EFFECTS ON THE DYNAMICS OF INSULIN ANALOGUES IN DIABETES USING TWO TIME DELAYS

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Abstract: ***Management of type 1 diabetes and severe type 2 diabetes rely on exogenous insulin or insulin analogues to control raised blood glucose concentration. Insulin lispro and insulin aspart are rapid acting insulin analogue which have a shortened delay of onset and are easily absorbed in the bloodstream. Insulin analogue exists in hexameric, dimeric and monomeric states and hexameric form dissociates into dimeric and monomeric form which can penetrate the capillary membrane and can be absorbed into plasma. For different insulin analogues the transformation of hexameric state into dimeric and monomeric state takes different time which will be considered as first time delay in the present study. More the time it will take in this transformation, utilization of insulin in the body will be delayed which will be termed as second time delay. Therefore, an attempt has been made to find the ranges of these two time delays for the concoction of better rapid acting insulin analogues for better management of glucose and insulin concentration in diabetics through DDE model. The pro le of plasma insulin concentration level obtained from simulation of the model are in good agreement with previously observed results for the quantified range of both time delays.***

Keywords: ***Glucose, hexamer, dimer, monomer, delays, insulin analogues, mathematical model.***

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1. Introduction

The absorption kinetics of subcutaneously injected insulin has been widely studied by many researcher [1, 2, 3, 4, 5]. The absorption of insulin from the subcutaneous tissues is a very complex process and many factors are supposed to influence its absorption rate i.e. exercise [6, 7, 8], rate of injection [9, 10], technique of delivering injection [11], hot water baths, local massage, temperature of the body and smoking [12]. Absorption rate also depends on injection volumes [4] and concentration [9, 11]. Inspite of many theoretical and experimental research, the mechanism behind the subcutaneous absorption of insulin are still unknown.

In 1989, Mosekilde et al. [1] proposed a partial differential equation (PDE) mathematical model of the absorption process for soluble insulin by considering some suitable assumptions. It has been assumed that injected soluble insulin is present in the subcutaneous tissue in hexameric and dimeric form. Binder [13] assumed in his study that only dimeric form can penetrate the capillary membrane. The hypothesis was further supported by Brange et al. [14] and Kang et al. [15] in their studies with soluble human insulin and insulin analogues with reduced self-association. Inspite of considerable assumption, the mathematical model was not able to nd widespread clinical application. Later in 1993, Trajanoski et al. [6] modified the model of Mosekilde et al. [1] for monomeric insulin analogues and estimated the parametric form, the time course of plasma insulin following subcutaneous insulin injection.

Diabetes is a disease in which -cells of the pancreas does not produce sufficient amount of insulin or if produced sufficiently, then the cells of the body do not utilize insulin properly. Glucose is given through oral intake, food supplements etc. The hormone insulin produced by pancreas helps to convert glucose into energy. If insulin does not properly utilized by the cells of the body then the glucose level raised in the body, resulting a risk of diabetes occur. Raised level of glucose if persistent for long duration, the condition is known as hyperglycemia and it affects most organs of the body i.e. heart, eye, lungs, kidneys and nervous system.

Diabetes is classified into three types : type 1 diabetes, type 2 diabetes and gestational diabetes. In type 1 diabetes, cells of the pancreas are impaired in function and do not produce insulin. Type 1 diabetes is mostly detected in children and young adults and also known as Juvenile diabetes. In type 2 diabetes, either -cells do not produce sufficient amount of insulin or due to insulin resistance of the body the cell do not utilize insulin properly. Type 2 diabetes is detected after 40 years of age and majority of diabetics have type 2 diabetes. Gestational diabetes is detected in pregnant ladies, who had never have diabetes but develop high glucose level during pregnancy.

Normally insulin is secreted from cells of the pancreas in two time scales in an oscillatory manner : pulsatile oscillations accounting for the basal insulin and ultradian oscillations controlled by plasma glucose concentration levels [16, 17, 18, 19, 20, 21]. Several different types of insulin analogues have been produced and used in clinical practices [22, 23, 24, 25]. Basal dose and bolus dose are the two types of insulin doses which simulate the insulin pulsatile secretion and ultradian secretion in an oscillatory manner, respectively. The doses are given to the patients according to their daily physical activities and can be adjusted manually [16]. Insulin analogue exists in hexameric, dimeric and monomeric states and hexameric form is the predominant state after the subcutaneous injection of soluble insulin. The hexameric form dissociates into dimeric and monomeric form which can penetrate the capillary membrane and can be absorbed into plasma [26]. The conversion of hexameric into dimeric and monomeric state is shown in Figure 1.

Insulin lispro is a rapid acting insulin analogue and it was the first insulin analogue to enter in the

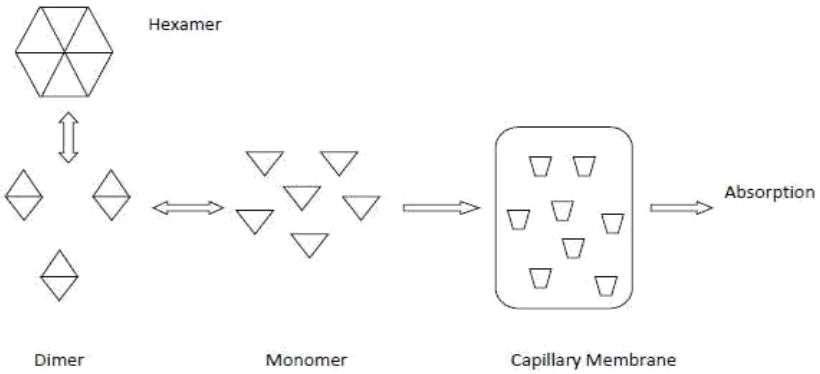

Figure 1: Conversion of hexamer to dimeric and monomeric state

market in 1996 [16]. Insulin lispro has a shortened delay of onset. Insulin aspart is also a rapid acting insulin analog and is manufactured from the human insulin by changing a single amino acid. This helps the rapid acting insulin analog to absorb into the bloodstream. Insulin glargine developed by rDNA technology in 2002 is a long acting basal insulin analogue, given once daily to help in controlling the raised blood glucose level. Insulin monomers are the functional and physiologically active unit of insulin. To mimic the normal physiological insulin secretion in type 1 diabetes, the best way is to use lispro or aspart as the bolus insulin and glargine as the basal insulin for pulsatile secretion of insulin stimulated by elevated plasma glucose concentration level [16].

This is clearly seen that insulin analogue are desirable to simulate the physiological pulsatile insulin secretion that observed in normal subjects [23, 24]. Several mathematical models have been proposed to understand the dynamics of the insulin analogues from the subcutaneous injection to absorption [16, 1, 6, 27, 28, 29, 30].

Here, our motive is to model the pro le of plasma insulin concentration level by incorporating two time delay terms in the previously developed insulin analogues model [1, 16]. To the time no one has considered the explicit time delays in model which are very necessary as delays are observed in the whole process from delivery of insulin injection to insulin absorption. The first delay is the delay observed in conversion of insulin analogues from hexameric state to dimeric and monomeric state and second delay is the delay observed in utilization of plasma insulin concentration.

We organise our paper into 5 sections : Introduction and biological background is given in section

1. A DDE mathematical model having two explicit time delays are discussed in section
2. Numerical simulation and results are found in section
3. The paper ends with brief discussion and conclusion in section 4 and 5.
4. **Mathematical Model**

In 2009, Li et al. [16] proposed the ODE mathematical models to stimulate the dynamics of rapid acting insulin analogue of the whole metabolic system. In 2009, Li and Johnson [31] considered the explicit delay > 0 for transformation of hexameric to dimeric form and demonstrate the plasma insulin concentration pro le and compared with the experimental data but the range of the delay term was not figured out in the paper. Here, we will modify the existing mathematical model proposed by Li et al.
[16] by incorporating two explicit time delay terms in the mathematical ODE models.

$_t$ is the time delay observed in the transformation of hexameric state to dimeric state and is incor-porated in eqn. (2) of the model (1- 3). $_u$ is the time delay observed in the utilization of plasma insulin concentration and is incorporated in eqn.(3) of the model (1- 3). We will observe the change in plasma insulin concentration level due to the presence of these two time delay terms in the model (1- 3).

The DDE mathematical model containing two explicit delay terms for the insulin analogues is :

$$\frac{dH}{dt} = pH(t) + pqD^3(t) \quad (1)$$

$$\frac{dD}{dt} = pH(t - \tau_t) - pqD^3(t) - \frac{bD(t)}{1 + I(t)} \quad (2)$$

$$\frac{dI}{dt} = \frac{rbD(t)}{1 + I(t)} - d_i I(t - \tau_u) \quad (3)$$

with initial conditions $H(0) = H_0 > 0$, $D(0) = 0$, $I(0) = I_0 \geq 0$, $\tau_t \geq 0$, $\tau_u \geq 0$, where H(t)(U=ml) represents the insulin analogue concentration in hexameric form, D(t)(U=ml) represents the insulin analogue concentration in dimeric form, I(t)(U=ml) represents the plasma insulin concentration at time t ≥ 0, p
(min ^{1}) is the transform rate from one hexameric molecule to three dimeric molecules [30], q (ml^2=U^2) represents chemical equilibrium constant [30], pq is the transform rate from three dimeric molecules to one hexameric molecule, b (U=min) is a constant parameter [1, 29, 30], r is the rate at which fractional molecules became plasma insulin [29], d_i(min ^{1}) is the insulin degradation rate.

Rate of dimers penetrating the capillary is inversely proportional to the plasma insulin concentration and is depicted by the term bD(t)=(1+ I(t)) in eqn.(2) equation and the term rbD(t)=(1+ I(t)) in eqn.(3) of the model (1- 3). This hypothesize is used as there is no experimental study is observed.

3. Numerical Analysis

In this section, we perform numerical simulation using parameters identified in the literature. We attempt to model the glucose insulin regulatory system of human body. Table (1) lists the values of all parameters used in model (1- 3) and the related references from which parameter values are determined.

We consider the delay differential equations (DDE) mathematical model to model the pro le of plasma insulin concentration. The calculation is simplified by using solver dde23 in Matlab 2012b. Bolus injection of insulin is the most commonly used in diabetics, but the continuous subcutaneous injection is more effective region for insulin delivery. Insulin is secreted from the pancreas in two oscillatory manners. Pulsatile oscillations having small amplitude and short period of 5 - 15 min and ultradian oscillations having large amplitude and long period of 50 - 150 min [16, 17, 18, 20, 32, 33].

We compare the pro le of plasma insulin concentration obtained from the numerical simulation of the model (1- 3) with the results obtained by Li et al. [16] and found that after incorporating the necessary time delay terms in the models, the pro le of plasma insulin concentration is compatible with the previous obtained results. Plasma insulin concentration is considered as a variable in simulation of both the models. The dynamics of plasma insulin concentration is in agreement with measured data [34, 35].

Insulin lispro and insulin aspart was injected subcutaneously in the experiments performed in [34], while the plasma volume was assumed to be 45 ml/kg [29]. Hence the initial value of $H(0) = H_0 = 0{:}0029$U=ml = 2900 U=ml, $D(0) = D_0 = 0$ and $I(0) = I_0 = 0{:}000006$U=ml = 6 U=ml [36] are considered to model the pro le of plasma insulin concentration in model (1- 3).

For model (1-3), the values of the parameters used are same as the value taken in [16]. The values of $b = 0{:}0060$, $d_i = 0{:}0775$ are considered for simulating insulin lispro and values of $b = 0{:}0068$, $d_i = 0{:}0081$ are considered for simulating insulin aspart [16]. The range of values of b and d_i are selected from range discussed in the best model 9 and model 10 proposed in [23] from Table III(a). Model is proposed for bolus injection only hence we compare the plasma insulin concentration of our model with the Li et al. [16] model.

We also quantify the range of two time delays in 3 cases at which the good pro le of plasma insulin concentration is obtained for model (1- 3).

Case 1 : $_t > 0$, $_u = 0$ (i.e delay in transformation of hexameric state to dimeric state but no delay in insulin utilization).

For $_t = 15$, $_u = 0$ we observe that I(t) = 10U=ml. In Figure (2) plasma insulin concentration level are plotted for aspart and lispro insulin which is also compatible to the pro le obtained by previous models [16, 31, 34].

Case 2 : $_t > 0$ min, $_u > 0$ min (i.e delay in transformation of hexameric state to dimeric state and delay in insulin utilization).

For $_t = 15$ min, $_u = 425$ min, we observe that I(t) = 12U=ml. In Figure (3) plasma insulin concentration level are plotted for aspart and lispro insulin which is also compatible to the pro le obtained by previous models [16, 31, 34].

Case 3 : $_t = 0$ min, $_u > 0$ min (i.e delay in transformation of hexameric state to dimeric state and delay in insulin utilization).

For $_t = 0$ min, $_u = 440$ min, we observe that I(t) = 6U=ml. Plasma insulin concentration level are plotted for aspart and lispro insulin which is again compatible to the pro le obtained by previous models [16, 31, 34] as seen in Figure (4).

In Figure (5), comparison of the simulated plasma insulin concentration produced by model (1- 3) for lispro having $_t = 15$ min, $_u = 0$ min and Li et al. [16] model is shown. In Figure (6), comparison of the simulated plasma insulin concentration produced by model (1- 3) for aspart having $_t = 15$ min, $_u = 0$ min and Li et al. [16] model is shown. Relationship of hexamer, dimer and plasma insulin concentration produced by model (1- 3) ($_t = 15$ min, $_u = 425$ min) can be seen in Figure (7).

Figures demonstrate the plasma insulin concentration after incorporating both the delays in model (1- 3). It can be seen clearly in figures that plasma insulin concentration pro le given by DDE model (1- 3) is compatible with the pro le of the previous models [16, 31].

4. Discussion

To maintain the normal blood glucose level in the body, regulation of glucose insulin endocrine system should work continuously. Lispro and aspart as the bolus insulin are the best form of insulin for the normal physiological secretion stimulated by elevated blood glucose concentration in type 1 diabetic patients while glargin as the basal insulin is considered to be the best [16]. To maintain the glucose concentration in physiological range, the exact timing and doses of subcutaneous insulin injection is required. Here our purpose is to solve the above problem by discussing the model (1- 3) with the help of two explicit time delays.

The pro le of plasma insulin concentration are modeled by many researchers time to time but no one has considered the time delays in the previous models. Here, we tried to make an attempt to model the plasma insulin concentration by incorporating necessary time delays and the obtained results are compatible with the results obtained by previous models.

The only limitation we can observe here is that the value of second delay ($_u$) is very large and sounds impractical in life. The obtained results also reveals the fact that there must be some hidden time delays which should also be considered and incorporated in the model so that more physiological results can be obtained. So in our future study we tried to deal with more number of time delays so that the range of all delays lies in physiological range.

5. Conclusion

The above discussed models (1- 3) having necessary time delay ($_t$ and $_u$) can form a foundation of an arti cial pancreas if integrated with continuous glucose monitoring system. The above model is simple in nature and can be proved helpful in clinical practices. Information obtained from the simulation of model may be useful in designing and development of artificial pancreas.

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Parameters	Explanantion	Units	Values	References
p	transfer rate of one hexameric molecule to three dimeric molecules	min^{1}	0.5	[6]
q	chemical equilibrium constant	ml^2U^{2}	0.13	[30]
r	rate at which fractional molecules became plasma insulin		0.2143	[29]
d_i	insulin degradation rate	min^{1}	0.081 (lispro)	[23]
d_i	insulin degradation rate	min^{1}	0.0775 (aspart)	[23]
b	constant parameter	min^{1}	0.0068 (lispro)	[23]
b	constant parameter	min^{1}	0.0060 (aspart)	[23]
H_0	insulin concentration in hexameric form at t=0	Uml^{1}	0.0029	[34]
D_0	insulin concentration in dimeric form at t=0	Uml^{1}	0	[16]
I_0	plasma insulin concentration at t=0	Uml^{1}	0.000006	[34]

Table 1: Parameters used in the mathematical model (1- 3).

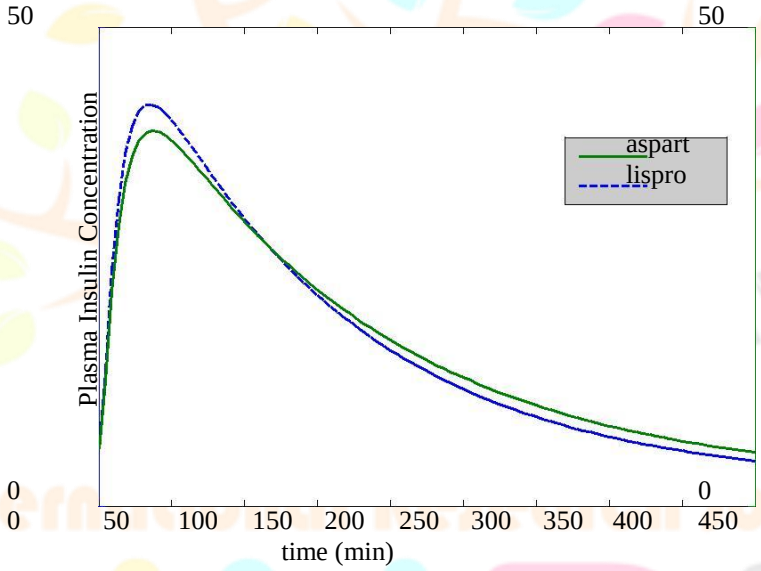

Figure 2: Plasma insulin concentration level produced by model (1- 3) having p=0.5, q=0.13, r=0.2143, d_i=0.0081, b=0.0068 $_1$ = 15, $_2$ = 0 for lispro (dashed line) and p=0.5, q=0.13, r=0.2143, d_i=0.0775, b=0.0060, $_1$ = 15, $_2$ = 0 for aspart (solid line)

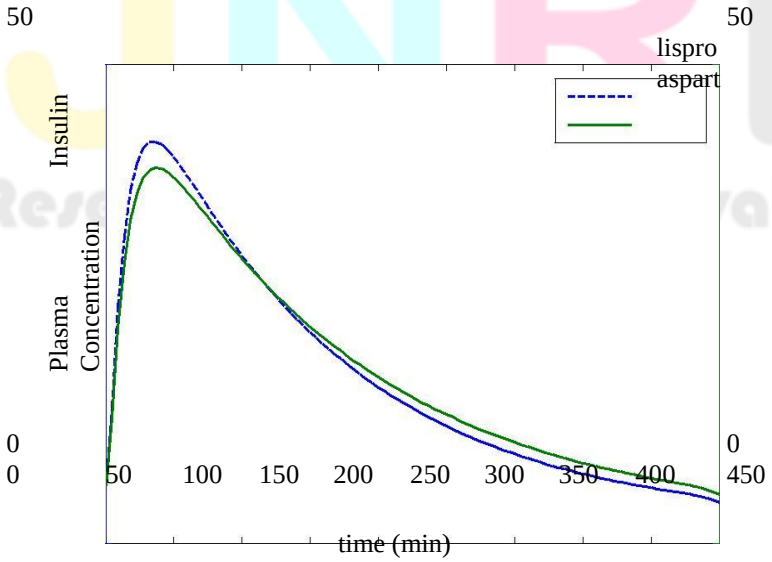

Figure 3: Plasma insulin concentration level produced by model (1- 3) having p=0.5, q=0.13, r=0.2143, d_i=0.0081, b=0.0068 $_1$ = 15, $_2$ = 425 for lispro (dashed line) and p=0.5, q=0.13, r=0.2143, d_i=0.0775, b=0.0060, $_1$ = 15, $_2$ = 425 for aspart (solid line)

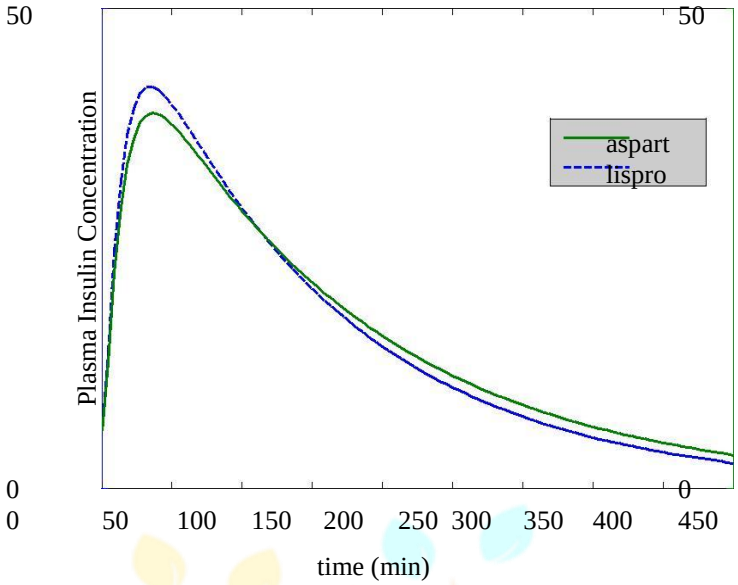

Figure 4: Plasma insulin concentration level produced by model (1- 3) having p=0.5, q=0.13, r=0.2143, d_i=0.0081, b=0.0068, $_1$ = 0, $_2$ = 440 for lispro (dashed line) and p=0.5, q=0.13, r=0.2143, d_i=0.0775, b=0.0060, $_1$ = 0, $_2$ = 440 for aspart (solid line)

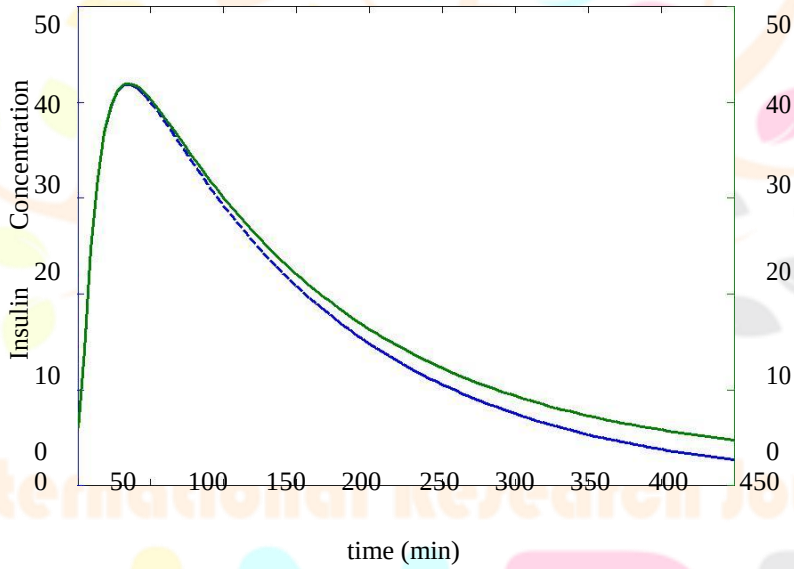

Figure 5: Comparison of the simulated plasma insulin concentration produced by model (1- 3) (solid line) for lispro having $_1$ = 15, $_2$ = 0 and dashed line is the simulation by model in [16]

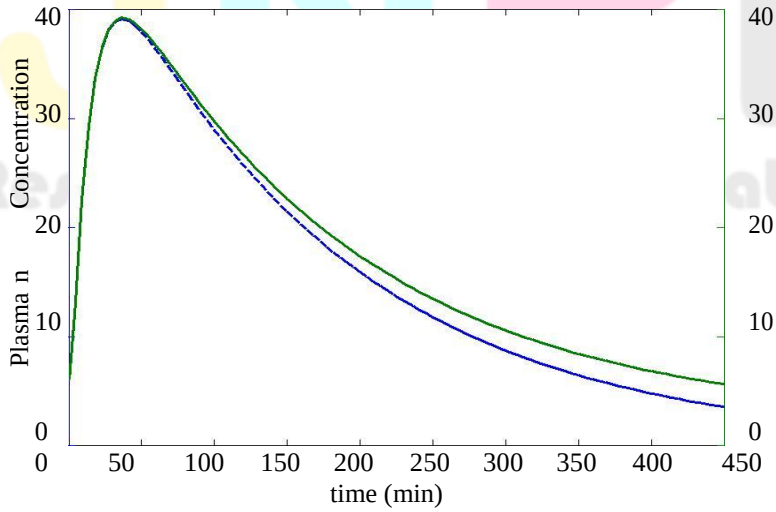

Figure 6: Comparison of the simulated plasma insulin concentration produced by model (1- 3) (solid line) for aspart having $_1$ = 15, $_2$ = 0 and dashed line is the simulation by model in [16]

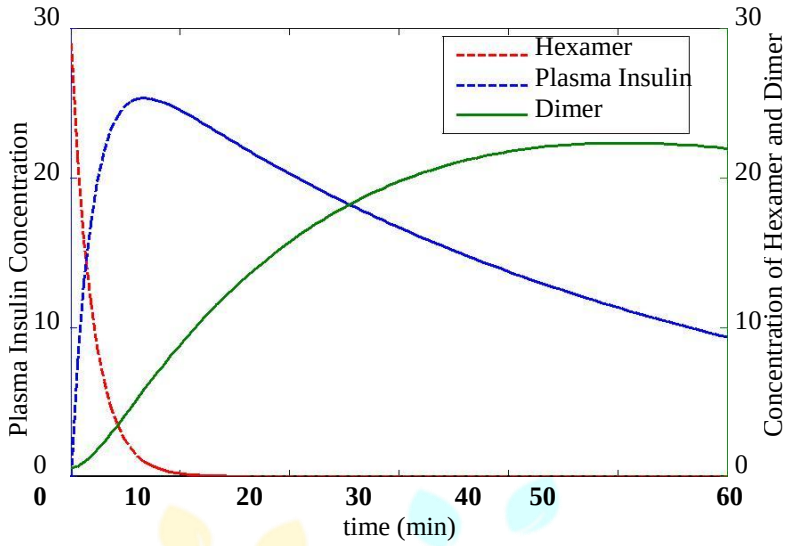

Figure 7: Dynamics of hexamer, dimer and plasma insulin concentration simulated by model (1- 3) ($_1$ = 15, $_2$ = 425)