Parameterizing Docking Candidates to Evaluate Binding Affinity for SHP2 *in silico*

Nate Kitzmiller Stephen Leonard W. Scott McCullough

Abstract

We report on CHARMM General Force Field parameterization of small organic inhibitors for the SHP-2 active site with a view to performing molecular dynamics docking studies. The inhibitors come from two classes of competitive general phosphatase inhibitors, isothiazolidinone (IZD) phosphate mimetics and oxindole scaffolds. We use the VMD Force Field Tool Kit (ffTK) plugin to implement the CHARMM workflow. The geometry and size of the molecules present difficulties in determining the CHARMM parameters.

Background

- SHP2 is a tyrosine phosphatase involved in cell-signaling pathways. Inhibiting its active site is one method of determining its range of functions in the cell.
- Inhibitor andidates are from a general class of tyrosine phosphatase inhibitors called isothiazolidinone molecules and oxindole scaffolds.
- The CHARMM force field was chosen to take advantage of the CHARMM General Force Field small molecule parameters.
- We use ffTK, a VMD tool that streamlines the CHARMM process of fitting quantum mechanical calculations to molecular mechanics data in order to determine parameters for each candidate.

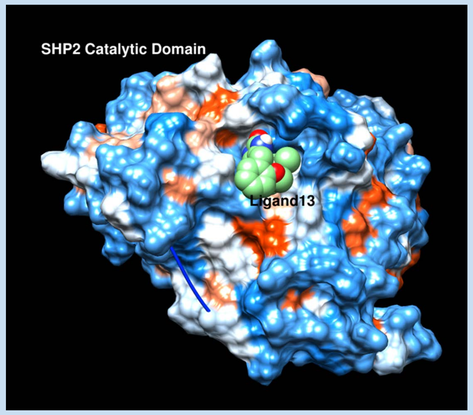

Figure 1: The SHP2 catalytic domain, displayed in the energy surface representation, with ligand 13, from Ref. 1. The ligand, shown in the Van der Waals representation, is occupying the active site of SHP2.

Methodology

We use the CHARMM general force field (CGenFF), summarized by the energy terms in Fig. 3, in order to capitalize on parameters optimized for a large set of common small molecules. The CGenFF approach allows the Lennard-Jones parameters and many more of these parameters to be set by analogy from the CGenFF parameter file. Further refinement involves choosing partial charges and parameters so that molecular mechanics reproduce vibrational and rotational frequencies calculated from quantum mechanics (QM). The QM frequencies are calculated using Gaussian software at the CHARMM-prescribed level of theory. We use the ffTK plugin from the VMD suite to guide the process and optimize parameter choices.

The basic CHARMM steps are

1. Construct a pdb file for the molecule and optimize its geometry at the MP2/6-31*G level of theory.
2. Optimize charge distribution using Hartree-Fock single point energy calculations for TIP3 water molecule interactions.
3. Optimize the force constants of each bond using QM vibrational data.
4. Optimize the dihedral angle parameters by matching them to QM-relaxed potential energy scans.

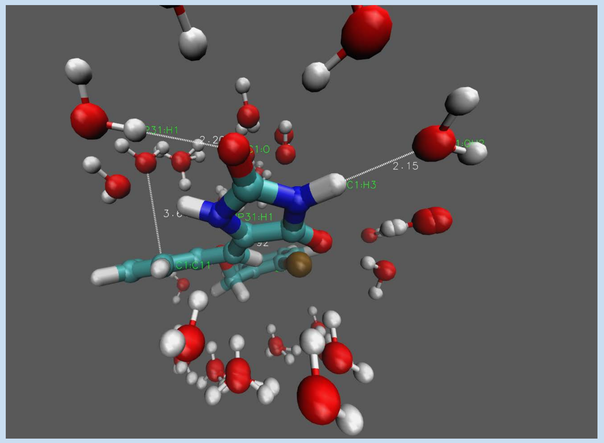

Figure 2: Geometry for single point energy calculations between the ligand atoms and TIP3 water molecules. Each atom was designated a hydrogen donor or acceptor in order to align the water molecule for interaction. The water molecules were constrained to move only in a straight line and change its dihedral angle in relation to a designated plane in order to implement the CHARMM criteria for parameterization.

$$U\left(\vec{R}\right) = \sum_{\text{bonds}} K_b\left(b-b_0\right)^2 + \sum_{\text{UB}} K_{UB}\left(S-S_0\right)^2 + \sum_{\text{angle}} K_\theta\left(\theta-\theta_0\right)^2 + \sum_{\text{dihedrals}} K_\chi\left(1+\cos\left(n\chi-\delta\right)\right) + \sum_{\text{impropers}} K_{\text{imp}}\left(\phi-\phi_0\right)^2 + \sum_{\text{nonbond}} \epsilon\left[\left(\frac{R_{min_{ij}}}{r}\right)^{12} - \left(\frac{R_{min_{ij}}}{r}\right)^{6}\right] + \frac{q_i q_j}{\epsilon_1 r_{ij}}$$

K_b, K_{UB}, K_θ, K_χ, K_{imp} are constants, b is the bond length, b_0 is the equilibrium bond length, S is the UB 1,3-distance, S_0 is the ideal UB 1,3-distnace, θ is the angle value, θ_0 is the equilibrium angle value, χ is the dihedral angle value, n is the periodicity, ϕ is the improper angle value, ϕ_0 is the ideal improper angle value, ϵ is the Lennard-Jones well depth, $R_{min_{ij}}$ is the distance at the Lennard Jones minimum, q_i and q_j are the atoms' charge ϵ_1 is the effective dielectric constant, r_{ij} is the distance between the atoms

Figure 3: CHARMM General Force Field potential energy function. http://cnx.org/resources/59c58b09f6fa8e02604473ed1e922f637638b96b/charmmfig.png

Status and Struggles

The ``small'' molecules are not always small and this sometimes makes the geometry optimization difficult. We apply usual remedies to get the QM calculations to converge.

We encountered difficulty in optimizing the charge distribution of candidates. Using too much or too little QM water data affects the minimization routine that optimizes the parameters.

The difficulty is compounded by geometries that result in steric clashes for the usual positioning of water molecules for single point energy calculations. We review all positioning and refine to avoid undesirable interactions with other atoms.

Lessons Learned

1. The “divide and conquer” approach of the CHARMM General Force Field is key to progress on molecules larger than 20 atoms.
2. It is essential to verify the results of quantum mechanical single point energy calculations and their effects on parameterization at every stage.
3. Too much quantum data or too little quantum data can impact convergence to determine partial charges.
4. Understanding the CHARMM philosophy in detail is essential to the parameterization process, even with a workflow tool like ffTK.

Future Direction

The goal is to rapidly characterize the candidate inhibitor molecules for binding affinity in order to prioritize experimental efforts to synthesize inhibitors in the laboratory.

References

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Contact Information

Dr. W. Scott McCullough
Indiana Wesleyan University
Marion, Indiana 46953
scott.mccullough@indwes.edu