Computational modelling of the interactions between therapeutics and metals in the progression of neurodegenerative diseases

Principal supervisor: Dr Shaun Mutter (LHCS)

Co-supervisor: Prof Jimena Gorfinkiel (SPS)

Location: The Open University, Milton Keynes, United Kingdom

Full-time study only.

Duration & Funding: 3-year and 3 months (39 months) studentship; Stipend £19,237 per annum; Training grant £1,100 per annum

Application due date: Monday, **10th February 2025**.

Interview: Week commencing **24th February 2025** via Microsoft Teams

Final Funding Decision: Week commencing **10th March 2025**. This is part of a pooled School process, so the selected applicant will be put forward to a reviewing panel for final decision. Applicants will be notified if they are selected and will be informed of the panel decision afterwards.

Start date: 1st October 2025

Science-related enquiries: shaun.mutter@open.ac.uk

Process-related enquiries: STEM-LHCS-PHD@open.ac.uk

Research area/keywords: Computational chemistry, Alzheimer's disease, Parkinson's disease, Molecular dynamics simulations

Project background and description

This project will utilise computational chemistry methodology and software to carry out simulations to explore the structure and aggregation dynamics of biomolecules associated with the progression of neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD).

The aggregation of several different proteins, to form abnormal deposits, has been shown to be an important factor in the progression of neurodegenerative diseases.[1,2] For example, amyloid-β and tau for AD and α-synuclein for PD, have been implicated in the disease's aetiologies.

The complex procedures by which these biomolecules undergo aggregation are poorly understood. Yet, current research identifies the importance of naturally occurring metals in the brain, such as copper and zinc, in the mechanisms leading to progression of the diseases.[3,4] Computational studies have already shown the impact these metal ions can have on the dynamics of amyloid-β and their impact on key structural motifs linked to aggregation, as shown in figure 1. This aggregation has also long been seen as an exploitable pathway for therapeutics. Several small molecules as well as many small peptides [5,6] have exhibited anti-aggregation properties and have therefore been considered as potential therapeutics in the treatment of neurodegenerative diseases.

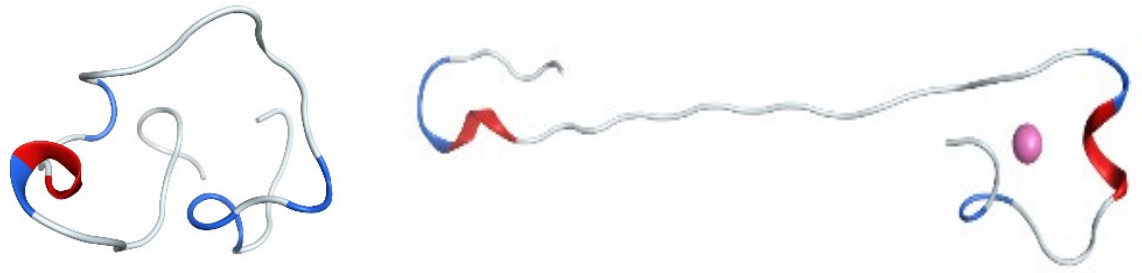

Figure 1: Simulated structure of amyloid-β: with no metal ions present (left), with a coordinated copper ion (right) [3]

This project aims to elucidate the mechanisms of how or why known therapeutics impact aggregation and if this is mediated via interaction with naturally occurring metals. This will take the form of computer simulations, predominantly using molecular dynamics simulations and electronic structure calculations with a variety of established software packages. We aim to (i) model the interactions between metal ions and therapeutics; (ii) simulate the structural dynamics of fragments of proteins linked to aggregation in the presence of therapeutics; and (iii) simulate the impact of therapeutics on aggregated structures.

A deeper understanding of the interplay between metals and aggregation inhibitors may open up avenues in development of therapeutics. Either through modification of current therapeutics or by rationale design of new therapeutics to explicitly target metals or metal binding sites.

Student Experience

A wide range of valuable skills and experience will be acquired through this project. This will include experience in running simulations in a high performance computing environment, the application and theory of multiple computational chemistry packages, coding in a variety of computer languages, design of computational simulations, data analysis and data presentation for national/international conferences and peer-reviewed publications.

References: [1] Breijyeh et al, Molecules, 2020, 25, 5789. [2] Dong-chen et al, Signal Transduct. Target. Ther., 2023, 8, 73. [3] Mutter et al, ACS Chem. Neurosci. 2018, 9, 2795. [4] Moons et al, Sci. Rep. 2020, 10, 16293. [5] Giorgetti et al, Int. J. Mol. Sci., 2018, 19, 2677. [6] Menon et al, Front. Neurol. 2022, 13, 852003

Eligibility

1. Applicants will have a First Class or Upper Second undergraduate degree or Masters degree (or equivalent experience) in Chemistry, Physics, or a related area.
2. The student would be required to live in the UK and within commuting distance to The Open University in Milton Keynes.
3. Both UK and overseas students may apply for this project. The registration for non-UK students will be covered by this project, but not visa or NHS costs.
4. Overseas applicants: Applicants from overseas will also be asked to verify their visa status with original documentation if you have a current visa allowing entry to the UK.
5. Overseas applicants: If you are not from a majority English-speaking country, you will need to demonstrate your competence in the English Language in all four elements: reading writing, speaking and listening. The University requires an overall IELTS score of 6.5 with no less than 6.0 in any of the four categories. You will need to submit this with your application for consideration. Further details and a list of approved providers of accreditation can be found on the UK Visas and Immigration website.

Desirable Criteria

Though previous experience in the following is not essential (all of the techniques required for this project can be learned), this project would be well-suited to candidates who:

1. Have experience of working in high-performance computing (HPC) environments.
2. Have experience in molecular dynamics simulations and/or electronic structure calculations.
3. Have experience in programming/coding.
4. Have excellent communication skills, the ability to conduct scientific literature searches independently, and data analysis experience.

Most importantly, applicants should demonstrate a commitment to interdisciplinary research and a willingness to learn new skills and techniques.

We are committed to widening participation and awarding PhD studentships to a diverse community of applicants. We particularly welcome applications from under-represented groups. Equal Opportunity is University policy.

How to apply

Please check this page for application entry requirements: https://www.open.ac.uk/postgraduate/research-degrees/degrees-we-offer/doctor-of-philosophy-phd

Please submit to STEM-LHCS-PHD@open.ac.uk:

- your CV,
- application form, and
- a personal statement (maximum 2 pages, outlining your suitability for the studentship, what you hope to achieve from the PhD and your research experience to date).

You do not need to submit a research proposal.

Information and the application form is found here: https://www.open.ac.uk/postgraduate/research-degrees/how-to-apply/mphil-and-phd-application-process. Note that as part of the application form, you will be asked to submit further documents (CV, degree transcripts, etc.)