MODELLING GLYCAEMIA IN ICU PATIENTS
A Dynamic Bayesian Network Approach

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Abstract: Presented in this paper is a Dynamic Bayesian Network (DBN) approach to predict glycaemia levels in intensive care patients. The occurrence of hyperglycaemia is associated with increased morbidity and mortality in critically ill patients. Due to the large inter-patient and intra-patient variability, the sparse nature of observations, inaccuracies in the data and the large number of factors that influence glycaemia, the system being modelled contains several sources of uncertainty. In the context of this uncertainty, the DBN-based system presented here performs extremely well. By using a DBN we integrate multiple strands of temporal evidence, arriving at varying time intervals, to determine the most probable underlying explanations. A key contribution of this work is that it presents a principled technique for recalibration of model parameters from general population-level values to patient-specific values, based entirely on standard real-time measurements from the patient. While in this paper we apply our approach to the glycaemia problem, this approach is equally applicable to other applications where unseen variables must be assessed and individualized in real time.

1 INTRODUCTION

Proper control of glycaemia (i.e., serum glucose levels) in critically ill patients in the intensive care unit (ICU) is a subject that is of great importance to physicians. Tight control of serum glucose levels has previously been demonstrated to improve outcome in a predominantly surgical population of critically ill patients (Van den Berghe et al. 2001). In contrast, the recent NICE-SUGAR study found that attempting to keep serum glucose levels within a tight range actually increases mortality rates (The NICE-SUGAR Study Investigators 2009). Therefore, the optimal target range for blood glucose and the optimal approach to controlling blood glucose levels in critically ill patients is still unclear.

The goal of this work is to develop a system that accurately predicts the glycaemia levels of a patient receiving insulin and glucose infusions. This would provide physicians with more accurate real-time estimates of glycaemia levels, which in turn would be useful in determining the optimal dosage for a given patient, through modelling the most likely effects of planned dosages.

To achieve this goal, we develop a Dynamic Bayesian Network (DBN) model that is derived from an existing differential equation model of glycaemia in ICU patients (see Section 2.1). By recasting it as a DBN, we provide a framework for computing solutions with continuous re-estimation of parameters, taking account of dependencies between variables and conditional distributions on them. In this way, it interprets the system as being a set of stochastic differential equations (SDEs). Unlike the original system of differential equations, in the DBN model all of the model terms are allowed to vary, and accordingly are automatically recalibrated to patient-specific values over time.

At a more general level, this paper introduces a method for mapping a system of differential

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equations directly to a DBN, so that they can be solved in a way that allows all model terms to vary, while directly incorporating both continuous and sporadic temporal evidence in the solutions.

1.1 Hyperglycaemia in an ICU Patient

Hyperglycaemia in non-diabetic patients is a common phenomenon in an ICU setting (Van den Berghe et al. 2001). The standard practice is to control a patient's glucose levels using glucose and insulin infusions. Each patient reacts differently to these insulin infusions depending on the nature of their illness, their insulin sensitivity and other medication they may be receiving. As well as inter-patient variability, there is intra-patient variability. A patient's condition and medication intake vary considerably while in the ICU, and hence so does the response to insulin.

To assess a patient's response to insulin, glucose levels are typically measured at intervals of between one and four hours in an ICU ward. When one considers that the half-life of insulin is only a few minutes, a lot can happen in a four hour interval. However, this is the only quantitative evidence available to physicians. From this sparse data, a physician must prescribe an appropriate dosage regime.

Another consideration is the quality of the data. There may be inaccuracies in the recorded dosage quantities and the time stamps on these records. Plasma glucose measurements are not always precise: depending on the method used error levels vary from 3% -12% (Chase et al. 2006).

1.2 Why use a DBN?

The challenge when building a model to predict an ICU patient's insulin/glucose dynamics reflects the challenge facing a physician trying to keep a patient's glucose levels within safe limits. Given the large inter-patient and intra-patient variability, the large number of factors that influence glucose levels and very sparse evidence, creating an accurate model is difficult.

Our objective in this work is to build a model capable of reasoning in the context of this uncertainty. However, as well as dealing with uncertainty, the temporal nature of the problem must also be addressed. A patient's glucose level depends not only on the current I.V. (intravenous) infusion rates but also past infusion rates and past glucose levels. Dynamic Bayesian Networks are an effective tool for modelling uncertainty in real time in a time-varying environment as was shown by Aleks et al. (2008). That paper describes an early application of full DBNs to analysing ICU data, and demonstrated very accurate detection and removal of artefacts in the arterial-line blood pressure sensor data.

Other DBN applications in the medical setting have used only discrete variables. The applications include a network to diagnose ventilator-associated pneumonia in ICU Patients (Charitos et al. 2009) and a prognostic model for carcinoid patients (van Gerven et al. 2008). In the separate, but related topic, of simulating human physiology, Abkai & Hesser (2009) recognised the need to use deterministic and probabilistic models. However unlike our approach, they separate ordinary differential equation solvers and DBN models.

It is assumed that readers are already familiar with Dynamic Bayesian Networks. They are described in a number of Artificial Intelligence textbooks, for example Russell & Norvig (2002).

2 A GLYCAEMIA MODEL

2.1 A Basic Mathematical Model of the Glucose/Insulin Dynamics

The first step in building the DBN model is to establish a relationship between the administered glucose and insulin and the resulting plasma levels. The ICU-Minimal Model (ICU-MM) developed by Van Herpe et al. (2007) is a mathematical model of this relationship. It is an adaptation of Bergman's Minimal Model (Bergman et al. 1981) specifically for ICU patients. The ICU-MM is described by a system of four differential equations:

$$dG(t)/dt = (P_1 - X(t))G(t) - P_1 G_b + F_G/V_G \quad (1a)$$

$$dX(t)/dt = P_2 X(t) + P_3(I_1(t) - I_b) \quad (1b)$$

$$dI_1(t)/dt = \alpha \max(0, I_2(t)) - n(I_1(t) - I_b) + F_I/V_I \quad (1c)$$

$$dI_2(t)/dt = \beta\gamma(G(t) - h) - nI_2(t) \quad (1d)$$

The terms are briefly explained in Appendix 1. However, for a detailed explanation of the model, please refer to Van Herpe et al. (2007).

Other models exist for describing the glucose/insulin interaction in critically ill patients. Chase et al. (2006) reviewed three different metabolic models used in critical care glycaemia control. Since then, other models have been proposed (Lin et al. 2008) (Hovorka et al. 2008).

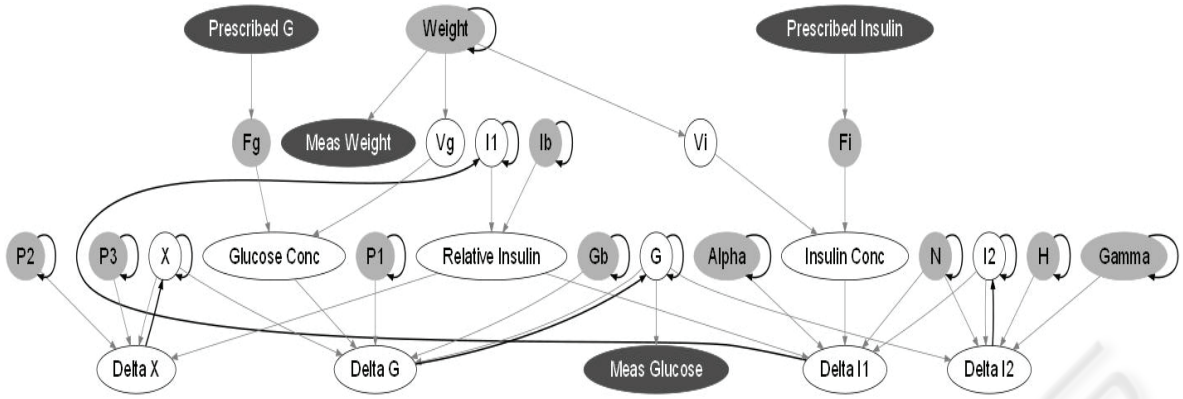

Figure 1: A Dynamic Bayesian Network for Glycaemia in ICU Patients. Grey nodes are conditionally Gaussian and vary over time. White nodes are deterministic and black nodes are observed. Grey arrows connect nodes within a time slice; black arrows connect nodes between time slices.

Both these models are of interest. The ICU-MM however is based on Bergman's Minimal Model. Bergman's model is the most well-known and well-understood model that exists of glucose metabolism. Indeed, Bergman's Minimal Model has previously been re-worked into a Bayesian graphical model (Anderson and Højbjerre 2003). Their approach is, however, significantly different to ours. They first derive a system of SDEs from the Minimal Model and then specify the SDEs as a DBN. As will be explained in Section 2.2, our approach does not require such transformation of a system of differential equations prior to constructing the DBN. It should also be noted that the Minimal Model is less complex than the ICU-MM. It was developed to assist in the diagnoses of diabetes and not for use in the ICU setting.

2.2 The DBN Model

A DBN is made up of a series of discrete time slices. In our model we use a one-minute time interval. Figure 1 shows one time slice of the DBN constructed based on the ICU-MM. Grey arrows connect nodes within a time slice; black arrows connect nodes from the previous time slice to the current time slice.

The DBN contains both observed and hidden variables. Given the history of observations up to the current time, the DBN can compute a probability distribution over the values of any or all of the hidden variables: past, present, or future. Observed nodes are coloured black in Figure 1. In our case, the prescribed insulin and glucose infusion rates and the measured weight of the patient are observed, and can be viewed as inputs to the DBN. The intermittent plasma glucose level measurements are also observed. These glucose observations ground the DBN in reality, so that the inferred values for the hidden variables are specific to the patient and take into account all of the measurements made. We are specifically interested in inferring current and future glucose levels, even when the most recent measurement may have been several hours in the past. By setting the values of nodes that correspond to hypothetical future actions and asking the DBN to predict future glucose levels for the patient, we can also evaluate and select among possible treatments.

The quantitative aspect of the DBN model consists of a conditional distribution for each node conditioned on its parents' values. In this system, a node is either deterministic (i.e. its value can be determined exactly from its parent values) or Gaussian (i.e. the conditional distribution is a Gaussian whose mean is a linear function of its parents' values). Gaussian nodes are shaded grey in Figure 1; deterministic nodes are clear with a black outline.

The observed value for plasma glucose (*Meas. Glucose* in the DBN) is assumed to contain a certain amount of measurement error. It is therefore modelled with a Gaussian distribution whose mean is its parent node, the true plasma glucose level, *G*. Likewise, the data from the ICU reflects the prescribed I.V. infusion rates for insulin and glucose; the actual administered rates may be different. Therefore we model the actual rates with Gaussian distributions whose means are the prescribed rates.

In many cases truncated Gaussian distributions are used, in order to constrain the DBN to postulate values that are not unrealistic for nodes. For example, the true I.V. infusion rate for insulin (F_i) cannot be a negative value, only positive values are

possible. The mean, standard deviation values and limits used for the Gaussian nodes are detailed in Appendix 2.

Similar limits were also placed on some deterministic nodes. For example, it is not possible to have a negative quantity of glucose in plasma, so a limit is placed on node *G* to reflect this.

In the DBN, all terms of the ICU-MM can vary over time as a patient's insulin sensitivity changes. Even terms that are fixed parameters in the original ICU-MM model are allowed to vary in the DBN.

The *delta* nodes capture changes in quantities over time. These changes are calculated using the differential equations of the ICU-MM. Each *delta* node has, as parent nodes, the various terms needed to solve the appropriate differential equation.

To illustrate this, Figure 2 shows a section of the DBN that is related to Eq. (1a) of the ICU-MM. Here, the *Delta G* node determines the per-minute change in plasma glucose levels. The current plasma glucose level is determined based on the glucose level and *Delta G* calculated in the previous time slice. Each of the terms in the differential equation for *G* is represented as a parent node of *Delta G*.

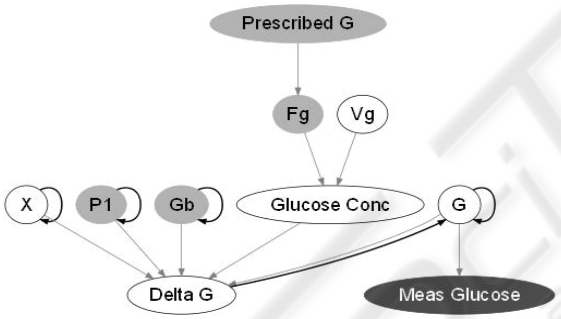

Figure 2: Section of DBN for predicting plasma glucose levels.

We used in-house software for building the DBN and for performing inference using particle filtering. Particle filtering is the means by which we determine the most probable states of the DBN nodes. We performed preliminary sensitivity analyses to determine that, for this DBN, using 50,000 particles gave an acceptable balance between execution time and accuracy.

2.3 Data Selection

In testing our model, we used data from real patients in the ICU of University Hospital Galway. Permission for extracting this data was given by the Galway Research Ethics Committee, UHG. All records were anonymised and stored on encrypted drives.

For this research, data from patients with the following characteristics was selected:

- Sepsis as a primary diagnosis
- Non-diabetic
- Not receiving steroids
- No major organ failure

In the next section, the results for one sample patient are presented.

2.4 DBN Glycaemia Prediction for a Sample Patient

Patient 23 was an ICU patient with acute pancreatitis who was administered N6 OliClinomel 900 E (glucose) and Actrapid (human soluble insulin) intravenously. As was explained in Section 2.2, the actual infusion rates are modelled as Gaussian distributions whose means are the prescribed infusion rates. The standard deviations on the nodes for the actual infusion rates, F_i and F_g, represent the expected error in the records. It was assumed that the records for the prescribed infusion rates were reasonably accurate therefore the standard deviations on the nodes F_i and F_g were set to relatively small values. The prescribed infusion rates are shown in Figure 3.

In the ICU, plasma glucose levels are measured at frequencies of between one and four hours. The square markers (coloured red) in Figure 4 show these measured glucose levels. These values are used as observations by the DBN to ground it in reality.

As can be seen in Figure 4, the observations for plasma glucose are intermittent; the DBN therefore makes internal predictions of plasma glucose levels in between observations. The accuracy of the predictions can be evaluated by comparing the predicted value at the time of a measurement to the actual value. In Figure 4, the dark blue lines are the mean values inferred by the DBN at each minute, and the lighter blue shaded areas show the standard deviations of inferred values, thereby giving a sense of the uncertainty associated with its predictions over time.

One can observe that the mean value often jumps when a new observation becomes available. There are factors which are unknown to the model that influence plasma glucose levels. Because of these unknown factors, the mean values predicted by the model can drift from reality in between observations. Once a new observation is available, the model realigns itself with reality. Although the

figures do not show it, the DBN can compute the distribution over past glucose levels given all previous and subsequent measurements; this "smoothed" estimate does not have jumps in the estimated value.

It is informative to consider the way that the standard deviations vary over time. Because the DBN always assumes some variability of values over time, and because actual observations of plasma glucose levels are available very intermittently (once every few hours), as the time from the last observation increases, so too does the range of possible values. Therefore the uncertainty of the predictions also increases. As uncertainty increases, the mean values also drift. This is why the standard deviations on the inferred plasma glucose grow between observations. Whenever an observation is provided, its plasma glucose prediction realigns to the actual level, and its uncertainty collapses.

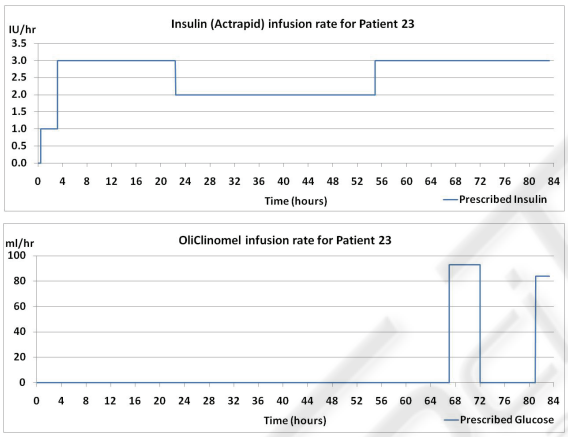

Figure 3: The prescribed infusion rates used as inputs to the DBN.

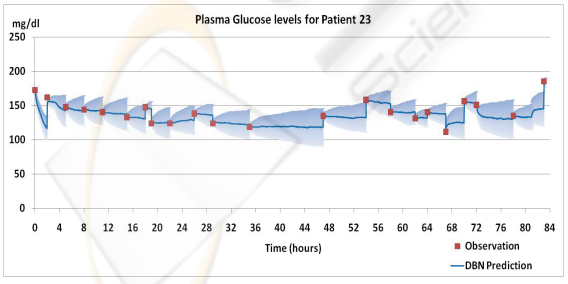

Figure 4: Glucose Levels inferred from the DBN.

It is interesting to observe the model terms to see how they vary over time. Take for example, the values inferred for h shown in Figure 5. Here, h represents the glucose threshold. When this threshold is reached, the body produces endogenous insulin. The model starts with a population average but quickly adjusts to a patient-specific value within the first 4 hours. Once the node adjusts to the patient-specific value, h does not vary to such a large degree.

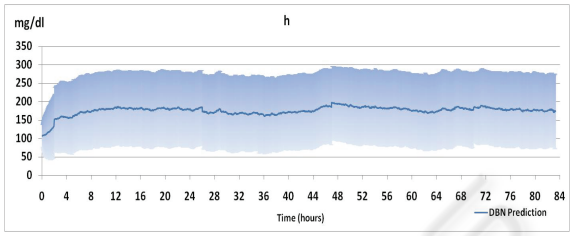

Figure 5: Values for h inferred by the DBN.

In contrast with this, other terms vary considerably over time. P_3 for example, shown in Figure 6, continues to rise over time. This variation reflects the changing condition of the patient and the possible effect of other medical interventions.

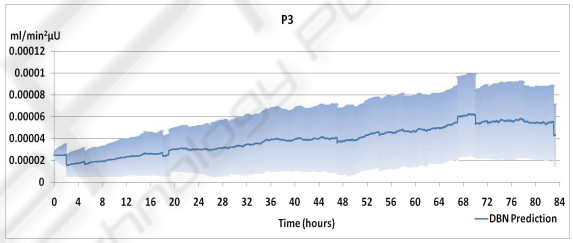

Figure 6: Values for P3 inferred by the DBN.

3 DISCUSSION

One of the difficulties with the mathematical model, on which the DBN is based, is that not only do the model terms vary quite considerably between patients, there is also a large intra-patient variability over time. In Figure 7 we compare the results for the DBN with those obtained by using just the differential equation model (1a)-(1d). For the latter, shown in the lower dashed line (coloured green), computed solutions were obtained by using the standard Euler's method (e.g., Iserles 2009). The DBN and the differential equation solutions both use the same initial values. Both use the I.V. infusion rates for glucose and insulin as inputs. Only the DBN considers the actual measured plasma glucose values. As can be seen, the solution to the differential equations on their own does not succeed in tracking the plasma glucose levels over time, since it does not include a mechanism to recalibrate to the measured values. By contrast the DBN performs reasonably well, because the DBN

considers real-time observations of the true state and because the DBN allows the model terms adjust to patient-specific values in each time step, so that its predictions are much closer to the true state than those of the simple mathematical model.

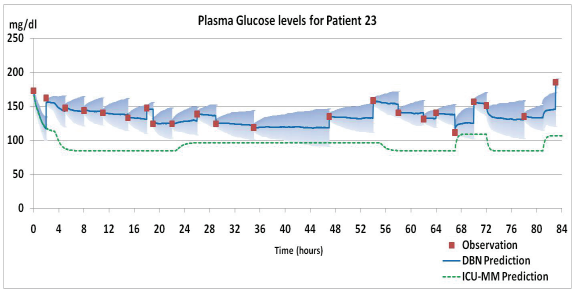

Figure 7: ICU-MM prediction using Euler's method vs. DBN prediction.

It should be noted that in the original implementation of the ICU-MM by Van Herpe et al. (2007), they did not simply use fixed values as was done for the solution of the differential equations in Figure 7. Their strategy for dealing with the large inter-patient and intra-patient variability was to choose patient-specific terms to fit the data offline, after analysing 24 hours of data for each patient, and then re-estimating these parameters every hour or every 4 hours.

Our DBN-based system uses quite a different approach for recalibration of model parameters from general values to patient-specific values. We select Gaussian distributions, suited to the cohort of patients in our dataset, as starting values for the model, and the DBN then adjusts these terms in each time-slice to find the best fit for the specific patient, given all the evidence up to that point. Often the first 24 hours in the ICU are the most critical and also the most unstable. Having a model that is calibrated to the patient in the first 24 hours is of clinical value.

Despite the large variance of the initial parameter estimates, the sparsity of the evidence, the prevalence of uncertainty in the model, and the omission of several factors from the model, the DBN performs remarkably well. For example, the predicted values for the hidden *Plasma Insulin* variable, shown in Figure 8, are strongly correlated with the prescribed insulin infusion rates as one would expect.

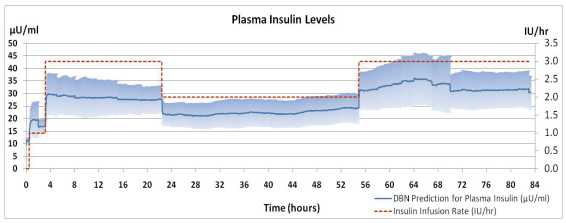

Figure 8: Plasma insulin levels inferred by the DBN are strongly correlated with the prescribed insulin infusion rates.

The underlying mathematical model is relatively simple. It does not fully describe the complexity of the system being modelled. The only inputs to the DBN model are the I.V. infusion rates and the patient's weight. Plasma glucose levels are the only sources of evidence available to help align the DBN to reality. This evidence is both sparse and intermittent. The dynamics of the system being modelled are constantly changing as the patient's insulin sensitivity changes. But by allowing the model terms to vary, the DBN can anticipate these changes, even though they are unobserved. The light blue shaded areas in Figure 4 show the range of possible values for plasma glucose predicted by the DBN. New observations are generally within this range.

4 FUTURE DIRECTIONS AND CONCLUSIONS

4.1 Future Directions

The DBN model presented in this paper is a relatively basic model. There are many factors that influence how a patient reacts to insulin and glucose infusions. These include the reason for which the patient was admitted to the ICU. For example, a patient with sepsis is more likely to have hyperglycaemia than a patient who was admitted following cardiac surgery (Chase et al. 2006). Then there are interactions with other medications. For example, steroids can reduce a patient's insulin sensitivity. Future models will incorporate these important factors that influence a patient's response to insulin.

The current model assumes that all glucose is administered intravenously. Many ICU patients are fed enterally. Gut absorption of glucose must be included if this model is to be of use in a clinical setting.

With these factors in mind we hope to work on new systems of differential equations to model the physical phenomena and also novel techniques to solve these numerically. This work will enable a comprehensive comparison of this DBN approach to numerical simulations.

Future work will also include additional validation of the model. We would like to validate the model on a larger number of patients and compare our methodology to other approaches.

4.2 Concluding Remarks

The system that has been presented in this paper, which uses a Dynamic Bayesian Network approach to modelling glycaemia in critically ill patients, shows great promise. The system performs extremely well in the context of great uncertainty, sparse observations and limited system knowledge.

Our approach demonstrates a principled technique for using standard real-time measurements from ICU patients, to recalibrate model parameters from general values to patient-specific values. This model has the potential to be used by physicians to individualise insulin dosage or to be incorporated into a control system to automate insulin delivery.

The approach demonstrated here is applicable to other applications where unseen variables must be assessed and individualized in real-time.

Finally, the methodology introduced in this paper, for mapping a system of differential equations directly to a DBN, can be applied to other systems of differential equations where all model terms vary, and both continuous and sporadic temporal evidence must be incorporated for an accurate solution.

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APPENDIX 1: THE ICU-MM

Van Herpe et al. (2007) define the model terms as:

G: Glucose concentration in blood plasma.

I_1: The insulin concentration in blood plasma.

X: The effect of insulin on net glucose disappearance. X is proportional to the insulin in the remote compartment.

I_2: The remote insulin. This variable does not have a strictly defined clinical interpretation but can be approached by the fraction of insulin concentration derived from the endogenous insulin secretion.

G_b: The basal value of plasma glucose.

I_b: The basal value of plasma insulin.

F_I and F_G: The intravenous rate of insulin and glucose are the two input variable to the model.

V_G: The glucose distribution space.

V_I: The insulin distribution volume.

P_1: The glucose effectiveness (i.e. the fractional clearance of glucose) when insulin remains at basal level.

P_2: The fractional rate of net remote insulin disappearance.

P_3: The fractional rate of insulin-dependent increase.

γ: The proportion by which endogenous insulin is released when glycaemia exceeds a threshold.

h: The glucose threshold. When this threshold is reached the endogenous insulin is produced.

n: The time constant for insulin disappearance.

β: An additional model coefficient to keep units correct. $\beta = 1$ min.

α: A scaling factor for the second insulin variable I_2.

APPENDIX 2: NODE VALUES AS USED IN THE DBN

Table 1 below specifies the values set in the DBN for the Gaussian nodes. Initially values were taken from Haverbeke et al. (2008), subsequently G_b, P_1, and P_3 were modified.

Table 1: The means, standard deviations and limits for the Gaussian nodes.

Node	Mean	Standard Deviation		Range
		Sensor Model	Transition Model	
G_b	135 mg/dl	5	1	0+
I_b	10.7 µU/ml	1	0.1	0+
P_1	-0.0371 per min	0.005	0.005	-1:0
P_2	-0.0224 per min	0.002	0.002	-1:0
P_3	2.5E-5 ml/(min^{2}µU)	2.0E-7	1.0E-6	0:1
h	107.4 mg/dl	30	10	0:360
N	0.2623 per min	0.1	0.001	0:1
Alpha	0.35	0.1	0.01	0+
Gamma	1.4001E-4 per min	1.0E-5	1.0E-5	0:1
F_i	Prescribed I	1		0+
F_g	Prescribed G	1		0+
Meas G	G	5		
Meas Weight	Weight	0.1		

The nodes V_g and V_i are modelled as deterministic nodes. Their values are calculated as 1.6*Weight and 120*Weight respectively.