**Section 1: Scientific and/or technical quality, relevant to the topics addressed by the call**

*(Maximum length for the whole of Section 1 – twenty pages. This does not include the Gantt chart, Pert diagram or tables 1.3a-e)*

**(...)**

**1.2 Progress beyond the state-of-the-art**

Describe the state-of-the-art in the area concerned, and the advance that the proposed project would bring about. If applicable, refer to the results of any patent search you might have carried out.

**2. Models**

It is often said that “all models are wrong, but some are useful”. Thus, the first step towards the selection or development of models is to set the purpose they are intended for. Broadly speaking, models can be used to deepen understanding on some phenomena, test hypotheses, estimate non-measurable variables, design controllers, etc., all requiring a different degree of complexity and accuracy. Whereas a model to shed light on some physiological process will generally be highly complex addressing gene expression, signal transduction, metabolic pathways, etc., a model for control will essentially capture the main dynamics at the systemic level. Indeed, cardinal principles of physiology like homeostasis, regulation and redundancy are systemic concepts [1]. The balance between model complexity and accuracy will also be imposed by the individualisation needs. Excessively complex models may be difficult to fit to an individual due to the limited data available in a practical domiciliary context, arising structural problems like lack of identifiability. The latter is especially important for the right interpretation of the identified model parameters and gaining predictive power.

This project aims at “the development of a new tool to induce healthier habits and better management of insulin therapy based on the prediction of glycaemic control indicators (e.g. risk of hypoglycaemia) and micro- and macro-vascular complications risk.” This implies the integration of a variety of models to describe:

1. Patient’s lifestyle, as a collection of probabilistic events (exercising, diet, snacking, etc.).
2. Glycaemic control achieved from the current insulin therapy and lifestyle. This requires the use of physiological glucoregulatory models, usually combined with data-driven components, able to predict the risk of hypoglycaemia, A1c levels, etc.
3. The development of micro- and macro-vascular complications, as a combination of physiological and epidemiological models. Interestingly, epidemiological and phenotypic data have provided more insight than genotype for instance in predicting the risk of type II diabetes [2].

Besides, models must be individualised to the patient from data collected through a monitoring system and kept continuously updated to counteract changes in patient’s behaviour. Intra-patient variability must also be accounted for.

In the following, the state-of-the-art on each of the above models is reviewed and the contribution of this project stated. For better readability, models will be classified according to its deterministic or probabilistic nature.

**2.1 Deterministic models**

**2.1.1. Glucoregulatory models**

Prediction of glycaemic control in type 1 diabetes implies the consideration of subcutaneous (s.c.) insulin absorption (for short- and long-acting insulin analogues to cover both Multiple Daily Injections –MDI– and Continuous Subcutaneous Insulin Infusion –CSII–), meal absorption, and the mechanisms of blood glucose regulation.

***S.c. insulin absorption.*** Modelling of s.c. insulin absorption dates back to the 80’s. In 1983, Kobayashi *et al.* published a model based on a one-compartmental delay differential equation for U40 Actrapid insulin [3]. Type 1 and type 2 diabetic patients were studied. No differences were found between CSII and MDI modes of administration, although insulin degradation at the injection/infusion site was observed as compared to intravenous administration. In 1984 Kraegen *et al.* [4] studied normal subject with endogenous insulin suppression proposing a two-compartmental model with degradation, which was quantified low (less that 10%/h). In 1989, Berger and Rodbard proposed a non-compartmental comprehensive model including regular, NPH, lente, and ultralente insulin depending on the model parameterisation [5]. In 1995 Puckett *et al.*[6] addressed modelling of short- and long-acting insulin (regular human insulin and ultralente insulin, respectively) in diabetic subjects following MDI therapy. Insulin degradation is considered as an effectiveness factor. Non-identifiability was addressed by a model re-parameterisation. Large inter- and intra-patient variability was reported. Modelling of U40 insulin lispro (fast-acting analogue) was addressed in [7] for CSII treated type 1 diabetic patients. Influence of the concentration of the insulin formulation for soluble insulin was addressed by Mosekilde *et al.* [8] by means of a partial differential equations model describing insulin dissociation, protein binding, diffusion and absorption. This model was later simplified by Trajanoski *et al.* [9]. Adoption of new insulin formulations (U100) and the development of new analogues opened new challenges in insulin absorption modelling. In 2005, Tarín *et al.* extended Trajanoski model to model the new long-acting analogue insulin glargine [10]. This work was followed by [11] where a new ODE-based model was presented for insulin glargine, lispro and aspart, and

[12], [13] where a comprehensive ODE model for monomeric, regular, NPH, lente, ultralente and glargine insulin was published Model validation was conducted from a meta-study of reported literature data in terms of time-to-peak and peak values for plasma insulin. Work on the artificial pancreas has also driven research on insulin pharmacokinetics modelling with a special focus of fast-acting insulin (lispro). In [14], a comparison of eleven alternative models for insulin lispro kinetics is conducted in seven type 1 diabetic patients, concluding that the best fit is obtained with a model comprising a slow and fast absorption route. However, a simplified two-compartmental model is used by this group in the Cambridge simulator for in silico testing of closed-loop glucose controllers [15], probably due to identifiability problems. A similar two-compartmental model but considering absorption from both compartments is used in the University of Virgina-Padova simulator in the same context [16].

***Meal absorption.*** Modelling of meal absorption has proven challenging due to the complex physiology of gastric emptying and intestinal absorption, with large variability reported [17]. Besides, glucose absorption rate is not directly measurable, unless complex tracer studies are conducted, with doubtful extrapolation to meals not considered in the study. An exponential model for gastric emptying is presented in [18], with emptying rate is made dependent on the volume and calorie density of the meal. The model is fitted from thirty-three studies of gastric emptying. The developed models for glucose absorption rate are carbohydrate-centric, all considering a one-compartmental model for intestinal absorption and differing on gastric emptying. In [19], a trapezoidal function is used to describe gastric emptying as a function of the grams of carbohydrates ingested. A model for Oral Glucose Tolerance Test (glucose load of 75 g) is presented in [20]. Besides the lack of extrapolation to a mixed meal, non-diabetic subjects are studied. However, delayed gastric emptying is frequent in type 1 diabetes [21]. In [22], input-output models are derived considering different absorption rates for monosaccharide, and fast- and slow-absorption polysaccharide. The abovementioned Cambridge simulator incorporates a two-compartmental model for glucose absorption [23]. The University of Virgina-Padova simulator incorporates a three-compartmental model with nonlinear gastric emptying allowing fast and slow absorption phases in carbohydrate emptying emulating the effect of fat. This model was fitted with triple tracer data, although in healthy subjects, with a meal consisting on traced jelly, eggs and bacon [24]. Limitations of meal models can be counteracted with the development of a library of glucose absorption profiles representing different types of mixed meals [25]. To this end, de-convolution methods for the estimation of glucose rate of appearance may be helpful [26].

***Glucose regulation.*** Since the seminal work of Bergman in 1979 for the estimation of insulin sensitivity from an Intravenous Glucose Tolerance Test in conscious dogs [27], several compartmental models have appeared in literature describing the role of insulin in glucose regulation. Unlike Bergman model, a two-compartment description for glucose was proven necessary to better estimate hepatic glucose production [28], where healthy subjects were studied. Although early works considered the role of glucagon [29], [30], current models are mainly insulin centred. Only in the last years interest in glucagon has been regained in the context of the bi-hormonal artificial pancreas [31]. Most accepted models are the ones included in the Cambridge [32] and University of Virgina-Padova [33] simulators. Cambridge simulator considers delayed insulin action on hepatic glucose production, glucose transport and glucose disposal. Time-varying parameters are considered to account for circadian variations and intra-patient variability. The model originated on data from healthy subjects [34]. University of Virgina-Padova simulator considers delayed insulin action on hepatic glucose production and glucose disposal following a Michaelis-Menten dynamics for the latter. Originally a model for healthy and type 2 diabetic patients was presented [33] from triple tracer data. Later, the model was adapted to represent a type 1 diabetic patient eliminating insulin secretion and retuning some parameters [35]. Both simulators have been validated for in silico evaluation of controllers, demonstrating comparable population clinical outcomes in the simulations and actual clinical trials. Additionally, models have appeared in literature addressing the influence of fat [36] and exercise

[37]-[39] in glucose regulation. However, further validation of these models is required.

**2.1.2. Prediction under intra-patient variability**

Large intra-patient variability has been reported in type 1 diabetic patients [6], [17], [40] and it must be accounted for when characterising and predicting patient’s behaviour. A natural way to express this variability is by means of interval-valued model parameters (interval models). Several techniques have been applied for the simulation of interval glucoregulatory models under uncertainty in inputs, parameters and initial state, such as modal interval analysis [41] and monotone systems theory [42]. Compared to Monte Carlo, these techniques are much more computationally efficient independently of the problem dimension. As result, an envelope containing all possible glucose trajectories (according to the model) is obtained. Interval models have been used to optimise insulin MDI therapy [43], compute the risk of postprandial hypo- and hyperglycaemia [44], the development of model-based CSII therapies [45] and fault detection with sensor augmented insulin pumps [46].

**2.1.3. Model individualisation**

Effectiveness of model-based tools depends on the accuracy of the individual model obtained for each patient. Individualization of glucoregulatory models (parameter identification) has been addressed both in data-based models [47]-[49] or physiology-based models [50]. There are two main challenges in model individualisation: error/noise sources in the measurement devices (especially with the use of continuous glucose monitoring devices for ambulatory data acquisition), and uncertainty/variability in the patient’s behaviour. Despite the high variability observed in the clinical practice parametric uncertainty has not generally been included into the identification process, leading to *average* models with poor predictive capabilities. Exceptionally, in [51] the identification of input-output models with interval parameters is considered , presenting an ad-hoc solution. In [52] a method is presented to identify interval physiological glucoregulatory models based on multiobjective identification and interval predictions. The data acquisition protocol and the cost index in the underlying optimization problem can be of great influence for the performance of the patients’ individual models. Several strategies have been proposed for improving the quality of the data acquired for model identification using optimal experiment design

[53], [54], although they are still rather complex for the patients. With regard to the cost index, the suitability of classical metrics such as Mean Square Error for model evaluation has recently been questioned in the context of diabetes [55] where clinical implications of prediction errors must be considered in order to better reduce the risk for patients when decisions are made based on the predictions performed. In this latter work new indices including a penalty based on clinical implications of model inaccuracies are introduced. Real-time state estimation and long-term model adaption are the next logical steps towards model individualisation to keep the models updated from real-time data after an initial identification is carried out [56]. This may allow for the detection of altered states of the patient and supply valuable information for control or decision making algorithms.

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