432n A Closed-Loop Monitoring Strategy for Type 1 Diabetes Patients

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Diabetes mellitus is a disease characterized by insufficient production of insulin by the pancreatic β-cells, leading to prolonged elevated concentrations of blood glucose. In 2000, diabetes was the sixth leading cause of death in the United States, accounting for over 69,000 deaths. The total national economic cost of diabetes in 2002 was estimated at $132 billion, approximately one out of every ten health care dollars spent.

Tight glycemic control is important because sustained high glucose levels (hyperglycemia) are responsible for many long-term diabetes-related complications, while very low glucose levels (hypoglycemia) can present immediate health threats such as insulin shock or even death [1]. Type 1 diabetics, also referred to as insulin-dependent diabetics, rely on exogenous insulin for survival. They typically control their blood sugar levels based on intermittent measurements (e.g., finger sticks) with basal insulin doses complemented by bolus injections administered coincidentally with glucose meals. By contrast, an "artificial pancreas" consisting of an in vivo glucose sensor, implantable insulin pump, and feedback control algorithm to automatically determine insulin delivery rate has the potential to significantly improve glycemic control in diabetic patients.

In order for an artificial pancreas to function in a routine and effective manner, it is essential that the control strategy be very robust and its performance carefully monitored. Clearly, safety issues are of the utmost importance, with safeguards against severe hypoglycemia a critical issue. Potential operating challenges include dealing with missing or erroneous data, sensor or actuator malfunctions, and the variability that is inherent in physiological systems. For example, the effect of insulin on a patient can exhibit changes over a wide range of time scales due to a variety of factors that include stress level, fitness level, time of day (e.g., the so-called "dawn phenomenon" is characterized by insulin resistance), general health, and menstrual cycles.

In this paper, a control system monitoring strategy is proposed and evaluated for type 1 diabetics. However, the proposed monitoring strategy can also be extended to type 2 diabetics. Multivariate statistical techniques such as principal component analysis (PCA) and pattern matching, in which similar patterns are sought in a large database, are used to distinguish between normal and abnormal closed-loop operation for a particular patient. Performance during normal operation, and some known faults, can be determined during the initial commissioning of the artificial pancreas. The database for pattern matching can be augmented with subsequent data for the patient. Also, simulated glucose responses for a wide variety of conditions from a dynamic model or bank of models can provide reasonably accurate descriptions of the current conditions.

The proposed monitoring strategy is evaluated in simulation studies for two different diabetes models and several feedback-feedforward control strategies. The two diabetes models used were a detailed model developed by Hovorka's research group [2] and the "minimal model" of Bergman [3]. Hovorka's model comprises three subsystems representing glucose, subcutaneous and plasma insulin, and insulin action. The glucose subsystem is divided into two compartments, a plasma compartment and a "non-accessible" compartment; the insulin subsystem is partitioned into three compartments and includes the dynamics of subcutaneous-to-intravenous insulin absorption. The insulin action subsystem takes into account the physiological effects of insulin on glucose distribution/transport, removal, and endogenous production. Hovorka's model was simulated using both its original insulin absorption system (OIAS) and updated alternate insulin absorption system (AIAS) [4]. In contrast to the detailed Hovorka model, the minimal model consists of only a few parameters and three differential equations. Although this

minimal model was developed to describe glucose-insulin interactions in non-diabetics, its attractive simplicity has made it the focus of numerous subsequent diabetes-related modeling studies.

To illustrate the potential capability of PCA to monitor diabetes patients and detect abnormal situations (i.e., "faults"), a dataset was simulated consisting of 11 days of data, with six runs representative of normal operation and five of abnormal or faulty operation. Realistic five-minute samples were simulated and saturation limits were imposed on the insulin infusion rate. The input profile consisted of breakfast, lunch, and dinner meal times and magnitudes, which were given reasonable distributions. The profile values for each simulation were generated randomly according to their respective distributions. Three faults were expressed as changes in model parameters, specifically insulin sensitivities. The signs (i.e., positive or negative) of these deviations were chosen arbitrarily, but the magnitudes were chosen on a physiological basis [5]. The other two faults simulated an insulin pump leak and glucose sensor bias. The PCA monitoring results demonstrated that a distinction could be made between normal operation and faults. Fault thresholds were also established and contribution plots used to diagnose the source of the fault.

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