A statistical approach to latent dynamic modelling with differential equations for individual disease trajectories

Maren Hackenberg
Institute of Medical Biometry and Statistics (IMBI), Faculty of Medicine and Medical Center, University of Freiburg

Current affiliation: European Molecular Biology Laboratory (EMBL)

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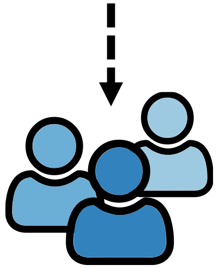
Disease trajectories of patients with spinal muscular atrophy (SMA)

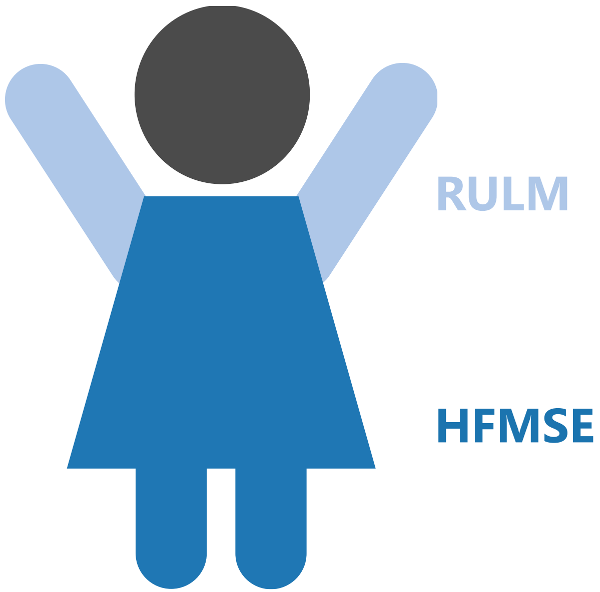
A prototypical application example from a rare disease cohort

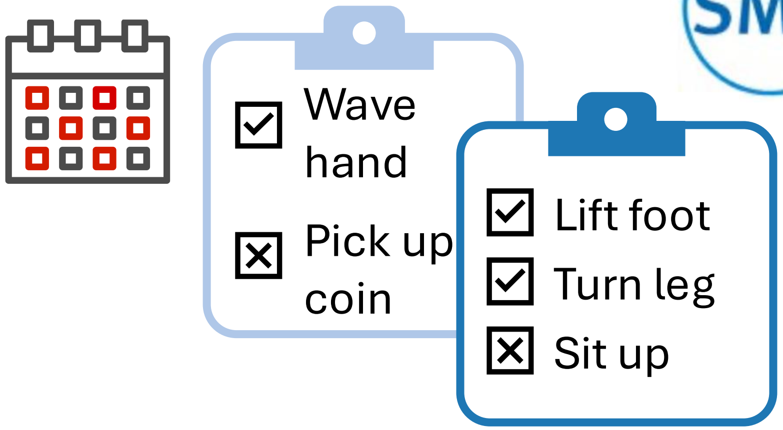
- age at symptom onset
- SMA subtype
- …

Baseline characterisation

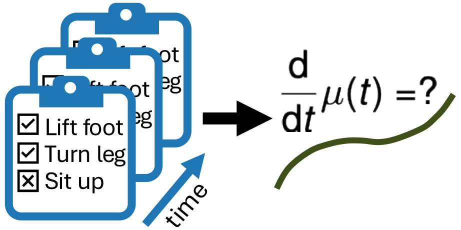


Heterogeneity
(3)

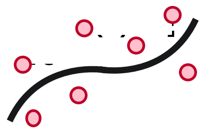




Motor function tests with different test items at irregular time points



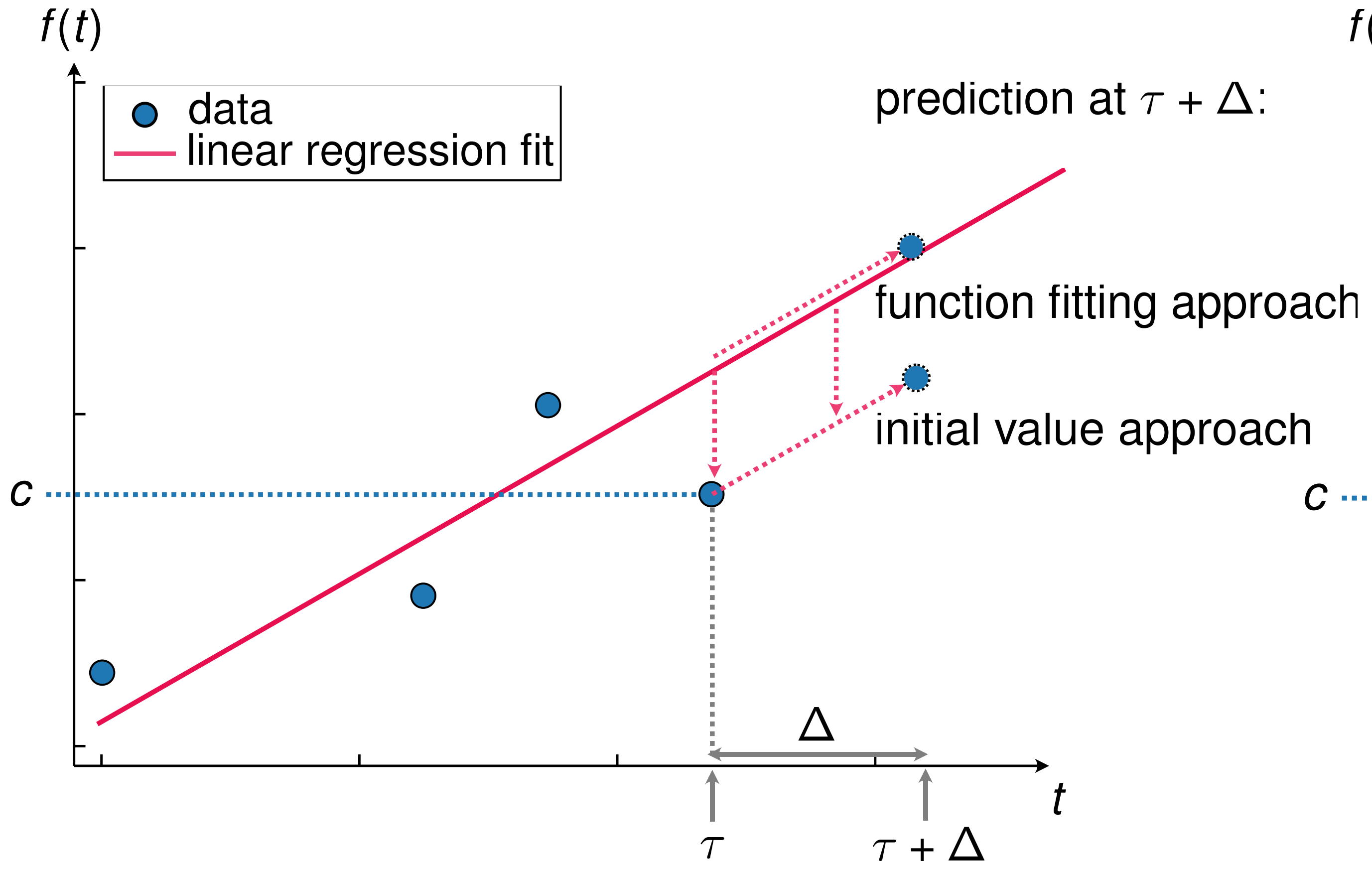
Underlying disease process unobserved
(1)

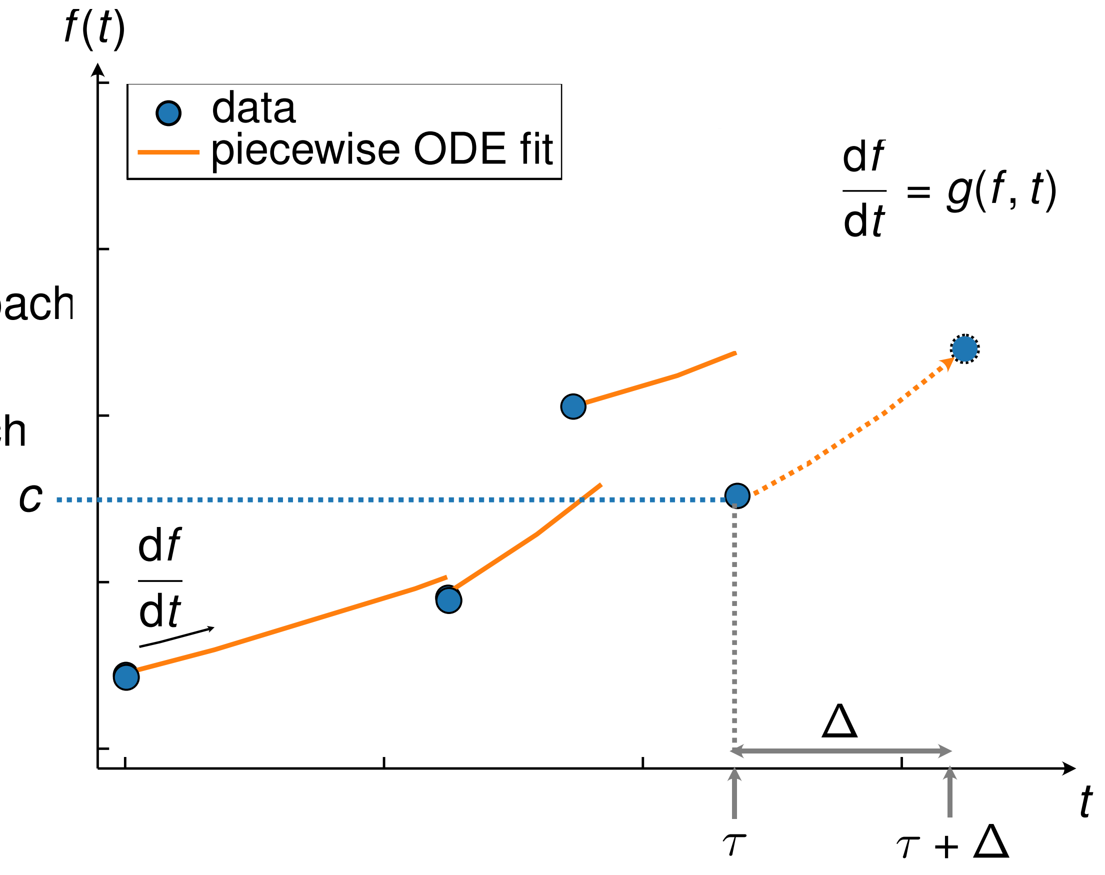


Large amount of noise
(2)

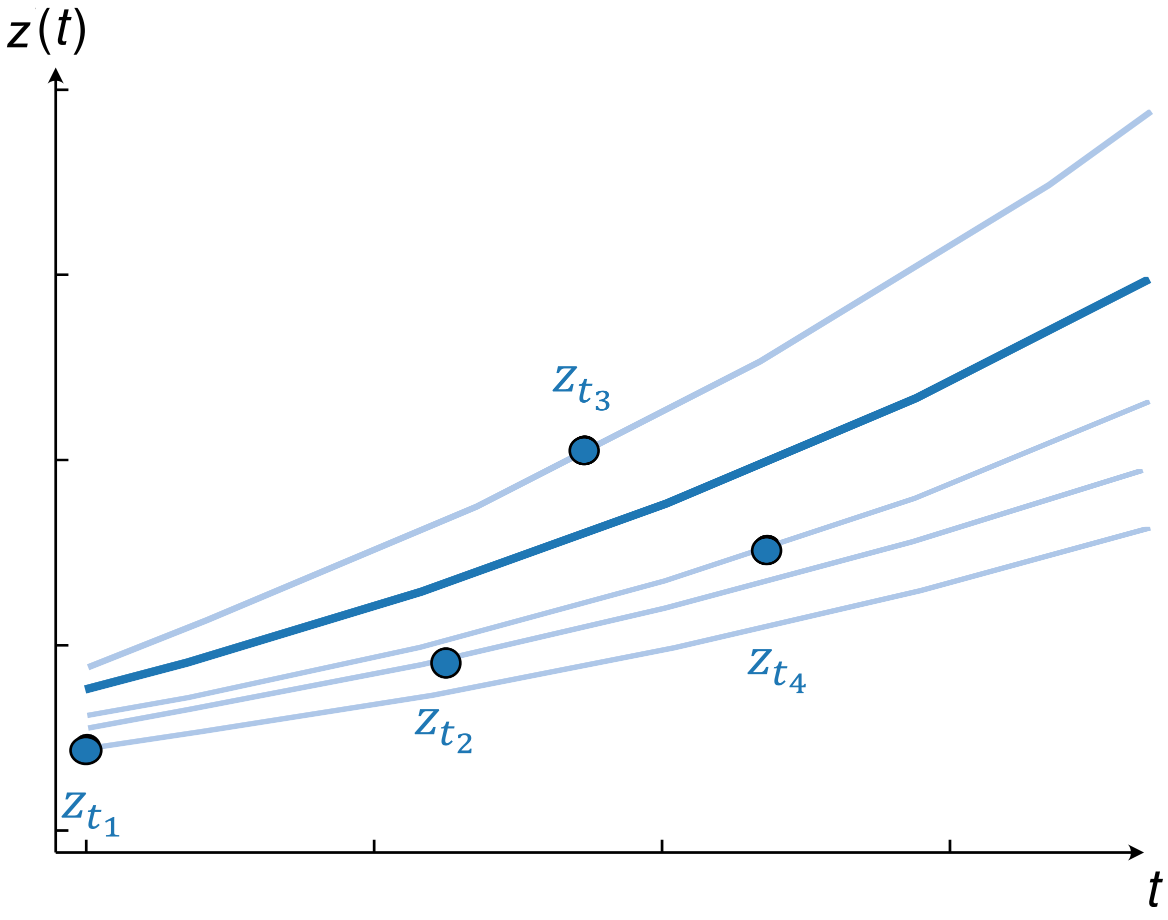
Different modeling communities have different perspectives on dynamic modelling

Function fitting vs. initial value approaches





A statistical approach based on ODEs



- time series $z_{t_0}, \dots, z_{t_K}; z_t \sim \mathcal{N}(\mu(t), \sigma)$
- initial value problem (IVP):

$$\frac{d}{dt} z(t) = A \cdot z(t) + c;\; z(t_k) = z_{t_k}$$

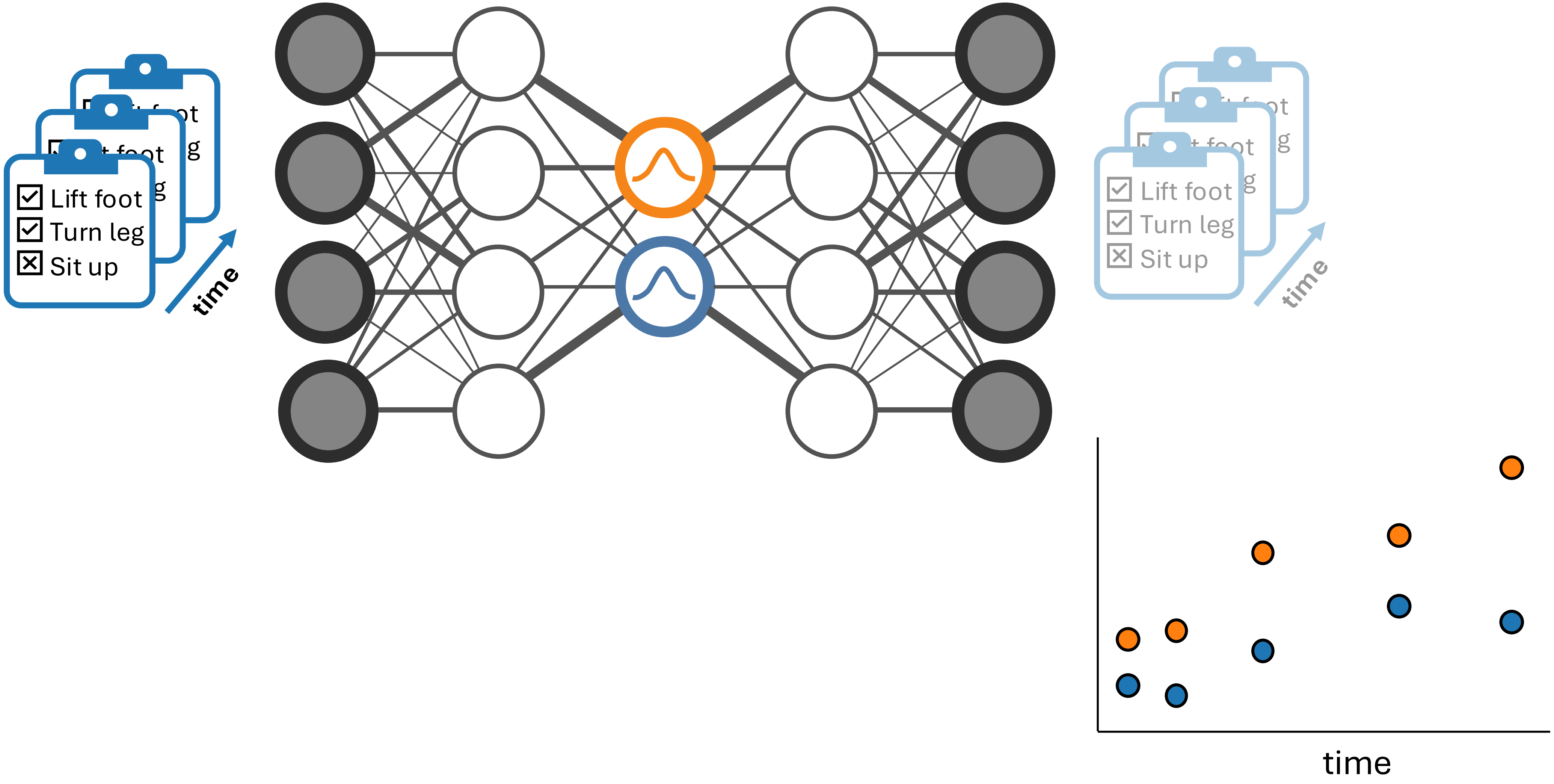
- analytical solution:

$$z_k(t) = \exp\big(A(t - t_k)\big) \cdot (A^{-1}c + z_k) - A^{-1}c$$

- solve IVP with each z_{t_k} as initial value
  → get solutions $z_k(t)$ for $k = 0, \dots, K$
- average individual solutions using time-dependent inverse-variance weights:

$$g(t) := \frac{\sum_{k=0}^{K} \mathrm{Var}[z_k(t)]^{-1} z_k(t)}{\sum_{k=0}^{K} \mathrm{Var}[z_k(t)]^{-1}}$$

Describing individual SMA trajectories as solutions of ODEs in a VAE latent space



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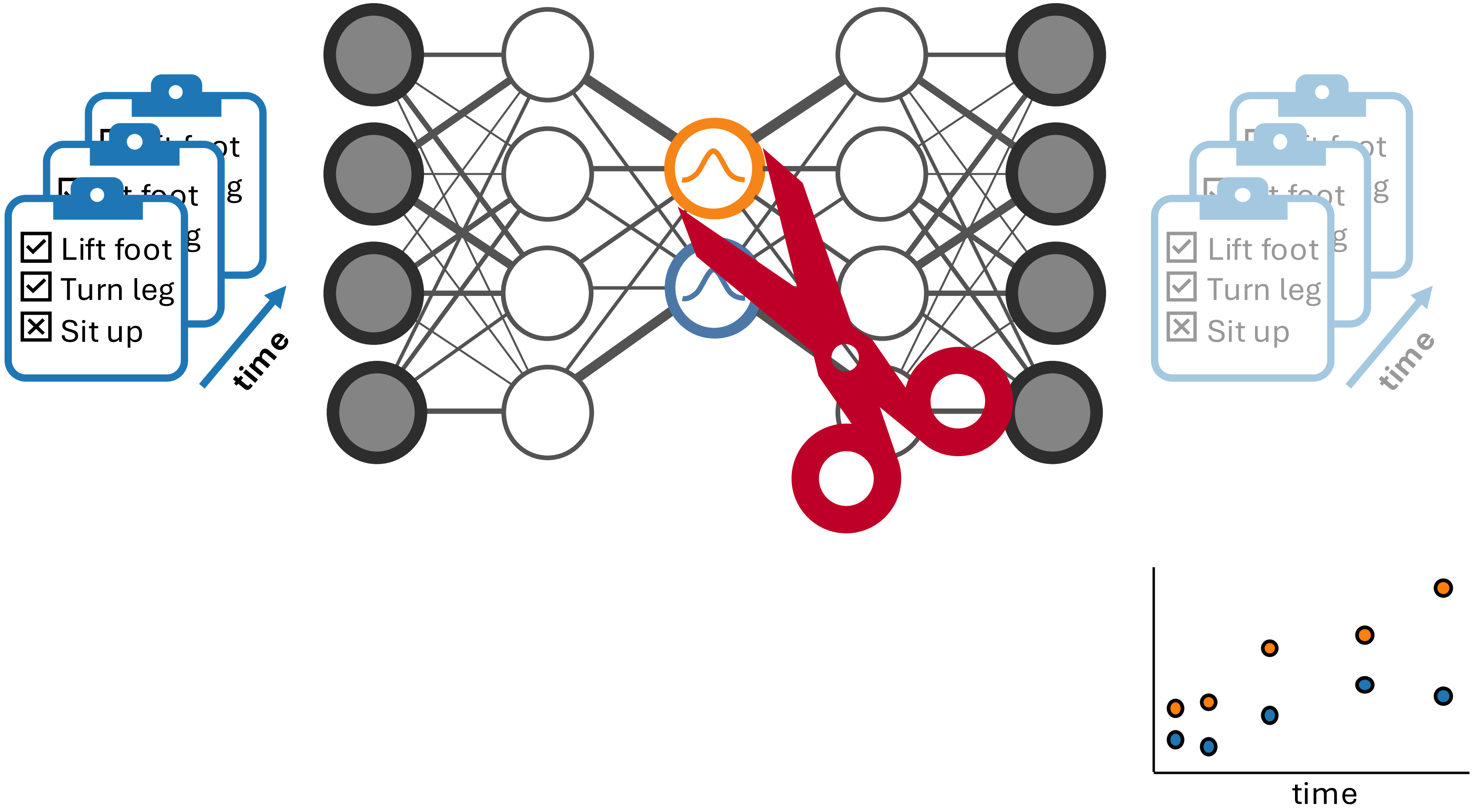

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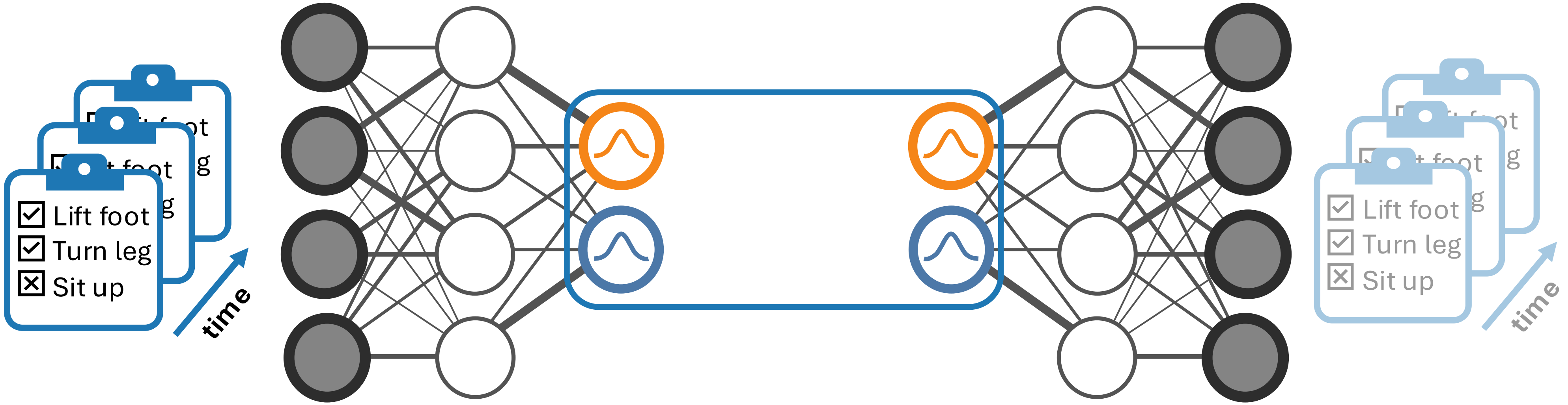

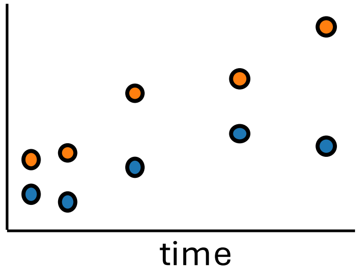

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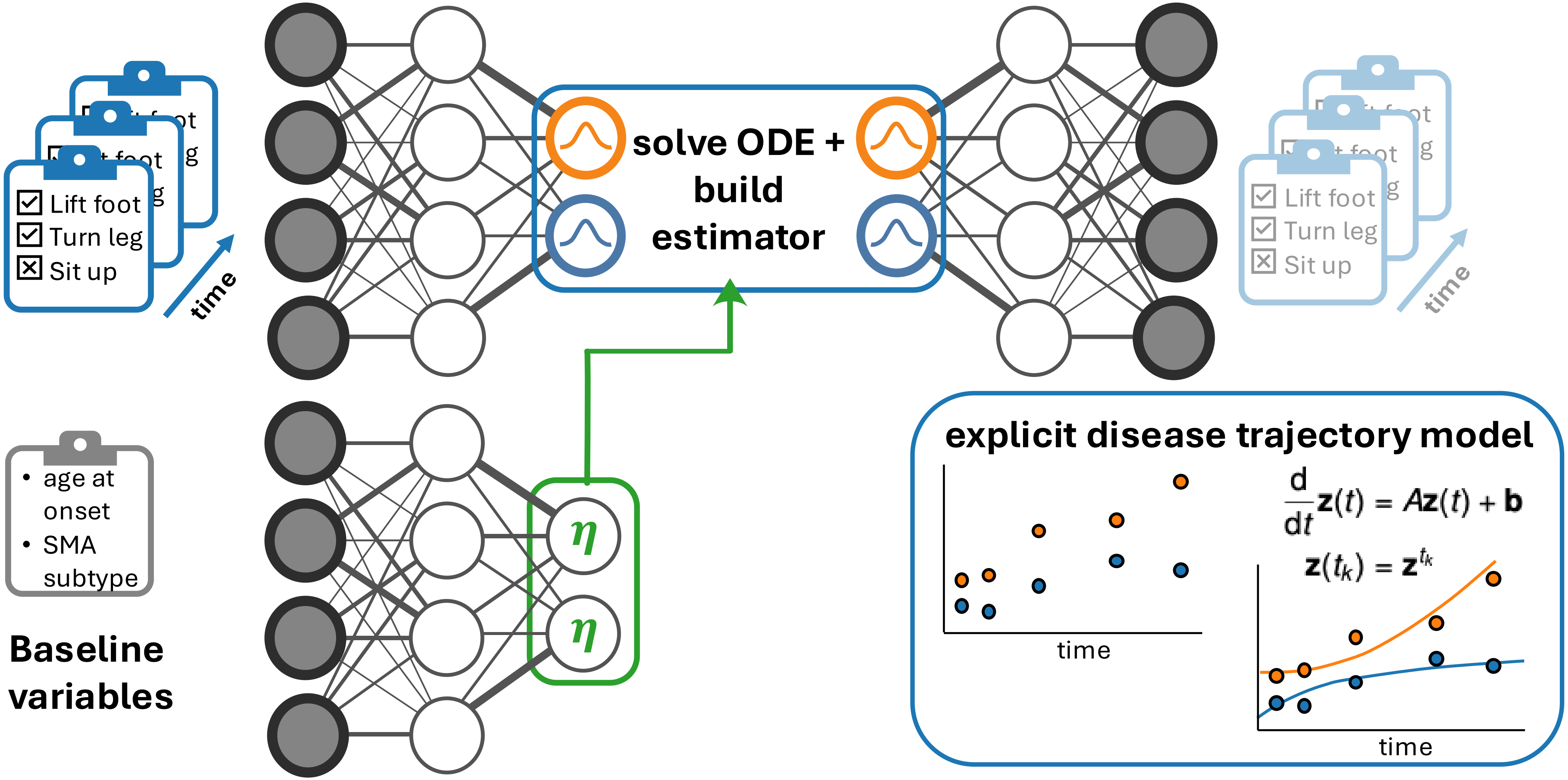
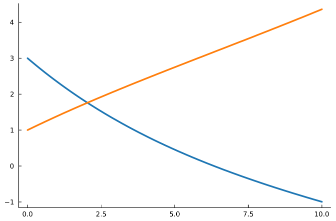
Describing individual SMA trajectories as solutions of ODEs in a VAE latent space



Simulation study results

Can the approach identify groups with different trends?

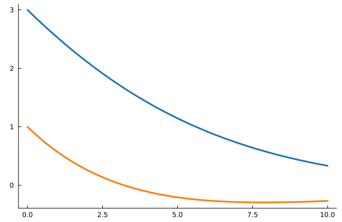


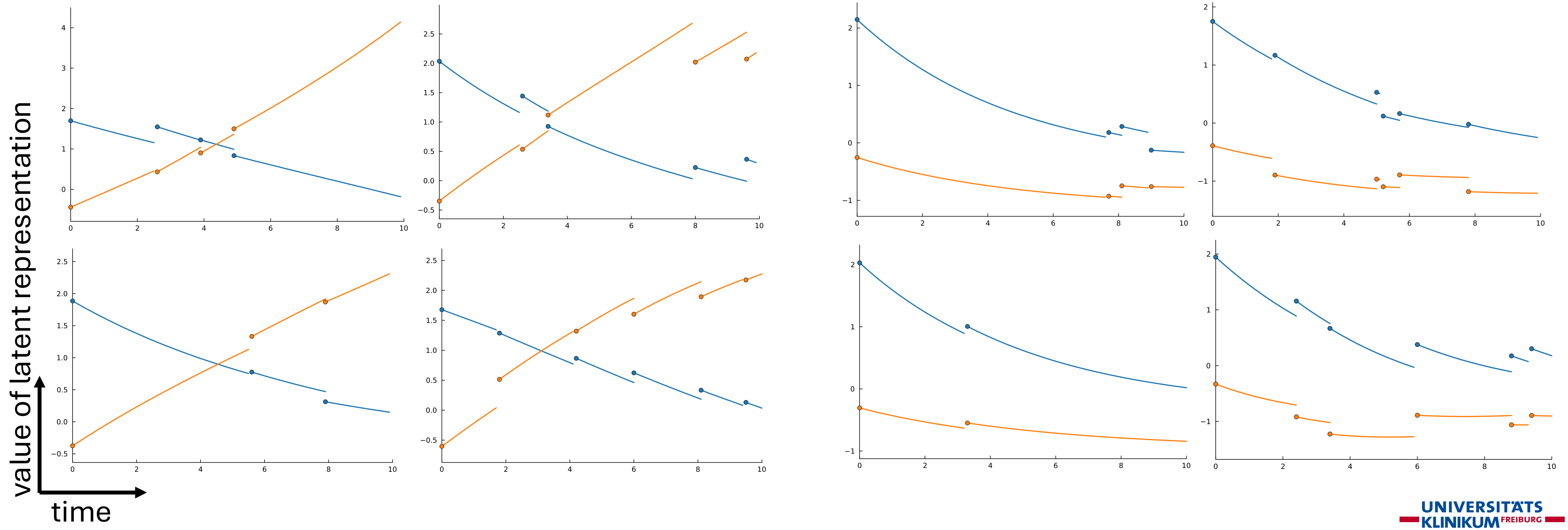
Individuals from group 1

local ODE solution $\widetilde{\mu}_1$ — μ_1 from encoder

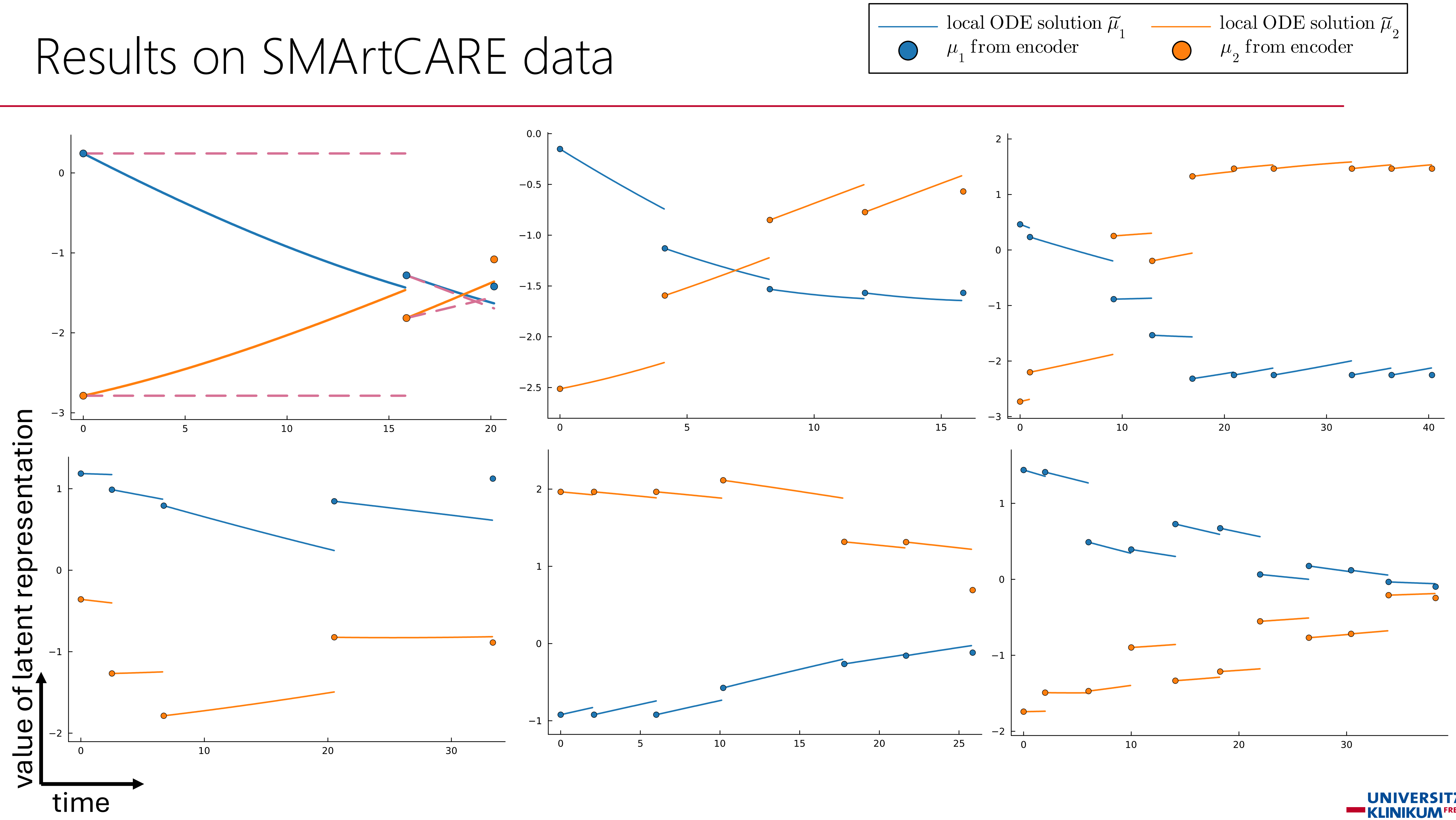
local ODE solution $\widetilde{\mu}_2$ — μ_2 from encoder

Individuals from group 2

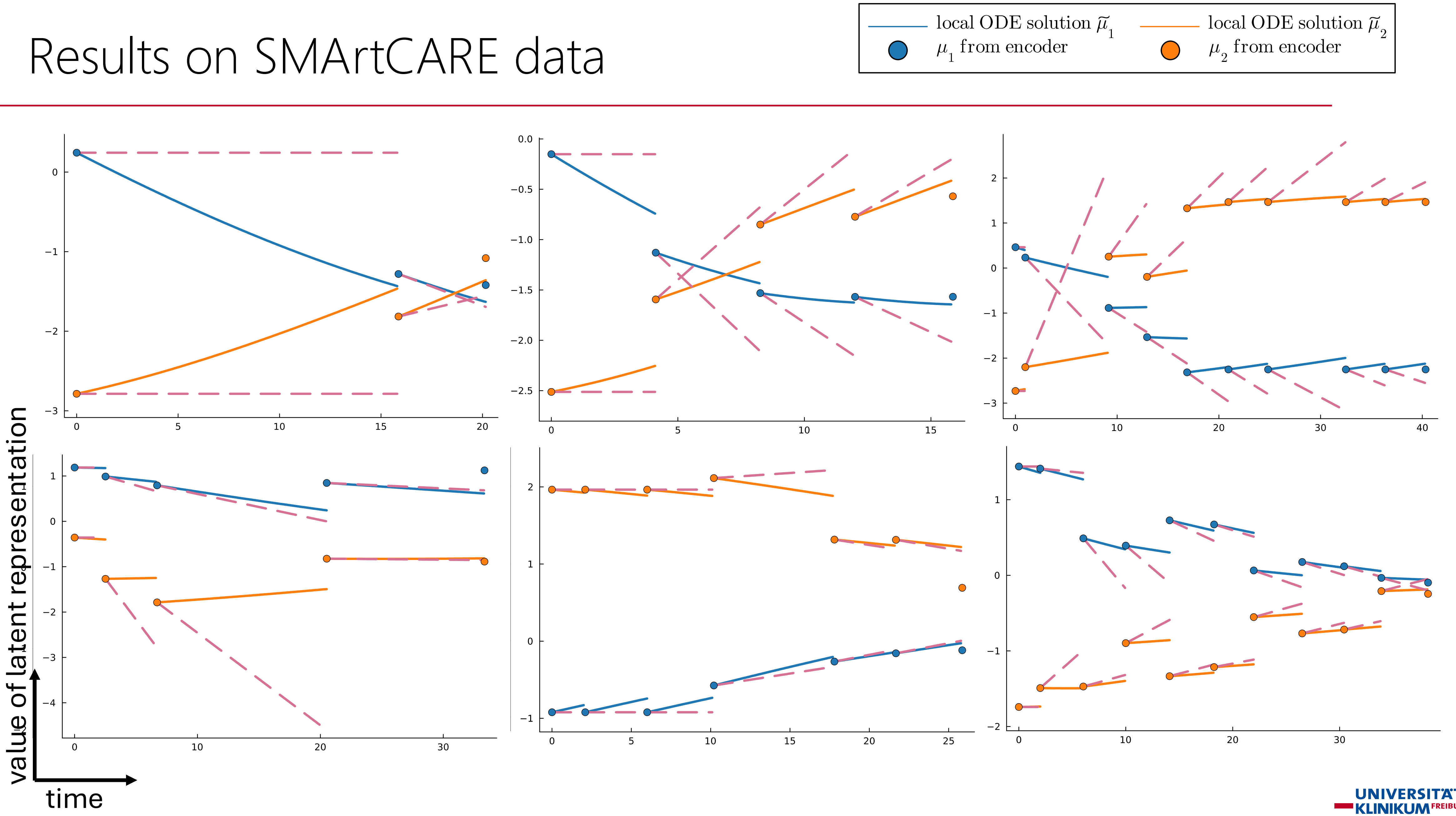




Results on SMArtCARE data

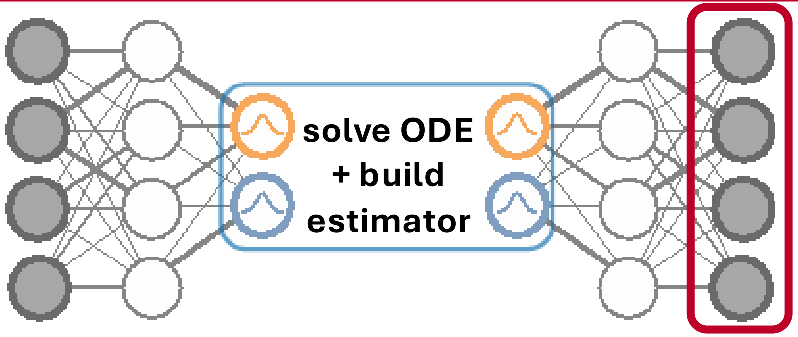


Results on SMArtCARE data



Benchmarking to alternative approaches

Model	Prediction in latent space
ODE	1.386
Regression with baseline variables	1.485
Regression with shift	3.523
Continuous autoregressive model	6.423



Model	Prediction on reconstructions
ODE	5.181
Functional PCA	19.611
Regression with shift	20.890

Summary

- Different modelling approaches correspond to different perspectives on dynamic modelling
- Our approach: ODEs for local predictions based on a patient‘s current status
  - Deep learning for identifying a low-dimensional latent health status **(1)**
  - Statistical framework for robustness to noise **(2)**
  - Patient-specific ODE parameters obtained from baseline variables **(3)**

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small data
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Kiana Farhadyar
Maria Krissmer
Niklas Brunn
Fabian Kabus

Thank you for listening!

… Questions?

If you're interested, take a look at our paper + package :

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A Statistical Approach to Latent Dynamic Modeling with Differential Equations

Maren Hackenberg[a], Astrid Pechmann[b], Clemens Kreutz[a,c,d], Janbernd Kirschner[b], and Harald Binder[a,c,d]

[a]Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg im Breisgau, Germany; [b]Department of Neuropediatrics and Muscle Disorders, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg im Breisgau, Germany; [c]Freiburg Center for Data Analysis, Modeling and AI, University of Freiburg, Freiburg im Breisgau, Germany; [d]Centre for Integrative Biological Signaling Studies (CIBSS), University of Freiburg, Freiburg im Breisgau, Germany

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maren.hackenberg@embl.de