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Ph.D. Dissertation Defense

Investigation of *E. coli* Biofilm Formation Dynamics Using Integrated *in silico* and *in vitro* Methods

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ABSTRACT:

Bacterial biofilm formation is a complex, organized collective response to biochemical cues, which transitively modulates gene expression, metabolite concentration, cellular function, and biofilm formation. Merging computational and experimental methods for studying biofilms is valuable in characterizing and understanding the connections between cellular-scale interactions, changing microenvironmental conditions, molecular-scale gene dynamics, and corresponding metabolic responses that modulate static culture biofilm formation. A simulation platform of *Escherichia coli* K12 MG1655's biofilm formation was first developed by using a multiscale agent based model (ABM) framework, which modeled the intracellular, extracellular, and cellular system levels. Global sensitivity analysis of the ABM's simulated biofilm formation was used characterize the cellular model impact on biofilm formation, and the simulated results were used to characterize attached and planktonic bacteria's metabolic response during biofilm formation.

Of the intracellular model's ~180 kinetic parameters, only ~14% were considered for parameter optimization, which denotes large model uncertainty. We characterized the intracellular model's uncertainty by integrating a biologically motivated modeling assumption, multi-phenotype modeling, with uncertainty quantification methods. Our novel procedure, multi-phenotype calibration, used shaken and static culture dynamics to identify the most probable parameter values and their corresponding uncertainties. Next, a static culture *in vitro* model of a *E. coli* GFP reporter strain library was used to generate high time resolution gene expression and biofilm formation empirical data. The empirical data was used to update the bacterial movement and growth rules. In addition, we characterized the impact of the intracellular and cellular model's parameter uncertainty on the simulated biofilm formation. Using the simulation results, we studied the impact of quorum sensing on bacteria movement.

The static culture ABM successfully predicted biofilm growth, and the discrepancy in simulated bacterial distribution was attributed to an uncharacterized interaction between bacterial movement and the presence of extracellular polymeric substances. In our analysis, GlycerAldehyde-3-phosphate Dehydrogenase demonstrated statistically significant sensitivities to biofilm formation, which has been documented as having an impact on bacteria growth and movement during biofilm formation. The model verified an increase in extracellular quorum sensing signaling molecule, AI2, concentration reduces bacteria movement during biofilm formation. Lastly, the *in silico* model demonstrates the discovery potential of integrating a dynamic intracellular model and a mechanistic movement rule within a biofilm ABM, and we outlined a framework for applying uncertainty quantification to help combat the model uncertainty introduced by using dynamic and mechanistically representative models.