Project Details	
Project Code	IIAR27Ba Iqbal
Title	Decoding the grammar of plasmid evolution: a hundred years of antibiotic resistance
Research Theme	Infection, Immunity & Antimicrobial Resistance
Project Type	Dry lab
Summary	Plasmids are mobile pieces of DNA that can spread between bacteria. They evolve by rearranging and swapping genes, and over the past century have emerged as a major source of antimicrobial resistance (AMR). Computational breakthroughs mean we can compute evolutionary distances between plasmids using DNA similarity, but we are missing a key piece of the puzzle: genes that look different (based on DNA) can have similar functions (based on protein structure). This project aims to incorporate functional similarity into models of plasmid evolution, testing the hypothesis that different plasmids follow a consistent evolutionary 'grammar'.
Description	BACKGROUND. Plasmids are mobile, self-replicating pieces of bacterial DNA and are responsible for the rapid spread of antibiotic resistance genes. Understanding how they evolve is central to understanding the spread of antimicrobial resistance (AMR). But plasmid evolution is notoriously hard to study: unlike chromosomes, plasmids evolve mainly through the rapid gain, loss and rearrangement of genetic material rather than gradual point mutation, and conventional sequence-alignment tools struggle to capture this. A new generation of computational tools have addressed this challenge by representing plasmid rearrangements directly. pling (Iqbal group) uses a Double-Cut-and-Join-Indel (DCJ-Indel) model to compute the number of structural "evolutionary events" separating any two plasmids, producing much more biologically meaningful distances than existing tools. However, pling, like other methods, currently defines relatedness purely at the level of DNA sequence homology. This misses an important biological phenomenon: two plasmid regions can be non-homologous in sequence while still being functionally equivalent i.e. they play the same or similar evolutionary role but are unrelated genetically. This is important, because we believe that most plasmids have highly modular genomes that can easily gain or lose functions. Incorporating information on protein structure into models of plasmid evolution may therefore give us important insights into how they evolve, particularly in response to selective pressures like antibiotics or bacterial defence systems such as CRISPR-Cas. RESEARCH QUESTION. This proejct will explore whether incorporating protein structure into rearrangement-distance models leads to a more comprehensive model of plasmid evolution. Is there a consistent "grammar" to plasmid modularity? If so, at what representational level does it operate: sequence blocks, individual genes, or structurally-defined protein clusters? And how does the evolution of AMR plasmids differ from other plasmids? OBJECTIVES. The project is structured into three parts. (1) Map structural equivalence across the plasmid protein universe (Year 1).

	Before rearrangement distances can incorporate structural equivalence, the scale of the phenomenon needs establishing: how often are non-homologous plasmid proteins structurally similar, meaning they may occupy similar functional niches despite a lack of shared sequence ancestry? Using structure-prediction and search tools (Foldseek, ESMFold/AlphaFold2), the student will systematically survey plasmid proteins to identify and characterise likely 'structural spare parts' of plasmids, providing the empirical foundation and candidate protein set that the model extension in WP2 is built against. This will be done first for high-quality reference genomes, before extending to >2.4 million genomes in AllTheBacteria (collaborative project led by Iqbal). (2) Extend the model with structural equivalence (Years 1–3). Using structure-prediction and search tools (e.g. Foldseek, ESMFold/AlphaFold2), the student will develop an extension to the DCJ-Indel framework to recognise structurally-equivalent, non-homologous protein regions as substitutable modules, and test this systematically against the standard sequence-based version (Frolova et al. 2024). The extended model will then be applied to specific plasmid families based on the student's own interests, testing whether plasmid rearrangement follows consistent rules, and at which representational level those rules are most stable (sequence block, gene, or structural cluster). (3) Track structural evolution across the antibiotic era (Years 3–4). Historical bacterial culture collections predating the widespread use of antibiotics provide a rare, directly-dated evolutionary timeline which shows that plasmids present before the antibiotic era followed one of three trajectories over the twentieth century: disappearance as intact backbones, preservation largely unchanged, or fusion into larger composite plasmids (Cazares et al. 2025). The student will apply the extended model from WP2 to these historical and modern plasmids, testing whether these evolutionary trajectories can be better explained by structural module exchange than by DNA-sequence homology alone, and whether AMR plasmids show a distinctive pattern of structural flexibility over this period compared with other plasmids. WIDER CONTEXT. This PhD project addresses work arising from the Iqbal and Shaw group, and the student will be working in an environment with close links to researchers interested in plasmid evolution. For example, research in the Shaw group funded by an ERC Starting Grant (PLEIADES, 2026–2031) is investigating the relationship between plasmids and bacterial defence systems which attack mobile DNA, and new computational methods for plasmid evolution will directly support this work. Other researchers at Bath and Bristol are working on bacterial evolution and AMR, giving a strong community of researchers to interact with. This project would suit a student with strong maths/physics/computational background and an interest in biology, or a student with a bioinformatics background and interest in algorithms. There are multiple opportunities to tailor the project to your interests, such as in choosing the specific plasmid families to focus on or in adding a wet-lab component if desired with the van Houte group. The initial objectives are more structured, but there is subsequent scope to change the direction of the project - for example, the project could develop to

	compare plasmids to other mobile genetic elements, explore the evolution of chromosomal regions and/or investigate correlations between evolution and environmental variables.
Can be completed part time?	Yes
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