

UVa/Padova T1DM Metabolic Simulator Simulation Services at The Epsilon Group

The Epsilon Group offers *in silico* simulation services for optimizing, testing and validating novel Type 1 Diabetes treatment strategies to the medical-scientific, pharmaceutical and device technology community.

The UVa/Padova Type 1 Diabetes Mellitus Metabolic Simulator (T1DMS) is a computer model of the human metabolic system based on the glucose-insulin dynamics in human subjects [1-3]. The T1DMS technology provides realistic computer simulation of clinical trials using an *in silico* population of 300 subjects with parameters derived from triple tracer metabolic studies that reflect the human metabolism found with Type 1 Diabetes Mellitus. It has been validated against actual clinical data and is accepted by the FDA as a substitute for pre-clinical animal trials in the testing of certain control strategies for T1DM.

The Epsilon Group collaborates with biopharmaceutical and medical device companies who are actively developing medications and glucose control strategies to treat diabetes. T1DMS simulations can: (i) provide invaluable information about the safety and the limitations of glucose control strategies; (ii) guide and focus the emphasis of clinical studies; and (iii) rule-out ineffective scenarios prior to human use. These simulations can save years and millions of dollars in pre-clinical development and testing.

Simulation results can be used to document safety and support FDA IDE submission for planned hospital-based/CRC clinical study. To date, five (5) IDEs have been granted by the FDA based on *in silico* simulation studies performed by The Epsilon Group employing the UVA/Padova T1DM Metabolic Simulator.

Representative Simulation Services

Integration of medical devices *in silico*

- Modeling of insulin sensors and insulin pumps to match the unique properties of medical devices and implementation into the T1DM Simulator for use in simulations
- *In silico* testing of point of care medical devices under clinical scenarios

The T1DM Metabolic Simulator has been used extensively for development of the Artificial Pancreas System among members of the JDRF Artificial Pancreas Consortium. Several standardized pumps and sensors are implemented in the model, and commercial devices have been implemented for optimization and testing. Additionally performance under various clinical scenarios can demonstrate safety and efficacy under real-life conditions prior to testing in humans with T1DM.

Integration of Insulin-Dosing Algorithms

- Integration and implementation of insulin-dosing control algorithms into the T1DM Simulator for use in simulations
- *In silico* testing of control algorithms under clinical scenarios that can be used in early-stage clinical trials

The T1DM Metabolic Simulator can test performance of control algorithms in a test population and a population of larger sample size and range of variability.

Implement Closed-Loop Control Treatment Protocols testing the system under real-life situations

- Subject-specific basal dosing
- “Manual” Meal Bolus
 - ❖ Timing of bolus injection with respect to meal time
 - ❖ Optimal/Over-Bolus/Under-Bolus variability to simulate real world situations
 - ❖ Missed Meal Bolus
- Meal Amounts
 - ❖ Total grams CHO/CHO per Kg body weight
 - ❖ Minimum/maximum meal amounts may vary at each meal
- Inclusion of temporary insulin-resistance
- Inclusion of exercise component as it affects insulin sensitivity
 - ❖ Include an exercise period during the simulation
- “Manual” correction boluses (variable dosing & timing)
- “Rescue Carbohydrates” in response to hypoglycemia under “person in the loop” control

Implement Treatment Protocols to design proposed clinical studies

- Provide *in silico* simulations and results data for proposed clinical study
- Provide analyses and graphics as outlined by the FDA guidance for *in silico* studies

In Silico Populations

Several *in silico* populations are available for in-depth testing of optional treatments

Available in the software:

- N=30 Test Population
 - ❖ 10 Adolescents
 - ❖ 10 Adults
 - ❖ 10 Children

Available through simulation services:

- N=300 Test Population
 - ❖ 100 Adolescents
 - ❖ 100 Adults
 - ❖ 100 Children
- N=300 “FDA Accepted” Population
 - ❖ 100 Adolescents
 - ❖ 100 Adults
 - ❖ 100 Children

Detailed Data Analysis

- Safety and efficacy endpoints to demonstrate performance across the *in silico* population
 - ❖ Mean BG
 - ❖ % time in extreme hypoglycemia (BG<50 mg/dL)
 - ❖ % of time and incidence below range (any BG < 70 mg/dL)
 - ❖ % time within the 70-180 mg/dL target range
 - ❖ % of time above range in hyperglycemia (BG > 180 mg/dL)
 - ❖ % of time in extreme hyperglycemia (BG > 300 mg/dL)
 - ❖ Low Blood Glucose Risk Index (LBGI)
 - ❖ High Blood Glucose Risk Index (HBGI)
 - ❖ BGRisk Index (BGRi)

- Control Variability Grid Analysis (CVGA) figures with each subject represented by one data point
- Number of subjects experiencing episodes (including duration and severity) of extreme hypoglycemia, hypoglycemia, hyperglycemia, extreme hyperglycemia and total number of events per population.
- Insulin pump and sensor error analysis
- Device accuracy analysis, Clarke error Grid Analysis for continuous and interval measurement devices.

Graphical Representations (per subject)

- Blood Glucose Trace Graphs
- Analysis graphs tailored to specific testing representation

Reports

- Detailed reporting, analysis and comparison of control strategies
- A comprehensive report for the *in silico* testing of the controls that can be included in IDE submissions to the FDA

Raw Data

- Raw data from simulations can be provided for client review and in-house analysis; Data points are available for each simulated minute unless data interval is modified.
 - Blood Glucose (mg/dL), Glucose Sensor (CGM and/or SMBG) Readings (mg/dL), Manual/Pump Insulin Bolus Doses (manual & algorithm controlled), Basal Insulin dosing, Insulin Pump delivery

FDA Submissions and Proposed Clinical Studies

- Provide *in silico* simulations and results data for protocols identical to a proposed clinical study using the “FDA Accepted” population
- Provide analyses and graphics as outlined by the FDA for submission of IDE’s to the FDA

Expert Consultants

The Epsilon Group retains consultancies to support access and ongoing collaboration with the primary scientists and engineers who contributed to the creation of the model:

- Claudio Cobelli, PhD and Chiara Dalla Man, PhD, University of Padova, Padova, Italy
- Stephan Patek, PhD, Marc Breton, PhD, and Boris Kovatchev, PhD, University of Virginia, Charlottesville, Virginia, USA
- Francis Doyle III, PhD, Howard Zisser, MD, and Eyal Dassau, PhD, University of California, Santa Barbara, California, USA
- Lalo Magni, PhD, University Di Pavia, Pavia, Italy

References

1. Chiarra Dalla Man, Robert A. Rizza, and Claudio Cobelli Meal Simulation Model of the Glucose-Insulin System *IEEE Transactions of Biomedical Engineering*, 2007 54(10): 1740-1749
2. Dalla Man C, Camilleri M, Cobelli C. A system model of oral glucose absorption: validation on gold standard data. *IEEE Trans Biomed Eng.* 2006 53(12): 2472-2478.

3. Marc Breton, Ph.D. and Boris Kovatchev, Ph.D. Analysis, Modeling, and Simulation of the Accuracy of Continuous Glucose Sensors J Diabetes Sci Technol 2008; 2(5): 853-862
4. Boris P. Kovatchev, Ph.D., Marc D. Breton, Ph.D., Chiarra Dalla Man, Ph.D., and Claudio Cobelli, Ph.D. In Silico Preclinical Trials: A Proof of Concept in Closed-Loop Control of Type 1 Diabetes J. Diabetes Sci Technol 2009 3(1): 44-45
5. Stephen D. Patek, PhD., Wayne Bequette, PhD., Marc Breton, PhD., Bruce A. Buckingham, M.D., Eyal Dassau, PhD., Francis J. Doyle III, PhD., John Lum, Lalo Magni, PhD., and Howard Zisser, M.D. In Silico Preclinical Trials: Methodology and Engineering Guide to Closed-Loop Control in Type I Diabetes Mellitus J. Diabetes Sci Technol 2009 3(2): 269-282.
6. William Clarke, M.D. and Boris P. Kovatchev, Ph.D. Statistical Tools to Analyze Continuous Glucose Monitor Data Diabetes Technol Ther. 2009 11(S1): S45-S54
7. Lalo Magni, Ph.D., Davide M. Raimondo, M.S., Chiarra Dalla Man, Ph.D., Marc Breton, Ph.D., Steven Patek, Ph.D., Guissepe De Nicolao, Ph.D., Claudio Cobelli, Ph.D., and Boris P. Kovatchev, Ph.D. Evaluating the Efficacy of Closed-Loop Glucose Regulation via Control-Variability Grid Analysis J. Diabetes Sci Technol 2008 2(4): 630-635.
8. Eyal Dassau, Ph.D., Howard Zisser, M.D., Cesar C. Palerm, Ph.D., Bruce A. Buckingham, M.D., Lois Jovanovič, M.D., and Francis J. Doyle III, Ph.D. Modular Artificial B-Cell System: A Prototype for Clinical Research J. Diabetes Sci Technol 2008 2(5): 863-872.