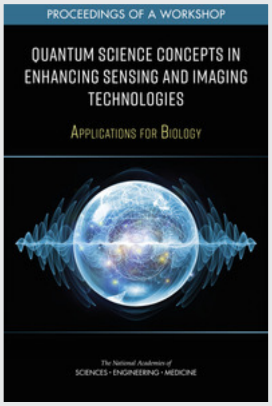

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QUANTUM SCIENCE CONCEPTS IN ENHANCING SENSING AND IMAGING TECHNOLOGIES

Applications for Biology

PROCEEDINGS OF A WORKSHOP

Anne Frances Johnson, Steven M. Moss, Andrew Bremer,
and Frances Sharples, *Rapporteurs*

Board on Life Sciences

Division on Earth and Life Studies

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This Proceedings of a Workshop was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published proceedings as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the charge. The review comments and draft manuscript remain confidential to protect the integrity of the process.

We thank the following individuals for their review of this proceedings:

YUN CHEN, Johns Hopkins University
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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the content of the proceedings nor did they see the final draft before its release. The review of this proceedings was overseen by **MARK SCHNITZER,** Stanford University. He was responsible for making certain that an independent examination of this proceedings was carried out in accordance with standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the rapporteurs and the National Academies.

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Overview

Quantum concepts hold the potential to enable significant advances in sensing and imaging technologies that could be vital to the study of biological systems. The workshop Quantum Science Concepts in Enhancing Sensing and Imaging Technologies: Applications for Biology, held online March 8–10, 2021, was organized to examine the research and development needs to advance biological applications of quantum technology. Hosted by the National Academies of Sciences, Engineering, and Medicine, the event brought together experts working on state-of-the-art, quantum-enabled technologies and scientists who are interested in applying these technologies to biological systems. Through talks, panels, and discussions, the workshop facilitated a better understanding of the current and future biological applications of quantum-enabled technologies in fields such as microbiology, molecular biology, cell biology, plant science, mycology, and many others.

The workshop was organized around three main themes. The first, quantum *in* biology, examined quantum concepts that are hypothesized to be important for life processes and that researchers are working to observe through biological imaging and sensing. The second, quantum *for* biology, addressed ways to use quantum concepts to enhance technologies for biological imaging and sensing. The third, biology for quantum, offered a wider discussion of how the frontiers of biological imaging and sensing could enable future study using quantum concepts, tools, or technologies.

Throughout the workshop, participants identified a wide range of emerging approaches and opportunities at the intersection of quantum physics and biological sensing and imaging. During the workshop, there were some differences in how each speaker defined the term *quantum*. During one of the panels, Prem Kumar offered thoughts on what phenomena are classical versus quantum, explaining that techniques get progressively more quantum as you move from just having superposition to having superposition with measurement and entanglement. Another explanation from Clarice Aiello delineates the definition into several levels. This includes a base level of "quantum-ness," which reflects that all matter is made of atoms, and when these particles are isolated they behave based on quantum mechanical principles. A second level is related to quantum coherence, where a single quantum object might be found in a coherent superposition state. A final level, which she described as the quantum-entangled level, involves multiple quantum systems which are entangled among themselves. Overall, the workshop touched on concepts such as superposition, entanglement, and squeezing and their potential implications for communication, computing, and simulation, in addition to the workshop's main focal area, biological sensing and imaging.

At the opening of the workshop, Thorsten Ritz of the University of California, Irvine, identified two questions at the heart of quantum biology: Is the machinery of life quantum mechanical, and can quantum mechanics be used to study the machinery of life in new ways? Participants highlighted systems in which researchers have explored these questions, from the vast array of molecular interactions involved in biological processes such as photosynthesis, to the mechanics involved in cellular functions such as differentiation and aggregation, to the role of oscillating magnetic fields in flight orientation among birds.

Sensing and imaging technologies are crucial to biological research; these technologies could both enhance the study of quantum effects and be enhanced by quantum concepts. A critical challenge in biological research is to develop imaging and sensing tools that do not damage or interfere with the often fragile and fleeting systems being studied. Attendees discussed a variety of established and emerging technologies that could enhance noninvasive biological imaging, including single- and two-photon spectroscopy, single-molecule spectroscopy, quantum illumination, ghost imaging, and cryo-electron microscopy. One example came from Marlan Scully who gave a keynote address on the first day of the workshop. Scully emphasized the use of different laser technologies, which exhibit coherence and other quantum properties, in moving toward real-world biological applications, such as the detection of SARS-CoV-2.

Both tools and theory will play an important role in advancing quantum biology research and applications. Several participants suggested theorists and experimentalists should work in tandem to understand and model biological processes. While physics often reduces systems to their simplest forms for fundamental insights, participants also noted the value of observing and understanding biological systems in all their "messiness," capturing both the inner workings of biological systems and the complex interactions that occur within and between organisms.

In discussions among participants, several attendees stressed the need to match emerging tools with the right scientific questions. Rather than developing quantum technologies as "a hammer looking for a nail," participants emphasized a focus on exploring the problems these technologies are best suited to address. For example, it is important to consider the size of the phenomenon being studied, the timescales that are important in answering the scientific question, and other relevant considerations. Every tool along the spectrum from classical to quantum involves its own set of trade-offs. For example, Ted Laurence of the Lawrence Livermore National Laboratory said that quantum measurements, such as single photon counting, fluorescence transitions, and lasers, can take longer to produce the same results as classical measurements. These quantum measurements, however, do not require calibration and can enable new research questions to be answered. Prem Kumar, Northwestern University, noted that, despite their promise, quantum approaches should not be used simply for the sake of using quantum, especially in situations where classical approaches better meet the needs of the researcher.

Understanding and applying quantum concepts could enable advances in a wide range of application areas including energy, synthetic biology, medicine, and sustainability. For example, Michelle O'Malley, University of California, Santa Barbara, described how improved noninvasive imaging approaches could help capture the complex interactions and functions involved in the breakdown of organic matter by microbial communities and lead to new technologies for capturing valuable products from plant waste. Several other participants discussed needs in tracking the movement of metabolites and molecules in microbial communities for insights into nutrient cycling in environments such as soil. Margaret Ahmad, Sorbonne University, discussed potential opportunities to leverage the magnetic properties of cryptochromes to advance new treatment approaches for diseases such as COVID-19 and cancer.

Looking toward the future development of the field, participants discussed challenges to advancing quantum biology that arise from disciplinary disconnects between physicists and biologists. The siloing of academic research disciplines represents a significant barrier to progress. Disconnects in terminology, motivations and priorities, and structural barriers to collaborative work underscore the need for concerted efforts to bridge these divides. Attendees and speakers offered suggestions for resolving these divergences, establishing a shared language, moving the field forward, and fostering meaningful feedback between disciplines. Overall, participants stressed a need for balance, open communication, collaboration, unity, and clear dialogue on trade-offs between quantum and classical approaches. Keiko Torii, The University of Texas at Austin, said that the best collaborations happen when the project provides mutual advantages that can show off everyone's talents, each team finds the work interesting, and partners develop a camaraderie to pursue new knowledge. To enable near- and long-term opportunities in this space, participants suggested that exploratory, high-risk funding could improve existing instrumentation to explore quantum enhancement collaboratively. They also emphasized the need for collaboration between quantum physicists and sensing/imaging scientists, which could be advanced through a dedicated quantum biology investigator program.

People, even more than technology, will be crucial to the future of quantum biology. Participants explored training, education, and workforce needs to further develop this burgeoning field and cultivate the next generation of scientists. While many programs are still in their nascent stages, participants highlighted examples of approaches and programs being developed at various types of institutions to engage students and professional scientists in quantum biology research.

Several participants stressed the need for an inclusive approach, spanning disciplines as well as communities to foster a diverse field fueled by the intellectual contributions of a wide range of people, including historically under-resourced schools and students. To increase awareness and excitement about quantum physics and related areas of biology, attendees suggested capitalizing on the "buzz" around quantum. Several participants emphasized the need to start early, introducing students to quantum concepts and their appealing "weirdness" in K–12 education. Engaging students early—before they become entrenched in traditional disciplinary siloes as typically happens in graduate school—could help to galvanize interest in the area and foster a generation of scientists with the interdisciplinary mindset and skills needed to advance this interdisciplinary field. While these efforts could be advanced at many levels and across multiple sectors, several participants suggested a national quantum biology center could be a valuable hub to coordinate and support quantum biology education and workforce development across academia, industry, and government.

1
Introduction

The principles of quantum mechanics—the study of the smallest units of matter, such as molecules, atoms, and subatomic particles—are being applied to an increasingly broad array of scientific areas. In biology, quantum concepts and tools can help improve the study and understanding of biological processes and systems.

The Quantum Concepts in Enhancing Sensing and Imaging Technologies: Applications for Biology workshop brought experts from multiple fields together to consider the potential impact of quantum technologies on the future of biological sensing and imaging. The workshop provided a forum to consider current and future imaging and sensing applications for quantum approaches in biology; examine the advantages, disadvantages, and technical needs of quantum strategies; and establish a common terminology spanning multiple areas of expertise. Participants explored broader impacts for quantum technologies in biology along with training, education, and workforce needs to further develop this burgeoning field. These objectives are closely tied to the National Academies of Sciences, Engineering, and Medicine's forthcoming decadal survey on Biological Physics/Physics of Living Systems.[1]

The workshop was organized by the National Academies at the request of the U.S. Department of Energy's (DOE's) Office of Science. DOE's Office of Science supports basic and applied research across a wide range of scientific disciplines and has established a Quantum Information Science effort to advance quantum science and applications.[2] Todd Anderson of the Biological Systems Sciences division, which uses genomic science to identify promising renewable resources, provided an introduction explaining DOE's hopes for the workshop. He described DOE's focus on the nonclassical behavior of quantum concepts, such as superposition, entanglement, and squeezing, and the potential implications for communication, computing, simulation, and sensing and imaging. Understanding more about quantum concepts and their biological applications can broaden the spectrum of bioenergy research, especially synthetic biology, imaging and sensing, and environmental microbiome research. Anderson expressed his hope that the workshop, with its collaborative spirit, could uncover additional innovative ideas.

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[1] See https://www.nationalacademies.org/our-work/biological-physicsphysics-of-living-systems-a-decadal-survey.

[2] See https://science.osti.gov/Initiatives/QIS.

The workshop organizing committee[3] was chaired by Taekjip Ha from Johns Hopkins University. Ha offered an overview of the workshop's goals and organization. The workshop was held virtually over 3 days and included a series of keynote speeches, themed panels, discussion periods, and breakout sessions. Day 1, with a theme of quantum *in* biology, examined quantum concepts that are important for observing biological processes. Day 2, focusing on quantum *for* biology, addressed ways to use quantum concepts to enhance technologies for biological imaging and sensing. Day 3, with a theme of biology *for* quantum, offered a wider discussion of how the frontiers of biological imaging and sensing could enable future study with quantum concepts.

This Proceedings of a Workshop was prepared by the rapporteurs as a factual summary of what occurred at the workshop. The statements made are those of the rapporteurs or individual workshop participants and do not necessarily represent the views of all workshop participants; the organizing committee; or the National Academies.

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[3] The organizing committee biographies can be found in Appendix C.

2

Quantum *in* Biology

The first day of the workshop focused on quantum *in* biology, which examined the study of quantum concepts that drive biological processes. The day started with a keynote address by Thorsten Ritz, professor of physics at the University of California, Irvine, which reviewed the history of research and theory in quantum biology and discussed emerging work. Following the keynote, three panel discussions covered probing intracellular and intercellular correlations in biology, bioelectromagnetic fields, and quantum photonics in biological systems. Each discussant on the panels was asked to give 7 minutes of opening remarks, which were followed by a moderated audience question and answer session. (See the workshop agenda in Appendix B.)

OLD AND NEW QUANTUM BIOLOGY

Thorsten Ritz

Ritz began his keynote talk by noting that quantum biology is defined by two closely connected questions: Is the machinery of life quantum mechanical, and can quantum mechanics be used to study the machinery of life in new ways? The design of new quantum tools could be bio-informed, meaning that the tools can incorporate an improved understanding of the biological systems and processes that are under study.

Quantum biology has been studied for decades by researchers siloed by disciplines. To make progress, Ritz urged that new collaborative, cross-cutting studies are needed to inform the entire array of interested communities. Using his own field, magnetic sensing via coherent electron spin reactions, as a focal point, Ritz highlighted “old” quantum findings, presented future opportunities in “new” quantum, and suggested open questions in each realm.

“Old” Quantum Biology Findings

Klaus Schulten’s early work on the impact of Earth-strength magnetic fields on chemical reactions at room temperature demonstrated that it was possible to set up molecular pairs to create targeted effects, an approach that has been consistently validated (Hore and Mouritsen, 2016; Schulten et al.,1978). This work has helped move three separate fields forward: physical chemistry, molecular biology and genetics, and animal navigation and orientation.

In physical chemistry, several studies were able to design a radical pair sensitive to Earth-strength magnetic field effects (Hiscock et al., 2016; Maeda et al., 2008; Procopio and Ritz, 2020; Timmel and Hore, 1996). However, Ritz said that there are other measures beyond the radical pair that should be investigated, such as response times and signal-to-noise (SNR) ratios.

In molecular biology and genetics, several studies have suggested that cryptochromes, a class of photoreceptors, are also a potential magnetic receptor. These receptors are unique because they are light receptors that respond to the stimulus of light on a biological timescale, which gives a direct coupling of light to the biological responses (Maeda et al., 2012; Ritz et al., 2000). There are still many unknowns about cryptochromes, but multiple studies have shown that they can affect circadian rhythms in *Drosophila* (Green et al., 2014; Helfrich-Förster et al., 2001).

Magnetic resonance experiments have shown that birds' orientation instincts can be disrupted (Emlen and Emlen, 1966; Wiltschko and Wiltschko, 1972; Wiltschko et al., 1994) (see Figure 2-1), but oscillating magnetic fields at varying intensities can also disrupt avian orientation (Ritz et al., 2004; Wiltschko et al., 2005).

"New" Quantum Biology Opportunities

Cross-cutting research ideas, such as enzymatic actions in the protein environment, are pushing quantum biology forward. Dynamic, non-equilibrium collective responses in proteins, such as cryptochromes, may be necessary to produce quantum features, such as tunneling, and it may also be possible to control these responses and activate similar mechanisms.

In addition, looking at cryptochromes structurally with newer, more advanced tools could produce greater knowledge about biological functionality and answer many open questions about photosynthesis. Integrated platforms, such as those described by Kush Paul and co-authors (2017), could be used to investigate other open questions. These open questions include the effects of light conditions on phenotypical responses. One challenge, however, is that the connection between cryptochromes and neuronal response is poorly understood. One possible explanation for the connection is that cryptochromes may directly affect rhodopsin, the most prominent light-responsive protein in the eye (Paul et al., 2017; Stoneham et al., 2012).

Another potential area of study is NV-center diamonds, which could be emulators for cryptochromes because the physics of their spin effects is very similar. Bringing physicists, engineers, and biologists together to look at these systems in a unified, collaborative way would create progress in understanding—and potentially drive research in—biological systems.

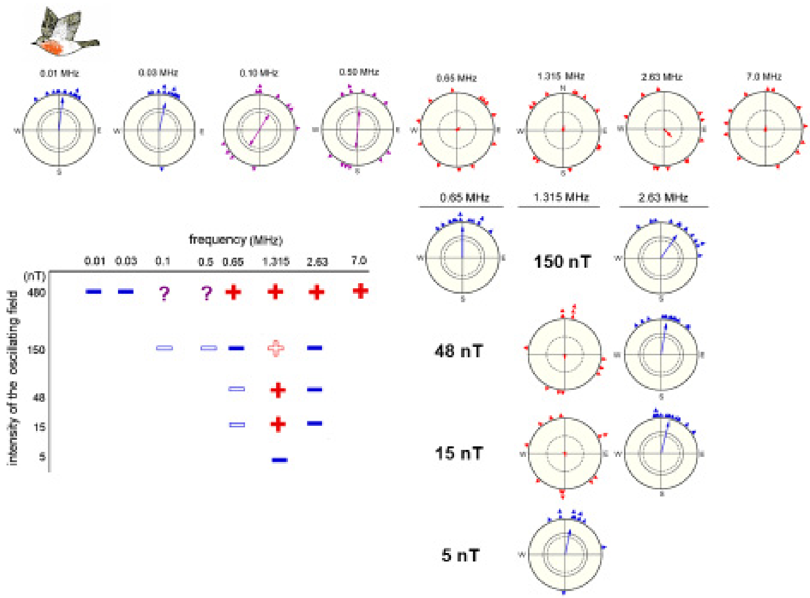

FIGURE 2-1 Orientation of robins tested under different magnetic resonance wavelengths. The figure shows the results of birds in “Emlen funnels,” small cages in which the birds leave scratch marks when trying to fly in a specific direction. Each red or blue mark indicates a scratch (quantal flux about 0.8 [UV] and 8 × 10^{15} quanta/s).
SOURCE: Reprinted from *Biophysical Journal*, Vol 96, Ritz et al., Magnetic Compass of Birds Is Based on a Molecule with Optimal Directional Sensitivity, pp. 3451–3457, Copyright (2009), with permission from Biophysical Society. Published by Elsevier, Inc.

Ritz concluded that quantum technology has come a long way due to the original work by Shor (1994), and the time is right to think beyond individual, siloed research and work together to push the field forward.

Discussion

A participant asked if it was possible to have evolved receptors wherein the unpaired electron is encased in a molecular edifice and the stabilized nucleus spins. Ritz answered that he believes it is possible for nature to work in harmony with the quantum state, at least on very short timescales, which is the case in enzymes. Although this is an important question, the available evidence is insufficient to provide a definitive answer at this point.

When asked how to test if the spectral density of an enzyme is an evolved property, Ritz replied that it is important to find the right ladder upon which to construct an answer. He suggested dynamical modes in thermal conduits in the context of adaptations of amino acid substitutions as a starting place. He also added that very short coherence times are critical to biological functions. The transition from classical to quantum thinking will improve as more is learned about how quantum science matters in biology.

PROBING INTRACELLULAR AND INTERCELLULAR CORRELATIONS IN BIOLOGY

Philip Kurian, founding director of the Quantum Biology Laboratory at Howard University, moderated the workshop's first session. The panelists were Marco Pettini, professor at Aix-Marseille University; Allyson Sgro, assistant professor of biomedical engineering at Boston University; Martin Plenio, director of the Institute of Theoretical Physics and the Center for Quantum Bio-Sciences, Ulm University; and Gürol Süel, professor of molecular biology, University of California, San Diego.

Long-Range Electrodynamic Interactions Among Biomolecules

Marco Pettini

There are an incredibly large number of biological reactions continuously taking place in living organisms, and thousands of metabolic interactions occur within each molecule. The fundamental question that drives Pettini's work is, how do these biochemical cognate partners meet so efficiently and successfully?

The current explanation is that they meet randomly via Brownian motion, but a different possibility builds off Fröhlich's (1968) idea that collective vibrations can be induced. Pettini's team has observed this possibility in several proteins by exciting cryptochromes with lasers, creating protein quakes observed at the Terahertz level (Nardecchia et al., 2018). Another possibility for exciting long-range reactions is electrodynamic interactions, such as DNA–protein and protein–protein interactions (Preto et al., 2015).

Manipulating and Controlling Molecular-Scale Processes to Engineer Multicellular Biological Behaviors

Allyson Sgro

Manipulating molecular processes could be a means to control multicellular systems and create a paradigm for synthetic biology (see Figure 2-2). First, however, it is necessary to quantify a single cell's behavior and engineer those behaviors to create protein-based tools and techniques to understand and exploit quantum biology.

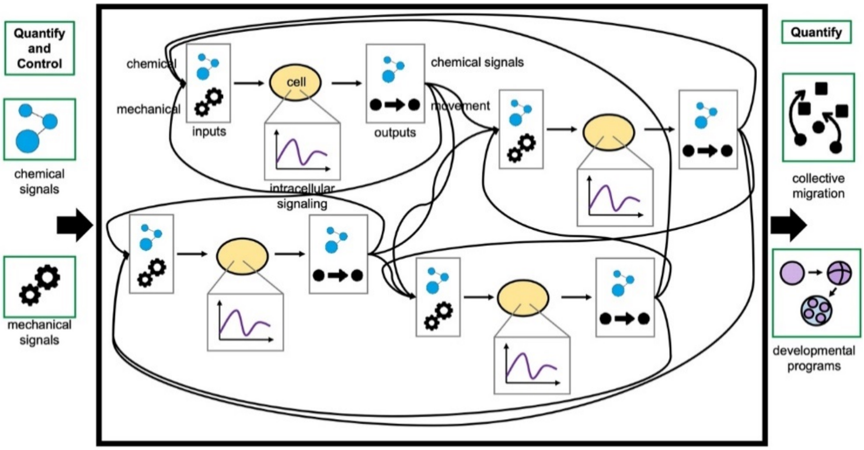

FIGURE 2-2 Manipulating molecular processes could be a means to control multicellular systems and create a paradigm for synthetic biology.
SOURCE: Image by Allyson Sgro and Mark Aronson.

Cells take internal action and signal to other cells based on inputs they receive. To understand how these inputs affect group behaviors, such as the collective scaling of vibration modes, Sgro's team uses microfluidics and optogenetics to control and quantify cell inputs and link them to quantified outputs. For example, Sgro's team used optogenetics to instruct a cell to initiate tissue repair.

New protein-based tools would illuminate ways that quantum effects are important in cell behavior. Existing imaging and sensing technologies have spatial and temporal limits that make it hard to capture ultrafast dynamic biological processes or relay instructions quickly enough. Other limitations are resolution, sampling frequency, depth, SNR ratio, and toxicity.

Quantum Sensing and Dynamics for Biology

Martin Plenio

Biological processes such as photosynthesis or magnetoreception can be viewed as very small, fast thermodynamic engines that have quantum potential. Some of the interactions that drive these processes happen at nanosecond and smaller timescales, and current open questions are how quantum mechanics might play a role in biological systems, how the interactions can be modeled, and how these interactions could be verified through experimentation (Huelga and Plenio, 2013). Direct quantum effects have not been observed over longer time ranges of days or years, but Plenio noted that there may be indirect effects.

Using color centers in diamonds is a promising way to examine the quantum effects of individual spin dynamics in biological systems at micro- and nanoscales. This makes it theoretically possible to search for magnetoreceptors in birds, detect redox reactions, and execute protocols for high-precision spin sensing (Barton et al., 2020; Cao et al., 2020; Müller et al., 2014; Schmitt et al., 2017; Schwartz et al., 2019; Wu et al., 2016). Collaborative efforts with biologists in these areas could answer important quantum effects questions.

Importance of Ionic Interactions

Gürol Süel

Inorganic ions, which are essential to life, underlie the majority of a cell's composition and interactions (Milo and Phillips, 2015) (see Figure 2-3). The study of ionic interactions has enormous and exciting potential for the future of quantum biology, but it has been neglected for several reasons.

First, there is a lack of tools to study ionic interactions, which are noncovalent, making these interactions the unmeasurable "dark matter" of biology (Ross, 2016). In addition, the concept of ion homeostasis is misleading; the concentrations and locations of metal ions are frequently in flux. Finally, cells cannot make or destroy ions; they must regulate their ion content through channels and transporters. Although quantum effects have not explicitly been defined or tested, Süel noted that much more needs to be done to determine the role of quantum in cellular systems that regulate ion fluctuations.

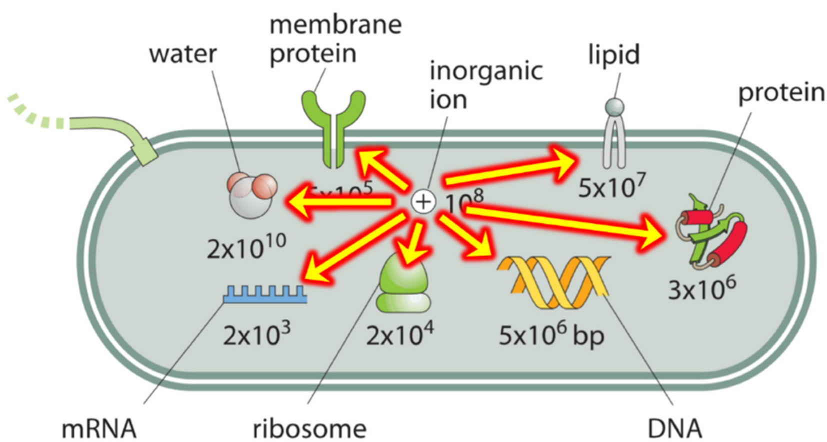

FIGURE 2-3 The vast majority of interactions in the cell are ionic.
SOURCE: *Cell Biology by the Numbers*, Ron Milo and Rob Phillips, © 2015, Garland Science. Reproduced by permission of Taylor & Francis Group.

Süel posited that the lack of knowledge or tools for studying inorganic ions poses an important challenge for many reasons. At the cellular level, certain ions can influence antibiotic resistance; for example, bacterial cells can protect their ribosomes from antibiotics by controlling the amount of magnesium ions inside the cell (Lee et al., 2019). At the population level, bacteria use ion channels to orchestrate community stress responses (Humphries et al., 2017; Prindle et al., 2015). Süel urged increased attention to this area at both the technical and theoretical levels.

Discussion

Kurian moderated a discussion that covered the need for new tools and theory, quantum effects versus quantum underpinnings, and probing ionic enhancements.

New Tools and Theory

Kurian asked what tools the panelists needed to pursue their work. Süel replied that beyond new tools and techniques, new theoretical frameworks are needed to understand cellular-level actions and predict cell behavior to design and use new tools. Sgro agreed, adding that theorists and experimentalists should work in tandem to build the tools to test these predictions in a closed loop.

Plenio, a theorist, added that the presence of so many unknowns in biological systems makes it difficult to formulate theories. Theorists and experimentalists working closely together could make progress by making, testing, and adjusting models. Pettini agreed that the theory–experiment gap is large, and noted that he is studying basic mechanics, such as cryptochromes and optogenetic molecules, to develop theory and design experiments around those building blocks.

Quantum Effects Versus Quantum Underpinnings

In response to a question, Sgro stated her belief that cell aggregation might be a quantum effect for two reasons. First, cell aggregation relies on a number of molecular-driven processes, which may be quantum-based. Second, the tools used to study cell aggregation are dependent on quantum phenomena but are not yet optimized to understand quantum properties. Kurian added that even phenomena that can be described classically may still have quantum underpinnings.

Sgro also noted that it can be challenging to tell which gene systems are activated during cell interactions. Different genes control internal cell activities than those that govern external interactions, and these external interactions could have quantum underpinnings. She stressed the importance of improving research tools to better understand external processes.

Probing Ionic Enhancements

Süel stated that because so little is known about the inner workings of cells, nothing can be ruled out. The fact that life has evolved with inorganic ions and cannot live without them, however, points to their being essential. Solving these important questions will require a community-wide effort, he concluded.

BIOELECTROMAGNETIC FIELDS

In Session 2, Clarice Aiello, leader of the Quantum Biology Technology Laboratory at the University of California, Los Angeles, introduced the topic of the exploration of how organisms interact with electromagnetic fields. Such bioelectromagnetics might involve quantum properties, which points to the possibility that organisms may, for a short time, be living quantum sensors.

Aiello went on to explain what she meant by *quantum*, noting that she delineates the definition into several levels. This includes a base level of "quantum-ness," which reflects that all matter is made of atoms, and when these particles are isolated they behave based on quantum mechanical principles. A second level is related to quantum coherence, where a single quantum object might be found in a coherent superposition state. A final level, which she described as the quantum-entangled level, involves multiple quantum systems which are entangled among themselves. Aiello noted that the area of bioelectromagnetism mostly touches on the quantum coherence level of quantum-ness, and she explained that the speakers would touch on the topic of spin, relating it to magnetic field sensing and the coherent superposition of spin states.

The speakers were Margaret Ahmad, research director of Centre National de la Recherche Scientifique (CNRS), Sorbonne University; Wendy Beane, associate professor of biological sciences at Western Michigan University; Douglas Wallace, geneticist and evolutionary biologist at the University of Pennsylvania; and Michael Levin, director of the Allen Discovery Center at Tufts University and the Tufts Center for Regenerative and Developmental Biology.

How Are Organisms Regulated by Electromagnetic Fields?

Margaret Ahmad

The class of photoreceptors known as cryptochromes, found throughout biology, are good candidates for magnetoreceptors because they absorb the blue light that migratory birds need to orient (Ritz et al., 2000). Many animals' cryptochromes can be manipulated by magnetic fields, which indicates that they can perceive magnetic signals (Ozturk, 2017). This is possible because cryptochromes undergo photoreduction to form oxidation reduction (redox) states, a process that requires oxygen, and then generate protein changes, which produce measurable biological signals (Ritz et al., 2010). Reactive oxygen species (ROS), which are highly active cellular messengers, are also produced. Even though much is known about this process, there are still many unanswered questions that need to be addressed to enable predictions of cell behavior. There is also a need for further development of imaging technology, Ahmad said.

Understanding these quantum forces also has potential therapeutic applications. Light and electromagnetic fields stimulate short bursts of ROS, making them anti-inflammatory agents (Sherrard et al., 2018). This raises the possibility that they could be used to defeat cytokine storms, which are highly modulated by ROS. A cytokine storm is an overreaction of the immune system to an invading pathogen and plays an important role in the pulmonary effects seen in the lungs of some COVID-19 patients as well as others affected by infectious organisms. Ahmad suggested that such approaches could also potentially work for other noninfectious diseases that are modulated by ROS, such as cancer and many chronic diseases.

Quantum Control of Stem Cells

Wendy Beane

Beane and colleagues study whether quantum effects can regulate stem cell activity in planarian flatworms. These organisms are notable for their large number of stem cells in adult tissues, and their high capacity to regenerate (Oviedo et al., 2008; Sánchez Alvarado, 2007). Specifically, Beane and colleagues explore how external magnetic fields can be used to manipulate the radical pair spin state to either increase or decrease ROS levels. Using this approach, they found that magnetic field strength regulates stem cell activity through relative threshold levels of ROS. Weak magnetic fields, which lower the level of ROS present, inhibit new tissue growth, gene expression, and downstream gene proliferation, while strong magnetic fields and the resulting high levels of ROS increase growth (Van Huizen et al., 2019) (see Figure 2-4).

The sensing of weak magnetic fields is more influential in biology than previously thought and could hold promise for developing noninvasive therapeutic applications for regenerative medicine and cancer treatment. However, Beane said, more research is needed to advance knowledge about quantum sensing in cells. She added that a shared language and improved, organism-specific imaging tools are needed to facilitate productive interdisciplinary work in this area.

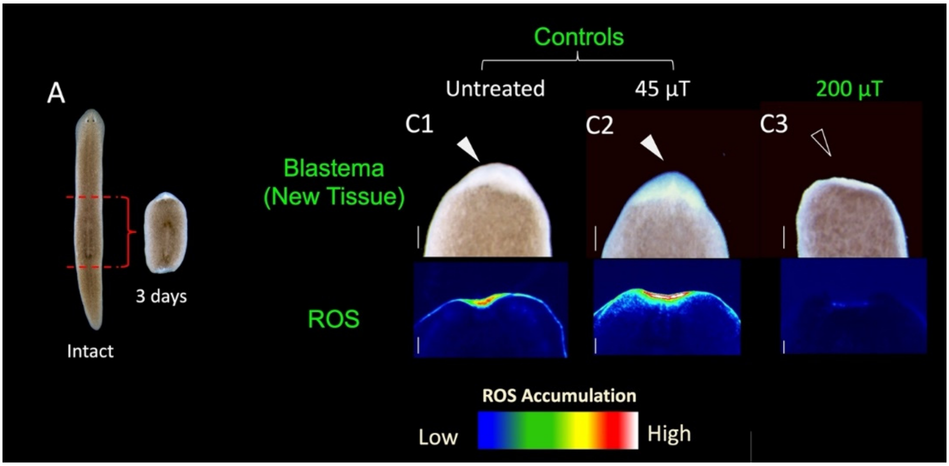

FIGURE 2-4 In planarian flatworms, exposure to a weak magnetic field (200 µT) prevents blastema or new tissue growth during regeneration due to an inhibition of ROS accumulation after injury.
SOURCE: Van Huizen et al., 2019. CC by 4.0.

Are Mitochondria the Source of Electromagnetic Radiation That Emanates from the Brain?

Douglas Wallace

Electromagnetic wave measurements that are used to diagnose neurodegenerative diseases have been assumed to come from neuronal cells. However, Wallace raised the possibility that oscillating electromagnetic fields of mitochondria could be generating the electromagnetic radiation seen in electroencephalograms (EEGs) or magnetoelectroencephalography (MEG). This could be because mitochondria have a higher membrane potential than neurons and because there are far more of them than neurons.

The brain emanates oscillatory electromagnetic radiation, and MEG measurements in the brains of patients with autism show a marked difference from those of patients without autism (Port et al., 2015). Wallace's team created a mouse with features that mimic autism and have an altered electroencephalogram pattern. This model was created by introducing a single point mutation in the mitochondrial DNA. The team then determined that the mitochondria communicate to generate an intense, oscillating electromagnetic field, similar to what is found in patients with autism (Yardeni et al., 2021). In addition, mitochondria align via electrostatic repulsion, creating an oscillating system along the mitochondrial membrane whose fluctuations generate the electromagnetic radiation that may be used in signaling (Brand et al., 2005).

Endogenous Bioelectric Pattern Memories in Embryogenesis, Regeneration, and Cancer

Michael Levin

Cells are incredibly competent at working together to create complex, three-dimensional morphologies. During development, a cell's genetic code acts not as a hard-wired set of instructions for anatomy, but as a system executing error minimization loops to achieve the correct target morphology in the organism as a whole. Studying this goal-directed process in tadpoles, Levin and colleagues found that the tadpole's craniofacial tissue will migrate to the appropriate locations during development to form normal frog faces, even when the tissues are artificially moved so that the eyes, nostrils, and mouth start in the wrong positions. This suggests that, rather than each cell following a preprogrammed path to its ultimate location in the face, cells make collective decisions about their arrangement and work together toward the correct formation. However, the mechanisms by which cell groups robustly implement specific anatomical goals are largely not understood.

In subsequent studies, Levin's team found that bioelectric signals likely form a key communication channel enabling these collective decisions. Tracing cellular conversations by monitoring bioelectric signals in developing frogs, the team was able to observe typical bioelectric patterns as cells cooperate normally, as well as abnormal bioelectric patterns that occur when oncogenic mutations cause cells to defect from the group and lead to abnormal morphology (Levin, 2021). This communication is not local but rather propagates across the whole body and does not depend on innervation (Busse et al., 2018). Levin noted that the nonlocal nature of the signal mirrors the types of event seen in quantum mechanics, but he did not suggest that there was evidence that these events were exhibiting quantum mechanical behavior.

To manipulate these bioelectric patterns, Levin's team uses molecular-level techniques to manage standing patterns of cellular voltage in tissues that instruct cell activity in multiple ways, including nonlocal activity, and creates computational models to guide the discovery of interventions that would normalize or repair damaged organs (Chernet et al., 2016).

This physiological "software" situated between the genome and anatomy can be read with voltage dyes and written by modulation of ion channels via drugs or light. Levin suggested that cracking the code of these quantum-esque bioelectric patterns represents a massive opportunity for biology and biomedicine, although better voltage imaging technologies will be needed.

Discussion

Aiello moderated a discussion covering other possible biomagnetic molecules, the need for more tools, and short-term electric field effects. Ritz also joined the panelists for the discussion.

Other Biomagnetic Molecules

A participant asked what other molecules, besides cryptochromes and ROS, might be affected by magnetic fields. Beane answered that anything with a magnetic dipole could be affected, and Ahmad added that any redox enzyme could be affected as well in the right environment. Wallace noted that if a mitochondrion's magnetic field could be modulated, it could regulate ROS.

Ritz added that to set up quantum effects, the radical pair has to be embedded in a meaningful way in order to drive magnetic field effects, which is challenging. He is currently studying metabolic responses to understand this process.

Need for More Tools

Aiello asked what is needed to say unambiguously that something is or is not a quantum effect. Ritz answered that multiple pieces are missing, such as integrated experiments with quantum tools alongside other system tools, and a way to turn off quantum-ness, perhaps via amino acid mutations.

Ahmad agreed that there is a dearth of necessary tools and said that studies conducted to date have not yet produced biological proof of quantum-ness. A good first step would be building the simplest possible biological model to pinpoint that a quantum effect is driving a meaningful response. Beane agreed, noting that while a clean, synthetic cell could help connect the dots, she would like to see inside real, messy, organism-level changes and to manipulate magnetic field spins to determine if they are working in a quantum manner.

Wallace cited several unanswered questions: Can physics modulate biology, and is that physics acting in a quantum way? What is generating and receiving the signal, and what is the signal structure, especially at a distance across an organism? Some questions can be answered with current tools, but confirming quantum effects would require more research and tool development, he said.

Short-Term Electric Field Effects

Aiello asked panelists to speculate about short-term electric field effects in cells. Levin replied that his work usually takes hours or days, but there may be ultrafast dynamics at play that go unnoticed. Beane suggested that local cellular communication may happen quickly, but the feedback loop takes longer. Wallace added that researcher Peter Burke is studying mitochondrial antennae and frequency signaling, and it may be that, as Beane suggested, a short-term signal gets repeated over a longer time frame.

QUANTUM PHOTONICS IN BIOLOGICAL SYSTEMS

Prineha Narang, assistant professor of computational materials science at Harvard University, moderated Session 3, which covered the roles of coherence, theory, and computation in biological systems. In addition, panelists described new quantum spectroscopy, optical, and photonic techniques to identify and differentiate these various mechanisms.

The panelists were Michelle Digman, associate professor in the Department of Biomedical Engineering at the University of California, Irvine; Scott Cushing, assistant professor of chemistry at the California Institute of Technology; Giuseppe Luca Celardo, professor at the Institute of Physics, Benemérita Universidad Autónoma de Puebla, and the Department of Mathematics and Physics, Università Cattolica del Sacro Cuore; and Tjaart Krüger, associate professor of physics at the University of Pretoria.

Quantum-Enabled Sensing and Imaging for Biology

Michelle Digman

Digman's laboratory uses imaging technologies, including fluorescence lifetime imaging microscopy (FLIM) and multiphoton excitation, to study biophysical cellular mechanisms and interactions, especially when cells are under stress. These technologies could also be developed to study quantum effects in biological systems. For example, total internal reflection fluorescence measures protein displacement and diffusion (Di Rienzo et al., 2014, 2016; Digman and Gratton, 2009; Digman et al., 2008). In addition, single plane illumination microscopy enables monitoring of molecular dynamics within a cell, not just at the membrane, to create a map of spatial and temporal dynamic molecule behavior (Unruh and Gratton, 2008).

Digman uses these tools to study voltage-gated potassium ion channels (Kv), which could play a crucial role in increasing the understanding of cellular system activity and may be influenced by cryptochromes (Dixit et al., 2020). Her team mapped and measured diffusion and the length of confinement in Kv to produce a quantitative measure of the dynamics of these proteins (Tedeschi et al., 2021).

Entangled Spectroscopy

Scott Cushing

Cushing posited that entangled photon spectroscopy could inspire new tools for detecting quantum effects (Szoke et al., 2020). Such tools could be as simple as a desktop device that analyzes data or a high-powered quantum spectrometry tool to stimulate activity and detect quantum effects.

Entangled photons can be created by taking one photon and splitting it into two photons, resulting in two photons with different spatial, temporal, and polarization domains (see Figure 2-5). Two entangled photons tend to act as one when interacting with matter. For example, two entangled photons leave the same side of the beam splitter or diffract on a grating at the wavelength of the original pump photon. Their entanglement also enables measurements of the quantum correlations of light (Kalashnikov et al., 2017; Ostermeyer et al., 2009). Nonlinear-type spectroscopy of entangled photons has recently demonstrated linear two-photon fluorescence and absorption (Dayan et al., 2005; Lee and Goodson, 2006). While the exact mechanics are still unknown, entangled photon spectroscopy is a promising method to see and measure quantum effects.

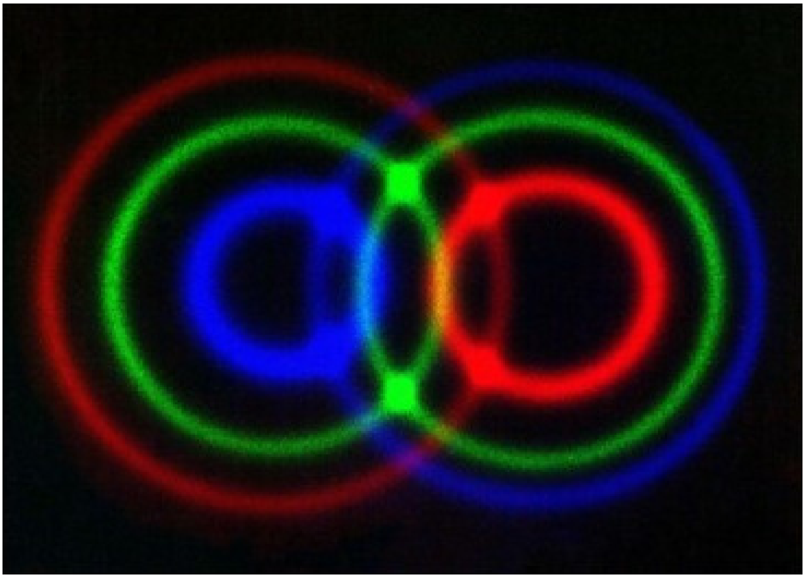

FIGURE 2-5 Entangled photons are generated by splitting one pump photon into two. SOURCE: Image by Paul Kwiat and Michael Reck.

To make an easy-to-use quantum spectrometer, very bright sources of entangled photons are needed, and they must work on short timescales to avoid disturbing the fragile entangled state in complex materials. For example, Cushing is studying whether on-chip sources with continuous wave diode lasers connected to a microscope could enable neural-type sensing.

Cooperativity Functionality and Sensing: A Bio-Inspired Sunlight Pumped Laser

Giuseppe Luca Celardo

Biological systems can process extremely weak energy sources and signals, such as the Earth's magnetic field or sunlight. To accomplish such efficient coherent effects, the systems have to be highly symmetrical and hierarchical. Using these principles, many teams have studied biomimetic quantum devices (Creatore et al., 2013; Dorfman et al., 2013; Higgins et al., 2014; Romero et al., 2017; Scully et al., 2011). More recently, researchers have increasingly focused on cooperative effects for their relevance to robustness and functionality, for example (Celardo et al., 2019; Chávez et al., 2020; Gullì et al., 2019; Mattiotti et al., 2020b).

Celardo's team is studying bio-inspired sunlight pumped lasers (Mattiotti et al., 2020a). A laser pumped by natural, renewable sunlight could collect, store, and distribute solar energy efficiently. Conventional sunlight-pumped lasers face technical challenges, but Celardo's biomimetic design works with natural, unconcentrated sunlight (Yabe et al., 2008). The technology's inspiration comes from bacterial photosynthesis, a process that relies on cooperative effects from the highly symmetrical and hierarchical organization of chlorophyll molecules that collect sunlight and efficiently transfer it.

Photosynthetic Light-Harvesting Complexes

Tjaart Krüger

Krüger posited that photosynthetic light harvesting complexes may be the best proof that biological systems use quantum effects to enhance function. Through subtle protein conformations, photosynthetic light-harvesting complexes use exciton-phonon coupling to dynamically tune the interplay between exciton delocalization and quantum decoherence. The level of tunability varies depending on the type of light-harvesting complexes that are used. Krüger's team is investigating this tunability via two experimental methods.

First, they use single-molecule spectroscopy with quantum techniques to investigate how single protein complexes perform the sensing and tuning of the light-harvesting efficiency. Second, they use ultrafast transient absorption spectroscopy to resolve energy transport, illuminating which pigments in the light-harvesting complexes, and which energy levels, participate at which time. By employing coherent control, it is also possible to actively tune the degree of light harvesting.

Two emergent technologies from this work, quantum illumination and ghost imaging, have promising biosensing and imaging advantages. Quantum illumination, in particular, can greatly enhance the signal-to-noise (SNR) ratio, improve accuracy and resolution, provide clarity in diagnostics, reveal protocol effectiveness, detect new pathways for optimizing biochemical processes, increase optical power, and minimize photodamage, all without being limited by combined time and frequency resolution. In practice, however, various sources of noise, such as interactions between excitons with vibrational modes in the immediate environment, severely limit the actual SNR enhancement, and the main benefit of these technologies lies in the use of fewer photons to obtain the same information as in classical measurements. In reply to a question, Krüger noted that his team has not studied quantum illumination for superresolution imaging but focuses instead on spectroscopic applications.

Discussion

Narang moderated a discussion touching on finding coherence signatures, quantum imaging, and entangled photons and spectrometry.

Finding Coherence Signatures

Narang asked the panelists how they could find coherence signatures, both theoretically and experimentally. Celardo answered that, first, these structures need to be fully understood and exploited, but it may be possible to simplify aggregates as dipoles through thermal relaxation and cooperativity. Exploiting hierarchy to understand the role of symmetry can also prove the efficiency of designed biomimetic structures and would be an indirect, theoretical hint at the role of coherence.

Cushing added that the biggest experimental challenge is whether the toll being induced is creating the effects seen. Separating combined quantum effects such as coherence and entanglement is difficult, but studying natural excitation, such as by sunlight, is promising. It is technically possible to excite something and determine if it is a quantum effect, but other tools are needed to study generic systems with varying properties.

Quantum Imaging

Ralph Jimenez, University of Colorado Boulder, asked Digman if quantum imaging could bolster her experiments. She replied that it is possible, for example, when monitoring a signaling event in Kv, an area widely under study. Digman also noted that although her laboratory does not measure quantum coherence, they do excite naturally occurring fluorescent molecules, and it may be possible to disentangle, monitor, and measure them. Cushing added that diffraction techniques for imaging still need improvement.

Entangled Photons and Spectrometry

A participant asked how entangled photons have different diffraction capabilities. Krüger replied that the improvement in the SNR ratio could apply to sensing and imaging, due to the soft Poissonian photon statistics. There is a limit, although the limit is lowered significantly with a very large number of photons.

Bern Kohler, The Ohio State University, asked Cushing if ultraviolet (UV) bandwidth could be increased in entangled light spectroscopy. Cushing replied that his laboratory is working on a prototype using a designed nonlinear element and diode lasers that he hopes can create ultrafast sources in UV. Celardo added that efficient photon sensing is key to learning more about biological processes.

BREAKOUT DISCUSSIONS

Attendees were invited to join several small breakout sessions for more in-depth discussion. For the first part of the breakout session, participants introduced themselves and discussed a range of topics, including the difference between coherence and entanglement, the role of ROS in wound healing, quantum versus classical coherence, different interpretations of *coherence*, different coherence timescales, and possible coherence measurements. For the second part, participants documented their thoughts on topics surrounding the concepts, technologies, and advancements to improve biological sensing and imaging. In addition, participants were asked to list outstanding questions they would like to see addressed during the remaining workshop sessions.

In these discussions, participants wondered if it were possible to reveal underlying quantum effects either by probing biosystems with quantum light or probing the quantum properties of the emitted light. Workshop participants pointed out several areas of importance for continued advancement of the field, including collaborations with synthetic chemists to create a bottom-up approach for building clean test systems to study entanglement, better readout mechanisms, and reaching *n* photon measurements. Finally, participants suggested future studies that could investigate using the ubiquity of ROS in metabolic signaling processes, the use of quantum squeezing to measure biological action potentials, and the uses for quantum illumination and ghost imaging. They listed the following outstanding questions for the workshop and the field in general:

1. What kinds of "quantum 2.0" techniques can enhance biological function?
2. What are the emergent properties of a system that can only come from quantum effects, such as nonlocality and entanglement?
3. Is the spectral density of motions in a biological system somehow tuned to enhance quantum effects?
4. What infrastructure at national laboratories would improve measurements on biosystems, such as flux, precision, and entanglement?
5. Can more be learned about photosynthetic systems with single photon measurements?
6. Is there a role for quantum measurements in looking at ion interactions?
7. How does a system transition from quantum to classical?
8. Does *nano* imply *quantum*?
9. Can coherent control techniques be used?
10. How can the lack of shared language be fixed?
11. What is the next improvement in resolution after quantum illumination?
12. What are the advantages of quantum light over increased laser power?

3

Quantum *for* Biology

The second day of the workshop focused on quantum *for* biology including the use of quantum tools and technologies for the sensing and imaging of biological processes. Although Marlan Scully, a member of the faculty in physics and astronomy at Texas A&M University, Princeton University, and Baylor University, spoke on the first day of the workshop, his keynote on applications of quantum laser spectroscopy are described here based on the topics covered. The second day opened with a joint keynote on the possibilities of quantum-enabled electron microscopy, given by Elizabeth Villa, assistant professor of biological sciences at the University of California, San Diego, and Karl K. Berggren, professor of electrical engineering, leader of the Quantum Nanostructures and Nanofabrication Group, and director of the Nanostructures Laboratory at the Research Laboratory for Electronics at the Massachusetts Institute of Technology. The keynote address was followed by three panel discussions covering the topics of quantum principles for enhanced measurement and imaging in microscopy, broadband spectroscopies of collective dynamics in biology, and ultrafast spectroscopy and biological reporters. During the panels, each discussant was given 7 minutes of opening remarks followed by a moderated audience question-and-answer session.

NEW QUANTUM THEORY APPLICATIONS FOR BIOLOGY

Marlan Scully

During this keynote address on the first day of the workshop, Scully delivered a presentation on quantum laser spectroscopy, COVID-19 applications, and superradiance.

Laser Spectroscopy

Scully engineered a laser spectroscopic technique, Femtosecond Adaptive Spectroscopic Technique for Coherent Anti-Stokes Raman Scattering (FAST CARS) which was used for rapid identification of anthrax spores (Scully et al., 2002). This technique was built using the Raman effect, the spontaneous effect of light scattering by a molecular system, a quantum mechanical process (see Figure 3-1).

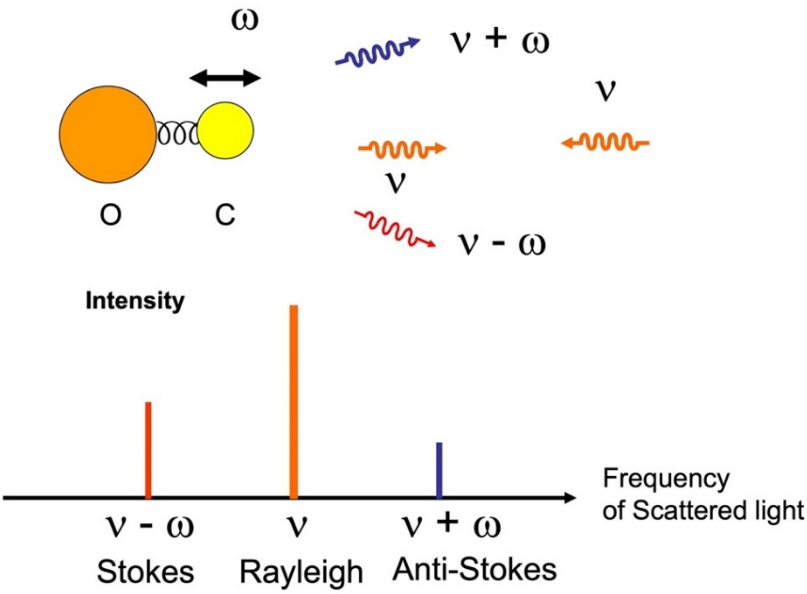

FIGURE 3-1 The Raman effect, a quantum mechanical process, is the spontaneous effect of light scattering a molecular system.
SOURCE: Image by Marlan Scully.[1]

The Raman effect is embodied by the coherence between a molecule's ground state and the first excited state. However, different molecules emit the same scattered frequency, making it hard to tell them apart (Pestov et al., 2007). Manipulating lasers via FAST CARS enhanced the signal and suppressed noise, and when FAST CARS was applied to surface Raman, it created astonishing improvements in sensitivity (Lis and Cecchet, 2014; Voronine et al., 2012).

COVID-19 Applications

Scully and his collaborators developed an enhanced technique, Femtosecond Adaptive Spectroscopic Technique with Enhanced Resolution for Coherent Anti-Stokes Raman Scattering (FASTER CARS) and applied it to identify SARS-CoV-2, the virus that causes COVID-19 (Deckert et al., 2020). FASTER CARS can scan a single RNA or DNA strand and measure the Raman signal to accurately determine the sequence of its nucleotide bases (He et al., 2020). Scully's team is currently investigating improvements to this technology to better understand the mechanics and increase its accuracy.

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[1] Thank you to Dr. Marlan Scully for allowing us to use his image.

Superradiance

Another topic under study is whether superradiance has any function in the brain, one of many ideas put forth by Fröhlich that several other researchers are pursuing (Fröhlich, 1968; Nardecchia et al., 2018; Reimers et al., 2009; Zhang et al., 2019). Scully outlined the differences between superradiance and laser coherence. Laser coherence is a dynamical stimulated emission, whereas superradiance is spontaneous, cooperative, and possibly coherent. The possibility of quantum coherence and superradiant states in brain microtubules inspired Scully to investigate timed Dicke states to create superradiance over long distances (Celardo et al., 2019; Jibu et al., 1994; Mavromatos, 2011; Scully and Svidzinsky, 2009). Scully said superradiance is still a very open topic, with exciting research advancements on the horizon.

Discussion

Taekjip Ha, Johns Hopkins University, asked about decay times. Scully responded that the superradiant state decays very quickly, before environmental phonon-induced decoherence can cause decay. He and Ha agreed that the short decoherence time may help couple quantum and biological processes.

When asked about the broader applications of this work, Scully replied that his team is one of several investigating improvements to antibody detection and methods to study SARS-CoV-2 surface proteins (Peng et al., 2020).

QUANTUM-ENABLED ELECTRON MICROSCOPY FOR BIOLOGICAL STUDY

Electron Microscopy and Cryogenic Electron Microscopy Development, Technologies, Applications, and Challenges

Elizabeth Villa

Cryogenic electron microscopy (Cryo-EM) could become the highest resolution technique for cell biology. For the first part of this joint keynote presentation, Villa discussed the development of the electron microscopy (EM) and cryo-EM technologies, current cryo-EM capabilities, and biomedical applications and challenges.

EM and Cryo-EM Development

Early electron microscopes were pioneered almost 100 years ago (see Figure 3-2) and led to the development of several tools enabling increasingly sophisticated three-dimensional (3D) reconstructions of two-dimensional (2D) biological images (Driest and Muller, 1935; Dubochet et al., 1988; Henderson and Unwin, 1975; Klug and Finch, 1965; Taylor and Glaeser, 1973; van Heel and Frank, 1981). Today, researchers can use single-particle cryo-EM to solve the structures of macromolecules with atomic resolution. In this technique, hundreds of thousands of structurally identical macromolecules are isolated, flash frozen in different spatial orientations on a monodispersed layer and photographed to create 3D reconstructions.

Solving structures with this level of atomic resolution can improve understanding of biochemical processes and aid drug design. However, the samples are very low contrast, making it hard to distinguish the images. Using higher doses of radiation to create higher contrast damages the materials, which are already very sensitive to radiation. Continuing to improve the quality of EM images requires finding a careful balance between higher contrast and radiation damage (Grant and Grigorieff, 2015).

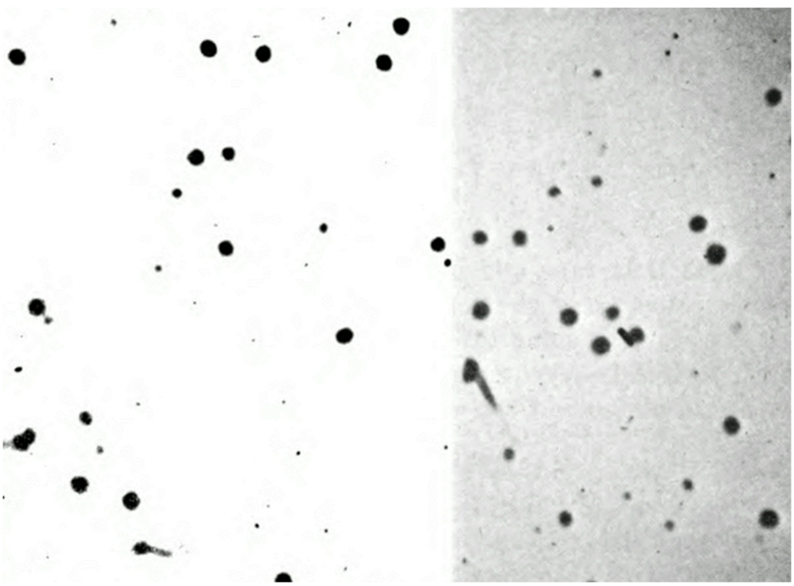

FIGURE 3-2 The first image of coronavirus (infectious bronchitis virus or *Avian coronavirus*) taken with electron microscope in 1948.
SOURCE: Courtesy of the U.S. National Library of Medicine.

After the "Resolution Revolution"

In the early 2010s, the cryo-EM "resolution revolution" brought faster direct detector devices and the ability to create high-resolution "movies" to review structures (McMullan et al., 2014). The signal-to-noise ratio (SNR) also increased, allowing the application of sophisticated algorithms to analyze data (Zhang et al., 2017). Cryo-EM leaped to the forefront of structural biology, without any advances in optics, and still has many facets where there is room for improvement. Adding quantum effects to cryo-electron tomography, an imaging technique used to make 3D reconstructions of entities such as cells, can allow for the analysis of thicker samples that have more crowded environments and low SNR (Villa et al., 2013).

EM Applications and Challenges

Villa's laboratory uses cryo-EM to study the Leucine-Rich Repeat 2 (LRRK2) protein, the most common mutations in genetically-driven Parkinson's disease, and thus a major drug target. Until recently, researchers have been unable to obtain its structure (Gaskill, 2019). By leveraging this protein's microtubule-binding properties, Villa's team successfully obtained the LRRK2 structure. The process involved computationally extracting sections of LRRK2-decorated microtubules, increasing resolution by subtomogram averaging, then using integrative modeling to determine the protein's architecture and study its interactions (Deniston et al., 2020; Kett et al., 2012; Watanabe et al., 2020).

Cryo-EM technologies have many other exciting applications, but there are challenges; studying macromolecules, including LRRK2, and their cellular pathways would be easier with higher-resolution tomography, minimal radiation, and improved SNR. Addressing those challenges will enable researchers to examine the entire molecular landscape in cells, transforming structural cell biology, Villa said.

EM Improvements, Applications, Challenges, and Opportunities

Karl K. Berggren

For the second part of this joint keynote, Berggren discussed improvements to EM, EM applications, and challenges and opportunities in this field.

Improvements to EM

Early EM designers were concerned about damage, quantum mechanics, and resolution limitations. However, resolution in biological systems is primarily limited not by optics, but rather by the maximum allowable dose of radiation

(Egerton, 2014). To make a microscope that causes less damage to biological samples, researchers turned to quantum mechanics, quantum measurements, and deeply counterintuitive concepts such as the quantum zeno effect, interaction-free measurement (IFM), and squeezed states of light (Bell, 1964; de Broglie, 1924; Degasperis et al., 1974; Einstein et al., 1935; Heisenberg, 1927; Yuen, 1975). In particular, IFM, which detects a sample without interacting with it, can be exploited with Mach–Zender interferometry and electrons (Agarwal et al., 2017; Elitzur and Vaidman, 1993; Turner et al., 2020).

EM Applications

Researchers have taken strides toward developing a microscope that effects a quantum zeno process by creating coupled waveguides and using mirrors to effectively create identical copies of a sample (Kwiat et al., 1995; Putnam and Yanik, 2009). This led Berggren and collaborators to pursue using free-space electron optics (including electron mirrors) for quantum EM (Kwiat et al., 1995; Putnam and Yanik, 2009). Finally, research suggests that an EM that does not require electron-splitting or a qubit-based system could be used as a coherent probe of quantum systems (Juffmann et al., 2017; Okamoto, 2012).

Challenges and Opportunities

Berggren's electron mirror could be developed for in-depth biological or environmental applications. Entanglement and quantum coherence also offer opportunities to improve performance and broaden scientific approaches. However, there are challenges. Electron optics such as mirrors, switches, and appropriate beam splitters are not widely available, and theoretical work around black-and-white versus grayscale approaches needs further development.

Discussion

Prineha Narang, Harvard University, moderated a discussion between attendees, Villa, and Berggren that addressed quantum-enabled EM and tracking coherence and cell interactions.

Quantum-Enabled EM

Narang asked how to build quantum-enabled EM for imaging cells. Berggren replied that Juffman and colleagues' (2017) multipass approach combined with multiparticle EM is the most promising technique to improve SNR and build real quantum tools in the next 5 to 10 years, although it may not work with fixed or thick samples. Berggren said that EMs with single-pass and multipass IFM could see small-percentage improvements in SNR, but an idea analogous to squeezing is needed to go further. Prem Kumar, Northwestern University, noted that increasing dosing and resolution can be problematic, and Berggren agreed that those were issues that needed more analysis, although he said that he is nevertheless convinced that nonclassical mechanisms are involved.

In response to a question, Berggren noted that challenges to using quantum systems to image every single molecule in a cell include a lack of instrument automation (especially for slicing thin films), unknown data pathways, and the arbitrary orientation of molecules. Villa agreed, adding that if quantum systems can enable a balance of SNR and dosing, they could create pattern-matching technology improvements over the current exhaustive 2D matching process. Villa noted that a transformation in data quality is also needed to bring this goal closer to reality, but as the field's landscape currently stands, it is expensive and likely out of reach.

Philip Kurian, Howard University, asked if it mattered whether protein data bank files were derived from cryo-EM instead of x-ray crystallography. Villa replied that the process was less important than the resulting resolution and interpretation of the structure, which rely on original data and can be of varying resolution depending on the sample. One important advantage to cryo-EM is that this method can more easily examine large and complex samples, such as membrane proteins.

Tracking Coherence

Asked what would help improve coherence with EM, Berggren responded that lens scale and adaptive measuring tools are more important than the EM itself for tracking coherence. In the initial stages, the resolution limitations will be challenging, but adding computing power and prior information will create SNR improvements and enable subangstrom resolution that could improve coherence.

Cell Interactions

When asked if the hierarchy of cell interactions was settled, Villa replied that exactly how electrons interact with biological matter is an open question with no consensus yet, for example, in the case of beam-induced motion. There is an opportunity to enhance the qualitative study of how imaging is affected by the interactions of the electron beam with the vitrified sample.

QUANTUM PRINCIPLES FOR ENHANCED MEASUREMENT AND IMAGING IN MICROSCOPY

Prem Kumar, Northwestern University, moderated the workshop's fourth session and gave a short introduction to the panel topic. The other panelists were Theodore Goodson III, Richard Barry Bernstein College Professor of Chemistry and Molecular Science and Engineering at the University of Michigan; Ted Laurence, deputy group leader for laser materials interaction science at the Lawrence Livermore National Laboratory; and Kevin Eliceiri, investigator at the Morgridge Institute for Research and associate professor of biomedical engineering at the University of Wisconsin–Madison and leader of the Laboratory for Optical and Computational Instrumentation at the University of Wisconsin–Madison Carbone Cancer Center.

Quantum Imaging

Prem Kumar

The concepts of squeezed light and quantum imaging microscopy have existed for decades (Kolobov, 1999; Kolobov and Kumar, 1993; Kumar and Kolobov, 1994). Kumar said that key issues in the field include raster casting versus multimode image rendering, ghost imaging and its variants, quantum illumination, and the Laser Interferometer Gravitational Wave Observatory, which is unusual because it can go beyond unique quantum effects (Barzanjeh et al., 2015; Ferri et al., 2010; Lloyd, 2008; Padgett and Boyd, 2017; Shapiro, 2020; Shapiro and Boyd, 2012; Shih, 2008; Tsang, 2013).

Some concepts are progressively more quantum than classical (see Figure 3-3). For example, superposition can occur as a classical behavior, but a superposition of single particles, where particle duality comes into place, is on the classical–quantum boundary. Concepts such as quantum computing are truly quantum when they require superposition, measurement, and entanglement. Kumar said that progress in imaging and microscopy will require innovation at the classical–quantum boundary despite fundamental quantum limits and varying environments.

Finally, Kumar urged attention to fair comparisons between classical and quantum approaches by considering improvements at a system level: a quantum digit offering 1,000× improvement should not be chosen over a classical digit offering 1,000,000× improvement. He also noted that there are unique scenarios where the quantum nature of the digit takes a higher priority, and he urged the consideration of all difference factors when making decisions about the utility of different methods.

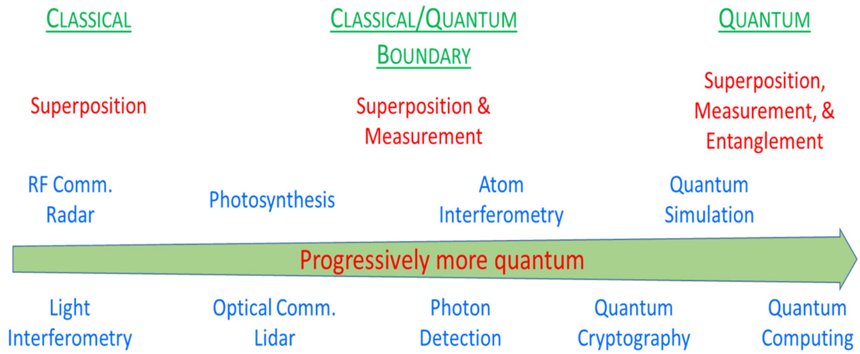

FIGURE 3-3 Spectrum from classical to quantum concepts and applications.
NOTE: RF Comm. = radio frequency communication.
SOURCE: Image by Prem Kumar.

Quantum Light Spectroscopy

Theodore Goodson III

Goodson's laboratory uses quantum light spectroscopy with photon entanglement to create new tools for investigating biological systems. This emerging field is an alternative to classical excitation, with both challenges and promise for biological imaging, especially if coupled with theoretical advances in quantum light.

Quantum light spectroscopy with entangled photon pairs has many uses. As Goodson noted, these include the high degree of correlation that can be leveraged to achieve enhanced sensitivity; entanglement transfer that could enable new material states; entangled photon pairs that could enable new dimensions to study, such as time, area, pathways, or dynamics; new molecular properties that could be activated and probed; and noise characteristics that can be improved. In addition, the lower number of photons needed to see quantum effects resolves past issues such as tissue transparency.

Goodson's team has studied two-photon absorption and linear dependence in organic molecules, entangled-photon fluorescence, and biological systems such as flavoprotein structures. They have used those findings to construct a microscope that offers nonlinear imaging capabilities with excitation intensity 10^6 lower than that necessary for classical light (Eshun et al., 2018; Harpham et al., 2009; Lee and Goodson, 2006; Upton et al., 2013; Varnavski and Goodson, 2020; Varnavski et al., 2017; Villabona-Monsalve et al., 2018).

Quantum Principles for Enhanced Measurement and Imaging

Ted Laurence

Developing correlations from quantum measurements, such as single photon counting, fluorescence transitions, and lasers, can take longer to produce the same results as classical measurements. They do not require calibration, however, and can enable new research areas, such as photon antibunching and quantum-entangled photons. For example, fluorescence correlation spectroscopy was combined with photon antibunching to determine the number of apolipoprotein A-1 proteins in one nano lipoprotein in a hydrated state (Ly et al., 2011). Laurence suggested that antibunching could be impacted by cooperative effects such as superradiance.

Laurence's group is also pursuing ghost imaging, a technique where light being measured has never directly interacted with the object of interest, using correlations between entangled photon pairs and polarizations to produce an image. Ghost imaging produces the same images as classical means but could provide different observables with quantum measurements, higher resolution, and higher sensitivity. The two detectors require a correlation, however, which presents a challenge; in addition, Laurence said that higher-rate sources, better detectors, and better detection strategies are needed.

Imaging Cell Autofluorescence for Clinical Treatment Guidance

Kevin Eliceiri

Quantum optics in cell imaging has potential for improving the understanding of the role that cells and their autofluorescent signatures play in cancer progression. Adapting multiphoton-based technologies to exploit intrinsic metabolic signatures from human tumor biopsies, Eliceiri's team has found that the levels of nicotinamide adenine dinucleotide hydrogen (NADH), an autofluorescent coenzyme that can be both free and protein-bound, can detect the Warburg effect, one of cancer's principal metabolic actions (Stringari et al., 2017; Yu and Heikal, 2009).

These multiphoton-based imaging techniques can achieve very specific excitation at the focal spot, deeper imaging, and better viability than one-photon methods. However, the required low excitation intensity can limit imaging speeds and imaging depth and there is a risk of photodamage. In addition, better techniques are needed to use FLIM to differentiate nicotinamide adenine dinucleotide phosphate hydrogen from NADH, Eliceiri noted.

Engaging with the quantum community could solve some of these problems and bring enhanced tools to biological imaging. Autofluorescence-based quantum imaging could improve optical sectioning, depth, and viability. Several studies have demonstrated proof of concept of entangled photon microscopy but not yet in a biological context (Lemos et al., 2014; Magaña-Loaiza et al., 2019; Scarcelli and Yun, 2007; Varnavski and Goodson, 2020).

Discussion

Kumar moderated a discussion that covered quantum light receivers, quantum light resolution, and sensitivity and entangled light.

Quantum Light Receivers

Bern Kohler, The Ohio State University, asked about the best receiver for quantum light spectroscopy. Goodson answered that for two-photon spectroscopy, he has tried aggregates, polymers, dimers, and more. He has found that what is most important is the ability to image large molecular cross-sections and understand energy levels, excitation, and intermediate states. Laurence added that for one-photon excitation, nothing special is needed.

Kumar asked the panelists what would enable quantum light to advance practical quantum sensing and imaging. Goodson replied that theory and experimentation need to create a better shared understanding of the structural and functional relationship between molecules.

Quantum Light Resolution

Asked about the theoretical resolution of quantum light techniques, Goodson replied that it could be used for spatial resolution, but would not necessarily create dramatic increases. A bigger impact in biological systems would be a reduction in the number of photons, although the field is still in the early stages.

Sensitivity and Entangled Light

Kumar, asking about sensitivity, reiterated that quantum does not always have a speed advantage over classical techniques. Goodson agreed, adding that low efficiency is one challenge of using entangled photons, and low-light excitation is still out of reach. Kumar suggested using the low number of photon pairs in innovative ways, and Goodson supported this idea, noting that nonclassical light is still an emerging area.

Berggren asked how relevant the transparency window is for entangled light, and Goodson replied that while the issue is still being investigated, it appears to be a trade-off between the molecule absorption and the number of photons. Photodamage can be extensive, and reducing it requires shifting the wavelength and examining different spectral regions outside the linear absorption to find molecules that have promising entangled two-photon cross-sections.

BROADBAND SPECTROSCOPIES OF COLLECTIVE DYNAMICS IN BIOLOGY

Narang moderated the workshop's fifth session, which focused on how the nonclassical properties of light can be used in metrology, microscopy, and biological system dynamics to improve quantum-enhanced sensing and imaging.

The panelists were Philip Hemmer, professor of electrical and computer engineering at Texas A&M University; Prem Kumar, Northwestern University; Kim Lewis, professor of physics and associate dean of research at Howard University; and Michelle O'Malley, professor in the Department of Chemical Engineering at the University of California, Santa Barbara.

Nanoparticles for Biosensing

Philip Hemmer

Nanoparticles can be used to amplify a target molecule's signal to enable identification and tracking. They offer advantages over fluorescent proteins, but also have some disadvantages. For example, although nanoparticles last longer than fluorescent proteins and are less prone to bleaching or blinking, they cannot be programmed into or expressed by genes the way proteins can.

For magnetic sensing, nitrogen-vacancy-center (NV-center) diamonds have proved effective because they have up to 30 percent suppressed fluorescence, depending on magnetic spin state. This large fluorescent contrast is what distinguishes them from the competition, but its precise mechanism is still not known (Nizovtsev et al., 2003). Nonetheless NV-center in diamonds has already been applied to magnetic resonance imaging (MRI), a superresolution technique, by replacing the complex MRI apparatus with a single molecule that can sense external spins and image molecules (Grotz et al., 2011). Researchers are still working on a way to image complex molecules, and Hemmer suggested that novel color centers in diamond are a promising avenue.

Hemmer's team also avoids biofluorescence interference by using upconversion nanoparticles. These particles sense temperature and certain biochemicals with high sensitivity (Hao et al., 2011). Here multimodal sensing is critical for accuracy because it identifies false signals. In the future, nanoparticles may also work in cell membranes, for electric field sensing. Hemmer aims to create novel multimodal sensors by growing diamond shells around upconversion particles and vice versa. Hemmer pointed out that these and other sensors have potential for quantum-enhanced imaging applications (Kolesov et al., 2012), but to use them to look for innate quantum effects in biological systems will require new protocols.

Generation of Photonic Entanglement in Green Fluorescent Proteins

Prem Kumar

Genetic engineering techniques may be able to optimize physical characteristics that are quantumly, but not classically, heuristic. Kumar's group studies quantum biology techniques and processes, such as photosynthesis and light harvesting, that have nonbiological applications (Engel et al., 2007; Li et al., 2005; Maeda et al., 2008; Sarovar et al., 2010; Sharping et al., 2006).

Because green fluorescence proteins (GFPs) can be used to generate entanglement, they are a promising method for creating a heuristic approach to study new sources of entangled photon pairs for nonbiological applications (Shaner et al., 2007; Yang et al., 1996). Although their molecular structure and behavior are still not fully understood, polarization filtering does improve the coincidence-to-accidental ratio (a measurement reflecting the number of pulse excitations of four-wave mixing in which a coincidence count was detected in the signal and idler arms versus what could have been attributed to accidental coincidence) (Shi et al., 2014, 2016). Knowing that photon pairs can be generated from a protein, Kumar's team, turning energy time entanglement into polarization entanglement by delayed choices, was able to create and measure the quantum interference of the generated entangled photon pairs (Shi et al., 2017, 2018). Future collaborations will explore why GFPs performed better than ordinary dyes and how they can be fused to other biological systems.

Broadband Spectroscopies of Collective Dynamics

Kim Lewis

Scanning tunneling microscopy, conductive atomic force microscopy, electromigration, and inelastic electron tunneling spectroscopy (IETS) are techniques to study electron transport and nanoscale junctions in order to build molecular electronics (i.e., electronic circuits that behave like conventional silicon devices). With these techniques, researchers have identified conductance mechanisms, extracted the electron attenuation coefficient, and investigated electron-phonon coupling and molecular vibration modes (Esposito, 2017; Saha et al., 2011).

IETS, the most relevant of these techniques to biology, tracks molecule changes in nanojunctions, enabling identification of vibrational modes linked to electron transport or electron-phonon coupling, to prove the presence of a molecule in a junction (Troisi and Ratner, 2006). Challenges abound: a well-defined molecular junction has yet to be fabricated, good results require very low temperatures in a vacuum, there needs to be a way to ensure that measurements come from the device in use, and molecules need to be properly attached to electrodes. Once those challenges are met, theoretical calculations are needed to determine chemical structure or bonds. Finally, once scientists can understand and control a molecule, Lewis said, new instrumentation will be needed to create short- and long-term biological sensing and imaging applications.

Unlocking the Biotech Potential of "Weird" Microbes

Michelle O'Malley

Better, noninvasive imaging approaches are needed to understand complicated systems, such as how microbial communities in the digestive tracts of herbivores accomplish lignocellulose hydrolysis, a very complex and slow decomposition process. GFPs do not work well because they require oxygen and this system is anaerobic.

Microbes employ a divide-and-conquer strategy to accomplish big tasks such as carbon recycling and plant and plastic degradation. Better imaging would enable researchers to understand the 3D structures and behavior involved and then replicate it to create value out of commingled waste. Researchers have investigated the process, but many questions remain regarding how enzymes and other proteins break down plant matter, their behavior and unpredictability, polymer resistance, and the role of the environment (Rubin, 2008).

Lignocellulose microbes thrive in the digestive tract of large herbivores, where a very diverse structure of anaerobic microorganisms live in a cross-kingdom relationship (Haitjema et al., 2014; O'Malley et al., 2011). New sequencing tools have contributed some insights, but O'Malley said that more imaging tools are needed to capture gut microbes' interactions and enable researchers to engineer microbial communities that create added value.

Discussion

Narang moderated a discussion that covered new techniques, isotopic effects and chlorophyll, the brain–gut microbe connection, and vibrational modes and high-temperature limits.

New Techniques

Narang asked the panelists what techniques could be developed to improve the understanding of complex, multicomponent systems. Kumar answered that minimizing loss of all kinds would open a quantum advantage for studying any system. In addition, some molecule behavior is captured in the reconstructive density matrix, which could provide a photonic readout of short-timescale electronic processes. Hemmer added that nanoparticles can follow and study molecules, but they cannot determine quantum properties.

Ralph Jimenez, University of Colorado Boulder, asked if photosynthetic systems required photon-limited sensitive samples. Kumar replied that sensitive detectors that can measure single photons, pixelate, and accomplish spatial resolution were more important.

Isotopic Effects and Chlorophyll

A participant asked Hemmer if he had studied isotopic effects in NV-center diamonds for biological imaging. He replied that at low temperatures, diamonds without carbon-13s work best.

Brain–Gut Microbiome Connection

Kurian asked O'Malley about the brain–gut microbiome connection, and she theorized that research into how memory proteins and serotonin receptors relay responses between the brain and gut during the divide-and-conquer process would be valuable. One promising idea is to use biosensors made from G protein–coupled receptors to mediate and understand communication.

Vibrational Modes and High-Temperature Limits

In response to a question, Lewis said that it is possible to excite specific vibrational modes, but it depends on the material and environment in use. In addition, IETS has a high-temperature limit of 77 K. At that level, it gets very noisy, and researchers have been testing various methods to reduce the noise. This temperature optimization would be critical for more extensive use of IETS in biological settings.

ULTRAFAST SPECTROSCOPY AND BIOLOGICAL REPORTERS

Kurian moderated the workshop's sixth session, focused on ultrafast spectroscopy and biological reporters. He noted that intrinsic chromophores could be used in quantum reporting to examine local and distributed quantum effects across the brain and gut, which could have several implications for nutrition and disease. Applying ultrafast spectroscopy to biological systems is moving research to the femtoscale, elucidating the complex, subtle effects of electromagnetic field and relaxation on biology.

The panelists were Majed Chergui, head of the Laboratory of Ultrafast Spectroscopy and founding director of the Lausanne Centre for Ultrafast Science at École Polytechnique Fédérale de Lausanne; Dongping Zhong, Robert Smith Professor in the Department of Physics and professor in the Department of Chemistry and Biochemistry at The Ohio State University; Michelle Y. Sander, associate professor in the Department of Electrical and Computer Engineering, Boston University; and Bern Kohler, professor in the Department of Chemistry and Biochemistry at The Ohio State University.

Probing Interchromophoric Interactions in Biosystems

Majed Chergui

The deep UV range of light occurs below 300 nanometers, and is important because DNA, RNA, and amino acids absorb at that wavelength or below. To use naturally occurring chromophores to prove biosystem dynamics, researchers have developed two deep-UV spectroscopic techniques with femtosecond to picosecond resolution: one-dimensional (1D) and 2D transient absorption spectroscopy and time-resolved circular dichroism, in addition to broadband fluorescence spectroscopy (Auböck et al., 2012a,b; Cannizzo et al., 2007; Oppermann et al., 2019).

With these tools, Chergui's group was able to learn more about intraprotein transient electric fields, intraprotein energy–electron transfer and energy transfer, spin and structural dynamics in heme proteins, and excited-state chirality (Bacellar et al., 2020; Consani et al., 2013; Kinschel et al., 2020; Leonard et al., 2009; Monni et al., 2015; Schenkel et al., 2006). Chergui's team plans to extend these techniques to monitor spectroscopic changes that could be used as markers of drug–target and protein–protein interactions.

Biological Photoenzymes and Photoreceptors

Dongping Zhong

Nature repairs UV-induced DNA damage with photolyases. Using femtosecond spectroscopy combined with absorption and fluorescence, Zhong's team was able to reverse DNA damage and produce high-resolution detailed movies of the electron tunneling and hopping that took place during the repair process (Li et al., 2010; Zhang et al., 2016). Zhong has also studied photoreceptors with femtosecond spectroscopy to investigate details of light harvesting and energy transfer for dynamic proteins (Li et al., 2020).

In response to a question, he noted that his experiments used adenine, but it is not the adenine itself that is critical, but the unusual fact that its flavin is folded instead of stretched, which has many functions and plays an important role in biology.

Photothermal Material Interactions for Modulation and Imaging Using Infrared Light

Michelle Y. Sander

Infrared nerve manipulation and vibrational infrared photothermal amplitude and phase signal (VIPPS) imaging are two optical techniques based on spatiotemporal temperature gradients for either label-free neuronal modulation or chemical identification and microscopy. The waveform of action potentials (APs) is reduced or completely blocked by pulsed infrared light (Zhu et al., 2019), impacting neuronal communication and downstream physiological outputs. Blocked APs result in complete and reversible termination of the muscle response while suppressed AP waveforms can recover, leaving the synaptic transmission unchanged (Zhu et al., 2020).

VIPPS imaging can be used to explore structural and chemical composition based on infrared vibrational bands. Relying on thermal lensing effects, detection can occur at visible and near-infrared wavelengths, thus resulting in subdiffraction-limited resolution (Samolis and Sander, 2019; Totachawattana et al., 2015, 2017). In addition, this technique is able to capture, distinguish, and characterize weakly absorbing features and can offer insights into thermal diffusion dynamics (Samolis et al., 2020). When applied to cell imaging, both the nanoscale cell and nuclear membrane can be localized and secondary protein conformation can be monitored (Timmel and Hore, 1996).

These multidimensional, label-free modulation and imaging techniques could be integrated across different platforms to offer novel capabilities to simultaneously analyze biological phenomena across different spatial and temporal resolutions and obtain quantum molecular, cellular, and ensemble information, Sander said.

Photodamage and DNA

Bern Kohler

The constant photodamage of DNA by UV light happens over many timescales and is a problem of great biological importance (Schreier et al., 2007). To learn about the photophysics of monomeric nucleobases, Kohler's team used femtosecond transient absorption methods and discovered that their excited states have very short lifetimes. These short lifetimes are associated with a lower risk of photodamage and are several hundred femtoseconds in duration (Crespo-Hernández et al., 2004; Middleton et al., 2009; Pecourt et al., 2000, 2001). The special photoproperties of the DNA nucleobases may be the legacy of repeated cycles of absorption, synthesis, and destruction, which led to intrinsically photostable building blocks critical to the start of life on Earth (Beckstead et al., 2016).

DNA is a multichromophoric assembly, and because of this, its structure takes a role in dissipating electronic energy (Ostroumov et al., 2013). Using infrared spectroscopy to detect DNA radicals has provided rich information about charge transfer states (Zhang et al., 2015, 2016a,b). These states move rapidly from more delocalized excited states known as excitons, but the precise events are unclear. There is interest in whether there is quantum mechanical or coherent transport of DNA excitons that affect photodamage. There are different kinds of coherence, and it is important to consider coherences that arise from natural sunlight. Coherence *within* eigenstates, a quantum mechanical value, can create delocalized excited states using solar illumination, but sunlight cannot create coherences *between* eigenstates (Mukamel, 2013). This distinction is important for understanding how electronic energy deposited by sunlight can move about in DNA. Kohler noted that quantum biology effects must be driven by mechanisms that are evolutionarily advantageous.

Discussion

Kurian moderated a discussion covering applications for quantum reporting, longer timescales, UV absorption, channel-forming proteins, and melanin.

Applications for Quantum Reporting

Kurian asked what applications for quantum reporting with intrinsic biological chromophore networks were most promising. Chergui pointed to in vitro studies of interactions between biological systems. Sander added that at the neuronal level, it is important that in vitro experiments optimize the environment and eliminate perturbations to elicit accurate measurements and signal interpretations to be closer to in vivo quantum measurements and scalable to neuronal communication.

Longer Timescales

Noting that it will be important to understand how ultrafast technology can report on longer-scale biological time lengths, Kurian asked the panelists how scientists can bridge the gap between femtoscale measurements and nano or microscale biology. Chergui answered that there are many examples of longer-timescale biological cascades that are induced by an initial action of light-driven processes such as photosynthesis. Kohler added that one challenge of ultrafast spectroscopy is that outcomes, while rare and short-lived, are biologically significant; therefore, the timescales must be bridged.

Zhong stated that for photoreceptors, inducing long-range changes by ultrafast approaches can help, but first it is necessary to understand the initial dynamics and then trace conformation changes. Sander agreed, noting that longer timescales are found in larger biological hierarchies and systems. To image and manipulate these events, it is necessary to understand how individual mechanisms interact.

UV Absorption

Alistair Nunn, University of Westminster, asked about the effect of plant compounds that absorb UV light on electric fields. Chergui noted that in his research, he sensed chromophore response in the UV. Zhong replied that he had the same result.

Channel-Forming Proteins

When asked if she had studied channel-forming proteins, Sander replied that several unknowns in the biophysical mechanisms need to be clarified first. Currently, classical microscopy is used to understand the chain of events that trigger an output, but drilling deeper into the individual protein or channel response level is promising. In addition, her team has considered studying solitonic vibrations, but has not yet been able to monitor them.

Melanin

Kurian asked how Kohler would design an entangled photon experiment with melanin. He replied that melanin is especially challenging, because it is one of the last biopolymers whose complex microscopic structure and individual chromophores are unknown. His team is using spectroscopy to deepen the understanding of melanin, which he said is a very rich, heterogeneous system that overlaps with carbonaceous nanomaterials (Ju et al., 2019).

4

Biology *for* Quantum

The third day had a theme of biology *for* quantum, which focused on the current state of biological imaging in order to understand where quantum advances might be most useful. Michelle O'Malley, professor of chemical engineering at the University of California, Santa Barbara, gave a keynote on imaging and sensing needs for anaerobic microbes. Following the keynote, there were two panel discussions that covered the topics of current capabilities and limitations in plant imaging, and measurement and sensing needs for microbial communities. During the panels, each discussant was given 7 minutes of opening remarks, followed by a moderated audience question-and-answer session.

EXPLOITING ANAEROBES FOR BIOMASS BREAKDOWN AND SUSTAINABLE CHEMISTRY

Michelle O'Malley

O'Malley started the day with a keynote presentation on research into processes for sustainable chemistry. If researchers could understand and overcome the ability of lignans, energy-rich plant metabolites, to avoid the decomposing processes of microbes and enzymes, they could engineer enzymes that would enable plant waste to become value-added material. Studying these organisms can also fill important gaps in understanding biology and help to engineer sustainable energy sources.

The natural breakdown process of plants is slow, messy, and difficult to study (Rubin, 2008). One promising environment for research is the digestive tract of large herbivores. In this environment, teams of anaerobic microorganisms work in a cross-kingdom partnership to break through lignans to extract nutrition from forage (Haitjema et al., 2014; O'Malley et al., 2011). O'Malley's group has isolated, investigated, and analyzed anaerobes from the digestive tracts of herbivores, and is now building imaging tools as a step toward bioengineering microorganisms that can degrade plant waste faster (see Figure 4-1).

Isolate and Investigate

First, O'Malley's team needed to isolate and investigate the actions of biomass-degrading microorganisms. *Neocallima stigomycota*, a phylum of anaerobic fungi, are primitive and, thus far, found only in large herbivores' stomachs (Doi, 2008; Grigoriev et al., 2011; Orpin, 1975; Trinci et al., 1994).

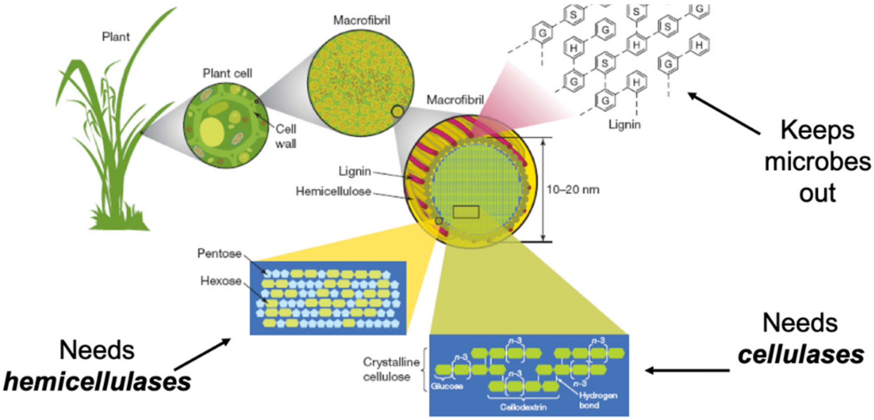

FIGURE 4-1 Replicating the process by which microbes degrade waste material could inform new ways to capture value from waste.
SOURCE: Reprinted by permission from RightsLink: Springer Nature, Genomics of cellulosic biofuels by Rubin et al., © 2008.

Studying the growth and behavior of these fungi was very difficult, because there was no genomic information, proteomic characterization, or lab-ready strain available. In addition, these fungi are difficult to grow, cryopreserve, and genetically transform. Overcoming these challenges, O'Malley's team isolated anaerobic fungal spores directly from their animal sources, cultured them, and sequenced their genomes. Within these fungi's genomes, they found the largest and most comprehensive array of biomass-degrading enzymes among sequenced microorganisms, a genomic profile that likely enables these fungi to assist in the breakdown of lignans (Haitjema et al., 2017; Henske et al., 2017; Mondo et al., 2017; Solomon et al., 2016). A growing community of researchers is studying these enzymes' biotechnological potential, but there is still much to learn.

Analyze

Next, her team focused on understanding the function of these biomass-degrading enzymes via transcriptomic- and genomic-based ("omics") analyses. They discovered unique enzymes that interweave with the substrate they degrade and leave behind unidentifiable materials, but the structure, composition, and enzyme-tethering mechanism within cellulosome scaffolding is still unknown (Gilmore et al., 2015; Haitjema et al., 2014). Combining several "omics" approaches, the team discovered approximately 400 genes involved in the process, most of which are carbohydrate-active enzymes originating in bacteria through horizontal gene transfer (Haitjema et al., 2017).

Build

This work still has many unanswered questions, making the building of tools very challenging. However, O'Malley said that her laboratory is working with the U.S. Department of Energy to build imaging tools capable of nondestructively capturing anaerobic enzyme actions in vivo to demystify the lignan degradation process. They plan to synthesize quantum dots attached to nanobodies, direct these nanobodies to cellulosomes in vivo, image their kinetics via multimodal methods, and adapt existing imaging techniques to create 3D structures (Podolsky et al., 2019). Those structures will then be used as a platform to measure kinetics and enzyme rearrangement. The team is also transforming anaerobic fungi to conjugate quantum dots to cellulosomes for enzyme tracking in real time. More broadly, this process could accelerate in vivo imaging characterization (Lillington et al., 2021).

O'Malley concluded that developing new, real-time, nondestructive bioimaging techniques will advance the understanding of microbe communities, and requires interdisciplinary collaborations and an openness to learning about understudied, real-world systems. The payoff is that these advances can fill critical gaps in biological research and have wide-ranging health, energy, and sustainability applications.

Discussion

Asked if the spatial organization of these microbes mattered, O'Malley answered that she had not studied the question directly, but suspected that microorganism location and spread were very important as they spread out and appear to form films when cultured. In reply to another question, she noted that she had not studied the potential quantum electron transport function of ferritin.

CURRENT CAPABILITIES AND LIMITATIONS IN PLANT IMAGING

Jason West, professor of ecology and conservation biology at Texas A&M University, moderated the workshop's seventh session, covering advances and limitations for imaging plant biology.

The panelists were Ross Sozzani, professor of plant and microbial biology and director of the plant improvement platform for the North Carolina Plant Sciences Initiative at North Carolina State University; Keiko Torii, Johnson & Johnson Centennial Chair in Plant Cell Biology at The University of Texas at Austin, a Howard Hughes Medical Institute Investigator, and member of the Institute of Transformative Biomolecules at Nagoya University in Japan; and Christopher Topp, assistant investigator at the Donald Danforth Plant Research Center.

The Goldilocks Principle: Just the Right Amount of Growth

Ross Sozzani

The root of the model plant *Arabidopsis* has many features that reduce complexity, making it a tractable system to study (Fisher and Sozzani, 2016). It also presents biologists with the opportunity to collaborate with mathematical modeling and imaging experts, whose work is crucial to learning more about biological systems, improving imaging techniques, and advancing the field.

One key aspect of *Arabidopsis* root stem cell regulation is its transcription factors. These move between cells and form protein complexes with different stoichiometries to create the “just right” conditions for stem cell division (Benfey et al., 1993; Cruz-Ramírez et al., 2012; Di Laurenzio et al., 1996; Sozzani et al., 2010). Quantifying the movement of transcription factors makes it possible to create space, time, and stoichiometric maps, and fluorescence correlation spectroscopy sheds light on transcription factors’ diffusion coefficient, oligomeric state, and protein interactions (Clark and Sozzani, 2017; Clark et al., 2016).

Quantitative measurements of transcription factors’ specific movements also show differential representation of both the movements and the factors’ interacting partners, justifying close examination of cell types’ specific mechanisms (Clark et al., 2020). In addition, the measurements make it possible to create accurate multiscale hybrid models at the molecular and cellular level that track and predict cell divisions, and then validate those predictions (Van den Broeck et al., 2021). Imaging these movements required building microfluidic devices and software to track cell division (Buckner et al., 2018, 2020; de Luis Balaguer et al., 2016; Madison et al., 2020).

Visualizing the Cellular Decision-Making Process During Plant Epidermal Development

Keiko Torii

Stomata, a plant’s epidermal pores, can teach researchers important lessons about how cells differentiate. When a precursor cell divides into stem cells and neighboring cells, either could become stomata, but at some point this flexibility ends and a cell’s fate is determined. During this time, the plant cells cannot move or rearrange themselves, and the process cannot be regained, even if researchers disturb it.

Torii’s team learned that the key regulators of this process are the polarity component and peptide signaling that enforce proper transcription factor actions. To better understand peptide functions, Torii and collaborators developed a tool that visualizes peptides to monitor cell activity and determine how receptors move, a collective set of actions that determines the cell’s fate (Zeng et al., 2020). Some of this process can be visualized in real time or with time-lapse imaging, but will require bridging the imaging technology gap for visualization over different scales.

Technical challenges to this work include strong autofluorescence from chlorophyll, organelle behavior, and interference from some of the techniques employed, such as optogenetics or optophysiology, which can affect a plant's ability to sense and respond to low-level light. In addition, most imaging tools are optimized for animals, not plants. More collaborations with physicists, chemists, computer scientists, and engineers are needed to use quantum imaging to more fully understand plant cell dynamics.

Deep Phenotyping of Root and Rhizosphere Biology

Christopher Topp

Understanding the molecular and growth processes of plant roots, and how they affect whole-plant functioning, holds enormous potential for enhanced crop productivity and sustainable agriculture. Modern agriculture's drive for high yields with unsustainable inputs ignores the plant's root system, which provides all of the water and nutrients for the shoots and grain (Donald, 1968). As a primary source of carbon, roots also drive physical, chemical, and biological changes in the soil.

Studying roots is very difficult, especially given that methods to access and observe root systems in the field have not substantively changed in the last century. Furthermore, root–soil–microbe interactions are complex and dynamic, one primary root can lead to hundreds of thousands of roots, and each root has local temporal processes and interactions that add to the macro-level process. A better understanding of time dimensions will enable the creation of models for interactions, growth patterns, and environmental conditioning.

Through x-ray microscopy and large-format, high-resolution x-ray tomography, Topp is able to identify root systems' structural details, functional information, and interactions (Duncan et al., 2020). Using positron emission tomography, it is possible to measure a whole plant's carbon and nitrogen allocation dynamics in real time, as well as other dynamic physiological processes, although the resolution is not fine enough to enable differentiation.

Current limitations, such as studying plants in natural soil, could be overcome with emerging quantum technologies such as quantum dots or other nanoparticles. Topp's lab is working to capture the 3D structure of an entire freely grown root system via multimodal sensing to create digital models that can be used to study plant–environment dynamics. The ability to bridge timescales and design functional, high-resolution imaging systems would enable in situ, thick-sample imaging and sensing and further advance knowledge of whole-plant, root and shoot, systems.

Discussion

West moderated a discussion that covered tools, facilitating collaborations, and remote plant sensing.

New Versus Existing Tools

West asked the panel which was needed more—new tools or adaptations to existing tools? Sozzani replied that both were necessary. Some animal tools work well for plants, but she suggested that scientists should collaborate with engineers to develop plant-specific sensing tools as needed, especially because they could have a large societal and economic impact.

Torii agreed, adding that she has learned about good tools from both animal scientists and stem cell biologists. There are challenges, such as timescale and detecting underground behavior, but large, free-growing plants cannot yet be studied in the wild. Tools that bridge timescales, combine and analyze data, and are optimized for plants will make the study of whole-plant organisms possible, she suggested. Topp also agreed that plant science can and should adapt advanced medical tools, with the understanding that there will be limitations.

Facilitating Collaborations

West asked how best to facilitate collaborations to advance research in this space. Torii replied that the best collaborations happen when the project has mutual advantages that are able to show off everyone's talents, each team finds the work interesting, and partners develop a camaraderie to pursue new knowledge.

Sozzani suggested that funding agencies, which are starting to understand that the most impactful collaborations integrate basic and applied research, could recommend including an industry partner to prioritize solution-driven science. Topp added that funders should recognize that this work requires continuous long-term commitment and mutual learning. In addition, he said collaborations should be incentivized and recognized, because successes can elevate each field.

Remote Plant Sensing

Margaret Ahmad, Sorbonne University, asked if remote plant sensing was possible. Topp replied that reporters attached to autonomous robots and low-flying drone sensors, built in collaboration with engineers, have worked well. Not every prototype has been successful, and investment here is risky, but more tools, and experts who can help build them, are needed.

Sozzani agreed, adding that in addition to time and expense, sensing tools create questions about data, data management, and cyber infrastructure. On the plus side, data enable predictions, and if plant science becomes more interdisciplinary, it can take advantage of those abilities. Torii also agreed, noting that hyperspectral camera drones are being tested for monitoring plant health, but more analysis and machine learning techniques are needed to correlate images and measurements and provide meaningful information.

MEASUREMENT AND SENSING NEEDS FOR MICROBIAL COMMUNITIES

Jennifer Pett-Ridge, leader of the Environmental Isotope Systems Group at the Lawrence Livermore National Laboratory, moderated the workshop's eighth session, which focused on critical knowledge gaps in the understanding of microbial communities and their interactions in the environment, and the tools needed to address these gaps.

The panelists were Victoria Orphan, James Irvine Professor of Environmental Science and Geobiology, Allen V. C. Davis and Lenabelle Davis Leadership Chair at the Center for Environmental Microbial Interactions, and director of the Center for Environmental Microbial Interactions at the California Institute of Technology; Alice Dohnalkova, environmental microbiologist in the Environmental Molecular Science Laboratory at the Pacific Northwest National Laboratory; and Elizabeth Shank, professor of microbiology and physical systems at the University of Massachusetts Medical School.

Syntrophic Interspecies Microbial Interactions and Extracellular Electron Transfer in the Environment

Victoria Orphan

Orphan studies how microorganism interactions—specifically the direct passage of electrons between organisms known as extracellular electron transfer—affect the cycling of carbon and nutrients through the biosphere. This cycling process is known to be important in microbial metal respiration and was recently discovered to be important to interspecies syntrophy, the process by which different species pass metabolites and nutrients to each other. For example, in methane-oxidizing archaea, the full range of this process is responsible for sequestering up to 80 percent of methane flux from ocean sediments.

These microorganisms are challenging to study because they are uncultured and live in deep-sea sediment in diverse communities, coexisting with hundreds of other species. Orphan and colleagues use multiple techniques to identify, isolate, and glean knowledge about interaction constraints of extracellular electron transfer within methane-consuming syntrophic associations (He et al., 2021). In the future, her team plans to use multimodal imaging to study these microorganisms at different scales in their environmental context, one of the Grand Challenges of environmental microbial ecology.

In situ microbial communities are inherently complex, and to study them will require field-portable, nondestructive, precise tools to identify microbes, track their dynamics, and image and sample them in opaque environments over time, space, and varied chemical, mineral, and metabolic processes. Although technologies such as quantum dots and gas vesicles are promising, Orphan noted that these are still in the very early stages of development, and there exists a need for more advanced sensing capabilities to tackle these challenges (Farhadi et al., 2019; Whiteside et al., 2019).

Revealing Mechanisms for Stabilizing Organic Carbon by Microbial–Mineral Interactions: Innovative Chemical Imaging

Alice Dohnalkova

Dohnalkova uses electron microscopy, its coupled analyses, multiscale imaging correlated with multiple methodologies, and chemical imaging to study microbial processes in biogeochemical environments such as soil. Although they appear on the macroscale, most biogeochemical processes are driven by micro- or nanoscale processes that must be studied to be understood.

To learn how microbes stabilize carbon in soil, Dohnalkova's team sequenced and imaged microbial–mineral associations naturally recruited from forest soil. Imaging and analyzing organic macromolecules is challenging with electron beam methods, making correlation a labor-intensive process. Using scanning transmission x-ray microscopy with x-ray absorption near edge structure, a quantum-based method, the team was able to trace the signatures for calcium and carbon in the microbe and the extracellular polymeric substance, demonstrating the role of calcium bridges in carbon stabilization in soils (Lawrence et al., 2003).

With aloof beam electron energy loss spectroscopy, originally developed for materials science, her team was also able to image away from samples (thus avoiding sample degradation) with very high energy resolution, adding more unprecedented insights from microbe–environment interactions. In addition, Dohnalkova noted that machine learning and artificial intelligence techniques, increasingly applied to microscopy, are promising ways to manage the large amounts of data that automated robotics processes generate (Broderick et al., 2018).

Microbial Interactions and Quantum Bioimaging

Elizabeth Shank

Quantum bioimaging may enhance the study of microbial interactions, carbon degradation, and interkingdom interactions in complex, heterogeneous, opaque environments such as soil. These processes happen on a microscale but have large impacts on an ecosystem's biogeochemistry, plant health, and soil health.

Natural soil is a challenging study environment for bioimaging. However, Shank's team can use bioimaging tools on transparent soil model systems (see Figure 4-2) to realistically and nondestructively investigate the physiology and transcriptional states of microbial interactions, and how they affect the larger, heterogeneous environment over time (Downie et al., 2012; Sherrard et al., 2018). Transparent soil also enables the use of fluorescence microscopy, Raman spectroscopy, and mass spectrometry to get a spatial and temporal image of the entire 3D microcosm, including microbes, cells, and the activity of metabolites and molecules (Sharma et al., 2020).

Advancements are needed in identifying and tracking microbes within complex, native communities; imaging multiple organisms simultaneously; combining multiple types of datasets; and imaging more deeply in live samples, over longer timescales, and with wild microbes. Two-photon quantum approaches may be able to image deeper into samples, study larger interaction areas, and identify transcriptional states of different microbes and their heterogeneous gene expression. Quantum dots are promising because they have been used to monitor multiple fluorophores over longer lifetimes, but they can be destructive. These may also be useful in studying carbon degradation because they can track nitrogen movement through plants and fungi, Shank noted (Whiteside et al., 2009).

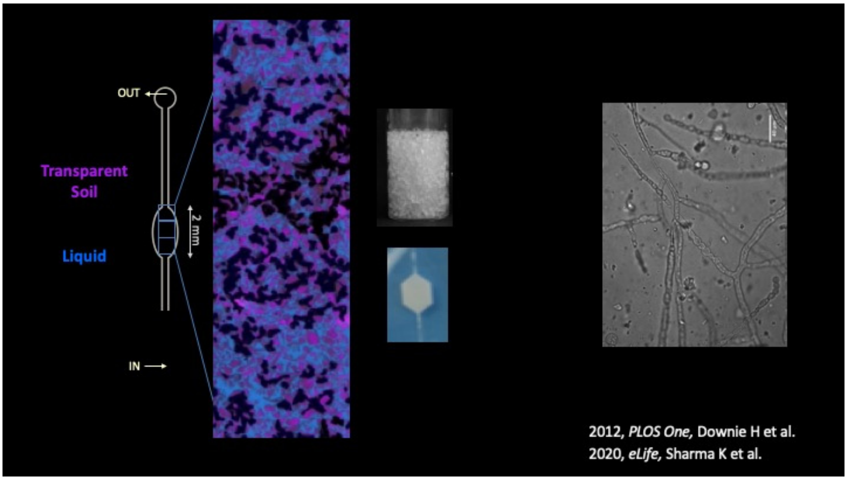

FIGURE 4-2 Transparent soil model systems allow nondestructive investigation of microbial interactions within a heterogeneous environment over time.
SOURCE: Credit for this image goes to Kriti Sharma and Elizabeth Shank (left); Downie et al., 2012 CC by 4.0 (top middle); Sharma et al., 2020 CC by 4.0 (bottom middle and right).

Discussion

Pett-Ridge moderated a discussion touching on current hurdles, quantum trade-offs, bioluminescence versus fluorescence, short-term interactions, and infrared photodetectors.

Current Hurdles

Pett-Ridge asked panelists to name current hurdles to advancing their work. Orphan pointed to the inability to replicate the wild environment in the laboratory, which necessitates new quantum tools and sensors to image deep structures in real ecosystems. Dohnalkova agreed that the laboratory environment is different, adding that the dehydration process, required for imaging, unnaturally collapses plant systems.

Shank also agreed that laboratory work is extrapolation, although she noted the value of building model systems. She also noted the importance of achieving unlabeled identification of wild microbes, noninvasive and long-term natural-environment study methods, and more sensitive detection methods as critically needed advances.

Quantum Trade-offs

Pett-Ridge asked the panelists if quantum approaches are truly needed, and what trade-offs would be acceptable. Dohnalkova replied that while researchers are pushing the limits, and there is a strong drive for bigger and better tools, many fields may be able to improvise with existing tools.

Shank stated that trade-offs already exist for every technique, so in most places they would be acceptable. As to whether quantum approaches are needed, she expressed ambivalence. Quantum dots could be more widely used, and striving to design new tools can add to an existing suite of techniques for answering different questions, she said.

Orphan agreed that a suite of imaging tools that includes quantum techniques would advance the field, but the biggest hurdle would be to correlate images across different platforms, each with its own limitations and benefits. Adding computational power in the post-processing stage would also advance the field.

Pett-Ridge asked if tools should be more widely accessible. Shank replied that many tools are not used enough to require wider distribution, and there is a value in having experts who understand the tools' full capabilities. She and Orphan agreed that increased awareness of these tools' existence could close communication and technology gaps among scientists.

Bioluminescence Versus Fluorescence

Shank noted that she has used bioluminescence as a reporter, and although it is better than fluorescence at detecting weak signals, it is only one-color and thus cannot be used to look at multiple moieties simultaneously, like fluorescence. In addition, microscopes are not set up for bioluminescence, and so imaging and sensing only work for bulk cellular measurement, not individual cells.

Orphan noted that in her work, she gets around fluorescence issues by using deep UV Raman to image mineral substrates outside the usual range for fluorescence. She added that some solutions developed for aerospace applications could be adapted for environmental systems. Pett-Ridge agreed that the current fluorescence techniques are tedious and require customization.

Short-Term Interactions

Pett-Ridge asked how it may be possible to see fluxes and compounds that are short-lived. Orphan replied that some researchers are using genetically tractable organisms as sensors to create readouts. Fast interactions may drive carbon and nutrient cycling, and their study could yield more insight than studying chemical residues. Shank noted that items of low abundance are very difficult to measure or retrieve without disrupting system balance.

Infrared Photodetectors

An attendee asked Shank if infrared photodetectors could help penetrate soil opacity. She replied that it may be possible, and Dohnalkova added that the challenges are with imaging and detecting speed and resolution. Pushing the technology into the femtosecond range, or faster, which is when these processes occur, would be a major development, she added.

5

Education, Training, and Workforce Needs

EDUCATION, TRAINING, AND WORKFORCE NEEDS FOR USE OF QUANTUM CONCEPTS IN BIOLOGICAL SENSING AND IMAGING

Clarice Aiello, University of California, Los Angeles, moderated the final session of the workshop, a discussion of ways to explore and create training and workforce opportunities to establish a truly interdisciplinary quantum biology community.

The panelists were Johnjoe McFadden, professor of molecular genetics at the University of Surrey and co-director of the Leverhulme Quantum Biology Doctoral Training Centre; Wendy Beane, professor of biological sciences at Western Michigan University; Thomas A. Searles, Martin Luther King Visiting Professor of Physics at the Massachusetts Institute of Technology, professor of physics and astronomy at Howard University, and director of the IBM-HBCU Quantum Center; and Thorsten Ritz, professor of physics at the University of California, Irvine.

Leverhulme Quantum Biology Doctoral Training Centre

Johnjoe McFadden

The Leverhulme Quantum Biology Doctoral Training Centre is a unique cross-disciplinary program that McFadden suggested can serve as a model for formal quantum biology education. It has roughly 20 doctoral students whose supervisors come from biology, physics, engineering, computer science, and mathematics. Students and supervisors engage in national and international collaborations with several research institutes.

Starting the Centre involved multiple challenges. It was difficult to secure buy-in from faculty unfamiliar with quantum biology, recruit external collaborators, select the right students, and set up and deliver a dedicated, interfaculty doctoral program, McFadden said. To attract a diverse and inclusive quantum biology workforce, the Centre focuses on media publicity, interesting projects, and careful student selection. They have achieved gender balance for students, but not supervisors.

To ensure truly interdisciplinary education, all students share a single office space. They are required to teach each other both basic and advanced topics in their fields to improve cross-disciplinary communication and understanding and create a shared language. The Centre also emphasizes continuous, wide-ranging learning and strong mentoring and support programs.

Quantum Biology Interdisciplinary Trainee Exchange Program

Wendy Beane

Beane is in the initial stages of launching the Quantum Biology Interdisciplinary Trainee Exchange (QBITE) program, which she said was inspired by her experiences collaborating with engineers and physicists, who use very different tools, language, and knowledge.

QBITE will enable biology graduate students and postdoctoral researchers to work in quantum laboratories in other disciplines, such as physics, engineering, or chemistry, to gain an understanding of the knowledge, experiences, and challenges in those fields. Another main goal of the program is to reduce siloing of labs and researchers who work on quantum and those who work in biology. She reported that student recruitment has been strong; the next step is to recruit laboratories for the exchanges.

Diversity, Inclusivity, and the Quantum-Smart Workforce

Thomas A. Searles

When asked what they want to be when they grow up, kids often cite STEM fields (Fatherly, 2018). The challenge is to harness that early enthusiasm and encourage science-loving high school students and undergraduates to choose a path in quantum science.

Howard University has a long history of providing top-rate educational opportunities for Black students and has trained generations of Black scientists and engineers (Branson, 1942). Searles now has the opportunity to train Black scientists for the quantum age, where talent is needed.

Although more Black students overall are earning bachelor's degrees, there has been little growth in the number of Black students in physics. Searles suggested that successful strategies from computer science and bioengineering can help diversify physics. For example, bioengineering is more diverse than other areas of engineering because it meshes engineering, which is historically not very diverse, with biology, which is historically more diverse. He noted a partnership between IBM and 23 historically Black colleges and universities (HBCUs), centered at Howard University and led by Searles. This IBM-HBCU Quantum Center is trying to diversify the quantum sciences, which he noted has even less Black representation than physics (Howard University, 2020).

Creating an Interdisciplinary Quantum Biology Workforce

Thorsten Ritz

Ritz argued that quantum has an appeal that should be capitalized on to create and support new interdisciplinary graduate programs to train the future quantum biology workforce. One such program, the Mathematics and Computational and Systems Biology Program at the University of California, Irvine, was built by an interdisciplinary faculty team with the goal of training students who can take a multidisciplinary approach toward research in quantum biology.

In addition, Ritz posited that the United States needs a national quantum biology center that can be a focal point for initiating national-scale collaborations and guiding educational programs. Such a center could also advocate for the integration of quantum biology work into every quantum initiative to encourage collaboration and discourage the siloing and knowledge gaps that are seen in every aspect of the quantum sciences.

Discussion

Aiello moderated a discussion that covered specialization and siloing, starting quantum education earlier, and how to support quantum biology.

Specialization and Siloing

When asked how McFadden convinced specialists to support quantum biology research, he answered that it has been hard for different faculty members to understand each other, and there are few shared definitions of even simple terms, such as *fast*. Learning to collaborate outside of one's specialty and overcome intimidation early on is important, which is why the Centre exists. Ritz added that successful collaborations recognize and accommodate different fields' unique cultures. In addition, quantum scientists need to be clearer about why their research is exciting.

Beane noted that siloing is a large problem even within disciplines. Biologists in different subdisciplines can find each other's work indecipherable. She sees two separate issues: the need to create a quantum biology workforce and the lack of quality communication to other scientists about how quantum biology can advance their research. Inviting speakers, sharing ideas, and laboratory exchange programs can improve awareness and help remove barriers. Searles agreed, noting that those practices can also be applied to undergraduates, who should be encouraged to explore quantum fields.

Starting Quantum Education Earlier

Aiello asked the panelists when quantum mechanics should be introduced in education. McFadden agreed that this should happen earlier than it generally does, and he expressed his belief that a lack of knowledge related to general quantum concepts is one reason biologists are not more interested in pursuing quantum biology. Younger students, who are not yet indoctrinated into a particular field's culture, may be more open to quantum's fascinating aspects than practicing scientists.

Searles also agreed, stating that K–12 students should be introduced to quantum as early as possible, emphasizing the field as a future job opportunity. They may not all get doctorates, but the field's breadth and diversity will improve. McFadden and Searles also shared that although Black women are relatively well represented, they both have had difficulty recruiting Black men and suggested that sharing quantum messaging with younger students may help. McFadden suggested that a course encapsulating the wonder and weirdness of quantum mechanics would benefit undergraduates and K–12 students, and Beane added that a program that does the reverse—teaching physicists about biology—would also have value.

How to Support Quantum Biology

Aiello asked what institutions and the federal government can do to support quantum biology. Searles replied that a national quantum biology center would be a great start, especially as a place for less-resourced schools and students, and a meeting point for institutes and initiatives, such as the IBM-HBCU Quantum Center, to work together.

Beane answered that both federal and industry funding would be helpful. In addition, it may be possible for institutions to create interdisciplinary, undergraduate quantum-focused biology programs, stitched together from existing courses and staff that could generate interest and feed into doctoral programs.

Ritz noted that training centers are a better model for branding, outreach, and curricula creation than research institutes. He argued that building a prestigious, fully supported, decentralized, national model would be a worthwhile endeavor.

BREAKOUT DISCUSSIONS

To wrap up the workshop, attendees convened for small-group breakout sessions, where they were encouraged to voice any final thoughts on future directions and structures for using quantum technologies to enhance biological sensing and imaging.

Participants were asked to explore technical hurdles; additional existing or emerging quantum concepts, tools, theory, and experiments; near- and long-term opportunities to advance biological sensing and imaging; and ideas for expanding quantum education.

Overall, participants stressed the importance of balance, open communication, collaboration, unity, and understanding trade-offs between quantum and classical approaches.

Participants mentioned a number of technical hurdles, including the inability to measure the quantum properties of light in instruments; lack of simulation of developed-, single-, or few-photon cellular differentiation events; and clumping and toxicity in quantum dots.

Attendees identified a need for more research in a variety of areas. They suggested the following topics as potentially fruitful areas for exploration:

- single-photon measurements of time-correlated spatial properties that enable superresolution imaging and single-photon measurements of light emitted by living cells
- coupling between light and spins
- whether ultrafast biophysics events enable seeing quantum properties of light
- studying coherence timescales in biological systems
- quantum sensing for protein recognition or ion fields
- identifying quantum optics opportunities
- ability to differentiate entangled photons from classical photons
- the gut as a quantum organ
- enhancing cryptochrome fluorescence
- quantum properties of disease, microbes, consciousness, and anesthesia
- nontraditional model systems and plants
- Godel’s theorem to describe self-referential biofeedback loops
- isotopes as chemical tracers
- redox processes
- tracking complex molecules and fluxes

Participants cited the need for new tools and upgrades to existing ones, including the following:

- microscopy and spectroscopy with undetected photons
- conductive atomic-force microscopy of tissues
- single-photon detectors
- devoted quantum microscopes
- use of x-ray free electron laser technology
- advanced UV biophoton-counting platforms
- multimodal imaging methods
- modified organisms to manipulate environments
- targeted sampling of live intact systems
- biosensors for quantum imaging or magnetic field alterations

To enable near- and long-term opportunities, many participants suggested that exploratory, high-risk funding could improve existing instrumentation to collaboratively explore quantum enhancement. They also emphasized the need for collaboration between quantum physicists and biological sensing and imaging scientists, which could be advanced through a dedicated quantum biology investigator program.

To expand quantum education and continue to grow the field, participants suggested

- holding follow-up meetings and workshops to facilitate additional interdisciplinary collaborations across multiple institutions;
- assembling a group to bring quantum education to K–12 students;
- forming a quantum biology society to create a core community and platform for further workshops and training;
- reaching youth through comics, games, incentives, focus groups, and myth busting;
- using visualization tools to engage students; and
- integrating molecular biological approaches for math and physics education fostering cross-disciplinary training.

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A

Statement of Task

At the request of the U.S. Department of Energy's Office of Biological and Environmental Research (BER), the National Academies of Sciences, Engineering, and Medicine will appoint an ad hoc planning committee to organize and convene a workshop on research and development needs to advance the use of quantum-enabled sensing, imaging, and instrumentation technologies for biological applications. The main emphasis will be on applications of quantum sensing and imaging technologies at the cellular and molecular levels in plant science, microbiology, and mycology to conform to the areas of most interest in BER. However, speakers and attendees will also be asked to discuss quantum-enabled sensing and imaging technologies meant to advance these and other fields of biological science. The workshop will draw on research, information, and ideas from key stakeholders representing the quantum sensing scientific community, the engineers and scientists developing biological sensors, imaging, and instrumentation technologies, basic scientists who apply biological sensing technologies for imaging, and experts in other relevant fields. The goal of this workshop is to bring together practitioners and thought leaders from these diverse scientific areas to determine mutual interests and knowledge gaps and investigate ways to use their combined expertise to overcome current challenges in biological sensing and imaging. The presentations and discussions may explore the following:

- The history of and terminology for quantum sensing and imaging technologies, as well as any established biological applications.
- Descriptions of current biological applications of quantum sensing and imaging, as well as other potential areas of biology where these technologies might be applied.
- Understanding what advantages are imparted by quantum-enabled sensing and imaging technologies over their classical counterparts. For example, will these technologies provide a better signal-to-noise ratio, better depth of interaction (to image deep-seated signals), or increase the spatial and temporal resolution of imaging cellular and molecular functionalities?
- Determining what disadvantages, strategies, feasibility, and technical needs must be addressed for applying the principles of quantum sensing and imaging to advance the fields of interest in biology. How might the demonstrated uses of quantum approaches in other fields be adaptable to plant science, microbiology, and mycology, especially for work in

intracellular molecular phenomena and intercellular interactions? What impediments must be overcome for these applications to succeed, and what investments could help drive the convergence of these disparate fields forward?

- Exploring how the applications of these technologies could have broader impacts in areas such as the development of renewable energy sources, understanding the effects of earth systems changes on biota, and the advancement of biotechnology.
- Identifying the education, training, and workforce needs for advancing quantum sensing and imaging technologies in biology.

The workshop presentations and discussions will be documented in a workshop proceedings authored by rapporteurs in accordance with National Academies guidelines.

B

Workshop Agenda

MONDAY, MARCH 8

10:30 **Virtual Platform Opens**

11:00 **Opening Remarks**
Steven Moss, National Academies of Sciences, Engineering, and Medicine
Todd Anderson, U.S. Department of Energy
TJ Ha, Johns Hopkins University (Organizing Committee Chair)

11:15 **Keynote Address:** Quantum Concepts in Biology
Thorsten Ritz, University of California, Irvine

11:45 **Keynote Address:** New Quantum Theory Applications for Biology
Marlan Scully, Texas A&M University

12:15 **Break**

12:20 **Session 1:** Probing Intracellular and Intercellular Correlations in Biology

Description: Biological systems are characterized by the dynamic organization of multiscale physical processes in nonequilibrium environments. Sensing and imaging tools derived from terahertz spectroscopy, fluorescence correlation spectroscopy, optogenetics, nuclear magnetic resonance, and various arenas of quantum information science are important to understanding these characterizations. We aim to further understand: (1) How these technologies may be poised to elucidate a range of phenomena across intracellular and intercellular domains and (2) how such novel approaches could be transformative in shaping our ability to manipulate and engineer biological systems for energy and information processing applications.

Moderator: *Philip Kurian*, Howard University
Panelists:
Marco Pettini, Aix-Marseille University
Allyson Sgro, Boston University
Martin Plenio, University of Ulm
Gürol Süel, University of California, San Diego

1:15 **Break**

1:30 **Session 2:** Bioelectromagnetic Fields

Description: Nanoscale interactions with electromagnetic fields might be impactful for biology. Through the study of these interactions, we aim to answer the following questions: (1) What are needed and existing tools to demonstrate the presence, causality, and consequences of such interactions? (2) To which extent are these interactions "quantum"? (3) How might organisms regulate them in vivo? (4) How can they be manipulated to technological and therapeutic advantage?

Moderator: *Clarice Aiello*, University of California, Los Angeles
Panelists:
Michael Levin, Tufts University
Margaret Ahmad, Sorbonne University
Douglas Wallace, University of Pennsylvania
Wendy Beane, Western Michigan University

2:25 **Break**

2:30 **Session 3:** Quantum Photonics in Biological Systems

Description: Quantum optics and photonics intersect at various scales in biological systems. Related to this, scientists are seeking to unravel the role of coherence in the spatial and temporal dynamics of these systems. To study these coherences, researchers are bridging across spectroscopy approaches to understand these biological quantum systems, and further understand energy and charge transfer. This session will explore how different techniques are advancing the study of photonics in biological systems, and what the major challenges are to advancing this research.

Moderator: *Prineha Narang*, Harvard University
Panelists:
Michelle Digman, University of California, Irvine
Scott Cushing, California Institute of Technology
Giuseppe Luca Celardo, Benemérita Universidad Autonóma de Puebla
Tjaart Krüger, University of Pretoria

3:25 **Transition to Breakout Groups**

During this transition time we encourage participants to move around the ePosterboards virtual platform and explore the different rooms and capabilities. Please join a breakout group within 5–10 minutes.

4:00 **Adjourn Day 1**

5:00 **Virtual Platform Closes**

TUESDAY, MARCH 9

10:30 **Virtual Platform Opens**

11:00 **Joint Keynote Address**
Karl K. Berggren, Massachusetts Institute of Technology
Elizabeth Villa, University of California, San Diego

11:45 **Break**

11:50 **Session 4:** Quantum Principles for Enhanced Measurement and Imaging in Microscopy

Description: Advances in microscopy have managed to unlock details of biology on a number of different scales, from single-molecule observations to multicellular imaging. This session will explore advances in using quantum-enabled microscopy to understand properties of biological systems, as well as the potential that exists in applying emerging microscopy technologies to explore different biological entities.

Moderator: *Prem Kumar*, Northwestern University
Panelists:
Theodore Goodson III, University of Michigan
Ted Laurence, Lawrence Livermore National Laboratory
Melissa Skala, University of Wisconsin–Madison (replaced by Kevin Eliceiri, University of Wisconsin–Madison, during the workshop)

12:45 **Break**

1:00 **Session 5:** Broadband Spectroscopies of Collective Dynamics in Biology

Description: Quantum-enhanced measurement and imaging is a multifaceted and rapidly expanding field of research that promises to shed new light on biological systems. The aim of this session is to discuss metrology and microscopy of dynamics in biological systems in conditions of low-light, special spectral ranges, and the promise of using the nonclassical properties of light for quantum-enhanced imaging.

Moderator: *Prineha Narang*, Harvard University
Panelists:
Prem Kumar, Northwestern University
Philip Hemmer, Texas A&M University
Kim Lewis, Howard University
Michelle O'Malley, University of California, Santa Barbara

1:55 **Break**

2:00 **Session 6:** Ultrafast Spectroscopy and Biological Reporters

Description: Networks of aromatic molecules, characterized by specific delocalized charge responses, are ubiquitous in biology. The fundamental principles of fluorescence for these quantum reporters of biological behavior have been understood for decades. More recently, work has started to explore properties across the entire ultraviolet light-visible-infrared spectrum at subpicosecond scales. This session looks to understand how multidimensional spectroscopies probing the cooperative and coherent behaviors of protein and nucleic acid complexes could be game changing in studies of the interaction of light and living systems.

Moderator: *Philip Kurian*, Howard University
Panelists:
Majed Chergui, École Polytechnique Fédérale de Lausanne
Dongping Zhong, The Ohio State University
Michelle Y. Sander, Boston University
Bern Kohler, The Ohio State University

2:55 **Break**

3:10 **Poster Session**

4:00 **Adjourn Day 2**

5:00 **Virtual Platform Closes**

WEDNESDAY, MARCH 10

10:30 **Virtual Platform Open**

11:00 **Welcome and Summary from Days 1 and 2**
TJ Ha, Johns Hopkins University

11:15 **Keynote Address**
Michelle O'Malley, University of California, Santa Barbara

11:45 **Break**

11:50 **Session 7:** Current Capabilities and Limitations in Plant Imaging

Description: Microscopy allows us to visualize and quantify those fundamental processes that govern plant growth, cell division and differentiation, sensing and response to the environment, protection from pathogens, and the wide array of interactions that constitute symbioses. A varied and exciting range of tools are being developed to allow ever more precise characterization of organellar, cellular, and tissue-scale processes. This session will examine new and emerging approaches to plant imaging that exist on either side of the quantum–classical boundary, with an effort to explore as-yet unattainable information that may be found using quantum approaches.

Moderator: *Jason West*, Texas A&M University
Panelists:
Ross Sozzani, North Carolina State University
Keiko Torii, The University of Texas at Austin
Christopher Topp, Donald Danforth Plant Research Center

12:45 **Break**

1:00 **Session 8:** Measurement and Sensing Needs for Microbial Communities

Description: This session will discuss the critical knowledge gaps in our understanding of functionality and interactions in environmental microbiomes and current limitations of existing imaging techniques—specifically time resolution, 3D imaging, molecular sensitivity, and phototoxicity—that could be overcome with quantum approaches.

Moderator: *Jennifer Pett-Ridge*, Lawrence Livermore National Laboratory

Panelists:

Victoria Orphan, California Institute of Technology
Alice Dohnalkova, Pacific Northwest National Laboratory
Elizabeth Shank, University of Massachusetts Medical School

1:55 **Break**

2:00 **Session 9:** Education, Training, and Workforce Needs to Move the Quantum Biology Community Forward

Description: In this session, we will discuss what the community building and education needs are in working to establish a quantum biology workforce. We aim to answer the following questions: (1) What are current models for quantum biology education? (2) How are interdisciplinary challenges addressed during the training of the workforce? (3) How do we attract and establish a diverse and inclusive quantum biology workforce?

Moderator: *Clarice Aiello*, University of California, Los Angeles
Panelists:

Johnjoe McFadden, University of Surrey
Thomas A. Searles, Howard University
Thorsten Ritz, University of California, Irvine
Wendy Beane, Western Michigan University

2:55 **Closing Remarks and Breakout Session Instructions**
TJ Ha, Johns Hopkins University

3:00 **Town Hall–Style Breakout Group and Informal Networking Time**

4:00 **Adjourn Workshop**

C

Organizing Committee Biographies

Taekjip "TJ" Ha (NAS), *Chair*, is the Bloomberg Distinguished Professor of Biophysics and Biomedical Engineering at Johns Hopkins University and an investigator with the Howard Hughes Medical Institute. He develops and uses single-molecule and single-cell measurement tools to study life at high resolution. Dr. Ha received a bachelor's degree in physics from Seoul National University in 1990 and a doctoral degree in physics from the University of California, Berkeley, in 1996. After postdoctoral training at Stanford University, he was a physics professor at the University of Illinois at Urbana-Champaign until 2015. Dr. Ha serves on the editorial boards for *Science.* He is a member of the National Academy of Sciences and a fellow of the American Academy of Arts & Sciences. He received the 2011 HoAm Prize in Science.

Clarice D. Aiello is a Brazilian quantum engineer, the leader of the University of California, Los Angeles (UCLA), Quantum Biology Tech Lab, and interested in how quantum physics informs biology at the nanoscale. She holds a Diplôme d'Ingénieur from the École Polytechnique (France), a physics M.Phil. from the University of Cambridge (UK), and a Ph.D. from the Massachusetts Institute of Technology (MIT) in electrical engineering. Prior to joining UCLA, Dr. Aiello held postdoctoral appointments in bioengineering at Stanford University and in chemistry at the University of California, Berkeley. Throughout her career, she has received fellowships and awards from institutions such as the Moore Foundation, the Schlumberger Foundation, Fulbright, UNESCO, and the French Ministry of Foreign Affairs. Dr. Aiello was also recognized by MIT's School of Engineering's Award for Extraordinary Teaching and Mentoring. She is actively engaged in fostering the quantum biology field as organizer of an international series of trainee-focused weekly talks about quantum biology and also as the chair or keynote speaker in venues such as the National Science Foundation Nanoscale Science and Engineering Grantees Conference (2019); the Australian and New Zealand Conferences on Optics and Photonics (2019); the IEEE MIT Undergraduate Research Technology Conference (2019); MindshareLA (2020); HRL Laboratories (2020); and the 2020 American Physical Society March Meeting.

Prem Kumar is a professor of information technology in the McCormick School of Engineering and Applied Science at Northwestern University. He holds a Ph.D. in physics from the State University of New York at Buffalo. Although Dr.

Kumar's primary appointment is in the Department of Electrical and Computer Engineering, a courtesy appointment in the Department of Physics and Astronomy allows him to recruit students from both disciplines into his research group, a privilege that has proven extremely beneficial for his research interests that lie at the interface of basic quantum science and applied information technology. His primary research focus is on photonic devices and their applications utilizing the principles of nonlinear and quantum optics. Recent projects have included generation, distribution, and ultrafast processing of photonic entanglement for applications in quantum information networks; novel quantum light states for precision measurements, imaging, and sensing; and novel optical amplifiers and devices for networked classical optical communications. From February 2013 to January 2017, Dr. Kumar was on leave from Northwestern University to be at the Defense Advanced Research Projects Agency (DARPA), where he served as a program manager in the Defense Sciences Office. Prior to joining DARPA, Dr. Kumar served on the National Academies' committee that issued the 2012 landmark report *Optics and Photonics: Essential Technologies for Our Nation*, which spawned the National Photonics Initiative (NPI). Presently, Dr. Kumar serves on the NPI Steering Committee, lending his expertise to issues pertaining to the National Quantum Initiative. Dr. Kumar is a fellow of the Optical Society, the American Physical Society, IEEE, the Institute of Physics (UK), the American Association for the Advancement of Science, and the Society of Photo-optical Instrumentation Engineers. He has been a distinguished lecturer for the IEEE Photonics Society, a Hermann A. Haus Lecturer at the Massachusetts Institute of Technology, a recipient of the Quantum Communication Award from Tamagawa University in Tokyo, Japan, and the Walder Research Excellence Award from the provost's office at Northwestern University.

Philip Kurian is a theoretical physicist, a translational scientist, and the founding director of the Quantum Biology Laboratory (QBL) at Howard University. Dr. Kurian is the recipient of awards from the U.S.–Italy Fulbright Commission, the Oak Ridge and Argonne Leadership Computing Facilities, the Whole Genome Science Foundation, the National Physical Science Consortium, and the U.S. National Institutes of Health. He serves as the principal investigator (PI) for a federal study examining how optical pumping of aqueous proteins far from equilibrium can produce collective restructuring of their internal mechanical degrees of freedom, and as the co-PI for the conceptualization of a National Science Foundation "quantum leap" challenge institute to develop novel platforms for quantum sensing and information processing in complex biological environments. His QBL was the first group outside the United Kingdom to receive a grant from the Guy Foundation, which was established in 2018 to facilitate exploration into quantum biology and the role it could play in advancing medicine globally. Dr. Kurian's vision is to uncover how fundamentally quantum interactions can produce biological manifestations at the mesoscopic and clinical scales, including in neurodegeneration, cancer, immunodiversity, oxidative metabolism, and human consciousness. As a board member for the Science for Seminaries program of the American Association for the Advancement of Science, Dr. Kurian also advises seminary professors on how to integrate frontier science topics into theological conversations. He received a Ph.D. in physics from Howard University.

Prineha Narang is an assistant professor at the John A. Paulson School of Engineering and Applied Sciences at Harvard University. Prior to joining the faculty, she came to Harvard University as a Ziff Fellow and worked as a research scholar in condensed matter theory at the Massachusetts Institute of Technology (MIT) Department of Physics. Dr. Narang received an M.S. and a Ph.D. in applied physics from the California Institute of Technology. Her work has been recognized by many awards and special designations, including a National Science Foundation Faculty Early Career Development Award in 2020, being named a Moore Inventor Fellow by the Gordon and Betty Moore Foundation, a CIFAR Azrieli Global Scholar by the Canadian Institute for Advanced Research, a Top Innovator by MIT Tech Review, and a Young Scientist by the World Economic Forum in 2018. In 2017, Dr. Narang was named by *Forbes* magazine on its "30 under 30" list for her work in quantum engineering. Dr. Narang's lab's research at Harvard University focuses on how quantum systems behave, particularly away from equilibrium, and how these effects can be harnessed. By creating predictive theoretical and computational approaches to study dynamics, decoherence, and correlations in matter, Dr. Narang's lab's work would enable technologies that are inherently more powerful than their classical counterparts, ranging from scalable quantum information processing to ultrahigh-efficiency optoelectronic and energy conversion systems.

Jennifer Pett-Ridge is a senior staff scientist and the group leader at the Lawrence Livermore National Laboratory (LLNL) who uses the tools of systems biology and biogeochemistry to link, identity, and function in environmental microbial communities. Recently awarded a U.S. Department of Energy (DOE) Early Career award to study the responses of tropical soil microbes to climate change, she has also pioneered the use of NanoSIMS isotopic imaging in the fields of microbial biology and soil biogeochemistry. As the lead scientist of the LLNL Genomic Science Program Biofuels Scientific Focus Area (SFA) from 2009 to 2018 and more recently the LLNL Soil Microbiome SFA, Dr. Pett-Ridge helps to coordinate multidisciplinary teams that integrate biogeochemistry, stable isotope probing, NanoSIMS imaging, molecular microbial ecology, and computational modeling to understand biotic interactions and energy flow in microbial communities critical to the soil carbon cycle, nutrient cycling, and sustainable biofuel production. She is the group lead for the Environmental Isotope Systems group in the Nuclear and Chemical Sciences Division at LLNL and manages a portfolio of more than $10 million in DOE, the National Science Foundation, the National Aeronautics and Space Administration, and other funding. Dr. Pett-Ridge helps to mentor a group of staff scientists, postdocs, and graduate students working on terrestrial and marine carbon cycling, plant–soil interactions, and the development of new isotope tracing methods (El-FISH, Chip-SIP, STXM-SIMS) and collaborates frequently with scientists at academic institutions and other national labs. She has published more than 85 peer-reviewed articles, including a return-on-investment patent for the ChipSIP approach linking microbial identity and function using NanoSIMS analysis of microarrays. Dr. Pett-Ridge was awarded a Ph.D. in soil microbial ecology from the University of California, Berkeley, and an M.S. in forest science and a B.A. in biology and studies in the environment from Yale University.

Jason B. West is an associate professor in the Department of Ecology and Conservation Biology at Texas A&M University. He is a plant physiological ecologist who studies the ecological and evolutionary causes of trait variation across a range of organizational and spatiotemporal scales as well as the ecosystem-scale impacts of that variation. He has worked in a number of ecological systems in North and South America and collaborates with colleagues around the world in many others. Dr. West is an internationally recognized expert in plant physiological ecology and spatial modeling of plant isotopes and seeks transdisciplinary solutions to difficult scientific questions. He obtained a Ph.D. from the University of Georgia and a B.S. from Utah State University, has held research positions at the University of Minnesota and The University of Utah, and was a visiting scientist at INRAE Nouvelle–Aquitaine-Bordeaux.

D

Poster Presentations

Symmetries and Spin Dynamics in Posner Molecules: Theoretical and Experimental Approaches

Shivang Agarwal

Description: We wish to study the spin coherence properties of Posner molecules and investigate whether the molecule exists in a six-fold symmetry that is conducive to higher coherence times or not.

Quantum Biology in the Treatment of Inflammation—Relevance to COVID-19?

Margaret Ahmad

Description: Both light and magnetic field exposure regulate intracellular reactive oxygen species (ROS), possibly also by spin chemical mechanisms involving radical pairs generated during redox reactions. Intriguingly, ROS have potential therapeutic applications, including in the treatment of inflammation. Here we examine the effect of static magnetic fields and infrared light exposure on relieving hyperinflammation in cell cultures of the type causing respiratory distress in COVID-19 patients.

Photonic Cooperativity and Coherence in Tubulin Architectures

Nathan Babcock

Description: Microtubules are ubiquitous in life, and ultraviolet light can be used to control the reorganization of these structures. We use numerical and experimental methods to explore coherent, collective excitation effects in microtubules. This work may have implications for various health and disease processes.

Entanglement Measure Based on the Geometry of Quantum States

Ghofrane Bel-Hadj-Aissa

Description: To exploit the advantages of quantum entanglement in different areas in science, we need a thorough characterization of it. We developed an entanglement measure that is based on a distance deriving from an adapted application of the Fubini-Study metric. This entanglement measure has an explicit computable expression and can be computed either for pure states or mixed states and for qubit or qudit hybrid systems.

An Ultrahigh-Bandwidth Nano-Electronic Interface to the Interior of Living Cells with Integrated Fluorescence Readout of Metabolic Activity

Peter Burke

Description: We show an ultrahigh-bandwidth nano-electronic interface to the interior of living cells with integrated fluorescence readout of metabolic activity. On-chip or on-petri dish nanoscale capacitance calibration standards are used to quantify the electronic coupling from bench to cell from DC to 26 GHz (with cell images at 22 GHz).

Bioelectrodynamics

Michal Cifra

Description: Our mission is to probe and influence biosystems using an electromagnetic field at the biomolecular level. Our vision is to design novel electromagnetic methods for benign and more efficient bionanotechnology and medicine to bring us closer to a world where electromagnetic technologies can painlessly prevent, detect, and cure diseases.

Energy Transfer to the Phonons of a Macromolecule Through Light Pumping

Elham Faraji

Description: In our paper we address the problem of the energy down-conversion of the light absorbed by a protein into its internal vibrational modes.

Dynamics of Viral Evolution

Barbara Jones

Description: We study the evolution of viruses as they enter cells, are impacted by the host immune system, and finally reproduce with mutations. The viral quasispecies then goes on to try to infect other cells. We find a phase transition as a function of host immunity and cell properties. We ask at this workshop: Can this phase transition be imaged by cell-based quantum sensing? There are clear applications of this model to both plants and humans.

Molecules for Second Quantum Revolution

Manoj Kolel-Veetil

Description: Molecules containing unpaired electron on a transition metal or a lanthanide can function as a platform for quantum materials. Avenues for their creations are described.

Expanding the Utility and Range of Quantum and Polymer Dots for Multiplexed Superresolution Fluorescence Imaging in Plants

Zeev Rosenzweig

Description: In this work, we are developing a novel near-infrared superresolution fluorescence imaging microscopy system for monitoring plasma membrane receptor dynamics in plant cells. Semiconducting polymer dots doped with near-infrared–emitting organic dyes are used as near-infrared fluorescence imaging probes of these membrane receptors. We aim to conjugate these polymer dots to antibodies against membrane receptors in plant cells and use these selective imaging probes for multiplex imaging of binding events with nanoscale resolution.

Conductive Atomic Force Microscopy Testing of Substantia Nigra Pars Compacta Tissue

Chris Rourk

Description: Ferritin has physical parameters similar to those of engineered quantum dots and has been shown to support electron tunneling and hopping, using conductive atomic force microscopy (CAFM). There are significant accumulations of ferritin and neuromelanin, another substance that also has physical parameters similar to those of engineered quantum dots, in the substantia nigra pars compacta (SNc). CAFM tests were performed on SNc tissue and provided indications of electron tunneling or hopping.

Synchrotron Infrared Spectral Imaging of Biomineral Microenvironments

Patricia Valdespino

Description: At the Berkeley Synchrotron Infrared Structural Biology Imaging Project we use quantum mechanics of infrared spectroscopy to study biological systems. Our poster is focused on the synchrotron–Fourier-transform infrared spectroscopy study of biomineral microenvironments. The transfer of carbon from the atmosphere to the lithosphere is an urgent need in an increasing CO_2 world. In the quest for science solutions to this need, we find inspiration in microbial systems, which have been developing and optimizing biomineral formation for over a billion years. Our model systems are carbonate-forming aquatic microbial assemblages. Our insights into microbial systems and biomineral formation will help to inspire and optimize future carbon sequestration technologies, which is critical to face climate change.

Quantum Sensing in a Warm, Noisy Environment: Understanding Spin-Mediated Effects in Biological Systems

Sam Vizvary

Description: This research aims to explore multiple aspects of the radical pair (RP) quantum phenomena in cryptochrome (CRY) at the nanoscale. Our goal is to confirm both the RP mechanism and CRY's ability to accurately sense magnetic fields. We will present advances in the building of a lattice light sheet microscope with magnetic excitation capabilities, synchronized excitation and detection, and fast single-photon detection.

E

Acronyms and Abbreviations

AP	action potential
cryo-EM	cryogenic electron microscopy
EM	electron microscopy
FAST CARS	Femtosecond Adaptive Spectroscopic Technique for Coherent Anti-Stokes Raman Scattering
FASTER CARS	Femtosecond Adaptive Spectroscopic Technique with Enhanced Resolution for Coherent Anti-Stokes Raman Scattering
FLIM	fluorescence lifetime imaging microscopy
GFP	green fluorescence protein
HBCU	historically Black college and university
IETS	inelastic electron tunneling spectroscopy
IFM	interaction-free measurement
LRRK2	Leucine-Rich Repeat 2
MEG	magnetoelectroencephalography
MRI	magnetic resonance imaging
NADH	nicotinamide adenine dinucleotide hydrogen
NV-center	nitrogen-vacancy center
QBITE	Quantum Biology Interdisciplinary Trainee Exchange
ROS	reactive oxygen species
SNR	signal-to-noise
UV	ultraviolet
VIPPS	vibrational infrared photothermal amplitude and phase signal

F
Tools and Technologies

Aloof beam electron energy loss spectroscopy: A variation of electron energy loss spectroscopy in which the beam is aimed away from the sample itself in order to measure energy loss (and thereby determine the elemental composition of a sample) without damaging the sample.

Autofluorescence: The natural emission of fluorescent light by biological structures.

Conductive atomic force microscopy: A microscopy technique combining optical imaging with measures of electrical current.

Cryogenic electron microscopy: A type of electron microscopy that uses samples cooled to cryogenic temperatures, affording the ability to locate individual atoms in biomolecules.

Electroencephalogram: A record of the electrical activity in the brain.

Electromigration: The movement of atoms through a material when a current flows through it.

Entangled photon spectroscopy: A nonlinear-type spectroscopy of entangled photons that may be used to detect quantum correlations.

Femtosecond adaptive spectroscopic technique for coherent anti-Stokes Raman scattering: A technique for rapid identification of preselected molecules (e.g., airborne contaminants) based on analyzing molecular vibrations.

Fluorescence correlation spectroscopy: A method for tracking fluorescent particles in living systems through the analysis of fluctuations in fluorescence intensity over time.

Fluorescence lifetime imaging microscopy: An imaging technique based on analyzing the decay rate of fluorophores in a sample.

Fluorescent proteins: Proteins that exhibit fluorescence when exposed to certain wavelengths of light, commonly used as tags to visualize the activity of genes and proteins in a cell using fluorescence microscopy.

Ghost imaging: An imaging technique that combines information from a conventional detector that does not view the object being imaged with a singlepixel detector that does view the object, thus reconstructing an image with light that never directly interacts with the object.

Inelastic electron tunneling spectroscopy: A method for studying the junctions where electrons move among molecules when a bias voltage is applied, yielding information about the chemical elements that are present.

Infrared nerve manipulation: A method for stimulating nerve cells using short pulses of infrared light.

Infrared spectroscopy: A spectroscopy method that measures how infrared light interacts with a substance, thus yielding information about its components.

Magnetic resonance imaging: An imaging technique that measures how atoms in the body respond to strong magnetic fields and radio waves, creating detailed images deep into living tissues.

Magneto electroencephalography: A technique for mapping brain activity based on measuring magnetic fields produced by electrical currents.

Multiphoton excitation microscopy: A microscopy technique that simultaneously excites a sample (and any fluorescent dyes it contains) with multiple photons, allowing imaging at a greater depth and with less background signal compared to other microscopy techniques.

Nanoparticles: A particle small enough to be measured in nanoparticles, usually between 1 and 100 nanometers across.

Nitrogen-vacancy-center (NV-center) diamonds: A defect occurring in diamonds that can be used to cause a quantum spin state to interact with magnetic fields, enabling magnetic measurements at the nanoscale and forming a building block for quantum technologies.

Optogenetics: A method for manipulating the activity of neurons through genetic modifications that make certain nerve cells fire when exposed to light.

Optophysiology: A method for studying the mechanisms governing an organism's movements by combining optogenetics with electrophysiological techniques and behavioral observations.

Positron emission tomography: An imaging technique that measures physiological and metabolic activity by tracing the movement of radioactive substances in the body's tissues.

Quantum dots: Engineered particles of semiconducting material a few nanometers in diameter, capable of converting light into different colors.

Quantum illumination: A method for signaling or imaging based on the spatial correlations between pairs of photons even after entanglement is broken.

Quantum spectroscopy: Spectroscopy techniques that use quantum light sources or the quantum-optical fluctuations of light to assess quantum dynamics or reveal information about a sample.

Scanning tunneling microscopy: A technique that takes advantage of the quantum mechanical effect of tunneling, the piezoelectric effect, and feedback loops to enable imaging of surfaces at the atomic level.

Single-molecule spectroscopy: A range of spectroscopy methods that allow the study of individual molecules.

Superradiance: A high-intensity pulse created when a group of emitters interacts with a common light field.

Time-resolved broadband fluorescence spectroscopy: A technique of time-resolved spectroscopy that measures photons emitted by a sample to measure ultrafast processes in biological systems.

Transient absorption spectroscopy: A technique of time-resolved spectroscopy that uses two laser pulses to measure absorption by a sample to detect ultrafast processes in biological systems.

Ultrafast spectroscopy: Spectroscopic techniques that use ultrashort pulse lasers to measure molecular dynamics at timescales of attoseconds to nanoseconds

Vibrational infrared photothermal amplitude and phase signal imaging: An imaging method that targets the resonances of compounds in the mid-infrared region, allowing the identification of chemicals in biological samples without using of labels.

X-ray microscopy: A technique that uses x-rays to generate images of the features of microscopic samples.

X-ray tomography: Methods that use x-rays to recreate a virtual model of a three-dimensional object.