Lecture 10: Geometric Modeling and Visualization

Integrals & Integral Equations:
Molecular Energetics & Forces

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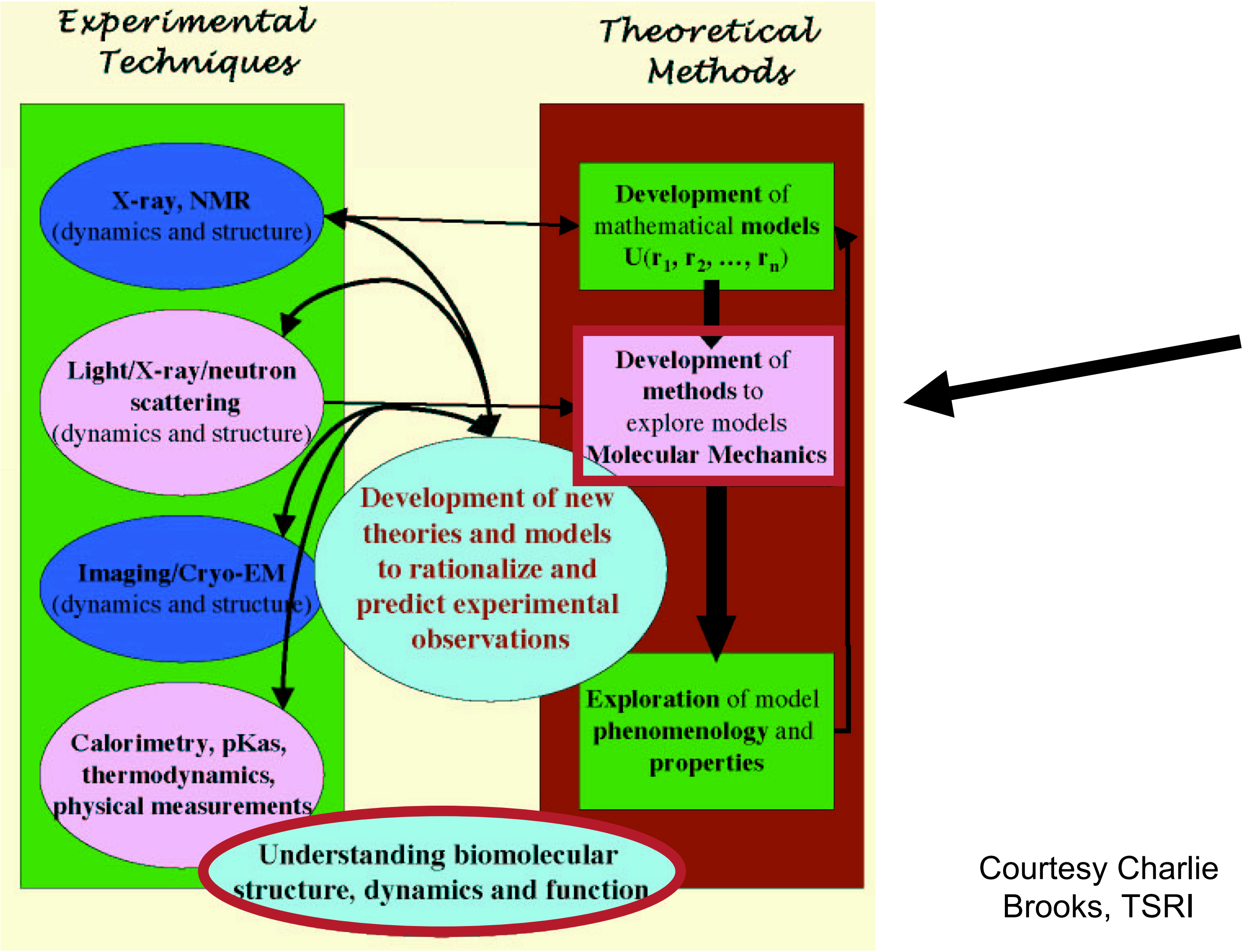
Molecular Mechanics and Modeling



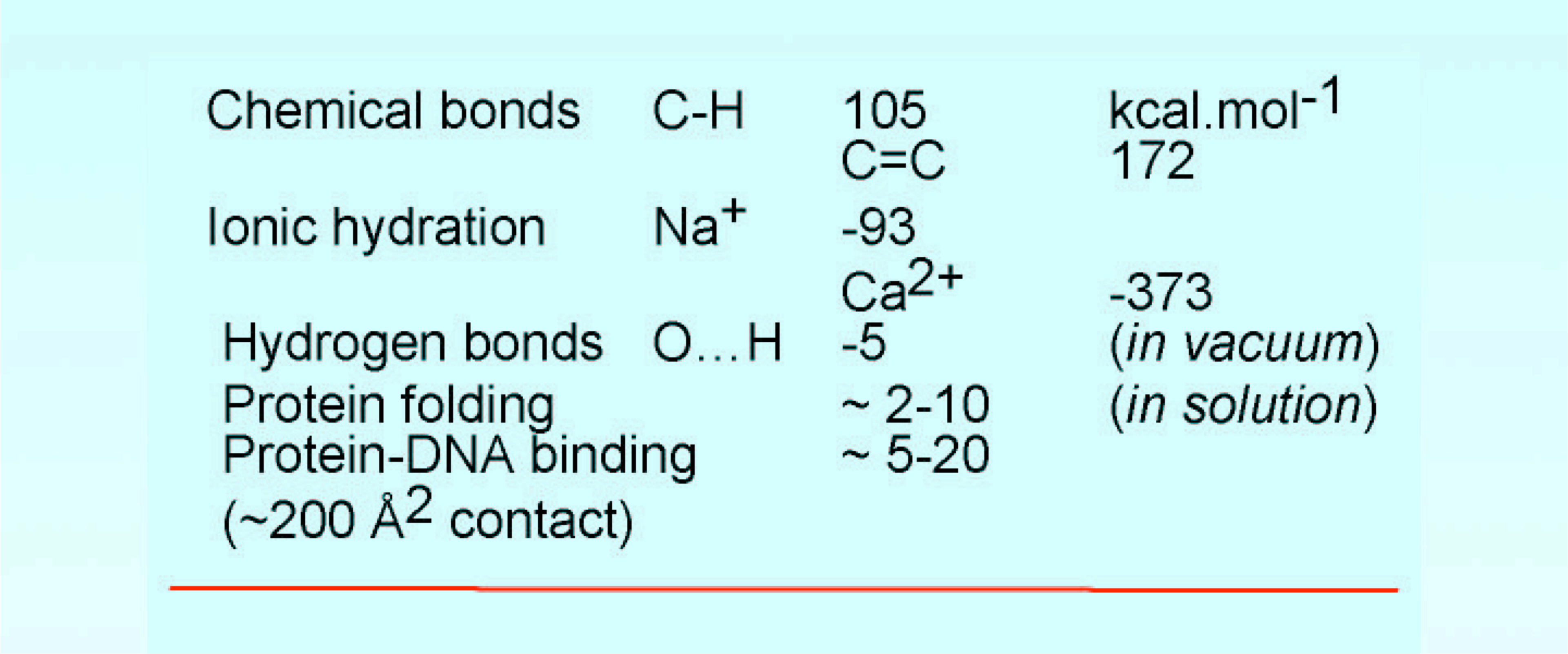
Courtesy Charlie Brooks, TSRI

Biological Time scale

Bond vibrations	1 fs	(10^{-15} s)
Sugar repuckering	1 ps	(10^{-12} s)
DNA bending	1 ns	(10^{-9} s)
Domain movement	1 ms	(10^{-6} s)
Base pair opening	1 ms	(10^{-3} s)
Transcription	2.5 ms / nucleotide	
Protein synthesis	6.5 ms / amino acid	
Protein folding	~ 10 s	
RNA lifetime	~ 300 s	

Courtesy David Case, TSRI

Biological energy scale



Chemical bonds	C-H	105	kcal.mol^{-1}
		C=C	172
Ionic hydration	Na^{+}	-93	
		Ca^{2+}	-373
Hydrogen bonds	O…H	-5	(*in vacuum*)
Protein folding		~ 2-10	(*in solution*)
Protein-DNA binding		~ 5-20	
(~200 Å^{2} contact)			

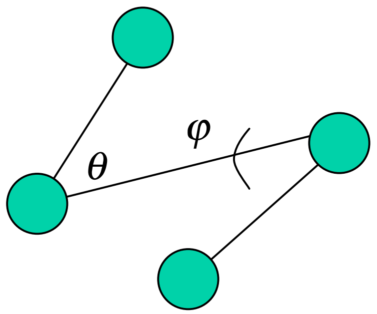
Courtesy David Case, TSRI

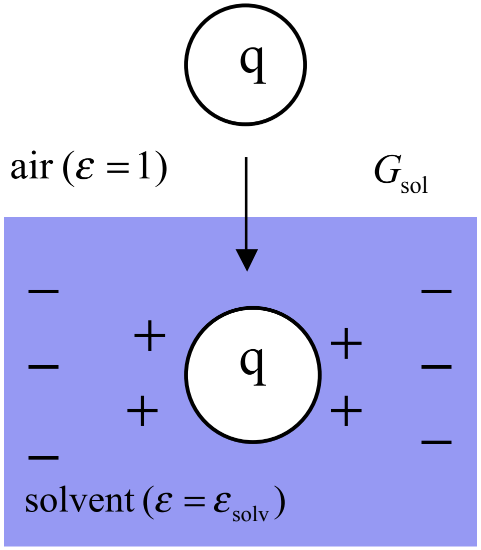
Free Energy of a Macromolecule in Solvent

Total free energy : $G = \boxed{E_{MM}} + \boxed{G_{\text{sol}}} - TS$

$$E = E_b + E_\theta + E_\varphi + E_{vdw} + E_{elec}$$

$$G_{\text{sol}} = G_{\text{cav}} + G_{\text{vdw}} + \boxed{G_{\text{pol}}}$$



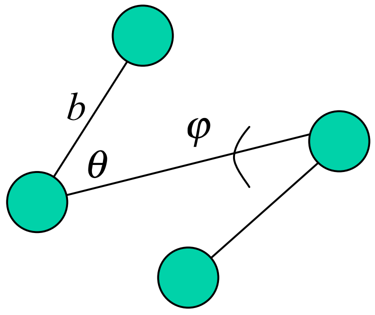


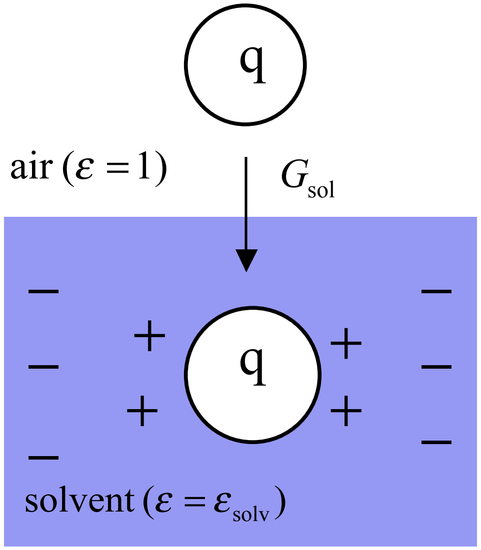
Free Energy of a Single Molecule in Solvent

Total free energy : $G = \boxed{E_{MM}} + \boxed{G_{\text{sol}}} - TS$

$$E_{MM} = \underbrace{E_b + E_\theta + E_\varphi}_{\text{bonded}} + \underbrace{E_{vdw}}_{\text{non-bonded}} + E_{elec}$$

$$\boxed{G_{\text{sol}}} = G_{\text{cav}} + G_{\text{vdw}} + G_{\text{pol}}$$





Free Energy of a Single Molecule in Solvent

- bonded

$$\begin{cases} E_b = \sum_b k_b (r_b - r_b^0)^2 \\ E_\theta = \sum_a k_a (\theta_a - \theta_a^0)^2 \\ E_\varphi = \sum_t k_t (1 + \cos n(\varphi_t - \varphi_t^0)) \end{cases}$$

r, r_0 : covalent bond and minima

θ, θ_0: valence angle and minima

φ, φ_0: torsion and minima

- non-bonded

$$\begin{cases} E_{vdw} = \sum_{i<j} \frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{6}} \\ E_{elec} = \sum_{i<j} \frac{q_i q_j}{r_{ij}} \end{cases}$$

C, D : Lennard-Jones parameters

r_{ij} : distance between atoms

q : atomic charge

- $G_{\mathrm{cav}} + G_{\mathrm{vdw}} = \gamma S$ γ, S : surface tension and surface area

Binding Energy of Macromolecules

In structure based drug design, binding of a drug (ligand) to a receptor (protein/nucleic acid), usually causes the ligand to either enhance or inhibit the activity of the receptor.

Binding energy:

$$\Delta G_{\text{bind}} = G_{\text{protein+ligand}} - (G_{\text{protein}} + G_{\text{ligand}})$$

Variation of binding energy:

$$\Delta\Delta G_{\text{bind}} = \Delta G_{\text{bind}}^{\text{wildtype}} - \Delta G_{\text{bind}}^{\text{mutant}}$$

receptor protein

ligand

How to Compute G_{pol} ?

$$G_{\text{pol}} = \frac{1}{2}\int [\phi_{\text{solvent}}(\mathbf{r}) - \phi_{\text{air}}(\mathbf{r})]\rho(\mathbf{r})\,dV$$

ε	dielectric constant
ϕ	electrostatic potential
ρ	solute charge density
λ	ion accessibility parameter
c_j^∞	ion bulk concentration
q_j	ion charge
k_B	Boltzmann's constant
T	temperature

- Poisson-Boltzmann (PB) Theory

$$-\nabla\cdot[\varepsilon(\mathbf{r})\nabla\phi(\mathbf{r})] = 4\pi\rho(\mathbf{r}) + 4\pi\lambda(\mathbf{r})\sum_{j=1} c_j^\infty q_j \exp(-q_j\phi(\mathbf{r})/k_B T)$$

finite difference, finite element

- Generalized Born (GB) Theory
  - Born formula (Born 1920)
    generalized Born formula (Still 1990)
  - methods to compute the Born radii:
    - pairwise summation : fast but not easy for force calculation
    - analytic, nFFT, and higher order quadrature [Bajaj, Zhao 2006]

$$R_i^{-1} = \frac{1}{4\pi}\int_\Gamma \frac{(\mathbf{r}-\mathbf{x}_i)\cdot\mathbf{n}(\mathbf{r})}{|\mathbf{r}-\mathbf{x}_i|^4}\,dS$$

GB Theory

Born formula: (single ion)

$$G_{\mathrm{pol}} = -(1-\frac{1}{\varepsilon})\frac{q^2}{2a}$$

ε	dielectric constant
a	atomic radius
q	atomic charge

Generalized Born formula: (molecule)

$$G_{\mathrm{pol}} = -\frac{\tau}{2}\sum_{ij}\frac{q_i q_j}{[r_{ij}^2 + R_i R_j \exp(-\frac{r_{ij}^2}{4R_i R_j})]^{\frac{1}{2}}}$$

$$\tau = 1 - \frac{1}{\varepsilon_{\mathrm{solv}}}$$

r_{ij} : distance between atom i and j

q_i : charge of atom i

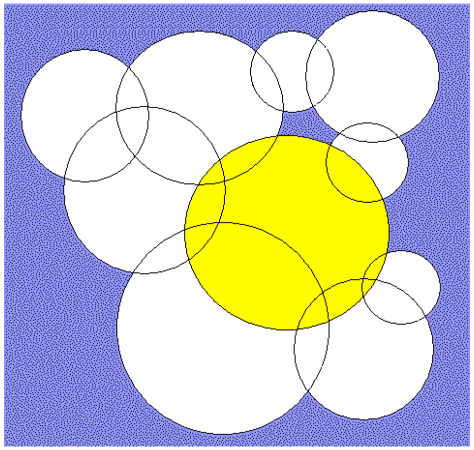
R_i : effective Born radius of atom i

W. C. Still et al., JACS (1990), 112, 6127-6129

Calculation of Born Radius

A single charge q_i located at the center of atom i in the molecule.

$$G_{\mathrm{pol}} = -\frac{\tau}{2}\frac{q_i^2}{R_i}$$ (by GB)



On the other hand, by approximating the electric field as the Columbic field,

$$G_{\mathrm{pol}} = -\tfrac{1}{8\pi}\tau\int_{\mathrm{ex}}\frac{q_i^{\,2}}{|\mathbf{r}-\mathbf{x}_i|^4}\,dV$$

Therefore $$R_i^{-1} = \frac{1}{4\pi}\int_{\mathrm{ex}}\frac{1}{|\mathbf{r}-\mathbf{x}_i|^4}\,dV$$

ex: exterior of the molecule

via Gauss' Divergence Thm

$$R_i^{-1} = \frac{1}{4\pi}\int_{\Gamma}\frac{(\mathbf{r}-\mathbf{x}_i)\cdot\mathbf{n}(\mathbf{r})}{|\mathbf{r}-\mathbf{x}_i|^4}\,dS$$

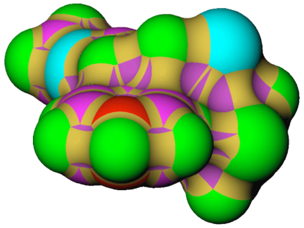
Γ : molecular surface

Fast Computation of Born Radii

$$R_i^{-1} = \frac{1}{4\pi}\int_\Gamma \frac{(\mathbf{r}-\mathbf{x}_i)\cdot\mathbf{n}(\mathbf{r})}{|\mathbf{r}-\mathbf{x}_i|^4}\,dS \approx \frac{1}{4\pi}\sum_{k=1}^{N} w_k \frac{(\mathbf{r}_k-\mathbf{x}_i)\cdot\mathbf{n}(\mathbf{r}_k)}{|\mathbf{r}_k-\mathbf{x}_i|^4}, \qquad \mathbf{r}_k \in \Gamma$$

Algorithm:

1. Generate a model for the molecular surface Γ.
2. Cubature: choose w_k and $\mathbf{r}_k$ properly so that higher order accuracy can be obtained for small N.
3. Fast summation to evaluate R_i , $i = 1, \ldots, M$.



Convex/Concave Spherical Patches

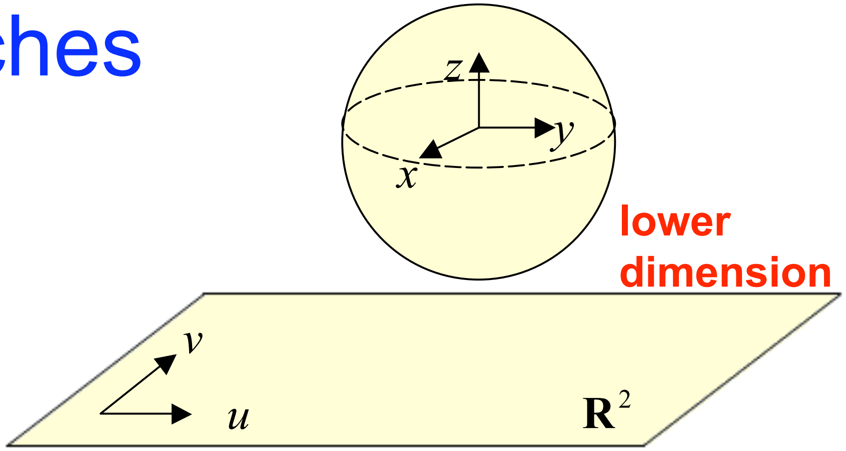
The rational map $\mathbf{g}:(u,v)\rightarrow(x,y,z)$

$$x=\frac{2ru}{u^2+v^2+1}$$

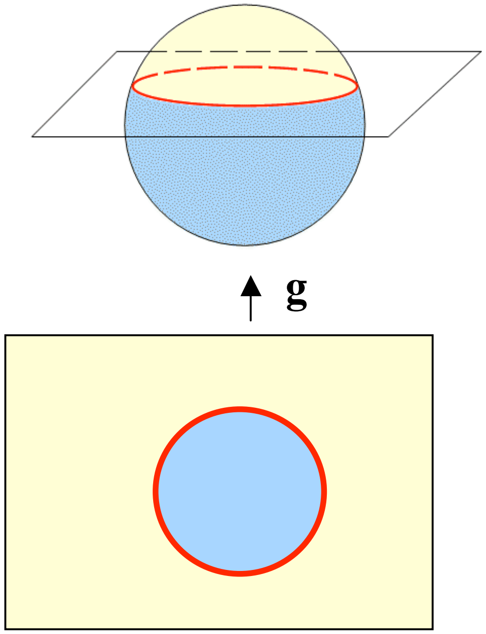
$$y=\frac{2rv}{u^2+v^2+1}$$

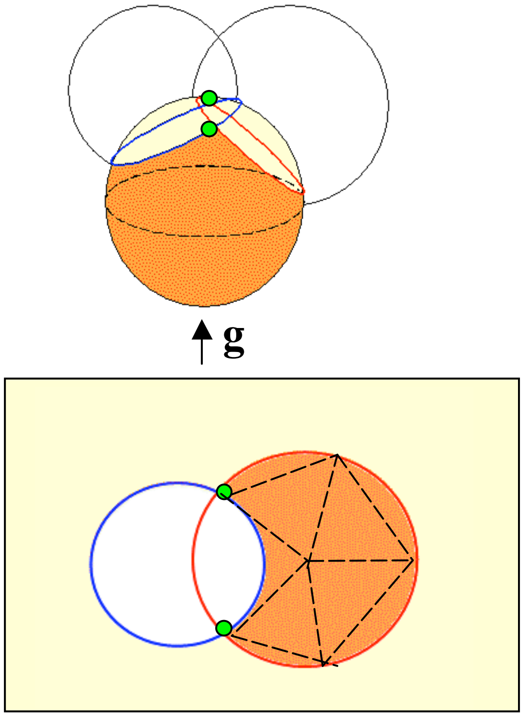
$$z=\frac{r(u^2+v^2-1)}{u^2+v^2+1}$$

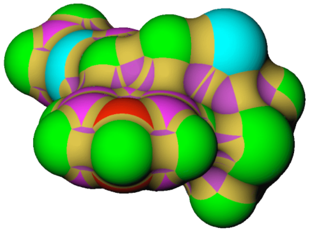
$(r=1,$ for unit sphere$)$



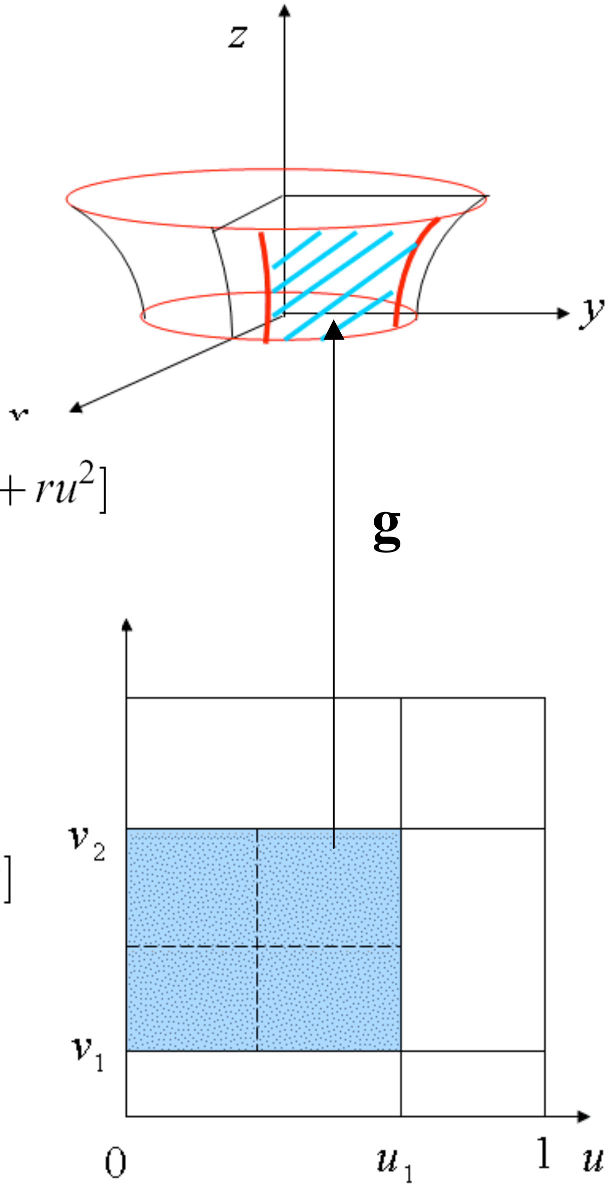
lower dimension







Toroidal Patches



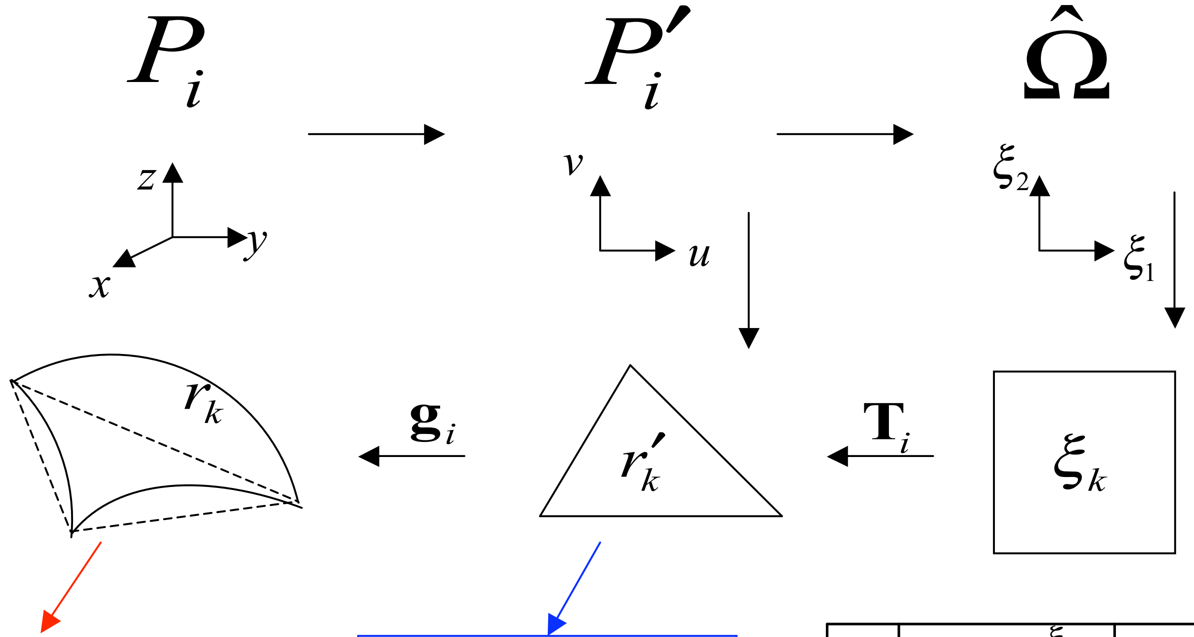
$$\mathbf{g}:(u,v)\rightarrow(x,y,z)$$

For $x\geq 0, y\geq 0, z\geq 0$

$$\begin{cases} x=\frac{1}{\Sigma}[(1-v)^2+\sqrt{2}v(1-v)][a[(1-u)^2+\sqrt{2}u(1-u)+u^2]+ru^2] \\ y=\frac{1}{\Sigma}[v^2+\sqrt{2}v(1-v)][a[(1-u)^2+\sqrt{2}u(1-u)+u^2]+ru^2] \\ z=\frac{r[u^2+\sqrt{2}u(1-u)]}{(1-u)^2+\sqrt{2}u(1-u)+u^2} \\ \Sigma=[(1-u)^2+\sqrt{2}u(1-u)+u^2][(1-v)^2+\sqrt{2}v(1-v)+v^2] \end{cases}$$

where $u\in[0,1], v\in[0,1]$

Cubature over LR Molecular Surface



$$r_k = \mathbf{g}_i(\mathbf{T}_i(\xi_k))$$

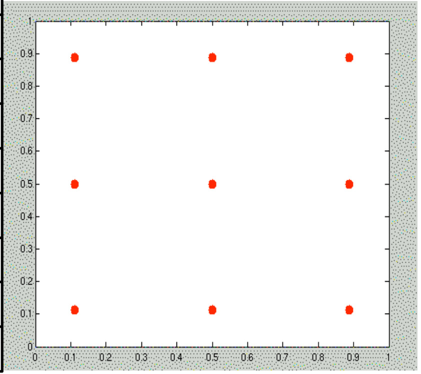
$$w_k = |J(\mathbf{g}_i)J(\mathbf{T}_i)|\,\hat{w}_k$$

$$r'_k = \mathbf{T}_i(\xi_k)$$

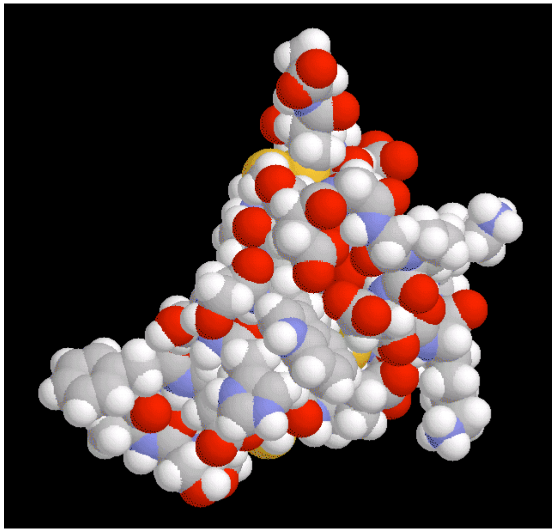
$$w'_k = |J(\mathbf{T}_i)|\,\hat{w}_k$$

$$\int_{P_i} f(\mathbf{r})dS \approx \sum_k |J(\mathbf{g}_i)J(\mathbf{T}_i)|\,\hat{w}_k f(\mathbf{g}_i(\mathbf{T}_i(\xi_k)))$$

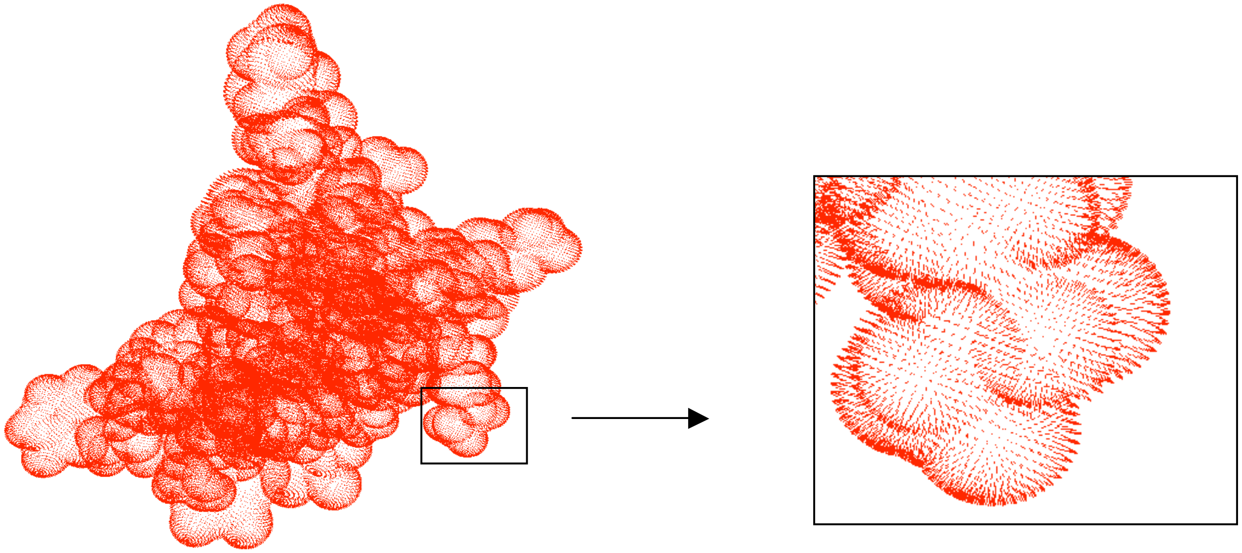
	Nodes ξ_k	Weights $\hat{w}_k$
1	(0.1127, 0.1127)	0.3087
2	(0.5, 0.1127)	0.4939
3	(0.8873, 0.1127)	0.3087
4	(0.1127, 0.5)	0.4939
5	(0.5, 0.5)	0.7901
6	(0.8873, 0.5)	0.4939
7	(0.1127, 0.8873)	0.3087
8	(0.5, 0.8873)	0.4939
9	(0.8873, 0.8873)	0.3087



Cubature Sampling



1AJJ, 514 atoms



(50x25)

Fast Fourier Summation

After we find the weights w_k and the nodes $\mathbf{r}_k$ by sampling over the LR surface or the analytic surface, we apply error-bounded fast Fourier summation methods to evaluate

$$R_i^{-1} = \frac{1}{4\pi} \sum_{k=1}^{N} w_k \frac{(\mathbf{r}_k - \mathbf{x}_i) \cdot \mathbf{n}(\mathbf{r}_k)}{|\mathbf{r}_k - \mathbf{x}_i|^4} \qquad i = 1, \ldots, M$$

Force Calculation

The electrostatic force acting on atom α which is part of the forces driving Molecular dynamics is

$$\mathbf{F}_{\alpha}^{\text{elec}} = -\frac{\partial G_{\text{pol}}}{\partial \mathbf{x}_{\alpha}}$$

$$\frac{\partial G_{\text{pol}}}{\partial \mathbf{x}_{\alpha}} = \sum_{i} \sum_{j \neq i} \frac{\partial G_{\text{pol}}}{\partial r_{ij}} \frac{\partial r_{ij}}{\partial \mathbf{x}_{\alpha}} + \sum_{i} \frac{\partial G_{\text{pol}}}{\partial R_i} \frac{\partial R_i}{\partial \mathbf{x}_{\alpha}}$$

$$R_i^{-1} = \frac{1}{4\pi} \int_{\text{ex}} \frac{1}{|\mathbf{r} - \mathbf{x}_i|^4} \, dV$$, or $$R_i^{-1} = \frac{1}{4\pi} \int_{\Gamma} \frac{(\mathbf{r} - \mathbf{x}_i) \cdot \mathbf{n}(\mathbf{r})}{|\mathbf{r} - \mathbf{x}_i|^4} \, dS$$

The integration domain depends on $\mathbf{x}_{\alpha}$.

Volumetric Analytic Density Function

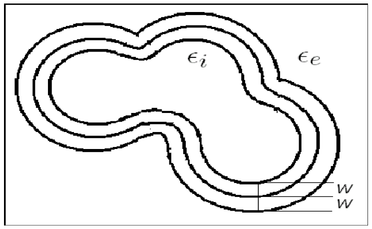
Introduce a differentiable molecular volumetric density function $\rho(\mathbf{r})$ such that

$$\int_{\text{ex}} \frac{1}{|\mathbf{r}-\mathbf{x}_i|^4}\, dV \approx \int_{\mathbf{R}^3} \frac{1-\rho(\mathbf{r})}{|\mathbf{r}-\mathbf{x}_i|^4}\, dV$$

For atom i, define $$\rho_i(x) = \begin{cases} 1 & x \le a_i - w \\ \frac{1}{4w^3}(x-(a_i-w))^3 - \frac{3}{4w^2}(x-(a_i-w))^2 + 1 & a_i - w < x < a_i + w \\ 0 & x \ge a_i + w \end{cases}$$

where $x = \|\mathbf{r}-\mathbf{x}_i\|$

Then define $$\rho(\mathbf{r}) = \sum_i \rho_i - \sum_{i<j} \rho_i\rho_j + \sum_{i<j<k} \rho_i\rho_j\rho_k - \sum_{i<j<k<l} \rho_i\rho_j\rho_k\rho_l$$

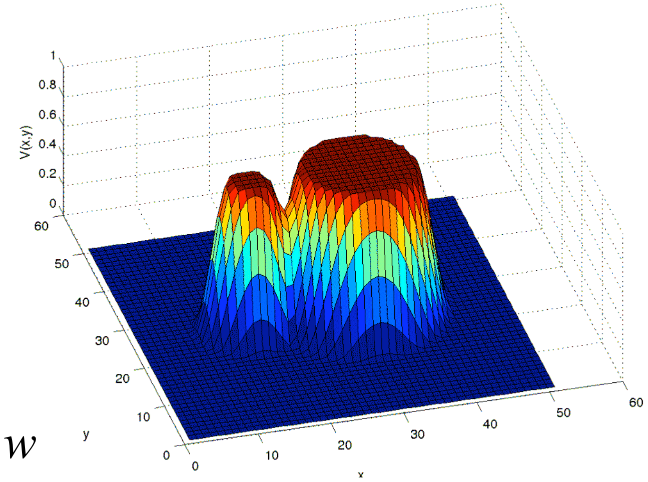


Molecular Skin

Let $\bar{\rho} = 1-\rho$, then $$R_i^{-1} \approx \frac{1}{4\pi}\int_{\mathbb{R}^3} \frac{\bar{\varrho}(\mathbf{r},\{\mathbf{x}_j\})}{|\mathbf{r}-\mathbf{x}_i|^4}\, dV$$

How to define the analytic volume function?

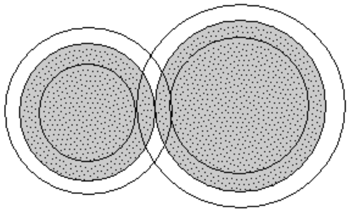
Im, Lee and Brooks (2003):



$$V(\mathbf{r}) = 1 - \mathrm{H}(\mathbf{r})$$

where $\mathrm{H}(\mathbf{r}) = \prod_j H_j(|\mathbf{r} - \mathbf{x}_j|)$

$$H_j(x) = \begin{cases} 0, & x \le a_j - w \\ \frac{1}{2} + \frac{3}{4w}(x - a_j) - \frac{1}{4w^3}(x - a_j)^3, & a_j - w < x < a_j + w \\ 1, & x \ge a_j + w \end{cases}$$



$\mathbf{x}$: distance between the spatial point and center of atom j
$2w$: smoothing length (less than 1 A)
a_j : the van der Waals radius of atom j

In such a model, $V(\mathbf{r}) \in C^1$

Force Calculation

$$-\frac{1}{R_i^2}\frac{\partial R_i}{\partial \mathbf{x}_\alpha} = \frac{1}{4\pi}\int_{\mathbb{R}^3}\frac{\partial}{\partial \mathbf{x}_\alpha}\frac{\bar{\varrho}(\mathbf{r},\{\mathbf{x}_j\})}{|\mathbf{r}-\mathbf{x}_i|^4}\,dV$$

$$\frac{\partial R_i}{\partial \mathbf{x}_\alpha} = -\frac{R_i^2}{4\pi}\left(\boxed{\int_{\mathbb{R}^3}\frac{\frac{\partial}{\partial \mathbf{x}_\alpha}\bar{\varrho}(\mathbf{r},\{\mathbf{x}_j\})}{|\mathbf{r}-\mathbf{x}_i|^4}\,dV} + \int_{\text{ex}}\frac{\partial}{\partial \mathbf{x}_\alpha}\frac{1}{|\mathbf{r}-\mathbf{x}_i|^4}\,dV\right)$$

$$\|$$

$$\boxed{-4\mathbf{x}_i 3\int_{\Gamma}\frac{(\mathbf{r}-\mathbf{x}_i)\cdot\mathbf{n}(\mathbf{r})}{|\mathbf{r}-\mathbf{x}_i|^6}\,dS}$$

$$\frac{\partial}{\partial \mathbf{x}_\alpha}\bar{\varrho} = -\frac{\partial}{\partial \mathbf{x}_\alpha}\tilde{\varrho} = \frac{\partial \varrho_\alpha}{\partial \mathbf{x}_\alpha}\left(1-\sum_j \varrho_j + \sum_{j<k}\varrho_j\varrho_k - \sum_{j<k<l}\varrho_j\varrho_k\varrho_l\right)$$

Molecular surface

Since $\frac{\partial \rho_\alpha}{\partial \mathbf{x}_\alpha} \neq 0$ only if $a_\alpha - w < |\mathbf{r}-\mathbf{x}_\alpha| < a_\alpha + w$

Molecular skin

$$\int_{\mathbb{R}^3}\frac{\frac{\partial}{\partial \mathbf{x}_\alpha}\bar{\rho}(\mathbf{r},\{\mathbf{x}_j\})}{|\mathbf{r}-\mathbf{x}_i|^4}\,dV = \boxed{\int_{|\mathbf{r}-\mathbf{x}_\alpha|=a_\alpha-w}^{|\mathbf{r}-\mathbf{x}_\alpha|=a_\alpha+w}\frac{\partial \rho_\alpha}{\partial \mathbf{x}_\alpha}\frac{1-\sum_j\rho_j+\sum_{j<k}\rho_j\rho_k-\sum_{j<k<l}\rho_j\rho_k\rho_l}{|\mathbf{r}-\mathbf{x}_i|^4}}$$

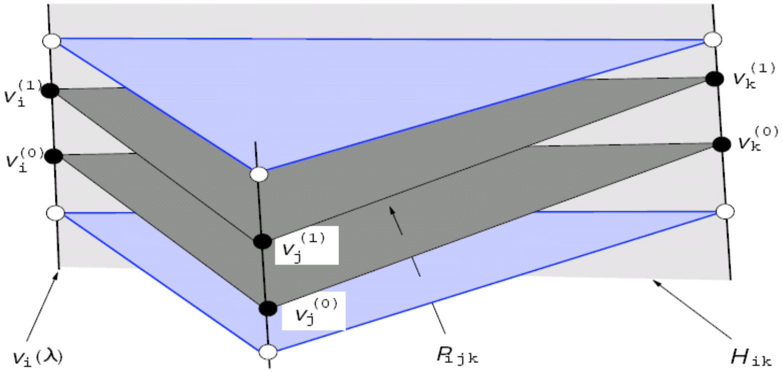
Force Calculation – *Integration over A-shells*

- Triangulate the molecular surface with attached normal at each vertex.
- For each triangle, along the normal direction at the vertices, construct prism A-shells:

$$P_{ijk}(I) = \{p := b_1 v_i(\lambda) + b_2 v_j(\lambda) + b_3 v_k(\lambda),\ b_1 + b_2 + b_3 = 1, \lambda \in I\}$$

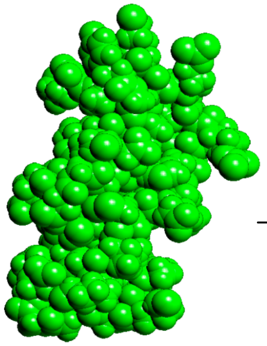
where I is a specified interval

- For a λ sampling, we obtain $\{\lambda_l\}$ For each λ_l, $\{v_i(\lambda_l), v_j(\lambda_l), v_k(\lambda_l)\}$ is a parametric A-patch

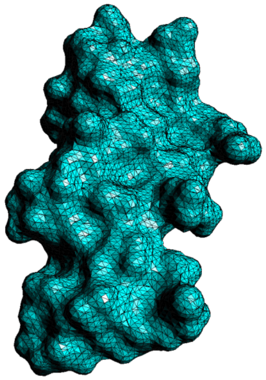


Bajaj and Xu, CAGD (2002), 89-112

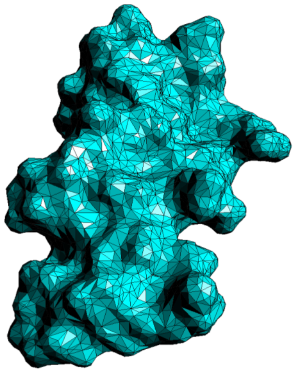
Continuum Approximation via A-Spline



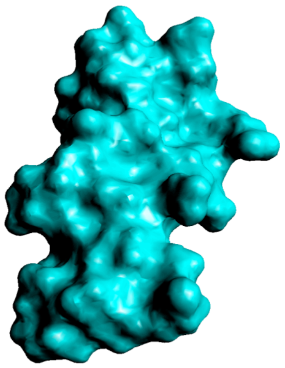
atomic/quasi-atomic structure



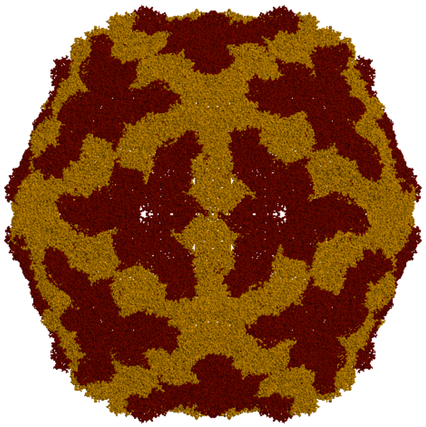
molecular surface triangulation



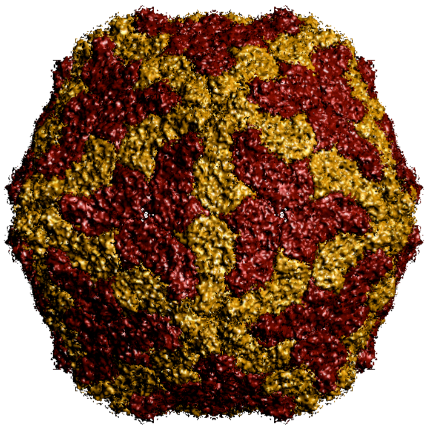
coarse mesh



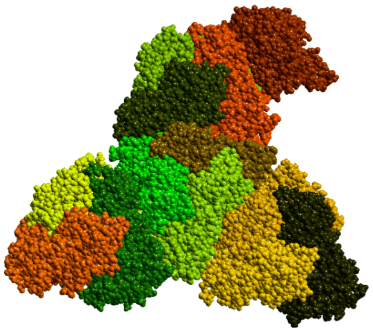
A-Spline



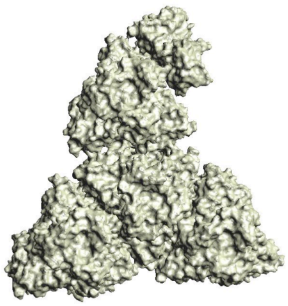
atomic structure of P3



A-Spline

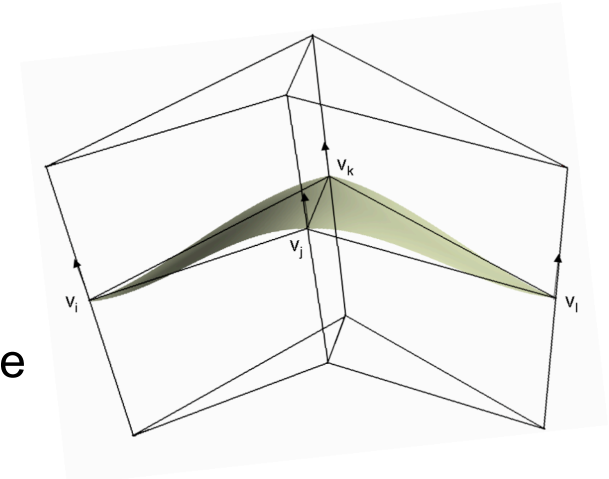


atomic structure asymmetric subunit P8



A-Spline

A-Spline



A-Spline model:

$S := \{\mathbf{p}(b_1,b_2,b_3,\lambda) : F(b_1,b_2,b_3,\lambda) = 0, \mathbf{p} \in D_{ijk}\}$ where

- $D_{ijk} = \{\mathbf{p}(b_1,b_2,b_3,\lambda) : \mathbf{p} = b_1\mathbf{v}_i(\lambda) + b_2\mathbf{v}_j(\lambda) + b_3\mathbf{v}_k(\lambda), \lambda \in I_{ijk}\}$
- I_{ijk} is an interval containing 0
- $F(b_1,b_2,b_3,\lambda) = \sum_{i+j+k=n} b_{ijk}(\lambda) B^n_{ijk}(b_1,b_2,b_3)$
- $B^n_{ijk}(b_1,b_2,b_3) = \frac{n!}{i!\,j!\,k!} b_1^i b_2^j b_3^k$
- n>2 so that S is smooth. We consider the case n=3. $b_{ijk}(\lambda)$ are determined so that C^1 continuity is obtained across the patch boundaries.

Parametrization for FEM/BEM

To evaluate $\int_\Gamma f(\mathbf{x})\, dS = \sum_j \int_{\Gamma_j} f(\mathbf{x})\, dS$, where Γ_j is the jth surface element

$$\int_{\Gamma_i} f(\mathbf{x})\, dS = \int_{\sigma_i} f(x(b_1,b_2), y(b_1,b_2), z(b_1,b_2))\sqrt{EG-F^2}\, db_1 db_2$$

where

$$E = (\frac{\partial x}{\partial b_1})^2 + (\frac{\partial y}{\partial b_1})^2 + (\frac{\partial z}{\partial b_1})^2$$

$$F = \frac{\partial x}{\partial b_1}\frac{\partial x}{\partial b_2} + \frac{\partial y}{\partial b_1}\frac{\partial y}{\partial b_2} + \frac{\partial z}{\partial b_1}\frac{\partial z}{\partial b_2}$$

$$G = (\frac{\partial x}{\partial b_2})^2 + (\frac{\partial y}{\partial b_2})^2 + (\frac{\partial z}{\partial b_2})^2$$

Apply the quadrature over the planar triangle,

$$\int_{\sigma_i} f(b_1,b_2)\sqrt{EG-F^2}\, db_1 db_2 \approx \sum_{k=1}^{n} W_k f(b_1^k, b_2^k)\sqrt{EG-F^2}|_{b_1^k, b_2^k}$$

Force Calculation

- The method to compute the surface integral is as same as the electrostatic solvation energy calculation.
- For volume integral in the force calculation, cubature over a spherical shell needs to be generated and fast summation method can be applied to evaluate the numerical cubature.
- For symmetric structures, both the surface integral and the volume integral can be sped up by doing the sampling over a single subunit and applying transformations for other subunits.

Error Estimation (I)

$$\left|\underset{\substack{\uparrow\\ \text{exact}\\ \text{value}}}{I(\mathbf{x}_i)}-\underset{\substack{\uparrow\\ \text{computed}\\ \text{value}}}{\tilde{I}(\mathbf{x}_i)}\right| \le \underbrace{\left|I(\mathbf{x}_i)-I_1(\mathbf{x}_i)\right|}_{\substack{\text{quadrature}\\ \text{error}}}+\underbrace{\left|I_1(\mathbf{x}_i)-I_2(\mathbf{x}_i)\right|}_{\substack{\text{Fourier series}\\ \text{truncation error}}}+\underbrace{\left|I_2(\mathbf{x}_i)-\tilde{I}(\mathbf{x}_i)\right|}_{\substack{\text{NFFT}\\ \text{error}}}$$

Error Estimation (II)

A) NFFT error

$$\left| I_2(\mathbf{x}_i) - \widetilde{I}(\mathbf{x}_i) \right| \leq E_f(\mathbf{x}_i) + E_t(\mathbf{x}_i)$$

$$\| E_f \|_\infty \leq \| \hat{f} \|_1 \max_{\grave{\mathbf{u}} \in I_n} \sum_{r \in \mathbf{Z}^3 \setminus \{0\}} | \hat{\phi}(\grave{\mathbf{u}} + nr) / \hat{\phi}(\grave{\mathbf{u}}) |$$

$$\| E_t \|_\infty \leq \| \hat{f} \|_1 \, n^{-3} (\max_{\grave{\mathbf{u}} \in I_n} | \hat{\phi}(\grave{\mathbf{u}}) |^{-1}) \sum_{\mathbf{l} \in I_{\sigma n}} | \phi(\mathbf{x} - \tfrac{\mathbf{l}}{\sigma n}) - \psi(\mathbf{x} - \tfrac{\mathbf{l}}{\sigma n}) |$$

where $\| \hat{f} \|_1 = \sum_{\grave{\mathbf{u}} \in I_n} | \hat{f}_{\grave{\mathbf{u}}} |$

Steidl, ACM (1998), 337-352

Error Estimation (III)

B) Cubature error

By Peano’s theorem, the Gaussian Cubature error for $f \in C^{2m}$ is

$$E_m(f) = \left| \int_a^b f(x)dx - \sum_{k=1}^{m} w_k f(x_k) \right| = \frac{(b-a)^{2m+1}(m!)^4}{(2m+1)[(2m)!]^3} \left| f^{(2m)}(\xi) \right|$$

For 2D quad patches:

$$E_{m_1m_2}(f) = \left| \int_{a_1}^{b_1}\int_{a_2}^{b_2} f(x,y)dydx - \sum_{i=1}^{m_1}\sum_{j=1}^{m_2} A_iB_j f(x_i,y_j) \right| \le (b_2-a_2)E_{m_1} + (b_1-a_1)E_{m_2}$$

Let $m_1 = m_2 = m$, N_P be the number of patches, $M = \max\{\|\frac{\partial^{2m}h}{\partial u^{2m}}\|_\infty, \|\frac{\partial^{2m}h}{\partial v^{2m}}\|_\infty\}$

$h(u,v) = f(\mathbf{g}(u,v))\,|J(\mathbf{g})|$

$$|I(\mathbf{x}_i) - I_1(\mathbf{x}_i)| \le N_P \frac{(u_2-u_1)(v_2-v_1)(m!)^4}{(2m+1)[(2m)!]^3} M({h_u}^{2m} + {h_v}^{2m})$$

Bajaj, Zhao (2006)

Error Estimation (IV)

C) Fourier series truncation error

$$R_n = I_1(\mathbf{x}) - I_2(\mathbf{x}) = \sum_{\boldsymbol{\omega} \in I_\infty \setminus I_n} b_{\boldsymbol{\omega}} e^{2\pi i \boldsymbol{\omega} \cdot \mathbf{x}}$$

In one dimension,

$$|R_n| \le \sum_{\omega=n+1}^{\infty} (|b_\omega| + |b_{-\omega}|)$$, where $$b_\omega = \int_{-\frac{1}{2}}^{\frac{1}{2}} K(x) e^{-2\pi i \omega x} dx$$

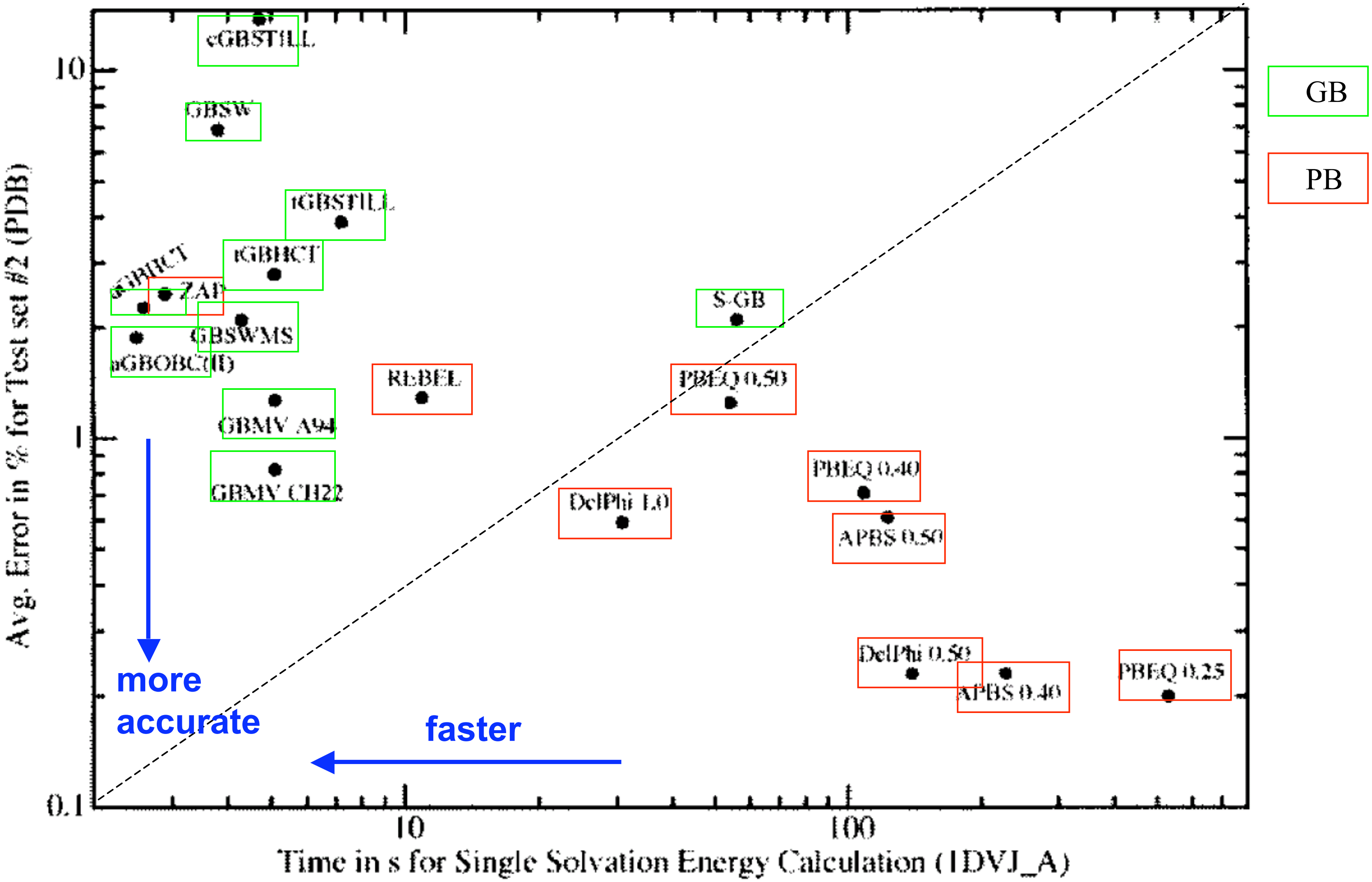
If $K \in C^{2m}$, $m \ge 1$, by successive integration by parts,

$$|b_\omega| \le \left(\frac{1}{2\pi\omega}\right)^{2m} \int_{-\frac{1}{2}}^{\frac{1}{2}} |K^{(2m)}(x)|\, dx = \left(\frac{1}{2\pi\omega}\right)^{2m} \mu_{2m}$$

$$|R_n| \le \frac{2\mu_{2m}}{(2\pi)^{2m}} \sum_{\omega=n+1}^{\infty} \frac{1}{\omega^{2m}} \le \frac{2\mu_{2m}}{(2\pi)^{2m}} \int_n^\infty \frac{1}{\omega^{2m}} d\omega = \frac{2\mu_{2m}}{(2\pi)^{2m}(2m-1)n^{2m-1}}$$

Bajaj, Siddahanavalli (2005)

GB versus PB



more accurate

faster

Center for Computational Visualization
Institute of Computational and Engineering Sciences
Department of Computer Sciences

Feig et al, JCC(2004), 25, 265-284

University of Texas at Austin

November 2007

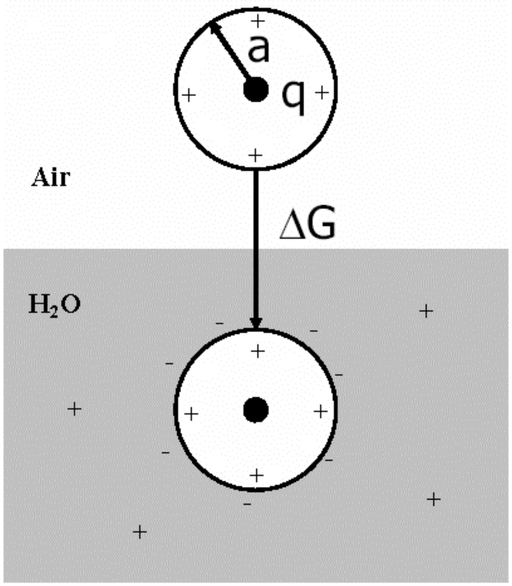
Generalized Born Energetics

Name	Year	Authors	Program	Calculation of Born radii	CFA Corr.	Dielectric Boundary
GB GB/SA	1990	Still, Tempczyk, Hawley, Hendrickson	Macromodel	FDPB	Yes	Molecular surface
GB	1995	Hawkins, Cramer, Truhlar	Amber, Tinker	Pairwise descreening	No	Overlapping spheres
ACE	1996/ 2001	Schaefer, Karplus	CHARMM	Pairwise sum of atomic volumes	No	Overlapping Gaussians
GB	1997	Qiu, Shenkin, Hollinger, Still	Macromodel, Tinker	Pairwise sum of atomic volumes	No	Overlapping spheres
S-GB	1998	Ghosh, Rapp, Friesner	Impact	Surface integral formulation	Yes	Overlapping spheres
GB1	1999	Dominy, Brooks	CHARMM	Pairwise sum of atomic volumes	No	Overlapping spheres
GBMV	2002/ 2003	Lee, Salsbury, Feig, Brooks	CHARMM	Numerical integration	Yes	Molecular surface
GBSW	2003	Im, Lee, Brooks	CHARMM	Numerical integration	Yes	Overlapping spheres + smooth boundary
AGB	2004	Gallicchio, Levy	Impact	Pairwise descreening	No	Overlapping spheres
GB	2004	Onufriev, Case	Amber	Pairwise descreening, radius rescaling	No	Molecular surface

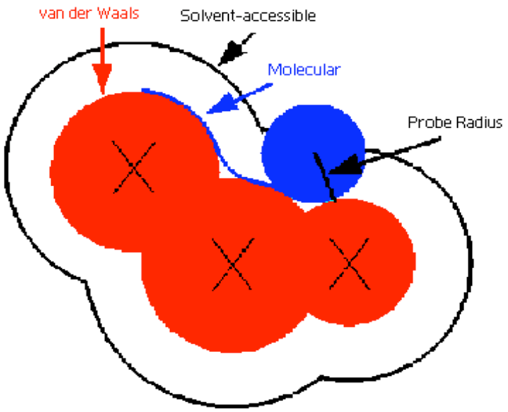
The solvation energy consists of three components:

- solute-solvent cavity formation
- solute-solvent hydrophobicity (van der Waals interaction)
- solute-solvent electrostatic polarization

$$G_{sol} = G_{cav} + G_{vdw} + G_{pol}$$



$$G_{sol} = G_{cav} + G_{vdw} + G_{pol}$$



- $G_{cav} + G_{vdw} = \sum_k \sigma_k SA_k$

  σ_k : empirical parameter

  (7.2 cal/(mol Å^2), *still et al, 1990*)

  SA_k: solvent-accessible surface area

- G_{pol} : Poisson theory

  or generalized Born (GB) theory

Given an accurate calculation of the Born radii, GB energy can reproduce Poisson energy within 1% error. (Lee et al, 2002)

Poisson theory

Model:

Solvent: high-dielectric continuum, e.g. water $\varepsilon = 81.5$ $(14^0\mathrm{C})$

Solute: a macromolecule of lower dielectric embedding charges

The electrostatic potential ϕ in such a system is

$$-\nabla \cdot [\varepsilon(\mathbf{r})\nabla\phi(\mathbf{r})] = 4\pi\rho(\mathbf{r}) \qquad \text{(Poisson equation)}$$

$\rho(r)$: charge density at the position r

$$\varepsilon(r) = \begin{cases} \varepsilon_{in} & \text{if r is in the molecule interior} \\ \varepsilon_{ex} & \text{if r is in the exterior} \end{cases}$$

For gas phase (air), $\varepsilon_{ex} = 1 \quad \Rightarrow \quad \phi = \phi_{vac}(\mathbf{r})$

For solvent phase, $\varepsilon_{ex} = \varepsilon_{solvent} \quad \Rightarrow \quad \phi = \phi_{sol}(\mathbf{r})$

} finite difference or
boundary element method
(expensive calculation!)

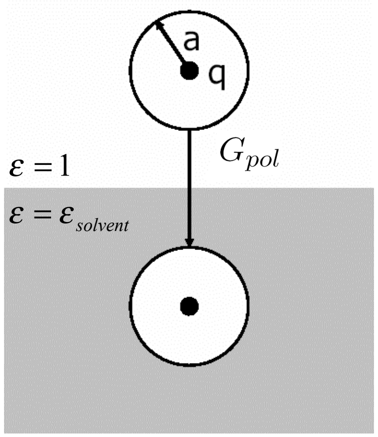
The electrostatic energy is equivalent to the work required to assemble a charge distribution, so

$$G = \frac{1}{2} \int \rho(\mathbf{r})\phi(\mathbf{r})\ dV$$

The electrostatic component of the solvation energy is

$$G_{pol} = \frac{1}{2} \int (\phi_{sol}(\mathbf{r}) - \phi_{vac}(\mathbf{r}))\rho(\mathbf{r})\ dV$$

Generalized Born theory



Simple case: one ion of radius a and charge q

The electrostatic solvation energy is

$$G_{pol} = \frac{q^2}{2a}\left(\frac{1}{\varepsilon_{solvent}} - 1\right) \qquad \text{(Born formula)}$$

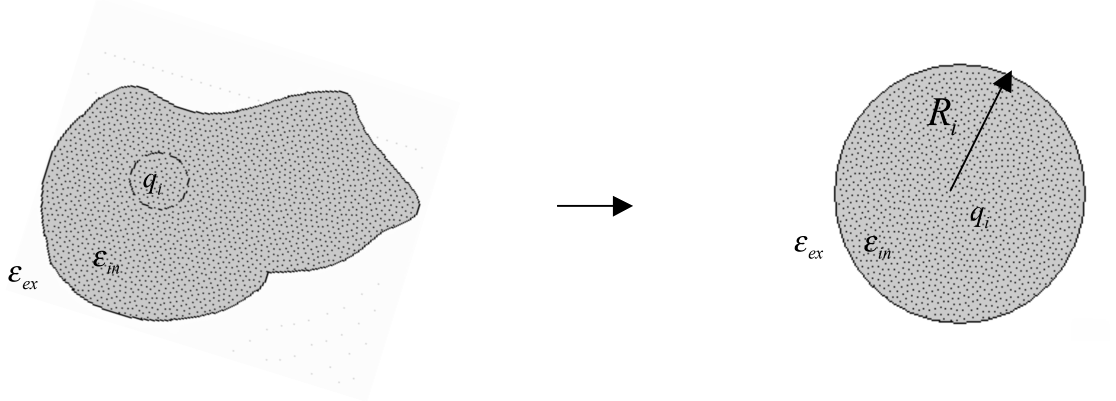
General case: A molecule consists of atoms of radii $a_1 \ldots a_N$ with charges $q_1 \ldots q_N$, and r_{ij} is the distance between atom i and j, the electrostatic solvation energy is

$$G_{pol} = \frac{1}{2}\left(\frac{1}{\varepsilon_{solvent}} - 1\right) \sum_{i,j} \frac{q_i q_j}{[r_{ij}^2 + R_i R_j \exp(-\frac{r_{ij}^2}{4R_i R_j})]^{\frac{1}{2}}}$$

R_i : Born radius of atom i

(Still et al, 1990)

Born radius



The Born radius is chosen in this way: we assume that there is a single charge q_i located at the center of atom i in the molecule. We solve the Poisson equation for this system. If we let it be equivalent to another system where there is a sphere of radius R_i with charge q_i at its center, then R_i is the effective Born radius of atom i. So

$$\frac{1}{2}q_i(\phi_{sol} - \phi_{vac}) = \frac{q_i^2}{2R_i}(\frac{1}{\varepsilon_{solvent}} - 1)$$

Not practical !

A practical approach to compute R_i : (Donald Bashford et al, 2000)

In classical electrostatics the work required to assemble a continuous charge distribution is

$$W = \frac{1}{2}\int \rho(\mathbf{r})\phi(\mathbf{r})\ dV$$

From Poisson equation, we know that

$$\rho = \frac{\varepsilon}{4\pi}\nabla \cdot \mathbf{E}$$

So

$$W = \frac{1}{8\pi}\int \varepsilon\phi\nabla \cdot \mathbf{E}\ dV$$

Because of the fact that $\nabla \cdot (\mathbf{E}\phi) = \phi\nabla \cdot \mathbf{E} + \mathbf{E} \cdot \nabla\phi$ and $\nabla\phi = -\mathbf{E}$

therefore

$$W = \frac{1}{8\pi}[\int \varepsilon\nabla \cdot (\mathbf{E}\phi)\ dV + \int \varepsilon\mathbf{E} \cdot \mathbf{E}\ dV]$$

$$W = \frac{1}{8\pi}[\int \varepsilon \nabla \cdot (\mathbf{E}\phi)\, dV + \int \varepsilon \mathbf{E} \cdot \mathbf{E}\, dV]$$

Apply Gauss' theorem: $\int_V (\nabla \cdot \mathbf{F})\, dV = \int_{\partial V} \mathbf{F} \cdot d\mathbf{S}$

$$W = \frac{1}{8\pi}[\oint_S \varepsilon \mathbf{E}\phi\, d\mathbf{S} + \int_V \varepsilon \mathbf{E} \cdot \mathbf{E}\, dV]$$

Assume the solute is embedded in an infinite water dielectric. The electric field at far distance from the charge distribution looks like the field of a point charge, so

$$E \sim \frac{1}{r^2} \qquad \phi \sim \frac{1}{r} \qquad S \sim r^2 \qquad \oint_S \varepsilon \mathbf{E}\phi\, d\mathbf{S} \sim \frac{1}{r}$$

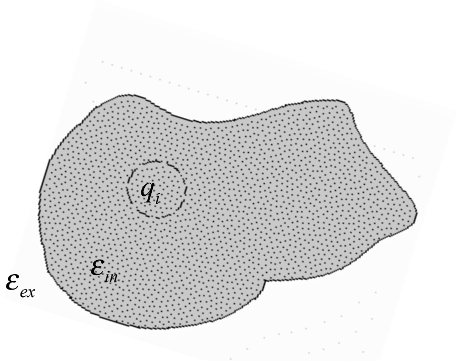
As $r \rightarrow \infty$

$$W = \frac{1}{8\pi}\int \varepsilon \mathbf{E} \cdot \mathbf{E}\, dV$$

The electric field due to charge q_i (lying on the origin) is

$$\mathbf{E}_{\text{i}} = \frac{q_i \mathbf{r}}{\varepsilon r^3} \qquad \text{(Coulombic electric field)}$$

The electrostatic energy of the system :

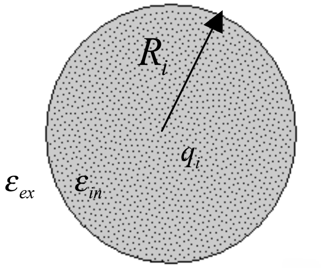


$$G_i = \frac{1}{8\pi} \int \varepsilon \mathbf{E} \cdot \mathbf{E} \, dV \approx \frac{1}{8\pi} \int_{in} \frac{q_i^2}{r^4 \varepsilon_{in}} \, dV + \frac{1}{8\pi} \int_{ex} \frac{q_i^2}{r^4 \varepsilon_{ex}} \, dV$$

The electrostatic solvation energy of this system is

$$G_{pol}^{i} = G_{i,solvent} - G_{i,air} = \frac{1}{8\pi} \left(\frac{1}{\varepsilon_{solvent}} - 1 \right) \int_{ex} \frac{q_i^2}{r^4} \, dV$$

The electrostatic solvation energy of the system:



$$G_{pol}^{i} = \frac{q_i^2}{2R_i} \left(\frac{1}{\varepsilon_{solvent}} - 1 \right)$$

$$\frac{1}{8\pi}\left(\frac{1}{\varepsilon_{solvent}}-1\right)\int_{ex}\frac{q_i^2}{r^4}\,dV=\frac{q_i^2}{2R_i}\left(\frac{1}{\varepsilon_{solvent}}-1\right)$$

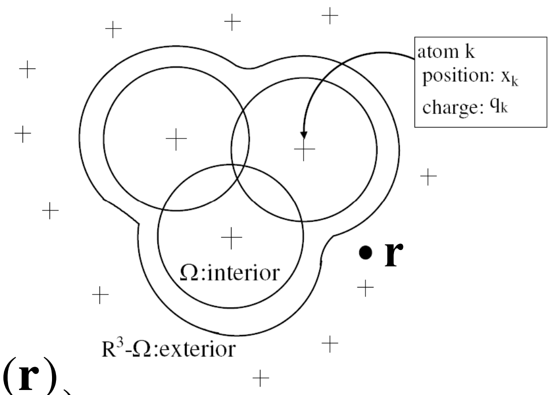
$$\Longrightarrow$$

$$\begin{aligned}
R_i^{-1} &= \frac{1}{4\pi}\int_{ex}\frac{1}{r^4}\,dV \\
&= \frac{1}{4\pi}\left(\int_{V,r>a_i}\frac{1}{r^4}\,dV-\int_{in,r>a_i}\frac{1}{r^4}\,dV\right) \qquad \left(\int dV=\iint r^2dr\,d\Omega\right) \\
&= a_i^{-1}-\frac{1}{4\pi}\int_{in,r>a_i}\frac{1}{r^4}\,dV
\end{aligned}$$

A sphere of radius a_i (the van der Waals radius of atom i) is excluded from the integration domain to avoid singularity at 0.

Electrostatic Solvation Energy

- $$G_{\text{pol}} = \frac{1}{2}\int [\phi_{\text{solvent}}(\mathbf{r}) - \phi_{\text{air}}(\mathbf{r})]\rho(\mathbf{r})\,dV$$



Poisson-Boltzmann (PB) theory:

$$\nabla \cdot [\varepsilon(\mathbf{r})\nabla\phi(\mathbf{r})] = \rho_c(\mathbf{r}) + \rho_b(\mathbf{r})$$

$$\rho_c(\mathbf{r}) = -4\pi\sum_{k=1}^{M} q_k\delta(\mathbf{r}-\mathbf{x}_k), \qquad \rho_b(\mathbf{r}) = \kappa^2(\mathbf{r})\left(\frac{k_B T}{e_c}\right)\sinh\left(\frac{e_c\phi(\mathbf{r})}{k_B T}\right)$$

where

$\varepsilon(\mathbf{r})$	dielectric coefficient at $\mathbf{r}$	q_k	charge of atom k
$\mathbf{x}_k$	position of charge point q_k (center of atom k)	M	the number of point charge
$\kappa(\mathbf{r}) = \sqrt{\frac{8\pi e_c^2 I(\mathbf{r})}{k_B T}}$	modified Debye-Huckel parameter	e_c	charge of an electron
k_B	Boltzmann's constant	T	absolute temperature
$I(\mathbf{r}) = \frac{1}{2}\sum_i c_i z_i^2$	ionic strengths at $\mathbf{r}$	c_i, z_i	concentration and charge of i^{th} ionic species

Electrostatic Solvation Energy

PB theory: (cont.)

After we solve the PB equations, we could calculate the reaction field energy

$$G_{rf}(\kappa,\varepsilon_e) = \frac{1}{2}\sum_{k=1}^{M}\phi(\mathbf{x}_k)q_k$$

and the electrostatic solvation energy

$$G_{pol}(\kappa,\varepsilon_e) = G_{rf}(\kappa,\varepsilon_e) - G_{rf}(0,1)$$

Linear Poisson-Boltzmann Equation

The LPB equation is formally correct when $q_i\phi(r)/kT \ll 1$

$$\nabla(\epsilon(\vec{x})\nabla\phi(\vec{x})) = \rho_c(\vec{x}) + \rho_b^L(\vec{x})$$

Where $\rho_b^L(x)$ is the first term of Taylor expansion of $\rho_b(x)$

$$\begin{aligned}\rho_b(x) &= \frac{k_B T}{e_c}\sinh\left(\frac{e_c\phi(\vec{x})}{k_B T}\right)\\ &= \phi(\vec{x}) + \frac{k_B T}{e_c}\left(\frac{1}{3!}\left(\frac{e_c\phi(\vec{x})}{k_B T}\right)^3 + \frac{1}{5!}\left(\frac{e_c\phi(\vec{x})}{k_B T}\right)^5 + \ldots\right)\end{aligned}$$

Boundary Element Solution to LPBE

The boundary element representation of the solution:

$$\nabla(\epsilon(x)\nabla\phi(x)) = -4\pi\sum_{k=1}^{n_c} q_k\delta(x - x_k) \qquad x \in \Omega$$

$$\nabla(\epsilon(x)\nabla\phi(x)) = \kappa^2\phi(x) \qquad x \in R^3 \setminus \Omega$$

The interface continuous condition on the boundary Γ of Ω

$$\phi(\vec{x}) = \phi_1(\vec{x}) = \phi_2(\vec{x}) \qquad x \in \Gamma$$

$$\frac{\partial\phi}{\partial n_x}(\vec{x}) = \frac{\partial\phi_1}{\partial n_x}(\vec{x}) = \frac{\epsilon_e}{\epsilon_i}\frac{\partial\phi_2}{\partial n_x}(\vec{x}) \qquad x \in \Gamma$$

Nonderivative Boundary Integral Equations

Apply Green's second identity to the above equations

$$\int_\Omega (\phi \nabla^2 \psi - \psi \nabla^2 \phi) \cdot d\Omega = \int_\Gamma (\phi \nabla \psi - \psi \nabla \phi) \cdot d\Gamma$$

We can get the boundary integral equations:

$$\frac{1}{2}\phi(x) + \int_\Gamma \frac{1}{4\pi} \left(\frac{\partial}{\partial n_y} \frac{1}{|x-y|} \phi(y) - \frac{1}{|x-y|} \frac{\partial \phi(y)}{\partial n_y} \right) d\Gamma = \sum_{k=1}^{n_c} \frac{q_k}{4\pi \epsilon_i |x - x_k|}$$

$$\frac{1}{2}\phi(x) + \int_\Gamma \frac{1}{4\pi} \left(\frac{\epsilon_e}{\epsilon_i} \frac{e^{-\kappa|x-y|}}{|x-y|} \frac{\partial \phi(y)}{\partial n_y} - \frac{\partial}{\partial n_y} \frac{e^{-\kappa|x-y|}}{|x-y|} \phi(y) \right) d\Gamma = 0$$

Derivative Boundary Integral Equations

Let $G_0(x,y) = \frac{1}{4\pi|x-y|}$ and $G_\kappa(x,y) = \frac{e^{-\kappa|x-y|}}{4\pi|x-y|}$

Then

$$\begin{aligned}\frac{1}{2}\left(1+\frac{\epsilon_e}{\epsilon_i}\right)\phi(x) \quad & + \int_\Gamma \left(\frac{\partial G_0(x,y)}{\partial n_y} - \frac{\partial G_\kappa(x,y)}{\partial n_y}\right)\phi(y)d\Gamma \\ & - \int_\Gamma (G_0(x,y) - G_\kappa(x,y))\frac{\partial\phi(y)}{\partial n_y}d\Gamma = \sum_{k=1}^{n_c}\frac{q_k}{\epsilon_i}G_0(x,x_k)\end{aligned}$$

$$\begin{aligned}\frac{1}{2}\left(1+\frac{\epsilon_i}{\epsilon_e}\right)\frac{\partial\phi(x)}{\partial n_x} \quad & + \int_\Gamma \left(\frac{\partial^2 G_0(x,y)}{\partial n_x \partial n_y} - \frac{\epsilon_e}{\epsilon_i}\frac{\partial^2 G_\kappa(x,y)}{\partial n_x \partial n_y}\right)\phi(y)d\Gamma \\ & - \int_\Gamma \left(\frac{\partial G_0(x,y)}{\partial n_x} - \frac{\epsilon_i}{\epsilon_e}\frac{\partial G_\kappa(x,y)}{\partial n_x}\right)\frac{\partial\phi(y)}{\partial n_y} = \sum_{k=1}^{n_c}\frac{q_k}{\epsilon_i}\frac{\partial G_0(x,x_k)}{\partial n_x}\end{aligned}$$

Numerical Treatment of Boundary Integral Equations using A-Spline

The numerical treatment of the boundary integral equations of the LPBE:

$$\begin{aligned}
&\tfrac{1}{2}(1 + \tfrac{\epsilon_e}{\epsilon_i})\phi(x) \\
&= \textstyle\sum_{e=1}^{E} \tfrac{\partial \phi}{\partial n}(x_e) \sum_k W_{kf} J(b_1^k, b_2^k)(G_0(x, b_1^k, b_2^k) - G_\kappa(x, b_1^k, b_2^k)) \\
&- \textstyle\sum_{e=1}^{E} \phi(x_e) \sum_k W_{kf} J(b_1^k, b_2^k)(\tfrac{\partial G_0}{\partial n}(x, b_1^k, b_2^k) - \tfrac{\partial G_\kappa}{\partial n}(x, b_1^k, b_2^k)) \\
&+ \textstyle\sum_{k=1}^{n_c} \tfrac{q_k}{\epsilon_i} G_0(x, x_k)
\end{aligned}$$

where

x_e: center of the eth element

E: number of elements

x: collocation point

Numerical Treatment of Boundary Integral Equations using A-Spline

Since $y = \sum_{i=1}^{3} b_i v_i(\lambda)$, we have

$$G_0(x,y) = \frac{1}{4\pi|x-\sum_{i=1}^{3} b_i v_i(\lambda)|}$$

$$G_\kappa(x,y) = \frac{e^{-\kappa|x-\sum_{i=1}^{3} b_i v_i(\lambda)|}}{4\pi|x-\sum_{i=1}^{3} b_i v_i(\lambda)|}$$

$$\frac{\partial G_0(x,y)}{\partial n_y} = \frac{-(x-\sum_{i=1}^{3} b_i v_i(\lambda))\cdot n_y(\lambda)}{4\pi|x-\sum_{i=1}^{3} b_i v_i(\lambda)|^3}$$

$$\frac{\partial G_\kappa(x,y)}{\partial n_y} = \frac{-e^{-\kappa|x-\sum_{i=1}^{3} b_i v_i(\lambda)|}(1+\kappa|x-\sum_{i=1}^{3} b_i v_i(\lambda)|)(x-\sum_{i=1}^{3} b_i v_i(\lambda))\cdot n_y}{4\pi|x-\sum_{i=1}^{3} b_i v_i(\lambda)|^3}$$

Numerical Treatment of Boundary Integral Equations using A-Spline

The boundary integral equations become

$$\begin{aligned}
\frac{1}{2}\left(1+\frac{\epsilon_e}{\epsilon_i}\right)\phi(x) &= \sum_{e=1}^{E} \frac{\partial\phi}{\partial n}(x_e) \sum_k W_{kf} J(b_1^k, b_2^k) \frac{1-e^{-\kappa|x-\sum b_i v_i(\lambda)|}}{4\pi|x-\sum b_i v_i(\lambda)|} \\
&\quad - \sum_{e=1}^{E} \phi(x_e) \sum_k \Big(W_{kf} J(b_1^k, b_2^k) \\
&\quad \times \frac{(-1+(1.0+\kappa|x-\sum b_i v_i(\lambda)|)e^{-\kappa|x-\sum b_i v_i(\lambda)|})(x-\sum b_i v_i(\lambda))\cdot n_y(\lambda)}{4\pi|x-\sum b_i v_i(\lambda)|^3} \Big) \\
&\quad + \sum_{k=1}^{n_c} \frac{q_k}{\epsilon_i} \frac{1}{4\pi|x-x_k|}
\end{aligned}$$

where

$$n_y(\lambda) = \nabla F = T^{-1}\left(\frac{\partial F}{\partial b_1}, \frac{\partial F}{\partial b_2}, \frac{\partial F}{\partial \lambda}\right)^T$$

Boundary Element Solver to LPBE

The linear system of LPBE boundary element solver are

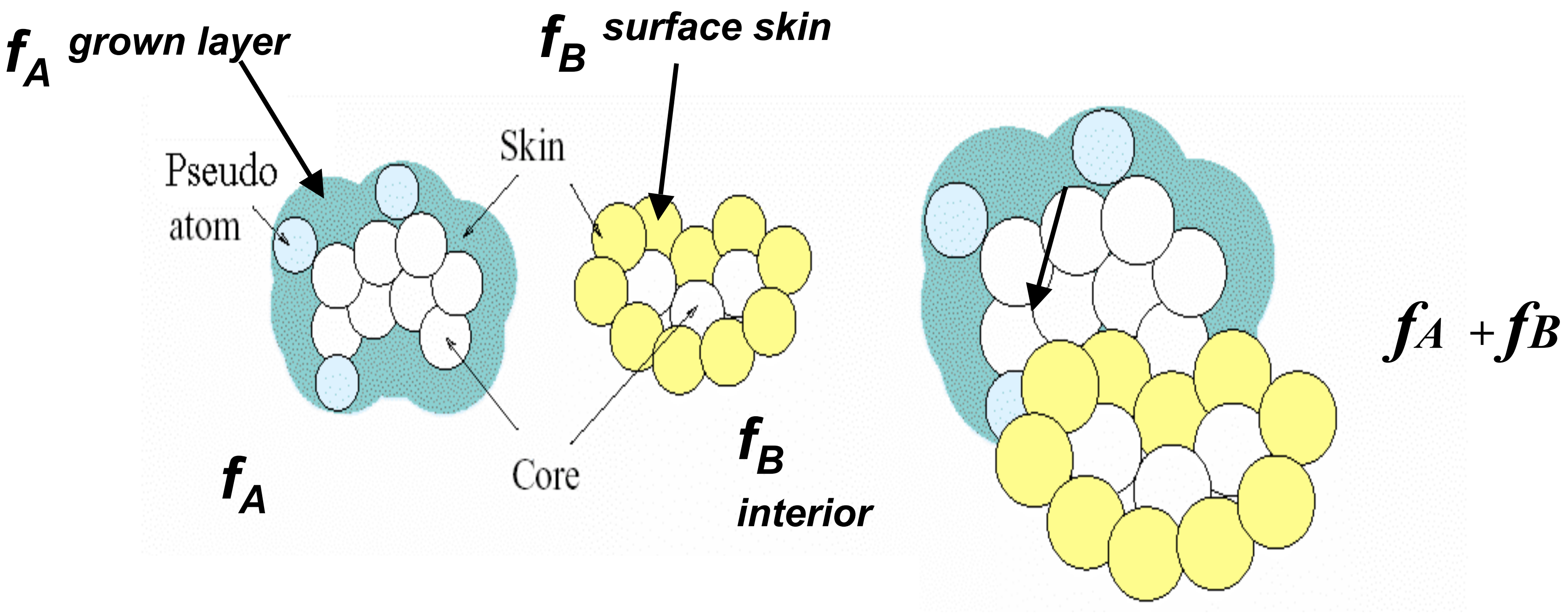
$$\frac{1}{2}\left(1+\frac{\epsilon_e}{\epsilon_i}\right)\phi_j = \sum_{e=1}^{E}\frac{\partial\phi}{\partial n}^{e} A_j^e + \sum_{e=1}^{E}\phi^e B_j^e + \sum_{k=1}^{n_c} q_k G_0(x_j, x_k)$$

$$\frac{1}{2}\left(1+\frac{\epsilon_i}{\epsilon_e}\right)\frac{\partial\phi_j}{\partial n} = \sum_{e=1}^{E}\frac{\partial\phi}{\partial n}^{e} D_j^e + \sum_{e=1}^{E}\phi^e C_j^e + \sum_{k=1}^{n_c} q_k \frac{\partial G_0}{\partial n}(x_j, x_k)$$

where

$$\begin{aligned}
A_i^e &= \textstyle\sum_k W_{kf} J(b_1^k, b_2^k)(G_0(x, b_1^k, b_2^k) - G_\kappa(x, b_1^k, b_2^k)) \\
B_i^e &= \textstyle\sum_k W_{kf} J(b_1^k, b_2^k)(\frac{\partial G_0}{\partial n_i}(x, b_1^k, b_2^k) - \frac{\epsilon_e}{\epsilon_i}\frac{\partial G_\kappa}{\partial n}(x, b_1^k, b_2^k)) \\
C_i^e &= \textstyle\sum_k W_{kf} J(b_1^k, b_2^k)(\frac{\partial^2 G_0}{\partial n_i \partial n}(x, b_1^k, b_2^k) - \frac{\partial^2 G_\kappa}{\partial n_i \partial n}(x, b_1^k, b_2^k)) \\
D_i^e &= \textstyle\sum_k W_{kf} J(b_1^k, b_2^k)(\frac{\partial G_0}{\partial n_i}(x, b_1^k, b_2^k) - \frac{\epsilon_i}{\epsilon_e}\frac{\partial G_\kappa}{\partial n_i}(x, b_1^k, b_2^k))
\end{aligned}$$

F^3 Dock: Fast Flexible Fourier Docking



- ***fA* grown layer:** Sampled SAS with pseudo atom centers
- ***fA***: Atom centers of the protein
- ***fB surface skin***: Surface atoms
- ***fB* interior**:Atoms of B which are not surface atoms

Affinity based Scoring I

- Summation of Weighted Gaussians with following coefficients:

Region	**Function**	**Coeff. weights**
$f_A^{\text{grown layer}}$	positive real	1
f_A	positive imaginary	2i
$f_B^{\text{surface skin}}$	positive real	1
$f_B^{\text{interior atoms}}$	positive imaginary	2i

- Affinity:
  - $(f_A, f_B^{\text{interior atoms}})$ overlap: **pos imag. * pos imag. = (-)ve real**
  - $(f_A^{\text{grown layer}}, f_B^{\text{surface skin}})$ overlap: **pos real * pos real = pos real**
  - $(f_A, f_B^{\text{surface skin}})$ && $(f_A^{\text{grown layer}}, f_B^{\text{interior atoms}})$ overlap: **ignore**

  - Maximal values indicate regions of high skin overlaps and low interior clashes, and therefore highly plausible docking sites.

Affinity based Scoring II

$$f_1(\vec{x}) = F_A^{grown\ layer}(\vec{x}) + F_A(\vec{x}) = F_A^{Re}(\vec{x}) + F_A^{Im}(\vec{x})$$

$$f_2(\vec{x}) = F_B^{surface\ skin}(\vec{x}) + F_B^{interior\ atoms}(\vec{x}) = F_B^{Re}(\vec{x}) + F_B^{Im}(\vec{x})$$

- The score of the overlap of two functions , one shifted by **x** is given by the integral of their product.

$$s(\vec{x}) = \int_{\vec{y} \in R^3} f_1(\vec{y}) f_2(\vec{x} - \vec{y}) d\vec{y}$$

- If we rotate the second function by **R**, we get the overlap score to be:

$$s(\vec{x}) = \int_{\vec{y} \in R^3} f_1(\vec{y}) (\Delta_R(f_2))(\vec{x} - \vec{y}) d\vec{y}$$

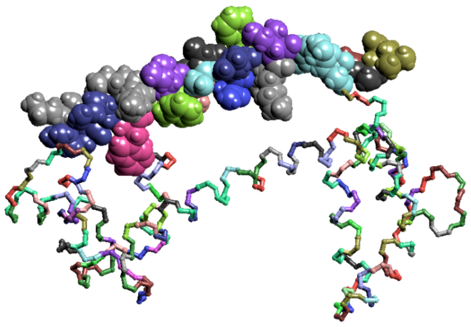
Location of the maximum score, over all **R** and **x** is recorded as a potential docking position:

$$\boxed{pos = arg\ max_{[\vec{x}, R]} \int_{\vec{y} \in R^3} f_1(\vec{y}) (\Delta_R(f_2))(\vec{x} - \vec{y}) d\vec{y},\ \forall\, [\vec{x}, R]}$$

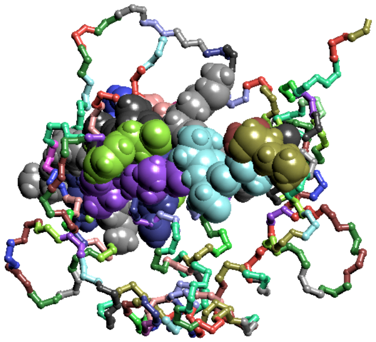
F^3 Dock: results

Calmodulin (1CLL.PDB) with a peptide (myosin light chain kinase)

148, 36 residues
98 conformation samplings to keep <2A difference.
Used 32^3 Fourier coefficients



Open pos: 6.2769



Closed pos: 9.8430

The docking position is in the list of the top 10% of all combinations checked

More Reading

- Molecular modelling: Principles and applications, A.R. Leach 2001, Prentice-Hall
- Molecular modeling and simulation: An interdisciplinary guide, T. Schlick 2003, Springer-Verlag
- Understanding molecular simulation: From algorithms to applications, D. Frenkel, B. Smit 1998 Academic Press
- Computer simulation of biomolecular systems, W.F. van Gunsteren et al. 1997 Kluwer

Further Reading: GB Theory

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6. A. Ghosh, C. Rapp, R. Friesner. Generalized Born model based on a surface integral formulation. J. Phys. Chem. B, 102, 10983-10990, 1998.

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Protein-protein docking

- **Early sphere matching by Kuntz et al.:**
  Irwin D. Kuntz, Jeffrey M. Blaney, Stuart J. Oatley, Robert Langridge, and Thomas E. Ferrin.
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- **Hashing based scheme:**
  Daniel Fischer, Raquel Norel, Ruth Nussinov, and Haim J. Wolfson.
  3-d docking of protein molecules.
  In CPM ’93: Proceedings of the 4th Annual Symposium on Combinatorial Pattern Matching, pages 20–34, London, UK, 1993. Springer-Verlag.
- **FFT grid based**:
  Ephraim Katchalski-Katzir, Isaac Shariv, Miriam Eisenstein, Asher A. Friesem, Claude Aflalo, and Ilya A. Vakser.
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- **ZDock:** (same algorithm as above)
  Rong Chen, Li Li, and Zhiping Weng. Zdock:
  An initial-stage proteindocking algorithm.
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- **Harmonics based algorithms:**
  Willy Wriggers and Pablo Chacon.
  Modeling tricks and fitting techniques for multiresolution structures.
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- **Hex:**
  D. Ritchie.
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Further Reading: Virtual Screening

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  D. S. Goodsell and Arthur J. Olson,
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