Bol. Soc. Paran. Mat.
©SPM – E-ISSN-2175-1188
SPM: www.spm.uem.br/bspm

(3s.) **v. 2025 (43) 3** : 1–12.
ISSN-0037-8712
doi:10.5269/bspm.78366

A Novel Fractional-Order Approach for Modelling Glucose Regulation with Meal Spikes and Periodic Noise

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ABSTRACT: In this work, we develop a novel fractional order model for glucose-insulin-lactate dynamics in diabetic patients, incorporating both time-varying noise and meal-induced glucose spikes to enhance the realism of the system. This framework is about non-linear fractional differential equations that capture the chaotic behaviour of glucose regulation in the presence of noise and periodic fluctuations. To simulate real-world conditions, time-varying noise is introduced as physiological variability, including noise levels that fluctuate based on circadian rhythms and metabolic processes. In addition, we introduce meal spikes as a sudden increase in glucose levels, reflecting the physiological response to food intake. The glucose surge is modelled using a Gaussian function, with intensity and duration adjustable to simulate different meal patterns. The proposed model successfully captures the complex, real-world behaviour of glucose metabolism, providing insights into the effectiveness of control strategies under realistic conditions. From this approach, we offer a more comprehensive representation of the metabolic control system in diabetic patients and provide a practical method to examine intervention strategies.

Key Words: Fractional-order dynamics, glucose-insulin-lactate system, time-varying noise, meal-induced glucose spikes.

Contents

1. Introduction

The human glucose-insulin regulatory system is a biologically complex and dynamic network, constantly adjusting to internal metabolic cues and external stimuli such as meals, stress, and circadian variations. In people affected by diabetes mellitus, this regulatory network is impaired, leading to uncontrolled glycemic excursions and long-term complications. In recent years, the modeling of this physiological system has seen major developments, transitioning beyond traditional linear representations to embrace more biologically faithful approaches, such as nonlinear fractional-order differential equations (FODEs), chaotic systems theory, and noise-driven dynamics. These advanced models have become instrumental in simulating real-world glucose-insulin-lactate interactions, capturing physiological unpredictability, and aiding the development of intelligent therapeutic systems.

Wang, Y., and Wang, H. laid foundational work by using dynamical system modeling to simulate glucose-insulin interactions. Their model captured glucose response curves and introduced nonlinear feedback relationships [1]. A key evolution came with the concept of closed-loop systems for insulin infusion. Hovorka et al. conducted a randomized controlled trial demonstrating the safety and efficacy of overnight artificial pancreas systems, marking a shift from simulation to real-world implementation. This clinical work emphasized the critical need for robust and adaptive control algorithms, particularly in the presence of physiological variability [2].

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2010 *Mathematics Subject Classification:* 34H05, 34H10, 34H15, 34H20.
Submitted August 12, 2025. Published October 02, 2025

To address model instability under unpredictable metabolic states, N'Doye et al. introduced a fractional-order control strategy, demonstrating enhanced stability through fractional dynamic feedback [3]. Alongside this, Bequette reviewed core challenges in artificial pancreas development, including modeling of delayed insulin action and postprandial glucose surges-problems that were inadequately addressed by earlier integer-order systems [4]. In complementary work, N'Doye et al. designed an unknown input fractional-order observer, enhancing state estimation in the presence of unmeasurable disturbances-a frequent issue in real-time diabetes monitoring [5].

These approaches emphasized the need to embed real-time responsiveness and physiological adaptability into diabetic management [6]. In industrial biotechnology, Craven et al. applied nonlinear model predictive control (NMPC) to regulate glucose in fed-batch bioreactors, offering useful cross-domain insights for medical glucose regulation [7].

Cho et al. introduced a fractional-order extension of the MINMOD Millennium model, enhancing its capability to simulate long-term glucose-insulin memory effects, such as those seen in insulin resistance [8]. Heydarinejad and Delavari observed a robust glucose control, even in systems subjected to sudden meal spikes or irregular hormonal activity [9]. Oviedo et al. conducted a comprehensive review of personalized blood glucose prediction strategies, advocating for the use of patient-specific physiological models rather than generic, population-based ones. They highlighted the role of adaptive algorithms and data-driven personalization in glucose modeling [10]. In parallel, Panahi et al. developed a fractional chaotic model for glucose-insulin dynamics, showing how chaos theory could replicate postprandial surges and hormonal variability more accurately than traditional models [11].

To handle system uncertainty, Heydarinejad et al. applied fuzzy type-2 controllers in conjunction with fractional observers. Their model integrated learning mechanisms for adaptive response and observer correction [12]. Paiva et al. improved both transient and steady-state performance by managing the blood sugar levels governs by fractional order method [13]. Munoz-Pacheco and Posadas-Castillo demonstrated the effectiveness of non-local fractional operators, further refining the modeling of metabolic memory and delay propagation in glucose-insulin systems [14].

Expanding on these control strategies, Ivanov et al. introduced the concept of network physiology, advocating for integrative modeling across cardiovascular, endocrine, and neural networks. This holistic view redefined diabetes as a system-level disorder [15]. Fernández-Carreón and Munoz-Pacheco implemented this thinking in their time-delay fractional-order glucose-insulin model, successfully simulating the delayed insulin response post-meal intake [16].

Askariand Mohammad Reza developed adaptive insulin delivery modules that incorporated chaotic glucose patterns and predictive models to offer real-time insulin adjustments [17]. Saleem and Iqbal introduced a complex-order PID controller for improved glycemic control, capable of handling high variability in unstructured daily activities [18]. Vijaya et al. extended diabetic prediction capabilities using metaheuristic optimization algorithms, enhancing control performance through global optimization of controller parameters [19].

Meal-induced glucose spikes-among the most difficult variables to manage in diabetic patients-received special focus in 2024. Batool et al. introduced a Mittag-Leffler kernel-based glucose-insulin-glucagon model, which modeled postprandial spikes as Gaussian pulses, capturing their sharp onset and gradual decay [20]. Kamat and Sweet validated this mathematically through biological experiments demonstrating that glucose surges lead to hypertonicity-induced insulin release, consistent with Gaussian-shaped models [21]. Ganguly et al. highlighted the integration of such models into biosensor ecosystems, advocating for sensor-driven control loops [22].

The evolution of fractional modeling continued with Alhazmi, who compared Caputo and Caputo-Fabrizio operators, recommending modeling strategies based on desired memory depth and computational efficiency [23]. Selma et al. further introduced a model-free feedback control strategy for meal-induced glucose spikes, by passing the need for explicit meal announcement and supporting autonomous artificial pancreas operations [24].

More recent efforts in 2025 focused on refining fractional control frameworks. Toopchi et al. presented a backstepping-based nonlinear control design optimized for the fractional-order nature of glucose-insulin dynamics [25]. Nisar and Farman formulated a PID feedback synthesis approach for closed-loop glucose control, while their second work demonstrated formal controllability analysis of such fractional systems-an essential criterion for ensuring robust clinical performance [26].

Additional control innovation was shown by Dagher and Haggege, who developed a genetic fuzzy controller to manage glycemic variability [27]. Nisar and Farman explored hybrid control techniques for fractional-order models, showing enhanced performance under both meal-based disturbances and sensor noise [28]. Finally, Saber and Mirgani presented fractional disease-informed neural networks, combining data-driven AI with fractional model structures for adaptive learning in diabetic systems [29].

In this reseacrh work, we will use the neural network method for the proposed model due to their strong generalization capabilities and adaptability. The application of neural networks spans multiple domains, including visual perception, language modeling, biomedical data analysis, diagnostic systems, and dynamic control processes. The conceptual foundation of neural networks was established by McCulloch and Pitts, who introduced a simple computational model of a neuron [30]. Later, Rosenblatt developed the Perceptron, a learning algorithm capable of binary classification, sparking early interest in artificial neural systems [31]. However, due to limitations in solving non-linear problems (e.g., XOR), highlighted in Minsky and Papert's work, research declined, leading to the first "AI winter" [32]. Interest was revived in the 1980s with the development of the backpropagation algorithm by Rumelhart, Hinton, and Williams, which enabled multi-layer networks to learn effectively [33].

This progress, along with growing data availability and computational power, resulted in transformative models like transformer-based architectures found in [34]. Neural networks play a vital role in cancer detection and prognosis by learning complex patterns from medical images and genomic data. Kourou et al. highlighted the effectiveness of neural networks in predicting cancer outcomes using clinical and molecular data [35]. Also, Esteva et al. showed that CNNs can classify skin cancer at a dermatologist-level [36]. Neural networks have been validated as effective across numerous diseases beyond oncology, offering enhanced diagnostic and prognostic capabilities. In ophthalmology, neural networks are widely utilized for diagnosis of diabetic patients with high sensitivity, supporting early intervention and screening programs Gulshan et al. [37].

In this paper, we introduce a fractional-order model for glucose-insulin-lactate dynamics in diabetic patients, incorporating time-varying noise and meal-induced glucose spikes to reflect real-life metabolic fluctuations. The model uses nonlinear fractional differential equations to capture chaotic glucose regulation influenced by circadian and metabolic noise. Meal spikes are modeled with adjustable Gaussian functions to simulate various dietary patterns. Results show the model effectively represents complex glucose behavior, offering a realistic tool for analyzing and optimizing therapeutic strategies in diabetes management.

2. Mathematical Model

A growing body of research has proposed models to capture the dynamic behavior of glucose regulation in diabetic patients, often structured based on multiple physiological compartments [38]. The study conducted by us specifically focused on non-linear glucose-insulin-lactate interactions in diabetic conditions, where the inter-system feedback between glucose, insulin, and lactate was taken into consideration. To achieve this, we will design a three-dimensional dissipative system of fractional order which incorporates: non-linear interactions between glucose, time varying noise, meal spikes and no equillibrium points ensuring potentially hidden or transient chaotic attractors. For this, we made a compartmental model for which the state variables as: x(t), y(t) and z(t) represented glucose concentration, insulin concentration and lactate concentration, which governs by the following postulates:

- System has no equillibrium point
- Meal spike acts as external time dependent input into the glucose particularly Gaussian input
- Noise is time varying particularly Gaussian noise
- The fractional orders lies in the interval (0.9,1)

In compliance with this fundamental postulates, the proposed mathematical model consists three compartments, corresponding to each state variables as shown in the Figure 1

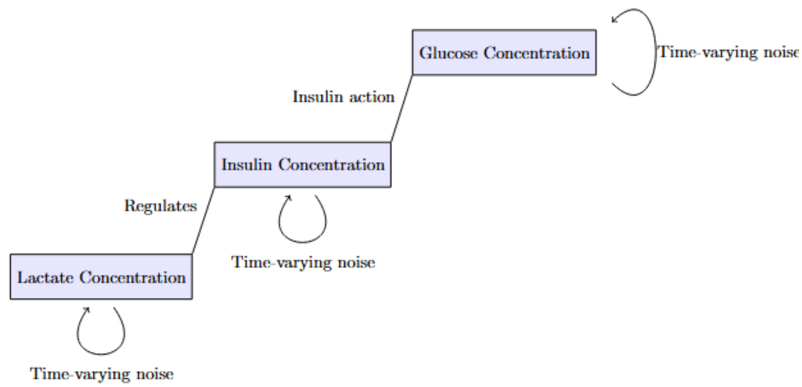

Figure 1: Comparmental Diagram of Proposed Mathematical Model

Based on the Figure 1 and interactions between glucose, insulin and lactate, we have designed a novel dynamical system by employing the above postulates.The model comprising a set of ordinary differential equation which is expressed as:

$$\begin{aligned} D^{\alpha}x &= \sigma(y-x) + k_1xz + M(t) + \eta_x(t) \\ D^{\alpha}y &= x(\rho-z) - y + k_2yz + M(t) + \eta_y(t) \\ D^{\alpha}z &= xy - \beta z + k_3x^2 + M(t) + \eta_z(t) \end{aligned} \tag{2.1}$$

where $M(t)$ = meal spike function (at some time t_0) considered as $A\exp^{-\frac{(t-centerofaspike)^2)}{twice(widthofspike)^2}}$, A$(mmolL^{-1})$ is an amplitude, $\eta_x(t)(mmolL^{-1}), \eta_y(t)(pmolL^{-1})$ and $\eta_z(t)(mmolL^{-1})$ are time varying noise (small Gaussian noise). Further, $\sigma(min^{-1}), \rho(mmolL^{-1}), \beta(min^{-1})$ are the control parameters and k_1, k_2, $k_3((mmolL^{-1})^{-1}min^{-1})$ are the small nonlinear perturbation parameters. Biologically the terms in the system 2.1 interpreted as $\sigma(y-x)$ represents insulin–glucose regulatory feedback; xz as lactate's modulatory effect on glucose; $x(\rho-z)$ as glucose stimulates insulin secretion (ρ as threshold); $-y$ as natural insulin clearance from the bloodstream; yz as interaction where lactate modulates insulin release or degradation; xy as interaction term indicating lactate production linked to glucose metabolism under insulin action (glycolysis); βz as natural lactate clearance via liver (Cori cycle); x^2 as extra lactate production under high glucose load (anaerobic metabolism). The phase portrait of the system (2.1) illustrates the existence of chaos and attractor which was observed in the Figure 2. Moreover, for a particular choice of parameter $\sigma = 10, \rho = 28, \beta = 8/3, k_1 = 0.05, k_2 = 0.03, k_3 = 0.02, \alpha = 0.95$ and the initial condition is $X(0) = (1, 1, 1)$, we have made a phase portrait of the system (2.1) and it's projection represented in Figure 2 and 3. In addition, we have observed the dissipative nature of the system in Figures (5 - 7) through the variation in the value of α.

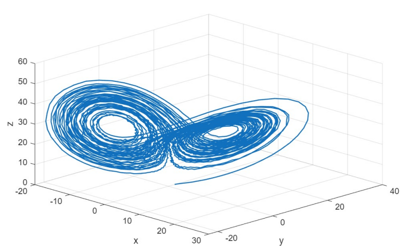

Figure 2: Phase portrait of the system (2.1)

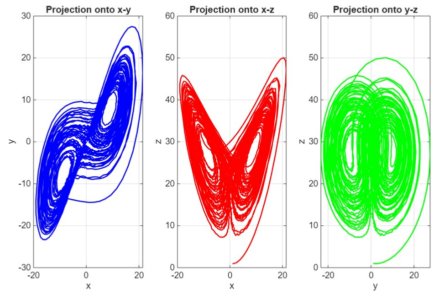

Figure 3: Projection of the system (2.1)

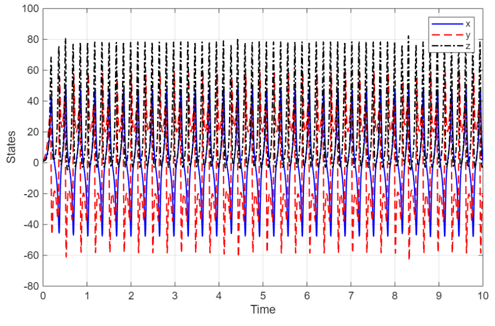

Figure 4: Time- series of the state variable x, y and z when $\alpha = 0.85$

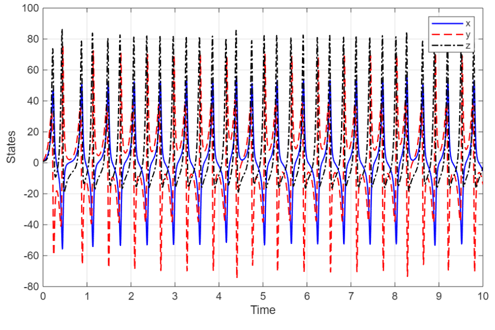

Figure 5: Time- series of the state variable x, y and z when $\alpha = 0.90$

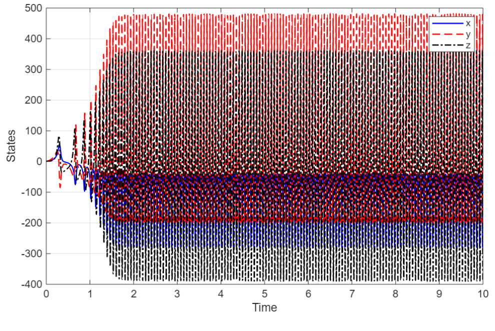

Figure 6: Time- series of the state variable x, y and z when $\alpha = 0.98$

3. Chaotic Dynamics

In the upcoming analysis, we establish that the system displays dissipative behavior under the selected set of parameters. We provide evidence of Shilnikov-type connections and present the computed Lyapunov exponents along with the corresponding Lyapunov dimension to support this claim.

Chaotic dynamics in a system can be characterized through Lyapunov exponents, which quantify how small variations in initial conditions evolve over time. These exponents reflect the system's sensitivity to initial perturbations. To numerically estimate the Lyapunov exponents, one must perform multiple iterations using fine time intervals, sampling different locations on the attractor. The Lyapunov exponent can be computed by tracking how an initial separation d_0 between nearby trajectories changes with respect to time step t.

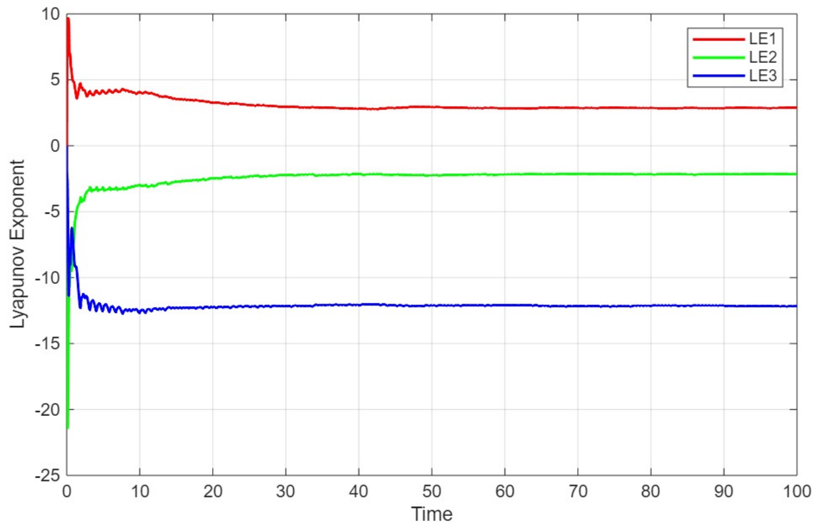

Figure 7: Lyapunov Spectrum of system (2.1) when $x_0 = 3$, $y_0 = 2$, $z_0 = 1$

The Figure 7 illustrates the time evolution and convergence of the three Lyapunov exponents indicate that the nonlinear dynamical system exhibits dissipative behaviour. Chaos can be quantified, if one of the Lyapunov exponent is positive and Lyapunov exponents corresponding to the proposed model are computed as $(2.72, -2.18, -11.96)$ which have been observed in Figure 7. In the initial part of the simulation (for small values of time), the exponents display rapid fluctuations, which means system does not evolved towards equilibrium into its long-term behavior. During this phase, the numerical method is still adapting to the local geometry of the attractor, and the exponents are still evolving and have not converged to their final asymptotic behavior.

As time progresses, all three curves begin to stabilize. By approximately t= 30–40, the values of the Lyapunov exponents level off, indicating convergence. This convergence confirms that the system has converged to its asymptotic regime and that the computed exponents are reliable indicators of its long-term behavior. Together, the spectrum of Lyapunov exponents shown in the figure- one positive, one near zero, and one negative- is a classic indicator of chaotic behavior in continuous dynamical systems. The convergence of these exponents over time not only confirms the chaotic nature of the proposed model but also validates the performance of the numerical algorithm used in their computation.

The bifurcation diagram shown in Figure 8 depicts the evolution of the system's long-term behavior as modulated by the control parameter ρ, with the variable z plotted along the vertical axis. Each point on the diagram represents a value of z at a steady state or during the long-term oscillatory regime for a given ρ, after discarding transients. As the parameter ρ increases from 20 to 40, the system undergoes a sequence of qualitative changes in its dynamics. For lower values of ρ (approximately $\rho< 22$), the system converges to a stable fixed point, as indicated by a single point at each ρ-value. This reflects regular and non-chaotic behavior.

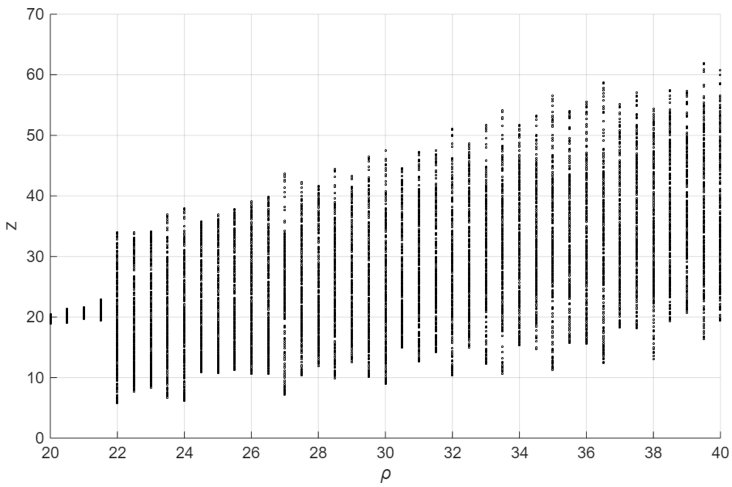

Figure 8: Bifurcation Diagram for Fractional-Order System (2.1)

However, as ρ increases, the diagram begins to show multiple discrete points for each ρ, signifying the emergence of period-doubling bifurcations. These bifurcations are characteristic of systems transitioning from periodic to chaotic regimes. The increased density and vertical spread of points reflect the growth in dynamical complexity. In the range $\rho \approx 24$ to $\rho \approx 40$, the system exhibits high sensitivity to initial conditions and aperiodic trajectories-hallmarks of chaos. The irregular and fragmented vertical structures in this region suggest the presence of chaotic attractors, where the system no longer follows a predictable cycle, and the trajectories diverge exponentially over time within a bounded region.

The presence of such chaotic bands is strong visual evidence of chaotic dynamics in the fractional-order system. This is unvarying with the known behavior of nonlinear systems, where parameter variations lead to complex transitions through bifurcations into chaos. The bifurcation diagram thus serves as a powerful diagnostic tool, revealing the onset and range of chaotic behavior in relation to the control parameter ρ. Further, we have observed bifurcation structure in a fractional-order system under appropriate parameter conditions.

4. Designing of Controller using Neural Network Method

The fundamental operation of a neural network involves computing a weighted sum of inputs, adding a bias term, and applying a non-linear activation function. Through this layered structure, the network is capable of approximating complex and highly non-linear relationships between inputs and outputs. The network "learns" these relationships by adjusting the weights and biases based on a defined loss function.

The original fractional-order model is augmented by introducing control inputs $u_1(t), u_2(t), u_3(t)$ into the respective differential equations:

$$\begin{aligned} D^\alpha x &= \sigma(y-x) + k_1 xz + M(t) + \eta_x(t) + u_1(t) \\ D^\alpha y &= x(\rho - z) - y + k_2 yz + M(t) + \eta_y(t) + u_2(t) \\ D^\alpha z &= xy - \beta z + k_3 x^2 + M(t) + \eta_z(t) + u_3(t) \end{aligned} \tag{4.1}$$

Let us denote:

$$\begin{aligned} e_1(t) &= x(t) - x_d(t) \\ e_2(t) &= y(t) - y_d(t) \\ e_3(t) &= z(t) - z_d(t) \end{aligned} \tag{4.2}$$

where $x_d(t), y_d(t), z_d(t)$ are the desired trajectories.

Apply the Caputo derivative to each error term of system (4.2), we have

$$\begin{aligned} D^\alpha e_1 &= D^\alpha x - D^\alpha x_d \\ D^\alpha e_2 &= D^\alpha y - D^\alpha y_d \\ D^\alpha e_3 &= D^\alpha z - D^\alpha z_d \end{aligned} \tag{4.3}$$

Using system (4.2) and (4.3), error dynamical system written as

$$\begin{aligned} D^\alpha e_1 &= \sigma(y-x) + k_1 xz + M(t) + \eta_x(t) + u_1(t) - D^\alpha x_d \\ D^\alpha e_2 &= x(\rho - z) - y + k_2 yz + M(t) + \eta_y(t) + u_2(t) - D^\alpha y_d \\ D^\alpha e_3 &= \beta z + k_3 x^2 + M(t) + \eta_z(t) + u_3(t) - D^\alpha z_d \end{aligned} \tag{4.4}$$

The goal is to design u_1, u_2, u_3 such that:

$$\lim_{t\to\infty} e_i(t) = 0 \qquad \text{where } i = 1, 2, 3 \tag{4.5}$$

4.1. Neural Network Approximation

We approximate the unknown dynamics f(x), f(y) and f(z) using Radial Basis Function (RBF) Neural Networks:

$$\begin{aligned} \hat{f}_1(x) &= \hat{W}_1^\top \Phi(x) \\ \hat{f}_2(y) &= \hat{W}_2^\top \Phi(y) \\ \hat{f}_3(z) &= \hat{W}_3^\top \Phi(z) \end{aligned} \tag{4.6}$$

where:

- $\Phi(\cdot) \in \mathbb{R}^N$ is the RBF vector,
- $\hat{W}_i \in \mathbb{R}^N$ is the estimated weights,

Each radial basis function is defined by:

$$\phi_j(s) = \exp\left(-\frac{(s-c_j)^2}{2\sigma^2}\right), \quad j = 1, 2, \ldots, N \tag{4.7}$$

Control Law Designed (RBF-NN + Feedback) as:

$$\begin{aligned} u_1(t) &= -\hat{W}_1^\top \Phi(x(t)) - k_{e_1} e_1(t) \\ u_2(t) &= -\hat{W}_2^\top \Phi(y(t)) - k_{e_2} e_2(t) \\ u_3(t) &= -\hat{W}_3^\top \Phi(z(t)) - k_{e_3} e_3(t) \end{aligned} \tag{4.8}$$

- $\hat{W}_i^\top \Phi(\cdot)$ is the NN approximation of unknown dynamics,
- k_{e_i} is the error feedback gain.

Weight Adaptation Laws described as

$$\begin{aligned} \dot{\hat{W}}_1 &= -\Gamma_1 \Phi(x) e_1(t) \\ \dot{\hat{W}}_2 &= -\Gamma_2 \Phi(y) e_2(t) \\ \dot{\hat{W}}_3 &= -\Gamma_3 \Phi(z) e_3(t) \end{aligned} \tag{4.9}$$

where:

- Γ_i is the learning rate matrix (usually $\Gamma_i = \gamma I$).

Controller Expressions:

$$u_i(t) = -\sum_{j=1}^{N} \hat{w}_{ij}(t) \exp\left(-\frac{(s_i(t) - c_j)^2}{2\sigma^2}\right) - k_{ei} e_i(t) \tag{4.10}$$

- For u_1: $s_1(t) = x(t)$, $e_1(t) = x(t) - x_d(t)$
- For u_2: $s_2(t) = y(t)$, $e_2(t) = y(t) - y_d(t)$
- For u_3: $s_3(t) = z(t)$, $e_3(t) = z(t) - z_d(t)$

Radial Basis Function Vector:

$$\Phi(s) = \begin{bmatrix} \exp\left(-\frac{(s-c_1)^2}{2\sigma_{\text{rbf}}^2}\right) \\ \exp\left(-\frac{(s-c_2)^2}{2\sigma_{\text{rbf}}^2}\right) \\ \vdots \\ \exp\left(-\frac{(s-c_N)^2}{2\sigma_{\text{rbf}}^2}\right) \end{bmatrix} \tag{4.11}$$

(centres c_j and width σ_{rbf} were set in the script).
Weight Update Laws:

$$\begin{aligned} \dot{\hat{W}}_1(t) &= -\Gamma_1 \Phi(x(t))\, e_1(t), \\ \dot{\hat{W}}_2(t) &= -\Gamma_2 \Phi(y(t))\, e_2(t), \\ \dot{\hat{W}}_3(t) &= -\Gamma_3 \Phi(z(t))\, e_3(t), \qquad \Gamma_i = \gamma I_N. \end{aligned} \tag{4.12}$$

The simulation is carried out in MATLAB and Mathematica with the particular set of parameters and initial conditions, we found the controller u_1, u_2, u_3 equipped with the system (2.1), controlled the chaotic behaviour and the error dynamical system (4.4) converged towards zreo after sometime observed in Figures 9 and 10.

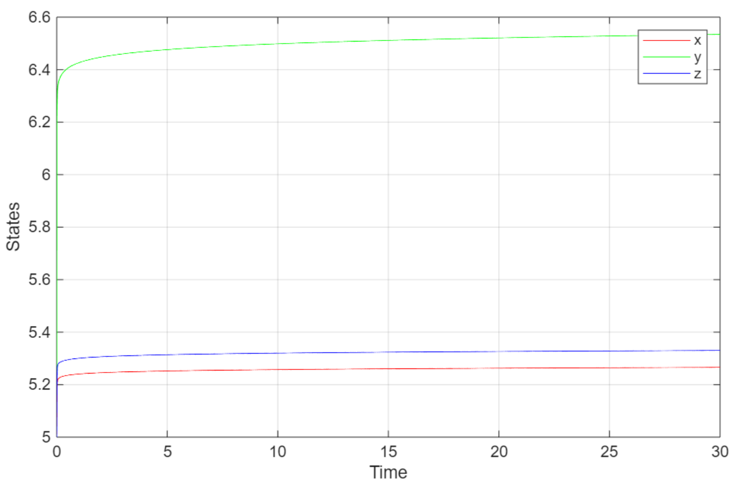

Figure 9: Controlled Fractional Order Chaotic System under the Updated Controller (4.10)

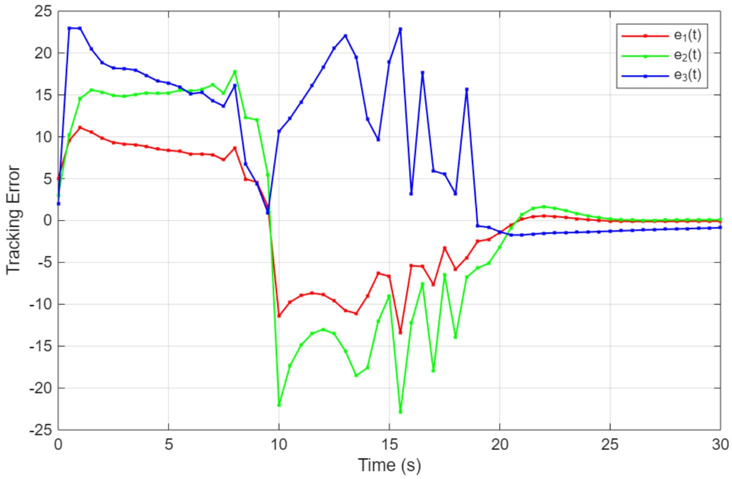

Figure 10: Convergence of Error Dynamical System (4.4)

5. Conclusion

The purpose of this study is to propose the non-linear chaotic system of novel fractional order Glucose regulation with meal spikes and periodic noise. In contrast to the work of Shaban Mohammadi and S. Reza Hejazi (2022), our proposed model demonstrates a more rapid convergence toward disease regulation. While their framework consists of two fractional-order equations and one integer-order equation, our approach employs three fully fractional-order equations, thereby capturing system memory and hereditary properties more comprehensively. Furthermore, unlike most existing models in the literature that rely on the existence of equilibrium points, our proposed model operates without any equilibrium point, offering a new perspective on the chaotic dynamics of glucose-insulin regulation. Moreover, this modeling approach offers the potential to improve prediction of glucose fluctuations under realistic conditions that include irregular meal patterns and physiological noise. In future, this framework will be integrated with advanced stochastic control strategies to optimize insulin dosing in real time, followed by rigorous validation against large-scale clinical trial datasets.

References

1. Chen, C.-L., Tsai, H.-W., and Wong, S.-S., *Modeling the physiological glucose–insulin dynamic system on diabetics*, J. Theor. Biol., 265(3), 314–322, (2010).

2. Hovorka, R., Kumareswaran, K., Harris, J., Allen, J. M., Elleri, D., Xing, D., Kollman, C., Nodale, M., Murphy, H. R., Dunger, D. B., et al., *Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies*, BMJ, 342, (2011).

3. N'Doye, I., Voos, H., Darouach, M., Schneider, J. G., and Knauf, N., *Static output feedback stabilization of nonlinear fractional-order glucose-insulin system*, Proc. 2012 IEEE-EMBS Conf. Biomed. Eng. Sci., 589–594, (2012).

4. Bequette, B. W., *Challenges and recent progress in the development of a closed-loop artificial pancreas*, Annu. Rev. Control, 36(2), 255–266, (2012).

5. N'Doye, I., Voos, H., Darouach, M., Schneider, J. G., and Knauf, N., *An unknown input fractional-order observer design for fractional-order glucose-insulin system*, Proc. 2012 IEEE-EMBS Conf. Biomed. Eng. Sci., 595–600, (2012).

6. Ghorbani, M., and Bogdan, P., *A cyber-physical system approach to artificial pancreas design*, Proc. 2013 Int. Conf. Hardware/Software Codesign Syst. Synth. (CODES+ISSS), 1–10, (2013).

7. Craven, S., Whelan, J., and Glennon, B., *Glucose concentration control of a fed-batch mammalian cell bioprocess using a nonlinear model predictive controller*, J. Process Control, 24(4), 344–357, (2014).

8. Cho, Y., Kim, I., and Sheen, D., *A fractional-order model for MINMOD millennium*, Math. Biosci., 262, 36–45, (2015).

9. Heydarinejad, H., and Delavari, H., *Fractional order back stepping sliding mode control for blood glucose regulation in type I diabetes patients*, Theory Appl. Non-Integer Order Syst., Zakopane, Poland, 187–202, (2016).

10. Oviedo, S., Vehí, J., Calm, R., and Armengol, J., *A review of personalized blood glucose prediction strategies for T1DM patients*, Int. J. Numer. Meth. Biomed. Eng., 33(6), e2833, (2017).

11. Shabestari, P. S., Panahi, S., Hatef, B., Jafari, S., and Sprott, J. C., *A new chaotic model for glucose-insulin regulatory system*, Chaos, Solitons & Fractals, 112, 44–51, (2018).

12. Heydarinejad, H., Delavari, H., and Baleanu, D., *Fuzzy type-2 fractional backstepping blood glucose control based on sliding mode observer*, Int. J. Dyn. Control, 7, 341–354, (2019).

13. Paiva, H. M., Keller, W. S., and da Cunha, L. G. R., *Blood-glucose regulation using fractional-order PID control*, J. Control Autom. Electr. Syst., 31(1), 1–9, (2020).

14. Muñoz-Pacheco, J. M., Posadas-Castillo, C., and Zambrano-Serrano, E., *The effect of a non-local fractional operator in an asymmetrical glucose-insulin regulatory system: Analysis, synchronization and electronic implementation*, Symmetry, 12(9), 1395, (2020).

15. Ivanov, P. C., *The new field of network physiology: building the human physiolome*, Front. Netw. Physiol., (2021).

16. Fernández-Carreón, B., Muñoz-Pacheco, J. M., Zambrano-Serrano, E., and Félix-Beltrán, O. G., *Analysis of a fractional-order glucose-insulin biological system with time delay*, Chaos Theory Appl., 4(1), 10–18, (2022).

17. Askari, M. R., *Developing Adaptive and Predictive Modules for the Second Generation of Multivariable Insulin Delivery System for People with Type-1 Diabetes*, PhD thesis, Illinois Institute of Technology, (2023).

18. Saleem, O., and Iqbal, J., *Complex-order PID controller design for enhanced blood-glucose regulation in Type-I diabetes patients*, Meas. Control, 56(9–10), 1811–1825, (2023).

19. Vijaya, J., Chandra, S., and Baghel, P., *Diabetes disease prediction using various metaheuristic optimization algorithms*, Proc. 2023 IEEE 8th Int. Conf. Convergence Technol. (I2CT), 1–6, (2023).

20. Batool, M., Farman, M., Ghaffari, A. S., Nisar, K. S., and Munjam, S. R., *Analysis and dynamical structure of glucose insulin glucagon system with Mittage-Leffler kernel for type I diabetes mellitus*, Sci. Rep., 14(1), 8058, (2024).

21. Kamat, V., and Sweet, I. R., *Hypertonicity during a rapid rise in D-glucose mediates first-phase insulin secretion*, Front. Endocrinol., 15, 1395028, (2024).

22. Ganguly, A., Churcher, N., Upasham, S., Dhamu, V., and Prasad, S., *Sensor ecosystems for health self-monitoring: Focus on diabetes management*, Org. Inorg. Mater. Based Sensors, 3, 1013–1054, (2024).

23. Alhazmi, M., *Comparing the numerical solution of fractional glucose–insulin systems using generalized Euler method in sense of Caputo, Caputo–Fabrizio and Atangana–Baleanu*, Symmetry, 16(7), 919, (2024).

24. Selma, B., Selma, B., Abouaïssa, H., Chouraqui, S., Kadem, H., Mehdeb, D., and Elaffifi, M., *Toward a model-free feedback control of blood glucose induced by meals for type-1 diabetics: In silico studies*, Iran J. Comput. Sci., 7(2), 217–227, (2024).

25. Noshad, E., Toopchi, Y., Abbasi Nozari, H., Sadati Rostami, S. J., Castaldi, P., and Hedayati, S., *A backstepping-based nonlinear controller for glucose-insulin system dynamics in type-1 diabetes patients*, Int. J. Robust Nonlinear Control, 35(5), 1687–1704, (2025).

26. Nisar, K. S., Farman, M., Jamil, K., Jamil, S., and Hincal, E., *Fractional-order PID feedback synthesis controller including some external influences on insulin and glucose monitoring*, Alex. Eng. J., 113, 60–73, (2025).

27. Dagher, K. E., and Haggege, J., *Development of a cognitive blood glucose–insulin control strategy design for a nonlinear diabetic patient model*, Nonlinear Eng., 14(1), 20250135, (2025).

28. Nisar, K. S., and Farman, M., *Investigation of fractional order model for glucose-insulin monitoring with PID and controllability*, Scientific Reports, 15(1), 8128, (2025).

29. Igiri, C. P., and Shikaa, S., *Monkeypox transmission dynamics using fractional disease informed neural network: A global and continental analysis*, IEEE Access, (2025).

30. McCulloch, W. S., and Pitts, W., *A logical calculus of the ideas immanent in nervous activity*, The Bulletin of Mathematical Biophysics, 5, 115–133, (1943).

31. Rosenblatt, F., *The perceptron: a probabilistic model for information storage and organization in the brain*, Psychological Review, 65(6), 386, (1958).

32. Minsky, M., and Papert, S., *An introduction to computational geometry*, Cambridge Tiass., HIT, 479(480), 104, (1969).

33. Rumelhart, D. E., Hinton, G. E., and Williams, R. J., *Learning representations by back-propagating errors*, Nature, 323(6088), 533–536, (1986).

34. Vaswani, A., Shazeer, N., Parmar, N., Uszkoreit, J., Jones, L., Gomez, A. N., Kaiser, Ł., and Polosukhin, I., *Attention is all you need*, Adv. Neural Inf. Process. Syst., 30, (2017).

35. Kourou, K., Exarchos, T. P., Exarchos, K. P., Karamouzis, M. V., and Fotiadis, D. I., *Machine learning applications in cancer prognosis and prediction*, Computational and Structural Biotechnology Journal, 13, 8–17, (2015).

36. Esteva, A., Kuprel, B., Novoa, R. A., Ko, J., Swetter, S. M., Blau, H. M., and Thrun, S., *Dermatologist-level classification of skin cancer with deep neural networks*, Nature, 542(7639), 115–118, (2017).

37. Gulshan, V., Peng, L., Coram, M., Stumpe, M. C., Wu, D., Narayanaswamy, A., Venugopalan, S., Widner, K., Madams, T., Cuadros, J., et al., *Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs*, JAMA, 316(22), 2402–2410, (2016).

38. Gassem, F., Zahir, A., Dawood, A., Almalahi, M., Ali, A., and Aldwoah, K., *Mathematical analysis of modified blood glucose insulin model through fractal fractional operators*, Scientific Reports, 15(1), 1–20, (2025).

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