Original article

Analysis of the Behavior of Glucose in Diabetic and Pregnant Rats at Two Weeks of Gestation

Análisis del comportamiento de la glucosa en ratas diabéticas y preñadas a las dos semanas de gestación

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ABSTRACT
An application of a study to various data collected from an experimental model of diabetes in Wistar rats developed by the *Unidad de Investigaciones Biomédicas* of the *Universidad de Ciencias Médicas de Villa Clara*, which is based on the proposal of a mathematical model that is analyzed in previous works, is shown here. In this way, the real behavior of blood glucose is approximated to each instant of time for the course of 5 hours, once the ingestion of a dose for each rat has been carried out. The curves obtained from the model in the different cases can be compared between them. In addition, with graphic representations, several parameters of great importance for decision making are identified and the difference is represented when we are in the presence of diabetic and pregnant rats with their respective controls.
Keywords: insulin and glucose interaction; pregnancy diabetes; gestational diabetes; behavior of insulin-glucose through differential equations; insulin-glucose dynamics; expected value for variation of glucose concentration.

RESUMEN
Se muestra una aplicación de un estudio a diversos datos recolectados de un modelo experimental de diabetes en ratas Wistar desarrollado por la Unidad de investigaciones biomédicas de la Universidad de Ciencias Médicas de Villa Clara, el cual se basa en la propuesta de un modelo matemático que se analiza en trabajos previos. De esta manera, se aproxima el comportamiento real de la glucosa en sangre en cada instante de tiempo durante el transcurso de 5 horas una vez realizada la ingesta de una dosis para

cada rata. Las curvas obtenidas en los diferentes casos a partir del modelo se pueden comparar entre sí. Además, con las representaciones gráficas se identifican varios parámetros de gran importancia para la toma de decisiones y se representa la diferencia cuando estamos en presencia de ratas diabéticas y gestantes con sus respectivos controles.
Palabras clave: interacción insulina-glucosa; diabetes gestacional; comportamiento insulina-glucosa a través de ecuaciones diferenciales; dinámica insulina-glucosa; valor esperado para la variación de la concentración de glucosa.

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Introduction

Diabetes is one of the diseases that most affect people worldwide, exceeding 422 million cases according to World Health Organization (WHO) 2021 statistics. It is also one of the diseases that causes the most problems, thus reducing life expectancy, since in 2019, it was the ninth most important cause of death (1.5 million, American Diabetes Association, 2021).

One of the problems that doctors face today is predicting the critical moment when the maximum glucose value is reached in order to apply insulin to patients as well as what value can be at that critical moment. [(1)] Hence, this implies that the treatment must be more individualized to be more precise when making medical guidelines.

Various mathematical models can be found in the literature that simulate situations where both the insulin-glucose interaction and the intervention of other molecules are analyzed. Almost all the cases are too complex and lack practical sense. Conjectures that are presented may be the impossibility of identifying any real-life examples.

Moreover, there are logical bioethical limitations that are associated with research in humans, mainly during pregnancy. Therefore, the application of biological and mathematical models is an essential step in biomedical studies. [(2)] As far as we are concerned, a model that we have worked in previously is applied to the data collected in the previously mentioned biological model of moderate diabetes. The purpose of this paper is to analyze the interaction between insulin and glucose in rats from this mathematical model.

All the simulations were carried out thanks to the collaboration of the *Unidad de Investigaciones Biomédicas* of the *Universidad de Ciencias Médicas de Villa Clara*, Cuba, which works with an experimental model of moderate diabetes in Wistar rats, which includes the study of pregnancy and its complications associated with the disease.

In general, it is possible to find the time point of maximum concentration for glucose, and the radical changes that are generated in each individual and predict insulin without the need to do an additional laboratory test in Wistar rats in the different case studies.

Biological Considerations

It is known so far that there are three main types of diabetes:
Type 1 which consists of deficient production of insulin. It usually develops at an early age, especially in children and young people, and its symptoms are known as the 3 P's: polydipsia (excessive thirst), polyuria (excessive desire to urinate), and polyphagia (constant hunger). [3]
Type 2 diabetes is characterized by the ineffective use of insulin by the body, mainly because its quality is worse. The causes of type 2 diabetes (DM2) are overweight, a sedentary lifestyle (very little physical activity), and an unbalanced diet rich in sugars and fats. That is why it tends to occur with a higher prevalence in people with an advanced age. [4]
Gestational diabetes: consists mainly of hyperglycemia that occurs in some pregnant women.[5]

Glucose

Glucose is an aldohexose that is the main source of energy for the cell. It is the only source of energy for the brain and nervous system. It must be maintained at relatively constant concentrations in the blood. The tissues that have enzymes for glucose synthesis are the liver and kidneys (Genova et al, 2007). Glucose concentrations are higher in plasma than in erythrocytes. Thus, hypertriglyceridemia and hyperproteinemia decrease the concentration of water in the blood sample, which can lead to falsely decreased glucose results (Orazio et al, 2005). On the other hand, glucose is higher in arterial than in capillary blood and higher in capillary than in venous blood due to the rate of glucose consumption in the tissues. [6]

Insulin

Insulin is a hormone that is secreted by the pancreas. Its mission is to carry out the metabolism of carbohydrates, lipids, and proteins and to facilitate the glucose circulating in the blood to penetrate the cells to be used as energy. It is a small protein that contains 51 amino acids arranged in two chains (A and B) which are linked by disulfide bridges.

Pregnant Diabetes

Mother's systems change during pregnancy at all levels like the cardiovascular, respiratory, and metabolic ones. This happens in response to the need to maintain an adequate balance between the mother and the fetus. Hence, this will guarantee an adequate development of the baby. These adaptations occur to ensure correct glucose shunting to promote fetal development while maintaining adequate maternal nutrition in the context of glucose metabolism. [7]
Balance in glucose regulation is essential for maternal-fetal health during all trimesters of gestation. Firstly, fasting blood glucose levels decrease during pregnancy; this is partly due to dilution effects as the mother's blood volume increases and these remain constant in the second trimester and decrease further during the third trimester. [8]
In addition, pregnancy represents an extremely delicate risk to both the mother and the developing fetus of a diabetic person. High blood glucose levels before and during pregnancy can worsen long-term diabetes-related problems such as eye problems, heart disease, and kidney disease. The baby may have problems such as being born prematurely, being overweight, having breathing problems or low blood

glucose right after birth, or other health problems. Furthermore, the risk of losing the baby increases due to miscarriage, that is, losing the baby before 20 weeks, or retained stillbirth, that is, when the baby dies in the womb after 20 weeks of pregnancy.

Rat Experimentation

In recent decades, many researchers have studied DM using experimental models since they allow us to understand pathophysiological mechanisms and evaluate diagnostic and therapeutic strategies that limit the development of the disease and its complications.

Although no biological model completely reproduces the disease in humans, it is necessary to work on the characterization of these animals so that the results obtained from their use are as valuable as possible. Nonetheless, there is no research about animal models of moderate diabetes where the impact of moderate hyperglycemia in Wistar rats and their offspring is comprehensively evaluated on all the scientific literature reviewed.

However, the etiology, pathogenesis, and prevention of diabetes-induced complications require constant efforts in basic and clinical research. Animal models of diabetes and pregnancy are an important tool for studying the complications caused by the disease in pregnant women and their offspring, given the complexity of carrying out these studies in humans. [9],[10]

Mathematical Considerations

Mathematical Models

Attempts to develop the dynamics of glucose and insulin have led to the formulation of various mathematical models. These models range from simple expressions to more complex equations that describe glucose and insulin metabolism. The three general groups of these mathematical models are:

Bolie 's model: One- compartment model that illustrates the mathematical relationship between the kinetics of glucose and insulin in blood plasma. It is based on the feedback between glucose and insulin that was previously defined where appropriate assumptions are made to determine which physiological sensitivity coefficient dominates the mathematical characteristics of normal glucose and insulin tolerance curves. They find from experimental data that these physiological coefficients approximate the known critical damping criteria of servomechanism theory. [11]

Ackerman 's model: Ackerman proposed a model of tolerance and utilization of oral glucose and another for intravenous insulin infusion. It is a simplification of the physiological control system. Well, it derives from a simplification of a general correlation diagram between the known physiological functions that the organism performs to regulate blood glucose and insulin. The proposed equations are based on linear equations with two noise channels J and$K$

$$\begin{cases} \frac{dg}{dt} = m_1 g - m_2 h + J(t) \\ \frac{dh}{dt} = m_3 g - m_4 h + K(t) \end{cases} \quad (1)$$

where $m_i$are positive constants and $J$and $K$are the degree of glucose and external insulin influencing the change. [12]

Sorensen 's model: Sorensen proposed a physiological model of glucose metabolism in patients with type I diabetes. Compartment technique is used to represent the main organs of the human body involved in glucose and insulin dynamics. The result was a non-linear mathematical model represented by a system of 19 first-order ordinary differential equations, divided into three subsystems that represent the dynamics of glucose, insulin, and glucagon, respectively. [13]

Cobelli Model: The Cobelli model is the only computer simulator accepted by the Food and Drug Administration (FDA) as a substitute for test. It consists of twelve differential equations, and its resolution by numerical methods demands great equipment capacity, which is reflected in the simulation time. It consists of a metabolic plant (glucose), and two regulatory hormones (insulin and glucagon). The glucose subsystem is described as a model of single-compartment (extracellular fluid) metabolism and distribution, with the balanced net participation of hepatic glucose (i.e., the difference between hepatic glucose production in the liver, and absorption), renal glucose excretion, insulin-dependent glucose utilization (mainly in muscle and adipose tissue), and non-insulin-dependent glucose utilization (mainly in the central nervous system and red blood cells). [14],[15]

Material and Method

Proposed Model

The model that is proposed is a continuation of several works that have been developed at the Universidad de Oriente regarding the study of the behavior of insulin-glucose through the development of differential equations. [16] It was initially proposed by Dr. C Antonio Iván Ruiz Chaveco where he himself manages the insulin-glucose dynamics in the case of a healthy individual and a diabetic individual, which is subsequently analyzed and applied in experimental models of Wistar rats. [17], [18] The model in general is described by the following system of equations:

$$\begin{cases} \frac{dG}{dt} = aG - bI + G_p(g,h,t) \\ \frac{dI}{dt} = eG - fI + H_p(g,h,t) \end{cases} \quad (2)$$

Where $G_p(g,h,t)$ and $H_p(g,h,t)$ represent the external variation rate of the concentration of glucose and insulin in blood, respectively; these represent disturbances in the system and will depend on momentary unforeseen events (food or any emotional state), in addition to the health of the individual (if they are diabetic or non-diabetic).[17]

A special case would be:

$$\begin{cases} \dot{x}_1 = ax_1 - bx_2 - c{x_1}^2 - dx_1x_2 \\ \dot{x}_2 = ex_1 - fx_2 + gx_1x_2 \end{cases} \quad (3)$$

where $\dot{x}_1 = \frac{dG}{dt}$and $\dot{x}_2 = \frac{dI}{dt}$, also the parameters a, b, c, d, e, f, g represent: coefficient of variation of glucose proportional to its concentration, coefficient of variation of glucose proportional to the concentration of insulin, coefficient of reaction of glucose proportional to its concentration, coefficient of reaction between glucose and insulin proportional to the concentration of glucose, coefficient of variation of insulin proportional to the concentration of glucose, coefficient of variation of insulin proportional to its concentration (this case takes into account only the metabolism of the body) and

coefficient of reaction between glucose and insulin proportional to the insulin concentration respectively.[16]

Estimate Parameters

For this case, due to the characteristics of the data, only the linear part of the proposed equation (3) would be taken and its parameters are estimated.

Let $\Theta \subseteq R^p$ and be $f: [t_0, T] \times \Theta \to R^n$ a function with a control variable $t \in [t_0, T]$ and a vector of parameters $\theta \in \Theta$ in such a way that they determine a model with a response variable y, that is to say

$$y = f(t; \theta), (t, \theta^{Tr})^{Tr} \in [t_0, T] \times \Theta \quad (4)$$

The problem lies in estimating the vector of parameters θ, in such a way that the "surface" defined by (4) is "fit" in the best possible way to a collection of observations given by the table:

$$T = \{(t_i, {y_i}^{Tr})^{Tr} \in [t_0, T] \times R^n \vee y_i = f(t_i; \theta) + \varepsilon_i, i = 1{:}m\} \quad (5)$$

where $\varepsilon_i \in R^n$ are errors of observations, with $mn > p$.

In addition to the identification of the coefficients or parameters that accompany the equation, other parameters are important for the diagnosis and clinical study that are defined from the curve.

Evaluation Parameters

There are other parameters that are linked to the equation and used to evaluate the development of the illness.

A value is given by measuring the distance of the curve from the limit curve or Difference Value (VD), which is defined as:

$$\int_0^5 \big(G(x) - G\big|1(x)\big)dx$$

where G is the limit glucose concentration and G_1 represents the test being performed.[18] The limit curve is developed from the limit values recommended by the doctor at the different measurement times after glucose ingestion. According to the definition, if g_1 is predominantly higher, then the value is negative and therefore the person may have diabetes and should be evaluated by a specialist.

The other factor is the expected value for the time of variation of the glucose concentration (VETVCG), which is defined as:

$$\int_0^5 tG'(t)dt$$

where $G'(t)$ is the derivative of the glucose concentration curve.[18] Its objective is to measure the variability of the speed with which the states of blood glucose concentration change. A value far from that which is measured on the limit curve may infer that patients have clinical problems.

From Table 1, a development of the borderline model can be constructed by taking the maximum values where the person begins to develop diabetes.

Table 1- Maximum values of glycemia after overload for 3 hours. American Diabetes Association 2021.

Time (minutes)	Max value _ (glycemia in plasma) Baseline
(fast)	105mg/dl
60 min	190mg/dl
120 min	165mg/dl
180 min	145mg/dl

In figure 1, the prediction for glucose and insulin in a 5 hour after an 8-hour fast is observed. It takes 5 hours since it is the average time when an individual returns to feed and starts the cycle again. The coefficients obtained in this case are $a = -4.90, b = -42.42, f = -0.15, e = -1.11$ [18]

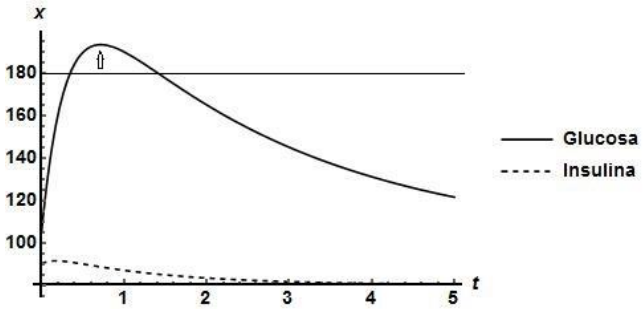

Fig.1- Simulation of the model for the limit data at 60, 120, 180 and fasting for 5 postprandial hours. Taken from Pérez Pérez et al, 2022.

In figure 1, it can be read that the time when the glucose critical point is reached is approximately 42 minutes after the ingestion of food for a maximum value of 193.39. The maximum glucose values begin after 21 minutes and last for 1 hour and 27 minutes. The data for the latter were taken taking into account considering the normal accumulated insulin in the blood of a person. Finally, the (VETVG) is from 165.15.[18]

The first of the tests consists of carrying out an analysis of the behavior of postprandial glucose for both diabetic and non-diabetic rats and diabetic and non-diabetic pregnant rats.
The test is carried out in two formats; the first consists of the study of 20 diabetic rats and 10 rats that do not present diabetic symptoms. After performing a fasting diabetes test, the glucose ingestion of 2 grams per 0.25 kg average weight of the rat is performed and measurements are taken at 30, 60, and 120 minutes after concentration is being applied. With these, you can infer the simulations. The second format would be similar to the previous one, but in this case, another sample of rats in the gestational stage, the diabetic group, and the control one are used. In this way, a descriptive analysis of the data is carried out where the mean and standard deviation are measured, and normality tests are carried out in the four stages of the study.

Results and Discussion

Statistical Analysis

Table 2 shows the results obtained from the exploratory analysis performed on the 20 non-pregnant diabetic rats. It is observed that the tests used to verify if the data conform to a normal distribution induce positive results in the Gaussian sense since the calculated P-values are greater than 0.05. Hence, it is feasible to take the mean as a result of the general behavior of the population for each of the times sampled. A change of variability in the data is also observed after 60 minutes, not affecting the results.

Table 2- Exploratory results of non-pregnant diabetic rats.

Sampling of non-pregnant diabetics	mean ± SD	Standard deviation	normality tests		Normality test type
			Statistical test	P-Value	
0	125.38	27.12	0.961	0.580	Shapiro-Wilk
30 minutes	309.32	25.99	0.957	0.494	Shapiro-Wilk
60 minutes	284.82	42.58	0.975	0.863	Shapiro-Wilk
120 minutes	203.96	65.4	0.97	0.774	Shapiro-Wilk

On the other hand, Table 3 shows the exploratory analysis for the control rats that are not pregnant, which in general has a normal behavior in the four measurement moments with little variability, suggesting that the average can be taken in this case as a representation of general measurements for the population.

Table 3- Exploratory results of non-pregnant control rats.

Sampling of non-pregnant diabetics	mean ± SD	Standard deviation	normality tests		Normality test type
			Statistical test	P-value	
0	102.29	3.96	0.947	0.637	Shapiro-Wilk
30 minutes	136.87	15.76	0.038	0.771	Shapiro-Wilk
60 minutes	117.06	10.32	0.965	0.853	Shapiro-Wilk
120 minutes	96.17	7.88	0.846	0.051	Shapiro-Wilk

Ahmed *et al. (*2015) takes 12 rats to do a study of experimental diabetes where 6 were normal control and the other six as diabetic induced. There, the rats were injected with 50mg/kg dose of Streptozotocin to induce diabetes. On week later, blood glucose levels were measured with a glucometer and it was

found that in normal rats the glucose levels were 125+10mg/dl, and in diabetic rats it was 386+45mg/dl. (19)

Table 4 shows the results in the case that the rat is diabetic or pregnant, as observed at the time of 30 minutes; the results of the hypothesis test for Anderson-Darling do not coincide with Shapiro-Wilk since the distribution of their data is not a normal variable for this, although if it is taken into account that the latter is more exact for small samples, then normality is accepted.

Table 4- Exploratory results of pregnant diabetic rats.

Sampling of non-pregnant diabetics	mean ± SD	Standard deviation	normality tests		Normality test type
			Statistical test	P-value	
fast	101.93	7.97	0.983	0.98	Shapiro-Wilk
30 minutes	266.9	34.82	0.856	0.068	Shapiro-Wilk
60 minutes	226.38	23.46	0.92	0.356	Shapiro-Wilk
120 minutes	133.99	23.34	0.871	0.101	Shapiro-Wilk

Table 5 shows the results of the exploratory analysis for the pregnant control rats. Only in the measurements for 30 minutes there is a case similar to that observed in Table 4. This may be conditioned by the physiological needs required by the fetus. However, normality is accepted since the samples are small.

As the variability that is measured is not so wide, it is considered to take the average as a representation of the population.

Table 5- Exploratory results of the pregnant control rats.

Sampling of non-pregnant diabetics	mean ± SD	Standard deviation	normality tests		Normality test type
			Statistical test	P-Value	
fast	84.57	7.62	0.958	0.768	Shapiro-Wilk
30 minutes	162.27	13.13	0.746	0.003	Shapiro-Wilk
60 minutes	130.03	11.63	0.873	0.106	Shapiro-Wilk
120 minutes	105.17	9.46	0.936	0.513	Shapiro-Wilk

Descriptive analysis is where the main data is taken to estimate the parameters of the general equation of the insulin-glucose interaction process. For each of the populations, the average of each measured time is used.

Behavior of Rats

From Tables 2, 3, 4, and, 5 the data is obtained to carry out the simulation of the different processes where the means of the samples and the standard deviation are taken. Figure 2 shows the results of applying the parameter identification of equation 3 to the data collected with the experimental models. In this case, it is considered that the ingestion is part of the metabolism which does not cause disturbances.

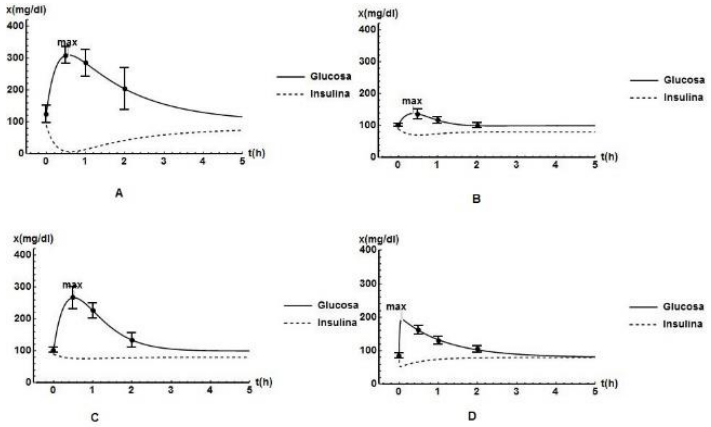

Fig.2- Simulation of the concentration of insulin and glucose for the different situations in the postprandial period. The points on the curves are the values measured at different times; their confidence intervals are also added. (A): Non-pregnant diabetic, (B): Non-pregnant control, (C): Pregnant Diabetic, (D): Pregnant Control.

Figure 2 shows that in cases where the rats are diabetic, both pregnant and non-pregnant, there is a gradual increase in blood glucose concentration with a slower decrease. On the contrary, case for the data from the control tests is not the same since the increase in the concentration of glucose in the blood is more regulated and tends to decrease more rapidly. The figure also recreates the instant when the maximum values are reached and the control points with their confidence intervals (mean $\pm$SD), which are the measurements at the four moments of the tests.

In Figueroa-García et al. (2016) the results were similar after the obtaining of a case of experimental diabetes. Hence, glucose tolerance curves show the development in 150 minutes where the highest point is approximately 18 mmol/L (324 mg/dl) for diabetic rats and 8 mmol/L (144 mg/dl) for the control group and this happens close to the 30 minutes. Furthermore, the problem in this study is that the results are showed with a lineal curve where it is not possible to predict the values that are mentioned in this work.[20]

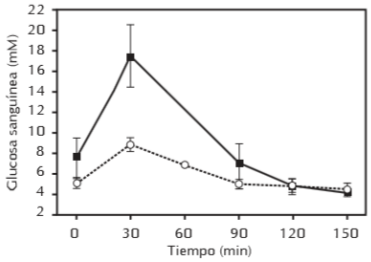

Fig. 3- Glucose tolerance curves in Wistar rats (diabetes: black point; control: white point). (Figueroa-García et al, 2016).

Trujillo Arriaga (2007) presents in his work a smoother curve than the linear example before, but he does not take into account the law of interaction of glucose, then his results are less exact. Even so, this test is applied to only one person. [21]

Fig. 6 shows the previously defined parameters which will define the decisions to be taken to analyze the clinical status of the rats in the four variants. There, it is observed that the maximum values (VM) are reached for diabetic rats as expected, where the non-pregnant diabetic is the highest. Consequently, the estimated times where the maximum value (TMV) is reached for diabetic rats exceed the 30 minutes, which are greater than the case of the controls.

Day trial	coef . a	coef . b	coef . e	coef . f	VD	VETVG	MV	TMV
non-pregnant diabetic	18.22	−52.41	−7.85	22.45	−193.4	381.17	310.39	33.6
Non-pregnant control	5.09	−22.7	−2.46	9.52	3.51	33.88	138.46	22.8
Pregnant diabetic	1.72	−85.05	−0.15	5.47	4.46	228.28	267.01	30.6
pregnant control	150.5	−626.66	−50.7	210.7	1.78	133.01	194.51	4.2
Mean	-	-	-	-	-	194.08	227.59	22.8

Fig. 6 - Parameters of the four tested models.

In the case of the VETVG parameter, four cases reach very different values. Furthermore, four cases of curves are different; it can be observed in Figures 2 and 6.

Conclusions

A biological and mathematical analysis of the behavior of blood glucose for both diabetic and healthy people was carried out. After that, a model which predicts the behavior of glucose 5 hours after food ingestion is proposed. Then, the model provides as a result a curve where various parameters can be extracted to help make clinical decisions. Hence, once the model and analysis have been formulated, they are applied to the data collection that is carried out in the *Unidad de Investigaciones Biomédicas*

of the *Universidad de Ciencias Médicas de Villa Clara* on Wistar rats. In this way, the behavior of glucose in sick, healthy and pregnant rats is obtained in order to also make comparisons and reach clinical decisions.

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Conflicts of Interests

En el presente documento se declara que no existe conflicto de interés por parte de los autores.

Authorship Statement

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