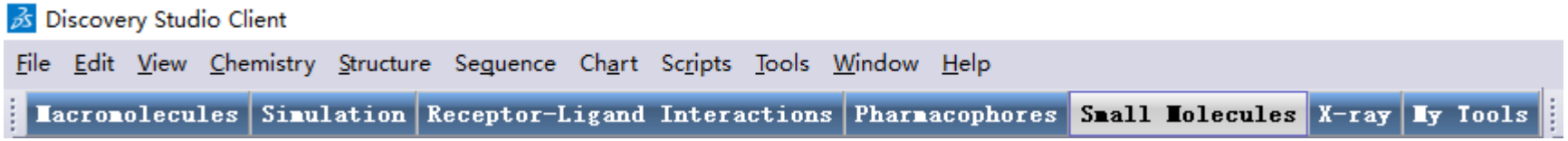
分子力学优化及动力学模拟

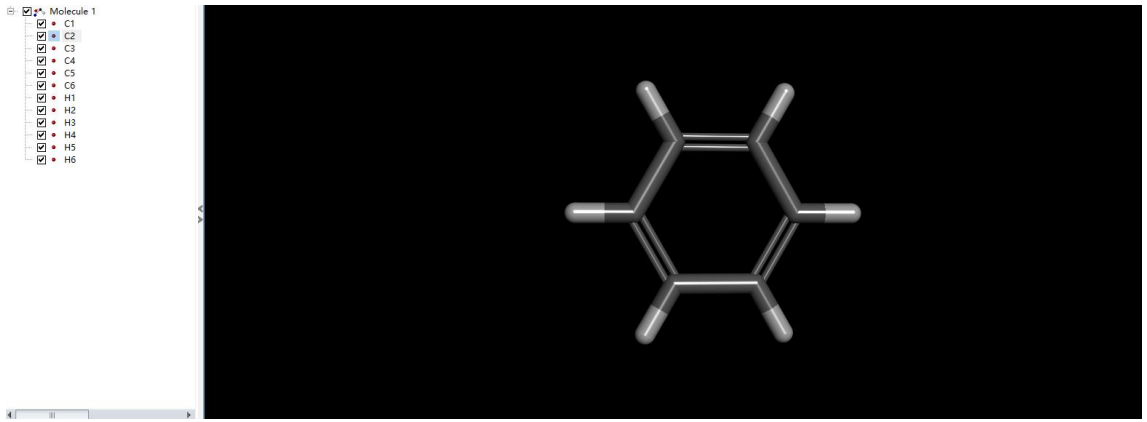
Discovery Studio模块组成与基本操作

（1）菜单栏



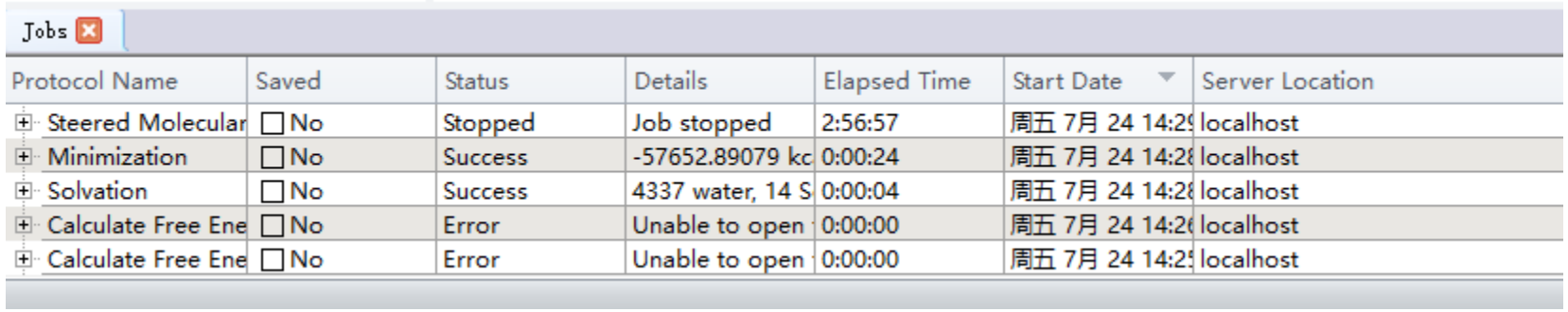
（2）工具栏

（3）窗口栏

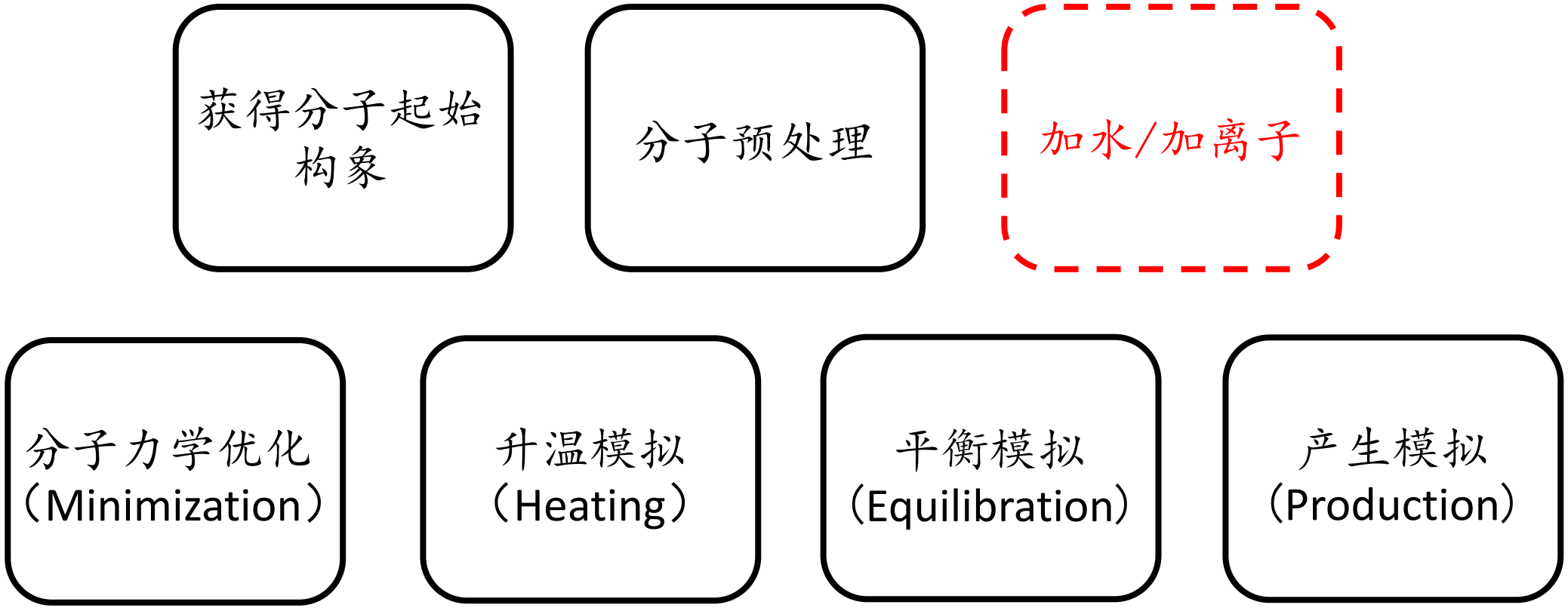


（4）具体分子模拟模块

（5）任务执行监测



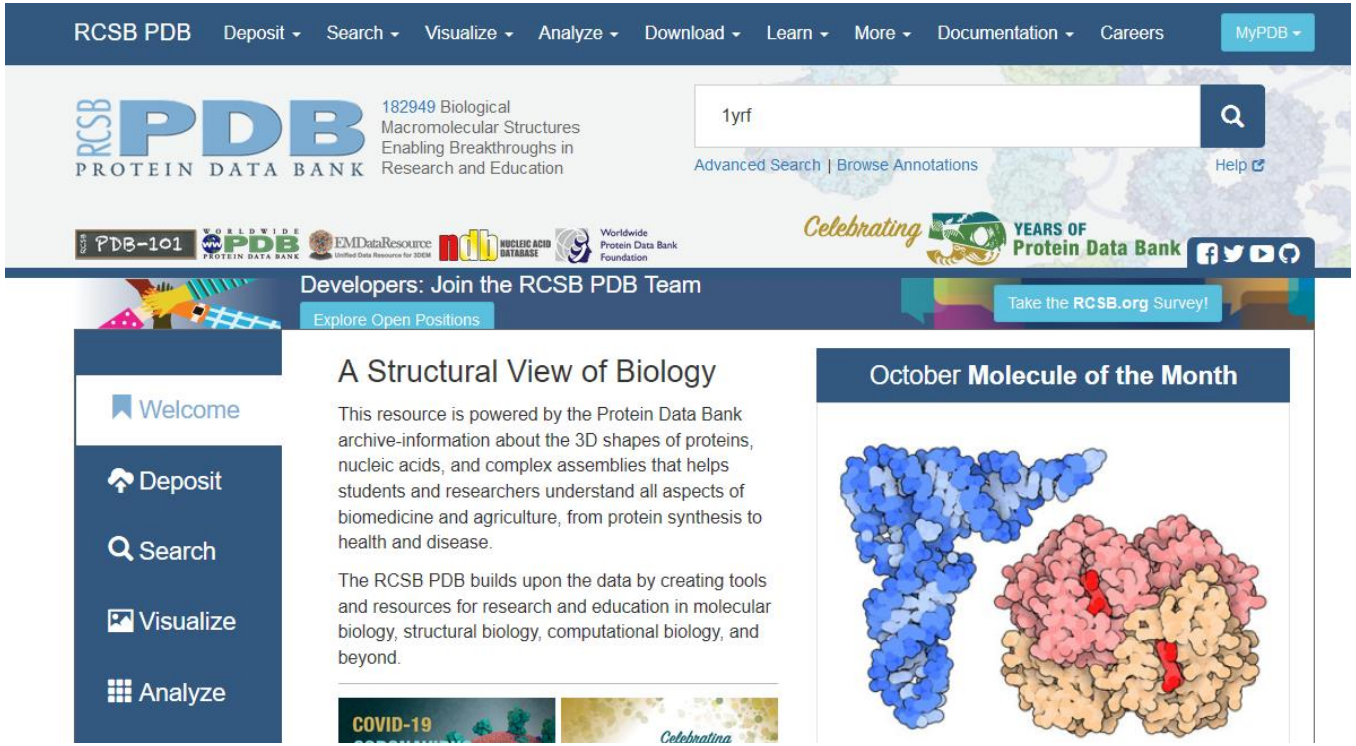
分子力学优化与动力学的一般操作流程

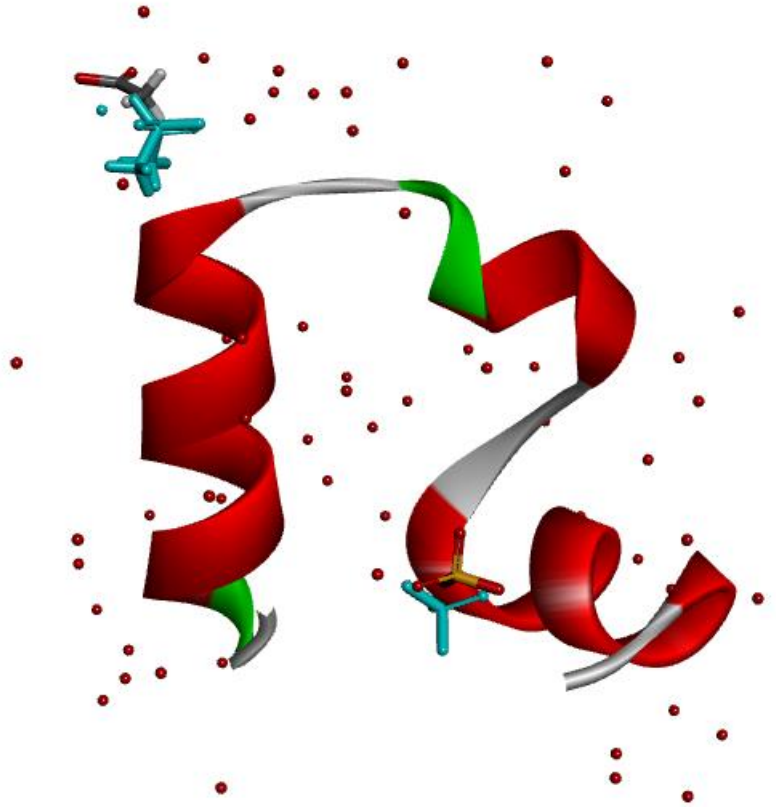


（1）分子初始构象获取

PDB数据库获取蛋白晶体结构

（https://www.rcsb.org/）





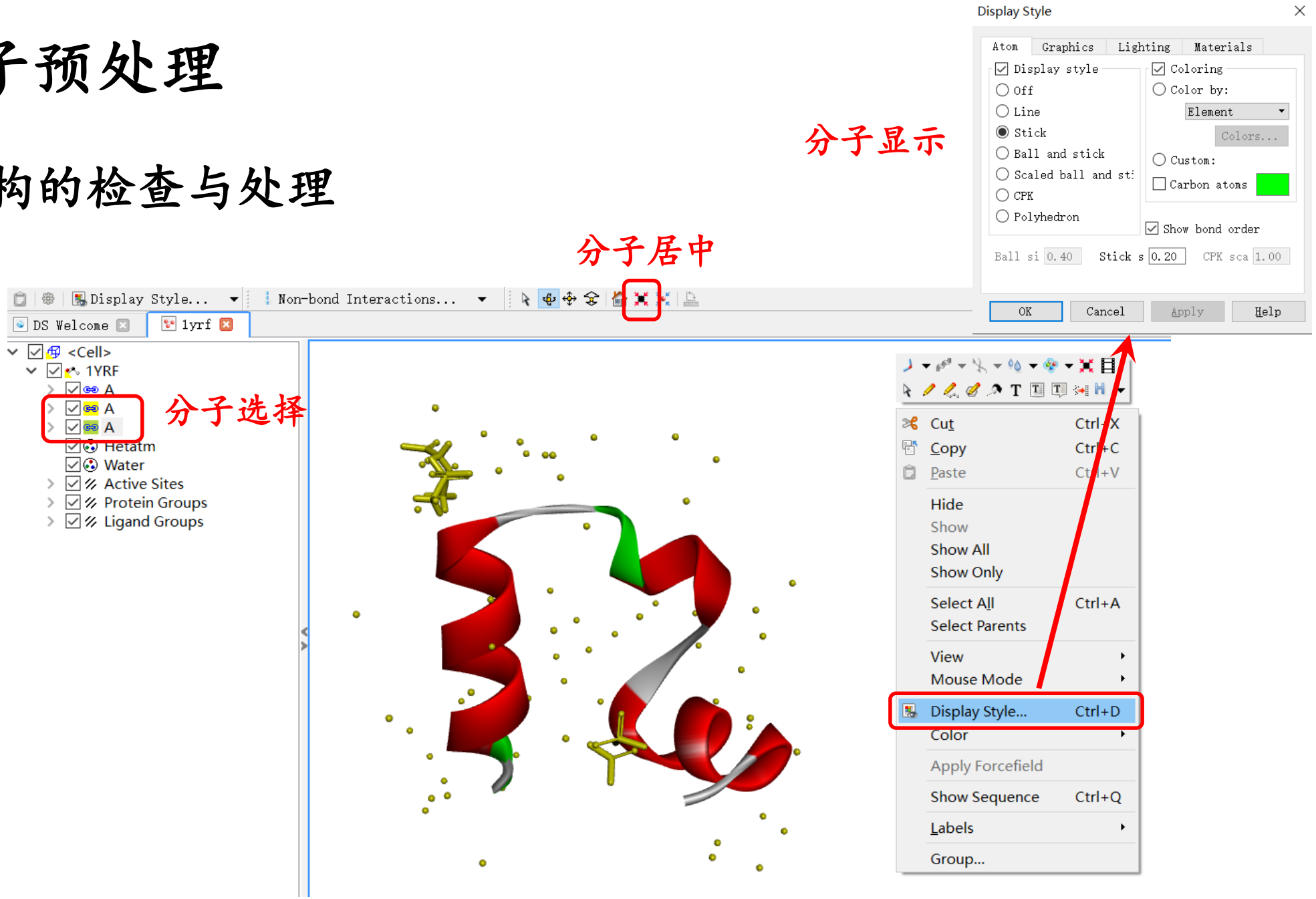
HP53 (PDB code: 1yrf)

（2）分子预处理

1. 初始结构的检查与处理

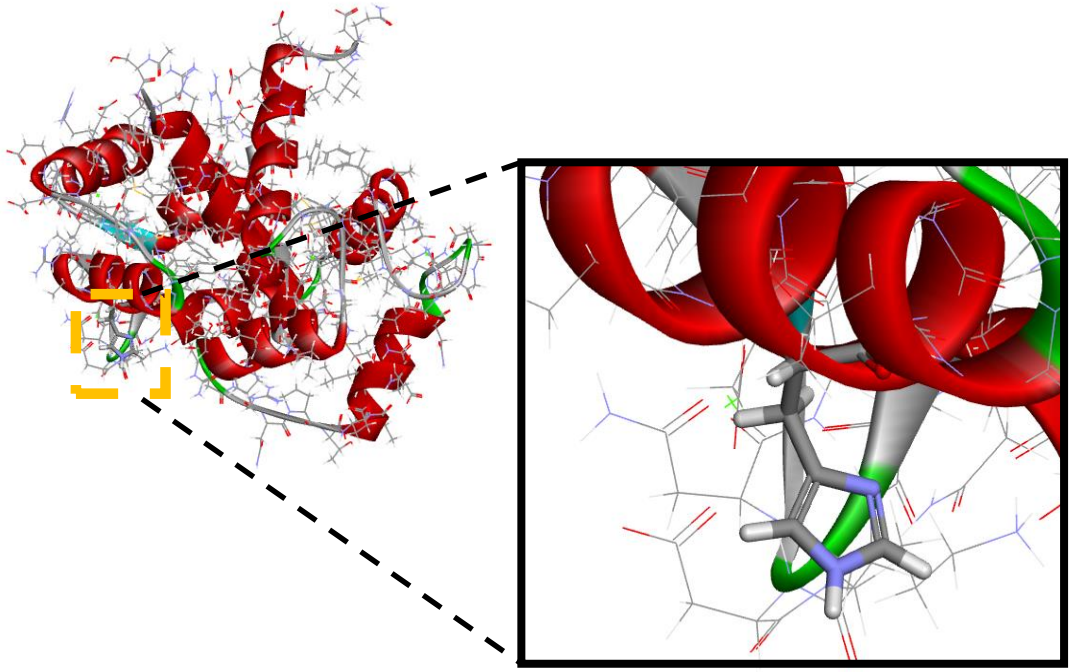
分子的

- 选择
- 居中
- 旋转
- 删除
- 显示



2. 分子的精细化处理

- 蛋白结构检测（主、侧链修复等）
- 质子化状态确定



Macromolecules

the protein structure.

Clean Protein

Prepare Protein

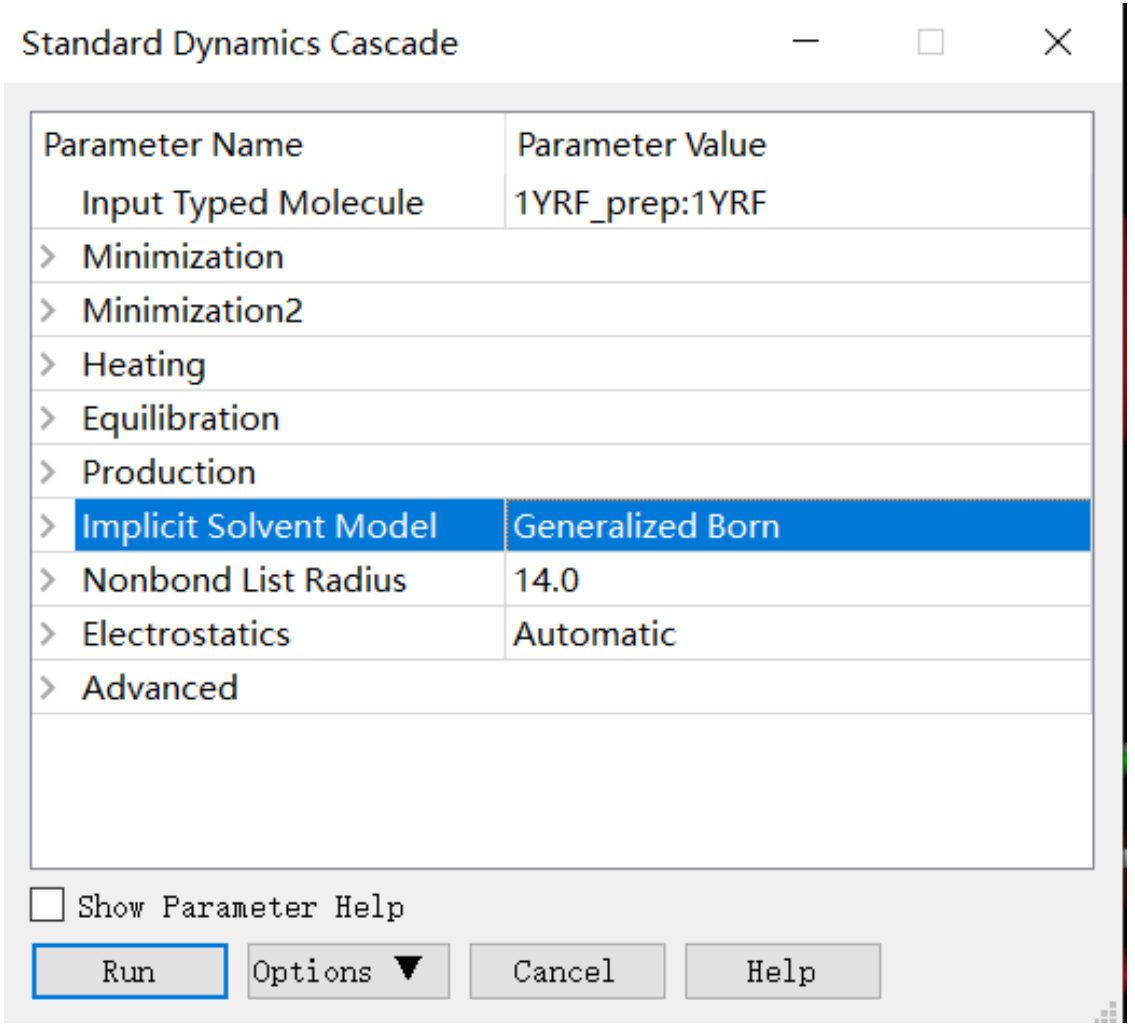
Parameter Name	Parameter Value
Input Protein	3gp2_deal:3gp2_deal
⊟ Build Loops	True
⊞ Loop Definition	SEQRES
Maximal Loop Length	20
⊞ Use Looper	False
Use CHARMm Minimi...	True
Flexible Stem Residues	0
⊟ Protonate	True
Protein Dielectric Con...	10
pH for Protonation	7.4
Ionic Strength	0.145
Energy Cutoff	0.9
⊟ Advanced	
Forcefield	CHARMm
Keep Ligands	True
Keep Water	None
Disulfide Bridges	

☐ Show Parameter Help

Run | Options ▼ | Cancel | Help

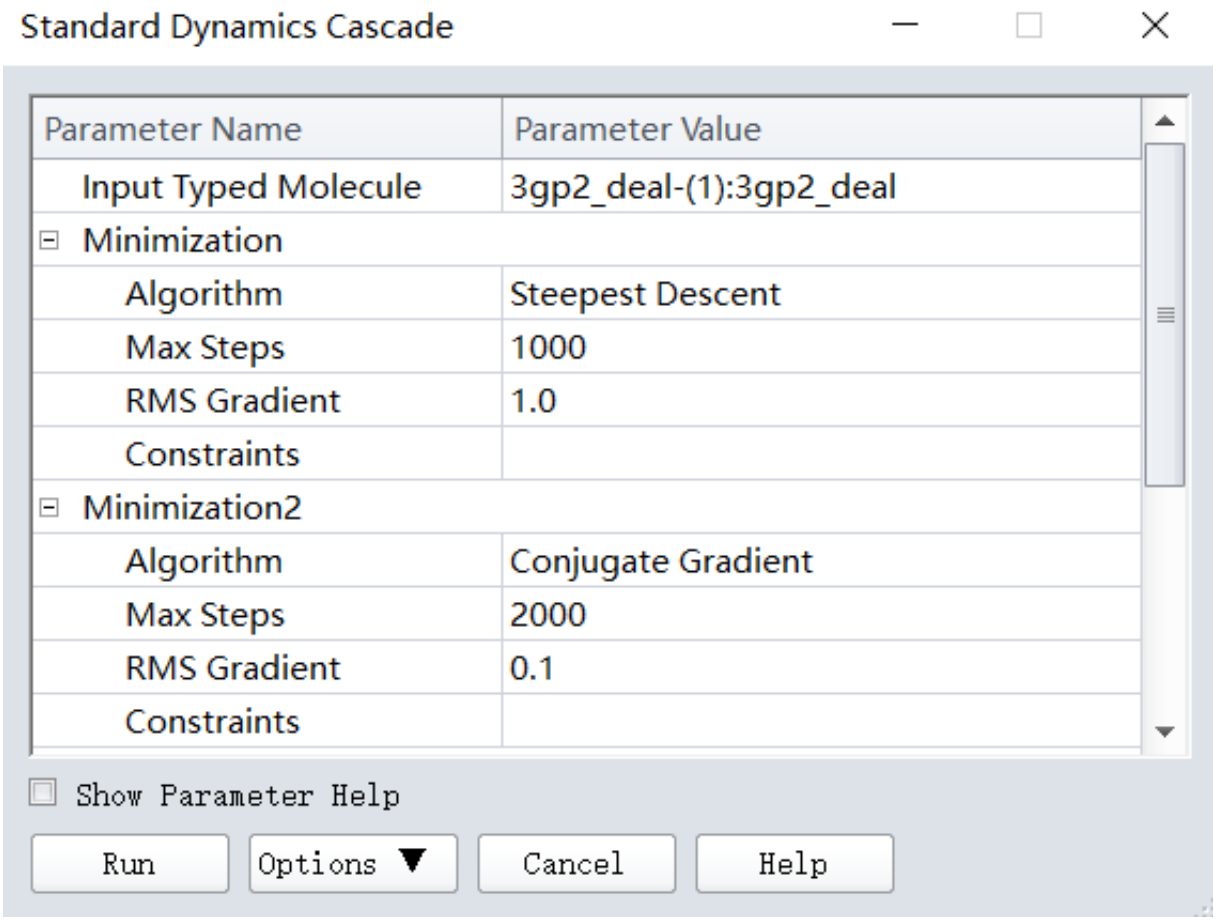
Standard MD Cascade

- 分子力学优化（Minimization and Minimization2）
- 升温期模拟（Heating）
- 平衡期模拟（Equilibration）
- 产生期模拟（Production）



（3）体系能量优化（ Minimization ）

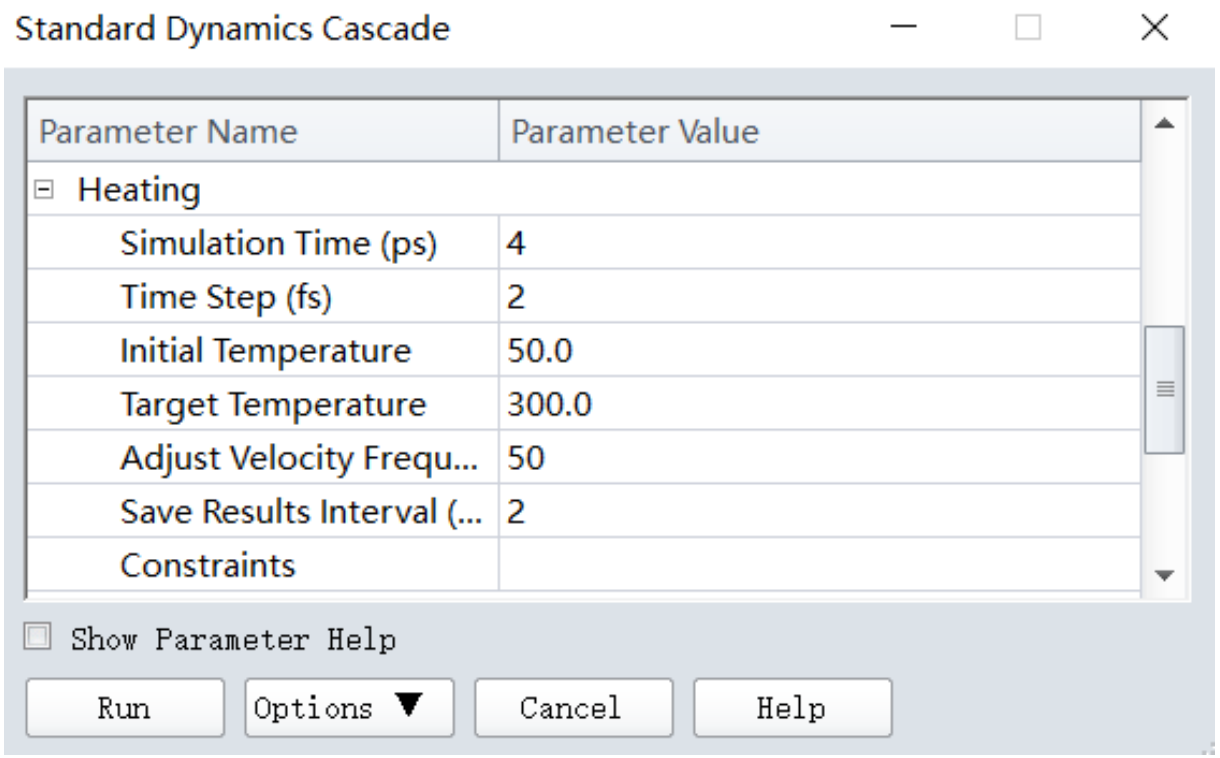
- 结构优化的目的在于优化分子中因实验（低精度结构）或模建（加氢或蛋白修复等）产生的结构触碰
- 最陡下降法与共轭梯度法联合优化分子结构，以获得稳定初始状态



（4）升温模拟（Heating）

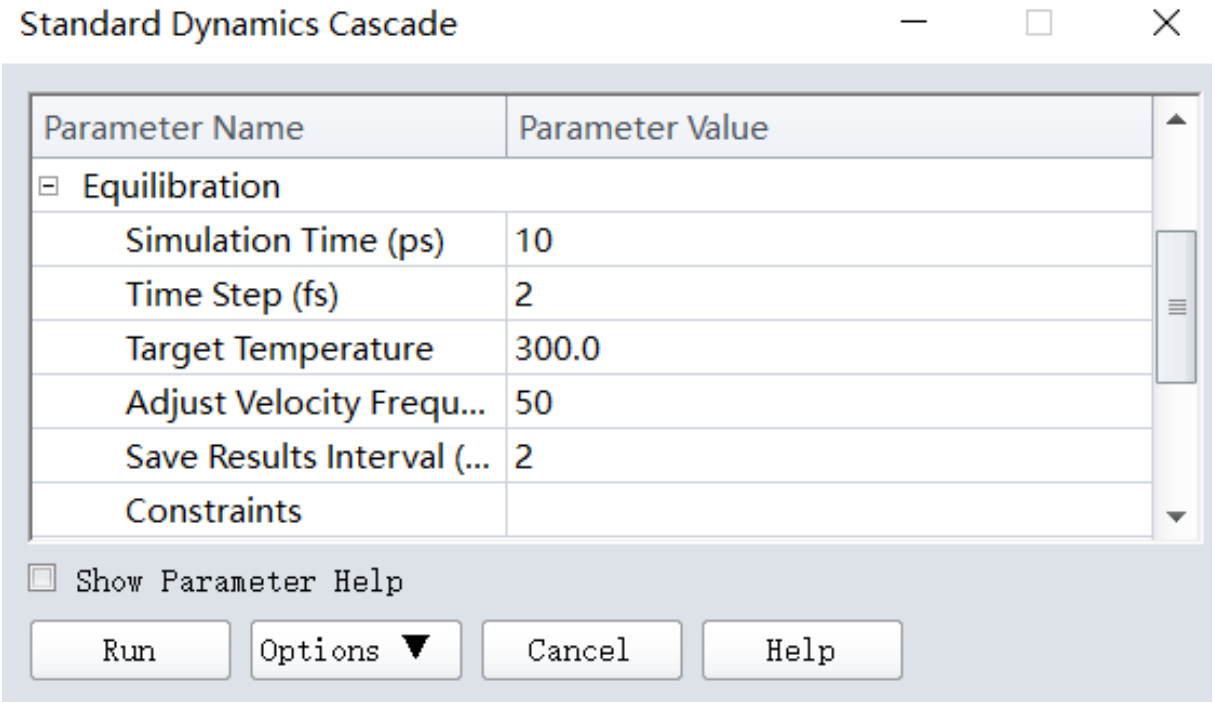
- 通过Maxwell-Boltzmann分布随机生成初速度

- 升温过程需逐步缓慢进行，以防止体系不稳定



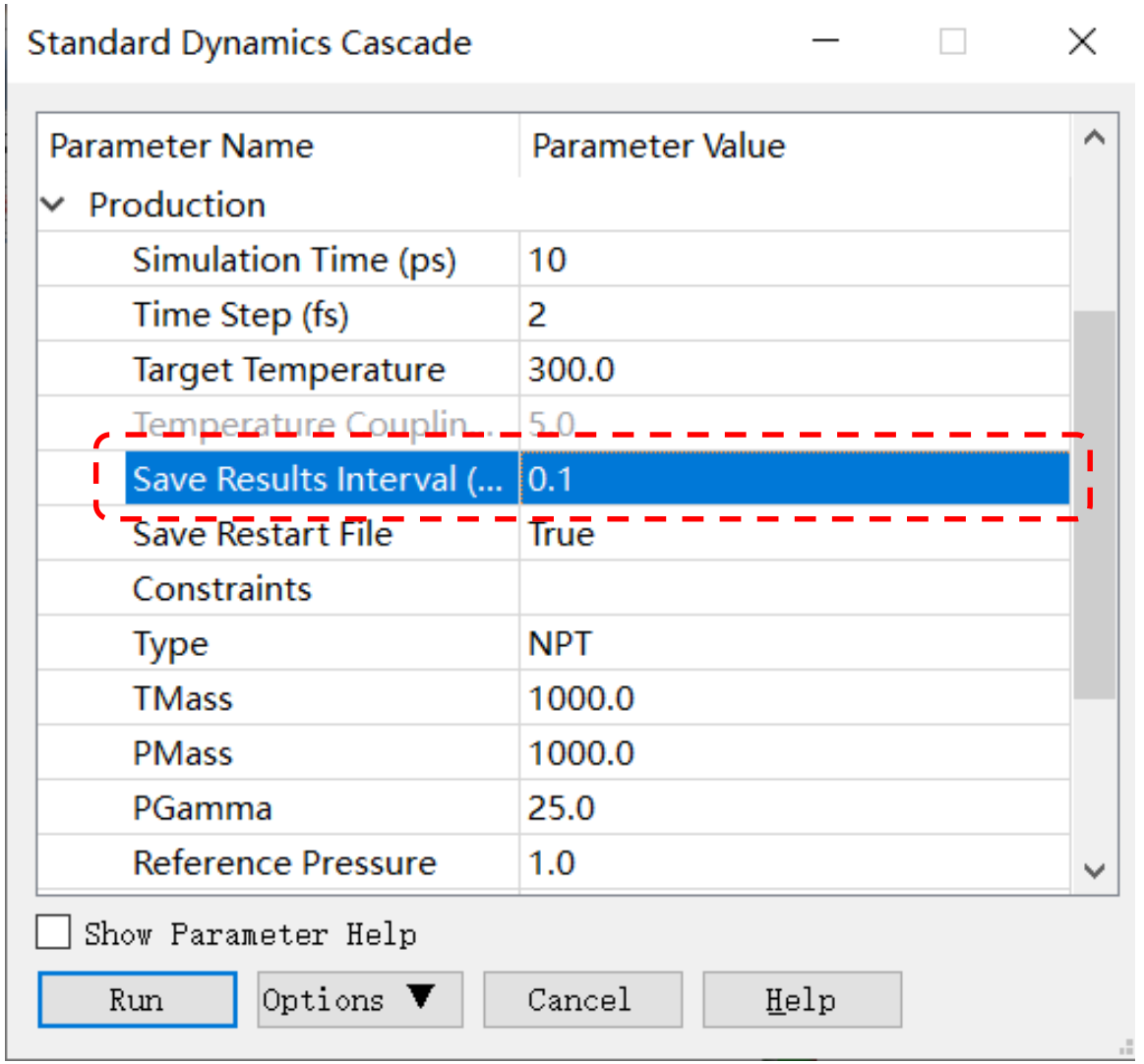
（5）平衡模拟（Equilibration）

- 平衡期模拟的主要作用在于避免加热过程中产生的局部或全局不稳定构象
- 一般而言，经过平衡期后，体系趋于稳定，可以开始后续的采样及分析



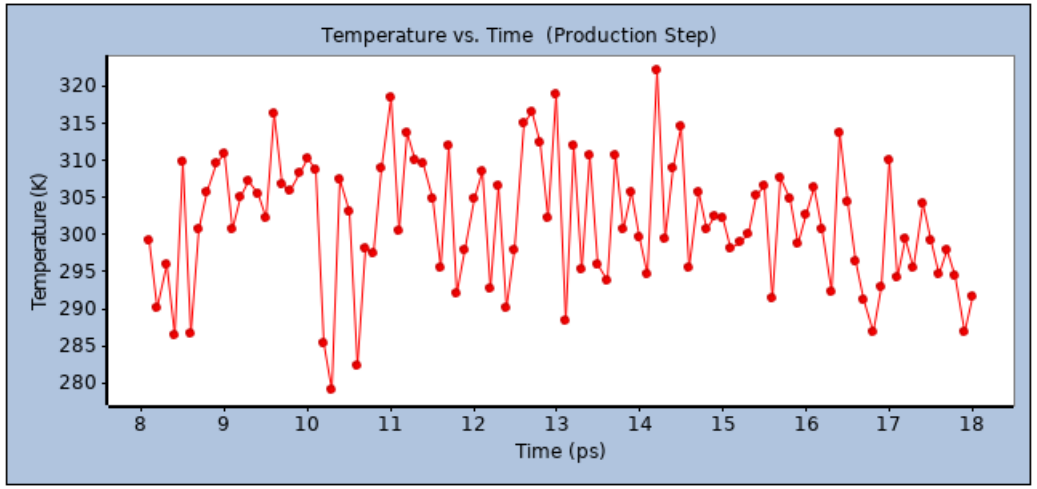
（6）产生模拟（Production）

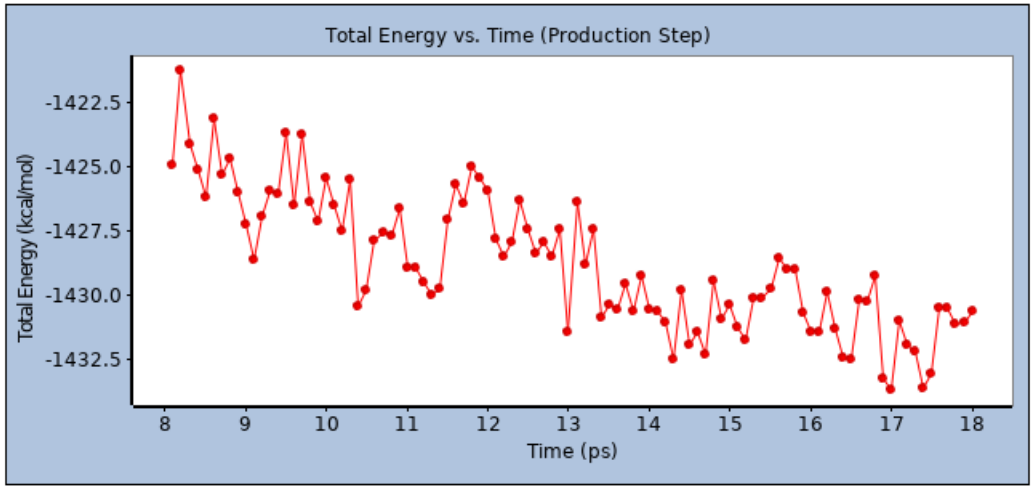
- 产生模拟又称为采样模拟，是一个MD模拟有效数据的来源，也是MD模拟整个过程中耗时最长阶段



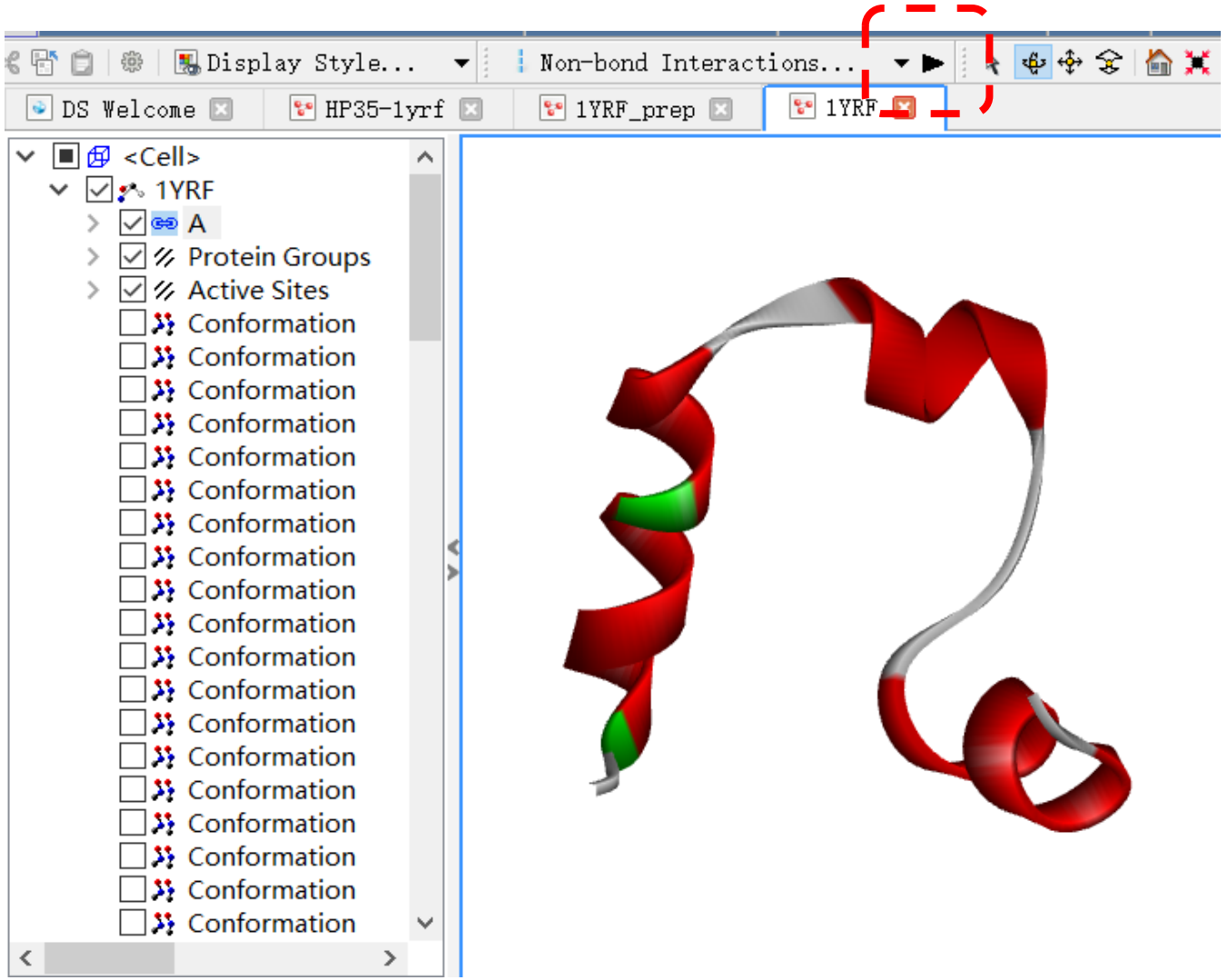
结果分析—DS自动生成结果

Name	Stage	Forcefield	Start Time (ps)	End Time (ps)	Initial Potential Energy (kcal/mol)	Total Energy (kcal/mol)	Potential Energy (kcal/mol)	Kinetic Energy (kcal/mol)	Temperature (K)	Van der Waals Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	Initial RMS Gradient (kcal/(mol x A))	Final RMS Gradient (kcal/(mol x A))
1YRF	Minimization	CHARMm			-2112.216		-2221.783			-245.241	-1342.316	10.857	0.906
1YRF	Minimization2	CHARMm			-2221.783		-2287.575			-260.837	-1168.394	0.906	0.093
1YRF	Heating	CHARMm	0.000	4.000	-2287.575	-1453.956	-1880.728	426.772	296.837	-209.999	-1123.988	1.579	18.385
1YRF	Equilibration	CHARMm	4.000	8.000	-1880.728	-1422.640	-1849.158	426.518	296.660	-202.850	-967.363	18.385	18.563
1YRF	Production	CHARMm	8.000	18.000	-1849.158	-1430.614	-1849.775	419.161	291.543	-176.022	-1071.813	18.563	19.374

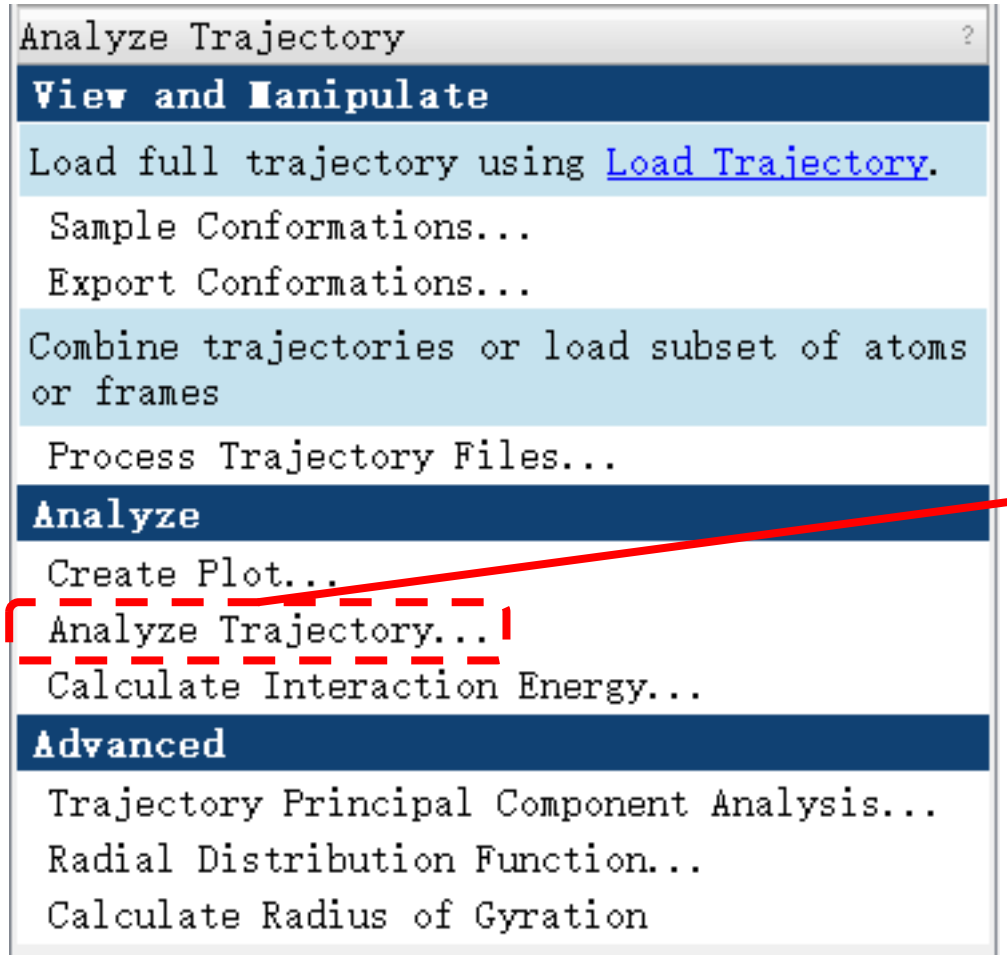


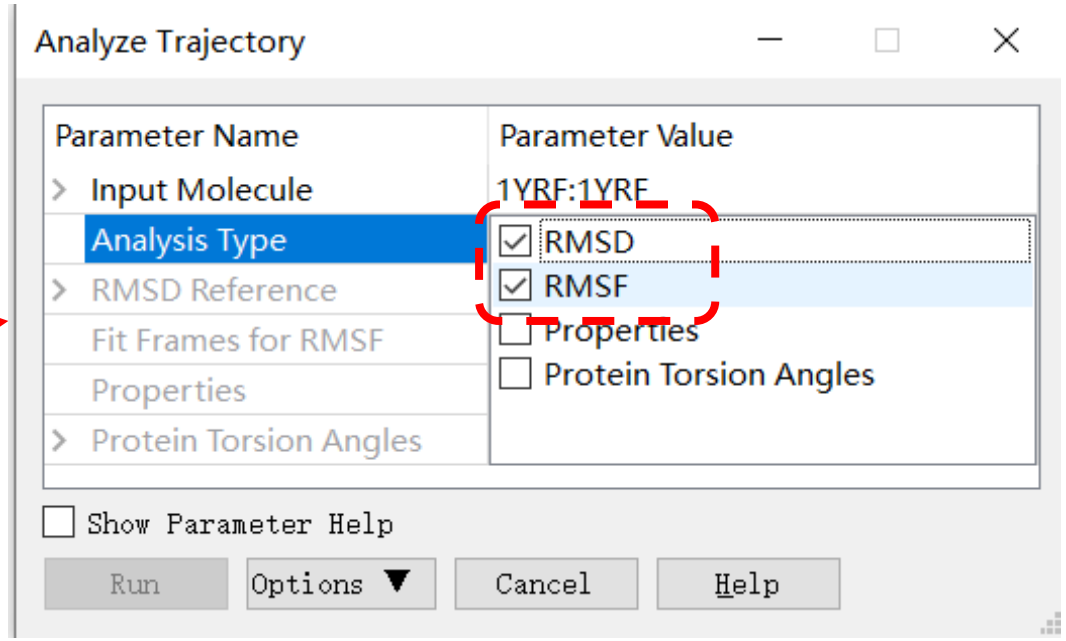


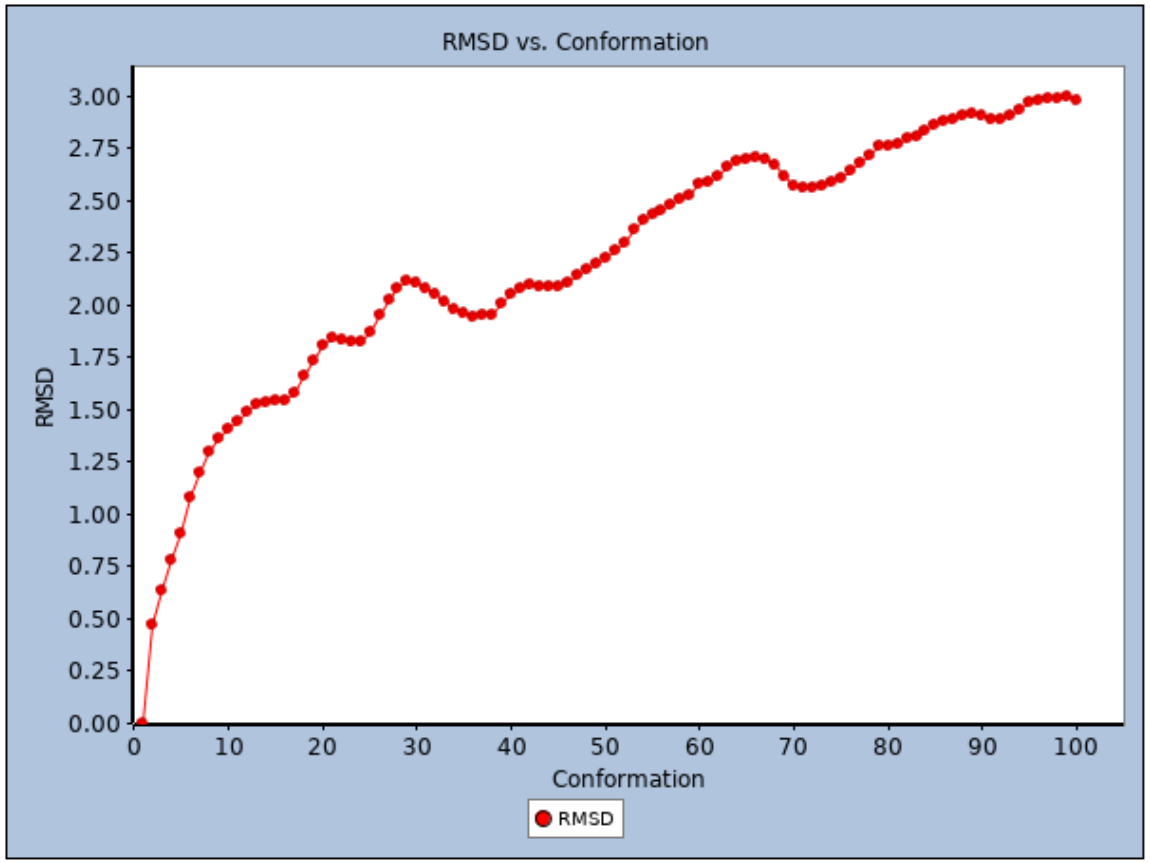
结果分析—动力学轨迹观察

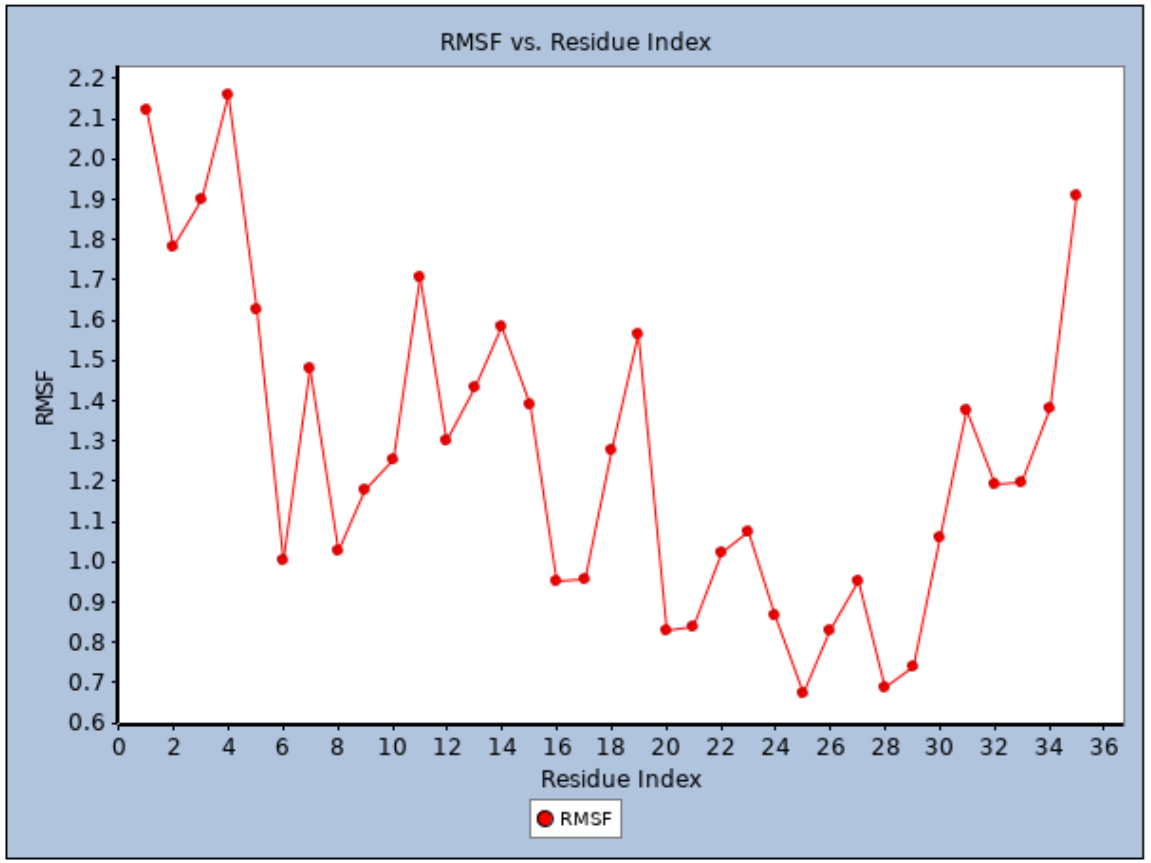


结果分析—RMSD、RMSF计算






RMSD vs. Conformation
RMSD
Conformation
RMSD
0.00
0.25
0.50
0.75
1.00
1.25
1.50
1.75
2.00
2.25
2.50
2.75
3.00
0
10
20
30
40
50
60
70
80
90
100


RMSF vs. Residue Index
RMSF
Residue Index
RMSF
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
1.9
2.0
2.1
2.2
0
2
4
6
8
10
12
14
16
18
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26
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34
36

任务：

（1）熟悉DS的基本操作

（2）从PDB数据库获取感兴趣蛋白结构，如HP35（PDB：1YRF）

（3）目标体系预处理（蛋白预处理）

（4）目标体系动力学模拟

（体系结构优化、升温模拟、平衡模拟、采样模拟）

（5）结果分析（体系能量变化、RMSD、RMSF等）

实验报告：

（1）实验目的

分子动力学模拟，观测体系构象变化

（2）操作流程

蛋白下载、蛋白预处理、标准MD流程模拟（优化、升温、平衡、采样）

（3）结果与讨论

观测体系能量、RMSD、RMSF变化情况，并展示模拟结果