Coupling Monte Carlo, Variational Implicit Solvation, and Binary Level-Set for Simulations of Biomolecular Binding

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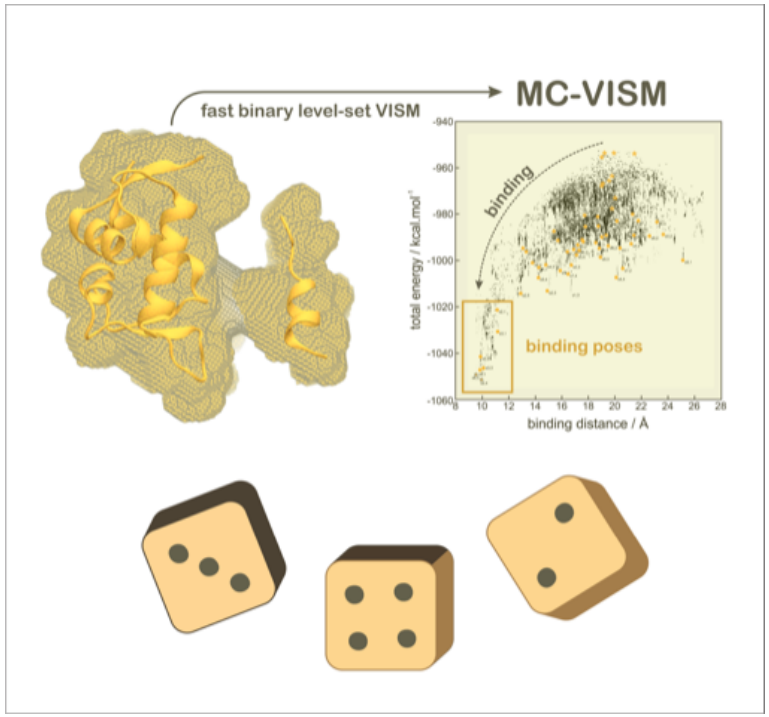
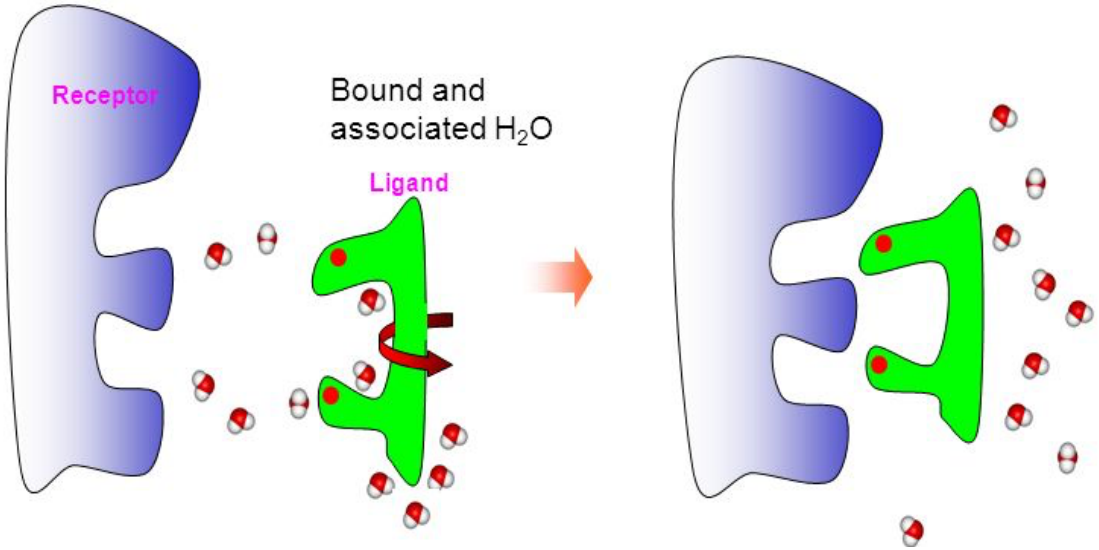
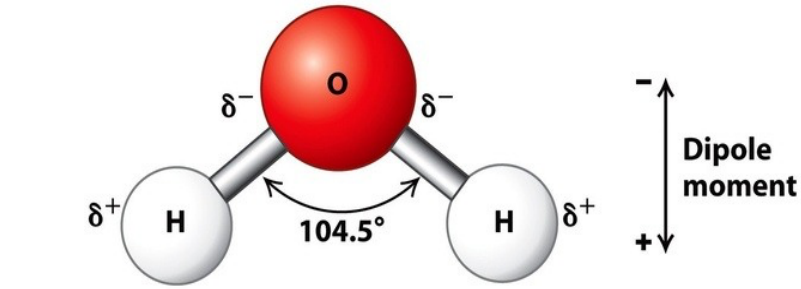
Outline

- Background
- A Variational Approach
- Fast Level-Set Monte Carlo Simulations
- Conclusions

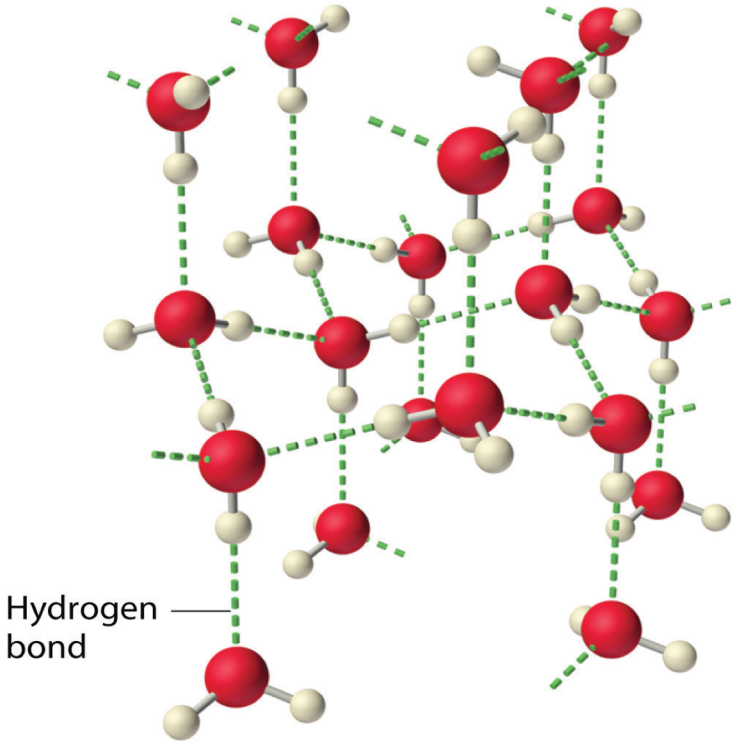


Biomolecular Binding and Unbinding



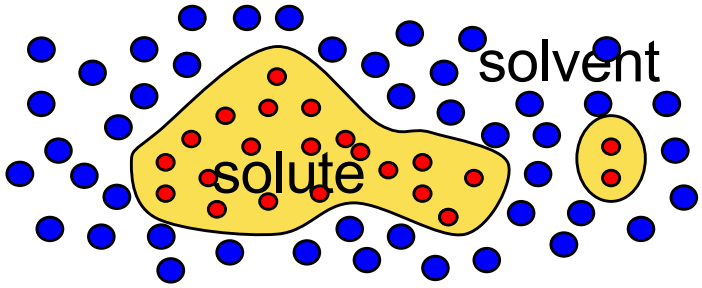


Displaced H_2O

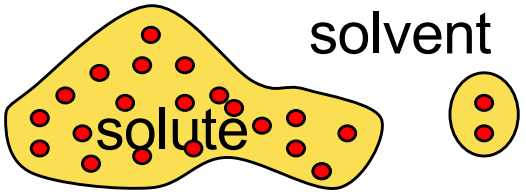


- **Binding affinity** – thermodynamics, free energy, and stability.
- **Binding/unbinding kinetics** – fast/slow, residence time, etc.
- **Binding modes:** Lock-and-key? Conformational selection? Induced fit?
- **Role of water** – polarization, fluctuations, dry-wet transitions, etc.
- **Application** in rational drug design.

Biomolecular Modeling: Explicit vs. Implicit



Explicit-water MD simulations



Dielectric-boundary based Implicit-solvent models

Born's model (1920)

$$\Delta G = -\frac{q^2}{8\pi\varepsilon_0 R}\left(\frac{1}{\varepsilon_m} - \frac{1}{\varepsilon_w}\right)$$

Solute-solvent interface or dielectric boundary

- Protein-water interface ~ vaper-liquid interface
- Abrupt change of dielectric environment

Hasted, Ritson, & Collie, JCP 1948.

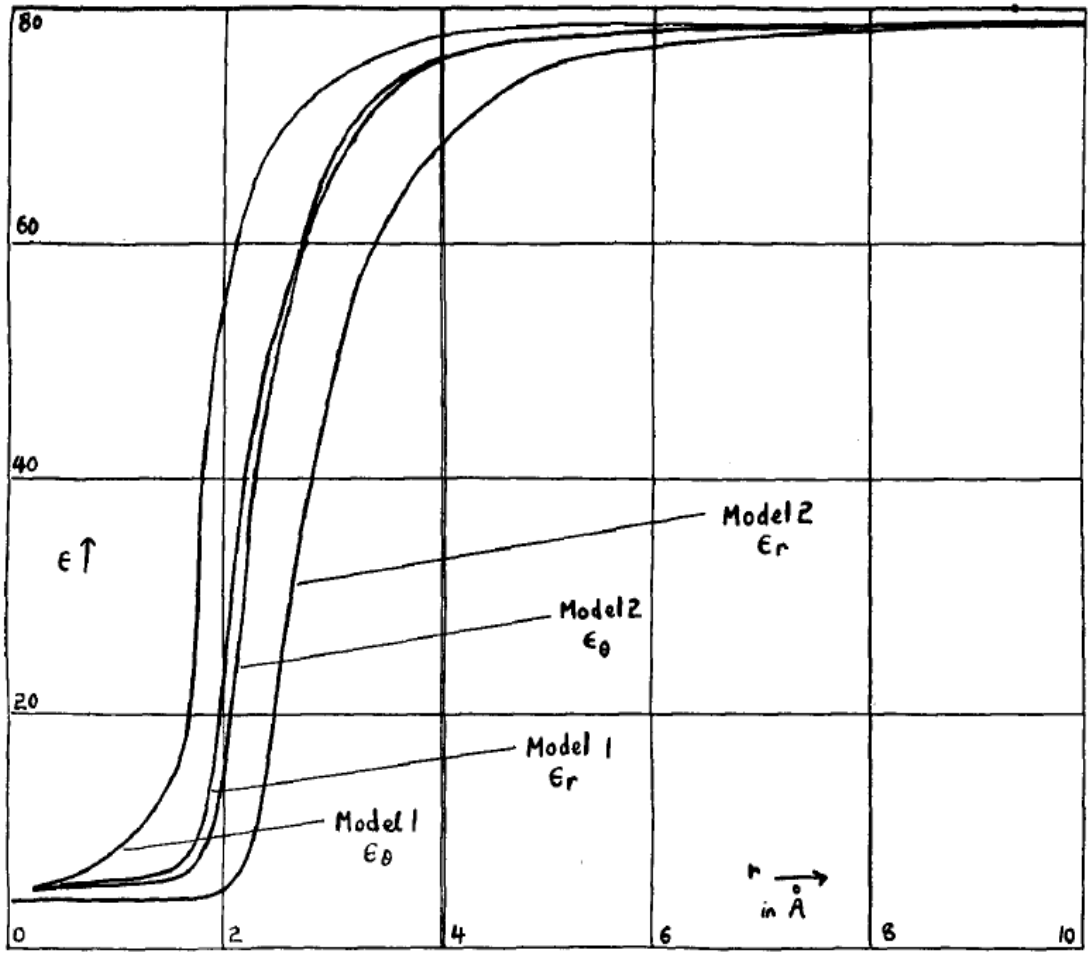
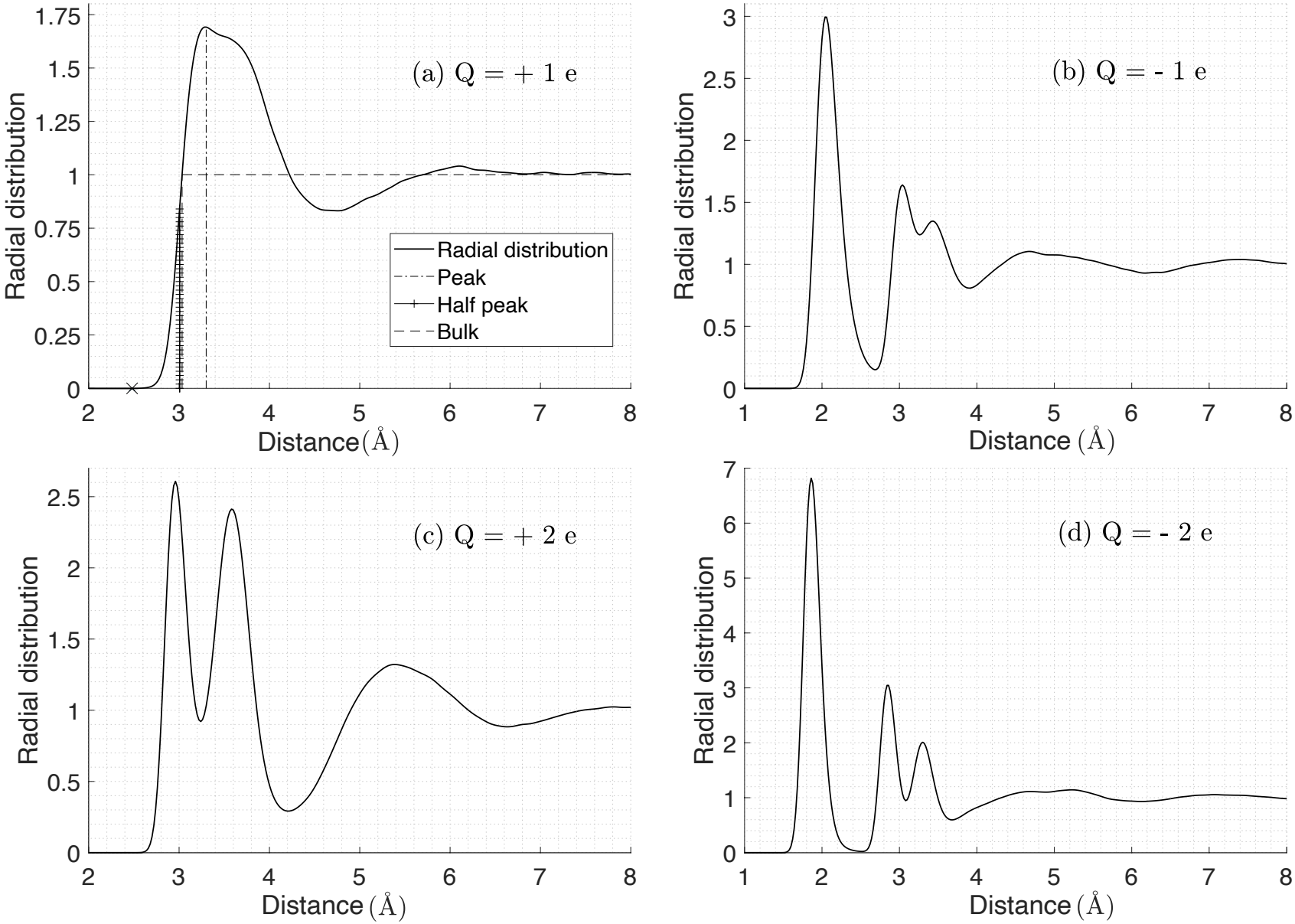


FIG. 1. Plot of dielectric constants ϵ_r, ϵ_θ against distance r in angstroms from an ion.

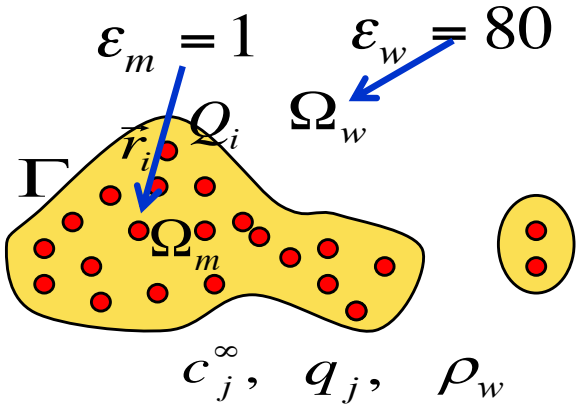
The Radius of an Ion (Fan-Li-White, SIAP 2021)



Variational Implicit-Solvent Model (VISM)

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

Γ : solute-solvent interfaces



Solvation free-energy functional

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

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

surface energy

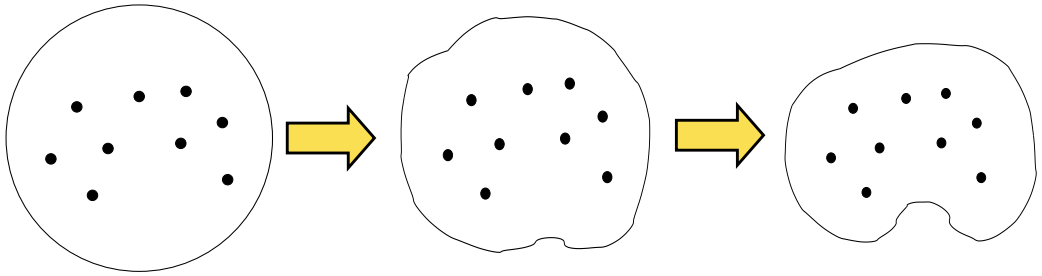
solute-solvent interactions

$G_{elec}[\Gamma]$: Poisson-Boltzmann (PB) theory

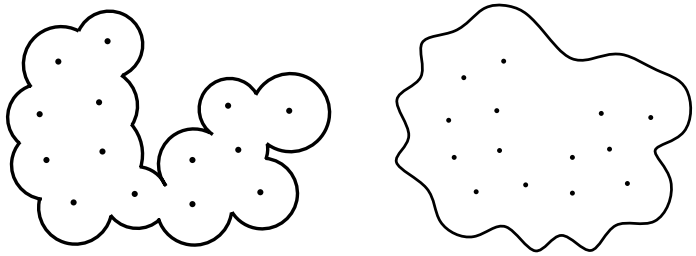
Coulomb-field approximation (CFA)

Theorem. Minimizers exist. (Dai-Li-Lu, ARMA 2018)

Level-set numerical method



Relaxation

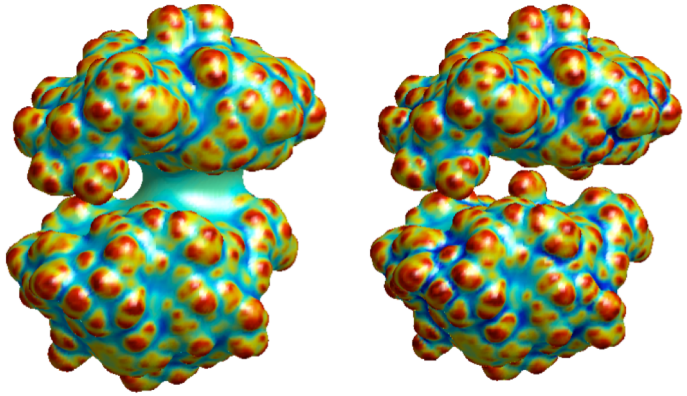


Tight initial

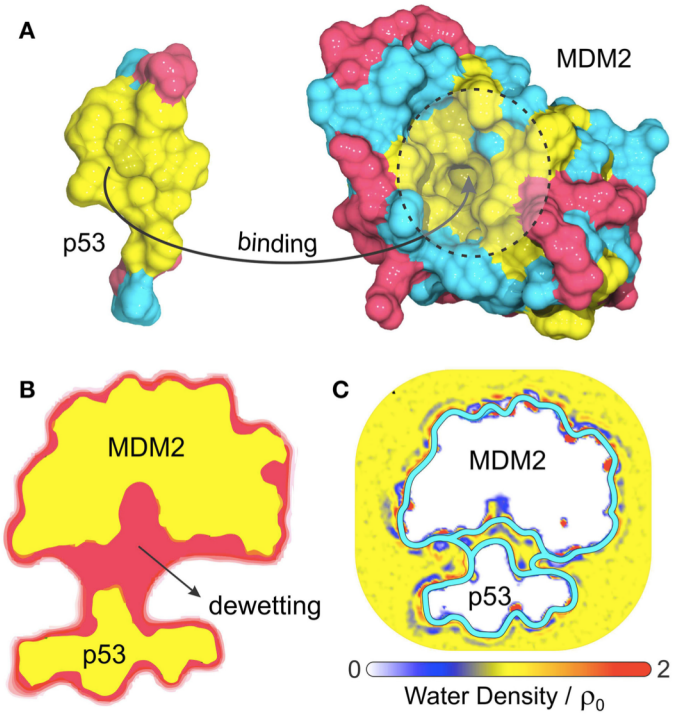
Loose initial

Dry and Wet States

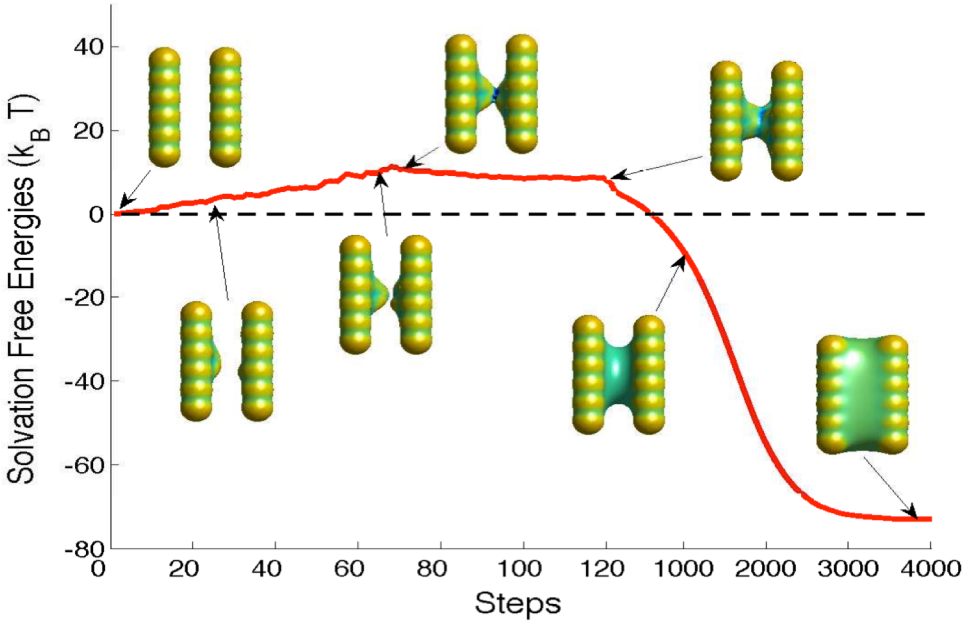
BphC



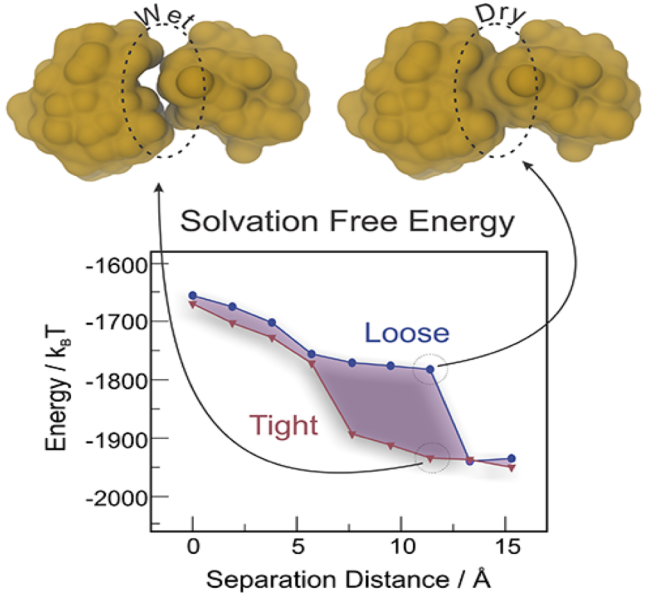
p53/MDM2



Stochastic level-set VISM for dewetting transition



Martini-VISM: Barstar-barnase

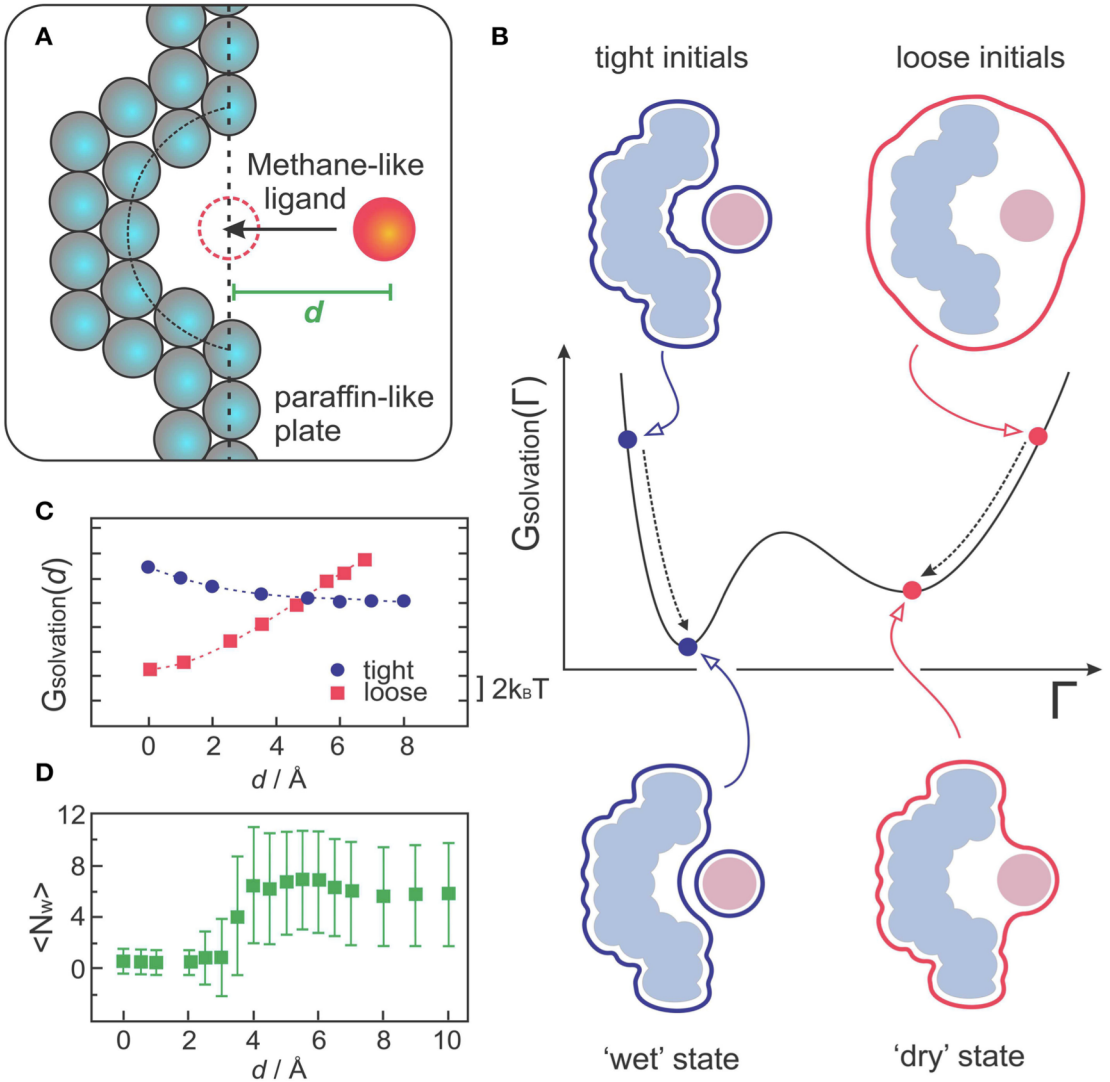


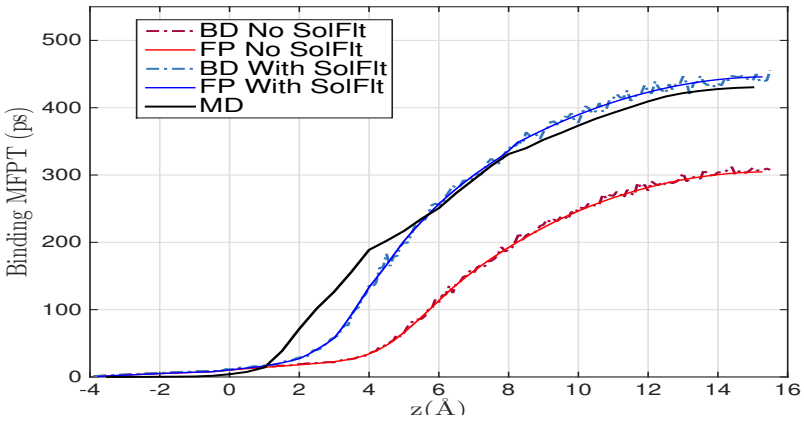
Predict the kinetics by VISM-string method-BD simulations

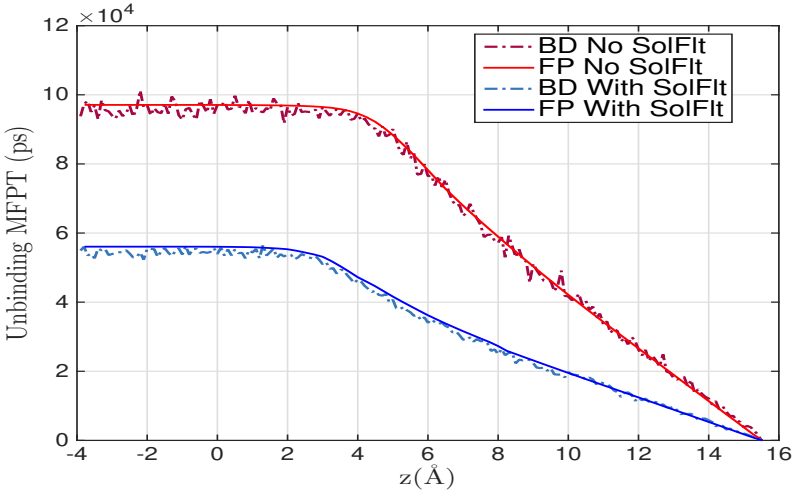
(Zhou, *et al*, PNAS 2019)

A Model System

- Dry and wet states, PMF
- Transition paths and energy barriers
- BD simulations for MFPT

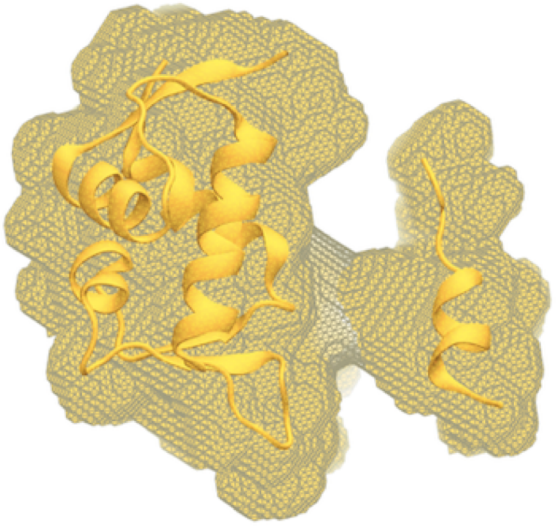






Monte Carlo-VISM-Level Set for Binding

(Zhang, Ricci, *et al.* JCTC 2021)



The total interaction free energy

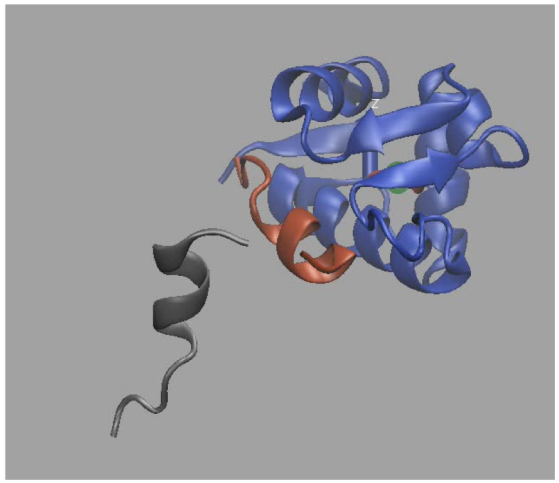
$$G_{\text{total}} = G_{\text{vdW,sol-sol}} + G_{\text{elec,sol-sol}} + G_{\text{solvation}}$$

$$G_{\text{vdW,sol-sol}} = \sum_{i=1}^{M}\sum_{j=1}^{N} 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{|\mathbf{r}_i^A - \mathbf{r}_j^B|}\right)^{12} - \left(\frac{\sigma_{ij}}{|\mathbf{r}_i^A - \mathbf{r}_j^B|}\right)^{6}\right]$$

$$G_{\text{elec,sol-sol}} = \frac{1}{4\pi\varepsilon_0\varepsilon_w}\sum_{i=1}^{M}\sum_{j=1}^{N}\frac{Q_i^A Q_j^B}{|\mathbf{r}_i^A - \mathbf{r}_j^B|}$$

$$G_{\text{solvation}} = \min_{\Gamma} G_{\text{VISM}}[\Gamma]$$

CFA: $$G_{\text{elec}}[\Gamma] = \frac{1}{32\pi^2\varepsilon_0}\left(\frac{1}{\varepsilon_w} - \frac{1}{\varepsilon_m}\right)\int_{\mathbb{R}^3\setminus\Omega_m}\left|\sum_{i=1}^{L}\frac{Q_i(\mathbf{r}-\mathbf{r}_i)}{|\mathbf{r}-\mathbf{r}_i|^3}\right|^2 dV_{\mathbf{r}}$$



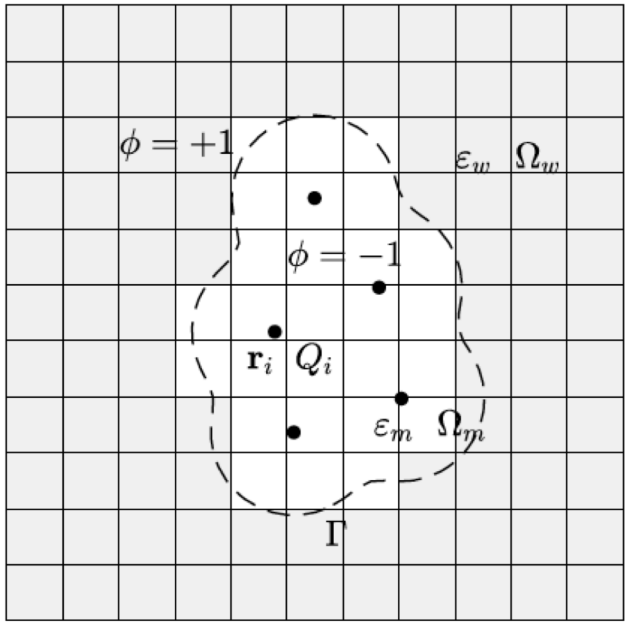
Rigid-body Monte Carlo simulations

- Fix Molecule A.
- Random move of the center of Molecule B.
- Calculate the change of the binding free energy
- Accept or reject the move by the Metropolis criterion

T	298	K
ρ_w	0.0333	Å^{-3}
γ_0	0.174	$k_B T/\text{Å}^2$
ε_m	1	
ε_w	80	

A Fast Binary Level-Set Method (BLSM)

- Kernel based expression of area
- Area is approximated as the volume difference with respect to an overlapped infinitesimally thin layer
- Binary level set function: 1 (solvent) and -1 (solute)
- Flipping grid boxes: 1 → -1 or -1 → 1
- Fast evaluation of energy changes

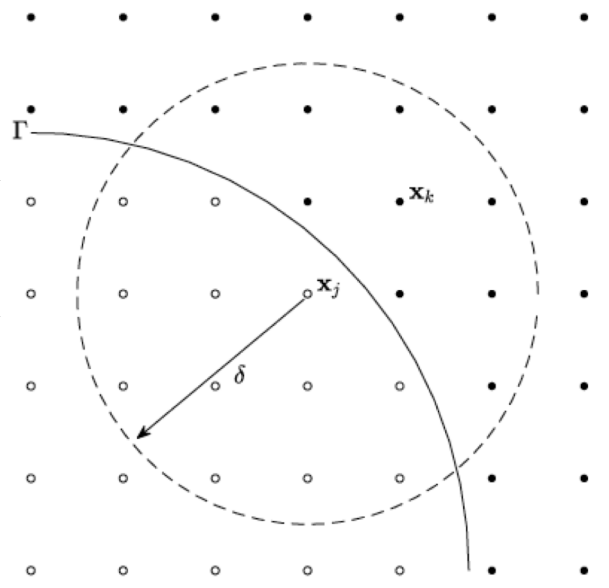


$$\text{Area}(\Gamma) = C(\delta) \int_{\mathbf{x}\in\Omega_m} \int_{\mathbf{y}\in\Omega_w} K\left(\frac{\mathbf{x}-\mathbf{y}}{\delta}\right) d\mathbf{y}d\mathbf{x} + O(\delta^2)$$

$$C(\delta) = \left(\delta^4 \int_0^1 a_0(s)ds\right)^{-1} \text{ and } a_0(s) = \int_{B_1(\mathbf{0})\cap\{y_3>s\}} K(\mathbf{y})d\mathbf{y}$$

$$K(\mathbf{x}) = \begin{cases} \sin^2(\pi|\mathbf{x}|) & \text{if } |\mathbf{x}| \le 1 \\ 0 & \text{otherwise} \end{cases}$$

$$\delta \sim \sqrt{h}$$



BLSM: Accuracy and Efficiency

Table 3. Solvation Free Energy (in k_BT) for Each of the Single Ions K^+, Na^+, Cl^-, and F^-: The Level-Set VISM Calculations vs Experiment[83]

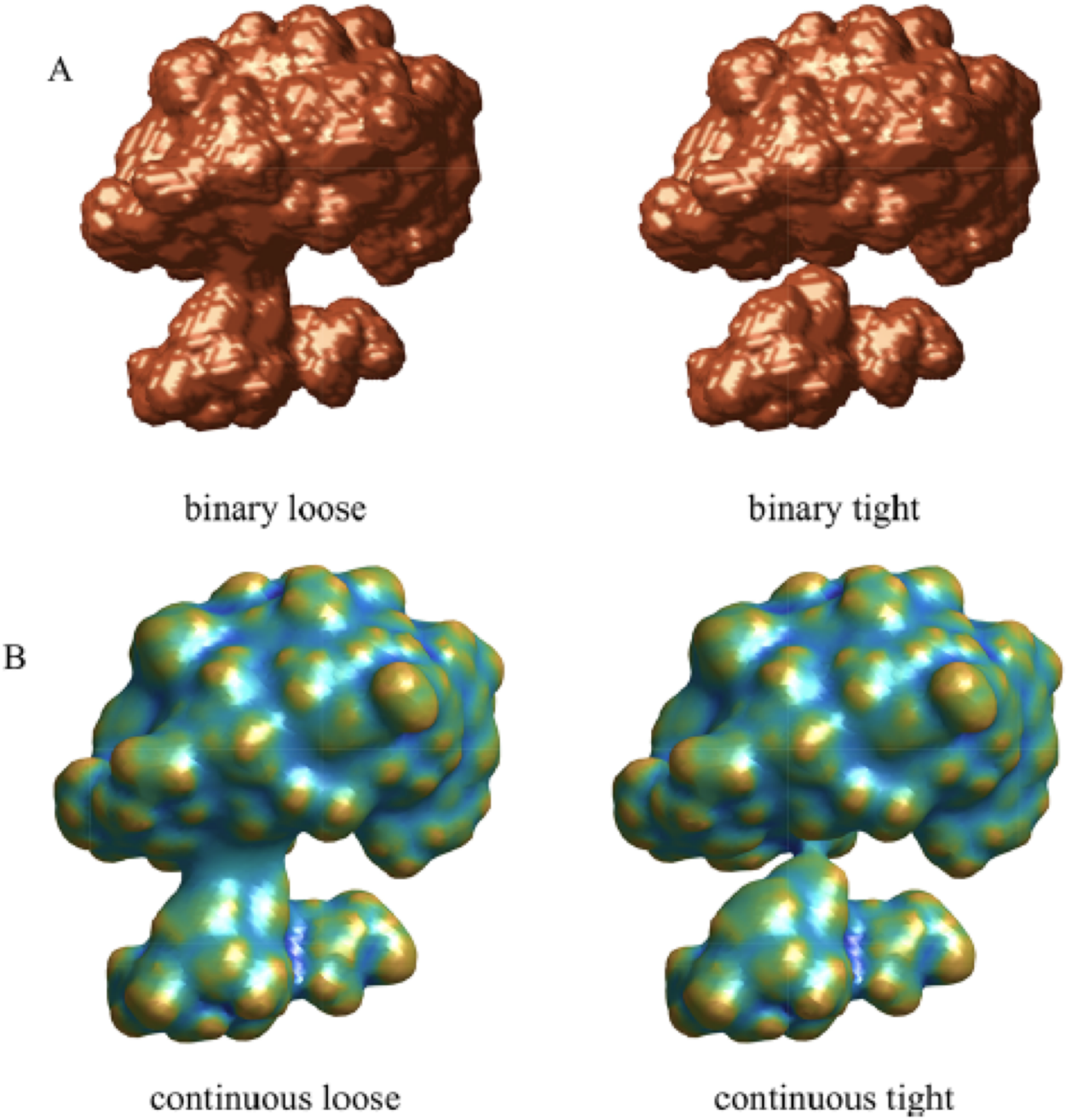
ions	ε (k_BT)	σ (Å)	experiment	continuous level-set	binary level-set
K^+	0.008	3.85	−117.5	−112.3	−103.1
Na^+	0.008	3.49	−145.4	−131.1	−123.1
Cl^-	0.21	3.78	−135.4	−126.7	−113.4
F^-	0.219	3.3	−185.2	−171.9	−158.7

Table 4. Solvation Free Energy (k_BT) and Computation Time (s) for Different Grid Numbers with $Q = 0$[a]

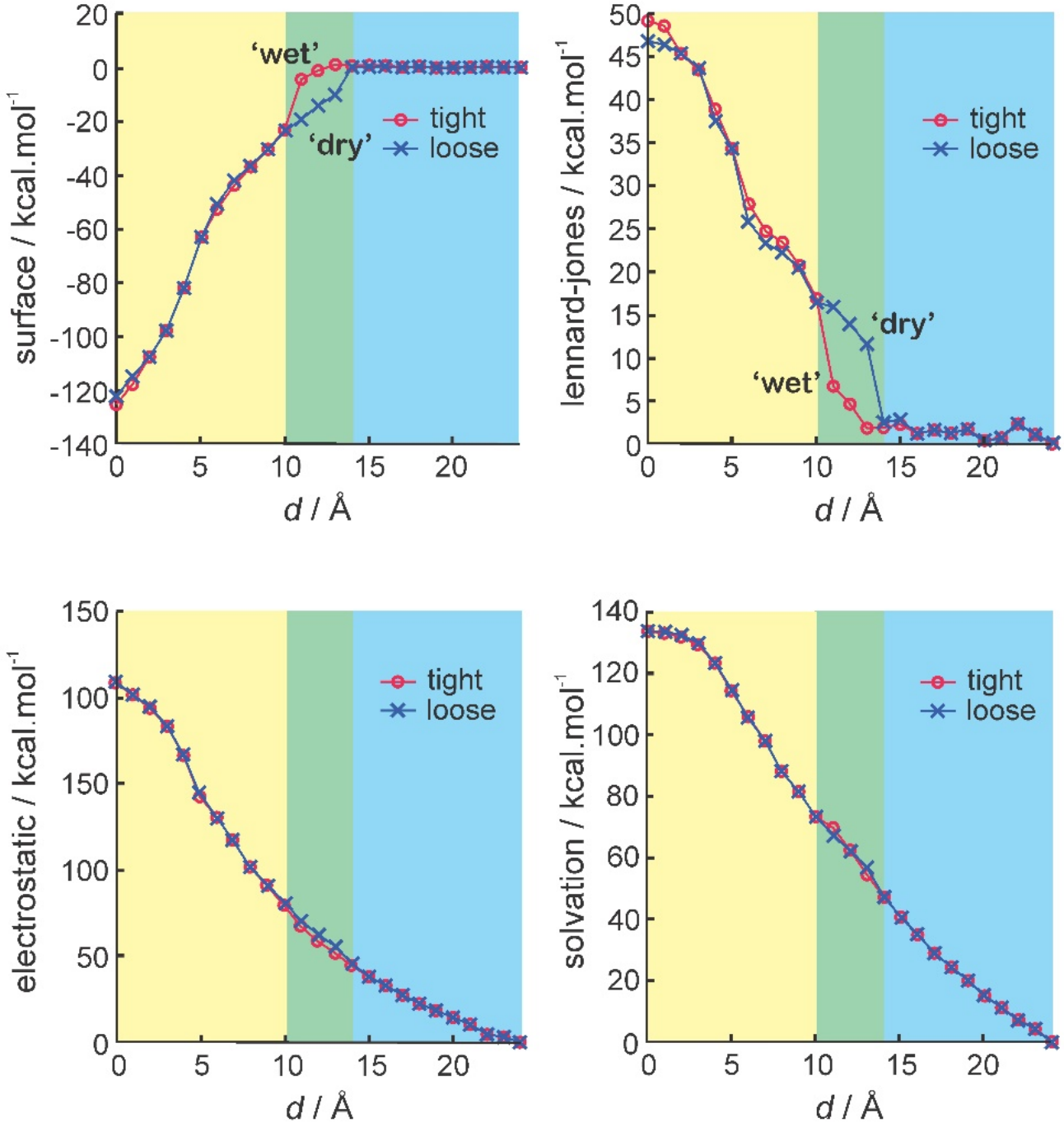
	surface energy		vdW energy		time	
grid no.	cont	binary	cont	binary	cont	binary
25^3	21.46	20.64	−2.86	−3.31	1.10	0.01
50^3	20.87	20.45	−2.78	−3.02	11.97	0.10
100^3	20.68	20.28	−2.76	−2.66	186.44	1.15
200^3	20.80	20.37	−2.91	−2.68	5032.03	21.21

[a]Here, cont stands for the continuous level-set method, and binary stands for the binary level-set method.

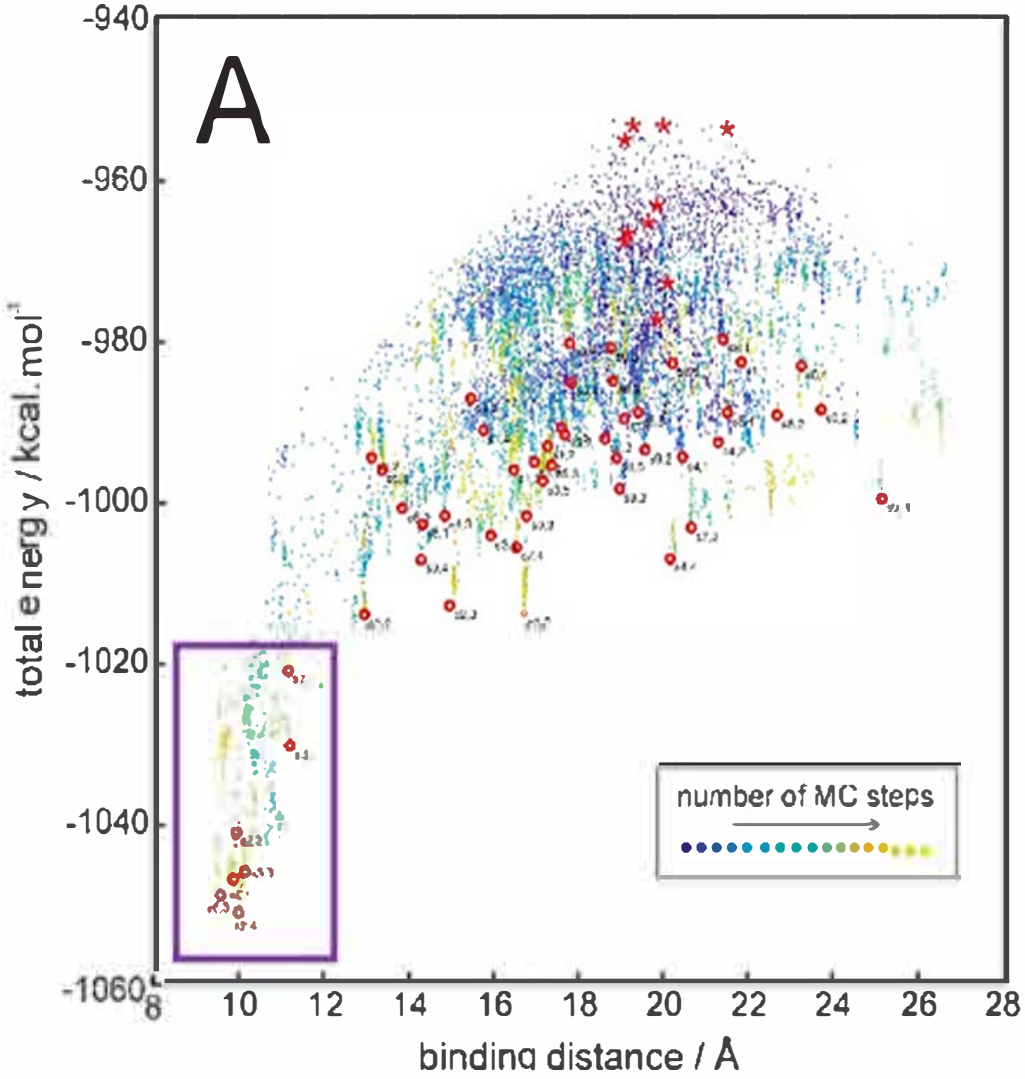
Binary vs. Cont. LSM for Dry-Wet States of p53-MDM2

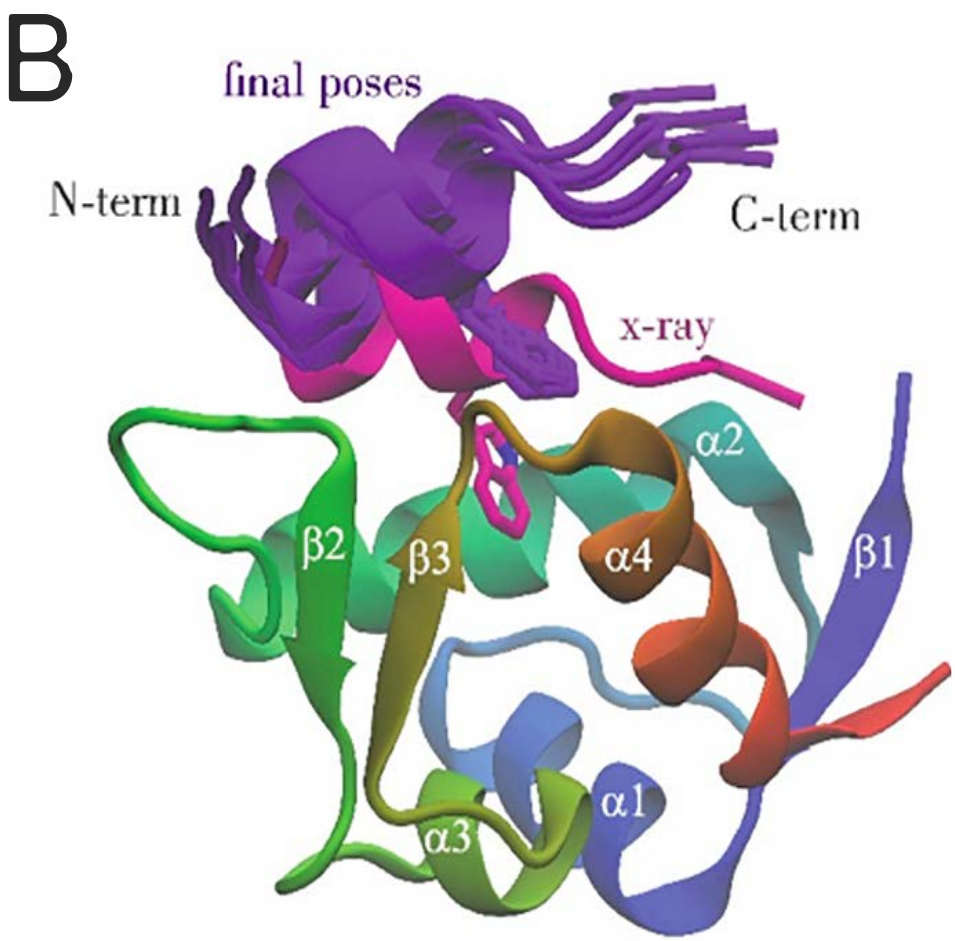


BLSM-VISM Solvation Free Energy of p53-MDM2



Rigid-Body MC Simulations of p53-MDM2





Superposition of productive encounters

- Red asterisks: initial configurations
- Red circles: final configurations
- Blue to yellow: configurations sampled throughout simulations
- Small window: productive encounters

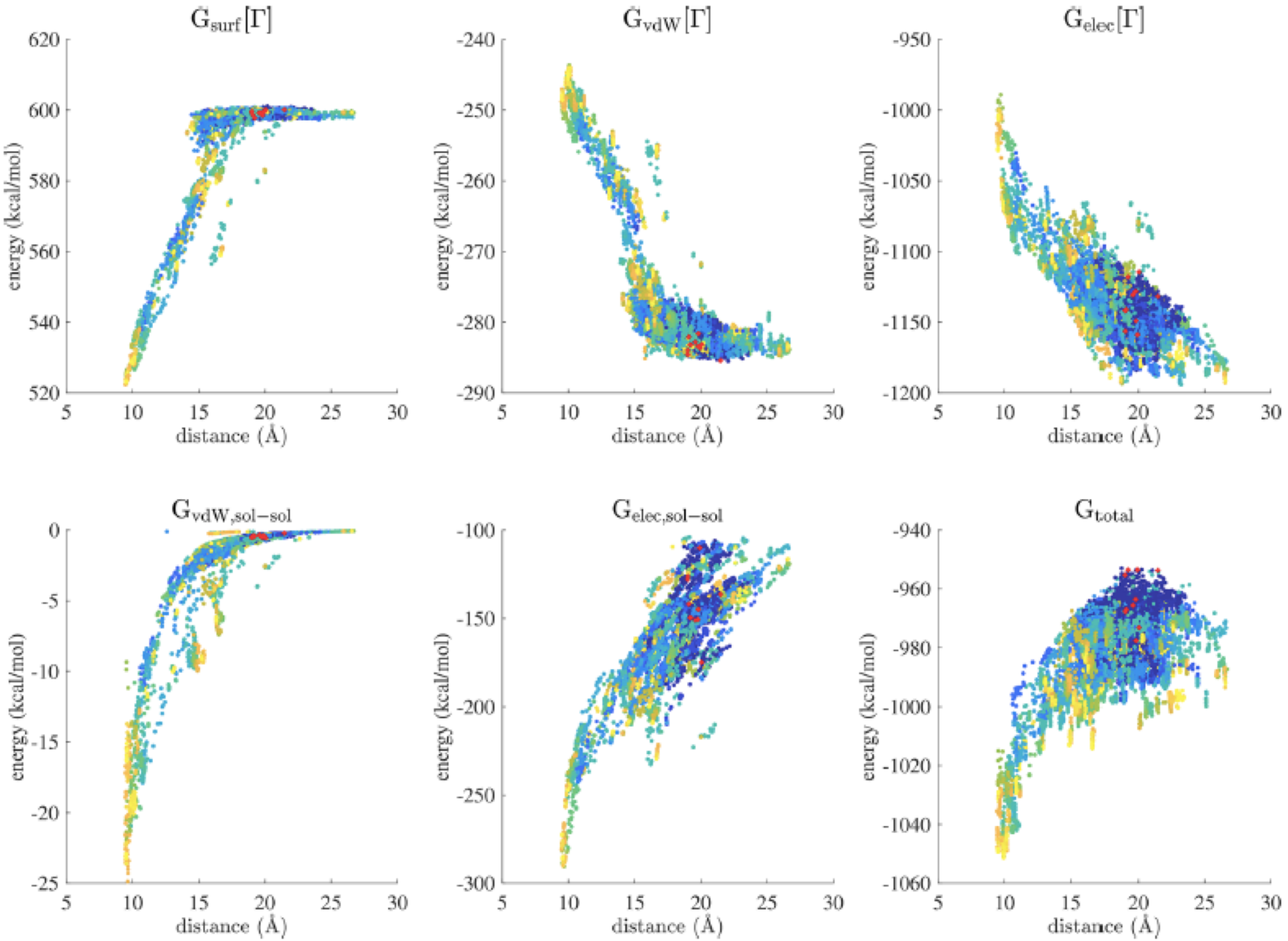
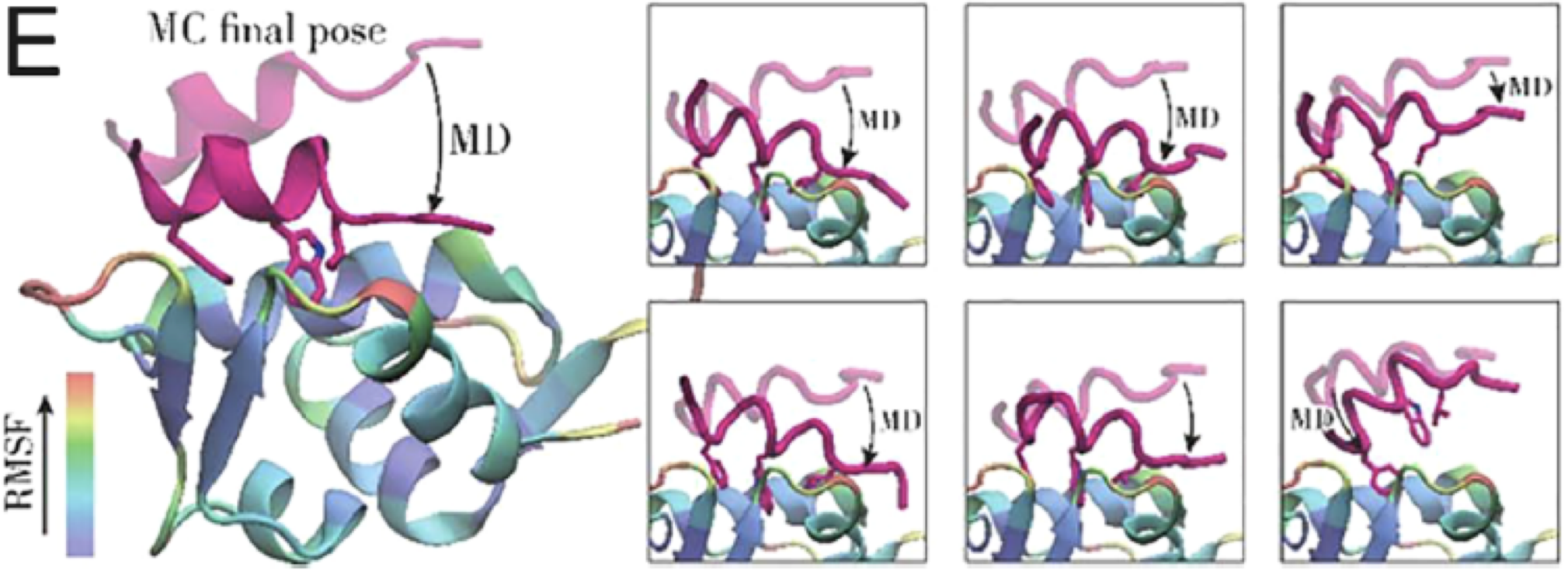


Figure 8. Scatterplot of individual energy components of the total binding energy versus the binding distance for all MC-VISM simulations. Initial (randomly generated) configurations are marked by red circles, and configurations sampled throughout the simulations are colored from blue to yellow.

Observations (so far)

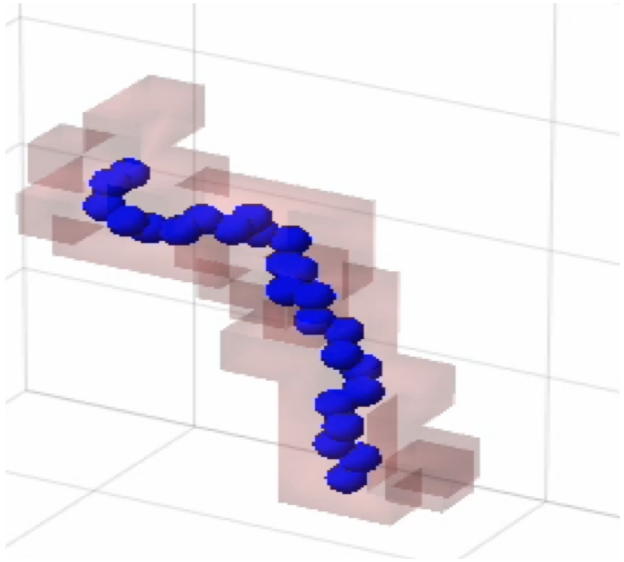
- VISM-binary level set predicts dry and wet states
- The binary level set method is fast enough for MC simulations
- Rigid-body MC-VISM simulations are fast but provide only approximate bound states
- Models are not flexible and difficult to overcome energy barriers

MD simulations from the approximate MC-VISM bound states quickly reach the final bound state!



Conclusions

- Development of a variational solvation approach, capturing dry and wet states
- VISM-string method predicts transition paths, energy barriers, and the binding/unbinding kinetics
- Construction of a hybrid modeling framework: MC-VISM-LS for binding simulations
- Design, implement, and test of a fast binary level-set method
- Rigid-body VISM MC simulations provide approximate bound states that can be used for fast MD simulations



Current and future studies

- Electrostatics
- Parameter optimization
- Improving sampling techniques
- Binding pathways
- More flexibilities
- More applications: binding, folding, etc.

Thank You!