Mathematical models for Continuous Glucose Monitoring: deterministic and stochastic approaches

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Outline

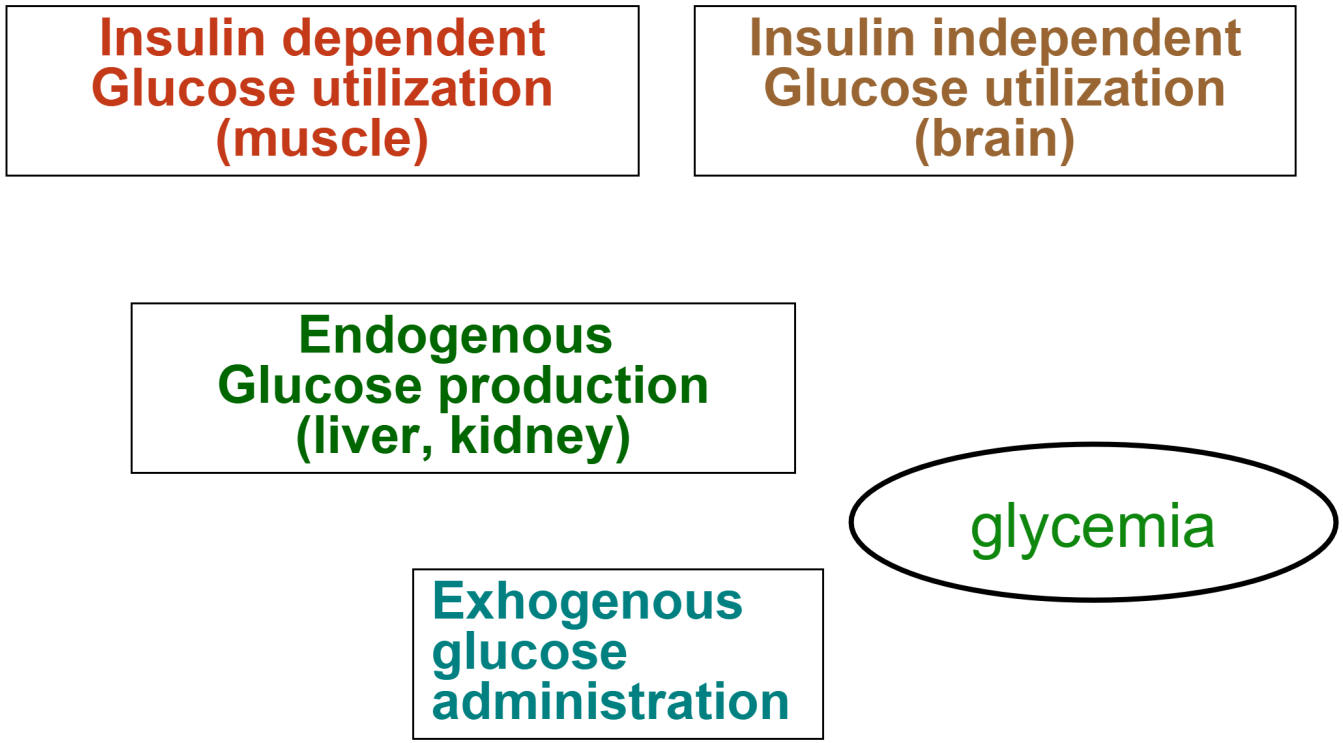
Introduction

Abstract

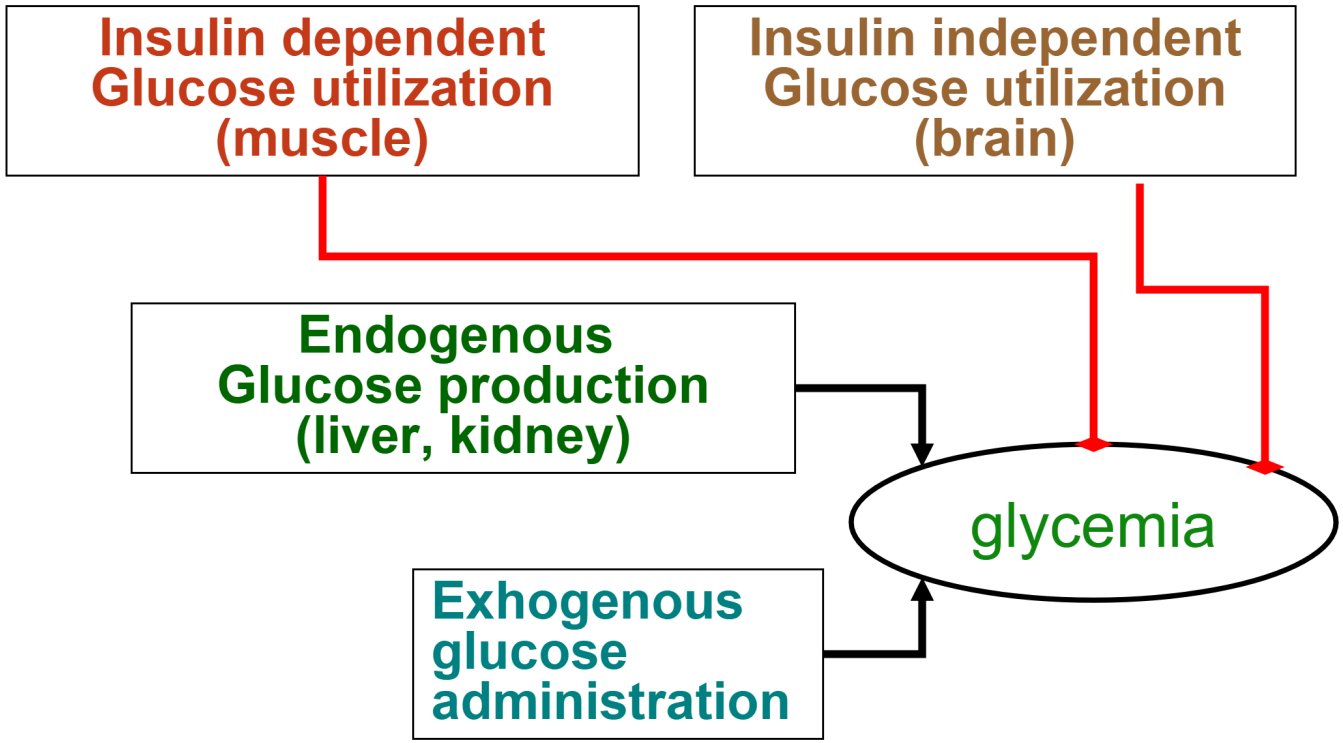
In the quest for progressively more realistic mathematical representations of biomedical processes, fractional differential equations have the potential of summarizing, with an order that can in principle be estimated from data, different (presumably integer-order) interacting controls or influences upon the observed variable of interest. This is the case, for example, of transcutaneously measured glycemia, where besides glycemia itself (possibly decaying by first-order elimination) also unobserved factors (insulinemia, other hormones) may exert higher order effects. The problem is complicated by the fact that random events (hormonal oscillations and emotions, besides food intake or exercise) may affect glycemia as well, leading to the eventual formalization of the problem as a Fractional Stochastic Differential Equation. We discuss the rationale and the techniques for progressing from ODE's to more complex deterministic and stochastic models. We use a simple FSDE model of glycemic control to exemplify a possible approach to model parameter estimation in this context: advances both in model structure and in parameter estimation techniques are the topic of future research at Obuda University. Once satisfactory modeling and estimation methods are obtained, their incorporation in devices or add-on apps for the analysis of Continuous Glucose Measurement tracings would greatly improve patient-specific tailoring of therapy, with better glycemia prediction and reduction of the frequency of occurrence of dangerous hypoglycemic episodes in the fragile, often juvenile Type 1 Diabetes Mellitus population.

Physiological glucose control 1/7

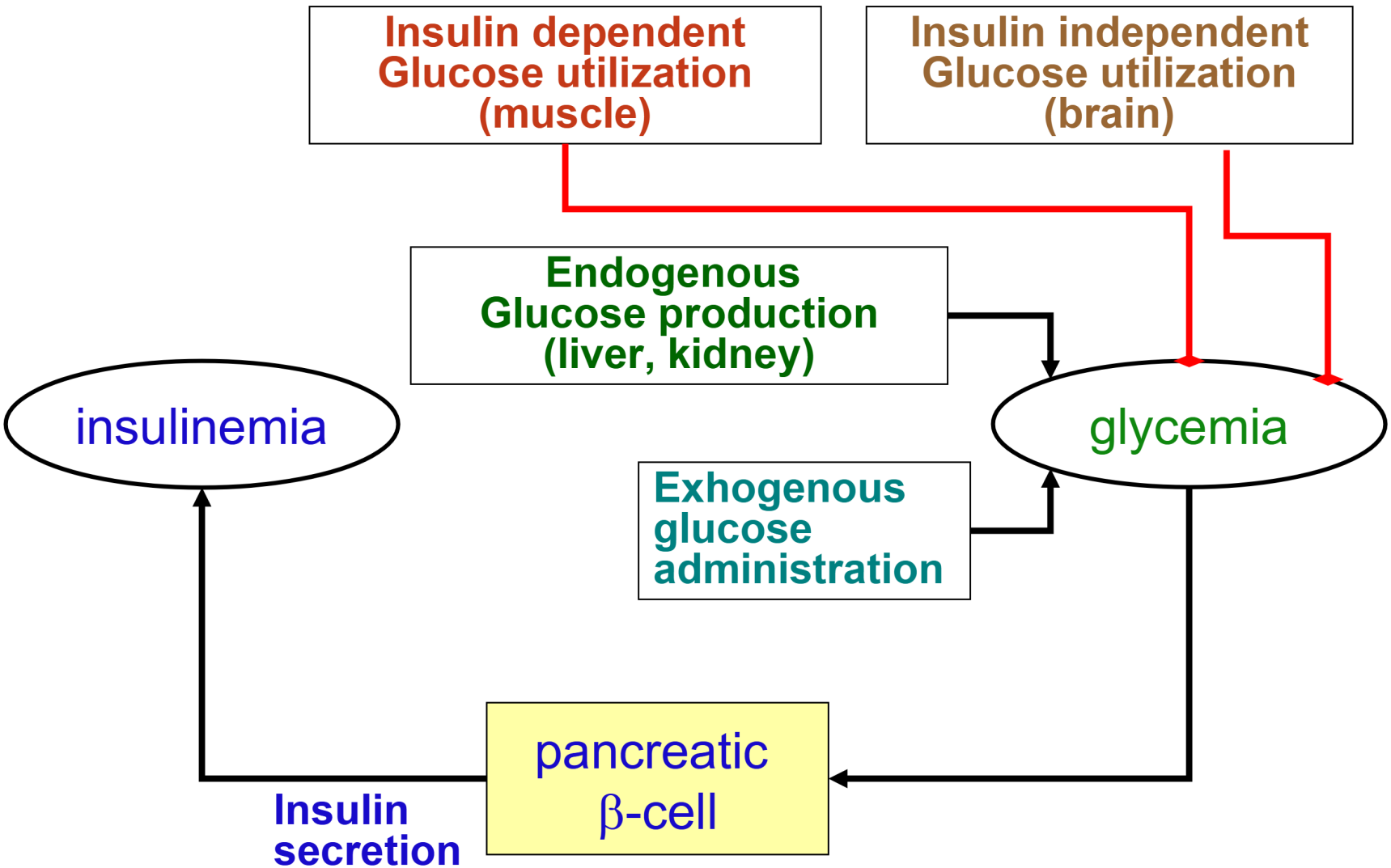
Physiological glucose control 2/7



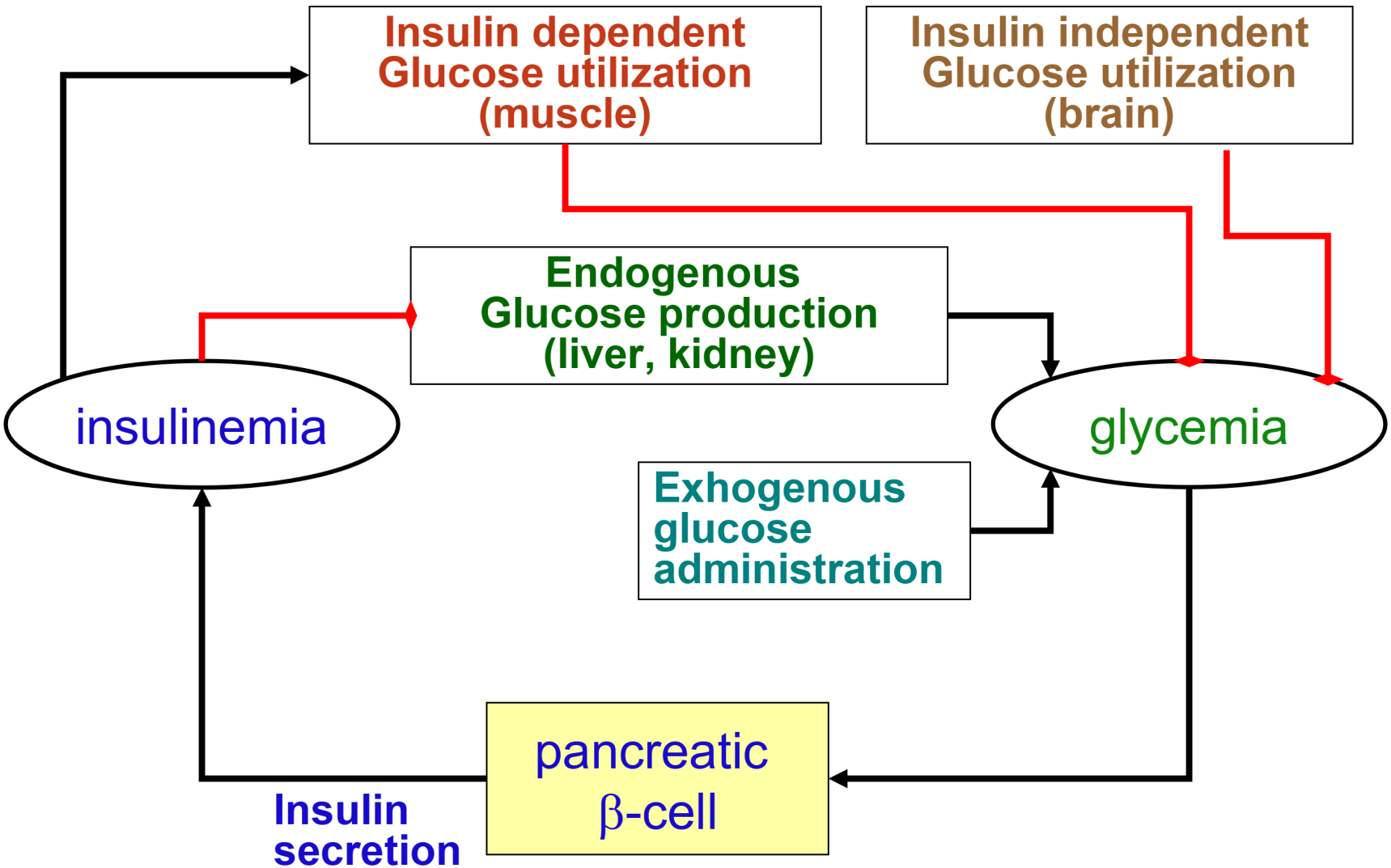
Physiological glucose control 3/7



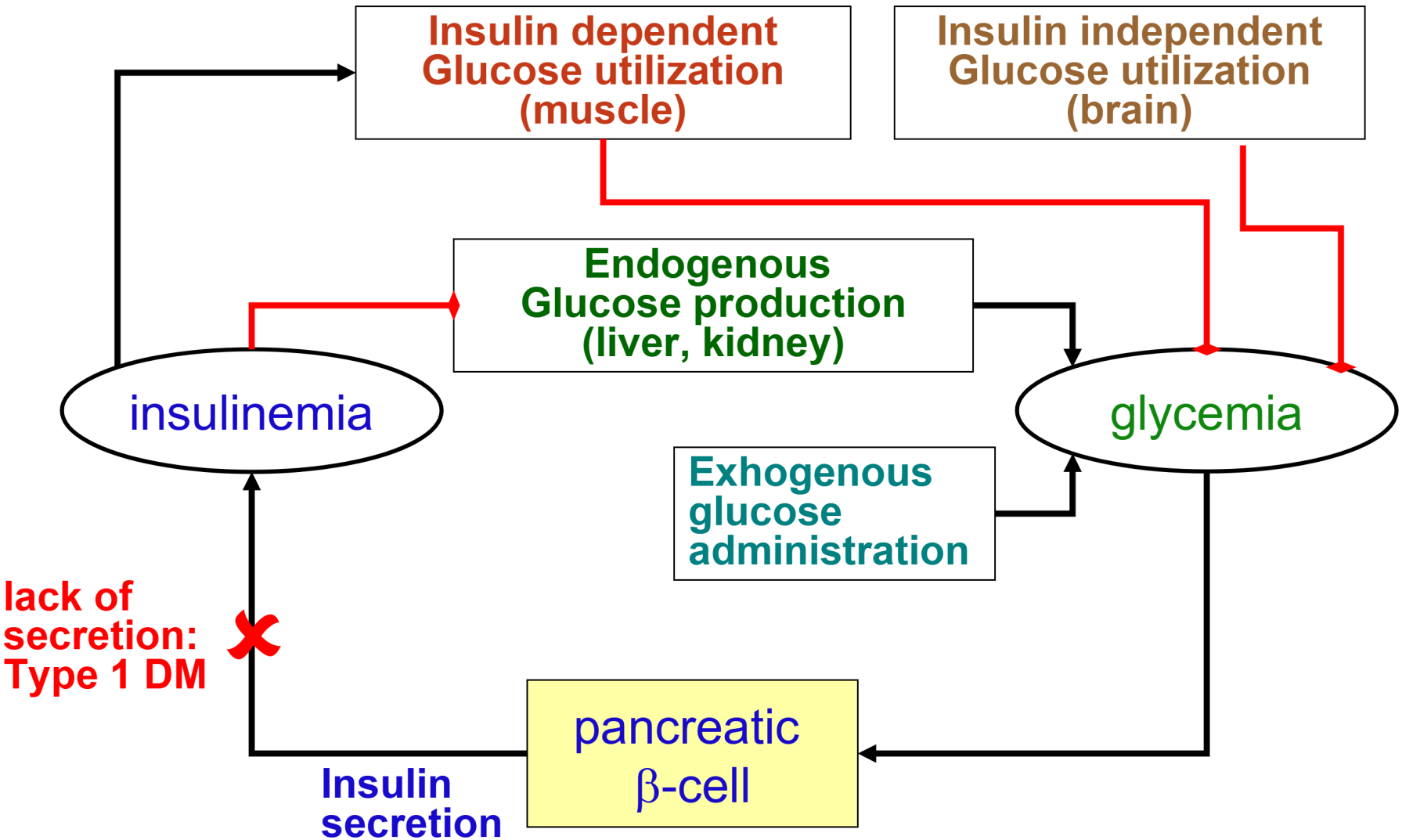
Physiological glucose control 4/7



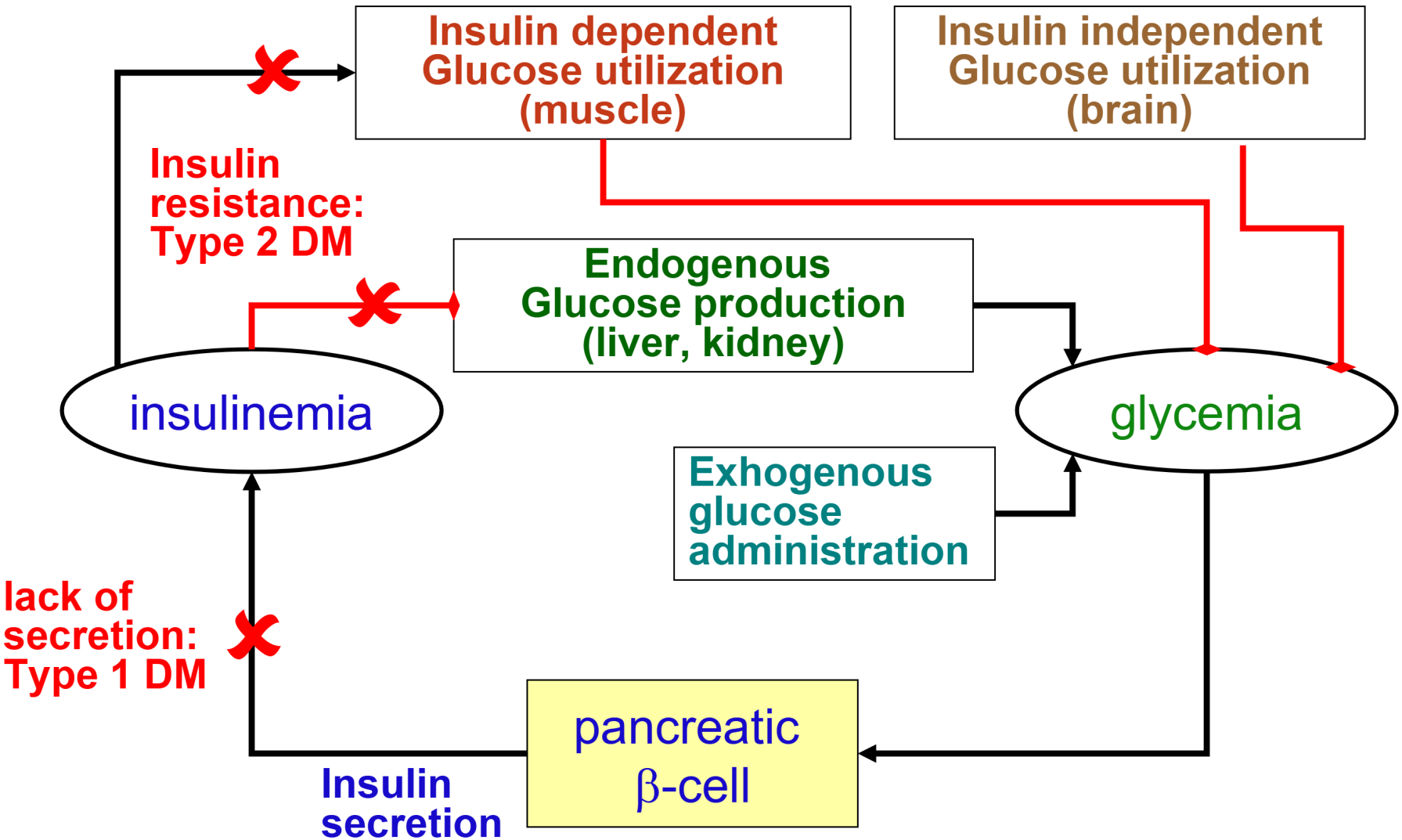
Physiological glucose control 5/7



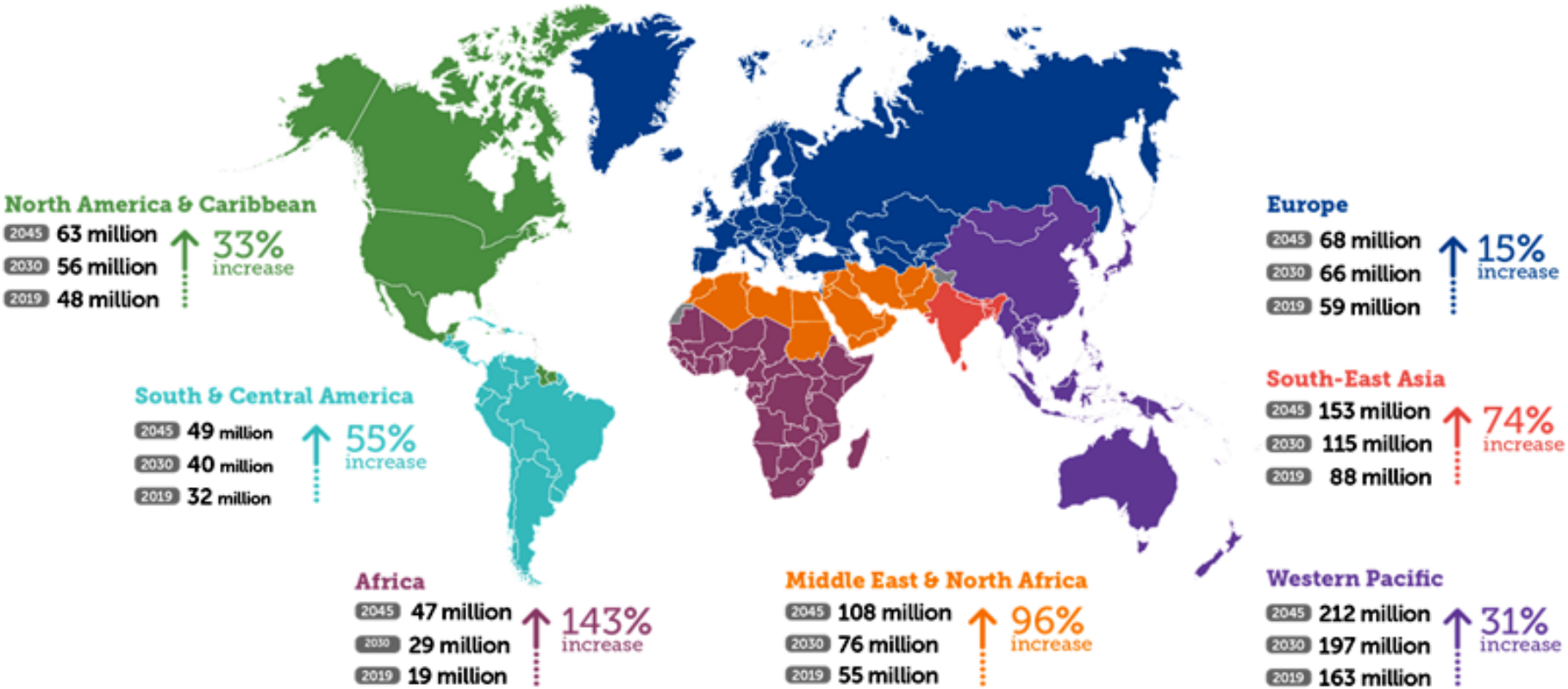
Physiological glucose control 6/7



Physiological glucose control 7/7

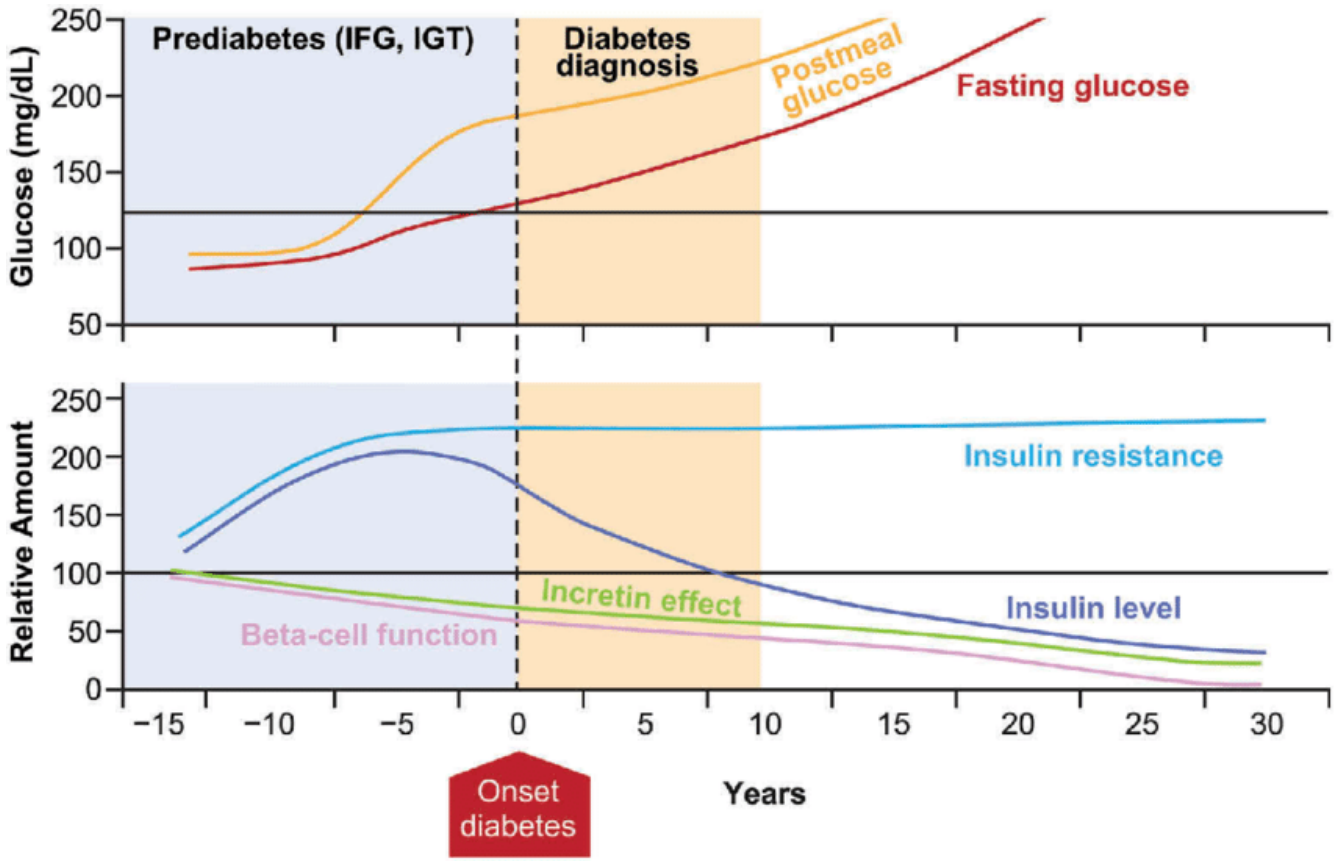


Diabetes Prevalence (ages 20-79)

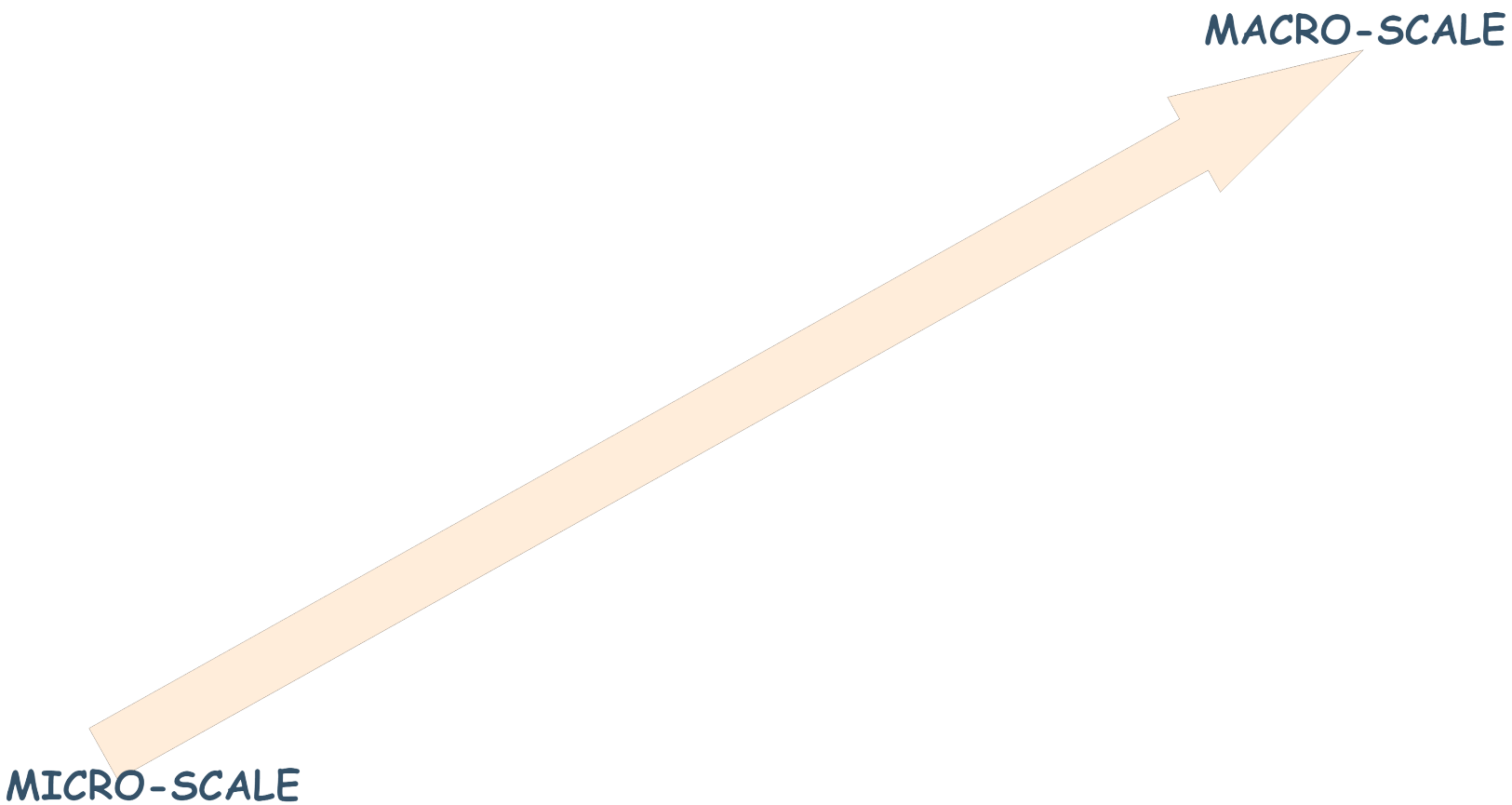


Hungary: 661,400 people with Diabetes in 2021 (7 % of population) + maybe 110,300 undiagnosed cases.

Natural history of T2DM

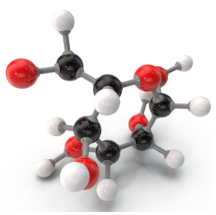


Multi-scale modeling in Biomedicine 1/9



Multi-scale modeling in Biomedicine 2/9

MACRO-SCALE

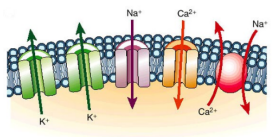


Molecular level

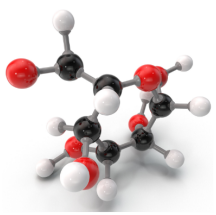
MICRO-SCALE

Multi-scale modeling in Biomedicine 3/9

MACRO-SCALE



Cellular level

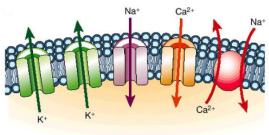


Molecular level

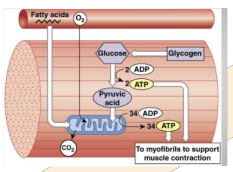
MICRO-SCALE

Multi-scale modeling in Biomedicine 4/9

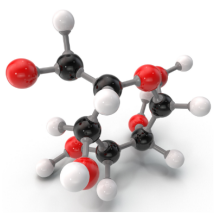
MACRO-SCALE



Cellular level



Tissue level



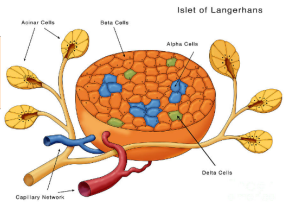
Molecular level

MICRO-SCALE

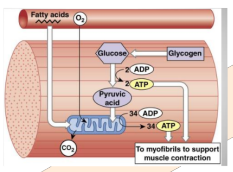
Multi-scale modeling in Biomedicine 5/9

MACRO-SCALE

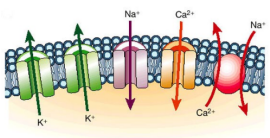
Organ level



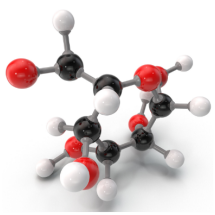
Tissue level



Cellular level



Molecular level

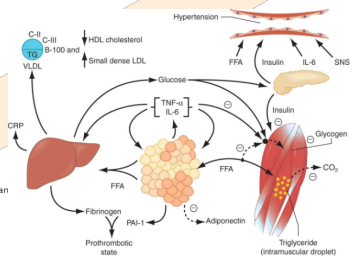


MICRO-SCALE

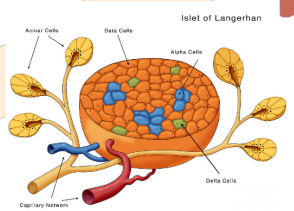
Multi-scale modeling in Biomedicine 6/9

MACRO-SCALE

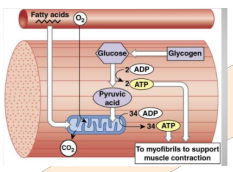
Organism level



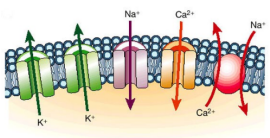
Organ level



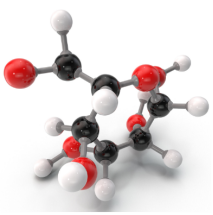
Tissue level



Cellular level

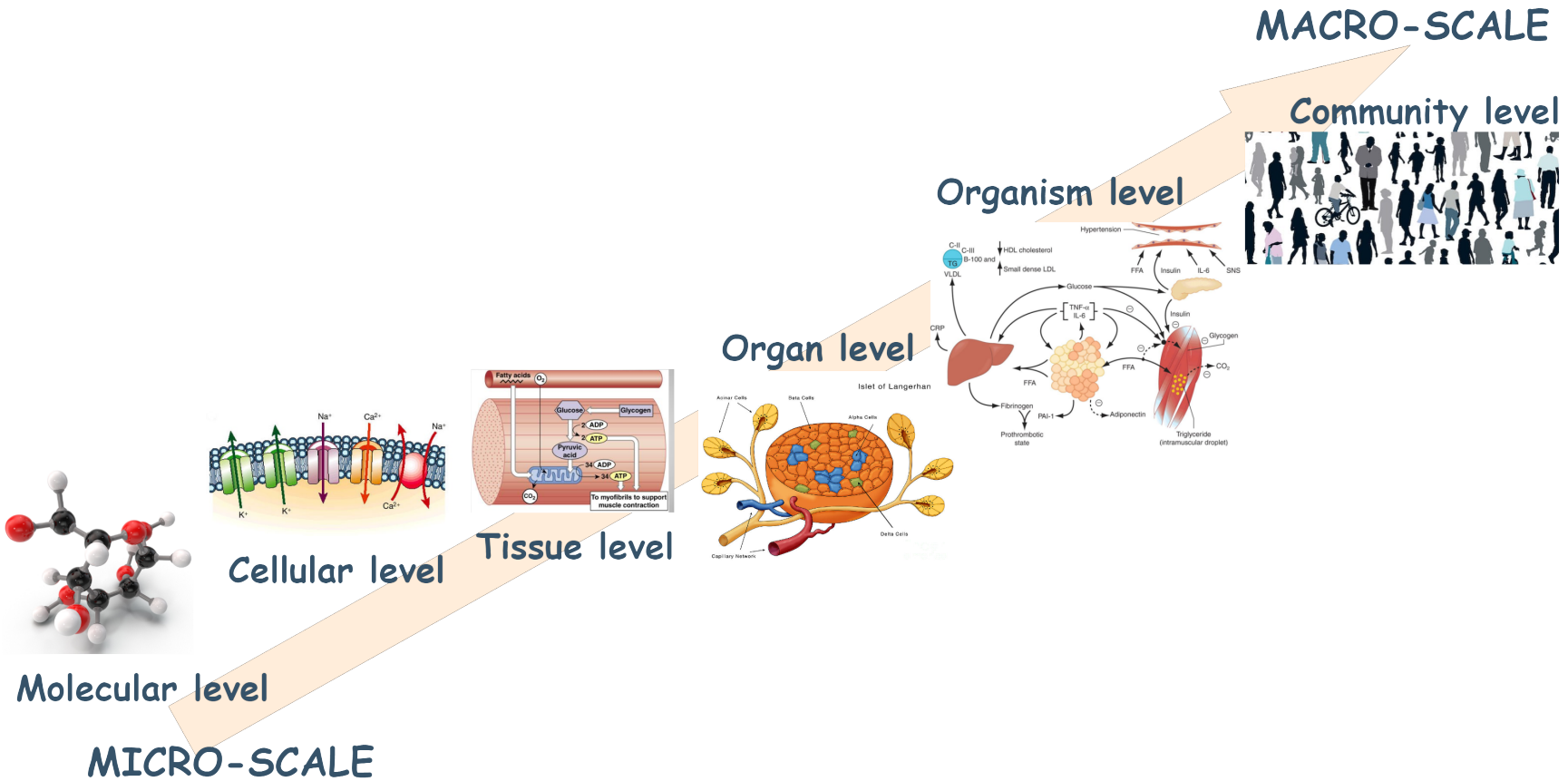


Molecular level

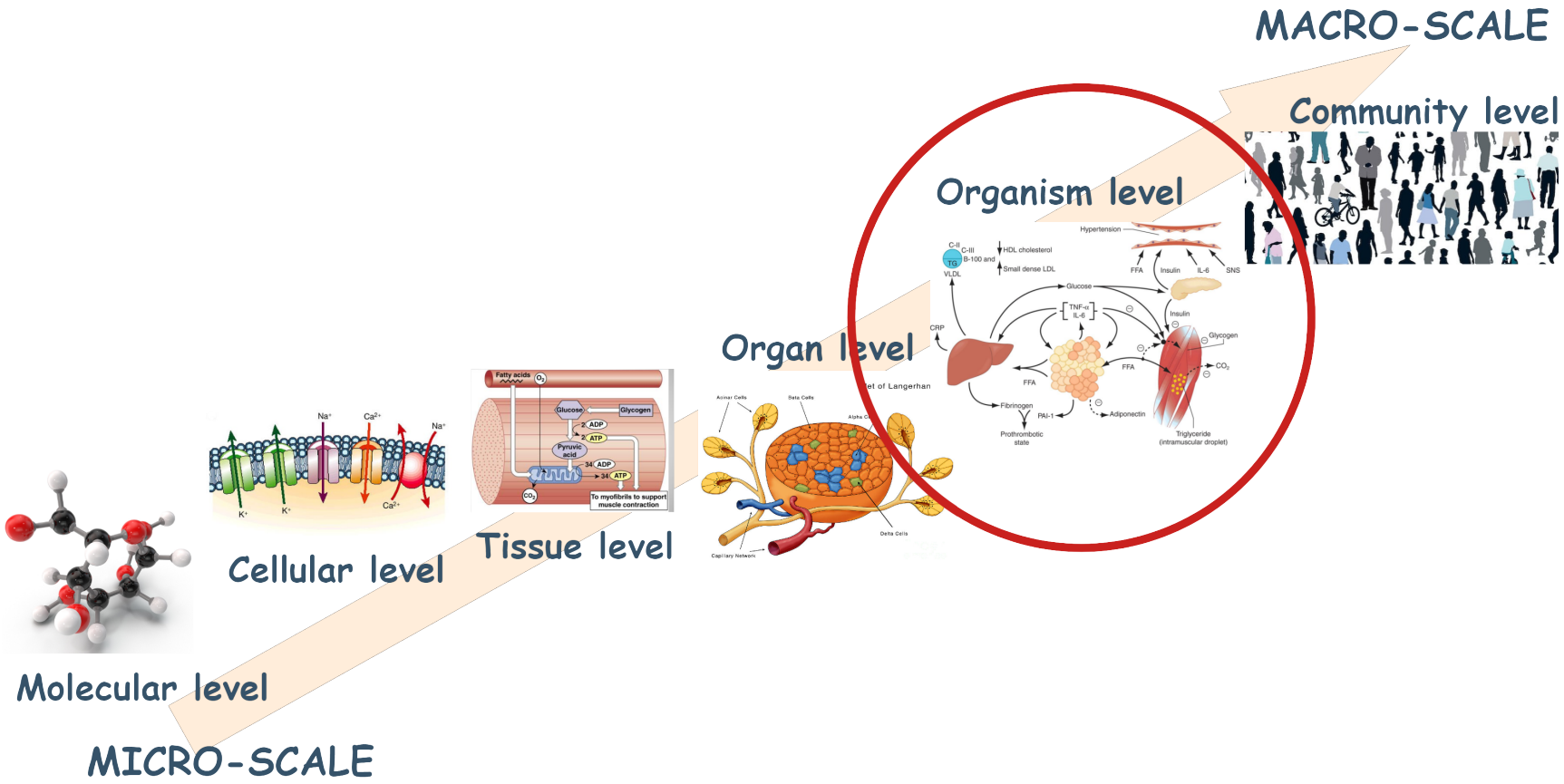


MICRO-SCALE

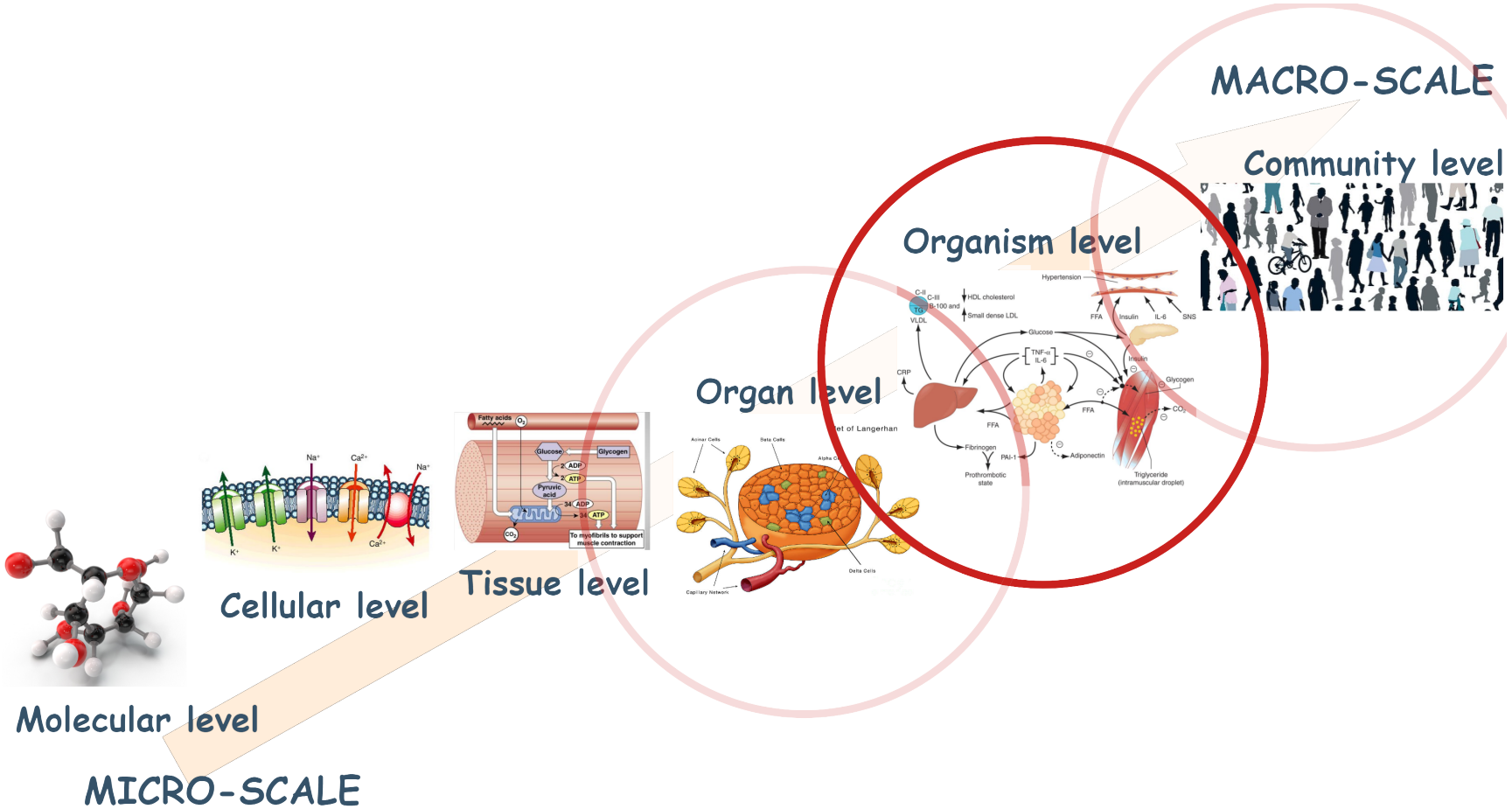
Multi-scale modeling in Biomedicine 7/9



Multi-scale modeling in Biomedicine 8/9



Multi-scale modeling in Biomedicine 9/9



What have we done so far?

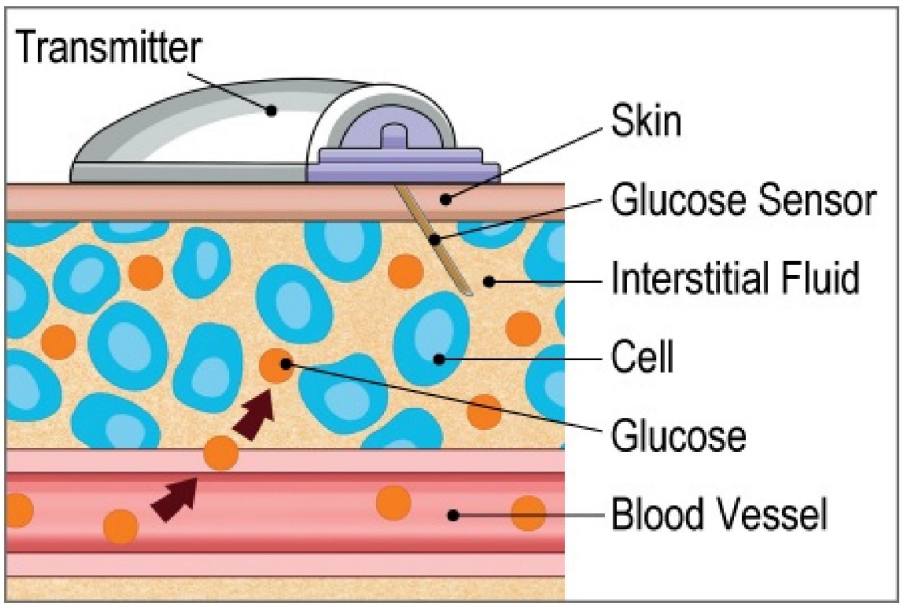
- how the pancreas works (*organ/organism-level*)
- efficient estimation of insulin sensitivity from perturbation experiments (*organism-level*)
- natural history of T2DM (*organism-level*)
- population evolution of insulin sensitivity (*organism/community-level*)

What are we going to do next?

- T2DM evolves to insulin dependence
- T1DM evolves to insulin resistance
- **NEED**: identify patient current condition from real-life data

Continuous Glucose Monitoring (CGM)

A device records glucose concentration in the dermal tissue (in the deep layers of the skin). In diabetic patients recorded glucose concentrations drive an insulin pump through some automatic control algorithm.

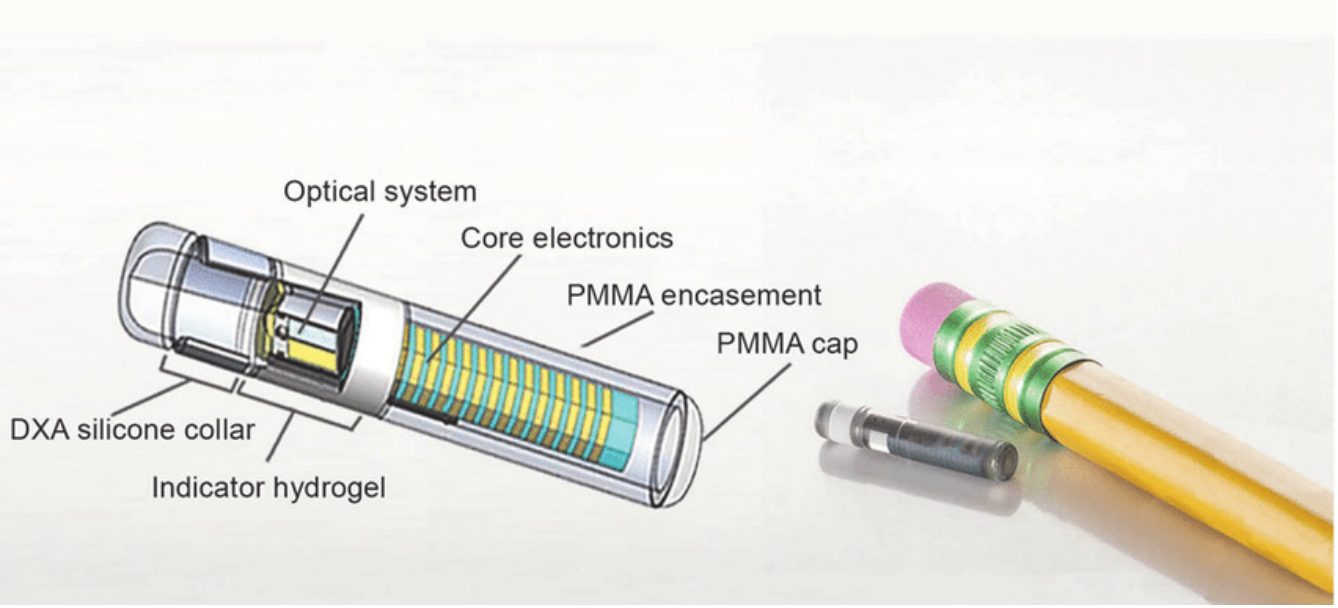


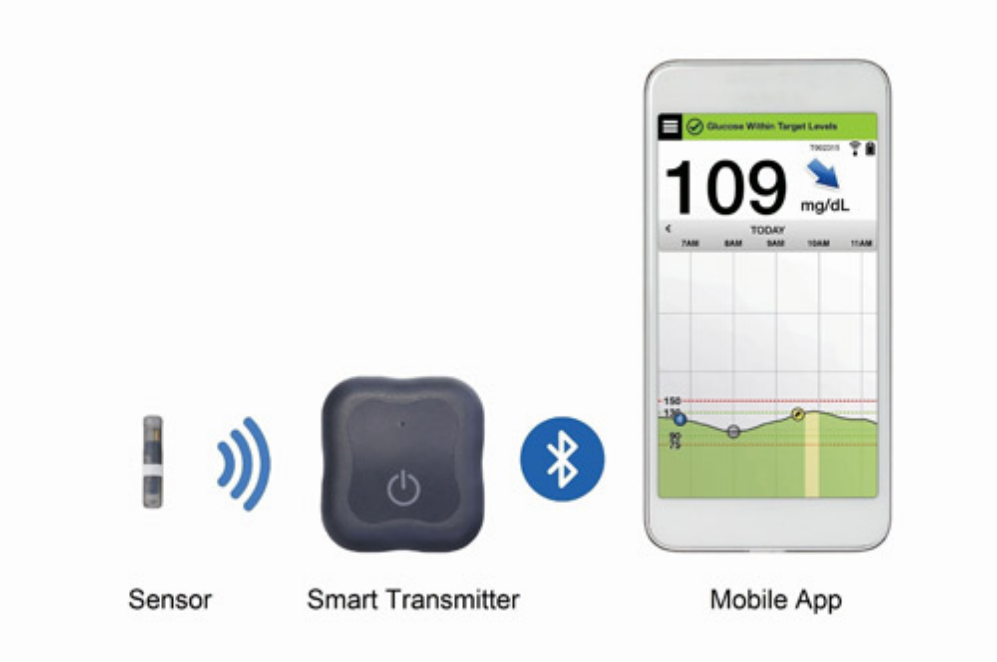
The monitor usually stores the data every 5 minutes. Glucose concentrations measured by the device refer to the dermis, but they reflect with good approximation blood glucose concentrations (glycemia).

CGM and cellphone

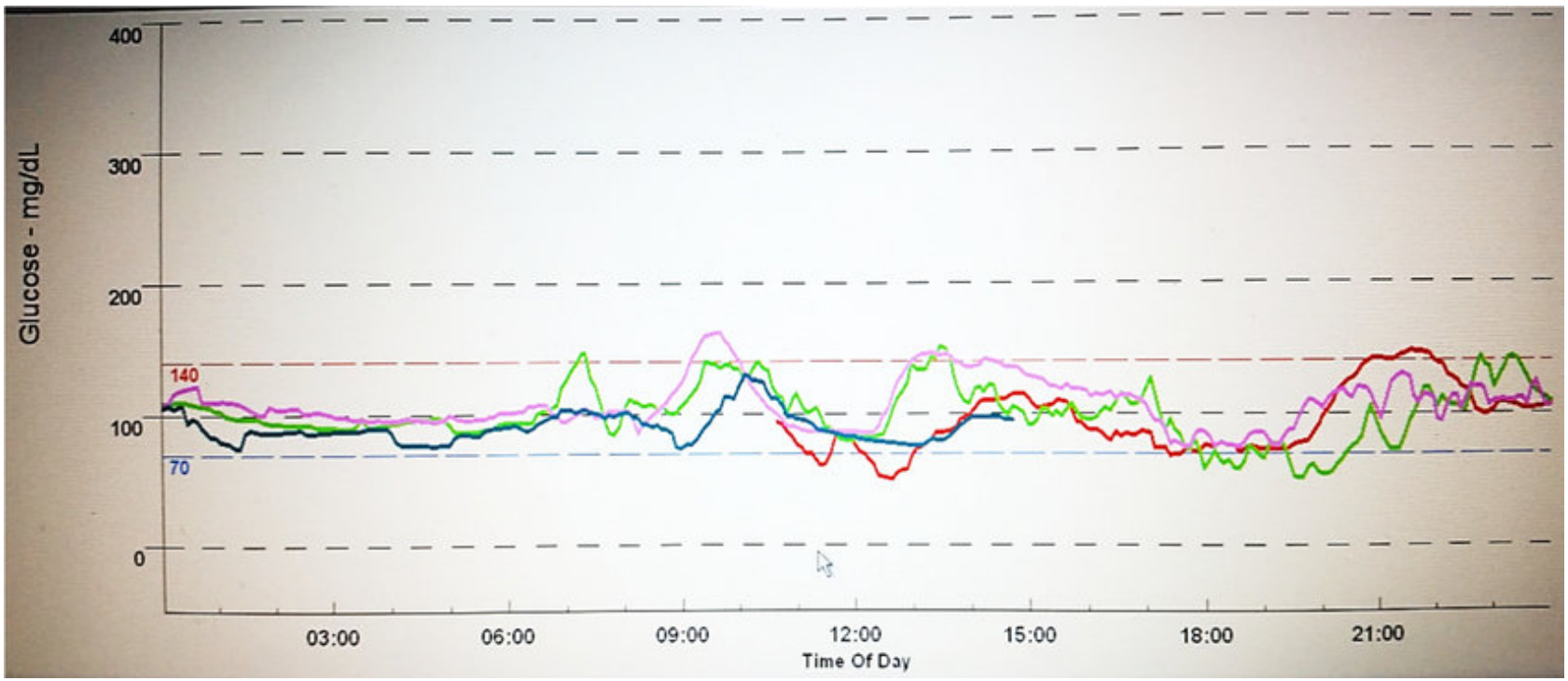
CGM and insulin pump

Implantable CGM

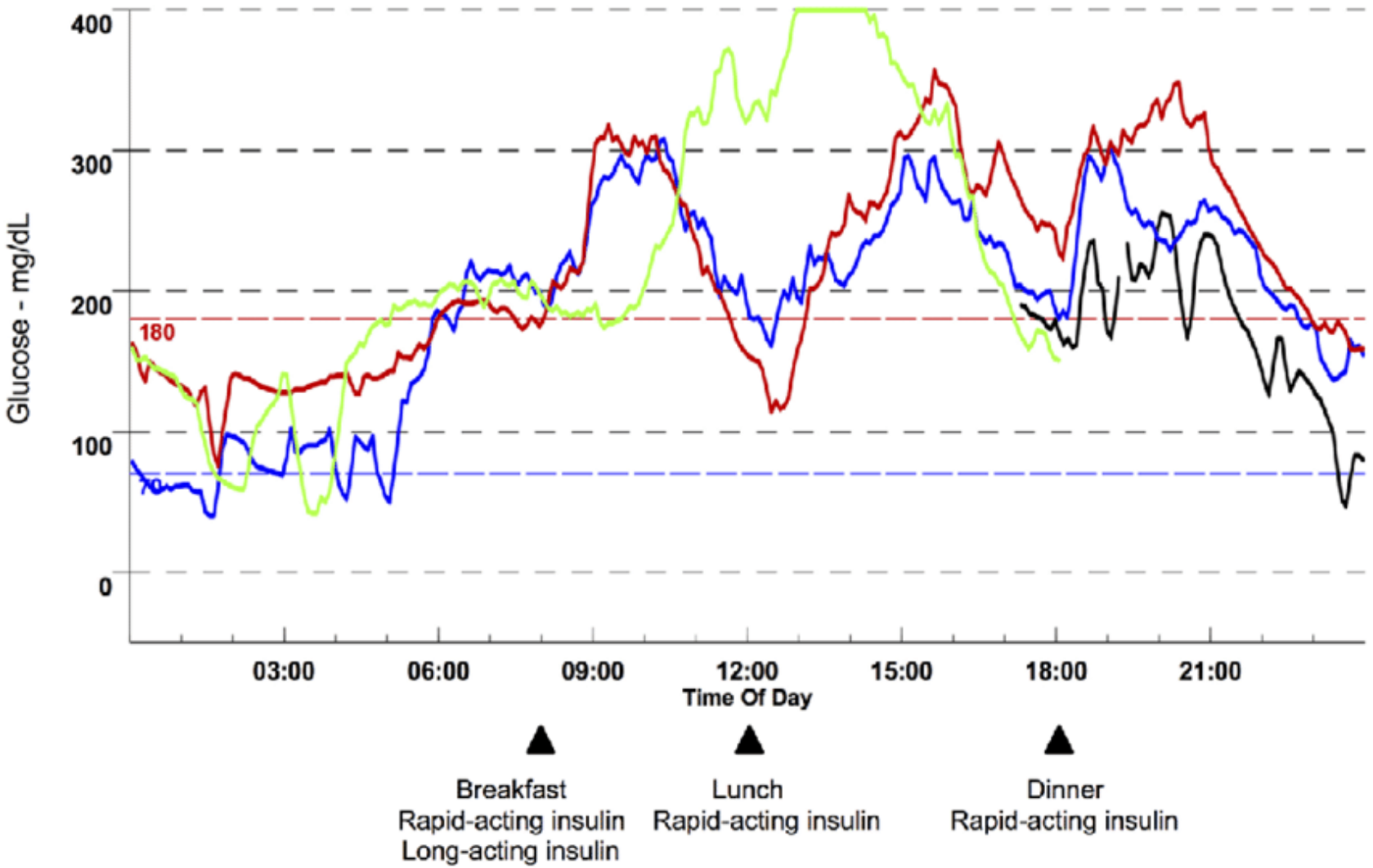




CGM profile: non-diabetic pregnant woman



CGM profile: T1DM



Our goal

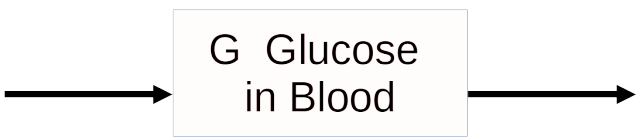
- **Forecasting**? not meaningful
- **Control**? robust
- hence: **diagnostics**! (*post-hoc*)

Methodology

Standard approach:

Ordinary (nonlinear) **Differential Equations**

Glucose Metabolism 1a/10

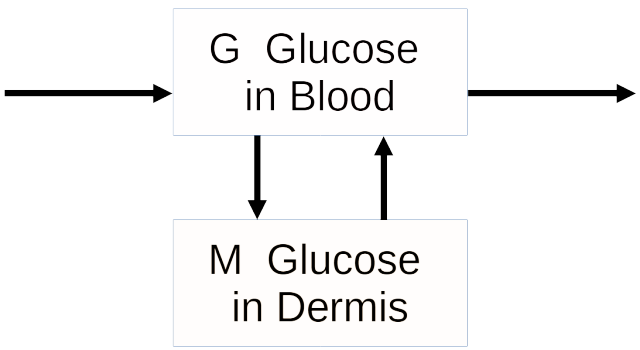


Glucose Metabolism 1b/10

$$\frac{dG}{dt} = k_G - k_{EG}G, \quad G(t_0) = G_0$$

(2 free parameters)

Glucose Metabolism 2a/10

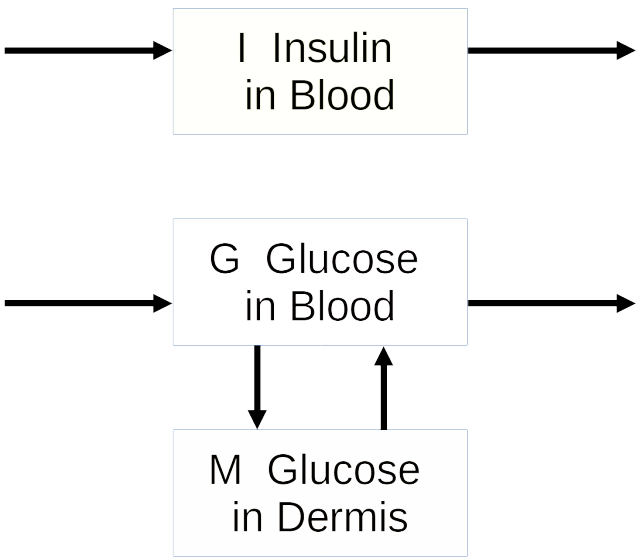


Glucose Metabolism 2b/10

$$\frac{dG}{dt} = k_G - k_{EG}G - k_{MG}G + k_{GM}M, \quad G(t_0) = G_0$$
$$\frac{dM}{dt} = k_{MG}G - k_{GM}M, \quad M(t_0) = M_0 = G_0$$

(3 free parameters)

Glucose Metabolism 3a/10

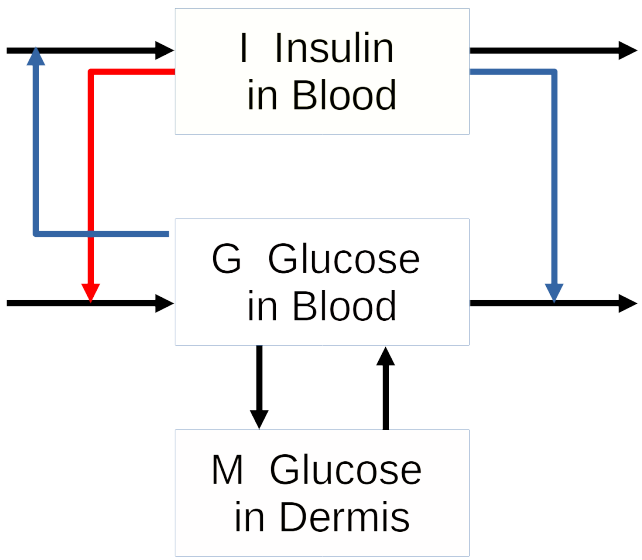


Glucose Metabolism 3b/10

$$\frac{dG}{dt} = k_G - k_{EG}G - k_{MG}G + k_{GM}M, \quad G(t_0) = G_0$$
$$\frac{dM}{dt} = k_{MG}G - k_{GM}M, \quad M(t_0) = M_0 = G_0$$
$$\frac{dI}{dt} = k_I - k_{EI}I, \quad I(t_0) = I_0$$

(5 free parameters)

Glucose Metabolism 4a/10

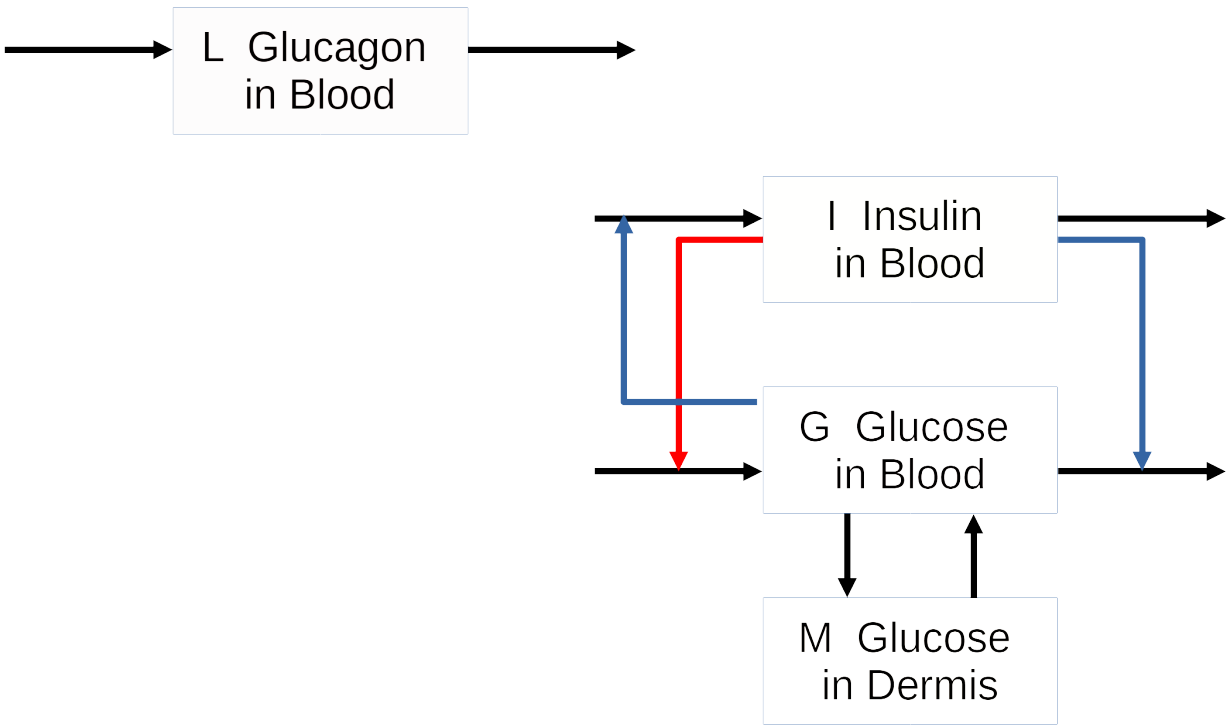


Glucose Metabolism 4b/10

$$\frac{dG}{dt} = k_G(I) - k_{EG}G - k_{MG}G + k_{GM}M - k_{EGI}IG, \quad G(t_0) = G_0$$
$$\frac{dM}{dt} = k_{MG}G - k_{GM}M, \quad M(t_0) = M_0 = G_0$$
$$\frac{dI}{dt} = k_I - k_{EI}I + k_{IG}G, \quad I(t_0) = I_0$$

($\geqslant 7$ free parameters)

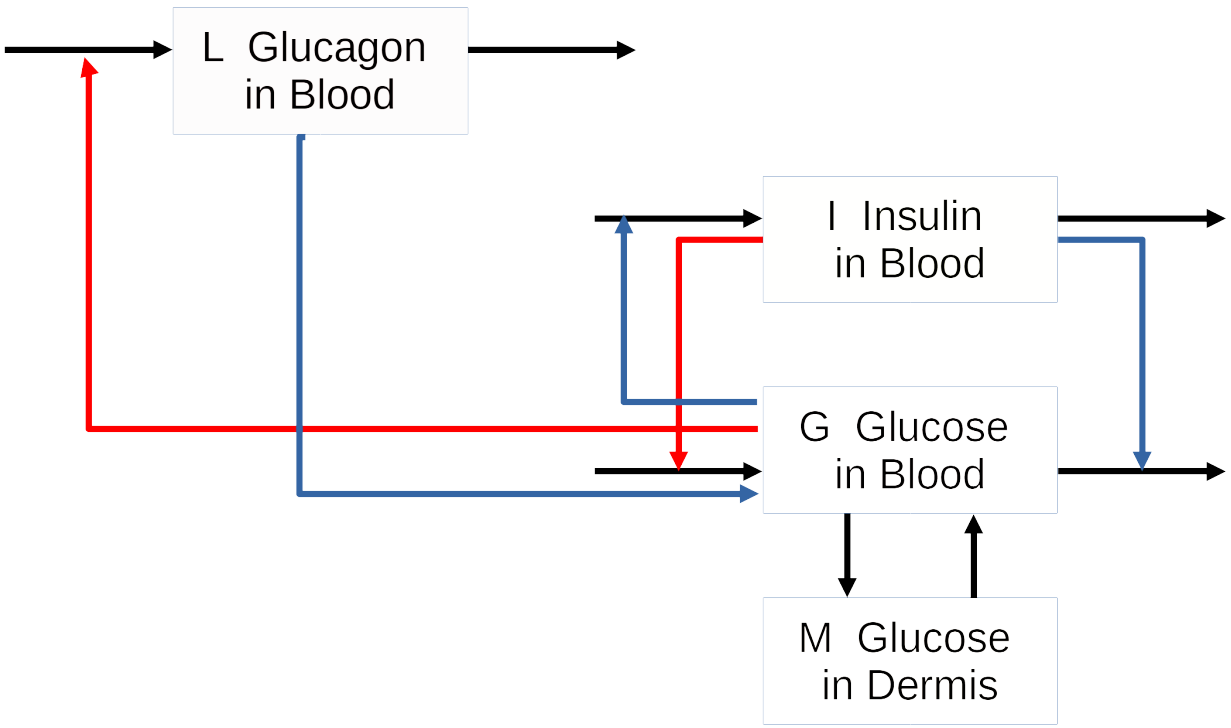
Glucose Metabolism 5a/10



$$\frac{dG}{dt} = k_G(I) - k_{EG}G - k_{MG}G + k_{GM}M - k_{EGI}IG, \quad G(t_0) = G_0$$
$$\frac{dM}{dt} = k_{MG}G - k_{GM}M, \quad M(t_0) = M_0 = G_0$$
$$\frac{dI}{dt} = k_I - k_{EI}I + k_{IG}G, \quad I(t_0) = I_0$$
$$\frac{dL}{dt} = k_L - k_{EL}L, \quad L(t_0) = L_0$$

($\geqslant$ 9 free parameters)

Glucose Metabolism 6a/10

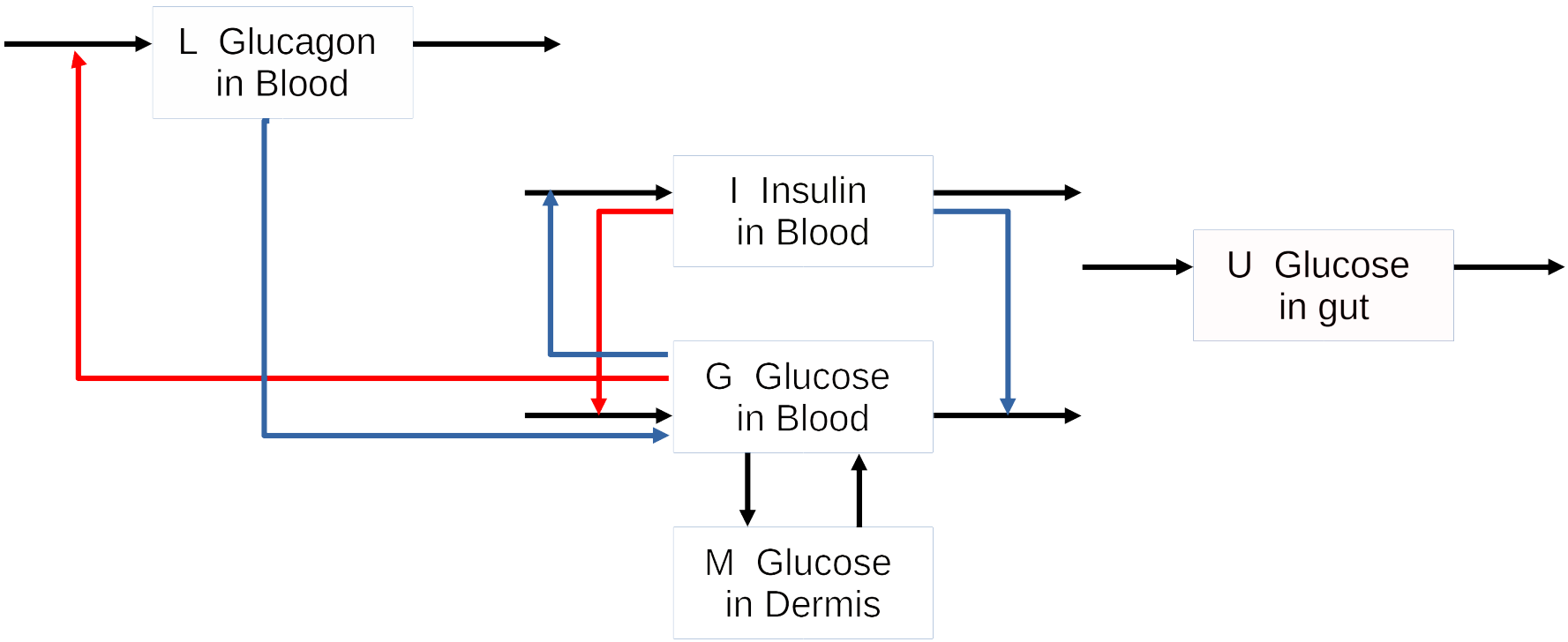


Glucose Metabolism 6b/10

$$\frac{dG}{dt} = k_G(I) - k_{EG}G - k_{MG}G + k_{GM}M - k_{EGI}IG + k_{GL}L, \quad G(t_0) = G_0$$
$$\frac{dM}{dt} = k_{MG}G - k_{GM}M, \quad M(t_0) = M_0 = G_0$$
$$\frac{dI}{dt} = k_I - k_{EI}I + k_{IG}G, \quad I(t_0) = I_0$$
$$\frac{dL}{dt} = k_L(G) - k_{EL}L, \quad L(t_0) = L_0$$

($\geqslant$ 11 free parameters)

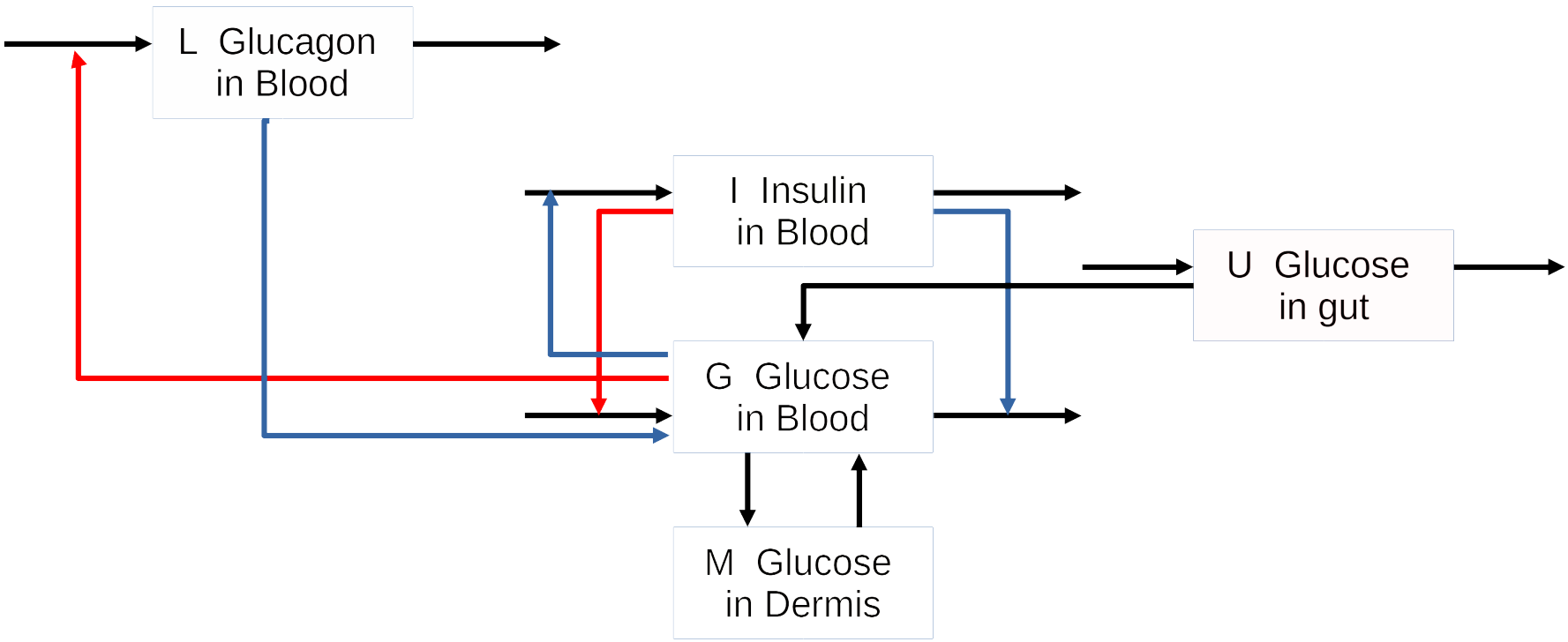
Glucose Metabolism 7a/10



$$\frac{dG}{dt} = k_G(I) - k_{EG}G - k_{MG}G + k_{GM}M - k_{EGI}IG + k_{GL}L, \quad G(t_0) = G_0$$
$$\frac{dM}{dt} = k_{MG}G - k_{GM}M, \quad M(t_0) = M_0 = G_0$$
$$\frac{dI}{dt} = k_I - k_{EI}I + k_{IG}G, \quad I(t_0) = I_0$$
$$\frac{dL}{dt} = k_L(G) - k_{EL}L, \quad L(t_0) = L_0$$
$$\frac{dU}{dt} = \sum_{m=1}^{n_U} U_m \, \delta(t - t_m) - k_{EU}U, \quad U(t_0) = U_0$$

($\geqslant$ 15 *free parameters*)

Glucose Metabolism 8a/10



$$\frac{dG}{dt} = k_G(I) - k_{EG}G - k_{MG}G + k_{GM}M - k_{EGI}IG + k_{GL}L + k_{GU}U(t-\tau), \quad G(t_0) = G_0$$

$$\frac{dM}{dt} = k_{MG}G - k_{GM}M, \quad M(t_0) = M_0 = G_0$$

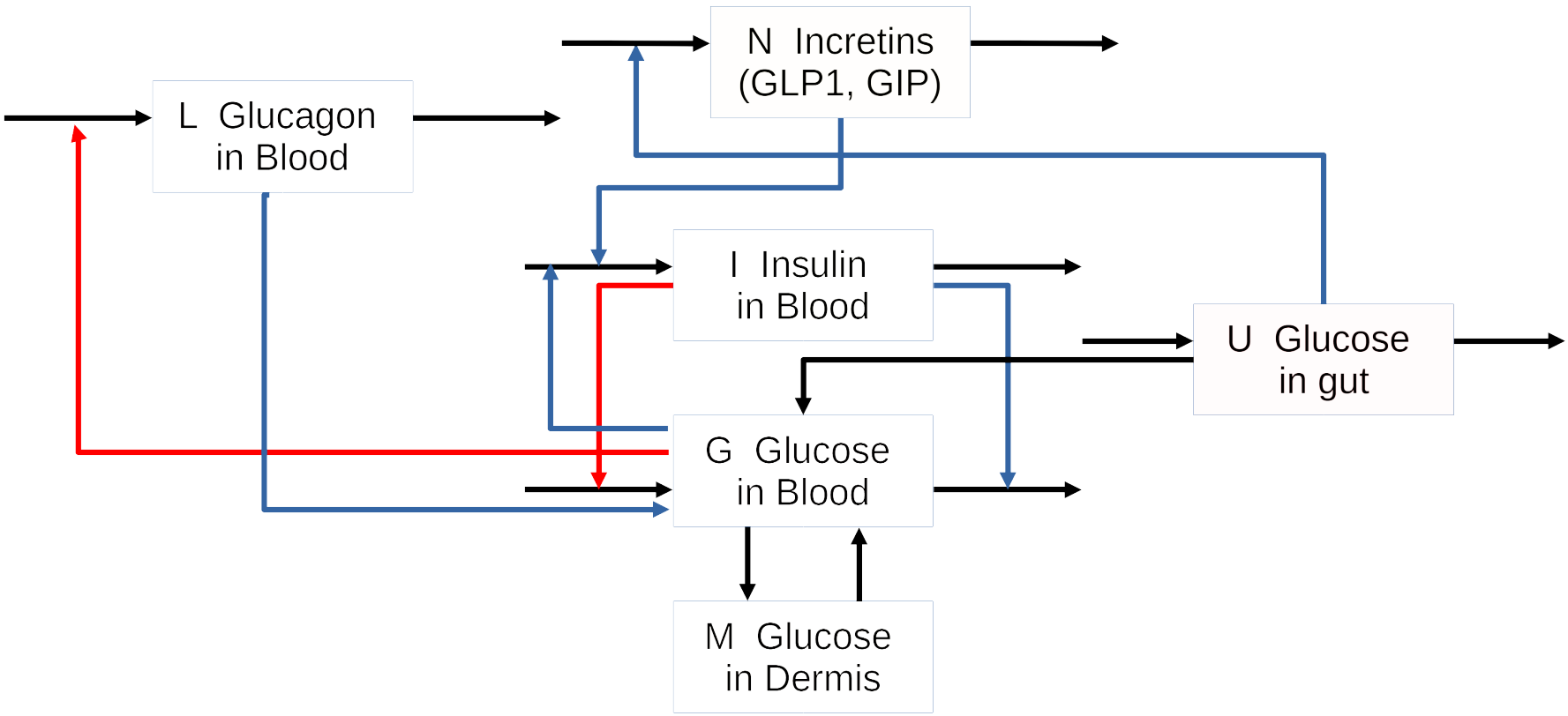
$$\frac{dI}{dt} = k_I - k_{EI}I + k_{IG}G, \quad I(t_0) = I_0$$

$$\frac{dL}{dt} = k_L(G) - k_{EL}L, \quad L(t_0) = L_0$$

$$\frac{dU}{dt} = \sum_{m=1}^{n_U} U_m\,\delta(t-t_m) - k_{EU}U, \quad U(t_0) = U_0$$

($\geqslant$ 17 *free parameters*)

Glucose Metabolism 9a/10



Glucose Metabolism 9b/10

$$\frac{dG}{dt} = k_G(I) - k_{EG}G - k_{MG}G + k_{GM}M - k_{EGI}IG + k_{GL}L + k_{GU}U(t-\tau), \quad G(t_0) = G_0$$

$$\frac{dM}{dt} = k_{MG}G - k_{GM}M, \quad M(t_0) = M_0 = G_0$$

$$\frac{dI}{dt} = k_I - k_{EI}I + k_{IG}G + k_{IGN}NG, \quad I(t_0) = I_0$$

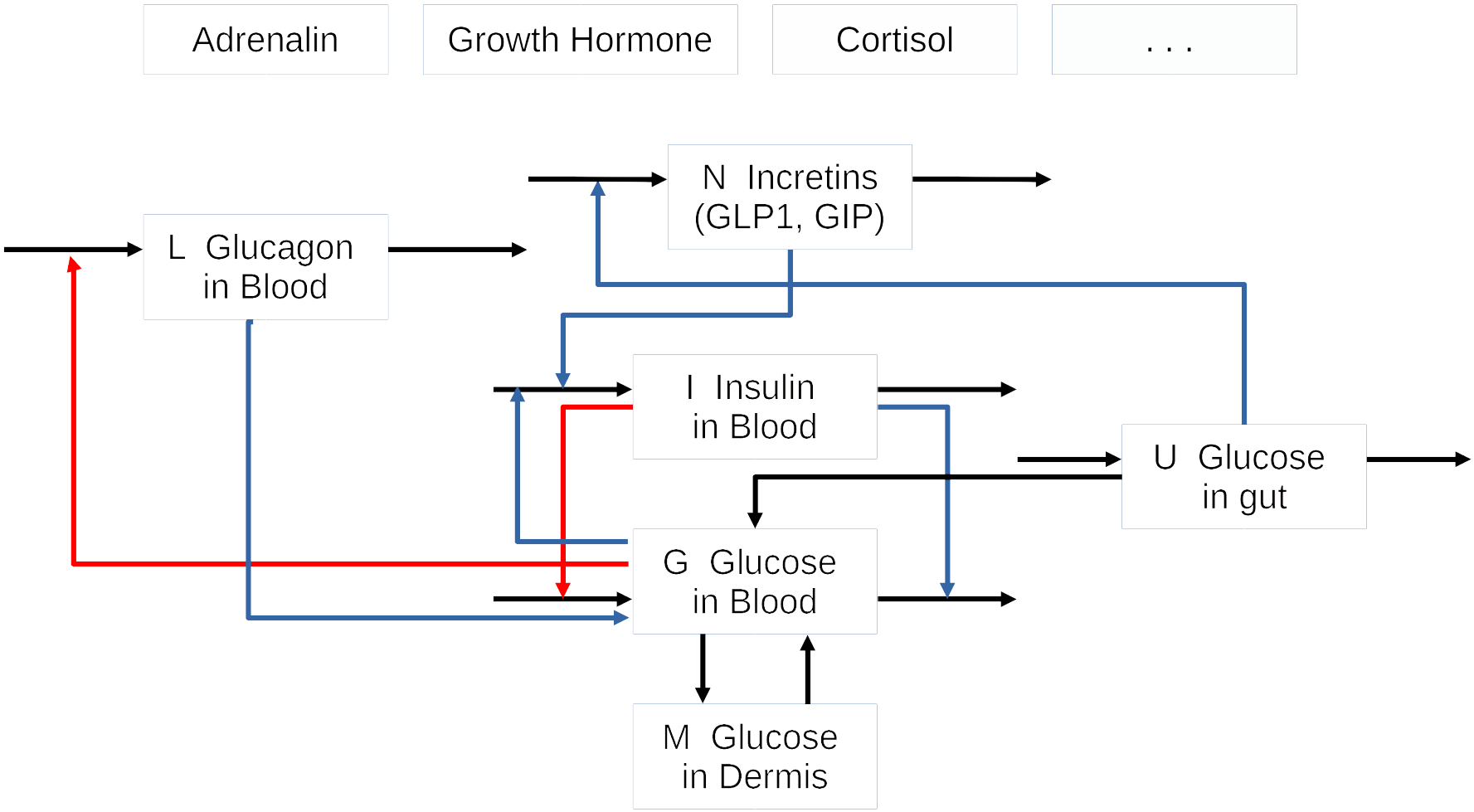
$$\frac{dL}{dt} = k_L(G) - k_{EL}L, \quad L(t_0) = L_0$$

$$\frac{dU}{dt} = \sum_{m=1}^{n_U} U_m\,\delta(t-t_m) - k_{EU}U, \quad U(t_0) = U_0$$

$$\frac{dN}{dt} = k_{NU}U - k_{EN}N, \quad N(t_0) = N_0$$

($\geqslant$ 20 free parameters)

Glucose Metabolism 10/10



... does not work!

- MANY parameters to be estimated from
- the tracing of a SINGLE variable

- need some synthetic approach...

order of control

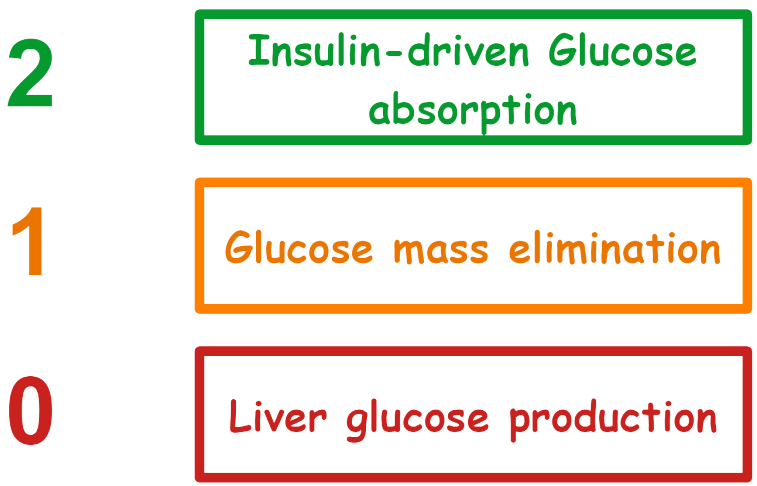
0 Liver glucose production

order of control

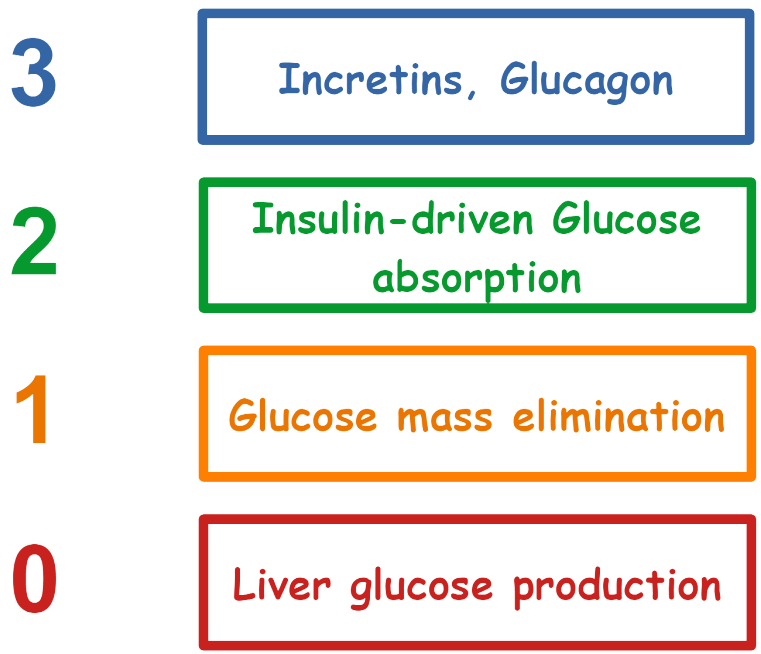
1 Glucose mass elimination

0 Liver glucose production

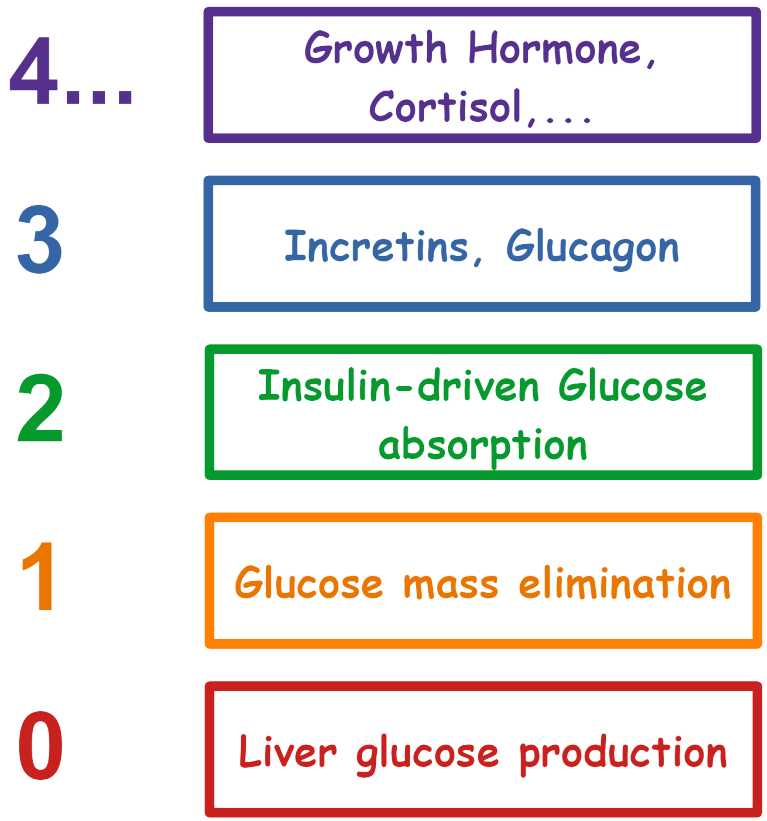
order of control



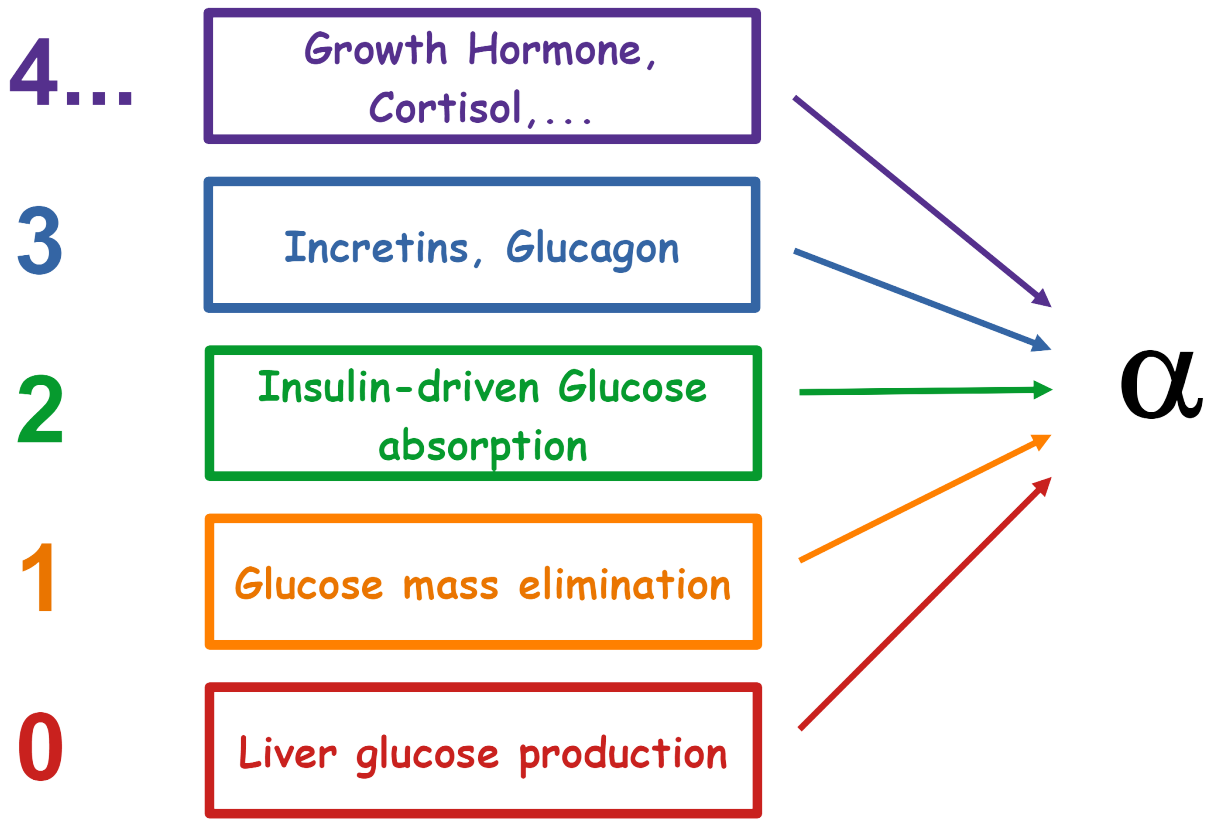
order of control



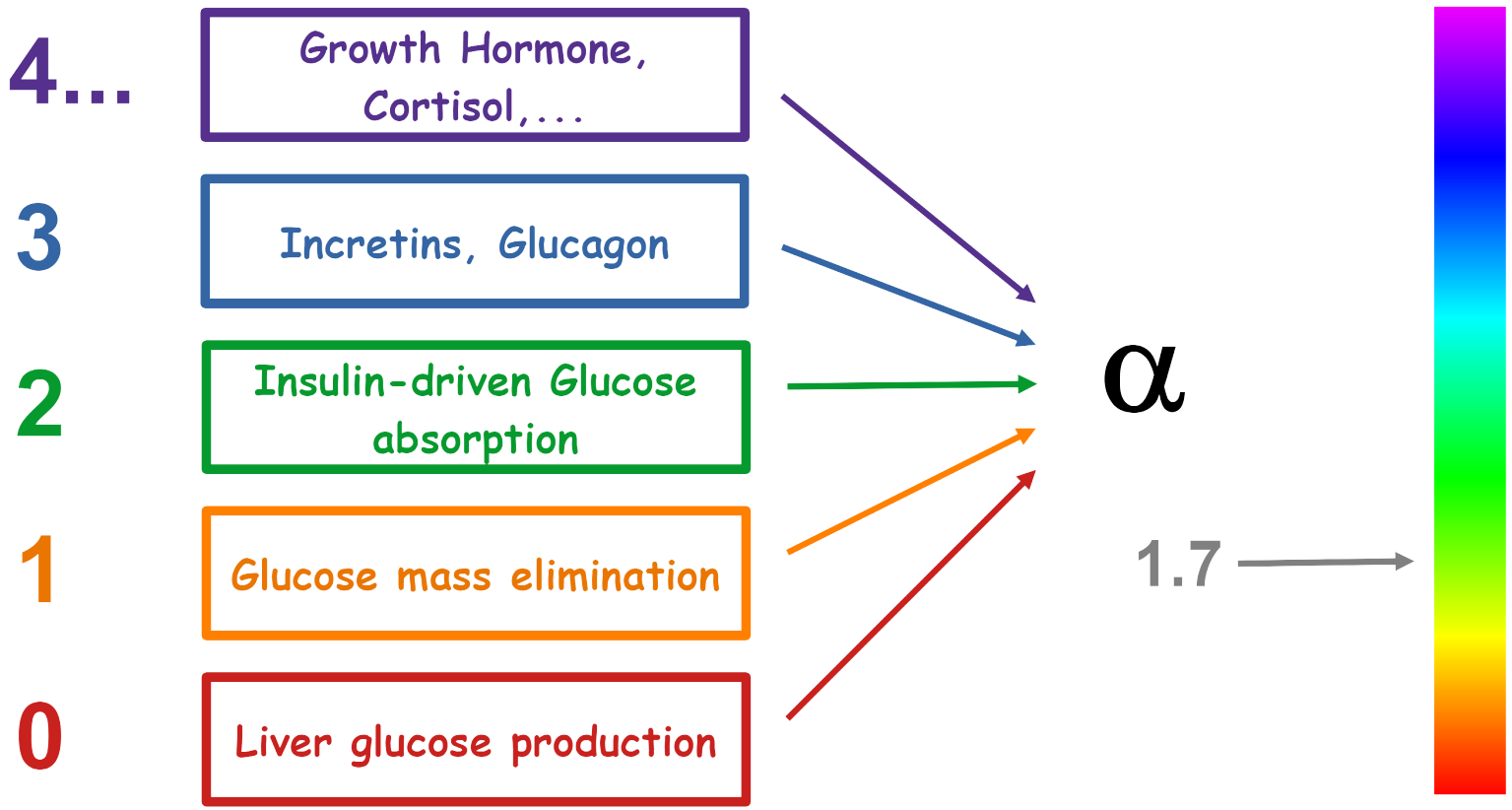
order of control



order of control



order of control



Fractional differential equations?

- Grünwald-Letnikov
- Riemann-Liouville
- Caputo

In the case of **deterministic** fractional differential equations we might use the Caputo definition:

$$ {}_{t_0}^{C}D_t^{\alpha} y(t) = \frac{1}{\Gamma(m-\alpha)} \int_{t_0}^{t} (t-u)^{m-\alpha-1} y^{(m)}(u) du, $$

with

$$ y^{(0)} = y(t), \qquad y^{(k)} = \frac{d^k y(t)}{dt^k}, \quad k = 1, 2, \ldots, m-1, $$

where $m := \lceil \alpha \rceil \in \mathbb{Z}$, $m \in \mathbb{Z} : 0 < (m-1) < \alpha < m$.

Rome Italy CGM experimental set-up

- subject is at rest and meals have not been eaten for a relatively long time (e.g. during the night)
- near-constant, zero-order glucose production occurs in the liver
- Glucose elimination from the bloodstream may be proportional to glycemia, with an apparently first-order, linear elimination rate
- Insulin exerts a second-order effect
- other hormonal influences (cortisol, growth-hormone, counter-regulatory hormones like adrenalin, noradrenalin and glucagon) may exert third-order effects
- Furthermore: random (system) noise

... we tried, does not work very well :(

- Sakulrang, Moore, Sungnul, ADG - A fractional differential equation model for continuous glucose monitoring data, Advances in Difference Equations 2017
- ADG, Sakulrang, Borri, Pitocco, Sungnul, Moore - Modeling continuous glucose monitoring with fractional differential equations subject to shocks, Journal of Theoretical Biology 2021

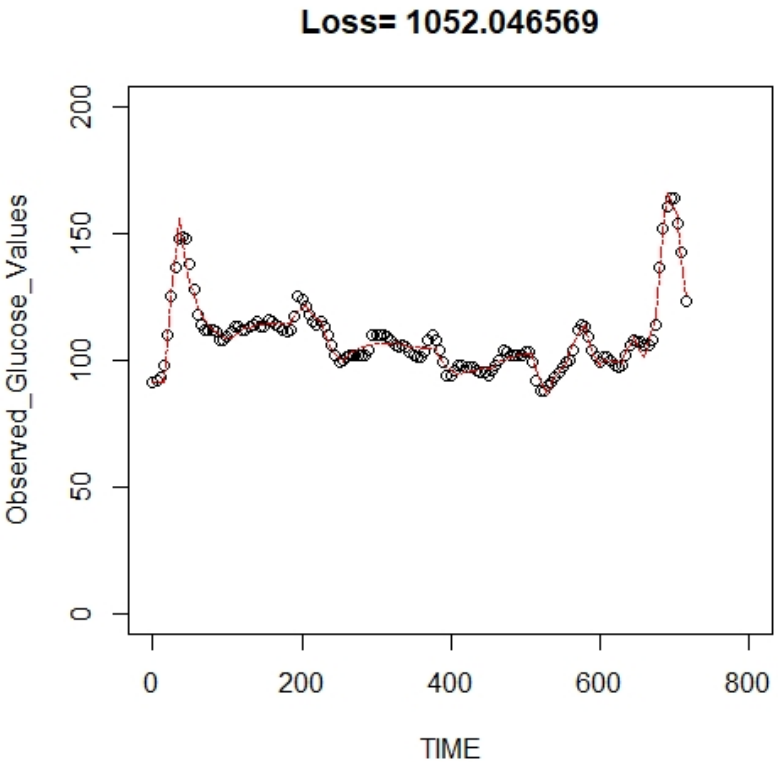
Unless "shocks" are added, model does not capture oscillations, same as integer-order ODE.

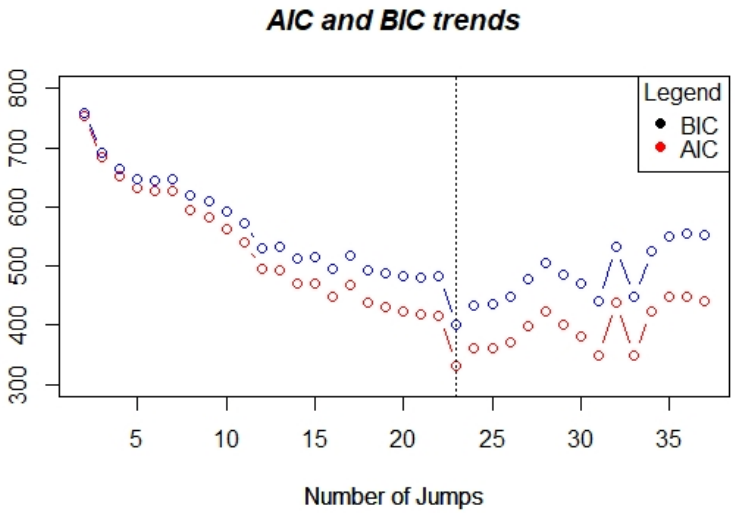
If it is shocks you need, you might as well be ODE between-shocks!!! $\Rightarrow$ RODE's

$$\frac{dG}{dt} = blablabla(G, X), G(t_0) = G_0$$
$$\frac{dX}{dt} = blablabla(X, Y), X(t_0) = X_0$$
$$\frac{dY}{dt} = blablabla(Y, Z), Y(t_0) = Y_0$$
$$\frac{dZ}{dt} = -k_{EZ}Z + \sum_{m=1}^{nShocks} z_m \delta(t - t_m), z(t_0) = 0$$

where $\Delta t_m := t_{m+1} - t_m \sim exp(\lambda)$ and $z_m \sim N(0, \sigma_z^2)$

One CGM subject by RODE





RODE's

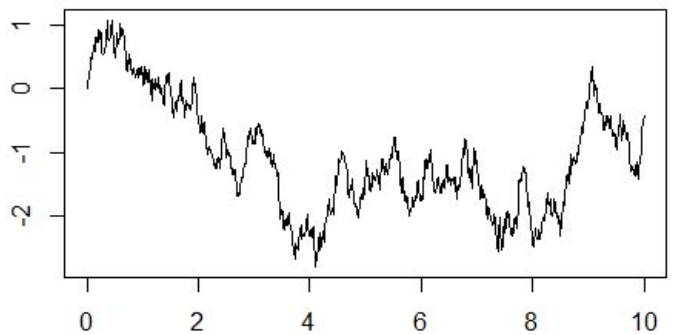
- *nShocks* is determined by AIC or BIC
- kind of works, presumes a shock-generating mechanism (plausible)
- the (many!) other parameters are estimated by standard methods (OLS, WLS,...)
- the (meta) parameters λ and σ_z^2 are estimated directly from the sample of estimated Δt_m's and z_m's.
- ... questionable approach?

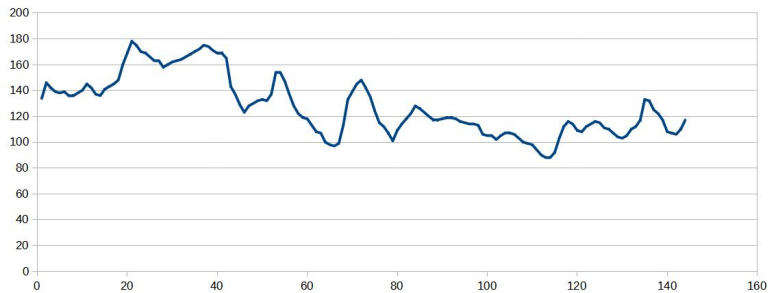
In the case of **integer order** Stochastic Differential Equations we might use the Itô definition:

$$dy = f(t, y(t))dt + \sigma(t, y(t))dW_t, \quad 0 \leq t \leq T,$$

where $\sigma(t, y(t))$ is the time and state dependent variance of a standard Gaussian $\mathcal{N}(0, \sigma^2(t, y(t))$ and $W_t = W(t)$ is a standard Wiener process.

... we tried, does not work at all :(:(





Wiener process (by definition) does not capture high autocorrelation between increments.

Fractional Stochastic Differential Equations: first attempt

In the present situation the time-course of transcutaneously, continuously measured glycemia (CGM) depends both on superposed, different orders of control, and on random system noise.

We thus formalize the problem as a **process controlled by a deterministic drift** (of integer order in this case), **driven by a fractional Brownian diffusion**:

$$\begin{cases} dG(t) &= (k_G - k_{XG}G(t))dt + \sigma\sqrt{G(t)}dB^H(t) \\ G(0) &= G_0 \end{cases}$$

$B^H(t)$ is the fractional-order Brownian Motion of Hurst index H.

The fractional process $B^H(t)$ of Hurst index $H \in (0,1)$ is defined in terms of the standard Wiener process $B(t)$ via the Weyl integral

$$
\begin{aligned}
B^H(t) &= B^H(0) \\
&+ \frac{1}{\Gamma(H+1/2)} \left\{ \int_{-\infty}^{0} \left[(t-s)^{H-1/2} - (-s)^{H-1/2} \right] dB(s) \right. \\
&+ \left. \int_{0}^{t} (t-s)^{H-1/2} dB(s) \right\},
\end{aligned}
$$

Numerical approximation

A number of efficient numerical tools are available for the generation of fractional noise, based e.g. on the frequency-domain interpretation of fBm as white noise subject to a fractional order integration, or on the use of wavelets. Here the sequence of increments $\{\Delta B_k^H\}$ is approximated using the "circulant embedding method" (Kroese 2015, implemented in MATLAB™):

$$B_{k+1}^H := B_k^H + \Delta B_k^H, \qquad k = 0, 1, ..., \quad B_0^H = 0$$

We also derived a stochastically exact method to generate discrete-time samples of a fractional Brownian motion (follows the definition in the Weyl integral and conforms to autocorrelation, but is slower).

Parameter estimation

We employed a moment-based approach, by Weighted Least Squares approximation of the characterizing moments (mean, variance, autocorrelations of lag $1 - 20$) of the fractional Brownian motion, depending on the free model parameters.

Weights were set to the inverse of the fitted autocorrelations and of the fitted first two moments respectively.

The free parameters to be estimated are k_{XG}, σ and the Hurst index H: glycemia at time 0 was fixed at the observed concentration, whereas the parameter k_G was determined, assuming (average) steady state conditions at t_0:

$$k_G = k_{XG}\, G_0$$

Results

Provisional Results

Clearly the results of the optimization procedure depend on the realization of the driving process. Therefore the optimization was repeated for each of 1000 realizations of the driving Brownian motion.

The first two observed moments were 78.1 $[mg/dl]$ and 82.6 $[(mg/dl)^2]$ (mean and variance respectively); the respective mean $\pm$ SD values computed on the predictions were 82.8 and 82.5 (loss $\leqslant$ 95-th percentile), respectively 83.9 and 200.9 (all realizations).

Autocorrelation structure

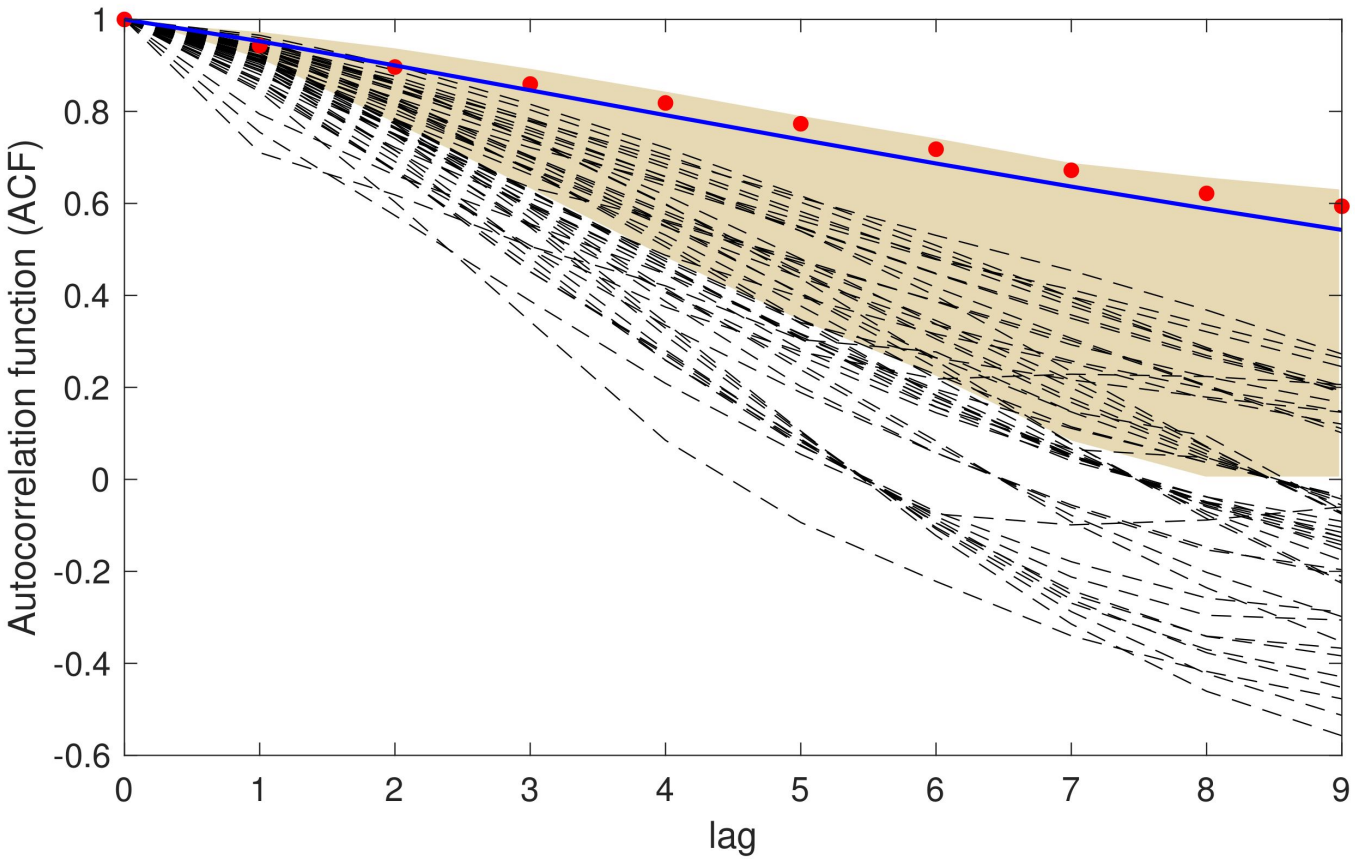


Figure: Observed (red circles) and fitted autocorrelation functions (dashed black lines), in tan the 95% loss envelope

Stochastic solution process

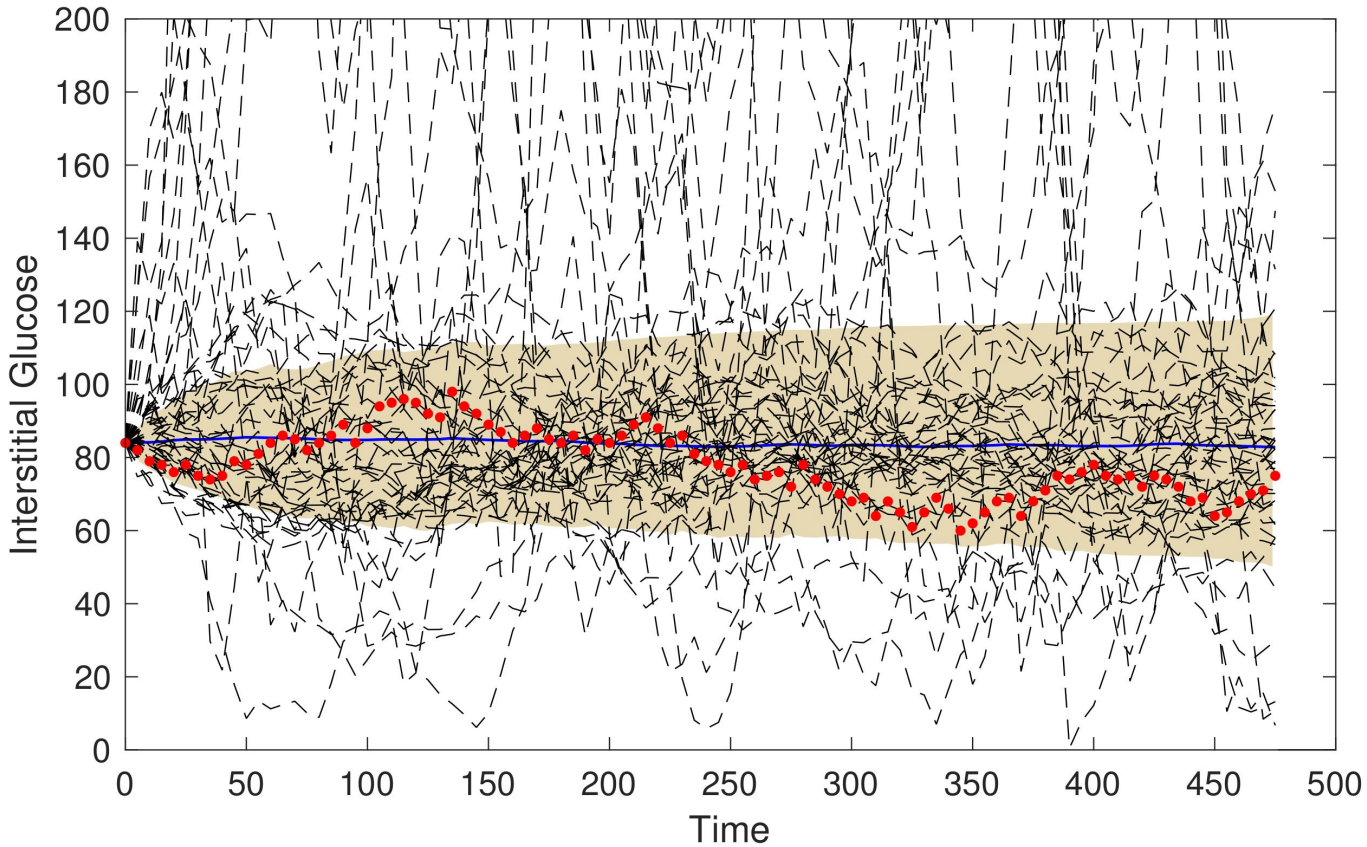
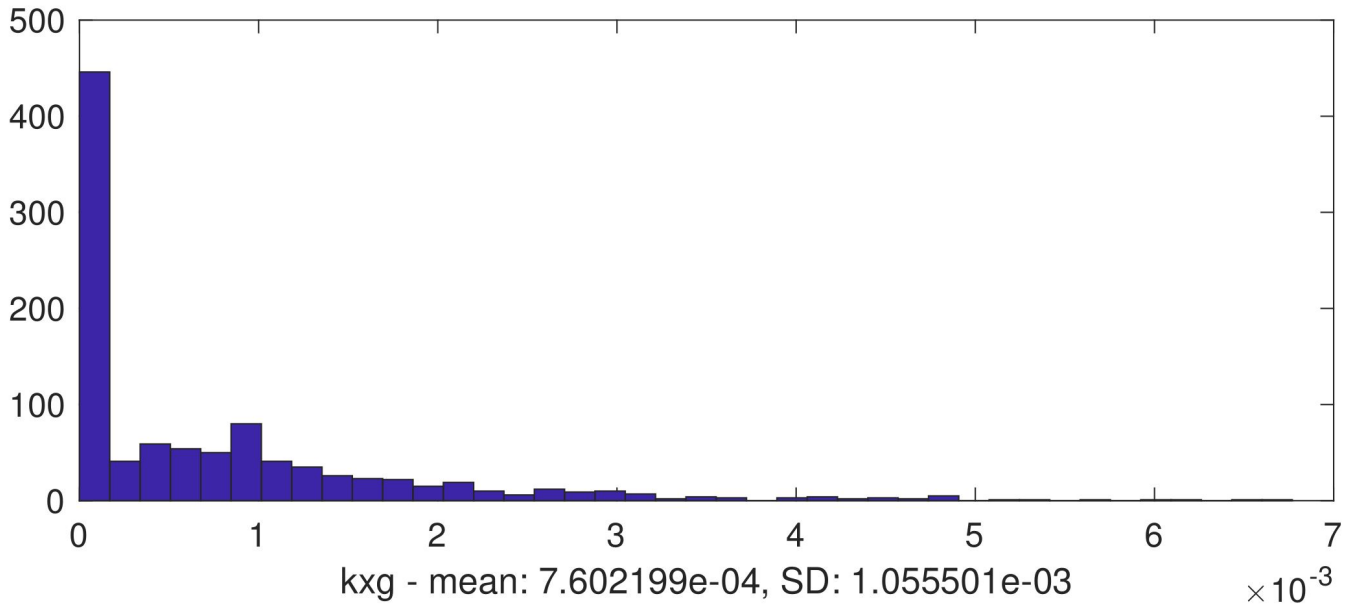
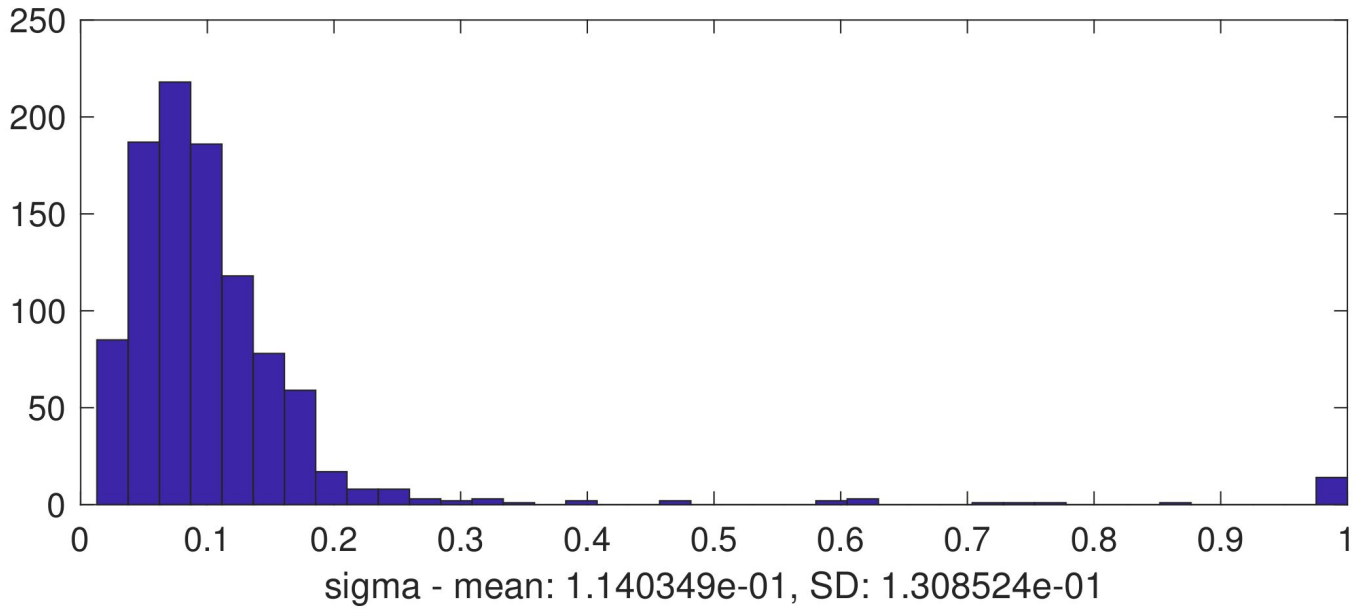


Figure: Observed (red circles) and solution processes (dashed black lines), in tan the 95% loss envelope

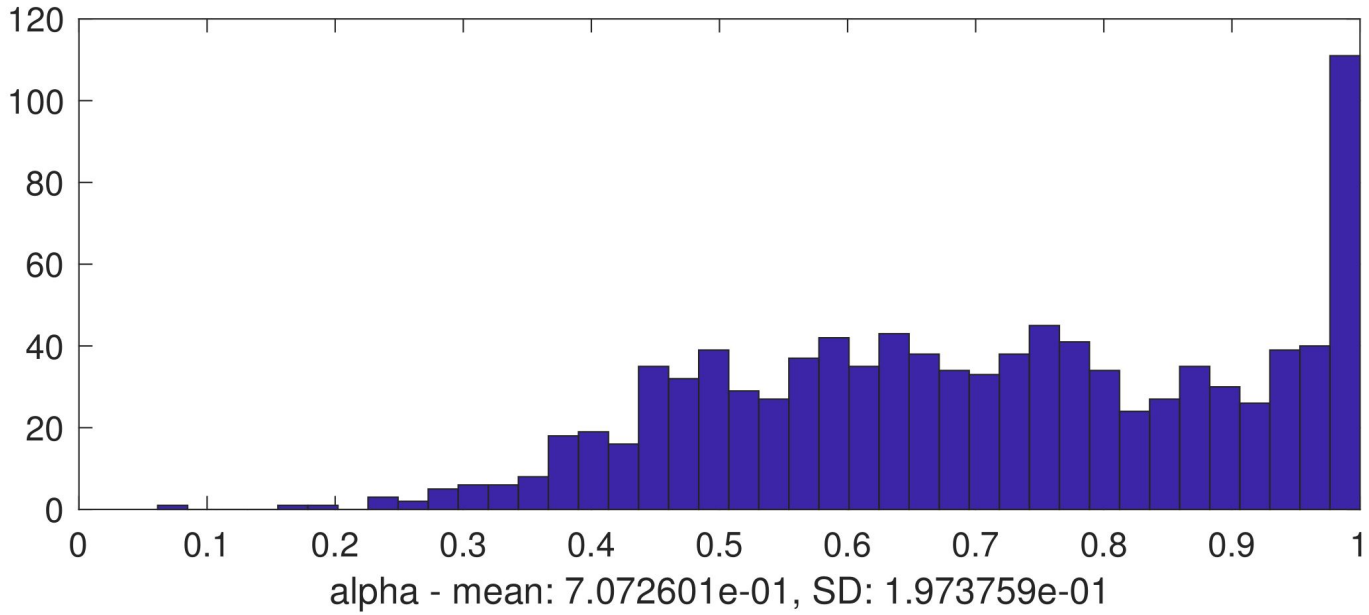
Parameter estimates: k_{XG}



Parameter estimates: σ



Parameter estimates: α, the Hurst index



Conclusions

there are many ways to skin a cat

Where we are ...

- There is an inherent limitation in the information carried by the observation of a single variable relatively to a complex and noisy control system.
- Each single patient is characterized by a specific control signature, due to lifestyle habits, body weight, muscle mass, and psychological setup. The goal of CGM analysis is to identify this signature: while glycemia prediction is practically unfeasible, modeling allows the diagnosis of the compensation state of each patient.
- a Fractional Stochastic Differential Equations model is consistent with observed Continuous Glucose Monitoring (*proof of concept*).

... and where we want to go

- Mathematics: fractional **drift** together with fractional **diffusion**
- Physics/Biology: **meaning** of coefficients.
- Statistics/Optimization: numerically intensive **correct** parameter estimation

- Specific goal: incorporation of diagnostic modeling within Continuous Glucose Monitors, allowing patients to directly follow their disease evolution and assess the effect of mitigation measures.
- General goal: coherent mathematical representation of the different aspects of energy metabolism, allowing *in-silico* tailored predictions of the effects of different therapy schemes.

Thank you!

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- Dept. of Biomatics, Óbuda University, Budapest Hungary