THE EPSILON GROUP
Driven by Modeling

UVa/Padova

T1DMS

Type 1 Diabetes Metabolic Simulator

v3.2

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References and Acknowledgements

The T1DMS Type 1 Diabetes Mellitus Metabolic Simulator referenced herein is the 'Distributed Version' of the ***UVa/Padova Type 1 Diabetes Mellitus Metabolic Simulator***. The following references cover some of the scientific literature describing the development of the T1DMS.

References

1. Chiara 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., Chiara 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., Chiara 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. Chiara Dalla Man, Ph.D., Francesco Micheletto, Ph.D., Dayu Lv, Ph.D., Marc Breton, Ph.D., Boris Kovatchev, Ph.D., and Claudio Cobelli, Ph.D. The UVA/PADOVA Type 1 Diabetes Simulator: New Features J. Diabetes Sci Technol 2014 8(1): 26-34.
9. Dayu Lv, Ph.D., Marc D. Breton, Ph.D., and Leon S. Farhy, Ph.D. Pharmacokinetics Modeling of Exogenous Glucagon in Type 1 Diabetes Mellitus Patients Diabetes Technol Ther. 2013 15(11): 935-941.

Sample Scenario.scn and ctrlsetup.m Files

Annotated Scenario.scn

```
An ANNOTATED Scenario File
Note: "*" Indicates default values
Note: "%" Required for variables to be read, NOT => comment
File Name will be available in sim_results.mat data.scenario file

TIME_of_Simulation_Information
Tsimul     Model Run Time – in QTsimul units
%Tsimul=1440
QTsimul    Tsimul Units – min*, hour, day
%QTsimul=min
simToD     Time of Day at start of sim – 0* in minutes after midnight
%simToD=0

Initial Blood Glucose Value in mg/dl
BGinit not specified* =>subject specific fasting or Specify in mg/dl
Such as this example: %BGinit=[100]

MEALS INFO _ Timing, Amount Carbs in total or perkg, Duration of meals
Tmeals     Time of Meals VECTOR in time after start of simulation
%Tmeals=[[8 12 19 23]
QTmeals    Tmeals unit – min*, hour, day
%QTmeals=hour
Meal_Amounts VECTOR matching_Tmeals_CHO in Total grams or g/KG BW
%Ameals=[40 60 80 10]
DURATION of meals_Fixed* minutes(15*) or Dmeals VECTOR to match Tmeals
%Dmeals=[15]
Qmeals is Ameals Unit_total g cho or g/Kg body weight =total* or perkg
%Qmeals=total

START CLOSED LOOP TREATMENT
Time after start of sim in QTclosed units – min*, hour, day
%Tclosed=0
%QTclosed=hour

START REGULATION _Time past start of the simulation in minutes
REGULATION => data is included in analysis calcs of results data
Built-in Data Analysis
%Treg=0

OPEN_LOOP Basal injections
basal Fixed _ set "basal=[XX]" – Units of Insulin per minute
Qbasal uses subject-specific basal rate (quest overrides basal=)
%Qbasal=quest
```

OPEN_LOOP SQ insulin BOLUS Treatment

```
OB on uses subject-specific Unit Insulin/g CHO to compute meal bolus
%OB=on
User specified Boluses - OB on set overrides any Abolus info
Abolus     Vector of bolus amounts in Units Insulin (total or perkg)
Tbolus     Time_Vector of bolus injections in QTbolus units
QTbolus    Tbolus Units – min*, hour, day
Qbolus     Units of Bolus:'total' Units Insulin or 'perkg' U/Kg B.W.
```

OPEN LOOP INSULIN INJECTION INFO – IV

```
TIVINS     Time_Vector - IV insulin injection begin & end times in minutes
           after start of simulation
QIVins     Dosage Units - IV insulin: 'perkg' b.w. or total 'total'
AIVINS     a vector of IV insulin injection rates (U insulin/minute)
```

OPEN LOOP DEXTROSE INJECTION INFO – IV

```
TIVD       Time_Vector of IV dextrose injections begin & end times in
           minutes after start of simulation
QIVD       units of IVdextrose injections: per kg of of body weight
           ('perkg') or ('total')
AIVD       a vector of IV dextrose injection rates (grams of CHO/min)
```

This Annotated Scenario and several sample scenarios are included in the
T1DMS Type 1 Diabetes Simulator model folder

Annotated ctrlsetup.m

```
function ctrller=ctrlsetup(Quest,hd,sc,ctrller,struttura)

% OPTIONAL add a name for auditing; can be checked in sim_results
% load sim_results.mat and see data.ctrlsetup
% NOTE actual required filename is always ctrlsetup.m
ctrller.ctrlname='ctrlsetup_Annotated_v3_2';  % user-specified

%% Controller Dosing Algorithm Robustness Analysis Modifiers - Required
% % user can use these parameters explore & evaluate response to stress
% NOT included in FDA master file
% SImult will apply for the entire Tsimul
ctrller.SImult=1; % modify SI, insulin sensitivity

% Mealmult will apply for the entire Tsimul
ctrller.Mealmult=1; % modify meal speed (<1=slower) (>1=faster)

% test with mis-announcement of the meals amount in the controller
ctrller.meal_announce_modifier=[0 1]; % multiplicative time dependent modifier
% modifier on meal_announce amount, set = 0 for no meal announcement
% first column contains time (minutes) from which to apply the values in the second column
% modified meal amount will be used in meal bolus calculation as applicable

% ADD additive and/or multiplicative Bias to the CGM sensor
ctrller.CGM_bias=[0 0]; % additive time dependent modifier on CGM signal,
% first column contains time from which to apply the values in the second column
ctrller.CGM_bias_rel=[0 1]; % multiplicative time dependent modifier on CGM signal,
% first column contains time from which to apply the values in the second column

%% write your code below
% Subject-Specific: Quest information available to the controller
%Optimal Basal, Optimal Carb Ratio, Max.BG.Drop/Unit Insulin
ctrller.basal=Quest.basal; % U/hr
ctrller.CR=Quest.OB; % Carb Ratio, gCHO/U insulin
ctrller.CF=Quest.MD;   % Correction Factor max BG drop/U insulin

ctrller.name=Quest.names; % subject name- determine if adult, teen or child
ctrller.BW=Quest.weight; % subject weight, kg
ctrller.fastingBG=Quest.fastingBG; % subject fasting BG mg/dL w/basal

%% Some potential controller specific parameters
% Subject independent values can be specified directly in Controller

% Target & Threshhold values generally used w/correction bolus calculation
ctrller.corr.tgt=100; % set correction bolus target mg/dL
ctrller.corr_thresh=150; % set correction bolus threshhold mg/dL
ctrller.corr_CFmeal=0; % Correction Bolus w/Meal; =0 => off, =1 => 100%
```

An Annotated ctrlsetup.m file is included in the
T1DMS Type 1 Diabetes Simulator model folder (controller setup folder)

Outcome Measures & Outcome Graphs (can be selected in the GUI)

Outcome Measures

The T1DM simulator can create the "per subject" Glucose Control-relevant analyses as selected by the user and calculated at the end of the simulation (see create_output.m for calculation methods).
All of the results are evaluated between the start of regulation (Treg) and the end of the simulation.

Mean blood glucose reading:
Per-subject average of glucose readings (mg/dl).

Mean pre-meal blood glucose values:
Average per-subject glucose values (mg/dl) during the hour prior to meal times.

Mean post-meal blood glucose values:
Average per-subject glucose values (mg/dl) over one hour beginning 60 minutes after a given meal.

Per cent time in Severe Hypoglycemia (BG ≤ 50 mg/dL):
Percentage of time (per-subject) spent with a glucose level less than or equal to 50 mg/dL.

Per cent time in Hypoglycemia (BG ≤ 70 mg/dL) (user-selected low target):
Percentage of time (per-subject) spent with a glucose level less than or equal to 70 mg/dL.

Per cent time in Euglycemia (Low Target mg/dL < BG ≤ High Target mg/dL)
Percentage of time (per-subject) spent with a glucose level within the user specified target range.

Per cent time in Hyperglycemia (BG > High Target mg/dL) (user-selected high target):
Percentage of time (per-subject) spent with a glucose level greater than 180 mg/dL.

Per cent time in Severe Hyperglycemia (BG > 300 mg/dL):
Percentage of time (per-subject) spent with a glucose level greater than 300 mg/dL.

Post Prandial AUC per gram of CHO:
Post prandial Area Under the Curve (> pre-meal BG) divided by the total grams of carbohydrates consumed averaged over all of the meals (during regulation).
Mean[(Sum(BG- pre-meal mean BG))/gCHO].

Low BG Index (LBGI):
LBGI is a measure of the frequency and extent of low BG readings. The LBGI provides a per-subject analysis of long-term risk for hypoglycemia. These risk values can be used to identify Minimal (LBGI<1.1), Low (1.1 ≤ LBGI < 2.5), Moderate (2.5 ≤ LBGI < 5), and High-risk groups (LBGI>5.0).

High BG Index (HBGI):
HBGI is a measure of the frequency and extent of high BG readings. The HBGI provides a per-subject analysis of long-term risk for hyperglycemia. These risk values can be used to identify Minimal (HBGI<5.0), Low (5.0 ≤ HBGI < 10.0), Moderate (10.0 ≤ HBGI < 15), and High-risk groups (HBGI>15.0).

BG Risk Index (BGRI):
The BG Risk Index is simply the per-subject sum of the HBGI and LBGI values. The BGRI provides a metric for identifying individual subjects who are prone to extreme Glucose Control-related events.

SD of BG Rate of Change:
The BG Rate of Change is computed as the ratio of glucose readings over intervals of 15 minutes during the simulation's execution. The standard deviation of these values is calculated to provide a measure of the stability of closed-loop control within the model.

Outcome Graphs

The Distributed T1DMS creates the following Glucose Control-relevant graphs:

Blood Glucose (Trace) -- Population/Subject:
The blood glucose trace graph provides a per-subject or per-population BG trace for the simulation time. BG values are represented as a black line prior to regulation and as a green line during regulation.

Blood Glucose (Density) -- Population/Subject:
The blood glucose density graph provides a probability distribution of glucose values. The graph is divided into three sections based on the simulation's target range. The calculated probabilities of the glucose readings are displayed, numerically, within each target area.

Risk Trace -- Population/Subject:
The glucose risk trace graphs display the fluctuations of LBGI (plotted as < zero) and HBGI (plotted as > 0) for each hour of the simulation (during the regulation period). This graph emphasizes large excursions and suppresses fluctuations within the target range in order to highlight the critical variances in blood glucose throughout the simulation.

Aggregated BG Trace -- Subject:
The Aggregated Glucose Trace provides a per-hour graphical display of the clinical zone of glycemic control.

Histogram of BG Rate of Change -- Population/Subject:
The Histogram of Glucose Rate of Change plots the frequency and distribution of various rates of glycemic change (in mg/dL per-minute) during regulation.

Poincare Plot -- Subject:
The Poincare plot provides a graphical summary of a given subject's glucose stability. A smaller and more concentrated collection of values indicates high glucose stability, whereas a widely dispersed region indicates BG-related irregularity (i.e. frequent and extreme glucose excursions).

Control Variability Grid Analysis (per-day/per-subject) -- Population/Subject:
The Control Variability Grid Analysis (CVGA) points represent per-subject glucose extremes. The individual points are computed as follows: for each subject a point is plotted with an x-coordinate and y-coordinate equal to the minimum and maximum BG values over a given observation period, respectively. NOTE: To reject sensor errors the confidence bounds of the x and y values have been set to a 95% spread of the overall BG distribution.

T1DMS OUTPUT file: sim_results.mat structured data mat file
provides per minute per subject data:
G (mg/dL), state (see below), time (minutes), injection (pmol/min), sensor (mg/dL), CHO (g/min), BOLUS (pmol/min), BASAL (pmol/min), To_PUMP (pmol/min)

INPUT to metab_model in the Simulink Model (includes conversions from scenario & control setup files)
(this exact input data may not be automatically collected)
u(1) meals CHO carbohydrates in (mg CHO/minute)
u(2) Subcutaneous insulin injection (pmol/per Kg body weight)/minute
u(3) qstot = qsto(t) glucose in the stomach in mg
u(4) Insulin IV injection in (pmol/minute)
u(5) Glucose/Dextrose IV injection in (mg CHO/Kg body weight)/minute
u(6) Pramlintide (Not used in current model) [mcg/minute]
u(7) Glucagon SQ injection in (mg/Kg body weight)/minute

data.results(i).state.signals.values (i = subject # by order of simulation)
sys(1) Plasma glucose concentration mg/dL.
sys(2) Subcutaneous glucose concentration mg/dL.
sys(3) Plasma insulin concentration pmol/L.
sys(4) Rate of appearance mg/kg/min.
sys(5) Endogenous glucose production rate mg/kg/min.
sys(6) Glucose utilization rate at all tissues mg/min.
sys(7) Rate of appearance of insulin pmol/L/min.
sys(8) Glucagon rate of appearance ng/L/min.
sys(9)-sys(26) **Model States or Compartments**
sys(27) Total carbs in stomach (*Qsto*).

Model States or Compartments
sys(9) = x(1) Carbs in first phase of stomach (mg).
sys(10) = x(2) Carbs in second phase of stomach (mg).
sys(11) = x(3) Carbs in intestine (mg).
sys(12) = x(4) Glucose in plasma and insulin-independent tissues (mg/kg).
sys(13) = x(5) Glucose in insulin-dependent tissues (mg/kg).
sys(14) = x(6) Insulin in plasma (pmol/kg).
sys(15) = x(7) Insulin action, X (pmol/L).
sys(16) = x(8) Delay compartment for insulin action on glucose production (pmol/L).
sys(17) = x(9) Insulin action on glucose production, Id (pmol/L).
sys(18) = x(10) Insulin in the liver (pmol/kg).
sys(19) = x(11) Insulin in first subcutaneous compartment (pmol/kg)
sys(20) = x(12) Insulin in second subcutaneous compartment (pmol/kg)
sys(21) = x(13) Subcutaneous glucose (mg/kg)
sys(22) = x(14) Plasma glucagon (ng/L)
sys(23) = x(15) Glucagon action (ng/dL)
sys(24) = x(16) Delayed static glucagon secretion (mg/kg per min)
sys(25) = x(17) Glucagon in first subcutaneous compartment (mg/kg)
sys(26) = x(18) Glucagon in second subcutaneous compartment (mg/kg)