J Prev Alz Dis 2023;1(10):1-4
Published online January 5, 2023, http://dx.doi.org/10.14283/jpad.2023.1

Editorial

Accelerating Innovations for Enhanced Brain Health. Can Artificial Intelligence Advance New Pathways for Drug Discovery for Alzheimer's and other Neurodegenerative Disorders?

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Artificial intelligence/machine learning (AI/ML) offers new solutions to untangle the complexity involved in discovery of new intervention targets for neurodegenerative disorders

The International Neurodegenerative Disorders Research Center (INDRC), a private, non-profit research institute, based in Prague, Czech Republic was established to address the challenges facing the identification and validation of new interventions for neurodegenerative disorders. This perspective describes the INDRC use of a transparent governance model that includes committed international partners from the European Union and North America comprising universities, research institutes, clinical centers, and for-profit/non-profit companies. The Institute applies artificial intelligence/machine learning (AI/ML) to develop novel and integrated analytical methods from many different disciplines including basic neuroscience, applied/theoretical biophysics/biochemistry, computer science, computer/electrical engineering, mathematics, and clinical/population-based research. INDRC is interdisciplinary by design, addressing research bottlenecks and enabling convergence of dispersed knowledge, and developing new analytical approaches to discover and model the non-linear dynamics between biology, disease, man, and environment.

The first scientific initiative of the Institute is to address the major public health demand for improved understanding of biology of neurodegeneration and new interventions to treat neurodegenerative diseases. The search for effective interventions remains slow due to lack of understanding of the complex inter-relationship of brain structure and brain function, as well as limited knowledge of the precise pathogenic pathways that impair or destroy neurons and their connections.

A key obstacle to the development of new therapies is understanding the complex non-linear networked relationships between the behavioral and clinical features of a given brain disorder with the underlying neurobiological mechanism (1-3). Researchers do not currently possess adequate conceptual models, the requisite research mapping tools, and the knowledge visualization systems to investigate new and promising therapeutic pathways that account for these complex dynamics – including positive/negative feedback systems – that connect the biology and clinical expression of neurodegenerative disorders.

The development of novel therapeutics aimed at slowing and eventually preventing progression of Alzheimer's disease (AD) and other neurodegenerative disorders remains a critically important international public health goal (4). Despite the recent struggles of clinical trials to demonstrate efficacy in modifying the clinical course of AD, delaying the onset of disabling symptoms remains a viable and near-term strategic objective (1-3).

In the AD realm, the leading clinical development programs are generally focused on interventions designed to interfere with the putative pathobiological processes of the disease. Although this strategy shows some promise, given the heterogeneity of the onset, progression, and clinical phenotypes, an important question remains. How can we develop additional intervention strategies to slow, to alter, or even to stop the progression of AD?

One important innovation for the Alzheimer's research field will be to embrace an emergent neurobiological systems-based approach to collect, organize, and communicate knowledge about the disease (7). Unlike other chronic disorders such as cancer and heart disease, an important first step is the redefinition and reconceptualization of AD as a syndrome rather than as a disease. As a syndrome, both the pathological features and the clinical symptoms constitute ongoing processes of systems degradation and eventual systems failure for the overall brain architecture (5-9). The operational framework for an emergent neurobiological systems-based approach allows for multiple etiologic factors to describe multiple pathways for AD pathogenesis.

Received July 12, 2022
Accepted for publication October 16, 2022

There are two critical points. First, this conceptualization does not presuppose a single etiological trigger. As noted above, the approach acknowledges multiple pathways, multiple hierarchical scales of subsystems, and multiple time/temporal sequencing scales may ultimately lead to neuronal dysfunction and cell death.

Second, the framework requires understanding of key functional components of the overall brain architecture system. In doing so, the framework also places an emphasis on understanding interactions, mediation, and temporal sequencing among the various architectural elements (9). In this way, the systems approach seeks understanding of how crucial sub-systems of the overall brain architecture, such as genetic, environmental events, and temporal changes influence system performance. Further, the framework also permits exploration of how various elements and sub-systems may interact in sequence, or in parallel, and provide new therapeutic options to optimize overall system performance.

The explicit challenge for developing novel therapeutic interventions using a systems approach will be to solve the complex interaction for maintaining or restoring functionality or optimal performance of the system. In this way, a systems-based model of AD requires greater knowledge of the origin, the timing of upstream and downstream pathological changes, and how interactions couple/interface within different brain environments including heterogeneous genetic variants and clinical phenotypes. The systems-based approach allows for the possibility that different individuals come to experience brain failure for different reasons and through different paths. This is very likely to be one pathway toward individualized patient healthcare.

So, how will this be accomplished? INDRC seeks the establishment of a novel modelling framework to formally examine all current theories, as well as clinical and biological knowledge comprising Alzheimer's disease and neurodegeneration. This effort will:

1. Create an inventory of knowledge about various theories
2. Provide a knowledge management platform of these theories
3. Establish a common ontology to identify the most crucial aspects that provide linkages, coupling and/or interfaces between and among the various sub-systems within the complete brain-architecture
4. Construct a high-performance AI/ML model platform – "Modelbase" – to integrate conceptual knowledge and experimental data from topics including:

- Known risk factors, particularly age, genetic predisposition, life/health experiences, education, and cognitive reserve
- Progression and sequence of biological and clinical changes
- Selectivity vulnerability and anatomical specificity of brain regions with respect to various pathophysiological processes
- Issues of mixed pathologies and multiple clinical phenotypes
- Biological and digital markers of diagnosis, clinical assessment, and disease monitoring

Conceptual models for Alzheimer's disease based on general systems theory are likely to change the current paradigm of treatment development (5-9). The formulation of a multifactorial disorder model first requires recognizing Alzheimer's disease as a syndrome and then:

- Identifying key etiologic components,
- Understanding the evolution and interactions of pathological events, and
- Developing multi-modal therapeutic strategies to restore or maintain functionality throughout the illness process.

AI/ML solutions can dramatically improve understanding of pathogenesis of Alzheimer's and identification of effective treatments

Early detection of Alzheimer's disease is a challenge because of the lack of long-term data on how the disease develops over the lifespan. Because traditional studies on medical use cases tend to make only qualitative visual assessments of MRIs, valuable potential findings often go unrecognized or unconsidered if they are not relevant to the hypothesis under consideration. In contrast, by measuring the volume of brain structure, big data collections provide a promising quantitative basis to back up diagnoses. Data from different perspectives and points in time of disease development, disease progression, and therapeutic process must be captured. As a consequence, the data-centric approaches of AI/ML may act as a driver for knowledge discovery providing the basis to unfold the power of AI/ML aiming at the development of new agents and drugs to prevent and treat Alzheimer diseases.

More precisely, current treatment models relied on sometimes completely wrong, but at minimum, simplified models of brain function and disease pathogenesis. They do not contain a non-linear dynamic of complex interplay between heredity, behavior, the impact of treatment or prevention, and the ability of the brain system to maintain functions to some extent even in the event of damage. AI/ML can help us create more suitable models of brain architecture. At its core, AI/ML solutions are better optimized for model development of complex, multi-dimensional systems owing in part to the use of neural networks and the computational ability of AI/ML centers of excellence to process efficiently peta- and yottabytes of clinical and biological data.

One of the goals of INDRC is to build computational models that combine knowledge and expertise taken from biological sciences, clinical research, mathematics, biophysics/biochemistry, electrical engineering, and computer science to study and treat neurodegenerative disorders. This has been facilitated by bringing together leading experts from these fields. However, several important following tasks are necessary to bring together these seemingly disparate fields to tackle and solve the problems posed by neurogenerative disorders. These include:

- Trust and common understanding among all stakeholders
- Bridging the disciplines to develop the best the AI/ML and clinical medicine interfaces
- Adoption, validation, and verification of in silico clinical research methodology to support regulatory science health policy decision-making
- Discovery, qualification, and validation of AI/ML to reveal biomarkers and other surrogate clinical outcomes for:

1. Predicting disease/syndromic risk
2. Predicting disease/syndromic risk
3. Diagnosis
4. Monitoring disease/syndromic processes
5. Predicting disease/syndromic progression
6. Monitoring a treatment/therapeutic effect
7. Monitoring safety in clinical trials
8. Predicting clinically relevant outcomes
9. Predicting disease/syndromic risk of future events
10. Applying AI/ML solutions for new drug candidates and in silico trials
11. Data engineering, including the development of data integration pipelines and compute infrastructure for ETL (ETL stands for extract, transform and load and is used to combine data for long-term use into data warehouses, data hub or data lake structures); data curation; data documentation and metadata management; and data transformation and standardization to adhere to prespecified ontologies are all necessary components that must be established to provide input for data scientists to develop AI towards insight generation

Path forward: INDRC integrates capabilities and efforts to treat and prevent Alzheimer's disease and neurodegenerative disorders

The INDRC goal is to merge and advance the globally dispersed knowledge in Alzheimer's disease and other neurodegenerative disorders through research training fellowship programs of excellence, delivering outstanding independent research programs, building a world-class research community, and enabling technological/therapeutic innovations with genuine impact on society and humanity. No doubt, the identification of breakthrough novel interventions for neurodegenerative disorders will be greatly increased by international collaboration between North America, EU, and the rest of the world. INDRC will support this activity by bringing together leading experts from the fields of neurodegeneration and AI/ML. INDRC serves both as a research institute, collaborative platform, and a sponsor of the paradigmatic shift necessary to accelerate brain health research.

The INDRC concept offers new, synthetic views through deployment of AI/ML methods and technologies in all possible layers, such as:

1. AI/ML-enhanced powered diagnostics, e.g., autonomous cognitive assessment, audio & video analysis
2. Novel therapeutic solutions, e.g., machine learning for protein engineering and new biologically active molecules
3. AI/ML-enhanced assistance for patients and caregiver care, e.g., assistive devices for home care and telemedicine
4. Prevention and brain health insights for health systems, primary care physicians, and individuals, e.g., big data processing of social, professional, life-style impacts to individual

Putting together existing brain research and AI/ML computational expertise, encounters a number of challenges that INDRC was established to overcome. INDRC aims to mitigate knowledge dispersity by developing new methods, models, and algorithms to enable exploration of the complex non-linear dynamics between biology, environment, disease, and public health. Computational and scientific advances give us tremendous opportunity to advance our understanding of neurodegeneration and potential interventions to help patients suffering from devastating neurodegenerative disorders. INDRC represents an opportunity to integrate better collaboration and communication for the scientific community with scientific priorities for 2023 focused on the 1) the identification of unrecognized cognitive impairment, and 2) the development of a unified conceptual model of Alzheimer's disease. Also, INDRC aims to facilitate communication within research networks, initiatives, and teams, to enable partners to learn from each other, and generate synergies. The effort will update readers on this progress, and highlight as an early priority, the need to conduct a survey of available data sources that would enable this level of modeling. This is a topic of sufficient breath that the editors of JPAD should invite authors to submit comments, letters to the editor, to identify other potential sources of data. The ultimate aim will help alleviate unnecessary duplication of effort and improve the likelihood that the best AI/ML labs and clinical research centers work together. Perhaps, the most important outcome for INDRC will be to help introduce a new way to fuse conceptual knowledge obtained from neuroscience and to derive new high-performance computing applications to find novel solutions for preventing and treating Alzheimer's disease and other neurodegenerative disorders. JPAD and the entire neurodegenerative disorders research community is invited to submit projects, ideas, and visions and to join this endeavor.

Acknowledgements: Rhoda Au, Jean-Marie Bouteiller, Vít Dočkal, John Hey, Pavel Hroboň, Cezary Kaliszyk, Ara Khachaturian, Zaven Khachaturian, Barbora Klečková, Petr Kocis, Milan Kulhánek, Jaroslav Lískovec, Joseph Lombardo, Vladimír Mařík, Michelle Mielke, Paolo Maria Rossini, Václav Snášel, Martin Tolar, Eva Troppová, Bruno Vellas, Jort Vijverberg, Wolfgang Wahlster.

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How to cite this article: A.S. Khachaturian, A. Dengel, V. Dočkal, et al. Editorial: Accelerating Innovations for Enhanced Brain Health. Can Artificial Intelligence Advance New Pathways for Drug Discovery for Alzheimer's and other Neurodegenerative Disorders? J Prev Alz Dis 2023;1(10):1-4; http://dx.doi.org/10.14283/jpad.2023.1