

Working with Forcefield tools

Time: 15 minutes

Introduction

In molecular mechanics simulations, an essential step is to first assign a forcefield to the input molecule. For novice users, the CHARMM forcefield with automatic parameter estimation can be used to automatically assign complete forcefield parameters for almost any type of molecule. However, advanced users may find it desirable to modify and define their own forcefield parameters for certain residues. In addition, some other forcefields, such as charmm19 or charmm27, do not have automatic parameter estimation capability built in, so you must create new residue and atom types for systems other than common biomolecular monomers. For these forcefields, nonstandard residues may not be assigned forcefield parameters successfully, and manual customization of the residues is necessary to ensure complete forcefield assignment of the molecule. In Discovery Studio, you can use Forcefield tools to help the customization of residues during the forcefield assignment process.

In this tutorial, you will learn how to apply the charmm27 forcefield to proteins containing HEME residues, which cannot be typed automatically by charmm27. The following tasks are covered:

Applying charmm27 to a protein that contains a HEME residue

Customizing the HEME residue

Adding the customized HEME residue template to the charmm27 forcefield

Applying charmm27 to a protein that contains a HEME residue

Choose File | Open... from the menu bar and open Samples | Tutorials | Simulation | 1hho.pdb.

This opens the protein 1hho in the Molecule Window. The protein has an amino acid chain and a chain containing the HEME residue.

Open the Simulation | Change Forcefield tools.

From the Forcefield list, choose charmm27.

Click Apply Forcefield.

This applies charmm27 forcefield to the 1hho protein. Since charmm27 does not contain all parameters necessary, the following message appears: "1hho could not be typed with the current forcefield. See the Change Forcefield toolpanel for more information."

Click OK to dismiss the message.

The Forcefield Status tool panel displays "1hho is not fully typed with 1hho-charmm27". This is because the charmm27 forcefield does not have a residue template for the HEME residue.

Click More....

This brings up a Forcefield Window that details why 1hho cannot be fully typed with the charmm27 forcefield.

The Forcefield Window has two tabs: Residues and Atoms. The Residues tab lists all residues that cannot be typed by the standard residue template. For example, HEM143 is listed with a status of "No matching template" because it does not match any residue template of the charmm27 forcefield.

Click the Atoms tab.

The Atoms tab in the Forcefield Window lists all the atoms that do not have a forcefield type assigned. There are four atoms (NA, NB, NC, and ND) with a status of "Missing". Their forcefield type is unknown and listed as "?" in the table, as charmm27 forcefield failed to find an appropriate forcefield type for them.

Customizing the HEME residue

Now you can modify the HEME residue so it can be completely typed by charmm27 for use in simulation protocols. Begin by hiding everything except the HEME residue.

You can drag the tab of the Forcefield Window to the right side of the application to display the Molecule Window and the Forcefield Window side-by-side.

Click on the 1hho molecule window tab. Press CTRL+H to open the Hierarchy View if it is not already showing.

Expand the second chain A and select the HEM143 residue under the chain.

Right-click the Hierarchy View and choose Show Only.

Now only the HEME residue is shown in the Molecule Window.

Expand the HEM143 residue and select the NA, NB, NC, and ND atoms. You can also make this selection by clicking the row numbers in the Atom tab of the Forcefield Window, which causes the corresponding items in the Molecule Window to be selected, then click the Molecule Window tab to make it active again.

These are the four atoms in the Atoms tab of the Forcefield Window that do not have a forcefield type.

From the Forcefield Customization group of the Change Forcefield tool panel, click Modify Atom Type.

This opens the Choose a Forcefield Type dialog. This dialog allows you to either assign an existing or new forcefield type to the selected atoms.

Choose NPH as the Forcefield type for the four atoms, and then click OK.

In the Choose a Forcefield Type dialog, the Description field for type NPH is "heme pyrrole N", which matches the chemical environment for the four nitrogen atoms.

Alternatively, you may also define a new atom type by filling in the Type and Description fields.

Note: If you think the assigned atom type is incorrect, or you want to use your own parameters, you can choose a different forcefield type or define a new atom type for any atoms in the molecule. You can also modify the partial charges for the atoms in the Atoms tab.

Now all atoms have an assigned forcefield type and the Forcefield tool will automatically calculate the forcefield parameters needed for the molecule. Please check the Forcefield Window for any missing or estimated parameters that are not in the original forcefield.

The Forcefield Status tool panel now shows "1hho typed with 1hho-charmm27" since all atoms have forcefield type assigned, and all parameters are either provided or estimated by the charmm27 forcefield.

In the Forcefield Window, each of the four atoms in the Atoms tab now have the forcefield type as NPH. Notice that the Forcefield Window now has a few more tabs. In the Bonds, Angles, Torsions, and Improper tabs, estimated parameters associated with the HEME residue are listed. You can either accept these estimated parameters as is, or modify them appropriately based on other sources, such as accurate quantum mechanical calculations.

Once all parameters are acceptable, you can use the 1hho protein with charmm27 forcefield as input to Simulation protocols such as Minimization, or Standard Dynamics Cascade.

Adding the customized HEME residue template to the charmm27 forcefield

Once you have modified the HEME residue, you can also add it as part of your own forcefield library, so you do not have to manually assign the missing atom types each time when applying the charmm27 forcefield to HEME containing proteins.

In the Hierarchy View of the typed 1hho protein, select the HEM143 residue.

From the Change Forcefield tool panel, click Add Residue Template in the Forcefield Customization group.

This adds the HEME residue template along with any estimated parameters to your forcefield library. You can now use the template to type any other HEME containing proteins by charmm27 forcefield in the future.

You can check the residue template file (HEM143.rtf) and parameter file (HEM143.prm) for the HEME residue under your user's forcefield folder. The folder is stored in:

<Settings Folder>/Forcefield/charmm27

Note: For details about locations of folders in different operating systems, see Installation folders.

Note: If you are an advanced user who is familiar with the CHARMM file format, you can manually modify the RTF files under your Forcefield folder. You can also copy any new RTF and PRM files that are compatible with the corresponding forcefield to this folder. Any residue templates and parameter files placed under this folder will be used by the Forcefield engine after restarting the application. Be aware that a residue template will only be matched if the atom labels, order, and bonds of the residue are exactly the same as the RTF file.

Choose File | Open... from the menu bar and open Samples | Tutorials | Simulation | 2hhb.pdb.

From the Tools Explorer, click Apply Forcefield to apply the charmm27 forcefield.

The typing now complete without any messages and the Forcefield Status now displays "2hhb typed with 2hhb-charmm27".

Click More....

Although the HEME residue could not be typed by the original charmm27 forcefield, this molecule is now typed successfully because HEM has been added to the charmm27 forcefield's residue template library in the previous step. The Residues tab lists these as Matches custom template in the Status column of the Forcefield Window.

Further information

Work with forcefields

Forcefield Window

Choose a Forcefield Type dialog