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, which is good, since space is at a premium in this piece!

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

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 million cumulative premature deaths by 2050 with a loss of up to $100 trillion to the growing economy[1]. 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[2]. A strategy to maintain the efficacy of existing and future antibiotics is to constrain the paths towards resistance, which requires detailed 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 construct a multi-compartment mathematical model to explore the temporal population dynamics of bacteria during treatment with antibiotics.*

Intellectual Merit: Bacteria resist antibiotics by modifying their cell wall proteins or target of the drug, inactivating the antibiotic, or overexpressing their efflux pump proteins to expel the antibiotic and reduce its efficacy[2]. Engineering strategies to delay 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. These combination treatments typically lead to increased dosage and toxicity. Furthermore, progress towards overcoming antibiotic resistance has been encumbered by the lack of a high-throughput system to study antibiotic susceptibility and knowledge of compatible biomaterials for large-dose antibiotic delivery.

To approach this problem, I will understand how collateral sensitivity – whereby an organism resistant to one drug displays increasing sensitivity to a second drug – affects clearance of a bacterial population relative to treatment either with one drug or a combination of drugs simultaneously (Fig. 1A)[3]. I hypothesize that collateral sensitivity will minimize the evolution of resistance and increase the rate of clearance of bacterial pathogens. In my interdisciplinary project, which integrates microbiology, mechanical engineering, materials science, and mathematical biology, as part of [redacted] **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.**

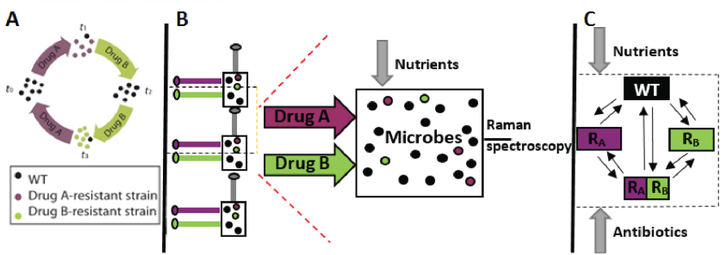

Fig. 1: (A) Collateral sensitivity includes cycling of two drugs, A and B, to result in increased sensitivity of the bacteria to the subsequent drug[3]. **(B)** The multiplexed microfluidics approach involves pumping drugs A and B with Raman spectroscopy as a readout for different regimens being tested simultaneously. **(C)** The microfluidics experiments can inform kinetics of a population-based mathematical model with bacteria that are susceptible to both drugs, *i.e.* wild-type (WT), resistant to drug A, resistant to drug B, or resistant to both drug A and drug B.

explicit references to project resources

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

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

explicit BI title

BI is a mix of global impact and local impact

Approach: With guidance from Dr. [redacted], I will leverage the resources of the [redacted] and [redacted] Laboratories [redacted] and the Center for [redacted] at [redacted] Additionally, I am currently advising three [redacted] 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 time-consuming established techniques for antibiotic susceptibility testing, I have started to fabricate a multiplexed microfluidics device with support from [redacted] (Fig. 1B)[4]. 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 engineered to express fluorescent proteins to elucidate whether inherent characteristics of the pathogen leads to different viability outcomes with various treatment regimens. This approach solely captures population effects without information of chemical compositions and structure of biological molecules. To overcome this limitation, I will utilize Raman spectroscopy and measure phenotypic heterogeneity at a single-cell level in genetically uniform microbial populations[5].

Aim 2: Develop biomaterials for gastric resident delivery device with a holding capacity of 50 grams of drug. In parallel to work outlined in Aim 1, I will explore various designs for large-dose delivery devices that can hold up to one month's worth of drugs (around 50 grams for tuberculosis) to minimize resistance due to nonadherence of treatment regimens. Design criteria include the following: the device should be made of biocompatible materials (available in the [redacted]), retained in the stomach, deployed orally, able to control release rates of drugs, and cycle drugs. *In vitro* device testing involves measuring drug release rates in simulated gastric fluid and ensuring robust mechanical properties over one month (using the Instron machine [redacted]).

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 switching of susceptible populations to drug-resistant populations when treated with antibiotic regimens (Fig. 1C). In particular, the model can inform the optimal period of cycling drugs for collateral sensitivity and determine when this approach is a better treatment relative to combination or monotherapy. To account for rare events of resistance, I will implement a stochastic model and incorporate fitness costs of resistance.

Broader Impacts: A high-throughput platform for rapid antibiotic susceptibility testing combined with a predictive mathematical model represents a significant step towards our understanding of treatments to quickly eradicate bacterial infections while minimizing resistance to current and future drugs. I will partner with industries through [redacted] Program and translate results of my research to the clinic for developing large-dose antibiotic delivery devices. Moreover, to inspire underprivileged middle- and high-school girls in the [redacted] to 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 project, such as microfluidics, biomaterials, and mathematical modeling. My research can be used as a platform for a general and systematic approach for understanding the interactions of antibiotics and microbes in addition to discovering novel materials for large-dose devices to overcome antibiotic resistance worldwide.

References: **1.** O'Neill, J. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations (2014). **2.** Dantas, G. & Sommer, M. O. A. *Am. Sci.* **102,** 42–51 (2014). **3.** Imamovic, L. & Sommer, M. O. A. *Sci. Transl. Med.* **5,** 204ra132 (2013). **4.** Mohan, R., et al. *Biosens Bioelectron* **49**, 118-25 (2013). **5.** Hermelink, A., et al. *Analyst* **134**, 1149-1153 (2009).