JOURNAL
COMPUTER SCIENCES INSTITUTE

JCSI 13 (2019) 272-278
Wysłane: 2019-11-18
Przyjęte: 2019-12-11

The insulin activity model based on insulin profiles

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Abstract. The purpose of the research was to propound an insulin activity model in a human body after a subcutaneous injection. A deterministic model in the form of a mathematical function was formulated. The research was based on pharmaceutic publicly available drug information published by the manufactures. The paper presents in detail the model. The obtained results can be used in computer simulations of diabetes mellitus therapy. They suggest that activity models may be assigned to types of insulin instead of separate products.

Keywords: insulin profiles; insulin activity; diabetes mellitus; computer therapy

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Uzyskanie modelu aktywności insuliny na podstawie profili insulinowych

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Streszczenie. Celem badań było opracowanie modelu aktywności insuliny w organizmie człowieka po wstrzyknięciu podskórnym. Sformułowano model deterministyczny w postaci funkcji matematycznej. Badanie oparto na publicznie dostępnych informacjach farmaceutycznych opublikowanych przez producentów. Artykuł szczegółowo przedstawia model. Uzyskane wyniki mogą być wykorzystane w komputerowych symulacjach terapii cukrzycy. Sugerują one również, że modele aktywności mogą dotyczyć grup insulin zamiast konkretnych preparatów.

Słowa kluczowe: krzywa insulinowa; aktywność insuliny; cukrzyca; terapia komputerowa

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1. Introduction

The insulin activity model presented in this paper is intended to assist development of computer systems supporting type 1 diabetes therapy. The type 1 diabetes is an incurable (nowadays) autoimmune disease with global occurrence. The consequence of getting this type is the patient's body inability to produce the insulin hormone. In this sense, a person with type 1 diabetes is a disabled person. Insulin is a crucial hormone for a metabolism, so it must be supplied from the outside a lifetime because the lack of it leads in short time to a coma and subsequently to death. The therapy with insulin is difficult and awkward. Proper doses of an insulin analog (artificial insulin used as a medicine) have to be injected a few times a day daily. Each overdose results in hypoglycemia (low blood sugar), which may even lead to sudden death. Contrarily, each under-dose brings hyperglycemia (high blood sugar), which in a longer time brings destruction of blood vessels, nerve tissues and kidneys. On the other hand a proper therapy means that the disability resulting from type 1 diabetes is almost imperceptible by the patient and his/her environment. Such a person is able to live a successful life including the professional and family sphere. Therefore, carrying out research on insulin dosing algorithms is reasoned.

Today there are many insulin analogs in use. Administering such insulin to a patient is realized by subcutaneous injections. After an injection the whole dose of the insulin does not become immediately available to a human body, but is released into the blood system gradually. The process takes place in time and can be described with a insulin profile (Fig. from 2 to 7). The profile (sometimes called an insulin curve) is a characteristic of an insulin analog and tells how blood insulin concentration changes over time after the injection of a certain dose. Although the profile depends on many different factors, it is necessary to assume one when predicting an insulin action in a body.

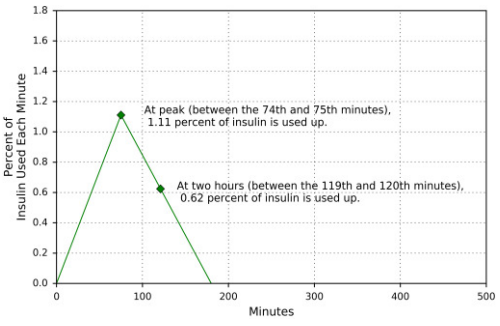

Fig. 1. Simplified insulin activity function applied in OpenAPS [1]

The insulin profiles themselves may be used in computer simulations but it would not be convenient because they refer to blood concentration. It is more usefully to know what fraction of the whole insulin dose will be released in subsequent minutes. Such a function is called the insulin activity function and because building one always needs making assumptions it is also named the insulin activity model.

Regrettably - from digital biohackers' point of view - pharmaceutical companies do not publish mathematical formulas for their insulin analogs. Therefore, software developers adopt simplified insulin activity functions. An example of such a function can be found in OpenAPS [1], which is a successful open-source artificial pancreas system that got ahead commercial equivalents a few years ago. The system has been created by volunteers and is publicly available under the MIT license. The system applies the simplest approximation that assumes linear increase and linear decrease in bioavailability of an insulin dose (Fig.1). The creators themselves agree that the model should be replaced with more precise one.

2. Analysis of insulin profiles

2.1. Common insulin analogs

Today the world demand for insulin is supplied by 6 private companies [2] (Table 1). From commercial medicine point of view it may be said that participation in the market of other suppliers is marginal. For this reason, this research has been limited to the products of the leading manufacturers. Tables form 2 to 7 enumerate insulin analogs offered by the group of interest excluding insulin mixes. In the tables next to the name of an insulin analog there is given its type and the information about its profile availability. Generally there are 4 types of insulin analogs defined by their time activity in a human body. The first group called „rapid acting" remains active up to 6 hours, the second one denoted „short acting" up to 9 hours, the next „intermediate acting" means about 12 hours of activity and the last group „long acting" stands over 20 hours. Having said that it must be noted that the given definition is rough.

Table 1. Major players in the world insulin market

Company	Origin	Web page
Novo Nordisk	Denmark	www.novonordisk.com
Sanofi	France	www.sanofi.com
Eli Lilly	USA	www.lilly.com
Biocon	India	www.biocon.com
Julphar	UAE	www.julphar.net

Table 2. Novo Nordisk essential insulin analogs offer

Name	Type	Profile published
Fiasp®	Rapid	Yes
NovoRapid®		
Actrapid®	Short	
Insulatard®	Intermediate	No
Tresiba®	Long	
Xultophy®		
Levemir®		

Table 3. Sanofi essential insulin analogs offer

Name	Type	Profile published
Apidra®	Rapid	Yes
Insuman Implantable®		
Insulin Lispro Sanofi®		No
Insuman R®	Short	
Insuman N®		
Lantus®	Long	
Toujeo®		

Table 4. Eli Lilly essential insulin analogs offer

Name	Type	Profile published
Humalog®	Rapid	Yes
Humulin R Short-acting®	Short	
Liprolog®		No
Humulin N®	Intermediate	
Abasaglar®	Long	

Table 5. Biocon essential insulin analogs offer

Name	Type	Profile published
Insugen®	Short	No

Table 6. Julphar essential insulin analogs offer

Name	Type	Profile published
Jusline N®	Intermediate	No
Jusline R®		

2.2. Recognition of insulin profiles

At the time of the research only for 7 insulin analogs there were insulin profiles included into the official information about the medical products [3-8]. The source graphs have been presented in the figures from 2 to 8.

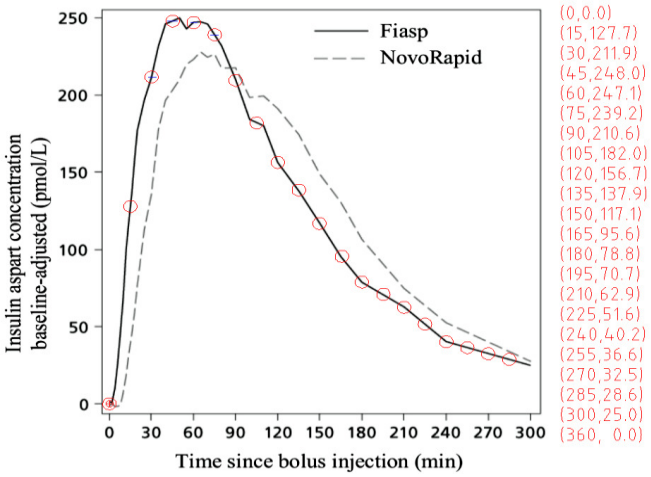

Fig. 2. Insulin profile for Fiasp including points (in red) used in polynomial fitting [3]

All the source graphs have been supplemented with points used in the calculations. The values have been obtain using the open-source graphical program LibreCad (www.librecad.org). According to the manufacturers the data came from clinical trials and was averaged before published. All the diagrams show how serum insulin concentration varies over time after a subcutaneous injection of a certain insulin dose. The diagrams are not standardized. The time is given in minutes or hours. The observation time ranges from 240 to 720 minutes. The first measurement is made at the time of the injection or before it. The insulin concentration is given in different units with or without baseline adjustment. Therefore there is a need to normalize the curves in order to use in any computer calculations.

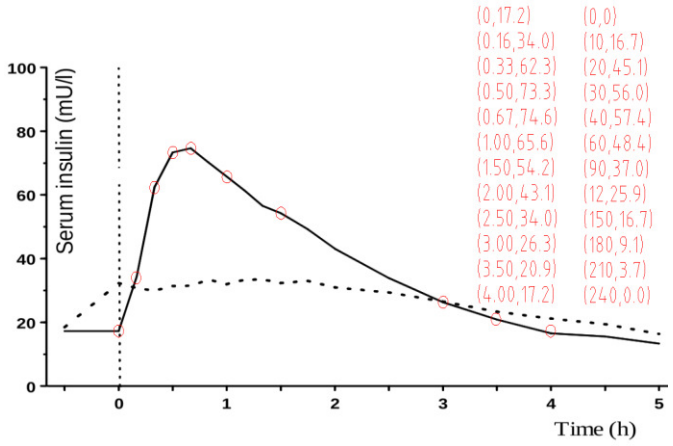

Fig. 3. Insulin profile for NovoRapid including points (in red) used in polynomial fitting. The left column gives data read from the graph, the right after baseline adjustment and time converted to minutes [4]

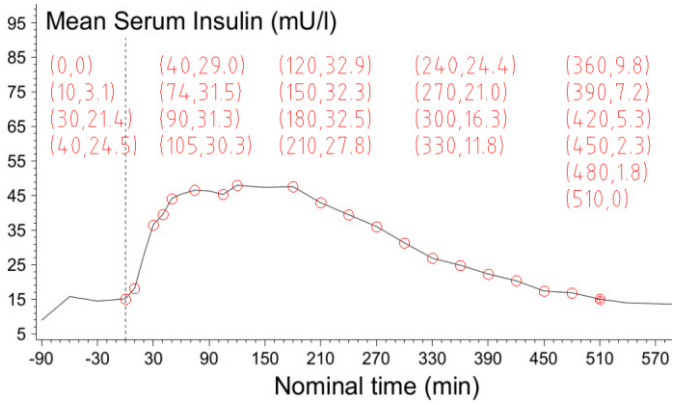

Fig. 4. Insulin profile for Actrapid including points (in red) used in polynomial fitting. Values given after baseline adjustment [5]

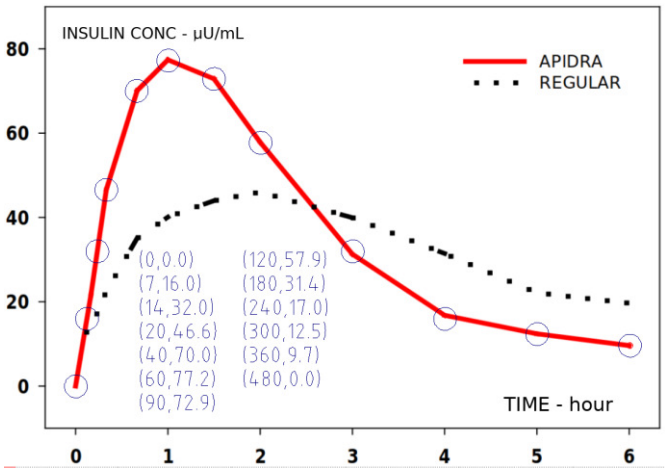

Fig. 5. Insulin profile for Apidra including points (in blue) used in polynomial fitting where hours has been converted to minutes [6]

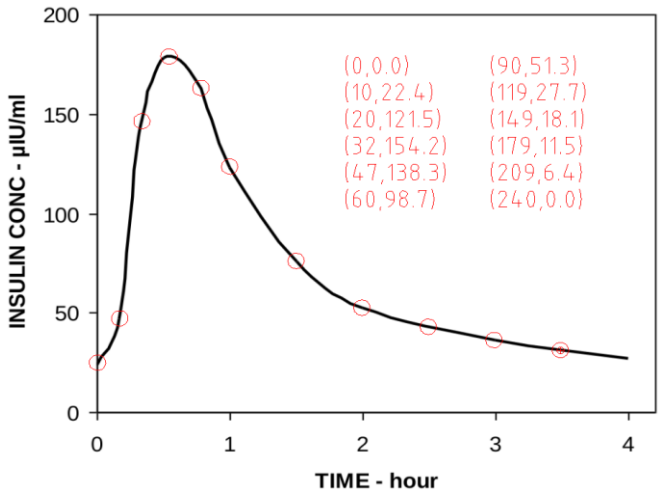

Fig. 6. Insulin profile for Insuman Implantable including points (in red) used in polynomial fitting- hours converted into minutes, concentration values given over the base level of 25 [7]

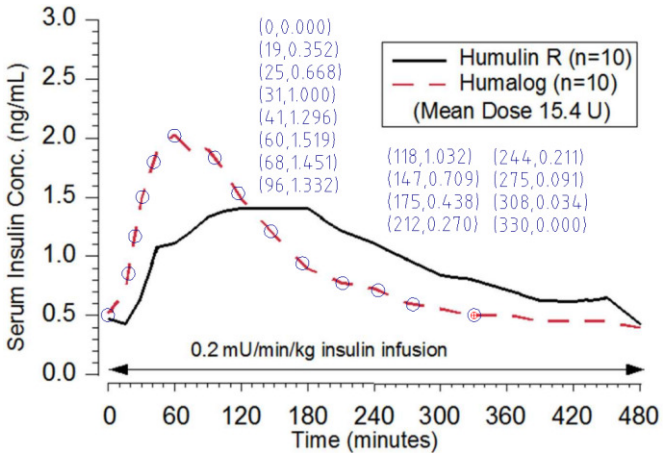

Fig. 7. Insulin profile for Humalog including points (in blue) used in polynomial fitting where serum insulin concentration is given over the base level of 0.5 [8]

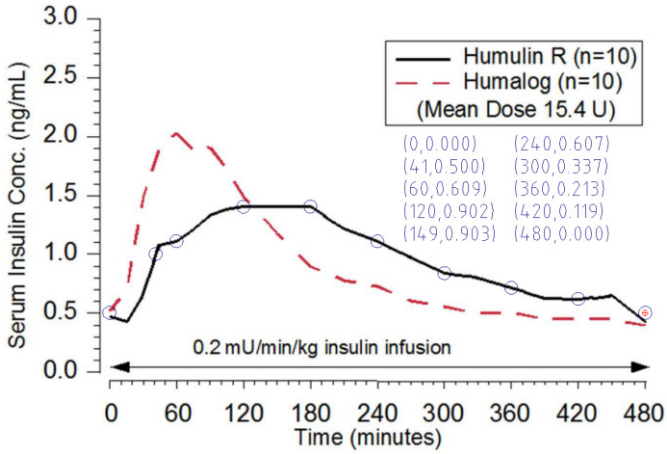

Fig. 8. Insulin profile for Humulin R Short-acting including points (in blue) used in polynomial fitting where serum insulin concentration is given over the base level of 0.5 [8]

It was assumed that the insulin curves can be approximated with polynomials. After preliminary tests (results unpublished) it was stated that the minimal degree of such a polynomial is 6:

$$C(T)=A_6\cdot T^6+A_5\cdot T^5+A_4\cdot T^4 +A_3\cdot T^3+A_2\cdot T^2+A_1\cdot T+A_0 \quad (1)$$

where: C is serum insulin concentration, T - time, A_i - individual coefficients for each insulin analog (i=0,1,..,6). The polynomial is valid for the range of insulin action starting with the time of application (injection) T_{APP} until it fades away at time point marked T_{FED}. The range of insulin action is denoted by $T_{SPAN} = T_{FED} - T_{APP}$. Within the considered range there is so called peak insulin activity. It is just maximum of the polynomial function and the time point for it is denoted by T_{PEAK} ($T_{APP} < T_{PEAK} < T_{FED}$). To simplify calculations, it was assumed that $T_{APP} = 0$.

Before fitting the polynomial (1) to the points from the diagrams (Fig. from 2 to 8) following restrictions had been imposed:

$$C\left(T_{APP}\right) = C\left(T_{FED}\right) = 0 \quad (2)$$

$$C\left(T_{APP} < T < T_{FED}\right) > 0 \quad (3)$$

$$C'\left(T_{PEAK}\right) = 0 \quad (4)$$

$$C'\left(T_{APP} < T < T_{PEAK}\right) > 0 \quad (5)$$

$$C'\left(T_{APP} < T < T_{PEAK}\right) > 0 \quad (6)$$

$$C'\left(T_{FED}\right) = 0 \quad (7)$$

The condition (2) along with (3) says that the increase in serum insulin concentration takes place from T_{APP} to T_{FED} and the injection itself cannot cause any decrease of the concentration. Satisfying the conditions (4), (5) and (6) together guarantees existence of one maximum within the range of insulin action i.e. existence of the insulin peak. Finally the condition (7) forces gradual asymptotic fading of the concentration, which can be noticed for all presented insulin analogs. Minutes were used as time unit and the point of the peak was searched for with 5 minutes resolution. This approach let keep the results practical with the therapeutic point of view. Moreover any greater accuracy would not have correspond with the source data, which had been after all averaged.

All the symbolic and numerical calculations were preformed using the open-source mathematics software SageMath (www.sagemath.org). The quality of fitting the polynomials to the points has been shown in figures from 9 to 15. The calculations resulted in finding the values of the A_i coefficients for all the insulins under study. Here the time T is given in minutes but the values of the polynomials correspond to the source units (see Fig. from 2 to 8). The symbol P in the descriptions under the figures stands for the area under the curve given in current units. These values were used in a normalization process.

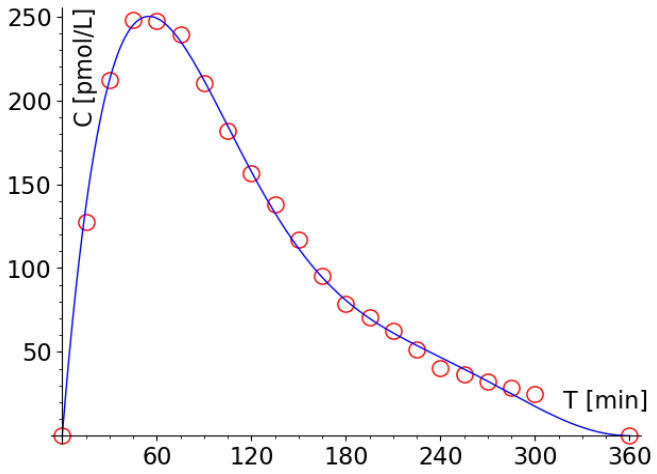

Fig. 9. Polynomial fitting for Fiasp: T_{PEAK}= 55, $C(T) = -4.408\times10^{-12}\ T^6 +6.756\times10^{-9}\ T^5 -4.073\times10^{-6}\ T^4 +1.218\times10^{-3}\ T^3 -0.1840\ T^2 +11.60\ T$, P=36452.5

3. The model of insulin activity

After the fitting calculations all the polynomials had been normalized. The normalization process consisted in transforming the polynomials to the range of [0,1] and reducing the area under the curve to 1. If the normalized form of (1) is described with (note small letters):

$$c(t)=a_6\cdot t^6+a_5\cdot t^5+a_4\cdot t^4 +a_3\cdot t^3+a_2\cdot t^2+a_1\cdot t+a_0 \quad (8)$$

where: c is unitless serum insulin concentration, t -unitless time in the range of [0,1], then the individual coefficients a_i for each insulin analog can be calculated using the formula:

$$a_i=\frac{A_i\cdot T_{SPAN}^{i+1}}{P} \quad (9)$$

Having the normalized insulin curves (Table 7) it is possible to determine insulin activity functions:

$$D(T)=\frac{DOSE}{T_{SPAN}}\cdot c\left(\frac{T}{T_{SPAN}}\right) \quad (10)$$

where: $DOSE$ is the amout of insulin injected (in any insulin unit). The model of insulin activity contains the following assumptions:

- Source diagrams (Fig. from 2 to 8) present the total consumption of the injected dose.
- Insulin serum concentration is directly proportional to the active fraction of the whole dose.
- The insulin dose size does not affect its profile.

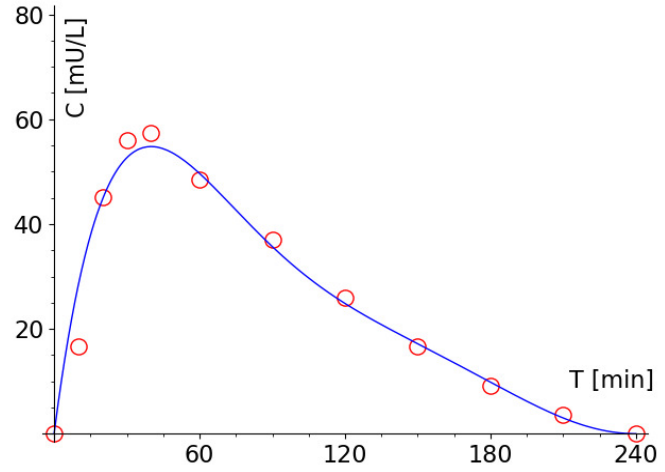

Fig. 10. Polynomial fitting for NovoRapid: T_{PEAK}= 40, $C(T) = -1.034\times10^{-11}\,T^6 + 1.035\times10^{-8}\,T^5 - 4.076\times10^{-6}\,T^4 + 8.018\times10^{-4}\,T^3 - 0.08134\,T^2 + 3.576\,T$, P=6048.19

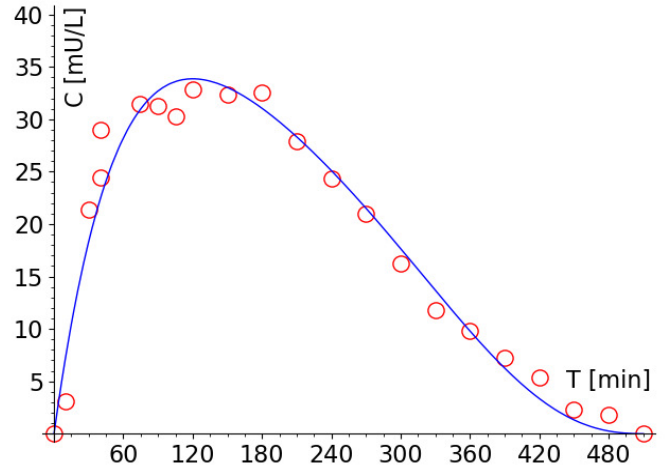

Fig. 11. Polynomial fitting for Actrapid: T_{PEAK}= 120, $C(T) = -5.669\times10^{-14}\,T^6 + 1.054\times10^{-10}\,T^5 - 7.818\times10^{-8}\,T^4 + 3.064\times10^{-5}\,T^3 - 0.006997\,T^2 + 0.7952\,T$, P=9190.88

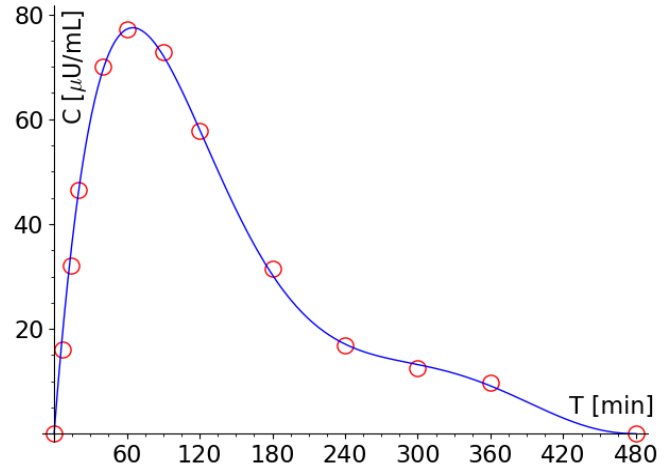

Fig. 12. Polynomial fitting for Apidra: T_{PEAK}= 65, $C(T) = -3.638\times10^{-13}\,T^6 + 7.160\times10^{-10}\,T^5 - 5.521\times10^{-7}\,T^4 + 2.090\times10^{-4}\,T^3 - 0.03926\,T^2 + 3.000\,T$, P=13354.3

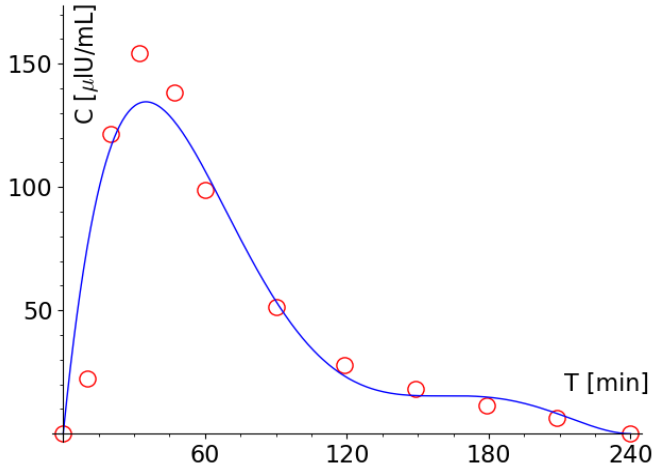

Fig. 13. Polynomial fitting for Insuman Implantable: T_{PEAK}= 35, $C(T) = -1.351\times10^{-11}\,T^6 + 1.846\times10^{-8}\,T^5 - 9.040\times10^{-6}\,T^4 + 2.060\times10^{-3}\,T^3 - 0.2239\,T^2 + 9.519\,T$, P=11320.0

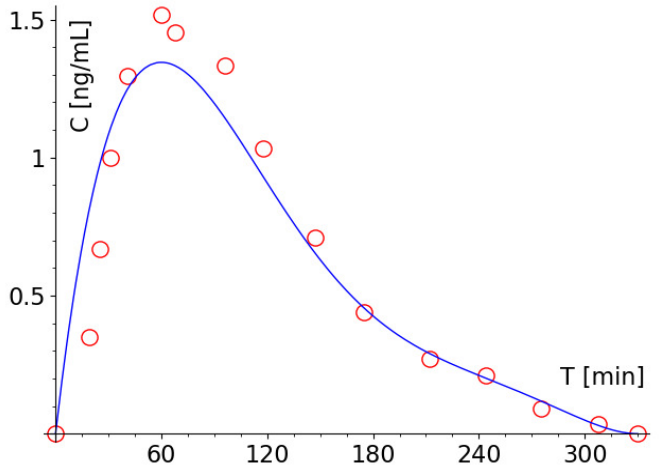

Fig. 14. Polynomial fitting for Humalog: T_{PEAK}= 60, $C(T) = -1.670\times10^{-20}\,T^6 + 9.683\times10^{-12}\,T^5 - 1.040\times10^{-8}\,T^4 + 4.214\times10^{-6}\,T^3 - 0.0007752\,T^2 + 0.05588\,T$, P=192.583

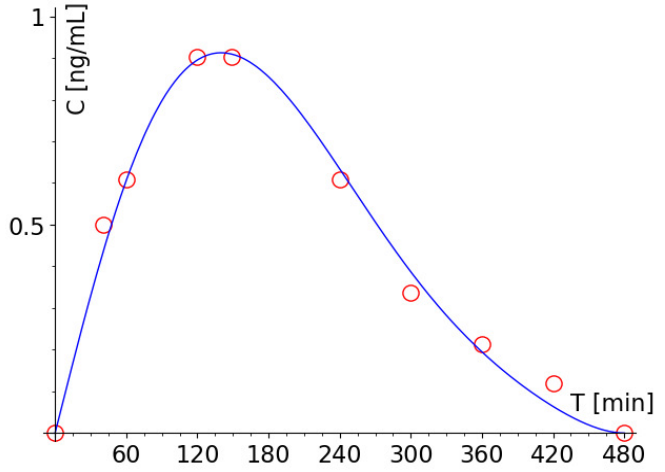

Fig. 15. Polynomial fitting for Humulin R Short-acting: T_{PEAK}= 140, $C(T) = +2.296\times10^{-15}\,T^6 - 3.739\times10^{-12}\,T^5 + 2.227\times10^{-9}\,T^4 - 5.197\times10^{-7}\,T^3 + 4.667\times10^{-6}\,T^2 + 0.0113\,T$, P=221.561

4. Results

The most valuable results of this work are the normalized insulin profiles given by polynomial coefficients a_i (Table 7).

The profiles enable standarized comparison of insulin analogs. Moreover they, along with the time ranges of insulin action $T_{SPAN,}$ let formulate the insulin activity model according to (10). The normalized curves have been depicted in the following figures. The Fig.16 presents the curves for the rapid acting insulin analogs under study, whereas the Fig. 17 shows the curves for the short acting analogs. It can be noticed that within the the same group the normalized insulin curves are similar. The differences between them may not go beyond measurement scatter. Let's take into consideration Fig. 2 and Fig. 3. They both show insulin profiles for NovoRapid. Using the data from the figures two different normalized curves for the same analog have been draw up (see Fig. 18). The disagreement is similar to that one seen between different rapid acting analogs (Fig. 16). This observation indicates a possible direction in further searching for insulin activity models. It suggests that it may be possible to use one normalized insulin curve for each group instead of individual for each product.

Example activity functions have been calculated according to (10) for DOSE = 1U (1unit) and presented at Fig. 19. The functions describe the action of 1U of an insulin analog injected at time T_{APP}=0. The figure shows how the analogs activates in a human body over time. In this case different types of insulin can be presented at the same graph, because here unitless time is scaled to real minutes using the given periods of activity T_{SPAN}. Looking at the figure is easy to point out the rapid acting group and the short acting group.

The case of Humalg needs to be commented. Looking at the Fig. 19 one can notice that its curve deviates from the rest of the rapid-acting group. The graph suggests that Humalog is the fastest insulin. The effect is not present in the Fig. 16 because it is the activity time range T_{SPAN} that has decided on the look of the activity function. The range for Humalog (see Table 7) is shorter then ranges of other rapid-acting analogs. The range was read form Fig. 6. The author of this paper recommends caution in this case.

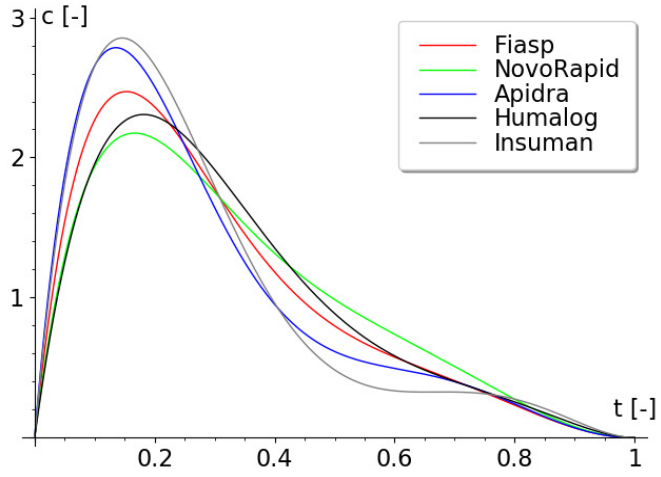

Fig. 16. Normalized insulin curves for rapid acting analogs under study

Table 7. Unitless coefficients a_i (i=1, 2, ..,6, a_0=0 for each case) of normalized insulin curves and time ranges of insulin action in minutes

Insulin	a_6	a_5	a_4	a_3	a_2	a_1	T_{SPAN}
Fiasp	−94.76	+403.4	−675.6	+561.2	−235.5	+41.25	360
NovoRapid	−78.44	+327.1	−536.6	+439.8	−185.9	+34.05	360
Actrapid	−55.35	+201.8	−293.5	+225.5	−101.0	+22.50	510
Apidra	−159.9	+655.7	−1053	+831.0	−325.2	+51.75	480
Insuman Implantable	−54.72	+311.7	−635.9	+603.9	−273.5	+48.43	240
Humalog	+0.000	+64.93	−211.3	+259.5	−144.7	+31.60	330
Humulin R	+60.84	−206.4	+256.1	−124.5	+2.329	+11.70	48

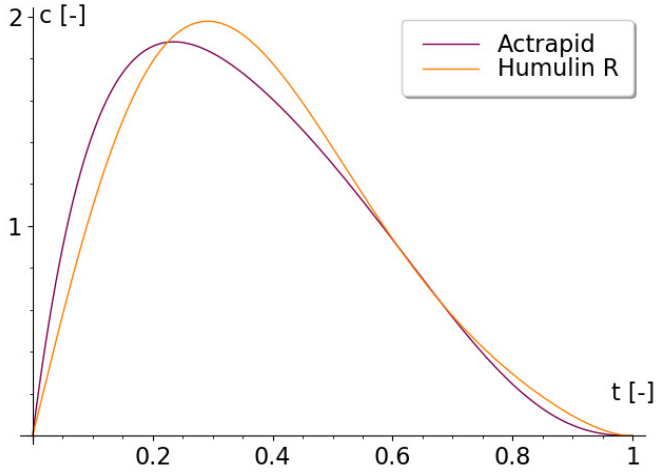

Fig. 17. Normalized insulin curves for short acting analogs under study

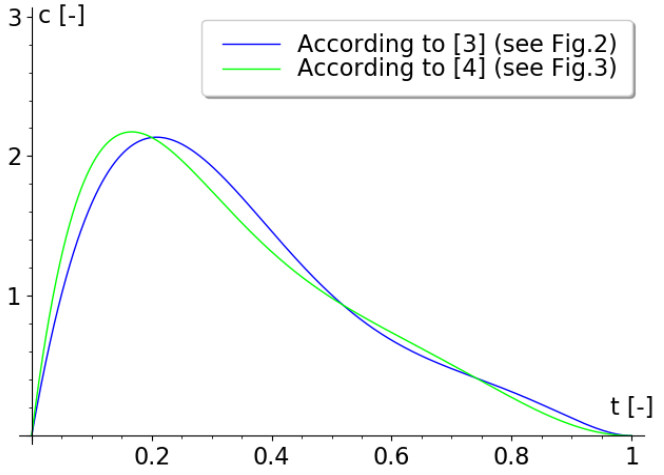

Fig. 18. Insulin profile for NovoRapid acc.to different data sources

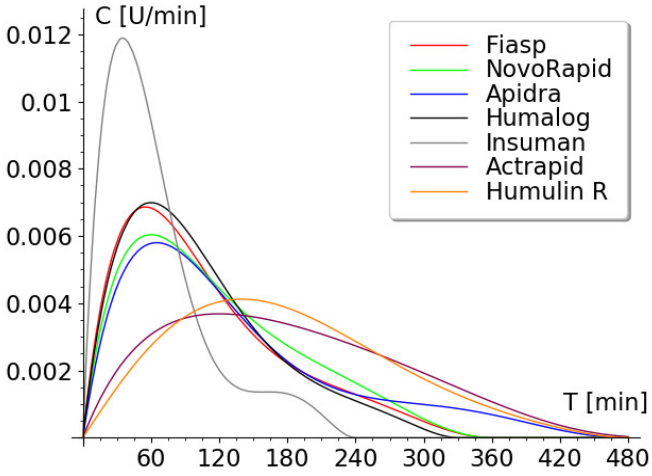

Fig. 19. Insulin activity functions acc.to (10) for the analogs under study after injection of 1U (unit) of insulin analog

5. Conclusion

In this paper 7 normalized insulin profiles have been evaluated based on the product information published by the manufactures. Followingly, the insulin activity model has been propounded. The model consists of a function formula which enables to predict insulin activity in a human body after an injection. The activity model may be used with limited trust (!) in computer aided therapy of type 1 diabetes. Moreover the results have opened a new direction for future research in the field of insulin activity models.

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