CLOSED-LOOP GLUCOSE CONTROL USING A PHYSIOLOGY-BASED PHARMACOKINETIC / PHARMACODYNAMIC MODEL KERNEL

Stephan Schaller[1,2], Joerg Lippert[1], Lukas Schaupp[3], Thomas Pieber[3], Andreas Schuppert[1,2], Thomas Eissing[1]

[1] Systems Biology, Bayer Technology Services GmbH, Leverkusen, Germany

[2] Aachen Institute for Advanced Study in Computational Engineering Sciences, RWTH Aachen, Aachen, Germany

[3] Department of Internal Medicine, Medical University of Graz, Graz, Austria

Motivation

Automated glucose control (AGC), even after decades of research, has not yet reached a clinical stage [1]. Major hurdles are the inter- and intra-individual variability of glucose dynamics, the uptake, kinetics, and response of insulin, and related pharmacological lag-times. The explicit distinction between substance and patient properties within physiology-based pharmacokinetic/ pharmacodynamic (PBPK/PD) models allows the use of prior knowledge, e.g. organ volumes and blood flow rates, for their individual pre-parameterization. Together with added mechanistic detail, the approach holds promise in alleviating remaining challenges in AGC.

Physiology-based pharmacokinetic modelling

PBPK models describe the mechanisms underlying the absorption, distribution, metabolism and excretion (ADME) of a substance within the body at an in-depth level of detail.

PBPK models are based to a large extend on prior information regarding an organism's anatomy and physiology. Most model parameters are either taken from collections of anatomical and physiological data or are calculated from drug-dependent properties. Based on such basic physicochemical parameters of a substance, generic PK prediction models are automatically parameterized. These models can then be used to simulate drug concentration profiles in various organs and tissues (Fig. 1) [2-4] .

PBPK models for glucose, insulin and glucagon were developed using the software tools PK-Sim® and MoBi®. For insulin and glucagon, the exchange across capillary walls is described by the two pore theory, assuming convection and diffusion through two types of pores [5]. For insulin only, saturating receptor-based trans-endothelial transport is taken into account [6,7]. Insulin crosses the endothelium via transcytosis. From the interstitial space, insulin and glucagon are transported back to circulation by lymph flow (Fig. 2).

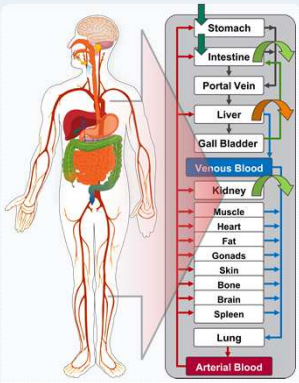


Figure 1: PBPK model structure implemented in PK-Sim®. The basic model structure can be extended by additional processes such as active transporters or enzyme-mediated metabolisation [2].

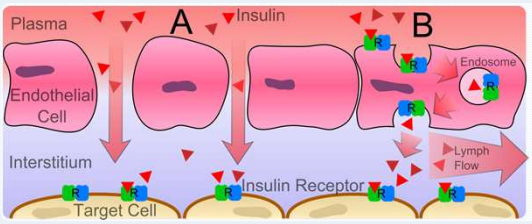


Figure 2: Schematic of trans-endothelial insulin transport. A) Two pore transport by convection and diffusion. **B)** Saturatable receptor-based transendothelial transport. Bound to its receptor and internalized, insulin is carried to interstitial space. Insulin and glucagon are transported back to circulation by lymph flow

PBPK/PD model of the glucose-insulin metabolism

A coupled PBPK/PD model was developed to describe the distribution and interaction of glucose, insulin and glucagon in individual patients. Mechanistic models of both insulin receptor dynamics [8,9] and subcutaneous insulin absorption [10] were integrated for dynamic representations of long- and short-term (stationary and dynamic) changes in insulin action and to accommodate for the application of all market relevant insulin derivatives (Fig. 3).

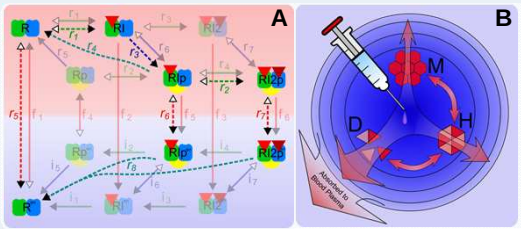


Figure 3: Insulin action and subcutaneous absorption mechanistics. A) Comparison of the insulin receptor model from [8] which was implemented (full colours, dotted arrows) with [9] (opaque, solid arrows). **B)** Mechanistics of subcutaneous absorption of dimeric/ monomeric insulin (D) and its transition into hexameric (H) and microprecipitated (M) structures as adapted from [10].

The model was parameterized using a variety of literature data [14,15,16] as well as an unpublished dataset from a clinical trial for closed-loop glucose control evaluation with subjects with type 1 diabetes at the Medical University of Graz. The coupled model is able to describe different standard scenarios including clamp studies, tolerance tests as well as complete clinical trials with patients with type 1 diabetes using one time-invariant parameter set, i.e. without continuous adaptations to intra-patient variability (Fig. 4).

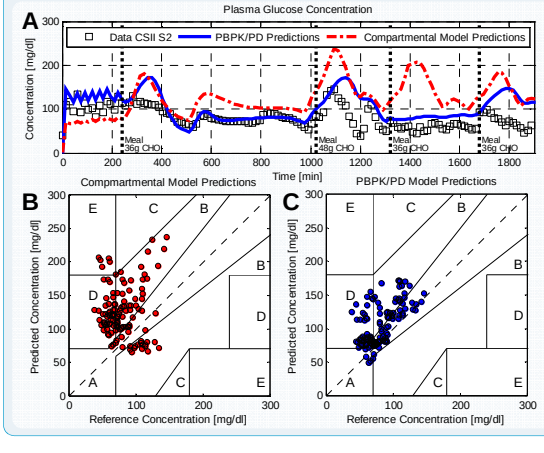
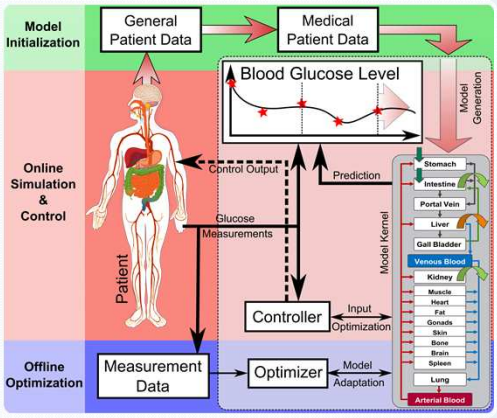


Figure 4: Comparison of predicted time concentration curves. Compared models are the PBPK/PD model and the compartmental model developed by Hovorka et al. [11,12] which was used for model predictive control in the clinical study from which the data was obtained (excerpts in [13]). Only **one representative individual** (Subj. 2) is shown. **A)** Exemplary prediction of glucose concentration of visit 1. The subject was fitted on data from visit 2. **B)&C)** Clarke's Error Grid Analysis of the predicted blood glucose time concentration curves from A). Most high-false predictions occur during a meal. The compartmental model was parameterized to our best knowledge.

Closed-Loop insulin delivery

For future applications, the coupled glucoregulatory PBPK/PD model will be used as a model kernel for automated insulin delivery, i.e. blood glucose control. To accommodate for the nonlinearities of the model kernel and the physiological/pharmacological lag-times of insulin absorption and action, a constrained and robust nonlinear model predictive control routine (MPC) [17], state of the art in blood glucose control [11,18], was chosen to derive the optimal insulin dose. The workflow setting is depicted in Figure 5.

Figure 5: Schematic of the workflow during continuous closed-loop glucose control. The PBPK/PD model kernel is initialized with the patients data (physiological parameters, e.g. weight, height, gender). Blood glucose measurements are taken frequently, stored and the most recent measurements are delivered to the controller. The process works on two time-frames: the online calculation of the optimal insulin dose ("control input" for closed-loop glucose control) based on recent glucose measurements on a short timeframe, and the offline "model adaptation" based on the full measurement data history on an extended time-frame.



A number of restrictions have been imposed to increase the robustness and safety of the control algorithm. The maximum insulin Infusion rate is constrained based on a threshold calculated from the saturation of effect of on-board insulin in hepatic and peripheral tissue. Thus, relative insulin Sensitivity of the subject can be accounted for. This was combined with a state-feedback controller for error correction to account for prediction errors. Overall, the evaluated control concept indicates the applicability for glycaemic control (Fig. 6)

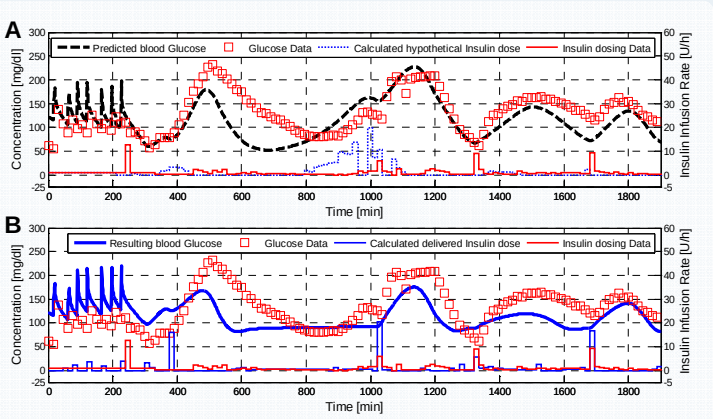


Figure 6: Evaluation of the blood glucose control concept using MPC. The chosen blood glucose concentration target value for control is 105 mg/dl. **A)** Evaluation of a "what-if" scenario. Blood glucose is predicted based on the original protocol of the clinical trial. In parallel, hypothetical insulin dosing suggestions are calculated at each time-step by the controller, but are not applied to the process, and therefore repeatedly high doses are recommended. This allows a qualitative comparison of the controller output under similar conditions (predictive error and glucose levels) **B)** Evaluation of an *in-silico* control run. Only carbohydrates (meals and IV / oral glucose) are administered based on the original protocol of the clinical trial. Information on carbohydrate intake is passed to the controller upon start of intake. The optimal insulin dose is calculated by the controller and applied to the process.

Conclusions

Overall the results promise that PBPK/PD models offer a more predictive approach than simpler compartmental models by mechanistically capturing process variability. In a next step, the meal absorption process will be improved, taking into account the nutritional composition of a meal. Currently, the effect of exercise on liver and muscle glucose metabolism is under investigation. All this should allow for a better control performance of insulin delivery as will be further investigated in a clinical setting.

References

[1] Hovorka, R., 2011, *Nat. Rev. Endocrinol.* 7: 385-95
[2] Eissing, T. et al., 2011, *Front. Physio.* 2
[3] Willmann, S. et al., 2003, *Biosilico* 1: 121-124
[4] PK-Sim® 4.2, 2010, www.systems-biology.com
[5] Rippe, B. and B. Haraldsson, 1994, *Physiol. Rev.* 74: 163-219
[6] Barrett, E.J., et al., 2011, *Am J Phys. Endo. Metab.* 301: 252-63
[7] Abbott, N.J. and I.A. Romero, 1996, *Mol Med Today* 2: 106-13
[8] Sedaghat, A.R. et al., 2002, *Am J Phys. Endo. Metab.* 283
[9] Koschorreck, M. and E.D. Gilles, 2008, *BMC Syst Biol* 2: 43
[10] Tarin, C., et al., 2005, *IEEE Trans Biomed Eng*, 52: 1994-2005
[11] Hovorka, R., et al., 2004, *Physiol Meas.* 25: 905-20
[12] Hovorka, R., et al., 2008, *Physiol Meas.* 29: 959-78
[13] Hovorka, R. et al., 2004, *Diabetes Technol Ther* 6: 307-18
[14] El-Khatib, F.H. et al., 2010, *Sci Transl Med.* 2: 27ra27
[15] Regittnig, W. et al., 1999 , *Diabetes* 48: 1070-81
[16] Sorensen, J.T., 1985, *PhD Thesis*, MIT.
[17] Mayne, D.Q., 2000, *Automatica* 36: 789-814
[18] Magni, L. et al., 2009, Biomed. Sig. Proc. & Contr. 4: 338-346

Acknowledgements

This work was performed in the framework of FP7 Integrated Project Reaction (Remote Accessibility to Diabetes Management and Therapy in Operational Healthcare Networks) partially funded by the European Commission under Grant Agreement 248590.

www.systems-biology.com