Dissecting peptide conformational transitions: unique water dynamics

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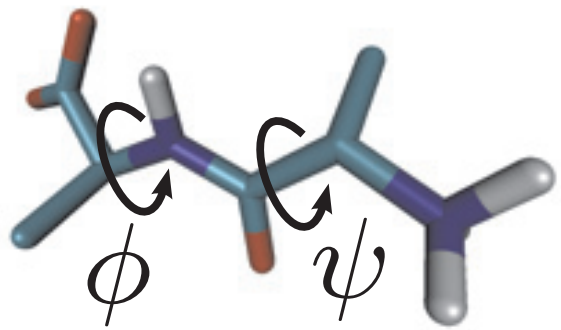
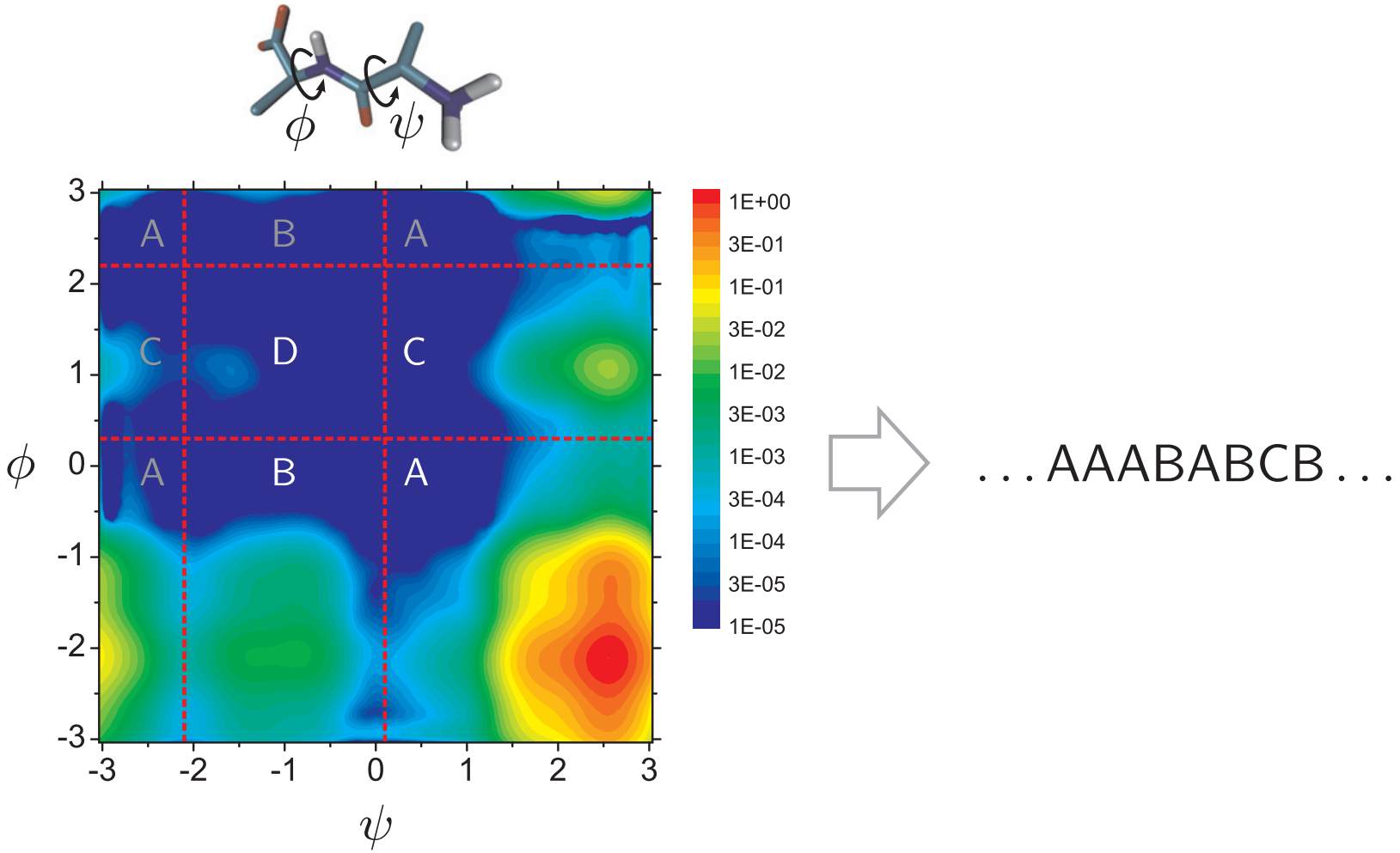
L-alanyl-L-alanine zwitterion



We do classical MD in explicit water.

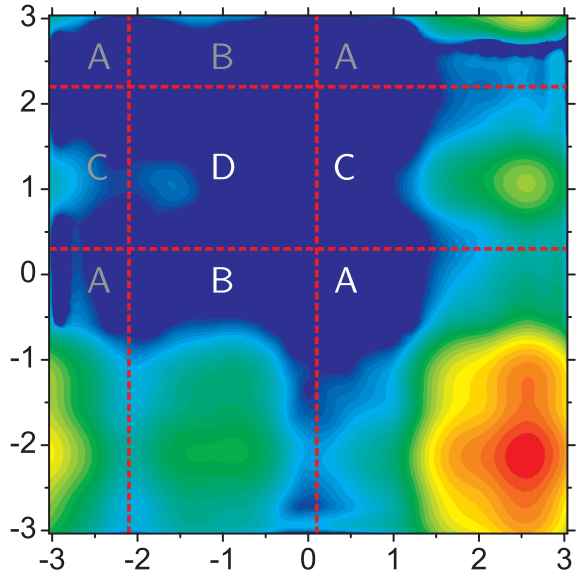
The conformational changes of the peptide is the focus of the investigation.

L-alanyl-L-alanine zwitterion conformational dynamics



Probabilities of conformations for a 1μs trajectory and its symbolisation

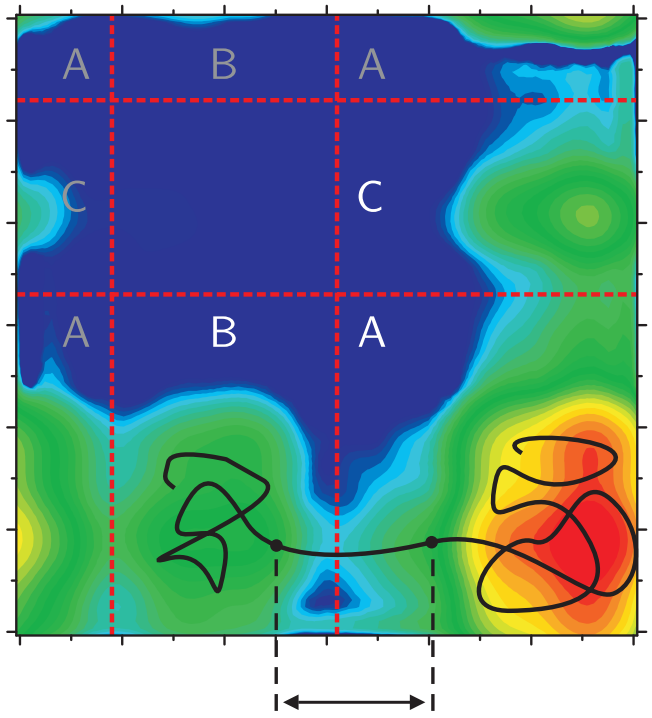
Markov State Model



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

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

Markov State Model



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

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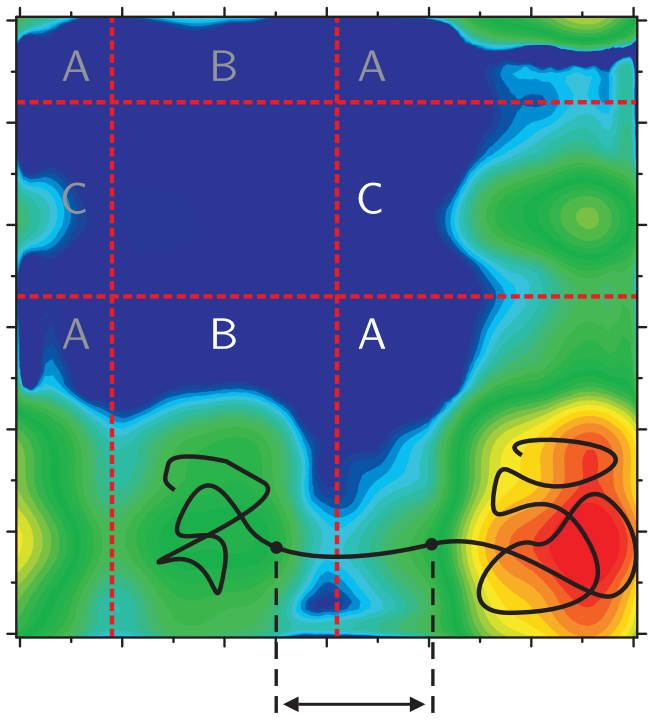

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It does not say anything about *how* and *why* the transitions happen.

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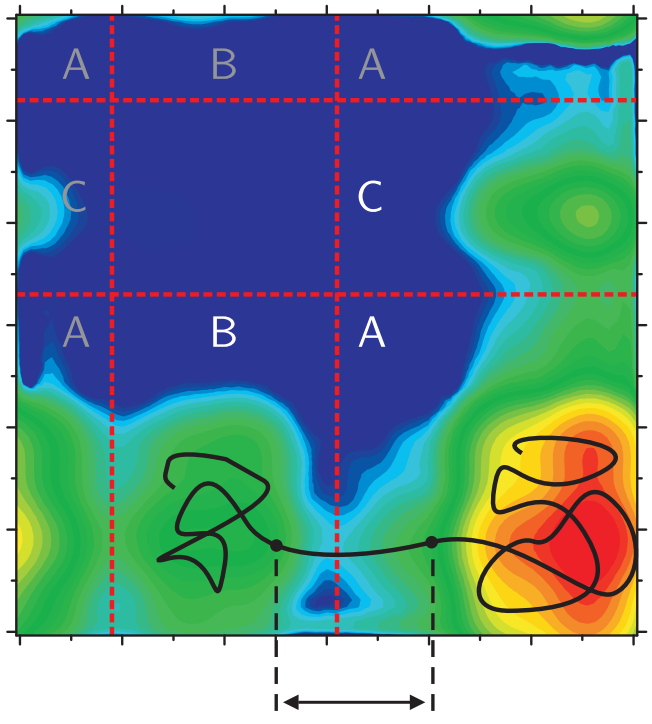

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Solution: build a model that works for smaller time steps.

Hidden Markov model

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

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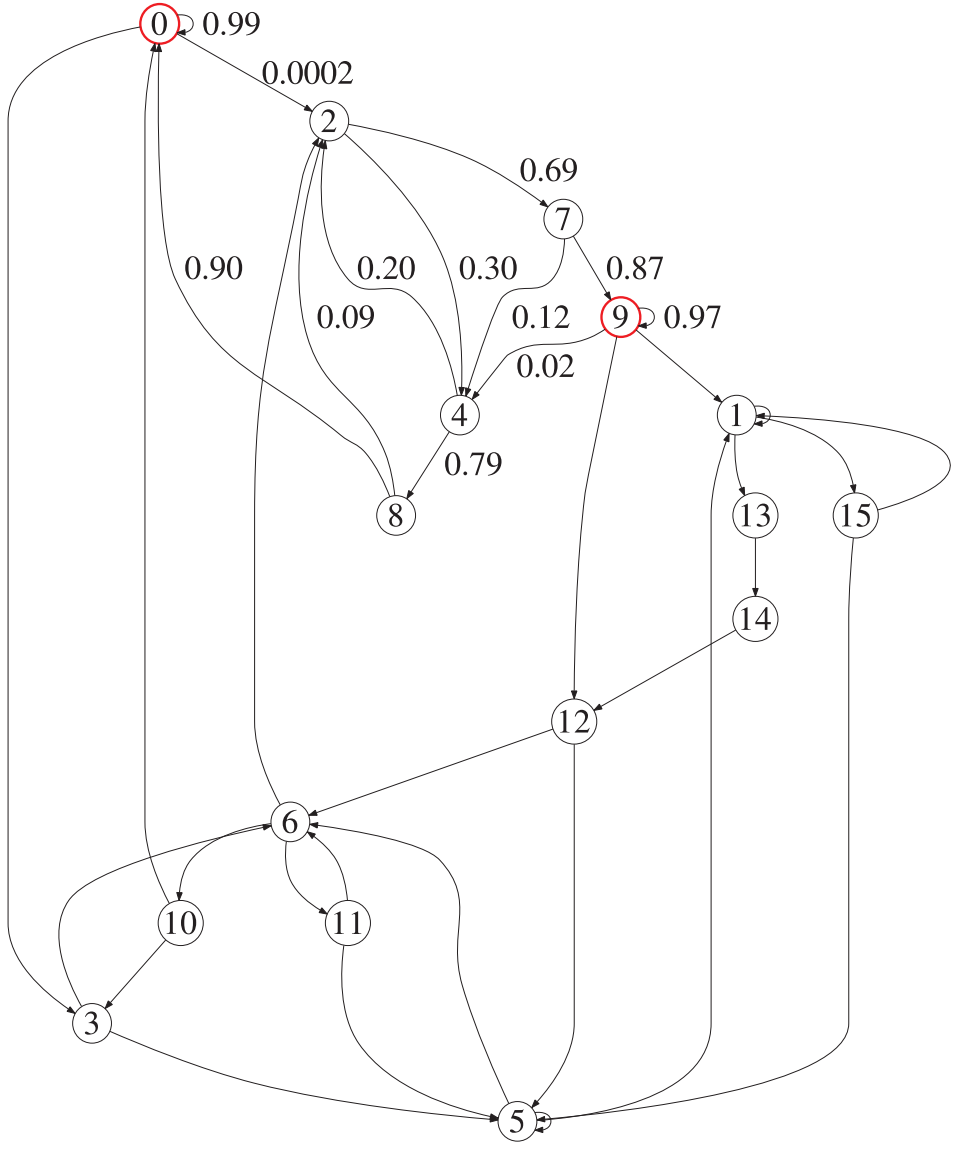
We build a Markov model on these states.

Hidden Markov model

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



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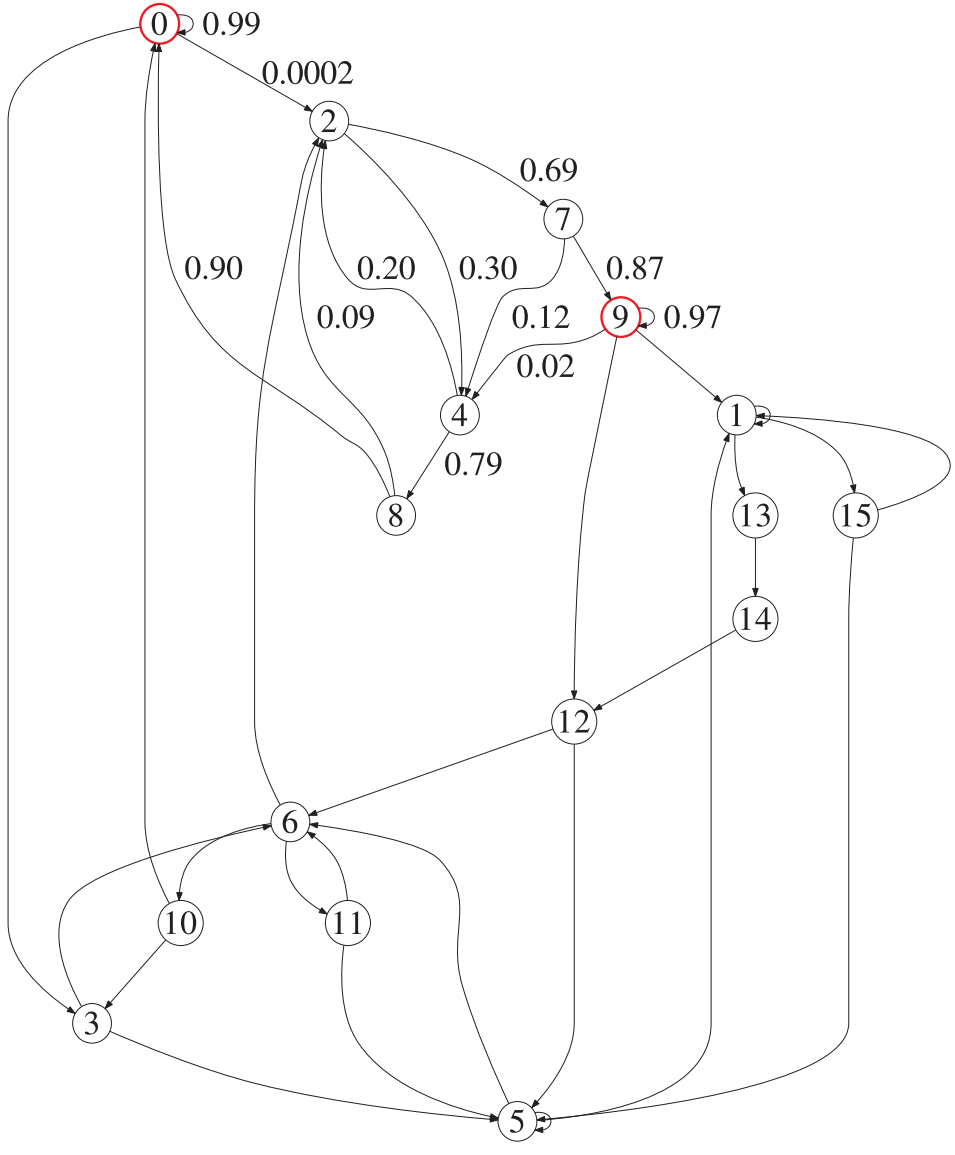
State '0' corresponds to the original state 'A': it consists of the sequences $AAAA$.

State '9' corresponds to 'B'.



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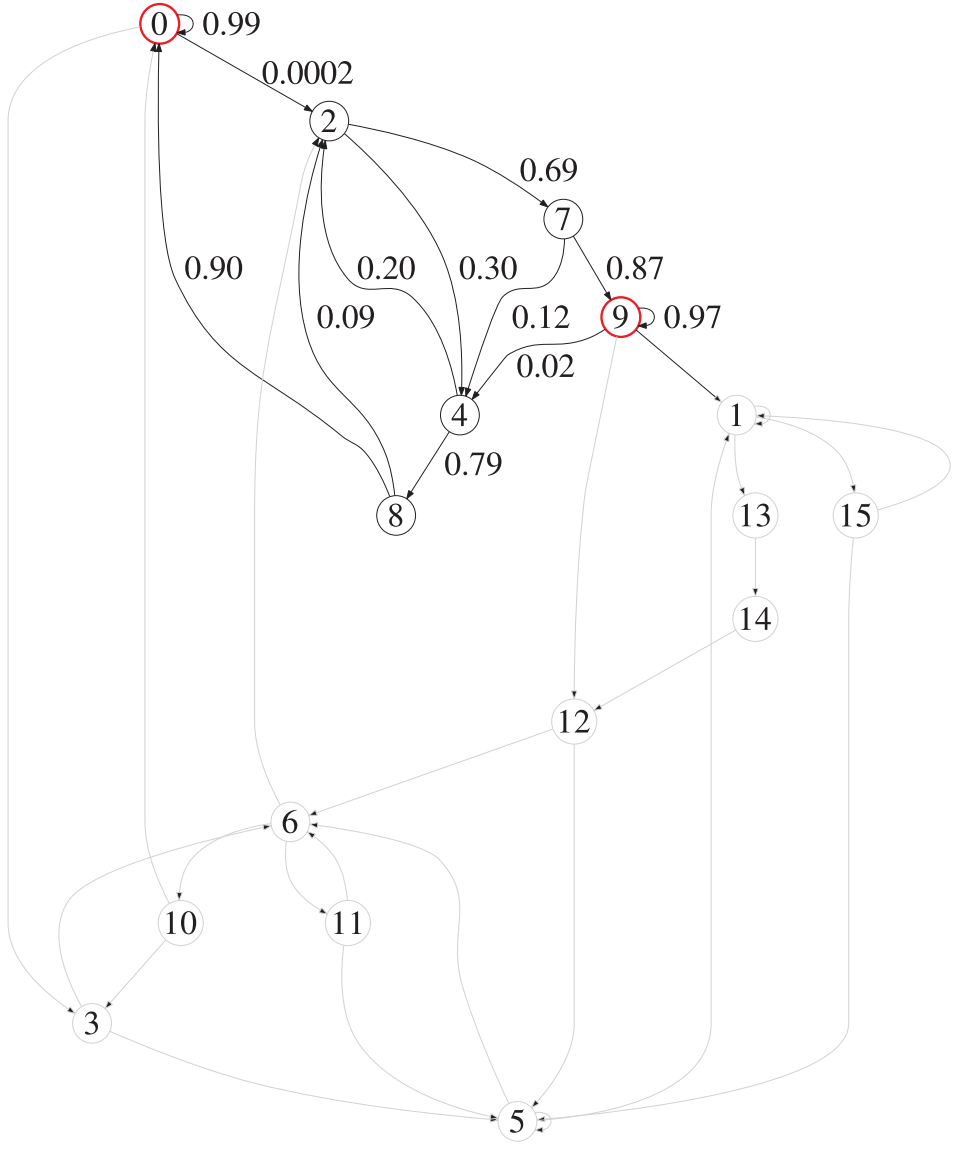
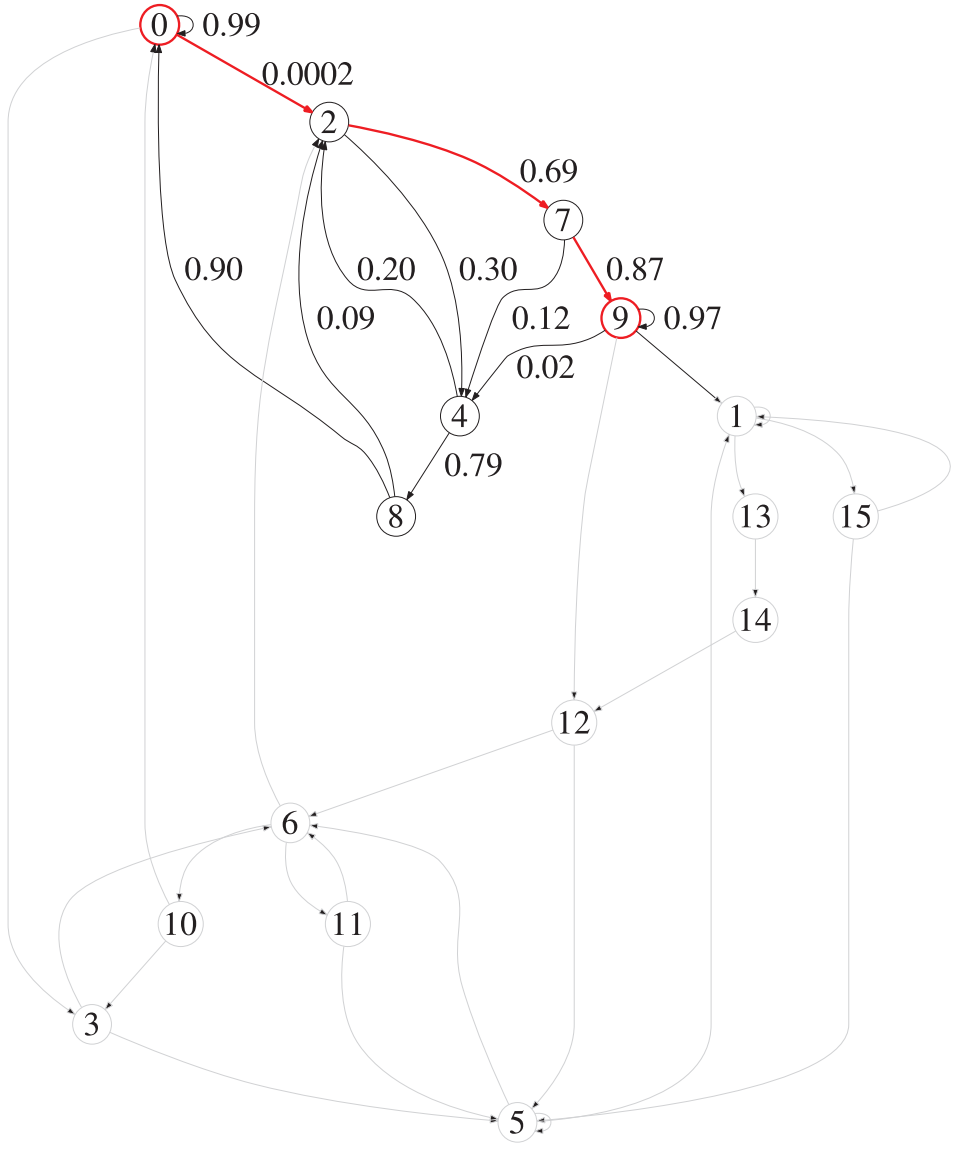
The states '$2, 7, 4, 8$' are the transition states, they describe the mechanism (pathways) of the transition.



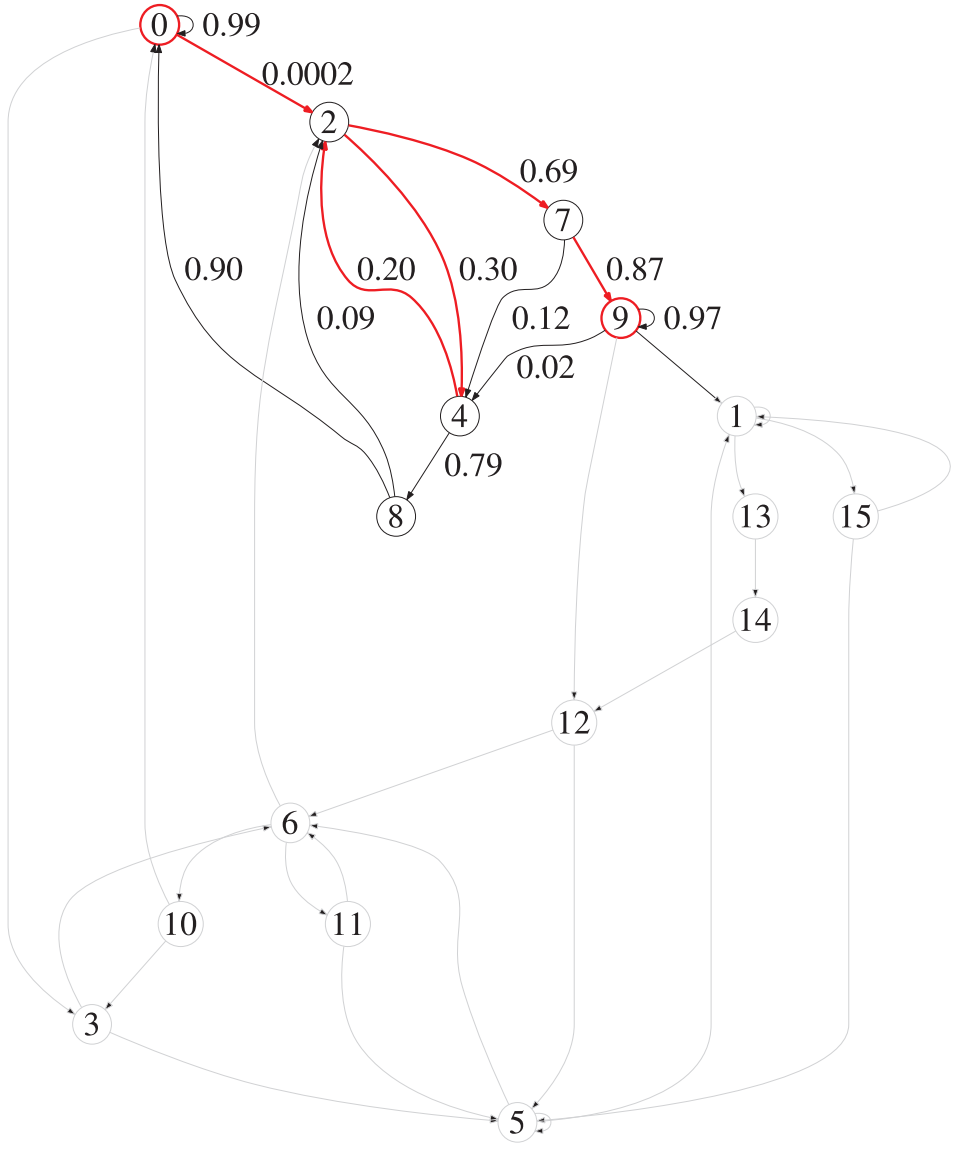
Hidden Markov model

Direct transition



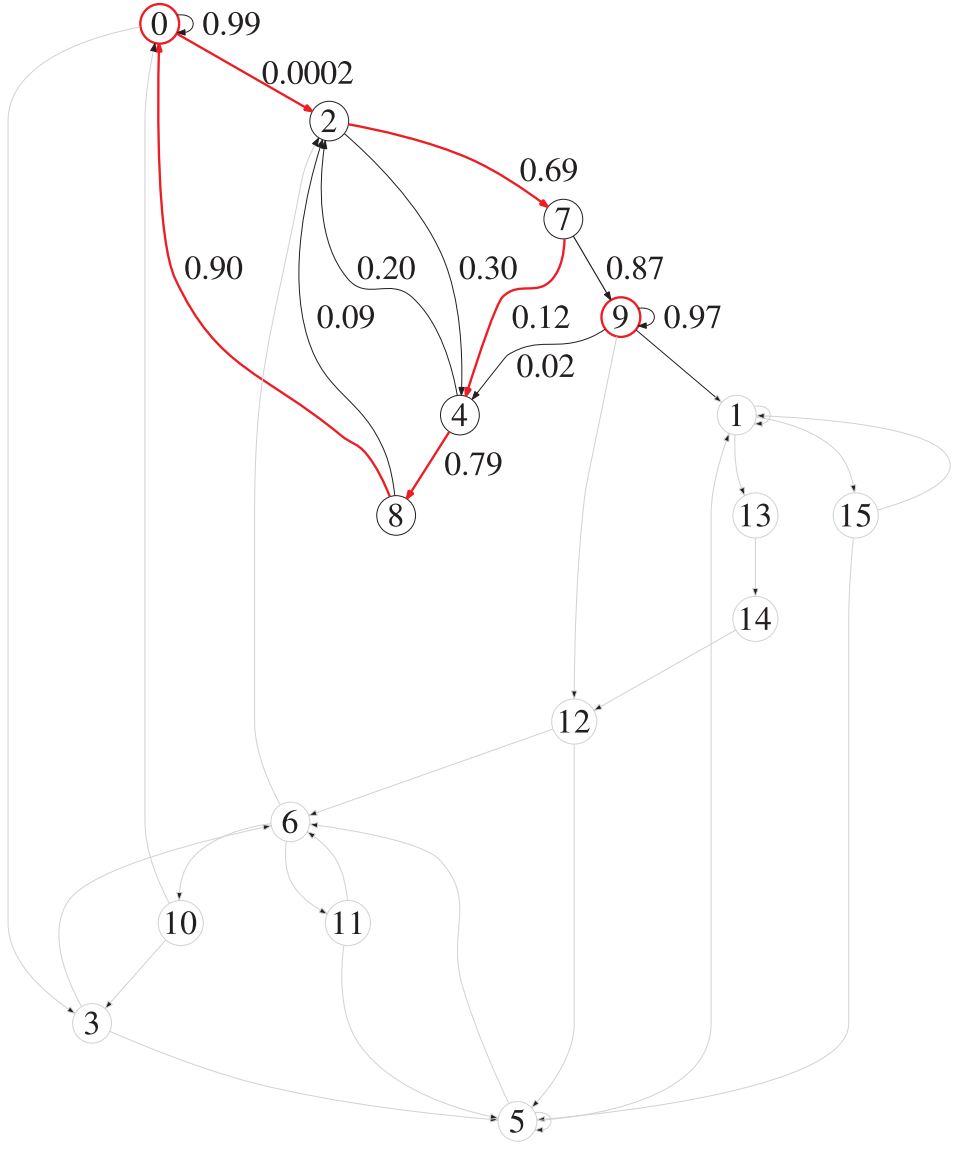
Hidden Markov model

With several recrossings



Hidden Markov model

Failed attempts of transition



Hidden Markov model

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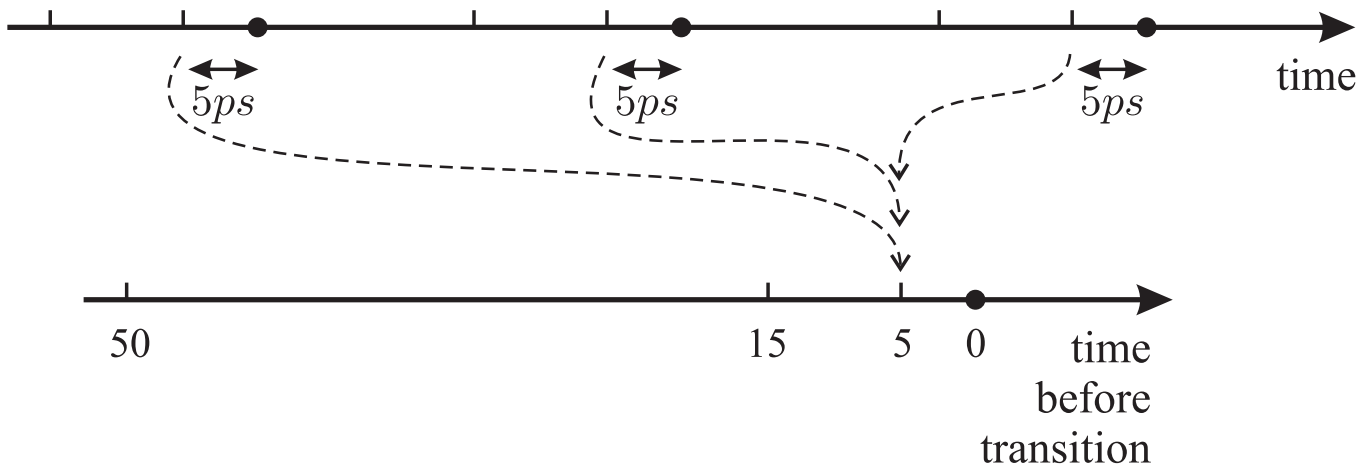
We collect the time frames at specific times *before* the transitions.



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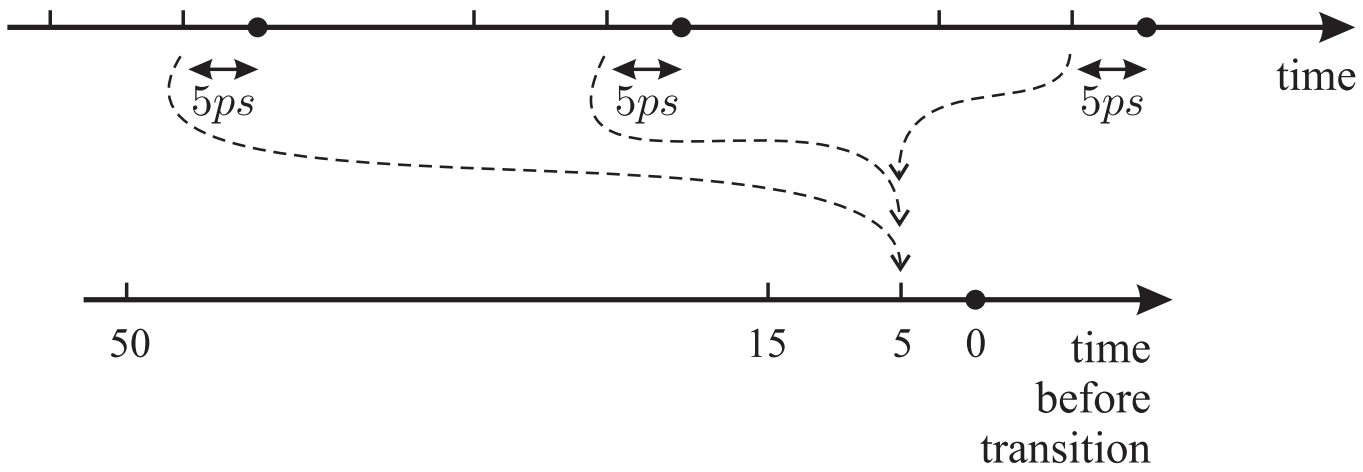
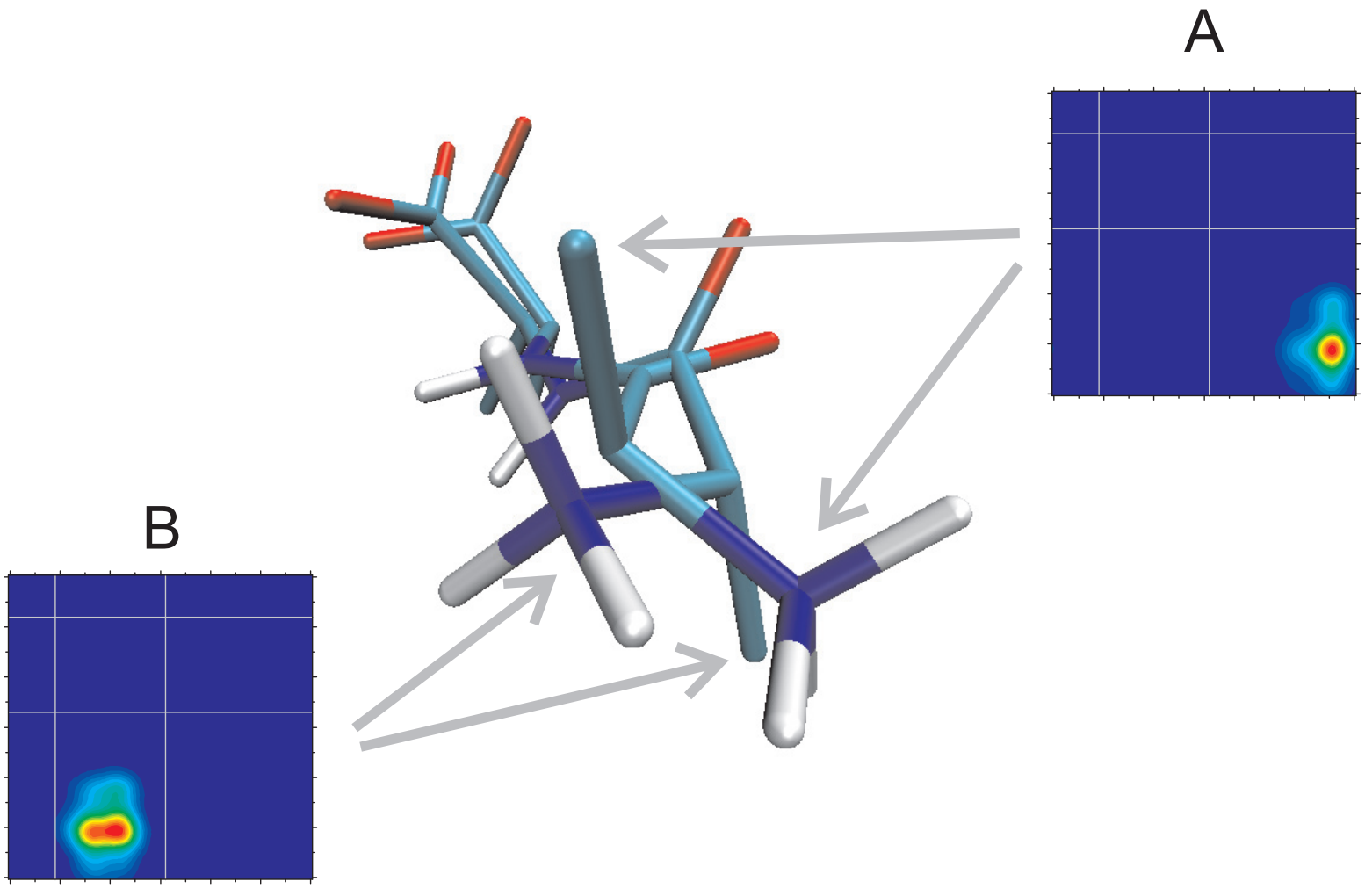


The transitions do not happen in vacuum. We analyse the behaviour of water at various times before the transitions.

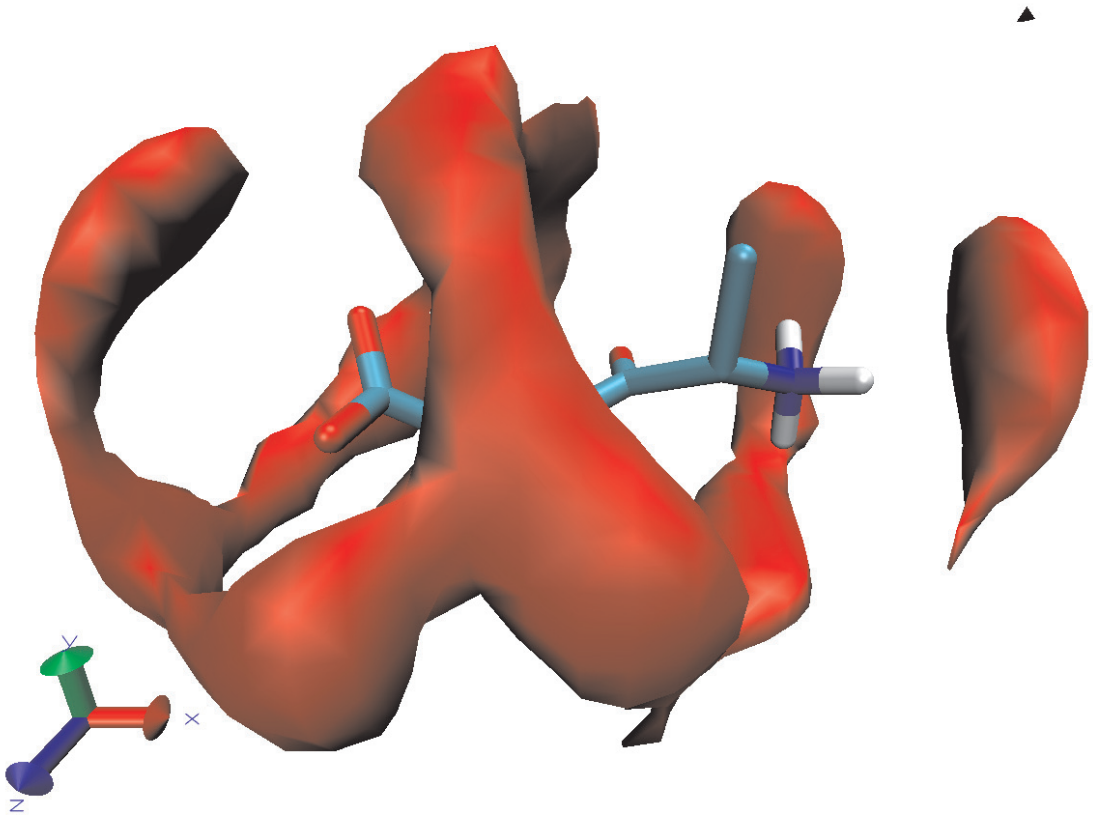
How water contributes to the transition from A to B



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.

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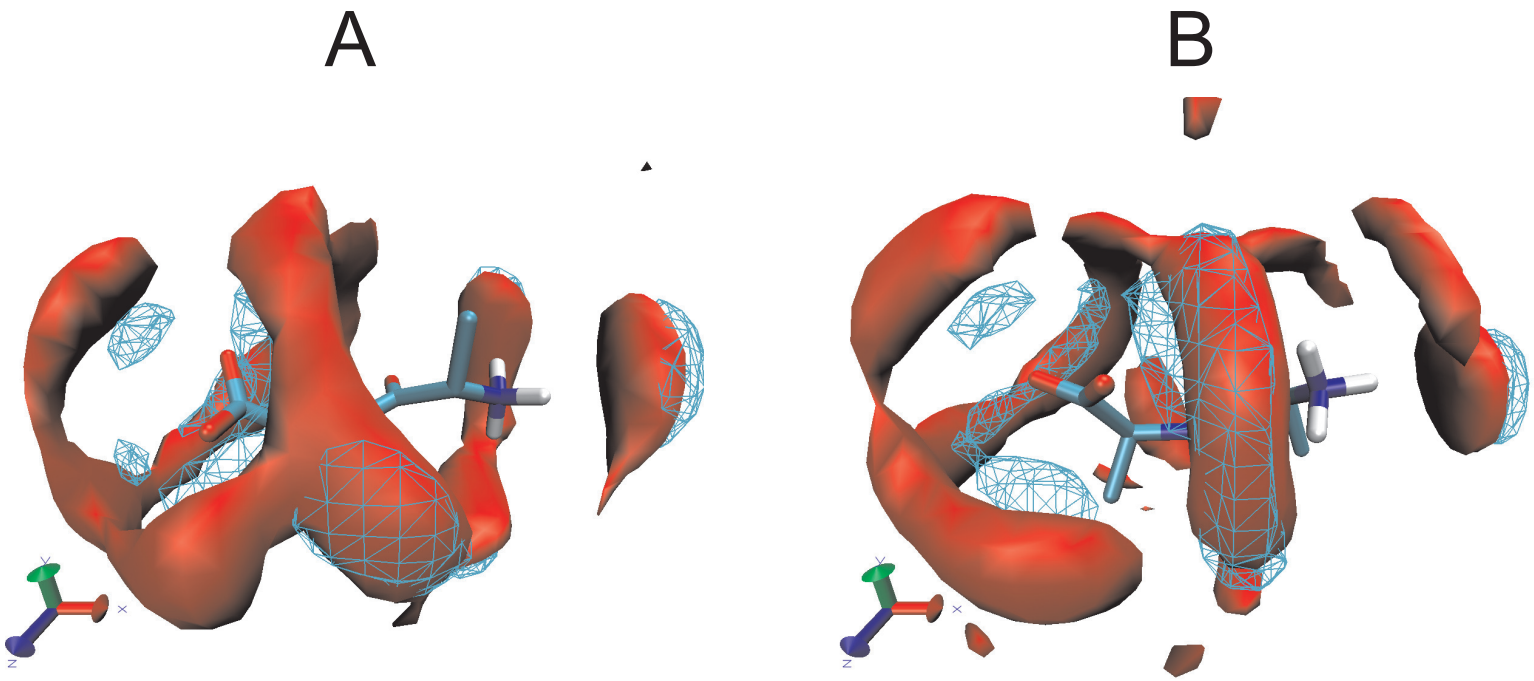
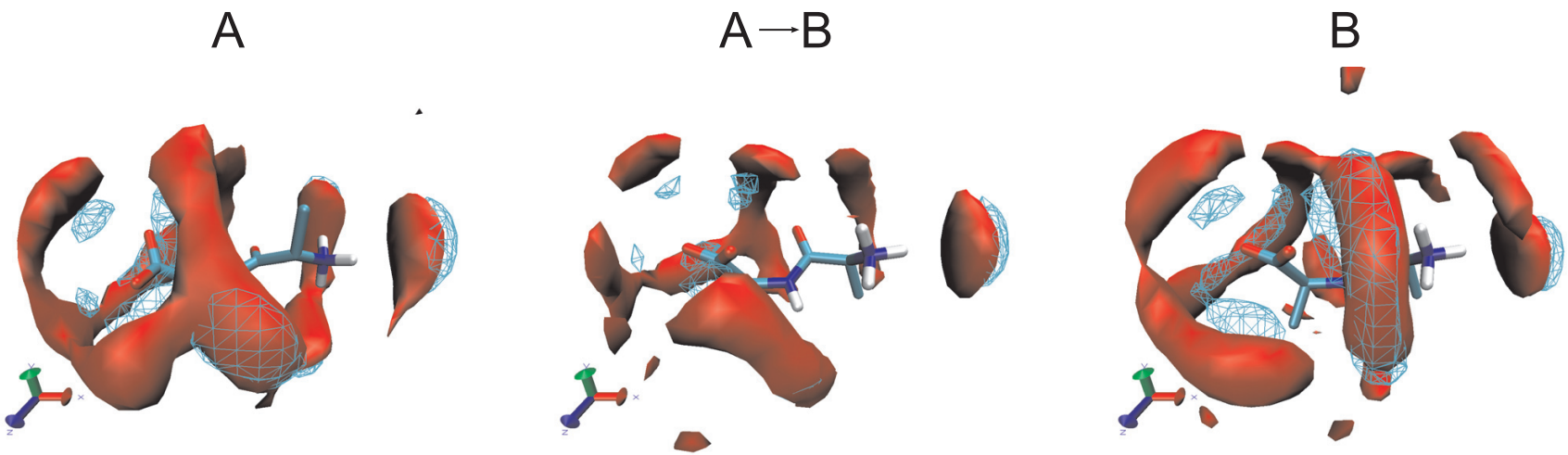


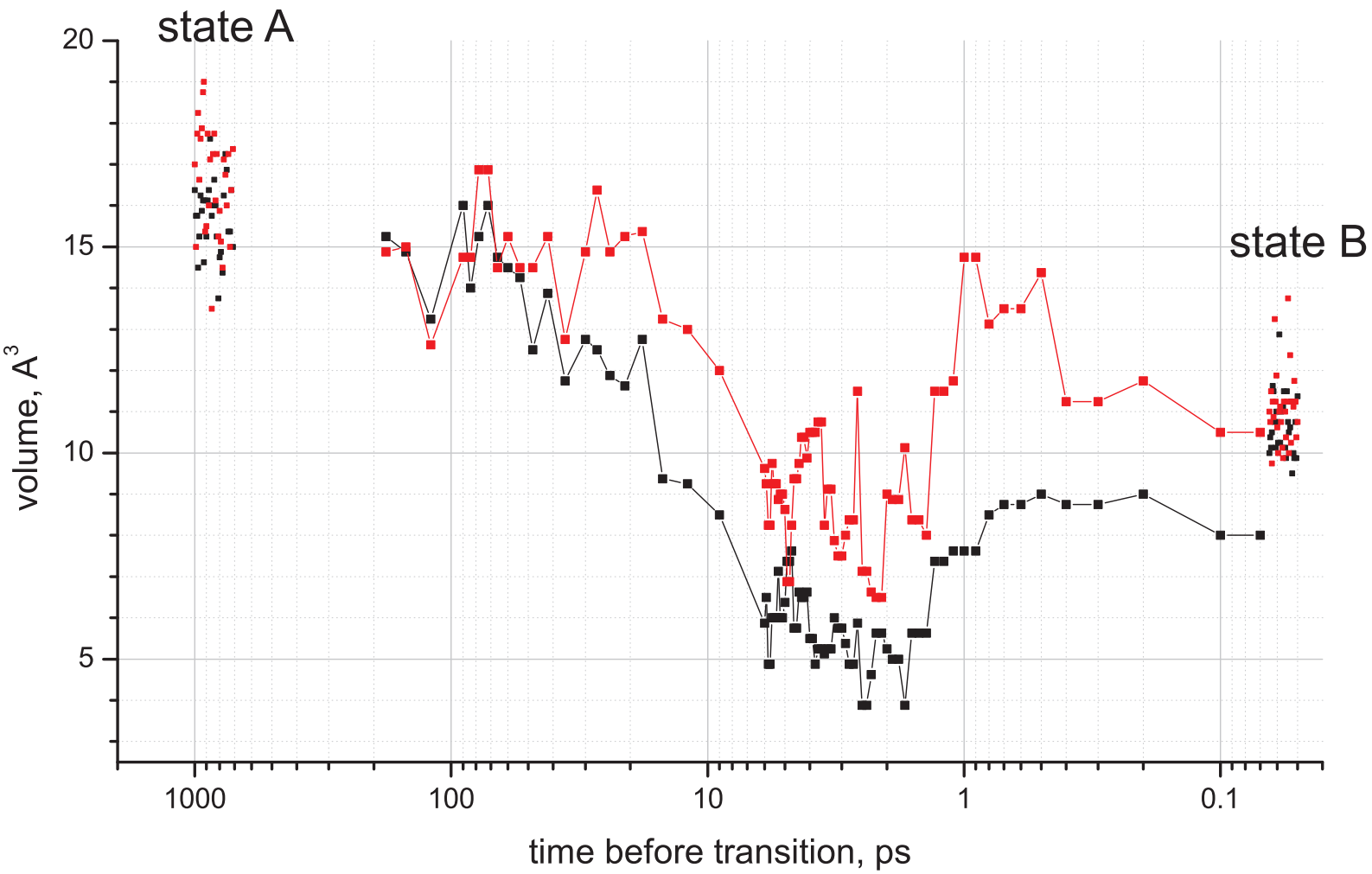
Density isosurfaces for states A and B

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

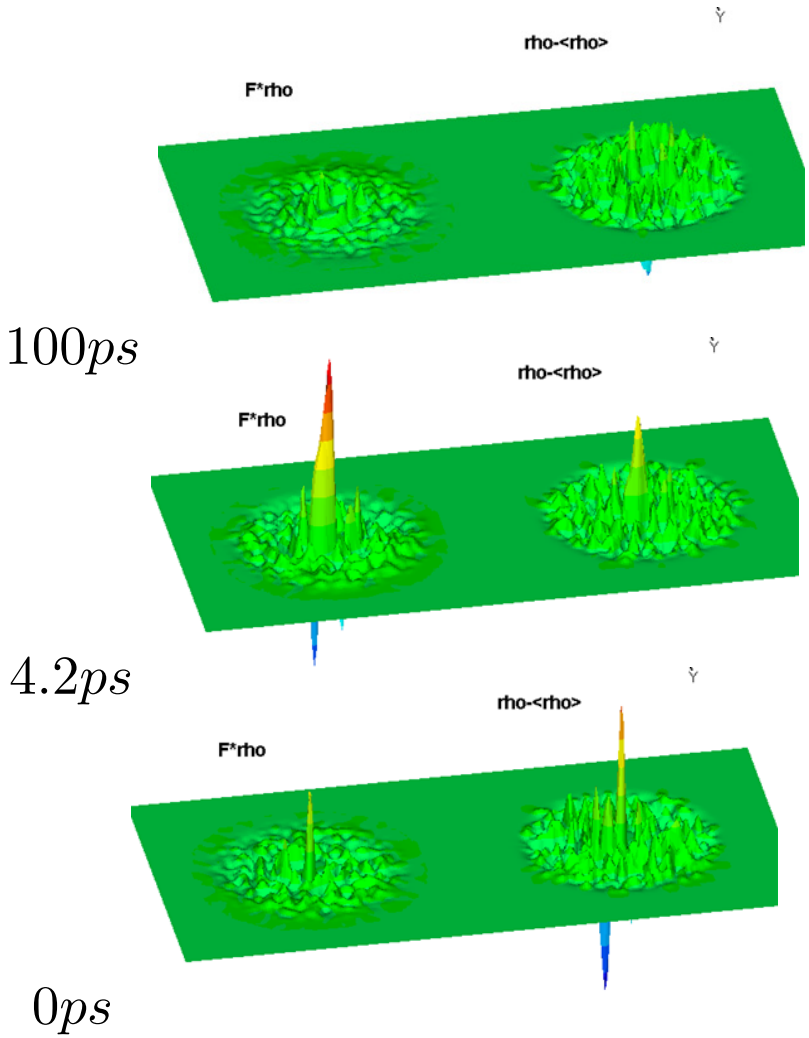


The volume of high oxygen (black) and hydrogen (red) density during the transition from state A to state B

Water density correlation with the peptide motion

The water density is represented as the linear function of the peptide angles:

$$\rho_i = \langle \alpha_i \psi + \beta_i \phi \rangle_{time}.$$



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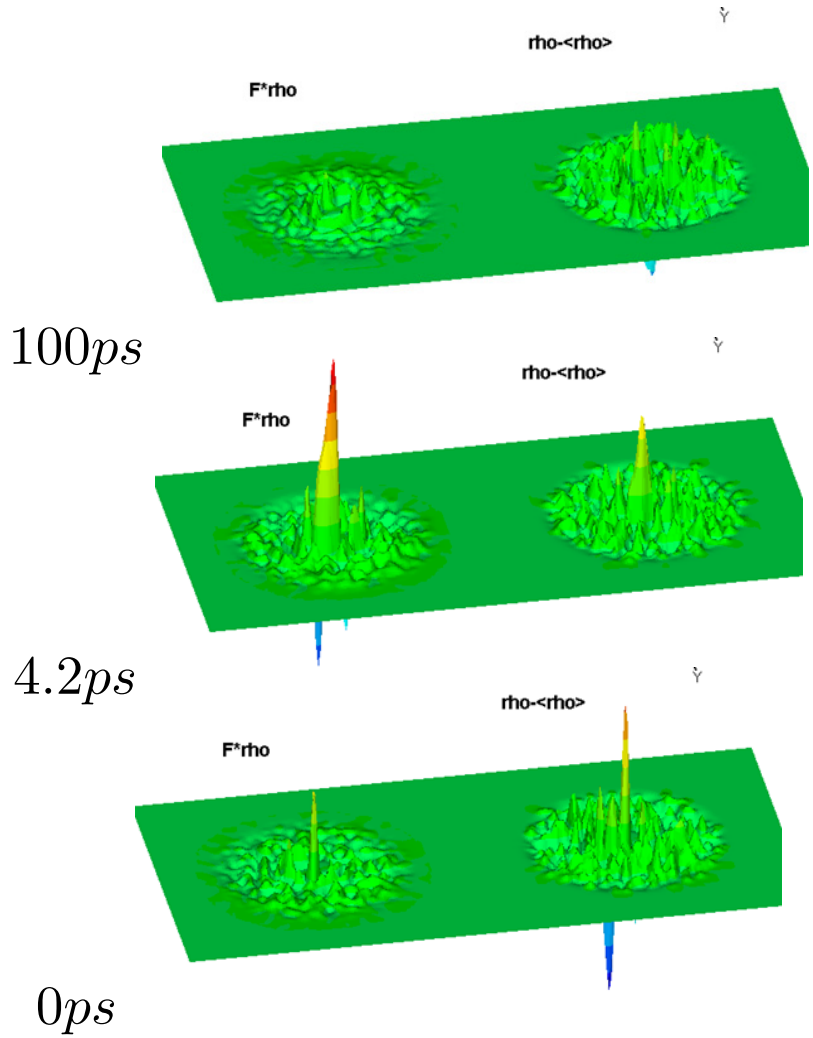
There are no correlations at the times well in advance of transitions.

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
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