strong intellectual merit AND broader impacts right out of the gate!

explicit call-out to IM helps the panelists

sets out a knowledge/engineering gap

states a hypothesis, restates goals

figure is information-dense, since space is at a premium in this piece!

figure might have benefited from some simplification (what are the dotted lines?). Overall, the document could use more whitespace

note that "how it's done" is only half of the document! The rest is intro, background, IM, BI

explicit BI title

note that "methods" are much broader than what you read in a paper or lab report!

explicit references to project resources

Pathogenic microbes continually evolve to acquire resistance to antibiotic treatments, creating an enormous global health crisis. The consequences are extreme – a recent report projected the human cost of antimicrobial resistance to be $300 trillion cumulative premature deaths by 2050 with a loss of up to $1000 trillion to the growing economy. Despite the prevalence of antibiotic resistance rising rapidly, the rate of development of novel antibiotics substantially lags behind the rate at which pathogens evolve resistance to them. A strategy to maintain the efficacy of existing and future antibiotics is to continue the paths towards pathogen resistance, which is to improve knowledge of genetics, ecological conditions, evolutionary landscapes, and mechanisms of drug actions. I propose to create a high-throughput system to evaluate sensitivity of microbes to various antibiotic regimens, engineer a novel biocompatible device for implementation of large-dose antibiotic delivery, and cultivate a mathematical model to explore the temporal evolution of resistance of bacteria during treatment with antibiotics.

Intelectual Merit: Bacteria resist antibiotics by modifying their cell wall proteins or target of the drug, modulating the antibiotic, or expressing efflux pumps to expel the antibiotic and reduce its effects. Thus, strategies to develop antibiotic resistance and eventually overcome it are critical now. Currently, researchers are attempting to do this by studying drug interactions, with regards to synergy and antagonism to optimize killing of microbes. A mathematical model for bacterial growth and drug sensitivity will enable us to understand how a drug can affect bacterial resistance and increase the rate of bacterial pathogens in my interdisciplinary project, which integrates microbiology, mechanical engineering, materials science, and mathematical biology, as part of this project. I intend to create a microfluidics system to study the effectiveness of collateral sensitivity, develop a large-scale drug delivery device to be tested in vitro, and provide a mathematical basis for understanding the dynamics of bacterial treatment and resistance.

Fig. 1 (A) Collateral sensitivity includes cycling of two drugs, A and B, to result in increased sensitivity of the bacteria to the subsequent drug. (B) The multiphase microfluidics approach involves pumping drugs A and B with human apoptosis as a readout for different regimens being tested simultaneously. (C) The microfluidics experiments can inform scientists of a population-based multidrug resistance strategy. Both drugs, i.e. wild type (WT), resistant to drug A, resistant to drug B, or resistant to both drugs, A and drug B.

Approach: With guidance from Dr. , I will leverage the resources of the laboratory and the Center for . Additionally, I am currently involving three undergraduate students to work with me on Aim 1 and Aim 2 of this project.

Aim 1: Evaluate different antibiotic regimens with bacteria using microfluidics. To circumvent these limitations, I will fabricate a multiphased microfluidics device with support from . This enables simultaneous monitoring of the effects of multiple antibiotics at different concentrations, as well as their combination and cycling regimens. Several bacterial strains will be grown in a lab-designed microfluidics chip and measured using flow cytometry. I will characterize resistance and measure phylogenetic heterogeneity at a single-cell level in genetically similar populations.

Aim 2: Develop biomaterials for gastric resident delivery device with a holding capacity of 50 nanograms of drug. In parallel to workflow outlined in Aim 1, I will explore various designs for large-dose drug delivery devices that can hold up to one month’s worth of drugs (around 50 grams of tubing). These will be tested in vitro using gastric fluid and ensuring robust mechanical properties over one month using the strain machine.

Assessment: I will use the following devices: biocompatible materials (available in the form of a disk) that will be placed in the stomach, deployed really quickly, able to control release rates of drugs, and cycle devices. The drug delivery involves measuring drug release rates in simulated gastric fluid and ensuring robust mechanical properties over one month using the strain machine.

Aim 3: Construct a mathematical model to validate interactions of bacteria and antibiotics. With results from the high-throughput system in Aim 1, I will provide a mathematical basis for understanding and predicting the kinetics of susceptible populations to drug-resistant populations when treated with antibiotic regimens. The model is influenced by the optimal period of cycling drugs for collateral sensitivity and determine when this approach is a better treatment option than static treatment. To account for the resistance of bacteria, I will implement a stochastic model and incorporate fitness costs of resistance.

Broad Impacts: A high-throughput platform for rapid antibiotic susceptibility testing combined with a predictive mathematical model represents a significant step towards understanding treatments to quickly eradicate bacterial infections while minimizing resistance to current and future drugs. I will partner with industries through the program and translate results of my research to the clinic for developing large-dose antibiotic delivery devices. Moreover, to respond to the rising global challenges, I will pursue higher education and expose them to a variety of research topics. I am organizing bioengineering workshops through the College Connection program in my capacity as a Society of Women Engineers graduate student leader. These will incorporate interdisciplinary techniques used in my projects, such as microbiology, biotechnology, and mechanical engineering research. This plan will be used as a platform for a general and systematic approach for understanding the interactions of bacteria and antibiotics. In addition to discovering novel materials for large-dose devices to antibiotic-resistant pathogens worldwide.