Stereochemical statistics in Crystallography Open Database

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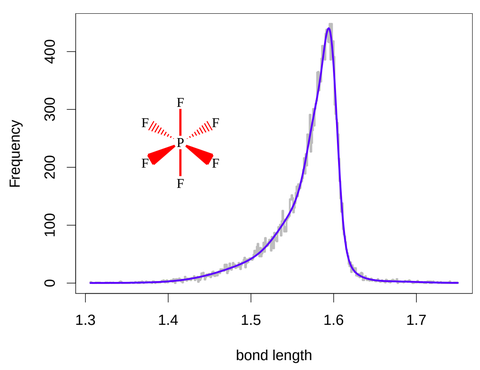
Abstract

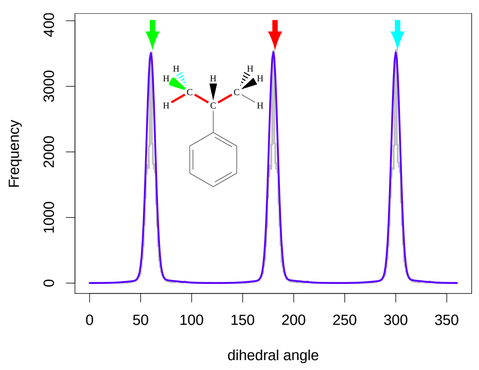
Libraries of small molecule stereochemical information, used for refinement and validation of small molecules and macromolecule-ligand complexes, are subjected to two limitations: licensing and possibility to become outdated [5]. A novel library of small molecule stereochemical information is constructed from the Crystallography Open Database [4], harnessing a new method for description of the variety of small molecule chemical environments and Bayesian framework. Means for automatic renewal of the library in the real time are devised. The result of the research is comparable to the previous works [1, 2] and proves to be useful in the detection of unusual geometric features in small molecules.

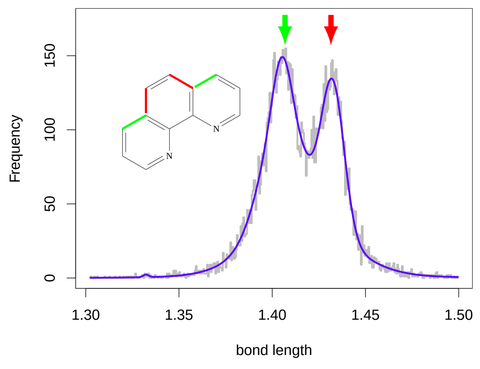
Materials and methods

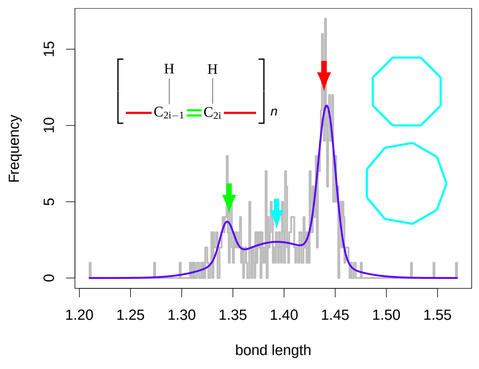
- Data source: Crystallography Open Database (COD)
- Stereochemistry extracted from ∼160 K structures:
  - ∼11 M bond lengths;
  - ∼22 M valence angle sizes;
  - ∼39 M dihedral angle sizes;
- Harnessing SMILES-like algorithm to describe atom chemical environment:
  - ∼1 M classes of bonds;
  - ∼3.5 M classes of valence angles;
  - ∼8 M classes of dihedral angles;
- Fitting mixtures to distributions:
  - Using Gaussian and Cauchy mixtures for bond lengths and valence angles;
  - Using von Mises mixtures for dihedral angles;
- Estimating mixture parameters with expectation-maximisation algorithm [3];
- Selecting best models using Bayesian information criterion [6].

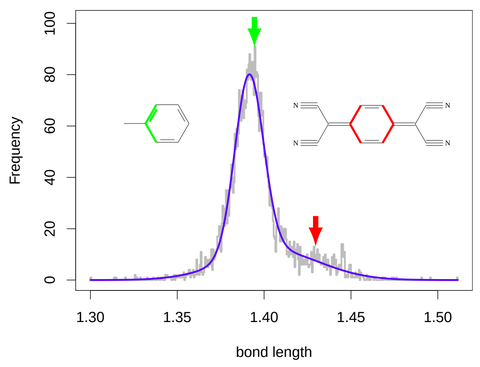
Fitting the distributions

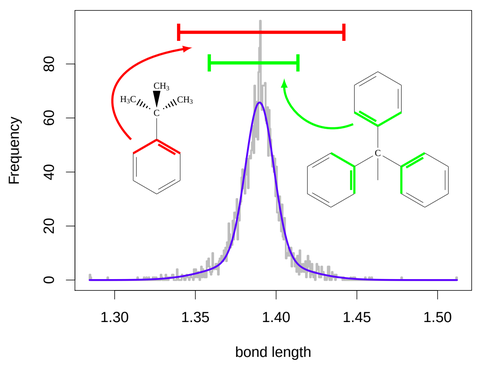












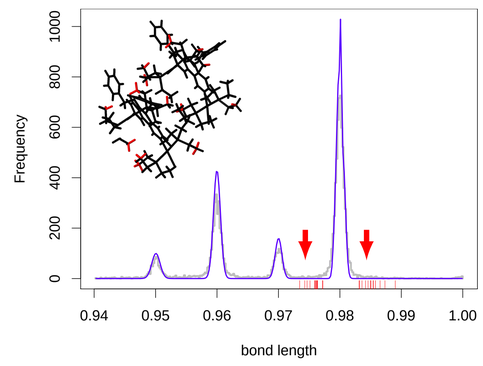
- Complex distributions can be described (*fig. a,b*);
- Information is preserved even when classification algorithm is not accurate enough (*fig. c,d,e,f, coloured bars represent* $\pm 3\sigma$).

a	b
c	d
e	f

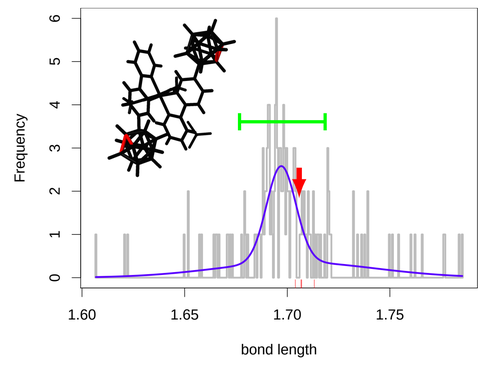
Detecting unusual features in molecular models

- Depends on a set of models defining ”normal” geometry;
- ”Unusual” does not necessarily mean ”wrong”.

- COD structure 4027109
  - Methyl C-H bond lengths deviate from ”optima” (*up right*);
  - Do deviations notify about structure anomalies or represent previously unobserved albeit normal bond lengths?

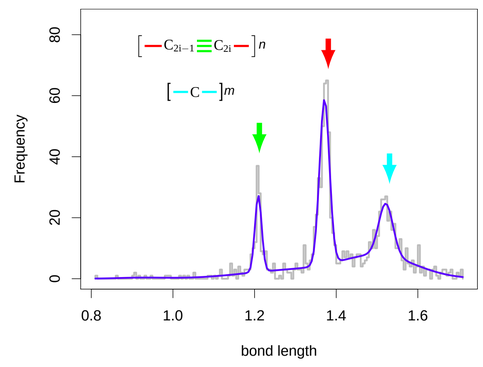


- COD structure 7109296
  - Carborane C-B bonds fall in ”credible” interval (*down right, green bar marks* $\pm 3\sigma$ *from the centre of the sharpest peak*);
  - Formally, carborane carbon is hexavalent, though such structures are reliably observed.

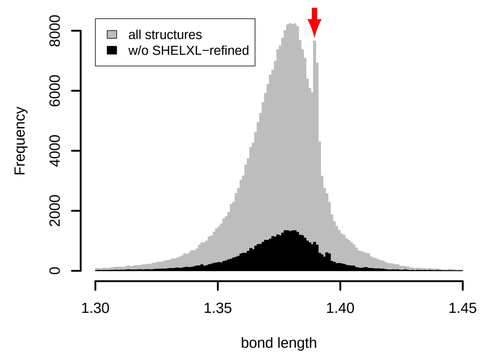


Insights in aggregated published material

- Problems with model representation introduce non-physical modes:
  - Example: cyan peak in linear carbon bond histogram (*up right*) marks bonds from alkanes without covalent-bounded hydrogens;
  - Such models should undergo special treatment or be removed from dataset;
  - Requires attention of an expert to be detected.



- Refinement constraints bias the distributions
  - Example: red-marked peak in benzene C-C bonds histogram (*down right*);
  - Removing observations of constrained models suppresses bias.



Conclusions

- Fully automatic and unsupervised methods to collect and process the stereochemical parameters are devised;
- Over 160 K small molecule structures were used to build stereochemical database;
- Database proved to be useful for the detection of unusual geometric features in molecular models;
- May be applied for maximum likelihood refinement of structures of macromolecule/ligand complexes.

Acknowledgements

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