Brunel University of London

ONE-DAY SCIENTIFIC MEETING

Programme & Abstract Booklet

Wednesday, 4 November 2026

Newton Room (Hamilton Centre)
Brunel University of London
Uxbridge, United Kingdom

Hosted by:
Antimicrobial Innovations Centre (AMIC), Brunel University of London

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Organising Committee

Prof Philip Biggin, University of Oxford
Prof Garrett Morris, University of Oxford
Dr Philip Fowler, University of Oxford
Dr Michelle Sahai, Brunel University of London

Meeting Programme:

TIME	SESSION / SPEAKER
09:30–09:45	Registration
09:45–10:00	Welcome and introduction
10:00–10:40	**Alice McHardy | Helmholtz Centre for Infection Research (remote)** ***Towards Data-Driven Infection Diagnostics***
10:40–11:00	Poster / Lightening flash talks
11:00–11:30	Morning coffee, networking and poster viewing
11:30–12:10	**Paul Finn | Oxford Drug Design** ***The Discovery of a Novel Class of Antibacterial Agents with Potent Gram-Negative Activity***
12:10–12:50	**Tania Dottorini | King's College London** ***Harnessing Artificial Intelligence to reshape research in antimicrobial resistance and infectious diseases***
12:50–14:00	Lunch, poster viewing and networking; **DeepMirror: dd4gh (Drug Design for Global Health) at 1.20pm**
14:00–14:40	**Shozeb Haider | University College London** ***Dynamic Driven Design of β-lactamase inhibitors***
14:40–15:20	**Angelo Frei | University of York** ***Harnessing Metal Complexes for Antibacterial Use***
15:20–15:50	Afternoon coffee, networking and poster viewing
15:50–16:30	**Marc van der Kamp | University of Bristol** ***Insights into serine β-lactamase activity through multiscale simulations***
16:30–17:00	Poster voting and best poster prize
17:00–18:00	Reception and networking

Lightening Talks/Poster Numbers:

1	Juliana F Vilacha	Exploring The Structural Aspects Of Roda In The E.Coli Elongasome
2	Amy Gill	Uncovering The Molecular Mechanism Of Undecaprenyl Phosphate Recycling Within Bacterial Membranes By Deda Family Proteins
3	Reza Talandashti	Lateral Dynamics Within The E. Coli Outer Membrane: The Impact Of Protein Density And Antibiotics
4	Barbara Abreu	Evaluation Of Cyclic Peptide Inhibitors With Antimicrobial Effects Using Molecular Modelling
5	Mingyu Qin	Designing Pamam Dendrimers As Antimicrobial Agents Against Gram-Negative Bacteria
6	Andrej Nikolić	Atomistic Insights Into Porphyrin-Conjugated Antimicrobial Peptides: Environment-Dependent Coil–Helix Balance, Macrocycle Stacking And Bacterial Membrane Target Engagement
7	Carlos Henrique Bezerra Da Cruz	De Novo Design Of Functionalisable Peptide-Based Virus-Like Particles For Antimicrobial Applications
8	Salome Llabres	Multiscale Modelling Of Antibiotic Efflux Through The Macabtolc Pump
9	Thomas Allam	Better Understanding Of Heteroresistance Through Computational Analysis Of Mic Experiments
10	Hershna Patel	Discovery Of Inhibitors Targeting Conserved Regions Of Influenza A Ns1, Nep And Pb2 Proteins.

11	Morgan Alderman-Bowen	Microplastics As Trojan Horses, Ai And Engineering Approaches To Antibiotic Pollution
12	Mayar Al Mohajer	Computational Surveillance Of Antimicrobial Resistance In 7.8 Million Older Adults Using Electronic Health Records
13	Michael Beer	A Transition State-Like Acylenzyme Conformation Distinguishes Carbapenemase Activity In Class A B-Lactamases
14	Linda Phan	Structure-Based Design Of Molecular Glues Targeting Mycobacterium Tuberculosis Isocitrate Lyase (Icl2)
15	Asal Khoshravan Azar	Trimerization Of Nitrite Reductase Ania Is Allosterically Regulated By Copper Binding
16	Salma Darwish	Anti-Microbial Resistance And Molecular Dynamics: Using Md To Compare Drug Binding Sites In The Same Target Enzyme From Different Species
17	Maxim Tsenkov	Bringing Community Predictions And Complexes Together: The Alphafold Database For Antimicrobial Resistance Research
18	Wei-Tse Hsu	Exploring Oligomeric Interfaces Of *Mycobacterium Tuberculosis* Isocitrate Lyase 1 For Inhibitor Discovery
19	Sarath Dantu/ Lyna Benbouabdellah	Protein Dynamical Units organise collective motion and mediate allosteric communication

Title: Towards Data-Driven Infection Diagnostics

Prof. Dr. Alice Carolyn McHardy is Head of the Department of Computational Biology for Infection Research at the Helmholtz Centre for Infection Research (HZI) and Full Professor of Bioinformatics at TU Braunschweig, Germany.

Her research focuses on developing computational methods for the analysis of large-scale biological and epidemiological data, combining machine learning, statistical modeling, comparative genomics, and metagenomics. Her work addresses major challenges in infectious disease research, including antimicrobial resistance, pathogen identification and characterization, microbial community dynamics, and the evolution and spread of viral pathogens. Current research priorities include precision infection medicine, novel anti-infective strategies, and pandemic preparedness.

McHardy obtained her doctorate in bioinformatics from Bielefeld University in 2004, following studies in biochemistry. She subsequently worked at IBM's T.J. Watson Research Center in the United States, led an independent research group at the Max Planck Institute for Informatics, and held the Chair of Algorithmic Bioinformatics at Heinrich Heine University Düsseldorf before assuming her current positions in 2014.

Talk Title: The Discovery of a Novel Class of Antibacterial Agents with Potent Gram-Negative Activity

Dr. Paul W. Finn is Chief Scientific Officer at Oxford Drug Design, a spin-out company from the Chemistry Department of the University of Oxford, where he lead the company's research into the development of new computational methods to support drug discovery and their application to the development of new medicines in the therapeutic areas of oncology and infectious diseases. He has 40 years of experience in drug discovery at major Pharma companies and Biotechs, including leading the team that discovered Beleodaq, a marketed drug for the treatment of peripheral T-cell lymphoma.

https://oxforddrugdesign.com/index.php/who-we-are/

Talk Title: Harnessing Artificial Intelligence to reshape research in antimicrobial resistance and infectious diseases

Professor Tania Dottorini is Professor of Artificial Intelligence in Infectious Diseases at King's College London. She progressed from Assistant Professor to Full Professor between 2016 and 2025 at the University of Nottingham, following a Marie Curie European Fellowship at Imperial College London. Her research integrates artificial intelligence, bioinformatics and big data mining to address to address complex challenges in antimicrobial resistance (AMR) and infectious diseases. She aims to identify key drivers and causal mechanisms underlying the emergence, evolution, and transmission of new genetic variants of resistant pathogens and novel AMR traits, while exploring how host, co-infections, ecological, environmental and climate interactions influence the dynamics of infections and resistance across interconnected systems.

She uses artificial intelligence and large-scale data mining frameworks to integrate heterogeneous clinical, genomic, microbiome, environmental and climate data, to investigate antimicrobial resistance emergence and spread across interconnected systems. Her work drives advancements in diagnostics, surveillance, monitoring, early warning systems, and treatment selection. She has secured more than £17 million in research funding as Principal Investigator and is currently leading several major international programmes. These include an MRC funded project focused on AI driven discovery of novel therapeutic targets for resistant infections together with research organisations and governmental agencies in Bangladesh; a BBSRC programme integrating multi omics, microbiome science and precision farming to investigate AMR dynamics within One Health; a JPIAMR European initiative developing a cloud based, AI powered One Health surveillance platform across Europe and Africa; and an EU EDCTP consortium spanning Europe and Sub Saharan Africa to tackle AMR and diarrhoeal diseases in partnership with hospitals, companies and public health agencies. Professor Dottorini serves on numerous international scientific advisory boards and funding panels, including UKRI, EU, NIHR, Human Frontiers Advisory Panel.

Talk Title: Dynamic Driven Design of β-lactamase inhibitors

Professor Shozeb Haider is a distinguished professor of Computational Biophysics, currently at the UCL School of Pharmacy. Professor Haider's academic journey began at Aligarh Muslim University in India, where he earned his undergraduate and master's degrees in Biochemistry. He moved to the UK to do MRes in Bioinformatics from the University of Leeds. He later obtained his PhD from The Institute of Cancer Research, London. Before joining UCL, he held positions at the University of Oxford and Queen's University Belfast. He also holds the position of an Adjunct Professor at Mount Sinai School of Medicine in New York. He is a currently a senior editor at *eLife*. Professor Haider is an elected Fellow of the Royal Society of Chemistry and has published extensively, with his work being cited over 12,000 times. His research interests include understanding the relationship between molecular structure and function, with applications in drug discovery, with a main focus on β-lactamase enzymes, antimicrobial resistance and quadruplex structures.

Talk Title: Harnessing Metal Complexes for Antibacterial Use

Dr Angelo Frei obtained his PhD at the University of Zurich in Switzerland in 2018 working on theranostic metal complexes for the diagnosis and treatment of cancer. He then secured a Swiss National Science Foundation Grant for a postdoctoral stay in the group of Professor Mark Blaskovich at The University of Queensland in Australia from 2018 to 2020.

After that he moved to London for a second postdoc in the group of Prof. Nicholas Long at Imperial College. Since 2022 he has started his independent group in Bern Switzerland as an Ambizione Fellow.

In 2024, he joined the University of York in the United Kingdom as a lecturer. His group is interested in discovering, exploring and understanding metal-based compounds as antimicrobial agents using state-of-the-art techniques such as machine learning and robotics.

Talk Title: Insights into serine β-lactamase activity through multiscale simulations

β-lactam antibiotics are widely used to treat bacterial infections and have saved numerous human lives. However, the effectiveness of *β*-lactam antibiotics is rapidly declining due to the emergence of antibiotic resistance, mainly driven by *β*-lactamases (BLs), enzymes produced by bacteria to hydrolyse the *β*-lactam ring, leading to inactivation. Quantum mechanical / molecular mechanical (QM/MM) molecular dynamics simulations of the reaction can be used as a computational assay to predict serine *β*-lactamase variants that break down certain antibiotics and those that cannot. Through analysis of these detailed atomic-level simulations, it becomes possible to pinpoint the exact, often very subtle, effects that cause certain variants to be more effective than others in breaking down specific antibiotics. Examples of this will include all classes of serine *β*-lactamases: A, C and D [1,2,3].
Using multi-scale simulations to directly predict resistance-conferring variants and assist with antibiotic selection and optimisation remains a challenge. Both increases in efficiency and accuracy are important, whereas for QM/MM simulations, there is a trade-off between the two. Replacing QM by machine-learning (ML) potentials canhelp solve this but requires appropriate treatment of the crucial electrostatic interactions between ML and MM regions. Here, we show that with our recently developed "electrostatic ML embedding" (EMLE) scheme, ML/MM simulations capture enzyme catalysis accurately *and* efficiently [4], including for antibiotic hydrolysis by *β*-lactamases [5].

1. Chudyk *et al.* (2022) *ACS Infect. Dis*. 8, 1521–1532; Jabeen *et al.* (2024) *ACS Catal.* 14, 7166–7172.
2. Lima and Van der Kamp (2025) *ACS Catal.* 15, 11739–11748.
3. Hirvonen *et al.* (2020) *ACS Catal.* 10, 6188-6196; Wang *et al.* (2026) *J. Chem. Inf. Model.*, 66, 5416–5428.
4. Gradisteanu *et al.* (2026) *Chem. Sci.* 2026, 17, 8542-8556.
5. Chan *et al.* (2026) *ChemRxiv*, DOI: 10.26434/chemrxiv.15008538

Professor **Marc van der Kamp** is Professor of Computational Biochemistry in the School of Biochemistry and Biomedical Sciences at the University of Bristol, having started there in 2015 as a BBSRC David Phillips Fellow. He leads a research group focused on understanding the molecular basis of enzyme function through advanced computational approaches. Research centres on computational enzymology, with particular interests in elucidating enzyme catalysis and biosynthesis, understanding β-lactamase-mediated antibiotic resistance, and uncovering how protein dynamics, intermolecular interactions, and conformational changes influence biological activity. The group uses and develops state-of-the-art atomistic biomolecular simulation techniques, including quantum mechanical/molecular mechanical (QM/MM) methods and enhanced-sampling molecular dynamics simulations. Working closely with experimental collaborators in Bristol, across the UK, and internationally, computational and experimental data are integrated to address fundamental questions in enzyme catalysis, aid design of biocatalysts, and understand and predict antimicrobial resistance.

POSTER ABSTRACTS

POSTER 1:

Exploring the structural aspects of RodA in the *E.coli* elongasome

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The peptidoglycan (PG) is a key component in bacteria due to its role in maintaining bacterial shape and it is also known as the cell wall. The cell wall is a polymer product from transglycosylation and transpeptidation action of protein complexes located in the inner membrane of bacteria; two major complexes contribute to the polymerization process, the elongasome and the divisome. Both complexes polymerize lipid II though transglycosylation of the glycan units and incorporate the growing polymer to the existing PG through the transpeptidase reactions using the pentapeptide stem, with the undecaprenol pyrophosphate being a subproduct of the reaction.

In *E.coli, during the elongation*, the PG polymerization is performed by the elongasome, an assembly of protein containing protein MreC, MreD, MreB and the pair RodA-PBP2. The RodA protein is part of the SEDS (Shape, Elongation, Division and Sporulation) family and is responsible for the transglycosylation (TG) reaction, being characterized by ten transmembrane helices and two main cavities responsible for Lipid II binding. The Penicillin Binding Protein 2 (PBP2) is a class B monofunctional TPase responsible for incorporating the newly synthesized PG to the existing cell wall through, mostly, 4-3 crosslinks, connecting the D-Ala of the growing chain to the mDAP or L-Lys of the PG. While MreB form filaments and regulate the PG synthesis and cell shape, MreC and MreD are believed to regulate the transglycosylation and transpeptidase reactions indirectly through PBP2 modulation. Alongside these two proteins, RodZ acts as an inner membrane (IM) bounded connection of the cytoskeletal complex MreBCD proteins.

Despite the increasing interest on the elongasome, there is still a need to understand the mechanism of lipid II polymerization on a molecular and structural level, allowing for further exploration of possible druggable pockets. In this context, we propose a detailed exploration of the E. coli RodA and its mechanism of Lipid II binding and transglycosyaltion.

Aiming to provide atomistic insight on the conformational changes and structural aspects regulating lipid II polymerization, our experimental design comprises molecular dynamics simulations of RodA, either apo or in presence of a growing chain of lipids, and either alone or in the presence of other proteins of the elongasome. Our studies are a combination of AI tools such as AlphaFold3 and ChaiDiscovery and molecular dynamic (MD) simulations. The MD simulations were performed using GROMACS (v 2024.3) and were performed either using atomistic force fields CHARMM 27 (v 2021) or coarse grained force field MARTINI3 in triplicates for 500 nanoseconds or 10 microseconds, respectively.

Our main findings show a high flexibility of the transmembrane helix (TM) 7, in accordance with previous reports of lipid II binding. Additionally, we identified hotspots of intramolecular interactions with special attention to salt bridge between residues on TM4, E114 and K117. Given that TM4 is locate between the two main cavities of RodA, we mutated either or both residues and analysed the impact of mutations on protein flexibility and volume of both cavities.

Our analyses of RodA-LipidII contact indicate a role for the flexible TM7 as a modulator of the cavity A volume and regulation of the subproduct release. Further mutagenesis studies indicate a major role of charged residues on a juxta membrane helix neighbouring TM7 in stabilizing the bounded lipid II.

Additionally, our analysis indicate that RodA flexibility is dependent not only on the presence of the PBP2 transmembrane helix but on its conformation, either upwards, in an active state, or resting on top of RodA, in an inactive state, as previously demonstrate by the cryo EM structure (PDB code 8tJ3). Our mutagenesis studies showed that single mutations into alanine have a higher impact on the flexibility of the catalytic loop, especially when located on position K117.

These finding shed light into the transglycosylation process identifying the role of highly conserved residues in the binding and processivity of lipid II into a polymer.

POSTER 2:

Uncovering the Molecular Mechanism of Undecaprenyl Phosphate Recycling within Bacterial Membranes by DedA Family Proteins

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The DedA protein family is a large group of bacterial inner membrane proteins whose structures and functions remain largely uncharacterised. *Bacillus subtilis* UptA has been implicated in the recycling of the lipid carrier molecule undecaprenyl phosphate (UndP) - a molecule which is integral to bacterial cell envelope synthesis processes such as peptidoglycan synthesis. Such lipid transport processes represent attractive targets for antimicrobial intervention, as cell envelope synthesis and maintenance are essential for bacterial growth and survival.

This study investigates the molecular mechanism by which *B. subtilis* UptA recycles UndP from the membrane upper leaflet to the lower leaflet. A combination of coarse-grained and atomistic molecular dynamics simulations suggests a proton-motive force driven mechanism of transport, involving key membrane-embedded acidic residues and highly conserved arginine residues at the core of the DedA fold. Additionally, a role for the flexible C-terminal helix of UptA in the recycling mechanism is revealed. Preliminary simulations of other DedA family proteins suggest that *Escherichia coli* YabI and YghB, and *Staphylococcus aureus* UptA are also capable of flipping UndP *in silico*. This approach provides insight into the previously unknown mechanism of lipid transport by these proteins, enhancing our understanding of these potential antimicrobial targets.

POSTER 3:

Lateral Dynamics within the *E. coli* Outer Membrane: the Impact of Protein Density and Antibiotics

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Recent experiments suggest that the *E. coli* outer membrane is laterally heterogeneous, with protein-rich regions enriched in outer membrane proteins (OMPs) and lipid-rich regions dominated by lipids and lipopolysaccharide (LPS). Here, we introduce a molecular model of the *E. coli* outer membrane that enables both protein-rich and lipid-regions to be represented explicitly. We use this model comprising 10.8 M particles, to examine how lipid–protein interactions shape outer-membrane organization and how this organization is affected by the last-resort antimicrobial peptide polymyxin B. Large-scale coarse-grained molecular dynamics simulations reveal distinct behaviour of the two domain types. In protein-rich regions, OMPs show slow lateral motion and are associated with coordinated movement of nearby LPS molecules, leading to collective dynamics. In contrast, LPS-rich regions show faster and less coordinated lateral LPS motion. When polymyxin B is introduced into the system, it disrupts the coordinated LPS flow in protein-rich regions and reduces the overall coherence of the membrane. Furthermore, we find that polymyxin B penetrates more deeply into lipid-rich regions compared to protein-rich regions. This deeper penetration may indicate that lipid-rich domains present a lower kinetic barrier to polymyxin B insertion, while OMP crowding and coordinated LPS organization in protein-rich regions hinders the progress of polymyxin B1 into the outer membrane. Together, these results show how the lateral organisation of the *E. coli* outer membrane gives rise to distinct local dynamics and suggest that polymyxins perturb the Gram-negative envelope in a region-dependent manner.

POSTER 4:

Evaluation of cyclic peptide inhibitors with antimicrobial effects using molecular modelling

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Antimicrobial resistance has risen as one of the major public health concerns worldwide, leading to resistance from previously susceptible bacteria. Therefore, novel antibiotic molecules are needed that can circumvent the current resistance mechanisms.
Gram-negative bacteria possess a cell wall consisting in a double membrane with a layer of cross-linked peptidoglycan in between. The outer leaflet of the outer membrane is composed by lipopolysaccharide (LPS) further contributing for their pathogenicity. While a plethora of protein complexes are involved in the biosynthesis and maintenance of the cell wall, the divisome and the Lpt complexes stand out due to their key roles in synthesizing peptidoglycan and in the LPS transport to the outer leaflet, respectively.
Belonging to the divisome complex, FtsI is a transmembrane transpeptidase responsible for the cross-linking of peptidoglycan units at the time of cell division, and the main target of beta-lactam antibiotics, while the LptDEM subcomplex is responsible for flipping LPS to the outer leaflet.
In this work, we investigated the binding of cyclic peptides with a central scaffold to both FtsI and LptDE as potential inhibitors of both of these proteins. For LptDE we were able to obtain an optimal cyclic peptide which binds with nanomolar affinity to the LptDE complex and interacts with the surrounding lipids. On the other hand, binding of a different cyclic peptide to FtsI insertion mutants revealed a stable binding mode, by interacting thoroughly with the protein, displaying increased binding in comparison with a beta-lactam inhibitor.
Therefore, the usage of cyclic peptides with a central scaffold can pave new ways to counter antibiotic resistance and may provide new therapeutic approaches to tackle this public health concern.

POSTER 5:

Designing PAMAM Dendrimers as Antimicrobial Agents against Gram-Negative Bacteria

Mingyu Qin[1], Reza Talandashti[1] and Syma Khalid[1]

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Antimicrobial resistance (AMR) is a major threat to global health, and multidrug-resistant Gram-negative bacteria are among the most difficult pathogens to treat. Much of their resilience derives from the outer membrane (OM), an asymmetric bilayer whose outer leaflet is composed predominantly of lipopolysaccharide (LPS). This tightly packed LPS layer forms a selective permeability barrier that excludes many conventional antibiotics, motivating the search for new therapeutic strategies.

Poly(amidoamine) (PAMAM) dendrimers are synthetic, hyperbranched polymers with a precisely defined structure and a multivalent surface that can carry a high density of tuneable functional groups. These features make them attractive antimicrobial candidates, yet two obstacles limit their development: the cytotoxicity associated with high cationic charge, and the lack of quantitative principles relating surface chemistry to OM interaction. Here, we use coarse-grained molecular dynamics simulations as a design tool to address this problem. Drawing on the physicochemical features of antimicrobial peptides, we systematically vary the terminal-group chemistry and charge distribution of the dendrimer to identify the molecular features that enhance OM engagement while keeping net charge, and hence toxicity, low.

The study is carried out at two levels of complexity. Using simplified LPS and phospholipid membrane models, we show that cationic charge and hydrogen-bonding capacity act synergistically to anchor dendrimers to the OM, and that clustering surface charges supports stable binding at a lower net charge than distributing them evenly. The most promising designs are then examined in a large, biologically realistic OM model containing outer membrane protein (OMP) “islands”, which reproduces the co-organisation of OMPs and LPS reported in recent experimental studies of the *E. coli* outer membrane.[1,2] In this heterogeneous setting, cationic dendrimers accumulate in anionic pockets on OMP surfaces and form long-lived electrostatic bridges, acting as a “molecular glue” that slows the lateral diffusion of both LPS and OMPs by up to an order of magnitude. In line with the charge-distribution principles established above, clustered-charge dendrimers additionally bridge neighbouring proteins into stable dimers and trimers, whereas scattered-charge variants leave them largely monomeric. Together, these results link dendrimer surface chemistry to membrane-scale perturbation, providing transferable design principles for potent, low-toxicity dendrimer

antimicrobials and suggesting a mechanism by which they may impair the integrity and transport function of the Gram-negative OM.

[1]Benn, G. *et al.* Phase separation in the outer membrane of *Escherichia coli*. *PNAS* 118, e2112237118 (2021).
[2]Webby, M. N. *et al.* Lipids mediate supramolecular outer membrane protein assembly in bacteria. *Sci. Adv.* 8, eadc9566 (2022).

POSTER 6:

Atomistic Insights into Porphyrin-Conjugated Antimicrobial Peptides: Environment-Dependent Coil–Helix Balance, Macrocycle Stacking and Bacterial Membrane Target Engagement

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Membrane-targeting antimicrobial peptides (AMPs) are attractive candidates against resistant bacteria, but their therapeutic application can be limited by various factors including proteolytic instability (1). Conjugation of a porphyrin to an AMP may offer certain peptide protection from proteolysis and introduce complementary modes of action: light-independent membrane partitioning and light-activated photodynamic activity (2). However, the porphyrin also adds a bulky hydrophobic group that can potentially alter the peptide's conformation and the way it engages bacterial membrane targets. Here, we examined how strongly peptide conformation depends on the attached porphyrin, and whether this dependence persists from solution to the membrane interface.

Following a QM-informed parameterization of the porphyrin, all-atom molecular dynamics simulations using AMBER ff19SB, GAFF2 and Lipid21 with OPC water were performed on free peptides and their porphyrin conjugates. The peptides differ in length, amphipathicity and intended target (lipid membrane or lipopolysaccharide (LPS)). The simulated environments included aqueous multi-copy systems, an SDS micelle, a POPE/POPG bilayer and an LPS target. Well-tempered metadynamics was additionally applied to probe the porphyrin-dependent coil–helix balance. Trajectories were analyzed for secondary structure, insertion depth and local bilayer thickness, and interaction energies were estimated by MM/PBSA.

In water, the effect of conjugation on helix persistence was sequence-dependent, and porphyrin-stacked dimers formed spontaneously. On the micelle, the conjugates remained helical as in the case of lipid bilayer and LPS simulated interactions. Additionally, in the bilayer, the porphyrin penetrated deeper than the peptide backbone, consistent with a hydrophobic anchoring role, while local bilayer thinning was maintained. Moreover, the LPS-simulated interactions retained favorable LPS contacts after conjugation, although MM/PBSA indicated a weaker interaction.

Together, these findings highlight the sequence- and environment-dependent effects of porphyrin attachment on peptide conformation, self-association and membrane interactions. Ongoing work is assessing conformational sampling across different starting states and extending comparison between simulated ensembles and experimental far-UV circular dichroism data. This study provides an atomistic outline for interpreting the structural consequences of porphyrin conjugation, while experimental validation is needed to determine their implications for antimicrobial activity and selectivity.

ACKNOWLEDGMENTS

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[2] D. A. Mendonça et al. Bioconjug Chem. **2021**, 32 (6) ,1067.

POSTER 7:

De novo design of functionalisable peptide-based virus-like particles for antimicrobial applications

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Abstract

The growing prevalence of antimicrobial resistance is creating an urgent need for new therapeutic strategies that can complement or overcome conventional antibiotics. Antimicrobial peptides (AMPs) are promising candidates because of their diverse mechanisms of action and their potential to retain activity against drug-resistant bacteria. Here, we explore virus-inspired peptide nanostructures as modular platforms for the delivery and presentation of antimicrobial functionality.

β-annulus (βA) peptides derived from *Sobemovirus* capsid proteins are known to self-assemble into virus-like particles capable of encapsulating a range of molecular cargos. Building on this principle, we previously combined protein engineering and coarse-grained molecular dynamics simulations to design βA-derived assemblies functionalised with antimicrobial motifs, demonstrating stable nanocapsule formation and favourable interactions with bacterial membrane models *in silico*.

In this work, we extend this strategy using machine-learning-guided protein design to generate novel trigonal peptide assemblies based on the βA motif from Sesbania mosaic virus (SeMV). Candidate sequences were designed to preserve self-assembly while providing a scaffold suitable for subsequent functionalisation with antimicrobial peptides. Their structural stability and assembly behaviour were assessed through extensive coarse-grained molecular dynamics simulations, followed by experimental characterisation using atomic force microscopy.

This integrated computational–experimental approach provides a route towards the rational design of programmable peptide-based virus-like particles and supports their development as adaptable nanostructures for antimicrobial applications.

References

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POSTER 8:

Multiscale modelling of antibiotic efflux through the MacABTolC pump

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Active drug efflux is one of the main drivers of multidrug resistance in Gram negative bacteria. It relies on the expression of tripartite efflux pumps, which are specialised protein complexes able to expel drugs from the periplasm. Understanding their function is of great interest, as their inhibition may restore the efficacy of a wide range of existing antibiotics. MacABTolC, which exports macrolide antibiotics and toxins, belongs to a recently characterized superfamily of tripartite efflux pumps containing ABC transporters[1]. Their unique structure suggests a novel mechanism of efflux. The current hypothesis states that MacB works as a set of molecular bellows fuelled by ATP [2] that pushes substrates across the MacA gating ring. However, it is not clear whether the binding or the hydrolysis of ATP provides the power stroke needed for efflux [3]. Here, we have employed state-of-the-art molecular modelling methods to study the function of the MacABTolC pump. Computational modelling methods have enabled us to understand the role of the MacA gating ring, which prevents the backflow of substrates [2]. Also, we are we are currently investigating the activation of the pump using enhanced sampling and multiscale modelling methods.

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[2] Crow A et al (**2017**) *PNAS*, 114, 12572-12577
[3] Souabni H et al (**2021**) *Comms Bio*. 4, 493.

POSTER 9:

Better understanding of heteroresistance through computational analysis of MIC experiments.

Thomas Allam,[1] Caleb Marsh,[2] Charlotte Hind,[2] Mark Sutton,[2] Samantha Pearman-Kanza,[1] and Jeremy Frey[1]

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Keywords: MIC assay, Data curation, Data analysis, Heteroresistance

Global Antimicrobial Resistance (AMR) related deaths are predicted to rise to 10 million per year by 2050 from 4.71 million in 2019.[1] Therefore the need for FAIR (Findable, Accessible, Interoperable, and Reusable)[2] minimum inhibitory concentration (MIC) datasets have never been greater, to better understand the causes of AMR.[3]

In this work we share our experience working with UKHSA to curate 2350 complete MIC assay experiments into a FAIRer computationally accessible format and the frameworks used to do so. The dataset is then explored for growth by strain and edge effects. Finally non-inhibitory concentration is algorithmically called and used to screen the dataset for heteroresistance trends.

References

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POSTER 10:

Discovery of inhibitors targeting conserved regions of Influenza A NS1, NEP and PB2 proteins.

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Influenza A is a prevalent infectious virus capable of causing significant respiratory illness worldwide. The virus genome encodes several proteins and upon infection, antiviral drugs targeting the neuraminidase surface protein, the acid polymerase subunit and M2 transmembrane proteins are the only treatment options available. However, emergence of antiviral resistance due to mutations highlights the requirement of investigating other proteins as targets for antivirals. Therefore, this research aims to identify 1) highly conserved regions of influenza A viral proteins that overlap with potential ligand binding sites and 2) inhibitor molecules that can bind to those sites. Sequences of the influenza A non-structural 1 protein (NS1), nuclear export protein (NEP) and basic polymerase 2 (PB2) were aligned and the degree of amino acid conservation was calculated for each protein. Missing parts of the experimental structures were predicted and molecular dynamics (MD) simulations performed to improve the accuracy of the protein models. Potential binding hot spots were identified with computational solvent mapping based on the FTMap algorithm. Selected binding sites were subjected to virtual screening against a library of ~50,000 chemical compounds from the ZINC database using a combination of two docking algorithms, namely AutoDock Vina and AutoDock 4. Several highly conserved areas that overlap with ligand binding sites were located and mapped onto the protein structures. MD simulations revealed conformationally flexible regions of the NS1 and NEP models, and virtual screening results revealed drug-like compounds with predicted binding affinities up to approximately -10.0 kcal/mol. Compounds targeting evolutionary conserved regions are less likely to undergo mutations that could render antiviral drugs ineffective. The predicted drug-like compounds could serve as laboratory tools to investigate protein functions and/or be developed into antivirals.

POSTER 11:

Microplastics as Trojan Horses, AI and Engineering Approaches to Antibiotic Pollution

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Environmental persistence of micropollutants, such as antibiotics, is a growing threat to human health and contributes to future antimicrobial resistance (AMR) risk. Microplastics (MPs) interact with these environmental pollutants and influence their transport through environments, persistence and bio-accumulation in food webs. The interactions of 'pristine' polymers and anti-biotics is well-studied however, we hypothesise that protist ingestion, digestion and egestion alter the chemical environment of MP surfaces and subsequent interactions.

This PhD project will employ engineering biology principles and AI-driven molecular modelling techniques to investigate the molecular interactions between environmentally-relevant antibiotics and biologically-processed MP surfaces. We will design molecular dynamics simulations and validate models with in-vitro studies involving model protist species such as Tetrahymena pyriformis. With our industrial partner DeepMirror, we will identify molecular interaction fingerprints to improve the accuracy of models integrated into our workflow.

POSTER 12:

COMPUTATIONAL SURVEILLANCE OF ANTIMICROBIAL RESISTANCE IN 7.8 MILLION OLDER ADULTS USING ELECTRONIC HEALTH RECORDS

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Background Large electronic health record (EHR) networks offer opportunities for computational antimicrobial resistance (AMR) surveillance. We assessed phenotype-specific resistance patterns and associations with social vulnerability among older adults.

Methods We conducted a serial cross-sectional analysis of Epic Cosmos records from US adults aged ≥65 years during 2016–2025, retaining the first susceptibility-tested record per patient, phenotype and calendar year. Six phenotypes were evaluated: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* spp. (VRE), extended-spectrum beta-lactamase phenotype/proxy (ESBL), and carbapenem-resistant *Enterobacterales* (CRE), *Pseudomonas aeruginosa* (CRPA) and *Acinetobacter* spp. (CRAB). Aggregated Poisson models with tested-record offsets, state fixed effects and location-clustered robust standard errors estimated adjusted positivity ratios (APRs), controlling for year, demographics, payer, specimen, care setting and residential ZIP-code-linked Social Vulnerability Index (SVI).

Results Analysis included 21,427,196 tested records from 7,750,830 patients across 57,108 anonymous clinical locations. Positivity was 43.5% for MRSA, 29.6% for ESBL, 19.0% for CRAB, 6.0% for CRPA, 4.1% for VRE and 0.4% for CRE. Between 2016 and 2025, VRE positivity declined from 6.2% to 3.5% and CRPA from 8.6% to 5.1%; MRSA remained broadly stable. Compared with the least vulnerable SVI quintile, the most vulnerable had higher adjusted positivity for five phenotypes, including MRSA (APR 1.18; 95% CI 1.17–1.20), but lower ESBL positivity (0.92; 0.89–0.95). Noninpatient settings generally had lower adjusted positivity. Tested volumes and contributing locations increased for every phenotype.

Conclusions EHR-based computational analyses identify heterogeneous AMR patterns that may inform targeted surveillance and stewardship. Findings describe positivity among tested records, not population incidence; temporal trends remain sensitive to changing network composition.

POSTER 13:

A transition state-like acylenzyme conformation distinguishes carbapenemase activity in class A β-lactamases

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Carbapenems are the most potent β-lactams, key antibiotics for healthcare-associated infections by Gram-negative bacteria and evade hydrolysis by most β-lactamases; but are increasingly threatened by emergence of enzymes exhibiting hydrolytic activity towards them. Of the four recognised β-lactamase subclasses, class A (active-site serine enzymes that hydrolyse β-lactams via a covalent acylenzyme intermediate) is the most widely disseminated and, while the majority of such enzymes react with carbapenems to form long-lasting acylenzyme complexes, several possess carbapenem-hydrolysing activity (carbapenemases). Here, we investigate the basis for these differences in a panel of class A beta-lactamases using molecular dynamics (MD) simulations of the respective acylenzyme complexes and tetrahedral intermediates (TI). The simulations reveal multiple features associated with catalytic activity across the spectrum of enzymes tested, including more extensive interactions of the carbapenem acylenzyme carbonyl and generally increased lifetimes of active site water molecules positioned for deacylation. Analysis of the dynamic trajectories shows carbapenemases to have reduced root mean-squared fluctuation (RMSF) differences between the acylenzyme and TI, that are not limited to the active site, indicating that the acylenzyme complex is pre-organised for reaction in carbapenemases but not in carbapenem-inhibited enzymes. Similarly, Principal Component Analysis (PCA) of acylenzyme and TI dynamics shows greater overlap between the two states in carbapenemases, providing further evidence for acylenzyme pre-organisation. Such simulations may represent an effective computational assay able to identify enzymes with carbapenemase activity at relatively modest computational cost.

POSTER 14:

STRUCTURE-BASED DESIGN OF MOLECULAR GLUES TARGETING MYCOBACTERIUM TUBERCULOSIS ISOCITRATE LYASE (ICL2)

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Addressing the urgent global health challenge of drug-tolerant *Mycobacterium tuberculosis* (*Mtb*) requires therapeutic strategies that extend beyond traditional targets towards previously undrugged proteins. During latent infection, *Mtb* survives within host macrophages by engaging the glyoxylate shunt via isocitrate lyase (ICL), a metabolic bypass entirely absent in humans, presenting an attractive drug target. There are two isoforms of ICL (ICL1 and ICL2), with ICL1 playing a dominant role during active growth and infection, while the structurally distinct ICL2 contributes more under stress conditions associated with latent and chronic infection. Inhibition of both isoforms is required to fully eliminate *Mtb*.

Existing drug discovery efforts have mainly targeted the active site of ICL1, but no compounds have progressed through clinical trials. Recent structural resolution of ICL2 [1], together with insights into its acetyl-CoA–mediated allosteric activation mechanism [2], highlights it as a promising drug target. To leverage this, we present an integrated structure-based workflow for molecular glue discovery that targets the allosteric mechanism of *Mtb* ICL2, locking its inactive state. We used molecular dynamics (MD) simulations to map conformational ensembles and pocket flexibility, incorporating these features into a conformationally aware pharmacophore model to screen the ZINC database for novel molecular glues capable of modulating enzyme function.

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POSTER 15:

Trimerization of Nitrite Reductase AniA is allosterically regulated by copper binding

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Metalloenzymes play essential roles in biological processes, yet the interplay between metal binding, structural dynamics, and oligomerisation remains poorly understood. This gap is particularly relevant for ***Neisseria gonorrhoeae***, an increasingly antibiotic-resistant pathogen that survives under anaerobic conditions by reducing nitrite to nitric oxide via the copper-dependent enzyme AniA. Targeting AniA therefore represents a potential strategy to circumvent conventional antibiotic treatments. AniA exists as a monomer in its apo form and assembles into a functional trimer upon metal loading. It contains two distinct copper sites: a Type-1 site within each monomer and a Type-2 site at the interface between subunits, which constitutes the catalytic centre. A key unresolved question is whether copper binding drives trimerisation or whether trimer formation is a prerequisite for copper incorporation, especially given that both processes are slow and effectively irreversible in vitro. To address this, we performed molecular dynamics simulations combined with quantum-mechanical parameterisation of copper-coordinating residues, analysing both apo and holo states of the monomer and trimer. Our results reveal pronounced structural rearrangements centred on a flexible C-terminal segment. This region is highly dynamic in the apo state and remains disordered in the holo monomer; only becoming stabilised upon trimer formation in the holo state. These findings demonstrate that copper binding alone is insufficient to stabilise the protein, and that oligomerisation is required for ordering of the C-terminal region. This suggests a cooperative mechanism in which Type-1 copper loading and trimer assembly are interdependent processes that enable formation of the catalytic Type-2 site.

POSTER 16:

Anti-microbial resistance and molecular dynamics: using MD to compare drug binding sites in the same target enzyme from different species.

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Globally around 2M people die yearly from invasive fungal infections, particularly the immunocompromised (e.g., following chemotherapy). Resistance to antifungals has increased due to overuse of medications. *Candida* species are major causes of life-threatening infections and are increasingly resistant to available antifungal drugs. *Candida auris*, first reported in Japan in 2009 since spreading globally, is not only multi-resistant but also survives extreme cleaning regimens. Our lab is working with F2G - a UK biotech SME that develops new antifungal drugs. They have discovered Orotomides, a new class of antifungals, the first lead compound being Olorofim. Orotomides target dihydroorotate dehydrogenase (DHODH), which carries out the rate limiting step in pyrimidine synthesis, oxidising dihydroorotate (DHO) to orotate. Fungal death ensues since fungal cells have no pyrimidine rescue program. However, while Olorofim is highly active against *Aspergillus fumigatus*, it is inactive against most *Candida* species, even though they have a highly homologous enzyme. The goal of this project has been to design and test a new Orotomide that inhibits *Candida albicans* DHODH.
Since the *Aspergillus* and *Candida* enzymes share conserved binding sites for ubiquinone, their oxygen acceptor, which is the site of Orotomide binding, it is feasible to modify Olorofim to develop a new antifungal drug active against *Candida* species .Using homology models of both enzymes, we identified key differences in the active sites and performed molecular dynamics simulations using GROMACS to compare the binding interactions of olorofim in each enzyme and analyse these to ubiquinone binding. PLIF analysis identified key residue interactions, while MM/PBSA calculations estimated relative binding free energies, identifying differences between olorofim and coenzyme Q binding in *Candida* and *Aspergillus* DHODH. These findings provide a basis for rational optimisation of olorofim to improve activity against *Candida* species.

POSTER 17:

BRINGING COMMUNITY PREDICTIONS AND COMPLEXES TOGETHER: THE ALPHAFOLD DATABASE FOR ANTIMICROBIAL RESISTANCE RESEARCH

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We hypothesise that broad structural coverage of bacterial proteins and their complexes could accelerate antimicrobial resistance (AMR) research, yet experimental structures cover only a fraction of bacterial proteomes and even fewer of their protein complexes. To help provide this missing piece, the AlphaFold Protein Structure Database (AFDB) has evolved from a single-source monomer archive into a community platform for predicted protein and complex structures.

We present three developments relevant to AMR. First, AFDB now integrates large-scale third-party datasets through the AFDB-Integration-Toolkit, which helps contributors convert diverse outputs into harmonised, consistency-checked entries, available via web, API and bulk download. Second, this toolkit enabled integration of the AllTheBacteria dataset: 17.7 million predictions for hypothetical proteins from over 2.4 million bacterial and archaeal genomes spanning 11,824 species. Derived directly from genome assemblies, 90.6% have no identical sequence in UniProt, extending structural coverage to hypothetical proteins absent from the core AFDB. Third, AFDB now provides quaternary structures. Approximately 31 million homo- and heterodimers were predicted and filtered using benchmarked interface-confidence criteria, with bacterial complexes among the most confidently predicted across taxonomic groups. For AMR-relevant bacteria, this yields 533,038 homodimers and 9,793 heterodimers at high confidence.

The new AFDB Portal View groups predictions by global health topic. Its AMR category brings together over 169 million bacterial entries from multiple contributors, including WHO Global Health bacterial proteomes, UniProt-derived monomers and dimers, and AllTheBacteria. Where several contributors have modelled the same sequence, independent predictions are retained as alternative structural hypotheses. Together, these resources offer an open, searchable structural starting point for target identification, mechanistic hypotheses and molecular modelling in AMR research. We want to work with the AMR community to identify what would help most and where gaps remain, and then address them, including by integrating community-contributed datasets.

POSTER 18:

Exploring oligomeric interfaces of *Mycobacterium tuberculosis* isocitrate lyase 1 for inhibitor discovery

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Mycobacterium tuberculosis isocitrate lyase 1 (ICL1) is a metabolic enzyme of interest for antitubercular drug discovery. Binding sites outside its catalytic pocket could offer alternative opportunities for inhibition, but their structural accessibility and suitability for ligand binding remain poorly characterized. Here, we integrate molecular dynamics simulations, pocket characterization, solvent mapping, and pharmacophore-based virtual screening to investigate an interfacial cavity in ICL1 and identify candidate compounds for experimental evaluation.

Our analyses identified a central cavity at the ICL1 oligomerization interface that remained structurally stable in both dimeric and tetrameric simulations. Multiple pocket detection methods identified this cavity, while independent solvent mapping revealed favorable sites for interactions with small organic probes. Computational alanine scanning identified predicted contributors to dimer–dimer association that were spatially distinct from the cavity, suggesting that ligand binding may influence function through mechanisms beyond directly disrupting these contacts.

To translate the solvent-mapping results into screening models, we developed acs2ph4, a tool that converts E-FTMap atomic consensus sites into pharmacophore features. We used the resulting pharmacophores to screen the ZINC database and applied additional computational filters to prioritize candidate compounds. Experimental validation of the selected compounds is currently underway.

This work connects characterization of a potential binding site with compound prioritization, providing a basis for testing whether an interfacial cavity can be exploited to modulate ICL1 activity.

POSTER 19:

Protein Dynamical Units organise collective motion and mediate allosteric communication

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Proteins use multi-time-scale dynamics to deliver biological functions. While existing approaches describe collective motions, correlated fluctuations and kinetic states, these representations do not necessarily establish if a protein can be decomposed into interacting residue-supported subsystems with reproducible predictive properties. In this study, we develop a mathematical framework for Protein Dynamical Units (PDUs), a proposed organisational layer between residue-level descriptions and global protein dynamics. A candidate PDU is characterised by two properties: 1) the ability of its member residues to predict each other's dynamics and 2) its effective incoming and outgoing communication with the surrounding system. In a finite-lag linear reference model, the subsystem–environment coupling is represented by off-diagonal blocks of a partitioned dynamical operator. Resolution-dependent effective rank measures the interface widths, while predictive dimension characterises the complexity of the subsystem's predictive states. These quantities motivate a criterion for the identification of candidate units with restricted effective interfaces.

We demonstrate that a Channel Optimization growth algorithm, implemented based on the above two defining properties of PDUs, can detect units in T4 Lysozyme and Synaptotagmin-C2A with established communication channels from molecular dynamics data. With channels switched off, the recovery of kinetic rates of the global modes significantly deteriorates.

This work establishes a testable mathematical and computational basis for investigating whether PDUs constitute a reproducible organisational layer of protein dynamics. In addition, it motivates future investigation of whether time-dependent residue pathways can be exploited for rational protein design.