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DIABETES COMPUTING & INTERNET WATCH

Incorporating a Generic Model of Subcutaneous Insulin Absorption into the AIDA v4 Diabetes Simulator

2. Preliminary Bench Testing

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Abstract

Background:
The AIDA interactive educational diabetes simulator has been available without charge for over a decade via the Internet (see www.2aida.org). Part 1 of this report [J Diabetes Sci Technol. 2007;1(3):423-35] described the model components to be integrated to enhance the utility of the software, with the aim being to provide enhanced functionality and educational simulations of regimens utilizing insulin analogues, as well as insulin doses greater than 40 units. This report provides some preliminary subcutaneous insulin absorption bench testing results for the updated modeling prototype.

Methods:
An analysis has been done of the spatial distribution of insulin in the region of the injection site for different classes of insulin preparations and times after the administration of a set insulin injection. Demonstrations of the proportion of residual insulin in depot versus time after a subcutaneous bolus have also been simulated for different insulin injection volumes and concentrations, as well as to show the proportions of hexameric, dimeric, and bound insulin over time after an injection.

Results:
Some early bench testing results are highlighted 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 insulins (both Semilente and neutral protamine Hagedorn types), and a very long-acting insulin analogue (such as glargine/Lantus). The transformation, dissociation/association, and absorption processes by which insulin moves from the subcutaneous injection site to the plasma are also illustrated.

continued →

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Abbreviations: (IU) international units [of insulin], (NPH) neutral protamine Hagedorn

Keywords: absorption, computer, diabetes, insulin, model, simulation, software

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Abstract cont.

Discussion:
This report demonstrates how enhanced capabilities may be added to AIDA once a new model of subcutaneous insulin absorption is incorporated. The revised approach, once fully implemented, should permit the simulation of plasma insulin profiles for rapidly acting and very long-acting insulin analogues, as well as insulin injections greater than 40 units.

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Introduction

The AIDA interactive educational diabetes simulation program has been in widespread general use for more than a decade.[1–4] As computer technology has evolved, and medical advancements such as insulin analogues and new oral hypoglycemic agents have been made, so the need for enhancements to the software has grown.[5] One of the most requested updates has been for the addition of new insulin analogues to the program in order to permit the simulation of any insulin management regimen currently used in clinical practice. Therefore, it has been decided that as a first step to updating the software, efforts will focus on extending the scope of insulin preparations that can be simulated with AIDA v4.

The updated release of AIDA is intended to cover rapidly acting insulin analogues (e.g., lispro/Humalog or aspart/NovoLog), short-acting (regular) insulin, intermediate-acting insulins [Semilente and neutral protamine Hagedorn (NPH) types], and very long-acting insulin analogues (e.g., glargine/Lantus), as well as premixed biphasic insulin preparations involving combinations of rapidly acting analogues and intermediate-acting insulin, such as Humalog Mix75/25, Humalog Mix50/50, and NovoLog Mix70/30.

Obviously these extensions require the insulin part of the model simulator to be modified. In Part 1 of this report[6] a prospective collaborative development plan was described aimed at providing such enhancements to the existing AIDA v4.3a educational simulator. The plan consisted of integrating a novel, generic, and physiological subcutaneous insulin absorption model[7,8] and developing a methodology by which this can be substituted in place of the previously adopted insulin absorption model while retaining the existing functions of the glucoregulatory system currently used in AIDA v4.3a. Part 1 of this report[6] also overviewed the generic insulin absorption I_{ex} model and illustrated preliminary simulations using the generic model showing temporal patterns of insulin absorption following the subcutaneous injection of different insulin preparations, including rapidly acting and very long-acting insulin analogues.

In this report (Part 2), preliminary bench testing of insulin absorption following subcutaneous insulin injections is presented. This includes presentation of the kinetics of the transformation, dissociation/association, and absorption processes by which insulin moves from the subcutaneous injection site to the plasma. An analysis has been undertaken of the spatial distribution of insulin in the region of the injection site (the diffusion spheres) for different classes of insulin preparations and time instants after the administration of a set dose of insulin. The proportion of residual insulin in the form of hexameric, dimeric, and bound insulin versus time after bolus injection has also been simulated for different increasing insulin injection volumes and concentrations.

Methods

The dynamics and intensity of insulin action depend primarily on the kinetics of insulin absorption and elimination (disposition). The time course of insulin absorption into the circulation is described according to the generic subcutaneous model of Tarín and colleagues[7,8] using insulin preparation-specific parameters as described in Part 1 of this report.[6] The approach is based on previous work by Trajanoski *et al.*[9] and Mosekilde *et al.*[10] Contrary to other existing insulin absorption models reported in the literature, this model is able to characterize for educational purposes, via adequate parameterization, the different physical and chemical processes associated with insulin absorption for a wide range of usual insulin formulations, including more

recent insulin analogues such as insulin glargine. This novel generic subcutaneous insulin absorption model overcomes the problems that arise with other existing models when dealing with flat-profiled insulin. Thus, simulation of insulin absorption ranging from rapidly acting to very long-acting formulations should now become possible.

In the generic model,[7,8] a new (bound) insulin state was introduced in order to account for the substantial delay in insulin absorption with very long-acting insulin analogues. This new state should not be confused with inactive insulin *bound* to other molecules, but is a virtual state representing the decreased solubility at physiological pH and insulin precipitation or crystallization of very long-acting analogues such as insulin glargine. No such bound insulin is assumed for rapidly acting, short-acting, and intermediate-acting insulin formulations for which a delay is not needed. Modeling of inactive insulin actually bound to other molecules has been disregarded, since, as concluded by Trajanoski and colleagues,[9] it is only significant for very small insulin doses.

As described in Part 1 of this article,[6] the generic model adopted represents the diffusion of insulin through the subcutaneous depot, transformation between the different insulin states, and absorption. A graphical depiction of the subcutaneous insulin absorption model is shown in **Figure 1**, which also shows how the concentrations of different insulin forms affect the different transport and chemical processes. The initial values of the different concentrations correspond to those of the injection, but represent different states depending on the preparation injected. It is considered that for a very long-acting insulin preparation, such as glargine, all the insulin is initially in the bound state. Then bound insulin will transform gradually to the hexameric state and diffuse from the injection site (not shown in **Figure 1**). This transformation will saturate when a given concentration of hexameric insulin has been reached (called $c_{h,\max}$).[6] Simultaneously, hexameric insulin molecules will dissociate into three molecules of dimeric insulin, and three molecules of dimeric insulin will aggregate into a single molecule of hexameric insulin until chemical equilibrium is reached. As dimeric insulin diffuses away from the injection site, a constant fraction will be absorbed into the systemic circulation. When dimeric insulin is absorbed, a decrement of hexameric insulin is induced and the transformation bound-hexameric desaturates.

For rapidly acting, short-acting, and intermediate-acting insulin formulations, no bound insulin exists, as

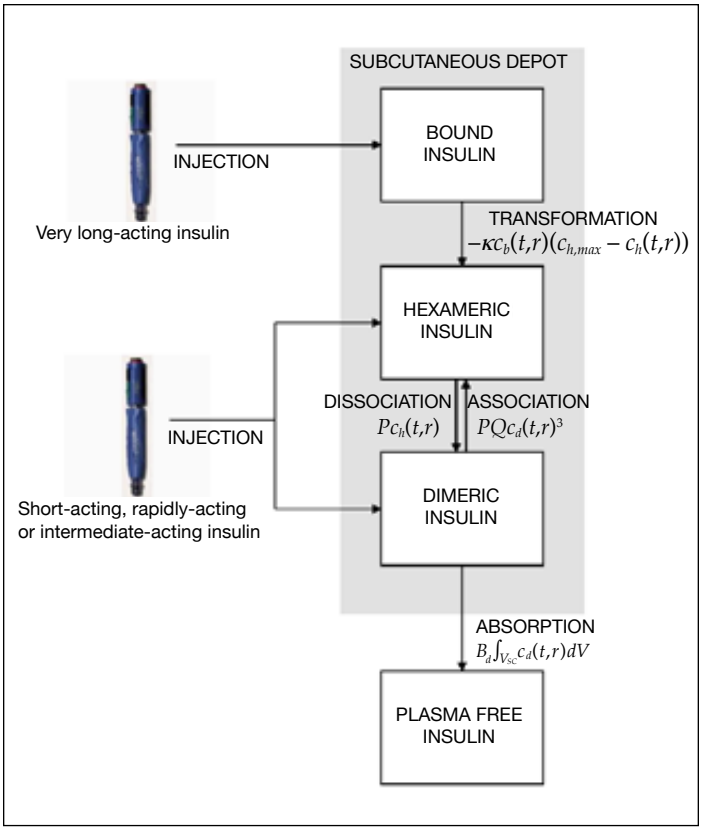

Figure 1. Graphical depiction of the generic subcutaneous insulin absorption model of Tarín and colleagues[7] intended for incorporation within AIDA v4.5. Expressions have been included for flux functions between insulin states. For a very long-acting insulin analogue, injected insulin is initially in the bound state ("precipitated"). Then it gradually converts to a hexameric form, beginning a process of dissociation/association between hexameric and dimeric forms, until equilibrium is reached. Only the dimeric form will be absorbed. For the rest of the insulin preparations, injected insulin is considered to be in equilibrium between hexameric and dimeric forms.

the injected dose is in hexameric and dimeric forms. Initially it is considered that hexameric and dimeric insulin molecules are in equilibrium. As insulin diffuses from the injection site and dimeric insulin is absorbed, dissociation/association between hexameric and dimeric states continuously drives insulin concentrations toward a new chemical equilibrium.

Figures 2A and **2B** show how the rates of the different chemical transformations depend on the concentrations of the different insulin forms. As can be seen in **Figure 2A**, the bound-to-hexameric transformation corresponds to a linear process with a saturation point ($c_{h,\max}$). Hexameric insulin will range from 0 to $c_{h,\max}$ (15 IU/ml for insulin glargine). As long as the hexameric insulin concentration is smaller than $c_{h,\max}$, bound insulin is converted into the hexameric form following first-order kinetics. Once the saturation value is reached, the transformation stops. The transformation rate in **Figure 2A** is also zero at $c_{h,\max}$.

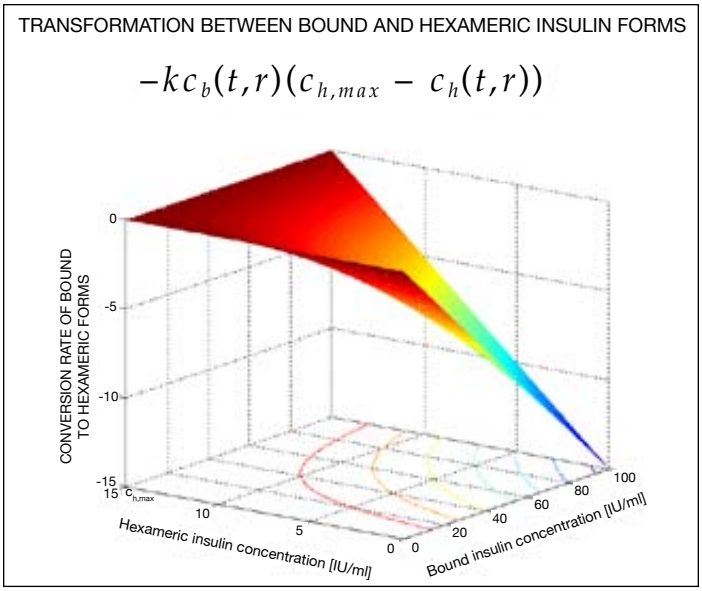

Figure 2A

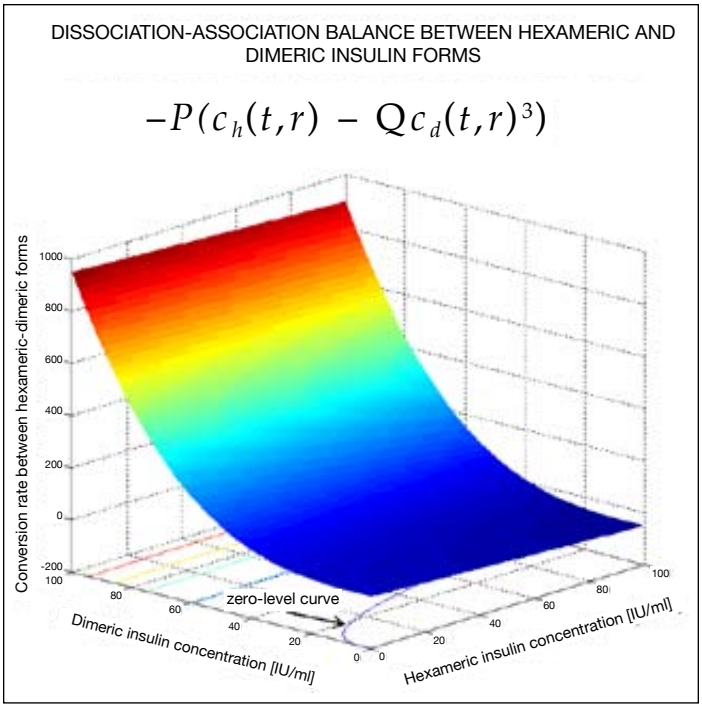

Figure 2B

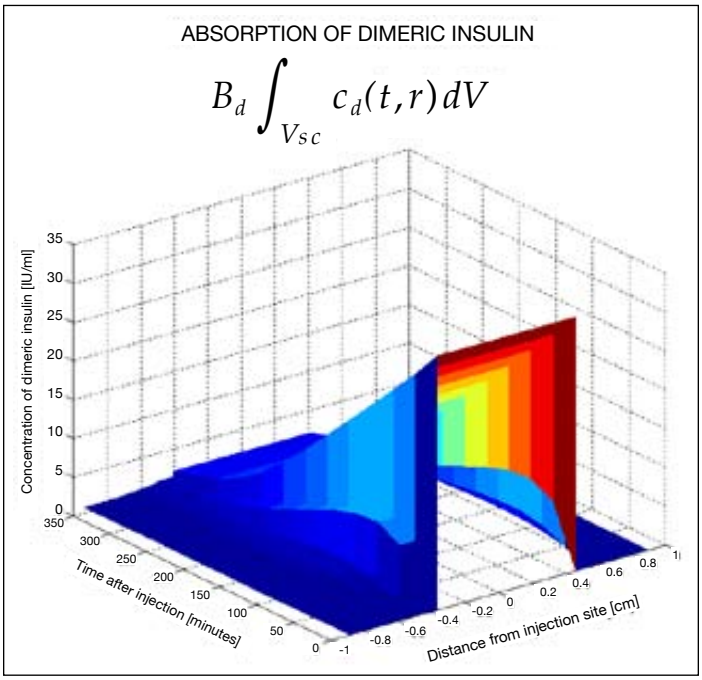

Figure 2C

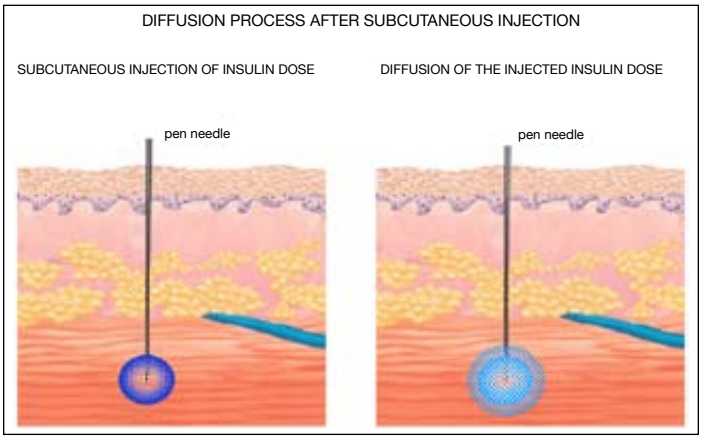

Figure 2D

Figure 2. (**A**) Transformation of bound insulin into the hexameric form. This corresponds to a linear process with a saturation point. Hexameric insulin will range from 0 to $c_{h,\max}$ (15 IU/ml for insulin glargine). At this value, the transformation process will stop until dimeric insulin is absorbed. This will induce a decrement of hexameric insulin, desaturating the bound-to-hexameric process. (**B**) Net difference between association and dissociation of hexameric insulin into the dimeric form. This process is linear in the hexameric concentration and is a third-order kinetic process in the dimeric concentration. A hexameric insulin molecule will dissociate into three molecules of dimeric insulin until chemical equilibrium is reached (zero-level curve of the shown surface). (**C**) The insulin absorption process. As dimeric insulin diffuses away from the injection site, a constant fraction of it will be absorbed into the systemic circulation. (**D**) Diffusion process after subcutaneous insulin injection. (**Left**) Initial injection. (**Right**) Diffusion of injected insulin dose. Color intensity represents insulin concentration.

The dissociation of hexameric insulin obeys first-order kinetics, whereas the association of dimeric insulin into the hexameric form is assumed to be a third-order chemical reaction. **Figure 2B** shows the net balance between the rate of dissociation of the hexameric form of insulin and the rate of association of the dimeric form. The zero-level curve (see **Figure 2B**) of these surfaces determines the chemical equilibrium between these insulin forms, which corresponds to $c_h^{eq} = Q\,(c_d^{eq})^3$, where c_h^{eq} and c_d^{eq} represent equilibrium concentrations of hexameric and dimeric insulins, respectively. P (in **Figure 2B**) denotes the first-order dissociation rate constant of hexameric insulin, and Q is the equilibrium constant of the reversible association/dissociation processes.

Figure 2C shows the absorption process and how the amount of dimeric insulin evolves in time and space. If a section of the surface is taken at a fixed time instant, a constant fraction (B_d) of the area under the curve of the resulting graph (total dimeric insulin at the diffusion volume at that time instant) will be absorbed into the systemic circulation.

Figure 2D schematically shows the injection site into which insulin is injected, the surrounding subcutaneous tissues into which different forms of insulin are diffused, and the absorption of dimeric insulin into the capillary circulation. The absorption of dimeric insulin obeys first-order kinetics.

As described in Part 1 of this report,[6] the model equations cannot be solved in closed form and numerical integration is required, involving discretization of variables in both *time* and *space*. With regard to space discretization, for simulation purposes the spherical diffusion volume is divided into n shells of equal volume. The number of shells to be considered will depend on the insulin class and injected insulin dose. The volume of individual shells is set to be equal to the injected volume,[9] which is calculated from the injected dose and concentration of the preparation used.

As part of the preliminary bench testing of the absorption model, an analysis of the effect of the volume and concentration of the injected preparation on the absorption process has been carried out. Simulations for the different insulin formulations have been run, first, considering a fixed concentration of 40 IU/ml and different injected volumes (0.01, 0.03, 0.1, and 0.3 ml, corresponding respectively to doses of 0.4, 1.2, 4, and 12 IU).

Simulations have been carried out in MATLAB™ using numerical implementation of the generic subcutaneous insulin absorption model. For time discretization the Euler method with a time step of 0.01 minutes has been used.

Results

In this section, insight is provided into how the insulin absorption model works, how the concentrations of the different insulin forms evolve over time and space, how this evolution is affected by the volume and dose of injected insulin, and how these temporal patterns affect the overall absorption rate of dimeric insulin, which basically determines the plasma levels of the hormone that controls glucose metabolism. Simulation results are presented from different perspectives.

How Much Insulin Is Not Yet Absorbed Over Time?

Figures 3 and **4** illustrate the temporal profile of the amount of insulin remaining at the injection site following injection and how these patterns are affected by the injected volume. **Figure 3A** shows the profile of the percentage of insulin remaining at the injection site for short-acting (regular) insulin. The same results are plotted in **Figure 3B** using a logarithmic scale. It may be observed that absorption rates follow an exponential profile, and the process is completed after 6 to 7 hours, depending on the dose. **Figure 3B** reveals that the exponential phase (straight line on the logarithmic scale, the slope of which defines the absorption rate constant) is preceded by a slower absorption phase. The maximum deviation is observed at around 1.5 hours, with a difference of approximately 15% between minimum and maximum injected doses/volumes.

Figure 4 shows results obtained for the rest of the insulin formulations. For rapidly acting insulin (see **Figure 4A**), the initial absorption phase is shorter than with regular insulin, and after 2 to 3.25 hours less than 1% of the injected insulin has not yet been absorbed. Also the influence of the injected volume on the absorption rate in the exponential phase is greater. This latter influence seems to disappear for intermediate and very long-acting insulin, where parallel straight lines appear in **Figures 4B–4D**. For an intermediate-acting insulin (Semilente type), after 6 to 9.5 hours less than 1% of the injected insulin still remains in the subcutaneous depot (**Figure 4B**). This happens after 8 to 16 hours for an intermediate-acting insulin of NPH type (**Figure 4C**) and after around 8.5 to 17 hours for a very long-acting insulin (**Figure 4D**). Surprisingly, the behavior described by the model for

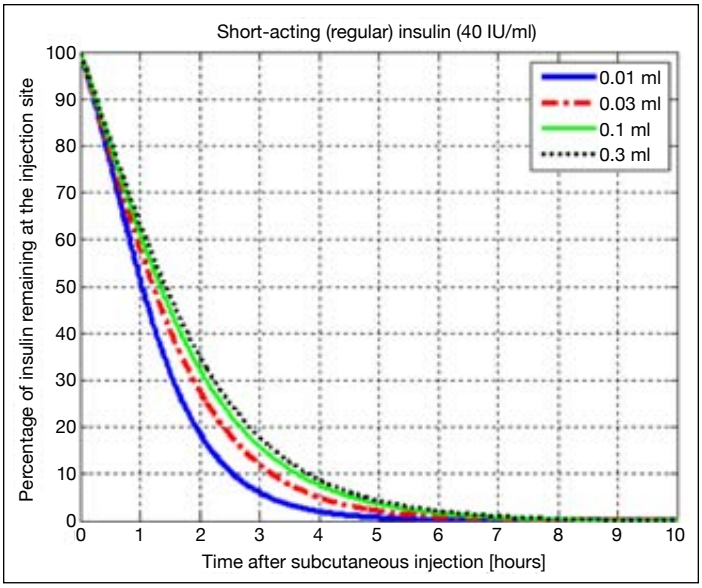

Figure 3A

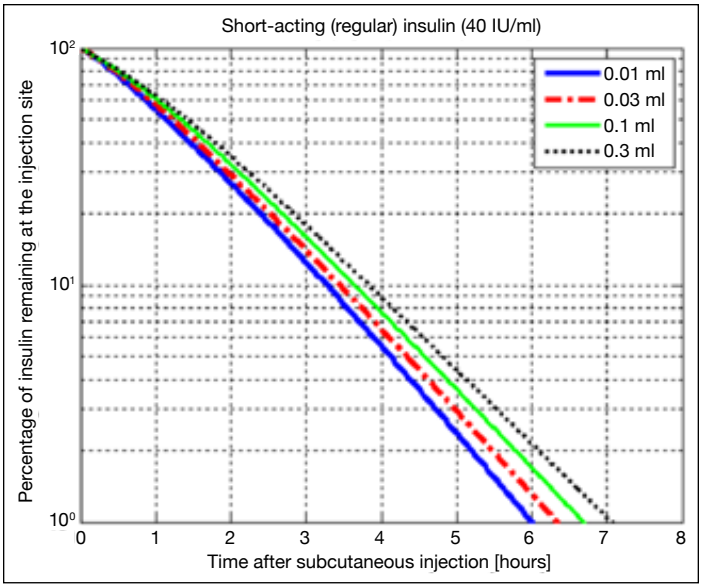

Figure 3B

Figure 3. (**A**) Percentage of insulin remaining at the injection site after an injection of 0.01, 0.03, 0.1, and 0.3 ml of a preparation of short-acting (regular) insulin with a concentration of 40 IU/ml. (**B**) Display of data shown in **Figure 3A** using a logarithmic scale. After an initial slow absorption phase, an exponential phase is observed (straight line).

intermediate-acting insulin (NPH type) and very long-acting insulin (insulin glargine) at 40 IU/ml is similar, except for a slightly longer initial slower absorption phase observed for very long-acting insulin.

The difference between the absorption patterns of intermediate-acting (NPH type) and very long-acting insulin becomes more transparent when the concentration of the insulin preparation is raised to 100 IU/ml, as in current commercially available preparations (see **Figures 5A** and **5B**). The injected volumes have been kept as in the previous simulation, corresponding to injected doses of 1, 3, 10, and 30 IU. In this case, for intermediate-acting insulin (NPH type), less than 1% of the injected insulin still remains in the subcutaneous depot after 9 to 21.5 hours. However, this happens for very long-acting insulin after 10.5 to 29.5 hours. In this latter case, for a dose of 10 IU, insulin is still not yet absorbed after more than 20 hours following the injection. This issue is addressed further in the next section, where the balance between different insulin states is investigated.

Dose Dependency of Insulin Absorption

A second set of bench testing simulations have been run, considering now a fixed injected volume of 0.3 ml and different concentrations of the insulin preparation (1, 4, 10, and 40 IU/ml, corresponding respectively to 0.3, 1.2, 3, and 12 IU). It may be observed that final insulin doses are quite similar to those used in the previous analysis.

Figure 6 shows simulation results for the different classes of insulin preparations. As may be observed, sensitivity to the concentration of the preparation is negligible for rapidly acting insulin (**Figure 6A**). For all the injected doses, around 3.25 hours after the injection, 1% of the injected insulin dose still remains at the injection site. For short-acting (regular) insulin (**Figure 6B**), this happens after 6.5 to 7 hours. Variations in the concentration of the preparation produce a simulated difference of just 0.5 hours. This influence is nonlinear, with the effect of 1-, 4-, and 10-IU/ml concentrations being very similar. The time difference observed is more significant for the rest of the insulin classes, although the same nonlinearity in the concentration influence is seen as before. For intermediate-acting insulin (Semilente type)(see **Figure 6C**), 1% of the injected insulin will still remain at the injection site after approximately 6.25 to 9.5 hours (time span of 3.25 hours). This happens for intermediate-acting insulin (NPH type)(see **Figure 6D**), after 7 to 16 hours (time span of 9 hours), and for very long-acting insulin (see **Figure 6E**), from 7 to 17.5 hours (time span of 10.5 hours). It is worth noting that for preparations with small insulin concentrations (1, 4, and 10 IU/ml), the behavior of NPH-type insulin and very long-acting insulin analogues is similar (e.g., when comparing **Figures 6D** and **6E**) for the injected volume. As before, differences become apparent only when preparations with higher insulin concentrations (e.g., 100 IU/ml) are administered.

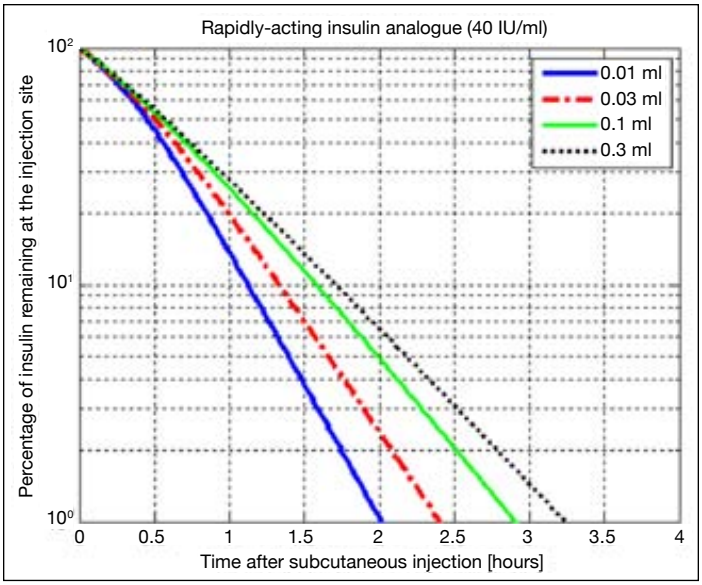

Figure 4A

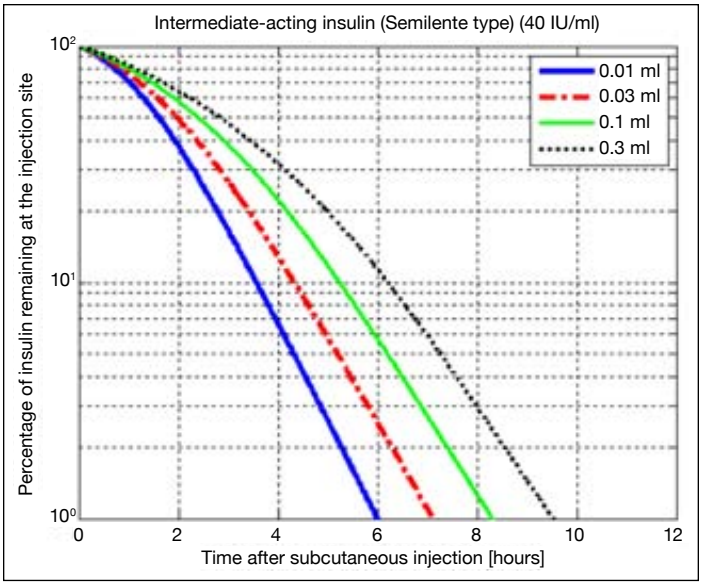

Figure 4B

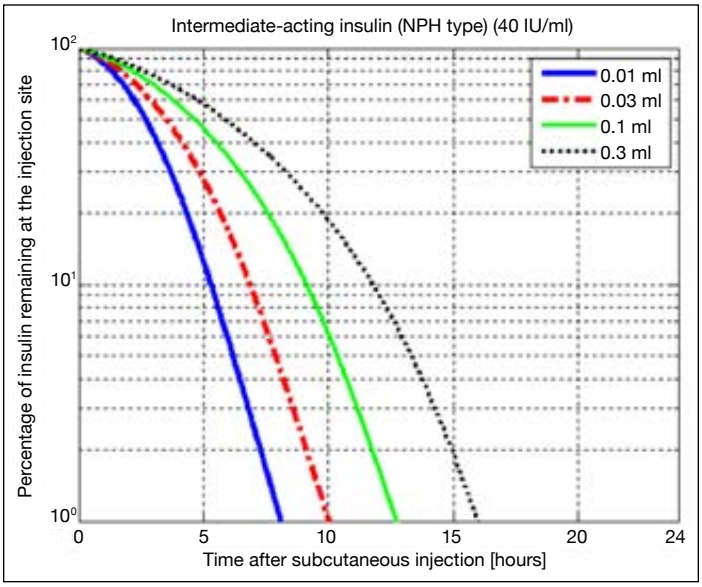

Figure 4C

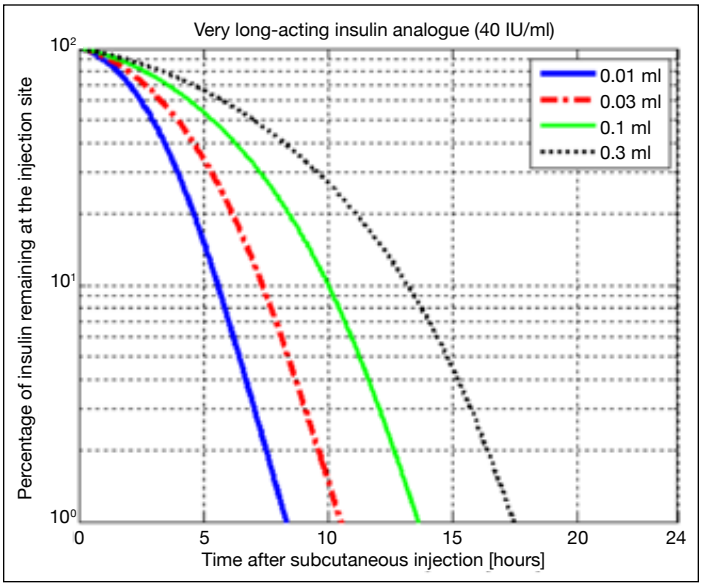

Figure 4D

Figure 4. Percentage of insulin remaining at the injection site under the same conditions as **Figure 3A** with (**A**) a rapidly acting insulin analogue, (**B**) an intermediate-acting insulin (Semilente type), (**C**) an intermediate-acting insulin (NPH type), and (**D**) a very long-acting insulin analogue.

In all cases, no influence of the concentration of the insulin preparation on the absorption rate appears in the exponential phase. It may also be noted, comparing the results of the previous run (see, for instance, **Figure 4B** and **Figure 6C** for intermediate-acting insulin of Semilente type), that different behaviors are observed for an injection of 0.03 ml, 40 IU/ml and an injection of 0.3 ml, 4 IU/ml (dashed line) with a dose of 1.2 IU in both cases. For each insulin preparation, higher insulin concentrations result in a longer initial phase of slower absorption.

Balance between Different Insulin States

Figure 7 shows the percentage of the amount of insulin remaining in depot in the different insulin states for injection of a volume of 0.3 ml and a concentration of 40 IU/ml for the preparation (dose of 12 IU). The fraction of dimeric insulin with respect to the total amount of insulin is also shown. It may be observed that big differences in the initial balance of hexameric and dimeric insulin are found for rapidly acting (28% hexameric), short-acting (45% hexameric), intermediate-acting Semilente-type (80% hexameric), and intermediate-

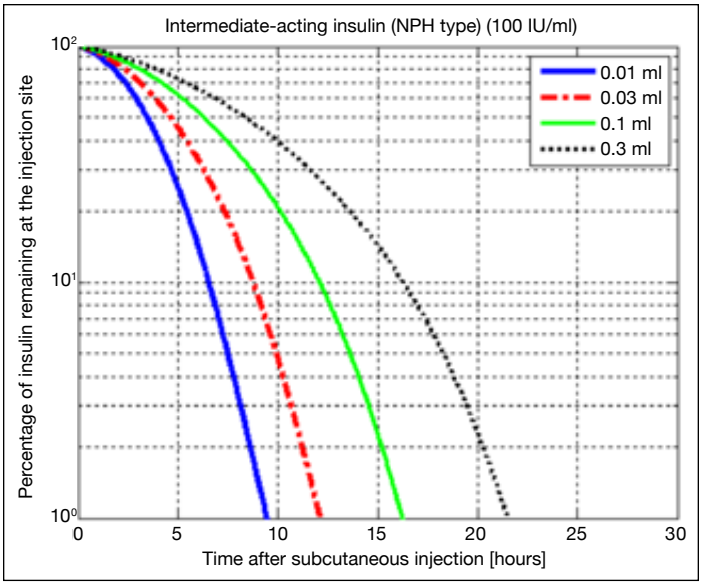

Figure 5A

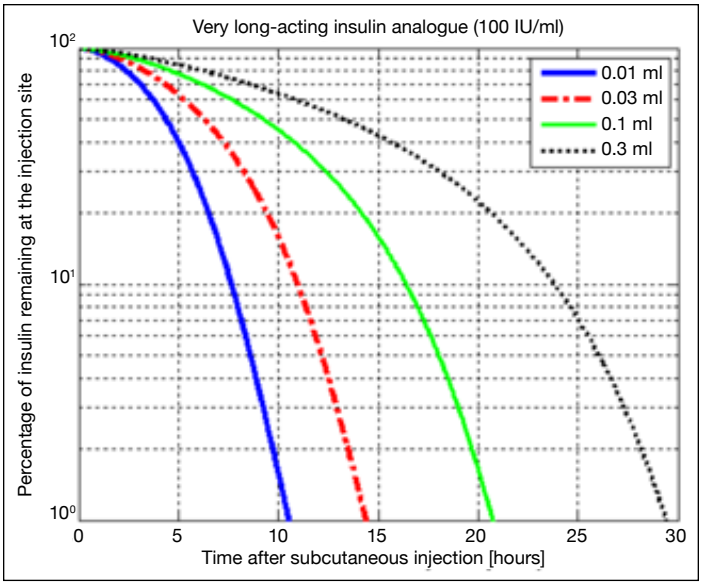

Figure 5B

Figure 5. Percentage of insulin remaining at the injection site after an injection of 0.01, 0.03, 0.1, and 0.3 ml of a 100-IU/ml preparation of (**A**) intermediate-acting insulin (NPH type) and (**B**) a very long-acting insulin analogue.

acting NPH-type (94% hexameric) insulins. This seems to be a key difference between the absorption profiles of the different classes of insulin preparations.

It may also be noted that, comparing **Figures 6A–6E** with **Figures 7A–7E**, respectively, the exponential phase corresponds to the practical disappearance of hexameric insulin, implying a predomination of dimeric insulin. This happens, for the injected volume and concentration of the preparation under consideration, after around 1 hour for rapidly acting insulin (**Figure 7A**), 3 hours for short-acting insulin (**Figure 7B**), 7 hours for intermediate-acting insulin of Semilente type (**Figure 7C**), 15 hours for intermediate-acting insulin of NPH type (**Figure 7D**), and 16 hours for very long-acting insulin (**Figure 7E**). In this latter case, it may be observed that bound insulin is only significant in the first 7 hours and a peak of hexameric insulin of approximately 48% appears after around 4 hours (**Figure 7E**). This peak is characteristic for this kind of insulin, as a steadily decreasing decay of hexameric insulin is observed in the rest. When comparing dimeric insulin profiles with intermediate-acting insulin (NPH type) and very long-acting insulin (**Figures 7D** and **7E**), it may be seen that for a preparation of 40 IU/ml these are quite similar, which will give rise to similar absorption profiles.

Figures 8A and **8B** show the same profiles after the injection of 100 IU/ml of an insulin preparation.

The hexameric insulin profile for a very long-acting insulin analogue has a plateau, which produces the characteristic delay in absorption of this kind of insulin (see **Figure 8B** compared with **Figure 8A**). This phenomenon can be attributed to saturation of the bound-to-hexameric insulin transformation. Initially, bound insulin is converted very fast to hexameric insulin until saturation occurs and chemical equilibrium between hexameric and dimeric forms is reached. This can be seen most easily in **Figure 8B**, where a fast rise in hexameric insulin takes place during the first minutes until the 15% level, i.e., 15 IU/ml, is reached, which corresponds to the value of $c_{h,\max}$. Please note that this is different from the approximately 24% of insulin remaining at the injection site (plateau level of hexameric insulin in **Figure 8B**).

Hexameric insulin will be located mostly at the innermost shell of the diffusion volume. As it diffuses and dimeric insulin is absorbed, new bound insulin will be converted more slowly to hexameric insulin, again reaching saturation. Saturation or near-saturation of the innermost shell, which lasts approximately 15 hours in the case under consideration, will continue until bound insulin is not significant (see **Figure 9**). This prolonged saturation produces a smaller concentration profile of dimeric insulin than intermediate-acting insulin (NPH type) and thus a slower absorption profile.

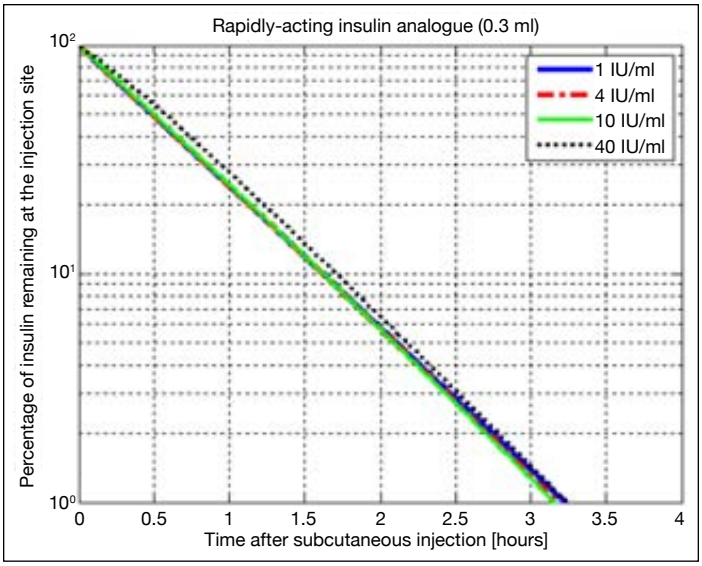

Figure 6A

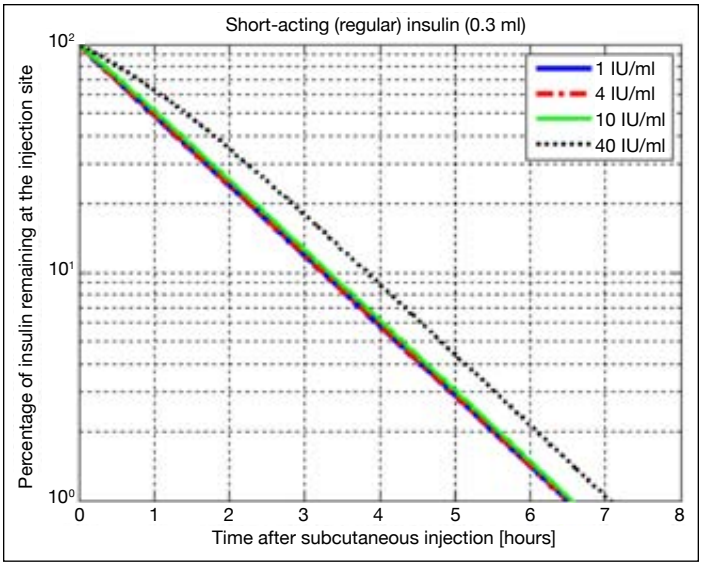

Figure 6B

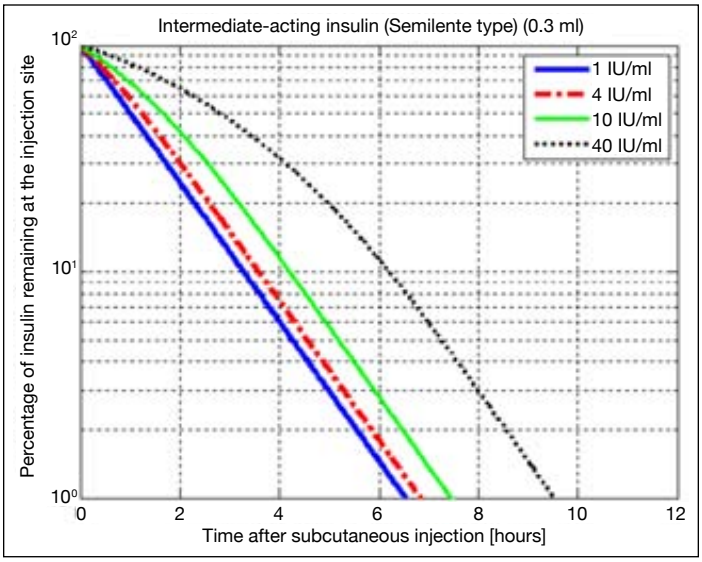

Figure 6C

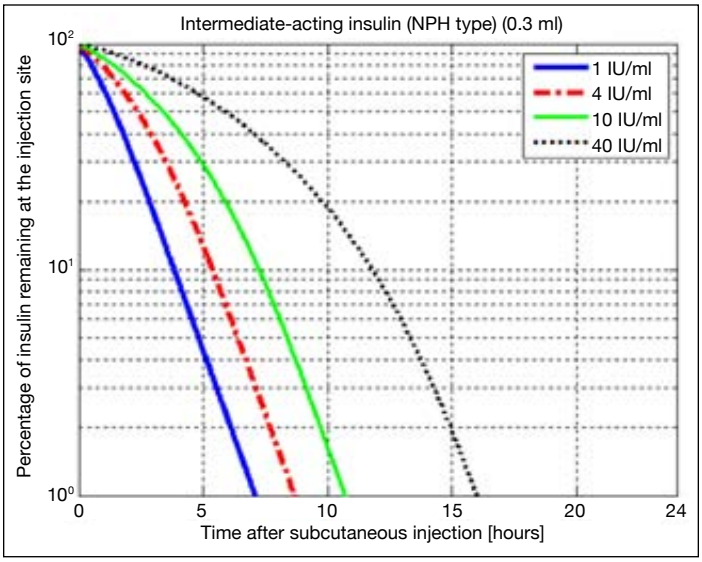

Figure 6D

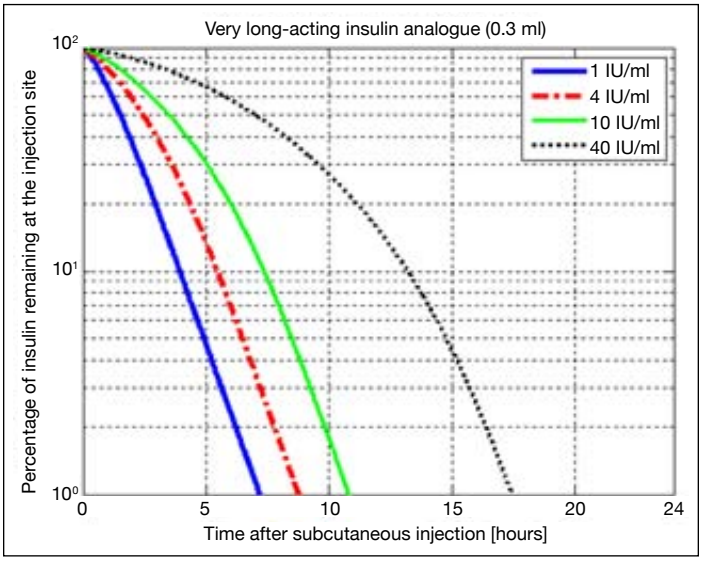

Figure 6E

Figure 6. Percentage of insulin remaining at the injection site after an injection of 0.3 ml of a preparation with concentrations of 1, 4, 10, and 40 IU/ml of (**A**) a rapidly acting insulin analogue, (**B**) a short-acting (regular) insulin preparation, (**C**) an intermediate-acting insulin (Semilente type), (**D**) an intermediate-acting insulin (NPH type), and (**E**) a very long-acting insulin analogue.

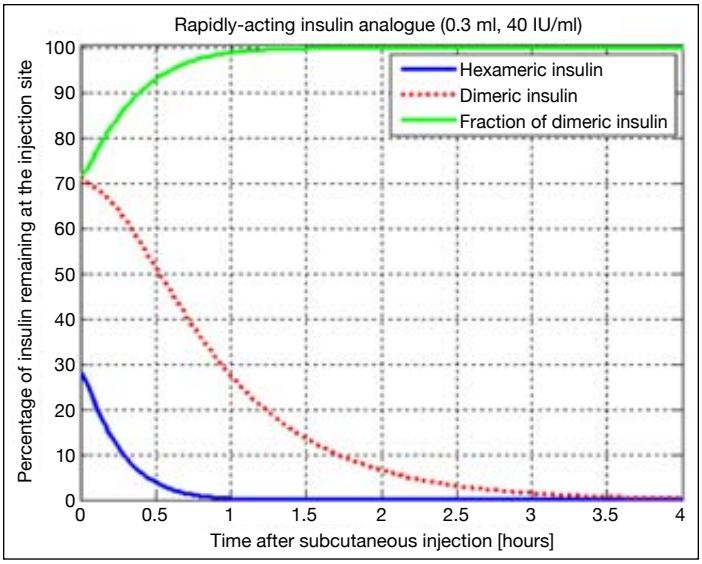

Figure 7A

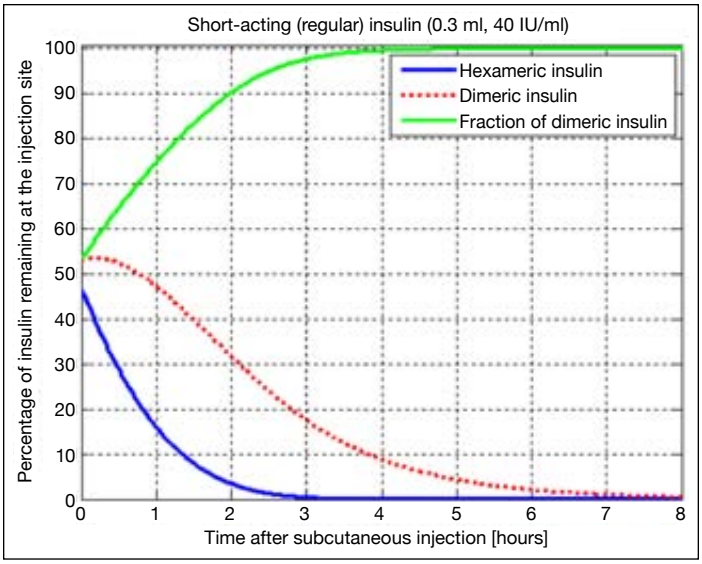

Figure 7B

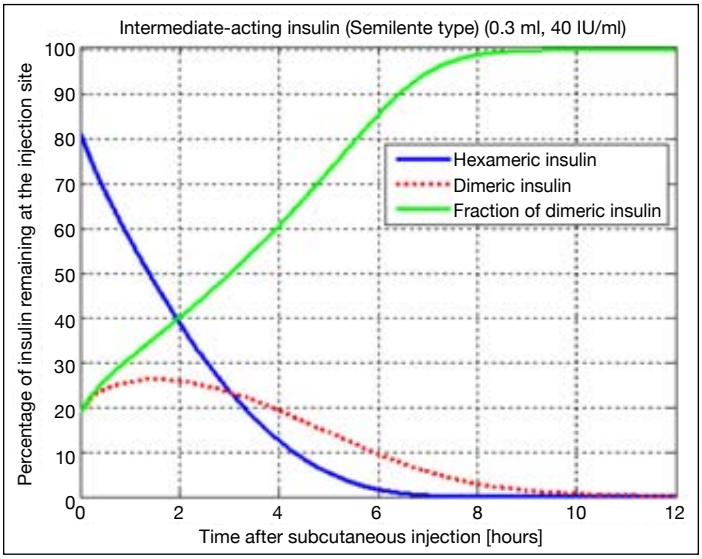

Figure 7C

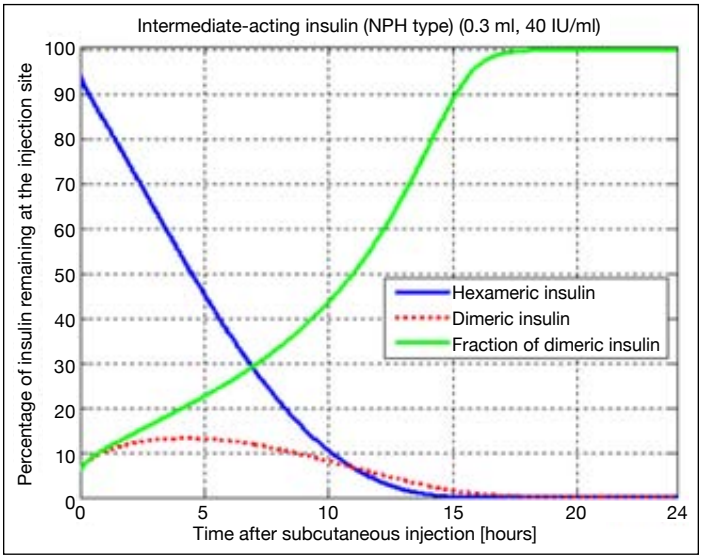

Figure 7D

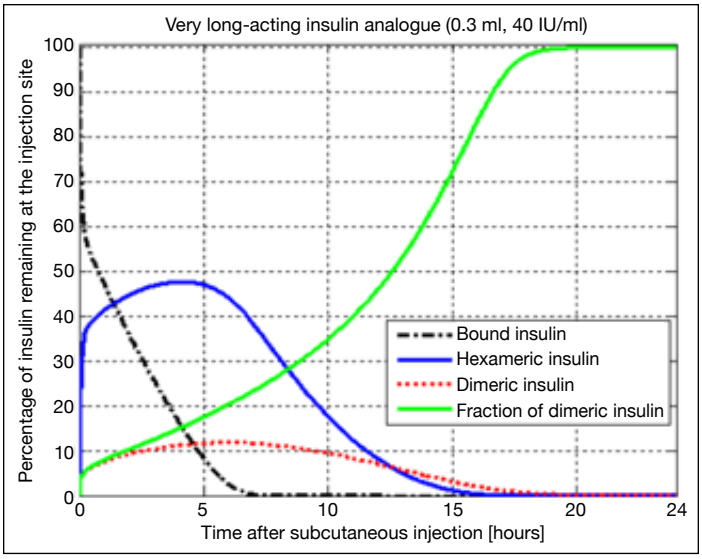

Figure 7E

Figure 7. Percentage of insulin in bound, hexameric, and dimeric states remaining at the injection site after an injection of 0.3 ml of a preparation with 40 IU/ml of (**A**) a rapidly acting insulin analogue, (**B**) a short-acting (regular) insulin preparation, (**C**) an intermediate-acting insulin (Semilente type), (**D**) an intermediate-acting insulin (NPH type), and (**E**) a very long-acting insulin analogue.

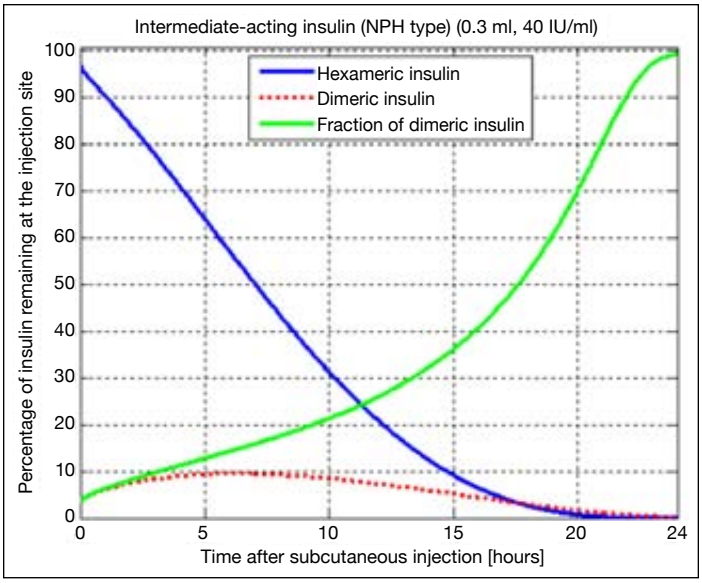

Figure 8A

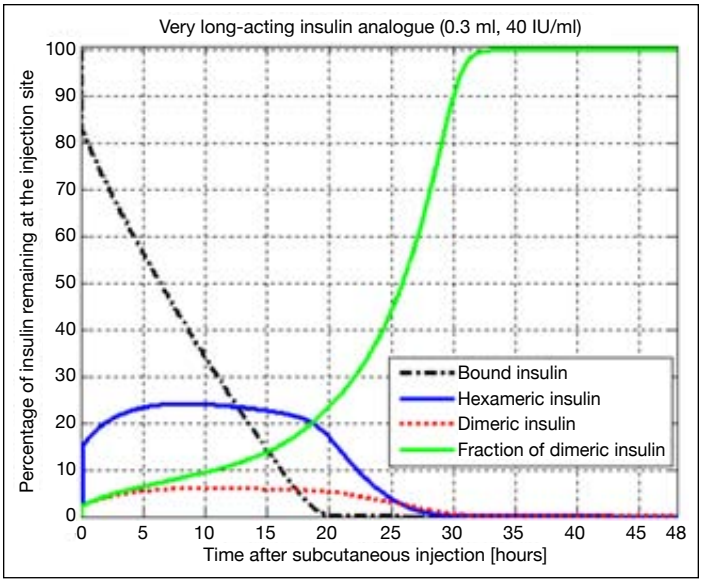

Figure 8B

Figure 8. Percentage of insulin in bound, hexameric, and dimeric states remaining at the injection site after an injection of 0.3 ml of a preparation with 100 IU/ml of (**A**) an intermediate-acting insulin (NPH type) and (**B**) a very long-acting insulin analogue.

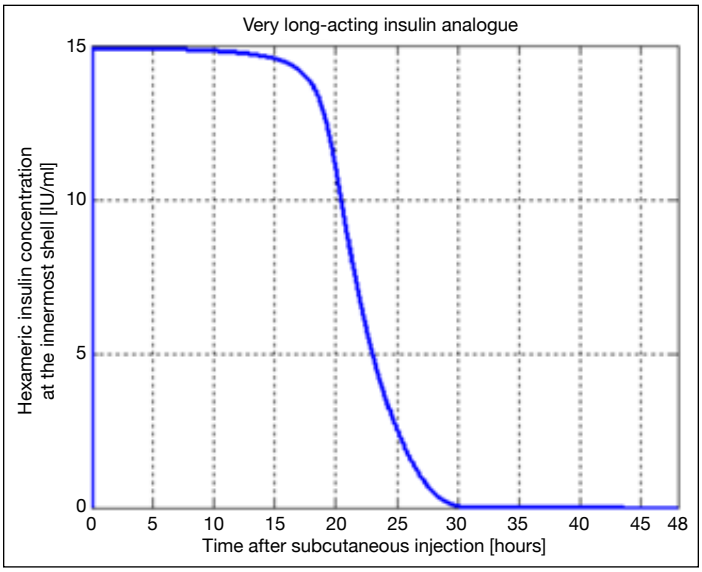

Figure 9. Hexameric insulin concentration at the innermost shell of the diffusion volume after an injection of 0.3 ml of a preparation with 100 IU/ml of a very long-acting insulin analogue.

Insulin Diffusion into the Surrounding Tissues

Figure 10 shows a comparison of the spatial distribution of insulin in the region of the injection site (the diffusion spheres) for different classes of insulin preparations at $t = 0$, 60, 120, 180, 240, and 300 minutes after the administration of 20 IU of an U100 preparation. Transverse sections of the sphere are represented unidimensionally by the distance from the injection site due to the homogeneity consideration inside a shell. It may be observed that for all insulin types, at time $t = 0$ minutes, the concentration of the innermost shell equals that of the preparation, i.e., all the insulin is in this shell. As time goes on, insulin diffuses to neighboring shells and is absorbed. For a rapidly acting insulin analogue, after 1 hour, the concentration in the innermost shell has decreased by more than 80% and after 2 hours the spatial distribution is almost flat, as most of the insulin has already been absorbed. For a short-acting (regular) insulin preparation, the decrease in the initial concentration after 1 hour is approximately 40%, 25% for an intermediate-acting insulin (NPH type), and less than 10% for a very long-acting insulin analogue. During the first 5 hours, the diffusion process is more significant for intermediate-acting insulins. It can also be observed that during the first 5 hours, and for all insulin preparations, insulin farther than 8 millimeters from the injection site is considered negligible. As expected, the shorter acting the injected insulin, the more rapidly the insulin disappears from the innermost shell, as shown in Part 1 **Figure 5**.[6]

Discussion

Data presented in this report offer detailed insight into the intricacies of the absorption process that should enable users to follow (i) what is going on both in space and in time after insulin has been injected subcutaneously and (ii) what happens to the injected insulin prior to absorption. Simulation studies reveal

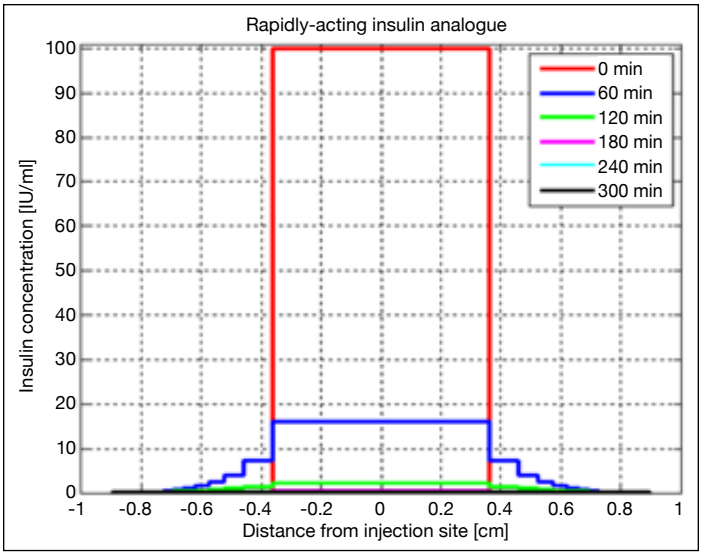

Figure 10A

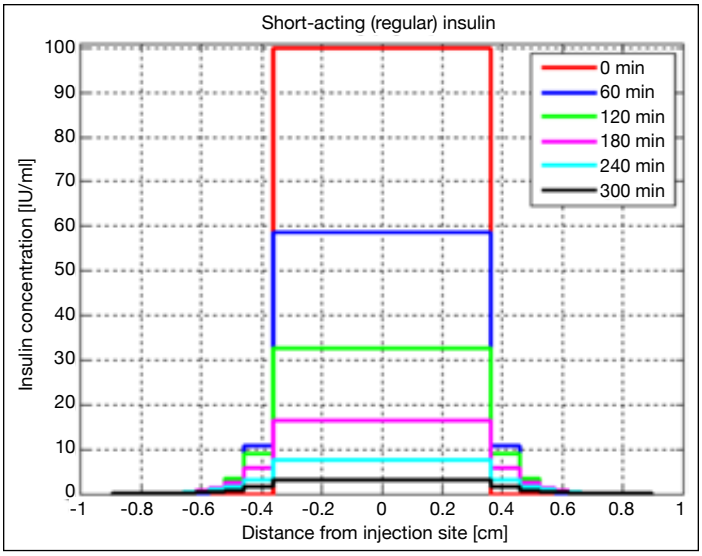

Figure 10B

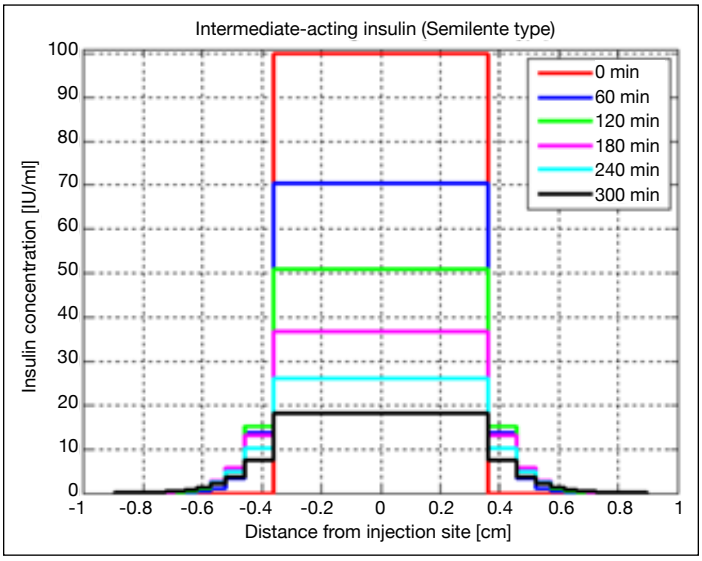

Figure 10C

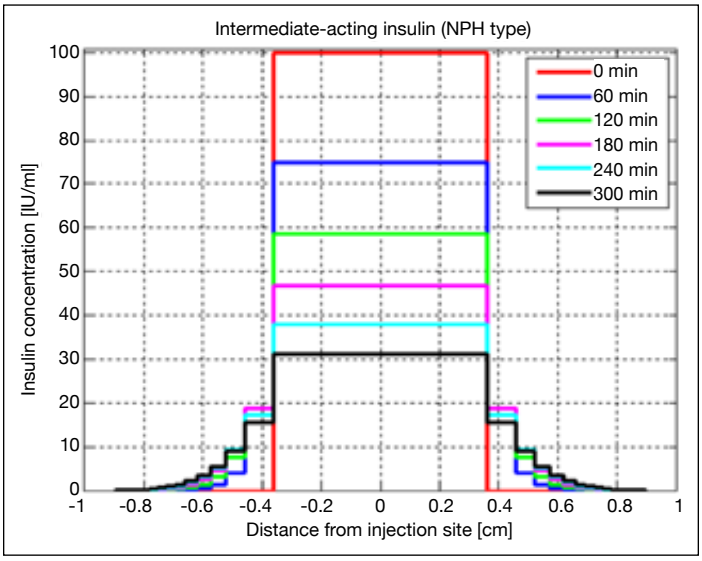

Figure 10D

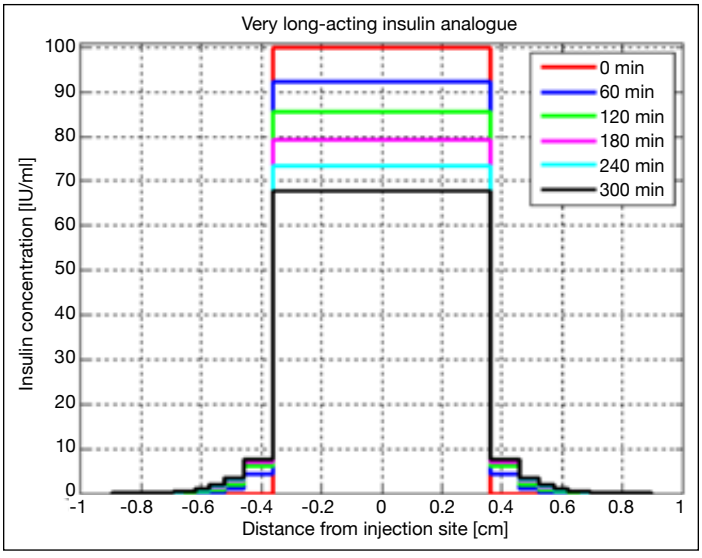

Figure 10E

Figure 10. Diffusion of insulin from the injection site as described by discretization of the model [explained in **Figure 5B** (Part 1)[6]]. Spatial distribution of insulin after an insulin injection of 20 IU. Insulin concentration at every shell of the diffusion volume is represented for time instants t = 0, 60, 120, 180, 240, and 300 minutes and 100 IU/ml insulin formulations of (**A**) a rapidly acting insulin analogue, (**B**) a short-acting (regular) insulin preparation, (**C**) an intermediate-acting insulin (Semilente type), (**D**) an intermediate-acting insulin (NPH type), and (**E**) a very long-acting insulin analogue. Diffusion is considered to be spherical and homogeneous, and the diffusion volume is discretized into concentric shells of equal volume. The x axis represents distance from the injection site in any direction. The y axis represents the concentration of insulin in each shell. Transverse sections of the sphere are represented unidimensionally by the distance to the injection site.

that insulin absorption obeys dose-dependent kinetics with an initial phase of reduced absorption. The length of the initial absorption phase is closely related to the preparation used. This was also observed by Mosekilde and colleagues.[10]

For rapidly acting insulin, the sensitivity of the absorption process to the insulin concentration is negligible. Regardless of the injected dose, around 3.25 hours after the injection time, only 1% of the injected insulin is still left at the injection site.

For preparations with small insulin concentrations (1, 4, and 10 IU/ml), the behavior of NPH-like insulin and glargine-like insulin analogues is similar, with differences becoming apparent only when preparations with higher insulin concentrations, as available commercially, are administered (e.g., 100 IU/ml).

In all cases no influence of the concentration of the insulin preparation on the absorption rate appears in the exponential phase. It has been concluded that the exponential phase of absorption corresponds to the practical disappearance of hexameric insulin, implying a predomination of dimeric insulin.

For very long-acting insulin analogues, bound insulin is only significant in the first 7 hours and a peak of hexameric insulin of approximately 48% appears around 4 hours. This peak is characteristic for this kind of insulin, as with the other classes of insulin preparations, a steadily decreasing decay of hexameric insulin is observed.

When comparing dimeric insulin profiles for intermediate-acting insulin (NPH type) and very long-acting insulin analogues, it may be seen that for a preparation of 40 IU/ml they are quite similar, which gives rise to the similar absorption profiles. However, if a preparation of 100 IU/ml is considered, then the hexameric insulin profile for very long-acting insulin analogues demonstrates a plateau, which produces the characteristic delay in absorption for this kind of insulin. This can be attributed to saturation of the bound-to-hexameric insulin transformation. Initially, bound insulin is converted very fast to hexameric insulin until saturation happens and a chemical equilibrium between hexameric and dimeric forms is reached. A fast rise in hexameric insulin takes place until the level of 15 IU/ml is reached.

This hexameric insulin will be located mostly at the innermost shell of the diffusion volume. As it diffuses and dimeric insulin is absorbed, new bound insulin will be converted more slowly to hexameric insulin, reaching saturation again. Saturation or near-saturation of the innermost shell will continue until the amount of bound insulin becomes insignificant. This prolonged saturation produces a smaller concentration profile of dimeric insulin than NPH-type insulin and hence a slower absorption profile.

The influence of the insulin preparation on the diffusion process reveals that as time passes, insulin diffuses to neighboring shells and is absorbed. For a rapidly acting insulin analogue preparation, after 1 hour, the concentration in the innermost shell has decreased by more than 80% and after 2 hours spatial distribution is almost flat, as most of the insulin has already been absorbed. For a short-acting (regular) insulin preparation, the decrease in the initial concentration after 1 hour is approximately 40%. The reduction in percentage is 30% for intermediate-acting insulin (Semilente type), 25% for intermediate-acting insulin (NPH type), and less than 10% for a glargine-like insulin analogue. This opportunity to study and follow what happens to the injected insulin before it is absorbed clearly enhances the possible scope of the AIDA software.

Incorporation of the novel insulin absorption model is in harmony with the intention to build a modular glucose–insulin model in which unit processes are clearly identified and interactions are formulated in a systematic way. The new absorption model appears physiologically based with parameter values that are reasonable and have physiological meaning or that can be interpreted physiologically. This implies that the new insulin absorption model should therefore allow the whole spectrum of currently available insulin preparations to be catered for within the AIDA program.

What to Expect in the Third Part of This Article?

In Part 3 of this report,[11] further data from integration of the generic subcutaneous insulin absorption model, and the currently implemented model in AIDA for insulin kinetics/elimination, will be presented. Plasma insulin simulations will be provided for all currently available insulin preparations, including a rapidly acting insulin analogue (e.g., Humalog/lispro), a short-acting (regular) insulin preparation (e.g., Actrapid), intermediate-acting insulins (both Semilente and NPH types), and a very long-acting insulin analogue (e.g., Lantus/glargine), as well as for doses greater than 40 IU. Furthermore, issues surrounding the use of the detemir/Levemir very long-acting insulin analogue will be discussed.

The methodology to be adopted to actually implement the generic absorption model within AIDA v4 will be overviewed, and the logistical steps required to program this in Pascal will be described. Technical issues concerning the operation of AIDA v4 under the Windows Vista™ operating system and relating to resolving certain display problems that manifest themselves on some of the latest generations of notebook personal computers will also be addressed.

System Availability

Following completion of further bench testing work,[11] it is expected that a new, improved version of AIDA (v4.5) will become available at the http://www.2aida.org Web site 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.

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Disclosure:

The AIDA v4 software referred to in this report is an independent, noncommercial development that is being made available free of charge via the Internet—at a dot org (.org) not-for-profit Web site—as a noncommercial contribution to continuing diabetes education. Dr. Lehmann and Dr. Deutsch are codevelopers of the original AIDA v4 diabetes simulator, and Dr. Lehmann is webmaster of the www.2aida.org Web site. However, none of the authors have any financial conflicts of interest in this work.

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