Insulin dosage based on risk index of Postprandial Hypo- and Hyperglycemia in Type 1 Diabetes Mellitus with uncertain parameters and food intake

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SWIM’09 Small Workshop on Interval Methods
June 2009.
Intensive insulin therapy

- Emulate the insulin secretion by the pancreas with injection of basal and bolus insulin
  - Basal insulin: the insulin that controls blood glucose levels between meals and overnight. It controls glucose in the fasting state
  - Bolus insulin: the insulin that is released when food is eaten or to correct a high blood glucose
- The patient calculates the adjusted insulin dose according to some rules prescribed by the physician in the therapy plan
- Counter-action: risk of severe hypoglycemia episodes if doses not properly calculated
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Motivation

- The poorly controlled diabetes leads to chronic complications with an important morbidity and mortality.

- The mathematical models of glucose metabolism are approximations.

- Realistic conditions must be considered during the prediction.
  - Food intake information is estimated and thus uncertain. *Grams of CHO?*
  - The model must consider intra-patient variability: uncertain parameters (intervals). *Insulin Sensitivity?*
  - Initial state of the patient also uncertain. *Current plasma insulin concentration?*

- The Diabetes Control and Complications Trial (DCCT) showed that a suitable intensive insulin therapy achieved blood glucose levels closer to normoglycemia and that this was associated with reduced frequency and severity of blood vessel damage.
Objectives

- To calculate all possible glucose excursions suffered by the patient for a given preprandial glucose measurement, a given insulin dose and considering all uncertainty sources

- To estimate the risk of hyper- and hypoglycemia episodes

- To provide the optimum insulin dosage and injection-to-mealtime with the lowest risk
The Model of the Healthy Subject

Scheme of the glucose-insulin control system which puts in relation the measured plasma glucose and insulin concentrations, glucose and insulin fluxes

(Dalla Man 2007)
The Type 1 Diabetes Model

To simulate a type 1 diabetic subject the insulin secretion module is substituted by a subcutaneous insulin infusion module

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(Dalla Man 2007)
Glucose-Insulin System

- Insulin subcutaneous absorption
- Gastric emptying
- Digestion
- Absorption

- Insulin kinetics

- Glucorregulation

- Plasma glucose

- Insulin type
- Dose
- Injection time

- Quantity
- Nutritional content
- Ingestion time

- Exogenous Insulin flow
- Exogenous Glucose flow
Glucose-Insulin System

Dalla Man et al, TBME, 54(10), 2007
Tarín et al, TBME, 52(12), 2005
Hovorka et al, PM, 25, 2004
Trajanoski et al, BT, 38, 1993
Berger et al, DC, 12, 1989
Glucose-Insulin System

Dalla Man et al, TBME, 54(10), 2007
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Dalla Man et al, TBME, 54(10), 2007
Roy et al, EMBS, 2006
Hovorka et al, PM, 25, 2004
Lehmann et al, JBE, 14, 1992
Glucose-Insulin System

Introduction

Interval models
Risk Index
Insulin dosage

Glucose-Insulin System

Interval simulation

Dalla Man et al, TBME, 54(10), 2007
Tarín et al, TBME, 52(12), 2005
Hovorka et al, PM, 25, 2004
Trajanoski et al, BT, 38, 1993
Berger et al, DC, 12, 1989

Insulin type
Dose
Injection time

Insulin subcutaneous absorption

Exogenous Insulin flow

Insulin kinetics
Glucorregulation

Gastric emptying
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Absorption

Exogenous Glucose flow

Plasma glucose

Dalla Man et al, TBME, 54(10), 2007
Hovorka et al, PM, 25, 2004
Vicini et al, TBME, 46(2), 1999
Parker et al, TBME, 46(2), 1999
Lehmann et al, JBE, 14, 1992
Bergman et al, AJPEM, 236, 1979

Dalla Man et al, Roy et al,
Hovorka et al,
Lehmann et al,
Uncertainty in Gluoregulatory Interval models

- Food intake information is estimated and thus uncertain. *Grams of CHO?*
- The model must consider intra-patient variability: uncertain parameters (intervals). *Insulin Sensitivity?*
- Initial state of the patient also uncertain. *Current plasma insulin concentration?*

Interval model

\[ \dot{x} = f(x, u, p, t) \] uncertain in:

- Parameters \( p \in P = [P, \bar{P}] \).
- Input \( u \in U = [\underline{U}, \bar{U}] \).
- Initial Conditions \( x(0) \in X(0) = [\underline{X}(0), \bar{X}(0)] \).
Interval simulation

Modal Interval analysis (MIA)

- Logical formulas equivalent to interval inclusions
- Logic for envelope calculation

\[ x_{t+1} = f(x_t, p_t, u_t, \Delta t) \]
\[(\forall x_t \in X_t')(\forall p_t \in P')(\forall u_t \in U_0')(\exists x_{t+1} \in X'_{t+1}) x_{t+1} = f(x_t, p_t, u_t, \Delta t) \]
\[
\begin{align*}
\downarrow
\end{align*}
\]

\[ f^*(X_t, P_t, U_t, t) \subseteq X_{t+1} \rightarrow \text{Modal Interval library (IvalDb) or } f^*\text{algorithm} \]
Bergman interval model

\[ I(t + 1) = I(t) - n \Delta t \left( \text{Dual}(I(t)) + I_b \right) + \left( I_{ex} / V_i \right) \Delta t \]

\[ X(t + 1) = X(t) \left( 1 - p_2 \Delta t \right) + p_3 \Delta t \left( I(t) - I_b \right) \]

\[ G(t + 1) = G(t) \left( 1 - p_1 \Delta t \right) - X(t) \left( \text{Dual}(G(t)) + G_b \right) \Delta t + D(t) \Delta t \]

with the constraints:

\[ \Delta t < \min \left( \frac{1}{n}, \frac{1}{p_1 + X(t)} \right) \]

Uncertainty:

- Insulin sensitivity index \( S_i = \frac{p_3}{p_2} \)
- Meal glucose disturbance given by \( D(t) = \frac{F_G}{V_G} \)
Hovorka interval model (1)

\[ Hovorka \ Model = \begin{cases} 
\text{Glucose subsystem} \\
\text{Insulin subsystem} \\
\text{Insulin action subsystem} 
\end{cases} \]

Insulin subsystem: Plasma insulin concentration is described as:

\[ I(t + 1) = \frac{I_{ex}(t)}{V_I} + I(t)(1 - ke) \]

Insulin action subsystem:

\begin{align*}
    x_1(t + 1) &= x_1(t)(1 - k_{a1}) + k_{a1}S_{it}I(t) \\
    x_2(t + 1) &= x_2(t)(1 - k_{a2}) + k_{a2}S_{id}I(t) \\
    x_3(t + 1) &= x_3(t)(1 - k_{a3}) + k_{a3}S_{ie}I(t)
\end{align*}

Uncertainty: Insulin sensitivities \( S_{it}, S_{id} \) and \( S_{ie} \).
Hovorka interval model (2)

Subsystem Glucose:
- Hovorka Model: State variables $Q_1$ and $Q_2$ which represent the masses of glucose in the accessible and non-accessible compartments
- New function in Hovorka Model: State variables $Q_1$ and $S$. Due to $Q_1(t+1)$ and $Q_2(t+1)$ aren’t monotonous with respect to $X_i(j)$ for $j = 0, 1, ..., t$.

Applying coercion theorem the equations of the model are:

$$Q_1(t+1) = (1 - \Delta t(k_{12} + X_1(t)))Q_1(t) - \Delta t(Dual(F_{01}^C(t)) + Dual(F_R(t))) + \Delta t k_{12} S(t) + \Delta t B(t)$$

$$S(t+1) = \Delta t Dual(X_2(t))Q_1(t) - \Delta t(Dual(F_{01}^C(t)) + Dual(F_R(t))) + (1 - \Delta t X_2(t)) S(t) + \Delta t B(t)$$

$$B(t) = U_G(t) + EGP_0(1 - X_3(t))$$

$$G(t) = \frac{Q_1(t)}{V_G}$$

with the constraints:

$$\Delta t < \min \left( \frac{1}{k_{12} + X_1(t) + FC(t)}, \frac{1}{k_{12} + X_2(t)} \right) \quad \text{and} \quad X_2(t) - FC(t) > 0$$

Uncertainty: Amount of carbohydrates digested ($D_G$)
Interval simulation. Uncertainty: 10% $A_G$ and 10% $t_{max,G}$

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>CHO (g)</th>
<th>Basal Insulin</th>
<th>Bolus Insulin</th>
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<td>8:40</td>
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<td>21:30</td>
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(SIMOSI 2007)
Interval Simulation. Variation in insulin sensitivities

- 10% variation in peripheral and hepatic insulin sensitivity
- 10% variation in peripheral and hepatic insulin sensitivity and 8 IU at 12:15 instead of 9 IU
- 20% variation in peripheral and hepatic insulin sensitivity

The model predicts hyperglycemia episodes.

The model predicts a risk of hypoglycaemia for 9IU.

By decreasing in 1IU the bolus dose no risk is predicted.

* 3 days simulated. Envelopes for third day

(EMBC 2007)
**Risk Index**

- Using Modal Interval Analysis (MIA), the upper and lower envelopes of all the possible glucose excursions suffered by the patient for each glucose absorption model are predicted.
- A suitable cost function $J$ which quantifies the safety of the predicted manifold of postprandial glucose responses must be considered.
- The inputs are the upper ($G_{max}$) and lower ($G_{min}$) envelopes of the glucose excursions.
- A normalized area-under-the-curve of the worst-case is obtained.
- The risk index is computed as a weighted sum of the risk for each occurrence of mild and severe hypoglycemia and hyperglycemia event.
Cost Function

\[ J_{Hs} = \frac{\int_{A} \gamma(t) (G_{max}(t) - H_m) \, dt}{H_s - H_m} \]

\[ J_{Hm} = \frac{\int_{B} \gamma(t) (G_{max}(t) - H_m) \, dt}{H_s - H_m} \]

\[ A = \{ G_{max}(t) \geq H_s \} \]

\[ B = \{ H_m \leq G_{max}(t) < H_s \} \]

\[ J := \alpha_{Hs} J_{Hs} + \alpha_{Hm} J_{Hm} + \alpha_{hs} J_{hs} + \alpha_{hm} J_{hm} \]

*Medical support: Hospital Josep Trueta and Hospital de Sant Pau*
Examples of risk indexes for each pre-prandial glucose with different combinations of bolus insulin and mealtime

<table>
<thead>
<tr>
<th>Pre-prandial Glucose (mg/dl)</th>
<th>Risk</th>
<th>Bolus (IU)</th>
<th>Meal (gr)</th>
<th>Meal (min)</th>
<th>Severe Hypoglycemia Index</th>
<th>Mild Hypoglycemia Index</th>
<th>Severe Hyperglycemia Index</th>
<th>Mild Hyperglycemia Index</th>
<th>Total Index</th>
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</table>
Insulin dosage

a Initial dose of bolus insulin 5 IU, initial injection before eating 30 min indicate by a point in grid

b Relationship between bolus insulin and injection-to-meal-time with the low risk index in circle
### Insulin dosage optimization. 11% $S_{IT}$, 8% $S_{ID}$, 2% $S_{IE}$ and 5% $D_{G}$

- Initial: $II=5$ IU, $MI=30$ min, $RI=5.14$
- Optimal: $d_i=6$ IU, $t_{im}=30$ min, $RI=1.95$

The initial and optimal mealtimes are the same; however, the optimization suggests a higher bolus dose of insulin reducing the risk index.

### Insulin dosage optimization. 11% $S_{IT}$, 8% $S_{ID}$, 2% $S_{IE}$ and 5% $D_{G}$

- Initial: $II=5$ IU, $MI=0$ min, $RI=15.48$
- Optimal: $d_i=5$ IU, $t_{im}=-15$ min, $RI=8.98$

The optimal risk index is higher than in the other scenario due to the presence of hypoglycemia episodes. The minimum risk index is obtained injecting 15 minutes after the ingestion, decreasing in this way the time in hypoglycemia resulting from the initial estimation.

*Using interval model Hovorka et al. 2004.*
Conclusions

- MIA has successfully been applied to the prediction of glucose excursions in patients with type 1 diabetes face to uncertain information.
- Considering intra-patient variability and uncertainty in the food intake, a safer prediction of possible hyper- and hypoglycemia episodes induced by the tested insulin therapy can be calculated, leading to a reduction in the number of false-negatives.
- The interval simulation is integrated in a dosage-evaluation system of bolus insulin doses and injection time minimizing the risk of postprandial hyper- and hypoglycemia in patients with type 1 diabetes.
- To apply the methodology presented in this work in a patient-specific scenario, it is necessary to adjust the model to this patient.
- The system is built modularly and can be used with other glucoregulatory model.
Thank you for your attention