

# A toolbox to improve algorithms for insulin-dosing decision support

K. Donsa<sup>1</sup>; P. Beck<sup>1</sup>; J. Plank<sup>2</sup>; L. Schaupp<sup>2</sup>; J. K. Mader<sup>2</sup>; T. Truskaller<sup>1</sup>; B. Tschapeller<sup>1</sup>; B. Höll<sup>1</sup>; S. Spat<sup>1</sup>; T. R. Pieber<sup>1,2</sup>

<sup>1</sup>HEALTH – Institute for Biomedicine and Health Sciences, JOANNEUM RESEARCH Forschungsgesellschaft mbH, Graz, Austria;

<sup>2</sup>Division of Endocrinology and Metabolism, Department of Internal Medicine, Medical University of Graz, Graz, Austria

## Keywords

clinical decision support systems, workflow; algorithms; computer simulation; diabetes mellitus type 2

## Summary

**Background:** Standardized insulin order sets for subcutaneous basal-bolus insulin therapy are recommended by clinical guidelines for the inpatient management of diabetes. The algorithm based GlucoTab system electronically assists health care personnel by supporting clinical workflow and providing insulin-dose suggestions.

**Objective:** To develop a toolbox for improving clinical decision-support algorithms.

**Methods:** The toolbox has three main components. 1) Data preparation: Data from several heterogeneous sources is extracted, cleaned and stored in a uniform data format. 2) Simulation: The effects of algorithm modifications are estimated by simulating treatment workflows based on real data from clinical trials. 3) Analysis: Algorithm performance is measured, analyzed and simulated by using data from three clinical trials with a total of 166 patients.

**Results:** Use of the toolbox led to algorithm improvements as well as the detection of potential individualized subgroup-specific algorithms.

**Conclusion:** These results are a first step towards individualized algorithm modifications for specific patient subgroups.

## Correspondence to:

Peter Beck, PhD  
JOANNEUM RESEARCH-HEALTH  
Elisabethstraße 5  
8010 Graz  
Austria  
E-mail: peter.beck@joanneum.at

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## 1. Introduction

Poor glycemic control has been associated with poor clinical outcome and increased mortality in patients with and without history of diabetes [1]. Recently performed audits in Great Britain demonstrated that glycemic control is not established satisfactorily. Nearly 40% of patients included in the audit experienced at least one diabetes medication error while in hospital. Patients with medication errors were more than twice as likely to experience a severe hypoglycemic episode (16.8%) than patients who did not have a medication error (7.5%) [2]. Implementing a standardized subcutaneous insulin order set promoting the use of scheduled basal and nutritional insulin therapy is a key intervention in the inpatient management of diabetes. Observational and randomized controlled studies indicate that when glycemic control improves, hospital complication rates are lowered in general medical and surgery patients [3–7].

GlucoTab, an algorithm based workflow and decision support system for non-critically ill patients with diabetes mellitus type 2, was developed in the EU-funded project REACTION. It is a mobile Android-based tablet PC which interacts with a Java Enterprise server to provide workflow and insulin dosing support to physicians and nurses directly at the point of care. The GlucoTab system was developed by an interdisciplinary team of engineers, physicians and nurses. Design input was provided by clinical specialists and technical experts, and the system was improved in an iterative approach involving end user feedback.

Four clinical trials regarding patient safety, efficacy of glycemic control and usability have already been performed using the GlucoTab system. The first trial evaluated the underlying workflow-integrated algorithm for basal-bolus insulin therapy in a paper-based form. The algorithm was effective in establishing glycemic control, and was well accepted by medical staff [8]. Subsequently, this algorithm was integrated into the GlucoTab system and applied and evaluated in clinical trials. Although the overall glycemic control was good (73% of blood glucose readings in the accepted glycemic range 70–180 mg/dl), some patient subgroups did not reach the glycemic target range or experienced hypoglycemic episodes.

We now report on a new toolbox for analyzing and simulating GlucoTab system modifications. The ultimate aims of this toolbox development were: to improve the GlucoTab algorithm which in its initial form lacked flexibility, to test and optimize new ideas and hypotheses for algorithm modifications to draw maximum benefit from future clinical studies, and to identify individualized algorithm and workflow improvements for specific patient subgroups. We have now incorporated several heterogeneous clinical data sources and implemented a standard procedure for statistical analysis.

## 2. Methods

This section summarizes the methods and technologies and the iterative process used to develop the toolbox for improving the algorithms for insulin-dosing-decision support. The toolbox consists of three main components (► Figure 1):

- **Data preparation:** Data from several heterogeneous sources is extracted, cleaned and stored in a uniform data format.
- **Simulation:** Modified versions of the algorithm are applied in simulations of the treatment workflow, based on real data from clinical trials.
- **Analysis:** The algorithm performance is measured and visualized for all patients or patient subgroups.

### 2.1 Data preparation

The purpose of this component is to extract, transform and load (ETL) data from clinical trials and other sources into a uniform data structure in a standardized process. One major challenge in the performance of pooled data analyses is the varying structure of data from different clinical trials. We designed a multi-step process to monitor and clean the data: the first steps are performed routinely as part of clinical trial data management according to Good Clinical Practice (GCP) and Inter-

national Conference on Harmonisation (ICH) [9]. In each clinical trial data is extracted from the sources and transformed into a standardized format according to standard data management: data is first checked for consistency and quality; applying for example summary statistics and row checks in the form of if clauses. Inconsistent, implausible or missing values are discussed with the clinical trial team in the database release meeting to achieve a clean dataset for statistical analysis. As part of the toolbox, during the data preparation step, the data is extracted, cleaned and stored in a uniform data format for pooled statistical analyses. Type and unit conversions as well as preparations for the simulations and analyses are performed in this step. Patient-specific profiles with baseline characteristics, concomitant diagnoses and medications, overall glycemic information (mean blood glucose levels, glucose variability, hypo- and hyperglycemic events) and information on the algorithm version used are generated. “Virtual insulin sensitivity” profiles are also generated which are required for blood glucose estimations, performed in the simulation component (see chapter 2.2 Simulation).

## 2.2 Simulation

Simulation aims to estimate the effect of insulin dose changes on blood glucose values due to algorithm modifications. Simulations are performed with a simulator application implemented in Java which integrates and uses original components from the GlucoTab server implementation. This approach was chosen because building on the original, well tested medical device software components is much more reliable and resource-effective compared to completely rebuilding the entire workflow and decision support algorithm in its full complexity in statistics software and keeping it in synchronization with future modifications of the server. Furthermore, the source code developed for the simulation is already available for implementation into the GlucoTab system, in case of adopting algorithm modifications after the simulation. After additional reviews and testing, the code can be included in the medical device software.

Simulations are performed in two steps, with real patient data from the GlucoTab clinical trials. In the first step, the simulator uses blood glucose measurements and insulin dose calculations, as well as therapy adaptations, based on the original entries into the GlucoTab system by the clinical personnel. Sequentially new insulin dose calculations are performed by using the new algorithm. In a second step the blood glucose estimations are performed. We identified several methods for blood glucose estimations from a structured literature research. Neural networks have been shown to be the most promising technologies [10, 11]. However, neural networks could not be used to achieve accurate blood glucose estimations using our data. The GlucoTab approach for type 2 diabetes mellitus does not involve exact carbohydrate counting. Therefore, exact amounts of carbohydrates consumed were not available and could account for the inaccurate estimations achieved with neural networks. Thus we developed a new method for blood glucose estimations in the toolbox by using “virtual insulin sensitivity” profiles. “Virtual insulin sensitivity” was defined as the difference between two blood glucose measurements divided by the injected insulin dose. A „virtual insulin sensitivity“ value is estimated for every measurement interval (e.g. noon to evening) for every patient on each hospital day. The simulator uses the “virtual insulin sensitivity” profile of the patients and calculates the estimated blood glucose value for the next interval alongside the new insulin dose. An example of how blood glucose estimations due to algorithm modifications are performed is illustrated in ► Figure 2. A patient with a noon blood glucose level of 200 mg/dl, an evening blood glucose level of 160 mg/dl received 10 insulin units (IU) injected at noon, and thus has a “virtual insulin sensitivity” of 4 mg/dl/IU. In this example, one unit of insulin lowers the blood glucose level by 4 mg/dl. In the simulation the patient receives 15 IU at noon, following the dose suggestion of the modified algorithm. Considering the “virtual insulin sensitivity” of the patient the simulation estimates that the additional 5 IU would have lowered the blood glucose level by additional 20 mg/dl resulting in an evening blood glucose level of 140 mg/dl.

All records resulting from the simulations are stored in the relational GlucoTab database, and are then extracted by the data preparation component and prepared for pooled statistical analysis in the analysis component.

## 2.3 Analysis

In the analysis component, different methods of the toolbox (e.g. patient hazard analysis, what-if analysis) are combined depending on the specific research question. Results from the analysis component are summarized in a reporting tool. The following use cases demonstrate the possibilities of the toolbox by using data from three clinical trials and comprise datasets from the following data sources:

- **Glucotab server:** 5,218 blood glucose measurements (Roche Accu-Chek) from 166 patients on 1,124 patient days, suggested and confirmed bolus and basal insulin doses and information on consumption of meals and insulin sensitivity
- **Clinical trial data management system (OpenClinica):** Diagnoses, medications and baseline characteristics of 166 patients
- **Laboratory information system:** Hospital laboratory data of 99 patients
- **Continuous Glucose Monitoring (CGM):** 14,140 hours recorded with CGM (Medtronic iPro2) of 97 patients

### Pooled data

The first use case demonstrates methods for the retrospective analysis of pooled patient data. It aims to detect the quality of glycemic control when using the GlucoTab system by identifying individualized versions of insulin-dosing algorithms for specific patient subgroups. A penalty scoring system evaluates the therapy of each patient considering the average blood glucose levels, hypo- and hyperglycemic events and glucose variability. If the patient's glycemia is within the target range the scoring system rewards credit points whereas blood glucose values outside the target range are given penalty points. Penalty points are weighted according to the severity of hypo- or hyperglycemia. Hypoglycemia has a higher impact on the score. Subgroup analyses using hierarchical clustering allow the detection of "responder" or "non-responder" patient subgroups and their distinctive properties.

### Algorithm modification

The second use case aims to evaluate algorithm modifications. In what-if analyses, outcomes regarding blood glucose levels and suggested insulin doses are investigated and visualized for interpretation by clinical specialists. Patient hazard analyses for patients with low glycemic events are performed to identify the safest version of the modified algorithm: insulin dose calculations are simulated by using new variants of the algorithm. To detect potentially dangerous changes in the algorithm, a potential increase of insulin doses prior to a low glycemic event is investigated. Patient hazard analyses are discussed with diabetes specialists to ensure that only safe variants of a new algorithm are implemented.

### Continuous glucose-monitoring data

The third use case considers additional input from continuous glucose monitoring (CGM) data for algorithm evaluation. The clinical standard for monitoring the patient's blood glucose levels is point of care testing (POCT) [12]. POCT provides only a snapshot of the patient's glycemic profile. With the use of CGM we investigated if these snapshots are sufficient for the patient's therapy. We identified low glycemic episodes using CGM data. A low glycemic episode was defined as a signal drop below the threshold level of 70 mg/dl for at least three consecutive measurements (5 min sampling). If the sensor level was above the threshold for less than one hour between two below-threshold episodes, this was counted as one episode. Additionally, to compensate data processing of the CGM sensor manufacturer, offset correction was applied to the CGM sensor data to increase the sensitivity for detection of low glycemic events in a post-processing step. The sensitivity is defined as the relative number of true low glycemic episodes that have been detected. It is calculated as the proportion of the number of detected true low glycemic episodes divided by the number of detected and missed low glycemic episodes [13]. Another aim is to relate CGM to the algorithm: in a subsequent what-if analysis the patient's outcome is investigated regarding suggested insulin doses and patient hazard.

The **reporting tool** generates automated PDF reports using the R project for Statistical Computing [14] with Sweave and LaTeX. A multitude of customized graphic output functions has been de-

veloped using ggplot and ggplot2 packages. Results can be reported as text, tables or figures by using the customizable PDF reports (e.g. ►Figure 3 and ►Figure 4 in this paper).

### 3. Results

#### Pooled data

Since low glycemic events are the most dangerous in blood glucose management, first analyses were conducted to investigate and visualize the glycemic range which is most likely resulting in low blood glucose events. ►Figure 3 shows data from all patients treated with the first version of the algorithm ( $n = 52$ ), revealing that low glycemic events do not only emerge from patients with low blood glucose levels but also occur in patients with initially high blood glucose values.

#### Algorithm modification

An example of validating the simulation results of the toolbox is demonstrated in ►Figure 4. The use of the first version of the algorithm in previous clinical trials has resulted in relatively high mean blood glucose values at noon [8] (►Figure 4a). A blood glucose estimation was performed to simulate a change of the bolus ratio for morning, noon and evening, for all 52 patients treated with the first version of the algorithm (►Figure 4b). The new algorithm (v2) was clinically validated after implementing the proposed bolus ratio changes into the GlucoTab system. The results for the first 15 patients (►Figure 4c) showed a significantly reduced mean noon blood glucose level (t-test,  $p = 0.014$ ).

#### Continuous glucose-monitoring data

The toolbox was used to assess if POCT provides all necessary information for the patient's glycemic control, especially low glycemic events. Low glycemic events were identified according to the method described (see CGM in the methods section) using 1,480 paired blood glucose sensor readings (8,578 hours recorded with CGM) of 59 patients. After adjusting for the offset of sensor data, 134 events below 70 mg/dl were detected with CGM compared to 35 detected by blood glucose POCT. The majority of low glycemic events that were detected with CGM occurred during the night. Sensitivity to detect low glycemic events using CGM was 42%.

### 4. Discussion

This work created a toolbox with three main components to improve an insulin dosing algorithm used in a decision support system. The data preparation component enabled a fast and standardized way to incorporate additional clinical data for the simulation component and the analysis component. Based on the uniform data structure and standardized processes, algorithm changes were simulated, evaluated and optimized before being implemented in the decision support system. Three particularly important examples for the use of the analysis component during algorithm development are demonstrated in this paper.

The toolbox was used for pooled data analyses and indicated that low glycemic events occur not only in patients with low blood glucose levels but also in patients with initially high blood glucose levels. A further increase of insulin doses would lead to an increased hypoglycemia risk in some patients. Pooled data analyses and visualization of results were successfully used to investigate a hypothesis and discuss results with clinical experts for a further improvement of the algorithm.

Simulated bolus ratio changes and blood glucose estimations in the toolbox were confirmed with real patient data after the algorithm changes had been implemented in the GlucoTab system. Algorithm changes resulted in a statistically significant reduction of blood glucose levels at noon as estimated by the toolbox, but might have also been affected by the difference in glycemic control prior to the trial. HbA1c in patients treated with the initial version of the algorithm was  $76 \pm 30$  mmol/mol

compared to  $62 \pm 18$  mmol/mol in the first 15 patients treated with the modified version of the algorithm. Further analyses with a bigger sample size are still ongoing.

CGM data indicate that a high number of low glyceemic events ( $<70$  mg/dl) are not detected with standard glucose POCT, in particular during the night when fewer POCT reference measurements are available for confirmation. The high number of low glyceemic events has to be interpreted cautiously due to the low sensitivity of the commercially available CGM sensor. The sensitivity of the CGM sensor system applied in the studies to detect low glyceemic events (42%) is comparable to a recently published study using a similar CGM system (CGM-sensor sensitivity: 37.5%) [13].

The presented toolbox provides the technical foundation for the development of more individualized algorithms. Already planned clinical trials using the GlucoTab system will provide more data for the toolbox and enable us to perform simulations of algorithm changes for various patient subgroups. We will continue in-depth analyses and carefully test algorithm modifications by simulations, before any changes are implemented in the software, and are applied in the therapy of patients in clinical evaluation trials.

### **Clinical Relevance**

Algorithm based decision support systems directly influence clinical practice and have the potential to achieve significant and clinically relevant improvements. The developed toolbox has successfully been used to derive modifications of a treatment algorithm from clinical data in an effective and reproducible way. The safest and best performing algorithms can be identified by simulation, before being implemented in medical device software and being applied in the therapy of patients.

### **Conflict of Interest**

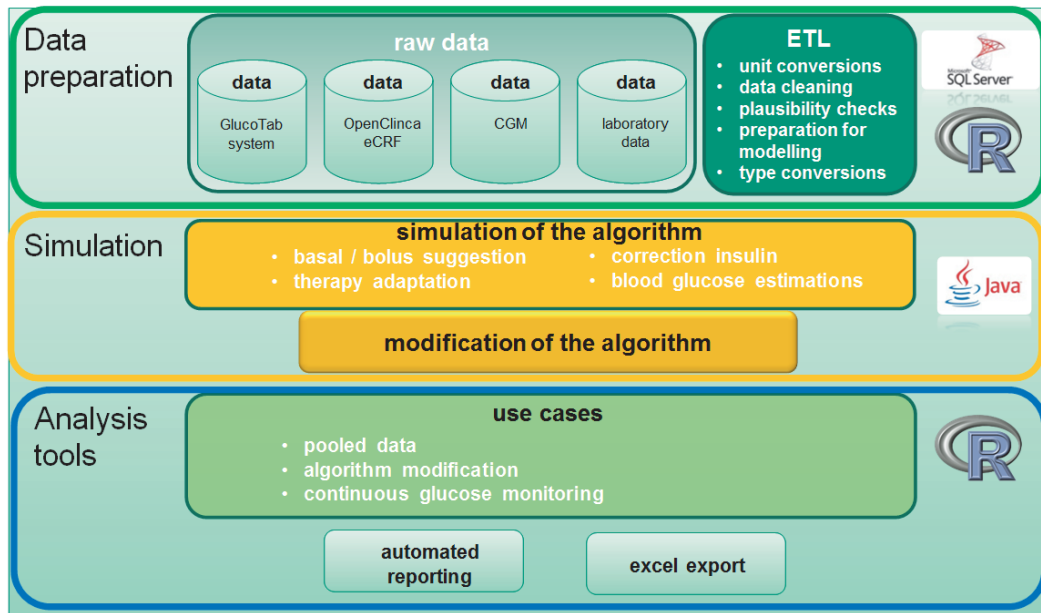
The authors declare that they have no conflicts of interest in the research.

### **Human Subjects Protections**

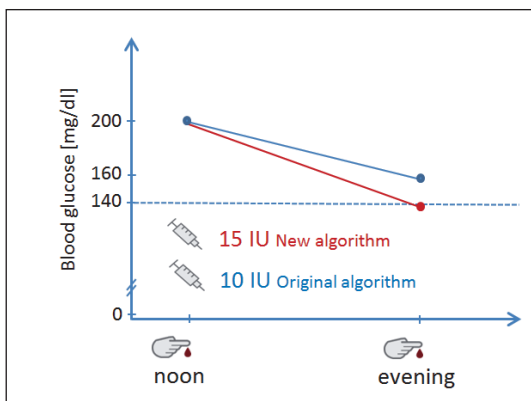
The procedures used have been reviewed in compliance with ethical standards of the responsible committee on human experimentation.

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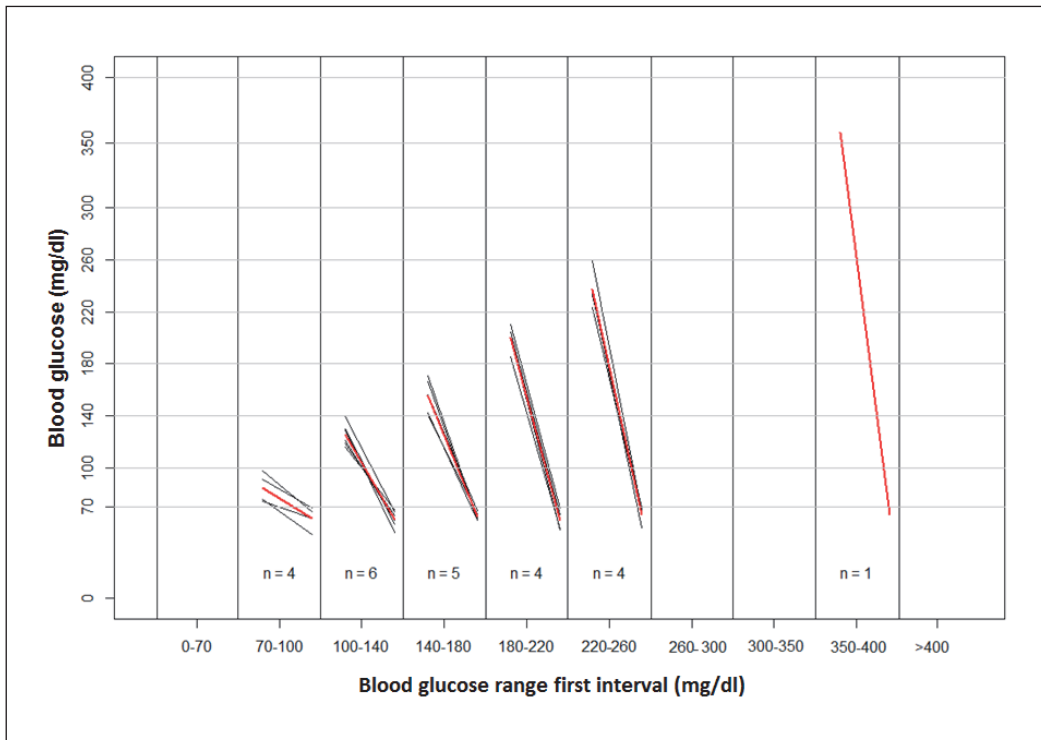
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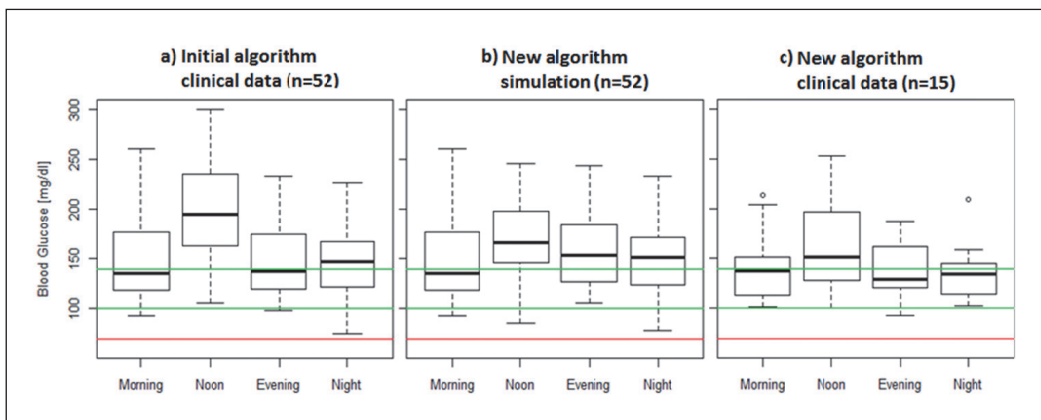
**Fig. 1** Structure of the toolbox for improving algorithms for insulin-dosing decision support. ETL (extract, transform and load)



**Fig. 2** Example of blood glucose estimations due to algorithm modifications. IU (insulin unit)



**Fig. 3** Blood glucose values preceding low glycemic events (<70 mg/dl). Black lines denote changes of blood glucose values over the measurement interval that resulted in a blood glucose value <70 mg/dl. Red lines are averages



**Fig. 4** Mean blood glucose per hospital stay – clinical data and simulation results



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