Insulin-Glucose Dynamics a la Deterministic models
Biomath Summer School and Workshop 2008
Denmark

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Outline

- About Diabetes
- Insulin-Glucose Network
- Deterministic Mathematical models

About Diabetes

Insulin/Glucose Interaction

Mathematical models

Summary

Diabetes is characterized by **high blood glucose** levels resulting from insufficient metabolization by **insulin**

- Type 1: autoimmune destruction of insulin producing β cells
- Type 2: reduced insulin production and/or insulin resistance
- Gestational Diabetes: similar to type 2 and usually temporary

Glucose - a monosaccharide created when digestion breaks down ingested food. Body's main source of energy.

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Glucose - a monosaccharide created when digestion breaks down ingested food. Body's main source of energy.

Insulin - a hormone made in the pancreas. Plays a role in:

- glucose uptake from blood by cells (muscle,liver and fat tissue cells)
- storing of glucose in liver
- regulation of use of fat as an energy source (liver and adipose tissue)
- vascular compliance (blood vessels)
- promotion of protein synthesis and growth (general effect)

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Some facts about Diabetes

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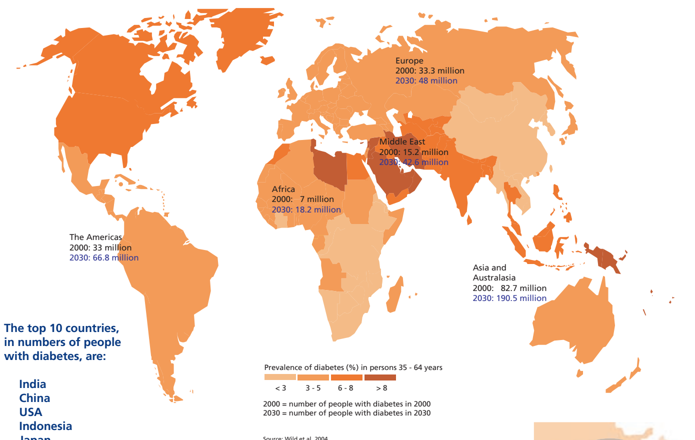
- Type 2 Diabetes- correlated to overweight/ lack of exercise (Obesity in 55% diabetics)
- Sugar consumption does not cause diabetes. Sustained high-carb diet can impair insulin sensitivity
- Type 2 can be controlled by regular exercise/ balanced diet

Prevalence of diabetes

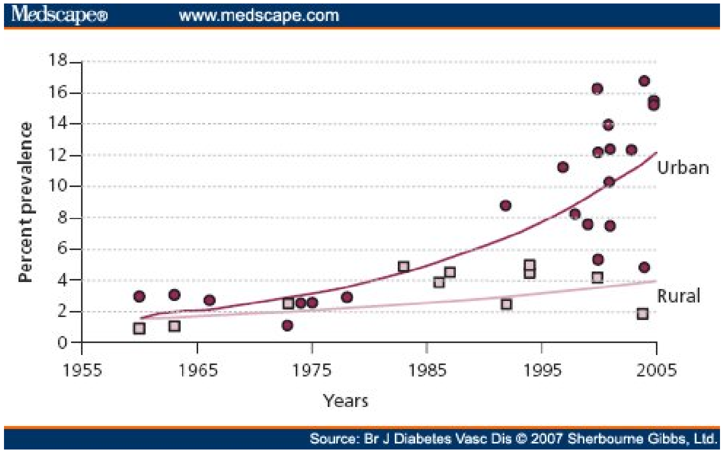


The top 10 countries, in numbers of people with diabetes, are:

India
China
USA
Indonesia
Japan
Pakistan
Russia
Brazil
Italy
Bangladesh

Year		2000	2030
Ranking	*Country*	*People with diabetes (millions)*	
1	India	31.7	79.4
2	China	20.8	42.3
3	United States of America	17.7	30.3

30 million **reported** diabetics in India today



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Definition of Diabetes

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Definition of Diabetes

- No specific biological marker known to define diabetes
- WHO defines Diabetes by plasma glucose levels. Fasting plasma glucose levels of $\geq$ 126mg/dL or 2 hours plasma glucose of $\geq$ 200mg/dL

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Diagnosis of Diabetes

- Symptoms - fatigue, frequent thirst and urination, sweet urine (in Greek diabetes = 'to flow honey')
- Fasting plasma glucose test and Oral Glucose Tolerance Test (OGTT) are used for diagnosis

Testing for Diabetes

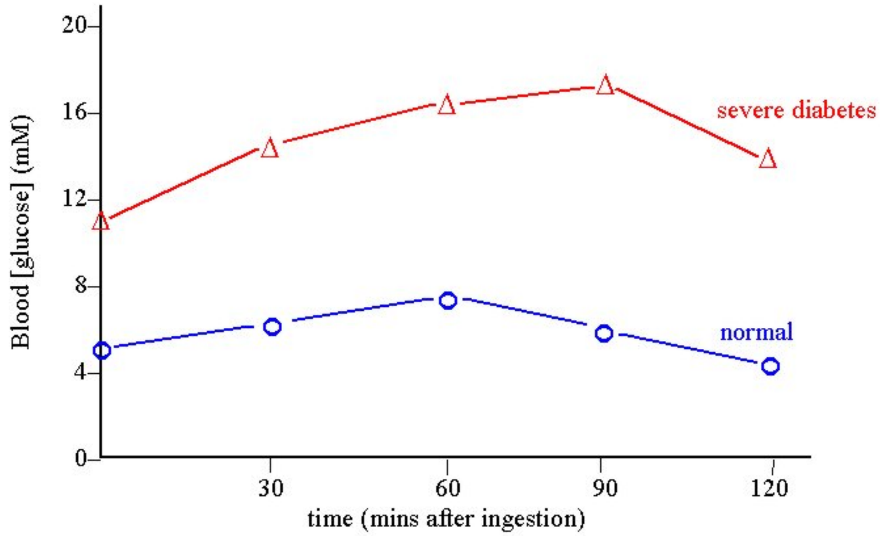
Fasting Plasma Glucose Test:

- 8-10 hours fast
- Then blood glucose measurement

OGTT:

- 8 hr fast.
- I/G measured
- Ingest 75 grams glucose
- Then measure I/G hourly over 3 hr period

SAMPLE RESULTS FROM OGTT



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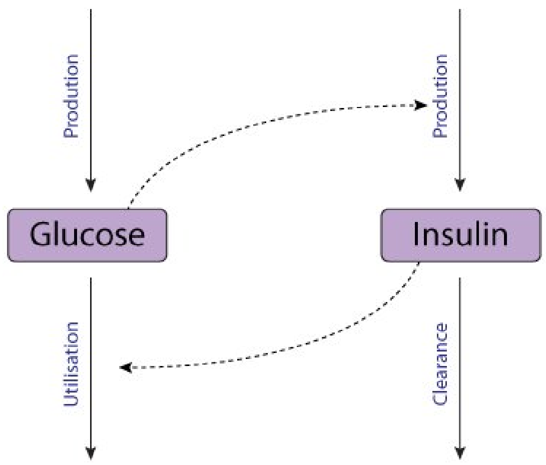
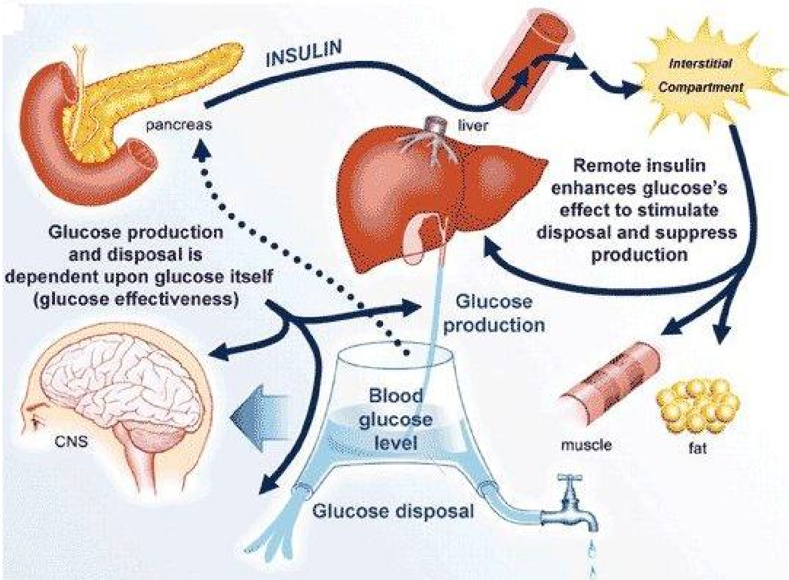
GLUCOSE/INSULIN RELATIONSHIP - SIMPLIFIED



GLUCOSE/INSULIN DYNAMICS - MAJOR ORGANs



Important Measurements
Insulin Sensitivity/Glucose Effectiveness

- **Glucose Effectiveness:** Insulin-independent rate of tissue glucose uptake.
- **Insulin Sensitivity:** - the responsiveness to insulin of glucose utilizing cells i.e. the ability of insulin to enhance glucose disappearance.

Measurement of Insulin Sensitivity/glucose effectiveness

IVGTT: 10-12 hrs Fast

- I/G measurements at t =-30,-15,0
- Glucose bolus injection at $t = 0$
- 26 to 30 I/G measurements over 3 hours

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Physiology corresponding to IVGTT:

- glucose mixing in blood plasma for $7 \leq t \leq 10$
- insulin production in pancreas stimulated
- cessation of glucose production by liver
- glucose disposal for $10 \leq t \leq 30$ is glucose mediated
- glucose disposal is insulin mediated for $t > 30$

Measurement of Insulin Sensitivity/Glucose Effectiveness

Euglycemic Hyperinsulinemic Clamp: 10-12 hr fast

- I/G measurements at t =-30,-15,0
- Fixed Insulin dosage infused starting at $t = 0$ to simulate post-prandial levels.
- Variable amt of G infused to maintain post-prandial insulin plateau for 2 hours, keeping the patient euglyceimic
- Blood I/G measured every 5 to 15 minutes for 3 hours
- Goal is to suppress hepatic glucose production to isolate measurements for glucose effectiveness and insulin sensitivity

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Types of mathematical models:

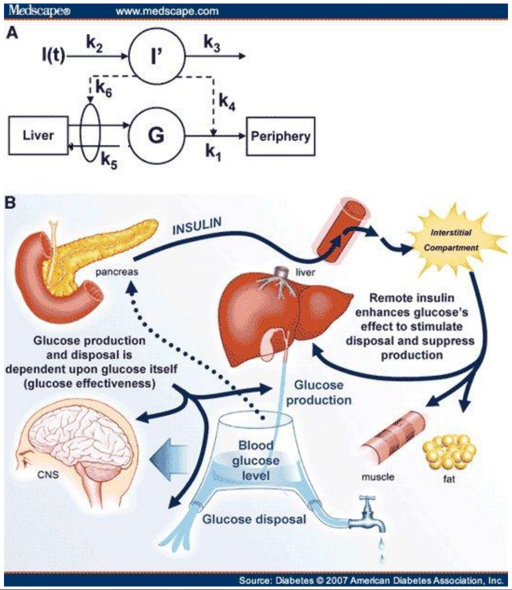
- Ordinary differential equation (ODE) models
- Delay differential equation (DDE) models
- Partial differential equation (PDE) models
- Fredholm integral equation (FIE) models
- Stochastic differential equation (PDE) models
- Integro-differential equation (IDE) models

References:

Makroglou Et Al, Applied Numerical Mathematics,56 (2006)

Boutayeb and Chetouani, BioMedical Engineering Online, June 2006.

Bergman et al Minimal Model flow diagram (IVGTT)



Minimal Model

Goal of model:

- to analyze the plasma glucose and insulin dynamics during IVGTT
- determine parameters like 'insulin sensitivity' and 'glucose effectiveness' at an individual level

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Model

- uses a system of ODEs
- estimates parameters for ODEs using non-linear least squares

Bergman's Minimal Model- Glucose Kinetics

$$\frac{dG(t)}{dt} = -p_1\left[G(t) - G_b\right] - X(t)G(t) \quad G(0) = p_0$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3\left[I(t) - I_b\right] \quad X(0) = 0$$

G: Plasma glucose concentration

X: Insulin-excitable glucose uptake rate in remote compt.

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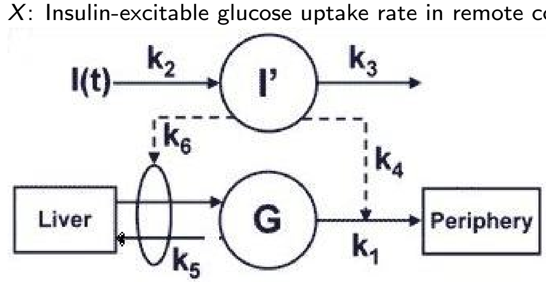
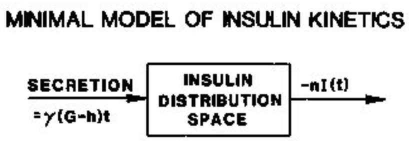


Bergman et al - Insulin Kinetics



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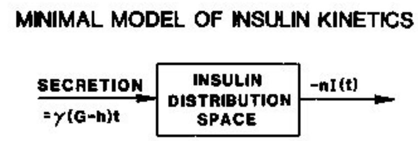

$$\frac{dI(t)}{dt} = p_4 \left[G(t) - p_5\right]^+ t - p_6 \left[I(t) - I_b\right] \quad I(0) = p_7 + I_b$$

$I(t)$: Blood insulin concentration

Coupled Minimal Model Equations

$$\frac{dG(t)}{dt} = -p_1 G(t) - X(t)G(t) + p_1 G_b \quad G(0) = p_0$$

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Analysis of Bergman's Minimal model

- Formal analysis done by De Gaetano et al in 2000
- Parameter values where stable equilibrium exists determined

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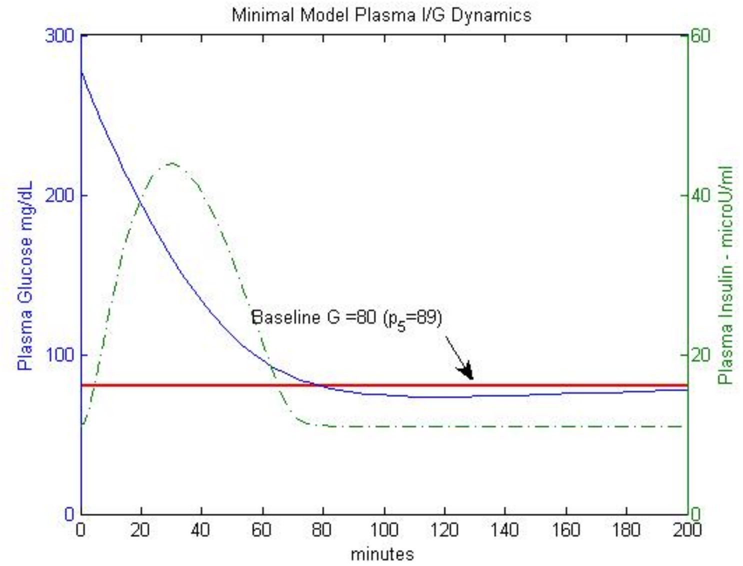
Coupled Minimal Model



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Bergman's Minimal model

Drawbacks

- X is not measurable
- Assumption that insulin secretion linearly increases with time is not physiologically tested
- 'Glucose Effectiveness' is over-estimated and 'Insulin Sensitivity' is underestimated
- no stable equilibrium for certain realistic parameters

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DeGaetano and Arino -2000

$\frac{dG}{dt}$ equation in minimal model changed to

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DeGaetano and Arino -2000

$\frac{dG}{dt}$ equation in minimal model changed to

$$\frac{dG}{dt} = -b_1 G(t) - b_4 X(t) G(t) + b_7, \; G(t) \equiv G_b \forall t \in [b_5, 0), \; G(0) = G_b + b_0$$

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$\frac{dX}{dt}$ equation is eliminated

$\frac{dI}{dt}$ equation changed to:

$$\frac{dI}{dt} = \frac{b_6}{b_5} \int_{t-b_5}^{t} G(s) ds - b_2 I(t), \quad I(0) = I_b + b_3 b_0$$

DeGaetano and Arino -2000

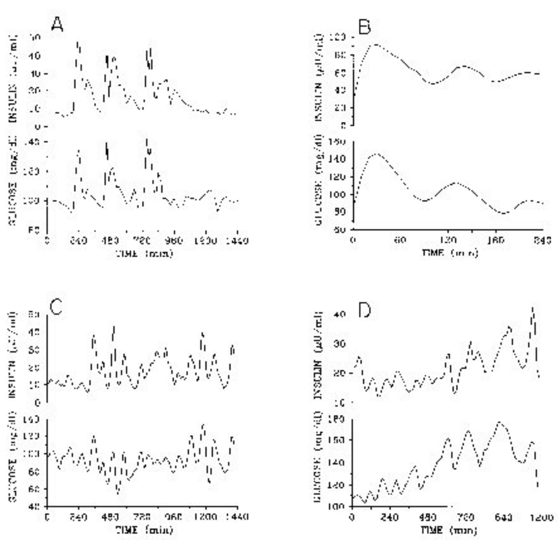
- Model has a unique equilibrium point
- Equilibrium is asymptotically stable
- Numerical fitting to individual data was good

Sturis Et Al -1991/2000- Insulin-Glucose feedback model

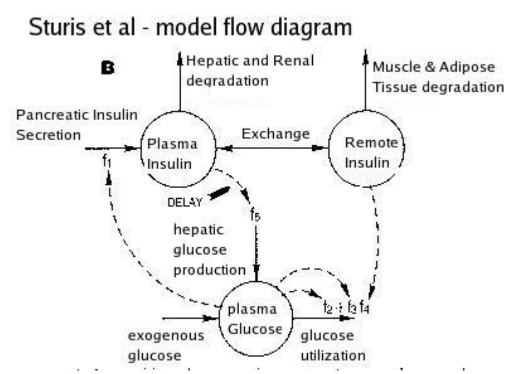
Goal:

- to develop a model for slow (ultradian) oscillations in insulin secretion
- to examine the reasons for slow Oscilltions in Insulin Supply

Sturis et al- Ultradian Oscillations



Sturis Et Al - 1991/2000 - Insulin-Glucose feedback



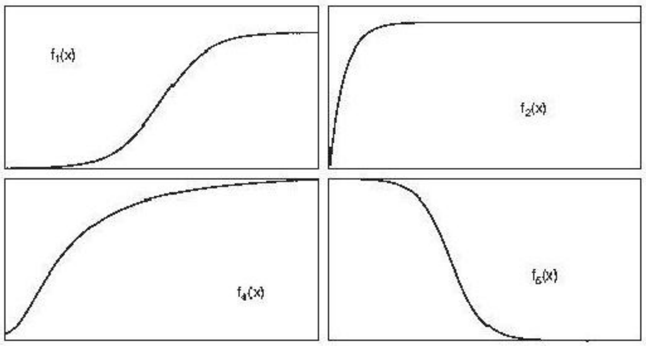
circles represent state variables
dashed arrows denote functional relationships
solid arrows represent output flows/input flows/exchanges

Sturis Et Al - Insulin-Glucose feedback model

$$\begin{aligned}
\frac{dG}{dt} &= G_{in} - f_2(G(t)) - f_3(G(t))f_4(I_i(t)) + f_5(x_3(t)) \\
\frac{dI_p}{dt} &= f_1(G(t)) - E\left(\frac{I_p(t)}{V_p} - \frac{I_i(t)}{V_i}\right) - \frac{I_p(t)}{t_p} \\
\frac{dI_i}{dt} &= E\left(\frac{I_p(t)}{V_p} - \frac{I_i(t)}{V_i}\right) - \frac{I_i(t)}{t_i} \\
\frac{dx_1}{dt} &= \frac{3}{t_d}\left(I_p(t) - x_1(t)\right) \\
\frac{dx_2}{dt} &= \frac{3}{t_d}\left(x_1(t) - x_2(t)\right) \\
\frac{dx_3}{dt} &= \frac{3}{t_d}\left(x_2(t) - x_3(t)\right)
\end{aligned}$$

I_p/I_i: mass of insulin in plasma/intercellular space. x_1, x_2, x_3: delayed effect of insulin on hepatic glucose production with time t_d

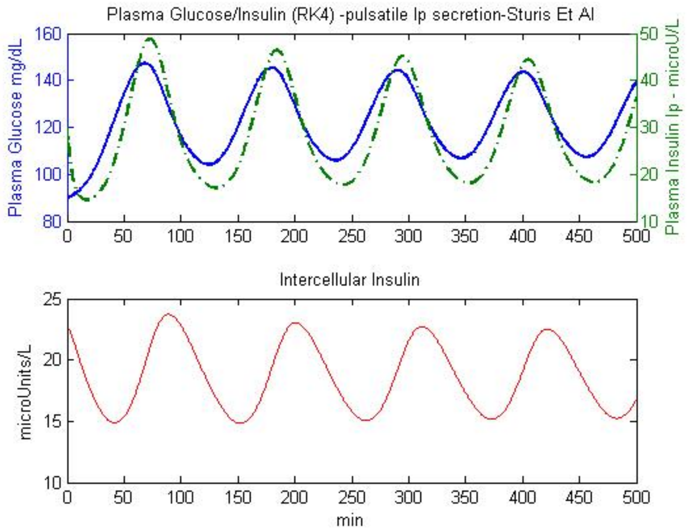
Sturis et al - shapes of the functions f_i



Shapes of the functions are more important than the exact forms

f_3 is linear in G

Sturis et al



Sturis et Al

- Numerical Analysis suggested that oscillations *could* arise from a bifurcation in the model
- Oscillations are dependent on hepatic glucose production
- self-sustained oscillations occur when hepatic glucose time-delay is in $25 - 50$ min range

Li et al 2006 - feedback model with two time delays

Sturis et al model reduced to two compartments

$$\frac{dG}{dt} = G_{in} - f_2(G(t)) - f_3(G(t))f_4(I(t)) + f_5(I(t-\tau_2))$$
$$\frac{dI}{dt} = f_1(G(t-\tau_1)) - \frac{I(t)}{t_i}$$

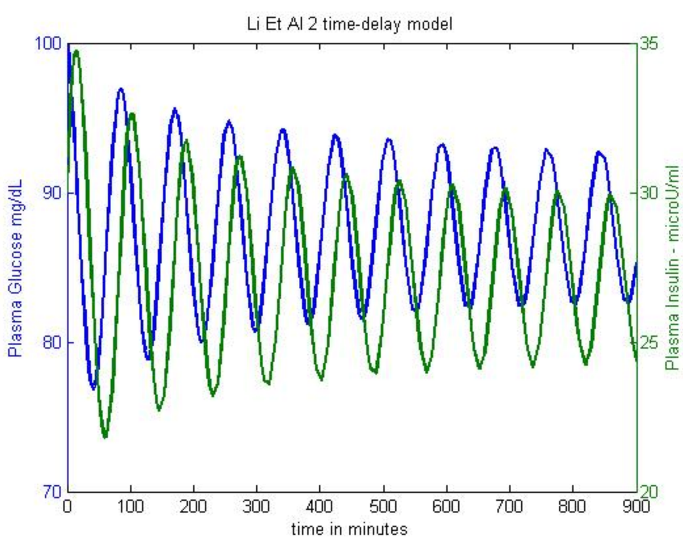
I: mass of insulin in plasma and inter-cellular space
G: mass of glucose in blood

Li Et Al

Goals/Findings

- comparison with other ultradian oscillation models for self-sustained oscillations
- found ranges of time delays in their model where sustained oscillations occur

Li et al simulations



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SUMMARY

- Minimal Model-ODE
  - models the IVGTT
  - quantifies 'glucose effectiveness' and 'insulin sensitivity'
- DeGaetano and Arino improvement on Minimal model
- Ultradian oscillations - ODE + DDE
  - ODE model - efficacy of oscillatory insulin
  - DDE model- attributes oscillations to both time delays with τ_2 playing a more important role

Hands on simulations (in Matlab and R) of models presented this afternoon

Thanks to my summer student PRABHAT KUMAR for programming help!