Project Details	
Project Code	IIAR27Br Oliveira
Title	Deciphering Intramolecular Communication Networks to Identify New Antibiotic Targets in Multidrug-Resistant Bacteria
Research Theme	Infection, Immunity & Antimicrobial Resistance
Project Type	Other
Summary	Bacteria are becoming resistant to many of our most important antibiotics, creating an urgent need for new treatments. This project will investigate how proteins communicate internally to control their function, focusing on DNA gyrase, a key bacterial enzyme and major antibiotic target. Using advanced computer simulations alongside experiments, this project will uncover how structural changes travel through this molecular machine, how resistance mutations alter these pathways, and how new drugs could disrupt them. The project offers training at the interface of computational chemistry, biophysics, structural biology, and antibiotic discovery, opening the door to the next-generation antibacterial therapies.
Description	Antibiotic resistance is one of the major global health challenges of the twenty-first century, yet the development of new antibacterials has failed to keep pace with the emergence and spread of resistant pathogens. Given the difficulty of identifying entirely new antibacterial targets, an attractive alternative is to develop novel ways of targeting well-validated enzymes. Bacterial type II DNA topoisomerases, DNA gyrase and topoisomerase IV, are particularly important in this regard. These essential enzymes regulate DNA topology during replication, transcription and chromosome segregation through an ATP-driven cycle involving DNA binding, cleavage, strand passage and religation. While fluoroquinolone antibiotics successfully target the DNA breakage-reunion reaction, resistance to this class is now widespread, highlighting the need for alternative approaches to inhibiting topoisomerase function. This project addresses the fundamental questions of how long-range communication within DNA gyrase coordinates the distinct biochemical events (i.e., ATP binding/hydrolysis and DNA binding/cleavage/translocation/relegation) required for enzyme function and how these communication networks can be exploited to identify new opportunities for antibacterial inhibition. Specifically, the project will investigate how structural and dynamical changes are transmitted between key functional regions of DNA gyrase, including the ATPase site, DNA breakage-reunion site and known allosteric sites. Understanding these pathways will provide insight into how this complex molecular machine operates and reveal new strategies for disrupting its activity using small molecules. The project builds on our recently developed dynamical-nonequilibrium molecular dynamics (D-NEMD) simulation approach, which enables the identification of communication pathways within proteins. D-NEMD introduces a perturbation (e.g. ligand removal) into an equilibrium simulation and monitors how the resulting response propagates through a protein structure. This approach has successfully revealed functionally important communication networks in diverse biological systems, including human nicotinic receptors, SARS-CoV-2 proteins and antibiotic-

	resistance β-lactamases. In the latter case, we used D-NEMD to predicted remote sites involved in functional communication and subsequently validated their importance experimentally. More recently, we applied D-NEMD to the ATPase domains of Mycobacterium tuberculosis DNA gyrase, identifying communication pathways within these domains and providing the foundation for the proposed work. The project will initially focus on M. tuberculosis DNA gyrase, an important target for anti-tuberculosis drug development. This system offers an ideal training platform because high-quality structural data are available and our previous D-NEMD studies provide a strong foundation for the student to learn simulation setup, execution and analysis. Following training in biomolecular simulation, the student will extend D-NEMD studies to larger and more biologically relevant gyrase assemblies, including complexes with DNA and small-molecule inhibitors such as the allosteric inhibitor evybactin. These simulations will identify communication networks operating both within and between gyrase subunits, revealing residues and structural regions that play key roles in long-range functional coupling across the enzyme. Based on these analyses, we will predict sites where mutation is expected to disrupt information transfer between functional centres, as well as identify potential allosteric pockets that may be amenable to small-molecule binding. The functional importance of these regions will then be assessed experimentally through targeted mutagenesis and DNA gyrase activity assays. In parallel, molecular docking and virtual screening approaches will be employed to identify and prioritise small molecules capable of binding to these sites and perturbing the communication networks that underpin gyrase function. The project has four main objectives: 1- Characterise communication networks within DNA gyrase using D-NEMD simulations to determine how ATP binding and hydrolysis are coupled to DNA cleavage, strand passage and religation. 2- Identify communication pathways linking active and allosteric sites by investigating how signals are transmitted between the ATPase site, DNA breakage-reunion site and inhibitor-binding regions, including the evybactin-binding site. 3- Test the functional importance of predicted communication networks by identifying residues whose mutation is predicted to disrupt information transfer and experimentally evaluating these predictions using DNA gyrase activity assays. 4- Explore opportunities for inhibitor discovery by combining simulation results with molecular docking and virtual screening to identify small molecules capable of disrupting key communication pathways through novel mechanisms of action. The student will receive interdisciplinary training in computational biophysics, structural biology, molecular simulation, antibacterial drug discovery and experimental enzymology, supported by Bristol's world-class High-Performance Computing facilities. Importantly, they will be encouraged to take ownership of the project from an early stage by, e.g., selecting the most relevant gyrase structures/conformations/complexes for investigation, prioritising communication pathways and allosteric sites for study, designing mutations for experimental validation,

	determining the balance between computational and experimental work, and exploring opportunities to extend their studies to other type II topoisomerases from additional clinically-important pathogens. This project combines methodological innovation, mechanistic insight and translational relevance, providing an exciting interdisciplinary research programme at the interface of computational chemistry, structural biology and antibacterial drug discovery, while offering substantial scope for scientific independence and creativity.
Can be completed part time?	Yes
Supervisory Team	
Lead Supervisor	
Name	Dr Sofia Oliveira
Affiliation	Bristol
College/Faculty	Faculty of Science and Engineering
Department/School	School of Chemistry
Email Address	sofia.oliveira@bristol.ac.uk
Co-Supervisor 1	
Name	Professor James Spencer
Affiliation	Bristol
College/Faculty	Faculty of Life Sciences
Department/School	School of Cellular and Molecular Medicine
Co-Supervisor 2	
Name	Professor Adrian Mulholland
Affiliation	Bristol
College/Faculty	Faculty of Science and Engineering
Department/School	School of Chemistry
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	