Continuum electrostatics

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Topics

- Polarization in electrostatics
- Continuum electrostatics:
  - Finite difference method, Generalized Born equation, boundary element method
  - Combination with molecular dynamics
- Some special topics:
  - pK_a calculations from Monte Carlo simulation and continuum electrostatics
  - 2D Lekner summation technique in membrane affinity calculations

Energy and forces of a collection of charges

Amount of work required to assemble a charge distribution (from infinity)

$$\varphi_i(\boldsymbol{r}_i) = \sum_j \frac{q_j}{4\pi\epsilon_0 |\boldsymbol{r}_i - \boldsymbol{r}_j|}$$

$$W_N(\boldsymbol{r}_1, \boldsymbol{r}_2, \ldots, \boldsymbol{r}_N) = \sum_{i<j} \frac{q_j q_i}{4\pi\epsilon_0 |\boldsymbol{r}_i - \boldsymbol{r}_j|} = \frac{1}{2}\sum_i q_i \varphi(\boldsymbol{r}_i)$$

$$\boldsymbol{F}_i(\boldsymbol{r}_i) = q_i \sum_j \frac{q_j(\boldsymbol{r}_i - \boldsymbol{r}_j)}{4\pi\epsilon_0 |\boldsymbol{r}_i - \boldsymbol{r}_j|^3}$$

Total electrostatic potential at $\mathbf{r}_i$

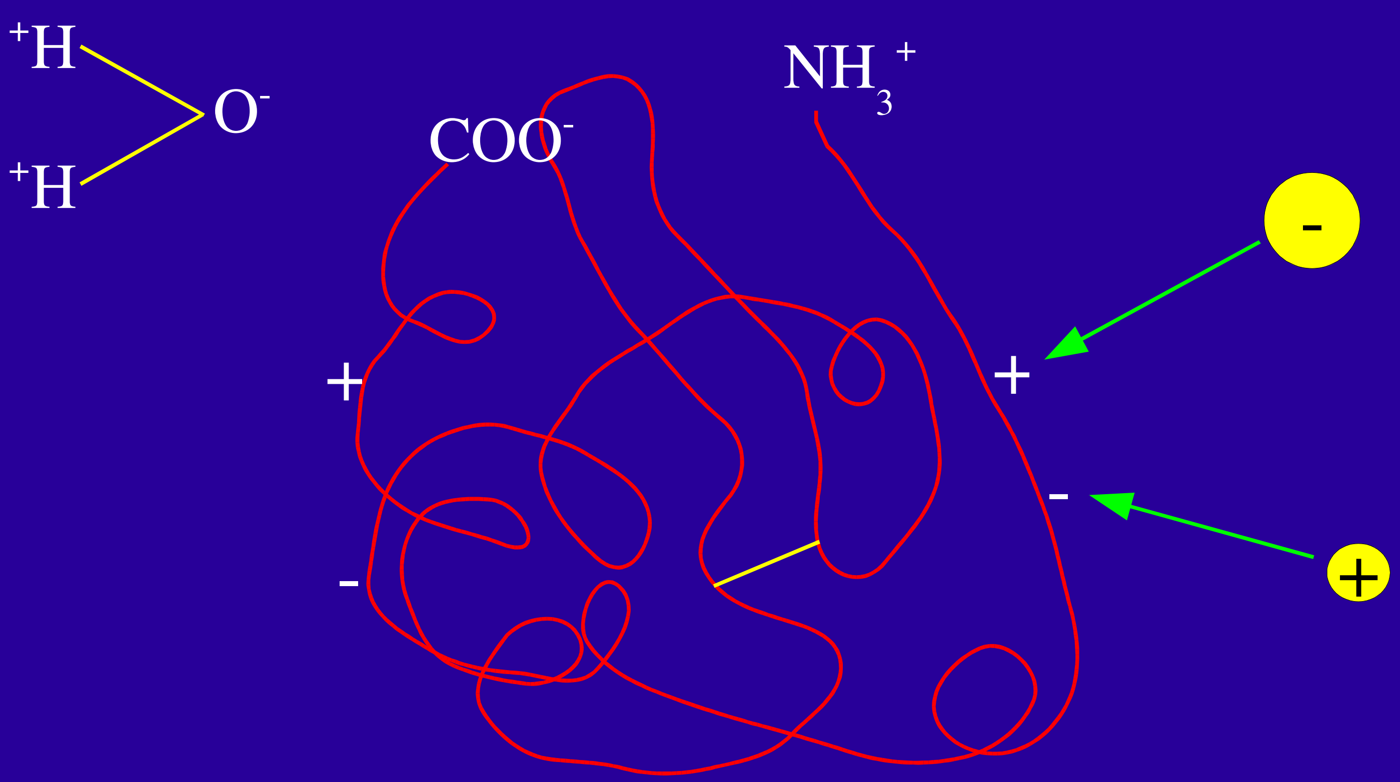
Computation of electrostatic interactions

- Problem: interactions are long-ranged
- Standard cutoff approaches will not work
- Requires special techniques:
  - Summation techniques: Ewald, Particle Mesh, Lekner, etc.
  - Continuum electrostatics

Protein charge distribution

- Charged groups:
  - Lys (+), Arg (+), Glu (-), Asp (-), ...
  - Cterm (-), Nterm (+)
- Polar groups:
  - Ser (OH), Tyr (OH), peptide-bond, ...
  - His (imodazol group), Cys (SH), ...
- Titrating sites may change their protonation state (charge distribution) as a function of the p*H*.
- Asymmetric molecular charge distribution

Protein in solvent



p*H* effects

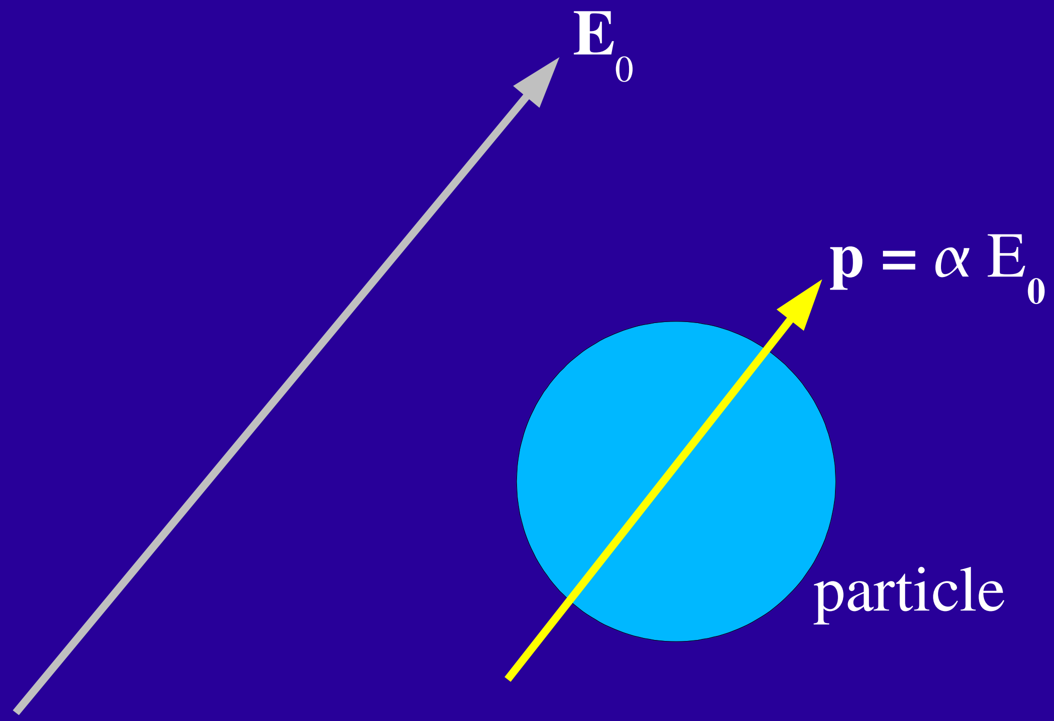
Polarization

- Response of material to external possibly time-dependent electric fields
- Solvent polarization:
  - Solvent reorientation (orientation polarization)
  - Ion redistribution (added ionic strength, 0.15 M)
  - Electronic polarization (redistribution of electron density in atoms and molecules):
    - Induced dipoles, quadrupoles, etc.
- Solute polarization:
  - Electronic polarization
  - Reorientation of groups.

Molecular dynamics and polarization

- Includes contributions to polarization to some degree, except for:
  - Electronic polarization
  - Ion redistribution:
    - Time scale issue ↔ statistics

Electronic polarization



$\mathbf{E}_0$: 'External' field due to external sources (external with respect to particle)

p : Induced dipole moment : measure for distortion of electron cloud

α : polarizability : tensorial quantity, frequently assumed to be a scalar

Collection of polarizable particles

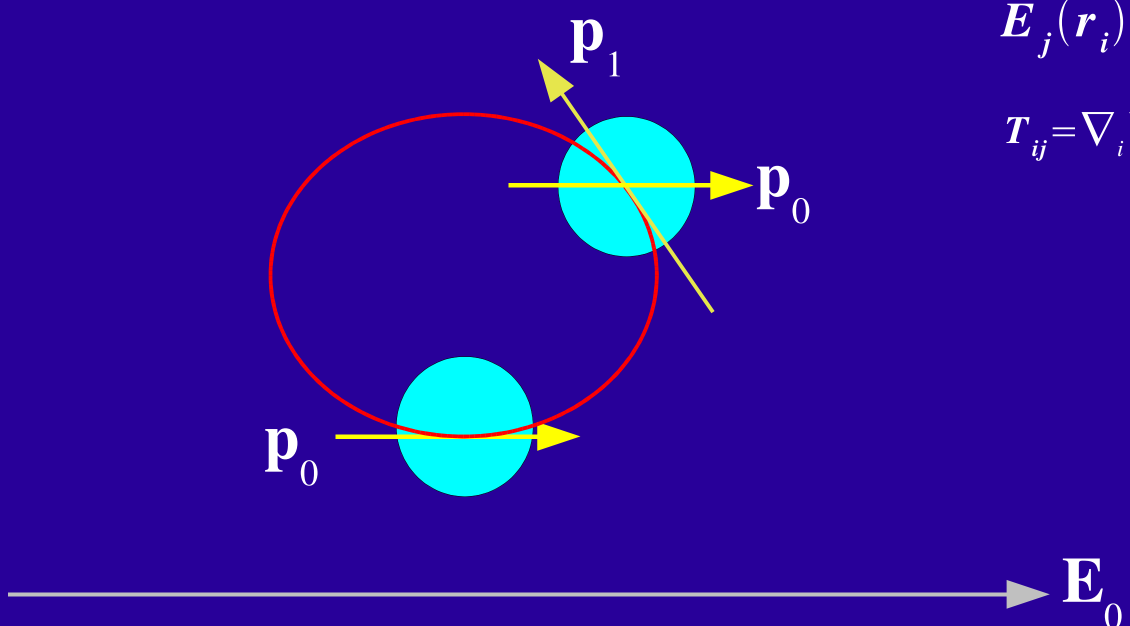
$$\boldsymbol{p}_i = \alpha_i \boldsymbol{E}(\boldsymbol{r}_i) = \alpha_i \left(\boldsymbol{E}_0 + \sum_{i \neq j} \boldsymbol{E}_j(\boldsymbol{r}_i)\right)$$

Total electric field

Electric field of dipole

$$\boldsymbol{E}_j(\boldsymbol{r}_i) = -\boldsymbol{T}_{ij} \boldsymbol{p}_j$$

$$\boldsymbol{T}_{ij} = \nabla_i \nabla_i \frac{1}{|\boldsymbol{r}_i - \boldsymbol{r}_j|}$$



Collection of polarizable waters

- External field is due to sources (permanent charges, dipoles, etc) on other molecules
- Dipole – dipole interactions within and between molecules

$$\boldsymbol{p}_i = \alpha_i \boldsymbol{E}(\boldsymbol{r}_i) = \alpha_i \left(\boldsymbol{E}_0 + \sum_{i \neq j} \boldsymbol{E}_j(\boldsymbol{r}_i) \right)$$

Numerical calculation

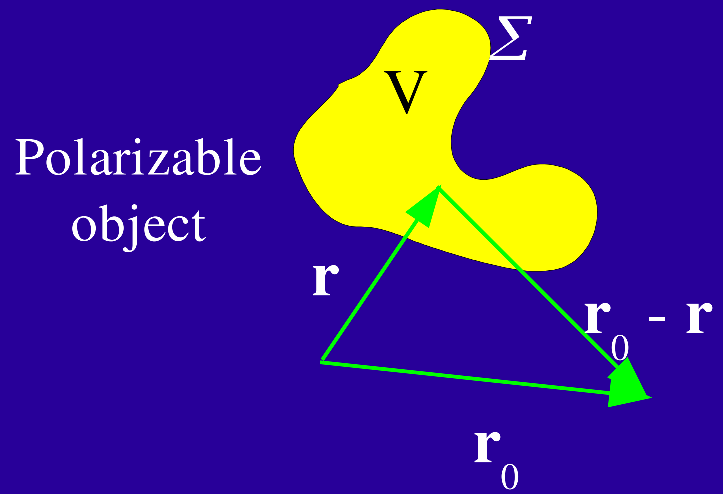
$$\boldsymbol{p}_i = \alpha_i \boldsymbol{E}(\boldsymbol{r}_i) = \alpha_i (\boldsymbol{E}_{\mathbf{0}} - \sum_{i \neq j} \boldsymbol{T}_{ij} \boldsymbol{p}_j) \rightarrow \alpha^{-1}(\mathbf{1} + \alpha \boldsymbol{T}) \boldsymbol{p} = \boldsymbol{E}_{\mathbf{0}}$$

- Vector – matrix equation: $\mathbf{Ap}=\mathbf{E}_0 \Leftrightarrow \mathbf{p}=\mathbf{A}^{-1}\mathbf{E}_{0:}$
  - Dimension **A** is $3N \times 3N$, if N number of polarizabilities
- Self consistent solution to be obtained by direct methods (e.g. LU decomposition) or iterative procedures.
- Energy W:
  - $\varphi(\mathbf{r}_i)$: Total potential: sum of external potentials and potentials due to induced dipoles

$$W = \frac{1}{2} \sum_i q_i \varphi(\boldsymbol{r}_i)$$

$$\varphi(\boldsymbol{r}_{\mathbf{0}}) = \frac{1}{4\pi\epsilon_0} \sum_i \frac{q_i}{|\boldsymbol{r}_{\mathbf{0}} - \boldsymbol{r}_i|} + \frac{1}{4\pi\epsilon_0} \sum_j \frac{\boldsymbol{p}_j(\boldsymbol{r}) \cdot \boldsymbol{r}}{|\boldsymbol{r}_{\mathbf{0}} - \boldsymbol{r}_j|^3}$$

Potential of a macroscopic polarizable object



Collection of induced dipoles →

Dipole density or Polarization **P**

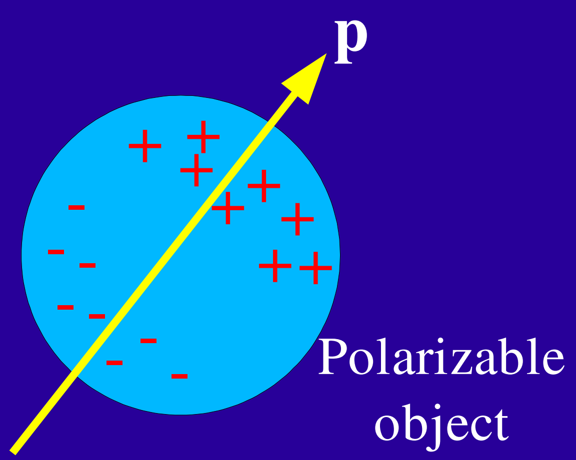
P generally includes all types of polarization

$$\varphi(\boldsymbol{r}_0)=\frac{1}{4\pi\epsilon_0}\int_V\frac{\boldsymbol{P}(\boldsymbol{r})\cdot\boldsymbol{r}}{|\boldsymbol{r}_0-\boldsymbol{r}|^3}d\tau=\frac{1}{4\pi\epsilon_0}\int_\Sigma\frac{\boldsymbol{P}(\boldsymbol{r})\cdot\boldsymbol{n}}{|\boldsymbol{r}_0-\boldsymbol{r}|}d\sigma+\frac{1}{4\pi\epsilon_0}\int_V\frac{\nabla\cdot\boldsymbol{P}(\boldsymbol{r})}{|\boldsymbol{r}_0-\boldsymbol{r}|}d\sigma$$

$$\varphi(\boldsymbol{r}_0)=\frac{1}{4\pi\epsilon_0}\int_\Sigma\frac{\sigma_b(\boldsymbol{r})}{|\boldsymbol{r}_0-\boldsymbol{r}|}d\sigma+\frac{1}{4\pi\epsilon_0}\int_V\frac{\rho_b(\boldsymbol{r})}{|\boldsymbol{r}_0-\boldsymbol{r}|}d\sigma$$

Bound charges: $\sigma_b(\boldsymbol{r})=\boldsymbol{P}(\boldsymbol{r})\cdot\boldsymbol{n}$ $\quad\rho_b(\boldsymbol{r})=\nabla\cdot\boldsymbol{P}(\boldsymbol{r})$

Interpretation of bound charges



$$\rho(\boldsymbol{r}) = \rho_f(\boldsymbol{r}) + \rho_b(\boldsymbol{r})$$

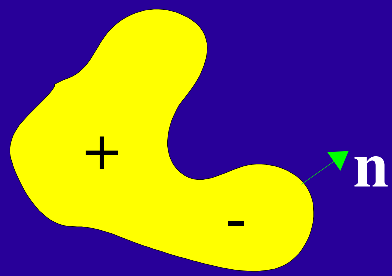
Total charge density / distribution

Free charge density

Bound / polarization / induced charge density:
- “difference” density: reflects change in charge density
- volume and surface charge density

Gauss' Law in polarizable media

Polarizable object



$$\epsilon_0 \int_{\Sigma} \boldsymbol{E}(\boldsymbol{r}) \cdot \boldsymbol{n} = Q_{encl} \qquad \epsilon_0 \nabla \cdot \boldsymbol{E}(\boldsymbol{r}) = \rho(\boldsymbol{r})$$

No external field: $\epsilon_0 \nabla \cdot \boldsymbol{E}(\boldsymbol{r}) = \rho_f(\boldsymbol{r})$

With external field: $\epsilon_0 \nabla \cdot \boldsymbol{E}(\boldsymbol{r}) = \rho_f(\boldsymbol{r}) + \rho_b(\boldsymbol{r}) = \rho_f(\boldsymbol{r}) - \nabla \cdot P(\boldsymbol{r})$

Define: $\boldsymbol{D} = \epsilon_0 \boldsymbol{E} + \boldsymbol{P}$

$$\nabla \cdot \boldsymbol{D}(\boldsymbol{r}) = \rho_f$$

Linear dielectric media

Linear response, if total field is weak and fairly constant in space and time:

$$\boldsymbol{P}(\boldsymbol{r}) = \epsilon_0 \chi_e \boldsymbol{E}(\boldsymbol{r})$$

$$\boldsymbol{D}(\boldsymbol{r}) = \epsilon_0 \boldsymbol{E}(\boldsymbol{r}) + \boldsymbol{P}(\boldsymbol{r}) = \epsilon_0 (1 + \chi_e) \boldsymbol{E}(\boldsymbol{r}) = \epsilon_0 \epsilon \boldsymbol{E}(\boldsymbol{r})$$

χ_e: Electric susceptibility of the medium (no units, usually positive): describes macroscopic response of medium.

ϵ: Dielectric constant / relative permittivity.

$$\rho_b = -\nabla \cdot \boldsymbol{P} = -\frac{\epsilon - 1}{\epsilon} \rho_f$$

Linear dielectric media

$$\nabla \cdot \boldsymbol{D}(\boldsymbol{r}) = \epsilon_0 \epsilon \nabla \cdot \boldsymbol{E}(\boldsymbol{r}) = \rho_f(\boldsymbol{r})$$

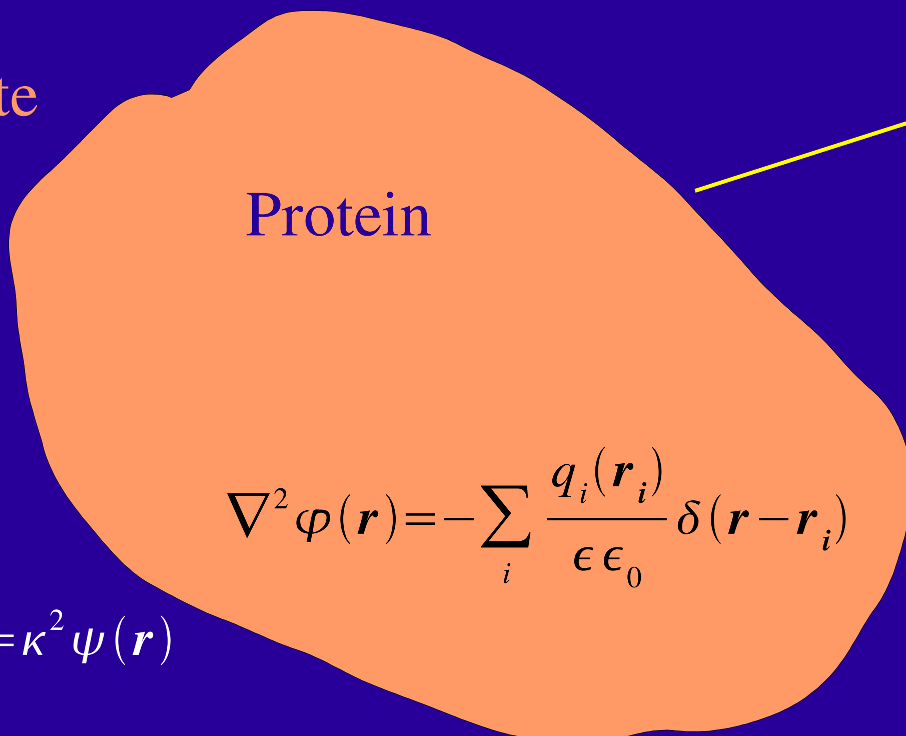
$$\boldsymbol{E}(\boldsymbol{r}) = -\nabla \varphi(\boldsymbol{r})$$

Poisson equation: $$\nabla^2 \varphi(\boldsymbol{r}) = -\frac{\rho_f(\boldsymbol{r})}{\epsilon \epsilon_0}$$

Starting equation for continuum electrostatics

Polarizable protein in polarizable electrolyte solution

Electrolyte



Dielectric boundary

$$\varphi(\boldsymbol{r}) = \psi(\boldsymbol{r})$$

$$\frac{\partial \varphi(\boldsymbol{r})}{\partial n} = \frac{\epsilon_P}{\epsilon_S} \frac{\partial \psi(\boldsymbol{r})}{\partial n}$$

$$\nabla^2 \varphi(\boldsymbol{r}) = -\sum_i \frac{q_i(\boldsymbol{r}_i)}{\epsilon \epsilon_0} \delta(\boldsymbol{r} - \boldsymbol{r}_i)$$

$$\nabla^2 \psi(\boldsymbol{r}) = \kappa^2 \psi(\boldsymbol{r})$$

Poisson-Boltzmann equation

κ : Inverse Debye Length $\kappa(\epsilon_S, I)$

Electrostatic energy and forces:

$$W(\{\boldsymbol{r}_i\}) = \frac{1}{2} \sum_i q_i \varphi(\boldsymbol{r}_i)$$

$$F_{el,i}(\boldsymbol{r}_i) = -\nabla_i W(\{\boldsymbol{r}_i\})$$

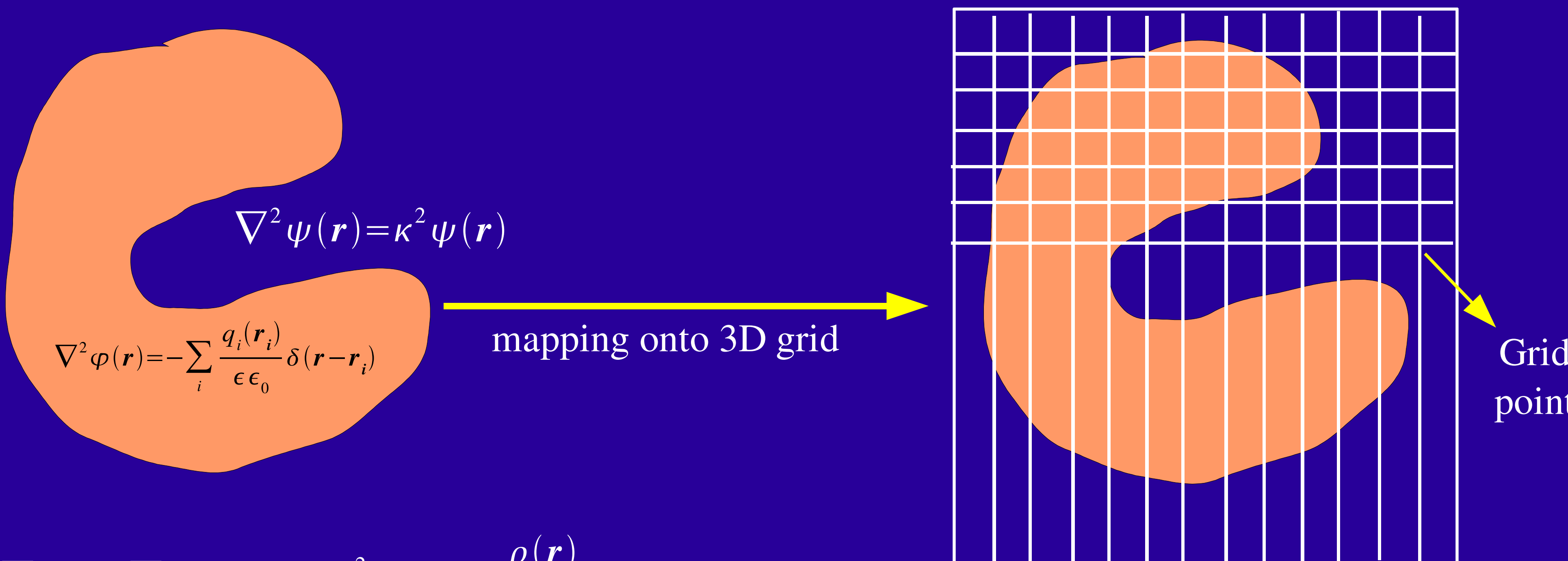
Dielectric constant of a protein

- Between 4 to 30, according to
  - Molecular dynamics simulations
  - pK_a calculations
- Describes polarization of protein due to the presence of a polarizable solvent:
  - Charge distribution itself already contains in an average way polarization effects of bringing atoms together

Numerical solutions

- Finite difference method
- Generalized Born equation
- Boundary element method
- Finite element method
- ....

Finite Difference Method

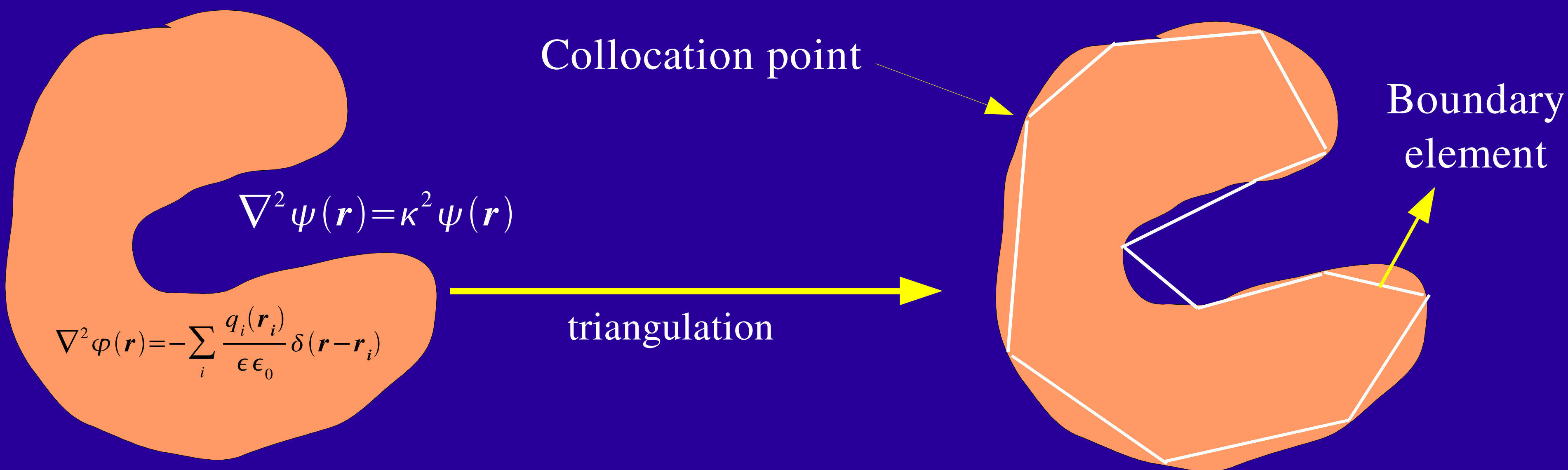


$$\nabla \cdot [\epsilon(\boldsymbol{r}) \nabla \varphi(\boldsymbol{r})] - \kappa(\boldsymbol{r})^2 \varphi(\boldsymbol{r}) = -\frac{\rho(\boldsymbol{r})}{\epsilon_0}$$

$$\varphi_j = \frac{\sum_{i=1}^{6} \epsilon_i \varphi_i + \frac{Q_i}{\epsilon_0 h}}{\sum_{i=1}^{6} \epsilon_i + \bar{\kappa}_j^2 h^2} \qquad \bar{\kappa} = \epsilon^{\frac{1}{2}} \kappa$$

- Charges have to be mapped onto the grid
- Regularity conditions are not exactly satisfied
- Forces / fields more difficult to compute

Boundary element method



$$\boldsymbol{E}(\boldsymbol{r}_i) = -\nabla_i \varphi(\boldsymbol{r}_i)$$

$$\varphi(\boldsymbol{r}_i) = \int_\Sigma \left(L_1(\boldsymbol{r}, \boldsymbol{r}_i)\varphi(\boldsymbol{r}) + L_2(\boldsymbol{r}, \boldsymbol{r}_i)\frac{\partial \varphi(\boldsymbol{r})}{\partial n}\right) d\sigma + \sum_{j \neq i} \frac{q_j}{\epsilon_0 \epsilon_P} \frac{1}{4\pi |\boldsymbol{r}_j - \boldsymbol{r}_i|} \longrightarrow \varphi = \boldsymbol{R}\boldsymbol{x} + \boldsymbol{D}$$

$$\frac{1}{2}\left(1 + \frac{\epsilon_S}{\epsilon_P}\right)\varphi(\boldsymbol{r}_0) = \int_\Sigma \left(L_1(\boldsymbol{r}, \boldsymbol{r}_0)\varphi(\boldsymbol{r}) + L_2(\boldsymbol{r}, \boldsymbol{r}_0)\frac{\partial \varphi(\boldsymbol{r})}{\partial n}\right) d\sigma + \sum_i \frac{q_i}{\epsilon_0 \epsilon_P} \frac{1}{4\pi |\boldsymbol{r}_i - \boldsymbol{r}_0|}$$

$$\frac{1}{2}\left(1 - \frac{\epsilon_P}{\epsilon_S}\right)\frac{\partial \varphi(\boldsymbol{r}_0)}{\partial n_0} = \int_\Sigma \left(L_3(\boldsymbol{r}, \boldsymbol{r}_0)\varphi(\boldsymbol{r}) + L_4(\boldsymbol{r}, \boldsymbol{r}_0)\frac{\partial \varphi(\boldsymbol{r})}{\partial n}\right) d\sigma + \sum_i \frac{q_i}{\epsilon_0 \epsilon_P} \frac{(\boldsymbol{r}_i - \boldsymbol{r}_0)\cdot n_0}{4\pi |\boldsymbol{r}_i - \boldsymbol{r}_0|^3}$$

$$\longrightarrow \boldsymbol{A}\boldsymbol{x} = \boldsymbol{b}$$

Generalized Born equation

$$W = \frac{1}{2}\sum_i q_i \varphi(\boldsymbol{r}) = \frac{1}{2}\sum_{i,j} \frac{q_i q_j}{\epsilon_0} g(\boldsymbol{r}_i, \boldsymbol{r}_j)$$

$g(\mathbf{r}_i, \mathbf{r}_j)$: 'Green Function'

$$g(\boldsymbol{r}_i, \boldsymbol{r}_j) = \frac{1}{4\pi r_{ij}} + \Delta g(\boldsymbol{r}_i, \boldsymbol{r}_j) \rightarrow \frac{1}{4\pi \epsilon r_{ij}}$$

(in homogeneous system)

Generalized Born attempts to construct simple analytical approximations to Δg

$$\Delta g_{GB}(\boldsymbol{r}_i, \boldsymbol{r}_j) = \left(\frac{1}{\epsilon_w} - 1\right)\left(r_{ij}^2 + R_{ij}^2 \exp\left(-\frac{1}{A R_{ij}^2}\right)\right)^{-\frac{1}{2}}$$

A, R_{ij} : parameters of the model

Continuum electrostatic and MD

- Combination with MD is 'easy'
- Attractive: considerable reduction of number of degrees of freedom:
  - Long time simulation possible
- Usually is mixing two extreme levels of descriptions:
  - Protein : full detail
  - Solvent : no detail at all (full continuum)