# EPSRC Centre for Doctoral Training (CDT) in Molecular Sciences for Medicine (MoSMed)

# Neural networks for modelling protein conformational space: Application to inhibitor design exploiting an enzyme's mobile regulatory element.

## [Newcastle University, School of Natural & Environmental Sciences]


**Supervisory Team**

- **Dr Daniel Cole (Newcastle University)**
- **Dr Matteo Degiacomi (Durham University)**
- **Prof Wyatt Yue (Newcastle University)**


## Project overview/context

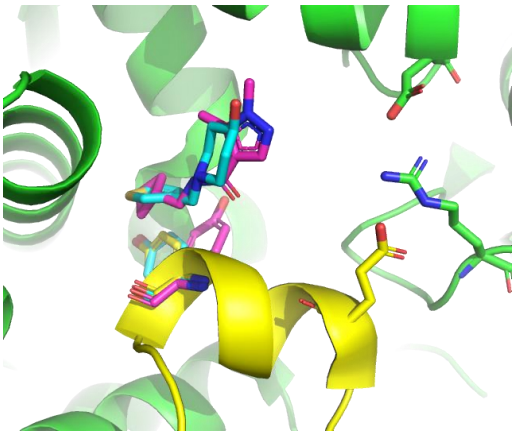
Computational structure-based drug design techniques, such as de novo design or docking, typically base predictions on a static crystal structure of the target of interest. Yet biological structures are anything but static. This collaborative computational / bioscience project seeks to use the latest advances in neural network-based machine learning to generate ensembles of protein binding pocket structures that are both diverse and physically plausible. The method will be applied to the characterisation of and inhibitor design for human haem biosynthetic enzyme 5'-aminolevulinate synthase (ALAS2), which appends an autoinhibitory loop to its active site and exhibits conformational dynamics during catalysis.

## Research Project

Proteins are dynamic structures, and their conformations can be shifted by binding to other molecules. Hence, when performing structure-based drug design against flexible targets, it would be ideal to consider not just a single structure, but instead an ensemble of plausible structures that the target may adopt.

In our previous work, the supervisory team have shown that machine learning can play an important role in i) producing physically reasonable intermediate structures along an enzyme's opening pathway and ii) learning accurate molecular interactions and dynamics (force fields) from quantum mechanical data.

In this project, the student will work to improve the use of quantum mechanical data in training models that describe molecular dynamics and interactions at the atomic scale (in collaboration with the Open Force Field Initiative). State-of-the-art force fields will be incorporated into neural network-based methods for structure prediction, in particular focusing on accurate modelling of flexible protein binding pockets.



The combined computational methodology will be applied by the student to a novel therapeutic target, the human metabolic enzyme ALAS2 (pictured), which was recently crystallised in Prof Yue's lab. An ensemble of binding pocket structures of this flexible target will be generated and structure-based design will be carried out with the goal of inhibiting enzyme activity.

**Further reading**

[1] www.dx.doi.org/10.1103/PhysRevX.11.011052
[2] https://doi.org/10.1039/D0FD00028K
[3] https://doi.org/10.1038/s41467-020-16586-x

## Training & Skills

The student will work closely with the MoSMed CDT with the goal of establishing these workflows as a standard tool in the drug discovery pipeline. The supervisory team will provide highly sought-after training in the fields of computational medicinal chemistry, machine learning and structural biology (at both Newcastle and Durham Universities). As such, this project is ideal for a candidate with ambitions towards a career in the pharmaceutical industry or academic drug discovery.

## Further Information

Please contact Dr Daniel Cole with any enquiries (daniel.cole@ncl.ac.uk), https://blogs.ncl.ac.uk/danielcole/

## How to Apply

You must apply through the University's online application system.

When applying to Newcastle University please select the Course Code **8207F (PhD in Molecular Sciences)** You will need to:
- Insert the **programme code 8207F** in the programme of study section
- Select '**PhD in Molecular Sciences'** as the programme of study
- Input (only) the **studentship reference code (e.g. 22_05)** that you are applying for in the studentship/partnership reference field when prompted (all codes are outlined in the individual project adverts and can be found on the MoSMed website: https://research.ncl.ac.uk/mosmed/phdstudentships/)
- Attach all documents that are requested including a CV and cover letter. The cover letter must **clearly** state the project reference code, the full title of the studentship and state how your interests and experience relate to the project
- Attach degree transcripts and certificates and, if English is not your first language, a copy of your English language qualifications

Should you have any queries regarding the application process to Newcastle University please contact Selina McCarthy, MoSMed CDT Manager: Selina.McCarthy@newcastle.ac.uk or email mosmed.cdt@newcastle.ac.uk

Within the MoSMedCDT we are committed to building a diverse community based on excellence and commitment. To that end in our recruitment of Doctoral Researchers we welcome applications from outstanding candidates of all backgrounds regardless of ethnicity, disability, gender identity, sexual orientation and will consider all applications equally based on merit.

Newcastle University · Durham University · UKRI Engineering and Physical Sciences Research Council