Nicholas J. Fowler

njf16@leicester.ac.uk
njfowler.com
+44(0)7503 769286

Education

PhD Biophysics, University of Manchester — 2014–2018
Thesis: Investigating the role of electrostatic interactions in modulating protein function
Supervisors: Jim Warwicker, Sam de Visser and Chris Blanford

MSc Physics, University of Manchester — 2012–2014
Thesis: Experimental confirmation of a Kibble-Zurek scaling law in a nematic liquid crystal
Supervisors: Ingo Dierking and Tobias Galla

PGCE Physics Secondary, University of Manchester — 2011–2012
Dissertation: Teaching strategies enabling pupils with moderate learning difficulties to learn science more effectively

BSc Physics, University of Manchester — 2007–2010
Dissertation: The physics of traffic jams

Research Experience

Research Associate, Molecular and Cell Biology, The University of Leicester — 2021–present
Being able to resolve the structural conformational heterogeneity of biomolecules is vital for understanding their functionality and crucially important for structure-based drug design. My current research involves working out how to extract the dynamical properties of proteins from readily available NMR data (e.g. NOEs, chemical shifts), and how to use this information to construct dynamic ensembles which simultaneously represent protein structure and dynamics. A key aim is to test using the dynamic ensembles generated for small molecule docking. This could improve structure-based drug design pipelines by revealing cryptic binding sites that would be missed using static structures produced using conventional structural approaches. An important step to achieving this aim will be to find a way to reliably validate dynamic ensembles, as structural models are only useful if they are accurate and can be shown to be accurate. I am investigating how the validation method I developed at Sheffield - Accuracy of NMR Structures Using Rigidity and RCI (ANSURR) can be extended to do this.

Research Associate, Molecular Biology and Biotechnology, The University of Sheffield — 2018–2021
I developed a method (ANSURR) to validate protein structures solved using NMR. NMR protein structures are important because they represent proteins in solution and include a high proportion of small proteins with under-represented folds. However, there is no reliable way to determine the accuracy of NMR protein structures deposited into the Protein Data Bank (PDB). This means that many researchers simply do not use them e.g. for structure-based drug discovery. My method addresses this need. It works by comparing protein flexibility obtained from chemical shifts, with that predicted from the structure, using the mathematical theory of rigidity. A noteworthy conclusion was that the most common measure of structural similarity, backbone RMSD, misses many important differences relating to side chain position and hydrogen bond geometry - which my method is sensitive to. ANSURR can therefore guide NMR spectroscopists to improve this crucial aspect of their structures. The method is freely available here: github.com/nickjf/ANSURR, and validation scores for structures deposited in the PDB can be found on my webserver - ansurr.com. I am now working on how ANSURR can be used to identify and fix errors in structures predicted by the latest AI-based methods (e.g. AlphaFold2, RosettaFold).

PhD Biophysics, School of Chemistry, The University of Manchester   2014–2018
I applied different computational methods (QM/DFT, molecular dynamics and continuum electrostatics) to model metalloproteins with potential biotechnological applications. I developed a method to predict the reduction potential of copper protein mutants and experimentally tested these predictions using techniques in molecular biology and electrochemistry. In collaboration with EPR spectroscopists at Aix-Marseille University, I performed molecular dynamics simulations in a combined experimental/computational study looking for the hypothesised closed conformation of a fruit-ripening enzyme. My simulations revealed that we had not observed a closed conformation and instead found multiple different open conformations.

MSc Physics, School of Physics, University of Manchester   2012–2014
I used nematic liquid crystals to validate a scaling relation for the formation of topological defects that occur during symmetry-breaking phase transitions, such as those in cosmological theories of the early universe, superfluids and other condensed matter systems.

Publications

LD Gahan, **NJ Fowler**, AIP Taylor, R Hawkins, RA Staniforth. Simulating amyloid formation in the context of neurodegenerative disease. *In preparation* (2022).

NJ Fowler, MF Albalwi, S Lee, AM Hounslow, MP Williamson. Improved methodology for protein NMR structure calculation using hydrogen bond restraints and ANSURR validation: the SH2 domain of SH2B1. *In preparation* (2022).

NJ Fowler, MP Williamson. The accuracy of protein structures in solution determined by AlphaFold and NMR. *Structure - Accepted* [bioRxiv 10.1101/2022.01.18.476751] (2022).

NJ Fowler, A Sljoka, MP Williamson. The accuracy of NMR protein structures in the Protein Data Bank. *Structure* 29(12), 1430-1439 (2021).

NJ Fowler, A Sljoka, MP Williamson. A method for validating the accuracy of NMR protein structures. *Nature Communications* 11, 6321 (2020). **(Featured in Editors' Highlights)**

N Iwakawa, NJ Baxter, DCC Wai, **NJ Fowler**, RAV Morales, K Sugase, RS Norton, MP Williamson. Conformational exchange in the potassium channel blocker ShK. *Scientific Reports* 9(1), 1-8 (2019).

E Fournier, S Tachon, **NJ Fowler**, G Gerbaud, P Mansuelle, P Dorlet, SP de Visser, V Belle, AJ Simaan, M Martinho. The Hunt for the Closed Conformation of the Fruit-Ripening Enzyme 1-Aminocyclopropane-1-carboxylic Oxidase: A Combined Electron Paramagnetic Resonance and Molecular Dynamics Study, *Chemistry–A European Journal* 25(60), 13766-13776 (2019). **(A 'Hot Paper' as chosen by editors)**

A Timmins, **NJ Fowler**, J Warwicker, GD Straganz, SP de Visser. Does substrate positioning affect the selectivity and reactivity in the hectochlorin biosynthesis halogenase? *Frontiers in chemistry* 6, 513 (2018).

NJ Fowler, CF Blanford, SP de Visser, J Warwicker. Features of reactive cysteines discovered through computation: from kinase inhibition to enrichment around protein degrons. *Scientific Reports* 7(1), 1-12 (2017).

NJ Fowler, CF Blanford, J Warwicker, SP de Visser. Prediction of reduction potentials of copper proteins with continuum electrostatics and density functional theory. *Chemistry–A European Journal* 23(61), 15436-15445 (2017).

NJ Fowler, I Dierking. Kibble–Zurek scaling during defect formation in a nematic liquid crystal. *ChemPhysChem* 18(7), 812-816 (2017).

Funding, Prizes and Awards

Poster Prize, The Astbury Conversation, University of Leeds	2022
Poster Prize, Advances and Challenges in Biomolecular Simulations EMBO Workshop	2021
Summer Student Bursary (£2080), Physics of Life Network 2	2019
Biomedical Vacation Scholarship (£1600), Wellcome Trust (awarded, but I declined)	2019
Travel Award, NMR in Biophysics and Molecular Biology, University of Leeds	2019
Talk Prize and Travel Award, MGMS Young Modellers Forum, University of Greenwich	2017
Talk Prize, School of Chemistry PhD Conference, Univrsity of Manchester	2017
Talk Prize, BBSRC/MRC DTP PhD Conference, University of Manchester	2017
Poster Prize, Reson8 2nd Biophysical and Biochemical Symposium, University of Leeds	2017
Outstanding Contribution to Public Engagement, Better World Awards, University of Manchester	2016
Talk Prize, Computational and Evolutionary Biology Symposium, University of Manchester	2015
BBSRC DTP PhD Studentship	2014–2018

Invited Talks

CCPN Conference 2022, University of Bath	July 2022
Title: The role of NMR in the structural biology world after the advent of Alphafold	
Molecular and Cellular Biology cluster seminar series, University of Sheffield	May 2022
Title: NMR structure calculation post AlphaFold2. Why bother?	
CCPN Conference 2021, University Of Cumbria	Aug 2021
Title: Validating NMR proteins structures with ANSURR	
RPI NMR Methods Workshop, Rensselaer Polytechnic Institute (online)	Jun 2021
Title: Protein structure validation Assessment with ANSURR	
ICMRBS ECR Webinar Series (online)	Apr 2021
Title: Is your NMR protein structure accurate? We have the ANSURR!	
European Bioinformatics Institute (EMBL-EBI), Cambridge	Jun 2019
Title: Validation of NMR protein structures using structural rigidity theory and random coil index	
Reson8 4th Biophysics and Biochemistry Symposium, University of Sheffield	Jan 2019
Title: Validation of NMR protein structures using structural rigidity theory and random coil index	

Conference presentations

Poster/Flash Talk The Astbury Conversation, University of Leeds	2022
"The accuracy of protein structures in solution determined by AlphaFold and NMR"	
Talk ICMRBS ECR Webinar	2021
"Is your NMR protein structure accurate? We have the ANSURR!"	
Poster Advances and Challenges in Biomolecular Simulations EMBO Workshop (Online)	2021
"Are protein structures predicted by AlphaFold more accurate than NMR structures? TLDR: yes"	
Talk CCPN Conference 2021, University of Cumbria	2021
"Validating NMR proteins structures with ANSURR"	
Poster/Flash Talk Reson8 5th Biophysics and Biochemistry Symposium, University of York	2020
"Is your NMR protein structure accurate? We have the ANSURR!"	

Summer Student Poster Physics of Life Town Meeting, The Royal Society   2019
"Investigating the flexibility of protein regions containing post-translationally modified cysteines"

Poster European Conference on Computational Biology, University of Basel   2019
"Validating NMR protein structures using structural rigidity theory and random coil index"

Poster NMR in biophysics and molecular biology, University of Leeds   2019
"Validation of NMR protein structures using structural rigidity theory and random coil index"

Talk Reson8 4th Biophysics and Biochemistry Symposium, University of Sheffield   2019
"Validation of NMR protein structures using structural rigidity theory and random coil index"

Poster/Flash Talk Reson8 3rd Biophysics and Biochemistry Symposium, University of Manchester   2018
"Prediction of reduction potentials of copper proteins with continuum electrostatics and DFT"

Talk MGMS Young Modellers Forum, University of Greenwich   2017
"Prediction of reduction potentials of copper proteins with continuum electrostatics and DFT"

Poster QM/MM Methods and Applications, University of Manchester   2017
"Prediction of reduction potentials of copper proteins with continuum electrostatics and DFT"

Talk BBRSC/MRC DTP PhD Conference, University of Manchester   2017
"Biophysical correlates of lysine acetylation"

Talk School of Chemistry PhD Conference, University of Manchester   2017
"Prediction of reduction potentials of copper proteins with continuum electrostatics and DFT"

Poster Reson8 2nd Biophysics and Biochemistry Symposium, University of Leeds   2017
"Modulating the reduction potential of copper proteins"

Poster Protein Electrostatics, Freie Universität Berlin   2016
"Modulating the reduction potential of copper proteins"

Poster Dalton 2016: Inorganic Reaction Mechanisms DG, University of Oxford   2016
"Modulating the reduction potential of copper proteins"

Talk Computational and Evolutionary Biology Symposium, University of Manchester   2015
"Modulating the reduction potential of copper protein mutants"

Poster British Liquid Crystal Society Annual Conference, Durham University   2014
"Experimental confirmation of the Kibble-Zurek mechanism in a nematic liquid crystal"

Conference and seminar organisation

ICMRBS ECR webinar series   2020–present
– I jointly organise the monthly International Council on Magnetic Resonance in Biological Systems (ICMRBS) Early Career Researcher Webinars which was highlighted in an editorial in the Journal of Magnetic Resonance (10.1016/j.jmr.2020.106854).

PhD and postdoc seminars   2019–2020
– I organised and chaired a monthly seminar for PhD students and postdocs for department of Molecular Biology and Biotechnology at the University of Sheffield.

Manchester Energy PhD conference   2017
– Organised and chaired the inaugural Manchester Energy PhD conference.
– Secured funding from the University for printing, catering and prizes.

Peer Review

Biochemical Society Transactions, Pacific Symposium on Biocomputing (PSB) Proceedings

Teaching Experience

Level 1/level 2 tutor, Molecular Biology and Biotechnology, Uni. of Sheffield 2018–2021
- Six six-student tutorials per year.
- I set scientific essays, gave written feedback and facilitated discussion in seminars on how to write an excellent scientific essay.

Student supervision, Uni. of Manchester and Uni. of Sheffield 2015–present
- Devised and ran an 8 week project for an undergraduate Summer student, who used this experience to secure a PhD at the University of Cambridge.
- Day-to-day supervision of PhD, MSc and undergraduate students.

Teaching assistant, Uni. of Manchester 2015-2017
- Supported the delivery of maths workshops for BBSRC PhD students.
- Facilitated "Introduction to reaction mechanisms" tutorials for first year students.
- Demonstrated how to run and analyse computational chemistry simulations in a workshop for final year students.

Teacher of science, Loreto High School, Chorlton, Manchester 2012-2014
- Taught physics, chemistry and biology to pupils aged 11-16.
- Graded 'Outstanding' according to Ofsted criteria.
- Continued to teach weekend GCSE revision sessions during my PhD (2014-2018) on a freelance basis.

Academic mentor 2012–present
- Mentored a student during their A levels and physics degree at the University of Oxford. They are now doing their PhD at the University of Bristol.

Private tutor 2012-2018
- Taught maths and physics at A level and maths, physics and chemistry at GCSE level.

Outreach and Public Engagement

Widening participation fellow, Uni. of Manchester 2014–2018
- Created and delivered workshops, talks and tutorials for University events, schools and science festivals aimed at children less likely to be considering higher education. Topics included astrobiology, protein synthesis, computational population dynamics, rocket building and electrochemical cells.

Outreach events, Uni. of Manchester 2014–2018
- Participated in numerous outreach activities outside of my role as a widening participation fellow including training and managing science busking teams, presenting my research to the public at SciBAR events and judging a national science competition at the Big Bang Fair.

Other Experience

Maintenance of Linux cluster 2018-2021
- I maintained a cluster of 12 Linux computers used by the bioNMR group at the University of Sheffield.
- Involved software/hardware installation, data backup and writing programs to automate workflows.

Motivational speaker, various schools and colleges in Manchester 2017–2018
- Wrote and delivered interactive lectures talking about my experience of higher education and why all students should consider going to University.

Internship at Manchester Energy, Uni. of Manchester 2015
- Developed a 'Sim City' style computer game where the player controls the National Grid while trying to meet 2050 environmental targets.
- I led a team presenting an idea for how Greater Manchester should invest in future energy generation to an audience comprising local council members, energy companies and the general public. For this, I received a "Making a Difference" award for outstanding contribution to public engagement.