Finite temperature analysis of stochastic networks

Maria Cameron

University of Maryland
USA
Stochastic networks with detailed balance

* The generator matrix

\[ L = (L_{ij})_{i,j \in S}, \quad \begin{cases} 
L_{ij} \geq 0, & \forall i, j \in S, \ i \neq j \\
\sum_{j \in S} L_{ij} = 0, & \forall i \in S 
\end{cases} \]

* If the process is at state \( i \) at time \( t \), then

\[ L_{ij} \Delta t + o(\Delta t) \]

is the probability to jump from state \( i \) to state \( j \) in the time interval \([ t, t+\Delta t ]\).

* The equilibrium probability distribution \( \pi = (\pi_i)_{i \in S} \) satisfies

\[ \pi^T L = 0 \]

* The detailed balance: \( \pi_i L_{ij} = \pi_j L_{ji} \)

* Then \( L \) can be decomposed as

\[ L = \Pi^{-1} E, \quad \text{where } E = (E_{ij} = \pi_i L_{ij})_{i,j \in S} \text{ is symmetric, and } \Pi^{-1} = diag(\pi_1, \ldots, \pi_N) \]
Stochastic networks and energy landscapes

* Freidlin and Wentzell: mathematical justification
* D. Wales et al: networks for molecular clusters
* D. Hartl et al: networks for protein evolution

\[ dx = -\nabla V(x) dt + \sqrt{2T} dw \]

\[ T = \text{temperature, a small parameter} \]

The equilibrium probability distribution:

\[ \pi = \left( \pi_i = Z^{-1} k_i e^{-V_i/T} \right)_{i \in S}, \quad Z = \sum_{i \in S} k_i e^{-V_i/T} \]
Goal

Suppose we are interested in the transition process between two selected states (or two subsets of states) A and B.

- Developing computational tools to quantify the transition process between A and B
- in the limit $T \to 0$
- in the case where $T$ is low for studying the process by direct simulations but the zero-temperature asymptotic analysis is no longer valid
Motivation: Wales’s networks

D. Wales’s group (Cambridge University, UK) created a number of stochastic networks representing energy landscapes of molecular clusters.

Example: LJ$^{38}$ network:
over $10^6$ local minima.
Its subset of the lowest $10^5$ minima and 13888 saddles is available via the Wales’s group web site.

The lowest minimum: face-centered cubic truncated octahedron, point group $O_h$

The second lowest minimum: incomplete icosahedron, point group $C_{5v}$

Figure from Wales’s group web page
Approaches to finding transitions in LJ$_{38}$

- Discrete path sampling (Wales, 2002) (Build a network representing the energy landscape and then study it)

- Direct transition current sampling (Picciani, Athenes, Kurchan, Taileur, 2011)

- Molecular dynamics and temperature accelerated molecular dynamics (Hamilton, Siegel, Uberuaga, Voter, 2011)

- Parallel tempering (Neirotti, Calvo, Freeman, Doll, 2000)
Difficulties

- Stochastic networks are large, complex and irregular
  - \( \text{LJ}_{38} \): \( 10^5 \) states, degrees vary from 1 to 839

- Pairwise transition rates vary widely at small temperature
  - \( \text{LJ}_{38} \): from \( \sim 1 \) to \( \sim \exp(-100) \)

- The transition process becomes diverse as the temperature increases. It is not clear how to effectively describe it.


Critical temperatures:
- \( T=0.12 \) - solid-solid transition,
- \( T=0.18 \) - the outer layer melts
- \( T=0.35 \) - the cluster melts completely
Results

• Zero-temperature asymptotic analysis:
  • Characterization of the asymptotic zero-temperature pathway
  • An algorithm for computing it

• Finite temperature analysis
  • Range of validity of the zero-temperature asymptotic analysis
  • Effective description of transition process
  • Analysis of the temperature-dependence of the transition rate
  • A simple two-state model mimicking the complex LJ$_{38}$ network
Zero-temperature asymptotic analysis

Freidlin’s cycles


\[ dx = b(x)dt + \sqrt{2T} \sigma(x)dw \]

In the case of multiple attractors the system is reduced to a discrete-space continuous-time Markov chain and its dynamics of the system is characterized by the hierarchy of cycles

Cameron, 2013

\[ dx = -\nabla V(x)dt + \sqrt{2T} dw \]

In the case of the overdamped Langevin dynamics, the hierarchy of cycles is a full binary tree
Example: a three-well potential

\[ dx = -\nabla V(x) dt + \sqrt{2T} dw \]

Idea:

For \( k=1,2,... \)

Form a (generalized) rate matrix \( Q^{(k)} \).
Convert it into a (generalized) jump matrix \( \Pi^{(k)} \).
Take the zero temperature limit to find a (generalized) limiting jump matrix \( \Pi^{(k)}_0 \).
Extract \( k \)-th order cycles from \( \Pi^{(k)}_0 \) and treat them as macro-states.

End
Stage 1

Rate matrix

\[ Q^{(1)} = \begin{bmatrix} -q_{AB} - q_{AC} & q_{AB} & q_{AC} \\ q_{BA} & -q_{BA} - q_{BC} & q_{BC} \\ q_{CA} & q_{CB} & -q_{CA} - q_{CB} \end{bmatrix} \]

Jump matrix

\[ \Pi^{(1)} = \begin{bmatrix} 0 & \frac{q_{AB}}{q_{AB} + q_{AC}} & \frac{q_{AC}}{q_{AB} + q_{AC}} \\ \frac{q_{BA}}{q_{BA} + q_{BC}} & 0 & \frac{q_{BC}}{q_{BA} + q_{BC}} \\ \frac{q_{CA}}{q_{CA} + q_{CB}} & \frac{q_{CB}}{q_{CA} + q_{CB}} & 0 \end{bmatrix} \]

Limiting jump matrix

\[ \Pi_0^{(1)} := \lim_{\beta \to \infty} \Pi^{(1)} = \begin{bmatrix} 0 & 0 & 1 \\ 0 & 0 & 1 \\ 0 & 1 & 0 \end{bmatrix} \]

\{B, C\} is a 1st order cycle
Stage 2

Calculate probability distribution in the 1st order cycle \{B, C\} and update the rate matrix

\[
P(B | BC) = \frac{\tau_B}{\tau_B + \tau_C} \times \frac{\beta(V_{BC} - V_B)}{e^{\beta(V_{BC} - V_B)} + e^{\beta(V_{BC} - V_C)}}
\]

\[
P(C | BC) = \frac{\tau_C}{\tau_B + \tau_C} \times \frac{\beta(V_{BC} - V_C)}{e^{\beta(V_{BC} - V_B)} + e^{\beta(V_{BC} - V_C)}}
\]

\[
k_{BA} \equiv \lim_{t \to \infty} \frac{N_{BA}}{\tau_B + \tau_C} = P(B | BC)Q_{BA}^{(1)} \propto \frac{e^{-\beta V_{AB}}}{e^{-\beta V_B} + e^{-\beta V_C}}
\]

\[
k_{CA} \equiv \lim_{t \to \infty} \frac{N_{CA}}{\tau_B + \tau_C} \propto P(C | BC)Q_{CA}^{(1)} \propto \frac{e^{-\beta V_{AC}}}{e^{-\beta V_B} + e^{-\beta V_C}}
\]

Generalized rate matrix

\[
Q^{(2)} = \begin{bmatrix}
-q_{AB} - q_{AC} & q_{AB} & q_{AC} \\
k_{BA} & -k_{BA} - k_{CA} & -k_{BA} - k_{CA} \\
k_{CA} & -k_{BA} - k_{CA} & -k_{BA} - k_{CA}
\end{bmatrix}
\]

Generalized limiting jump matrix

\[
\Pi_{0}^{(2)} := \lim_{\beta \to \infty} \Pi^{(2)} = \begin{bmatrix}
0 & 0 & 1 \\
0 & 0 & 0 \\
1 & 0 & 0
\end{bmatrix}
\]

Generalized jump matrix

\[
\Pi^{(2)} = \begin{bmatrix}
0 & \pi_{AB}^{(2)} & \pi_{AC}^{(2)} \\
\pi_{BA}^{(2)} & 0 & 0 \\
\pi_{CA}^{(2)} & 0 & 0
\end{bmatrix},
\]

where

\[
\pi_{AB}^{(2)} \propto \frac{e^{-\beta V_{AB}}}{e^{-\beta V_{AB}} + e^{-\beta V_{AC}}}
\]

\[
\pi_{AC}^{(2)} \propto \frac{e^{-\beta V_{AC}}}{e^{-\beta V_{AB}} + e^{-\beta V_{AC}}}
\]
The structure of the hierarchy of cycles

Theorem

Suppose the system evolves according to

$$dx = -\nabla V(x) dt + \sqrt{2\beta^{-1}} dw$$

where the potential $V(x)$ satisfies certain nonrestrictive conditions. Then

**Claim 1.** The escape rate from the maximal cycle $C^{(k-1)(i)}$ containing state $i$ via the edge $ij$ is

$$Q_{ij}^{(k)} \sim \frac{\exp(-\beta V_{ij})}{\exp(-\beta \min_{m \in C^{(k-1)(i)}} V_m)}$$

**Claim 2.** Each cycle (except for the largest one) is exited via the lowest saddle adjacent to it

**Claim 3.** Each cycle of order $\geq 1$ can be decomposed to exactly two maximal subcycles of lower orders.
The asymptotic zero-temperature pathway connecting states 1 and 7:

\[
V_{i_p,i_q} = \max_{(i_p,i_q) \in w} \left( \min_{w(i_k,i_l) \in W} \max_{(i_p,i_q) \in w(i_k,i_l)} V_{q,r} \right)
\]
Hierarchy of cycles and the minimal spanning tree

Claims 2 and 3 imply that the set of cycles of order \( \geq 1 \) is isomorphic to the set of edges of the minimal spanning tree with the cost function \( c_{ij} = V_{ij} \).

Goal

Find the pathway in the minimal spanning tree between two given states without computing the minimal spanning tree itself.
Algorithm for finding the minimax pathway between two given states

This algorithm recursively builds a tree of minimax edges using, as a building block, the Dijkstra method with

- the cost function

\[ c_{ij} = \begin{cases} V_{ij}, & \text{if } i \text{ and } j \text{ are connected by an edge} \\ \infty, & \text{otherwise} \end{cases} \]

- the value function

\[ u(j) = \min_{w} \max_{(k, l) \in w} V_{kl} \]

- and the update rule

\[ u(j) = \min \left\{ u(j), \max \left\{ u(i), c_{ij} \right\} \right\} \]

\[ u(7) = V_{37} - V_{1} \]
Step 1: build a tree of minimax edges.

// The structure “MyTreeNode” contains 4 components:
// minimax edge, parent, left child, and right child.

Function MyTreeNode = TreeNode(initial state \(i_0\), terminal state \(i_t\), parent NULL)

\[\text{MyTreeNode.Parent} = \text{NULL};\]
\[\text{[u, parent-child relationship]} = Dijkstra(\text{initial state } i_0, \text{terminal state } i_t);\]
\[\text{minimax edge } (i,j) = \text{FindMinimaxEdge}(i_t, i_0, u, \text{parent-child relationship});\]
\[\text{MyTreeNode.Edge} = (i,j);\]
\[\text{if } i \text{ coincides with } i_0 \text{ then}\]
\[\quad \text{MyTreeNode.LeftChild} = \text{NULL};\]
\[\text{else}\]
\[\quad \text{MyTreeNode.LeftChild} = \text{TreeNode}(\text{initial state } i_0, \text{terminal state } i_t, \text{parent MyTreeNode});\]
\[\text{end}\]
\[\text{if } j \text{ coincides with } i_t \text{ then}\]
\[\quad \text{MyTreeNode.RightChild} = \text{NULL};\]
\[\text{else}\]
\[\quad \text{MyTreeNode.RightChild} = \text{TreeNode}(\text{initial state } j, \text{terminal state } i_t, \text{parent MyTreeNode});\]
\[\text{end}\]
\[\text{return MyTreeNode};\]

Step 2: sort the tree into the asymptotic zero-temperature pathway.
(1) Dijkstra( $i_s = 7$, $i_t = 1$ )

(2) Dijkstra( $i_s = 3$, $i_t = 1$ )

(3) Dijkstra( $i_s = 3$, $i_t = 2$ )

(4) Sort the tree into a path

(7,3)  (2,1)  (3,2)
Application to Lennard-Jones-38 cluster
D. Wales’s LJ$_{38}$ network

Double-funnel of LJ$_{38}$

The lowest minimum: face-centered cubic truncated octahedron, point group $O_h$

The second lowest minimum: incomplete icosahedron point group $C_{5v}$

Over $10^6$ minima.

$10^5$ minima and 138888 transition states are available via Wales’s group web site
The hierarchy of cycles involved into the minimax pathway

The minimax pathway =
the asymptotic zero-temperature pathway

Legend

- $n$: The number of states in the smallest macrostate (cycle) containing $a$ and $b$.
- $a, b$: The smallest macrostate (cycle) containing the states $a$ and $b$.
- $c, d$: The edge corresponding to the highest saddle in this macrostate.
- $r$: The number of states in the largest macrostate (cycle) containing the states $a$ but not containing $b$.

$r = \nabla(saddle\ separating\ c\ and\ d) - \nabla(\text{the\ lowest\ minimum\ in\ the\ macrostate})$

The average number of transitions between $a$ and $b$ per time unit is logarithmically equivalent to $\exp(-r/T)$, where $T$ is the temperature.
The asymptotic zero-temperature pathway

The highest barrier: $V = -169.709$ or 4.219 relative to FCC
Finite temperature analysis

Joint work with E. Vanden-Eijnden
The discrete Transition Path Theory

Metzner, P., Schuette, Ch., and Vanden-Eijnden, E., 2008

Key concepts
- The committor function \( q(i) \) = the probability to reach \( B \) prior to \( A \) starting from the state \( i \);

\[
\sum_{j \in S} L_{ij} q_j = 0, \quad i \in S \setminus (A \cup B)
\]

\( q_i = 0, \quad i \in A, \quad q_i = 1, \quad i \in B \)

- The probability current of reactive trajectories

\[
f_{ij}^{AB} = \begin{cases} 
\pi_i (1 - q_i) L_{ij} q_j, & i \neq j, \\
0, & \text{otherwise}
\end{cases}
\]

- The reactive (a.k.a. effective) current

\[
F_{ij} = f_{ij}^{AB} - f_{ji}^{AB} = \pi_i L_{ij} (q_j - q_i)
\]

- The signed effective current

\[
f_{ij}^+ = \max\{F_{ij}, 0\}
\]
An analogy with electricity

\[ \varphi_A = 1 \]
\[ q_A = 0 \]
\[ A \]

\[ \varphi_B = 0 \]
\[ q_B = 1 \]
\[ B \]


- Committor = 1 - electric potential
- Effective current = electric current
- \[ \pi_i L_{ij} = \text{resistance} \]
Reactive trajectories vs reaction pathways

- Solve the committor equation
- Calculate the probability current of reactive trajectories
- Calculate the reactive current (a. k. a. the effective current)
- Generate the reaction pathways
  - Jump probabilities:  \( p_{ij} = \frac{f_{ij}^+}{\sum_{k \sim i} f_{ik}^+} \)
- Calculate the transition rate

\[ q(A) = 0 \quad q(B) = 1 \]
**LJ\(_{38}\) network: settings**

The generator matrix:

\[
L_{ij} = \begin{cases} 
\sum_{e_k \in E_{ij}} \frac{O_i \bar{V}_i^k}{O_{ij} (\bar{V}_{ij}^k)^{\kappa-1}} e^{-\frac{(V_{ij}^k - V_i)}{T}}, & \text{if } i \sim j \\
0, & \text{otherwise}
\end{cases}
\]

The equilibrium probability density:

\[
\pi_i = Z^{-1}(T) \frac{e^{-V_i/T}}{O_i \bar{V}_i^\kappa},
\]

where \(Z(T) = \sum_{i \in S} e^{-V_i/T} \frac{O_i \bar{V}_i^\kappa}{O_{ij} (\bar{V}_{ij}^k)^{\kappa-1}}\)

\(O = \) the order of the point group
\(\bar{v} = \) the mean vibrational frequency
\(\kappa = 3 \cdot 38 - 6 = 108\)

= the number of vibrational degrees of freedom

Wales’s network:
connected component:
71887 states

\(A = IC\)
\(B = FCC\)
Solving the committor equation

\[ \sum_{j \in S} L_{ij} q_j = 0, \quad i \in S \setminus (A \cup B) \]

\[ q_i = 0, \quad i \in A, \quad q_i = 1, \quad i \in B \]

**Symmetrization:**

\[ \sum_{j \in S} \pi_i L_{ij} q_j = 0, \quad i \neq \text{ICO, FCC} \]

\[ q(\text{ICO}) = 0, \quad q(\text{FCC}) = 1 \]

**Method:**

Conjugate gradient with incomplete Cholesky preconditioning

| Temperature | Barrier | The # of states | |S||
|-------------|---------|-----------------|----------------|
| 0.05        | 4.428   | 1604            |               |
| 0.055       | 5.428   | 15056           |               |
| 0.06 ... 0.065 | 5.928 | 28486           |               |
| 0.07        | 6.928   | 53566           |               |
| 0.075 ... 0.08 | 7.428 | 61706           |               |
| 0.085       | 8.428   | 69302           |               |
| 0.09 ... 0.095 | 8.928 | 70552           |               |
| 0.10 ... 0.12 | 9.928 | 71609           |               |
| 0.125 ... 0.18 | Inf   | 71887           |               |
Cartoon of the transition process at $T=0.05$:

Good agreement with the LDT prediction:

The **dominant representative pathway** coincides with the **minimax pathway**

- $0 \leq q < 0.2$
- $0.2 \leq q < 0.4$
- $0.4 \leq q < 0.6$
- $0.6 \leq q < 0.8$
- $0.8 \leq q \leq 1$

$\begin{array}{c}
q(7)=0 \\
q(8)=3.8e-9 \\
q(312)=7.0e-7 \\
q(313)=2.3e-5 \\
q(375)=4.5e-5 \\
q(376)=1.4e-4 \\
q(342)=4.4e-4 \\
q(354)=3.4e-1 \\
q(958)=3.5e-1 \\
q(2831)=9.996e-1 \\
q(1)=1
\end{array}$

$0 \leq q < 0.2$

$0.2 \leq q < 0.4$

$0.4 \leq q < 0.6$

$0.6 \leq q < 0.8$

$0.8 \leq q \leq 1$
Cartoon of the transition process at $T=0.06$:

Still good agreement with the LDT prediction:

The **dominant representative pathway** coincides with the **minimax pathway**

<table>
<thead>
<tr>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ≤ $q$ &lt; 0.2</td>
<td>○</td>
</tr>
<tr>
<td>0.2 ≤ $q$ &lt; 0.4</td>
<td>○</td>
</tr>
<tr>
<td>0.4 ≤ $q$ &lt; 0.6</td>
<td>⚫</td>
</tr>
<tr>
<td>0.6 ≤ $q$ &lt; 0.8</td>
<td>⚫</td>
</tr>
<tr>
<td>0.8 ≤ $q$ ≤ 1</td>
<td>●</td>
</tr>
</tbody>
</table>
Cartoon of the transition process at $T=0.09$:

No longer good agreement with the LDT prediction:

The effective current is distributed among many different pathways.
Cartoon of the transition process at $T=0.12$:

The transition process becomes diverse

The effective current is distributed among many different pathways
Cartoon of the transition process at $T=0.15$: 

Even more diverse …

The effective current is distributed among many different pathways
Cartoon of the transition process at $T=0.18$:

And even more diverse …

The dominant representative pathway $q(3223)=6.2\times10^{-2}$

The effective current is distributed among many different pathways

$0 \leq q < 0.2$
$0.2 \leq q < 0.4$
$0.4 \leq q < 0.6$
$0.6 \leq q < 0.8$
$0.8 \leq q \leq 1$
The distribution of the highest barriers along the reaction pathways.

- **$T = 0.05$**: 53% for $342 - 354$, 24% for $351 - 354$, 9% for $354 - 958$, 4% for $396 - 5162$, 1% for $958 - 1$.
- **$T = 0.06$**: 38% for $958 - 607$, 24% for $3886 - 354$, 13% for $351 - 354$, 11% for $3223 - 354$, 7% for $396 - 5162$.
- **$T = 0.09$**: 32% for $958 - 1$, 16% for $3886 - 354$, 14% for $351 - 354$, 7% for $342 - 354$, 7% for $396 - 5162$.
- **$T = 0.12$**: 54% for $958 - 1$, 24% for $351 - 354$, 11% for $3886 - 354$, 10% for $3223 - 354$, 5% for $396 - 5162$.
- **$T = 0.15$**: 82% for $958 - 607$, 7% for $3886 - 354$, 5% for $351 - 354$, 1% for $342 - 354$, 1% for $3223 - 354$.
- **$T = 0.18$**: 94% for $958 - 1$, 1% for $3886 - 354$, 1% for $351 - 354$, 1% for $342 - 354$, 1% for $3223 - 354$.
The distribution of highest barriers along the reaction pathways
Transition rate fits the Arrhenius law

\[ r = C e^{-\Delta/T} \]

\[ \log(r) = \log(C) - T^{-1} \Delta \]

\[ k_A = 9.81 \times 10^4 \exp\left\{-\frac{3.525}{T}\right\}, \quad k_B = 1.03 \times 10^4 \exp\left\{-\frac{4.289}{T}\right\} \]

Compare to: \[ V_{342,354} - V_{ICO} = 3.543, \quad V_{342,354} - V_{FCC} = 4.219 \]
Does the Large Deviation Theory explain the transition rate?

\[ r = Ce^{-\Delta/T} \]

\[ T \log r = T \log C - \Delta \]

Black - full network
Blue - reduced network: maximal barrier - 169.5
Cuts and transition rate

Metzner, P., Schuette, Ch., and Vanden-Eijnden, E.,

\[ r = \sum_{i \in A, j \in S} f_{ij}^{AB} = \sum_{i \in S, j \in B} f_{ij}^{AB} = \frac{1}{2} \sum_{i, j \in S} \pi_i L_{ij} (q_j - q_i)^2 \]

**Theorem** (Cameron & Vanden-Eijnden, 2013)

For any cut \( C \), separating the sets \( A \) and \( B \), the transition rate is given by

\[ r = \sum_{i \in C_L, j \in C_R} F_{ij} = \sum_{i \in C_L, j \in C_R} \left( f_{ij}^{AB} - f_{ji}^{AB} \right) \]
Isocommittor cuts and reactive tubes

T=0.06

T=0.09

T=0.12

T=0.18
The distribution of the committor
Reactive flux distribution in the isocommittor cut $C(0.5)$
The transition rate in LJ$_{38}$: two opposite effects:

1. Growth of $Z(T)$
2. Widening of the reactive tube

**Modified Arrhenius law:** $v_{AB}(T) = Z^{-1}(T)Ce^{-V_{eff}(T)/T}$, then $T \log(Z(T)v_{AB}(T)) = T \log(C) - V_{eff}(T)$

**FCC:** $O_{FCC} = 48$

**ICO:** $O_{ICO} = 10$

**Most states:** $O_i = 1$
A two-state model mimicking the reactive tube in LJ$_{38}$

The two-state model:

\[ f_k(T) = Re^{-V_k/T} \]

The LJ$_{38}$ network, in the isocommittor section C(0.5):

\[ f_k(T) = C(T)k^{b(T)+ka(T)} \]

To match these formulas, we need:

\[ C(T) = Re^{-V_1/T}, \quad a(T) = \alpha / T, \quad b(T) = \beta / T \]

We check: these relationships hold

Then, in the two-state model

\[ V_k = V_1 + (\beta + \alpha k)\log(k), \quad k = 1,2,\ldots \]
Transition rate in the LJ$_{38}$ and in the two-state model

\[ V_{\text{eff}} (T) = V_1 - \gamma T^2 \]
Conclusion

- The Arrhenius law holds for the LJ38 network due to a fine balance of two opposite effects
  - The growth of $Z(T)$ inhibits the transition rate
  - The widening of the reactive tube accelerates it
Asymptotic zero-temperature path

Reactive tube at higher temperature

\[ V(x) \sim (\beta + \alpha |x|) \log |x| \]
Experiment: all prefactors in the LJ38 are set to 1

Suppose all prefactors = 1. Then $V_{\text{eff}}$ grows quadratically with $T$. 

![Graph](image-url)
Asymptotic zero-temperature path

Reactive tube at higher temperature

\[ V(x) \sim (\beta + \alpha |x|) \log |x| \]