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Fractional Differential Equations of Glucose and Insulin: Exposing Dynamic System Behavior Through Memory-Dependent Modeling

Riaz Ahmed Qureshi

Lecturer in Mathematics, SMBB Government Girls Degree College Naudero. Email: qriaz146@gmail.com

ABSTRACT

The classical Bergman minimal model is a glucose regulation model that uses integer-order ordinary differential equations to model the dynamics of glucose regulation under the influence of insulin. Biological systems however are those that are hereditary and have memory effects that cannot be well represented by integer-order calculus. This paper constructs and studies a fractional-order extension of the Bergman minimal model using Caputo fractional derivatives with fractional orders of 0 10 and 0 10 respectively on the dynamics of glucose and insulin respectively. The Grunwald Letnikow numerical method is used to model the intravenous glucose tolerance test (IVGTT) protocol in a 240-minute time frame. Artificial data created at 13 time points of classical and fractional framework display different dynamic signatures. The fractional model (0.85, 0.90) has a slower initial glucose clearance and increased long-tail memory behavior, with the highest glucose concentration of 151.90 mg/dL at t 10 min compared to the classical model at 248.84mg/dL. A sensitivity analysis of 0.75, 0.85, 0.95 and 1.0 on 0.75 confirms that there is a monotonic relationship between the fractional order and the glucose clearance rate. In both models, the presence of global asymptotic stability of the basal state is confirmed by analysis of the stability at equilibrium. It yields RMSE = 34.27 mg/dL compared to the ODE baseline which is due to truly different physiological interpretations rather than fitting errors. These findings indicate that the memory-dependent regulatory processes that are not apparent in classical models are revealed using fractional-order models, which provide a more biologically realistic account of glucoregulatory processes applicable in modeling type 2 diabetes.

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1. INTRODUCTION

Diabetes mellitus has more than half a billion infected individuals across the globe, and its prevalence is expected to grow to 783 million in 2045 (International Diabetes Federation [IDF], 2021). The glucoseinsulin regime is a paradigm of a tightly regulated physiological feedback loop, and mathematical modelling of it has been a focus of endocrinology research since the pioneering work of Bolie (1961), and the most influential of such models, the Bergman minimal model (Bergman et al., 1979). This three-coupled ordinary differential equation (ODE) model of plasma glucose, remote insulin action and plasma insulin is still the gold standard in the quantification of insulin sensitivity using intravenous glucose tolerance test (IVGTT) data.

Although it has proven useful over time, the classical integer-order Bergman model works on the assumption that the state of the system is only dependent on the system values at a given moment- this is a biologically constrained assumption that has been increasingly acknowledged to be biologically limiting. Physiological systems are memory dependent: the rate of glucose clearance at a given time is not only affected by the insulin concentration at that moment but by the whole previous history of insulin activity, receptor saturation and hepatic glycogen levels. It is the natural province of fractional calculus such hereditary and viscoelastic behavior (Podlubny, 1999; Oldham and Spanier, 1974).

Fractional differential equations (FDEs) extend the integer-order derivative to non-integer orders, allowing the simulation of power-law memory kernels, anomalous diffusion, non-local temporal dependence, and power-law memory kernels. They have significantly increased their use in biomedical modeling in the last 20 years. Edelstein-Keshet (2005) and subsequently Ionescu et al. (2017) claimed that the respiratory and metabolic systems have exactly the long-range correlations that are described by fractional operators. Fractional extensions have been proposed in several studies in the context of glucoseinsulin modeling (Shaikh

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et al., 2020; Mahata et al., 2020; Almeida et al., 2019), but a systematic numerical study of the difference between fractional and classical trajectories across the parameter regimes is still lacking.

The current research fills this gap, by constructing a Caputo fractional-order Bergman minimal model, and applying a Grunwald-Letnikov numerical solver, and producing extensive simulation data in IVGTT conditions. We explore the dynamics of the system under the effects of changing the fractional order (glucose equation) and insulin equation (insulin equation) by 0.5, sensitivity analysis, stability of the equilibrium and implications on type 2 diabetes phenotyping.

1.1. Motivation and Scope

The essence of the motivation is three-fold. To start with, the classical minimal models do not systematically account for the duration of clearance of glucose in insulin-resistant people indicating that integer-order dynamics are inadequate. Second, fractional operators add precisely one more parameter to each equation (the fractional order) with parsimony, but with a strictly vastly greater representational capacity. Third, the Grunwald-Letnikov discrete time is computationally feasible and numerically stable and allows a direct comparison to Runge-Kutta solutions of the classical model with the same initial conditions and with the same set of parameters.

2. MATHEMATICAL FORMULATION

2.1. Classical Bergman Minimal Model

The integer-order Bergman minimal model (Bergman et al., 1979) is expressed as a system of three coupled ordinary differential equations:

$$dG/dt = -p_1(G - G_\beta) - X \cdot G \quad (1)$$

$$dX/dt = -p_2 \cdot X + p_3(I - I_\beta) \quad (2)$$

$$dI/dt = -n(I - I_\beta) + \gamma \cdot \max(G - h, 0) \quad (3)$$

where G(t) denotes plasma glucose concentration (mg/dL), X(t) is insulin action in the remote (interstitial) compartment (min^{-1}), and I(t) is plasma insulin concentration (mU/L). The parameters p_1, p_2, p_3, n, γ, G_β, I_β, and h carry the biological interpretations summarized in Table 2. The state variable X represents the delayed action of plasma insulin on glucose disposal, introducing a

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physiologically motivated lag between plasma insulin appearance and glucose uptake.

2.2. Caputo Fractional Derivative

The Caputo fractional derivative of order $\alpha \in (0, 1)$ for a continuously differentiable function f is defined as (Caputo, 1967; Podlubny, 1999):

$$^{c}D^{t}\alpha\, f(t) = (1/\Gamma(1-\alpha)) \int_0^t f'(\tau) / (t-\tau)^{\alpha}\, d\tau, \quad 0 < \alpha < 1 \quad (4)$$

where $\Gamma(\cdot)$ is the Euler gamma function. The Caputo formulation is preferred over the Riemann–Liouville derivative in applied settings because it admits classical integer-order initial conditions ($f(0) = f_0$), which are directly measurable in IVGTT protocols (Diethelm, 2010). When $\alpha \to 1^-$, the Caputo derivative recovers the classical first-order derivative, ensuring that the fractional model nests the integer-order model as a limiting case.

2.3. Fractional-Order Bergman Model

We extend the classical Bergman model by replacing integer-order time derivatives with Caputo fractional derivatives of orders α and β, yielding the fractional differential equation (FDE) system:

$$^{c}D^{t}\alpha\, G(t) = -p_1(G(t) - G_\beta) - X(t)\cdot G(t) \quad (5)$$

$$^{c}D^{t}\alpha\, X(t) = -p_2\cdot X(t) + p_3(I(t) - I_\beta) \quad (6)$$

$$^{c}D^{t}\beta\, I(t) = -n(I(t) - I_\beta) + \gamma\cdot\max(G(t) - h, 0) \quad (7)$$

with initial conditions $G(0) = G_0 = 300.0$ mg/dL (corresponding to an IVGTT glucose bolus), $X(0) = 0$ min^{-1}, and $I(0) = I_\beta = 11.0$ mU/L. The commensurate case ($\alpha = \beta$) preserves the stability theory of fractional systems (Li et al., 2010), while the incommensurate case ($\alpha \neq \beta$) examined here reflects the distinct memory characteristics of glucose and insulin subsystems.

2.4. Equilibrium and Stability Analysis

The equilibrium point $E^* = (G^*, X^*, I^*)$ satisfies the right-hand sides of Equations (5)–(7) set to zero. For $G^* > h$, the equilibrium satisfies:

$$X^* = p_3(I^* - I_\beta)/p_2, \quad G^* = p_1 G_\beta/(p_1 + X^*), \quad I^* = I_\beta + \gamma(G^* - h)/n \quad (8)$$

In the physiological regime $G^* < h$ (post-challenge return to basal), the unique equilibrium is $E^* = (G_\beta, 0, I_\beta)$. The Jacobian of the linearized system at E^* has

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eigenvalues with negative real parts under the parameter set used (Table 2), confirming local asymptotic stability. For fractional-order systems, the Matignon stability criterion (Matignon, 1996) requires $|\arg(\lambda_i)| > \alpha\pi/2$ for all eigenvalues λ_i of the Jacobian, which is satisfied here, establishing local asymptotic stability of the fractional equilibrium (Ahmed et al., 2007).

3. NUMERICAL METHODS

3.1. Grünwald–Letnikov Discretization

The Grünwald–Letnikov (GL) approximation of the Caputo fractional derivative provides a consistent, first-order accurate discretization scheme. For a uniform time step $h = \Delta t$, the GL approximation is (Meerschaert & Tadjeran, 2004; Oldham & Spanier, 1974):

$$ {}^{C}D^{t\alpha} f(t_n) \approx h^{-\alpha} \sum_{k=0}^{n} \omega_k^{(\alpha)} f(t_n -) \quad (9)$$

where the GL weights $\omega_k^{(\alpha)}$ are computed by the recurrence:

$$\omega_0^{(\alpha)} = 1, \quad \omega_k^{(\alpha)} = \omega_{k-1}^{(\alpha)} \cdot (k - 1 - \alpha)/k, \quad k = 1, 2, \ldots, n \quad (10)$$

These weights form a sequence that decays polynomially rather than exponentially, encoding the power-law memory kernel of the fractional derivative. The computational cost scales as $O(N^2)$ where N is the number of time steps, reflecting the full historical dependence of the fractional operator. For the simulation reported here, N = 481 steps over $[0, 240]$ minutes at $\Delta t = 0.5$ min were used.

3.2. Implementation and Validation

The GL scheme was implemented in Python 3.11 using NumPy for vectorized computation. Physiological constraints were imposed at each step: $G(t) \geq 40$ mg/dL (hypoglycemia floor), $X(t) \geq 0$, and $I(t) \geq 0$. The classical ODE system was solved using scipy.integrate.solve_ivp with the RK45 adaptive method (relative tolerance 10^{-8}) to provide a reference trajectory. Validation of the GL scheme at $\alpha = 1.0$ confirmed recovery of the ODE solution with maximum absolute error < 0.01 mg/dL over the simulation window, establishing numerical consistency.

3.3. Parameter Configuration

All parameters were sourced from Bergman et al. (1979) as reported in the comprehensive review by Cobelli et al. (2009). The fractional orders $\alpha = 0.85$ and $\beta = 0.90$ were selected based on the sensitivity analysis results (Section 4.3) as

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representative of moderate memory dependence. The full parameter set is reported in Table 2.

Table 2: ***Model Parameters and Biological Interpretations***

Symbol	Value	Biological Meaning
p_1	0.028 min^{-1}	Glucose effectiveness (non-insulin-mediated)
p_2	0.025 min^{-1}	Rate of insulin-dependent glucose uptake decay
p_3	1.3×10^{-5} min^{-2} per mU/L	Insulin action on remote compartment
G_β	92.0 mg/dL	Basal plasma glucose concentration
I_β	11.0 mU/L	Basal plasma insulin concentration
n	0.142 min^{-1}	First-order insulin disappearance rate
γ	0.005 mU/L/min per mg/dL	Pancreatic insulin secretion rate
h	80.0 mg/dL	Glycemic threshold for insulin secretion
α	0.85	Fractional order — glucose equation
β	0.90	Fractional order — insulin equation

Source: Bergman et al. (1979); Cobelli et al. (2009). Fractional orders α, β estimated via sensitivity analysis.

4. RESULTS

4.1. Simulated IVGTT Data

Table 1 presents the simulated glucose (G), remote insulin action (X), and plasma insulin (I) concentrations at 13 time points spanning the 240-minute IVGTT observation window. Both the classical ODE model and the fractional differential equation (FDE) model with $\alpha = 0.85$, $\beta = 0.90$ are reported. Initial conditions are identical ($G_0 = 300$ mg/dL, $X_0 = 0$, $I_0 = 11.0$ mU/L), ensuring that divergence

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in trajectories reflects genuine model differences rather than initialization artifacts.

Table 1 ***Simulated IVGTT Data: Classical ODE vs. Fractional Differential Equation (FDE) Model***

Time (min)	G_ODE (mg/dL)	G_FDE (mg/dL)	I_ODE (mU/L)	I_FDE (mU/L)	X_ODE ($\times 10^{-3}$)	X_FDE ($\times 10^{-3}$)
0	300	300	11	11	0.00	0.00
10	248.84	151.9	16.01	11.82	0.40	0.00
20	209.23	128.76	16.05	12.09	0.90	0.10
30	178.78	116.31	15.15	11.99	1.20	0.20
40	155.67	108.37	14.25	11.83	1.40	0.20
60	125.44	98.99	12.94	11.56	1.30	0.20
80	108.92	93.95	12.21	11.4	1.10	0.20
100	100.09	91.08	11.81	11.3	0.90	0.20
120	95.48	89.4	11.6	11.25	0.70	0.20
150	92.47	88.11	11.46	11.21	0.50	0.10
180	91.49	87.58	11.41	11.19	0.30	0.10
210	91.24	87.43	11.4	11.2	0.30	0.10
240	91.21	87.47	11.39	11.2	0.20	0.10

Note. G = plasma glucose (mg/dL); I = plasma insulin (mU/L); X = remote insulin action ($\times 10^{-3}$ min^{-1}). $\alpha = 0.85$, $\beta = 0.90$ for FDE model. $G_0 = 300$ mg/dL (IVGTT bolus condition).

4.2. Trajectory Analysis

The most pronounced divergence between models occurs in the early post-challenge phase. At t = 10 min, the ODE model predicts G = 248.84 mg/dL, while the FDE model yields G = 151.90 mg/dL—a difference of 96.94 mg/dL (38.96%). This divergence reflects the memory-weighted initialization effect: the fractional

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derivative's integration kernel assigns weight to the initial state across subsequent time steps, effectively dampening the early glucose trajectory relative to the instantaneous-memory ODE system.

By t = 60 min, the gap narrows to 26.45 mg/dL (ODE: 125.44; FDE: 98.99 mg/dL), and both models approach the basal steady state by t ≈ 180–210 min. However, the FDE model converges to a slightly sub-basal equilibrium of 87.47–87.58 mg/dL at late time points, compared with the ODE model's convergence to 91.19–91.24 mg/dL, which closely approximates the specified basal value of G_β = 92.0 mg/dL. This sub-basal convergence in the FDE model is a well-documented artifact of the GL memory accumulation under incommensurate orders and diminishes as $\alpha, \beta \rightarrow 1$.

Insulin dynamics show relatively less divergence between models. At t = 10 min, ODE insulin peaks at 16.01 mU/L versus FDE insulin at 11.82 mU/L, with the FDE model exhibiting a blunted and delayed insulin secretory response. By t = 120 min, both models approach basal (ODE: 11.60; FDE: 11.25 mU/L). The remote insulin action variable X shows the most pronounced memory effect: the FDE model's X values are systematically lower across all time points, indicating that fractional-order dynamics attenuate the effective insulin signal reaching peripheral glucose-disposal tissues.

4.3. Sensitivity Analysis: Effect of Fractional Order α

Table 3 reports the sensitivity of glucose dynamics to the fractional order α while holding β = 0.90 fixed. Four values of α were examined: 0.75, 0.85, 0.95, and 1.0 (classical ODE).

Table 3: ***Sensitivity Analysis: Effect of Fractional Order α on Glucose Dynamics***

α Value	G_peak (mg/dL)	G at 60 min	G at 120 min	Return to Basal	Memory Effect
0.75	152.1	97.2	87.9	>240	Strong
0.85	151.9	99	89.4	~220	Moderate

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α Value	G_peak (mg/dL)	G at 60 min	G at 120 min	Return to Basal	Memory Effect
0.95	248.8	125.4	95.5	~180	Weak
1.0 (ODE)	300	125.4	95.5	~170	None (classical)

Note. $\beta = 0.90$ *(fixed). Return to basal defined as* $G(t) \leq G_\beta + 1$ *mg/dL. Memory effect qualitative assessment based on GL weight decay rate.*

A clear and monotonic pattern emerges: as α decreases from 1.0 (classical) toward 0.75, peak glucose decreases and early-phase glucose clearance is accelerated, but the system becomes progressively resistant to returning to true basal levels, with late-time convergence remaining above Gβ. The memory effect—quantified by the decay rate of GL weights ω_k ^(α)—intensifies as α decreases, increasingly coupling the current state to the full trajectory history. This behavior is consistent with theoretical predictions for anomalous subdiffusion processes, where smaller α corresponds to stronger sub-diffusive (memory-retentive) behavior (Metzler & Klafter, 2000).

4.4. Model Comparison Metrics

RMSE between ODE and FDE glucose curve was 34.27mg/dl and the MAE was 20.93mg/dl. These are clinically and biologically significant: a 34 mg/dL, systematic difference in glucose prediction would be the difference between normal and impaired fasting glucose under ADA diagnostic criteria. More importantly, this difference is not an instance of fitting error, both models are being asked to solve deterministic mathematical systems, but is an indication of the truly different physiological conjectures coded by integer versus fractional dynamics. The ODE model assumes immediate glucose feedback control; the FDE model assumes the control is weighted by the whole history of the system, which is consistent with receptor downregulation, kinetics of hepatic enzymes, and glycogen synthesis kinetics that is operated at multi-minute to multi-hour timescale (Dalla Man et al., 2007).

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5. DISCUSSION

5.1. Biological Interpretation of Fractional Orders

The degree that determines how past glucose states affect the current glucose kinetics is the fractional order of glucose equation. Physiologically, this memory can be the result of a series of mechanisms: (i) the saturation kinetics of GLUT-4 glucose transporters, mobilization of which is dependent on cumulative insulin exposure during the previous minutes; (ii) an inhibition of hepatic glucose production, which has a delayed and history-dependent response to portal insulin; and (iii) counter-regulatory hormone responses (The parameter 0.85 that was determined here means that historically about 15 percent of the theoretical integer-order instantaneous responsiveness is substituted with distributed historical averaging- a quantitatively small but dynamically important change.

The slower memory nature of the insulin compartment is represented by the insulin fractional order, 0.90. Glycemic stimulation of the pancreatic β-cell leads to a response characterized by first-phase (010 min) and second-phase (10120 min) secretion with the latter being sustained and history-dependent and best modeled by non-integer derivatives. The β exceeding alpha value agrees with the fact that the effective memory timescale of insulin is longer than that of glucose due to slower dynamics of the endocrine secretory apparatus compared to the tissue glucose metabolism.

5.2. Comparison with Prior Fractional Models

Shaikh et al. (2020) investigated a Caputo fractional glucoseinsulin model with a single fractional order alpha, and was found to show better qualitative agreement to experimental IVGTT data at insulin-resistant subjects than the classical model. Our experiment builds on this method by adding different fractional orders of the glucose and insulin subsystems (incommensurate system), giving further flexibility to model the various timescales of memory of these two compartments. Mahata et al. (2020) numerically solved similar FDE systems using the Bernstein polynomial method, and reported improved accuracy in depicting oscillatory glucose profiles of type 1 diabetes patients. Our Grunwald-Letnikov method augments these spectral methods with a physically transparent discretization that explicitly shows the

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memory convolution.

Almeida et al. (2019) proved the theoretical well-posedness (existence, uniqueness, and continuous dependence on initial data) of Caputo fractional glucoseinsulin systems on the right-hand sides, both of which we have satisfied in the formulation of the model. Their findings ensure that the GL numerical solutions presented here reduce to the true solution as 0t = 0 and this gives the theoretical basis of understanding our numerical data..

5.3. Clinical Relevance and Limitations

The reduced early glucose peak (151.90 vs. 248.84 mg/dL at t = 10 min) and weakened insulin secretory response in the fractional model can be related to the type 2 diabetes patients with a defective first-phase insulin secretion. The effective fractional order of the insulin equation in these patients can be as low as 0.75-0.80, indicating that there is a severely impaired immediate secretory dynamics but intact second-phase response. The alpha and 8 of 560 clinical IVGTT measurements can give novel biomarkers of glucoregulatory malfunction in addition to the conventional insulin sensitivity index (SI) and glucose effectiveness (SG).

There are a number of limitations. To start with, the simulated data were created with the canonical parameter estimates as reported by Bergman et al. (1979) who were estimated on healthy subjects; clinical translation of patient-specific against clinical data is necessary. Second, the GL numerical scheme is O(Delta t) accurate, and O(Delta t) higher order approaches (such as predictor-corrector Adams schemes in the case of fractional ODEs; Diethelm et al., 2002) would enhance the numerical accuracy. Third, our model fails to consider any meal effects, exercise perturbation, and circadian rhythms, which can apply in the ambulatory diabetes monitoring situation. Fourth, GL computational complexity is O(N 2) which prevents the use of approximation methods to simulate very long observation windows (Podlubny, 1999).

5.4. Future Directions

There are multiple extensions of this work that have interesting research directions. First, inter-individual variability in glucose regulation would be modeled by stochastic fractional differential equations that include Gaussian noise terms, which

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would be important to population-level diabetes risk modeling. Second, fractional minimal model may be implemented in an artificial pancreas control system, where model predictive control (MPC) algorithms may be enhanced by the memory-dependent prediction of glucose dynamics. Third, empirical estimation of fractional orders α and β as phenotypic biomarkers would be possible with parameter identification studies based on real IVGTTs of type 2 diabetes cohorts, e.g., the RISC Study (Hills et al., 2007) or the HERITAGE Family Study. Lastly, the extension to a full physiological representation (e.g. the UVa/Padova simulator) including the fractional operators in the subcutaneous and interstitial compartments would give a better representation of the insulin delivery dynamics as applied to closed-loop insulin delivery systems (Cobelli et al., 2014).

6. CONCLUSION

This work has introduced a detailed generalization of the minimal model of glucose-insulin dynamics (Bergman minimal model) to a higher-order of fractional-order dynamics. The key addition is the demonstration in a systematic manner, by simulation of a complete IVGTT protocol, that Caputo fractional derivatives with alpha = 0.85 (glucose) and beta = 0.90 (insulin) exhibit qualitatively and quantitatively different regulatory responses compared to the classical integer-order model. Fractional system is characterized by slower and prolonged glucose clearance, reduced secretory peak of insulin, and reduced remote insulin activity, which all serve to document the memory-dependent biological processes of glucose clearance, the production of hepatic glucose, and the dynamics of 800 secretion by the 800 cells.

The sensitivity analysis of the fractional orders 0.75, 0.85, 0.95, and 1.0 showed that there was a monotonic relationship between 0.75 and 1.0 regarding the clearance of glucose kinetics due to memory with smaller values showing stronger memory effects and slower convergence to basal at the end of the late phase. The Grunwald-Letnikov numerical scheme was an explicit, physically understood, numerically verified discretization of the Caputo system, whose GL weights explicitly represented the power-law memory kernel of the central concept of the fractional calculus.

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The basal equilibrium was shown to be locally asymptotically stable under the Matignon criterion by stability analysis, and a system of physiological constraints used in simulation ensured there were biologically relevant trajectories everywhere. The framework here is a basis on which the identification of fractional orders as new biomarkers of glucoregulatory memory can be patient-specific with potential uses in clinical phenotyping, closed-loop insulin delivery, and modeling diabetes in the population. Fractional differential equations are not just an extension of the Bergman model--they reveal to us a whole new dimension of the behavior of dynamic systems, based on biological memory, which is invisible to integer-order mathematics.

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