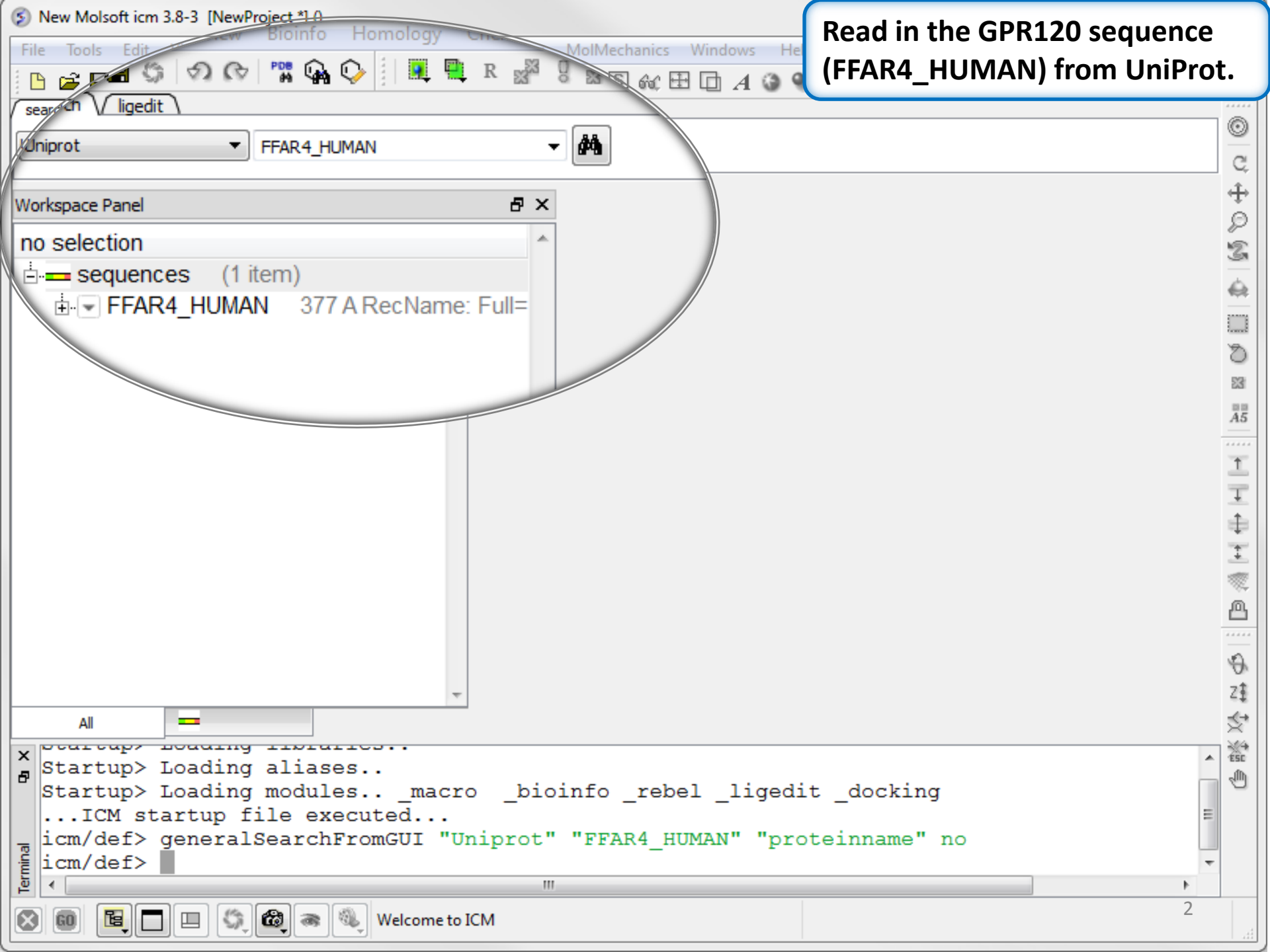
Homology Modeling

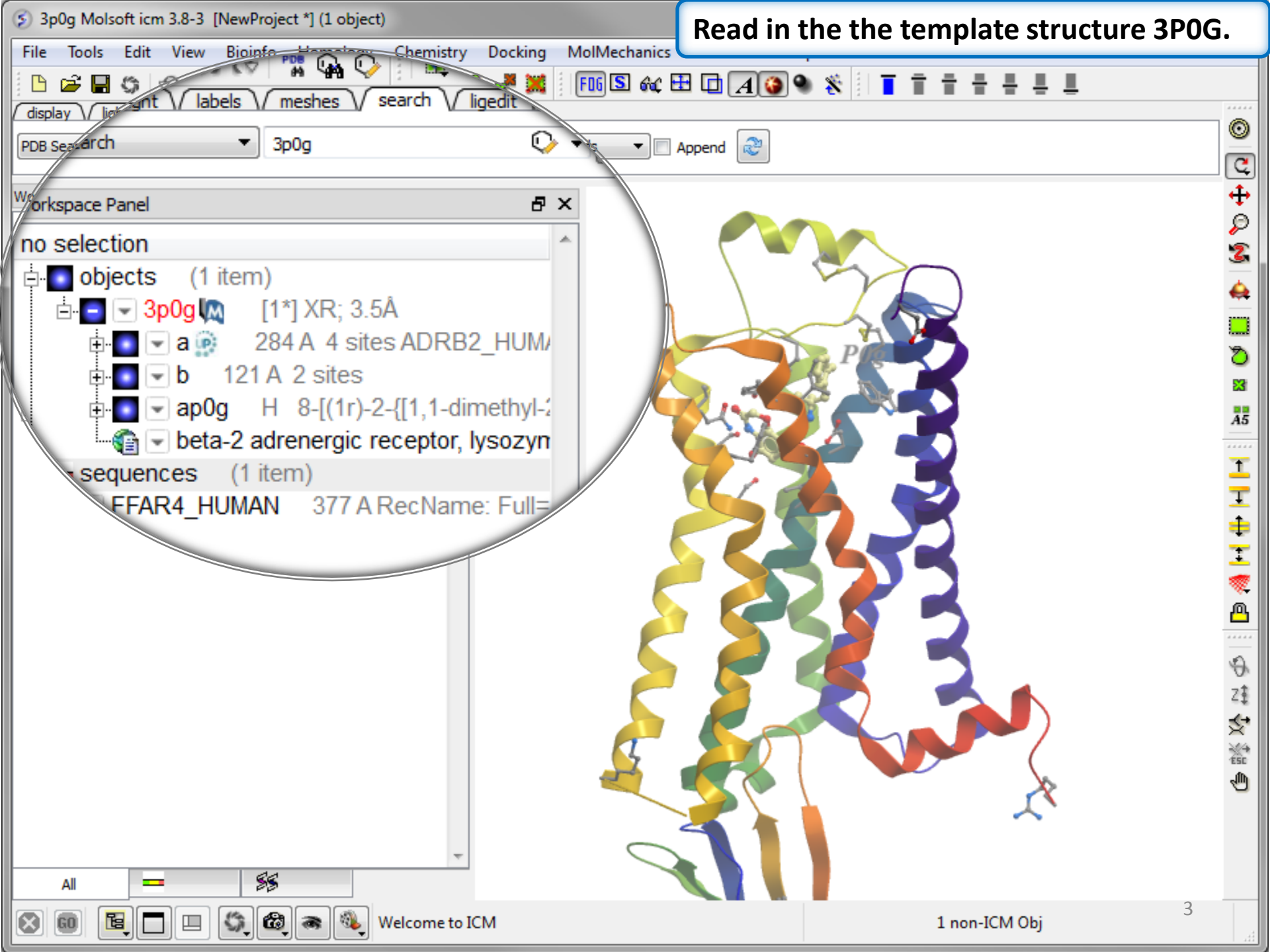
GPR120 Model – GPCR Modeling

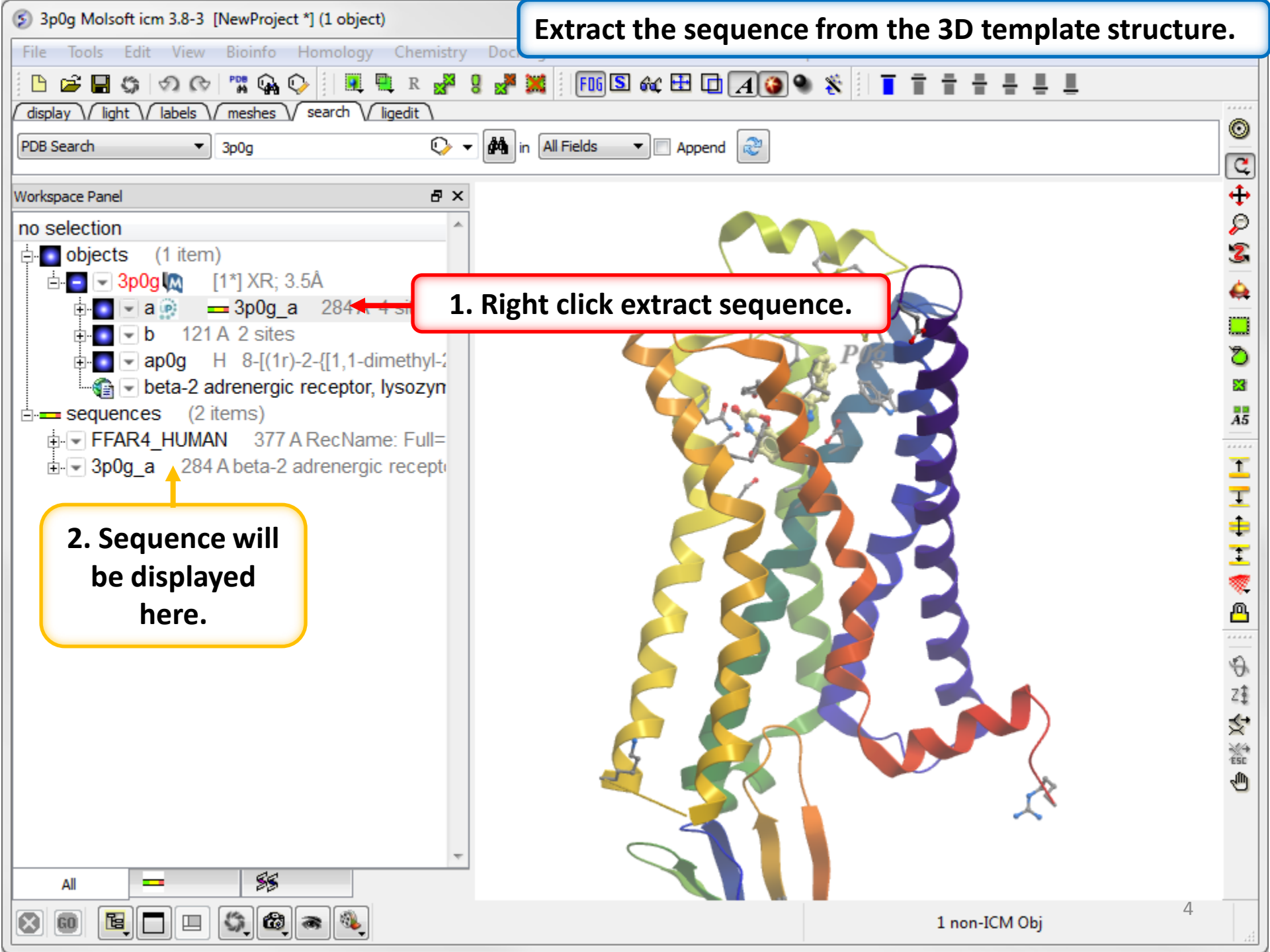
GPR120 is a member of the Class A GPCRs. It is gaining particular interest because it has been shown to be involved in the insulin-sensitizing effects of omega 3 fatty acids as well as inflammation. GPR120 dysfunction is responsible for reduced fat metabolism, thereby leading to obesity.

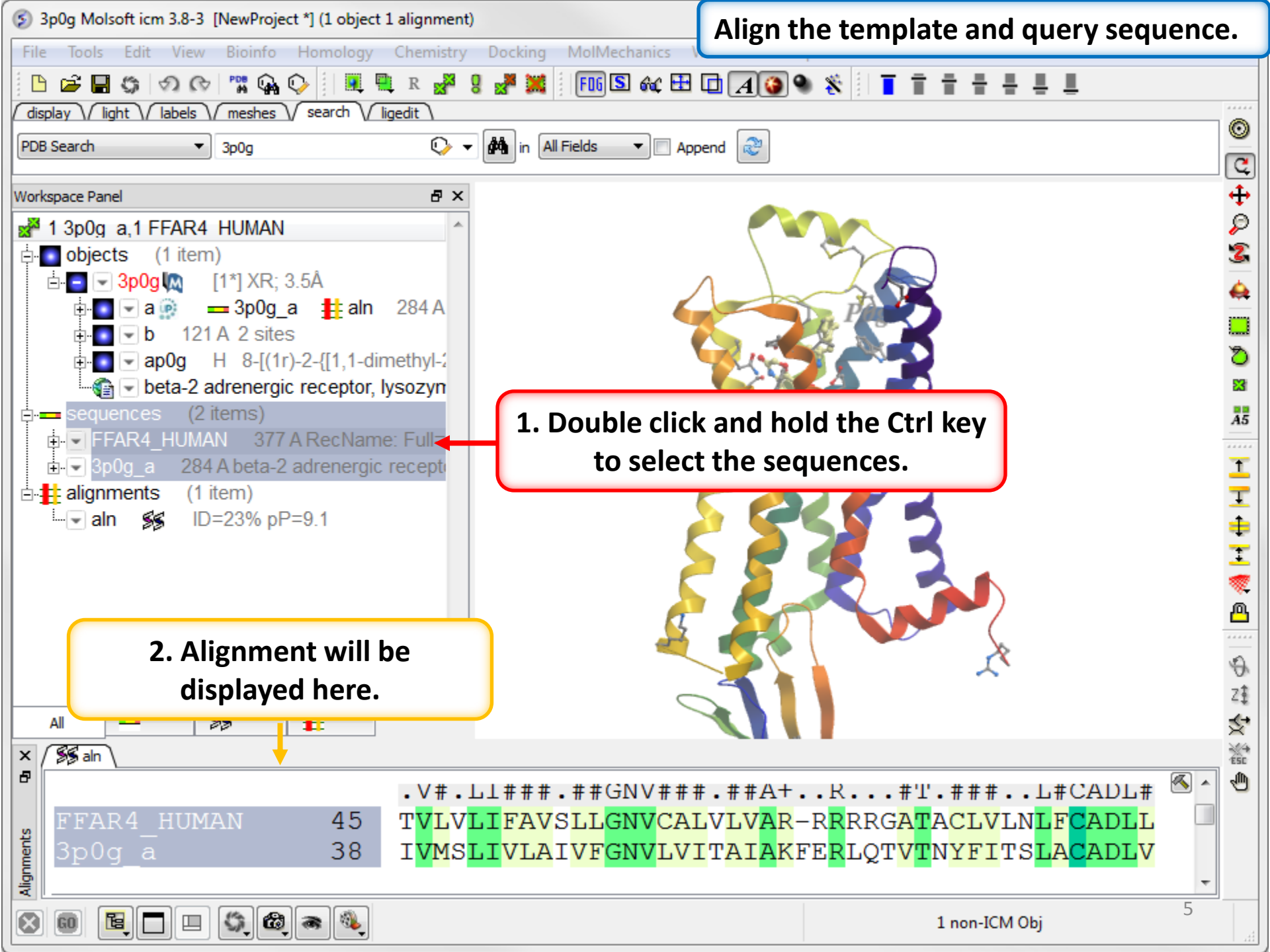


Read in the GPR120 sequence (FFAR4_HUMAN) from UniProt.

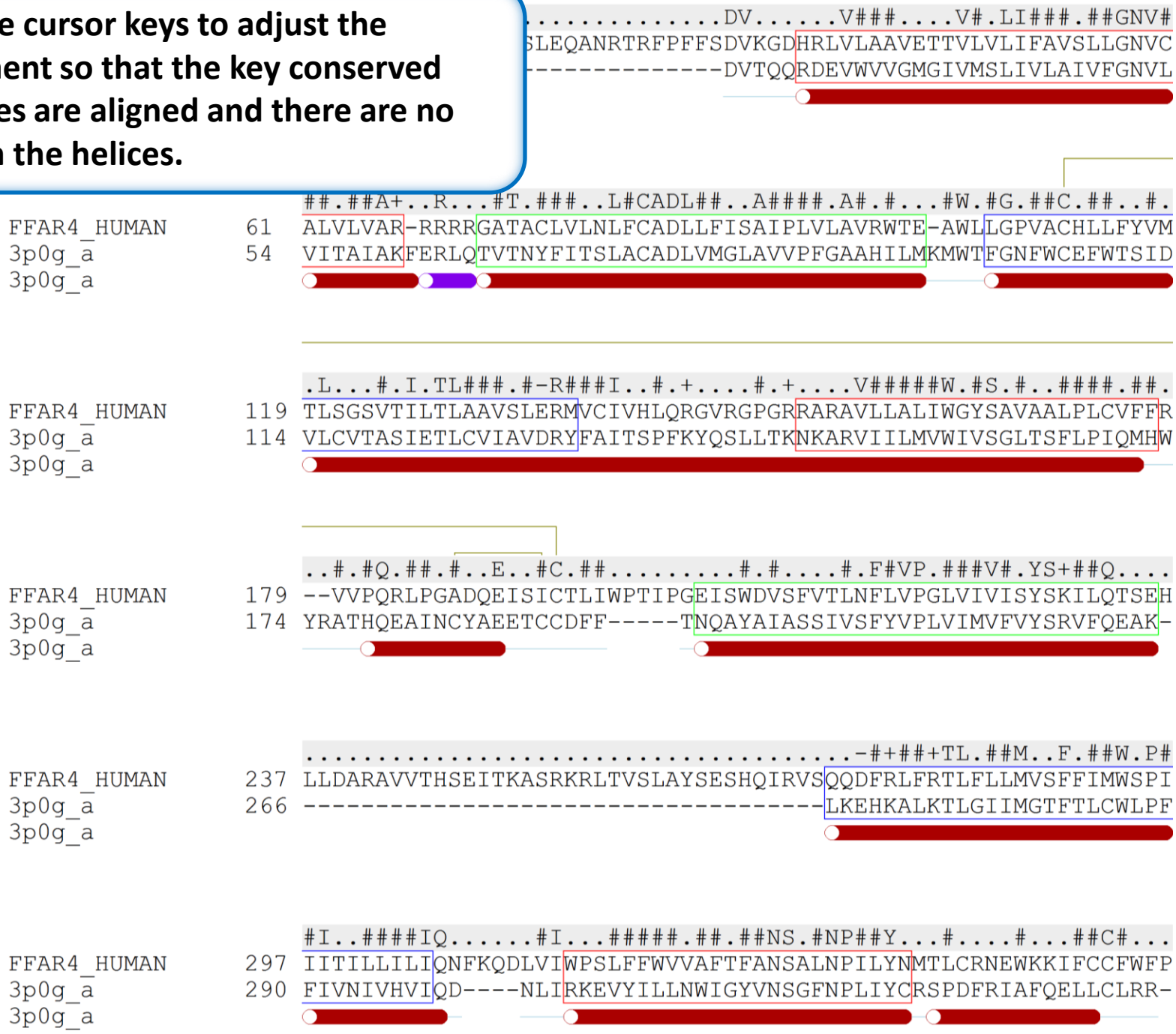
Read in the the template structure 3P0G.



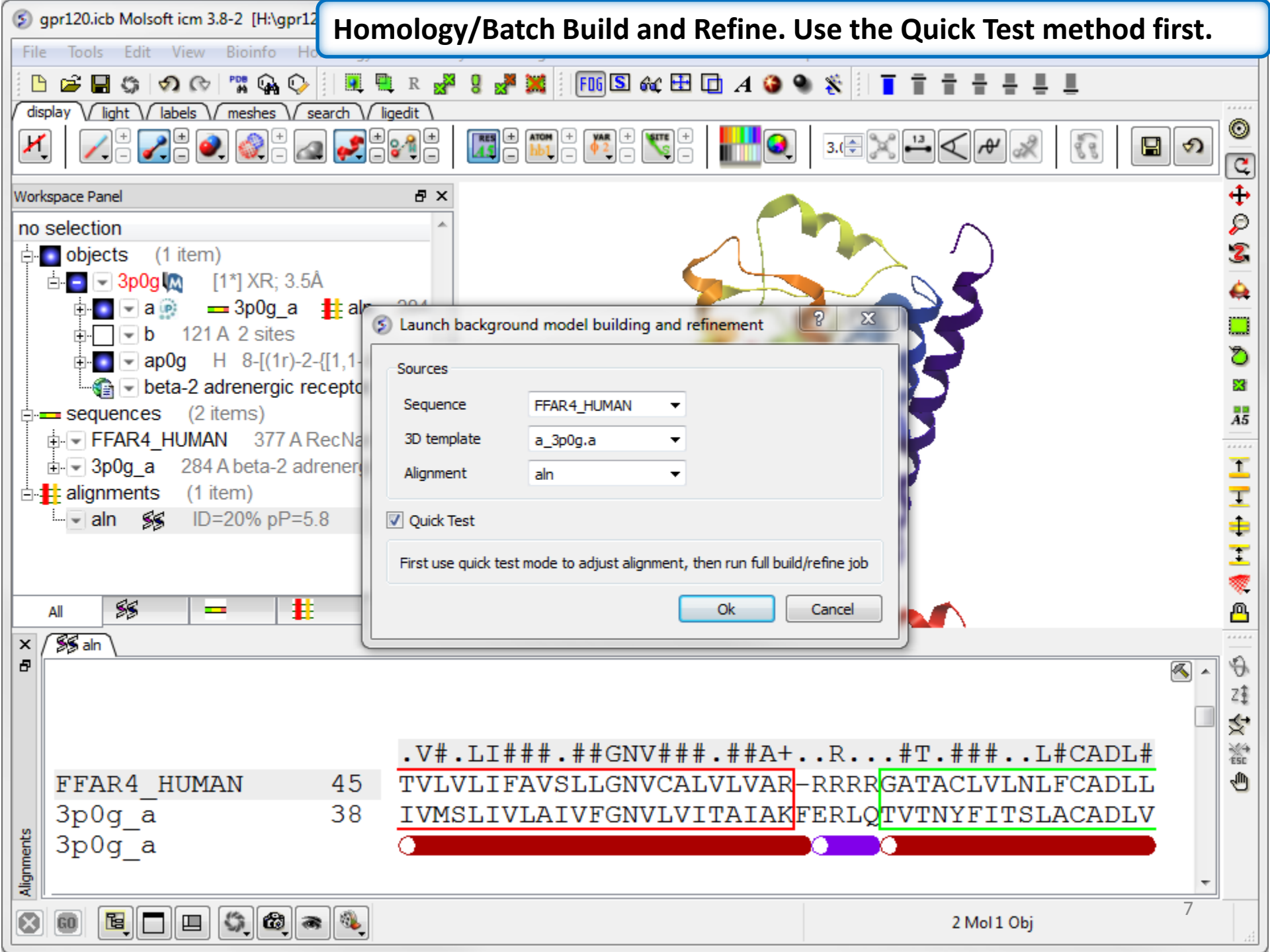

3p0g Molsoft icm 3.8-3 [NewProject *] (1 object)
Extract the sequence from the 3D template structure.
File Tools Edit View Bioinfo Homology Chemistry
display light labels meshes search ligedit
PDB Search
3p0g
in
All Fields
Append
Workspace Panel
no selection
objects (1 item)
3p0g [1*] XR; 3.5Å
a 3p0g_a
b 121 A 2 sites
ap0g H 8-[(1r)-2-{[1,1-dimethyl-
beta-2 adrenergic receptor, lysozyn
sequences (2 items)
FFAR4_HUMAN 377 A RecName: Full=
3p0g_a 284 A beta-2 adrenergic recept
1. Right click extract sequence.
2. Sequence will be displayed here.
All
1 non-ICM Obj


3p0g Molsoft icm 3.8-3 [NewProject *] (1 object 1 alignment)
Align the template and query sequence.
File Tools Edit View Bioinfo Homology Chemistry Docking MolMechanics
display light labels meshes search ligedit
PDB Search
3p0g
in
All Fields
Append
Workspace Panel
1 3p0g a,1 FFAR4 HUMAN
objects (1 item)
3p0g [1*] XR; 3.5Å
a 3p0g_a aln 284 A
b 121 A 2 sites
ap0g H 8-[(1r)-2-{[1,1-dimethyl-
beta-2 adrenergic receptor, lysozyn
sequences (2 items)
FFAR4_HUMAN 377 A RecName: Full
3p0g_a 284 A beta-2 adrenergic recept
alignments (1 item)
aln ID=23% pP=9.1
1. Double click and hold the Ctrl key to select the sequences.
2. Alignment will be displayed here.
All
aln
FFAR4_HUMAN 45 TVLVLIFAVSLLGNVCALVLVAR-RRRRGATACLVLNLFCADLL
3p0g_a 38 IVMSLIVLAIVFGNVLVITAIAKFERLQTVTNYFITSLACADLV
Alignments
1 non-ICM Obj
5

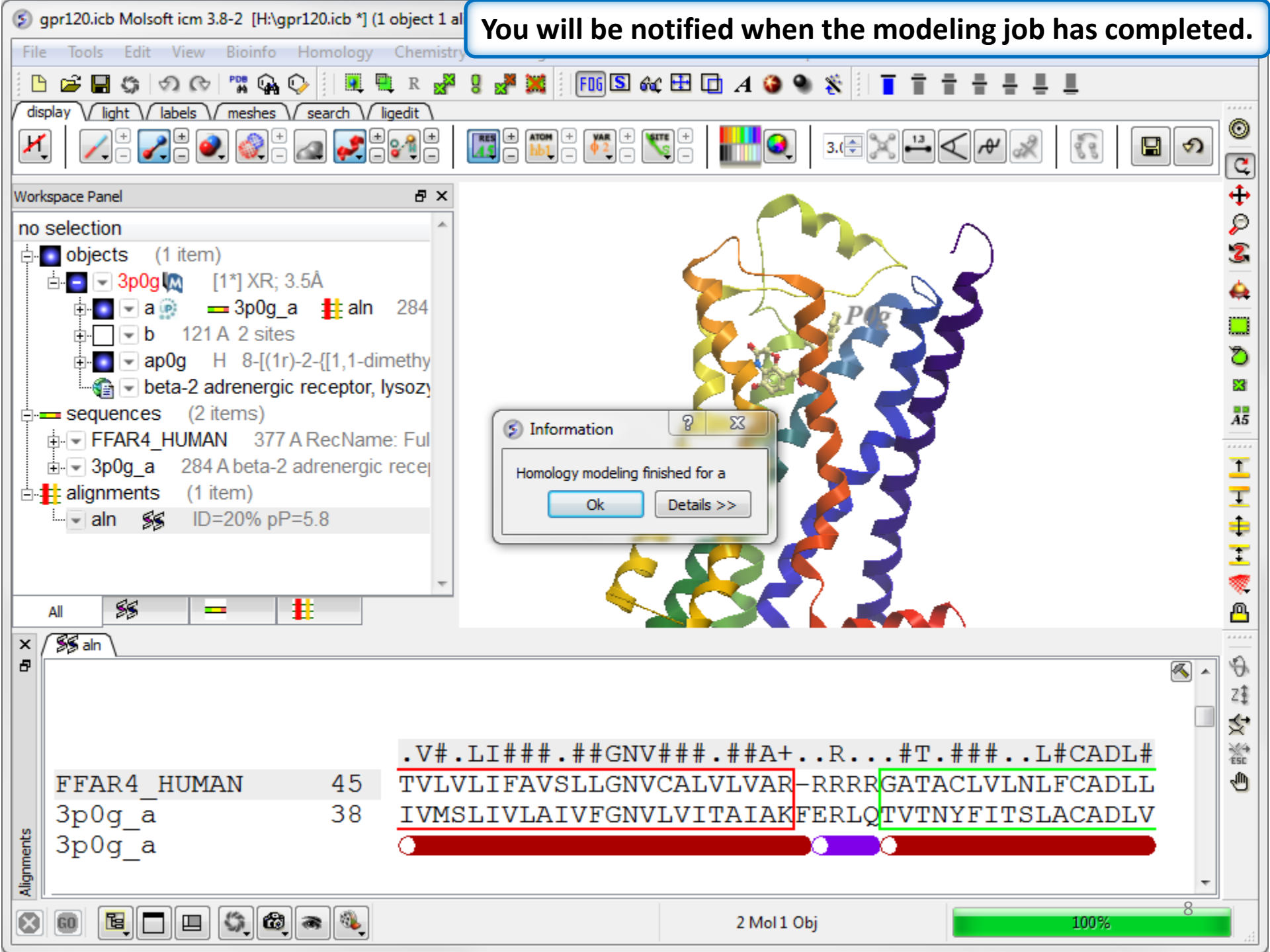
Use the cursor keys to adjust the alignment so that the key conserved residues are aligned and there are no gaps in the helices.



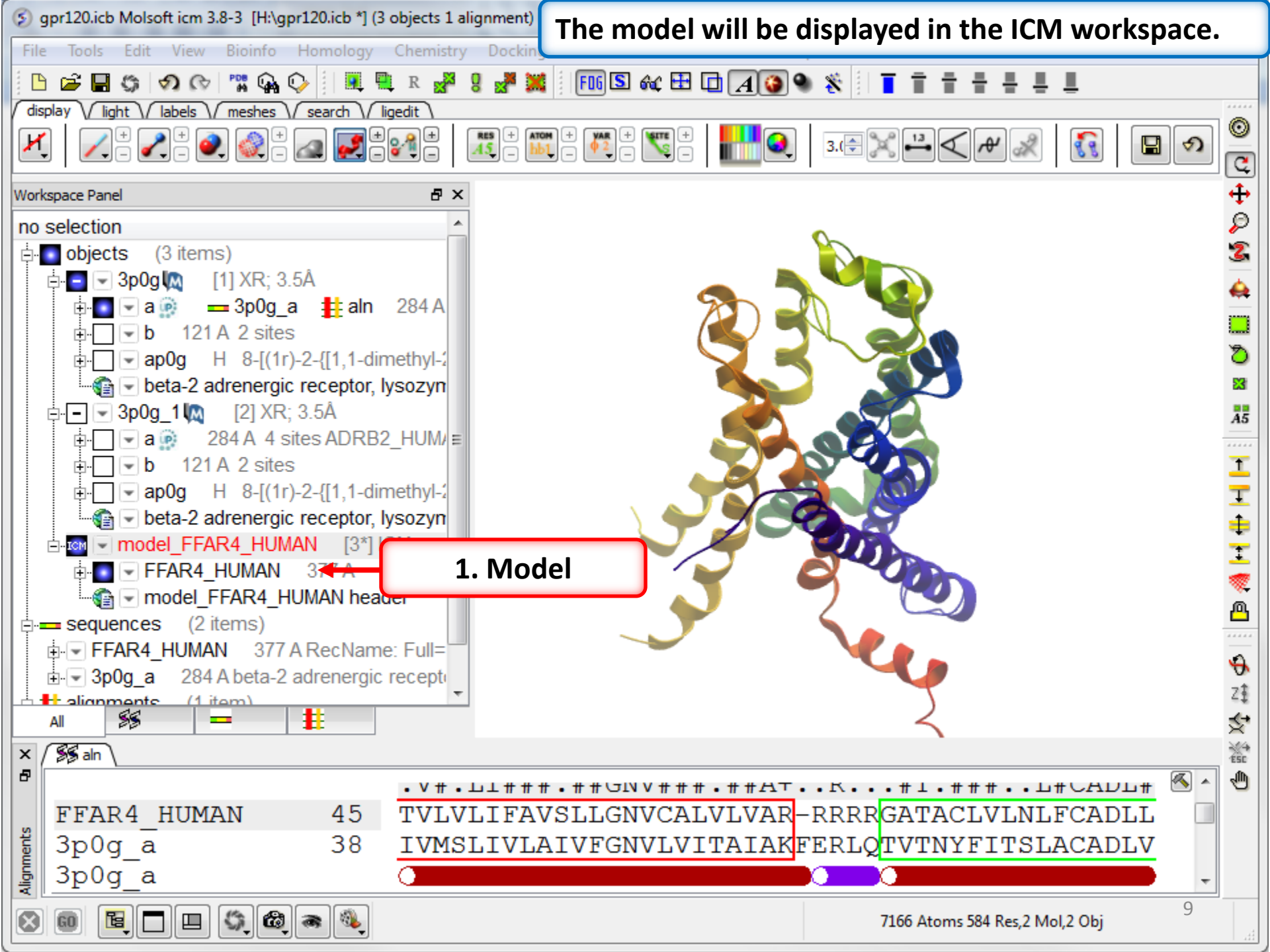
Homology/Batch Build and Refine. Use the Quick Test method first.



You will be notified when the modeling job has completed.

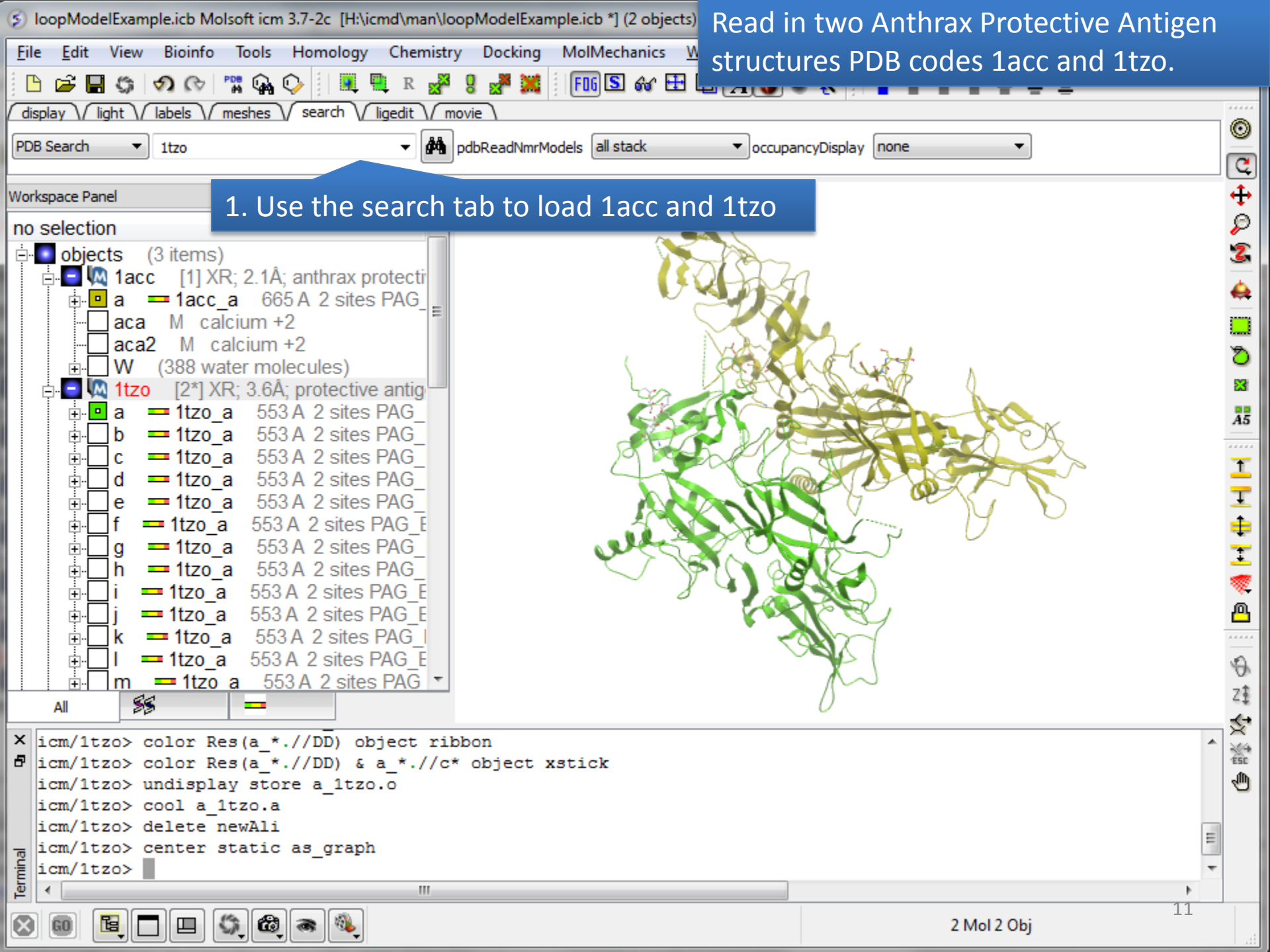


The model will be displayed in the ICM workspace.

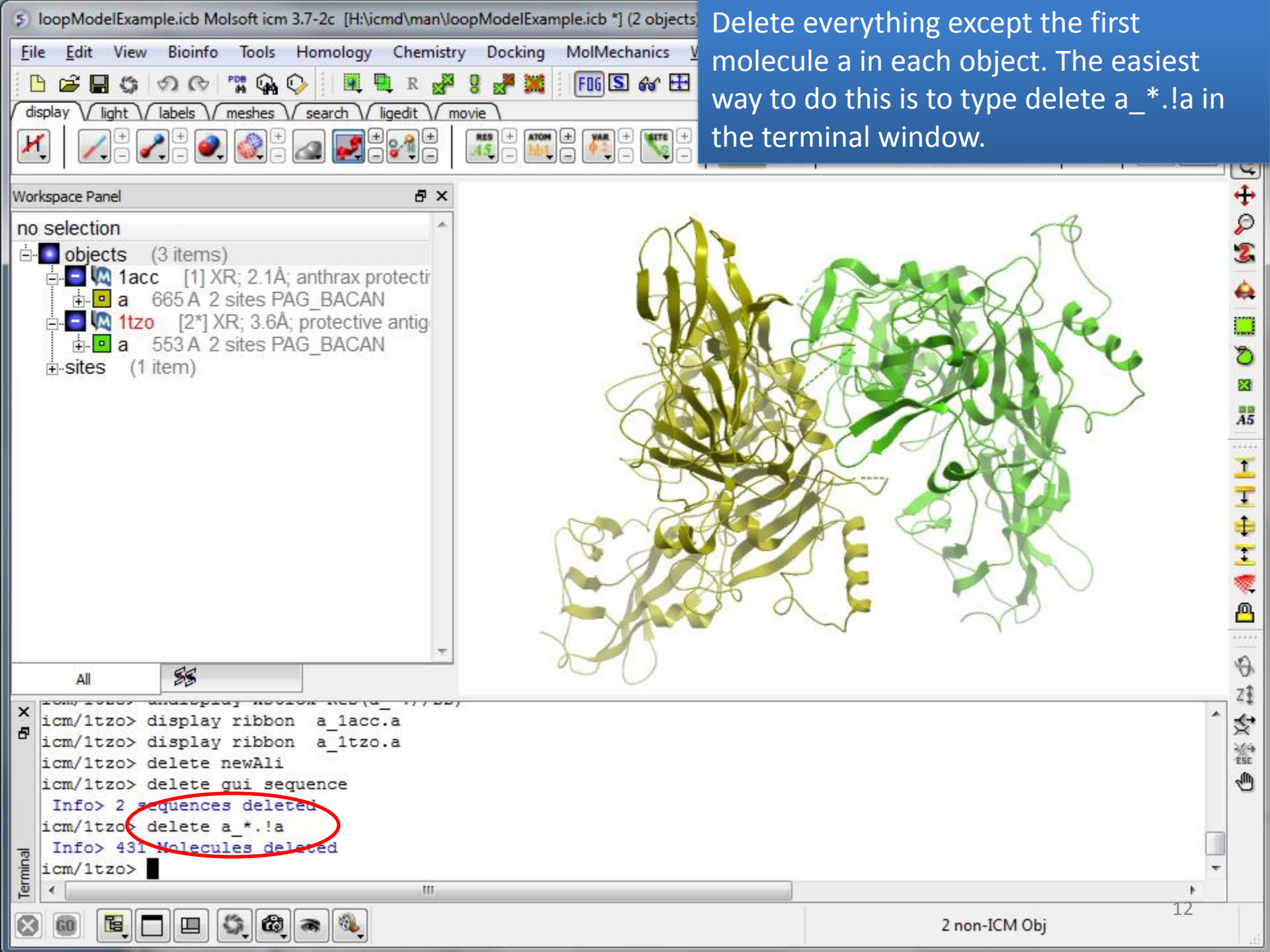


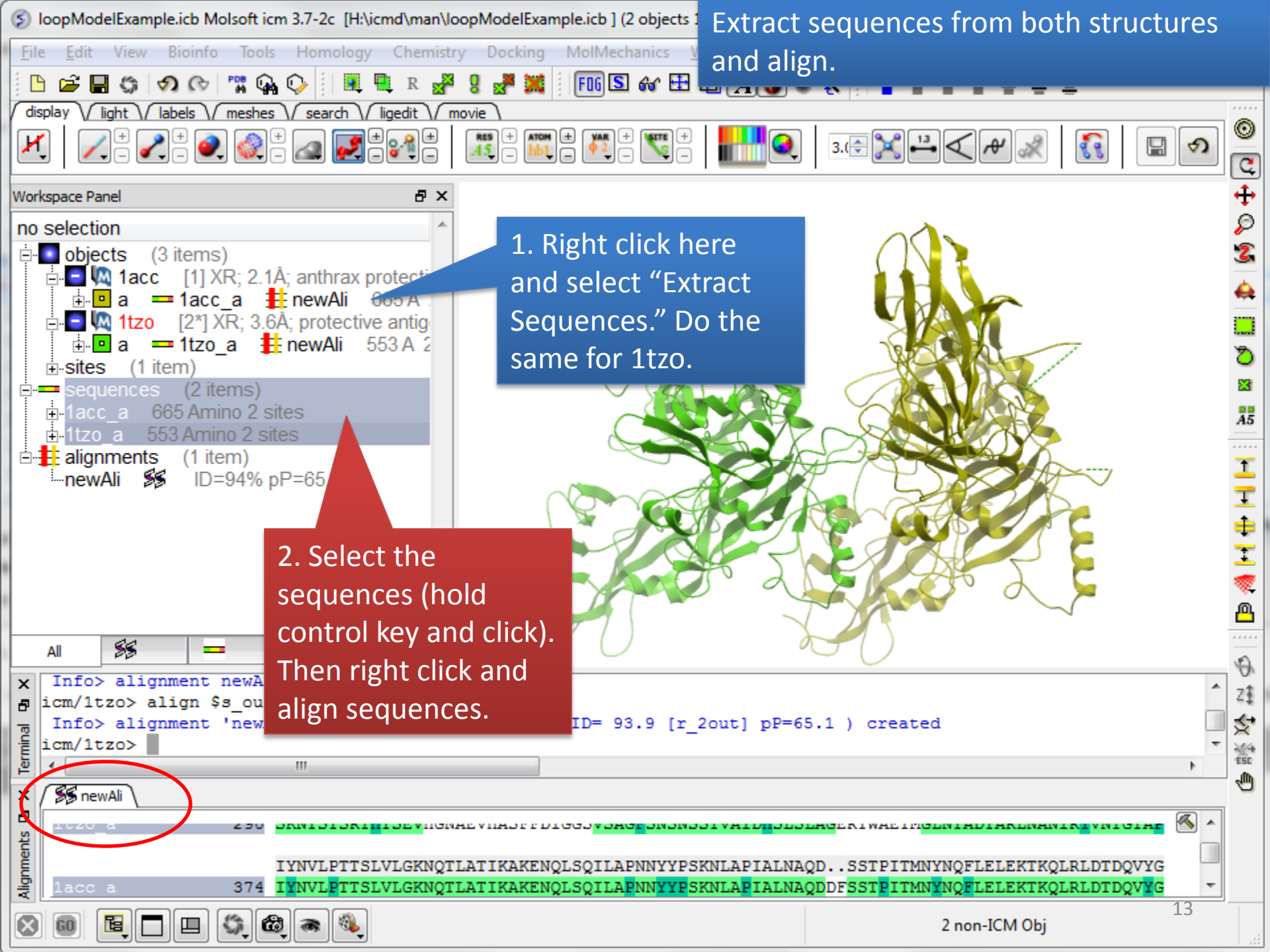
Loop Modeling

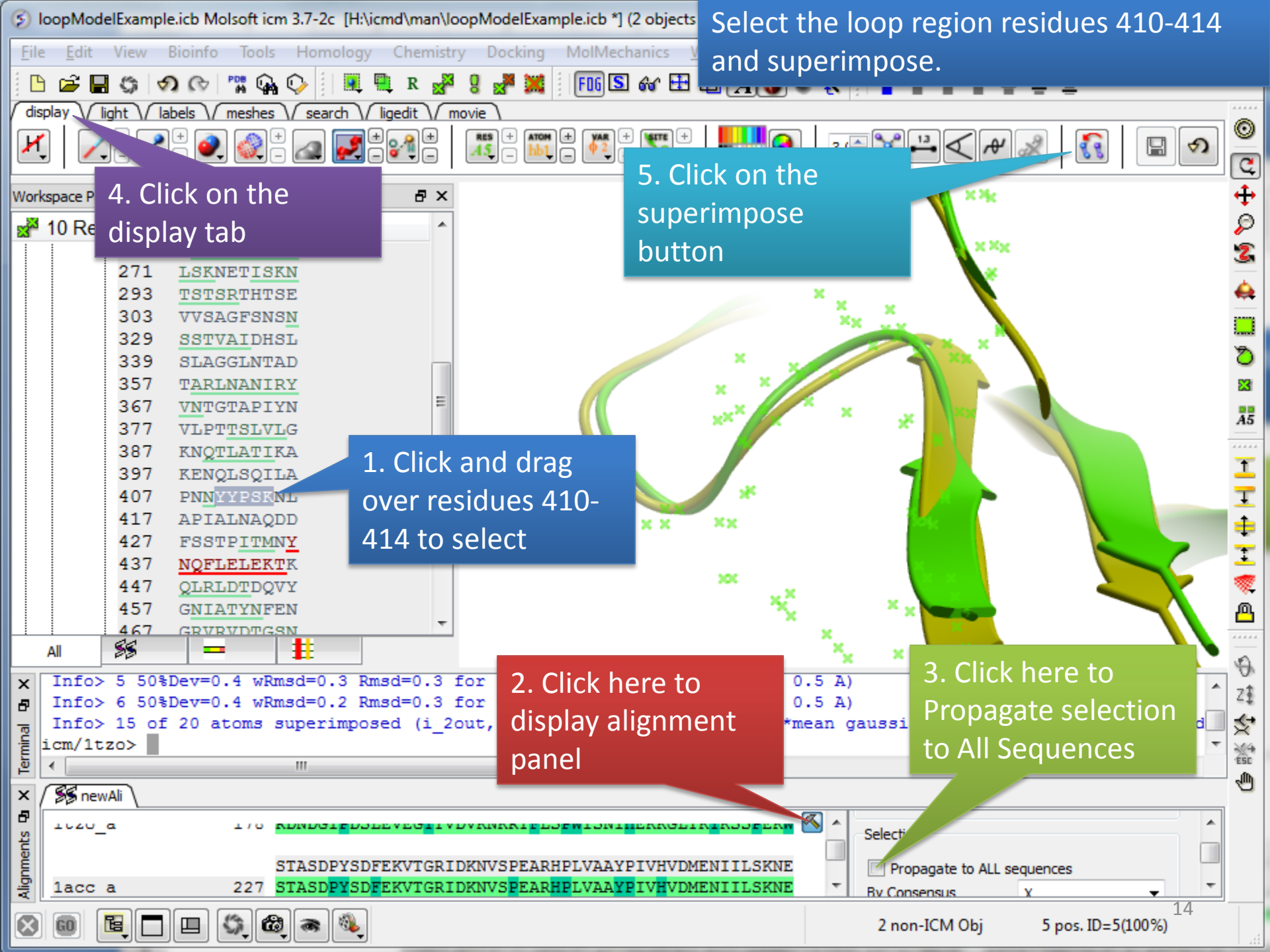
- In this example we will use the high precision loop modeling method Arnautova *et al* Proteins. 2010, 79:477.
- We will model a loop region in Anthrax Protective Antigen which contains a proline residue where the cis/trans conformation is not clear from the available X-ray crystal structures.
- We will determine the most energetically favorable conformation of the proline and the neighboring loop residues.

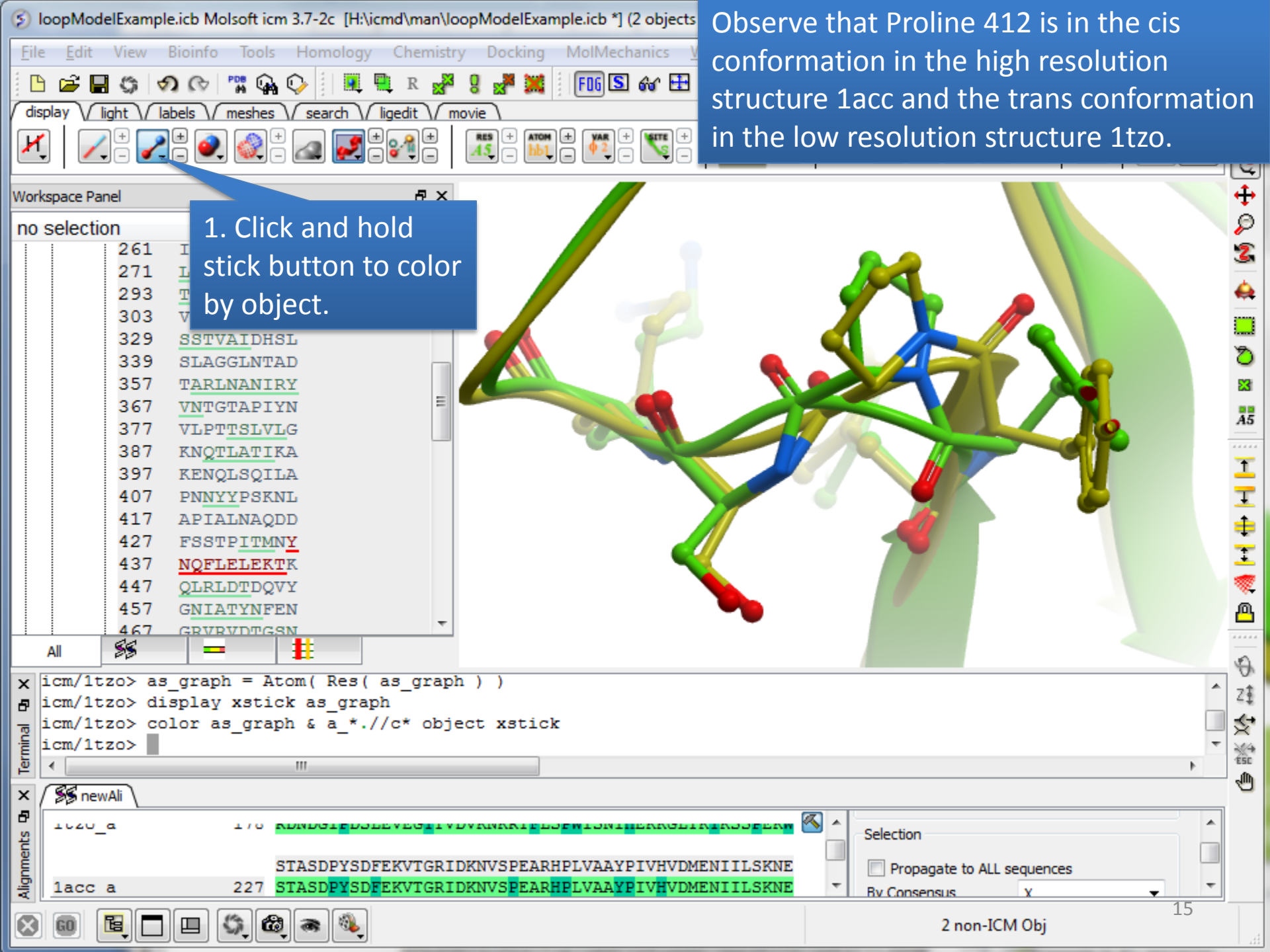

loopModelExample.icb Molsoft icm 3.7-2c [H:\icmd\man\loopModelExample.icb *] (2 objects)
Read in two Anthrax Protective Antigen structures PDB codes 1acc and 1tzo.
File Edit View Bioinfo Tools Homology Chemistry Docking MolMechanics
display light labels meshes search ligedit movie
PDB Search
1tzo
pdbReadNmrModels
all stack
occupancyDisplay
none
1. Use the search tab to load 1acc and 1tzo
Workspace Panel
no selection
objects (3 items)
1acc [1] XR; 2.1Å; anthrax protecti
a 1acc_a 665 A 2 sites PAG_
aca M calcium +2
aca2 M calcium +2
W (388 water molecules)
1tzo [2*] XR; 3.6Å; protective antig
a 1tzo_a 553 A 2 sites PAG_
b 1tzo_a 553 A 2 sites PAG_
c 1tzo_a 553 A 2 sites PAG_
d 1tzo_a 553 A 2 sites PAG_
e 1tzo_a 553 A 2 sites PAG_
f 1tzo_a 553 A 2 sites PAG_E
g 1tzo_a 553 A 2 sites PAG_
h 1tzo_a 553 A 2 sites PAG_
i 1tzo_a 553 A 2 sites PAG_E
j 1tzo_a 553 A 2 sites PAG_E
k 1tzo_a 553 A 2 sites PAG_
l 1tzo_a 553 A 2 sites PAG_E
m 1tzo_a 553 A 2 sites PAG
All
icm/1tzo> color Res(a_*.//DD) object ribbon
icm/1tzo> color Res(a_*.//DD) & a_*.//c* object xstick
icm/1tzo> undisplay store a_1tzo.o
icm/1tzo> cool a_1tzo.a
icm/1tzo> delete newAli
icm/1tzo> center static as_graph
icm/1tzo>
Terminal
2 Mol 2 Obj

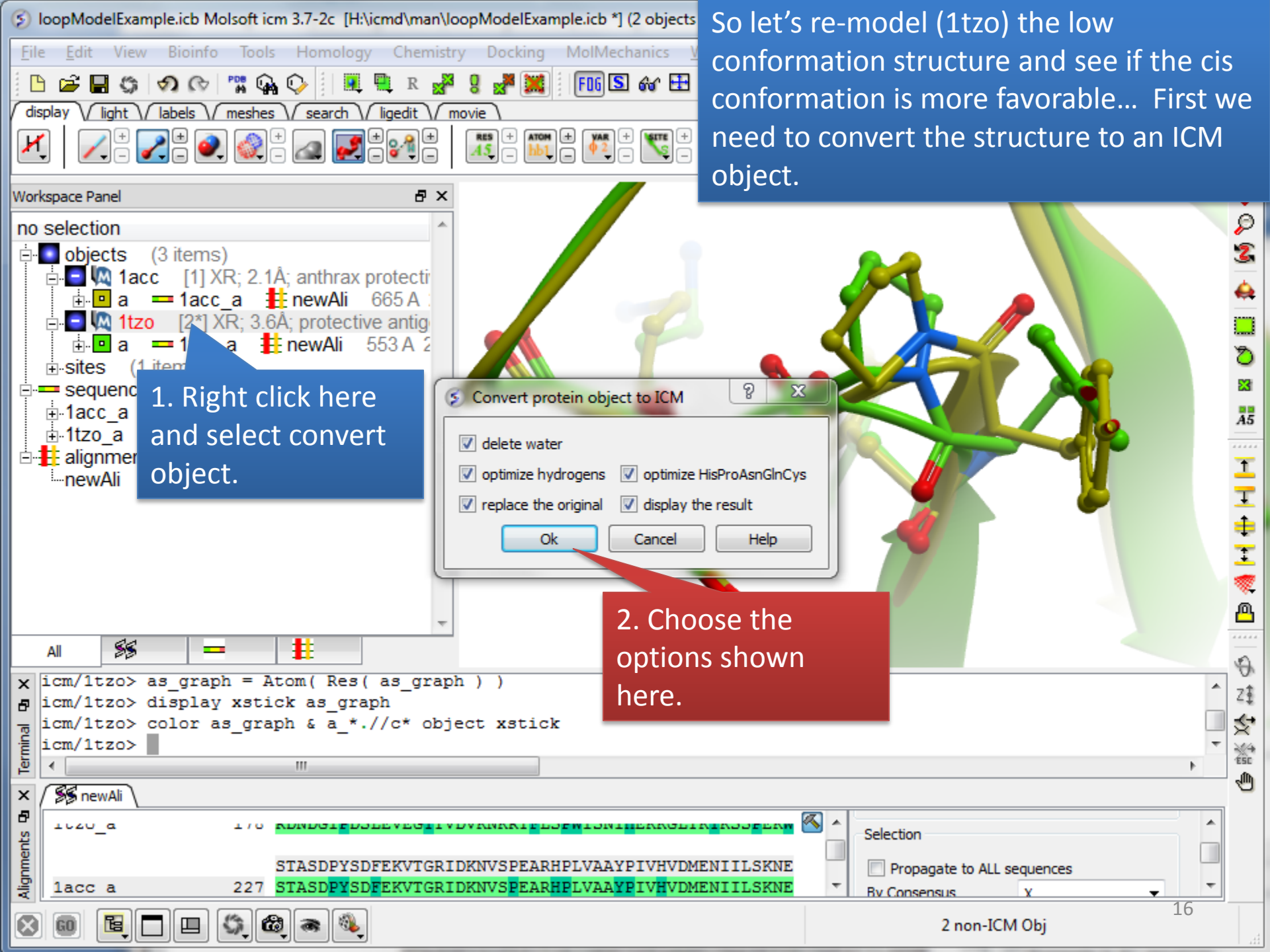
Delete everything except the first molecule a in each object. The easiest way to do this is to type delete a_*.!a in the terminal window.



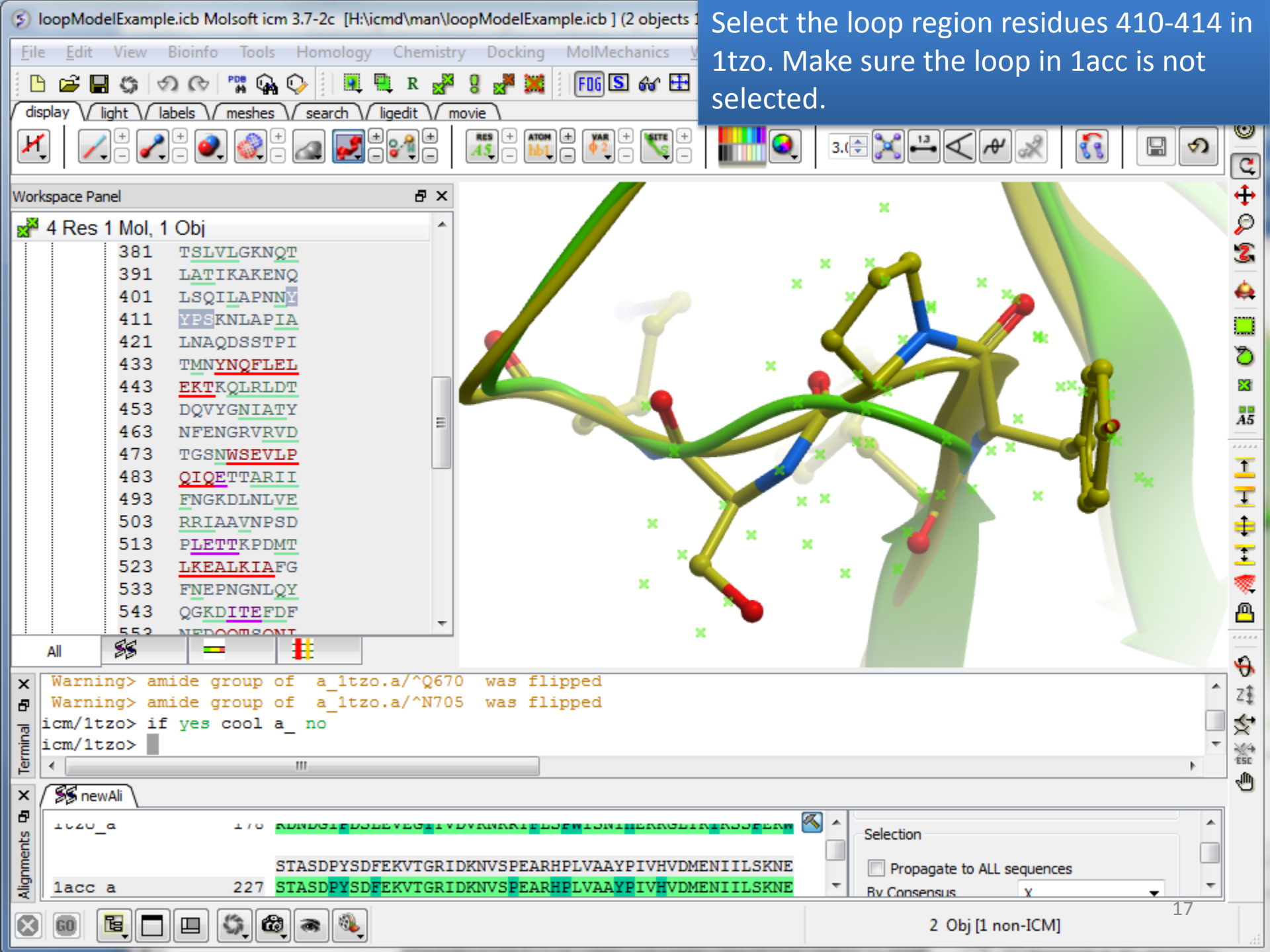

Extract sequences from both structures and align.
1. Right click here and select “Extract Sequences.” Do the same for 1tzo.
2. Select the sequences (hold control key and click). Then right click and align sequences.
Workspace Panel
no selection
objects (3 items)
1acc [1] XR; 2.1Å; anthrax protecti
a 1acc_a newAli
1tzo [2*] XR; 3.6Å; protective antig
a 1tzo_a newAli 553 A
sites (1 item)
sequences (2 items)
1acc_a 665 Amino 2 sites
1tzo_a 553 Amino 2 sites
alignments (1 item)
newAli ID=94% pP=65
Info> alignment newA
icm/1tzo> align $s_ou
Info> alignment 'new
ID= 93.9 [r_2out] pP=65.1) created
icm/1tzo>
newAli
1acc_a 374 IYNVLPTTSLVLGKNQTLATIKAKENQLSQILAPNNYYPSKNLAPIALNAQDDFSSTPITMNYNQFLELEKTKQLRLDTDQVYG
2 non-ICM Obj

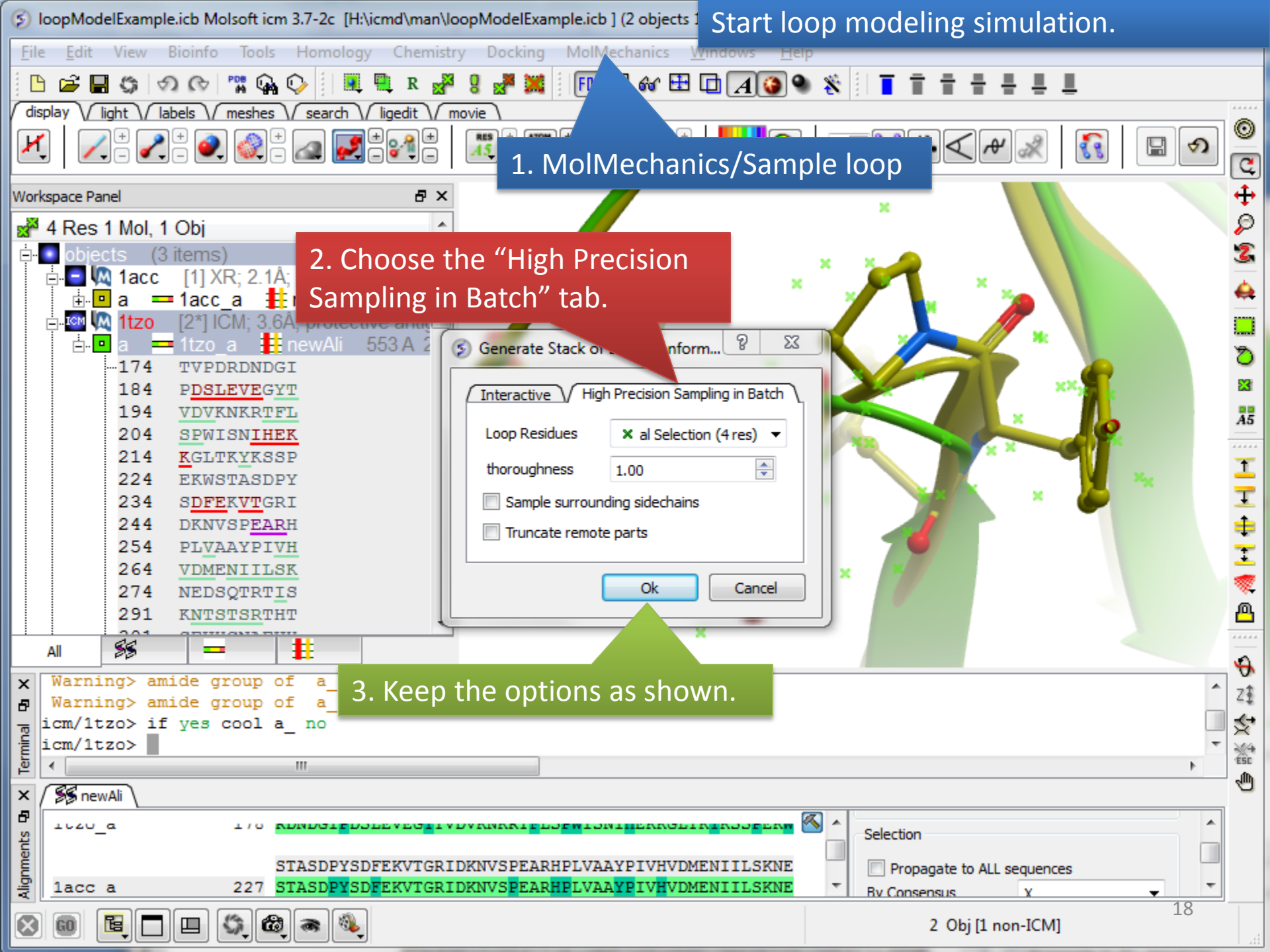

Select the loop region residues 410-414 and superimpose.
4. Click on the display tab
5. Click on the superimpose button
1. Click and drag over residues 410-414 to select
2. Click here to display alignment panel
3. Click here to Propagate selection to All Sequences
loopModelExample.icb Molsoft icm 3.7-2c [H:\icmd\man\loopModelExample.icb *] (2 objects
File Edit View Bioinfo Tools Homology Chemistry Docking MolMechanics
display light labels meshes search ligedit movie
Workspace P
10 Re
271 LSKNETISKN
293 TSTSRTHTSE
303 VVSAGFSNSN
329 SSTVAIDHSL
339 SLAGGLNTAD
357 TARLNANIRY
367 VNTGTAPIYN
377 VLPTTSLVLG
387 KNQTLATIKA
397 KENQLSQILA
407 PNNYYPSKNL
417 APIALNAQDD
427 FSSTPITMNY
437 NQFLELEKTK
447 QLRLDTDQVY
457 GNIATYNFEN
All
Info> 5 50%Dev=0.4 wRmsd=0.3 Rmsd=0.3 for
Info> 6 50%Dev=0.4 wRmsd=0.2 Rmsd=0.3 for
Info> 15 of 20 atoms superimposed (i_2out,
0.5 A)
0.5 A)
*mean gaussi
icm/1tzo>
Terminal
newAli
STASDPYSDFEKVTGRIDKNVSPEARHPLVAAYPIVHVDMENIILSKNE
1acc a 227 STASDPYSDFEKVTGRIDKNVSPEARHPLVAAYPIVHVDMENIILSKNE
Propagate to ALL sequences
By Consensus
Alignments
2 non-ICM Obj
5 pos. ID=5(100%)
14

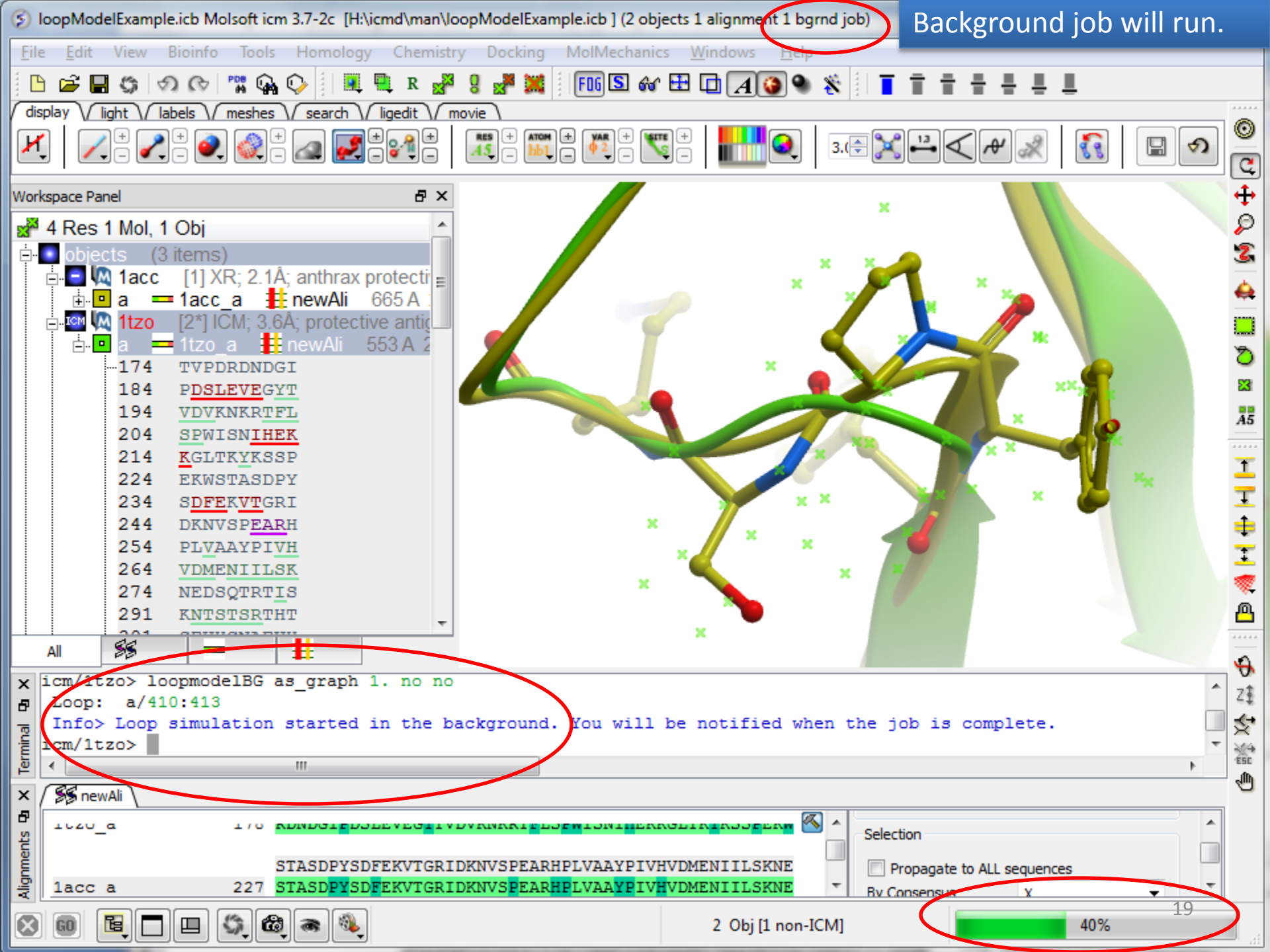

loopModelExample.icb Molsoft icm 3.7-2c [H:\icmd\man\loopModelExample.icb *] (2 objects
File Edit View Bioinfo Tools Homology Chemistry Docking MolMechanics
display light labels meshes search ligedit movie
Observe that Proline 412 is in the cis conformation in the high resolution structure 1acc and the trans conformation in the low resolution structure 1tzo.
1. Click and hold stick button to color by object.
Workspace Panel
no selection
261 I
271 L
293 T
303 V
329 SSTVAIDHSL
339 SLAGGLNTAD
357 TARLNANIRY
367 VNTGTAPIYN
377 VLPTTSLVLG
387 KNQTLATIKA
397 KENQLSQILA
407 PNNYYPSKNL
417 APIALNAQDD
427 FSSTPITMNY
437 NQFLELEKTK
447 QLRLDTDQVY
457 GNIATYNFEN
All
icm/1tzo> as_graph = Atom(Res(as_graph))
icm/1tzo> display xstick as_graph
icm/1tzo> color as_graph & a_*.//c* object xstick
icm/1tzo>
Terminal
newAli
STASDPYSDFEKVTGRIDKNVSPEARHPLVAAYPIVHVDMENIILSKNE
1acc a 227 STASDPYSDFEKVTGRIDKNVSPEARHPLVAAYPIVHVDMENIILSKNE
Alignments
Selection
Propagate to ALL sequences
By Consensus
2 non-ICM Obj
15


So let's re-model (1tzo) the low conformation structure and see if the cis conformation is more favorable… First we need to convert the structure to an ICM object.
loopModelExample.icb Molsoft icm 3.7-2c [H:\icmd\man\loopModelExample.icb *] (2 objects
File Edit View Bioinfo Tools Homology Chemistry Docking MolMechanics
display light labels meshes search ligedit movie
Workspace Panel
no selection
objects (3 items)
1acc [1] XR; 2.1Å; anthrax protecti
a 1acc_a newAli 665 A
1tzo [2*] XR; 3.6Å; protective antig
a newAli 553 A
sites
sequenc
1acc_a
1tzo_a
alignmer
newAli
1. Right click here and select convert object.
Convert protein object to ICM
delete water
optimize hydrogens
optimize HisProAsnGlnCys
replace the original
display the result
Ok
Cancel
Help
2. Choose the options shown here.
All
icm/1tzo> as_graph = Atom(Res(as_graph))
icm/1tzo> display xstick as_graph
icm/1tzo> color as_graph & a_*.//c* object xstick
icm/1tzo>
Terminal
newAli
Alignments
STASDPYSDFEKVTGRIDKNVSPEARHPLVAAYPIVHVDMENIILSKNE
1acc a 227 STASDPYSDFEKVTGRIDKNVSPEARHPLVAAYPIVHVDMENIILSKNE
Selection
Propagate to ALL sequences
By Consensus
2 non-ICM Obj

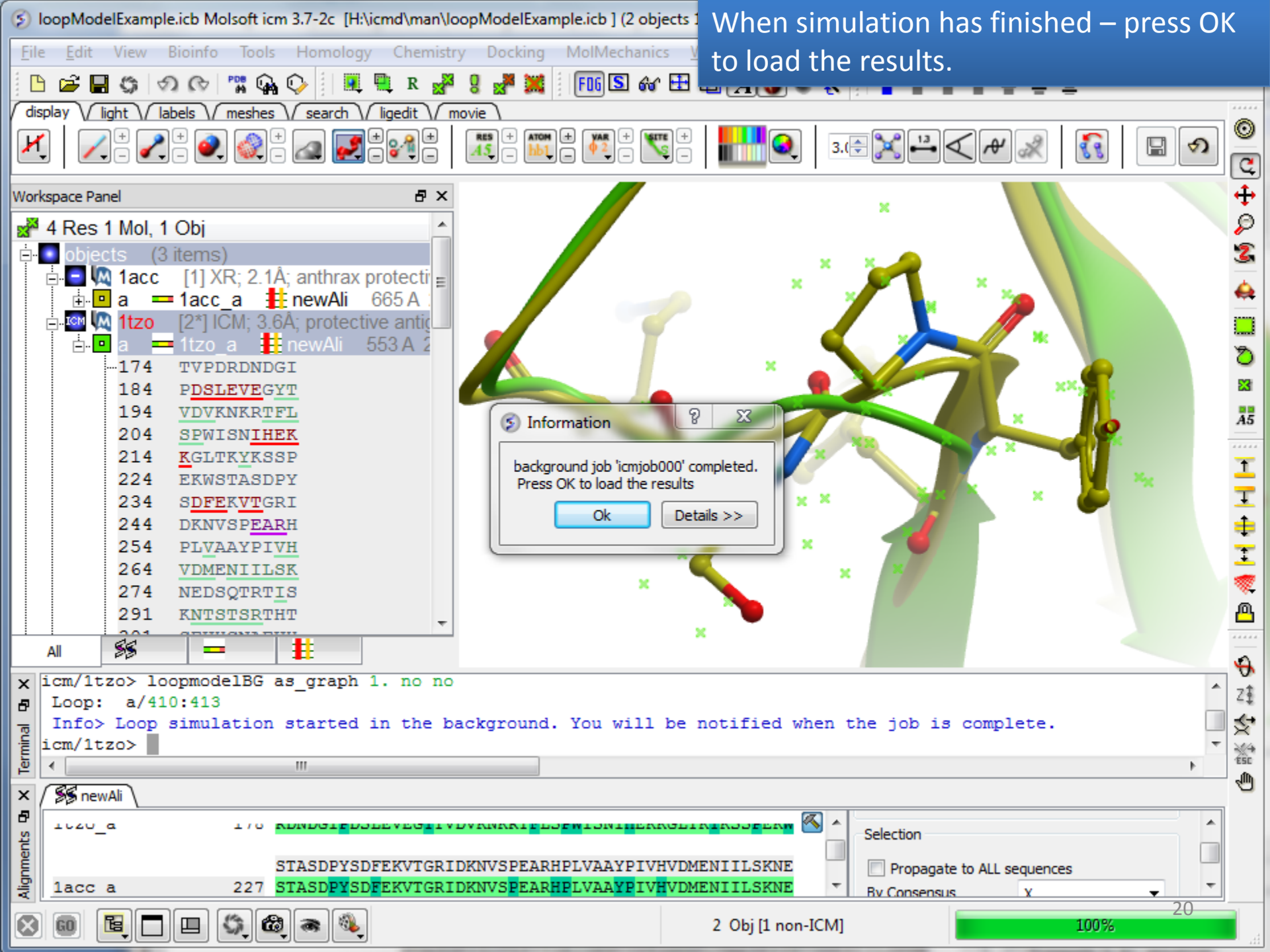
Select the loop region residues 410-414 in 1tzo. Make sure the loop in 1acc is not selected.

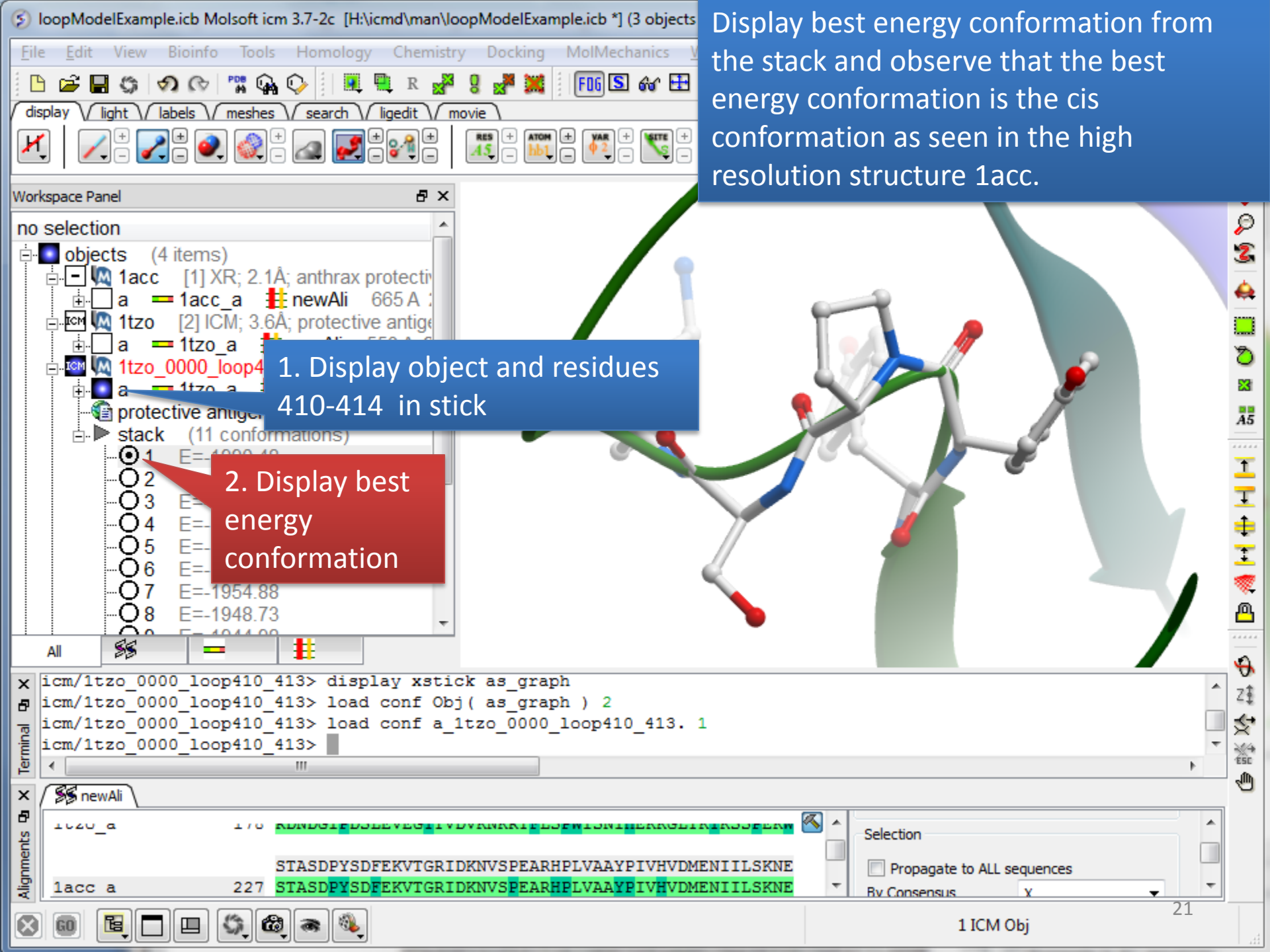



Start loop modeling simulation.
1. MolMechanics/Sample loop
2. Choose the “High Precision Sampling in Batch” tab.
3. Keep the options as shown.
Interactive
High Precision Sampling in Batch
Loop Residues
thoroughness
1.00
Sample surrounding sidechains
Truncate remote parts
Ok
Cancel


loopModelExample.icb Molsoft icm 3.7-2c [H:\icmd\man\loopModelExample.icb] (2 objects 1 alignment 1 bgrnd job)
Background job will run.
File Edit View Bioinfo Tools Homology Chemistry Docking MolMechanics Windows Help
display light labels meshes search ligedit movie
Workspace Panel
4 Res 1 Mol, 1 Obj
objects (3 items)
1acc [1] XR; 2.1Å; anthrax protecti
a 1acc_a newAli 665 A
1tzo [2*] ICM; 3.6Å; protective anti
a 1tzo_a newAli 553 A 2
174 TVPDRDNDGI
184 PDSLEVEGYT
194 VDVKNKRTFL
204 SPWISNIHEK
214 KGLTKYKSSP
224 EKWSTASDPY
234 SDFEKVTGRI
244 DKNVSPEARH
254 PLVAAYPIVH
264 VDMENIILSK
274 NEDSQTRTIS
291 KNTSTSRTHT
All
icm/1tzo> loopmodelBG as_graph 1. no no
Loop: a/410:413
Info> Loop simulation started in the background. You will be notified when the job is complete.
icm/1tzo>
Terminal
Alignments
newAli
1tzo_a 170 KDNDGIPDSLEVEGYTVDVKNKRTFLSPWISNIHEKKGLTKYKSSPEAH
STASDPYSDFEKVTGRIDKNVSPEARHPLVAAYPIVHVDMENIILSKNE
1acc a 227 STASDPYSDFEKVTGRIDKNVSPEARHPLVAAYPIVHVDMENIILSKNE
Selection
Propagate to ALL sequences
By Consensus
2 Obj [1 non-ICM]
40%
19

When simulation has finished – press OK to load the results.




loopModelExample.icb Molsoft icm 3.7-2c [H:\icmd\man\loopModelExample.icb *] (3 objects
File Edit View Bioinfo Tools Homology Chemistry Docking MolMechanics
display light labels meshes search ligedit movie
Workspace Panel
no selection
objects (4 items)
1acc [1] XR; 2.1Å; anthrax protecti
a 1acc_a newAli 665 A
1tzo [2] ICM; 3.6Å; protective antige
a 1tzo_a
1tzo_0000_loop4
a
protective antige
stack (11 conformations)
1
2
3
4
5
6
7 E=-1954.88
8 E=-1948.73
All
Display best energy conformation from the stack and observe that the best energy conformation is the cis conformation as seen in the high resolution structure 1acc.
1. Display object and residues 410-414 in stick
2. Display best energy conformation
icm/1tzo_0000_loop410_413> display xstick as_graph
icm/1tzo_0000_loop410_413> load conf Obj(as_graph) 2
icm/1tzo_0000_loop410_413> load conf a_1tzo_0000_loop410_413. 1
icm/1tzo_0000_loop410_413>
Terminal
newAli
Alignments
STASDPYSDFEKVTGRIDKNVSPEARHPLVAAYPIVHVDMENIILSKNE
1acc a 227 STASDPYSDFEKVTGRIDKNVSPEARHPLVAAYPIVHVDMENIILSKNE
Selection
Propagate to ALL sequences
By Consensus
1 ICM Obj
21