Theory of Solutions in Energy Representation in NPT-ensemble: Derivation Details

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Abstract

Theory of solutions in energy representation (ER method) developed by Matubayasi and Nakahara provides with an approximate way of calculating solvation free energies (or, identically, the excess chemical potentials) from atomistic simulations. In this document we provide some derivation details of this, to our opinion, theoretically involved method, which will help a non-specialist to follow. There are three points which differ this document from a regular textbook on statistical mechanics or research articles:

1. Derivation is detailed and all approximations are explicitly stated;
2. Statistical mechanics derivations are performed in NPT-ensemble;
3. We perform the derivations for the case when a molecule is represented as a set of (atomic) sites interacting via spherically symmetric potentials (a classical Force Field representation).

In ER method, a new collective coordinate is introduced - the interaction energy of a solute and a solvent molecule. The excess chemical potential is expressed as a functional of the solute-solvent density distribution defined over the collective variable. The functional can be approximated by the Percus’s method of functional expansion, which leads to the end-point (not dependent on the $\lambda$-coupling path) free energy expression.

As a side result, we prove that the solvation free energy is always equivalent to the excess (over ideal) chemical potential, and not only at infinite dilution or when internal molecule degrees of freedom are not affected by solvation as it is sometimes wrongly believed.
1 Introduction

We provide detailed derivation of the theory of solutions in energy representation (ER method) developed by Matubayasi and Nakahara [1, 2, 3, 14, 15]. ER method provides with an approximate way of calculating solvation free energies (or, identically, the excess chemical potentials) from atomistic simulations. The method can be seen as bridge between the molecular simulations and the classical density functional theory (DFT). It is quite common nowadays to model molecular interaction on the level of the classical force field approximation, which implies that a molecule is represented as a set of (atomic) sites interacting via spherically symmetric potentials.

In the first part of the manuscript we define and derive the expression for solvation free energy (SFE) in NPT-ensemble for the case of classical force field representation of molecular interactions. We prove that SFE is identical to the excess chemical potential. Also, we obtain the Kirkwood’s charging formula expressing the excess chemical potential via the solute-solvent density distribution.

In the second part of the manuscript we provide details on some important relations of ER method for the case of NPT-ensemble. In ER method, a new collective coordinate is introduced - the interaction energy of a solute and a solvent molecule. We show that the Kirkwood’s charging formula is valid also for the solute-solvent distribution function in energy representation. Later this expression is reformulated as a functional of density distribution. The Percus method of functional expansion is used to obtain the hypernetted chain (HNC)- and Percus-Yevick (PY)-like approximations of this functional. The final formula for the excess chemical potential
heuristically combines expressions from different approximations and employs different input functions.

2 Excess chemical potential in NPT-ensemble

2.1 Some definitions

We consider a system with \(N_s = 1\) solute and \(N_w\) solvent molecules in isothermo-isobaric ensemble (NPT-ensemble).

We describe the interactions between the molecules in the force field approximation at the level of classical mechanics. Each molecule is represented as a set of atoms (better to say interaction sites), which interact with each other via bonded and nonbonded potentials present in the given force field (e.g. OPLS, CHARMM, AMBER, etc). Each interaction site is considered as a separate object, which has its own translational degrees of freedom and translational partition function. Therefore, when we talk about a set of coordinates which define the position of a molecule \(x_i\), we mean the positions of all atoms which belong to this molecule, where index \(\alpha\) runs over all atoms \((n_t)\) of the molecule of type \(t\):

\[
x_i = \{r_{i,\alpha}\}_{\alpha=1}^{n_t}
\]

where \(t\) is the molecule type, e.g. \(s\) denotes solute, \(w\) denotes solvent, and the coordinates of atom \(\alpha\) of \(i^{th}\) molecule:

\[
r_{i,\alpha} = \{x_{i,\alpha}, y_{i,\alpha}, z_{i,\alpha}\}
\]

Each atom has its own momentum: \(p_{i,\alpha}\)

2.2 Parametrized Hamiltonian

Here and after we mostly adopt the notations used in the Appendix of the Shirts et al. publication [6].

The excess chemical potential can be calculated in the process of gradual switching on the intermolecular interactions between a solute molecule and the solvent. We introduce \(\lambda\) parameter which controls the degree of coupling between the solute and solvent molecules, such that when \(\lambda=0\) the interactions are absent and when \(\lambda=1\) interactions are at full coupling. Since, only solute-solvent interaction potential \(u_{sw,\lambda}(x_s, x_{w,i})\) depends on \(\lambda\), the potential energy function of the system can be written as follows:

\[
U_\lambda(x_s, x_{N_w}^w) = \Psi(x_s) + \sum_{i=1}^{N_w} u_{sw,\lambda}(x_s, x_{w,i}) + U_{ww}(x_{N_w}^w)
\]

where subscript \(s\) denotes solute, subscript \(w\) denotes solvent, \(\Psi(x_s)\) is the potential energy of the solute molecule, \(x_{w,i}\) is the position of \(i^{th}\) solvent molecule, \(N_w\) is the number of solvent molecules, \(u_{sw,\lambda}\) is the \(\lambda\)-dependent solute-solvent interaction potential, \(U_{ww}\) is the potential energy of the solvent molecules, \(x_{N_w}^w\) is the short notation of positions of all solvent molecules.

The total Hamiltonian can be written as:

\[
H_\lambda = K(p_s, p_{N_w}^w) + U_\lambda(x_s, x_{N_w}^w)
\]
where the kinetic energy is written as:

\[ K(\mathbf{p}_s, \mathbf{p}_w^N) = \sum_{\alpha=1}^{n_s} \frac{p_{s,\alpha}^2}{2m_{s,\alpha}} + \sum_{i=1}^{N_w} \sum_{\alpha=1}^{n_{w,i}} \frac{p_{w,i,\alpha}^2}{2m_{w,\alpha}} \]  

(4)

where \( m_{s,\alpha} \) and \( m_{w,\alpha} \) are the masses of \( \alpha \)th atoms of solute and solvent molecules, correspondingly.

2.3 Partition functions with non-parameterized Hamiltonian

Keeping in mind that we consider the system with a single solute molecule \( N_s = 1 \), we will write explicitly the terms with \( N_s \) in the derivations. Later this will help us to show that the SFE is always equal to the excess chemical potential.

2.3.1 Case of solution

The partition function in NPT ensemble can be written as:

\[
\Delta(N_s, N_w, P, T) = \int_0^\infty \frac{dV}{V'} e^{-\beta PV Q(N_s, N_w, V, T)}
\]

(5)

where \( V' \) is an arbitrary constant which makes the partition function dimensionless, \( \beta = \left(\frac{k_B T}{\hbar}\right)^{-1} \), \( k_B \) is the Boltzmann constant, \( Q(N_s, N_w, V, T) \) is the canonical partition function, which has the following form:

\[
Q(N_s, N_w, V, T) = \frac{1}{h^{3N_w N_w! N_s!}} \int_{-\infty}^{+\infty} d\mathbf{p}_s^{N_s} d\mathbf{p}_w^{N_w} \int_V dx_s^{N_s} dx_w^{N_w} \exp \left[-\beta \mathcal{H}(\mathbf{p}_s^{N_s}, \mathbf{p}_w^{N_w}, \mathbf{x}_s^{N_s}, \mathbf{x}_w^{N_w})\right]
\]

where \( h \) is the Planck’s constant. Multiplication by \( h^{-1} \) serves as a quantum correction for purely classical partition function [7]. The factorials of number of atoms in the system appear due to indistinguishably of atoms belonging to the molecules of the same type. Each integration symbol denotes integration over multiple coordinates. Differential \( d\mathbf{x}_w^{N_w} \) is the short notation for \( dx_{w,1}...dx_{w,N_w} \). Symbol \( V \) at the integration sign - \( \int_V \) - reflects that integration limits are bound by the system’s volume.

In the case of classical statistical mechanics the momenta degrees of freedom are independent and can be analytically integrated [8]:

\[
h^{-3} \int_{-\infty}^{+\infty} d\mathbf{p}_{x,\alpha} e^{-\beta \frac{p_{x,\alpha}^2}{2m_{x,\alpha}}} = \frac{\hbar^2}{2\pi m_{x,\alpha} k_B T}^{-1.5} = \Lambda_{x,\alpha}^{-3}
\]

where \( \Lambda_{x,\alpha} \) is the thermal de Broglie wavelength for atom \( \alpha \) in molecule of type \( x \).

Therefore we get:

\[
Q(N_s, N_w, V, T) = \prod_{\alpha=1}^{N_s} \Lambda_{s,\alpha}^{-3N_s} \prod_{\alpha=1}^{N_w} \Lambda_{w,\alpha}^{-3N_w} \cdot Z(N_s, N_w, V, T)
\]

(6)

where \( Z \) is the configuration integral of the system:

\[
Z(N_s, N_w, V, T) = \int_V dx_s^{N_s} dx_w^{N_w} \exp \left[-\beta U(x_s^{N_s}, x_w^{N_w})\right]
\]

(7)
The Gibbs free energy is:

\[ G(N_s, N_w, P, T) = -k_B T \ln \Delta(N_s, N_w, P, T) \]

The chemical potential of solute in the system can be written as:

\[ \mu = G(N_s, N_w, P, T) - G(N_s - 1, N_w, P, T) = -k_B T \ln \frac{\Delta(N_s, N_w, P, T)}{\Delta(N_s - 1, N_w, P, T)} \] (8)

2.3.2 Case of ideal gas

For later derivations we will use the expression for the chemical potential of non-interacting solute molecules at given \( T, V \) and \( N_s \). Therefore, we derive it here. Firstly, let us find the configuration integral for a single solute molecule:

\[ Z(N_s = 1, N_w = 0, V, T) = \int_V d\mathbf{x}_s \exp \left[-\beta \Psi_s(\mathbf{x}_s)\right] \] (9)

The potential energy in the force field (FF) representation is a function only of distances between particles and does not depend on their absolute positions. Additionally, we consider homogeneous liquid phase. These two facts allow us to change the coordinates of the system such that one atom of the solute molecule is located in the origin \([7\)\]. Coordinates of all solute’s atoms are written as (see Eq. 1):

\[ \mathbf{x}_s = \{\mathbf{r}_{s,1}, \mathbf{r}_{s,2}, \ldots, \mathbf{r}_{s,n_s}\} \]

Therefore, we may rewrite Eq. 9:

\[
\int_V d\mathbf{x}_s \exp \left[-\beta \Psi_s(\mathbf{x}_s)\right] = \int_V d\mathbf{r}_{s,1} d\mathbf{r}_{s,2} \ldots d\mathbf{r}_{s,n_s} \exp \left[-\beta \Psi_s(0, \mathbf{r}_{s,2}, \ldots, \mathbf{r}_{s,n_s})\right] =
\]

\[
= V \int_V d\mathbf{r}_{s,2} \ldots d\mathbf{r}_{s,n_s} \exp \left[-\beta \Psi_s(0, \mathbf{r}_{s,2}, \ldots, \mathbf{r}_{s,n_s})\right] =
\]

\[
= V \int_V d\mathbf{r}_{s,2} \ldots d\mathbf{r}_{s,n_s} \exp \left[-\beta \Psi_s(0, \mathbf{r}_{s,2}, \ldots, \mathbf{r}_{s,n_s})\right] =
\]

where we, firstly, integrated out the position of the first atom of the solute molecule which released the volume, and, secondly, we dropped the ′ marks for simplicity.

To proceed we introduce the following approximation. The bonded potentials in FF representation do not allow atoms belonging to the same molecule to move far from each other. Therefore, the limits of integration for the rest of solute’s atoms with very high accuracy can be reduced to a small volume around the first atom (we denote it as \( V_s \)). Please note that, since we consider a single molecule here these do not affect the combinatorial prefactor of the canonical partition function. Therefore we write:

\[
\int_V d\mathbf{x}_s \exp \left[-\beta \Psi_s(\mathbf{x}_s)\right] = V \int_{V_s} \ldots \int_{V_s} d\mathbf{r}_{s,2} \ldots d\mathbf{r}_{s,n_s} \exp \left[-\beta \Psi_s(0, \mathbf{r}_{s,2}, \ldots, \mathbf{r}_{s,n_s})\right]
\]

For simplicity we will use the following notations: \( \mathbf{x}^*_s = \{\mathbf{r}_{s,2}, \ldots, \mathbf{r}_{s,n_s}\} \), and correspondingly, \( d\mathbf{x}^*_s = d\mathbf{r}_{s,2} \ldots d\mathbf{r}_{s,n_s} \). With these notations we have:

\[
\int_V d\mathbf{x}_s \exp \left[-\beta \Psi_s(\mathbf{x}_s)\right] = V \int_{V_s} d\mathbf{x}^*_s \exp \left[-\beta \Psi_s(0, \mathbf{x}^*_s)\right] = V \cdot q_s(T) \] (10)
where we introduced new function $q_s(T)$, which is in some sense corresponds to the internal partition function of a solute molecule in FF representation:

$$q_s(T) = \int_{V_s} d\mathbf{x}_s^* \exp \left[ -\beta \Psi_s(0, \mathbf{x}_s^*) \right]$$ (11)

However, one should note that in this definition all conformations of the molecule are taken into account in contrast to the usual $q(T)$ definition based on vibrational, rotational, electronic, etc. partition functions, which are defined for a single molecular conformation [9].

With the help of Eq. 10 we may write the configuration integral (Eq. 7) for non-interacting solute molecules as:

$$Z_{id}(N_s, N_w = 0, V, T) = \int_V d\mathbf{x}_s^{N_s} \exp \left[ -\beta \sum_{i=1}^{N_s} \Psi(\mathbf{x}_{s,i}) \right] = (V \cdot q_s(T))^{N_s}$$ (12)

And the corresponding canonical partition function (see Eq. 6) is:

$$Q_{id}(N_s, N_w = 0, V, T) = \prod_{\alpha=1}^{n_s} \Lambda_{s,\alpha}^{-3N_s} \cdot V^{N_s} \cdot q_s^{N_s}(T)$$ (13)

The chemical potential for the ideal gas case at given $V$ is written as:

$$\mu_{id} = -k_B T \ln \frac{Q_{id}(N_s, N_w = 0, V, T)}{Q_{id}(N_s - 1, N_w = 0, V, T)} = -k_B T \ln \frac{\prod_{\alpha=1}^{n_s} \Lambda_{s,\alpha}^{-3N_s}}{\prod_{\alpha=1}^{n_s} \Lambda_{s,\alpha}^{-3N_s-1}} \cdot V^{N_s} \cdot q_s^{N_s}(T)$$

$$= -k_B T \ln \left[ \frac{V q_s(T)}{N_s} \cdot \prod_{\alpha=1}^{n_s} \Lambda_{s,\alpha}^{-3} \right]$$ (14)

### 2.4 Solvation free energy and excess chemical potential

The solvation free energy (SFE) can be defined as a reversible work required to switch on the interactions between a solute molecule and the rest [7]. In NPT ensemble this can be written as:

$$\Delta G_{solv} = -k_B T \ln \frac{\Delta(N_s, N_w, P, T, \lambda = 1)}{\Delta(N_s, N_w, P, T, \lambda = 0)}$$ (15)

where the $\lambda$ in the brackets indicate that the partition functions are written with the $\lambda$-parameterized Hamiltonian (Eq. 3).

In the next transformation of Eq. 15 the $N_s^{n_s}$ factor in the nominator appears because of the dissemination process [7]. When we write the parameterized Hamiltonian we scale the solute-solvent interactions only for one solute molecule, which makes this solute molecule distinguishable from the rest. This switch from assimilated and disseminated solute molecule changes the combinatorial prefactor of the canonical partition function (Eq. 6). Inside a single molecule we consider atoms being physically different, however atoms of the same type from identical molecules are physically identical. Therefore the $N_s^{n_s}$ factor appears:

$$\Delta G_{solv} = -k_B T \ln \frac{\Delta(N_s, N_w, P, T)}{\Delta(N_s - 1, N_w, P, T)}$$ (16)

$$= \int_0^\infty d \left( \frac{V}{\mathcal{V}} \right) e^{-\beta PV} Q(N_s = 1, N_w = 0, V, T)Q(N_s - 1, N_w, V, T)$$
where $\Delta(N_s, N_w, P, T)$ is the partition function with non-parameterized Hamiltonian and the canonical partition function in the denominator factorizes into canonical partition function for the single solute molecule and the system with $N_s - 1$ solvent molecules.

The denominator in Eq. (16) can be further simplified:

$$
\int_0^\infty d \left( \frac{V}{V'} \right) e^{-\beta PV} Q(N_s = 1, N_w = 0, V, T)Q(N_s - 1, N_w, V, T) =
$$

(please, again, note that one solute molecule is not identical to the rest and the corresponding combinatorial factor reduces by one:)

$$
= \prod_{\alpha=1}^{n_s} \frac{\Lambda_{s,\alpha}^{-3N_s}}{(N_s - 1)!} \prod_{\alpha=1}^{n_w} \frac{\Lambda_{s,\alpha}^{-3N_w}}{N_w!} \cdot \int_0^\infty d \left( \frac{V}{V'} \right) e^{-\beta PV} Z(N_s = 1, N_w = 0, V, T)Z(N_s - 1, N_w, V, T) =
$$

(for a large number of molecules in the system only integration of large system volumes contribute to the NPT partition function (Eq. 5), and therefore integration over small volumes comparable to $V_s$ can be safely neglected. Thus, the integrals over small volumes $V_s$ and, consequently, $Z(N_s = 1, N_w = 0, V, T)$ become independent on total volume $V$. Therefore, using Eqs. (10) we can rewrite Eq. (17) as:)

$$
= \left( \frac{q_s(T) \cdot \prod_{\alpha=1}^{n_s} \Lambda_{s,\alpha}^{-3}}{V^*} \right) \cdot \Delta(N_s - 1, N_w, P, T)
$$

(multiplication and division of Eq. (18) by $\Delta(N_s - 1, N_w, P, T)$ leads to the following:)

$$
= \left( \frac{q_s(T) \cdot \prod_{\alpha=1}^{n_s} \Lambda_{s,\alpha}^{-3}}{V^*} \right) \cdot \Delta(N_s - 1, N_w, P, T)
$$

where $V^*$ is the average volume of the $(N_s - 1, N_w, P, T)$ system.

Finally, we write SFE (Eq. 16) as:

$$
\Delta G_{solv} = -k_B T \ln \left[ \frac{\Delta(N_s, N_w, P, T)}{\Delta(N_s - 1, N_w, P, T)} \cdot \frac{N_s^{n_s}}{q_s(T) \cdot V^* \cdot \prod_{\alpha=1}^{n_s} \Lambda_{s,\alpha}^{-3}} \right] =
$$

(using Eq. 8 we get:)

$$
= \mu + k_B T \ln \frac{q_s(T) \cdot V^* \cdot \prod_{\alpha=1}^{n_s} \Lambda_{s,\alpha}^{-3}}{N_s^{n_s}} =
$$

(we add $k_B T \ln \frac{V_1}{V_1}$, where $V_1$ is the mean volume of $(N_s, N_w)$ system:)

$$
= \mu + k_B T \ln \frac{q_s(T) \cdot V_1 \cdot \prod_{\alpha=1}^{n_s} \Lambda_{s,\alpha}^{-3}}{N_s^{n_s} V_1} + k_B T \ln \frac{V^*}{V_1}
$$

(19)

where the last term is the work required for one ideal gas particle to expand the volume from $V^*$ to $V_1$. In thermodynamic limit the ratio of two volumes tends to 1 and therefore the term
vanishes. The first term is the chemical potential of the ideal gas of solute molecules (see Eq. 14) with the average volume of \((N_s, N_w, P, T)\) system \(V_1\). Therefore, Eq. 19 is rewritten as:

\[
\Delta G_{\text{solv}} = \mu - \mu^{id}
\]  

(20)

Eq. 20 shows that the SFE is always equal to the excess (over ideal) chemical potential. This also proves that the excess chemical potential is the reversible work of switching the solute-solvent interactions, as defined in Eq. 16. Therefore, we may write:

\[
\Delta G_{\text{solv}} \equiv \mu_{ex}
\]  

(21)

We would like to note two things here. Firstly, SFE equals to the excess chemical potential not only at infinite dilution, as it is sometimes wrongly believed. Secondly, there is a wrong statement (at least for the present case of the FF models of molecules) in the book of Ben-Naim (Ref. [7], page 200) that "... only when \(q_s\) is unaffected by the solvation process, \(\mu_{ex}\) becomes identical with the solvation Gibbs energy ...". In our derivation of Eq. 21 we explicitly considered the case when internal degrees of freedom of molecules, represented by sets of interaction sites, are coupled to other degrees of freedom.

2.5 Kirkwood charging formula

In order to make the forthcoming derivations simpler, from now we explicitly consider the case of infinite diluted solution: \(N_s = 1\). The point here is that we will express the excess chemical potential of solute via the particle density distributions. Therefore, considering many solute molecules in the system will require to introduce the solute-solute density distribution, which will unnecessarily complicate the derivations. Note, that all the forthcoming derivation can be straightforwardly extended to the case of multicomponent solvent (see Ref. [10]).

Let us define the excess chemical potential for the system with parameterized Hamiltonian (Eq. 3) at a certain \(\lambda\) value. With Eqs. 16 and 21 we get:

\[
\mu_{ex,\lambda} = -k_B T \ln \frac{\Delta(N_s, N_w, P, T, \lambda)}{\Delta(N_s, N_w, P, T, \lambda = 0)}
\]

Since the denominator does not depend on \(\lambda\) one can write:

\[
\frac{\partial \mu_{ex,\lambda}}{\partial \lambda} = -k_B T \int_0^\infty d\left(\frac{V}{T}\right) e^{-\beta PV} \int V d\mathbf{x}_s d\mathbf{x}_w \frac{\partial u_{\text{sw},\lambda}}{\partial \lambda} \exp \left[ -\beta U_\lambda(\mathbf{x}_s, \mathbf{x}_w) \right] \frac{\Delta(N_s, N_w, P, T, \lambda)}{\Delta(N_s, N_w, P, T, \lambda = 0)} = \left\langle \frac{\partial U_\lambda}{\partial \lambda} \right\rangle_{\lambda}
\]

With the explicit form of the potential function (Eq. 2) we have:

\[
\frac{\partial \mu_{ex,\lambda}}{\partial \lambda} = \left\langle \sum_{i=1}^{N_w} \frac{\partial u_{\text{sw},\lambda}(\mathbf{x}_s, \mathbf{x}_{w,i})}{\partial \lambda} \right\rangle_{\lambda} = \left\langle \int_{-\infty}^{+\infty} d\mathbf{x}_s' d\mathbf{x}_w' \frac{\partial u_{\text{sw},\lambda}(\mathbf{x}_s', \mathbf{x}_{w,i})}{\partial \lambda} \sum_{i=1}^{N_w} \delta(\mathbf{x}_s - \mathbf{x}_s')\delta(\mathbf{x}_{w,i} - \mathbf{x}_{w,i}') \right\rangle_{\lambda}
\]

where \(\langle \cdot \rangle_{\lambda}\) denotes ensemble average in isothermo-isobaric condition at given \(\lambda\). We can change order of integration and take out the derivative from the ensemble average:

\[
\frac{\partial \mu_{ex,\lambda}}{\partial \lambda} = \int_{-\infty}^{+\infty} d\mathbf{x}_s' d\mathbf{x}_w' \frac{\partial u_{\text{sw},\lambda}(\mathbf{x}_s', \mathbf{x}_{w,i})}{\partial \lambda} \sum_{i=1}^{N_w} \delta(\mathbf{x}_s - \mathbf{x}_s')\delta(\mathbf{x}_{w,i} - \mathbf{x}_{w,i}') \right\rangle_{\lambda}
\]

(22)

In the right hand side there is the pair solute-solvent density distribution in NPT-ensemble by definition (see e.g. Eq. (2.5.13) of Ref. [8], but mind that for density distributions of non-identical particles the sum should include terms with \(i = j\):
\[
\frac{\partial \mu_{\text{ex} \lambda}}{\partial \lambda} = \int d\mathbf{x}_s' d\mathbf{x}_w' \frac{\partial u_{\text{sw} \lambda}(\mathbf{x}_s', \mathbf{x}_w')}{\partial \lambda} \rho_{\text{sw} \lambda}(\mathbf{x}_s', \mathbf{x}_w')
\]

Finally, the excess chemical potential can be written as an integral over lambda:

\[
\mu_{\text{ex}} = \int_0^1 d\lambda \frac{\partial \mu_{\text{ex} \lambda}}{\partial \lambda} = \int_0^1 d\lambda \int_{-\infty}^{+\infty} d\mathbf{x}_s' d\mathbf{x}_w' \frac{\partial u_{\text{sw} \lambda}(\mathbf{x}_s', \mathbf{x}_w')}{\partial \lambda} \rho_{\text{sw} \lambda}(\mathbf{x}_s', \mathbf{x}_w')
\tag{23}
\]

Note, that Eq. (23) is different from Eq. (3) of Ref. [10], where the delta function for the solute-solvent potential at full coupling \( u_{\text{sw}}(\mathbf{x}_s, \mathbf{x}_w) \), irrespective of the ensemble and Hamiltonian which were used to generate this configuration:

\[
v_{\text{sw}}(\mathbf{x}_s, \mathbf{x}_w) = u_{\text{sw}, \lambda = 1}(\mathbf{x}_s, \mathbf{x}_w)
\tag{24}
\]

**3 Energy representation (ER)**

### 3.1 Basic definitions in ER

**Collective coordinate.** We define a new collective coordinate which is the interaction energy between a solute molecule and a solvent molecule: \( \epsilon \). We make this coordinate \( \lambda \)-independent, such that this coordinate is calculated with the solute-solvent potential at full coupling \( u_{\text{sw}}(\mathbf{x}_s, \mathbf{x}_w) \), irrespective of the ensemble and Hamiltonian which were used to generate this configuration:

\[
v_{\text{sw}}(\mathbf{x}_s, \mathbf{x}_w) = u_{\text{sw}, \lambda = 1}(\mathbf{x}_s, \mathbf{x}_w)
\tag{24}
\]

**Microscopic density.** For a single configuration of the system the microscopic density in energy representation can be written as:

\[
\bar{\rho}^e_{\text{sw}}(\epsilon) = \sum_{i=1}^{N_w} \delta \left( v_{\text{sw}}(\mathbf{x}_s, \mathbf{x}_w) - \epsilon \right) = \\
= \int_{-\infty}^{+\infty} d\mathbf{x}_s' d\mathbf{x}_w' \delta(\mathbf{x}_s', \mathbf{x}_w') - \epsilon \sum_{i=1}^{N_w} \delta(\mathbf{x}_s' - \mathbf{x}_s) \delta(\mathbf{x}_w' - \mathbf{x}_w) = \\
= \int_{-\infty}^{+\infty} d\mathbf{x}_s d\mathbf{x}_w \delta(\mathbf{x}_s, \mathbf{x}_w) - \epsilon \bar{\rho}_{\text{sw}}(\mathbf{x}_s, \mathbf{x}_w)
\tag{25}
\]

**Potential in ER.** The potential in energy representation can be written as:

\[
u^e_{\text{sw}, \lambda}(\epsilon) = \int_{-\infty}^{+\infty} d\mathbf{x}_s d\mathbf{x}_w \delta \left( u_{\text{sw}}(\mathbf{x}_s, \mathbf{x}_w) - \epsilon \right) u_{\text{sw}, \lambda}(\mathbf{x}_s, \mathbf{x}_w)
\tag{26}
\]

It is important for the following derivation that we choose the lambda path in such a way that \( u_{\text{sw}, \lambda}(\mathbf{x}_s, \mathbf{x}_w) \) is constant on each equi-energy surface of \( v_{\text{sw}}(\mathbf{x}_s, \mathbf{x}_w) \). This can be achieved, for instance, when \( u_{\text{sw}, \lambda}(\mathbf{x}_s, \mathbf{x}_w) = \lambda v_{\text{sw}}(\mathbf{x}_s, \mathbf{x}_w) \). With this restriction of the \( u_{\text{sw}, \lambda} \) potential we can write the following identity:

\[
u_{\text{sw}, \lambda}(\mathbf{x}_s, \mathbf{x}_w) = \int_{-\infty}^{+\infty} d\epsilon \cdot \delta \left( v_{\text{sw}}(\mathbf{x}_s, \mathbf{x}_w) - \epsilon \right) u^e_{\text{sw}, \lambda}(\epsilon)
\tag{27}
\]

Taking the partial derivative of the both sides of equation we obtain the formula, which will be used later on:

\[
\frac{\partial u_{\text{sw}, \lambda}(\mathbf{x}_s, \mathbf{x}_w)}{\partial \lambda} = \int_{-\infty}^{+\infty} d\epsilon \cdot \delta \left( v_{\text{sw}}(\mathbf{x}_s, \mathbf{x}_w) - \epsilon \right) \frac{\partial u^e_{\text{sw}, \lambda}(\epsilon)}{\partial \lambda}
\tag{28}
\]
Solute-solvent density distribution in ER. Solute-solvent density distribution in NPT ensemble is written as:

\[ \rho_{\text{sw},\lambda}^\epsilon(\epsilon) = \langle \hat{\rho}(\epsilon) \rangle_\lambda \]

Using the definition of microscopic density in ER (Eq. 27) and writing explicitly its ensemble average we get:

\[
\rho_{\text{sw},\lambda}^\epsilon(\epsilon) = \frac{\int_0^\infty d \left( \frac{V}{V'} \right) e^{-\beta PV} \int_V d x_s d x_w^N \left[ \int_{-\infty}^{+\infty} dx'_s d x'_w \delta(v_{\text{sw}}(x'_s, x'_w) - \epsilon) \hat{\rho}_{\text{sw}}(x'_s, x'_w) \right] \exp \left[ -\beta U_\lambda(x_s, x_w^N) \right]}{\int_0^\infty d \left( \frac{V}{V'} \right) e^{-\beta PV} \int_V d x_s d x_w^N \exp \left[ -\beta U_\lambda(x_s, x_w^N) \right]}
\]

Change of the integration order:

\[
\rho_{\text{sw},\lambda}^\epsilon(\epsilon) = \int_{-\infty}^{+\infty} dx'_s d x'_w \delta(v_{\text{sw}}(x'_s, x'_w) - \epsilon) \rho_{\text{sw},\lambda}(x'_s, x'_w)
\]

(31)

The ratio gives us the definition of the solute-solvent density distribution (see Comment after Eq. 22):

\[ \rho_{\text{sw},\lambda}(x'_s, x'_w) = \int_{-\infty}^{+\infty} dx'_s d x'_w \delta(v_{\text{sw}}(x'_s, x'_w) - \epsilon) \rho_{\text{sw},\lambda}(x'_s, x'_w) \]

(32)

### 3.2 Kirkwood charging formula in energy representation

#### 3.2.1 Kirkwood charging formula via density distribution

Let us obtain the charging formula in energy representation. We start from coordinate representation (Eq. 23):

\[
\mu_{\text{ex}} = \int_0^1 d \lambda \int_{-\infty}^{+\infty} dx'_s d x'_w \frac{\partial u_{\text{sw},\lambda}(x'_s, x'_w)}{\partial \lambda} \rho_{\text{sw},\lambda}(x'_s, x'_w) =
\]

Using Eq. 30 we obtain:

\[
\mu_{\text{ex}} = \int_0^1 d \lambda \int_{-\infty}^{+\infty} dx'_s d x'_w \left[ \int_{-\infty}^{+\infty} d \epsilon \left( v_{\text{sw}}(x'_s, x'_w) - \epsilon \right) \frac{\partial u_{\text{sw},\lambda}(\epsilon)}{\partial \lambda} \right] \rho_{\text{sw},\lambda}(x'_s, x'_w)
\]

We change the integration order:

\[
\mu_{\text{ex}} = \int_0^1 d \lambda \int_{-\infty}^{+\infty} d \epsilon \frac{\partial u_{\text{sw},\lambda}(\epsilon)}{\partial \lambda} \left[ \int_{-\infty}^{+\infty} dx'_s d x'_w \delta(v_{\text{sw}}(x'_s, x'_w) - \epsilon) \rho_{\text{sw},\lambda}(x'_s, x'_w) \right]
\]

We use the relation Eq. 32 to obtain:

\[
\mu_{\text{ex}} = \int_0^1 d \lambda \int_{-\infty}^{+\infty} d \epsilon \frac{\partial u_{\text{sw},\lambda}(\epsilon)}{\partial \lambda} \rho_{\text{sw},\lambda}(\epsilon)
\]

(33)

Eq. 33 is the Kirkwood’s charging formula in energy representation.
3.2.2 Indirect part of potential of mean force (IPMF)

We can introduce an auxiliary function $w_{sw,\lambda}^e(\epsilon)$, which is an analogue of the indirect part of potential of mean force in coordinate representation:

$$\rho_{sw,\lambda}^e(\epsilon) = \rho_{sw,\lambda=0}^e(\epsilon) \cdot \exp \left[ -\beta \left( u_{sw,\lambda}^e(\epsilon) + w_{sw,\lambda}^e(\epsilon) \right) \right] \quad (34)$$

The potential then can be rewritten as:

$$u_{sw,\lambda}^e(\epsilon) = -k_B T \ln \frac{\rho_{sw,\lambda}^e(\epsilon)}{\rho_{sw,\lambda=0}^e(\epsilon)} - w_{sw,\lambda}^e(\epsilon) \quad (35)$$

3.2.3 Kirkwood charging formula via IPMF

Let us rewrite the Kirkwood’s charging formula (Eq. 33) via $w_{sw,\lambda}^e(\epsilon)$:

$$\mu_{ex} = \int_0^1 d\lambda \int_{-\infty}^{+\infty} d\epsilon \frac{\partial u_{sw,\lambda}^e(\epsilon)}{\partial \lambda} \rho_{sw,\lambda}^e(\epsilon)$$

Change of the integration order:

$$\mu_{ex} = \int_{-\infty}^{+\infty} d\epsilon \int_0^1 d\lambda \frac{\partial u_{sw,\lambda}^e(\epsilon)}{\partial \lambda} \rho_{sw,\lambda}^e(\epsilon)$$

Integration by parts for the inner integral:

$$\mu_{ex} = \int_{-\infty}^{+\infty} d\epsilon \left[ \rho_{sw,\lambda=1}^e(\epsilon) u_{sw,\lambda=1}^e(\epsilon) - \int_0^1 d\lambda \frac{\partial \rho_{sw,\lambda}^e(\epsilon)}{\partial \lambda} u_{sw,\lambda}^e(\epsilon) \right]$$

Change of the integration order back. Mind that $u_{sw,\lambda=1}^e(\epsilon) = \nu_{sw}^e(\epsilon) = \epsilon$ according to the definition (Eq. 24 and Eq. 28):

$$\mu_{ex} = \int_{-\infty}^{+\infty} d\epsilon \rho_{sw,\lambda=1}^e(\epsilon) \epsilon - \int_0^1 d\lambda \int_{-\infty}^{+\infty} d\epsilon \frac{\partial \rho_{sw,\lambda}^e(\epsilon)}{\partial \lambda} u_{sw,\lambda}^e(\epsilon) \quad (36)$$

Let us denote the last term as a functional of the potential and the solute-solvent density distribution:

$$\mathcal{F}\left[\rho_{sw,\lambda}^e(\epsilon), u_{sw,\lambda}^e(\epsilon)\right] = \int_0^1 d\lambda \int_{-\infty}^{+\infty} d\epsilon \frac{\partial \rho_{sw,\lambda}^e(\epsilon)}{\partial \lambda} u_{sw,\lambda}^e(\epsilon) \quad (37)$$

The functional can be written via IPMF. Here and after, we use the following simplified notations:

$$\rho_{sw,0}^e \equiv \rho_{sw,\lambda=0}^e$$

$$\rho_{sw}^e \equiv \rho_{sw,\lambda=1}^e$$

Similar notations are adopted for other functions.

Using Eq. 36 and changing the integration order we obtain from Eq. 37:

$$\mathcal{F}\left[\rho_{sw,\lambda}^e(\epsilon), u_{sw,\lambda}^e(\epsilon)\right] = \int_{-\infty}^{+\infty} d\epsilon \int_0^1 d\lambda \frac{\partial \rho_{sw,\lambda}^e(\epsilon)}{\partial \lambda} \left( -k_B T \ln \frac{\rho_{sw,\lambda}^e(\epsilon)}{\rho_{sw,\lambda=0}^e(\epsilon)} - w_{sw,\lambda}^e(\epsilon) \right) \quad (38)$$

The first integral in Eq. 38 can be taken analytically by parts:

$$\int_0^1 d\lambda \frac{\partial \rho_{sw,\lambda}^e(\epsilon)}{\partial \lambda} \ln \frac{\rho_{sw,\lambda}^e(\epsilon)}{\rho_{sw,0}^e(\epsilon)} = \rho_{sw,\lambda}^e(\epsilon) \ln \frac{\rho_{sw,\lambda}^e(\epsilon)}{\rho_{sw,0}^e(\epsilon)} \bigg|_0^1 - \int_0^1 d\lambda \frac{\partial \rho_{sw,\lambda}^e(\epsilon)}{\partial \lambda} \rho_{sw,\lambda}^e(\epsilon)$$
\[
\rho_{sw,\lambda}^e(\epsilon) = \rho_{sw,0}^e(\epsilon) \ln \frac{\rho_{sw}^e(\epsilon)}{\rho_{sw,0}^e(\epsilon)} - (\rho_{sw}^e(\epsilon) - \rho_{sw,0}^e(\epsilon))
\] (39)

Therefore, we rewrite Eq. 38 using Eq. 39 as:

\[
\mathcal{F}[\rho_{sw,\lambda}^e(\epsilon), u_{sw,\lambda}^e(\epsilon)] =
\int_{-\infty}^{+\infty} d\epsilon \left[-k_B T \left(\rho_{sw}^e(\epsilon) \ln \frac{\rho_{sw}^e(\epsilon)}{\rho_{sw,0}^e(\epsilon)} - (\rho_{sw}^e(\epsilon) - \rho_{sw,0}^e(\epsilon))\right) + \int_{0}^{1} d\lambda \frac{\partial \rho_{sw,\lambda}^e(\epsilon)}{\partial \lambda} (-u_{sw,\lambda}^e(\epsilon))\right]
\]

Regrouping the terms we get:

\[
\mathcal{F}[\rho_{sw,\lambda}^e(\epsilon), u_{sw,\lambda}^e(\epsilon)] = k_B T \int_{-\infty}^{+\infty} d\epsilon \left[(\rho_{sw}^e(\epsilon) - \rho_{sw,0}^e(\epsilon)) - \rho_{sw}^e(\epsilon) \ln \frac{\rho_{sw}^e(\epsilon)}{\rho_{sw,0}^e(\epsilon)} - \beta \int_{0}^{1} d\lambda \frac{\partial \rho_{sw,\lambda}^e(\epsilon)}{\partial \lambda} w_{sw,\lambda}^e(\epsilon)\right]
\] (40)

This expression can be further simplified if we choose the \(\lambda\)-dependence of the potential such that the density distribution is a linear function of \(\lambda\):

\[
\rho_{sw,\lambda}^e(\epsilon) = \lambda \rho_{sw}^e(\epsilon) + (1 - \lambda) \rho_{sw,0}^e(\epsilon)
\] (41)

With this restriction (Eq. 41) the \(\lambda\)-derivative is:

\[
\frac{\partial \rho_{sw,\lambda}^e(\epsilon)}{\partial \lambda} = (\rho_{sw}^e(\epsilon) - \rho_{sw,0}^e(\epsilon))
\]

and the functional (Eq. 40) becomes:

\[
\mathcal{F}[\rho_{sw,\lambda}^e(\epsilon), u_{sw,\lambda}^e(\epsilon)] =
\int_{-\infty}^{+\infty} d\epsilon \left[(\rho_{sw}^e(\epsilon) - \rho_{sw,0}^e(\epsilon)) - \rho_{sw}^e(\epsilon) \ln \frac{\rho_{sw}^e(\epsilon)}{\rho_{sw,0}^e(\epsilon)} - \beta \int_{0}^{1} d\lambda \frac{\partial \rho_{sw,\lambda}^e(\epsilon)}{\partial \lambda} w_{sw,\lambda}^e(\epsilon)\right]
\] (42)

Finally, the excess chemical potential (Eq. 33) reads:

\[
\mu_{ex}[\rho_{sw,\lambda}^e(\epsilon), u_{sw,\lambda}^e(\epsilon)] = \int_{-\infty}^{+\infty} d\epsilon \rho_{sw}^e(\epsilon) e - \mathcal{F}[\rho_{sw,\lambda}^e(\epsilon), u_{sw,\lambda}^e(\epsilon)]
\] (43)

### 3.2.4 Density functional

For further derivations we would like to consider the functional \(\mathcal{F}\) as a unique functional of \(\rho_{sw,\lambda}^e(\epsilon)\). This can be the case if the solute-solvent interaction potential is a unique functional of \(\rho_{sw,\lambda}^e(\epsilon)\). This implies that there should be only one \(u_{sw,\lambda}^e(\epsilon)\) to which a given \(\rho_{sw,\lambda}^e(\epsilon)\) corresponds. Both in coordinate and energy representation it is not the case if we consider ensembles where the number of particles is fixed \([3, 10, 11, 12]\). This can be easily seen from the definition of \(\rho_{sw,\lambda}^e(\epsilon)\) (Eq. 31 and Eq. 2): if one adds a constant to the solute-solvent interaction potential \(u_{sw,\lambda}\) the resulting \(\rho_{sw,\lambda}^e(\epsilon)\) function does not change (mind, that there is a one-to-one correspondence between the potential in energy and coordinate representations (Eqs. 29 and 28)). The lack of the one-to-one correspondence between \(\rho\) and \(u\) results to the fact that the density-density correlation matrix is not invertible and has a singular eigenvalue \([3, 10, 11]\).
Matubayasi proposed a way how to retain the one-to-one ρ - u correspondence by introducing additional condition based on the physical sense. Firstly, he showed that the potentials giving different density profiles can differ from each other only by an additive constant (see Appendix of Ref. [10] and Ref. [3]). Secondly, he set the additive constant to ensure that the chemical potential is an intensive property of the system. This can be achieved by ensuring that the solute-solvent pair potential reaches zero when particle separation tends to infinity.

With this approach a one-to-one correspondence between \( u_{sw,\lambda}(\epsilon) \) and \( \rho_{sw,\lambda}(\epsilon) \) achieved both in coordinate and energy representation. This allows us to consider the potential \( u_{sw,\lambda}(\epsilon) \) as a functional of \( \rho_{sw,\lambda}(\epsilon) \) in a fixed-N ensemble and use the functional calculus to obtain approximate free energy functionals.

Therefore, the excess chemical potential (Eq. 43) can be written as a density functional of the solute-solvent density distribution:

\[
\mu_{ex}[\rho_{sw,\lambda}(\epsilon)] = \int_{-\infty}^{+\infty} d\epsilon \rho_{sw}^{e}(\epsilon)\epsilon - \mathcal{F}[\rho_{sw,\lambda}(\epsilon)]
\]  

(44)

### 3.3 Approximate free energy functional.

The exact free energy functional (Eq. 12) contains the term which depends on \( \lambda \). To eliminate the \( \lambda \)-dependence we apply the Percus’s method of functional expansion to obtain approximate free energy functionals.

#### 3.3.1 Hypernetted chain (HNC) - like approximation.

Following Percus [13] we obtain the HNC-like approximation by expanding the following functional in powers of density fluctuations \( \rho_{sw}(\epsilon') - \rho_{sw,0}(\epsilon') \):

\[
\ln \rho_{sw}^{e}(\epsilon) + \beta u_{sw}^{e}(\epsilon) \approx \ln \rho_{sw,0}^{e}(\epsilon) + \int_{-\infty}^{\infty} d\epsilon' \left( \rho_{sw}^{e}(\epsilon') - \rho_{sw,0}^{e}(\epsilon') \right) \frac{\delta \ln \rho_{sw}^{e}(\epsilon) + \beta u_{sw}^{e}(\epsilon)}{\delta \rho_{sw}^{e}(\epsilon')} \bigg|_{\rho_{sw}(\epsilon') = \rho_{sw,\lambda}(\epsilon')}
\]

(45)

With the help of Eq. 35 we rewrite the left hand side of Eq. 45 via IPMF. Therefore, IPMF in HNC-like approximation can be written as:

\[
u_{sw}^{e,HNC}(\epsilon) = -k_{B}T \int_{-\infty}^{+\infty} d\epsilon' \left( \rho_{sw}^{e}(\epsilon') - \rho_{sw,0}^{e}(\epsilon') \right) \left[ \frac{\delta(\epsilon - \epsilon')}{\rho_{sw}^{e}(\epsilon')} + \beta \frac{\delta u_{sw}^{e}(\epsilon)}{\delta \rho_{sw}^{e}(\epsilon')} \right]^{\rho_{sw}(\epsilon') = \rho_{sw,\lambda}(\epsilon')}
\]

(46)

Let us show that the functional derivative in Eq. 46 is a functional inverse of the density-density correlation function. For that we start from the definition of solute-solvent distribution function at full solute coupling:

\[
\rho_{sw}^{e}(\epsilon) = \langle \hat{\rho}(\epsilon) \rangle_{\lambda=1} = \frac{\int_{0}^{\infty} d \left( \frac{\epsilon}{\nu_{sw}} \right) e^{-\beta PV} \int_{V} d\mathbf{x}_{s} d\mathbf{x}_{w}^{N_{w}} \hat{\rho}^{e}(\epsilon)e^{-\beta U(\mathbf{x}_{s},\mathbf{x}_{w}^{N_{w}})}}{\int_{0}^{\infty} d \left( \frac{\epsilon}{\nu_{sw}} \right) e^{-\beta PV} \int_{V} d\mathbf{x}_{s} d\mathbf{x}_{w}^{N_{w}} e^{-\beta U(\mathbf{x}_{s},\mathbf{x}_{w}^{N_{w}})}}
\]

(47)

Let us denote nominator of Eq. 47 as \( f \) and denominator as \( g \). Then, find the functional derivative of distribution function with respect to solute-solvent potential:

\[
\frac{\delta \rho_{sw}^{e}(\epsilon)}{\delta u_{sw}^{e}(\epsilon')} = \frac{\delta f}{\delta u_{sw}^{e}(\epsilon')} g = -\frac{\delta g}{\delta u_{sw}^{e}(\epsilon')} f
\]

(48)
Both in \( f \) and \( g \) only potential energy \( U \) depends on \( u_{sw}^{e} \). To write its explicit dependence on \( u_{sw}^{e} \) we use the relation between the solute-solvent interaction potentials in coordinate and energy representations (Eq. 29): 

\[
U(x_s, x_w^{N_w}) = \Psi(x_s) + \sum_{i=1}^{N_w} u_{sw}(x_s, x_{w,i}) + U_{ww}(x_w^{N_w}) = \\
= \Psi(x_s) + \sum_{i=1}^{N_w} \int_{-\infty}^{+\infty} d\epsilon'' \cdot \delta(v_{sw}(x_s, x_{w,i}) - \epsilon'') u_{sw}^{e}(\epsilon'') + U_{ww}(x_w^{N_w}) \tag{49}
\]

Therefore, we find the following derivative which will be used in later derivations:

\[
\frac{\delta e^{-\beta U}}{\delta u_{sw}(\epsilon')} = -\beta e^{-\beta U} \sum_{i=1}^{N_w} \int_{-\infty}^{+\infty} d\epsilon'' \cdot \delta(v_{sw}(x_s, x_{w,i}) - \epsilon'') \delta(\epsilon'' - \epsilon') = \\
= -\beta e^{-\beta U} \sum_{i=1}^{N_w} \delta(v_{sw}(x_s, x_{w,i}) - \epsilon') = -\beta e^{-\beta U} \rho_{sw}(\epsilon') \tag{50}
\]

where we used Eq. 28.

With this relation (Eq. 50) the first term in Eq. 48 then can be written as:

\[
\frac{\delta f}{\delta u_{sw}(\epsilon')} = -\beta \langle \rho_{sw}(\epsilon) \rho_{sw}(\epsilon') \rangle_{u_{sw}} \tag{51}
\]

where \( \langle \cdot \rangle_{u_{sw}} \) denotes the ensemble average with the Hamiltonian where the solute-solvent interaction potential is \( u_{sw} \).

Also, with relation Eq. 50 we see that \( g' = -\beta f \). With this Eq. 50 is written as:

\[
\frac{\delta \rho_{sw}(\epsilon)}{\delta u_{sw}(\epsilon')} = -\beta \left[ \langle \rho_{sw}(\epsilon) \rho_{sw}(\epsilon') \rangle_{u_{sw}} - \langle \rho_{sw}(\epsilon) \rangle_{u_{sw}} \langle \rho_{sw}(\epsilon') \rangle_{u_{sw}} \right] \tag{52}
\]

Which equivalently can be written as:

\[
\frac{\delta \rho_{sw}^{e}(\epsilon)}{\delta u_{sw}^{e}(\epsilon')} = -\beta \left[ \rho_{sw}^{e}(\epsilon, \epsilon') + \rho_{sw}^{e}(\epsilon) \delta(\epsilon - \epsilon') - \rho_{sw}^{e}(\epsilon) \rho_{sw}^{e}(\epsilon') \right] = -\beta \chi_{sw}^{e}(\epsilon, \epsilon') \tag{53}
\]

where \( \chi_{sw}^{e}(\epsilon, \epsilon') \) is the density-density correlation function, and \( \rho_{sw}^{e}(\epsilon, \epsilon') \) is the three molecule distribution density distribution defined by analogy to the two molecule density distribution in coordinate representation (see Eq. (2.5.13) of Ref. [8]) as:

\[
\rho_{sw}^{e}(\epsilon, \epsilon') = \left\langle \sum_{i=1}^{N_w} \sum_{j \neq i} \delta(v(x_s, x_{w,i}) - \epsilon) \delta(v(x_s, x_{w,j}) - \epsilon') \right\rangle_{u_{sw}} \tag{54}
\]

From Eqs. 52 and 53 we obtain:

\[
\frac{\delta u_{sw}^{e}(\epsilon)}{\delta \rho_{sw}^{e}(\epsilon')} = \left( \frac{\delta \rho_{sw}^{e}(\epsilon)}{\delta u_{sw}^{e}(\epsilon')} \right)^{-1} = -k_B T (\chi_{sw}^{e})^{-1}(\epsilon, \epsilon') \tag{55}
\]

where \( (\chi_{sw}^{e})^{-1} \) is the functional inverse of the density-density correlation function defined as (see Eq. (3.5.8) of Ref. [8]):

\[
\int_{-\infty}^{+\infty} d\epsilon'' \cdot \chi_{sw}^{e}(\epsilon, \epsilon'') (\chi_{sw}^{e})^{-1}(\epsilon'', \epsilon') = \delta(\epsilon - \epsilon') \tag{56}
\]
With Eq. \((55)\) we can rewrite the HNC-like approximation of the indirect part of potential of mean force (Eq. \((18)\)) as:

\[
w_{\text{sw},\text{HNC}}^e(\epsilon) = -k_B T \left[ \frac{\rho_{\text{sw}}^e(\epsilon) - \rho_{\text{sw},0}^e(\epsilon)}{\rho_{\text{sw},0}^e(\epsilon)} - \int_{-\infty}^{+\infty} d\epsilon' \cdot \left[ \rho_{\text{sw}}^e(\epsilon') - \rho_{\text{sw},0}^e(\epsilon') \right] \cdot (\chi_{\text{sw},0}^e)^{-1}(\epsilon, \epsilon') \right]
\]

\[(57)\]

3.3.2 Percus-Yevick (PY) - like approximation.

Again, following Percus \((13)\) we obtain the Percus-Yevick-like (PY-like) approximation by expanding the following functional:

\[
\rho_{\text{sw}}^e(\epsilon) e^u_w(\epsilon) \approx \rho_{\text{sw},0}^e(\epsilon) + \int_{-\infty}^{+\infty} d\epsilon' \cdot \left( \rho_{\text{sw}}^e(\epsilon') - \rho_{\text{sw},0}^e(\epsilon') \right) \cdot \frac{\delta \left[ \rho_{\text{sw}}^e(\epsilon) e^u_w(\epsilon) \right]}{\delta p_{\text{sw}}^e(\epsilon')}
\]

\[(58)\]

We rewrite Eq. \((58)\) via IPMF (Eq. \((34)\)):

\[
w_{\text{sw}}^e,\text{PY}(\epsilon) = -k_B T \ln \left( 1 + \int_{-\infty}^{+\infty} d\epsilon' \cdot \left[ \frac{\delta (\epsilon - \epsilon')}{\rho_{\text{sw},0}^e(\epsilon)} + \beta \frac{\delta u_w^e(\epsilon)}{\delta p_{\text{sw}}^e(\epsilon')} \right] \right)
\]

\[(59)\]

With the help of Eq. \((46)\) we can rewrite the PY-like approximation via the HNC-like \(w\):

\[
w_{\text{sw}}^e,\text{PY}(\epsilon) = -k_B T \ln \left( 1 - \beta w_{\text{sw}}^e,\text{HNC}(\epsilon) \right)
\]

\[(60)\]

3.3.3 Lambda-integral in HNC-like approximation.

When \(u_\lambda^e\) is the solute-solvent interaction potential the corresponding IPMF is written as:

\[
w_{\text{sw},\lambda}^e,\text{HNC}(\epsilon) = -k_B T \left[ \frac{\rho_{\text{sw},\lambda}^e(\epsilon) - \rho_{\text{sw},0}^e(\epsilon)}{\rho_{\text{sw},0}^e(\epsilon)} - \int_{-\infty}^{+\infty} d\epsilon' \cdot \left[ \rho_{\text{sw},\lambda}^e(\epsilon') - \rho_{\text{sw},0}^e(\epsilon') \right] \cdot (\chi_{\text{sw},0}^e)^{-1}(\epsilon, \epsilon') \right]
\]

\[(61)\]

With the linear dependence of \(\rho_{\text{sw},\lambda}^e\) on \(\lambda\) (Eq. \((11)\)) Eq. \((61)\) can be written via \(w_{\text{sw}}^e,\text{HNC}\) at full solute coupling:

\[
w_{\text{sw},\lambda}^e,\text{HNC}(\epsilon) = \lambda \cdot w_{\text{sw}}^e,\text{HNC}(\epsilon)
\]

\[(62)\]

The \(\lambda\)-integral in Eq. \((62)\) can be written in HNC-like approximation as:

\[
\beta \int_0^1 d\lambda w_{\text{sw},\lambda}^e,\text{HNC}(\epsilon) = w_{\text{sw}}^e,\text{HNC}(\epsilon) \cdot \beta \int_0^1 d\lambda \cdot \lambda = \frac{1}{2} \beta w_{\text{sw}}^e,\text{HNC}(\epsilon)
\]

\[(63)\]

3.3.4 Lambda-integral in PY-like approximation.

When \(u_\lambda^e\) is the solute-solvent interaction potential the corresponding IPMF in PY-like approximation is written as (see Eq. \((60)\)):

\[
w_{\text{sw},\lambda}^e,\text{PY}(\epsilon) = -k_B T \ln \left( 1 - \beta w_{\text{sw}}^e,\text{HNC}(\epsilon) \right) = -k_B T \ln \left( 1 - \lambda \cdot \beta w_{\text{sw}}^e,\text{HNC}(\epsilon) \right)
\]

\[(64)\]

Now, we use the following known tabulated relation:

\[
\int dx \cdot \ln(ax + b) = \frac{(ax + b) \cdot \ln(ax + b) - ax}{a}
\]
to find the $\lambda$-integral:

$$
\beta \int_{0}^{1} d\lambda w_{s,w,\lambda}^{e,PY}(\epsilon) = -\frac{[\beta w_{s,w}^{e,HNC}(\epsilon) + 1] \cdot \ln[\beta w_{s,w}^{e,HNC}(\epsilon) + 1] + \beta w_{s,w}^{e,HNC}(\epsilon)}{-\beta w_{s,w}^{e,HNC}(\epsilon)}
$$

(65)

Next, we use the relation between $w$ in PY and HNC-like approximations at full solute coupling $\lambda = 1$ (see Eq. 64):

$$
w_{s,w}^{e,PY}(\epsilon) = -k_B T \ln(1 - \beta w_{s,w}^{e,HNC}(\epsilon)) \Rightarrow -\beta w_{s,w}^{e,HNC}(\epsilon) = e^{-\beta w_{s,w}^{e,PY}(\epsilon)} - 1
$$

(66)

Using Eq. 66 we rewrite Eq. 65 as:

$$
\beta \int_{0}^{1} d\lambda w_{s,w,\lambda}^{e,PY}(\epsilon) = -\ln[1 - \beta w_{s,w}^{e,PY}(\epsilon)] + 1 + \frac{\ln[1 - \beta w_{s,w}^{e,PY}(\epsilon)]}{\beta w_{s,w}^{e,PY}(\epsilon)}
$$

(67)

### 3.3.5 Constructing hybrid functional.

The approximate functional is developed by Matubayasi and Nakahara [2] based on the following considerations. To make an end-point expression of $\mu_{ex}$ we need to approximate the $\lambda$-integral in Eq. 42. Beforehand, we would like to note that the approximate expression of the $\lambda$-integral combines four parts.

Firstly, the $\lambda$-integration can be analytically performed both in PY-like and HNC-like approximations (see Eqs. 67 and 68). There is a general knowledge in the field that in the case of simple liquids the PY approximation works better for short range repulsive potentials, while HNC approximation performs better for long-range attractive potentials [8]. Matubayasi and Nakahara [2] decided to use the PY-like expression for the $\lambda$-integral in the unfavorable region of solvation ($w_{s,w}^{e} \geq 0$) and HNC-like expression for the $\lambda$-integral in the favorable region of solvation ($w_{s,w}^{e} < 0$).

Secondly, the indirect part of potential of mean force $w_{s,w}^{e}$ can be determined from unbiased molecular simulations (regular MD or Monte-Carlo) only outside of the solute-core region (region of very large solute-solvent interaction energies: $\epsilon$). Matubayasi and Nakahara [3] proposed to use HNC-approximation of the potential of mean force when $w_{s,w}^{e}$ is not resolved from molecular simulations. In HNC-like approximation $w_{s,w}^{e,HNC}$ is determined by the solute-solvent density distribution $\rho_{s,w,0}^{e}$ and the inverse of the density-density correlation function $(\chi_{s,w,0}^{e})^{-1}$ in the case of the zero solute-solvent coupling (this can be seen from Eq. 57, where the difference $\rho_{s,w}^{e} - \rho_{s,w,0}^{e}$ can be safely approximated by $-\rho_{s,w,0}^{e}$ since in the core region $\rho_{s,w}^{e} << \rho_{s,w,0}^{e}$). Therefore, $w_{s,w}^{e,HNC}$ in the core-region can be calculated with high resolution in the ensemble, where solute and solvent are fully decoupled and the probability to find solvent molecule in the core region is high. The later can be in the most convenient way realized by the insertion of the solute molecule configurations into the ensemble of precalculated pure solvent configurations.

Combination of the two different expression for the $\lambda$-integral and the two different input $w$ functions results into functional consisting of four parts. The final expression for the excess chemical potential (Eq. 44) is:

$$
\mu_{ex}[\rho_{s,w}^{e}(\epsilon), \rho_{s,w,0}^{e}(\epsilon), \chi_{s,w,0}^{e}(\epsilon, \epsilon')] = \int_{-\infty}^{+\infty} d\epsilon \rho_{s,w}^{e}(\epsilon) - \mathcal{F}[\rho_{s,w}^{e}(\epsilon), \rho_{s,w,0}^{e}(\epsilon), \chi_{s,w,0}^{e}(\epsilon, \epsilon')]
$$

where

$$
\mathcal{F}[\rho_{s,w}^{e}, \rho_{s,w,0}^{e}, \chi_{s,w,0}^{e}] =
$$
\[ k_B T \int_{-\infty}^{+\infty} d\epsilon \left[ (\rho_{sw}^e(\epsilon) - \rho_{sw,0}^e(\epsilon)) - \rho_{sw}^e(\epsilon) \ln \frac{\rho_{sw}^e(\epsilon)}{\rho_{sw,0}^e(\epsilon)} - (\rho_{sw}^e(\epsilon) - \rho_{sw,0}^e(\epsilon)) \cdot I[\rho_{sw}^e, \rho_{sw,0}^e, \chi_{sw,0}] \right] \]

where \( I \) is the approximated \( \lambda \)-integral:

\[ \beta \int_{0}^{1} d\lambda w_{sw,\lambda}^e(\epsilon) \simeq I[\rho_{sw}^e, \rho_{sw,0}^e, \chi_{sw,0}] = \alpha(\epsilon) \cdot F_w(\epsilon) + [1 - \alpha(\epsilon)] \cdot F_{w,HNC}(\epsilon) \]

where the functions \( F_w \) and \( F_{w,HNC} \) are in turn written as the combination of PY and HNC-like expressions for the \( \lambda \)-integral:

\[ F_w(\epsilon) = \begin{cases} \frac{\beta w_{sw}^e(\epsilon)}{2}, & \text{when } w_{sw}^e(\epsilon) \geq 0 \\ \beta w_{sw}^e(\epsilon) + 1 + \frac{\beta w_{sw}^e(\epsilon)}{e^{\beta w_{sw}^e(\epsilon)} - 1}, & \text{when } w_{sw}^e(\epsilon) < 0 \end{cases} \]

and

\[ F_{w,HNC}(\epsilon) = \begin{cases} \frac{2}{\beta w_{sw}^e,HNC(\epsilon)}, & \text{when } w_{sw}^e,HNC(\epsilon) \geq 0 \\ - \ln \left[ 1 - \beta w_{sw}^e,HNC(\epsilon) \right] + 1 + \frac{\ln \left[ 1 - \beta w_{sw}^e,HNC(\epsilon) \right]}{\beta w_{sw}^e,HNC(\epsilon)}, & \text{when } w_{sw}^e,HNC(\epsilon) < 0 \end{cases} \]

The parameter \( \alpha(\epsilon) \), which is responsible for merging parts with different \( w \) functions, is set heuristically [5] as [2]:

\[ \alpha(\epsilon) = \begin{cases} 1, & \text{when } \rho_{sw}^e(\epsilon) \geq \rho_{sw,0}^e(\epsilon) \\ 1 - \left( \frac{\rho_{sw}^e(\epsilon) - \rho_{sw,0}^e(\epsilon)}{\rho_{sw}^e(\epsilon)} \right)^2, & \text{when } \rho_{sw}^e(\epsilon) < \rho_{sw,0}^e(\epsilon) \end{cases} \]
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