PARAMETER UNIQUENESS/IDENTIFIABILITY

QUANTIFYING INSULIN RESISTANCE FROM WEARABLE SENSORS

VITAL Training School 1,
Delft University of Technology.

March 19th 2025

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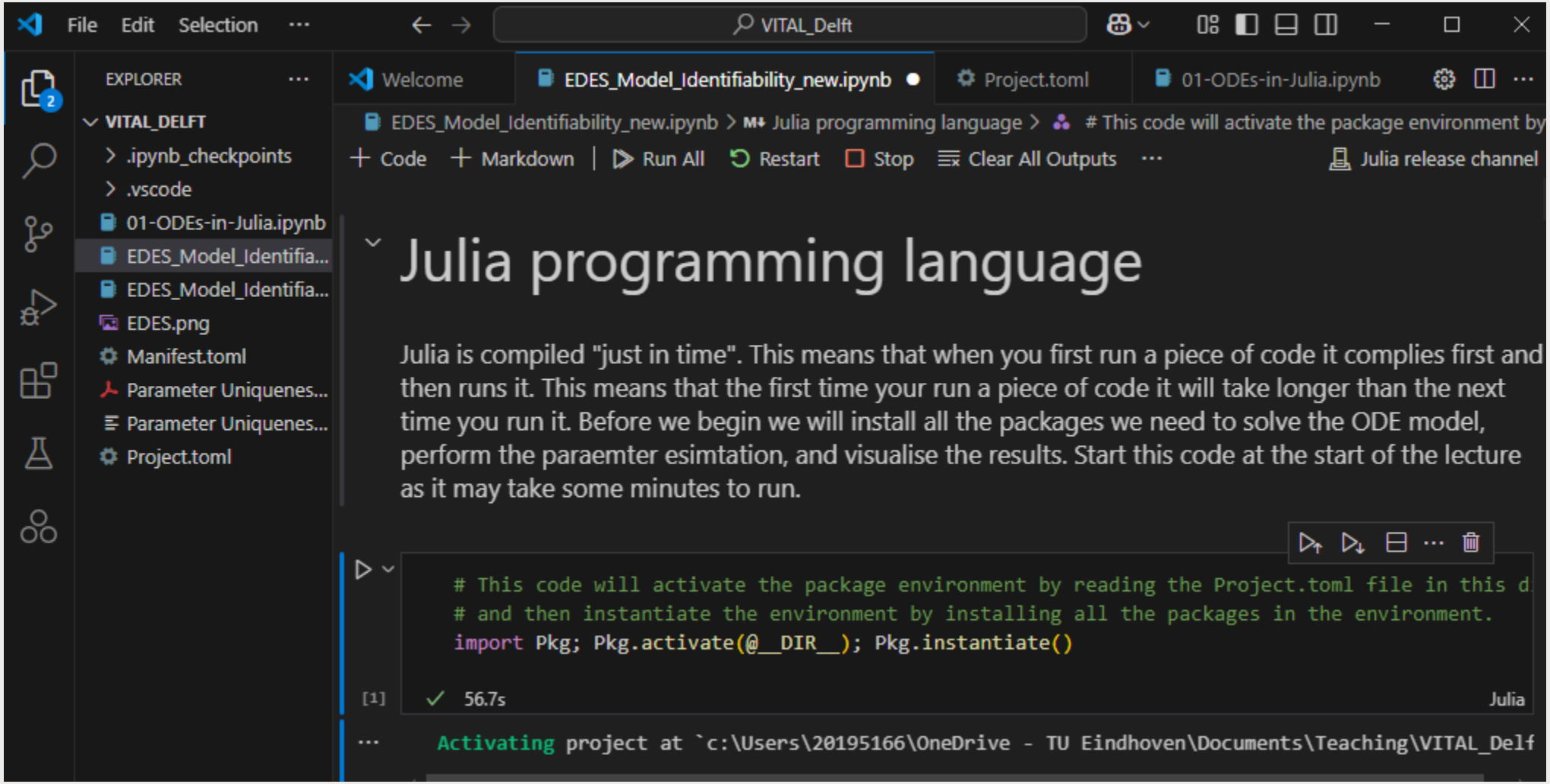
Parameter Indentifiability: Personalising the Eindhoven Diabetes Education Simulator

This is the repository for the Tutorial on parameter uniqueness/identifiability as part of the VITAL Training School 1, Delft University of Technology on March 19th 2025.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01-ODEs-in-Julia.ipynb
EDES_Model_Identifiability_new.ipynb > Julia programming language > # This code will activate the package environment by
Code
Markdown
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Julia release channel
Julia programming language
Julia is compiled "just in time". This means that when you first run a piece of code it complies first and then runs it. This means that the first time your run a piece of code it will take longer than the next time you run it. Before we begin we will install all the packages we need to solve the ODE model, perform the paraemter esimtation, and visualise the results. Start this code at the start of the lecture as it may take some minutes to run.
# This code will activate the package environment by reading the Project.toml file in this d
# and then instantiate the environment by installing all the packages in the environment.
import Pkg; Pkg.activate(@__DIR__); Pkg.instantiate()
[1]
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Julia
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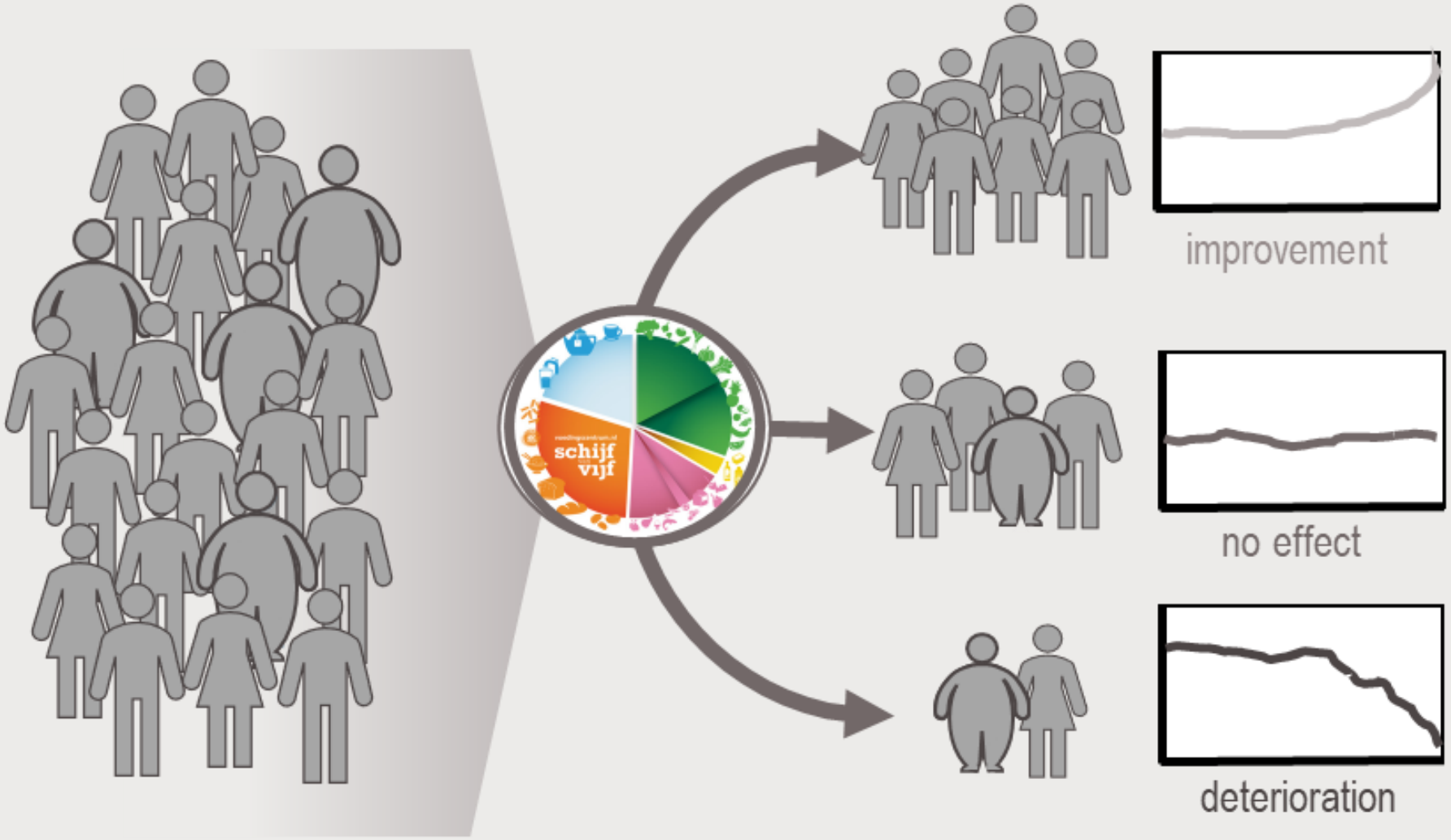
Current medicine

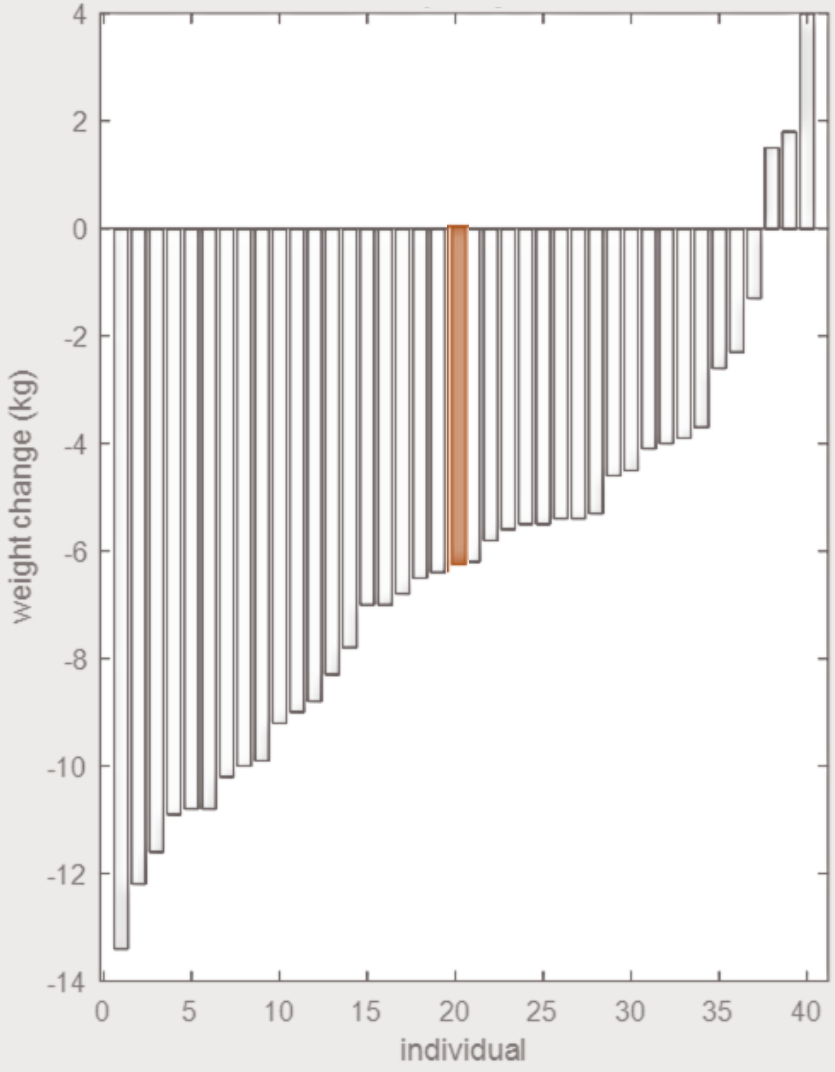
One-size-fits-all



Current medicine

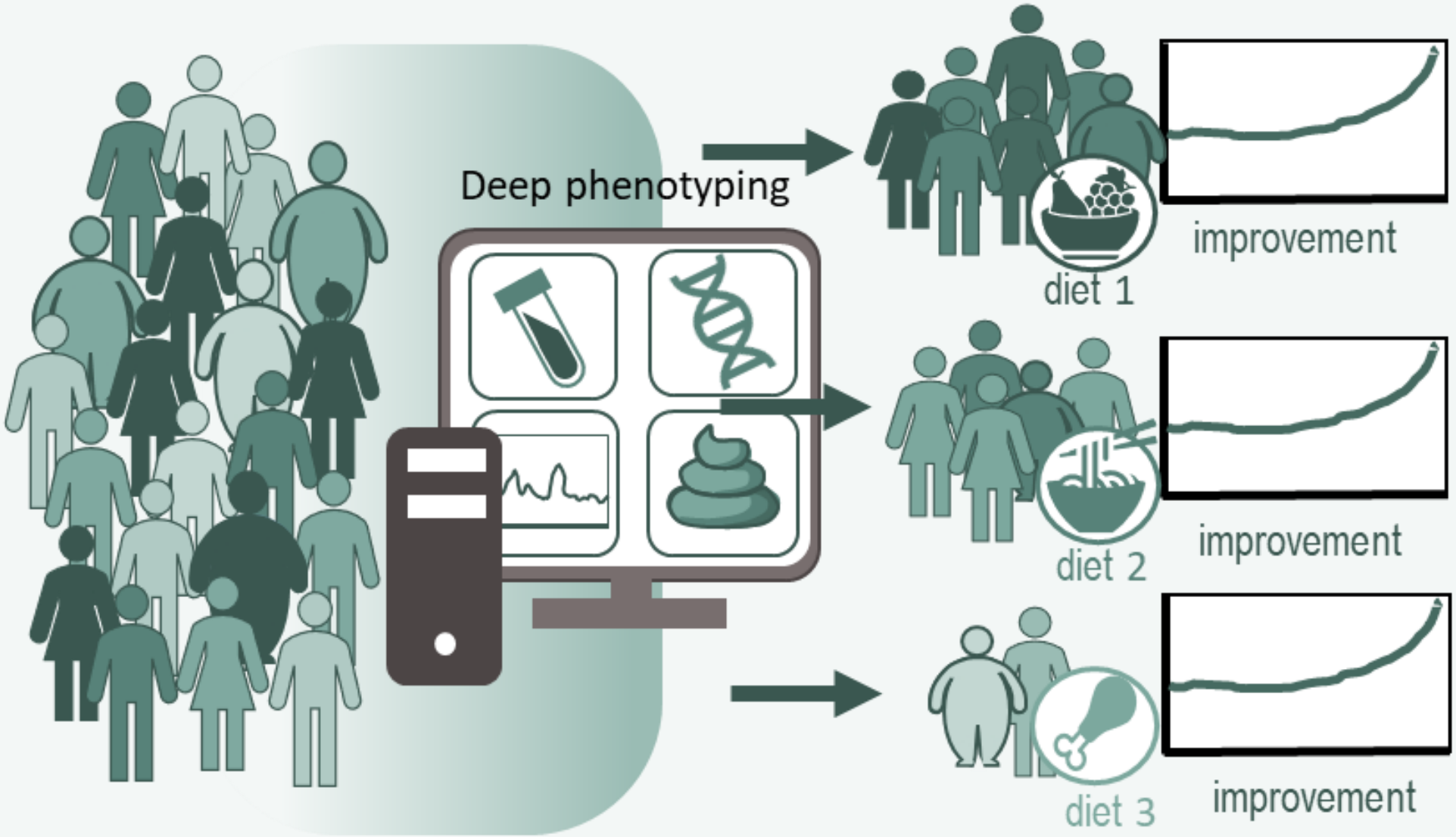
One-size-fits-all

20% caloric restriction



Future of medicine

Personalised treatment strategies



WHAT IS HEALTH?

Health was once considered the **absence of disease or injury**.

More recently, the concept of health has been redefined as the **ability** of an individual to **respond and adapt** to **physical, emotional, or social challenges**, referred to as **resilience**.

WHAT IS HEALTH?

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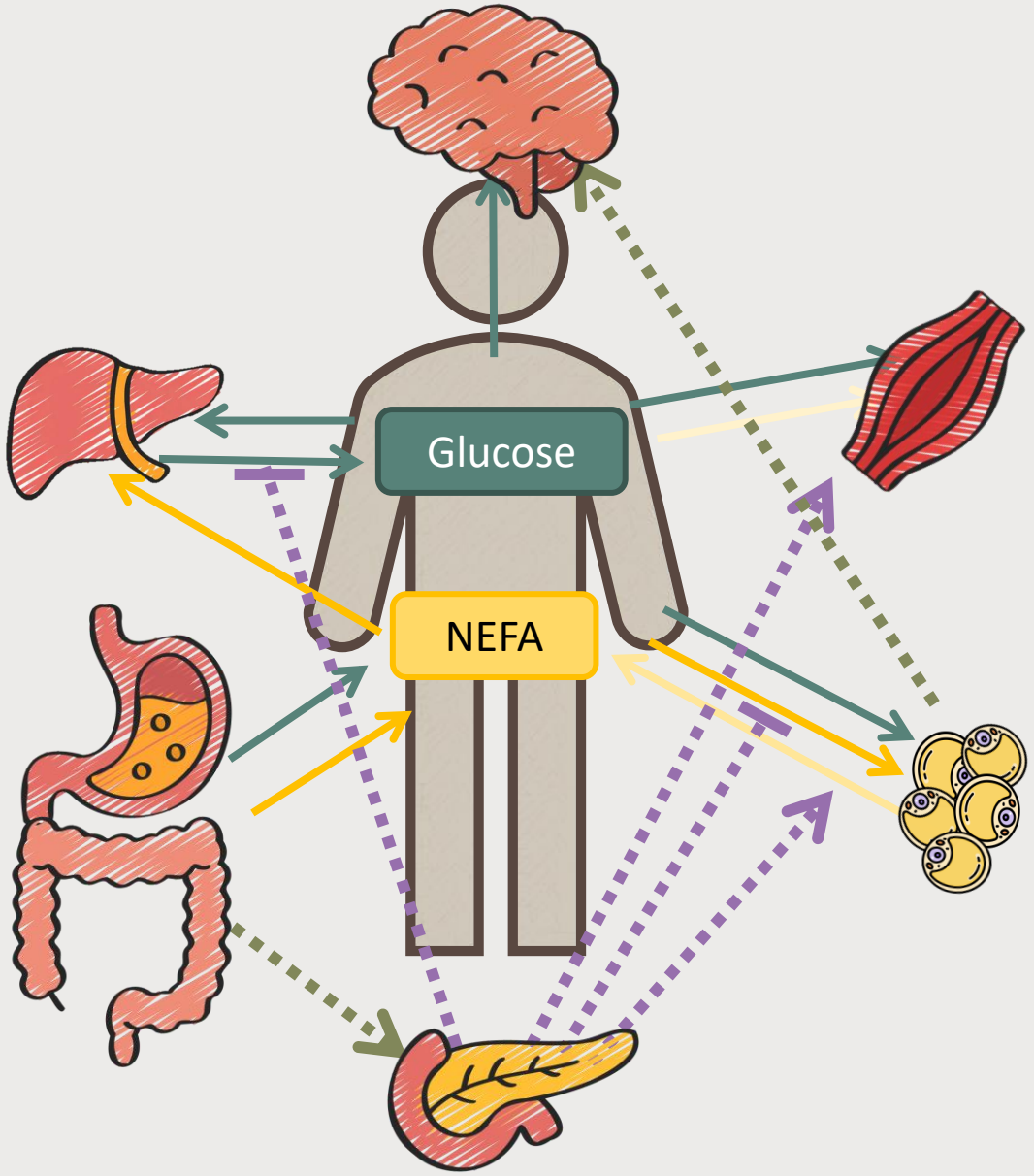
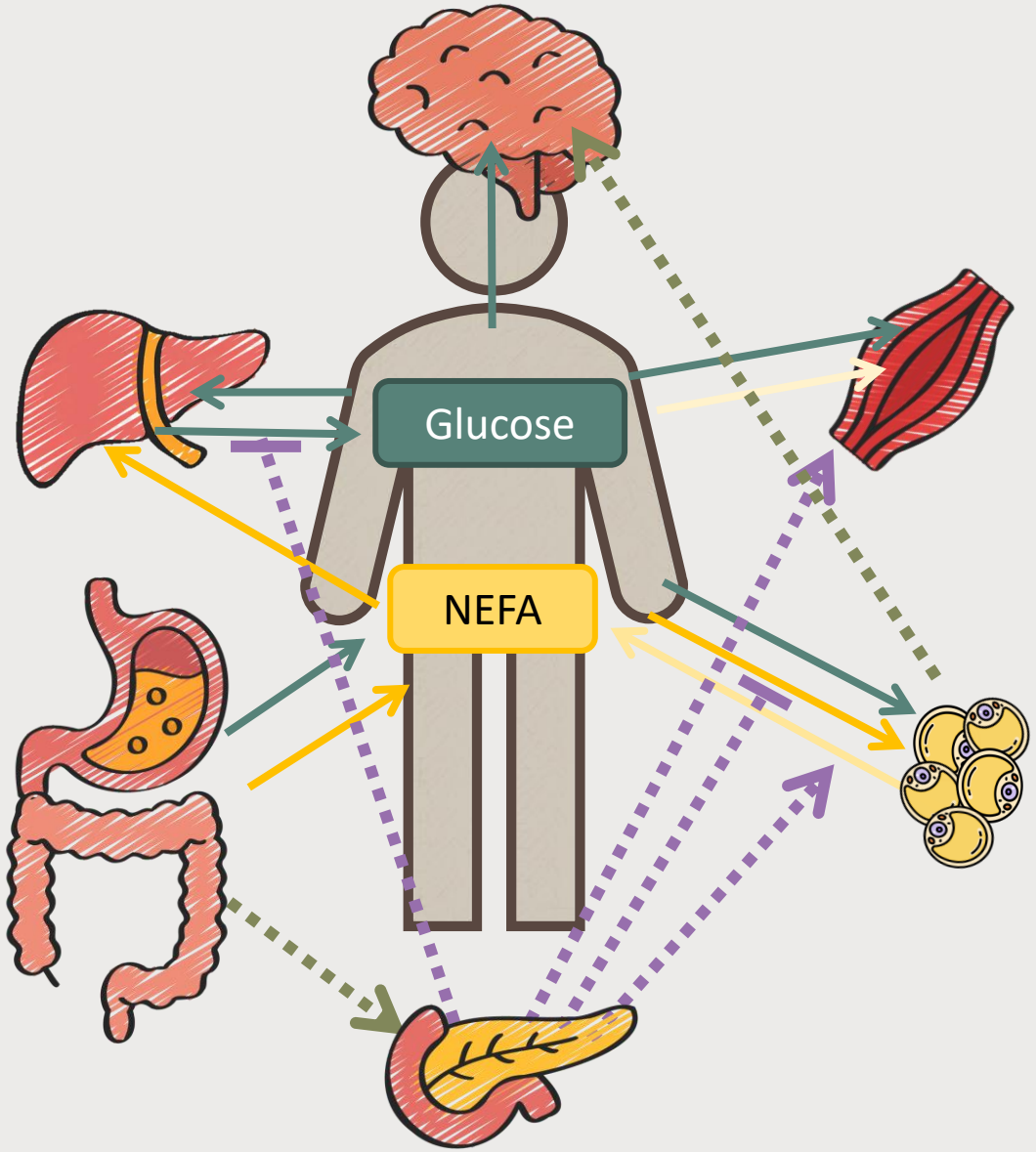
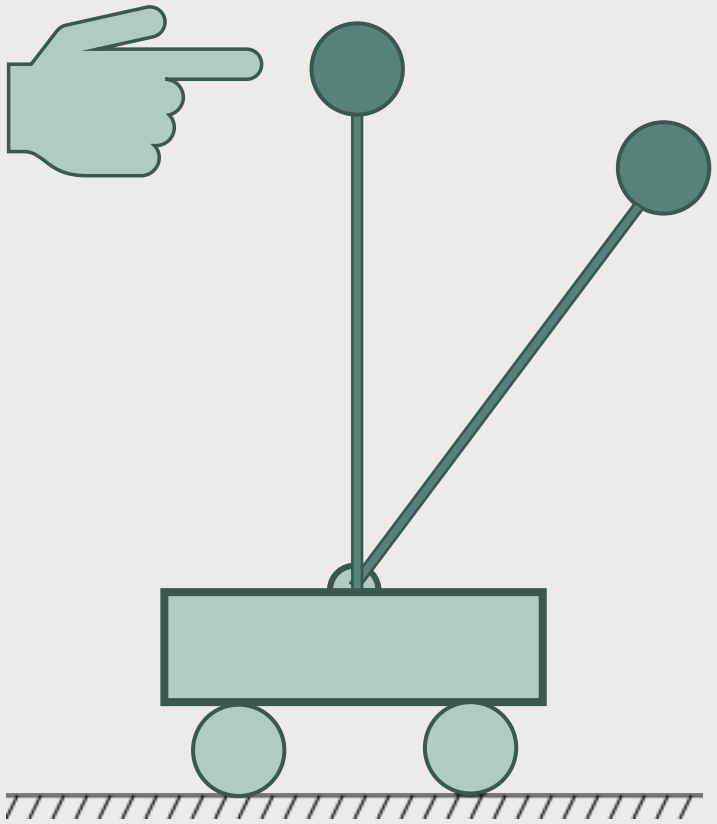
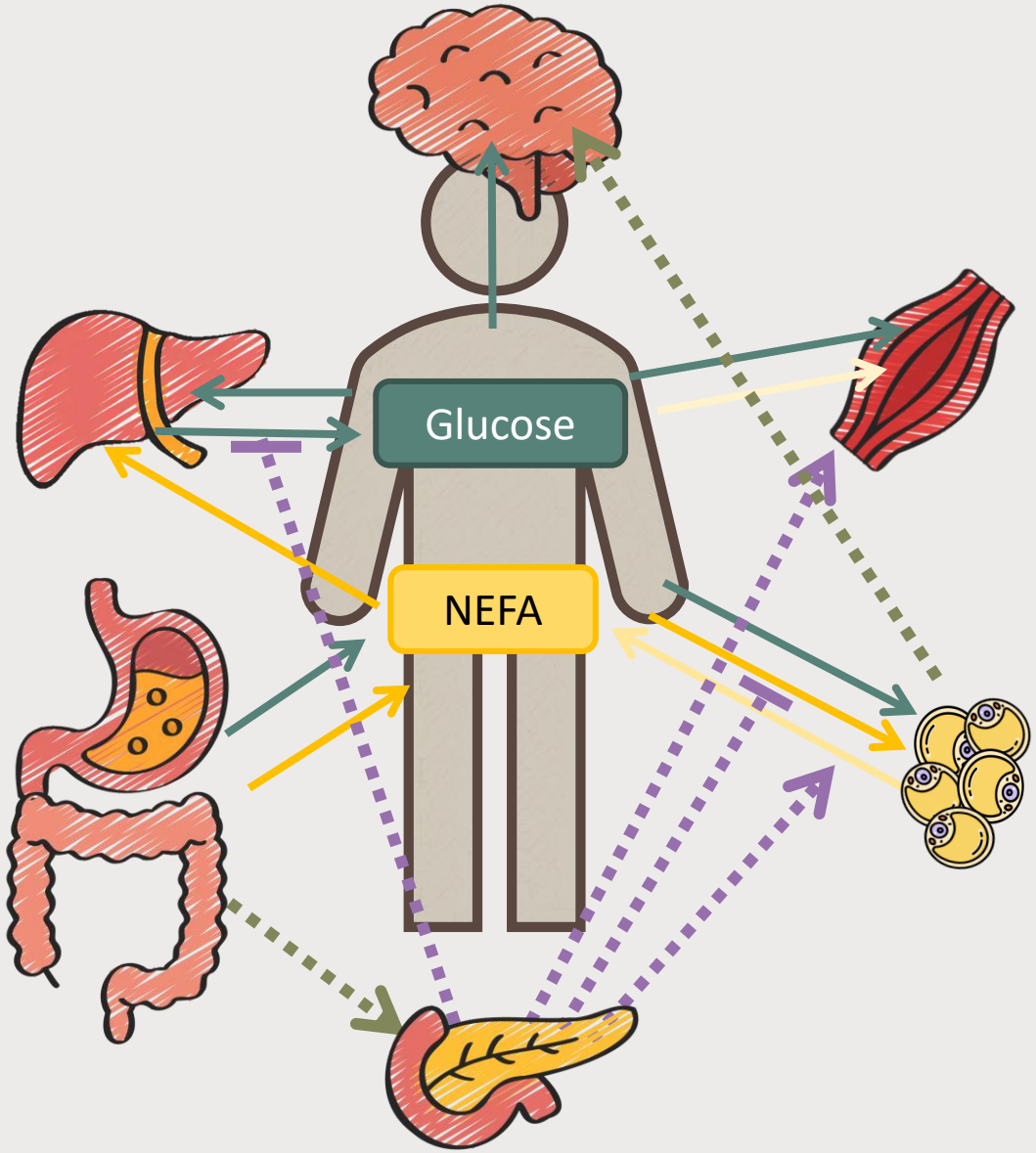


METABOLIC RESILIENCE



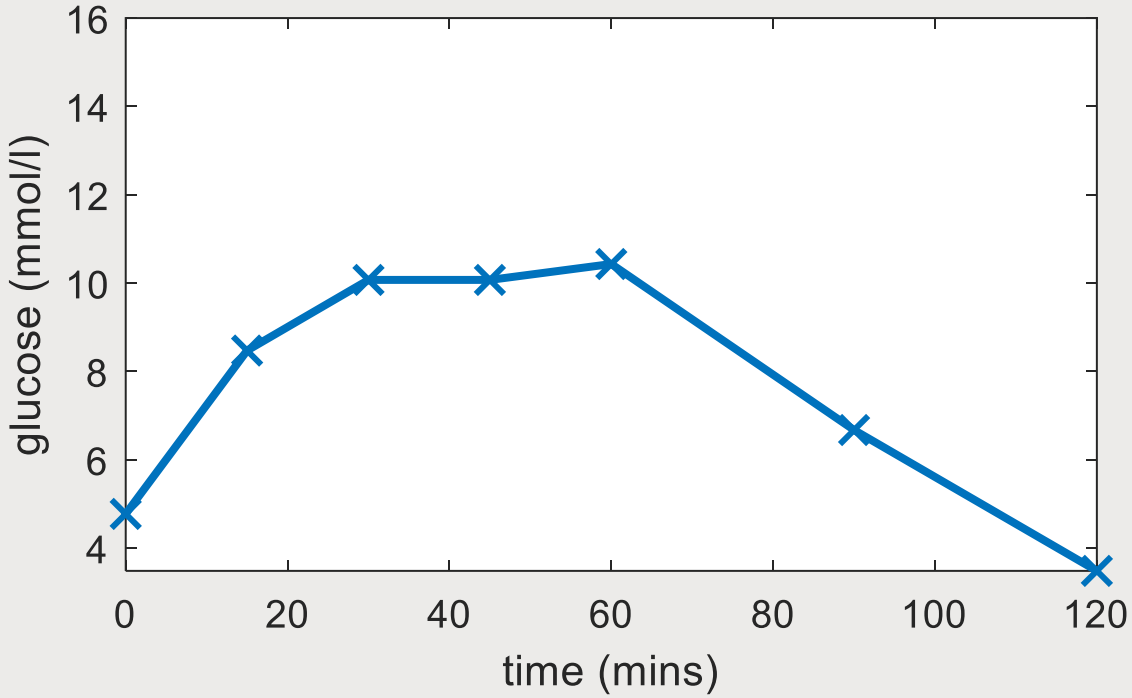


METABOLIC RESILIENCE

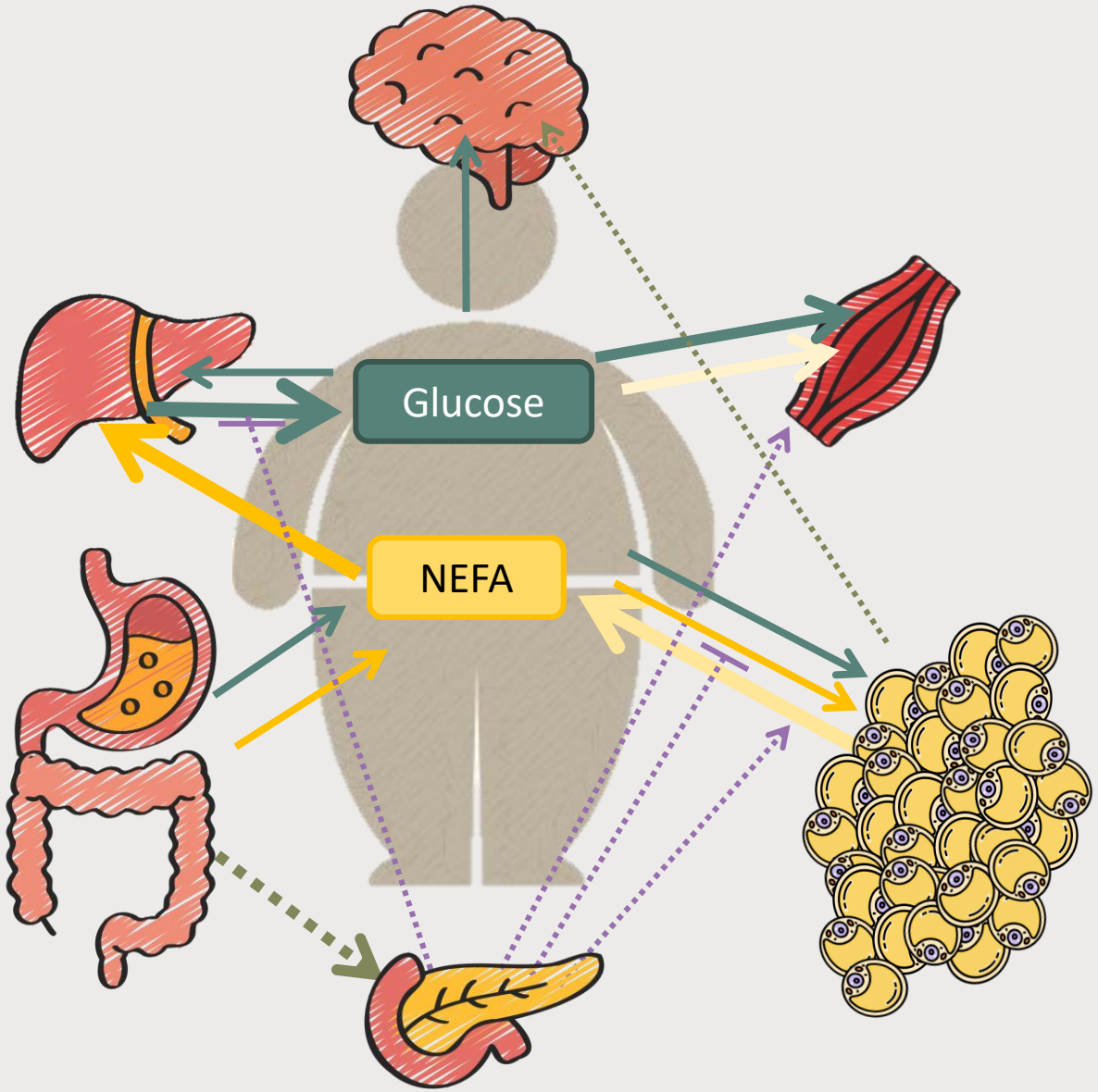


Healthy individual

Meal Response



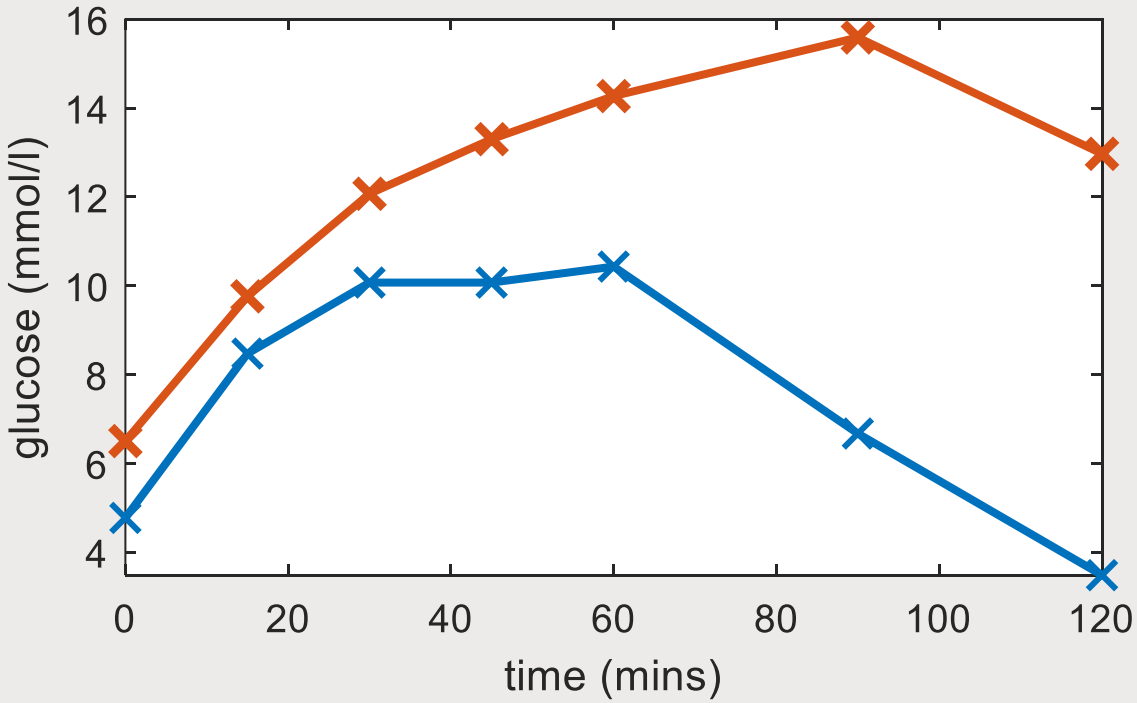
METABOLIC RESILIENCE



Healthy individual

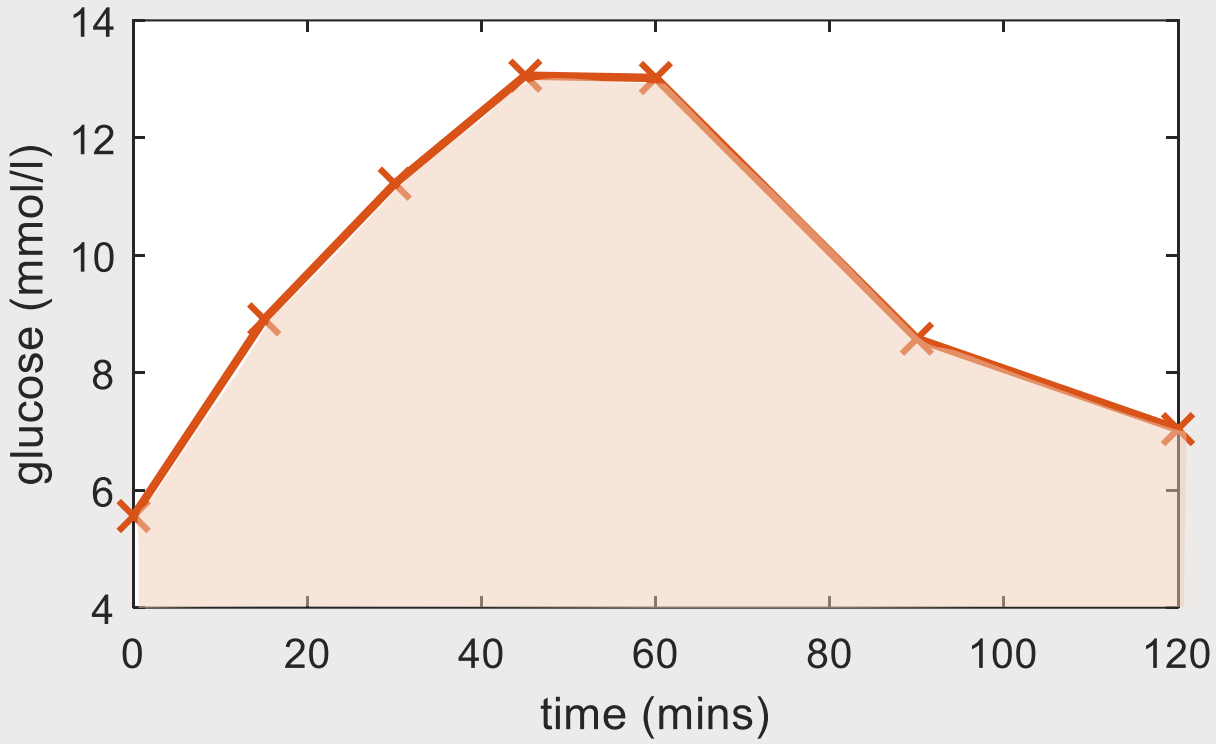
Individual with insulin resistance.

Meal Response



HOW TO QUANTIFY METABOLIC RESILIENCE

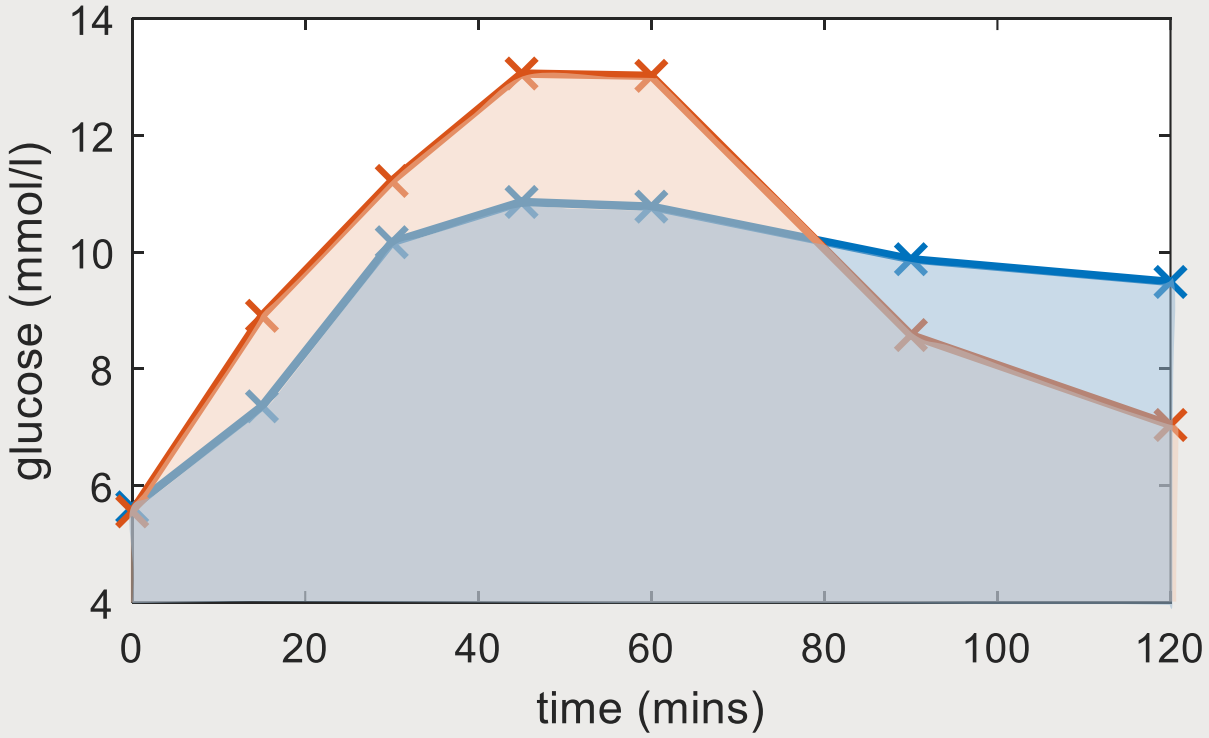
- Fasting values
- 2hour values
- Mean value
- Area under curve



HOW TO QUANTIFY METABOLIC RESILIENCE

- AUC reduces dynamic information to a single value.
- Two curves with very different dynamics may have very similar AUC values.

	Person 5	person1 6
AUC	1175	1169
Peak heigh	13.06	10.86
Glucose 120	7.04	9.49
Slope decline	-0.09	-0.02

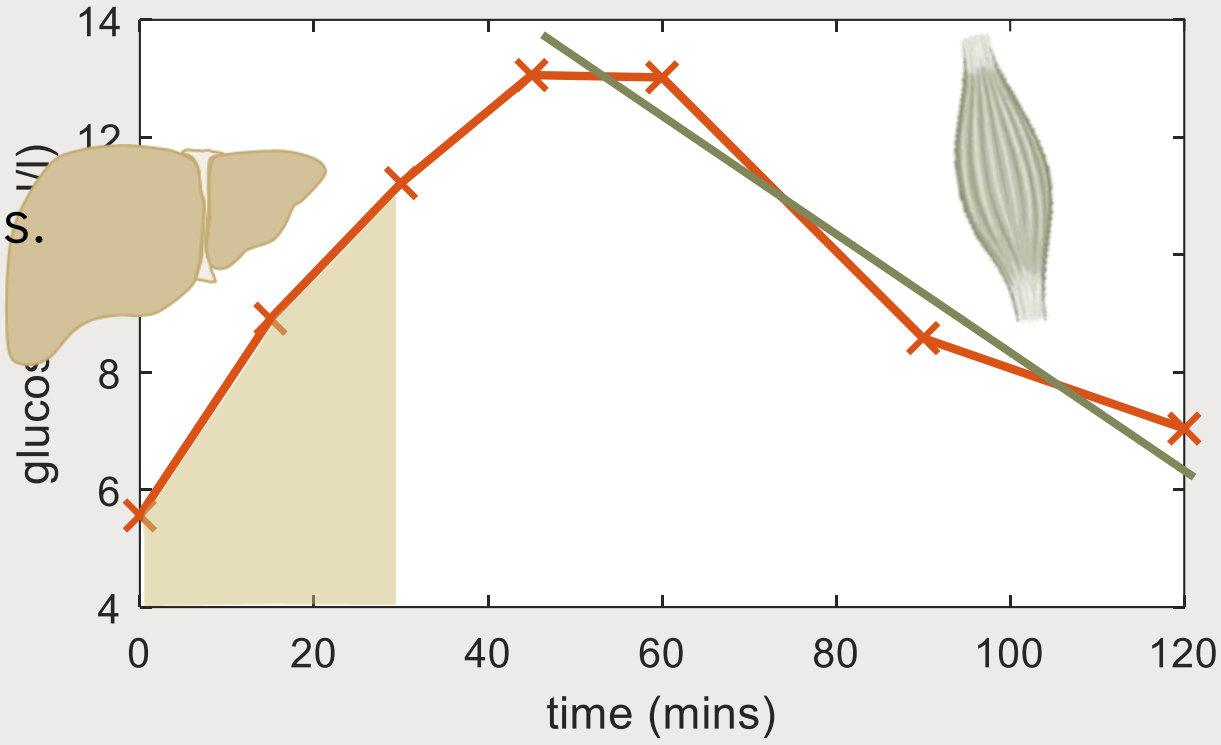


HOW TO QUANTIFY METABOLIC RESILIENCE

Different parts of the meal response curve tell us something about the health of individual tissues and organs.

Early phase of glucose response is governed by liver insulin sensitivity.

Later phase of glucose response is indicative of skeletal muscle health.

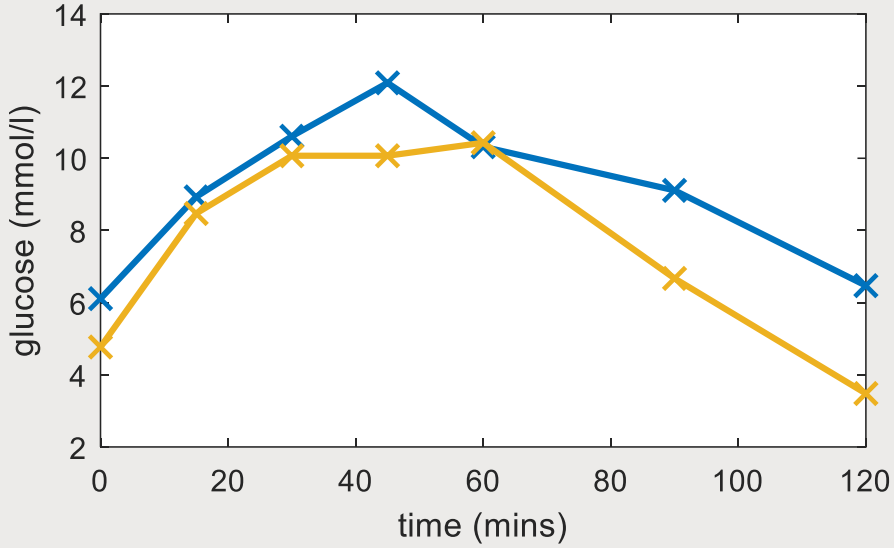


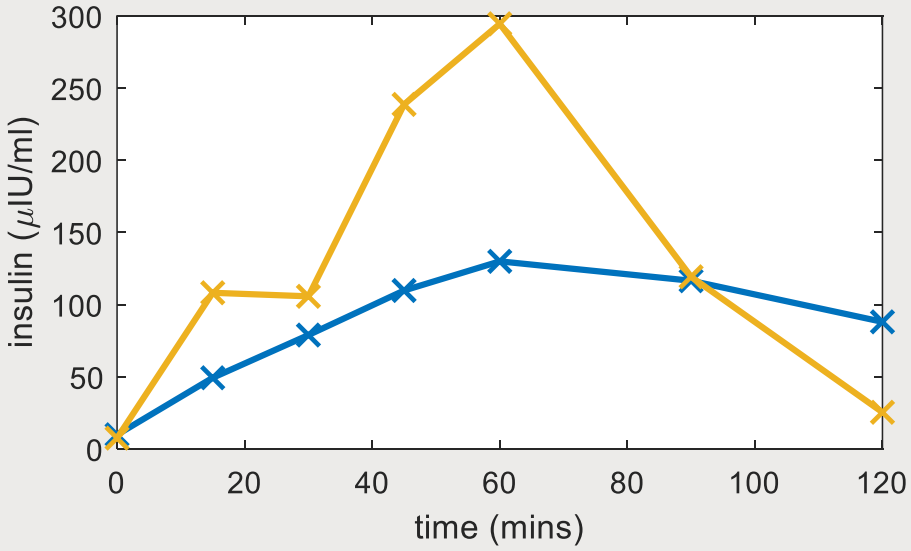
O'Donovan, Lenz et al. (2019) Scientific Reports

HOW TO QUANTIFY METABOLIC RESILIENCE

The relative plasma levels of **multiple metabolites and hormones** may be needed to provide a complete picture of metabolic resilience.

The yellow individual requires much higher insulin levels to maintain glycemic control, suggesting they have insulin resistance.





MATHEMATICAL MODELS OF GLUCOSE-INSULIN SYSTEM

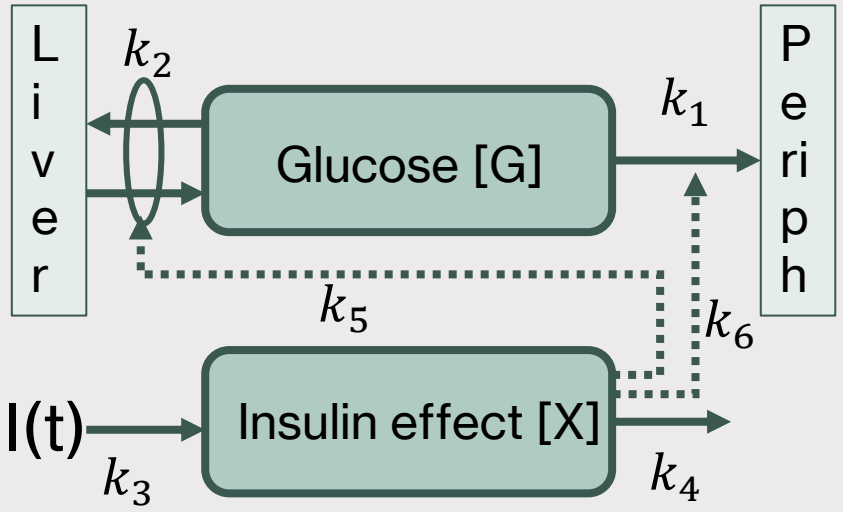
IDENTIFICATION OF A MINIMAL MODEL OF GLUCOSE DISAPPEARANCE FOR ESTIMATING INSULIN SENSITIVITY

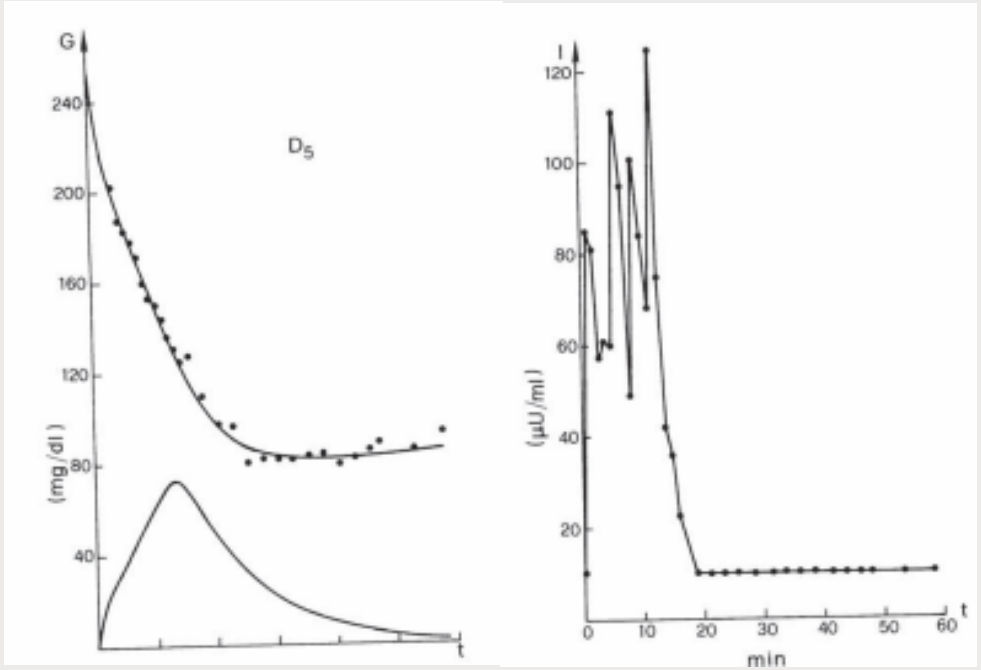
R. N. Bergman*, G. Bortolan**, C. Cobelli** and G. Toffolo**

*Biomedical Engineering Center, The Technological Institute, Northwestern University, Evanston, Illinois 60201, U.S.A.
**Laboratorio per Ricerche di Dinamica dei Sistemi e di Bioingegneria, Consiglio Nazionale delle Ricerche, Padova, Italy and Istituto di Elettrotechnica e di Elettronica, Università di Padova, Padova, Italy

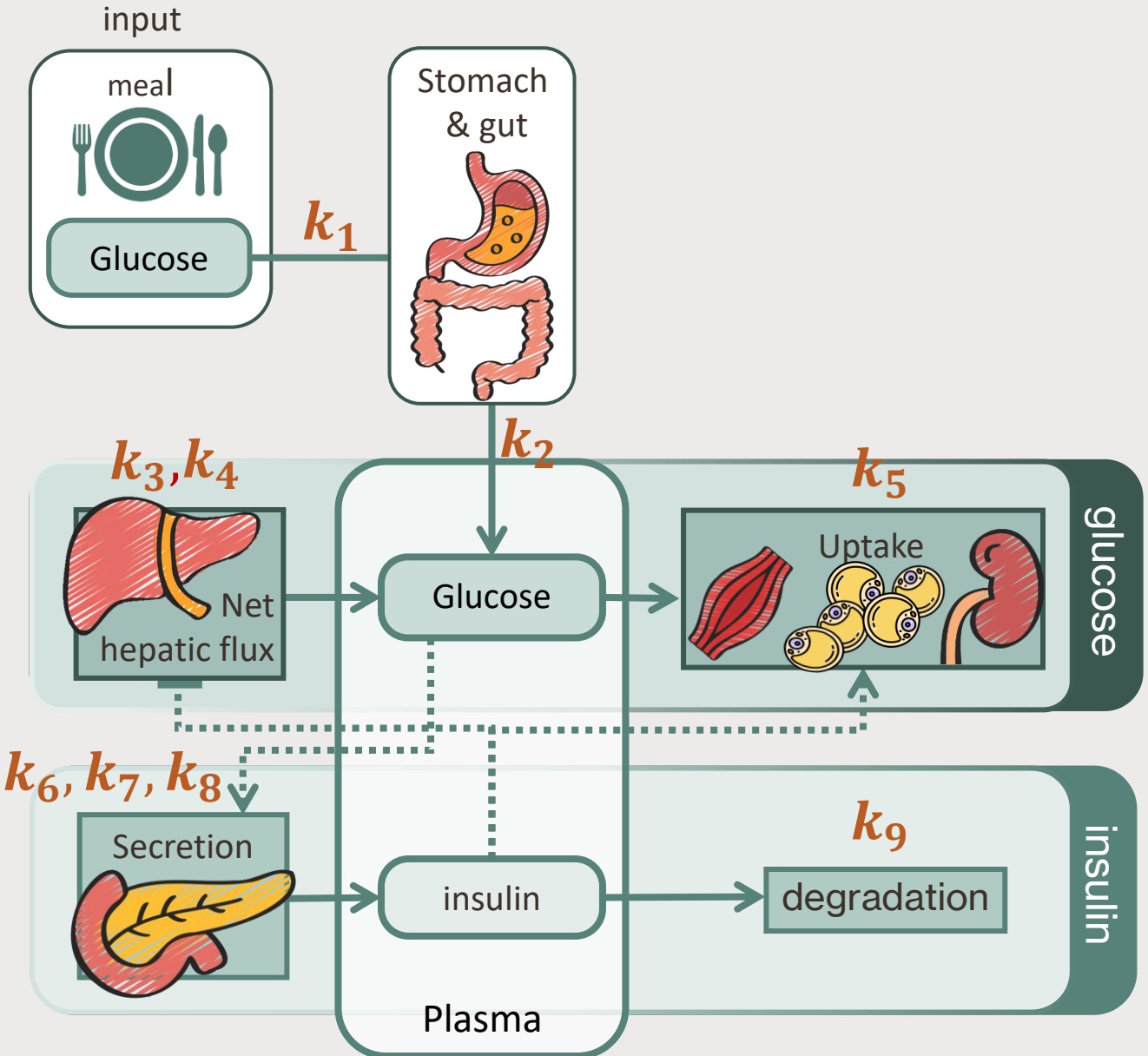
$$\frac{d[G]}{dt} = k_2 \cdot k_5[X] - (k_1 \cdot k_6[X] + k_2 \cdot k_5[X])[G]$$

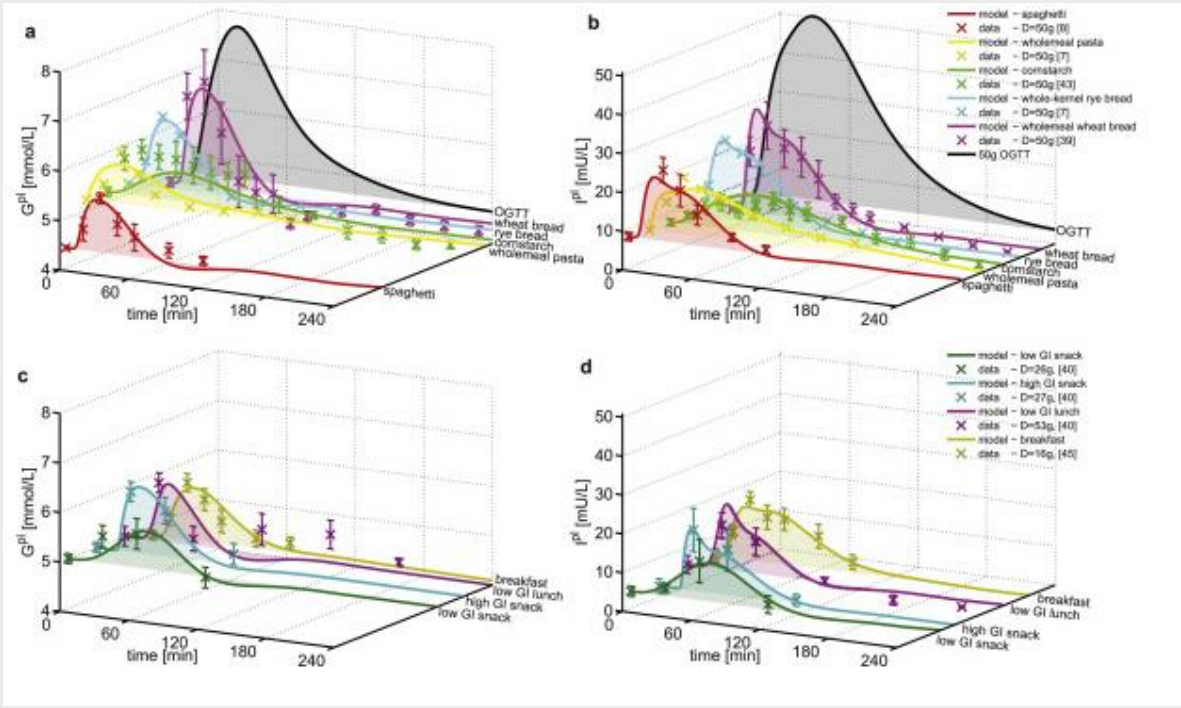
$$\frac{d[X]}{dt} = k_3[I] - k_3[X]$$





EINDHOVEN DIABETES EDUCATION SIMULATOR

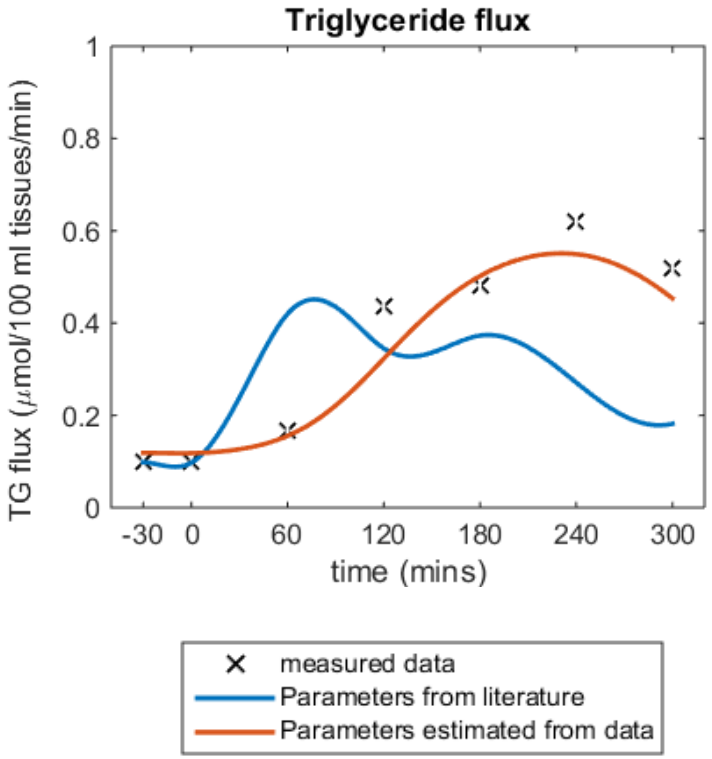




Maas AH, Rozendaal YJ et al. A physiology-based model describing heterogeneity in glucose metabolism: the core of the Eindhoven Diabetes Education Simulator (E-DES). J Diabetes Sci Technol. 2015 Mar;9(2):282-92. doi: 10.1177/1932296814562607.

MAXIMUM LIKELIHOOD ESTIMATION

$$\frac{d[TG_{PL}]}{dt} = \theta_{0.0096} \frac{d[VLDL_{PL}]}{dt}[TG_{PL}]$$



Model can be described as

$$y(t) = f(u(t), \theta) + \xi(t)$$

residuals

$$\Rightarrow \xi(t) = y(t) - f(u(t), \theta)$$

Probability density function

$$p(\xi(t)) = \frac{1}{\sqrt{2\pi\sigma}} e^{\xi(t)^2}$$

Maximise the likelihood

$$\hat{\theta} = \max_{\theta} L(y(t)|\theta)$$

Landscape of parameter estimation

HOW TO SELECT WHICH PARAMETER TO ESTIMATE?

Go to **literature** to determine which parameters are most influential.

Use a combination of local and global **sensitivity analysis** and **AIC/BIC** to determine optimal parameter set **from data**.

HOW TO SELECT WHICH PARAMETER TO ESTIMATE?

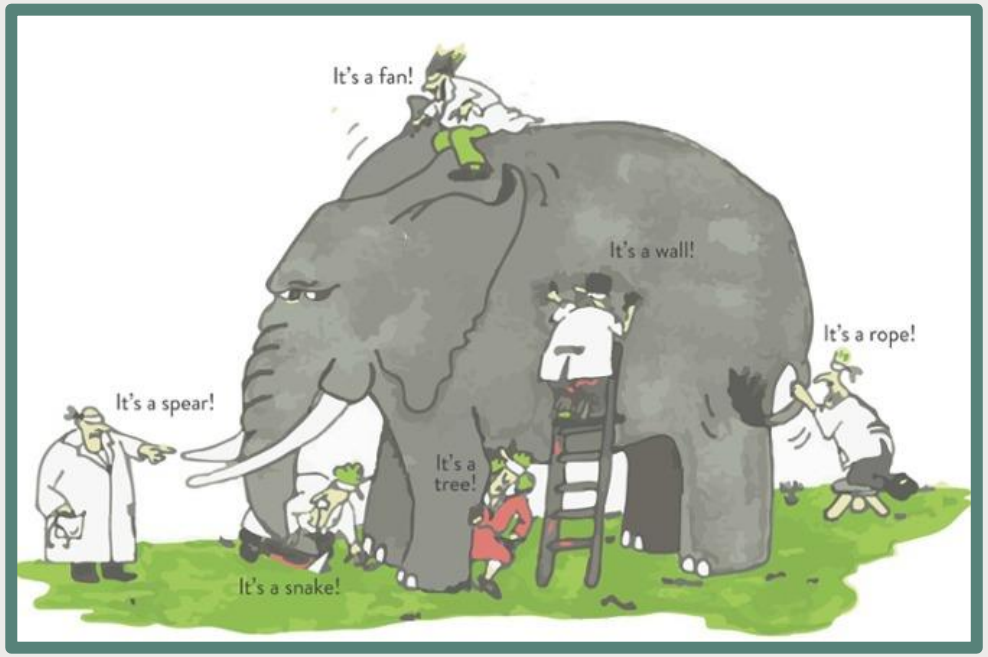
Occam's razor

"Entities should not be multiplied unnecessarily"

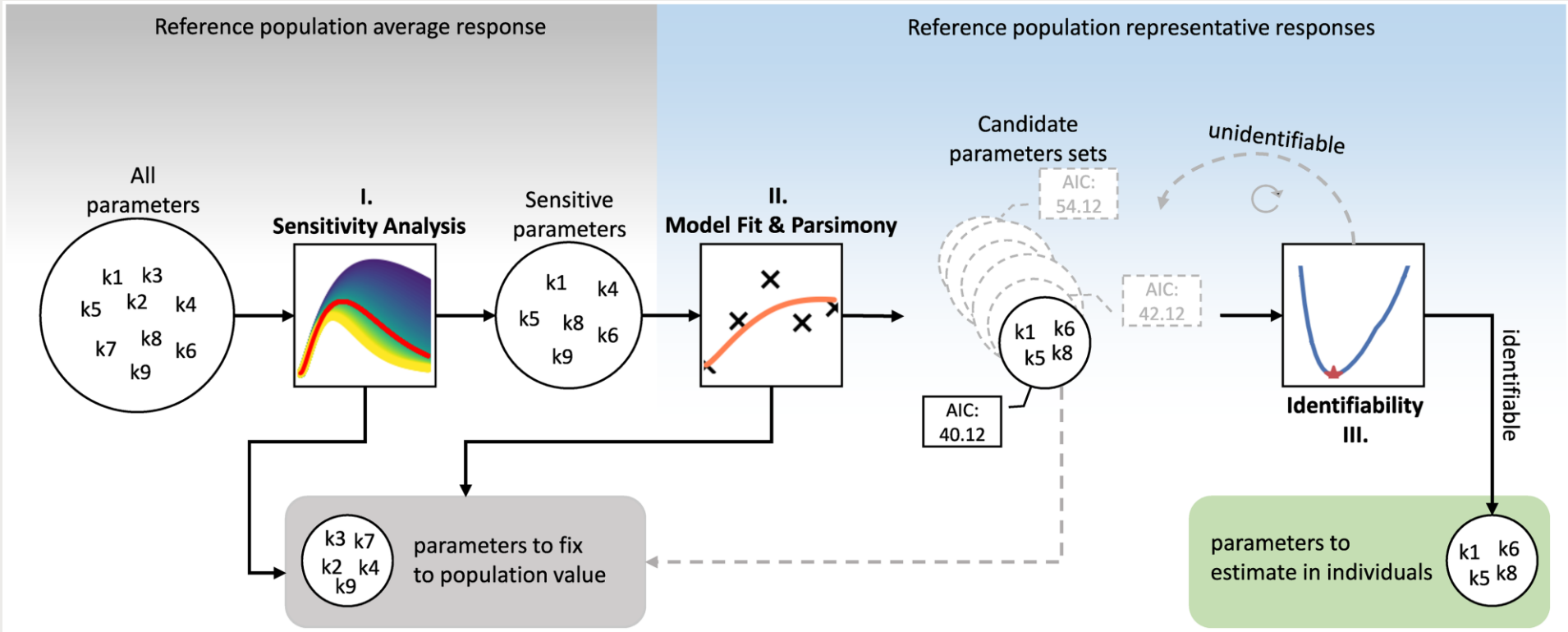
when you have two competing theories that make exactly the same predictions, the simpler one is the better.

"With four parameters I can fit an elephant, and with five I can make him wiggle his trunk."

John von Neumann

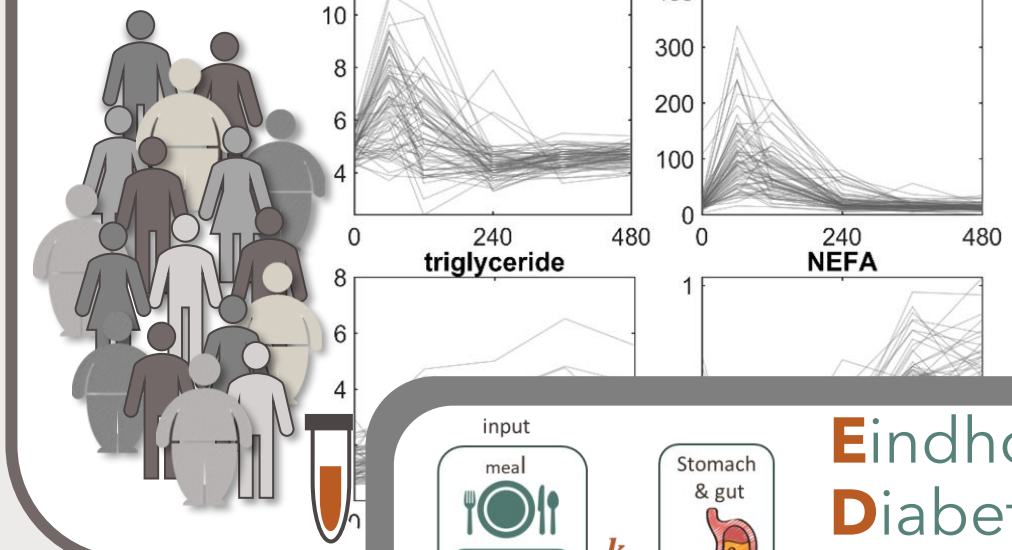


HOW TO SELECT WHICH PARAMETER TO ESTIMATE?

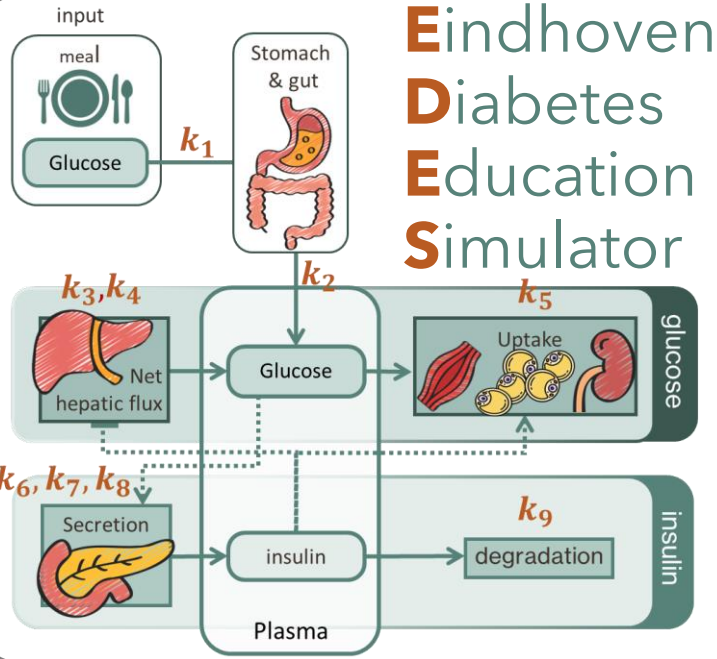


Erdős B, van Sloun B, Adriaens ME, O'Donovan SD et al. (2021) Personalized computational model quantifies heterogeneity in postprandial responses to oral glucose challenge. PLoS Comput Biol 17(3): e1008852. https://doi.org/10.1371/journal.pcbi.1008852

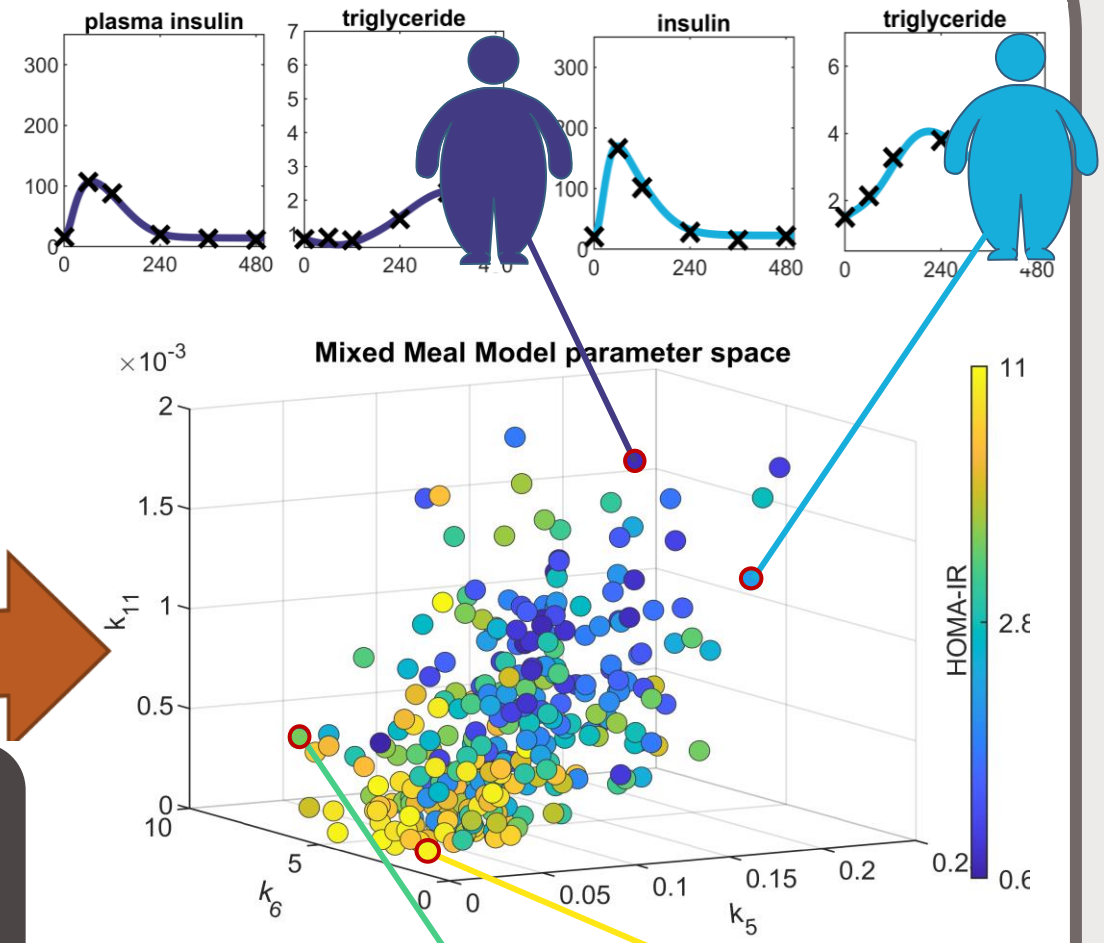
Meal challenge responses



Eindhoven Diabetes Education Simulator



Metabolic resilience phenotype



O'Donovan SD, Rundle M, et al. Quantifying the effect of nutritional interventions on metabolic resilience using personalized computational models. iScience. 2024 Feb 29;27(4):109362. doi: 10.1016/j.isci.2024.109362.

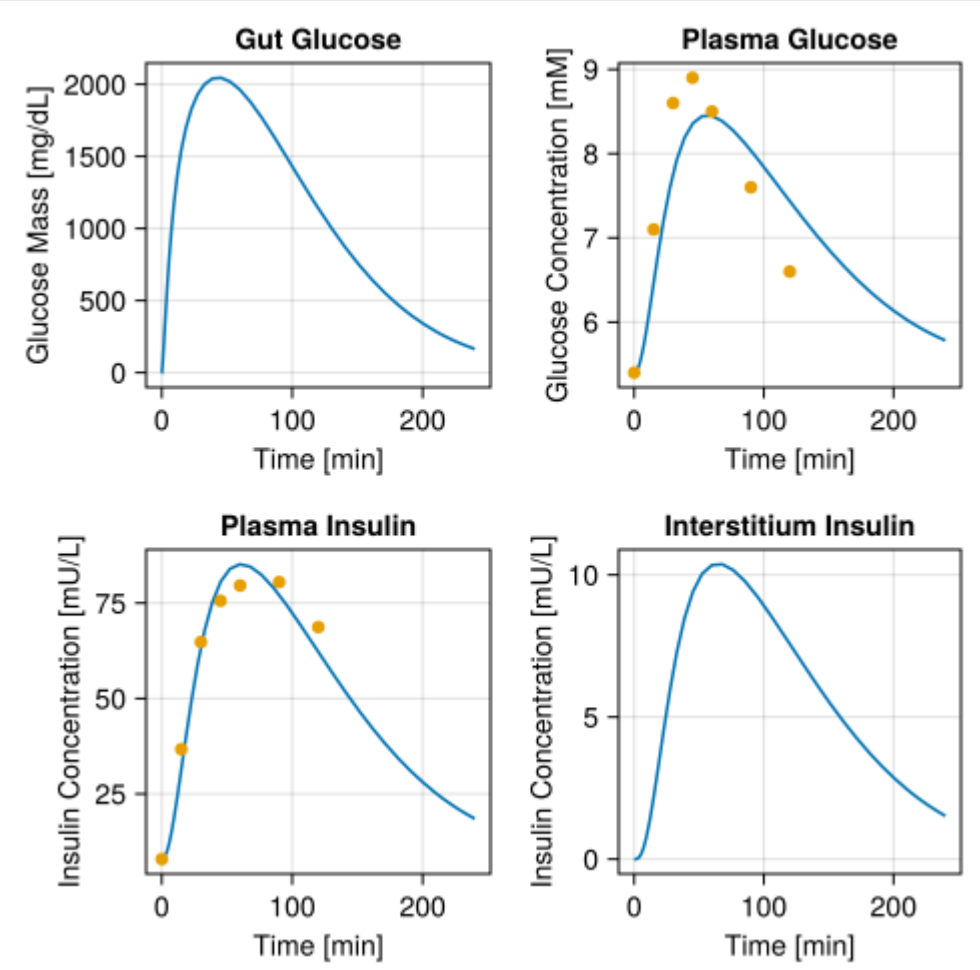
PRACTICAL EXERCISE

The analysis of Erdos et al. identified a four-parameter EDES model as being the most parsimonious.

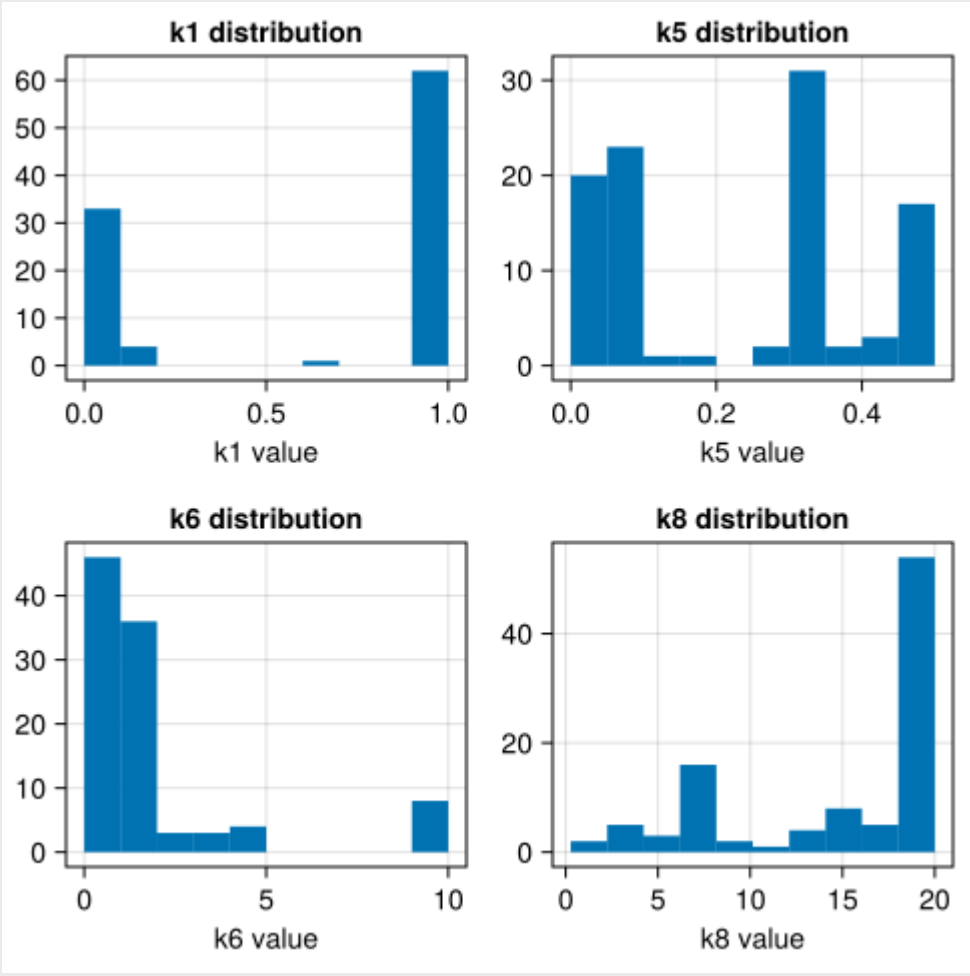
Parameter	Function
k_1	Rate of glucose appearance from gut
k_5	Rate of insulin dependent glucose uptake to tissues
k_6	Insulin secretion in response to glucose (proportional)
k_8	Insulin secretion in response to glucose (derivative)

Estimate these parameters for two individuals using a multi-start approach.

Visualization of fit to average data



Distribution of parameter estimates



PROPERTIES OF ESTIMATED PARAMETER VALUES.

If we are estimating parameters from data what properties do we want these parameters to have?

IDENTIFIABILITY

Parameters are said to be **identifiable** if it is theoretically possible to learn the **true value** from **data**.

Due to technical limitations (availability of specific antibodies, or ability to measure specific fluxes in vivo) **biological networks are often only partially observable** – not all model species can be measured.

Given a certain amount and quality of experimental data **can a parameter be estimated unambiguously (uniquely) from the data**.

IDENTIFIABILITY

Parameters are said to be **identifiable** if it is theoretically possible to learn the **true value** from **data**.

Given a certain amount and quality of experimental data **can a parameter be estimated unambiguously (uniquely) from the data**.

$$\text{if } f(p) = f(p') \Rightarrow p = p'$$

TYPES OF NON-IDENTIFIABILITY

- **Global identifiability**

$$\text{if } f(p) = f(p') \Rightarrow p = p' \; \forall \; p$$

- **local identifiability**

$$\exists \; \{p' \subset \text{P}\} \text{ where if } f(p) = f(p') \Rightarrow p = p' \; \forall \; p$$

TYPES OF NON-IDENTIFIABILITY

If a parameter cannot be inferred with an infinite amount of data we say it is **structurally non-identifiability**. Structural non-identifiability arises from functionally related parameters and is **independent of the data availability.**

A parameter is said to be **practically non-identifiable** if it cannot be reliably estimated given **the amount or quality of data available.** Practical non-identifiability can be resolved by collecting **higher-quality data.**

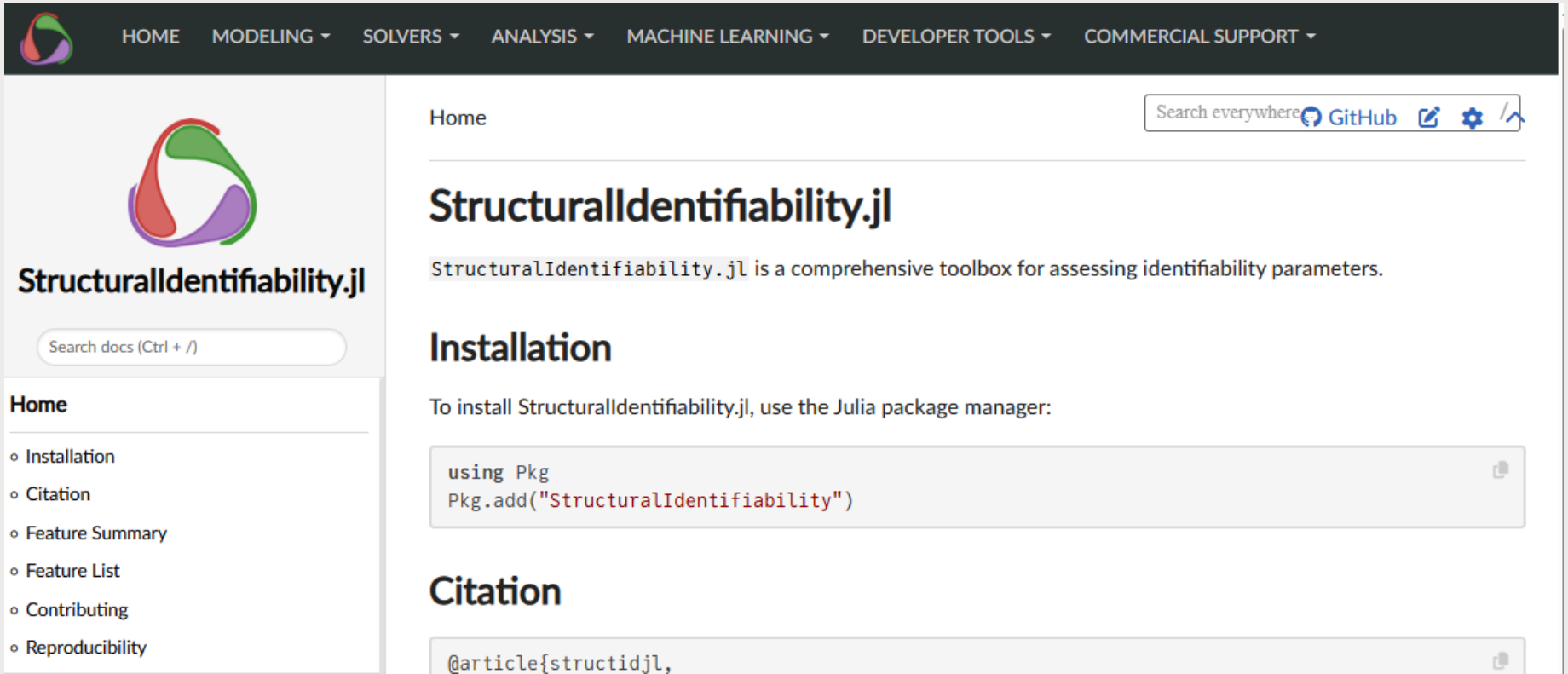
STRUCTURAL IDENTIFIABILITY

If a parameter cannot be inferred with an infinite amount of data we say it is **structurally non-identifiability**.

- Structural non-identifiability occurs when the model makes the **same prediction for more than one value of the parameter**.
- Structural non-identifiability is a **problem with the model structure independent of the data availability.**
- Structural non-identifiability can only be **resolved** by introducing **qualitatively new measurements** (i.e. increase the number of observed variables) or **changing the structure of the model.**

STRUCTURAL IDENTIFIABILITY

The StructuralIdentifiability.jl package is a function in Julia that allows you to assess if the parameters of a model are structurally identifiable given theoretically ideal data availability.



Structural Identifiability Analysis

A cool feature of ModelingToolkit, is the automatic structural identifiability analysis. We can import this with `StructuralIdentifiability`. For this, we first need to define our model using `ModelingToolkit`.

> There is currently a bug in StructuralIdentifiability, which prevents using Greek symbols in the ModelingToolkit model. Therefore, we use the names of the greek symbols. ModelingToolkit will parse them as Greek symbols anyway, while StructuralIdentifiability will remain working

```
using ModelingToolkit, StructuralIdentifiability

@variables t S(t) I(t) R(t) Y(t)
@parameters beta gamma
d = Differential(t)

equations = [
  d(S) ~ -beta*S*I,
  d(I) ~ beta*S*I - gamma*I,
  d(R) ~ gamma*I
]

sirsystem = ODESystem(equations, t, name = :SIRModel)
```

2]

Julia

$$\frac{\mathrm{d}S\left(t\right)}{\mathrm{d}t} = -\beta I\left(t\right)S\left(t\right) \tag{1}$$

$$\frac{\mathrm{d}I\left(t\right)}{\mathrm{d}t} = -\Gamma I\left(t\right) + \beta I\left(t\right)S\left(t\right) \tag{2}$$

$$\frac{\mathrm{d}R\left(t\right)}{\mathrm{d}t} = \Gamma I\left(t\right) \tag{3}$$

We then define an array of measured quantities. In the `@variables` macro, we added an extra variable `Y(t)`, which is our measurement. In the measured quantities array, we can define the correspondence between a measurement and the model state variables. In this case, our measurement directly corresponds to `I`. We then call the `assess_identifiability` function on the system and specify the measured quantities. We then see that it starts computing and shows that all of our parameters are globally identifiable.

```
measured_quantities = [Y ~ I]
sir_identifiability = assess_identifiability(sirsystem, measured_quantities=measured_quantities)
```

9]

Julia

```
Dict{SymbolicUtils.BasicSymbolic{Real}, Symbol} with 2 entries:
  gamma => :globally
  beta  => :globally
```

PRACTICAL IDENTIFIABILITY

Practical non-identifiability considers if parameters can be uniquely estimated given the amount and quality of the available data.

- A structurally identifiable parameter may still be practically non-identifiable given the available data.
- Practical non-identifiability can be **resolved by collecting more frequently sampled/higher quality data**.
- Practical indentifiability can be used to **inform experimental design** (determine how many and/or which time points should be sampled)

PROFILE LIKELIHOOD ANALYSIS

BIOINFORMATICS ORIGINAL PAPER

Vol. 25 no. 15 2009, pages 1923–1929
doi:10.1093/bioinformatics/btp358

Systems biology

Structural and practical identifiability analysis of partially observed dynamical models by exploiting the profile likelihood

A. Raue[1,*], C. Kreutz[1], T. Maiwald[2], J. Bachmann[3], M. Schilling[3], U. Klingmüller[3] and J. Timmer[1,4]

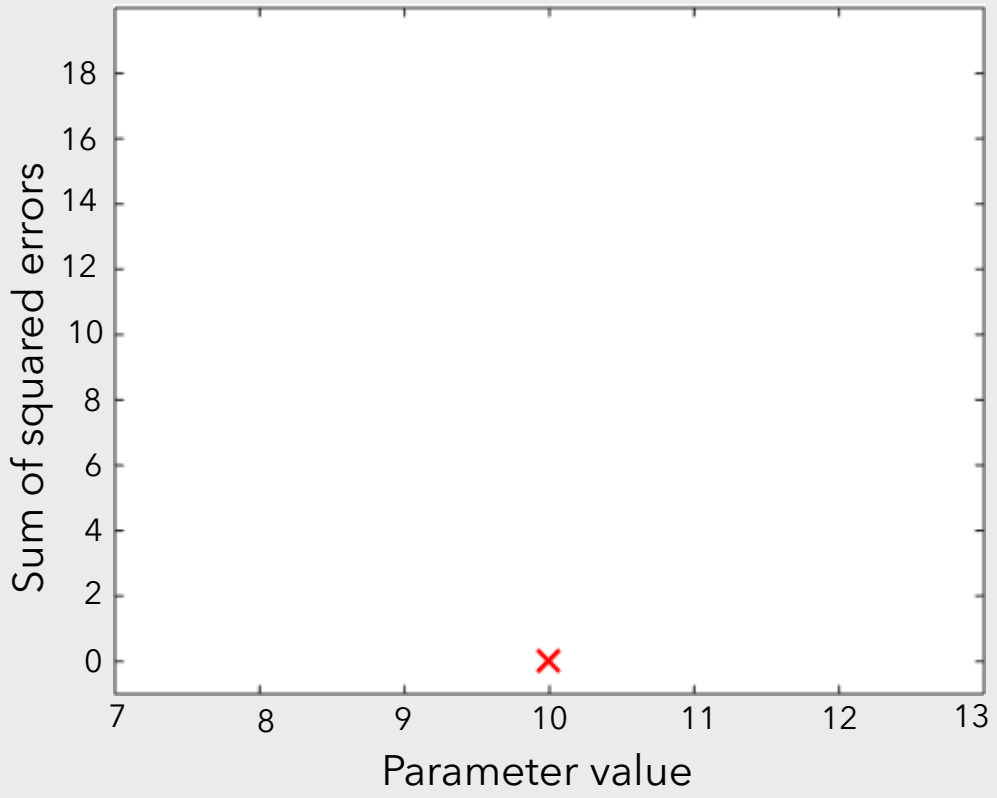
[1]Physics Institute, University of Freiburg, 79104 Freiburg, Germany, [2]Department of Systems Biology, Harvard Medical School, 02115 Boston, MA, USA, [3]Division of Systems Biology of Signal Transduction, DKFZ-ZMBH Alliance, German Cancer Research Center, 69120 Heidelberg and [4]Freiburg Institute for Advanced Studies, University of Freiburg, 79104 Freiburg, Germany

Received on April 14, 2009; revised on May 21, 2009; accepted on June 3, 2009

Advance Access publication June 8, 2009

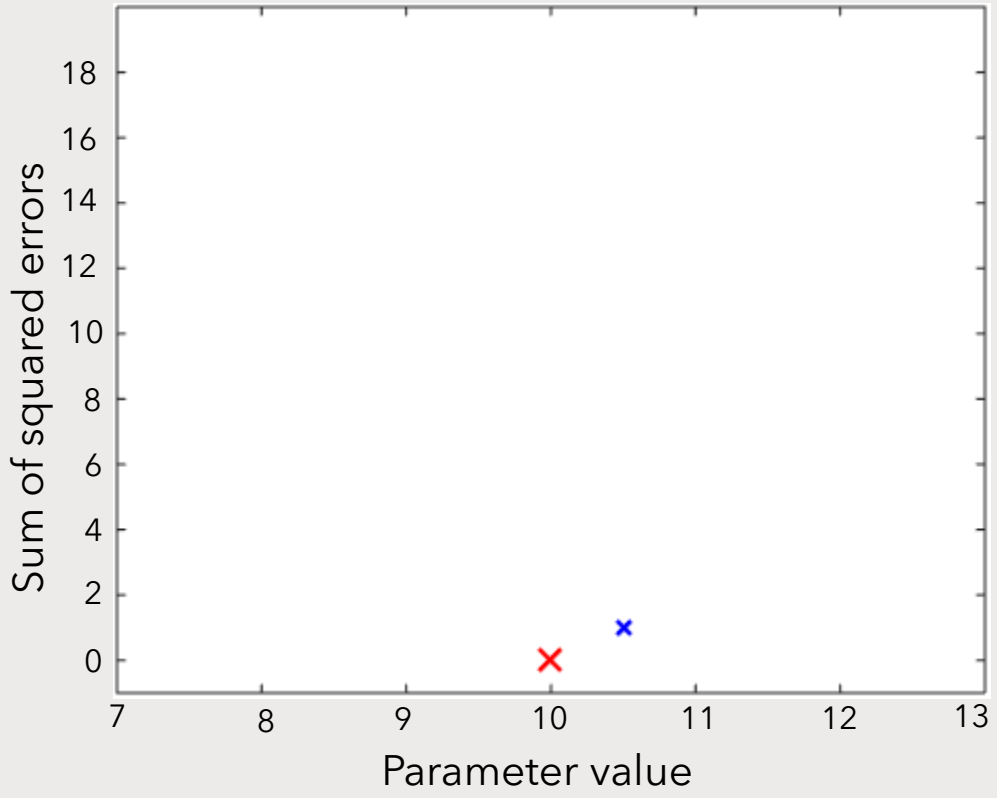
Associate Editor: Martin Bishop

PROFILE LIKELIHOOD ANALYSIS



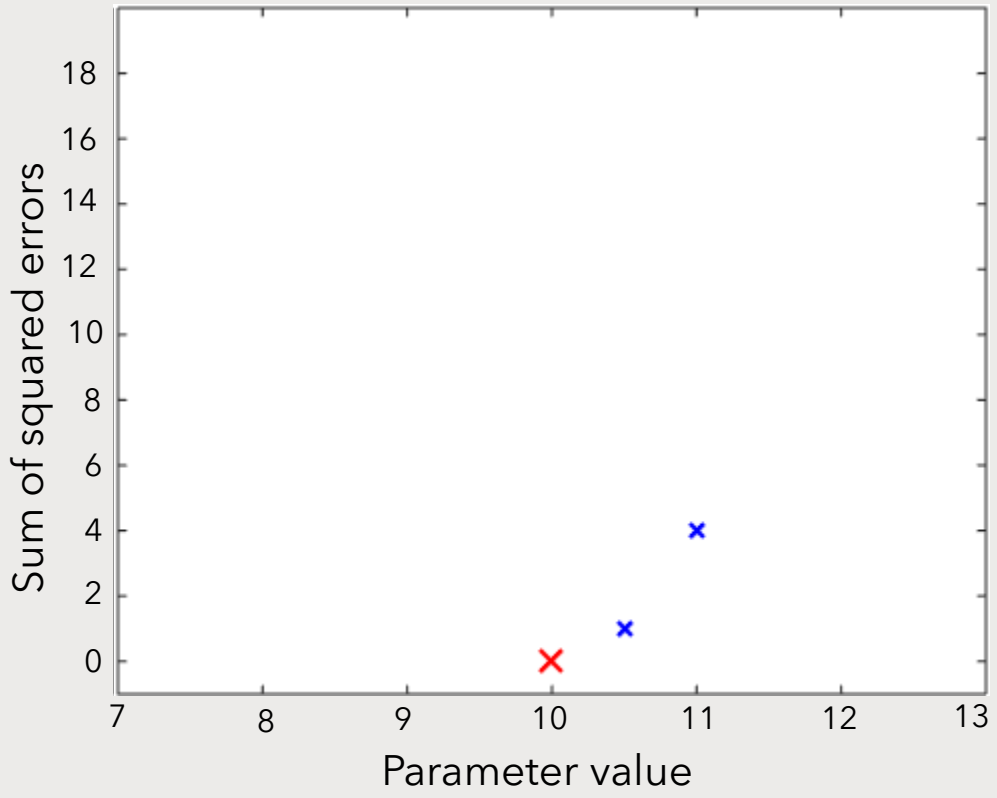
Calculate the **cost function** (sum of squared error) for the **optimal parameter set** found during parameter estimation.

PROFILE LIKELIHOOD ANALYSIS



Iteratively **change the value of one parameter and re-estimate the remaining parameters** and compare the value of the **cost function** (sum of squared error).

PROFILE LIKELIHOOD ANALYSIS



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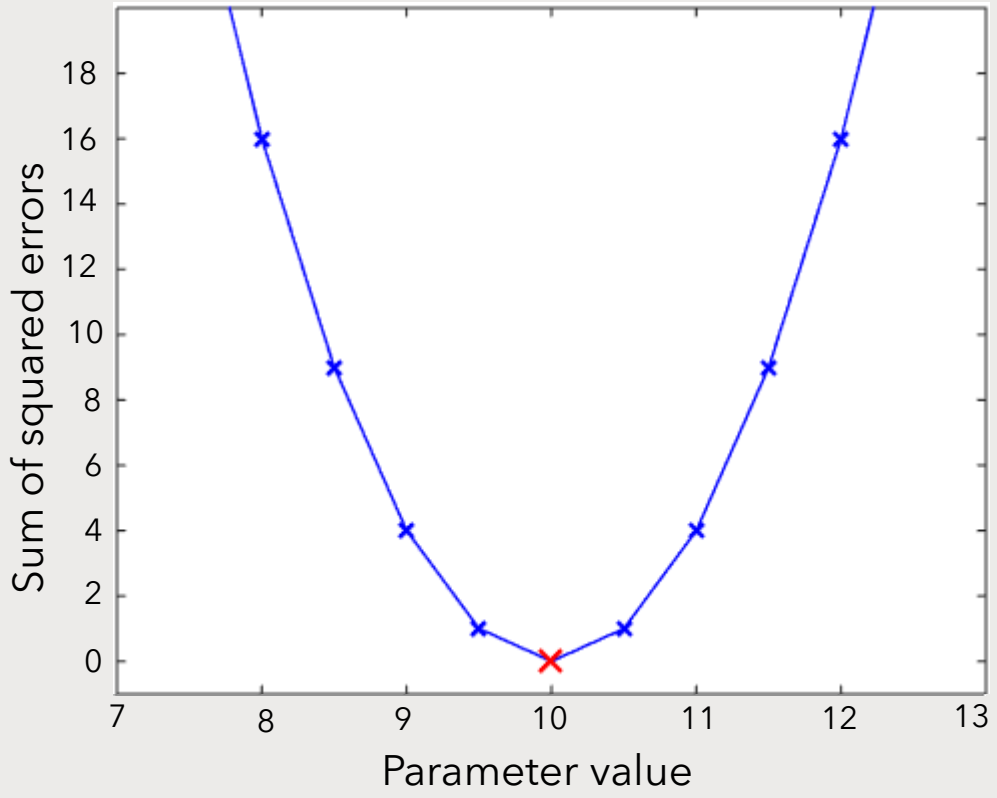
PROFILE LIKELIHOOD ANALYSIS



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PROFILE LIKELIHOOD – CONFIDENCE INTERVAL

Confidence intervals of estimated parameters can be derived using a **threshold in the likelihood**.

Likelihood ratio is a statistical test used to compare the fit of two models M_o (the null model) is a special case of M_1 (the alternative model)

$$D = -2 \ln \left(\frac{L(M_o)}{L(M_1)} \right)$$

Where the null hypothesis represents a special case of the alternative hypothesis the distribution of the test statistic is approximately a chi-squared distribution $\chi^2_{1-\alpha,p}$

A. Raue, C. Kreutz et al.; Structural and practical identifiability analysis of partially observed dynamical models by exploiting the profile likelihood, *Bioinformatics*, (2009) 25(15);1923–1929,

PROFILE LIKELIHOOD – CONFIDENCE INTERVAL

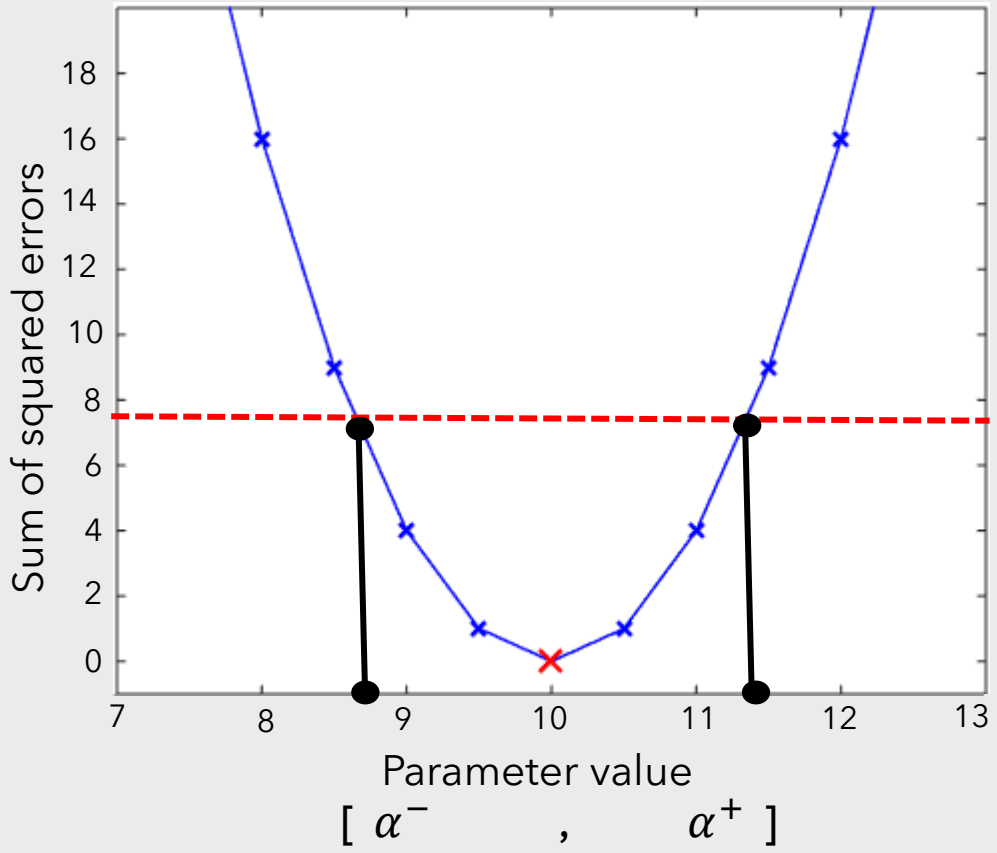
$$threshold = \chi^2_{1-\alpha,df}$$

Where df are the degrees of freedom,
α the desired significance level.

Pointwise confidence intervals hold individually for each parameter
=> df=1

Simultaneous confidence intervals that hold jointly for all parameters can be computed by setting df=number of parameters

PROFILE LIKELIHOOD ANALYSIS



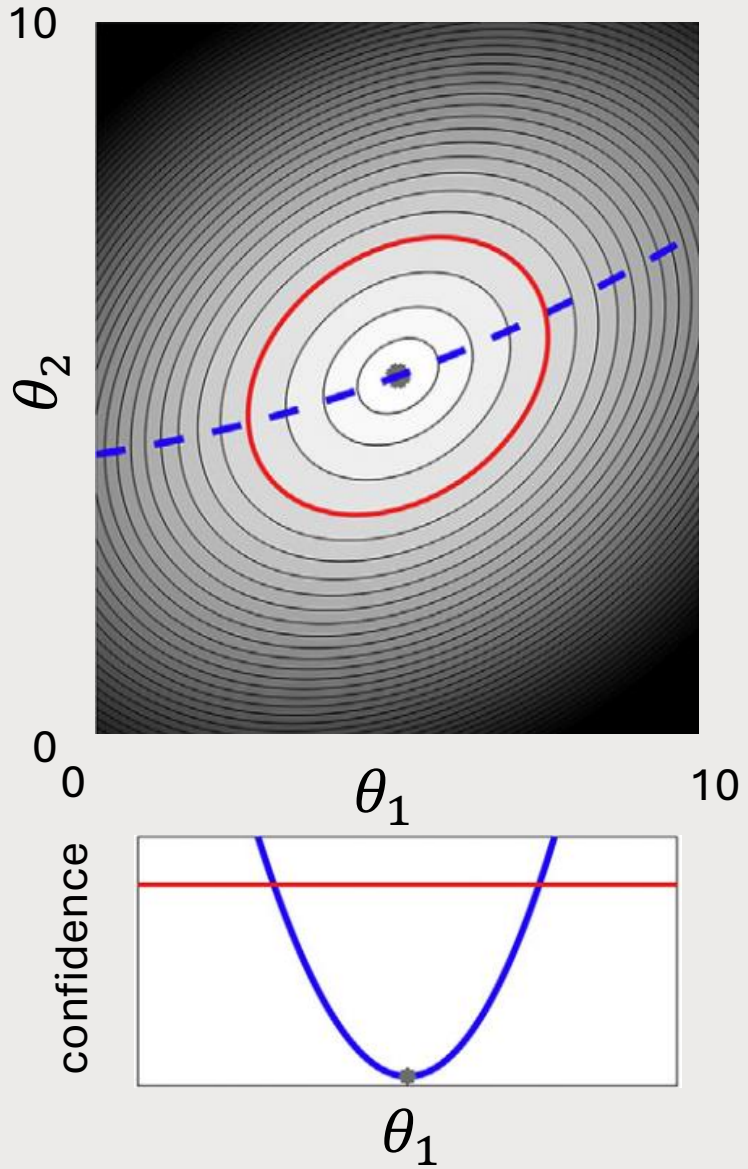
Confidence intervals of estimated parameters can be derived using a **threshold in the likelihood**.

Threshold = $\chi^2_{1-\alpha,df}$

A parameter is considered **identifiable** when it has a **finite confidence interval**.

Landscape of parameter identifiability

PROFILE LIKELIHOOD ANALYSIS



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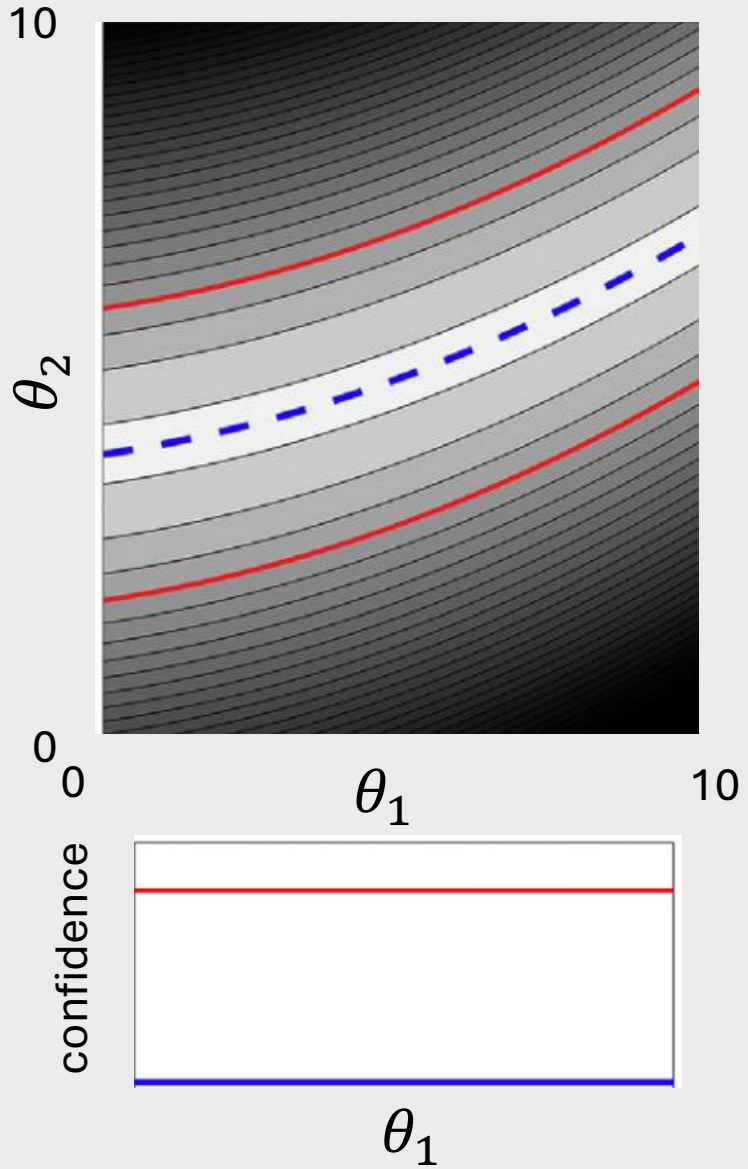
PROFILE LIKELIHOOD ANALYSIS



Structural non-identifiability arises from a redundant parameterisation in the model.

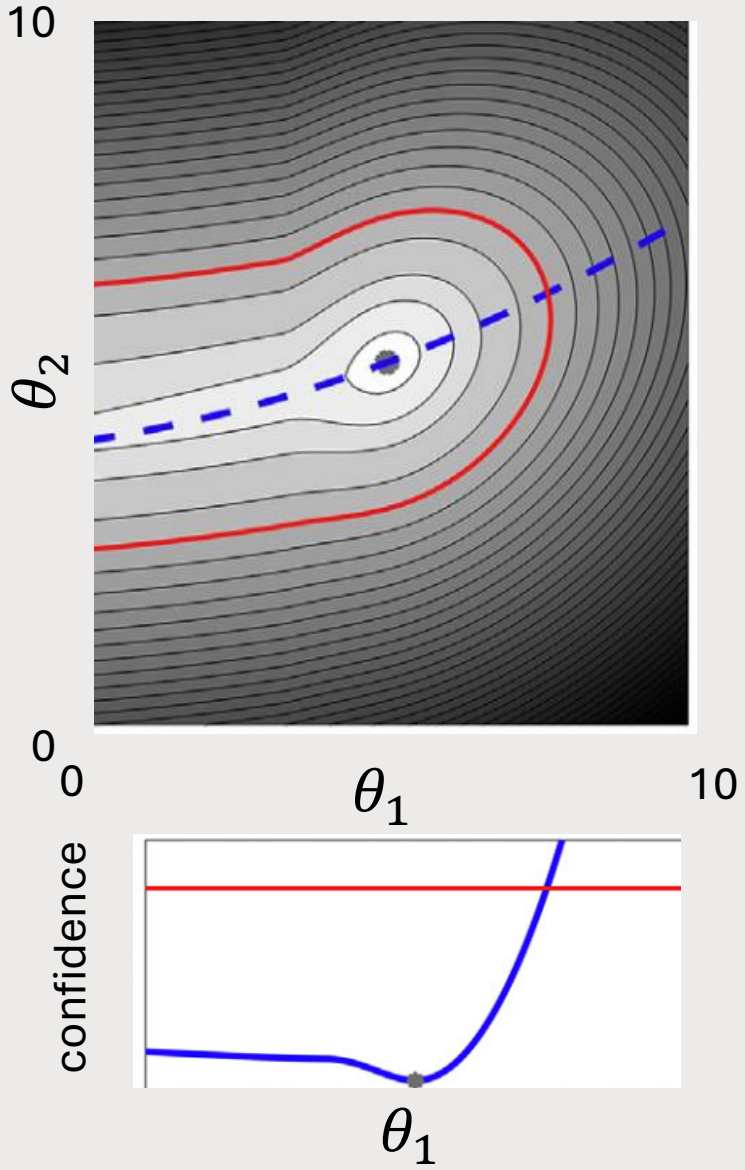
- I.e. A set of parameters $\theta_{sub} \subset \theta$ may be varied without changing the model prediction.
- The confidence interval for structurally non-identifiable parameters are infinite $[-\infty, +\infty]$.

Structurally non-identifiability is **independent of the accuracy of available** experimental **data**. The only remedy is a **qualitatively new measurement** or **modification of model structure**.

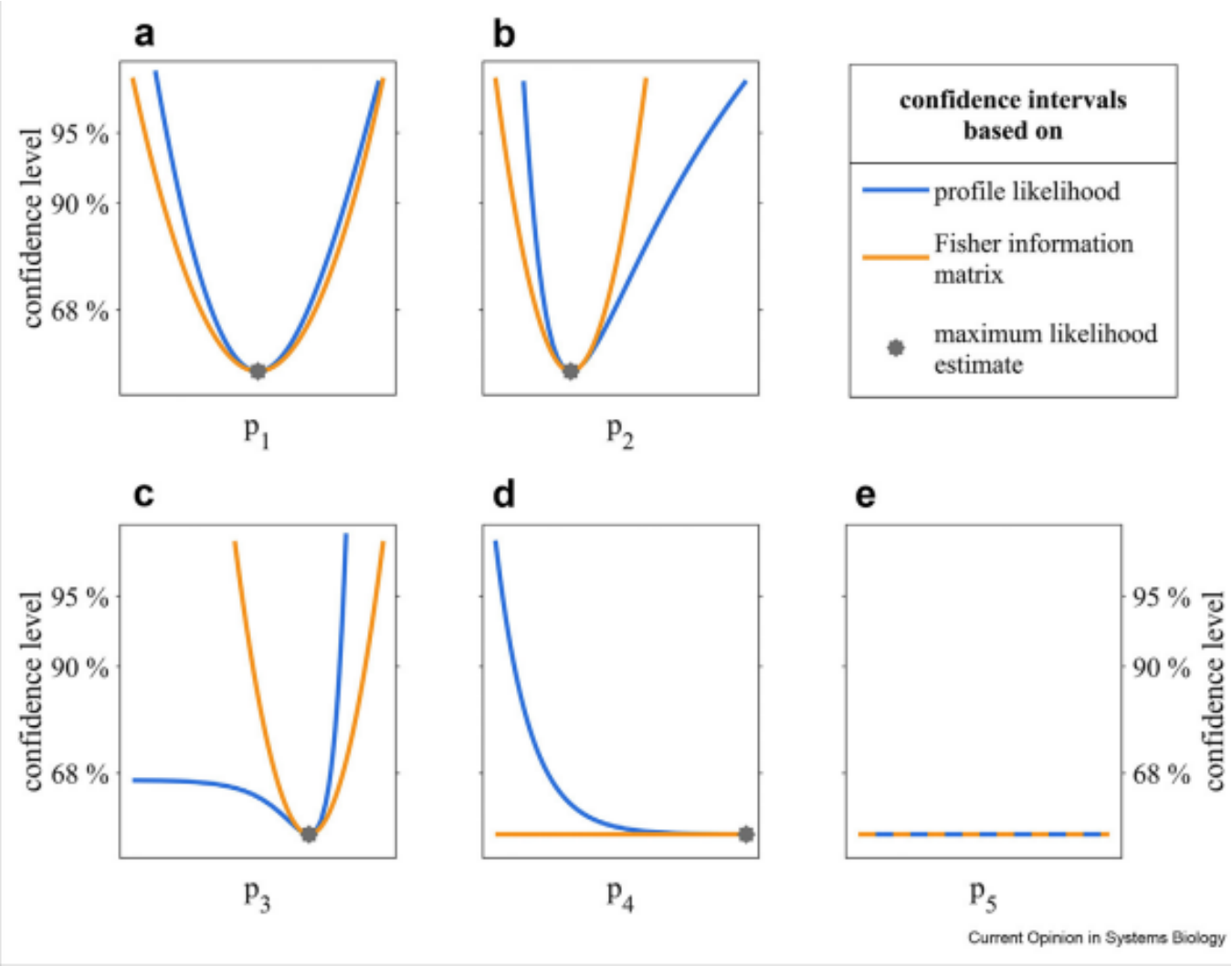
PROFILE LIKELIHOOD ANALYSIS

- A parameter estimate $\widehat{\theta_i}$ is ***practically non-identifiable*** if the likelihood-based confidence region is infinitely extended in increasing and/or decreasing direction of θ_i, although the likelihood has a unique minimum for this parameter.

- **Increasing the amount** and **quality of measured data** and/or the choice of measurement time points will ultimately **resolve practical non-identifiability**.



PROFILE LIKELIHOOD ANALYSIS –V- FISHER INFORMATION MATRIX



- Fisher information matrix is a traditional methods to calculate confidence intervals for linear regression models.
- Solutions of ODES models are **non-linear in their parameters** -> using FIM in such instances is questionable.
- FIM produces symmetric confidence intervals, **PLA-based confidence intervales can by asymmetric**.

Wieland FG, Hauber AL, Rosenblatt M, Tönsing C, Timmer J. On structural and practical identifiability. CURR OPIN SYST BIOL. 2021, 25:60–69

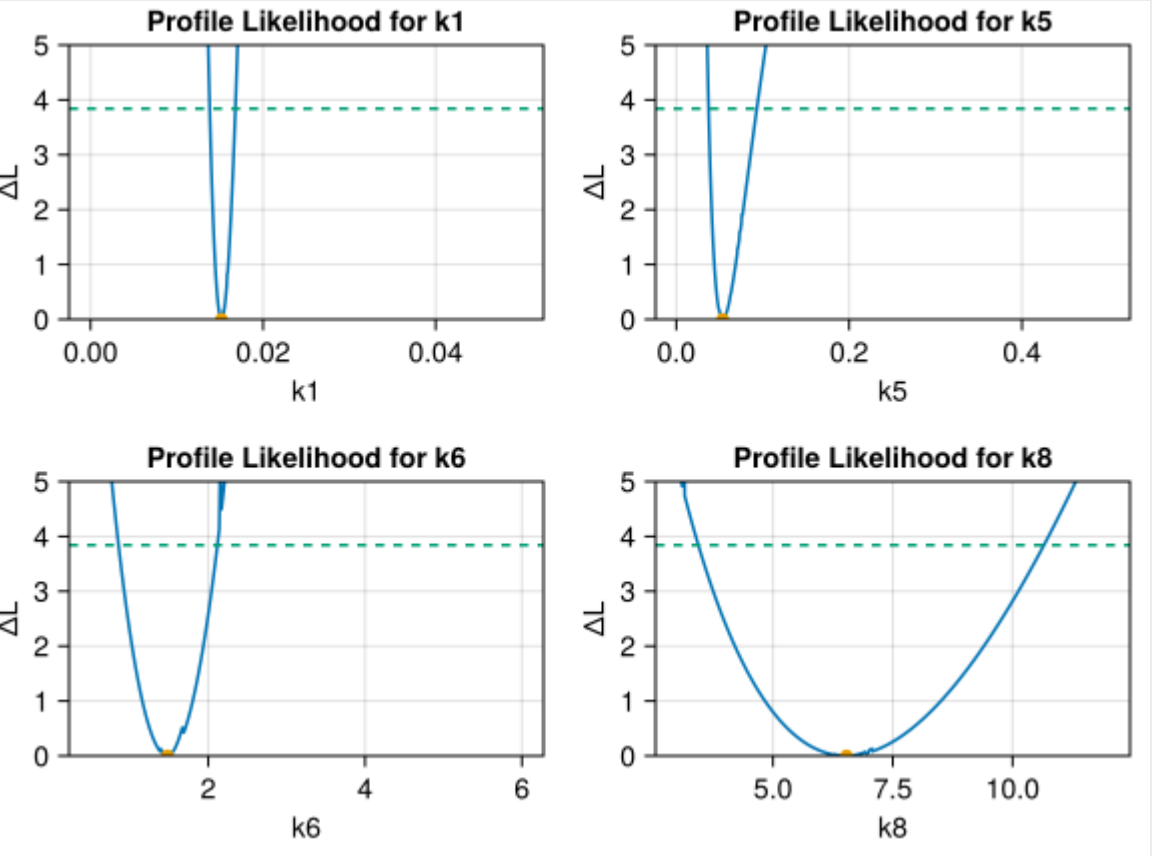
PRACTICAL EXERCISE

Use the PLA algorithm in Julia to assess the structural and practical identifiability of the four-parameter EDES model.

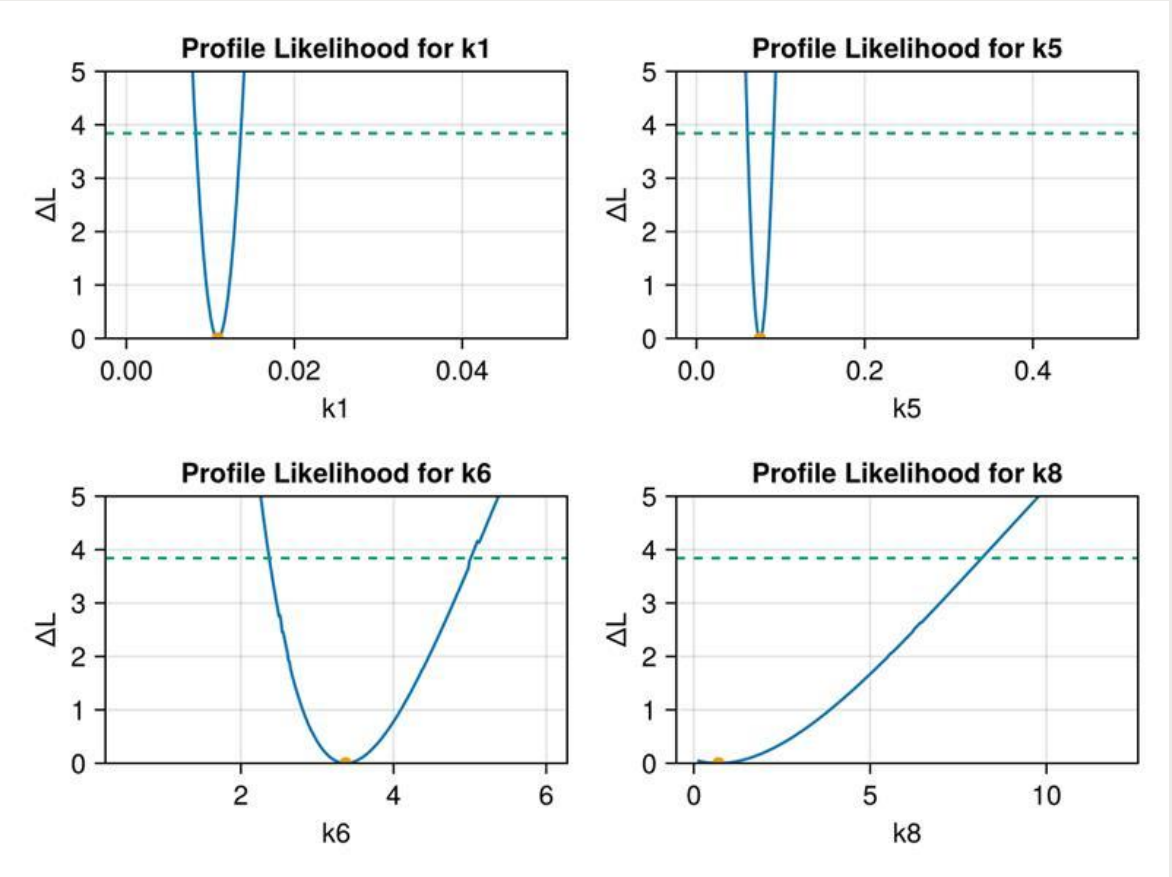
Fix $k_8 = 7.25$ and evaluated the identifiability of the three parameter EDES model.

PRACTICAL EXERCISE

PLA for fit to average data

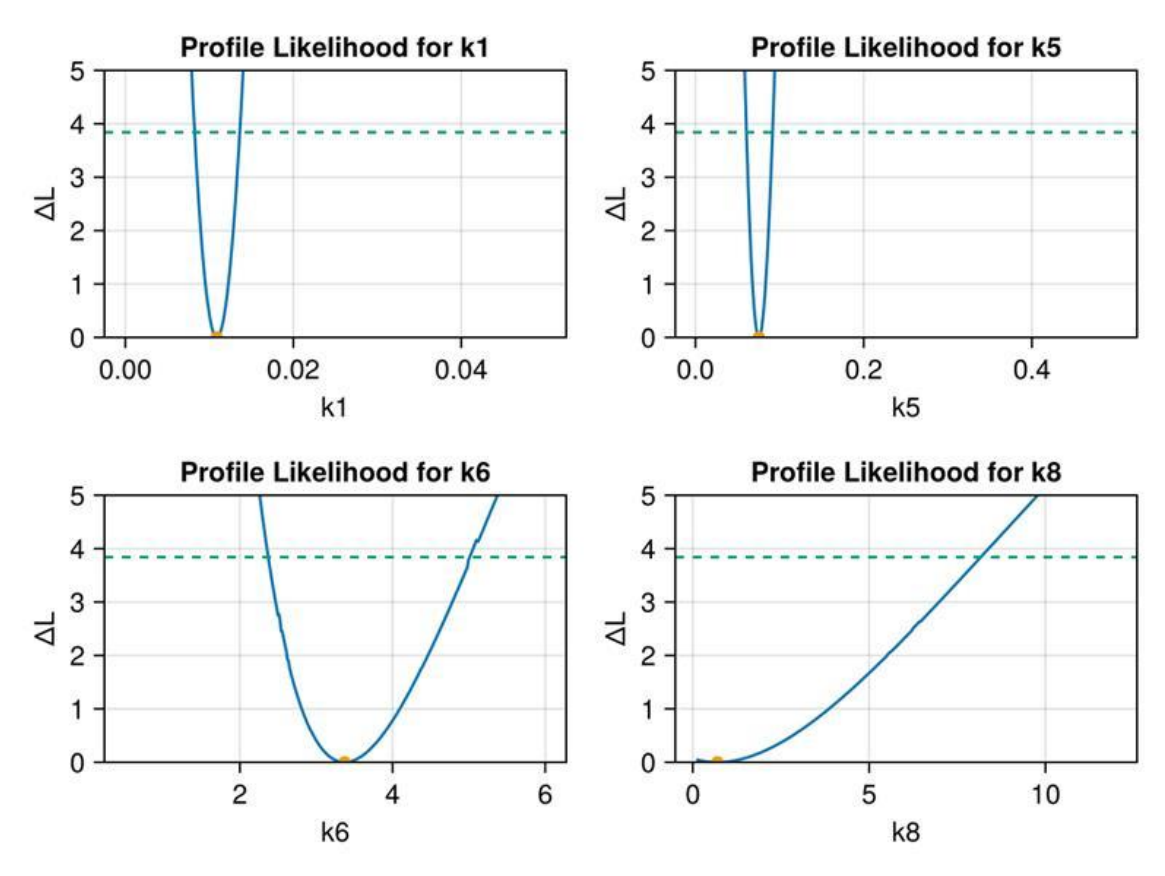


PLA for fit to data for individual A

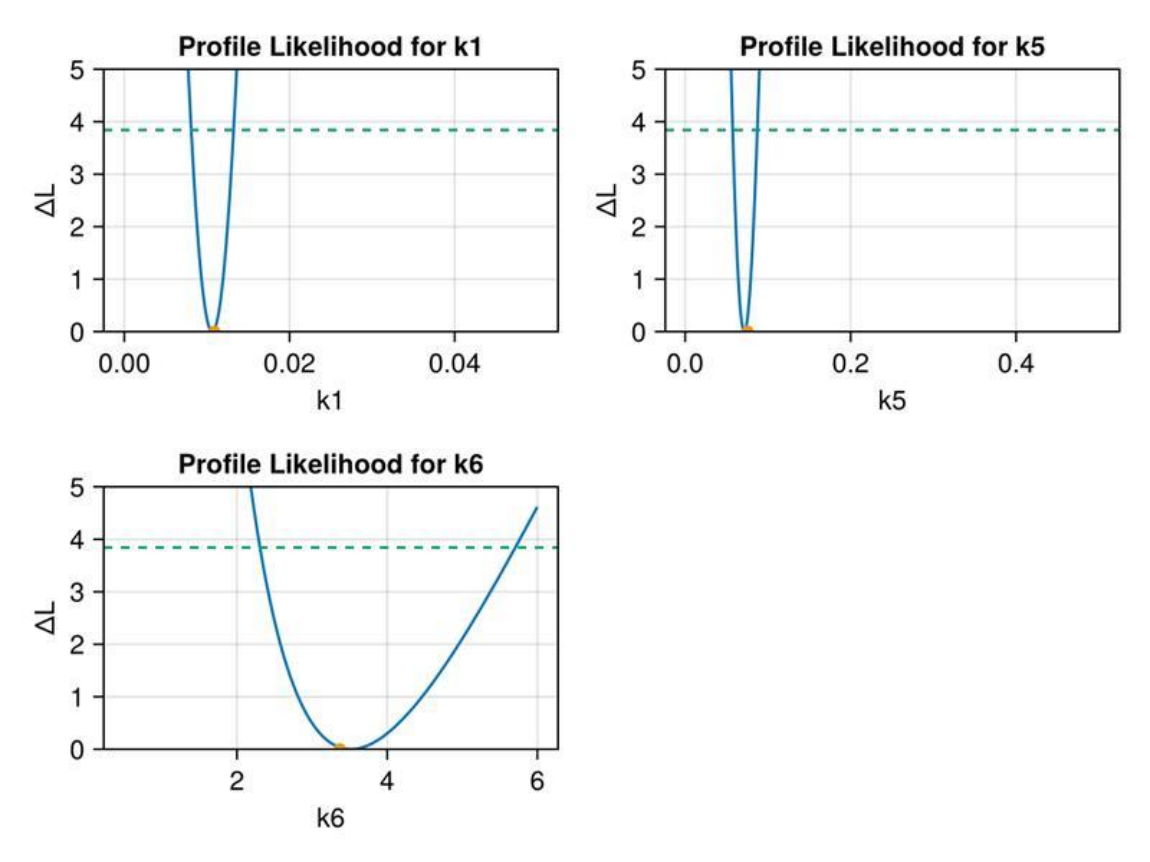


PRACTICAL EXERCISE

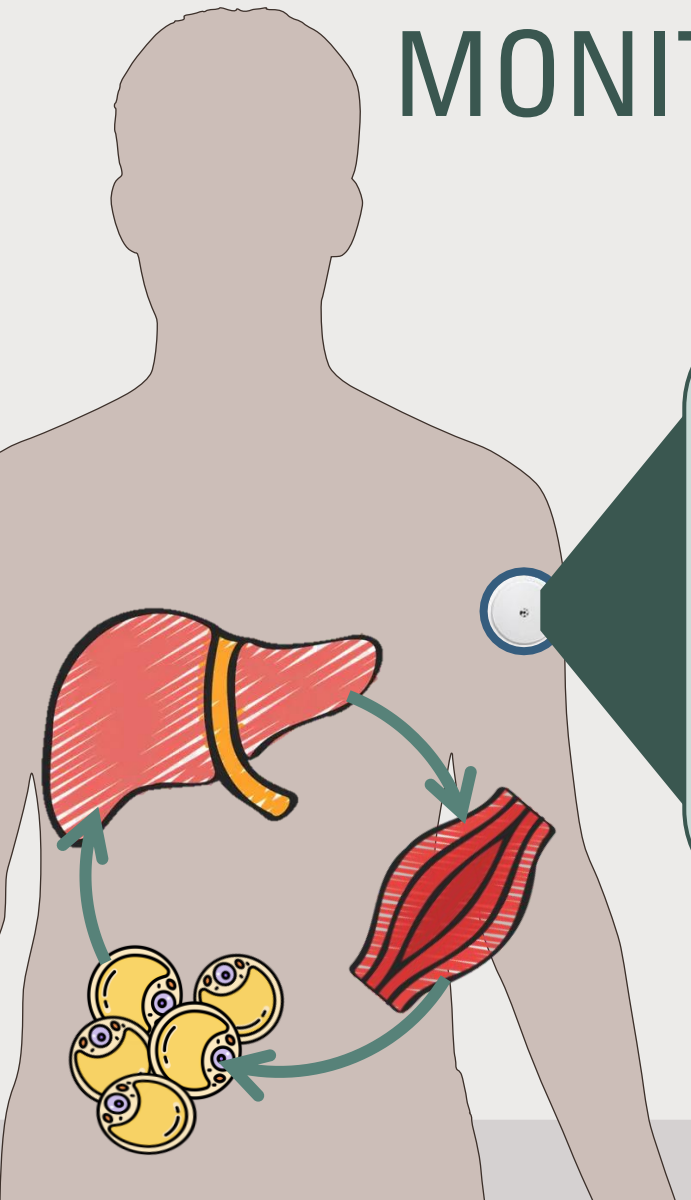
PLA for fit to individual A – four parameter model



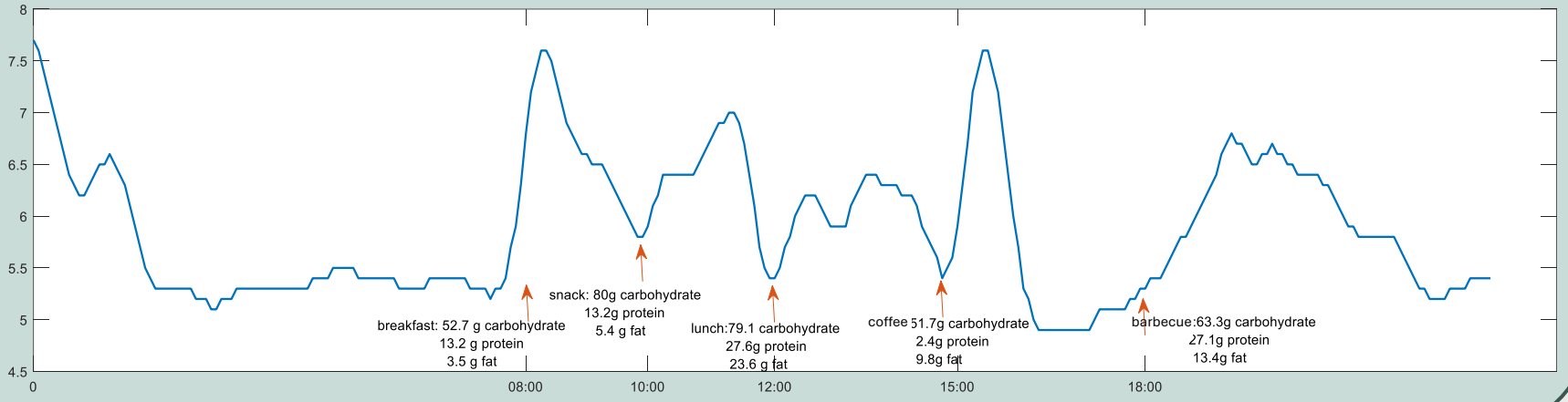
PLA for fit to individual A– three parameter model



WEARABLE CONTINUOUS GLUCOSE MONITORS.



Wearable continuous glucose monitoring data

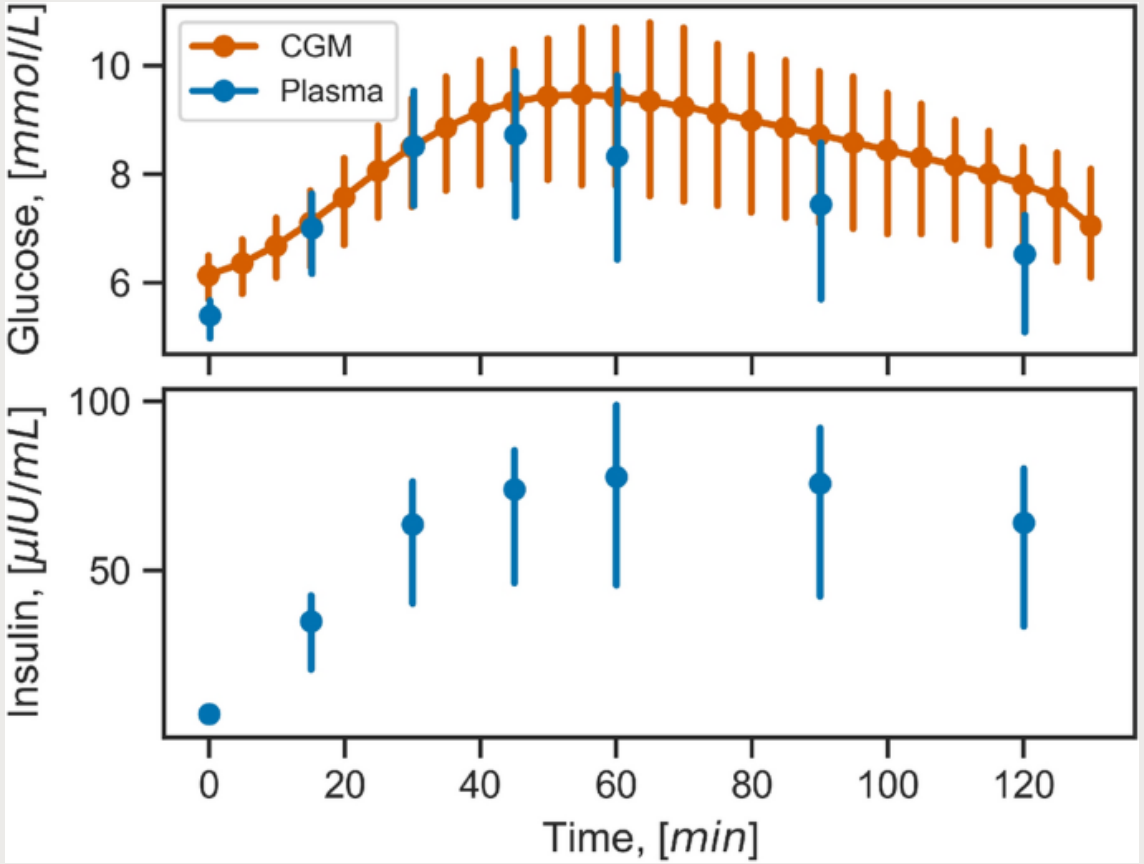


WEARABLE CONTINUOUS GLUCOSE MONITORS.

Extensive time series of glucose in free living conditions.

- Meal composition
- Meal context (time of day)
- Sleep quality
- Physical activity

Have glucose data only – no insulin.



Erdős B, O'Donovan SD *et al.* Leveraging continuous glucose monitoring for personalized modeling of insulin-regulated glucose metabolism. *Sci Rep* **14**, 8037 (2024). https://doi.org/10.1038/s41598-024-58703-6

PRACTICAL EXERCISE

Can the EDES model be parameterized using only CGM data?

How does this impact the identifiability of model parameters?

PARAMETER UNIQUENESS/IDENTIFIABILITY

- Model selection
- Parameter identifiability
  structural unidentifiability
  Practical unidentifiability
- Toolboxes in Julia – StructuralIdentifiability.jl
- Profile Likelihood Analysis – chi-squared threshold

Parameter Uniqueness/identifiability

QUANTIFYING INSULIN RESISTANCE FROM WEARABLE SENSORS

VITAL Training School 1,
Delft University of Technology.

March 19th 2025

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