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How to Assign CHARMM Parameters to Desmond-generated System with viparr4

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1 Works for me dx.doi.org/10.17504/protocols.io.bp53mq8n

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ABSTRACT

You can use the Schrödinger software suite to prepare systems for molecular dynamics simulations, however, only the OPLS _2005 and OPLS3e force fields can be automatically assigned. This tutorial will show you how to use Desmond with third-party force fields like CHARMM, using the Viparr utility from D.E. Shaw Research.

You will prepare a protein-ligand complex, generate custom CHARMM parameters for the ligand, and use the Viparr utility to convert the generated CHARMM parameters into a viparr-formatted template, that can be used for simulations.

You can find the input files for this tutorial here: **desmond_viparr_charmm-IPB_files.tgz**

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KEYWORDS

Molecular Dynamics, MD, Desmond, CHARMM, Amber, Force Field, Simulations

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MATERIALS TEXT

- Schrödinger Software version 2020-4 or newer installed on a supported platform with Linux
- Bash shell
- Optional: git

In order to run MDs with Desmond, you'll also need a GPU.

DISCLAIMER:

The converter tool described in this document is not supported by either Schrödinger Inc. or D.E. Shaw Research. For help please consult other Desmond users via Google Desmond Group.

ABSTRACT

You can use the Schrödinger software suite to prepare systems for molecular dynamics simulations, however, only the OPLS _2005 and OPLS3e force fields can be automatically assigned. This tutorial will show you how to use Desmond with third-party force fields like CHARMM, using the Viparr utility from D.E. Shaw Research.

You will prepare a protein-ligand complex, generate custom CHARMM parameters for the ligand, and use the Viparr utility to convert the generated CHARMM parameters into a viparr-formatted template, that can be used for simulations.

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BEFORE STARTING

You should have a working installation of the Schrödinger Software suite version 2020-4 or newer on a supported version of a supported Linux distribution. See Supported Platforms for more information.

Set the environment variable SCHRODINGER to the installation directory of the Schrödinger software. For example, for a bash shell, enter the following:

```
export SCHRODINGER=/path/to/schrodinger2020-4
```

Setting up a Schrödinger Python Environment

1 ⚠

Set up a Python Virtual Environment

In order to avoid compatibility issues with the Python modules, and ensure interoperability with Schrödinger's Python modules, use the Schrödinger software to create a new virtual environment.

1.1 Initialize a new Python virtual environment using the Schrödinger software:

```
%> $SCHRODINGER/run schrodinger_virtualenv.py schrodinger.ve
```

1.2 Activate the virtual environment:

```
%> source schrodinger.ve/bin/activate
```


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1.3 Upgrade pip:

```
[schrodinger.ve] %> pip install --upgrade pip
```

2 ⚠

Install the Viparr and Msys Utilities

Viparr is a utility developed by D.E. Shaw Research to assign force field parameters to systems, which can then be used to perform MD simulations with Desmond.

2.1 Download these two Python packages from D.E. Shaw Research's GitHub repository:

- Msys
- Viparr

These packages are distributed in the Python 'wheel' format, compatible with 'manylinux2014' Linux distributions.

2.2 Install the packages into the virtual environment

```
[schrodinger.ve] %> pip install msys-1.7.318-cp38-cp38-manylinux2014_x86_64.whl
[schrodinger.ve] %> pip install viparr-4.7.35-cp38-cp38-
manylinux2014_x86_64.whl
```

2.3 Clone the public Viparr parameters from D.E. Shaw Research's GitHub repository:

```
[schrodinger.ve] %> git clone git://github.com/DEShawResearch/viparr-
ffpublic.git
```

Alternatively, you can download the repository as ZIP archive: viparr-ffpublic

2.4 Set the VIPARR_FFPATH environment variable

```
[schrodinger.ve] %> export VIPARR_FFPATH=`pwd`/viparr-ffpublic/ff
```

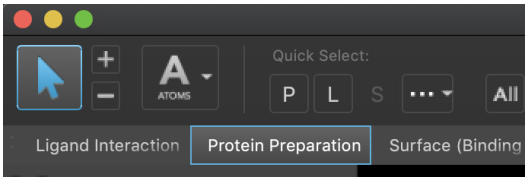
Preparing the Protein-Ligand Complex for Simulation

3 First, we download a structure from the protein data base (PDB) and prepare the protein-ligand complex. This tutorial uses a PDB structure for the human adipocyte lipid-binding protein FABP4 in complex with (S)-ibuprofen (PDB ID: 3p6h).We build the system with Schrödinger's Maestro and Desmond tools. The default force field used by the Schrödinger software is OPLS_2005 (OPLS3e if you have a license). After building the system for MD simulations, we can reassign the forcefield using Viparr.

To prepare the system for MD, open Maestro and follow these steps:

3.1 **Prepare the Protein-Ligand Complex**

In Maestro, go to **Tasks** → **Protein Preparation and Refinement** → **Protein Preparation Wizard** or click **Protein Preparation** in the toolbar.



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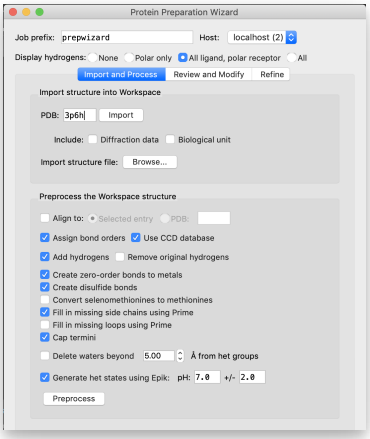
In the Protein Preparation Wizard, enter '3p6h' in the **PDB** text box, and click **Import** to download the structure from the PDB database and import it into Maestro.



Protein Preparation Wizard

After the PDB has been imported into the 3D workspace, preprocess the protein and the ligand. In the Protein Preparation Wizard, make sure the following options are selected:

- Assign bond orders
- Add hydrogens
- Create disulfide bonds
- Cap termini
- Fill in missing side chains using Prime (requires a Prime license)

Click **Preprocess**.

The Protein Preparation Wizard runs structural sanity checks and displays potential issues in a warning. In this tutorial, you can safely ignore these warnings and click OK to close the warning. In real applications, you should pay close attention to these warnings and resolve issues that may lead to problems during the MD simulations.

> For the 3p6h structure, the Protein Preparation Wizard shows missing atoms on the terminal residues. Since we cap the terminals, this is not an issue. Further, overlapping atoms and alternative residue positions can be ignored for this tutorial.

After the Protein Preparation Wizard finishes, a protein-ligand complex is added to Maestro's Workspace where formal charges, protonation states and bond orders are assigned and hydrogen atoms are added to the protein, ligand and crystallographic water molecules.

3.2 Solvate and Neutralize the Protein-Ligand Complex

Now that we have a protein-ligand complex loaded in the Workspace, we can solvate and neutralize the complex to prepare it for MD simulations.

In Maestro, go to **Tasks → Desmond → System Builder** to open the System Builder.

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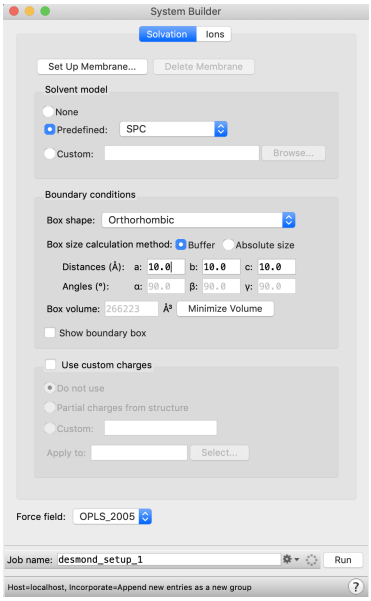

System Builder

Click **Run** to build the system with the default settings. By default, a water buffer of 10 Å and neutralizing counterions are added to the protein-ligand complex. The System Builder also assigns OPLS_2005 force field parameters (or OPLS3e if you have a license) to the protein-ligand atoms using SPC as the model for water.

After the System Builder finishes, a solvated system is added to Maestro's Workspace. The solvated system is also saved to a file *desmond_setup_1-out.cms*.

Generating Custom CHARMM parameters

4 To simulate a molecule that is not covered by the standard CHARMM parameter set, you first need to obtain topology and parameter files for that molecule. You can obtain parameters from one of these sources:

- Search the CHARMM message board to see if anyone else is willing to share their parameters: CHARMM forums
- Adopt parameters from the literature
- Use other computational chemistry tools to generate parameters, see the following:

1. A. D. MacKerrel's slide deck: PDF link
2. N. Foloppe and A. D. MacKerell (2000). JCC 21 (2): DOI link

- Use the CHARMM General Force Field (CGenFF) facility: website, DOI link
- Use the Paratool plugin for VMD: website
- Use the SwissParam server: website, DOI link

You can use any of the above methods to generate CHARMM-compatible parameters.

> To ensure that the parameters you intend to use are the ones that are being assigned, it is best if the topology and parameter files are self-contained and do not depend on other parameter files.

In this tutorial, we use the SwissParam server to generate topology and parameter files. Please refer to the original SwissParam documentation for more details on parameterization methods.

4.1 Export the Ligand as Mol2 File

The 3p6h complex contains a ligand: *Ibuprofen* (IBP). This ligand is not part of the standard CHARMM

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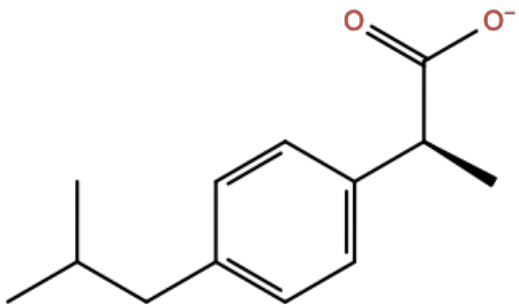
parameter set so you have to get its parameters from the SwissParam web server.



A 2D representation of *Ibuprofen*

The SwissParam server requires the ligand structure in a **.mol2** file. To prepare a .mol2 file with the prepared ligand structure, follow these steps:

1. Select the ligand atoms in Maestro's Workspace, right-click the selected atoms and select **Create New Entry by → Copying Selected Atoms**. This creates a new entry in Maestro only containing the ligand atoms.
2. Select the ligand entry in the **Entry List** on the left side of Maestro, right-click and select **Export → Structures**
3. Enter *'ibp.mol2'* as file name.

4.2 Generate Custom CHARMM Parameters with SwissParam

Upload the file **ibp.mol2** to the SwissParam web server and click **Submit**.

After the SwissParam web server finishes, a ZIP file **ibp.zip** is generated which contains these results:

- CHARMM topology file: **ibp.rdf**
- CHARMM parameter file: **ibp.par**

Extract these files from the ZIP archive.

4.3 Convert the CHARMM Parameters to a Viparr Template

The parameters need to be converted into a format that you can use with Desmond, enter the following command to generate a viparr-formatted template:

```
[schrodinger.ve] %> viparr-convert-charmm -p ibp.par -t ibp.rtf IBP
```

After the program finishes, a new directory **IBP** is created, which contains the viparr-formatted CHARMM template for Ibuprofen.

> The SwissParam web server renames the ligand's residue name to 'LIG'. Since viparr uses structure-matching to assign force field parameters, this is not an issue.

Assigning CHARMM Force Fields to the Molecular System

5 Now, we can reassign the CHARMM force field to the CMS file. **go to step #3.2**

The viparr utility comes with standard sets of protein parameters which we can use for the protein. For the ibuprofen ligand, we can use the viparr template in the directory IBP. **go to step #4.3**

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5.1 Run Viparr

To reassign the force field to CHARMM, enter the following command:

```
[schrodinger.ve] %> viparr desmond_setup_1-out.cms charmm-start.cms -f
aa.charmm.c36m -f ions.charmm36 -f water.tip3p_charmm -d IBP

Importing forcefield from /home/user/viparr-ffpublic/ff/aa.charmm.c36m
Importing forcefield from /home/user/viparr-ffpublic/ff/ions.charmm36
Importing forcefield from /home/user/viparr-ffpublic/ff/water.tip3p_charmm
Importing forcefield from IBP
Importing structure from desmond_setup_1-out.cms
WARNING: will NOT fix prochiral atom names because rename_atoms or
rename_residues was not enabled
Exporting parametrized system to charmm-start.cms
VIPARR exited successfully
```

This command assigns the CHARMM36m parameters to the proteins and ions, uses CHARMM's Tip3p water model, and uses the template directory IBP for the ibuprofen ligand. After viparr finishes, a new file: **charmm-start.cms** is created which contains the structure and CHARMM force field information.

5.2 Clean Properties and Prepare for MD

To prepare the converted system for MD simulations, certain properties need to be removed from the CMS file and the full-system structure needs to be prepared. Run the Python program:

gen_fsys.py

```
%> $SCHRODINGER/run gen_fsys.py charmm-start.cms
```

This script will overwrite the file **charmm-start.cms**. The system is now ready for simulation.

Running an MD Simulation with Desmond

6 Now that the system is prepared with CHARMM parameters, Desmond can minimize, equilibrate, and run an MD simulation of the system. For further information check the *Desmond User Manual.*

6.1 Set up an MD Simulation

In Maestro, go to **Tasks → Desmond → Molecular Dynamics** to open the **Molecular Dynamics** panel.

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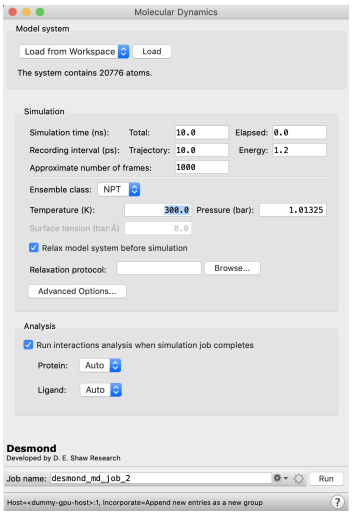

Molecular Dynamics Panel

In the **Model system** section, choose Import from a file, and click Browse to locate and load **charmm-start.cms**

1. In the **Model system** section, select **Import from file**, browse to the file **charmm-start.cms**, and click **Load**.
2. *Optional:* Adjust simulation parameters, such as simulation time.
3. Ensure the **Relax model system before simulation** checkbox is selected.
4. *Optional:* Enter a job name, click the gear icon to change job settings, or click the **?** icon to open the Help for more information.
5. Click **Run** to start the MD simulation.

6.2

Analyze the Results

In Maestro, go to **Tasks → Desmond → Simulation Interactions Diagram** (SID) and run the analysis.

For comparison, we ran a 10 ns MD simulation. The SID report is attached as PDF:
desmond_md_job_1.pdf

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