A New Model for Evaluating Oral Glucose Tolerance Tests

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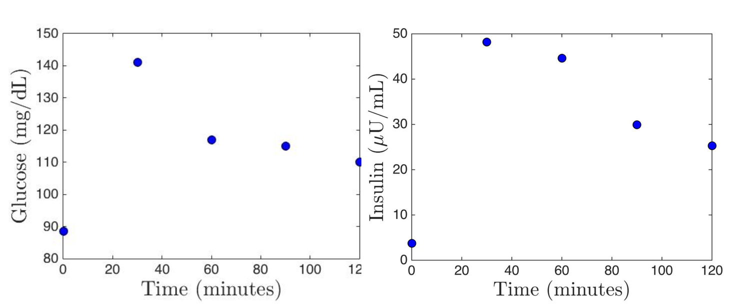
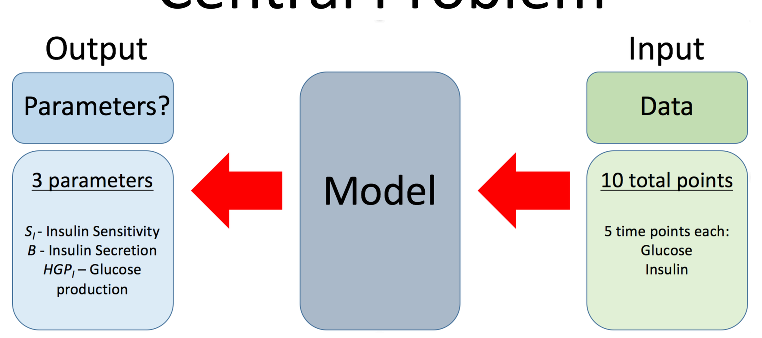
Introduction

- **Current quantitative methods in diabetes**:
  - Plasma glucose tests (fasting and random)
  - HbA1c
  - Glucose tolerance test (OGTT and IVGTT)
  - Glucose clamp
- **Goal**: obtain clinical information from OGTTs using mathematical model with physiological basis
- **Big picture:** use long-term features of model to link OGTTs from same subject, predict subject's trajectory, suggest treatment

Typical Oral Glucose Tolerance Test Data



Central Problem



Model

Two main ordinary differential equations:

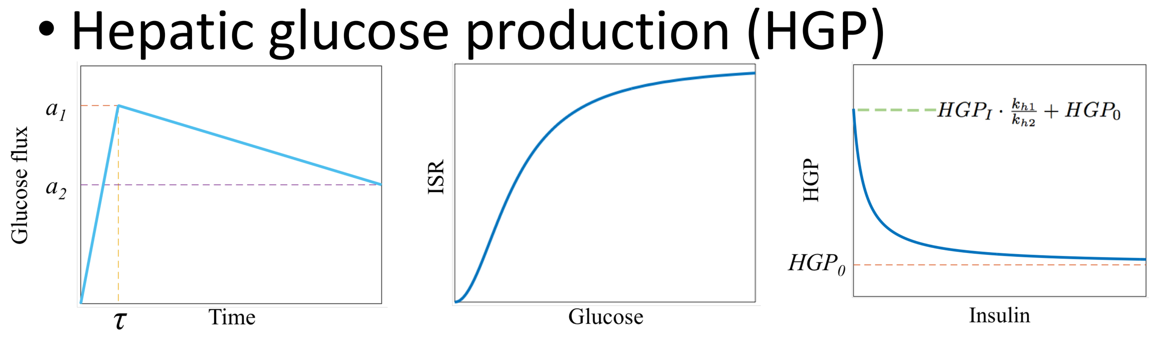
$$\frac{dG}{dt} = HGP + OGTT - (k_G + S_I \cdot I)G$$

$$\frac{dI}{dt} = B \cdot ISR - k_I \cdot I$$

Parameter	Meaning
HGP	Hepatic glucose production
OGTT	Glucose flux
k_G	Basal glucose uptake
S_I	Insulin sensitivity
B	Maximal beta cell function
ISR	Insulin secretion rate
k_I	Insulin disappearance rate

Three main auxiliary variables:

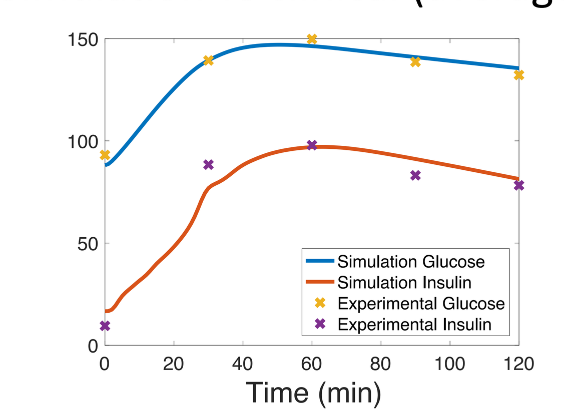
- Glucose influx (OGTT)
- Insulin secretion rate (ISR)
- Hepatic glucose production (HGP)



Results

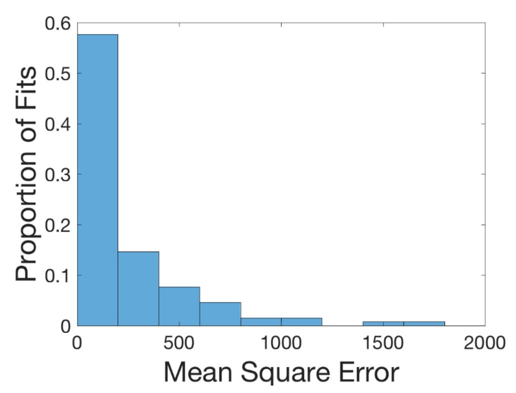
Fitting to Federal Women's Study

Simulation vs clinical (average)

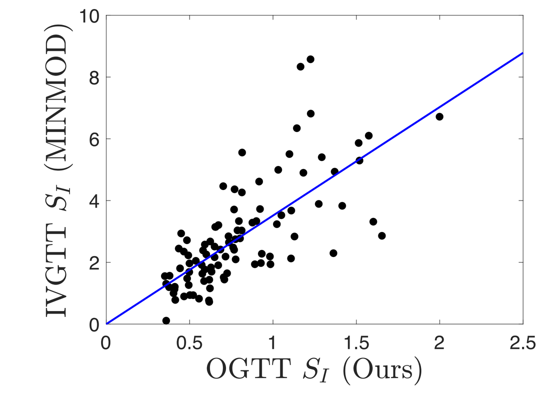


Units - Glucose: mg/dL, Insulin: μU/mL

Errors (Individual Fits)



Comparison to MINMOD S_I



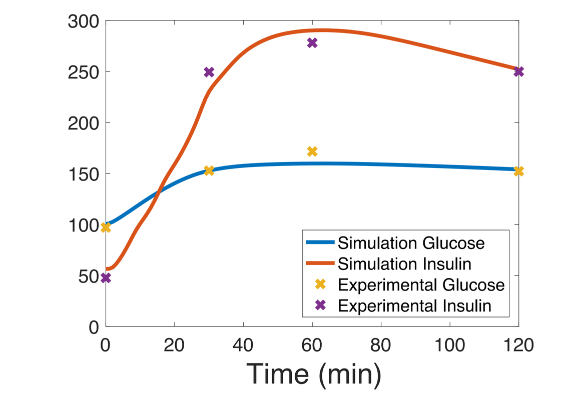
Correlation with MINMOD S_I

Index	R^2
Ours	0.51
Matsuda	0.55
HOMA-IR	0.36

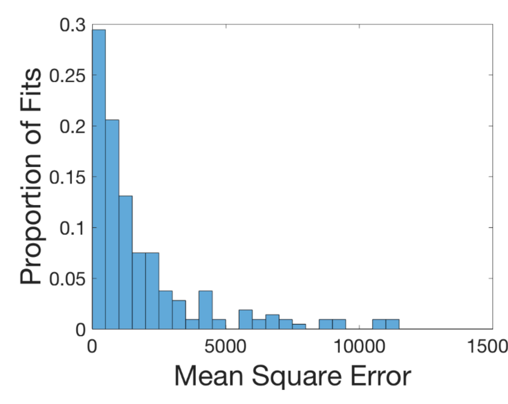
Data courtesy of Chung and Sumner (Protocol Number: 13-DK-0090)

Fitting to Pima Indian Data

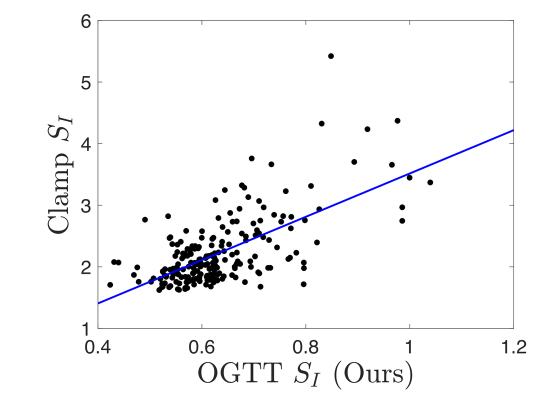
Simulation vs clinical (average)



Errors (Individual Fits)



Comparison to Clamp S_I



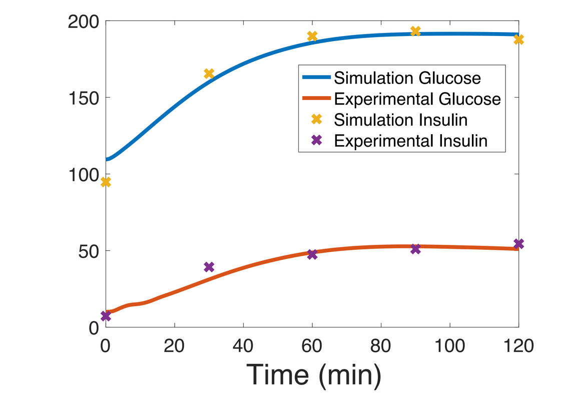
Correlation with Clamp S_I

Index	R^2
Ours	0.45
Matsuda	0.58
HOMA-IR	0.26

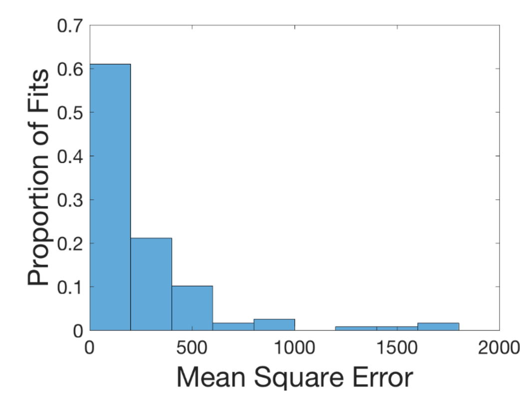
Data courtesy of Bogardus (Protocol Number: 82-DK-0136)

Fitting to Japanese Data

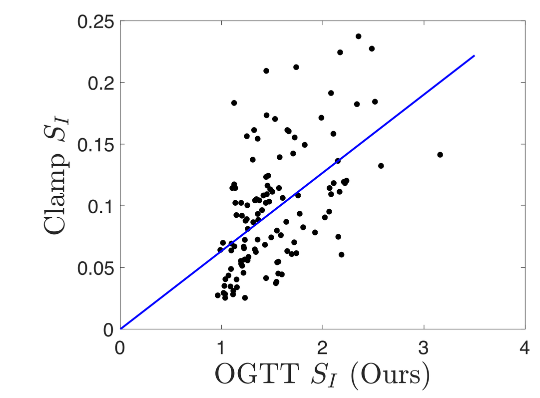
Simulation vs clinical (average)



Errors (Individual Fits)



Comparison to Clamp S_I

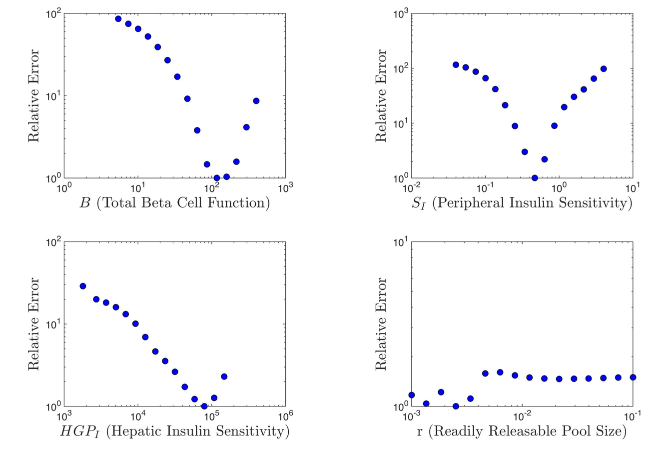


Correlation with Clamp S_I

Index	R^2
Ours	0.28
Matsuda	0.05
HOMA-IR	0.21

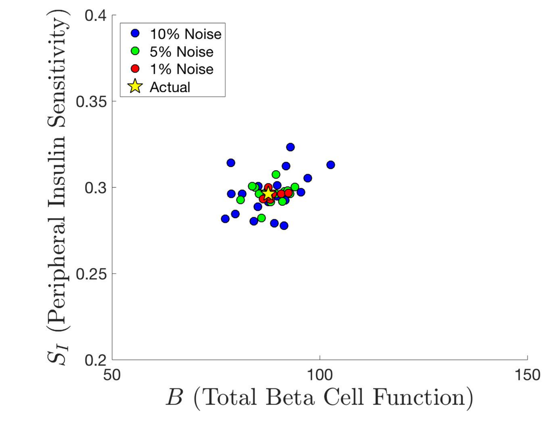
Data courtesy of Ref. 2

Error Dependence on Parameters



Valley-shaped error indicates best fit parameters are tightly constrained.

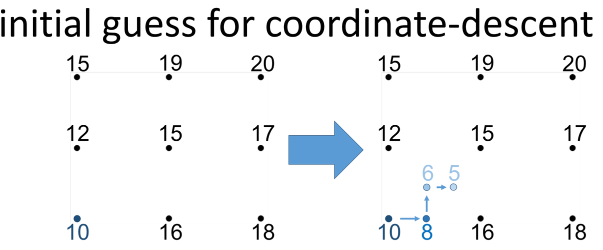
Parameter Sensitivity to Noise



Parameters were robust to random Gaussian noise added to glucose and insulin data

Methods

- **Simulating single OGTT**: OGTT glucose flux was added to steady state solution and integrated up to 120 minutes
- **Fitting model to data**: precomputed database was used to provide an initial guess for coordinate-descent minimization



- **Error function analysis**: optimal fits and their errors were computed for fixed values of parameters
- **Noise analysis**: parameters were estimated for data sets with random Gaussian noise added to each data point
- **Computational Tools**: MATLAB, MacBook Pro, Biowulf

Conclusions

- New model to obtain insulin sensitivity and beta cell function from OGTT (simpler and less invasive than IVGTT/Clamp)
- More physiological basis
  - More detailed characterization of insulin secretion
  - Both hepatic and peripheral insulin sensitivity
- Measurements consistent with Clamp and MINMOD across variety of subjects

Future Work

- Longitudinal analysis/prediction of OGTTs of same patient
- Comparison between three main methods of S_I measurement (OGTT, IVGTT, clamp) in same subjects

References

1. Ha, Satin, and Sherman, 2016; *Endocrinology* 157(2):624-635.
2. Ohashi et al., 2015; *Plos ONE* 10(12):e0143880.

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