Combined peptide-water energy landscape: the dynamics of rare conformational transitions

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Conformational transitions in dialanine zwitterion - explicit water system have been investigated using MD. The conformational states of the peptide and transitions between them are described in the framework of hidden Markov State Model, an extension of popular MSM approach. The distribution of water molecules around the peptide is investigated at different moments in advance of a chosen transition. We have found that the surrounding water molecules make an integral part of the system for the process of conformational changes. Water degrees of freedom must be explicitly included in the reaction coordinates when analysing the energy landscape on which the dynamics takes place. It is also likely that water drives the transitions in the peptide.

Motivation

Recent investigations of protein dynamics indicate that water plays the major role in protein motion. Frauenfelder and colleagues have experimentally shown that protein dominant conformational motions are slaved by the hydration shell and the bulk solvent, while the protein molecule itself provides an 'active matrix' necessary for guiding the water's dynamics towards biologically relevant conformational changes.

Despite extensive research on protein dynamics the investigations of *elementary conformational motions* are rare. In this work we analyse molecular dynamics (MD) simulated peptide focusing on the moments of elementary conformational changes including explicit water molecules. We show that water indeed drives the changes and elucidate the specific mechanisms of this phenomenon.

Methodology

MD simulation details and the molecular system

We study a zwitterion L-alanyl-L-alanine, Fig. 1. Two different MD models (SPC and OPLS) of the peptide in explicit water have been studied.

Analysing the conformational dynamics

Three well separated metastable states, Fig. 1, allow one to introduce a simple natural discretisation of the conformations which we designate as 'A', 'B', or 'C'.

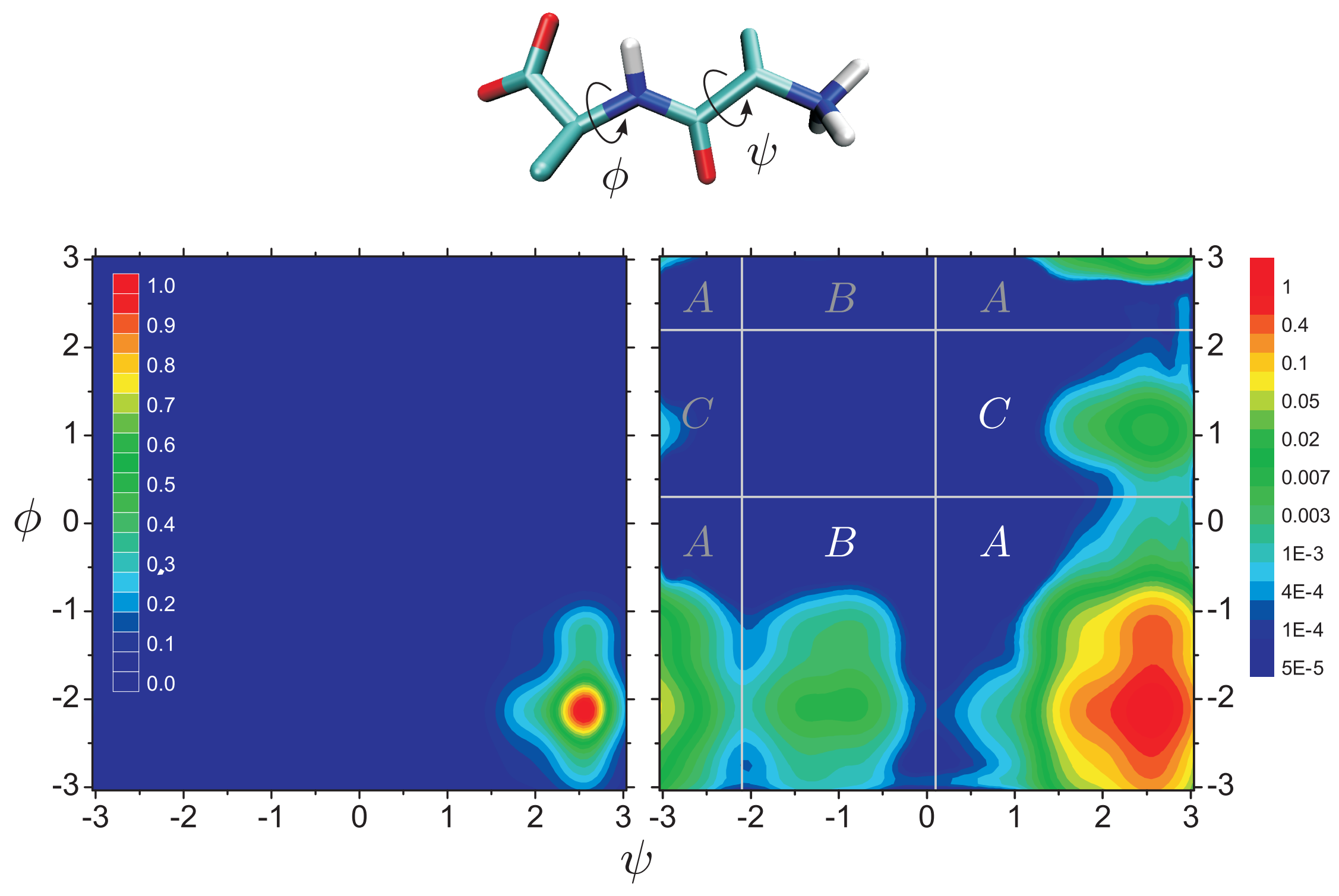

Figure 1: Top: L-alanyl-L-alanine zwitterion and its normalised probabilities of conformations

It is now possible to identify the moments of transitions. The described discretisation defines boundaries of the states. However, individual pieces of the trajectory do not go directly from one state to another, instead they wind in a complicated manner, often crossing the boundaries many times before settling in a new conformation.

The problem can be solved by increasing the time step between state observations, such that the step becomes larger than the time required for the transition to complete. Thus, by discretising time with a step Δt the continuous MD trajectory is converted into a string of symbols $\{s_i\}, i = 0 \dots N$, where s_i equals to 'A', 'B', or 'C' depending on where the trajectory point falls at the time moment t_i, N is the number of such steps in the simulation. This sequence of symbols can be analysed using a model that becomes very popular recently is the Markov State Model (MSM).

We build a variant of the *hidden Markov model* using the same conformational states of the peptide. Specifically, we use the 'ϵ-machine' by Crutchfield et al. Instead of the conformational states s_i themselves we consider the l-long *sequences* of states $\overleftarrow{s}_i \equiv \{s_{i-l+1} \dots s_{i-2}s_{i-1}s_i\}$. The advantage of such description is that for a small time step, even if the original states are correlated over several steps, for long enough sequences $\overleftarrow{s}_i$, these new states (the sequences) are uncorrelated. We, therefore, can build a Markov model on these new states.

Using our hidden Markov model the time step can be reduced to $0.3ps$ providing a tool to investigate what happens at different moments *before* the transition including the details of the process of transition. For this we collect the time frames at specific times before the transitions, Fig. 2.

Results

We study the behaviour of water. We calculate the distribution of oxygen (hydrogen) atoms in space *by averaging over the selected time frames.* The calculated field $f(\mathbf{x}, t)$ gives the probability to find an oxygen (hydrogen) atom in a small volume around the location $\mathbf{x}$ at time t *in advance of the transition.* The calculated quantity is *not* density as the latter is obtained by dividing the number of atoms (times their mass) by the volume.

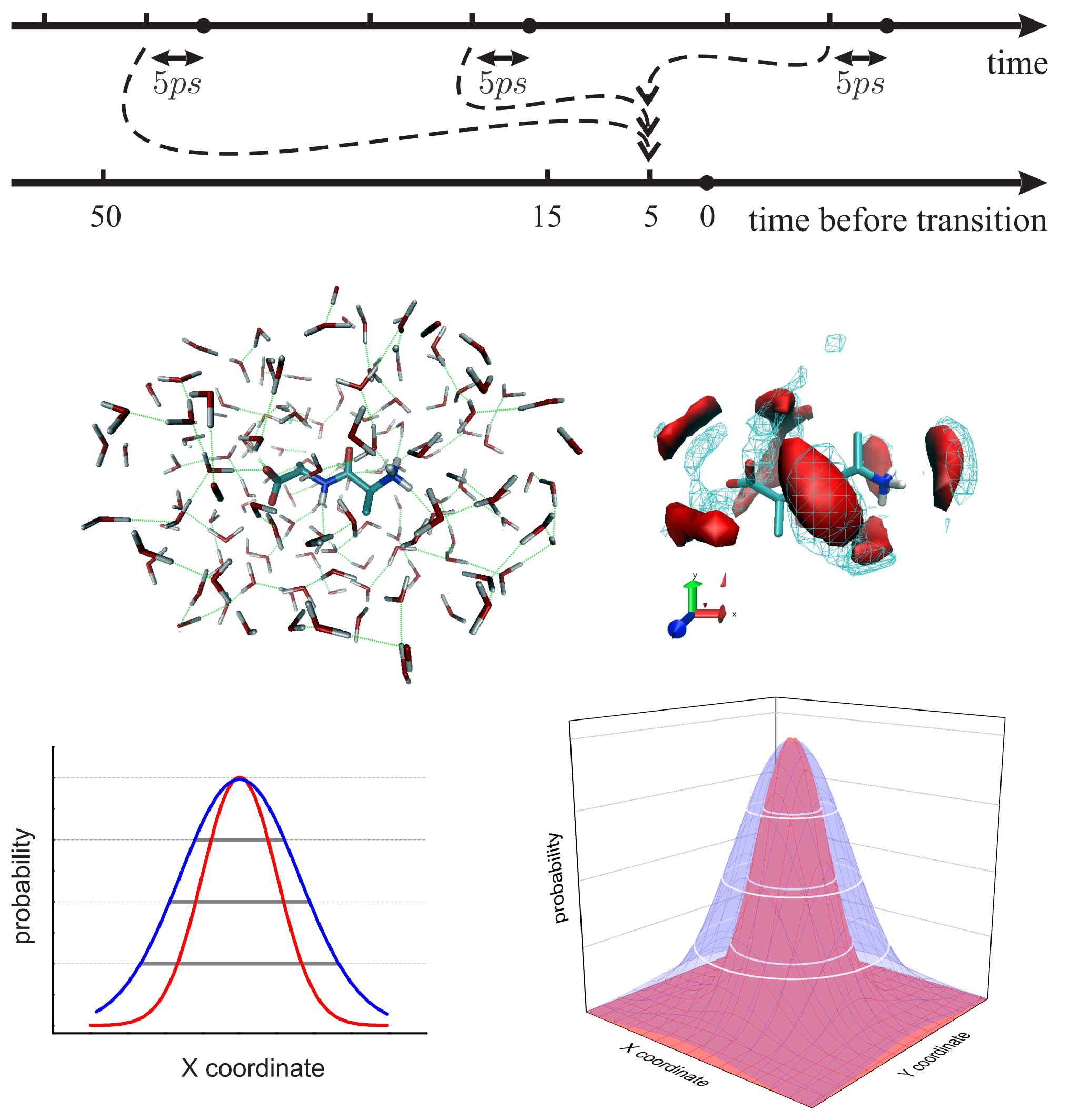

Figure 2: Collecting the time frames for the analysis

The structure of water is defined by the hydrogen bonds network, which implies approximately the same distance between water molecules everywhere (and, hence, the same local density), Fig. 2, middle left. The probabilities, however, can be significantly different at different locations indicating the preferred positions of the atoms, Fig. 2, middle right.

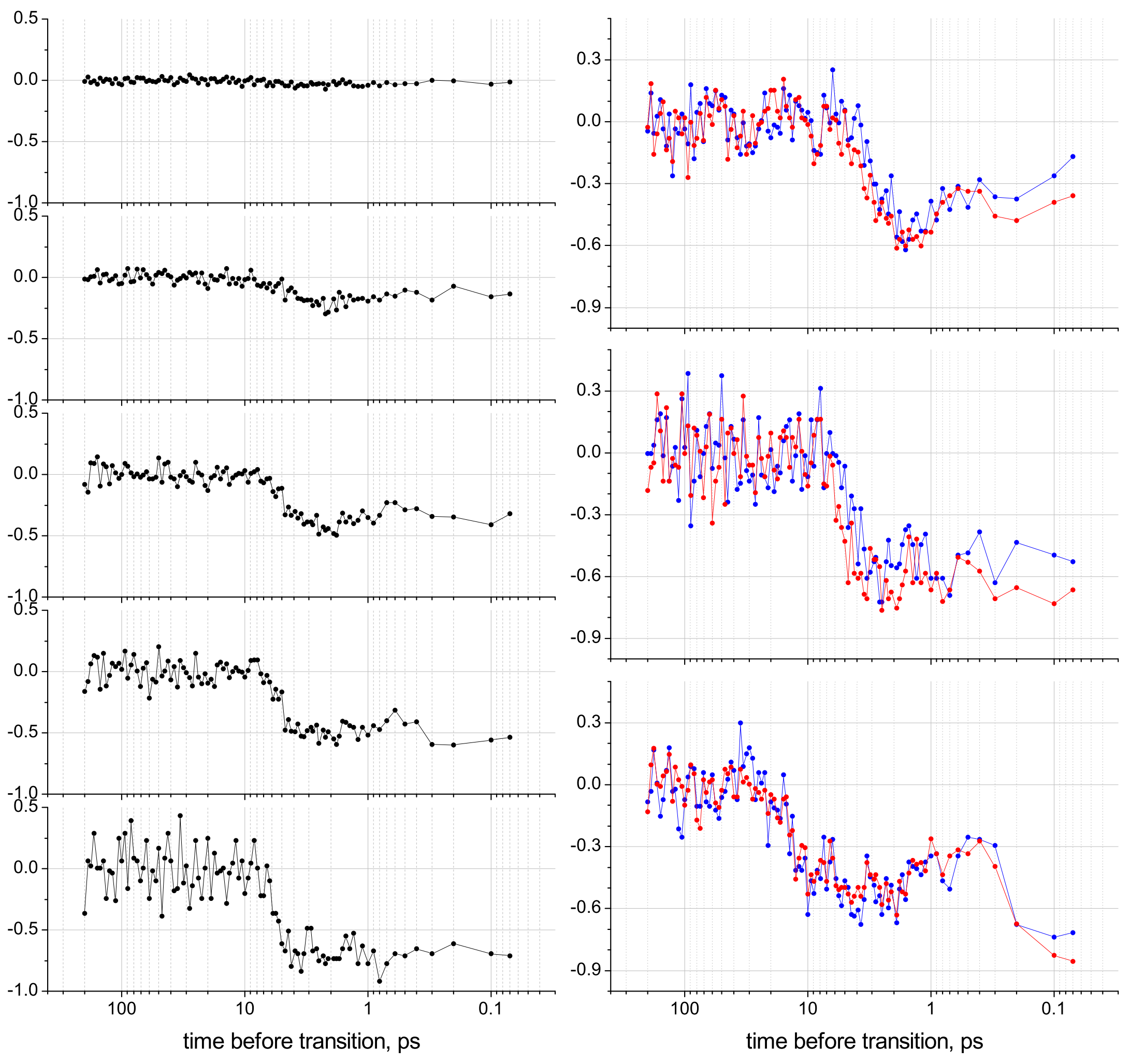

Figure 3: High probability volumes of water

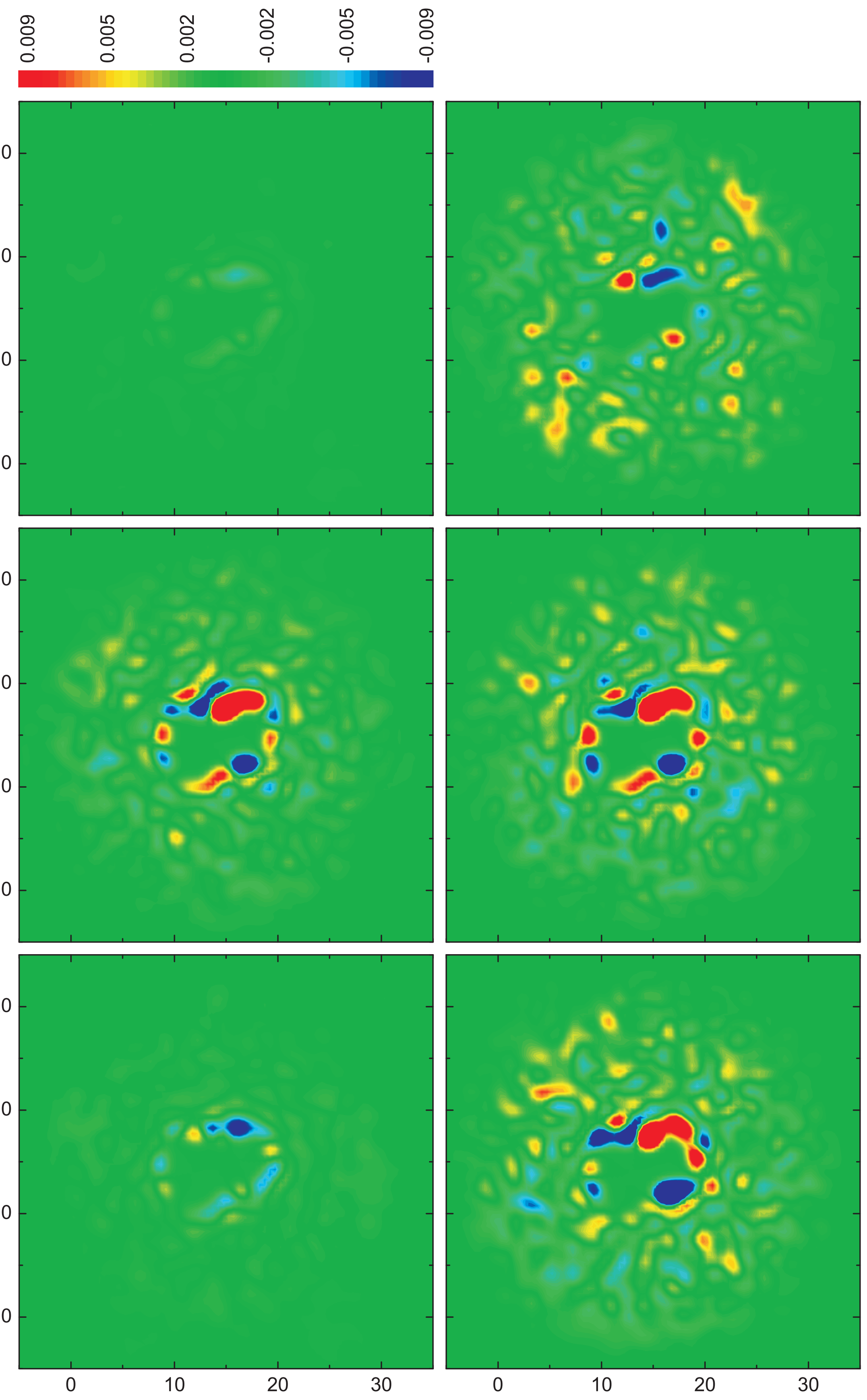

Figure 4: Correlations between the water probability and peptide angles

Conclusions

We have found that (i) from 10 to 1ps before the transition, when the dihedral angles change the most, the water molecules tend to be located at more specific positions around the peptide compared to more uniform distribution at other times; (ii) during the transition the dynamics of water distribution becomes highly correlated with the dynamics of the dihedral angles; and (iii) these correlations are completely absent during the stable conformation periods.

We conclude that water and the peptide behave as an integral dynamical system. During the conformational transition the peptide and the surrounding water undergo transitions together. This is in contrast to the metastable periods when their dynamics is essentially decoupled. The transition is characterised by a more specifically defined hydrogen bonds network of water.