

# Conformational Sampling of Macrocycles: Recent Progress

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## Macrocycles explore different property space

- non-Ro5 property space
  - Membrane permeability

Doak et al., *J. Med. Chem.*, **59**, 2313 (2016).

### extended Ro5

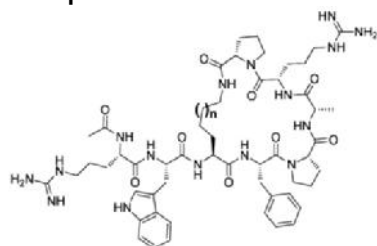
all of:

MW 500-700 Da, ClogP 0-7.5  
HBD  $\leq 5$ , HBA  $\leq 10$ , PSA  $\leq 200 \text{ \AA}^2$   
NRotB  $\leq 20$

### beyond Ro5

MW  $> 500$  Da and at least one of:  
MW 700-3000 Da, ClogP  $< 0$  or  $> 7.5$   
HBD  $> 5$ , HBA  $> 10$ , PSA  $> 200 \text{ \AA}^2$   
NRotB  $> 20$

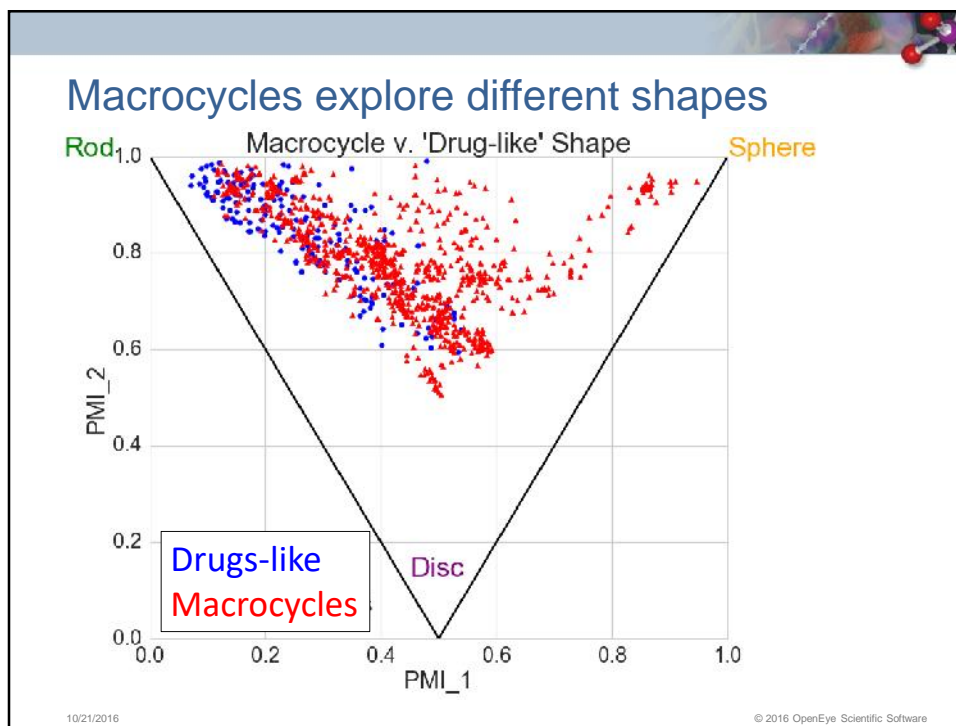
- Protein-protein interaction inhibition

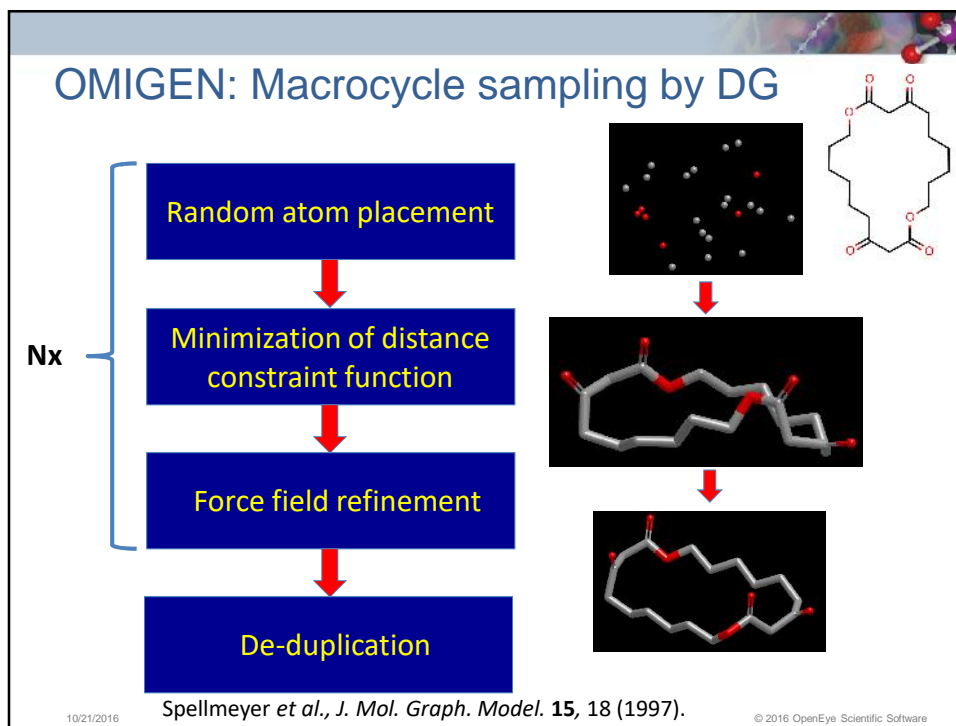


Zhou et al., *J. Med. Chem.*, **56**, 1113 (2013).

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### Quantity v. quality in macrocycle sampling

- Quantity
  - Time
  - # Conformers produced
    - Downstream processing
- Quality
  - Reproduction of solid-state structures
  - Diversity of conformer space sampling

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## Data sources

- CSD
  - “Training”
    - What are best # attempts and RMSD?
- PDB
  - “Testing”
    - Are CSD parameters transferable?
- BIRD
  - “Validation”
    - Can we reduce the problem space?

H  
a  
r  
d  
e  
r

<http://www.wwpdb.org/data/bird>

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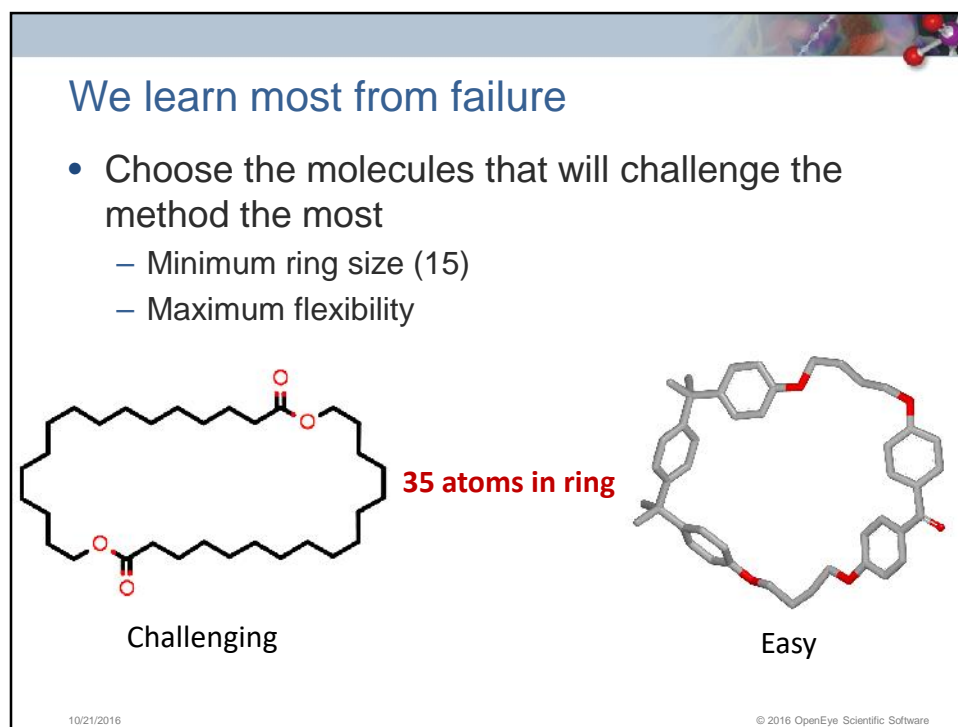
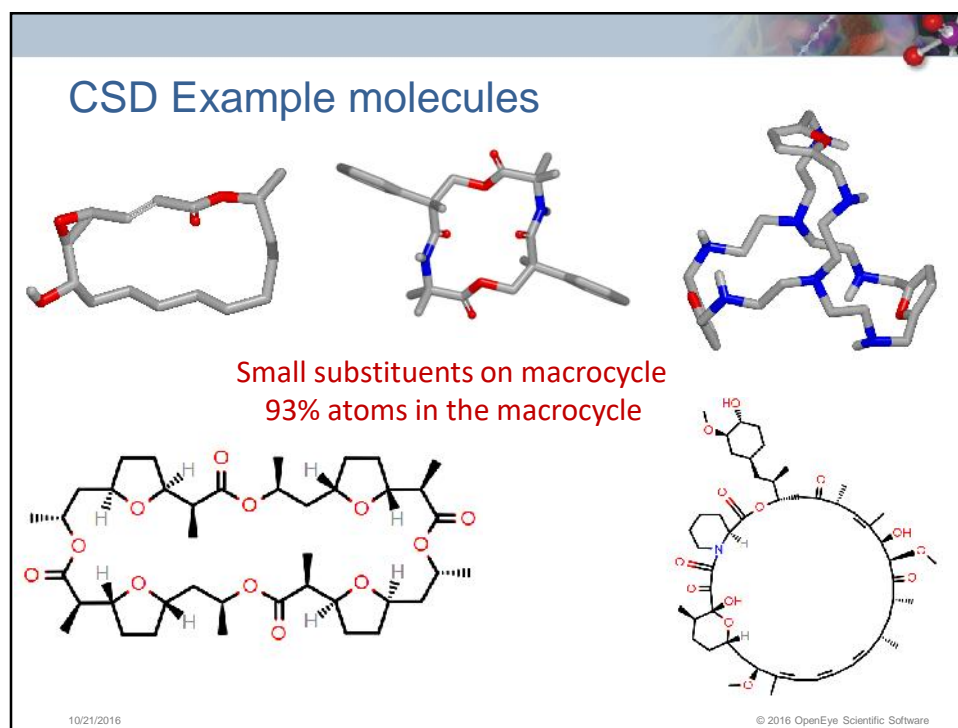
## CSD: Reliable & high quality

1657 structures

- Molecule “quality” — 1650
- Duplicates — 1575
- Clashes — 1542
- Diverse — 1477 (89.1%)

1269 unique rings

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### Scoring ring flexibility

- Constraining groups (high penalty)

$$(R)(R')C=C(R'')(R''')$$

$$R-C\#C-R'$$

$$C1*C1$$

- Restraining groups (lower penalty)
  - Exo alkene, Ketone; ester; amide; urea

=                      -                      -

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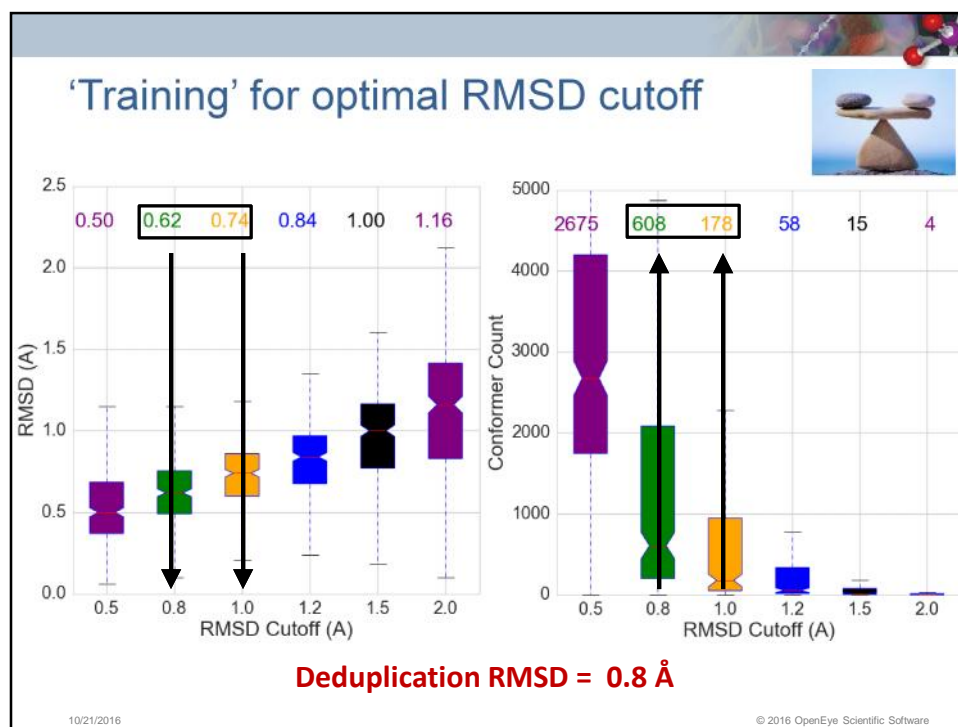
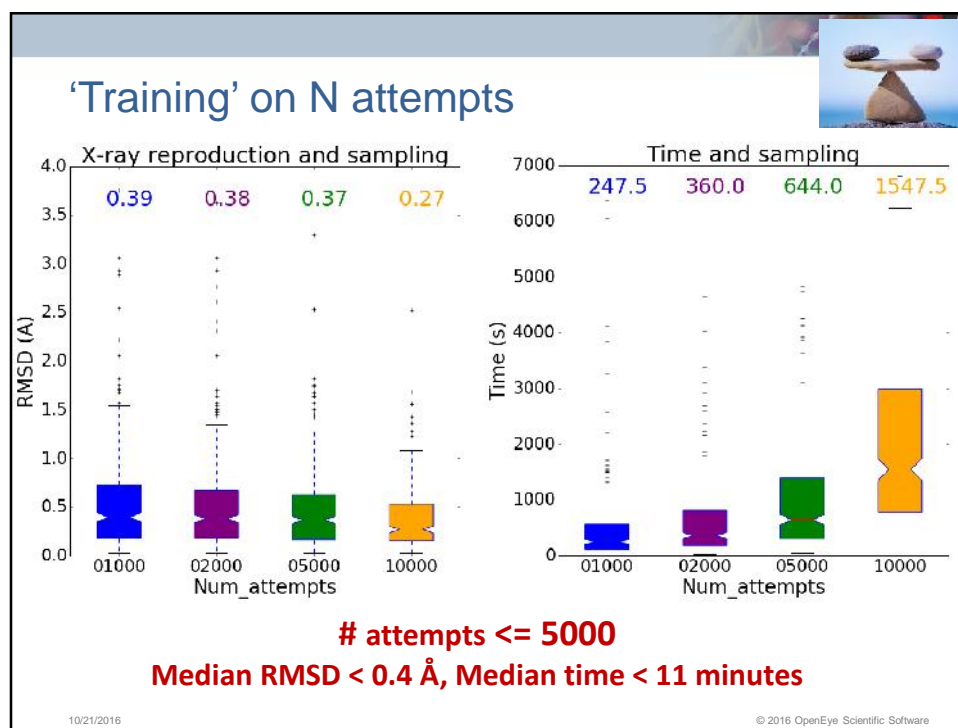
### Filtering with flexibility heuristics

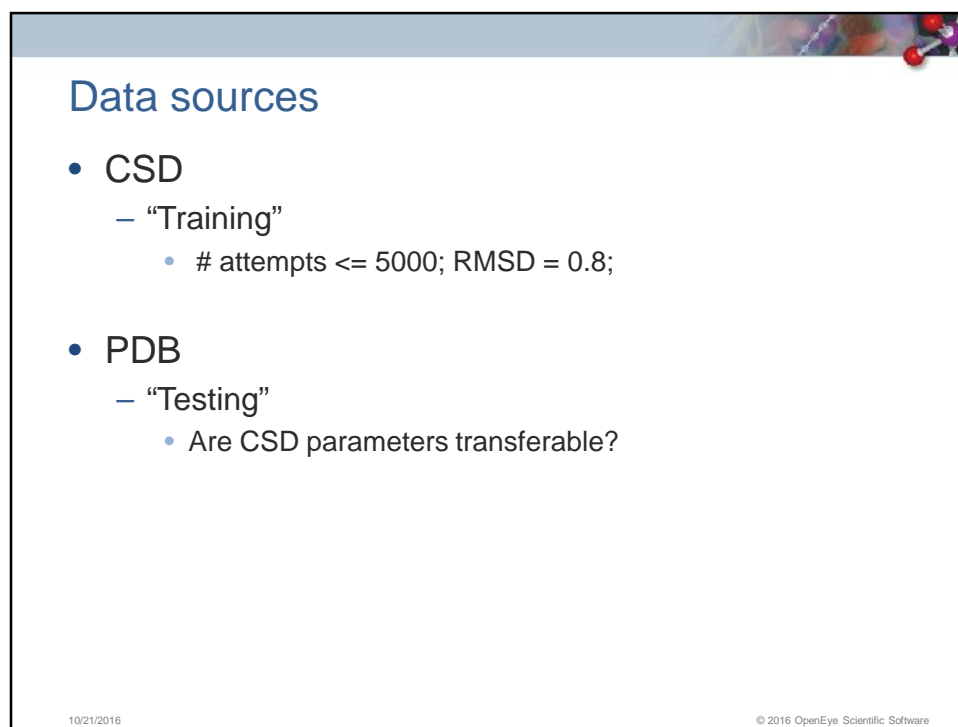
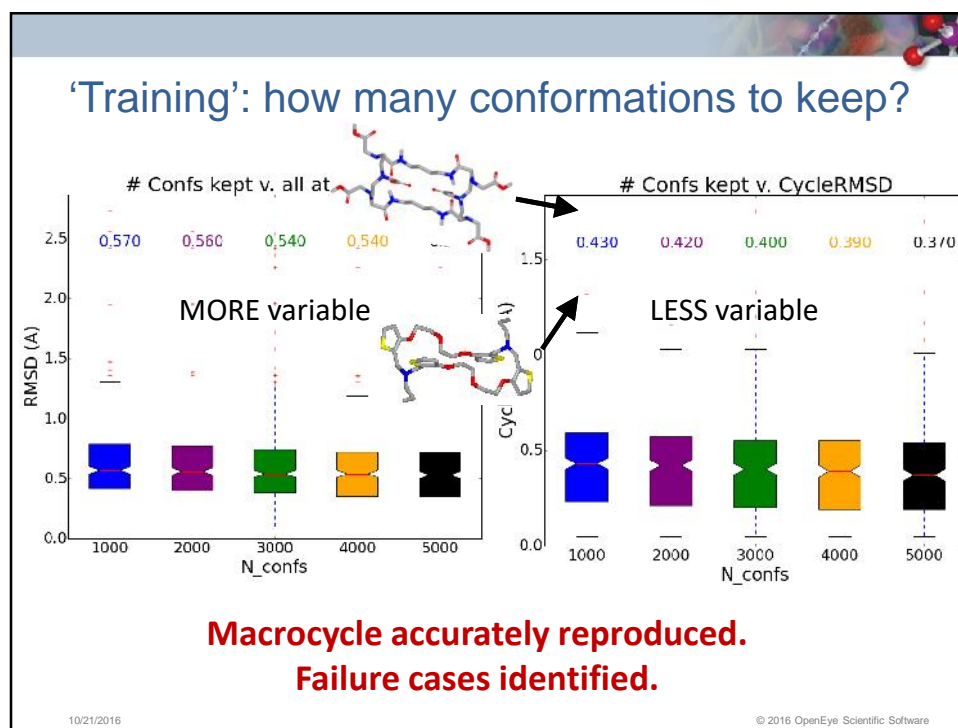
24 atoms in largest ring.  
**Removed.**

24 atoms in largest ring.  
**Retained.**

1477 -> 333 molecules  
270 unique rings

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## PDB: Finding good quality ligand models

- Well fit to data
  - Globally ( $R$ ,  $R_{\text{free}}$ )
  - Locally (RSCC, RSR, OWAB)
- Ligand not obviously badly solved
  - No clashes
  - Appropriate relationship between chemistry and geometry
- Low inherent coordinate error
  - If RMSD < coordinate error, indistinguishable difference

Hawkins et al., *J. Chem. Inf. Model.*, **50**, 572 (2010).

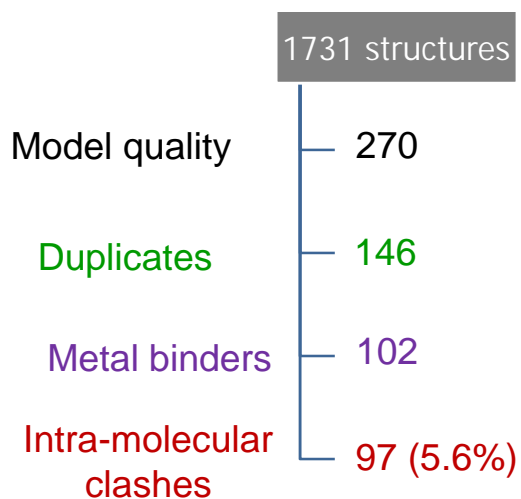
Warren et al., *Drug Disc. Today.*, **17**, 1270 (2012).

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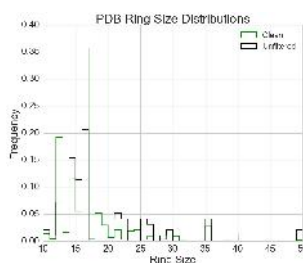
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## Sieving the PDB

For comparison:  
LigandExpo: 989270  
Surviving: 53420 (5.4%)

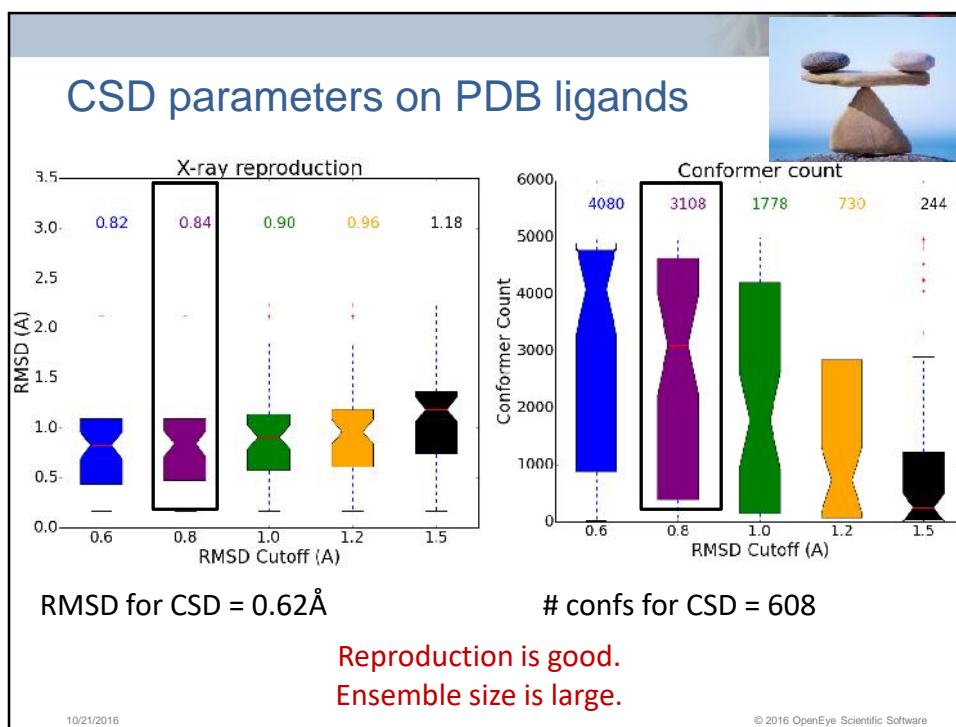
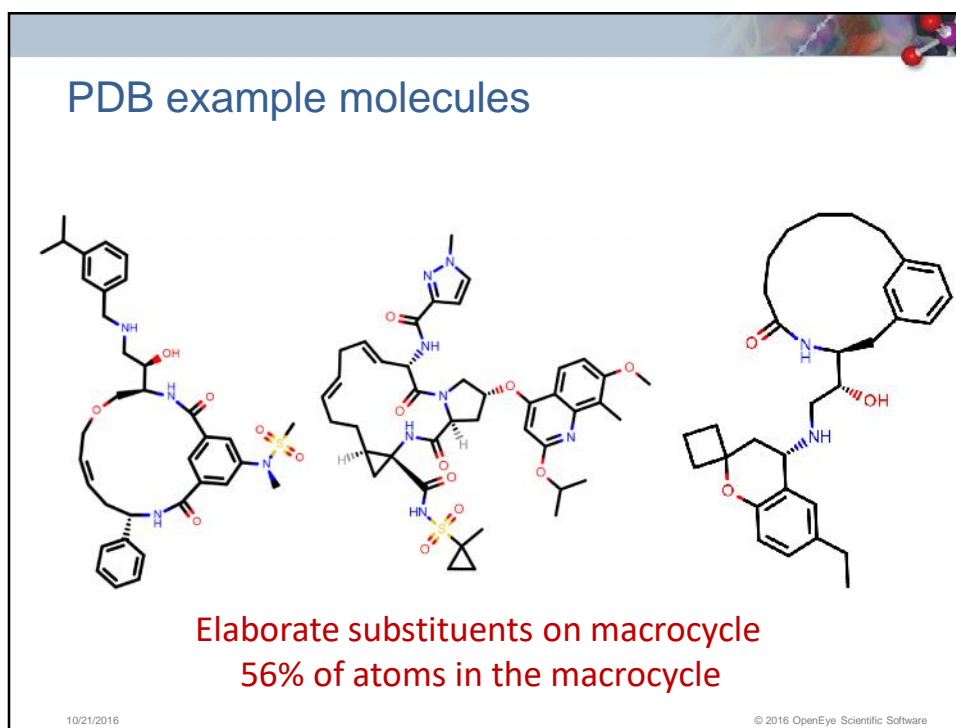


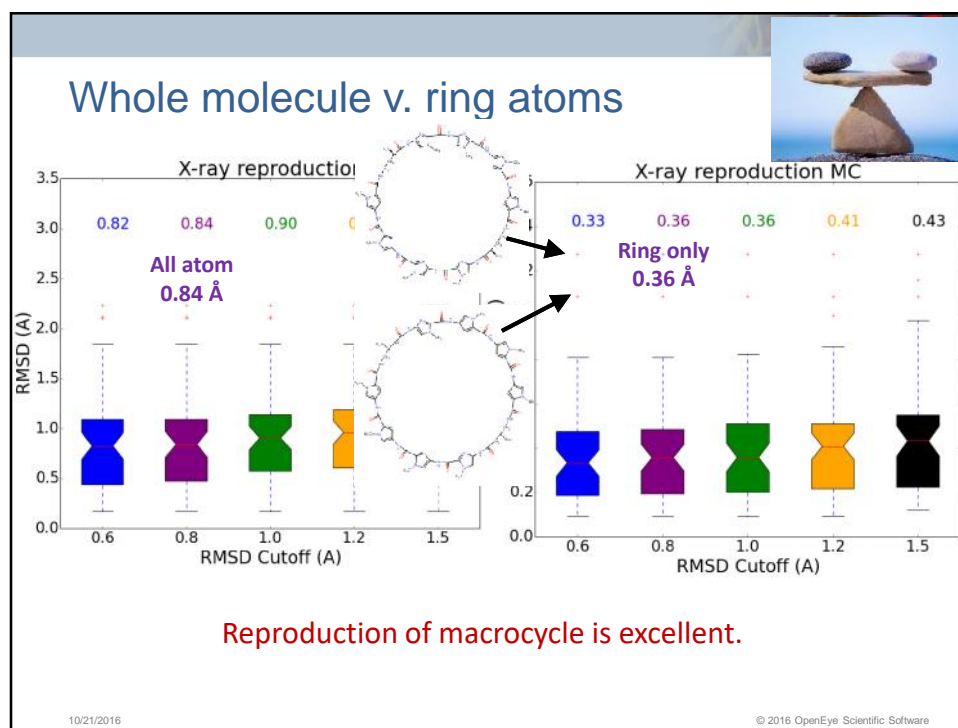
53 unique rings



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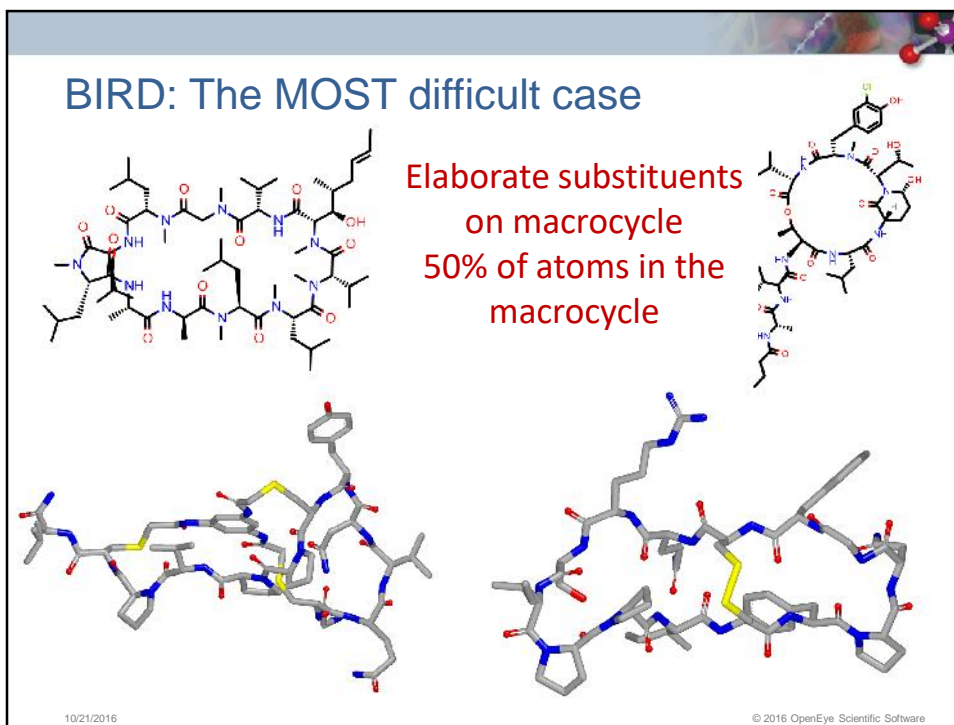
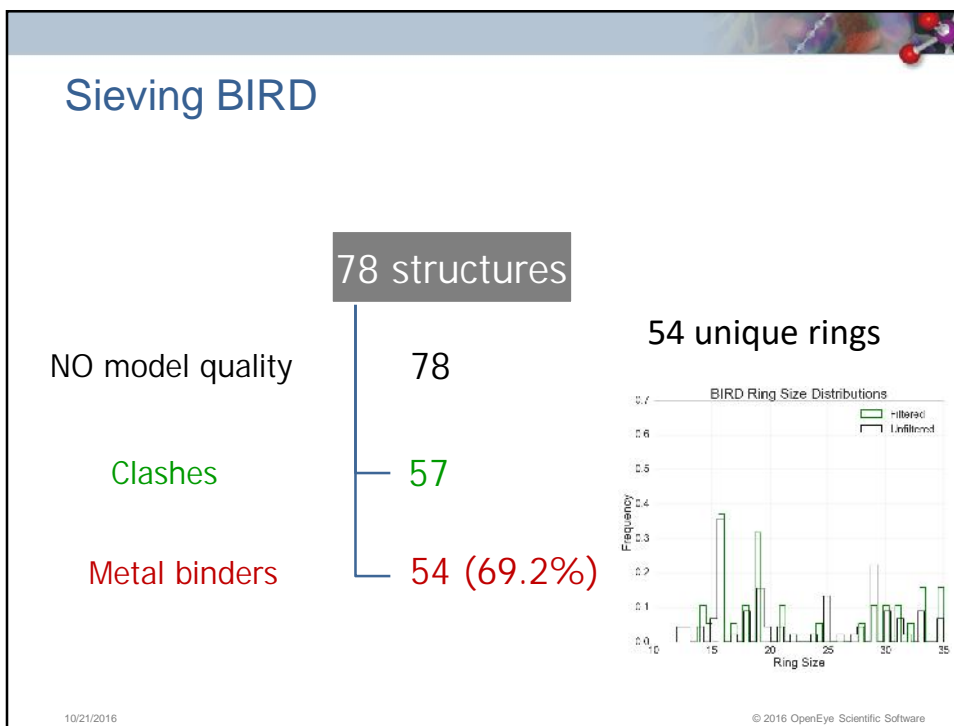


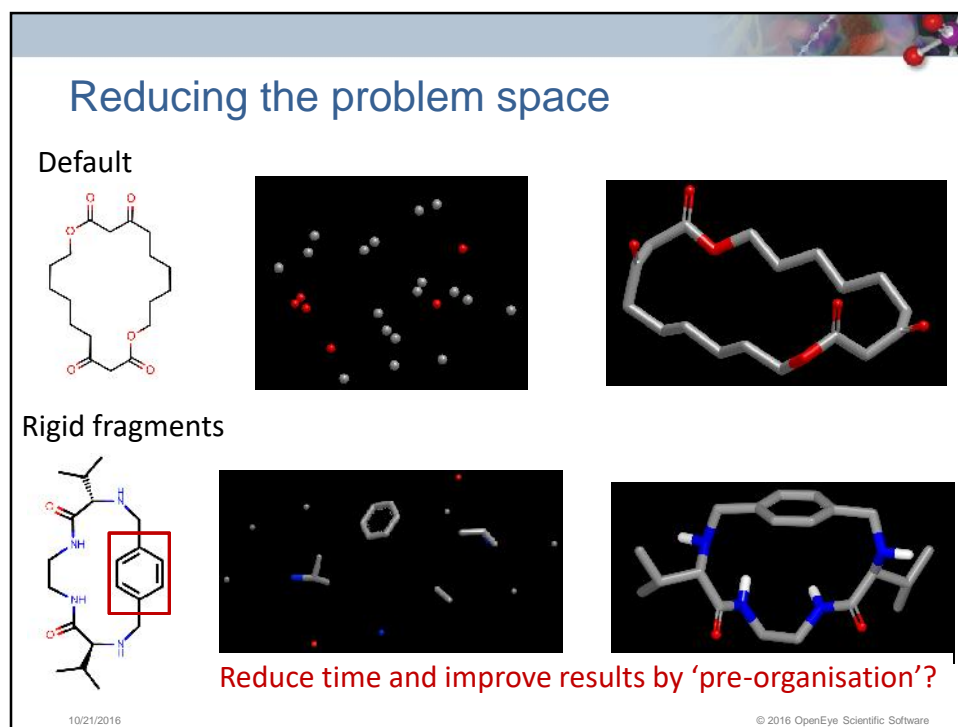
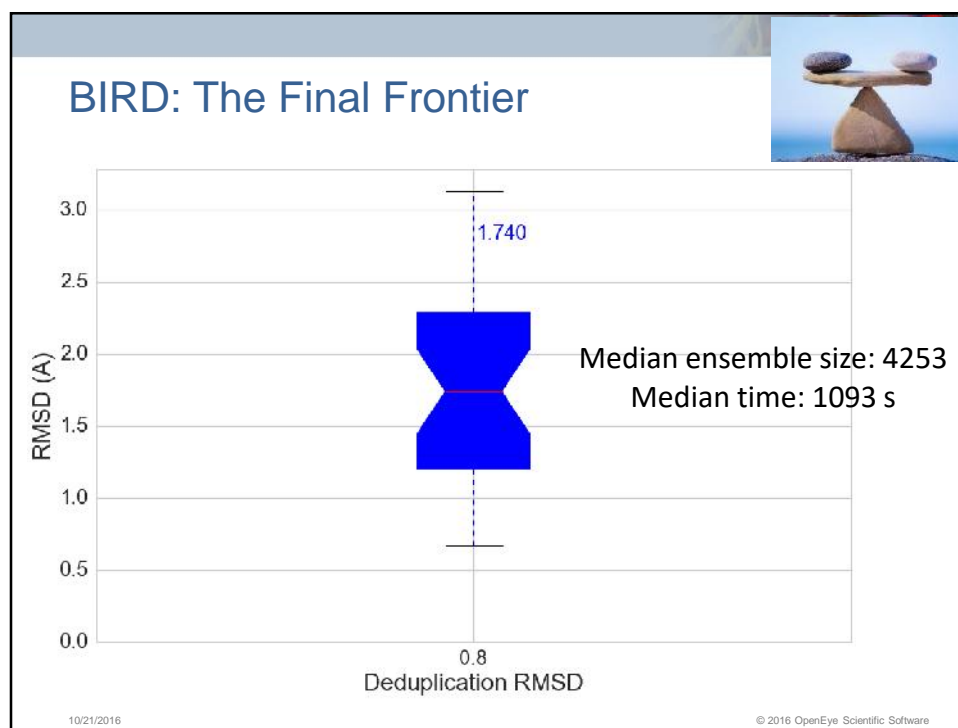
### Data sources

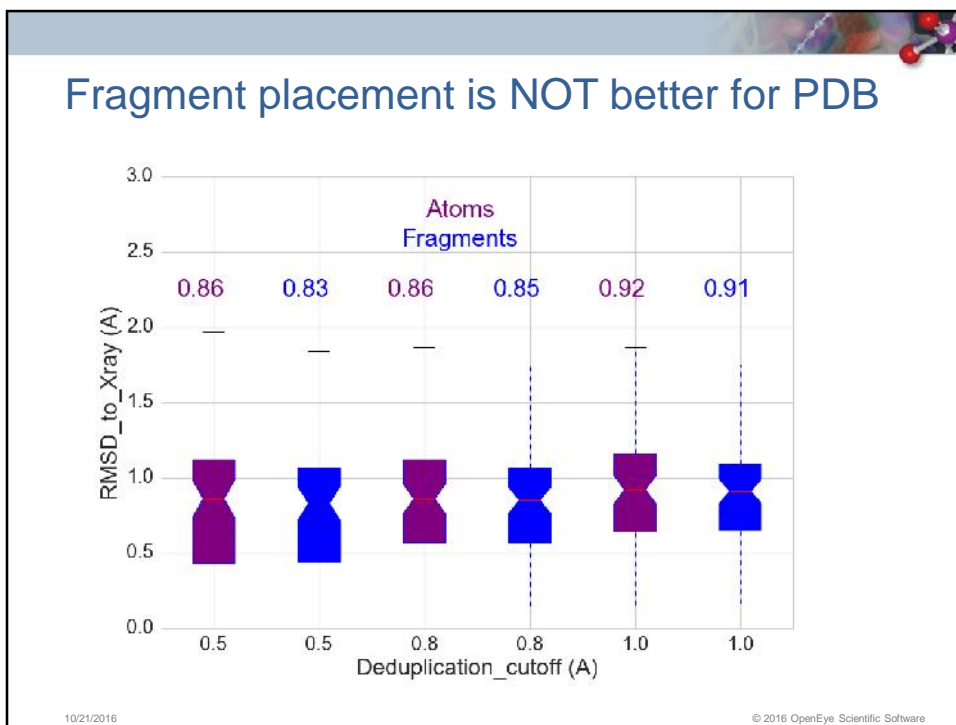
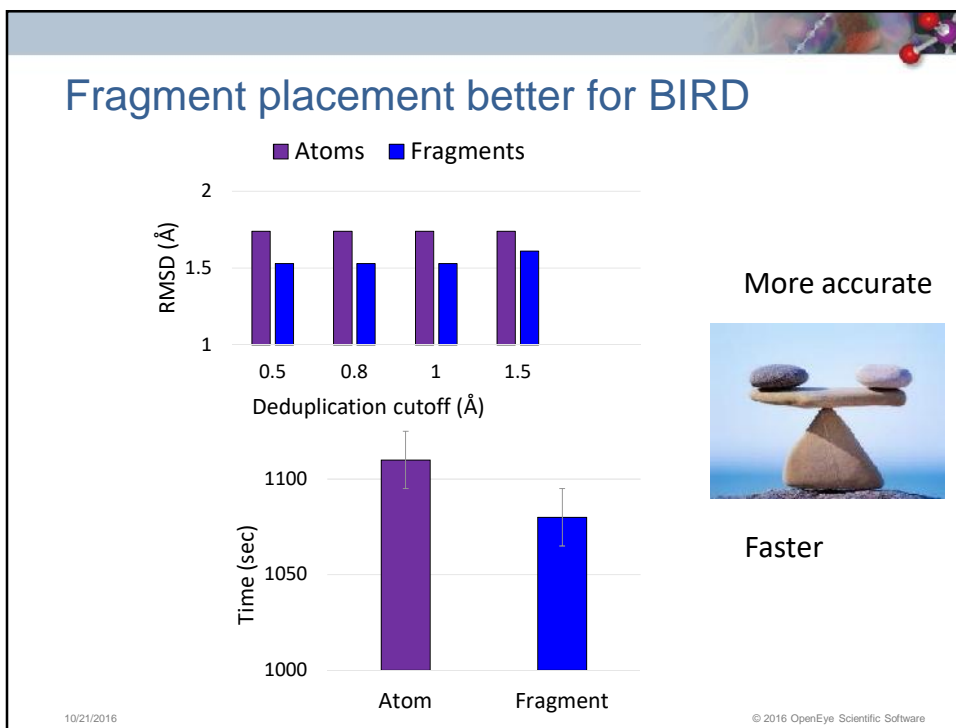
- CSD
  - "Training"
    - # DG attempts  $\leq$  5000, RMSD = 0.8
- PDB
  - "Testing"
    - CSD parameters work fairly well
- BIRD
  - "Validation"
    - Can we reduce the problem space?

<http://www.wwpdb.org/data/bird>

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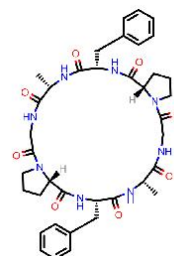
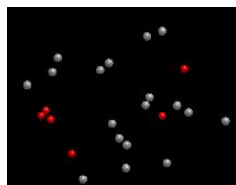




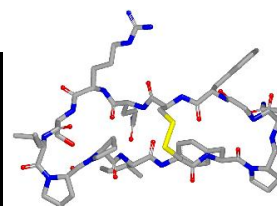


## Atom v. fragment placement

- Lightly elaborated
  - ATOM placement



- Heavily elaborated, large
  - FRAGMENT placement

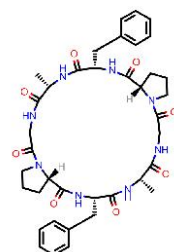
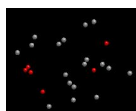
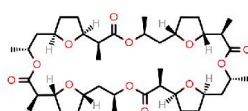


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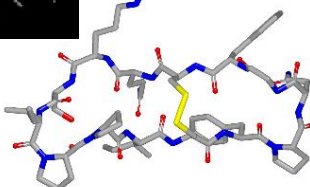
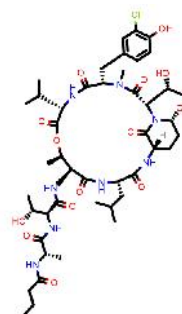
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## Key conclusions

- There are two kinds of molecule in the world...

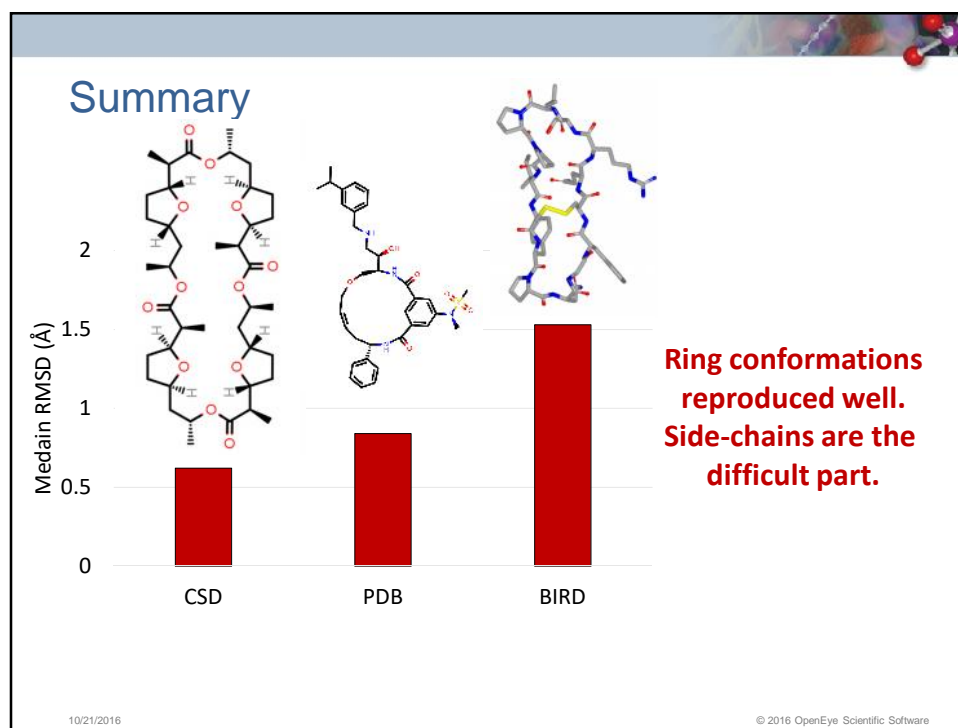


All atom RMSD:  $< 0.85\text{\AA}$   
MC RMSD:  $< 0.5\text{\AA}$   
Time: 11 minutes



All atom RMSD:  $1.5\text{\AA}$   
MC RMSD:  $0.9\text{\AA}$   
Time: 18 minutes

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- BMS
  - Shana Posy
  - Steve Spronk

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