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SYMPOSIUM

In Silico Preclinical Trials: A Proof of Concept in Closed-Loop Control of Type 1 Diabetes

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Abstract

Arguably, a minimally invasive system using subcutaneous (s.c.) continuous glucose monitoring (CGM) and s.c. insulin delivery via insulin pump would be a most feasible step to closed-loop control in type 1 diabetes mellitus (T1DM). Consequently, diabetes technology is focusing on developing an artificial pancreas using control algorithms to link CGM with s.c. insulin delivery. The future development of the artificial pancreas *will* be greatly accelerated by employing mathematical modeling and computer simulation. Realistic computer simulation is capable of providing invaluable information about the safety and the limitations of closed-loop control algorithms, guiding clinical studies, and out-ruling ineffective control scenarios in a cost-effective manner. Thus computer simulation testing of closed-loop control algorithms is regarded as a prerequisite to clinical trials of the artificial pancreas.

In this paper, we present a system for *in silico* testing of control algorithms that has three principal components: (1) a large cohort of $n = 300$ simulated "subjects" ($n = 100$ adults, 100 adolescents, and 100 children) based on real individuals' data and spanning the observed variability of key metabolic parameters in the general population of people with T1DM; (2) a simulator of CGM sensor errors representative of Freestyle Navigator™, Guardian RT, or Dexcom™ STS™, 7-day sensor; and (3) a simulator of discrete s.c. insulin delivery via OmniPod Insulin Management System or Deltec Cozmo® insulin pump.

The system has been shown to represent adequate glucose fluctuations in T1DM observed during meal challenges, and has been accepted by the Food and Drug Administration as a substitute to animal trials in the preclinical testing of closed-loop control strategies.

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Abbreviations: (BG) blood glucose, (CGM) continuous glucose monitoring, (CHO) carbohydrate, (CVGA) control-variability grid analysis, (FDA) Food and Drug Administration, (i.v.) intravenous, (IDE) investigational device exemption, (JDRF)Juvenile Diabetes Research Foundation, (MPC) model-predictive control, (PID) proportional integral derivative, (s.c.) subcutaneous, (T1DM) type 1 diabetes mellitus

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