Drug design package software with in silico drug discovery

MolDesk Basic Ver.1.1.105

Quick Manual



Table of Contents

1.	MD	Calo	culations	3
1	.1.	Mol	ecular Input	3
1	.2.	Aut	omatic MD calculation	4
1	.3.	Tra	jectory Analysis	6
	1.3.	1.	When MD calculation is performed in GROMACS	6
	1.3.	2.	MD calculation by other than GROMACS	7
1	.4.	3D.	Animation Display and File Output	7
2.	Doc	king	calculations	8
2	.1.	Mol	ecular Input	8
2	.2.	Aut	omatic docking	9
	2.2.	1.	Select receptor and ligand molecules	9
	2.2.	2.	Create a pocket	0
	2.2.	3.	Docking execution	$\lfloor 2$
2	.3.	Con	firmation of Results1	12
3.	Sav	ing a	nd Loading Projects	13
3	.1.	[Fil	e] - [Save As]1	13
3	.2.	[Fil	e] - [Open Project]	4
4.	3D '	View	of Molecular Structure	15
4	.1.	Mou	use Operation1	15
4	.2.	Sele	ect molecule, chain, residue, atom1	15
4	.3.	Sele	ect a display model	16
4	.4.	How	v to color1	16
5.	MD	Calo	culations in GROMACS	17
5	.1.	[Pre	eference] - [Molecular dynamics] settings	17
	5.1.	1.	If [GROMACS] is selected	17
	5.1.	2.	If [Use chiral server=Yes] is selected	18

1. MD Calculations

For the Windows version, MD calculations (molecular dynamics calculations) with GROMACS can be performed with a few clicks of the mouse.

The following is an example of the simplest automated MD calculation.

The procedure is as follows.



1.1. Molecular Input



If you are connected to the Internet, click the [PDB] or [TEST] button on the top page.

Each has the following functions.

[PDB]: Input the molecule of the PDB ID specified by the user.

[TEST]: Input molecules with any PDB ID 4kn6.



When the [PDB] button is clicked, the screen shown in the figure is displayed, so enter 4kn6 and click [OK].

4kn6 will be entered. The same applies when you click the [TEST] button. * If you are not connected to the Internet, click [File] - [Open Molecular File] to load the sample / PDB / 4KN6.pdb file.

1.2. Automatic MD calculation



Next, click the [MD] button shown in the figure. The process is performed in the following order.

- * Add missing hydrogen atoms to all molecules (default is the dissociated state in water)
- * Gasteiger charge added to all compounds or sugars
- * Molecules other than compounds or sugars are charged based on the force field selected in [Help] [Preference] [Molecule] [tplgeneX]

Solvate			×	
set water				
☑ set water	crystal water ☑ use crystal water in PDB ☐ predict precise placement	system size shape Cube \checkmark size Margin from molecular size \checkmark margin(A): 3.00 \clubsuit	center coordinate	Displays a dialog box for selecting water solvents and ion addition methods.
add ion	method			Click the [OK] button.
	in human cell (10mh//bla) 100	The water solvents and ions		
☑ add ion	in numan cell (10mm//Na+, 100	are added.		
			OK Cancel	



- **Solvent:** A rectangular box with the center of gravity of the system as the center of the solvent and a size of 3 Å from the solute boundary.
- **Ions:** Na+, K+, and Cl- are added at the ion concentration of a human cell.

ZMIN 1	loop limit MIN 1 (ste	eps): 5000 💂
MIN 2	loop limit MIN 2 (ste	2ps): 5000 👻
4IN 1 N	IIN 2	
Method :		Steepest descent 🛛 🗸
	n restraint	Heavy atoms (proteins & DNA/RNA) 🛛 🗸
🗌 Positio		

Click [OK] to display the dialog box for setting conditions for energy minimization calculations.

Two energy minimization calculations will be performed in succession.

The first one is the steepest descent method with 5000 steps. No position constraint The second one is the conjugate gradient method, 5000 steps. No position constraint

When the energy minimization calculation is completed, the MD Calculation Condition Setting dialog box is displayed.

Global Dynamics	×
MD 1 20000 \$ steps MD 2 20000 \$ steps MD 3 2000 MD 4 20000 \$ steps MD 5 20000 \$ steps MD 6 2000 MD 7 20000 \$ steps MD 8 20000 \$ steps MD 9 2000 MD 10 20000 \$ steps MD 11 20000 \$ steps MD 12 2000	0 ÷ steps 0 ÷ steps 0 ÷ steps 0 ÷ steps
MD 1 MD 2 MD 3 MD 4 MD 5 MD 6 MD 7 MD 8 MD 9 MD 10 MD 11 MD Use restart file Ensemble : NPT Pressure (bar): 1.000 + Temperature (init) (K) : 300.000 + Temperature (const) (K) : 300.000 + Position restraint Heavy atoms (proteins & DNA/RNA) >	12 Typical setting O None O Globular Membrane O RNA
constraint (LINCS) : h-bonds ∨ Time step (fsec) : 2.000 Cutoff length (A) : 10.00 Output trajectory 2000 ÷ ✓ MD energy (every steps): 2000 ÷ ✓ Coordinate (every steps): 2000 ÷ ✓ Velocity (every steps): 2000 ÷	
ОК	Cancel

Click the [OK] button.

The MD calculation starts with the following conditions.

- * Execute only once.
- * The number of steps is 20000.
- * NPT ensemble
- * Pressure is 1 bar.
- * Initial temperature 300K
- * Constant temperature of 300K
- * No position constraint
- * Constraints of LINCS: h-bonds
- * Time step is 2.0 fsec
- * Cutoff radius is 10.0 Å.
- * Energy file output (every 2000 steps)
- * Trajectory file output (every

2000 steps)

This completes the entire process of calculating MD for molecules in aqueous solution.

* The force field is set by default to AMBER GAFF2 for compounds or sugars and AMBER ff99SB for others (e.g. proteins).

(Force field can be changed by [Help] - [Preference] - [Molecule] - [tplgeneX])

- * The [MD] button is equivalent to the mics [Dynamics] -[Auto Solvate and Dynamics] button.
- 1.3. Trajectory Analysis
- 1.3.1. When MD calculation is performed in GROMACS

Click the [2D plot] button to run the trajectory analysis in GROMACS and display a graph with time axis linked to the movie.





gmx energy

gmx rms

8	
General	PCA Analysis
(1) gmx energy	(8) gmx covar
(2) gmx rms	(9) gmx anaeig
(3) gmx rmsf	
(4) gmx gyrate	
(5) gmx mindist	
(6) gmx hbond	
(7) gmx rama	

Executable gmx commands

- * For details on usage, please refer to the MolDesk Basic manual.
- * For details on trajectory analysis with GROAMCS, refer to the GROMACS manual.

1.3.2. MD calculation by other than GROMACS

* For details on usage, refer to the MolDesk Basic manual.

1.4. 3D Animation Display and File Output



By operating the Animation controller on the MD Analysis screen, you can animate the time variation of atom movement (trajectory) on the 3D screen.

Click the [Save Animation] button to output the animation as a GIF file. The frame time interval can also be set.

Click the [Save PDB] button to save a snapshot of all trajectories in a PDB file.

2. Docking calculations

The following is an example of the simplest docking calculation performed by automation.

The procedure is as follows.



* Docking to nucleic acid molecules in addition to proteins is available in ver. 1.1.78 and later. Proteins or nucleic acid molecules can be specified as acceptors.

2.1. Molecular Input



If you are connected to the Internet, click the [PDB] or [TEST] button on the top page.

Each has the following functions.

[PDB]: Input the molecule of the PDB ID specified by the user.

[TEST]: Input molecules with any PDB ID 4kn6.

iternet	
DB ID 4kn6	: 4 characters starting with a number[1-9]

When the [PDB] button is clicked, the screen shown in the figure is displayed, so enter 4kn6 and click [OK].

4kn6 will be entered. The same applies when you click the [TEST] button.

* If you are not connected to the Internet, click [File] - [Open Molecular File] to load the sample / PDB / 4KN6.pdb file.

2.2. Automatic docking



Next, click the [DOCK] button in Fig. The process is performed in the following order.

- * Adds a missing hydrogen atom to all molecules (default is the dissociated state in water).
- * Add Gasteiger charge for all compounds or sugars
- * For molecules other than compounds or sugars, add charges based on the force field selected in [Help] [Preference] [Molecule] [tplgeneX]
- * The [DOCK] button is equivalent to Dock [Dock] [Auto Docking].

2.2.1. Select receptor and ligand molecules

A message dialog will appear prompting you to select a receptor.

lease select Recentor Molecule(s) including at least one Protein/Nucleotide, and	
cuse select neceptor molecule(s) including at least one moterly redecoded, and	d click [OK
ease select neceptor molecule(s) menduing at least one froten, rudecolide, and	r click [c

Select **I** pro1 in the tree view screen and click OK.



* The receptor molecule must contain at least one protein or nucleic acid molecule. It may contain compounds, sugars or metals.

2.2.2. Create a pocket

After specifying the receptor, a dialog box will appear to select the pocket creation method.

OCoc	ordinates of	the ligand	
Mail	ke Pocket		
○ Find	Pocket		

In this case, leave [Make Pocket] as it is and click [OK].

The following is a description of the items in the dialog box for selecting the pocket generation method.

Item	Item
[Coordinates of the ligand]	The coordinates of the selected molecule are used as the probe
	point for the pocket.
	Multiple molecules other than protein or nucleic acid molecules
	can be selected and batch probed.
[Make Pocket]	Places a pocket sphere on the surface of the selected receptor
	and generates a pocket probe point inside the sphere.
[Find Pocket]	Performs a pocket search on the surface of the selected receptor
	and automatically generates multiple probe points in score
	order.

* For details on usage, please refer to the MolDesk Basic Manual.

The protein becomes a space-fill display model and displays a pocket selection dialog.



Click around the ligand molecule in the 3D screen.



- 0

The selected pocket is displayed as a yellow translucent sphere.

Click the [OK] button.



Display **D** point4 in the tree view screen,



Add the probe points (red points) of the pocket in the yellow translucent sphere.

A message dialog prompting the user to select a ligand is displayed.



In this example, **1** lig2 is selected in the tree view screen and [OK] is clicked.

2.2.3. Docking execution

A dialog box for setting the conditions for docking calculations appears.



In this example, leave the default conditions as they are and click OK. The docking calculation is executed.

All docking calculations are now complete.

2.3. Confirmation of Results

When the docking calculation is completed, the Docking Info screen displays a list of the 10 molecular structures predicted by the docking calculation in order of best score. The values of the molecular structure attributes are as follows

 ΔG value (deltaG, free energy)

Score (score, docking score)

RMSD (value for the ligand used in the docking calculation input)





Select a candidate structure in the Docking Info screen (Ctrl+click for multiple selections), right-click, and select "Add Selected Docking Result" to add the candidate structure to the Ligand Info screen, Add Selected Docking Result" to add the candidate structure to the

Ligand Info screen. The result will be added to the calculation system and can be used for MD calculations, etc.

3. Saving and Loading Projects

3.1. [File] - [Save As]

Saves the displayed system with a project name. The command history is also saved.

Execute [File] - [Save As] and in the [Make PROJECT directory] dialog, select [Create New Folder] or [New Folder]or [New] - [Folder] from the right-click menuand enter a folder name. This folder name will become the new project name.

All data (including command history) of the currently displayed system will be saved in the created folder.

[Please note that if you specify an existing folder without creating a new folder, the following folders and files will be output directly under the folder.

original folder work folder cif and pdb files downloaded via internet

* If you are interested in the details of the files stored in the project, please refer to the MolDesk Basic Manual.

3.2. [File] - [Open Project]

Open a project that has been saved in the past via [File] - [Save As], or

MoldeskProject00000 MoldeskProject00001 MoldeskProject00002 ... in the directory set in the Default Project Directory under [Help] - [Preferences] - [8. Other].

Select the existing project folder (including "original" and "work" folders directly below) and click [OK].

The tab names on the tree display screen (blue box "P2- L1- W" in the figure below) indicate the number of proteins and compounds.

P indicates protein chain, L indicates compounds, W indicates the presence of crystal water, and M indicates metals and ions.

In the tree view, denotes protein, denotes compound, denotes water, denotes metal ion, and denotes sugar.

The last command is indicated by the tab name on the 3D screen ("proj001 : 5 Global Minimize" in the red frame in the figure below).

The tab name indicates [Project name : History number Execution command name].



4. 3D View of Molecular Structure

4.1. Mouse Operation

Movement	Mouse Operation	
X-axis (left/right axis) rotation		
Y-axis (vertical axis) rotation	Left drag	
Z-axis (depth axis) rotation	Shift + right drag (left/right direction)	
Move in X-axis (left/right) direction	Right drag	
Move in Y-axis (up/down) direction		
Mana in 7 anis (dauth) dimetian (aroun in/ant)	Shift + left drag	
Move in Z-axis (depth) direction (zoom in/out)	Or, rotate the wheel	

* For MAC, Left click = click

Right click = [Command] + click

4.2. Select molecule, chain, residue, atom

The selection of molecules, chains, residues, and atoms is performed with the mouse, but the operation differs between the 3D screen and the tree view screen.

Operation	3D Screen	Tree view screen	
Multiple selection	Ctrl + click	Ctrl + click	
Consecutive			
multiple selections	-	Shift + click	
Select residues	Double click	Click residue name	
Select Chain	Triple click	Click on chain name	
Select molecule	-	Click on molecule name	

P2-L1-\	N 🛛 🗌	🗖 🗖 Command V
~	Chain : A	A De Dyna
>	4 SER	sign mics
>	5 PR(Show Atom
>	6 GL	Hide Atom
>	7 VAI	Show All
>	8 VAI	3100 All
>	9 ILE	Receptor On
>	10 SE	Receptor Off
>	11 AS	· · · · · · · · · · · · · · · · · · ·
>	12 AS	Export PDB
>	13 Gl	Export mmCIF
>	14 PF	Export Single PDB
>	15 Gl	Export Single mmCIE
>	16 TY	Export single mindle
>	17 AS	Export Single Mol2
>	18 LE	Export Single Tpl
>	19 ASP	Add
	20 L EU	

Multiple molecules, chains, residues, and atoms can be displayed or hidden together.

Select multiple molecules, chains, residues, and atoms in the tree view and right-click [Show Atom] or [Hide Atom].

Click [Show All] to show all residues and atoms.

4.3. Select a display model



By selecting a molecule, chain, residue, or atom, and then selecting a model from the [Display] menu, you can change the display model to Line, Stick, etc.

The meaning of the options are as follows[Only] : Display only this display model in 3D.[On] : Overlays this display model on other display models.

[Off]: Erase this display model.

For other display models, please refer to the following site of MolDesk https://www.moldesk.com/moldesk-basic-commands/#Display

4.4. How to color

You can change the color of molecules, chains, residues, and atoms.

	MolDesk	Basic							
File	Select	Display	Color	Option	Expert	Simple	Screening	Preparat	tion \
6			A	toms		>	Cpk	N	1
□ P1-L1-W X		Bonds		>	Struc	Structure			
		Backbone >			Chai	Chain			
~ I	💶 pro 1		Т	ube Ribbo	n Cartoor	n >	Resid	lue	
l '	✓ CI	hain : A	н	Bond		>	Char	ge	ł
	~	4 SEK 5 PRO	s	S Bond		>	B-Fa	ctor	
	5	6 GLY	A	II Surface		>	Shap	ely	
	>	7 VAL	В	ackgroun	d	>	Grou	p	
	>	8 VAL		-		Incentif	Any		
	>	9 ILE				insert f	· · ·		
	>	10 SER							

Select a molecule, chain, residue, or atom, and choose a color from the [Color] menu to change its color.

You can also change the color and transparency of all molecular surfaces at the same time by selecting [Color] - [All Surface].

For more information on each item in the [Color] menu, please refer to the following site of MolDesk.

https://www.moldesk.com/moldesk-basic-commands/#Color

5. MD Calculations in GROMACS

5.1. [Preference] - [Molecular dynamics] settings

5.1.1. If [GROMACS] is selected

In the [Help]-[Preference]-[Molecular dynamics] screen, select [GROMACS] under [Molecular Dynamic Program :].

Performs energy minimization and MD calculations with GROMACS on a computer with MolDesk Basic installed.

Preferences			– o x
	1. Molecular dynamics		(> ▼ => ▼ 8
1. Molecular dynamic	Molecular Dynamics Program :	_	
2. Screening	no MPI (cosgene) • GROMACS	s	
3. Docking		-	
4. H bond	CDOMACS directory	C:VBrogram FilesVMalDackBasicVgromassVuin64Vgromass 2021 7	Proviso
5. 3D view	GROWACS directory		browse
6. Molecule	Steps to be automatically devided	1000000	
7. Internet			
8. Other	Use chiral server :		
ANSI Support	○ Yes ● No		
	Chiral Server User ID		
	Chiral Server API Key		
		Restore Defaults	Apply
		Apply and Close	Cancel

On Windows 10 and Windows 11, this setting is not necessary since the GROMACS executable program is implemented beforehand.

On Linux and MAC, the user must install GROMACS and configure the [GROMACS directory] setting in the installed GROAMCS. The installation procedure is explained below.

https://www.moldesk.com/faq/faq16/

For [GROMACS directory], set the directory where **share** and **bin** exist.

* In the current version, GROMACS is executed in bin/gmx without specifying the number of parallelism.

If bin/gmx does not exist in the installation directory, GROMACS cannot be executed.

The parallel number of OpenMP and thread MPI depends on the function of automatically specifying the parallel number of GROMACS.

5.1.2. If [Use chiral server=Yes] is selected

When Yes is selected for [Use chiral server :] in the [Help]-[Preference]-[Molecular dynamics] screen

m Preferences			– D X
	1. Molecular dynamics		<p 8<="" th="" ₹="" ⇒="" ▼=""></p>
 Molecular dynamic Screening Docking H bond 	Molecular Dynamics Program : Ono MPI (cosgene) • GROMACS		
5. 3D view	GROMACS directory	C:¥Program Files¥MolDeskBasic¥gromacs¥win64¥gromacs-2021.7	Browse
6. Molecule	Steps to be automatically devided	1000000	
7. Internet			
8. Other	Use chiral server :		
ANSI Support	○Yes ⁰No		
	Chiral Server User ID		
	Chiral Server API Key		
		Restore Defaults	Apply
		Apply and Close	Cancel

The energy minimization and MD calculations are performed by GROMACS on the cloud server provided by Chiral. A separate contract between the user and Chiral is required.

Enter the [Chiral Server User ID] and [Chiral Server API Key] issued by Chiral.