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California Institute of Technology
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$1,200,000

The Fragment Generation Hypothesis to explain a cause and function of sleep

Sleep occupies a third of our lifespan, is universal among animals, and is essential for life. Several functions of sleep have been proposed, but evidence for each is limited, and none provide a satisfying explanation for the ubiquity and necessity of sleep. The fundamental molecular function of sleep, and molecular mechanisms that underlie sleep, also remain unclear. This team previously proposed the Fragment Generation Hypothesis (FGH), in which protein-sized protein fragments accumulate during wake when higher levels of calcium transients in neurons increase the activity of calpain proteases. The FGH posits that during sleep, the proteolytic elimination of protein fragments is faster owing to fewer calcium transients, and hence decreased calpain activity, and possibly also due to higher activities of proteolytic pathways that eliminate protein fragments. According to the FGH, the accumulation of protein fragments during wake increases homeostatic sleep pressure, while more efficacious protein fragment removal during sleep accounts for a molecular function of sleep, since an unchecked accumulation of protein fragments would be toxic. The team will experimentally test the fragment generation hypothesis using larval zebrafish, which have specific advantages for this goal. In Aim 1, they will determine whether accumulation of protein fragments is both necessary and sufficient to promote sleep. In Aim 2, they will test the FGH prediction of an interdependence between sleep pressure, calpain activity, and protein fragment levels. In Aim 3, they will identify genetic and neuronal mechanisms through which protein fragments promote sleep. These experiments have the potential to transform our understanding of both the cause and function of sleep.

Stevens Institute of Technology
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Towards single graviton detection with quantum acoustic cavities

The two fundamental theories of modern physics – general relativity and quantum mechanics – are seemingly incompatible with each other, and it remains unknown how they merge into a unified framework. To date, research on quantum gravity has proceeded largely without direct experimental input. One central prediction of any quantum theory of gravity is the existence of “gravitons” – the fundamental quantum particles that underlie gravity. For decades, however, the detection of gravitons was considered far beyond the reach of any conceivable experiment, until recent work by PI Pikovski (Stevens Institute of Technology) demonstrated how this long-standing challenge can be overcome. By combining new techniques in quantum measurement of macroscopic systems with the now-routine detection of passing gravitational waves, it becomes possible to resolve the absorption of discrete energy quanta from these waves, and thereby detect a single graviton. In this project, carried out in close collaboration between theory and experiment, the team will realize a proof-of-principle demonstration of the detection scheme, while also developing a refined understanding of what graviton experiments can reveal about quantum gravity and its possible alternatives. The detector will be implemented using the superfluid helium quantum optoacoustic devices developed by PI Harris (Yale University). Its realization will open the door to the first direct experimental studies of graviton physics, analogous to the earliest demonstrations of quantum phenomena of light at the turn of the twentieth century.

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Molten carbonates: chemical platforms for activation of strong chemical bonds

The selective cleavage of C–C and C–H bonds in alkanes is a frontier of modern chemistry central to chemical energy conversion and the upcycling of plastics waste. Cleavage of strong C–C and C–H bonds necessitates elevated reaction temperatures (300-900°C) which are prohibitively high for conventional solvents (water, toluene). Consequently, alkane activation has historically relied on use of solid catalysts which are far more difficult to chemically tune relative to solution-phase (homogeneous) analogs. Practical alkane conversions have, therefore, remained largely unchanged over the past several decades. The limitations imposed by high reaction temperatures and solid catalysts could be overcome through the use of a high-temperature-stable solvent with modular chemical functionality and homogeneous catalysts suited for selective C–C and C–H cleavage. This investigator and his team propose that molten carbonates satisfy this need by combining thermal stability with (i) solvation of structurally well-defined molecular catalysts, (ii) tunable acid-base and redox properties, and (iii) stabilization of a wide array of otherwise elusive chemical intermediates (peroxides, peroxycarbonates) potent for C–C and C–H activation. The proposed research program establishes chemical, electrochemical, and spectroscopic protocols to monitor and control homogeneously-catalyzed alkane–O2 reactions in molten carbonates that have transformative potential for hydrocarbon chemistry and the new field of molecular catalysis in molten salts. They envision the learnings established in this research program will broadly inform the use of molten carbonates, and other redox-active molten salts, as versatile chemical platforms for a diverse range of important catalytic transformations, including plastics waste upcycling.

University of California, Merced
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Exposing the role of metamorphic proteins in temperature adaptation by bacteria

Metamorphic proteins, capable of reversibly switching between distinct folds, are hypothesized here to hold the key to understanding how bacteria and other ectotherms sense and adapt to environmental temperature changes. Despite over 200,000 entries in the Protein Data Bank, fewer than 100 metamorphic proteins have been confidently identified, mainly because their conformational flexibility and fold-switching behavior are not detectable under conventional experimental conditions. Leveraging nuclear magnetic resonance (NMR) spectroscopy and high-throughput screening by mass spectrometry (MS), this investigator and his team will examine the entire Escherichia coli proteome to systematically identify and characterize metamorphic proteins. E. coli offers a tractable and well-annotated model system, and our preliminary studies support the feasibility and transformative potential of this approach.

This team's interdisciplinary effort, combining expertise in NMR, MS, protein design, proteomics, genome editing and cell assays, is well-suited to identify and characterize metamorphic proteins in the E. coli proteome. By manipulating newly identified metamorphic proteins using genome editing and subjecting the resulting strains of E. coli to varying thermal conditions, the investigators aim to reveal new classes of metamorphic proteins involved in temperature sensing and adaptation. This transformative, high-risk/high-reward research will advance our understanding of protein evolution and the mechanisms of ecological resilience, with implications for predicting how microbial life adapts to a changing climate. Deciphering the "metamorphome" will not only challenge the prevailing dogma about protein folding but also broaden the foundation for innovative biotechnologies and inform global strategies for climate adaptations.

University of California, San Diego
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Spatiotemporal mapping of ultrafast electronic relaxation dynamics in molecules

Understanding and controlling energy flow in molecules is a core goal of modern chemistry. When a molecule absorbs a photon, its electrons can be excited to a higher energy state, followed by electronic relaxation (de-excitation) to release the energy. One common form of de-excitation is radiative, such as fluorescence, occurring over *picoseconds (10-12 seconds) to nanoseconds (10-9 seconds). However, in many systems, like DNA bases or retinal in the human eye, non-radiative electronic relaxation occurs. This ultrafast process is mediated by conical intersections (CIs), where potential energy surfaces (PESs) intersect, enabling rapid conversion of electronic energy into atomic motion in less than a few hundreds of femtoseconds (10-15 seconds). The precise timing and pathway of the molecular wave packet through a CI remain elusive due to a lack of direct experimental observables. The PI will pursue a novel technique, ultrafast twisted x-ray diffraction, to directly detect correlated electron oscillations that arise during CI passage. These oscillations, driven by electronic coherence between quantum states, are a sensitive marker of CI dynamics and can persist for tens of femtoseconds. By using helical dichroism measurements, this method isolates these coherence signals from nuclear motion, offering a clear view of CI passage dynamics. He will investigate how the landscape of PESs influences chemical reaction outcomes, aiming to reveal the true timescale and quantum nature of CI transitions, thereby opening a new window into visualizing molecular quantum dynamics.*

University of Colorado Boulder
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$1,000,000

Resolving the femtosecond local structural dynamics driving solid-state ion transport

Solid-state ion conductors are a ubiquitous requirement for many modern and emerging technologies such as batteries, separation membranes, sensors, and solid oxide fuel cells. Materials design strategies for fast ion conductors increasingly exploit collective lattice dynamics that flatten the free energy surface for facile ion diffusion. However, our understanding of the local dynamics that define atomic-scale ion diffusion remains confined to theory and largely indirect experiments due to the sub-picosecond and Å-scale nature of ion hopping phenomena. This lack of empirical insight has limited the de novo design of fast ion conductors that can revolutionize a broad range of technologies such as electrified transportation and ion-selective membranes for the separation of critical materials. This team of researchers from the University of Colorado, Argonne National Laboratory, and the University of California Santa Barbara will pursue a transformational and ambitious approach to directly resolve the dynamic local structure that defines ion conduction pathways in solid-state ion conductors with an initial focus on fast Na-ion conducting compounds for solid-state electrolytes. These are excellent model materials due to their lattice dynamical properties as well as their technological relevance. Combining for the first time THz excitation of optical phonons that drive ion hops with ultrafast X-ray total scattering, they will use ultra-fast X-ray pair-distribution function (ufPDF) to measure the transient local structural states that underpin atomic-scale ion conduction mechanisms creating quantitative “movies” of the collective atomic motions associated with the ion hopping. A time-resolved local structure characterization method sensitive to ion hopping events represents a fundamental advance by providing empirical access to the atomic-scale diffusion mechanisms presently inaccessible.

University of Rochester
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$1,300,000

Quantum electrodynamics for selective transformations

A grand challenge for chemistry is to control chemical bond formation at any stage in a reaction. A team of researchers from the University of Rochester, the University of Wisconsin – Madison, and North Carolina A&T will tackle this challenge by showing how strongly coupling matter to the electric field of an optical cavity can enable a level of control over chemical reactions that is not currently possible. Their general approach is to couple the quantum light of an optical cavity to the electronic states of matter, forming a hybrid light-matter state called an electron-polariton. Polariton chemistry has been predicted, including by the PIs, to allow for unprecedented chemical reactivity because for polaritons, light can be used to modify the chemical bonding properties of matter. However, electron-polariton chemistry has significant technical and fundamental challenges, which they aim to directly address in this project. The researchers will perform groundbreaking, proof-of-principle experiments that will verify for the first time crucial theoretical predictions about how polaritons affect chemical reactivity, allowing for a direct determination of the fundamental effectiveness and general applicability of polariton chemistry. With this project the PIs aim to establish the fundamental tenets of this nascent field, eventually allowing chemists to break free from currently established rules of reactivity and establishing quantum-light as a simple tool with which one can tune the products of a chemical reaction. This project has the potential to someday enable a complete paradigm shift in chemical synthesis to produce molecules and material of tremendous value to society.