

Educational software for understanding integrated blood glucose effects

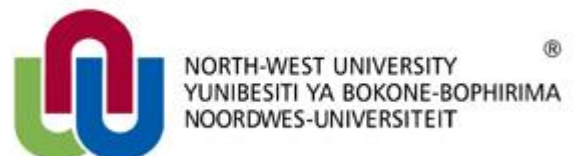
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Summary

The World Health Organisation considers diabetes mellitus as a fast-growing epidemic. The number of documented cases increase each year; together with the number of patients hospitalised due to complications associated with the disease. These long- and short-term complications can include blindness, kidney failure, circulatory diseases, neuropathy, to name a few.

The management of diabetes is a lifelong procedure that can become very expensive. Often patients lapse in their efforts. The education of diabetics, family members and care providers is therefore essential to ensure that lifelong accurate, continuous blood glucose control is achieved. This can decrease the occurrence or severity of complications.

Simulation models describing the human blood glucose system became more popular as the twenty-first century approached and computers became part of everyday life. These models are often used to educate diabetics rather than using conventional educating methods. Several such models exist, however, none offers an integrated approach to incorporate all the external and internal influences on the blood glucose system. These models were developed to simulate blood glucose response to several of these influences, but not in an integrated manner.

To fill this gap, an integrated simulation model was developed that incorporates the equivalent teaspoons sugar (ets) concept. ets is a newly developed generic energy unit used to determine the energy value of food, beverages, exercise, stress as well as the regulation and counterregulation hormones. This simplifies the mathematical model of the blood glucose system and is also easy for diabetics to implement in their everyday lives.

This led to the development of the educational simulation model, *Edutool* diabetes simulator, that incorporates the ets concept. The *Edutool* is an educational program for people with diabetes, non-diabetic people, care providers and medical professionals. The mathematical model behind the simulator has been experimentally validated. Due to the many simulation models that currently exist, it is essential to validate the model to determine its user-friendliness and educational value.

This experimental validation and evaluation of the *Edutool* was questionnaire-based and the results statistically analysed. The validation of the questionnaire was done by three experts in the field of diabetes and endocrinology. Three questionnaires were developed to evaluate the educational value of the *Edutool*, assess its ease-of-use and compare it to another educational diabetes simulator (AIDA).

A quick-start guide presentation was also developed to assist the user in understanding the basic diabetes and blood glucose concepts as well as show the user how the *Edutool* works. This presentation was developed so that a primary school child would understand the concepts being explained. The next step was to set up the trials.

The trials took place at Curro Hazeldean Primary and Curro College Hazeldean, both situated in Pretoria. A trial protocol was set up to explain the exact order of events in the trial. Information release forms were also required for all minors participating in the trials. These were signed by parents or guardians of the participants and returned prior to the start of the trial.

In the primary school trial, the increase in total test results was 40% after watching the quick-start guide presentation and working on the *Edutool*. After working on the AIDA simulator, all participants preferred the *Edutool*. The secondary school trial was also very successful. The results showed a 35% increase in the total test score. In this group all the participants also preferred the *Edutool* to the AIDA program. For both trials the p -value was smaller than 0.001, which indicates that the increase in total test scores for the trials are statistically significant.

From these results it can be concluded that the *Edutool*, together with the quick-start guide presentation, has improved the knowledge of the participants in both trials significantly. This validates the educational value of the *Edutool*. The ease-of-use of the program was also validated by the results of the open-ended questions, and therefore the *Edutool* can be regarded as a validated educational software program.

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List of symbols

ΔBG_{meal}	Blood glucose increase after consuming a meal (mmol/L)
$\Delta BG_{insulin}$	Measured blood glucose decrease after a given amount of bolus insulin
\widetilde{ets}	Equivalent teaspoons sugar
\widetilde{ets}_{meal}	The amount of \widetilde{ets} in a meal (ets)
$\widetilde{ets}_{absorbed}$	Amount of \widetilde{ets} absorbed into the blood as a result of digestion of a meal containing \widetilde{ets}_{meal} (ets)
$\widetilde{ets}_{effective}$	Effective amount of \widetilde{ets} consumed in a meal (ets)
f_{CHO}	Specific person's CHO absorption efficiency
$f_{BG/ets\ food}$	Person-specific \widetilde{ets} sensitivity factor
$f_{BG/insulin}$	Specific person's insulin sensitivity factor
\dot{G}	Glucose energy flow (mmol/L.min)
\dot{G}_{basal}	Glucose energy required for everyday living (mmol/L.min)
G_{blood}	Blood glucose concentration (mmol/L)
$G_{Blood(t)}$	Blood glucose concentration at a specific time interval (mmol/L)
$G_{Blood(t-1)}$	Blood glucose concentration at the previous time interval (mmol/L)
\dot{G}_{Digest}	Glucose energy flow from the digestion system to the bloodstream (mmol/L.min)
$\dot{G}_{Exercise}$	Glucose energy flow from the bloodstream to the energy expenditure (mmol/L.min)
$\dot{G}_{Exercise-Min}$	Minimum value of $\dot{G}_{Exercise}$ (mmol/L.min)
$\dot{G}_{Storage}$	Glucose energy flow between the primary storage and secondary storage (mmol/L.min)

$G_{Storage(t)}$	Glucose energy storage flow at a specific time interval (mmol/L)
$G_{Storage(t-1)}$	Glucose energy storage flow at the previous time interval (mmol/L)
$\dot{G}_{Store-IN}$	Glucose energy flow from the bloodstream to the primary storage (mmol/L.min)
$\dot{G}_{Store-OUT}$	Glucose energy flow from the primary storage to the bloodstream (mmol/L.min)
I_{Basal}	Basal insulin level (U)
I_{Bolus}	Amount of bolus insulin administered (U)
$I_{Control}$	Amount of regulation hormone in the system (U)
$\dot{I}_{Control}$	Change in the amount of regulation hormone in the system (U/min)
$I_{Control(t)}$	Amount of regulation hormone in the system at a specific time interval (U)
$I_{Control(t-1)}$	Amount of regulation hormone in the system at the previous time interval (U)
$\dot{I}_{Exercise}$	Insulin consumed from the blood when exercising (U/min)
$I_{Injected}$	Short-acting insulin requirement (U)
$k_{BG/ets\ food}$	Person-specific equivalence factor
η_{cho}	Metabolic efficiency of the specific CHO
t_{Digest}	Total digestion time of the specific meal (min)
$t_{Elapsed}$	Time elapsed up to current time (min)
T_{Meal}	Time of day a meal is taken
t_{Total}	Duration of the release function (min)

Glossary

α -cells: The cells situated in the islets of Langerhans in the pancreas that produce the hormone glucagon. ¹

β -cells: Cells situated in the islets of Langerhans in the pancreas. They produce the hormone insulin. ^{2,3}

Basal insulin: Slow-releasing insulin used to control the blood glucose for longer periods, such as during the night and between meals. ⁴

Blood glucose (BG): Glucose is the main energy source of the body. It is also often referred to as blood sugar. ⁴

Blood glucose level (BGL): This is the amount of glucose in the blood, measured in mmol/L or mg/dL.

Bolus insulin: “An extra amount of insulin taken to cover an expected rise in blood glucose, often related to a meal or snack”. ⁴

Carbohydrate (CHO): Carbohydrates are chemical substances synthesised from carbon dioxide and water. They play a significant role in the metabolism of animals and plants. The most important CHO is glucose, which is a major metabolic fuel. CHOs are classified into four types, namely, monosaccharides, disaccharides, oligosaccharides and polysaccharides. ⁵

¹ Sorensen JT: A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes. Doctor of Science thesis, Massachusetts Institute of Technology, Department of Chemical Engineering, 1985.

² García-Jaramillo M, Calm R, Bondia J, Tarín C, Vehí J: Insulin dosage optimization based on prediction of postprandial glucose excursions under uncertain parameters and food intake. *Computer Methods and Programs in Biomedicine* 2010; (Article in press): 1-9.

³ Thain, M: *Penguin Dictionary of Human Biology*. Penguin Books, London, 2009.

⁴ American Diabetes Association. 2011. <http://www.diabetes.org/diabetes-basics/common-terms/> (Accessed: April 11, 2011).

⁵ Murray RK, Granner DK, Rodwell VW: *Harper's Illustrated Biochemistry*, 27th Edition. Lange Medical Books/McGraw-Hill, New York, 2003.

Circadian profile: A graph that displays a 24-hour timeline on the x-axis, with the y-axis displaying the desired variable as it changes during this time period. ⁶

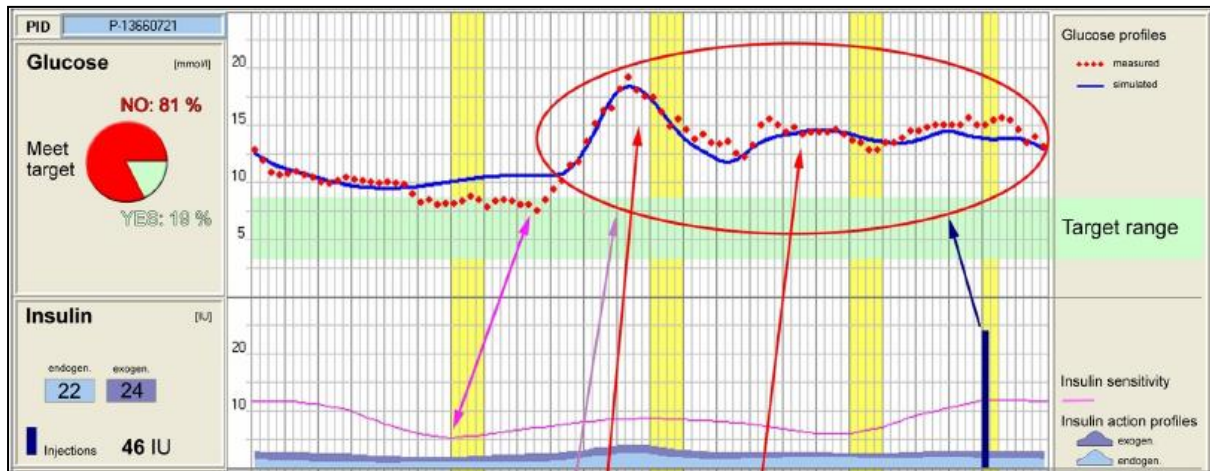


Figure 1: Circadian profiles of blood glucose and insulin concentrations.

Continuous glucose monitor (CGM): The continuous glucose monitor consists of a sensor to measure BG in the fluid under the skin on a continuous basis; a monitor to display the measurements and alert the patient in case of low or high BG; and a transmitter that connects to the sensor inserted in the body. The transmitter sends the collected data to the monitor. The BG data, which is stored, can be downloaded to a computer and analysed. ⁷

Counterregulation hormones: These hormones work against the actions of insulin to raise the BGL when it gets too low. The main counterregulation hormones include glucagon, epinephrine (adrenaline), growth hormone and cortisol. ⁸

Counterregulatory neuroendocrine response: The regulation of glucose by hormonal and neural regulatory mechanisms to raise the BGL if it gets below the lower limit of the normal human BG range, i.e. 3.9 mmol/L. Both the pancreas and hypothalamus/vagus are involved in this process. ³

⁶ Salzsieder E, Augstein P, Vogt L, Kohnert K, Heinke P, Freyse E, Azim AA, Metwali Z, Salman I, Attef O: Telemedicine-based KADIS combined with CGMS has high potential for improving outpatient diabetes care. *Journal of Diabetes Science and Technology* 2007; 1: 4: 511-521.

⁷ Medtronic: Guardian Real-time Continuous Glucose Monitoring System Users Guide. Medtronic MiniMed Inc., Northridge, California, 2006.

⁸ Diabetes Self-Management, 2006. Counter Regulatory Hormones. http://www.diabetesselfmanagement.com/Articles/Diabetes-Definitions/counterregulatory_hormones/ (Accessed: April 14, 2011).

Endogenous insulin: The hormone, insulin, produced within the human body by the β -cells of the islets of Langerhans in the pancreas. When a rise in BG is sensed, the response is the release of insulin.³

Euglycaemia/normoglycaemia: The normal range in which a healthy person's BG concentration varies throughout the day is defined as 3.9 – 6.6 mmol/L.^{3,4}

Exogenous insulin: Exogenous is defined as “originating outside the system concerned”.³ Therefore, exogenous insulin is insulin injected into the body.

Glucagon: A hormone that counters the action of insulin on the BGL, i.e. glucagon inhibits the production of glycogen and activates the breakdown process of glycogen (glycogenolysis) to produce glucose and the release of plasma glucose by liver cells. Glucagon is produced in the α -cells of the islets of Langerhans in the pancreas.³

Glucose absorption curve: An example of a glucose absorption curve is depicted in Figure 2:

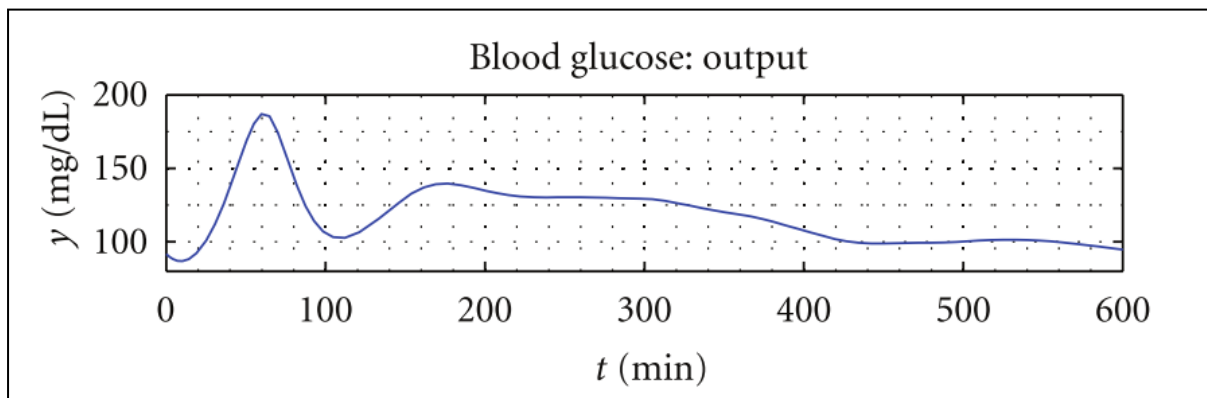


Figure 2: Glucose absorption curve.⁹

Glucose/insulin metabolism: When the plasma glucose concentration level becomes low, the β -cells stop releasing insulin. Instead, the α -cells, also contained in Langerhans islets, start to release glucagon. Glucagon exerts control over pivotal metabolic pathways in the liver and leads the liver to break down the glycogen (glycogenolysis) stores and dispense

⁹ György A, Kovács L, Szalay P, Drexler D, Benyó B, Benyó Z: Quasi-Model-Based Control of Type 1 Diabetes Mellitus. Journal of Electrical and Computer Engineering 2011; 1-12. (doi:10.1155/2011/728540)

glucose. As opposed to the fact that glucagon secretion triggers the liver to dispense glucose, insulin secretion inhibits glucose production by the liver.¹⁰

Glycogen: The main storage of glucose within liver cells and skeletal muscle.³

Glycaemic index (GI): “On a ‘glycaemic’ scale of 0 to 100, the GI compares carbohydrates weight for weight in individual foods, providing a physiologic rather than structural basis for ranking glycaemic potential (Table 1). A food with a lower GI contains starches and sugars that are more slowly digested and absorbed, or less glycaemic by nature (e.g. fructose).”¹¹

HbA_{1c}: “Haemoglobin (Hb) is the part of a red blood cell that carries oxygen to the cells and sometimes joins with the glucose in the bloodstream. Also called haemoglobin A_{1c} or glycosylated haemoglobin, if tested, shows a person's average blood glucose level over the past 2 to 3 months. The test shows the amount of glucose that [attaches] to the red blood cell, which is proportional to the amount of glucose in the blood”.⁴

Insulin: The hormone produced by the β -cells of the islets of Langerhans in the pancreas that controls the glucose uptake of muscles and adipose tissue and inhibits the breakdown of glycogen in the liver.³

Insulin action profiles: The insulin action profiles for the different types of short-, intermediate- and long-acting insulin available.

¹⁰ Li J, Kuang Y: Analysis of a Model of the Glucose-Insulin Regulatory System with Two Delays. Society for Industrial and Applied Mathematics 2007; 67: 3: 757-776.

¹¹ Brand-Miller J, Dickinson S, Barclay A, Celermajor D: The Glycemic Index and Cardiovascular Disease Risk. Current Atherosclerosis Reports 2007; 9: 479-485.

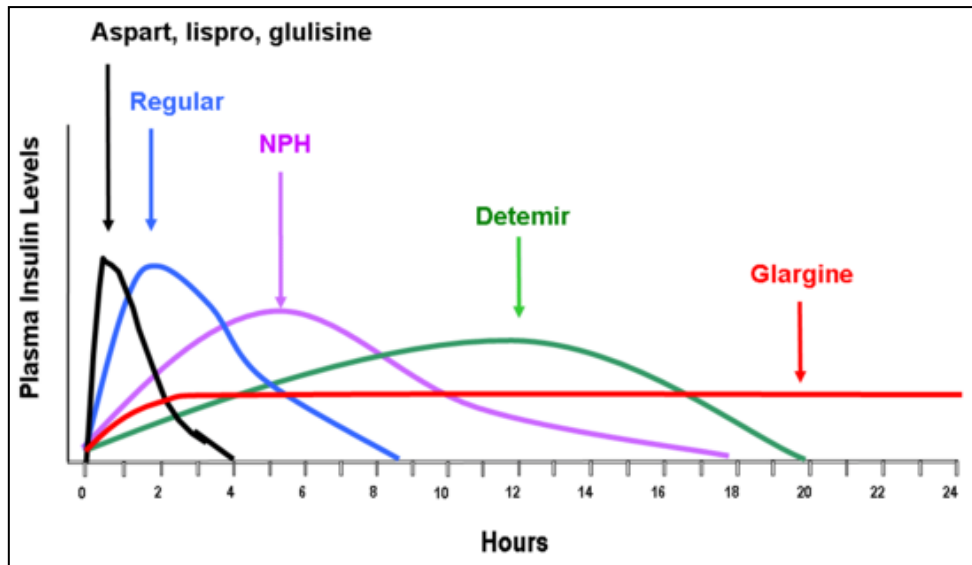


Figure 3: Insulin action profiles for the different types of insulin available.¹²

Insulin protocol: Is defined by Bellazzi *et al.* (1994) as the timing, type and total amount of insulin administered to a specific diabetes patient. This protocol is usually based on different factors affecting the patient in everyday life, such as meal planning, physical activity and BG levels.⁴

Insulin pump: “An insulin-delivering device about the size of a deck of cards that can be worn on a belt or kept in a pocket. An insulin pump connects to narrow, flexible plastic tubing that ends with a needle inserted just under the skin. Users set the pump to give a steady trickle of insulin or basal amount of insulin continuously throughout the day. Pumps release bolus doses of insulin (several units at a time) at meals and at times when blood glucose is too high, based on programming done by the user”.⁴

PDA: PDA is an acronym for Personal Digital Assistant. It is a small, hand-held computer that is used as a data manager.

Postprandial: Occurring after a meal.¹²

Preprandial: Occurring before a meal.¹³

Subcutaneous: Putting a fluid into the tissue under the skin.⁴

¹² Hirsch IB, Kyler JS: 2006. Chapter 20: The Management of Type 1 Diabetes. <http://www.endotext.org/diabetes/diabetes20/ch01s06.html> (Accessed: April 14, 2011).

¹³ Merriam Webster, 2011. Medline Medical Dictionary. <http://www2.merriam-webster.com/cgi-bin/mwmednlm?book=Medical&va=postprandial> (Accessed: April 14, 2011).

Abbreviations

ANFIS	Adaptive Neuro-fuzzy Inference System
ANN	Artificial Neural Networks
BG	Blood Glucose
BGL	Blood Glucose Level
BI	Blood Insulin
CBR	Case-based Reasoning
CDE	Centre for Diabetes and Endocrinology
CGM	Continuous Glucose Monitor
CHO	Carbohydrate
CM	Compartmental Model
CRH	Counterregulation Hormone
DM	Diabetes Mellitus
DEMS	Diabetes Electronic Management System
ENCDOR	Edgar National Centre for Diabetes and Obesity Research
FR	Free-run
FSIGTT	Frequently Sampled Intravenous Glucose Tolerance Test
GI	Glycaemic Index
HCI	Human-centred Informatics
HLM	High-level Module
IDDM	Insulin-dependent Diabetes Mellitus

IVGTT	Intravenous Glucose Tolerance Test
LLM	Low-level Module
MBR	Model-based Reasoning
MIA	Modal Interval Analysis
MMR	Multi-modal Reasoning
OGTT	Oral Glucose Tolerance Test
PDA	Personal Digital Assistant
PID	Proportional-integral-derivative
RH	Regulation Hormone
RMS	Root Mean Square
RNN	Recurrent Neural Networks
RTRL	Real-time Recurrent Learning
SC	Subcutaneous
TF	Teacher-forming
WHO	World Health Organisation

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