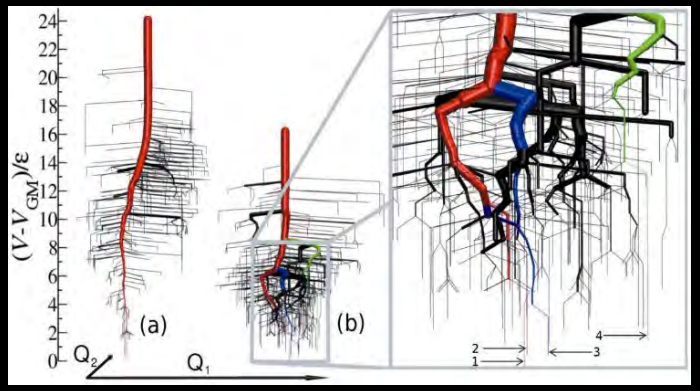
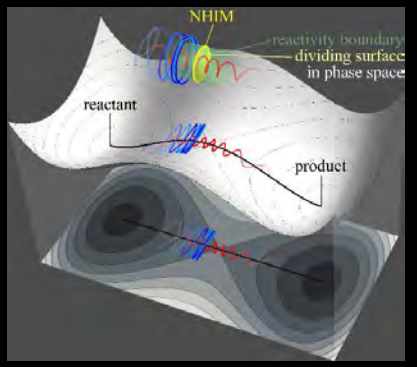
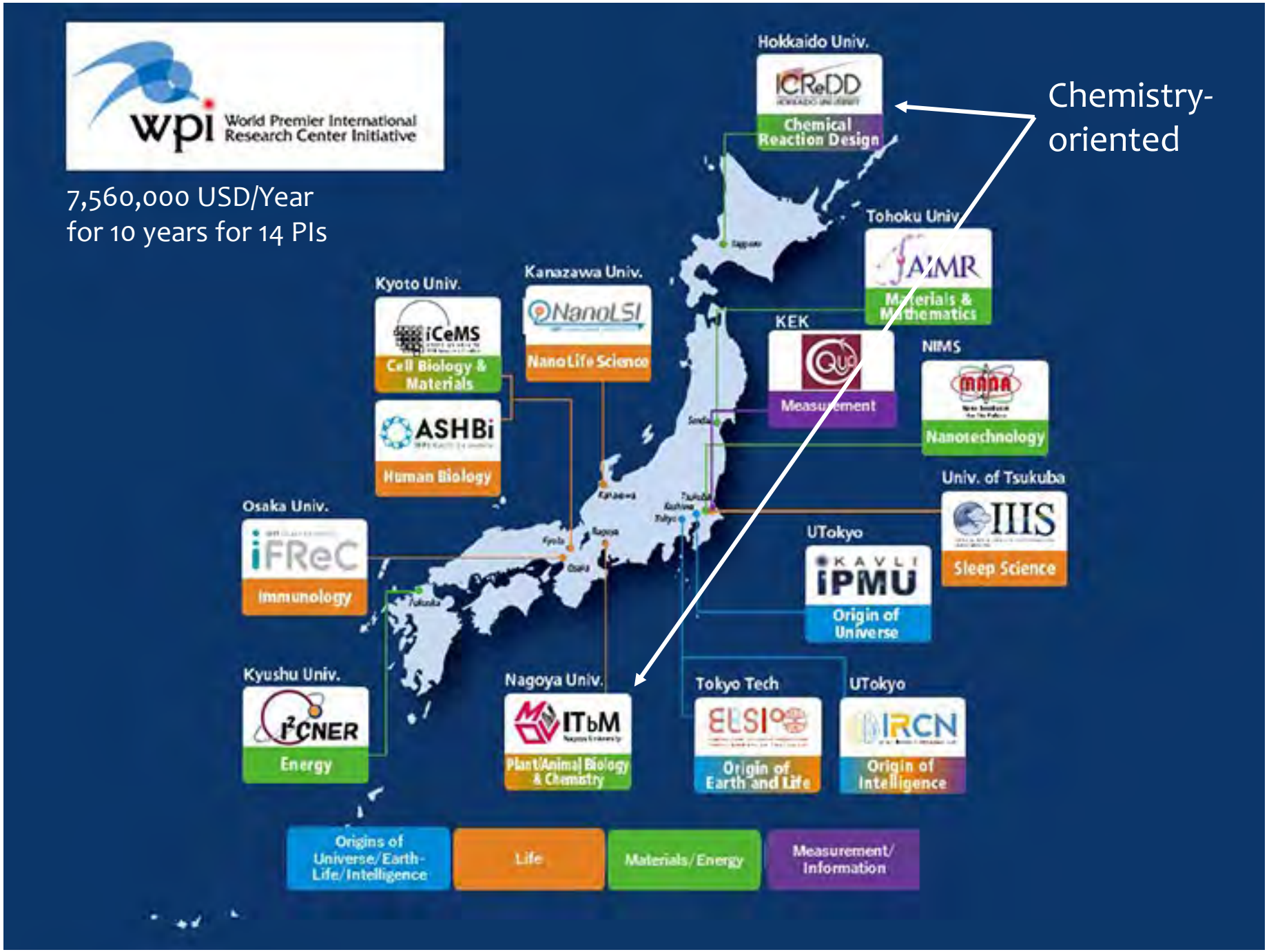


A Structure of Kinetic Hierarchy in Reaction Network



Tamiki Komatsuzaki
Institute for Chemical Reaction Design and Discovery (WPI-ICReDD)
Research Center of Mathematics for Social Creativity
Research Institute for Electronic Science (RIES)
Hokkaido University, Japan
Adjunct, The Institute of Scientific and Industrial Research, Osaka University
Adjunct, Institute for Open and Transdisciplinary Research Initiatives, Osaka University


wpi World Premier International Research Center Initiative
7,560,000 USD/Year
for 10 years for 14 PIs
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ICReDD
Chemical Reaction Design
Chemistry-oriented
Tohoku Univ.
AIMR
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Kyoto Univ.
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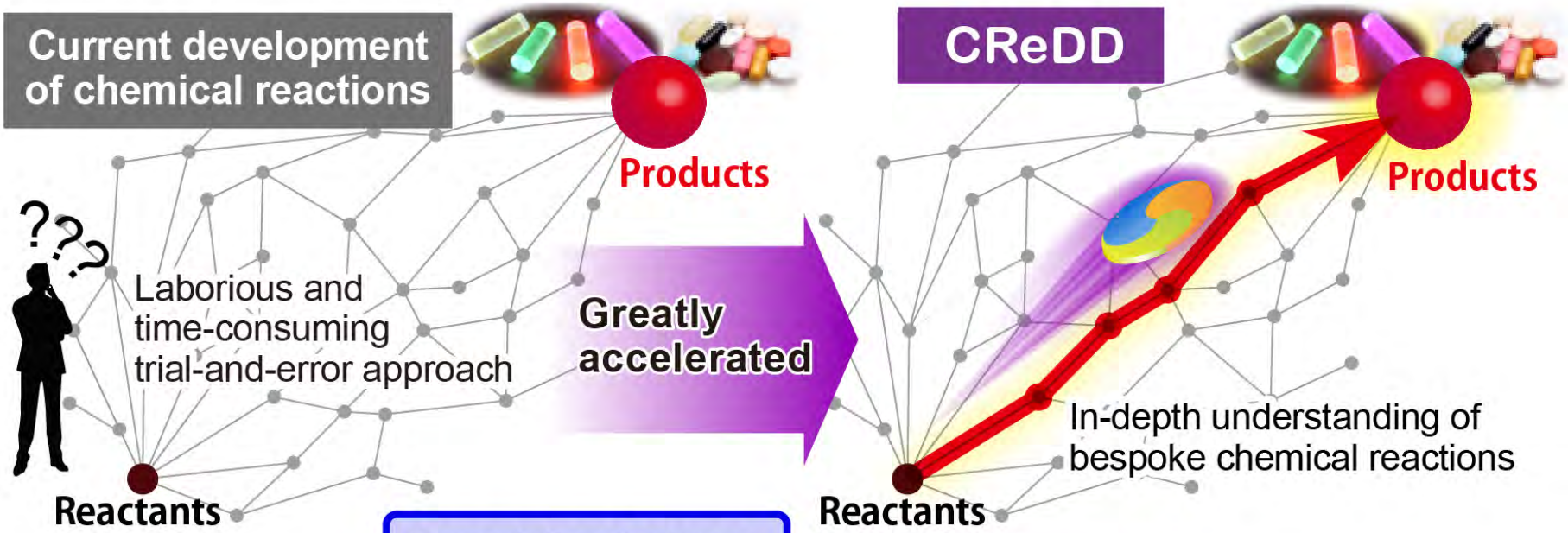
Cell Biology & Materials
ASHBi
Human Biology
Kanazawa Univ.
NanoLSI
Nano Life Science
KEK
Measurement
NIMS
Nanotechnology
Univ. of Tsukuba
IIIS
Sleep Science
Osaka Univ.
iFReC
Immunology
UTokyo
KAVLI IPMU
Origin of Universe
Kyushu Univ.
I²CNER
Energy
Nagoya Univ.
ITbM
Plant/Animal Biology & Chemistry
Tokyo Tech
ELSI
Origin of Earth and Life
UTokyo
IRCN
Origin of Intelligence
Origins of Universe/Earth-Life/Intelligence
Life
Materials/Energy
Measurement/Information

Institute for Chemical Reaction Design and Discovery

Hokkaido University from 2018 Oct 1



Hokkaido University

Collaborative research among top researchers from each field has begun

Computational science
Predict the chemical reaction path through the automated reaction path search method

Infromation science
Optimize experimental conditions from the extensive predicted reaction paths

Experimental science
Realize the reactions derived from computational and information sciences

Institute for Chemical Reaction Design and Discovery

https://www.icredd.hokudai.ac.jp/

Information Science

AI, Machine Learning, Network theory,
Information Theory, Applied Mathematics














Computational Science

Quantum Chemistry
MD simulation

Experimental Science

Synthetic Chemistry,
Biology, Medicine

ICReDD Organization of 2022

Calculation
Information
Experiment
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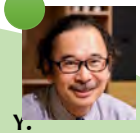

Y. HASEGAWA


TAKETSUGU


Collaborator
J. HASEGAWA


RUBINSTEIN


VARNEK

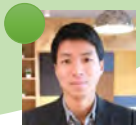

KOMATSUZAKI


TAKIGAWA


Co-PI
TSUJI

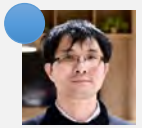

INOKUMA

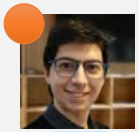

TANAKA


Junior-PI
HUANG


Junior-PI
JIN


Junior-PI
GAO


Co-PI
YAMAMOTO


Co-PI
STAUB

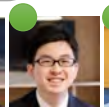

YOSHIOKA


IWATA


Junior-PI
SIDOROV


MITA


HAYASHI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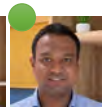
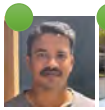
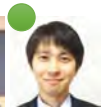

MANGAONKAR


MANDALI


KATSUYAMA

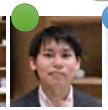

HIGASHIGA


SHIMIZU


MASUDA


JAISWAL


NAGADA


AKIYAMA

HARABUCHI

SUZUKI

KOBAYASHI

PIRILLO

MIZUNO

TABATA

HU

GANTZER

KUBOTA

ISSHIKI

GAO

WANG

RAUT

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TSUDA

TANIKAWA

IMAJO

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POLY

SARTYOUNGKUL

IWASA

OZEN

LYALIN

SAHA

LI

NAGAHATA

TSITSVERO

HANDE

KITAGAWA

SHOJI

WANG

IDE

YONEDA

KINOSHITA

KILINGARU

NAKAJIMA

FAN

ZHENG

HANE

MIKHERDOV

ICHINO

ONO

AKAMA

GWEE

CLEMENT

MATSUMURA

NATH

1. Background and Motivation
2. Transition Disconnectivity Graph
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4. Lumping Theory to Preserve Hierarchical Timescales
5. Outlooks

Lagrangian Coherent Structure

H. Teramoto et al ., ***Chaos* 23**, 043107 (2013)
P. Nag et al. ***J. Chem. Phys.* 141**, 104907(2014)

Higher rank saddles

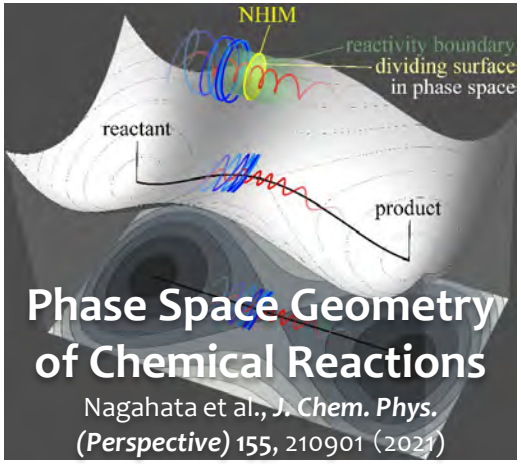
Y. Nagahata et al. ***Phys. Rev. E* 87**,62817 (2013); ***ibid.* 88**, 42923 (2013)

Bifurcation of NHIM

C.-B.Li, T. Komatsuzaki, ***J. Chem. Phys.* 130**,124116, (2009)

multidimensional Energy Landscape Based on single molecule time series

A. Baba et al., ***PNAS* 104**,19297 (2007); ***PCCP*, 13**, 1395 (2011); K. Kamagata et al., ***JACS* 134**, 11525 (2012); J.N. Taylor et al., ***Sci. Rep*. 5**, 9174 (2015) J. Alfermann et al., ***Nature Chem. Bio.* 13**, 1009 (2017)



Origin of Stochasticity in Transitions

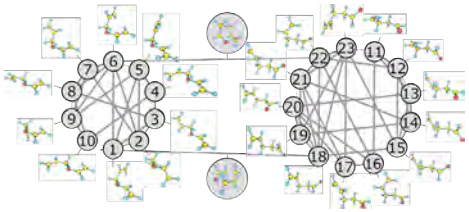
Komatsuzaki et al. ***PNAS* 98** 7666 (2002), C.-B.Li et al., ***PRL* 97**, 028302 (2006); H. Teramoto et al., ***PRL* 106**, 054101 (2011); **115**, 093003 (2015); ***Nonlinearity* 28**, 2677 (2015) ; ***PRL***, 054101 (2015)

Phase Space in Wells

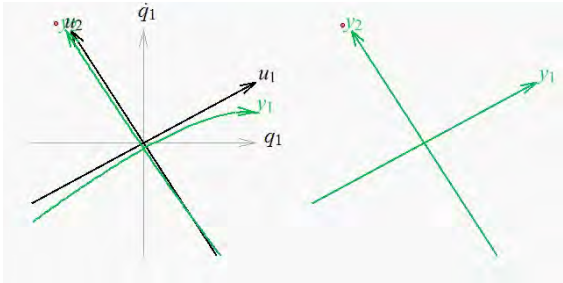
A. Shojiguchi et al. ***Phys. Rev. E* 76**, 056205 (2007); ***ibid.*75**, 035204(R) (2007); H. Teramoto et al. ***J. Chem. Phys.* 129**, 094302 (2008); ***Phys. Rev. E* 78**, 017202 (2008); ***Theor. Chem. Acc.* 133**, 1571, (2014)(invited); Y. Mizuno et al., ***Physica D* 428**, (2021) (*invited*)

TS in Complex Network

Y. Nagahata, S. Maeda, H. Teramoto, T. Horiyama, T. Taketsugu, T. Komatsuzaki et al. ***JPCB* 120**(8), 1961-1971 (2015).

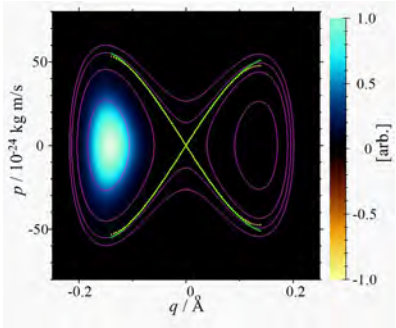


No-return TS in Dissipative systems



S. Kawai, T. Komatsuzaki, ***Phys. Chem. Chem. Phys. (Perspective)* 13**, 21217 (2011); ***Phys. Chem. Chem. Phys.* 12**, 15382 (2010); ***ibid.* 12, 7626 (2010); *ibid.* 12**, 7636 (2010); ***J. Chem. Phys.* 134**, 114523, (2011); ***ibid.* 131**, 224505 (2009) ***ibid.* 131**, 224506 (2009); Nagahata et al., ***J. Chem. Phys. (Perspective)* 155**, 210901 (2021) *(invited)* (**selected as cover art**)

Optimal control theory in chemical reactions

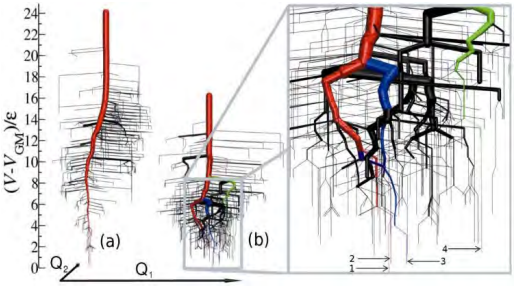


S. Kawai, T. Komatsuzaki, ***Bull. Chem. Soc. Japan* 85**, 854 (2012); ***J. Chem. Phys.* 134**, 024317 (2011)

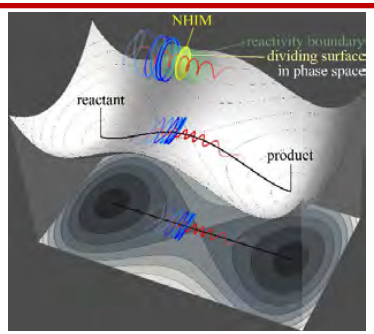
To understand chemical reactions including structural transitions

1：Describe the "space/scaffold" where chemical reactions take place （static）

- ✓ Electronic structure theories （e.g., HOMO-LUMO theory, QM/MM）
- ✓ Energy landscape or reaction (conformation) network representation



***PNAS* 103,** 18551 (2006)



2：Understand why and how fast reaction takes place （kinetic, dynamic）

- ✓ Transition state theories in Gas/Condensed Phase, or more in general in Phase Space

***PNAS* 98** 7666 (2002) ; ***PRL* 97**, 028302 (2006); ***PRL* 105**,048304, (2010); ***PRL* 106**, 054101 (2011); ***PRL* 115**, 093003 (2015); ***Nonlinearity* 28**, 2677 (2015) ; ***JCP (Perspective)* 155**, 210901 （2021）

3： Constructing energy landscape/network from Experimental data （data science）

- ✓ Single Molecule Time series Analysis for Molecular Science

***PNAS* 104**,19297 (2007); ***PNAS* 105**, 536 (2008); ***PRL* 111**, 58301(2013); ***Sci. Rep.* 5**, 9174 (2015); ***Nature Commun.* 6**,10223 (2015); ***JCP* 148**, 123325 (2018) (special issue on single molecule biophysics)

4：Accelerate designing experiments via adaptive feedback between measurement/computation and data analysis （reinforcement learning） **Mach. Learn. 109**, 327-372 (2020); **AISTATS**, Volume 206, 29pages (2023). **PNAS** under revision

Inferring cell-cell interactions from images

S. Sattari et al., ***Sci. Adv.*** **8**(6), abj1720 (2022) (***Chosen as featured on-line article***)

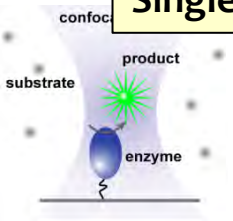
U. Basak et al, ***PRE*** **102**, 012404 (2020); ***JCP*** **154**, 034901 (2021)

Fluorescence imaging

Facts and artifacts in interpreting dynamic disorder of enzymatic turnover reactions

T. Terentyeva et al., ***ACS Nano*** **6** 346-354(2012)

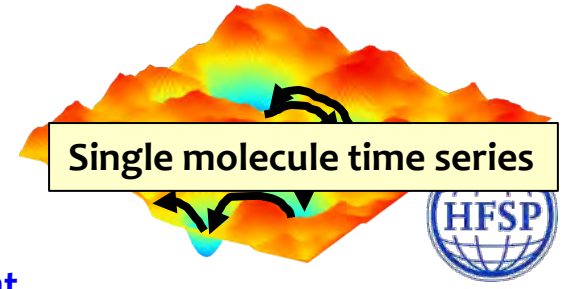
Single molecule time series



Single molecule time series

C.-B. Li et al., ***PRL*** **111**, 58301(2013)

multidimensional Energy Landscape



Single molecule time series

A. Baba et al., ***PNAS*** **104**,19297 (2007); ***PCCP***, **13**, 1395 (2011); K. Kamagata et al., ***JACS*** **134**, 11525 (2012); J.N. Taylor et al., ***Sci. Rep.*** **5**, 9174 (2015)
J. Alfermann et al., ***Nature Chem. Bio.*** **13**, 1009 (2017)

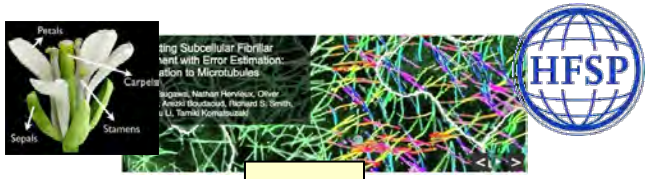
Cell state defined by single cell Ramar

Raman imaging

K. M. Helal, et al., ***FEBS Lett.*** **593**, 2535-2544 (2019)(***Chosen as cover art & highlight article***)
J. Nicholas Taylor, et al. *J. Phys. Chem. B* **123**, 4358-4372 (2019)

Let the Systems Speak for Themselves

Coordination of microtubules beyond single cells in sepals



AFM

S. Tsugawa et al., ***J.*** **110**, 1836 (2016) (***Chosen as highlighted article***)
L. Hong et al., ***Dev. Cell*** **38**, 15 (2016) (***Chosen as cover art & Highlight***)

New change point analysis & m... AT...

Single molecule time series of F1 motor

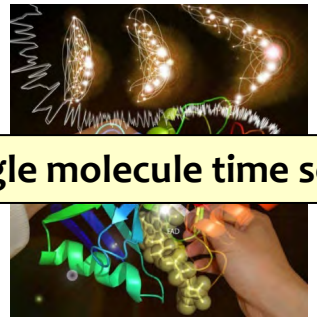
C.-B. Li et al., ***Nature Commun.*** **6**,10223 (2015)

Logr... conc...

Single molecule time series of F1 motor

Yagi...
(***Chosen as highlighted article***)

Nonequilibrium steady state network



Single molecule time series

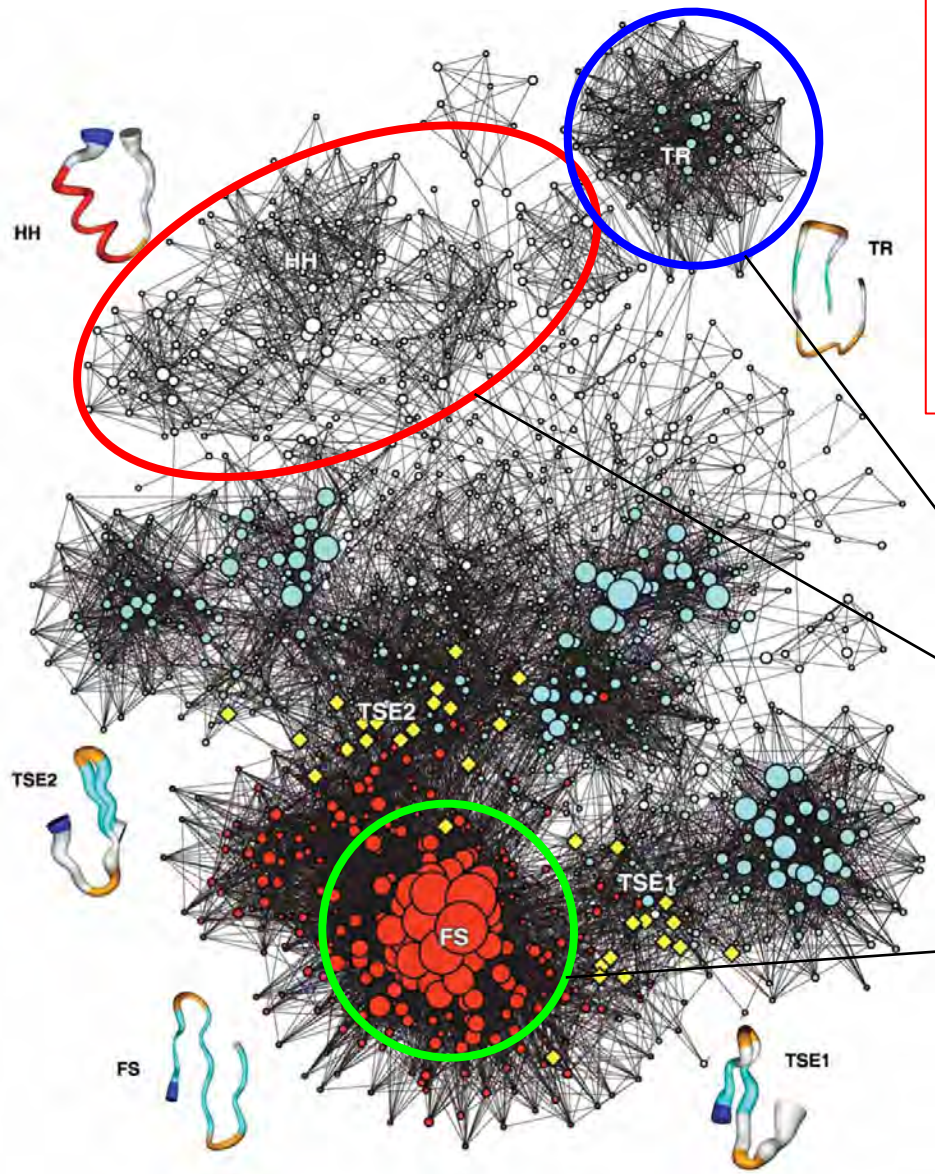
C.-B. Li et al., ***PNAS*****,105**, 536 (2008); C.-B. Li et al., ***JPC B*****, 113**, 14732 (2009) ; T. Sultana et al. ***JCP*** **139**, 245101(2013)

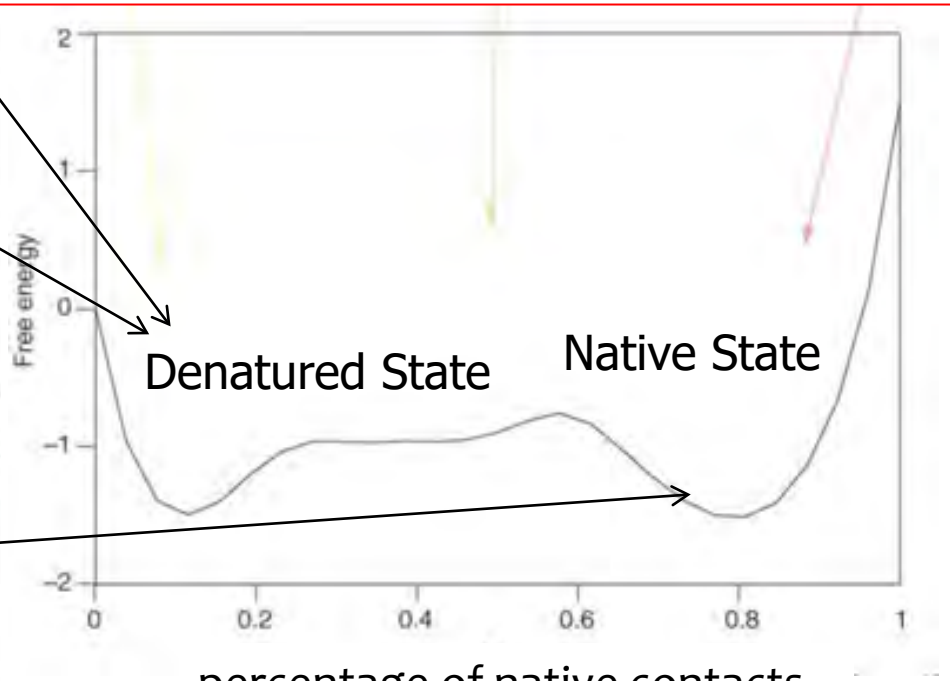
Energy Landscape: confo

F. Rao and A. Caflisch, *J. Mol. Biol.* (2004) **342**,299
Krivov, Muff, Caflisch, Karplus , *JPCB* **112**, 8701 (2008

The complexity of conformation space network is masked by a projection

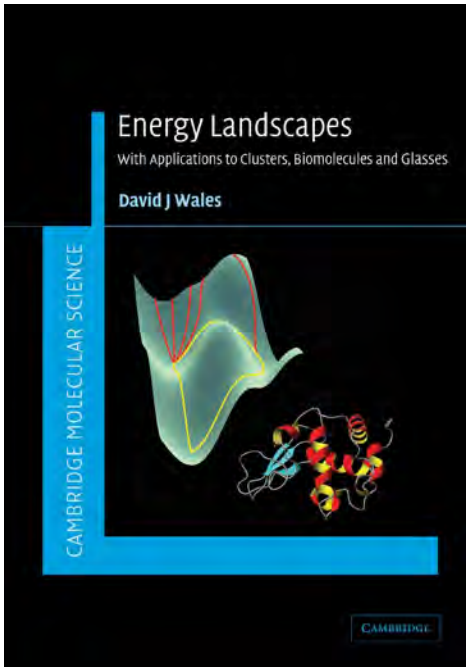
How can one elucidate multiple paths from an energy basin to one another?





Disconnectivity Graph: Visualization of Complexity of Energy Landscape

Disconnectivity Graph



D. J. Wales, *Energy Landscapes*
(Cambridge University Press, Cambridge, 2004).

Disconnectivity Graph

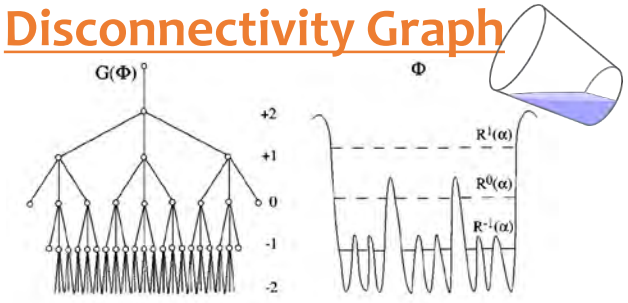


FIG. 2. A schematic one-dimensional partial cross section through a rough $3N$-dimensional potential energy hypersurface Φ (triadic Koch curve). The horizontal lines on the PES Φ correspond to the energies used by the map $M^{\alpha}(\mathbf{r};E)$ to define the $R(\alpha)$ basins. These energies determine the corresponding levels on the disconnectivity graph $G^{E}(\Phi)$.

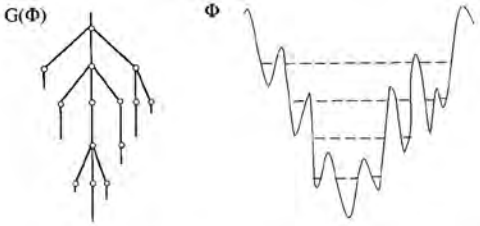


FIG. 4. A schematic representation of a funnel potential energy surface Φ and its corresponding $G^{E}(\Phi)$ graph.

O. M. Becker and M. Karplus,
J. Chem. Phys. **106**, 1495 (1997)

connectivity tree

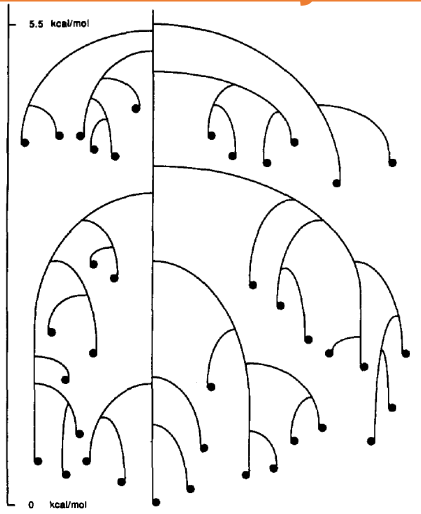


FIG. 9. A schematic representation of the connectivity tree (Cayley tree) of the minima and the transition states in the tetrapeptide IAN. Only the vertical direction which denotes the energy in kcal/mol is meaningful. The black circles (●) are the minima and the tree junctions are the barriers. We emphasize that only the lowest energy path between the minima or clusters is shown and no conclusions on the topology of the connectivities should be drawn from the figure.

R. Czerminski and R. Elber,
J. Chem. Phys. **92**, 5580 (1990)

1. Background and Motivation
2. Transition Disconnectivity Graph
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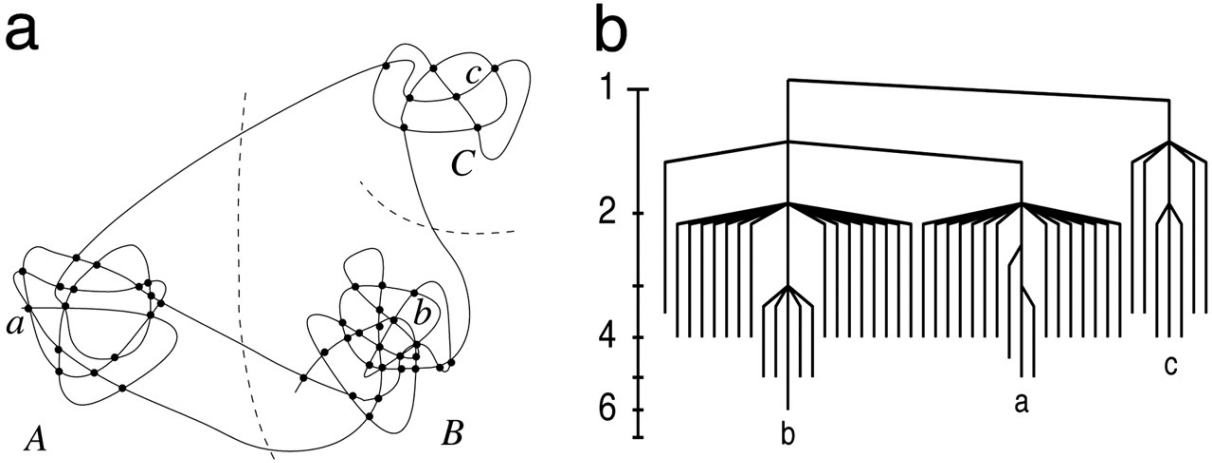
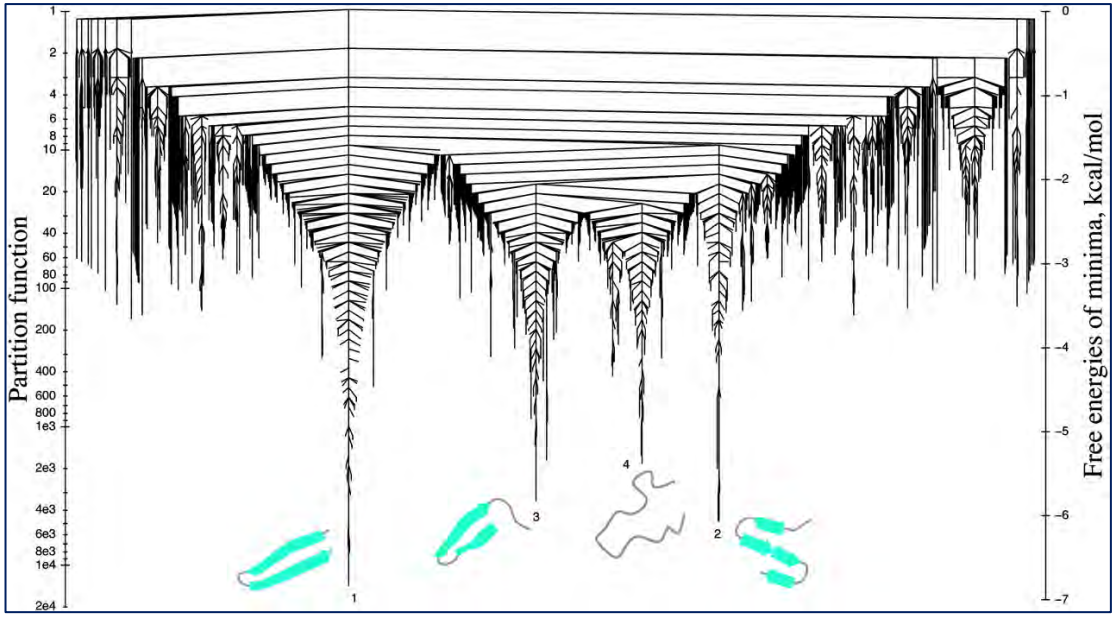
4. Lumping Theory to Preserve Hierarchical Timescales
5. Outlooks

Transition disconnectivity graph (TRDG)

S.V. Krivov & M. Karplus, Proc. Natl. Acad. Sci. USA **101** 14766 (2004)
Krivov, Muff, Caflisch, Karplus , JPCB **112**, 8701 (2008)

Transforming a conformation space network into a new type of disconnectivity graph in terms of a network theory using rates among conformations

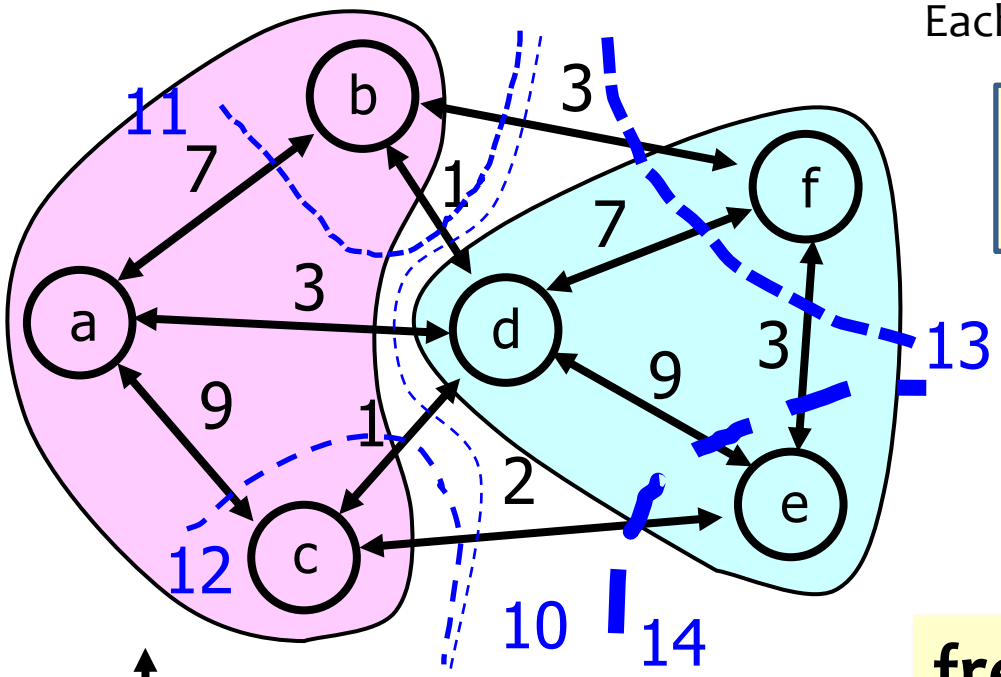


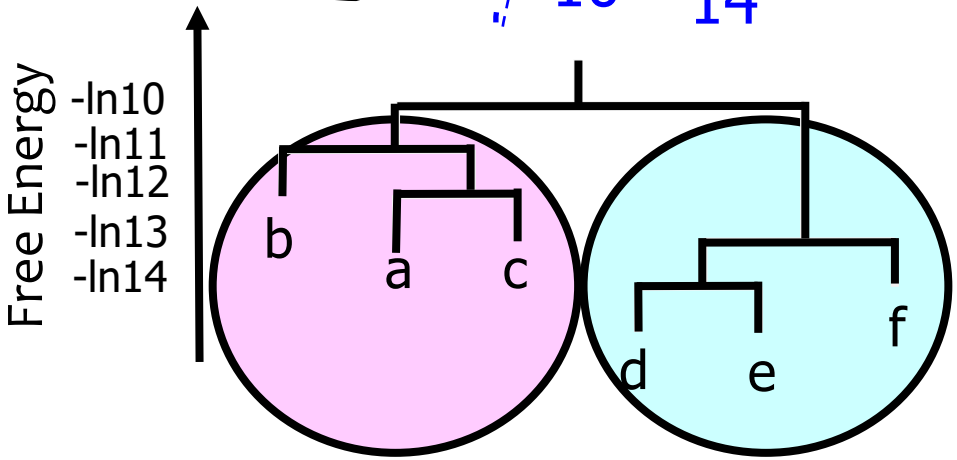


TRDG of β-hairpin at 360 K.

Transformation from Network to Energy Landscape

S. V. Krivov and M. Karplus, *J. Chem. Phys.*, **117**, 10894 (2002); *Proc. Natl. Acad. Sci. USA* **101** 14766 (2004)





Each sub region has its own bottleneck.

Energy Barrier $\propto -k_B T \ln\left(k_{i\to j} P_i\right)$

Hierarchical grouping

free energy disconnectivity graph can be constructed by taking into account all possible pathways in the network

Free energy of the state i $F_i = -k_B T \ln\left(\frac{\sum_j N_{i\to j}}{N}\right) = -k_B T \ln\left(\frac{N_i}{N}\right) = -k_B T \ln P_i$

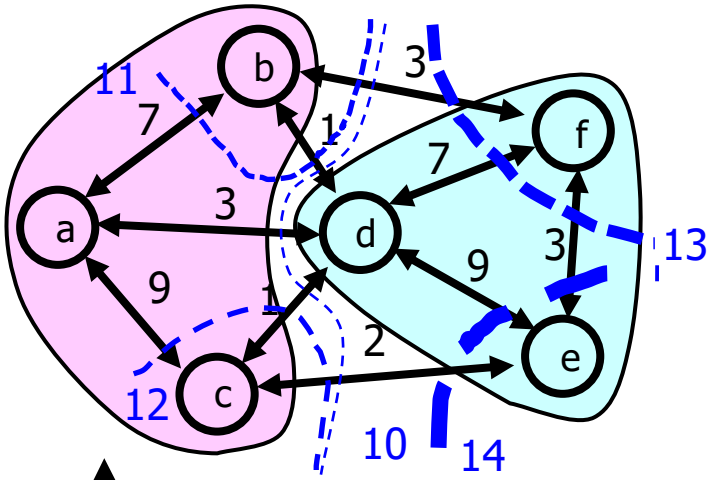
Kramers rate theory $k_{i\to j} \approx \frac{1}{\tau_0}\exp\left(-\frac{F_{ij}-F_i}{k_B T}\right)$

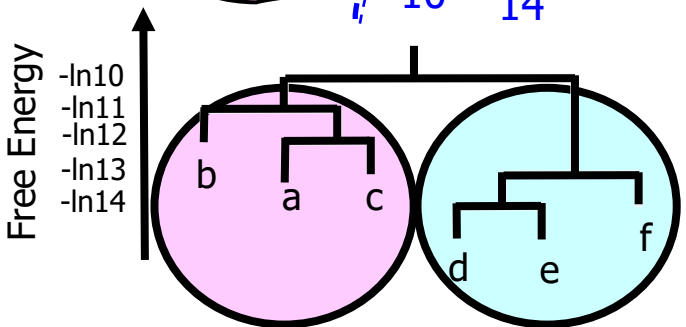
τ_0: the decay timescale of the autocorrelation for motion exerted by friction from the environment.

$$k_{i\to j}P_i = \left(\frac{N_{i\to j}}{N_i}\frac{1}{\tau_{obs}}\right)\left(\frac{N_i}{N}\right) = \frac{1}{\tau_0}\exp\left(-\frac{F_{ij}-F_i}{k_B T}\right)\exp\left(-\frac{F_i}{k_B T}\right) = \frac{1}{\tau_0}\exp\left(-\frac{F_{ij}}{k_B T}\right).$$

Timescale of observation

$$F_{ij} = -k_B T \ln\left(\tau_0 k_{i\to j}P_i\right) = -k_B T \ln\left(\frac{N_{i\to j}}{N}\frac{\tau_0}{\tau_{obs}}\right)$$

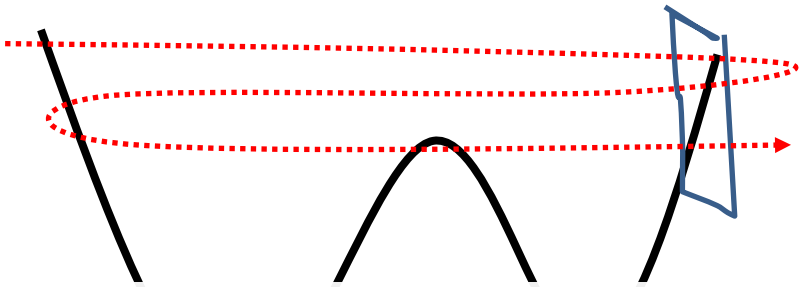


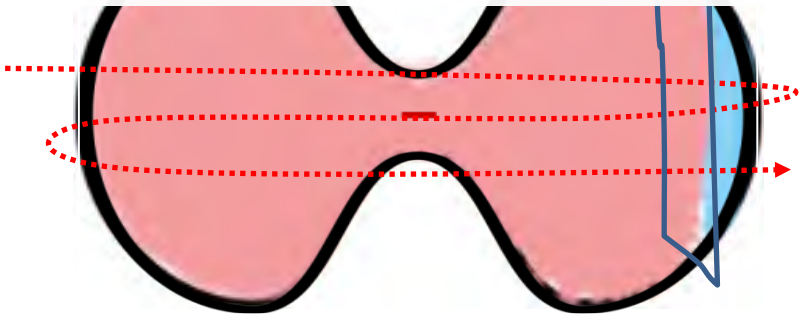


in order to validate the free energy at the barrier, $F_{ij} = F_{ji}$

$k_{i\to j}P_i = k_{j\to i}P_j$ should hold.

Why does the minimum flux approach miss the "transition state" in network?





$$p[S] \gg p[S^C]$$

When the space of optimization is the entire one, the minimum flux surface can be located near the "edge"

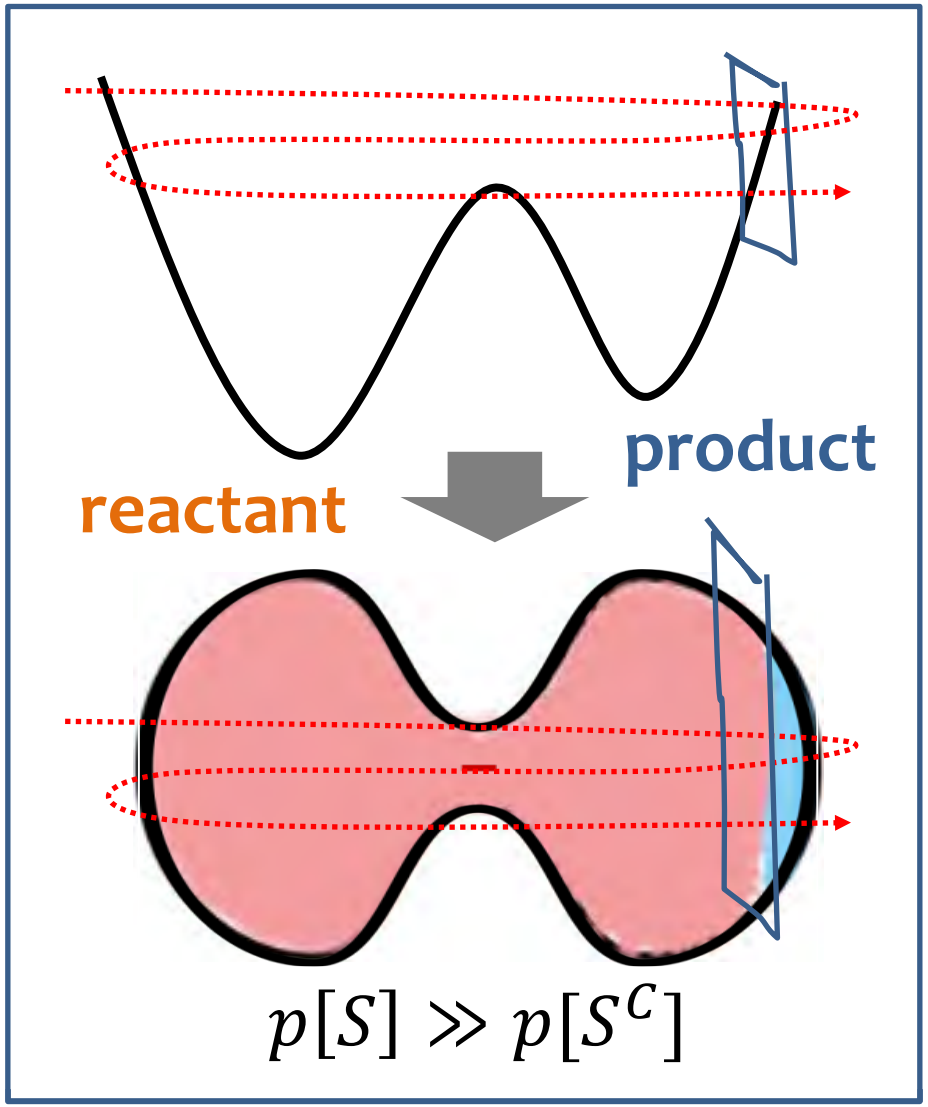
However, "Balanced min-cut is not unique and can break balance in some cases"

Nagahata, Wales, Komatsuzaki, *prepared for publication*

*Krivov-Karplus' choice

Balanced min-cut

Why does the minimum flux approach miss the "transition state" in network?



When the space of optimization is the entire one, the minimum flux surface can be located near the "edge"

Can one infer the region of dividing surface over an entire network?

*Krivov-Karplus' choice
Balanced min-cut

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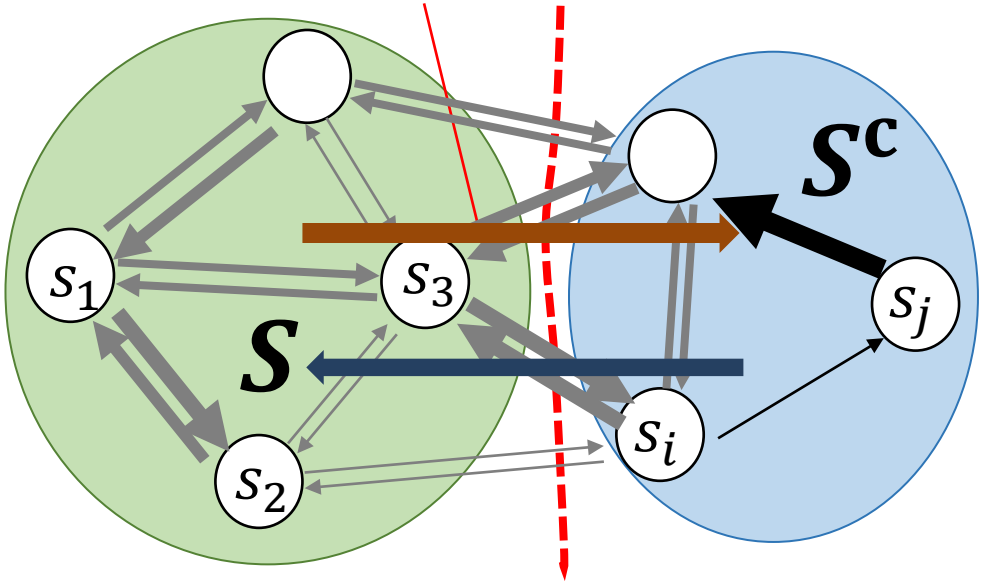
TS in network is defined as a dividing surface across which passage is slowest

$k_{\text{network}}(S \to S^c) = p_{\Delta t}[S^c, S]/p[S]$



Y. Nagahata et al. ***J. Phys. Chem. B* 120**, 1961(2015)

The quantity to be minimized is NOT the flux BUT the gross rate constant between the subsets of the network

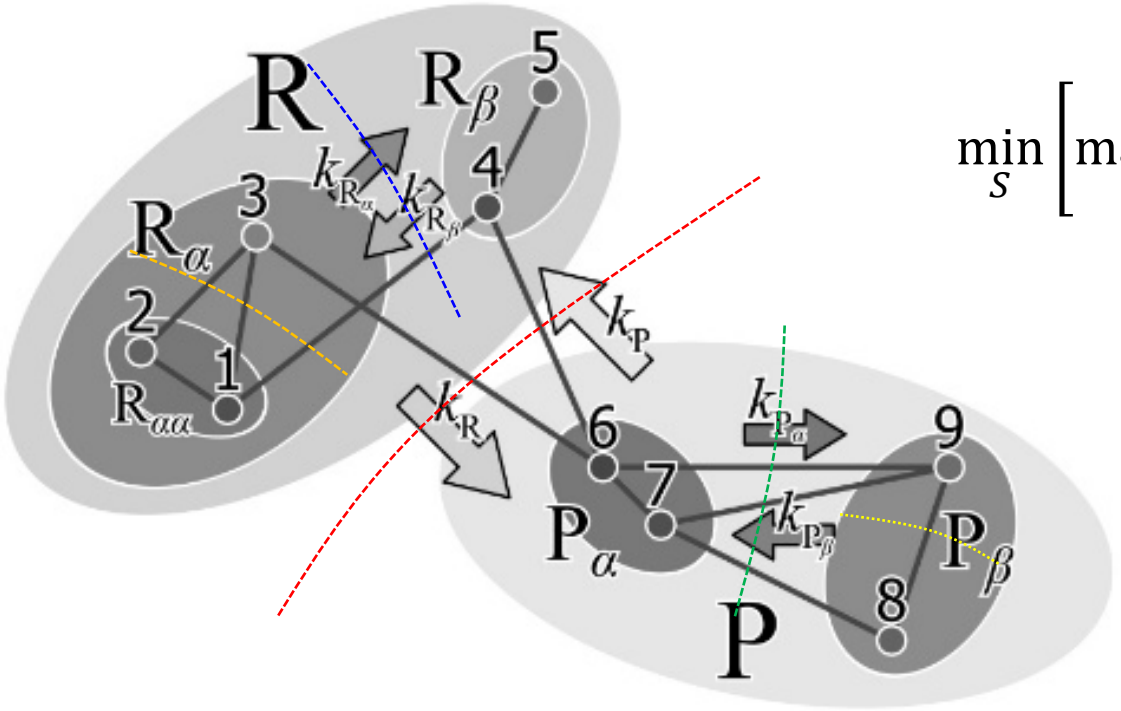
Gross rate constants of $S \to S^c$ and $S \to S^c$

Gross rate (in time Δt) of $S \to S^c$ and $S \to S^c$

$$\min_S \left[\max \left\{ \frac{p_{\Delta t}[S^c, S]}{p[S]}, \frac{p_{\Delta t}[S, S^c]}{p[S^c]} \right\} \right]$$

taking into account "the volume"

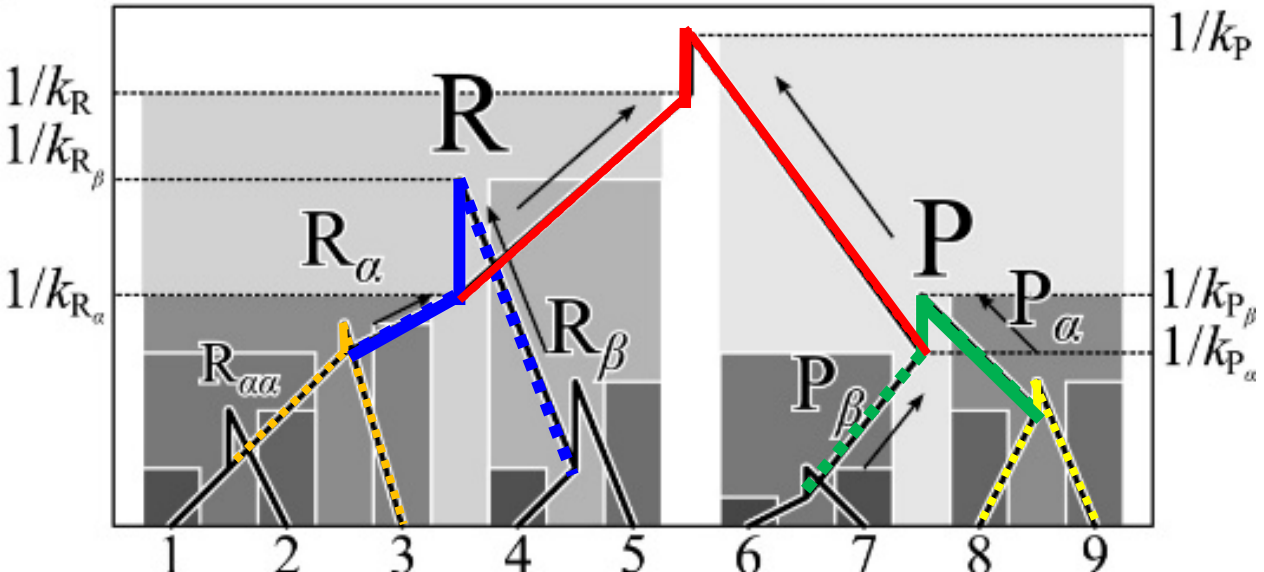
(a)



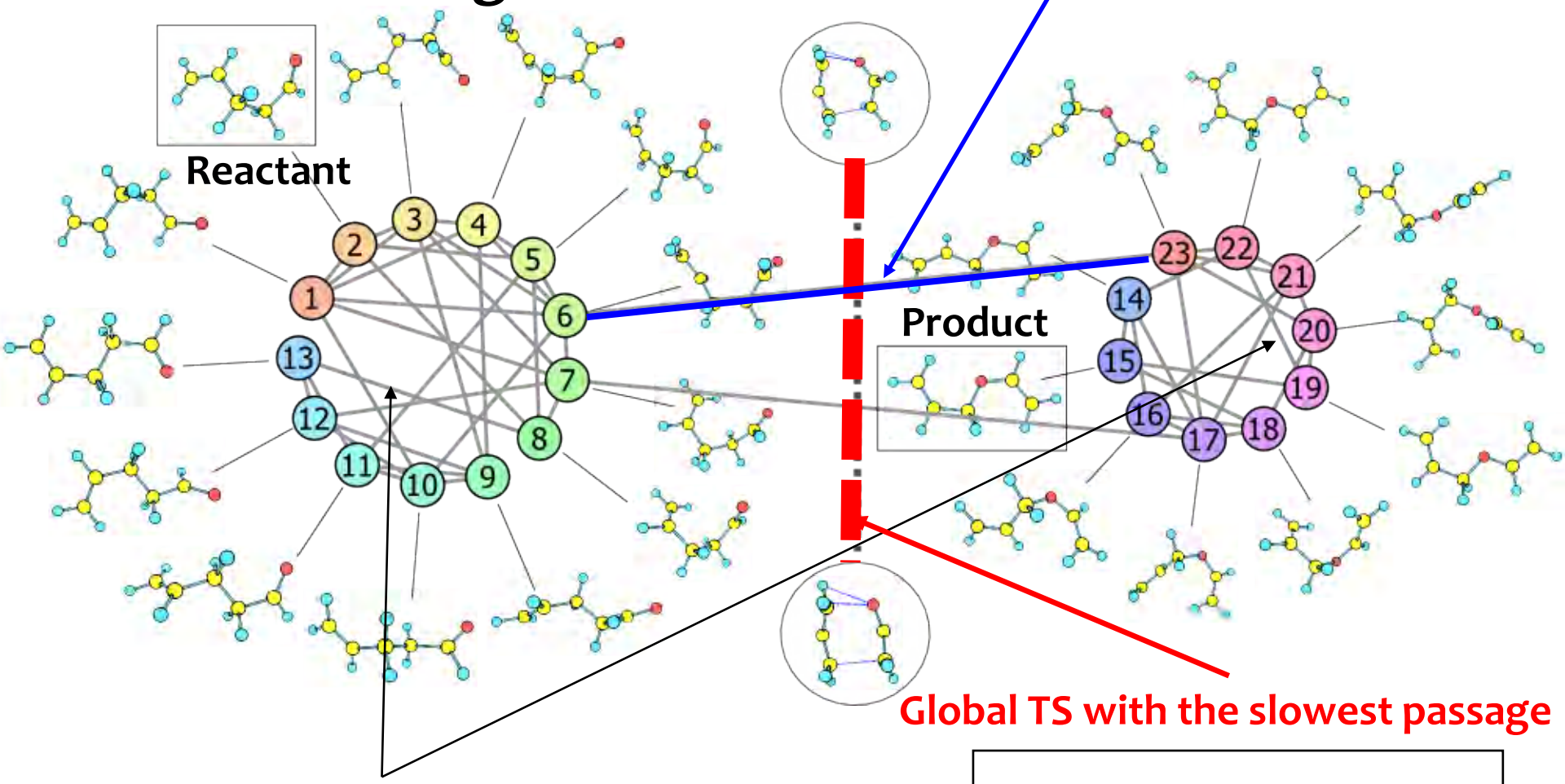
$$\min_S \left[\max \left\{ \frac{p_{\Delta t}[S^c, S]}{p[S]}, \frac{p_{\Delta t}[S, S^c]}{p[S^c]} \right\} \right]$$

$$p[S] \left(= \sum_{s_i \in S} p_{eq}[s_i] \right)$$

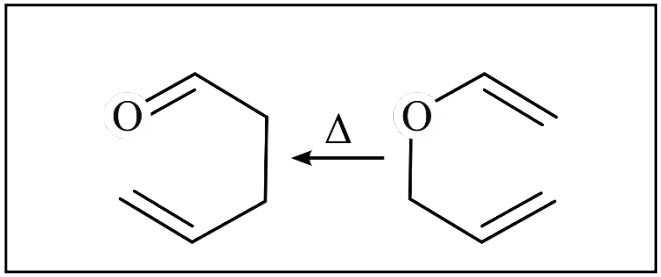
(b) escaping timescale = $1/k$ ($\propto \ln[\Delta F^{\ddagger}]$)



Reaction Network of Claisen Rearrangement

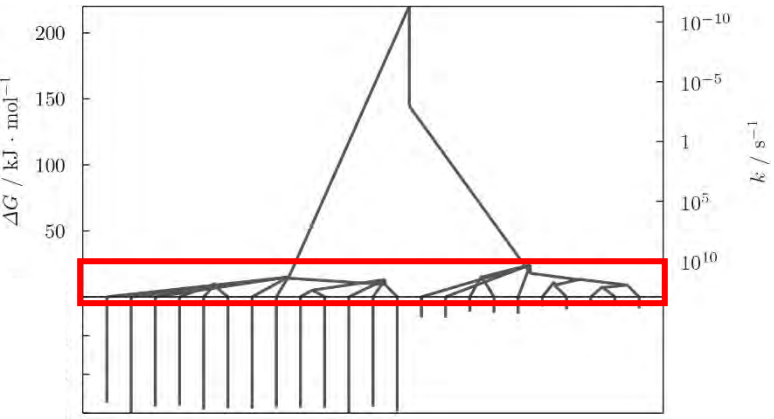


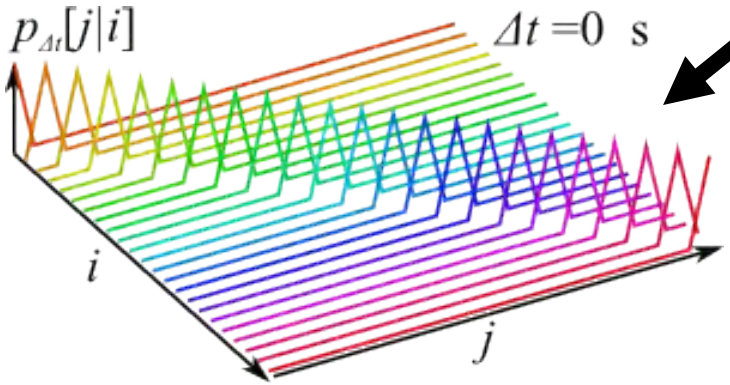
Each edge between nodes has a saddle linking the two minima & an estimated TST rate constant at 473.15 K

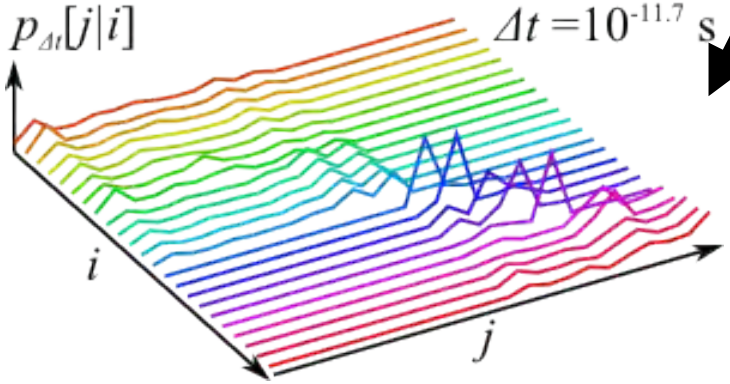


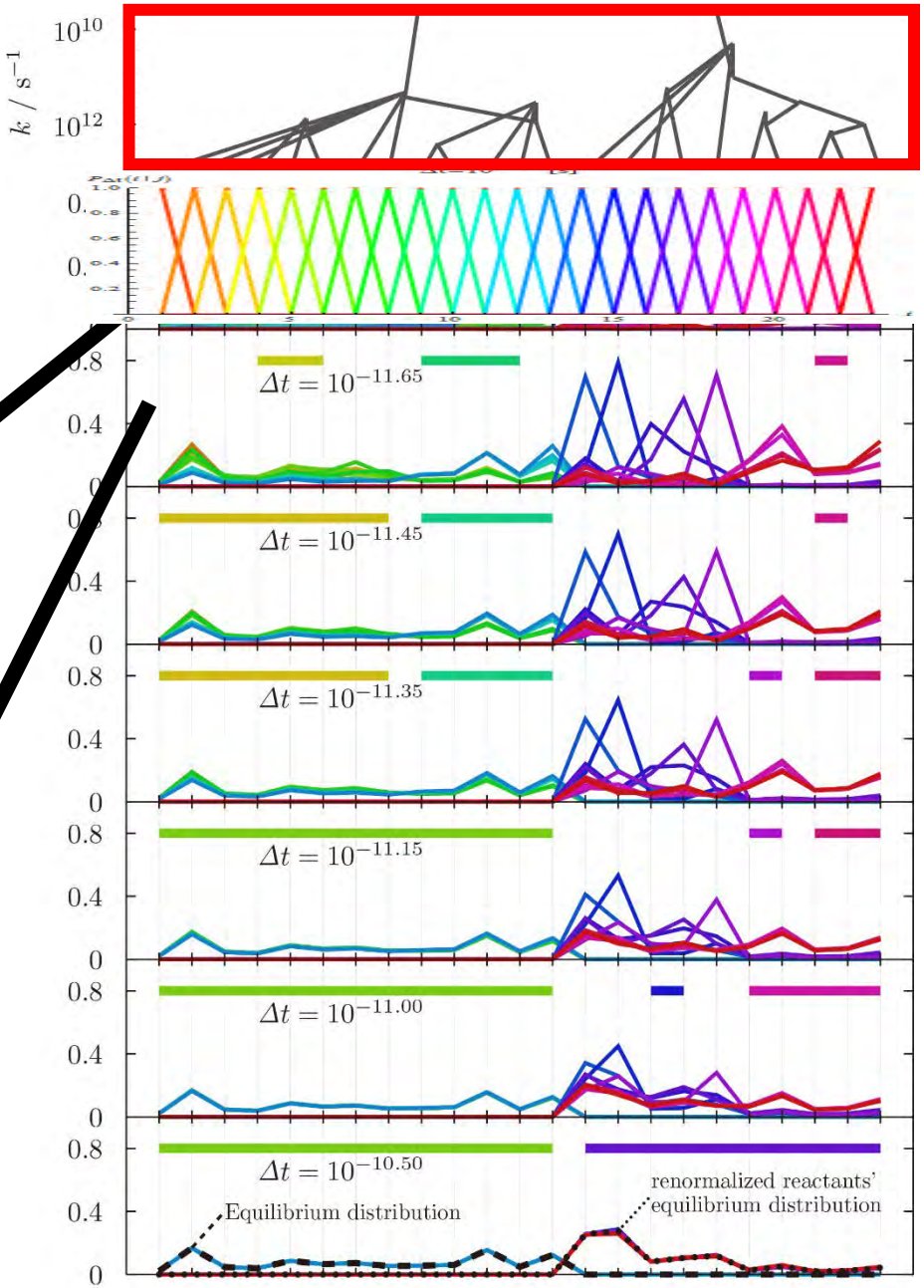
By Maeda & Taketsugu, GRRM/SC-AFIR with CCSD(T)/jun-cc-pVTZ//M062X/6-311+G(2d,p)

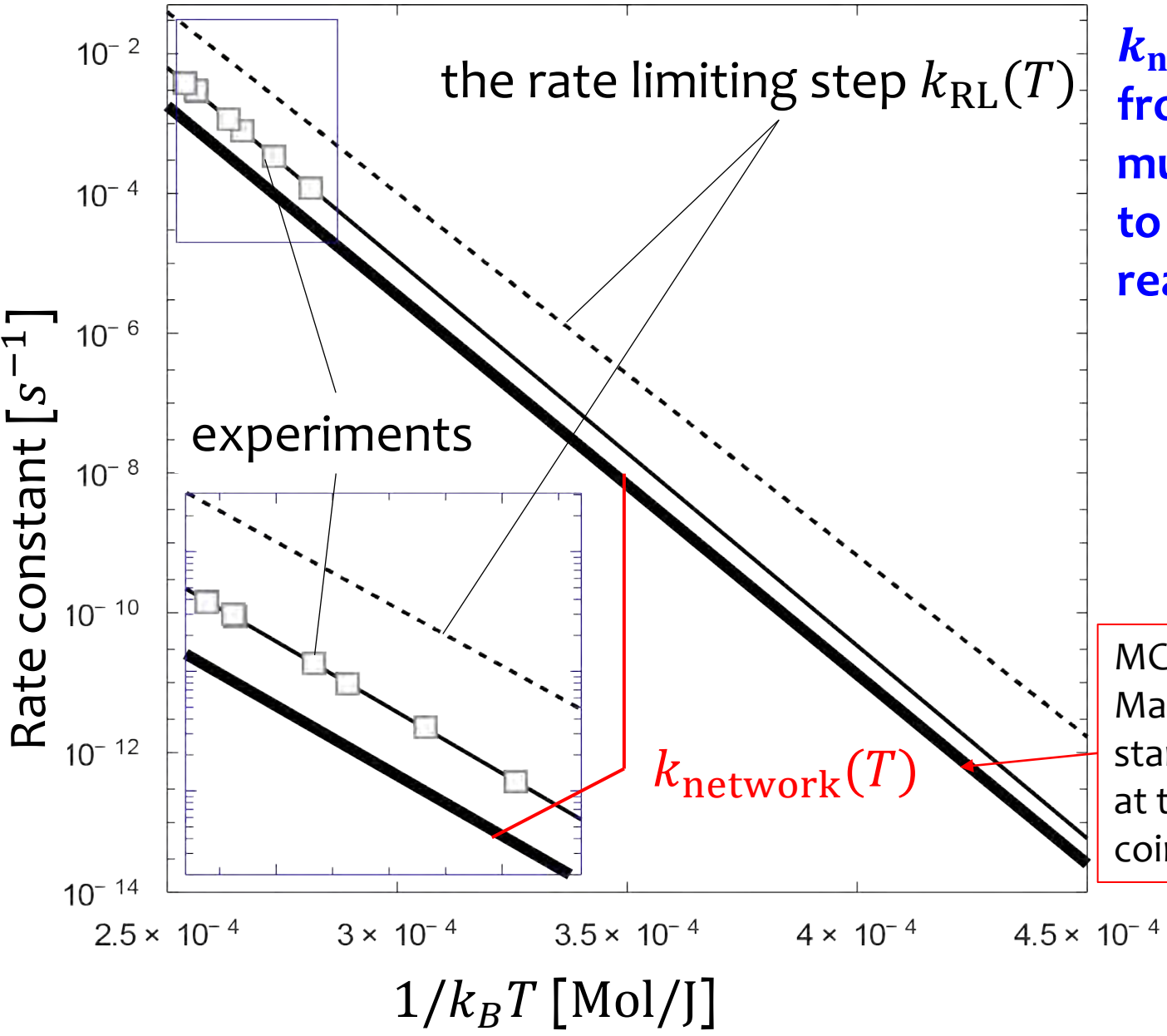
Kinetic disconnectivity graph and Markov kinetics







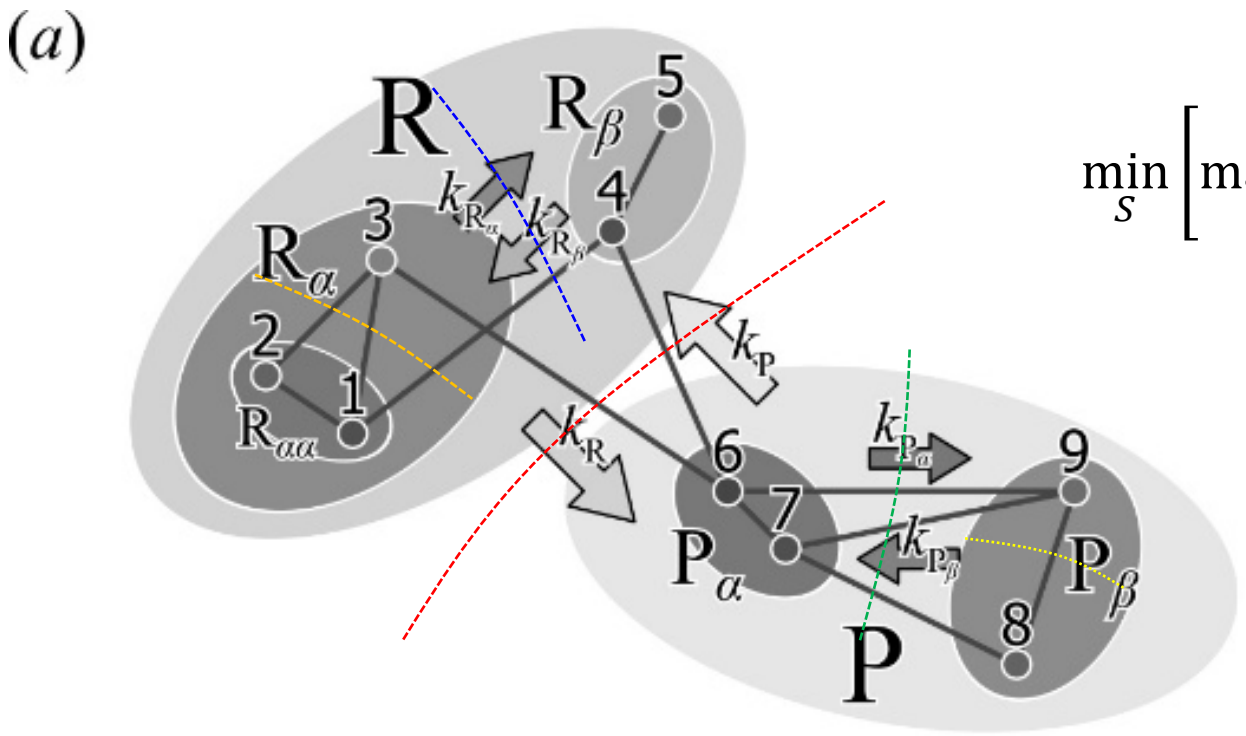




$k_{\mathrm{network}} < k_{RL}$ arises from the existence of multiple pathways to connect the reactant and product

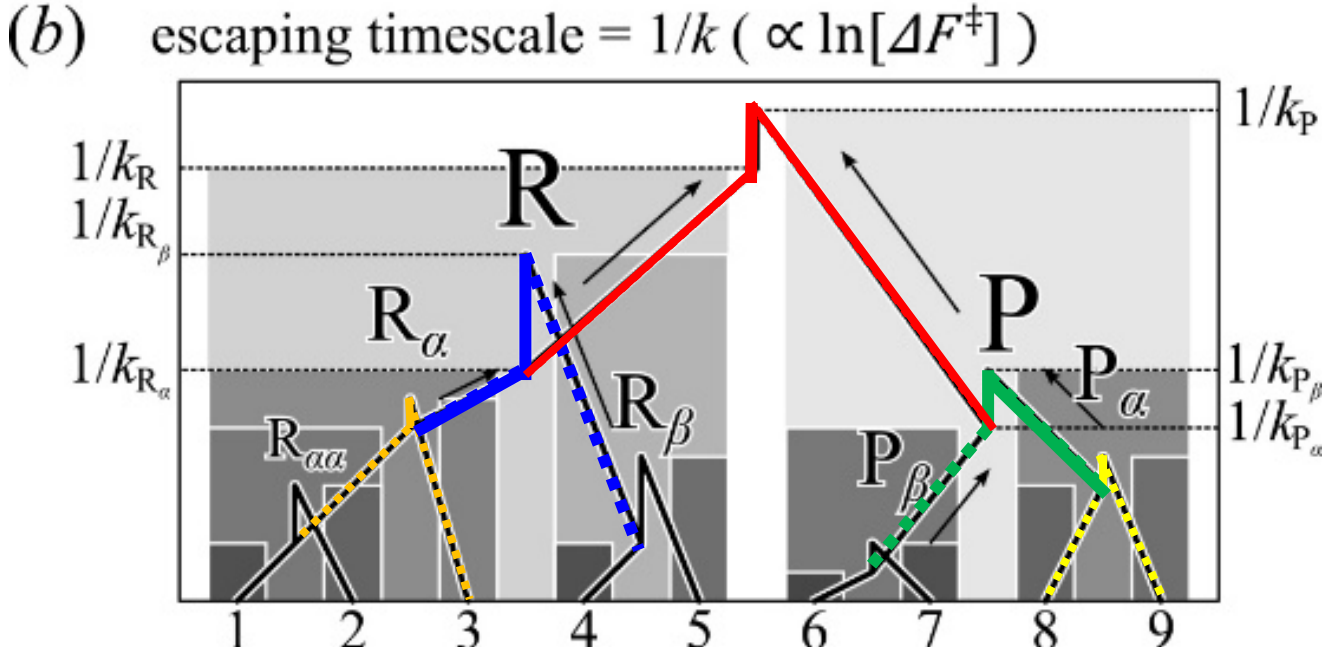
MC Simulation on the Markovian network started from $p[t=0]=1$ at the reactant node coincides with $k_{\mathrm{network}}(T)$

Experimental data F. W. Schuler and G. W. Murphy, J. Am. Chem. Soc. 72, 3155 (1950).



$$\min_S \left[\max \left\{ \frac{p_{\Delta t}[S^c, S]}{p[S]}, \frac{p_{\Delta t}[S, S^c]}{p[S^c]} \right\} \right]$$

$$p[S] \left(= \sum_{s_i \in S} p_{eq}[s_i] \right)$$



This requires the assumption of thermal equilibrium irrespective of the pair of S, S^c

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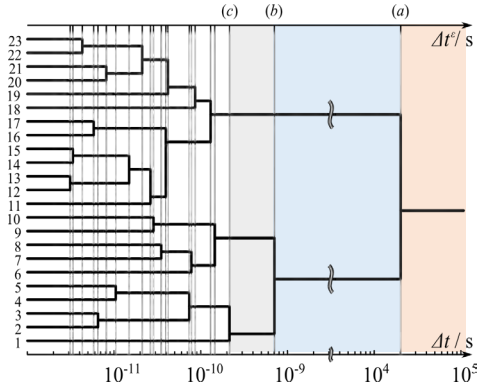
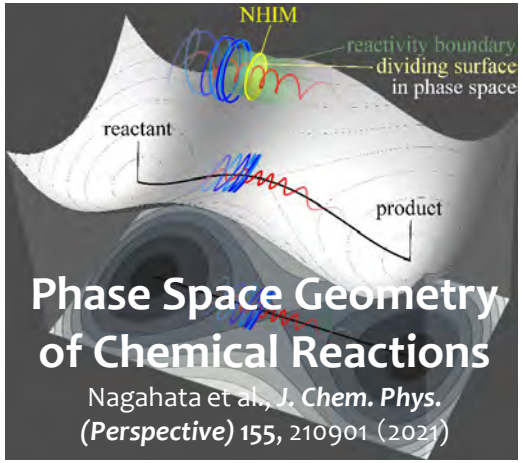
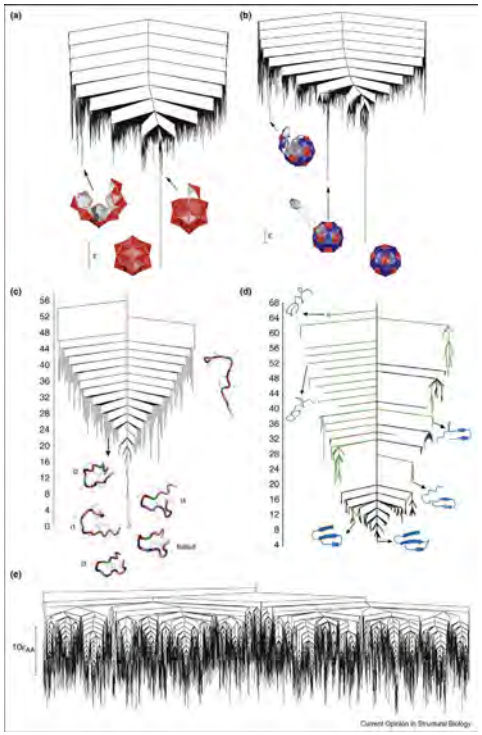




Dynamics

Representation of Kinetic Hierarchies not necessarily based on equilibrium

Free from stationarity, timescale separation, Predefining subnetworks



D. J. Wales,
Curr. Opin. Struct. Biol. **20**, 3 (2010).

Landscape

Lumpability diagram vs kinetic DG

Lumpability diagram

Identifying ϵ-indistinguishability of dynamics under a given timescale of observation.

Computational costs:

Solving ODE:

diagonalization $\mathcal{O}(n^3)$

Find Δt^{ϵ}:

matrix multiplication $\mathcal{O}(n^3)$

matrix arithmetic $\mathcal{O}(n^2)$

multi-precision

root finding $\times\ \mathcal{O}(n^2)$

Constructing diagram

complete linkage $\mathcal{O}(n^2)$

Kinetic disconnectivity graph

Showing whether each subnetwork is connected under a given threshold of timescale

Computational costs:

Computing rate constants:

arithmetic $\times\ \mathcal{O}(n^2)$

Constructing diagram

single linkage $\mathcal{O}(n^2)$

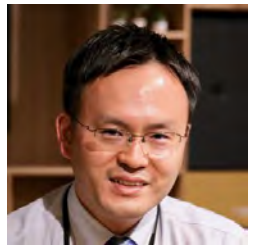
Dr. Yutaka Nagahata

ICReDD

Institute for Chemical Reaction Design and Discovery

北海道大学 化学反応創成研究拠点

Prof. Tetsuya Taketsugu



Prof. Satoshi Maeda