Reliable adaptive method for electrostatic computations in biomolecular systems governed by the Poisson-Boltzmann equation

Prof. Johannes Kraus, Svetoslav Nakov, Prof. Sergey Repin

Johann Radon Institute for Computational and Applied Mathematics (RICAM)
Austrian Academy of Sciences (ÖAW)
Linz, Austria

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Outline

1 Setting of the problem

2 Well posedness and error estimation

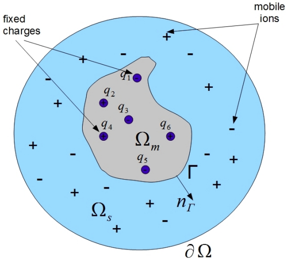
3 Numerical examples

4 Summary

Poisson-Boltzmann equation of electrostatics

Notation: $\Omega \subset \mathbb{R}^3$ is a truncation of $\mathbb{R}^3$ (the computational domain).
Ω_m is the molecule domian, and Ω_s is the solvent domain.
$\Omega, \Omega_m, \Omega_s$ are bounded Lipschitz domains and $\partial\Omega_m = \Gamma$.
The equation for the dimensionless potential $\tilde{\phi} = \frac{e_c \phi}{k_B T}$ is:

$$
\begin{aligned}
-\nabla \cdot \left(\epsilon(x)\nabla\tilde{\phi}\right) + k^2(x)\sinh\left(\tilde{\phi}\right) &= \frac{4\pi e_c^2}{k_B T}\sum_{i=1}^{N} z_i \delta_{x_i}(x) \quad \text{in } \Omega_m \cup \Omega_s, \\
\left[\tilde{\phi}\right]_\Gamma &= 0, \\
\left[\epsilon \nabla \tilde{\phi} \cdot n\right]_\Gamma &= 0, \\
\tilde{\phi} &= g \quad \text{on } \partial\Omega,
\end{aligned}
$$



where g is Lipschitz on $\partial\Omega$ and the coefficients $k(x)$, $\epsilon(x)$ are given by

$$
k^2(x) = \begin{cases} k_m^2 = 0, & x \in \Omega_m, \\ k_s^2 = \dfrac{8\pi c^\infty q^2}{kT}, & x \in \Omega_s, \end{cases}
\qquad
\epsilon(x) = \begin{cases} \epsilon_m, & x \in \Omega_m, \\ \epsilon_s, & x \in \Omega_s. \end{cases}
$$

2-term regularization: $\tilde{\phi} = G + u$

$\tilde{\phi} = G + u$, where

$$\begin{aligned} G &= \frac{e_c^2}{\epsilon_m k_B T} \sum_{i=1}^{N} \frac{z_i}{|x - x_i|} \\ -\nabla \cdot (\epsilon_m \nabla G) &= \frac{4\pi e_c^2}{k_B T} \sum_{i=1}^{N} z_i \delta_{x_i}(x), \quad \text{on } \mathbb{R}^3. \end{aligned}$$

Then u satisfies

$$\begin{aligned} -\nabla \cdot (\epsilon \nabla u) + k^2 \sinh(u + G) &= 0 \quad \text{in } \Omega_m \cup \Omega_s, & \text{(2a)} \\ [u]_\Gamma &= 0, & \text{(2b)} \\ [\epsilon \nabla u \cdot n]_\Gamma &= -[\epsilon \nabla G \cdot n]_\Gamma =: g_\Gamma, & \text{(2c)} \\ u &= g - G \quad \text{on} \quad \partial\Omega. & \text{(2d)} \end{aligned}$$

Definition 1 (Weak formulation of (2))

We call u a weak solution of (2) if $u \in H^1(\Omega)$ with $u = g - G$ on $\partial\Omega$ and u is such that $k^2 \sinh(u+G)v \in L^1(\Omega), \forall v \in H_0^1(\Omega) \cap L^\infty(\Omega)$ and

$$\int_\Omega \epsilon \nabla u \cdot \nabla v dx + \int_\Omega k^2 \sinh(u+G) v dx = \int_\Gamma g_\Gamma v ds = \int_\Omega (\epsilon_m - \epsilon) \nabla G \cdot \nabla v dx, \tag{3}$$

$\forall v \in H_0^1(\Omega) \cap L^\infty(\Omega)$.

Proposition 2 (Kraus,Nakov,Repin 2018)

Problem (3) *has a unique weak solution* $u \in H^1(\Omega)$ *with* $u = g - G$ *on* $\partial\Omega$, *which belongs to* $L^\infty(\Omega)$. *As a consequence, the test functions in* (3) *can be taken in* $H_0^1(\Omega)$.

Main ingredient for the proof of boundedness and uniqueness:

Theorem 3 (H. Brézis and F. Browder, 1978)

Let Ω be a domain in $\mathbb{R}^d$, $T \in H^{-1}(\Omega) \cap L^1_{loc}(\Omega)$, and $v \in H^1_0(\Omega)$. If there exists a function $f \in L^1(\Omega)$ such that $T(x)v(x) \geq f(x)$, a.e in Ω, then $Tv \in L^1(\Omega)$ and the duality product $\langle T, v\rangle$ in $H^{-1}(\Omega) \times H^1_0(\Omega)$ coincides with $\int_\Omega Tvdx$.

Remark 4

In other words, we have the following situation: a locally summable function $b \in L^1_{loc}(\Omega)$ defines a bounded linear functional T_b over the dense subspace $D(\Omega) \equiv C_0^\infty(\Omega)$ of $H^1_0(\Omega)$ through the integral formula $\langle T_b, \varphi\rangle = \int_\Omega b\varphi dx$. It is clear that the functional T_b is uniquely extendable by continuity to a bounded linear functional $\overline{T}_b$ over the whole space $H^1_0(\Omega)$. Now the question is whether this extension is still representable by the same integral formula for any $v \in H^1_0(\Omega)$ (if the integral makes sense at all). If $v \in H^1_0(\Omega)$ is a fixed element, Theorem 3 gives a sufficient condition for bv to be summable and for the extension $\overline{T}_b$ evaluated at v to be representable with the same integral formula as above, i.e $\langle \overline{T}_b, v\rangle = \int_\Omega bvdx$.

3-term regularization $\tilde{\phi} = G + u^H + u$ (Holst 2012)

$\tilde{\phi} = G + u^H + u$, such that $\tilde{\phi} = u$ in Ω_s, i.e. $u^H = -G$ in Ω_s.

$$
\begin{aligned}
-\Delta u^H &= 0 \quad \text{in} \quad \Omega_m, \\
u^H &= -G \quad \text{on} \quad \Gamma = \partial\Omega_m,
\end{aligned}
$$

$$
\begin{aligned}
-\nabla \cdot (\epsilon \nabla u) + k^2 \sinh(u) &= 0 \quad \text{in } \Omega_m \cup \Omega_s, && \text{(4a)} \\
[u]_\Gamma &= 0, && \text{(4b)} \\
\left[\epsilon \frac{\partial u}{\partial n}\right]_\Gamma &= g_\Gamma, && \text{(4c)} \\
u &= g, \quad \text{on } \partial\Omega. && \text{(4d)}
\end{aligned}
$$

$$
\left[\epsilon \frac{\partial u}{\partial n}\right]_\Gamma = -\gamma_\Gamma \left(\epsilon_m \frac{\partial \left(u^H + G\right)}{\partial n} \restriction_{\Omega_m} \right) =: g_\Gamma
$$

If ∇u^H is only in $H(\text{div}; \Omega_m)$, then the functional $g_\Gamma \in H^{-1/2}(\Gamma)$ is defined as follows

$$
\langle g_\Gamma, v \rangle_\Gamma = -\langle \gamma_{n,\Omega_m}(\epsilon_m \nabla u^H), v \rangle_\Gamma + \langle \gamma_{n,\Omega_s}(\epsilon_m \nabla G), v \rangle_\Gamma, \; \forall v \in H^{1/2}(\Gamma), \qquad (5)
$$

$\tilde{\phi} = G + u^H + u$, where $u^H \in H^1(\Omega)$ with $u^H = -G$ on Γ, $u^H = -G$ in Ω_s and

$$\int_{\Omega_m} \nabla u^H \cdot \nabla v dx = 0, \forall v \in H_0^1(\Omega)$$

Definition 5

Then u satisfies the integral identity

$$\int_{\Omega} \epsilon \nabla u \cdot \nabla v dx + \int_{\Omega} k^2 \sinh(u) v dx = \\ = -\int_{\Omega_m} \epsilon_m \nabla u^H \cdot \nabla v dx + \int_{\Omega_s} \epsilon_m \nabla G \cdot \nabla v dx, \text{ for all } v \in H_0^1(\Omega) \cap L^\infty(\Omega). \quad (6)$$

Proposition 6 (Kraus, Nakov, Repin 2018)

Problem (6) has unique weak solution $u \in H^1(\Omega)$ with $u = g$ on $\partial\Omega$ which is also in $L^\infty(\Omega)$.

3-term regularization in practice

- $$\tilde{\phi} = \begin{cases} G + u^H + u, & x \in \Omega_m, \\ u, & x \in \Omega_s, \end{cases}$$
- Find a conforming approximation $\tilde{u}^H$ to $u^H \in H^1(\Omega_m)$ with $u^H = -G$ on Γ, where $\int_{\Omega_m} \epsilon \nabla u^H \cdot \nabla v dx = 0, \; \forall v \in H_0^1(\Omega_m)$
- Flux reconstruction: $T : \nabla \tilde{u}^H \mapsto T(\nabla \tilde{u}^H) \in H(\text{div}; \Omega_m)$
- Find a conforming approximation $\tilde{u}_h$ to $\tilde{u} \in H^1(\Omega)$ with $\tilde{u}_h = g$ on $\partial\Omega$, where

$$\int_\Omega \epsilon \nabla u \cdot \nabla v dx + \int_\Omega k^2 \sinh(u) v dx = -\int_{\Omega_m} \epsilon_m \nabla u^H \cdot \nabla v dx + \int_{\Omega_s} \epsilon_m \nabla G \cdot \nabla v dx, \text{ for all } v \in H_0^1(\Omega).$$

$$\int_\Omega \epsilon \nabla \tilde{u} \cdot \nabla v dx + \int_\Omega k^2 \sinh(\tilde{u}) v dx = -\int_{\Omega_m} \epsilon_m \nabla T(\nabla \tilde{u}^H) \cdot \nabla v dx + \int_{\Omega_s} \epsilon_m \nabla G \cdot \nabla v dx, \text{ for all } v \in H_0^1(\Omega).$$

Overall error in u is:

$$|||\nabla(u - \tilde{u}_h)||| \leq \sqrt{\epsilon_m} M_{\oplus,H}\left(\tilde{u}^H, T(\nabla \tilde{u}^H)\right) + \sqrt{2} M_\oplus(\tilde{u}_h, \tilde{y}^*), \qquad (7)$$

where $\|\nabla u^H - T(\nabla \tilde{u}^H)\|_{L^2(\Omega_m)} \leq M_{\oplus,H}\left(\tilde{u}^H, T(\nabla \tilde{u}^H)\right)$ and $|||\nabla(\tilde{u} - \tilde{u}_h)||| \leq \sqrt{2} M_\oplus(\tilde{u}_h, \tilde{y}^*)$.

Functional a posteriori error estimates

Find $u \in H_0^1(\Omega)$ such that

$$(P) \quad J(u) = \inf_{v \in H_0^1(\Omega)} J(v), \text{ where } J(v) = G(\Lambda v) + F(v). \tag{8}$$

$$D_G(\Lambda v, p^*) + D_F(v, -\Lambda^* p^*) + D_G(\Lambda u, y^*) + D_F(u, -\Lambda^* y^*) = M_\oplus^2(v, y^*) \tag{9}$$

where $\Lambda := \nabla : H_0^1(\Omega) \to \left[L^2(\Omega)\right]^3$, $\Lambda^* := -\operatorname{div} : \left[L^2(\Omega)\right]^3 \to H^{-1}(\Omega)$ the adjoint operator to Λ,

$$D_G(\Lambda v, y^*) := G(\Lambda v) + G^*(y^*) - (y^*, \Lambda v)$$

$$D_F(v, -\Lambda^* y^*) := F(v) + F^*(-\Lambda^* y^*) + \langle \Lambda^* y^*, v \rangle$$

are the *compound* functionals for G and F, respectively (see Repin 2000 , Neittaanmaki & Repin 2004).

$$J(v) - I^*(p^*) = D_G(\Lambda v, p^*) + D_F(v, -\Lambda^* p^*), \tag{10a}$$

$$J(u) - I^*(y^*) = D_G(\Lambda u, y^*) + D_F(u, -\Lambda^* y^*). \tag{10b}$$

$$J(v) - I^*(y^*) = D_G(\Lambda v, y^*) + D_F(v, -\Lambda^* y^*) = M_\oplus^2(v, y^*). \tag{10c}$$

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A model semilinear equation

$$\begin{aligned} -\nabla \cdot (A(x)\nabla u) + u &= f, \text{ in } \Omega \\ u &= 0, \text{ on } \partial\Omega \end{aligned}$$

$$\begin{aligned} D_G(\Lambda v, p^*) = \frac{1}{2}|||\nabla(v-u)|||^2, \quad D_F(v, -\Lambda^* p^*) = \frac{1}{2}\|v-u\|^2_{L^2(\Omega)}, \\ D_G(\Lambda u, y^*) = \frac{1}{2}|||y^* - p^*|||^2_*, \quad D_F(u, -\Lambda^* y^*) = \frac{1}{2}\|\text{div}(y^* - p^*)\|^2_{L^2(\Omega)}. \end{aligned} \tag{11}$$

$$|||\nabla(v-u)|||^2 := \int_\Omega A\nabla(v-u)\cdot\nabla(v-u)dx$$ is the energy norm

$$|||y^* - p^*|||^2_* := \int_\Omega A^{-1}(y^* - p^*)\cdot(y^* - p^*)dx$$ is the dual energy norm.

$$M^2_\oplus(v, y^*) = D_G(\Lambda v, y^*) + D_F(v, -\Lambda^* y^*)$$

The error identity becomes:

$$\begin{aligned}&|||\nabla(v-u)|||^2+\|v-u\|^2_{L^2(\Omega)}+|||y^*-p^*|||^2_*+\|\operatorname{div} y^*-\operatorname{div} p^*\|^2_{L^2(\Omega)}\\ &=\underbrace{|||A\nabla v-y^*|||^2_*+\|-\operatorname{div} y^*+v-f\|^2_{L^2(\Omega)}}_{D_G(\Lambda v,y^*)+D_F(v,-\Lambda^* y^*)}\end{aligned} \tag{12}$$

For general convex problems, the following relations hold:

$$|||A\nabla v-y^*|||^2_*=|||\nabla(v-u)|||^2+|||y^*-p^*|||^2_*-\underbrace{2\int_\Omega(y^*-p^*)\cdot\nabla(v-u)dx}_{\approx 0(\text{from numerics})},$$

$$2D_F(v,-\Lambda^*y^*)=\underbrace{2D_F(v,-\Lambda^*p^*)}_{\approx\|v-u\|^2_{L^2(\Omega)}}+\underbrace{2D_F(u,-\Lambda^*y^*)}_{\approx\|\operatorname{div}(y^*-p^*)\|^2_{L^2(\Omega)}}+\underbrace{2\int_\Omega(y^*-p^*)\cdot\nabla(v-u)dx}_{\approx 0(\text{from numerics})}$$

Example: $-\nabla \cdot (\epsilon \nabla u) + k^2 \sinh(u + w) = f$.

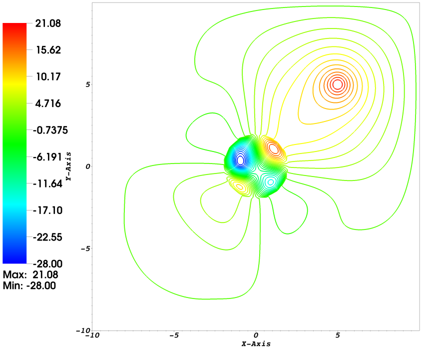

Figure: Reference solution.

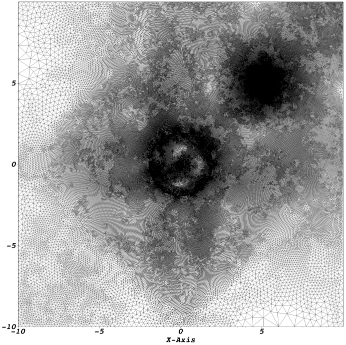

Figure: Mesh with 555 489 elements, obtained by AMR using the error indicator $|||\epsilon \nabla v - y^*|||^2$ with flux equilibration for y^*.

$$2D_F(v, -\Lambda^* y^*) \approx \|-\operatorname{div} y^* + k^2 \sinh(v+w) - f\|^2_{L^2(\Omega)}$$

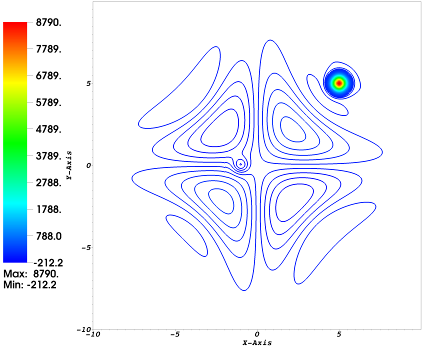

Figure: Function

$f = -k^2 \sinh(u+w) + l$.

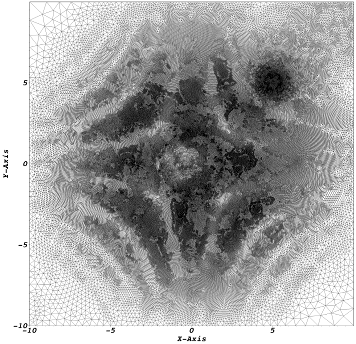

Figure: Mesh with 395 935 elements, obtained by AMR using the error indicator $|||\epsilon \nabla v - y^*|||^2_* + 2D_F(v, -\Lambda^* y^*)$ with flux equilibration for y^*.

Significantly improved efficiency indeces !

Near best approximation result

Galerkin approximation $\tilde{u}_h$ in a finite element space $V_h \subset H_0^1(\Omega)$ ($g = 0$ on $\partial\Omega$):

Find $\tilde{u}_h \in V_h$ such that

$$\int_\Omega \epsilon \nabla \tilde{u}_h \cdot \nabla v dx + \int_\Omega k^2 \sinh(\tilde{u}_h) v dx = -\int_{\Omega_m} \epsilon_m \nabla T(\nabla \tilde{u}^H) \cdot \nabla v dx + \int_{\Omega_s} \epsilon_m \nabla G \cdot \nabla v dx,$$

for all $v \in V_h$. (13)

where $\tilde{u}^H$ is an approximation to u^H and $T(\nabla \tilde{u}^H)$ is an approximation of the dual variable $\nabla \tilde{u}^H$ (T is a "Flux reconstruction operator").

Theorem 7 (Kraus,Nakov,Repin 2018)

Let $V_h \subset L^\infty(\Omega)$ be a closed subspace of $H_0^1(\Omega)$ and $\tilde{u}_h \in V_h$ be the Galerkin approximation of $\tilde{u}$ defined by (13). Then

$$|||\nabla(\tilde{u}_h - \tilde{u})|||^2 \leq \inf_{v \in V_h} \left\{ |||\nabla(v - \tilde{u})|||^2 + \int_{\Omega_s} k^2 (\sinh(v) - \sinh(\tilde{u}))^2 dx \right\} \quad (14)$$

Proof:

$$J(v) = G(\Lambda v) + F(v), \quad G(\Lambda v) := \int_\Omega \frac{\epsilon}{2} |\nabla v|^2 \, dx,$$

$$F(v) := \int_\Omega k^2 \cosh(v) dx + \int_{\Omega_m} \epsilon_m T(\nabla \tilde{u}^H) \cdot \nabla v dx - \int_{\Omega_s} \epsilon_m \nabla G \cdot \nabla v dx$$

For any $v \in V_h$:

$$|||\nabla(\tilde{u}_h - \tilde{u})|||^2 + \underbrace{2D_F(\tilde{u}_h, -\Lambda^* \tilde{p}^*)}_{\geq 0} = 2\left(J(\tilde{u}_h) - J(\tilde{u})\right)$$

$$\leq 2\left(J(v) - J(\tilde{u})\right) = |||\nabla(v - \tilde{u})|||^2 + 2D_F(v, -\Lambda^* \tilde{p}^*).$$

$$2D_F(v, -\Lambda^* \tilde{p}^*) = \int_{\Omega_s} k^2 \left(\cosh(v) - \cosh(\tilde{u}) + \tilde{u}\sinh(\tilde{u}) - v\sinh(\tilde{u})\right) dx$$

$$\leq \int_{\Omega_s} k^2 (\sinh(v) - \sinh(\tilde{u}))^2 dx \overset{\|v\|_{L^\infty} \leq 2\|\tilde{u}\|_{L^\infty}}{\leq} C\|v - \tilde{u}\|^2_{L^2(\Omega)} \leq C|||\nabla(v - \tilde{u})|||^2$$

Proof:

$$J(v) = G(\Lambda v) + F(v), \quad G(\Lambda v) := \int_\Omega \frac{\epsilon}{2} |\nabla v|^2 \, dx,$$

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For any $v \in V_h$:

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More generally

Find $u \in H_0^1(\Omega)$ such that for all $v \in H_0^1(\Omega)$ (15)

$$\int_\Omega A\nabla u \cdot \nabla v dx + \int_\Omega k^2(x) b(u) v dx = \int_\Omega \left(f_0 v + f_1 \frac{\partial v}{\partial x_1} + \ldots + f_d \frac{\partial v}{\partial x_d} \right) dx.$$

where $k^2 \in L^\infty(\Omega)$, $f_0 \in L^2(\Omega)$, $f_1, \ldots, f_d \in L^s(\Omega)$, $s > d$, $b : \mathbb{R} \to \mathbb{R}$ is a continuous and strictly increasing function (ensure a convex problem and strong duality): Then:

$u \in L^\infty(\Omega)$ with $\|u\|_{L^\infty(\Omega)} \leq M$, M depending only on the data, not on the nonlinearity b (for this we only need $f_0 \in L^r(\Omega)$, $r > \frac{d}{2}$).

$$D_F(v, -\Lambda^* p^*) = \int_\Omega k^2 \left(B(v) - vb(u) + ub(u) - B(u)\right) dx \qquad (16)$$

Near best approximation result

Let $V_h \subset L^\infty(\Omega)$ be a closed subspace of $H_0^1(\Omega)$ and $\tilde{u}_h \in V_h$ be the Galerkin approximation of the solution u of (15). Then for any $M > \|u\|_{L^\infty(\Omega)}$ exists a constant $C > 0$ such that

$$|||\nabla(u_h - u)|||^2 \leq \inf_{\substack{v \in V_h \\ \|v\|_{L^\infty(\Omega)} \leq M}} \left\{ |||\nabla(v - u)|||^2 + \int_\Omega C(v - u)^2 dx \right\} \qquad (17)$$

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where $k^2 \in L^\infty(\Omega)$, $f_0 \in L^2(\Omega)$, $f_1, \ldots, f_d \in L^s(\Omega)$, $s > d$, $b : \mathbb{R} \to \mathbb{R}$ is a continuous and strictly increasing function (ensure a convex problem and strong duality): **Then:**

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$$D_F(v, -\Lambda^* p^*) = \int_\Omega k^2 \left(B(v) - vb(u) + ub(u) - B(u) \right) dx \tag{16}$$

Near best approximation result

Let $V_h \subset L^\infty(\Omega)$ be a closed subspace of $H_0^1(\Omega)$ and $\tilde{u}_h \in V_h$ be the Galerkin approximation of the solution u of (15). Then for any $M > \|u\|_{L^\infty(\Omega)}$ exists a constant $C > 0$ such that

$$|||\nabla(u_h - u)|||^2 \leq \inf_{\substack{v \in V_h \\ \|v\|_{L^\infty(\Omega)} \leq M}} \left\{ |||\nabla(v - u)|||^2 + \int_\Omega C(v-u)^2 dx \right\} \tag{17}$$

More generally

Find $u \in H_0^1(\Omega)$ such that for all $v \in H_0^1(\Omega)$ (15)

$$\int_\Omega A\nabla u \cdot \nabla v dx + \int_\Omega k^2(x) b(u) v dx = \int_\Omega \left(f_0 v + f_1 \frac{\partial v}{\partial x_1} + \ldots + f_d \frac{\partial v}{\partial x_d} \right) dx.$$

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For computing $F^*(-\Lambda^* y^*)$ when $f_0 \notin L^\infty(\Omega)$ we need additional assumptions. For example:

- b^{-1} is AC,
- $|b^{-1}(s)| \leq C_1 + C_2|s|, \forall s \in \mathbb{R}$.
- $b(s_0) = 0$ for some $s_0 \in \mathbb{R}$

or

- b^{-1} is AC,
- $|b(s)| \leq C_1 + C_2|s|, \forall s \in \mathbb{R}$,
- $B(s) := \int_0^s b(t)dt + C \geq 0$ for some $C > 0$.
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$$= \sup_{z\in H_0^1(\Omega)} \int_\Omega \left[(\operatorname{div} y_0^* + f_0) z - k^2 B(z)\right] dx \qquad (1)$$

(finite if $\operatorname{div} y_0^* + f_0 = 0$ in $\{x \in \Omega : k^2(x) = 0\}$)

$$\leq \int_\Omega \sup_{\xi\in\mathbb{R}} \left[(\operatorname{div} y_0^*(x) + f_0(x))\,\xi - k^2 B(\xi)\right] dx$$

$$= \int_\Omega k^2 \left[\left(\frac{\operatorname{div} y_0^* + f_0}{k^2}\right) b^{-1}\left(\frac{\operatorname{div} y_0^* + f_0}{k^2}\right) - B\left(b^{-1}\left(\frac{\operatorname{div} y_0^* + f_0}{k^2}\right)\right)\right] dx \qquad (2).$$

With the assumptions above, we can show that $(1) = (2)$!

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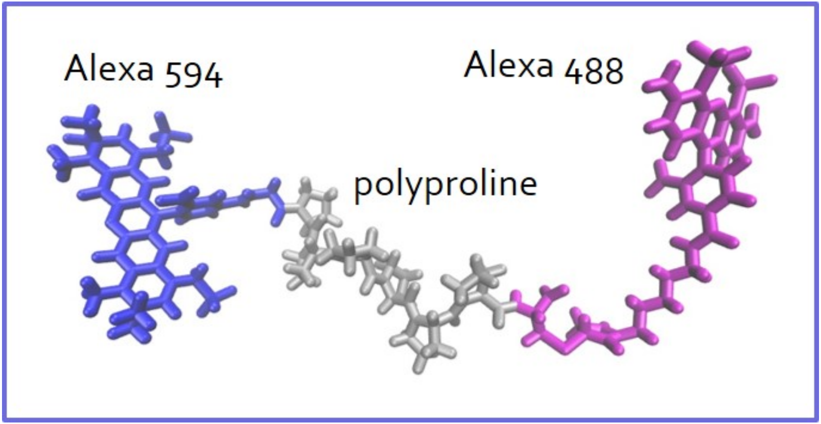
With the assumptions above, we can show that (1) = (2)!

Example 1: Alexa 488 and Alexa 594



Example 1: Alexa 488 and Alexa 594 (**2-term**)

Example 1: $k_m^2 = 0,\ k_s^2 = 10,\ \epsilon_m = 2,\ \epsilon_s = 80$					
level i	#elements	upper bound of energy error [%]	lower bound of CEN [%]	practical estimation of CEN [%]	upper bound of CEN [%]
0	667 008	31.9	14.7	20.9	22.3
1	1 619 690	10.0	4.78	6.88	7.04
2	3 624 678	6.97	3.33	4.79	4.89
3	6 830 130	5.37	2.56	3.69	3.76
4	9 861 226	4.60	2.20	3.16	3.23
5	12 982 453	4.12	1.97	2.83	2.89
6	16 420 992	3.76	1.80	2.59	2.64
7	20 636 057	3.46	1.66	2.38	2.43
8	25 937 013	3.20	1.53	2.20	2.24
9	32 602 138	2.96	1.41	2.04	2.07
10	40 972 275	2.74	1.31	1.88	1.92
11	51 409 492	2.53	1.21	1.74	1.77

Example 2: Insulin protein (PDB ID: 1RWE) (**2-term**)

Example 2: $k_m^2 = 0,\ k_s^2 = 10,\ \epsilon_m = 20,\ \epsilon_s = 80$					
level i	#elements	upper bound of energy error [%]	lower bound of CEN [%]	practical estimation of CEN [%]	upper bound of CEN [%]
0	724 737	40.67	16.24	25.81	27.54
1	1 523 717	27.39	10.95	17.07	18.54
2	2 325 989	23.33	9.33	14.47	15.80
3	3 082 380	21.12	8.45	13.07	14.30
4	3 880 178	19.54	7.81	12.08	13.23
5	4 785 000	18.26	7.30	11.28	12.36
6	5 850 441	17.17	6.86	10.59	11.62
7	7 140 525	16.17	6.46	9.97	10.95
8	8 713 471	15.26	6.10	9.41	10.33
9	10 625 629	14.42	5.77	8.89	9.77
10	12 948 272	13.64	5.46	8.40	9.24

Harmonic component u^H is computed on a mesh with 31971835 elements with a relative error $\leq 6.53\%$ and $M_{\oplus,H}(\tilde{u}^H, T(\nabla\tilde{u}^H)) = 9.17$.

$$|||\nabla(u - \tilde{u}_h)||| \leq \sqrt{\epsilon_m} M_{\oplus,H}\left(\tilde{u}^H, T(\nabla\tilde{u}^H)\right) + \sqrt{2} M_{\oplus}(\tilde{u}_h, \tilde{y}^*) = \sqrt{20} \times 9.17 + 67.08 = 108.08$$

resulting in no more than approximately 19.3% relative error in the regular component u ($|||\nabla\tilde{u}_h||| = 558.63$).

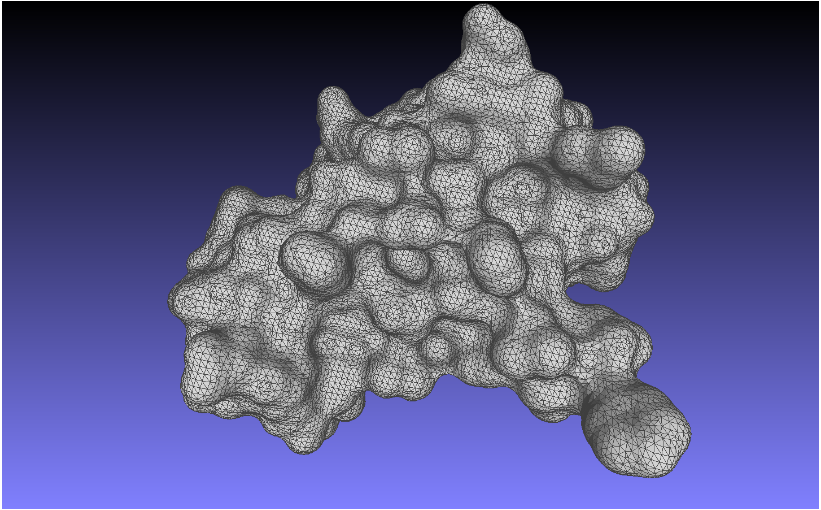
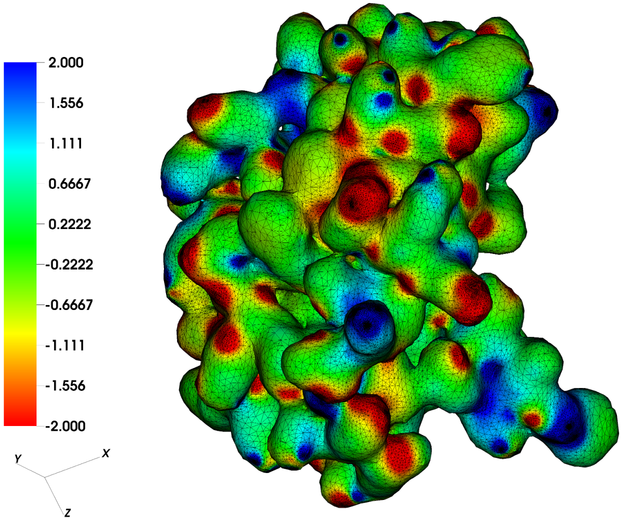


Figure: Connolly surface mesh of the insulin protein created with NanoShaper.


2.000
1.556
1.111
0.6667
0.2222
-0.2222
-0.6667
-1.111
-1.556
-2.000
Y
X
Z

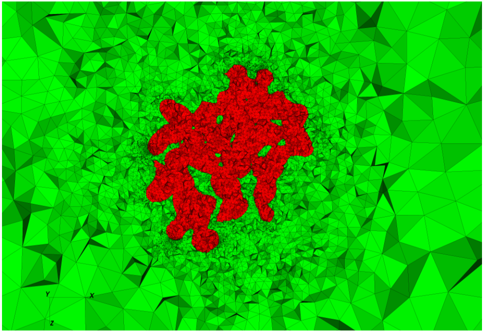


Figure: Cross section of the mesh with the plane $y = 15$ at level 2 in the mesh refinement procedure for finding the component $\tilde{u}^N$ in Example 2. The molecule region Ω_m is marked red.

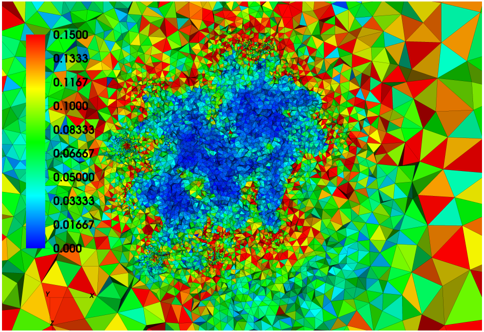


Figure: Cross section of the mesh with the plane $y = 15$ at level 2 in the mesh refinement procedure for finding the component $\tilde{u}^N$ in Example 2. Error indicator as a piecewise constant function.

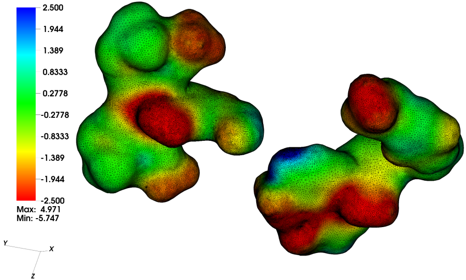


Figure: Full potential surface map with the 3-term regularization for the system Alexa 488 and Alexa 594 in units $k_B T / e_c$.

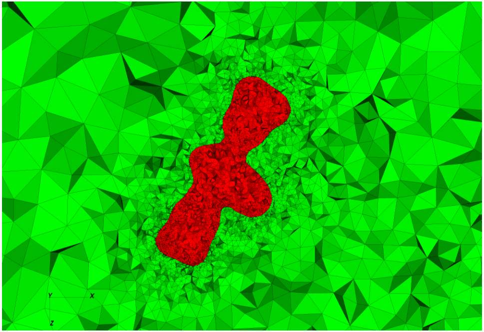


Figure: Cross section of the mesh with the plane $y = 3$ at level 1 in the mesh refinement procedure for finding the component $\tilde{u}$ in Example 3. The molecule region Ω_m is marked red (Alexa 594).

$$2M_{\oplus}^{2}(\tilde{u}_h, \tilde{y}^*) = |||\epsilon\nabla\tilde{u}_h - \tilde{y}^*|||_* + 2D_F(\tilde{u}_h, -\Lambda^*\tilde{y}^*) \qquad (18)$$

Error Indicator: the integrand of $M_{\oplus}^{2}(\tilde{u}_h, \tilde{y}^*)$ which is nonnegative in Ω.

How to choose $\tilde{y}^* \in H(\mathrm{div};\Omega)$?

$\epsilon\nabla\tilde{u}_h \in [L^2(\Omega)]^d$ and $\epsilon\nabla\tilde{u}_h \notin H(\mathrm{div};\Omega)$!

- Flux reconstruction by gradient averaging
- Patchwise flux reconstruction with equilibration in RT_0, RT_1 (for example Braess and Schoberl 2006 - easy to implement in parallel)
- Minimization of the majorant $M_{\oplus}^{2}(\tilde{u}_h, \tilde{y}^*)$ with respect to $\tilde{y}^*$ in a subspace of $H(\mathrm{div};\Omega)$ (for example $[Vh]^d$, $RT0$, $RT1$,..)

Summary

- Well posedness (2-term and 3-term regularizations)
- Convergence of the finite element method under uniform refinement (2-term and 3 -term regularizations)
- A posteriori error estimates (2-term and 3-temr regularizations)
  - Valid for any conformal approximation (P_1, P_2, IGA,...)
  - No local or global constants are present in the estimate
  - Guaranteed bound on the global error (even equality in the full nonlinear measure for the error)
  - The more is invested in constructing a better $\tilde{y}^*$, the tighter the bound on the energy and CEN error is
  - Efficient error indicator
- Efficient construction of the "free variable" $\tilde{y}^*$

Thank you for listening!

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