Molecular mechanism of activity in hyperthermophilic versus mesophilic enzymes

Objective:

- Understand the mechanism behind the activity of mesophilic proteins. This knowledge can be employed to engineer enzymes used to deconstruct biomass. Thermal stability and solvent (water) stability also have common mechanisms.

Approach:

- Explain using Molecular Dynamics simulations why the mesophilic pyrophosphatase (EcPPase) functions at high (non-native) temperatures whereas the hyperthermophilic homolog (TtPPase) is inactive at room temperature (non-native).

Results:

- Solvent accessibility of EcPPase is reduced at 353K compared to 298K, whereas that of TtPPase remains unaffected with this temperature change.
- At high temperatures, EcPPase adapts by reducing the number of hydrogen bonds with water molecules in its catalytic pocket and maintains its local flexibility which is necessary for activity.

Significance:

- Engineering of the active site of enzymes so that it becomes less solvent exposed while retaining local flexibility at high temperatures may increase enzymatic activity at high temperatures, a trait desirable for biofuels production.

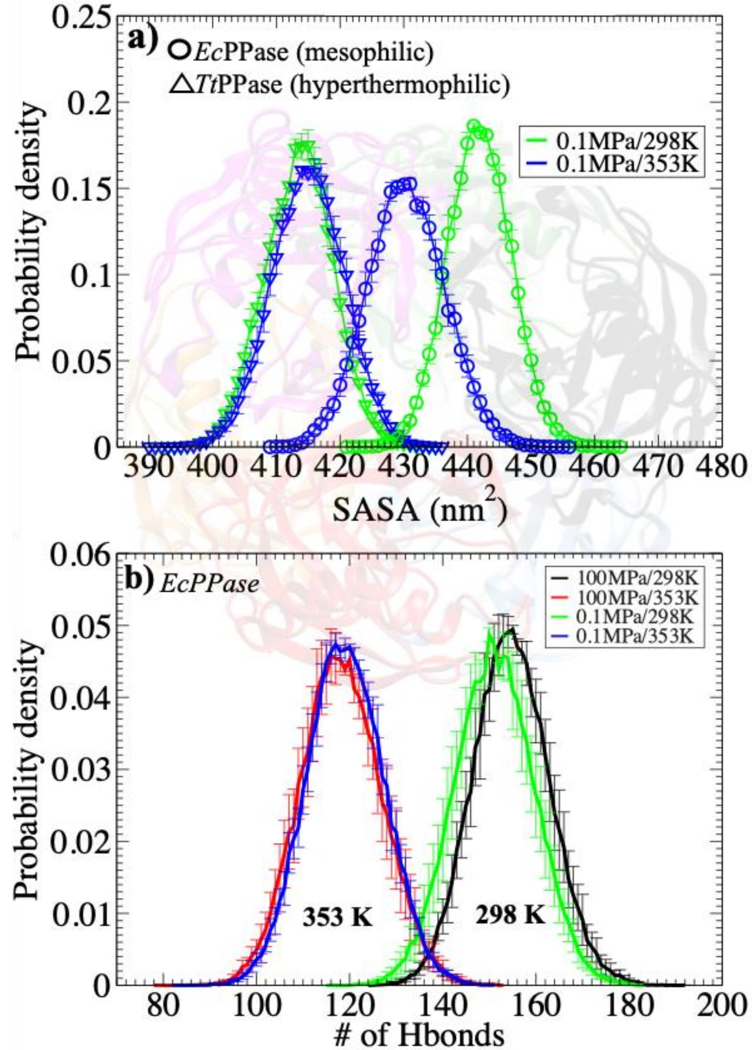

Figure: Histograms at different conditions: (a) solvent accessible surface area (SASA) of *Ec*PPase vs. *Tt*PPase and (b) hydrogen bonds (Hbond) between catalytic pocket residues of *Ec*PPase and water molecules.

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