

# Harnessing Computational Approaches to Advance Aging and AD/ADRD Research

*National Institute on Aging*

March 1-2, 2023

Virtual Meeting

*September 28, 2023*



This meeting summary was prepared by Rose Li and Associates, Inc., under contract to the National Institute on Aging. The views expressed in this document reflect both individual and collective opinions of the meeting participants and not necessarily those of NIA. Contributions to and reviews of this meeting summary by the following individuals are gratefully acknowledged: Elizabeth A. Finch, Martin Sabandal, Christina Tricou, Dana Carluccio, Dave Frankowski, Karolina Lempert, Sparsha Muralidhara, Angela Radulescu, Paola Sebastiani, Janine Simmons, Ana Solodkin.

# Table of Contents

|                                                                                                                      |            |
|----------------------------------------------------------------------------------------------------------------------|------------|
| <b>Acronym Definitions.....</b>                                                                                      | <b>iii</b> |
| <b>Executive Summary .....</b>                                                                                       | <b>iv</b>  |
| <b>Computational Analysis of Molecular and Cellular Systems .....</b>                                                | <b>iv</b>  |
| <b>Computational Analysis of Large-Scale Brain Systems .....</b>                                                     | <b>v</b>   |
| <b>Computational Analysis of Complex Behavior .....</b>                                                              | <b>v</b>   |
| <b>Gaps, Opportunities, and Future Directions .....</b>                                                              | <b>vi</b>  |
| <b>Meeting Summary .....</b>                                                                                         | <b>1</b>   |
| <b>Opening Remarks and Overview.....</b>                                                                             | <b>1</b>   |
| <b>Session I: Computational Analysis of Molecular Systems .....</b>                                                  | <b>2</b>   |
| Quantifying Aging .....                                                                                              | 2          |
| Engineering Longevity – Computationally-Guided Reprogramming of Single-Cell Aging .....                              | 3          |
| Computational Challenges in Extreme Longevity Studies.....                                                           | 5          |
| Microscopic Imaging of Epigenetic Age and Chromatin Heterogeneity .....                                              | 7          |
| Moderated Discussion.....                                                                                            | 8          |
| <b>Session 2: Computational Analysis of Large-Scale Brain Systems .....</b>                                          | <b>10</b>  |
| From Clockwork to Emergence: A New View of the Brain .....                                                           | 11         |
| How a Biophysical Generative Model Gives Unique Insights into Aging and Dementias .....                              | 12         |
| Clinical Utility of a Global Information Processing Model for Mental Functions.....                                  | 13         |
| Using Network Control Theory to Formally Model the Energetics of Brain Function .....                                | 15         |
| Moderated Discussion.....                                                                                            | 16         |
| <b>Session 3: Computational Analysis of Complex Behavior .....</b>                                                   | <b>19</b>  |
| Using Computational Modeling Approaches to Reveal Cognitive Processes Underlying Changes<br>Across the Lifespan..... | 19         |
| Computation Conquers Complexity – Decomposing Behavior to Understand the Components of<br>Cognition .....            | 20         |
| Towards Naturalistic Reinforcement Learning in Health and Disease .....                                              | 21         |
| Relating Individual Differences in Learning to Markers of Alzheimer’s Disease .....                                  | 22         |
| Moderated Discussion.....                                                                                            | 23         |
| <b>Final Discussion: Gaps and Opportunities .....</b>                                                                | <b>25</b>  |
| <b>Closing Remarks .....</b>                                                                                         | <b>29</b>  |
| <b>Appendix: Agenda .....</b>                                                                                        | <b>30</b>  |

## Acronym Definitions

|          |                                                                              |
|----------|------------------------------------------------------------------------------|
| AD       | Alzheimer's disease                                                          |
| ADRC     | Alzheimer's Disease Research Center                                          |
| ADRD     | Alzheimer's disease and related dementias                                    |
| AI       | artificial intelligence                                                      |
| AITC     | Artificial Intelligence and Technology Collaboratories                       |
| AMP      | Accelerating Medicines Partnership                                           |
| CEE      | control energy estimate                                                      |
| COVID-19 | Coronavirus disease 2019                                                     |
| DCNN     | deep computational neural network                                            |
| DDM      | drift-diffusion model                                                        |
| DTI      | Diffusion Tensor Imaging                                                     |
| EF       | electric field                                                               |
| FDG-PET  | fluorodeoxyglucose positron emission tomography                              |
| fMRI     | functional MRI                                                               |
| FTD      | frontotemporal dementia                                                      |
| iPSC     | induced pluripotent stem cell                                                |
| iRFP     | infrared fluorescent reporter                                                |
| LBD      | Lewy body disease                                                            |
| LFP      | local field potential                                                        |
| MCI      | mild cognitive impairment                                                    |
| ML       | machine learning                                                             |
| MODEL-AD | Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease |
| MSM      | multiscale modeling                                                          |
| NIA      | National Institute on Aging                                                  |
| NIAGADS  | NIA Genetics of AD Data Storage                                              |
| NIH      | National Institutes of Health                                                |
| PBMC     | Peripheral blood mononuclear cells                                           |
| PCA      | principal component analysis                                                 |
| PD       | Parkinson's Disease                                                          |
| PE       | prediction error                                                             |
| PET      | positron emission tomography                                                 |
| PFC      | prefrontal cortex                                                            |
| rDNA     | ribosomal DNA                                                                |
| RL       | reinforcement learning                                                       |
| SNP      | single nucleotide polymorphism                                               |
| TREAT-AD | Target Enablement to Accelerate Therapy Development for AD                   |
| TVB      | The Virtual Brain                                                            |

## Executive Summary

On March 1-2, 2023, the National Institute on Aging (NIA) Divisions of Neuroscience, Aging Biology, and Social and Behavioral Research held a workshop that convened stakeholders on aging, Alzheimer’s disease (AD), and Alzheimer’s disease and related dementias (ADRD) research. The workshop goal was to explore and harness computational approaches to advancing the study of aging and AD/ADRD. The workshop highlighted three major areas in computational approaches and analyses to brain aging and AD/ADRD: molecular and cellular systems, large-scale networks and brain systems, and complex behavior and cognition. Current and potential applications of computational approaches to the study of aging and AD/ADRD were also explored to help better understand key questions in the field, identify critical gaps and opportunities, and provide a forum for the scientific community to offer input about the resources, guidance, and opportunities that will strengthen and accelerate NIA-supported computational research.

Meeting participants presented on new and emerging technologies and research findings, and engaged in moderated discussions that included the following topics:

- identifying computational techniques uniquely suited to answer aging and neurodegeneration research questions;
- developing computational models of biological and behavioral changes across the lifespan;
- determining resources and techniques required to effectively interrogate large- and multi-scale datasets;
- generating strategies to promote collaboration between computational scientists and aging researchers.

## Computational Analysis of Molecular and Cellular Systems

During the presentations in this section, workshop participants

- learned about studies on quantifying aging that use biomarker aging signatures to develop and apply epigenetic and other biological “clocks” to analyze biological or functional age;
- discussed integrating quantitative, single-cell image-based measurements of replicative aging in budding yeast with dynamic mechanistic predictive models to understand how gene regulatory networks drive the aging process and to guide the design of intervention strategies that promote longevity;
- addressed modeling approaches and computational challenges in studies of extreme longevity aimed at integrating multi-omic molecular signatures, genetics, and phenotypes to identify molecular profiles that correlate with the delayed disability, morbidity, and mortality;

- reviewed a new method for fluorescence microscopic imaging of epigenetic age and chromatin heterogeneity for uncovering novel characteristics of cellular and organ level biological and functional aging.

Discussion topics included causality and heterogeneity in aging, bias in biological age prediction, issues related to different scales across the biological hierarchy, issues related to modeling biological dynamics across timescales, and key challenges for using computational approaches to model aging.

## Computational Analysis of Large-Scale Brain Systems

During the presentations in this section, workshop participants

- described a paradigm shift for large-scale brain organization based on multi-electrode recordings from millions of neurons, which has shown that neural activity underlying cognition is complex, dynamic, and rhythmic, with emergent properties (e.g., brain waves) that organize brain activity and play key roles in cognition and consciousness;
- discussed biophysical and biologically based computational models, including a multi-scale neuroinformatics platform called The Virtual Brain, that use *in silico* simulations of brain activity to study macroscale mechanisms in order to discover the mechanistic principles of human brain function and dysfunction;
- presented a computational behavioral neurology framework using fluorodeoxyglucose positron emission tomography (FDG-PET) imaging to address clinical questions about brain-behavior mapping, describe specific brain patterns in patients, and distinguish brain patterns between clinically normal individuals and those with a variety of dementia syndromes;
- examined recent expansions of measurement, modeling, and conceptual approaches that provide a richer understanding of how the brain's structural network constrains the flow of activity and the use of network control theory for modeling brain energetics.

Discussion topics included the hierarchy of scales across time and space, challenges unique to modeling brain aging using computational approaches, and key gaps and opportunities in computational analysis of large-scale brain systems.

## Computational Analysis of Complex Behavior

During the presentations in this section, workshop participants

- identified the benefits, risks, and limitations of using computational modeling to understand behavior and the power of these approaches to reveal cognitive processes that underlie cognitive changes across the lifespan;
- characterized the development of computational and mathematical models that capture a wide range of simple lab-based to complex real-world behaviors and their use to understand the components of cognition;

- assessed studies that combine naturalistic behavior and modeling aimed at determining whether similar cognitive processes are used across tasks and whether and how those processes change with age;
- noted studies of economic decision-making in older adults focused on understanding whether diminished learning abilities in cognitively normal older adults contribute to suboptimal decision-making and whether individual differences in learning processes might indicate pathological heterogeneity.

Discussion topics included the impact of aging on learning and decision-making, the generalizability of findings from specific behavioral tasks, temporal discounting, and ecological validity and task simplicity.

## Gaps, Opportunities, and Future Directions

Workshop participants also discussed the gaps, opportunities, and future directions for developing and implementing computational approaches to study of aging and AD/ADRD that emerged from the workshop, including:

- approaches to integrating computational models across biological and temporal scales and levels of analysis;
- limitations, barriers, and opportunities for computational approaches to inform experimental work;
- barriers to bridging across scales;
- education and training barriers;
- opportunities for advancing collaboration across areas of expertise;
- and questions specific to aging and neurodegeneration for which computational approaches are uniquely suited.

Several key common themes that emerged from the discussion provided a unifying framework for the workshop. Applying computational approaches across all levels of brain function, from molecules to complex behaviors, relies on the bidirectional interplay between modeling approaches and experimental data—as well as modelers and experimentalists. In addition, developing multi-scale modeling approaches and strategies for bridging and integrating across the multilevel biological and temporal scales is critical for harnessing computational modeling approaches to understand brain function and its dysfunction in aging and AD/ADRD.

## Meeting Summary

### Opening Remarks and Overview

*Amy Kelley, MD, MSHS, Deputy Director, National Institute on Aging*

*Matt Sutterer, PhD, Program Director, National Institute on Aging*

The workshop on Harnessing Computational Approaches to Advance Aging and AD/ADRD Research was a collaborative effort co-sponsored by the National Institute on Aging (NIA) Divisions of Neuroscience, Aging Biology, and Social and Behavioral Research. The goal of the workshop was to explore computational approaches to advancing the study of aging and AD/ADRD. Recent years have seen the rapid development of computational biology, imaging and modeling, systems and bioinformatics, advances in machine learning (ML) and artificial intelligence (AI), and the availability of large-scale datasets that, together, have facilitated an explosion of research across many levels of biology and behavior. These advances have led to the growth of computational neuroscience as an interdisciplinary field for the development, simulation, and analysis of multiscale models and theories of neural function. As reflected in the three workshop sessions, computational approaches span multiple levels of analysis from molecules and cells to networks to cognition and behavior. The workshop explored current and potential applications of computational approaches to the study of aging and AD/ADRD to better understand key questions in the field and to provide an opportunity to hear from the community about resources, guidance, and opportunities that will strengthen and accelerate NIA-supported computational research.

Dr. Kelley advocated for the workshop's focus, which aligns with NIA's mission to understand the aging process and diseases and conditions associated with aging to extend the healthy and active years of life for older adults. NIA is committed to advancing the most innovative areas of science by investing in projects and infrastructure that apply novel and cutting-edge approaches to (1) fill critical gaps in research and discovery and (2) facilitate the broad sharing of research data and the resources developed with public funds.

To accomplish this mission, NIA has established initiatives including Target Enablement to Accelerate Therapy Development for AD (TREAT-AD), which develops high quality research tools and technology needed to validate and advance the next generation of drug targets for AD by through the open dissemination of data, research methodologies, and computational and experimental tools to the AD research community. Another initiative is the new Artificial Intelligence and Technology Collaboratories (AITC), which are dedicated to helping Americans live longer and healthier lives through the application of AI and emerging technologies. These AITCs will serve as a national resource to promote the development and implementation through partnerships across industry, healthcare systems, and other stakeholders.

In addition, NIA recognizes the importance of data sharing to ensure the rigor, reproducibility, and transparency of research findings. Sharing scientific data can also accelerate biomedical research discovery by (1) enabling the validation of research results and (2) promoting data re-use for additional research studies. NIA already has generated robust resources including the

NIA Genetics of AD Data Storage (NIAGADS), the NIA Knowledge Portal created through the Accelerating Medicines Partnership (AMP), and the Aging Research Biobank. These resources provide a wide range of new opportunities for researchers to conduct computational research with existing data sources.

## Session I: Computational Analysis of Molecular Systems

*Session Chair: Vadim Gladyshev, Ph.D., Harvard University*

### Quantifying Aging

*Vadim Gladyshev, Ph.D., Harvard University*

Dr. Gladyshev's lab focuses on quantifying aging, longevity, and rejuvenation while generating signatures of these processes that can be used to identify and validate candidate interventions that target aging and promote rejuvenation. Studies to quantify aging illustrate the power of this approach. The development of human and mouse epigenetic, transcriptomic, proteomic, microbiome, and ionome biomarkers of aging, known as biological "clocks," has revolutionized the study of aging over the past ten years. Dr. Gladyshev's team developed the first mouse epigenetic clock by sequencing 200 mice in 16 age groups from very young to 35 months of age. By applying ML methods (e.g., elastic net regression) to millions of common CpG sites identified by sequencing, they were able to develop a mathematical model that could correctly assign biological age to mouse cohorts, detect the effects of calorie restriction and gene knockouts on longevity, and report rejuvenation of fibroblast-derived induced pluripotent stem cells (iPSCs) based on DNA methylation patterns.

More recently, Dr. Gladyshev's lab developed a probabilistic clock, which provides a flexible and scalable probabilistic framework for epigenetic age prediction at single-cell resolution, called "scAge." scAge correctly predicts the age of mouse hepatocytes and embryonic fibroblasts at the single cell level. Analysis using scAge suggests that cells age at different rates; although many cells age at similar rates, some cells age faster (e.g., senescent cells) or slower (e.g., muscle stem cells), which leads to heterogeneity in the biological age of individual cells within tissues. This complexity requires new thinking about cell and tissue aging and the development of new methods to identify and predict cell age.

Several examples illustrate the power of epigenetic clocks to quantify aging. In one application, biological age was reversibly increased by severe stress (e.g., major surgery, severe COVID-19 infection, pregnancy, parabiosis), which suggests that biological age does not continuously progress like chronological age, but instead fluctuates depending on physiological conditions. In another study, epigenetic clocks were applied to determine if parabiosis could reverse aging in mice. In this study, connecting the vasculature of young and old mice to establish common blood circulation for three months resulted in the old mice living longer, and applying epigenetic clocks supported that they were truly rejuvenated (i.e., predicted biological age was reduced) across several tissues (e.g., liver, blood).

One fundamental challenge with using features of aging to develop biological clocks is determining which aging characteristics are causal and which are adaptive responses that do not influence aging per se (e.g., using glasses, graying hair), marking the importance of distinguishing age-related changes as aging, neutral, or adaptive. By applying Mendelian randomization to age-related changes, the team identified a subset of CpG DNA methylation sites that were either detrimental (i.e., reduced lifespan) or protective/adaptive (i.e., increased lifespan) during aging. These sites were used to make separate clocks for damaging and adaptive changes—DamAge and AdaptAge—both of which can be used to predict age. However, in the rejuvenation context (i.e., reprogramming fibroblasts to iPSCs), DamAge revealed rejuvenation, whereas AdaptAge did not. This finding highlights key challenges in the field, including how to quantify aging and when clocks can be appropriately applied to understand directional changes from young to old and from old to young.

Additional challenges with using aging biomarkers to study aging to be resolved include:

1. **Omics:** Determining which omics methods are optimal for different applications (e.g., epigenetics, transcriptomics, proteomics, multi-omics).
2. **Phenotypes:** Determining how to relate omics results to phenotypic measurements (e.g., frailty, cell composition, morphology, systemic changes).
3. **Training:** Determining optimal aging manifestations for training clocks (e.g., damage accumulation, loss of function, appearance of diseases, mortality, rate of change)
4. Determining how to relate aging at the levels of single cells, tissues, and organisms.
5. Understanding aging versus adaptation.
6. Understanding how to separate features of aging versus development.
7. Understanding how stochastic versus regulatory features contribute to clocks.
8. Understanding mechanistic differences between sites with increased versus increased DNA methylation.
9. Understanding differences between aging and rejuvenation and whether clocks can be applied in both directions.
10. Reducing costs of sequencing by 10- to 100-fold to make use of biological clocks widely applicable.

To take advantage of opportunities for major advances brought about by the biomarker revolution (e.g., the ability to quantify various aspects of aging and to test longevity interventions) and begin to address remaining challenges, a [Biomarkers of Aging Consortium](#) was launched on February 28, 2023. In addition, Dr. Gladyshev's lab released an online platform called [ClockBase](#) to help the community explore and analyze biological age across 300,000 GEO databased samples under 7,000 experimental conditions.

### **Engineering Longevity – Computationally-Guided Reprogramming of Single-Cell Aging**

*Nan Hao, PhD, University of California at San Diego*

Recent studies by Dr. Hao's lab are integrating quantitative, single-cell measurements with dynamic mechanistic predictive models to understand how gene regulatory networks drive the aging process and the ways in which these models can be used to guide the design of

intervention strategies to promote longevity. The system used for these studies is the replication of the aging process in budding yeast, a genetically tractable model for the aging of mitotic cell types in mammals (e.g., stem cells) in which replicative lifespan is measured as the number of mother cell divisions before death. Through over 60 years of investigation, studies in yeast have identified many well-conserved genes that influence longevity among eukaryotes. Emerging challenges are to understand how those genes interact and how their interactions change dynamically to drive the aging process.

To overcome the labor-intensive challenge of manually separating daughter and mother cells after each division, Dr. Hao's lab developed a microfluidic device to separate daughter cells from trapped mother cells, which allows mother cells to bud continuously throughout their lifespan until they become sick, stop budding, and die. This methodology enables tracking of molecular and cellular changes during the aging process of many single cells. Using this approach, Dr. Hao's group found that isogenic yeast cells exhibit two distinct types of phenotypic changes during aging, with approximately half of the cells producing elongated daughters ("Mode 1"), and half of the cells producing small round daughters ("Mode 2"). Mode 2 aging features a more dramatic slowdown of cell cycle rate and a shorter lifespan than Mode 1 aging. Tracking of organelles during aging revealed that nucleoli become dramatically enlarged and fragmented in old Mode 1 cells (but not Mode 2 cells), whereas mitochondria became aggregated in old Mode 2 cells (but not Mode 1 cells). These findings show that different modes of aging specifically target different organelles, with Mode 1 leading to nucleolar decline and Mode 2 leading to mitochondrial decline.

To investigate how the pathways underlying Mode 1 and Mode 2 operate together to drive the aging process, Dr. Hao's lab developed single-cell fluorescent reporters to monitor nucleolar and mitochondrial decline. For Mode 1 aging, a GFP reporter for ribosomal DNA (rDNA) silencing, rDNA-GFP, was developed to monitor Sir2-mediated chromatin silencing, which regulates the nucleolar rDNA instability underlying nucleolar decline. For Mode 2 aging, a nuclear anchored infrared fluorescent reporter, nuclear iRFP, was developed to monitor the HAP transcriptional complex, which plays a key role in heme-regulated mitochondrial function in yeast. The rDNA-GFP and nuclear iRFP reporters were then used to simultaneously track Sir2 and HAP activities in the same cells during aging. Analysis of many cells revealed that isogenic cells initially had relatively uniform fluorescence levels for both reporters, but those levels diverged early in life and progressed in opposite directions. Mode 1 cells ended their life at a low Sir2, high HAP state, consistent with nucleolar decline, while Mode 2 cells ended at a high Sir2, low HAP state, consistent with mitochondrial decline. The aging of genetically identical cell populations age toward two discrete ending states with anti-correlated Sir2 and HAP activities suggested that mutual inhibition between Sir2 and HAP mediates the early-life divergence of aging processes, which the Hao lab confirmed using genetic analysis.

Based on this circuit, the Hao lab developed a simple deterministic mathematical model that simulates how Sir2 and HAP activities change during aging. In this model, the aging process is viewed as a progression from unstable fixed points to stable fixed points, or steady states, and a Sir2-HAP phase plane (i.e., a vector field from model simulations) that illustrates how Sir2 and

HAP activities change over time. To address the stochastic nature of aging in single cells, a stochastic version of the model was used to compute a potential landscape, where the stable fixed points from the deterministic model correspond to local wells on the landscape and the well depth reflects its fate decision probability. In this way, the aging process of each single cell can be seen as a divergent progression toward different wells (i.e., different steady states) on the Sir2-HAP landscape, with the low Sir2 high HAP well corresponding to the ending state of Mode 1 aging and low HAP wells corresponding to the ending state of Mode 2 aging.

Genetic perturbations further showed that 2-fold overexpression of Sir2 generates a third aging mode that ends at a high Sir2, high HAP state, called Mode 3 aging. Mode 3 cells have a lifespan about twice the average wildtype lifespan, and, unlike Mode 1 and Mode 2 cells, retain a normal cell cycle rate throughout the entire lifespan. In the model, a 2-fold increase in Sir2 activity partially counteracts inhibition from HAP, leading to the emergence of a new fixed stable point on the phase plane and a new well on the landscape corresponding to the long-lived Mode 3 aging observed experimentally. Using computationally guided reprogramming, additional genetic manipulations to enrich Mode 3 aging in a large fraction of cells effectively promoted longevity of the entire cell population. Most recently, Dr. Hao's lab combined mathematical modeling and network engineering to rewire the Sir2-HAP circuit and create a synthetic oscillator for longevity in which periodic switching of Sir2 and HAP activities avoids cell fate commitment to detrimental states and extends cell lifespan by 82 percent.

Together, these studies have revealed that aging is more of a programmable decision process than a simple accumulation of deleterious events. More broadly, this work highlights the power of an integrated systems biology and computational framework for enabling new discoveries in aging biology and could drive future innovations in intervention development.

### **Computational Challenges in Extreme Longevity Studies**

*Paola Sebastiani, PhD, Tufts Clinical and Translational Science Institute*

In the field of extreme human longevity, genetics affect the ability of individuals to reach extreme old age, often in the absence of physical and cognitive impairments. Although genetics provide information about unmodifiable risk factors, recent studies have focused on the translation of genetic variants into molecular profiles, which are modifiable. Many large-scale studies are collecting a range of biological samples using harmonized protocols to generate multi-omics data as well as phenotypic data from centenarians and healthy agers. The goal is to integrate molecular signatures with genetics and phenotypes to identify the molecular profiles that correlate with the delayed disability, morbidity, and mortality of centenarians to try to understand the protective profiles that are correlated with having adaptive genetic mutations and to identify targets for intervention using anti-aging therapeutics.

To tackle this complex challenge, Dr. Sebastiani's group is building models to understand mechanisms, predict outcomes, and eventually identify targets for anti-aging therapeutics. Thus far, Dr. Sebastiani's group is collecting pieces of the puzzle. For genetics, these pieces include a growing catalogue of genetic mutations associated with the ability of people to reach extreme old ages and protective variants that are correlated with maintenance of good cognitive

function in centenarians. Molecular signatures of good genetic variants associated with longevity have also been identified, including a signature of the APOE2 allele correlated with maintaining healthy cognitive function during aging and a specific APOE2-related metabolomic signature associated with long life. Additional transcriptomic, proteomic, and serum metabolomic studies are yielding analogous findings. The emerging picture is that while many biomarkers of aging at the level of transcriptomics, proteomics, and metabolomics are consistent with what would be expected, centenarians also exhibit unique omics profiles, although distinguishing the omics signatures that are causes versus effects remains a challenge.

Dr. Sebastiani's group is using Bayesian Networks (BNs) to model the complex interactions between genetics, multi-omics, and multi-phenotypes in observational studies. BNs consist of probability distributions (i.e., vectors) of multiple random variables that can represent, for example, SNPs, risk factors, omics, and outcomes. These networks are advantageous because they decompose a complex probability distribution into factors, leveraging marginal and conditional independencies. In practice, this means that a complex model can be factorized into small modules, which are easier to learn from data and to use for probabilistic reasoning. Once a model is assembled, it can be used for predicting the consequences of perturbing nodes in the network (e.g., genes genetic variants, aging traits) to predict outcomes or identify the most likely path to outcomes. Probabilistic networks are known as the "Ferrari" of machine learning because of their numerous advantages for modeling complex systems, the many years of work that shape their learning structure and network parameters, and their incorporation of probabilistic reasoning. Importantly, one model can be used for a variety of tasks. However, the massive size of omics data presents unique challenges for BN-based modeling—while datasets may be ready for ML algorithm modeling, the algorithms themselves may need further development to process that data fast enough. Further work also needs to adapt ML methods to the unique needs of multi-omics data, in part by accommodating for both observational studies and the development of interoperable omics summaries.

The complex BN networks generated by compiling genetic, multi-omic, and multi-phenotype data in a BN algorithm can be simplified using data reduction and summarizing techniques. To work with massive omics datasets, Dr. Sebastiani's group is adapting the work in genetics that developed polygenic risk scores to develop omics risk scores for DNA methylation, proteomics, metabolomics, and transcriptomics. These scores are not only linked to aging but can be linked to any aging trait. However, the development of standards is needed to generate omics summaries that are scale-free and platform- or study-independent. To better summarize phenotypic data obtained from the administration of multiple neuropsychological tests, Dr. Sebastiani's group is using cluster analysis to identify cognitive signatures that can be used to stratify individuals into subgroups based on patterns of performance in different cognitive domains. This type of analysis has revealed patterns of variables associated with good multi-domain cognitive performance that are clearly related to genetics.

Many additional challenges remain for modeling the interactions between genetics, multi-omics, and multi-phenotypes. To address issues related to developing BNs from correlated data (e.g., data from related family members), Dr. Sebastiani's group developed "mixed effects BNs"

to learn and quantify networks from family data; they are now developing resampling methods to learn Gaussian networks from clustered data to improve computation efficiency. Furthermore, one big challenge is shifting to build dynamic models that can address the complexities of massive multi-omic and multi-phenotype datasets that are influenced by the range of environmental exposures and change over the life course. Additional challenges include adapting ML methods to challenges in observational data (rather than adapting challenging data to existing methods), issues related to data-sharing with the ELITE program that is part of the AD Knowledge Portal, and the need for benchmark data (e.g., synthetic data) to enable objective and robust evaluation of methods.

### **Microscopic Imaging of Epigenetic Age and Chromatin Heterogeneity**

*Alexey Tersikh, PhD, Sanford Burnham Prebys Medical Discovery Institute*

Quantitating biological age or functional age—the aging that occurs with gradual accumulation of damage to cells and tissues in the body—is of key importance for understanding aging and potentially much more important than knowing chronological age. It is now well understood that aging is a complex phenomenon and much of the complexity is related to epigenetics, with a set of genes that faithfully maintain function early in life then begin to fail in later life. Several tools and approaches have been developed to study biological or functional age, including DNA methylation clocks and serum analytes. To overcome limitations of these approaches, Dr. Tersikh's group developed an approach to image epigenetic age in single cells, which they call "miEpiAge." The fundamental concept behind this approach is that the global landscape of epigenetic modifications confers a specific chromatin state that is essential to cell identity and can be microscopically imaged to understand the trajectory with aging.

The miEpiAge approach is based on determining the distance matrix between individual measurements with no prior assumption of connectivity (e.g., aging linearity). miEpiAge has single-cell resolution by design, employs all possible epigenetic modifications (including DNA methylation), and is combinatorial in nature (e.g., by using multiple markers), cost effective, and uniquely suitable for *in situ* analysis of aging. The miEpiAge method entails staining cells using antibodies to epigenetic markers for methylation and acetylation (e.g., DAPI, H3K4me3, H3K27me3), high throughput imaging using a multi-well format, and image feature extraction to extract about 250 features per channel, followed by computational ML approaches.

Dr. Tersikh's group has demonstrated the usefulness of miEpiAge for identifying different cell types, drug screening, analyzing effects of environmental compounds, and, more recently, to study aging. Initial studies of single cells from liver demonstrated that analyzing epigenetic signatures using miEpiAge could reproducibly separate young and old hepatocytes. Subsequently, Dr. Tersikh's group investigated the emergence of epigenetic age in mouse CD3+ peripheral blood mononuclear nucleus cells (PBMCs) from 53 to 968 days of age. Plotting the data as the distance from the centroid of young mice to the distance from the centroid of old mice showed that cells fell on a line, which they called the epigenetic age ("EpiAge") axis. Based on simple linear regression, progression along the EpiAge axis was correlated with chronological age in PBMCs and CD3+ PBMCs. Aging trajectories were further analyzed using

two independent approaches. First, principal component analysis (PCA) was used to plot the signatures along the PC1 and PC2 components. The PC1 component easily separated CD3+ and CD3- cells, whereas the PC2 component extracted the aging axis, like the EpiAge axis. Second, hyperbolic space was used, which is an emergent type of embedding that can better handle multidimensionality and is particularly suitable for hierarchically organized biological data. Geodesic projections of both CD3+/CD3- cells and age-labelled cells in hyperbolic space revealed the emergence of an epigenetic trajectory with age like that seen with simple PCA analysis. Together, these analytical approaches suggest that imaging of the epigenetic landscape in PBMCs and CD3+ cells result in emergence of the intrinsic epigenetic aging trajectory without additional regression or other mathematical techniques.

Several examples further illustrate the power of the miEpiAge approach. Imaging of five solid organs (brain, heart, kidney, liver, and skeletal muscle) from mice 2 to 27 months of age also revealed the progression and emergence of the aging trajectory. The brain, which ages slower than other organs based on the DNA methylation clock, also aged slower using the EpiAge approach. In addition, aging of brain and heart was also correlated, consistent with findings using other methods. Studies of functional perturbations known to affect health span and lifespan showed that mice treated with doxorubicin (a chemotherapy agent known to accelerate aging) have an older epigenetic signature than untreated mice and that mice subjected to caloric restriction (an intervention known to slow aging) have a younger epigenetic signature than untreated mice. To investigate whether epigenetic age in skeletal muscle was correlated with muscle function in individual mice, skeletal muscle function was assessed using multiple behavioral and metabolic tests. Plotting EpiAge versus a linear combination of organismal readouts revealed that epiAge was correlated with locomotor and metabolic circadian rhythms. Finally, the heterogeneity of chromatin topography in a large population of cells increased exponentially with age. Further, prediction of the maximum lifespan limit of circulating CD3+ T cells from the asymptote of the hyperbolic function yielded an estimated maximum lifespan that fell between that observed in C57BL/6J mice and wild type mice in captivity.

This body of work demonstrates that miEpiAge is capable of uncovering novel characteristics of biological and functional aging. Together, the findings using miEpiAge suggest that epigenetic trajectory and chromatin heterogeneity travel through time and space of the epigenetic trajectory such that the heterogeneity of chromatin increases with age until it reaches the maximum variance compatible with life.

### **Moderated Discussion**

Presenters shared unpublished data including the applied computational tools to analyze large datasets in the field of aging research, discussed the causality and heterogeneity in aging, and raised several challenges, summarized below.

#### ***Bias in Biological Age Prediction***

Various speakers noted difficulties in predicting biological age using transcriptomic, epigenetic, and other biological clocks; a bias appears to exist toward overestimating the age of younger individuals and underestimating the age of older individuals. Furthermore, this bias might be

due to issues with the clocks, survival bias in the population, or both. Dr. Jones and colleagues found this issue to be related to a bias towards the mean in the training dataset. Although computational approaches can be used to address the issue (e.g., regressing out the effect and using the corrected age gap), no one-fits-all solution currently exists, which remains an important area to address in the next several years.

***Issues Related to Scale Across Biological Clocks and Biological Aging***

Data at different scales across the biological hierarchy are currently being used to generate biological clocks. Speakers agreed that there should not be a preferred scale for which biological clocks are built, because physiology of interest at different scales should be modeled, although a common framework for modeling across and between scales probably exists. A major challenge for the field is to determine the best ways to model across scales.

Dr. Gladyshev shared a survey conducted at a Gordon Conference which revealed that scientists in the field of aging have very disparate views of what aging is. Biomarkers of aging built on these different views would therefore be built for different manifestations of aging and have different specific meanings (e.g., a transcriptomic clock versus an EEG clock in cardiology). Dr. Terskikh explained that their approach for imaging epigenetic age does not entail training or regression, but instead (1) images the actual signatures and (2) inquires about information the signatures can provide.

Although Dr. Hao's work addresses the fundamental questions of scale at the basic level of changes in single yeast cells, their goal is to connect to higher organizational levels, including mammalian tissue and animal aging. Although yeast is a good starting point, moving to slightly more complex systems will undoubtedly lead to unexpected challenges, such as the types of data that are needed and can be generated, and will require the gradual building of multi-scale models to help understand the aging process.

***Issues Related to Modeling Dynamics Over Different Time Scales***

Modeling of biological dynamics across a range of timescales is important for understanding changes that span temporal scales from subseconds to decades. A notable example is that epigenetic and transcriptomic biomarkers work at different time scales. Dr. Solodkin suggested that a biophysical modeling approach could yield scaleless universal principles that could be applied, with numerical adjustment, to span the entire hierarchy of temporal and biological scales. Drs. Gladyshev and Jones agreed that applying physical principles and a dynamics complex systems approach is a very promising strategy to go across scales in studies of aging. Although each scale will have unique aspects, developing models at each scale and an understanding of how to relate them in a unified framework would enable robust temporal scaling. Dr. Hao agreed that the nonlinear dynamic models can be applied to different time scales. Dr. Sebastiani noted that studies at the cellular level look at a snapshot in time and not the dynamics or lifecourse of individual cells, suggesting that it might be easier to model the hierarchy of events in a lifecourse experiment at the cellular level that evolve over seconds to hours compared to modeling a human lifespan that evolves over decades and years. Dr.

Terskikh responded that he and his colleagues are building genetically engineered probes that could enable longitudinal monitoring of changes in live cells.

### ***Key Challenges for Using Computational Approaches to Model Aging***

Each speaker addressed what they view as the single most important challenge to overcome that unique to modeling aging using computational approaches and what it would take to overcome that challenge, summarized below.

- Dr. Sebastiani noted that the biggest challenge for modeling human data is to transition from modeling one point in time to modeling dynamical systems with many feedback loops. Overcoming this challenge requires more temporal data and consideration of sampling frequency as well as the development of new computational tools.
- Dr. Terskikh explained that the most important challenge is to understand causality and causal phenomena; he suggested two things that could help overcome this challenge. First, longitudinal studies and dynamical modeling are critical. Second, the Granger causality test could be used to determine whether one time series can predict another and evaluate causality among two co-regulated phenomena.
- Dr. Hao speculated that technology advancement for generating data is the key tool needed to measure, characterize, and perturb systems dynamically and thus enable building dynamic mechanistic models.
- Dr. Gladyshev reiterated the Gordon Conference survey, which found that the most important question to scientists in the aging field is to “understand aging.” Dr. Gladyshev agreed that reaching a common understanding about what the essence of aging is required to be able to target and treat aging-related diseases. Dr. Gladyshev suggested that NIA could consider developing new initiatives to address this issue.

Speakers from both Session 1 and 2 shared additional thoughts about these challenges. In addition, Dr. Jones agreed that developing a definition of aging is the most important question and suggested that once that question is answered, all the issues related to data collection, scale, interventions, and how and what to model can be addressed. If, for example, the appropriate framework is dynamic oscillatory phenomena that maintain balance or function within healthy limit cycles and avoid degenerative or unhealthy states, then Dr. Hao’s approach could apply across many scales.

Furthermore, Dr. Sebastiani observed that as multi-dimension data is obtained, data integration is very difficult and has many unexpected challenges. Dr. Terskikh thinks that it is important (1) to advance the integration of different datasets and knowledge from single cells to understand how it affects the function of an organ and an organism and, (2) in the context of aging, to understand which functions are causal. Dr. Hao suggested that the next big question is to determine whether the principles learned from single cells can be applied across scales to understand tissues, organisms, and aging.

## **Session 2: Computational Analysis of Large-Scale Brain Systems**

*Session Chair: David Jones, MD, Mayo Clinic University*

## **From Clockwork to Emergence: A New View of the Brain**

*Earl Miller, Ph.D., Massachusetts Institute of Technology*

Technological advances in recording electrical activity in the brain over the past couple of decades have led to an evolution in our view of how the brain processes information. The advent of multiple-electrode recording approaches to simultaneously record from hundreds to millions of neurons has enabled an increased understanding of the brain at the network level and the emergent properties and mechanisms that can only be discerned when the parts interact as a wider whole. This technology enables the recording of local field potentials (LFPs), which are the averaged activity a targeted group of neurons, and electric fields (EFs), which represent the activity of large groups of neurons, rather than simply recording spikes from single neurons. Studies using the multiple-electrode approach have revealed that information relevant to function is present at each of these levels.

To understand cognition and its dysfunction in disease, Dr. Miller's lab studies executive brain functions (e.g., planning, focusing attention, learning, organizing thoughts) by recording electrical signals from the brains of non-human primates and uses computational modeling and analytics to make sense of the signals. Through a series of studies aimed at explaining how the brain learns abstract concepts or principles, Dr. Miller's lab found that the prefrontal cortex (PFC) absorbs and uses top-down information to control the flow of activity across cortex and that its neurons throw away irrelevant details to learn tasks at the level of rules and principles, as would be expected for goal-directed behavior. The subsequent use of multiple-electrode technology to simultaneously record from hundreds of neurons in the PFC and other higher cortical areas revealed that specific tasks produced activity in 30 to 40 percent of randomly recorded neurons, as if the task took over the brain. These findings countered the 20<sup>th</sup> century paradigm that every neuron had one function, which predicts a diverse group of specialized neurons with distinct functions rather than large populations of neurons that seem to have the same function. Many years of subsequent investigation has shown that cortical neurons do not have one function but are instead selective for complex non-linear combinations of many features with no obvious relationship—a property called “mixed selectivity”—and that individual neurons are multifunctional, exhibiting different functions in different tasks.

Why are mixed selectivity neurons so important for high level top-down information? Mixed selectivity provides computational horsepower to the brain by enabling a wide range of information to be combined in a single population of networked neurons. This property provides a high dimensional representation of space that makes the brain smarter, increases storage capacity, and enables faster learning and cognitive flexibility. However, mixed selectivity requires a new way of thinking about the brain in which neurons have more than one function and are members of multiple networks rather than anatomically unique neuronal ensembles, which raises the question of how individual multifunctional neurons are selected to form a particular network and participate in specific tasks. One hypothesis is that the brain self-organizes through the generation of neural oscillations—or “brain waves”—a property that emerges from the synchronized activity of millions of neurons. This type of large-scale organization is precisely what is needed for top-down executive control, which requires

coordinating and directing large parts of cortex toward a specific task. Dr. Miller's lab recently showed that the contents of working memory can be read from electric fields near the brain independent of representational drift by individual neurons.

Substantial evidence now supports the idea that brain activity is organized by brain waves, such that neurons that “hum together, wire together (temporarily)”, and that brain anatomy provides the infrastructure that underlies where neural signals can flow. However, patterns of brain waves direct the moment-to-moment flow of neural activity (e.g., thoughts) through this underlying anatomical infrastructure. For example, task-switching studies revealed that different neuronal ensembles based on synchronized LFP dynamics emerged during different tasks. Furthermore, different brain wave frequencies were found to carry distinct types of information (e.g., sensory signals, executive control). Finally, studying the precise patterns of traveling brain waves provided insight into their role in computations during working memory tasks. Together, this body of work has led to a paradigm shift in our understanding of the brain by showing that the neural activity underlying cognition is complex, dynamic, and rhythmic and that the emergent properties like brain waves that organize brain activity play key roles in cognition and consciousness.

## **How a Biophysical Generative Model Gives Unique Insights into Aging and Dementias**

*Ana Solodkin, PhD, University of Texas at Dallas*

Biophysical and biologically based computational models use *in silico* simulations of brain activity to study multiscale questions in neuroscience, with the aim of using reverse engineering of the human brain to discover the mechanistic principles of brain function and dysfunction. These models use mathematical algorithms associated with the biophysics underlying the neural activity that governs brain dynamics and simulations that reflect the spatio-temporal evolution of the system. Dr. Solodkin and colleagues aimed to address these issues using a multi-scale neuroinformatics platform called [The Virtual Brain](#) (TVB).

TVB generates simulations of native brain signals (e.g., neuronal firing rate, LFPs, seizures) that are derived from the estimation of biophysical parameters. These parameters are associated with two different scales: 1) interactions between brain regions and information transfer delays derived from individualized DTI structural connectomes and 2) local level (mesoscopic) brain dynamics generated by a set of mathematical algorithms that were developed through the years based on basic neuroscience research. The simulated brain signals are validated by generating simulated rsfMRI, EEG, and MEG signals via a forward solution that allows the fitting of simulated and empirical signals. Once the model is validated, reverse engineering is then used to identify the local and global biophysical parameters associated with brain function and dysfunction linking activity across scales.

Dr. Solodkin illustrated this approach by describing a proof-of-concept study that included individuals with cognitive assessments categorizing them as healthy controls, mild cognitive impairment (MCI), or AD. Modeling was done on both the whole brain and in eight subregions of the limbic subnetwork associated with Braak and Braak stages of Alzheimer's disease (entorhinal cortex, hippocampus, amygdala, etc.). The bottom line is that the simulation

obtained in the limbic subnetwork resulted in a more sensitive measure of early brain changes that occur during the progression to AD, with two parameters showing the most dramatic changes. First, at the local dynamical level, inhibition was decreased locally leading to higher excitability. Second, there was an increase in one parameter associated with the interaction between regions, called global coupling, which can be interpreted biologically as brain modulation produced by a change in the gain of the weights of the structural connections. One interesting feature that emerged from this study was a high degree of variance in the limbic subnetwork of the MCI group; this finding likely reflects the heterogeneity of the MCI cohort, which clinically is composed of converters and non-converters to AD. In addition, the covariance between the model parameters and cognition was much higher than the covariance between the structural and functional connectomes and cognition, suggesting that the model parameters predicted cognition better than current neuroimaging data metrics.

The physiology of the system was studied by using mathematical modeling to untangle the local dynamics and global dynamics to obtain a representation of individualized brain function. In this model, progressively increasing the strength of the structural connections yielded a bifurcation point unique to each individual where the system changed states and the phase transitioned from disordered activity to synchronized oscillations. This finding is consistent with evidence that complex systems undergo phase transitions that produce systemic changes in functional connectivity. The oscillations were only observed in the posterior cingulate region, which is intriguing in the context of AD, given that its changes in metabolic rates have been used as a biomarker for vulnerability to AD.

Together, these studies show that TVB provides a multi-scale method for investigating the brain's dynamic repertoire as a function of structure that is geared to characterizing realistic biological mechanisms of brain function and dysfunction. Profile measures can also be repeated in individual participants to monitor aging or disease progression. The approach is translatable and can test inputs derived from animal models and can also be used clinically for designing novel interventions and implementing virtual therapies. This type of approach provides the opportunity to gain insight into the mechanisms underlying aging and AD that can be combined with observations at other scales.

### **Clinical Utility of a Global Information Processing Model for Mental Functions**

*David Jones, MD, Mayo Clinic*

The computational behavioral neurology framework is grounded in a pragmatic scientific process for mental functions, with the goal of providing an explanatory model to ask questions about clinically relevant functions. Within neuroscience field, this framework consists of mental functions that correspond to biophysical dynamics occurring in the brain during an organism's intrinsic and extrinsic interactions, and, in the context of an aging and AD/ADRD research, consists of age-related degeneration of mental functions that correspond to a gradual and progressive failure in biophysical dynamics occurring in the brain during an organism's intrinsic and extrinsic interactions that lead to disability. Various levels of abstractions for these biophysical dynamics exist in genes, molecules, cells, circuits, large-scale systems, mental

functions, and activities of daily living. Dr. Jones and his colleagues focus on using large scale patterns in the brain, referred to as “modes of function” or “eigenbrains,” which are analogous to global traffic patterns superimposed on brain structure. These modes of function can be used to answer clinical questions about brain-behavior mapping, to describe specific brain patterns in patients, and to accurately separate clinically normal individuals from those with a variety of dementia syndromes.

Large-scale patterns in the brain can be described in multiple ways. Although early work focused on “networks,” more recent descriptions include “co-activation patterns,” “functional connectivity gradients,” “quasi-periodic patterns,” “propagating waves,” and “superposition of standing waves.” The historical origins of these neuroscience patterns come from fluorodeoxyglucose positron emission tomography (FDG-PET), which reflects spatial patterns of brain glucose uptake and metabolism. As early as 1983, work using FDG-PET suggested that the abnormal behavior associated with dementia may be related more to disturbed functioning of surviving tissue than to the loss of brain substance itself. Since then, evidence has continued to accrue to support this idea. For example, studies using FDG-PET have revealed characteristics of brain metabolism across the AD spectrum, including a clinically relevant preservation of metabolism in primary cortices and subcortical structures. In addition, some areas of the brain were found to be less metabolically active during certain cognitively demanding tasks and called the “default-mode network.” Subsequent studies found that the default-mode network is abnormal in early AD. Although the field has not arrived at a consensus for what to name these large-scale patterns, clustering analysis reveals four distinct patterns in FDG-PET images in AD.

Comparisons of brain FDG-PET and tau-PET images from patients with AD revealed corresponding and overlapping patterns of glucose uptake and tau protein across several AD modalities, including memory, language, visuo-spatial, executive, motor, and behavioral predominant disorders. Alongside other studies on more focal modalities, these findings demonstrated that data from FDG-PET negated the necessity of tau-PET. The sufficiency for FDG-PET was supported such that Dr. Jones and colleagues were able to use FDG-PET to build a deep neural network that simulated a tau-PET scan. More recent work shows, for example, that FDG-PET can identify mixed patterns and pathology corresponding to mixed dementias and can also reveal structural problems corresponding to dysregulated CSF dynamics rather than neurodegenerative disease, which is a clinically important distinction. Using dimensionality reduction of pattern variability, Jones and colleagues found that ten simple underlying patterns were sufficient to describe all the features they observed in brain scans. Further, patient brain scans can be described as a combination of these ten eigenbrains that can be related to neural networks seen in fMRI, cognition, symptoms, and syndromes.

Based on this evidence, Dr. Jones and colleagues propose that FDG-PET can play an important role in the evaluation of patients and can answer three categories of etiological questions: (1) whether a disorder is neurologic or non-neurologic; (2) if neurologic, whether it is degenerative or non-degenerative; and (3) if degenerative, whether it is AD, LBD, or FTD spectrum. Defining the etiology of brain disorders based on relatively simple underlying patterns allows for targeted therapeutics, counseling, management, and clinical trials. This body of work suggests a

new paradigm for neurodegenerative diseases that is based on degeneration of large-scale population dynamics rather than network-based structural neurodegeneration.

## **Using Network Control Theory to Formally Model the Energetics of Brain Function**

*Dani Bassett, PhD, University of Pennsylvania*

The human brain is a notable example of a networked biological system that is composed of regions that perform specific functions and engage computations. Those regions are interconnected by tracts of neuronal axons along which information-bearing electrical signals propagate. Recent work has focused on using a variety of statistical measures to characterize patterns of activity, with the goal of understanding how those patterns constrain the passage of information. Because the pattern of information flow determines the sorts of functions the brain can support, understanding structural network constraints is key to understanding healthy human brain function and its alteration in disease.

Recent efforts have expanded the investigation of structural constraints in several ways. First, the field has seen an increase in the sensitivity of measurements. Diffusion-weighted MRI, which is typically used in humans, has become increasingly sensitive to microstructural integrity, and provides estimates of tract locations at finer and finer spatial resolutions, an advance made possible by increased scan time, an increasing number of diffusion directions, and improved analysis algorithms.

Second, the field has focused on developing data-informed computational models that allow investigation of structural constraints differently and quantitative assessments of how network architecture affects the brain's potential or actual dynamical repertoire. One promising example of such a model is the network control model, which is based on theoretical work in systems engineering. The idea of network control theory is that it provides a mathematical framework that determines which perturbations can drive a networked dynamical system to a desired state and enables the study of how exogenous input (e.g., via sensory input) can change the state of the system. Network control theory asks questions about the types of inputs that can drive the system from some initial state to some final state, what sorts of final states are possible to get to, and how those final states are achieved.

A network control model stipulates precisely how activity flows along structural connections, which is made possible by defining the dynamics of the system according to the location of the structural constraints. Conceptually, the model formalizes the idea that the state of the brain in the future (i.e., patterns of activity) depends on the current state of the brain and where its current activity can flow along structural connections. That dependence is modulated by exogenous input in a way that takes energy, with the amount of energy required depending on structural constraints. Therefore, state transitions depend not just on patterns of activation, but also the network of neurons underlying those patterns. Network control theory allows questions to be asked about the amount of energy required to move the brain from an initial state to a final state.

The third reason that recent efforts have expanded the investigation of structural constraints is a conceptual shift in explanations for cognition. Although considerable progress has been made from activity-based explanations for cognition, recent work is also studying a complementary structure-based explanation, which suggests that a dynamical process is constrained by the structural network that connects the regions involved. Therefore, the cognitive process is explained by both the pattern of activation and the relation between that pattern and the pattern of connectivity underneath. Dr. Bassett illustrated this idea using the example of “cognitive effort,” a term that refers to the engaged proportion of limited-capacity central processing, and is correlated with task difficulty, task novelty, and a variety of individual factors (e.g., age, neural differences). Among the potential ways to measure cognitive effort, Bassett described how the cost of orchestrating complex activity dynamics on a network can be operationalized by network control theory, and specifically by the control energy estimate (CEE). The resulting data showed that transitioning from a less cognitively demanding state into a more cognitively demanding state (e.g., from an attention state to a working memory state) required more control energy than transitioning out of a more cognitively demanding state.

These three expansions of measurement, modeling, and conceptual approaches provide a richer understanding of how the brain’s structural network constrains the flow of activity through the brain, thereby influencing the types of computations and functions that can be performed. These computational advancements are enabling new insights into the cognitive processes that mediate healthy brain function and its dysfunction in aging and disease.

## Moderated Discussion

### ***Energy Requirements and Costs for State Transitions and Changes During Aging***

Dr. Bassett clarified that the cognitive effort study aimed to both understand the energy required for state transitions from lower to higher cognitively demanding tasks and to evaluate the dual-state theory of dopamine function, which suggests that dopamine receptor function can alter the brain’s energy landscape and change the flexibility of state transitions. This study found that distinct type 2 dopamine receptor function, either through genetic or pharmacological manipulations, can explain the energy difference and, importantly, enables connecting brain and neurotransmitter function.

Dr. Bassett also addressed the relationship between different cost measures and frequency bands, and whether insight can be gained from investigating the energy costs of switching from alpha- to gamma-dominated states. Although most of Dr. Bassett’s work thus far has used fMRI, one study that examined power states across regions, particularly frequency bands, suggested that the model is relevant to addressing changes in power across frequency bands, although they have not yet examined the energy required to move from or to alpha.

Dr. Solodkin asked about the energy construction during aging, noting that despite subtle structural changes, network stability tends to become less dynamic, and, specifically, about the relevant considerations for capturing functional changes that are modified in very subtle ways over an extended period. Dr. Bassett explained that the CEE depends on changes in both structures, which can be very small, or in activation patterns, and that the combination of those

two variables informs the (CEE). Because changes in both activation profiles and structure occur during aging, the CCE would sense that. One way to ask which variable is the stronger CEE driver during aging is to compare the energy required using a structural connectivity template derived from young healthy adults to the energy required using an aging individual's true structural connectivity; this will provide an estimate of the consequences of structural changes on the CEE as well as the effects of activation pattern changes.

Regarding the broader issue of changes in control energy with age, in youth between 8 and 22 years of age, Dr. Bassett observed a marked decrease in the CEE for activation of frontoparietal cortex with age, which is consistent with individual differences in executive function and suggests that the CEE approach can be used across timescales in the lifespan. Drs. Bassett and Solodkin discussed whether this observation might be related to developmental increases in myelination and thus produce increased synchrony of signals; this could be addressed by determining the degree to which myelination estimates from T1/T2 ratios and control energy are correlated.

### ***Hierarchy of Scales Across Time and Space***

Presenters discussed issues related to time scales and length scales in the context of larger-scale networks, including stability and representational drift, and whether there are preferred time and length scales or a hierarchy of scales, and how different computations and behaviors are represented at different time and length scales. Dr. Miller recommended that oscillation bands of different frequencies not be thought of as having specific functions. Frequency bands were arbitrarily designated over 150 years ago and do not correspond to true functional differences; rather, they should be viewed as different energy states of the network that are compatible with different functions. Generally, gamma occurs during high levels of spiking, whereas beta and alpha occur during low levels of spiking. Thus, for example, lower frequencies that act on a larger spatial scale are thought to be used as a top-down control mechanism and higher frequencies carry feed-forward sensory information to create motor output.

### ***Challenges Unique to Modeling Brain Aging Using Computational Approaches***

Each speaker addressed unique challenges and limitations in the specific context of applying computational approaches to brain aging, summarized below.

Dr. Jones and colleagues apply age-prediction models to data (e.g., FDG-PET) and use deep neural networks to predict biological age, compare that to chronological age, and explore features the model uses to make that prediction. This approach can provide information about biological mechanisms at the scale and physiology of the data being used. With FDG-PET, which uses changes in brain energy, and functional MRI data, a transition is observed where age-prediction in younger individuals is more dependent on the frontal lobe and in older individuals is more dependent on the back of the brain. However, age-prediction using structural MRI uses different features (e.g., CSF dynamics). One challenge is to develop a framework for understanding what the gap between biological age estimates and chronological age using these approaches and perspectives means for brain function.

Dr. Solodkin remarked that challenges unique to aging come up repeatedly in modeling brain aging and is an extremely relevant issue. One role of modeling is to identify the bare bones in messy real-world data that are relevant to a specific situation. Thus, modeling will never be perfect, but can be useful. Key metrics of a model's usefulness are its predictive value and its ability to generate testable mechanistic hypotheses. The bidirectional link between models and basic research data—from molecular to the whole brain—is fundamental.

Dr. Miller whole-heartedly agreed with Dr. Solodkin's comments, noting that many of the hypotheses regarding dynamics he and his colleagues are testing are based on computational models. Although figuring out cognition from first principles is extremely difficult, models can identify unanticipated properties and predictions that can be tested experimentally. This interplay between modeling and experimentation enables an iterative process of refining models and making predictions. Dr. Jones agreed with this view and added that, pragmatically, models can be used to ask clinically useful questions about the relationship between large-scale brain organization and cognition, which is difficult to understand at the cellular or circuit levels. For example, the tight correlation between FDG-PET patterns and the cognitive symptoms and syndromes indicates that this link is important. Models provide a framework for asking questions, even if the models are not absolutely "true."

### ***Making Predictions Using Computational Tools***

Presenters discussed the types of predictions, particularly those beyond cognition, that can be made using computational tools. Dr. Jones described recent work showing that FDG-PET can be used to classify subphenotypes of dysexecutive AD and predict clinical trajectories. Dr. Miller's lab has developed a model of sensory overload in autism caused by an imbalance between low and high frequencies in which weak low frequencies cannot filter out unwanted sensory signals and result in sensory overload. A series of investigations is now underway to use closed-loop electrical stimulate to manipulate the rhythms to crease a disease-like model of sensory overload and test treatment paradigms. Dr. Jones thinks that Dr. Miller's modeling approach ties together Dr. Bassett's work in brain energetics to diagnose and prognose with models of potential treatment paradigms. For example, it may be possible to identify and enable less energetic state transitions to treat patients so they can achieve a functional space to perform executive functions again. Dr. Miller described experiments using the new technology of ultra-fast closed loop stimulation, which is aimed at using non-invasive electrical stimulation as a viable path towards actual treatment.

### ***Takeaway Gaps and Opportunities***

Each speaker shared their thoughts about the biggest takeaway gap or opportunity in computational analysis of large-scale brain systems.

- Dr. Miller noted that the 21<sup>st</sup> Century is the century of understanding the brain's emergent properties because the pieces are now well enough understood to look at that level.
- Dr. Solodkin recommended a paradigm shift to address mechanisms of both aging and brain dysfunction; the approach should include individualization of measures because that might be a way to push towards precision medicine.

- Dr. Jones suggested that the field needs an ontology for the large-scale organization of the brain that everyone understands and agrees upon and that relates to certain clinical syndromes and symptoms. A model of ontology would facilitate developing relevant cognitive measures and interventions.
- Dr. Bassett indicated the need to evaluate, understand, and connect brain energetics from different perspectives. The multiple measurements, models, and perspectives of brain energetics provide a constraint on the system that has the potential to push the field forward.

## Session 3: Computational Analysis of Complex Behavior

*Session Chair: Anne Collins, PhD, University of California at Berkeley*

### Using Computational Modeling Approaches to Reveal Cognitive Processes Underlying Changes Across the Lifespan

*Anne Collins, PhD, University of California at Berkeley*

Dr. Collins presented the benefits and risks of using computational modeling to understand behavior. Even simple behaviors and decisions employ a multitude of behavioral facets. For example, choosing between two food items will include processing the history of reward, short-term memory, episodic memory, exploration, and heuristics. One benefit of computational modeling is the ability to compare and validate models against individual patient data. Comparison and validation then enable researchers to quantitatively arbitrate among hypotheses regarding cognitive processes. The ability to use parameters, which may allude to neural mechanisms, to tune models and experimental processes is a second major benefit of computational modeling. A third benefit of computational modeling is access to latent variables, which may probe cognitive processes as neural mechanisms.

However, computational modeling has limitations. A model may pass all validation checks in an experiment without being meaningful or generalizable. This lack of meaning and generalizability may result from poor experimental design or may result from the model being “overexpressive” and thus failing to properly relate components of cognition. Alternatively, a model may over-attribute behavior to one group of processes. Similar learning tasks may be well fit by reinforcement learning (RL) despite recruiting different underlying processes; these fits may thus lead to failure of generalizability. Different models may also capture the same behavior similarly well, leading to a lack of clarity on the actual underlying processes. To avoid these limitations, modelers should bridge to lower levels of computational modeling and should test generalizability, as well as designing experimental tasks while considering different processes.

Sufficiently sophisticated computational modeling approaches that account for these limitations may elucidate how aging and disease affect decision making or other behaviors. Modeling may identify differences in how processes are recruited across age groups or modulated with age. Dr. Collins described a mathematical cognitive modeling approach that uses the framework of RL, in which a person makes choices based on estimated value of the outcome; feedback leads to updating the valuation. Simple experiments in which subjects

repeatedly choose between two options enable researchers to manipulate load, short term delay, cumulative reward, and positive and negative outcomes. Results of such experiments indicate that the effect of set-size on learning performance is not fully accounted for by classic RL. These results were age-dependent; using a sample of populations aged 8 – 12, 13 – 17, and over 18 years, researchers found that the effect of set-size decreases with age. Simultaneously, increasing age correlates with an increase in accuracy. Tuning these parameters revealed that noise decreases with age and learning rate increases. Some data indicate that older adults have impaired learning relative to younger adults, and that their decision making is more affected by set-size. These analyses suggest that the group differences are best explained by differences in working memory function.

### **Computation Conquers Complexity – Decomposing Behavior to Understand the Components of Cognition**

*Robert Wilson, PhD, University of Arizona*

Dr. Wilson's research team develops computational and mathematical models that capture a wide range of behavior, from "simple" lab-based tasks (e.g., perceptual decisions, optimal training, exploration-exploitation) to real-world complex behaviors (e.g., navigation, detecting phishing emails). Dr. Wilson highlighted experiments and models of exploration-exploitation, which describes decisions that involve choosing between novel and familiar items (e.g., your food choice at a familiar restaurant). Choosing the familiar item exploits a known outcome, while choosing the novel item guarantees exploring an unknown, but potentially better, outcome. Inspired by computational and machine learning literature, Dr. Wilson's team proposed that people use two computational strategies to solve explore-exploit problems. Directed exploration is driven by information-seeking or choice, while random exploration is driven by behavioral variability or chance.

Dr. Wilson described a task that disentangles these two exploration strategies. Choosing between a familiar and a novel item is influenced by the chances of repeat opportunities. One means of testing these differences in the lab is using slot machine gambling. Rewards occur along a Gaussian distribution, and subjects only have information from outcomes. Using forced trials to present more information for one option than another, the researchers can identify how subject behavior varies as a function of the number of future choices. From this experiment, Dr. Wilson's lab can generate a psychometric choice curve. A simple model then quantifies the decision variable as a function of differences in reward, information bonuses, and decision noise. Current findings indicate that the information bonus and decision noise increase with "the horizon," providing evidence for the existence of directed and random variation. If little chance exists of encountering a given dilemma again, a person is facing a short horizon and is thus more likely to choose exploitation of the familiar item. In contrast, if the person expects to repeatedly encounter that dilemma, they face a long horizon and are more likely to choose exploration with a new item. Results also indicate that the effects of horizon length increase with age from young teenagerhood to middle age, that middle age and older adults are more ambiguity averse than teenagers, and that random exploration declines with age.

Dr. Wilson also described a set of experiments that indicate the likelihood of subjects detecting phishing emails. His team developed a Phishing Email Suspension Test (PEST) that involves subjects rating emails as safe or suspicious; results from the task are analyzed with signal detection theory to compute bias and discrimination scores. Comparison with real-world data confirms that individuals who are more susceptible to phishing are worse at the in-lab task, suggesting that similar cognitive components and computations are employed in both settings. Cognitive neuroscience methods can be added to these tasks to develop neural network models that capture the complexity of these decisions. Current low-dimensional neural network models can predict phishing susceptibility—or how an individual will respond to a given email—with 75 percent accuracy; Dr. Wilson noted that older adults are more likely to not recognize a phishing email.

### **Towards Naturalistic Reinforcement Learning in Health and Disease**

*Angela Radulescu, PhD, Icahn School of Medicine at Mt. Sinai, Center for Computational Psychiatry*

Dr. Radulescu's lab studies naturalistic behavior to determine whether similar cognitive processes are used across tasks and whether those processes change with age. Using virtual reality in combination with computational modeling facilitates these studies without sacrificing the controlled environment of laboratory experimentation.

To study how people identify goal-relevant features, Dr. Radulescu's thesis focused on a multidimensional RL task. In this task, subjects choose repeatedly among three stimuli (e.g., faces, landmarks, tools) and only sometimes receive rewards; choices are more likely to yield rewards if participants select a specific feature within the relevant dimension. Thus, efficient state representation of the task requires selective attention to only relevant states for representing stimulus categories. Dr. Radulescu and collaborators used eye-tracking and pattern classification methods of fMRI data to decode the probability that participants attended to each of the three dimensions on a given trial. This trial-by-trial index of selective attention was used in a behavioral modeling framework called attention-weighted RL. Attention-weighted RL assumes that, during choice, individuals compute the value of a particular stimulus as a linear combination of the features of the stimulus weighted by the attention index (i.e., how much attention each feature attracts). Then, during learning, people update expectations using a trial-and-error mechanism based on reward prediction error weighted by attention.

To determine how timing of attention interacts with learning, Dr. Radulescu and co-authors compared the ability of four models to predict the choices participants made. These four models were (1) uniform attention to all features, (2) attention at choice only, (3) attention at learning only, and (4) attention at choice and learning. Results of these comparisons suggested that individuals use attention at both choice and learning, selectively evaluating the world before acting and reflecting on features following action. This evaluation and reflection process can be formalized using statistical inference to develop inference-guided attention, a model that assumes that individuals have a finite memory cache in which they store recent

observations and rewards. Individuals subsequently use that cache to reflect on previous trials and to compute a proposed distribution for new hypotheses regarding the task, then redirect attention in accordance with those hypotheses. Eye-tracking data indicate that the dynamics of gaze data are more consistent with the inference model rather than trial-and-error learning. This experimental framework can be used to elucidate individual differences in RL across the lifespan; one such experiment indicated that, compared to younger adults, older adults may spread attention over a narrower set of features when learning in a multidimensional environment.

Dr. Radulescu's recent work aims to generalize models and ideas to natural decision making by modeling a well-studied behavior—visual search—in virtual reality. Participants search for a target object during eye-tracking, which enables researchers to determine which aspects of a realistic visual scene guide gaze behavior (e.g., contextual cues, object identity). Algorithmic approaches of RL models trained to complete this task can be compared to actual human gaze behavior. Model comparisons over different state representations indicate that individuals use both shape and color to conduct this task; however, the strategies used indicate that people use a higher order combination of features with a relatively low-dimensional representation.

### **Relating Individual Differences in Learning to Markers of Alzheimer's Disease**

*Karolina Lempert, PhD, Adelphi University*

Dr. Lempert's research team studies economic decision-making in older adults (e.g., estate planning, retirement savings, health care). Aging changes the neural systems associated with learning (e.g., medial temporal lobe), which affects the ability of older adults to reach decisions that involve new learning. Two central objectives guide Dr. Lempert's work: (1) a diminished ability to learn and update values in cognitively normal older adults may contribute to suboptimal decision-making in this group and (2) individual differences in those learning processes may indicate heterogeneity in pathologic alterations within older adults, even in the absence of functional impairment.

One means of learning the values of new stimuli is trial-and-error with probabilistic feedback. The striatum and amygdala are integral to this type of learning; notably, the amygdala, located in the medial temporal lobe, may be particularly susceptible to age-related neurodegeneration. To study this learning ability, Dr. Lempert's team uses a feedback-driven value learning task in which participants choose between two objects that represent lotteries and subsequently receive feedback on a payout associated with that object. Participants must determine the value of that payout; however, the feedback of the object's actual value is only accurate 60 percent of the time. Young adults (ages 18 – 39) outperform cognitively normal older adults (ages 61 – 92); however, older adults still outperform chance, indicating successful learning.

Dr. Lempert's team developed a reinforcement learning model using a hierarchical Bayesian method to determine the cognitive processes underlying behavior in this task. In this model, the expected value of any stimulus is updated based on prediction error (PE), or the difference between the reward on the trial and the expectation. The model that best fit these data included three free parameters that varied among subjects: positive PE learning rate, negative

PE learning rate, and a consistency parameter. Older adults were less consistent in choosing higher-valued stimuli compared to younger adults, even though the older adults update stimulus values from PE similarly. This finding supports the hypothesis that learning and updating values may impact economic decision-making, particularly via the consistency parameter.

To test the second hypothesis, Dr. Lempert's team recruited participants from a longitudinal cohort at the NIA-funded Alzheimer's Disease Research Center (ADRC). Many of these participants had existing structural MRI scans, which the team used to measure cortical thickness and volume. Using these data, the team identified an association between the consistency parameter and both task performance and amygdala thickness. This association did not extend to learning rate parameters and did not generalize to other medial temporal lobe structures, implying a specific role for the amygdala in feedback-driven learning. These findings exemplify how computational modeling can divide a complex learning process into component parts, which can then be linked to age and indicators of age-related decline. Dr. Lempert emphasized that task design must be optimized to draw strong conclusions regarding parameters in computational models.

## **Moderated Discussion**

### ***Impact of Aging on Learning and Decision-Making***

Speakers presented computational models using parameters that captured an element of randomness (e.g., noise parameter, random exploration). Notably, each speaker described the relationship of this parameter with age; Dr. Lempert reported a direct relationship, Dr. Wilson reported an inverse relationship, and Dr. Collins reported no change. Task differences may drive the discrepancy in these findings. For example, the task design used in Dr. Lempert's lab precludes distinguishing between directed and random exploration. Her findings may thus indicate either a higher error rate in older adults or greater exploration to reach conclusions. In Dr. Wilson's experiments, this error reduction correlates with slower reaction time, which itself correlates with increasing age. He proposed modeling the reaction time using a drift-diffusion model (DDM), in which a change in behavioral probability can be captured by either a change in decision bounds or in noise of the drift-diffusion process. A more sophisticated model that accounts for reaction time may successfully disentangle these concepts.

Dr. Collins conducts load manipulation of working memory, and Dr. Wilson manipulates the time horizon. These manipulations may facilitate identifying and quantifying parameters of interest. When Dr. Collins used a decay parameter in her model, results indicated no difference with age. Furthermore, the task demanded limited working memory, and thus a different design may have revealed changes of the decay parameter by age.

### ***Parameter Generalizability***

Traditional neuropsychological testing uses a range of tasks to comprehensively characterize behavior. Many of these tasks have been used for a large cohort of individuals; however, they may not be computationally well-defined. Most researchers do not use a battery of tasks, which

are costly. Moreover, they tend to use different or adjusted tasks, which reduces comparability across studies. Researchers must balance new learning with exploiting existing knowledge.

Dr. Wilson suggested that researchers using a battery of measures could determine shared features across a range of tasks. Dr. Russell Poldrack's team recently compared 40 tasks to identify shared features; however, the results were not easily interpreted. Dr. Collins' team has also compared three RL tasks that varied in several dimensions; the team found that although the noise parameter showed some generalizability, the learning rate parameter did not generalize at all.

The number of cognitive processes likely underlying any given behavior reduces generalizability of findings from any given task. Dr. Wilson asked whether a black box neural network approach could reveal generalizable parameters across tasks. Dr. Collins stated that the low number of participants ( $n=300$ ) in her experiments, which included three tasks, precludes successful machine learning training and learning. However, her team used some multiple regression approaches to determine predictability of both experimental parameters and summary statistics. Results indicated most shared generalizability was related to the noise factor, but Dr. Collins noted that predictability using this approach did not surpass other methods.

#### Overexpressivity

Dr. Collins explained that RL provides an example of overexpressive models. This family of models can explain multiple phenomena, including dopaminergic signaling as well as behavior across species. When a model clearly relates to multiple natural phenomena, researchers may assume that those phenomena are necessarily related. This assumption is false; the family of models can explain two different phenomena that are themselves unrelated. Dr. Collins suggested that the field has inappropriately overgeneralized RL models due to their ability to represent a range of tasks. This problem is further exacerbated if researchers inappropriately equate RL models.

#### Universal Task

Efforts to isolate the RL circuit with a specific task have failed. As a thought experiment, participants discussed developing a task from which a generalizable decay parameter, noise parameter, and learning rate could be successfully derived. Using this approach might reduce the likelihood of tasks having similarly named parameters that do not align across tasks. However, defining these parameters would pose interpretability challenges. Participants asked whether such a task could be added to the NIH Toolbox; Dr. Molly Wagster, who contributed to the development of the Toolbox, explained that it was intended to include a set of measures that were well-validated and normed using a wide range of ages, which could then be broadly used in studies. New additions to the Toolbox are unlikely.

#### Generalizable Learning Rate Parameter

To develop such a task, the field would need to reach agreement on whether the learning rate should describe neural processes or how people learn in real-world tasks, given that a statistic that predicts behavior successfully may not be related to a specific neural process. For NIA, the most useful learning parameter would predict changes in cognitive behavior during aging or

age-related diseases. However, behaviorally predictive variables or models that nonetheless are not predictive of underlying neural processes have clinical utility; such a variable may also reveal a site for intervention.

### ***Temporal Discounting***

Surveys and diagnostic strategies often include self-report components (e.g., executive function) that are more reliable than most neuropsychological testing. One publication from Dr. Poldrak described a temporal discounting task, which represents a hybridization between self-report and performance measures. It requires less memory sampling and self-awareness than other self-report measures. This construct might be predictive of changes, responses to treatment, or phenotypes. Temporal discounting has been validated and associated with other constructs, making it successful as a trait variable. Dr. Lempert noted that temporal discounting is not a changeable state variable and is difficult to manipulate experimentally; thus, this measure captures behavior effectively but is relatively inflexible.

### ***Ecological Validity and Task Simplicity***

Tasks tend to be biased toward simplicity to ensure tractability and easy modeling. However, such simple tasks may fail to reflect realistic behavior; ecologically valid behaviors are more complex but may be more revealing. Dr. Radulescu noted that her team's approach using the RL framework in studying ecologically valid behaviors included considering how the constructs applied in situations without tasks. The theory provides a means of identifying what can be studied (e.g., planning, attention) without considering those processes in isolation. Using ecologically valid tasks forces researchers to consider exactly what the task represents in terms of neural processes.

Dr. Collins suggested that a combination of complex and naturalistic tasks is necessary to fully understand the brain and to bridge levels of analysis. Tasks must be simple enough for analysis but complex enough to represent constructs and relate to real-world behaviors.

## **Final Discussion: Gaps and Opportunities**

Participants engaged in robust discussions of gaps, opportunities, and future directions that emerged from the workshop. Topics discussed included approaches to using computational modeling across levels of analysis, barriers to bridging across scales, the use of computational approaches to inform experimental work, opportunities for advancing collaboration across areas of expertise, and questions specific to aging and neurodegeneration for which computational approaches are uniquely suited.

### ***Approaches to Computational Modeling Across Scales and Levels of Analysis***

Speakers addressed issues related to modeling aging at different scales and integrating across levels of analysis. When addressing the issue of scale, Dr. Jones first asks what the question is and what framework will be used to answer that question. For example, if the framework is that mental functions emerge from biophysical dynamics in the brain and, within that framework, the question is about semantic function, then a biophysical rather than a cellular scale would be the most relevant approach. To address crossing scales within that framework, a

translation function is needed that involves theory and modeling. Dr. Jones referred to a recently published consensus paper ([On the Role of Theory and Modeling in Neuroscience](#)) that tackles question of scales and describes a pragmatic perspective in which descriptive, mechanistic, and normative models and theories each play a distinct role in defining and bridging levels of abstraction and crossing scales.

Dr. Wilson noted that for specific cases at the systems neuroscience level where the networks are relatively well-characterized and neural models have been developed that can make predictions at the level of behavior (e.g., the head direction system), it should be possible to build a hierarchy of models that span from neural circuits to behavior. However, for other systems (e.g., decision-making) more data are required about neuronal circuits model across scales.

Dr. Solodkin referred to the concept of emergence discussed by Dr. Miller that embodies a key issue with bridging scales, where emergence at a higher scale cannot be predicted based simply on the sum of the lower scale. An approach that considers the brain as an adaptive complex system allows models to be generated that implicitly translate the lower scale into the higher scale. This approach also amplifies small underlying changes that occur at lower scales, which enables their detection at higher scales. Biophysical modeling classically considers the brain as a complex system and provides an actual measure of the explicit links between scales. For models such as those mentioned by Dr. Wilson, linking scales is more challenging because they are based on assumptions rather than explicit quantification of emergence; however, linking scales can be done with appropriate experimental design.

### ***Limitations, Barriers, and Opportunities for Computational Approaches to Inform Experimental Work***

Dr. Gladyshev noted that it would be useful to bring molecular level analyses to behavioral and complex brain function studies. At the molecular level, it is easier to study causality and link those findings to genetics. Dr. Wilson agreed that trying to connect lower levels with higher level behavior is a big opportunity. With the increased availability of large datasets, a hidden structure is being discovered in behavior (e.g., personality factors). Ideally, individual differences are driven by cellular level processes and different genetic causes; making those connections is not yet an area of focus in the computational framework. Dr. Collins noted that some work along these lines has been done in domain of learning, where studies have tried to relate genetic polymorphisms to behavioral patterns (e.g., bridge mechanisms of dopaminergic signaling in learning). The limiting factors are the theory to bridge across these scales and the unknown appropriate behavioral tasks required.

Dr. Gladyshev pointed out the potential opportunity to use biobanks (e.g., the UK Biobank) as a resource because of their large cohorts that are well-characterized, including many kinds of behavioral phenotypes, genomics and omics data, and biological age assigned to individual samples.

Dr. Collins explained the additional complexity that the social sciences bring to this issue. Based on strong evidence that behavior is driven by the history of social environment and experiences

(e.g., long-term effects of early life adversity on decision making), Dr. Collins does not think that bridging in a single hierarchical pattern would capture the many feedback loops that involve the social and physical environment.

### ***Barriers to Bridging Scales in Computational Neuroscience***

Despite the recognized importance of bridging scales for understanding brain function, several barriers and challenges limit implementing these approaches. Dr. Collins described some of her challenges with bridging scales between biological networks and cognitive modeling, where she has successfully done this in only two papers in over 15 years of work. Bridging scales is difficult because it requires two types of modeling expertise and each type of modeling trades off different costs and benefits in ways that make them hard to pull together and makes it difficult to develop a coherent story or paper across a given question.

Dr. Solodkin thinks that a major roadblock for multi-scale approaches is that they require a change in the paradigm for thinking about the problem. It is not sufficient to have observations at different scales; the relationship *between* the scales must also be modeled. A fundamental change in thinking is required to model descriptors of these relationships.

Dr. Jones agreed that a paradigm shift is needed and proposed that the computational modeling across scales requires a common model (i.e., an agreement about the end goal of what is being modeled across the field that would provide a “base camp” for individuals to work towards across different scales). For example, to answer questions about his patients, the base camp Dr. Jones needs would be an agreement about how to think about large scale brain patterns. Then individuals working at different scales (e.g., neuronal cells, cognitive processes) could generate different models that produce those patterns (e.g., link cellular modeling or behavior data to large scale patterns). In Dr. Jones’ example, the ontology is encoded by only 50 to 60 eigenbrain patterns (i.e., numbers) generated by FDG-PET; those patterns can be used as the generative model to make patterns in other data.

### ***Education and Training Barriers***

Dr. Lempert clarified discussed broader barriers to computational methods that impact the field as a whole, noting that many people are intimidated by computational modeling because it requires programming skills and knowledge of math. This results in avoidance of the field altogether or application of modeling packages without a sufficient understanding of the model being used. Drs. Wilson and Solodkin agreed that the education barrier is huge; Dr. Solodkin encounters this problem when training individuals to use TVB. On the behavioral side, psychology undergraduates often are not required to learn coding or math that qualifies them to do modeling in graduate school. Dr. Solodkin thinks that the most important educational skill for students is to learn how to think clearly about the question being asked. Although math and coding can be learned, students need to be able to evaluate whether their results make sense in the context of the question. Otherwise, the danger of using modeling packages is “garbage in, garbage out.”

***Opportunities and Recommendations for Advancing Collaboration Across Areas of Expertise***

Dr. Dibattista informed participants about a current funding opportunity developed to bring together teams of experimental and computational researchers to start working together at the beginning of a research question ([RFA-AG-24-018](#)), and noted that NIA is interested developing ways to do more in this space.

Dr. Sebastiani agreed with the idea of using funding strategies to encourage collaboration across multi-disciplinary teams and approaches, particularly for complex issues such as aging and dementia, and noted that multi-disciplinary collaborations enrich the knowledge of all participants as well as promote an appreciation of how different areas of expertise complement a project. Dr. Sebastiani further clarified that the key is to train individuals to collaborate and not to train individuals with all competencies in all areas. One large gap is that work is often done in silos (e.g., neuroscience, behavior, omics) and communication is lacking among experts across disciplines.

Drs. Solodkin and Hao also applauded NIA's strategy of using funding opportunities to promote collaboration and convergence across fields to address complex issues such as aging and dementia. Dr. Hao described the immense impact receiving this type of team-based grant from NIA had on his own career by stimulating the formation of a long-term collaborative team to study the systems biology of aging, which has expanded to study a range of questions. Furthermore, Dr. Hao added that greater funding opportunities are required to trigger multi-disciplinary research.

Dr. Collins added a cautionary comment about collaborating across domains, where her experience is that the difficulties in each domain often do not add up, but instead multiply. Dr. Collins suggested that it is often useful to take small steps that do not complicate the protocol. For example, her first cross-disciplinary collaboration simply collected saliva samples to measure hormonal status in adolescents; for aging, she suggested that collecting a proxy of biological age might be a useful first step. While Dr. Jones thought this was an interesting idea, he cautioned that different biological functions have different biological ages (e.g., heart versus bone); he suggested that instead of biological aging, modelers should use the concept that oscillatory dynamics exist at different scales that relate to the aging physiology of interest.

***Questions Specific to Aging and Neurodegeneration for which Computational Approaches are Uniquely Suited***

Dr. Jones noted that Dr. Hao's solution to aging, by driving the system to healthy limit cycles, highlights the unique contribution of computational modeling to aging-related questions because no other paradigm outside of the computational paradigm thinks like that. If this type of solution can be applied at a cellular scale, it can be applied at any scale—provided the right ontology has been developed to measure at that scale. When applied at any scale, this solution would enable modeling as a dynamic process with degenerative dynamics and using that model to try to get to a healthy limit cycle. Dr. Jones does not know of another paradigm that can offer those novel approaches to address AD/ADRD research.

Dr. Hao suggested that another question related to healthy limit cycles that modeling can help address is regarding dynamic patterns of interventions. Although dynamic patterns of interventions are a huge parameter space, predictive modeling can help guide the design of the dynamic regime to promote effects; this could be scaled up from cellular to animal and human scales. This approach could reveal unifying patterns, although at different timescales, which is ideal from a modeling perspective.

Dr. Sebastiani suggested that integrating data on behavior, cognitive decline over time, and aging at the molecular level might address some of the many unsolved problems related to aging. A great deal of such data on large cohorts has been collected, but teams of experts need more opportunities to focus on these data and address difficult questions related to integrating and modeling them.

Dr. Solodkin thinks that computational generative models provide an opportunity to ask questions about whether common features—or fingerprints—exist in cognitive changes across different neurodegenerative diseases (e.g., AD, PD, spinocerebellar ataxias, vascular dementia) at the level of brain dynamics. The approach of focusing on commonalities across diseases, rather than individualization, could reveal similar dynamic roots or frameworks that span different diseases.

## **Closing Remarks**

On behalf of NIA, Dr. Sutterer thanked all participants for a robust set of presentations and discussions explicating the needs and opportunities for harnessing computational neuroscience to address aging and AD/ADRD. This workshop was clearly just the beginning of a larger conversation that he welcomed participants to continue.

## Appendix: Agenda

### Day 1: March 1, 2023

|                    |                                                                                                                                                            |
|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 12:15 pm           | <b>Welcome and Introductions</b><br><i>Amy Kelley, MD, MSHS, National Institute on Aging</i><br><i>Matt Sutterer, PhD, National Institute on Aging</i>     |
| <b>SESSION I:</b>  | <b>Computational Analysis of Molecular Systems</b><br><b>Session Chair:</b> <i>Vadim Gladyshev, PhD, Harvard University</i>                                |
| 12:30 pm           | <b>Quantifying Aging</b><br><i>Vadim Gladyshev, PhD, Harvard University</i>                                                                                |
| 12:50 pm           | <b>Engineering Longevity—Computationally-Guided Reprogramming of Single-Cell Aging</b><br><i>Nan Hao, PhD, University of California at San Diego</i>       |
| 1:10 pm            | <b>Break</b>                                                                                                                                               |
| 1:20 pm            | <b>Computational Challenges in Extreme Longevity Studies</b><br><i>Paola Sebastiani, PhD, Tufts Medical Center</i>                                         |
| 1:40 pm            | <b>Microscopic Imaging of Epigenetic Age and Chromatin Heterogeneity</b><br><i>Alexey Tersikh, PhD, Sanford Burnham Prebys Medical Discovery Institute</i> |
| 2:00 pm            | <b>Discussion of Session 1</b>                                                                                                                             |
| 2:45 pm            | <b>Virtual Coffee Break (Zoom attendees only)</b>                                                                                                          |
| <b>SESSION II:</b> | <b>Computational Analysis of Large-Scale Brain Systems</b><br><b>Session Chair:</b> <i>David Jones, MD, Mayo Clinic</i>                                    |
| 3:20 pm            | <b>From Clockwork to Emergence: A New View of the Brain</b><br><i>Earl Miller, PhD, Massachusetts Institute of Technology</i>                              |
| 3:40 pm            | <b>How a Biophysical Generative Model Gives Unique Insights Into Aging and Dementia</b><br><i>Ana Solodkin, PhD, University of Texas at Dallas</i>         |
| 4:00 pm            | <b>Break</b>                                                                                                                                               |
| 4:10 pm            | <b>Clinical Utility of a Global Information Processing Model for Mental Functions</b>                                                                      |

*David Jones, MD, Mayo Clinic*

4:30 pm **Using Network Control Theory to Formally Model the Energetics of Brain Function**

*Dani Bassett, PhD, University of Pennsylvania*

4:50 pm **Break**

5:00 pm **Discussion of Session 2**

5:45 pm **Closing Remarks:** *Leonid Tsap, PhD, National Institute on Aging*

5:50 pm **Adjourn**

## **Day 2: March 2, 2023**

**SESSION III: Computational Analysis of Complex Behavior**

**Session Chair:** *Anne Collins, PhD, University of California at Berkeley*

12:25 pm **Opening Remarks:** *Luke Stoeckel, PhD, National Institute on Aging*

12:30 pm **Using Computational Modeling Approaches to Reveal Cognitive Processes Underlying Changes Across the Lifespan**

*Anne Collins, PhD, University of California at Berkeley*

12:50 pm **Computation Conquers Complexity - Decomposing Behavior to Understand the Components of Cognition**

*Robert Wilson, PhD, University of Arizona*

1:10 pm **Break**

1:20 pm **Towards Naturalistic Reinforcement Learning in Health and Disease**

*Angela Radulescu, PhD, Icahn School of Medicine at Mt. Sinai, Center for Computational Psychiatry*

1:40 pm **Relating Individual Differences in Learning to Markers of Alzheimer's Disease Pathology in Older Adults**

*Karolina Lempert, PhD, Adelphi University*

2:00 pm **Discussion of Session 3**

2:45 pm **Break**

**Final Discussion**

|         |                                                                                |
|---------|--------------------------------------------------------------------------------|
| 3:00 pm | <b>Gaps and Opportunities: Breakout Session</b>                                |
| 3:15 pm | <b>Gaps and Opportunities: Final Discussion</b>                                |
| 4:00 pm | <b>Closing Remarks:</b> <i>Matt Sutterer, PhD, National Institute on Aging</i> |
| 4:05 pm | <b>Meeting Adjourns</b>                                                        |