

# How Regulatory-ready Biosimulation is Revolutionizing Neurodegenerative Drug Development

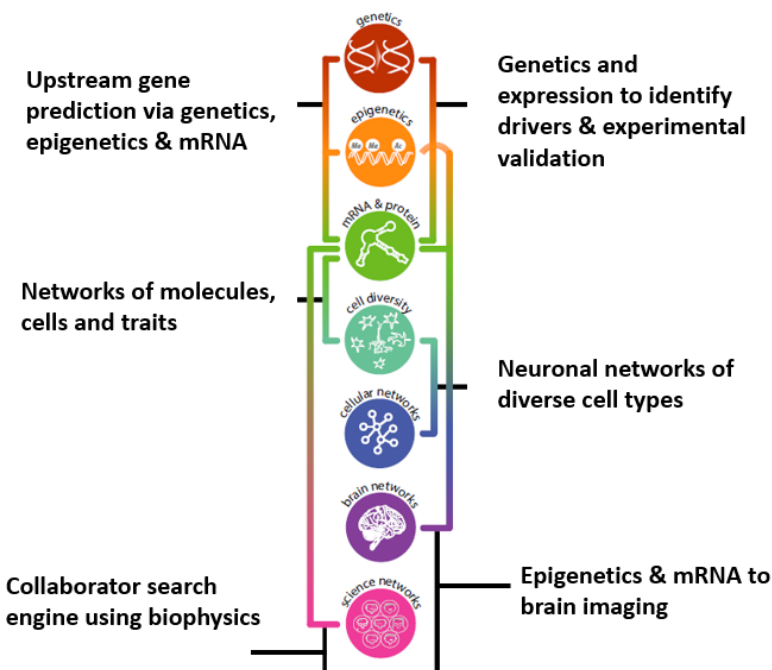
More than 30 million individuals worldwide suffer from neurodegenerative diseases (NDD). NDD is characterized by a loss of neurons, the building blocks of the nervous system that includes the brain and spinal cord. The subsequent decline in cognitive and motor function that patients experience in these diseases is associated with nerve cell loss. Neurons normally do not reproduce or replace themselves when they become damaged or die.

A surge of new therapeutic options, a focus on the interplay between the immune system and NDD, and the potential for combination therapies are facilitating a resurgence in this field.

***Biosimulation provides a unique and compelling technology approach to enhance our understanding of NDD and increase probability of success and time-to-market for new treatments.***

## NEURODEGENERATIVE DISEASE DRUG DEVELOPMENT: CHALLENGES & OPPORTUNITIES FOR BIOSIMULATION

Neurodegenerative diseases are complex and usually involve dysregulation in multiple biochemical pathways, as shown in diagram below. Typically, drug discovery projects focus on a single biophysical scale. The connections across these scales are obscured by the complexity of biological systems, causing an obstacle to building coherent disease models. Biosimulation is a proven technology to analyze these individual, integrated and combination challenges in silico.



Biosimulation facilitates the coupling of biophysical scales, which allows the 'scaling up' of molecular findings to the level of cognitive processes

Biosimulation can be also be used to simulate the interaction of different misfolded protein pathways with neuroinflammatory processes which is becoming increasingly important, not in the least by the identification of many microglia genes in large genetic studies.

## WHAT IS BIOSIMULATION AND HOW DO WE APPLY IT IN NDD

Encouraged by regulators and leveraged by the biopharma industry, biosimulation uses advanced technology to test, evaluate and create scenarios in silico, versus in vivo. Mechanistic biosimulation uses computer-based models of biological systems to predict how the body affects the drug and how the drug affects the body. Spanning the R&D cycle, global regulators have accepted its use to attain clinical trial waivers, extrapolate to untested populations, and reduce trial study size.

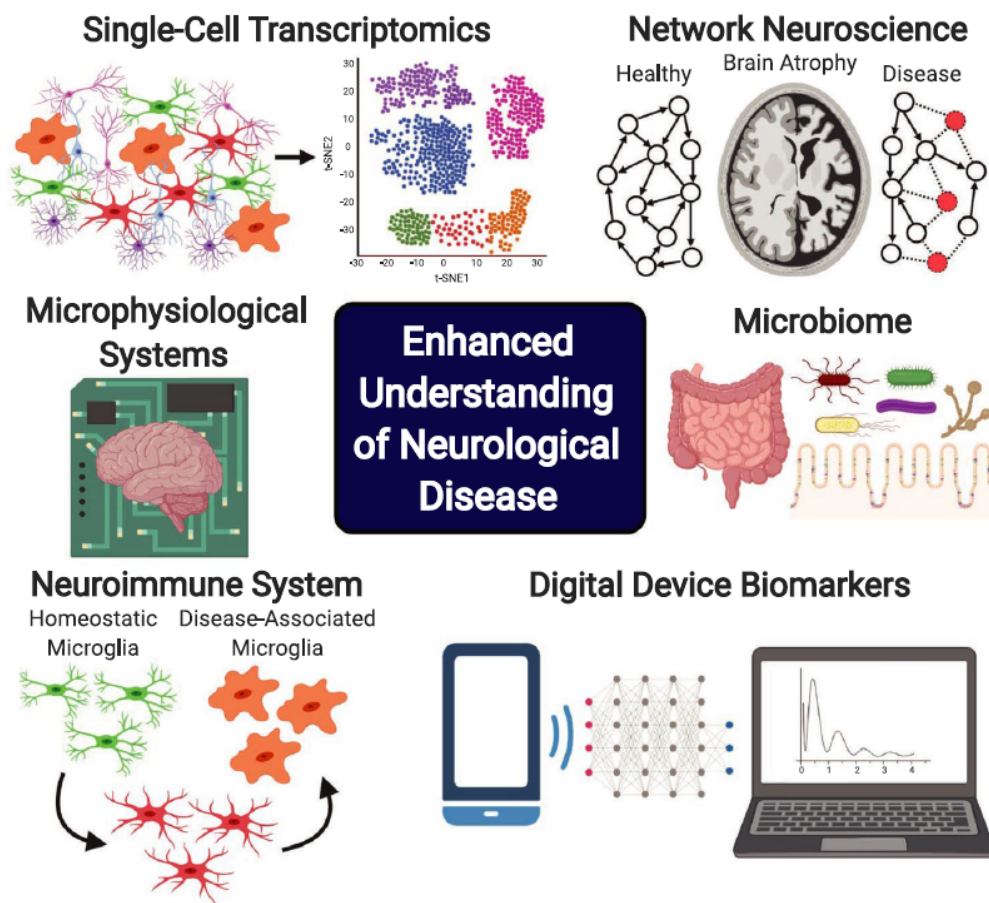
Biosimulation facilitates the understanding of the pharmacological effects of drugs on biological systems—in the case of NDD, the integration of complex interactions of different brain circuits across multiple biophysical scales. We can begin as early as the discovery phase, building from literature data, ‘learn and confirm’ the model via the addition of in vitro and animal data to inform first dose for IND submittal. As we gain further in vivo data, we advance the model to integrate diverse factors as shown in the diagram, providing a framework for predicting clinical outcomes.

Certara has a series of unique, qualified models for NDD, including:

- Blood-brain barrier
- Amyloid
- Tau
- Alpha-synuclein
- Misfolded proteins
- Neuroinflammation neurotoxicity
- Immunogenicity
- Clinically relevant scales

Models assess the integration of drugs, drug combinations with proteins, pathways and biomarkers

Technology is used for small molecule, biologics, gene and cell therapies and different routes of application, i.e. i.v., s.c., intrathecal.

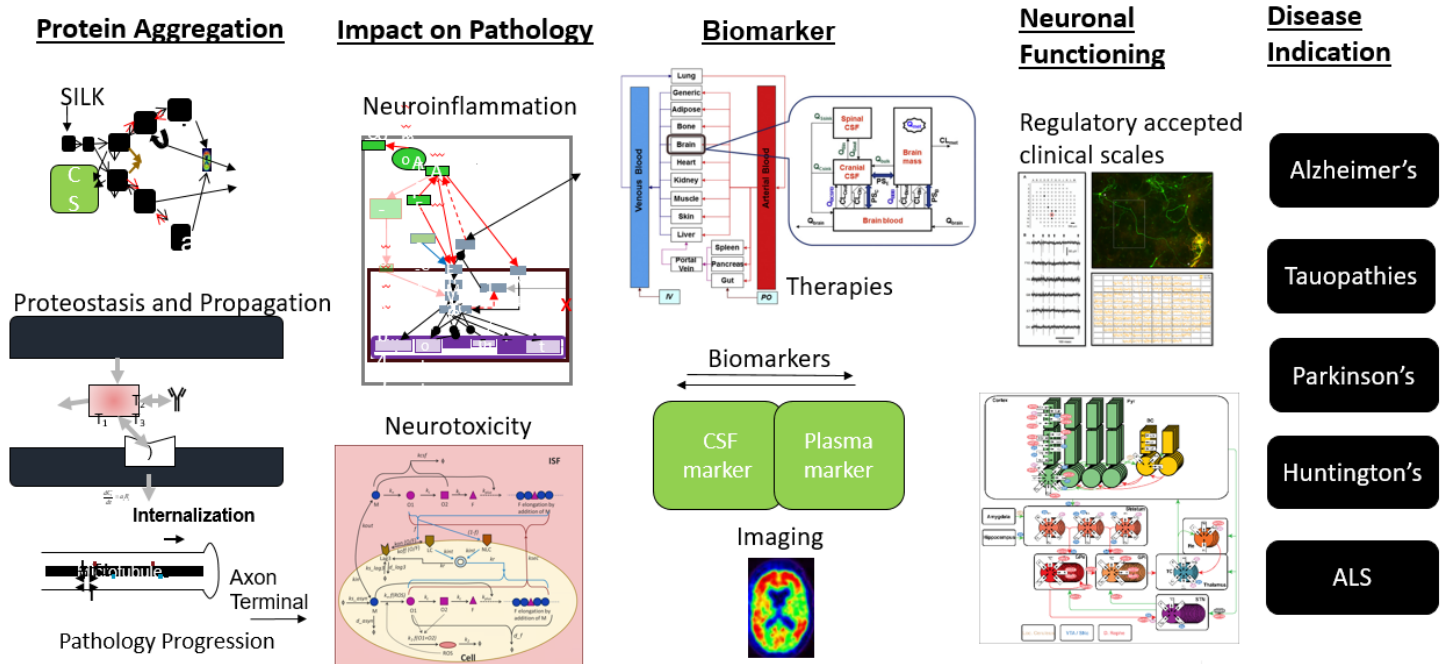


Select methodologies, technologies, and areas of research in neuroscience that can be leveraged and incorporated modeling workflows to enhance the quantitative understanding of pathophysiological processes in neurological disease and therapeutic effects of pharmacological treatment strategies  
(*CPT Pharmacometrics Syst. Pharmacol.*, Feb 2021)

## CERTARA'S NDD BIOSIMULATION PLATFORM

As shown in the figure below, Certara's platform links the pathologies on the left with neural function on the right, to derive functional clinical outcomes. The platform can integrate information on protein aggregation, Proteostasis and the impact of specific pathologies, including on neuroinflammation and neurotoxicity.

Although the platform is often used in discovery and pre-clinical work, it has been well qualified and calibrated with clinical data. Omics studies, Microphysiological systems experiments, neuroimaging, EEG and digital data can provide information on drug pharmacology and disease pathophysiology across multiple levels of biological organization and integrated into the model.



## PREDICTING BRAIN EXPOSURE FOR BIOLOGICALS

Due to the limited permeability of biologicals across brain barriers, the quantitative understanding of exposure in the CNS is a key factor in their design, development and dose prediction. We have developed a fit-for-purpose physiologically-based pharmacokinetic (mPBPK) model for brain biological therapeutics, which can be used to evaluate CNS target exposure and inform clinical dose selections. The model can be fully integrated with our other NDD platforms to enable comprehensive in-silico assessment of target engagement, modulation and clinical efficacy and safety.

## EXAMPLE CASE STUDIES

**Multiple System Atrophy:** Developed clinical pharmacology strategy and created the IND package for this first of a new generation of small molecule drugs designed to inhibit the aggregation of pathological proteins implicated in neurodegeneration. Performed model-based translation of animal models to predict human efficacy based on unbound brain concentrations to select human efficacious dose. Established safety and efficacy in phase 1. Combined animal data with human PK to select the phase 2 dose. Program is progressing.

**Huntington's Disease/Tardive Dyskinesia:** Implemented a model-informed drug development program for a vesicular monoamine transporter 2 inhibitor which is used for the treatment of chorea associated with Huntington's disease and tardive dyskinesia. Our analyses were used to assess individual systemic exposure, a lack of exposure-response relationship between daily dosing and key adverse events, and phase 3 efficacy. The drug package, which was approved by FDA in 2017, was delivered via Certara's regulatory publishing software.

**Parkinson's Disease:** Developed a multi-scale biosimulation model for determining target suitability in Parkinson's drug discovery. Created a biological map to assess the mechanisms implicated in disease propagation at the molecular level and disease progression in a small brain region. Modeling was used to quantify the spread of harmful proteins over time and prioritize targets that could lead to reduced propagation.

**Dravet and Lennox-Gastaut Syndrome:** Created integrated clinical pharmacology plan that maximized use of biosimulation for the development of a liquid formulation of pure plant-derived Cannabidiol (CBD), as a treatment for various orphan pediatric epilepsy syndromes. Approved under both FDA's orphan and fast track designations, the modeling approach leveraged the use of the Simcyp Simulator's unique pediatric module, which enables the prediction of clinical outcomes in neonates and small children.

**Alzheimer's Disease:** Developed a multi-scale computational model of amyloid aggregation and microglia-mediated clearance and the impact of therapeutic antibodies on biomarkers and ARIA-E side effects. Model was then extended with the impact of amyloid oligomers and misfolded tau proteins on ligand-gated and voltage-gated ion channels to estimate effect of interventions on CDR-SOB and used to explore various hypotheses on the disconnect between changes in biomarkers and clinical outcome.

## About Certara

Certara accelerates medicines using proprietary biosimulation software, technology, and services to transform traditional drug discovery and development. Its clients include more than 2,000 biopharmaceutical companies, academic institutions, and regulatory agencies across 62 countries.

For more information, visit [www.certara.com](http://www.certara.com).