In-silico Comparison of Intravenous, Intraperitoneal, Subcutaneous and Combined Approaches for Closed-Loop Glucose Control

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Motivation

Approaches for insulin infusion and glucose sensing

- **Subcutaneous (SC) approach:** Slow response, poor robustness towards local tissue effects (mechanical pressure, temperature etc), variable insulin absorption.
- **Intravenous (IV) approach:** Appealing, but only practically possible inside the hospital/ clinic.
- **Intraperitoneal (IP) approach:** Faster dynamics at both ends [1,2], while being more practically usable than intravascular sensors.

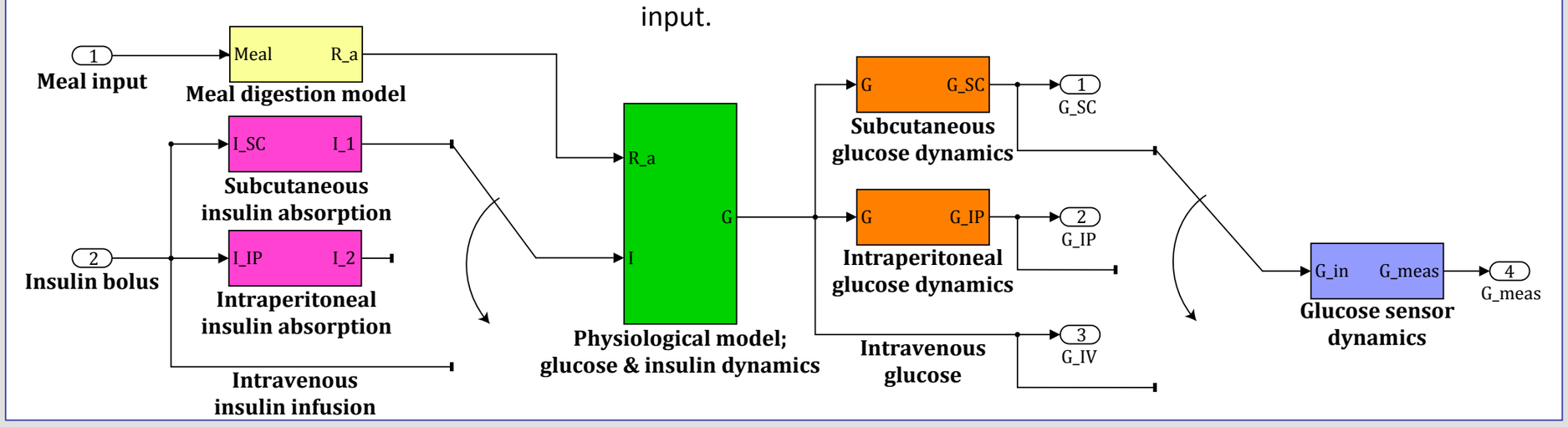
Methods

Modeling

- Modular mathematical model.
- Glucose and insulin dynamics based on existing models [3,4].
- Extended with IP insulin infusion [5].
- Extended with IP glucose sensing [1,2].
- Sensor dynamics for selected sensor types.
- Parameter sets for diabetes type 1 subjects and for non-diabetic subjects.

Control methods

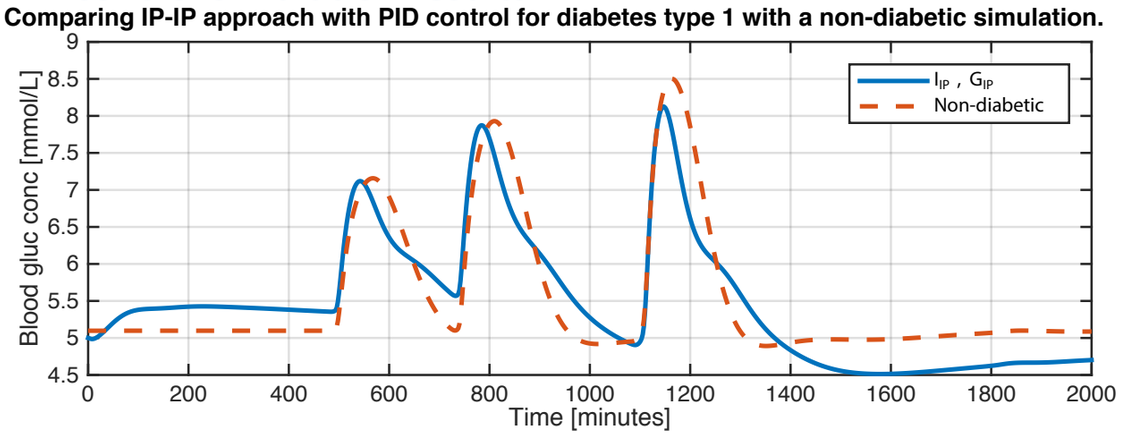
- Manually tuned proportional-integrative-derivative (PID) control. Only tested for a double IP approach.
- Model-predictive control (MPC). Tested for all approaches, including combined approaches (e.g. IV insulin infusion and IP glucose sensing).
- The “controller model” used by MPC is simplified/linearized compared to the simulator model. Additionally, some parameters are perturbed in the simulator model: Insulin sensitivity, insulin absorption and glucose dynamics (from blood to sensor site), in order to achieve more realistic results. Equal percent-wise perturbation in all approaches (IV, IP, SC).
- Simulated for 24 hours including 3 typical meals.
- Compared with simulations of non-diabetic subjects, with the same meal input.



Results

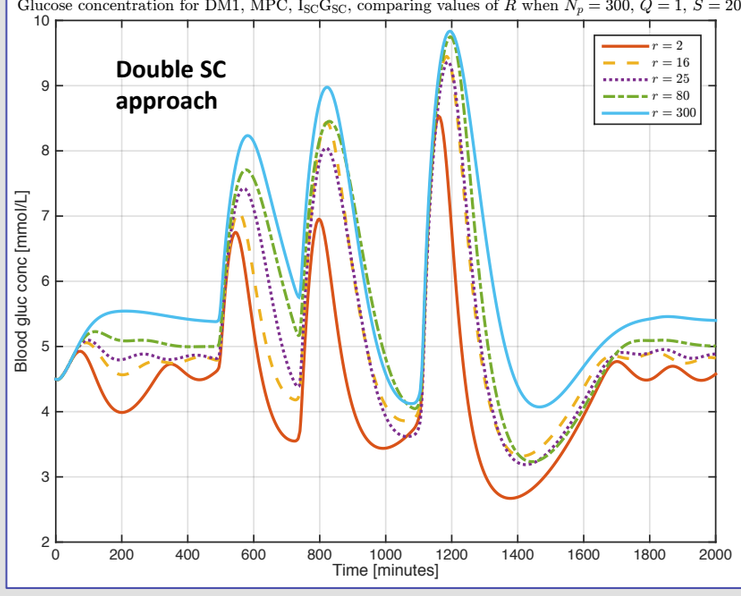
PID control simulation results

Comparing IP-IP approach with PID control for diabetes type 1 with a non-diabetic simulation.

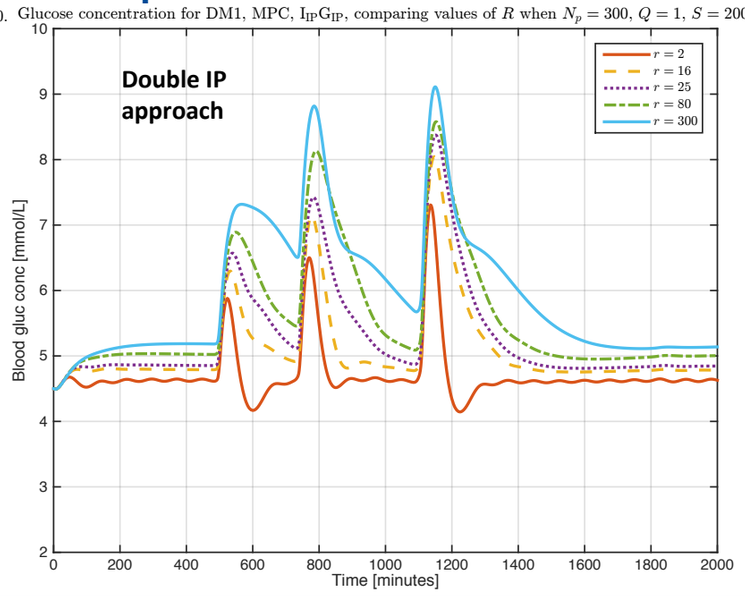


Examples of MPC simulation results with model perturbations

Glucose concentration for DM1, MPC, $I_{SC}G_{SC}$, comparing values of R when $N_p = 300$, $Q = 1$, $S = 200$.



Glucose concentration for DM1, MPC, $I_{IP}G_{IP}$, comparing values of R when $N_p = 300$, $Q = 1$, $S = 200$.



MPC simulation results summarized

Approach	R*	Gmin (mmol/L)	Area under low limit (< 4 mmol/L)	Gmax (mmol/L)	Area over high limit (> 8 mmol/L)	Mean glucose level (mmol/L)
I_sc, G_sc	2	2,67	7631	8,53	378	4,49
	16	3,14	2074	9,45	1717	5,16
	25	3,19	3064	9,37	1364	5,20
	80	3,23	2242	9,75	2635	5,53
	300	4,07	0	9,83	4065	5,96
I_ip, G_sc	2	3,35	904	7,44	0	4,78
	16	4,49	0	8,27	88	5,21
	25	4,49	0	8,47	251	5,43
	80	4,49	0	8,77	686	5,68
	300	4,49	0	9,16	1427	6,07
I_ip, G_ip	2	4,15	0	7,31	0	4,76
	16	4,49	0	8,04	5	5,21
	25	4,49	0	8,37	164	5,42
	80	4,49	0	8,58	380	5,73
	300	4,49	0	9,11	1321	6,06
I_iv, G_sc	2	4,19	0	6,53	0	4,67
	16	4,49	0	6,95	0	4,97
	25	4,49	0	7,19	0	5,09
	80	4,49	0	7,53	0	5,37
	300	4,49	0	7,94	0	5,66
I_iv, G_iv	2	4,21	0	6,64	0	4,69
	16	4,49	0	7,26	0	5,11
	25	4,49	0	7,67	0	5,24
	80	4,49	0	8,03	2	5,49
	300	4,49	0	8,30	82	5,82

(*) The R tuning parameter represents the input weighting for the MPC algorithm, but since Q (weighting of the deviation from reference, 4.5 mmol/L) is set to a constant value of 1, the variation of R is practically adjusting the Q/R ratio. The last parameter, S, is a weighting of a slack variable (breaking of the low and high limits).

Conclusion

- A simple PID controller may be sufficient for a double IP approach.
- A double intraperitoneal approach ($I_{IP}G_{IP}$) gives markedly smaller glucose excursions after meals compared to the state-of-the-art double subcutaneous approach ($I_{SC}G_{SC}$) on MPC.
- The difference is larger when tested on a MPC with induced model errors; the double IP approach is more robust to model errors, compared to SC approaches ($I_{SC}G_{SC}$, $I_{IP}G_{SC}$).
- Our results suggest that a double IP approach should be investigated further on the way towards a robust artificial pancreas.

References

[1] Velho, G., Froguel, P., and Reach, G., “Determination of Peritoneal Glucose Kinetics in Rats: Implications for the Peritoneal Implantation of Closed-loop Insulin Delivery Systems,” *Diabetologia*, vol. 32, no. 6, pp. 331–336, 1989.

[2] Burnett, D. R., Huyett, L. M., Zisser, H. C., Doyle, F. J., and Mensh, B. D., “Glucose Sensing in the Peritoneal Space Offers Faster Kinetics than Sensing in the Subcutaneous Space,” *Diabetes*, vol. 63, no. 7, pp. 2498–2505, July 2014.

[3] Dalla Man, C., Raimondo, D. M., Rizza, R. A., and Cobelli, C., “GIM, Simulation software of meal glucose-insulin model,” *Journal of Diabetes Science and Technology*, vol. 1, no. 3, pp. 323–330, 2007.

[4] Wilinska, M. E., Chassin, L. J., Schaller, H. C., Schaupp, L., Pieber, T., and Hovorka, R., “Insulin Kinetics in Type-1 Diabetes: Continuous and Bolus Delivery of Rapid Acting Insulin,” *IEEE Transactions on Biomedical Engineering*, vol. 52, no. 1, pp. 3–12, 2005.

[5] Matsuo, Y., Shimoda, S., Sakakida, M., Nishida, K., Sekigami, T., Ichimori, S., et al., “Strict Glycemic Control in Diabetic Dogs with Closed-loop Intraperitoneal Insulin Infusion Algorithm Designed for an Artificial Endocrine Pancreas,” *Journal of Artificial Organs*, vol. 6, no. 1, pp. 55–63, 2003.