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Interfacial solvation modelling with PCM

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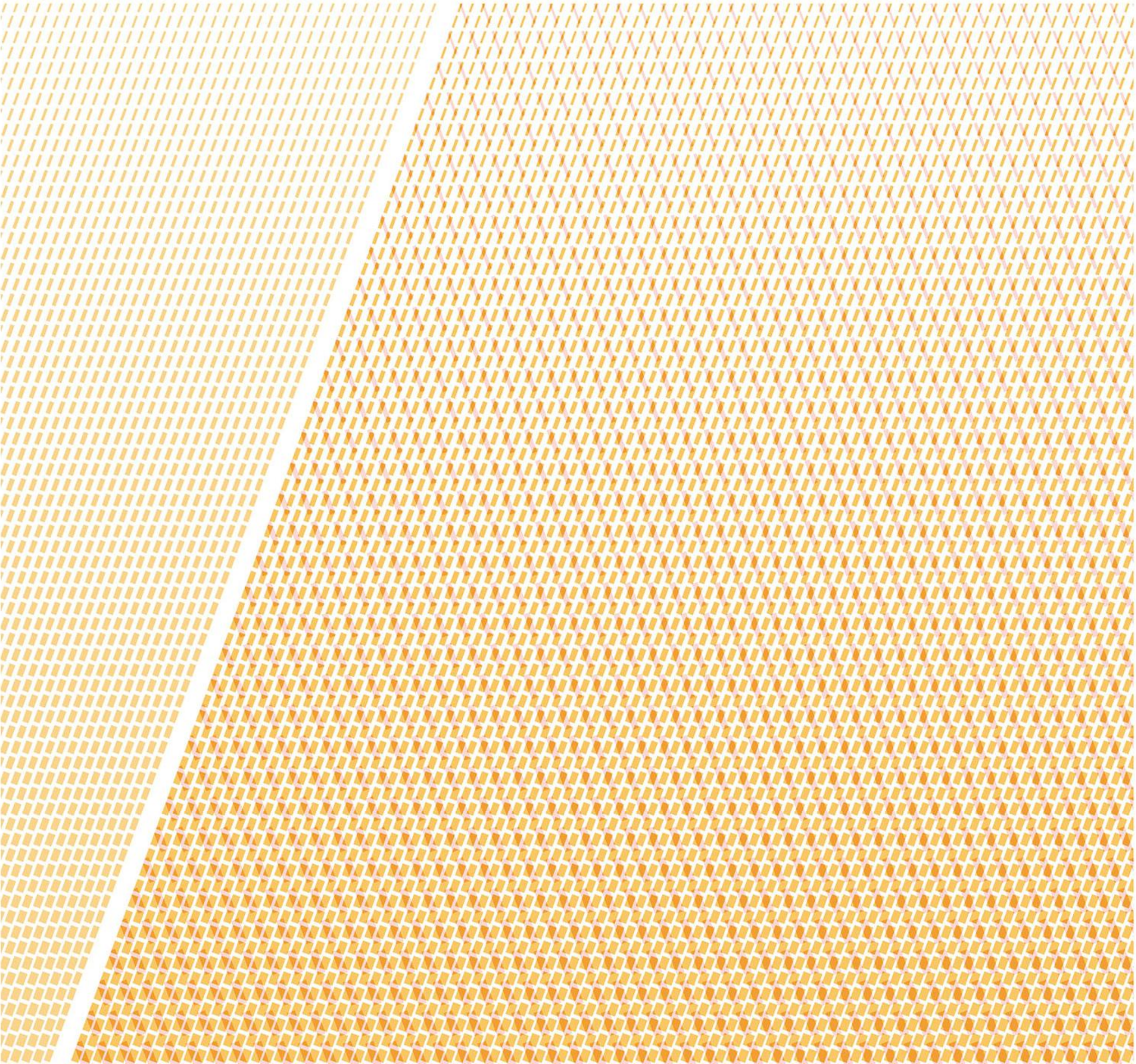

UNIVERSITY OF TROMSØ

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Contents

Preface

”So... you mix imaginary chemicals ?”

Satander Cole

While the raise of quantum chemistry can be attributed to many groups or individual scientists, perhaps one of the more outstanding and influential was paper by Kołos and Wolniewicz [1], regarding the hydrogen dissociation energy. At the time, computational chemistry was still deemed to be a budding, non-practical part of science. Because of that, no one was surprised that the results presented in the mentioned paper were in contradiction with the high-precision values obtained by the experimentalist and Nobel Prize winner, G. Herzberg [2]. After all, imperfect method produces imperfect results. The stunning outcome of that paper was that Herzberg, ten years after his initial paper, published a revision of his experimental hydrogen dissociation energies, in which his results were corrected in accordance with Kołos and Wolniewicz work [3]. It was the first, and perhaps the most vivid, situation in which the theoretical *ab initio* prediction for molecules was superior to the high-precision experimental measurement. Since then, quantum chemistry has flourished, especially with the exponentially increasing computational power and general development of technology. Applications of such predictive methods became quite broad, from technology [4] to even modeling of the real biological systems [5].

The gain in using quantum chemistry is, in the author’s opinion, two-fold. Firstly: the possibility of experimental examination of reaction mechanisms are currently limited to the most sophisticated of spectroscopic methods[6]. The most feasible option, currently, to examine chemical processes step by step lies within theoretical modeling. The second important factor is versatility and cost-efficiency of the computational methods. Experimental science usually requires a highly specialized and sophisticated apparatus for each observable or set of observables and a constant stream of non-reusable reagents and solvents. Conversely, quantum chemistry requires only one apparatus, a computer, which is limited only by available software and currently available performance of CPU and memory units (which still develop as stated in the Moore's Law [7]).

While many words of praise can be said about quantum chemistry, there are numerous problems associated with it. First and foremost, quantum mechanics is, because our limited capacity to solve its equations, approximate beyond the one-electron system, and the number of approximations increase as derivation of it elaborates. Because of that, usual calculations are limited to a singular, isolated molecule in its ground state, which is usually not very interesting for an experimental scientist.

This fact brings us to the solvation modeling. The motivation for it is simple: most of chemistry happens in solution, therefore a way to include solvent-related effects is necessary. Very often, the main focus is on a small part of the system (i.e. a single solute molecule, or a small cluster of molecules), for which a solvent interaction model is requited. The two very common approaches are: explicit (i.e. Molecular Mechanics (MM)[8]), and implicit models (i.e. Polarizable Continuum Model (PCM)[9]). Explicit models make use of classical mechanics to simulate real solvent environments and molecular systems, with all the solvent molecules in the simulation. In this particular approach calculations can be conducted on very large systems, too large for quantistic calculation, with a substantial amount of solvent molecules, which is vital for e.g. enzyme analysis and design. Some MM applications allow even for examination of small viruses [10]. Because of that, MM is often considered to be closer to the experiment and more practical than Quantum Mechanics (QM). Nevertheless, the most problematic factor of MM is very heavy dependence on the parametrization, which needs to be (usually) fitted empirically (this is also true for PCM, substantially fewer parameters are required for the latter).

Implicit models revolve around the idea that solute-solvent interaction can be simulated through the averaged effect, without investing a lot of computational power in simulating the solvent itself, in which we are not usually interested. This averaged effect is usually achieved through a set of image charges, interacting with the solute molecule as implied solvent. The strength of this approach is that it is both quantistic and computationally cheap. Due to the model's simplicity, more complex solvent environments, like surfaces and interfaces, can be also be simulated without huge additional computational cost [11]. The main drawback of continuum models is lack of all specific solvent-solute interactions, i.e. hydrogen bonding, although methods exist to re-introduce them, i.e. addition of small number of explicit solvent molecules or additional parametrization.

Both for PCM and MM, the majority of applications in quantum chemistry focuses on solvent effect in bulk solution. While for many applications this is sufficient, with the rise of nanotechnology and miniaturization of electronics, micellization of the pharmaceutical agents, applications of the quantum dots etc. surface and interface-related phenomena become more and more important. This fact becomes apparent with the realization, that when a cube of 1000 atoms is considered, 60% of them make the surface of the cube, which means that interfacial phenomena become more important than bulk properties of the system. Ergo, the smaller the system, the more important surfaces are, therefore the development of methods which will allow to simulate them is vital. Nevertheless, it is rather challenging to examine interfacial phenomena that do not involve a solid phase experimentally, apart from macroscopic properties like surface tension. The problematic factor of the interface lies in very small size of the system, which can be considered to be two-dimensional, thus rather sophisticated methods with pinpoint accuracy are necessary to examine interfacial region precisely, and not average of large part of the surrounding system. One of this method is circular dichorism, which have been used for that specific purpose [12]. Theoretical modeling of the interface, possible for both MM and implicit methods (see Section VII), is both feasible and offers substantial help. Apart from verification of the experimental results, theoretical models can predict certain interfacial behavior, even before the experiment is conducted, or even appropriate experimental procedure invented.

The introduction to this thesis is organized as follows. The basics of PCM are given in Section I to Section III. The Apparent Surface Charge methods and elaboration of specific version of PCM are given in Section IV to Section VI. Extension model to interfaces is covered in Section VII and corresponding subsections. Lastly, non-electrostatic effects and contributions are discussed in Section VIII and corresponding subsections. At the end of this introduction short summaries of papers included are given.

Theory

I Basics of the model

We begin by establishing an effective Hamiltonian for this method. Following Tomasi and Persico [13], we assume system in thermal and mechanical equilibrium, while allowing chemical reactions. For the solute **M** consisting of N_{el} electrons and N_{nuc} nuclei, Hamiltonian $\hat{H}_M^0$ will depend on electronic coordinates $q = q_1, q_2, q_3, ...q_{N_{el}}$ and nuclear coordinates $Q = Q_1, Q_2, Q_3, ...Q_{N_{nuc}}$, the latter as parameters. This establishes a ground state electronic Hamiltonian in the Born-Oppenheimer approximation. On top of that we have to include the interaction potential V_{int}, corresponding to the solvent effect on the system, which yields an effective Hamiltonian in the form

$$\hat{H}_M^{\text{eff}} = \hat{H}_M^0(q; Q) + V_{int}. \tag{1}$$

In continuum models we employ a simple version of the interaction potential, focused on electrostatics (which we will then expand to include other contributions). In methods centered around effective Hamiltonian using continuous distribution (EHCD) [14] more complicated interaction potentials are used, namely depending on the distribution of electronic charge of the solute ϱ_M and the thermally-averaged distribution function of solvent molecules g_S. In continuum methods, instead of using g_S, the solvent is assumed to be a linear isotropic continuum, characterized by a dielectric constant ϵ, which is solvent- and temperature-dependent. Therefore V_{int} can be described as

$$V_{int}(q, Q, \varrho_M, \epsilon) = \sum_{\alpha=1...N_{nuc}} Z_\alpha \Phi(Q_\alpha) - \sum_{i=1...N_{el}} \Phi(q_i), \tag{2}$$

where Z_α is the charge of nucleus α, and $\Phi(r)$ is the electrostatic potential generated by the polarized dielectric at the position r. If the solvated wavefunction, obtained by solving the Schrödinger's equation using effective Hamiltonian, is given by $\Psi^{(f)}(q;Q)$, then the solute-solvent interaction contribution to the total energy $E^{(f)}$ is given by

$$W_{MS} = \int_{allspace} \Psi^{(f)*} V_{int} \Psi^{(f)} dq1...dq_i = \int_{allspace} \varrho_M(r)\Phi(r)dr^3. \qquad (3)$$

This equation sets the foundation of the continuum model. For the derivation of the basic model, it is important to state some assumptions at this point at this point:

1. The model describes extremely diluted solution. In practice, only a single solute molecule in infinite solvent is considered.

2. The solvent is isotropic and in equilibrium at standard conditions (that is, 298 K and 1013 hPa). While true for the derivation, this will be extended in Section VII, where interfaces are introduced.

3. Interactions between solvent and solute are limited to electrostatics. This point is arbitrary, as other conventions (e.g. focusing on dispersion interaction first) could be considered with equally good outcome. Regardless of approach, for a good solvation model several interactions have to be considered (see Section VIII).

4. Solvent molecules are, and will only be considered, in the electronic ground state, and no dynamic effect are considered. This will be extended in Section VIII.3, where dispersion contribution, describing interaction between transition charge densities, is introduced.

II On the cavity

In all continuum models, which are implicit by definition, arises the problem of the boundary between the solute molecule and the continuum. In explicit models, this problem in not present, because the explicit solvent molecules and their interaction with the solute naturally establish space occupied by the solute. The uniform dielectric 'space' requires additional steps, namely to describe where solvent can or cannot enter. Following Onsager's comments [15], the cavity should not only have a physical meaning, but also contain the largest possible part of the solute charge distribution. The solute charge distribution vanishes only at infinity, which will have a bearing on our model later on (see Section V and Section VIII.2). The problem with the charge distribution and cavity can be then reformulated to "cavity containing largest *sensible* part of solute charge distribution". This is, of course, highly subjective, as there are many ways a cavity can be established using this guidelines, of which we will mention the three perhaps most representative formal definitions. The first approach is based on using a surface of constant electronic density as the cavity [16]. This cavity is unique for each electronic structure of examined solvent, so any possible deviation in it will result in a different cavity. This approach is not widely used.

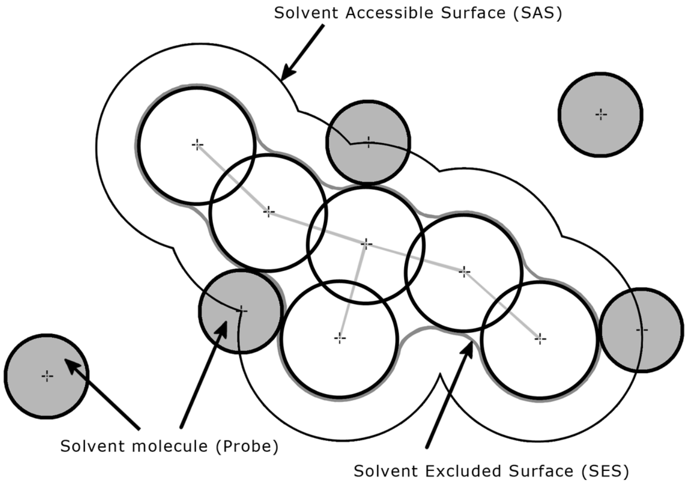

Figure 1: Illustration of solvent accessible surface (SAS) and solvent excluded surface (SES).

The second and third definition are based on rolling a spherical probe (see Fig. 1), representing the solvent molecule, on the van der Waals surface of the solute. The surface traced by the center of the probe defines the solvent accessible surface (SAS), or in different words, a boundary between regions where the solvent center can and cannot enter [17]. In principle, in this definition the cavity can be considered to be, approximately, a van der Waals surface in which radius of each sphere was increased by an additive factor. In a third approach, a solvent sphere is used as a contact probe, encasing a molecule in a surface solvent cannot penetrate. In this definition a cavity is called solvent excluded surface (SES), or Connolly surface [18]. The latter, while realistic, is challenging to parametrize and is rarely used [9].

In practice, a compromise between computational feasibility and SAS is used, that is, a cavity made of interlocking spheres with predefined radii. The three most common standards of radii are are: (1) radii proportional to van der Waals radii, proposed by Miertŭs, Scrocco and Tomasi [19], (2) radii obtained from crystallographic data by Bondi [20] and (3) the universal force field (UFF) [21] set included in Gaussian [22] program package, which, unlike the other two sets, covers the whole periodic table.

This approach, however, will sometimes lead to problems when sterical obstructions from the neighboring atoms groups should be taken into account (e.g. two or three neighboring methyl groups at the end of aliphatic chain). This problem can be countered by applying GEPOL algorithm (developed by Pascual-Ahuir *et al* [23])for building the molecular cavity. In this method, the distance between each pair of cavity spheres is compared with the solvent (probe) diameter. If this distance disallows a probe to pass between the spheres, additional spheres are placed, to simulate sterical obstruction. Alternative algorithms for the cavity creation, and solution of sterical problem, are available. Among those it is probably important to mention DEFPOL, developed by Pomelli [24], in which a big sphere containing entirety of solute is then deformed and reshaped in iterative procedure into a polyhedron with the desired number of triangular faces, and SES cavity adaptation for wavelet formulation of PCM [25], proposed by Randrianarivony [26], in which a non-uniform rational basis spline (NURBS) algorithm, employing Bézier curves, is used.

III The electrostatic problem

In the previous section we defined the possible shapes of the cavity, made of interlocking spheres with the set radii, possibly with some additional spheres when needed. We can now approach the solution of the electrostatic problem, following Tomasi *et al* [9].

First, the dielectric constant should assume two values: one inside the cavity Γ (equal to 1, as vacuum is assumed), and equal to ϵ outside. All the charge density is assumed to be confined within the cavity, which is strictly speaking not true (see Section II), and we will have to account for that later (see Section V).

With that assumption, we can write the Poisson equations for this model as:

$$-\nabla^2\Phi(r) = 4\pi\varrho_M(r) \qquad r \in \Gamma, \tag{4}$$

$$-\epsilon\nabla^2\Phi(r) = 0 \qquad r \notin \Gamma. \tag{5}$$

One should mention here that for a given charge distribution ϱ, the electrostatic potential will be different from the one calculated in vacuum, as it contains also the reaction potential generated by the dielectric medium.

For the equations just mentioned, there are two boundary conditions that we should explore: infinity, and the cavity boundary. For infinity we have

$$\lim_{r\to\infty} r\Phi(r) = \alpha, \tag{6}$$

$$\lim_{r\to\infty} r^2\frac{\partial\Phi(r)}{\partial r} = \beta, \tag{7}$$

where α and β are finite numbers. Those conditions will be automatically satisfied by this basic QM model.[9]

At the cavity surface, the conditions take form

$$[\Phi] = 0 \qquad \text{on} \quad \Gamma, \tag{8}$$

$$[\partial\Phi] = 0 \qquad \text{on} \quad \Gamma, \tag{9}$$

where $[\Phi]$ is given by

$$[\Phi] = \lim_{r \to r_\Gamma -} \Phi_{\text{in}}(r) - \lim_{r \to r_\Gamma +} \Phi_{\text{out}}(r), \tag{10}$$

where r_Γ is radius of the cavity Γ, and 'in' and 'out' stand for inside and outside of the cavity, respectively.

The jump condition in Eq. (8) describes the continuity of the potential across the surface. The second jump condition (Eq. (9)) involves the discontinuity of the component of the field perpendicular to the cavity surface. In the model considered here, as mentioned before, we have a cavity enclosing a space with the dielectric constant equal to 1, and an external medium with the dielectric constant of ϵ (considered to be a number greater than one). This leads to the equation

$$[\partial\Phi] = \lim_{r \to r_\Gamma -} \left(\frac{\partial\Phi}{\partial n}\right) - \lim_{r \to r_\Gamma +} \epsilon \left(\frac{\partial\Phi}{\partial n}\right) = 0, \tag{11}$$

where $\vec{n}$ is the outward-pointing vector perpendicular to the cavity surface.

As a side note: in the classical model, we recollect that

$$W_{MS} = \int_\Gamma \varrho_M(r)\Phi(r)dr^3, \tag{12}$$

but since we assume $\varrho = 0$ outside the cavity, integral boundaries are limited to the volume of cavity. Then, following Böttcher [27], for a rigid charge model where no polarization of solute and no relaxation is present we can write that

$$\Delta G_{el} = \frac{W_{MS}}{2}, \tag{13}$$

which defines an electrostatic contribution to the free energy of solvation. We will refine this approach in the following sections.

The solution of the electrostatic problem is not trivial, and at least six approaches can be named:

1. the multipole expansion (MPE) method, in which the interaction potential between set of classical charges of solute and polarizable dielectric solvent is presented in terms of the multipole expansion formalism [28],

2. the generalized Born approximation (GBA), in which the Born model [29] for the interaction free energy of a spherical ion with dielectric is extended to the many-atom case [30],

3. the image charge (IMC) method, in which solvent is approximated as a set of point charges distributed in space around the solute [31],

4. the finite difference method (FDM), in which the electrostatic problem is reformulated in terms of the Poisson equation, with a position-dependent permittivity, which is solved using a three dimensional grid over the whole space and a set of finite difference equations [32],

5. the finite elements method(FEM), in which the problem is reformulated similarly to FDM, but where the space is divided into a number of finite volumes (elements) for which a set of corresponding equations have to be solved [33],

6. the Apparent Surface Charge (ASC) method, represents the solvent polarization in terms of a surface charge density ϱ supported on the cavity surface [9]. This approach is the only one applied in this work and is described in detail in Section IV.

IV Apparent Surface Charge and BEM

In order to reformulate our problem in terms of the ASC, we first represent the total potential $\Phi_T(r)$ as a sum of the electrostatic potential $\Phi_M(r)$ generated by the charge density $\varrho_M(r)$ and the reaction potential $\Phi_R(r)$ generated by the dielectric medium due to its polarization. This reaction potential can be described in the formalism of classical electrostatics in terms of the apparent charge distribution $\sigma(s), s \in \Gamma$, supported on the cavity surface. While one can encounter various formulations of this method, the common point is to define a potential over whole space as [9]

$$\Phi(r) = \int_\Gamma \frac{\sigma(s)}{|r-s|} ds. \tag{14}$$

Treating the source of the reaction potential as a charge density on the cavity surface is a great simplification of the electrostatic problem.

To further simplify the solution, we employ the Boundary Elements Method (BEM). BEM is a technique widely used in physics, e.g. acoustics, in which only a surface of the given domain need to be represented, to numerically solve complex differential problems [34]. The application of BEM in our case approximates the cavity surface in terms of a finite number of triangular elements called tesserae. We can then describe the surface charge in terms of a set of point charges q_t, which can be viewed as a local value of $\varrho(s)$ multiplied by tessera area a_t. Thus, we can transform Eq. (14) as

$$\Phi(r) = \sum_t \frac{\sigma(s) a_t}{|r-s|} = \sum_t \frac{q_t}{|r-s|}. \tag{15}$$

BEM in this work is used as a way of performing integration, and to reduce a three-dimensional integral to a two-dimensional (and then summation) over the cavity surface. This approach is a good approximation for tesserae far away from each other. The problem arises for diagonal elements of singular operators, for which we resort to a fitting of the analytical result for a polar cap [35].

As the basis of this method will be the same, regardless of what particular equation is examined (namely, to exchange integration over cavity to summation over tesserae), we will continue to use the classical form of equations, i.e. the ones using continuous distribution of surface charge $\varrho(s)$ (unless specified otherwise). There are many approaches on how to calculate the ASC, from among which one should mention:

1. The Dielectric PCM (D-PCM) (also simply known as PCM), in which a scalar permittivity is used, and the surface charges are calculated using the field generated by a solute charge density and by a reaction potential, derived over the cavity surface [19],
2. The Conductor-like Screening Model (COSMO), in which the permittivity is initially considered infinite, which causes the electric potential to vanish at the cavity. The surface charge is then calculated using only the charge density of the solute. The reaction field is then reduced by a scaling factor depending on the actual applied permittivity (thus screening) [36],
3. the Integral Equation Formalism (IEF) formulation, in which PCM problem is reformulated in terms of Green's function and integral equations. This approach is the only one applied in this work and is discussed in detail in Section V.

V Integral Equation Formalism PCM

The IEF method has been originally formulated by Cancés and Mennuci [37]. Following their derivation, we begin by dividing the potential into two parts: the electrostatic potential Φ_M generated by the charge distribution ϱ_M, and the reaction potential of the solvent Φ_R. We define this potentials in terms of Green's functions. As a solution of the electrostatic problem, the Green's function $G(x, y)$ is a potential in a point $\vec{x}$ generated by a point charge in $\vec{y}$. This definition can be formally presented as

$$\Phi(x) = \int_{R^3} G^s(x, y)\varrho_M(y)\mathrm{d}y, \tag{16}$$

$$\Phi_M(x) = \int_{R^3} G(x, y)\varrho_M(y)\mathrm{d}y, \tag{17}$$

$$\Phi_R(x) = \int_{R^3} G^R(x, y)\varrho_M(y)\mathrm{d}y, \tag{18}$$

where $G(x, y)$ corresponds to a kernel of $-\nabla^2$ operator and $G^s(x, y)$ corresponds to a kernel of $-\nabla(\epsilon\nabla)$ operator. G^R is given by

$$G^R(x, y) = G^s(x, y) - G(x, y). \tag{19}$$

It can be proven that the reaction potential Φ_R can be represented as a single layer potential [38]

$$\Phi_R(x) = \int_{\Gamma} \frac{\sigma(y)}{|x - y|} dy, \tag{20}$$

where Γ is the cavity surface and σ is the surface charge $\sigma(y)$, which is a unique solution of the equation

$$A\sigma = -g, \tag{21}$$

where A and g are the integral operators given by

$$A = (2\pi - D_e)S_i + S_e(2\pi + D_i^*), \tag{22}$$

$$g = (2\pi - D_e)\Phi_M + S_e(\partial\Phi_M/\partial n), \tag{23}$$

where e and i stand for the exterior and interior of the cavity, respectively. Operators D_a and S_a ($a = e, i$) are given by

$$(S_a\sigma)(x) = \int_\Gamma G_a(x, y)\sigma_M(y)\mathrm{d}y, \tag{24}$$

$$(D_a\sigma)(x) = \int_\Gamma [(\epsilon_a \vec{\nabla}_y G_a(x, y)) \cdot \vec{n}(y)]\sigma(y)\mathrm{d}y, \tag{25}$$

$$(D_a^*\sigma)(x) = \int_\Gamma [(\epsilon_a \vec{\nabla}_x G_a(x, y)) \cdot \vec{n}(x)]\sigma(y)\mathrm{d}y. \tag{26}$$

We recall that $\epsilon_i = 1$, as we assume vacuum inside the cavity. The equations Eqs. (24) to (26) are the three components (out of four) of the Calderon projector [39], which is well known in the theory of integral equations. We can then make use of some of the known properties of this operators in order to simplify the working equations, namely that $S_i D_i^* = D_i S_i$, D_i^* is the adjoint of D_i, and that S_i is self-adjoint. Additionally, $S_e = S_i/\epsilon$, and $D_i = D_e$.

Firstly, knowing that [40]

$$(2\pi - D_i)\Phi_M + S_i(\partial\Phi_M/\partial n) = 0, \tag{27}$$

we can rewrite Eq. (23) as

$$g = [(2\pi - D_e) - S_e S_i^{-1}(2\pi - D_i)]\Phi_M, \tag{28}$$

thus removing the dependence of σ on the normal component of the field. This step is important for two reasons: it is an implicit correction of the outlying charge problem[41], and is numerically more feasible due to the fact that only the electrostatic potential has to be calculated (which is a scalar), without the need to additionally calculate the electric field (which is a vector).

Secondly, applying previously mentioned relations, we can further transform g and A for isotropic solvents as

$$A = (1 - 1/\epsilon) \left[2\pi \frac{\epsilon + 1}{\epsilon + 1} - D_i \right] S_i, \quad (29)$$

$$g = (1 - 1/\epsilon)(2\pi - D_i)\Phi_M. \quad (30)$$

Finally, equation Eq. (21) can be written in a more elaborate form [40]

$$\left[2\pi \frac{\epsilon + 1}{\epsilon + 1} - D_i \right] S_i \sigma = -(2\pi - D_i)\Phi_M. \quad (31)$$

This version of IEF is sometimes denoted as IEF(V) [9], as only the solute electrostatic potential is required to determine the ASC σ. This simplification is however only possible for an isotropic medium. For more complicated environments, like interfaces, the general Eq. (21) must be used instead.

The big strength of the IEF approach is in its generality. As can be seen from above, the IEF can be applied without any modifications to its equations to any environment for which Green's functions is known. For the cavity interior, the Green's function is always equal to

$$G(x, y) = 1/4\pi|x - y|, \quad (32)$$

as vacuum is assumed. The same Green's function, scaled by a factor $1/\epsilon$, can be used for a uniform dielectric medium. For other cases, either the analytical or a numerical form of the Green's function is required. The IEF approach can then be used for anisotropic systems, like a sharp [42] or a diffuse [11] planar interface (as we will see in Section VII), or even for biological membranes [43].

Another important point is that within this formalism no additional renormalization of the surface charges due to the outlying charge (see Section III) to the first order is necessary, as was confirmed by Cances and Mennucci [41]. This is a rather important point, since only IEF-PCM and another continuum method (called "surface and simulation of volume polarization for electrostatics" or SS(V)PE [44]) accounts for that inherently, and all other cavity-based methods must use the appropriate correction factors [9]. Nevertheless, the outlying charge gives rise to the repulsion free energy contribution, which will be discussed later (see Section VIII.2).

VI Quantum Mechanical Problem

With IEF general formulation in place, we can move to the solution of the QM problem, in a general form. As mentioned in Section I, the method starts with the Hamiltonian operator including solute-solvent interaction potential

$$\hat{H} = \hat{H}^0 + V(\Psi), \tag{33}$$

where we note that the potential V is dependent on the wavefunction, dbecause it depends on the electronic charge density of the solute. The expectation value of free energy is then given by

$$G = \langle \Psi | \hat{H}^0 + 1/2V(\Psi) | \Psi \rangle , \tag{34}$$

where the factor 1/2 is introduced due to the aforementioned dependence of the potential on the wavefunction [45]. The right hand side of Eq. (34) can be written as

$$\langle \Psi | \hat{H}^0 + 1/2V(\Psi) | \Psi \rangle = \langle \Psi | \hat{H}^0 + 1/2(\mathcal{J} + \mathcal{Y} + \mathcal{X} + U_{NN} | \Psi \rangle , \tag{35}$$

where $\mathcal{J}, \mathcal{Y}, \mathcal{X}$ and U_{NN} refer to the interaction energy between the potential and the charge distribution of, respectively, nuclei and electrons, electrons and nuclei, electrons and electrons, and nuclei with nuclei. By taking a derivative with respect to the density matrix we obtain the final form of the operators used for PCM in QM

$$\frac{\partial G}{\partial D_{\mu\nu}} = F^0_{\mu\nu} + 1/2(\mathcal{J}_{\mu\nu} + \mathcal{Y}_{\mu\nu}) + \mathcal{X}_{\mu\nu}, \tag{36}$$

where F^0 is the Fock matrix. The one-electron terms can be shown to be identical [13], therefore the final form of this equation is

$$\frac{\partial G}{\partial D_{\mu\nu}} = F^0_{\mu\nu} + \mathcal{J}_{\mu\nu} + \mathcal{X}_{\mu\nu}. \tag{37}$$

The two last terms define the PCM contribution to the Fock matrix, which can then be used in the SCF procedure.

VII Interfaces

We have now established the formalism to calculate the electrostatic effect of solvation on energy in a uniform medium. In order to extend this formulation to non-uniform media, like interfaces, we only need to find the appropriate Green's function, as mentioned in Section V.

VII.1 Sharp interfaces

The simplest case possible is the planar sharp interface, where the discontinuity in the solvent properties at the interface is introduced. For this case, we define z as the coordinate normal to the interface plane, which we locate at $z = 0$, between two phases with permittivities of ϵ_1 $(z < 0)$ and ϵ_2 $(z > 0)$, respectively. If we place a charge q on point d, $d \in z$, $d > 0$, then the Green's function for a point P given by cylindrical coordinates (r, θ, z) is given by [46]

$$G(P) = \begin{cases} \dfrac{1}{\epsilon_2}\left(\dfrac{q}{\sqrt{r^2+(d-z)^2}} + \dfrac{q'}{\sqrt{r^2+(d+z)^2}}\right) & \text{if } z > 0 \\ \dfrac{1}{\epsilon_2}\dfrac{q''}{\sqrt{r^2+(d-z)^2}} & \text{if } z < 0, \end{cases} \tag{38}$$

where q' and q'', are the image charges of q and q', respectively. The image charges can be found as

$$q' = -\left(\frac{\epsilon_2 - \epsilon_1}{\epsilon_2 + \epsilon_1}\right) q, \tag{39}$$

$$q'' = \left(\frac{2\epsilon_2}{\epsilon_2 + \epsilon_1}\right) q. \tag{40}$$

For the spherical sharp interface, the Green's function is slightly more complicated. One of the first works presenting the analytical form of Green's function for this case was done by Messina [47].

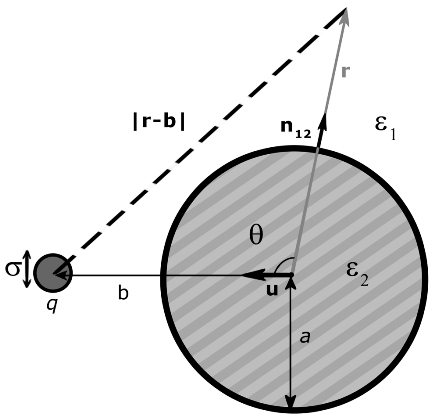

Figure 2: Illustration of sphere of dielectric medium with permittivity ϵ_2, submerged in second dielectric medium with permittivity ϵ_1.

Following the description of variables from Fig. 2, the Green's function for the sharp spherical interface is given by

$$G(r,\theta) = \frac{q}{4\pi\epsilon_0\epsilon_1}\left[\frac{1}{|r-b|} + \sum_{l=1}^{\infty}\frac{a^{2l+1}}{b^{l+1}}\frac{(\epsilon_1-\epsilon_2)l}{\epsilon_1(l+1)+\epsilon_2 l}\frac{1}{r^{l+1}}P_l(\cos\theta)\right], \quad (41)$$

where l is the order of angular momentum expansion, and P_l is Legendre polynomial of l-th order. While in theory $l \to \infty$, practically a value between 100 and 200 is employed.

VII.2 Diffuse interfaces

While it is possible to stop the derivation of the model at the sharp interface, such system is not physical. The usual problem with sharp interfaces is the divergence of the image charge potential close to the interface. In a physical system a divergence, if at all, can exist only a very short time, since induced reaction due to the entropy would immediately eliminate it. For the real systems, an interface can be seen as an intermediate area where medium gradually changes from the one solvent to another. For our use, it can be defined as a medium with position dependent permittivity, varying along z [11].

In order to use such a diffuse interface in IEF-PCM, the corresponding Green's function must be found. For this case, we cannot write it in the analytical form[11] (although it is possible to present analytical form of such function, if a specific shape of permittivity profile is chosen). Instead, a numerical procedure is employed to solve the following differential equation (following notation for Green's function from Section V)

$$\vec{\nabla}_x \cdot \left[\epsilon(x) \cdot \vec{\nabla}_x G^E(x,y)\right] = -4\pi\delta(x-y), \tag{42}$$

where the permittivity ϵ becomes position dependent.

In our case the permittivity does not change in the xy plane and varies only along z. The equation Eq. (42) can be reformulated as

$$G^E(x,y) = \int_0^\infty G^E(q_1,z,z') J_0(q_1|x_{||} - y_{||}|) q_1 dq_1, \tag{43}$$

where J_0 is the Bessel function of zeroth order, $x_{||}$ and $y_{||}$ are the projections of x and y on the interface plane. A more practical form of this equation, which can be solved numerically is

$$\frac{\partial}{\partial z}\left[\epsilon(z)\frac{\partial}{\partial z}G^E(q_1,z,z')\right] - q_1^2\epsilon(z)G^E(q_1,z,z') = -2\delta(z-z'). \tag{44}$$

In order to solve this equation, we must factor out the Coulomb singularity which is included in this Green's function. Finally, we obtain

$$G_e(q_1,z,z') = \frac{1}{c(z,z')q_1}e^{-q_1|z-z'|} + G^E_{img}(q_1,z,z'). \tag{45}$$

By employing the inverse Fourier transform, we obtain the final expression for the Green's function for the planar diffuse interface, which consists of the Coulomb term and the image potential term,

$$G_e(x,y) = \frac{1}{c(x,y)|x-y|} + G_{img}(x,y), \tag{46}$$

where $1/(c(x,y)|x-y|)$ is the Coulomb-like term, whereas $G_{img}(x,y)$ corresponds to the potential of the hypothetical image charge, due to the presence of the interface.

For the spherical diffuse interface, the starting point and methodology is similar to the one presented by Frediani *et al*[11] for a planar diffuse interface. The full derivation, presented for the first time in the literature, can be seen in Paper 3. Here only the final form of the Green's function, using spherical coordinates, is presented as follows

$$G(r,r') = \sum_{\ell=0}^{\infty} G_\ell(r,r') = \begin{cases} \displaystyle\sum_{\ell=0}^{\infty} \frac{-2\ell+1}{r'^2\ \epsilon|_{r'}} \frac{u_\ell|_r\ v_\ell|_{r'}}{W_\ell|_{r'}} P_\ell(\cos\gamma) & \text{if } r < r' \\ \displaystyle\sum_{\ell=0}^{\infty} \frac{-2\ell+1}{r'^2\ \epsilon|_{r'}} \frac{u_\ell|_{r'}\ v_\ell|_r}{W_\ell|_{r'}} P_\ell(\cos\gamma) & \text{if } r > r', \end{cases} \tag{47}$$

where again ℓ is the order of the angular momentum expansion, and P_ℓ is the Legendre polynomial of ℓ-th order, u_ℓ and v_ℓ are given by

$$u_\ell = r^\ell \qquad v_\ell = \frac{1}{r^{\ell+1}}, \tag{48}$$

W_ℓ is the Wronskian

$$W_\ell|_{r'} = \left.\frac{\mathrm{d}v_\ell}{\mathrm{d}r}\right|_{r'} u_\ell|_{r'} - \left.\frac{\mathrm{d}u_\ell}{\mathrm{d}r}\right|_{r'} v_\ell|_{r'}\,, \tag{49}$$

and $\cos\gamma$ is given by

$$\cos\gamma = \frac{r \cdot r'}{|r||r'|}. \tag{50}$$

We recall here that in theory $\ell \to \infty$, but in practice the value between 100 and 200 is employed.

As for the solvent-related parameters, like the permittivity, the most straightforward way to define it, is by linking it with the molecular fractions x of solvents 1 and 2,

$$\epsilon(z) = x_1(z)\epsilon_1 + x_2(z)\epsilon_2. \tag{51}$$

In order to model the shift in molar fractions across the interface we employ the hyperbolic tangent

$$x_1 = \frac{1}{2} + \frac{1}{2} tanh\left(\frac{(z) - (z_0)}{D}\right), \tag{52}$$

with the parameter D related to the width of the interface.

Finally, we arrive at the practical formula for calculating the permittivity for diffuse interfaces,

$$\epsilon(z) = \frac{\epsilon_1 + \epsilon_2}{2} + \frac{\epsilon_1 - \epsilon_2}{2} tanh\left(\frac{(z) - (z_0)}{D}\right). \tag{53}$$

The same strategy can be employed to any solvent-related parameter.

VIII Non-electrostatics

In the previous sections, the main focus of derivation was the electrostatic energy of solvation. This historically has been a main focus for theoretical development of continuum solvation models [48, 15]. This fact is understandable considering that polar solvents, i.e. water, for which electrostatic contribution is dominant, are the most important in chemical applications. Nevertheless, other early models were sometimes focused on the different aspects of the solute-solvent interaction, e.g. Claverie model including only dispersion [49].

Regardless of the privilege of the electrostatic term, non-electrostatics cannot be neglected. One of the most important reasons is that they tend to be of the same order of magnitude as the electrostatic term [50]. Secondly, in non-polar media the electrostatic contribution tends to be less important. Moreover, the inclusion of other solvation effects contributes to the improvement of the model, as nature is simulated more truthfully with more refinement. Additionaly, if a given contribution is included in the quantistic Hamiltonian, then its effect on properties can also be observed.

Following the definition given by Tomasi, Mennucci and Cammi [9], the solvation free energy of a solute molecule in a cavity in an infinite isotropic liquid solvent is given by the equation:

$$\Delta G_{\mathrm{sol}} = \Delta G_{\mathrm{el}} + G_{\mathrm{rep}} + G_{\mathrm{dis}} + G_{\mathrm{cav}} + \Delta G_{\mathrm{tm}} + P\Delta V \qquad . \tag{54}$$

We will now focus on defining and explaining each term, starting with electrostatics. We define that $\Delta G_{\mathrm{el}} = G_{\mathrm{el}} - E^0$, where E^0 is *ab initio* ground state energy of examined molecule(s) in the vacuum, within Born-Oppenheimer approximation, and G_{el} is the energy of the same system calculated with solvation effects(see Section VI). The extension of this contribution to interfaces was already discussed in Section VII.2.

G_{rep} is the repulsion contribution to the solvation free energy, that arises due to the charge density escaping the cavity boundary. The full description can be found in Section VIII.2.

G_{dis} is the dispersion interaction between the solute and the solvent. It is described in detail in Section VIII.3

G_{cav} is the cavitation term, which accounts for the energy required to form the cavity in the solvent. It will be discussed in more detail in Section VIII.1. It is also worth noting, that cavitation is the only contribution to the solvation free energy that is not included in the quantistic Hamiltonian, and is instead treated classically. While the recent work by Andreussi *et al*[51] proposes a quantistic approach to cavitation, it is not included in the model used in this work.

ΔG_{tm}, is connected to a difference in the vibrational energy between the solvated and the unsolvated case, analogously to the electrostatic contribution. This term is often neglected in the implementation due to the small extent[52]. Moreover, it is not obvious whether the current models can appropriately describe such an effect on interfaces, which are the main interest of this work. Therefore, this term has not been included in any results.

$P\Delta V$ term, or the adiabatic volume work, is also neglected in this work, because this contribution is very small, of order of 10^{-3} in terms of $(P\Delta V)/\Delta G$ ratio[53].

VIII.1 Cavitation

The problem of the cavity and cavitation was already mentioned in Section II. The cavitation energy contribution is usually defined as a reversible work necessary to create an empty space, a cavity, in the solvent medium. Historically, numerous strategies to obtain this contribution have been proposed. One of the earliest, by Uhlig [54], links the energy to create a bubble encasing solute of radius R_M to a surface tension γ between the solute and solvent

$$G_{\mathrm{cav}} = 4\pi\gamma R_M^2. \tag{55}$$

This approach is somewhat simplistic, considering that the surface tension is a macroscopic value used to describe the average interaction between two phases, and not between a singular molecule and the solvent.

According to a relatively recent review paper[9], it is very hard or impossible to find the experimental data on the energetics of cavitation process, that is, a creation of a perfect empty bubble in a liquid medium. While in chemistry this methods are of little (but existing) interest, there is perhaps the possibility of future collaborations with marine research, where cavitation in ship propulsion is a rather lively topic, and similar methods like BEM are employed to study cavitation[55, 56].

To obtain the results, we make use of a method called scaled particle theory (SPT) developed by Pierotti for the spherical cavities and hardsphere solvent [57]. In this method, the cavitation energy is considered in terms of an entropic effect of introduction of a sphere (or solute molecule) into the solvent volume: the solvent movement is restricted thus the entropy decreases. Cavitation is then considered to be proportional to this decrease in entropy. This method was originally developed in a statistical thermodynamics formalism for spherical cavities, and has been extended heuristically for multi-sphere cavities. The formula used in the implementation of the IEF-PCM used for this work is as follows. First we define an auxiliary function y

$$y = \frac{4\pi N R_S^3}{3V_S}, \tag{56}$$

where N is avogadro number, V_S and R_S are the molecule radius and the molar volume of the solvent, respectively. The cavitation free energy is then given by

$$G_{\text{cav}} = RT\left\{-\ln(1-y) + \frac{3y}{1-y}\left(\frac{R_M}{R_S}\right) + \left[\frac{3y}{1-y} + \frac{9}{2}\left(\frac{y}{1-y}\right)^2\right]\left(\frac{R_M}{R_S}\right)^2\right\}, \tag{57}$$

where R_M is the molecular radius of the solute, R is the gas constant and T is the temperature (standard conditions). This formula can be extended to cavities made of multiple interlocking spheres by calculating the contribution for each sphere and then weighting it by the solvent-exposed part of each sphere ω_n

$$G_{\text{cav}} = \sum_n \omega_n G_{\text{cav}} R_n, \tag{58}$$

where R_n is radius of the sphere n.

In order to extend this formalism to interfaces, we then employ BEM (see Section IV), and divide the cavity into t triangular tesserae. We assume here that only the solvent-exposed part of the cavity has been tesselated by an appropriate algorithm. The new formula reads

$$G_{\text{cav}} = \sum_t \frac{a_t}{4\pi R_t^2} G_{cav} R_t, \tag{59}$$

where a is the area of the t-th tesserae, and R_t is radius of the sphere that tesserae belongs to.

For sharp interfaces, cavitation can be considered to be the sum of contributions from each solvent, weighted by the part of cavity exposed to each solvent. For diffuse interfaces, we must account for the existence of the intermediate interfacial area. This is accomplished by including the position-dependent solvent density ρ ratio as weight

$$G_{\text{cav}} = \sum_{sol} \sum_{t} \frac{\rho(s_t)}{\rho_0} \frac{a_t}{4\pi R_t^2} G_{cav,sol}(R_t), \tag{60}$$

where s_t is the collocation point. We note an additional summation, which implies that the cavitation contribution needs to be calculated separately for each solvent and then summed. Certainly, if a given solvent is not present in the molecule's vicinity, $\rho(s_t) = 0$ and its contribution is zero.

With the inclusion of interface, an additional contribution, called surface term G_{surf}, arises[50]. If a molecule occupies part of the interfacial area, the solvent surface is reduced by a cross section of the cavity at the interface. This can be accounted for by using the formula

$$G_{\text{surf}} = \gamma_s A(z = 0), \tag{61}$$

where γ_s is the surface tension between the solvents, and $A(z = 0)$ is the mentioned cross section of the cavity at the interface. A is calculated as

$$A = \int_{\Gamma} \left(\rho(z)/\rho_0 - \frac{1}{2} \right) \hat{z}(s) \cdot \hat{n}(s) ds, \tag{62}$$

where the $\left(\rho(z)/\rho_0 - \frac{1}{2}\right)$ factor is introduced because the interface is a diffuse region rather than a two-dimensional plane.

VIII.2 Repulsion

The repulsion contribution arises because assumption that the entirety of the solute charge density is encased within the cavity is an approximation. This problem has been already mentioned in Section III. While the IEF-PCM accounts for the outlying charge in terms of an ACS correction to the electrostatic energy [41], the outlying charge gives rise to the energetic effect that we have to account for.

The method used within this work was developed by Amovilli and Mennucci [58], based on the exchange and penetration terms of the intermolecular interaction energy, and their decomposition. The basic idea is to start with the exchange energy of a dimer, considering solute to be the first part of dimer, and solvent, the second one. The electron density of the second partner is then replaced with the one-electron charge distribution, averaged over the whole solvent volume, which is taken as a constant factor. This reduces a double integral problem to a single integral over outlying charge

$$G_{rep} = \alpha \int_{r \notin C} dr \varrho_M(r), \tag{63}$$

where ϱ_M is charge density of solute and α is

$$\alpha = 0.063 \rho_S \frac{n_{val}^S}{M_S}, \tag{64}$$

where ρ_S, n_{val}^S, M_S are the density (relative to water at standard conditions), the number of valence electrons and the molar weight of the solvent, respectively. The integral in Eq. (63) is in practice obtained by calculating the difference between a total number of solute electrons and the charge encased in the cavity. If we employ the Gauss theorem, we obtain that the internal charge is equal to $1/2\pi \int_\Gamma \vec{E}_M(s)\vec{n}(s)d^2s$, where $\vec{n}$ is the vector perpendicular to the cavity at the cavity surface point s, and E_M is the solute electronic electric field. This contribution may then be included in our Fock matrix, by adding following repulsion operator in matrix form [9]

$$(h_{\mathrm{rep}})_{\mu\nu} = \alpha[S - S^{(\mathrm{in})}]_{\mu\nu}, \tag{65}$$

where S is the overlap matrix and $S^{(\mathrm{in})}$ is given by

$$S_{\mu\nu}^{(\mathrm{in})} = 1/4\pi \int_\Gamma \vec{E}_{\mu\nu}(s)\vec{n}(s)d^2s, \tag{66}$$

where $\vec{E}_{\mu\nu}$ are the electric field integrals. In order to obtain the repulsion contribution to the free energy, we can use the following formula

$$G_{\mathrm{rep}} = \mathrm{tr} D^{\mathrm{rep}} h_{\mathrm{rep}}, \tag{67}$$

where D^{rep} is the density matrix obtained by using the repulsion term operator from Eq. (65) in the SCF procedure. The last step is the application of BEM in order to simplify the integral in Eq. (66). This allows us to exchange integration with a summation of contributions from tesserae.

This approach is sufficient for a uniform medium, but for interfaces some modifications are necessary. The most important challenge is that we cannot assume that the escaped charge is distributed in a uniform way, because the medium is not isotropic due to the interface presence. A way to weight electron density to account for a position dependence of the escaped charges was proposed by Bondesson *et al* [59], who stated that the electron density, assuming symmetric radial decay with the distance r from the origin, can be written as

$$\varrho_M(r) = \varrho_M(R)\frac{e^{-\beta r^2}}{e^{-\beta R^2}}, \tag{68}$$

where R corresponds to the radius of cavity, and β is a parameter, which can be found considering that the integration of Eq. (68) outside of cavity yields number of outlying electrons, which can also be calculated using the Gauss' theorem

$$n_{out} = \varrho_M(R)\int_{r\notin C} dr\frac{e^{-\beta r^2}}{e^{-\beta R^2}}. \tag{69}$$

If radial decay is kept, but we assume that the electron density does not have to be constant on cavity surface we arrive at

$$n_{out} = \frac{1}{e^{-\beta R^2}}\int\int \varrho(\theta,\phi)\sin(\theta)\mathrm{d}\theta\mathrm{d}\phi\int\limits_R^\infty e^{-\beta r^2}r^2\mathrm{d}r, \tag{70}$$

which divides problem in a radial and an angular part, the latter over the cavity surface. If BEM is employed, one arrives at

$$n_{out} = \sum_t \varrho(s_t)f(s_t), \tag{71}$$

where f is given by

$$f(s_t) = \frac{a_t}{2\beta R_t^2 e^{-\beta R_t^2}}\left\{R_t^2 e^{-\beta R_t^2} + \sqrt{\frac{\pi}{4\beta}}[1 - erf(\sqrt{\beta}R)]\right\}, \tag{72}$$

where a_t is area of tesserae t, R_t is radius of the corresponding sphere. With that factor in place, we can write, again in terms of BEM

$$G_{\mathrm{rep}} = \alpha' \sum_t \varrho_M(s_t) f(s_t) n_{val}^S(s_t). \tag{73}$$

We note here that for interface calculations the number of valence electrons of the solvent becomes position dependent, and is parameterized in the same way as other solvent dependent properties at the interface are (see Section VII.2), and α' collects all the other constant factors. By using the delta function operator we arrive at

$$G_{\mathrm{rep}} = \alpha' \sum_t \varrho_M(s_t) f(s_t) n_{val}^S(s_t) \mathrm{tr} D\delta_t = \mathrm{tr} D h_{\mathrm{rep}}, \tag{74}$$

which we can use to obtain the final, interface-adapted repulsion operator, by taking a functional derivative

$$h_{\mathrm{rep}} = \frac{\partial G_{\mathrm{rep}}}{\partial D} = \alpha' \sum_t \varrho_M(s_t) f(s_t) n_{val}^S(s_t) \delta_t. \tag{75}$$

VIII.3 Dispersion

The dispersion contribution is usually described in terms of the fluctuation of local charge density, giving rise to an interaction between the temporarily induced dipole moments. The most common classical description of this contribution is the Lennard-Jones potential [60], or the van der Waals interaction energy. While this term is very often coupled with repulsion (especially in terms of van der Waals contribution), these two terms have different physical origins, therefore they should be discussed separately.

We start with the expression developed by Amovilli [61]

$$G_{\mathrm{disp}} = \frac{1}{\pi} \int \mathrm{d}\omega \sum_p \frac{\omega_p}{{\omega_p}^2 + \omega^2} \times \int \mathrm{d}r_1 \int_\Gamma \frac{\mathrm{d}r_2}{|r_1 - r_2|} \varrho_p(r_1) \Phi_S[\epsilon(i\omega), \varrho_p](r_2), \tag{76}$$

where p runs over all the excited states of the solute, and ω and ϱ are excitation energies and transition densities, respectively. The term $\Phi_S[\epsilon(i\omega), \varrho_p]$

corresponds to the ASC density of the cavity surface, induced by a transition charge density ϱ_p, which is calculated using a dielectric constant at the imaginary frequency $\epsilon(i\omega)$. This equation will serve both as a starting point and as reference for the future derivation.

We continue by assuming that $\Phi_S[\epsilon(i\omega), \varrho_p]$ is proportional to the corresponding electrostatic field generated by the ASC [58]

$$G_{\text{disp}} = -\frac{1}{8\pi}\frac{\eta_S^2 - 1}{\eta_S^2}\sum_p \frac{\Omega^S}{\Omega^S + \omega_p}\int_\Gamma \mathrm{d}s V_p(s)E_p(s), \tag{77}$$

where E_p and V_p are the electrostatic potential and the field induced by the transition charge density ϱ_p, respectively. $\Omega^S = \eta_S I$, where I is the first ionization potential of the solvent, and η_S is its refractive index. We then exchange the excitation energy ω_p and the summation over all excited states with an average excitation energy value ω_{ave}. Furthermore, a factor $\frac{1}{8\pi}$ is exchanged with an empirical factor c_f, which is solvent dependent [62]

$$G_{\text{disp}} = -c_f\frac{\eta_S^2 - 1}{\eta_S^2}\frac{\Omega^S}{\Omega^S + \omega_{\text{ave}}}\int_\Gamma \mathrm{d}s \sum_p V_p(s)E_p(s). \tag{78}$$

In order to compute ω_{ave}, Amovilli and Mennucci [58] suggested to average the energy of a subset of virtual and occupied orbitals. This approach is however very dependent on the method and basis set. Later, Weijo *et al* [62] proposed to compute ω_{ave} by imposing equivalence of the results between Eq. (76) and Eq. (78). With the average excitation energy in place, the last step is to collect all the factors before the integral into a constant factor β (note that this factor is different from and unrelated to the one used in Section VIII.2)

$$G_{\text{disp}} = -\beta\int_\Gamma \mathrm{d}s \sum_p V_p(s)E_p(s). \tag{79}$$

Eq. (79) can be transformed in terms of molecular orbitals [58] into the expression

$$G_{\text{disp}} = -\beta\sum_{\mu\nu\kappa\lambda}[\mu\nu|\kappa\lambda]D_{\mu\lambda}(S_{\nu\kappa}^{-1}) + \beta/2\sum_{\mu\nu\kappa\lambda}[\mu\nu|\kappa\lambda]D_{\mu\lambda}D_{\nu\kappa}, \tag{80}$$

where μ, ν, κ and λ run over the atomic orbitals, D is the density matrix and S is the overlap matrix. $[\mu\nu|\kappa\lambda]$ is given by (in terms of BEM)

$$[\mu\nu|\kappa\lambda] = 1/2 \sum_t \left[V_{\mu\nu}(s_t)E_{\kappa\lambda}(s_t) + V_{\kappa\lambda}(s_t)E_{\mu\nu}(s_t)\right]. \tag{81}$$

We can rewrite Eq. (80) in a matrix form as follows [9]

$$G_{\text{disp}} = \text{tr}D[h_{\text{disp}} + 1/2X_{\text{disp}}(D)], \tag{82}$$

where the new matrix elements are given by

$$(h_{\text{disp}})_{\mu\lambda} = -\beta \sum_{\nu\kappa} [\mu\nu|\kappa\lambda](S^{-1}_{\nu\kappa}), \tag{83}$$

$$(X_{\text{disp}})_{\mu\lambda} = \beta \sum_{\nu\kappa} [\mu\nu|\kappa\lambda]D_{\nu\kappa}. \tag{84}$$

With the formalism in place in order to account for dispersion energy in quantistic Hamiltonian, we can now extend it to planar diffuse interfaces. In case of dispersion, this is done simply by assuming position-dependence of β, which is achieved in the usual way, as described in Section VII.2,

$$\beta(z) = \frac{\beta_1 + \beta_2}{2} + \frac{\beta_1 - \beta_2}{2} tanh\left(\frac{(z) - (z_0)}{D}\right). \tag{85}$$

IX Properties

Now that the formalism for the full IEF-PCM model including non-electrostatic contributions has been established, we can proceed to the calculation of molecular properties.

In the presence of the external electric field $\mathcal{E}$ in the z-direction (axis choice is arbitrary for the sake of simplicity), the perturbation due to that field can be written as

$$\hat{H}^{(1)} = -\hat{\mu_z}\mathcal{E}, \tag{86}$$

where $\hat{\mu_z}$ is the dipole moment operator. Before we apply perturbation theory to obtain the expression for the dipole moment, polarizability and excitation energies, we must first use the Hellmann-Feynman theorem to link the energy E and the perturbation (external electric field)

$$\frac{\mathrm{d}E}{\mathrm{d}\mathcal{E}} = \left\langle \frac{\partial \hat{H}}{\partial \mathcal{E}} \right\rangle . \tag{87}$$

The partial derivative of the Hamiltonian is simply

$$\frac{\partial \hat{H}}{\partial \mathcal{E}} = \frac{\partial(-\mu_z \mathcal{E})}{\partial \mathcal{E}} = -\mu_z, \tag{88}$$

because $\hat{H}^0$ is not field dependent. This implies that

$$\frac{\mathrm{d}E}{\mathrm{d}\mathcal{E}} = -\left\langle \mu_z \right\rangle . \tag{89}$$

If we expand the energy in a Maclaurin series, in terms of the electric field derivative, and apply Eq. (89) we get

$$\langle \mu_z \rangle = -\left(\frac{\mathrm{d}E}{\mathrm{d}\mathcal{E}}\right)_0 - \left(\frac{\mathrm{d}^2E}{\mathrm{d}\mathcal{E}^2}\right)_0 \mathcal{E} - \cdots \tag{90}$$

The expectation value of the dipole moment operator is the permanent dipole moment and the additional contributions induced by the field, corresponding to the first, second, etc. (hyper)polarizability:

$$\langle \mu_z \rangle = \mu_z^{\mathrm{perm}} + \alpha_{zz}\mathcal{E} + \frac{1}{2}\beta_{zzz}\mathcal{E}^2 + \cdots \tag{91}$$

where α is the polarizability and β is the first hyperpolarizability, which measure of how strongly the dipole moment is affected by the external electric field.

In order to obtain the final expression for the dipole moment and polarizability, we first rewrite the energy E in terms of perturbative expansion for the ground state $|\Psi_0\rangle$

$$E_0 = E_0^{(0)} + \langle\Psi_0|\hat{H}^{(1)}|\Psi_0\rangle + \langle\Psi_0|\hat{H}^{(2)}|\Psi_0\rangle + \sum_{n\neq 0} \frac{\langle\Psi_0|\hat{H}^{(1)}|\Psi_n\rangle \langle\Psi_n|\hat{H}^{(1)}|\Psi_0\rangle}{E_0^{(0)} - E_n^{(0)}} + \cdots \tag{92}$$

Due to the absence of any second-order term in the zeroth order Hamiltonian $\hat{H}^0$ for the electric field perturbation, the third term in the expansion is zero. If we then apply Eq. (86), we obtain

$$E_0 = E_0^{(0)} + \langle\Psi_0|\mu_z|\Psi_0\rangle + \left(\sum_{n\neq 0} \frac{\langle\Psi_0|\mu_z|\Psi_n\rangle \langle\Psi_n|\mu_z|\Psi_0\rangle}{E_0^{(0)} - E_n^{(0)}}\right) \mathcal{E}^2 + \cdots \tag{93}$$

If we apply Eq. (90) and Eq. (91), respectively for the dipole moment and polarizability, we finally get

$$\mu_z^{\text{perm}} = -\left(\frac{\mathrm{d}E}{\mathrm{d}\mathcal{E}}\right)_0 = \langle\Psi_0|\mu_z|\Psi_0\rangle\,, \tag{94}$$

$$\alpha_{zz} = -2\left(\frac{\mathrm{d}^2E}{\mathrm{d}\mathcal{E}^2}\right)_0 = \sum_{n\neq 0} \frac{\langle\Psi_0|\mu_z|\Psi_n\rangle \langle\Psi_n|\mu_z|\Psi_0\rangle}{E_0^{(0)} - E_n^{(0)}}. \tag{95}$$

Eq. (94) can be reformulated for any dimension as

$$\alpha_{ij} = \sum_{n\neq 0} \frac{\langle\Psi_0|\mu_i|\Psi_n\rangle \langle\Psi_n|\mu_j|\Psi_0\rangle}{E_0^{(0)} - E_n^{(0)}}, \tag{96}$$

and the mean polarizability is then defined as

$$\alpha = \frac{1}{3}(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}). \tag{97}$$

With the mean polarizability defined, we can then link it to the spectroscopy. The oscillator strength of a given transition can be defined as [63]

$$f_{n\leftarrow 0} = \left(\frac{4\pi m_e}{3e^2\hbar}\right) \nu_{n\leftarrow 0} \left\langle \Psi_0 \middle| \mu \middle| \Psi_n \right\rangle \left\langle \Psi_n \middle| \mu \middle| \Psi_0 \right\rangle , \tag{98}$$

where ν corresponds to the frequency of a photon, e and m_e are electron charge and mass, respectively. If we apply Eq. (97), we then obtain

$$\alpha = \left(\frac{\hbar^2 e^2}{m_e}\right) \sum_{n\neq 0} \frac{f_{n\leftarrow 0}}{(E_0^{(0)} - E_n^{(0)})^2} \tag{99}$$

For the excitation energies, and to show how PCM is generally included in calculation of properties, we need to find an appropriate solution in the time-dependent framework. For this derivation, the Einstein convention for summation is adopted, that is, a repeated index implies summation over it. Following Olsen and Jørgensen[64], we start by defining a fully optimized time-dependent, single-determinant wavefunction in its ground state, $|\Psi(t)\rangle$, which is assumed to be the eigenfunction $|\Psi\rangle$ of the ground state Hamiltonian for $t = 0$, when no perturbations are present. We then write the time-dependent Schrödinger equation

$$\hat{H} \left|\Psi(t)\right\rangle = i\frac{\partial}{\partial t} \left|\Psi(t)\right\rangle , \tag{100}$$

with the total Hamiltonian operator $\hat{H} = \hat{H}_0 + V^t$, with V^t being time-dependent perturbation. This perturbation can contain time-independent frequency components V^ω.

At a finite time t, a perturbed wavefunction in the frequency domain is given by the perturbation expansion

$$\left|\Psi(t)\right\rangle = \left|\Psi\right\rangle + \int_{-\infty}^{\infty} \mathrm{d}\omega \left|\Psi_1^\omega\right\rangle e^{-i\omega t + \gamma t} + \cdots \quad , \tag{101}$$

where γ is a damping factor, and $|\Psi_1^\omega\rangle$ contains all terms which are linear in the perturbation. The time-dependent expectation value of the arbitrary operator $\hat{A}$ can be written as

$$\langle\Psi(t)|\hat{A}|\Psi(t)\rangle = \langle\Psi|\hat{A}|\Psi\rangle + \int\limits_{-\infty}^{\infty} \mathrm{d}\omega_1 \, |\Psi_1^{\omega}\rangle \, e^{-i\omega t+\gamma t} \, \langle\langle A; V^{\omega_1}\rangle\rangle_{\omega_1} + \cdots \quad , \tag{102}$$

where $\langle\langle A; V^{\omega_1}\rangle\rangle_{\omega_1}$ is called the linear response function, which contains all terms linear in V^{ω}. In the simple case of a monochromatic field at frequency ω the perturbation operator can be written as

$$V^t = V^{\omega} e^{-i\omega t+\gamma t} + V^{-\omega} e^{i\omega t+\gamma t} \tag{103}$$

The expectation value of the operator $\hat{A}$, at a finite time, can be written as

$$\langle\Psi(t)|\hat{A}|\Psi(t)\rangle = \langle\Psi|\hat{A}|\Psi\rangle + \frac{1}{2}\sum_i \langle\langle A; V^{\omega_1}\rangle\rangle_0 \, . \tag{104}$$

In order to obtain the expectation value of a property in time-dependent domain we need to find the linear response function. It can be shown [64] that the aforementioned function can be expressed in terms of eigenfunctions of $\hat{H}_0$ in a form similar to Eq. (95)

$$\langle\langle A; V^{\omega_1}\rangle\rangle_0 = \sum_{n\neq 0} \frac{\langle\Psi_0|\hat{A}|\Psi_n\rangle \, \langle\Psi_n|V^{\omega}|\Psi_0\rangle}{\omega - (E_n^{(0)} - E_0^{(0)})} - \sum_{n\neq 0} \frac{\langle\Psi_0|V^{\omega}|\Psi_n\rangle \, \langle\Psi_n|\hat{A}|\Psi_0\rangle}{\omega + (E_n^{(0)} - E_0^{(0)})} . \tag{105}$$

This equation has poles for frequencies equal to excitation energies, which can be used to obtain the latter.

To show how PCM is included in calculation of properties a more technical explanation is required . In order to obtain the linear response function we first expand the variational parameters $\alpha(t)$, which describe the response of the wavefunction to the perturbation, in powers of perturbation V^t [65]

$$\alpha_l(t) = \alpha_l^{(1)} + \alpha_l^{(2)} + ... \tag{106}$$

We note here that the zeroth term vanishes, because $|\Psi\rangle$ satisfies the generalized Brillouin theorem. In order to obtain linear response properties only term $\alpha^{(1)}$ need to be considered. It is given by

$$iS_{jl}\alpha_l^{(1)}(t) - G_{jl}\alpha_l^{(1)}(t) = -iV_j^{t[1]}, \tag{107}$$

where S_{jl} is given by

$$S_{jl} = \mathrm{sgn}(l)\delta_{jl}. \tag{108}$$

G_{jl} obtained by diagonalization of the following matrix

$${}^{e}\mathbf{G} = \begin{pmatrix} A & B \\ B^* & A^* \end{pmatrix}, \tag{109}$$

where A and B collect the second derivatives of the free energy with respect to non-redundant orbital rotations (that is, between occupied and virtual orbitals)

$$\mathbf{A}_{aj,bl} = \frac{\partial^2 G}{\partial \kappa^*_{aj} \partial \kappa_{bl}} \quad = \quad \frac{\partial G}{\partial \rho} \frac{\partial^2 \rho}{\partial \kappa^*_{aj} \partial \kappa_{bl}} + \frac{\partial^2 G}{\partial \rho^2} \frac{\partial \rho}{\partial \kappa^*_{aj}} \frac{\partial \rho}{\partial \kappa_{bl}}, \tag{110}$$

$$\mathbf{B}_{aj,bl} = \frac{\partial^2 G}{\partial \kappa^*_{aj} \partial \kappa^*_{bl}} \quad = \quad \frac{\partial G}{\partial \rho} \frac{\partial^2 \rho}{\partial \kappa^*_{aj} \partial \kappa^*_{bl}} + \frac{\partial^2 G}{\partial \rho^2} \frac{\partial \rho}{\partial \kappa^*_{aj}} \frac{\partial \rho}{\partial \kappa^*_{bl}}. \tag{111}$$

The exact form of this contributions can be seen in Paper 2. After the derivation, we finally obtain

$$\langle\langle A; V_1^{\omega} \rangle\rangle_{\omega_1} = \frac{\mathrm{sgn}(l) A_k^{[1]} V_k^{\omega[1]}}{\omega_1 - \mathrm{sgn}(k)\omega_k + i\gamma}, \tag{112}$$

where

$$A_k^{[1]} = - \langle \Psi | [\mathcal{X}_k, A] | \Psi \rangle, \tag{113}$$

where $\mathcal{X}$ are the basis set elements.

Papers

Three papers are included in this thesis, and will now be discussed briefly.

1. ”Solvation at Surfaces and Interfaces: A Quantum-Mechanical/ Continuum Approach Including Nonelectrostatic Contributions”,
   K. Mozgawa, B. Mennucci and L. Frediani
   Journal of Physical Chemistry C, 2014, **118**, 4715-4725

   This paper is a benchmark of a full approach to IEF-PCM, with non-electrostatic contributions, against other computational results. Two sets of molecules have been investigated, one being methane halides at the water-hexane interface, and second - a subset of (mainly) organic molecules investigated by Pohorille and Wilson [66] at the water-air interface. Additionally, orientational analysis has been performed on phenol and ethanol at water-air interface. For this paper, additionally, c_f parameter value (see Section VIII.3) has been established for the solvents used. The results show a good qualitative agreement with the other computational work. Features, like preferred solvation at interface due to the energetic minimum, can be observed with the non-electrostatic contributions, unlike in simpler PCM approaches with electrostatics only.

2. ”Electronic structure of small surfactants: a continuum solvation study”,
   K. Mozgawa and L. Frediani
   Manuscript

   This paper extends the work done in Paper 1. Firstly, a Boltzmann averaging scheme was implemented. The approach exploits Leopardi sampling[67] in order to generate a spherical coordinates used in averaging over rotational degrees of freedom. With that established, energies and properties for several organic molecules (formaldehyde, benzaldehyde, *o*-cyanophenol, valine, glycine) are calculated. For first three of the organic molecules, additional properties were calculated, namely dipole moments and excitation energies and compared with work done within Quantum Mechanics/Molecular Mechanics (QM/MM) formalism. Similarities and discrepancies compared to QM/MM/MD simulations are discussed and motivated.

3. "A Polarizable Continuum Model for Molecules at Spherical Diffuse Interfaces",
   R. Di Remigio, K. Mozgawa, H. Cao, V. Weijo and L. Frediani
   Manuscript

   In this paper, a framework for the IEF-PCM calculations at the spherical diffuse interface is presented. A full derivation of Green's function is shown, together with a discussion of the implementation within LS-DALTON. Additionally, results of calculations of the electrostatic contribution to the free energy of solvation for ions (Li^+, Br^-), acetone, paranitrioaniline and L0 dye from [68], are presented. The effect of curvature on the solvation energy has been investigated and presented. Non-electrostatic contributions to the free energy of solvation have not been included yet in this implementation. No comparison with other work has been performed because we mainly focused on the development and implementation of the model.

Paper not included in this thesis:

- "Wavelet formulation of the polarizable continuum model. II. Use of piecewise bilinear boundary elements",
  M. Bugeanu, R. Di Remigio, K. Mozgawa, S.S. Reine, H. Harbrecht and L. Frediani
  Physical Chemistry Chemical Physics, 2015, **15**, 31566-31581

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Paper 1

Paper 2

Paper 3