Modeling Intestinal Glucose Absorption from D-Xylose Data

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Section 1

Introduction

Motivations

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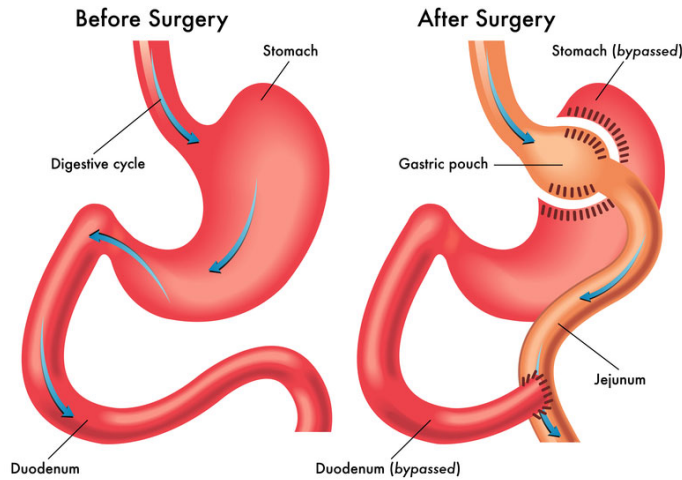
More recent observation: abnormal Intestinal Glucose Absorption (IGA)

Motivations

- bariatric surgery is primarily used to reduce stomac and intestinal size to manage obesity

RYGB surgery



[Baud et al., Cell Metabolism, 2016]

Motivations

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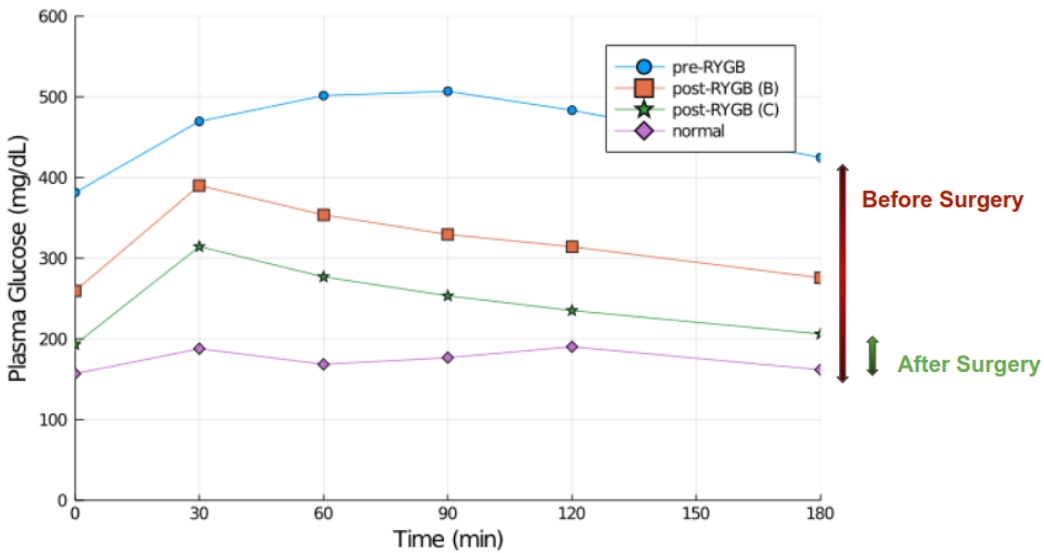
- but is also has a strong (side) effect on metabolism

Postprandial glucose response



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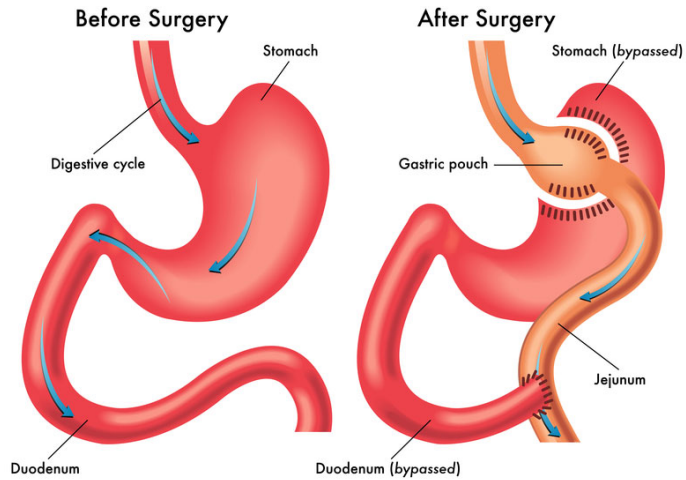

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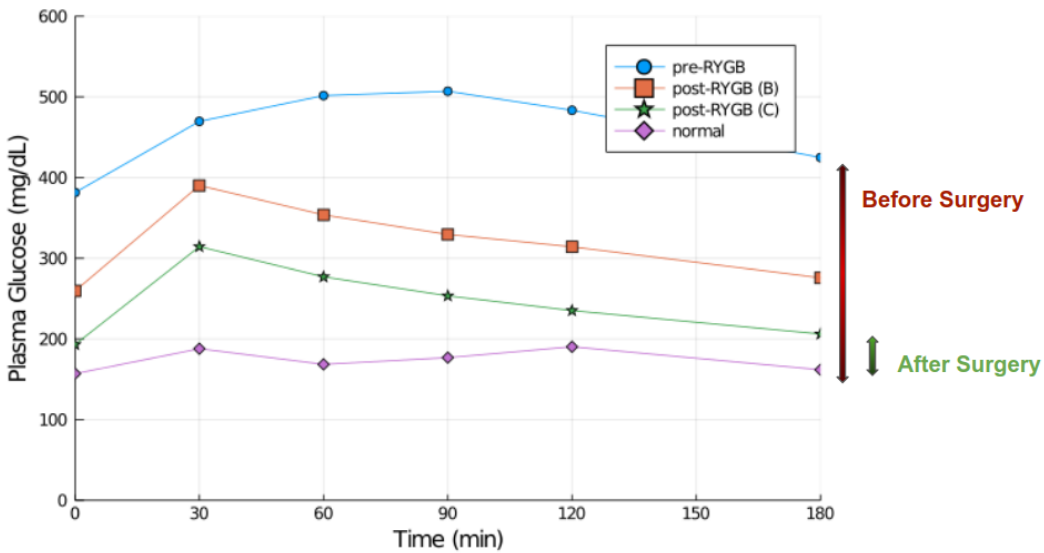

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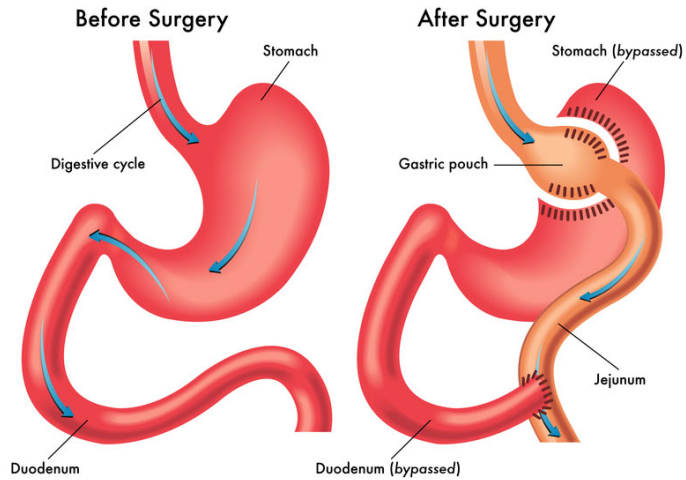

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⇒ RYGB reduces IGA which improves glucose homeostasis restoration

Objectives

- (*long term*) model-based understanding of the role of IGA in postprandial glucose response
- (*now*) predict the rate of IGA from postprandial data

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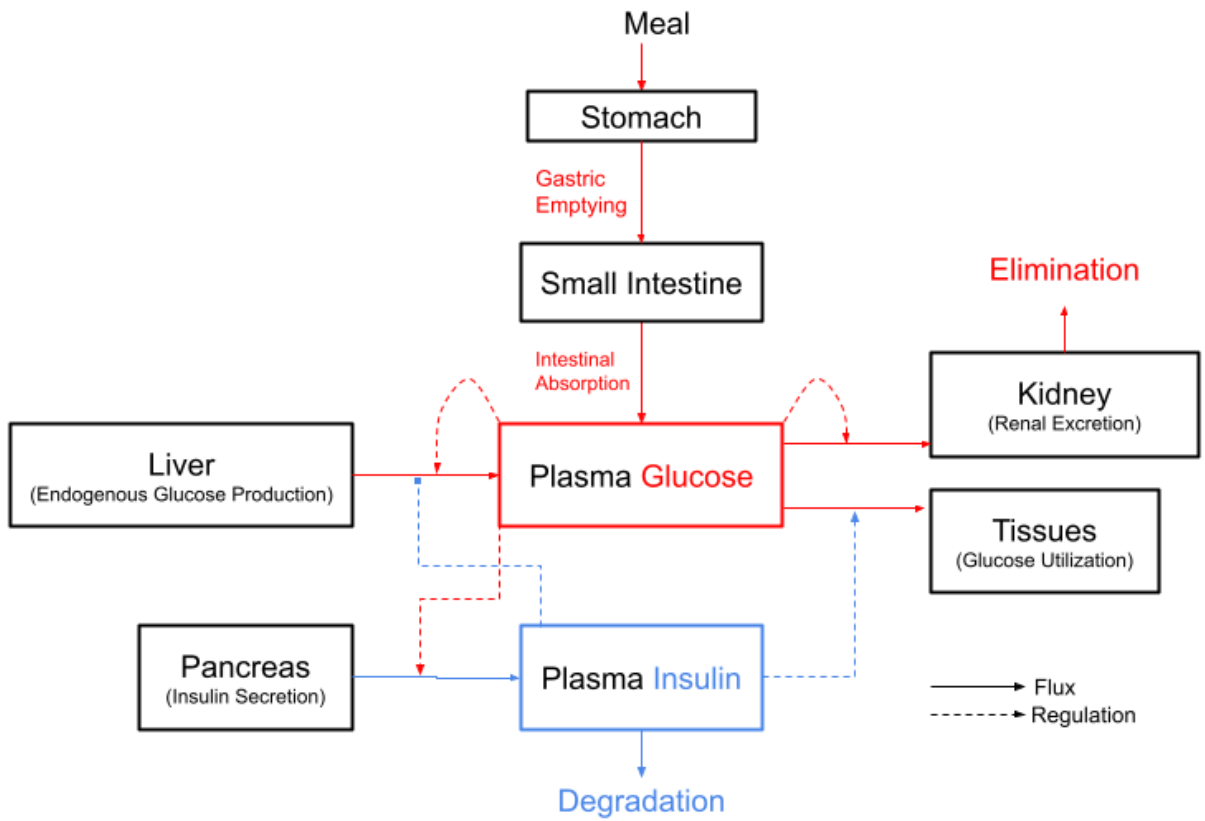

Model-based understanding of IGA

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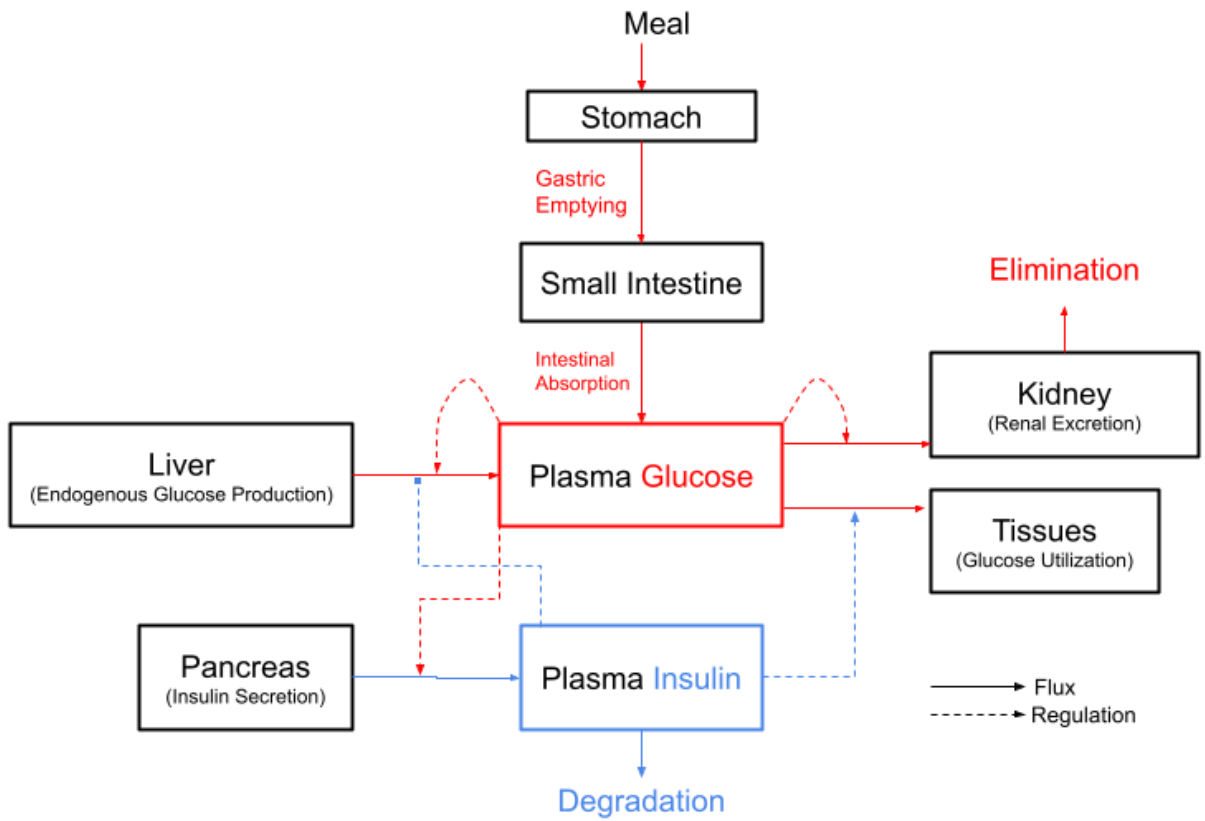
- State of the art model of postprandial glucose dynamics [Dalla Man et al., 2007]
- complex ODE model (12 variables, 36 parameters)



Model-based understanding of IGA

Dalla Man's model can hardly predict bariatric surgery [Dursoniah et al. BIOTECHNO 2021] because of

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Also, its calibration needs monitoring of IGA which either requires:

- access to portal vein (almost impossible), or
- use of tracer protocols (too complex to set up in a clinical context).

Predicting IGA from D-Xylose data

Instead, we propose:

- to use a molecular marker (D-Xylose) simple to use in the clinical setting
- to design a simple model that focusses on intestinal absorption
- solve identifiability issues based on minipig experimental data

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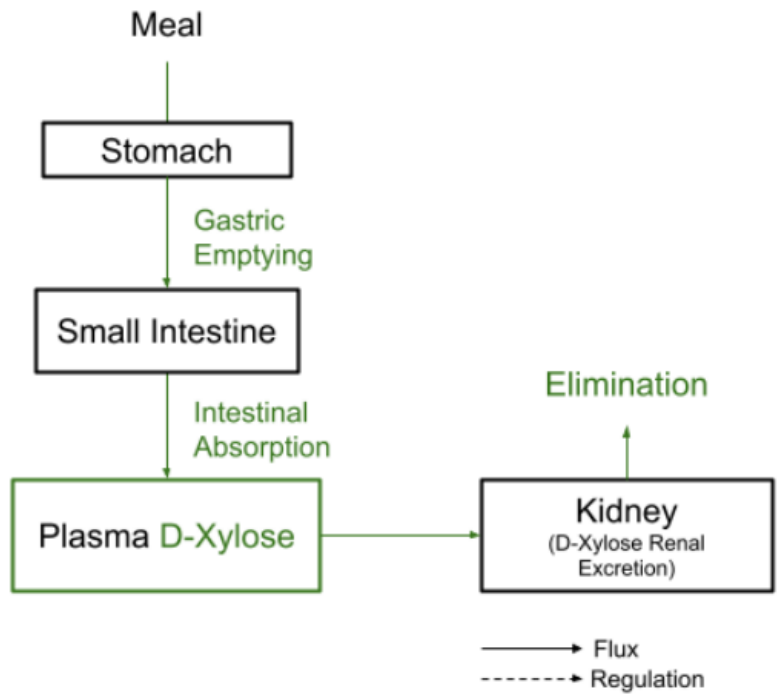

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- unlike glucose, it is not metabolized
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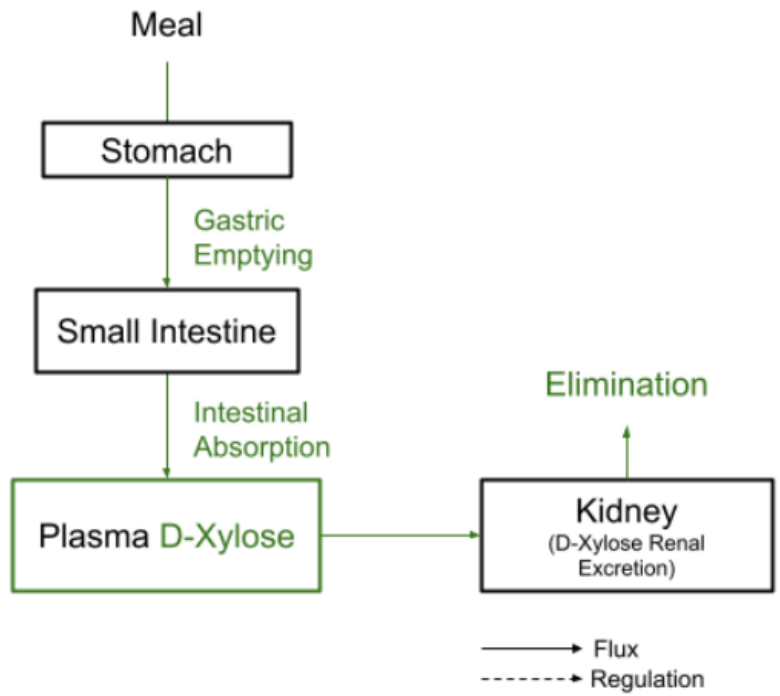

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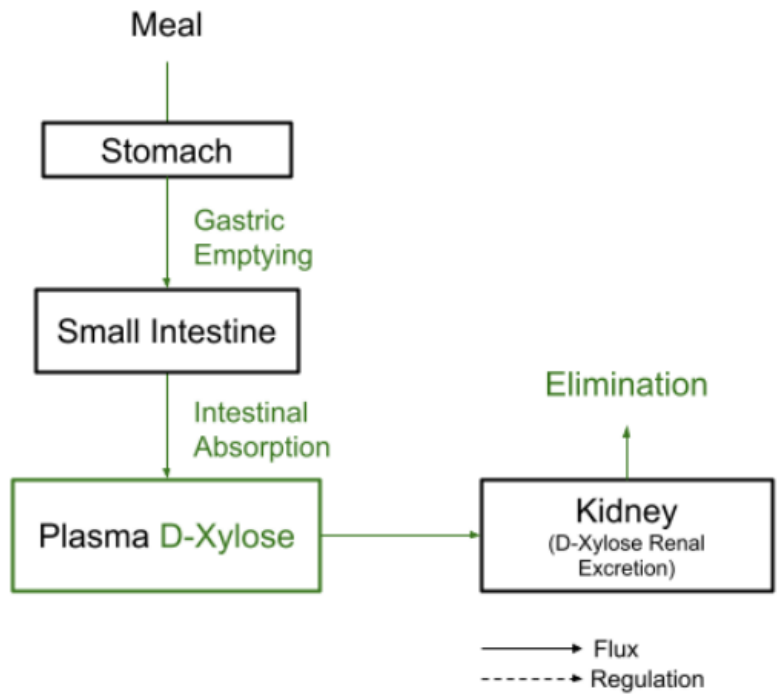

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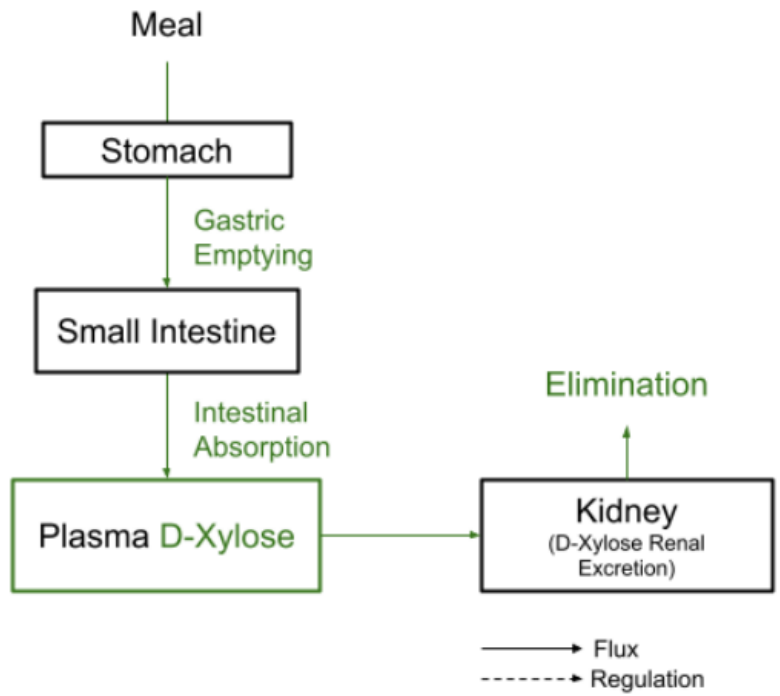

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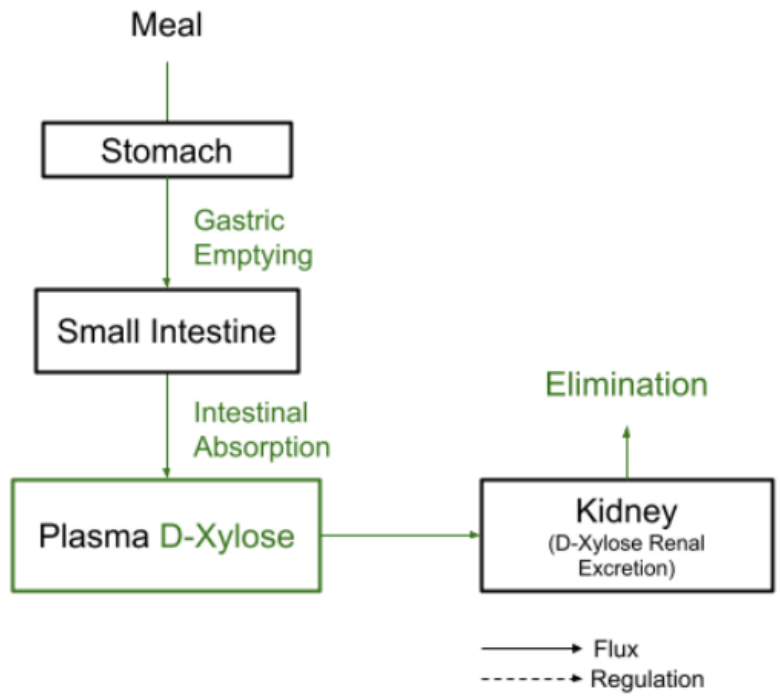


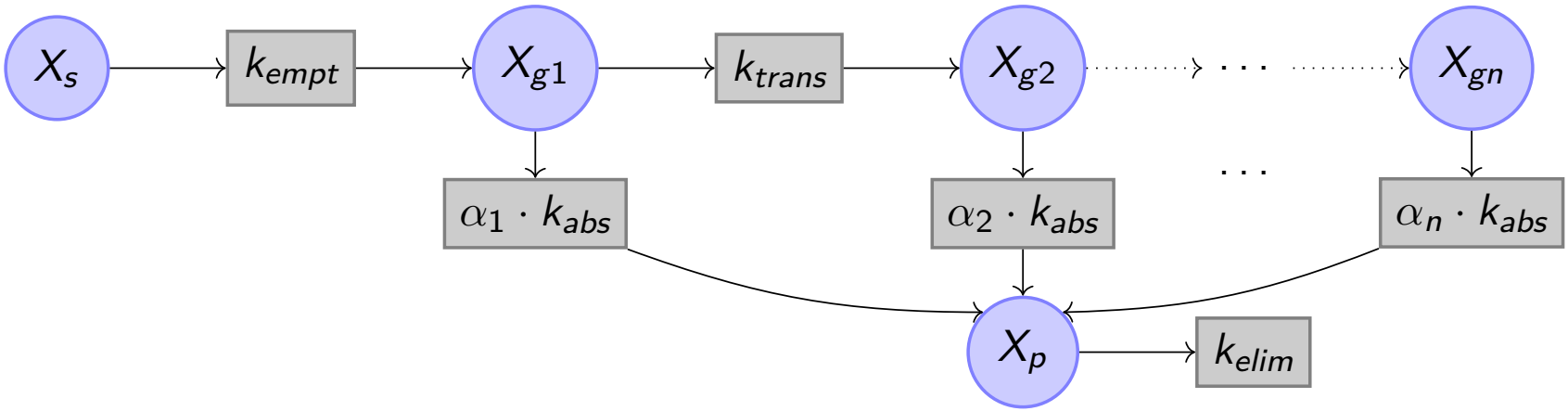
What can we learn about intestinal absorption from the observation of D-Xylose concentration in blood ?

Section 2

D-Xylose Mechanistic Model and Calibration

D-Xylose model

Chemical Reaction Network



3 main parts:

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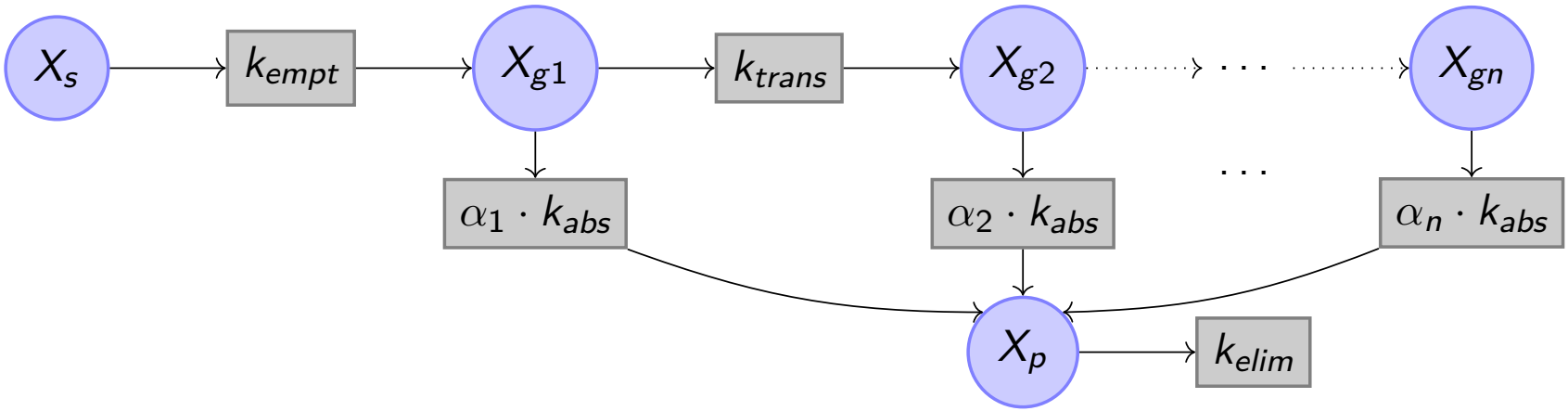

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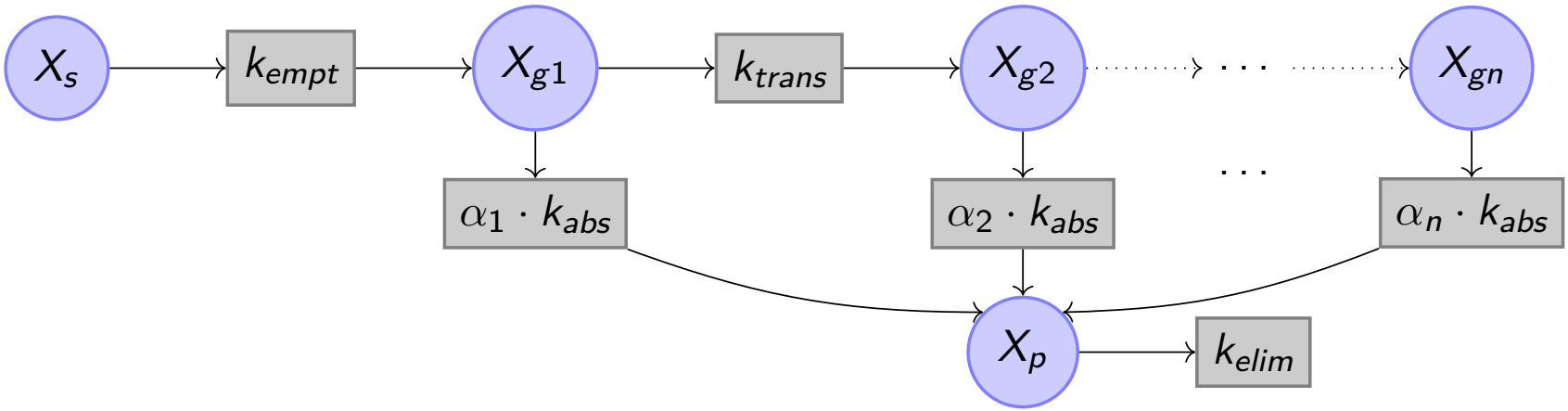

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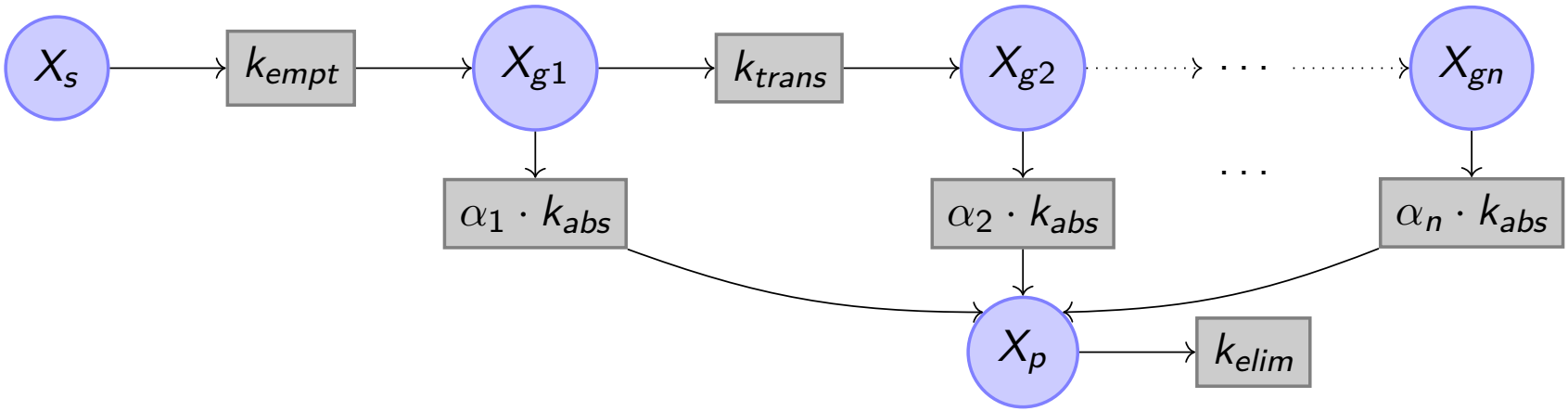

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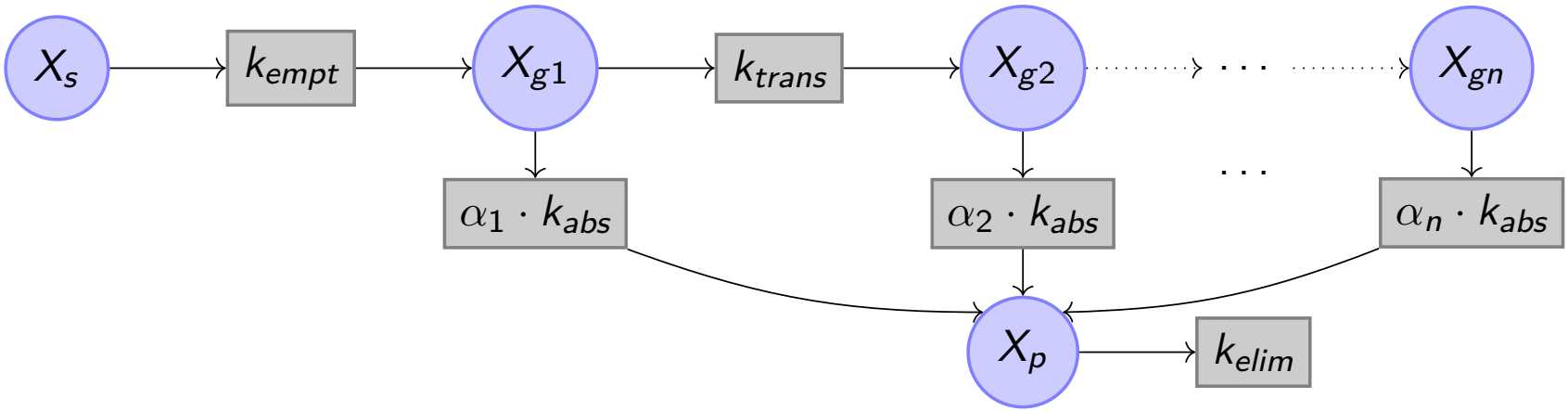

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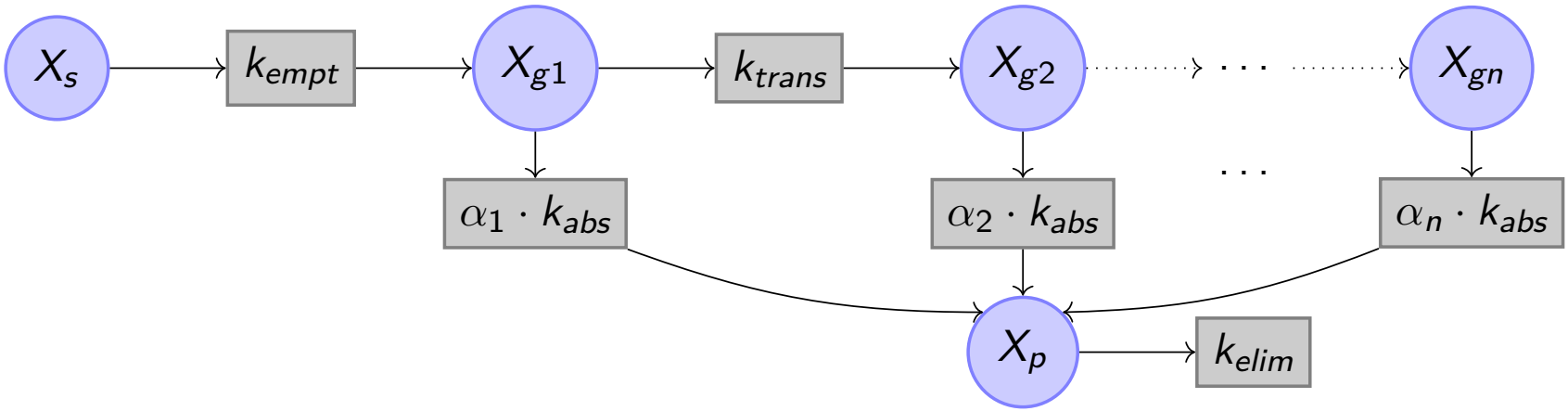

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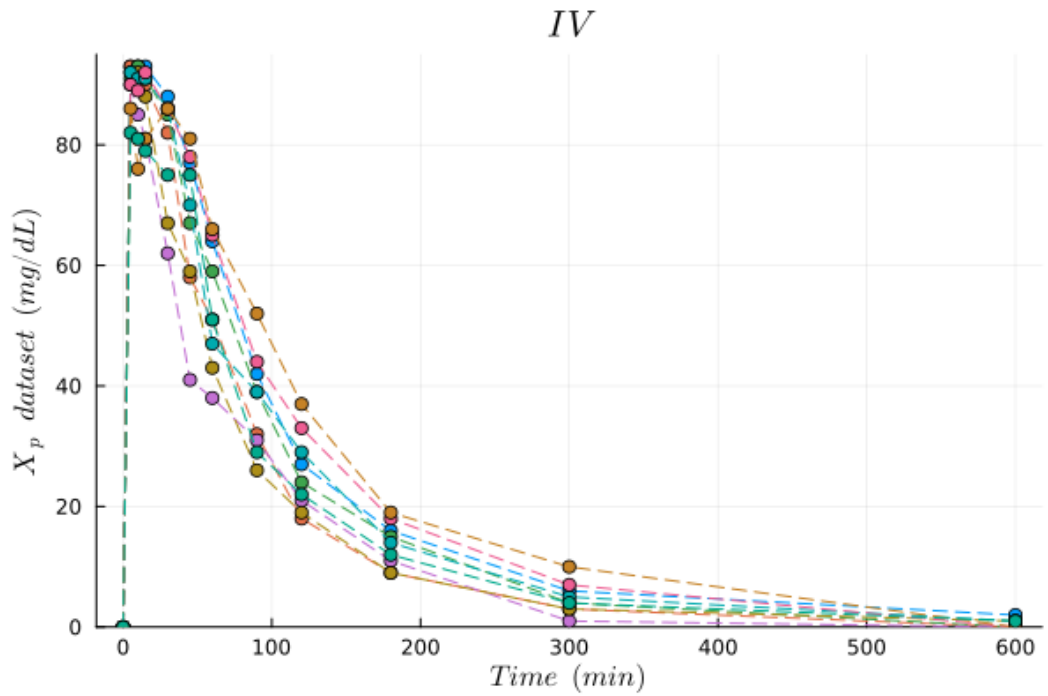
- 3 parameters of interest: k_{empt}, k_{abs} and k_{elim}

Minipig Experimental Datasets

Intravenous administration of 30g D-Xylose



Used to estimate the rate k_{elim} of D-Xylose elimination

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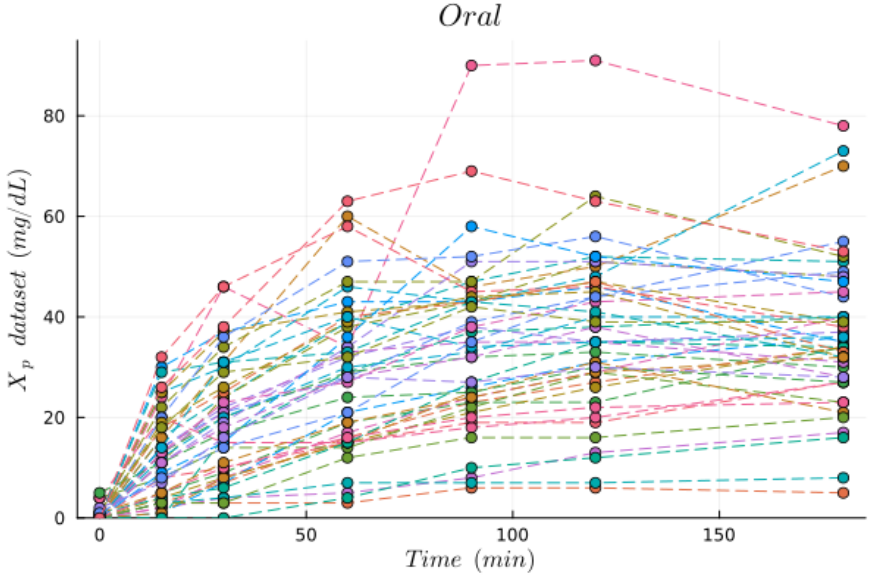

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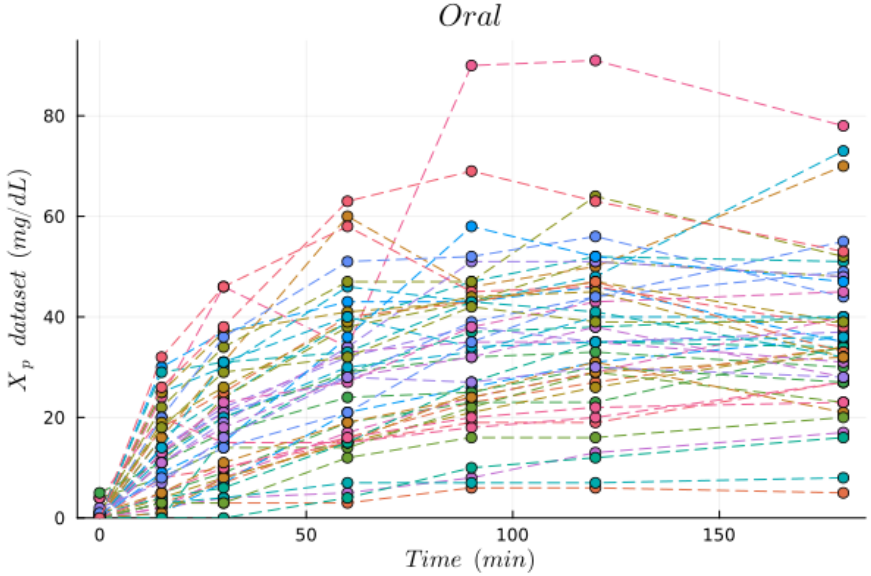
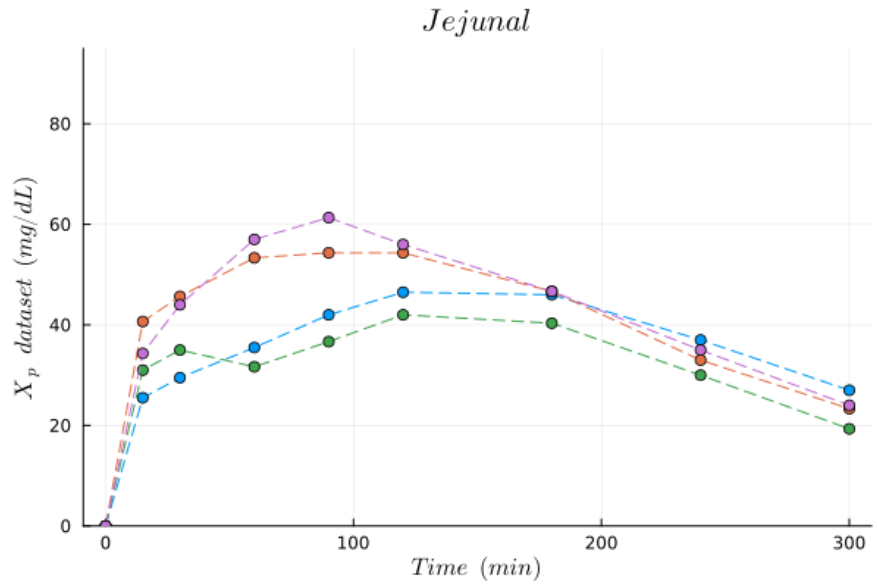


Jejunal administration



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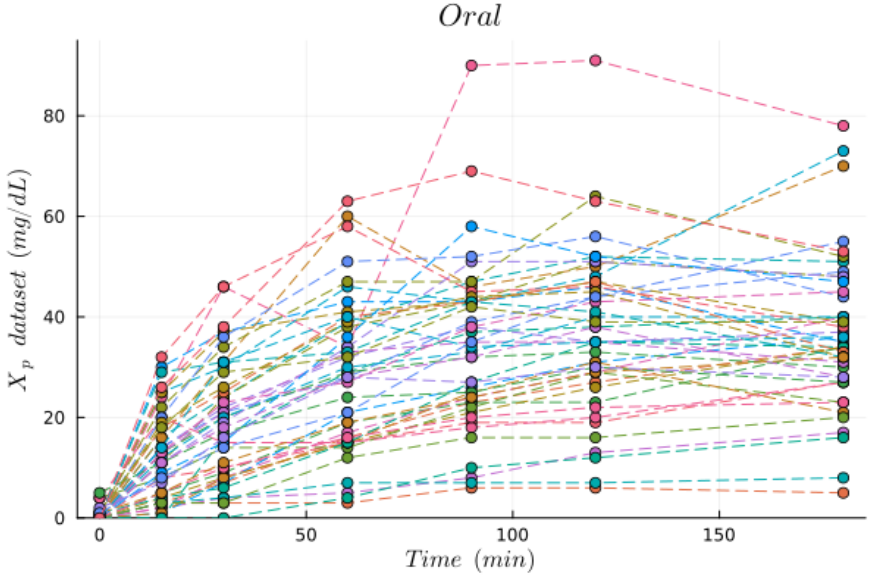

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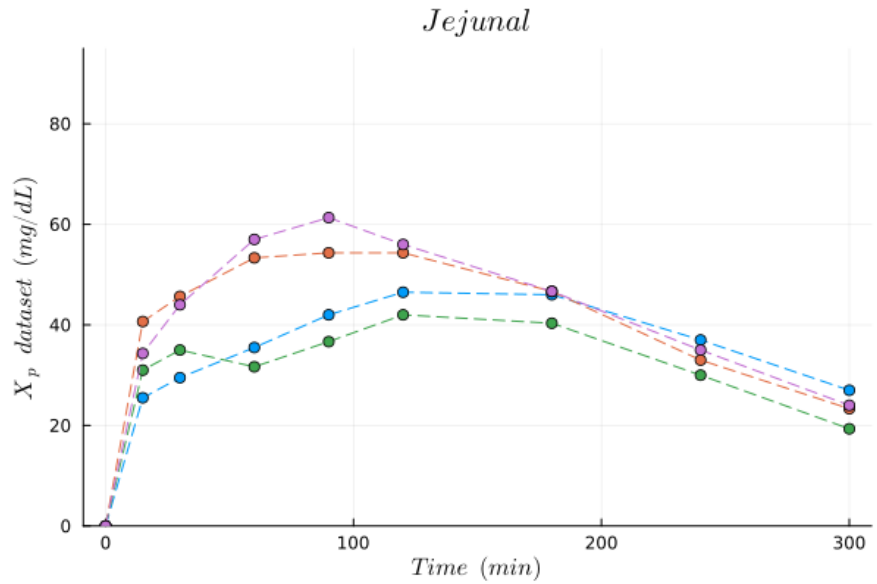
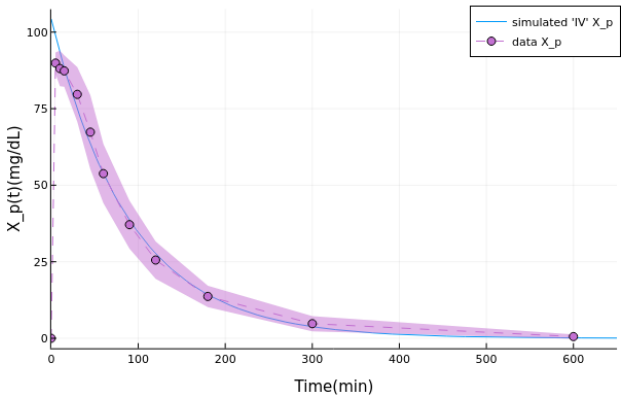


Used to estimate the rates k_{empt} of gastric emptying and k_{abs} of intestinal absorption.

Parameter Estimation



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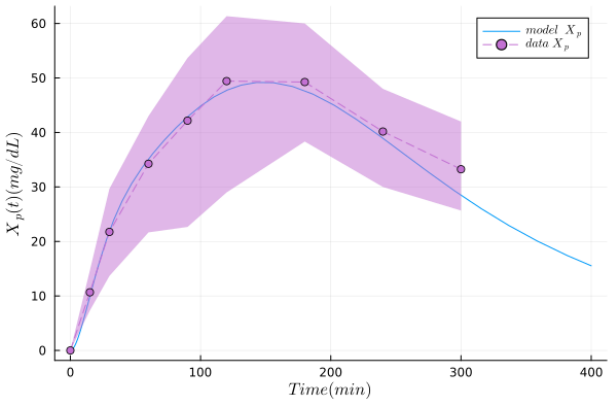

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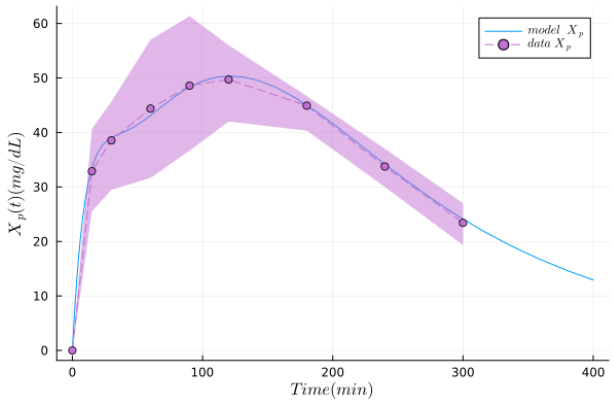

Jejunal

Very good fitting of (mean) intravenous, oral and jejunal datasets

Parameter Estimation

Profil likelihood method was applied to study parameter identifiability

Parameters	C.I. lower bounds	C.I. upper bounds
k_{empt}	0.03737	0.09202
k_{abs}	0.22197	0.32798
k_{elim}	0.00622	0.00708

Our 3 parameters of interest are identifiable

Section 3

Gastric Emptying vs. Intestinal Absorption

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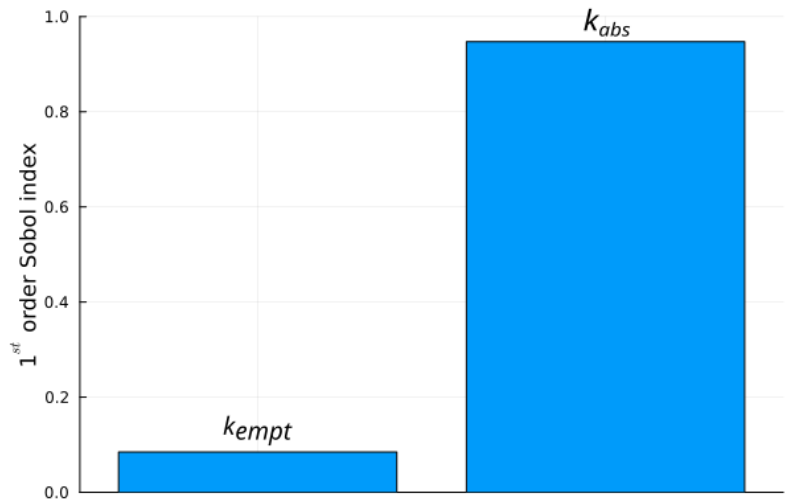
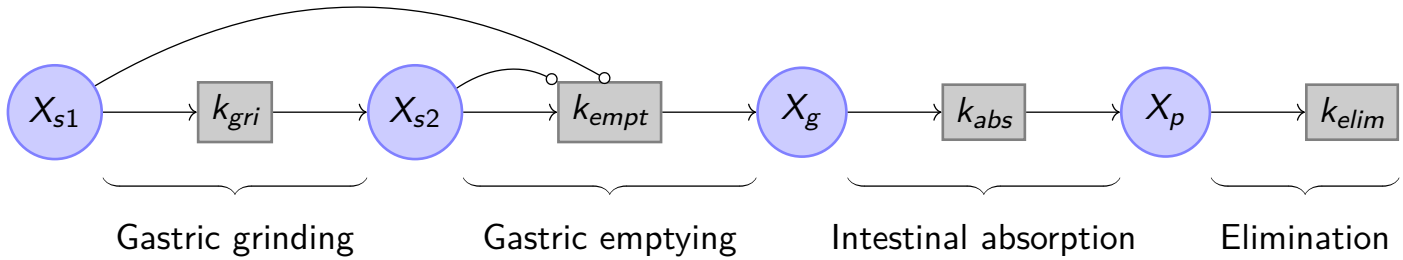
- Sensitivity analysis of AUC_{Ra_X} w.r.t. k_{empt} and k_{abs}



AUC_{Ra_X} is more sensitive to intestinal absorption than to gastric emptying

Model with complex gastric emptying

Alternative model focusing on gastric emptying [Dalla Man et al. 2006]



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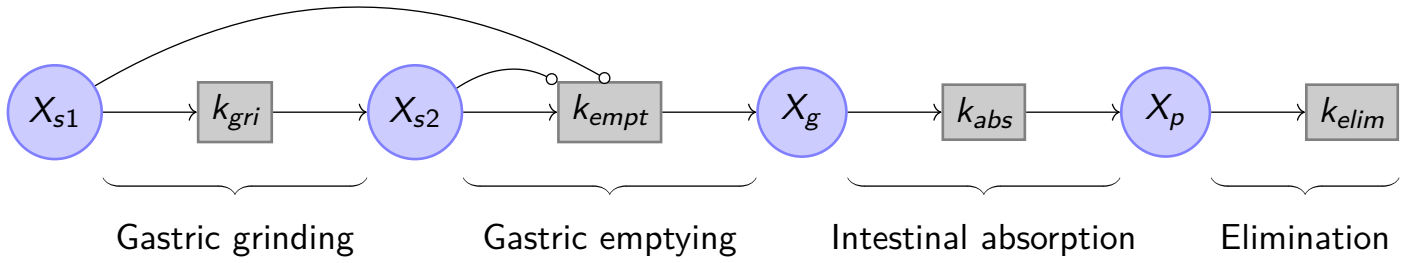

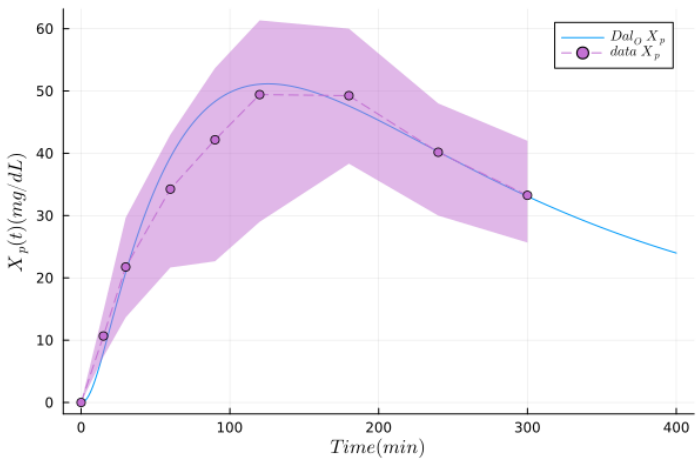

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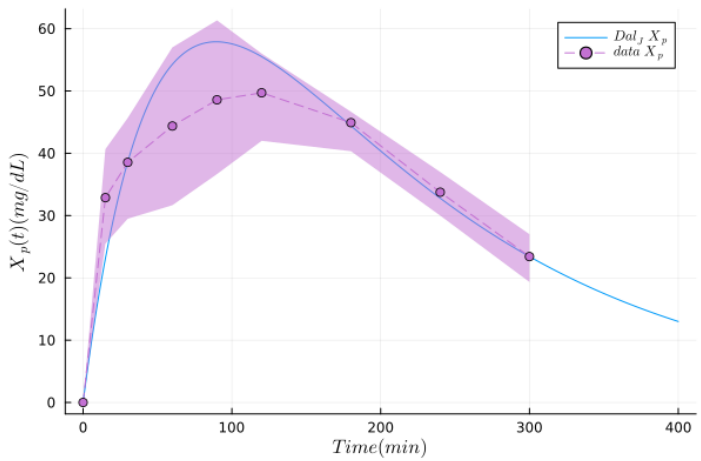

Jejunal

Much less satisfying fitting

Conclusion and future work

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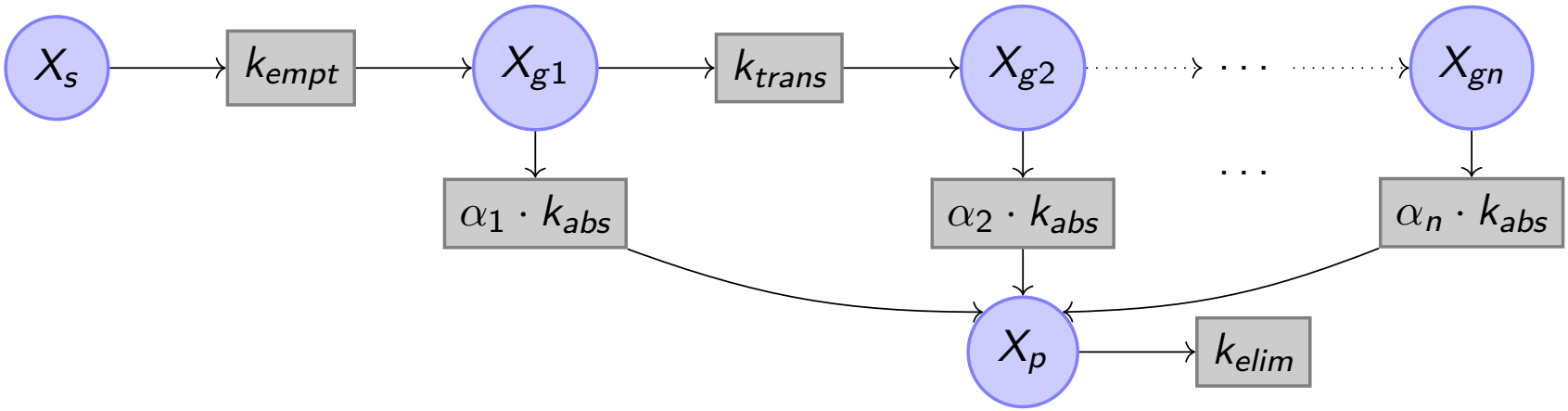
- Use DXylose model to predict glucose dynamics

Thank you for you attention

Any question ?

D-Xylose variables and parameters



Variables:

- X_s : stomach
- $X_{g1} \ldots X_{g_n}$: n gut compartments
- X_p : plasma

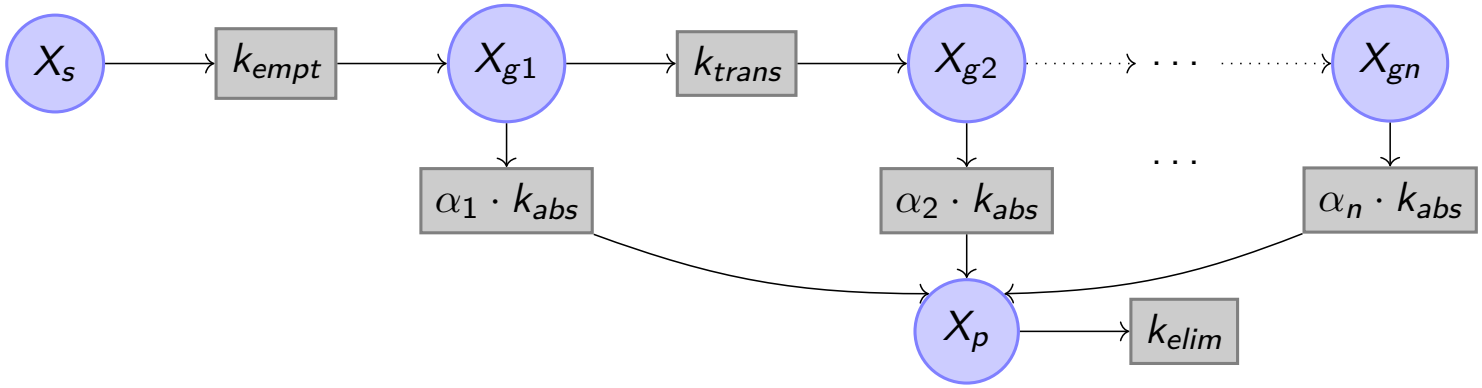
Parameters of interest:

- k_{empt} : rate of gastric emptying
- k_{abs} **: rate of intestinal absorption**
- k_{elim} : rate of xylose elimination

Other parameters:

- $\alpha_1 \ldots \alpha_n$: distribution of absorption
- k_{trans} : rate of intestinal transit

From reaction network to ODEs



$$\dot{X}_s(t) = -k_{empt} \cdot X_s(t)$$
$$\dot{X}_{g1}(t) = k_{empt} \cdot X_s(t) - (\alpha_1 \cdot k_{abs} + k_{trans}) \cdot X_{g1}(t)$$
$$\vdots$$
$$\dot{X}_{gn}(t) = k_{trans} \cdot X_{g_{n-1}}(t) - \alpha_n \cdot k_{abs} \cdot X_{gn}(t)$$
$$\dot{X}_p(t) = Ra_X(t) - k_{elim} \cdot X_p(t)$$

$$X_s(0) = \frac{D_X}{BW \cdot V_{D_X}(BW)}$$
$$X_{g1}(0) = 0$$
$$\vdots$$
$$X_{gn}(0) = 0$$
$$X_p(0) = 0$$

$$Ra_X(t) = k_{abs} \cdot \left(\sum_{i=1}^{n} \alpha_i \cdot X_{gi}(t)\right)$$