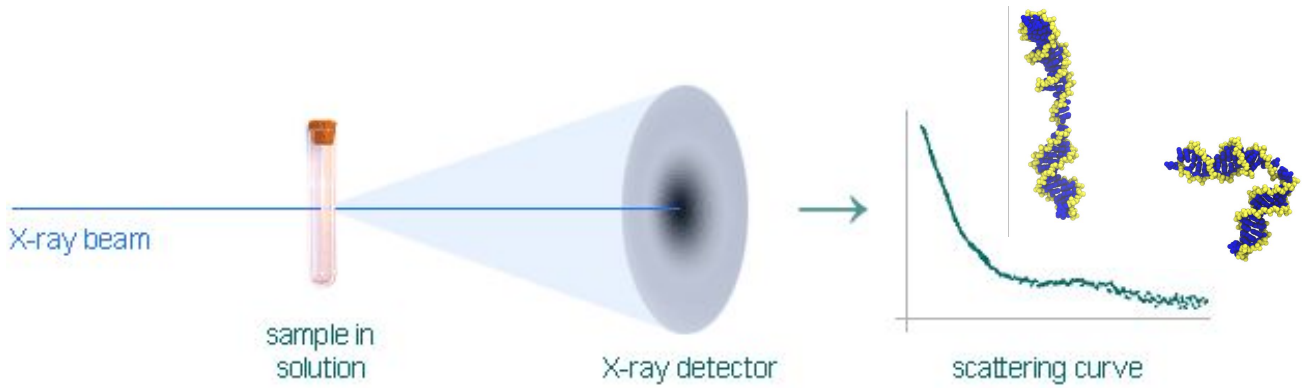
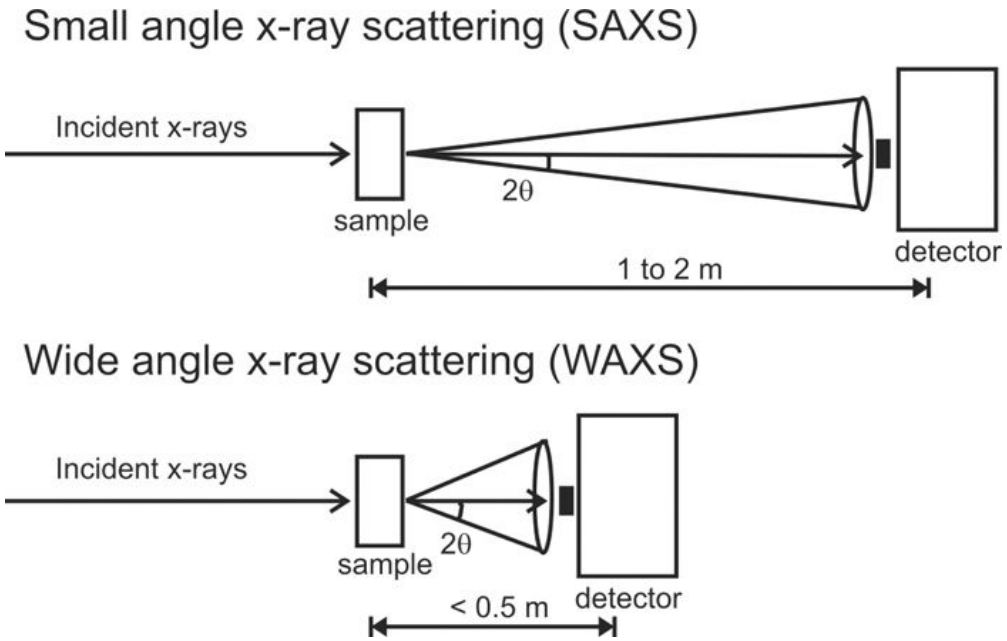
NYU

Interpretation of Solution X-Ray Scattering by Explicit-Solvent Molecular Dynamics



Introduction



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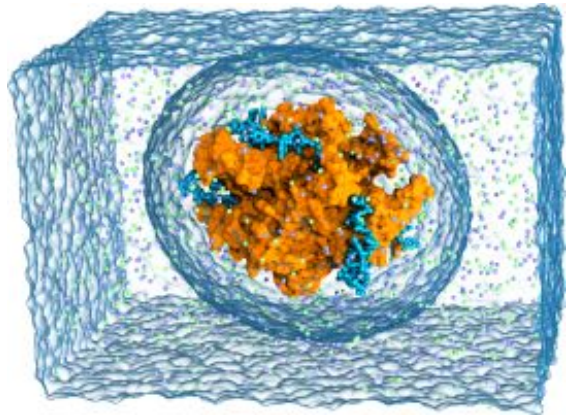


= **SWAXS-driven MD**

~~**Foreknowledge of reaction paths**~~

S/WAXS

- SAXS: overall shape and size of the molecules
- WAXS: changes in tertiary and secondary structures
  - Data interpretation is challenging.

MD simulations

- Atomic level details of molecular structures
  - Sampling issue
  - Force field bias

Theory: coupling potential

The coupling of the MD simulation to experimental target SWAXS curve

$$E_{\text{hybrid}} = E_{\text{FF}} + E_{\text{SWAXS}}$$

- E_{FF} : energy from MD force field
- E_{SWAXS} : energy penalty from disagreement

Quantifying the deviation between EXP and MD

$$E_{\text{SWAXS}}^{(\log)}(t) = \alpha(t) k_c \frac{k_B T}{n_q} \sum_{i=1}^{n_q} [\log I_c(q_i, t) - \log I_e(q_i)]^2$$

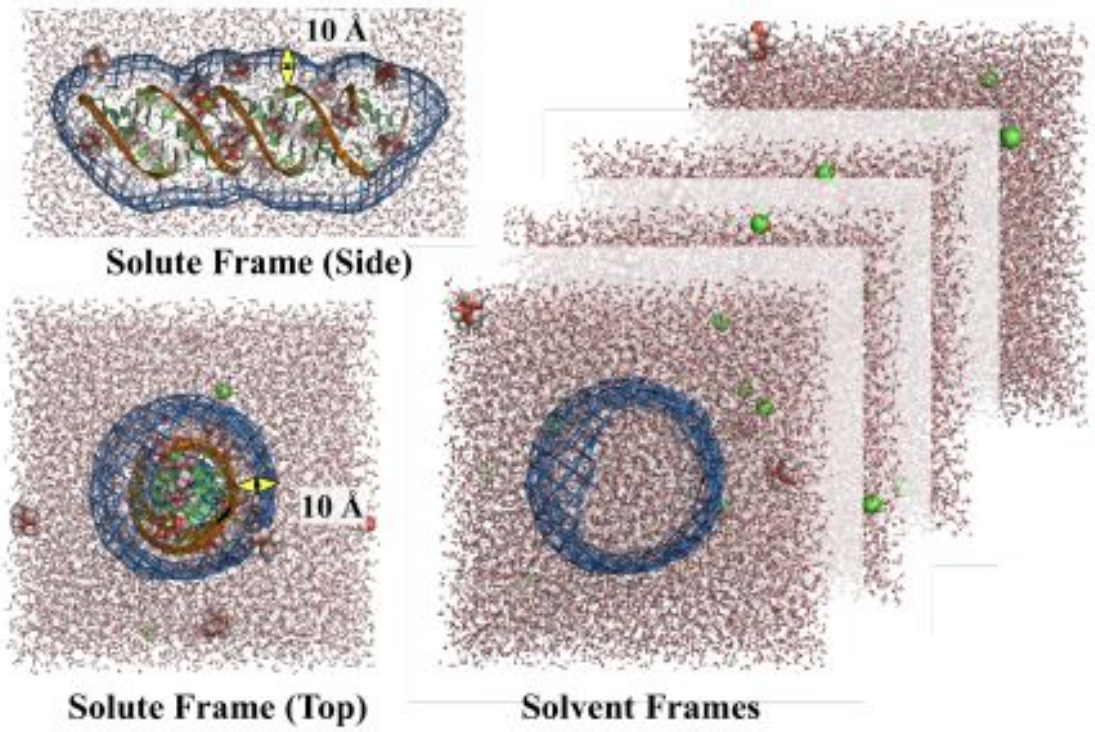
$$E_{\text{SWAXS}}^{(w)}(t) = \alpha(t) k_c \frac{k_B T}{n_q} \sum_{i=1}^{n_q} \frac{[I_c(q_i, t) - I_e(q_i)]^2}{\sigma^2(q_i)}$$

$$\sigma^2(q_i) = \sigma_e^2(q_i) + \sigma_c^2(q_i) + \sigma_{\text{buf}}^2(q_i).$$

- I_c : computed SWAXS from simulations, on the fly
- I_e : target SWAXS from experiment
- n_q : intensity points
- k_c : coupling strength/constant
- $\alpha(t)$: time-dependent function
- σ^2: errors

Po-chia Chen and Jochen S. Hub, Biophysical Journal, 108, 25730-2584, (2015)

Theory: calculation of SWAXS curves



Computed SWAXS scattering:

$$I_c(q,t) = I_A(q,t) - I_B(q)$$

$$I_c(q,t) = \left\langle \left\langle \left|\tilde{A}(\mathbf{q})\right|^2 \right\rangle_{t;\tau}^{(\omega)} - \left\langle \left|\tilde{B}(\mathbf{q})\right|^2 \right\rangle^{(\omega)} \right\rangle_{\Omega}.$$

$\tilde{A}(\mathbf{q})$ and $\tilde{B}(\mathbf{q})$

Fourier transforms of the instantons electron density of the system A and B

$\langle \bullet \rangle \Omega$ Orientational average $\langle \bullet \rangle^{(\omega)}$ Conformational average

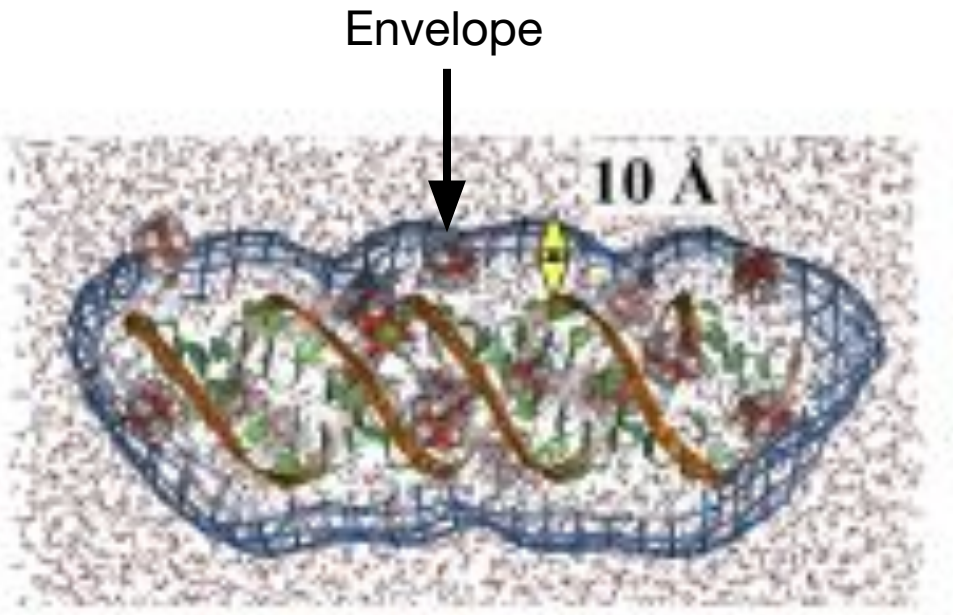
Conformational average:

$$\left\langle \left|\tilde{A}(\mathbf{q})\right|^2 \right\rangle_{t;\tau}^{(\omega)} = \mathcal{N}(t)^{-1} \int_0^t \left|\tilde{A}(\mathbf{q},t')\right|^2 e^{(t'-t)/\tau} \mathrm{d}t'.$$

$$\mathcal{N}(t) = \int_0^t \exp[(t'-t)/\tau] \mathrm{d}t'$$

$$\mathcal{N}(t) \to \tau \text{ as } t >> \tau.$$

Methods: on-the-fly calculation



$$I_c(q,t) = \langle D(\mathbf{q},t)\rangle_\Omega,$$

$$D(\mathbf{q},t) = \left|\left\langle \tilde{A}_i(\mathbf{q})\right\rangle_{t;\tau}^{(\omega)} - \left\langle \tilde{B}_i(\mathbf{q})\right\rangle\right|^2 + \left[\left\langle \left|\tilde{A}_i(\mathbf{q})\right|^2\right\rangle_{t;\tau}^{(\omega)} - \left|\left\langle \tilde{A}_i(\mathbf{q})\right\rangle_{t;\tau}^{(\omega)}\right|^2\right] - \left[\left\langle \left|\tilde{B}_i(\mathbf{q})\right|^2\right\rangle^{(\omega)} - \left|\left\langle \tilde{B}_i(\mathbf{q})\right\rangle^{(\omega)}\right|^2\right].$$

$$\langle D(\mathbf{q},t)\rangle_\Omega := (4\pi)^{-1}\int d\Omega_q D(\mathbf{q},t)$$

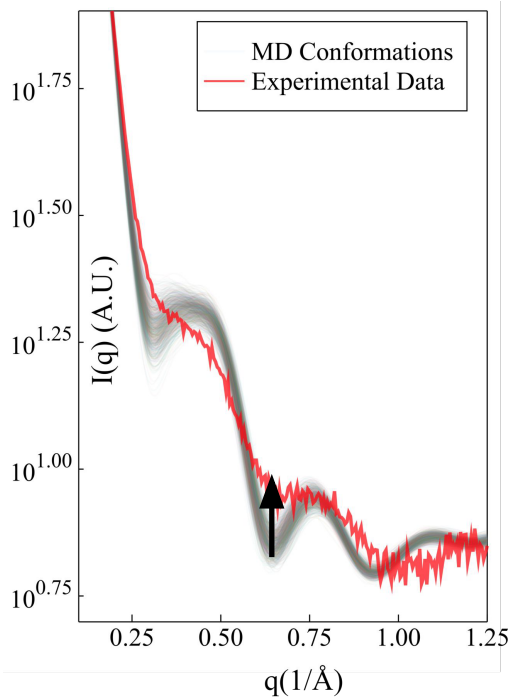
$$\tilde{A}_i(\mathbf{q}) = \sum_{j=1}^{N_A} f_j(q) e^{i\mathbf{q}\cdot\mathbf{r}_j},$$

- N_A : atoms in envelop
- $f_i(q)$: atomic form factor
- $\mathbf{r}_j$: position of atom j

$$f(q) = c + \sum_{k=1}^{4} a_k \exp[-b_k(q/4\pi)^2],$$

a_k , b_k , c_k: Cromer-Mann parameters

Methods: SWAXS-driven forces



$$\mathbf{F}_k(t) = -\nabla_k E^{(log)}_{\mathrm{SWAXS}}(t)$$

$$= -2\frac{\alpha(t)k_c k_B T}{n_q}\sum_{i=1}^{n_q}\frac{\log I_c(q,t) - \log I_e(q)}{I_c(q)}\nabla_k I_c(q,t),$$

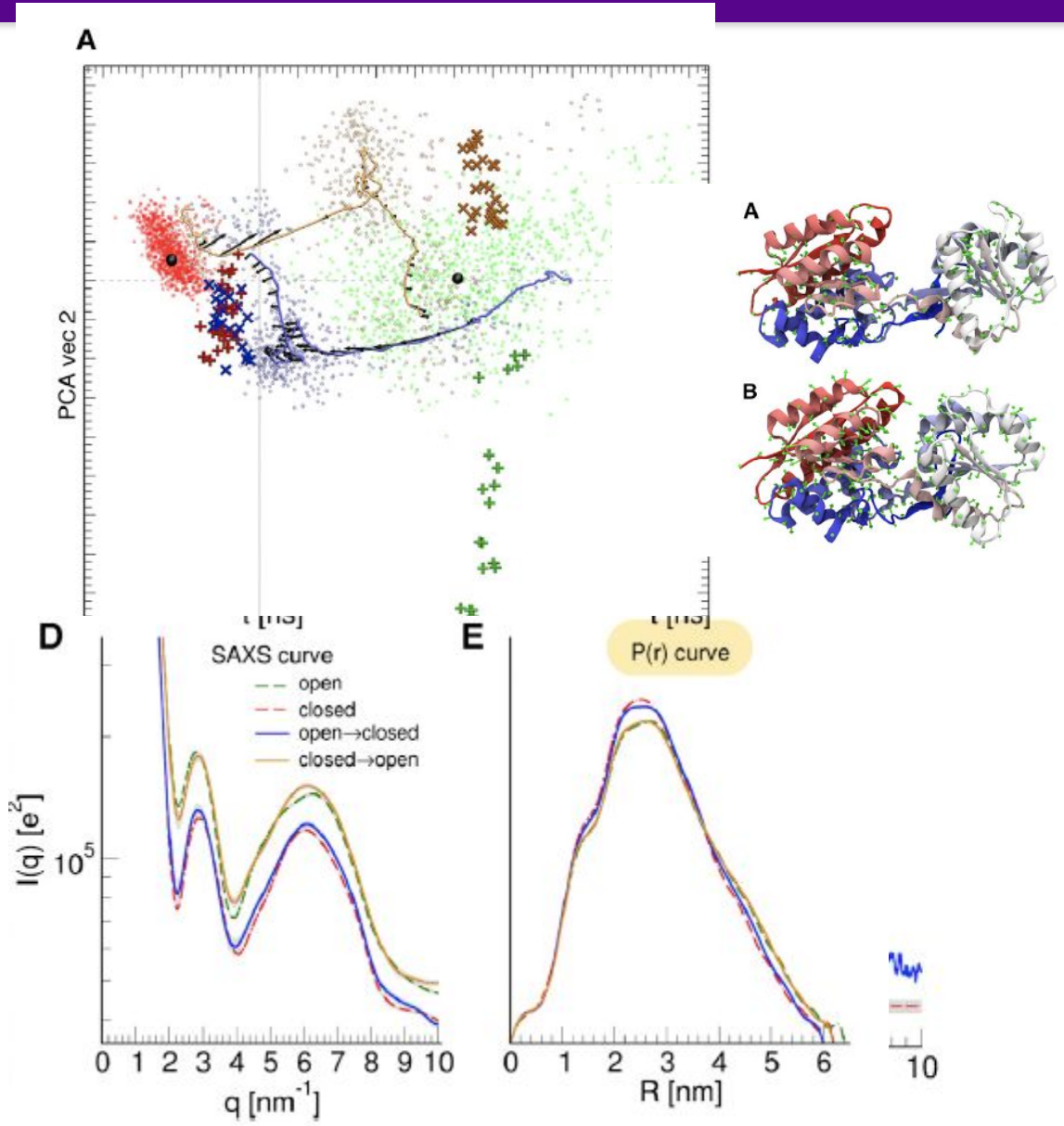
$$\nabla_k I_c(q) = \frac{1}{4\pi}\int d\Omega_{\mathbf{q}}\nabla_k D(\mathbf{q}),$$

$$\nabla_k D(\mathbf{q}) = 2\,\mathrm{Re}\Big[\Big\langle \tilde{A}_i(\mathbf{q})\nabla_k \tilde{A}_i^*(\mathbf{q})\Big\rangle^{(\omega)}_{t;\tau}$$

$$- \Big\langle \nabla_k \tilde{A}_i^*(\mathbf{q})\Big\rangle^{(\omega)}_{t;\tau}\Big\langle \tilde{B}_i(\mathbf{q})\Big\rangle^{(\omega)}\Big].$$

Shannon sampling limit: $q_{max}D_{max}$

Discussion: LBP



Red and green dots :

the ensembles of unbiased simulations of closed (red) and open (green) LBP

Black dots:

Cluster center of closed and open ensembles used for the RMSD analysis in subplots (B and C)

Orange/blue dots:

Conformations during SWAXS-driven MD in the opening (orange) and closing simulation (blue).

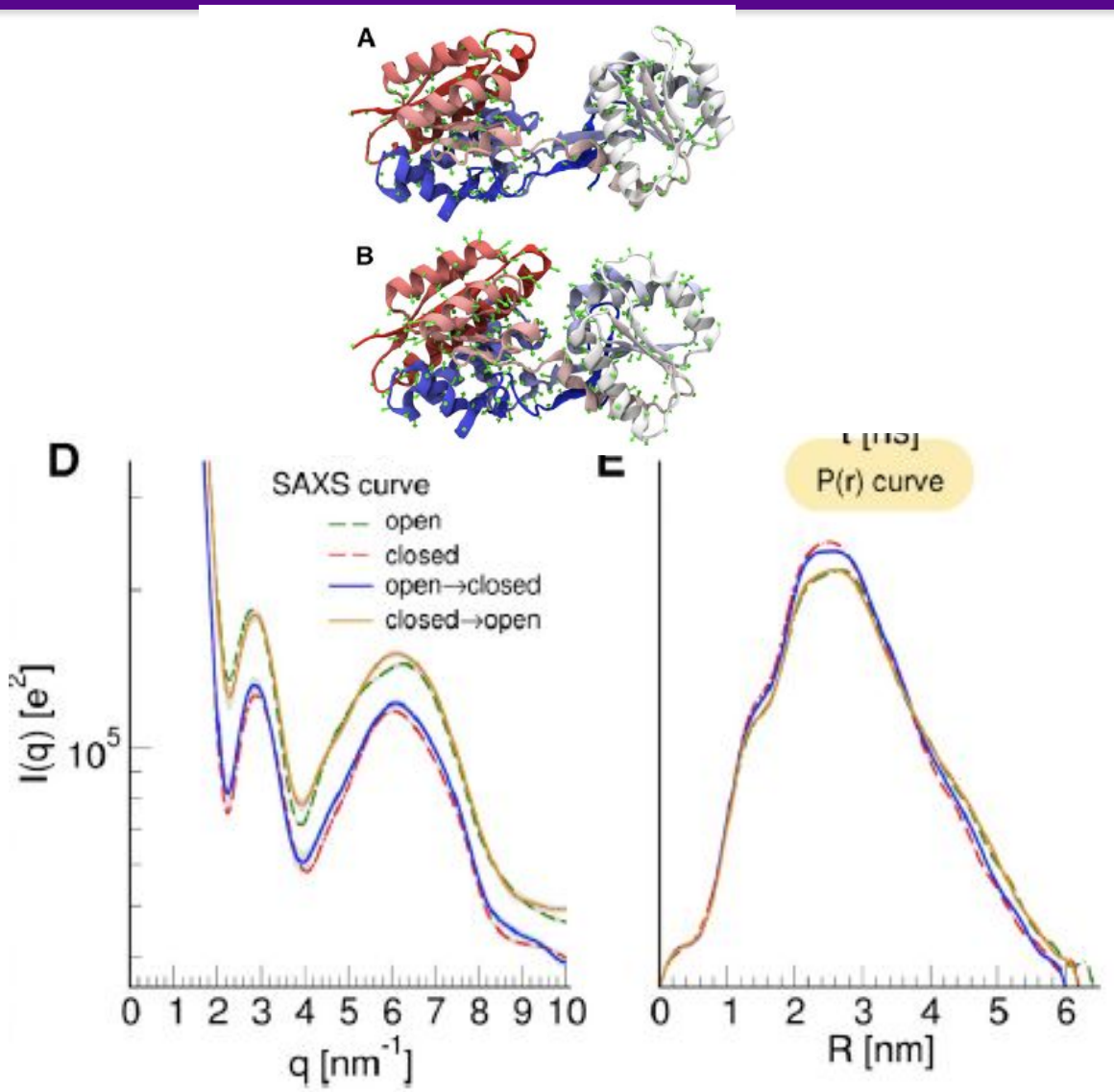
Orange and blue lines:

To guide the eye, smoothed SWAXS-driven trajectories are shown.

Black arrows:

Forces derived from E_{SWAXS}, mainly acting along the opening motion.

Discussion: LBP



- Scattering-curves of SWAXS-driven trajectories at t =10 ns, as compared to the target curves
- The SWAXS curves and pair distribution functions P(r) computed from the final frames of the SWAXS-driven MD are in close agreement to the target curves