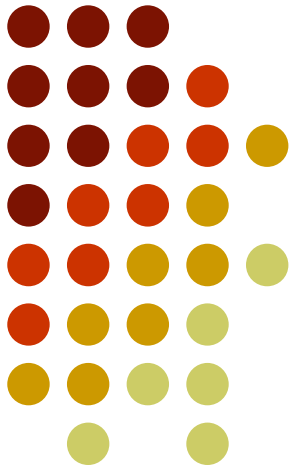
Implementing Spherical Harmonics in the Poisson Boltzmann Equation for the Electrostatic-Potential



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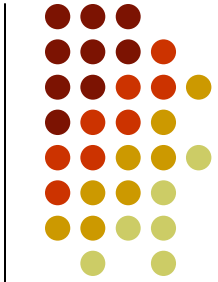
Mentors: Dr. Madura

Dr. Fleming

Background - Potential



Electrostatic Potential why important?

-electrostatic forces are derived from this

-changes with each configuration change

- clearly the potential is a vital yet complex calculation which needs to be performed optimally

-solved with the Poisson Boltzmann equation

Background – Poisson Boltzmann Equation

The Poisson Boltzmann Equation (PBE) is a *complex second order non-linear partial differential equation used the electrostatic potential*. It takes the following form.

$$-\nabla \cdot (\epsilon(\mathbf{r})\nabla\Phi(\mathbf{r})) + \bar{\kappa}^2 \left(\frac{k_B T}{e_c}\right) \sinh\left(\frac{e_c \Phi(\mathbf{r})}{k_B T}\right) = 4\pi \sum_{i=1}^{N_m} q_i \delta(\mathbf{r} - \mathbf{r}_i)$$

The hyperbolic sine term can be linearized resulting in the Linearized PBE (LPBE)

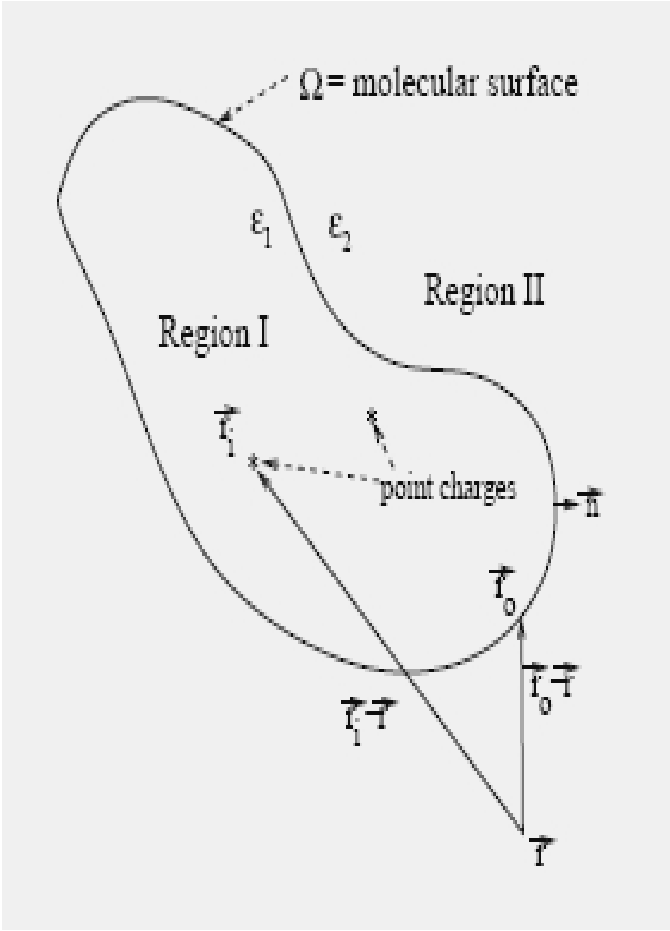
$$-\nabla \cdot (\epsilon(\mathbf{r})\nabla\Phi(\mathbf{r})) + \bar{\kappa}^2\Phi(\mathbf{r}) = 4\pi \sum_{i=1}^{N_m} q_i \delta(\mathbf{r} - \mathbf{r}_i).$$

Background- Molecular Case of the LPBE

- Discontinuous piecewise constant dielectric term
- Discrete individual point charges on molecule
- The LPBE splits into the following system

$$\nabla^2 \varphi_1(\vec{r}) = -\sum_{i=1}^{n_c} \frac{q_i}{\varepsilon_1} \delta(\vec{r} - \vec{r}_i) \quad \text{(Region I)}$$

$$\nabla^2 \varphi_2(\vec{r}) - \kappa^2 \varphi_2(\vec{r}) = 0 \quad \text{(Region II)}$$



Background- Boundary Element Method

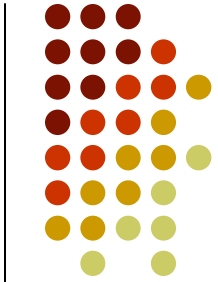
- Using Green's function we can convert the previous system of 2nd order PDEs to a system of *surface integrals* of the following form

$$\varphi_1(\vec{r}) = \int_\Omega \left[G_1(\vec{r};\vec{r}\,') \frac{\partial \varphi_1}{\partial n}(\vec{r}\,') - \varphi_1(\vec{r}\,') \frac{\partial G_1}{\partial n}(\vec{r};\vec{r}\,') \right] d\vec{r}\,' + \sum_{i=1}^{n_c} \frac{q_i}{\varepsilon_1} G_1(\vec{r};\vec{r}_i),$$

$$\varphi_2(\vec{r}) = \int_\Omega \left[-G_2(\vec{r};\vec{r}\,') \frac{\partial \varphi_2}{\partial n}(\vec{r}\,') + \varphi_2(\vec{r}\,') \frac{\partial G_2}{\partial n}(\vec{r};\vec{r}\,') \right] d\vec{r}\,',$$

This system is approximated using finite element methods creating a non sparse matrix

Project Idea



- Computational Speed and Efficiency
  - -Matrix Compression :

    ACA algorithm
- Accuracy
  - -Flexible approximation techniques:

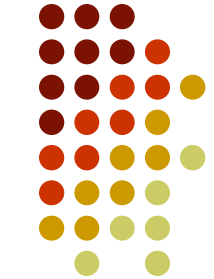
    we can specify the order of approximating polynomial
  - -Accurate functional representation:

    Spherical Harmonics

Project Idea part 1: Implementing ACA Algorithm

- Matrix manipulations are often the most computationally expensive
- Finite Element and Finite Difference Methods
  - Sparse large matrices
- Boundary Element Method
  - Smaller matrix but *not sparse*
- ACA compresses nearly singular portions of a surface integral matrix
- ACA programming and setting up the surface integral matrix consists of the bulk of the project

Project Idea part 2: Implementing Spherical Harmonics



- Clearly the solution of the PBE hinges on surface integrals
- To integrate over the surface we need a functional representation of the surface
- previously naive attempts were made fitting an ellipse over target molecule
- Spherical Harmonics can produce better shapes

Spherical Harmonics-What are they?

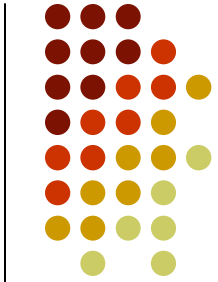
- an ortho-normal series of functions defined on the unit sphere (defined for all (phi,theta))
- a generalization of the Fourier series to the sphere
- an infinite dimension basis for all continuous functions defined on the unit sphere

$$Y_\ell^m(\theta,\varphi) = \sqrt{\frac{(2\ell+1)}{4\pi}\frac{(\ell-m)!}{(\ell+m)!}}\,P_\ell^m(\cos\theta)\,e^{im\varphi}$$

Spherical Harmonics-Why use them?

- we can express the radius of a star surface with a central point as a function of (phi,theta)
- this function can be then be written as an infinite sum of spherical harmonics
- we can specify the degree of accuracy by the adding harmonics
- for star shaped objects the spherical harmonics should converge to the shape

Spherical Harmonics- Coefficients



For each function there exists a unique spherical harmonic ***coefficient*** for each harmonic

$$f_\ell^m = \int_\Omega f(\theta, \varphi)\, Y_\ell^{m*}(\theta, \varphi)\, d\Omega$$

The coefficients obey the following property

$$f(\theta, \varphi) = \sum_{\ell=0}^{\infty} \sum_{m=-\ell}^{\ell} f_{lm}\, Y_{lm}(\theta, \varphi).$$

The coefficients also minimize the following quantity

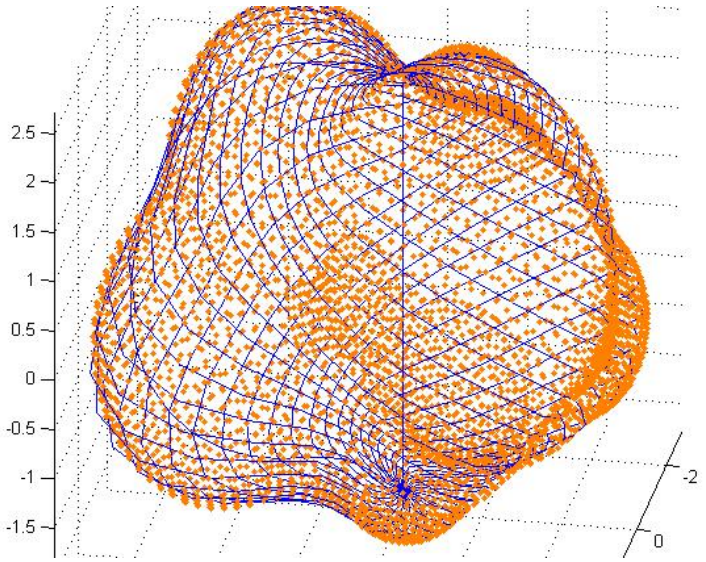
$$\int_H (r(\theta, \varphi) - \sum C_{nk} Y_{nk}(\theta, \varphi))^2 d\omega$$

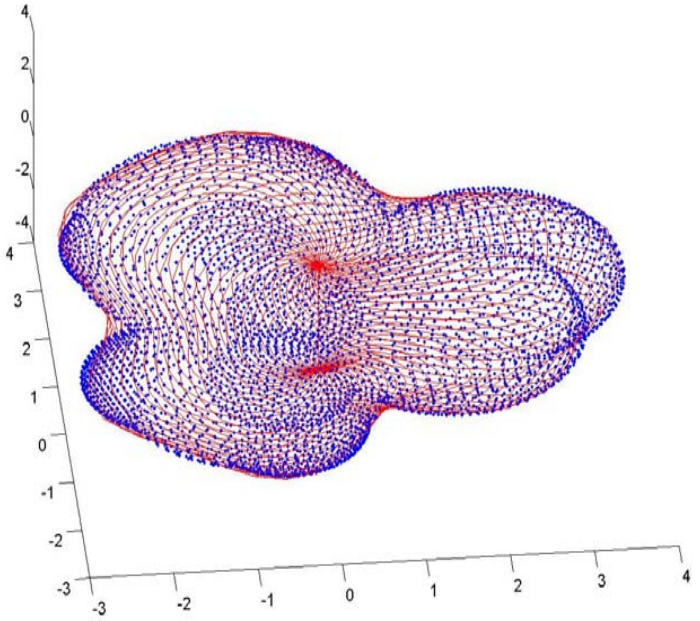
Spherical Harmonics- Process

- Start with a PDB file containing atomic coordinates of the nuclei of the molecule/protein
- Use Dr. Connolly's msroll program to generate a larger series of coordinates representing the dot surface of the molecule/protein
- Run spherical harmonics approximation of the desired degree

Results : Simple Amino Acids

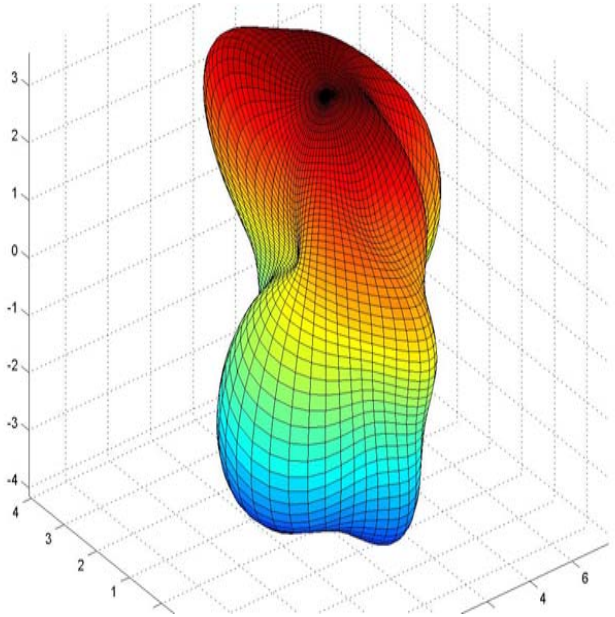
- Alanine: only 13 atoms, a common residue

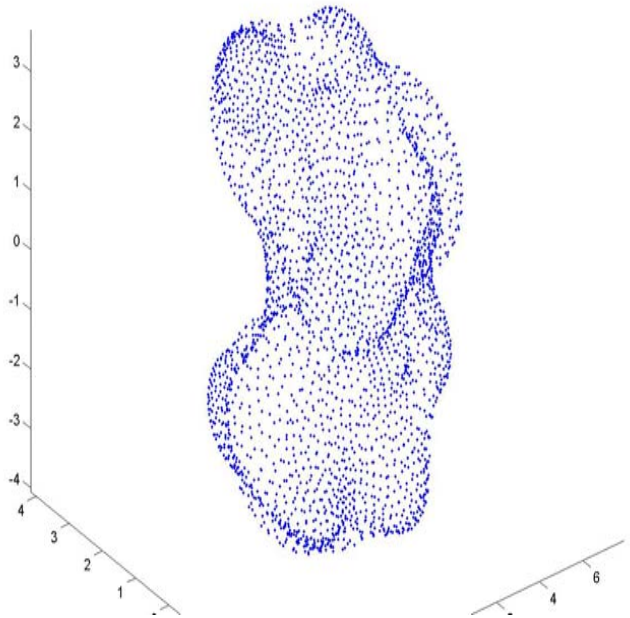




Results : Complex Amino Acids

- Tryptophan: 27 atoms

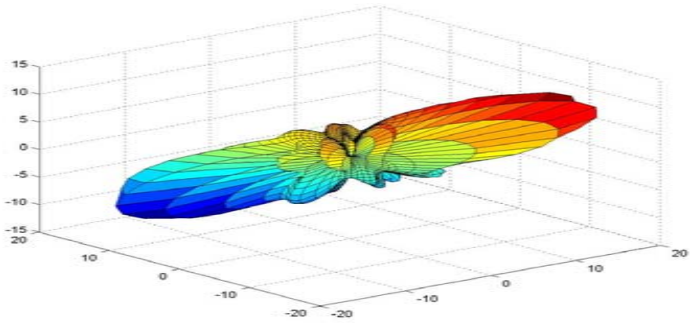


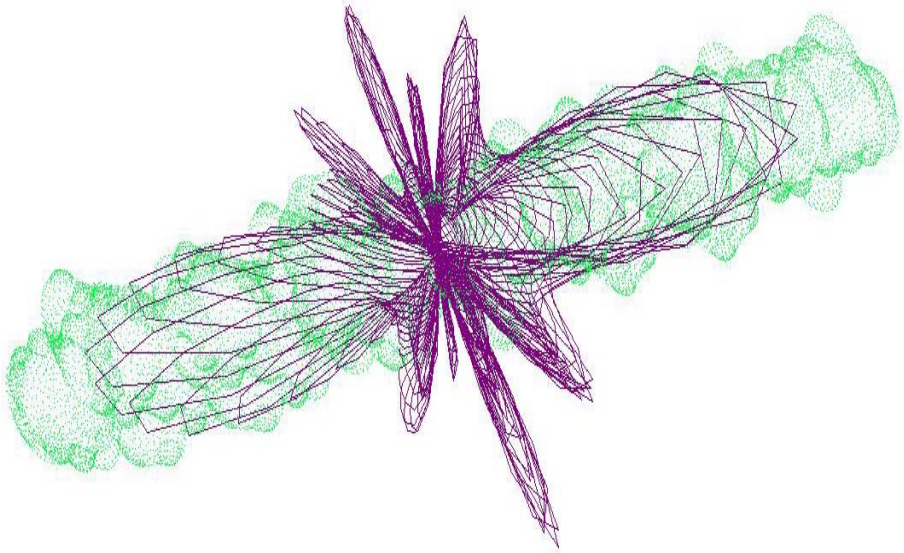


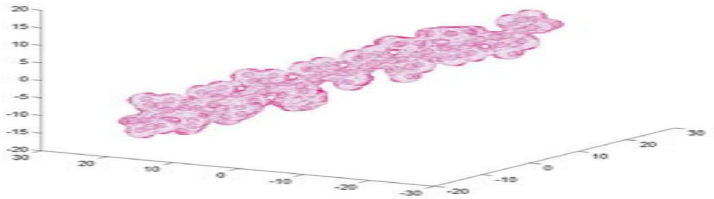
Results: Secondary Structure

Beta Pleated Sheets

~ 15 residues

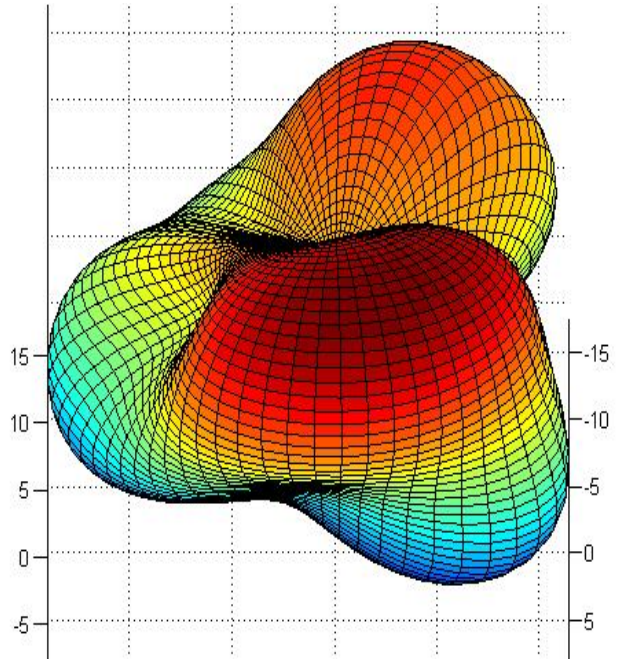


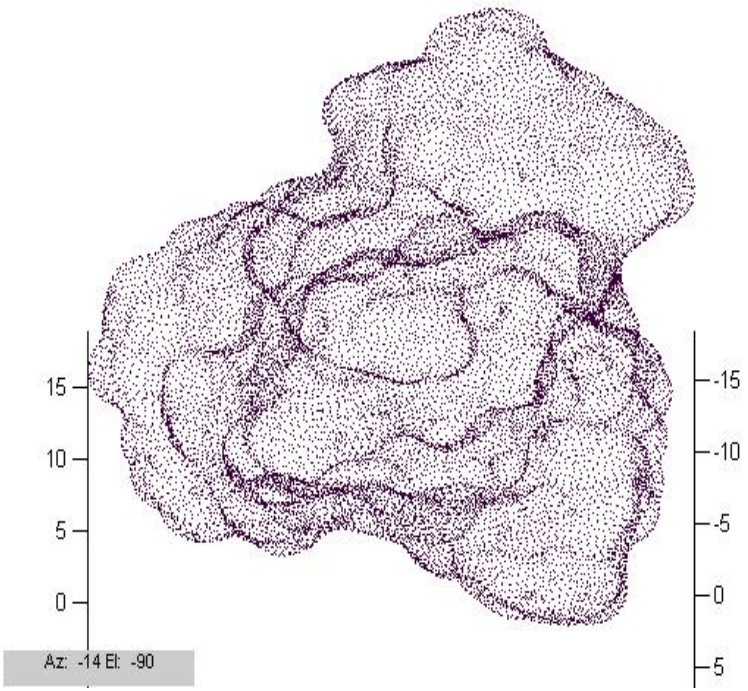




Results- Simple Proteins

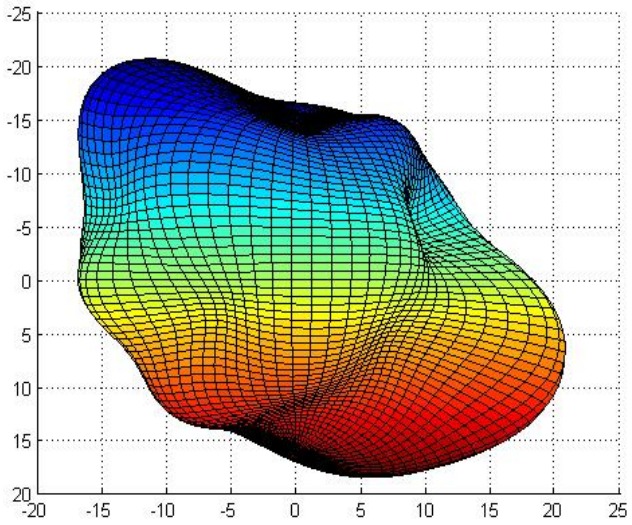
Due to slightly more regular shape these fit fairly well
Crambin: only 46 residues

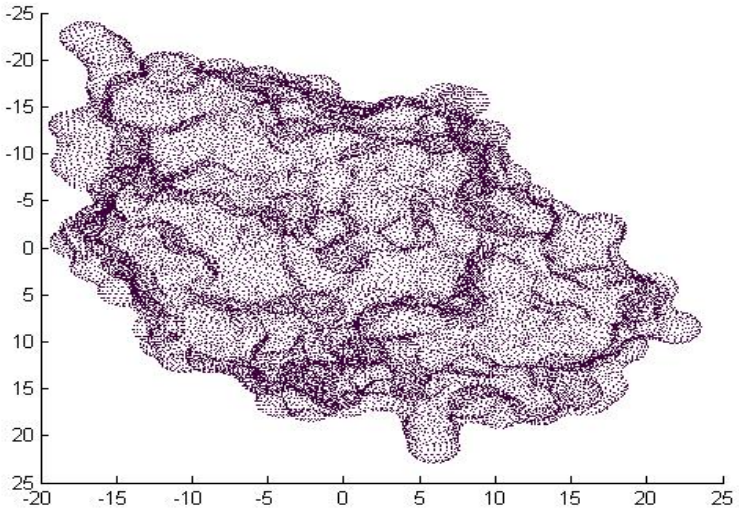




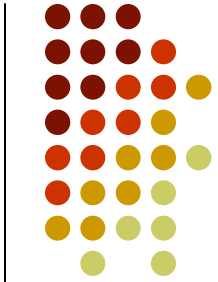
Results –Not so simple protein

- Lysozyme: 129 Residues



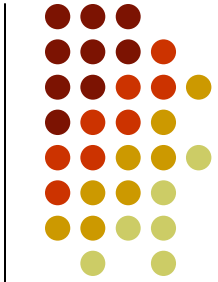


Results - Summary



- Single Amino Acids: excellent fit
- Secondary Structure: way off because of poor shape
- Proteins: doesn’t capture everything, but gives a pretty good general idea
- Overall fairly successful attempt

Thank You Slide



I would like to thank my mentors

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Dr. Fleming of Duquesne University

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I would also like to thank Dr. Michael L. Connolly for letting me use the Biohedron program to generate dot surfaces

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References

- Altman, Bardhan, Kuo, Tidor and White “Fast Methods for Simulation of Biomolecule Electrostatics,” *IEEE* 2002.
- Baker, Holst and Wang “Adaptive Multilevel Finite Element Solution of the Poisson-Boltzmann Equation 1 Algorithms and Examples,” *Journal of Computational Chemistry*, 2000.
- Boschitsch, Fenley and Zhou “Fast Boundary Element Method for the Linear Poisson-Boltzmann Equation,” *Journal of Physical Chemistry,* 2002.
- Connolly, “Solvent-Accessible Surface of Proteins and Nucleic Acids,” *Science*, Aug. 1983.
- Getzoff and Max “Spherical Harmonic Molecular Surfaces,” *IEEE Computer Graphics & Applications,* July, 1988.
- Grandison, Penfold and Vanden-Broeck “A rapid boundary integral equation technique for protein electrostatics,” J*ournal of Computational Physics,* 2006.
- Lee, Vouvakis and Zhao “The Adaptive Cross Approximation Algorithm for Accelerated Method of Moments Computations of EMC Problems,” *IEEE* 2005.