ABSTRACT

Many classes of simulations including all atom molecular dynamics (MD) were developed to study the detailed atomic motions of proteins. Validating these simulations using hydrogen exchange (HX), which monitors the breaking of individual H-bonds, is an important step. The HX rates and their denaturant dependence provide information on individual H-bond stabilities and the structural fluctuations that lead to their breakage, which can be compared with simulation. Previous studies to compare with simulation and HX were focused on matching the protection factor with either site-specific NMR data or peptide level mass spectroscopy data. Here we provided a method and web-server, which can compare not only protection factor but also local structural fluctuation, by calculating correlation function and denaturant dependence which are tested for simple model system. Also we applied the tool on several different simulations. These comparisons provide a general protocol for validating the ability of simulations to accurately capture conformational fluctuations involving partial or complete unfolding of a protein.

MD2HX, a web-server calculating Hydrogen Exchange Results from Molecular Dynamics Simulation

WooKyung Yu, Karl F Freed,3,5, Tobin R. Sosnick1,4,6
1Department of Biochemistry and Molecular Biology, 2Department of Chemistry, 3James Franck Institute, 4Institute for Biophysical Dynamics, 5Computation Institute, University of Chicago, Chicago, IL 60637, USA.

MD2HX Webserver

APPLICATION TO MODEL SYSTEM

H-bonds can be broken through solvent H or D’s. Spontaneous thermal fluctuations validate the ability of simulations to accurately capture simulations. These comparisons provide a general protocol for validating the ability of simulations to accurately capture conformational fluctuations involving partial or complete unfolding of a protein.

Comparison (Prediction) Experiments from Simulations

Level of model

H-bonds to be measured

Simulation

Experiment

Global information

Adhami et al. PNAS (2012)

Lindorff-Larsen et al. Science (2011)

Skinner et al. PNAS (2014)

HX: Measuring thermodynamics of backbone H-bonds

Local information

Slope: m values

Global information

Spontaneous thermal fluctuations break H-bonds permitting exchange with solvent H or D’s.

H-bonds can be broken through solvent H or D’s.

K\text{observed} = K_{D_{observed}} \frac{K_{H_{observed}}}{K_{D_{observed}}}

observed rate = (% open/total rate when open)

ΔG = RT ln K

Subglobal-local

Protection Factor = K_{observed}/K_{free} = K_{observed}/K_{H}

What and How can we compare?

- Protection Factor: Most of previous works studied based on protection definition.

- H-bond - SASA of N

- % of water

- Local/Global Fluctuation based on subglobal/global behavior

- Open state Correlation function

- Denaturant dependent AG:

  - After defining m, for each microstate i, reweighting each microstate according to P(i|den)

  - Example of open state correlation function and denaturant dependent AG

Conclusions

We have developed a method to compare simulations to HX data, according to protection factors and their denaturant dependence. We applied the tool to model systems and real simulations. For real simulations, it is challenging to observe subglobal behavior, which it may related with (1) many local behaviors hide the subglobal signal, (2) it’s hard to see the subglobal behavior in native protein data, (3) our simulation is not good enough to replicate experimental HX results.

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