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A DYNAMIC BEHAVIOR OF HYPERGLYCEMIA MODEL BASED ON REACTION- DIFFUSION CELLULAR NONLINEAR NETWORKS (RD-CNN)

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***Abstract*:** *Diabetes Mellitus (DM) is a disorder resulting from a malfunction in the glucose-insulin interaction dynamic inside the human body. To model such pathophysiology (DM), we suggest a new mathematical model for the insulin-glucose regulation system is introduced based on the well-known Lokta-Volterra model. The proposed system is then converted using RD-CNN for introducing 3D forms presenting such system behavior as unpredictable pattern formation. To further studies, as all the system parameters can be controllable, one can consider the efficiency of newly proposed drugs by considering the relevant parameter in this model. This paper's overall result may help a better understanding of the diabetes mellitus regulation system, including diseases such as Hyperglcymia related to the polycystic ovary (PCOS) based RD-CNN which is called the pre-diabetes disease of Type2 DM.*

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Keywords: Biological complex modeling. Nonlinear dynamics systems. Chaos. PCOS pre-diabetes.

I. INTRODUCTION

Due to an increase in life expectancy, inactive lifestyles, and obesity in the last decades, Diabetes Mellitus (DM) has become a global epidemic worldwide. In type2 diabetes, the body cannot be using the insulin hormone in its proper way. This is called insulin resistance. In the beginning, the pancreas secretes insulin to increase it up. However, the glucose is not digested into the cells because the insulin receptors are not working correctly, causing the glucose to be increased in the blood [1]. This case is called "Hyperglcymia," which is the pre-stage of so-called type2 diabetes. However, many risk factors are associated with type2 diabetes as physical activities, obesity, blood pressure, and family history. PCOS is the sign of increased risk as an apparent disease related to insulin resistance, and T2DM these disorders are connected with risk factors such as metabolic syndrome, dyslipidemia, and hypertension [2, 3]. Moreover, gestational diabetes mellitus GDM happed with women having PCOS rather than women without PCOS. However, we are pointed to study the insulin-glucose interaction, its dynamic behavior, and a specific dynamical disease "PCOS" in 2D and 1D bifurcation diagrams and its unpredictable 3D form shape RD-CNN within the whole proposed system model.

This paper proposes a new model to explain the glucose, insulin, and β-cells dynamics in the regulatory system with dynamic diseases. A novel computational model introduces to represent Hyperglcymia due to Polycystic Ovary Syndrome PCOS is expressed in detail depending on Reaction-Diffusion Cellular Nonlinear Network RD-CNN. In Sec.III we propose new mathematical model. In Sec.III, we analyze both statistical and dynamical properties of this system using the stability analysis, bifurcation diagram, and Lyapunov exponents of the system for related physiologically meaningful system parameters. Finally, the conclusion of the paper has been discussed in Sec.VI.

II. MATHEMATICAL MODEL

A. Prey-Predator Model

Volterra was a significant mathematician that proposed the prey-predator model composed of two simple differential

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equations, which can describe the behavior dynamics in terms of measurable variables known as the Lotka-Volterra model [4].

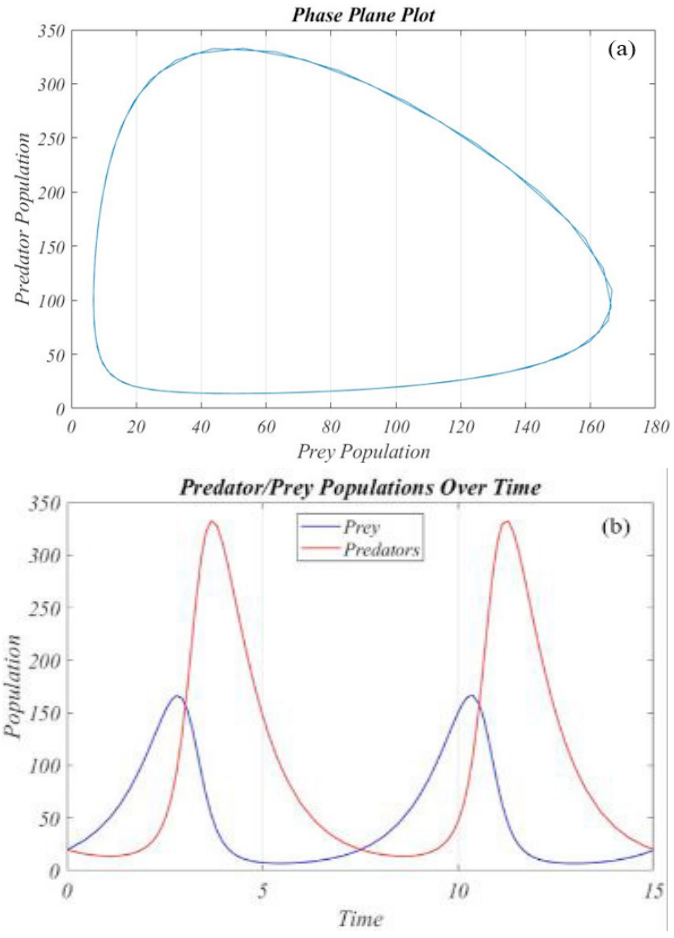

Fig.1 (a) Cyclic relationship between prey and predator as $\delta = \gamma = 1, \alpha = 0.01$ and $\beta = 0.02$ and (b) Time delay between prey and predator.

$$\frac{dG}{dt} = \delta G(t)(1 - G) - \alpha G(t)I(t)$$
$$\frac{dI}{dt} = -\gamma I(t) + \beta G(t)I(t) \quad (1)$$

Where G(t) is the population density of prey, I(t) is the population density of predator, and a,b,c, and d are parameters. Fig. 1 shows such model behavior.

B. Historical Mathematical model of insulin-glucose physiological systems

Many scientists in different fields have been proposed studying the interaction and the relationship between insulin and glucose in the body and made predictions for diabetic therapy. The mathematical model (2) suggested by Ackerman in 1964 with six constants [5]:

$$\frac{dG}{dt} = -a_1 G(t) + a_2 I(t) + C_1$$
$$\frac{dI}{dt} = -a_3 I(t) + a_4 G(t) + a_5 + T(t) \quad (2)$$

Where G(t) is glucose concentration, I(t) is insulin concentration, and T(t) is the rate of increase of blood glucose due to absorption in the GIT system. Also, a_1 represents an average rate of glucose removal independent of insulin. a_2 represents a rate of released glucose into the blood. c_1 represents a net increase in the average rate of glucose. a_3 represents insulin removal independent of glucose. a_4 represents a net increase in the rate of insulin due to glucose. a_5 represents the release rate of insulin by the pancreas independent of glucose.

Later, it has been discovered that the main function of β-cell is to store and secret insulin. So the mathematical model (3) proposed by Bajaj studied three ODE's that embody β-cells [6]as:

$$\frac{dG}{dt} = R_1 G(t) - R_2 I(t) + C_1$$
$$\frac{dI}{dt} = \frac{R_3 N}{z} - R_4 I(t) + C_2$$
$$\frac{dZ}{dt} = R_5 G(t)\big(T - z(t)\big) + R_6 z\big(T - z(t)\big) - R_7 z(t) \quad (3)$$

Where G(t) is insulin concentration, I(t) is glucose concentration, and z(t) is the population density of β-cell. R_1 represents the increased rate of insulin concentration in response to the blood glucose increase. R_2 represents the insulin reduction rate, which is independent of glucose concentration and based on the current level. R_3 shows the decrease rate of glucose in response to insulin secretion. R_4 shows the rate of increase in β-cells dividing due to interaction between blood glucose levels above the fasting level. R_5 shows the increase of β-cells due to interaction between dividing and non-dividing β-cells. R_6 is the decrease rate of β-cells toward its current level. C_1 is the rate of increase of G in the absence of G and I. C_2 is the increase rate of I in the absence of G, and Z. Mentioned models have common properties which they are omitting many factors that may affect the insulin-glucose interaction and all of them are suggested to in an isolated environment.

C. New Mathematical Chaotic Model for an insulin-glucose regulatory system with PCOS

We consider the dynamical relationship between insulin, glucose, and β-cells concentrations to propose a new model. In this context, physiologically meaningful parameters have been considered to suggest three-dimensional differential equations. It should be noted that the proposed model will be expected to show behavioral responses of the insulin-glucose regulatory system. So the values of the parameters should be set as these responses will be meaningful. For example, all three variables of this system show concentration of the particular materials in the body. The proposed computational model for the insulin-glucose regulatory system is as follows:

$$\begin{aligned}\frac{dI}{dt} &= -R_1\, I(t) + R_2\, G(t) + R_3 G^2(t) + R_4 G^3(t) + R_5\, z(t) \\ &\quad + R_6\, z^2(t) + R_7 z^3(t) + R_{18} \\ \frac{dG}{dt} &= -R_8\, I(t) - R_9\, I^2(t) - R_{10} I^3(t) - R_{11} z(t) \\ &\quad - R_{12}\, z^2(t) - R_{13} z^3(t) + R_{19} + 0.5^I \\ \frac{dZ}{dt} &= R_{14}\, G(t) + R_{15} G^2(t) + R_{16} G^3(t) - R_{17} Z(t)\end{aligned} \tag{4}$$

Where I(t) is insulin concentration, G(t) is blood glucose concentration, and z(t) is the population density of β-cells. Also, R_1 represents the reduction rate of insulin concentration which is based on its current level. R_2 , R_3, and R_4 show the increased rate of insulin when glucose concentration increases. R_5, R_6, and R_7 show the increased insulin concentration rate when the β-cells' level increases. R_8, R_9, and R_{10} represent the rate of glucose reduction to increase the insulin level. R_{11}, R_{12}, and R_{13} show the reduction rate of glucose concentration because of β-cells' activity. R_{14}, R_{15}, and R_{16} represent the increase in β-cells due to increased glucose concentration. R_{17} shows the rate of decrease in β −cells due to its current level. R_{18} represents the decrease rate of β-cells, and R_{19} shows an increased glucose rate in the absence of insulin and β-cells. Fig. 2 shows the chaotic attractor response and its time series.

III. STABILITY ANALYSIS OF THE PROPOSED SYSTEM

To study the dynamic system, we regard Table-I- firstly. The chaotic system's dynamical behavior can be tracked by evaluating the eigenvalues of the corresponding Jacobian matrix at each equilibrium point. Because of the variables' biological meaning, the only positive fixed points (Time series must be positive). The system has only one positive equilibrium point *E (x, y, z)* = (1.6400,0.900,1.4500).The Jacobian matrix of the system in (5) yields eigenvalues as $\lambda_1 = 0.2640 - \mathrm{j}\,3.0705$, $\lambda_2 = 0.2640 + \mathrm{j}\,3.0705$, $\lambda_3 = -2.2580$. So, stability analysis indicates that it is a unstable equilibrium.

A. Bifurcations and Lyapunov Exponents Diagrams

In this section, both bifurcation and Lyapunov exponents diagrams for R8 are plotted, and the biological meaning of such parameters is discussed, as shown in Fig. 3. As observed in previous studies, whenever a system demonstrates a chaotic behavior, it yields and introduces some disorders [7]. In the present study, the system exhibits some chaotic behavior. According to both bifurcation and Lyapunov exponents, that we specify it as a biological disorder, whenever the insulin decreasing may cause such biological disorder as shown in Fig. 3. Lyapunov exponents spectrum is a way to analyze the dynamical system's nonlinear behavior, which measures the exponential rates of the divergence and convergence of nearby trajectories in the chaotic system's phase space. If there is at least one positive Lyapunov exponent, the system is chaotic [7]. The chaotic attractor and the tendency of the state variables identical to this suitable set of parameters. It can be realized that any slight fluctuation in model parameters leads to the undesired behavior of the system. In the bifurcation diagram of the system, we discovered that the appearance of a period-doubling route to chaos is similar to the prey and predator model.

$$J = \begin{pmatrix} (-R_1) & (R_2 + 2R_3 G + 3R_4 G^2) & (R_5 + 2R_6 z + 3R_7 z^2) \\ (-R_8 - 2R_9 I - 3R_{10} I^2 - 0.69(0.5^I)) & (0) & (-R_{11} - 2R_{12} z - 3R_{13} z^2) \\ (0) & (R_{14} + 2R_{15} G + 3R_{16} G^2) & (-R_{17}) \end{pmatrix} \tag{5}$$

B. Basin of Attraction

Dynamical systems are categorized into systems with self-excited and systems with hidden attractors. When an attractor's basin of attraction involves equilibrium, such attractor is called a "Self-excited" attractor. Otherwise, the attractor is hidden [8]. An attractor is called a self-excited attractor if its basin of attraction intersects with any open neighborhood of an unstable fixed point. Otherwise, it is called a hidden attractor. The Basin of attraction for a hidden attractor is not connected with any unstable fixed point [9, 10]. Fig. 4 shows the Basin of attractions of the proposed system. Fig.4, shows regions of different behavior of the system in xy-projection with $z = 1.02$ and parameters set as in Fig. 3 (a). Where there is no fixed point appears, so the chaotic attractor is hidden. In Fig. 4 unbounded region is shown in (red), periodic (limit cycle) in (green) and quasiperiodic (tours) in (black) with $z = 1.04$ and in xy-projection.

IV. Reaction-Diffusion Cellular Nonlinear Networks (RD-CNNs)

Spatial-temporal patterns occur widely in physics, biology, and chemistry. In many situations, it seems to be generated spontaneously. These behaviors have encouraged a high degree of mathematical modeling that led to a greater understanding of different mechanisms. PDE's of diffusion type work for pattern formation in many living cells. Some autonomous CNN represents an excellent approximation to nonlinear PDE's, producing a real-time solution of such systems [11]. The CNN models most extraordinary is to use dynamical nonlinear circuits' advantages of cooperation behavior to get complex, comprehensive missions. It has illustrated that the development of the 3D-CNN dynamics introduces compatible unexpected emergence shapes.

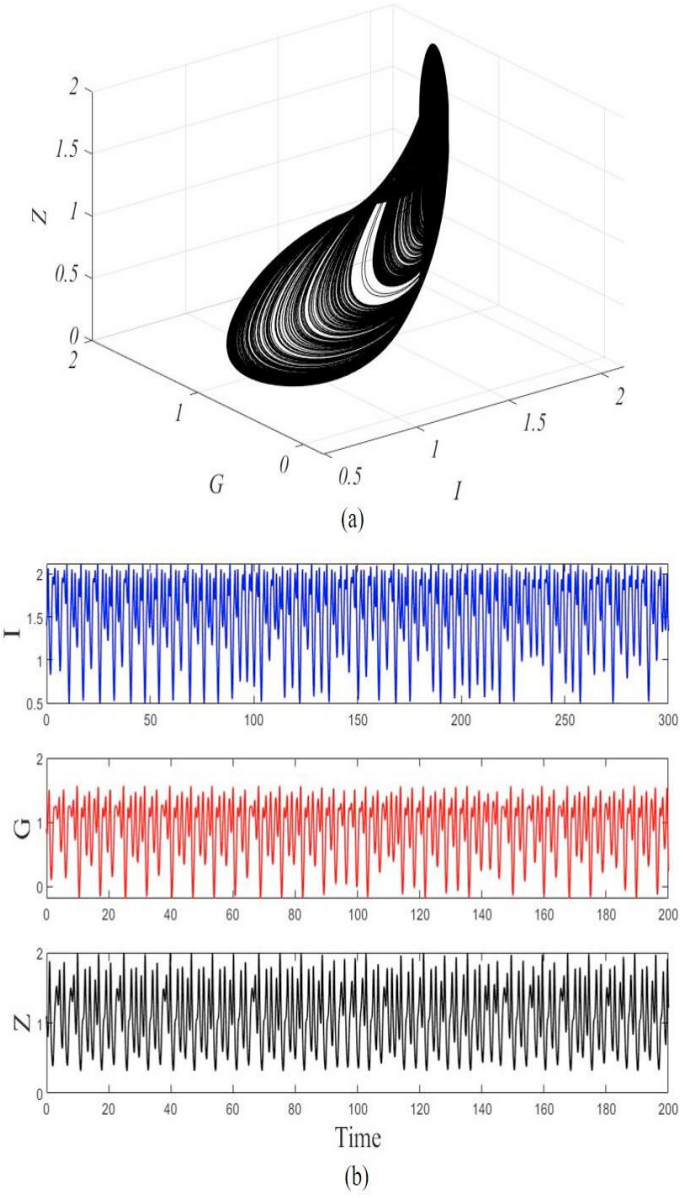

Fig. (2) (a) 3D view of the chaotic response of the insulin-glucose regulatory system and (b) Positive time series of the system.

Table I: Parameters values of chaotic system

Parameter	Value	Parameter	Value	Parameter	Value	Parameter	Value
R_1	0.30	R_6	-0.62	R_{11}	1.95	R_{16}	1.25
R_2	0.69	R_7	-0.10	R_{12}	0.75	R_{17}	1.43
R_3	0.27	R_8	1.24	R_{13}	-0.02	R_{18}	-0.83
R_4	0.92	R_9	-1.06	R_{14}	0.83	R_{19}	1.93
R_5	0.98	R_{10}	-0.29	R_{15}	1.01		

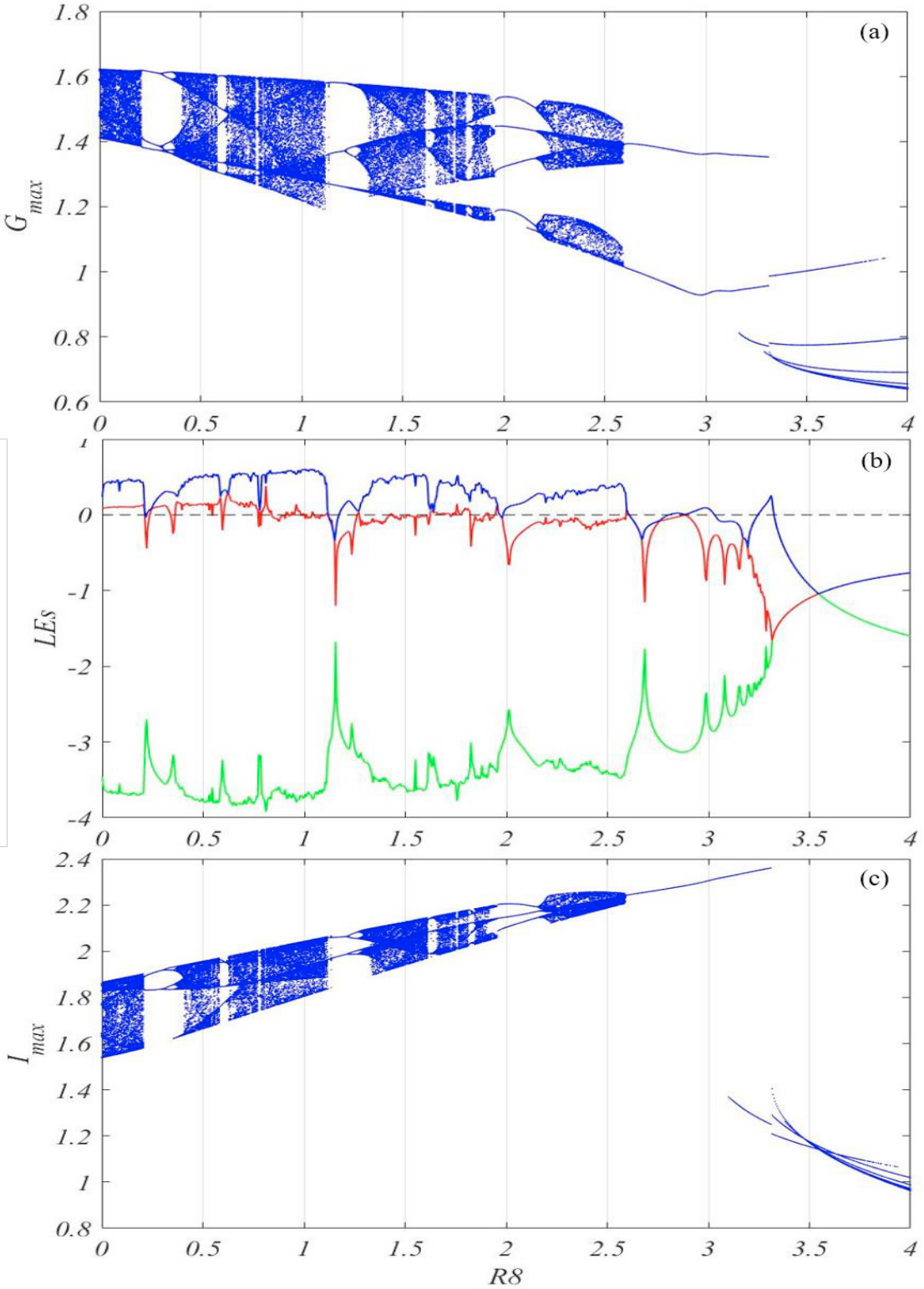

Fig. (3) (a) Bifurcation diagram of the system with $\boldsymbol{G_{max}}$ as the parameter R_8 changes. (b) Lyapunov diagram concerning R_8. (c) Bifurcation diagram of the system with $\boldsymbol{I_{max}}$ as the parameter R8 changes. This parameter shows the change rate of insulin concentration may cause the biological disorder.

RD-CNN is suitable to reintroduce complicated phenomena in bio-science, neuro-dynamics, and chemistry. CNN is a convenient agent to introduce shapes and patterns to associated shape emergence of dynamical systems and introduce actual arch over between circuits and art [12]. The well-known PDE of reaction-diffusion equation:

$$\frac{\partial \boldsymbol{u}}{\partial t} = F(\boldsymbol{u}) + D\nabla^2 \boldsymbol{u} \tag{6}$$

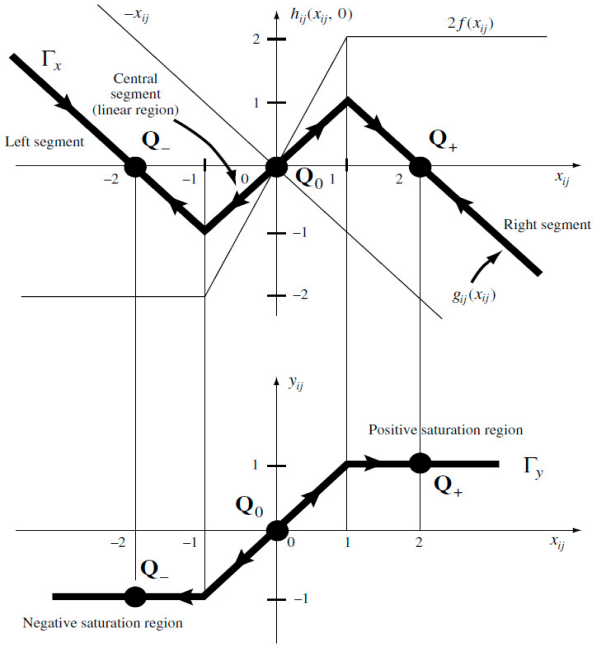

Fig. (5) Dynamics rout of both the state x_{ij} and output Y_{ij} with zero offset level ($w_{ij} = 0$).

where $\boldsymbol{u} \in \mathbb{R}^N$, $F \in \mathbb{R}^N$, D is a diagonal matrix of coupled diffusion, and $\nabla^2 u$ is the Laplacian operator in $\mathbb{R}^2$. There are various ways to estimate the ∇^2in discrete space by a CNN synaptic law with a convenient A-template. The 3D-CNN paradigm drives us to the architecture's comprehensive features as both arrangement and emergent dynamical behavior. The comprehensive interior dynamics can be recognized by combining the 3D-CNN observation of the forms. A split occurs in the shape proliferation abilities of the CNNs are confirmed, and the shape is a fractional condition of the emergent phenomena in the nonlinear dynamical models. A graphical illustration of 3D-CNN is shown in Fig. (6), in which a small cube presents each cell, and the connections with each other are sketched [12].

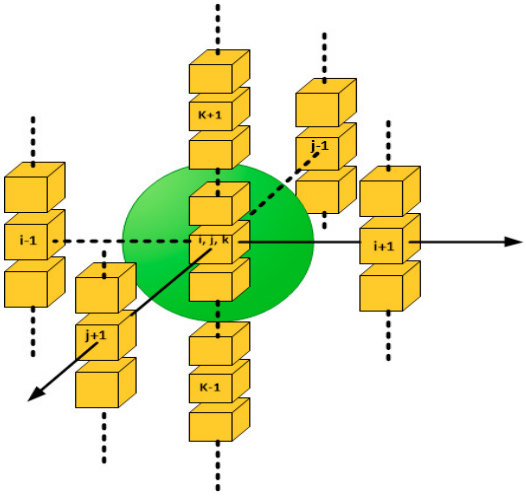

Fig. (6) Schematic representation of 3D-CNN array in Cartesian coordinates i, j, k, that each cube represents a single cell and reacts to others spatially.

Now, regarded the diffusion law is assumed as [12]:

$$c_{i,j,k}(\boldsymbol{x}_{ijk}) = D\nabla^2_{ijk}\boldsymbol{x} \tag{7}$$

In which the discrete Laplacian operator in 3D spatial-configuration is known by the relation [12] :

$$\nabla^2_{ijk}\boldsymbol{x} = \boldsymbol{x}_{i-1,i,k} + \boldsymbol{x}_{i+1,j,k} + \boldsymbol{x}_{i,j-1,k} + \boldsymbol{x}_{i,j+1,k} + \boldsymbol{x}_{i,j,k-1} + \boldsymbol{x}_{i,j,k+1} - 6\boldsymbol{x}_{i,j,k} \tag{8}$$

With all the assumptions above, the system of equations (11) can be rewritten as follows [12]:

$$\dot{x}_{ijk} = f(x_{ijk}) + D(x_{i-1,j,k} + x_{i+1,j,k} + x_{i,j-1,k} + x_{i,j,k-1} + x_{i,j,k+1} - 6x_{ijk}) \tag{9}$$

There are several ways to approximate the Laplacian operator in discrete space by a CNN synaptic law with a convenient template. So, model (4) , according to (6-9), become:

$$\frac{dI}{dt} = -R_1 I(t) + R_2 G(t) + R_3 G^2(t) + R_4 G^3(t) + R_5 z(t) + R_6 z^2(t) + R_7 z^3(t) + R_{18} + D_1\nabla^2 I(t)$$

$$\frac{dG}{dt} = -R_8 I(t) - R_9 I^2(t) - R_{10} I^3(t) - R_{11} z(t) - R_{12} z^2(t) - R_{13} z^3(t) + R_{19} + 0.5^I + D_2\nabla^2 G(t)$$

$$\frac{dZ}{dt} = R_{14} G(t) + R_{15} G^2(t) + R_{16} G^3(t) - R_{17} Z(t) + D_3\nabla^2 Z(t) \tag{10}$$

Now, our new Insulin-Glucose model (7) can be converted to CNN with three dimensions as:

$$\dot{I}_{ijk} = -R_1 I(t)_{ijk} + R_2 G(t)_{ijk} + R_3 G^2(t)_{ijk} + R_4 G^3(t)_{ijk} + R_5 z(t)_{ijk} + R_6 z^2(t)_{ijk} + R_7 z^3(t)_{ijk} + R_{18} + D_1[I_{i+1,j,k} + I_{i-1,j,k} + I_{i,j+1,k} + I_{i,j-1,k} + I_{i,j,k+1} + I_{i,j,k-1} - 6I_{ijk}]$$

$$\dot{G}_{ijk} = -R_8 I(t)_{ijk} - R_9 I^2(t)_{ijk} - R_{10} I^3(t)_{ijk} - R_{11} z(t)_{ijk} - R_{12} z^2(t)_{ijk} - R_{13} z^3(t)_{ijk} + R_{19} + 0.5^{x(t)_{ijk}} + D_2[G_{i+1,j,k} + G_{i-1,j,k} + G_{i,j+1,k} + G_{i,j-1,k} + G_{i,j,k+1} + G_{i,j,k-1} - 6G_{ijk}]$$

$$\dot{Z}_{ijk} = R_{14} G(t)_{ijk} + R_{15} G^2(t)_{ijk} + R_{16} G^3(t)_{ijk} - R_{17} z(t)_{ijk} + D_3[Z_{i+1,j,k} + Z_{i-1,j,k} + Z_{i,j+1,k} + Z_{i,j-1,k} + Z_{i,j,k+1} + Z_{i,j,k-1} - 6Z_{ijk}] \quad (11)$$

where $D_1 = 0.5, D_2 = 0.2$ *and* $D_3 = 0.3$ are diffusion coefficients and ∇^2 is three-dimensional discretized Laplacian operator. The cells' chaotic behavior represented by the beauty of the strange attractor is reflected in the beauty of the 3D form shown in Fig.7.

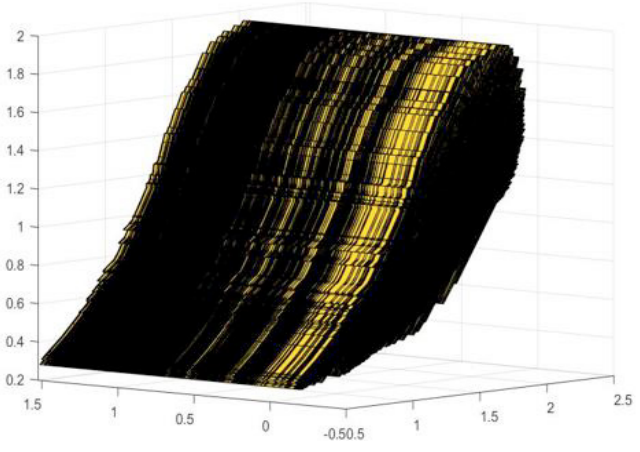

Fig.7 behavior of 3D form obtained by a 3D-CNN made of the proposed Insulin-Glucose regulation chaotic system.

V. INSULIN RESISTANCE DUE TO PCOS

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among reproductive of aged females, with prevalence up to 5% and 18% in recent studies [13]. The underlying mechanism of PCOS remains unclear mainly, and it is complex and multifactorial. The hormone disturbance created by a combination of hyperandrogenism and insulin resistance plays a vital role in such a disease's pathophysiology. Many factors contributed to such hormone disturbance as genetic and environmental cause combined with other factors, including obesity, ovarian dysfunction, and hypothalamic-pituitary abnormalities, related to the etiology of PCOS [14]. It has been suggested that some diabetes risk factors, including insulin resistance, impaired fasting glucose that common among women with PCOS than in the general female population. This led to the hypothesis that women with PCOS also have an elevated risk of diabetes mellitus (DM). To consider dynamical changes in the system in this type of diabetes, we can consider parameter R8 changing rate in equation $\dot{G}$. This parameter shows the changing insulin concentration rate. As we consider this decreasing parameter grows, dynamical changes of the glucose, insulin, and β-cells during type 2 diabetes can be derived. Fig.2 shows the bifurcation diagram of the insulin concentration as parameter R8 decreases. Regards to Fig. 2, the insulin concentration has a chaotic attractor while the decreasing rate of insulin secretion due to many reasons. In our hypothesis, these chaotic variations are normal and physiological limits as the insulin level changes in a day. However, in the case of more destruction of β-cells, theses variation vanishes and insulin dynamics becomes ordered through period halving bifurcation.

VI. CONCLUSIONS

Diabetes Mellitus (DM) is one of the common diseases in the world. In this disease, insulin and glucose concentration in the blood are not in their normal range. We propose a new model which represents the interaction of the glucose, insulin, and β-cells. In this differential equation computational model, we analyze the effect of the physiologically meaningful parameter (R_8) on the model's statistical and dynamical properties. Considering the system's bifurcation diagram for one parameter of the system derives dynamical changes in hyperglycemia due to PCSO. Also, Lyapunov exponent analysis was done to show the exact behavior of the biological system in many different control parameters. Finally, the system's dynamical properties were investigated by using the Basin of attraction, indicating that the proposed system is newly introduced concerning hidden attractor.

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