

Research Article

Development of AIDA v4.3b Diabetes Simulator: Technical Upgrade to Support Incorporation of Lispro, Aspart, and Glargine Insulin Analogues

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Introduction. AIDA is an interactive educational diabetes simulator available on the Internet without charge since 1996 (accessible at: <http://www.2aida.org/>). Since the program's original release, users have developed new requirements, with new operating systems coming into use and more complex insulin management regimens being adopted. The current work has aimed to design a comprehensive diabetes simulation system from both a clinical and information technology perspective. *Methods.* A collaborative development is taking place with a new generic model of subcutaneous insulin absorption, permitting the simulation of rapidly-acting and very long-acting insulin analogues, as well as insulin injections larger than 40 units. This novel, physiological insulin absorption model has been incorporated into AIDA v4. Technical work has also been undertaken to install and operate the AIDA software within a DOSBox emulator, to ensure compatibility with Windows XP, Vista and 7 operating systems as well as Apple Macintosh computers running Parallels PC emulation software. *Results.* Plasma insulin simulations are demonstrated following subcutaneous injections of a rapidly-acting insulin analogue, a short-acting insulin preparation, intermediate-acting insulin, and a very long-acting insulin analogue for injected insulin doses up to 60 units of insulin. *Discussion.* The current work extends the useful life of the existing AIDA v4 program.

1. Introduction

Interest in the use of information technology (IT) in diabetes care is increasing [1, 2]. The rationale underlying this interest is the hope that computers may provide a way of improving the therapy offered to diabetic patients—permitting more patients to be managed more intensively—in line with the experience of the Diabetes Control and Complications Trial (DCCT) [3]. However, in addition to the landmark DCCT study [3], there have been other randomised controlled trials that have highlighted the potential benefits of a more flexible approach to diabetes care. The

DAFNE (dose adjustment for normal eating) approach has been pioneered in Dusseldorf [4] and since the trialled in Bucharest [5] and elsewhere [6], as well as more recently in the UK [7]. This has shown that a structured training course designed to maintain blood glucose (BG) control while enabling dietary freedom—teaching diabetes self-management skills to patients with insulin-dependent (type 1) diabetes mellitus—can be effective in improving metabolic control [4–7]. The hypothesis underlying this approach is that more comprehensive teaching may lead to attainment of the practical goals achieved in the DCCT. Furthermore, the DAFNE educational model, which focuses

on teaching patients the skills to self-adjust insulin dosages for carbohydrate intake, seems also to be associated with an improved sense of self-efficacy and treatment satisfaction [8].

The working hypothesis underlying the AIDA interactive educational diabetes simulation approach is that there are not enough diabetes educators to provide the sort of intensive insulin therapy offered in the DCCT, and even DAFNE-style structured teaching sessions can be workforce-intensive and time-consuming. Therefore, perhaps computer-assisted learning tools may be able to help in the transfer of knowledge from health-care professionals to patients [9], particularly if there becomes a need to offer repeat education to people with diabetes over a longer period of time.

There are many different aspects to diabetes education; however, learning facts is only one of these [10]. The ability to gain experience is also of great importance. It is well recognised that it is not ideal for patients to learn about diabetes control solely from real-life experiences because of the long time frames involved, aside from the possible very real dangers of hypo- or hyper-glycemia [11]. For this reason, it has been suggested that an interactive simulation of a diabetic patient might offer one solution [12].

1.1. AIDA Background. AIDA is a freeware computer program that permits the interactive simulation of plasma insulin and BG profiles for demonstration, teaching, self-learning, and research purposes. It has been made available since March/April 1996, without charge, on the World Wide Web as a noncommercial contribution to continuing diabetes education. In the 14+ years since its original Internet launch, over two million visits have been logged to the AIDA Web pages at <http://www.2aida.org/> and <http://www.2aida.net/> and over 345,000 copies of the program have been downloaded, *gratis* (Figures 1(a) and 1(b)). Further copies have been made available, in the past, on diskette by the system developers [13–17] and from the British Diabetic Association, London, UK [18].

When AIDA is run, a dialog box opens and asks the user to select the status and individual characteristics of the subject for simulation, including body weight and main metabolic indices, such as renal threshold of glucose, creatinine clearance, and peripheral and hepatic insulin sensitivities (Figure 2(a)). These parameters serve to specify patients with different degrees of insulin resistance and various degrees of glycaemic impairment.

Once all the fields are set and new values are saved, the simulation can be run. Simulation results are presented in a graphical format (Figure 2(b)), showing blood glucose and plasma insulin concentrations. Users can specify nearly unlimited numbers of virtual diabetic patients and test how different types of treatments, doses and dosing regimens, and even lifestyle (dietary) changes affect the daily BG profile (Figure 2(c)). If a simulated regimen is found unable to keep glycaemia within desired limits, users can experiment with alternative management regimens to try and improve the daily BG pattern [19].

An estimate of medium-term BG control which will be familiar to patients/software users is provided by the AIDA program via the glycosylated haemoglobin (HbA_{1c} level)

which is estimated on the basis that if the simulated BG profile was maintained for approximately 8–12 weeks this is the expected glycaemic control (HbA_{1c} index) that would result [20, 21]. People with diabetes, ideally, would be aiming for an HbA_{1c} of 6.0%–6.5%.

A major benefit of using AIDA is that it offers an opportunity to try and use the patient's own data, in an attempt to improve their understanding of their own diabetes. The AIDA software and underlying model have been previously described in detail elsewhere in the literature [10, 22, 23].

1.2. Rationale for Revising the Current AIDA Program. Based on the large number of downloads, user comments clearly demonstrate that the AIDA educational software has so far stood the test of time [24–26]. Like other software products more than 14 years after their original launch, however, the time is ripe to consider potential revisions to the existing AIDA program. Developments both in the clinical and computational arena clearly point to the need to revise and extend the current software. User comments have prompted the systematic revision of the description and spectrum of diabetes types, as well as interventions/lifestyle events, handled by the AIDA model.

From a clinical perspective the existing AIDA v4 software does not cater for the latest insulin analogue preparations which have become increasingly used in the therapy of people with insulin-dependent (type 1) diabetes mellitus. Furthermore, the existing program is unable to simulate either non-insulin-dependent (type 2) diabetic patients with endogenous insulin secretion or management regimens involving insulin infusions in addition to subcutaneous boluses of insulin. New insights into the processes involving carbohydrate metabolism should also appear in an updated version of the educational simulator in order to fully reflect the complexity of modern day diabetes therapy.

For instance, in clinical practice the regulation of the BG concentration is mainly achieved by the action of three control variables: insulin, meals, and oral hypoglycaemic agents, but also modified by the effects of other factors, such as physical exercise and stress. This implies a need to extend the scope of input variables included in the underlying AIDA model.

There are also a number of technical issues to be resolved about the current software. The AIDA program, being DOS-based, is now becoming somewhat dated, and there can be issues about making use of the AIDA v4.3a downloadable software under the Microsoft Windows XP, Windows Vista, and Windows 7 operating systems. Furthermore, it is necessary to respond to some technical requests of AIDA users and resolve certain Turbo Pascal display problems that seem to manifest themselves on the latest notebook computers. The flexibility and user friendliness of the user interface could also clearly be improved. The main features of the current and future planned versions of the AIDA software are contrasted in Table 1.

It is evident that AIDA should remain a user-friendly program that implements a novel physiological model of the glucose-insulin system. This paper aims to present both the

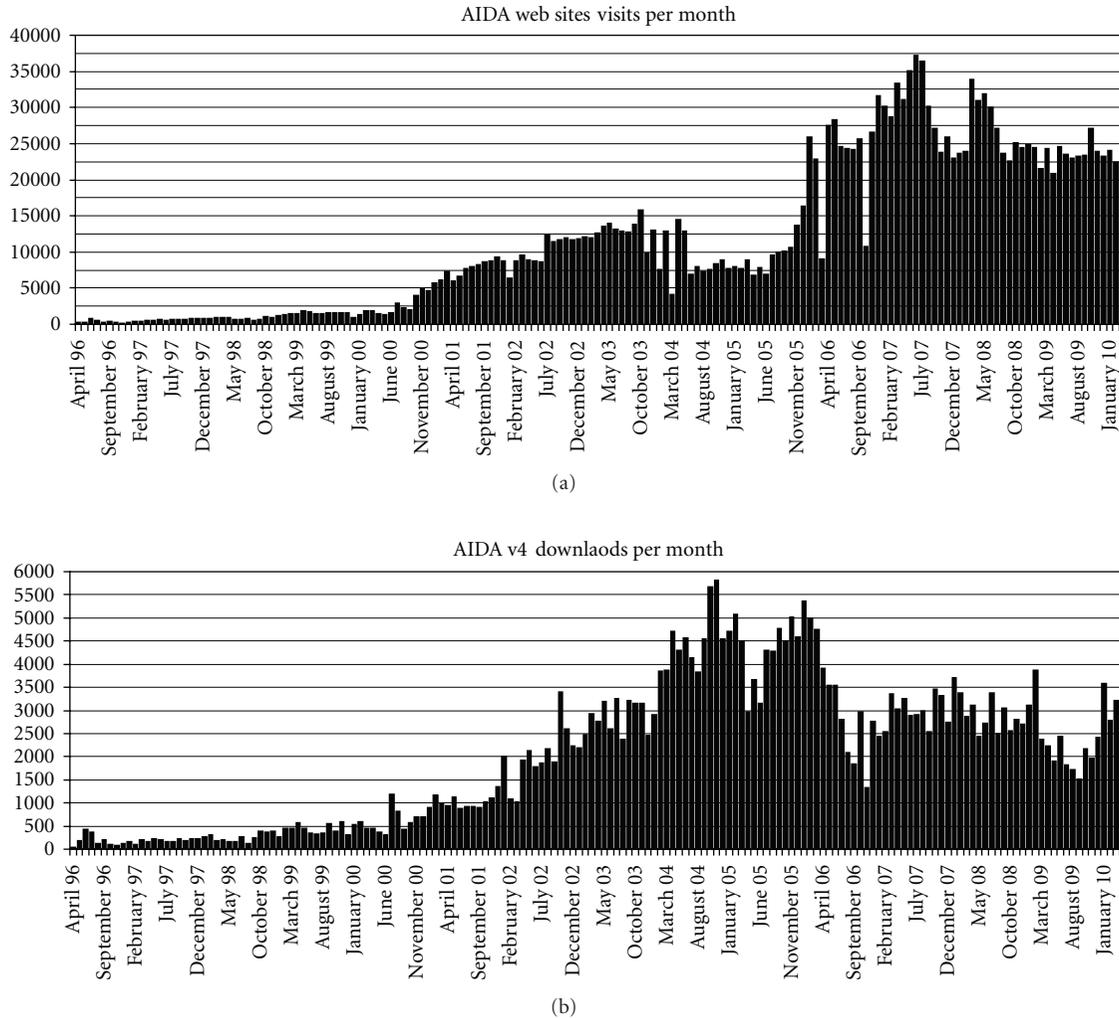


FIGURE 1: Number of (a) visits and (b) downloads per month at the two AIDA websites (<http://www.2aida.org/> and <http://www.2aida.net/>) since March/April 1996 when AIDA first went live on the Internet—up to March/April 2010—just before the web launch of AIDA v4.3b. Despite the age of the software, there continues to be considerable interest in the program with a large number of site visitors and downloads.

clinical and technical results achieved to date in the current phase of the revision process.

2. Methods

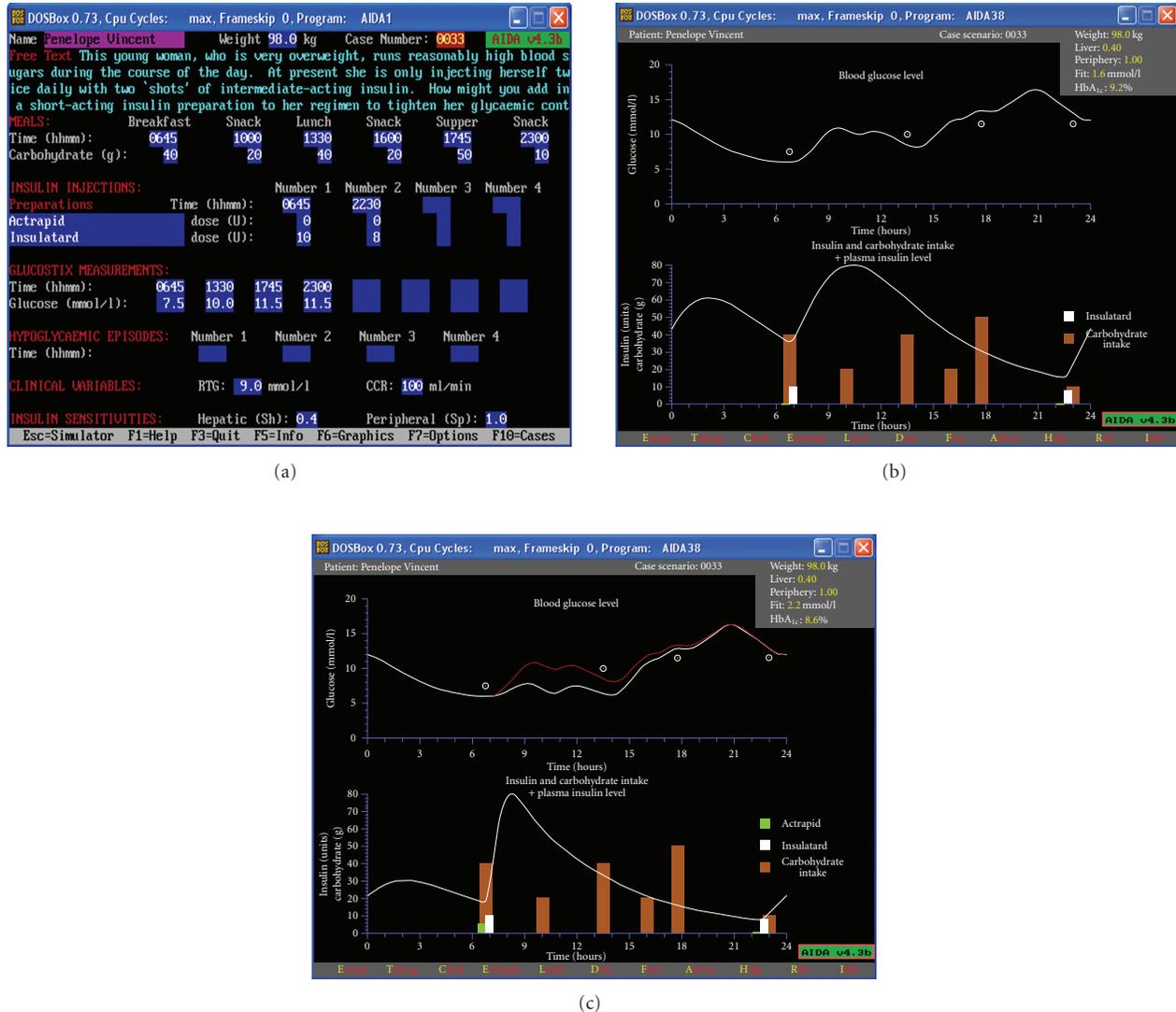
The first update to the AIDA v4.3a program relies on several new methods which are related to modelling, programming, and technical issues. These novel developments will be overviewed in turn.

2.1. Modelling Methods. The underlying AIDA model consists of glucose and insulin submodels. The glucose submodel describes the temporal evolution of the concentration of glucose in the blood stream based on the simulated patient's management regimen as well as lifestyle (dietary) information. BG levels are controlled by various glucose fluxes into and out of the blood stream. These fluxes are complex functions of glucose and insulin levels, some of which vary according to a diurnal rhythm [23]. The glucose submodel

has not been revised in the first phase of the program's revision.

The insulin submodel encapsulates equations according to which insulin molecules enter the circulation from subcutaneous depots (insulin absorption) and are distributed/eliminated. As a first stage to updating the AIDA simulator, a decision was taken to focus on the appearance of insulin in the plasma following a subcutaneous injection—thereby incorporating more novel insulin analogues into the program. In a survey of 200 users of the AIDA v4 software this was an often requested “wish list” feature for a new release of the program [24–26].

Subcutaneous insulin absorption is a complex process which is affected by many factors including tissue blood flow, injection site/depth, injected volume, and concentration [27]. Following a subcutaneous injection, soluble insulin forms a subcutaneous depot, where it is present in several multimeric, primarily hexameric and dimeric, forms. The subcutaneous depot is cleared by absorption



of dimeric insulin molecules into the vasculature [28]. Although absorption of hexameric insulin has been reported, it is considered not significant as compared to dimeric insulin [29, 30].

Various insulin absorption models have been proposed which vary in their degree of complexity. Virtually all of them handle short-acting (regular) insulin preparations, while

a few handle intermediate-acting insulin and novel insulin analogues [28, 31, 32].

The Berger-Rodbard model [33] adopted in AIDA v4.3a was a simple and flexible tool that enabled the estimation of plasma insulin levels for various insulin preparations. However, this model was developed at the end of the 1980s and thus insulin analogues were not included.

TABLE 1: Comparison of features in current release of AIDA v4 diabetes simulator (on left) with planned features in future versions of the software (v4.5) and later (on right). IDDM: insulin-dependent (type 1) diabetes mellitus. NIDDM: non-insulin-dependent (type 2) diabetes mellitus.

AIDA v4 current version	AIDA v4.5 (and later) future versions
Model building/structure	New features
(i) Interconnected insulin-glucose submodels	(i) Comprehensive insulin/glucose model built from unit processes (diabetes “lego”-land)
(ii) Empirical models for insulin/glucose dynamics and control	(ii) Physiologically based model of insulin absorption (generic) and kinetics
(iii) Linear insulin disposition/elimination (superposition principle applies)	(iii) Fewer (only necessary and realistic) assumptions
(iv) Use of fictive compartment (“active” insulin)	(iv) Patient specification with minimal number of identifiable parameters
(v) Over parameterisation of patients (use of nonidentifiable parameters such as separate hepatic and peripheral insulin sensitivities)	(v) Specification of typical patient types (insulin sensitive versus resistant, etc.) parameterised accordingly
Limitations	Overcoming limitations
(i) IDDM only	(i) Both IDDM and NIDDM
(ii) No insulin analogues	(ii) Both rapidly acting and very long-acting insulin analogues added
(iii) Insulin dose ≤ 40 units	(iii) Insulin dose ≤ 60 units
(iv) Carbohydrate intake/meal ≤ 80 g	(iv) Carbohydrate intake/meal ≤ 120 g
(v) Oral hypoglycaemic drugs not incorporated	(v) Different types of oral hypoglycaemic drugs included
(vi) Lifestyle events/effects <i>not</i> included (stress, physical activity, menstrual cycle, etc.)	(vi) Lifestyle events (stress, physical activity, menstrual cycle, etc.) included
Technical	New features
(i) Menu driven data entry (nongraphical)	(i) Intuitive graphical user interface

A more comprehensive model, which has focused more on physiology and pharmacokinetics, has been described by Mosekilde and colleagues [34]. This approach was later modified by Trajanoski et al. [35] and Wach et al. [36] in an attempt to allow for parameter estimation based on plasma insulin profiles. The model was also extended to support monomeric insulin analogues. Being more physiologically based, the model proposed by Mosekilde et al. [34] and modified by Trajanoski and colleagues [35] was chosen as the basis for the insulin absorption model of Tarin and colleagues [37, 38] and the current collaborative development work with AIDA v4 [39–41]. The Trajanoski

TABLE 2: Parameter set derived from Mosekilde et al. [34].

Parameter	Value	Description
$Q/\text{mL}^2 \text{IU}^{-2}$	0.13	Chemical equilibrium constant
B/min^{-1}	$1.3 \cdot 10^{-2}$	Absorption rate constant
$D/\text{cm}^2 \text{min}^{-1}$	$0.9 \cdot 10^{-4}$	Diffusion constant for soluble insulin in water at 37°C
$C/\text{IU cm}^3$	0.05	Binding capacity for insulin in the tissue
T/min	800	Average life time for insulin in its bound state

model was extended to deal with the long-acting insulin analogue glargine, thereby covering the whole range of insulin preparations currently used in medical therapy. Later works have subsequently appeared in the literature that also consider insulin glargine, but where the diffusion process is neglected or approximated [42–44].

The generic insulin absorption model planned for inclusion in AIDA v4 [37, 38] represents diffusion of insulin through the subcutaneous depot, transformation between the different insulin states—hexameric, dimeric, and crystallized (in the case of the insulin glargine)—and absorption through capillary walls. Due to diffusion, the model is no longer a set of ordinary differential equations, but partial differential equations (PDEs) dependent on both time and space. Since the diffusion process is considered homogeneous and isotropic, the system of PDEs is unidimensional in space (distance from the injection site).

The generic model is based on published data from the literature. As described by Tarin and colleagues [37, 38] the parameters of the absorption model for insulin glargine were found through an iterative identification process, while the parameters for the rest of formulations were obtained from the previous works of Mosekilde et al. [34], Trajanoski et al. [35], Höfig [45], and Gessler [46].

In the study by Mosekilde et al. [34] the model was adjusted to fit available experimental data and to determine the effective diffusion constant D for subcutaneous insulin, the absorption rate constant B for dimeric insulin, the equilibrium constant Q between hexameric and dimeric insulin, the typical binding capacity C for insulin in the tissue, and the average lifetime T for insulin in its bound state (not to be confused with the new “bound state” of insulin glargine). Typical values for insulin injection into the thigh of a fasting person with type 1 diabetes are summarized in Table 2.

As reported by Trajanoski et al. [35], due to the model structure, the formal identification techniques cannot be adopted for the modified model (i.e., the model is theoretically unidentifiable [47]). Further model simplification like linearization or aggregation of distributed effects cannot be performed, since the essential characteristics of the model

would be lost if linearization was done. On the other hand, model decomposition is not possible, as it is impossible to measure insulin with different association states in the subcutaneous depot. Therefore, a parameter set has been chosen from published *in vivo* and *in vitro* experiments as shown in Table 3.

- (i) Values for the diffusion coefficients of insulin and insulin analogues published by Moeller et al. [48] were used (the diffusion constant D was measured in water or tissue biopsies at 37°C).
- (ii) The absorption rate constant for monomeric insulin was calculated from the slope of the absorption curves observed by Kang et al. [47]. According to the assumptions of Trajanoski et al. [35] during the last phase of the absorption only dimers are absorbed. Therefore, for the absorption rate constant Bd for soluble insulin, the final slope of the absorption curve of Kang et al. [47] is adopted.
- (iii) In the study by Mosekilde et al. [34] it was assumed that the hexameric-dimeric balance is always near equilibrium, and a large value was chosen for the parameter P compared to the absorption rate constant Bd . Since even large changes of P do not alter the results significantly, in the study by Trajanoski et al. [35] the same value was used.
- (iv) For the distribution-elimination model for soluble insulin, parameters reported by Kraegen and Chisholm [49] were used for the calculations (Ks and Vp).
- (v) The plasma elimination rate constant Km for monomeric analogues was taken from the study by Robertson et al. [50].

In the studies by Höfig [45] and Gessler [46] the parameter Q was modified in order to mimic the absorption curves measured with different insulin preparations such as rapidly acting analogues and NPH (see the studies by Kang et al. [51] and Binder [52]). Readers are referred to the report by Tarin et al. [37] for a detailed description of the mathematics underlying the generic insulin absorption model.

As the insulin flow into the blood stream is markedly slower than the elimination of insulin from the plasma, plasma insulin kinetics are typically described as a single compartment model representing the blood pool and some extravascular space from where there is a first-order elimination of insulin. This is the modeling approach that has been used for the insulin model [33] incorporated within the existing AIDA v4 program.

2.2. Programming Issues. The model of glucose-insulin interaction includes a set of differential equations, algebraic expressions, and parameters which helps to make it more case-/patient-specific. Model equations are integrated by separately computing the glucose and insulin submodels.

For simulating type 1 diabetic patients the insulin submodel is considered independent of the glucose part of the model. As none of the parameters associated with the kinetics

TABLE 3: Parameter set derived from Trajanoski et al. [35].

Parameter	Value	Description
$Q/\text{mL}^2 \text{ IU}^{-2}$	76	Chemical equilibrium constant
B_d/min^{-1}	$1.18 \cdot 10^{-2}$	Absorption rate constant for dimeric insulin
B_m/min^{-1}	$1.22 \cdot 10^{-2}$	Absorption rate constant for monomeric insulin
P/min^{-1}	0.5	Rate constant
$D/\text{cm}^2 \text{ min}^{-1}$	$8.4 \cdot 10^{-5}$	Diffusion constant for soluble insulin
$D_m/\text{cm}^2 \text{ min}^{-1}$	$1.66 \cdot 10^{-4}$	Diffusion constant for monomeric insulin analogues
K_s/min^{-1}	0.09	Plasma insulin elimination rate
V_p/l	12	Volume of plasma insulin compartment
K_m/min^{-1}	55	Plasma insulin elimination rate constant for monomeric insulin analogues

are assumed to be patient-specific, the insulin concentrations can be precomputed for any possible insulin delivery and stored prior to use by AIDA. Insulin levels resulting from any particular insulin regimen are computed by summing up the precomputed individual contributions corresponding to the preparations and doses as used in the particular insulin regimen.

This technique allows the glucose subsystem exhibiting slower dynamics to be simulated with a 15-minute step size. It is noted that integrating insulin equations in real time would require a much smaller step size (less than 1 minute) due to the short halftime (about 5 minutes) of insulin in the plasma.

Simulations start with a BG level of 100 mg/dL (5.6 mmol/L). Insulin and glycaemic responses are simulated for 48 hours, and the results of the second day's simulation are displayed as the steady state response to the current therapy.

2.3. Precomputing Insulin Levels. Although insulin levels corresponding to different types and doses of subcutaneous insulin preparations need to be determined only once, these calculations are still time-consuming because of the complexity of the generic insulin absorption model. As the coupled PDEs have no closed solution, integration should be done numerically. It is considered that insulin after the injection forms a spherical volume in the adipose tissue and starts to diffuse out symmetrically. Hence, a numerical implementation has been carried out by means

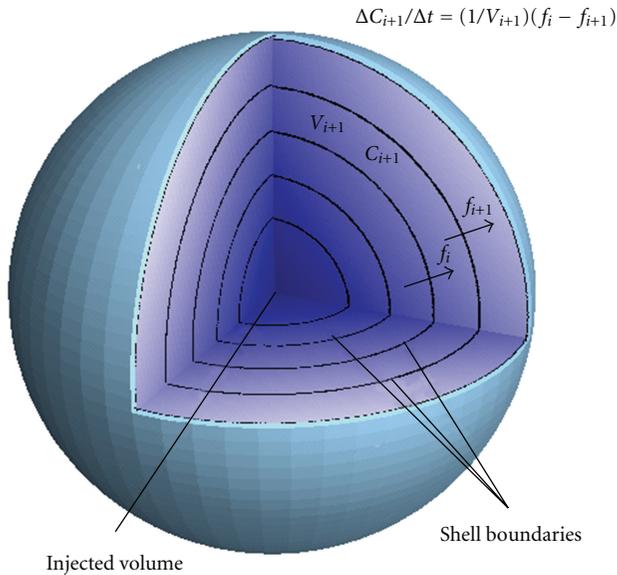


FIGURE 3: Injected volume with shells. Diffusion takes place over shell boundaries, that is, the surface of the shells, and it is approximated by the balance of insulin flows entering and leaving the shell (c : concentration; f : insulin flow; V : volume). The flows are computed according to the first Fick's law.

of a spatial discretisation consisting of spherical shells with equal volume, based on the work of Trajanoski et al. [35].

In this solution, an approximation of Fick's diffusion law as a balance of flows at each discrete shell is carried out (Figure 3 [35]).

Initial conditions are provided by the amount (dose) and type of the injected insulin. For rapidly acting, short-acting, and intermediate-acting insulin, it is considered that all the insulin is in the inner shell in chemical equilibrium between hexameric and dimeric forms. The volume of the inner shell corresponds to the injected volume. For the outermost spherical shell it is considered that the insulin concentration is null outside the considered spherical depot.

It was demonstrated by Tarín et al. [38] that a fixed number of fifteen shells, as considered by Trajanoski et al. [35], is not sufficient for all insulin types and doses. Thus, a varying number of shells is considered here depending on the dose and type of insulin. To calculate the required number of shells, the absorbed insulin flow is computed in two different ways that become equivalent for a large enough spherical depot (Figure 4):

- absorbed insulin flow at a given time t is the collection of insulin absorption flows from each spherical shell;
- absorbed insulin flow at a given time t is the decrement of total insulin in the spherical depot per unit time.

In the first case (a), if the insulin concentration outside the considered spherical depot is significant, the computed value will underestimate the actual insulin absorption flow, since this insulin will be neglected. However, in the second

case (b), the insulin concentration will be considered as absorbed, yielding an overestimation. Profiles computed by each of the methods will converge as the number of shells is increased, and thus the radius of the spherical depot increases. As computational time will increase with the number of shells considered, the solution is accepted as a compromise between efficiency and precision. The number of shells is considered adequate when the area under the curve of the calculated absorption profile (i.e., the sum of absorption flows from each shell), computed as described in item (a) above, and the injected dose, differ by less than 1%.

One percent can be considered adequate given that these losses only occur for small doses that are hardly ever administered. This represents a good compromise between speed and precision.

Figure 5 shows the number of shells required for each insulin type, and doses ranging from 1 to 60 IU, with a concentration of the preparation of 100 mIU/L (U100).

- For rapidly-acting insulin analogues, 20 shells is regarded as enough for doses higher than 20 IU, but for smaller doses the number of shells required increases dramatically, reaching 180 shells for 2 IU. Computation for 1 IU with a 1% target difference was not possible due to memory constraints.
- For short acting insulin preparations, doses higher than 10 IU require 10 shells or less; for smaller doses the number of shells increases up to 120 shells for a dose of 1 IU.
- For intermediate-acting insulin preparations and very long-acting insulin analogues, doses higher than 20 IU require only 20 shells, while for doses below 3 IU the number of shells exceeds 100, reaching 180 shells for a dose of 1 IU of insulin.

For smaller doses the injected volume is small, too. This automatically leads to rather small shell radii. Since the volume is kept constant, the further from the injection site, the thinner the shell will be. Furthermore, the smaller the radii the higher the diffusion speed and the higher the ratio between shell surface and volume. Therefore, for small injection doses, the insulin diffuses very quickly from the inner to the outermost shell and beyond, which leads to the loss if the number of shells is not sufficient. However as the AIDA v4 software only handles integer insulin injection doses, less than 1 IU insulin injection simulations are not required for the current version of the program. Although for future paediatric use such issues about fractional insulin injection dosages may potentially become of greater significance.

Table 4 shows radii of the 15th sphere around the injected volume for various doses of U100 (100 mIU/L) insulin preparations. As can be seen, the radii are within a reasonable range with respect to the thickness of the subcutaneous tissue.

Regarding time discretisation, the Euler method is applied with a time step of 0.01 minute. The computational burden to actually calculate insulin absorption flows is not trivial but does not exceed the capabilities of modern personal computers either. Calculating the absorption flow

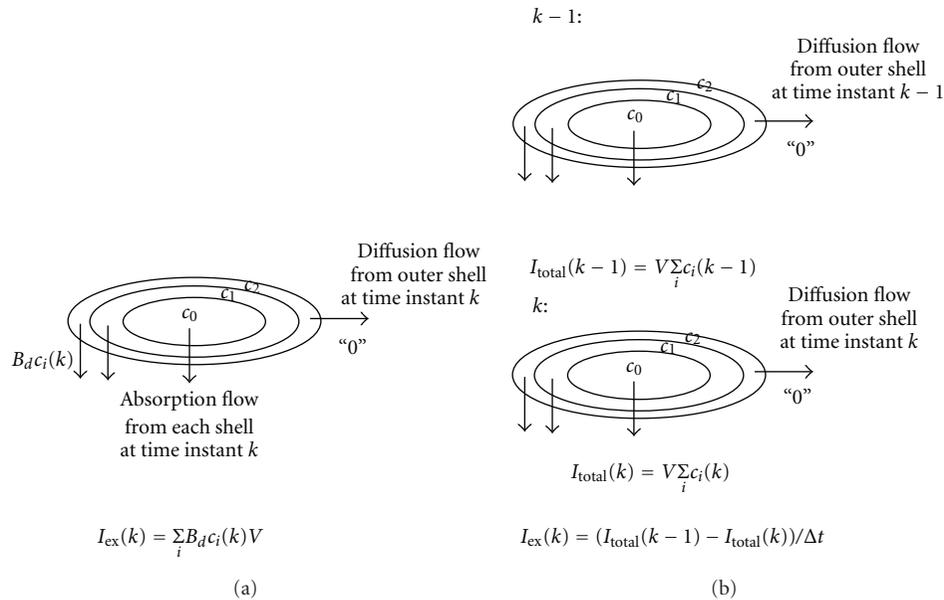


FIGURE 4: Two methods of approximation of the absorbed insulin flow: (a) the absorbed insulin flow I_{ex} is obtained as the collection of absorbed insulin at each shell; (b) the absorbed insulin is obtained as the decrement of total insulin per unit time. If the number of shells is adequate, the diffusion flow from the outer shell is null and both methods are equivalent.

TABLE 4: Radius of the 15th sphere for various injected volumes of U100 (100 mIU/L) insulin.

Injected dose/IU	Injected volume/mL	Radius of 15th sphere/mm
1	0.01	3.4 mm
2	0.02	4.2 mm
5	0.05	5.8 mm
10	0.1	7.3 mm
20	0.2	9.1 mm

of one 18 IU injection of glargine, for example, needs roughly three seconds on a 1.4 GHz Pentium class PC without any effort in the implementation. Doing the same on a portable device like a PocketPC or smart phone, equipped with a 200 MHz StrongArm CPU, will require more patience but can be done in less than ten seconds especially if a highly optimized implementation is used. This remains true for the vast majority of insulin injection doses. It is only when calculating extremely low doses that much longer computational times are observed. As can be seen, the number of required shells may increase dramatically for low insulin doses (Figure 5).

At low insulin doses computational time can become excessive, and running the simulations in “real time” may not be appropriate. For this reason, AIDA v4 relies on precomputed insulin profiles.

2.4. Technical Issues. There have been some reported display issues with the existing AIDA v4 software operating under Windows XP, particularly with the latest laptop/notebook PCs. Also Microsoft Windows Vista and Windows 7 do not

allow legacy Disk Operating System (DOS) applications to switch to full-screen display mode, as required by AIDA v4. Therefore, in order for AIDA to run optimally under Windows XP—and operate under Windows Vista and Windows 7—an alternative display approach has been investigated. Instead of trying to execute AIDA directly as a standalone application, as has been done previously, the idea has been developed to run AIDA using a DOS emulator. This emulator is a Windows application itself that mimics the behaviour of the 16-bit DOS operating system for which AIDA was originally designed. The concept is that AIDA should then in turn run within this emulator, hidden from the Windows XP/Vista/7 operating systems, yet in a way that would be transparent to the user. This approach is similar to a method adopted previously to permit AIDA v4 to operate on Apple Macintosh computers, using SoftWindows or PowerPC emulation software on Apple Macs (<http://www.2aida.org/applemac/>) [53]. The approach has been investigated for notebook and desktop PCs running Windows XP, Vista, and 7 to prolong the useful “shell life” of the existing AIDA v4 software and permit people to continue making good use of the program.

DOSBox is a lightweight DOS emulator that has gained wide acceptance in the DOS gaming community. It is published under a General Public Licence (GPL) and can be used and distributed freely without charge or fee. Packed with a handy installer, it comes as a 1.5 Mb download, which is acceptable even for users with slow Internet connections. It is freely available from <http://www.dosbox.com/>.

Installing and starting DOSBox is a straightforward process. DOSBox also offers a convenient way to configure itself. Upon running DOSBox, it scans the directory in which

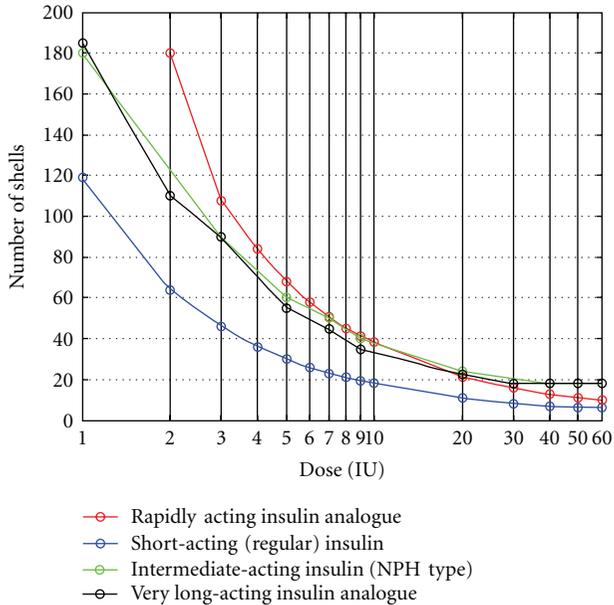


FIGURE 5: A bench test study concerning spatial discretization reveals that a fixed number of shells is not appropriate for any insulin class, dosage, or preparation. Accurate simulation results depend on the insulin preparation and the dose. The number of shells required for an insulin absorption profile computation with an area under the curve (AUC) error below 1% is shown. The time step considered for 2 IU of rapidly acting insulin was reduced to 0.002 to avoid numerical instabilities. The value for 1 IU could not be computed due to memory resources limitations (number of shells greater than 250 are estimated).

it is located for a file called “dosbox.conf.” Within this file, various settings can be prespecified. Among these are the keyboard layout, the emulation speed, and all the steps to be executed automatically right after starting DOSBox. In this way, DOSBox can be tailored to suit the hardware and software environments found on the host computer. All possible settings are documented at the DOSBox website (<http://www.dosbox.com/>).

The possibility to configure the keyboard layout is especially important as AIDA is used internationally. By exploiting the “autorun” section mechanism in the “dosbox.conf” file, DOSBox can also be configured to start emulating AIDA upon invocation. Therefore, usage of the DOSBox DOS emulator can be implemented in a way that is entirely transparent to the AIDA user.

Interestingly, the display problems, AIDA v4.3a can show on some of the latest notebook PCs are not experienced when AIDA is run within DOSBox. As these problems might be related to missing UNICODE support of the compiler with which AIDA was compiled, the solution of this problem does not come as a surprise as DOSBox emulates the ASCII environment for which AIDA v4 was compiled.

Installation of a combined AIDA/DOSBox application can also be streamlined. In order to emulate AIDA, not all files that the standard DOSBox installer copies to the host computer are actually needed. As neither special

sound output nor game-relevant hardware support (e.g., for joysticks) are required, it is sufficient to copy the DOSBox executable, the “dosbox.conf” file for the host computer, and the two Simple DirectMedia Layer (SDL) library files which provide cross-platform multimedia capabilities designed to offer fast access to the graphics frame buffer.

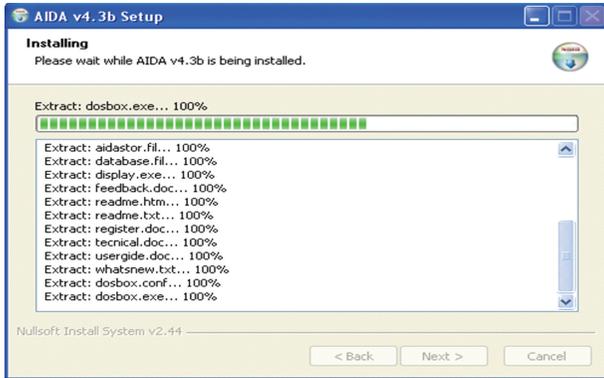
If the AIDA installer then updates the “dosbox.conf” file with the path to the AIDA executables and the keyboard layout autoidentified at install time and lets the created links in the start menu folder point to the DOSBox executable instead of the AIDA executable, then AIDA can be used in a streamlined manner on any Microsoft Windows PC operating system, including Windows XP, Windows Vista and Windows 7.

The installer for AIDA has been created with the Nullsoft Scriptable Install System (NSIS). This is an advanced open source installation system that can be used for free. NSIS is especially suited for the AIDA installation as it allows more complex tasks to be performed than mere file unpack and copy routines (Figure 6(a)). Instead, via its inherent script system, it can, for instance, call any operating system application programming interface (API) functions. In this way, it is possible to query, for example, the keyboard layout of the computer on which AIDA is to be installed. Moreover, NSIS supports several handy script functions to edit text files. Thus, it can perform all the configurations of the DOSBox environment. Furthermore, being open source software and freeware it is very compatible with the AIDA freeware ethos.

The DOSBox/NSIS approach has been extensively trialed, and a technical update to AIDA (called AIDA v4.3b) has been developed which provides a “turnkey” streamlined installation of AIDA v4 incorporating the DOSBox functionality in a user friendly format for Windows XP, Vista, and 7 users.

The new version of AIDA v4.3b has been released on the Internet in April 2010. Figure 6 shows AIDA v4.3b operating in this way successfully under the (b) Windows XP, (c) Windows Vista, and (d) Windows 7 operating systems.

The AIDA v4 simulator itself comes accompanied by a second application, called AIDADEMO, which provides a demonstration of what AIDA can do for users who are not sure whether to download the full program. The AIDADEMO guides the user through a series of slides which explain usage and the theoretical background of the simulator, thereby pointing out the program’s capabilities and limitations. As AIDADEMO has originally been created using a similar development environment to AIDA v4 itself, it naturally may have similar operating system issues to the parent AIDA application. However, just as with AIDA, these issues have been addressed by use of the DOSBox approach bundled with the NSIS installer. Figure 6(e) shows a screenshot from the AIDADEMO application demonstrating for a different person (“Joy Wilson”), a 70 kg insulin-dependent diabetic patient, the effect of missing the usual morning insulin injection before breakfast with the profound hyperglycaemia (raised blood glucose) that is predicted to occur in the afternoon. The DOSBox/NSIS packaged release of AIDADEMO is accessible at the AIDA website at the end of viewing the web-based demo at <http://www.2aida.org/demo/> or directly at <http://www.2aida.org/aidademo/> (Figure 6(f)).



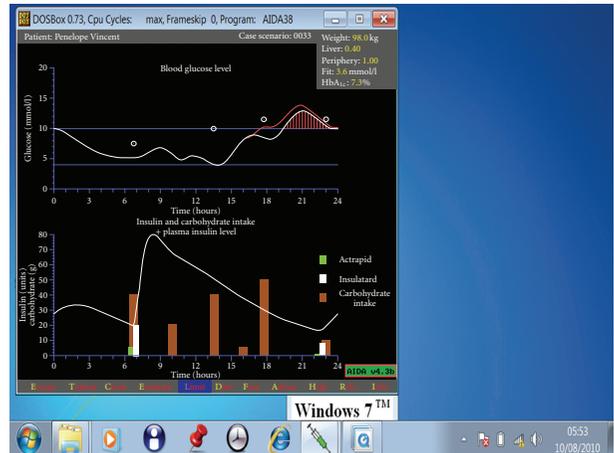
(a)



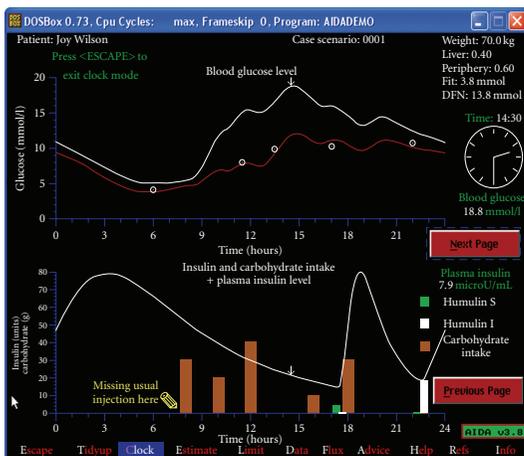
(b)



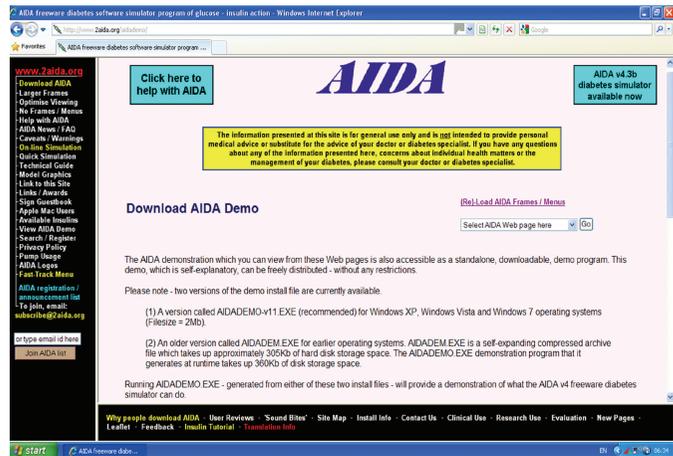
(c)



(d)

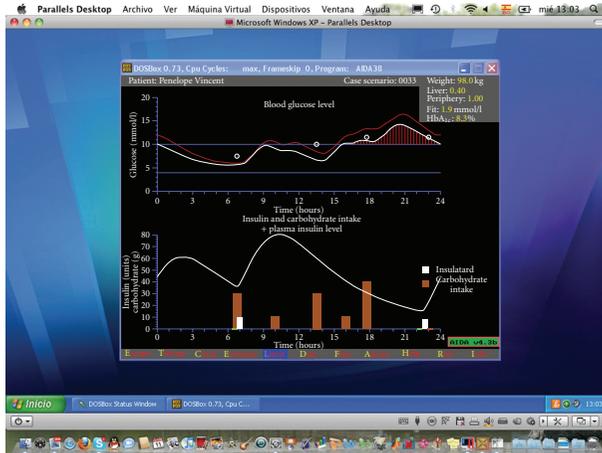


(e)

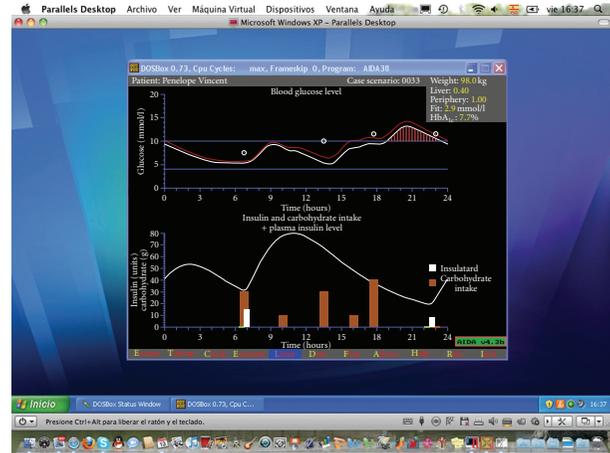


(f)

FIGURE 6: Continued.



(g)



(h)

FIGURE 6: (a) shows the Nullsoft Scriptable Install System (NSIS) in operation—which is used to set up and install AIDA v4.3b on Windows XP, Windows Vista, and Windows 7 PCs, as well as on Apple Macs running PC emulation software. (b) shows AIDA v4.3b operating successfully within a window on a PC running the Windows XP operating system. The effect of increasing the 6:45 am Insulatard insulin injection dose from 10 IU to 15 IU is shown—with a concomitant reduction in the blood glucose (BG) profile. The resulting estimated HbA_{1c} is calculated by AIDA v4.3b to be improved at 8.0% (down from 8.6% for the previous simulation from Figure 2(c) which is shown as the red BG curve for comparison). (c) AIDA v4.3b operating successfully within a window on a PC running the Windows Vista operating system. The effect of increasing the 6:45 am Insulatard insulin injection dose by 5 more units of insulin to 20 IU is shown—with a concomitant further reduction in the blood glucose (BG) profile. The resulting estimated HbA_{1c} is calculated by AIDA to be further improved at 7.5%. The previous two simulations from Figures 2(c) and 6(b) are shown as the red BG curves for comparison. A user specifiable normoglycaemic range is also shown demonstrating the target range that the user might aim for. BG values are shown in units of mg/dL—much used in North America and other countries around the world. AIDA can present simulation results in both mmol/L and mg/dL. 1 mmol/L of glucose = 18 mg/dL. (d) AIDA v4.3b operating within a window on a PC running the Windows 7 operating system. The effect of a change in the carbohydrate intake has been simulated, with a reduction in the size of the 4pm snack from 20 grams of carbohydrate to 5 grams of carbohydrate being shown. This change results in a reduction in the estimated HbA_{1c} to 7.3% (from 7.5% for the simulation shown in Figure 6(c)—the simulation from which is shown as the red blood glucose curve for comparison on this graph). (e) shows a screenshot from the AIDADEMO application demonstrating for “Joy Wilson,” a 70 kg insulin-dependent diabetic patient, the effect of missing her usual morning insulin injection before breakfast with the profound hyperglycaemia (raised blood glucose) that is predicted to occur in the afternoon. (f) shows where the new DOSBox/NSIS packaged release of AIDADEMO is available for freeware download at the AIDA website from <http://www.2aida.org/aidademo/>. (g) AIDA v4.3b software operating within a window on an Apple Macintosh computer running the Parallels Windows emulation software. The original simulation from Figure 2(b) has been used as the baseline for this example and the effect of reducing each meal and snack by 10 grams of carbohydrate is simulated. As can be seen, this improves the estimated HbA_{1c} from 9.2% (Figure 2(b)) to 8.3% with a 50 gram per day reduction in carbohydrate intake. (h) A further example of AIDA v4.3b operating within a window on an Apple Macintosh computer running the Parallels Windows emulation software. The simulation from Figure 6(g) is shown as a baseline (in red), and the concomitant effect of increasing the 6:45 am Insulatard insulin injection by 5 IU from 10 IU to 15 IU is shown with an improvement in the overall blood glucose profile, with a reduction in estimated HbA_{1c} from 8.3% (Figure 6(g)) to 7.7%.

2.5. Running AIDA v4.3b on Apple Macintosh Computers. Since the year 2000 the AIDA website has supported the use of AIDA v4 under SoftWindows and PowerPC emulation software on Apple Macintosh computers [53], and see <http://www.2aida.org/apple/mac/>. Since the adoption of Intel microprocessors by Apple in 2006, Windows applications can be executed even more efficiently on Mac operating systems OSX. This requires the installation of Windows on the Mac machine, and the use of Boot Camp (if it is intended to start the machine under Windows), or a virtualization application (like Parallels or VMware Fusion). In the first case, Windows will have access to all the resources of the Mac machine. In the second case, a virtual Windows machine will be created, sharing resources with Mac OS X.

Virtualization is based on the creation of virtual hardware by means of software. Although this will consume more resources since Mac OS X and Windows will be running at the same time, it is convenient if the user does not want to restart the machine every time they need to execute a Windows application. VMware Fusion and Parallels require an Intel Mac, a minimum of Mac OS X v10.4.6 Tiger, and 1 Gb of RAM. Boot Camp is a built-in function from Mac OS X v10.5 Leopard. Parallels Desktop 5 and VMware Fusion 3 for Mac OS X v10.6 Snow Leopard both offer compatibility with Windows 7.

The use of any of the above tools will allow the execution of AIDA v4.3b on any Intel-based Mac machine. By way of illustration, the execution of AIDA v4.3b on a Mac OS X Tiger

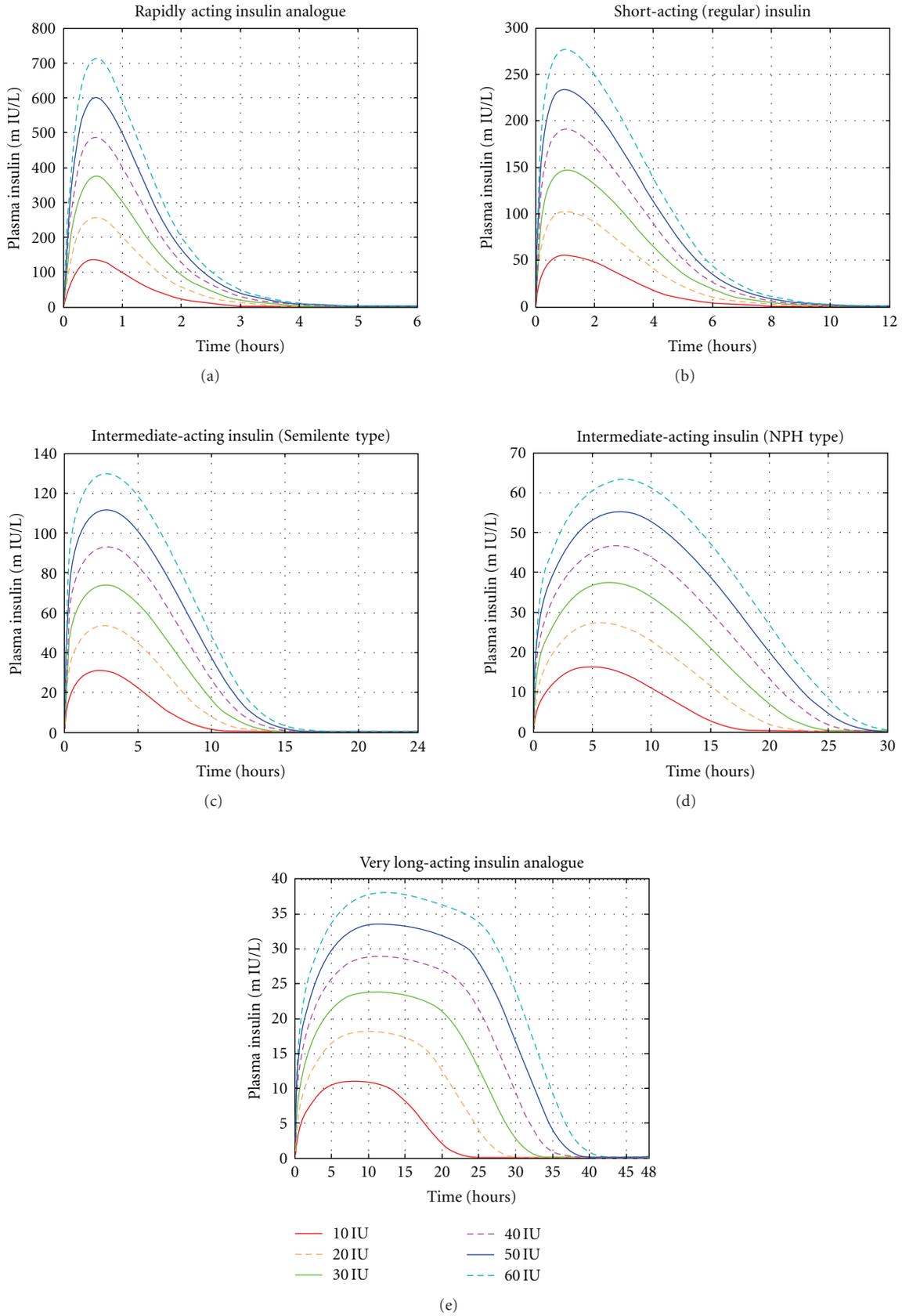


FIGURE 7: Plasma insulin simulations following subcutaneous injections of (a) a rapidly acting insulin analogue (such as lispro/Humalog or aspart/NovoLog), (b) a short-acting (regular) insulin preparation (e.g., Actrapid), intermediate-acting insulin (both (c) Semilente and (d) NPH types), and (e) a very long-acting insulin analogue (such as glargine/Lantus) for injected insulin doses up to 60 units of insulin.

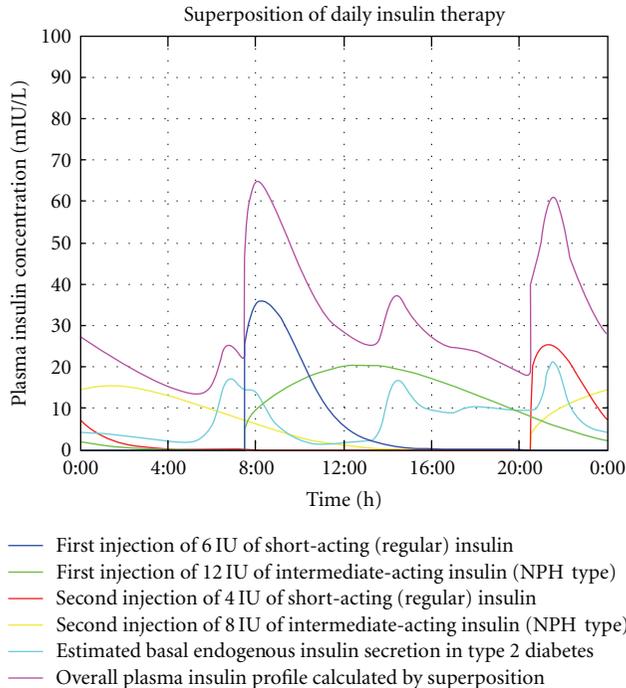


FIGURE 8: Prototype simulation using the superposition principle to calculate a plasma insulin profile based on exogenous insulin injections and estimated basal endogenous insulin secretion in a type 2 diabetic patient who takes 6 units of short-acting (regular) insulin and 12 units of intermediate-acting (NPH type) insulin in the morning with a further 4 units of short-acting (regular) insulin and 8 units of intermediate-acting (NPH type) insulin in the evening. The estimated basal endogenous insulin secretion is shown by the light blue (cyan) line—and the overall plasma insulin profile is superimposed.

machine with Parallels is shown in Figures 6(g) and 6(h). This approach has been tested on a Macbook Pro and on an iMac—using Parallels to execute a virtual machine with Windows XP.

AIDA v4.3b, like AIDA v4.3a before it, is intended for use on PC platforms, or Apple Macintosh computers running suitable PC emulation software. A further freeware upgrade, called AIDA v4.5 (currently under development), is planned incorporating the generic insulin model into the AIDA v4 software—allowing the interactive simulation of lispro, aspart, and glargine insulin analogues.

3. Results

Figure 1 shows the AIDA Website logstats for the number of visitors and AIDA v4 downloads since the software went on freeware Internet release—demonstrating the large number of site visitors and downloads that have taken place.

Figures 2 and 6 show a case study using AIDA v4.3b—which demonstrates some of the ways in which the software can be applied as an educational/demonstration/teaching tool. “Penelope Vincent”—case scenario number 0033 in the AIDA database—is a young woman, who is overweight

(98 kg) and runs reasonably high blood sugars during the course of the day. At present she is only injecting herself twice daily with two “shots” of intermediate-acting insulin. The AIDA software asks the user “How might you add in a short-acting insulin preparation to her regimen to tighten her glycaemic control? Alternatively, see if you can decrease her carbohydrate intake—thereby perhaps helping her to lose weight—and at the same time improving her blood glucose control...” Various examples of ways in which Penelope’s glycaemic control might be improved are simulated for educational purposes in Figures 2(c) and 6. The AIDA v4.3b freeware software is shown running on personal computers under the Windows XP, Windows Vista and Windows 7 operating systems in a DOSBox environment (Figures 6(b)–6(d)), as well as under Parallels on Apple Macs (Figures 6(g) and 6(h)).

Plasma insulin simulations are also demonstrated using the novel generic model following subcutaneous injections of a rapidly acting insulin analogue (such as lispro/Humalog or aspart/NovoLog), a short-acting (regular) insulin preparation (e.g., Actrapid), intermediate-acting insulin (both Semilente and NPH types), and a very long-acting insulin analogue (such as glargine/Lantus) for injected insulin doses up to 60 units of insulin (Figure 7).

4. Discussion

Interactive simulators offer users the chance to test the behaviour of the simulated object without risk. Diabetes simulators can animate an underlying model of glucose metabolism and may help to train users to manage “virtual diabetic patients” with the possibility of changing decisions or starting again in the case of failure.

Numerous models of the human glucoregulatory system have been reported [22, 54–57] However, these models may not be so useful for individual patients, their relatives, health-care professionals, or students without some sort of program (a “simulator”) to allow easy access to, and interaction with, the model. A range of interactive simulation programs of glucose-insulin interaction in diabetes have also been described in the literature [12, 28, 33, 57–62]. A few notable simulators have been circulated on diskette for use by select health-care professional/research users [13–17, 19]. Some authors [22, 33, 63, 64] have also developed a simulation program which could be obtained upon request.

However, for the majority of simulation programs [28, 58–61], it would seem that readers have been wholly dependent on the authors’ own descriptions of their prototypes in research articles, since no versions appear to be available for general use by others.

With AIDA, the program has been made widely available, *gratis*, via the Internet, from its own Websites—<http://www.2aida.org/> and <http://www.2aida.net/>—as a non-commercial contribution to continuing diabetes education. This has led to a substantial experience with the program—globally—with over 347,000 downloads of the software taking place from more than 100 countries worldwide. Independent reviews of AIDA can be found on the Web at <http://www.mendoza.com/aida.htm> and

<http://www.2aida.net/aida/review.htm> as well as in a range of publications [65–69].

The AIDA diabetes simulator provides a user-friendly way of making use of the AIDA model in an interactive, intuitive, and freeware manner. It would assist research into the use of such applications in this area, as well as possibly benefit the wider diabetes community, were more such diabetes simulation programs made available for free on the Internet.

4.1. Future Work. Table 1 shows the directions in which the AIDA software is intended to be developed. Revisions will affect the model, coverage of disease types, and the management and lifestyle events affecting BG levels.

The current hardwired mathematical model will be replaced by a modular (“lego”-like) design in which unit processes are clearly identified and interactions are formulated in a systematic and formal way. The revised/extended model aims to be physiologically based using parameters with values that are reasonable and which permit physiological interpretation. The insulin absorption model implemented in the revised diabetes simulator offers a description of what happens after the subcutaneous injection of different insulin preparations, including insulin analogues, with realistic assumptions and a minimal number of model parameters. Similar revisions of the glucose submodel are anticipated.

In due course it is planned to update AIDA further to make it possible to simulate glycaemic responses in non-insulin-dependent (type 2) diabetic patients. The superposition principle adopted within the AIDA model [23], of course, could also apply to insulin that has been secreted by pancreatic beta cells. Such endogenous secretion evolves over time corresponding to the temporal variations in BG concentrations. The insulin levels arising from endogenous insulin sources at any time can be computed as the sum of effects of all insulin that has been secreted in the preceding four hours (insulin levels are known to fall nearly to zero within four hours following a short intravenous bolus of insulin). For this computation the plasma and “active” insulin levels in response to a reference constant rate of insulin infusion delivered to the plasma over a short time period would be required. In each 15-minute integration step the average endogenous insulin secretion would be computed as the response to the average BG level in that period. The overall effect of endogenous insulin secretion would be computed by adding together individual contributions, in a similar way to that done currently with exogenous insulin injections.

Figure 8 shows a prototype simulation using the superposition principle to calculate a plasma insulin profile based on exogenous insulin injections and estimated basal endogenous insulin secretion in a type 2 diabetic patient.

The patient takes 6 units of short-acting (regular) insulin and 12 units of intermediate-acting (NPH type) insulin in the morning with a further 4 units of short-acting (regular) insulin and 8 units of intermediate-acting (NPH type) insulin in the evening. The estimated basal endogenous insulin secretion is shown—and the overall plasma insulin profile is superimposed.

It is intended to implement a similar facility within AIDA to provide simulations and a representation for insulin-treated type 2 diabetic patients.

Further inputs such as carbohydrate intake/meals up to 120 grams in size as well as different types of oral hypoglycaemic agents and lifestyle events (stress, physical activity, menstrual cycle, etc.) will also be added. Finally the revised AIDA simulator should be easily used via an intuitive graphical user interface.

5. Conclusion

In this paper the development and freeware Internet launch of AIDA v4.3b has been described. This incorporates technical work ensuring the diabetes simulation software, and a runtime demonstration program, continue to operate seamlessly under the Windows Vista, Windows 7, and Apple Macintosh operating systems. Plasma insulin simulations are demonstrated following subcutaneous injections of a rapidly acting insulin analogue (such as lispro/Humalog or aspart/NovoLog) and a very long-acting insulin analogue (such as glargine/Lantus) for injected insulin doses up to 60 units of insulin. Further work is planned to validate the generic model of insulin absorption in parallel with its incorporation into an updated release of the freeware AIDA software (AIDA v4.5).

5.1. System Availability. AIDA v4.3b is freely available for download from <http://www.2aida.org/>. Following completion of further programming, validation, and bench testing work, it is expected that a new, improved version of AIDA (v4.5)—incorporating Humalog/lispro and Lantus/glargine insulin analogues—will become available at the same website for freeware download and educational use. Readers who wish to be automatically informed by email when the new software is launched are welcome to join the very low volume AIDA registration/announcement list by sending a blank email note to subscribe@2aida.org.

Please note that “Penelope Vincent” and “Joy Wilson” are pseudonyms.

Abbreviations

BG: Blood glucose

PC: Personal computer

IU: International units (of insulin).

References

- [1] E. D. Lehmann, Ed., “Application of information technology in clinical diabetes care. Part 1. Databases, algorithms and decision support,” *Medical Informatics*, vol. 21, no. 4, pp. 255–378, 1996.
- [2] E. D. Lehmann, Ed., “Application of information technology in clinical diabetes care. Part 2. Models and education,” *Medical Informatics*, vol. 22, no. 1, pp. 1–120, 1997.
- [3] H. Shamooin, H. Duffy, N. Fleischer et al., “The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent

- diabetes mellitus," *The New England Journal of Medicine*, vol. 329, no. 14, pp. 977–986, 1993.
- [4] I. Muhlhauser, V. Jorgens, and M. Berger, "Bicentric evaluation of a teaching and treatment programme for type 1 (insulin-dependent) diabetic patients: improvement of metabolic control and other measures of diabetes care for up to 22 months," *Diabetologia*, vol. 25, no. 6, pp. 470–476, 1983.
 - [5] I. Muhlhauser, I. Bruckner, M. Berger et al., "Evaluation of an intensified insulin treatment and teaching programme as routine management of type 1 (insulin-dependent) diabetes. The Bucharest-Dusseldorf study," *Diabetologia*, vol. 30, no. 9, pp. 681–690, 1987.
 - [6] K. Howorka, *Functional Insulin Treatment*, Springer, Berlin, Germany, 2nd edition, 1996.
 - [7] S. Amiel, S. Beveridge, C. Bradley et al., "Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial," *British Medical Journal*, vol. 325, no. 7367, pp. 746–749, 2002.
 - [8] K. Howorka, J. Pumprla, D. Wagner-Nosiska, H. Grillmayr, C. Schlusche, and A. Schabmann, "Empowering diabetes outpatients with structured education: short-term and long-term effects of functional insulin treatment on perceived control over diabetes," *Journal of Psychosomatic Research*, vol. 48, no. 1, pp. 37–44, 2000.
 - [9] E. D. Lehmann, "Preliminary experience with the Internet release of AIDA—an interactive educational diabetes simulator," *Computer Methods & Programs in Biomedicine*, vol. 56, no. 2, pp. 109–132, 1998.
 - [10] E. D. Lehmann, "Experience with the Internet release of AIDA v4.0—an interactive educational diabetes simulator," *Diabetes Technology & Therapeutics*, vol. 1, no. 1, pp. 41–54, 1999.
 - [11] E. D. Lehmann, "Interactive educational diabetes simulators: future possibilities," *Diabetes, Nutrition & Metabolism*, vol. 12, no. 6, pp. 380–387, 1999.
 - [12] E. D. Lehmann, "Interactive educational simulators in diabetes care," *Medical Informatics*, vol. 22, no. 1, pp. 47–76, 1997.
 - [13] E. D. Lehmann, T. Deutsch, E. R. Carson, and P. H. Sonksen, "Combining rule-based reasoning and mathematical modelling in diabetes care," *Artificial Intelligence in Medicine*, vol. 6, no. 2, pp. 137–160, 1994.
 - [14] E. D. Lehmann, T. Deutsch, E. R. Carson, and P. H. Sonksen, "AIDA: an interactive diabetes advisor," *Computer Methods & Programs in Biomedicine*, vol. 41, no. 3–4, pp. 183–203, 1994.
 - [15] E. D. Lehmann, I. Hermanyi, and T. Deutsch, "Retrospective validation of a physiological model of glucose-insulin interaction in type 1 diabetes mellitus," *Medical Engineering and Physics*, vol. 16, no. 3, pp. 193–202, 1994.
 - [16] E. D. Lehmann, I. Hermanyi, and T. Deutsch, "Erratum: Retrospective validation of a physiological model of glucose-insulin interaction in type 1 diabetes mellitus," *Medical Engineering and Physics*, vol. 16, no. 4, pp. 351–352, 1994.
 - [17] E. D. Lehmann and T. Deutsch, "Computer assisted diabetes care: a 6-year retrospective," *Computer Methods & Programs in Biomedicine*, vol. 50, no. 3, pp. 209–230, 1996.
 - [18] E. D. Lehmann, T. Deutsch, and D. Broad, *AIDA. An Educational Simulator for Insulin Dosage and Dietary Adjustment in Diabetes*, British Diabetic Association, London, UK, 1997.
 - [19] E. D. Lehmann, *Development, evaluation, and usage of 'AIDA'—an interactive educational diabetes simulator*, Ph.D. thesis, University of London/Imperial College of Science, Technology and Medicine, 2004.
 - [20] E. D. Lehmann, "Simulating glycosylated hemoglobin (HbA_{1c}) levels in diabetes using an interactive educational virtual diabetes patient simulator," *Diabetes Technology & Therapeutics*, vol. 3, no. 3, pp. 517–524, 2001.
 - [21] E. D. Lehmann, "The freeware AIDA interactive educational diabetes simulator—<http://www.2aida.org>—(2) simulating glycosylated haemoglobin (HbA_{1c}) levels in AIDA v4.3," *Medical Science Monitor*, vol. 7, no. 3, pp. 516–525, 2001.
 - [22] E. D. Lehmann and T. Deutsch, "A physiological model of glucose-insulin interaction," in *Proceedings of the 13th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, pp. 2274–2275, November 1991.
 - [23] E. D. Lehmann and T. Deutsch, "A physiological model of glucose-insulin interaction in type 1 diabetes mellitus," *Journal of Biomedical Engineering*, vol. 14, no. 3, pp. 235–242, 1992.
 - [24] E. D. Lehmann, S. S. Chatu, and S. S. H. Hashmy, "Retrospective pilot feedback survey of 200 users of the AIDA version 4 educational diabetes program—1: quantitative survey data," *Diabetes Technology & Therapeutics*, vol. 8, no. 3, pp. 419–432, 2006.
 - [25] E. D. Lehmann, S. S. Chatu, and S. S. H. Hashmy, "Retrospective pilot feedback survey of 200 users of the AIDA version 4 educational diabetes program—2: qualitative feedback data," *Diabetes Technology & Therapeutics*, vol. 8, no. 5, pp. 602–608, 2006.
 - [26] E. D. Lehmann, S. S. Chatu, and S. S. H. Hashmy, "Retrospective pilot feedback survey of 200 users of the AIDA version 4 educational diabetes program—3: discussion," *Diabetes Technology & Therapeutics*, vol. 9, no. 1, pp. 122–132, 2007.
 - [27] C. Binder, T. Lauritzen, O. Faber, and S. Pramming, "Insulin pharmacokinetics," *Diabetes Care*, vol. 7, no. 2, pp. 188–199, 1984.
 - [28] S. Plougmann, O. K. Hejlesen, and D. A. Cavan, "DiasNet—a diabetes advisory system for communication and education via the internet," *International Journal of Medical Informatics*, vol. 64, no. 2–3, pp. 319–330, 2001.
 - [29] M. C. Storm and M. F. Dunn, "The Glu(B13) carboxylates of the insulin hexamer form a cage for Cd²⁺ and Ca²⁺ ions," *Biochemistry*, vol. 24, no. 7, pp. 1749–1756, 1985.
 - [30] P. Kurtzhals and U. Ribel, "Action profile of cobalt(III)-insulin: a novel principle of protraction of potential use for basal insulin delivery," *Diabetes*, vol. 44, no. 12, pp. 1381–1385, 1995.
 - [31] T. Kobayashi, S. Sawano, and T. Itoh, "The pharmacokinetics of insulin after continuous subcutaneous infusion or bolus subcutaneous injection in diabetic patients," *Diabetes*, vol. 32, no. 4, pp. 331–336, 1983.
 - [32] W. R. Puckett and E. N. Lightfoot, "A model for multiple subcutaneous insulin injections developed from individual diabetic patient data," *American Journal of Physiology*, vol. 269, no. 6, pp. E1115–E1124, 1995.
 - [33] M. Berger and D. Rodbard, "Computer simulation of plasma insulin and glucose dynamics after subcutaneous insulin injection," *Diabetes Care*, vol. 12, no. 10, pp. 725–736, 1989.
 - [34] E. Mosekilde, K. S. Jensen, C. Binder, S. Pramming, and B. Thorsteinsson, "Modeling absorption kinetics of subcutaneous injected soluble insulin," *Journal of Pharmacokinetics & Biopharmaceutics*, vol. 17, no. 1, pp. 67–87, 1989.
 - [35] Z. Trajanoski, P. Wach, P. Kotanko, A. Ott, and F. Skraba, "Pharmacokinetic model for the absorption of subcutaneously injected soluble insulin and monomeric insulin analogues," *Biomedizinische Technik*, vol. 38, no. 9, pp. 224–231, 1993.

- [36] P. Wach, Z. Trajanoski, P. Kotanko, and F. Skrabal, "Numerical approximation of mathematical model for absorption of subcutaneously injected insulin," *Medical and Biological Engineering & Computing*, vol. 33, no. 1, pp. 18–23, 1995.
- [37] C. Tarín, E. Teufel, J. Picó, J. Bondia, and H. J. Pfeleiderer, "Comprehensive pharmacokinetic model of insulin glargine and other insulin formulations," *IEEE Transactions on Biomedical Engineering*, vol. 52, no. 12, pp. 1994–2005, 2005.
- [38] C. Tarín, J. Bondia, E. Teufel, and J. Vehi, "On spatial discretisation in the calculus of subcutaneous insulin absorption profiles," in *Proceedings of the 2nd European Modeling and Simulation Symposium (EMSS '06)*, pp. 379–384, Barcelona, Spain, 2006.
- [39] E. D. Lehmann, C. Tarín, J. Bondia, E. Teufel, and T. Deutsch, "Incorporating a generic model of subcutaneous insulin absorption into the AIDA v4 diabetes simulator: 1. A prospective collaborative development plan," *Journal of Diabetes Science & Technology*, vol. 1, no. 3, pp. 423–435, 2007.
- [40] E. D. Lehmann, C. Tarín, J. Bondia, E. Teufel, and T. Deutsch, "Incorporating a generic model of subcutaneous insulin absorption into the AIDA v4 diabetes simulator: 2. Preliminary bench testing," *Journal of Diabetes Science & Technology*, vol. 1, no. 5, pp. 780–793, 2007.
- [41] E. D. Lehmann, C. Tarín, J. Bondia, E. Teufel, and T. Deutsch, "Incorporating a generic model of subcutaneous insulin absorption into the AIDA v4 diabetes simulator: 3. Early plasma insulin determinations," *Journal of Diabetes Science & Technology*, vol. 3, pp. 190–201, 2009.
- [42] J. Wong, J. G. Chase, C. E. Hann et al., "A subcutaneous insulin pharmacokinetic model for computer simulation in a diabetes decision support role: model structure and parameter identification," *Journal of Diabetes Science & Technology*, vol. 2, no. 4, pp. 658–671, 2008.
- [43] J. Wong, J. G. Chase, C. E. Hann et al., "A subcutaneous insulin pharmacokinetic model for computer simulation in a diabetes decision support role: validation and simulation," *Journal of Diabetes Science & Technology*, vol. 2, no. 4, pp. 672–680, 2008.
- [44] J. Li and Y. Kuang, "Systemically modeling the dynamics of plasma insulin in subcutaneous injection of insulin analogues for type 1 diabetes," *Mathematical Biosciences & Engineering*, vol. 6, no. 1, pp. 41–58, 2009.
- [45] B. Höfig, *Physiologische Modellierung des menschlichen Glukose-Metabolismus für die simulationsgestützte Therapie des insulinabhängigen Diabetes Mellitus*, Ph.D. dissertation, Universität Stuttgart, Stuttgart, Germany, 1996.
- [46] R. Gessler, *Ein portables System zur subkutanen Messung und Regelung der Glukose bei Diabetes Mellitus Typ-I*, Ph.D. dissertation, Universität Ulm, Ulm, Germany, 2000.
- [47] S. Kang, J. Brange, A. Burch, A. Volund, and D. R. Owens, "Subcutaneous insulin absorption explained by insulin's physicochemical properties. Evidence from absorption studies of soluble human insulin and insulin analogues in humans," *Diabetes Care*, vol. 14, no. 11, pp. 942–948, 1991.
- [48] U. Moeller, P. Sejrnsen, J. F. Hansen, and P. Hougaard, "Determination of diffusion coefficients of insulin and insulin analogues in relation to physical and absorption properties," *Diabetes*, vol. 37, supplement 1, p. 163A, 1988 [abstract].
- [49] E. W. Kraegen and D. J. Chisholm, "Insulin responses to varying profiles of subcutaneous insulin infusion: kinetic modelling studies," *Diabetologia*, vol. 26, no. 3, pp. 208–213, 1984.
- [50] D. A. Robertson, B. M. Singh, P. J. Hale, I. Jensen, and M. Nattrass, "Metabolic effects of monomeric insulin analogues of different receptor affinity," *Diabetic Medicine*, vol. 9, no. 3, pp. 240–246, 1992.
- [51] S. Kang, D. R. Owens, J. P. Vora, and J. Brange, "Comparison of insulin analogue B9AspB27Glu and soluble human insulin in insulin-treated diabetes," *The Lancet*, vol. 335, no. 8685, pp. 303–306, 1990.
- [52] C. Binder, "Absorption of injected insulin. A clinical-pharmacological study," *Acta Pharmacologica et Toxicologica*, vol. 27, supplement 2, pp. 1–84, 1969.
- [53] E. D. Lehmann, "The freeware AIDA interactive educational diabetes simulator—<http://www.2aida.org>—(1) a download survey for AIDA v4.0," *Medical Science Monitor*, vol. 7, no. 3, pp. 504–515, 2001.
- [54] C. Cobelli and R. N. Bergman, Eds., *Carbohydrate Metabolism: Quantitative Physiology and Mathematical Modelling*, Wiley, Chichester, UK, 1981.
- [55] A. M. Albisser and M. Schulz, "Simulating human intermediary metabolism: OMNI et al," in *Clinical Biochemistry Nearer the Patient II*, V. Marks and K. G. M. M. Alberti, Eds., pp. 59–67, Bailliere Tindall, London, UK, 1986.
- [56] R. N. Bergman, "Toward physiological understanding of glucose tolerance. Minimal-model approach," *Diabetes*, vol. 38, no. 12, pp. 1512–1527, 1989.
- [57] C. Dalla Man, R. A. Rizza, and C. Cobelli, "Meal simulation model of the glucose-insulin system," *IEEE Transactions on Biomedical Engineering*, vol. 54, no. 10, pp. 1740–1749, 2007.
- [58] W. I. Sivitz, P. C. Davidson, D. Steed, B. Bode, and P. Richardson, "Computer-assisted instruction in intense insulin therapy using a mathematical model for clinical simulation with a clinical algorithm and flow sheet," *The Diabetes Educator*, vol. 15, no. 1, pp. 77–79, 1989.
- [59] J. Hedbrant, J. Ludvigsson, and K. Nordenskjöld, "Sarimner: a computer model of diabetes physiology for education of physicians and patients," *Diabetes Research and Clinical Practice*, vol. 14, no. 2, pp. 113–122, 1991.
- [60] J. Hedbrant and J. Ludvigsson, "Use of computer simulator training in the education of diabetic teenagers," *Practical Diabetes International*, vol. 12, no. 1, pp. 18–21, 1995.
- [61] A. Rutscher, E. Salzsieder, and U. Fischer, "KADIS: model-aided education in type I diabetes," *Computer Methods & Programs in Biomedicine*, vol. 41, no. 3-4, pp. 205–215, 1994.
- [62] E. D. Lehmann, "Usage of a diabetes simulation system for education via the internet," *International Journal of Medical Informatics*, vol. 69, no. 1, pp. 63–69, 2003 [letter].
- [63] E. Biermann and H. Mehnert, "DIABLOG: a simulation program of insulin-glucose dynamics for education of diabetics," *Computer Methods & Programs in Biomedicine*, vol. 32, no. 3-4, pp. 311–318, 1990.
- [64] E. Biermann, "DIACATOR: simulation of metabolic abnormalities of type II diabetes mellitus by use of a personal computer," *Computer Methods & Programs in Biomedicine*, vol. 41, no. 3-4, pp. 217–229, 1994.
- [65] D. M. Wilson, "Diabetes simulators: ready for prime time?" *Diabetes Technology & Therapeutics*, vol. 1, no. 1, pp. 55–56, 1999.
- [66] Website Review, "The virtual diabetic patient: AIDA on-line," *Diabetes/Metabolism Research and Reviews*, vol. 15, p. 226, 1999.
- [67] A. B. Chausmer, "Diabetes management tools for patients and physicians," *Medical Software Reviews CRI Health Care Publications*, September-October 2002.

- [68] G. R. Parslow, "Websites of note," *Biochemical Education*, vol. 32, no. 3, pp. 207–209, 2004.
- [69] P. Tatti, "AIDA: un nuovo strumento educativo per il paziente con diabete," in *Proceedings of the 1st National Congress of Progetto Diabete*, p. 31, Genova, Italy, 2006.