

# MODELING TREATMENT WITH METFORMIN, WITH AND WITHOUT INSULIN IN A VIRTUAL T2DM POPULATION IN AN ENVIRONMENT WITH THE VARIABILITY OF COMMON SELF-MANAGEMENT BEHAVIORS

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## Background

The DMMS (Diabetes Mellitus Metabolic Simulator) with the *in silico* T2DM population of 100 adults is used to demonstrate how daily metformin treatment with an add-on insulin bolus can improve glycemic control for subjects with T2DM under daily life style variability.

## Introduction

Insulin therapy is increasingly acknowledged as an important component of glucose control for T2 Diabetes (T2DM)<sup>1</sup>. Despite the efficacy of metformin, over half of T2 patients would benefit from the addition of long-acting insulin therapy<sup>2,3</sup>. However, many barriers exist for assessing the optimal combination treatment of daily metformin and use of insulin in a clinical T2DM population under the variability of self-management behaviors. Also, factors such as glucose meter error, carbohydrate counting errors and medication noncompliance cannot be controlled in population studies and the individual or combined effects confound the understanding of direct relationships between the medications and blood glucose (BG) control. Simulation studies can be used to improve the understanding of the interactions of metformin, add-on insulin and common variability in daily T2 diabetes self-management patterns.

## Methods

We examined the impact of metformin<sup>4</sup>, with and without long-acting insulin on clinical outcomes with daily lifestyle factors, in a virtual T2DM population of 100 adults, (DMMS; The Epsilon Group, www.tegvirginia.com). We applied *in-silico* models of the variability of daily life activities and diabetes self-management behaviors, including exercise, and inconsistency of meal sizes and timing, designed to reflect common self-management patterns as reported in the literature<sup>5,6</sup>. The Diabetes Mellitus Metabolic Simulator (DMMS) is an *in-silico* simulation environment which supports design of "clinical" interventions that affect the glucose-insulin response of virtual subjects. The simulation, which is built on a compartmental metabolic Human model<sup>1</sup>, generates results that include continuous signal values representing all of the model's compartments. These can be extracted for further examination of the individual or the population.

## T2DM Daily Life Scenarios

The protocols were designed to reflect usual T2DM daily life experiences and common self-management patterns. The study simulations began at 5 a.m. and lasted for 7 days for all scenarios. Three meals and a random afternoon snack were included, with breakfast meals consisting of 30g carbohydrates (CHO), lunch was 40 g CHO, and dinner was 50 g CHO. Random errors were applied to the time, amount, and duration of each standard meal (breakfast, lunch, and dinner). The variation of meal time had a normal random error with zero mean and standard deviation = 10 minutes. The meal amount had normally distributed random error with CV = 10%, 7.5% and 6% of carbohydrate count for breakfast, lunch, and dinner, respectively. Durations of the standard meals were 5, 10, and 15 minutes, and a uniformly distributed random error with CV = 0.5% was applied to these. The probability of an afternoon snack was 0.5 in each day of simulation. The scenario also included a period of afternoon physical activity that could raise the sensitivity of insulin (via increasing the insulin action parameter on the liver by 25%) for about 30 minutes.

There were three protocols with different medical treatment plans: no medical treatment, metformin alone, or metformin with add-on long-acting insulin. All subjects in the simulations had the same life style scenario settings and the medication treatment was the only variable that was different.

Protocol 1. This scenario served as the control group with no medical treatment.

Protocol 2. Subjects were taking long term metformin treatment (1000 mg/day).

Protocol 3. Subjects were taking long term metformin treatment (1000 mg/day) and injected long acting insulin at 7:00 a.m. every morning. The injected subcutaneous insulin dose was calculated to be ideal and the efficacy (the effective insulin per minute) of the long-acting insulin is assumed to be a perfect constant. The dose for each subject was optimized to maintain the plasma fasting glucose concentration within a range of 120 - 130 mg/dl.

## Simulation Results

The target range was defined as 70 – 180 mg/dl. The hypoglycemia event was counted when any BG measure below the target range was observed and the hyperglycemia event was counted when any BG measure above the target range was observed. The time in each glycemic zone is represented as a percentage. Results of T2DM population metrics analysis are presented in Table 1.

We compared the impact of treatment with metformin alone (protocol 2) and with add-on insulin (protocol 3) in the same T2DM subjects with no treatment (protocol 1) under identical daily life events. Glucose control in a virtual T2DM population was significantly improved with metformin alone over no treatment, and was even more improved with combined metformin and long-acting insulin treatment. See Table 1. The box plot (Fig 2), which demonstrates the average BG distribution for the population between the three protocols, confirms the significant improvement in glucose control for the population in protocol 2 and 3.

Protocol 3 (metformin with add-on insulin treatment) resulted in fewer hyperglycemia events and shorter time in compared to other protocols. The subjects' glucose levels also remained in the target BG range longer in protocol 3 when compared to protocol 1 and 2. Although the significant reduction in average glucose increased the risk for hypoglycemia, there were no hypoglycemic events in these simulation protocols.

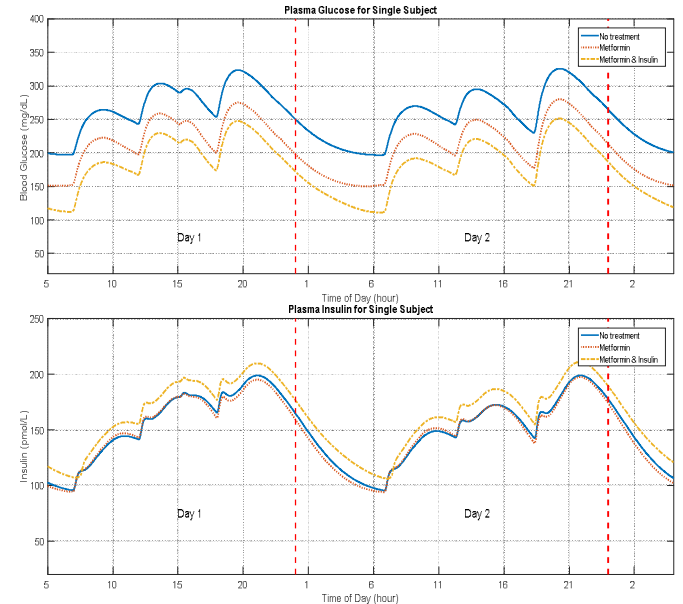


Figure 1. Trace Plots for Various Signals Under Different Treatment Protocols

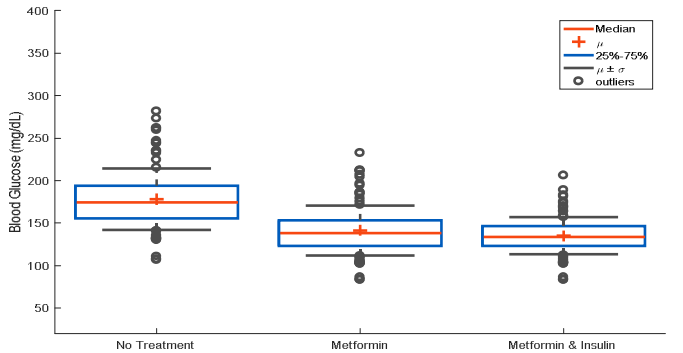


Figure 2 Box Plot for Population Average Glucose Among Treatment Protocols

The individualized add-on insulin and metformin combined treatment shows the best glycemic control in average glucose over the simulation period and exhibits a significant difference in the paired t-test between other protocols.

Population Metric (mean ± SD)	No Treatment	Metformin	Metformin and Daily Long Acting Insulin Bolus
BG mean (mg/dl)	178 ± 36	141 ± 29	135 ± 22
BG max (mg/dl)	244 ± 50	211 ± 45	205 ± 40
BG min (mg/dl)	147 ± 28	110 ± 22	99 ± 13
# Hypoglycemia events	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
% Time in hypoglycemia	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
# Hyperglycemia events	13.8 ± 8.7	9.6 ± 8.5	9.0 ± 8.2
% Time in hyperglycemia	42.1 ± 32.3	16.0 ± 21.6	11.3 ± 14.9
% Time in target	57.4 ± 31.9	71.8 ± 25.8	76.2 ± 23.1
LBG1	0.01 ± 0.04	0.25 ± 0.61	0.25 ± 0.61
Estimated HbA 1c	7.8 ± 1.2	6.6 ± 1.0	6.3 ± 0.8

Table 1 Glucose Control Metrics for Type 2 Adult Population

The statistical analysis for BG includes essential measures such as mean, maximum, minimum, percent time in events, and total number of events, to assist the glucose control assessment. The statistical analysis table is a standard feature included in DMMS.R.

## Conclusions

- This T2DMS study demonstrates how *in-silico* modeling and simulation allows for examination of co-administration of metformin and insulin in an environment that includes models of real-life variability factors.
- We have observed that a treatment protocol that combines metformin and daily long acting insulin bolus showed the best glycemic control for *in-silico* T2DM subjects. The result is consistent with clinical studies<sup>2,3</sup>.
- With careful modeling and validation processes, this type of simulation can be useful in examining various treatment approaches to self-management behaviors and their effect on glucose control in a safe environment.

## References

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