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| **Research Theme: Computational Biology; AI; MIcrobiology** |
| **PhD Research Project Title:**  **Predicting Bacterial Environmental Sensing via AI to Enhance Bacteria-Based Cancer Therapy** |
| **Scholarship category (Please indicate the source of funding for this project):**   1. **SBS Research Student Scholarship (for SBS faculty only)** |
| **Principal Investigator/Supervisor: Anni Zhang** |
| **Co-supervisor/ Collaborator(s) (if any):** |
| **Project Description**  **a) Background:**  Cancer is the leading cause of death in Singapore, responsible for 28.2% of all deaths from 2017 to 2021 (National Registry of Diseases Office 2023). Bacteria-based cancer therapy aims to mitigate the side effects of contemporary cancer therapy via engineered bacteria. However, a critical challenge remains: to precisely focus the bacteria to effectively target a tumor without damaging the host (Nemunaitis *et al.* 2003; Le *et al.* 2015). The precise control of microbes can be done by engineering bacteria to detect tumor-specific environmental signals and subsequently activate anticancer drug production via two-component systems. While many studies have been conducted to identify environmental stimuli that activate two-component systems, such as transcriptomic experiments under various stimuli (Xie *et al.* 2022), most of them only test one two-component system or one bacterial strain. Computational prediction is challenging due to the significant diversity of sensing domains in two-component systems (Zschiedrich, Keidel and Szurmant 2016), which are responsible for binding environmental stimuli. Thus, neither experimental nor computational methods can efficiently predict two-component systems in bacteria that respond to particular environmental signals. Thus, there exists a *critical need* to design novel methods that effectively predict the binding interaction between environmental stimuli, e.g. chemical ligands, and the sensing domains of two-component systems. In the absence of such methods, moving bacteria-based cancer therapy beyond preclinical models to clinical use remains a formidable challenge.  **b) Proposed work:**  Our *long-term goal* is to design advanced bacteria genomes guided by AI computation to enhance tumor sensing and drug production in bacterial-based cancer therapies. Our *overall objective in this proposal* is to design computational methods to predict binding affinity between diverse environmental stimuli and bacterial two-component systems. Our *central hypothesis* is that AI models, such as language models and deep learning methods, allow accurate prediction of binding affinity between environmental chemical ligands and sensing domains of two-component systems, especially under-characterized ones with limited prior knowledge. We have based our central hypothesis upon previous work:   1. A study using the deep learning model trained on protein and ligand sequences outperformed traditional methods in predicting protein–ligand binding affinity, achieving a strong correlation (R = 0.789) between predicted and experimentally measured values (Wang *et al.* 2021). 2. Deep neural network models exhibited exceptional predictive performance in protein-ligand binding affinity (Pearson’s r = 0.83 and Root Mean Square Error of 1.23 compared to the experimental results) (Rezaei *et al.* 2020). 3. A interpretable machine learning model accurately predicted binding affinity between transcription factors and DNA (Pearson’s r2 ranging from 0.974 to 0.998 compared to experimental measurements) (Rube *et al.* 2022). 4. Fine-tuning pretrained language models on protein-ligand binding datasets resulted in high predictive accuracy for binding affinity (correlation R ranging from 0.722-0.737 between the predicted and experimental data) (Zhang *et al.* 2023).   **c) Preferred skills:**  **A curiosity about microbes;**  **An interest in coding;**  **A dedication to research** |
| **Supervisor contact:**  **If you have questions regarding this project, please email the Principal Investigator: anni.zhang@ntu.edu.sg** |
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