesimal transition probabilities (transition rates): can be obtained from the transition probabilities:

\[
q_{ii} = 0
\]

\[
q_{ij} = \lim_{s \to t} \frac{p_{ij}(s,t)}{t-s} \quad (i \neq j)
\]

(29)

Example: a birth-and-death process

\[
\emptyset \overset{k_1}{\rightarrow} A_1
\]

\[
A_1 \overset{k_2}{\rightarrow} 2A_1
\]

\[
A_1 \overset{k_3}{\rightarrow} \emptyset
\]

\[
p_{i,i+1}(t, t+h) = \lambda_i h + o(h)
\]

\[
p_{i,i-1}(t, t+h) = \mu_i h + o(h)
\]

\[
p_{i,i}(t, t+h) = 1 - (\lambda_i + \mu_i)h + o(h)
\]

\[
p_{i,j}(t, t+h) = o(h) \quad \text{if } j \neq i \text{ and } j \neq i \pm 1 \quad h \to 0.
\]

(31)

\[
\frac{dP_0(t)}{dt} = -\lambda_0 P_0(t) + \mu_1 P_1(t)
\]

(32)
Continuous time discrete state stochastic models

Chemical Master equation: general case

transition rate of reaction $j$ starting from state $(a_1, a_2, \ldots, a_n)$: combinatorial kinetics; "$kn(n - 1)$"

The full master equation of the process: summing all transition rates relevant to a given state:

$$\frac{dP_f(a_1, a_2, \ldots, a_n)}{dt} = -\sum_{j=1}^{m} v_j(a_1, a_2, \ldots, a_n)P_f(a_1, a_2, \ldots, a_n)$$

$$+ \sum_{j=1}^{m} v_j(a_1 - v_{j,1}, a_2 - v_{j,2}, \ldots, a_n - v_{j,n})P_f(a_1 - v_{j,1}, a_2 - v_{j,2}, \ldots, a_n - v_{j,n})$$

$$\frac{dP(t)}{dt} = \Omega P(t)$$
Continuous time discrete state stochastic models

Solutions of the master equation

• Direct matrix operations
• Laplace transformation
• Generating functions
• Other techniques ($Q$-functions, Poisson representation)
• Stationary distributions
• Simulation method
Continuous time discrete state stochastic models

Solutions of the master equation

Generating function:

\[ G(z_1, z_2, \ldots, z_n, t) = \sum_{\text{all states}} z^{a_1} z^{a_2} \cdots z^{a_n} P_{f(a_1, a_2, \ldots, a_n)}(t) \]

\[ z_i \in C \quad i = 1, 2, \ldots, n \]  \hspace{1cm} (35)

WHY?

all the individual variables of interest in the stochastic description can be obtained from it in a relatively straightforward manner

The expectation of the number of \( A_i \) molecules can be generated using first partial derivatives:

\[ \langle a_i \rangle(t) = \frac{\partial G(1, 1, \ldots, 1, t)}{\partial z_i} \]  \hspace{1cm} (36)

Second order moments and correlations can be given with a using second and mixed partial derivatives as follows:

\[ \langle a_i^2 \rangle(t) = \frac{\partial^2 G(1, 1, \ldots, 1, t)}{\partial z_i^2} + \frac{\partial G(1, 1, \ldots, 1, t)}{\partial z_i} \]  \hspace{1cm} (37)

\[ \langle a_i a_j \rangle(t) = \frac{\partial^2 G(1, 1, \ldots, 1, t)}{\partial z_i \partial z_j} \quad i \neq j \]  \hspace{1cm} (38)

transient solutions for *compartmental systems* fully known

Master equation (differential-difference equation ->
Partial DE for the generating function
(can be solved if linear)
Stationary distributions

• A stationary distribution is a vector, usually denoted as \( \pi \), and satisfies the following equation, which is derived from equation (34) by setting the left side 0:

\[
0 = \Omega \pi
\]  

(39)

• In typical cases, the stationary distribution \( \pi \) can also be thought of as the limit of the vector of probability functions with time approaching infinity:

\[
\pi_f(a_1,a_2,\ldots,a_n) = \lim_{t \to \infty} P_f(a_1,a_2,\ldots,a_n)(t)
\]  

(40)

• unimodality versus multimodality

• stochastic theory of bistable reactions
Stationary distributions

Schlögl reaction of the first-order phase transition

\[ A + 2X \xrightleftharpoons[k_1]{k_2} 3X \]  \hspace{2cm} (41)

\[ B \xrightleftharpoons[k_3]{k_4} X, \]  \hspace{2cm} (42)

deterministic model is

\[ \frac{dx(t)}{dt} = k_1 ax^2 - k_2 x^3 - k_4 x + k_3 b; \quad x(0) = x_0. \]  \hspace{2cm} (43)

three stationary states: bistability

master equation is given as

\[ \frac{dP_n(t)}{dt} = \lambda_{n-1} P_{n-1} + \mu_{n+1} P_{n+1} - (\lambda_n + \mu_n) P_n, \]  \hspace{2cm} (44)

for \( n = 1 \ldots \infty \), and

\[ \frac{dP_0}{dt} = \mu_1 P_1 - \lambda_0 P_0. \]  \hspace{2cm} (45)

Here \( \lambda_n = \hat{k}_3 n_B + \hat{k}_1 n_A (n - 1) \) and \( \mu_n = \hat{k}_4 n + \hat{k}_2 n (n - 1) (n - 2) \), \( \lambda_n \) and \( \mu_n \) are the birth and death rates, respectively.

The stationary distribution calculated by using the detailed balance assumption \( \lambda_{n-1} P_{n-1}^{ss} = \mu_n P_n^{ss} \) as

\[ P_n^{ss} = P_0^{ss} \prod_{i=0}^{n-1} \frac{\lambda_i}{\mu_{i+1}}, P_0^{ss} = 1 - \sum_{j=1}^{\infty} P_j^{ss}. \]  \hspace{2cm} (48)

Figure 8: The volume-dependence of the modality

volume \( V \) is explicitly taken into account: \( \hat{k}_i = \frac{k_i}{V_m T} \).
Continuous time discrete state stochastic models: Simulation methods

The Doob-Hanus-Hárs-Tóth-Érdi-Gillespie algorithm

- when will the next reaction occur?
- what kind of reaction will it be?
- Doob theorem
- \( P(\tau, \mu) \): reaction probability density function
- variations, accelerated, hybrid etc methods.

\[ P(\tau, \mu) d\tau \] means the probability at time \( t \) that the next reaction in \( V \) will occur in the differential time interval \( (t + \tau, t + \tau + d\tau) \), and it will be an \( R_\mu \) reaction.

- simulation softwares: Cain
- algorithms
- visualization methods

Figure 9: Realization

Figure 10: Histogram
A more satisfactory way of dealing with this problem could be called **stochastic mapping** (G. Lente), which attempts to identify the part of the parameter space of a given kinetic scheme in which only the stochastic approach is viable. A convenient definition of this stochastic region is the set of parameter values for which the stochastic approach shows that the relative standard error of the target variable is larger than a pre-set critical value (often 1% because of the usual precision of analytical methods used for concentration determination). Although there is no general proof known yet, a small standard deviation of the expectation of a variable calculated based on the stochastic approach seems to ensure that the stochastic expectation is very close to the deterministic solution.
Systems Biological Applications

- Fluctuations near instabilities
- Enzyme kinetics
- Signal processing in biochemical networks
- Calcium signaling
- The beneficial role of noise: fluctuation-dissipation theorem and stochastic resonance
- Stochastic models of gene expression
- (Chiral symmetry)
Fluctuations near instabilities

CCD vs CDS models

\[ A + X \xrightarrow{\lambda'} 2X \]  
\[ X \xrightarrow{\mu} 0. \]  

\[ \frac{dx(t)}{dt} = (\lambda - \mu)x(t); \quad x(0) = x_0, \]  
(51)

(Here \( \lambda = \lambda'[A]. \)) The solution is

\[ x(t) = x_0 \exp(\lambda - \mu)t. \]  
(52)

If \( \lambda > \mu \), \( x \) is exponentially increasing function of time.

\( \lambda = \mu \):

\[ x(t) = x_0. \]  
(53)

\[ \frac{dP_k(t)}{dt} = -k(\lambda + \mu)P_k(t) + \lambda(k - 1)P_{k-1}(t) + \mu(k + 1)P_{k+1}(t) \]  
(54)

\[ P_k(0) = \delta_{kx_0}; k = 1, 2, \ldots N \]  
(55)

\[ E[\xi(t)] = x_0 \exp(\lambda - \mu)t, \]  
(56)

\[ D^2[\xi(t)] = (\lambda + \mu)t. \]  
(57)

For the case of \( \lambda = \mu \)

\[ D^2[\xi(t)] = 2D\lambda t, \]

Figure 11: Amplifications of fluctuations might imply instability. While the expectation is constant, the variance increases in time.
Enzyme kinetics

\[
E + S \xrightarrow{k_1} ES \xrightarrow{k_2} E + P \quad (58)
\]

\[
\frac{dP_{e,s}(t)}{dt} = -[\kappa_1 e_s + (\kappa_{-1} + \kappa_2)(e_0 - e)] P_{e,s}(t) + \\
\kappa_1 (e + 1)(s + 1) P_{e+1,s+1}(t) + \\
\kappa_{-1} (e_0 - e + 1) P_{e-1,s-1}(t) + \\
\kappa_2 (e_0 - e + 1) P_{e-1,s}(t) \quad (59)
\]

Figure 12: Stochastic map of the Michaelis-Menten mechanism with the number of product molecules formed as the target variable.
Enzyme kinetics

Figure 13: An overlooked very important paper

Figure 14: Comparison of CDS and CCD model
Enzyme kinetics

Oxidation of molecular hydrogen by HynSL hydrogenase from *Thiocapsa roseopersicina*

\[
\begin{align*}
E_2 + E_3 & \xrightarrow{k_b} 2E_3 \\
E_3 & \xrightarrow{k_c} E_4 \\
E_4 + H_2 + 2M_o & \xrightarrow{k_d} E_2 + 2M_r
\end{align*}
\]

(60)

three step catalytic cycle

E₂, E₃ and E₄ are different enzyme forms in the catalytic cycle, H₂ is hydrogen, whereas M₀ and Mᵣ are the oxidized and reduced form of the electron acceptor compound benzyl viologen. State: E₂, E₃ and Mᵣ molecules as e₂, e₃ and p. The master equation can then be stated as using m and h for the number of Mᵣ and H₂ species, and introducing the constant n as the total number of all enzyme forms (n = e₂ + e₃ + e₄): It is possible to find rate constants leading to extinction.

\[
\frac{dP_{e₂,e₃,p}(t)}{dt} = -[k_be₂e₃ + k_ce₃ + k_d(n - e₂ - e₃)m(m - 1)h]P_{e₂,e₃,p}(t)
\]

+ kₐ(e₂ + 1)(e₃ - 1)P_{e₂+1,e₃-1,p}(t) + kₐ(e₃ + 1)P_{e₂+1,e₃+1,p}(t)

+ kₐ(n - e₂ - e₃ + 1)(m + 2)(m - 1)(h + 1)P_{e₂-1,e₃,p-2}(t)

(61)

Extinction in autocatalytic system, which occurs when the molecule number of the autocatalytic species falls to zero in a system that involves a pathway for the decay of the autocatalyst. This phenomenon is unknown in deterministic kinetics, as an initially nonzero concentration can at no time be exactly zero there.
Signal processing in biochemical networks

Evaluation of signal transfer by mutual information

- Biochemical networks map time-dependent inputs to time-dependent outputs.
- The efficiency of information transmission: mutual information between the input signal $I$ and output signal $O$

\[
M(I, O) = H(O) - H(O|I)
\]  

\[
H(O) \equiv - \int p(O) \log p(O) \, dO
\]

is the information-theoretical entropy of the output $O$ having $P(O)$ probability distribution, and $H(O|I) \equiv - \int p(I) dI \int p(O|I) \log p(O|I) \, dO$ is the average (over inputs $I$) information-theoretical entropy of $O$ given $I$, with $p(O|I)$ the conditional probability distribution of $O$ given $I$.

Input species $S$ and output species $X$ (Tostevin and ten Wolde (2009)):

\[
M(S, X) = \int DS(t) \int DX(t) p(S(t), X(t)) \log \frac{p(S(t), X(t))}{p(S(t))p(X(t))}
\]  

(63)
Systems Biological Applications

Signal processing in biochemical networks

Analytical results: small Gaussian fluctuations:
Mutual information rate: \( R(s,x) = \lim_{T \to \infty} \frac{M(s,x)}{T} \) - calculated from the power spectra of the fluctuations:

\[
R(s,x) = -\frac{1}{4\pi} \int_{-\infty}^{\infty} d\omega \ln \left\{ 1 - \frac{|S_{ss}(\omega)|^2}{S_{ss}(\omega)S_{xx}(\omega)} \right\} \tag{64}
\]

\( R(s,x) \): temporal correlations between the input and output signals. Equation 64 is exact for linear systems with Gaussian noise. Detection of input signals may generate correlations between the signal and the intrinsic noise of the reactions. If there is NO correlation: **spectral addition rule** (65).

\[
S_{xx}(\omega) = N(\omega) + g^2(\omega)S_{ss}(\omega) \tag{65}
\]

Here \( N(\omega) \): internal fluctuation; \( S_{ss}(\omega) \): the power spectrum of the input signal, \( g^2(\omega) = \frac{|S_{sx}(\omega)|^2}{S_{ss}(\omega)} \): frequency-dependent gain.

The spectrum of transmitted signal: as \( P(\omega) = g^2(\omega)S_{ss}(\omega) \), so equation (64):

\[
R(s,x) = -\frac{1}{4\pi} \int_{-\infty}^{\infty} d\omega \ln \left\{ 1 + \frac{P(\omega)}{N(\omega)} \right\} \tag{66}
\]
Signal processing in biochemical networks

The effect of external noise (on $E_+$): addition of a correction (diffusion) term to the deterministic result ($\sigma$ is the forward enzyme noise strength)

$$R_N(\sigma)(X_{ss}, E_+; E_-) = E_+ - \frac{k_- E - (X_0 - X_{ss})(K_+ + X_{ss})}{K_+ X_{ss}(K_+ + X_0 - X_{ss})} + \frac{\sigma^2 k_+ K_+}{(K_+ + X_{ss})^2} = 0$$

(67)

Figure 15: The enzymatic futile cycle reaction mechanism. Adapted from Šamoilov 2005

Figure 16: Transition between uni- and multistaionarity. The bifurcation parameter $p$ is the exponent of $E_+$ in a relationship connecting the variance $E_+$ and $E_+$. (Šamoilov 2005)
Figure 17: Stochastic bifurcation plot of the fractional steady-state values of activated kinase, as a function of the volume $V$. The solid curves represent the maxima of the steady-state distribution, and the dashed curve represents the minimum of the distribution. $V = 1.67$ is the critical value, where the bistability disappears. (Bishop-Qian 2010).
Calcium signaling

Hierarchy of spatiotemporal events

- single channel opening (blip)
- the opening of several closely packed channels (puff)
- cooperation of puffs may set off a wave traveling through the cell
- Waves may occur periodically, so they can be seen as global oscillations

Figure 18: A lumped kinetic scheme of the channel kinetics. $X_{00}$: state with no $Ca^{2+}$ bound; $X_{10}$: activated state; $X_{11}$ and $X_{01}$: inhibited states. An index is 1 if an ion is bound and 0 if not. Transition rates are shown at the edges of the rectangle. Falcke03.

Figure 19: Distributions of clusters and of receptors involved obtained with simulations of intercluster dynamics with calcium accumulation. Power law distribution can be rather well fitted. Based on Lopez 2012.
Systems Biological Applications

The beneficial role of noise: fluctuation-dissipation theorem and stochastic resonance

- Estimation of rate constants from equilibrium fluctuations
- Chemical fluctuations measurements: electric conductance; fluorescence correlation spectroscopy
- Membrane noise analysis

For the association-dissociation reaction of the beryllium sulfate described by the reaction $X \xrightleftharpoons[k_1]{k_{-1}} Y$, the spectrum of the electric fluctuation (which reflects the concentration fluctuation) was found to be

$$S_\nu = \frac{\text{const}}{1 + (2\pi \nu (k_1 + k_2))^2}.$$  \hfill (68)

Since from deterministic equilibrium the ratio $\frac{k_1}{k_{-1}}$ is given, therefore, the individual rate constants can be calculated.
Fluorescence correlation spectroscopy is able to measure the fluctuation of the concentration of fluorescent particles (molecules). Temporal changes in the fluorescence emission intensity caused by single fluorophores are recorded. The autocorrelation function $C(t) := E[\xi(t)\xi(t - \tau)]$ of the signal $\xi(t)$ is calculated, and from their time-dependent decay of the fluorescence intensity the rate parameters can be calculated. Higher order correlations $C_{mn}(t) := E[\xi(t)^m\xi(t - \tau)^n]$ were used to study the details of molecular aggregation. To extract more information from the available data beyond average and variance at least two efficient methods were suggested. **Fluorescence-intensity distribution analysis** is able to calculate the expected distribution of the number of photon counts, and **photon counting histogram** gives an account of the spatial brightness function. Forty years after, fluorescence fluctuation spectroscopy still is a developing method.
Parameter estimation for stochastic kinetic models: beyond the fluctuation-dissipation theorem

- time-dependent data
- maximum likelihood estimator for the rate constants
- kinetic parameters of biochemical reactions, such as gene regulatory, signal transduction and metabolic network, generally cannot be measured directly,

\[
L(k) = \prod_{j=1}^{m} \prod_{i=1}^{n} f(o_j^i, t_i; k), \quad (69)
\]

where the \(j^{th}\) experimental replicates \(o_1^j, o_2^j, \ldots, o_n^j\) are taken at time points \(t_1, t_2, \ldots, t_n\) for \(j = 1, 2, \ldots, m\) (i.e. the experiments are done in \(m\) replicates). \(f(o_i^j, t_i; k)\) is the likelihood function determined by the density function histogram constructed from the realizations of the stochastic process specified by the master equation. The maximization of the likelihood function (actually from numerical reasons the minimization of the negative log-likelihood function) gives the best estimated parameters (i.e. it gives the greatest possible probability to the given data set): training data.

\[
k^* = \arg \min_k -\log L(k) = \arg \min_k \sum_{j=1}^{m} \sum_{i=1}^{n} -\log P(o_j^i, t_i), \quad (70)
\]

where \(P(o_i^j, t_i)\) is the conditional probability density function reconstructed from the simulated realizations.
Stochastic resonance

Figure 20: A typical curve of stochastic resonance shows a single maximum of the output performance as a function of the intensity of the input noise.

Figure 21: Signal-to-noise ratio as a function of the width of the double well. Since width can be identified as the noise parameter, the peak is the feature of stochastic resonance. From Leonard 1994

Figure 22: (a) One-parameter system: a threshold is constant in time and the system generates a response if the sum of the signal and additive noise exceeds the threshold. (b) Two-parameter system: a periodic modulation in one parameter changes a threshold of the other parameter, and the system generates response when noise in the latter parameter exceeds the modulated threshold. From Tomo Yamaguchi’s lab: 1998.
Stochastic resonance of aperiodic signals

Not only periodic, but aperiodic signals might be the subject of amplification by noise, both in experimental (actually electrochemical) and model studies. Information transfer is quantified by the $C_0$ cross correlation function

$$C_0 = \langle (x_1 - \langle x_1 \rangle_t)(x_2 - \langle x_2 \rangle_t) \rangle_t,$$

where $x_1$ and $x_2$ represents the time series of the aperiodic input signal, and the noise induced response of the electrochemical system, respectively. $\langle \rangle$ denotes the respective time averages.

Figure 23 illustrates the existence of optimal noise level for information transfer.

![Cross-correlation as a function of noise level](image)

Figure 23: Cross-correlation as a function of noise level. Parma-show 2005.
Stochastic models of gene expression: second encounter

A three-stage model of gene expression (say: Paulsson 2005):

\[
\begin{align*}
\text{inactive gene} \xrightarrow{\lambda_1^+} & \text{active gene} \xrightarrow{\lambda_2} \text{mRNA} \xrightarrow{\lambda_3} \text{protein} \\
\text{supplemented with two degradation steps} \text{ (the second also called as proteolysis):} & \\
\text{mRNA} \xrightarrow{\gamma_m} 0 & \quad \text{protein} \xrightarrow{\gamma_p} 0
\end{align*}
\] (72) (73)
1. Canonical stochastic models of gene expression

Gene activation: \( n_1^+ \frac{a}{n_1} + 1 \)
Gene inactivation: \( n_1^- \frac{a}{n_1} - 1 \)
Transcription: \( n_2 \frac{a}{n_2} + n_2 - 1 \)
mRNA degradation: \( n_2^- \frac{a}{n_2} + n_2 - 1 \)
Translation: \( n_3 \frac{a}{n_3} + n_3 + 1 \)
Proteolysis: \( n_3^- \frac{a}{n_3} + n_3 - 1 \)

2. Circular Gene Expression Hypothesis

The skeleton network model of coordinated mRNA degradation and synthesis

3. Direct Kinetic measurements are missing

A possible test:
HOW does the feedback mechanism influence protein fluctuation?

4. Stochastic Simulation

5. Simulation Results – Canonical Model

Figure 1. The stationary distribution of the number of protein particles at t=50,000 for n=100,000 simulated stochastic trajectories of the canonical model with a normal transcription rate (propensity=0.0231). The resulting distribution is statistically well-modeled by a Poisson distribution with expected value \( \lambda = 3,270 \).

Figure 2. The stationary distribution of the number of protein particles at t=50,000 for n=100,000 simulated stochastic trajectories of the canonical model with an elevated transcription rate (propensity=0.1155). The resulting distribution is statistically well-modeled by a Poisson distribution with expected value \( \lambda = 3,270 \).

5. Simulation Results – Feedback Model

Figure 3. The stationary distribution of the number of protein particles at t=50,000 for n=100,000 simulated stochastic trajectories of the feedback model with a normal transcription rate (propensity=0.0231). The resulting distribution is statistically well-modeled by an exponential distribution.

Figure 4. The stationary distribution of the number of protein particles at t=50,000 for n=100,000 simulated stochastic trajectories of the feedback model with an elevated transcription rate (propensity=0.1155). The resulting distribution is statistically well-modeled by an exponential distribution.

6. Where are we now?

- PROTEIN FLUCTUATION seems to be sensitive
- mRNA FLUCTUATION is smaller but shows similar tendencies
- MODEL DISCRIMINATION seems to be possible
- Some ANALYTICAL calculations look feasible
- The justification of the circular gene expression hypothesis needs kinetic studies

7. A Similar Project

Investigation of transmitter-receptor interactions by analyzing postsynaptic membrane noise using stochastic kinetics
Erdi, P., Ropolyi, L.

Abstract
The stoichiometric and kinetic details of transmitter-receptor interaction (the number of conformations and the rate constants of conformation changes) in synaptic transmission have been investigated analyzing postsynaptic membrane noise by the aid of the fluctuation-dissipation theorem of stochastic chemical kinetics. The main assumptions are the following: (i) the transmitter-receptor model interactions are modelled by a closed compartment system (a special complex chemical reaction) of unknown length, (ii) the number of transmitter is maintained at a constant level, (iii) the conductance is a linear function of the conformation quantity vector. The main conclusion is the conductance spectral density function is determined by three qualitatively different factors, (ii) the length of the compartment system, (iii) the precise form of the conductance-conformation quantity vector, (iv) the matrix of the reaction rate constants.

8. References
Chiral symmetry: An important topic: Gábor Lente

- Molecular chirality: lack of certain symmetry elements in the three dimensional structures of molecules
- Homochirality or biological chirality: mirror image counterparts have very different roles: typically, only one of them is abundant and it cannot be exchanged with the other one.
- Racemic mixtures (R and S)

\[
P(r, s) = \binom{r+s}{r} (0.5 + \varepsilon)^r (0.5 - \varepsilon)^s \tag{74}
\]

Here, \( P(r, s) \) is the probability that \( r \) molecules of the R enantiomer and \( s \) molecules of the S enantiomer occur in an ensemble of \( r + s \) molecules. Parameter \( \varepsilon \) is characteristic of the degree of inherent difference between the two enantiomers (\( \varepsilon \leq 0.5 \)), and is connected to the energy difference (\( \Delta E \)) between the R and S molecules as follows:

\[
\varepsilon = \frac{e^{\Delta E/RT} - 1}{2(e^{\Delta E/RT} + 1)} \tag{75}
\]

The expectation and standard deviation for the number of R enantiomers from this distribution is given by straightforward formulae:

\[
\langle r \rangle = (0.5 + \varepsilon)(r + s) \tag{76}
\]

\[
\sigma_r = \sqrt{(r + s)(0.5 + \varepsilon)(0.5 - \varepsilon)} \tag{77}
\]
Chiral symmetry

Figure 24: The classical Frank model (1953)
\[
\frac{dP(a, r, s, t)}{dt} = -\left\{ 2a\kappa_u + ar\kappa_c + as\kappa_c + rs\kappa_d + (n-a)\kappa_f \right\} P(a, r, s, t) + \\
+ \left\{ (a+1)\kappa_u + (a+1)(r-1)\kappa_c \right\} P(a+1, r-1, s, t) + \\
+ \left\{ (a+1)\kappa_u + (a+1)(s-1)\kappa_c \right\} P(a+1, r, s-1, t) + \\
+ \left\{ (r+1)(s+1)\kappa_d \right\} P(a, r+1, s+1, t) + (r+1)\kappa_f P(a-1, r+1, s, t) + \\
+ (s+1)\kappa_f P(a-1, r, s+1, t) + (n-a-r-s+1)\kappa_f P(a-1, r, s, t)
\]
Figure 26: Final probability distributions in the Frank model in a closed system