Dynamical systems

Modeling the human glucose metabolism

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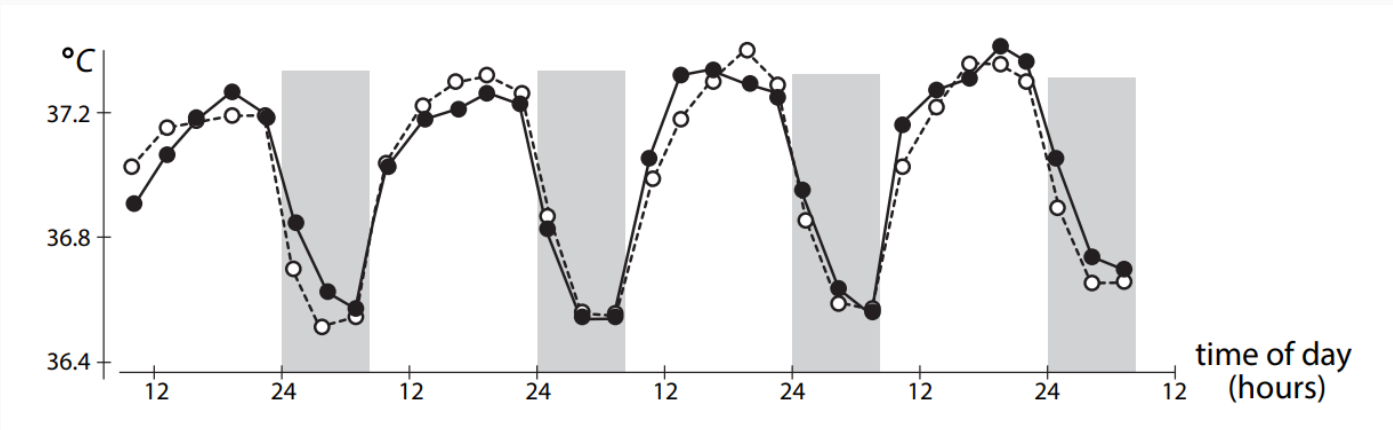
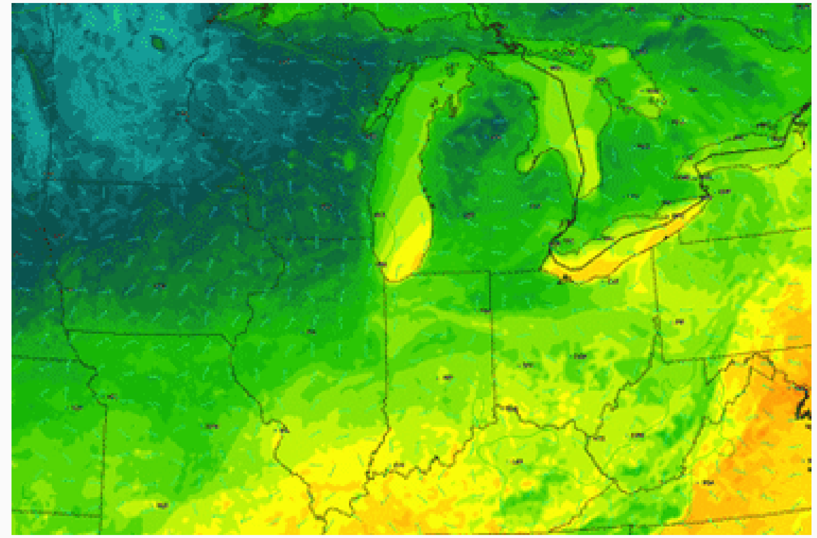
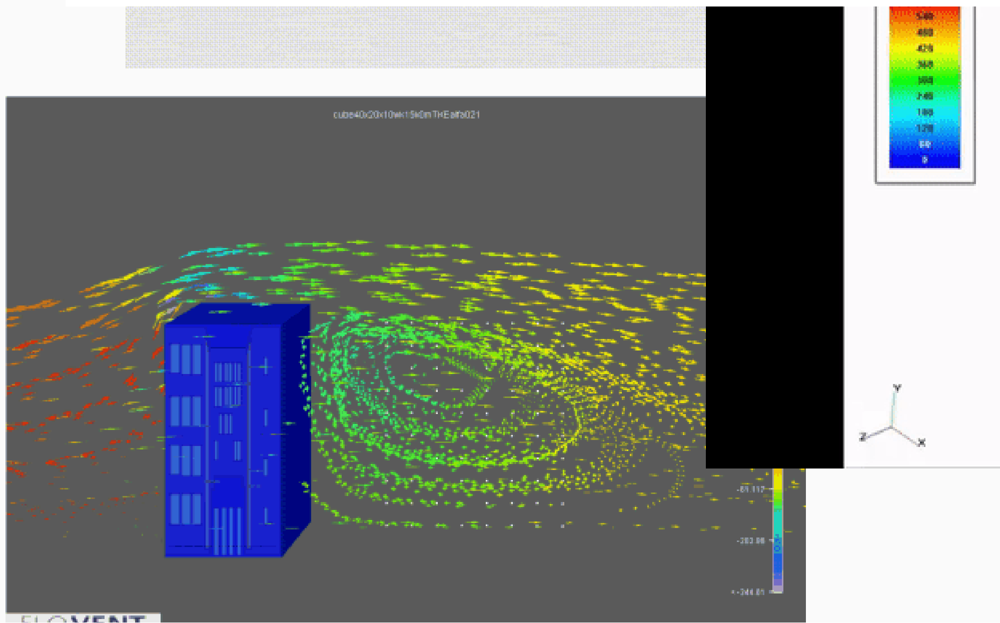
11/14/22

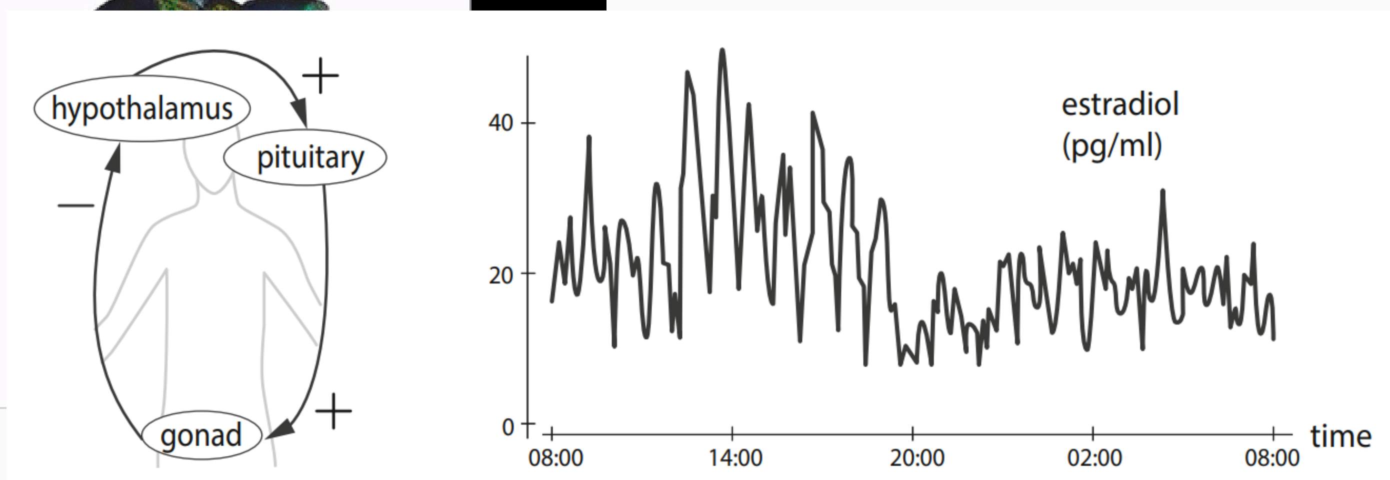
Dynamical systems

Steady-state?



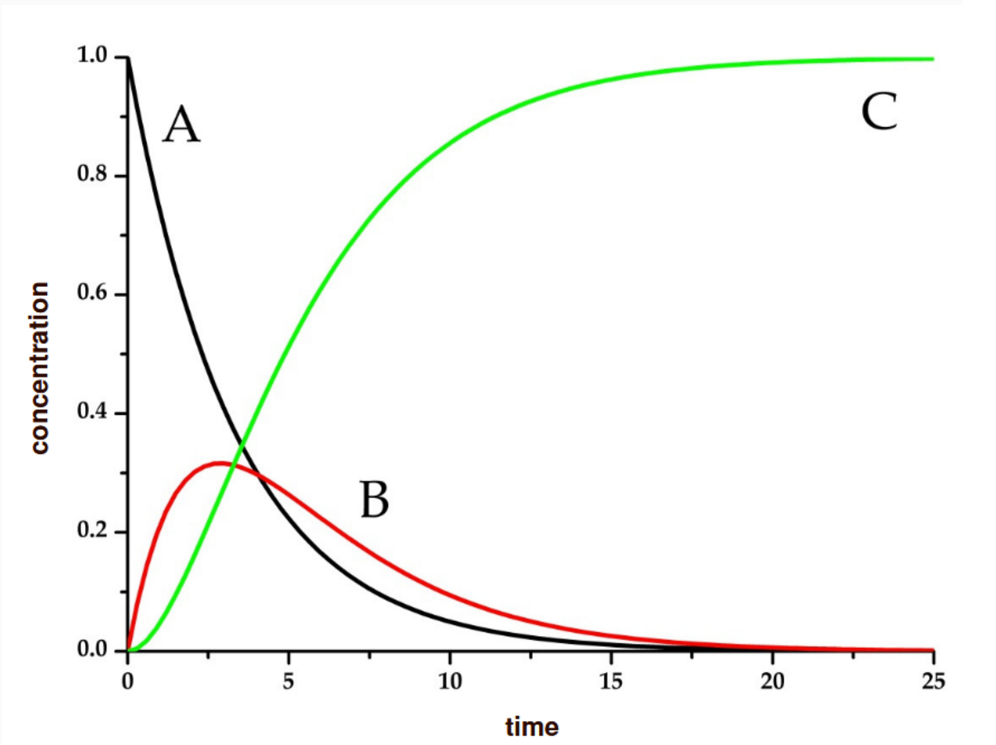


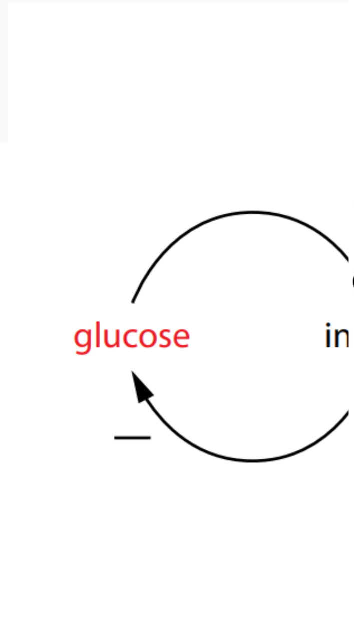


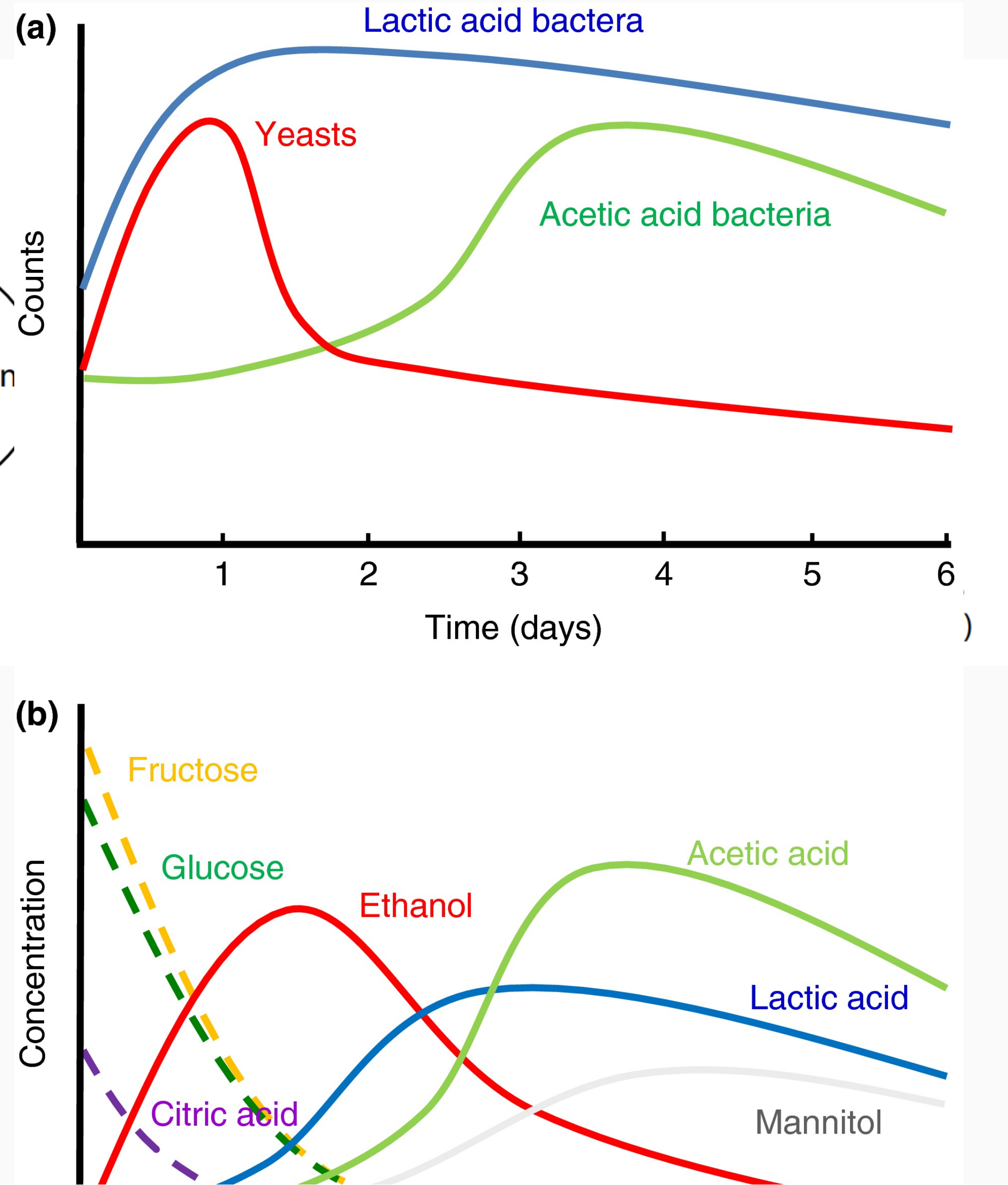


What about metabolism?

Are concentrations of metabolites static?







~~Steady state~~

- SS can be a useful simplification, but is usually wrong!
- most often point-of-interest is the dynamics; e.g. to answer questions of: **why**, **how**, and **when**, typically requires some understanding of the dynamics
- metabolism is dynamic

Describing dynamical systems mathematically

State variable(s): number(s) that characterize the system at a time

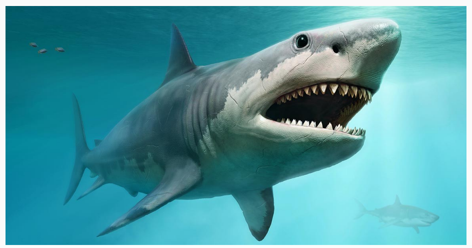
State space: the space within which the state variables exist

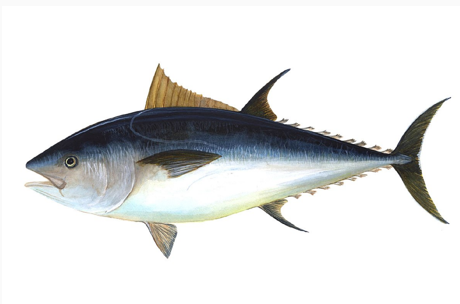
Change: trajectory through state-space

Describing dynamical systems mathematically

What tells a system where to go? the **MODEL**!

$$\frac{dx}{dt} = +\text{makes } x \text{ go up} \uparrow -\text{makes } x \text{ go} \downarrow$$





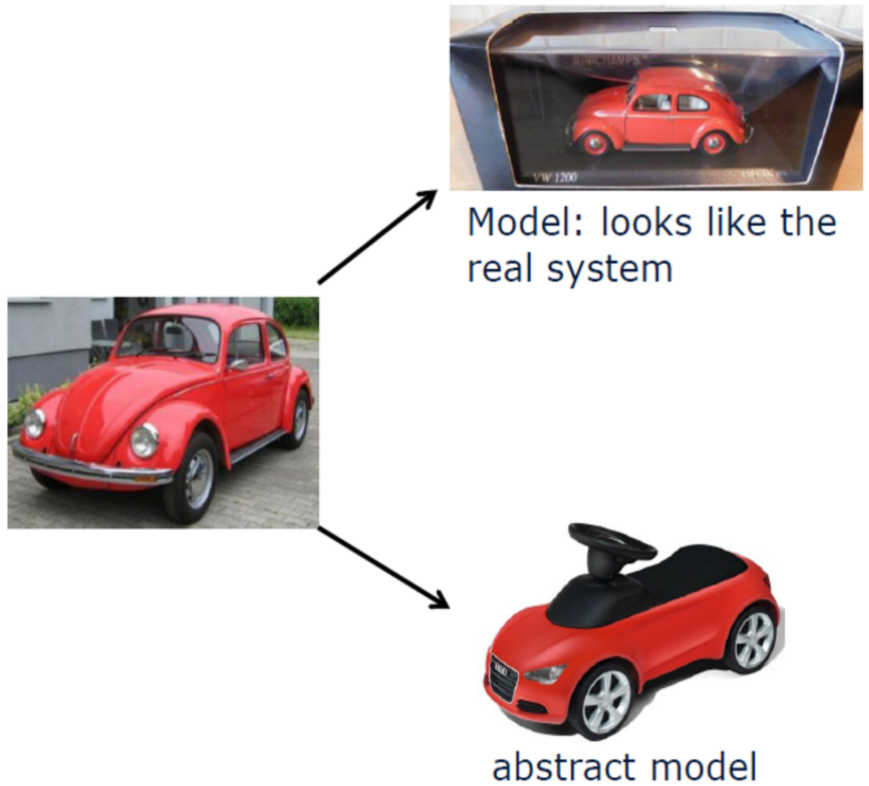
Why make models?

- Organize disparate information into a coherent whole
- To think (and calculate) logically about what components and interactions are important in a complex system
- To discover new strategies
- To make important corrections in the conventional wisdom
- To understand the essential, qualitative features

J.E. Bailey, 2008. Mathematical Modeling and Analysis in Biochemical Engineering: Past Accomplishments and Future Opportunities

What is a model?

All models are wrong, but some are useful!



- 4 wheels
- No steering wheel
- Shape is the same
- Size is different
- No engine etc.
- Can't transport humans

- 4 wheels
- Steering wheel
- Shape is different
- Size is different
- No engine etc.
- Can transport humans

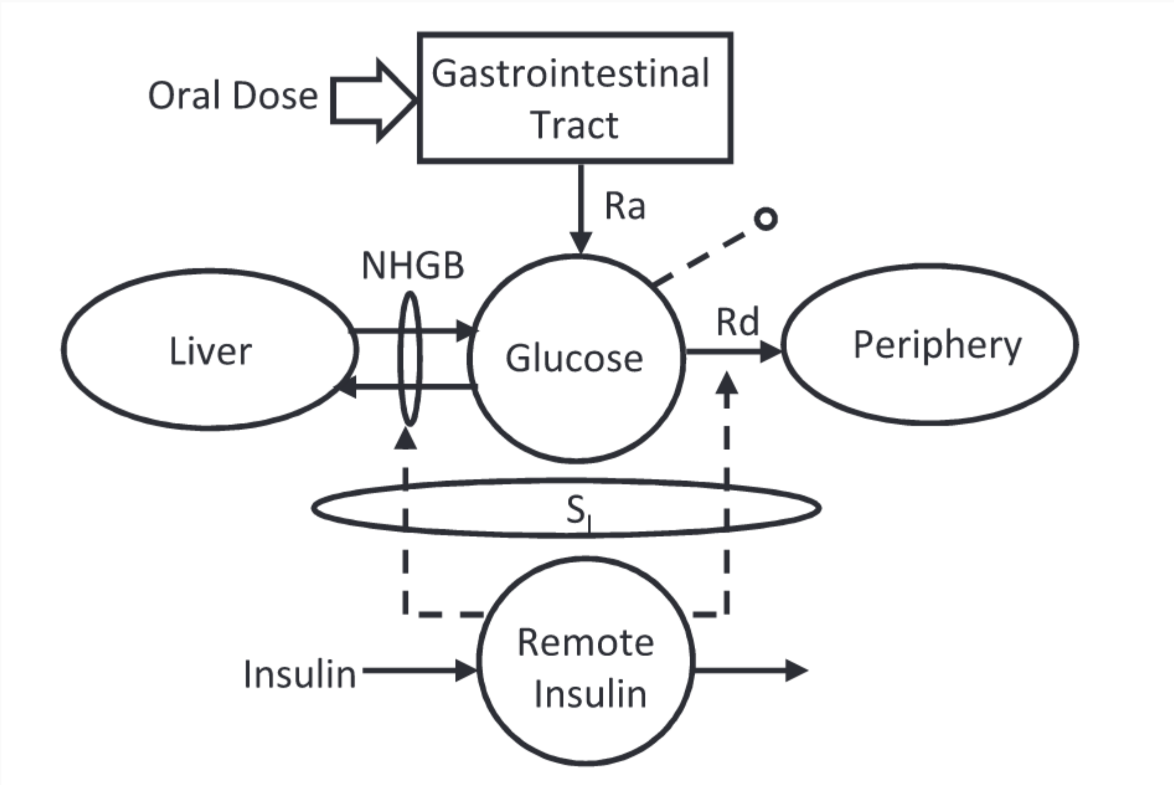
What is a model?

A representation of the system that is:

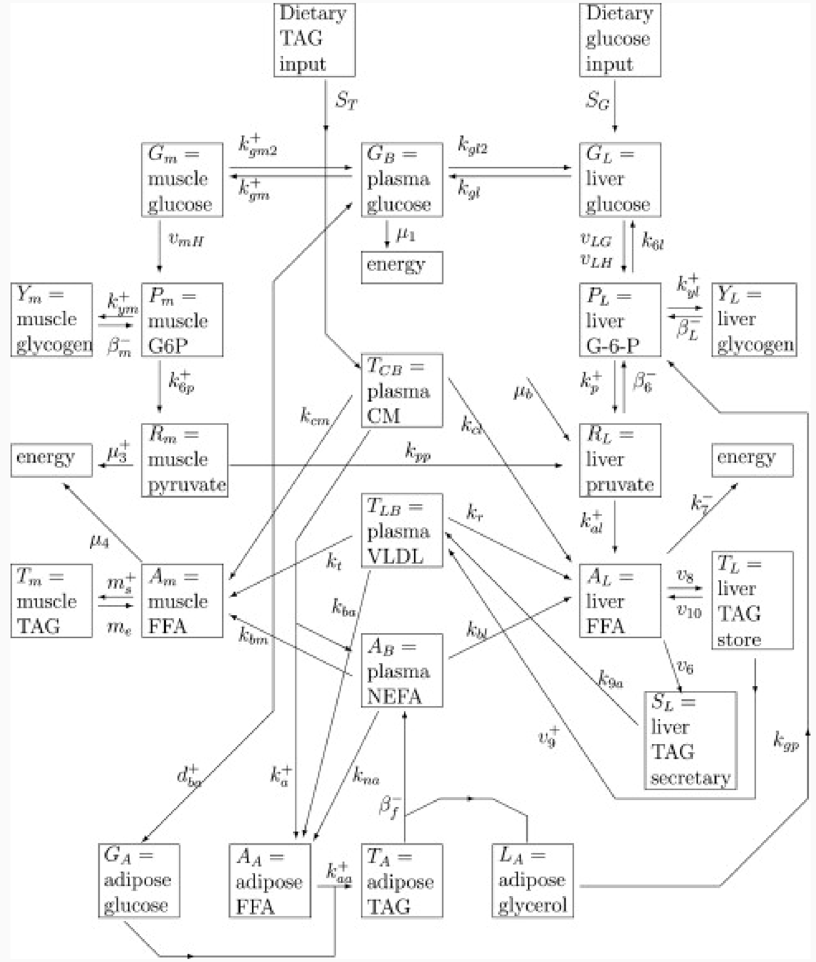
- never equal to the system (incomplete)
- less complex than the system
- focuses on the *relevant* features of the system

How complex?

Depends on scope and use-case!



Cobelli et al. 2014



Pratt et al. 2014

How complex?

Models to measure

- minimal
- only contain the key components
- few parameters
- can be identified from data
- i.e. quantify crucial processes

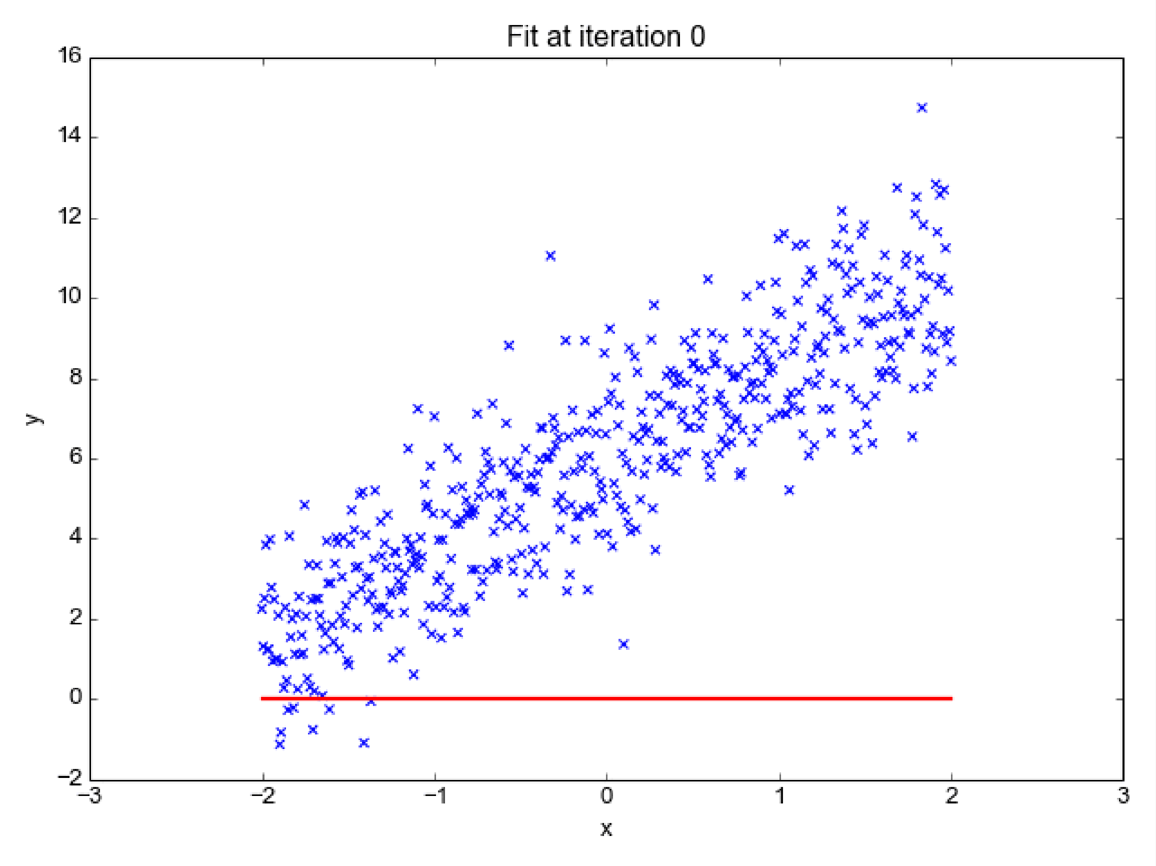
Models to simulate

- fine-grained
- comprehensive description
- many parameters
- in general cannot be identified from data
- can be used to simulate the system

Cobelli et al., 2014. Advancing our understanding of the glucose system via modeling: a perspective

How to parameterize your model?

- guess
- measure kinetic parameters
- values from literature
- **estimate from data** (model calibration)



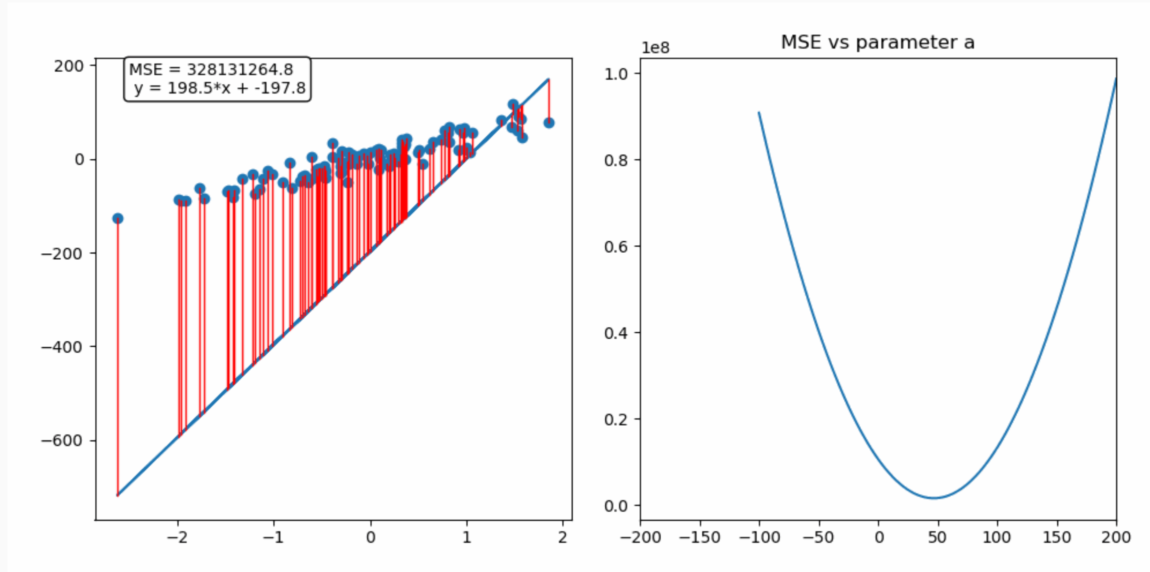
- Minimize the sum of squared model errors by varying model parameters
- optimal parameters <- minimal error

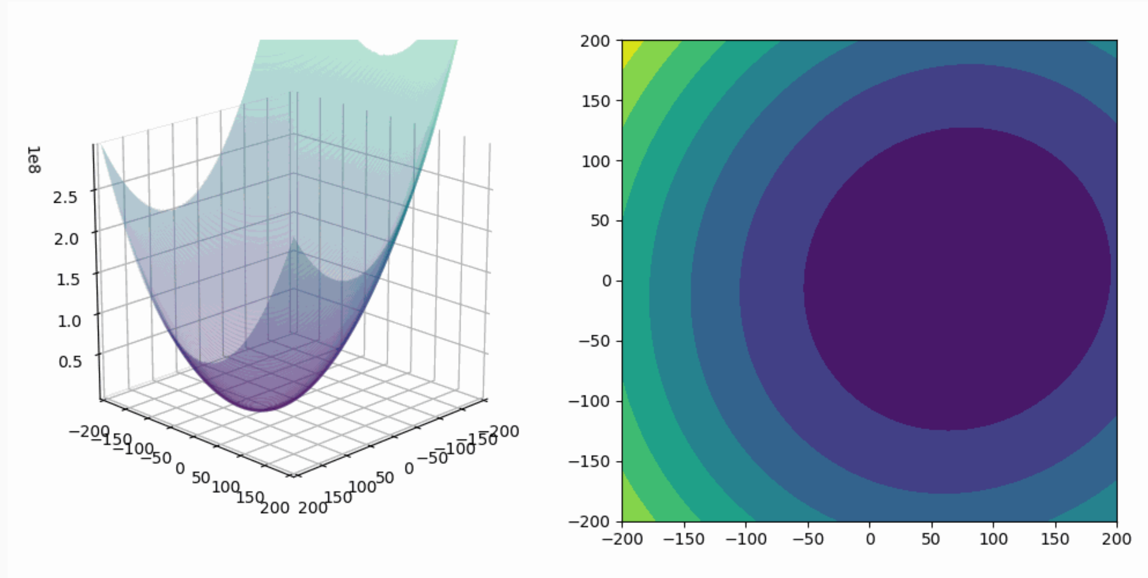
Parameter estimation

Minimize the error between the data points and the simulation

$$C = \sum_{i=1}^{N} (f((y_i|\theta) - d_i))^2$$

$$\operatorname*{argmin}_{\theta} C(\theta)$$




1e8
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1.0
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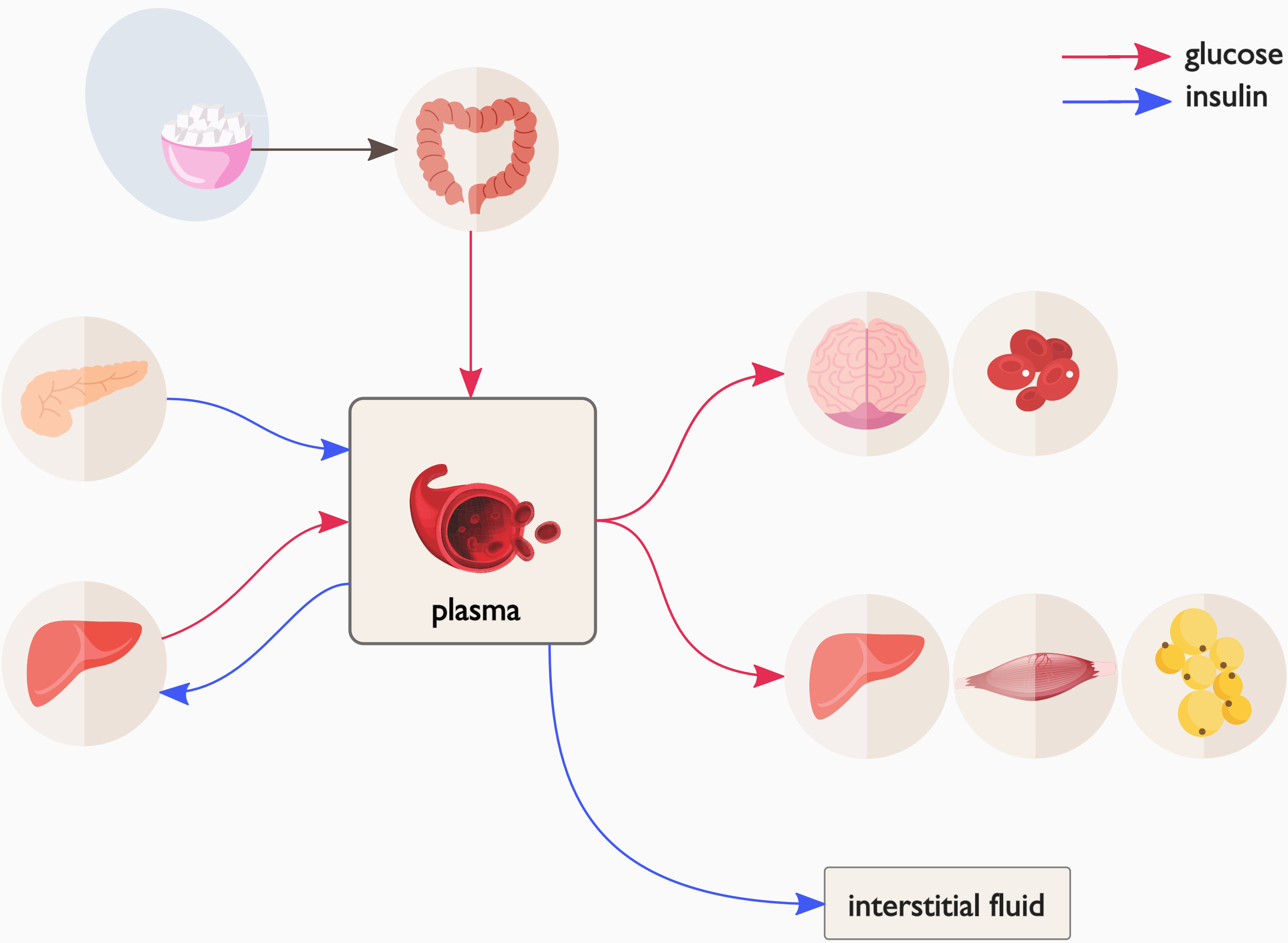
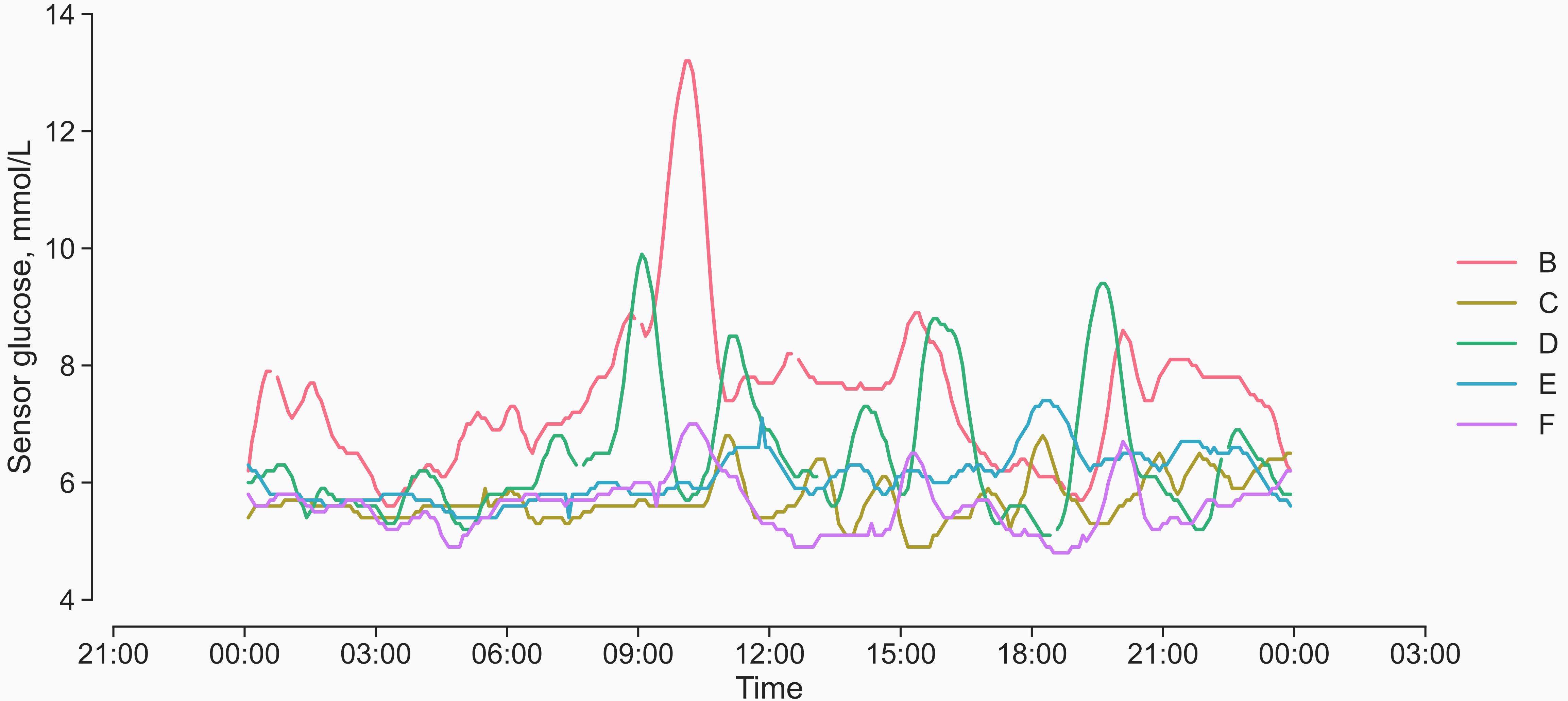
Glucose regulation



- plasma glucose concentrations are tightly regulated
- too low or too high glucose levels are harmful for the body (Diabetes)
- regulatory system is complex, involving several organs, hormones, and metabolites

readouts of glucose regulation?

Glucose regulation



How is (pre)diabetes diagnosed?

…by measuring blood glucose levels!

oral glucose tolerance test (OGTT): After measuring fasting glucose, a glucose-rich drink. Blood is sampled at time intervals to see how the body is processing the glucose.

Table 3 Diagnostic criteria for diabetes

Measurement	Diagnostic cut-off value	Comment
Fasting venous or capillary plasma glucose**	≥7.0 mmol/L (126 mg/dL)	Least costly but difficulties with ensuring a fasting state
2-hour post-load venous plasma glucose	≥11.1 mmol/L (200 mg/dL)	Cumbersome and costly, difficulties with ensuring a fasting state
2-hour post-load capillary plasma glucose**	≥12.2 mmol/L (220 mg/dL)	Cumbersome and costly, difficulties with ensuring a fasting state
Random plasma glucose	≥11.1 mmol/L (200 mg/dL)	To be used only in the presence of symptoms
HbA1c***	6.5% (48 mmol/mol)	• Less intra-individual variability than plasma glucose • Does not require the fasting state but substantially more costly than glucose measurements • Is an indirect method • Can be inaccurate in some conditions (haemoglobinopathies, renal failure, some anaemias, conditions with rapid red blood cell turnover)

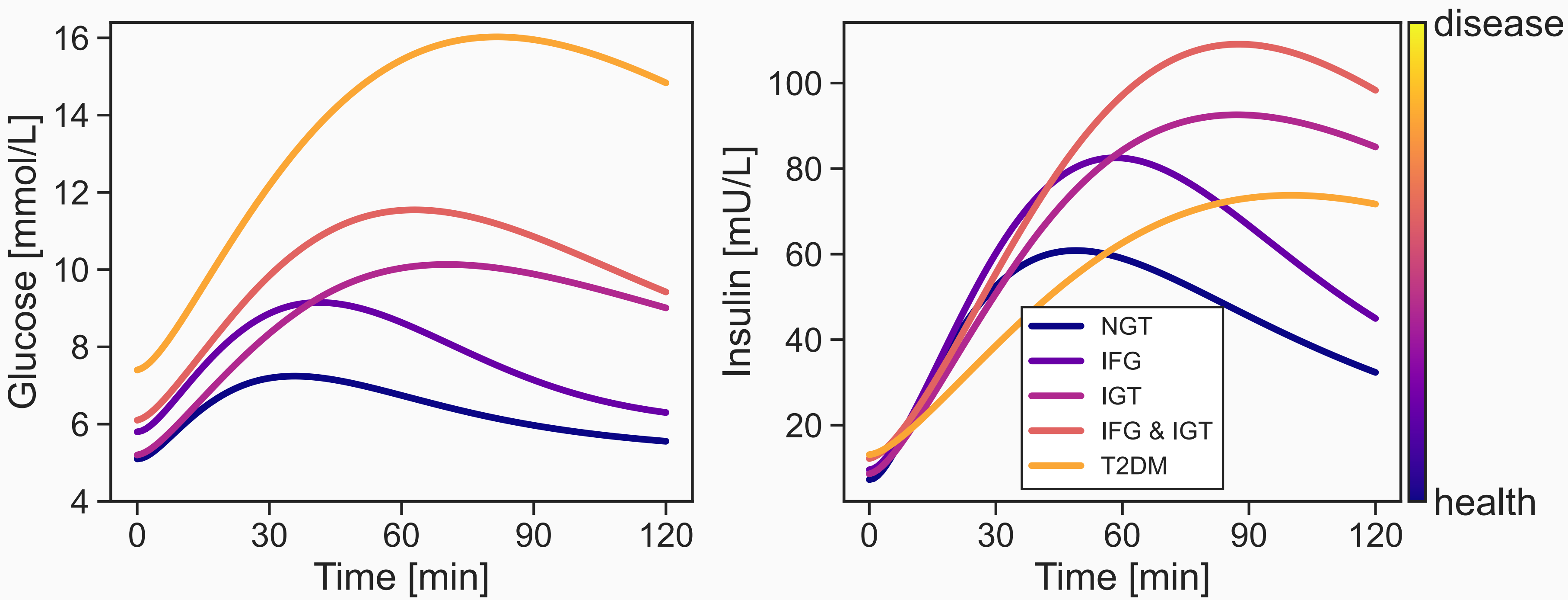
* Overnight fast of 8–14 hours.
** If laboratory measurement is not available, point of care, (“finger stick”) devices can be used (they report glucose values in capillary plasma).
*** Plasma glucose is preferred in people with symptoms who are suspected of having type 1 diabetes.

Diagnosis and Management of Type 2 Diabetes

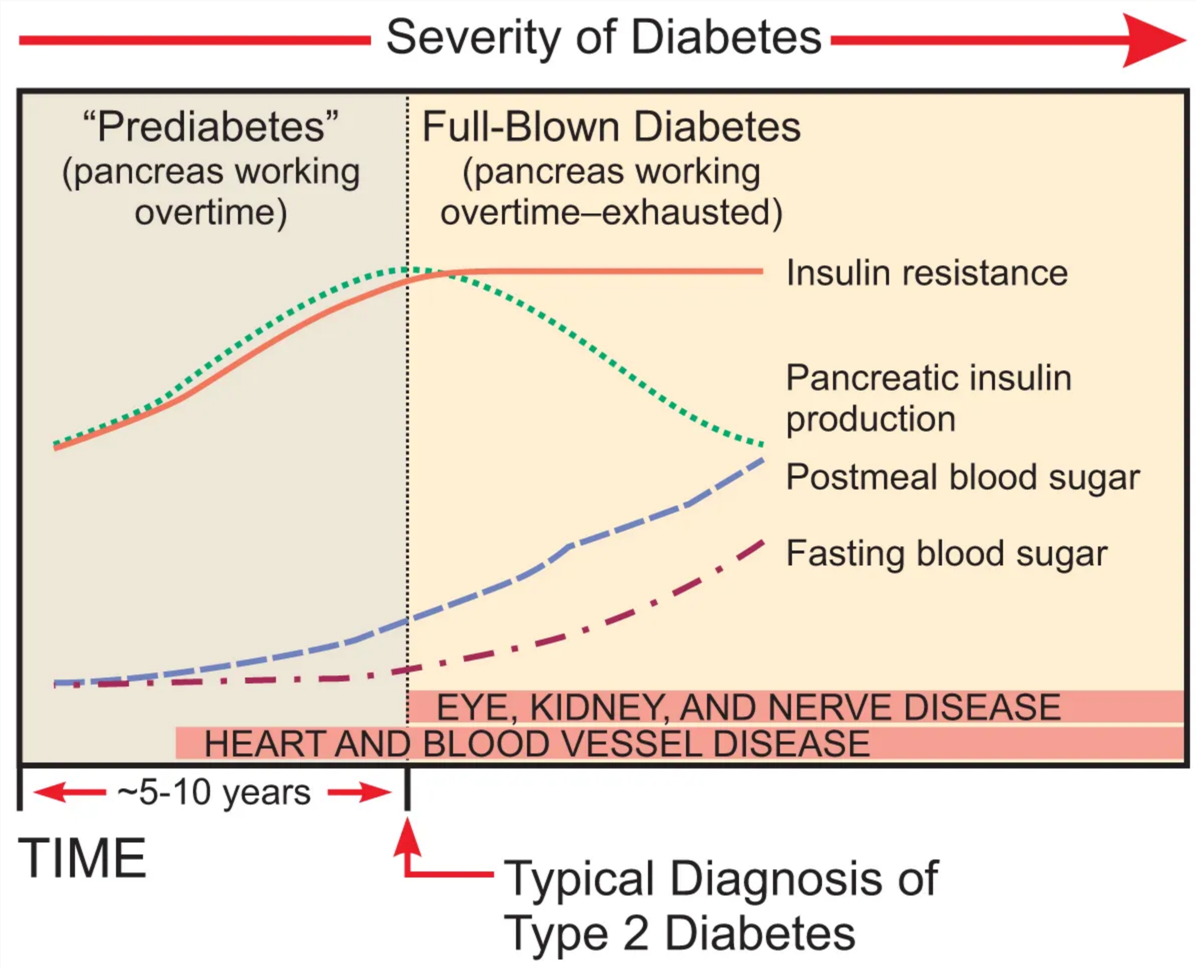
WHO, 2022

Why are the dynamics important?

Response to the OGTT



Development of type 2 diabetes

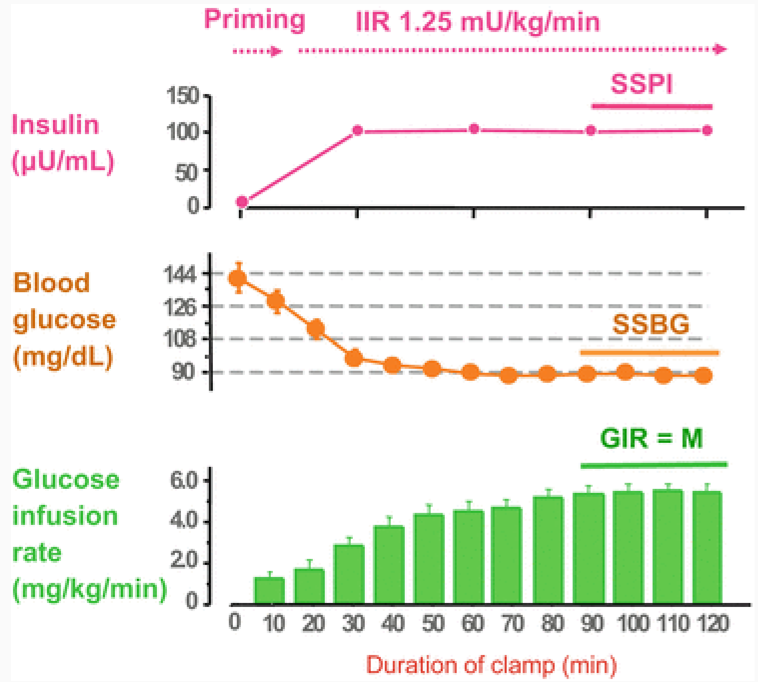


- quantifying **insulin sensitivity/insulin resistance** is key!

Quantifying insulin sensitivity

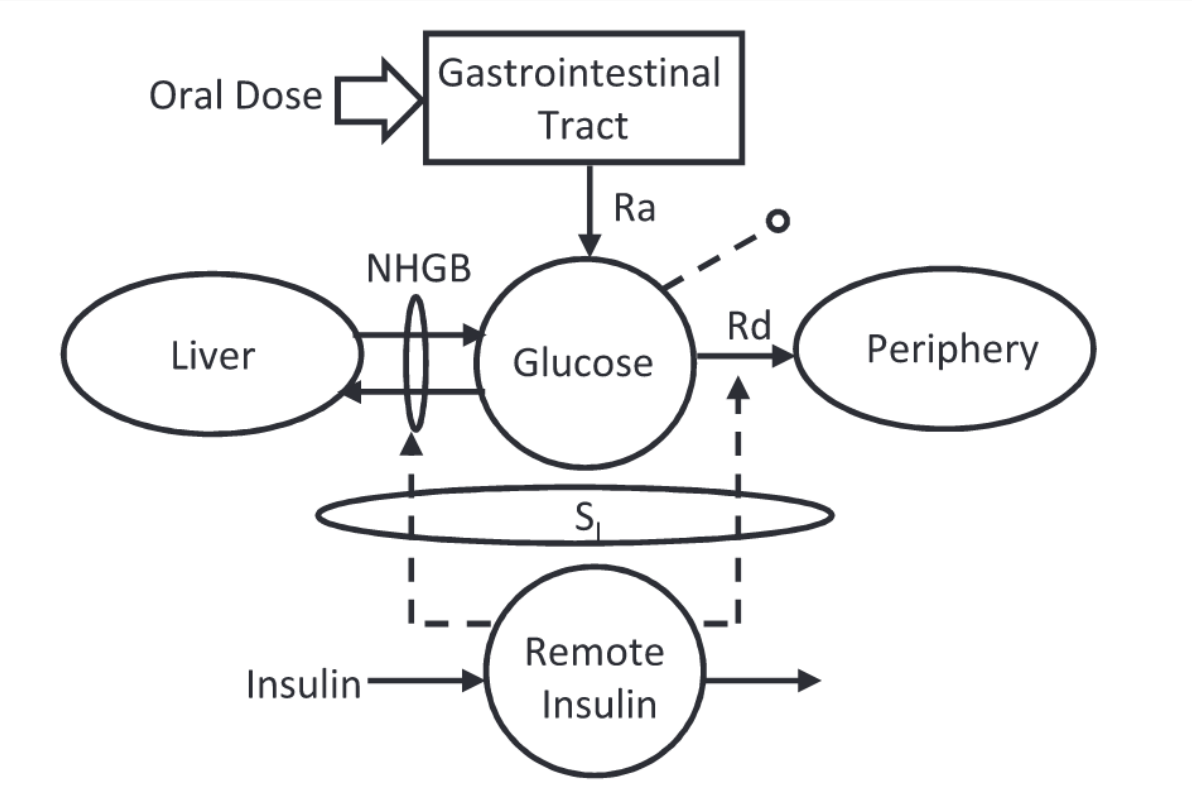
Gold standard: “hyperinsulinemic euglycemic clamp”

- measures the amount of glucose necessary to compensate for an increased insulin level without causing hypoglycemia[1]
- costly, invasive, not representative of normal physiology
- **alternative:** quantify from **OGTT** via **dynamic model** of the glu-ins system



1. DeFronzo, 1979. Glucose clamp technique: a method for quantifying insulin secretion and resistance

The oral glucose minimal model

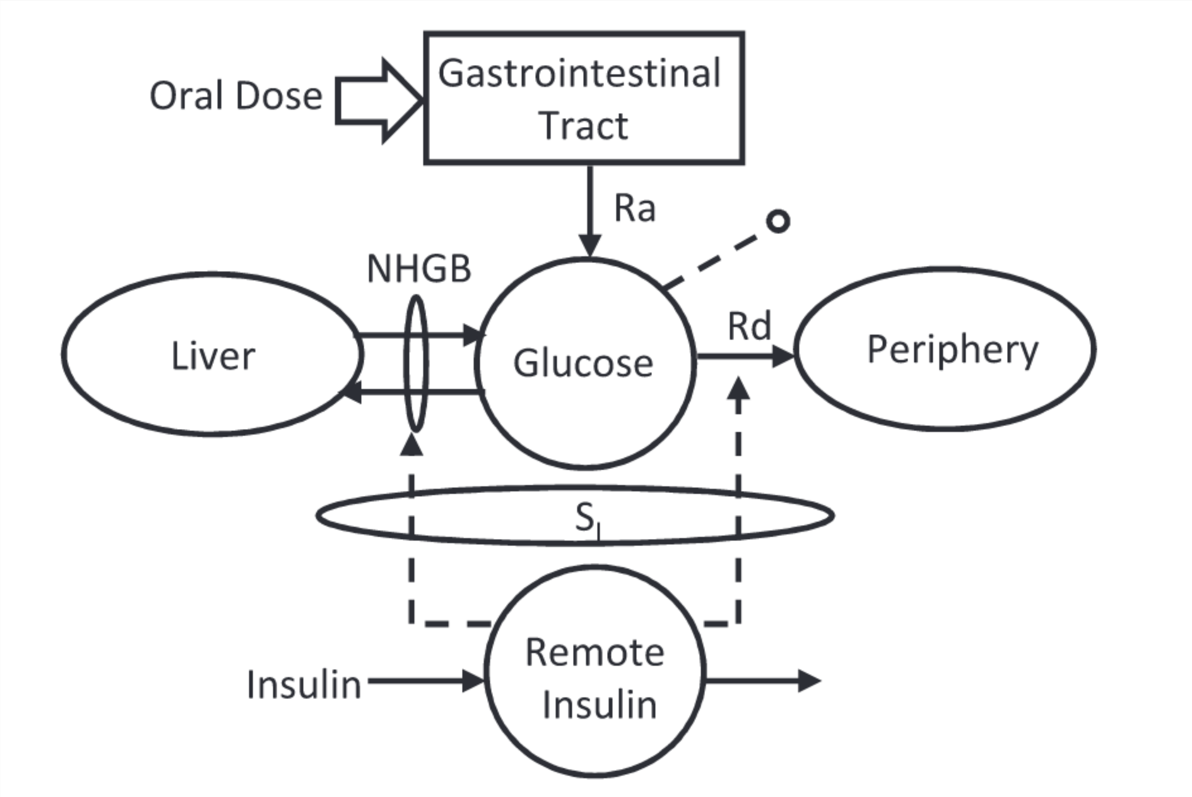


Main concepts:

1. model predicts evolution of glucose given measured time series of insulin

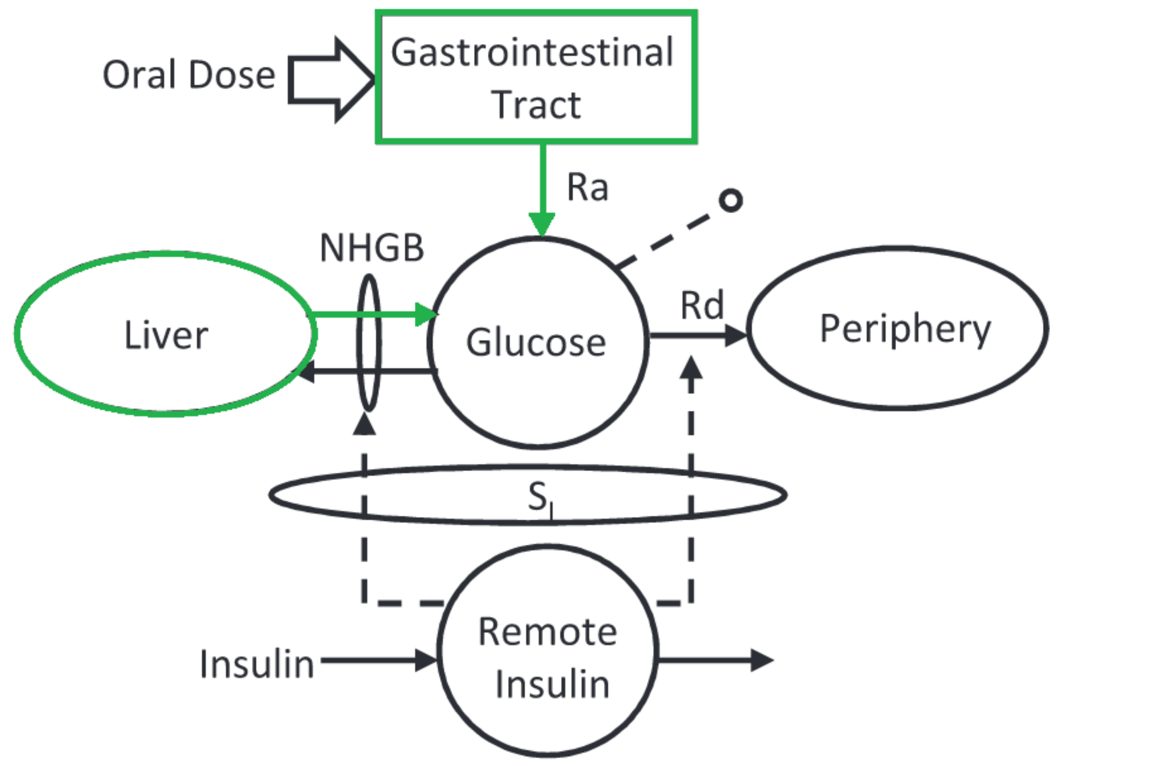
2. estimate model parameters that describe insulin sensitivity

The oral glucose minimal model



$$\frac{dQ}{dt} =$$

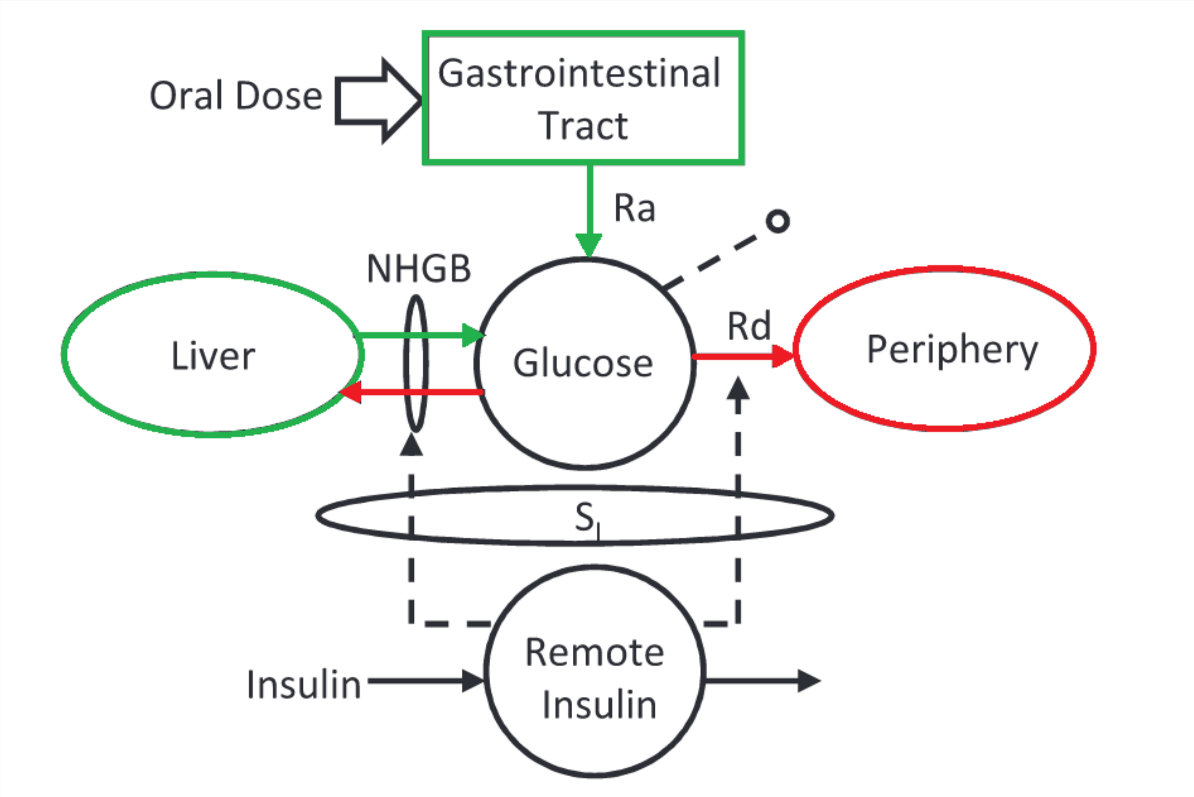
The oral glucose minimal model



$Ra(t)$ - glucose from gut
$NHGB(t)$ - glucose from liver

$$\frac{dQ}{dt} = Ra(t) + NHGB(t)$$

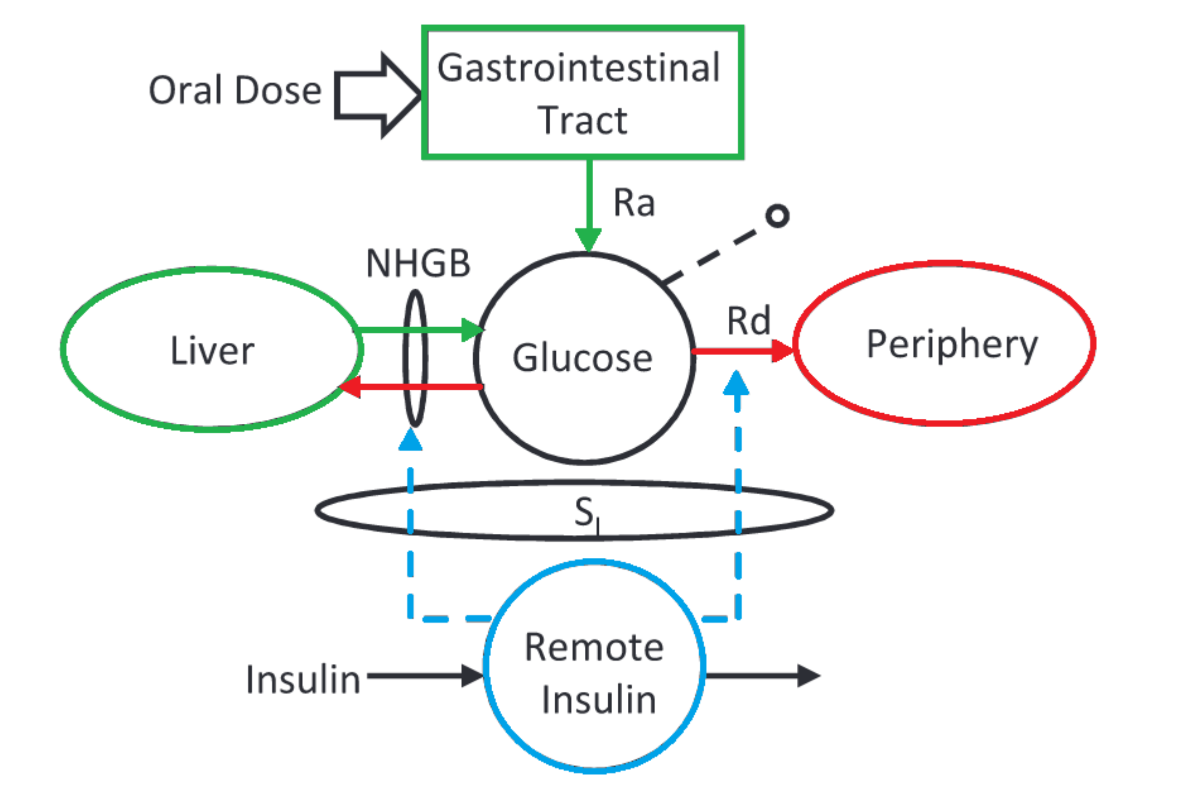
The oral glucose minimal model



$Ra(t)$ - glucose from gut
$NHGB(t)$ - glucose from liver
$NHGB(t)$ - glucose to liver
$Rd(t)$ - glucose to periphery

$$\frac{dQ}{dt} = Ra(t) + NHGB(t) - Rd(t)$$

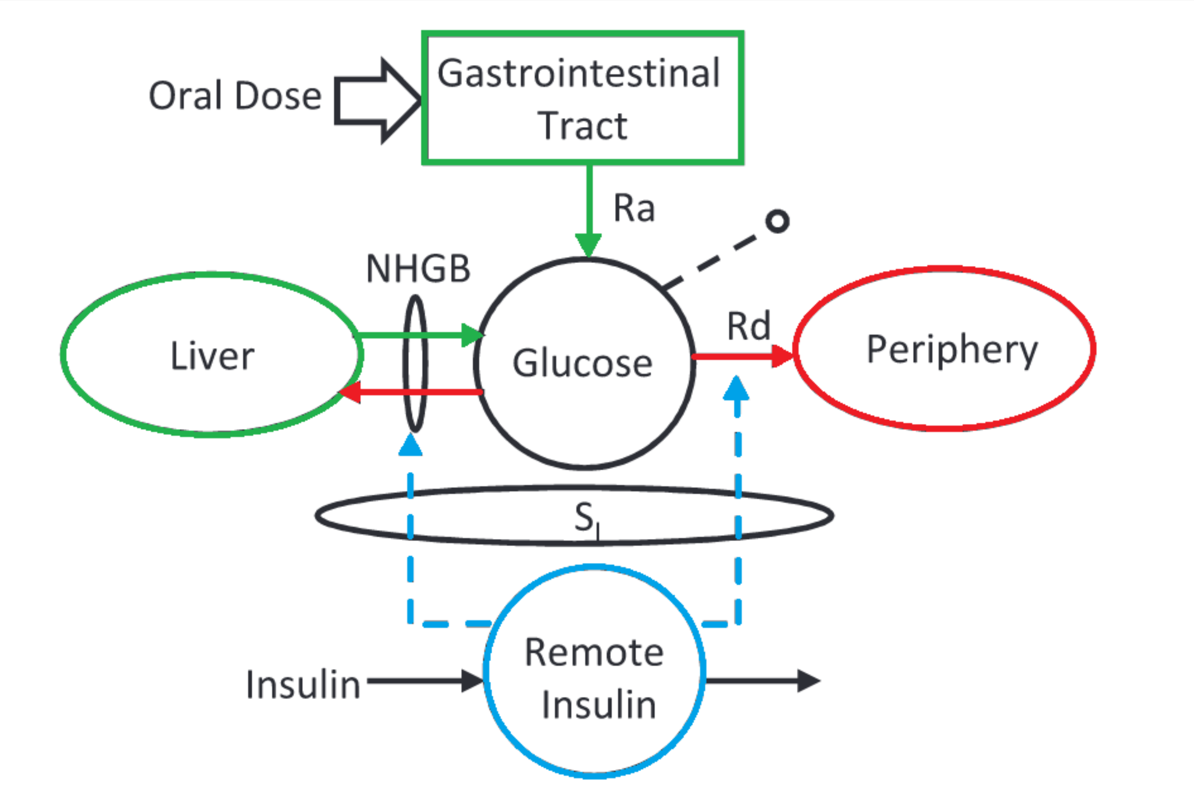
The oral glucose minimal model



$$Ra(t) = Ra(\alpha, t)$$

$$\frac{dQ}{dt} = Ra(t) + NHGB(t) - Rd(t)$$

The oral glucose minimal model

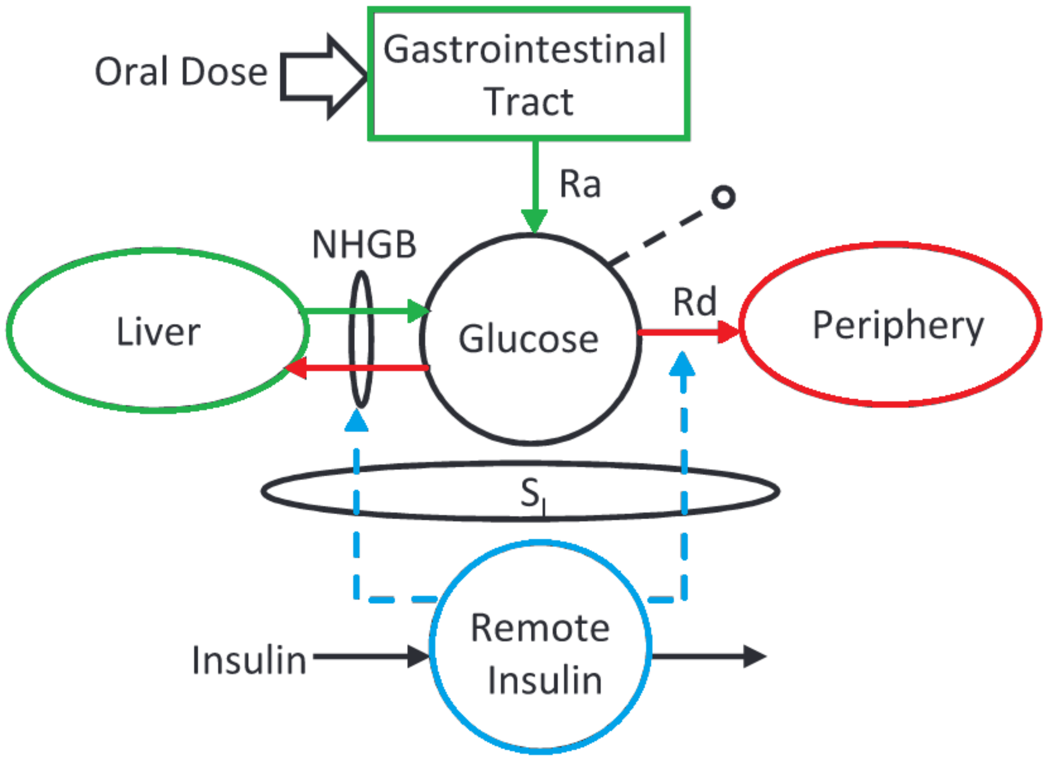


$$Ra(t) = Ra(\alpha, t)$$

However! $NHGB(t)$ and $Rd(t)$ are both mediated by insulin action $X(t) \rightarrow$

$$\frac{dQ}{dt} = Ra(t) + NHGB(t) - Rd(t)$$

The oral glucose minimal model



$Ra(t) = Ra(\alpha, t)$

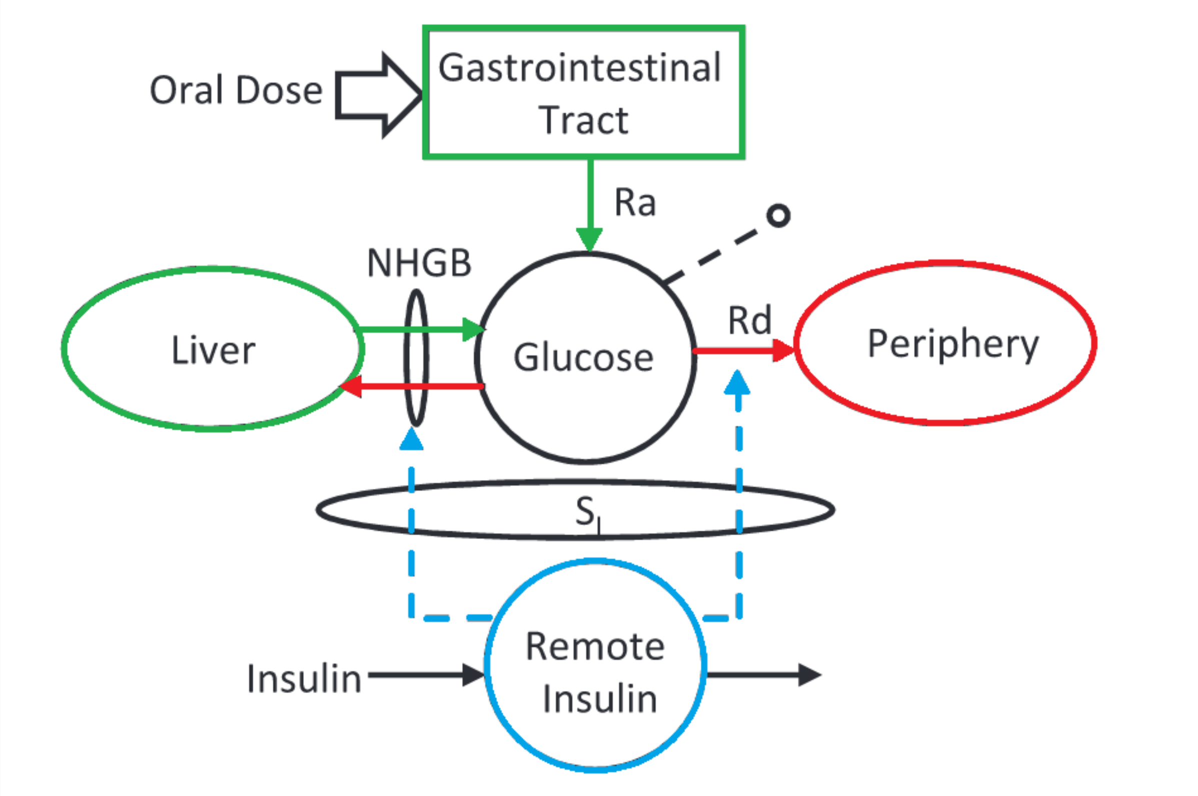
However! $NHGB(t)$ and $Rd(t)$ are both mediated by insulin action

$X(t) \rightarrow$

$+S_g Q_b - S_g Q(t) - X(t)Q(t)$

$$\frac{dQ}{dt} = Ra(t) + NHGB(t) - Rd(t)$$

The oral glucose minimal model



$$Ra(t) = Ra(\alpha, t)$$

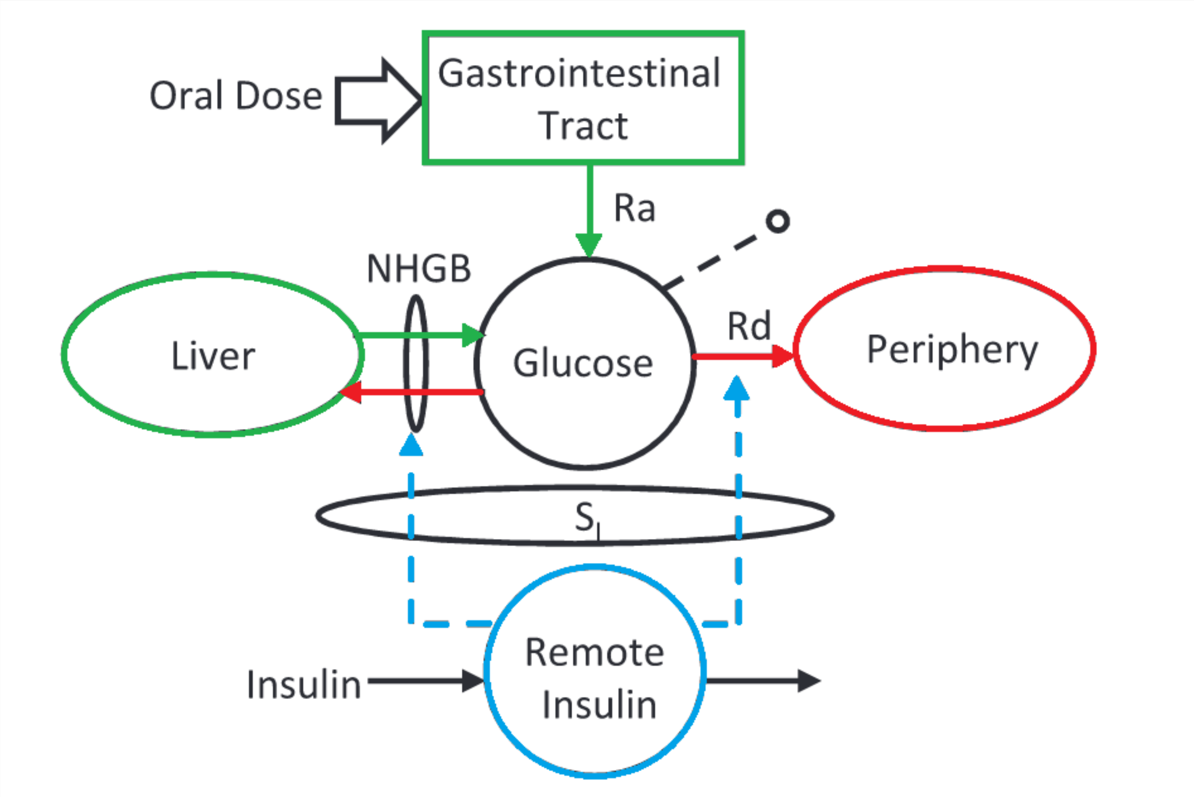
However! $NHGB(t)$ and $Rd(t)$ are both mediated by insulin action $X(t) \rightarrow$

$$+S_g Q_b - S_g Q(t) - X(t)Q(t)$$

$$\frac{dQ}{dt} = Ra(\alpha, t) + S_g Q_b - (S_g + X(t)Q(t))$$

$$\frac{dX}{dt} = p_3(I(t) - I_b) - p_2 X(t)$$

The oral glucose minimal model



$Ra(t) = Ra(\alpha, t)$

However! $NHGB(t)$ and $Rd(t)$ are both mediated by insulin action

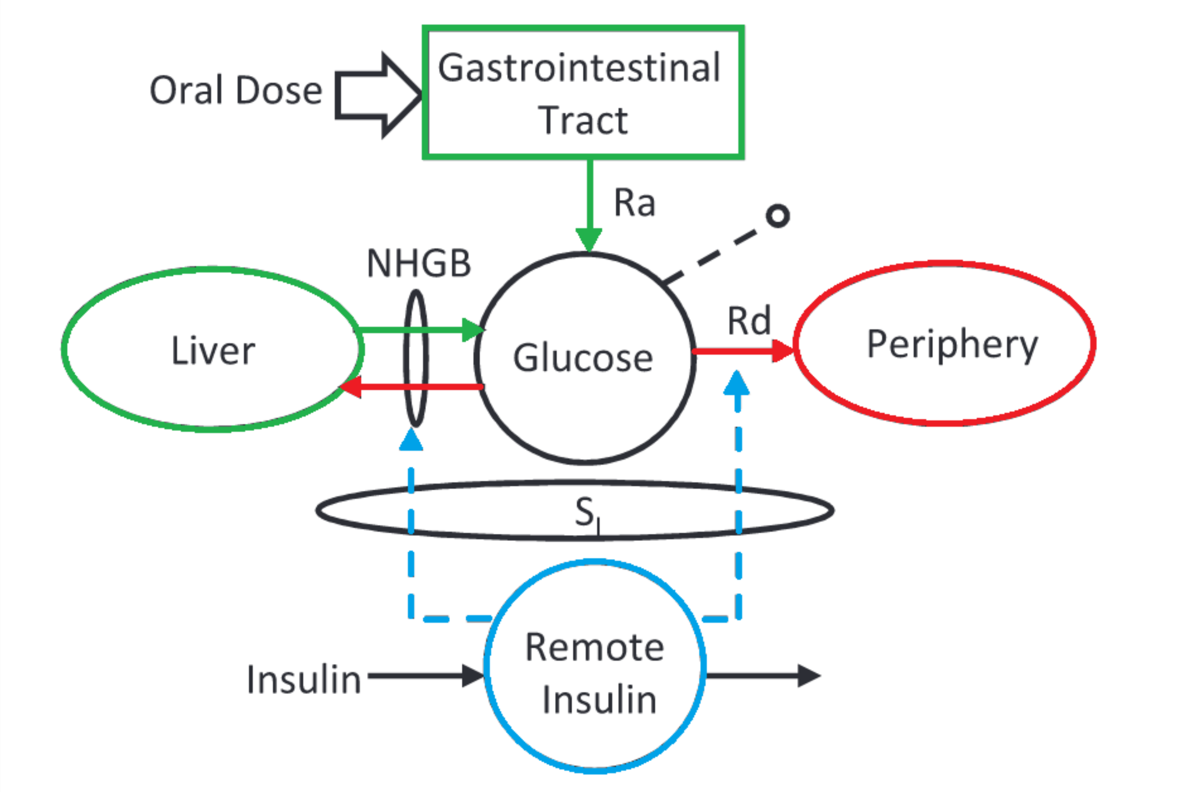
$X(t) \rightarrow$

$+S_g Q_b - S_g Q(t) - X(t)Q(t)$

$$\frac{dQ}{dt} = Ra(\alpha, t) + S_g Q_b - (S_g + X(t)Q(t))$$
$$\frac{dX}{dt} = p_3(I(t) - I_b) - p_2 X(t)$$

$$G(t) = \frac{Q(t)}{V}$$

The oral glucose minimal model



α, S_g, p_2, p_3 are model parameters. They can be estimated from data! In particular a measure of insulin sensitivity can be derived as:

$$S_I = \frac{p_3}{p_2} V$$

$$\frac{dQ}{dt} = Ra(\alpha, t) + S_g Q_b - (S_g + X(t)Q(t))$$
$$\frac{dX}{dt} = p_3(I(t) - I_b) - p_2 X(t)$$

$$G(t) = \frac{Q(t)}{V}$$

The oral glucose minimal model in MATLAB

$$\frac{dQ}{dt} = Ra(\alpha, t) + S_g Q_b - (S_g + X(t)Q(t))$$

$$\frac{dX}{dt} = p_3(I(t) - I_b) - p_2 X(t)$$

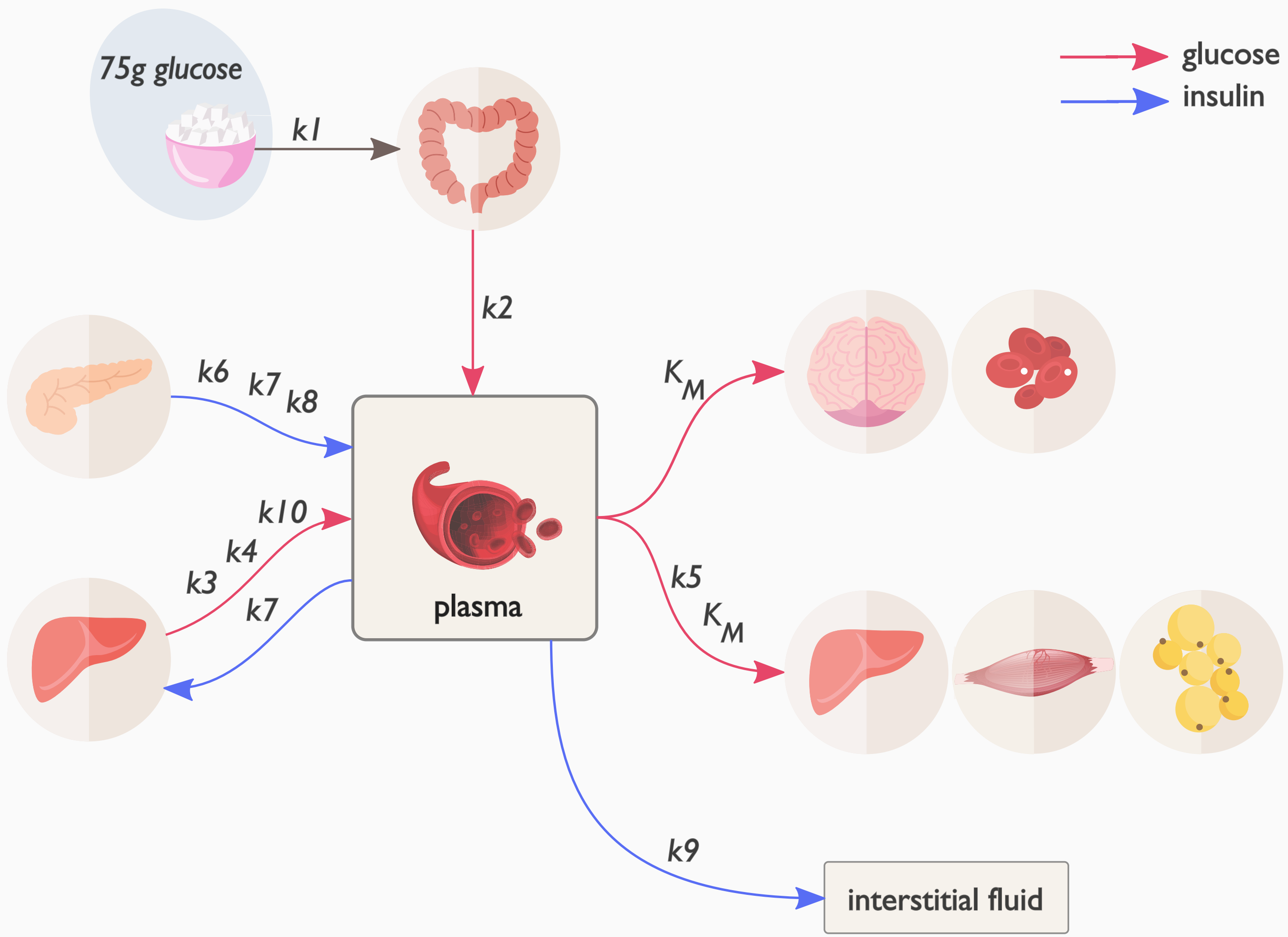
```
% state variables:
Q = x(1);
X = x(2);

% glucose in plasma:
dx(1) = Ra + SG*Qb - (SG + X)*Q;
% insulin action:
dx(2) = p3*(I-datIns(1)) - p2*X;
```

more in Thursday's practical!

Dynamic models of metabolism

Can we go beyond quantifying a single index?



eDES model[1]

- 2 compartments
- 13 parameters
- calibrated on OGTT
- estimating only 4 parameters

→

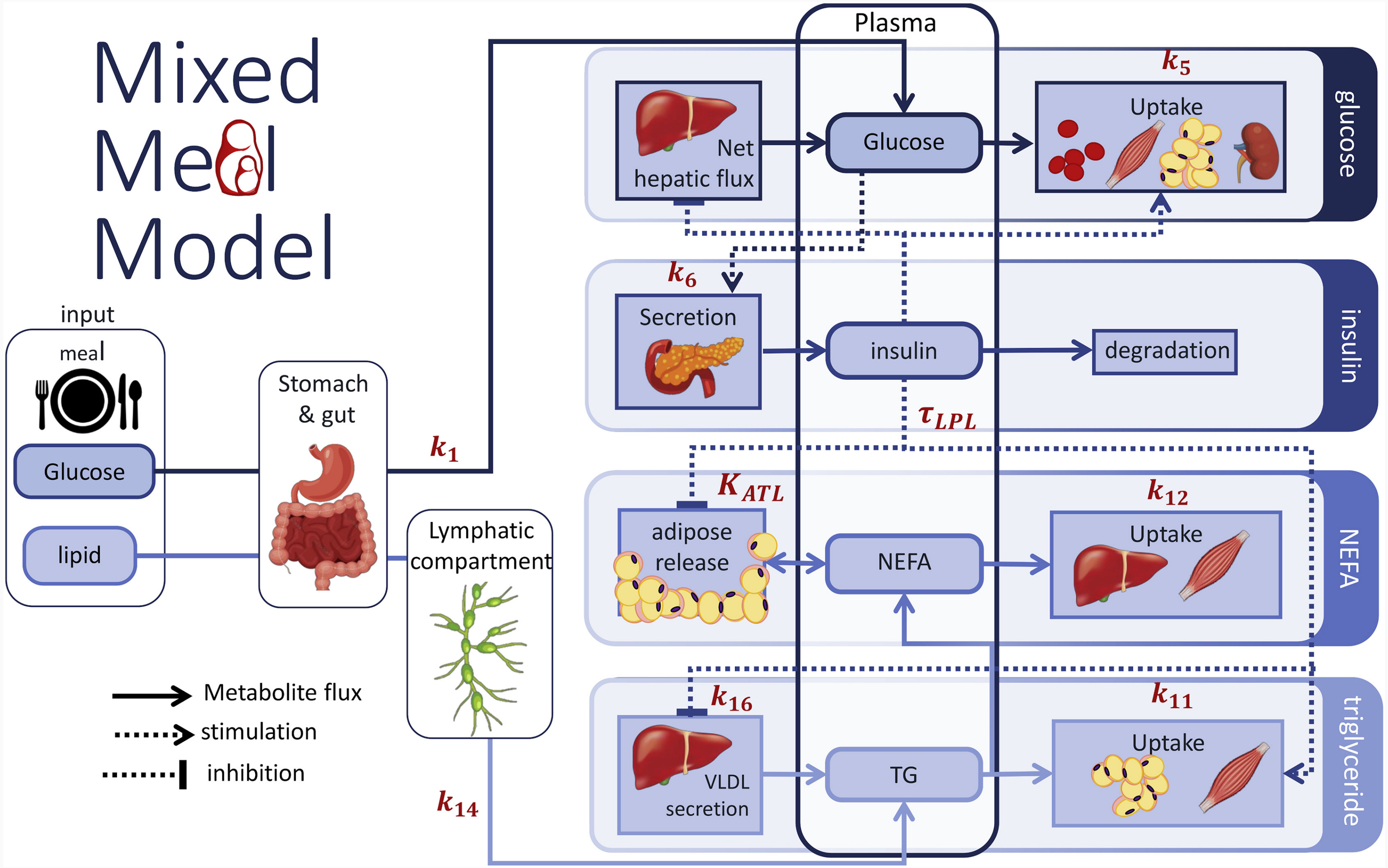
1. Maas et al.2017; Erdős et al., 2021

Dynamic models of metabolism

Erdős et al., 2021

Dynamic models of metabolism

Dynamic models of metabolism



O'Donovan et al., 2022

Modeling in systems biology

…to whole organisms and physiology

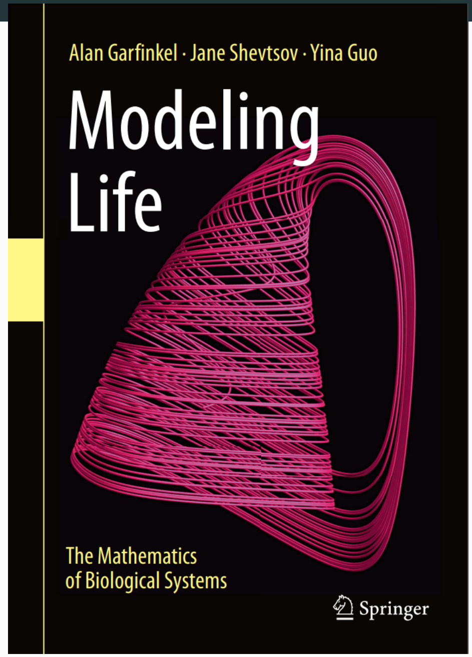
data-driven (machine learning)

Conclusion

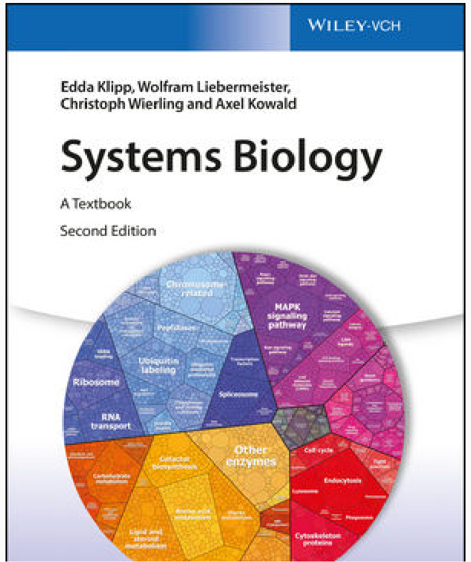
- metabolism is a **dynamical system**
- questions of how, why, and when systems **change** can only be answered if we look at the dynamics!
- **differential equation** models are a convenient and flexible way to model these systems
- development of **T2DM** occurs over time as the **glucose-insulin system deteriorates**
- dynamic models of the glu-ins system allow insight into glucose regulation

Further reading and resources

- Alan Garfinkel, Jane Shevtsov, Yina Guo - “Modeling Life: The Mathematics of Biological Systems”
  - book available online, lectures on youtube



- Edda Klipp, Wolfram Liebermeister, Christoph Wierling, Axel Kowald - “Systems Biology: A textbook”



Thank you for your attention!