碱基修饰对RNA三级结构的影响研习

Get to know the Roles of modified nucleosides in RNA 3D structure

Group18

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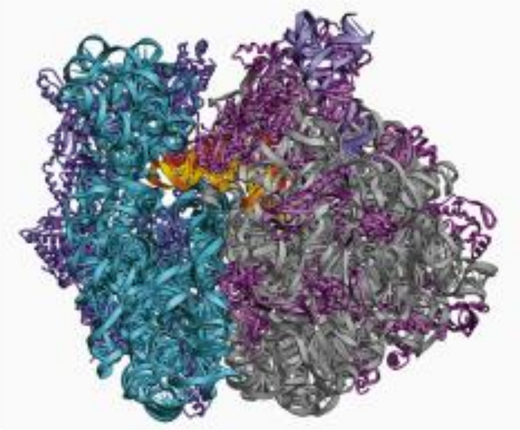
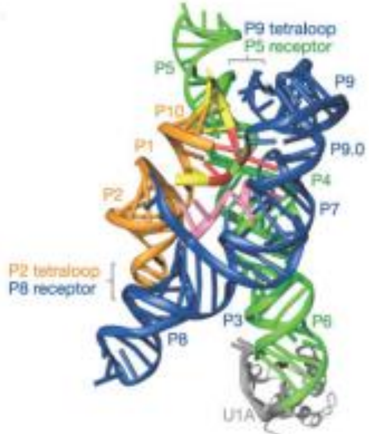
提纲

1. 背景
    - RNA三级结构是功能的基础
    - 核酸碱基修饰
    - 核酸碱基修饰对RNA三级结构的影响
    - 研究意义
2. 研习方案
3. 数据检索
    - PDB数据库的使用
4. 数据处理
    - PDB-viewer
    - Chimera

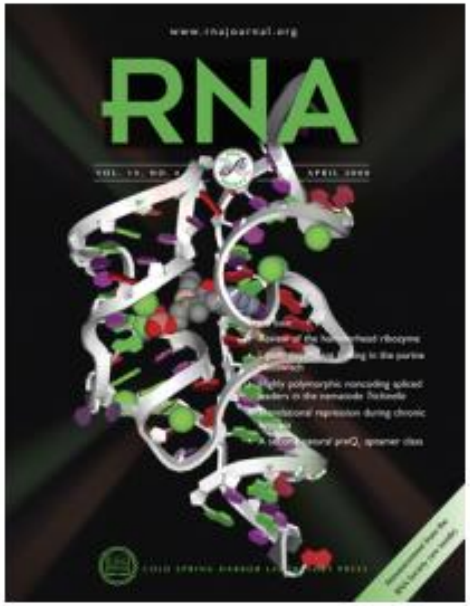
功能型RNA范例



rRNA



Group I Intron

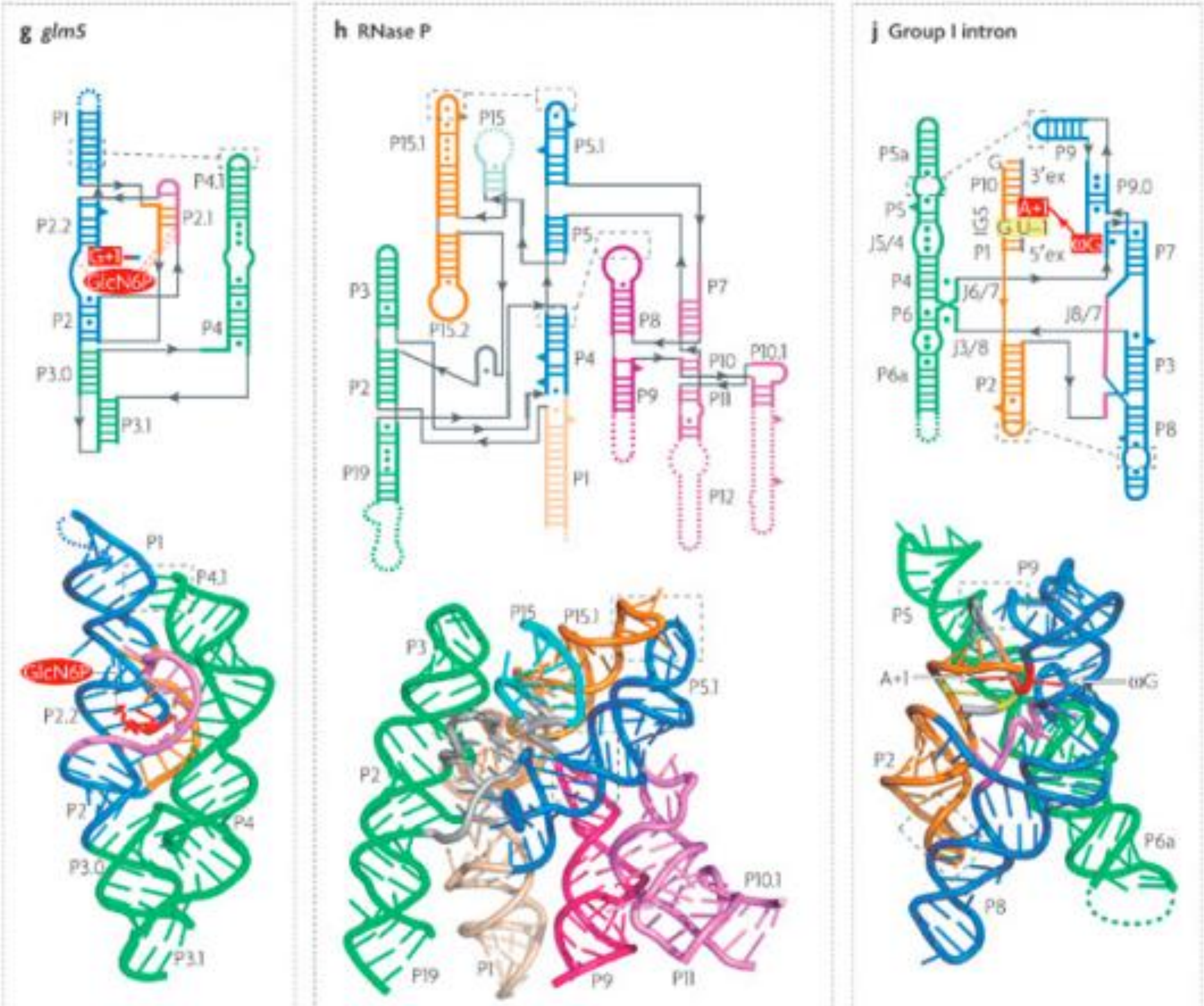


Riboswitch

SRP

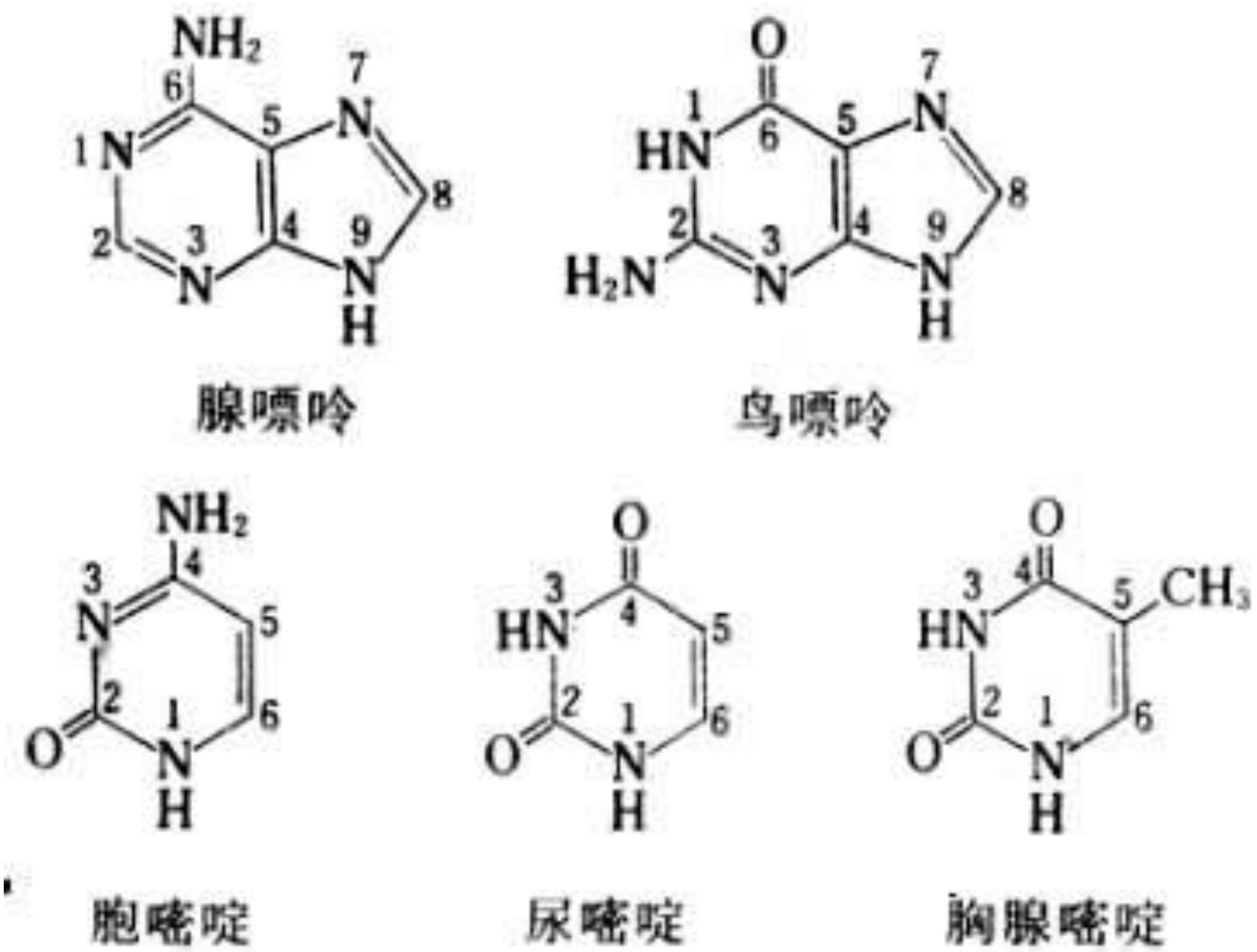
tRNA

功能RNA结构的形成



Serganov & Patel, Nature Reviews Genetics,2007

主要碱基结构式

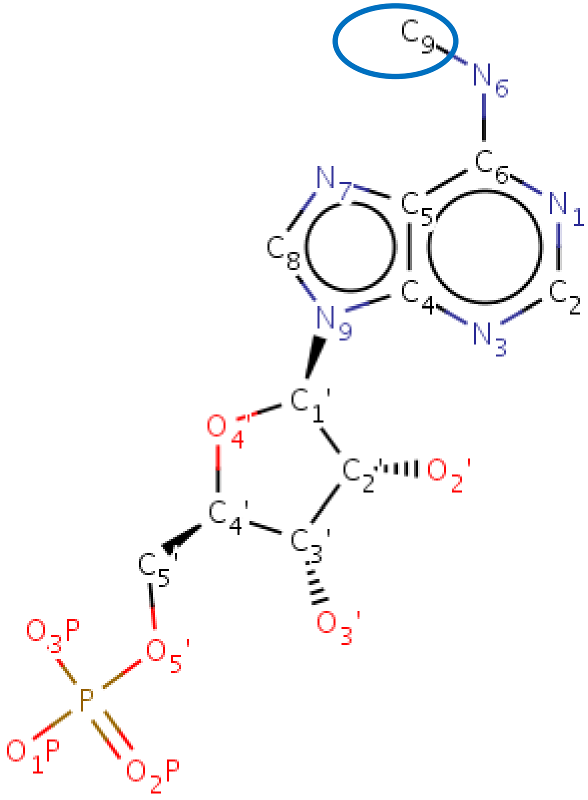


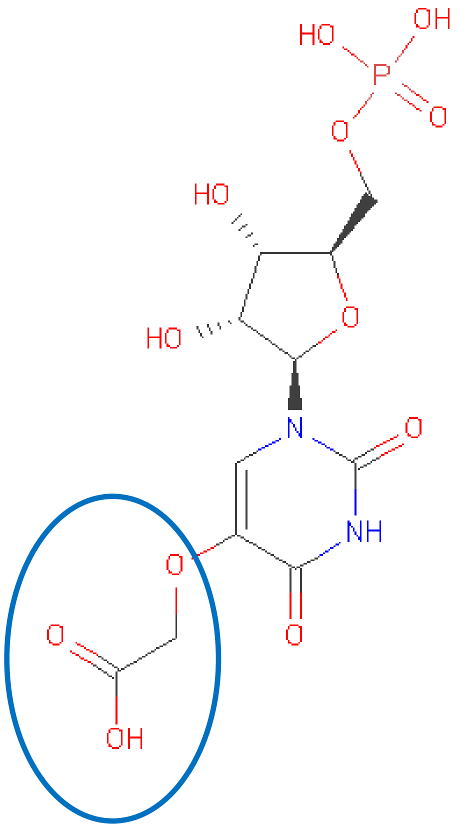
腺嘌呤　鸟嘌呤

胞嘧啶　尿嘧啶　胸腺嘧啶

图 1　5 种主要碱基的结构式

碱基修饰分子结构示例

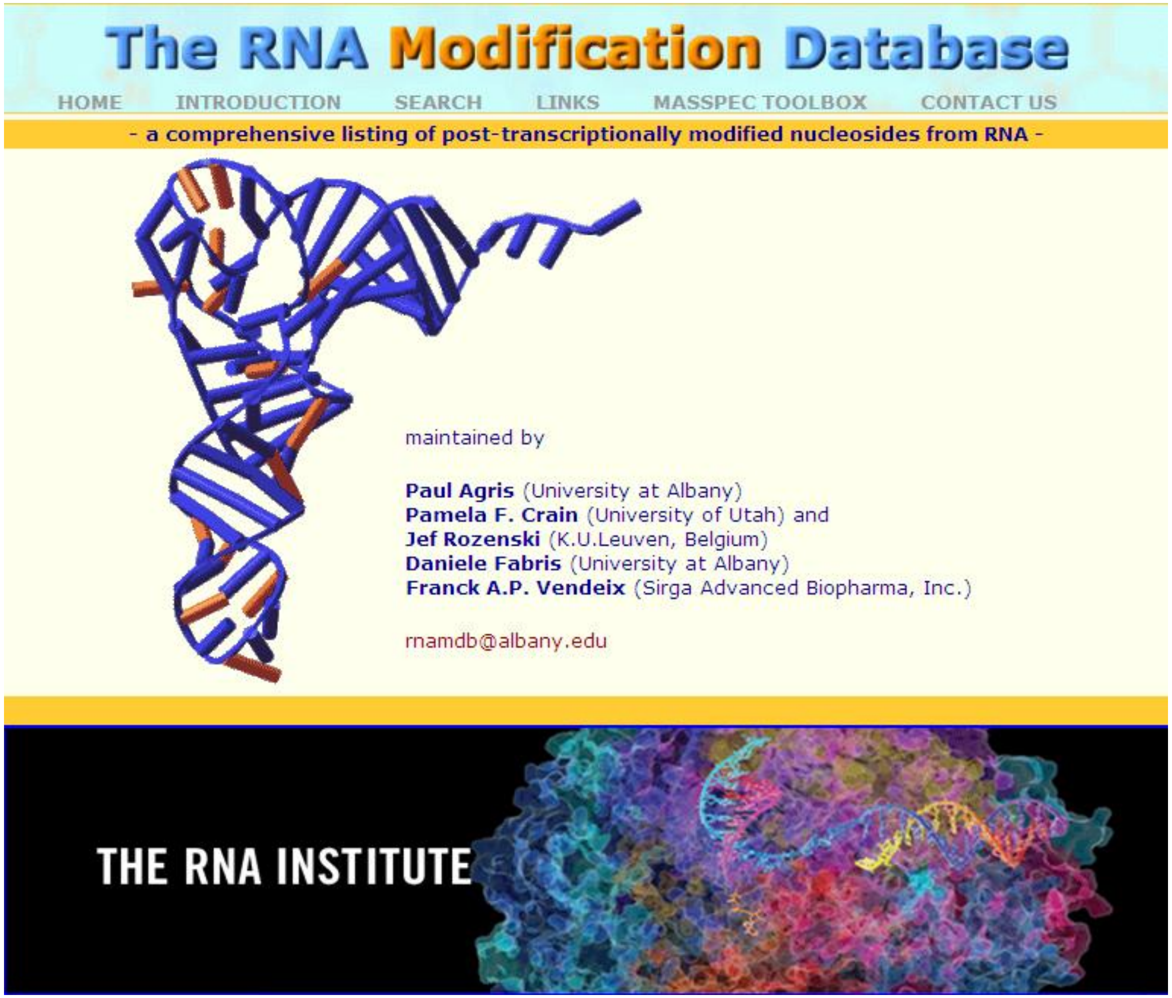




6-methyladenine(6mz)

uridine-5-oxyacetic(cmo)

RNA修饰数据库



The RNA Modification Database

- a comprehensive listing of post-transcriptionally modified nucleosides from RNA -

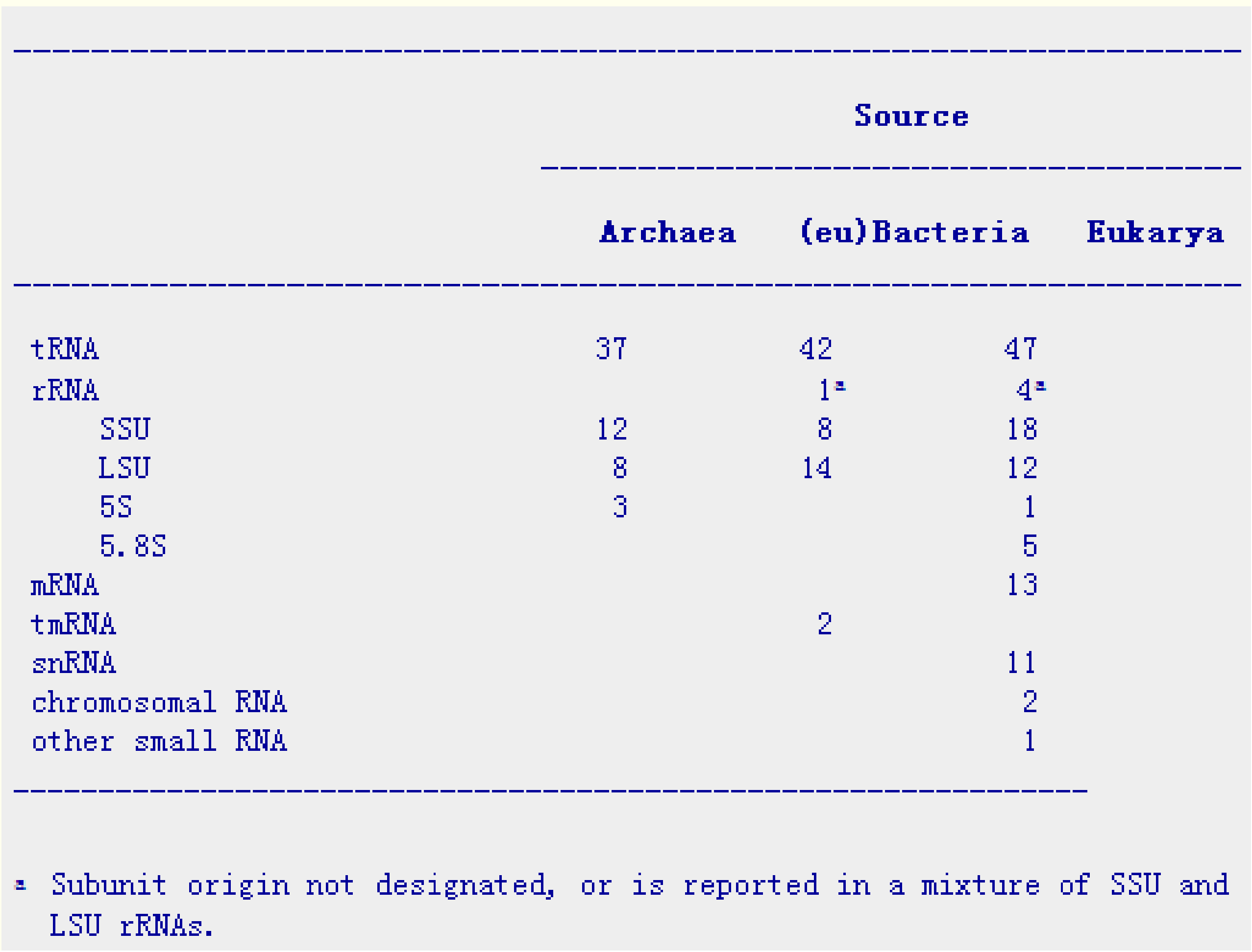
maintained by

Paul Agris (University at Albany)
Pamela F. Crain (University of Utah) and
Jef Rozenski (K.U.Leuven, Belgium)
Daniele Fabris (University at Albany)
Franck A.P. Vendeix (Sirga Advanced Biopharma, Inc.)

rnamdb@albany.edu

http://rna-mdb.cas.albany.edu/RNAmods/

核糖核苷酸修饰在不同RNA中分布



	Source		
	Archaea	(eu)Bacteria	Eukarya
tRNA	37	42	47
rRNA		1*	4*
SSU	12	8	18
LSU	8	14	12
5S	3		1
5.8S			5
mRNA			13
tmRNA		2	
snRNA			11
chromosomal RNA			2
other small RNA			1

* Subunit origin not designated, or is reported in a mixture of SSU and LSU rRNAs.

核酸碱基修饰对RNA三级结构的影响

- 修饰对RNA结构和动力学的影响？
- 单个RNA分子中研究不同修饰的相互作用的高分辨率的RNA结构 （少）

研究意义

- 使人们重新认识RNA结构的3–D构象。
- 有利于合理掌握RNA的结构从而控制其活性，利用RNA 分子设计小分子药物，以及设计可根据使用者指定的方式而改变结构的RNA 传感器等。
- 本研究兴趣虽然不能直接找到RNA三级结构形成规则，但是可以从影响RNA三级结构的因素出发，为揭示问题提供些线索。

研习方法

- 在PDB数据库中寻找存在N6-甲基腺苷(m6A，N6-methyladenosine)配基的RNA分子结构，然后寻找相应的未修饰RNA分子结构
- 使用chimera，pymol，PDB-viewer等软件查看同一种RNA被修饰前后结构是否有变化

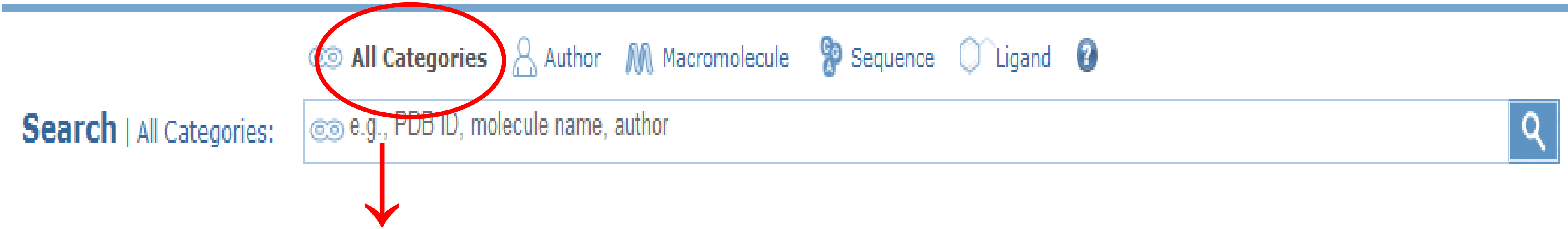
PDB数据库的使用

- 高级检索
- Ligand search

http://www.rcsb.org/pdb/home/home.do

直接检索

--PDB结构文件出现的关键字或其组合

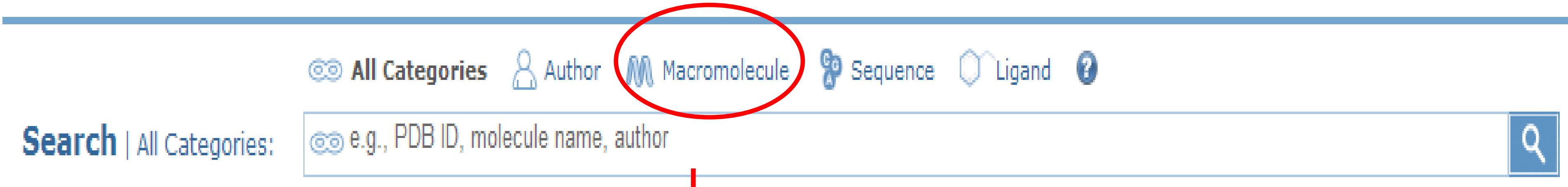


默认检索模式：

1. PDB ID：4个字符组成 每一个新结构对应一个PDB ID，字符无特殊含义
2. 关键词：出现在mmCIF 格式的结构数据文件中的词
3. AND OR NOT 以及 “ ” （）的使用

直接检索

--PDB结构文件出现的关键字或其组合

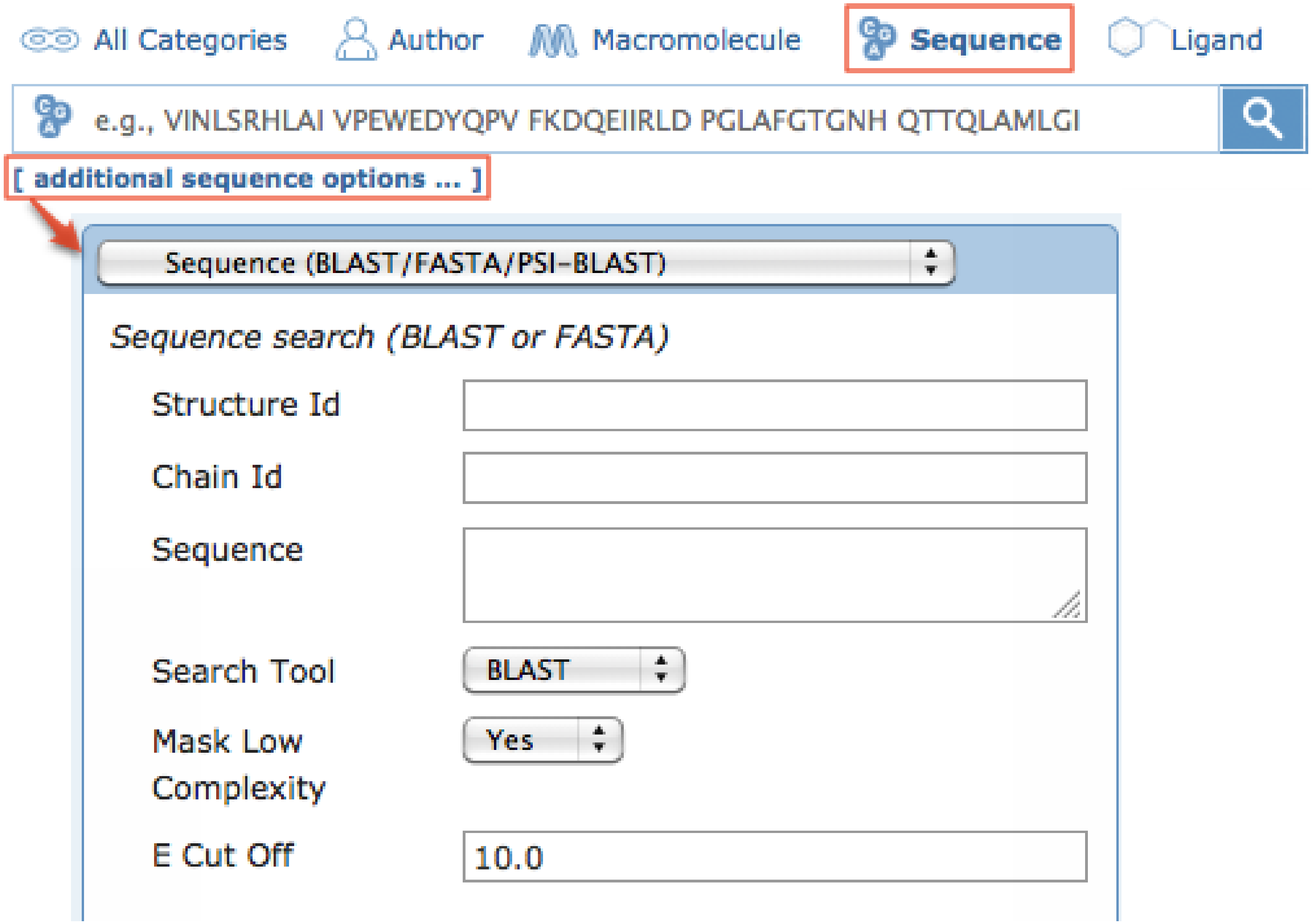


生物大分子

1. 可以检索由其他序列综合数据库，如uniprot，定义的生物大分子如Hemoglobin subunit alpha
2. 通过检索，可以得到该分子在不同物种中的结构数据，并都与uniprot有交叉链接

直接检索

--PDB结构文件出现的关键字或其组合



e.g., VINLSRHLAI VPEWEDYQPV FKDQEIIRLD PGLAFGTGNH QTTQLAMLGI

Sequence (BLAST/FASTA/PSI-BLAST)

Sequence search (BLAST or FASTA)

Structure Id

Chain Id

Sequence

Search Tool: BLAST

Mask Low Complexity: Yes

E Cut Off: 10.0

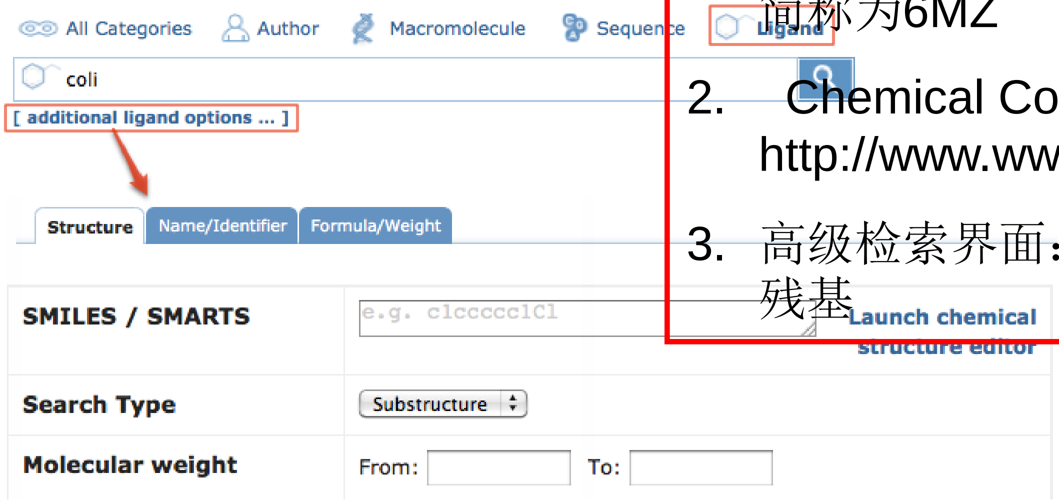
直接检索

--PDB结构文件出现的关键字或其组合

Search | All Categories: e.g., PDB ID, molecule name, author

小分子残基：

1. 小分子或其三个字母的简称含义，如N6-METHYLADENOSINE-5‘-MONOPHOSPHATE，简称为6MZ
2. Chemical Component Dictionary：http://www.wwpdb.org/ccd.html
3. 高级检索界面：通过化学结构、名字和分子式检索残基



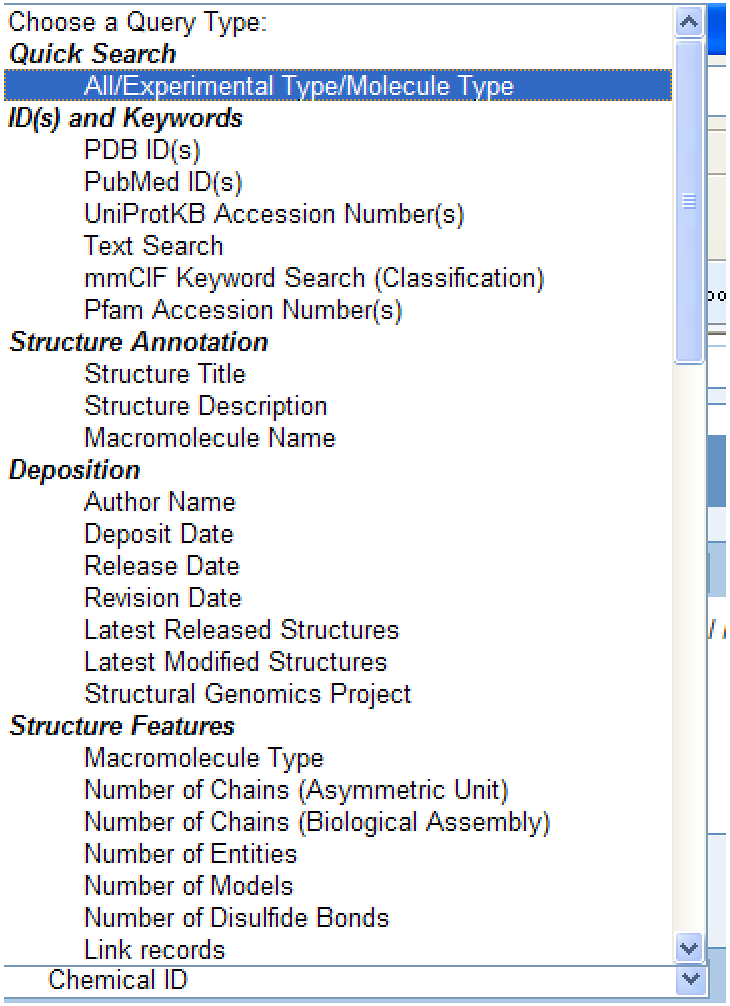
coli

SMILES / SMARTS: e.g. c1ccccc1Cl

Search Type: Substructure

Molecular weight From: To:

高级检索



Choose a Query Type:

Quick Search

- All/Experimental Type/Molecule Type

ID(s) and Keywords

- PDB ID(s)
- PubMed ID(s)
- UniProtKB Accession Number(s)
- Text Search
- mmCIF Keyword Search (Classification)
- Pfam Accession Number(s)

Structure Annotation

- Structure Title
- Structure Description
- Macromolecule Name

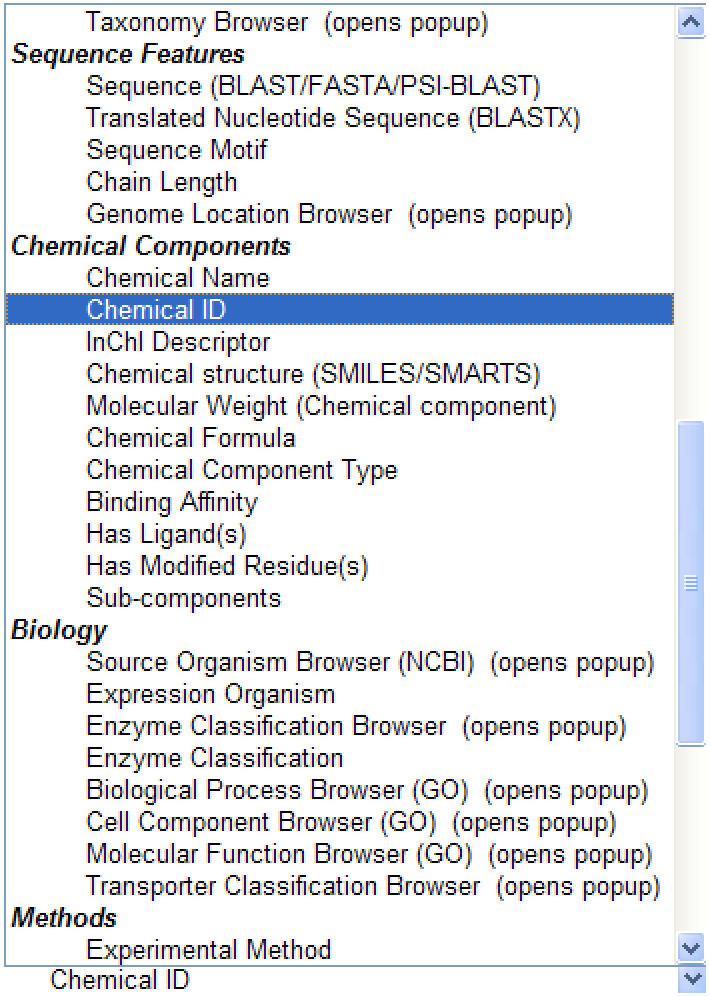
Deposition

- Author Name
- Deposit Date
- Release Date
- Revision Date
- Latest Released Structures
- Latest Modified Structures
- Structural Genomics Project

Structure Features

- Macromolecule Type
- Number of Chains (Asymmetric Unit)
- Number of Chains (Biological Assembly)
- Number of Entities
- Number of Models
- Number of Disulfide Bonds
- Link records

Chemical ID



- Taxonomy Browser (opens popup)

Sequence Features

- Sequence (BLAST/FASTA/PSI-BLAST)
- Translated Nucleotide Sequence (BLASTX)
- Sequence Motif
- Chain Length
- Genome Location Browser (opens popup)

Chemical Components

- Chemical Name
- Chemical ID
- InChI Descriptor
- Chemical structure (SMILES/SMARTS)
- Molecular Weight (Chemical component)
- Chemical Formula
- Chemical Component Type
- Binding Affinity
- Has Ligand(s)
- Has Modified Residue(s)
- Sub-components

Biology

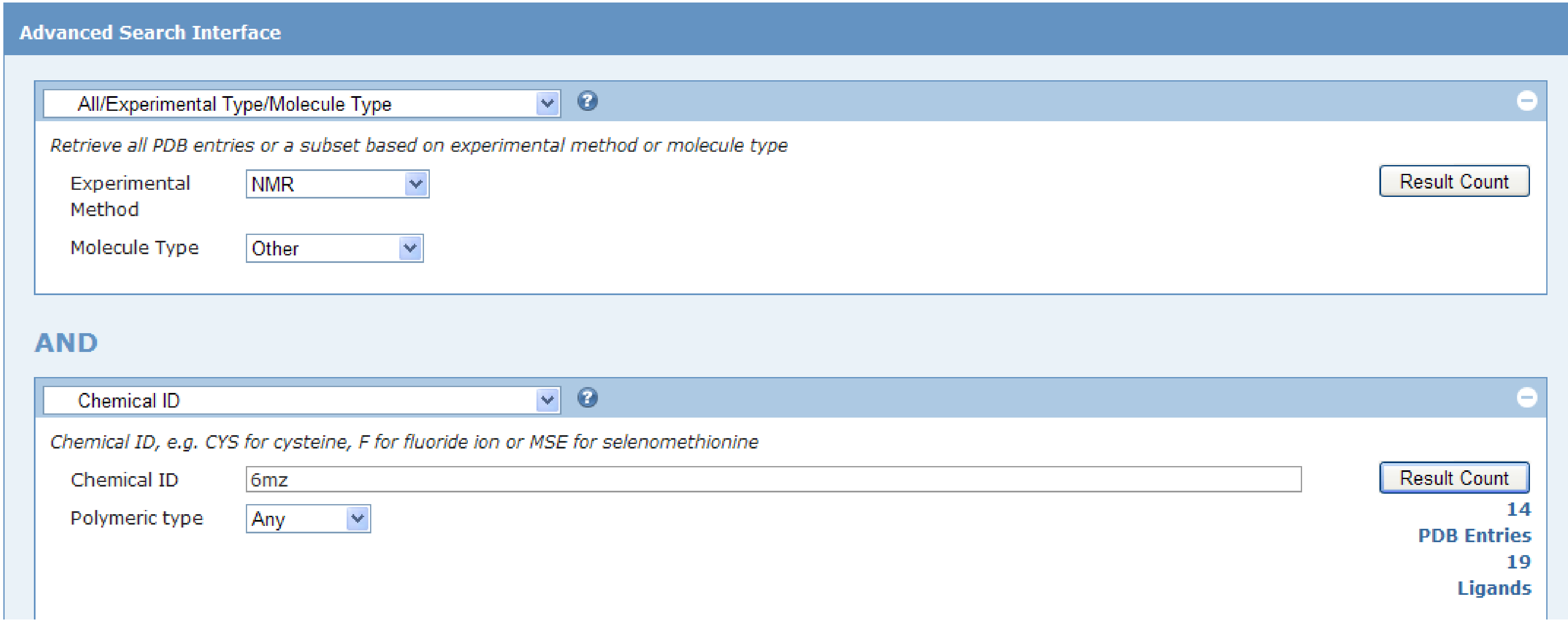
- Source Organism Browser (NCBI) (opens popup)
- Expression Organism
- Enzyme Classification Browser (opens popup)
- Enzyme Classification
- Biological Process Browser (GO) (opens popup)
- Cell Component Browser (GO) (opens popup)
- Molecular Function Browser (GO) (opens popup)
- Transporter Classification Browser (opens popup)

Methods

- Experimental Method

Chemical ID

高级检索



Advanced Search Interface

All/Experimental Type/Molecule Type

Retrieve all PDB entries or a subset based on experimental method or molecule type

Experimental Method: NMR

Molecule Type: Other

AND

Chemical ID

Chemical ID, e.g. CYS for cysteine, F for fluoride ion or MSE for selenomethionine

Chemical ID: 6mz

Polymeric type: Any

14
PDB Entries
19
Ligands

PDB数据库检索结果

- NMR Solution Structure of the Anticodon of E.coli TRNA-VAL3
- 2JR4: without modification（缺）
- 2JSR: with 1 modification, 6mz
- 2JRQ: with 1 modification, cmo
- 2JRG: with 2 modifications, 6mz and cmo

PDB-viewer的使用

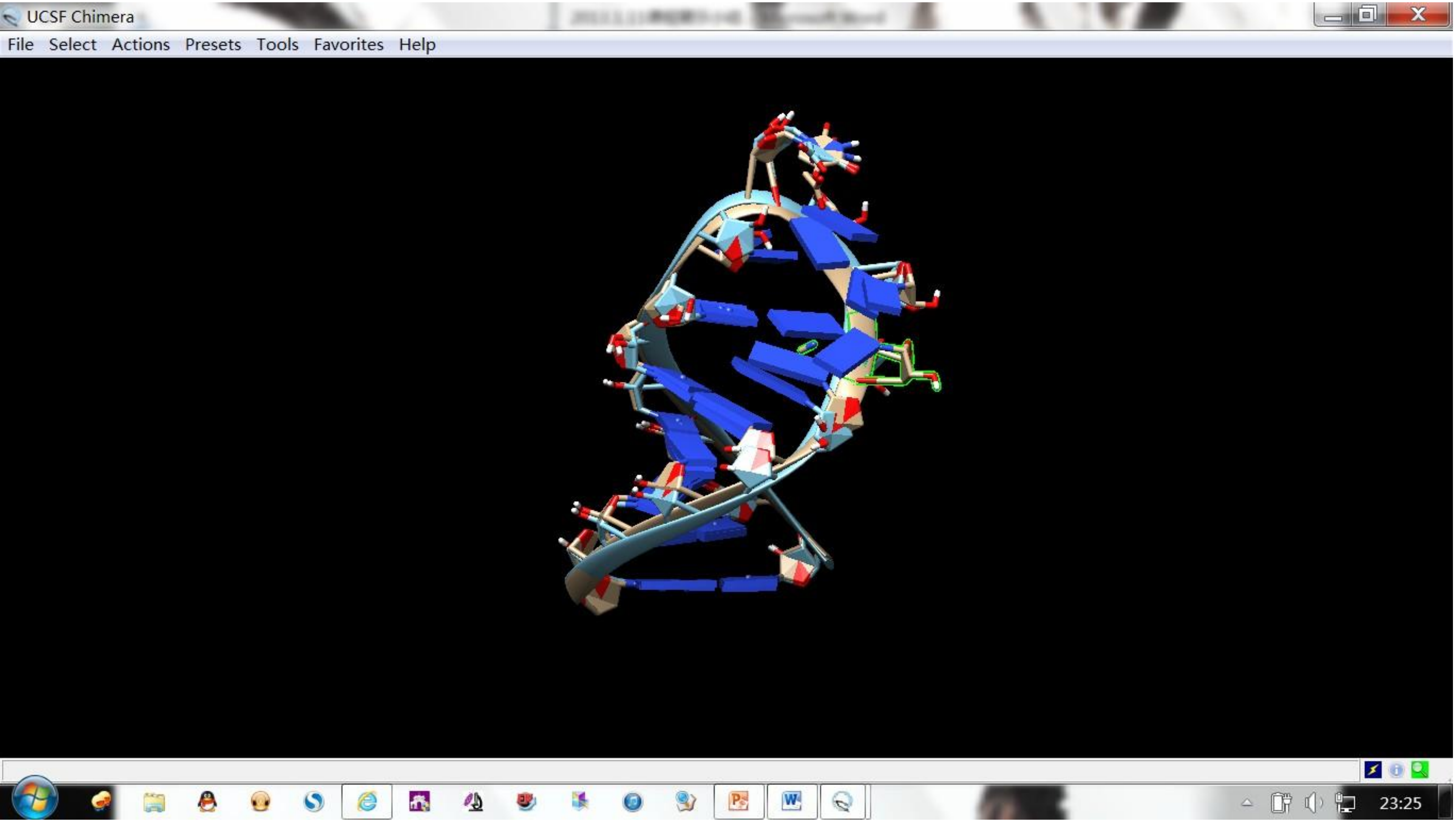
- 使用pdb-viewer查看四个结构，并作两两比对，并归纳结论
- 6MZ 影响程度
  - 2JR4&2JSR
  - 2JRG&2JRQ
- cmo影响程度
  - 2JRG&2JSR
  - 2JR4&2JRQ

PDB-viewer

Chimera

RMSD between 16 atom pairs is 0.912 angstroms

Chimera


UCSF Chimera
File
Select
Actions
Presets
Tools
Favorites
Help
23:25

Anticodon modifications enhanced order in the loop

- m (6)A 37 exhibited high affinities for its cognate and wobble codons GUA and GUG, and for GUU in the A-site of the programmed 30S ribosomal subunit, whereas the unmodified ASL (Val3) UAC bound less strongly to GUA and not at all to GUG and GUU.
- m (6)A 37 bound to all four of the valine codons in the A-site of the ribosome's 30S subunit
- xo (5)U 34-type modifications order the anticodon loop prior to A-site codon binding for an expanded codon reading, possibly reducing an entropic energy barrier to codon binding

http://www.ncbi.nlm.nih.gov/pubmed/18473483

Thanks!