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Best time of year to rotate in your lab: Rotations available any time.

Wiring Cells: Control of Microbial Behavior using Protein Nanowires

"Life is nothing but an electron looking for a place to rest." - Nobel Laureate A. Szent-Gyorgi

How can we monitor and control the growth of microbes deep inside the Earth and in human cells? This ability is central to understanding basic microbial function in their native environment with various applications such as reducing microbial methane emissions and treating multi-drug-resistant bacteria.

Controlling microbial growth is challenging. Established optogenetics and fluorescent proteins have limited use in studying microbial communities due to their low penetration depth and inability to work in anoxic environments. Directing electrons derived from metabolism is an ideal tool to control microbial growth because all life processes are driven by electrons. However, proteins and cell surfaces are non-conductors.

To bridge this gap, **we are studying proteins that allow microbial growth to be imaged and controlled with electrons**. This work is enabled by our discovery that diverse microbes use chains of heme or aromatic moieties to export electrons to partner or host cells (*Cell* 2019, *Nature* 2021, *Nature Micro.* 2023). This allows microbes to switch metabolism to respiration, and promote growth and colonization, without oxygen-like soluble electron acceptors. We found that microbes overexpress nanowire genes by sensing natural electric fields, allowing electronic control of gene expression (*Nature Chem.Bio.* 2020). Together, electron-conducting proteins and electrogenetics are the **electronic analogs of GFP and optogenetics.**

We hope to lay a foundation for far-reaching benefits to basic research as well as environmental and human health. To realize this vision, we are identifying mechanisms of nanowire biosynthesis, redox regulation for metabolic reprogramming, conductivity, and interaction partners that charge nanowires.

The ability to wire any microbe and electronically control metabolism, communication, and host colonization stands to reduce methane emissions that contribute to climate change and deliver novel classes of treatments that prevent the adhesion of or outcompete microbes to defeat infectious diseases.

1. FUNDAMENTAL ADVANCES: Elucidating how bacteria assemble and use nanowires. We are focused on understanding how microbes respire without oxygen-like, soluble, electron acceptors.

1A. *Understanding nanowire biosynthesis as a step towards reconstituting protein nanowires*. We are identifying the nanowire assembly machinery using genetics combined with cryo-electron microscopy/tomography to reconstitute into new species (*Nature Micro.* 2023, *Nature Comm.* 2022).

1B. *Defining ultrafast conductivity mechanism*: We are determining how nanowires move electrons, ions, spins and excitons at ultrafast (< 200 fs) rates (*Nature Comm.* 2022) and over centimeter distances unprecedented in biology (*Nature Chem.Bio.* 2020). We have found a novel electron escape route in proteins to avoid oxidative damage (*PNAS* 2021) and how cooling speeds up electrons (*Science Adv.* 2022).

2. ENVIRONMENTAL HEALTH: Controlling electron exchange syntrophic microbial communities to lower atmospheric methane and thus, global temperatures. Microbes use protein nanowires to control methane generation and consumption. This leads us to hypothesize that it would be possible to construct microbial communities interconnected via protein nanowires in a way that consumes atmospheric methane. Ultimately, solutions to lower methane levels will have a positive effect on our ability to slow down climate change and repair damage to our environment. Towards this long-term goal, our two short-term goals are:

2A. *Understanding interspecies nanowire connections* using our electron imaging methods (*Nature Nano.*) combining with cryo-electron microscopy and tomography (with Jun Liu lab)

2B. Analyzing nanowires in soil and marine samples. Ultimately, this work will allow us to build and study communities of electron exchanging methane consuming microbes, optimizing them for methane consumption. The envisioned platform will be a fully autonomous microbial community that can be installed in areas with high atmospheric methane levels.

3. HUMAN HEALTH. Control bacterial metabolic switching and host colonization via nanowires.

3A. Antibiotics: Disrupting electron export to inhibit growth and adhesion of pathogens.

3B. Probiotics: Accelerating electron export to promote growth and adhesion of commensals.

Small wires, big opportunities. Protein nanowires provide unprecedented ability to control microbial function and design custom microbial communities. We are establishing a fundamentally new class of electron-conducting protein nanowires, and electrogenetics, making it possible and electronically control any microbe as **electronic analogs of GFP and optogenetics,** to monitor and control the growth, communication, and colonization of microbes deep inside the Earth and in human cells. By developing electronic monitoring and control of microbial behavior, these fundamental studies will enable countless innovations in fundamental as well as environmental and clinical research.

Projects involve structural studies, genetically engineering nanowire conductivity, nanoscale electron transfer measurements in nanowires and living biofilms, spectroelectrochemistry as well as building and experimentally-testing computational models, through ongoing collaborations with **Batista** and **Brudvig** (Yale, Chem.) and **Lisa Craig (Canada), Olivera Francetic (France),** and **Carlos Salgueiro (Portugal)**.

We have several interdisciplinary projects embedded in these larger goals that would be great rotation projects as they provide training in a variety of biophysical, molecular, and synthetic biology as well as biochemical techniques and are likely to yield positive results/publications within the rotation.

Please come chat with me or with one of my laboratory members to match your interests with our training opportunities. Rotation projects are experimentally or computationally oriented with possibilities of combining both and no prior background in a specific discipline is necessary.

Join our lab meetings either in person or via zoom: Tuesdays 2:30 PM (Computation); Friday 10 AM (Experiments). We can adapt our lab meeting schedule to accommodate your class schedule.

Lab's policy on career development: Among lab's foremost goals is the development of the next generation of interdisciplinary scientists who will play vital roles in advancing biological sciences. Our My philosophy is to train students to be self-directed learners by building a core set of discipline-specific expertise first, and then encourage them to expand beyond their core discipline to appreciate and incorporate other disciplines. We encourage all careers, especially industry and teaching (see here). E.g. we have received patents and Blavatnik Innovation Award to commercialize various nanowire-based technologies.