**MOE GPCR Induced Fit Docking Tutorial**

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The following table outlines the steps required to dock a small molecule into a GPCR receptor structure using MOE 2020.

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| **Step** | **Description** | **Figure** |
| 1 | Click *File* 🡪 *Open* and then click on the PDB icon on the left-hand side of the window. Type in your 4 letter PDB ID code in the *Codes* box and then click *OK*. Alternatively, download your desired structure from <https://gpcrdb.org/structure/> or https://www.rcsb.org/downloads. |  |
| 2 | Open the sequence editor by clicking *SEQ* in the top right corner of the MOE window. At this point, some things may or may not need to be deleted from the downloaded crystal structure.   * If the structure you’ve downloaded contains non-GPCR sequence segments (e.g. fusion partners) they will need to be deleted. These are typically numbered starting at 1001 and can be deleted by selecting the non-GPCR sequence segment residues and using the Delete key. If your sequence is not showing numbers, make sure to click the “13A ALA” box in the bottom right of the sequence editor to show the residue numbers. * Waters (represented by a “W” residue) will also need to be deleted. * If your crystal structure contains ligands that are not located within the receptor’s binding pocket (i.e. ligands you do not wish to dock), they should also be deleted. |  |
| 3 | The structure can then be energetically minimized and pronated using the *QuickPrep* function in MOE that is located on the upper right side of the MOE window. Open the *QuickPrep* panel and click *OK* to prepare the structure using default settings. |  |
| 4 | To ensure correct protonation at pH 7.4, the *Protonate 3D* function can be used. Click *Compute* 🡪 *Prepare* 🡪 *Protonate 3D…* to open the *Protonate 3D* window, change the pH to 7.4, and click *OK*. |  |
| 5 | Two methods can be used to select a site for docking:   1. The first uses the *Site Finder* function to identify a probable binding site. Click *Compute* 🡪 *Site Finder…* to open the *Site Finder* window. In the *Site Finder* window, click *Apply* to identify probable binding sites within your receptor structure. After ensuring that *Select Contact Atoms* is checked, click the first binding site and then click *Close*. Open the sequence editor and ensure that the selected residues are within the extracellular portion of the receptor (at the top of the receptor structure near extracellular loops 1, 2, and 3). If the first selected binding site isn’t located toward the extracellular side of the receptor structure, use *Site Finder* again but click the second binding site instead. Repeat this process as necessary until a probable binding site is elucidated. 2. If you wish to dock at a specific set of residues, they can be selected using the sequence editor. Open the sequence editor and then *Ctrl+*click each residue you wish to dock at. |  |
| 6 | Open the docking menu by clicking *Compute* 🡪 *Dock*. By default, MOE will set the receptor and ligand to those currently opened in MOE. Some settings here will need to be changed in order to dock at the desired site as well as ensure that induced fit docking is utilized. Provided that the ligand shown is the ligand you wish to dock, the following changes should be made in the docking window:   * **Site** should be changed from Ligand Atoms to **Selected Atoms** * **Placement Poses** should be changed from 5 to **400** * **Refinement** should be changed from Rigid Receptor to **Induced Fit**   Next, enter the desired name of your output database in the **Output** section of the panel (example\_dock.mdb in this case) and then click *Batch…* to open the *Batch:Dock* window. In the *Batch:Dock* window, click *OK*. In the window that pops up, click *Yes* and then *OK*. |  |

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| 7 | In the directory that was created, there should now be 3 files: lig.moe, rec.moe, and run.sh. In order to run the docking job on the University’s HPC cluster, a batch file must be created. Create a new text file using a text editor (I recommend Notepad++) and paste the following:  #! /bin/csh  #SBATCH --ntasks=4  #SBATCH --partition=computeq  #SBATCH --job-name=dock  /public/apps/moe/moe2020/bin-lnx64/moebatch -exec "run 'run.sh'"  The above code names the job “dock”, though it can be changed to better describe the job. In the directory containing the lig.moe, rec.moe, and run.sh files, save the text editor file as “dock.sh” from your text editor and then close the text editor. |  |
| 8 | Prior to performing any docking, the necessary files must be present within a folder on the HPC. Use Filezilla (or an alternate SFTP client) to log in to the HPC and transfer job files. Here is how to login:   * Host: type “sftp://username@hpclogin.memphis.edu”. Make sure to change the “username” string to your U of M username. The SFTP string is important since it is the HPC’s preferred method of file transfer. * Username: can be left blank * Password: Your account password * Port: blank |  |
| 9 | Move the folder containing the lig.moe, rec.moe, run.sh, and dock.sh files into a folder on your HPC directory. In the left pane (local directory), navigate to the directory containing the folder containing your docking files (example\_dock in this case). In the right pane (HPC directory), create a folder you wish to run your jobs in or navigate to a pre-existing folder. Drag the folder containing the docking files from the left pane into the right pane and wait for the upload to complete. |  |
| 10 | Once the docking files are present on the HPC, a command line must be opened using an SSH client. In this case, PuTTY will be used (<https://www.putty.org/>). Once installed, PuTTY can be configured as follows:   * - Hostname:   username@hpclogin.memphis.edu, where username is your HPC account username.  Click *Open* and type your password into the window that is created once prompted for it. |  |
| 11 | Once logged into your HPC directory, use the command cd to navigate to the folder containing the files that were moved using Filezilla. (ex. cd example\_dock). The ls command can be used to list the files in the folder you are currently located in. Reminder: the folder you should be in at this step should contain the rec.moe, lig.moe, run.sh, and dock.sh files. |  |
| 12 | The job can be run using the following command:  sbatch -D . dock.sh  If sbatch returns an error due to line break formatting, use the command dos2unix dock.sh to correctly format the job file. Once the job is finished, a new .mdb file will be present in the job directory that contains the docking results. This file can be downloaded with FileZilla and opened in MOE.  The progress of jobs can be checked using the command squeue -u username, where “username” is your username. This command will display the status of a user’s current jobs and is helpful for determining which jobs are done and which are still pending/running. |  |