Slides/Gist

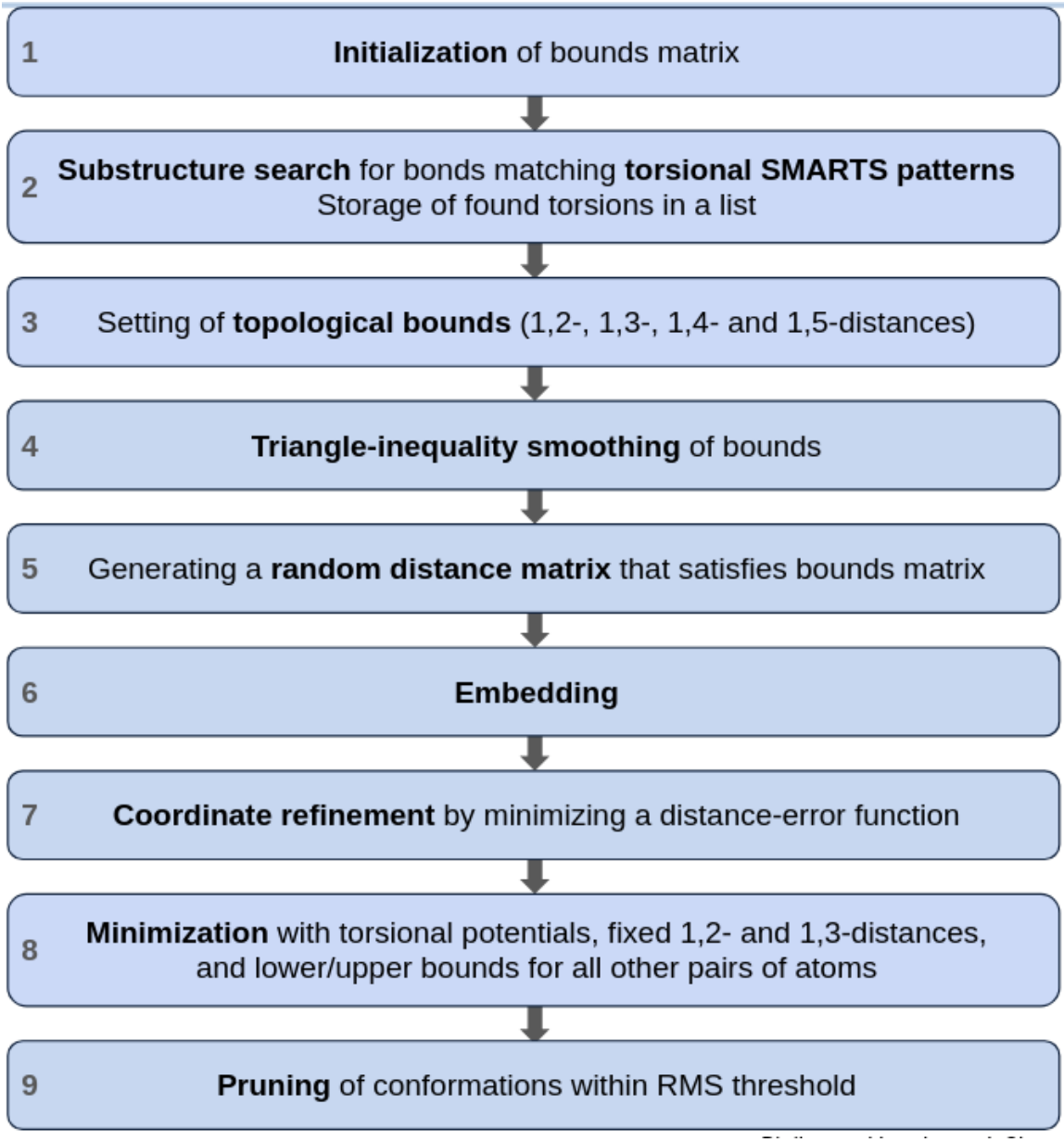
`Background`

Experimentally obtained molecular structures are not always readily available.

Therefore, in order to do modelling (e.g. static docking, dynamical simulation, quantum calculation), computationally generate molecular conformations is highly desired.

Conformer Generation

- Obtain 3D structure from molecular connectivity and other (optional) information
- **E**xperimental **T**orsion **K**nowledge **D**istance **G**eometry(ETKDG) method [reading]



Bound Matrix

- Atom pair distances
  - Lower bounds are usually Van der Waals radii sums
  - Upper bounds are based on lower bounds with added tolerance (here 0.5 Å)
- Satisfy triangle inequality: e.g. O-C2 distance ≤ (O-C1 + C1-C2)

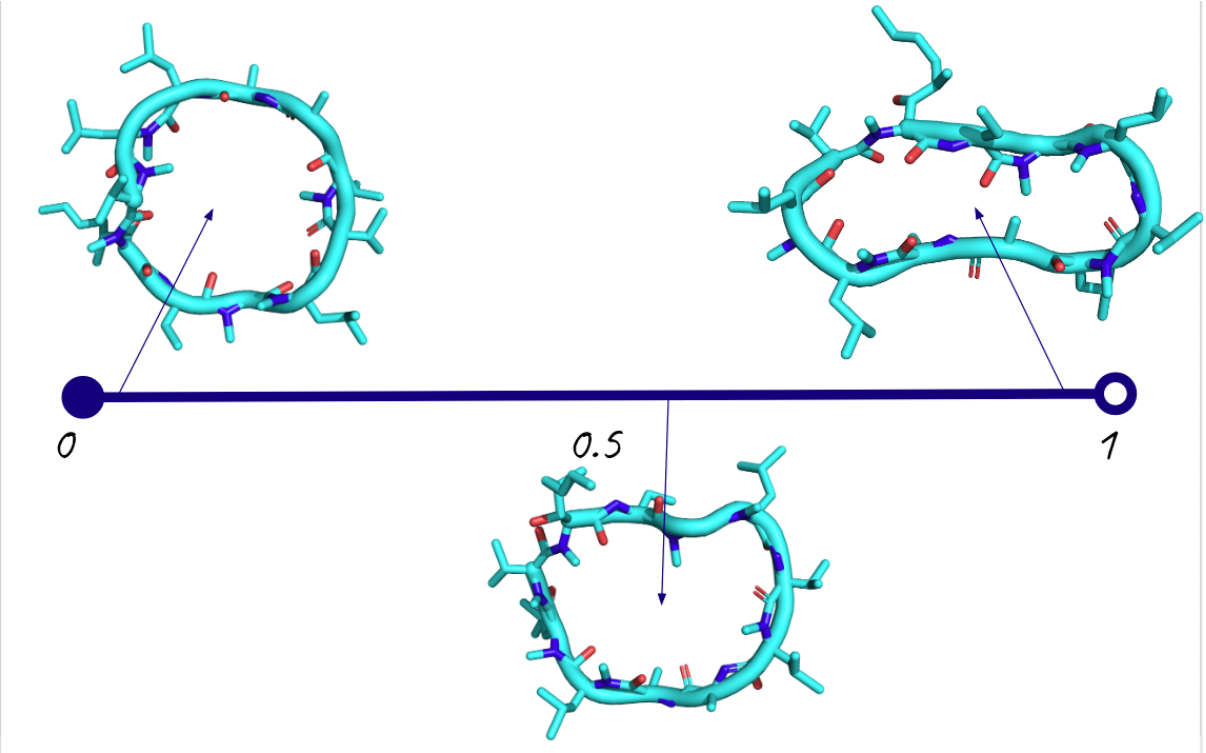
	O	C1	C2	C3
O	0	1.9	3.5	1.9
C1	1.4	0	2.1	3.7
C2	1.4	1.6	0	2.1
C3	1.4	1.6	1.6	0

Upper bound

Lower Bound

Using the Bound Matrix: Eccentricity

- Conformational space spanned by the bound matrix can be vast when the number of atoms increase
- Restricting the search space to the chemical meaningful regions is important
- The eccentricity scale [reading]:



`Main Idea`

- **Incorporate experimental nuclear overhauser effect data for conformer generation of macrocycles (previous section)**

Table S1: NOE upper distance bounds of CsE in CCl_4. The atom labels are shown in Fig. S1.

Index	Residue 1	Residue 2	Upper bound [nm]
1	1 HA	6 HA	0.424
2	1 HA	7 HN	0.421
3	2 HN	5 HN	0.438
4	11 HN	8 HN	0.533
5	2 HN	5 HB	0.552
6	6 HD	1 HA	0.592
7	2 HB	5 HB	0.509
8	8 HN	6 HB	0.462
9	1 HG1	3 HCN	0.505
10	8 HA	6 HD	0.352
11	8 HN	7 HN	0.386
12	7 HN	6 HA	0.361
13	10 HA	10 HCN	0.404
14	1 HCN	2 HA	0.472
15	4 HCN	5 HN	0.310
16	3 HCN	3 HA	0.384
17	1 HA	2 HG	0.473
18	9 HG	8 HA	0.361

Primary Goals

1. Build up a pipeline for automated NOE constraint incorporation
    - standardise and parse NOE tabulated data
    - allow an *importance* ranking of NOE data
    - assign the parsed NOE data into the conformer generation (start with bound matrix)
    - validating the workflow on test macrocycle molecules
2. Sub-selection of conformational ensemble based on NOE fulfillment
3. Survey literature for additional test molecules (e.g. NOE databases)
4. As a post-processing, MD simulational refinement of generated conformers
5. Connecting/compatibility checking between NOEs and eccentricity
6. A benchmark against NMR softwares

TODOs

- Read papers to understand ETKDG conformer generator:
    1. https://pubs.acs.org/doi/abs/10.1021/acs.jcim.5b00654
    2. https://pubs.acs.org/doi/abs/10.1021/acs.jcim.0c00025
- Get to know Python

- Install rdkit：https://www.rdkit.org/docs/index.html
- Run example: https://github.com/rdkit/rdkit/blob/master/Docs/Book/Cookbook.rst#conformer-generation-with-etkdg
- Understand Git/GitHub & Docker

Secondary TODOs

- CYANA reading : https://link.springer.com/article/10.1007%2Fs10858-015-9924-9
- Think about various NMR expertise of yours that can be useful (e.g. J-coupling information as validation)