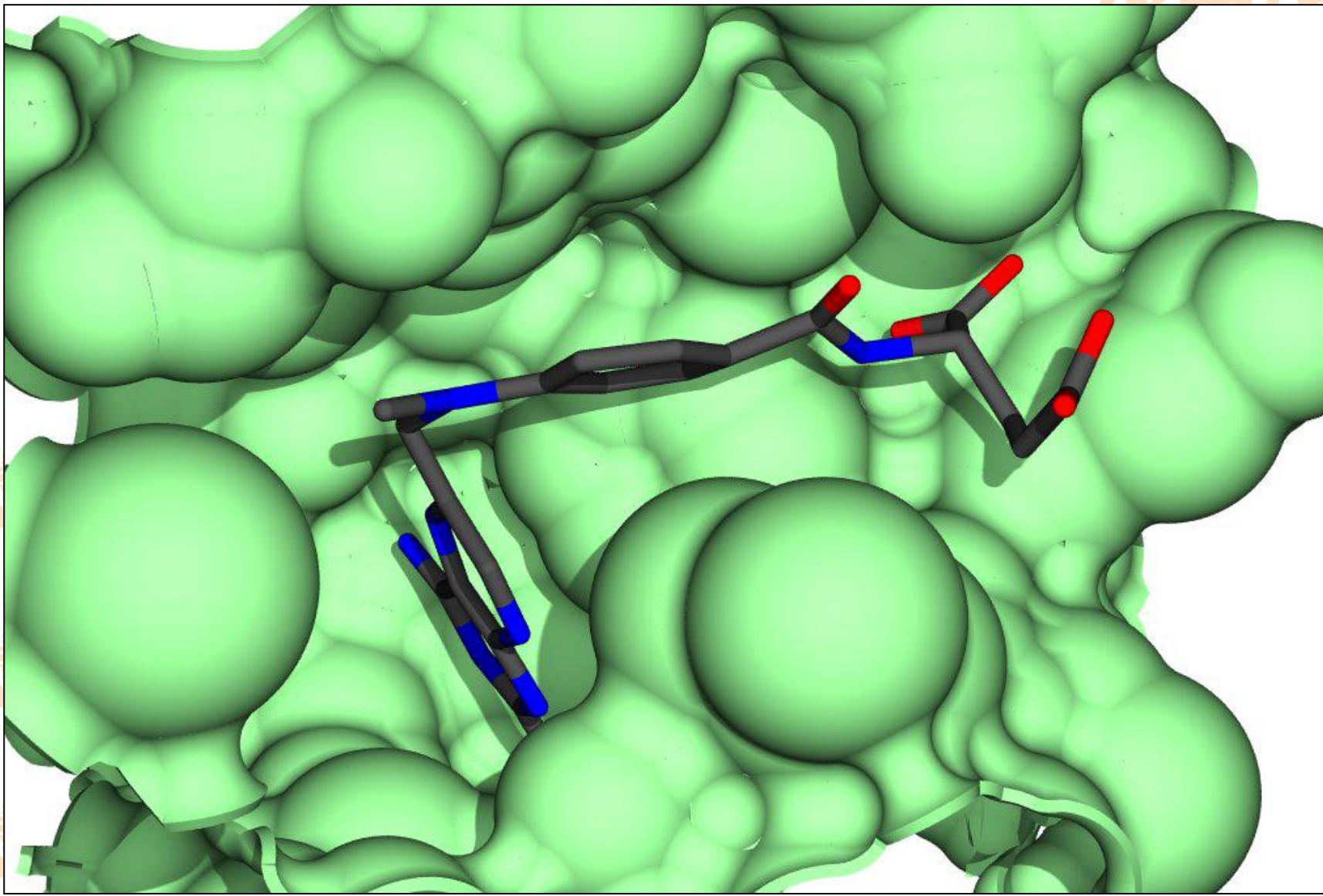


虚拟筛选

分子对接与虚拟筛选



Molecular Docking





分子对接的概念

Ⅱ 预测受体和配体分子形成的复合物结构

分子对接分为两类

蛋白—蛋白分子对接

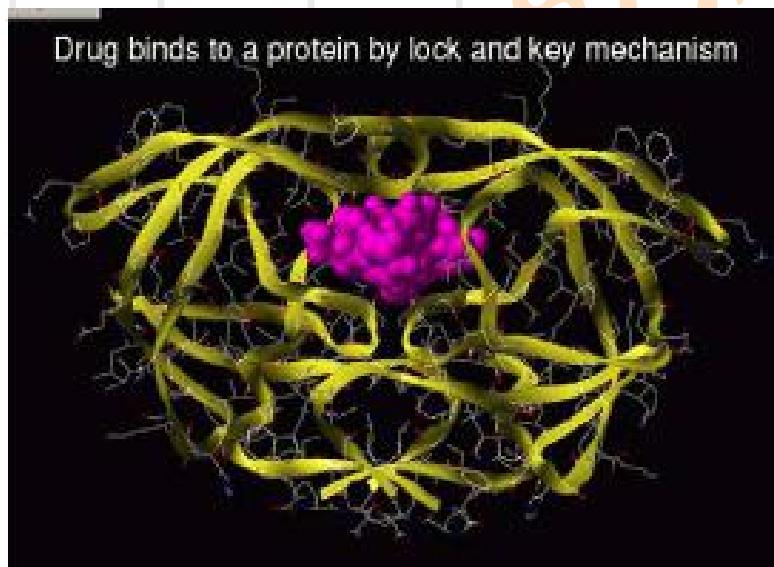
蛋白—小分子的对接



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分子对接的原理

- 【 理论基础:
- “锁和钥匙模型”
- “诱导契合模型”



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重要原则:

【 互补性: 决定识别过程的选择性

【 预组织性: 决定识别过程的结合能力

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分子对接的基本原理

配体与受体的结合强度取决于结合的自由能变化

$$\Delta G_{\text{结合}} = \Delta H_{\text{结合}} - T\Delta S_{\text{结合}} = -RT \ln K_i$$

许多分子对接法忽略了熵效应，而在焓效应也只考虑配体与受体的相互作用能，即：

$$E_{\text{interaction}} = E_{\text{vdw}} + E_{\text{electrostatic}} + E_{\text{h-bond}}$$





分子对接的原理



搜索算法：如何找到最佳的结合位置

遗传算法

模拟退火



能量函数：如何评估结合强度



基于分子力场的方法

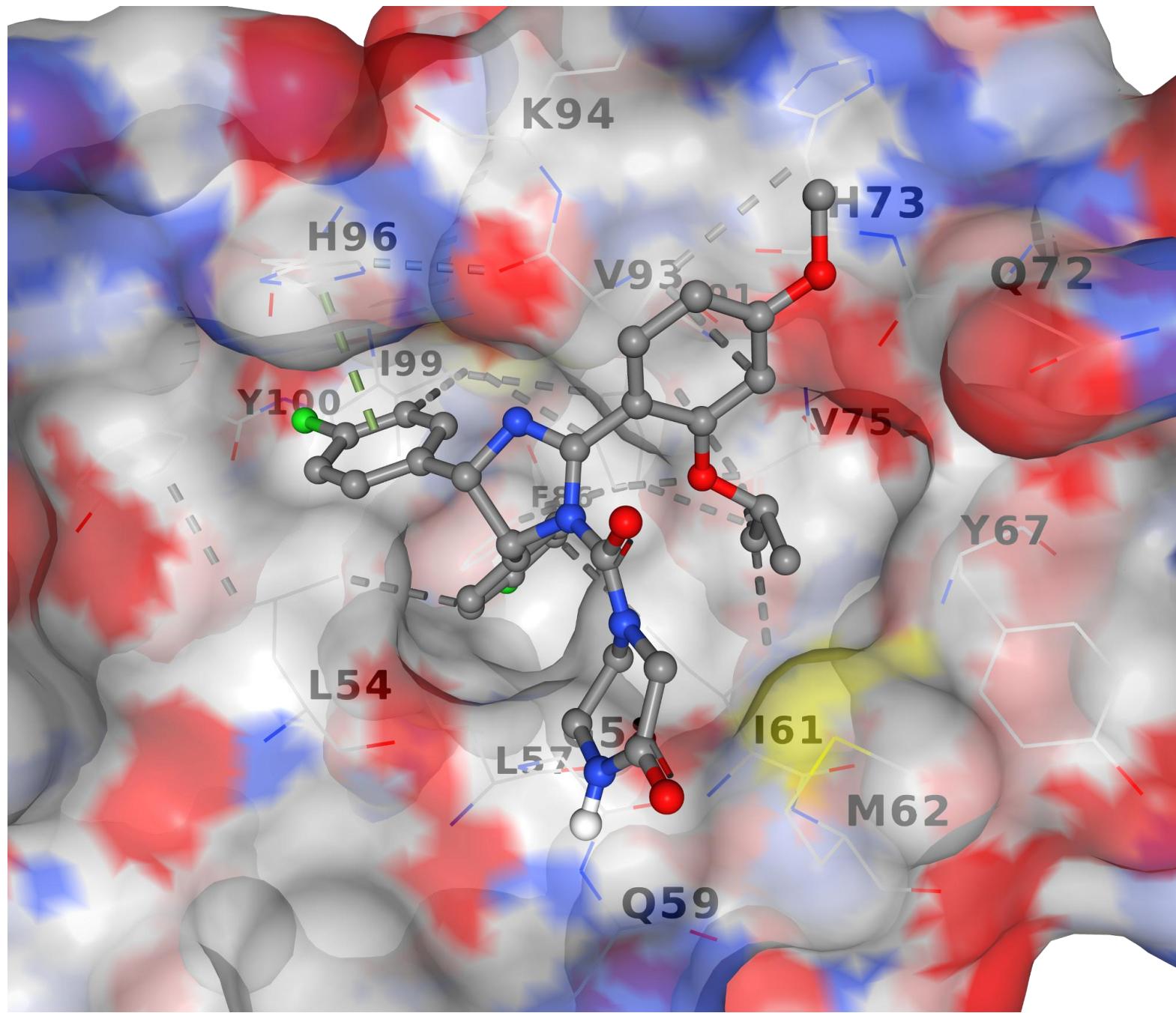


基于经验的方法



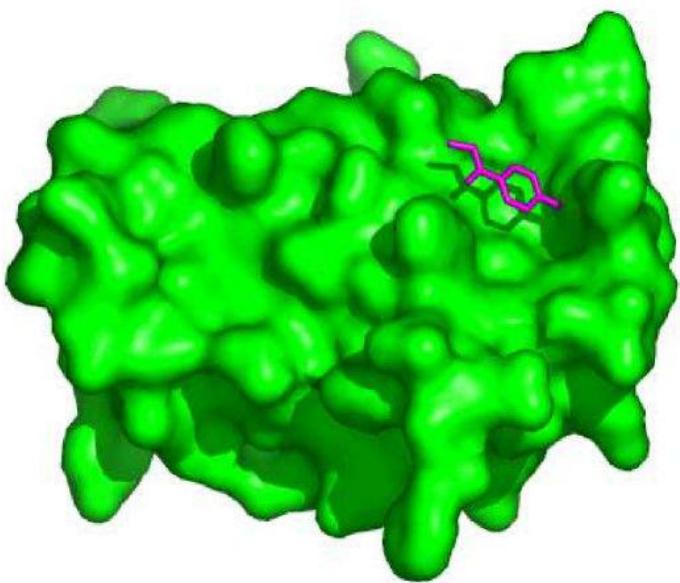
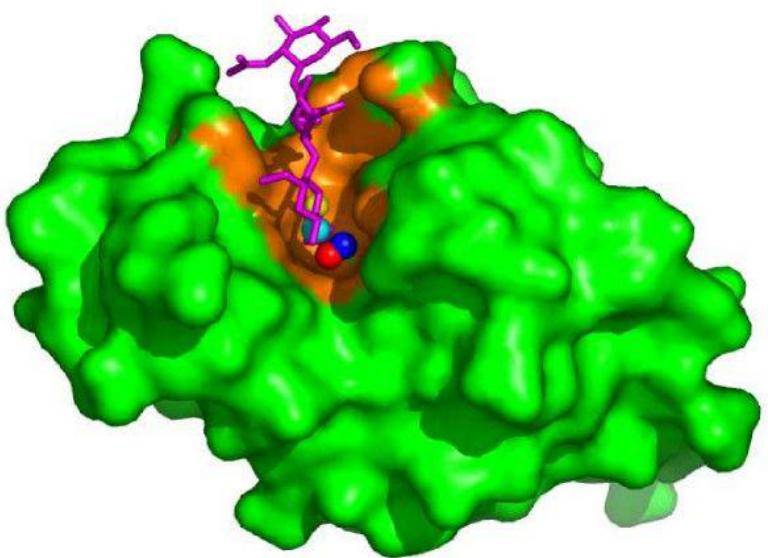
基于知识统计的打分函数





吉祥如意

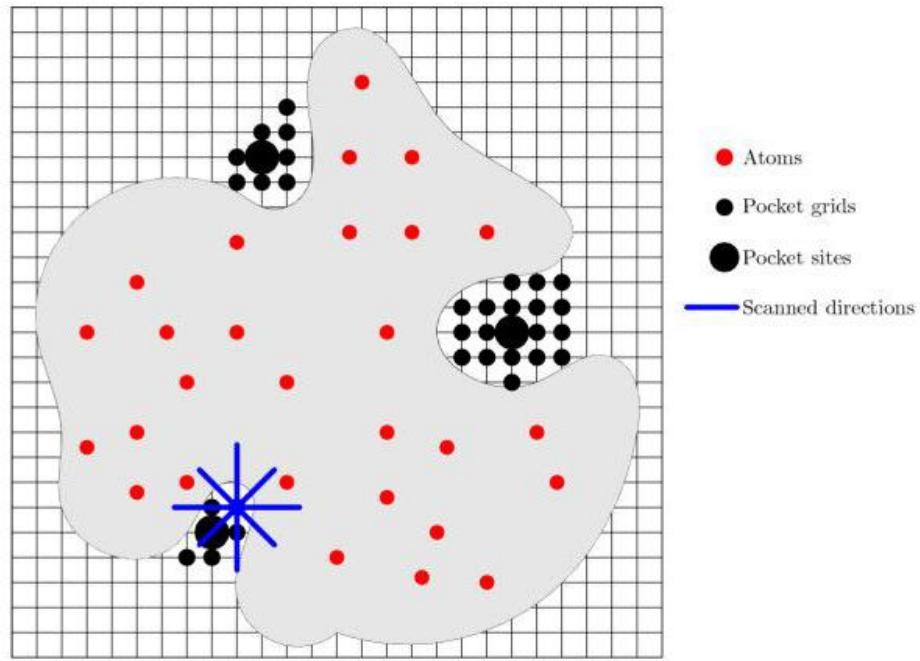
发现结合口袋



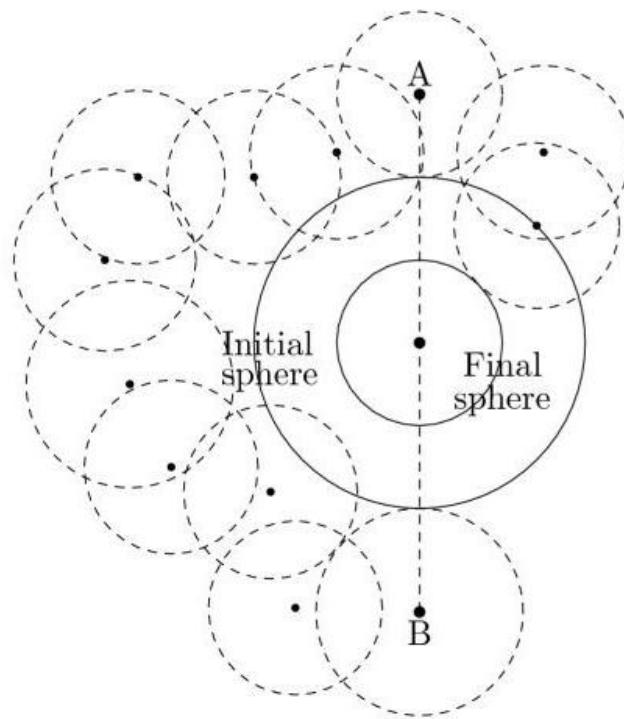
发现结合口袋：几何分析法

吉祥如意

a. POCKET, LIGSITE, LIGSITE^{csc}



b. SURFNET



吉祥如意

发现结合口袋：综合信息法

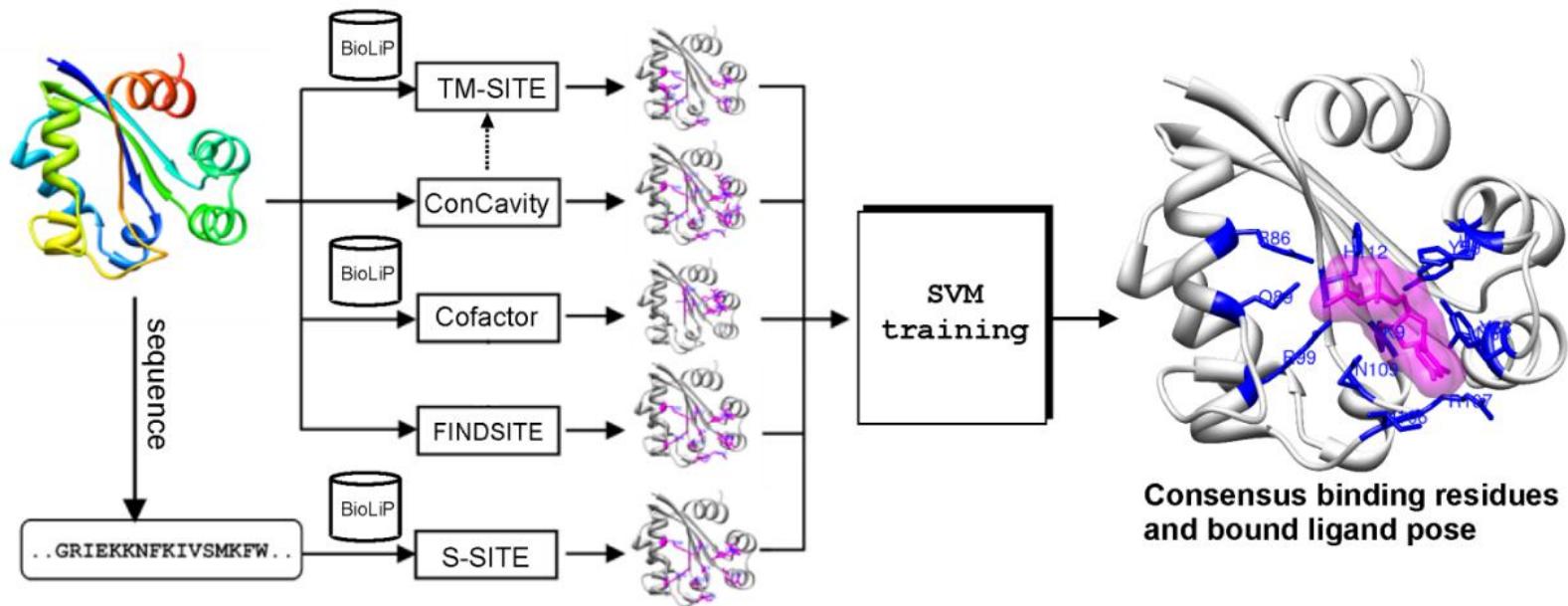


Figure S1. Flowchart of the COACH algorithm. COACH combines complementary predictions from TM-SITE, S-SITE, COFACTOR, FINDSITE and ConCavity.

<https://zhanglab.ccmb.med.umich.edu/COACH/>

Home Research Services Publications People Teaching Job Opening Facilities News Forum Lab Only

Online Services

- I-TASSER
- QUARK
- LOMETS
- COACH
- COFACTOR**
- MetaGO
- MUSTER
- SEGMER
- FG-MD
- ModRefiner
- REMO
- SPRING
- COTH
- BSpred
- SVMSEQ
- ANGLOR
- BSP-SLIM
- SAXSTER
- ThreaDom
- ThreaDomEx
- EvoDesign
- GPCR-I-TASSER
- BindProf
- BindProfX
- ResQ
- IonCom
- STRUM
- DAMPred
- TM-score
- TM-align
- MM-align

COACH for Protein-ligand binding site prediction

COACH is a meta-server approach to protein-ligand binding site prediction. Starting from given structure of target proteins, COACH will generate complementary ligand binding site predictions using two comparative methods, TM-SITE and S-SITE, which recognize ligand-binding templates from the [BioLIP protein function database](#) by binding-specific substructure and sequence profile comparisons. These predictions will be combined with results from other methods (including [COFACTOR](#), [FINDSITE](#) and [ConCavity](#)) to generate final ligand binding site predictions. Users are also allowed to input primary sequence, where [I-TASSER](#) will be used to generate 3D models first which are then fed into the COACH pipeline for ligand-binding site prediction. The COACH algorithm was ranked as the best method in the [weekly CAMEO ligand Binding Site Prediction Experiments](#).

Please post questions and suggestions about the COACH server at the [Service System Discussion Board](#).

[Download the standalone COACH Package through I-TASSER Suite.](#)

[\[Download\]](#) [\[Queue\]](#) [\[Library\]](#) [\[Example\]](#) [\[Forum\]](#)

Please copy and paste your data below (either structure in [PDB format](#) or sequence in [FASTA format](#) is acceptable)

[Click for an example PDB input](#) [Click for an example FASTA input](#)

Or upload the structure/sequence file:

No file selected.

Email: (Mandatory, where results will be sent to)

ID: (Optional, your given name to this protein)



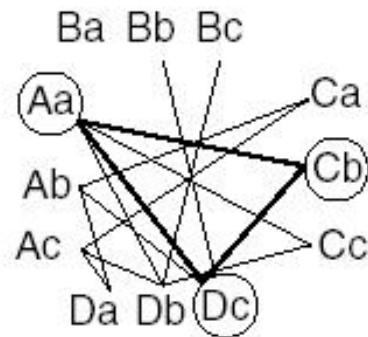
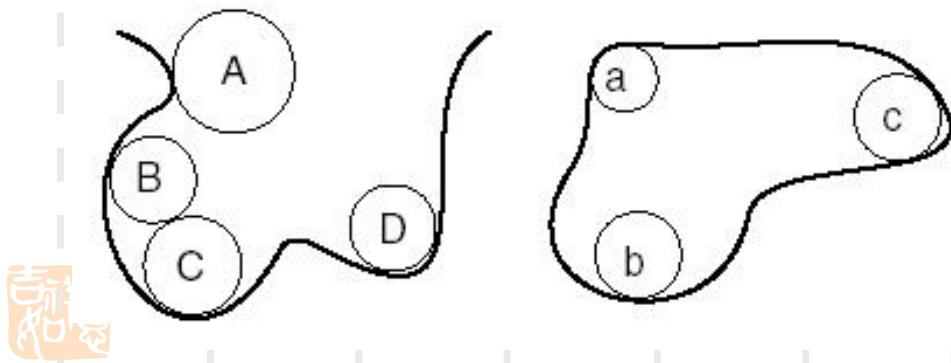
分子对接的分类

- 【 刚性对接：研究体系的构象不发生变化。
- 【 柔性对接：研究体系的构象是可以自由变化的。



刚性分子对接的算法举例

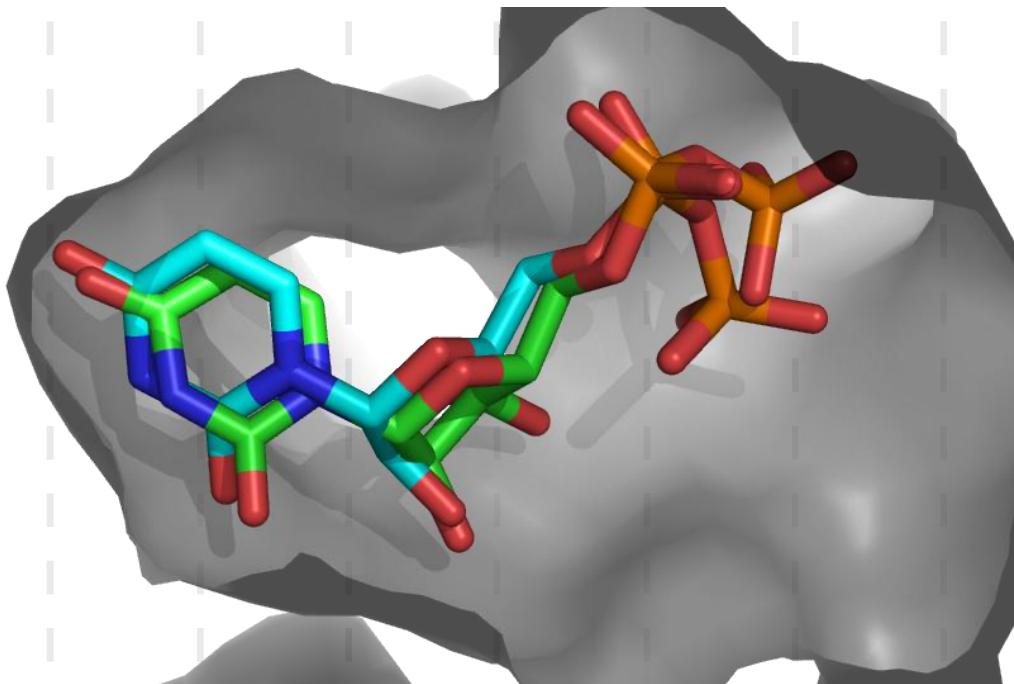
吉祥如意



柔性分子对接

吉祥如意

- 【 片段生长 (DOCK和FlexX)
- 【 锚定搜索 (AutoDock、GOLD、GLIDE)
- 【 构象群对接 (MDock、FRED)





代表性对接软件

名称	构象搜索方法	结合评价方法	速度
Flex X	片段生长法	半经验自由能	快
LigandFit	蒙特卡罗模拟	半经验自由能	快
Glide	系统搜索	半经验自由能	一般
Gold	遗传算法	半经验自由能	快
AutoDock	遗传算法	半经验自由能	一般
Dock	片段生长法	分子力场	快
ICM-Dock	随机全局优化	半经验自由能	快
Fred	系统搜索	半经验自由能	快





CB-Dock

http://cao.labshare.cn/cb-dock/

CB-Dock

Cavity-detection guided Blind Docking

Home

Dock

Results

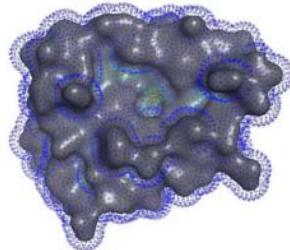
Manual

Contact

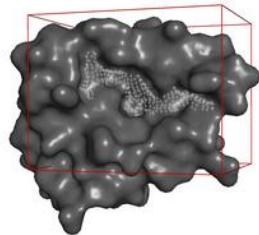
Register Login

CB-Dock is a new blind docking method based on cavity detection. A new method of cavity detection based on the curvature value of protein surface has been used in CB-Dock. We have designed the procedure to automatically identify binding sites, calculate the center and size, and customize the docking box size according to the query ligands, and then perform the molecular docking with [AutoDock Vina](#). Large-scale benchmarking calculations show that docking in small selected sites can enhance the hit ratio and accuracy of blind docking. Accordingly, CB-Dock can improve the facilitation and accuracy as predicting the binding sites of target proteins and the binding poses of query ligands using AutoDock Vina.

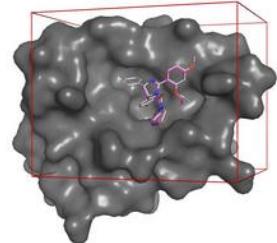
Curvature of protein surface



Cavity detected by clustering



Docking with AutoDock Vina



Programs

[AbRSA](#)

[Cyscore](#)

[PDB Tools](#)

[DrugScreen](#)

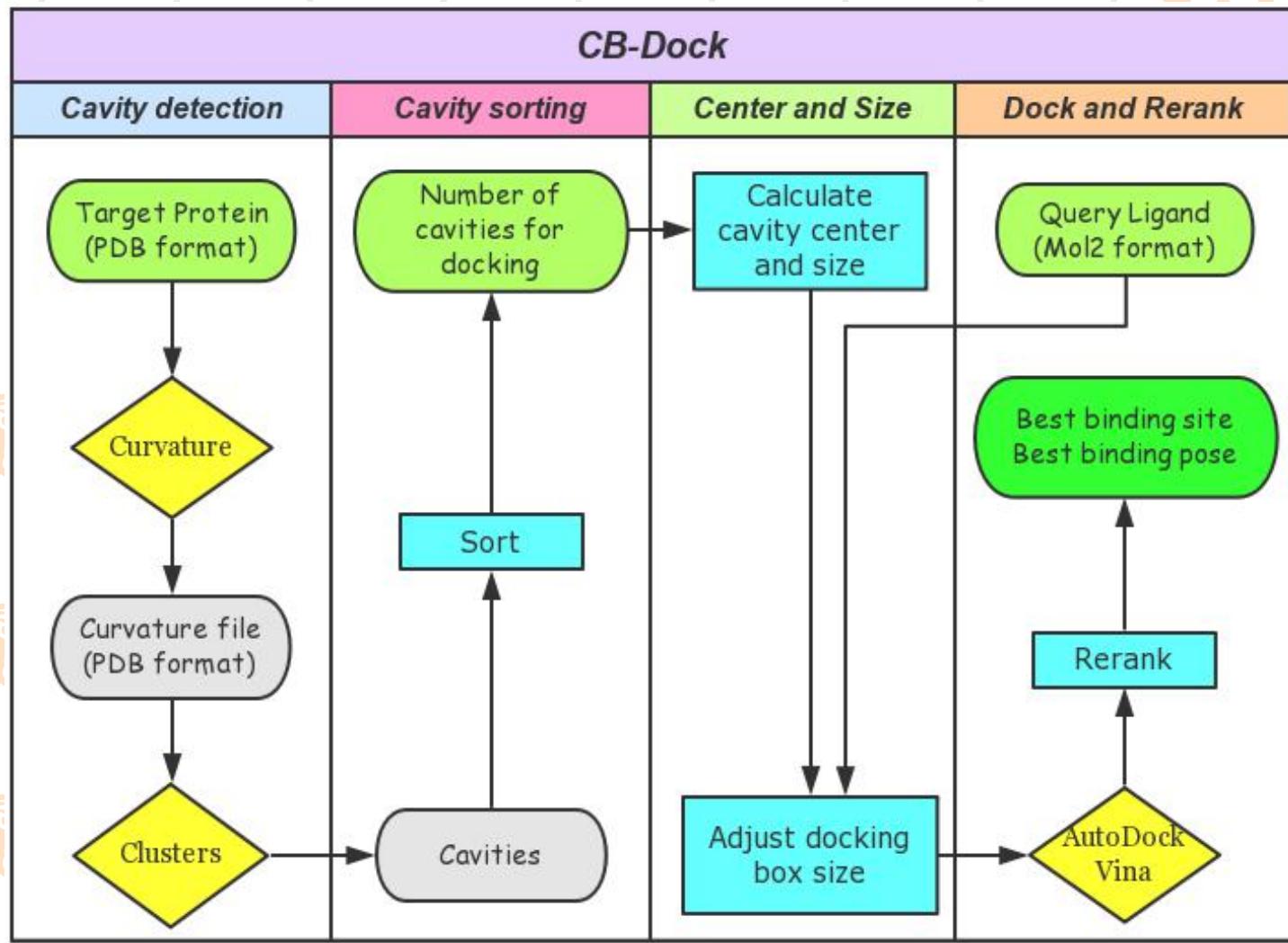
Institute

Compounds Database

Proteins Database

吉祥

算法流程





分子对接计算的注意点

【小分子问题】

起始构象对对接结果有一定影响

对分子进行加电荷和加氢处理

【蛋白质问题】

如何选择合理的蛋白质活性位点

【对接问题】

搜索结合模式的正确性、对接的效率、评分的正确性

采用多个软件进行评价，减少结合模式搜索误差

定量指标，需要结合分子动力学进一步评价



吉祥如意

分子对接方法未来需要解决的问题：

- 溶剂化效应
- 分子的柔性
- 打分函数

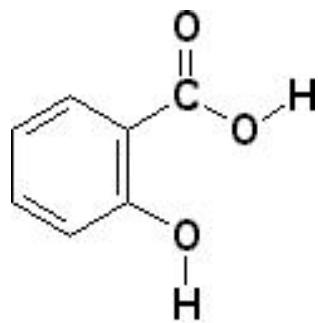


吉祥如意

传统的药物开发方法



- 经验的有效天然产物

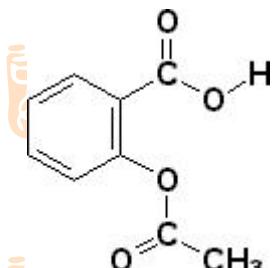
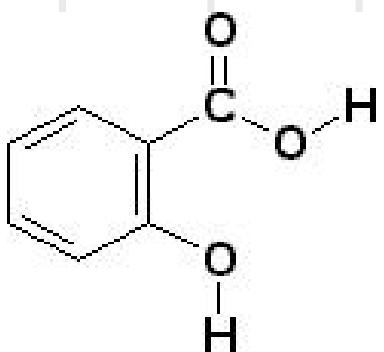


- 分离活性物质

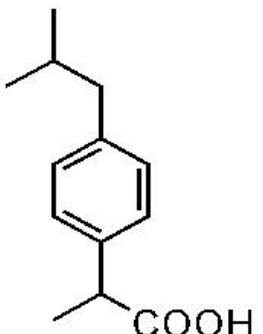


吉比特

- 合成化合物



Aspirin



Ibuprofen

布洛芬是公认的儿童首选抗炎药。



- 化合物的修饰
(更有效,降低副作用)

吉祥如意

药物设计与发现

- drug **targets** (usually proteins)
- binding of **ligands**
-
- “rational” drug design
- (benefits = saved time and **\$\$\$\$**)



基于靶点的药物开发方法

- 区别在哪里？
- 药物开发从疾病入手 (而不是已有的治疗方法)
- 应用疾病模型去寻找可能的药物靶点

NEW and IMPROVED!

现代的药物开发方法

疾病 → 生物学模型界定的靶点



高通量（虚拟）筛选



发现先导化合物（亲和力高，有修改潜力）



亲和力优化、药代性质优化



安全性评价、临床实验



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祥
医

现状

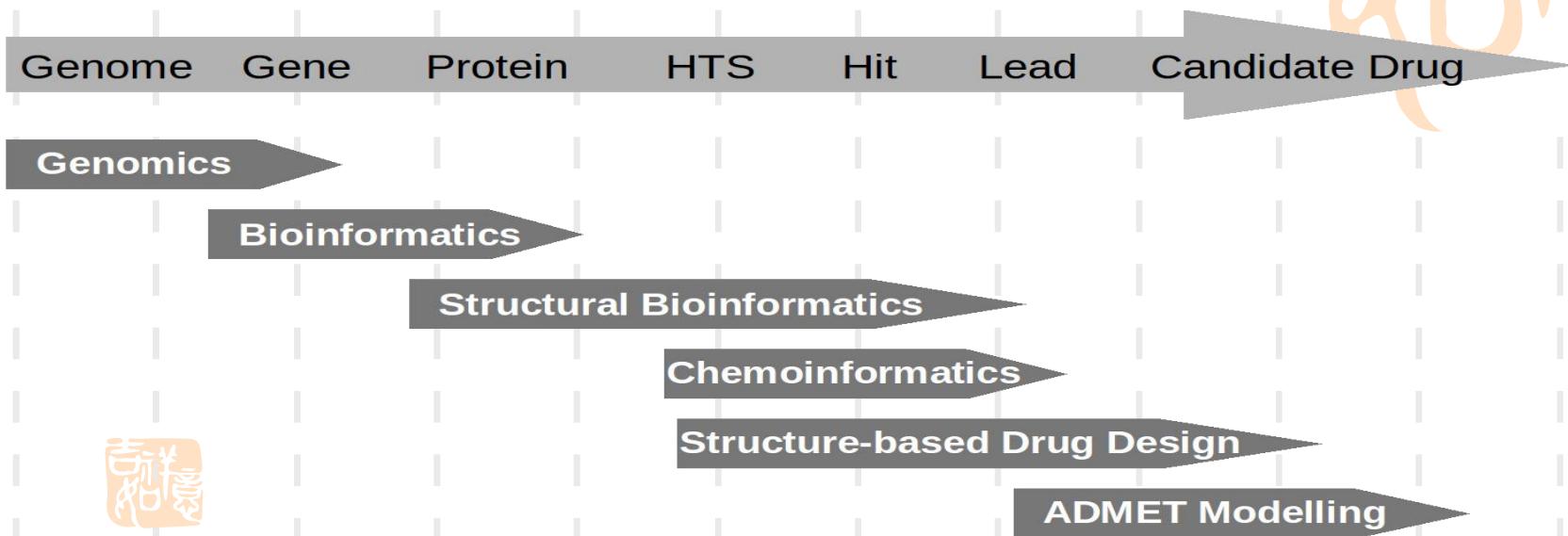
- 超过90% 的药物不能通过临床实验而被枪毙



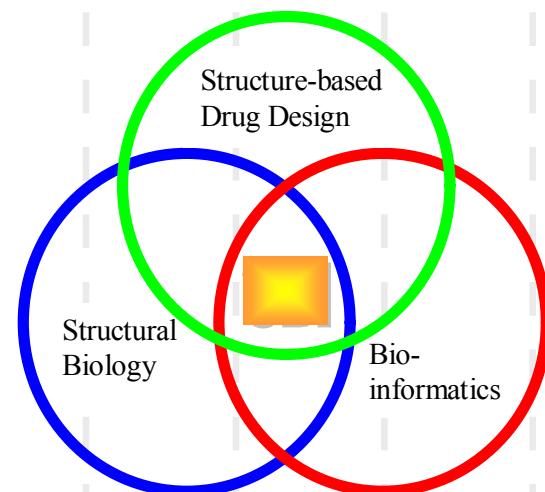
- 平均一款全新药物的研发耗资超过数亿美元，耗时12年



结构生物信息学对药物开发的影响



Speeds up key steps in DD process by combining aspects of bioinformatics, structural biology, and structure-based drug design



吉祥如意

谢谢

