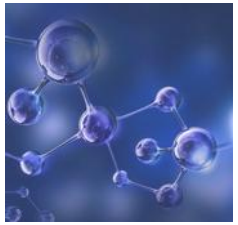
DP Technology 深势科技

基于AI for Science新范式的

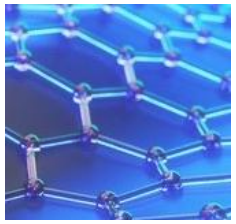
新一代药物计算设计平台Hermite

马鹏宇
深势科技药物设计平台解决方案总监

传统分子模拟面临维数灾难瓶颈

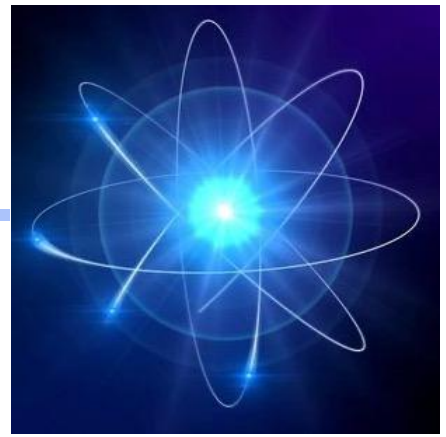


药物设计



材料设计

化工设计

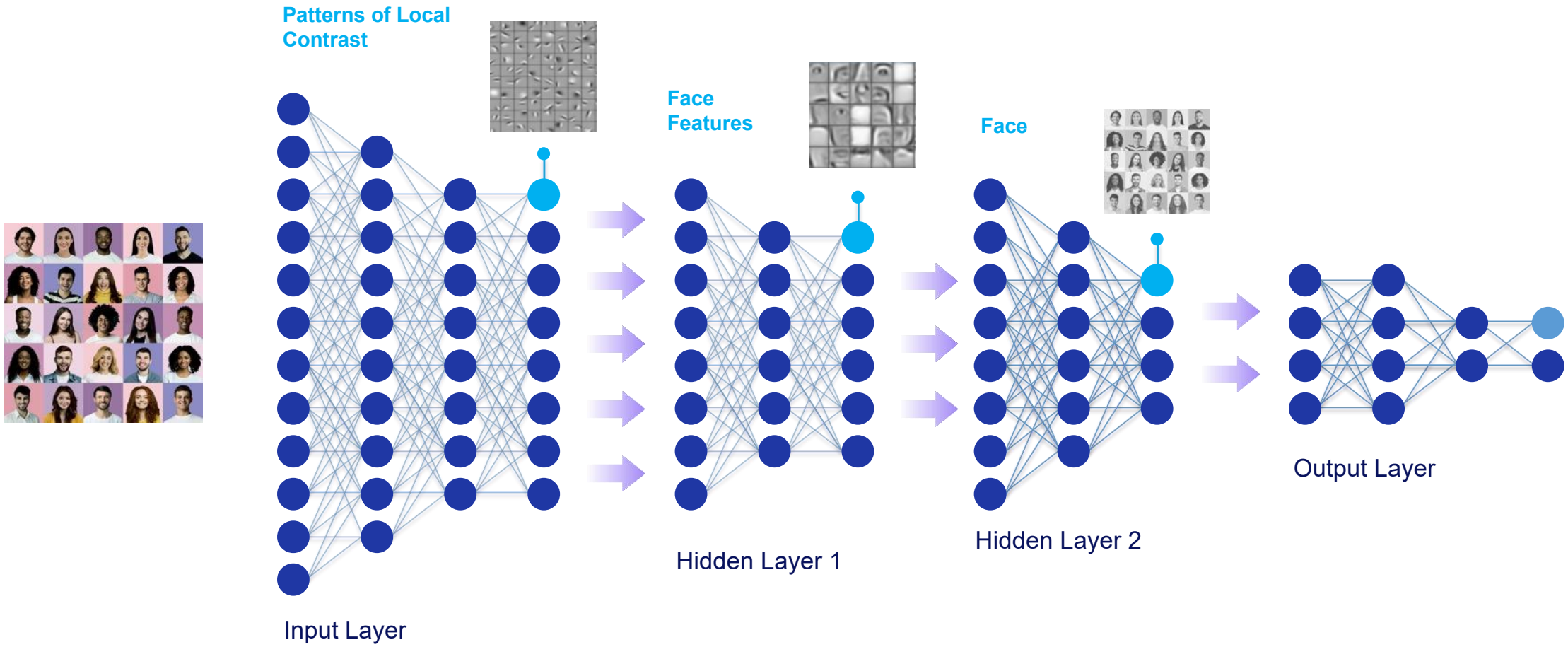


微观粒子复杂多体作用

核心困难

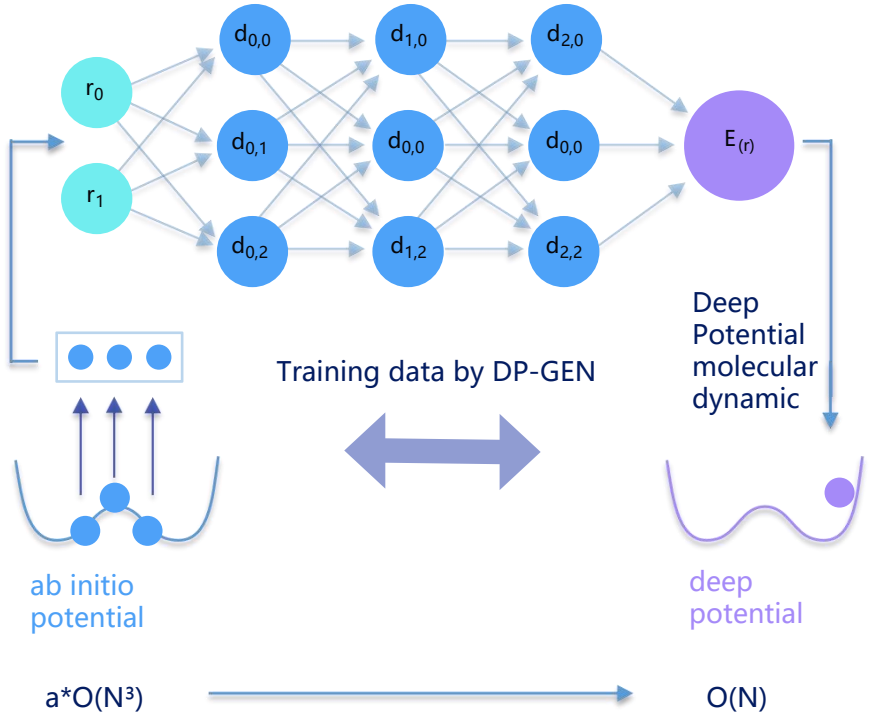
维数灾难

AI的本质是高维函数的拟合和求解工具



AI for Science新范式
突破传统分子模拟计算局限

第一性原理精准建模，深度学习方法拟合高维函数

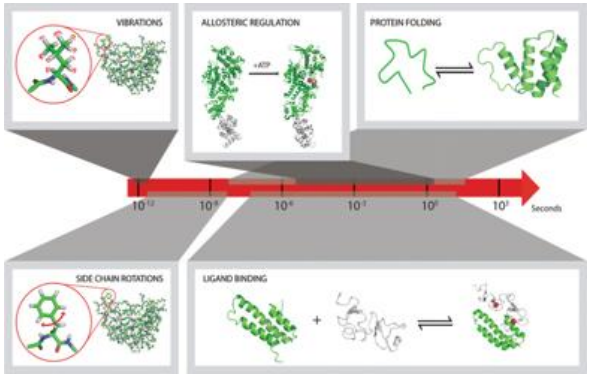


实现计算速度与精度的统一

AI for Science新范式
大幅提升分子模拟采样效率

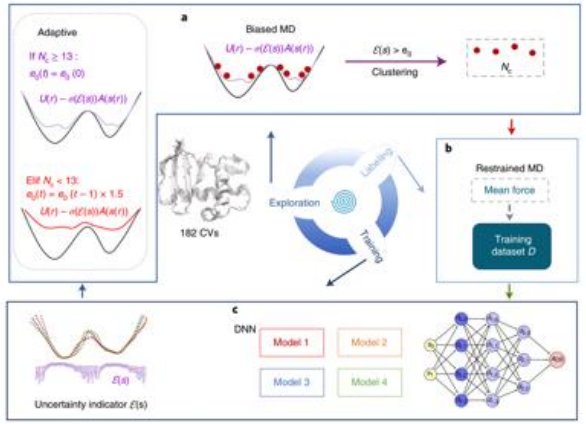
RiD高效探索高维反应坐标空间

Cellular & Molecular Life Sciences, 2009, 66(14):2231-2247.



◆ **cMD：**

- 易限于局域能量低点
- 难以对蛋白质慢运动进行有效描述



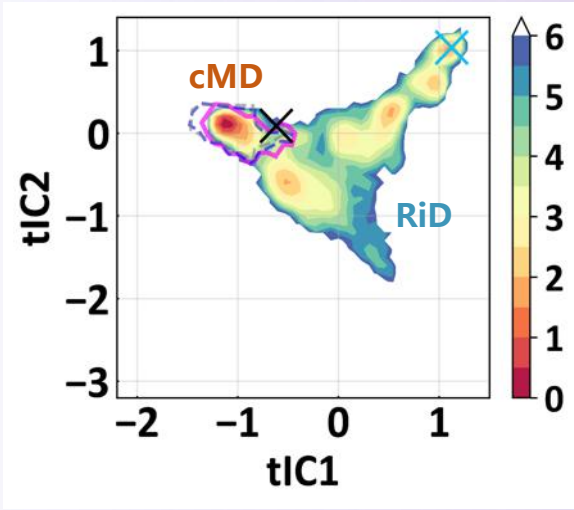
◆ **RiD：**

- 基于AI方法高效填充势能面
- 可选取上百个慢自由度进行充分采样

RiD
Reinforced Dynamics

RiD大幅提升对蛋白构象的采样效率

充分探索势能面
得到更多蛋白亚稳态构象

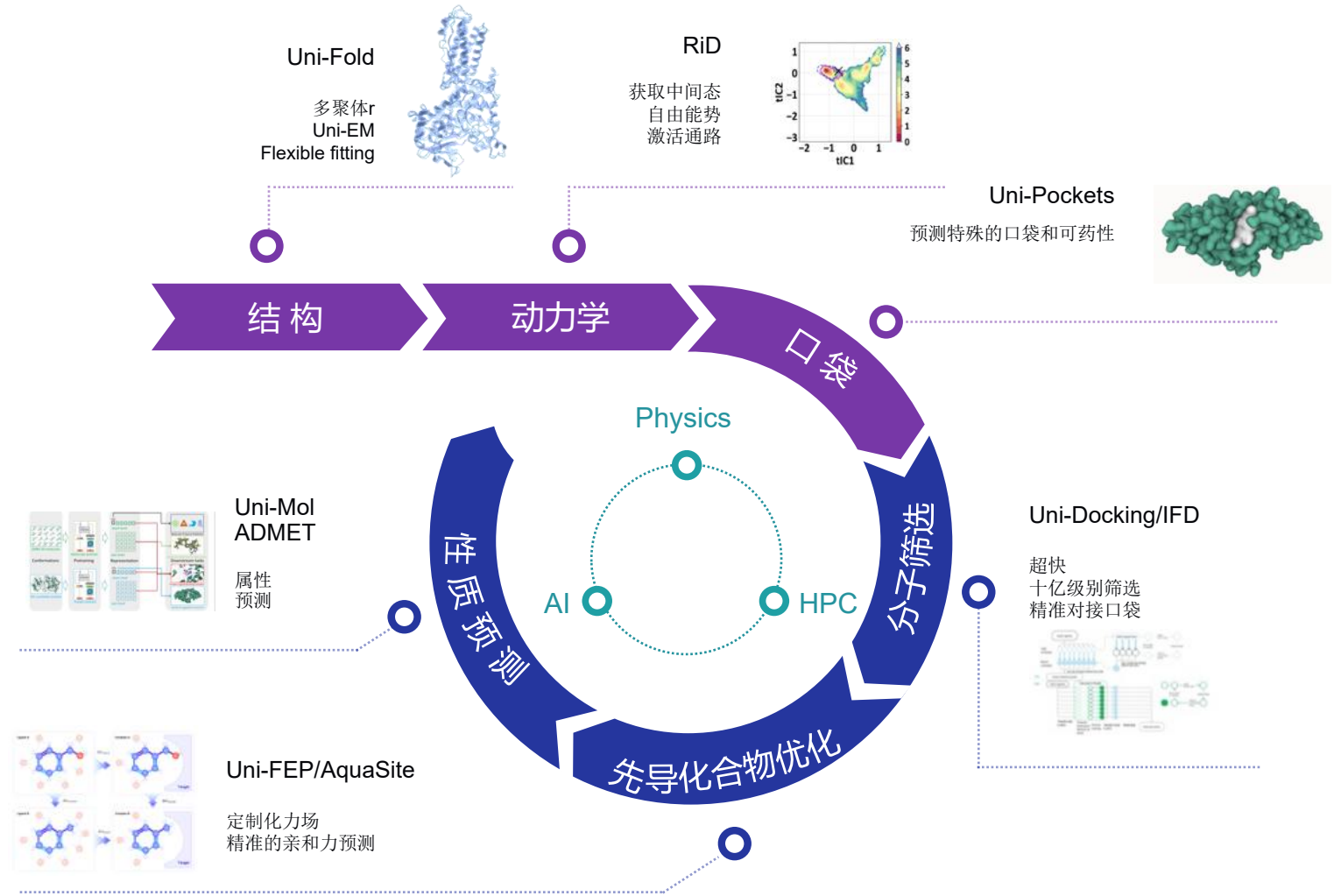


Efficient sampling of high-dimensional free energy landscapes using adaptive reinforced dynamics. Nature Computational Science, 2021, 2, 20.

新一代药物计算设计平台

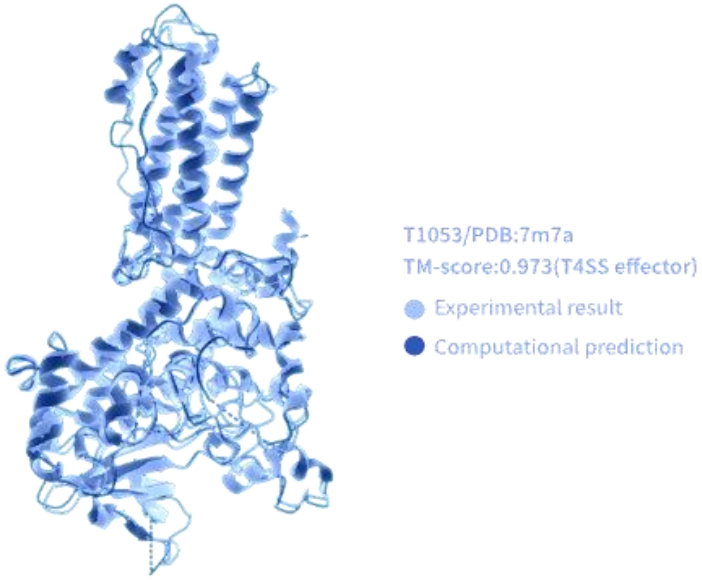
Hermite

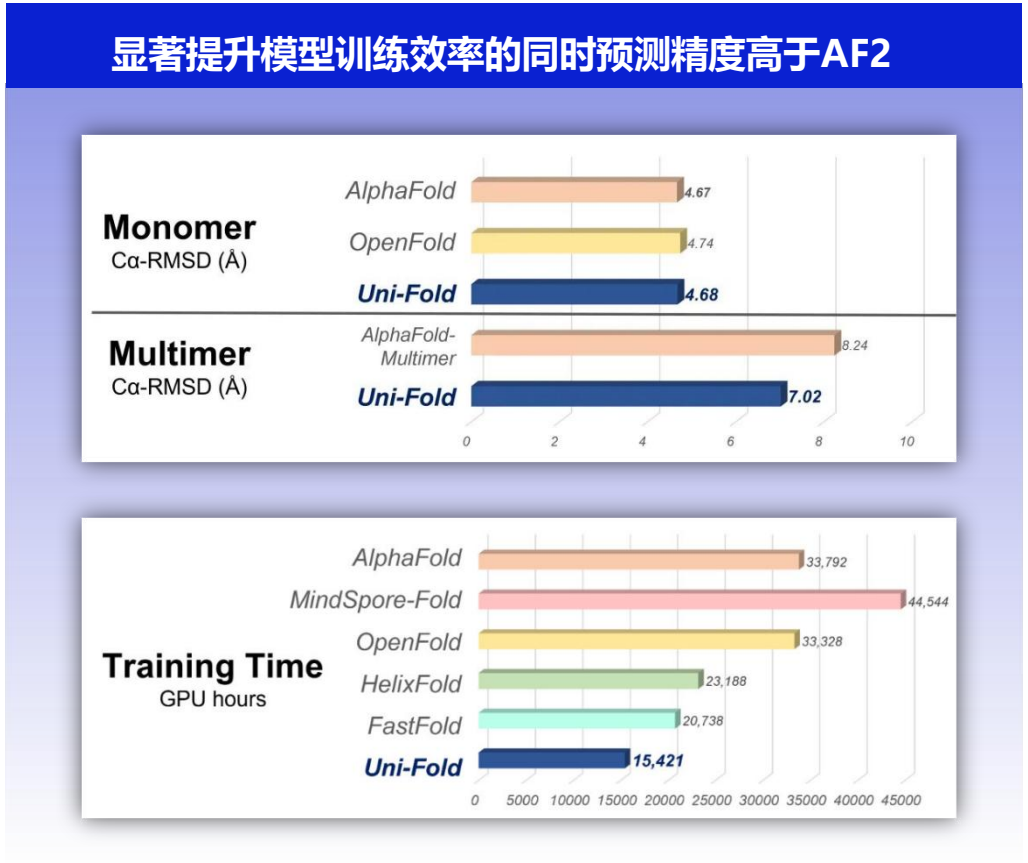
基于人工智能、物理建模和高性能计算的
新一代药物计算设计平台



Uni-Fold蛋白结构预测，超越AlphaFold2

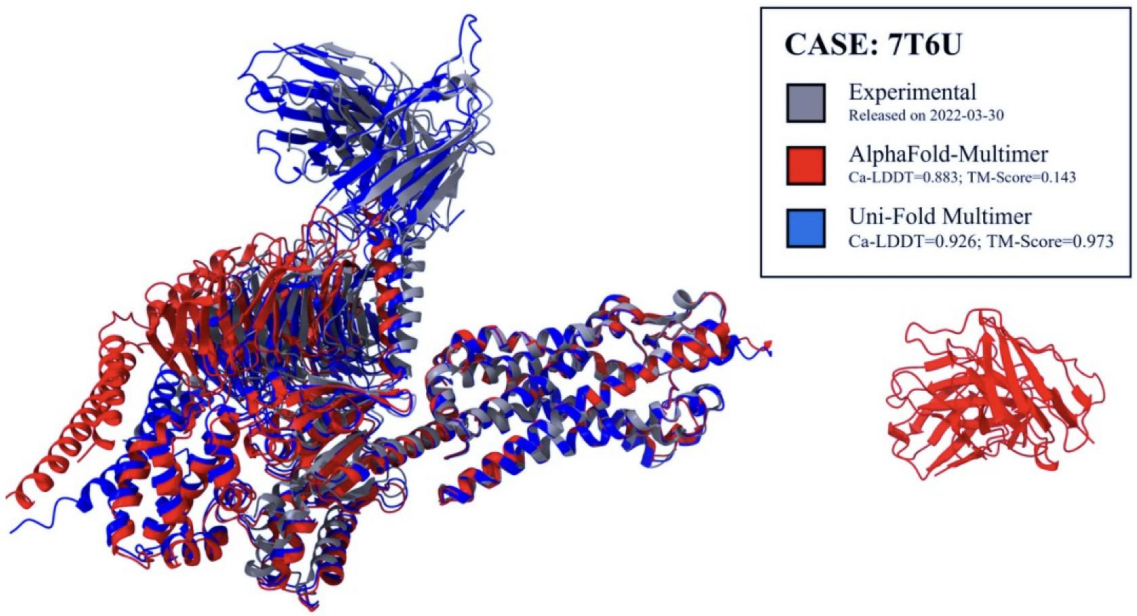
The first protein 3D structure prediction model that open-sourced both inference codes and training codes in the world.



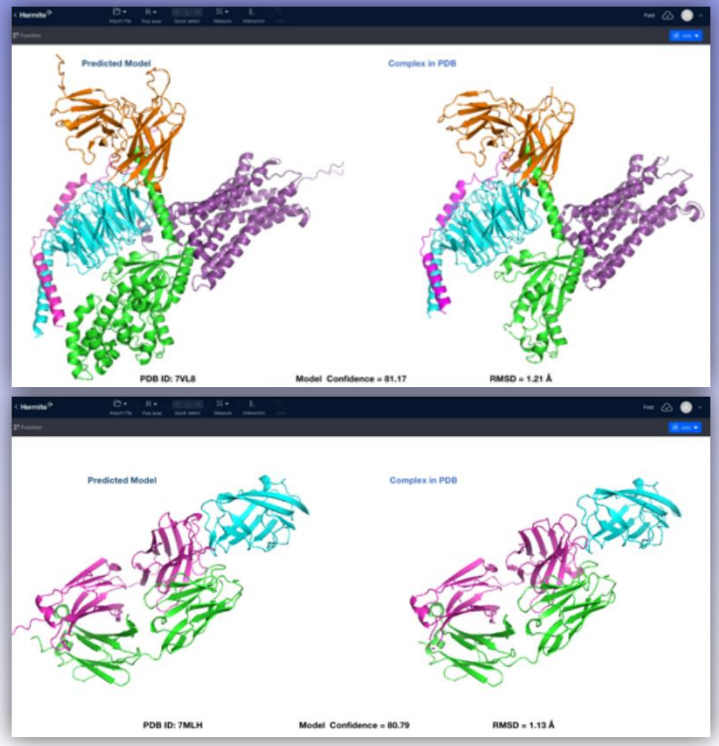


Uni-Fold蛋白结构预测，超越AlphaFold2

多聚体结构预测能力超越AF2-multimer



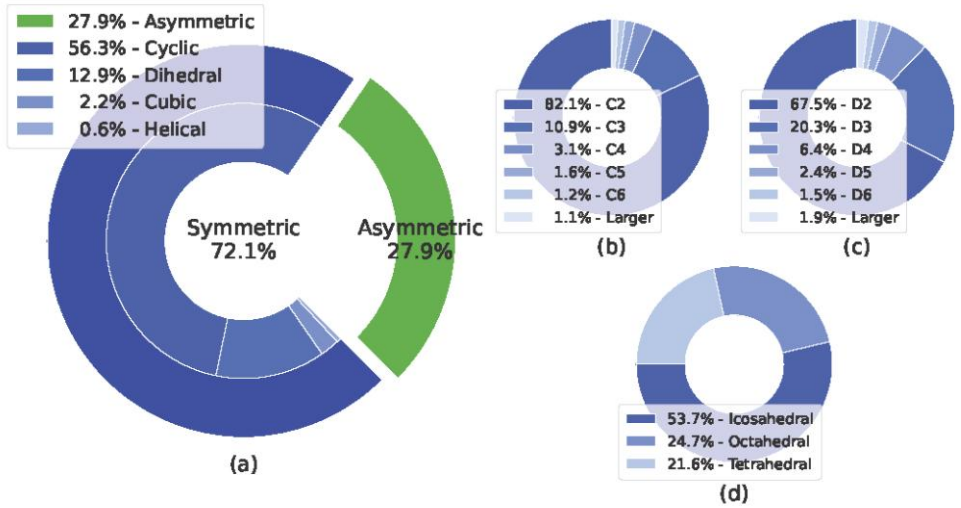
开源，开放，开箱即用



DP Technology 深势科技

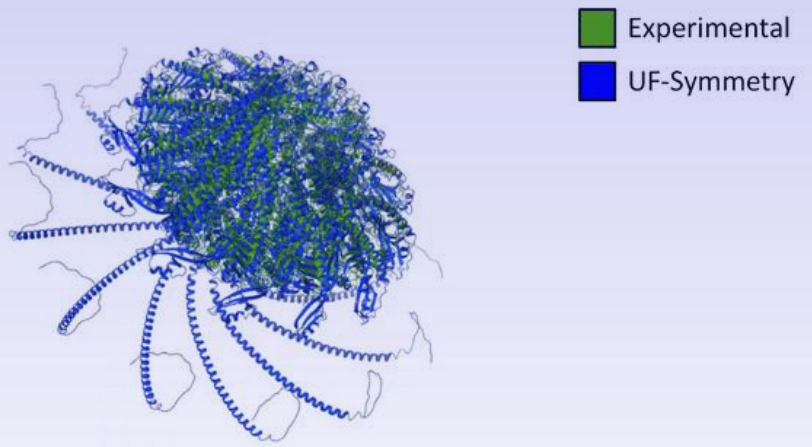
Uni-Fold Symmetry预测超大对称性蛋白高聚体结构

多数重要蛋白具有全局对称性



目前PDB中近10万个蛋白复合物中，有**72%**具有全局对称性，如病毒刺突蛋白、离子通道蛋白、酶等，对生命起重要作用。

成功预测超大蛋白复合物，模型推理加速20倍



PDB-ID: 7SYA, Residue Count: 8460, TM-Score=0.922

Uni-Fold Symmetry成功预测的超大蛋白复合物（同源12聚体，共8460个残基）；AlphaFold因显存限制无法预测

Uni-Fold+RiD赋能无结构靶标结构预测与解析

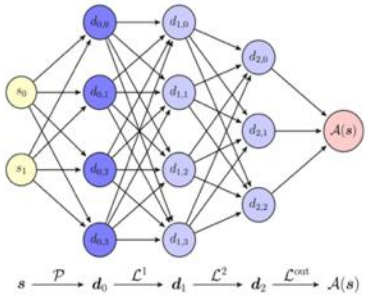
Uni-Fold算法快速预测蛋白质三维结构

RiD对蛋白结构进一步精准优化

Protein Sequence

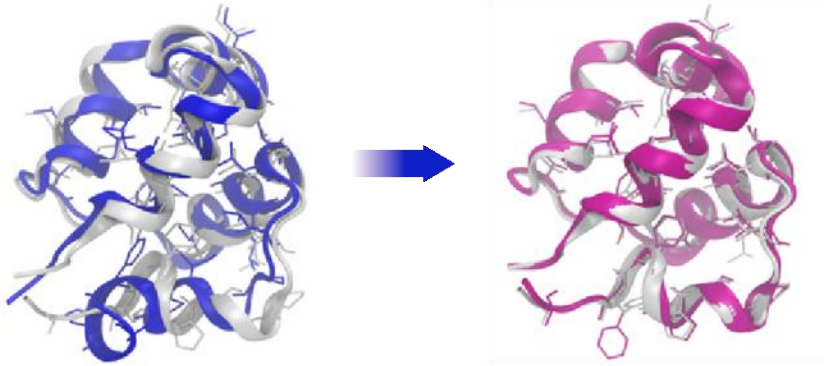
EKETSESRGI
SRFIPPWLK
KQKSYTLVV
AKDGGDD
...

Uni-Fold



Predicted Structure
RMSD: 2.1 Å

Finally Structure
RMSD: 0.5 Å

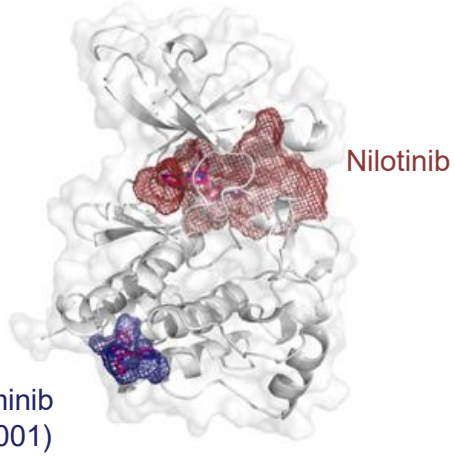


Efficient sampling of high-dimensional free energy landscapes using adaptive reinforced dynamics. Nature Computational Science, 2021, 2, 20.

RiD辅助寻找别构位点

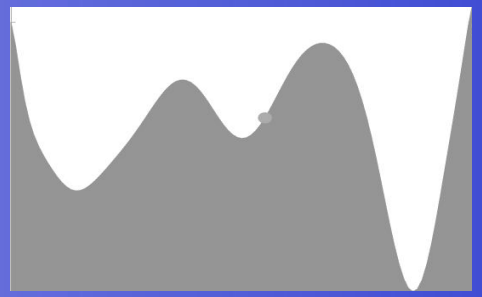
蛋白质构象变化由RiD采样，而后计算可能的口袋及correlation从而找到与正构口袋correlation高的别构口袋

BCR-ABL1

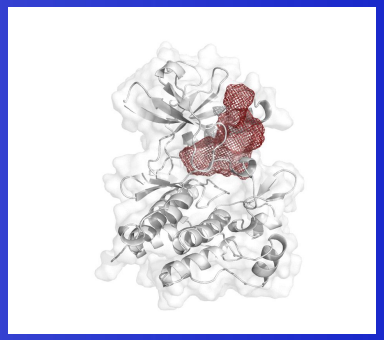


Protein: 1fpu
Ligand: 5mo4

传统采样易限于局域能量低点

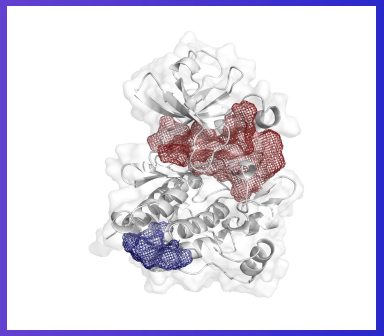


Classical MD 计算50ns



RiD采样高效探索自由能面

RiD 计算50ns

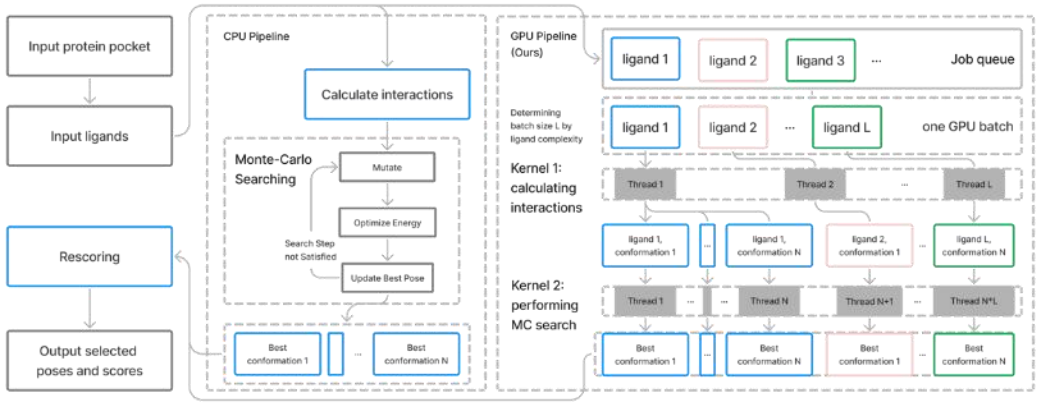


DP Technology 深势科技

Uni-Docking

极致加速的分子对接引擎

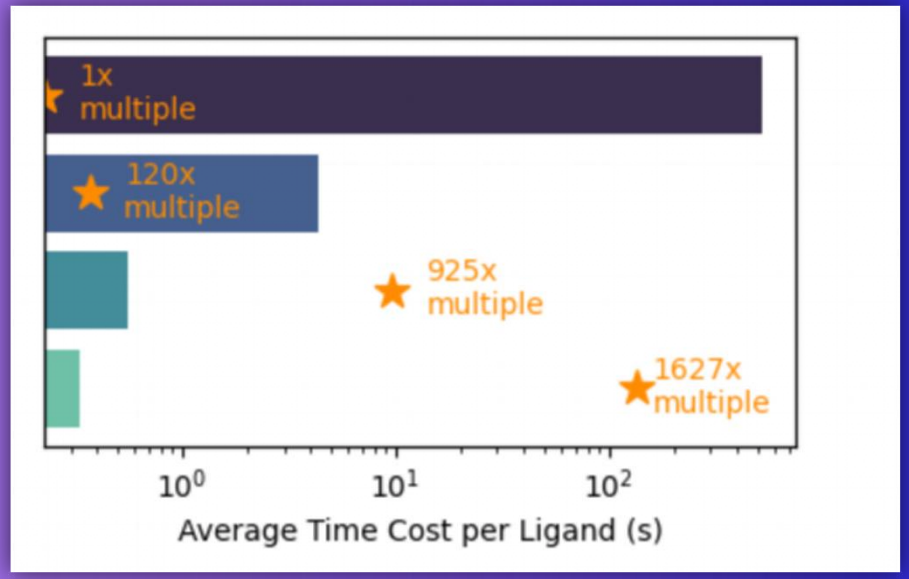
基于GPU的多配体、多搜索线程并行
全面覆盖搜索空间、极大提升搜索效率



YU, Yuejiang, et al. Uni-Dock: A GPU-Accelerated Docking Program Enables Ultra-Large Virtual Screening. 2022.

与AutoDock Vina保持一致的精度下，速度提升1600余倍

并行调度100卡NVIDIA V100 GPU，
完成**38 million**分子数据库的多级分子对接仅用**11.3小时**

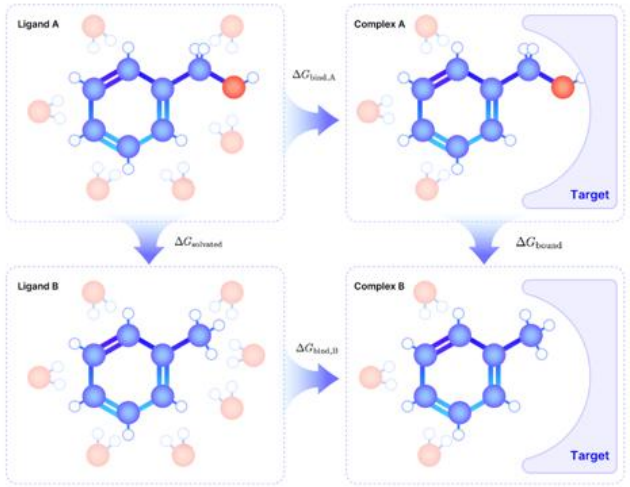


Uni-FEP

Computational Assay

以**化学精度**（±1 kcal/mol）预测修饰配体造成的活性改变

精确评估配体-蛋白结合自由能



- ✓ **活性提升：**先导化合物活性优化
- ✓ **其他性质优化：**保持活性同时修饰化合物以改进ADME/T性质

Uni-FEP可大幅提高**药物优化效率**，批量推出优质PCC药物分子

计算1000-5000次FEP

合成100个分子

实验验证确定PCC分子

自由能微扰理论

分子动力学

01100
10110
11110

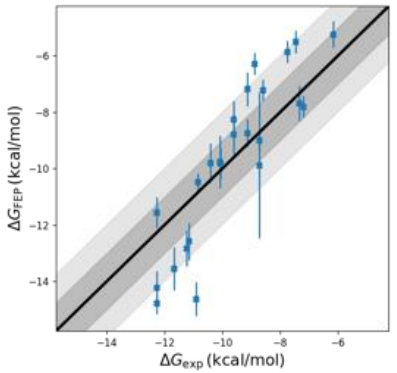
增强采样算法

高性能计算

Hermite

Uni-FEP 自由能计算技术驱动的药物研发

计算与实验结果高度吻合



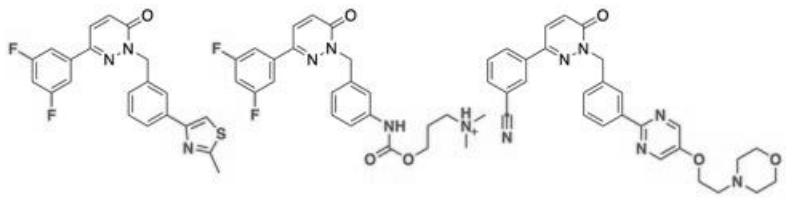
Case:

c-Met inhibitor

R^2 = 0.79

Note: dark grey and grey represent 1 and 2 kcal/mol error lines respectively

Tepotinib



Experiment (kcal/mol)	-6.17	-10.06	-12.27
Uni-FEP (kcal/mol)	-5.24	-9.82	-11.56

Series \ R^2	Hermite FEP	Schrodinger FEP+	Vina Score
BACE	0.55	**0.61**	0.01
CDK2	**0.49**	0.23	0.10
JNK1	0.62	**0.72**	0.14
MCL1	0.50	**0.60**	0.05
p38	**0.54**	0.43	0.01
PTP1B	0.50	**0.64**	0.01
thrombin	**0.70**	0.50	0.18
Tyk2	0.72	**0.79**	0.46
Average	**0.58**	**0.57**	**0.12**

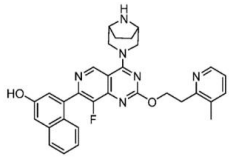
Hermite

Uni-FEP 针对KRAS G12D的回顾性验证

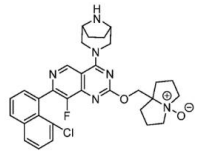
计算与实验结果高度吻合

Ten compounds in the patent

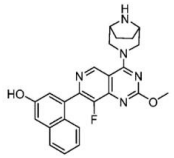
MRTX 6



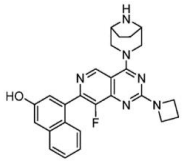
MRTX 60



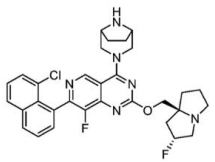
MRTX 105



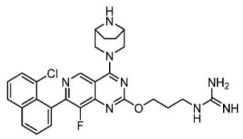
MRTX 119



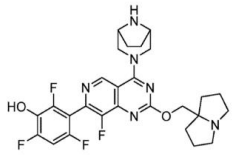
MRTX 134



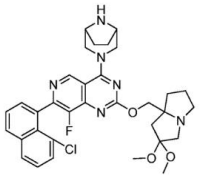
MRTX 177



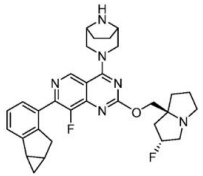
MRTX 350

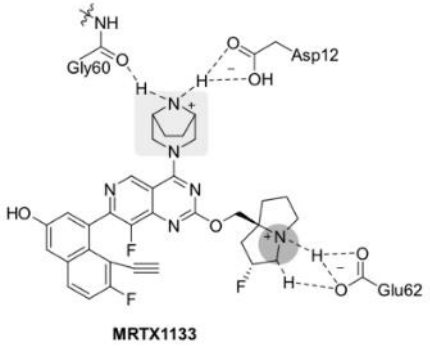


MRTX 404

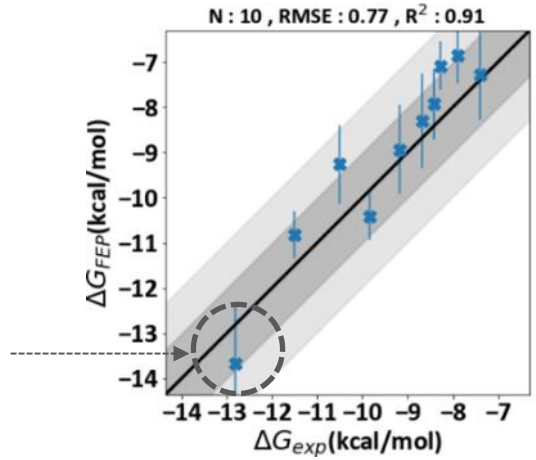


MRTX 438





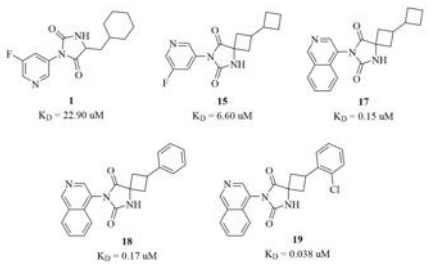
MRTX1133



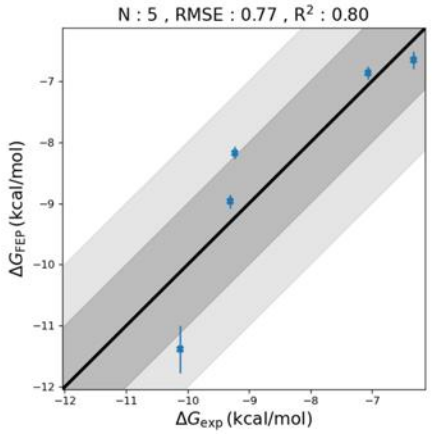
Compound	ΔG_{exp} (kcal/mol)	$\Delta G_{Uni-FEP}$ (kcal/mol)	Deviation (kcal/mol)
MRTX60	-7.88	-6.87 ± 0.62	1.01
MRTX105	-8.27	-7.10 ± 0.54	1.17
MRTX350	-7.39	-7.30 ± 0.99	0.09
MRTX119	-8.41	-7.94 ± 0.77	0.47
MRTX6	-8.68	-8.32 ± 1.04	0.36
MRTX177	-9.17	-8.95 ± 0.98	0.22
MRTX438	-10.50	-9.28 ± 0.87	1.22
MRTX404	-9.84	-10.42 ± 0.52	0.58
MRTX134	-11.50	-10.83 ± 0.52	0.67
MRTX1133	-12.81	-13.68 ± 1.28	0.87

更多案例：Uni-FEP靶点“探月”计划

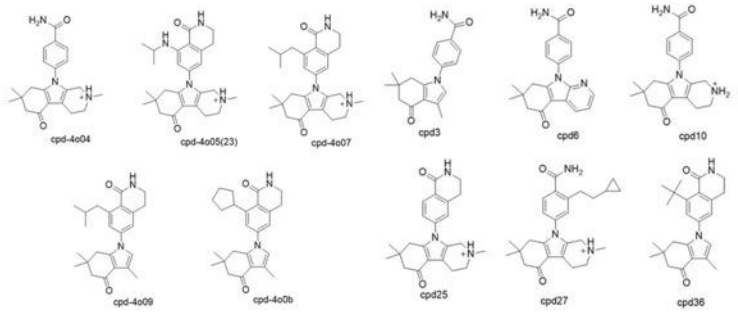
3CLpro

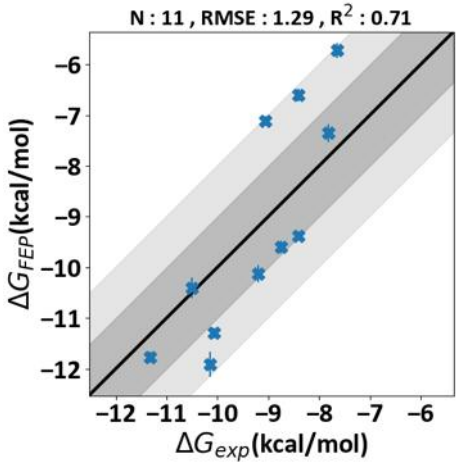


Compound	ΔG_{exp} (kcal/mol)	$\Delta G_{Uni-FEP}$ (kcal/mol)	Deviation (kcal/mol)
1	-6.33	-6.66 ± 0.15	0.33
15	-7.06	-6.87 ± 0.11	0.19
18	-9.23	-8.17 ± 0.11	1.06
17	-9.31	-8.97 ± 0.10	0.34
19	-10.12	-11.38 ± 0.39	1.26

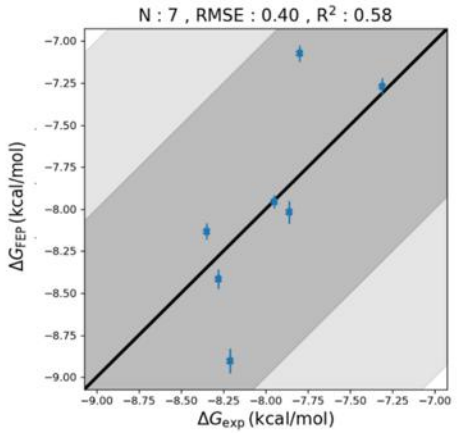


HSP90

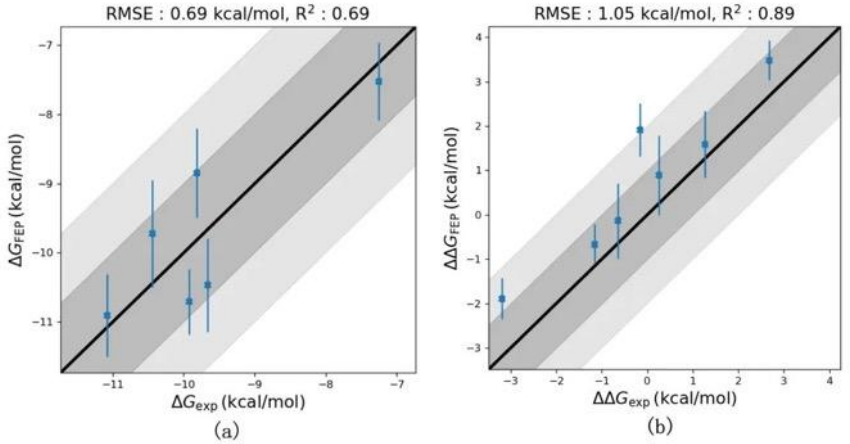




EG5



FXR



Partners

豪森药业 HANSOH PHARMA

InventisBio 益方生物

加科思 Jacobio

Pharma Resources

. . .

分子模拟未来

Molecule Simulates the Future

DP Technology 深势科技