# Gromacs蛋白模拟的力场简介

惠成功

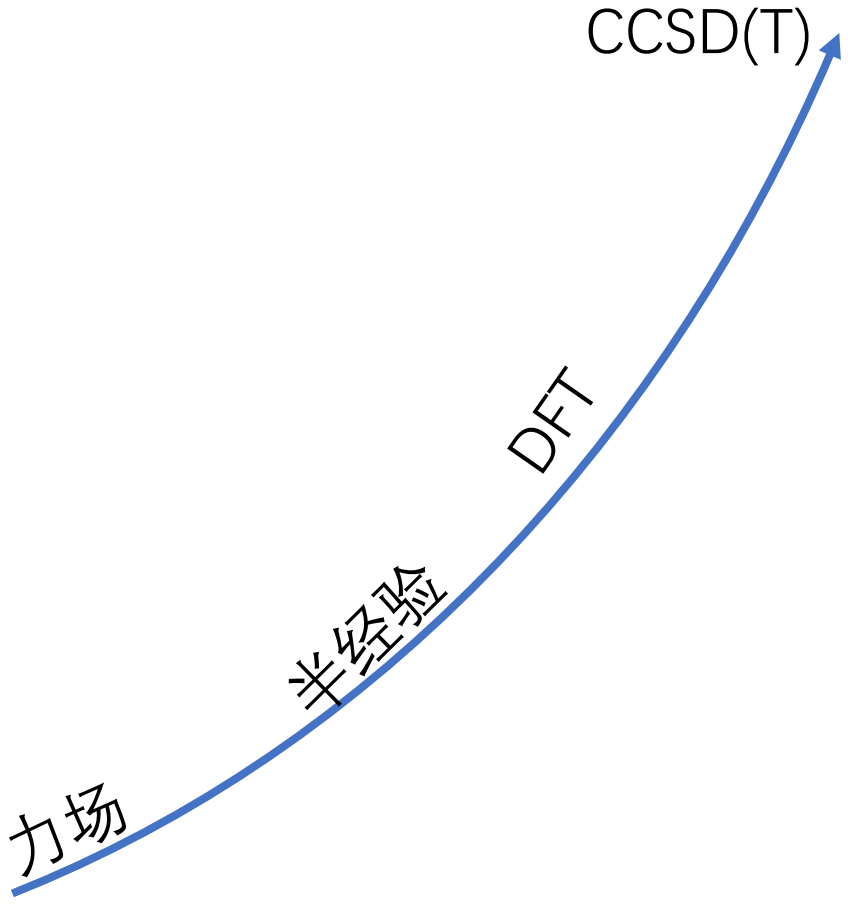
Computational Biomolecular Dynamics

Max Planck Institute for Multidisciplinary Sciences

Bilibili
Chenggong_CC

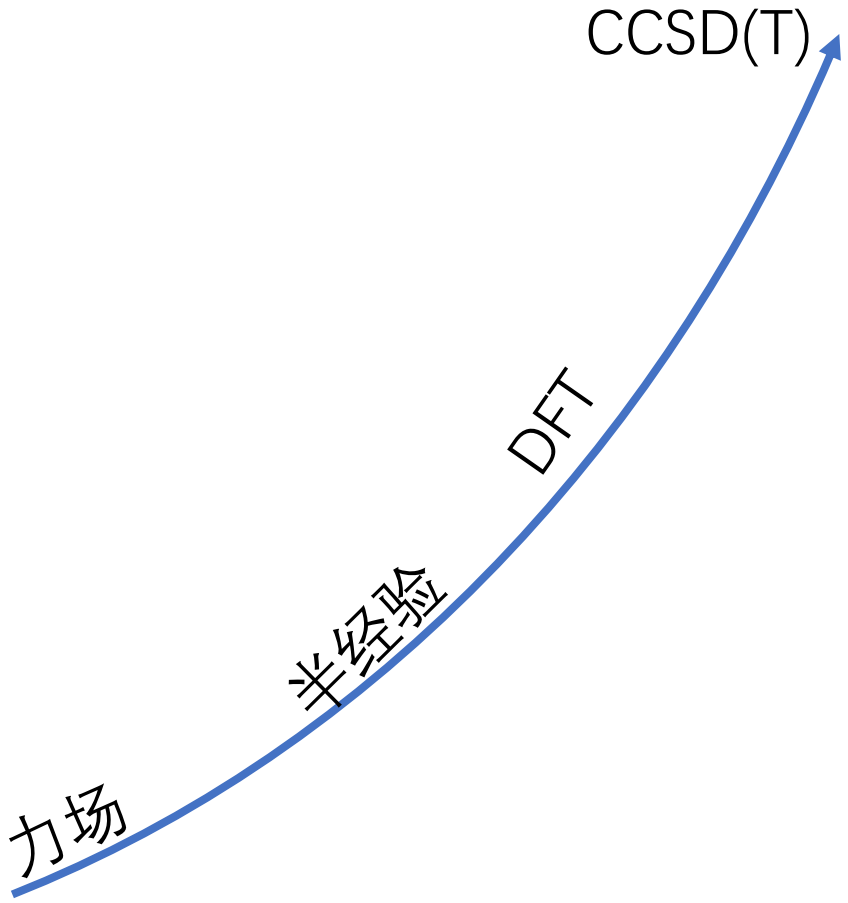
# 力场究竟有多准确?

- A 1kcal/mol
- B 10kcal/mol
- C 100kcal/mol



# 力场在XXX问题上究竟有多准确?

- A 1kcal/mol
- B 10kcal/mol
- C 100kcal/mol



# 力场在“**计算蛋白配体结合自由能**”时？

1. Wang, L.; Wu, Y.; Deng, Y.; Kim, B.; Pierce, L.; Krilov, G.; Lupyan, D.; Robinson, S.; Dahlgren, M. K.; Greenwood, J.; Romero, D. L.; Masse, C.; Knight, J. L.; Steinbrecher, T.; Beuming, T.; Damm, W.; Harder, E.; Sherman, W.; Brewer, M.; Wester, R.; Murcko, M.; Frye, L.; Farid, R.; Lin, T.; Mobley, D. L.; Jorgensen, W. L.; Berne, B. J.; Friesner, R. A.; Abel, R., Accurate and Reliable Prediction of Relative Ligand Binding Potency in Prospective Drug Discovery by Way of a Modern Free-Energy Calculation Protocol and Force Field. *J. Am. Chem. Soc.* **2015,** *137* (7), 2695-2703.

**2015 Schrodinger FEP+ AUE=0.73 kcal/mol**

2. Gapsys, V.; Pérez-Benito, L.; Aldeghi, M.; Seeliger, D.; van Vlijmen, H.; Tresadern, G.; de Groot, B. L., Large scale relative protein ligand binding affinities using non-equilibrium alchemy. *Chem. Sci.* **2020,** *11* (4), 1140-1152.

**2020 Open source software (gromacs, pmx, Amber/GAFF, Charmm/cgenff) AUE=0.87 kcal/mol**

3. Grimme, S., Supramolecular Binding Thermodynamics by Dispersion-Corrected Density Functional Theory. *Chemistry – A European Journal* **2012,** *18* (32), 9955-9964.

**2012 Sampl4 challenge, DFT+D3 AUE ~ 2kcal/mol**

4. Goerigk, L.; Hansen, A.; Bauer, C.; Ehrlich, S.; Najibi, A.; Grimme, S., A look at the density functional theory zoo with the advanced GMTKN55 database for general main group thermochemistry, kinetics and noncovalent interactions. *Phys. Chem. Chem. Phys.* **2017,** *19* (48), 32184-32215.

**2017 CCSD(T) 1kcal/mol, DFT ~5kcal/mol**

# 提要

- 一些关于力场的基础知识，是什么？
- 蛋白力场进化的过程，从哪里来？
- 一些在Gromacs里的操作经验，怎么用？
- 一些general的建议，怎么选？

# 一些基础知识

- 力场包含2部分
  - 势函数
  - 势函数的参数

- 蛋白尺度上的有趣的问题

往往既需要精确的能量，也需要充分的采样

- 精度/速度

# 一些基础知识——势函数

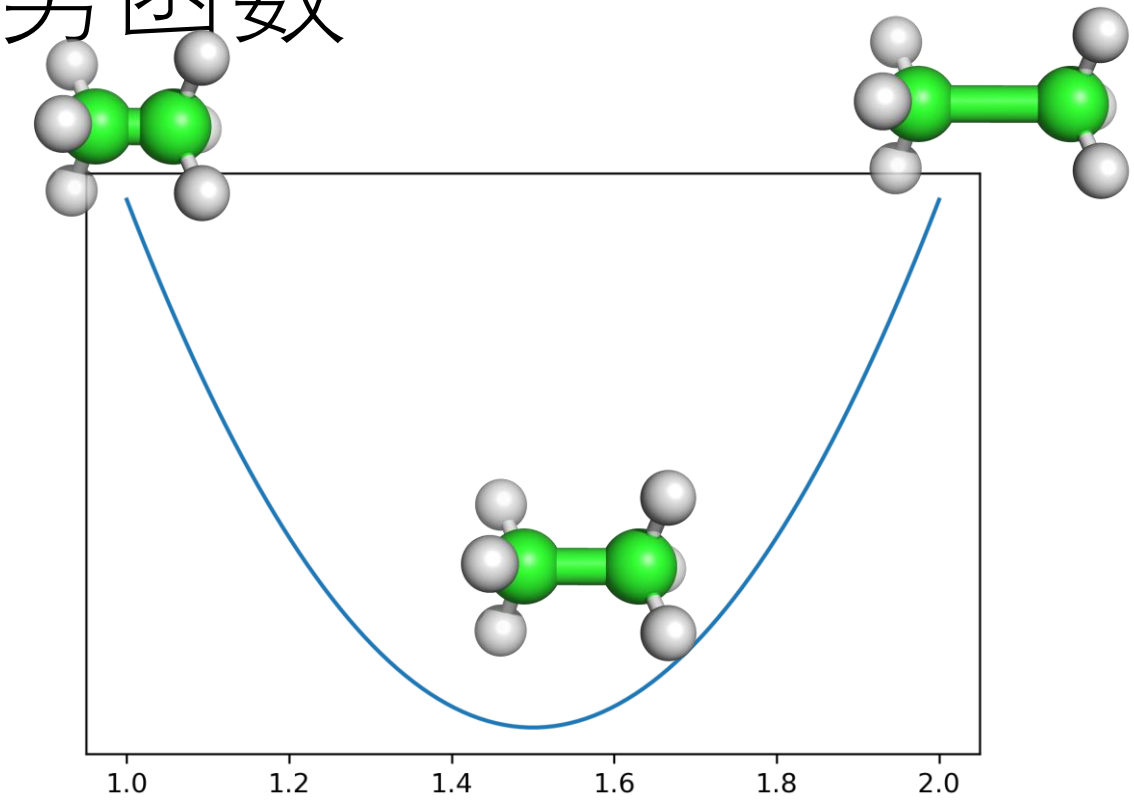
**Bond**

Angle

Dihedral

Vdw

Coulomb




$E=1/2\ k\ (x-x_0)^2$

# 一些基础知识——势函数

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**Angle**

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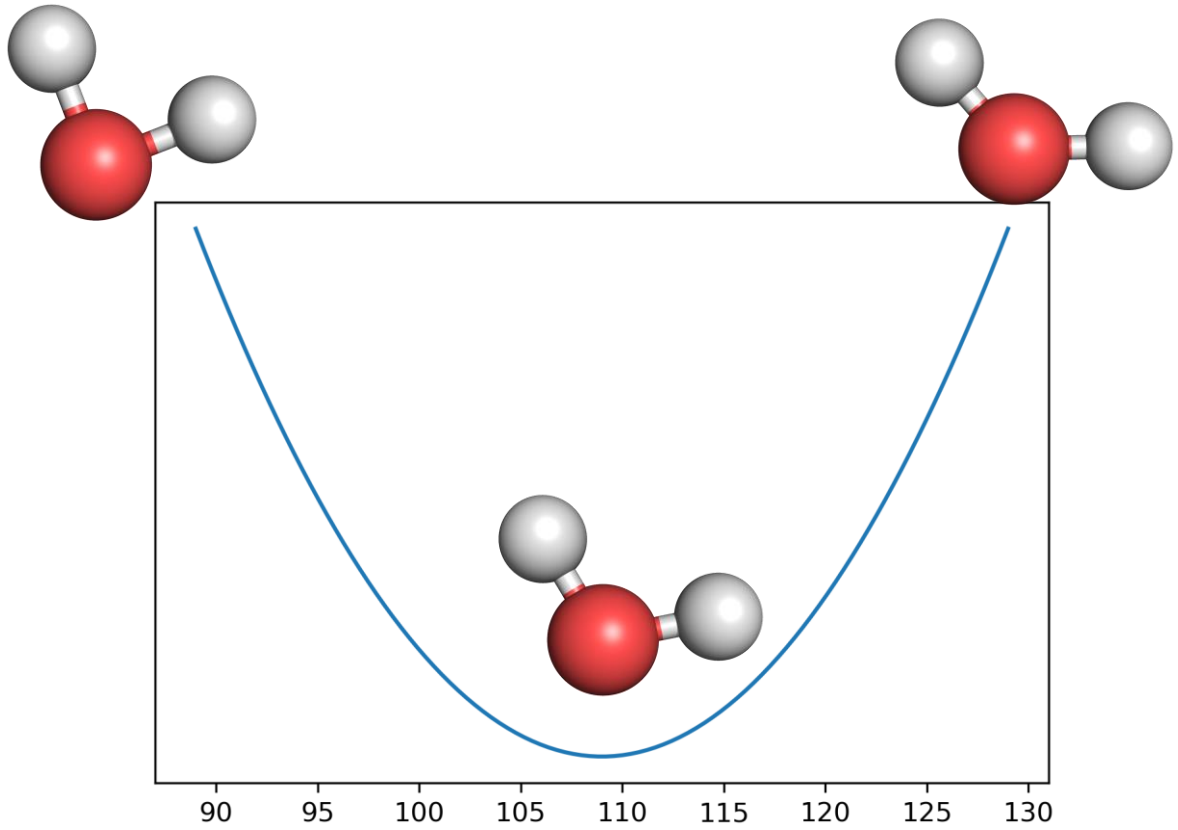
Vdw

Coulomb




$E=1/2\ k(\theta-\theta_0)^2$

# 一些基础知识——势函数

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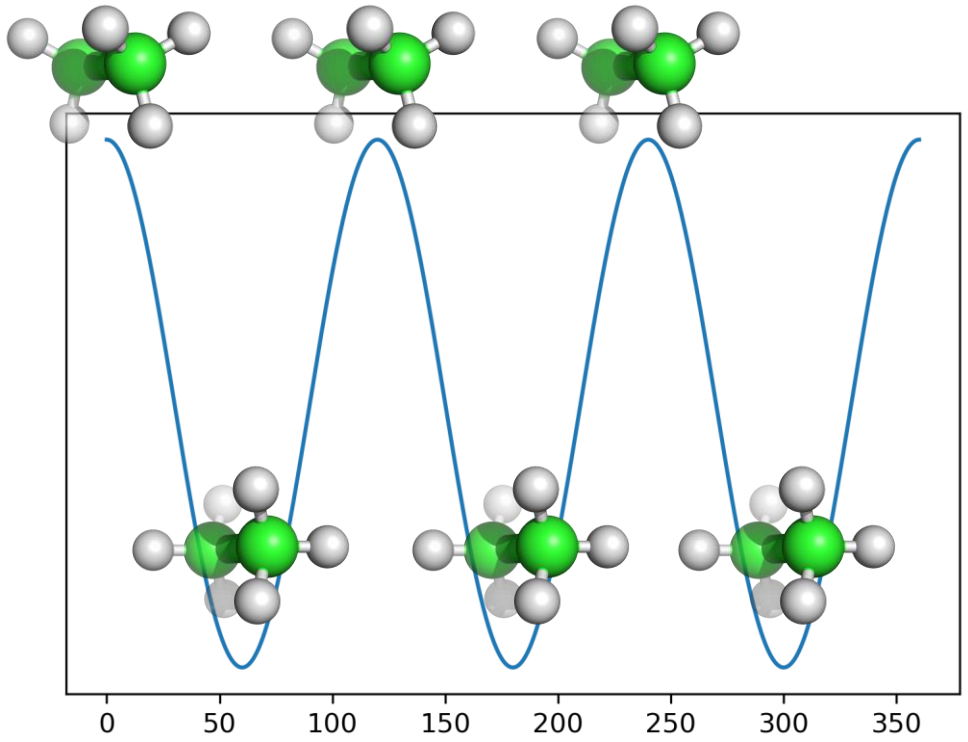
Angle

**Dihedral**

Vdw

Coulomb



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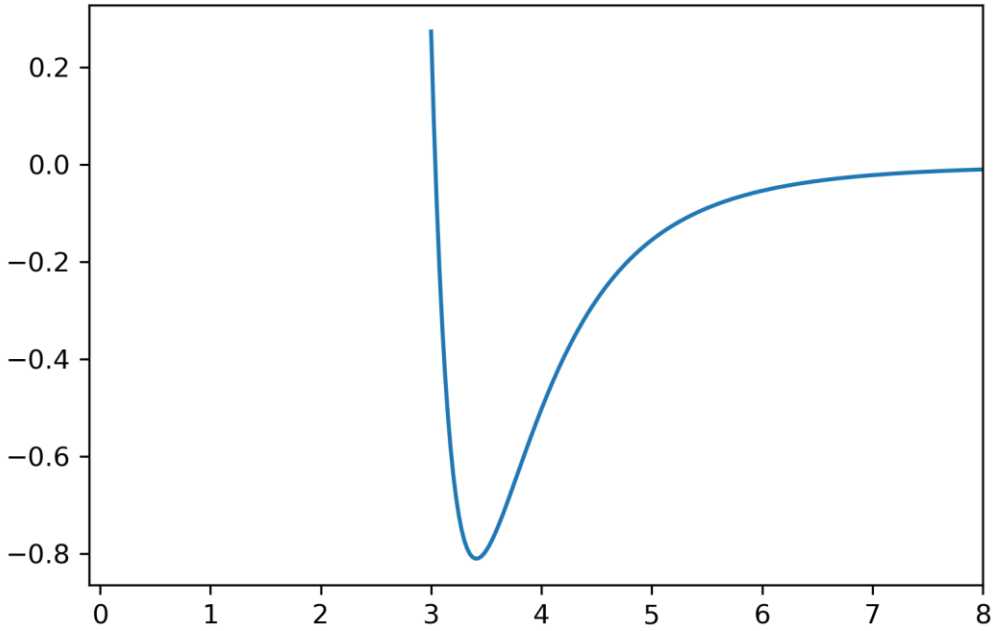



$$V_{\mathrm{LJ}}(r) = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right]$$

# 一些基础知识——势函数

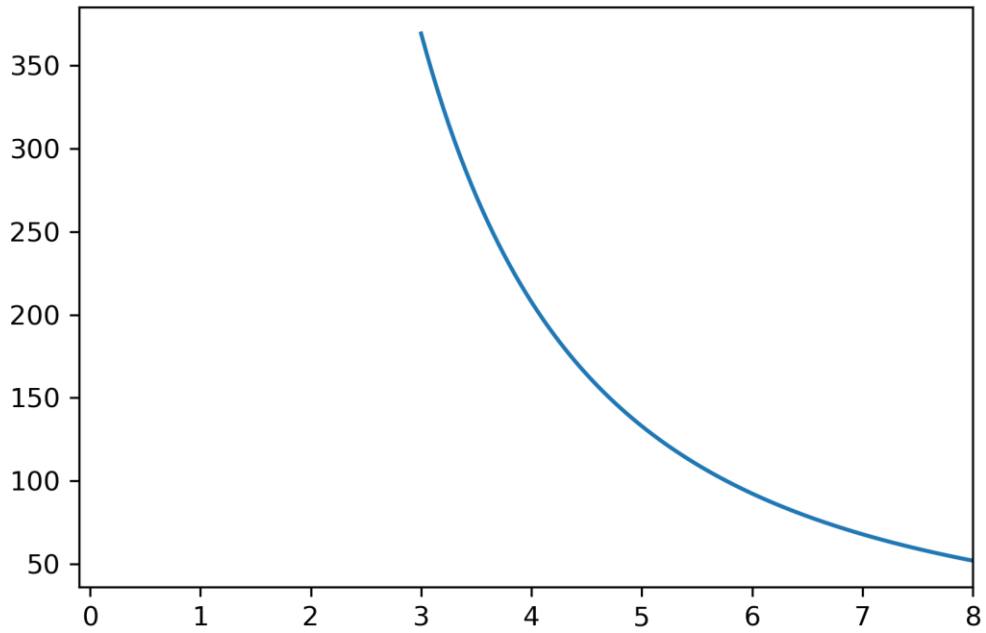
Bond

Angle

Dihedral

Vdw

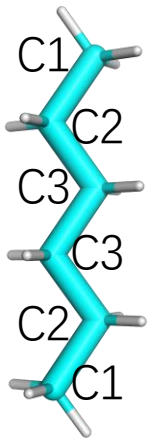
**Coulomb**



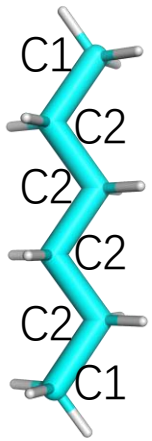

$E = k\, q_1 q_2 / r^2$

# 一些基础知识——原子类型

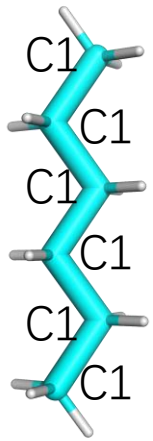
- 参数化与普适性




Bond
C1-C2
C2-C3
C3-C3
Angle
C1-C2-C3
C2-C3-C3
Dihedral
C1-C2-C3-C3
C2-C3-C3-C2
Vdw
3




Bond
C1-C2
C2-C2
Angle
C1-C2-C2
C2-C2-C2
Dihedral
C1-C2-C2-C2
C2-C2-C2-C2
Vdw
2




Bond
C1-C1
Angle
C1-C1-C1
Dihedral
C1-C1-C1-C1
Vdw
1

更多参数
更低普适

更少参数
更高普适

# 蛋白模拟力场

- Amber
- Charmm
- OPLS-AA
- ~~GROMOS~~

- 力场与软件（除了OPLS）
- 都经历过联合原子力场到全原子的发展过程
- 开始与~1970-1980年

# 蛋白模拟力场——已经参数化了吗？

- 蛋白
- 磷脂膜
- 糖蛋白（有没有？）
- 糖磷脂（有没有？）
- DNA-RNA?
- 小分子
- 水
- $K^+$，$Cl^-$, $Na^+$,…

# Amber ff99SB (2006), ff14SB ff (2015), 19SB (2019)

ff14SB

Maier, J. A.; Martinez, C.; Kasavajhala, K.; Wickstrom, L.; Hauser, K. E.; Simmerling, C., ff14SB: Improving the Accuracy of Protein Side Chain and Backbone Parameters from ff99SB. *J Chem Theory Comput* **2015,** *11* (8), 3696-3713.

重新拟合主链/侧链的二面角参数

HF/6-31G* MP2/6-31+G** （不要模仿）

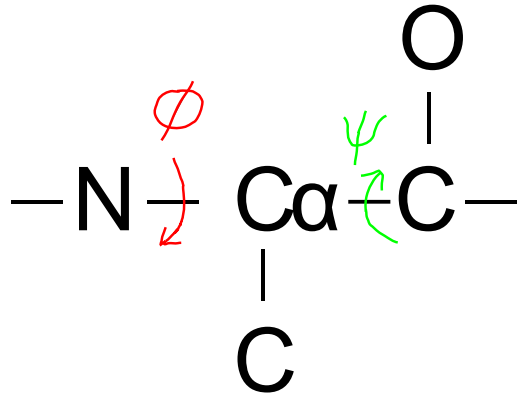
# Amber ff99SB (2006), ff14SB ff (2015), 19SB (2019)

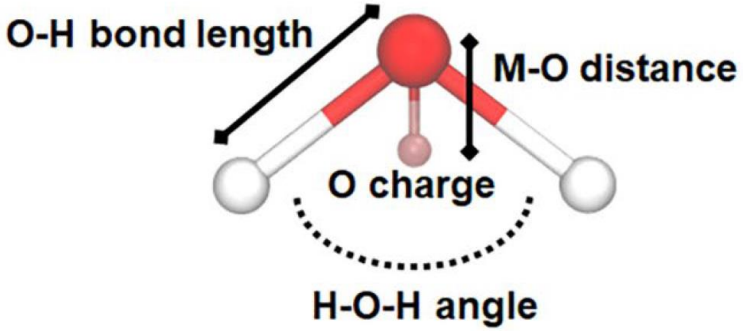
## ff19SB

Tian, C.; Kasavajhala, K.; Belfon, K. A. A.; Raguette, L.; Huang, H.; Migues, A. N.; Bickel, J.; Wang, Y.; Pincay, J.; Wu, Q.; Simmerling, C., ff19SB: Amino-Acid-Specific Protein Backbone Parameters Trained against Quantum Mechanics Energy Surfaces in Solution. *J Chem Theory Comput* **2020,** *16* (1), 528-552.

CMAP （$\varphi$ $\psi$）

OPC water （4 point water）



# Charmm 22 27 36 36m

- Charmm27 （CMAP）

Mackerell Jr., A. D., Empirical force fields for biological macromolecules: Overview and issues. *J. Comput. Chem.* **2004,** *25* (13), 1584-1604.

- Charmm36 （再次拟合二面角）

Best, R. B.; Zhu, X.; Shim, J.; Lopes, P. E. M.; Mittal, J.; Feig, M.; MacKerell, A. D., Optimization of the Additive CHARMM All-Atom Protein Force Field Targeting Improved Sampling of the Backbone Φ, ψ and Side-Chain χ1 and χ2 Dihedral Angles. *J Chem Theory Comput* **2012,** *8* (9), 3257-3273.

- Charmm36m （改进IDP）

Huang, J.; Rauscher, S.; Nawrocki, G.; Ran, T.; Feig, M.; de Groot, B. L.; Grubmüller, H.; MacKerell, A. D., CHARMM36m: an improved force field for folded and intrinsically disordered proteins. *Nature Methods* **2017,** *14* (1), 71-73.

* Charmm TIP3P

# 在gromacs中使用最新的力场?

gmx pdb2gmx -f C6.pdb

Select the Force Field:

From '/home/cheng/Software/GMX/2021.5-CPU/share/gromacs/top':

1: AMBER03 protein, nucleic AMBER94 (Duan et al., J. Comp. Chem. 24, 1999-2012, 2003)
2: AMBER94 force field (Cornell et al., JACS 117, 5179-5197, 1995)
3: AMBER96 protein, nucleic AMBER94 (Kollman et al., Acc. Chem. Res. 29, 461-469, 1996)
4: AMBER99 protein, nucleic AMBER94 (Wang et al., J. Comp. Chem. 21, 1049-1074, 2000)
5: AMBER99SB protein, nucleic AMBER94 (Hornak et al., Proteins 65, 712-725, 2006)
6: AMBER99SB-ILDN protein, nucleic AMBER94 (Lindorff-Larsen et al., Proteins 78, 1950-58, 2010)
7: AMBERGS force field (Garcia & Sanbonmatsu, PNAS 99, 2782-2787, 2002)
8: CHARMM27 all-atom force field (CHARMM22 plus CMAP for proteins)
9: GROMOS96 43a1 force field
10: GROMOS96 43a2 force field (improved alkane dihedrals)
11: GROMOS96 45a3 force field (Schuler JCC 2001 22 1205)
12: GROMOS96 53a5 force field (JCC 2004 vol 25 pag 1656)
13: GROMOS96 53a6 force field (JCC 2004 vol 25 pag 1656)
14: GROMOS96 54a7 force field (Eur. Biophys. J. (2011), 40,, 843-856, DOI: 10.1007/s00249-011-0700-9)
15: OPLS-AA/L all-atom force field (2001 aminoacid dihedrals)

Outdated

# 在gromacs中使用最新的力场?

- Charmm36m
  - http://mackerell.umaryland.edu/charmm_ff.shtml (charmm36-jul2021)
- Amber14SB
  - Community support https://www.gromacs.org/Downloads/User_contributions/Force_fields
- Slipid
  - http://www.fos.su.se/~sasha/SLipids/Downloads.html

# 在gromacs中使用最新的力场？其他选择

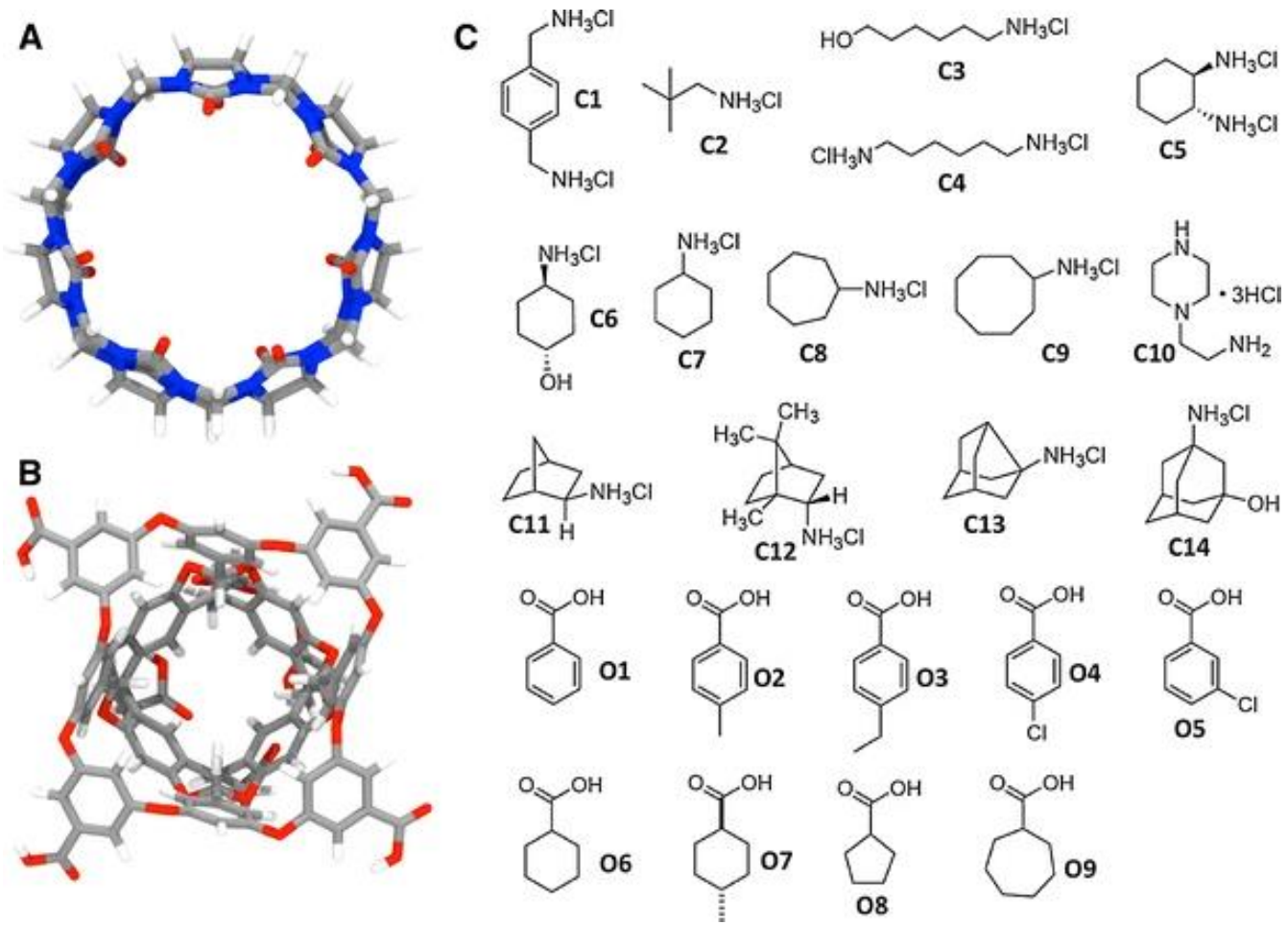
- Charmm-GUI
- Acpype
- parmed

不可信，自行测试

# 一些我没有用过的力场

- OPLS-AA
  - http://zarbi.chem.yale.edu/oplsaam.html
- DES-amber and DES-amberSF1.10
  - Piana et al., 2020, J. Chem. Theory Comput., 4, 2494–2507
- A99SB-disp / TIP4P-D
  - Piana et al., 2015, J. Phys. Chem. B, 119, 5113-5123
- ?
- ?

# 凭什么MD能做到1kcal/mol, QM不行




SAMPL4 challenge

# 一些建议

- 拿来之前考虑力场是如何参数化的
- 不要混合未经检验的参数
  - Amber/GAFF
  - Charmm/CGenFF
  - ion, water
- 使用力场开发时候的mdp参数
- 没有唯一正确的答案
- 实验对比

# Acknowledgement


- Bert de Groot
- Dirk Matthes
- 钰沐菡

# Other ref

1. Kadaoluwa Pathirannahalage, S. P.; Meftahi, N.; Elbourne, A.; Weiss, A. C. G.; McConville, C. F.; Padua, A.; Winkler, D. A.; Costa Gomes, M.; Greaves, T. L.; Le, T. C.; Besford, Q. A.; Christofferson, A. J., Systematic Comparison of the Structural and Dynamic Properties of Commonly Used Water Models for Molecular Dynamics Simulations. *Journal of Chemical Information and Modeling* **2021,** *61* (9), 4521-4536.

**MM water benchmark**