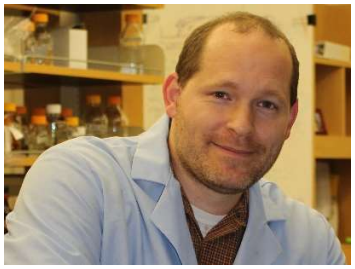
Using synthetic biology to explore bacterial tolerance, persistence, and antibiotic resistance



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Abstract

Antibiotic tolerance is a widespread phenomenon that renders antibiotic treatments less effective and facilitates antibiotic resistance. Recently, we explored the role of proteases in antibiotic tolerance, short-term population survival of antibiotics, using queueing theory (i.e. the study of waiting lines), computational models, and a synthetic biology approach. Proteases are essential cellular components that degrade proteins and play a key role in a multi-drug tolerant subpopulation of cells, called persisters. We found that queueing at the protease ClpXP increases antibiotic tolerance ~80 and ~60 fold in an *E. coli* population treated with ampicillin and ciprofloxacin, respectively. There does not appear to be an effect on antibiotic persistence, which we distinguish from tolerance based on population decay. These results demonstrate that proteolytic queueing is a practical method to probe bacterial tolerance and related genes, while limiting the unintended consequences frequently caused by gene knockout and overexpression. To get a better understanding, we are currently focusing on the proteolytic queue, and using microfluidic devices and our custom pipeline to quantify 1000s of single-cell response over time. This pipeline takes advantage of recent advances in imaging and machine learning, and allows us to identify, track, and quantify single cells before and after antibiotic treatment.

Brief Biography

Dr. Butzin joined the Department of Biology and Microbiology at South Dakota State University in 2017 as an Assistant Professor. He previously was a Research Scientist and postdoc in the Department of Physics, Virginia Tech, and a postdoc in the Department of Molecular & Cell Biology, University of Connecticut. The Butzin lab explores microbial systems using an evolutionary perspective and a synthetic biology approach. His goal is to understand the principles behind robustness in both natural and synthetic microbial systems. He is particularly interested in how individual cells cope with constant fluctuations in natural environments and limited enzymatic resources. Although his lab has several ongoing projects ranging from the development of new robust synthetic circuits to the study of antibiotic resistance and biofilms, all projects utilize synthetic biology to understand natural phenomena or to develop products for industrial and medical applications. His lab uses mathematical and computational approaches along with wet-lab experiments to probe and develop a more comprehensive understanding of the mechanisms that generate cellular plasticity and robustness. As a PI, he was recently awarded a 4-year NSF grant (Award Number: 1922542) entitled '*Using a queueing framework to explore the design principles of synthetic circuits in microorganisms.*'

Brief CV

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Education

PhD: Biological Sciences, University of Wisconsin-Milwaukee, USA, 2009
MS: Biological Sciences, University of Wisconsin-Milwaukee, USA, 2005
BS: Biological Sciences, University of Wisconsin-Platteville, USA, 2002

Professional Career

2017-present: Assistant Professor of Synthetic Biology, Department of Biology and Microbiology, South Dakota State University, USA
2016-2017: Research Scientist, Department of Physics, Virginia Tech, USA
2012-2016: Postdoctoral Research Fellow, Department of Physics, Virginia Tech, USA
2009-2012: Postdoctoral Research Fellow, Department of Molecular & Cell Biology, University of Connecticut, USA
2005-2009: Graduate Research Assistant, Department of Biological Sciences, University of Wisconsin-Milwaukee, USA

Research Interests

1. Metabolic engineering and synthetic biology.
2. Molecular microbial physiology and evolution.
3. Natural and synthetic microbial networks: oscillators, biosensors, etc.
4. Robustness and fitness of microbial life and biological systems: antibiotic resistance, tolerance, and persistence; microbial adaptation; microbial ecology.
5. Life at the extreme (extremophilic organisms) and the origin of cellular life.

Selected publications (*Butzin is the corresponding author)

1. Deter* et al. 2019, Under Review. *Nature Communications*. https://www.biorxiv.org/content/10.1101/680504v1
2. Deter* et al. 2019, In Press. *Springer's Methods in Molecular Biology*.
3. Butzin* and Mather. 2018. *ACS Synth Biol*. 7:54-62.
4. Butzin* et al. 2017* NC. *ACS Synth. Biol*. 6:455-462.
5. Datla* et al. 2017. *Scientific Reports*. 7:16071.
6. Deter* et al. 2017. *Toxins* (Basel). 9.
7. Butzin et al. 2016. *Reviews in Cell Biology and Molecular Medicine.*
8. Butzin et al. 2016. *ACS Synth. Biol*. 5:146-153.