

Hybrid Neural and Numerical Inverse Identification of Fractional Memory and Regulatory Parameters in a Caputo Glucose Insulin Beta Cell Model

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Running title: Hybrid neural numerical inversion

Abstract

Fractional-order models introduce memory into nonlinear dynamical systems but also turn parameter estimation into a computationally expensive inverse problem because each objective evaluation requires a history-dependent forward solve. We develop a hybrid neural–numerical framework for simultaneous identification of the Caputo order and selected regulatory parameters in a three-state glucose–insulin–beta-cell model. A fractional Adams–Bashforth–Moulton predictor–corrector method generates reference trajectories, while a local scaled-sensitivity analysis is used to screen candidate unknowns before inversion. The screening reveals near-collinearity between the sensitivities associated with two regulatory coefficients (correlation -0.986); excluding the redundant coefficient reduces the sensitivity-matrix condition number from approximately 38.6 to 3.46. A parametric neural surrogate with inputs (t, α, a_1, a_{15}) is then trained on 220 Latin-hypercube trajectories using trajectory-level train/validation/test separation. On the 20 held-out trajectories, statewise coefficients of determination exceed 0.9997 and RMSEs are below 9.7×10^{-4} . In a synthetic inverse benchmark with 20 independent noise realizations at each nonzero level, the surrogate-assisted method obtains median mean parameter errors of 0.76%, 1.39%, and 2.47% at 1%, 3%, and 5% observation noise, respectively; direct numerical inversion gives 0.86%, 1.52%, and 2.40%. Across 12 additional unseen parameter triples at 1% noise, the surrogate inversion has a median mean parameter error of 1.75%. Every recovered parameter set is independently verifiable with the fractional numerical solver. The experiments use dimensionless synthetic data and do not constitute clinical calibration; rather, they demonstrate a reproducible strategy for combining identifiability screening, a learned forward map, regularized inversion, and independent numerical verification in a nonlinear fractional system.

Keywords: inverse problems; Caputo fractional dynamics; glucose–insulin regulation; parameter identification; neural surrogate; fractional Adams–Moulton; scientific machine learning.

MSC 2020: 34A08; 65L09; 65K10; 68T07; 92C30.

1 Introduction

Inverse identification in fractional differential equations combines two difficulties: the unknown parameters influence a nonlinear dynamical response, and each evaluation of that response contains a nonlocal memory operator. This makes repeated optimization substantially more expensive than the corresponding integer-order problem. At the same time, the inverse map

can be poorly conditioned when several parameters produce similar trajectory perturbations. These two issues—computational cost and identifiability—must be addressed together if machine learning is to accelerate an inverse problem without obscuring its numerical reliability.

Caputo models are attractive in applications because they retain classical pointwise initial conditions while introducing a power-law memory kernel [1, 2]. Predictor–corrector schemes of Adams type provide a well-established numerical route for nonlinear fractional initial-value problems [3]. In parallel, neural approximations have become important tools for forward and inverse scientific computing. Physics-informed neural networks combine observations with differential-equation residuals [4], and fractional extensions have demonstrated inverse identification of fractional orders and transport parameters [5]. The present work follows a different hybrid route: the network does not replace the governing equations or define a physics-informed residual. Instead, it learns a parametric forward map generated by a conventional fractional solver and is embedded in a regularized inverse optimization. The recovered parameters are then reinserted into an independent high-resolution fractional solve.

Glucose–insulin regulation provides a useful nonlinear test system. Mathematical models of glucose homeostasis have long been used to study endocrine feedback, parameter sensitivity, and control [6–8]. Shabestari et al. [9] proposed a three-state polynomial regulatory model involving insulin-related, glucose-related, and beta-cell-related states. Here we use the coefficients and initial condition from that source as a dimensionless computational benchmark and introduce a common Caputo order $0 < \alpha < 1$ to represent history dependence. No patient observations, dimensional calibration, or clinical thresholds are used.

The contribution of this study is fourfold:

- (i) the forward model is transcribed and audited against the source coefficient table before fractionalization;
- (ii) a scaled local-sensitivity analysis identifies a near-collinear parameter pair and motivates a better-conditioned three-unknown inverse problem;
- (iii) a trajectory-level neural surrogate learns the map $(t, \alpha, a_1, a_{15}) \mapsto (x, y, z)$ over a parameter box rather than fitting isolated time series; and
- (iv) the inverse estimates are tested under increasing noise, incomplete observations, and unseen parameter triples, with direct fractional inversion and independent numerical verification as baselines.

The resulting framework is designed for the intersection of inverse problems, numerical methods, and artificial intelligence: learning accelerates the repeated forward evaluations, whereas the classical solver remains the verification authority.

2 Fractional glucose–insulin–beta-cell model

Let $x(t)$, $y(t)$, and $z(t)$ denote dimensionless insulin-related, glucose-related, and beta-cell-related states. The polynomial model of Shabestari et al. [9] is

$$\begin{cases} \dot{x} = -a_1x + a_2xy + a_3y^2 + a_4y^3 + a_5z + a_6z^2 + a_7z^3 + a_{20}, \\ \dot{y} = -a_8xy - a_9x^2 - a_{10}x^3 + a_{11}y(1 - y) - a_{12}z - a_{13}z^2 - a_{14}z^3 + a_{21}, \\ \dot{z} = a_{15}y + a_{16}y^2 + a_{17}y^3 - a_{18}z - a_{19}yz. \end{cases} \quad (1)$$

The coefficient values used throughout the numerical study are listed in Table 1. The signs in Eq. (1) and the signed numerical values in the table are kept separately; this avoids changing the model inadvertently when a coefficient itself is negative.

Table 1: Dimensionless coefficient set used for the computational benchmark, transcribed from Shabestari et al. [9].

a_1	a_2	a_3	a_4	a_5	a_6	a_7
2.04	0.10	1.09	-1.08	0.03	-0.06	2.01
a_8	a_9	a_{10}	a_{11}	a_{12}	a_{13}	a_{14}
0.22	-3.84	-1.20	0.30	1.37	-0.30	0.22
a_{15}	a_{16}	a_{17}	a_{18}	a_{19}	a_{20}	a_{21}
0.30	-1.35	0.50	-0.42	-0.15	-0.19	-0.56

We replace each first derivative by a Caputo derivative of common order $\alpha \in (0, 1)$,

$${}^C D_t^\alpha \mathbf{u}(t) = \mathbf{F}(\mathbf{u}(t); \mathbf{a}), \quad \mathbf{u}(0) = \mathbf{u}_0 = (0.53, 1.31, 1.03)^\top, \quad (2)$$

where $\mathbf{u} = (x, y, z)^\top$ and $\mathbf{F}$ is the right-hand side of Eq. (1). For a sufficiently smooth scalar function v ,

$${}^C D_t^\alpha v(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t (t-s)^{-\alpha} v'(s) ds. \quad (3)$$

The order α is treated here as a mathematical memory parameter. Because the model variables and coefficients are dimensionless and are not calibrated to individual physiology, estimates of α or a_j must not be interpreted as clinical biomarkers.

Figure 1 illustrates the corrected fractional forward model for three orders. The trajectories remain in a compact range on the benchmark interval $0 \leq t \leq 1$, which is important for the bounded inverse experiments that follow.

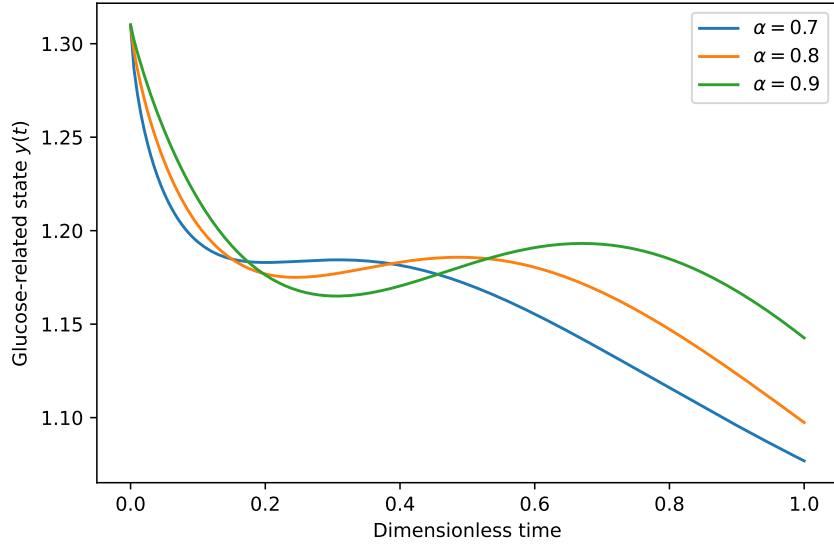


Figure 1: Glucose-related state $y(t)$ from the audited fractional forward model for three memory orders.

3 Fractional reference solver

The reference trajectories are generated by the fractional Adams–Bashforth–Moulton predictor–corrector method of Diethelm, Ford, and Freed [3]. For the generic system

$${}^C D_t^\alpha \mathbf{u}(t) = \mathbf{F}(t, \mathbf{u}(t)), \quad \mathbf{u}(0) = \mathbf{u}_0, \quad (4)$$

with $t_n = nh$, the predictor is

$$\mathbf{u}_{n+1}^P = \mathbf{u}_0 + \frac{h^\alpha}{\Gamma(\alpha+1)} \sum_{j=0}^n b_{j,n+1} \mathbf{F}(t_j, \mathbf{u}_j), \quad (5)$$

where

$$b_{j,n+1} = (n+1-j)^\alpha - (n-j)^\alpha. \quad (6)$$

The corrector is

$$\mathbf{u}_{n+1} = \mathbf{u}_0 + \frac{h^\alpha}{\Gamma(\alpha+2)} \left[\mathbf{F}(t_{n+1}, \mathbf{u}_{n+1}^P) + \sum_{j=0}^n a_{j,n+1} \mathbf{F}(t_j, \mathbf{u}_j) \right], \quad (7)$$

with

$$a_{0,n+1} = n^{\alpha+1} - (n-\alpha)(n+1)^\alpha, \quad (8)$$

$$a_{j,n+1} = (n-j+2)^{\alpha+1} + (n-j)^{\alpha+1} - 2(n-j+1)^{\alpha+1}, \quad 1 \leq j \leq n. \quad (9)$$

A step-refinement check at $\alpha = 0.85$ compares each solution with an $h = 0.00125$ reference. Table 2 shows systematic error decay, with empirical maximum-error orders between approximately 1.87 and 2.19 over the tested refinements. The inverse computations use $h = 0.01$ for repeated direct solves and $h = 0.0025$ for independent verification.

Table 2: Step-refinement audit for the fractional predictor–corrector solver at $\alpha = 0.85$.

h	maximum error	RMS error	empirical order (max.)
0.0200	5.3261×10^{-4}	2.1487×10^{-4}	—
0.0100	1.4624×10^{-4}	5.9408×10^{-5}	1.865
0.0050	3.8643×10^{-5}	1.5769×10^{-5}	1.920
0.0025	8.4809×10^{-6}	3.4703×10^{-6}	2.188

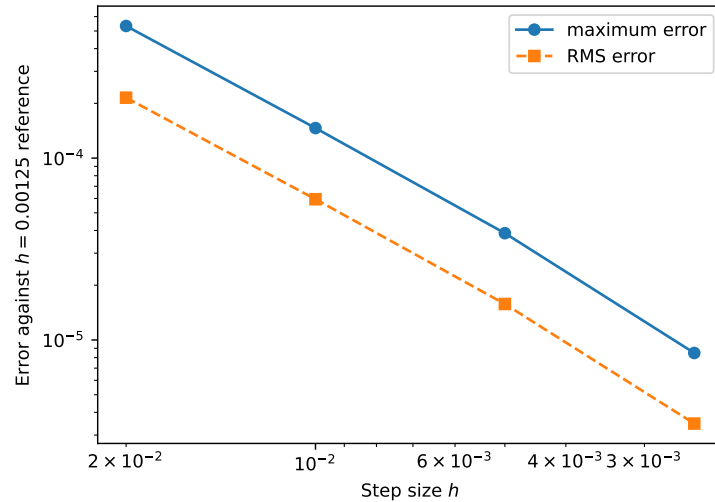


Figure 2: Step-refinement error of the fractional reference solver.

4 Inverse formulation and identifiability screening

Suppose that observations are available at times t_i through an observation operator $\mathcal{H}$,

$$\mathbf{y}_i^\delta = \mathcal{H}\mathbf{u}(t_i; \mathbf{q}) + \boldsymbol{\varepsilon}_i, \quad i = 1, \dots, N_{\text{obs}}, \quad (10)$$

where $\mathbf{q}$ collects the unknown fractional order and regulatory coefficients. The inverse estimate minimizes a scaled Tikhonov functional [11],

$$\hat{\mathbf{q}} = \arg \min_{\mathbf{q} \in \mathcal{Q}} \left\{ \sum_{i=1}^{N_{\text{obs}}} \left\| \mathbf{W} [\mathcal{H}\mathbf{u}(t_i; \mathbf{q}) - \mathbf{y}_i^\delta] \right\|_2^2 + \lambda \left\| \mathbf{D}(\mathbf{q} - \mathbf{q}_0) \right\|_2^2 \right\}. \quad (11)$$

Here $\mathbf{W}$ and $\mathbf{D}$ are diagonal scaling matrices whose entries are the reciprocals of the state RMS magnitudes and the admissible parameter-interval widths, respectively; $\mathbf{q}_0$ is the nominal parameter vector, and $\lambda = 10^{-2}$ in all reported tests.

4.1 Scaled local sensitivity matrix

Before solving Eq. (11), we examine four plausible unknowns,

$$\mathbf{q}_4 = (\alpha, a_1, a_7, a_{15})^\top. \quad (12)$$

Let $\mathbf{Y}(\mathbf{q})$ be the stacked three-state observations at 21 equally spaced times. Each sensitivity column is approximated by a centered finite difference and nondimensionalized by the parameter range and state RMS. The resulting matrix $\mathbf{S}$ is used to inspect column norms, correlations, and subset condition numbers.

The strongest warning is the a_1 – a_7 sensitivity correlation, -0.98637 . Although both columns have substantial norms, their effects are nearly collinear over the observation window. Retaining both produces a poorly conditioned inverse subproblem. Table 3 shows that replacing a_7 by a_{15} reduces the condition number by more than one order of magnitude. We therefore identify

$$\boxed{\mathbf{q} = (\alpha, a_1, a_{15})^\top} \quad (13)$$

and keep a_7 fixed at its nominal value.

Table 3: Identifiability screening based on the scaled local sensitivity matrix.

Candidate unknown set	$\kappa_2(\mathbf{S})$
(α, a_1, a_7)	38.45
(α, a_1, a_{15})	3.46
(α, a_7, a_{15})	4.34
$(\alpha, a_1, a_7, a_{15})$	38.63

The admissible box is

$$0.70 \leq \alpha \leq 0.95, \quad 0.85a_1^{(0)} \leq a_1 \leq 1.15a_1^{(0)}, \quad 0.85a_{15}^{(0)} \leq a_{15} \leq 1.15a_{15}^{(0)}. \quad (14)$$

This screening is local and does not prove global uniqueness; its purpose is to prevent an avoidable ill-conditioned parameterization before neural training and inversion.

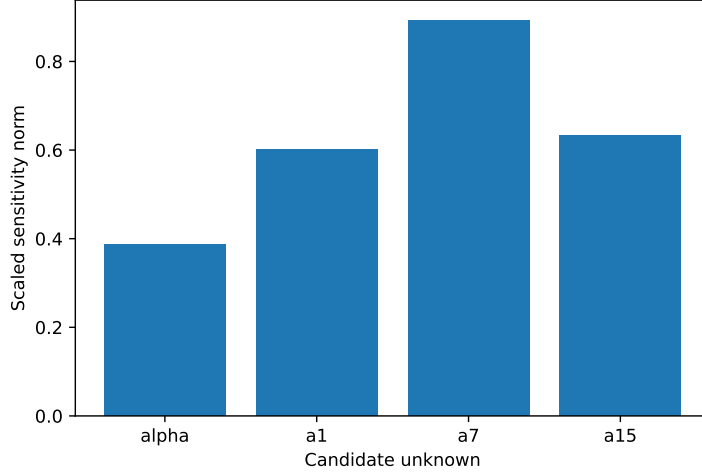


Figure 3: Scaled sensitivity norms for the four screened candidate unknowns. Large norm alone does not imply identifiability; the a_1 and a_7 columns are nearly collinear.

5 Parametric neural forward surrogate

The surrogate approximates the solution operator

$$\mathcal{N}_\theta : (t, \alpha, a_1, a_{15}) \mapsto (x, y, z). \quad (15)$$

A Latin hypercube design [10] supplies 220 parameter triples in the box (14). For each triple, the fractional solver with $h = 0.01$ generates 101 states on $t \in [0, 1]$. Crucially, the split is made by complete trajectories: 180 parameter triples are used for training, 20 for validation, and 20 for testing. No time points from a held-out parameter triple appear in the training data.

The network has architecture 4–64–64–64–3 with hyperbolic-tangent hidden activations and a linear output layer. Inputs are mapped to $[-1, 1]$ using the parameter bounds, outputs are standardized from the training trajectories, and the network is optimized with Adam. The loss is a supervised state error rather than a fractional-equation residual. Accordingly, the model is a solver-trained parametric surrogate, not a PINN. This distinction is intentional: the governing model is enforced by the training database and by the independent numerical verification step rather than by automatic differentiation of a nonlocal operator.

On the 20 held-out trajectories, the surrogate errors are summarized in Table 4. All R^2 values exceed 0.9997. The glucose-related state has the largest RMSE, 9.60×10^{-4} , and the largest pointwise error, 1.26×10^{-2} .

Table 4: Held-out trajectory accuracy of the parametric neural surrogate.

State	RMSE	maximum absolute error	R^2
x	5.116×10^{-4}	5.156×10^{-3}	0.999822
y	9.599×10^{-4}	1.264×10^{-2}	0.999722
z	4.160×10^{-4}	3.101×10^{-3}	0.999923

6 Hybrid inversion and verification

The direct baseline evaluates Eq. (11) by calling the fractional solver at each trial parameter vector. The hybrid method replaces that repeated forward solve by $\mathcal{N}_\theta$ during optimization,

$$\hat{\mathbf{q}}_{\text{NN}} = \arg \min_{\mathbf{q} \in \mathcal{Q}} \left\{ \sum_i \left\| \mathbf{W}[\mathcal{H}\mathcal{N}_\theta(t_i, \mathbf{q}) - \mathbf{y}_i^\delta] \right\|_2^2 + \lambda \left\| \mathbf{D}(\mathbf{q} - \mathbf{q}_0) \right\|_2^2 \right\}. \quad (16)$$

Both minimizations use a bounded nonlinear least-squares algorithm initialized at $\mathbf{q}_0 = (0.85, 2.04, 0.30)^\top$. After surrogate inversion, the estimate is never accepted solely from the neural output: the fractional solver is rerun at $\hat{\mathbf{q}}_{\text{NN}}$ with $h = 0.0025$ and compared with the observations or synthetic reference. The workflow is therefore

fractional solver $\rightarrow$ trajectory database $\rightarrow$ neural surrogate
 $\rightarrow$ inverse optimization $\rightarrow$ fractional verification.

7 Numerical inverse experiments

7.1 Noise robustness and comparison with direct inversion

The primary synthetic truth is

$$(\alpha^\dagger, a_1^\dagger, a_{15}^\dagger) = (0.83, 2.15, 0.315), \quad (17)$$

which is not one of the nominal parameter vectors. Twenty-one equally spaced three-state observations are generated by the $h = 0.0025$ fractional solver. For each state, independent zero-mean Gaussian noise has standard deviation δ times that state’s RMS. The nonzero levels $\delta = 1\%, 3\%, 5\%$ each use 20 independent realizations; the noise-free case is deterministic.

Table 5 compares the median parameter-recovery errors. Both methods degrade smoothly with noise. The two methods have comparable median errors over the tested noise range: the surrogate is slightly lower at 1% and 3% noise, whereas the direct solver is slightly lower at 5% noise. The surrogate’s principal advantage is computational: it avoids the history-dependent solve during the optimization loop.

Table 5: Inverse recovery under synthetic observation noise. Errors are medians across 20 realizations for each nonzero noise level. “Mean error” is the mean of the three relative parameter errors within each run, followed by the median across runs.

Noise	Method	E_α (%)	E_{a_1} (%)	$E_{a_{15}}$ (%)	mean error (%)
0%	Direct	0.93	0.29	0.49	0.57
0%	Surrogate	0.85	0.40	0.48	0.58
1%	Direct	1.28	0.40	0.67	0.86
1%	Surrogate	0.54	1.06	0.54	0.76
3%	Direct	2.23	1.36	1.42	1.52
3%	Surrogate	1.41	1.77	1.08	1.39
5%	Direct	3.99	1.11	2.05	2.40
5%	Surrogate	2.06	2.69	2.39	2.47

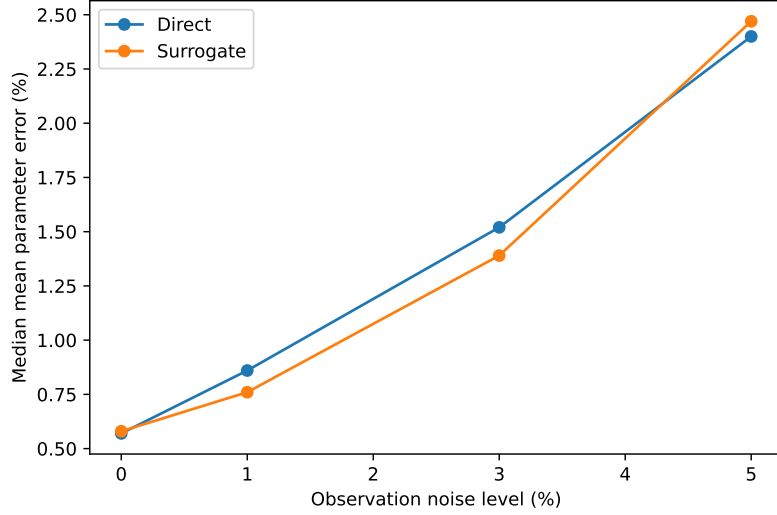


Figure 4: Median mean parameter error versus observation noise for direct and surrogate-assisted inversion.

7.2 Incomplete observations

To probe information loss, the surrogate inverse is repeated at 1% noise with three observation operators: all three states; only (x, y) ; and only y . Table 6 shows that the full-state inverse remains below 1% median mean error, whereas glucose-only observation raises the error to approximately 4%. This is consistent with the sensitivity analysis: reducing the observation operator removes information needed to distinguish memory and regulatory effects.

Table 6: Surrogate-assisted inversion with incomplete observations at 1% noise (20 realizations).

Observed states	E_α (%)	E_{a_1} (%)	$E_{a_{15}}$ (%)	mean error (%)
x, y, z	0.81	0.87	0.68	0.79
x, y	2.12	1.95	2.06	2.04
y only	2.81	3.92	4.61	3.79

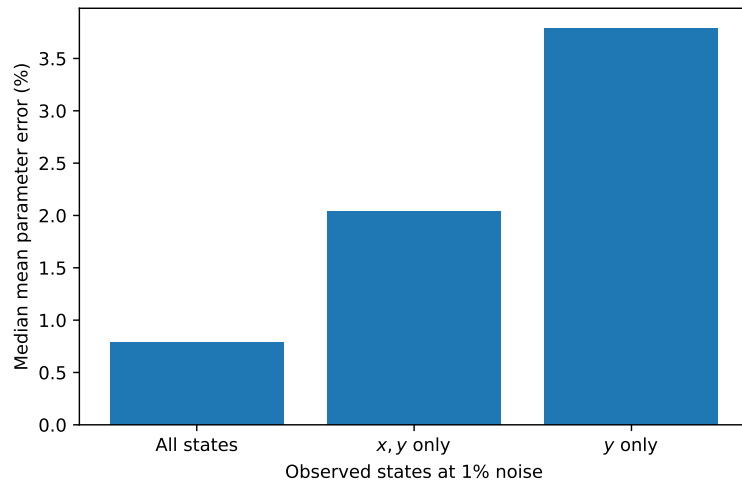


Figure 5: Effect of reducing the observation operator on inverse recovery at 1% noise.

7.3 Generalization to unseen inverse truths

A single inverse truth can conceal parameter-specific bias, so the surrogate is also tested on 12 additional parameter triples drawn from the held-out design. Each case uses 1% synthetic observation noise and was excluded from neural training. The median of the casewise mean parameter errors is 1.75%, the mean is 2.09%, and the worst case is 4.11%. The fractional order is the most difficult of the three quantities in this experiment, with a median relative error of 3.42%; the corresponding median errors for a_1 and a_{15} are 1.11% and 0.92%.

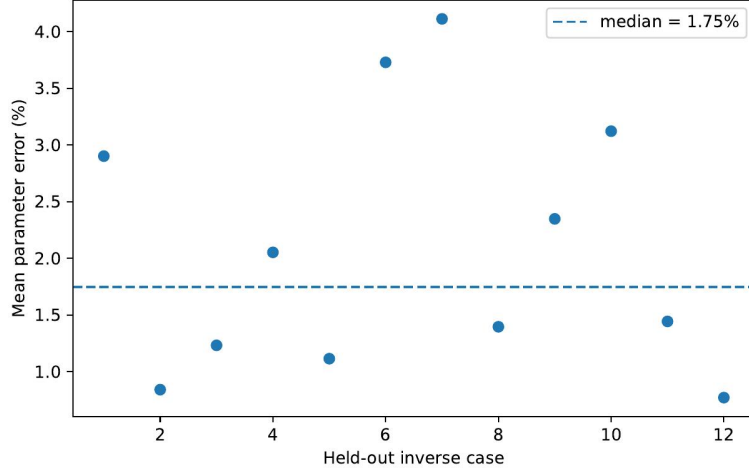


Figure 6: Casewise mean parameter error for 12 unseen inverse truths at 1% observation noise. The dashed line is the median across cases.

7.4 Forward-evaluation cost

A simple timing benchmark over 101 time points gives approximately 3.64×10^{-3} s per fractional forward solve with $h = 0.01$ and 1.77×10^{-4} s per neural-surrogate evaluation in the execution environment used for this audit, corresponding to an approximately 20.6-fold forward-evaluation speedup. These values are hardware- and software-dependent and should be interpreted only as an implementation benchmark. The inverse wall-clock advantage depends additionally on optimizer evaluations and batching.

8 Discussion

The numerical evidence supports three conclusions. First, inverse parameter selection matters before machine learning is introduced. The sensitivity matrix shows that two individually influential coefficients can nevertheless be jointly unidentifiable because their trajectory derivatives are almost collinear. The large condition number of (α, a_1, a_7) would have made a four-parameter neural inverse appear more difficult for reasons unrelated to neural approximation. Screening the parameterization first yields a better-posed numerical experiment.

Second, a supervised forward surrogate can be useful in a fractional inverse loop even though it is not a physics-informed network. The distinction is methodological. A PINN attempts to enforce the governing operator during network training [4, 5]; our network instead approximates a family of trusted numerical forward solutions. Its role is computational acceleration. Reliability is recovered by keeping the classical fractional scheme in the workflow as both data generator and post-inversion verifier.

Third, inverse performance must be assessed beyond random pointwise train/test splits. All neural tests here are separated at the trajectory level, and the inverse benchmarks include noise,

incomplete observation operators, and unseen parameter triples. The resulting degradation under glucose-only observation is particularly informative: excellent forward interpolation does not imply that all inverse quantities remain recoverable from limited data.

The framework also has limitations. The benchmark interval is short and dimensionless; the coefficient set is inherited from a theoretical model rather than calibrated from clinical data; only three parameters are identified; the sensitivity analysis is local; uncertainty is summarized through repeated synthetic noise rather than a posterior distribution; and the neural architecture has not been exhaustively optimized. A biologically stronger study would require dimensional reconstruction, real glucose/insulin observations, model discrepancy treatment, structural identifiability analysis, and external validation. A mathematically stronger extension could combine global identifiability diagnostics, Bayesian inversion, adaptive surrogate refinement, or a residual-aware fractional operator in the learning stage.

9 Conclusions

We presented a hybrid neural–numerical inverse framework for a nonlinear Caputo glucose–insulin–beta-cell model. The workflow begins with an audited fractional forward system and a converged Adams-type solver, uses sensitivity geometry to select a better-conditioned unknown set, trains a parametric neural forward surrogate on complete trajectories, performs bounded regularized inversion, and finally verifies the inferred parameters with the classical fractional solver.

For the synthetic benchmarks considered here, the surrogate accurately generalizes across held-out forward trajectories and recovers (α, a_1, a_{15}) with median mean parameter errors below 0.8% at 1% observation noise and approximately 2.5% at 5% noise. Across 12 additional unseen inverse truths, the median casewise mean error is 1.75%. The main methodological message is not that a neural network replaces the fractional solver, but that a verified neural forward map can reduce repeated-solve cost while the numerical method preserves an auditable connection to the governing equations.

Acknowledgments

The authors acknowledge the computational resources used to perform the numerical experiments. No patient-level or clinical data were used.

Author contributions (CRediT)

Alvaro H. Salas: Conceptualization; Methodology; Formal analysis; Software; Validation; Writing – original draft; Writing – review and editing; Supervision. **Gilder Cieza Altamirano:** Methodology; Investigation; Validation; Visualization; Writing – review and editing. Both authors approved the submitted version and accept responsibility for the integrity of the work.

Declarations

Funding

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests

The authors declare no competing interests.

Data Availability Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request. All datasets used in the numerical experiments are simulated from the dimensionless mathematical model described in this article.

Ethics approval

Not Applicable.

Consent to Participate

Not Applicable.

Consent for Publication

Not Applicable.

AI-assisted preparation disclosure

Generative artificial-intelligence tools assisted language editing and organization of the computational workflow. The authors reviewed the manuscript, equations, code, references, and numerical outputs and take responsibility for the final content.

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