(number) density field $\rho(r; x)$, i.e. the number of fluid molecules within each of the cells centered around point x discretizing the space. $\rho(r; x)$ is a convenient Σ_{LB} proxy in the atomistic description of multi-phase systems [38]. The intrusion/extrusion path and the associated free energy profile for field observables can be obtained by the string method in collective variable [71]. This approach has been successfully applied to intrusion/extrusion of simple porous systems revealing the analogies and differences with respect to the simpler description in terms of $N(r)$ (V_B) (Figure 5) [27,40,41,45,72].

3.2.2. Umbrella sampling

As in RMD, US provides a way to compute the probability distribution $P_\xi(\xi^*)$ and, ultimately, the corresponding free energy, by enhancing the sampling of states that are rarely observed in a typical equilibrium simulation. To accomplish this task, US modifies the potential of the system by adding a ξ-dependent term that restricts sampling to desired regions of ξ-space. This *biasing* potential modifies the systems Hamiltonian to $\mathcal{H}_{bias}(\Gamma) = \mathcal{H}(\Gamma) + V_{bias}(\xi(\Gamma))$, where $\mathcal{H}(\Gamma)$ is the original Hamiltonian and $V(\xi(\Gamma))$ is the biasing potential that depends on the order parameter ξ. Biasing the system in this manner shifts the probability distribution of the order parameter as $P_b(\xi) \propto P(\xi)e^{-\beta V_{bias}(\xi)}$, such that the original distribution is *reweighted* by the biasing potential. We take advantage of this reweighting in US by performing many simulations with different values of $V(\xi)$ to
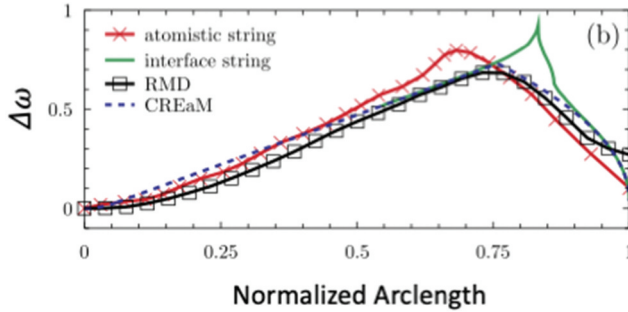

Figure 5. Comparison between the free energy profile of a single variable, number of water molecules in a square 2D cavity (Figures 2, 3), or the corresponding liquid volume, for atomistic (RMD) and continuum (CREaM) models, vs the density profile $\rho(x)$ (atomistic string), an atomistic proxy of the liquid/bubble interface Σ_{LB} (interface string). $\Delta\omega = \Delta\Omega/(V\Delta p_{max})$, with $\Delta p_{max} = -2\gamma_{LB}\cos\vartheta_Y/l$, where l is the characteristic length of the texture (see Figure 3). To make the comparison between the different calculations feasible, the free energy is reported as a function of the distance from the initial state, normalized for the total length of the path (normalized arc length). Here 'distance' is understood as the Euclidean distance in the space of the variables: N and $\rho(x)$ for the atomistic calculations and V_B and Σ_{LB} for the continuum ones. This distance has not an immediate and intuitive physical sense; rather, it is a measure of the separation between states of the system along the process, which is more conveniently represented in its normalized form, with values contained between 0 (initial state) and 1 (final state). Adapted from Refs. 28 and 45.
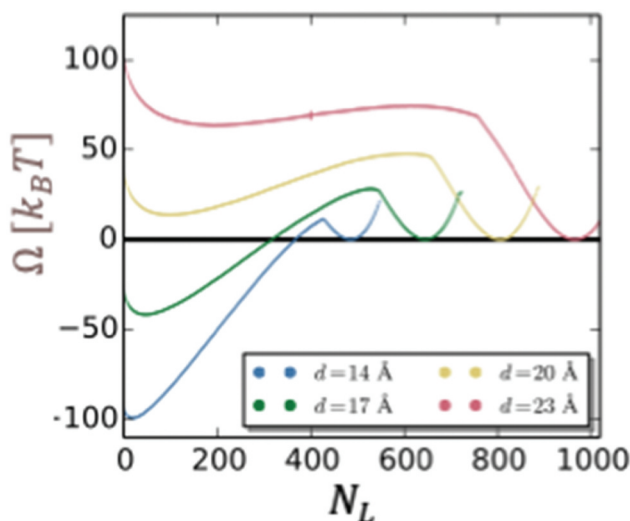
Figure 6. Free energy profile, in thermal units [k_BT], as a function of the number of water molecules between hydrophobic plates as obtained by INDUS. The free energy arbitrary constant is chosen such that the value at the filled (meta)stable state is zero. The relative stability of the filled and empty state and the barrier separating them depends on the distance between the plates. Adapted from Ref. [44].

extrusion and instead order parameters like the number of molecules in a region of space or the water density are used. In these cases, dynamical effects must be taken into account in simulation estimates of rate constants. While various approaches exist for doing this, rate constants for intrusion/extrusion have been predicted using forward flux sampling (FFS) [89].

FFS is a path sampling technique that applies no bias to the system in order to accurately describe the system's dynamics. In FFS, one first chooses an order parameter that can distinguish between reactant (A) and product (B) states; for extrusion, A is the wet state and B is the dry state. Then, the order parameter is used to divide the state-space between A and B into many states or 'milestones' with different values of the order parameter. Many trajectories of a specified length are then initiated from A, and the corresponding transition probability to reach the first milestone can be computed from the fraction of trajectories that start from state A and reach the first milestone. More trajectories are initiated from the first milestone to compute the transition probability to the second milestone, and this procedure is repeated until the transition probabilities between all the milestones spanning A to B are computed. The product of all these probabilities with the flux of trajectories out of state A into the first milestone yields the rate constant for the transition from A to B. Piecewise reactive trajectories can be analyzed to identify the process' mechanism (Figure 7).