Predictions of Molecular Binding/Unbinding Kinetics

Geometrical Flows, Transition Paths, and Multi-State Brownian Dynamics

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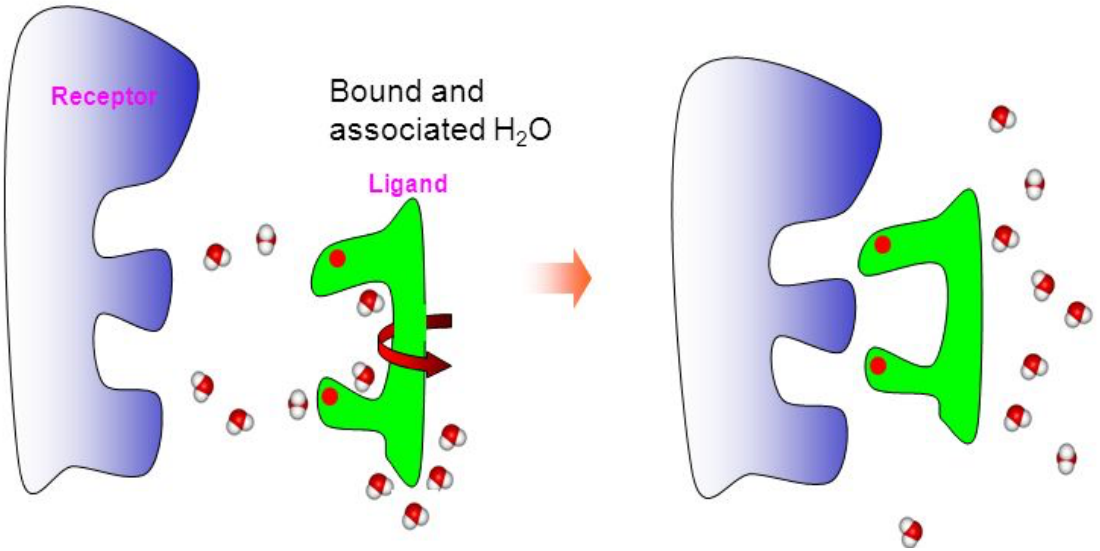
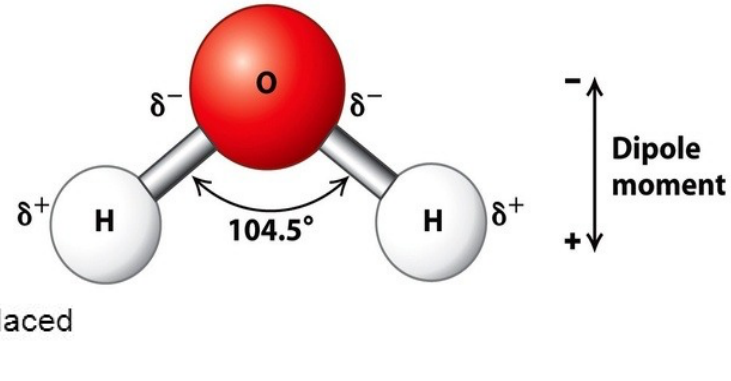
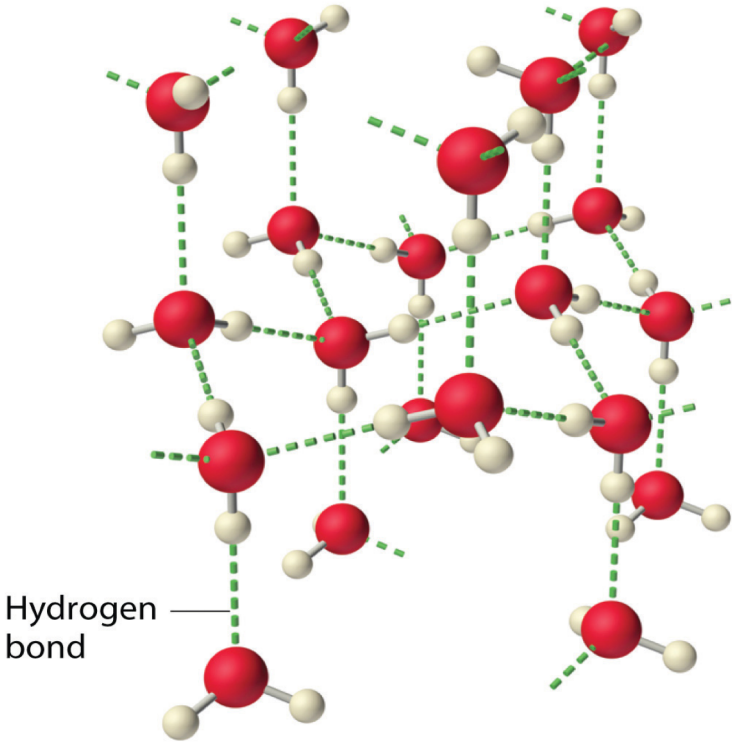
Reference

Zhou, *et al.* PNAS, 116, 14989-14994, 2019.

Ligand-Receptor Binding/Unbinding

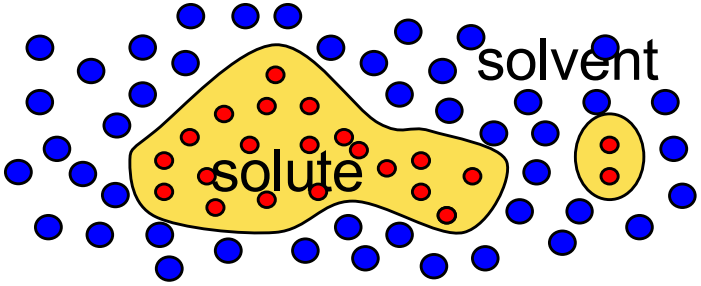






- **Binding affinity** – thermodynamics, free energy, binding sites, and stability.
- **Binding/unbinding kinetics** – fast/slow, residence time, etc.
- **Role of water** – fluctuations, dry-wet transitions, and polarization.
- **Application** in rational drug design.

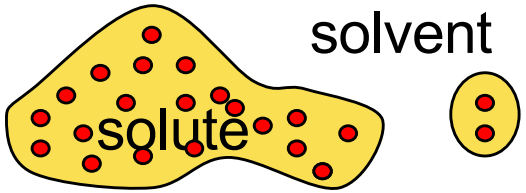
Biomolecular Modeling: Explicit vs. Implicit



MD simulations

$$m_i \ddot{r}_i = -\nabla_{r_i} V(r_1, \ldots, r_N)$$

$$\langle A \rangle = \frac{1}{Z} \iint A(p,r) e^{-\beta H(p,r)} dp dr = \langle A \rangle_{time}$$



Statistical mechanics

$$P(X,Y) = P_0 e^{-U(X,Y)/k_B T}$$

$$U(X,Y) = U_{uu}(X) + U_{vv}(Y) + U_{uv}(X,Y)$$

$$\overline{P}(X) = \int P(X,Y)\, dY = \overline{P}_0 e^{-W(X)/k_B T}$$

$W(X)$: **Potential of Mean Force**

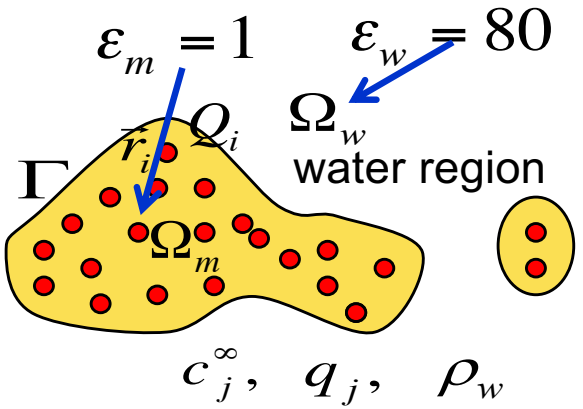
Our approach

- **V**ariational **I**mplicit-**S**olvent **M**odel (**VISM**)
- The string method for transition paths
- Brownian dynamics (BD) and Fokker-Planck equation (FPE) with multi-state fluctuations

Variational Implicit-Solvent Model (VISM)

Dzubiella, Swanson, & McCammon, PRL and JCP, 2006.

Γ : solute-solvent interfaces



Free-energy functional

$$G[\Gamma] = Pvol(\Omega_m) + \gamma_0 \int_\Gamma (1 - 2\tau H) dS$$

$$+ \rho_w \int_{\Omega_w} \sum_i U_{LJ,i}(|\vec{r} - \vec{r}_i|) dV + G_{elec}[\Gamma]$$

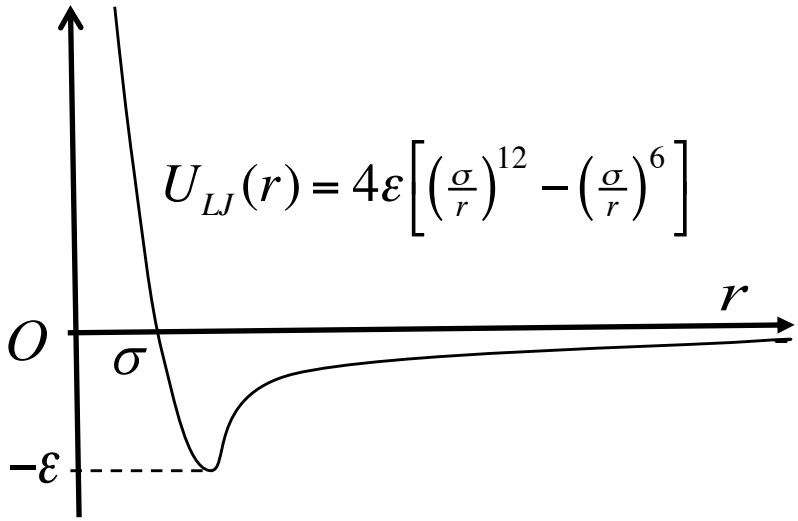
τ : the Tolman length, a fitting parameter

Poisson-Boltzmann (PB) theory

$$G_{elec}[\Gamma] = \int \left[-\frac{\varepsilon\varepsilon_0}{2} |\nabla\psi|^2 + \rho_f \psi - B(\psi) \right] dV$$

$$\nabla \cdot \varepsilon\varepsilon_0 \nabla\psi - B'(\psi) = -\rho_f \quad \text{(PBE)}$$

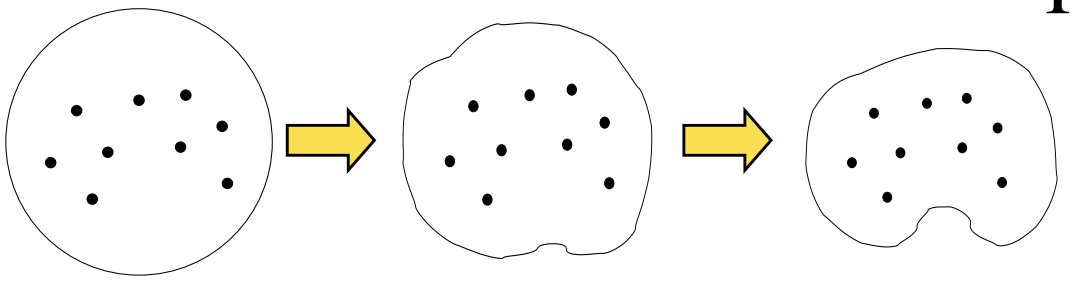
$$B(\psi) = \beta^{-1} \sum_{j=1}^{M} c_j^\infty \left(e^{-\beta q_j \psi} - 1 \right)$$



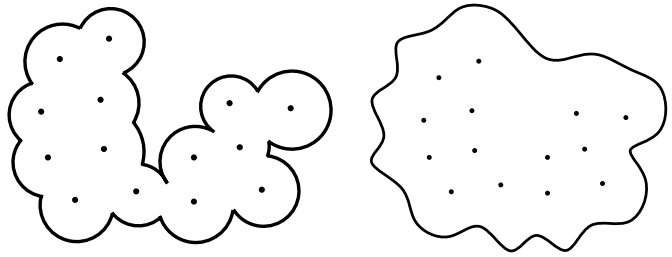
The Level-Set Method

$$\varphi_t + V_n |\nabla \varphi| = 0$$

$$\Gamma(t) = \{\vec{r} \in \Omega : \varphi(\vec{r}, t) = 0\}$$



Relaxation



Tight initial Loose initial

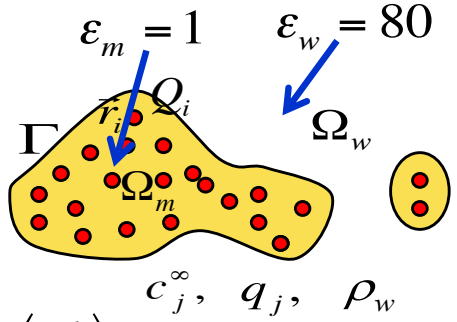
Normal velocity (i.e., boundary force)

Gaussian curvature

$$V_n = -\delta_\Gamma G[\Gamma](\vec{r}) = -P - 2\gamma_0[H(\vec{r}) - \tau K(\vec{r})] + \rho_w U(\vec{r}) - \delta_\Gamma G_{elec}[\Gamma]$$

$$G_{elec}[\Gamma] = \int \left[-\frac{\varepsilon\varepsilon_0}{2} |\nabla\psi|^2 + \rho_f \psi - B(\psi) \right] dV$$

$$\nabla \cdot \varepsilon\varepsilon_0 \nabla\psi - \chi_w \sum_{j=1}^{M} q_j c_j^\infty e^{-\beta q_j \psi} = -\rho_f$$

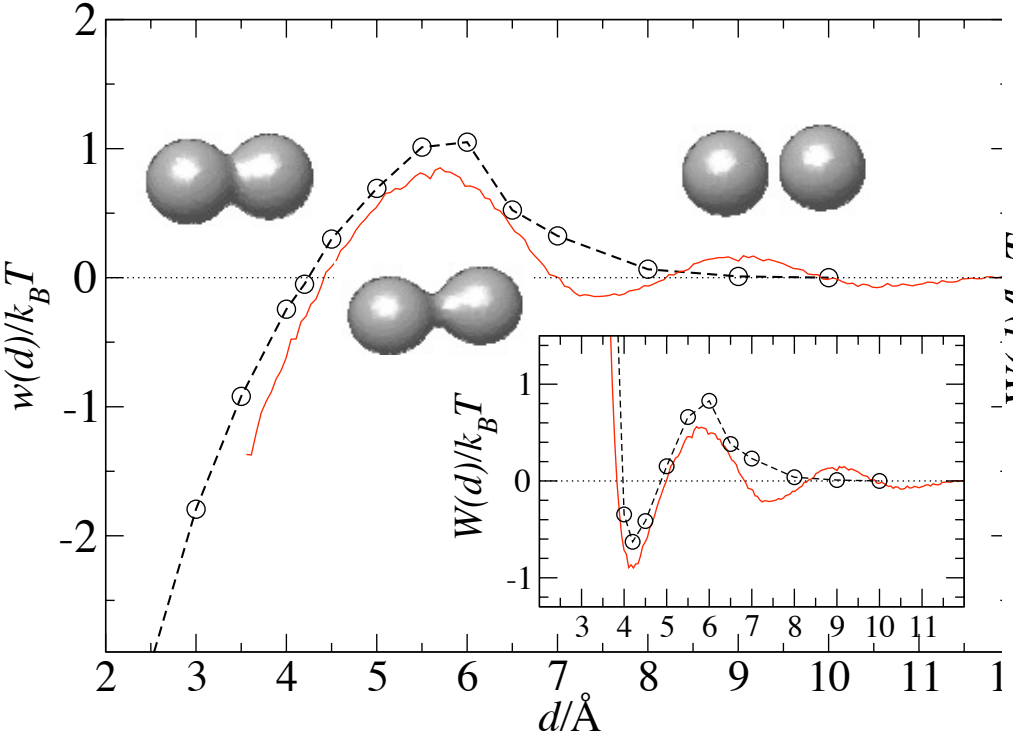


$$\Gamma_t \Rightarrow \text{PBE: } \psi_t \Rightarrow G_{elec}[\Gamma_t] \Rightarrow \delta_\Gamma G_{elec}[\Gamma] = \left(\frac{d}{dt}\right)_{t=0} G_{elec}[\Gamma_t]$$

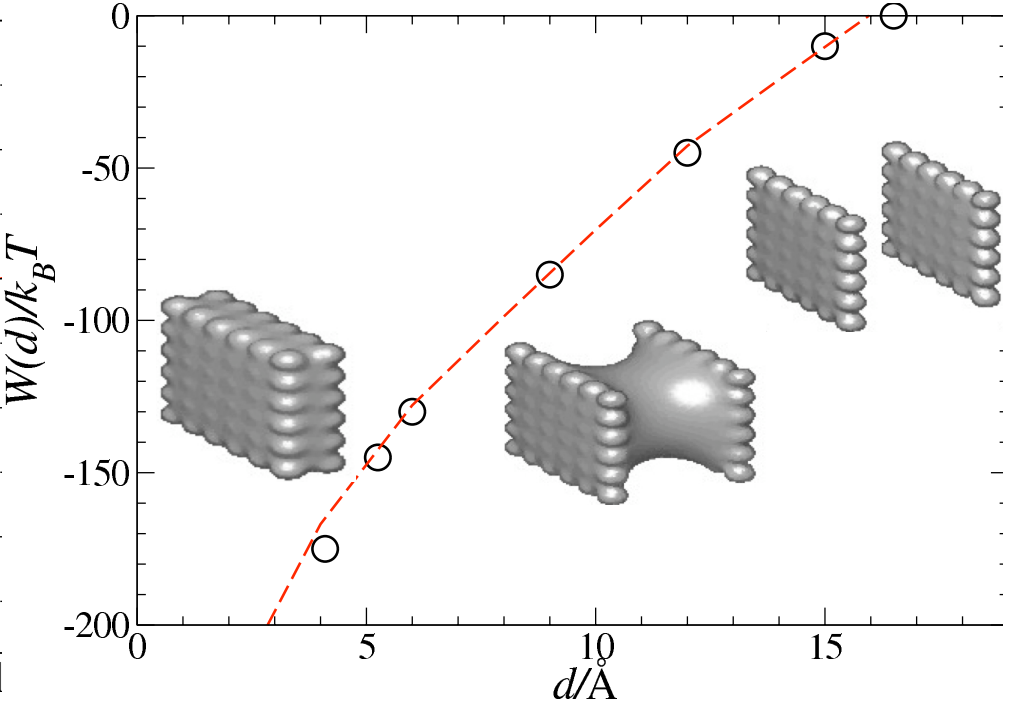
$$-\delta_\Gamma G_{elec}[\Gamma] = \frac{\varepsilon_0}{2}\left(\frac{1}{\varepsilon_w} - \frac{1}{\varepsilon_m}\right) |\varepsilon \partial_n \psi|^2 + \frac{\varepsilon_0}{2}(\varepsilon_m - \varepsilon_w)\left|(I - n \otimes n)\nabla\psi\right|^2 - B(\psi).$$

Estimation of Solvation Free Energies

Two xenon atoms



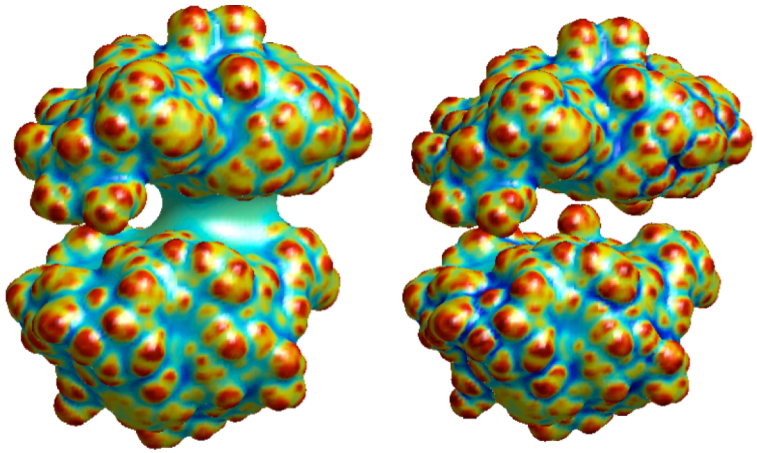
Two paraffin plates



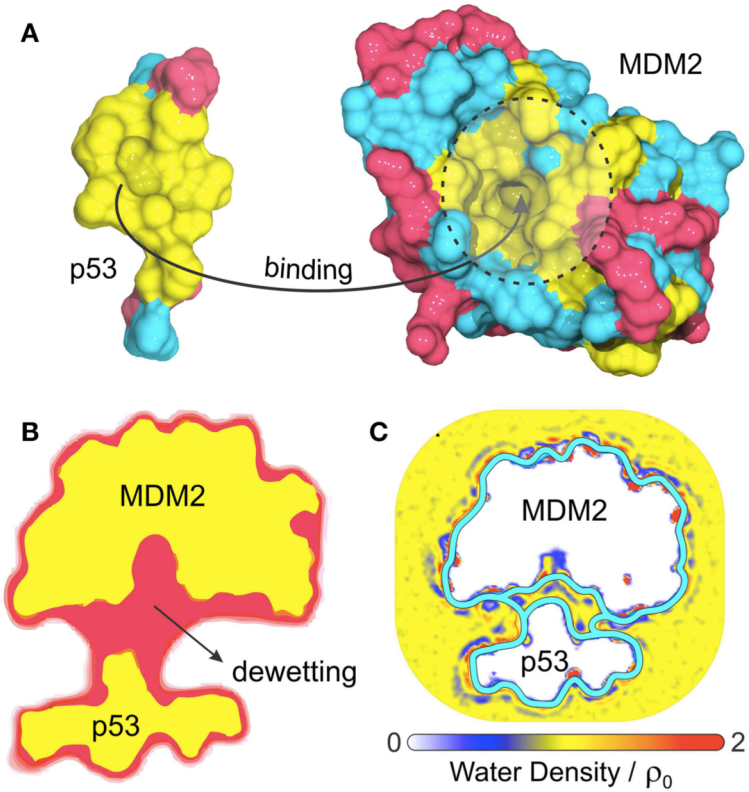
PMF: Level-set (circles) vs. MD (solid line).

MD: Paschek, JCP 2004. Koishi *et al.* PRL 2004; JCP 2005.

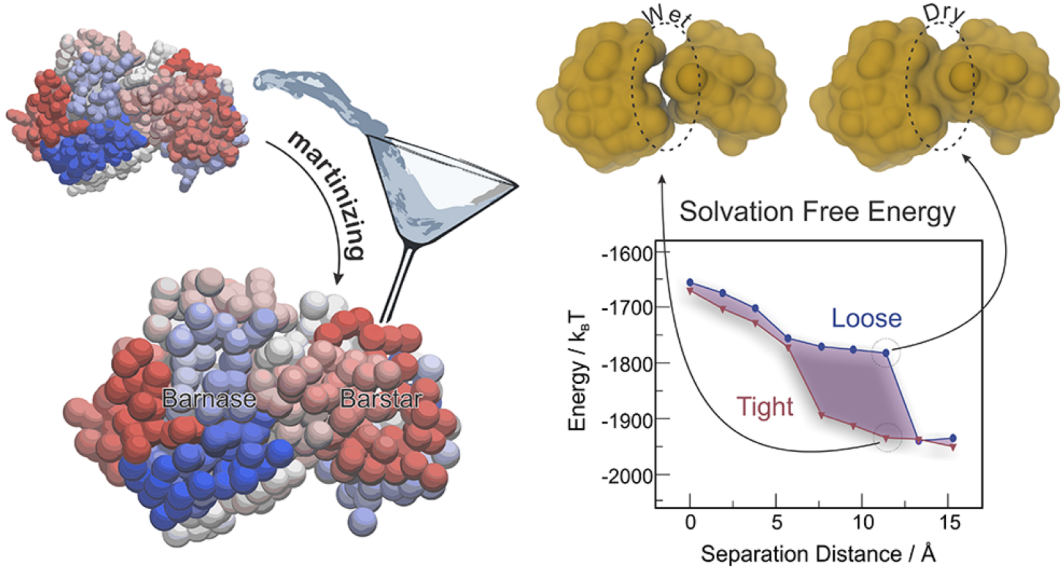
BphC



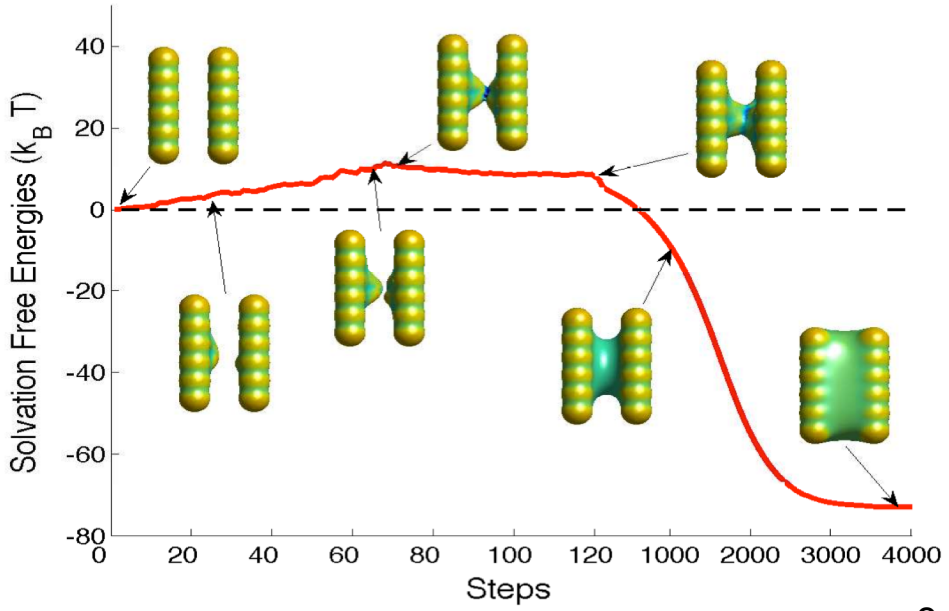
p53/MDM2



Martini-VISM: Barstar-barnase



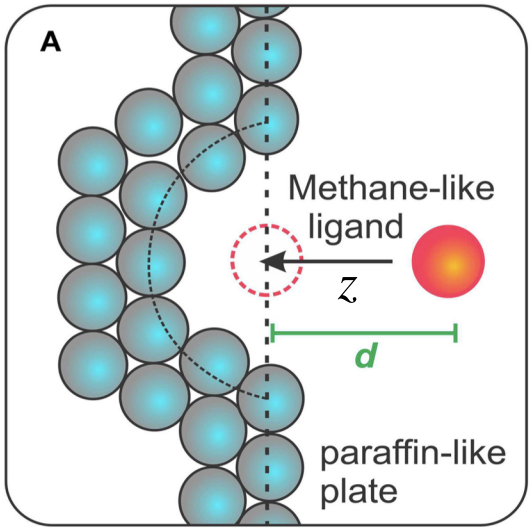
Stochastic level-set VISM for dewetting transition

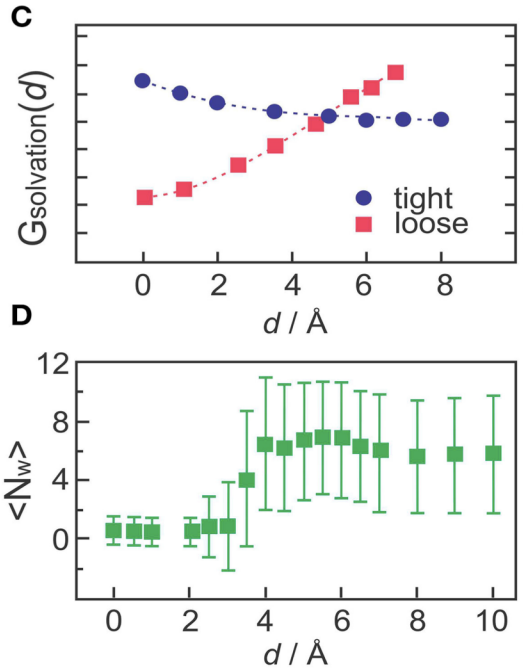


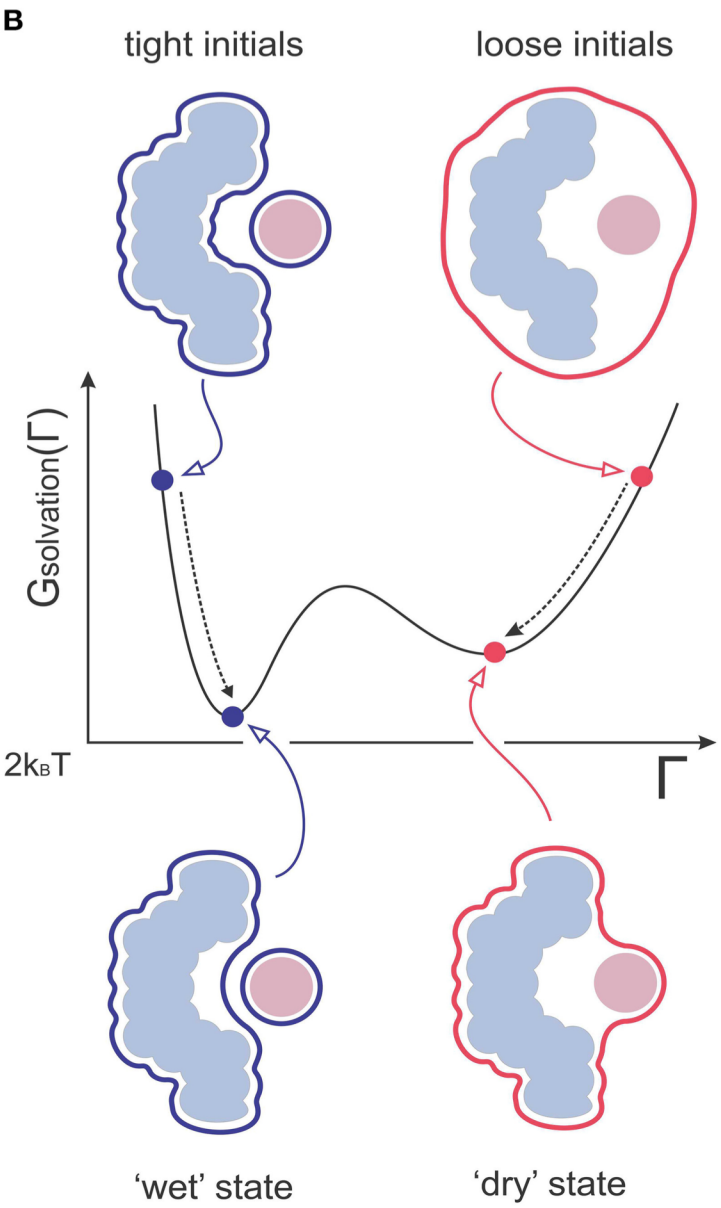
Binding/Unbinding: A Model System

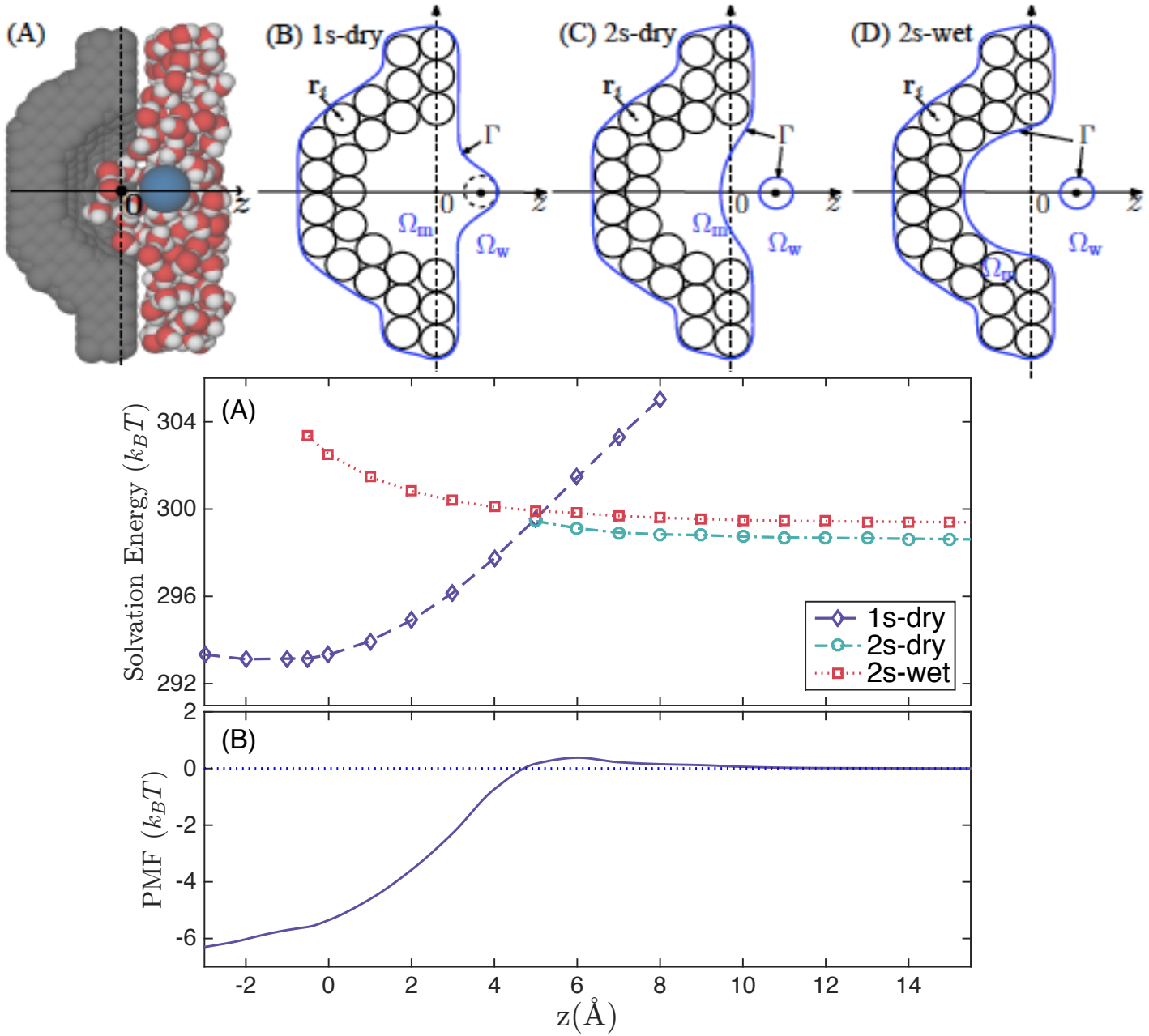
Outline

- Dry and wet states, PMF
- Transition paths, energy barriers, and kinetic rates
- BD simulations and FPE calculations









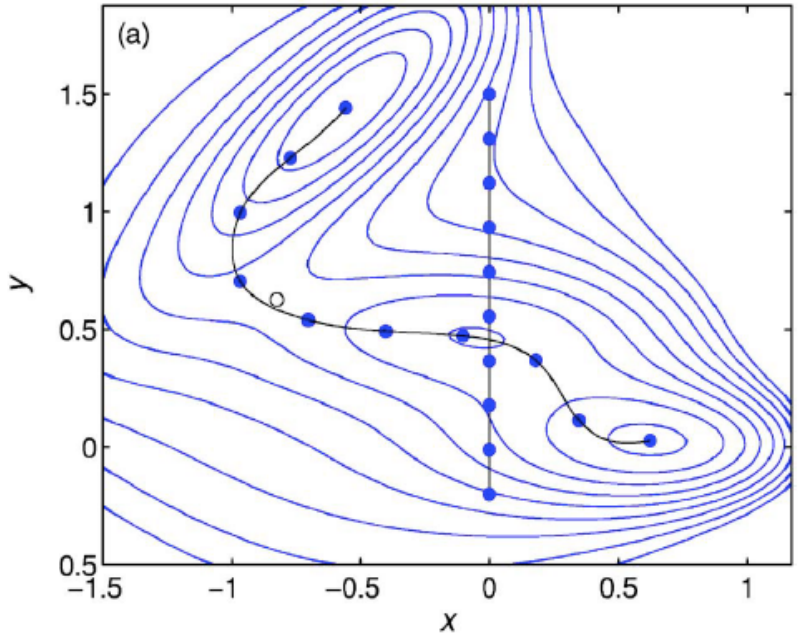
(A) Solvation free energies. (B) The total PMF.

$$V_{\mathrm{tot}}(z) = -k_{\mathrm{B}}T \ln \left(\sum_{\Gamma(z)} e^{-G[\Gamma(z)]/k_{\mathrm{B}}T} \right) + U_{\mathrm{vdW}}(z) + V_{\mathrm{tot},\infty}$$

The String Method

(E, Run, & Vander-Eijnden, 2000s)

MEP: minimum energy path



VISM-(Simplified) String Method

String: $\phi_\alpha = \phi_\alpha(x,t) \qquad (0 \le \alpha \le 1)$

$\phi_0 =$ First State, $\quad \phi_1 =$ Second State.

$$\partial_t \phi_\alpha = -V_n(\phi_\alpha)|\nabla \phi_\alpha| + \lambda_\alpha \frac{\partial_\alpha \phi_\alpha}{|\partial_\alpha \phi_\alpha|} \qquad (0 < \alpha < 1)$$

α is the normalized arc length and λ_α is a Lagrange multiplier.

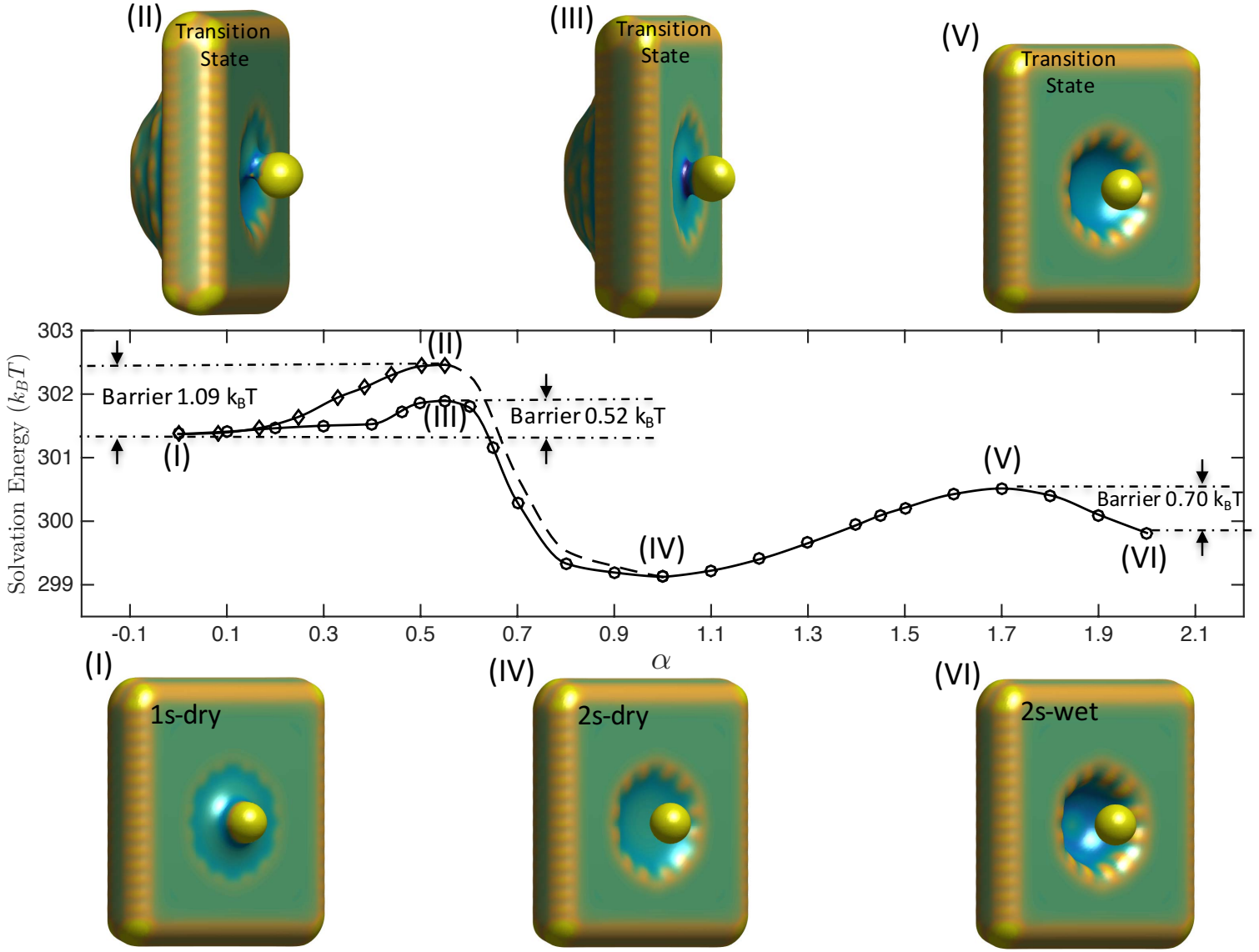
Discretization $\quad 0 = \alpha_0 < \alpha_1 < \cdots < \alpha_M < \alpha_{M+1} = 1$

Iteration $\quad \{(\alpha_j^k, \phi_j^k)\}_{j=1}^M \Rightarrow \{(\alpha_j^*, \phi_j^*)\}_{j=1}^M \Rightarrow \{(\alpha_j^{k+1}, \phi_j^{k+1})\}_{j=1}^M$

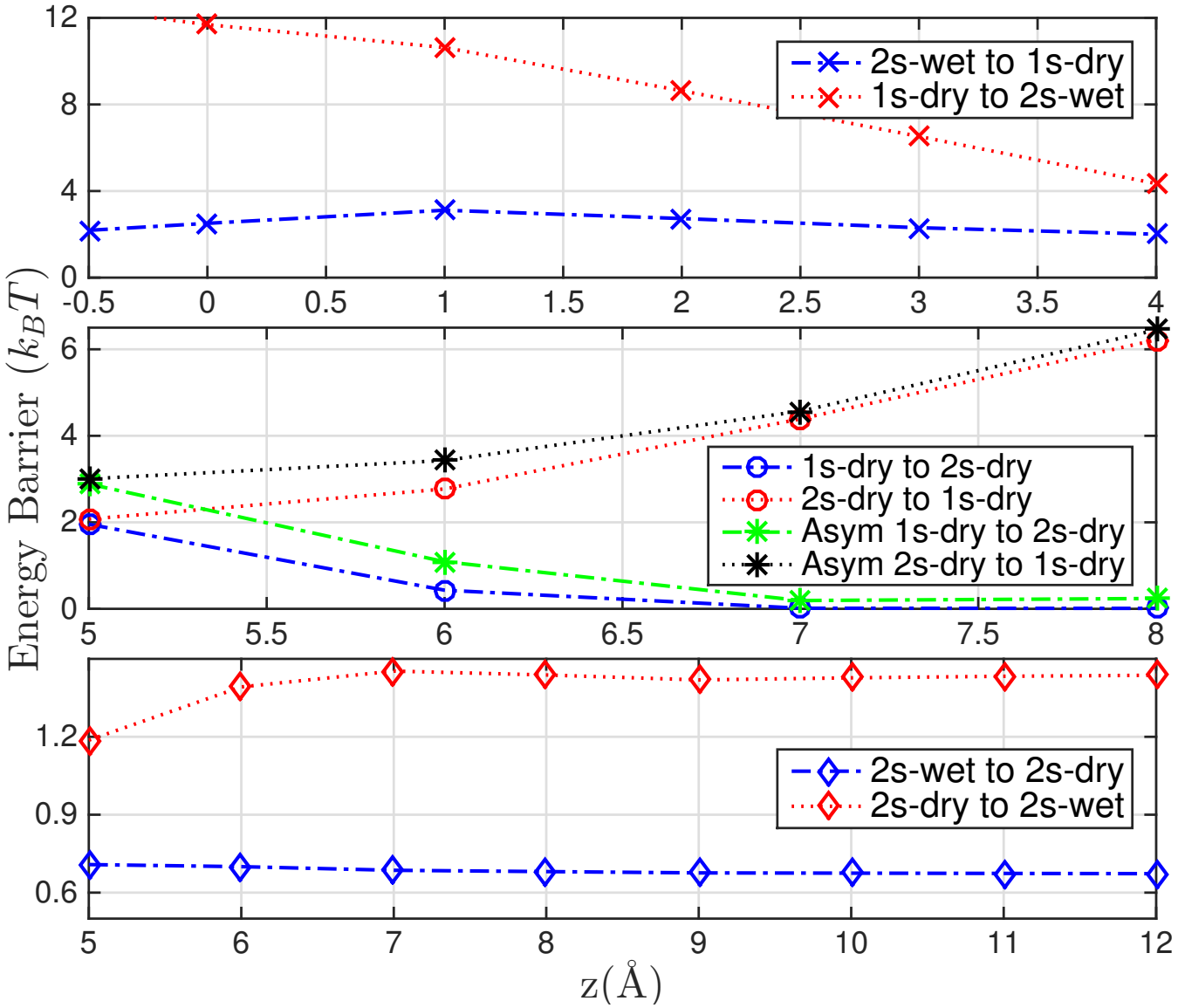
$$s_0 = 0 \text{ and } s_j = s_{j-1} + \|\phi_j^* - \phi_{j-1}^*\| \ (j = 1, \ldots, M)$$

$$\alpha_j^* = s_j / s_M \ (j = 1, \ldots, M)$$

$$\alpha_j^{k+1} = j/(M+1) \quad (j = 1, \ldots, M)$$



Two MEPs connecting “1s-dry", “2s-dry”, and “2s-wet" at $z = 6$ Å with axi-asymmetric (II) and axisymmetric (III) transition states.



Transition energy barriers used to define the transition rates:

$R_{\mathrm{dw}}(z) \sim \exp\{ -$ (dry-wet transition energy barrier at $z)/k_{\mathrm{B}}T$ $\}$

$R_{\mathrm{wd}}(z) \sim \exp\{ -$ (wet-dry transition energy barrier at $z)/k_{\mathrm{B}}T$ $\}$

Brownian dynamics (without dry-wet fluctuations)

$$dz_t = \left[-\frac{1}{k_{\mathrm{B}}T} D_{\mathrm{eff}}(z_t) V'_{\mathrm{tot}}(z_t) + D'_{\mathrm{eff}}(z_t) \right] dt + \sqrt{2D_{\mathrm{eff}}(z_t)}\, d\xi_t$$

$z_t = z(t)$: ligand position at time t .

$D_{\mathrm{eff}} = D_{\mathrm{eff}}(z)$: effective diffusion coefficient;
$D_{\mathrm{eff}} \approx 0.25$ Å/ps outside and 1 Å/ps inside the pocket.

Constraint: $z(t) \in [z_{\mathrm{L}}, z_{\mathrm{R}}]$

For binding simulation: reset $z(t)$ to be $2z_{\mathrm{R}} - z(t)$ if $z(t) \geq z_{\mathrm{R}}$,
stop the simulation if $z(t) \leq z_{\mathrm{L}}$.

For unbinding simulation: reset $z(t)$ to be z_{L} if $z(t) \leq z_{\mathrm{L}}$,
stop the simulation if $z(t) \geq z_{\mathrm{R}}$.

The mean first passage time **(MFPT)**: Average over many simulations.

A Continuous Time Markov Chain (CTMC) Model for the Brownian Dynamics with Pocket Dry-Wet Fluctuations

$$\begin{cases} dz_t = \left[-\dfrac{1}{k_{\mathrm{B}}T} D(z_t) \dfrac{\partial V_{\mathrm{fluc}}(\eta(z_t), z_t)}{\partial z} + D'(z_t) \right] dt + \sqrt{2D(z_t)}\, d\xi_t, \\ \eta(z_t) \in \{0, 1, 2\} \text{ is a CTMC with the transition rate matrix} \\ \begin{pmatrix} -\left[R_{01}(z_t) + R_{02}(z_t)\right] & R_{01}(z_t) & R_{02}(z_t) \\ R_{10}(z_t) & -\left[R_{10}(z_t) + R_{12}(z_t)\right] & R_{12}(z_t) \\ R_{20}(z_t) & R_{21}(z_t) & -\left[R_{20}(z_t) + R_{21}(z_t)\right] \end{pmatrix} \end{cases}$$

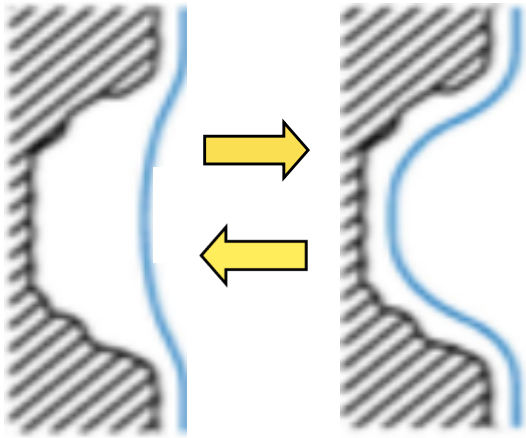
$$V_{\mathrm{fluc}}(\eta, z) = G_i(z) + U_0(z) \quad \text{if } \eta = i$$

$$R_{ij}(z) = R_0 e^{-B_{ij}(z)/k_{\mathrm{B}}T}$$

$\eta(z, 0)$: equilibrium distribution

$$P_i^{\mathrm{eq}}(z) = \frac{e^{-G[\Gamma_i(z)]/k_{\mathrm{B}}T}}{\sum_{j=0}^{2} e^{-G[\Gamma_j(z)]/k_{\mathrm{B}}T}}$$

Constraint: $z(t) \in [z_{\mathrm{L}}, z_{\mathrm{R}}]$

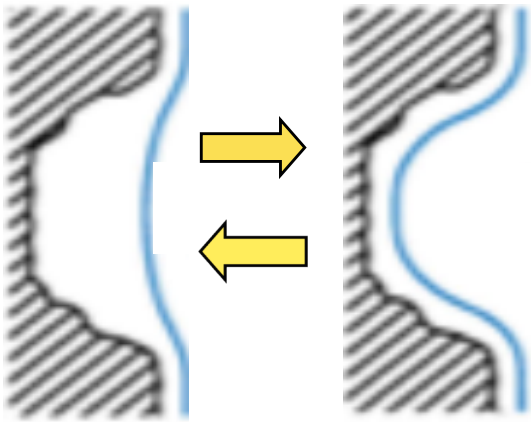


Pocket dry-wet fluctuations

FPE without dry-wet fluctuations

$$\frac{\partial \bar{P}(z,t)}{\partial t} = \frac{\partial}{\partial z}\left\{ D_{\text{eff}}(z)\left[\frac{\partial \bar{P}(z,t)}{\partial z} + \frac{1}{k_{\text{B}}T} V'_{\text{tot}}(z)\bar{P}(z,t)\right]\right\}$$

$\bar{P}(z,t)$: Density of probability of the ligand at position z at time t



Pocket dry-wet fluctuations

FPE with dry-wet Fluctuation

$P_i(z,t)$: PDF of probability of the ligand at location z at time t with the system being in the *i*-th state.

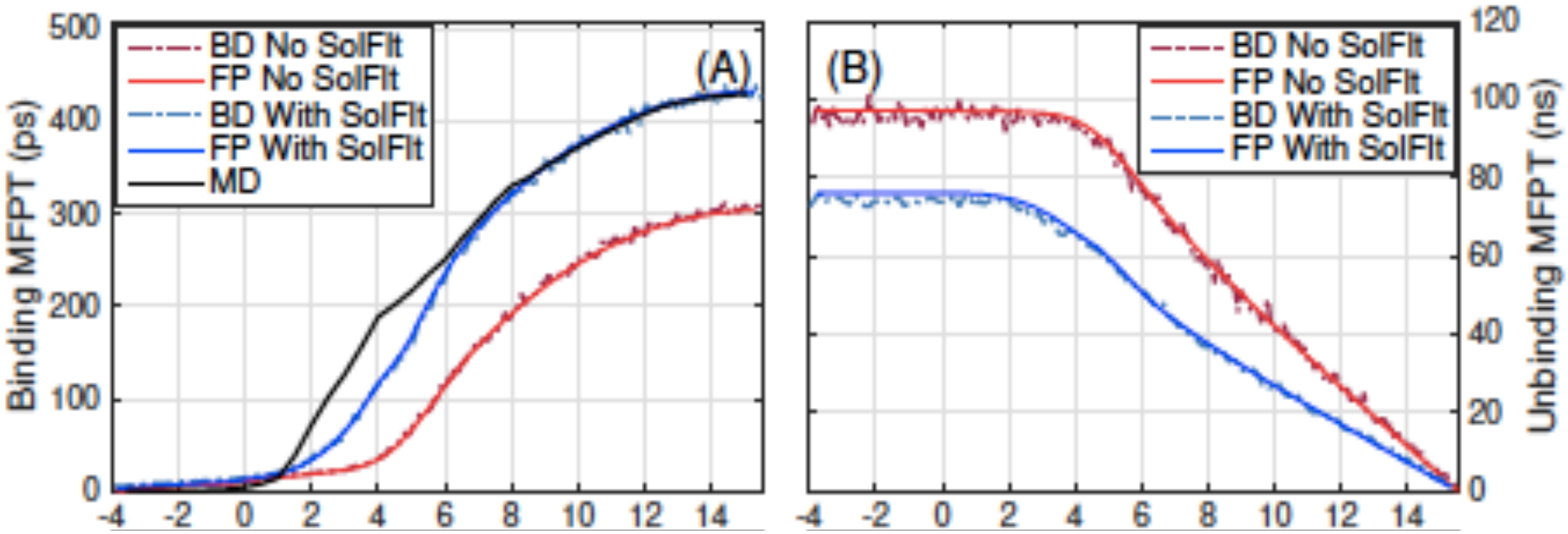
$$\frac{\partial P_i}{\partial t} = \frac{\partial}{\partial z}\left\{ D(z)\left[\frac{\partial P_i}{\partial z} + \frac{1}{k_{\text{B}}T} V'_i(z)P_i\right]\right\} + \sum_{0\le j\le 2,\, j\neq i} R_{ji}(z)P_j - \left(\sum_{0\le j\le 2,\, j\neq i} R_{ij}(z)\right) P_i$$

Boundary conditions

$$\bar{P}(z_{\text{L}},t) = 0 \quad \text{and} \quad \frac{\partial \bar{P}(z_{\text{R}},t)}{\partial z} = 0 \qquad \text{for binding,}$$

$$\frac{\partial \bar{P}(z_{\text{L}},t)}{\partial z} + \frac{1}{k_{\text{B}}T} V'_{\text{tot}}(z_{\text{L}})\bar{P}(z_{\text{L}},t) = 0 \quad \text{and} \quad \bar{P}(z_{\text{R}},t) = 0 \quad \text{for unbinding.}$$

MFPT $\tau_{\text{MFPT}} = \int_0^{\infty}\int_{z_{\text{L}}}^{z_{\text{R}}} P(z,t)\, dz\, dt$



The MFPT for: (A) the binding of ligand that starts from *z* and reaches the pocket at –4 Å; and (B) the unbinding of ligand that starts from z and reaches 15.5 Å.

Note: The time unit in (B) is ns while that in (A) is ps.

Conclusions

A new and efficient approach to the binding/unbinding kinetics.

- Level-set VISM for equilibrium states and PMFs.
- Level-set VISM-string method for transition paths and rates.
- A CTMC model and FPE for the stochastic dynamics with the dry-wet fluctuation.

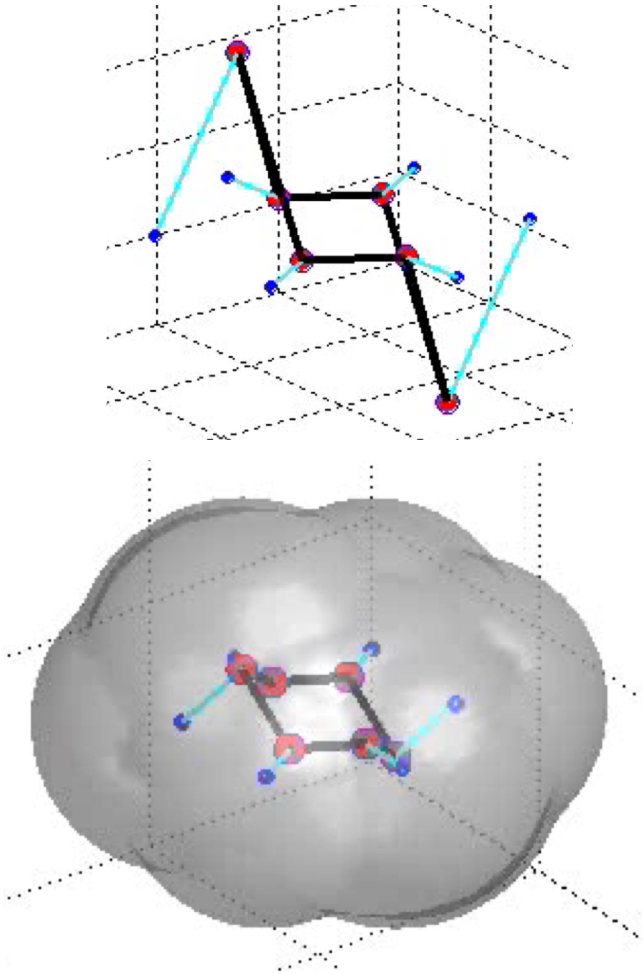
No tracking of individual water molecules!

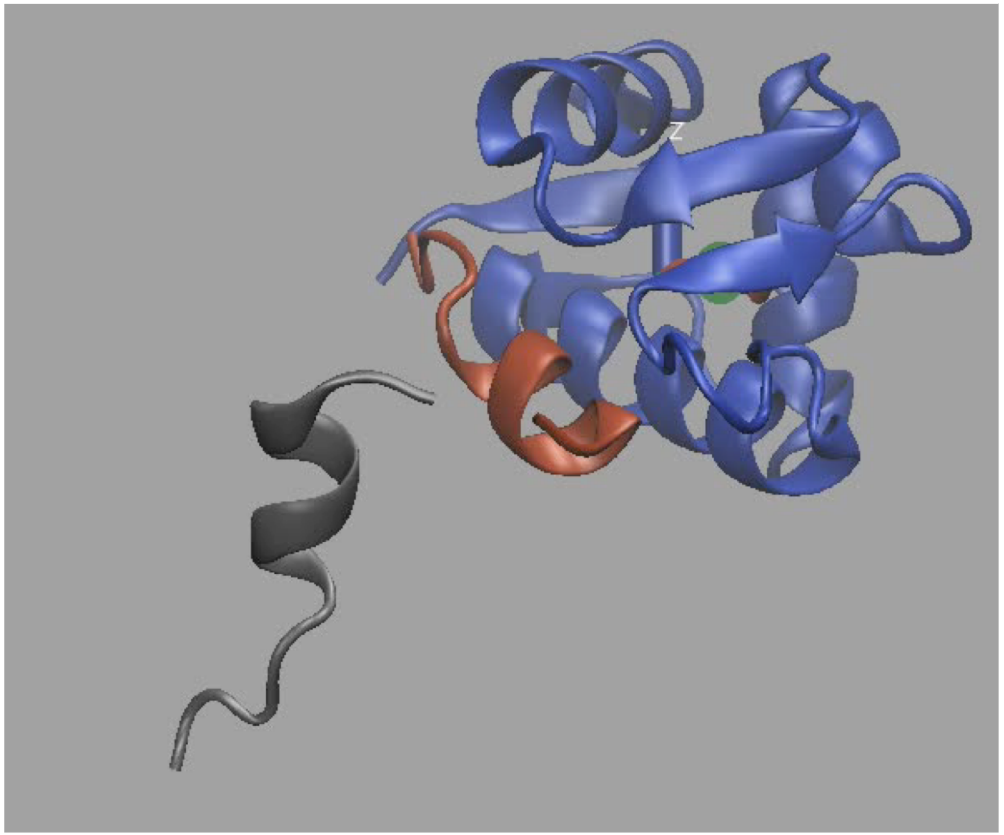
Our studies have predicted

- PMF and MFPT (for binding) agreeing with MD simulations.
- The dry-wet fluctuation is crucial to the binding/unbinding kinetics: decelerates binding but **accelerates unbinding**.

Current and Future Work

- Coupling solute molecular mechanics with coarse-grained VISM.
- Fast algorithms and advanced Monte Carlo sampling. Numerical energy landscapes. Convergence.
- Real systems, e.g., beta-cyclodextrin, p53/MDM2, etc. More general reaction coordinates.





Thank You!