New variational analysis on the sharp interface of multiscale implicit solvation: general expressions and applications

Elizabeth Hawkins, Yuanzhen Shao, and Zhan Chen

The interface definition between regions of different scales becomes a key component of a multiscale model in mathematical biology and other fields. Differential geometry based surface models have been proposed to apply the theory of differential geometry as a natural means to couple polar-nonpolar and solute-solvent interactions. As a consequence, the variational analysis of such models heavily relies on the variation of the interface. In this work, we provide a new variational approach to conduct the variational analysis on the sharp interface of multiscale implicit solvation models. It largely simplifies the computations of variations of the area and volume functionals. Moreover, general expressions of the second variation formulas of the solvation energy functional are obtained and used for the stability analysis of the equilibrium interface. Finally, we establish a reasonable concept of stability which generalizes the well-known results in minimal surfaces with constant volume and then the necessary and sufficient condition for stability. Our work paves the way to conducting stability analysis for a general energy functional especially with constant volume.

1. Introduction

Multiscale modeling becomes imperative in mathematical biology as the description of complex natural phenomena usually involves a large number of variables in hierarchical scales. In the fields of chemistry and biochemistry, multiscale models become popular alternatives to more computationally expensive approaches. For example, in the well-known hybrid model developed by Martin Karplus et al. [1], the central part is described by quantum mechanics, while the surrounding is described by molecular mechanics (e.g. atoms or group of atoms), and the entire molecular system is embedded in a dielectric continuum.

For the spatial multiscale modeling in mathematical biology, a crucial component lies in how to describe the interactions among regions of different scales in a physically meaningful way. Thus, the interface definition between regions of different scales becomes a key component of a multiscale model. For instance, in an implicit solvent model of a biomolecule, the molecule of interest is described at the atomic level while the surrounding environment is treated as a continuum. The separation and interaction of discrete and continuum domains require an interface to indicate the boundary between

Table 1: Notations of Terms Related to Geometry

Ω	:	the computational domain.
Ω_m	:	the solute region.
Ω_s	:	the solvent region.
Ω_ρ	:	the perturbation of Ω_m by a function ρ.
Ω_e	:	$\Omega \setminus \Omega_\rho$.
Σ	:	the solute-solvent interface, equipped with the metric inherited from the Euclidean metric in $\mathbb{R}^3$.
Σ_ρ	:	the normal graph given by a function $\rho \in C^2(\Sigma)$ over Σ, equipped with the metric inherited from the Euclidean metric in $\mathbb{R}^3$.
ν_Σ	:	the outward unit normal field of Σ pointing into Ω_s.
ν_{Σ_ρ}	:	the outward unit normal field of Σ_ρ pointing into Ω_e.
$d\Sigma$	:	the surface element of Σ.
$d\Sigma_\rho$	:	the surface element of Σ_ρ.
$Area$	:	the surface area of Σ.
Vol	:	the volume of the solute region Ω_m.
A_ρ	:	the surface area of Σ_ρ.
V_ρ	:	the volume of Ω_ρ.
$\mathbb{B}(x,r)$	:	the open ball at x with radius r in $\mathbb{R}^3$.
p	:	a generic point on Σ.
a	:	the width of the tubular neighbourhood of Σ.
G	:	the first fundamental form on Σ.
g	:=	$\det G$.
L	:	the second fundamental form on Σ.
K	:	the shape operator of Σ.
G_{Σ_ρ}	:	the first fundamental form on Σ_ρ.
g_{Σ_ρ}	:=	$\det G_{\Sigma_\rho}$.
H_ρ	:=	$G - 2\rho L + \rho^2 L G^{-1} L$.
h_ρ	:=	$\det H_\rho$.
$\mathrm{adj}(A)$	:	the adjunct matrix of A.
$\mathrm{tr}(A)$	:	the trace of a matrix A.
$\mathcal{K}$	:	the Gaussian curvature of Σ.
κ	:	the normalized mean curvature of Σ.
∇_Σ	:	the surface gradient of Σ.
div_Σ	:	the surface divergence of Σ.
Δ_g	:	the Laplace-Beltrami associated with the metric G.

solute atoms and the surrounding solvent. Moreover, the definition of interface plays a vital role in determining the performance of the implicit solvent model, as many physical properties of interest are very sensitive to interface definitions, including electrostatic free energies, biomolecular surface areas, molecular cavitation volumes, solvation free energies, and pK_a values [2, 3, 4, 5].

Therefore, it is highly desirable to have a interface definition between regions of different scales in a physically realistic way for a system of interest. Variational based interface models of implicit solvation have recently drawn attention [6, 7, 8, 9, 10, 11]. In particular, differential geometry based surface models have been proposed to apply the theory of differential geometry as a natural means to couple polar-nonpolar and solute-solvent interactions [6, 12, 13, 14]. The main idea is to obtain an optimal sharp interface by the minimization of a total energy functional of the system to encompass energies of interest. As a result, interface equations are obtained via the first variation of a proposed energy functional. Moreover, the second variation can be used for the stability analysis of the targeted equilibrium surface shape.

The energy of a spatial multiscale model in mathematical biology usually consists of contributions from both energies from the bulk regions and that from the separating interface. As a consequence, the variational analysis of such a model heavily relies on the variation of the interface. If one considers variations of C^2-hypersurfaces, it suffices to look at normal variation of the interface, see Section 2.2. This largely simplifies the computations of variations of the area and volume functionals based on the work of J. Prüss and G. Simonett [15, 16]. In previous literature, variations of spatial multiscale models are mainly considered among those with constant velocities, conditions on critical points of the corresponding energy functional were found and stability were investigated. However, the inclusion of a constant volume constraint changes the story in a fundamental way. In particular, it is technically hard to find necessary and sufficient conditions for a reasonable notion of stability if one confines oneself to variations of constant velocities. Therefore, a major goal of our work is to formulate and analyze the stability of a sharp interface in a general spatial multiscale model with constant volume. Last but not least, the constant volume constraint can be viewed as a conservation of mass condition under the constant density assumption. From a physical point of view, if the materials in the two bulk regions are immiscible, a conservation of mass condition should be an indispensable part of the modeling.

The objective of this work is threefold. First, we provide a new variational approach to conduct the variational analysis on the sharp interface of a multiscale implicit solvation model. The method can be verified by some benchmark examples such as variations of area and volume. Second, by the new approach, the first variation of a general energy functional involving both surface and bulk energies leads to optimal interface equations which are consistent with the literature. Moreover, general expressions of the second variation formulas of the solvation energy functional are obtained for the

first time. It can be used for the stability analysis of the equilibrium interface through calculating the sign of the formula. Third, based on the obtained variational method, we introduce the stability concept for a general energy functional with constant volume constraint and establish the necessary and sufficient condition of a stable interface, c.f. Theorems 4.2 and 4.4, which does not seem to be accessible via the traditional variational methods in previous literature on biological modeling. The new stability concept turns out to be a generalization of the well-known stability of minimal surfaces with constant volume.

The rest of this paper is organized as follows. We first describe a basic solvation free energy functional and related notations and formulas for our new approach of variation analysis on the sharp interface in Section 2. The first and second variational formulas for area and volume are examined as benchmark examples to verify current new method in Section 2. It is followed by the applications of our method to solvation free energy functionals in Section 3. Finally, the variational analysis on a functional with constant volume is explored in Section 4 in which existence of energy minimizing surface with constant volume is also shown.

2. Solvation energy functional and the first fundamental form G

2.1. Notations

In this article, we use $x = (x_1, x_2, x_3)$ to denote the coordinates in $\mathbb{R}^3$ and p to denote a generic point on a reference manifold Σ.

Given a manifold Σ and an interval I (possibly degenerate), $BC^2(I \times \Sigma)$ stands for the Banach space of all functions with bounded and continuous derivatives up to second order. When I is non-degenerate, for a function $\rho \in BC^2(I \times \Sigma)$, $\dot{\rho} = \frac{\partial}{\partial t}\rho$ and $\ddot{\rho} = \frac{\partial^2}{\partial t^2}\rho$ are the time derivatives of ρ.

Given $U \subseteq \mathbb{R}^3$, $\mathring{U}$ denotes the interior of U and $\overline{U}$ stands for the closure of U. The boundary of U is denoted by ∂U.

2.2. Sharp interface based solvation energy functional

We define the region of computation $\Omega = \Omega_m \cup \Omega_s \subset \mathbb{R}^3$ as a bounded Lipschitz domain consisting of solute region Ω_m and solvent region Ω_s. See Figure 1 for the 2D and 3D domain definition and decomposition.

The interface $\Sigma = \partial\Omega_m = \partial\Omega_m \cap \partial\Omega_s$ is an embedded closed hypersurface of class C^2. In this article, a closed manifold always means one that is compact and without boundary. In addition, we assume that Σ has no contact
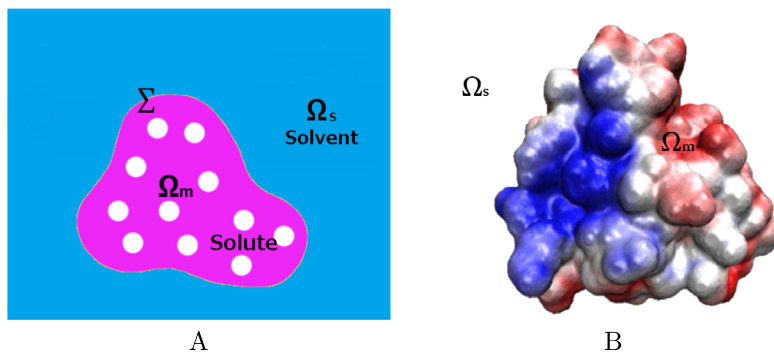
Figure 1: Illustrations of model domain definition and decomposition: Ω_m: solute (molecular) region; Ω_s: solvent region; Σ: solute-solvent sharp interface: A: a 2D view; B: A protein (ID 1frd) is immersed into solvent Ω_s with electrostatic potential projected onto the sharp interface Σ [12].

with $\partial\Omega$, i.e. $\Sigma \cap \partial\Omega = \emptyset$. Σ is equipped with the Riemannian metric inherited from the Euclidean metric in $\mathbb{R}^3$. It is known that a C^2-hypersurface satisfies the *uniform ball condition of radius* a > 0 for some a > 0, which means at each point $p \in \Sigma$, the open balls $\mathbb{B}(p \pm a\nu_\Sigma(p), a)$ do not intersect Σ. See for instance [17, Exercise 2.11]. Here ν_Σ is the outward point unit normal field of Σ pointing into Ω_s. A hypersurface satisfies the uniform ball condition of radius a > 0 iff it admits a tubular neighborhood of radius a, cf. [18, Remark 3.1]. This property allows us to express closed hypersurfaces that are close enough to (in some sense to be defined below) Σ as normal graphs on Σ.

   We want to give some explanations to the reason that we confine our discussions to C^2-hypersurfaces in $\mathbb{R}^3$. The set $\mathcal{MH}^2$ of all C^2-closed connected C^2-hypersurfaces Σ in $\mathbb{R}^3$ forms a Banach manifold with respect to the metric $d_{\mathcal{MH}^2}$ defined in the following way. Let $\mathcal{N}\Sigma = \{(p, \nu_\Sigma(p)) : p \in \Sigma\}$ denote their associated normal bundles. The second normal bundle of $\mathcal{N}^2\Sigma$ is defined by

$$\mathcal{N}^2\Sigma = \{(p, \nu_\Sigma(p), \nabla_\Sigma \nu_\Sigma(p)) : p \in \Sigma\},$$

where ∇_Σ is the surface gradient on Σ. The metric $d_{\mathcal{MH}^2}$ is defined by $d_{\mathcal{MH}^2}(\Sigma_1, \Sigma_2) = d_H(\mathcal{N}^2\Sigma_1, \mathcal{N}^2\Sigma_2)$ with d_H being the Hausdorff distance. Then given $\Sigma \in \mathcal{MH}^2$, any Γ that is close enough to Σ_1 with respect to the metric $d_{\mathcal{MH}^2}$ can be expressed as a normal graph on Σ. More precisely, there exists $\rho \in C^2(\Sigma)$ such that

$$\Phi_\rho : \Sigma \to \mathbb{R}^3 : p \mapsto p + \rho(p)\nu_\Sigma(p)$$

is a C^2-diffeomorphism between Σ and Γ. We would like to refer interested readers to the Monograph [19] by J. Prüss and G. Simonett for more details.

To define suitable concepts of variations of Σ, we consider a C^2-family of embedding $\Lambda_t : \Sigma \to \mathbb{R}^3$ of Σ into $\mathbb{R}^3$ defined on $\mathcal{MH}^2$ with $t \in I := (-\varepsilon, \varepsilon)$ for some sufficiently small $\varepsilon > 0$ and $\Lambda_0 = \mathrm{id}_\Sigma$. The vector field defined by

$$\xi(p) = \frac{d}{dt}\Lambda_t(p)|_{t=0}, \quad p \in \Sigma$$

is called the *variation vector* of Λ_t. A variation is called *normal* if $\xi(p) = \phi(p)\nu_\Sigma(p)$, where $\phi \in C^2(\Sigma)$. From the discussion in the previous paragraph, every C^2-family of embedding of Σ into $\mathbb{R}^3$ defined on $\mathcal{MH}^2$ is associated with a function $\rho \in BC^2(I \times \Sigma)$ with $\rho(0, \cdot) = 0$ in the format

$$\Lambda_t(p) = p + \rho(t, p)\nu_\Sigma(p), \quad p \in \Sigma. \tag{1}$$

Its variation vector is exactly $\dot{\rho}\nu_\Sigma$. Therefore, every variation of Σ on $\mathcal{MH}^2$ is normal. Conversely, given any $\rho \in BC^2(I \times \Sigma)$ with $\rho(0, \cdot) = 0$, (1) gives a C^2-family of embedding of Σ into $\mathbb{R}^3$ defined on $\mathcal{MH}^2$. Based on this observation, by restricting the variations on $\mathcal{MH}^2$, it suffices to consider normal variations of Σ.

A typical solvation free energy functional in Ω can be written in the form

$$E_{Gen} = \int_\Sigma f \, d\Sigma + \int_{\Omega_m} M(x)dx + \int_{\Omega_s} N(x)dx, \tag{2}$$

where f is the density function of surface energy and M, N are the bulk energy densities in Ω_m and Ω_s, respectively. In addition, $d\Sigma$ is the surface element on Σ.

A prototype of (2) that is of particular interest to us is the following functional of solvation free energy introduced in [12],

$$E = \gamma(Area) + p(Vol\,) + \int_{\Omega_m} \left[\rho_m\psi - \frac{\epsilon_m}{2}|\nabla\psi|^2\right] dx$$

$$+ \int_{\Omega_s} \left[\rho_s U^{\mathrm{vdW}} - \frac{\epsilon_s}{2}|\nabla\psi|^2 - k_B T \sum_{i=1}^{N_c} c_i \left(e^{-\psi q_i/k_B T} - 1\right)\right] dx. \tag{3}$$

Here *Area* and *Vol* represent the surface area and volume of the macromolecule; and other terms can be considered as volume functionals of the form $\int_{\Omega_i} F(x)dx$ with $i \in \{m, s\}$. The term $\gamma(Area)$ is the surface energy; it measures the disruption of intermolecular and/or intramolecular bonds that

occurs when a surface is created. The term $p(Vol)$ is the mechanical work of creating the vacuum of a biomolecular size within the solvent. We have that ψ is the electrostatic potential whose domain is the whole computational domain Ω. We define γ to be the constant surface tension, p pressure, ϵ_s and ϵ_m the dialectic constants of the solvent and solute respectively, ρ_s solvent bulk density, T the absolute temperature in Kelvin, k_B the Boltzmann constant, c_i and q_i the bulk concentration and charge of the i-th ionic species respectively, N_c the number of ionic species, and similar to [9], we take $\rho_m : \Omega \to \mathbb{R}$ as an L^∞-approximation of $\sum_j Q_j \delta(r - r_j)$, which is the density of the molecular charges with Q_j being the partial charge on an atom located at r_j. Note that $\epsilon_m < \epsilon_s$. U^{vdW} represents the attractive dispersion effects near the solvent-solute interface which has been shown to play an important role in accurate nonpolar solvation analysis [20].

2.3. Perturbation of the first fundamental form G

Let U be an open set in $\mathbb{R}^2$. We then define $f : U \to \Sigma \subset \mathbb{R}^3$ to be a surface patch on Σ. Given any $\rho \in BC^2((-\varepsilon, \varepsilon) \times \Sigma)$ for some $\varepsilon > 0$ satisfying $\rho(0) = 0$, by taking ε sufficiently small, we may assume $\|\rho\|_\infty \leq$ a, where a is the width of tubular neighbourhood of Σ asserted in the introduction. We use (t, p) to denote the arguments of ρ. Put

$$\dot\rho(0) = \frac{\partial}{\partial t}\rho|_{t=0} = \phi \quad \text{and} \quad \ddot\rho(0) = \frac{\partial^2}{\partial t^2}\rho|_{t=0} = \zeta.$$

The map

$$\Psi_\rho : (-\varepsilon, \varepsilon) \times \Sigma \to \mathbb{R}^3 : (t, p) \mapsto p + \rho(t, p)\nu_\Sigma,$$

is a C^2-diffeomorphism onto its image. Put $\Sigma_\rho(t) := \Psi_\rho(\Sigma \times t)$. In this article, for an objective F depending on ρ and thus on t, we usually omit the time variable. For instance, we usually write Σ_ρ instead of $\Sigma_\rho(t)$. Denote by Ω_ρ the region enclosed by Σ_ρ and $\Omega_e = \Omega \setminus \Omega_\rho$. In addition, we use $d\Sigma_\rho$ to denote the surface element of Σ_ρ. Let ν_{Σ_ρ} be the outward unit normal field of Σ_ρ pointing into Ω_e.

Then $f + \rho\nu_\Sigma$ is a surface patch on the perturbed surface Σ_ρ. Let G be the first fundamental form on Σ and $g = \det G$. It follows from J. Prüss and G. Simonett [21, 19] that the perturbation of G by ρ, the first fundamental form on Σ_ρ, is given by

$$G_{\Sigma_\rho} = G - 2\rho L + \rho^2 L G^{-1} L + \nabla_\Sigma\rho \otimes \nabla_\Sigma\rho,$$

where L denotes the second fundamental form of Σ. For compactness, let

$$H_\rho := G - 2\rho L + \rho^2 L G^{-1} L \quad \text{and} \quad h_\rho = \det(H_\rho);$$

and denote by $K = G^{-1} L$ the shape operator of Σ. So

$$H_\rho := G[I - 2\rho G^{-1} L + \rho^2 (G^{-1} L)^2] = G(I - 2\rho K + \rho^2 K^2) = G(\rho K - I)^2.$$

We may rewrite the perturbation as

$$G_{\Sigma_\rho} = H_\rho (I + H_\rho^{-1} \nabla_\Sigma \rho \otimes \nabla_\Sigma \rho),$$

where ∇_Σ is the surface gradient on Σ. Let $g_{\Sigma_\rho} := \det G_{\Sigma_\rho}$. Then we have the perturbation of g given by

$$g_{\Sigma_\rho} = h_\rho \det(I + H_\rho^{-1} \nabla_\Sigma \rho \otimes \nabla_\Sigma \rho).$$

2.4. Derivatives of the perturbation of G

We can now take the derivatives of the perturbations of g to simplify later calculations. The first order derivative is

$$\dot{g}_{\Sigma_\rho} = \frac{\partial}{\partial t} g_{\Sigma_\rho} = \dot{h}_\rho \det(I + H_\rho^{-1} \nabla_\Sigma \rho \otimes \nabla_\Sigma \rho) + h_\rho \frac{\partial}{\partial t} \det(I + H_\rho^{-1} \nabla_\Sigma \rho \otimes \nabla_\Sigma \rho).$$

Clearly, $h_\rho(0) = g$ and $\det(I + H_\rho^{-1} \nabla_\Sigma \rho \otimes \nabla_\Sigma \rho)(0) = \det(I) = 1$. Then

$$\dot{g}_{\Sigma_\rho}(0) = \dot{h}_\rho(0) + g \frac{\partial}{\partial t} \det(I + H_\rho^{-1} \nabla_\Sigma \rho \otimes \nabla_\Sigma \rho)|_{t=0}.$$

For any two vectors $a, b \in \mathbb{R}^n$, we have the identity $\det(I + a \otimes b) = (1 + a \cdot b)$. So

$$\frac{\partial}{\partial t} \det(I + H_\rho^{-1} \nabla_\Sigma \rho \otimes \nabla_\Sigma \rho)|_{t=0} = \frac{\partial}{\partial t}(1 + H_\rho^{-1} \nabla_\Sigma \rho \cdot \nabla_\Sigma \rho)|_{t=0} = 0.$$

Hence,

$$\begin{aligned}
\dot{g}_{\Sigma_\rho}(0) &= \dot{h}_\rho(0) = g \frac{\partial}{\partial t} \det(\rho K - I)^2|_{t=0} \\
&= 2g \det(\rho K - I)|_{t=0} \frac{\partial}{\partial t} \det(\rho K - I)|_{t=0} \\
&= 2g \frac{\partial}{\partial t} \det(\rho K - I)|_{t=0}.
\end{aligned}$$

Using Jacobi's formula and the notation $\mathrm{adj}(B)$ for the adjunct matrix of B, we have

$$
\begin{aligned}
\frac{\partial}{\partial t}\det(\rho K - I)|_{t=0} &= \mathrm{tr}(\mathrm{adj}(\rho K - I)|_{t=0}\phi K)\\
&= \mathrm{tr}(\mathrm{adj}(-I)\phi K)\\
&= -\phi\mathrm{tr}(K).
\end{aligned}
$$

Given that the Gaussian curvature $\mathcal{K} = \det K$ and the normalized mean curvature $\kappa = \frac{1}{2}\mathrm{tr}(K)$ of Σ, we then have the first order derivative of the perturbations of g given by

$$
(4)\qquad \dot{g}_{\Sigma_\rho}(0) = \dot{h}_\rho(0) = -2g\phi\mathrm{tr}(K) = -4g\phi\kappa.
$$

Now the second order derivative of the perturbation of g is given by

$$
\begin{aligned}
\ddot{g}_{\Sigma_\rho}(0) = {}&\ddot{h}_\rho(0)\,\det(I + H_\rho^{-1}\nabla_\Sigma\rho\otimes\nabla_\Sigma\rho)|_{t=0}\\
&+ h_\rho(0)\frac{\partial^2}{\partial t^2}\,\det(I + H_\rho^{-1}\nabla_\Sigma\rho\otimes\nabla_\Sigma\rho)|_{t=0}\\
&+ 2\dot{h}_\rho(0)\,\frac{\partial}{\partial t}\,\det(I + H_\rho^{-1}\nabla_\Sigma\rho\otimes\nabla_\Sigma\rho)|_{t=0}.
\end{aligned}
$$

Since $\frac{\partial}{\partial t}\,\det(I + H_\rho^{-1}\nabla_\Sigma\rho\otimes\nabla_\Sigma\rho)|_{t=0} = 0$, we have

$$
\ddot{g}_{\Sigma_\rho}(0) = \ddot{h}_\rho(0) + g\frac{\partial^2}{\partial t^2}\,\det(I + H_\rho^{-1}\nabla_\Sigma\rho\otimes\nabla_\Sigma\rho)|_{t=0}.
$$

Consider now

$$
\begin{aligned}
\ddot{h}_\rho(0) = {}&g\frac{\partial^2}{\partial t^2}\,\det(\rho K - I)^2|_{t=0}\\
={}&2g\left[\left(\frac{\partial}{\partial t}\,\det(\rho K - I)|_{t=0}\right)^2 + \frac{\partial^2}{\partial t^2}\,\det(\rho K - I)\Big|_{t=0}\right]\\
={}&2g\left(\phi^2\mathrm{tr}^2(K) + 2\phi^2\det K - \zeta\mathrm{tr}K\right).
\end{aligned}
$$

Then

$$
(5)\qquad \ddot{h}_\rho(0) = 8g\phi^2\kappa^2 + 4\phi^2 g\mathcal{K} - 4g\zeta\kappa.
$$

It remains to find

$$\frac{\partial^2}{\partial t^2} \det(I + H_\rho^{-1}\nabla_\Sigma\rho \otimes \nabla_\Sigma\rho)|_{t=0} = \frac{\partial^2}{\partial t^2}\Big(1 + H_\rho^{-1}\nabla_\Sigma\rho \cdot \nabla_\Sigma\rho\Big)\Big|_{t=0}$$
$$= 2H_\rho^{-1}(0)\nabla_\Sigma\phi \cdot \nabla_\Sigma\phi$$
$$= 2|\nabla_\Sigma\phi|^2.$$

Finally by combining this and (5), we have that the second order derivative of the perturbation of g is

(6) $$\ddot{g}_{\Sigma_\rho}(0) = g\left(8\phi^2\kappa^2 + 4\phi^2\mathcal{K} - 4\zeta\kappa + 2|\nabla_\Sigma\phi|^2\right).$$

2.5. Benchmarks: variations for area and volume

In this subsection, the above proposed new variational approach will be validated by two benchmark examples: one is variational analysis on Area, another is on Volume.

We set

$$A_\rho = \int_{\Sigma_\rho} d\Sigma_\rho \quad \text{and} \quad V_\rho = \int_{\Omega_\rho} dx,$$

which are the surface area of Σ_ρ and the volume enclosed by Σ_ρ, respectively. In particular,

$$A_\rho(0) = \int_\Sigma d\Sigma \quad \text{and} \quad V_\rho(0) = \int_{\Omega_m} dx$$

are the surface area of Σ and the volume of Ω_m, respectively. The variations of A_ρ and V_ρ are determined by using the derivatives of g_{Σ_ρ}.

Using (4), we can compute the first variation of the area functional by

$$A_\rho'(0) = \frac{d}{dt}\int_\Sigma g_{\Sigma_\rho}^{1/2} g^{-1/2} d\Sigma\Big|_{t=0} = \frac{1}{2}\left(\int_\Sigma g_{\Sigma_\rho}^{-1/2}\frac{\partial}{\partial t}g_{\Sigma_\rho} g^{-1/2} d\Sigma\right)\Big|_{t=0}$$
$$= \frac{1}{2}\int_\Sigma g^{-1}\frac{\partial}{\partial t}g_{\Sigma_\rho}(0) d\Sigma = \frac{1}{2}\int_\Sigma g^{-1}(-4g\phi\kappa) d\Sigma$$

(7) $$= -2\int_\Sigma \phi\kappa \, d\Sigma;$$

and by using (4) and (6), the second variation of the area functional is

$$A_\rho''(0) = \frac{1}{2}\left\{\int_\Sigma\left[\frac{-1}{2}g_{\Sigma_\rho}^{-3/2}\left(\frac{\partial}{\partial t}g_{\Sigma_\rho}\right)^2 + g_{\Sigma_\rho}^{-1/2}\frac{\partial^2}{\partial t^2}g_{\Sigma_\rho}\right]g^{-1/2} d\Sigma\right\}\Big|_{t=0}$$

$$= \int_{\Sigma} \left[2\phi^2 \mathcal{K} - 2\zeta\kappa + |\nabla_{\Sigma}\phi|^2 \right] d\Sigma$$

By the divergence theorem, we have

$$\int_{\Sigma} |\nabla_{\Sigma}\phi|^2 \, d\Sigma = -\int_{\Sigma} (\mathrm{div}_{\Sigma}\nabla_{\Sigma}\phi)\phi \, d\Sigma = -\int_{\Sigma} (\Delta_G\phi)\phi \, d\Sigma,$$

where div_{Σ} is the surface divergence operator on Σ and Δ_G denotes the Laplace-Beltrami operator associated with the metric G. Therefore,

$$(8) \qquad A''_{\rho}(0) = \int_{\Sigma} \left[2\phi^2 \mathcal{K} - 2\zeta\kappa - (\Delta_G\phi)\phi \right] d\Sigma.$$

Given a sufficiently smooth function $F : \Omega \to \mathbb{R}$, the volume functional

$$F_{\rho} := \int_{\Omega_{\rho}} F(x) \, dx$$

can be considered as the energy installed in Ω_{ρ} with energy density F. We will compute the derivatives of F_{ρ} at $t = 0$.

It is proved in [21, Formula (28)] that

$$(9) \qquad \nu_{\Sigma_{\rho}} = \beta_{\rho}(\nu_{\Sigma} - a_{\rho}),$$

where

$$a_{\rho} = (I - \rho L)^{-1}\nabla_{\Sigma}\rho \quad \text{and} \quad \beta_{\rho} = (1 + |a_{\rho}|^2)^{-1/2}.$$

Direct computations show

$$a_{\rho}(0) = 0, \quad \dot{a}_{\rho}(0) = \nabla_{\Sigma}\phi, \quad \beta_{\rho}(0) = 1, \quad \dot{\beta}_{\rho}(0) = 0.$$

By viewing the parameter t as the time variable, with a little arbitrariness, one can say that the normal velocity of the moving hypersurface Σ_{ρ} is

$$(10) \qquad v = (\nu_{\Sigma_{\rho}}|\nu_{\Sigma})\dot{\rho} = (\beta_{\rho}(\nu_{\Sigma} - a_{\rho})|\nu_{\Sigma})\dot{\rho} = \dot{\rho}\beta_{\rho}$$

in view of (9), where $(\cdot|\cdot)$ is the inner product in $\mathbb{R}^3$. The continuity equation and (10) show that

$$(11) \qquad F'_{\rho} = \frac{d}{dt}F_{\rho} = \int_{\Sigma_{\rho}} F\dot{\rho}\beta_{\rho} \, d\Sigma_{\rho} = \int_{\Sigma} F\dot{\rho}\alpha_{\rho} \, d\Sigma$$

with $\alpha_\rho = \beta_\rho g_{\Sigma_\rho}^{1/2} g^{-1/2}$. Direct computations show

(12) $$\alpha_\rho(0) = 1 \quad \text{and} \quad \dot{\alpha}_\rho(0) = -2\phi\kappa.$$

This implies that

(13) $$F'_\rho(0) = \frac{d}{dt} \int_{\Omega_\rho} F(x)\, dx \Big|_{t=0} = \int_\Sigma \phi F \, d\Sigma.$$

In particular, choosing $F \equiv 1$, it yields

(14) $$V'_\rho(0) = \int_\Sigma \phi \, d\Sigma.$$

The second order derivative of F_ρ can be computed by

$$F''_\rho = \frac{d^2}{dt^2} F_\rho = \frac{d}{dt} \int_\Sigma F \dot{\rho} \alpha_\rho \, d\Sigma$$
$$= \int_\Sigma \left[\frac{\partial}{\partial t}(F \circ \Psi_\rho)\dot{\rho}\alpha_\rho + F\ddot{\rho}\alpha_\rho + F\dot{\rho}\alpha'_\rho \right] d\Sigma.$$

Recalling (12), we find the second variation of F_ρ given by

(15) $$F''_\rho(0) = \int_\Sigma \left[\phi^2(\partial_{\nu_\Sigma} F - 2F\kappa) + F\zeta \right] d\Sigma,$$

with $\partial_{\nu_\Sigma} F = (\nabla F | \nu_\Sigma)$. In the particular case of $F \equiv 1$, we have

(16) $$V''_\rho(0) = \int_\Sigma (-2\phi^2\kappa + \zeta) \, d\Sigma.$$

Over the entire computational domain Ω, we have that $\dfrac{d}{dt} \displaystyle\int_\Omega F(x)\, dx = 0$ and $\Omega = \Omega_m \cup \Omega_s$. If we set $F_e(t) = \int_{\Omega_e(t)} F(x)\, dx$, then

(17) $$F'_e(0) = \frac{d}{dt} \left(\int_\Omega F(x)\, dx - \int_{\Omega_m} F(x)\, dx \right) \Big|_{t=0} = -\int_\Sigma \phi F \, d\Sigma.$$

Similar to (17), we conclude that

(18) $$F''_e(0) = -\int_\Sigma \left[\phi^2(\partial_{\nu_\Sigma} F - 2F\kappa) + F\zeta \right] d\Sigma.$$

Note that the first and second variations of Area (7) (8) and volume (14) (16) are consistent with the literature [22] and verify our variational approach.

3. Applications to the variation of solvation energy functionals

In this subsection, it is shown that with the above-derived formula, one can easily find the variations of a general energy functional involving both surface and bulk energies. As a particular application, we consider the solvation energy functional proposed by Chen et al. [12]. It turns out for both simplified non-polar part E_{np} and the full energy functional E, the necessary condition for the extremum and the second variation matches the existing generalized formula [12].

3.1. Variation of a general energy functional

Let $M, N \in C^1(\overline{\Omega})$. Then we consider a general energy functional of the form

$$(19) \qquad E_{Gen} = C(Area) + D(Vol\ ) + \int_{\Omega_m} M(x)dx + \int_{\Omega_s} N(x)dx$$

for constants C and D. The variation of E_{Gen} with respect to ρ is given by

$$(20) \qquad E_{Gen,\rho} = C(A_\rho) + D(V_\rho) + \int_{\Omega_\rho} M(x)dx + \int_{\Omega_e} N(x)dx.$$

(7), (14), (13) and (17) imply

$$E'_{Gen,\rho}(0) = CA'_\rho(0) + DV'_\rho(0) + M'_\rho(0) + N'_e(0)$$
$$= \int_\Sigma \left[C(-2\phi\kappa) + D\phi + \phi M - \phi N \right] d\Sigma$$
$$(21) \qquad\qquad = \int_\Sigma \phi(-2C\kappa + D + M - N)\, d\Sigma.$$

So at a critical point of E_{Gen}, it holds

$$(22) \qquad\qquad D = 2C\kappa - M + N \quad \text{on } \Sigma.$$

Similar computations lead to the second variation

$$E''_{Gen,\rho}(0) = \int_\Sigma \left[\phi^2\left(C\mathcal{K} + \frac{1}{2}\partial_{\nu_\Sigma}(M-N) - (M-N+D)\kappa\right) - \frac{1}{2}C(\Delta_G\phi)\phi\right]d\Sigma$$

in view of (8), (16), (15) and (18). Using (22), the above expression simplifies to

$$(23) \quad E''_{Gen,\rho}(0) = \int_\Sigma \left[\phi^2\left(2C(\mathcal{K} - 2\kappa^2) + \partial_{\nu_\Sigma}(M-N)\right) - C(\Delta_G\phi)\phi\right]d\Sigma$$

at a critical point of E_{Gen}. Note that an equivalent form of $\mathcal{K} - 2\kappa^2$ is

$$\mathcal{K} - 2\kappa^2 = \frac{1}{2}\text{tr}(G^{-1}\text{III}),$$

where III is the third fundamental form of Σ.

3.2. Variation of nonpolar energy functional E_{np}

We will first simplify E by considering just the non-polar part E_{np} defined by

$$E_{np} = \gamma(Area) + p(Vol\ ) + \int_{\Omega_s} \rho_s U^{\text{vdW}}\,dx$$

and its variation by ρ given by

$$E_{np,\rho} = \gamma(A_\rho) + p(V_\rho) + \int_{\Omega_\rho} \rho_s U^{\text{vdW}}\,dx.$$

Using (21), we have the first variation is

$$E'_{np,\rho}(0) = \int_\Sigma \phi(-2\gamma\kappa + p - \rho_s U^{\text{vdW}})d\Sigma;$$

at a critical point of E_{np}, it holds

$$p = 2\gamma\kappa + \rho_s U^{\text{vdW}} \quad \text{on } \Sigma.$$

Using (23), the second variation is

$$E''_{np,\rho}(0) = \gamma \int_\Sigma \left[\phi^2(2\mathcal{K} - \frac{\rho_s}{\gamma}\partial_{\nu_\Sigma}U^{\text{vdW}} - 4\kappa^2) - (\Delta_G\phi)\phi\right]d\Sigma$$

at a critical point of E_{np}.

3.3. Variation of full solvation functional E

We now take the first and second variations of E using the general formulas previously found. Denote the variation of E by

$$E_\rho = \gamma(A_\rho) + p(V_\rho) + \int_{\Omega_\rho} \left(\rho_m \psi - \frac{\epsilon_m}{2} |\nabla \psi|^2 \right) dx$$

$$+ \int_{\Omega_e} \left[\rho_s U^{\text{vdW}} - \frac{\epsilon_s}{2} |\nabla \psi|^2 - k_B T \sum_{i=1}^{N_c} c_i \left(e^{-\psi q_i / k_B T} - 1 \right) \right] dx.$$

For compactness, let $\epsilon_c := |\epsilon_s - \epsilon_m|$. Then the first variation is

$$E_\rho'(0) = \int_\Sigma \phi [p - 2\gamma\kappa - \rho_s U^{\text{vdW}} + \rho_m \psi + \frac{\epsilon_c}{2} |\nabla \psi|^2$$

$$+ k_B T \sum_{i=1}^{N_c} c_i \left(e^{-\psi q_i / k_B T} - 1 \right)] d\Sigma;$$

so at a critical point of E, it holds

$$p = 2\gamma\kappa + \rho_s U^{\text{vdW}} - \rho_m \psi - \frac{\epsilon_c}{2} |\nabla \psi|^2 - k_B T \sum_{i=1}^{N_c} c_i \left(e^{-\psi q_i / k_B T} - 1 \right) \quad \text{on } \Sigma;$$

and at a critical point of E, the second variation is

$$E_\rho''(0) = \gamma \int_\Sigma \left[2\phi^2 (\mathcal{K} - 2\kappa^2) - (\Delta_G \phi)\phi + \frac{\phi^2}{\gamma} \partial_{\nu_\Sigma} \left(\rho_m \psi - \rho_s U^{\text{vdW}} + \frac{\epsilon_c}{2} |\nabla \psi|^2 \right. \right.$$

$$\left. \left. + k_B T \sum_{i=1}^{N_c} c_i \left(e^{-\psi q_i / k_B T} - 1 \right) \right) \right] d\Sigma.$$

The above general expression of the second variation provides the basis for analyzing the stability and fluctuation of optimal surfaces. An optimal equilibrium interface is stable if $E_\rho''(0)$ is positive for any $C^\infty(\Sigma) \ni \phi \neq 0$. But it is difficult to determine the sign for the general case. However, the general expression can be applied to provide an efficient tool for numerical implementation as well as some simple cases which can even be evaluated analytically.

4. Variation of energy functional with constant volume

As described in Introduction, from a physical point of view, if the materials in the two bulk regions are immiscible, a conservation of mass condition should be an natural part of the problem. The constant volume constraint can be considered as a conservation of mass condition under the constant density assumption. Therefore, it is interesting to theoretically explore the variational analysis on the sharp interface for the variational solvation models with constant volume.

4.1. Variations of a general energy functional with constant volume

The concept of stability was introduced for minimal hypersurfaces with fixed volume in [23]. In this section, we will generalize the concept of stability to a general energy functional on the Banach manifold $\mathcal{MH}^2$ and obtain the criterion for stability.

Let

$$\mathcal{V} = \{\rho \in BC^2(I \times \Sigma) : \rho(0, \cdot) \equiv 0 \text{ and } \int_\Sigma \dot\rho \alpha_\rho \, d\Sigma = 0\}, \quad I := (-\varepsilon, \varepsilon).$$

Note that $\int_\Sigma \dot\rho \alpha_\rho \, d\Sigma = 0$ implies $\int_\Sigma \phi \, d\Sigma = 0$.

First, we will show that there is a one-one correspondence relationship between volume-preserving variations of Σ and elements in $\mathcal{V}$.

Proposition 4.1. *Every C^2-family of volume-preserving variation Λ_t of Σ on $\mathcal{MH}^2$ with $t \in I$ is associated with an element in $\mathcal{V}$ via (1) and vice versa.*

Proof. Given a C^2-family of volume-preserving variation Λ_t of Σ on $\mathcal{MH}^2$ with $t \in I$, Λ_t can be expressed by (1) for some $\rho \in BC^2(I \times \Sigma)$. It follows from (11) that

$$V_\rho'(t) = \int_\Sigma \dot\rho(t)\alpha_\rho(t) \, d\Sigma.$$

Λ_t is volume-preserving iff $V_\rho' \equiv 0$. So $\rho \in \mathcal{V}$. The proof for the conversed direction is similar. □

Given a general energy functional (19), we consider the variation (20) under the constant volume constraint

(24) $$V_\rho \equiv M_0 \quad \text{for some } M_0 > 0.$$

Utilizing the Lagrangian multipliers method and (21), the necessary condition for an extremum is

$$(25) \qquad D - \lambda = 2C\kappa - M + N \quad \text{on } \Sigma \quad \text{for some } \lambda \in \mathbb{R}.$$

We set

$$J_\rho = E_{Gen,\rho} - \lambda V_\rho.$$

Theorem 4.2. *Suppose that Σ satisfies* (25). *$E''_{Gen,\rho}(0) \geq 0$ (> 0, resp.) for every C^2-family of volume-preserving variation of Σ on $\mathcal{MH}^2$ given by ρ iff $J''_\rho(0) \geq 0$ (> 0, resp.) for every $\rho \in \mathcal{V}$.*

Proof. First we assume $E''_{Gen,\rho}(0) \geq 0$ for every C^2-family of volume-preserving variation. Given any $\rho \in \mathcal{V}$, from Proposition 4.1, we know that (1) gives a C^2-family of volume-preserving normal variation. Then

$$J''_\rho(0) = E''_{Gen,\rho}(0) - \lambda V''_\rho(0) = E''_{Gen,\rho}(0) \geq 0.$$

Conversely, assume that $J''_\rho(0) \geq 0$ for every $\rho \in \mathcal{V}$. Given any C^2-family of volume-preserving variation of Σ on $\mathcal{MH}^2$ given by ρ, Proposition 4.1 implies $\rho \in \mathcal{V}$. Then

$$E''_{Gen,\rho}(0) = J''_\rho(0) + \lambda V''_\rho(0) = J''_\rho(0) \geq 0.$$

The strict inequality case follows by a similar argument. $\qquad\square$

Based on these discussions, it is reasonable to introduce the notion of stability as follows.

Definition 4.3. *Suppose that Σ satisfies* (25). *We say that the energy functional* (19) *is stable (strictly stable, resp.) at Σ if $E''_{Gen,\rho}(0) \geq 0$ (> 0, resp.) for every C^2-family of volume-preserving variation of Σ on $\mathcal{MH}^2$ given by ρ.*

Theorem 4.4. *The energy functional* (19) *is stable (strictly stable, resp.) at Σ iff*

$$(26) \qquad \int_\Sigma \left[\phi^2 \Big(2C(\mathcal{K} - 2\kappa^2) + \partial_{\nu_\Sigma}(M - N) \Big) - C(\Delta_G \phi)\phi \right] d\Sigma \geq 0 \ (> 0),$$

respectively, for any $\phi \in C^2(\Sigma)$ with $\int_\Sigma \phi \, d\Sigma = 0$.

Proof. Assume that (26) holds for all $\phi \in C^2(\Sigma)$ with $\int_\Sigma \phi \, d\Sigma = 0$ and Σ satisfies (25). Given any $\rho \in \mathcal{V}$ with $\phi = \dot\rho(0)$, using (23) and (25), it is not

hard to see

$$J_\rho''(0) = \int_\Sigma \left[\phi^2 \Big(2C(\mathcal{K} - 2\kappa^2) + \partial_{\nu_\Sigma}(M - N) \Big) - C(\Delta_G \phi)\phi \right] d\Sigma \geq 0 \ (> 0).$$

Then Theorem 4.2 and Definition 4.3 imply that (19) is stable (strictly stable, resp.) at Σ.

For the converse part, we will apply the implicit function theorem argument in [23, Lemma 2.4]. Assume that (19) is stable (strictly stable, resp.) at Σ with $Vol = M_0$. Given $\phi \in C^2(\Sigma)$ with $\int_\Sigma \phi \, d\Sigma = 0$, we will show that there exists a C^2-family of volume-preserving normal variation Λ_t on $\mathcal{MH}^2$ with variational vector $\phi\nu_\Sigma$ and $t \in (-\varepsilon, \varepsilon)$ for sufficiently small $\varepsilon > 0$. Put

$$\Lambda_{t,\bar{t}}(p) = p + (t\phi + \bar{t}h)(p), \quad p \in \Sigma$$

for some $h \in C^2(\Sigma)$ with $\int_\Sigma h \, d\Sigma \neq 0$. Let $\Gamma(t, \bar{t}) := \Lambda_{t,\bar{t}}(\Sigma)$ and $V(t, \bar{t})$ be the volume of the region enclosed by the C^2-hypersurface $\Gamma(t, \bar{t})$ for $t, \bar{t} \in (-\varepsilon, \varepsilon) =: I$ with sufficiently small ε. Recall

$$V(0, 0) = M_0 > 0.$$

By (14)

$$\frac{\partial}{\partial \bar{t}} V(0, 0) = \int_\Sigma h \, d\Sigma \neq 0.$$

Therefore, it follows from the implicit function theorem that by possibly shrinking ε, there exists a smooth function $\varphi : I \to \mathbb{R}$ such that $\varphi(0) = 0$ and

$$V(t, \varphi(t)) = M_0, \quad t \in I.$$

Moreover,

$$\varphi'(0) = \left(\int_\Sigma h \, d\Sigma \right)^{-1} \int_\Sigma \phi \, d\Sigma = 0.$$

Then $\Lambda_t = \Lambda_{t,\varphi(t)}$ is the claimed family of volume-preserving variation. $\quad\square$

4.2. Variation of area with constant volume

We will apply the results in the previous subsection to some simple case, namely the well-known example of minimal surface with fixed constant volume. It can be shown that our variational approach and resulted general expressions of first and second variations can be directly used for the stability analysis of the equilibrium surface which turns out to be a sphere.

Now we consider a special case of (19) with $C = 1$, $D = 0$, $M \equiv 0$ and $N \equiv 0$, i.e the variation of *Area* with the constant volume constraint. (25) shows that the necessary condition for an extremum is

$$-2\kappa = \lambda \quad \text{hence} \quad \kappa = -\frac{\lambda}{2} = -C$$

for a constant C. A. D. Alexandrov proved that a closed embedded surface in $\mathbb{R}^3$ with constant mean curvature $\kappa \neq 0$ must be a sphere. Assume that Σ is a sphere of radius r. Then

(27) $$\kappa = \frac{1}{r} \quad \text{and} \quad \mathcal{K} = \frac{1}{r^2}.$$

By Theorem 4.4, a sphere Σ is stable iff

(28) $$\int_{\Sigma} \left[2\phi^2 (\mathcal{K} - 2\kappa^2) - (\Delta_G \phi)\phi \right] d\Sigma \geq 0$$

for all $\phi \in C^2(\Sigma)$ with $\int_{\Sigma} \phi \, d\Sigma = 0$. We may use the spherical coordinates

$$(r \cos\theta \sin\varphi, r \sin\theta \sin\varphi, r \cos\varphi), \quad 0 \leq \theta < 2\pi, \ 0 \leq \varphi < \pi$$

on Σ. Using this with (27) and the usual Laplace-Beltrami operator Δ_s on the sphere, (28) becomes

(29)
$$F(\phi) := \int_{\Sigma} \left[2\phi^2 \left(\frac{1}{r^2} - 2\frac{1}{r^2} \right) - (\Delta_s \phi)\phi \right] d\Sigma = -\int_{\Sigma} \left[\phi^2 \frac{2}{r^2} + (\Delta_s \phi)\phi \right] d\Sigma \geq 0.$$

For $l = 0, 1, \dots$ and $|m| \leq l$, we use the spherical harmonics $\phi = \sum_{l,m} a_{lm} Y_{lm}(\varphi, \theta)$ where a_{lm} are constants and Y_{lm} is the normalized real spherical harmonics of degree l and order m, which forms an orthonormal basis of $L^2(\Sigma)$. Using this expression, the fact that $\Delta_s Y_{lm} = -l(l+1)Y_{lm}/r^2$ and (29),

$$F(\phi) = -\frac{1}{r^2} \int_{\Sigma} \left[2 \left(\sum_{l,m} a_{lm} Y_{lm} \right)^2 - \left(\sum_{l,m} a_{lm} l(l+1) Y_{lm} \right) \sum_{l,m} a_{lm} Y_{lm} \right] d\Sigma$$

$$= \frac{1}{r^2} \int_{\Sigma} \left[\sum_{l,m} [l(l+1) - 2] |a_{lm}|^2 Y_{lm}^2 \right] d\Sigma$$

$$= \frac{1}{r^2} \sum_{l,m} [l(l+1) - 2] |a_{lm}|^2.$$

Note that $Y_{00} = 1$ does not have mean zero on Σ. It suffices to consider the case $l \geq 1$. For $l = 1$

$$F(\phi) = 0,$$

and for $l \geq 2$,

$$F(\phi) = \frac{\gamma}{r^2} \sum_{l,m} [l(l+1) - 2] |a_{lm}|^2 > 0.$$

Therefore, spheres are stable.

4.3. Variation of E with constant volume

We now take the first and second variations of E under the constraint of constant volume under the assumption that Σ is an embedded closed hypersurface of class C^2.

Using (21) and the Lagrangian multiplier method, the necessary condition for Σ to be a minimizer of E under the constraint (24) is
(30)
$$p - \lambda = 2\gamma\kappa + \rho_s U^{\text{vdW}} - \rho_m\psi - \frac{\epsilon_c}{2}|\nabla\psi|^2 - k_B T \sum_{i=1}^{N_c} c_i \left(e^{-\psi q_i/k_B T} - 1 \right) \quad \text{on } \Sigma$$

for some $\lambda \in \mathbb{R}$. By Theorem 4.4, E is stable at Σ iff

(31)
$$\int_{\Sigma} \left[|\nabla_\Sigma \phi|^2 + 2\phi^2(\mathcal{K} - 2\kappa^2) \right.$$
$$\left. + \frac{\phi^2}{\gamma} \partial_{\nu_\Sigma} \left(\rho_m\psi - \rho_s U^{\text{vdW}} + \frac{\epsilon_c}{2}|\nabla\psi|^2 + k_B T \sum_{i=1}^{N_c} c_i \left(e^{-\psi q_i/k_B T} - 1 \right) \right) \right] d\Sigma \geq 0$$

for all $\phi \in C^2(\Sigma)$ satisfying $\int_{\Sigma} \phi \, d\Sigma = 0$, which always holds if

$$\frac{1}{\gamma} \partial_{\nu_\Sigma} \left(\rho_m\psi - \rho_s U^{\text{vdW}} + \frac{\epsilon_c}{2}|\nabla\psi|^2 + k_B T \sum_{i=1}^{N_c} c_i \left(e^{-\psi q_i/k_B T} - 1 \right) \right)$$
$$+ 2\mathcal{K} - 4\kappa^2 + 1/C_p^2 \geq 0,$$

where C_p is the sharp constant in the Poincaré inequality

$$\|u - \bar{u}\|_2 \leq C_p \|\nabla_\Sigma u\|_2, \quad u \in H^1(\Sigma)$$

with $\bar{u}$ being the mean of u on Σ.

4.4. Existence of energy minimizing interface with constant volume

Using the language of Geometric Measure Theory, we can rewrite (3) in the form

$$E = \gamma \text{Per}(\Omega_m; \Omega) + \int_{\Omega_m} \left(p + \rho_m \psi - \frac{\epsilon_m}{2} |\nabla \psi|^2 \right) dx$$

$$+ \int_{\Omega_s} \left[\rho_s U^{\text{vdW}} - \frac{\epsilon_s}{2} |\nabla \psi|^2 - k_B T \sum_{i=1}^{N_c} c_i \left(e^{-\psi q_i / k_B T} - 1 \right) \right] dx.$$

Here $\text{Per}(\Omega_m; \Omega)$ is the perimeter of Ω_m in Ω.

In this section, we will consider the problem of minimizing E depending on two arguments Ω_m and ψ. We require, in addition, that ψ satisfies the the boundary value problem of the generalized Poisson-Boltzmann equation (GPBE)

$$(32) \quad \begin{cases} \text{div}(\alpha \nabla \psi) + \chi_{\Omega_s} \sum_{i=1}^{N_c} c_i q_i e^{-\psi q_i / k_B T} + \rho_m \chi_{\Omega_m} = 0 \quad \text{in} \quad \Omega; \\ \\ \psi = \psi_\infty \quad \text{on} \quad \partial \Omega \end{cases}$$

for some $\psi_\infty \in W^{1,\infty}(\Omega)$ with $\alpha = \frac{1}{2}(\epsilon_m \chi_{\Omega_m} + \epsilon_s \chi_{\Omega_s})$. This is the only section that we consider an undetermined electrostatic potential ψ. In all other sections, ψ is taken to be a known function.

By possibly enlarging Ω a little, without loss of generality, we may assume that there exists some $U \subset\subset \Omega$, i.e. $\overline{U} \subset \Omega$, such that $\Omega_m \subset \overline{U}$. Recall that the solute atoms are located at r_j inside Ω_m. We may further assume that there is a $\delta > 0$ such that $\bigcup_j B(r_j, \delta) \subseteq \Omega_m$.

We seek an optimal set D of finite perimeter minimizing

$$M(D) = \gamma \text{Per}(D; \Omega) + \int_D \left(p + \rho_m \psi - \frac{\epsilon_m}{2} |\nabla \psi|^2 \right) dx$$

$$(33) \qquad + \int_{\Omega \setminus D} \left[\rho_s U^{\text{vdW}} - \frac{\epsilon_s}{2} |\nabla \psi|^2 - k_B T \sum_{i=1}^{N_c} c_i \left(e^{-\psi q_i / k_B T} - 1 \right) \right] dx$$

subject to Constrain (32) and the conservation of mass condition

$$(34) \qquad |D| := \int_D dx = M_0 \quad \text{for some constant } M_0 > 0$$

in the admissible space

$$\mathcal{M} = \{D \subset \overline{U} \text{ is of finite perimeter such that } \bigcup_j B(r_j, \delta) \subseteq D\}$$

and

$$\mathcal{A} = \{\psi \in H^1(\Omega) : \psi|_{\partial\Omega} = \psi_\infty\}.$$

To validate the choice of the space $\mathcal{M}$, of course, we will require

$$\left|\bigcup_j B(r_j, \delta)\right| < M_0 < |U|.$$

Let

$$I_D := \int_D \left(\frac{\epsilon_m}{2}|\nabla\psi|^2 - \rho_m\psi\right) dx$$
$$+ \int_{\Omega\setminus D} \left[\frac{\epsilon_s}{2}|\nabla\psi|^2 + k_B T \sum_{i=1}^{N_c} c_i \left(e^{-\psi q_i/k_B T} - 1\right)\right] dx.$$

Proposition 4.5.
(1) *Given any $D \in \mathcal{M}$, there exists a unique $\psi_D \in \mathcal{A}$ such that*

$$I_D[\psi_D] = \min_{\psi \in \mathcal{A}} I_D[\psi] < \infty.$$

Moreover, ψ_D is the unique weak solution to (32). *Further, ψ_D satisfies*

(35) $$\|\psi_D\|_{H^1} + \|\psi_D\|_\infty \le M_1 = M_1(\psi_\infty).$$

In particular, the constant M_1 in (35) *is independent of D.*
(2) *Let $D_k, D \in \mathcal{M}$ be such that*

$$\chi_{D_k} \to \chi_D \quad \text{in } L^1(\Omega).$$

Let $\psi_k, \psi \in \mathcal{A}$ be the corresponding electrostatic potentials, i.e.,

$$I_{D_k}[\psi_k] = \min_{w \in \mathcal{A}} I_{D_k}[w] \quad \text{and} \quad I_D[\psi] = \min_{w \in \mathcal{A}} I_D[w].$$

Then $I_{D_k}[\psi_k] \to I_D[\psi]$.

Proof. They are just special cases of [24, Theorems III.1 and III.2] by taking $u = \chi_D$ and $u_k = \chi_{D_k}$. $\square$

Theorem 4.6. *There exists some $D \in \mathcal{M}$ minimizing* (33) *and satisfying the constrains* (32) *and* (34) *such that $M(D)$ is finite.*

Proof. For any fixed $D \in \mathcal{M}$, it follows from (35) that

$$I_D[\psi_u] < I_D[\psi_\infty] \leq C_0 < \infty$$

for some C_0 independent of D. Therefore,

$$(36) \qquad M(D) \geq \gamma \mathrm{Per}(D; \Omega) + p|D| + \int_\Omega \rho_s U^{\mathrm{vdW}} \, dx - C_0 > C_1 > -\infty,$$

which implies $C_M := \inf_{D \in \mathcal{M}} M(D)$ is finite. Now we can find a minimizing sequence $\{D_k\}_{k=1}^\infty \subset \mathcal{M}$ satisfying (34) such that

$$\lim_{k\to\infty} M(D_k) = C_M.$$

Further, we may assume $M(D_k) \leq C_M + 1$. Together with (36), this implies that

$$\|\chi_{D_k}\|_{BV(\Omega)} \leq C < \infty.$$

By the compactness and lower semi-continuity of BV-functions, cf. [25, Theorems 5.1 and 5.4], there exists $D \in \mathcal{M}$ such that

$$(37) \qquad \chi_{D_k} \to \chi_D \quad \text{in } L^1(\Omega) \quad \text{and} \quad \mathrm{Per}(D; \Omega) \leq \liminf_{k\to\infty} \mathrm{Per}(D_k; \Omega).$$

Together with Proposition 4.5, (37) implies that

$$M(D) \leq \liminf_{k\to\infty} M(D_K) \implies M(D) = C_M.$$

Moreover, (37) shows that D satisfies (34). $\qquad\qquad \square$

5. Conclusion

This work introduces a new mathematical method to approach the problem of taking the first and second variations of solvation energy functionals on a sharp interface. The variations are useful for finding the necessary conditions for extrema and analyzing the stability of an extremum once it has been found. This approach for the variations of energy functionals utilizes the variational formula of the first fundamental form proposed by J. Prüss and G. Simonett [15, 16] to find the variations of *Area*. Further, the

continuity equation and the formula for the variational normal vector field found in [15, 16] allow for a general formula for the variations of any volume functional. Utilizing the general formula, the variations of a general energy functional involving both surface and bulk energies can be quickly found. As an application, we consider the solvation energy functional proposed by Chen et al. [12]; first, we consider the simplified non-polar part E_{np} and then the full energy functional E. For both, the necessary condition for the extremum and the second variation matches the generalized formula. Based on these results, we further investigate the stability of a critical point of a general energy functional under constant volume constraint. To be precise, we establish a reasonable concept of stability which generalizes the well-known results in minimal surfaces with constant volume and then we establish the necessary and sufficient condition for stability. Our work paves the way to conducting stability analysis for a general energy functional with constant volume. But, as expected, the stability condition is in general hard to check numerically. As a simplified example as well as a verification of our work, we consider the well-known case of area-minimizing surface with constant volume. Using the general formula, we find that the minimal surface must be a sphere; this is a well known result for this isoperimetric problem and can be taken as a benchmark example for our variational approach and the derived first and second variation formulas. Then by using the spherical harmonics and the second variation, we analyze the stability of spheres and the result coincides with the classic ones. In the final part, we study the stability problem of the solvation energy functional. Surface equations of critical points are obtained; based on the stability criteria derived earlier, we find the equivalent condition for a critical point to be stable. In addition, the existence of energy minimizing surface with constant volume is also shown. For the future work, we will try to apply the general expression of the first and second variations numerically for the stability analysis of an equilibrium shape which should be resulted from the computational implementation of variational models of solvation with constant volume. Meanwhile, the local minimality condition of the equilibrium will be explored in more depth under the conservation of mass condition for the variational solvation model.

Acknowledgments

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ELIZABETH HAWKINS
DEPARTMENT OF MATHEMATICAL SCIENCES
GEORGIA SOUTHERN UNIVERSITY
STATESBORO, GA
USA
E-mail address: eh03511@georgiasouthern.edu

YUANZHEN SHAO
DEPARTMENT OF MATHEMATICS
UNIVERSITY OF ALABAMA
TUSCALOOSA, AL
USA
E-mail address: yshao8@ua.edu

ZHAN CHEN
DEPARTMENT OF MATHEMATICAL SCIENCES
GEORGIA SOUTHERN UNIVERSITY
STATESBORO, GA
USA
E-mail address: zchen@georgiasouthern.edu