

Molecular Simulations Workshop: Proteins (protein drugs) simulations: (3)

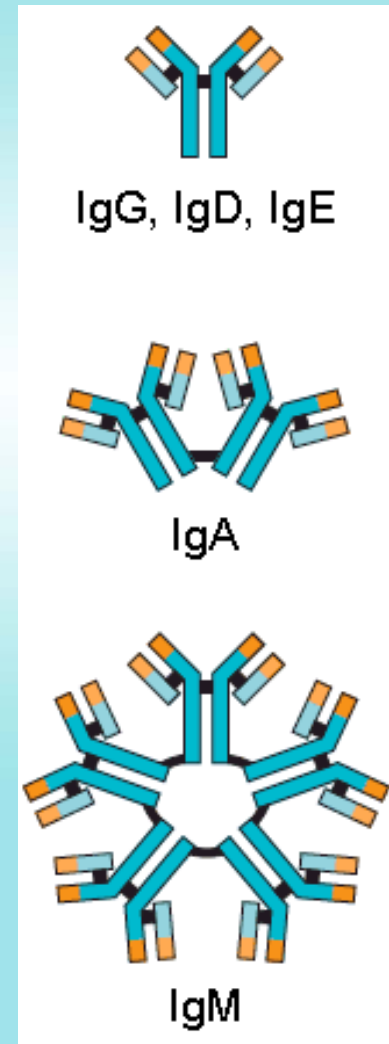
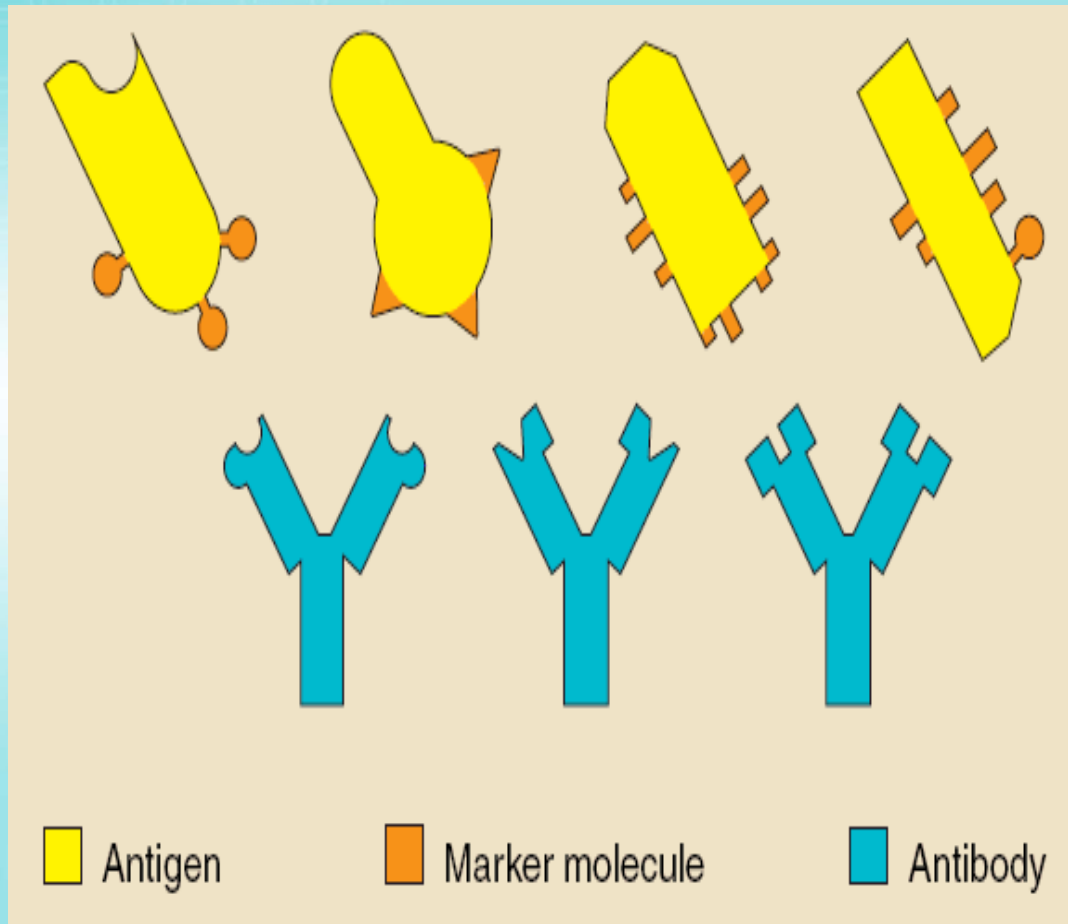
Applied Scientific Computing Division, National Center
for High-Performance Computing

Yeng-Tseng Wang

Email: c00jsw00@gmail.com



Binding hot spots: Antibody-antigen



Binding hot spots: Antibody-antigen

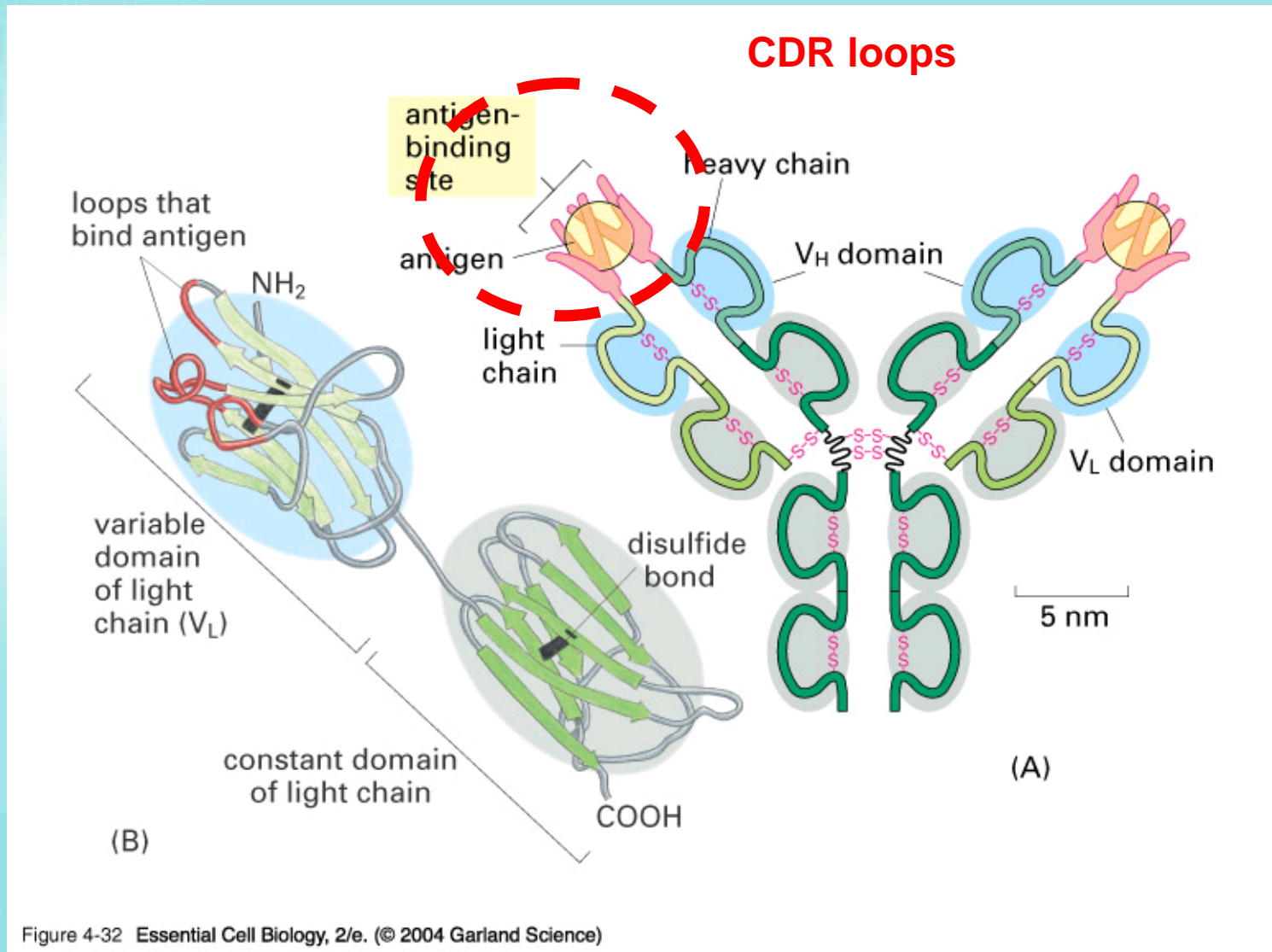
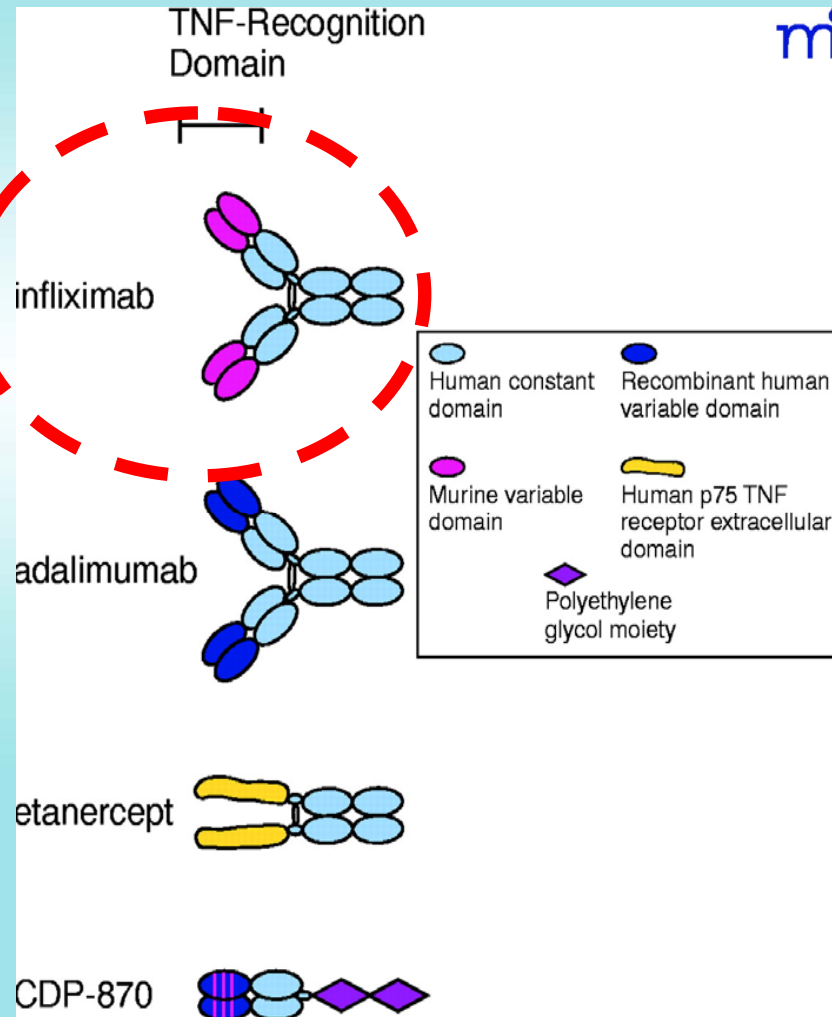
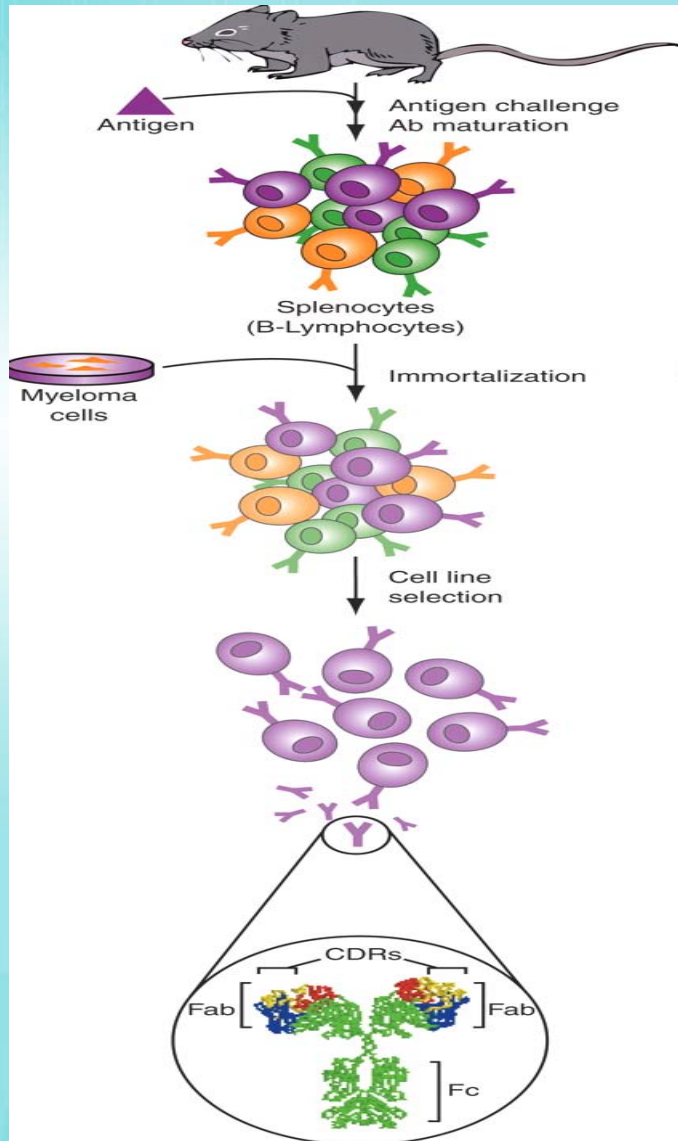


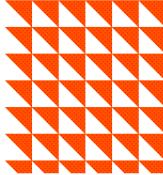
Figure 4-32 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Binding hot spots: Antibody-antigen

Rheumatoid arthritis




Binding hot spots: Antibody-antigen



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Please cite the following reference:

Tuncbag N, Gursoy A, Keskin O. Identification of computational hotspots in protein interfaces: combining solvent accessibility and inter-residue potentials improves the accuracy. *Bioinformatics*. 2009 Jun 15;25(12):1513-20. [\[Link\]](#)

Below you can try our prediction algorithm by entering the four letter PDB code of a protein or uploading your own structure file that is in the PDB format with the chain identifiers. Please do not submit PDB files containing only one chain. This will return an error! Hotpoint requires two chain identifiers which corresponds to a protein interface.

Run our prediction algorithm for a particular input protein.

Enter the four letter PDB code for automatic download from PDB:

Or load your structure file from disk:

Enter the one letter chain identifiers for interface generation.

Chain1: Chain2:

Enter the distance threshold to fetch the interface residues.

Default:The sum of van der Waals radii of two atoms + 0.5Å

User defined distance threshold (Å):

<http://prism.cccb.ku.edu.tr/hotpoint/>

Binding hot spots: Antibody-antigen

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Here are [instructions](#) in case you run into trouble. They will help you avoid common mistakes, such as uploading a file with only one chain, files with odd naming conventions, or files that contain non-amino/nucleic acid groups at ATOM records.

Required input

<input type="text" value="Username (or type 'guest')"/>	AND	<input type="text" value="Email Address"/>
<input type="text" value="Upload Complex"/> 瀏覽...	OR	<input type="text" value="PDB Code"/>
<input type="text" value="Protein 1 Chainlist"/>		<input type="text" value="Protein 2 Chainlist"/>
<input type="text" value="Job Name"/>		<input type="button" value="Submit"/>


Note: You may leave the chain identifiers blank if your PDB file contains a complex of exactly two chains separated by a TER record. Do not upload structures containing only a single chain, as this will return an error.

Optional input

<input type="text" value="Consurf Scores"/> 瀏覽...	<input type="text" value="Rosetta AlaScan"/> 瀏覽...	<input type="text" value="Experimental Data"/> 瀏覽...
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Upload Instructions

Please [register](#) if you wish to maintain an archive of your KFC jobs. Users may also submit jobs using the login name **guest**, with or without an email address. If you do not provide an email address, your results will only be accessible via the job queue.

Place your mouse over the  icon for information about each field.

Please **do not** submit PDB files containing only one chain! The KFC model requires a protein **interface**, meaning **two** or more chains in contact with one another. If you want to predict functional residues for a single protein chain, we highly recommend that you look into [Consurf](#) or [Evolutionary Trace](#) or one of the many websites mentioned in this [paper](#).

<http://kfc.mitchell-lab.org/>

Tutorial 3: Ibalizumab

Creating proteins structure:

- 1.Pdb ID: 3O2D (TMB355)
- 2.Submitting 3O2D file to H++ server

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Friday
September 30th 2011
02:31:31 AM EST

VERIFY YOUR STRUCTURE

The information retrieved from your structure:

Title: 3NU6.1.pdb: unknown
pH: unknown
Model Count: 1
ESTIMATED RUN TIME: 0 hrs 1 min 19 sec (Actual time will vary depending on load on the H++ server)
0

Titratable sites (estimated): 44
Model Number: 1
Chain Count: 1
Chain Number: 1
Number of Amino Acids: 99
Number of Nucleic Acids: 0

Calculations will be performed using the following physical conditions:

Salinity:
Internal Dielectric:
External Dielectric:

The pdb structure will be protonated assuming pH of:

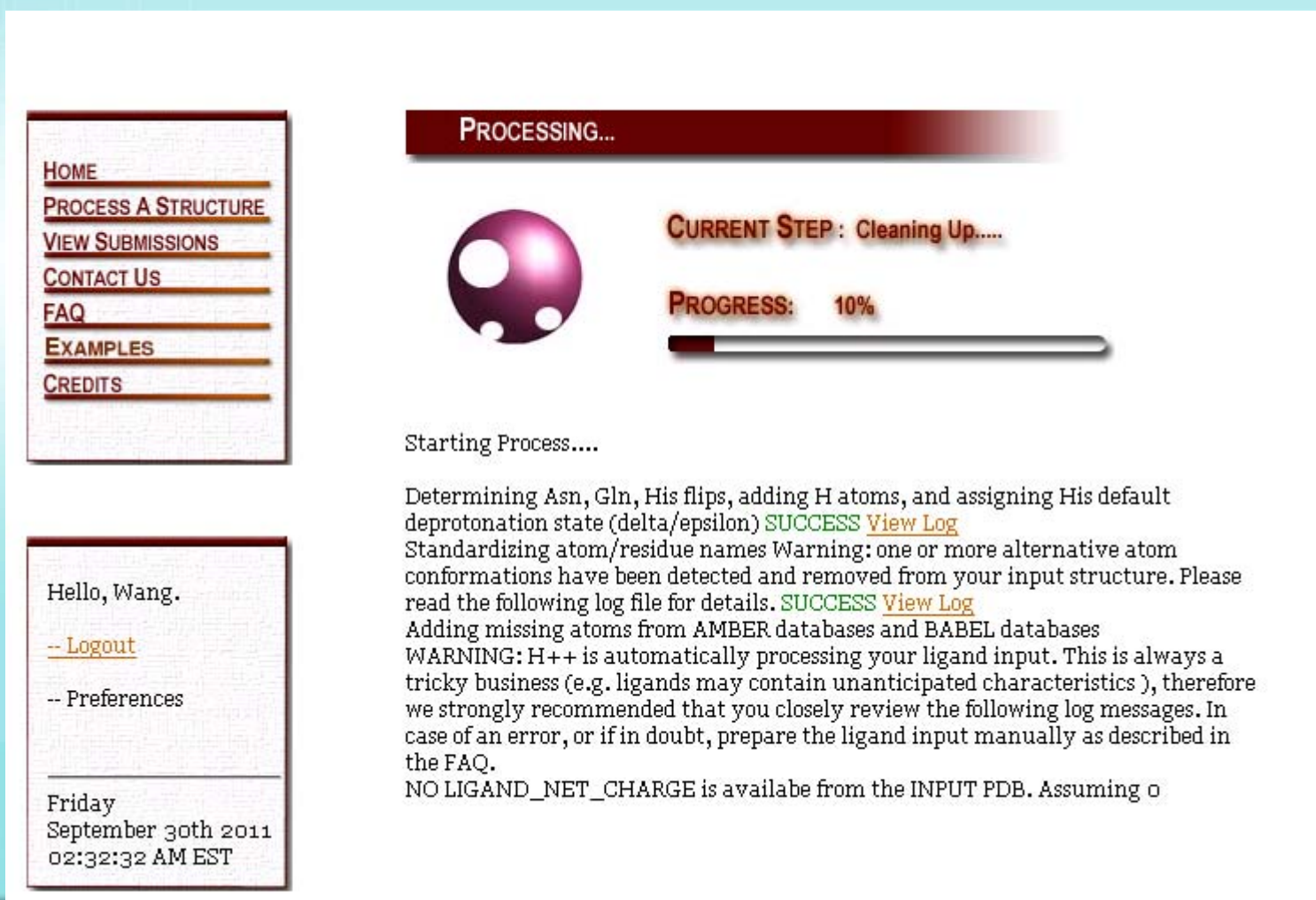
Correct orientation of ASN, GLN and HIS groups, add H atoms, and assign HIS H atoms to the δ or ϵ O, based on van der Waals contacts and H-bonding.

Output Options:
Prepare explicit solvent box topology/coordinate files (AMBER):

Tutorial 3: Ibalizumab

Creating proteins structure:

3. Waiting for the H++ server ~10 min



The screenshot displays the H++ web interface during a protein structure processing task. On the left, a navigation menu includes links for HOME, PROCESS A STRUCTURE, VIEW SUBMISSIONS, CONTACT US, FAQ, EXAMPLES, and CREDITS. Below the menu, a personalized greeting reads "Hello, Wang." with links for "-- Logout" and "-- Preferences". The date and time are shown as "Friday September 30th 2011 02:32:32 AM EST".

The main content area features a dark red header with the text "PROCESSING...". Below this is a purple and white circular logo. To the right of the logo, the text "CURRENT STEP: Cleaning Up...." is displayed above a progress bar that is 10% full. Below the progress bar, the text "PROGRESS: 10%" is shown.

Starting Process....

Determining Asn, Gln, His flips, adding H atoms, and assigning His default deprotonation state (delta/epsilon) **SUCCESS** [View Log](#)
Standardizing atom/residue names **Warning:** one or more alternative atom conformations have been detected and removed from your input structure. Please read the following log file for details. **SUCCESS** [View Log](#)
Adding missing atoms from AMBER databases and BABEL databases
WARNING: H++ is automatically processing your ligand input. This is always a tricky business (e.g. ligands may contain unanticipated characteristics), therefore we strongly recommended that you closely review the following log messages. In case of an error, or if in doubt, prepare the ligand input manually as described in the FAQ.
NO LIGAND_NET_CHARGE is available from the INPUT PDB. Assuming o

Tutorial 3: Ibalizumab

Creating proteins structure:


4. Downloading GB and TIP3 files


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PROCESSING...



CURRENT STEP: Done. 

PROGRESS: 100%


Starting Process....

Determining Asn, Gln, His flips, adding H atoms, and assigning His default deprotonation state (delta/epsilon) [SUCCESS View Log](#)
Standardizing atom/residue names Warning: one or more alternative atom conformations have been detected and removed from your input structure. Please read the following log file for details. [SUCCESS View Log](#)
Adding missing atoms from AMBER databases and BABEL databases
WARNING: H++ is automatically processing your ligand input. This is always a tricky business (e.g. ligands may contain unanticipated characteristics), therefore we strongly recommended that you closely review the following log messages. In case of an error, or if in doubt, prepare the ligand input manually as described in the FAQ.
NO LIGAND_NET_CHARGE is available from the INPUT PDB. Assuming o
[SUCCESS View Log](#)
Optimizing positions of the added hydrogens [SUCCESS View Log](#)
Adding atomic charges and radii from AMBER databases [SUCCESS View Log](#)
Checking file for consistency [SUCCESS View Log](#)
Identifying titratable sites... [SUCCESS: found 46 sites. View Log](#)
Setting up Electrostatic Calculations [SUCCESS View Log](#)
Calculating using Poisson-Boltzmann... [SUCCESS View Log](#)
Computing partition sum via clustering algorithm... [SUCCESS View Log](#)
Number of sites is more than 25, no energy diagram available Adding/Removing protons according to the computed pKs... Preparing AMBER coordinate/topology files... Re-optimizing positions of the added hydrogens... [SUCCESS View Log](#)
Reindexing... Collecting data ... [SUCCESS](#)
DONE

Structure has been processed. [VIEW RESULTS.](#)

Tutorial 3: Ibalizumab

Creating proteins structure:

4. GB and Tip3 water box simulations (the same as before)

Reference to the files

(gb.md.in gb.min.in polyAT_wat_md1.in polyAT_wat_md2.in polyAT_wat_min1.in polyAT_wat_min2.in 3O2D.sh 3O2D.TIP3.sh)

5. \$BRIMM_ROOT/bin/sietraj -pt 3O2D.top -trj 3O2D.md.x -sf 1 -ef 100 -inc 10 -tr 1-6633 -lr 6634-9434 -o gb.sie.out -sie

6. \$BRIMM_ROOT/bin/sietraj -ave gb.sie.out

```
Energies in kcal/mol:
```

	Average	StdErr	Stdev
Inter vdW	-127.27	2.31	7.31
Inter Coulomb	13.13	3.77	11.92
Reaction Field	-0.40	2.83	8.94
Cavity	-24.51	0.31	0.97
Constant	-2.89	0.00	0.00

Delta G	-17.46	0.35	1.11

Tutorial 3: Ibalizumab

further study

1. Mutating the residues of CDR loops/ binding-hot spots residues and running MD simulations.
2. Using the same methods to analyze the potential energies and RMSD profiles.

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Enter the distance threshold to fetch the interface residues.

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 User defined distance threshold (Å):

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Required input

Username (or type 'guest'): AND Email Address:

Upload Complex: OR PDB Code:

Protein 1 Chainlist: Protein 2 Chainlist:

Job Name:

Note: You may leave the chain identifiers blank if your PDB file contains a complex of exactly two chains separated by a TER record. Do not upload structures containing only a single chain, as this will return an error.

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