### Disease Progression Aspects

#### AD and PD Progression Models

Meemansa Sood AETIONOMY Final Symposium 29<sup>th</sup> Nov 2018 Bonn, Germany



#### Mission

To increase knowledge of the causes of Alzheimer's and Parkinson's Disease by generating a mechanism-based taxonomy; to validate the taxonomy in a prospective clinical study that demonstrates its suitability for identifying patient subgroups (based on discrete disease mechanisms); to support future drug development and lay the foundation for improved identification and treatment of patient subgroups currently classified as having AD or PD.









Introduction



Pathways and BEL mechanistic models have no time dimension  $\geq$ 

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## Introduction

#### **Challenges:**

- > Understand disease progression (over time) at a mechanistic level
- Multiscale level data: temporal interdependency













## **Crosstalk between IMI Projects: EPAD**

- > Target the disease at early stage
- Trial infrastructure for prevention trials
- Trigger to the longitudinal aspects, prompted us to look at the time dimension















## Introduction

**Challenges:** 

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**Hypothetical Model** 



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#### **Reality Check**











## **Hypothetical Model vs. Reality**

#### **Fundamental Question:**

Do ADNI biomarkers show the same trajectories like the hypothetical model published for AD?















## **Longitudinal Model**

> Computation of Trajectories: Individual biomarkers in ADNI data



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http://epad.scai.fraunhofer.de/longitudinal-adni





## **Hypothetical Model: Computable**



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#### **Computation of Trajectories**

AD pathological cascade model based on ADNI data



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## **Computation of Trajectories**



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#### **Challenges:**

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#### **Longitudinal Bayesian Modeling**

- Represents conditional dependency over time
- Resource to represent ADNI and PPMI in a graph model
- Allows for risk modelling
- Association of mechanistic models with patient level graph models









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## **Bayesian Network Structures Reflect Expected Causal Associations**



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## **Application: Virtual Dementia Cohort (VDC)**



 Classifier cannot detect virtual patients significantly better than chance level

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# Application: Simulating a VDC with an Intervention

- Shift of diagnoses towards more healthy outcomes
  - Moving cognition scores to median normal scores shows
- Our approach allows for simulating "what-if" scenarios









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## **Conclusion and Future Outlook**

#### Longitudinal Trajectory Model:

- Reality check between hypothetical model and ADNI
- Provides interoperability between real data and hypothetical model by normalizing the axes
- Will serve as a common metric to include trajectories from other studies like AddNeuroMed and AIBL

\* Sood et al. "Longitudinal Data Modeling as an Approach to Enable the Prediction of Biomarker Trajectories for Alzheimer's Disease", Journal of Alzheimer's disease : JAD, 2018. (in preparation)













## **Conclusion and Future Outlook**

#### **Longitudinal Bayesian Modeling:**

- Represents complex clinical datasets in longitudinal conditional graph models
- > Will be used for mechanism enrichment
- First approach for realistic simulation of virtual clinical subject trajectories across multiple biological scales and data modalities

\*Sahay and Sood et al. "Realistic Simulation of Virtual Multi-Scale, Multi-Modal Patient Trajectories using Bayesian Networks and Sparse Autoencoders", Scientific Reports, Nature, 2018 (In preparation)











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## Thank you









