**PARAMFIT:**
A program for automated forcefield parameter generation using a genetic algorithm

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The parameter-fitting algorithm was applied to a methylamine (NMe), and the fitted parameters were used to produce potential energy surfaces that were compared with both the default AMBER forcefield and one obtained using a quantum package.

*The parameter fitting was very effective in locating the correct parameter set.*

The algorithm's function evaluation rate was very effective in both locating the correct parameter set and providing estimates of missing data.

**Introduction**
Classical molecular dynamics simulations rely on a forcefield that characterizes each type of bond, angle, and dihedral in the system. Without accurate forcefield parameters, simulations will produce incorrect results that do not match experimental data. Furthermore, when existing forcefields fail to provide an accurate description, the accuracy of the simulation is difficult to improve because the parameters are difficult to change.

Although AMBER's ab initio program can be used to assign atom types to new species and provide estimates for missing parameters, it often cannot provide even an approximation for missing data.

**The lack of good parameters is especially problematic for protein or other simulations that rely on accurate peptide backbone dynamics.** NMR calculations can be used to assign the quantum parameters, but they are computationally intensive. When evaluated over a number of conformations, quantum programs can be used to make spectroscopic predictions, which will be similarly inaccurate when lacking parameters. The equilibrium dynamics of a simulated system can be performed using molecular dynamics data, and can give incorrect results even when the forcefield parameters are known.

**Geometry become especially evident.** When comparing the two optimized structures below, differences in N-H bond angles are especially evident. The graphs show the relative differences in energy of each structure, with the structure on the left being the reference structure.

**Algorithm**
A variety of conformations of the system are sampled using a quantum package to obtain the force for each atom using various methods. A minimization algorithm can be used to adjust the parameters. The result of the force calculations is then inserted back into the equations.

**Function Evaluation**
The difference between the MD and quantum methods is summed for each atom involved with the parameters to be optimized. The sum of the square of these values is the function value.

**Iteration**
The genetic algorithm progresses until there is no improvement after many generations, after which it is considered converged, and the best of past parameter sets is stored.

**Methodology**
Parameter-fitting may be accomplished to a limited degree by using quantum programs to sample each system and measuring parameters, but the potential surface will present a large number of minima and maxima. The quantum calculations are only feasible for small molecules, and it is often not for conducting protein or lipid simulations.

**Dihedral Geometry**
All-atomic quantum methods provide much greater accuracy, but at great computational cost, rendering them infeasible for all but the smallest of molecules. The accuracy of quantum methods can be greatly improved by using the assumption of classical methods to correct quantum methods. A minimization algorithm can be used to adjust the quantum parameters in order to improve calculations in simulations.

**Results**

**Conclusion**

Parameters for classical molecular dynamics simulations is difficult due to the many coupled degrees of freedom inherent in the problem. However, knowledge of the energy derivatives between evaluations with test parameters and quantum data for a variety of input structures is an effective means of improving parameters. Implementing a genetic algorithm to accomplish the minimization resulted in a program that can refine parameters at once with efficiency. The algorithm handles the large, multidimensional search space with ease, and provided that there are enough input configurations to provide an adequate sampling of the parameter space. A fitting of bond-angle, and dihedral parameters for a methyl amine has been done, and the final parameters are very effective in locating the correct parameter set and providing estimates of missing data. The parameter-fitting algorithm follows a simple five-step process. The algorithm runs efficiently on a desktop computer, and has been parallelized to run on multicore or multiple processors. High-performance computing resources may be used for the quantum energy calculations and the final evaluations.