**24.2.2.8 分子力场的发展**

在过去数十年的时间里，分子力场得到不断发展（表x1），被广泛地应用于蛋白质、核酸、有机小分子、糖分子和磷脂的模拟，并被证明能够很好地解释化学和生物体系上的问题1, 2。目前分子力场类型主要可分为固定电荷力场和可极化力场。固定电荷力场由于其不考虑原子周围化学微环境的变化所产生的极化作用等，极大减少了计算量，因此在复杂的生物大分子体系中应用最为广泛。

目前发展较为成熟的四种固定电荷分子力场分别是AMBER(Assisted Model Building and Energy Refinement)、CHARMM(Chemistry at HARvard Macromolecular Mechanics)、GROMOS(GROningen MOlecular Simulation)和OPLS(Optimized Potential for Liquid Simulations)力场。

AMBER力场最初是由美国加州大学的Peter A. Kollman团队发展（1984年）3，应用于蛋白质和核酸体系，之后又相继发展了可应用于磷脂、糖分子和有机小分子体系的力场参数，目前在分子动力学模拟中比较主流的AMBER力场版本分别是ff14SB4，Lipid175，GAFF26和GLYCAM\_06j7。CHARMM力场最初是由美国哈佛大学的Martin Karplus团队发展（1983年）8，可适用于蛋白质、核酸、磷脂、糖和有机小分子得模拟，目前比较主流的CHARMM力场版本是CHARMM369-14和CGenFF15。GROMOS力场最初由荷兰格罗宁大学的van Gunsteren团队发展（1984）16，包含蛋白质、核酸、磷脂、糖和有机小分子的力场参数，目前GROMOS力场的发展由瑞士苏黎世联邦理工等团队共同推进。OPLS力场最初由美国耶鲁大学的William L. Jorgensen团队发展（1988）17，根据对氢原子的不同处理方式，可将OPLS力场分为全原子力场OPLA-AA(OPLS All Atoms)，和联合原子力场OPLS-UA(OPLS Unit Atom)，于上述3类力场不同的是，OPLS力场最初的版本是应用于有机溶剂等液相体系，而后逐渐发展出适用于蛋白质等生物大分子体系的力场参数。

此外，随着计算机硬件的发展，可极化力场也逐渐发展起来，并能够用于模拟复杂的生物大分子体系18。与固定电荷力场相比，可极化力场考虑了原子周围化学微环境的变化对原子上电荷分布的影响，从原理上更准确，但也增加了计算复杂度。华东师范大学的张增辉等开发了线性标度量子化学计算方法MFCC(分子碎片共轭帽子)用于计算蛋白质的特异性极化电荷19。目前比较主流的可极化力场有AMOEBA(Atomic Multiple Optimized Energetics for Biomolecular Applications)20和CHARMM Drude力场21等。

表x1. 近十年固定电荷力场的发展

|  |  |  |  |
| --- | --- | --- | --- |
| **力场类型** | **年份** | **力场版本** | **适用范围** |
| AMBER | 2008 | GLYCAM067 | 糖分子 |
| 2012 | GAFFlipid22 | 磷脂 |
| 2014 | Lipid1423 | 磷脂 |
| 2015 | ff14SB4 | 蛋白质、核酸 |
| 2016 | GAFF26 | 有机小分子 |
| 2018 | Lipid175 | 磷脂 |
| 2020 | ff19SB24 | 蛋白质 |
| 2021 | Lipid2125 | 磷脂 |
| CHARMM | 2010 | C36 Lipids9 | 磷脂 |
| 2011 | C36 RNA10 | RNA |
| 2012 | Carbohydrates26 | 糖分子 |
| 2012 | C36 DNA12 | DNA |
| 2012 | C36 Protein14 | 蛋白质 |
| 2016 | CGenFF15, 27, 28 | 有机小分子 |
| 2017 | C36m Protein13 | 蛋白质 |
| GROMOS | 2011 | 54A729 | 蛋白质、核酸、磷脂 |
| 2011 | ATB1.030 | 有机小分子 |
| 2012 | 54A831 | 蛋白质、核酸、磷脂 |
| 2012 | 53A6GLYC32 | 糖分子 |
| 2014 | ATB2.033 | 有机小分子 |
| 2016 | 56A6CARBO\_R34 | 糖分子 |
| OPLS | 2012 | OPLS235 | 蛋白质、有机小分子 |
| 2015 | OPLS-AA/M Protein36 | 蛋白质 |
| 2016 | OPLS337 | 蛋白质、有机小分子 |
| 2017 | LigParGen38 | 有机小分子 |
| 2019 | OPLS-AA/M RNA39 | RNA |

**参考文献：**

1. Wang, W., Recent advances in atomic molecular dynamics simulation of intrinsically disordered proteins. *Physical Chemistry Chemical Physics* **2021,** *23* (2), 777-784.

2. Riniker, S., Fixed-Charge Atomistic Force Fields for Molecular Dynamics Simulations in the Condensed Phase: An Overview. *J Chem Inf Model* **2018,** *58* (3), 565-578.

3. Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Ghio, C.; Alagona, G.; Profeta, S.; Weiner, P., A new force field for molecular mechanical simulation of nucleic acids and proteins. *Journal of the American Chemical Society* **1984,** *106* (3), 765-784.

4. 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. *Journal of Chemical Theory and Computation* **2015,** *11* (8), 3696-3713.

5. Case, D.; Ben-Shalom, I.; Brozell, S. R.; Cerutti, D. S.; Cheatham, T.; Cruzeiro, V. W. D.; Darden, T.; Duke, R.; Ghoreishi, D.; Gilson, M.; Gohlke, H.; Götz, A.; Greene, D.; Harris, R.; Homeyer, N.; Huang, Y.; Izadi, S.; Kovalenko, A.; Kurtzman, T.; Kollman, P. A., *Amber 2018*. 2018.

6. Case, D.; Betz, R.; Cerutti, D. S.; Cheatham, T.; Darden, T.; Duke, R.; Giese, T. J.; Gohlke, H.; Götz, A.; Homeyer, N.; Izadi, S.; Janowski, P.; Kaus, J.; Kovalenko, A.; Lee, T.-S.; LeGrand, S.; Li, P.; Lin, C.; Luchko, T.; Kollman, P., *Amber 16, University of California, San Francisco*. 2016.

7. Kirschner, K. N.; Yongye, A. B.; Tschampel, S. M.; González-Outeiriño, J.; Daniels, C. R.; Foley, B. L.; Woods, R. J., GLYCAM06: A generalizable biomolecular force field. Carbohydrates. *Journal of Computational Chemistry* **2008,** *29* (4), 622-655.

8. Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; States, D. J.; Swaminathan, S.; Karplus, M., CHARMM: A program for macromolecular energy, minimization, and dynamics calculations. *Journal of Computational Chemistry* **1983,** *4* (2), 187-217.

9. Klauda, J. B.; Venable, R. M.; Freites, J. A.; O’Connor, J. W.; Tobias, D. J.; Mondragon-Ramirez, C.; Vorobyov, I.; Mackerell, A. D.; Pastor, R. W., Update of the CHARMM All-Atom Additive Force Field for Lipids: Validation on Six Lipid Types. *The Journal of Physical Chemistry B* **2010,** *114* (23), 7830-7843.

10. Denning, E. J.; Priyakumar, U. D.; Nilsson, L.; Mackerell, A. D., Impact of 2′-hydroxyl sampling on the conformational properties of RNA: Update of the CHARMM all-atom additive force field for RNA. *Journal of Computational Chemistry* **2011,** *32* (9), 1929-1943.

11. Guvench, O.; Mallajosyula, S. S.; Raman, E. P.; Hatcher, E.; Vanommeslaeghe, K.; Foster, T. J.; Jamison, F. W.; Mackerell, A. D., CHARMM Additive All-Atom Force Field for Carbohydrate Derivatives and Its Utility in Polysaccharide and Carbohydrate–Protein Modeling. *Journal of Chemical Theory and Computation* **2011,** *7* (10), 3162-3180.

12. Hart, K.; Foloppe, N.; Baker, C. M.; Denning, E. J.; Nilsson, L.; Mackerell, A. D., Optimization of the CHARMM Additive Force Field for DNA: Improved Treatment of the BI/BII Conformational Equilibrium. *Journal of Chemical Theory and Computation* **2012,** *8* (1), 348-362.

13. 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.

14. 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. *Journal of Chemical Theory and Computation* **2012,** *8* (9), 3257-3273.

15. Soteras Gutiérrez, I.; Lin, F.-Y.; Vanommeslaeghe, K.; Lemkul, J. A.; Armacost, K. A.; Brooks, C. L.; Mackerell, A. D., Parametrization of halogen bonds in the CHARMM general force field: Improved treatment of ligand–protein interactions. *Bioorganic & Medicinal Chemistry* **2016,** *24* (20), 4812-4825.

16. Hermans, J.; Berendsen, H. J. C.; Van Gunsteren, W. F.; Postma, J. P. M., A consistent empirical potential for water-protein interactions. *Biopolymers* **1984,** *23* (8), 1513-1518.

17. Jorgensen, W. L.; Tirado-Rives, J., The OPLS [optimized potentials for liquid simulations] potential functions for proteins, energy minimizations for crystals of cyclic peptides and crambin. *Journal of the American Chemical Society* **1988,** *110* (6), 1657-1666.

18. Jing, Z.; Liu, C.; Cheng, S. Y.; Qi, R.; Walker, B. D.; Piquemal, J.-P.; Ren, P., Polarizable Force Fields for Biomolecular Simulations: Recent Advances and Applications. *Annual Review of Biophysics* **2019,** *48* (1), 371-394.

19. Zhang, D. W.; Zhang, J. Z. H., Molecular fractionation with conjugate caps for full quantum mechanical calculation of protein–molecule interaction energy. *J. Chem. Phys.* **2003,** *119*, 3599-3605.

20. Peng, X.; Zhang, Y.; Chu, H.; Li, Y.; Zhang, D.; Cao, L.; Li, G., Accurate Evaluation of Ion Conductivity of the Gramicidin A Channel Using a Polarizable Force Field without Any Corrections. *Journal of Chemical Theory and Computation* **2016,** *12* (6), 2973-2982.

21. Lemkul, J. A.; Huang, J.; Roux, B.; Mackerell, A. D., An Empirical Polarizable Force Field Based on the Classical Drude Oscillator Model: Development History and Recent Applications. *Chemical Reviews* **2016,** *116* (9), 4983-5013.

22. Dickson, C. J.; Rosso, L.; Betz, R. M.; Walker, R. C.; Gould, I. R., GAFFlipid: a General Amber Force Field for the accurate molecular dynamics simulation of phospholipid. *Soft Matter* **2012,** *8* (37), 9617.

23. Dickson, C. J.; Madej, B. D.; Skjevik, Å. A.; Betz, R. M.; Teigen, K.; Gould, I. R.; Walker, R. C., Lipid14: The Amber Lipid Force Field. *Journal of Chemical Theory and Computation* **2014,** *10* (2), 865-879.

24. 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. *Journal of Chemical Theory and Computation* **2020,** *16* (1), 528-552.

25. D.A. Case, H. M. A., K. Belfon, I.Y. Ben-Shalom, S.R. Brozell, D.S. Cerutti, T.E. Cheatham, III, G.A. Cisneros, V.W.D. Cruzeiro, T.A. Darden, R.E. Duke, G. Giambasu, M.K. Gilson, H. Gohlke, A.W. Goetz, R. Harris, S. Izadi, S.A. Izmailov, C. Jin, K. Kasavajhala, M.C. Kaymak, E. King, A. Kovalenko, T. Kurtzman, T.S. Lee, S. LeGrand, P. Li, C. Lin, J. Liu, T. Luchko, R. Luo, M. Machado, V. Man, M. Manathunga, K.M. Merz, Y. Miao, O. Mikhailovskii, G. Monard, H. Nguyen, K.A. O’Hearn, A. Onufriev, F. Pan, S. Pantano, R. Qi, A. Rahnamoun, D.R. Roe, A. Roitberg, C. Sagui, S. Schott-Verdugo, J. Shen, C.L. Simmerling, N.R. Skrynnikov, J. Smith, J. Swails, R.C. Walker, J. Wang, H. Wei, R.M. Wolf, X. Wu, Y. Xue, D.M. York, S. Zhao, and P.A. Kollman, Amber 2021. **2021**.

26. Mallajosyula, S. S.; Guvench, O.; Hatcher, E.; Mackerell, A. D., CHARMM Additive All-Atom Force Field for Phosphate and Sulfate Linked to Carbohydrates. *Journal of Chemical Theory and Computation* **2012,** *8* (2), 759-776.

27. Vanommeslaeghe, K.; Mackerell, A. D., Automation of the CHARMM General Force Field (CGenFF) I: Bond Perception and Atom Typing. *Journal of Chemical Information and Modeling* **2012,** *52* (12), 3144-3154.

28. Vanommeslaeghe, K.; Raman, E. P.; Mackerell, A. D., Automation of the CHARMM General Force Field (CGenFF) II: Assignment of Bonded Parameters and Partial Atomic Charges. *Journal of Chemical Information and Modeling* **2012,** *52* (12), 3155-3168.

29. Schmid, N.; Eichenberger, A. P.; Choutko, A.; Riniker, S.; Winger, M.; Mark, A. E.; Van Gunsteren, W. F., Definition and testing of the GROMOS force-field versions 54A7 and 54B7. *European Biophysics Journal* **2011,** *40* (7), 843-856.

30. Malde, A. K.; Zuo, L.; Breeze, M.; Stroet, M.; Poger, D.; Nair, P. C.; Oostenbrink, C.; Mark, A. E., An Automated Force Field Topology Builder (ATB) and Repository: Version 1.0. *Journal of Chemical Theory and Computation* **2011,** *7* (12), 4026-4037.

31. Reif, M. M.; Hünenberger, P. H.; Oostenbrink, C., New Interaction Parameters for Charged Amino Acid Side Chains in the GROMOS Force Field. *Journal of Chemical Theory and Computation* **2012,** *8* (10), 3705-3723.

32. Pol-Fachin, L.; Rusu, V. H.; Verli, H.; Lins, R. D., GROMOS 53A6GLYC, an Improved GROMOS Force Field for Hexopyranose-Based Carbohydrates. *Journal of Chemical Theory and Computation* **2012,** *8* (11), 4681-4690.

33. Koziara, K. B.; Stroet, M.; Malde, A. K.; Mark, A. E., Testing and validation of the Automated Topology Builder (ATB) version 2.0: prediction of hydration free enthalpies. *Journal of Computer-Aided Molecular Design* **2014,** *28* (3), 221-233.

34. Plazinski, W.; Lonardi, A.; Hünenberger, P. H., Revision of the GROMOS 56A6CARBOforce field: Improving the description of ring-conformational equilibria in hexopyranose-based carbohydrates chains. *Journal of Computational Chemistry* **2016,** *37* (3), 354-365.

35. Shivakumar, D.; Harder, E.; Damm, W.; Friesner, R. A.; Sherman, W., Improving the Prediction of Absolute Solvation Free Energies Using the Next Generation OPLS Force Field. *Journal of Chemical Theory and Computation* **2012,** *8* (8), 2553-2558.

36. Robertson, M. J.; Tirado-Rives, J.; Jorgensen, W. L., Improved Peptide and Protein Torsional Energetics with the OPLS-AA Force Field. *Journal of Chemical Theory and Computation* **2015,** *11* (7), 3499-3509.

37. Harder, E.; Damm, W.; Maple, J.; Wu, C.; Reboul, M.; Xiang, J. Y.; Wang, L.; Lupyan, D.; Dahlgren, M. K.; Knight, J. L.; Kaus, J. W.; Cerutti, D. S.; Krilov, G.; Jorgensen, W. L.; Abel, R.; Friesner, R. A., OPLS3: A Force Field Providing Broad Coverage of Drug-like Small Molecules and Proteins. *Journal of Chemical Theory and Computation* **2016,** *12* (1), 281-296.

38. Dodda, L. S.; Israel; Tirado-Rives, J.; Jorgensen, W. L., LigParGen web server: an automatic OPLS-AA parameter generator for organic ligands. *Nucleic Acids Research* **2017,** *45* (W1), W331-W336.

39. Robertson, M. J.; Qian, Y.; Robinson, M. C.; Tirado-Rives, J.; Jorgensen, W. L., Development and Testing of the OPLS-AA/M Force Field for RNA. *Journal of Chemical Theory and Computation* **2019,** *15* (4), 2734-2742.