Contraction of stochasticity on hierarchical kinetic networks

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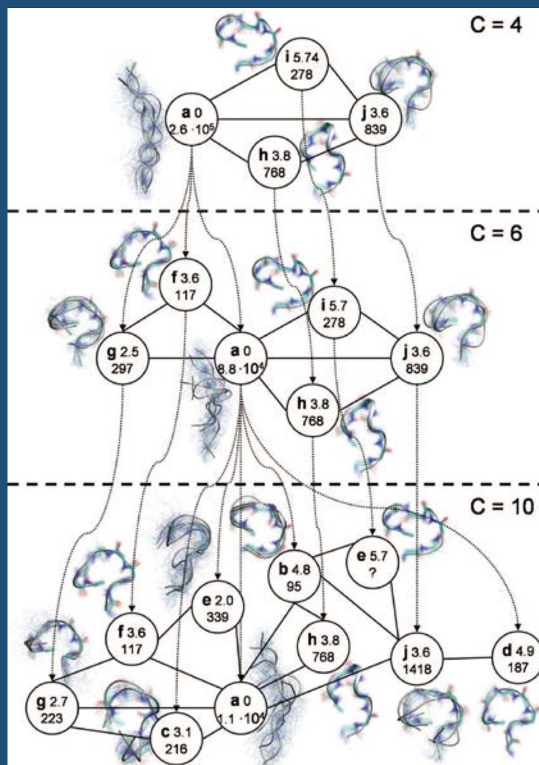
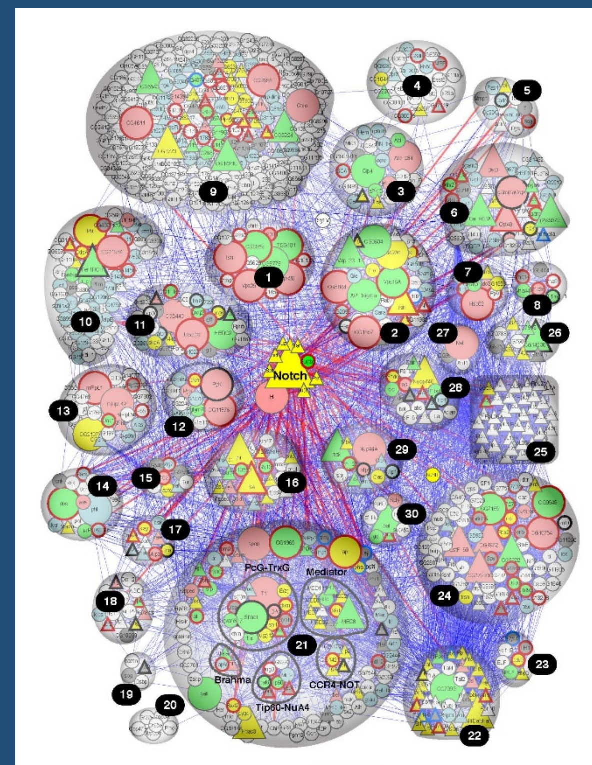
Motivation:

Kinetic networks are widely used for studying complex systems,

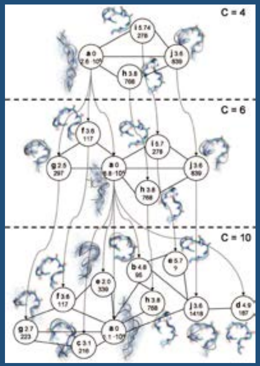
e.g., structural biology systems biology.



Noé, et al JCP (2007)
metastable states



Saj, et al (2010)
modules

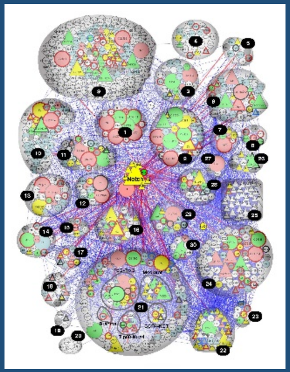


small system

share the same mathematics

⟺

what are states and transition rates between states?

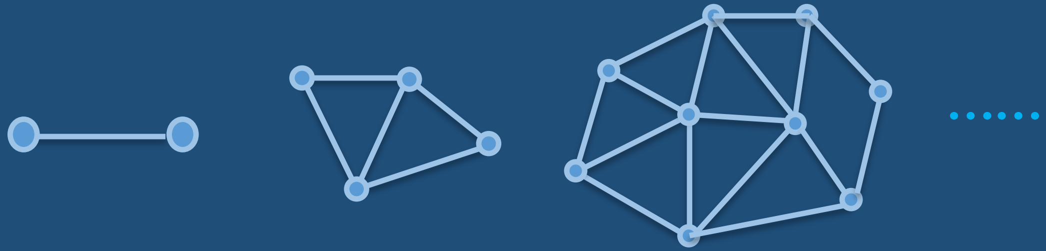


large system

Q: How fine we should coarse grain a system?

A: Unfortunately, no *a priori* rule.

➔ Hierarchical networks

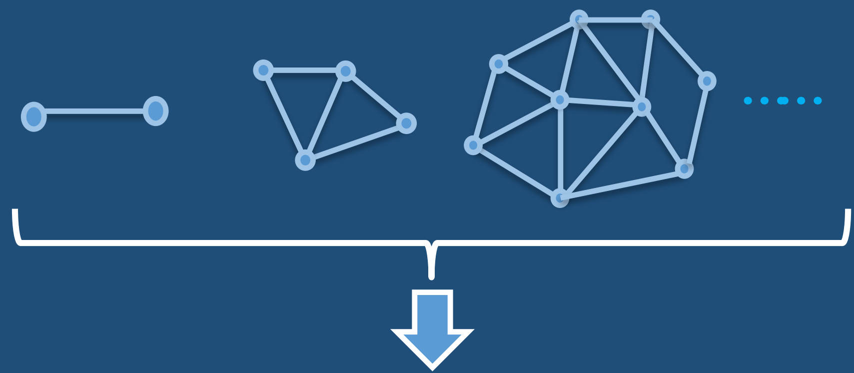


experimental data

unique

models

non-unique



“equivalence class”

(“equivalence relation”: identical after being projected to the same dimension)

Which kinds of equivalence?

- thermodynamical (mean at $t \to \infty$) ➔ textbook level
- kinetical (mean at all t) ➔ lumping analysis (LA)
- complete (mean & fluctuations at all t) ➔ stochastic LA

Stochastic LA introduces stochasticity into traditional LA.

Traditional lumping analysis (deterministic dynamics)

rate equations (RE)

Stochastic lumping analysis (stochastic process)

chemical master equations (CME)
(for intrinsic noises)

stochastic differential equations (SDE)
(for intrinsic & extrinsic noises)

Traditional lumping analysis

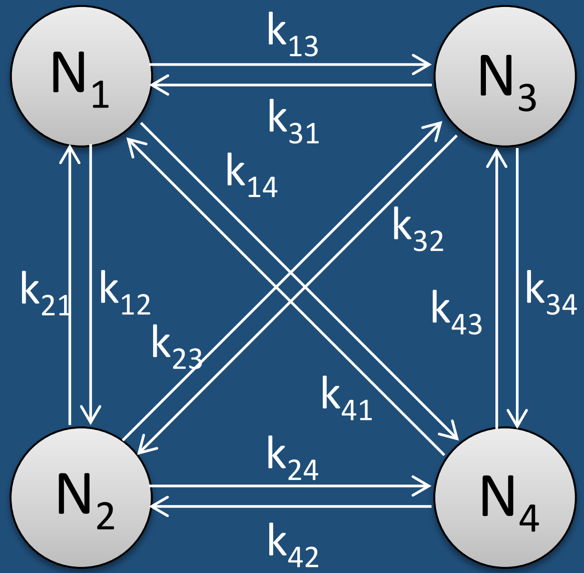
(on rate eq.)

Kinetic model

Rate equation (RE)

$$\frac{d\mathbf{N}}{dt} = \mathbf{MN}$$

$$\frac{dN_i}{dt} = \sum_{j=1}^{n} \left(k_{ji}N_j - k_{ij}N_i\right) \equiv \sum_{j=1}^{n} M_{ij}N_j$$



N_i : the concentration (or prob.) of the i-th state

$\sum_{i=1}^{n} N_i$ = constant (conservation law)

Exact and approximate lumpings

Suppose system A has a RE

$$\frac{d\mathbf{N}}{dt} = \mathbf{MN} \qquad n\text{–dim.} \qquad (1)$$

If there exists an $n' \times n$ lumping matrix $\mathbf{U}$ such that $\mathbf{N}' = \mathbf{UN}$ fulfills

$$\frac{d\mathbf{N}'}{dt} = \mathbf{M}'\mathbf{N}' + \cancel{f(\mathbf{N})} \qquad n'\text{-dim } (n' < n), \qquad (2)$$

then A is exactly lumpable.

If the memory $f(\mathbf{N}) \approx 0$ but $\neq 0$ ➔ A is approximately lumpable.

Condition for (exact) lumpability (Wei & Kuo 1969)

(1) ➔ $\frac{d(\mathbf{UN})}{dt} = \mathbf{UMN}$

(2) ➔ $\frac{d\mathbf{N}'}{dt} = \mathbf{M}'\mathbf{UN}$

$$\Leftrightarrow \boxed{\mathbf{UM} = \mathbf{M}'\mathbf{U}} \qquad (3)$$

Lumpability condition in terms of rate constants

$\mathbf{U}$ groups N_i into n' sets S_a, $a = 1, \ldots, n'$.

$$k'_{ba} = \sum_{i \in S_a} k_{ji} \qquad (4)$$
$$\forall \;\; a, b \text{ with } j \in S_b \text{ and } b \neq a$$

A and A' fulfill (4).

$\Longleftrightarrow$ A can be (exactly) lumped into A' (mathematical term)

$\Longleftrightarrow$ A is kinetically equivalent (KE) to A' (physical term)

$\Longleftrightarrow$ $\mathbf{UN}$ and $\mathbf{N}'$ are identical.

$\Longleftrightarrow$ $\mathbf{N}$ and $\mathbf{N}'$ are indistinguishable (after $\mathbf{N}$ is projected by $\mathbf{U}$).

Stochastic lumping analysis

(on chemical master eq. & stochastic differential eq.)

Chemical master equation (CME)

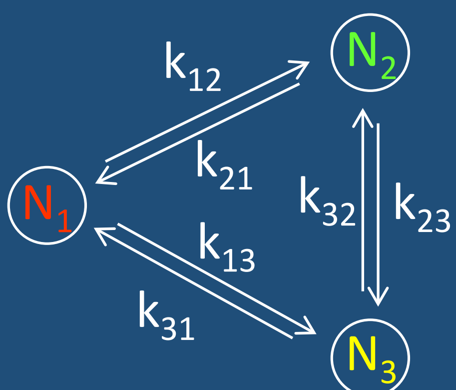
$$\frac{dP(\mathbf{N},t)}{dt} = \sum_{i,j}^{n} k_{ij}\left[(N_i+1)P\left(\mathbf{N}-\boldsymbol{\omega}_{ij},t\right) - N_i P\left(\mathbf{N},t\right)\right] \quad (5)$$

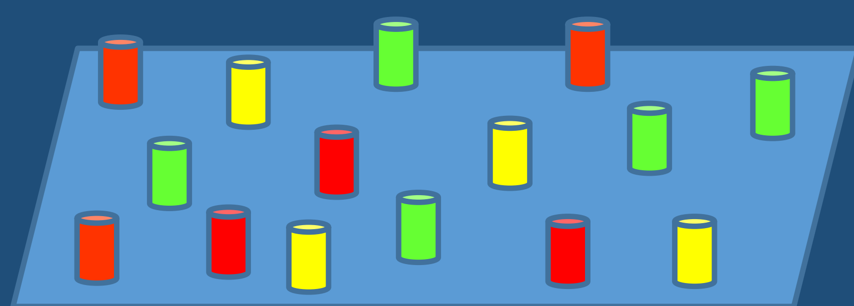
$$d\mathbf{P}(t)\,/dt = \boldsymbol{\mathcal{L}}\,\mathbf{P}(t)$$

$\boldsymbol{\omega}_{ij}$ = number change of N_i and N_j

Evolution of joint probability $P(\mathbf{N},t) = P\left(\begin{pmatrix} N_1 \\ N_2 \\ N_3 \end{pmatrix}, t\right)$

$P(\mathbf{N},t) \equiv 0$ if any $N_i < 0$.





$N_1 = 6$

$N_2 = 5$

$N_3 = 4$

Protein with three conformations (n = 3)

Lumping matrix U associated lumping operator $\hat{\mathbf{U}}$

For each matrix $\mathbf{U} : \mathbf{N} \rightarrow \mathbf{N}'$ for lumping the rate equation, there exists an associated operator $\hat{\mathbf{U}}$: $\mathbf{P} \rightarrow \mathbf{P}'$ for lumping the chemical master equation.

$$\begin{aligned}
&[\hat{\mathbf{U}}\mathbf{P}]_{\mathbf{N}'} \\
&\quad \equiv \sum_{\mathbf{N}'=\mathbf{U}\mathbf{N}} P(\mathbf{N}, t) \\
&\quad = \sum_{\{N_i\}} P(\mathbf{N}, t) \prod_{c=1}^{n'} \delta\left(N_c' - \sum_{k \in S_c} N_k\right) \qquad (6) \\
&\quad = [\mathbf{P}']_{\mathbf{N}'}
\end{aligned}$$

Theorem 1:

$$\frac{d\mathbf{N}}{dt} = \mathbf{M}\mathbf{N} \xrightarrow[\text{rate eq.}]{\mathbf{N}' = \mathbf{U}\mathbf{N}} \frac{d\mathbf{N}'}{dt} = \mathbf{M}'\mathbf{N}'$$

$$\downarrow\uparrow \qquad\qquad\qquad\qquad \downarrow\uparrow$$

$$\frac{d\mathbf{P}}{dt} = \mathcal{L}\,\mathbf{P} \xrightarrow[\text{chem master eq.}]{\mathbf{P}' = \hat{\mathbf{U}}\mathbf{P}} \frac{d\mathbf{P}'}{dt} = \mathcal{L}'\,\mathbf{P}'$$

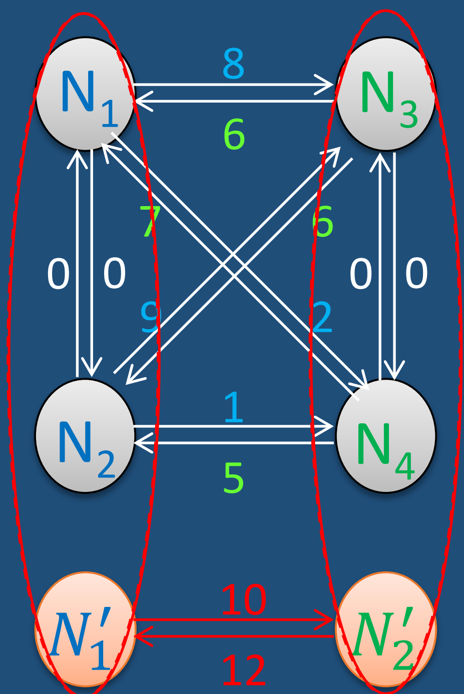
Implications:

- Lumpability of RE $\Leftrightarrow$ Lumpability of CME
  $\mathbf{N}$ and $\mathbf{N}'$ indist. $\Leftrightarrow$ $\mathbf{P}$ and $\mathbf{P}'$ indist.
  Weak indist. (1st moment) ➔ strong indist. (all moments)
  e.g., covariance & variance, …
- For intrinsic noises, fluctuation measurements cannot be used to judge whether a system has internal states.

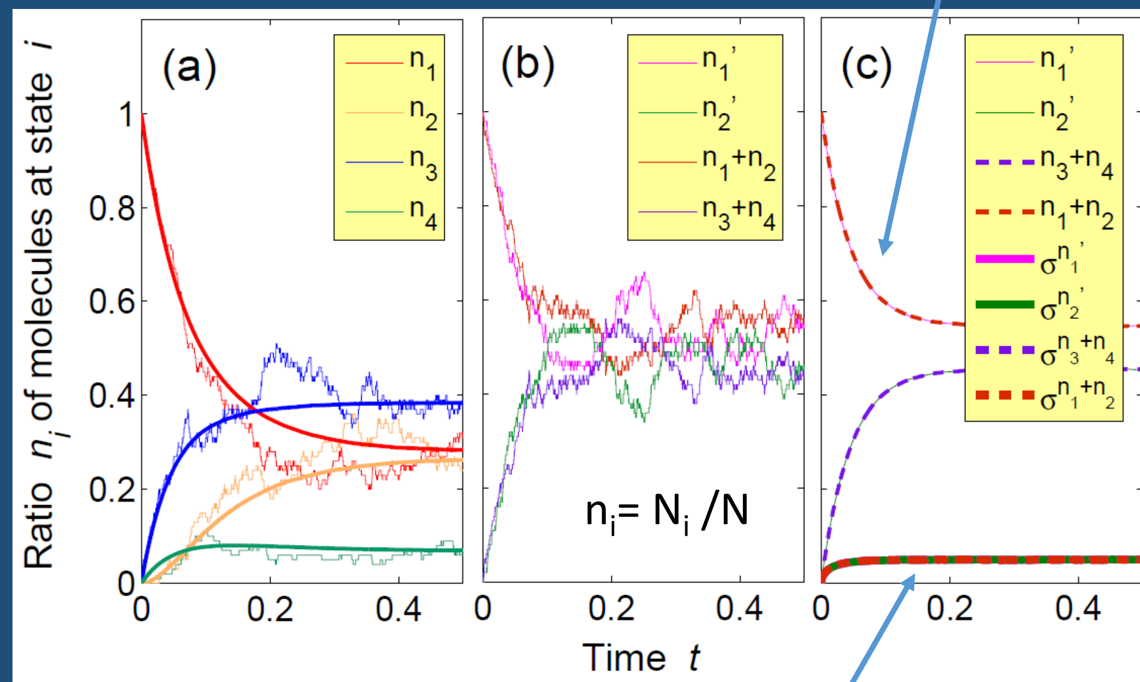
Numerical confirmation (to Theorem 1)

A is KE to A', indist. means between n_1+n_2 and n_1'.

4-state model A



2-state model A'



indist. variances.

(automatically)

Thermodynamically equivalence (TE)

If systems A and A’ are TE to each other, their states $\mathbf{N}$ and $\mathbf{N}'$ are indist. at t → ∞, i.e.,

$$\mathbf{U}\mathbf{N}^s = \mathbf{N}'^s \quad (s = \text{stationary}).$$

TE is weaker than KE (KE implies TE, but not vice versa).

Stationary joint prob. TL Hill (1971), YD Chen (1973), N Saito (1974)

(closed) $$P^s(\mathbf{N}) = \frac{N!}{\prod_{i=1}^n N_i!} \prod_{j=1}^n \left(\frac{\langle N_j^s \rangle}{N}\right)^{N_j}$$

(open) $$P^s(\mathbf{N}) = \prod_{i=1}^n \frac{\langle N_i^s \rangle^{N_i}}{N_i!} e^{-\langle N_i^s \rangle}$$

Since P^s only depends on the means N_j^s, infinitely many k_{ij} can generate the same P^s.

Theorem 2:

If the RE of A is thermodynamically equivalent to that of A’ (not necessarily kinetically equivalent), then

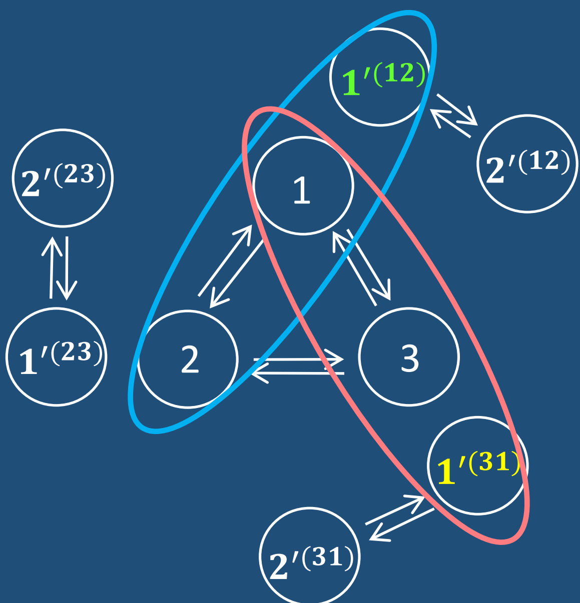
$$\widehat{\mathbf{U}}\mathbf{P}^s = \mathbf{P}'^s.$$

Implications:

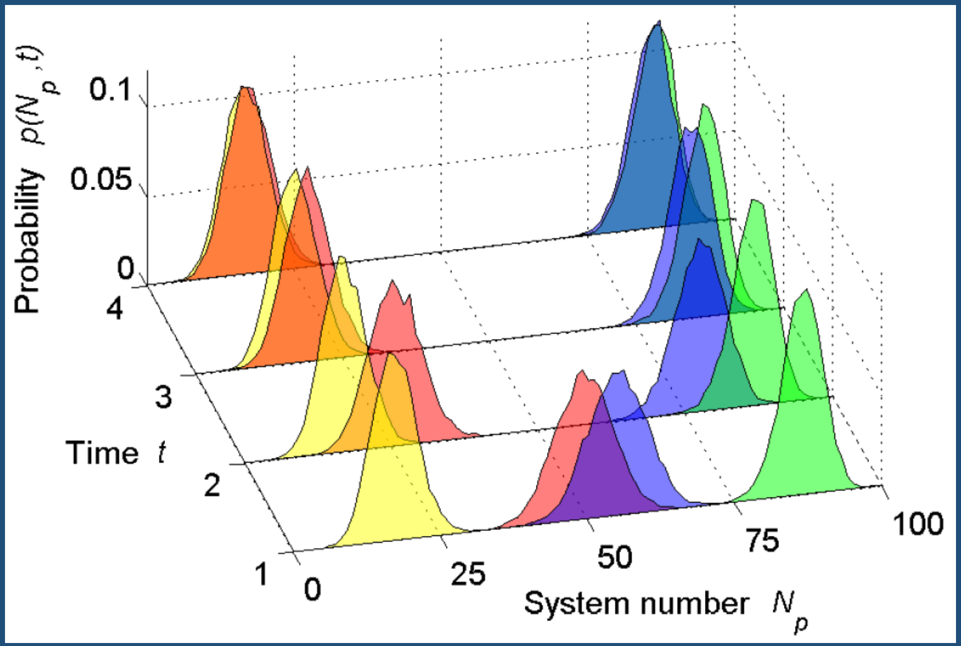
- Even if $\mathbf{N}$ and $\mathbf{N}'$ ($\mathbf{P}$ and $\mathbf{P}$’) of two TE networks are initially dist., they will become indist. at $t \to \infty$. ➔ asymptotic lumpability
- “Lumpability” seems to play the same role as a Lyapunov function for characterizing entropy production. Kullback-Leibler divergence may be a measure.

Numerical confirmation (to Theorem 2)

100 realizations of a system of 100 molecules



TE but not KE



$\boldsymbol{p(N_1 + N_3, t)}$ $\boldsymbol{p(N_1 + N_2, t)}$

$\boldsymbol{p(N_{1'(31)}, t)}$ $\boldsymbol{p(N_{1'(12)}, t)}$

Note: $p(N_i, t) \neq$ joint prob. $P((N_1, \ldots, N_n)^T, t)$.

Stochastic differential equation (SDE)

$$\frac{d\widehat{\mathbf{N}}}{dt} = \mathbf{M}\widehat{\mathbf{N}} + \mathbf{f}(t) \qquad \begin{aligned}&\langle \mathbf{f}(t) \rangle = 0 \\ &\langle \mathbf{f}(t)\mathbf{f}(t')^{\mathbf{T}} \rangle = \mathbf{\Gamma}\delta(t - t')\end{aligned} \qquad (7)$$

$$\widehat{\mathbf{N}}(t) = \mathbf{e}^{\mathbf{M}t}\widehat{\mathbf{N}}(0) + \int_0^t \mathbf{e}^{\mathbf{M}\tau}\,\mathbf{f}(t-\tau)\,\mathrm{d}\tau,$$

Covariance of fluctuations of $\widehat{\mathbf{N}}$:

$$\boldsymbol{\sigma}(\mathrm{t}) = \left(\widehat{\mathbf{N}} - \mathbf{N}\right)\left(\widehat{\mathbf{N}}^{\mathbf{T}} - \mathbf{N}^{\mathbf{T}}\right) = \int_0^{\mathrm{t}} \mathbf{e}^{\mathbf{M}\tau}\,\mathbf{\Gamma}\left(\mathbf{e}^{\mathbf{M}\tau}\right)^{\mathbf{T}}\mathrm{d}\tau \qquad (8)$$

Covariance of fluctuations of $\mathbf{U}\widehat{\mathbf{N}}$: (generally $\mathbf{U}\widehat{\mathbf{N}}$ has a memory term)

$$\begin{aligned}\mathbf{U}\boldsymbol{\sigma}\mathbf{U}^{\mathbf{T}} &= \mathbf{U}\left(\widehat{\mathbf{N}} - \mathbf{N}\right)\left(\widehat{\mathbf{N}}^{\mathbf{T}} - \mathbf{N}^{\mathbf{T}}\right)\mathbf{U}^{\mathbf{T}} \qquad (9)\\ &= \left(\mathbf{U}\widehat{\mathbf{N}} - \mathbf{U}\mathbf{N}\right)\left(\left(\mathbf{U}\widehat{\mathbf{N}}\right)^{\mathbf{T}} - (\mathbf{U}\mathbf{N})^{\mathbf{T}}\right) = \mathbf{U}\int_0^t \mathbf{e}^{\mathbf{M}\tau}\,\mathbf{\Gamma}\left(\mathbf{e}^{\mathbf{M}\tau}\right)^{\mathbf{T}}\mathrm{d}\tau\,\mathbf{U}^{\mathbf{T}}.\end{aligned}$$

If A can be lumped into A’ by $\mathbf{U}$,

$$\mathbf{U\sigma U^T} = \int_0^t \mathbf{e}^{\mathbf{M}'\tau}\,\mathbf{U}\,\mathbf{\Gamma}\,\mathbf{U}^{\mathbf{T}}\left(\mathbf{e}^{\mathbf{M}'\tau}\right)^{\mathbf{T}} \mathrm{d}\tau\,. \qquad (10)$$

Covariance of fluctuations of $\widehat{\mathbf{N}}'$ of A’:

$$\boldsymbol{\sigma}' = \int_0^t \mathbf{e}^{\mathbf{M}'\tau}\,\mathbf{\Gamma}'\left(\mathbf{e}^{\mathbf{M}'\tau}\right)^{\mathbf{T}} \mathrm{d}\tau\,. \qquad (11)$$

Covariance difference between (11) of A’ and (10) of A,

$$\boldsymbol{\sigma}_{\mathbf{diff}} \equiv \boldsymbol{\sigma}' - \mathbf{U\sigma U^T} = \int_0^t \mathbf{e}^{\mathbf{M}\tau}\,\mathbf{\Gamma}_{\mathbf{diff}}\left(\mathbf{e}^{\mathbf{M}\tau}\right)^{\mathbf{T}} \mathrm{d}\tau\,, \qquad (12)$$

with $\mathbf{\Gamma}_{\mathbf{diff}} \equiv \mathbf{\Gamma}' - \mathbf{U\Gamma U^T}$.

Variance difference

$\boldsymbol{V}_{\mathbf{diff}} \equiv$ diagonal part of $\boldsymbol{\sigma}_{\mathbf{diff}}$,

(12) ➔ Even when A and A’ have indist. means, their fluctuations, which depend on $\mathbf{\Gamma}_{\mathbf{diff}}$, could be different.

Theorem 3: (for varaince)

Variance ordering between two KE systems A and A'

driving

$$\Gamma_{\mathrm{diff}} \geq \mathbf{0} \Rightarrow \mathbf{V}_{\mathrm{diff}} \geq \mathbf{0}$$
$$\Gamma_{\mathrm{diff}} = \mathbf{0} \Rightarrow \mathbf{V}_{\mathrm{diff}} = \mathbf{0} \qquad (13)$$
$$\Gamma_{\mathrm{diff}} \leq \mathbf{0} \Rightarrow \mathbf{V}_{\mathrm{diff}} \leq \mathbf{0}$$

response

where $\geq \mathbf{0}$ ($\leq \mathbf{0}$) denotes positive (negative) semi-definite.

stronger than (13)

The derivative of covariance differnce (12):

$$\boldsymbol{\sigma}_{\mathrm{diff}} = \int_0^t \mathbf{e}^{\mathbf{M}\tau}\, \Gamma_{\mathrm{diff}} \left(\mathbf{e}^{\mathbf{M}\tau}\right)^{\mathbf{T}} d\tau$$

is

$$\frac{d\boldsymbol{\sigma}_{\mathrm{diff}}}{dt} = \mathbf{e}^{\mathbf{M}'t}\Gamma_{\mathrm{diff}}\left[\mathbf{e}^{\mathbf{M}'t}\right]^{\mathbf{T}} \quad (\mathbf{e}^{\mathbf{M}'t} \text{ reversible})$$

$\Rightarrow$

$\boldsymbol{\sigma}_{\mathrm{diff}} = \mathbf{0}$
iff
$\Gamma_{\mathrm{diff}} = \mathbf{0}$

Theorem 4: (for covariance)

If A can be lumped into another KE system A', with the corresponding $\boldsymbol{\sigma}'$ and $\boldsymbol{\Gamma}'$, then

$$\boldsymbol{\Gamma}' = \mathbf{U}\boldsymbol{\Gamma}\mathbf{U}^{\mathrm{T}} \quad \Leftrightarrow \quad \boldsymbol{\sigma}' = \mathbf{U}\boldsymbol{\sigma}\mathbf{U}^{\mathrm{T}} \tag{14}$$

Implication:

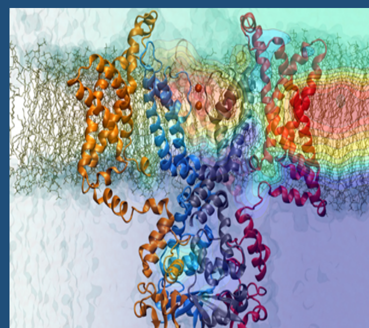
- (14) is a generalization of Keizer's contraction* from the invertible transformation to the lumping transformation.

* J. Keizer (1987)
"Statistical Thermodynamics of Nonequilibrium Processes"

Application I:
Intrinsic noises in ion channels

FJ Sigworth (J. Physiol, 1980)

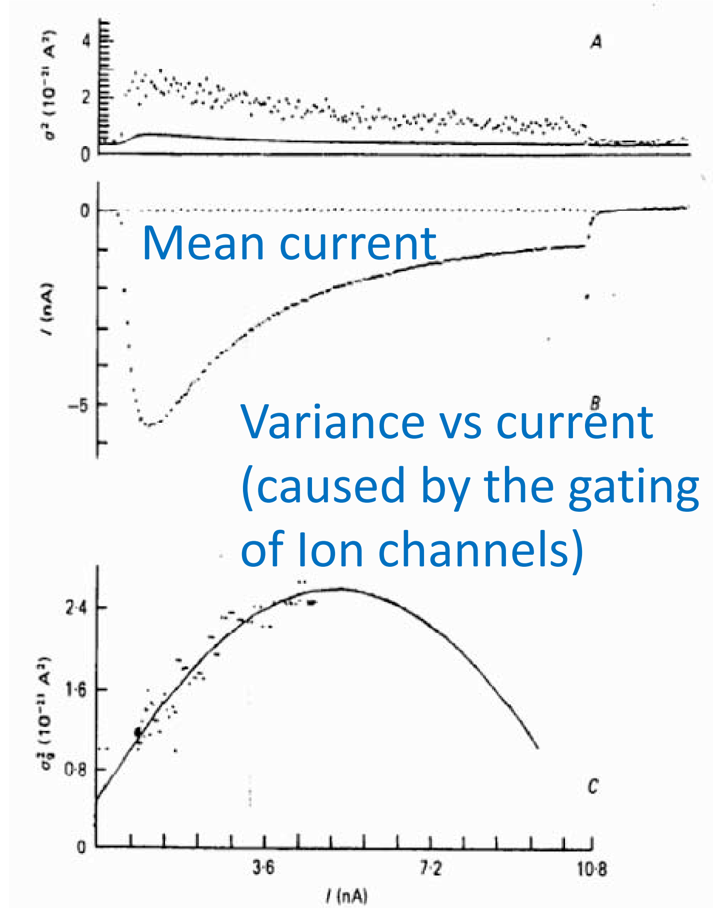
The variance of Na current fluctuations at the node of Ranvier



Voltage-clamped single myelinated nerve fibers from *Rana pipiens*

➔ N=20,400 Na channels

Variance from the stochastic gating of Na channels (dots) & thermal noise (solid line)



SDE approach to ion channel

For that problem, the covariance of stochastic force in the SDE is

$$\Gamma_{ij} = \sum_{k=1}^{n} (k_{ki} N_k + k_{ik} N_i)\, \delta_{ij} - k_{ji} N_j - k_{ij} N_i \qquad (15)$$

J. Keizer (1987): Canonical theory for transition rates
Van Kampen (2007): linear noise approximation

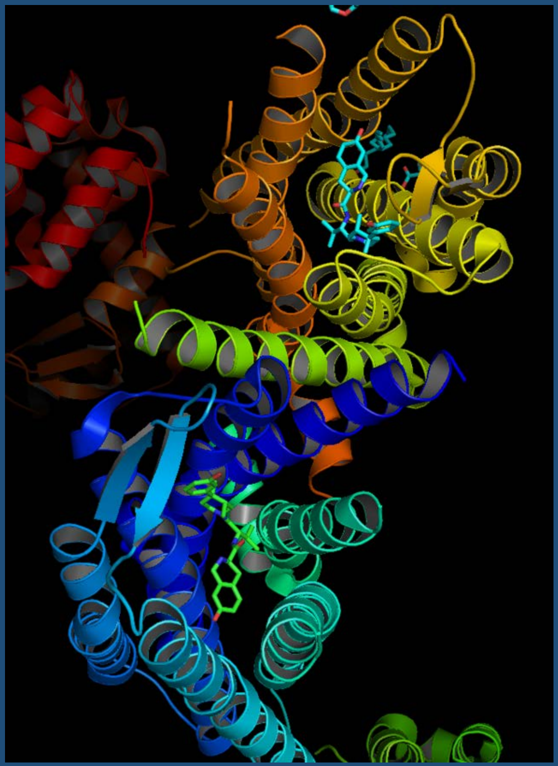
If two KE networks A and A' are used to describe the intrinsic noises of an ion channel, we can prove that their $\mathbf{\Gamma}$ and $\mathbf{\Gamma}'$ are indist. (also for the chemical Langevin eq. of DT Gillespie (2000)).

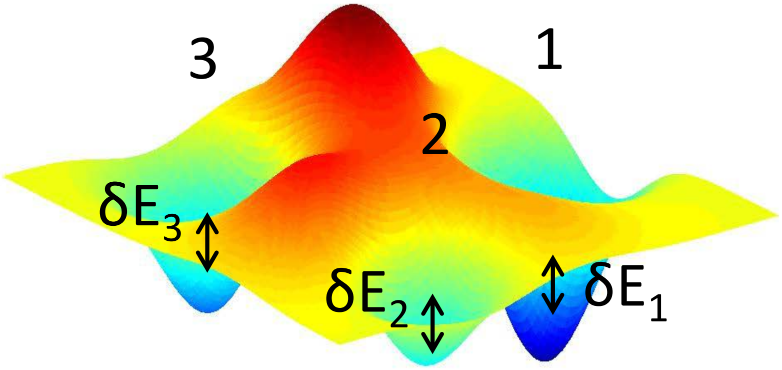
According to Theorem 4, $\boldsymbol{\sigma}$ and $\boldsymbol{\sigma}'$ are also indist..

Consistent "indist. $\boldsymbol{\sigma}$ and $\boldsymbol{\sigma}'$" from SDE and CME for intrinsic noises.

Application II:
Extrinsic noises in signal receptors

Free energy surface variations of receptor

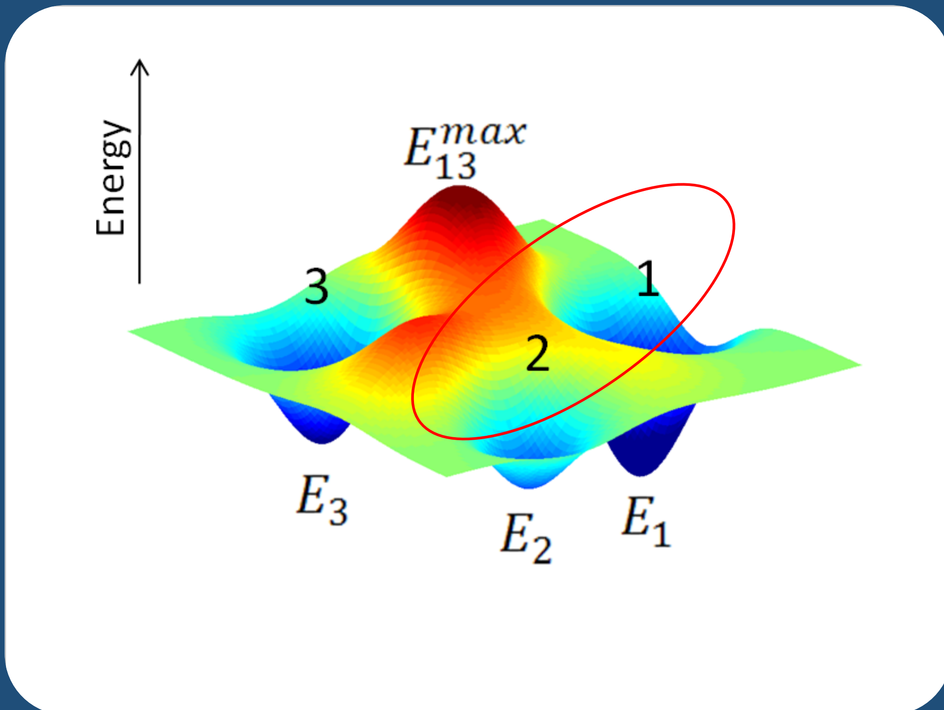


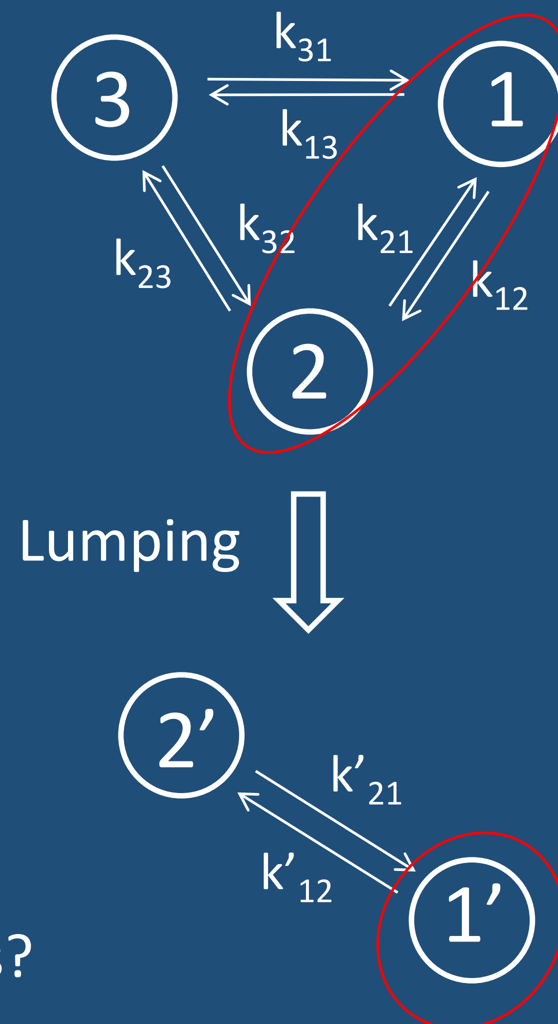


external noises

State fluctuations?

Lumping minima of free energy surface





If there exists two KE models,

do $\mathbf{N}$ and $\mathbf{N}'$ have indist. fluctuations?

Ordering relation of state variances

It's a special case of Theorem 3 and 4 at equilibrium (t → ∞)

$$\tilde{\boldsymbol{\Gamma}}_{\mathbf{diff}} \equiv \mathbf{D}_{\mathbf{N}^{e\prime}}\tilde{\boldsymbol{\Gamma}}'\mathbf{D}_{\mathbf{N}^{e\prime}} - \mathbf{U}\mathbf{D}_{\mathbf{N}^{e}}\tilde{\boldsymbol{\Gamma}}\mathbf{D}_{\mathbf{N}^{e}}\mathbf{U}^{\mathbf{T}}$$

$$\tilde{\boldsymbol{\sigma}}_{\mathbf{diff}} \equiv \tilde{\boldsymbol{\sigma}}' - \mathbf{U}\tilde{\boldsymbol{\sigma}}\mathbf{U}^{\mathbf{T}} = \beta^2 \int_0^\infty \mathbf{e}^{\mathbf{M}'\tau}\mathbf{M}'\tilde{\boldsymbol{\Gamma}}_{\mathbf{diff}}\mathbf{M}'^{\mathbf{T}}\left[\mathbf{e}^{\mathbf{M}'\tau}\right]^{\mathbf{T}} d\tau$$

$\tilde{\mathbf{V}}_{\mathbf{diff}} \equiv$ diagonal part of $\boldsymbol{\sigma}_{\mathbf{diff}}$

The distinguishiability of variances depends on $\tilde{\boldsymbol{\Gamma}}_{\mathbf{diff}}$:

$$\tilde{\boldsymbol{\Gamma}}_{\mathbf{diff}} \geq \mathbf{0} \Rightarrow \tilde{\mathbf{V}}_{\mathbf{diff}} \geq \mathbf{0}$$
$$\tilde{\boldsymbol{\Gamma}}_{\mathbf{diff}} = \mathbf{0} \Rightarrow \tilde{\mathbf{V}}_{\mathbf{diff}} = \mathbf{0}$$
$$\tilde{\boldsymbol{\Gamma}}_{\mathbf{diff}} \leq \mathbf{0} \Rightarrow \tilde{\mathbf{V}}_{\mathbf{diff}} \leq \mathbf{0}$$

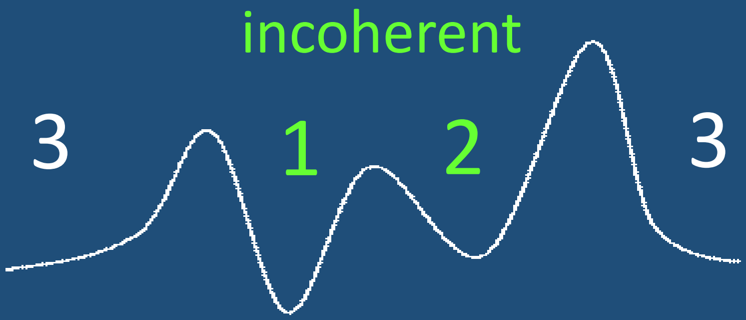
Q: Which $\tilde{\boldsymbol{\Gamma}}$ and $\tilde{\boldsymbol{\Gamma}}'$ would appear in real biological systems?

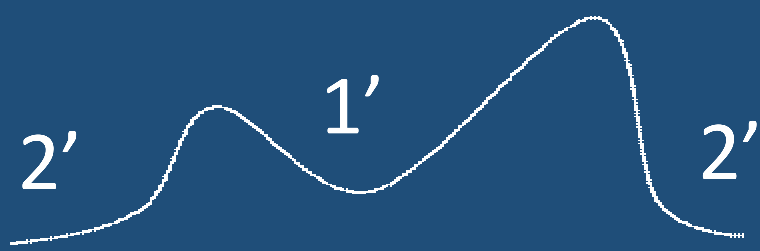
Criterion I (incoherent driving)

$\tilde{\boldsymbol{\Gamma}} = \mathbf{I}_{\mathbf{n}\times\mathbf{n}}$ and $\tilde{\boldsymbol{\Gamma}}' = \mathbf{I}_{\mathbf{n}'\times\mathbf{n}'}$ then $\tilde{\boldsymbol{\Gamma}}_{\mathbf{diff}} \geq \mathbf{0}$ and $\mathbf{V}_{\mathbf{diff}} \geq \mathbf{0}$

System A $\tilde{\Gamma}_3 \equiv \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$

System A’ $\tilde{\Gamma}_1 \equiv \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$





Smaller networks ⇒ larger state fluctuations.

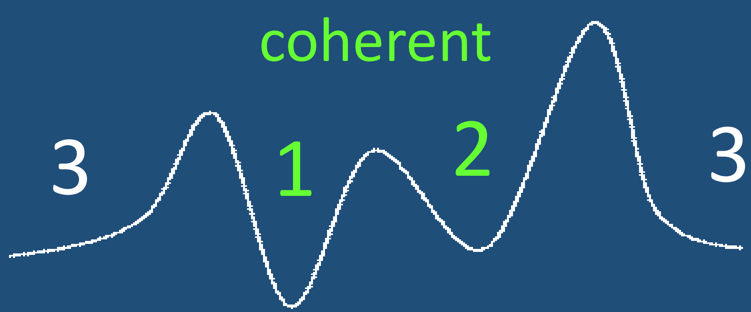
Criterion II (coherent driving)

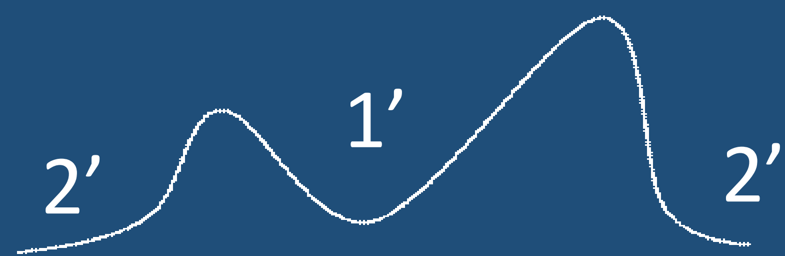
e.g., ion channels with symmetric conformations

$$\boldsymbol{\delta \mathbf{E} = \mathbf{U}^{T} \delta \mathbf{E}'} \quad \text{then} \quad \tilde{\boldsymbol{\Gamma}}_{\mathbf{diff}} = \mathbf{0} \quad \text{and} \quad \mathbf{V}_{\mathbf{diff}} = \mathbf{0}$$

System A $\quad \tilde{\Gamma}_2 \equiv \begin{bmatrix} 1 & 1 & 0 \\ 1 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$

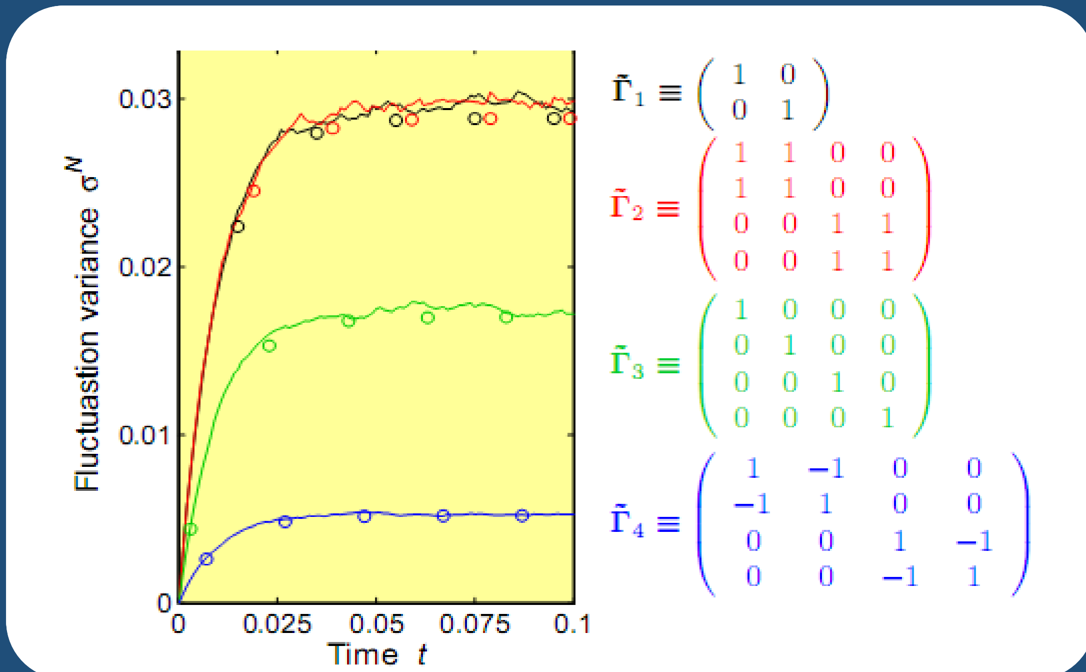
System A’ $\quad \tilde{\Gamma}_1 \equiv \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$

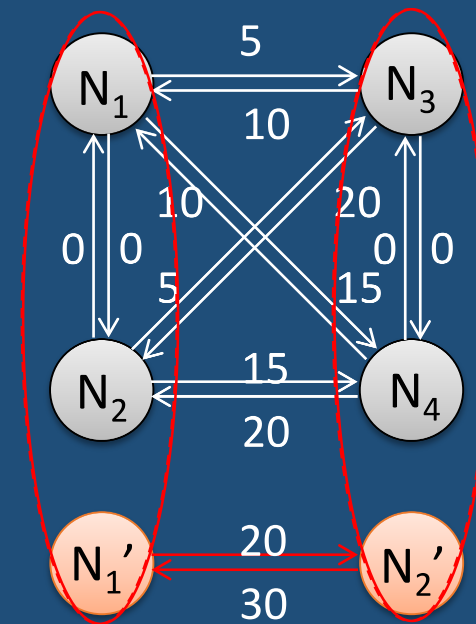




A and A’ are indistinguishable in variance.

Numerical confirmation (to Theorem 4 & Corollary I, II)





$$\frac{d\boldsymbol{\delta}\mathbf{N}}{dt} = \mathbf{M}(\boldsymbol{\delta}\mathbf{N} + \beta \mathbf{D}_{\mathbf{N}}^{e} \boldsymbol{\delta}\mathbf{E})$$ (solid curves, simulation of 10^2 molecules)

$$\tilde{\boldsymbol{\sigma}}_{\mathbf{diff}} = \beta^2 \int_0^t \mathbf{e}^{\mathbf{H}'\tau} \tilde{\boldsymbol{\Gamma}}_{\mathbf{diff}} \left[\mathbf{e}^{\mathbf{H}'\tau}\right]^{\mathrm{T}} d\tau$$ (circles, analytical solution)

Both follow the ordering predicted by the theorems & criteria.

Summary:

This work

- generalizes lumping analysis from deterministic dynamics to stochastic processes.
- introduces lumping technique from systems biology to structural biology.
- opens a possibility of identifying correct network models by observing extrinsic noises.
- goes beyond traditional contractions under “fast relaxation” assumption.
- provides a theoretical basis for the legitimate use of low-dim models for fluctuations.

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Stochastic lumping theory

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Stochastic lumping analysis for linear kinetics and its application to the fluctuation relations between hierarchical kinetic networks

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Conventional studies of biomolecular behaviors rely largely on the construction of kinetic schemes. Since the selection of these networks is not unique, a concern is raised whether and under which conditions hierarchical schemes can reveal the same experimentally measured fluctuating behaviors and unique fluctuation related physical properties. To clarify these questions, we introduce stochasticity into the traditional lumping analysis, generalize it from rate equations to chemical master equations and stochastic differential equations, and extract the fluctuation relations between kinetically and thermodynamically equivalent networks under intrinsic and extrinsic noises. The results provide a theoretical basis for the legitimate use of low-dimensional models in the studies of macromolecular fluctuations and, more generally, for exploring stochastic features in different levels of contracted networks in chemical and biological kinetic systems. © *2015 AIP Publishing LLC.* [http://dx.doi.org/10.1063/1.4919952]

I. INTRODUCTION

Kinetic schemes are widely used for studying the thermodynamic, dynamic, and stochastic properties of macromolecules.[1] These schemes are usually selected to be as simple as possible, such as the 2-state schemes for the bound and unbound states of enzymes or receptors and the open and closed states of ion channels. Nevertheless, they can also be rather sophisticated (e.g., 8-state inositol trisphosphate receptors,[2] the 10-state hemoglobin,[3] and the 56-state chloride channels[3]). The selection of kinetic schemes is mainly determined by the desired accuracy and the measurable quantities.[4,5] Since a low-dimensional scheme can usually be contracted from higher-dimensional ones, there exists a cascade of hierarchical Markovian network models suitable for describing the time evolution of the populations of a macromolecule's functional states.[6] These networks are anticipated to have indistinguishable kinetics, exhibiting identical mean trajectories after being projected to the low-dimensional network space. However, models with indistinguishable means do not necessarily have indistinguishable fluctuations. A question that arises is that which schemes will give more relevant fluctuations to a real system and under which conditions unique fluctuation features can be obtained from different levels of contracted schemes. These issues are essential for the reliability of various biological properties derived in terms of the fluctuations of a selected kinetic scheme, such as chemoreception,[7,8] membrane conductance,[9] and ion channel density.[10]

The inter-network fluctuation relations arise from a comparison between different coarse-grained dynamical systems. It resembles the comparison between different rate equations in the lumping analysis, widely used in systems biology and general chemical engineering.[11–15] A central issue in that analysis is finding the lumping conditions for eliminating unimportant events or time scales in a large network, of typically over 10^1 species in systems biology, to reduce its complexity.[16] Interestingly, this contraction is mathematically analogous to merging experimentally indistinguishable states to obtain simple transition networks for the conformational change of a macromolecule. For instance, the Hodgkin-Huxley potassium ion channel has 16 configurations depending on whether its individual four gates are open or closed.[4] However, this channel is often regarded as a 2-state system, described by whether or not ions can pass through it in a patch-clamp recording. The contraction from a 16-state to a 2-state model is because the gating current recording is incapable of resolving the detailed structure of the channel configuration. In terms of lumping analysis, this contraction is an approximate lumping.[17]

Despite that correspondence, the original lumping analysis focuses on the relations between mean dynamics and is not concerned with fluctuations. To extract this stochastic component, we generalize the lumping theory from original rate equations (RE) to chemical master equations (CME) and stochastic differential equations (SDE) and study kinetically equivalent (KE) and thermodynamically equivalent (TE) hierarchical kinetic schemes, under intrinsic and extrinsic noises. The results go beyond the conventional assumption of "fast relaxations" and contribute to our understanding of why a kinetic system can be contracted. In the case of extrinsic noise, different kinetic schemes can give different fluctuations even when their average trajectories are the same. This opens a possibility of identifying a correct kinetic model by observing fluctuations. Notably, lumping conditions here are used for generating complex KE or TE networks from simple networks, in opposite to their original goal of reducing complex networks to simple networks. Furthermore, for the conformational change of macromolecules discussed below, it is sufficient to focus on linear REs and linear lumping transformations.

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