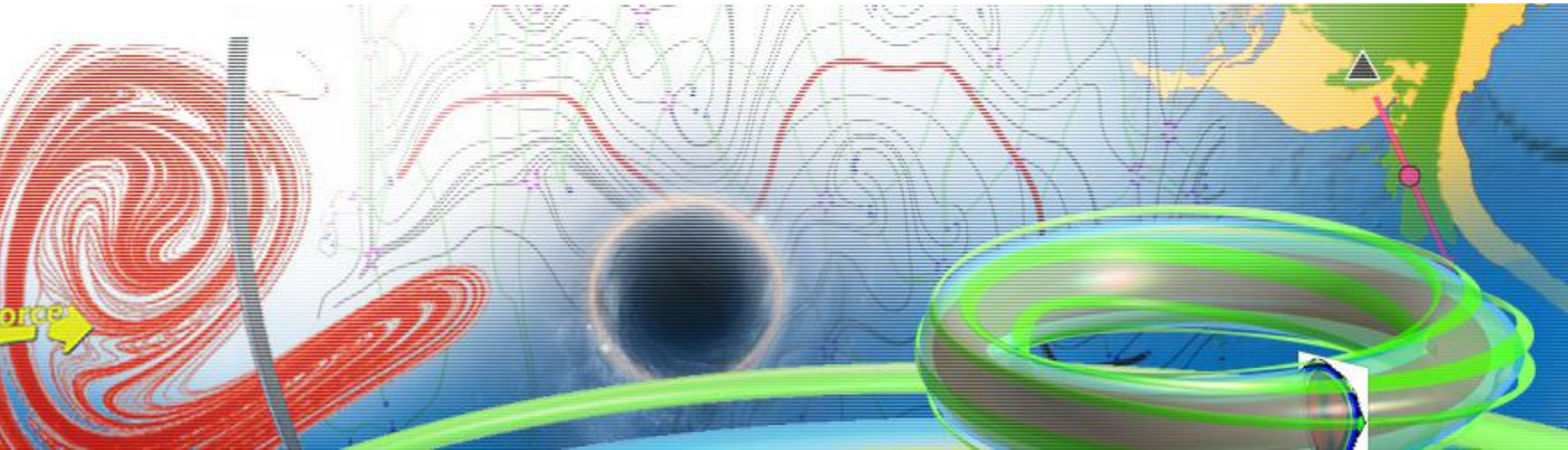
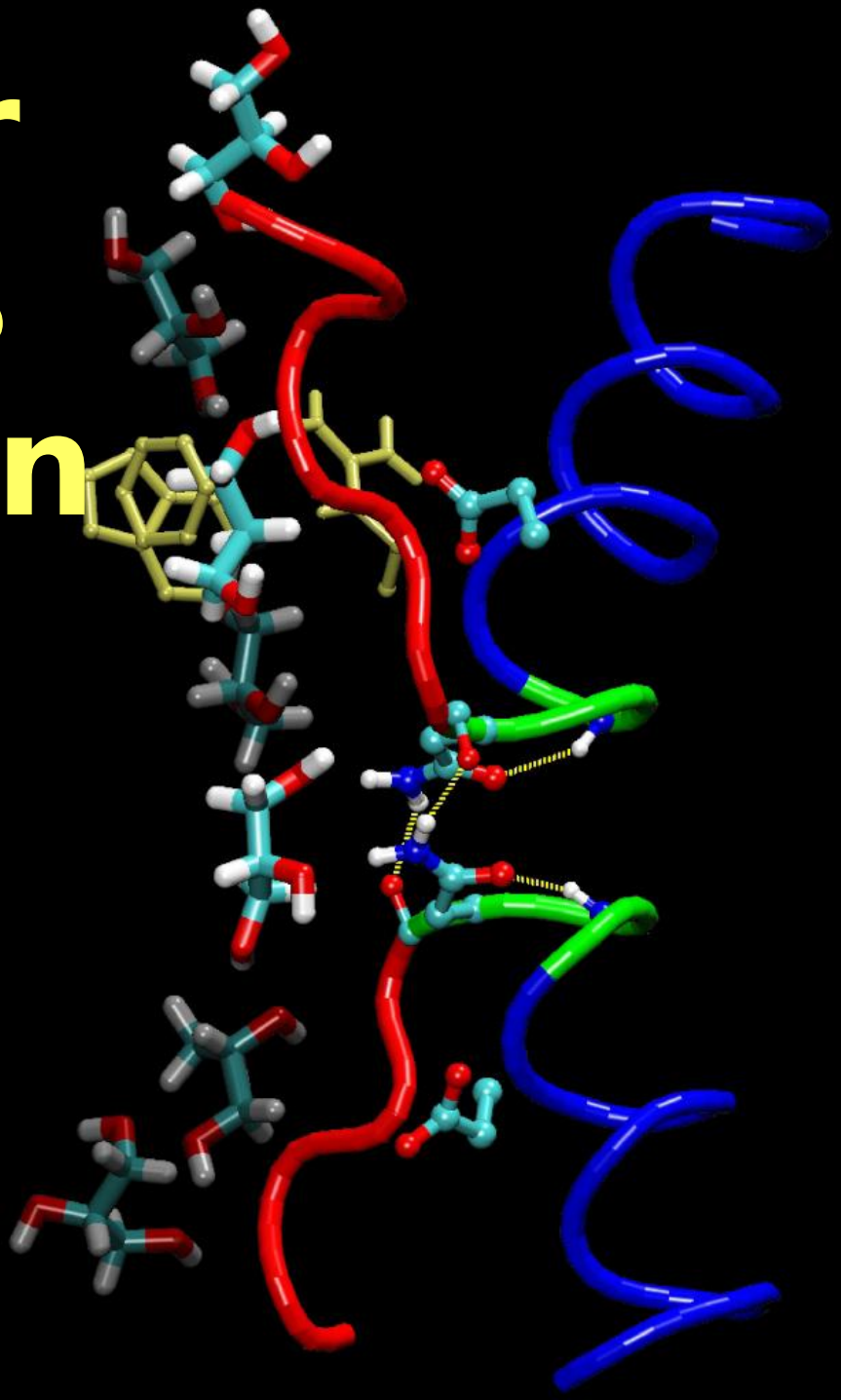
生物动力系统模拟

王冠宇 18665955633
wanggy@sustc.edu.cn



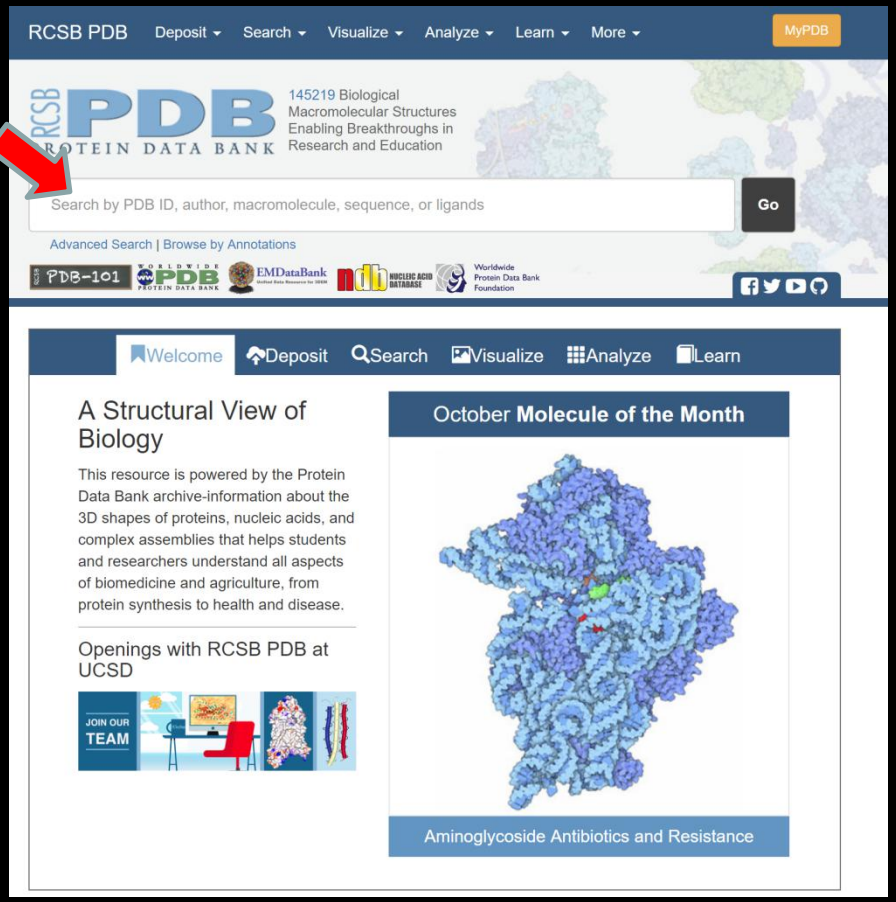
Molecular Dynamics Simulation



- Homolog modeling
- Protein together with inhibitor

• Homolog modeling

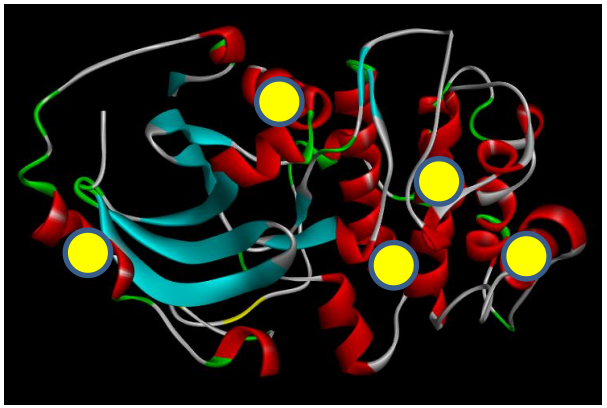
- Suppose you want to study human protein X
- You search PDB database https://www.rcsb.org/



Unfortunately you can only find mouse protein 2X39

Fortunately, your major is biology so you know mouse X protein should be ve
human X, probably a few differences of residues

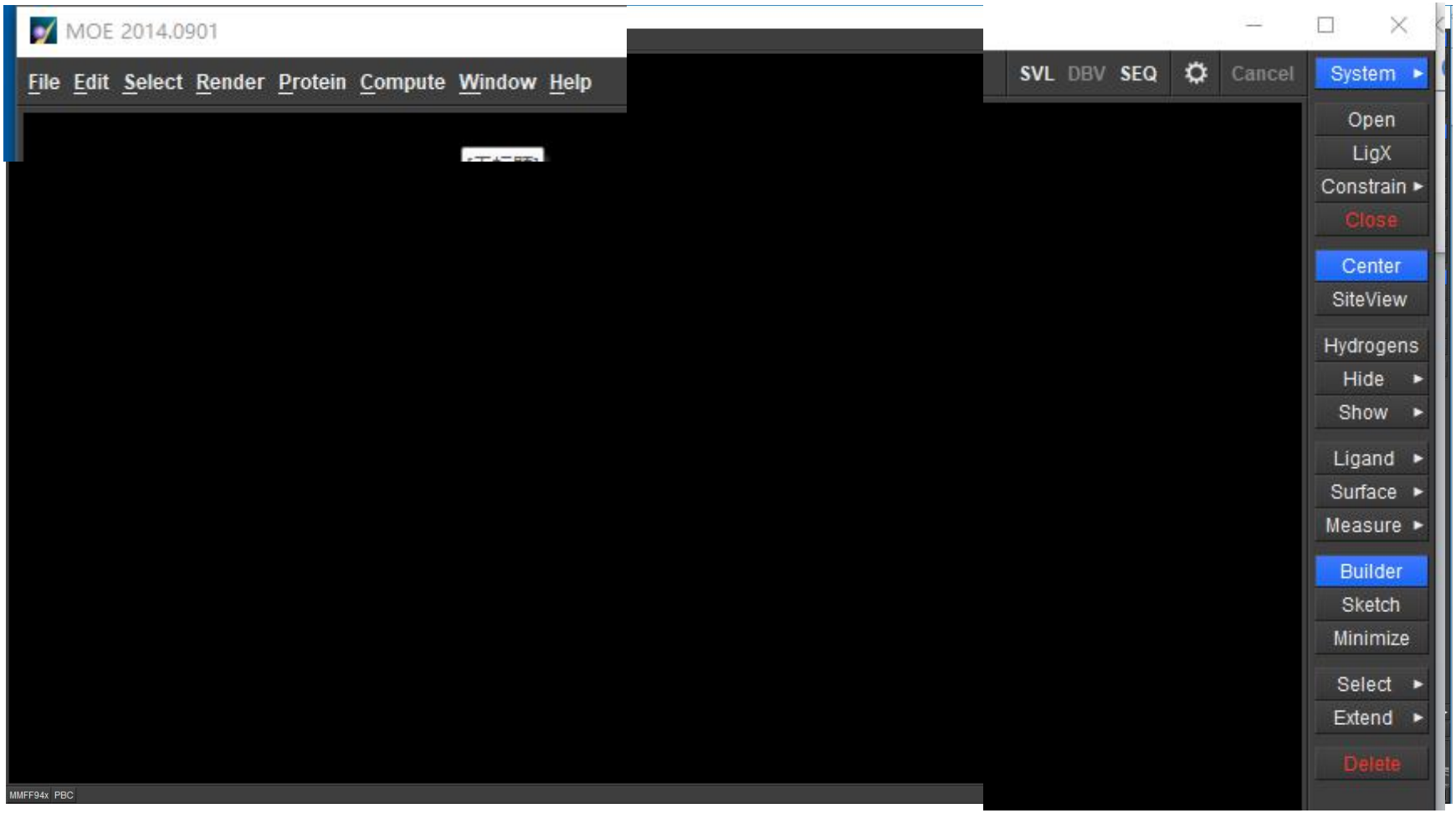
So you can just use mouse X structure, but just replace the different residue



Homolog modeling!

Then you do minimization to obtain a more realistic human X.

Many softwares can do homolog modeling, here we use MOE as an e



- **File Open** X**.pdb**

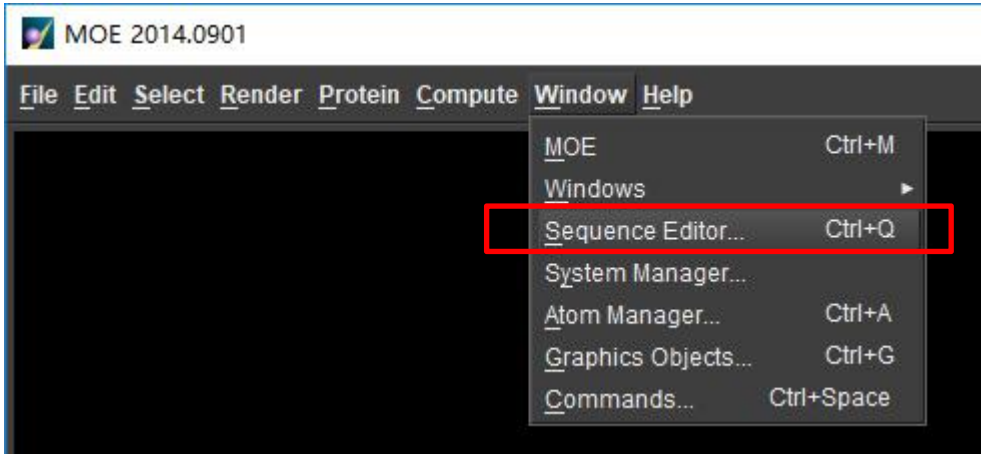
You see that there are few unimportant chains, which should be deleted

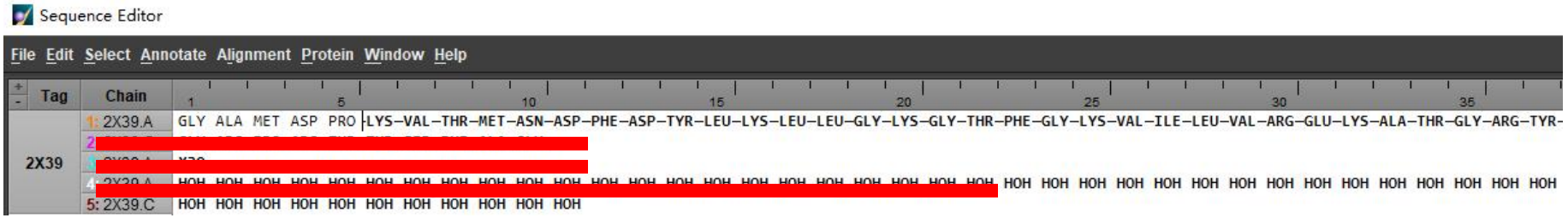
Description of the chains can often be found in the pdb file.

Check the file to determine things unwanted.

- **Delete the unwanted.**

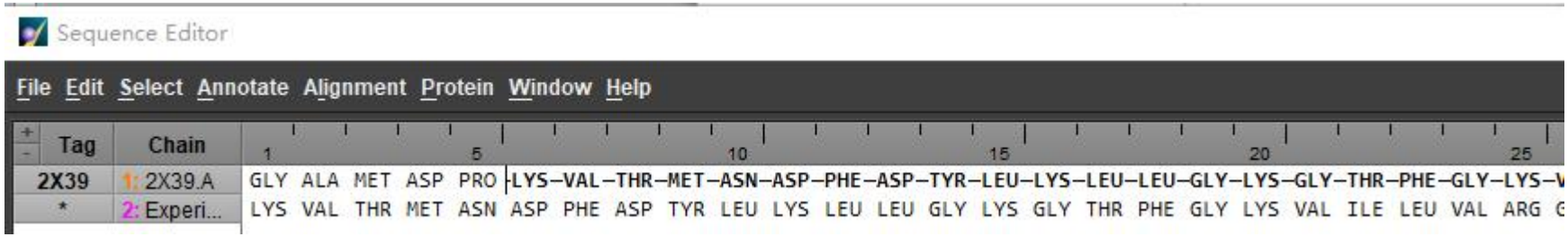
Click **Windows** **Sequence Editor**





- **In Sequence Editor, open the human X amino acid sequence**

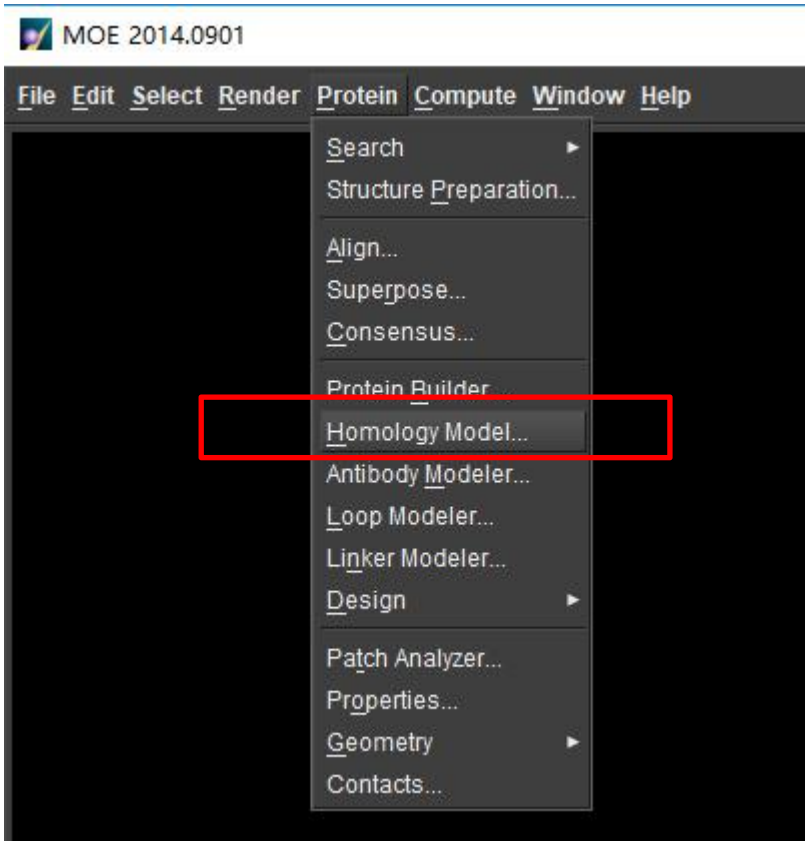
File Open HumanX

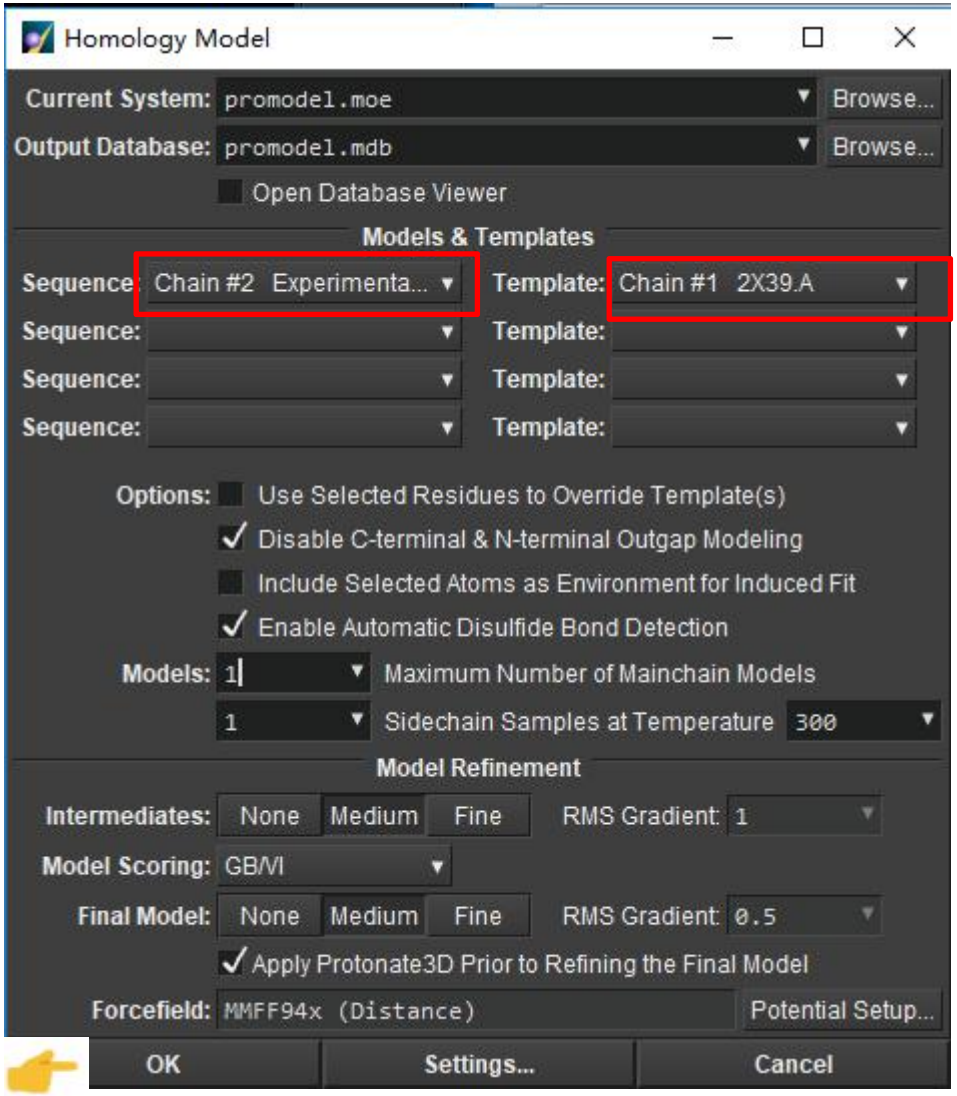


Through procedures such as Alignment, make the two as similar as pos

Details are case dependent. You can always click Help

- **Homolog modeling begins …**





- **Save into HumanX.pdb**

HumanX.pdb

X.pdb

- **Now we want to add an inhibitor to Human X protein**

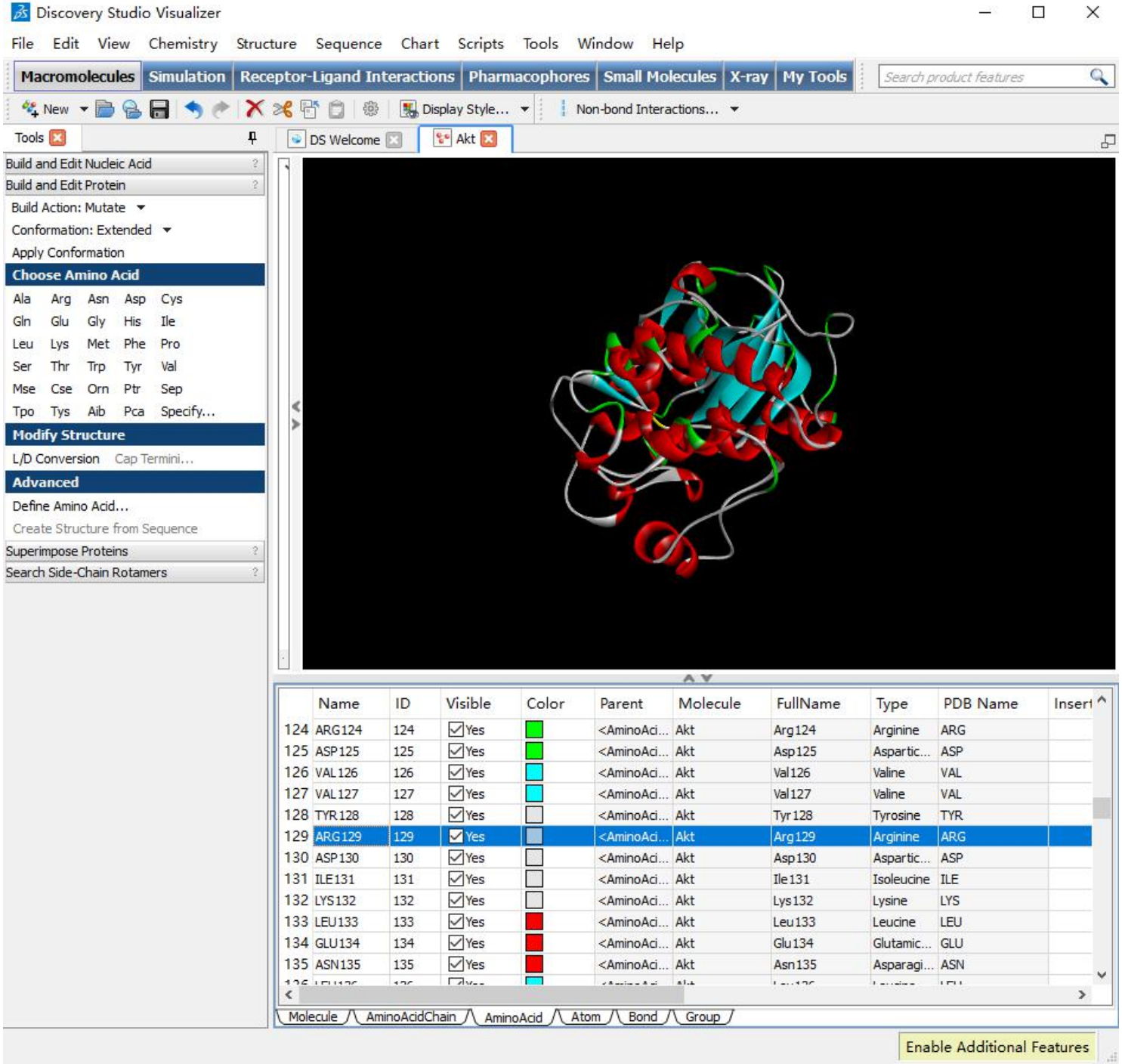
  Of course, we would not inhibit a normal protein.

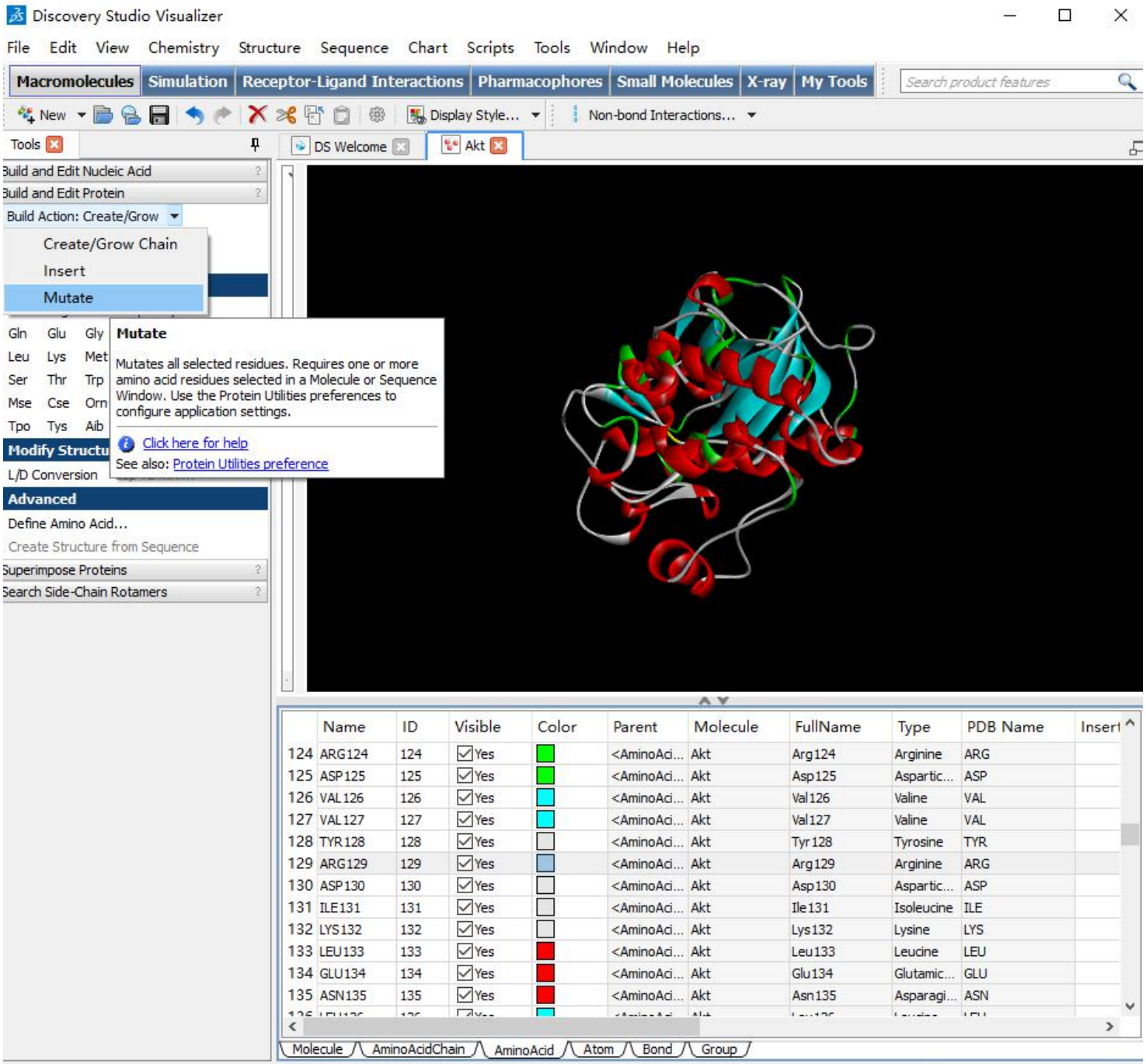
  We only inhibit a mutated protein that may cause problems like cancer

  So we first show how to mutate a amino acid

  R129H

  You can directly modify the pdb file (just change the residue #129 from A
  Or use a software


Discovery Studio Visualizer
File Edit View Chemistry Structure Sequence Chart Scripts Tools Window Help
Macromolecules Simulation Receptor-Ligand Interactions Pharmacophores Small Molecules X-ray My Tools
Search product features
New
Display Style...
Non-bond Interactions...
Tools
DS Welcome
Akt
Build and Edit Nucleic Acid
Build and Edit Protein
Build Action: Mutate
Conformation: Extended
Apply Conformation
Choose Amino Acid
Ala Arg Asn Asp Cys
Gln Glu Gly His Ile
Leu Lys Met Phe Pro
Ser Thr Trp Tyr Val
Mse Cse Orn Ptr Sep
Tpo Tys Aib Pca Specify...
Modify Structure
L/D Conversion Cap Termini...
Advanced
Define Amino Acid...
Create Structure from Sequence
Superimpose Proteins
Search Side-Chain Rotamers
Name ID Visible Color Parent Molecule FullName Type PDB Name Insert
124 ARG124 124 Yes <AminoAci... Akt Arg124 Arginine ARG
125 ASP125 125 Yes <AminoAci... Akt Asp125 Aspartic... ASP
126 VAL126 126 Yes <AminoAci... Akt Val126 Valine VAL
127 VAL127 127 Yes <AminoAci... Akt Val127 Valine VAL
128 TYR128 128 Yes <AminoAci... Akt Tyr128 Tyrosine TYR
129 ARG129 129 Yes <AminoAci... Akt Arg129 Arginine ARG
130 ASP130 130 Yes <AminoAci... Akt Asp130 Aspartic... ASP
131 ILE131 131 Yes <AminoAci... Akt Ile131 Isoleucine ILE
132 LYS132 132 Yes <AminoAci... Akt Lys132 Lysine LYS
133 LEU133 133 Yes <AminoAci... Akt Leu133 Leucine LEU
134 GLU134 134 Yes <AminoAci... Akt Glu134 Glutamic... GLU
135 ASN135 135 Yes <AminoAci... Akt Asn135 Asparagi... ASN
Molecule AminoAcidChain AminoAcid Atom Bond Group
Enable Additional Features


Discovery Studio Visualizer
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Search product features
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Display Style...
Non-bond Interactions...
Tools
DS Welcome
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Build and Edit Nucleic Acid
Build and Edit Protein
Build Action: Create/Grow
Create/Grow Chain
Insert
Mutate
Gln Glu Gly
Leu Lys Met
Ser Thr Trp
Mse Cse Orn
Tpo Tys Aib
Mutate
Mutates all selected residues. Requires one or more amino acid residues selected in a Molecule or Sequence Window. Use the Protein Utilities preferences to configure application settings.
Click here for help
See also: Protein Utilities preference
Modify Structu
L/D Conversion
Advanced
Define Amino Acid...
Create Structure from Sequence
Superimpose Proteins
Search Side-Chain Rotamers
Name ID Visible Color Parent Molecule FullName Type PDB Name Insert
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125 ASP125 125 Yes <AminoAci... Akt Asp125 Aspartic... ASP
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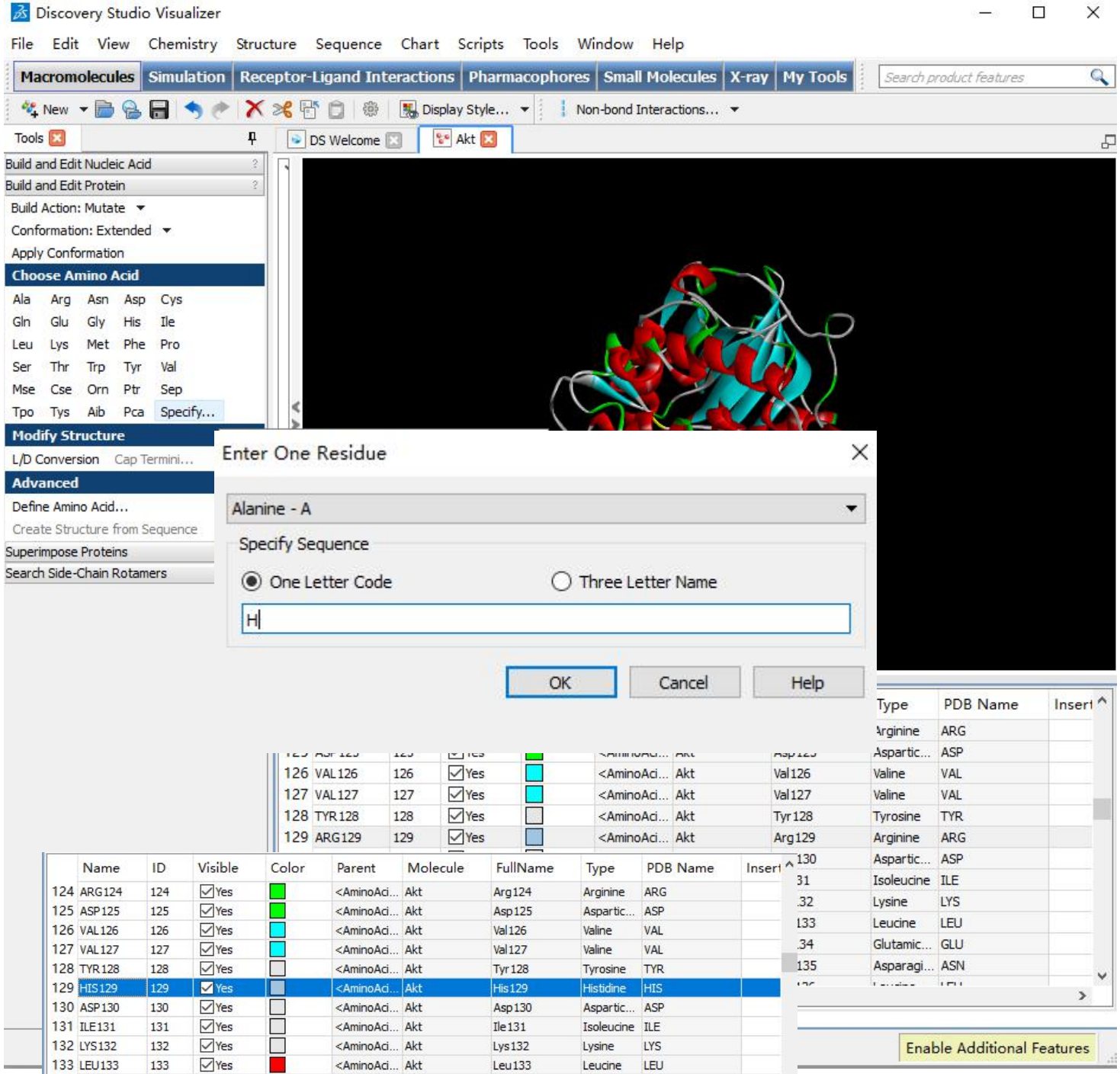
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Tpo Tys Aib Pca Specify...
Modify Structure
L/D Conversion Cap Termini...
Advanced
Define Amino Acid...
Create Structure from Sequence
Superimpose Proteins
Search Side-Chain Rotamers
Enter One Residue
Alanine - A
Specify Sequence
One Letter Code
Three Letter Name
H
OK
Cancel
Help
Type PDB Name
Arginine ARG
Aspartic... ASP
Valine VAL
Valine VAL
Tyrosine TYR
Arginine ARG
Aspartic... ASP
Isoleucine ILE
Lysine LYS
Leucine LEU
Glutamic... GLU
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Enable Additional Features

- **Now we want to add an inhibitor to Human X protein**

  Of course, we would not inhibit a normal protein.

  We only inhibit a mutated protein that may cause problems like cancer

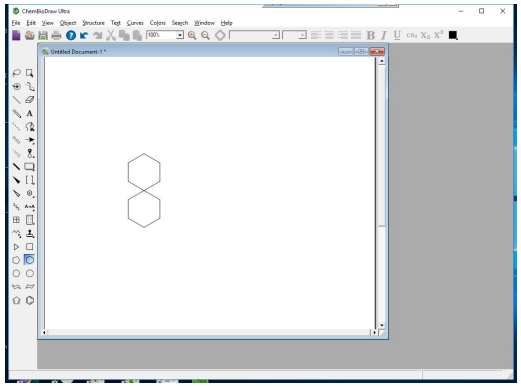
  So we first show how to mutate a amino acid

  R129H

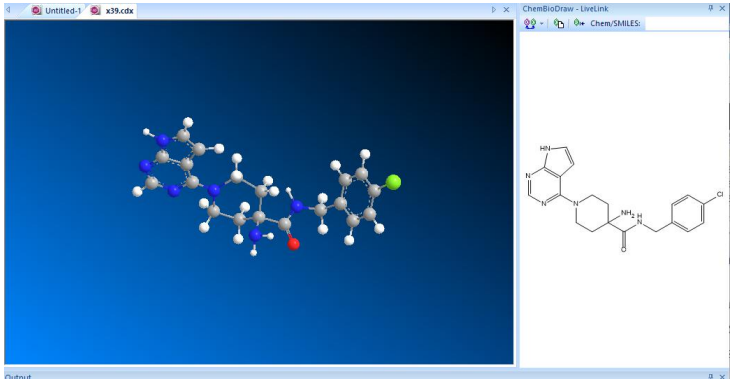
  You can directly modify the pdb file (just change the residue #129 from A
  Or use a software

  Save the file into Xm.pdb

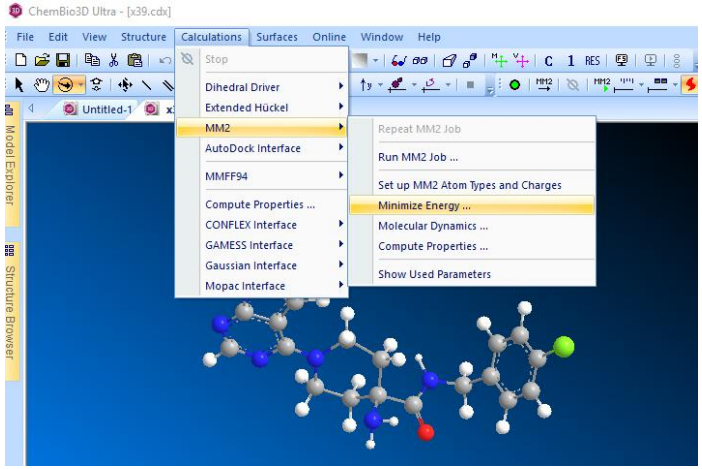
Now we design an inhibitor called inh



Firstly, use **Chemdraw** to draw the chemical structure of inh. Save it as inh.cdx.



You can use Chemdraw3D to visualize the inhibitor

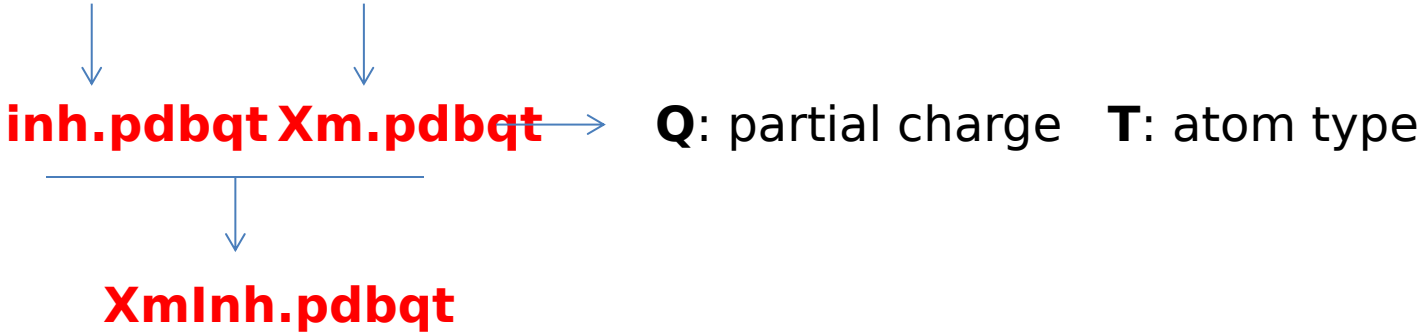


Minimization:

Calculations>MM2>Minimize Energy

Save inh.pdb

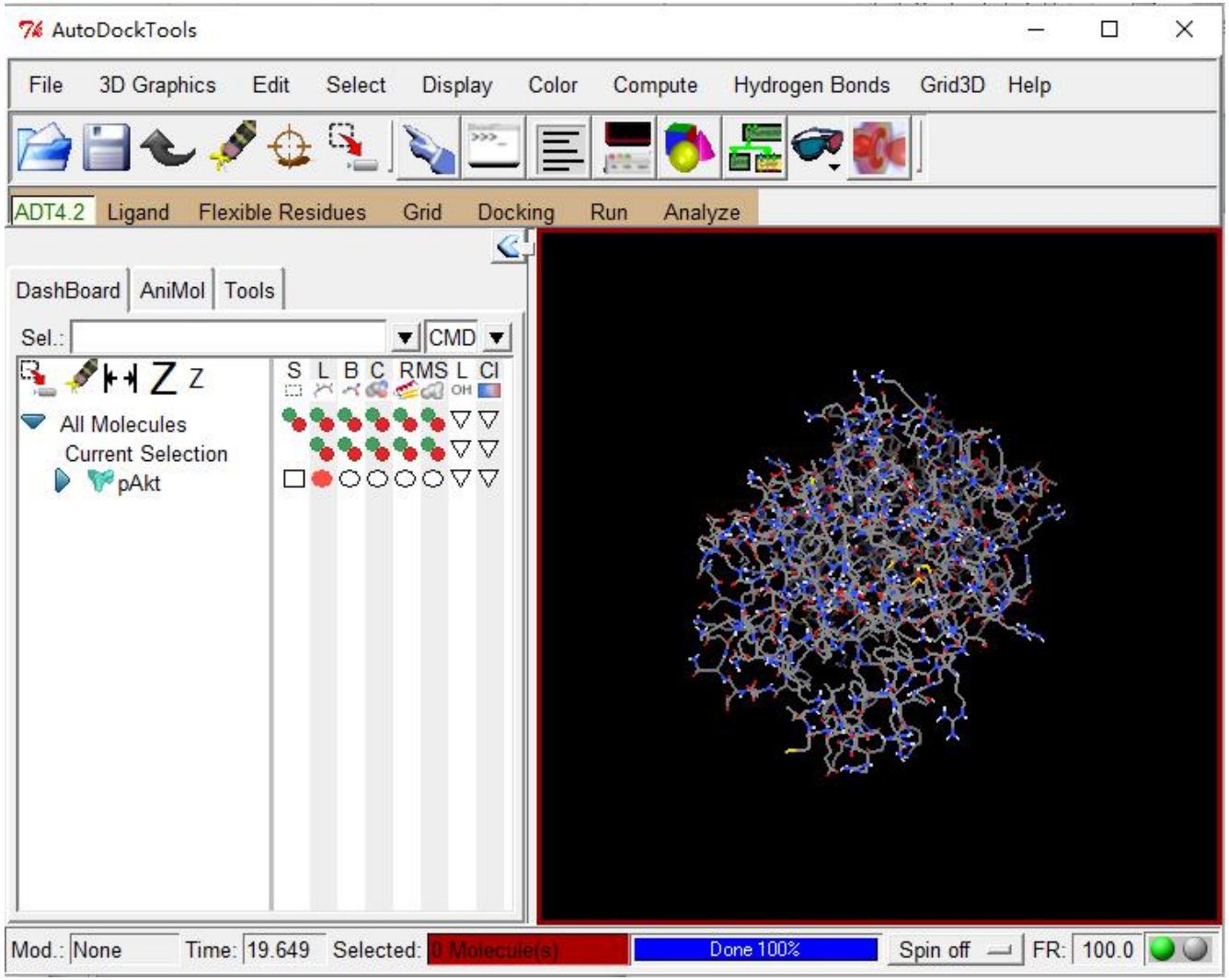
Now put inh.pdb into Xm.pdb (molecular docking)



We use another software called AutoDockTools

Note that docking is a minimization process

First, load Xm.pdb, after some operation, save it as Xm.pdbqt



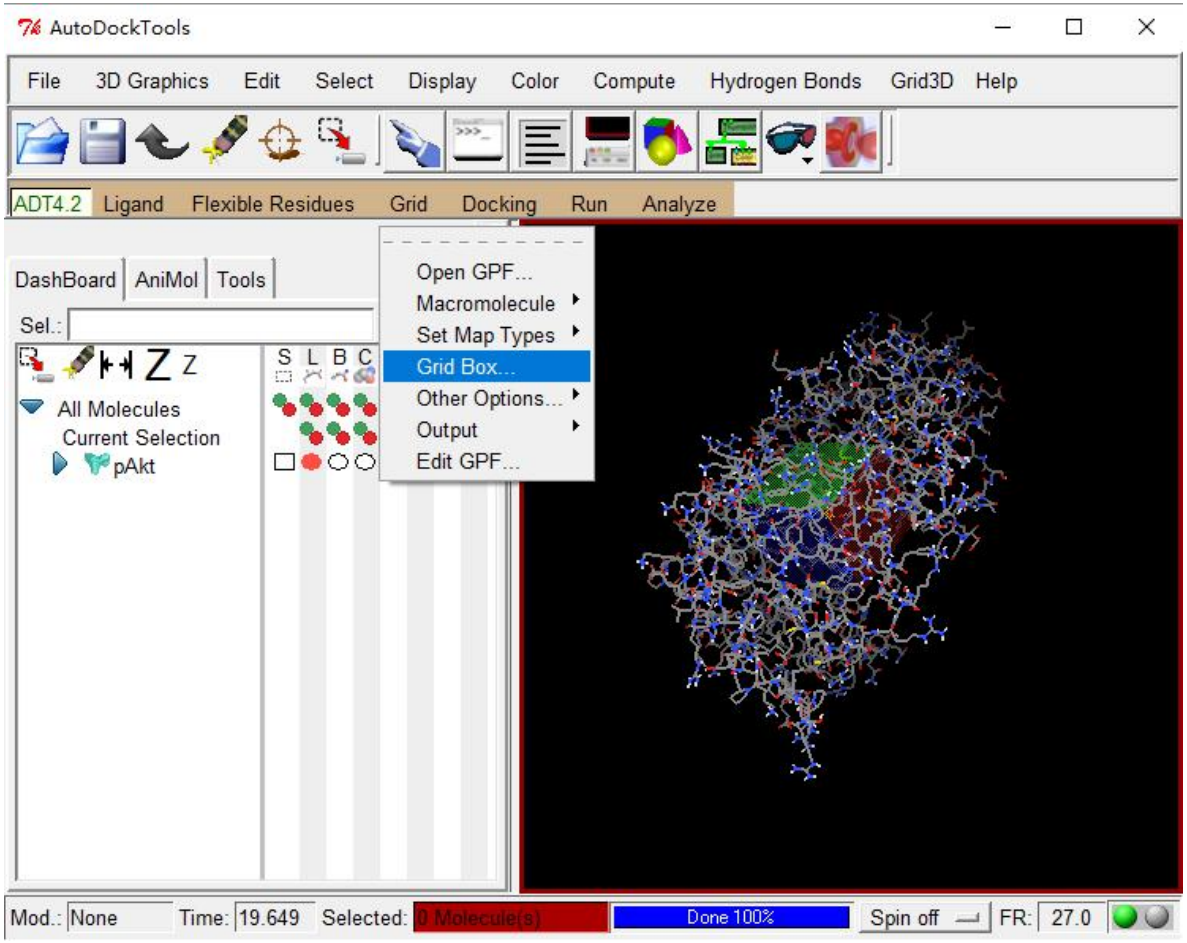
File>Read Molecule > Xm.pdb

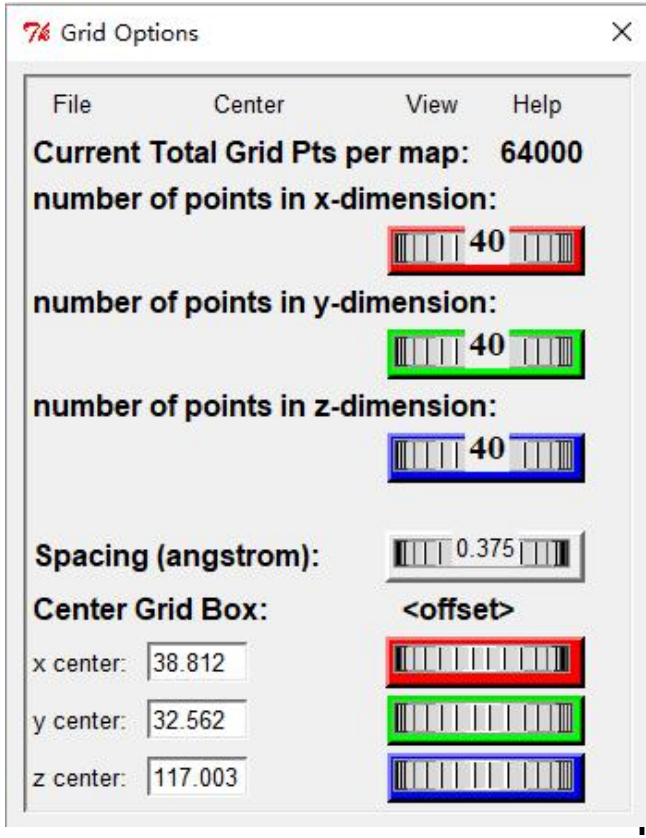
Edit>Hydrogens >add>polar only

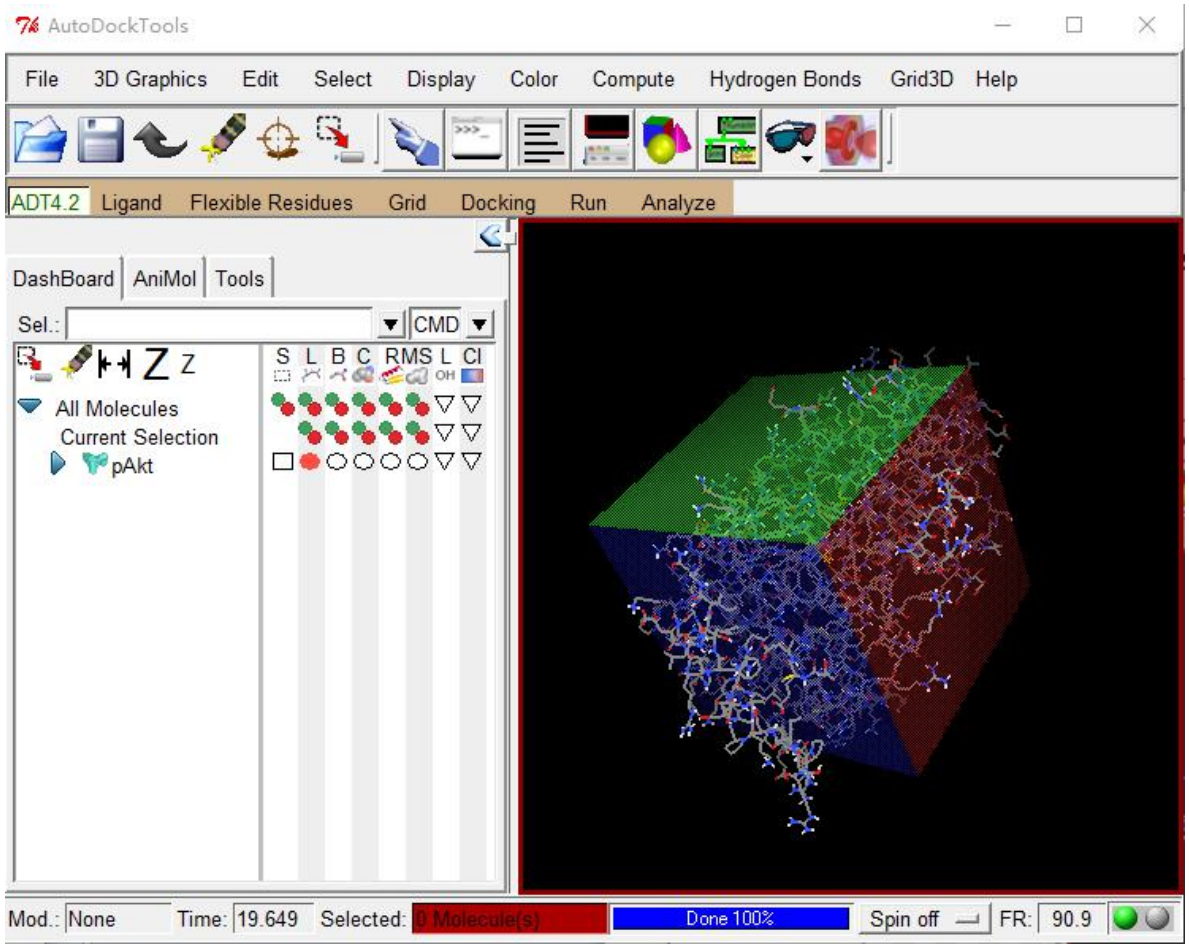
Grid>macromolecule >choose> Xm.pdb

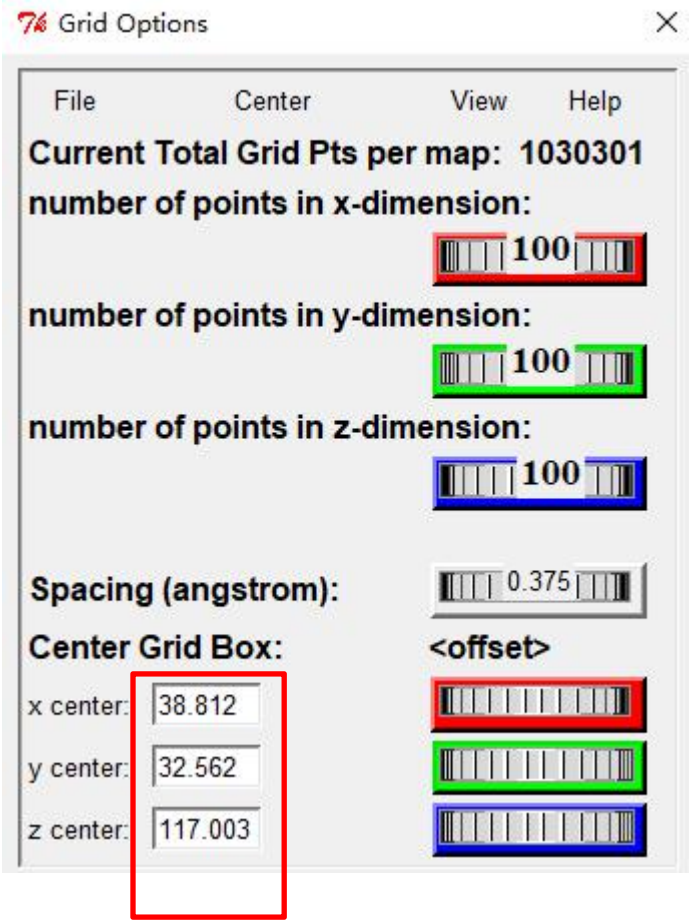
(Grid is to define search space for the upcoming

Now we use Grid to define the search space



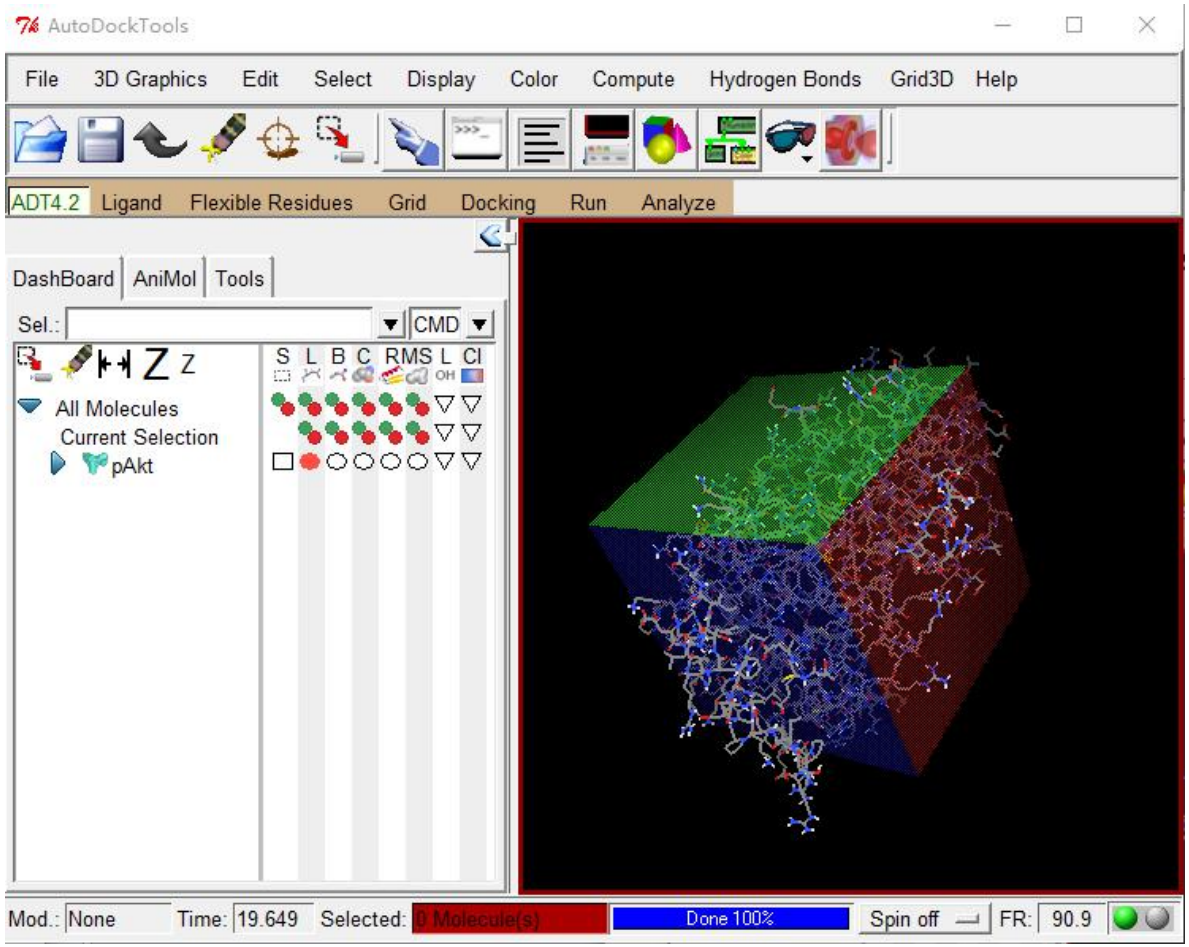






Write down the numbers

Load Inh.pdb, after some operation, save it as Inh.pdbqt



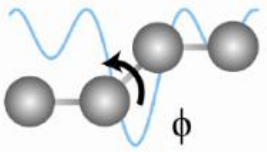
ligand>input>open

ligand>torsion Tree>
choose Torsions>Done

(Here all the torsion bonds are rotable;

There are options to make some bonds
Non-rotatable)

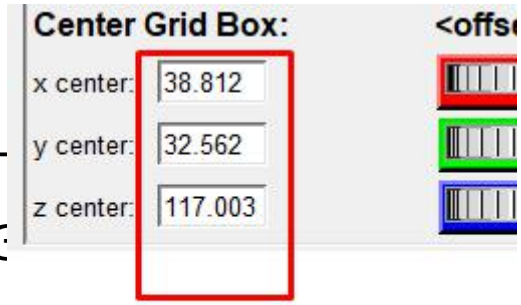
$$\sum_{dihedrals} \frac{V_n}{2}[1+\cos(n\phi-\gamma)]$$



ligand>output>save as

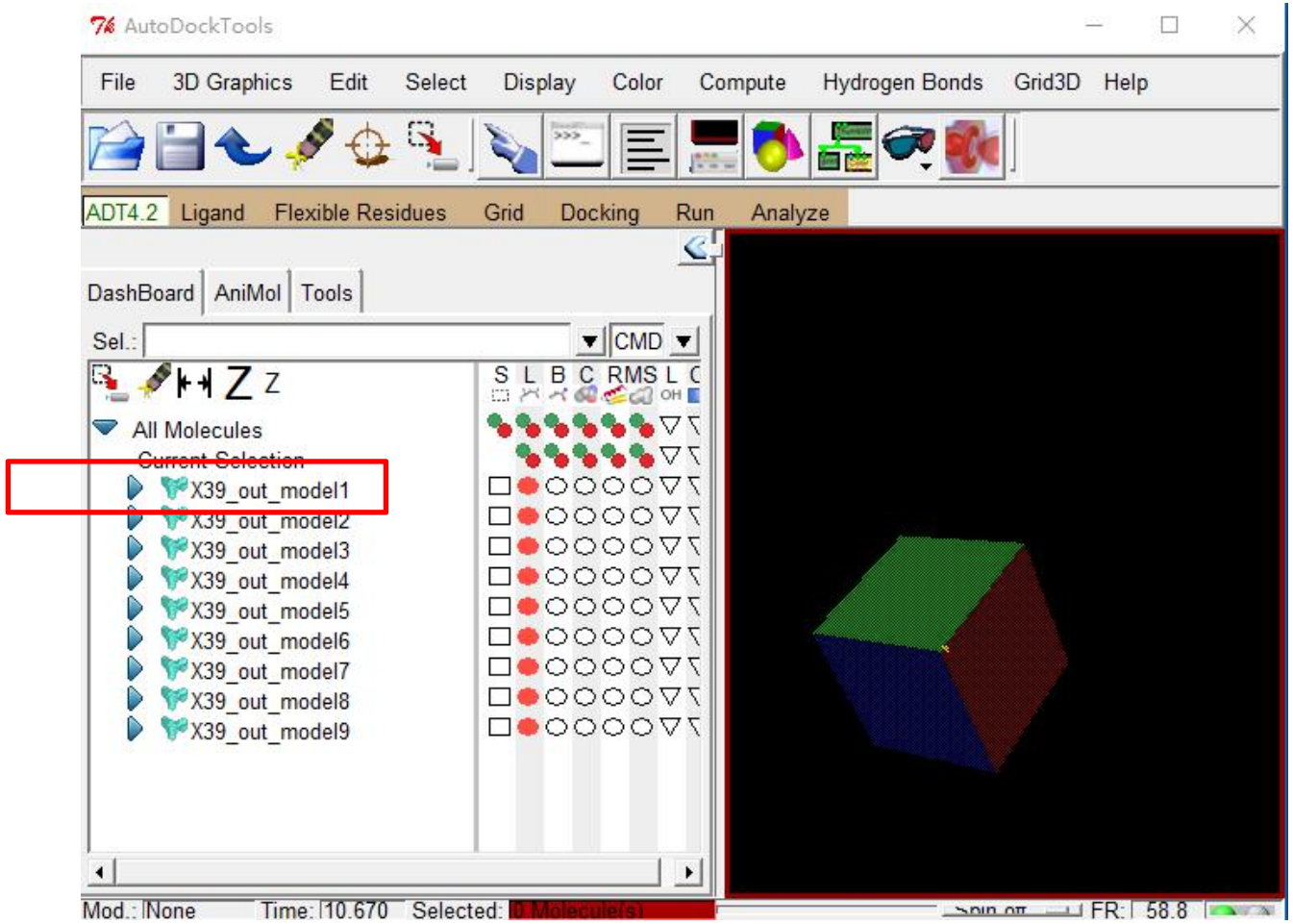
Now we do the docking …

```
$  vina --receptor Xm.pdbqt --ligand Inh.pdbqt

          --center_x 38.812 --center_y 32.562 --center_

          --size_x 100 --size_y 100 --size_z 100  --log x3
```



Write down the numbers

After a while, a new file Inh_out.pdbqt is generated, which contains 10 best inhibitors.



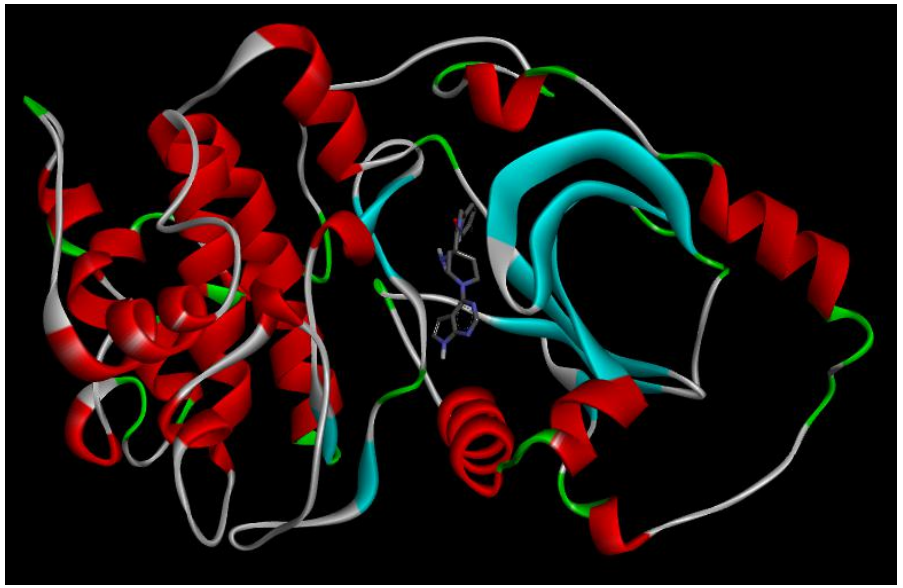
We usually choose the first one Inh_out_model1.pdb as the best of t

Now we can produce the complex

cat Inh_out_model1.pdb Xm.pdb > **XmInh.pdb**

cat A B > C is just a linux command to merge files A and B into C

Alternatively, you can do it by using text editor and copy paste.



XmInh.pdb

- **Generate a force field for the inhibitor**

With **XmInh.pdb**, one can begin MD simulation, following the same procedure

But there is a problem, i.e., there is no force field for the ligand.

Amber has two steps to produce a force field file *.frcmod

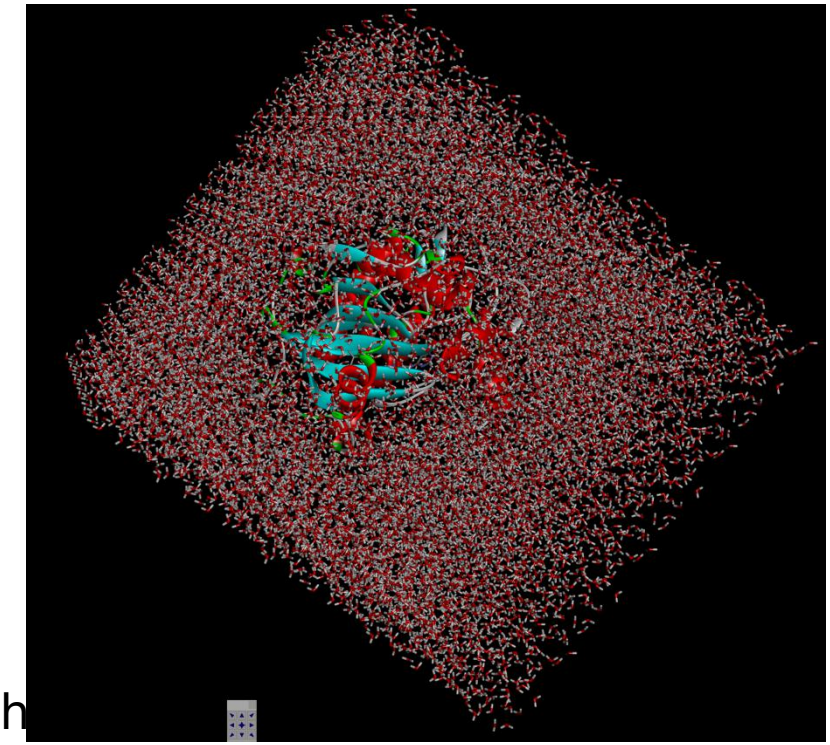
```
$ antechamber -i Inh.pdb -fi pdb -o Inh.mol2 -fo mol2
-c bcc -s 2
$ parmchk -i Inh.mol2 -f mol2 -o Inh.frcmod
```

- **Generate a library file Inb.lib for the inhibitor**

Generalized AMBER Force Field, a set of parameters used in simulating the interactions of small organic molecules

```
$ source leaprc.gaff

$ Inb = loadmol2 x39.mol2

$ check Inb

$ loadamberparams Inb.frcmod

$ saveoff Inb Inb.lib
```

- **Use xLeap to prepare: solvation, generating prmtop and inpcrd file**



source leaprc.protein.ff14SB
source leaprc.gaff
source leaprc.water.tip3p

loadoff lnh.lib

x = loadpdb **XmInh.pdb**

check x

addIons x Na+ 0 #neutralize th

solvatebox x TIP3PBOX 10.0 #add tip3p water model in the system

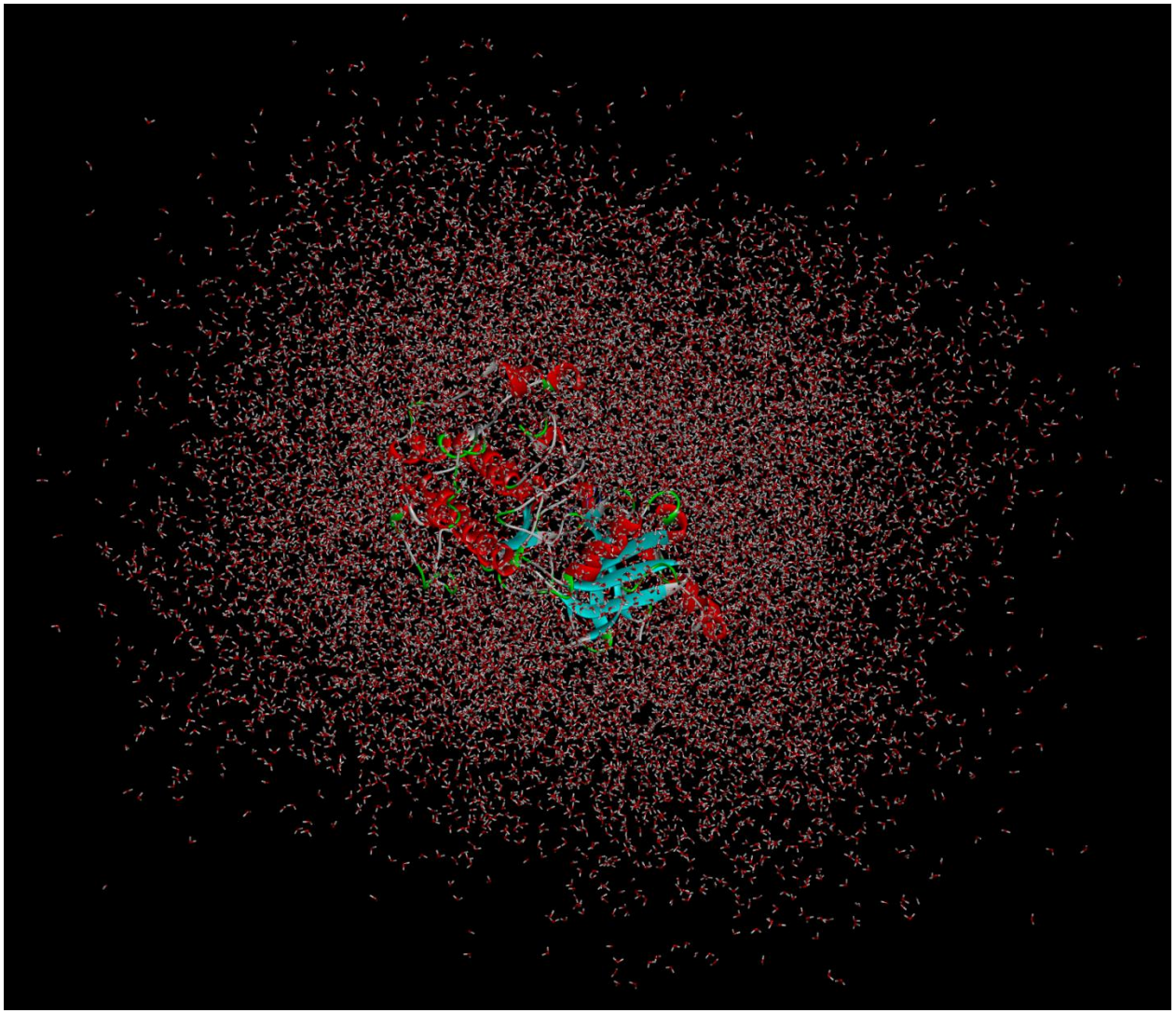
savepdb x **XmInhBox.pdb**

saveamberparm x **XmInh.**prmtop **XmInh.**inpcrd

quit

- **Minimizing, Heating, Production**

Prod.pdb



- **Minimizing, Heating, Production**

Prod.nc Tajectory file. Can show the simulation in VMD but not usual vide

Prod.mpg After conversion. It now can be played by standard video play

ProdNoWater.mpg