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MATHEMATICAL MODEL FOR DETECTING DIABETES IN BLOOD CELLS WITH THE INFLUENCE OF CORTISOL

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ABSTRACT

Diabetes is a disease that occurs when the body is unable to produce enough insulin or cannot effectively use the insulin it produces, resulting in an increase in blood glucose levels. One of the factors that affects the stability of glucose and insulin is the hormone cortisol, which is produced in response to stress. The purpose of this study is to develop a mathematical model of diabetes detection in blood cells by considering the influence of cortisol. The model is formulated as a system of linear differential equations and analyzed through equilibrium points and eigenvalue analysis. The results show that two eigenvalues form asymptotically stable spirals, while the other two are asymptotically stable nodes, indicating system stability. The novelty of this study lies in the inclusion of cortisol, which delays stabilization of glucose–insulin dynamics and provides a more realistic representation of physiological conditions under stress. A limitation of this study is that the model relies on simplifying assumptions without clinical validation. This research is expected to serve as a foundation for further model development by considering other regulatory factors, with implications for improving diabetes prevention and intervention strategies in stress-related conditions.

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1. INTRODUCTION

Diabetes is a disease that occurs when the body is unable to produce sufficient insulin or cannot effectively use the insulin it produces, leading to elevated blood glucose levels. Given its high prevalence and serious complications, it is urgent to develop mathematical models that can provide deeper insights into the regulation of glucose and support improved prevention and treatment approaches. This condition is further exacerbated by epinephrine, which stimulates glycogenolysis in the liver and inhibits insulin activity. The increase in epinephrine can be triggered by physiological or psychological stress, intense physical activity, and the body's response to hypoglycemia, all of which aim to maintain blood glucose levels under emergency conditions. To understand the dynamics of glucose regulation in the body, a mathematical model was developed by [1] that considers the interaction between glucose (g), insulin (h), and epinephrine (e). This model utilizes a system of linear differential equations to describe how insulin lowers glucose levels, how epinephrine raises them, and how epinephrine also affects insulin levels. The system provides insight into glucose regulation and how disruptions in this mechanism can contribute to the development of diabetes.

Cortisol is a hormone produced by the adrenal glands and plays a role in various bodily functions, including energy metabolism and the body's response to stress. Cortisol production is regulated by the hypothalamic-pituitary-adrenal (HPA) axis, which operates through a hormonal feedback system. When the body experiences stress, the hypothalamus releases CRH (Corticotropin-Releasing Hormone), which stimulates the pituitary gland to produce ACTH (Adrenocorticotropic Hormone). ACTH then stimulates the adrenal glands to produce and release cortisol into the bloodstream. Under normal conditions, cortisol follows a circadian rhythm, peaking in the morning and decreasing at night. However, prolonged stress, sleep deprivation, and metabolic disorders can cause excessive cortisol production. If cortisol levels remain high over the long term, it may disrupt the balance of other hormones, increase blood glucose levels, and lead to insulin resistance, increasing the risk of diabetes and other metabolic disorders [2].

The model developed by [1] aimed to understand how blood glucose levels are regulated by the interaction between insulin, which lowers them, and epinephrine, which raises them. The model demonstrated that maintaining a balance between these two hormones is crucial for preserving the body's metabolic stability, as disruptions in one component can lead to imbalances that contribute to hyperglycemia and insulin resistance. Moreover, the model emphasizes that changes in glucose levels are not only directly influenced by insulin and epinephrine but also by the interactions between them, creating a dynamic system for regulating blood sugar. However, the model does not consider cortisol, which also plays an important role in glucose regulation. Like epinephrine, cortisol can increase glucose levels by stimulating hepatic glucose production and inhibiting insulin activity. Over time, this can result in insulin resistance. Such conditions often occur during prolonged stress or hormonal disorders, where consistently elevated cortisol levels disrupt metabolic balance.

Several previous studies have explored the dynamics of glucose and insulin through various mathematical and computational models. One study developed a glucose–insulin dynamics model specifically for type 2 diabetes patients using ordinary differential equations (ODEs), but this model did not consider the influence of stress-related hormones, such as epinephrine or cortisol, which limits its physiological comprehensiveness [3]. Another investigation modeled glucose sensor error through a combination of diffusion models and time series analysis. However, this approach faced challenges due to non-Gaussian error distributions and temporal complexity, which made accurate modeling difficult [4].

A two-compartment model describing glucose and insulin interactions was proposed in [5], utilizing classical ODE formulations. While insightful, this model lacked the capacity for integrated multi-factor analysis and exhibited issues with global stability [6]. Meanwhile, [7] attempted to predict diabetic kidney disease (DKD) using genetic and clinical data through machine learning (ML) techniques. Although effective in prediction, the method did not incorporate dynamic or causal modeling, which are essential for understanding disease progression.

While [8] incorporated cortisol into glucose–insulin dynamics, no models have fully integrated neuroendocrine pathways—such as HPA-axis feedback loops—into β-cell dynamic models. Most models treat stress as an external parameter rather than an interactive hormonal system. Current literature [9] models β-cell decline as irreversible. There is a lack of dynamic modeling for β-cell regeneration or recovery, which is clinically relevant in early T2DM or post-treatment remission scenarios. Although some parameter estimation has been attempted [10], comprehensive global sensitivity or uncertainty quantification across time scales—particularly in multiscale β-cell models—remains limited.

An extension of the glucose–insulin model was introduced in [11] by incorporating external input energy into the ODE-based framework. Nevertheless, this model still failed to consider hormonal factors such as stress, which play a significant role in glucose regulation. Lastly, [12] proposed a model for the effects of epinephrine on glucose, insulin, and cell behavior using ODEs, but explicitly excluded cortisol from the modeling process, leaving a critical hormonal pathway unaddressed.

The novelty of this study lies in the addition of cortisol as a variable to the linear differential model previously developed by [1], resulting in a glucose regulation system that is more representative of actual physiological conditions, particularly in the context of chronic stress. From a medical perspective, cortisol plays a role in increasing glucose levels and inhibiting insulin function, particularly during periods of stress or hormonal imbalances. The objective of this research is to develop a mathematical model of glucose regulation that incorporates cortisol as a variable, in order to analyze its role as a potential indicator of diabetes risk and to evaluate its impact on system balance and glucose stability under different physiological conditions.

2. RESEARCH METHODS

The type of data used in this study is secondary data. These data are obtained from scientific literature that explores the biological interactions between glucose, insulin, epinephrine, and cortisol. The secondary data sources include experimental studies, such as those conducted by [13], which provide physiological parameter values, as well as numerical simulations from previous mathematical models, such as the work by [1], which offer insights into system dynamics and support model validation.

2.1 Modification of the Mathematical Model for Diabetes Detection in Blood Cells with Cortisol Influence

The modification of the mathematical model for diabetes detection in blood cells under the influence of cortisol is carried out through several systematic steps. The process begins by defining the model variables, namely $g(t)$ as the blood glucose concentration at time, $h(t)$ as the insulin concentration, $e(t)$ as the epinephrine concentration, and $k(t)$ as the cortisol concentration. Following this, new assumptions and problem boundaries are established to reflect the biological context. These assumptions are used to reformulate the linear differential equation system by incorporating the defined variables and parameters related to cortisol's effects. This study employs a linear system as a first-order approximation to capture the essential dynamics of glucose regulation. The linear framework was chosen because it allows analytical tractability through eigenvalue stability analysis, while acknowledging that the underlying biological processes are inherently nonlinear. Future work will extend this model into nonlinear formulations for greater physiological accuracy. The model is constructed based on the following assumptions:

1. Glucose intake from digestion is not considered, as external sources are excluded from the model.
2. The rate of change in glucose concentration depends on the levels of glucose, insulin, epinephrine, and cortisol.
3. Excessive or deficient blood glucose levels trigger the body's mechanisms to restore balance.
4. The effect of insulin on the changes in glucose, epinephrine, and cortisol levels is assumed to be linear.
5. A non-zero insulin concentration reflects active feedback mechanisms regulating glucose and insulin.
6. Epinephrine influences glucose and insulin regulation, particularly during stress.
7. The effect of cortisol on epinephrine is assumed to be independent, as both act via distinct mechanisms.
8. Cortisol concentration over time is not constant, as individuals vary in their physiological response to stress.
9. Cortisol plays a key role in regulating both glucose and insulin levels.

10. Chronic hyperglycemia can lead to prolonged cortisol secretion, potentially reducing insulin sensitivity and worsening diabetic conditions.
11. Cortisol is also assumed to be influenced by glucose and insulin levels. High blood glucose levels contribute to the reduction of cortisol through negative metabolic feedback, while insulin is assumed to stimulate cortisol secretion in line with experimental findings. These assumptions are supported by previous studies that demonstrated glucose-dependent cortisol regulation [21] and the role of insulin in enhancing cortisol release [18].

To enhance the clarity of the model, a compartment diagram is constructed to illustrate the dynamic interactions among the variables involved in regulating blood glucose under stress-related hormonal influences. The fundamental model equations are defined as [1]:

$$\frac{dg}{dt} = -ag(t) - bh(t) + fe(t),$$
$$\frac{dh}{dt} = cg(t) - jh(t) + ke(t),$$
$$\frac{de}{dt} = -l\,g(t) - mh(t) + ne(t),$$

where:

a : natural rate of change of glucose;

b : rate of glucose decrease due to insulin;

c : rate of insulin secretion in response to glucose;

j : natural rate of change of insulin;

f : rate of glucose increase induced by epinephrine;

k : rate of insulin secretion stimulated by epinephrine;

l : rate of epinephrine suppression due to glucose;

m : rate of epinephrine decrease caused by insulin;

n : natural rate of change of epinephrine.

2.2 Analytical Solution of the Mathematical Model for Diabetes Detection in Blood Cells with Cortisol Influence

The analytical solution of the mathematical model begins with determining parameter values to be used for numerical simulations. After the parameters are defined, the next step is to compute the equilibrium point of the system. Subsequently, the Jacobian matrix is evaluated at the equilibrium point to calculate its eigenvalues, which are used to analyze the system's stability. Lastly, the model is interpreted by examining how stress, through the hormone's epinephrine and cortisol, contributes to increased blood glucose levels and decreased insulin effectiveness. This highlights a greater risk of hyperglycemia and worsened diabetic conditions, particularly in individuals experiencing frequent stress.

3. RESULTS AND DISCUSSION

3.1 Model Modification

Cortisol is a steroid hormone produced by the adrenal cortex in response to stress and the body's metabolic needs. Its production is regulated by the hypothalamic-pituitary-adrenal (HPA) axis, where the hypothalamus releases Corticotropin-Releasing Hormone (CRH), stimulating the pituitary gland to secrete Adrenocorticotropic Hormone (ACTH), which in turn stimulates the adrenal cortex to produce and release cortisol into the bloodstream [13]. Cortisol plays a crucial role in regulating energy metabolism, immune responses, and blood pressure. The levels of cortisol follow a circadian rhythm, peaking in the morning and declining throughout the day to reach the lowest point at night [14]. The increase in cortisol levels is triggered by ACTH stimulation of the adrenal cortex, but cortisol is also rapidly degraded through natural and enzymatic mechanisms that maintain physiological balance [15].

Cortisol can elevate blood glucose levels by stimulating glucose production in the liver through the processes of gluconeogenesis and glycogenolysis. It enhances the activity of the enzyme glucose-6-phosphatase, which converts glucose-6-phosphate into free glucose and releases it into the bloodstream. Studies have shown that cortisol administration increases hepatic glucose output, particularly under conditions of low insulin levels. Cortisol elevates glucose by triggering the glucose/glucose-6-phosphate cycle, which plays a role in maintaining glucose balance in the liver. Data showed that glucose production was significantly higher after cortisol administration in the postabsorptive state (without insulin), with cortisol-treated subjects at 13.3 ± 0.5 μmol/kg·min compared to 12.2 ± 0.5 μmol/kg·min in saline-treated subjects ($P < 0.05$) [16].

Insulin is a hormone synthesized and secreted by pancreatic β-cells in response to elevated blood glucose levels, as well as other stimuli such as amino acids and parasympathetic nervous activity. It binds to receptors on the surface of target cells, activating intracellular signaling pathways via insulin receptor substrate (IRS) proteins. One of insulin's primary functions is to regulate short-term glucose metabolism by stimulating skeletal muscle and adipose tissue cells to absorb glucose from the bloodstream. This is achieved through the upregulation of GLUT-4 glucose transporters on the cell membrane, allowing glucose to enter cells for energy production or storage as glycogen, especially in the liver and muscles. In this way, insulin is essential for maintaining glucose homeostasis and supporting efficient energy metabolism [17].

Cortisol directly affects insulin action by reducing cellular sensitivity to insulin, thereby making it more difficult for cells to absorb glucose from the blood. Under normal conditions, insulin helps cells take up glucose for energy or store it as glycogen. However, when cortisol levels are elevated, such as during prolonged stress, cortisol inhibits insulin's effects by decreasing the number of insulin receptors and interfering with insulin signaling pathways. Consequently, cells become less responsive to insulin, leading to persistently high blood glucose levels. Over time, this condition may result in insulin resistance, one of the key factors in the development of type 2 diabetes and metabolic syndrome. Therefore, the balance between cortisol and insulin is crucial in maintaining glucose regulation in the body [18].

Cortisol has a direct effect on insulin function by reducing cellular sensitivity to insulin, making it more difficult for the body to absorb glucose from the bloodstream. Under normal conditions, insulin facilitates the uptake of glucose by cells for energy use or storage as glycogen. However, when cortisol levels are elevated—such as during prolonged stress—cortisol inhibits insulin action by decreasing the number of insulin receptors on cells and disrupting insulin signaling pathways. As a result, cells become less responsive to insulin, leading to persistently high blood glucose levels. If this condition persists, it may result in insulin resistance, which is one of the main contributing factors to the development of type 2 diabetes and metabolic syndrome. Therefore, the balance between cortisol and insulin is crucial for maintaining proper glucose regulation in the body [19].

Epinephrine (adrenaline) is a hormone secreted by the adrenal medulla in response to physical or emotional stress. Elevated levels of epinephrine in the bloodstream can cause a rapid increase in blood glucose by stimulating hepatic glycogenolysis as part of the body's adaptive response to emergency situations. A study by Shamoon et al. in 1980 demonstrated that epinephrine infusion increased glucose production by 60% within 15–30 minutes in healthy subjects, with an even greater and more prolonged response in individuals with type 1 diabetes.

Cortisol and epinephrine both play key roles in the body's stress response. Cortisol, the primary stress hormone produced by the adrenal cortex, directly regulates the biosynthesis of epinephrine by upregulating the expression of the enzyme phenylethanolamine N-methyltransferase (PNMT), which catalyzes the final step in epinephrine synthesis. This mechanism shows that cortisol released through HPA axis activation not only promotes gluconeogenesis but also ensures the availability of epinephrine by influencing its biosynthesis. This interaction confirms that cortisol and epinephrine work synergistically to maintain homeostasis during physiological and psychological stress [20]. To develop a mathematical model for detecting diabetes in blood cells that incorporates the influence of cortisol, the first step is to define the variables as follows:

$g(t)$: blood glucose concentration at time t;

$h(t)$: blood insulin concentration at time t;

$e(t)$: blood epinephrine concentration at time t;

$k(t)$: blood cortisol concentration at time t.

To illustrate the interactions among glucose, insulin, epinephrine, and cortisol, a compartment diagram is constructed, where each variable is represented as a node and arrows indicate the direction of regulatory effects within the model.

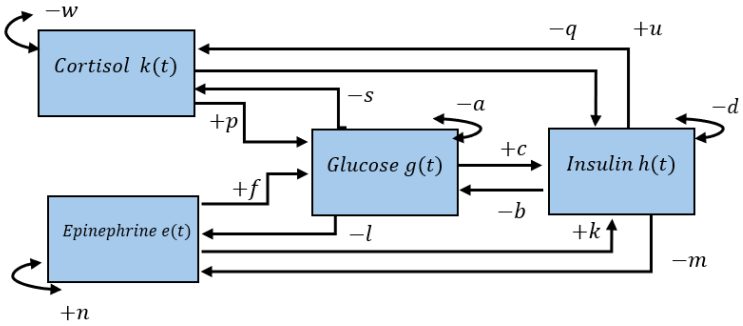


Figure 1. Compartment Diagram of the Diabetes Detection Model

From the diagram, each blue box represents a biological variable: glucose $g(t)$, insulin $h(t)$, epinephrine $e(t)$, and cortisol $k(t)$. The arrows connecting these variables indicate regulatory effects, either stimulatory (positive) or inhibitory (negative). When a variable has a self-loop labeled with a negative constant, it means there is a natural decay term reducing its value over time. Conversely, when another variable points into it with a positive constant, this indicates stimulation or production, while a negative arrow represents suppression or inhibition.

Starting with glucose $g(t)$, we see four contributions: a self-decay rate $-ag(t)$, inhibition from insulin $-bh(t)$, stimulation from epinephrine $+fe(t)$, and stimulation from cortisol $+pk(t)$. These terms combine to form the differential equation:

$$\frac{dg(t)}{dt} = -ag(t) - bh(t) + fe(t) + pk(t).$$

For insulin $h(t)$, the diagram shows that it is stimulated by glucose $(+cg(t))$, decays naturally $(-jh(t))$, is stimulated by epinephrine $(+ke(t))$, and is inhibited by cortisol $(-qk(t))$. Thus, the governing equation is:

$$\frac{dh(t)}{dt} = cg(t) - jh(t) + ke(t) - qk(t).$$

Epinephrine $e(t)$ is inhibited by glucose $(-lg(t))$, inhibited by insulin $(-mh(t))$, and has a natural self-dynamic growth term $+ne(t)$. No direct effect of cortisol is indicated, so its coefficient is zero. Therefore, the equation is:

$$\frac{de(t)}{dt} = -lg(t) - mh(t) + ne(t).$$

Finally, cortisol $k(t)$ receives inhibition from glucose $(-sg(t))$, stimulation from insulin $(+uh(t))$, and natural decay $(-wk(t))$. Since epinephrine has no effect, its coefficient is zero. This yields:

$$\frac{dk(t)}{dt} = -sg(t) + uh(t) - wk(t).$$

When these four equations are grouped together, they form a linear system of differential equations. By arranging the state vector as

$$X(t) = \begin{bmatrix} g(t) \\ h(t) \\ e(t) \\ k(t) \end{bmatrix},$$

we can express the model compactly as:

$$\dot{X(t)} = A\,X(t),$$

$$\begin{bmatrix} \frac{dg(t)}{dt} \\ \frac{dh(t)}{dt} \\ \frac{de(t)}{dt} \\ \frac{dk(t)}{dt} \end{bmatrix} = \begin{bmatrix} -a & -b & f & p \\ c & -j & k & -q \\ -l & -m & n & 0 \\ -s & u & 0 & -w \end{bmatrix} \begin{bmatrix} g(t) \\ h(t) \\ e(t) \\ k(t) \end{bmatrix},$$

where the system matrix is:

$$A = \begin{bmatrix} -a & -b & f & p \\ c & -j & k & -q \\ -l & -m & n & 0 \\ -s & u & 0 & -w \end{bmatrix}.$$

This matrix neatly summarizes all interactions: negative coefficients correspond to decay or inhibition, while positive coefficients correspond to stimulation. The absence of an arrow between two variables is represented by a zero entry. In this way, the diagram is systematically translated into both differential equations and a compact matrix representation.

3.2 Analytical Solution of the Model

Before conducting the stability analysis of the system, it is necessary to determine the parameter values that represent the rates of change between variables in the model. These parameters are derived from relevant previous studies, such as [1] and [21]. The values are used to simulate the dynamics of glucose, insulin, epinephrine, and cortisol concentrations in the human body. The details of the parameters used are presented in Table 1 below.

Table 1. Model Simulation Parameter Values

Parameter	Value	Definition	Source
a	2.92 mmol/l	Natural rate of glucose change	[1]
b	4.3 mmol/l	Rate of glucose decrease due to insulin	[1]
f	1.24 mmol/l	Rate of glucose increase due to epinephrine	[1]
c	0.208 mmol/l	Rate of insulin increase due to glucose	[1]
j	0.78 mmol/l	Natural rate of insulin change	[1]
k	0.14 mmol/l	Rate of insulin increase due to epinephrine	[1]
l	2.94 mmol/l	rate of epinephrine reduction from glucose	[1]
n	0.53 mmol/l	Natural rate of epinephrine change	[1]
m	0.98 mmol/l	Rate of epinephrine decrease due to insulin	[1]
p	7.1 mmol/l	Rate of glucose increase due to cortisol	[21]
q	0.000000031 mmol/l	Rate of insulin decrease due to cortisol	[18]
s	0.2 mmol/l	Rate of cortisol decrease due to glucose	[21]
u	0.66 mmol/l	Rate of cortisol increase due to insulin	[18]
w	3 mmol/l	Natural rate of cortisol change	[21]

The parameter values presented in Table 1 were obtained from experimental studies [13], [21] and adapted from previous mathematical models [1]. This ensures that the model remains consistent with physiological ranges reported in the literature. The eigenvalues were obtained by calculating the determinant using expansion along the first row [22].

$$\lambda_1 = -2.3034 + 1.7816\,i,$$
$$\lambda_2 = -2.3034 - 1.7816\,i,$$
$$\lambda_3 = -0.1817 + 0.0000i,$$
$$\lambda_4 = -1.3815 + 0.0000i.$$

Subsequently, the corresponding eigenvectors were determined:

$$k_1 = \begin{bmatrix} 0.7506 + 0.0000i \\ -0.0504 - 0.0885i \\ 0.5594 + 0.3212i \\ -0.0633 + 0.0782i \end{bmatrix},$$
$$k_2 = \begin{bmatrix} 0.7506 + 0.0000i \\ -0.0504 + 0.0885i \\ 0.5594 - 0.3212i \\ -0.0633 - 0.0782i \end{bmatrix},$$
$$k_3 = \begin{bmatrix} 0.1398 + 0.0000i \\ 0.2711 + 0.0000i \\ 0.9508 + 0.0000i \\ 0.0536 + 0.0000i \end{bmatrix},$$
$$k_4 = \begin{bmatrix} -0.5757 + 0.0000i \\ 0.3620 + 0.0000i \\ -0.6998 + 0.0000i \\ 0.2187 + 0.0000i \end{bmatrix}.$$

By using Maple software, the constants $c_1.\ c_2.c_3$and were computed as follows:

$$c_1 = 29.7022 - 11.1894i,$$
$$c_2 = 29.7022 + 11.1894i,$$
$$c_3 = -0.7073i + 0.0000i,$$
$$c_4 = 45.4949i - 0.0000i.$$

Thus, the particular solution for matrix A is obtained as follows:

$$\begin{aligned} g(t) = {} & (29.7022 - 11.1894i)e^{(-2.3034+1.7816\,i)t}(0.7506 + 0.0000i) \\ & + (29.7022 + 11.1894i)e^{(2.3034-1.7816\,i)t}(0.7506 + 0.0000i) \\ & + (-0.7073 + 0.0000i)e^{(-0.1817t+0.0000i)}(0.1398 + 0.0000i), \end{aligned}$$

$$\begin{aligned} h(t) = {} & (29.7022 - 11.1894i)e^{(-2.3034+1.7816\,i)t}(-0.0504 - 0.0885i) \\ & + (29.7022 + 11.1894i)e^{(-2.3034-1.7816\,i)t}(-0.0504 + 0.0885i) \\ & + (-0.7073 + 0.0000i)e^{(-0.1817+0.0000i)t}(0.2711 + 0.0000i) \\ & + (45.4949 - 0.0000i)e^{(-1.3815+0.0000i)t}(0.3620 + 0.0000i), \end{aligned}$$

$$\begin{aligned} e(t) = {} & (29.7022 - 11.1894i)e^{(-2.3034+1.7816\,i)t}(0.5594 + 0.3212i) + (29.7022 + \\ & 11.1894i)e^{(-2.3034-1.7816\,i)t}(0.5594 - 0.3212i) + (-0.7073 + \\ & 0.0000i)e^{-(0.1817+0.0000i)t}(0.9508 + 0.0000i) + (45.4949 - \\ & 0.0000i)e^{(-1.3815+0.0000i)t}(-0.6998 + 0.0000i), \end{aligned}$$

$$\begin{aligned} k(t) = {} & (29.7022 - 11.1894i)e^{(-2.3034+1.7816\,i)t}(-0.0633 + 0.0782i) \\ & + (29.7022 + 11.1894i)e^{(-2.3034-1.7816\,i)t}(-0.0633 - 0.0782i) \\ & + (-0.7073 + 0.0000i)e^{(-0.1817+0.0000i)t}(0.0536 + 0.0000i) \\ & + (45.4949 - 0.0000i)e^{(-1.3815+0.0000i)t}(0.2187 + 0.0000i). \end{aligned}$$

Thus, the changes in the model over time, using the parameter values from Table 1, are illustrated in the following graphs:

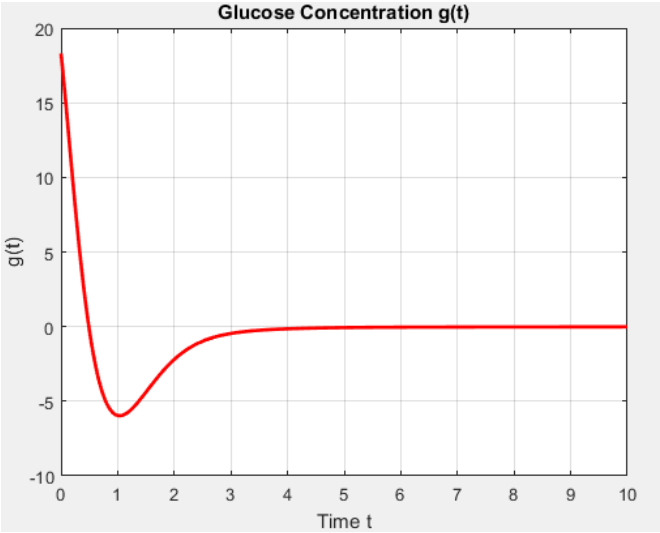


Figure 2. Blood Glucose Concentration for $t \in [0.10]$ Minutes with Initial Values $g(0) = 18.30$, $h(0) = 11.3$, $e(0) = 7.9093$, and $k(0) = 7.9$

Fig. 2 illustrates the behavior of blood glucose concentration $g(t)$ over the time interval $t \in [0,10]$. The curve is plotted in red and represents the dynamics of glucose levels in the bloodstream starting from an initial concentration of $g(0) = 18.30$. The graph shows that blood glucose concentration decreased sharply at the beginning of the interval and gradually approached stability, indicating the system's regulatory mechanism in lowering glucose after an initial spike.

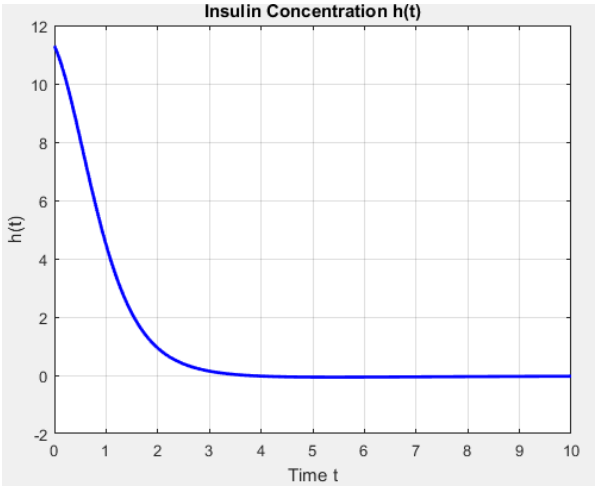


Figure 3. Blood Insulin Concentration for $t \in [0.10]$ Minutes with Initial Values $g(0) = 18.30$, $h(0) = 11.3$, $e(0) = 7.9093$, and $k(0) = 7.9$

Fig. 3 shows the concentration of blood insulin $h(t)$ over time $t \in [0,10]$, plotted in blue. Initially, the insulin level is quite high at $h(0) = 11.3$, then that level shows a declining trend toward equilibrium, reflecting the negative feedback relationship between glucose and insulin.

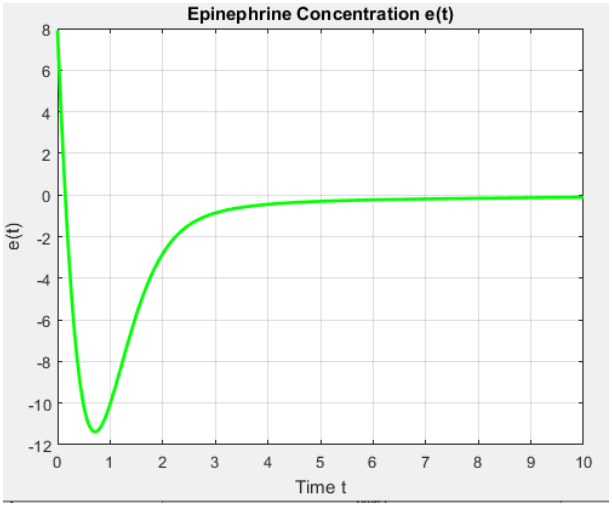


Figure 4. Blood Epinephrine Concentration for $t \in [0, 10]$ minutes with Initial Values $g(0) = 18.30$, $h(0) = 11.3$, $e(0) = 7.9093$, and $k(0) = 7.9$

Fig. 4 presents the blood epinephrine concentration $k(t)$ across the same time interval $t \in [0,10]$, represented by a green curve. The epinephrine level begins at $k(0) = 7.9$, experiences an initial dip, and then rises slightly before approaching a stable level. This behavior may model the acute stress response triggered by a sudden change in glucose levels.

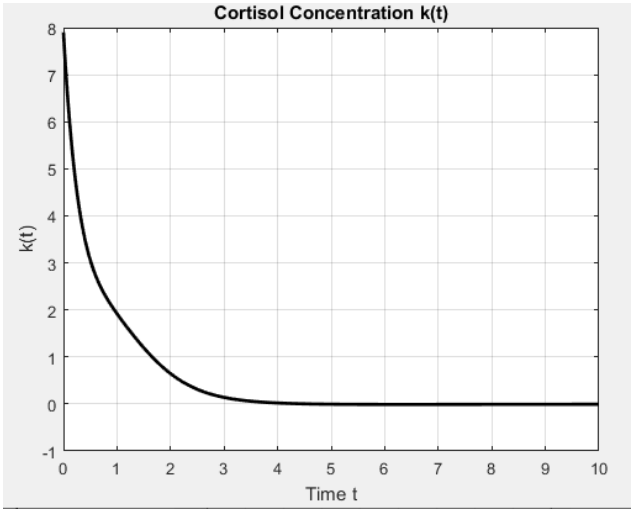


Figure 5. Blood Cortisol Concentration for $t \in [0, 10]$ with Initial Values $g(0) = 18.30$, $h(0) = 11.3$, $e(0) = 7.9093$, and $k(0) = 7.9$

Fig. 5 presents the variation of blood cortisol concentration k(t) over the time interval $t \in [0,10]$. The graph plots the function k(t)k(t)k(t) in black, starting from an initial value of $k(0)$=7.9. The curve demonstrates a rapid exponential decline in cortisol concentration, dropping sharply in the early phase (up to around $t = 2$), and then gradually approaching zero, where it stabilizes over time.

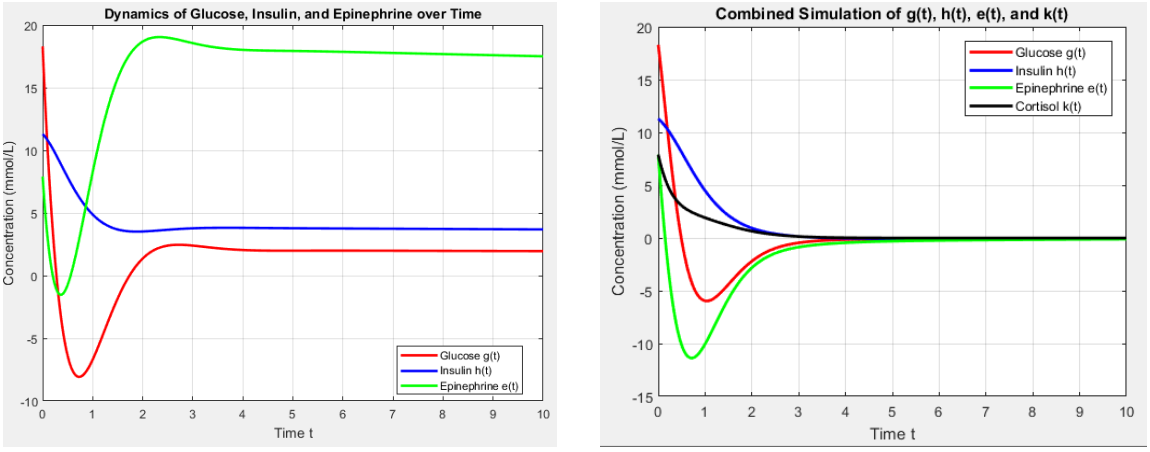
The initial parameter values used for the simulation are:

1. $g(0) = 18.30$ – initial glucose concentration;
2. $h(0) = 11.3$ – initial insulin concentration;
3. $e(0) = 7.9093$ – initial epinephrine concentration;
4. $k(0) = 7.9$ – initial cortisol concentration.

The initial values for glucose, insulin, and epinephrine were adopted from [1], while the initial cortisol level was assumed to be $k(0) = 7.9$ The cortisol value was intentionally set close to the initial epinephrine concentration to reflect their physiological similarity as stress hormones, both of which are elevated during

acute stress responses. This assumption provides consistency within the model and highlights the synergistic role of cortisol and epinephrine in glucose regulation.

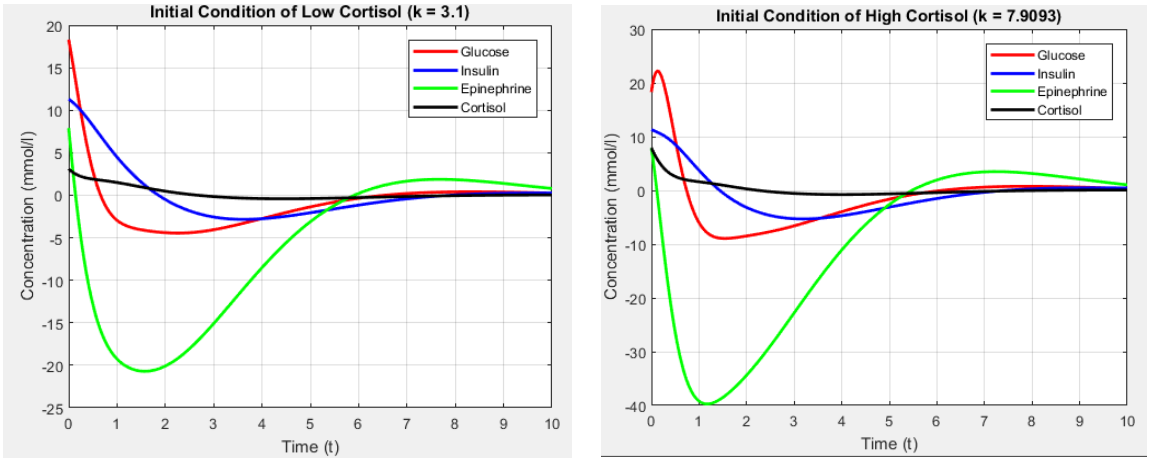
This graph illustrates the transient nature of cortisol secretion, which is typically elevated during stress responses and metabolic regulation, but decreases over time as homeostasis is achieved. The sharp decline suggests a rapid deactivation or clearance of cortisol after the initial regulatory response, such as after a glucose spike, aligning with its role as a stress hormone that modulates energy metabolism and temporarily suppresses insulin action. To provide a clearer illustration, the comparison graphs of glucose, insulin, and epinephrine before and after the addition of cortisol are presented below.



(a) **(b)**

Figure 6. Comparison of Glucose, Insulin, Epinephrine Graphs for $t \in [0, 10]$ minutes with Initial Values $g(0) = 18.30$, $h(0) = 11.3$, $e(0) = 7.9093$, and $k(0) = 7.9$
(a) without Cortisol (b) with Cortisol

The results demonstrate that the addition of cortisol slows down the rate at which the system reaches stability, keeps the system active for a longer period, and provides sufficient physiological time for the body's hormonal mechanisms to adjust. Incorporating cortisol into the model makes it more physiologically complete and more representative of real-world conditions. To further confirm the visible effect of cortisol, an additional test was conducted using a lower initial cortisol value, specifically $k(0) = 3.1$. The presence of cortisol suppresses insulin activity and increases glucose concentration, which requires the system to take more time to reach stability compared to the model without cortisol. This indicates that cortisol delays glucose–insulin regulation and plays an important role in glucose homeostasis during stress conditions. These findings are consistent with biological knowledge that chronic stress prolongs hyperglycemia and disrupts physiological balance.



(a) **(b)**

Figure 7. Comparison of Glucose Insulin Epinephrine Graphs with Initial $k(0) = 3.1$ and $k(0) = 7.9093$ for $t \in [0.10]$ minutes
(a) Low Cortisol (b) High Cortisol

The comparison of glucose, insulin, and epinephrine graphs with high and low initial cortisol values shows distinct patterns, indicating that initial cortisol levels influence the dynamics of glucose and insulin concentrations. In general, higher initial cortisol levels tend to suppress the early insulin response and slow down the reduction of blood glucose levels. In contrast, when the initial cortisol level is low, glucose and insulin exhibit more rapid fluctuations and reach equilibrium more quickly. Conversely, with high initial cortisol levels, the system response becomes slower, and the stabilization process takes longer.

The findings are supported by [20], who stated that cortisol plays a critical role in regulating the body's response to stress, not only through increased gluconeogenesis but also by influencing epinephrine biosynthesis via the upregulation of the PNMT enzyme. This mechanism highlights the significant hormonal influence of cortisol on the stress system. An imbalance in cortisol levels, particularly when prolonged, can potentially disrupt homeostatic mechanisms, including glucose regulation, by amplifying the stress response and extending hormonal activation that should be temporary. Therefore, cortisol not only triggers increased glucose levels but may also delay the body's metabolic system's return to normal conditions if its regulation is impaired. Overall, the simulation results demonstrate that incorporating cortisol into the glucose–insulin–epinephrine model provides a more realistic description of glucose regulation under stress, and these findings form the basis for the conclusions presented in the next section.

4. CONCLUSION

This study confirms that the addition of cortisol as a variable in the mathematical model for diabetes detection in blood cells provides a significant contribution to understanding the dynamics of glucose regulation in the body. The novelty of this work lies in the explicit integration of cortisol into the glucose–insulin–epinephrine model, which extends previous approaches and offers a more realistic representation of stress-related physiological conditions**.** By modeling the interaction among glucose, insulin, epinephrine, and cortisol using a system of linear differential equations and equilibrium point analysis through the eigenvalue approach, the study emphasizes that cortisol plays a crucial role in increasing glucose production and inhibiting insulin effectiveness, particularly during prolonged stress conditions.

Verification of the mathematical model at the fixed point (0,0,0,0) revealed that the first and second eigenvalues represent asymptotically stable spirals, while the third and fourth are asymptotically stable nodes. In the model's graphical results, stability is reached at time $t \geq 10$ indicating that the modified model incorporating cortisol is successful, as the stabilization time is longer compared to the previous model, which only included epinephrine. This finding aligns with biological and medical knowledge that cortisol is associated with chronic stress, which requires more time to achieve physiological balance. The implications of this research are substantial, not only as a foundation for the development of extended mathematical models involving other relevant variables but also as a reference for healthcare practitioners and researchers in designing more effective prevention and intervention strategies for diabetes, particularly in cases involving chronic stress that affects glucose homeostasis. However, this linear model is a first-order approximation and does not fully represent the biological dynamics, since in reality glucose, insulin, epinephrine, and cortisol concentrations never reach zero. Future research should therefore extend the model into nonlinear and multiscale formulations and incorporate clinical validation to achieve a more accurate physiological representation.

Author Contributions

Juhari: Conceptualization, Methodology, Software, Writing – Original Draft, Validation. Adelia Irma Feby Ariyanti: Data Curation, Resources, Draft Preparation. Imam Sujarwo: Formal Analysis, Validation, Supervision. Sutrisno: Visualization, Writing – Review and Editing. All authors contributed to the interpretation of the results, reviewed the manuscript, and approved the final version for publication.

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Declarations

The authors declare no competing interest.

Declaration of Generative AI and AI-assisted technologies

Generative AI tools (e.g., ChatGPT) were used solely for language refinement (grammar, spelling, and clarity). The scientific content, analysis, interpretation, and conclusions were developed entirely by the authors. The authors reviewed and approved all final text.

REFERENCES

[1] R. Kwach, B., Ongati, O., and Simwa, "MATHEMATICAL MODEL FOR DETECTING DIABETES IN THE BLOOD," *Appl. Math. Sci.*, vol. 5, no. 6, pp. 279–286, 2011, [Online]. Available: http://ir.mksu.ac.ke/handle/123456780/4414

[2] D. H. Hellhammer, S. Wüst, and B. M. Kudielka, "SALIVARY CORTISOL AS A BIOMARKER IN STRESS RESEARCH," *Psychoneuroendocrinology*, vol. 34, no. 2, pp. 163–171, Feb. 2009, doi: https://doi.org/10.1016/j.psyneuen.2008.10.026.

[3] M. Al Ahdab, J. Leth, T. Knudsen, P. Vestergaard, and H. G. Clausen, "GLUCOSE-INSULIN MATHEMATICAL MODEL FOR THE COMBINED EFFECT OF MEDICATIONS AND LIFE STYLE OF TYPE 2 DIABETIC PATIENTS," *Biochem. Eng. J.*, vol. 176, p. 108170, Dec. 2021, doi: https://doi.org/10.1016/j.bej.2021.108170.

[4] M. Breton and B. Kovatchev, "ANALYSIS, MODELING, AND SIMULATION OF THE ACCURACY OF CONTINUOUS GLUCOSE SENSORS," *J. Diabetes Sci. Technol.*, vol. 2, no. 5, pp. 853–862, Sep. 2008, doi: https://doi.org/10.1177/193229680800200517.

[5] A. De Gaetano and O. Arino, "MATHEMATICAL MODELLING OF THE INTRAVENOUS GLUCOSE TOLERANCE TEST," *J. Math. Biol.*, vol. 40, no. 2, pp. 136–168, Feb. 2000, doi: https://doi.org/10.1007/s002850050007.

[6] J. Juhari, "ON THE BEHAVIOR ANALYSIS OF SUSCEPTIBLE, INFECTION, RECOVERY (SIR) MEASLES SPREAD MODEL WITH AGE STRUCTURE," *BAREKENG J. Ilmu Mat. dan Terap.*, vol. 16, no. 2, pp. 427–442, Jun. 2022, doi: https://doi.org/10.30598/barekengvol16iss2pp427-442.

[7] R. K. Leung, Y. Wang, R. C. Ma, A. O. Luk, V. Lam, M. Ng, W. Y. So, S. K. Tsui and J. C. Chan., "USING A MULTI-STAGED STRATEGY BASED ON MACHINE LEARNING AND MATHEMATICAL MODELING TO PREDICT GENOTYPE-PHENOTYPE RISK PATTERNS IN DIABETIC KIDNEY DISEASE: A PROSPECTIVE CASE–CONTROL COHORT ANALYSIS," *BMC Nephrol.*, vol. 14, no. 1, p. 162, Dec. 2013, doi: https://doi.org/10.1186/1471-2369-14-162.

[8] M. Ma and J. Li, "DYNAMICS OF A GLUCOSE–INSULIN MODEL," *J. Biol. Dyn.*, vol. 16, no. 1, pp. 733–745, Dec. 2022, doi: https://doi.org/10.1080/17513758.2022.2146769.

[9] N. D. Pallab, "PANCREATIC B-CELL DYNAMICS WITH THREE-TIME-SCALE SYSTEMS," *arXiv Prepr.*, May 2025, [Online]. Available: http://arxiv.org/abs/2505.18837

[10] N. E. López-Palau and J. M. Olais-Govea, "MATHEMATICAL MODEL OF BLOOD GLUCOSE DYNAMICS BY EMULATING THE PATHOPHYSIOLOGY OF GLUCOSE METABOLISM IN TYPE 2 DIABETES MELLITUS," *Sci. Rep.*, vol. 10, no. 1, p. 12697, Jul. 2020, doi: https://doi.org/10.1038/s41598-020-69629-0.

[11] D. N. R. D. B. Gabriela Urbina, "MATHEMATICAL MODELING OF NONLINEAR BLOOD GLUCOSE-INSULIN DYNAMICS WITH BETA CELLS EFFECT," *Appl. Appl. Math. An Int. J.*, vol. 15, no. 1, pp. 171–191, 2020, [Online]. Available: https://digitalcommons.pvamu.edu/aam/vol15/iss1/10%0A

[12] I. I. Mohammed, I. I. Adamu, and S. J. Barka, "MATHEMATICAL MODEL FOR THE DYNAMICS OF GLUCOSE, INSULIN AND B-CELL MASS UNDER THE EFFECT OF TRAUMA, EXCITEMENT AND STRESS," *Model. Numer. Simul. Mater. Sci.*, vol. 09, no. 04, pp. 71–96, 2019, doi: https://doi.org/10.4236/mnsms.2019.94005.

[13] S. Khani and J. A. Tayek, "CORTISOL INCREASES GLUCONEOGENESIS IN HUMANS: ITS ROLE IN THE METABOLIC SYNDROME," *Clin. Sci.*, vol. 101, no. 6, p. 739, Dec. 2001, doi: https://doi.org/10.1042/CS20010180.

[14] M. Degering, R. Linz, L. M. C. Puhlmann, T. Singer, and V. Engert, "REVISITING THE STRESS RECOVERY HYPOTHESIS: DIFFERENTIAL ASSOCIATIONS OF CORTISOL STRESS REACTIVITY AND RECOVERY AFTER ACUTE PSYCHOSOCIAL STRESS WITH MARKERS OF LONG-TERM STRESS AND HEALTH," *Brain, Behav. Immun. - Heal.*, vol. 28, p. 100598, Mar. 2023, doi: https://doi.org/10.1016/j.bbih.2023.100598.

[15] K. Sriram, M. Rodriguez-Fernandez, and F. J. Doyle, "MODELING CORTISOL DYNAMICS IN THE NEURO-ENDOCRINE AXIS DISTINGUISHES NORMAL, DEPRESSION, AND POST-TRAUMATIC STRESS DISORDER (PTSD) IN HUMANS," *PLoS Comput. Biol.*, vol. 8, no. 2, p. e1002379, Feb. 2012, doi: https://doi.org/10.1371/journal.pcbi.1002379.

[16] D. P. Rooney, R. D. G. Neely, O. Beatty, N. P. Bell, B. Sheridan, A. B. Atkinson, E. R. Trimble and P. M. Bell., "CONTRIBUTION OF GLUCOSE/GLUCOSE 6-PHOSPHATE CYCLE ACTIVITY TO INSULIN RESISTANCE IN TYPE 2 (NON-INSULIN-DEPENDENT) DIABETES MELLITUS," *Diabetologia*, vol. 36, no. 2, pp. 106–112, Feb. 1993,

doi: https://doi.org/10.1007/BF00400689.
[17] R. C. Andrews and B. R. Walker, "GLUCOCORTICOIDS AND INSULIN RESISTANCE: OLD HORMONES, NEW TARGETS," *Clin. Sci.*, vol. 96, no. 5, pp. 513–523, May 1999, doi: https://doi.org/10.1042/cs0960513.
[18] A. Holmáng, E. Jennische, and P. BjÖrntorp, "THE EFFECTS OF LONG-TERM HYPERINSULINAEMIA ON INSULIN SENSITIVITY IN RATS," *Acta Physiol. Scand.*, vol. 153, no. 1, pp. 67–73, Jan. 1995, doi: https://doi.org/10.1111/j.1748-1716.1995.tb09835.x.
[19] H. Shamoon, R. Hendler, and R. S. Sherwin, "ALTERED RESPONSIVENESS TO CORTISOL, EPINEPHRINE, AND GLUCAGON IN INSULIN-INFUSED JUVENILE-ONSET DIABETICS: A MECHANISM FOR DIABETIC INSTABILITY," *Diabetes*, vol. 29, no. 4, pp. 284–291, Apr. 1980, doi: https://doi.org/10.2337/diab.29.4.284.
[20] D. L. Wong, "EPINEPHRINE BIOSYNTHESIS: HORMONAL AND NEURAL CONTROL DURING STRESS," *Cell. Mol. Neurobiol.*, vol. 26, no. 4–6, pp. 889–898, Jul. 2006, doi: https://doi.org/10.1007/s10571-006-9056-6.
[21] M. Salehi., "COMPARISON OF SALIVARY CORTISOL LEVEL IN TYPE 2 DIABETIC PATIENTS AND PRE-DIABETICS WITH HEALTHY PEOPLE," *Open Access Maced. J. Med. Sci.*, vol. 7, no. 14, pp. 2321–2327, Jul. 2019, doi: https://doi.org/10.3889/oamjms.2019.340.
[22] C. Anton, H., & Rorres, "ALJABAR LINEAR ELEMENTER VERSI APLIKASI," *PT Gelora Aksara Pratama*, 2000, [Online]. Available: https://lib.ui.ac.id/detail?id=20359146&lokasi=lokal