Deep Learning Scoring Function for Flexible Molecular Docking

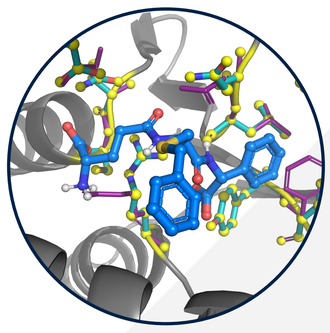
Rocco Meli,[1] Jocelyn Sunseri,[2] Philip C. Biggin,[1] David R. Koes[2]

[1] Department of Biochemistry, University of Oxford
[2] Department of Computational and Systems Biology, University of Pittsburgh

Introduction

Problems with standard docking studies:

- Semi-empirical or knowledge-based scoring functions
- Rigid receptor



Goals of this Google Summer of Code Project:

- **Train a CNN on docking with flexible side chains**
- **Implement CNN optimisation of flexible side chains**

Implemented in `gnina`*, a deep learning framework for molecular docking*

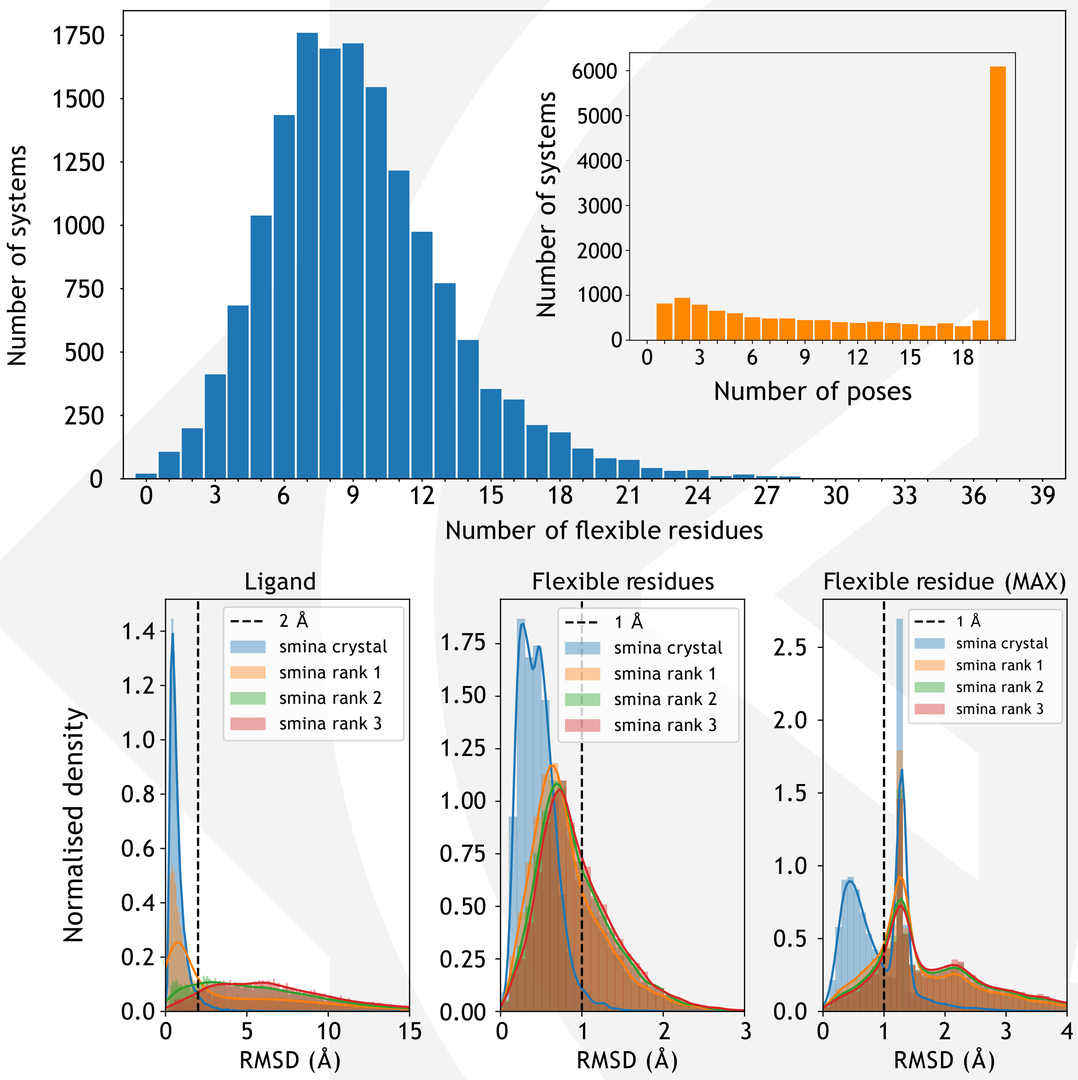
Flexible Docking

Flexible docking principles (with `smina`):

- Ligand rotations and translations
- Ligand rotatable bonds
- **Rotatable bonds of protein side chains**
- Fixed (rigid) backbone

PDBbind 2018 [4]:

- 16151 P-L complexes
- PDB and MOL2 files
- Binding affinity: K_i, K_d, IC_{50}



203786 (+ 15840) protein-ligand poses

Good
- Ligand RMSD < 2 Å
- Flex RMSD (MAX) < 1 Å

Bad
- Ligand RMSD > 4 Å
- Flex RMSD (MAX) > 1.5 Å

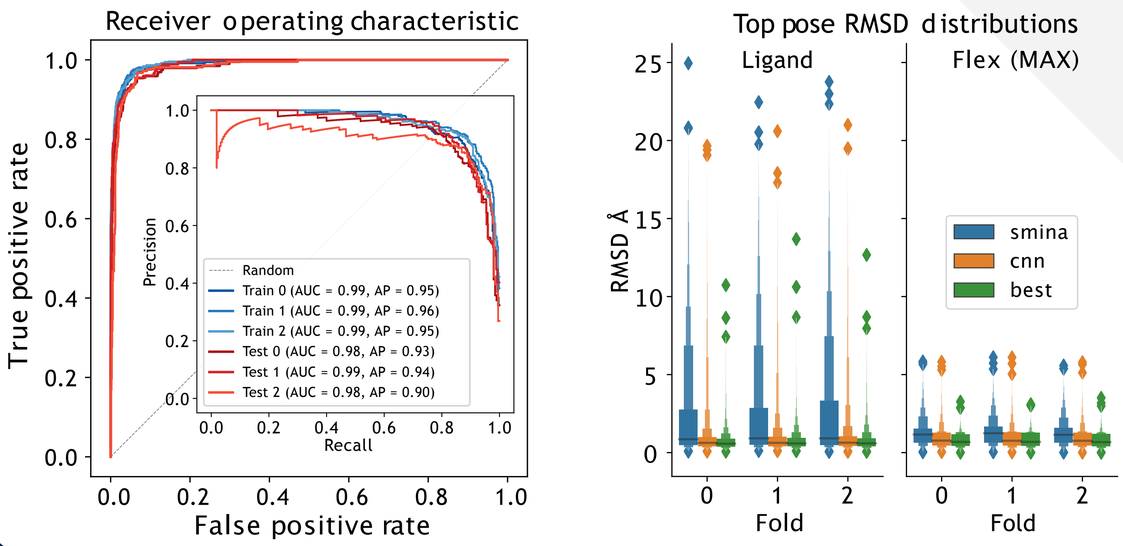
Training

RMSD-based annotation:

- **3232 (+ 8284) positive** examples
- **75404 (+ 25) negative** examples
- **Class imbalance** problem

3-fold **cross-validation**:

- Protein sequence distance
- Ligand similarity
- No. targets: [5598, 5639, 4889]



GNINA

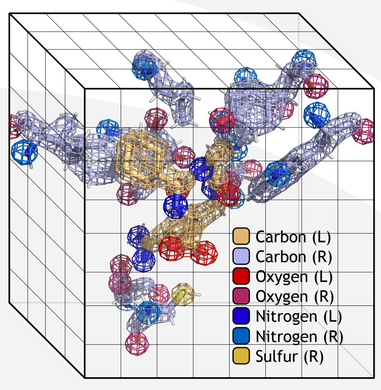
`gnina` [1]:

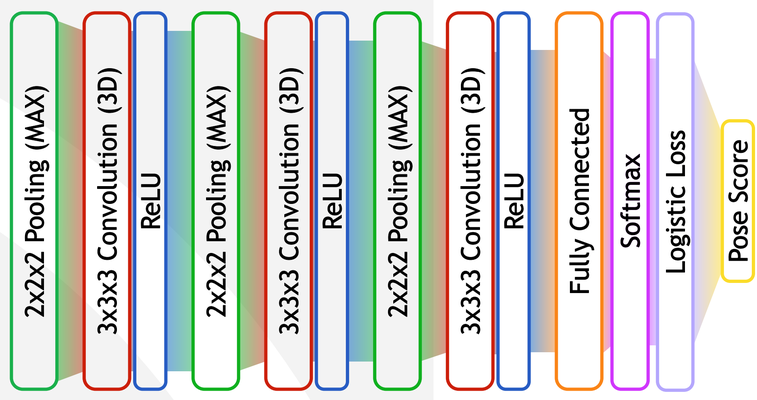
- **Deep learning framework for molecular docking**
- `caffe` [2] + `smina` [3] + `libmolgrid`
- Developed by David Koes' group

`github.com/gnina`

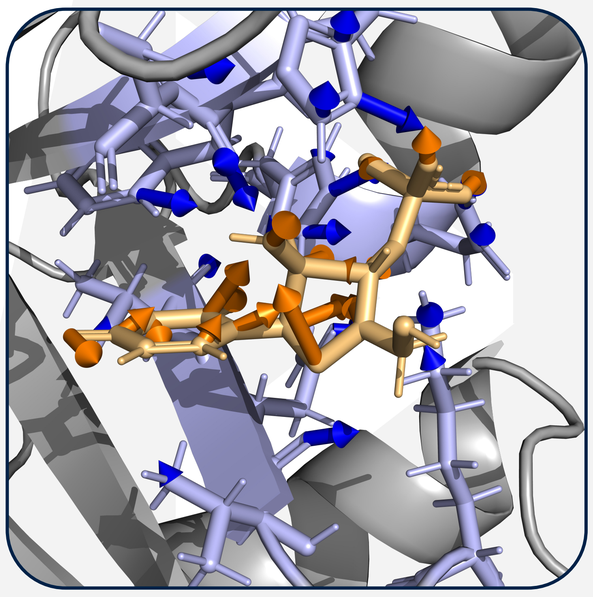
Workflow:

- **Discretisation** (gridding) if protein-ligand binding site (3D)
- Computation of **atomic densities** for different `smina` atom types
- **Standard CNN** machinery for computer vision (w/ data augmentation)





CNN Atomic Gradients



Backpropagation of gradients to ligand and receptor atoms [5].

$$\frac{\partial \mathcal{L}}{\partial \vec{a}} = \sum_{g \in G_{\vec{a}}} \frac{\partial \mathcal{L}}{\partial g} \frac{\partial g}{\partial d} \frac{\partial d}{\partial \vec{a}}$$

$$g(d;R) = \begin{cases} e^{-\frac{2d^2}{R^2}} & 0 \le d < R \\ \frac{4}{e^2 R^2} d^2 - \frac{12}{e^2 R} d + \frac{9}{e^2} & R \le d < 1.5R \\ 0 & d \ge 1.5R \end{cases}$$

Ligand — Ligand Gradients
Flexible Side Chains
Flexible Side Chains Gradients

Ligand pose and side chains optimisation, with respect to the CNN loss function, using standard optimisation techniques (BFGS).

CNN Optimisation

The CNN is trained on `smina` poses, which are physically sensible poses.

Problems:

- Ligand self-clashes
- Ligand receptor clashes
- Receptor-receptor clashes

CNN-optimised (L) — `smina` (L)
CNN-optimised (R) — `smina` (R)

Including CNN-optimised poses in the training set broadens the conformational space with unrealistic poses and may improve the CNN performance [5].

References

[1] M. Ragoza *et al.*, J. Chem. Inf. Model. **57**, 942-957 (2017)
[2] Y. Jia *et al.*, arXiv, arXiv:1408.5093 (2014)
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[4] Z. Liu *et al.*, Acc. Chem. Res. **50**, 302-309 (2017)
[5] M. Ragoza *et al.*, arXiv, arXiv:1710.07400 (2017)

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@RMeli
@RoccoMeli