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RESEARCH ARTICLE

Application of Jumarie-Stancu Collocation Series Method and Multi-Step Generalized Differential Transform Method to fractional glucose-insulin

1. Supplementary methodological clarifications and biological interpretations

1.1. Clarification of bifurcation parameters

Before proceeding with the bifurcation analysis, we identify the key parameters influencing the system's dynamic behavior. Specifically, the parameters a_{16} to a_{21} are selected for bifurcation analysis due to their physiological significance and their direct influence on the nonlinear terms governing the dynamics of β-cell function, glucose feedback, and insulin synthesis.

- a_{16}: Represents the inhibitory influence of elevated glucose levels on β-cell activity.
- a_{17}: Describes the enhancement of β-cell proliferation due to increasing glucose concentrations.
- a_{18}: Models the natural decay or degradation rate of β-cells.
- a_{19}: Captures the interaction between glucose and β-cell degradation (stress-related decay).
- a_{20}: A constant term modeling external input or perturbation in the glucose dynamics.
- a_{21}: Represents the baseline insulin production rate under normal physiological conditions.

The bifurcation ranges for these parameters (e.g., $a_{16} \in [-2, 0]$, $a_{17} \in [0, 1]$) were chosen based on physiological plausibility and prior modeling studies, particularly the work of Shabestari et al. [**?**]. These parameters are crucial in inducing transitions between different dynamical regimes such as equilibrium, oscillatory behavior, and chaotic dynamics and, thus, are analyzed to understand critical transitions in glucose-insulin regulation.

1.2. Discussion on the Use of Jumarie's fractional derivative

In this study, the Jumarie fractional derivative is employed to approximate the Caputo fractional derivative within the framework of the JSCSM. However, it is important to acknowledge that several works in the literature have questioned the mathematical validity of Jumarie's fractional calculus formulae, particularly for non-differentiable functions. Notably, the paper by Cheng-shi Liu [**?**] presents counterexamples that invalidate Jumarie's formulations in both differentiable and non-differentiable cases.

Despite this criticism, the impact on the findings of the present study remains limited for several reasons. Firstly, the JSCSM is used here primarily as a comparative numerical approach, while the main analytical and numerical findings—especially those related to bifurcation, chaos, and control—are validated through the MSGDTM, which does not rely on Jumarie's formulation. Secondly, the approximate solutions obtained via JSCSM exhibit strong agreement with those derived from MSGDTM and benchmark methods, as evidenced by the convergence and error analysis in Table 3.

Therefore, while the theoretical issues with Jumarie's derivative are acknowledged, they do not significantly undermine the core results or conclusions of this study. Nonetheless, we recommend a cautious interpretation of the results obtained solely through the JSCSM and suggest further exploration using rigorously validated formulations of fractional derivatives in future work.

1.3. Clarification on reference solution for error analysis

In the error analysis presented in this study (Section 4.3), the accuracy of the JSCSM and the MSGDTM is assessed by comparing their solutions to a high-accuracy reference solution. To

construct this reference solution, we employed the fractional-order Runge-Kutta method adapted for Caputo-type fractional derivatives. This method is a well-established numerical approach known for its precision in solving fractional differential equations with memory effects.

The fractional Runge-Kutta scheme used incorporates adaptive step-size control and higher-order accuracy, ensuring a reliable approximation of the true solution over the considered time interval. Specifically, the algorithm follows the predictor–corrector formulation based on the fractional Adams–Bashforth–Moulton method, which is widely recommended in the literature for Caputo fractional derivatives.

By solving the fractional glucose-insulin model using this method with a sufficiently small time step (e.g., $h = 10^{-4}$), we obtain a solution with negligible numerical error, which is then used as the benchmark for computing the L_2-norm errors of the JSCSM and MSGDTM approaches. This clarification ensures that the error analysis results are meaningful and can be reproduced or extended by interested readers.

1.4. Biological interpretation of negative parameters in Table 4

Table 4 presents the updated parameter values used in the glucose-insulin regulatory model. Among the 21 parameters, 10 are observed to have negative values: $a_4, a_6, a_9, a_{10}, a_{13}, a_{16}, a_{18}, a_{19}, a_{20}$, and a_{21}. It is essential to provide biological justification for these values to ensure the model's physiological plausibility.

- a_4: Represents a damping or saturating effect in insulin production due to high glucose concentrations. A negative value reflects a natural biological inhibition at elevated glucose levels, avoiding overproduction of insulin.
- a_6: Acts as a corrective factor in basal insulin release. A negative a_6 implies that at certain quadratic contributions, insulin release may plateau or diminish slightly, representing homeostatic regulation.
- a_9 and a_{10}: These correspond to higher-order negative feedback effects of insulin on glucose. Their negative signs represent enhanced glucose reduction through strong and secondary insulin-mediated mechanisms (quadratic and cubic terms), which are biologically consistent.
- a_{13}: Captures additional nonlinear reductions in glucose concentration due to insulin or β-cell activity. A negative value supports the physiological reality that beyond a threshold, insulin significantly suppresses glucose levels.
- a_{16}: Reflects the inhibitory effects of excessive glucose on β-cell function. A negative value aligns with the concept of glucotoxicity, where sustained hyperglycemia impairs β-cell regeneration.
- a_{18}: Models the natural loss rate of β-cells over time. Its negative value directly represents decay, consistent with aging or disease-related cell attrition.
- a_{19}: Represents glucose-induced stress on β-cells. A negative interaction term accounts for damage or suppression in β-cell function under persistent hyperglycemia.
- a_{20}: This constant term in glucose dynamics may reflect net loss due to external removal or metabolic demands exceeding input. A negative value is biologically plausible when overall glucose reduction dominates.
- a_{21}: Represents baseline insulin synthesis. A negative baseline may model pathological states (e.g., in type 2 diabetes) where insulin production is impaired even at rest.

The presence of negative parameters, therefore, does not invalidate the model. On the contrary, they reflect biologically meaningful inhibitory or decay processes. Overall, these interpretations affirm that the model is biologically feasible and captures both stimulatory and suppressive dynamics observed in real glucose-insulin physiology.

1.5. Justification for the range of fractional orders used in graphical results

In Figures 6–17, the fractional-order values α used in simulations range from 0.97 to 1.0, with time-dependent perturbations applied in some cases (e.g., $\alpha = 0.97 \pm 0.03 \times \sin(t/10)$, etc.). It is important to clarify that this range was intentionally chosen to focus on dynamics near the classical integer-order case ($\alpha = 1$), in order to highlight subtle changes in system behavior—particularly bifurcations and chaos suppression—when slight memory effects are introduced.

The rationale behind selecting fractional orders close to 1 is threefold:

(1) These values ($\alpha \approx 1$) mimic mild memory effects, which are often more biologically plausible in real physiological systems, like glucose-insulin interactions.

(2) The study aims to evaluate how small deviations from the classical model influence stability, oscillatory behavior, and chaotic transitions, which are key aspects for understanding potential therapeutic control strategies.
(3) Moreover, the effectiveness of the numerical methods (MSGDTM and JSCSM) is demonstrated in a range that remains computationally stable while still showing the richness of fractional-order dynamics.

Nonetheless, we acknowledge that lower fractional orders such as $\alpha = 0.7$, 0.8, and 0.9 offer deeper insights into strong memory effects and more pronounced nonlocal behaviors. Indeed, these values are already included in Table 2 through the Lyapunov exponent and Kaplan–Yorke dimension analysis, which supports the observation of increased system complexity and chaotic tendencies as α decreases.

Future extensions of this work will include full-scale simulations at lower fractional orders to systematically compare how varying α influences the long-term dynamics and control strategies of the glucose-insulin model.

1.6. The biological interpretation of the results

The simulations revealed that system behavior is highly sensitive to both the fractional order α and specific nonlinear interaction parameters. For instance, at fractional orders slightly less than one ($\alpha = 0.97$ to $\alpha = 1$), the model displays rich dynamic transitions, including oscillatory behavior and chaos, particularly under variations in parameters such as a_{16} to a_{21}, which regulate feedback, inhibition, and stress effects on glucose and β-cell function.

This suggests that even small memory effects can significantly influence glucose-insulin dynamics, providing deeper insights into pathological states like diabetes, where delayed or impaired responses are common. The bifurcation diagrams further reinforce that parameters like a_{16} (glucose-induced inhibition on β-cells) or a_{19} (stress-driven decay) are critical in destabilizing normal glucose regulation and can trigger complex or chaotic responses.

1.7. Advantages of the proposed techniques

From a computational standpoint, the MSGDTM demonstrated superior accuracy and convergence compared to JSCSM, as shown in the error analysis (Table 3). It was particularly effective in handling nonlinear terms and long-term simulations, making it a reliable tool for investigating fractional biological models. The JSCSM, although slightly less accurate, provided a computationally simpler approach suitable for moderate approximations.

The key advantages of the proposed MSGDTM technique include:

- Efficient handling of nonlinear and memory-intensive fractional systems.
- Faster convergence and lower approximation error compared to existing methods.
- Flexibility for long-time-interval simulations, essential for chronic conditions like diabetes.

1.8. Implications and future directions

Biologically, the results underscore the importance of considering fractional-order dynamics in glucose-insulin interaction models. Traditional integer-order models may overlook subtle delays and memory-driven feedback mechanisms present in real physiological systems. This fractional modeling approach opens avenues for designing more effective therapeutic strategies, such as timing insulin administration or optimizing feedback control based on the system's memory.

Future work may extend the model to include:

- Lower fractional orders ($\alpha = 0.7, 0.8, 0.9$) to assess strong memory effects.
- Stochastic or time-delay components to account for variability and uncertainty in biological responses.
- Patient-specific parameter estimation using real data to personalize and validate the model.

Overall, this study demonstrates how fractional-order modeling, supported by robust numerical schemes, like MSGDTM, can enhance our understanding of complex biomedical systems and contribute to the advancement of precision medicine.

1.9. Novelty and motivation

This study is among the first to apply and compare the effectiveness of the MSGDTM and the JSCSM to a fractional-order glucose-insulin system. These numerical methods are adapted to handle memory-driven, nonlinear systems over extended time intervals with high accuracy and convergence. The results provide deeper insights into how fractional-order parameters influence system dynamics and demonstrate the superiority of MSGDTM in solving biologically complex fractional models.

The main objective is to showcase how fractional-order modeling enhances the realism and analytical depth of glucose-insulin interaction

studies, offering a more robust framework for understanding pathological conditions such as diabetes and designing effective control mechanisms. This fractional framework not only broadens the scope of biomedical modeling but also establishes a foundation for future studies involving memory effects, variable-order systems, and real-time patient data integration.

1.10. Biological motivation

Glucose-insulin regulation is governed by complex interactions among glucose levels, insulin secretion, and pancreatic beta cells. Chronic conditions such as diabetes mellitus can result from disruptions in this regulatory mechanism. To study these interactions, traditional mathematical models are based on integer-order differential equations that ignore memory and hereditary effects.

Physiological responses—such as insulin secretion and glucose absorption—depend on the system's history, according to recent medical research. Fractional-order models incorporate memory effects through nonlocal operators, providing a more realistic representation of metabolic processes. In diseases like diabetes, where feedback loops and time-dependent responses substantially affect disease progression and treatment outcomes, fractional derivatives allow the modeling of long-term dependencies and delays.

The development and analysis of model (1) enhances our understanding of metabolic regulation while also enabling more accurate predictions and effective control strategies, essential to improving diabetes management and therapy.

1.11. Fractional-order derivatives: motivations

While classical glucose-insulin models based on integer-order derivatives have provided valuable insights, they are inherently limited in capturing the long-term memory and hereditary properties intrinsic to biological systems. Physiological processes such as insulin secretion, glucose absorption, and β-cell responses are not instantaneous and depend on the history of glucose levels over time. Integer-order differential equations assume local behavior, neglecting this temporal memory, which may result in oversimplified or less realistic predictions.

Fractional-order derivatives, particularly in the Caputo sense, naturally incorporate memory effects through nonlocal integration. This is especially advantageous in modeling chronic conditions such as diabetes, where the cumulative effect of glucose fluctuations significantly impacts insulin dynamics and β-cell function. Furthermore, fractional models provide additional flexibility by tuning the fractional order α, enabling the system to smoothly transition between memoryless (integer-order) and fully memory-dependent regimes. This tunability cannot be replicated using standard integer-order models. Thus, the use of fractional calculus is not only mathematically justified but also biologically motivated, as it aligns more closely with real physiological observations and enhances the model's predictive power.

In summary, the use of fractional-order derivatives in this study is essential for:

- Capturing memory effects and delayed feedback in glucose-insulin dynamics.
- Modeling complex nonlinear behaviors such as oscillations and chaos.
- Providing improved accuracy and adaptability over classical integer-order models.

1.12. Key factors influencing instability and glucose-insulin fluctuation dynamics

In the context of the model (1), "transmission potential" can be interpreted as the capacity of the system to propagate dynamic disturbances, such as oscillatory or chaotic behaviors, which may correspond to metabolic dysregulation or the onset of pathological states like diabetes. Several key model components influence this behavior:

- **Fractional order** α: It governs the strength of the memory effects. Lower α values increase the influence of past states, which can destabilize equilibrium and amplify oscillatory behavior, as confirmed by the Lyapunov exponents and bifurcation diagrams in this study.
- **Nonlinear feedback parameters**: Parameters such as a_2, a_8, a_{11}, and a_{16} play critical roles in amplifying or dampening responses to changes in glucose or insulin levels. In particular, a_{16} captures the glucotoxic effect on β-cells, contributing to instability when feedback fails.
- **β-cell regulation terms**: Parameters a_{17}, a_{18}, and a_{19} influence the rate of β-cell expansion or decay in response to glucose levels. Alterations in these rates can lead to a delayed insulin response or cellular burnout, which may lead to long-term instability.

- **Baseline and external inputs**: Parameters a_{20} and a_{21} represent external influences and baseline insulin synthesis. Variations here mimic environmental or pharmacological inputs, which can push the system toward stable or unstable regimes.
- **Initial conditions and perturbations**: Sensitivity to initial states is a hallmark of nonlinear dynamical systems. The model's chaotic attractors, demonstrated in the simulations, show that small perturbations can lead to significantly different system trajectories.

Collectively, these factors govern the ability of the glucose-insulin system to either suppress or transmit dynamic fluctuations over time. The proposed fractional-order model, by capturing these dependencies with higher fidelity, provides a deeper understanding of the underlying physiological processes and can inform control strategies to mitigate chaotic transitions.

1.13. Numerical simulations and parameter effects

To analyze the influence of key parameters on glucose-insulin dynamics, we performed numerical simulations of the fractional-order system using the MSGDTM and JSCSM. The simulations were conducted over a range of fractional orders $\alpha \in [0.97, 1]$, and parameter variations focused primarily on a_{16} to a_{21}, which govern feedback and regulatory mechanisms in the model.

The following key observations were drawn from the simulation results (Figures 6–17):

- **Effect of** a_{16}: This parameter represents inhibitory feedback on β-cell activity at higher glucose levels (glucotoxicity). When a_{16} is varied from -2 to 0, bifurcation diagrams show transitions from stable steady states to oscillatory and chaotic regimes, highlighting how impaired β-cell response can destabilize glucose regulation.
- **Effect of** a_{17}: Governing glucose-induced β-cell expansion, an increase in a_{17} (0 to 1) tends to stabilize the system, suggesting a protective role. Lower values are associated with delayed insulin responses and more complex dynamics.
- **Effect of** a_{18}: A decay term for β-cell populations, negative values (e.g., -1 to 0) represent cell loss due to aging or stress. Increasing $|a_{18}|$ induces irregular insulin release and unstable glucose levels, reflecting progression toward metabolic dysfunction.
- **Effect of** a_{19}: This interaction term captures stress-induced β-cell loss driven by elevated glucose. Negative values result in a feedback loop that exacerbates instability—glucose rises, causing more β-cell decay, which in turn reduces insulin availability.
- **Effect of** a_{20}: This parameter mimics external disturbances or baseline losses in glucose dynamics. Its variation affects the system baseline, with more negative values lowering glucose thresholds and amplifying system reactivity.
- **Effect of** a_{21}: Representing basal insulin production, lower (more negative) values model insulin-deficient conditions. Reductions in a_{21} lead to greater oscillations and even chaotic attractors, consistent with insulin-deficient diabetes states.

These findings collectively illustrate how physiological and pathological changes in key parameters can dramatically influence the system's dynamic behavior. The simulations validate the ability of the fractional-order model to replicate complex patterns such as chaos, oscillation, and stable regulation—offering valuable insight into the progression and control of glucose-related disorders.

Furthermore, the comparison between MSGDTM and JSCSM confirms that MSGDTM offers superior convergence and accuracy, especially in handling long-term memory effects and strong nonlinearities.

1.14. Parameter setup for simulations

The numerical simulations were carried out using the parameter values listed in Table 4, that are adapted from and calibrated based on the model of Shabestari et al. [**?**]. Unless otherwise stated, all simulations assume these parameter values to be fixed. For bifurcation and sensitivity analyses, selected parameters—particularly a_{16}, a_{17}, a_{18}, a_{19}, a_{20}, and a_{21}—were systematically varied within biologically meaningful ranges to examine their effect on system dynamics.

This approach allows us to isolate the influence of key feedback and regulatory mechanisms in the glucose-insulin-β-cell system, while maintaining physiological consistency for the remaining model components.

1.15. Advantages and unique features revealed by fractional-Order modeling

The use of fractional-order derivatives in this study has revealed several important dynamical

features of the model (1) that are not observable under classical integer-order formulations:

- **Memory-dependent dynamics**: Unlike integer-order models that assume instantaneous response, the fractional-order system incorporates memory effects, where the present rate of change depends on the entire past history of the system. This is particularly important in biological systems like glucose-insulin regulation, where insulin response to glucose is inherently delayed and influenced by prior metabolic states.
- **Smooth transition between dynamic regimes**: By tuning the fractional order α, the system smoothly transitions between stable, oscillatory, and chaotic behaviors. This tunable memory effect is a distinct feature of fractional systems that allows for finer control and richer dynamic exploration, which is not achievable using fixed-order classical models.
- **Earlier onset of chaos and bifurcations**: The bifurcation analysis shows that the onset of oscillatory and chaotic dynamics occurs at earlier parameter values when $\alpha < 1$. This sensitivity highlights the role of fractional memory in amplifying physiological feedback loops—potentially explaining early-stage diabetic dysregulation that would not be predicted by an integer-order system.
- **Higher fidelity to biological observations**: Many clinical and experimental studies report delayed insulin secretion, long recovery times, and complex glucose oscillations in diabetic patients. These phenomena are better replicated in the fractional model, where long-memory effects are naturally embedded in the system dynamics.
- **Improved control insights**: The fractional model also provides a more realistic testbed for developing control strategies (e.g., for insulin therapy or β-cell preservation). Because it better captures the delayed and cumulative impact of interventions, it can inform the timing and intensity of treatments more accurately than integer-order models.

Therefore, the fractional-order approach reveals dynamic richness, memory sensitivity, and control relevance that would otherwise remain obscured in traditional models, underscoring the value of fractional calculus in biomedical system modeling.

1.16. Biological and dynamic interpretation of figures

The biological and dynamic interpretation of the figures reveals how small variations in model parameters significantly impact glucose-insulin oscillations and system stability. Figures 6–9 display bifurcation diagrams for parameters a_{16} to a_{19}, showing that decreasing a_{16}, which represents glucotoxic inhibition of β-cells, transitions the system from steady to oscillatory and ultimately chaotic behavior, highlighting how impaired feedback at high glucose levels can trigger metabolic instability. Similarly, adjustments in a_{17} to a_{19} alter the amplitude and frequency of oscillations, reflecting the system's sensitivity to changes in β-cell function and stress responses. Figures 10–12 further demonstrate how variations in external glucose input (a_{20}) and basal insulin production (a_{21}) influence system dynamics, where decreasing basal insulin or increasing stress (more negative a_{20}) induces chaotic patterns akin to diabetic behavior, emphasizing the importance of carefully managing insulin dosage and timing to avoid instability. Time-series plots in Figures 13–15 illustrate the effects of different fractional orders ($\alpha = 0.97$, 0.98, 0.99, and 1) on system trajectories, revealing that small changes in α intensify memory effects and irregular oscillations, which is crucial for modeling delayed physiological responses and tailoring personalized treatments. Figures 16–17 present 3D attractors that visually confirm the emergence of complex, multi-scroll, or chaotic structures in the fractional model—less evident in the integer-order case—demonstrating the richer nonlinear dynamics enabled by fractional modeling. Collectively, these findings establish that the fractional-order model captures a broader range of dynamic behaviors, including periodic and chaotic oscillations, identifies critical physiological thresholds through bifurcation and Lyapunov analyses, and highlights the fractional order α as a tunable parameter controlling memory strength and the onset of chaos. Furthermore, the MSGDTM method outperforms JSCSM in long-term simulations and error convergence, validating its robustness for nonlinear fractional biological systems. Overall, this work demonstrates the power of fractional calculus in replicating realistic metabolic dynamics and guiding the design of precise, time-sensitive therapeutic strategies.

1.17. Impact of varying parameters and comparison with classical models

Varying the parameter values in the model (1) enables a deeper exploration of the system's sensitivity, feedback mechanisms, and potential for

complex behavior. In particular, the parameters a_{16} to a_{21}, which represent inhibitory feedback, stress-induced decay, external glucose input, and basal insulin synthesis, play a pivotal role in shaping system dynamics.

- For example, varying a_{16} reveals how glucotoxicity affects β-cell performance under hyperglycemic conditions, leading to transitions from stable glucose regulation to oscillations and chaos.
- Adjusting a_{19} shows how stress-related feedback loops, often present in diabetic states, can destabilize the system when not properly regulated.
- Modifying a_{21}, which represents basal insulin production, mimics physiological changes such as early-stage insulin resistance or treatment intervention.

These dynamic effects are further amplified when explored in the fractional-order context. The benefits of using fractional-order derivatives over classical derivatives include:

- **Memory and hereditary effects**: The fractional model accounts for the history of glucose and insulin levels, reflecting the delayed physiological responses more accurately than classical models.
- **Enhanced sensitivity to parameter variations**: Small changes in parameter values can lead to drastically different system behaviors (e.g., bifurcations or chaos), which are less apparent in integer-order models. This sensitivity allows for a better understanding of threshold behaviors and early detection of instability.
- **Improved Realism and Flexibility**: The ability to tune the fractional order α allows the model to capture both short-term (near-integer α) and long-term (lower α) memory dynamics. This flexibility is not possible in classical systems.
- **Biological relevance**: Many diseases like diabetes exhibit chronic feedback delays and long-term adaptation that are better modeled with fractional derivatives. Thus, the fractional framework leads to more biologically faithful simulations.

In summary, varying parameters within the fractional framework reveal richer, more realistic dynamics and system sensitivities that are difficult to observe using classical models. This enables a better understanding of disease mechanisms, risk thresholds, and intervention strategies, highlighting the superiority of fractional order modeling in biomedical applications.