Multi-level modelling of type 2 diabetes

why do we need a workshop in this?

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Overview

- **Practicalities**
- Backstory
- Is this really a good idea?
- The workshop

Welcome to Linköping!

- Linköping is the fifth biggest city in Sweden
- Almost equal distances from Stockholm, Gothenburg and Lund/Malmö
- University was founded in 1970
- Known for System Identification, and a clinically close research
- We have now put up the Linköping Centre for Systems Biology, focusing on these two areas. It involves approx 15 group from 7-8 departments.

Who am I

- M.Sc. in theoretical physics
- Worked with systems biology since my M.Sc. project
- My Ph.D. was spent at FS/ISY in Linköping, and at Fraunhofer-Chalmers in Gothenburg (both control engineering groups)
- 4-5 years ago I came back to Linköping, and has since then started up my own research group
- I have been travelling 2 x 1.5 months per year to other groups (Hiroaki Kitano (Tokyo), Jens Timmer (Freiburg), Stefan Hohmann (Gothenburg), Alejandro Coleman-Lerner (Buenos Aires)

The group: Diabetes and Integrated Systems Biology

www.isbgroup.eu

The theory and systems biology part

www.isbgroup.eu

First workshop

- In the EU-network BioSim there was one Workpackage devoted to fat cells, beta cells, muscle, and whole-body glucose homeostasis
- Why didn’t they talk to each other?
- I arranged a meeting with them, and some object-oriented modellers from engineering applications
- This was in January 2006

Amsterdam meeting

November 2006

More applications and meetings

- Malmö, January 10-11, 2008
- STREP application HIMOD, 2008
- DEEPINSIGHT, 2009
- The latest attempt was in 2010, M-INS...

M-INS

- Muscle: Riel, Zierath, Kiens/Richter
- Adipose: Cedersund, Strålfors, Arner
- Liver: Riel, Timmer, Bartholome, Holzhütter
- Whole-body: Cobelli, Adiels/Borén
- Omics: Cascante, Gunther, Kratchmarova
- Scientific advisory board: AstraZeneca, Novartis, Pfizer, NovoNordisk, Entelos

Let’s focus on getting things done as well!

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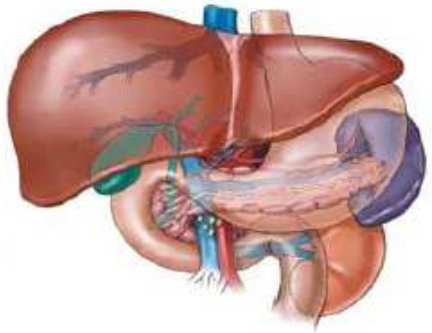
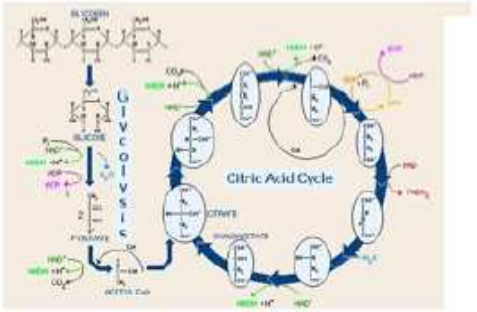
What is the idea?

Whole-body level

Organ modules



Detailed level



Can we then ever say anything more than this?

It could be like that

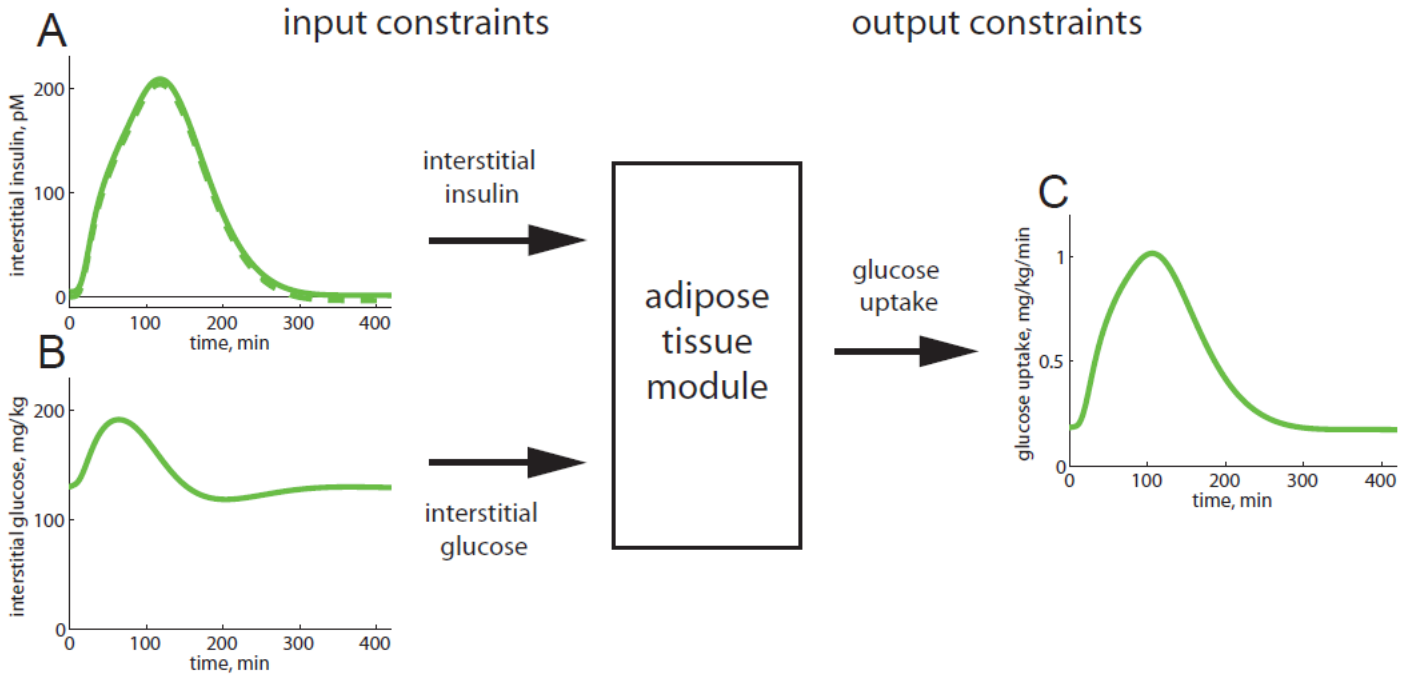
or.....

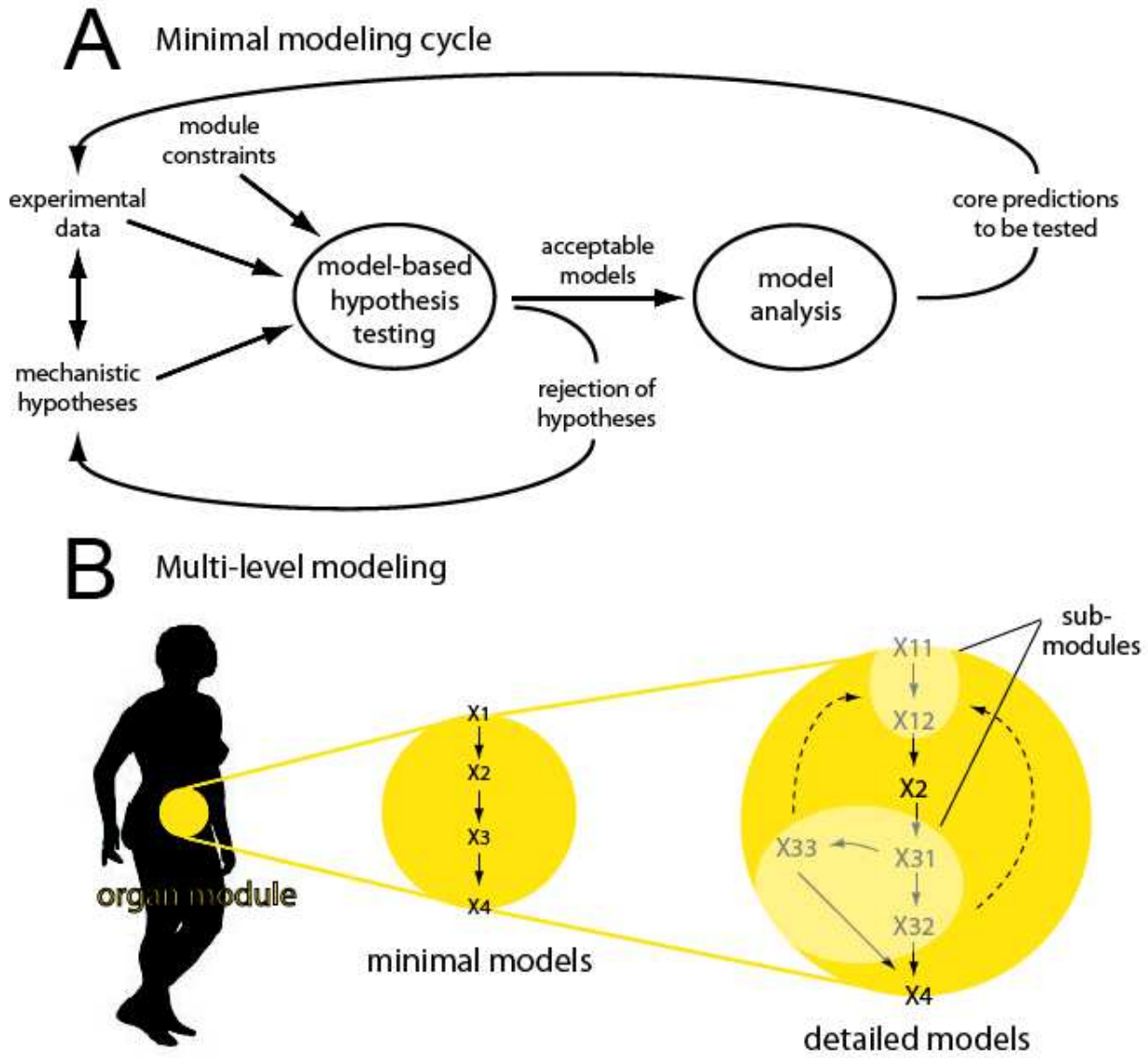
it could be in some other way

Actually we don’t even have a beach statement yet

- There are lots of pieces to the puzzle
- However, the pieces don’t match!
- And nobody bothers
- And type 2 diabetes remains an unresolved problem

And by organ constraints, we can draw conclusions




A
Minimal modeling cycle
module constraints
experimental data
model-based hypothesis testing
acceptable models
model analysis
core predictions to be tested
mechanistic hypotheses
rejection of hypotheses
B
Multi-level modeling
organ module
X1
X2
X3
X4
minimal models
sub-modules
X11
X12
X2
X33
X31
X32
X4
detailed models

Classical arguments

- Understanding such a complex multi-level disease as diabetes requires multi-level modelling
- The acceptance of the Dalla Man model for replacement of test animals is an indication that models are improving
- However, the Dalla Man model cannot do drug-simulations
- And one group does not have all the necessary competences

Other ongoing and future plans

- Add fatty acid homeostasis (ongoing)
- Model the brain better (see existing models)
- Model other states: diabetes and exercise
- Include more organs (beta cells are also already started)

This workshop

- Time to work!
- Disseminate knowledge
- Plan for the future
- Raise new ideas

This afternoon

- Elin Nyman, Multi-scale modelling incorporating insulin signaling in adipocytes and whole-body glucose homeostasis
- Fianne Sips, A whole-body model for both glucose and fatty acid homeostasis
- Britta Goebel, Brain centered whole-body model of the energy metabolism
- Clemens Kreutz, Modelling of hepatocyte insulin signalling

Monday morning

- Winston Garcia-Gabin, Multi-level modelling of glucose homeostasis and type 1 diabetes
- Peter Strålfors, Modelling as a tool to aid experiments in drawing conclusions and integrating knowledge regarding insulin signaling in primary human fat cells
- Natal van Riel, Modelling of muscle and liver metabolism
- Olof Dahlqvist Leinhard, Measuring local fat content on the whole-body scale

Monday afternoon

- Jan Krumsiek, Gaussian graphical modeling reconstructs pathway reactions from high-throughput metabolomics data

- Folke Sjöberg/Erik Tesselaar, Microdialysis to measure in vivo concentrations and fluxes in muscle, adipose, and liver