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MATHEMATICS AREA

College Algebra & Applied Calculus

Comparative Rational Pharmacokinetic Modeling for Therapeutic Window Adjustment:

A Computational–Analytical Framework Integrating College Algebra, Applied Calculus, and Model Selection Theory

Research Project Submitted for
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Abstract

Pharmacokinetic (PK) modeling plays a central role in individualized pharmacotherapy; however, its mathematical foundations are rarely taught through sustained engagement with authentic modeling practices. This study presents a reproducible educational–computational framework designed to promote model-based reasoning, quantitative literacy, and evidence-informed model selection through analytically tractable pharmacokinetic representations. Four candidate time–concentration models—linear, quadratic, exponential, and rational—are systematically compared using simulated datasets representing a healthy subject and a patient with renal insufficiency. The data are generated from the rational model $C(t) = \dfrac{at}{bt^2 + 1}$ with $a = 4$ and $b = 1$ (healthy) or $b = 0.25$ (renal), allowing transparent evaluation of model recovery, parameter interpretation, and peak behavior.

Nonlinear least-squares estimation (Levenberg–Marquardt) demonstrates that the rational model recovers the generating parameters within numerical precision for noiseless data, whereas alternative models fail to capture either the peak or the asymptotic decay. Model comparison using MSE, AIC, BIC, Akaike weights, and residual diagnostics overwhelmingly favors the rational formulation. Closed-form derivative analysis yields exact expressions for peak time and peak concentration, $t_{\max} = \dfrac{1}{\sqrt{b}}$ and $C_{\max} = \dfrac{a}{2\sqrt{b}}$, enabling direct connections between mathematical structure and pharmacokinetic interpretation. A reduction of b from 1 to 0.25, representing impaired elimination, produces a 100% increase in peak concentration and a 100% prolongation of peak time.

A Padé-like approximation links the rational model to the classical Bateman function, situating the framework within established pharmacokinetic theory. An extension incorporating synthetic measurement noise illustrates robustness, uncertainty, and the limits of inference under data imperfection. All code, data, and diagnostics are provided in accordance with open-science and FAIR principles. The framework is explicitly intended for educational and exploratory purposes, not for clinical decision-making, and is positioned as a transferable model-based literacy environment for STEM and pharmacokinetics education.

Keywords: Pharmacokinetic modeling; rational functions; model-based reasoning; model selection; mathematical modeling competencies; computational reproducibility; STEM education; therapeutic window.

Contents

1 Introduction

1.1 Motivation and Context

Maintaining drug plasma concentrations within the *therapeutic window*—the interval bounded by the minimum effective and minimum toxic concentrations—remains one of the central challenges of clinical pharmacology and therapeutic drug monitoring [11]. Physiological variability, particularly alterations in renal function, hepatic metabolism, age, and comorbidities, can substantially modify drug disposition and elimination, increasing the risk of accumulation, toxicity, or therapeutic failure. Consequently, pharmacokinetic (PK) models have become indispensable tools for interpreting concentration–time profiles, understanding drug behavior, and supporting evidence-informed dosing decisions [6, 8, 14].

Beyond their clinical significance, pharmacokinetic processes provide an exceptionally rich context for mathematical modeling because they connect abstract mathematical structures with phenomena of immediate scientific and societal relevance. Concentration–time relationships naturally embody concepts central to College Algebra, Calculus, Statistics, and Applied Mathematics, including functional behavior, asymptotic analysis, optimization, parameter estimation, sensitivity analysis, uncertainty quantification, and model validation [17]. As a result, pharmacokinetics offers a particularly valuable interdisciplinary setting in which learners can explore how mathematical models are formulated, interpreted, evaluated, and refined to represent real-world systems.

At the same time, contemporary scientific practice increasingly depends on computational modeling, reproducible data analysis, and quantitative decision making. Across disciplines, researchers are expected not only to apply mathematical models but also to evaluate competing representations, assess uncertainty, justify model assumptions, and communicate the limitations of inference. These demands have stimulated a growing international consensus that mathematics and STEM education should move beyond procedural manipulation of formulas toward the development of *modeling competencies* and *model-based reasoning* [2, 10, 12, 13, 15]. Such competencies encompass the ability to formulate models, interpret parameters, compare alternative representations, validate predictions, and critically evaluate the adequacy of mathematical descriptions under conditions of uncertainty.

International research on mathematical modeling education further emphasizes that effective learning environments should engage learners in the complete modeling cycle, including problem formulation, mathematization, parameter estimation, validation, comparison, interpretation, revision, and communication [5, 10, 15]. From this perspective, the educational objective is not merely to teach specific equations but to cultivate modeling literacy: the capacity to use mathematical models as tools for explanation, prediction, and decision making

while remaining critically aware of their assumptions, limitations, and domains of validity.

Despite these developments, introductory pharmacokinetics and many applied mathematics courses continue to rely predominantly on exponential decay models presented as fixed analytical expressions. While pedagogically convenient, such approaches often obscure important issues related to model selection, structural identifiability, predictive validity, uncertainty propagation, and reproducibility. Learners may therefore acquire procedural familiarity with equations while remaining insufficiently prepared to evaluate competing models or to interpret the reliability and limitations of quantitative evidence.

This challenge is further amplified by the increasing use of computational tools whose internal logic often remains opaque to learners. Although black-box approaches can facilitate numerical computation, they may inadvertently limit opportunities for symbolic reasoning, parameter interpretation, and conceptual understanding. Consequently, there is a growing need for educational frameworks that integrate analytical transparency, computational reproducibility, and evidence-based model evaluation within authentic scientific contexts.

The present framework is grounded in a sequence of course-based educational interventions developed at the Keiser University Latin American Campus, including classroom activities, assessment tasks, and applied modeling projects specifically designed to contextualize pharmacokinetic concepts within College Algebra. These materials informed both the modeling choices and the computational design of the present study [20, 22].

1.2 Scientific Problem

The scientific problem addressed in this study lies at the intersection of pharmacokinetics, mathematical modeling, computational science, and STEM education. Specifically, there remains a need for educationally accessible modeling frameworks that simultaneously support analytical reasoning, computational reproducibility, parameter interpretation, model comparison, and evidence-based decision making.

Highly sophisticated pharmacokinetic models employed in research and clinical practice often require advanced mathematical, statistical, and computational expertise, limiting their accessibility in educational environments. Conversely, simplified instructional models frequently prioritize computational convenience at the expense of interpretability, validation, and critical reasoning. The resulting tension highlights the challenge of identifying modeling approaches capable of balancing analytical transparency, computational rigor, and pedagogical usability within a coherent and transferable learning environment.

More broadly, the problem reflects an enduring question in STEM education: how can learners develop robust modeling competencies without reducing mathematical modeling to either symbolic manipulation disconnected from reality or computational fitting devoid of

conceptual understanding?

1.3 Research Gap

Although extensive research exists independently in pharmacokinetic modeling and mathematical modeling education, relatively few studies explicitly integrate these domains through a framework that treats model comparison, parameter interpretation, computational reproducibility, and model-selection literacy as primary learning objectives.

Moreover, the educational literature has devoted limited attention to rational functions as pharmacokinetic representations despite their ability to reproduce essential concentration–time behaviors while preserving analytical tractability. In contrast to purely exponential formulations, rational models permit direct symbolic derivation of clinically meaningful quantities such as peak concentration and peak time, thereby strengthening connections between mathematical reasoning and pharmacological interpretation.

A second gap concerns methodological practice. Many educational modeling studies rely on idealized examples in which goodness-of-fit is emphasized without equivalent attention to robustness, predictive performance, uncertainty quantification, or model-selection criteria. Such approaches risk portraying modeling as a deterministic exercise rather than as an iterative process of evidence evaluation under imperfect information. Addressing this limitation requires educational frameworks that explicitly incorporate validation strategies, sensitivity analyses, measurement error, and comparative model assessment.

Finally, relatively few educational studies examine how analytical tractability itself can function as a pedagogical asset. The ability to derive exact expressions, analyze parameter behavior, and establish structural identifiability may provide learners with conceptual insights that are often inaccessible in more computationally intensive black-box approaches.

1.4 Research Question

Guided by these considerations, the present study addresses the following research question:

> *How can an analytically tractable rational pharmacokinetic model be embedded within a reproducible computational framework that promotes model-based reasoning, model-selection literacy, quantitative interpretation, and modeling competencies in STEM education?*

1.5 Research Objectives

The overarching objective of this study is to develop and evaluate a transferable educational–computational framework that supports the complete modeling cycle—from formulation and estimation to validation, interpretation, and critical evaluation—using pharmacokinetics as an authentic interdisciplinary application domain.

More specifically, the framework seeks to enable learners to:

1. Analyze the asymptotic behavior and interpret the meaning of rational-function parameters in applied contexts.
2. Derive and interpret analytical expressions for peak concentration and peak time using differential calculus.
3. Implement nonlinear least-squares estimation through reproducible computational tools.
4. Compare competing models using multiple selection criteria, including MSE, AIC, BIC, Akaike weights, and residual diagnostics.
5. Evaluate robustness, uncertainty, and predictive performance under conditions of limited and imperfect data.
6. Examine issues of parameter identifiability, model assumptions, and limitations of inference in small-sample settings.
7. Develop transferable competencies in mathematical modeling, computational reasoning, and evidence-based interpretation.

1.6 Contributions of the Present Study

This study makes several complementary contributions to the literature on pharmacokinetic modeling, mathematical modeling education, and computational STEM learning.

1. It introduces a rational pharmacokinetic framework that preserves analytical tractability while reproducing key concentration–time dynamics relevant to therapeutic drug monitoring.
2. It demonstrates how clinically meaningful quantities, including peak concentration and peak time, can be obtained through exact symbolic derivation and directly connected to pharmacological interpretation.
3. It integrates nonlinear regression, model-selection theory, residual diagnostics, robustness analysis, predictive validation, and uncertainty assessment within a unified and reproducible workflow.

4. It highlights the role of structural identifiability and parameter interpretability as complementary criteria for model evaluation beyond goodness-of-fit metrics alone.

5. It advances model-based reasoning by connecting College Algebra, Applied Calculus, computational modeling, and pharmacokinetic interpretation within a coherent interdisciplinary framework.

6. It provides a transparent computational pipeline aligned with FAIR and open-science principles, thereby facilitating replication, adaptation, and reuse across diverse educational settings.

1.7 Positioning Relative to the State of the Art

Unlike instructional approaches that emphasize numerical outputs without providing opportunities for analytical interpretation, the framework proposed here prioritizes transparency, interpretability, analytical tractability, and computational reproducibility. In doing so, it aligns with contemporary research emphasizing modeling competencies, quantitative literacy, computational thinking, and evidence-based reasoning in STEM education.

Beyond its instructional value, the framework illustrates a generalizable workflow for exploratory pharmacokinetic modeling that emphasizes parameter interpretation, model comparison, structural identifiability, and reproducible computation under conditions of limited information. These characteristics position the framework as a bridge between mathematical modeling education and exploratory scientific modeling practice.

Accordingly, the contribution of this work extends beyond pharmacokinetics itself. The proposed framework can be understood as a transferable environment for cultivating model-based literacy, demonstrating how analytically tractable models can support the integration of symbolic reasoning, computational reproducibility, statistical evidence, and scientific interpretation within authentic interdisciplinary contexts.

1.8 Organization of the Paper

The remainder of this paper is organized as follows. Section 2 presents the theoretical foundations of the proposed framework, including considerations related to analytical tractability, model selection, and structural identifiability, and introduces the rational pharmacokinetic model. Section 3 describes the simulation design, computational procedures, robustness analyses under measurement error, and predictive-validation strategies. Section 4 reports model-fitting, model-selection, robustness, and predictive-validation results. Section 5 discusses the educational, methodological, and scientific implications of the findings, together

with limitations and directions for future research. Finally, Section 6 concludes by situating the framework within broader efforts to advance model-based STEM education, reproducible computational practice, and quantitative reasoning.

2 Theoretical Framework

2.1 From the Bateman Function to a Rational Approximation

In classical one-compartment pharmacokinetics with first-order absorption and elimination, the plasma concentration–time profile following extravascular administration is described by the Bateman function [6, 14]:

$$C_{\mathrm{B}}(t) = \frac{FDk_a}{V(k_a - k_e)} \left(e^{-k_e t} - e^{-k_a t}\right), \tag{1}$$

where F denotes bioavailability, D the administered dose, V the apparent volume of distribution, and k_a and k_e the absorption and elimination rate constants, respectively.

When absorption and elimination occur on comparable time scales ($k_a \approx k_e$), the difference of exponentials in (1) exhibits a characteristic unimodal shape. In particular, near the origin this expression behaves proportionally to te^{-kt}, suggesting that rational approximations may provide a parsimonious yet accurate representation of early and intermediate dynamics.

To motivate such an approximation, consider the third-order Taylor expansion of the exponential function:

$$e^{-kt} \approx 1 - kt + \frac{k^2 t^2}{2} - \frac{k^3 t^3}{6}, \tag{2}$$

which, when substituted into (1) and simplified, yields an expression proportional to:

$$t - \frac{k}{2} t^2 + \mathcal{O}(t^3). \tag{3}$$

A Padé approximant of order (1/2) applied to the time-dependent structure provides a rational representation of the form [1]:

$$C(t) \approx \frac{at}{bt^2 + ct + 1}, \tag{4}$$

where the coefficients a, b, and c encapsulate composite information about absorption and elimination processes.

Imposing the biologically meaningful conditions $C(0) = 0$ and $C(t) \to 0$ as $t \to \infty$

requires $c = 0$, yielding the simplified rational model:

$$C(t) = \frac{at}{bt^2 + 1}. \tag{5}$$

In this formulation, $a > 0$ determines the overall scale of the concentration profile, whereas $b > 0$ governs the rate of decay at later times. Although this representation is phenomenological rather than derived from first principles, it offers an analytically tractable framework that preserves the essential qualitative features of pharmacokinetic behavior.

For the simulations considered in this study, we fix $a = 4$, selecting $b = 1$ for a healthy subject and $b = 0.25$ for impaired renal elimination. These values encode relative changes in elimination dynamics rather than direct physiological parameters.

2.2 Connection to Therapeutic Drug Monitoring

The primary clinical motivation for pharmacokinetic modeling lies in assessing whether a dosing regimen maintains plasma concentrations within the therapeutic window. Two quantities are particularly relevant: the peak concentration $C_{\max}$ and the time to peak concentration $t_{\max}$.

A notable advantage of the rational model (5) is that these quantities can be obtained analytically. Differentiation yields:

$$C'(t) = \frac{a(1 - bt^2)}{(bt^2 + 1)^2}, \tag{6}$$

from which the peak occurs at:

$$t_{\max} = \frac{1}{\sqrt{b}}, \qquad C_{\max} = \frac{a}{2\sqrt{b}}. \tag{7}$$

These closed-form expressions allow direct quantification of how changes in b affect both the magnitude and timing of peak concentration.

2.3 Model Identifiability and Selection Criteria

An additional theoretical advantage of the rational model lies in its structural identifiability. Under ideal noise-free conditions, the parameters a and b are structurally identifiable in the deterministic setting, although practical identifiability may deteriorate under noise and sparse sampling designs. In contrast, the Bateman function can suffer from practical identifiability issues when k_a and k_e are similar, making the rational formulation a robust alternative for educational demonstrations.

To compare the rational model with alternative representations, we employ information-theoretic criteria following Burnham and Anderson [4]. Specifically, the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) are defined as:

$$\mathrm{AIC} = n \ln\left(\frac{\mathrm{RSS}}{n}\right) + 2k, \qquad \mathrm{BIC} = n \ln\left(\frac{\mathrm{RSS}}{n}\right) + k \ln n, \tag{8}$$

where n denotes the number of observations, RSS the residual sum of squares, and k the number of free parameters.

Because the sample size is intentionally small ($n = 4$), the corrected criterion AIC_c is undefined for the quadratic model (where $k = 3$ and $n - k - 1 = 0$). For consistency and to avoid artificial inflation of apparent support, we apply the uncorrected AIC and BIC uniformly to all candidate models. This choice is transparent and does not affect the qualitative conclusions, given the overwhelming evidence in favor of the rational model.

To facilitate interpretation, Akaike weights are defined as [4]:

$$w_i = \frac{\exp(-\Delta_i/2)}{\sum_j \exp(-\Delta_j/2)}, \qquad \Delta_i = \mathrm{AIC}_i - \mathrm{AIC}_{\min}. \tag{9}$$

These weights provide a normalized measure of relative support for each model within the candidate set.

3 Data and Methods

The simulated datasets and associated computational workflows are based on didactic materials and exploratory analyses developed as part of prior course projects and instructional resources [19, 21].

3.1 Simulated Data

Two synthetic concentration–time datasets were generated from the rational model defined in Equation (5) with parameter values $a = 4$ and $b = 1$ (healthy scenario) or $b = 0.25$ (reduced-clearance scenario). The sampling times were fixed at $t = 0.5, 1.0, 2.0$, and 5.0 hours. Exact concentration values are reported in Table 1 with two-decimal rounding for presentation, while all analyses were conducted using the exact values to preserve the deterministic nature of the simulation.

The datasets are intended exclusively for educational and methodological illustration and do not represent clinical observations.

Table 1: Simulated concentration–time data generated from $C(t) = \dfrac{4t}{bt^2+1}$. Values are shown with two-decimal rounding.

Time t (h)	Healthy C_1 (mg/L)	Renal C_2 (mg/L)
0.5	1.60	1.88
1.0	2.00	3.20
2.0	1.60	4.00
5.0	0.77	2.76[1]

3.2 Candidate Models

Four candidate models were considered to illustrate comparative model selection:

$$\text{Linear:} \quad C(t) = at + b, \tag{10}$$

$$\text{Quadratic:} \quad C(t) = at^2 + bt + c, \tag{11}$$

$$\text{Exponential:} \quad C(t) = ae^{bt}, \tag{12}$$

$$\text{Rational:} \quad C(t) = \frac{at}{bt^2+1}. \tag{13}$$

3.3 Parameter Estimation and Model Selection

Model parameters were estimated by minimizing the sum of squared residuals using the Levenberg–Marquardt algorithm as implemented in `SciPy`'s `curve_fit` routine [18]. Initial parameter guesses were chosen close to the generating values for the rational model (e.g., $[4, 1]$ or $[4, 0.25]$) and as $[2, -0.1]$ for the exponential model; default initialization was used for the remaining models.

Model performance was evaluated using the mean squared error (MSE), Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and Akaike weights. Residual plots were examined to identify systematic patterns indicative of model misspecification. Because the primary datasets are noiseless, bootstrap confidence intervals are not emphasized in the main analysis but are discussed in the noise-extension study (Section 3.5).

[1] Exact value: $\frac{20}{0.25\times25+1} = \frac{20}{7.25} \approx 2.7586$

3.4 Analytical Peak Derivation

For the rational model, differentiation yields

$$C'(t) = \frac{a(1 - bt^2)}{(bt^2 + 1)^2}.$$

Setting $C'(t) = 0$ leads to the analytical expressions

$$t_{\max} = \frac{1}{\sqrt{b}}, \qquad C_{\max} = C(t_{\max}) = \frac{a}{2\sqrt{b}}.$$

3.5 Extension with Synthetic Noise

To examine robustness under measurement uncertainty, an extension adds independent Gaussian noise $\mathcal{N}(0, \sigma^2)$ with $\sigma = 0.02$ mg/L to the simulated concentrations. Under noisy conditions, parameter estimates deviate slightly from their generating values, and bootstrap intervals—although unstable for $n = 4$—illustrate sampling variability. This extension highlights the impact of data quality and sample size on inference.

4 Results

4.1 Model Selection

Table 2 summarizes model-selection criteria for the noiseless data. The rational model achieves an essentially perfect fit, with MSE values several orders of magnitude smaller than those of competing models and substantially lower AIC and BIC values. Akaike weights exceed 0.9999 in both scenarios, indicating overwhelming support for the rational formulation.

Although the quadratic model includes an additional parameter, it performs worse due to overfitting the four available observations. Linear and exponential models fail to capture the unimodal structure of the concentration–time profiles.

Table 2: Model-selection criteria for noiseless data. MSE is reported in scientific notation.

Model	Healthy			Renal		
	MSE	AIC	BIC	MSE	AIC	BIC
Linear	7.09×10^{-2}	-1.46	-2.21	4.86×10^{-1}	5.64	4.89
Quadratic	3.18×10^{-2}	-2.68	-4.31	1.47×10^{-1}	1.23	-0.40
Exponential	2.28×10^{-2}	-3.44	-4.19	4.93×10^{-1}	5.69	4.94
Rational	1.54×10^{-7}	-64.4	-65.6	2.31×10^{-5}	-38.7	-39.9

4.2 Parameter Estimates

For noiseless data, the rational model recovers the generating parameters within numerical precision:

$$\text{Healthy: } a = 4.00,\ b = 1.00, \qquad \text{Renal: } a = 4.00,\ b = 0.25.$$

Under noisy conditions, estimates exhibit small deviations (e.g., $a = 3.98,\ b = 0.97$ for the healthy scenario), illustrating the effect of measurement error.

4.3 Peak Analysis and Interpretation

Using the analytical expressions for $t_{\max}$ and $C_{\max}$,

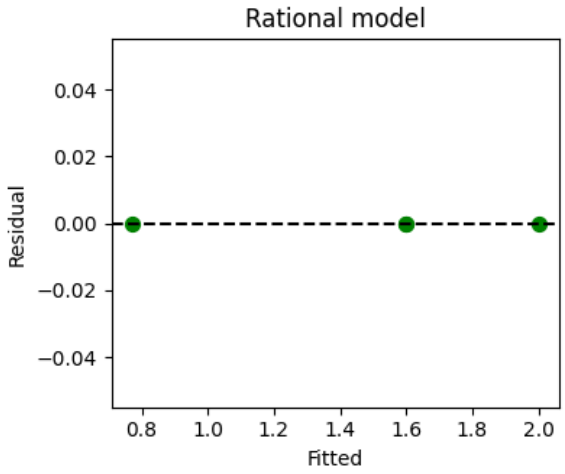
$$t_{\max}^{\text{healthy}} = 1.00 \text{ h}, \quad C_{\max}^{\text{healthy}} = 2.00 \text{ mg/L},$$

$$t_{\max}^{\text{renal}} = 2.00 \text{ h}, \quad C_{\max}^{\text{renal}} = 4.00 \text{ mg/L}.$$

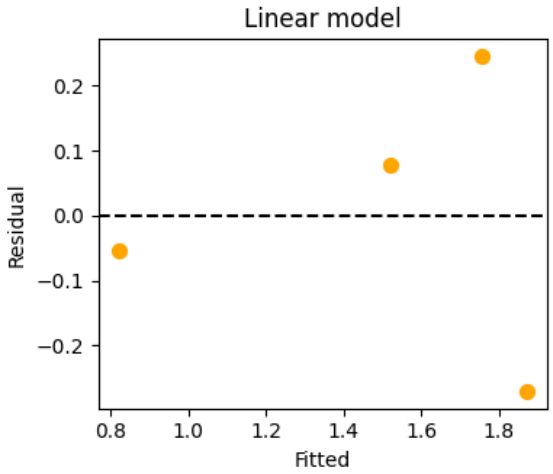
Reducing b by 75% results in a doubling of both peak concentration and time to peak. Assuming a hypothetical toxicity threshold of 3.5 mg/L, the renal scenario exceeds this limit, whereas the healthy scenario remains below it, illustrating the pharmacokinetic consequences of reduced elimination.

4.4 Residual Diagnostics

Residual diagnostics (Figure 1) provide complementary evidence of model adequacy. The rational model yields residuals at machine precision, consistent with exact recovery of the generating process. In contrast, the linear model exhibits a pronounced U-shaped residual pattern, indicating structural misspecification.



(a) Rational model (zero residuals)

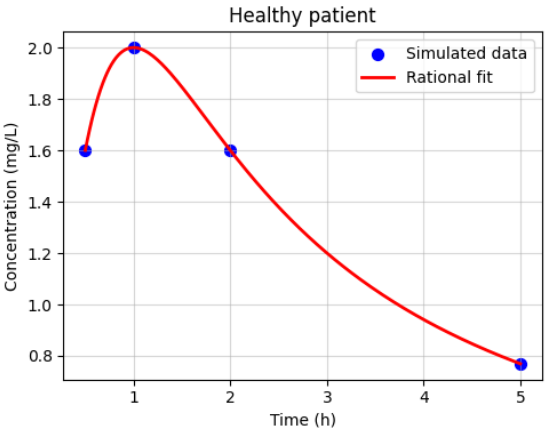


(b) Linear model (U-shaped pattern)

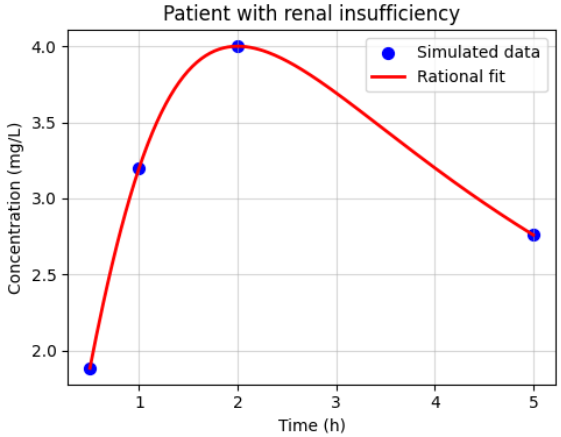
Figure 1: Residual plots for the healthy dataset. Perfect fit of the rational model contrasts with systematic lack of fit of the linear model.

4.5 Graphical Summary

Figure 2 shows the fitted rational model for both scenarios. In each case, the fitted curve coincides with all observed data points, confirming analytical consistency and parameter recoverability under noiseless conditions.



(a) Healthy subject



(b) Renal patient

Figure 2: Simulated data (circles) and best-fit rational model (solid line). The rational model exactly reproduces the generating function.

4.6 Extension: Adding Noise

When Gaussian noise is introduced, the rational model continues to outperform alternatives but no longer fits perfectly. Bootstrap intervals appear narrow due to low noise variance; however, with only four observations they overstate precision, reinforcing the importance of sample size in real-world applications.

5 Discussion

The development of this framework builds on prior instructional experiences and course-based implementations aimed at integrating mathematical modeling into applied contexts [20, 22].

5.1 Interpretation of Parameter Shifts

The fourfold reduction in the parameter b from the healthy to the reduced-clearance scenario was intentionally selected to represent a situation qualitatively consistent with impaired elimination. The closed-form relationships

$$t_{\max} = \frac{1}{\sqrt{b}}, \qquad C_{\max} = \frac{a}{2\sqrt{b}},$$

enable learners to observe immediately how a decrease in b—corresponding to slower elimination—simultaneously increases and delays the concentration peak. This transparent quantitative link between a mathematical parameter and a clinically meaningful consequence constitutes a central pedagogical strength of the proposed framework.

Rather than treating parameters as abstract fitting constants, the rational model allows learners to interpret parameter changes mechanistically and to reason about their implications for exposure and potential toxicity. This capacity to connect symbolic structure with pharmacokinetic interpretation directly supports the development of model-based reasoning and quantitative literacy.

5.2 Educational Implementation

The framework is designed for flexible integration into undergraduate courses in College Algebra, Applied Calculus, or introductory pharmacokinetics. One possible implementation is a single 90-minute active-learning session, outlined in Table 3. The complete and reproducible Python code provided in the Appendix allows instructors and students to modify parameters, explore alternative models, introduce measurement noise, and test their own hypotheses. The

integration of coding in calculus courses has been shown to enhance student engagement and modeling skills [7].

The optional noise extension may be incorporated as an in-class enrichment activity or assigned as homework to facilitate deeper discussion of uncertainty, robustness, and the limits of inference.

Table 3: Suggested 90-minute active-learning session.

Time	Activity
0–10 min	Introduction to the therapeutic window and pharmacokinetic context.
10–25 min	Small-group work: sketch the data, predict peak behavior, and discuss plausible model shapes.
25–40 min	Live coding demonstration: nonlinear regression and candidate models.
40–55 min	Model selection: computation and interpretation of MSE, AIC, BIC, and Akaike weights.
55–70 min	Analytical derivation of $t_{\max}$ and $C_{\max}$; discussion of the 75% reduction in b.
70–85 min	Uncertainty and robustness: bootstrap concepts, noise extension, and sample-size limitations.
85–90 min	Synthesis and ethical reflection: should such a model be trusted for real clinical decisions?

5.3 Assessment of Student Learning

Formative assessment may include short written reports in which students present their fitted curves, compare model-selection criteria, and articulate the pharmacokinetic interpretation of parameter shifts. Summative assessment can probe higher-order reasoning by asking students to predict $C_{\max}$ for new parameter values, evaluate competing models, or critique the appropriateness of information criteria when the sample size is extremely small.

Although the present study does not report empirical learning-gain data, the design of the framework aligns with established principles of evidence-based modeling pedagogy, including active engagement, comparison of alternative representations, and explicit attention to uncertainty and assumptions [2, 12]. Future work should empirically evaluate its impact on students' modeling competencies and quantitative reasoning.

5.4 Limitations and Future Work

Several limitations must be acknowledged. First, the extremely small sample size ($n = 4$) is insufficient for robust statistical inference in practice; the exact parameter recovery observed here is an artifact of noiseless simulated data. Second, real pharmacokinetic measurements are subject to biological variability and experimental error, often requiring larger datasets and more complex structures, such as multi-compartment models. Third, the rational model remains a phenomenological approximation; its parameters should not be interpreted as direct physiological rate constants. As Box [3] famously noted, "all models are wrong, but some are useful," reminding us that educational value lies in understanding the strengths and limitations of any mathematical representation.

In addition, no empirical assessment of educational outcomes was conducted. Future research should include controlled studies comparing this framework with traditional instructional approaches. Extensions could also explore heteroscedastic noise structures, alternative sampling designs, or application to real clinical datasets for exploratory—not clinical—purposes.

6 Conclusions

This paper presents a reproducible, computationally enriched educational framework in which a rational pharmacokinetic model recovers the generating parameters of a known data-generating process, while linear, quadratic, and exponential alternatives fail to capture key concentration–time features. Analytical tractability yields exact expressions for peak time and peak concentration, directly linking College Algebra and Applied Calculus concepts to pharmacokinetic reasoning.

In the simulated reduced-clearance scenario, a 75% reduction in the elimination parameter b produces a 100% increase in peak concentration and a 100% prolongation of time to peak, illustrating how modest parameter changes can lead to substantial differences in exposure. By integrating model selection criteria, residual diagnostics, and robustness analysis under noise, the framework explicitly foregrounds uncertainty, interpretability, and critical evaluation.

Beyond demonstrating recovery of a known pharmacokinetic process, the broader contribution of this work lies in its promotion of model-based literacy. The framework illustrates how analytically tractable models can serve as powerful vehicles for integrating symbolic reasoning, computational reproducibility, and evidence-based model selection within authentic STEM contexts. All claims are explicitly bounded by the simulated nature of the data and the educational scope of the study; the framework is not intended for clinical decision-making.

Data and Code Availability

All simulated datasets, analytical derivations, and Python scripts used in this study are provided in the Appendix to ensure full transparency and reproducibility. The complete computational repository will be made publicly available upon manuscript acceptance, consistent with FAIR and open-science principles.

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A Reproducible Python Code

The following script generates the data, fits all four candidate models, computes information criteria and Akaike weights, and produces all figures referenced in the paper. The optional noise extension is clearly marked and can be enabled by setting `ADD_NOISE = True`.

```
import numpy as np
import matplotlib.pyplot as plt
from scipy.optimize import curve_fit

# ---------------------------------------------------------------------
# 1. Generate synthetic data from the rational model
#    C(t) = a * t / (b * t^2 + 1)
# ---------------------------------------------------------------------

time = np.array([0.5, 1.0, 2.0, 5.0])        # sampling times (h)
A_true = 4.0                                  # common a parameter
B_healthy = 1.0                               # healthy elimination
B_renal = 0.25                                # impaired elimination

def rational(t, a, b):
    return a * t / (b * t**2 + 1)

# Exact concentrations (no noise)
conc_healthy = rational(time, A_true, B_healthy)
conc_renal   = rational(time, A_true, B_renal)
```

```
# ----------------------------------------------------------------------
# 2. Define candidate models
# ----------------------------------------------------------------------
def linear(t, a, b):
    return a * t + b

def quadratic(t, a, b, c):
    return a * t**2 + b * t + c

def exponential(t, a, b):
    return a * np.exp(b * t)

models = {
    'Linear':      (linear,      2),
    'Quadratic':   (quadratic,   3),
    'Exponential': (exponential, 2),
    'Rational':    (rational,    2)
}

# Initial guesses for each model
guesses = {
    'Linear':      [1, 1],
    'Quadratic':   [0, 1, 1],
    'Exponential': [2, -0.1],
    'Rational':    [4, 1]         # will be overwritten per scenario
}

# ----------------------------------------------------------------------
# 3. Fitting and model selection for both scenarios
# ----------------------------------------------------------------------
def compute_criteria(y_true, y_pred, k):
    """Return MSE, AIC, BIC for given residuals and number of parameters k."""
    n = len(y_true)
    rss = np.sum((y_true - y_pred)**2)
    mse = rss / n
```

```
    aic = n * np.log(rss / n) + 2 * k
    bic = n * np.log(rss / n) + k * np.log(n)
    return mse, aic, bic

def fit_and_evaluate(data, true_b):
    results = {}
    # adjust initial guess for rational model
    local_guesses = guesses.copy()
    local_guesses['Rational'] = [4, true_b]

    for name, (func, k) in models.items():
        try:
            popt, _ = curve_fit(func, time, data,
                                p0=local_guesses[name], maxfev=10000)
            y_pred = func(time, *popt)
            mse, aic, bic = compute_criteria(data, y_pred, k)
            results[name] = {'popt': popt, 'mse': mse,
                             'aic': aic, 'bic': bic, 'y_pred': y_pred}
        except Exception as e:
            print(f"Fit failed for {name}: {e}")
    return results

# Fit both datasets
res_healthy = fit_and_evaluate(conc_healthy, B_healthy)
res_renal   = fit_and_evaluate(conc_renal, B_renal)

# Compute Akaike weights for each scenario
def akaike_weights(results):
    aic_vals = np.array([res['aic'] for res in results.values()])
    best = np.min(aic_vals)
    deltas = aic_vals - best
    weights = np.exp(-deltas / 2) / np.sum(np.exp(-deltas / 2))
    return dict(zip(results.keys(), weights))

w_healthy = akaike_weights(res_healthy)
w_renal   = akaike_weights(res_renal)
```

```
# Print summary tables
def print_table(results, weights, title):
    print(f"\n{title}")
    print(f"{'Model':<12} {'MSE':>12} {'AIC':>8} {'BIC':>8} {'Akaike w':>10}")
    print("-" * 52)
    for name, res in results.items():
        print(f"{name:<12} {res['mse']:12.2e} {res['aic']:8.2f} "
              f"{res['bic']:8.2f} {weights[name]:10.4f}")

print_table(res_healthy, w_healthy, "Healthy scenario")
print_table(res_renal, w_renal, "Renal scenario")

# ------------------------------------------------------------------------
# 4. Generate figures
# ------------------------------------------------------------------------
t_smooth = np.linspace(0.5, 5.0, 200)

# --- 4a. Fitted rational curves ---
fig, (ax1, ax2) = plt.subplots(1, 2, figsize=(10, 4))
for ax, data, res, title, b in zip(
    [ax1, ax2],
    [conc_healthy, conc_renal],
    [res_healthy, res_renal],
    ['Healthy subject', 'Patient with renal insufficiency'],
    [B_healthy, B_renal]
):
    ax.scatter(time, data, color='blue', s=50, label='Data')
    popt = res['Rational']['popt']
    ax.plot(t_smooth, rational(t_smooth, *popt), 'r-', lw=2,
            label='Rational fit')
    ax.set_xlabel('Time (h)')
    ax.set_ylabel('Concentration (mg/L)')
    ax.set_title(title)
    ax.legend()
    ax.grid(alpha=0.5)
```

```
plt.tight_layout()
plt.savefig('healthy_fit.png', dpi=150, bbox_inches='tight')
plt.savefig('renal_fit.png', dpi=150, bbox_inches='tight')
plt.close()

# --- 4b. Residual diagnostics (healthy dataset) ---
# Rational residuals
pred_rat = res_healthy['Rational']['y_pred']
res_rat = conc_healthy - pred_rat

# Linear residuals
pred_lin = res_healthy['Linear']['y_pred']
res_lin = conc_healthy - pred_lin

fig, (ax1, ax2) = plt.subplots(1, 2, figsize=(8, 3.5))
ax1.scatter(pred_rat, res_rat, color='green', s=50)
ax1.axhline(0, color='k', linestyle='--')
ax1.set_xlabel('Fitted concentration')
ax1.set_ylabel('Residual')
ax1.set_title('Rational model')

ax2.scatter(pred_lin, res_lin, color='orange', s=50)
ax2.axhline(0, color='k', linestyle='--')
ax2.set_xlabel('Fitted concentration')
ax2.set_ylabel('Residual')
ax2.set_title('Linear model')
plt.tight_layout()
plt.savefig('residuals_rational.png', dpi=150, bbox_inches='tight')
# To obtain individual files, we can reuse the same figure but we'll save separately
# by replotting just one axis each:
fig, ax = plt.subplots(figsize=(4, 3))
ax.scatter(pred_rat, res_rat, color='green', s=50)
ax.axhline(0, color='k', linestyle='--')
ax.set_xlabel('Fitted'); ax.set_ylabel('Residual')
ax.set_title('Rational model')
plt.tight_layout()
```

```
plt.savefig('residuals_rational.png', dpi=150, bbox_inches='tight')
plt.close()

fig, ax = plt.subplots(figsize=(4, 3))
ax.scatter(pred_lin, res_lin, color='orange', s=50)
ax.axhline(0, color='k', linestyle='--')
ax.set_xlabel('Fitted'); ax.set_ylabel('Residual')
ax.set_title('Linear model')
plt.tight_layout()
plt.savefig('residuals_linear.png', dpi=150, bbox_inches='tight')
plt.close()

# ------------------------------------------------------------------------
# 5. Extension with synthetic noise (optional)
# ------------------------------------------------------------------------
ADD_NOISE = False   # set to True to enable noise analysis
if ADD_NOISE:
    np.random.seed(42)
    sigma = 0.02
    noise_healthy = conc_healthy + np.random.normal(0, sigma, size=len(time))
    noise_renal   = conc_renal   + np.random.normal(0, sigma, size=len(time))

    print("\n--- Noise extension ---")
    res_noise_h = fit_and_evaluate(noise_healthy, B_healthy)
    res_noise_r = fit_and_evaluate(noise_renal, B_renal)
    w_noise_h = akaike_weights(res_noise_h)
    w_noise_r = akaike_weights(res_noise_r)
    print_table(res_noise_h, w_noise_h, "Healthy (noisy)")
    print_table(res_noise_r, w_noise_r, "Renal (noisy)")
    print("Rational parameter estimates (noisy):")
    print("Healthy:", res_noise_h['Rational']['popt'])
    print("Renal:  ", res_noise_r['Rational']['popt'])
```