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MATHEMATICAL MODEL FOR SCHIZOPHRENIA: PARAMETER ESTIMATION

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Abstract: In this study, a fractional-order time-delay mathematical model for schizophrenia is investigated with a focus on parameter estimation. The model incorporates memory effects and delayed neural responses using Caputo fractional derivatives. A least squares approximation technique is employed to estimate unknown model parameters based on available data. Furthermore, the Fisher Information Matrix and profile likelihood methods are used to analyze parameter sensitivity and uncertainty. Numerical simulations are performed using MATLAB to validate the proposed approach. The results demonstrate that the fractional-order framework provides improved modeling accuracy and better representation of schizophrenia-related brain dynamics compared to classical integer-order models.

Keywords and Phrases: Parameter Estimation; Fractional differential equation, Caputo fractional derivative, Schizophrenia model.

2020 Mathematics Subject Classification: 93A30, 37N35, 34D20, 34E05,

34K28.

1. Introduction

A person's ability to think, feel, and interact with others is largely dependent on their mental health, which is a basic aspect of health. The World Health Organization [47] defines mental health as a state of well-being where an individual recognizes their abilities, effectively manages the normal stresses of life, works productively, and contributes to their community.

Schizophrenia is a severe mental disorder marked by significant and temporary disruptions in thinking, perception, and experience. Its effects can range from a diminished sense of reality to total impairment, as discussed by Marder, S. R. et al. [28]. Individuals affected by this disorder often experience disruptions across several areas, including motivation, emotional expression, attention, perception, thought processes, self-functioning, and psychomotor abilities, as reported by National Institute of Mental Health [30]. It may be challenging to engage in daily activities when suffering from symptoms of schizophrenia, as highlighted by Gaebel, W. and Wölwer, W. [18].

The diagnosis of schizophrenia predominantly hinges on subjective methods, including self-reports, clinical evaluations, and careful observations. These approaches are essential for accurately understanding the individual's experiences and manifestations of the disorder, as outlined by American Psychological Association [3]. Psychiatric diseases are frequently accompanied with sleep difficulties and related perturbations of the circadian rhythm, as discussed by Harvey, A. G. et al. [21] and Meyer, N. et al. [29]. Humans are aligned with the daily cycle of day and night through their circadian rhythm. This rhythm activates a complex network of interrelated biological patterns, which include the regulation of hormone levels, the sleep-wake cycle, shorter periods of rest and activity, and many other internal processes, as explained by Dibner, C. et al. [11]. A disrupted and unsynchronized circadian system is a common sign of schizophrenia, as reported by Delorme, T. C. et al. [10]. Both social rhythm patterns and the circadian system's daily changes in motor activity are known, as highlighted by Henson, P. et al. [22].

Due to its extensive applicability in a variety of domains, fractional differential equations and delay differential equations have developed into an emergent topic of study, as addressed and examined by Podlubny, I. [35], Györi, I. and Ladas, G. [20], Theyab, S. H. [45], Bekkouche, Z. et al. [5] and Joudha, Z. M. et al. [23]. The design of next generation matrices for compartmental epidemic models has been described by Diekmann, O. et al. [12]. The predictor-corrector approach has been used by Bhalekar, S. and Daftardar-Gejji, V. [6] to solve the fractional delay differential equations. Stability and Hopf bifurcation analyses were performed on the

fractional-order nonlinear financial model, the COVID-19 model, the RBC model, and the love dynamical model for a nonsynergic pair, which were modeled by Panigrahi, S. et al. [31, 34], and Panigrahi, S. and Chand, S. [32, 33]. Advancements in fractional-order mathematical modeling have introduced new derivative operators and frameworks for studying complex biological systems. In particular, piecewise modified Atangana–Baleanu–Caputo (ABC) fractional derivatives have been applied to model rotavirus infection dynamics, enabling the capture of time-varying transmission behavior, as studied by Shah, K. et al. [38]. Modified ABC fractional models have also been used in the analysis of breast cancer systems, providing improved representation of tumor growth processes, as investigated by Aldwoah, K. A. et al. [1]. In addition, piecewise fractional derivatives have been utilized to describe virus mutation dynamics, allowing better characterization of evolving biological systems, as described by Shah, K. et al. [39]. These approaches highlight the flexibility of fractional calculus in modeling complex biological phenomena.

The least squares approach is a powerful method for estimating parameters in regression analysis, focusing on minimizing the sum of the squares of the residuals. Residuals represent the differences between actual observed values and those predicted by the model. As the demand for accurate parameter estimation in linear and nonlinear system models continues to grow impacting critical fields such as signal processing, communication, biology, and control engineering, researchers are increasingly dedicated to advancing innovative techniques for system identification. Among these, the least squares method stands out as a vital tool for achieving precise and reliable model outputs, as discussed by Simkins, S. and Alexander, M. [44], Dang, J. S. et al. [9], Draper, N. R. [16], Raaijmakers, J. G. [36], Zivin, J. A. and Waud, D. R. [50], Dochain, D. and Vanrolleghem, P. A. [15], Guisasola, A. et al. [19], Raue, A. et al. [37], Ding, F. [13], Wang, D. Q. [46], Liu, Y. et al. [26] and Ding, J. and Ding, F. [14]. Fractional-order model parameter estimation has been covered by Wu, F. X. [48], Cois, O. et al. [8], Battaglia, J. L. et al. [4] and Khadhraoui, A. et al. [25]. Although estimation uncertainty has been expressed frequently for model parameters, prediction uncertainty is a crucial parameter for healthcare decision making, as highlighted by Boeker, M. et al. [7], Fröhlich, F. et al. [17] and Machado, V. C. et al. [27].

As such, delays are necessary in a realistic model of brain activity that considers dopamine's regulating function. Though modest, these delays may have ramifications beyond the nonlinearities we considered and explored in our original framework. Recent studies have focused on nonlinear delayed equations as a novel and significant method for simulating schizophrenia-like brain processes, as discussed by Zendehrouh, S. et al. [49]. Using a nonlinear mathematical model, Kaslik, E.

et al. [24] examined discrete time-delays in dopamine-modulated prefrontal-limbic connections in schizophrenia.

In recent years, artificial intelligence and neural network-based approaches have gained significant attention in the analysis of complex biological and medical systems. In particular, deep neural networks and fractal-fractional models have been successfully applied to study disease dynamics and predictive modeling. For example, neural network-based fractional models have been used to analyze chronic myeloid leukemia and eye disease infections, as studied by Shah, K. et al. [40] and Shah, K. et al. [41], while deep learning techniques have been applied for solving coupled fractional integro-differential systems and epidemic compartmental models, as investigated by Sher, M. et al. [43] and Shah, K. et al. [42]. Furthermore, artificial intelligence tools have also been employed in the mathematical modeling of psychological disorders, as described by Alqudah, M. A. et al. [2].

Recent studies on schizophrenia modeling have primarily focused on qualitative dynamics such as stability and bifurcation analysis using delay differential equations. However, parameter estimation in such nonlinear fractional models remains relatively unexplored. Fractional-order models naturally incorporate memory effects, while time-delays capture delayed neural responses, making them more suitable for modeling brain dynamics in schizophrenia. Despite these advantages, existing studies lack systematic parameter estimation frameworks and uncertainty analysis. This motivates the present study, where we address these challenges through least squares estimation and uncertainty quantification. To address these challenges, this study makes the following contributions:

- Proposes a fractional-order time-delay model for schizophrenia incorporating memory and delay effects.
- Develops a least squares based parameter estimation framework for the model.
- Utilizes Fisher Information Matrix and profile likelihood methods for parameter sensitivity and uncertainty analysis.
- Provides numerical validation through residual and cost function analysis.

The novelty of this work lies in the integration of fractional-order dynamics with time-delay modeling for schizophrenia, combined with a systematic parameter estimation framework using least squares, Fisher Information Matrix, and profile likelihood methods. While previous studies have primarily focused on qualitative analysis such as stability and bifurcation, the present study emphasizes quantitative parameter identification and uncertainty analysis, which are essential for improving

Table 1: Comparison of existing works and present study

Author	Model Type	Delay	Parameter Estimation	Uncertainty Analysis
Kaslik et al. (2020)	Integer-order	Yes	No	No
Panigrahi et al. (2021–2023)	Fractional	Yes	No	No
Other works	Fractional/Delay	Partial	Limited	No
Present Work	**Fractional + Delay**	**Yes**	**Yes (Least Squares)**	**Yes (FIM + Profile)**

model reliability and applicability. Unlike existing studies, which primarily focus on qualitative analysis such as stability and bifurcation, the present work provides a unified quantitative framework for parameter estimation and uncertainty analysis specifically for schizophrenia models. To the best of our knowledge, such a systematic integration of estimation and validation techniques has not been reported in the context of fractional-order time-delay schizophrenia models.

The structure of this paper is designed to provide a comprehensive exploration of our findings. In Section 2, we delve into the nonlinear fractional-order delay model for schizophrenia, laying the groundwork for our analysis. Sections 3, 4, and 5 present critical methodologies, including the least squares approximation, the Fisher information matrix approximation criteria, and an in-depth examination of parameter uncertainty through profile likelihoods. In Section 6, we showcase robust numerical simulations that powerfully validate our results. Lastly, Section 7 delivers insightful conclusions that encapsulate the significance of our research.

2. Mathematical Model

The human brain consists of interconnected regions that regulate emotional and cognitive responses. In schizophrenia, abnormal interactions between the amygdala, hippocampus, prefrontal cortex, and dopamine system are observed. These interactions can be effectively modeled using nonlinear dynamical systems.

The model considered in this study is based on dopamine-modulated prefrontal-limbic interactions with discrete time-delay, as studied by Kaslik, E. et al. [24]. The delay represents the time lag in neurotransmitter response, while nonlinear terms capture complex neural feedback mechanisms.

Each state variable represents the activity level of a specific brain region:

- $\chi_1(t)$: Amygdala activity
- $\chi_2(t)$: Hippocampus activity
- $\chi_3(t)$: Prefrontal cortex activity
- $\chi_4(t)$: Dopamine system activity

The interactions between these components are governed by the following system of equations:

$$\chi_1'(t) = -\mu_1\chi_1(t) - k_1\chi_2(t) - \gamma_1\chi_3(t) + I \tag{2.1}$$

$$\chi_2'(t) = k_2\chi_1(t) - \mu_2\chi_2 g(\chi_4(t-\eta)) + \frac{\gamma_2}{a_1 c(\chi_1)+1}\chi_3 \tag{2.2}$$

$$\chi_3'(t) = k_3\chi_2 g((\chi_4(t-\eta))^2) - a_2 c(\chi_1) \tag{2.3}$$

$$\chi_4'(t) = -\zeta_1\chi_1 g(\chi_4) + \zeta_2\chi_2 g(\chi_4) + \zeta_3\chi_3 g(\chi_4) \tag{2.4}$$

where $g(0) = 1$ and the function g is increasing, the parameter η signifies the critical delay in dopamine action, highlighting its significant impact on neurological responses, $c(\chi_1) = \frac{\beta e^{\chi_1}}{e^{\chi_1}+1}$, $c_2 = \frac{\gamma_2}{a_1 c(\chi_1)+1}$, μ_1 signify the level of anxiety, a_2 indicates the degree of vulnerability to stress as influenced by cortisol and positive system parameters, or the linear coefficients, indicate the strength of the connections between the different brain regions.

The fractional-order nonlinear model of dopamine-modulated prefrontal-limbic interactions in schizophrenia, which incorporates discrete time-delays, can be effectively developed using the Caputo fractional derivative (2.1)-(2.4),

$$D^\alpha\chi_1(t) = -\mu_1\chi_1(t) - k_1\chi_2(t) - \gamma_1\chi_3(t) + I \tag{2.5}$$

$$D^\alpha\chi_2(t) = k_2\chi_1(t) - \mu_2\chi_2 g(\chi_4(t-\eta)) + \frac{\gamma_2}{a_1 c(\chi_1)+1}\chi_3 \tag{2.6}$$

$$D^\alpha\chi_3(t) = k_3\chi_2 g((\chi_4(t-\eta))^2) - a_2 c(\chi_1) \tag{2.7}$$

$$D^\alpha\chi_4(t) = -\zeta_1\chi_1 g(\chi_4) + \zeta_2\chi_2 g(\chi_4) + \zeta_3\chi_3 g(\chi_4) \tag{2.8}$$

with the initial functions,
$\chi_1(t) = \omega_1(t)$, $\chi_2(t) = \omega_2(t)$, $\chi_3(t) = \omega_3(t)$, $\chi_4(t) = \omega_4(t)$ $t \in [-\eta, 0]$.

Equation (2.5) describes the dynamics of activation levels in the amygdala, while equation (2.6) models the activation levels in the hippocampus. Equation (2.7) addresses the activation dynamics of the prefrontal cortex, and equation (2.8) focuses on the activity of the dopamine system. In this context, μ_1 represents the level of anxiety, and a_2 signifies vulnerability to stress-related cortisol. Additionally, all other positive parameters indicate the strength of connections between the various brain regions.

The use of fractional derivatives is motivated by their ability to capture memory and hereditary properties inherent in biological systems. Unlike classical integer-order models, fractional-order derivatives incorporate the influence of past states on the present dynamics. This feature is particularly relevant in neurological disorders

such as schizophrenia, where brain activity depends not only on current stimuli but also on historical neural responses. Therefore, the fractional-order framework provides a more realistic and accurate representation of the underlying brain dynamics compared to integer-order models.

The coexistence of different brain regions such as the amygdala, hippocampus, prefrontal cortex, and dopamine system plays a crucial role in regulating normal cognitive and emotional functions. In schizophrenia, abnormal interactions among these regions lead to impaired neural signaling, cognitive dysfunction, and behavioral disturbances. Therefore, studying their coexistence and interaction dynamics is essential for understanding the progression and underlying mechanisms of the disease.

2.1. Remarks on Model Analysis

The stability and bifurcation analysis of the corresponding integer-order model has been studied in Kaslik, E. et al. [24]. However, the extension to fractional-order systems introduces additional memory effects, which significantly influence system dynamics and make analytical treatment more complex.

In this work, the primary focus is on parameter estimation and uncertainty quantification. Therefore, a detailed analytical stability study of the fractional-order model is beyond the scope of this paper. Instead, the model behavior is assessed through numerical simulations, residual analysis, and parameter estimation techniques.

Furthermore, parameter identifiability is investigated using profile likelihood analysis, while sensitivity is examined using the Fisher Information Matrix. These approaches provide quantitative insight into parameter influence and ensure the robustness of the estimation process.

3. Least squares Approximation

Least squares approximation is widely used for parameter estimation in nonlinear and fractional-order systems, as studied by Guisasola, A. et al. [19], Raue, A. et al. [37] and Ding, F. [13]. It minimizes the discrepancy between observed data and model predictions, making it suitable for biological models where analytical solutions are not readily available. In this study, least squares is employed to estimate the parameters of the proposed fractional-order schizophrenia model. This formulation ensures that the estimation process is both theoretically grounded and supported by existing literature.

The behavior of the dependent variable, χ, is accurately predicted by the robust nonlinear mathematical model (2.5)–(2.8), considering the independent variables'

values, t_1, t_2, t_3, t_4 are known quantities,

$$\chi^* = f(t;\theta) \tag{3.1}$$

where $t = (t_1, t_2, t_3, t_4)^T$ is the vector of the independent variable. The notation χ^* signifies the value that the model predicts for the dependent variable χ, highlighting the accuracy and reliability of our predictive capabilities.

$$\theta = (\mu_1, \mu_2, k_1, k_2, k_3, \zeta_1, \zeta_2, \zeta_3, \gamma_1, \gamma_2, a_1, a_2, \beta, I)^T$$

is the vector that holds the model's parameters; superscript T denotes the vector's transpose; f is a functional relationship.

The vector θ, which contains the model parameters, is calculated from field observations made up of four experimental data points $[(\chi_i, t_i); i = 1, 2, 3, 4]$. The experimental observations do not fully conform to equation (3.1) when the dependent variable is treated as random and subject to measurement error. This discrepancy underscores the complexity of accurately capturing random variability in such contexts. This introduces an error

$$\chi_i = f(t_i, \theta) + \epsilon_i, \quad (i = 1, 2, 3, 4) \tag{3.2}$$

where ϵ_i is defined as the absolute residual or error corresponding to the dependent variable for the ith observation. It is computed using the formula $\epsilon_i = \chi_i - \chi_i^*$, where χ_i represents the actual experimental value obtained for the ith observation, and χ_i^* is the theoretical or predicted value for that observation. t_i is used to denote the ith experimental observation of the variable χ. This categorization allows for a systematic approach to understanding how the observed values deviate from the expected values, and provides a basis for analyzing the consistency and accuracy of the experimental results. By evaluating these residuals, researchers can gain insights into the reliability of their data and potentially identify areas for refinement in their experimental methodologies.

The least squares approach has been widely applied for parameter estimation in biological and engineering systems, as studied by Simkins, S. and Alexander, M. [44] and Dang, J. S. et al. [9], supporting its applicability in the present study. The absolute least squares criterion is a least squares method that has been traditionally used in batch investigations on biodegradation. Time is the independent variable, and concentrations are the dependent variable. The absolute least squares criterion, commonly known as F_1, is a powerful mathematical technique designed to identify the optimal model parameters. It effectively minimizes the sum of the squares of the differences between observed values (χ_i) and predicted values (χ_i^*) for the

dependent variable. By applying this method, researchers can enhance the accuracy of their models, ensuring that predictions align closely with real-world data.

$$F_1 = \sum_{i=1}^{n} [\chi_i - \chi_i^*]^2$$

where n is the number of experimental observations.

Two presumptions form the basis of the absolute least squares criterion, as described by Draper, N. R. [16]. Initially, the random variable $E_i = \chi_i - \chi_i^*$ represents the absolute residual, which has a mean of zero and a constant variance. Secondly, there is no correlation between the residuals for distinct data. The variance of the absolute residual frequently rises as the value of the dependent variable rises, despite the fact that the second assumption is typically true for a large number of experiments, as discussed by Raaijmakers, J. G. [36]. Observations with large magnitude play a crucial role in accurately estimating least squares parameter estimates, far surpassing the significance of low magnitude observations. This is largely due to non-constant variance, which disproportionately weights experimental sites with higher values of the dependent variable. In the context of normal biodegradation batch tests, this challenge becomes even more pronounced when the connections differ by more than one order of magnitude, highlighting the importance of addressing these disparities for reliable results.

Normalizing the function to be reduced is one way to address the uneven-weight issue related to the absolute least squares criterion. Normalization is effectively accomplished by calculating the differences between the measured values and the model-projected values of the dependent variable, then dividing these differences by the measured value itself. This robust method, referred to as the relative least squares approach and denoted by the symbol F_2, offers a unique and powerful way to enhance data accuracy and reliability.

$$F_2 = \sum_{i=1}^{n} \left[\frac{\chi_i - \chi_i^*}{\chi_i} \right]^2$$

The relative least squares criterion has a clear benefit over the traditional absolute least squares criterion since it is in line with the observation that, in the majority of analytical assays, the relative error but not the absolute error as discussed by Zivin, J. A. and Waud, D. R. [50].

3.1. Parameter Estimation Algorithm

The parameter estimation procedure using least squares is summarized as follows:

1. Initialize parameter vector $\theta^{(0)}$ with initial guesses.
2. Solve the fractional-order system (2.5)–(2.8) numerically using MATLAB.
3. Compute predicted values $\chi^*(t_i, \theta)$.
4. Calculate residuals $\epsilon_i = \chi_i - \chi_i^*$.
5. Evaluate cost function:

$$J(\theta) = \sum_{i=1}^{n} (\chi_i - \chi_i^*)^2.$$

6. Update parameters θ using a least squares optimization routine (e.g., MATLAB `lsqnonlin` or `fminsearch`).
7. Repeat steps 2–6 until convergence criteria are satisfied.

4. Fisher information matrix approximation(FIM) Criteria

Since the FIM evaluates the variation in output variables due to model parameter variation, it provides an overview of the relative relevance of each model parameter over the outputs, as discussed by Dochain, D. and Vanrolleghem, P. A. [15] and Guisasola, A. et al. [19]. The representation of the FIM algebraically is

$$FIM = \sum_{i=1}^{N} Y_\theta(k) Q_k^{-1} Y_\theta^T(k) \tag{4.1}$$

The equation Q_k represents the 4×4 covariance matrix of the measurement noise. The vector θ consists of 14 parameters, and N denotes the total number of samples. The output sensitivity function matrix is represented by Y_θ and has dimensions 14×4. The Fisher Information Matrix (FIM) is calculated for four output variables and fourteen parameters, resulting in a 14×14 matrix. Which is,

$$Y_\theta^T = \left[\frac{\partial \chi(t_i, \theta_0)}{\partial \theta^T} \right]_{\theta_0}$$

where θ^T represents the transposed parameter vector that includes the key variables being analyzed, while θ_0 refers to the comprehensive model parameter vector utilized for the calculation of derivatives. This distinction is critical for understanding the nuances of the model's behavior and its response to changes in the parameters under investigation.

5. Parameter Uncertainty:Profile Likelihood

To derive the maximum likelihood estimates of the parameters effectively, it is essential to minimize the negative log-likelihood based on the measurement data, represented as $D = \{(t_i, \chi_i)\}_{i=1}^{n}$. This approach ensures a robust and accurate estimation, leading to more reliable outcomes in your analysis.

$$J_D(\theta) = -logp(D|\theta)$$

Given the parameter vector θ, the likelihood of θ is defined as the conditional probability $p(D|\theta)$, which quantifies the probability of observing the data D. This relationship underscores the crucial role of θ in determining how well our model explains the data we encounter. The expression $\tilde{\theta}^D = \arg\min_\theta J_D(\theta)$ identifies the most effective value of the parameter θ that minimizes the objective function $J_D(\theta)$, showcasing a precise alignment with the measurement data. This optimization improves model accuracy and reliability.

Confidence intervals serve as a powerful tool to convey the uncertainty inherent in estimating a parameter. When we calculate a confidence interval at the level of δ, we can confidently assert that it will encompass the true parameter θ^* in $(\delta \times 100)\%$ of instances, provided that these intervals are derived from genuine realizations of the true parameter θ^*. This statistical framework not only enhances our understanding but also solidifies our trust in the reliability of our estimates.

The aim is to enhance the analysis of confidence intervals by allowing for a seamless exploration of their widths across a diverse range of δ values. We will focus on a critical function that determines the minimum confidence level δ necessary to ensure that the parameter $\theta_i = c$ lies within the corresponding confidence interval $CI_{i,\delta}$. This function is articulated as follows:

$$R_{\theta_i}(c) = \min_\delta\{\delta : c \in CI_{i,\delta}\}$$

.

The sublevel set associated with the level $\log(\delta)$ of the objective function $J_D(\theta)$ provides a powerful interpretation of the confidence interval for the parameter θ_i at the confidence level δ. By employing the profile likelihood ratio, we can effectively quantify the size of these sublevel sets

$$R^{PL}_{\theta_i}(c) = \exp\left(\min_{\theta_j \neq i} J_D(\theta) - J_D(\tilde{\theta}^D)\right) \quad such \;\; that \;\; \theta_i = c,$$

which internally uses the profile likelihood, as discussed by Raue, A. et al.[**?**],

$$PL_{\theta_i}(c) = \min_{\theta_j \neq i} J_D(\theta)$$

6. Numerical Simulations

Using the least squares approximation, we have estimated parameters, as discussed by Wu, F. X. [48], Cois, O. et al. [8], Battaglia, J. L. et al. [4], Khadhraoui, A. et al. [25], Boeker, M. et al. [7], Fröhlich, F. et al. [17] and Machado, V. C. et al. [27]. MATLAB is used to generate the graphs. The parameter values of the model (2.5)-(2.8) are $\mu_1 = 3, \mu_2 = 1, k_1 = 2, k_2 = 1, \zeta_1 = 1, \zeta_2 = 1, \zeta_3 = 1, \gamma_1 = 1, \gamma_2 = 1, a_1 = 2, a_2 = 1, \beta = 0.8, I = 0.83$. The model's least-squares residual and relative residual are displayed in Figure 1. Finding the unknown parameters of the model that best fit a set of experimental data is the aim of parameter estimation. The procedure of estimating parameters should incorporate both a structural and a practical parameter identifiability study. Parameters that are not immediately quantifiable will be identified to ensure that the presented model fits the experimental data as closely as feasible. The parameter estimates for the model depicted in Figure 2 are as follows: μ_1, μ_2; k_1, k_2; ζ_1, k_3; ζ_2, ζ_3; γ_1, γ_2; a_1, a_2 and β, I, respectively. The estimated parameters for $\mu_1, \mu_2, k_1, k_2, k_3, \zeta_1, \zeta_2, \zeta_3, \gamma_1, \gamma_2, a_1, a_2, \beta$ and I are 2.2342, 0.3446, 1.0755, 1.9134, 1.0289, 1.0813, 1.05, 0.9, 1.0077, 1.0927, 1.07, 1.10, 0.3922, and 0.4613, respectively which is shown in figure 3.

Residuals represent the difference between observed and predicted values. A random distribution of residuals around zero indicates a good model fit, confirming that the model adequately captures the underlying data patterns. A good residual pattern validates the predictive and diagnostic power of the model in clinical settings.

$$Residual_i = \chi_i - \chi_i^*.$$

Figure 4 shows the residual plots of the model, which indicates that the model is appropriate for modeling the presented data. More accurate data for real-world performance is provided by a fractional real-life model.

The cost function measures the discrepancy between model outputs and observed data. Minimizing this function ensures optimal parameter estimation and improves the model fit. The used cost function is the least squares error function

$$J(\theta) = \sum_{i=1}^{n} [\chi_i - \chi_i^*]^2,$$

where $J(\theta)$ = The cost function(to be minimized), χ_i = Experimental data at time t_i, χ_i^* = Output of the fractional-order model with parameters θ, N = Total number of data samples and θ = Vector of unknown parameters. Fractional-order models represent systems with memory which is biologically relevant for diseases like schizophrenia that affect dynamic brain responses. Least squares error penalizes large deviations between observed patient data and model outputs and helps

in capturing time dependent dynamics, which is crucial in neuropsychiatric modeling. It allows quantitative comparison across different parameter sets, helping to identify the best fitting model that can simulate brain dynamics. After minimizing the cost function, a lower value of $J(\theta)$ implies a better fit. So the model closely replicates the observed data. The cost function value diagrams for the following are displayed in Figure 5: $\mu_1, \mu_2, k_1, k_2, k_3, \zeta_1, \zeta_2, \zeta_3, \gamma_1, \gamma_2, a_1, a_2, \beta$, and I, independently.

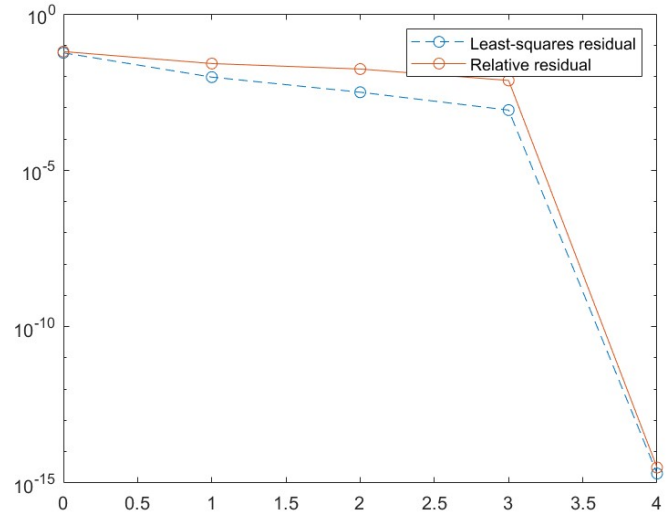


Figure 1: least squares approximation of the model

7. Results and Discussions

In Kaslik, E. et al. [24], authors have considered a time-delay nonlinear model of dopamine modulated prefrontal limbic interactions in schizophrenia and studied the stability and bifurcation analysis for the model. Their results reveal that the importance of time-delays in modulating dopamine reactivity. These results indicate that the model is not only statistically consistent but also dynamically stable under the estimated parameters. The observed behavior suggests that the interactions among brain regions are regulated in a balanced manner, which is crucial for maintaining normal cognitive function and is often disrupted in schizophrenia.

In this study, we have proposed a fractional-order time-delay nonlinear model of dopamine modulated prefrontal limbic interactions in schizophrenia and done the parameter estimation by using least squares approximation method, which min-

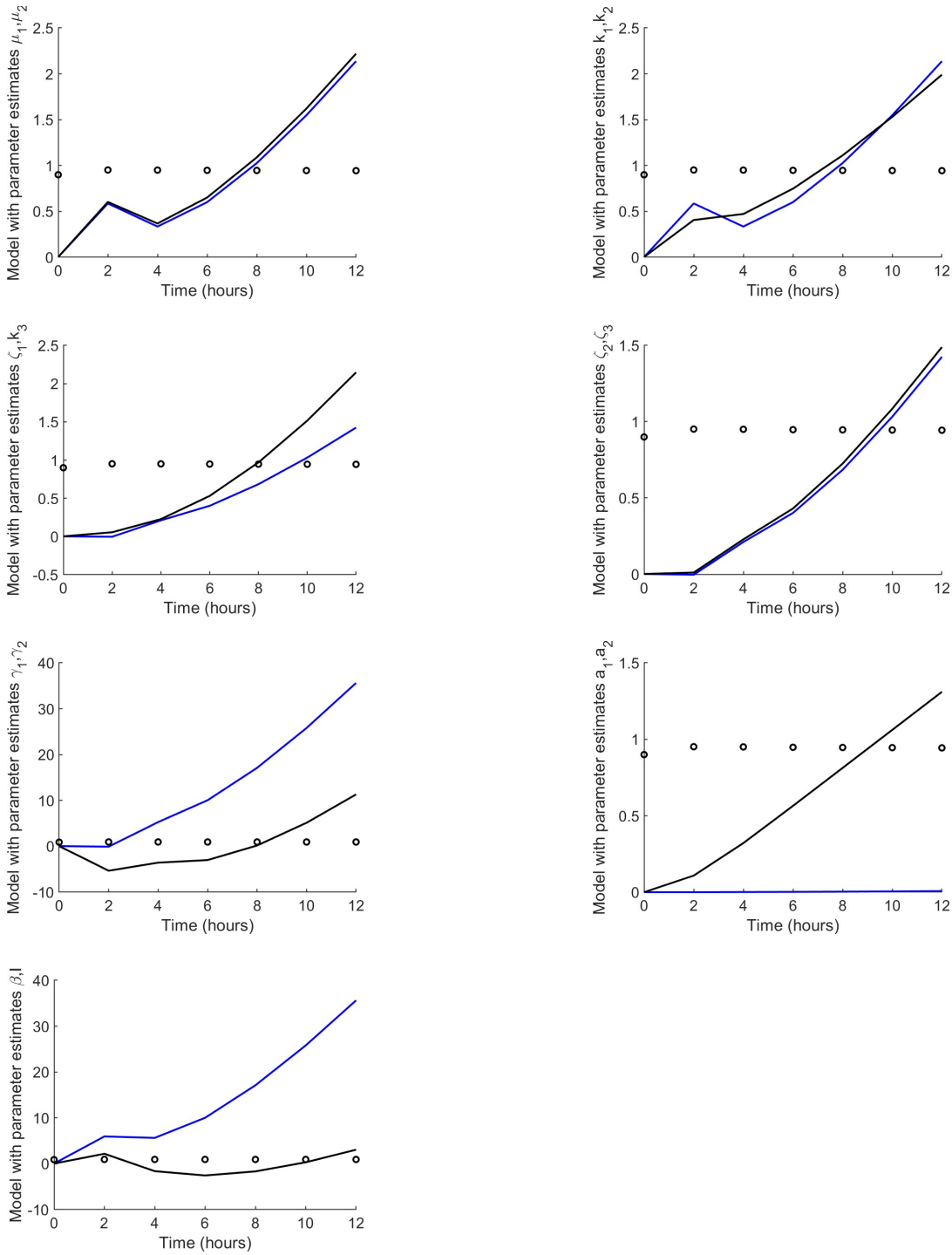
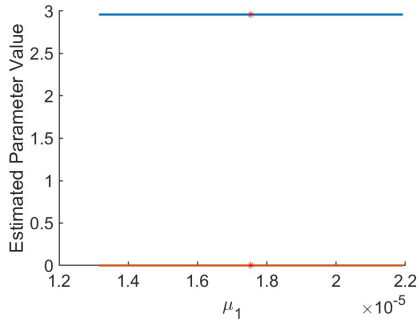
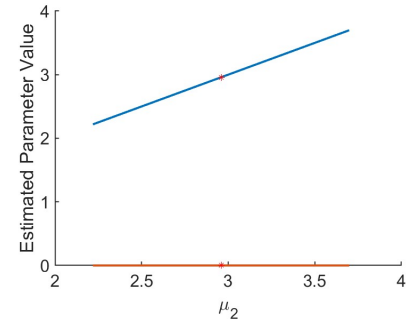
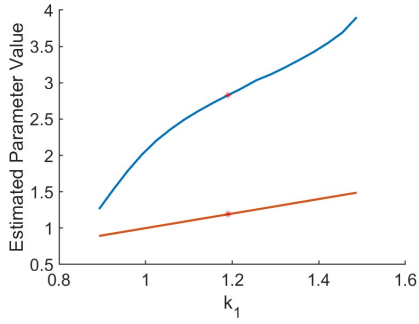
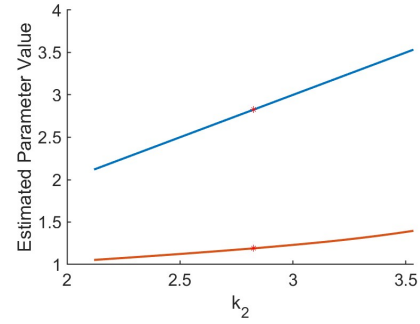


Figure 2: Model with Parameter Estimation


Estimated Parameter Value
μ_1
$\times 10^{-5}$


Estimated Parameter Value
μ_2


Estimated Parameter Value
k_1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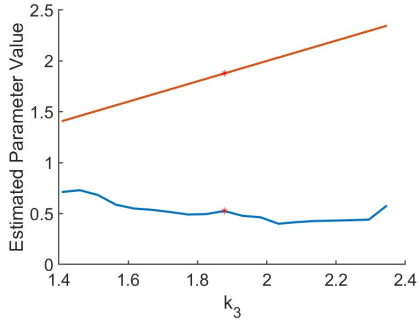
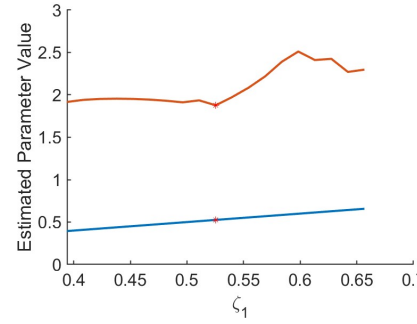
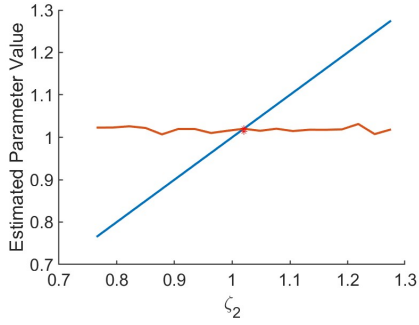

Estimated Parameter Value
k_3


Estimated Parameter Value
ζ_1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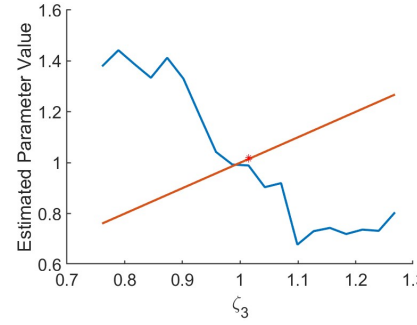
ζ_2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ζ_3

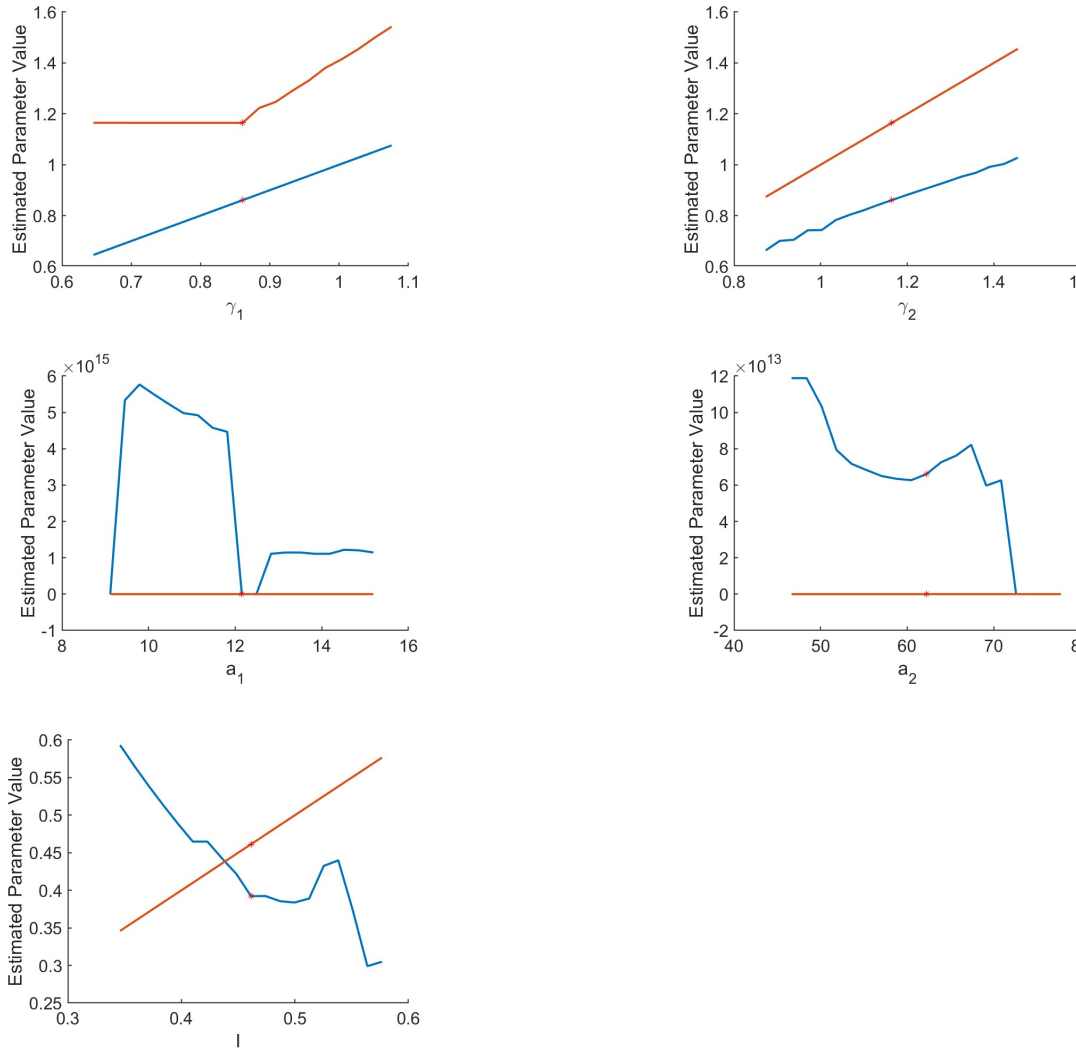


Figure 3: Parameter estimation of the model parameters

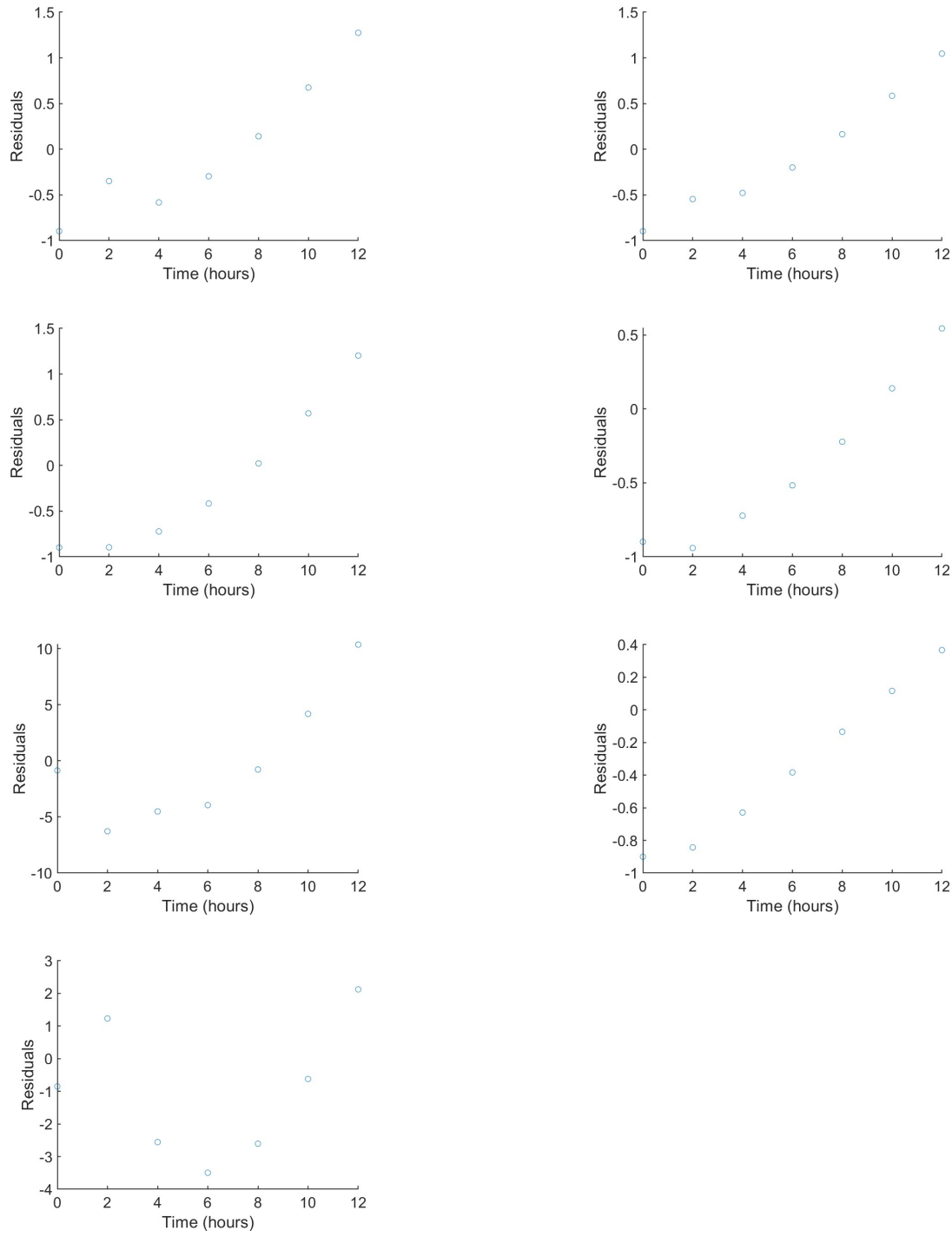
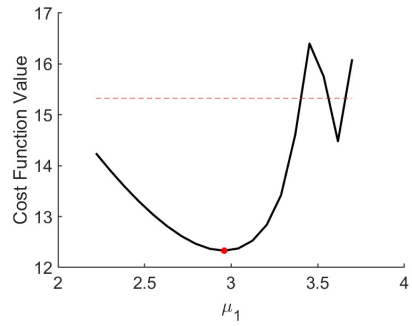
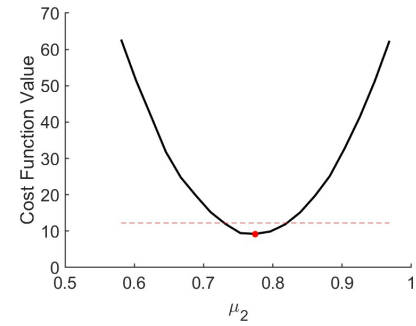
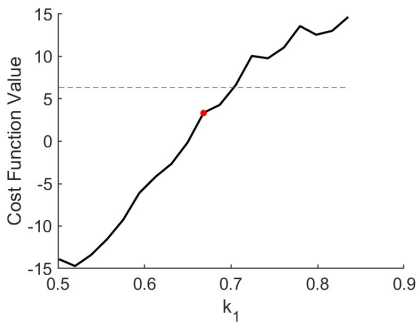
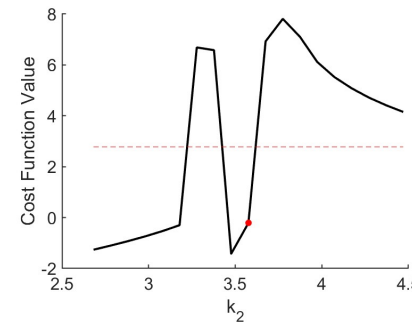


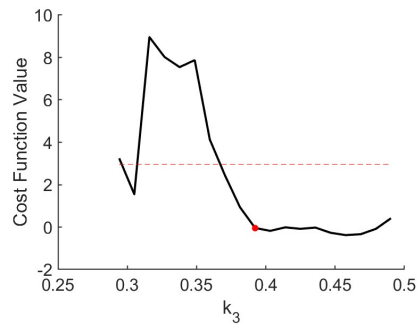
Figure 4: Residuals

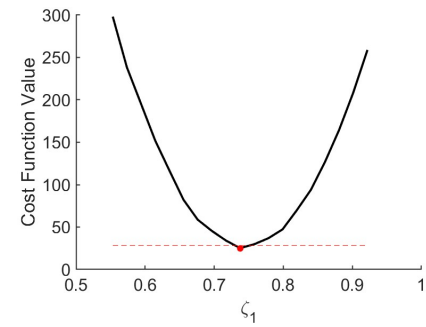

Cost Function Value
μ_1

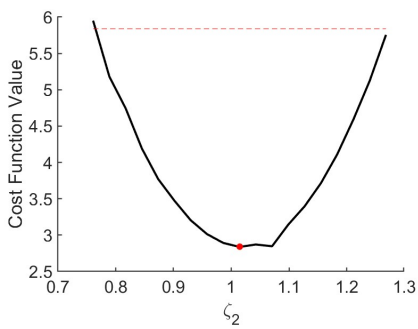

Cost Function Value
μ_2

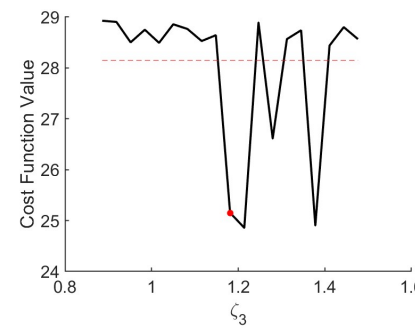

Cost Function Value
k_1


Cost Function Value
k_2


Cost Function Value
k_3


Cost Function Value
ζ_1


Cost Function Value
ζ_2


Cost Function Value
ζ_3

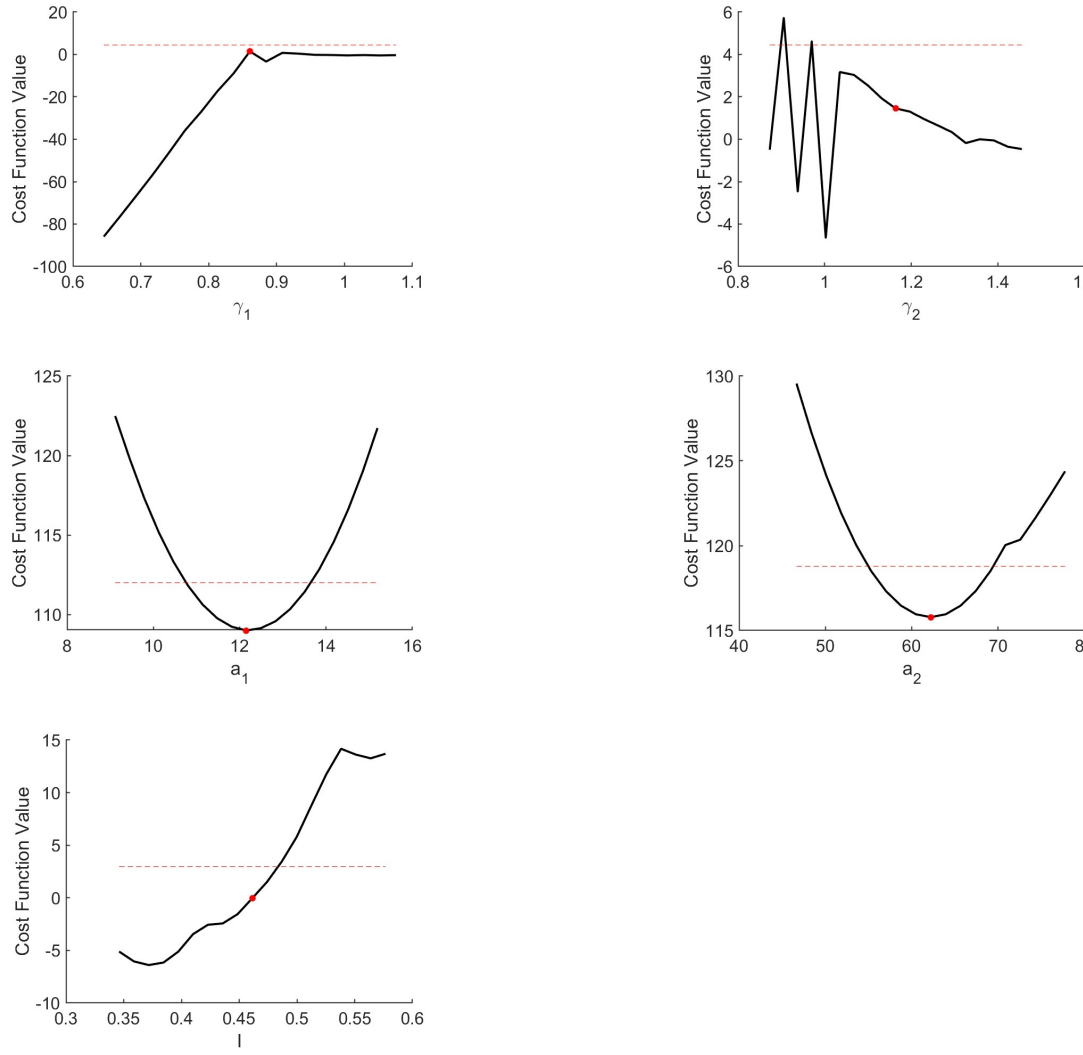


Figure 5: Cost function value

imized the discrepancy between model outputs and empirical observation. The proposed schizophrenia model has long memory behavior and delayed feedback, which traditional models can't capture. The fractional-order model is more realistic than the corresponding integer order model. Our results indicate that least squares parameter estimation in fractional-order time-delay model can meaningfully improve the representation of schizophrenia relevant brain circuits.

The graphical results provide important insights into the model performance. Figure 1 illustrates the least squares and relative residuals, showing a decreasing trend, which indicates convergence of the estimation process. Figure 2 demonstrates the model fitting with estimated parameters, where the predicted values closely follow the observed data, confirming model accuracy. Figure 3 presents the estimated parameter values, highlighting stability in parameter identification. Figure 4 shows residual plots, where residuals are randomly distributed around zero, indicating a good fit and absence of systematic error. Figure 5 depicts cost function profiles for different parameters. The presence of clear minima indicates optimal parameter estimation and model identifiability. These results indicate that the estimated parameters lead to stable neural interactions, where fluctuations in one brain region are regulated through feedback from other regions. This reflects the interconnected nature of brain dynamics in schizophrenia and supports the validity of the proposed model.

From a physiological point of view, the graphical results reflect the dynamic interactions among different brain regions involved in schizophrenia. The convergence observed in the model suggests stabilization of neural activity under the estimated parameters. The residual behavior indicates that the predicted neural responses closely follow the observed patterns, implying that the model effectively captures the underlying brain dynamics. The cost function profiles further indicate optimal parameter values corresponding to stable and consistent neural interactions. These results provide insight into how abnormalities in one brain region can influence the overall system behavior. This highlights the potential of the proposed model to capture pathological alterations in neural connectivity and provides a meaningful framework for understanding the progression of schizophrenia from a dynamical systems perspective.

7.1. Data Description and Validation

The data used for parameter estimation in this study is obtained from the model presented in Kaslik, E. et al. [24], which describes dopamine-modulated prefrontal-limbic interactions in schizophrenia. The dataset represents simulated observations of neural activity across four brain regions: amygdala, hippocampus, prefrontal cortex, and dopamine system.

The time-series data consist of discrete observations corresponding to different time points, which are used to estimate model parameters through the least squares method. Although the data are not derived from clinical experiments, they are consistent with previously validated models in the literature.

To validate the model, residual analysis and cost function minimization are performed. The residual plots demonstrate that the model predictions closely match the observed data, indicating a good fit. Furthermore, the convergence of the cost function confirms the reliability of the estimated parameters.

8. Conclusion

In this study, a fractional-order nonlinear schizophrenia model with time-delay has been analyzed, and its parameters have been estimated using the least squares method. The inclusion of fractional dynamics captures memory effects, while time-delay represents delayed neural responses, enhancing the realism of the model. Parameter estimation is supported by residual analysis, the Fisher Information Matrix (FIM), and profile likelihood. The results indicate that interactions among key brain regions evolve toward stable patterns, reflecting regulated neural activity, and the model provides a good fit to observed behavior. However, the study is limited by simplified assumptions and the absence of real clinical data, as well as the lack of detailed sensitivity and stability analysis. Future work will focus on incorporating clinical datasets, extending the model with additional biological factors, and performing sensitivity and stability analysis. The integration of artificial intelligence-based approaches may further improve predictive capability.

9. Data Availability

The data used for parameter estimation is taken from Kaslik, E. et al. [24].

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