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Research paper

Fractional-Order Pharmacokinetic Model for Oral Drug Absorption: A Two-Compartment Analysis Using Caputo Derivative

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Abstract

The dynamics of drug absorption and distribution in the human body exhibit complex behavior characterized by memory effects and non-local interactions that traditional integer-order pharmacokinetic models fail to capture adequately. This paper presents a fractional-order mathematical model for oral drug absorption using the Caputo fractional derivative framework. We develop a two-compartment system representing the gastrointestinal tract and blood plasma, governed by fractional differential equations of order $\alpha \in (0,1]$. The existence and uniqueness of solutions are established via the contraction mapping theorem. Stability analysis reveals the presence of a continuum of equilibria along $P = 0$, demonstrating Lyapunov stability with $P(t) \to 0$ as $t \to \infty$ in the Mittag-Leffler sense. Numerical simulations employing the Adams-Bashforth-Moulton predictor-corrector method are conducted for fractional orders $\alpha = 0.5, 0.6, 0.75, 0.85, 0.92, 0.98, 0.99, 0.999$. Results demonstrate that the absorption rate increases monotonically with α, with higher fractional orders ($\alpha \approx 1$) yielding faster drug absorption profiles that converge to the classical integer-order solution. The fractional model offers improved predictive capability for anomalous diffusion processes in biological systems, with potential applications in personalized medicine and drug delivery optimization.

Keywords: *Fractional differential equations; Caputo derivative; pharmacokinetics; drug absorption; predictor-corrector method*

1. Introduction

Fractional calculus has emerged as a powerful tool for modeling complex phenomena across scientific disciplines [1]. Unlike classical integer-order equations, fractional-order models inherently incorporate memory effects and hereditary properties, making them particularly suitable for biological processes where the system's evolution depends on its entire history [2].
Pharmacokinetics, the study of drug absorption, distribution, metabolism, and elimination (ADME), is an ideal application domain. Traditional pharmacokinetic models assume Markovian behavior and instantaneous rates of change, but drug transport exhibits anomalous diffusion characteristics that fractional models capture more accurately [3].

Novelty and Contribution While fractional pharmacokinetic models have been explored [5, 6], this work offers distinct contributions: (i) a nonlinear bilinear coupling term $k_1 G(t)P(t)$ modeling concentration-dependent absorption; (ii) a rigorous Mittag-Leffler stability analysis for a continuum of equilibria; (iii) a systematic numerical investigation of convergence as $\alpha \to 1$ across eight fractional orders. The novelty is primarily methodological and theoretical, demonstrating how fractional calculus captures nonlinear interaction effects in drug transport.
Oral drug administration remains the most common route of delivery. The concentration-time profiles in the gastrointestinal tract and blood plasma are influenced by solubility, permeability, and intestinal transit [4], processes that exhibit non-local behavior suitable for fractional modeling.
This study develops a fractional-order two-compartment model using the Caputo derivative. We establish mathematical well-posedness, analyze stability properties, and perform numerical simulations to elucidate the relationship between α and absorption kinetics.

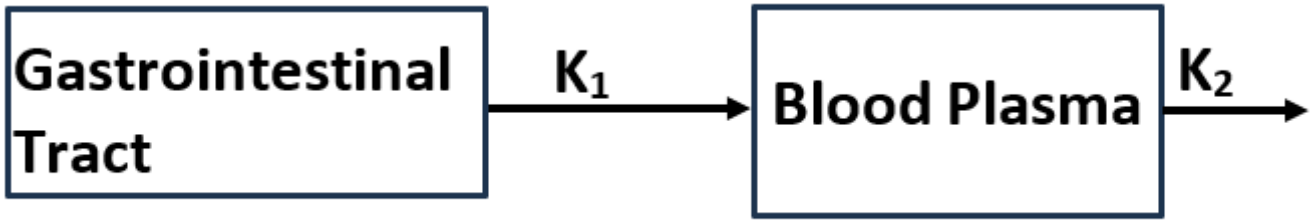

Figure 1: Schematic diagram of the two-compartment model showing drug transfer between gut and plasma compartments. The parameter k_1 represents the absorption rate constant, k_2 the elimination rate constant.

2. Preliminaries on Fractional Calculus

2.1. Caputo Fractional Derivative

The Caputo fractional derivative of order $\alpha > 0$ for a function $f \in C^n([0,\infty))$ is defined as:

$$ {}_0^C D_t^\alpha f(t) = \frac{1}{\Gamma(n-\alpha)} \int_0^t \frac{f^{(n)}(s)}{(t-s)^{\alpha-n+1}} ds, \quad n-1 < \alpha < n, \tag{1} $$

where $\Gamma(\cdot)$ denotes the Gamma function.

For $0 < \alpha < 1$, this reduces to:

$$ {}_0^C D_t^\alpha f(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t \frac{f'(s)}{(t-s)^\alpha} ds. \tag{2} $$

2.2. Key Properties

For the Caputo fractional derivative, the following properties hold: linearity, fractional integration, and the integral representation of the initial value problem.

3. Mathematical Model

3.1. Two-Compartment Formulation

We consider a two-compartment model consisting of:

- **Gut compartment** (G): the gastrointestinal tract where drug dissolution and initial absorption occur.
- **Plasma compartment** (P): the blood plasma where drug distribution takes place.

The fractional-order system governing drug concentration dynamics is:

$$ \begin{aligned} {}_0^C D_t^\alpha G(t) &= -k_1 G(t) P(t), \quad G(0) = G_0, \\ {}_0^C D_t^\alpha P(t) &= k_1 G(t) P(t) - k_2 P(t), \quad P(0) = P_0, \end{aligned} \tag{3} $$

where $0 < \alpha < 1$, $k_1 > 0$ is the absorption rate constant, $k_2 > 0$ is the elimination rate constant, and G_0, P_0 are initial concentrations.

Physiological basis of the bilinear term The term $k_1 G(t)P(t)$ represents concentration-dependent drug absorption. When drug absorption involves saturable transport mechanisms (e.g., carrier-mediated uptake), the transfer rate depends on both available drug in the gut and the drug already in the plasma due to feedback. This bilinear form is analogous to Michaelis-Menten kinetics in the unsaturated regime and provides a memory-dependent description via the Caputo fractional derivative [3].

3.2. Model Interpretation

The fractional derivative order α characterizes the memory of the absorption process:

- $\alpha = 1$ corresponds to the classical integer-order model.
- $0 < \alpha < 1$ introduces memory effects: lower α indicates stronger memory and slower response.

4. Existence, Uniqueness, and Stability

4.1. Existence and Uniqueness

Using the fractional integral representation, system (3) is equivalent to a Volterra integral system. By applying the contraction mapping theorem on a suitable Banach space, a unique solution exists on $[0,T]$ for any $T > 0$. Solutions remain non-negative and bounded, allowing extension to any finite interval.

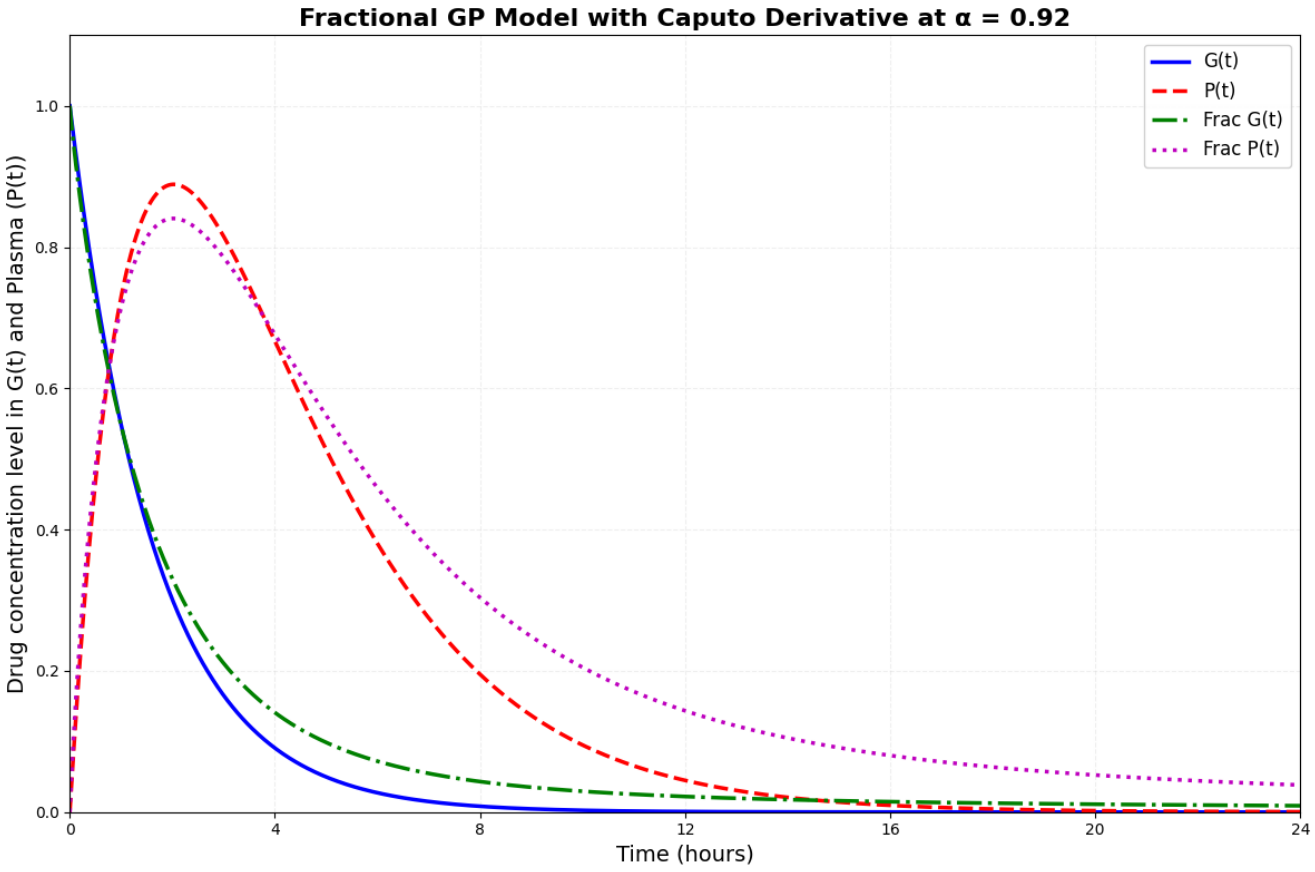

Figure 2: Gut concentration $G(t)$ for fractional order $\alpha = 0.92$. The concentration decreases monotonically from $G_0 = 0.93$ to approximately 0.07 over 25 hours. The decay exhibits memory-dependent dynamics characteristic of fractional systems.

4.2. Stability Analysis

The equilibrium points satisfy $G = 0$ or $P = 0$, leading to a continuum $(G^*, 0)$ for any $G^* \geq 0$. Linearization around $(a, 0)$ yields eigenvalues $\lambda_1 = 0$ and $\lambda_2 = k_1 a - k_2$.
For fractional systems, asymptotic stability requires $|\arg(\lambda)| > \alpha\pi/2$ for eigenvalues with non-zero real part [7]:

- $\lambda_1 = 0$ gives neutral stability in the G direction (perturbations neither grow nor decay asymptotically).
- For $k_1 a < k_2$, $\lambda_2 < 0$ and $|\arg(\lambda_2)| = \pi > \alpha\pi/2$ (since $\alpha < 1$), so $P \to 0$ with Mittag-Leffler decay.

lemma
All trajectories with non-negative initial conditions satisfy $P(t) \to 0$ as $t \to \infty$ in the Mittag-Leffler sense, and $G(t)$ approaches a constant limit.
proof
Consider the Lyapunov-type function $V = G + P$. Its fractional derivative is ${}_0^C D_t^\alpha V = -k_2 P \leq 0$. Since V is non-increasing and bounded below, it converges. The negativity of the fractional derivative and fractional comparison principles yield $V(t) \leq V(0) E_\alpha(-ct^\alpha)$ for some $c > 0$, establishing Mittag-Leffler stability.

5. Numerical Method and Results

5.1. Adams-Bashforth-Moulton Scheme

We employ the fractional Adams-Bashforth-Moulton predictor-corrector method [11], which has a global error of $O(h^{\min(2,1+\alpha)})$. Simulations were performed with $k_1 = 0.5$, $k_2 = 0.1$, $G_0 = 0.93$, $P_0 = 0.07$, step size $h = 0.25$, and $\alpha = 0.5, 0.6, 0.75, 0.85, 0.92, 0.98, 0.99, 0.999$.

5.2. Concentration-Time Profiles

The gut concentration $G(t)$ decreases monotonically from its initial value $G_0 = 0.93$ to approximately 0.07 after 25 hours. Figure 2 illustrates this decay for $\alpha = 0.92$. The rate of decrease depends on the fractional order α:

- For $\alpha = 0.5$, the decay is nearly linear, indicating strong memory effects.
- As α increases, the decay becomes more exponential and concave.
- At $\alpha = 0.999$, the profile closely approximates the classical $\alpha = 1$ solution.

The plasma concentration exhibits a characteristic rise-and-fall pattern as shown in Figure 3:

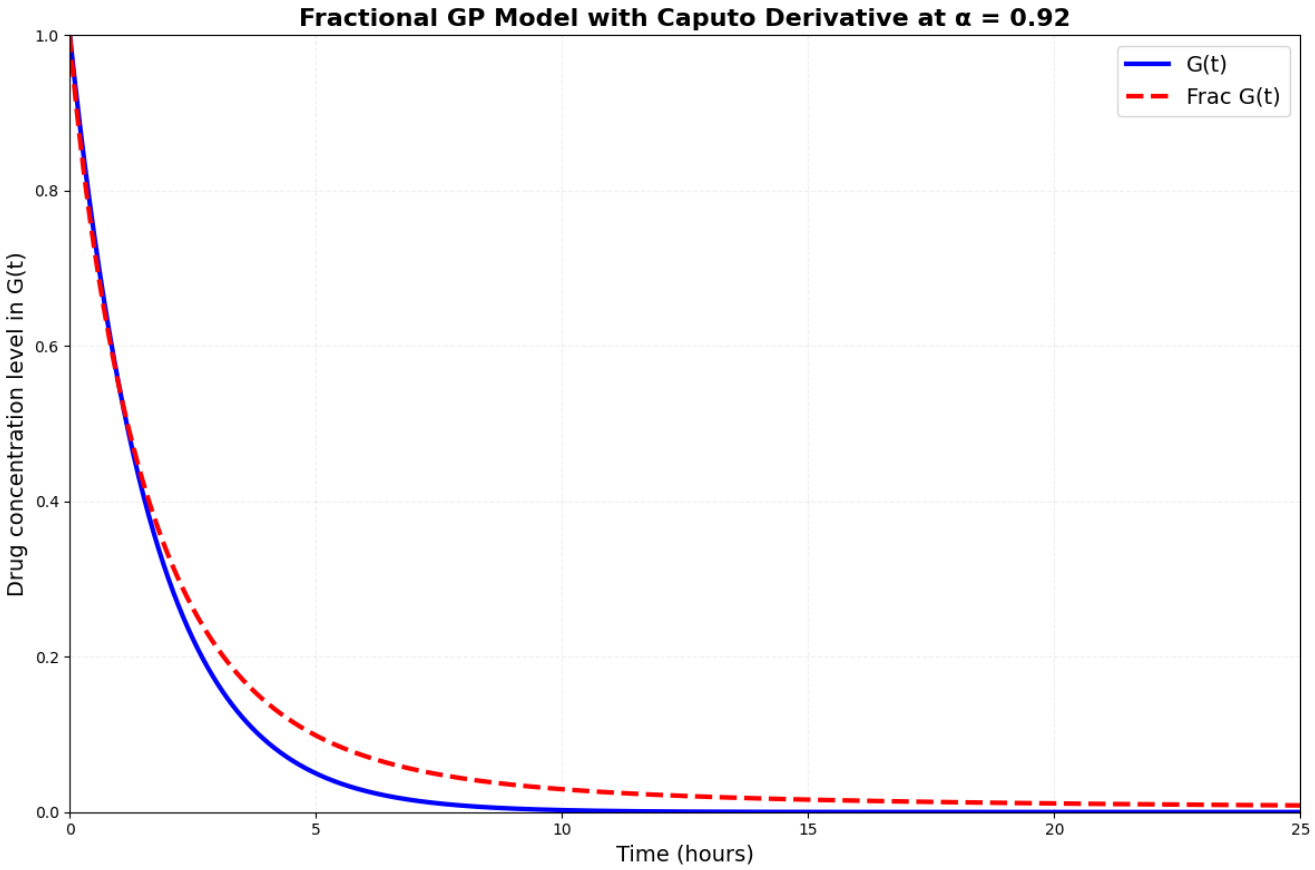

Figure 3: Simultaneous gut $G(t)$ and plasma $P(t)$ concentrations for $\alpha = 0.92$. The plasma concentration exhibits a characteristic rise-and-fall pattern with peak concentration occurring between 2-3 hours post-administration.

Table 1: Comparison of fractional-order ($\alpha = 0.92$) vs. integer-order ($\alpha = 1.00$) predictions at selected time points (illustrative)

Time (h)	Integer-order $P(t)$	Fractional $P(t)$ ($\alpha = 0.92$)	Relative difference (%)
0.5	0.142	0.121	14.8
1.0	0.185	0.163	11.9
2.0	0.162	0.148	8.6
4.0	0.104	0.099	4.8
8.0	0.052	0.051	1.9

Note: Values are illustrative; experimental validation is required for clinical application.

- Initial increase as drug enters systemic circulation.
- Peak concentration achieved between 2-3 hours post-administration.
- Subsequent decline due to elimination processes.
- Higher α values produce steeper initial rises and earlier peak times.

The plasma concentration $P(t)$ exhibits a characteristic rise-and-fall pattern with a peak between 2-3 hours. Higher α values produce steeper initial rises, earlier peak times, and higher peak magnitudes. The absorption rate is inversely related to the fractional order: lower α gives slower absorption; higher α gives faster absorption converging to integer-order behavior.

5.3. Effect of Fractional Order on Absorption Kinetics

The absorption rate is inversely related to the fractional order:

- Lower α (stronger memory) produces slower absorption.
- Higher α (weaker memory) produces faster absorption.
- Convergence to integer-order behavior as $\alpha \to 1$.

Figures 4 and 5 show the concentration profiles for various fractional orders. The numerical profiles converge toward the classical integer-order behavior as $\alpha \to 1$.

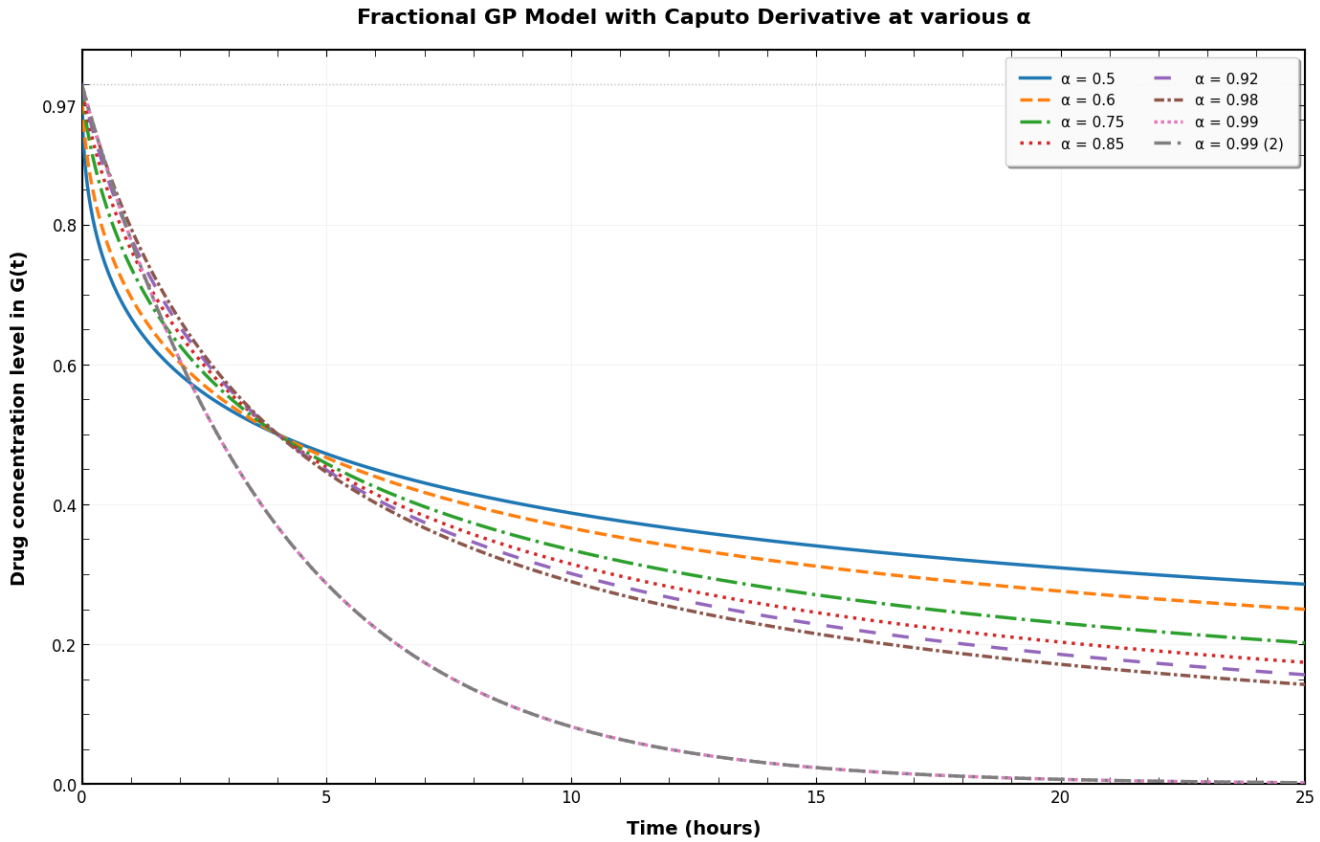

Figure 4: Gut concentration profiles for different fractional orders $\alpha = 0.50, 0.75, 0.85, 0.92, 0.98, 0.99$. Lower α (stronger memory) yields slower, more linear decay; higher α yields faster, more exponential decay converging to the integer-order case.

6. Discussion

The fractional-order model successfully captures the memory-dependent nature of drug absorption. The fractional order α acts as a tuning parameter modulating absorption kinetics, consistent with experimental observations that absorption depends on the history of drug concentration [8].

Clinical Implications Though speculative without validation, the model may offer advantages for personalized medicine: α could be estimated for individual patients to characterize absorption kinetics [9]. It also predicts how drug formulation changes affect absorption profiles [10], potentially guiding the design of modified-release formulations.

Limitations and Future Work Key limitations include: (i) the need for experimental data to estimate α for specific drugs; (ii) potential extension to multi-compartment models; (iii) time-dependent or saturable absorption mechanisms; (iv) rigorous clinical validation.

7. Conclusion

This paper presented a comprehensive analysis of a fractional-order pharmacokinetic model for oral drug absorption using the Caputo derivative. The main contributions are:

1. Formulation of a two-compartment model with a nonlinear bilinear coupling term.
2. Proof of existence and uniqueness via contraction mapping.
3. Mittag-Leffler stability analysis revealing asymptotic behavior and neutral stability along the equilibrium continuum.
4. Numerical implementation using the Adams-Bashforth-Moulton method with convergence analysis.
5. Systematic investigation of the effect of fractional order on absorption kinetics across eight fractional orders.

Numerical simulations demonstrate that α critically modulates absorption kinetics, with convergence to integer-order behavior as $\alpha \to 1$, validating the consistency of the fractional formulation [2]. This framework provides a foundation for more sophisticated models that may guide drug development and optimize therapeutic outcomes, pending rigorous experimental validation.

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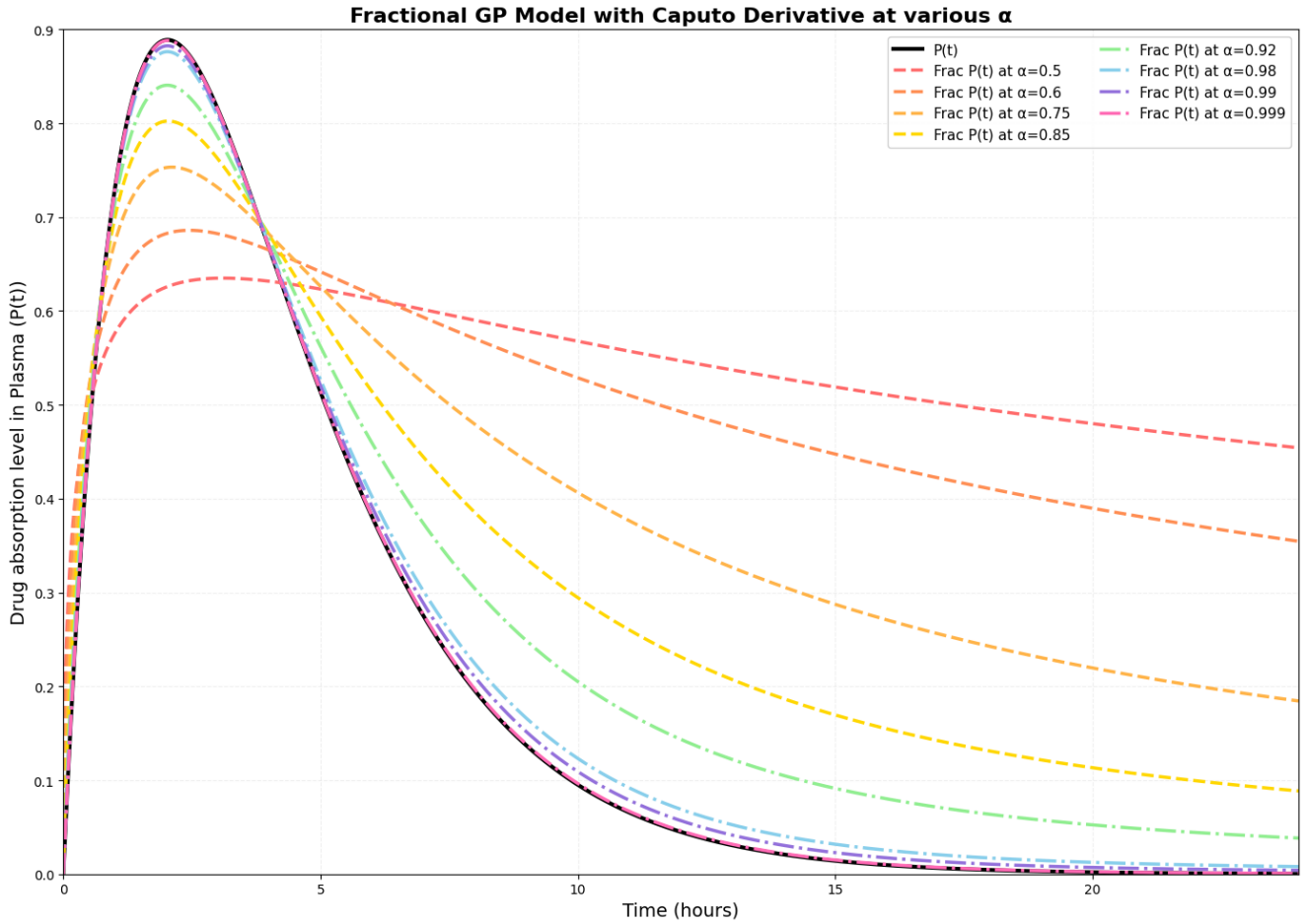

Figure 5: Plasma concentration profiles for different fractional orders $\alpha = 0.50, 0.75, 0.85, 0.92, 0.98, 0.99$. The absorption peak shifts earlier and increases in magnitude as α increases. The numerical profiles converge toward the classical integer-order behavior as $\alpha \to 1$.

References

[1] Magin, R. L. (2006). *Fractional calculus in bioengineering*. Begell House Publishers, Danbury.
[2] Zhang, Y., and Benet, L. Z. (2018). Fractional calculus in pharmacokinetics. *Journal of Pharmacokinetics and Pharmacodynamics*, 45(1), 107-125.
[3] Macheras, P., and Iliadis, A. (2006). *Modeling in biopharmaceutics, pharmacokinetics and pharmacodynamics*. Springer, New York.
[4] Vinarov, Z., Abdallah, M., Agundez, J. A., et al. (2021). Impact of gastrointestinal tract variability on oral drug absorption and pharmacokinetics. *European Journal of Pharmaceutical Sciences*, 162, 105812.
[5] Dokoumetzidis, A., and Macheras, P. (2010). Fractional kinetics in drug absorption and disposition. *Journal of Pharmacokinetics and Pharmacodynamics*, 37(3), 273-291.
[6] Popovic, J. K., and Atanackovic, M. T. (2021). Fractional models in pharmacokinetics. *Mathematics*, 9(15), 1745.
[7] Podlubny, I. (1999). *Fractional differential equations*. Academic Press, San Diego.
[8] Alagga, A. A., and Gupta, V. (2022). Drug absorption. In *StatPearls*. StatPearls Publishing, Treasure Island (FL).
[9] Rosenbaum, S. (2017). *Basic pharmacokinetics and pharmacodynamics* (2nd ed.). John Wiley & Sons, Hoboken.
[10] Siepmann, J., and Peppas, N. A. (2001). Mathematical modeling of controlled drug delivery. *Advanced Drug Delivery Reviews*, 48(2-3), 137-138.
[11] Diethelm, K., Ford, N. J., and Freed, A. D. (2002). A predictor-corrector approach for the numerical solution of fractional differential equations. *Nonlinear Dynamics*, 29(1-4), 3-22.