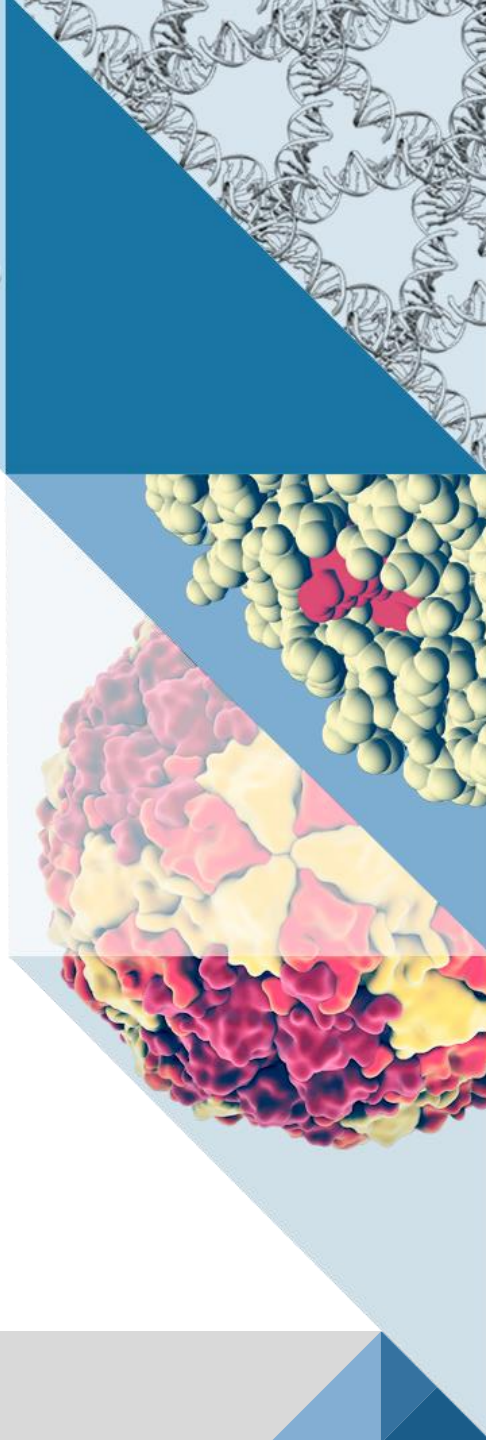
RCSB PDB
PROTEIN DATA BANK



Ligand Validation for the Protein Data Bank

Stephen K. Burley, M.D., D.Phil.
Director, RCSB Protein Data Bank
University Professor and Henry Rutgers Chair
Founding Director, Institute for Quantitative Biomedicine
Member, Rutgers Cancer Institute of New Jersey
Rutgers, The State University of New Jersey

AsCA, Auckland, New Zealand December 4th 2018

Protein Data Bank History (1971-2018)

- PDB 1st Open Access digital data resource in all of biology
- Single global **archive** for protein, DNA, and RNA experimental structures
- Today, Open Access to >146,000 structures
- wwPDB collaboration US (RCSB PDB), EU (PDBe), Japan (PDBJ), and BMRB

WORLDWIDE PDB
PROTEIN DATA BANK

RCSB PDB PROTEIN DATA BANK | BMRB | PDBe Protein Data Bank in Europe | PDBj Protein Data Bank Japan

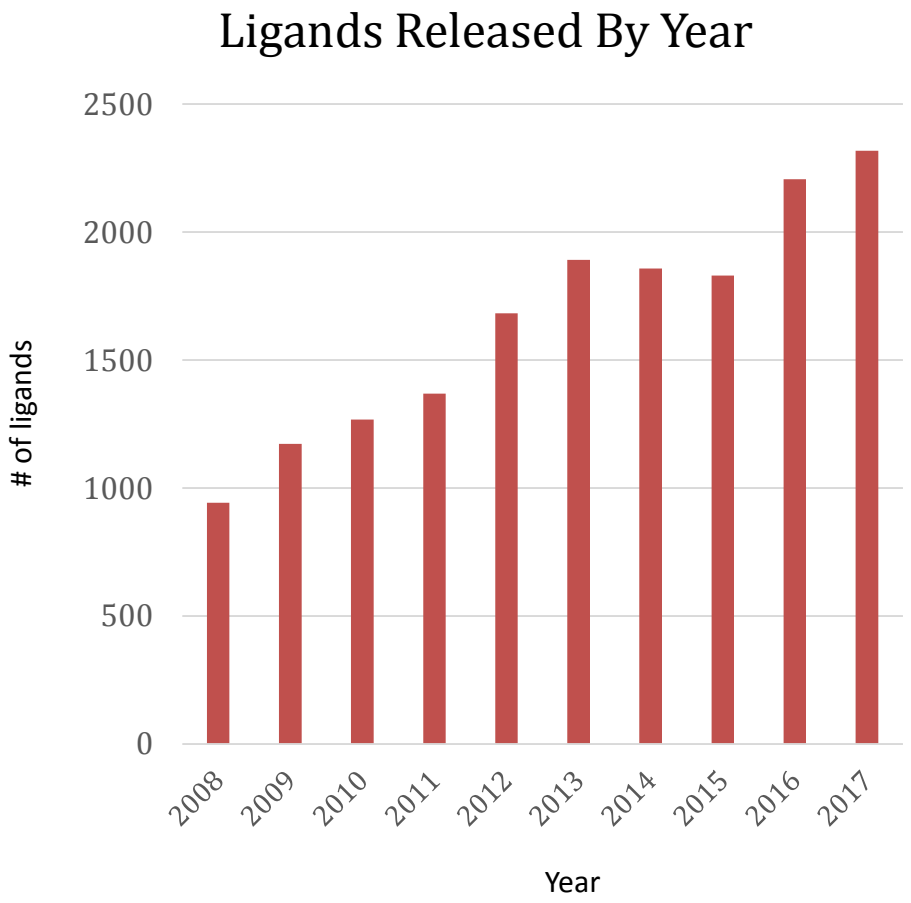
Outline

- wwPDB Chemical Component Dictionary
- Validating and Biocurating PDB Ligands
- Detecting PDB Ligand Outliers
- Correcting PDB Structures
- Impact of PDB on Drug Approvals

wwPDB Chemical Component Dictionary

wwPDB Chemical Component Dictionary

- wwPDB maintained library of all chemical components present in PDB archive
  - >26,400 chemical component definitions
  - 400 additional definitions of amino acid protonation variants
- ~2300 new components added in 2017

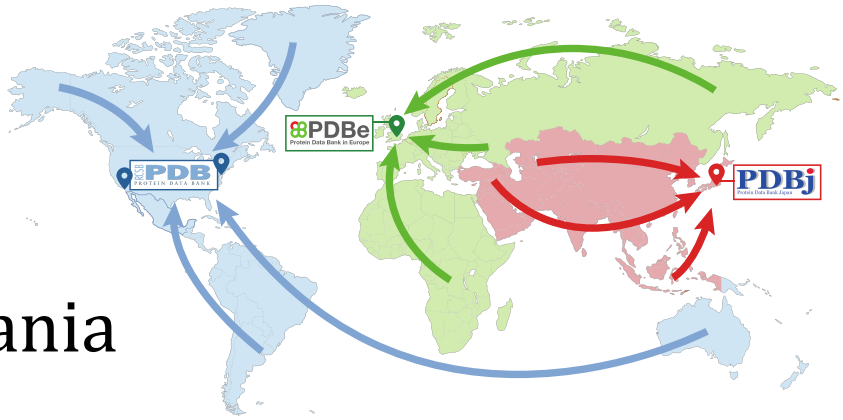


ftp.wwpdb.org/pub/pdb/data/monomers/components.cif

Validating and Biocurating PDB Ligands

wwPDB Deposition/Validation/Biocuration

- 13,049 new structures deposited in 2017
  - RCSB PDB processed 6,208 structures (~85% from US/Canada)
- Workload balanced among wwPDB Partners
  - RCSB PDB: Americas/Oceania
  - PDBe: Europe/Africa
  - PDBj: Asia/Middle East



OneDep Ligand Validation and Biocuration

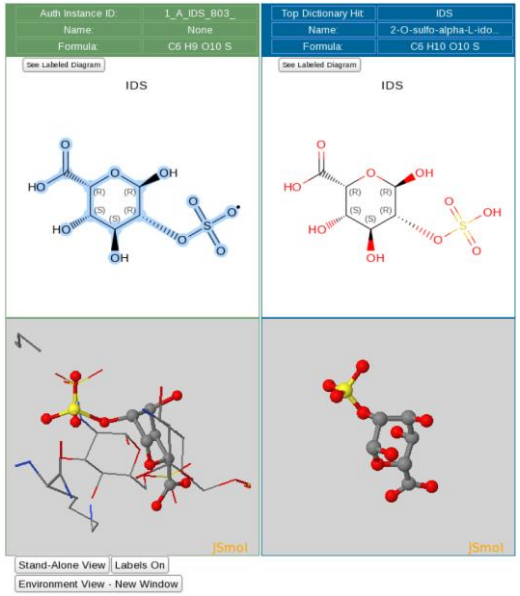
a). Automatic comparison of deposited component and the Chemical Component Dictionary (CCD)

- number of heavy atoms
- number of chiral centers
- chirality
- aromatic flags
- bond order

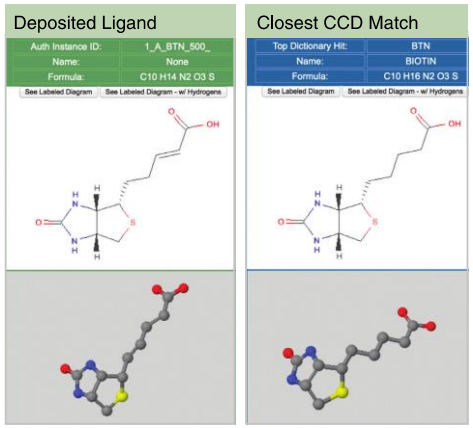
Passed	Instance is a match
Close Match	Analogue to CCD definition Discrepancy with component ID listed or in at least one criteria (not 100% match); manual review needed
No Match	Create new ligand

INSTANCE	TOP HIT	MATCH STATUS	SELECTION ■ ALL	COMPOSITE SCORE	ASSIGNMENT STATUS
1_C_MAN_1079_	BMA	close match	☑	100 / 100 / 100 / n.a. / 100	Not Assigned
1_C_NAG_1074_	NDG	close match	☑	100 / 100 / 100 / n.a. / 100	Not Assigned
1_C_NAG_1076_	NAG	close match	☑	100 / 100 / 80 / n.a. / 100	Not Assigned
1_C_MAN_1080_	MAN	passed	☑	100 / 100 / 100 / n.a. / 100	(MAN)
1_E_MES_1083_	MES	passed	☑	100 / n.a. / n.a. / n.a. / 100	(MES)
1_E_MES_1084_	MES	passed	☑	100 / n.a. / n.a. / n.a. / 100	(MES)

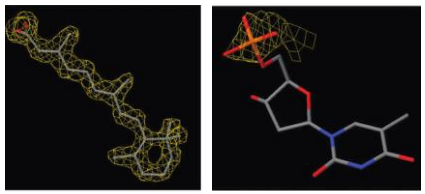
SUPPLEMENTAL INFO: Chiral center C1 has sp2 hybridization instead of sp3



b). 2D and 3D ligand comparison panel

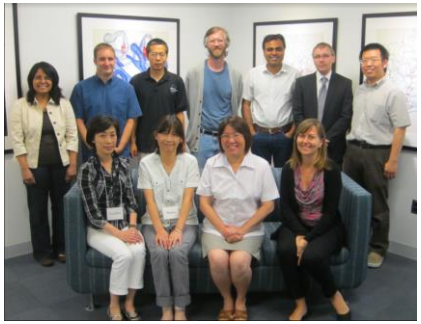


c). Local ligand density display (1.5 sigma omit map)



REA in entry 1CBS with LLDF=1.31 (RSR=0.10, CC=0.95)

TMP in entry 3HW4 with LLDF=6.77 (RSR=0.41, CC=0.70)



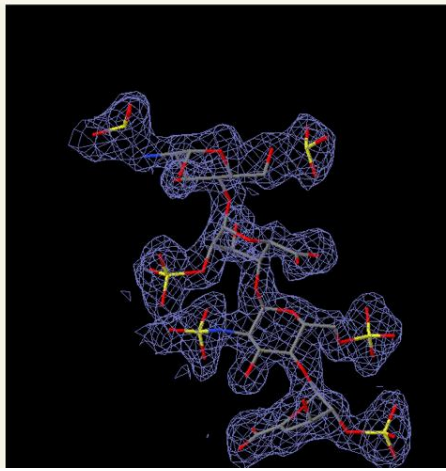
wwPDB Biocurators

Table of local electron density maps for non-polymer chemical components

View in JSMol	Residue Name
σ=2.0 | σ=1.5 | σ=1.0 | σ=0.8	UAP
σ=2.0 | σ=1.5 | σ=1.0 | σ=0.8	SGN
σ=2.0 | σ=1.5 | σ=1.0 | σ=0.8	IDU
σ=2.0 | σ=1.5 | σ=1.0 | σ=0.8	SGN

Table of local electron density omit maps for non-polymer chemical compor

View in JSMol	Residue Name
σ=2.0 | σ=1.5 | σ=1.0 | σ=0.8	UAP
σ=2.0 | σ=1.5 | σ=1.0 | σ=0.8	SGN
σ=2.0 | σ=1.5 | σ=1.0 | σ=0.8	IDU
σ=2.0 | σ=1.5 | σ=1.0 | σ=0.8	SGN



Young *et al*. (2017) *Structure 25*, 536-545.

Principal Ligand Validation Metrics

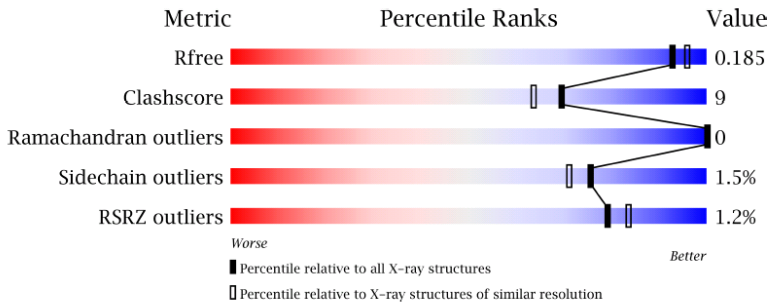
- **Agreement with Known Chemical Geometry**
  - Bond Lengths: RMSZ, # |Z|>2 (ref. CCDC Mogul)
  - Bond Angles: RMSZ, # |Z|>2 (ref. CCDC Mogul)
  - Plus analyses of Chirality, Torsions, and Rings (N.B.: Depends critically on choice of restraints.)

- **Agreement with Experimental Data (|Fobs|)**
  - RSR-Real Space R-factor
  - RSCC-Real Space Correlation Coefficient
  - Plus analyses of B-factors and Occupancy<0.9

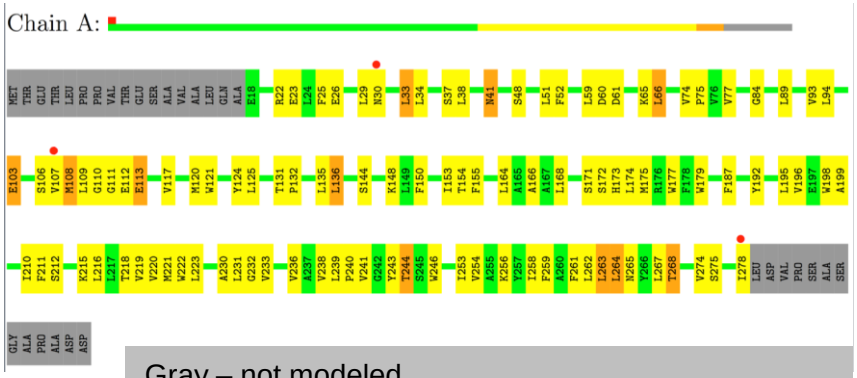
wwPDB Validation Report Version 1

- Detailed validation report based on community norms and input
- Overall quality sliders for 5 key metrics
- “Table 1” summary
- Tabulations of geometrical and experimental issues:
  - Macromolecules
  - Ligands
- Now required by some journals for manuscript review

Overall Quality Summary



Residue Plots

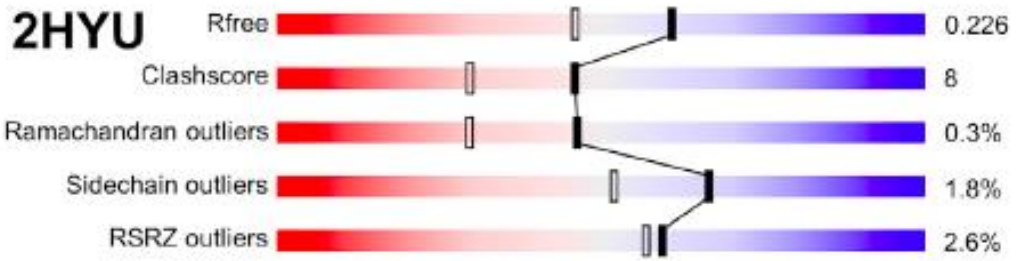


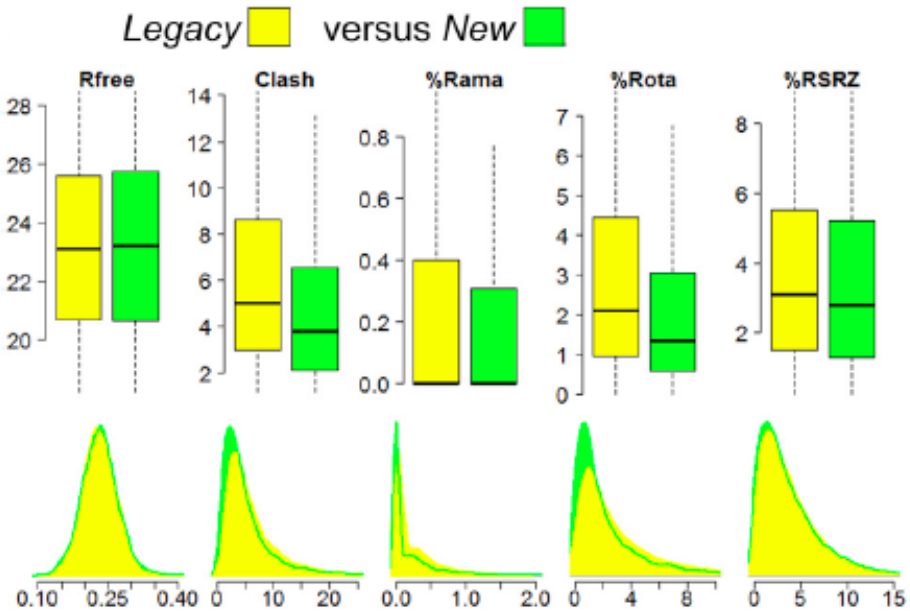
Gray – not modeled
Green, yellow, orange, red – 0,1,2, 3 or more issues
Red dot – poor fit to electron density

Gore *et al*. (2017) *Structure 25*, 1916-1927.

Version 1 Helped Improve Structure Quality

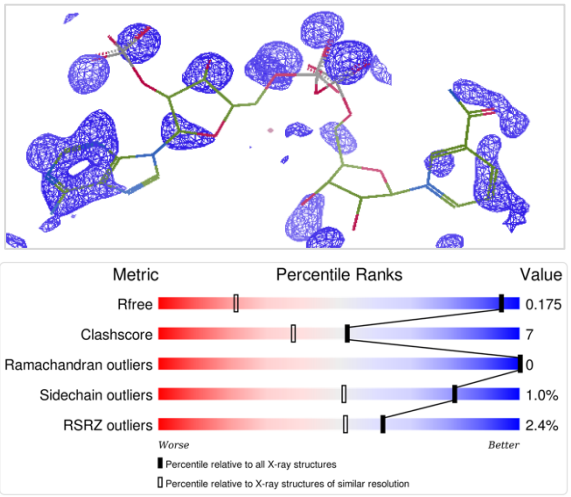
- Structures archived with *Legacy* (2012-2013) *vs*. *New* (2014-2015) Validation Systems compared
- Clashscores, Rotamers, Ramachandran violations, RSR Z-scores all improved!
- Median Rfree rose slightly



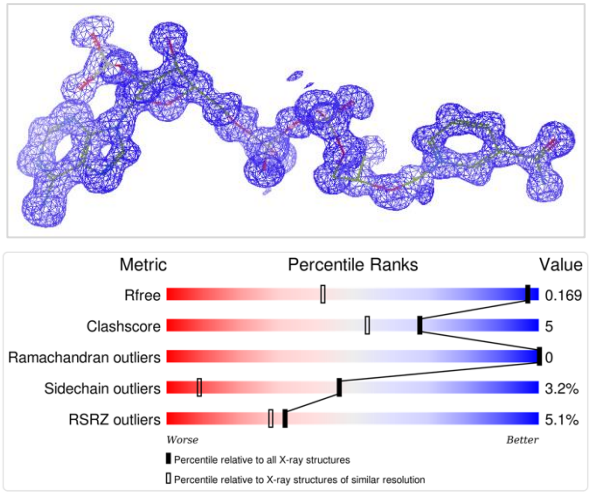


Version 1.0 No Impact on Ligand Quality

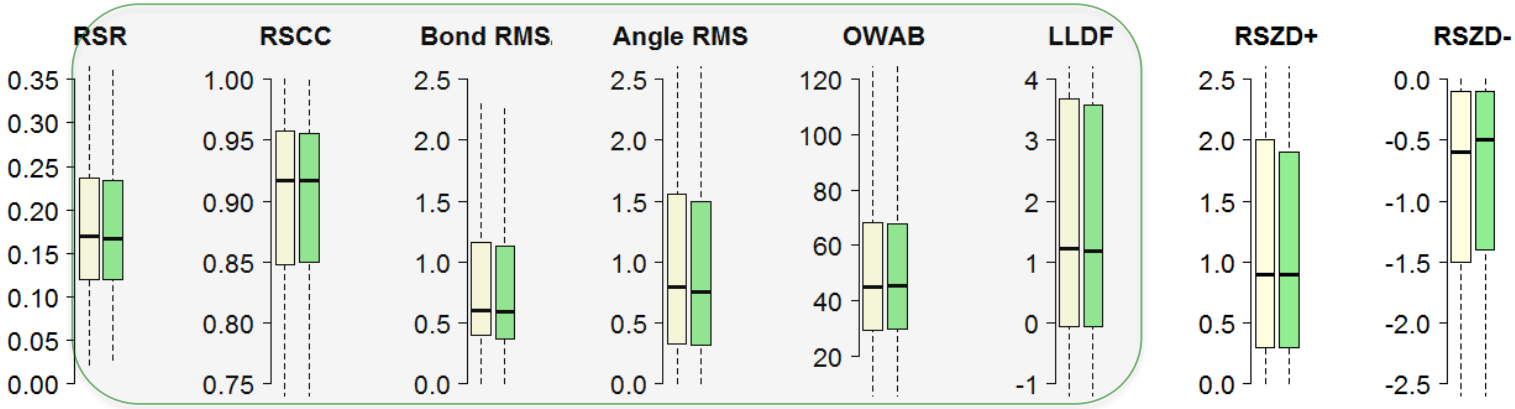
NADP in PDB 1ZK4:
2|Fo|-|Fc| map at 1σ
Schlieben et al., 2005



NADP in PDB 2FZD:
2|Fo|-|Fc| map at 1σ
Steuber et al., 2006



Overall Ligand Quality: *Legacy* 2012-2013 (yellow) *vs. New* 2014-2015 (green)



wwPDB Ligand Validation Workshop

Meeting Objectives: To bring together co-crystal structure determination experts from Academe and Industry with Crystallography and Computational Chemistry Software Developers to discuss, develop, and recommend:

- Best practices PDB deposition/validation of co-crystal structures
- Editorial/Refereeing/Publication standards for co-crystal structures
- Improvements in ligand representation across the PDB Archive
- Version 2 coming in 2019

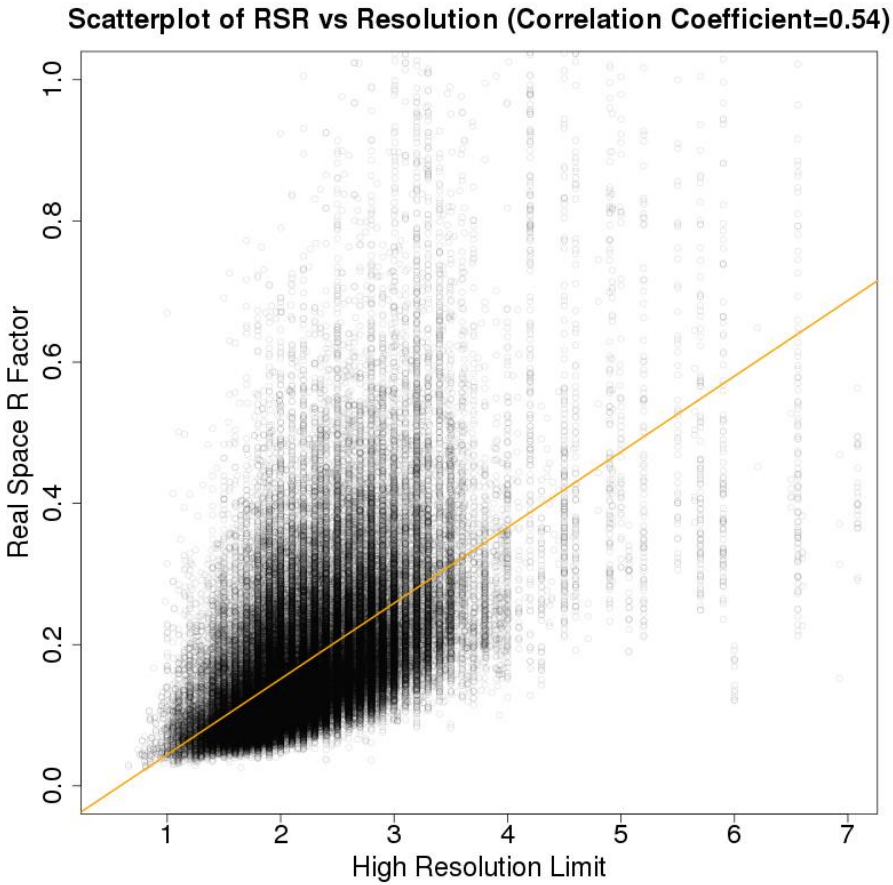
Adams *et al*. (2016) *Structure 24,* 502-408.

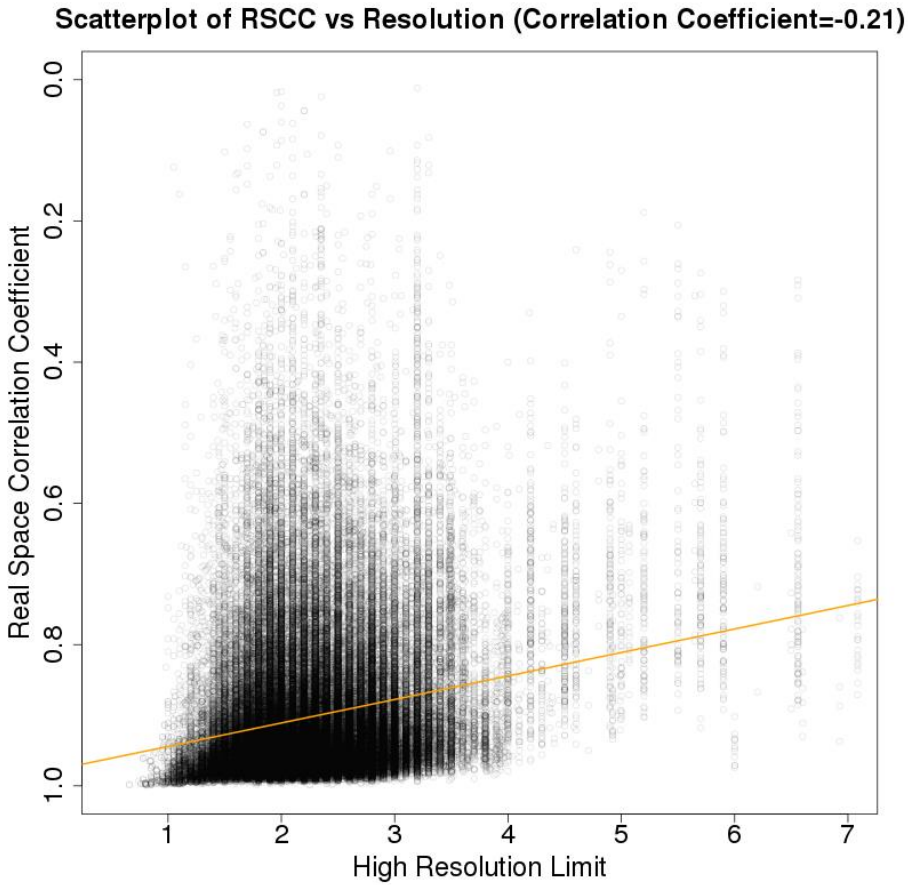
Detecting PDB Ligand Outliers

Identifying Outliers for Chemical Geometry

- For most PDB ligand structures, agreement with known chemical geometry depends almost entirely on refinement restraints and weighting schemes
- wwPDB Validation Report uses CCDC Mogul to identify outliers
- Available options:
  - Exact matches with the Cambridge Structural Database (~10% of the CCD)
  - Phenix AM1
  - CCP4 Acedrg
  - Higher level semi-empirical QM calculations

Identifying Outliers for RSR and RSCC





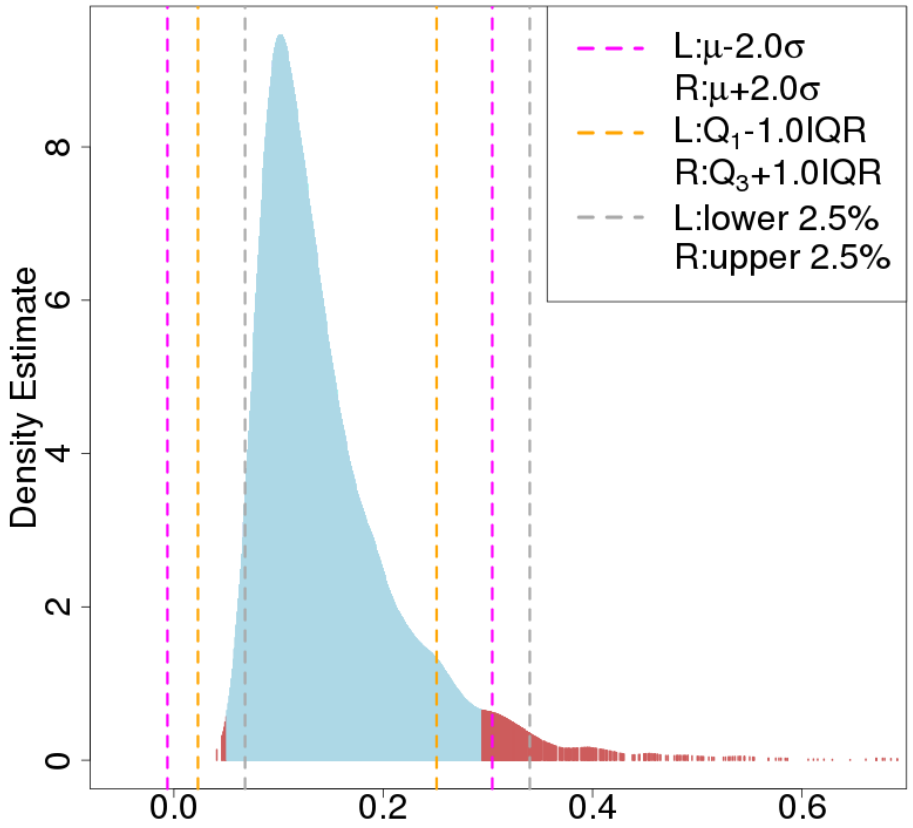
RSR and RSCC are Resolution Dependent!

109,368 Organic Ligands; MW=240-1000/Occup.>0.9

Shao *et al*. (2018) *Scientific Data,* in the press.

Analyzing RSR for Outliers (1.9-2.0A)

- Distribution of RSR values is not normal (skewed and bounded)
- Standard analyses using % cut-off, IQR, or Sigma cut-off entirely inappropriate
- Most-Probable-Range (95% blue) more appropriate

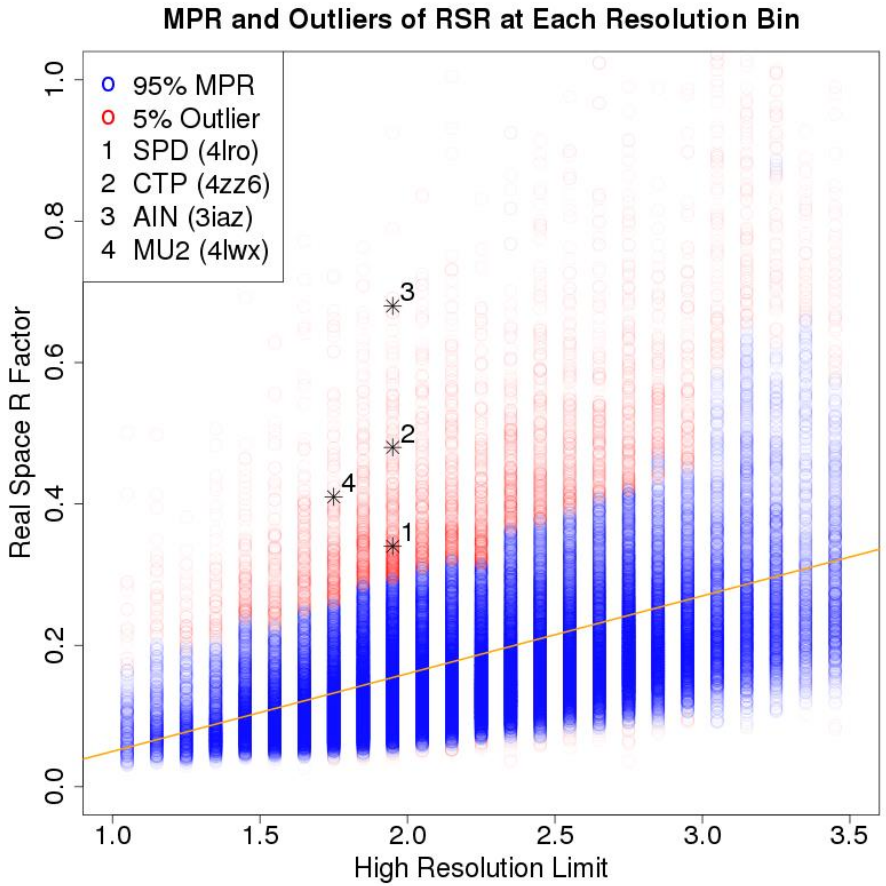


95% MPR(RSR)=0.040-0.295
(>10,000 ligands)

Shao *et al*. (2018) *Scientific Data,* in the press.

Analyzing RSR for Outliers (1.0-3.5A)

- 95% MPR(RSR) ranges vary with resolution
- This approach would have detected some notorious cases*
  1. 4lro(SPD): RSR=0.34
  2. 4zz6(CTP): RSR=0.48
  3. 3iaz(AIN): RSR=0.68
  4. 4lwx(MU2): RSR=0.41



*Wlodawer *et al.* (2018) *FEBS Journal 285*, 444-466.

Shao *et al*. (2018) *Scientific Data,* in the press.

Correcting PDB Structures

Coordinate Replacement by Depositor

- PDB archive is now fully versioned
- Starting in 2019, the Depositor of Record will be able to replace atomic coordinates for co-crystal structures using OneDep
- Your original PDB ID will be preserved!
- Numbers will be limited initially to ensure that RCSB PDB, PDBe, and PDBj do not get overwhelmed with corrected structures

Impact of PDB on Drug Approvals

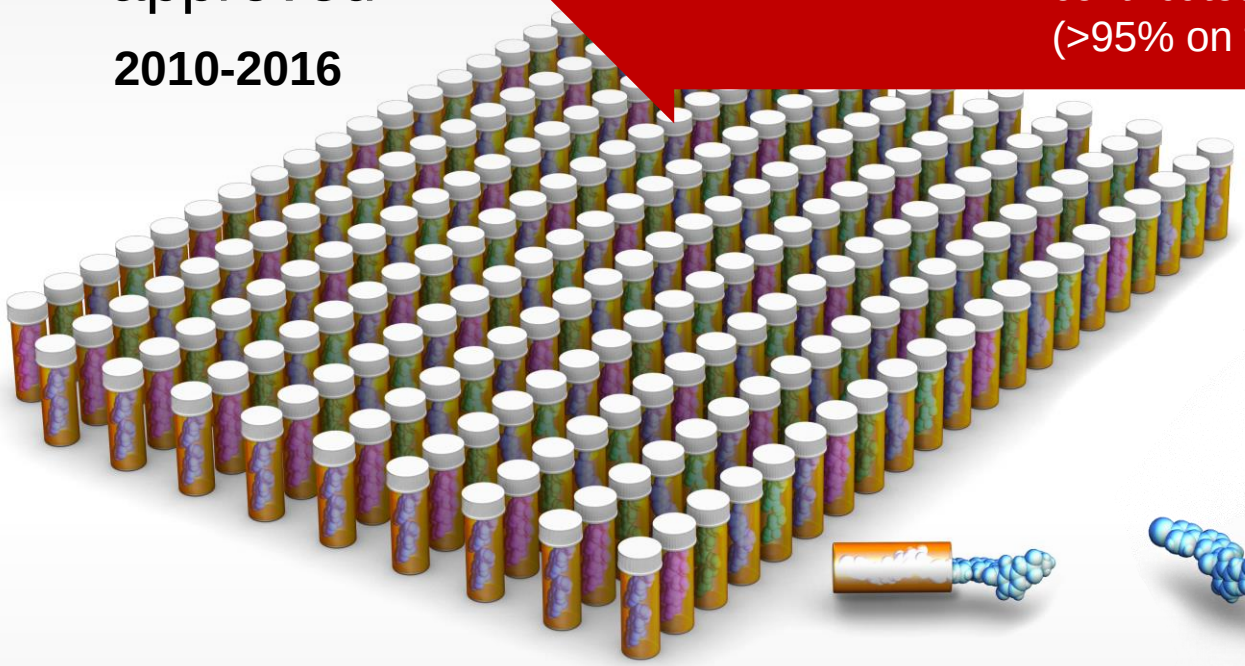
Impact of PDB on Drug Approvals[1]

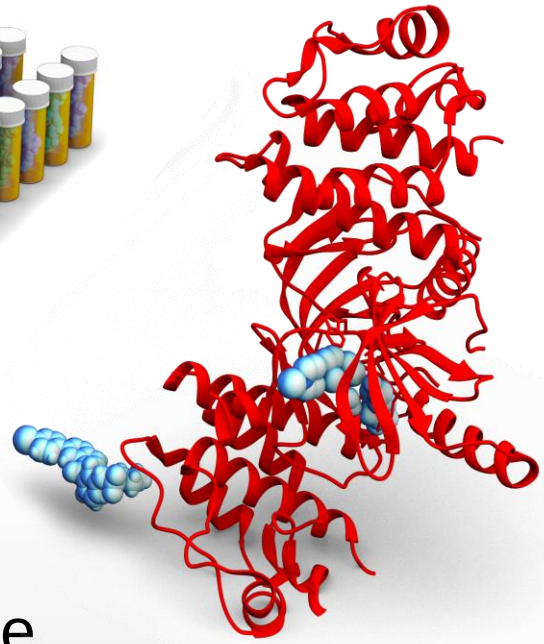
2000-2016

210 NEW DRUGS approved

2010-2016

>$100 BILLION **of NIH funding** contributed to these approvals (>95% on targets)[2]





B-Raf Kinase complex with Vemurafenib ***PDB ID 3og7***

5,914 PDB Structures contributed to **184** of these drug approvals

1. Westbrook and Burley (2018) *Structure,* in the press.
2. Galkina Cleary *et al.* (2018) *PNAS 115*, 2329-2334.

Acknowledgements

RCSB PDB PROTEIN DATA BANK

RCSB.ORG

info@rcsb.org

Funding

RCSB PDB is funded by a grant (DBI-1338415) from the National Science Foundation, the National Cancer Institute, the National Institute of General Medical Sciences and the US Department of Energy.

Management

The RCSB PDB is managed by:

RUTGERS UC San Diego SDSC SAN DIEGO SUPERCOMPUTER CENTER

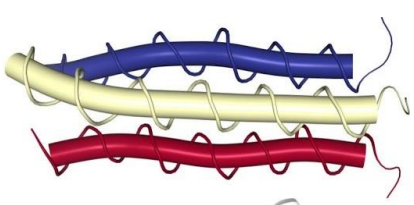
Follow us

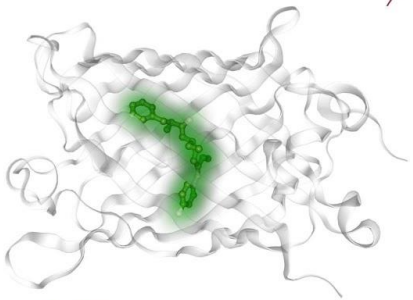
The RCSB PDB is a member of the Worldwide Protein Data Bank partnership (wwPDB; wwpdb.org).

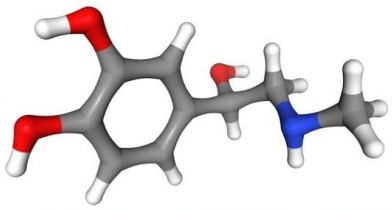
TIRED OF THE RAIN?
Join RCSB PDB at UCSD!

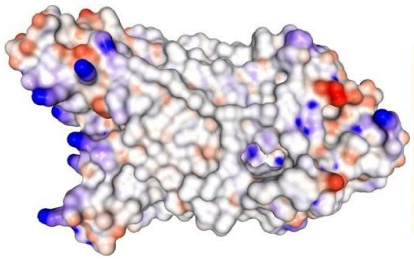
Postdoctoral Fellows

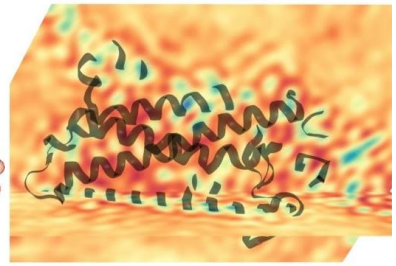
The Challenge:
Develop innovative **3D Visualization and Analysis** and **Bioassembly/Machine Learning** tools to help accelerate research and training in biology, medicine, and related disciplines.











Further inquiries:
rcsb.org *(More > Careers)*
info@rcsb.org

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