Appendix A - The Imperial College Artificial Pancreas Controller

The Imperial College Artificial Pancreas (ICAP) controller has been previously *in silico* and clinically validated [Herrero 2012, Reddy 2014, Reddy 2015]. The original ICAP controller has as core component a mathematical model of the beta-cell physiology [Pedersen 2010]. In addition, it incorporates an insulin feedback term [Steil 2004] to avoid insulin stacking by compensating for delays associated with subcutaneous insulin delivery. It also includes a low-glucose suspend (LGS) to minimize hypoglycemia.

In this work, an updated version of ICAP is introduced, where the the original pancreatic insulin secretion model [Pedersen 2010] is replaced by a most recent model [Riz 2014]. The motivation for changing such model was it better performance in simulation studies as well as the reduced complexity of the new model which significantly speeds up the computations.

The updated version of the ICAP controller is described by the equation

$$u(t) = SR(t) + SR_b - K_y I_p(t), \qquad (9)$$

where SR is the pancreatic insulin secretion (SR) above basal secretion, SR_b is the basal insulin secretion, and $K_y I_p$ is the insulin feedback term, which is proportional (K_y) to the plasma insulin estimation I_p .

As described in [Riz 2014], the pancreatic insulin secretion (SR) above basal secretion (SR_b) is assumed proportional (m) to the amount X of readily releasable insulin in the beta-cells

$$SR(t) = m\,X(t). \qquad (10)$$

The change in the insulin amount in the ready releasable pool (RRP) X results from the balance between the insulin secretion rate, the provision Y of insulin refilling the readily releasable pool, and recruitment of readily releasable insulin XD

$$\frac{dX(t)}{dt} = -mX(t) + Y(t) + X_D(t), \qquad X(0) = 0, \qquad (11)$$

where X_D is responsible for the first phase of secretion and is assumed to be proportional to the rate of increase of glucose via the constant parameter K_D and expressed as

$$X_D(t) = \begin{cases} K_D \frac{dG(t)}{dt}, & if\ \frac{dG(t)}{dt} > 0; \\ 0, & otherwise \end{cases} \qquad (12)$$

Remark: In the ICAP controller, the conditional statement in Equation (12) regarding the sign of the glucose derivative was eliminated. The rationale behind this modification is that delays in insulin absorption and glucose sensing due to the subcutaneous route make reducing insulin delivery when glucose is dropping desirable in order to minimize hypoglycemia.

The provision Y generates the slower second phase and is controlled by glucose according to the equation

$$\frac{dY(t)}{dt} = -\alpha[Y(t) - \beta(G(t) - G_b)], \qquad Y(0) = 0, \qquad (13)$$

where G_b represents the basal value of glucose, and α and β are parameters.

Parameter β is employed as a personalised tunable gain proportional to the subject's insulin sensitivity factor (ISF) used to overcome inter-subject variability. In particular, the following correlation was employed for this study, $\beta = 0.0225/\mathrm{ISF}$, where IFS is expressed in mg/dl per U.

For simulation purpose, the model was discretized using Euler method with an integration step of one minute. To attenuate the delays associated with subcutaneous glucose sensing [Facchinetti 2014], glucose measurements are forecasted 20 minute ahead using a linear regression of the last 6 glucose values (i.e. the preceding 30 minutes). The basal insulin term (SR_b) is set to the subject's basal insulin infusion profile. To tackle the perturbation introduced by the meals, a meal announcement strategy is used consisting of giving an insulin bolus calculated using a standard bolus calculator [Schmidt 2014] immediately before the ingestion of the meal.

To minimise hypoglycaemia, a low-glucose suspend (LGS) algorithm is incorporated on top of the controller. This LGS algorithm reduces the insulin delivery proposed by the controller

to 50% if the forecasted glucose value falls below a predefined threshold (TH1) and suspends the insulin delivery if it falls below a second lower predefined threshold (TH1). To prevent rebound hyperglycaemia, the insulin suspension is limited to 90 minutes, after which time the insulin delivery is resumed to 50% for 30 minutes and after this period total suspension is activated again if the hypoglycaemic condition is satisfied. It is important to remark that the LGS algorithm does not affect the meal bolus insulin. Figure 2 shows a schematic diagram of the ICAP controller.

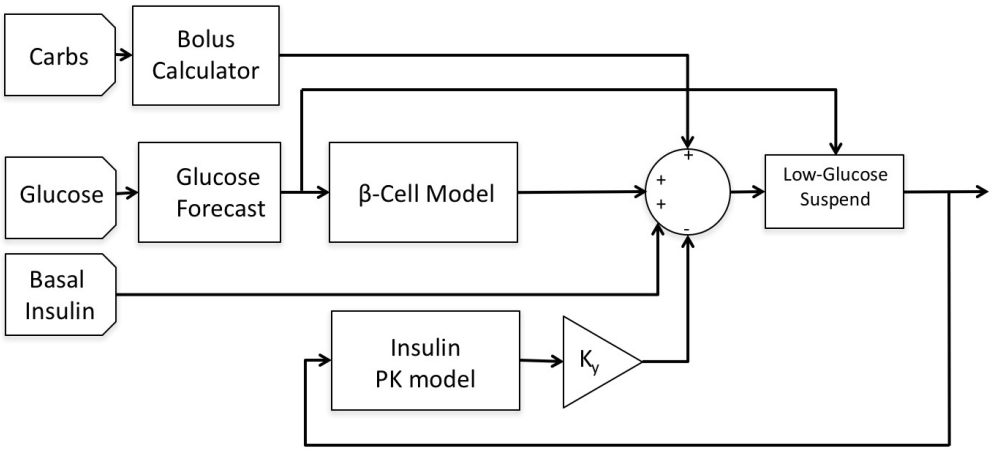

Figure 2. Block diagram of the ICAP controller, where inputs are the amount of ingested carbohydrates, the glucose concentration from a continuous glucose sensor, and the basal insulin rate for a given subject, and the output in the insulin dose to be delivered by the insulin pump.

Table 3 shows the values for the controller parameters employed for the simulation performed in this study. Such parameters where selected based on *in silico* tests. The mean population presented in [Hovorka 2004] were considered for the employed insulin absorption pharmacokinetic (PK) model to estimate plasma insulin concentration (I_p).

Table 3. Values for the parameters employed for the simulation performed in this study

Parameter	**Value**
m	0.5
α	m
β (U per mg/dl)	0.0225/ISF
K_D (min)	β·45
G_b (mg/dl)	117
K_y	50

TH1 (mg/dl)	81
TH2 (mg/dl)	99