Supporting Information:

Efficient Construction of Free Energy Profiles of Breathing Metal–Organic Frameworks Using Advanced Molecular Dynamics Simulations

Ruben Demuynck, Sven M. J. Rogge, Louis Vanduyfhuys, Jelle Wieme, Michel Waroquier, and Veronique Van Speybroeck*

Center for Molecular Modeling (CMM), Ghent University, Technologiepark 903, B-9052 Zwijnaarde, Belgium

E-mail: Veronique.VanSpeybroeck@UGent.be
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1 Theoretical background

1.1 Basic statistical physics

This section is devoted to the theoretical basis of the different free energy methods studied in this work. All methods find their basis in classical statistical physics. More in particular, the computation of the free energy can be related to the classical partition function and hence an integration over the entire phase space, i.e. the space spanned by the $N$ atomic positions $\mathbf{r}^N$ and the $N$ atomic momenta $\mathbf{p}^N$. Hence, the total partition function $Z$ and free energy $F$ of the global state of a molecular system at a temperature $T$ are defined as:

$$Z = \frac{1}{h^{3N}} \int e^{-\beta \mathcal{H}(\mathbf{r}^N, \mathbf{p}^N)} d\mathbf{r}^N d\mathbf{p}^N \quad (SI1.1)$$

$$F = -k_B T \ln Z \quad (SI1.2)$$

In this expression, $h$ is the Planck constant, $k_B$ is the Boltzmann constant and $\beta = 1/k_B T$. The Hamiltonian $\mathcal{H}(\mathbf{r}^N, \mathbf{p}^N)$ contains the kinetic energy of all particles and the potential energy $U(\mathbf{r}^N)$ of all particles.

Suppose we introduce a coordinate $Q(\mathbf{r}^N, \mathbf{p}^N)$ which is a function of all the degrees of freedom of the system. Furthermore, we are interested in the probability that the system is in a state for which $Q(\mathbf{r}^N, \mathbf{p}^N) = q$. In other words, this coordinate $Q(\mathbf{r}^N, \mathbf{p}^N)$ is a way of partitioning all the available microstates of the system (characterized by $\mathbf{r}^N, \mathbf{p}^N$) into a set of macrostates (characterized by $q$). This results in a partitioning of the partition function and free energy into contributions for every macrostate $q$:

$$Z(q) = C \int e^{-\beta \mathcal{H}(\mathbf{r}^N, \mathbf{p}^N)} \delta (Q(\mathbf{r}^N, \mathbf{p}^N) - q) d\mathbf{r}^N d\mathbf{p}^N \quad (SI1.3)$$

$$F(q) = -k_B T \ln Z(q) \quad (SI1.4)$$
with $C$ the normalization constant. Note that $Z(q)$ has the dimensions of $q^{-1}$. Furthermore, we can also partition the total probability for the system to be in the global state, which is 1, into a probability density $p(q)\, dq$ for the system to be in a macrostate $[q, q + dq]$ with:

$$p(q) = \int p(r^N, p^N) \delta \left( Q(r^N, p^N) - q \right) \, dr^N \, dp^N$$

$$= \frac{1}{Z} \int e^{-\beta H(r^N, p^N)} \delta \left( Q(r^N, p^N) - q \right) \, dr^N \, dp^N = \frac{Z(q)}{Z}$$

From the probability for each macrostate, the corresponding free energy can be determined:

$$F(q) = -k_B T \ln p(q) - k_B T \ln Z = -k_B T \ln p(q) + F$$

In practice, an integration over the entire phase space is unfeasible due to the large number of degrees of freedom. Hence, the partition function $Z$ and corresponding free energy $F$ cannot be computed. Nevertheless, the relative free energy difference between two macrostates can be computed by determination of the probability distribution: $F(q_2) - F(q_1) = -k_B T \ln [p(q_2)/p(q_1)]$. By means of molecular simulations, the relevant parts of the phase space are scanned allowing to determine the probability distribution in terms of the different macrostates. However, these molecular simulations are limited to short time scales, restricting the scan of the phase space to local minima. This results in a non-ergodic sampling if major free energy barriers are present. To overcome the limited sampling, several enhanced sampling techniques have been proposed: umbrella sampling, metadynamics, variationally enhanced sampling, free energy perturbation, and thermodynamic integration. All aforementioned sampling techniques enhance the sampling of the phase space in the direction of the partitioning coordinate, which in literature is often described as the collective variable or the reaction coordinate. Hence, those techniques will help to overcome free energy barriers in the direction of the collective variable, which are sampled poorly in classical
molecular dynamics (MD) simulations.

1.2 Umbrella sampling

As stated before, sampling by regular molecular simulations does not sufficiently sample the regions with low Boltzmann probability, \(\exp(-\beta H)\). In order to overcome this issue an external potential is introduced in the umbrella sampling method to enhance the sampling in these regions of low probability.\(^1\) The external potential depends on the partitioning coordinate \(Q\). Introducing this external potential in the simulation results in a biased free energy \(F_b\):

\[
Z_b(q) = C \int e^{-\beta(H(r^N,p^N)+U_b(Q))}\delta\left(Q(r^N,p^N) - q\right)dr^Ndp^N \tag{SI1.8}
\]

\[
F_b(q) = -k_B T \ln[Z_b(q)] \tag{SI1.9}
\]

\[
= -k_B T \ln p_b(q) + F_b \tag{SI1.10}
\]

The free energy of the unbiased system \(F(q)\) can be obtained from the free energy of the biased system \(F_b(q)\):

\[
F_b(q) = -k_B T \ln[Z_b(q)] \tag{SI1.11}
\]

\[
= -k_B T \ln[Z(q)e^{-\beta U_b(q)}] \tag{SI1.12}
\]

\[
= F(q) + U_b(q) \tag{SI1.13}
\]

In practice, a set of external potentials \(\{U_i^b\}\) is introduced. Here, each external potential focuses on a different region of the partitioning coordinate, such that the total set spans the entire region of interest. A popular choice for the external potential is a set of harmonic functions at uniformly distributed positions \(q_i\) over the sampling region: \(U_i^b(q) = \frac{k}{2}(q - q_i)^2\). For every external potential \(U_i^b\), a different simulation is performed yielding a set of histograms \(H_i(q)\). One finds the biased free energy profiles from the histogram by introducing
$p^i_b(q)\, dq = H_i(q)/M_i$ (with $H_i(q)$ the number of counts in the range $[q, q + dq]$ and $M_i$ the total simulation points in simulation $i$) in Equation SI1.10. In order to obtain a histogram for the unbiased system from the various biased histograms, two different schemes are considered in this work: the weighted histogram analysis method (WHAM)\textsuperscript{2,3} and the dynamic histogram analysis method (DHAM).\textsuperscript{4}

1.2.1 Weighted histogram analysis method (WHAM)

In principle, the unbiased probability can be written as a function of each of the biased probabilities:

$$p(q) = p^i_b(q)e^{\beta U^i_b(q)}\frac{Z^i_b}{Z}$$  \hspace{1cm} (SI1.14)

In practice, this will not work because, we can not compute $Z^i_b$ directly. In the weighted histogram analysis method, a weight $w_i$ is assigned to each count $H_i$ in the following way.\textsuperscript{2}

First off, the unbiased probability is written as a function of the weighted biased probabilities:

$$p(q) = \sum_i w_i p^i_b(q)e^{\beta U^i_b(q)}\frac{Z^i_b}{Z}$$  \hspace{1cm} (SI1.15)

where the weights add up to 1, $\sum_i w_i = 1$. The expression for the unbiased probability contains no information about the weights $w_i$ nor of the values of the ratios $\frac{Z^i_b}{Z}$.

Subsequently, an estimate of the weights is found by choosing them such that the variation of the unbiased probability is minimized. To that end, we assume the biased counts $H_i(q)$ to be distributed with according to a Poisson distribution, such that $\text{var}(p^i_b) = \text{var}(H_i)/M_i^2$ =
\[ E(H_i)/M_i^2 = E(p_b)/M_i \approx p_b/M_i. \]

\[ \sigma_p^2 = \text{var}(p) = \langle p(q)^2 \rangle - \langle p(q) \rangle^2 \quad \text{(SI1.16)} \]

\[ = \sum_i w_i^2 e^{2\beta U_i^b(q)} \left( \frac{Z_i}{Z} \right)^2 \left[ \langle p_b^i(q)^2 \rangle - \langle p_b^i(q) \rangle^2 \right] \quad \text{(SI1.17)} \]

\[ = \sum_i w_i^2 e^{2\beta U_i^b(q)} \left( \frac{Z_i}{Z} \right)^2 \frac{p_b^i(q)}{M_i} \quad \text{(SI1.18)} \]

\[ = p(q) \sum_i w_i^2 e^{\beta U_b^i(q)} \left( \frac{Z_i}{Z} \right) \frac{1}{M_i} \quad \text{(SI1.19)} \]

with \( M_i \) the number of sampling points obtained in simulation \( i \) with external potential \( U_b^i \).

Minimizing this expression for the weight functions yields:

\[ w_i = \frac{e^{-\beta U_i^b(q)} M_i Z/Z_b^i}{\sum_i e^{-\beta U_i^b(q)} M_i Z/Z_b^i} \quad \text{(SI1.20)} \]

Substituting these values yields a new expression for the unknown probability density \( p(q) \), with only the ratios \( \frac{Z_i}{Z} \) as unknown values:

\[ p(q) = \frac{\sum_i H_i(q)}{\sum_i e^{-\beta U_i^b(q)} M_i Z/Z_b^i} \quad \text{(SI1.21)} \]

with \( H_i(q) \) the counts in bin \([q, q + dq]\) in the simulation with external potential \( U_b^i(q) \).

Subsequently, an estimate for the ratios \( \frac{Z_i}{Z} \) is found by introducing a self-consistent cycle based up the definition of the partition function and the previous expression of the unbiased probability:

\[ Z_b^i = \int dr^N dp^N e^{-\beta (H + U_b^i(q))} \quad \text{(SI1.22)} \]

\[ = \int dq Z p(q) e^{-\beta U_b^i(q)} \quad \text{(SI1.23)} \]

\[ = \int dq e^{-\beta U_b^i(q)} \frac{\sum_i H_i(q)}{\sum_i e^{-\beta U_b^i(q)} M_i/Z_b^i} \quad \text{(SI1.24)} \]
Solving this self-consistent cycle for the unknown partition functions removes the last unknown values in the expression for the unbiased probability, allowing for the determination of the free energy profile (within a constant value). More details on the derivation of the WHAM method can be found in reference 5. In our manuscript, we employ the WHAM script provided in reference 6.

1.2.2 Dynamic histogram analysis method (DHAM)

In the dynamic histogram analysis method, the free energy profile is determined via the introduction of transition matrices, describing the transition probability between macrostates $Q$. First off, a Markov transition matrix for the biased simulations is constructed. Subsequently, this biased matrix is transformed into an unbiased Markov transition matrix which allows for the calculation of the free energy from the transition histogram. This idea was developed in biomolecular simulations where long time behavior predictions are made from short time molecular dynamics (MD) simulations. Before going into detail about the biased versus unbiased transition matrix, a brief introduction to the Markov state model is provided. A Markov state model assumes that two time steps $\{s, s + \tau\}$ in the trajectory that are well separated behave Markovian:

$$p (s + \tau|s) = p (s + \tau|s, s - \tau, s - 2\tau,...) \quad (\text{SI1.25})$$

That is, we assume that the state visited at time $s + \tau$ depends solely on the state at time $s$. Based on this property, a transition matrix $M$ can be constructed where the element in row $\beta$ and column $\alpha$ represents the probability to observe a transition from state $\alpha$ to state $\beta$ over a time $\tau$: $M_{\beta\alpha} = p(\alpha \rightarrow \beta)$.

The transition matrix allows for the determination of the change of the probability distribution over time. Given a probability distribution at time 0, the probability distribution at
time $n\tau$ is:

$$p(t = n\tau) = M(\tau)^n p(t = 0) \quad (SI1.26)$$

The free energy profile corresponds to the probability distribution which does not change over time. This non-changing probability is the eigenvector of the transition matrix corresponding with an eigenvalue 1. More information about the Markov state models can be found in the literature (for instance in reference 7).

In order to obtain the transition matrix from different biased simulations, Rosta and Hummer proposed to obtain the unbiased (and unnormalized) Markov transition matrix $M$ from a transition histogram $T^i$ of a simulation with external potential $U^i_b$:

$$M_{\beta\alpha} = \frac{\sum_i T^i_{\beta\alpha}}{\sum_i n^i_{\alpha} e^{-\beta(U^i_b(\beta) - U^i_b(\alpha)})/2} \quad (SI1.27)$$

with $n^i_{\alpha}$ the total amount of transitions initiated in state $\alpha$. After normalizing this matrix, the free energy profile is found from its eigenvector corresponding with eigenvalue 1.

1.3 Metadynamics

In regular dynamics the free energy for a certain macrostate $q$ is:

$$F(q) = -k_B T \ln \left[ C \int e^{-\beta H(r^N, p^N)} \delta \left[ Q(r^N, p^N) - q \right] dr^N dp^N \right] \quad (SI1.28)$$
In metadynamics, we apply a bias potential $U_b(q)$ which is a function of the macrostate. The biased free energy then becomes:

$$F_b(q) = -k_B T \ln \left[ C \int e^{-\beta H(r^N, p^N) + U_b(q)} \delta [Q(r^N, p^N) - q] \, dr^N dp^N \right]$$  \hspace{1cm} (SI1.29)

$$= -k_B T \ln \left[ e^{-\beta U_b(q)} C \int e^{-\beta H(r^N, p^N)} \delta [Q(r^N, p^N) - q] \, dr^N dp^N \right]$$  \hspace{1cm} (SI1.30)

$$= U_b(q) + F(q)$$  \hspace{1cm} (SI1.31)

In metadynamics, the bias potential is chosen such that the biased probability of each macrostate is equal for each macrostate $p(q) = \frac{1}{\Omega}$, with $\Omega$ a constant. This implicates that the free energy for each macrostate is also equal for each macrostate (see Eq. SI1.7):

$$F_b(q) = -k_B T \ln p(q) + F_b = k_B T \ln \Omega + F_b = cte$$  \hspace{1cm} (SI1.32)

Combining this with Eq. (SI1.31) yields:

$$cte = U_b(q) + F(q)$$  \hspace{1cm} (SI1.33)

$$F(q) = -U_b(q) + cte$$  \hspace{1cm} (SI1.34)

This means that after a metadynamics simulation has converged, i.e. when the biased probability is a constant as function of the partitioning coordinate, the free energy can be computed as minus the bias potential.

In practice, the bias potential is constructed on the fly by gradually adding Gaussian contributions. At certain points during the metadynamics simulation, one determines in which macrostate the system has been (i.e. which $q$) since the previous bias contribution. A new Gaussian contribution is added with a certain amplitude $h$ and width $w$. A metadynamics simulation has converged when the probability for each macrostate is equal. The bias
potential after the simulation becomes the sum of all Gaussians:

$$U_b(q|t) = h \sum_{i}^{N(t)} e^{-\frac{(q-q_i)^2}{2w_i^2}}$$  \hspace{1cm} (SI1.35)

The amplitudes $h_i$ and widths $w_i$ need to be well chosen to allow for an accurate and fast convergence. The smaller these values, the more accurate the results, but convergence will also take longer. This idea was empirically observed by Laio et al.\(^9\)

### 1.4 Variationally enhanced sampling

In the previous section about metadynamics we derived a relation between the free energy of a macrostate $F(q)$, a bias potential $U_t(q)$, and the biased free energy $F_t(q)$ (Eq. SI1.31):

$$F_t(q) = F(q) + U_t(q)$$  \hspace{1cm} (SI1.36)

Furthermore in Equation (SI1.7), we derived the relationship between the probability and free energy of a macrostate. Applying this relation to the biased free energy $F_t(q)$ gives:

$$F_t(q) - F_t = -k_B T \ln p_t(q)$$  \hspace{1cm} (SI1.37)

$$F_t(q) = -k_B T \ln p_t(q) + cte$$  \hspace{1cm} (SI1.38)

Combining the Equations (SI1.36) and (SI1.38) results in :

$$U_t(q) = -F(q) - k_B T \ln p_t(q) + cte$$  \hspace{1cm} (SI1.39)

This equation describes the relation (up to an irrelevant constant) between the unbiased free energy $F(q)$ of the system – the information we usually want to derive from a simulation – the biased probability $p_t(q)$, and the bias potential $U_t(q)$. In principle, this equation would allow us to determine the bias potential $U_t(q)$ associated with an a priori chosen target probability.
\( p_t(q) \). However, that would require \( F(q) \), which is the very thing we want to calculate. In this enhanced metadynamics method, a functional of a bias potential \( U_b \) is introduced:\(^{10}\)

\[
\Omega [U_b] = \frac{1}{\beta} \ln \frac{\int e^{-\beta[F(q)+U_b(q)]}dq}{\int e^{-\beta F(q)}dq} + \int p_t(q)U_b(q)dq \tag{SI1.40}
\]

This functional has three important properties:

- it has a stationary point at \( U_b(q) = -F(q) - k_B T \ln p_t(q) = U_t(q) \)
- it is a convex functional of \( U_b \)
- the functional value and its derivatives can be calculated from ensemble averages without the explicit value of the free energy:

\[
\Omega [U_b] = \frac{1}{\beta} \ln \frac{\int e^{-\beta[F(q)+U_b(q)]}dq}{\int e^{-\beta F(q)}e^{\beta U_b(q)}dq} + \int p_t(q)U_b(q)dq \tag{SI1.41}
\]

\[
= \frac{1}{\beta} \ln \frac{1}{\langle e^{\beta U_b(q)} \rangle_{U_b}} + \langle U_b(q) \rangle_{p_t} \tag{SI1.42}
\]

\[
= -\frac{1}{\beta} \ln \langle e^{\beta U_b(q)} \rangle_{U_b} + \langle U_b(q) \rangle_{p_t} \tag{SI1.43}
\]

\( \langle \cdot \rangle_{U_b} \) represents the ensemble average of the system biased with the potential \( U_b \) and can be calculated from a molecular simulation, while \( \langle \cdot \rangle_{p_t} \) represents the average according to the target probability distribution \( p_b(q) \) and can be calculated by means of numerical or analytical integration. The functional has a global minimum at the bias potential \( U_t \) that corresponds to the a priori chosen target probability \( p_t \). After finding the minimum of this functional, one also finds through Equation (SI1.39) the free energy \( F(q) \) of the unbiased system. The strength of this method is the fact that it also provides a well-defined procedure to construct an efficient bias potential through a variational principle.

A derivation of the functional is discussed in the work of Bilionis et al.,\(^{11}\) where the biasing of the dynamics and the estimation of the free energy profile are unified under the same objective of minimizing the Kullback-Leibler divergence between appropriately selected distri-
butions on the collective variable space. More in particular, the Kullback-Leibler divergence between the target and bias probability,

\[
\text{KL}(p_t|p_b) = \int dq \ p_t(q) \ln \left( \frac{p_t(q)}{p_b(q)} \right),
\]

(SI1.44)
is minimized, where KL = 0 represent matching distributions.

To optimize the functional, the bias potential is expanded into a finite basis set \(G_k\) and the variational principle is applied by varying the expansion coefficients \(\alpha_k\) until the stationary point \(\Omega\) is found. Due to the convex nature of \(\Omega\), we know that this stationary point is also the global minimum.

\[
U_b(q|\alpha) = \sum_k \alpha_k G_k(q)
\]

(SI1.45)

\[
\Omega(\alpha) = \frac{1}{\beta} \ln \left( \frac{\int e^{-\beta[F(q)+\sum_k \alpha_k G_k(q)]}dq}{\int e^{-\beta F(q)}dq} \right) + \int p_t(q) \sum_k \alpha_k G_k(q) dq
\]

(SI1.46)

\[
\frac{\partial \Omega}{\partial \alpha_k} = \frac{1}{\beta} \left( -\beta \int G_k(q)e^{-\beta[F(q)+\sum_k \alpha_k G_k(q)]}dq + \int p_t(q)G_k(q) dq \right)
\]

(SI1.47)

\[
= - \langle G_k \rangle_{U_b} + \langle G_k \rangle_{p_t}
\]

(SI1.48)
The stationary point is found when the gradient is zero, hence when the average of each basis function with respect to the bias potential \(U_b\) on the one hand and the target probability \(p_t\) on the other hand is equal. For efficient implementation of the minimizer, the second order derivatives are also required:

\[
\frac{\partial^2 \Omega}{\partial \alpha_k \partial \alpha_l} = \beta \left( \langle G_k G_l \rangle_{U_b} - \langle G_k \rangle_{U_b} \langle G_l \rangle_{U_b} \right)
\]

(SI1.49)

\[
= \beta \text{Cov} [G_k, G_l]_{U_b}
\]

(SI1.50)
The expansion coefficients can then be updated according to a stochastic gradient descent-based algorithm (due to the noise present in the MD simulation, one prefers to use a more
robust update scheme than straightforward conjugate gradient method) with update parameter $\mu$:

$$\alpha^{(n+1)} = \alpha^{(n)} - \mu \left[ \frac{\partial \Omega}{\partial \alpha} (\bar{\alpha}^{(n)}) + \frac{\partial^2 \Omega}{\partial \alpha^2} (\bar{\alpha}^{(n)}) (\alpha^{(n)} - \bar{\alpha}^{(n)}) \right] \quad (SI1.51)$$

Hence, a first order Taylor expansion of the gradient is constructed around the cumulative moving average $\bar{\alpha}^{(n)} = \frac{1}{n} \sum_{i=1}^{n} \alpha^{(i)}$ instead of evaluating the gradient directly at the instantaneous $\alpha^{(i)}$ to minimize the influence of the statistical fluctuations.

In the original work by Valsson and Parrinello exponential basis functions were proposed.\(^{10}\) In this work, we opt to use Gaussian basis functions instead of the exponential functions.

### 1.5 Free energy perturbation

Suppose a system has two states, $A$ and $B$, which can be described respectively by the Hamiltonians $\mathcal{H}_A$ and $\mathcal{H}_B$. The free energy of both states can be written as:

$$F_A = -k_B T \ln \left[ C \int e^{-\beta \mathcal{H}_A} dr^N dp^N \right] \quad (SI1.52)$$

$$F_B = -k_B T \ln \left[ C \int e^{-\beta \mathcal{H}_B} dr^N dp^N \right] \quad (SI1.53)$$

The difference in free energy becomes:

$$F_B - F_A = -k_B T \ln \left[ C \int e^{-\beta \mathcal{H}_B} dr^N dp^N \right] \quad (SI1.54)$$

$$= -k_B T \ln \left[ \frac{\int e^{-\beta (\mathcal{H}_B - \mathcal{H}_A)} e^{-\beta \mathcal{H}_A} dr^N dp^N}{\int e^{-\beta \mathcal{H}_A} dr^N dp^N} \right] \quad (SI1.55)$$

$$= -k_B T \ln \langle e^{-\beta (\mathcal{H}_B - \mathcal{H}_A)} \rangle_A \quad (SI1.56)$$

This means that the influence of a perturbation (going from $A$ to $B$) can be estimated by performing a single calculation in state $A$. 
1.6 Thermodynamic integration

Suppose the Hamiltonian depends on a partitioning parameter $\lambda$: $\mathcal{H}(r^N, p^N; \lambda)$.\textsuperscript{12,13} The free energy of the system and its derivative with respect to this parameter are given by

$$F(\lambda) = -k_B T \ln \left[ C \int e^{-\beta \mathcal{H}(r^N, p^N; \lambda)} \, dr^N \, dp^N \right]$$  \hspace{1cm} (SI1.57)

$$\frac{\partial F}{\partial \lambda} = -k_B T C \int \frac{e^{-\beta \mathcal{H}}}{C} \frac{\partial \mathcal{H}}{\partial \lambda} \, dr^N \, dp^N$$  \hspace{1cm} (SI1.58)

$$= \left\langle \frac{\partial \mathcal{H}}{\partial \lambda} \right\rangle_{\lambda}$$  \hspace{1cm} (SI1.59)

This results in the following expression for the free energy difference of the system between states $\lambda_2$ and $\lambda_1$:

$$F(\lambda_2) - F(\lambda_1) = \int_{\lambda_1}^{\lambda_2} \frac{\partial F}{\partial \lambda} \, d\lambda$$  \hspace{1cm} (SI1.60)

$$= \int_{\lambda_1}^{\lambda_2} \left\langle \frac{\partial \mathcal{H}}{\partial \lambda} \right\rangle_{\lambda} \, d\lambda$$  \hspace{1cm} (SI1.61)

The subscript $\lambda$ indicates that the average has to be computed in the ensemble where the Hamiltonian has a parameter value of $\lambda$. Hence, the ensemble changes during the integration, so that multiple ensembles have to be sampled for values of $\lambda$ in between $\lambda_1$ and $\lambda_2$.

2 Pulay stress

Based on the electronic energy profile, $E(V)$, and pressure, $P_{\text{VASP}}(V)$, as a function of the volume, a Pulay stress profile: $P_{\text{Pulay}}(V) = \frac{dE}{dV}(V) + P_{\text{VASP}}(V)$. To that end, we fit higher order polynomials to the energy and pressure profiles. After fitting those profiles, the energy profile can computed analytically and a polynomial fit can be computed for the Pulay stress. Figure SI1 shows the resulting Pulay stress as a function of the volume. The Pulay stress approximately follows a $1/V$ relation. By integrating the Pulay stress, we can compute the
corresponding free energy correction \( F_{\text{Pulay}}(V) \). Hence, we find an effective free energy by correcting the free energy obtained from umbrella sampling \( F_{\text{VASP}}(V) \) with the free energy induced by the Pulay stress: \( F(V) = F_{\text{VASP}}(V) - F_{\text{Pulay}}(V) \).

![Figure SI1](image-url)

**Figure SI1**: The volume dependent Pulay stress as a function of the volume, using an energy and pressure profile obtained via the PAW method in VASP.

### 3 Simulation parameters

Table SI1: Parameters for the construction of free energy profiles with the volume as the collective variable. The total simulation time is given by \( t \). \( \{V_0\} \) refers to the volume grid.

| Simulation Parameters | Analysis |
|-----------------------|----------|
| TI                    | \( t \)  | \( \{V_0\} \) | \( T \) | \( \Delta V \) |
| FEP                   | \( t \)  | \( \{V_0\} \) | \( T \) | \( \Delta V \) |
| US/WHAM               | \( t \)  | \( P \) | \( T \) | \( \{V_0\} \) | \( k \) | \( \Delta V \) | \( \Delta Z \) |
| US/DHAM               | \( t \)  | \( P \) | \( T \) | \( \{V_0\} \) | \( k \) | \( \Delta V \) |
| MTD                   | \( t \)  | \( P \) | \( T \) | \( w \) | \( h/T_u \) |
| VES                   | \( t \)  | \( P \) | \( T \) | \( \{V_0\} \) | \( w/\Delta V \) | \( \mu/T_u \) |

To perform advanced molecular simulations, several parameters need to be chosen, which are either related with the simulations or with the subsequent analysis (see Table SI1).
The simulation parameters can be divided into three groups: (i) the global MD parameters, (ii) the ensemble parameters, and (iii) the external potential parameters. The latter are only relevant for those simulations where an external bias potential is introduced in the simulation.

For the ensemble parameters, we distinguish between two ensembles, the \((N, V, \sigma_a = 0, T)\) and the \((N, P, \sigma_a = 0, T)\) ensemble (for notation, see reference 14). Hence, all simulations have a fixed temperature, fixed number of particles, and a fixed anisotropic stress. The \((N, V, \sigma_a = 0, T)\) ensemble is employed for thermodynamic integration (TI) and free energy perturbation (FEP), while the \((N, P, \sigma_a = 0, T)\) ensemble is used for umbrella sampling (US), metadynamics (MTD), and variationally enhanced sampling (VES). In FEP and TI, simulations are run at different volumes, i.e. a volume grid \(\{V_0\}\) is introduced.

In US, a similar volume grid is adopted to construct the harmonic potentials:

\[
U_b^i(V) = \frac{k}{2} (V - V_i)^2
\]  

(SI3.62)

where \(V_i \in \{V_0\}\) and \(k\) represents the force constant. In the MTD approach, the sampling is also governed by an external bias potential, consisting of Gaussian contributions:

\[
U_b(V | t) = h \sum_{i=1}^{N(t)} \exp \left( -\frac{(V - V_i)^2}{2w^2} \right)
\]  

(SI3.63)

where \(h\) is the height and \(w\) is the width of the Gaussian contribution which are fixed during a given simulation. The external bias potential is updated on-the-fly, every \(T_u\) time steps.

In VES, the Gaussian contributions are centered around the volume points on a volume grid \(\{V_0\}\). The height of the contributions is updated every \(T_u\) time steps with a stochastic optimization scheme with update parameter \(\mu\) (see Equation SI1.51).

A last type of parameters are the analysis parameters to determine a free energy profile from the advanced sampling simulations. These are \(\Delta V\), i.e. the grid spacing for the volume grid \(\{V_0\}\), and the convergence criterion \(\Delta Z\), which has to be fixed in WHAM.

In Table SI2 we summarize the numerical values which have been used in the different
procedures to construct the free energy profiles, displayed in Figure 3 of the main text. This parameter set for each free energy method yields the reference profile needed for the efficiency assessment, discussed in Section 7. In order to assess the efficiency of the simulation parameters, we subsequently lowered the total simulation time $t$ and increased the grid spacing $\Delta V$. The particular choice of the convergence criterion for WHAM is discussed in Section 8.

Table SI2: Numerical values for the various parameters tabulated in Table SI1. These parameters are employed in the computation of the free energy profiles displayed in Figure 3 of the main text.

| Simulation Parameters | Analysis |
|-----------------------|----------|
| MD Ensemble External Potential | |
| TI 500 ps [721,1551] Å$^3$ 300 K | 5 Å |
| FEP 500 ps [721,1551] Å$^3$ 300 K | 5 Å |
| US/WHAM 500 ps 1 MPa 300 K [721,1551] Å$^3$ $k_B T$ Å$^{-6}$ | 5 Å $\Delta Z$ |
| US/DHAM 500 ps 1 MPa 300 K [721,1551] Å$^3$ $k_B T$ Å$^{-6}$ | 5 Å |
| MTD 1 ns 1 MPa 300 K | $50 \text{ Å}^3$ $1 \text{ kJ} \text{ mol}^{-1} \text{ ps}^{-1}$ |
| VES 1 ns 1 MPa 300 K [600,1600] Å$^3$ | $50 \text{ Å}^3$ $1 \text{ kJ} \text{ mol}^{-1} \text{ ps}^{-1}$ |

4 Metastable structures and free energy differences

From the free energy profiles obtained using a force field description of the potential energy surface (see Figure 3 in the main text), several characteristic values for the unit cell volume of the closed pore (cp), large pore (lp) structure and transition (tr) structure can be extracted (see Table SI3). In addition, these properties can be compared to those obtained from the umbrella sampling simulations at several temperatures (100 K, 300 K and 500 K) using a DFT description for the potential energy surface (see Figure 5 of the main text). Table SI3 shows the obtained unit cell volumes for cp, lp and transition state from these free energy profiles. The free energy differences between those states are reported in Table SI4.
Table SI3: Unit cell volume of the closed pore (cp), large pore (lp) and transition (tr) structure in MIL-53(Al) extracted from the free energy profiles (see Figure 3 and Figure 5 of the main text). The upper part of the table reports unit cell volumes using the different free energy methods at the force field level, respecting a temperature of 300 K. The lower part of the table gives the DFT results obtained at the PBE+D3(BJ) level of theory.

| FF       | \(V_{cp} \text{ [Å}^3\)] | \(V_{lp} \text{ [Å}^3\)] | \(V_{tr} \text{ [Å}^3\)] |
|----------|---------------------------|---------------------------|---------------------------|
| TI       | 820.1                     | 1447.5                    | 1272.5                    |
| FEP      | 823.7                     | 1452.9                    | 1273.3                    |
| US/WHAM  | 820.4                     | 1447.3                    | 1270.9                    |
| US/DHAM  | 819.5                     | 1440.7                    | 1274.5                    |
| MTD      | 819.1                     | 1451.0                    | 1263.0                    |
| VES      | 814.0                     | 1454.5                    | 1265.1                    |
| average  | 819.4                     | 1448.9                    | 1269.8                    |

| DFT      | \(V_{cp} \text{ [Å}^3\)] | \(V_{lp} \text{ [Å}^3\)] | \(V_{tr} \text{ [Å}^3\)] |
|----------|---------------------------|---------------------------|---------------------------|
| 100 K    | 848                       | 1450                      | 1204                      |
| 300 K    | 869                       | 1449                      | 1196                      |
| 500 K    | 914                       | 1467                      | 1121                      |

Table SI4: Free energy differences for the different methods. Force field results are obtained at 300 K and DFT results are obtained using the PBE+D3(BJ) scheme.

| FF       | \(\Delta F_{lp-cp} \text{ [kJ/mol]} \) | \(\Delta F_{cp-\text{lp}}^{\ddagger} \text{ [kJ/mol]} \) | \(\Delta F_{lp-cp}^{\ddagger} \text{ [kJ/mol]} \) |
|----------|------------------------------------------|------------------------------------------|------------------------------------------|
| TI       | 26.16                                    | 28.25                                    | 2.09                                     |
| FEP      | 25.80                                    | 28.15                                    | 2.35                                     |
| US/WHAM  | 25.95                                    | 28.06                                    | 2.11                                     |
| US/DHAM  | 26.14                                    | 27.98                                    | 1.83                                     |
| MTD      | 26.94                                    | 29.77                                    | 2.82                                     |
| VES      | 26.51                                    | 28.88                                    | 2.36                                     |
| average  | 26.57                                    | 28.25                                    | 2.34                                     |

| DFT      | \(\Delta F_{lp-cp} \text{ [kJ/mol]} \) | \(\Delta F_{cp-\text{lp}}^{\ddagger} \text{ [kJ/mol]} \) | \(\Delta F_{lp-cp}^{\ddagger} \text{ [kJ/mol]} \) |
|----------|------------------------------------------|------------------------------------------|------------------------------------------|
| 100 K    | 18.67                                    | 24.75                                    | 6.14                                     |
| 300 K    | 9.74                                     | 15.49                                    | 5.75                                     |
| 500 K    | −0.67                                    | 6.41                                     | 7.08                                     |

5 Energy differences in literature

An overview of the energy differences between the large and closed pore phase in MIL-53(Al) based on published DFT results in literature is given in Table SI5. The energy difference depends significantly on the level of theory which comprises the choice of exchange correlation functional and the dispersion scheme. Moreover, the particular choice of code used to perform
the DFT calculations will impact the obtained energy difference, due to code-specific features such as the implementation of the basis sets. The relative stability of the two phases varies from 14 to 72 kJ/mol. A high-level theoretical study (beyond DFT) which could be regarded as a benchmark is still missing.

Table SI5: Energy difference between the large and closed pore phase of MIL-53(Al) reported in literature.

| level of theory       | $\Delta E_{lp-cp}$ [kJ/mol] | code     | reference |
|-----------------------|-----------------------------|----------|-----------|
| vdw-DF                | 71.9                        | SIESTA   | 15        |
| PBE+D2                | 38.8                        | CRYSTAL06| 15        |
| B3LYP+D2              | 41.6                        | CRYSTAL06| 15        |
| B3LYP+D2*             | 33.8                        | CRYSTAL06| 15        |
| PBE+D3(ATM)           | 15.7                        | CP2K     | 16        |
| HSE06+D3(ATM)         | 14.4                        | CP2K     | 17        |
| B3LYP+D2*             | 35.7                        | CRYSTAL09| 18        |

*re-parameterized by Civalleri et al.\textsuperscript{19}

6 Harmonic oscillator approximation

In this section, the free energy difference between the lp and the cp structure ($\Delta F_{cp-tp}$) is studied as a function of the temperature. A relation between the temperature and the free energy difference can be obtained either from the harmonic oscillator approximation or from dynamic simulation methods, constructing free energy profiles at different temperatures. The latter includes the anharmonic behavior related to framework breathing. Moreover, we would like to study this relationship with both methods employing two different descriptions for the potential energy surface: either at the force field level, or at the DFT level, adopting the PBE+D3(BJ) level of theory.

The free energy differences obtained from the harmonic oscillator approximation are compared with the free energy differences determined from the umbrella sampling simulations in Figure SI2. According to the force field results at 300 K, a difference in free energy $\Delta F_{cp-tp}$ of 32 kJ/mol and 26 kJ/mol is obtained with the harmonic oscillator approximation and the
umbrella sampling, respectively. Hence, not taking into account the anharmonic behavior overestimates the free energy difference between the cp and lp state. This observation is even more pronounced for the ab initio simulations, where a difference in free energy of 18 kJ/mol and 9 kJ/mol is observed for the harmonic approximation and the US simulations, respectively.

Moreover, inspection of Figure SI2 learns that the free energy difference from the force field simulations is overestimated with respect to the ab initio simulations. This observation clearly indicates the importance of the level of theory and the dispersion scheme on the determination of the free energy profile.

![Comparison of the free energy difference ∆F_{lp-cp} as a function of the temperature.](image)

Figure SI2: Comparison of the free energy difference ∆F_{lp-cp} as a function of the temperature. We use two descriptions for the potential energy surface, force field based (FF) and ab initio based (AI), and two free energy estimation methods, the harmonic oscillator approximation (HA) and umbrella sampling (US).

To partially take into account anharmonicity, one can employ a harmonic oscillator method at intermediate volume points. By means of a constrained volume optimization procedure, structures can be optimized at fixed volumes and corresponding Γ-point frequencies can be analytically derived with Yaff. Based on those frequencies a quasi-harmonic
(QHA) free energy profile can be computed. In Figure SI3, we compare the free energy profile at 300 K obtained with QHA with the free energy profile resulting from a dynamic method. Moreover, we also report the free energy difference between the lp and cp state obtained via NMA. The free energy differences between the lp and cp state is approximately 23 kJ/mol, 26 kJ/mol and 30 kJ/mol, using QHA, US and NMA, respectively.

The difference between NMA and QHA is due to the shift in equilibrium volume. Solely the latter is able to incorporate the volume shift due to thermal expansion. However, frequencies of large porous crystals such as MIL-53(Al) are hard to determine accurately, hence, QHA results can be prone to some noise. Especially around the lp phase, it is clear that there are some outliers when compared to US, which influence the free energy difference mentioned above. Overall, it can be concluded that QHA captures the most important temperature effects for this particular material. However those conclusions may not be generalized and need further testing in future studies.

Figure SI3: Comparison of the electronic energy profile, including dispersion corrections, (red curve) and the free energy profile at 300 K obtained from QHA (blue curve) and US (green curve). All profiles are based on the force field description of the potential energy surface.
7 Computational efficiency of each free energy method

In order to assess the computational efficiency of the different free energy methods, the computational effort to reach certain error thresholds is determined. We determine the errors generated by choosing less stringent parameter settings than the setting reported in Table SI2, which correspond to the reference free energy profiles. Lowering the parameters, and hence lowering the computational effort, will produce free energy profiles which deviate with respect to the reference free energy profile. Two types of errors were introduced in the main text: the error related to sampling along the direction of the collective variable and the error related to sampling of the degrees of freedom other than the collective variable. To compute those errors empirically, we use two empirical methods.

(i) To determine the error originating from incomplete sampling of all degrees of freedom apart from the collective variable, $n$ free energy profiles are constructed for each adapted parameter set. In the equilibrium methods, those $n$ free energy profiles are generated from bootstrapping the sample data. In the non-equilibrium methods, those $n$ free energy profiles stem from independent simulations. We generate 50 and 20 profiles for the equilibrium and non-equilibrium methods, respectively. Subsequently, an average free energy profile for each parameter set can be computed:

$$\hat{F}(V) = \frac{1}{n} \sum_{i=1}^{n} F_i(V)$$  \hspace{1cm} (SI7.64)

The sampling error related to the incomplete sampling of the degrees of freedom orthogonal to the collective variable is estimated from the standard deviation on the $n$ free energy profiles:

$$\hat{\sigma}^{(i)}(V) = \left[ \frac{1}{n-1} \sum_{i=1}^{n} (F_i(V) - \hat{F}(V))^2 \right]^{1/2}$$  \hspace{1cm} (SI7.65)
(ii) The sampling error along the collective variable can be determined from the squared deviation of the obtained free energy profiles with a fixed reference free energy profile.

\[ \sigma^{(ii)}(V) = \left[ (\hat{F}(V) - \hat{F}_{\text{ref}}(V))^2 \right]^{1/2} \]  

(SI7.66)

A third, more technical error, is the error related with fitting a polynomial to simulated data points, which is negligible compared to the sampling error.

As a measure of the efficiency of the different free energy methods, all errors are averaged over the volume range of interest and the computational time to reach a certain error threshold is determined for either \( \sigma^{(i)} \) or \( \sigma^{(ii)} \). The results are reported in Table SI6. A visual representation of the procedure to obtain both errors is provided in Figure SI4.

Table SI6: The minimal computational effort required for each free energy method to meet the threshold error of 0.5 kJ/mol and 0.7 kJ/mol.

|       | 0.7 kJ/mol | 0.5 kJ/mol |
|-------|------------|------------|
| TI    | 33 × 50.0 ps | 20 × 150.0 ps |
| FEP   | 165 × 50.0 ps | - |
| US/WHAM | 16 × 50.0 ps | 16 × 50.0 ps |
| US/DHAM | 23 × 50.0 ps | 16 × 100.0 ps |
| MTD   | 550.0 ps | - |
| VES   | 325.0 ps | - |
Figure SI4: Descriptive visualization of the two errors generated by an adaptive parameter set. The volume range of interest lies between the two vertical grey lines. The red curve represents the reference free energy profile, while the yellow curves represent the $n$ various free energy profiles and the blue curve is the average free energy profile $\hat{F}(V)$. The blue error bars correspond to the sampling of the orthogonal degrees of freedom. The red error bars correspond to the sampling of the collective variable.

In the particular case of the equilibrium free energy methods, the error $\sigma^{(i)}$ depends on the total simulation time of each simulation. By reducing the total simulation time, the degrees of freedom orthogonal to the collective variable are sampled to a lesser extent, resulting in a larger error. The error $\sigma^{(ii)}$ depends on the distance in between the simulations (i.e. the grid distance). To compare computational efficiencies, a set of simulations is run using the following set of total simulations times and grid distances: [50, 100, .., 500] ps $\times$ [5, 10, .., 50] Å³, yielding the efficiencies reported in Figure SI5. For each grid distance the minimum simulation time is plotted to get the error threshold and this for each of the considered equilibrium methods, i.e. TI, US/WHAM, US/DHAM and FEP. To illustrate, assuming a grid distance of 30 Å³ in the TI method, requires at least a simulation time of 150 ps to limit the error to 0.5 kJ/mol (see Figure SI5b). With a grid distance of 30 Å³, the volume range of interest is spanned by 28 windows. In each window, a MD simulation of 150 ps
in the \((N, V, \sigma_n = 0, T)\) ensemble is performed. Hence, the minimal computational effort to reach an error of 0.5 kJ/mol amounts to \(28 \times 150\) ps. The most optimal performance is obtained with a grid distance of 40 Å\(^3\) and a simulation time of 150 ps. In that case, the computational effort reduces to \(20 \times 150\) ps, agreeing with Table SI6. The minimal computational effort is marked by a square instead of a triangle in Figure SI5.

![Figure SI5](image)

**Figure SI5:** Lowest computational efficiency to reach the error thresholds of (a) 0.7 kJ/mol and (b) 0.5 kJ/mol for the different equilibrium free energy methods. Color coding is the following, blue: weighted histogram analysis method (WHAM), green: dynamic histogram analysis method (DHAM), red: thermodynamic integration (TI) and black: free energy perturbation (FEP).

In the non-equilibrium simulations, the error \(\sigma^{(i)}\) depends on the total simulation time. Hence, the latter determines whether the total range of interest was sampled sufficiently to yield a good estimate for the free energy profile. The error \(\sigma^{(ii)}\) depends on the work rate, defined as the ratio of the time in between two successive potential energy additions and the total amount of potential energy added to the system, i.e \(\frac{\tau_w}{h}\) in the case of MTD and \(\frac{\tau_w}{\mu}\) in the case of VES. For Gaussian contributions, the potential energy scales with both the Gaussian height, \(h\), and the Gaussian width, \(w\). Each addition of a Gaussian hill injects an energy of \(\int dx \cdot h e^{-x^2/(2w^2)} = \sqrt{2 \pi}wh\) into the system. A constant Gaussian width of 50 Å\(^3\) is adopted and the computational efficiency is reported in terms of the total simulation time and the work rate. For the two non-equilibrium methods, MTD and VES, the lowest
computational efficiency plots to reach the error threshold of 0.7 kJ/mol are depicted in Figure SI6. The interpretation of these plots is similar as in Figure SI5. In MTD, Gaussian heights of 0.5 kJ/mol are employed to estimate the computational efficiency, while a value of 1 kJ/mol is used in VES. The update times $T_u$ vary in the range $[1500 - 10000]$ time steps in MTD and in the range $[6000 - 30000]$. Considering a work rate of 18000 kJ/mol$^{-1}$ in VES requires a simulation time of 325 ps to obtain the best performance within the error threshold of 0.7 kJ/mol. A higher work rate will prevent the sampling of the whole phase space. A lower work rate will introduce too much bias in the system, creating a shooting effect. It explains why even 1 ns does not suffice to reach the 0.7 kJ/mol error threshold in those cases.

![Graphs showing computational efficiency](image)

Figure SI6: Lowest computational efficiency to reach the error thresholds of 0.7 kJ/mol with (a) metadynamics and (b) variationally enhanced sampling.

### 8 Convergence of WHAM

When using WHAM to determine the free energy profile from umbrella sampling data, the tolerance for the convergence of the self-consistent cycle, $\Delta Z$, is an important parameter. Since this tolerance is determined on the biased partition function, a good value for this tolerance is hard to estimate a priori. We have compared several tolerances in Figure SI7.
In general, lowering the tolerance for the self-consistent cycle until the free energy profile is no longer appreciably altered is a useful strategy. Nevertheless, it does not guarantee finding a correct free energy profile.\textsuperscript{21} In this work, a tolerance of 0.0004184 kJ/mol was used.

![Figure SI7: Free energy of MIL-53(Al) as a function of the unit cell volume determined with WHAM, using different values for the tolerance $\Delta Z$. The convergence criterion heavily influences the outcome of the final free energy. The legend represents the tolerance of the error on the partition function.](image)

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