PROJECT SUMMARY

Overview:

The end of Moore's Law and the impending end of the capacity of classical data storage devices have ushered an urgent need to discover revolutionary new means of programming 2D and 3D materials with sensing, data storage, and computing properties. The deluge of "big data" and computational demands emerging from diverse areas of biological sciences and engineering including genomics, transcriptomics, metabolomics, proteomics, functional imaging, and other scientific domains including ecology, sociology, climatology, oceanography, and astronomy have led to a tipping point whereby revolutionary solutions from materials science and data science are needed to meet societal needs for data storage, computing, and sensing. For these reasons, the time is ripe to initiate high-risk high-reward studies that bridge the gap between big data, data science, and materials science, as proposed here using functional neuronal imaging as a prototypical big dataset. Specifically, our ability to now reliably engineer structured nanomaterials using DNA origami, patchy nanoparticles, and silicon offer the opportunity to embed these materials with sensing, storage, and computing properties mapped from functional neuronal imaging datasets. Data-driven approaches to identify equivalence between dynamical neuronal datasets and energy transfer FRET networks in DNA-based materials, electronic and phononic transfer networks in nanoparticle-based materials, and phononic networks in silicon-based materials will establish a prototypical data-science platform for encoding arbitrary big datasets reliably into complex materials with sensing, storage, and computing properties. Once established, this framework may translate to meet worldwide societal demand for revolutionary solutions in these domains.

Intellectual Merit:

The proposed research explores a transformative data science approach to map functional neuronal datasets to emergent properties of soft and hard materials including DNA-based assemblies, patchy nanoparticle assemblies, and semi-conductors. Data reduction and coarse-graining techniques applied to massive neuronal datasets will reveal principles of data transformation to reveal sensing, storage, and computing properties that may be applied to diverse other big datasets. Principles for encoding neuronal sensing, data storage or memory, and computing in the soft and hard materials explored here may be transferred to diverse other materials with controllable electronic, photonic, phononic, magnonic, plasmonic, excitonic, and other emergent properties. Data-driven computational procedures for designing and exploring emergent sensing, storage, and computing properties of DNA-based, nanoparticle-based, and phononic materials will advance our understanding of how to use data-driven modeling and computation to encode these properties more generally in 1D, 2D, and 3D materials. Close integration of data scientists, neuroscientists, materials scientists, chemists, physicists, and biological engineers will enable a next-generation platform for discovering revolutionary new materials with embedded sensing, storage, and computing properties.

Broader Impacts:

The proposed research will result in three prototypes for revolutionary materials that encode arbitrary sensing, storage, and computing properties from big data. Translation of these prototypes to real-world settings may impact a range of industries ranging from wearable electronics and sensors to embedded solid-state devices. Graduate students and postdoctoral research associates involved in this highly interdisciplinary research program that spans multiple scientific and engineering domains will become well versed in interdisciplinary research and computation that will train them to be leaders in industry or academia in science and engineering. The PIs are actively involved in educational outreach and training of underrepresented minority scientists, engineers, and students from high school to university and post-graduate levels, and will actively promote outreach efforts to disseminate methodologies and results from the current project to non-technical groups and the broader public at large. The research team itself consists of a diverse group of scientists and engineers representing four ethnicities and both genders, which will promote diversity in science via leading by example.

Collaborative Research: Autonomous Computing Materials

1. Overview and Vision

Moore's Law has now ended [1] and silicon-based storage will reach its limit in the coming decade due to exponential growth in worldwide data [2], driving an imminent and urgent need for alternative forms of computing and data storage/retrieval platforms. Exabyte-scale datasets are increasingly being generated by numerous areas of biological science and engineering including genomics, transcriptomics, proteomics, metabolomics, imaging, as well as numerous other areas of science including climate science, ecology, astronomy, oceanography, sociology, and meteorology, amongst other fields. We are witnessing a data revolution in which increasingly massive amounts of data are being generated by diverse sources. It walks hand-in-hand with an increasing need for computational power that stores, processes, and computes using these datasets, and drives a major need for revolutionary new, alternative forms and substrates for computing and storage including distributed, embedded computing and storage media and devices.

Biological systems have evolved extraordinarily complex sensing, computation, and processing of information across all domains of life, with a hallmark of this capability represented by the human brain: The human brain stores approximately 1 petabyte of data and computes approximately at 1 exaflop, which is orders of magnitude faster than the fastest supercomputer [3]. Additional prominent features of the brain include: (1) near instantaneous random access memory; (2) long-term and short-term data storage; (3) extremely low latency as well as rapid, sub-millisecond sensing, computing, and response that enables human reactions to multiple and diverse external stimuli including visual, auditory, and physical cues or threats; (4) extremely low energy consumption per unit of computing power or data storage/retrieval; and (5) interfacing seamlessly with stimuli-sensing organs such as the eyes, ears, and nose, and actuating the musculature. In addition, the fully developed brain is an amorphous material that is capable of remodeling and repairing in response to some degree of damage, unlike any human-made data storage or computational material engineered to date. However, advanced materials can now be synthesized across numerous domains of science and engineering, ranging from advanced 2D and 3D phononic, photonic, excitonic, plasmonic, and magnonic materials. They can be implemented into soft or hard devices directly in pure form, coupled in heterogenous matrices or interfaced with one another, and paired with alternative forms of matter including the brain itself and other organs. ***In order to leverage the tipping point of the deluge of data and increased demand for computational power, in the present proposal we seek to harness this data revolution by discovering revolutionary new paradigms for data encoding, computing, and sensing in diverse forms of 2D and 3D materials that mimic the unique and powerful aspects of biological computing and data storage devices such as the human brain.***

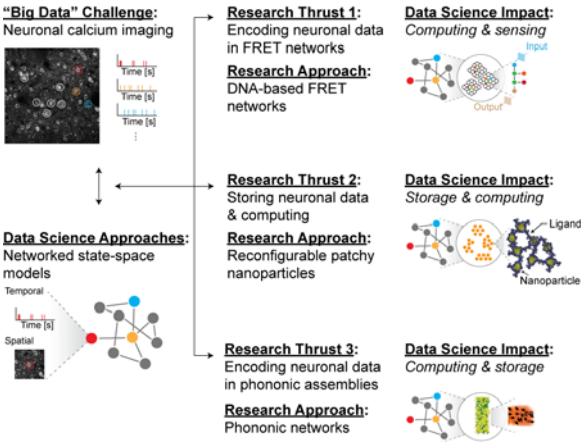

Figure 1. Overview of research approach. Three distinct prototypes are investigated as autonomous computing materials.

Specifically, we propose a revolutionary data science framework we term "*Emergence: Theme E*", in which large-scale data are recorded into both hard and soft solid-state materials, and these materials are additionally endowed with computational and sensing capabilities for deployment in non-traditional computing and sensing applications and environments. If successful, this autonomous computing materials framework will facilitate the encoding of arbitrary "big data" sets into diverse materials for data storage, sensing, and computing.

As a pilot project to prove feasibility of our vision, we demonstrate how complex spatial-temporal neuronal imaging datasets (co-PI ***Komiyama***) can be encoded (co-PI ***Machiraju***) into DNA-based (PI ***Bathe***), nanoparticle-based (co-PI ***Hernandez***), and phononic (co-PI ***Neogi***) 2D and 3D soft and hard

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materials. Computation, sensing, and data storage/retrieval are demonstrated as proofs-of-principle, with generalized data analysis and encoding frameworks that are applicable across each of these distinct materials domains. In any one of these domains, success would revolutionize our ability to encode arbitrarily complex, large-scale datasets into new materials, with potential to scale across diverse data domains, and materials frameworks. ***We pursue these three parallel, independent materials frameworks to mitigate risk and accelerate innovation through the exchange of ideas between the thrusts. Within this limited, two-year research project we seek to establish an overall framework based on a successful pilot study that is very likely to emerge from at least one of our three parallel, convergent research paths.***

This project is ***high impact*** because it seeks to discover a general, revolutionary new data-driven framework for encoding arbitrary big datasets, as well as complex and adaptable sensing and computing capabilities, into diverse materials. The envisioned non-traditional uses for 2D and 3D materials will have transformative impact on the data storage/retrieval, sensing, and computing communities and industries by offering new avenues for large-scale production of computing and data storage materials [2, 4]. The proposed research is unconventional and ***high risk*** because it proposes revolutionary new materials and computing/data-storage concepts that have not previously been tested or implemented. Notwithstanding, as noted above we mitigate this risk by proposing three parallel materials paradigms explored in three distinct **Research Thrusts** (**Research Thrust 1: DNA nanostructures**; **Research Thrust 2: Patchy nanoparticles**; and **Research Thrust 3: Phononic materials assembly**) for encoding sensing, data storage, and computing capabilities that will be pursued in this pilot project, with three prototypes emerging (**Figure 1**). Supporting these thrusts is a cross-cutting data science theme that will support them, namely **Theme E(quivalence): Learning autonomy**. Cross-cutting **Theme E** sets the stage by using data collected from the autonomous brain activity of live mice while responding to external stimuli. More importantly, **Theme E** will provide the tools to extract the elements of functioning dynamical systems and create a framework for conceiving equivalent systems in materials with significant and novel **sensing**, **data storage/retrieval**, and **computing** capabilities. The novel autonomous material systems will emulate these three preceding key aspects of functioning mammalian brains and any other system that generates large, dynamically varying data in response to external stimuli. Taken together, this project maximizes opportunities for disruptive new computing and data science concepts to emerge from our multi-disciplinary, collaborative team that spans data science, neuroscience, materials science, chemistry, physics, and biological engineering.

2. Technical Approach

2.1 Big Data Recording of Neuronal Activity

Neuroscience has experienced a technological revolution in the past two decades. In particular, *in vivo* two-photon calcium imaging has now made it possible to record in living animals the activity of hundreds of neurons simultaneously. This enables the application of cutting-edge data science approaches to extract emergent features of neuronal circuits. Toward this end, the pioneering neuroscience Lab of ***Komiyama*** will generate and process datasets from calcium imaging of neuronal ensembles from six cortical areas in live mice engaged in history-based decision making [5]. Each recording session contains ~500 neurons whose activities are simultaneously measured. These data span 2 hours of recording time and over 60,000 neurons [5], yielding 50 TB of raw data. We will refine these initial data using (1) correction of lateral motion artifacts [6]; (2) semi-automatic definition of ROI corresponding to individual neurons [7]; (3) extraction of fluorescence time series from individual neurons; and (4) deconvolution of calcium traces to infer individual neuron action potentials [8] (**Figure 2**). In addition, the ***Komiyama*** Lab will continue to refine each approach to more accurately estimate neuronal activity. Novel and equally robust techniques based on convolutional neural networks will also be explored in collaboration with the ***Machiraju*** Lab [9-11], who will leverage similar publicly available datasets from the *Allen Brain Observatory* (http://observatory.brain-map.org/visualcoding/). The Allen dataset will provide brain dynamics from brain regions different from the ***Komiyama*** dataset, namely from visual areas in response to various visual stimuli, expanding the breadth of available neuronal data.

While these simultaneous recordings of several hundred neurons are revolutionary, they still provide only a small glimpse into the neuronal circuit dynamics that consist of many more neurons (~100 billion in the human brain). In order to capture a more complete view of brain dynamics, the ***Komiyama*** Lab will collect additional data by using a state-of-the-art, large field-of-view, random-access two-photon microscope [12] recently installed in the ***Komiyama*** Lab. This new microscope expands the field of view of imaging and allows random-access imaging of the activity of ~3 brain areas simultaneously. Imaging will be done using transgenic mice (CaMKIIα-tTA::tetO-GCaMP6s) that express the calcium indicator GCaMP6s across cortical areas, with a large craniotomy that made most of dorsal cortex accessible for imaging [13]. During imaging sessions, mice are head-fixed in a behavior setup controlled by a real-time system. Imaging is performed at ~8 frames/sec, with excitation at 925 nm from a Ti-Sa laser (Newport). A typical field of view is 512×512 pixels covering ~500×500 μm containing ~1,000 labeled neurons in each of three selected cortical areas. These new, state-of-the-art functional imaging datasets will first be processed using the preceding data extraction methods to extract population activity in three distinct brain areas by the ***Komiyama*** Lab, which will then be input to the advanced data analysis framework described next in **Theme E**.

2.2 Theme E(quivalence): Learning for Equivalent Autonomous Computing Materials

Theme E is the data science mainstay of this proposal and glue between the three **Research Thrusts**. We demonstrate how equivalence is realized in three disparate systems for each of the three thrusts using a reference system. ***The proposed data science framework will provide a tipping point for crafting diverse autonomous computing materials explored here in this pilot project for Research Thrust 1: DNA origami; Research Thrust 2: Patchy nanoparticles; and Research Thrust 3: Phononic materials assembly.***

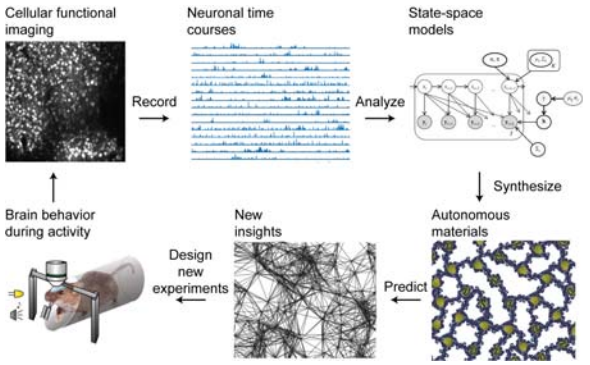

Figure 2. Workflow for processing raw image data of neuronal activity in a mouse brain, analyzing it for useful interpretation and synthesizing an equivalent system in materials. Any new insights will be used for new experiments and new hypotheses pertaining to functioning of the mammalian brain.

2.2.1 Building equivalent systems: A synthesis-from-analysis approach. To describe and characterize the functioning of systems composed of autonomous discrete elements we will use the lexicology of dynamic networks and state-space models. While networks richly describe changes in individual functions and spatial interactions of constituent elements in response to a stimulus, discrete state-space models describe the actual functioning of the system. The overall state provides an abstraction of a dynamical networked system as it learns and evolves in response to multiple inputs. In this two-year project, we will consider four systems of differing complexity. Our reference system is neuronal assemblies from the mouse brain as manifest in calcium (Ca^{2+}) imaging data from the ***Komiyama*** Lab and the *Allen Institute for Brain Science*, while our equivalent systems are the materials in the three **Research Thrusts**.

System equivalence requires that parameters or components of one system behave like parameters or components of a different system. Simple equivalent systems have been used to study large and expensive mechanical, thermal, and fluid systems [14]. It is well accepted that the mammalian brain is a complex yet unknown network of interconnected neurons [15]. This network may be described as a translational (transport-like) system through which information "flows". Because all systems that conserve energy can be described by energy-conserving analogues, the neuronal system may be cast as an equivalent flow system, namely as a FRET network transporting excitonic energy [16], or an assembly of electronic nanoparticles transporting electrons, or vibrational elements transporting phonons. It is not necessary that the two equivalent systems match elements-to-elements and connections-to-connections at all time points. **Theme E** will model neuronal assemblies as a dynamical network of interconnected neurons that transition from one descriptive state to another. State-space models allowing sufficient abstraction from unwanted

details will be learned from the Ca^{2+} imaging data. The charted state-space trajectory will subsequently be embedded into the equivalent systems in each **Research Thrust**.

The final state of the equivalent system will be the encoding of the input providing storage of a field property (light radiance, electronic energy, or vibrational energy) beyond the preceding context-free collection of bits and bytes. This representation in a physical network or assembly is akin to how deep networks represent data and processes[17, 18]. Sensed external inputs (photonic energy, electrical impulses, etc.) will drive the target system and each participating entity in the highly connected network will have adequate computing abilities (linear bandpass filtering, resonance matching, etc.). ***Thus, using a synthesis-by-analysis design process we will create autonomous materials that can sense and compute using extreme connectivity.*** This proposed two-year project will test the suitability of this approach using methodologies from the ***Machiraju*** Lab. Novel data analysis frameworks that build on this prototype will be considered in later stages of the project beyond the two-year pilot stage.

2.2.2 Analyzing Neuronal Processes. The goal of data analysis is to first "learn" correlative network and state descriptions of functioning neuronal assemblies. The following steps allow for the consideration of single neurons and their states, correlative pairs of neurons, an entire pattern as an undirected graph, clusters of network patterns and states, and finally a model of state transitions in response to stimuli.

Functional States in Neuronal Assemblies*:* Although a complex system such as the brain comprises many local functional states, they can be aggregated into global functional states or configurations at each point in time. Functional MRI (fMRI) data offer an analogy, whereby the ***Machiraju*** Lab showed that such an abstraction offers explanations of how the human brain engages in cognitive tasks like visual object recognition and mental arithmetic [19]. Brain-state labels for subjects of an fMRI study were easily elucidated with each state corresponding to a phase of the experiment. Descending to finer neuronal scale, a pertinent question to ask is: *Is the identification of similar instantaneous states from neuronal time courses as manifest in collected Ca^{2+} imaging data possible?* As explored by the ***Komiyama*** Lab, stable patterns have been shown to arise in neuronal assemblies of mice in response to continuous motor movements [20]. Thus, we postulate that learning proceeds dynamically through a cascade of "system states" and "network states" that will eventually converge to a stable network of an "expert". Other studies have already validated the usefulness of state-space approaches[21]. Further, a bottom-up and top-down characterization made strong assumptions of dynamic neuronal networks consisting of both excitatory and inhibitory neurons collectively traversing a salient state-space[22]. This observation lends even more credence to the development of state-space models with data from the ***Komiyama*** Lab and *Allen Institute for Brain Science*. Because Ca^{2+} imaging data are large (terabytes) and noisy [20, 23, 24], the extraction of states and networks will be computationally expensive. Consequently, there is a need for efficient and robust methods to create the materials prototypes described below.

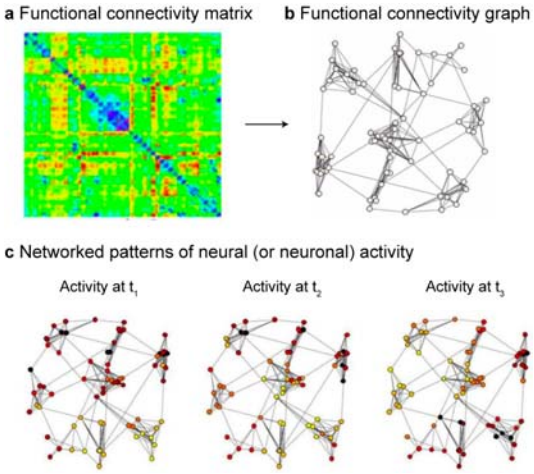

Figure 3. Functional connectivity in a dynamic system. An example of a functional connectivity network represented as a matrix of correlations in (a) and its graph–based representation in (b). (c) show the neuronal activity at three time–points from the data set.

Constructing Functional Connectivity Graphs. The functional connectivity of two neurons will be measured by the cross-correlations of their time-series. A suitably regularized functional connectivity map will be consistent, sparse, and positive definite. An example of such a functional connectivity matrix and its implied undirected graph are shown in **Figure 3**. Neurons represented as the graph's nodes are colored by the activity strength (black to yellow). Notwithstanding, the question remains: *How dissimilar are two neuronal assemblies in the patterns that they process?* As mentioned above, the neuronal networks offer transport of synaptic activity and rely on the connectivity of the network. Any suitable *functional distance metric* (FD) should estimate the amount of "*transport of synaptic activity*" over the neuronal assembly.

Thus, the difference between two activation patterns is quantified by the *transportation distance*, i.e., the minimal "transport" activity over the functional circuits to convert one pattern into another pattern [25]. Thus, for the networks at the three-time epochs in **Figure 3c**, because the network activated at time-point $t1$ is functionally more related (measured by their time-series correlations) to that at $t2$ than to that at $t3$, namely $FD(t_1, t_2) < FD(t_1, t_3)$.

Creating State-Space Models. Once the functional distance between each pair of acquisition time-points is computed, activation patterns at the T time-points are embedded in a lower dimension space and then grouped using hierarchical agglomerative clustering. Each cluster represents a characteristic distribution of activity in the neuronal activity, i.e., the *state of the assembly* at that timepoint and is labeled with an integer value using dynamic programming to minimize the overall label distance between clusters resulting in a time-series of labels. As described in [19], the ***Machiraju*** Lab will estimate the parameters of a reduced state-space model that will best explain the functioning of the neuronal assembly. Given the ease of interpretation of linear feature-spaces of neuronal time-courses, we will first construct one that employs a fast-to-compute and tractable linear approximation of "transportation metrics". Additionally, we will consider leveraging representations afforded by deep learning networks based on variable auto-encoders for providing a sparse and consistent feature set [26]. A first order Markov model (**Figure 4**) will thus include hidden states described by x_t, the activation patterns observed in the neuronal time-series data as a sequence y_t. Response functions will be chosen from the models derived from previous work [27]. The estimation problem is to determine the state marginal probabilities α and the state transition probabilities given by the $K \times K$ stochastic matrix π.

2.2.3 Synthesis of Equivalent Models in Materials. The state-space model will be used to create equivalent systems by the ***Bathe***, ***Hernandez***, and ***Neogi*** Labs. ***Machiraju*** will provide temporal network patterns and a state-space statistical model that describes the functioning of the complex neuronal assembly in response to motor, visual, and olfactory impulses. Further analyses can be conducted, with the networks easily further coarsened and other network properties and statistical estimators computed. In each of the **Research Thrusts** described below, methods to achieve equivalency will be addressed. Equivalency in our systems will require that the target material system when presented with an external input follows a state trajectory that is derivable from the neuronal reference system, as described in each **Research Thrust**.

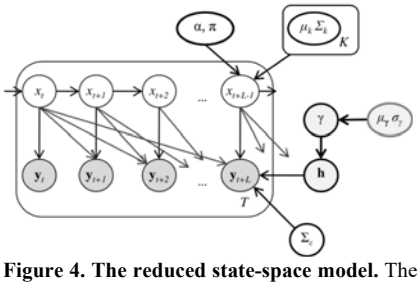

Figure 4. The reduced state-space model. The hidden brain–states are shown by $\{x_t\}$, the activation pattern is observed in the data $\{y_t\}$ (in feature–space after convolution with the response function).

2.3 Research Thrust 1: Encoding Neuronal Dynamics into DNA-Scaffolded FRET Networks

Overview. The overarching aim of this Research Thrust is to demonstrate that state-space trajectories from dynamical, spatial-temporal neuronal network signaling can be encoded within nanoscale DNA-based fluorophore networks. Specifically, the human brain consists of approximately 100 billion neurons organized into highly complex circuits that process external sensory information. While complete circuits of the brain are poorly understood, the function of small-scale neuronal circuits is considerably simpler, and can be modeled. At the most basic level, neurons transmit signals to neighboring neurons through synaptic connectivity, and this signal can either activate or inhibit other neurons depending on neuronal type and signal strength. By analogy, Förster resonance energy transfer (FRET) networks that occur in photosynthetic systems are similarly complex in structure and their spatial-temporal dynamics, but in contrast to neuronal circuitry, these networks can be approximated using phenomenological models [16, 28, 29]. Here, we aim to encode the salient features of neuronal circuits using FRET networks to investigate our ability to encode neuronal circuit sensing and processing into DNA-scaffolded fluorescent materials.

Sub-thrust 1.1 Developing a library of FRET circuits guided by state-space models.

Overview. While the brain comprises numerous local and global functional states on a hierarchy of spatial and temporal scales, we focus here on a limited spatial-temporal window of data from *in vivo* calcium imaging of mouse from the ***Komiyama*** Lab and the *Allen Institute for Brain Science*. We will employ the

state-space model that maximally captures the salient features from these data sets using the methodologies of **Theme E** from the ***Machiraju*** Lab.

Prototype. A state-space representation of the spatiotemporal neuronal firing patterns gleaned from *in vivo* calcium imaging data will guide the design and implementation of FRET network circuits using programmable DNA-based materials (**Figure 5**). We will characterize the computing and sensing functions that emerge from these encoded FRET network circuits to test their reproduction of the input, raw neuronal datasets. The resulting functional prototype from this **Research Thrust** will offer a new computing/sensing paradigm leveraging programmable molecular circuits that depart from von Neumann architectures, applicable to any network-like dataset containing complex spatial-temporal signaling dynamics.

Preliminary Results. The ***Bathe*** Lab has developed and implemented DNA-scaffolded networks that are aimed to rationally design synthetic light-harvesting systems and infer their photophysical dynamics [29-32](**Figure 5**). In one example, the ***Bathe*** Lab has used a phenomenological model to reproduce photophysical quantities that are experimentally measured using high-resolution time-resolved spectroscopic methods [29]. Using a master equation to describe the energy population dynamics, the ***Bathe*** Lab demonstrated models capture the temporal dynamics of energy transfer in light-harvesting circuits scaffolded by DNA duplexes and higher-order DNA assemblies. The ***Bathe*** Lab has also developed automated procedures to design 2D and 3D DNA nanostructures of arbitrary geometric shapes, which enable the design of arbitrary FRET circuits [33-35]. Methods of **Theme E** will be used to convert raw neuronal imaging data into network-models and state transition matrices that can be encoded into these FRET-based networks. In a manner similar to how field programmable gate arrays are used to realize complex combinatorial functions, FRET based networks can be deployed to process information.

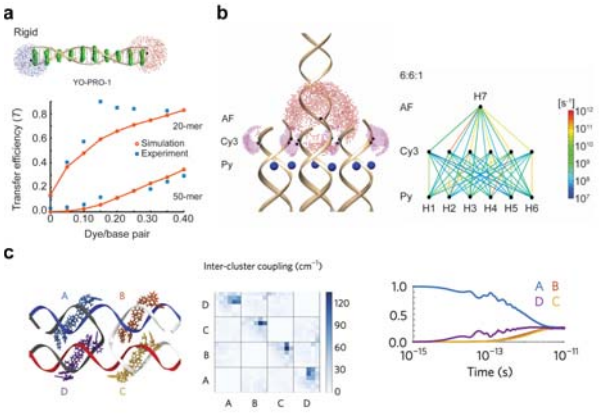

Figure 5. Experimental and computational approaches in developing synthetic light-harvesting circuits. Computational methods to analyze energy-transfer networks for (a) DNA duplexes (Pan *et al. Nucleic Acids Res*., 2014) and (b) DNA origami (Pan *et al*., *Nucleic Acids Res*., 2014). (c) Computational design of DNA-dye complexes with delocalized exciton states (Boulais *et al*., *Nat. Mater*., 2018).

Research Approach – Synthesizing and Programming a FRET Network. Calcium imaging data from the ***Komiyama*** Lab will be analyzed to extract key features of brain network activity. Specifically, the ***Machiraju*** Lab will apply state-based approaches to describe the functional connectivity of neurons to specific stimuli and identify network motifs that the ***Bathe*** Lab can use as design blueprints for building DNA-scaffolded FRET network motifs. While there are numerous ways to encode information using FRET, we will explore a subset of FRET network motifs that will have high fidelity for encoding. One specific example is through the use of pre-charge logic schemes (**Figure 6**). In this scheme, the excited-state dynamics of a subset of chromophores in the network can be toggled on or off to their "dark" or non-emissive states through photochemical perturbations [36, 37], which emulate the inhibitory function of neurons. The ***Bathe*** Lab will leverage its capabilities to synthesize 192 unique, modified DNA oligonucleotides in parallel and assemble these oligonucleotides to build libraries of DNA nanostructures in high-throughput using automated liquid handling. Assembled FRET networks will be validated using high-throughput fluorescence measurements performed on multi-well plates and then further investigated using microscopy. *Key questions include: What spatial and temporal resolutions of the neuronal data can be encoded in, and recovered from, DNA-based FRET networks? How efficient and robust are the preceding data reduction approaches for harnessing the spatial-temporal networks from neuronal datasets to faithfully represent them in DNA-based materials? And how can this data-science and materials-encoding framework be generalized to other types of spatial-temporal data from ecology, oceanography, etc.?*

Sub-thrust 1.2 Functional Higher-Order FRET Circuit Motifs Guided by Neuronal Circuitry.

Overview. Neurons form higher-order circuits that perform complex network operations through varying

degrees of connectivity among several neuronal network motifs. FRET as a programmable network offers a diverse molecular toolbox to build equivalent circuits. Key questions we explore in this section are: *can we reveal hidden connectivity patterns of neuronal circuits using the state-space models we have developed and embedded into FRET network circuits? What emergent computation and/or sensing function can we perform in these types of synthetic networks that are designed based on state-based representation of the spatiotemporal dynamics of neurons?*

Research Approach*.** Using the FRET circuits identified, constructed, and validated in **Sub-thrust 1.1**, we will construct higher-order energy transfer circuits to test our ability to recapitulate the hierarchical spatial-temporal dynamics of the brain, as elucidated by the ***Komiyama Lab using large-scale imaging of three distinct brain regions. The FRET circuits we outlined in **Figure 6** have parallels with existing neuronal circuit motifs that may already exist in the datasets provided by the ***Komiyama*** Lab (**Figure 2**). We will explore different combinations of these circuits to form higher-order FRET circuits that may uncover a hidden connectivity matrix of neurons as well as provide functional computing/sensing operations. To rationally design these higher-order FRET circuit arrays, the ***Machiraju*** Lab will derive network connectivity patterns from a large population of neurons. These patterns will provide guidance for the assembly of combinations of FRET circuits that contain a state-space representation of a neuronal subtype, as in **Sub-thrust 1.1**. These FRET circuits will be connected using published methods from the ***Bathe*** Lab to create coupled arrays of DNA nanostructures [38]. These higher-order FRET circuits will allow us to examine theoretically the functional connectivity of neuronal circuits for their efficient connections and the underlying mechanisms that drive their optimal combinations. We will investigate emergent computing and sensing from these higher-order FRET circuits by monitoring the fluorescence output of these circuits in the presence/absence of chemical perturbations using fluorometry and microscopy, as well as *in silico* simulation. *Leading questions this second sub-thrust addresses include: Can we effectively couple or transduce complex spatial-temporal dynamics between sub-modules of FRET networks, similarly to coupling between neuronal sub-circuits? And can we encode logic-based computing in higher-order FRET circuits that recapitulate logic-based signaling and circuitry from the brain?*

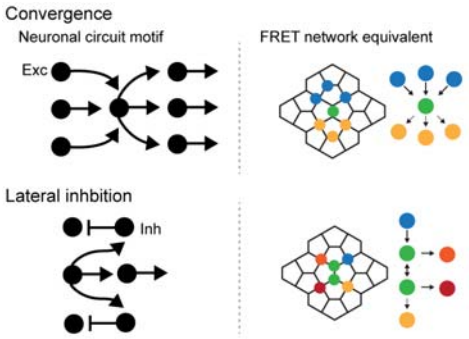

Figure 6. Realizing neuronal network motifs using FRET networks. The behavior of neuronal excitation (Exc) and inhibition (Inh) networks can be recapitulated in FRET circuits. Exciting chromophores in FRET is equivalent to excitatory processes. Neuronal inhibitory processes can be implemented in FRET networks either by biasing the energy-transfer pathways away from the desired chromophore or introducing fluorescence quenching mechanisms.

Summary of Research Thrust 1: The result of this sub-thrust will be a prototypical DNA-based FRET system that encodes arbitrary spatial-temporal dynamics from neuronal signaling data, including both inter-neuronal coupling and higher-order circuit dynamics that may include as-of-yet-unknown logic-based computing and sensing. This work is at a tipping point because arbitrary DNA-scaffolded FRET networks can now by synthesized reliably at scale, driven by large-scale neuronal datasets for the discovery of next-generation sensing and computing materials.

2.4 Research Thrust 2: Computing with Amorphous Nanoparticle/Polymer-Based Systems

Overview. The overarching aim of this Research Thrust is to demonstrate that neuronal spatial connectivity can be encoded in nanoparticle networks, which can be reconfigured to perform dynamic data storage and computation. Rational control of size, shape, and ligand association of engineered nanoparticles (ENPs) [39-43] will be used to generate 3D networks of these building blocks as amorphous computing and data storage elements with ultra-high density, as well as dynamic reconfigurability. Specifically, by controlling ligand attachment sites between nanoparticles, the degree of connectivity between distinct nanoparticles becomes an addressable register that may be used to encode information in a classical sense. On the other hand, the transport of vibrational or electronic energy between different

points of such an emergent network will also depend on this connectivity, offering computational and sensing capabilities. As a consequence, these ENP networks will be used to design hard-coded networks that perform computations given distinct input signals, in analogy to the synaptic transport observed by the ***Komiyama*** Lab and analyzed by the ***Machiraju*** Lab. In these ENP networks, we will use structural or functional connectivity as additional output readouts.

Prototype: We will design an amorphous assembly of polymer-wrapped ENPs that are attached either through chemical or physical bonds between the exterior ligands. **Figure 7** shows a cartoon of such a prototype in 2D to illustrate its key features: (1) The ENPs are amorphous and not tiled in a periodic array; (2) each ENP is connected to a varying number of ENPs and this degree may be used to encode information; and (3) the density of ligands between ENPs is heterogenous. The 3D prototype will be even more complex because it will necessarily have a more complex topology. In the simplest analogy between the ENP network and the neurons based only on structural equivalence, the components in the prototype would map directly to the complex networks produced by the ***Machiraju*** Lab with the ENPs acting as the nodes and the polymers as the links. A challenge in implementing these prototypes is whether we can control their spatiotemporal structure and the identification of the specific chemical identity of the components to create simpler architectures to match functional equivalence. We will solve this problem using the combination of multi-scale molecular models and equations of motion listed in **Figure 8,** applying deep-learning of the neuronal networks to identify optimal network architectures for our computing needs.

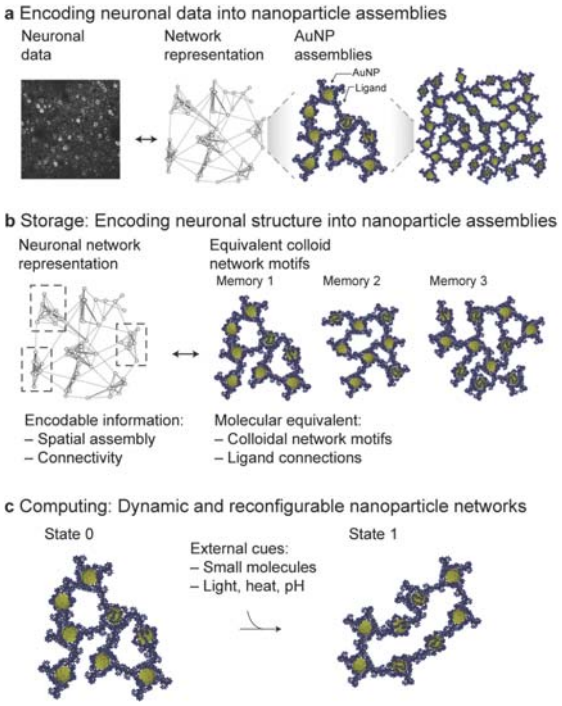

Figure 7. (a) A two-dimensional cartoon-drawn prototype of the networked-gold nanoparticle (AuNP) connected by polymeric ligands are shown in equivalence to a neuronal network. Note that the degree of variability would be enhanced in the *three-dimensional networked topologies* to be designed in this work. (b) A possible set of encodings of a networked-AuNP prototype for different memory states. (c) A possible schematic of a reconfigurable networked-AuNP prototype for effecting a computation from given inputs.

Preliminary Results*.** The ***Hernandez Lab has advanced multiscale models connecting molecules to devices that are both structurally consistent, i.e., yielding correct thermodynamics, and dynamically consistent, i.e., yielding correct dynamics at each scale [44-48]. Such frameworks are necessary for characterizing non-equilibrium chemical behavior such as reactions in heterogeneous environments [49, 50]. As an example of our use of data-centric approaches, we implemented neural nets with varying degrees of complexity to extend highly-accurate discrete data points to a global and smooth manifold that anchors non-recrossing dividing surfaces in an externally driven chemical reaction [51]. The ***Hernandez*** Lab has also characterized the interaction between ENPs coated with ligands and coronas at varying density [52, 53], with biological components such as membranes [43] using all-atom molecular dynamics and coarse-grained dissipative particle dynamics (DPD) [54]. In recent unpublished work, we verified that DPD could be used to construct vesicles which retained shape and degree of water content when mapped back to all-atom representation and benchmarked it to experiment. While this work has been, and will continue to be pursued in the NSF-funded Center for Sustainable Nanotechnology (CSN) as a separate and distinct research effort, it demonstrates that the ***Hernandez*** Lab has the necessary models and tools to explore and design complex ENP assemblies that can also be implemented experimentally downstream of this computational prototype.

Research Approach*.** The ***Hernandez Lab in collaboration with ***Bathe***, ***Komiyama***, and ***Machiraju*** will build the technology to create addressable networks of polymer-ligand connected nanoparticles illustrated

in **Figure 7**. The key technologies will be the use of molecular-based models at varying scales to accurately describe, predict, and design these amorphous ENP networks. Through the two approaches detailed below, we will optimize the nature of the ENPs and the chemical identity of the ligands. Initially, gold nanoparticles (AuNPs) will be used because their size and spectral properties can be controlled for laser-based spatiotemporal measurement. Initial ligands will be polyallylamine hydrochlorides (PAHs) because they exhibit heterogeneous structuring on AuNPs, making them ideal for implementing the target networks. We will vary both the nature of the ENP and the ligands to design for emergent properties of our prototypes including electron and phonon transport through the network.

Approach 1: Networked ENP Assemblies for Memory Storage. In the first approach, we will build assemblies of polymer-wrapped gold nanoparticles using multi-scale models to construct memory states as shown in **Figure 7b**. The equations of motion and examples of the representation of the particles at varying coarse-grained scales are shown in **Figure 8a**. We will design for variable attachment between the ENPs by varying the nature and density of the surface ligands. The objective will be to develop design rules for creating particular network topologies, and to establish the use of external stimuli such as light to induce isomerization (or intermolecular rearrangements) that can change the connectivity for electron and phonon transport in analogy to the state-to-state dynamics extracted by the ***Machiraju*** Lab from neuronal assemblies. Assuming that each nanoparticle contains a discrete set of data or memory, which may also represent a single neuron or subset of neurons, we will investigate our ability to mimic data storage and network topology harnessed by the ***Machiraju*** Lab from neuronal imaging datasets from the ***Komiyama*** Lab. Similar to the ability of the brain to store information in a dynamic, reconfigurable manner, we will explore an analogous ability of nanoparticle-based networks to realize this.

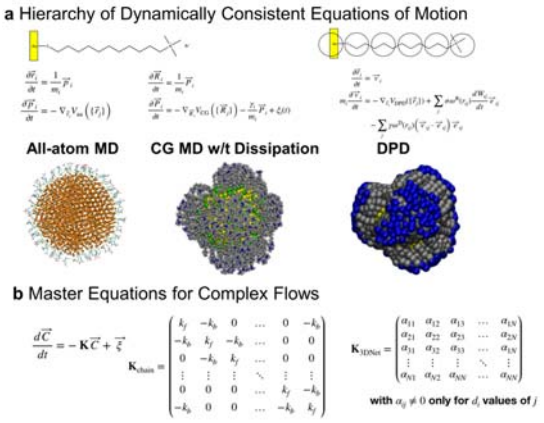

Figure 8. (a) In approach 1, we will use a series of representations with increasing coarse graining to represent the structure and dynamics of an assembly of ENPs connected by ligands. (b) In approach 2, we will model the flow of energy or electrons through a 3-dimensional networked ENP assembly that is sparsely connected with each ENP "node" connected to d_i other nodes, and is in contrast to the one-dimensional "chain" model in which each node is connected only to its nearest neighbor.

Approach 2: Networked ENP Assemblies for Computing. In the second approach, we will develop non-equilibrium master equations (**Figure 8b)** to describe the flow of vibrational energy, electronic energy, or electrons through a given networked architecture of ENPs. The goal is to establish the design rules for variations in output signals at certain nodes as a function of input signals, as a computing operation. In collaboration with the ***Machiraju*** Lab we will establish how different sets of these operations can be used to create a computing architecture. One possible solution to this problem will involve creating a big data set spanning a large number of networked architectures and their response profiles. Data science will be used to extract the underlying rules for these architectures. Key questions we seek to address include: *What ligands and ENPs are needed to specify complex transport operations? And to what degree can we control the requisite complex topologies, and the length and time scales necessary to measure the readouts?*

Summary of Research Thrust 2: The result of this sub-thrust will be a prototypical nanoparticle-based memory and computing system that encodes arbitrary structural data from neuronal signaling data, with emergent computational capabilities and reconfigurability in response to external cues. This work is at a tipping point for success because the multi-scale chemical tools required to model these complex networks with atomic and molecular specificity are just emerging now, and the emerging large data sets of neuronal networks can now teach us which complex networks to make.

2.5 Research Thrust 3: Encoding Collective Neuronal Dynamics into Phononic Assemblies

Overview. Neuromorphic Computing Systems (NCS) have seen great progress in recent years [55].

However, a major outstanding challenge in NCS design is how to build highly-interconnected systems using bulky computing subunits in high throughput. Here, we aim to prototype a new paradigm for phononic network computing to increase integration density as well as reduce power consumption and footprint of NCS. Like other quantum particles, phonons obey the laws of quantum mechanics and can be exploited as information carriers like electrons. Phonons couple the vibrational modes of distinct components in integrated heterogeneous systems, thereby providing a platform for information storage and transfer for autonomous computing materials. The goal of this final **Research Thrust** is to investigate emergent phononic properties of integrated heterogeneous materials as a new paradigm for information storage and transfer in integrated electronic devices that go beyond traditional electronic charge or spin. Toward this end, the ***Neogi*** Lab in collaboration with the ***Machiraju*** Lab and the ***Komiyama*** Lab will ***develop a prototypical computational framework to characterize the dynamics of phonons, the quanta of lattice vibrations, in order to mimic collective neuronal activity***. This will offer the revolutionary capability to encode low level computing from the brain into hard materials with controlled phononic properties. In this **Research Thrust**, we will prototype embedding collective neuronal dynamics into phononic states of pre-existing silicon-based integrated architectures. Once developed in silico and tested experimentally beyond this prototype-stage, this framework will be transferable to other hard and soft materials. If successful, this platform may initiate new means of computing using phonons as interconnects, beyond the scope of standard von Neumann architectures.

Our approach is inspired by the immense research activity in the field of neuroscience to develop mean field neuronal models [56-58] that show collective dynamics of neurons are central to adaptive cortical activity such as perception and behavior, as well as the determinants of large-scale neuroimaging data [59]. ***We hypothesize that the stimulus-response of phononic assemblies can similarly be regulated to exhibit collective dynamics of neuronal activity encoded in neuroimaging data.*** The fundamental assertion of this proposed work is that both neuronal and phononic assembly dynamics are stochastic processes [59, 60], and that probabilistic transition dynamics from one collective state to other accessible states can be modeled using a statistical master equation [61]. In ***Sub-thrust 3.1***, we will characterize these states and in ***Sub-thrust 3.2***, we will analyze the master equation to establish the equivalence between these two systems (**Figure 9**).

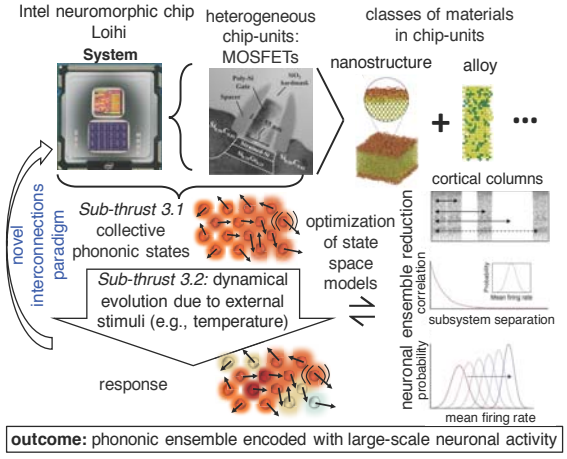

Figure 9. Embedding neuronal data in phononic states of solid-state integrated semiconductor systems.

Sub-thrust 3.1 Characterizing phononic states guided by deep learning algorithms

Overview. We can specify a phononic state using a set of 3N-dimensional state-variables = {n1, n2, ⋯, n3N} that represent the number of phonons at each of the 3N vibrational modes of a system of N atoms. Each vibrational mode may be described by the frequency, $\omega(\boldsymbol{k})$, group velocities, $v(\boldsymbol{k})$, and phonon lifetime ($\tau(\omega, \boldsymbol{k})$) due to scattering with other phonon modes, defects, boundaries or other quantum particles [62]. These descriptors reflect any modification of phononic state due to material transformation [63]. Significant progress has been made in recent years to analyze phonons in different classes of materials (e.g., crystalline, disordered, nanostructured) [64, 65]. However, the characterization about collective phonon states in an assembled material with heterogeneous components is missing [66]. In this **Research Thrust**, we will develop a data-driven framework to characterize emergent phononic states in a hetero-integrated system including different classes of materials.

Research Approach. Our initial guess of the collective phononic states will be a combination of the phonon descriptors of the individual classes of materials present in the system. The ***Neogi*** Lab has extensive expertise in theoretical design and simulation of phonon-engineered nanosystems [64, 67-70] and will use several numerical techniques [64, 67-72] to construct the initial phononic state and collaborate with the

Machiraju Lab to develop unsupervised deep learning frameworks based on stacked and Bayesian autoencoders to determine the collective emergent phononic states of the system in the absence of any external stimuli. *A key question we seek to address in this sub-thrust is: How can phononic states be reproducibly characterized within heterogeneous integrated materials to simulate a given response?*

Sub-thrust 3.2 Embedding neuronal ensemble activity into phononic assemblies

Overview. The collective response of a neuronal population to its inputs has been traditionally analyzed using the Fokker-Planck equation (FPE) [73-77]. There have been some recent efforts to describe phonon dynamics in terms of the FPE to analyze the thermal conductivity of complex systems [60, 78, 79] going beyond the popular phonon gas model, which assumes that interactions among vibrational modes are weak enough that the numbers of phonons of each mode follow the single-particle Bose-Einstein distribution at equilibrium [80-82]. The phonon FPE enables prediction of dynamics where interactions among vibrational modes are significant [83]. Thus, this framework enables us to model the dynamics of the system in response to external stimuli going beyond a single neuron or phonon.

Research Approach. Using the phononic states characterized and constructed in ***Sub-thrust 3.1***, we will develop state-space models based on the linear and non-linear FPE to describe the evolution of phononic states in response to external stimuli and analyze the equivalence between the phononic and neuronal data models using methods of the ***Machiraju*** Lab [19]. We will first measure the goodness of the phonon FPE model prediction against known thermal response characteristics of CMOS architectures, measured experimentally or predicted with Boltzmann transport equation framework [64, 84-86]. Once validated, we will compare the equivalence between the neuronal data and data embedded in the phononic states by measuring the similarity between the two state-space descriptions. The phononic state-space models acquired via optimization of the above-mentioned parameters between these two systems will provide insight about the phononic platform that will be able to evolve similarly to the neuronal assembly when responding to stimuli or perturbation, e.g., a driving current or applied temperature field. Given access to different neuronal models, e.g., motor, olfactory functions in a mouse brain, the ***Neogi***, ***Machiraju***, and ***Komiyama*** Labs will collaborate to examine which models are most amenable to adaptation in a phononic system. Such a dynamic framework will yield a conceptual transformation in understanding the emergence of hot spots and other complex behaviors of heterogeneous integrated architectures. This will establish a platform for information-embedding in phononic states that can be used more generally in photonics or plasmonics. *Key questions we seek to address include: How can we reveal hidden collective structure of neuronal activity and map them onto our interacting and evolving phononic assemblies? How can this communication platform help us reduce the power and footprint of NCS and improve integration density?*

Summary of Research Thrust 3: The result of this Thrust will be a prototypical phononic assembly that encodes arbitrary spatial-temporal dynamics from neuronal signaling data, representing large-scale collective neuronal activity that may include as-of-yet-unknown interconnecting paradigms in computing systems.

3. Management Plan

PI ***Bathe*** will be responsible for overall management of the research project, with administrative day-to-day support from a postdoctoral research associate to be identified at the time of award. Our Collaboration Plan reports in detail the manner in which our inter-disciplinary collaborative team will interact to advance the proposed research in the 2-year timeline proposed. ***Bathe*** and the postdoctoral lead will organize regular video-conferences for the participating research groups and personnel to share their research results on a regular, rotating basis. *Slack* will be used for day-to-day communication regarding each **Research Thrust** proposed, which involves distinct subsets of teams and personnel (**Figure 10**). Quarterly formal updates from each sub-thrust will be presented to the group in order to evaluate progress towards working prototypes for each of the three **Research Thrusts**. Four in-person meetings will be held at the participating institutions to offer interchange of research progress and plans. ***Bathe*** will focus on *in silico* design and *in vitro* synthesis and characterization of 2D and 3D DNA-based organic and inorganic FRET-based materials for **Research Thrust 1.** ***Hernandez*** will design networked systems of patchy particles *in silico* and use multi-scale modeling to predict their structure and dynamics with application to

memory encoding and computing for **Research Thrust 2**. ***Neogi*** will develop phonon engineering strategies for silicon-based material ensembles to embed arbitrary features from functional neuronal networks for **Research Thrust 3.** ***Komiyama*** will provide functional imaging data from mouse cortical networks. ***Machiraju*** will apply sophisticated data analysis techniques to extract key features and descriptors of neuronal datasets from ***Komiyama***. We also have identified key collaborators for this project that will enhance our joint capabilities further. Charles Leiserson in the MIT Computer Science and Artificial Intelligence Laboratory (CSAIL) and OSU Translational Data Analytics Institute (TDAI) have provided Letters of Collaboration for this project.

4. Synergy Between Scientists and Engineers

The PIs span both scientific and engineering disciplines including data science, materials science and engineering, computer science, chemistry, and biological engineering with strong publication track records in each discipline, including extensive collaborative publications across numerous disciplinary boundaries. PI ***Bathe*** works at the interface of experimental implementation and computational modelling of functional nucleic acid nanostructures. Co-PI ***Hernandez*** develops theoretical chemical models to understand the complex nature of nanoparticle self-assembly and predict their behavior. Co-PI ***Komiyama*** investigates neuronal behavior using state-of-the-art neuroscience techniques. Co-PI ***Machiraju*** develops computational models to identify salient features in "big data" sets. Co-PI ***Neogi*** develops physical models to understand and explain phonon behavior in materials. In the proposed two-year effort, the team of PIs will integrate their domain expertise, driven by data, to develop novel computing architectures the precise assembly of soft and hard materials. The ***Komiyama*** Lab will provide the neuronal imaging data that will be used to inspire the engineering of these novel computing architectures. The ***Machiraju*** Lab will distill the key features that are pertinent to describe the behavior of neurons based on the imaging data from the ***Komiyama*** Lab. ***Bathe***, ***Hernandez***, and ***Neogi*** will develop computational models and implement experimental prototypes that capture the neuronal spatiotemporal dynamics embedded in the coarse-grained network models from the ***Machiraju*** Lab. These prototypes would serve as proofs-of-principle to investigate emergent computing, sensing, and storage paradigms (**Figure 10**).

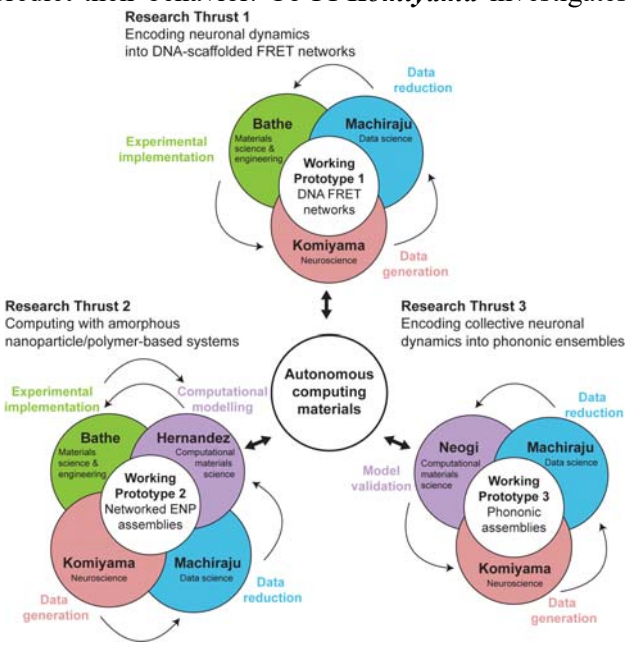

Figure 10. Overall team coordination, workflow management, and synergy between co-PIs.

5. Two-Year Timeline

Major milestones for the project will be presented at the 8-month intermediate PI meetings that occur twice during the lifetime of the project, followed by the capstone, final presentations at the end of the two-year mark when this pilot project would be converted into a full project proposal for a Data Science Institute. By the first 8-month meeting, the input neuronal data should be fully processed and converted to encodable sensing, computing, and data storage features for input to the three distinct materials systems, and all three materials systems should be ready for encoding. By the second 8-month meeting all three materials prototypes should be functional with the demonstrated ability to encode, process, and read-out the target functional neuronal datasets. The final 8-months of the project towards the closing PI meeting will then be focused on characterizing the success and failure points of the three prototypes and writing publications to disseminate results of the research, as well as formulating a broader vision and template for follow-on applications of our framework to other "big data" datasets from biology, ecology, imaging, etc., as well as other soft and hard materials systems.

6. Success Evaluation

The three functional prototypes form the central basis for success of the project, which will be evaluated at the end of the 16-month period, first, and at the final PI meeting at the end of 24-month project, second, including generalization of these prototypes to other type of data and materials systems. Specifically, the success of the project will demonstrate computing, storage, and sensing platforms using soft and hard materials encoding neuronal dynamics. From **Research Thrust 1**, the measurable outcome will be the demonstration of FRET network circuits that encode neuronal network motifs, both theoretically and experimentally, with FRET circuits performing sensing and computing operations. From **Research Thrust 2**, the measurable outcome will be a nanoparticle platform that stores and computes using self-assembly. From **Research Thrust 3**, phononic assemblies will encode neuronal data. Finally, for **Theme E**, the measurable outcome will be the scalable and robust extraction of dynamic networks and the construction of complementary lower-dimensional state-spaces from neuronal data. Further, the successful use of these state-spaces to create equivalent systems in three very different scientific settings will be a valuable outcome. Together, these three prototypes will clearly demonstrate success of the project that will result in a new paradigm for sensing, storage, and computing using distinct material properties.

7. Intellectual Merit

Advanced data science approaches will be explored to map functional neuronal datasets to emergent properties of soft and hard materials including DNA-based assemblies, patchy nanoparticle assemblies, and heterogeneous semi-conductors. Further data reduction and coarse-graining techniques applied to massive neuronal datasets will reveal principles of data transformation to reveal sensing, storage, and computing properties that may be applied to diverse other datasets. Principles for encoding neuronal sensing, data storage or memory, and computing in the soft and hard materials explored here may be transferred to diverse other materials with controllable electronic, photonic, phononic, magnonic, plasmonic, excitonic, and other emergent properties. Data-driven computational procedures for designing and exploring emergent sensing, storage, and computing properties of DNA-based, nanoparticle-based, and silicon-based materials will advance our understanding of how to use data-driven modeling and computation to encode these properties more generally in 1D/2D/3D materials.

8. Novelty of Approach, and Advanced Over State-of-the-Art

Data-driven functional materials design will be pursued based on massive biological datasets. Revolutionary new computing principles will be discovered, going beyond von Neumann architectures, applicable to synthetic sensing and computing machines embedded in synthetic materials. This two-year project will result in a generalized framework for the embedding of arbitrary biological and other datasets (genomic, transcriptomic, proteomic, metabolomic, imaging, ecological, etc.) into synthetic programmed materials that will be realized in three distinct material prototypes, and which will establish a new paradigm for autonomous computing.

9. Broader Impacts

The central mission of this proposal is to train graduate students and postdoctoral trainees in highly interdisciplinary research that spans multiple research areas, including neuroscience, data science, materials science, chemistry, physics and engineering. Our different research communities are active in disseminating our tools and data sets to scientists and engineers to expand the diversity of our research community and engage young researchers. In addition to their normal activities, the PIs are also active in a broad array of outreach and educational activities.

Outreach to Underrepresented Minorities and Women. All PIs have a strong track record, and will continue to engage, in outreach to local minority students. For example, ***Bathe*** has previously hosted in his lab several underrepresented minorities. Jaquesta Adams, an African-American student from Howard University, joined the ***Bathe*** Lab in summer of 2018 through the MIT Summer Research Program and subsequently received a Barry Goldwater Scholarship based in part on his recommendation letter. ***Komiyama***, ***Hernandez***, ***Machiraju***, and ***Neogi*** engage in similar outreach activities for minority and female students. ***Hernandez*** has led the chemistry community in changing policies and procedures in departments to advance inclusive excellence, and will partner with other PIs to extend these practices to

other disciplines. For example, he delivers over 10 lectures per year on "Advancing Science Through Diversity," at universities and conferences. ***Neogi*** is the Aerospace Engineering faculty liaison and creator of a faculty-student "Engineering Voices" dialogue series at the BOLD Center at the CU Boulder College of Engineering and Applied Science, created to prepare women and underrepresented minorities for success through graduation and beyond. ***Neogi*** has collaborated with the arts-sciences initiative NEST (Nature, Environment, Science, and Technology) to disseminate her research to the non-STEM community through data visualization and animation. The ***Machiraju*** Lab has 6 female undergraduate and graduate students and a female technical staff member. Further, the Translational Data Analytics Institute (TDAI) he leads holds summer camps on data science and analytics for young female middle and high school students from the inner city. Under his leadership, TDAI initiated new programs dedicated to workforce development in rural Ohio that targets disadvantaged groups. Lastly, OSU is the lead institution for the NSF Louis Stokes Alliance for Minority Participation in Ohio, and this project will provide research experiences to participating students enrolled at OSU. The ***Komiyama*** Lab has emphasized training of female students. The current female students include 3 PhD, 3 Masters and 7 undergraduate students who are trained with hands-on lab experiments. He will continue this effort with the PATHS program at UCSD.

Curricular Developments. The PIs will collaborate with local high school science teachers to build an interactive online course with the goal of introducing DNA nanotechnology to high-school students, undergraduate students, and the public. Similarly, ***Bathe*** collaborates with Dr. Gael McGill (Director of Molecular Visualization at Harvard Medical School) to develop molecular animations and simulations of structured DNA assemblies for undergraduate students. ***Bathe*** additionally develops and hosts numerous open source software programs that are accessible through web servers (DAEDALUS | daedalus-dna-origami.org, PERDIX | perdix-dna-origami.org, TALOS | talos-dna-origami.org, METIS | metis-dna-origami.org, and CanDo | cando-dna-origami.org) or through distributable software packages that offer high school and college students the opportunity to participate in the design of structured DNA assemblies both in independent Maker Space projects as well as in their coursework. The data analytics institute at OSU, TDAI, has been developing academic programming in data science and analytics at both the undergraduate, graduate and professional levels. The mainstay of these programs are the culminating capstone courses. It is likely that this project will create material for capstone courses in modeling and visualization. During the period of the proposed research, the Investigators will work together to build structure-based simulations of three different working prototypes proposed to produce visualizations and computational results that will help communicate the impact of computing, sensing, and storage to the broader scientific community.

10. Results of Prior NSF Support

Mark Bathe (PI) (a) DMREF CMMI-1334109, *Total Amount:* $1,706,468, *Period:* 01/15/2014–12/31/2017. **(b)** *Computational Design Principles for Functional DNA-Based Materials*. **(c)** This Designing Materials to Revolutionize and Engineer our Future (DMREF) grant provides funding for the development of a computational tool to determine optimal design parameters for the synthesis of DNA-based materials. ***Intellectual Merit.*** This grant supports research to develop an experimentally validated computational framework for the prediction of 3D structure and stability of programmed DNA assemblies, to develop generalized approaches for synthesis of programmed DNA architectures based on fundamental physical design principles are encoded in predictive computational models, and to expand the quantitative understanding of DNA tile-based self-assembly. The ***Bathe*** Lab has invented a generalized procedure to predict 3D structure of DNA assemblies programmed using multi-way junctions [87-89], which was applied to predict the solution structure of self-assembled micron-scale 2D arrays that templates plasmonic nanoparticles with nanometer precision [90]. We also developed a top-down computational design procedure DAEDALUS for scaffolded DNA origami nanoparticles based on the DX-edge motif to extend our ability to design arbitrary 3D shapes [35]. ***Broader Impacts.*** Computational and experimental results have been broadly disseminated worldwide through the preceding publications, online software tools, and servers, listed below. Because these computational tools dramatically reduce the cost and time associated with DNA origami synthesis, they have major impact on a variety of fields, disciplines, and industries leveraging structured DNA assemblies. **(d)** Pan et al. (2014) [87], Veneziano et al. (2016) [35]. Wang et al.

(2016) [90]. Pan et al. (2017) [91]. **(e)** Computational design and analysis tools are disseminated worldwide online, such as CanDo and DAEDALUS, with source code available from MIT or Open Source license.

Rigoberto Hernandez (Co-PI) (a) CHE 1503408 Hamers (PI), *Total Amount* to Hernandez: $948,000, *Period:* 7/1/2015– 6/30/2020. **(b)** *Dynamical Consistency in Multiscale Modeling of Sustainable Nanomaterials*, Subcontract to University of Wisconsin, Madison, "*Phase II Center for Chemical Innovation (CCI), A Molecular Basis for Sustainable Nanotechnology*" **(c)** This grant funds the development of computational models in close collaboration with experimentalists to elaborate on design principles for sustainable nanoparticles. **(d)** References: [48, 52, 53, 92-98]. ***Intellectual Merit*.** Through this grant, ***Hernandez*** is using simulation and design of specific nanoparticles to assess their properties and function in the context of environmental sustainability [48, 52, 53, 92-98].That work and what is proposed here are complementary to the advances the ***Hernandez*** Lab in making in the fundamentals of multiscale theory and methods through NSF CHE 1700749 [99-109]. ***Broader Impacts*.** The broader impacts of ***Hernandez***'s work can be summarized through his leadership of the field to address nonequilibrium behavior from molecular to large-scale heterogeneous assemblies with dynamical consistency, not just thermodynamic (or structural) consistency. The broader impacts of ***Hernandez***'s work beyond the impacts of his scientific work includes his roles in advocacy and mentoring of scientists from underrepresented groups (e.g., women, and under-represented minorities), his leadership in the profession through advisory board and professional service, dissemination through social media and traditional publication platforms, and his role as the Director of OXIDE [110-123].

Takaki Komiyama (Co-PI) (a) ECCS-1734940 (PI), *Total Amount:* $500,000, *Period:* 8/1/17−7/31/19. **(b)** *Super resolution Mapping of Multi-scale Neuronal circuits Using Flexible Transparent Arrays*. **(c)** ***Intellectual Merit*.** Development of methodologies to perform multimodal recording of neural activity with simultaneous electrophysiology and imaging holds promise to combine the advantages of both methodologies. The proposed computational approach could vastly increase the number of neurons that can be simultaneously recorded. We successfully developed and validated novel electrode arrays and performed multimodal recording, combining surface electrode recording with calcium imaging. We are refining our algorithm to infer underlying spikes of imaged neurons. ***Broader Impacts*.** Development of a technology to record all neurons in a brain area would have a transformative impact in neuroscience. Furthermore, the project is generating development opportunities to the graduate students involved in the collaboration across departments. **(d)** Lu et al. (2018) [124]. **(e)** We are working on disseminating the probes. The software for computation will be publicly available on GitHub.

Raghu Machiraju (Co-PI) (a) DBI-1262469 (PI), *Total Amount*: $411,434, *Period:* 06/01/2014–05/31/2018. **(b)** DBI-1262469: *BCSP: ABI Innovation: Collaborative research: Predicting changes in protein activity from changes in sequence by identifying the underlying biophysical conditional random field.* **(c)** ***Intellectual Merit*.** This project examines the Biological and Computing Shared Principle of a "Biophysical Conditional Random Field" underlying and predicting protein fitness and functionality, and proposes that this Biophysical CRF can be extracted, made tractable, and computed upon, to predict changes in protein fitness or functionality, from changes in protein sequence. ***Broader Impacts*.** The direct results will materially improve the ability of researchers working with proteins and protein mutations, to understand their data, predict the results of experiments, and engage in rational protein design. ***Results*.** The major results of the project are the development of mining and visualization tools to glean changes in function of salient proteins using data mining techniques and then validating them in the wet laboratory [125-128].

Sanghamitra Neogi (Co-PI)
No prior NSF support to report.

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