Transition Path Theory

Winterschool on
Theoretical Chemistry and Spectroscopy
9-13 December 2013, Han-sur-Lesse, Belgium

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Content

- Lecture 1: Markov processes
- Lecture 2: State clustering
- Lecture 3: Transition Path Theory
- Lecture 4: Sampling Reactive Events

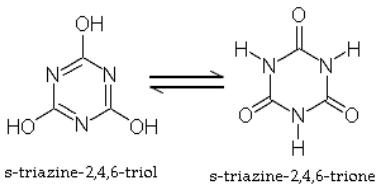
Friday, 13 December, 13

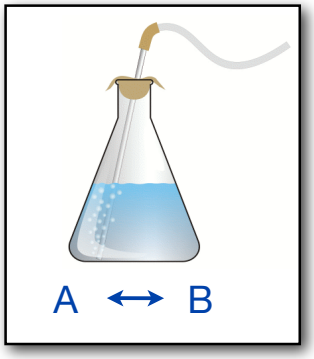
Stochastic processes

Chemical reaction:

$$A \leftrightarrow B$$

e.g. tautomerization reaction





At t=0

probability to measure molecule P(A) = 1.0
probability to measure molecule P(B) = 1.0-P(A) = 0.0

initial state distribution $S_0 = [1.0, 0.0]$

P(A) P(B)

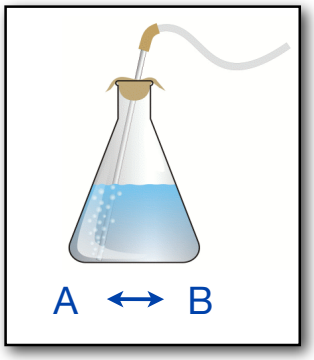
Stochastic processes

At t=0
initial state distribution $S_0 = [1.0, 0.0]$

e.g. a measurement every 30 minutes

Probability that A has converted to B after time τ

t(A→B) = 0.8
t(B→A) = 0.4



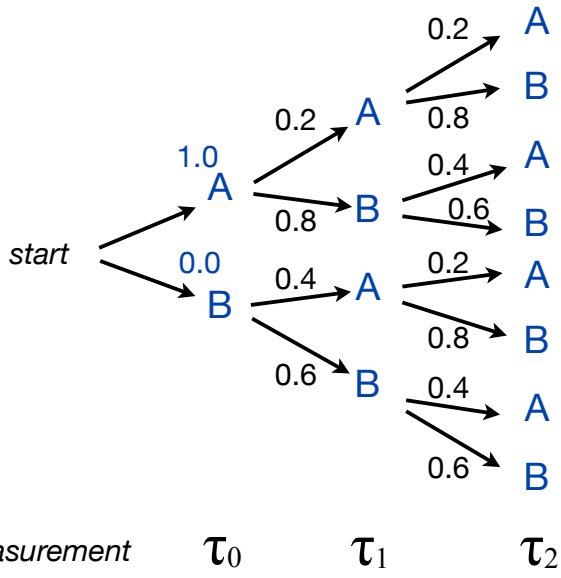
Transition matrix:

current state

$$T = \begin{bmatrix} 0.2 & 0.8 \\ 0.4 & 0.6 \end{bmatrix} \begin{matrix} A \\ B \end{matrix}$$

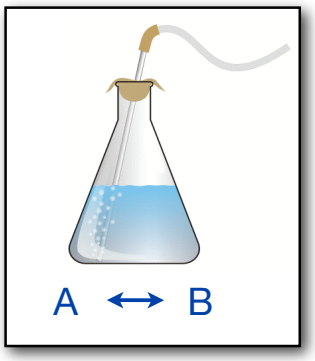
A B ← *next state*

Stochastic processes



$$S_0 = [1.0, 0.0]$$

$$\mathbf{T} = \begin{bmatrix} 0.2 & 0.8 \\ 0.4 & 0.6 \end{bmatrix}$$



$$S_1 = S_0 T = [1.0, 0.0] \begin{bmatrix} 0.2 & 0.8 \\ 0.4 & 0.6 \end{bmatrix} = [0.2, 0.8]$$

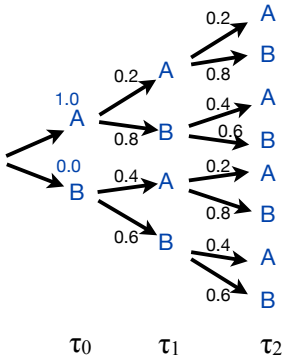
Stochastic processes

initial state distribution

$$S_0 = [1.0, 0.0]$$

transition matrix

$$\mathbf{T} = \begin{bmatrix} 0.2 & 0.8 \\ 0.4 & 0.6 \end{bmatrix}$$



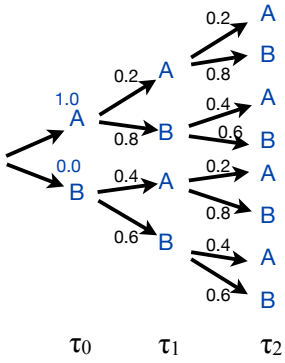
How does the distribution change in time?

$$S_1 = S_0 \mathbf{T} = [1.0, 0.0] \begin{bmatrix} 0.2 & 0.8 \\ 0.4 & 0.6 \end{bmatrix} = [0.2, 0.8]$$

$$S_2 = S_1 \mathbf{T} = [0.2, 0.8] \begin{bmatrix} 0.2 & 0.8 \\ 0.4 & 0.6 \end{bmatrix} = [0.36, 0.64]$$

$$S_3 = S_2 \mathbf{T} = [0.36, 0.64] \begin{bmatrix} 0.2 & 0.8 \\ 0.4 & 0.6 \end{bmatrix} = [0.328, 0.672]$$

Stochastic processes



How does the distribution change in time?

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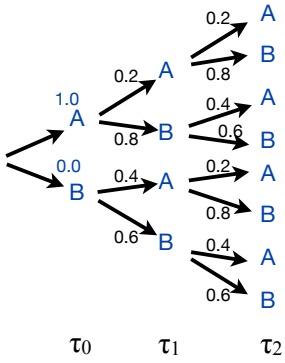
$$S_2 = S_0\mathbf{T}^2 = [1.0, 0.0]\begin{bmatrix} 0.2 & 0.8 \\ 0.4 & 0.6 \end{bmatrix}\begin{bmatrix} 0.2 & 0.8 \\ 0.4 & 0.6 \end{bmatrix} =$$

$$= [1.0, 0.0]\begin{bmatrix} 0.36 & 0.64 \\ 0.32 & 0.68 \end{bmatrix} = [0.36, 0.64]$$

Stochastic processes



$$S_0 = [1.0, 0.0]$$

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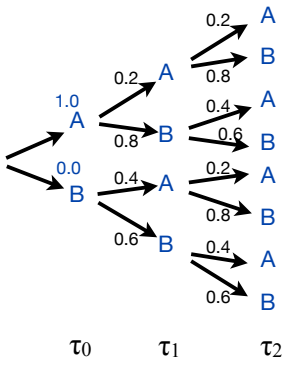
Does the distribution converge to a stable state?

Stochastic processes



$$S_0 = [1.0, 0.0]$$
$$S_1 = [0.2, 0.8]$$
$$S_2 = [0.36, 0.64]$$
$$S_3 = [0.328, 0.672]$$
$$S_4 = [0.3344, 0.6656]$$
$$S_5 = [0.33312, 0.66688]$$

$$S = \left[\frac{1}{3}, \frac{2}{3}\right]$$ *stationary matrix, steady state*

$$S\mathbf{T} = \left[\frac{1}{3}, \frac{2}{3}\right] \begin{bmatrix} 0.2 & 0.8 \\ 0.4 & 0.6 \end{bmatrix} = \left[\frac{1}{3}, \frac{2}{3}\right] = S$$

Markov process

Stochastic processes

- Poisson process:
  - number of events per time
  - no dependence between events
  - exponential decay
  - radioactive decay, earthquakes, jobs in printer queue
- Markov process:
  - stochastic process with simple relation between states X_1, X_2, X_3, X_4,...
  - probability to move to state X_{t+1} depends only on X_t (not on the past!)

formally: $P(X_{n+1=x}|X_1 = x_1, X_2 = x_2, \ldots, X_n = x_n) = P(X_{n+1=x}|X_n = x_n)$

- probability that it rains in your garden (X discrete, time continue)
- brain activity (X continue, time continue)
- game of goose, DNA base at position *t* (X discrete, “time” discrete)
- daily solar activity (X continue, time discrete)

Andrej Markov

Andrej Andrejevitsj Markov (Russisch: Андрей Андреевич Марков, Rjazan, 14 juni 1856 - Petrograd, 20 juli 1922) was een Russisch wiskundige, naar wie de Markovketens, de Markovprocessen en de Markov-ongelijkheid zijn vernoemd. Zijn zoon (1903-1979) draagt dezelfde naam en is op het gebied van de algebra, topologie, mechanica en logica eveneens een bekend Russisch wiskundige.

Markov chain

A Markov chain is a discrete time Markov process

A regular Markov chain has a regular transition matrix

A transition matrix, **T**, is regular if some power of it, $\mathbf{T}^n$, has only positive (non-zero) entries

$$\mathbf{T} = \begin{bmatrix} 0.2 & 0.8 \\ 0.4 & 0.6 \end{bmatrix}$$ *regular*

$$\mathbf{T} = \begin{bmatrix} 0.0 & 1.0 \\ 1.0 & 0.0 \end{bmatrix}$$ *not regular*

$$\mathbf{T} = \begin{bmatrix} 0.3 & 0.7 \\ 1.0 & 0.0 \end{bmatrix}$$ *regular*

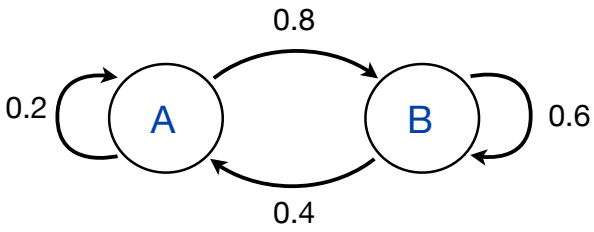
A regular Markov chain has a unique stationary state

Markov chain

Properties

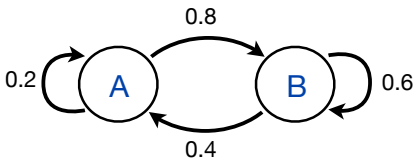
1. A regular Markov chain has a unique stationary state
2. The stationary state is found by solving: $S\,\mathbf{T} = S$
3. From any starting distribution S_0 the Markov chain will reach the stationary state
4. The matrices $\mathbf{T}^n$ approach a stationary matrix in which each row is the stationary state

Representation



Markov chain

Example, find the stationary state



$$S\,\mathbf{T} = S$$

$$S\,\mathbf{T} = [S_1, S_2] \begin{bmatrix} 0.2 & 0.8 \\ 0.4 & 0.6 \end{bmatrix} = [S_1, S_2] = S$$

$$0.2S_1 + 0.4S_2 = S_1$$
$$0.8S_1 + 0.6S_2 = S_2$$

1) and 2) are linear dependent

$$S_1 + S_2 = 1$$

3) extra rule: probabilities add up to 1

$$S_1 = 1/3$$
$$S_2 = 2/3$$

Markov chain

Other properties:

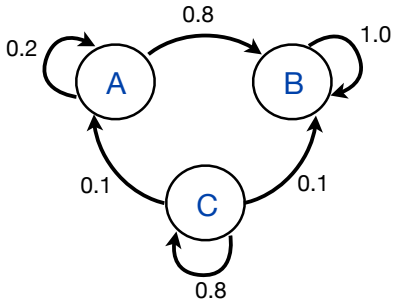
Time homogeneous Markov chain: transition matrix is time independent (otherwise time inhomogeneous).

Absorbing Markov chain: there is an absorbing state from which you cannot escape once you reach it.

n^{th} order Markov chain does not only depend on knowledge of the current state (=1st order) but also previous n-1 states.

A Markov chain is ergodic if there is a number of steps N in which each state can be reached from every other state (no loops, periodicity, absorbing state).

A Markov chain is reversible if it obeys detailed balance.



$$\mathbf{T} = \begin{bmatrix} 0.2 & 0.8 & 0.0 \\ 0.0 & 1.0 & 0.0 \\ 0.1 & 0.1 & 0.8 \end{bmatrix}$$

absorbing state: check diagonal for 1.0

Reversible Markov chains

Detailed balance

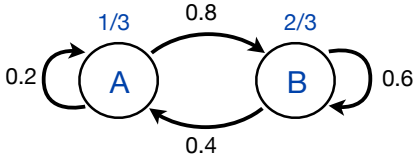
$$\rho_i \, P(X_{n+1} = j | X_n = i) = \rho_j \, P(X_{n+1} = i | X_n = j)$$

$$\rho_i \, t_{ij} = \rho_j \, t_{ji}$$

The probability be in state *i* times the probability to go to state *j* from state *i* is equal to be in state j times the probability to move from *j* to *i*.

The probability to be in state i, ρ_i , is an element of the equilibrium (stationary) state distribution S.

Example Reversible MC



$$\frac{1}{3} * 0.8 = \frac{2}{3} * 0.4$$

Detailed balance holds!

Reversible Markov chains

Example

$$\mathbf{T} = \begin{bmatrix} 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 \end{bmatrix}$$

transition matrix

Detailed balance

$$\rho_i \, t_{ij} = \rho_j \, t_{ji}$$

$$S = [0.25, 0.25, 0.25, 0.25]$$

stationary state solution

Detailed balance does not hold!

See also a chain sample: ...ABCDABCDABCD...
Reverse B–>C transitions do not occur.

Mind you, if the stationary state solution is uniform so that

$$\rho_i = \rho_j \, \forall \, i \neq j \longrightarrow t_{ij} = t_{ji}$$

then the transition matrix should be symmetric for a reversible MC

For a reversible Markov chain it is not possible to determine the direction of the process from the observed state sequence alone.

Chapman-Kolmogorov

Transition matrix **T**
An element of **T** gives the transition probality:

$$t_{ij} = P(X_{n+1} = j | X_n = i)$$

The probability of going from state i to state j in *k* time steps is:

$$t_{ij}^{(k)} = P(X_{n+k} = j | X_n = i)$$

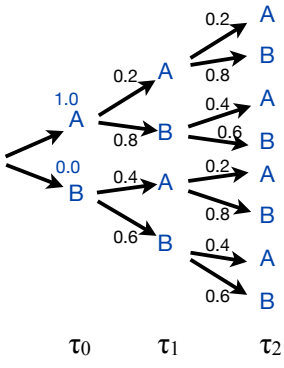
The Chapman–Kolmogorov equation says that for any *m* such that 0 < *m* < *k*,

$$p_{ij}^{(k)} = \sum_{r \in Z} p_{ir}^{(m)} p_{rj}^{(k-m)}$$

with the sum over all intermediate states *r* in the state space *Z*.

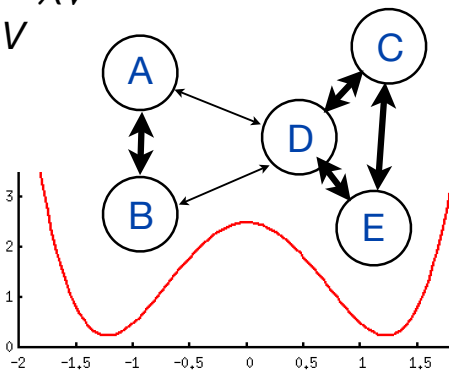
$$\mathbf{T} = \begin{bmatrix} 0.2 & 0.8 \\ 0.4 & 0.6 \end{bmatrix}$$

$$\mathbf{T}^{(k)} = \mathbf{T}^k$$



Spectral decomposition

Transition matrix **T** of dimension *d*
has *d* solutions of the linear equation: $\mathbf{T}\,V = \lambda V$
each with an eigenvalues λ with eigenvector *V*



Factorizing **T** in: $\mathbf{T} = \mathbf{V}\mathbf{\Lambda}\mathbf{V}^{-1}$

in which **Λ** is the diagonal matrix of eigenvalues, which can be ordered:

$$1 = \lambda_1 > |\lambda_2| \geq |\lambda_3| \geq \cdots \geq |\lambda_N| > 0$$

- Spectral decomposition allows to analyze how the system relaxes to equilibrium
- Eigenvalues close to 1 and significantly larger than the other eigenvalues indicate one or more slow relaxation times and metastability (rare events) between states.

Summary

part 1

A stochastic hopping between states is Markovian if the probability to reach the next state does not depend on the past (no memory)

- reversible Markov chains (detailed balance)
- ergodicity
- spectral decomposition (convergence to equilibrium)

Content

- Lecture 1: Markov processes
- Lecture 2: State clustering
- Lecture 3: Transition Path Theory
- Lecture 4: Sampling Reactive Events

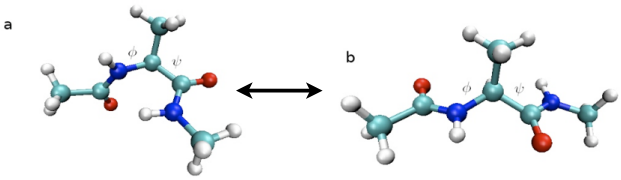
MSM of peptide dynamics

Markov State Modeling applied as analysis tool of the dynamics of a small peptide

- Analysis of molecular dynamics simulation
- Clustering based on structures
- Relation to free energy landscape
- Transition probability between clusters (states)

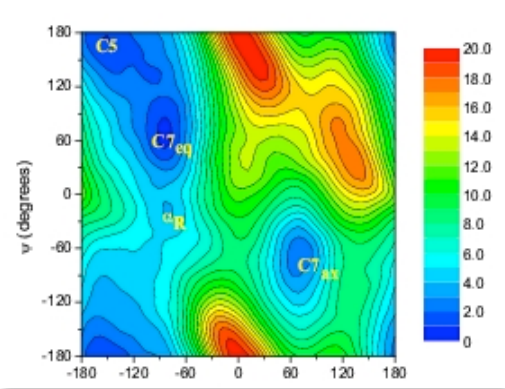
Is peptide dynamics Markovian?

How does a peptide (or protein) dynamically behave?



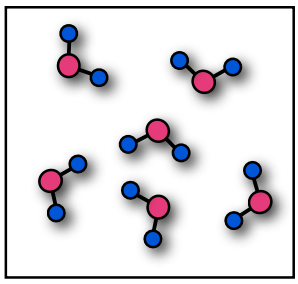
- can I distinguish characteristic structures/states?
- does it visit all states equally often?
- is there an order in visiting states?
- how do I know if it visited all possible states?
- can I compute the probability to visit a state?
- can I compute the probability to go from 1 state to any other state?

dipeptide



hexamer

FES of 12 torsions?



atom positions and velocities

$$r(t + \Delta t) = r(t) + v(t + \Delta t/2)\Delta t$$
$$v(t + \Delta t/2) = v(t - \Delta t/2) + \Delta t \frac{f(t)}{m}$$

Molecular Dynamics

Newtonian dynamics

$$f = m \cdot a$$
$$f = -\nabla V(r)$$

$$\Delta t \approx 1\,\text{fs} = 0.000000000000001\,\text{sec}$$

forcefield

$$V(\mathbf{r}) = \sum_{bonds} k_r(r - r_{eq})^2 + \sum_{angles} k_\theta(\theta - \theta_{eq})^2 + \sum_{dihedrals} \frac{1}{2}\nu_n(1 + cos(n\phi - \phi_0)) + \sum_{i<j} \left(\frac{a_{ij}}{r_{ij}^{12}} - \frac{b_{ij}}{r_{ij}^{6}} + \frac{q_i q_j}{\epsilon r_{ij}} \right)$$

bonds bends torsions non-bonded

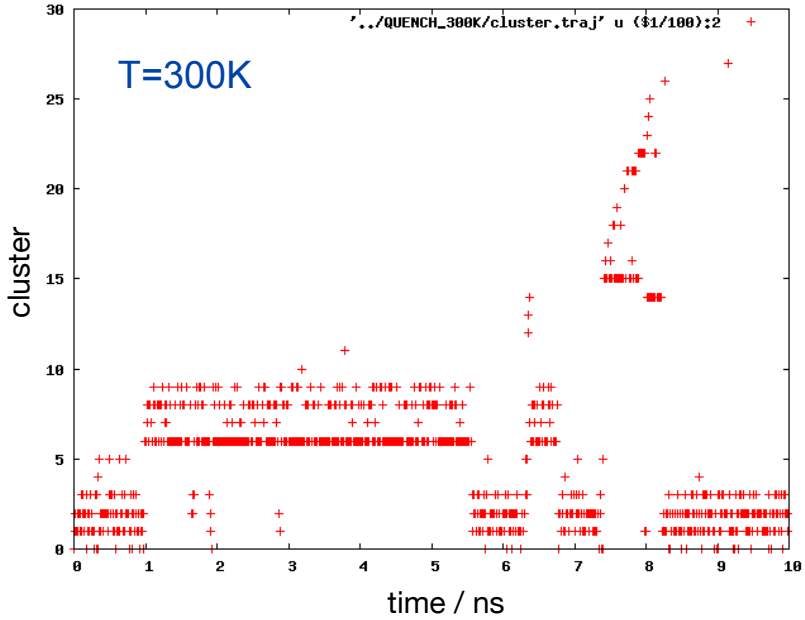
Cluster analysis

- 3x 10-20 ns simulations at T= 300, 400, and 500 K
- take a frame every 10 ps and quench in to zero Kelvin
- cluster quenched frames based on torsion angles

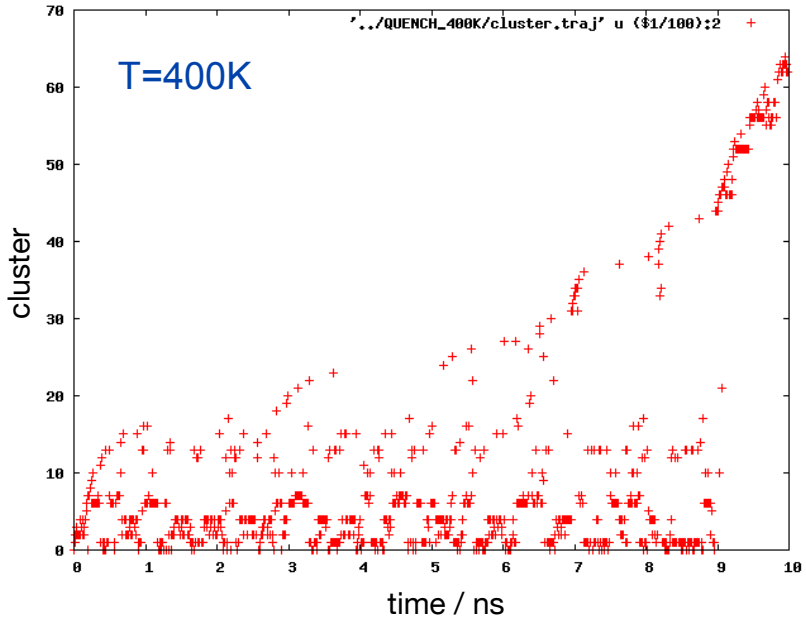
Clustering of structures based on resemblance between observed geometries in the trajectory,
e.g. RMSD(R_i,R_j) < TOLL

many flavors of clustering methods exist
typically involves an iterative procedure over the trajectory

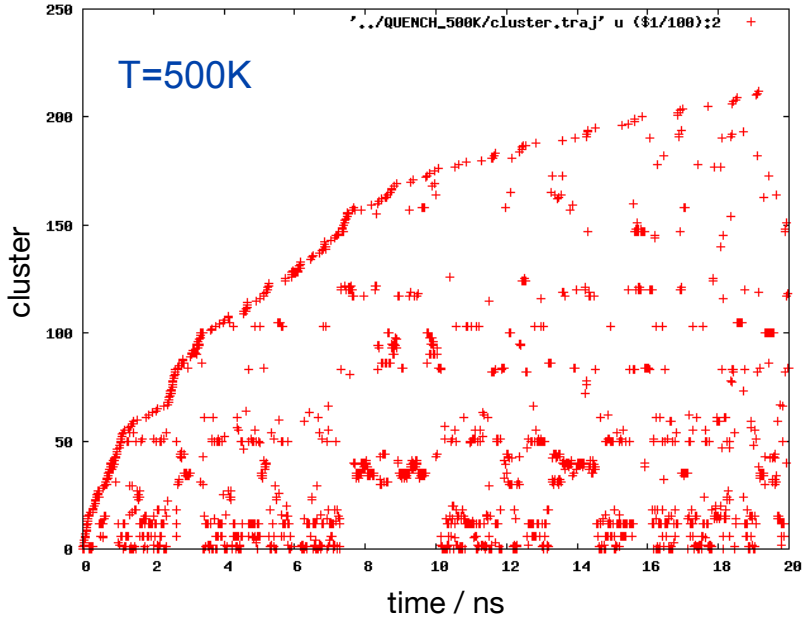
Cluster analysis



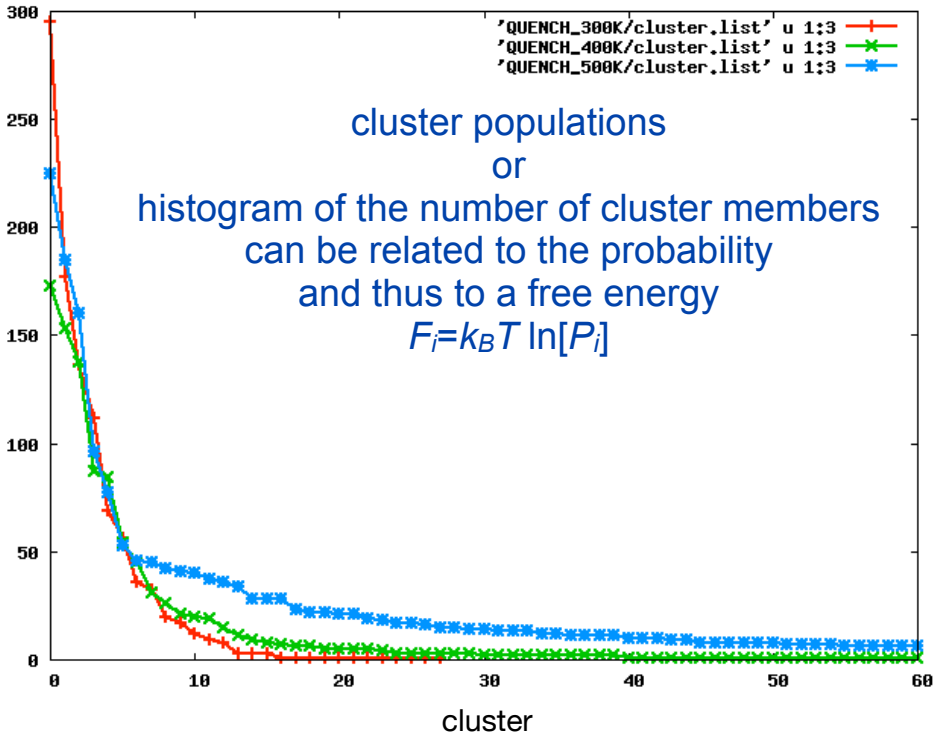
Cluster analysis



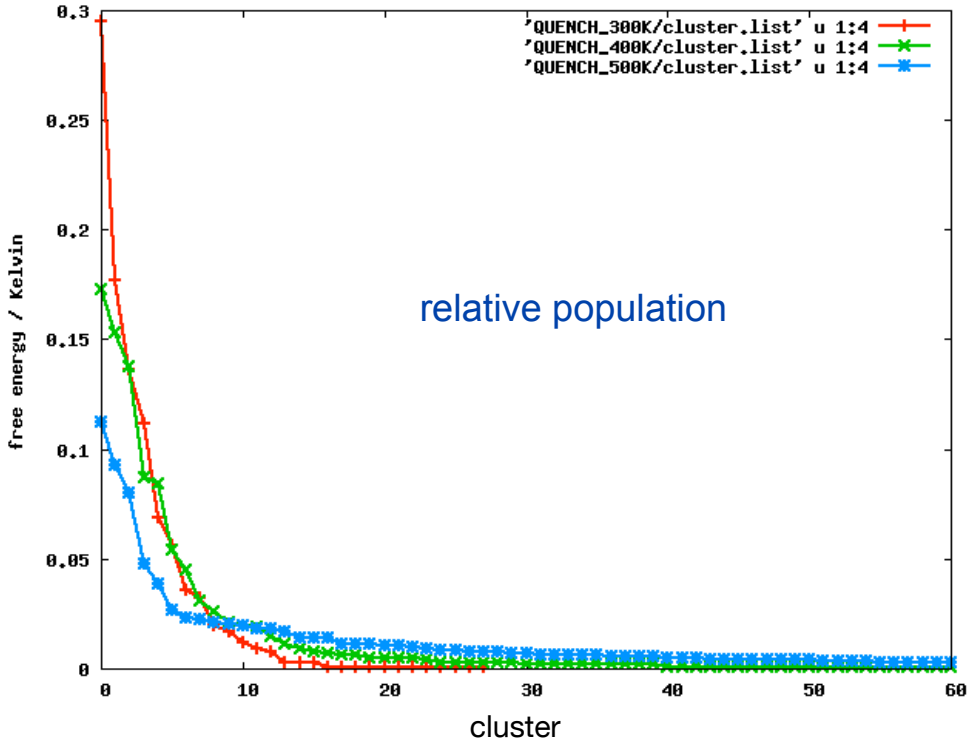
Cluster analysis



Cluster analysis



Cluster analysis



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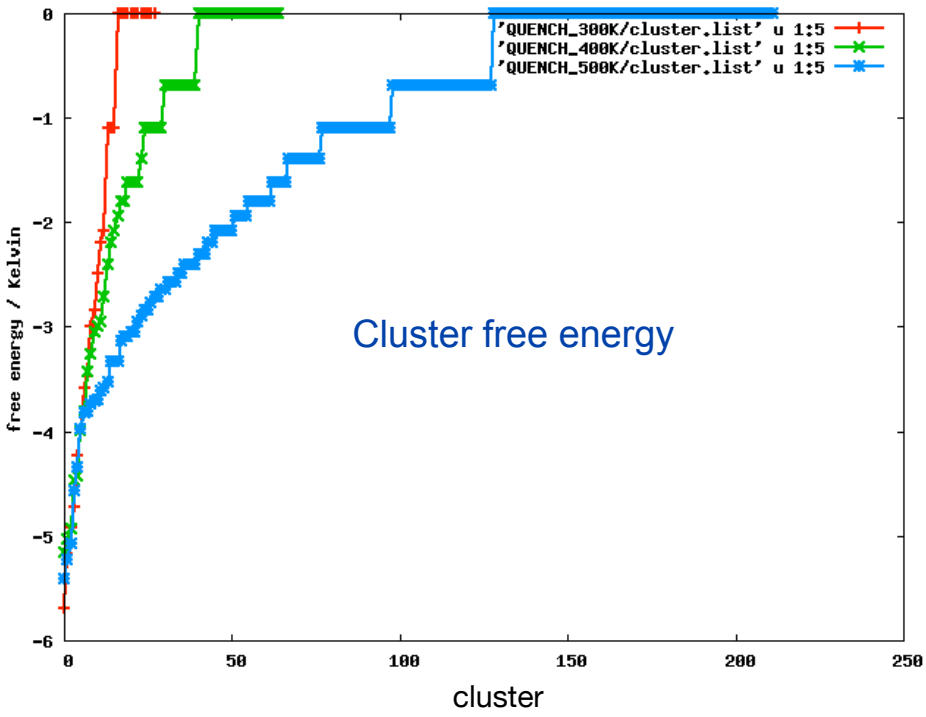
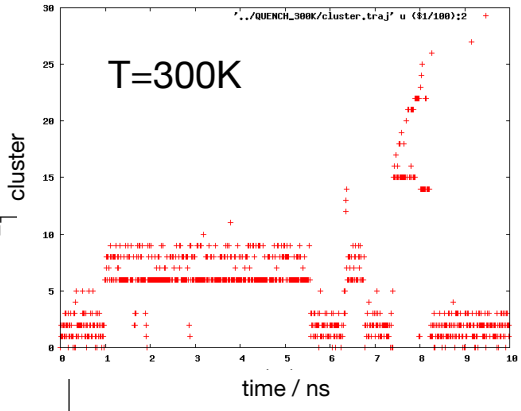
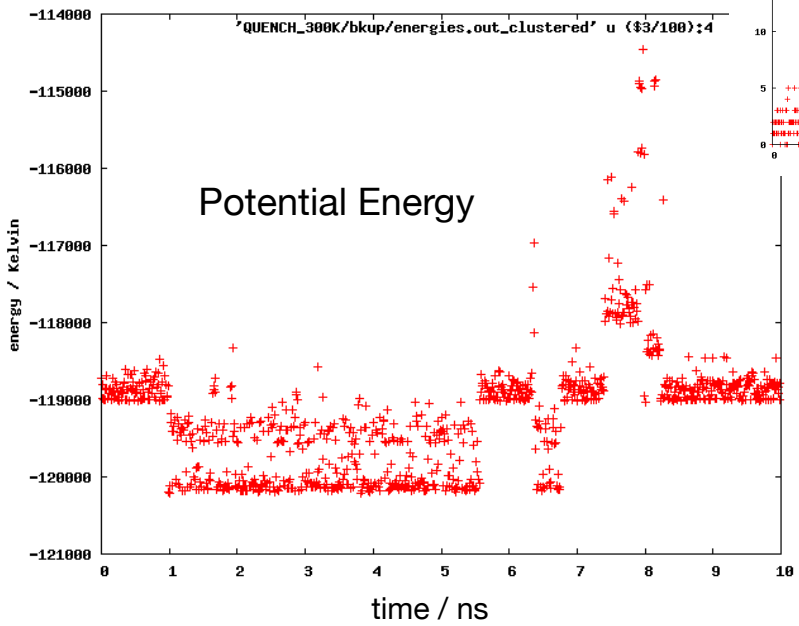
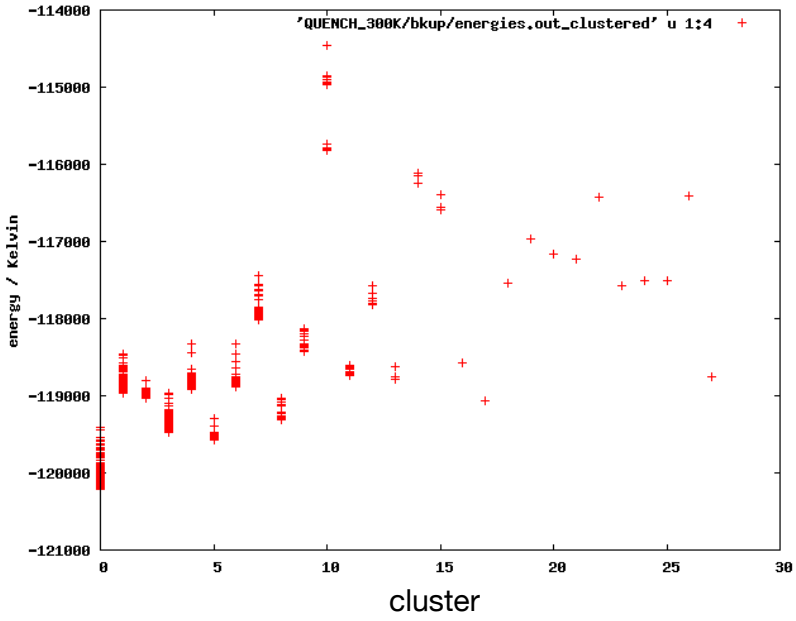


Do clusters with most members have the lowest potential energy?



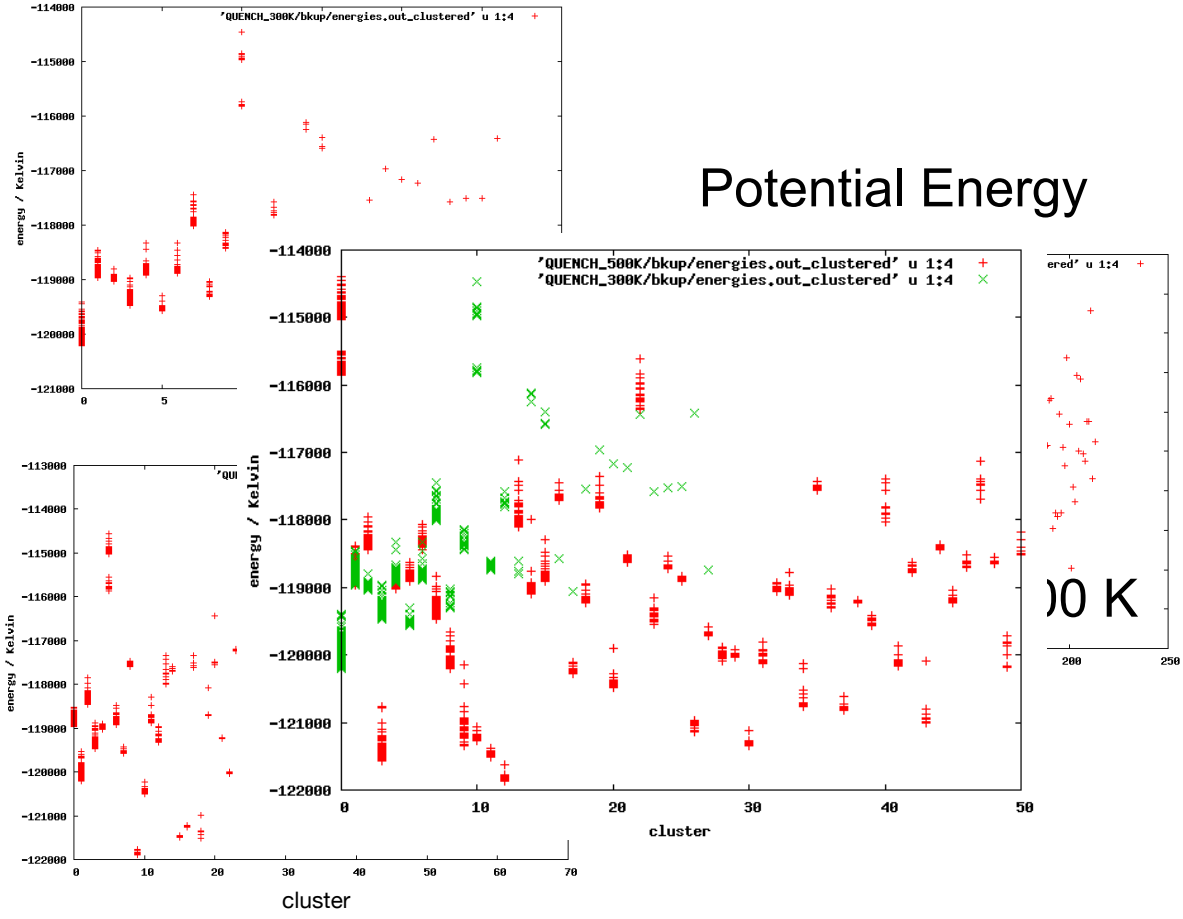


T=300K Potential Energy

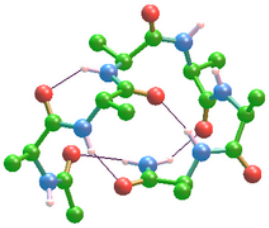


There is a correlation (cluster 1 has lowest E, but cluster 2 not second lowest).
Correlation not perfect, total energy not full story...

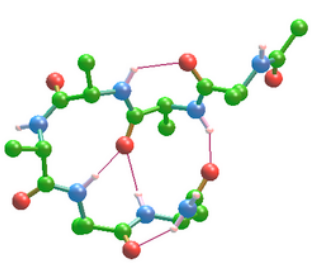
Potential Energy



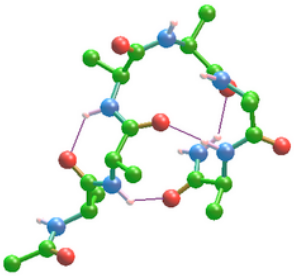
Cluster structures



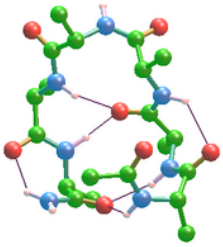
cluster 0



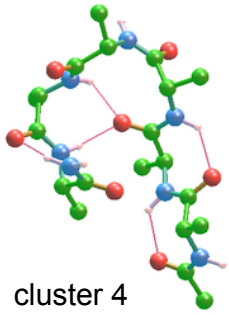
cluster 1



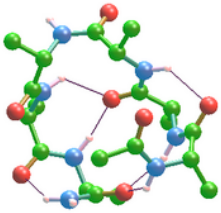
cluster 2



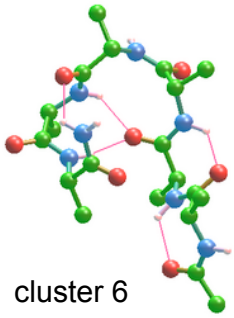
cluster 3



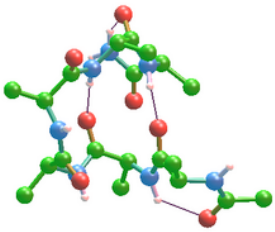
cluster 4



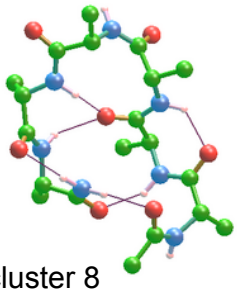
cluster 5



cluster 6



cluster 7



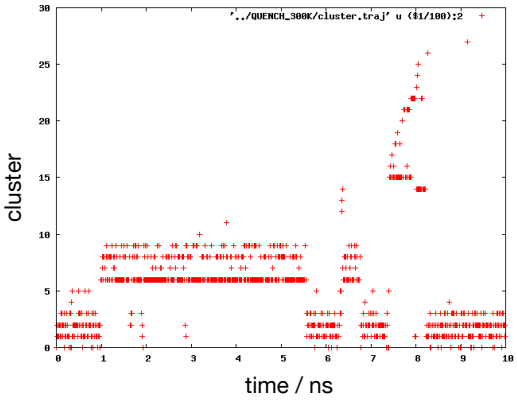
cluster 8

Cluster Dynamics

Transition matrix

Average Connection Frequency:

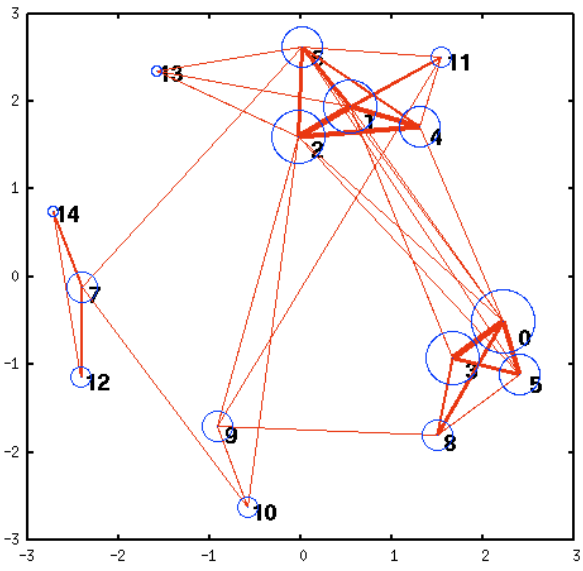
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
0	1	1	1	127	2	78	1	0	22	0	0	0	0	0	0
1		0	127	2	70	0	25	0	0	0	0	6	0	2	0
2			0	0	37	1	18	0	0	2	1	5	0	2	0
3				0	0	17	0	0	12	0	0	0	0	0	0
4					0	0	12	0	0	0	0	3	0	0	0
5						0	1	0	3	0	0	0	0	0	0
6							0	1	0	0	0	3	0	2	0
7								5	0	0	1	0	7	0	5
8									0	1	0	0	0	0	0
9										2	2	1	0	0	0
10											0	0	0	0	0
11												0	0	0	0
12													0	0	1
13														0	0
14															0



Free Energy Barriers:

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
0	-0.00	-0.00	-0.00	-4.84	-0.69	-4.36	-0.00	*	-3.09	*	*	*	*	*	*
1		*	-4.84	-0.69	-4.25	*	-3.22	*	*	*	*	-1.79	*	-0.69	*
2			*	*	-3.61	-0.00	-2.89	*	*	-0.69	-0.00	-1.61	*	-0.69	*
3				*	*	-2.83	*	*	-2.48	*	*	*	*	*	*
4					*	*	-2.48	*	*	*	*	-1.10	*	*	*
5						*	-0.00	*	-1.10	*	*	*	*	*	*
6							*	-0.00	*	*	*	-1.10	*	-0.69	*
7								-1.61	*	*	-0.00	*	-1.95	*	-1.61
8									*	-0.00	*	*	*	*	*
9										-0.69	-0.69	-0.00	*	*	*
10											*	*	*	*	*
11												*	*	*	*
12													*	*	-0.00
13														*	*
14															*

Network diagram



circle size: free energy of cluster

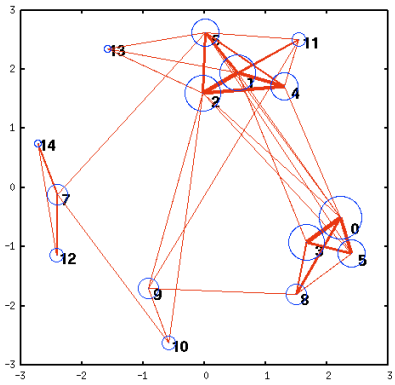
line thickness: transition probability

We can think of the peptide dynamics as a Markov chain at different levels:

- 14 small states
- 4 combined states

A Markov model

Are we allowed to apply a Markov model for analysis?
(mind you, the molecular dynamics was deterministic (not stochastic)).



We assume that the system jumps from state to state in a stochastic manner

- i.e. there is a separation of timescales such that the system stays long enough in metastable state to loose memory of the previous state ($\tau_{ij} >> \tau_{relax}$)

If the cluster analysis is not converged, we may find that the Markov chain is not reversible...

The Markov model can be stochastically sampled using Langevin dynamics, kinetic Monte Carlo, Fokker-Planck,....

Summary

part 1

A stochastic hopping between states is Markovian if the probability to reach the next state does not depend on the past (no memory)

- reversible Markov chains (detailed balance)
- ergodicity
- spectral decomposition (convergence to equilibrium)

part 2

Markov State Modeling applied as analysis tool of the dynamics of a small peptide

- Analysis of molecular dynamics simulation
- Clustering based on structures
- Relation to free energy landscape based on cluster size
- Transition probability between clusters (states)
- Using the MSM the dynamics can be sampled in a coarse-grain manner, e.g. using kinetic Monte-Carlo