The decisive role of water in elementary conformational transitions of a peptide

Dmitry Nerukh

Aston University
Birmingham

Motivation

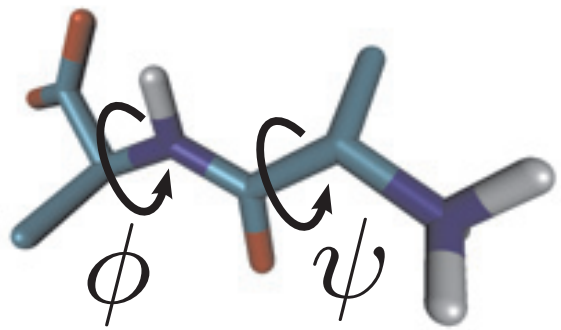
All biomolecular processes happen in solution: water is a key player.

Frauenfelder *et al* [1] have experimentally shown that protein conformational motions are slaved by water.

The protein molecule provides an 'active matrix' necessary for guiding the water's dynamics towards the biologically relevant conformational changes (the proteins 'function' or folding).

[1] H. Frauenfelder, et al, *PNAS*, **106**, 512 (2009)

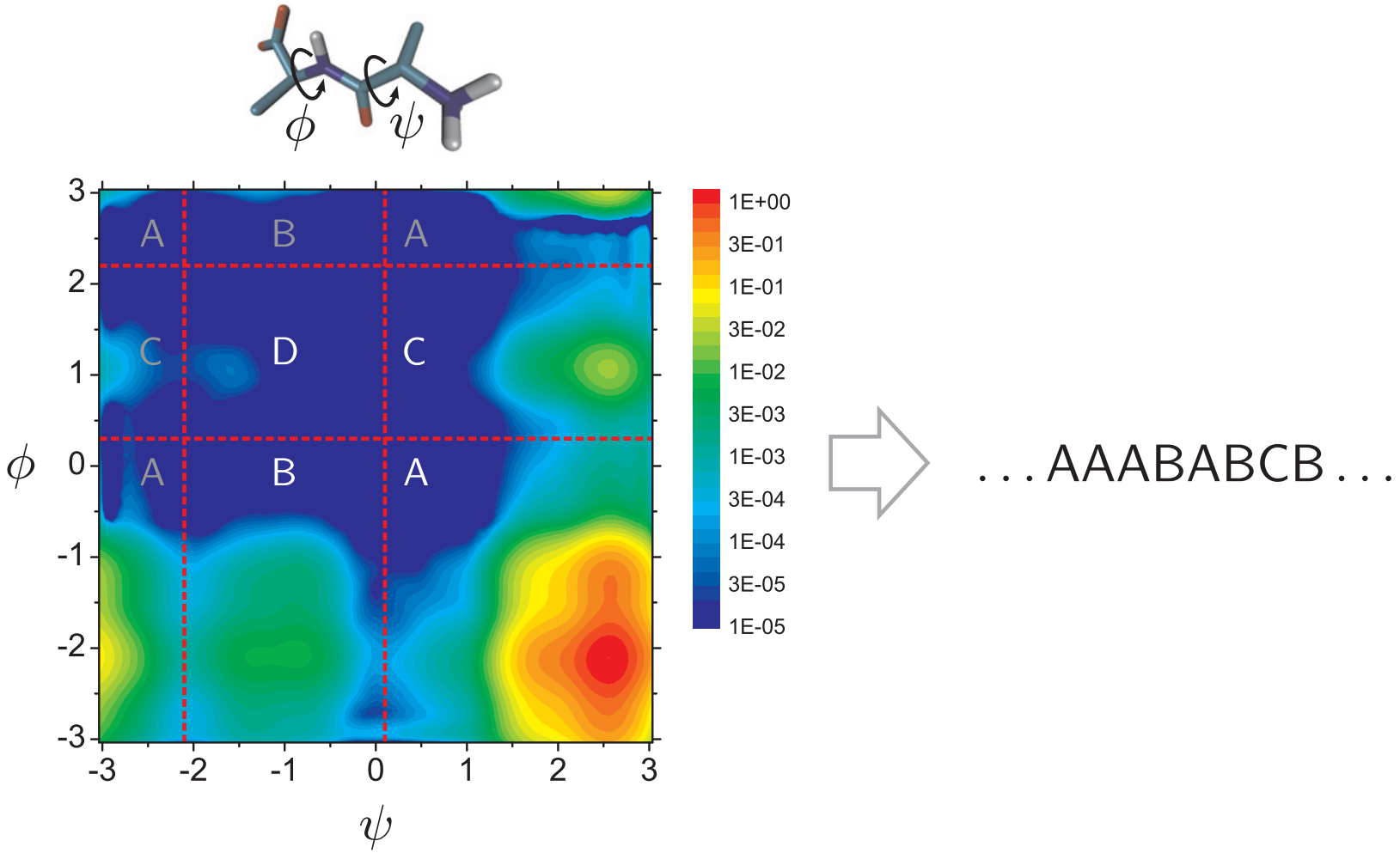
L-alanyl-L-alanine zwitterion



We do classical MD in explicit water.

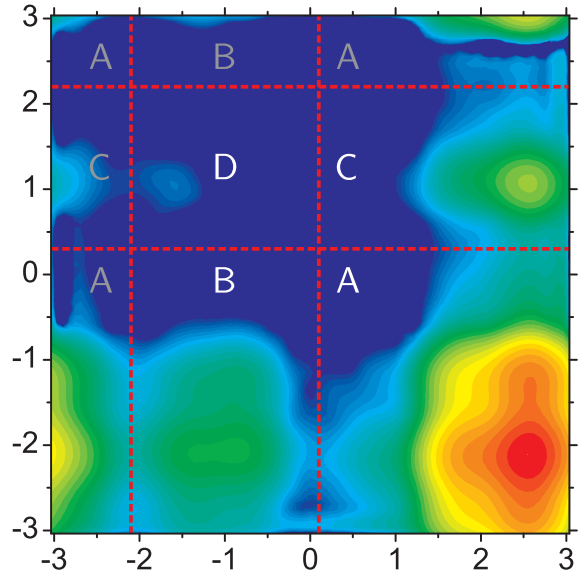
The conformational changes of the peptide is the focus of the investigation.

L-alanyl-L-alanine zwitterion conformational dynamics



Probabilities of conformations for a 1μs trajectory and its symbolisation

Markov State Model



s_i \ s_{i+1}	A	B	C
A	0.997	0.002	0.001
B	0.261	0.737	0.002
C	0.097	0.001	0.901

The time step is $6ps$.

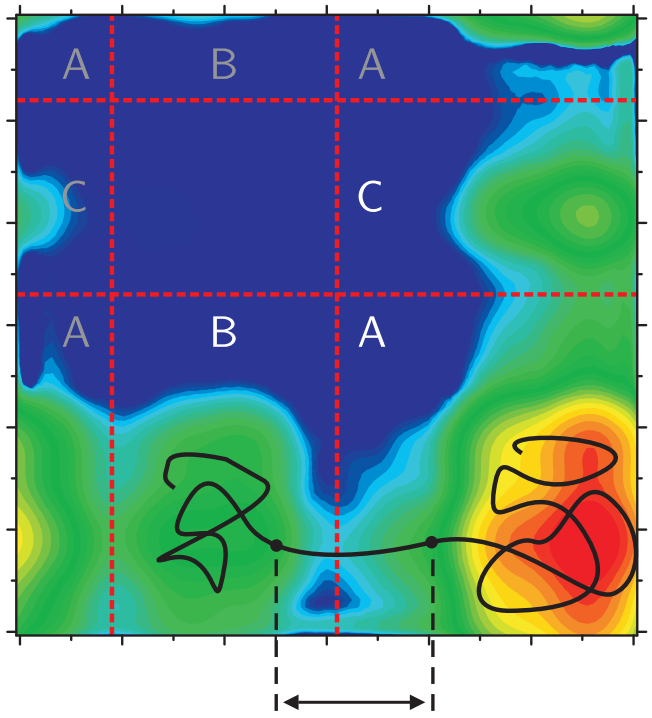
Markov State Model

A transition is when symbol 'A' at time step i changes to symbol 'B' at time step $i+1$.

s_{i+1} / s_i	A	B	C
A	0.997	0.002	0.001
B	0.261	0.737	0.002
C	0.097	0.001	0.901

$A \rightarrow B$ happens once in $2.8ns$ on average.

Markov State Model



Markov State Model is valid only for time steps longer than the length of the transition process.

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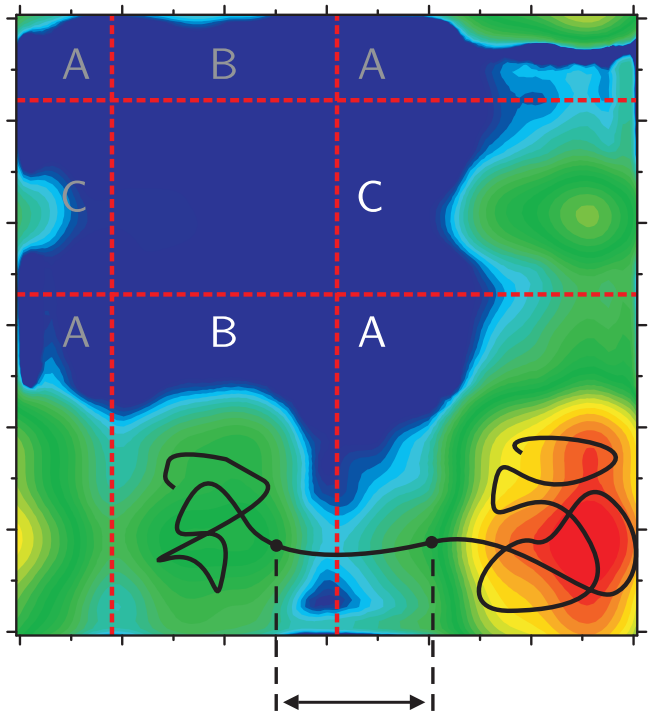

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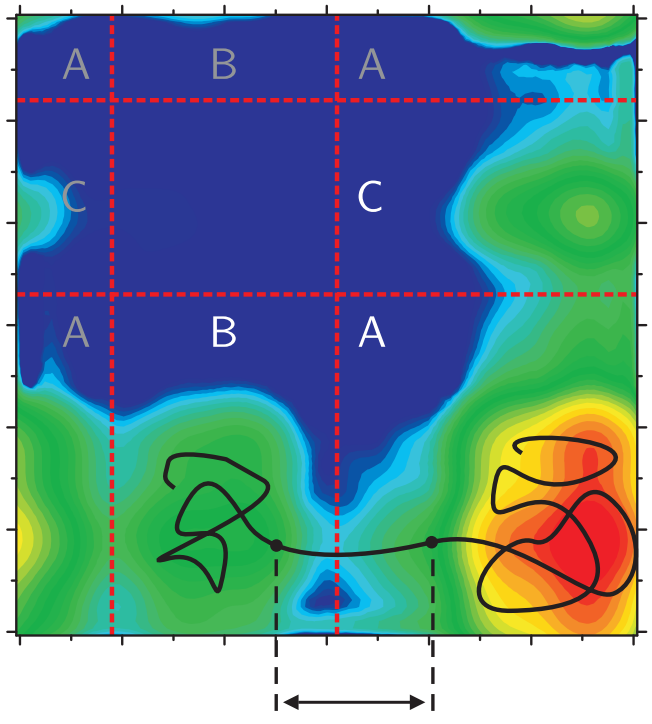

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It does not say anything about *how* and *why* the transitions happen.

Solution: build a model that works for smaller time steps.

Hidden Markov model

Instead of the conformational states, s_i, themselves (A,B,C) we consider the l-long *sequences* of states $\overleftarrow{s}_i \equiv \{s_{i-(l-1)} \ldots s_{i-2} s_{i-1} s_i\}$.

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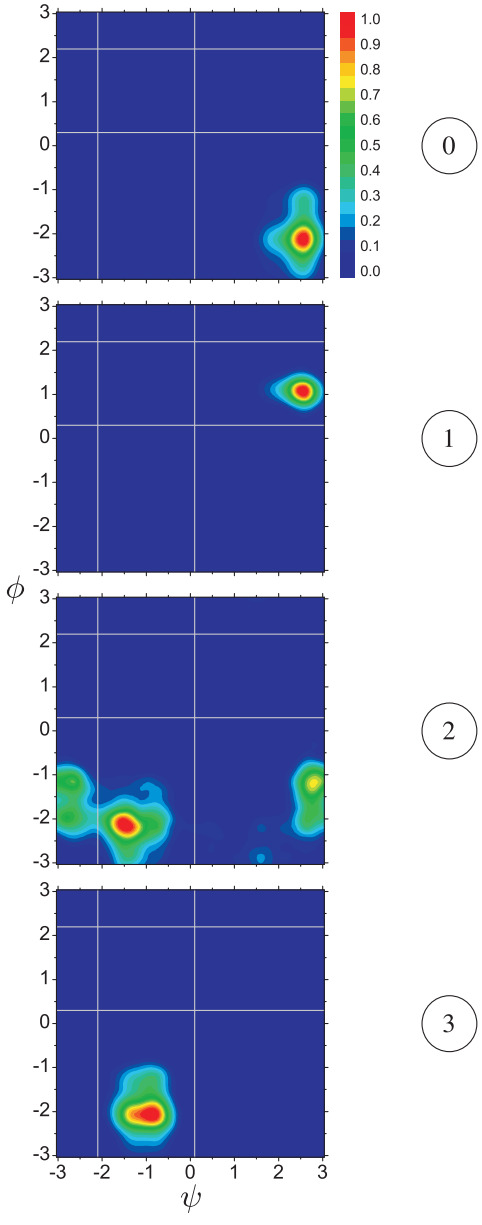
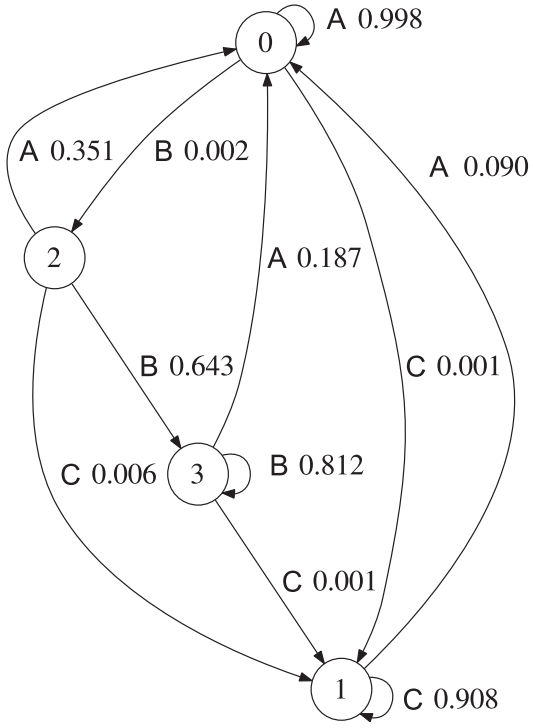
There are at most 3^l such states.

We build a Markov model on these states.

Hidden Markov model





For $5ps$ time step the model converges at $l = 2$.

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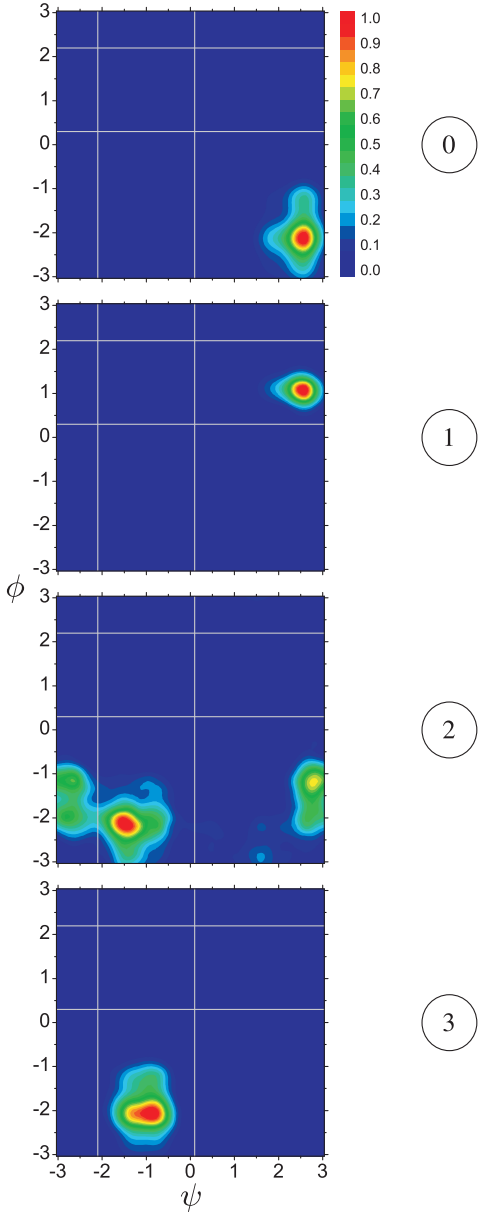
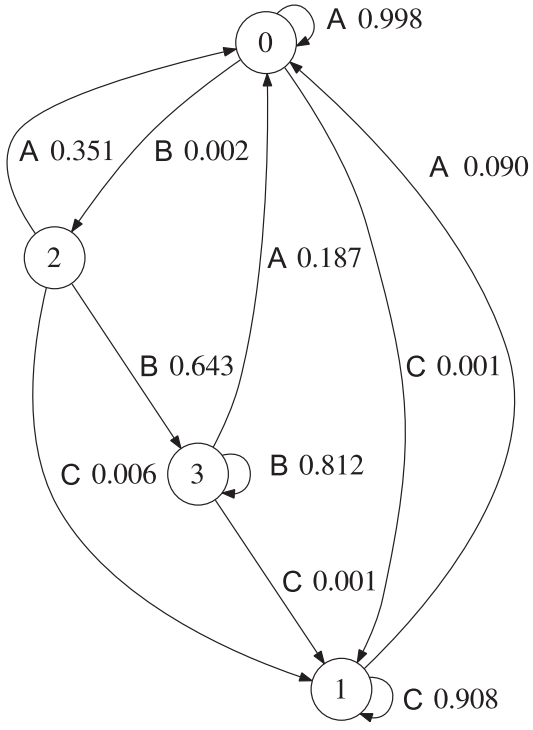
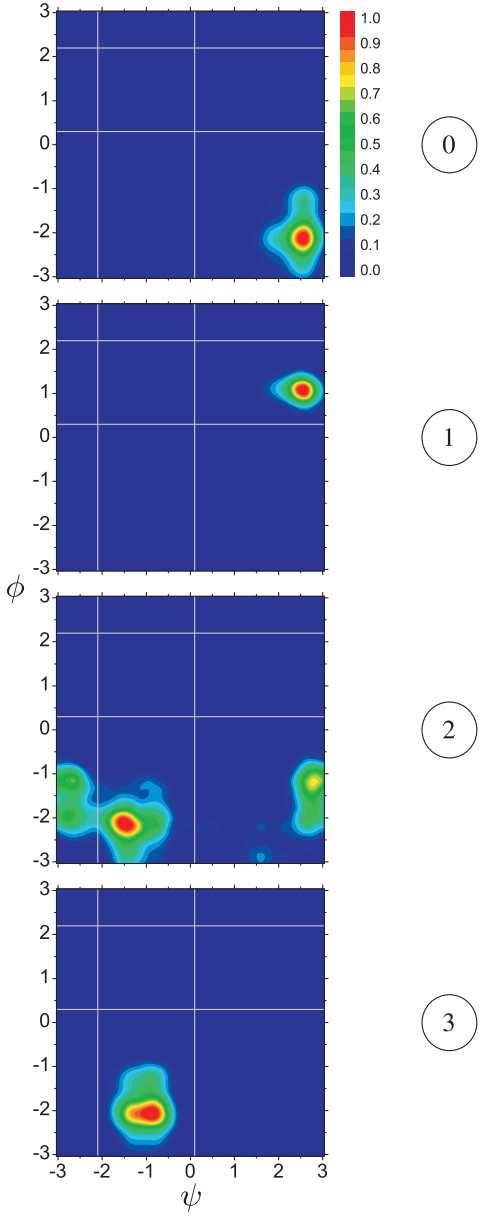
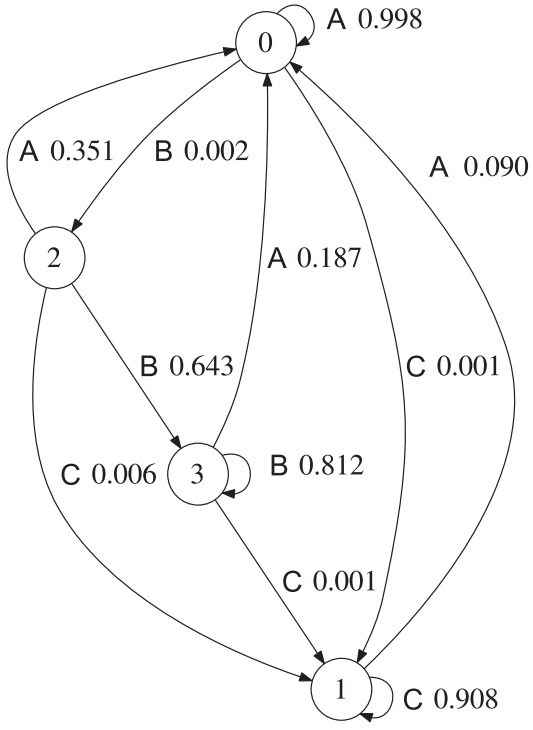




For $5ps$ time step the model converges at $l = 2$. State '0' corresponds to the original state 'A': it consists of the sequences 'AA'.

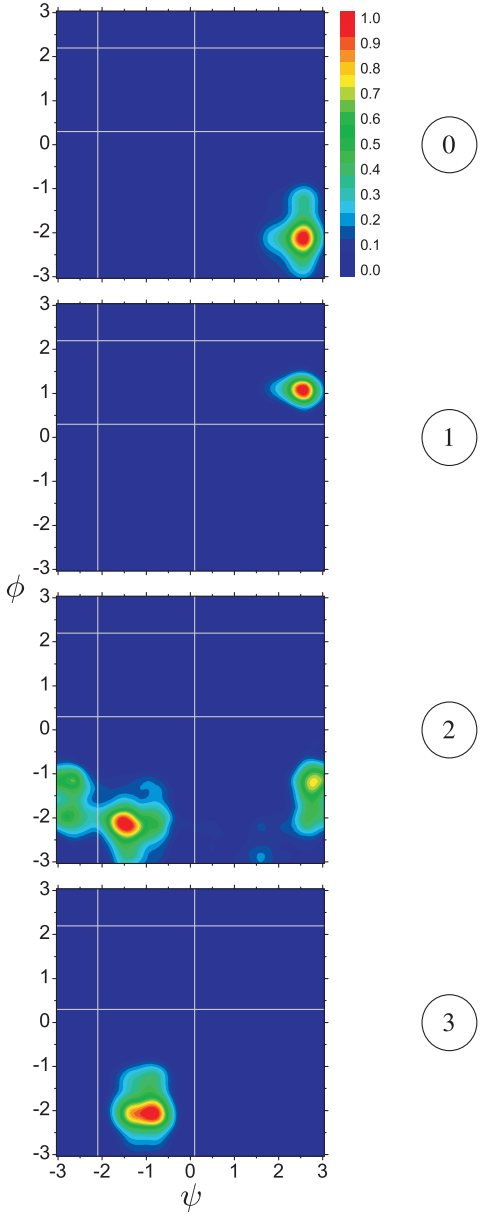
Hidden Markov model

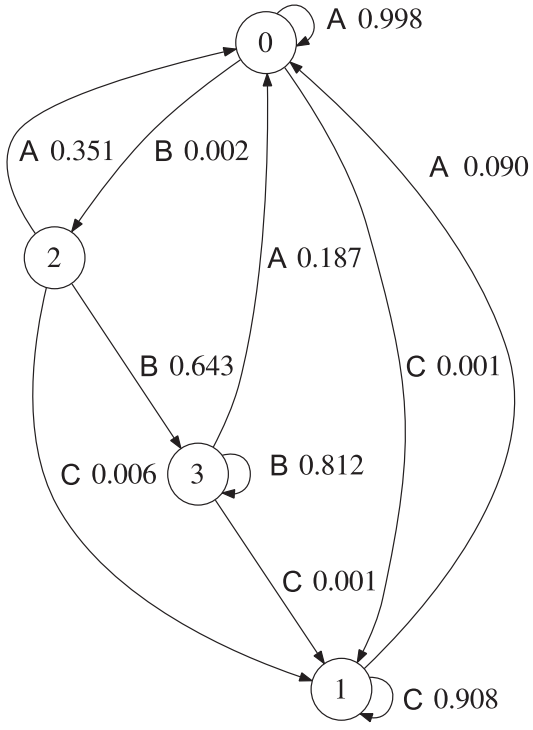




For $5ps$ time step the model converges at $l = 2$.
State '0' corresponds to the original state 'A':
it consists of the sequences 'AA'.
State '3' corresponds to 'B'.

Hidden Markov model

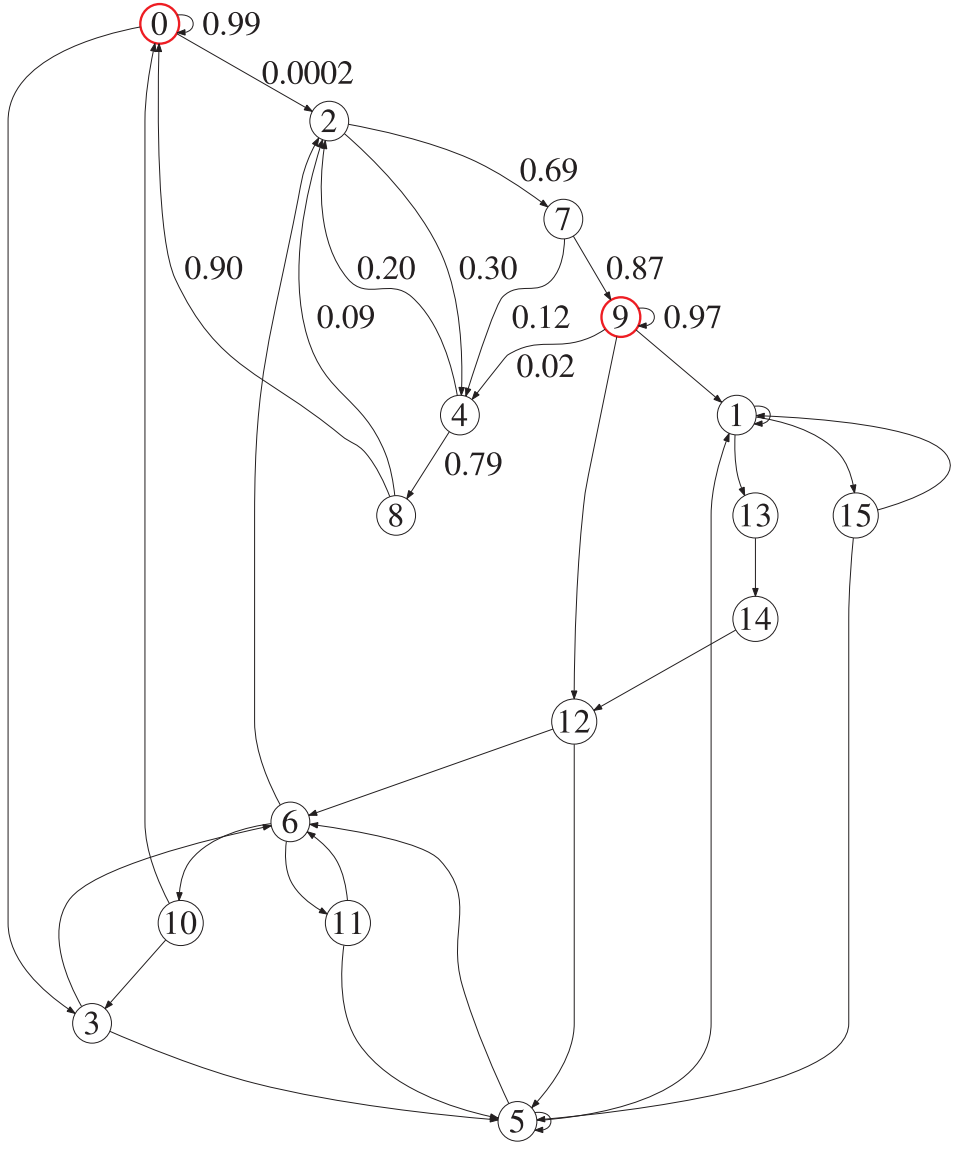




For $5ps$ time step the model converges at $l = 2$.
State '0' corresponds to the original state 'A': it consists of the sequences 'AA'.
State '3' corresponds to 'B'.
State '2' (sequences 'AB') describes the transition between 'A' and 'B'.

Hidden Markov model

For the time step $0.3ps$ the states are Markov for $l \geq 4$.



Hidden Markov model

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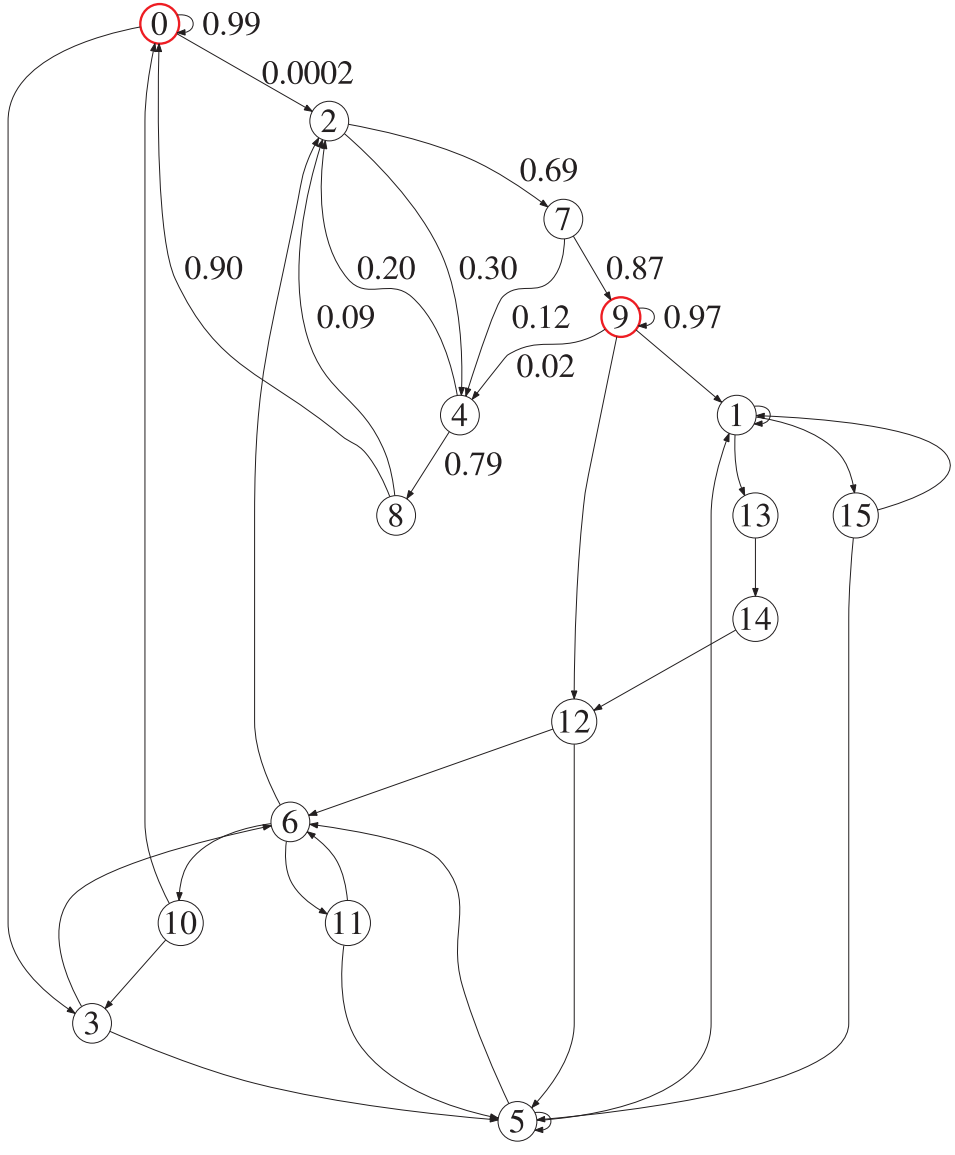
State '0' corresponds to the original state 'A': it consists of the sequences $AAAA$.

State '9' corresponds to 'B'.



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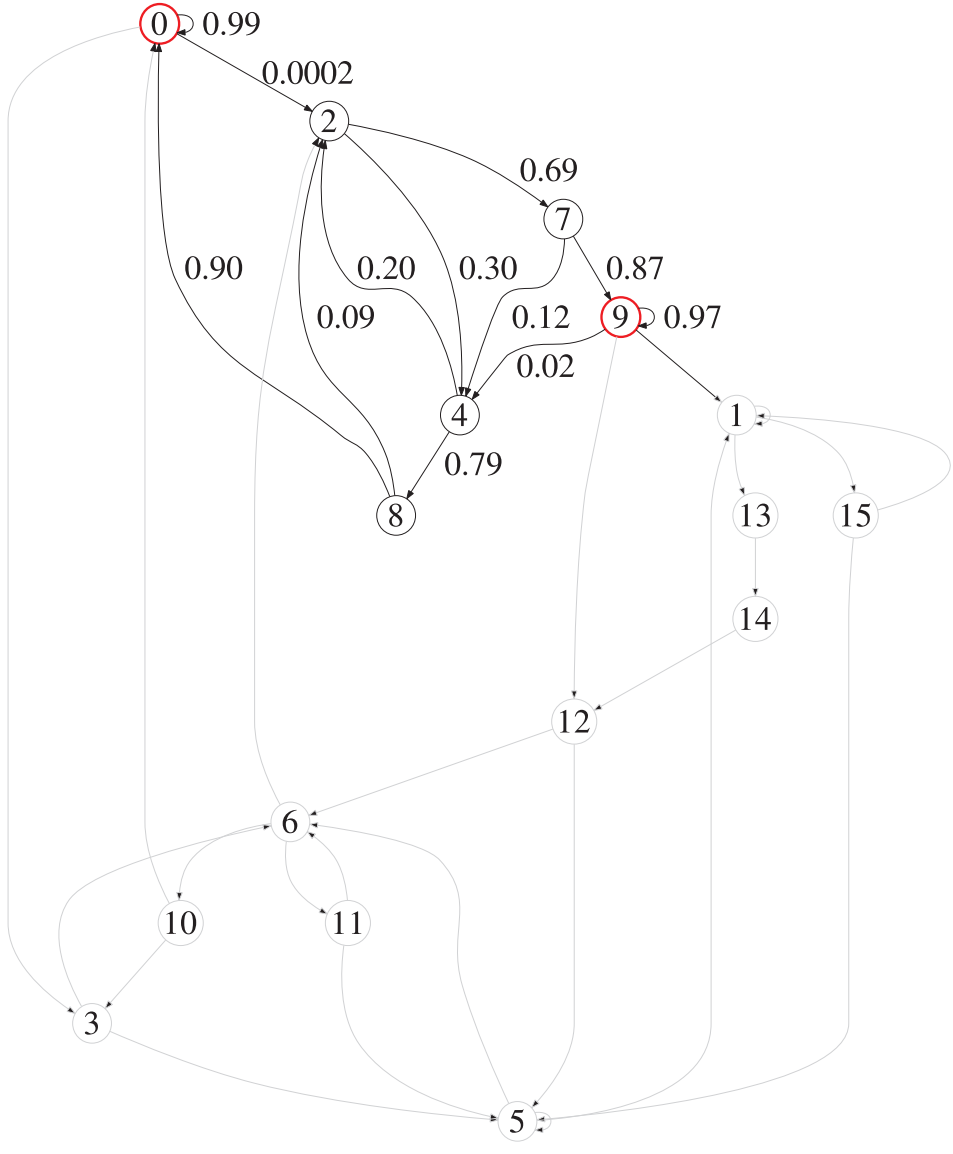
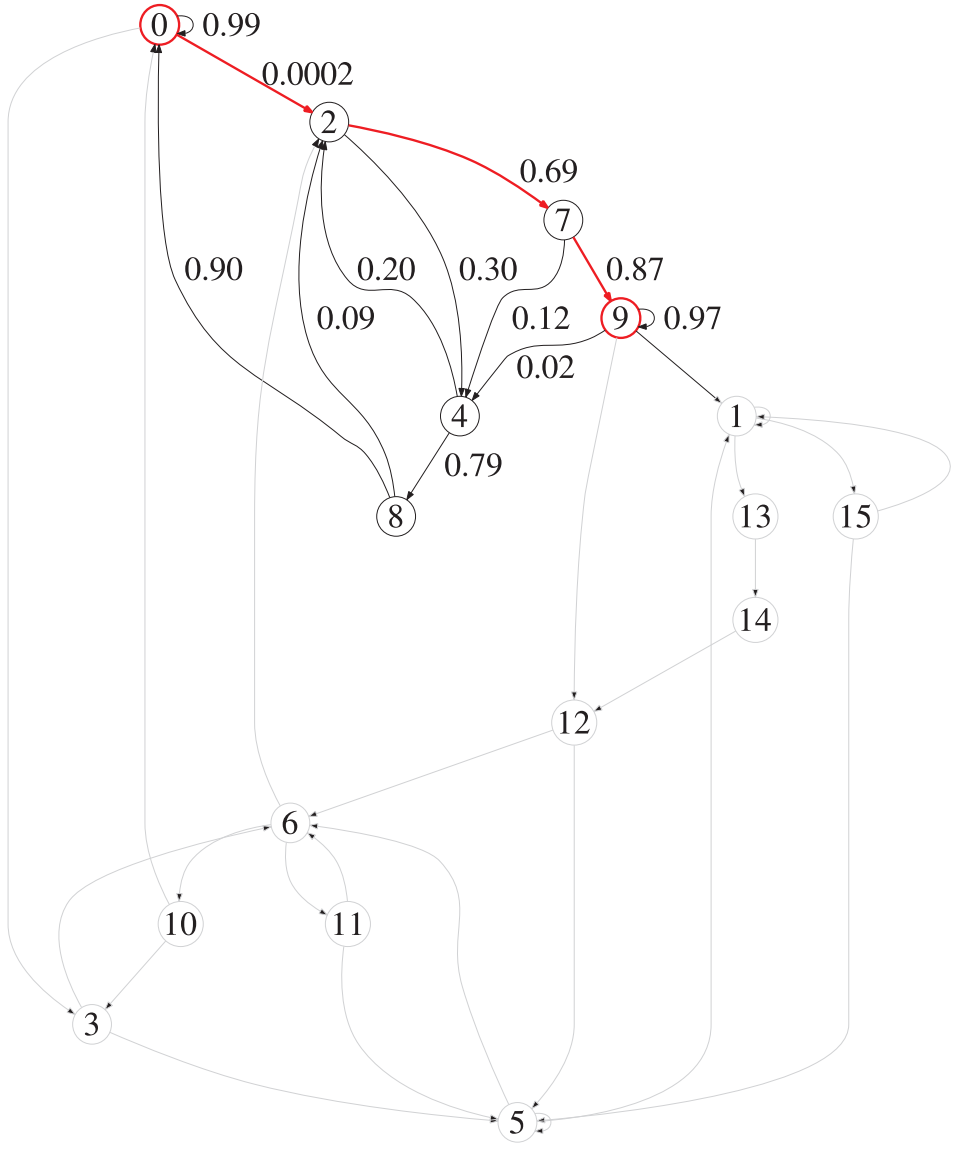
State '9' corresponds to 'B'.

The states '$2, 7, 4, 8$' are the transition states, they describe the mechanism (pathways) of the transition.



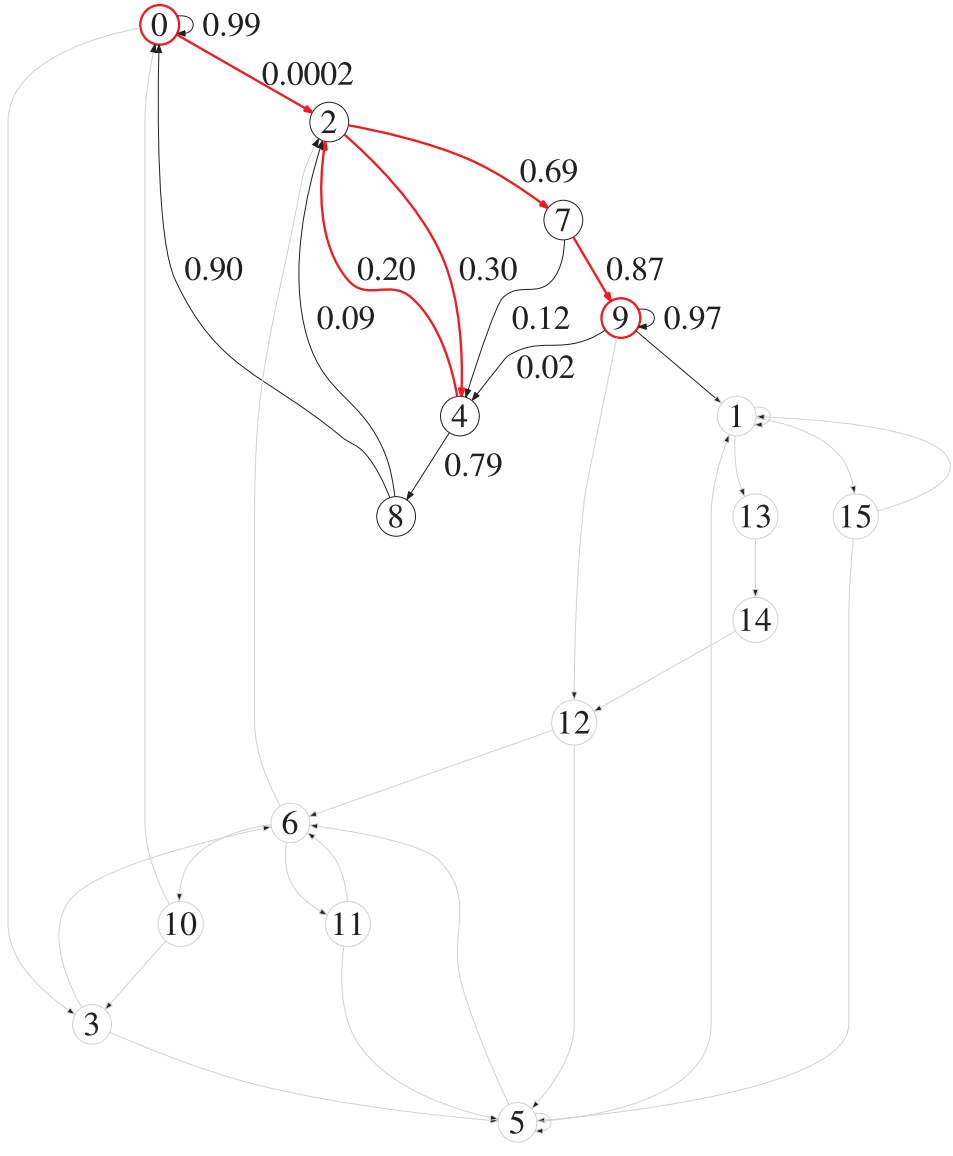
Hidden Markov model

Direct transition
(probability: 0.61)



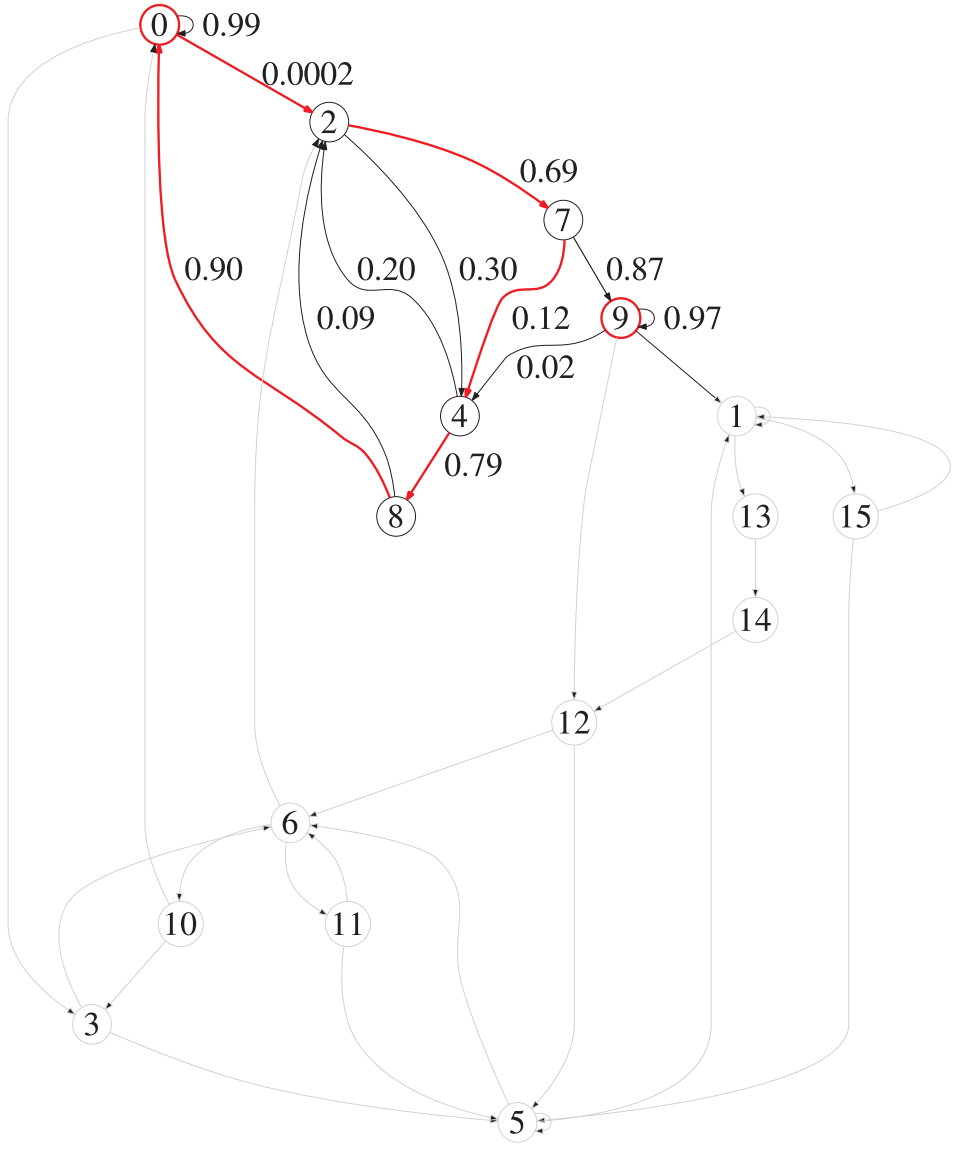
Hidden Markov model

With several recrossings
(probability: 0.04)



Hidden Markov model

Failed attempts of transition (probability: 0.07)



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Thus, we can identify the transitions with the precision of $0.3ps$.

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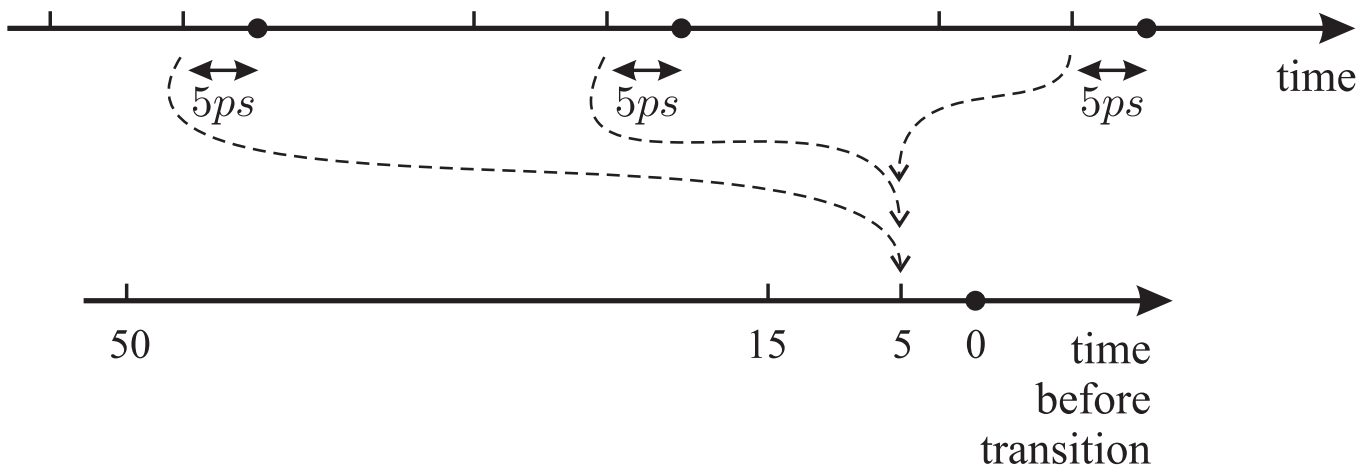
We collect the time frames at specific times *before* the transitions.



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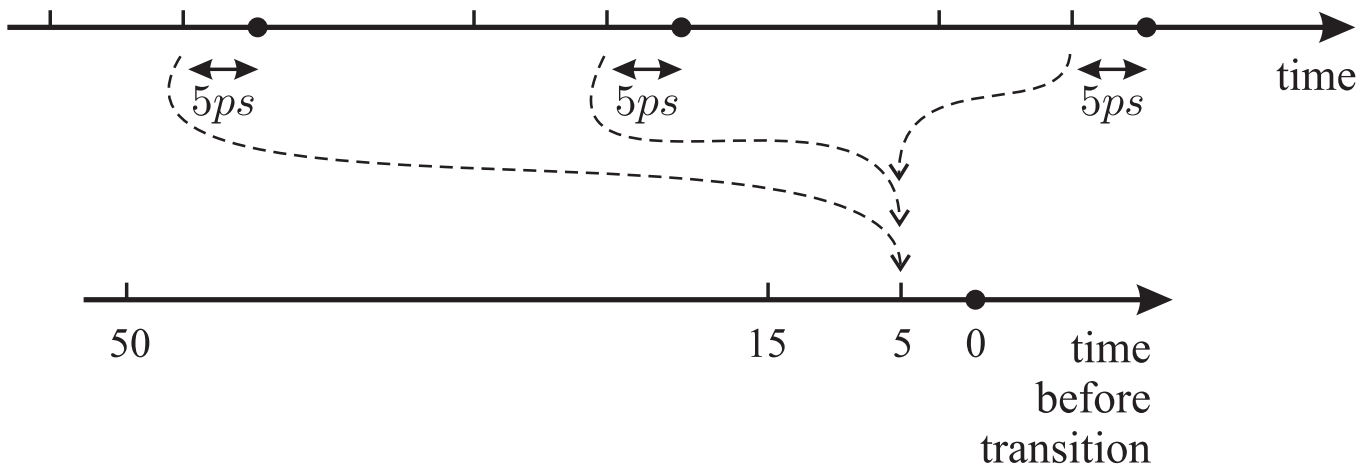
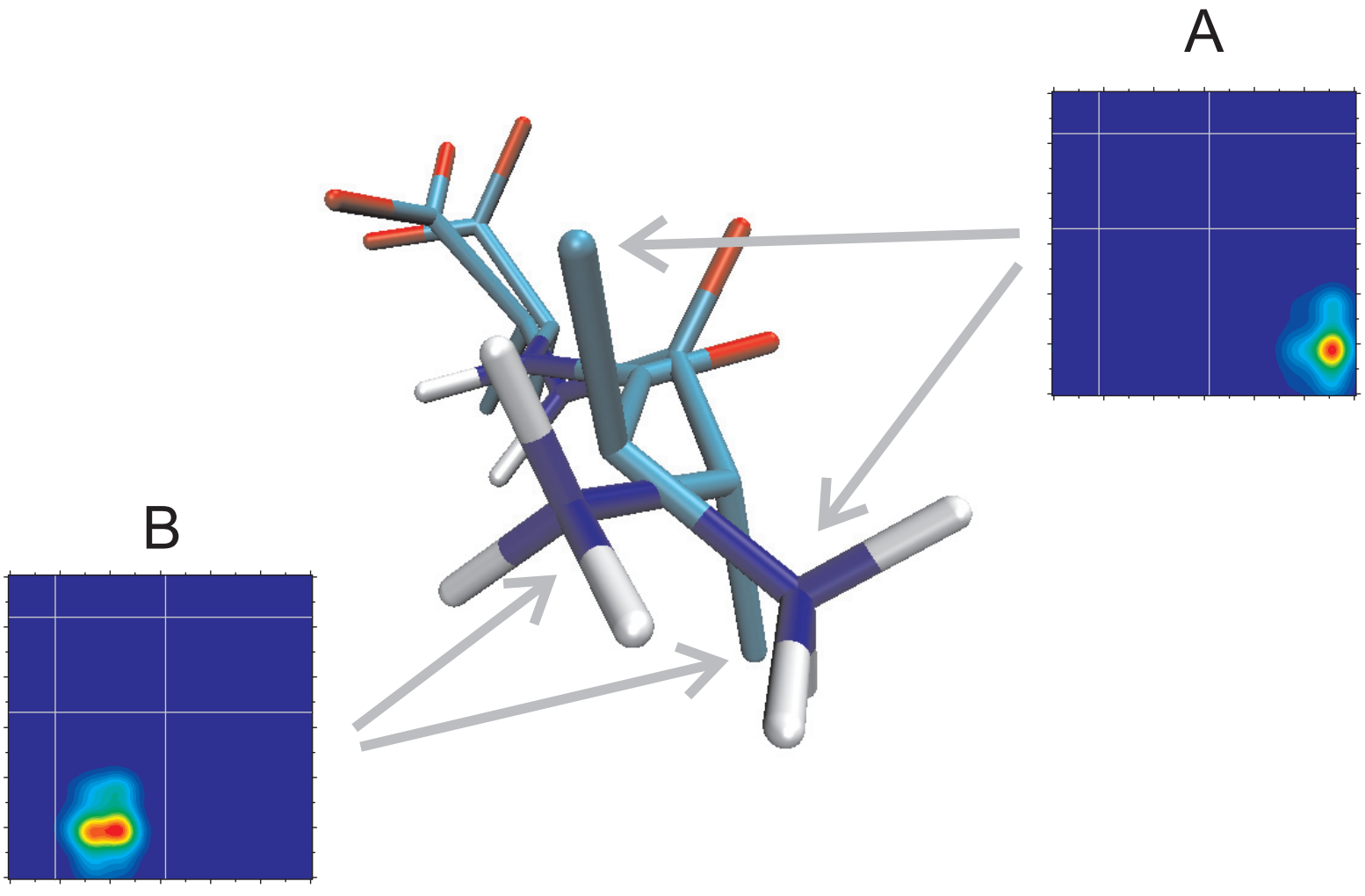


The transitions do not happen in vacuum. We analyse the behaviour of water at various times before the transitions.

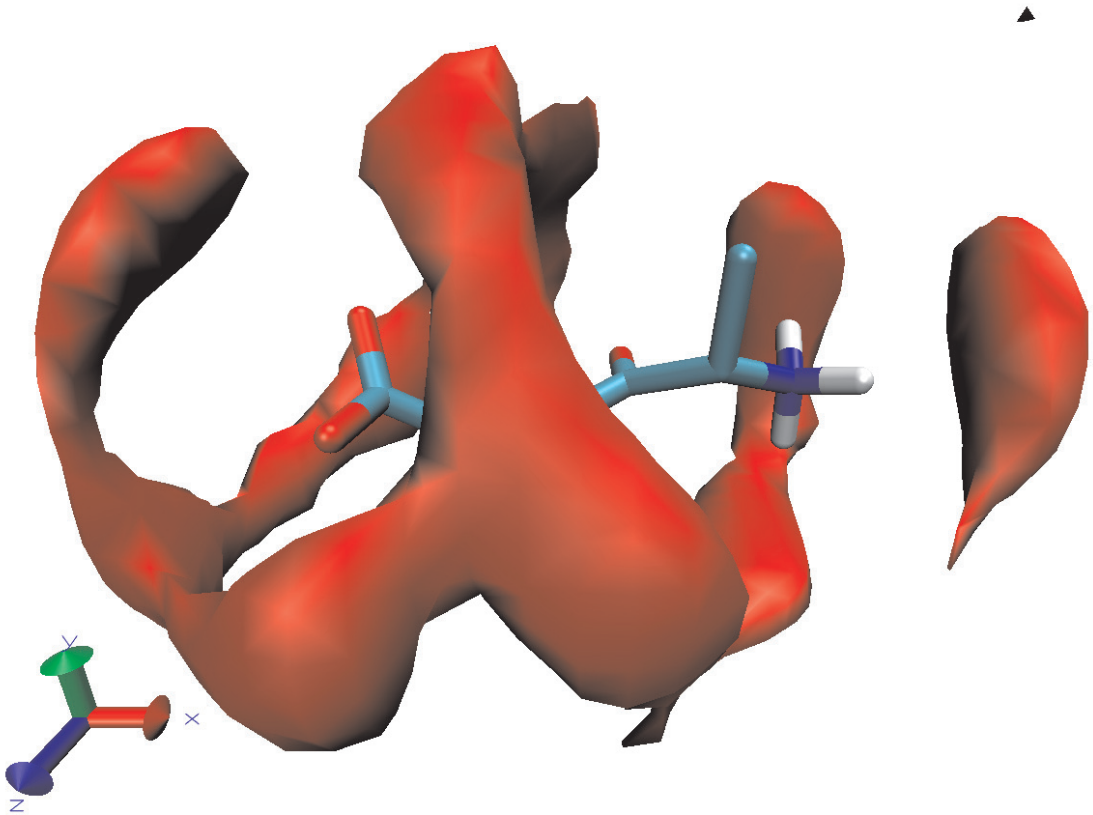
How water contributes to the transition from A to B



Transition from A to B corresponds to almost 180° flip

How water contributes to the transition from A to B

The density of oxygen (hydrogen) atoms is calculated by averaging over the selected time frames.

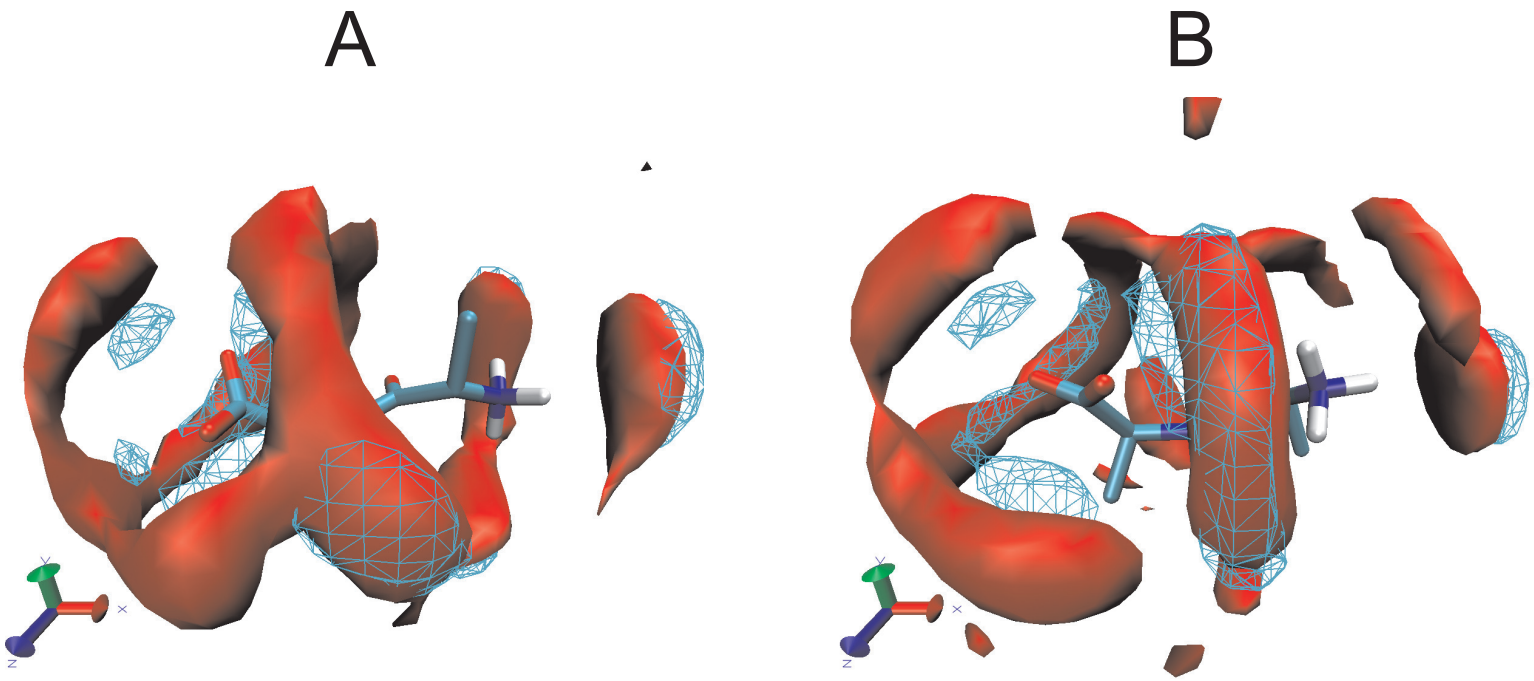


Density isosurface at 0.7 $\frac{am}{A^3}$ (average: 0.5) of oxygen of state A

How water contributes to the transition from A to B

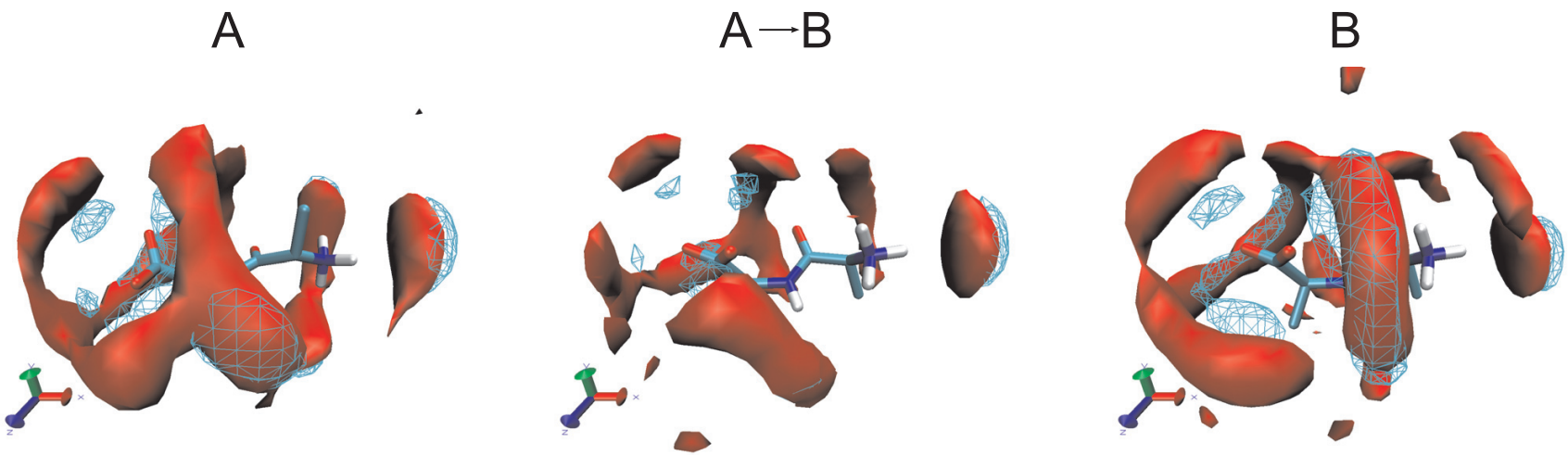
Dense areas of water correspond to *more stable structure*,
that is a more rigid hydrogen bonds network.

How water contributes to the transition from A to B



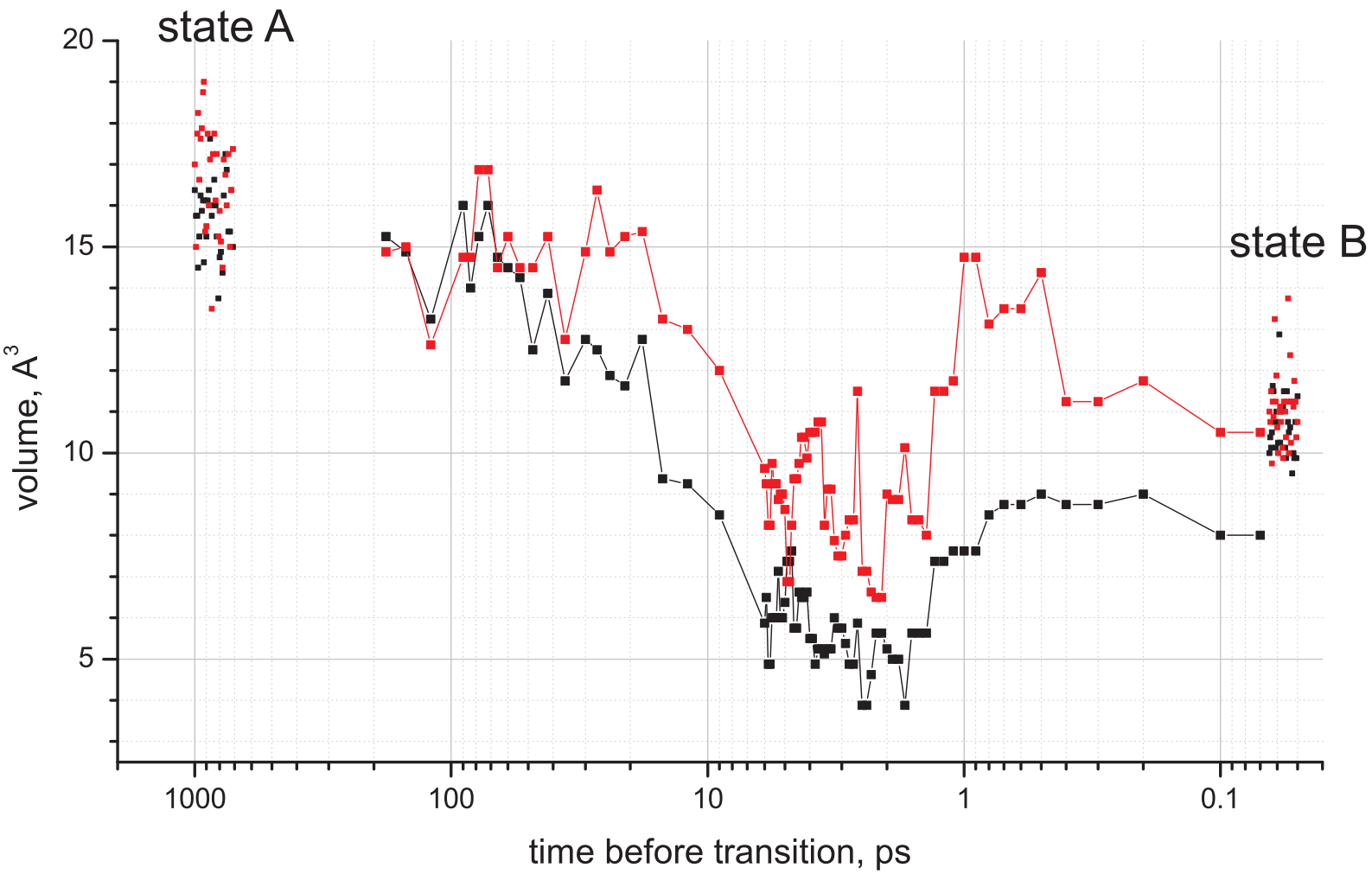
Density isosurfaces for states A and B

How water contributes to the transition from A to B



The density is significantly smaller at $\approx 3ps$ before the transition

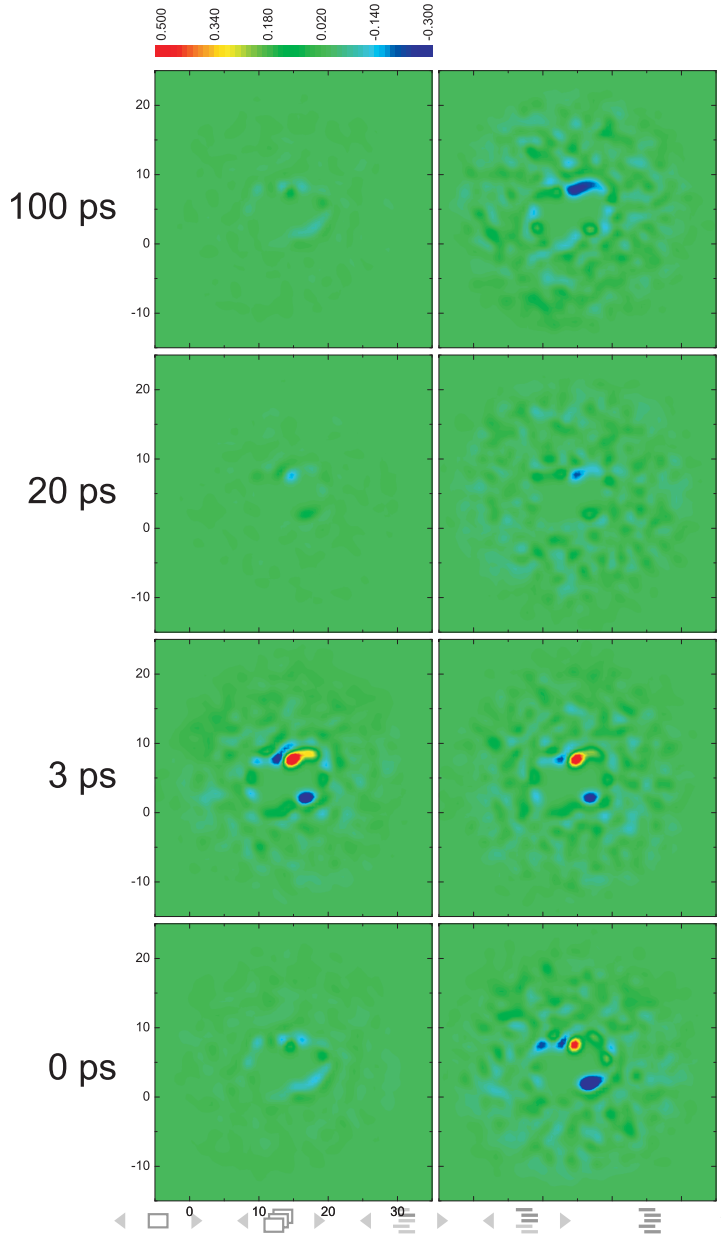
Water hydrogen bond network dynamics



The volume of high oxygen (red) and hydrogen (black) density during the transition from state A to state B

Water density correlation with the peptide motion

Linear Stochastic Estimation



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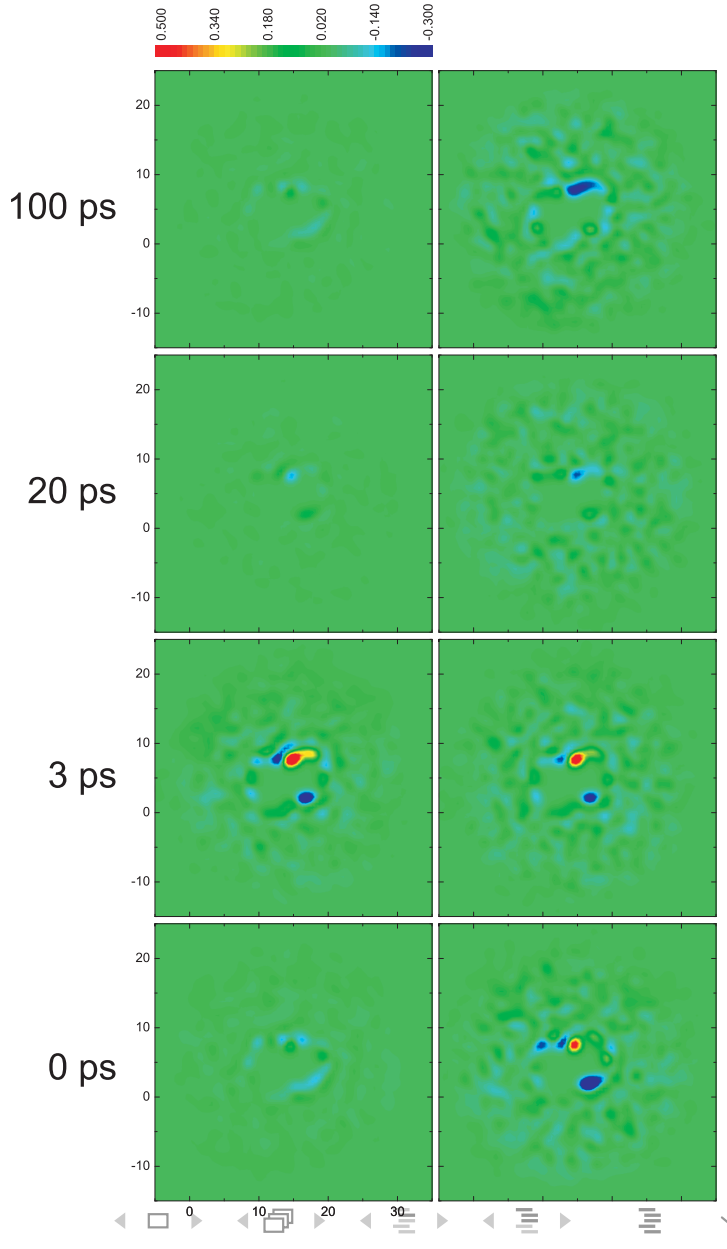
Linear Stochastic Estimation
The density field $\rho(\mathbf{x}, t)$ is converted to a time fluctuating field:

$$\rho'(\mathbf{x}, t) = \rho(\mathbf{x}, t) - \bar{\rho}(\mathbf{x}).$$

A linear approximation is calculated

$$\hat{\rho}(\mathbf{x}, t) = \alpha\bar{\phi}(t) + \beta\bar{\psi}(t)$$

that minimises the residual error $\langle \rho' - \hat{\rho} \rangle_t$.



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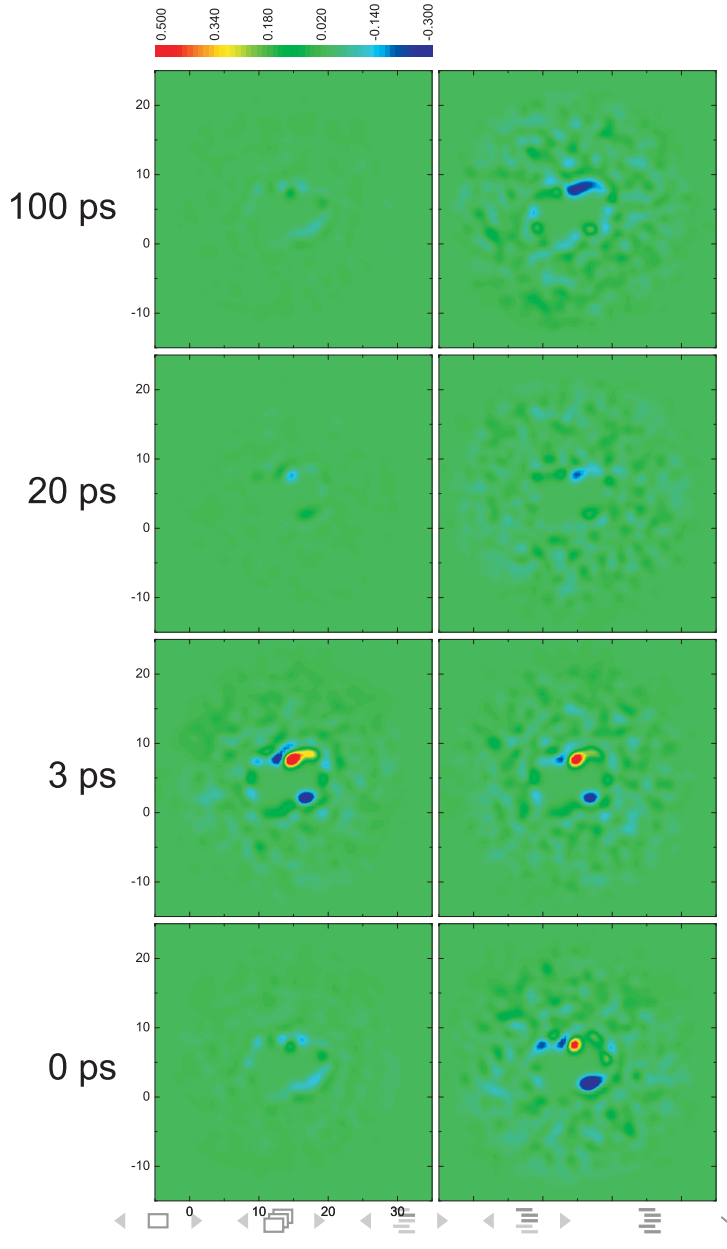
There are no correlations at the times well in advance of transitions.

Strong correlations exist at the moment just before the transition.



Conclusions

- $\approx 5ps$ before the transition, when the dihedral angles change the most, the water density significantly reduces;
- the change of water density begins at $\approx 50ps$ before the transition, 10 times earlier than the changes in the angles!
- during the transition the dynamics of water density becomes highly correlated with the dynamics of the angles;
- these correlations are completely absent during the stable conformations periods.

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Water drives (slaves) the conformational transitions.

Collaborators

Sergey Karabasov
Cambridge University

Makoto Taiji
RIKEN Institute

Vladimir Ryabov
Hakodate University

Vitaliy Bardik
Kiev University