In Silico Simulation of Dementia-Alzheimer-Syndrome: Application of hybrid computing approach to the study of emergent behavior

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INDRC
International Neurodegenerative Disorders Research Center

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Background

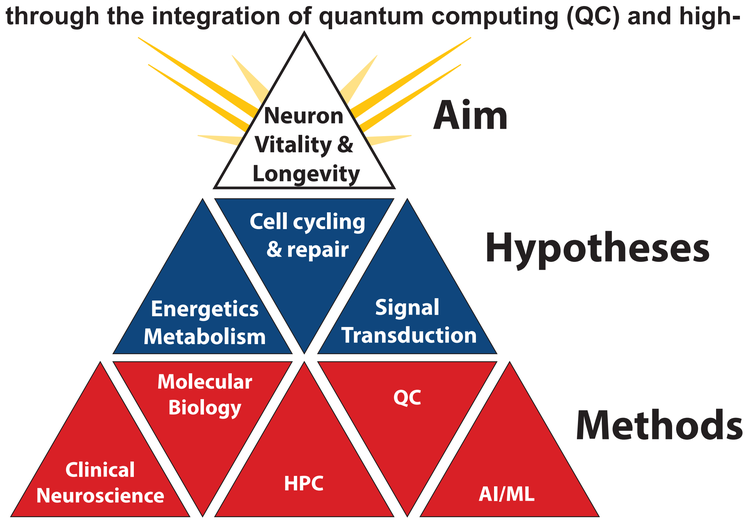
Efforts to find treatments for chronic brain disorders such as the dementia-Alzheimer syndrome are imperative, given the growing psycho-social challenges and escalating expenses associated with caring for affected individuals on a global scale. The aim of eradicating the dementia-Alzheimer syndrome from the world is a top priority for public health systems globally. Despite significant investments in research for over 40 years, there are only a few effective interventions available to slow down the progression of the disease or delay the onset of cognitive impairment and other disabling symptoms.

One of the main challenges in developing therapies for chronic brain disorders like dementia is the complexity of the neurobiology involved. Another is the lack of a conceptual framework connecting the components and variables involved. These two factors contribute to the difficulty of discovering effective interventions.

The grand challenge of vitality and longevity of neurons

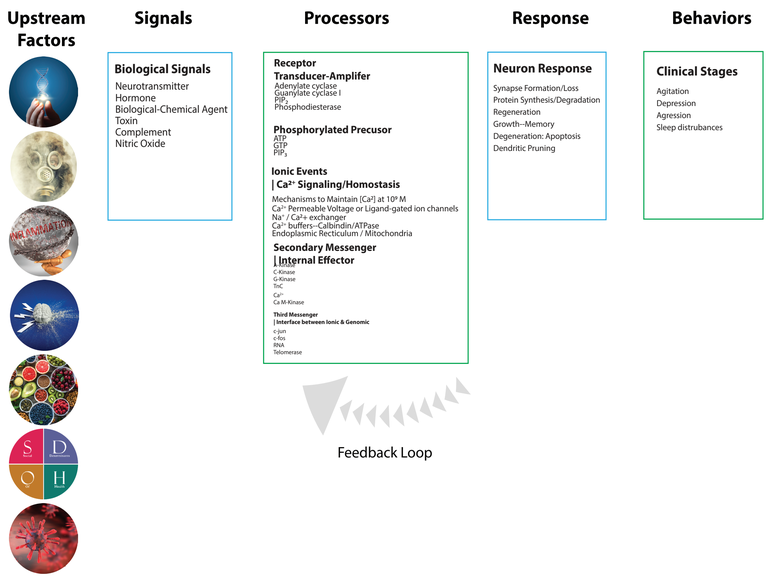
The conventional approach in dementia research to explain the pathophysiology of chronic brain disorders, such as Alzheimer's disease (AD), focuses on putative mechanisms of neuronal dysfunction leading to failure in particular neural systems. The CLARA-*Center for Artificial Intelligence and Quantum Computing in System Brain Research*-project represents a paradigm shift for neuroscience by asking a different research question. ***What are the necessary and sufficient conditions to maintain optimal function, vitality and longevity of a neuron to exceed 100 years?***

CLARA seeks to push the frontier of neurodegeneration research, particularly AD, by examining nonlinear interactions between the molecular, behavioral and clinical features of brain disorders through the integration of quantum computing (QC) and high-performance computing (HPC, together as hybrid computing or HPCQC) with AI/ML. Also, the project seeks deep field knowledge and processing of large-scale biological and clinical data that will enrich collective understanding of these emerging technologies to solve real-world challenges, thus accelerating innovations and the future of computing for the benefit of society. CLARA's use of quantum-accelerated supercomputing and AI/ML applications will expand neuroscience's capabilities to better understand, visualize and simulate the optimal performance of a neuron. This new knowledge will allow for innovative research into how, for example, energy disruptions are critical factors in neurodegenerative disease pathophysiology, progression, and as novel targets for therapeutic interventions. Finally, by building a domain specific HPCQC and data infrastructure platform based on current and future EuroHPC Joint Undertaking computing resources, CLARA will significantly contribute to the development of the European computing and data ecosystem in the field of system brain research.



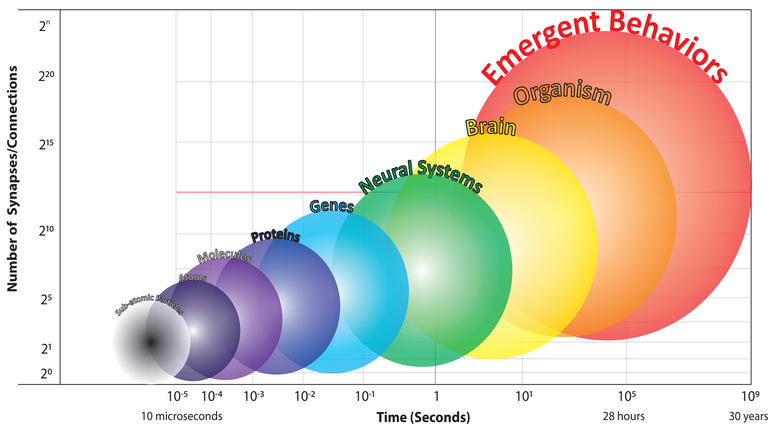
Reformulating the Calcium Hypothesis into a Systems Framework

One conceptualization of Alzheimer's disease is an accumulation of progressive system failures in interconnected brain networks. Using a systems perspective to characterize Alzheimer's disease goes beyond identifying a single etiologic factor leading to pathogenesis. The systems framework highlights the significance of explaining how the genetic and biological events interact within the entire system and how the temporal changes occur either in sequence or in parallel. Moreover, it emphasizes identifying the best possible ways to optimize the system's overall performance by examining its individual components. This approach provides a pathway to address the difficulties in conceptualizing and communicating non-linear relationships between the behavioral and clinical features of Alzheimer's disease and the underlying neurobiological mechanisms.



Rules and Regulatory Mechanisms Controlling Brain Molecular and Network Systems

The framework helps translate the phenomenological modeling of genome-scale, protein-scale, molecular-scale, and multiple other scales of information that influence the performance of neural systems. Under the modular network organization hypothesis, there is a likelihood that genomic, proteomic, and ionic processes form subsystems of insulated functions and that emergent characteristics/behaviors should self-organize to comprise progressively higher-scale systems. Further, these emergent characteristics will form higher-level regulatory networks with fewer interactions. From a computational and experimental perspective, this modeling schema may be calibrated so that the effective set of interactions is mathematically soluble given the data available.



Three Key Projects

1. Quantum-Supercomputing and Machine Learning to Address Protein Dynamics Aggregation Modulation by Small Molecules

The goal is to create new foundational models to study protein dynamics and aggregation in neurodegenerative diseases. These models will be trained using supercomputing and hybrid super/quantum computing for simulating large datasets of proteins. The project will establish and validate foundation models using model proteins, such as bioluminescent enzymes, to provide an easy functional readout. The group will then apply these models to crucial proteins and peptides involved in neurodegenerative diseases.

2. Expanding Standardized Systems Biology and Cellular Modeling Language, with Clinical Phenomenology of AD to Model Differential Time and Scale Coupling Parameters

Developing interventions for neurodegeneration is complicated due to complex molecular, biochemical, and patient-level data interactions. This makes assessing theories like the amyloid cascade and calcium theory of aging challenging. The project will define parameters, conditions, and models based on human energetics and metabolic systems to address this. We will integrate tools, models, and data to establish temporal sequencing parameters among various processes.

3. Develop Multiscale/Cross-Modal Patient/Deep-Learning Models of Alzheimer's Disease in Quantum Computing Environments

The project aims to create an e-diagram linking neurons, neuronal proteins, and network architecture to Alzheimer's symptoms. Then, deep learning models will be developed integrating clinical phenomenology, neurobiology, biophysics, and biochemistry to establish multiscale/cross-modal approaches. Currently, most simulations of genomic or other clinical-level data exceed the capacity of most current supercomputers. The derived data-driven functional abstractions (from #1 and #2), when used in conjunction with supervised deep learning and quantum computing (#3), should resolve challenging simulation tasks. At the cellular level, the effort will initially use a compartmental model of the CA1 pyramidal cell. The synaptic modeling platform EONS/ Rhenoms™ (Elementary Objects of the Nervous System) will be used to define the distribution and arrangement of molecular elements within a synaptic environment. We will develop novel predictive and generative deep learning models that can specifically tackle the challenge of crossmodal patient modeling (molecular, cellular, neuroimaging, cognitive, etc.). Novel hypotheses can be validated using this modeling and simulation environment such as why some neurons are more resilient than others, what are the critical clinical factors associated with selective neuronal vulnerability (SNV), and how whole genome expression studies may lead to further insights into the organization of SNV complexity that could lead to new therapeutic target discovery.

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Disclosures: Ara S. Khachaturian, Ph.D. is an Officer and director of the Campaign to Prevent Alzheimer's Disease (PAD 20/20) and; Officer, director and employee of Khachaturian and Associates: Founding executive-editor of Alzheimer's & Dementia, The Journal of the Alzheimer's Association (retired), Founding executive-editor of Alzheimer's & Dementia: Translational Research & Clinical Intervention (retired), Founding executive-editor of Alzheimer's & Dementia: Diagnoses, Assessment & Disease Monitoring (retired); Executive Officer and Director, Brain Watch Coalition; Senior Research Fellow, University of Nevada Las Vegas, National Supercomputing Institute & Dedicated Research Network; Received payments through organizational affiliations for grants, contracts, consulting fees, honoraria, meeting support, travel support, in-kind research/professional support over the last 36 months from the Alzheimer's Association, Acadia Pharmaceuticals, Alzheon, Biogen, Clinical Trials Alzheimer's Disease Conference, Davos Alzheimer's Consortium, Digicare Realized, Eisai, Eli Lilly & Company, Embic, RELX Plc, High Lantern Group, International Neurodegenerative Disorders Research Center, and Serdi Publishing.