Appendix

Description of the MDLAP System

We implemented the MDLAP system using Matlab R2008a (MathWorks Co., Natick, MA, USA). The following sections describe the main elements of the MDLAP system.

i) Pre-Processing

The MDLAP's input parameters are derived from the current glucose level (measured by a subcutaneous continuous glucose sensor [CGS]) and a log which includes all of the glucose levels and the insulin treatment history. The input to the MDLAP system is preprocessed in order to calculate trends in the glucose traces (past and future) and predict the future glucose trace in a given context. For our purposes, the trend of glucose levels is influenced by three factors: (a) the average rate of change in glucose level, measured in milligrams per deciliter per minute, within a certain time frame; (b) the direction of this change (ascending or descending); and (c) the duration of this change. The average rate of change within a certain time frame ($Avg\dot{G}\ t_i$) is calculated with the moving average method to determine the amplitude and the course of the trend. We defined the trend duration factor τ_{TD} as follows:

$$\tau_{TD} = \begin{cases} 1, 0 \le T_{SLTC} \le \tau_1 \\ 2\left(\frac{T_{SLTC} - \tau_1}{\tau_2}\right) + 1, \tau_1 < T_{SLTC} \le \tau_3 \\ 3, T_{SLTC} > \tau_3 \end{cases} \quad (1.1)$$

where T_{SLTC} [min] is the point in time when the glucose level trend changes from descending to ascending or vice versa, and τ_i is a time constant. The trend parameter is defined as a function of $Avg\dot{G}\ t_i$ and τ_{TD}.

The MDLAP prediction tool combines several methods in order to enhance accuracy. These include the auto-regressive model of Sparacino *et al.* (1) and a simple differential predictor which calculates the median rate of change in a certain time frame on the assumption that it will continue within the predefined predicted framework. On the basis of retrospective data, we defined the conditions for each type of predictor.

ii) Control to Range Module

The control to range module (CRM) is a Mamdani-type fuzzy logic controller with four inputs: past and future glucose trend ($\dot{BG}_{Past}$ and $\dot{\tilde{BG}}_{Future}$) as well as current and future glucose level (BG_{Curr} and $\tilde{BG}_{Future}$). The trend parameters include five member functions *(steep descent*, *descent*, *stable*, *ascent*, and *steep ascent)* that were defined over the range of -5 to 5 mg/dl/min. The glucose level parameters include six member functions (*very low*, *low*, *normal*, *normal high*, *high*, and *very high*) that were defined over the physiological range of glucose levels. A set of treatment rules was developed, with two outputs for each rule: (a) change in basal rate (Ba_P) and (b) portion of insulin bolus (B_P) (in percentages from the patient's basal plan and the calculated bolus, respectively). To translate the clinical meaning of the input variables in our fuzzy sets, each membership function for the inputs had to have an interval in which the function's value was “1”, followed by a smooth decrease to “0” outside this interval. Therefore, we selected two-sided Gaussian curve member functions. For the output variables, we selected Gaussian member functions in order to prevent redundancy and to maintain a smooth transition between member functions.

The fuzzy rules were defined in collaboration with the medical staff. The stated goal was to keep the glucose levels stable within a range of 80-120 mg/dl. To

evaluate the rule antecedents (i.e., the IF part of the rules), we used the AND fuzzy operation. The output ("defuzzification") was calculated by the centroid method. The CRM output treatment suggestion was then transferred to the control to target module (CTM).

iii) Control to Target Module

The initial recommendation received from the CRM is in a percentage. To determine the dosing amount of the two outputs in units or units/hour, the CTM considers both the recommendation of the CRM and the predefined glucose target level. Special glucose dynamics analysis is then applied, assuming the dosing regimen history and safety constraints related to the insulin pharmacodynamics, to yield the final dosing recommendation.

The characteristics of the glucose dynamics might be indicative of events that require special treatment (in classic control, this is known as a disturbance). A meal is a good example of an event that might alter the glucose dynamics. A detector in the system is designed to spot such special dynamics and adjust the dosing accordingly.

The CTM uses the history dosing regimes and safety constraints related to the pharmacodynamics of insulin to estimate the amount of on board insulin (in units). The results of Mudaliar et al (2) along with our preliminary study results were used to design a model for the pharmacodynamics of insulin aspart. We developed the following formula for the estimation of insulin on board:

$$f_{I/G}(t)[\%] = \begin{cases} 1 & t \le t_1 \\ P_2 & t_1 < t \le t_2 \\ \dfrac{P_3 \ t - t_3}{t_3 - t_2} & t_2 < t \le t_3 \\ 0 & t_3 < t \end{cases} \qquad (1.2)$$

where $P_{2\text{-}3}[\%]$ and $t_{1\text{-}3}[min]$ are taken from the patient treatment profile. Assuming K dosing incidents in the history log, the overall insulin on board I_{active} at t_0 is calculated using:

$$I_{active}[units] = \sum_{i=1}^{K} I[t_i] \cdot f_I(t_0 - t_i) \quad (1.3)$$

where, $I[t_i]$ is the insulin dosing (in units) at time t_i, and $f_i(t)$ is defined according to formula (1.2). The I_{active} is subtracted from the initial dosing recommendation to prevent overdosing.

Reference

1. Sparacino G, Zanderigo F, Corazza S, Maran A, Facchinetti A, Cobelli C: Glucose concentration can be predicted ahead in time from continuous glucose monitoring sensor time-series. *IEEE Trans Biomed Eng* 54:931-937, 2007

2. Mudaliar S, Lindberg F, Joyce M, Beerdsen P, Strange P, Lin A, Henry R: Insulin aspart (B28 asp-insulin): a fast-acting analog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. *Diabetes Care* 22:1501-1506, 1999