# Computation of Forces Arising from the Linear Poisson-Boltzmann Method in the Domain Decomposition Paradigm

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Joint work with M.Nottoli (Università di Pisa, Pisa), C. Quan (SUS Tech, China),

and B. Stamm (Universität Stuttgart, Stuttgart)

# Outline

# Solvation Models



- Ionic Solvation Models [1]
  - Explicit Solvation Models
    - Adopts molecular representation of both solute and solvent
    - Accurate results
    - Computationally expensive

[1] Zhang et. al.: JCTC, 13, 1034-1043, 2017

[2] Tomasci, Persico: CR 94, 2027-2094, 1994

[3] Honig, Nicholls: Sci. 268, 1144-1149, 1995

# Solvation Models



- Ionic Solvation Models [1]
  - Explicit Solvation Models
    - Adopts molecular representation of both solute and solvent
    - Accurate results
    - Computationally expensive
  - Implicit Solvation Models [2,3]
    - Microscopic treatment of solute
    - Macroscopic treatment of solvent using physical properties
    - Less computational cost

[1] Zhang et. al.: JCTC, 13, 1034-1043, 2017

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# Model Problem



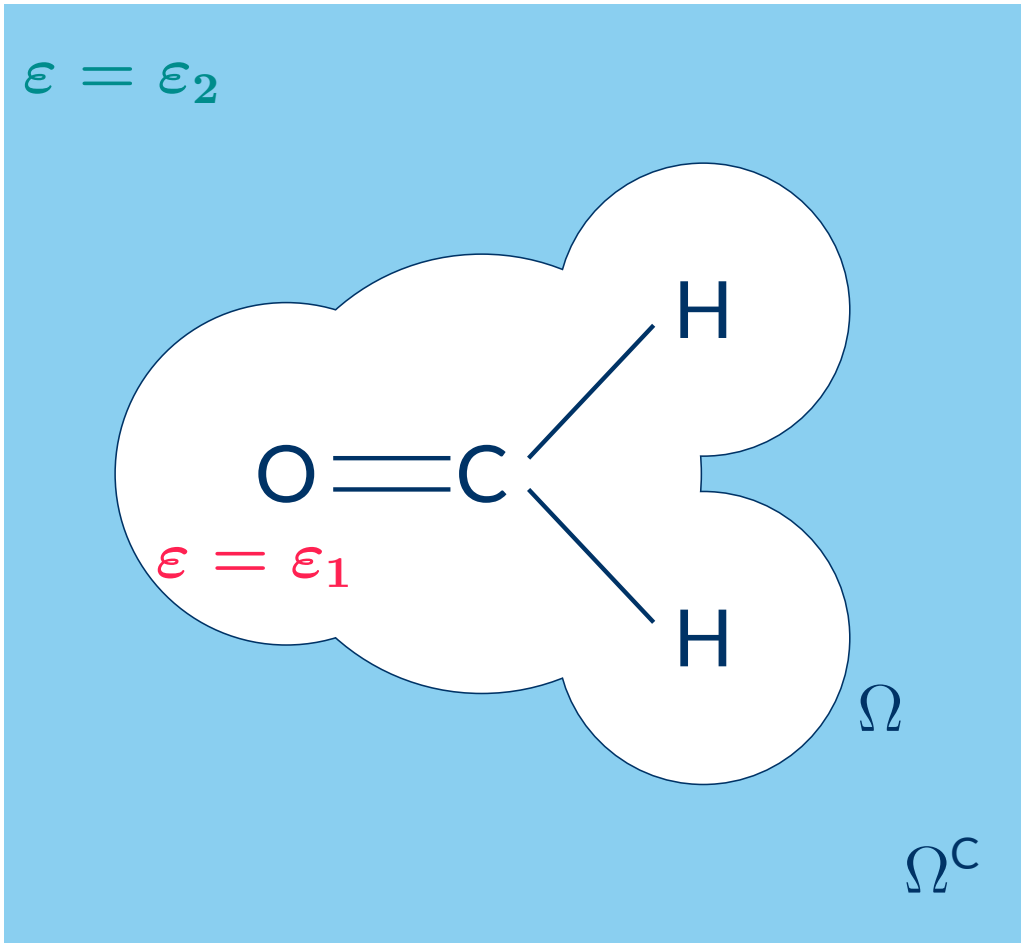


**Figure 1:** Formaldehyde molecule

- Linear Poisson-Boltzman (LPB) equation

$$-\nabla \cdot [\varepsilon(x)\nabla\psi(x)] + \bar{\kappa}(x)^2\psi(x) = 4\pi\rho_M(x) \quad \text{in } \mathbb{R}^3$$

  - $\psi(x)$ – Electrostatic potential

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  - $\psi(x)$– Electrostatic potential
  - $\varepsilon(x)$– Space-dependent dielectric permittivity

$$\varepsilon(x) = \begin{cases} \varepsilon_1 & \text{in } \Omega, \\ \varepsilon_2 & \text{in } \Omega^C := \mathbb{R}^3 \setminus \overline{\Omega} \end{cases}$$

  - $\Omega$– Solute Cavity

# Model Problem



- $\bar{\kappa}(\boldsymbol{x})$ – Modified Debye-Hückel parameter

$$\bar{\kappa}(\boldsymbol{x}) = \begin{cases} 0 & \text{in } \Omega, \\ \sqrt{\varepsilon_2}\kappa & \text{in } \Omega^{\mathsf{C}} \end{cases}$$

- $\kappa$ – Debye-Hückel screening constant

- $\bar{\kappa}(x)$ – Modified Debye-Hückel parameter

$$\bar{\kappa}(x) = \begin{cases} 0 & \text{in } \Omega, \\ \sqrt{\varepsilon_2}\kappa & \text{in } \Omega^c \end{cases}$$

- $\kappa$ – Debye-Hückel screening constant
- $\rho_M(x)$ – Solute charge distribution

$$\rho_M(x) = \sum_{i=1}^{M} q_i \delta(x - x_i)$$

- $M$ – Number of solute atoms
- $q_i$ – Partial charge on the $i^{\text{th}}$ atom

- Boundary Element Method (BEM) [1]

[1] Yoon, Lehnoff: JCC 11, 1080–1086, 1990

[2] Madura et.al.: CPC 91, 57–95, 1995

[3] Chen, Holst, Xu: SINUM 45, 2295–2320, 2007

[4] Cancés, Maday, Stamm: JCP 139, 054111, 2013

[5] Lipparini et.al.: JCP 141, 184108, 2014

[6] Quan, Stamm, Maday: SISC 41, B320–B350, 2019

[7] Lebedev, Laikov: DM 59, 477–481, 1999

# Review of numerical methods



- Boundary Element Method (BEM) [1]
- Finite Difference Method (FDM)[2]

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# Review of numerical methods



- Boundary Element Method (BEM) [1]
- Finite Difference Method (FDM)[2]
- Finite Element Method (FEM)[3]
- Domain Decomposition Methods [4,5,6]
  - Schwarz decomposition method
  - Does not rely on mesh but quadrature points[7]
  - Computation of forces becomes natural as spheres are centered at nucleus position

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- The LPB equation can be written in two equations

$$-\Delta\psi(x) = \frac{4\pi}{\varepsilon_1}\rho_M(x) \qquad \text{in } \Omega,$$
$$-\Delta\psi(x) + \kappa^2\psi(x) = 0 \qquad \text{in } \Omega^C,$$

with

$$[\![\psi(x)]\!] = 0 \qquad \text{on } \Gamma,$$
$$[\![\partial_{\mathbf{n}}\psi(x)]\!] = 0 \qquad \text{on } \Gamma$$

- Using potential theory the final equations are

$$\begin{aligned} -\Delta\psi_{\mathsf{r}}(x) &= 0 \quad \text{in } \Omega, \\ -\Delta\psi_{\mathsf{e}}(x) + \kappa^2\psi_{\mathsf{e}}(x) &= 0 \quad \text{in } \Omega, \end{aligned}$$

with

$$\begin{aligned} \psi_0 + \psi_{\mathsf{r}} &= \psi_{\mathsf{e}} && \text{on } \Gamma, \\ \sigma_{\mathsf{e}} &= \partial_{\mathsf{n}}\psi_{\mathsf{e}} - \frac{\varepsilon_1}{\varepsilon_2}\partial_{\mathsf{n}}(\psi_0 + \psi_{\mathsf{r}}) && \text{on } \Gamma \end{aligned}$$ [1]

[1] Sauter, Schwab, Springer, Berlin-2011, Thm. 3.3.1

# Problem Transformation



- Using potential theory the final equations are

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where

- $\psi_{\mathsf{r}}$ – Reaction potential in $\Omega$
- $\psi_0$ – Potential generated by $\rho_{\mathsf{M}}$ satisfying,

$$-\Delta\psi_0 = \frac{4\pi}{\varepsilon_1}\rho_{\mathsf{M}}$$

[1] Sauter, Schwab, Springer, Berlin-2011, Thm. 3.3.1

# Problem Transformation



- $\psi_e$ – Extended potential from $\Omega^C$ to $\Omega$
- $\sigma_e$ – Charge density generating $\psi_e$ satisfying

$$S_\kappa \sigma_e(x) := \int_\Gamma \frac{\exp\left(-\kappa|x-y|\right)\sigma_e(y)}{4\pi|x-y|} = \psi_e \quad \forall\, x \in \Gamma$$

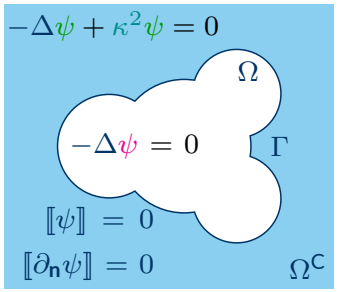
- $S_\kappa$ – Invertible single-layer potential operator [1]

$$S_\kappa : H^{-1/2}(\Gamma) \to H^{1/2}(\Gamma)$$

[1] Sauter, Schwab, Springer, Berlin-2011, 101-181

# ddLPB-Method





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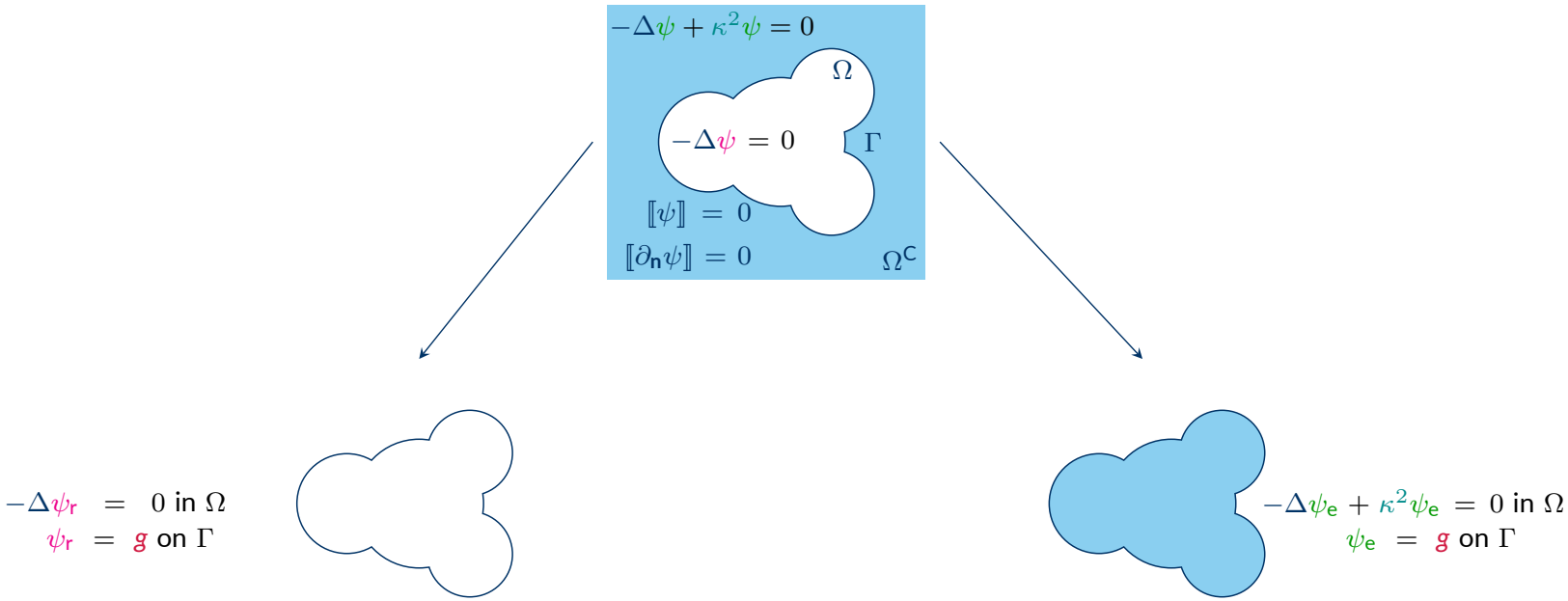

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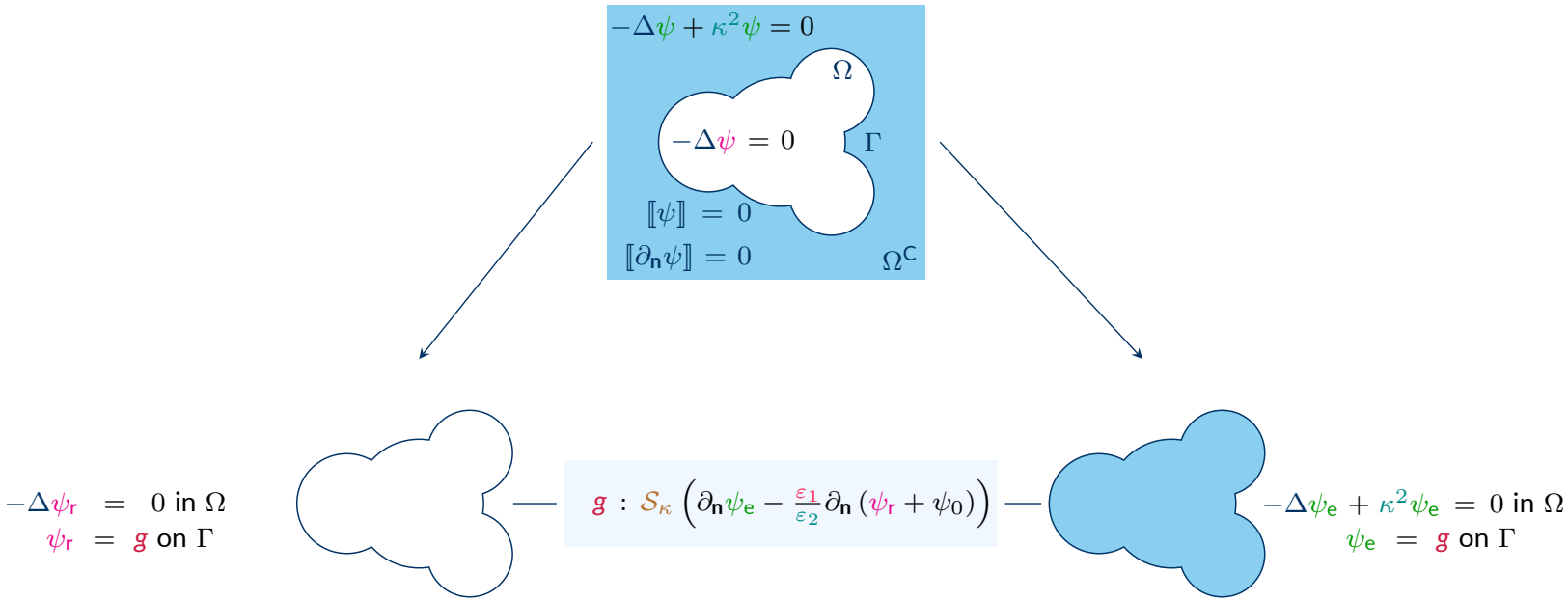
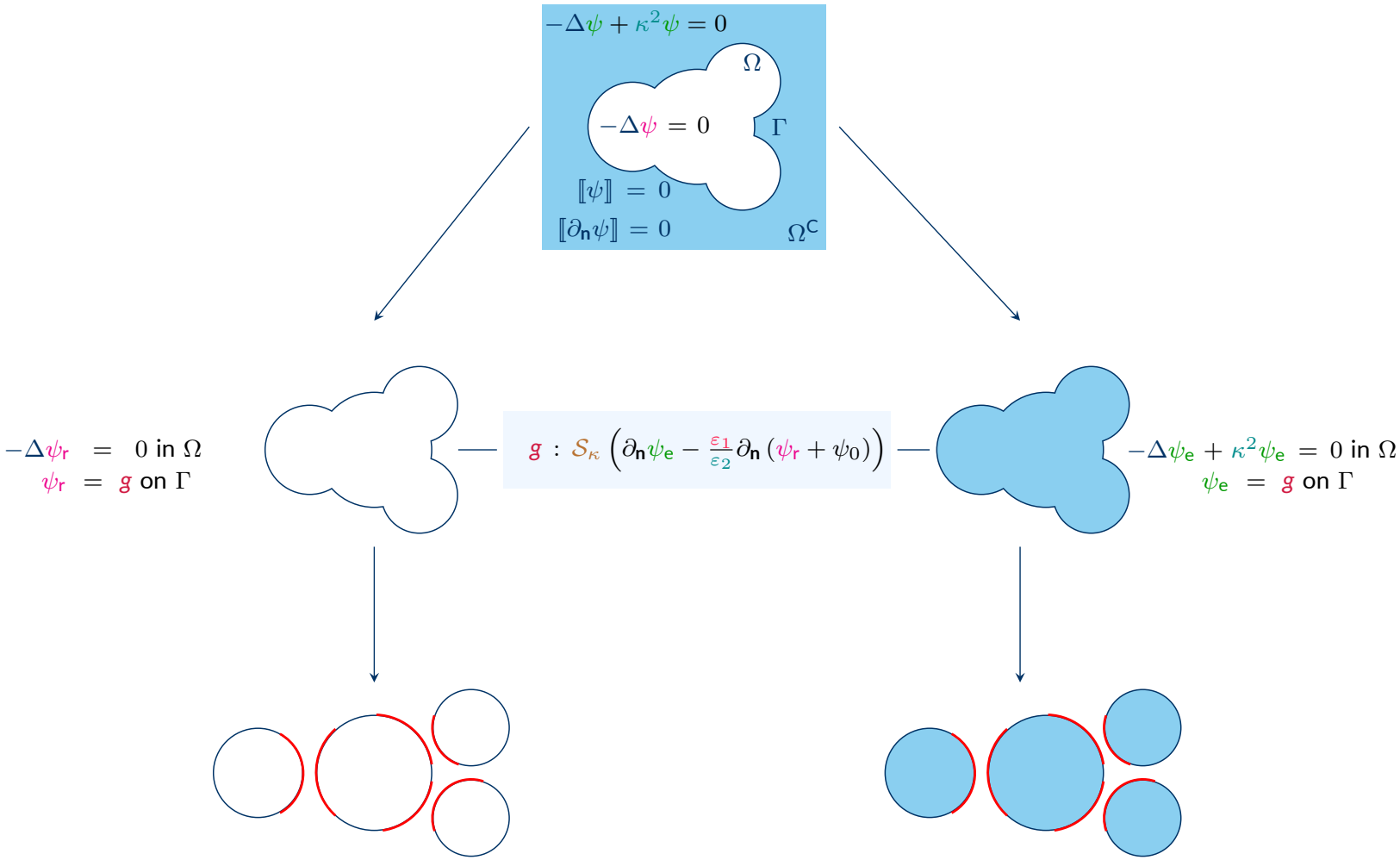


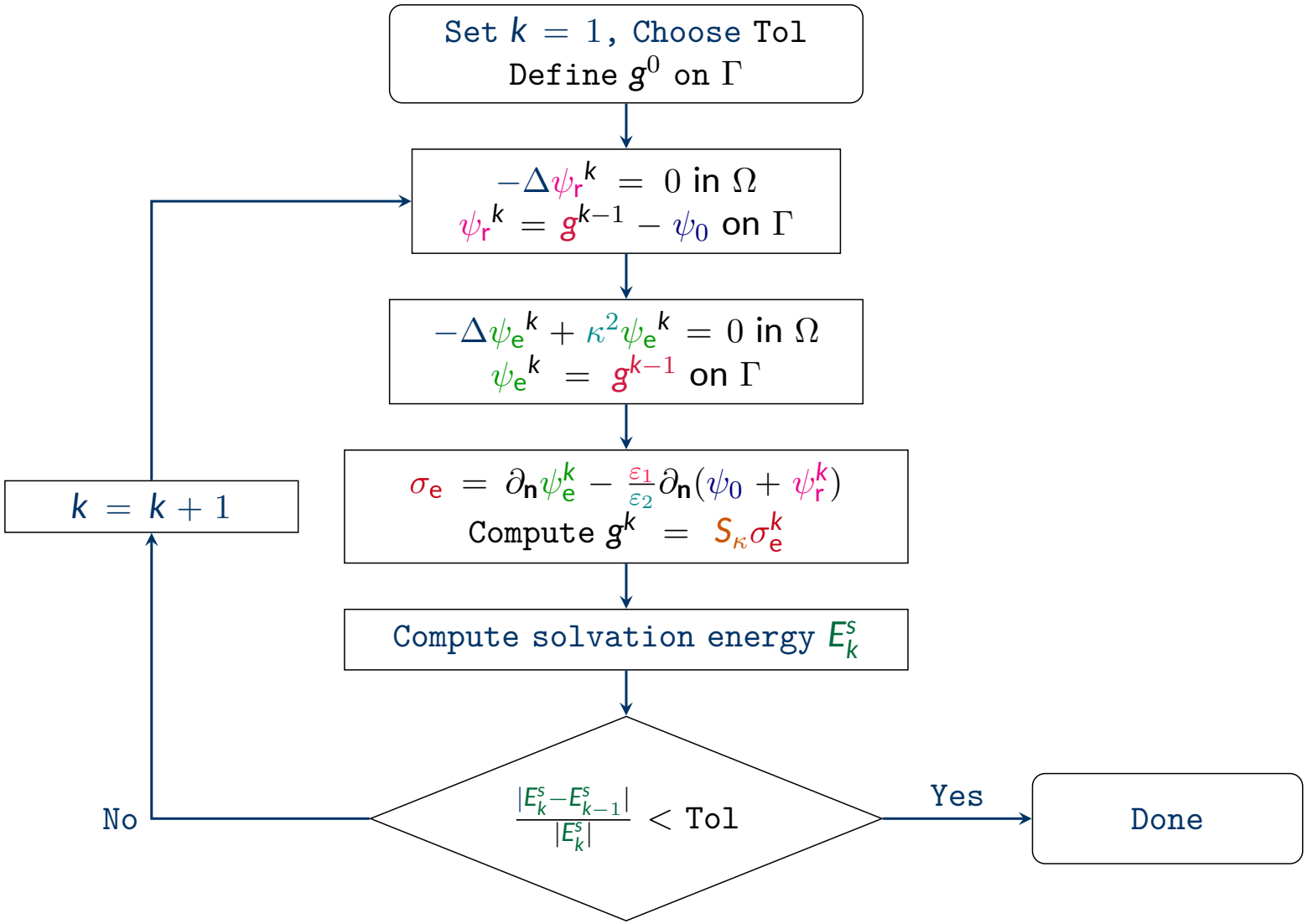
# ddLPB-Method





# Global strategy





- Energy for LPB equations[1]

$$E_s = \frac{1}{2} \langle \psi_r, \rho_M \rangle = \frac{1}{2} \sum_{j=1}^{M} \langle X, Q \rangle_j ,$$

where,

$$[Q]_{j\ell m} = \begin{cases} q_j \delta_{\ell 0} \delta_{m0}, & \text{if } 1 \leq j \leq M, \\ 0 & \text{if } M < j \leq 2M. \end{cases}$$

and

$$\langle X, Q \rangle_j = \sum_i [X]_{ji} [Q]_{ji} .$$

[1] Fogolari, Brigo, Molinari: JMR 15, 2002

# Computation of Forces



- Force with respect to $\lambda$

$$F_\lambda = \nabla^\lambda \left(E_s\right) = \frac{1}{2}\left(\left\langle \nabla^\lambda X, Q\right\rangle + \left\langle X, \nabla^\lambda Q\right\rangle\right) = \frac{1}{2}\left\langle \nabla^\lambda X, Q\right\rangle$$

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- Let $\mathsf{L}X = g$ be the ddLPB system

$$\begin{aligned} \nabla^\lambda \mathsf{L}X + \mathsf{L}\nabla^\lambda X &= \nabla^\lambda g \\ \nabla^\lambda X &= \mathsf{L}^{-1}\left(\nabla^\lambda g - \nabla^\lambda \mathsf{L}X\right). \end{aligned}$$

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- Substituting $\nabla^\lambda X$

$$\begin{aligned} F_\lambda &= \frac{1}{2}\left\langle \mathsf{L}^{-1}\left(\nabla^\lambda g - \nabla^\lambda \mathsf{L}X\right), \mathsf{Q}\right\rangle \\ &= \frac{1}{2}\left\langle \left(\nabla^\lambda g - \nabla^\lambda \mathsf{L}X\right), \left(\mathsf{L}^{-1}\right)^* \mathsf{Q}\right\rangle \\ &= \frac{1}{2}\left\langle \left(\nabla^\lambda g - \nabla^\lambda \mathsf{L}X\right), X_{\text{adj}}\right\rangle \end{aligned}$$

# System of Equations



- Linear System

$$LX = g,$$

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$$\mathbf{L}X = g,$$

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$$\mathbf{L} = \begin{bmatrix} \mathbf{A} & 0 \\ 0 & \mathbf{B} \end{bmatrix} + \begin{bmatrix} \mathbf{C}_1 & \mathbf{C}_2 \\ \mathbf{C}_1 & \mathbf{C}_2 \end{bmatrix}, \quad X = \begin{bmatrix} X_r \\ X_e \end{bmatrix}, \quad \text{and} \quad g = \begin{bmatrix} \mathbf{G}_0 + \mathbf{F}_0 \\ \mathbf{F}_0 \end{bmatrix}$$

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- Using the global strategy

$$\begin{bmatrix} \mathbf{A} & 0 \\ 0 & \mathbf{B} \end{bmatrix} \begin{bmatrix} {X_\mathrm{r}}^k \\ {X_\mathrm{e}}^k \end{bmatrix} = - \begin{bmatrix} \mathbf{C}_1 & \mathbf{C}_2 \\ \mathbf{C}_1 & \mathbf{C}_2 \end{bmatrix} \begin{bmatrix} {X_\mathrm{r}}^{k-1} \\ {X_\mathrm{e}}^{k-1} \end{bmatrix} + \begin{bmatrix} \mathbf{G}_0 + \mathbf{F}_0 \\ \mathbf{F}_0 \end{bmatrix}$$

where

- $k-$ Iteration
- $\mathbf{F}_0-$ Associated with $\partial_\mathbf{n}\psi_0$
- $\mathbf{C}_1-$ Associated with $\partial_\mathbf{n}\psi_\mathrm{r}$
- $\mathbf{C}_2-$ Associated with $\partial_\mathbf{n}\psi_\mathrm{e}$

# System of Equations



- Linear System

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- $\mathbf{A}, \mathbf{B}$ are sparse
- $\mathbf{C}_1, \mathbf{C}_2$ are not sparse

# Numerical Studies



- Comparison of Results
  - Adaptive Poisson-Boltzmann Solver[1]
    - Energy
    - Memory

[1] Jurrus et. al. : Protein Sci. 27 (1), 112-128, 2018

- Comparison of Results
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  - Analytical Forces vs Finite Difference

$$D_h[E_s](\lambda) = \frac{E_s(\lambda + h) - E_s(\lambda)}{h}$$

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$$D_h[E_s](\lambda) = \frac{E_s(\lambda + h) - E_s(\lambda)}{h}$$

    - $\ell^\infty$ error
    - $\ell^2$ error

$$\mathrm{Err}_{j,\alpha}(h) = D_h[E_s](x_{j,\alpha}) - \frac{\partial E_s}{\partial x_{j,\alpha}},$$

with

$$\mathbf{x}_j = (x_{j,1}, x_{j,2}, x_{j,3})^T$$

[1] Jurrus et. al. : Protein Sci. 27 (1), 112-128, 2018

- Constants in the Model
  - $\varepsilon_1 = 1, \varepsilon_2 = 78.54$
  - $\kappa = 0.104$ Å$^{-1}$

[1] ddX: https://github.com/ACoM-Computational-Mathematics/ddX

[2] Berman et. al. : NAR 28, 235-242, 2000

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- Stopping Criteria[1]
  - GMRES Tol$= 10^{-8}$
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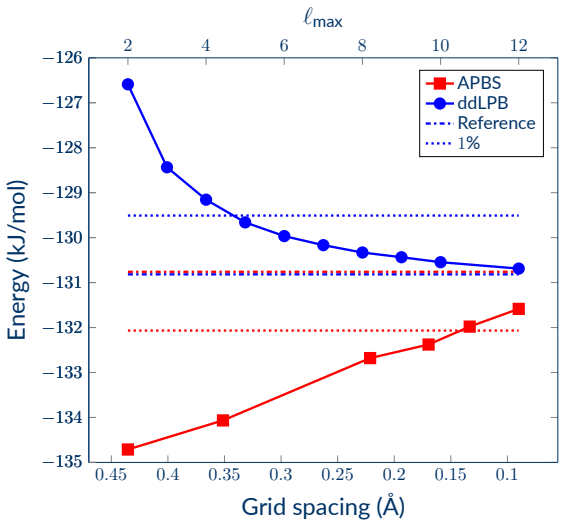
- Test Structure[2]

| PDB Code | M | Name |
|---|---|---|
| 1ay3 | 25 | Nodularin |
| 1etn | 180 | Enterotoxin |
| 1qjt | 9046 | EH1 Domain |

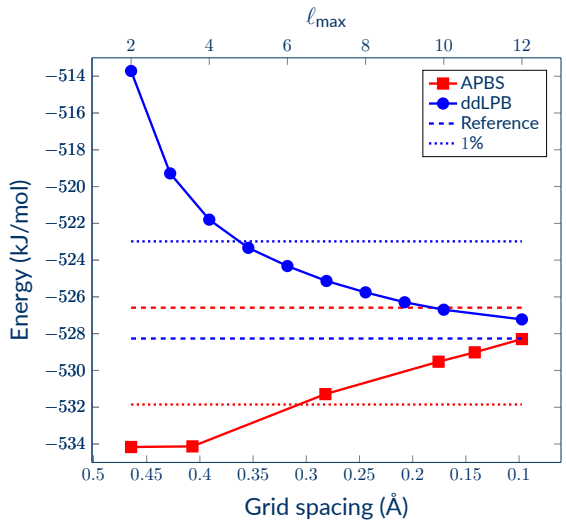
[1] ddX: https://github.com/ACoM-Computational-Mathematics/ddX

[2] Berman et. al. : NAR 28, 235-242, 2000

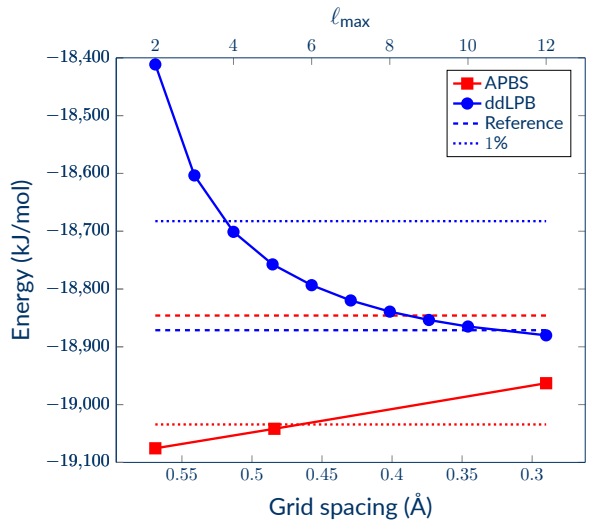
- Energy




**(a)** 1ay3




**(b)** 1etn




**(c)** 1qjt

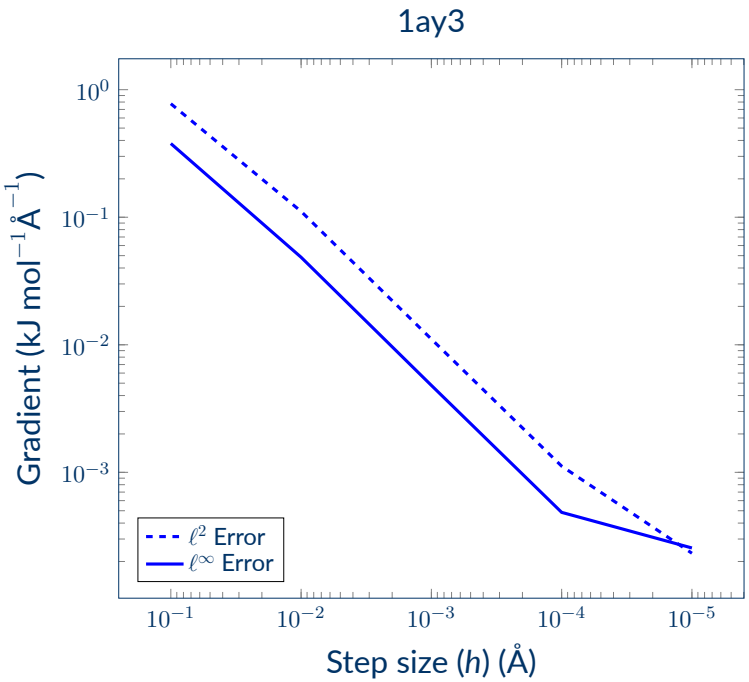
# Numerical Studies

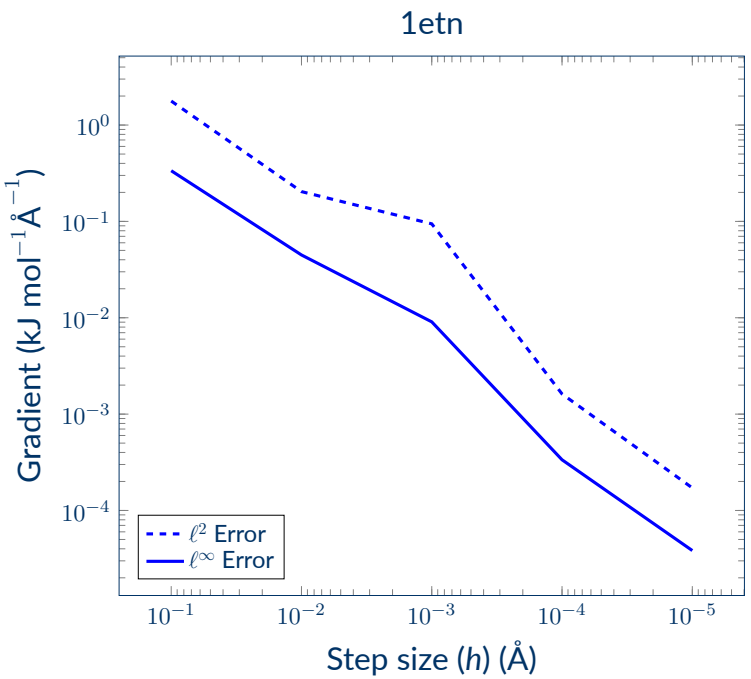


- Memory

| PDB Code | ddLPB | | | | | APBS | | | |
|---|---|---|---|---|---|---|---|---|---|
| | $\ell_{max}$ | Energy (kJ/mol) | Rel. En. | Mem. (GB) | Iter. | $h$ (Å) | Energy (kJ/mol) | Rel. En. | Mem. (GB) |
| 1ay3 (25) | 2 | −126.5891 | 0.0323 | 0.0347 | 5 | 0.4353 | −134.7127 | 0.0302 | 0.0215 |
| | 3 | −128.4347 | 0.0182 | 0.0463 | 6 | 0.0127 | −134.0656 | 0.0253 | 0.0218 |
| | 4 | −129.1554 | 0.0127 | 0.0416 | 6 | 0.2213 | −132.6796 | 0.0147 | 0.0638 |
| | 5 | −129.6607 | 0.0088 | 0.0473 | 6 | 0.1697 | −132.3780 | 0.0124 | 0.1244 |
| | 6 | −129.9653 | 0.0065 | 0.0569 | 6 | 0.1333 | −131.9791 | 0.0093 | 0.2448 |
| | 7 | −130.1668 | 0.0050 | 0.0752 | 6 | 0.0900 | −131.5849 | 0.0063 | 0.7906 |
| | 8 | −130.3308 | 0.0037 | 0.0922 | 6 | | | | |
| | 9 | −130.4356 | 0.0029 | 0.1249 | 6 | | | | |
| | 10 | −130.5462 | 0.0021 | 0.1525 | 6 | | | | |
| | 12 | −130.6886 | 0.0010 | 0.2873 | 6 | | | | |
| 1qjt (9046) | 2 | −18 411.4422 | 0.0244 | 1.2203 | 6 | 0.5690 | −19 075.6126 | 0.0122 | 2.9358 |
| | 3 | −18 603.4737 | 0.0142 | 3.1045 | 8 | 0.4840 | −19 041.8281 | 0.0104 | 4.7910 |
| | 4 | −18 701.0889 | 0.0090 | 6.9332 | 9 | 0.2900 | −18 962.9862 | 0.0062 | 24.8033 |
| | 5 | −18 757.4013 | 0.0060 | 13.7357 | 10 | | | | |
| | 6 | −18 793.3707 | 0.0041 | 24.7674 | 10 | | | | |
| | 7 | −18 819.8066 | 0.0027 | 41.5118 | 11 | | | | |
| | 8 | −18 839.1510 | 0.0017 | 65.6922 | 11 | | | | |
| | 9 | −18 853.5883 | 0.0009 | 99.2852 | 11 | | | | |
| | 10 | −18 864.8898 | 0.0003 | 144.5051 | 11 | | | | |
| | 12 | −18 880.1518 | 0.0005 | 279.6300 | 11 | | | | |

- Analytical Forces vs Finite Difference



# Conclusions and Outlook



- Conclusions[1]
  - Derivation of analytical forces for the ddLPB numerical method using the adjoint method

[1] J.,Nottoli, Quan, Stamm: arXiv : 2203.00552 , 2022

[2] ddX: https://github.com/ACoM-Computational-Mathematics/ddX

[3] Mikhalev,Nottoli, Stamm: chemrxiv : 10.26434 , 2022

[4] Geng,Kransy: JCP, 247, 62-78, 2013

# Conclusions and Outlook



- Conclusions[1]
  - Derivation of analytical forces for the ddLPB numerical method using the adjoint method
  - Implementation of the energy and forces validated by comparing results with APBS[2]

[1] J.,Nottoli, Quan, Stamm: arXiv : 2203.00552 , 2022

[2] ddX: https://github.com/ACoM-Computational-Mathematics/ddX

[3] Mikhalev,Nottoli, Stamm: chemrxiv : 10.26434 , 2022

[4] Geng,Kransy: JCP, 247, 62-78, 2013

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- Outlook
  - FMM implementation for linear scaling[3]
  - Comparison with other software[4]

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