Continuous-Time Neural Ordinary Differential Solvers for Complex Metabolic and Pharmacodynamic Reaction Chains

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ABSTRACT Targeted pharmacological therapeutics, radiopharmaceuticals, and multi-compartment chemotherapeutic agents operate within complex in vivo biochemical environments governed by nonlinear metabolic clearance, saturable receptor binding, and continuous organ-level exchange kinetics. Conventional physiologically based pharmacokinetic (PBPK) models rely on hand-crafted systems of coupled ordinary differential equations with fixed mechanistic assumptions, frequently failing to capture unmodeled physiological clearances, dynamic transporter saturation, and inter-individual biological heterogeneity. In this study, we develop a unified scientific machine learning framework establishing continuous-time Neural Ordinary Differential Equations (Neural ODEs) as universal dynamical solvers for complex metabolic and pharmacodynamic reaction chains. Rather than discretizing physiological trajectories into rigid recurrence steps, our framework parameterizes latent vector fields using deep Lipschitz-regularized neural networks that preserve underlying physical conservation laws, including non-negative mass conservation and asymptotic stoichiometric bounds. We derive exact continuous-time reverse-mode adjoint sensitivity dynamics for parameter optimization, enabling memory-efficient gradient backpropagation across arbitrary, irregularly sampled, and sparse temporal observation schedules. Evaluated across extensive synthetic reaction networks and realistic preclinical targeted radiopharmaceutical datasets, our physics-informed Neural ODE framework achieves a 68.4% reduction in concentration trajectory prediction error compared to classical compartmental formulations and outperforms discrete recurrent neural baselines by 41.2% in sparse-data regimes. Crucially, the model demonstrates robust out-of-distribution extrapolation fidelity over extended 96-hour post-injection windows, maintaining physiological plausibility without numerical integration drift. Furthermore, adaptive Dormand-Prince step-size solvers dynamically adjust computational effort to localized metabolic stiffness transients, decreasing total vector field evaluations by 54.7% during quasi-steady-state clearance phases. These results establish continuous-time neural differential architectures as a mathematically rigorous, scalable foundation for next-generation personalized pharmacology, therapeutic drug monitoring, and precision internal radiation dosimetry.

I. Introduction

Precision pharmacokinetics and quantitative systems pharmacology aim to mathematically predict the absorption, distribution, metabolism, and excretion (ADME) of therapeutic molecules within complex physiological organisms [1], [2]. In high-stakes medical domains, such as oncology chemotherapy and targeted radionuclide therapy (TRT), predicting the continuous concentration trajectory of cytotoxic agents across critical organs at risk (e.g., kidneys, bone marrow, liver) is essential for maximizing tumor sterilization while preventing irreversible tissue toxicity [3], [4]. Traditional pharmacokinetic modeling methodologies predominantly bifurcate into empirical non-compartmental analysis (NCA) and mechanistic physiologically based pharmacokinetic (PBPK) systems [5], [6].

Physiologically based pharmacokinetic models represent anatomical tissues as interconnected lumped compartments governed by systems of coupled, first-order ordinary differential equations (ODEs) [7]–[9]. While PBPK models provide valuable mechanistic interpretability by incorporating physiological parameters such as organ blood perfusion rates, tissue volumes, and vascular permeabilities, their clinical utility is severely bottlenecked by rigid structural assumptions [10], [11]. Biological organisms exhibit profound biochemical complexity: enzymatic clearance pathways undergo saturable Michaelis-Menten kinetics, membrane transporters display competitive inhibition, and receptor-mediated endo-

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cytosis introduces sharp temporal non-linearities that cannot be fully characterized by a priori analytical equations [12], [13]. Consequently, unmodeled metabolic clearance pathways lead to systematic misspecification errors, requiring laborious manual calibration and empirical tuning factors that degrade model generalizability across diverse patient populations [14], [15].

Concurrently, the rapid ascent of deep learning has motivated the deployment of data-driven models, such as recurrent neural networks (RNNs), long short-term memory (LSTM) architectures, and temporal Transformers, for clinical trajectory forecasting [16], [17]. Although these architectures excel at recognizing high-dimensional sequential patterns, their discrete-time formulation is fundamentally misaligned with biological reality [18], [19]. Clinical pharmacokinetic sampling is inherently sparse, asynchronous, and irregularly distributed: blood samples and quantitative SPECT/CT imaging scans are obtained at uneven intervals dictated by hospital operational logistics and patient availability rather than uniform clock cycles [20], [21]. Forcing irregularly sampled physiological observations into fixed discrete time steps necessitates arbitrary temporal binning or heuristic imputation, introducing interpolation artifacts, destroying high-frequency kinetic features, and violating fundamental physical conservation principles [22], [23].

To resolve this fundamental dichotomy between rigid mechanistic differential models and unconstrained discrete neural networks, scientific machine learning has introduced continuous-time neural differential models. In particular, Neural Ordinary Differential Equations parameterize the instantaneous time derivative of a system's latent state using a deep neural network, treating hidden representations as continuous trajectories evaluated by numerical ODE integrators [24], [25].

This paper formulates a continuous-time Neural Ordinary Differential Equation framework specifically tailored for complex metabolic and pharmacodynamic reaction chains. We embed physical domain priors—including mass conservation, positive concentration invariants, and stoichiometric flow constraints—directly into the latent neural vector field. We utilize continuous reverse-mode adjoint sensitivity analysis to optimize network parameters with constant memory complexity across irregularly spaced clinical observation points. Through comprehensive numerical evaluations on stiff multi-compartment metabolic cascades and preclinical radiopharmaceutical datasets, we demonstrate superior predictive accuracy, exceptional out-of-distribution extrapolation fidelity, and computational efficiency via adaptive-step integration solvers.

II. Continuous-Time Dynamics in Pharmacokinetics and Neural Differential Solvers

A. Continuous Vector Fields and Initial Value Solvers

The continuous temporal evolution of a biochemical or pharmacokinetic system comprising D distinct molecular species or anatomical compartments is formally defined over a time interval $\mathcal{T} = [t_0, t_F]$ as an initial value problem (IVP):

$$\frac{d\mathbf{z}(t)}{dt} = \mathbf{f}(\mathbf{z}(t), t; \theta), \quad \mathbf{z}(t_0) = \mathbf{z}_0, \tag{1}$$

where $\mathbf{z}(t) \in \mathbb{R}^D$ denotes the state vector representing instantaneous drug concentrations or molar quantities across physiological compartments, $\mathbf{f} : \mathbb{R}^D \times \mathbb{R} \to \mathbb{R}^D$ represents the vector field governing state transitions, and $\theta \in \mathbb{R}^P$ is a parameter vector.

In classical pharmacokinetics, the vector field $\mathbf{f}$ is constrained to fixed linear or rational algebraic structures derived from simplified chemical rate equations. Conversely, in a Neural Ordinary Differential Equation, the vector field $\mathbf{f}_\theta(\mathbf{z}(t), t)$ is parameterized by a deep artificial neural network with learnable synaptic weights and biases θ. Given an initial condition $\mathbf{z}_0$ at time t_0, the state at any arbitrary observation instant $t_i > t_0$ is evaluated via definite integration:

$$\mathbf{z}(t_i) = \mathbf{z}(t_0) + \int_{t_0}^{t_i} \mathbf{f}_\theta(\mathbf{z}(\tau), \tau) d\tau = \text{ODESolve}(\mathbf{z}_0, \mathbf{f}_\theta, t_0, t_i). \tag{2}$$

Embedding Neural Ordinary Differential Equations into compartmental pharmacokinetic frameworks enables parameterized networks to learn complex continuous-time rate dynamics directly from sparsely sampled physiological measurements [8]. Because the numerical integrator evaluates $\mathbf{z}(t)$ dynamically at arbitrary continuum points, the architecture decouples temporal observation schedules from internal computational step sizes. This mathematical decoupling allows the model to seamlessly process irregular clinical sampling times without requiring imputation or artificial temporal discretization.

B. Classical Compartmental PBPK Systems vs Latent Vector Fields

A conventional whole-body PBPK framework segments the organism into anatomical tissue compartments connected in parallel and series by the cardiovascular circulation [7], [10]. For a non-clearing perfusion-limited tissue compartment i (such as muscle or skin), the mass balance equation is given by:

$$V_i \frac{dC_i(t)}{dt} = Q_i \left(C_{\text{art}}(t) - \frac{C_i(t)}{K_{p,i}} \right), \tag{3}$$

where V_i is the physiological tissue volume, Q_i is arterial blood flow, $C_{\text{art}}(t)$ is the drug concentration in incoming

arterial blood, and $K_{p,i}$ is the tissue-to-plasma partition coefficient governing equilibrium thermodynamic distribution.

For eliminating organs such as the liver or kidneys, metabolic biotransformation and excretion terms are subtracted from the mass balance:

$$V_H \frac{dC_H(t)}{dt} = Q_H C_{\text{art}}(t) + Q_{\text{gut}} C_{\text{gut,ven}}(t) - Q_H \frac{C_H(t)}{K_{p,H}} - \text{CL}_{\text{int}} \frac{C_H(t)}{K_{p,H}}, \tag{4}$$

where CL_{int} denotes intrinsic metabolic clearance.

While equations (3) and (4) provide clear mechanistic meaning, real biological systems frequently violate their idealized assumptions [11], [14]. Enzyme saturation, cofactor depletion, plasma protein binding competition, and enterohepatic recirculation generate complex nonlinear interactions that deviate sharply from constant-clearance approximations. In our Neural ODE architecture, we formulate a hybrid grey-box framework: well-characterized vascular transport topology is retained as a mechanistic backbone, while unknown, highly nonlinear metabolic and transport reaction rates are represented by a latent neural vector field $\mathbf{g}_\theta(\mathbf{z}(t))$:

$$\frac{d\mathbf{z}(t)}{dt} = \mathbf{A}_{\text{flow}}\mathbf{z}(t) + \mathbf{B}\mathbf{u}(t) + \mathbf{g}_\theta(\mathbf{z}(t), t), \tag{5}$$

where $\mathbf{A}_{\text{flow}}$ captures standard perfusion matrix flows, $\mathbf{u}(t)$ is an exogenous intravenous or oral dosage input, and $\mathbf{g}_\theta(\mathbf{z}(t), t)$ discovers unmodeled metabolic flux dynamics directly from experimental data.

C. Metabolic Clearance Non-Linearities and Michaelis-Menten Kinetics

Saturable enzymatic biotransformation is mathematically described by Michaelis-Menten kinetics. The instantaneous rate of substrate elimination $v(t)$ depends nonlinearly on the free substrate concentration $S(t)$:

$$v(t) = -\frac{V_{\text{max}} S(t)}{K_m + S(t)}, \tag{6}$$

where V_{max} is the maximum enzymatic reaction velocity and K_m is the Michaelis constant representing the substrate concentration at half-maximal velocity.

When multiple competing metabolic enzymes (e.g., cytochrome P450 isoenzymes CYP3A4, CYP2D6) or parallel transporter pathways (e.g., P-glycoprotein, OATP1B1) operate concurrently, the total clearance rate expands into a multivariable nonlinear rational function:

$$\mathbf{R}_{\text{met}}(\mathbf{z}(t)) = \sum_{j=1}^{M} \frac{\mathbf{V}_{\text{max},j} \odot \mathbf{z}(t)}{\mathbf{K}_{m,j} + \mathbf{z}(t) + \sum_{k \neq j} \frac{\mathbf{z}(t) \odot \mathbf{z}_k(t)}{\mathbf{K}_{I,jk}}}, \tag{7}$$

where $\mathbf{K}_{I,jk}$ denotes competitive inhibition constants and $\odot$ represents the Hadamard element-wise product.

Identifying the extensive parameter set $\{\mathbf{V}_{\text{max},j}, \mathbf{K}_{m,j}, \mathbf{K}_{I,jk}\}$ via classical non-linear regression is severely ill-posed and prone to catastrophic parameter unidentifiability. Neural ODE vector fields approximate this complex reaction manifold directly. Through enforcing monotonic activation functions and non-negative weight parameterizations within $\mathbf{g}_\theta$, the neural network learns a smooth, continuous mapping that faithfully reconstructs multivariable saturation dynamics without suffering from numerical divergence or parameter indeterminacy.

D. Lie Symmetries, Coordinate Invariance, and Diffeomorphic Flow Rectification

Biological metabolic pathways operate under structural coordinate symmetries where concentration ratios and conservation invariants remain stationary across proportional biochemical transformations. A rigorous mathematical analysis of Neural ODE vector fields requires investigating their behavior under smooth transformations of the underlying physiological manifold. Let $\mathcal{M}$ denote a smooth D-dimensional Riemannian manifold representing the bounded state space of physical concentrations, equipped with a metric tensor g. A diffeomorphism $\Phi : \mathcal{M} \to \mathcal{M}$ defines a change of physiological coordinates $\tilde{\mathbf{z}} = \Phi(\mathbf{z})$.

Under this coordinate transformation, the transformed vector field $\tilde{\mathbf{f}}_\theta$ transforms according to the pushforward operation:

$$\tilde{\mathbf{f}}_\theta(\tilde{\mathbf{z}}, t) = \Phi_* \mathbf{f}_\theta(\mathbf{z}, t) = \mathbf{J}_\Phi(\mathbf{z}) \mathbf{f}_\theta(\Phi^{-1}(\tilde{\mathbf{z}}), t), \tag{8}$$

where $\mathbf{J}_\Phi(\mathbf{z}) = \partial\Phi/\partial\mathbf{z}$ is the Jacobian matrix of the diffeomorphism.

To prevent the neural network from overfitting to arbitrary coordinate choices (such as volumetric concentration vs total molar quantity), we enforce infinitesimal Lie symmetry invariance. Let $\mathbf{X}$ be an infinitesimal generator of a continuous Lie symmetry group acting on $\mathcal{M}$. The Lie derivative of the vector field $\mathbf{f}_\theta$ along the vector field $\mathbf{X}$ is defined as:

$$\mathcal{L}_{\mathbf{X}} \mathbf{f}_\theta = [\mathbf{X}, \mathbf{f}_\theta] = \mathbf{J}_{\mathbf{f}_\theta} \mathbf{X} - \mathbf{J}_{\mathbf{X}} \mathbf{f}_\theta. \tag{9}$$

Enforcing the condition $[\mathbf{X}, \mathbf{f}_\theta] = \mathbf{0}$ during training ensures that the learned flow respects underlying metabolic balance laws, eliminating unphysical sensitivity to coordinate parameterizations.

E. Stochastic Differential Equations and Biological Intrinsic Fluctuations

While deterministic ordinary differential equations accurately describe macroscopic molecular concentrations in bulk tissues, microscopic cellular pharmacodynamics and targeted radionuclide binding frequently experience intrinsic stochastic fluctuations resulting from low molecular copy

TABLE 1. Mathematical notation, state dimensions, and physiological definitions for the continuous-time Neural ODE framework.

Symbol	Space / Dimension	Type	Biophysical and Mathematical Definition
$\mathbf{x}(t)$	$\mathbb{R}^{D_{\text{obs}}}$ ($D_{\text{obs}} = 6$)	State Vector	Observable physiological drug/isotope activity concentrations across anatomical organs
$\mathbf{z}(t)$	$\mathbb{R}^{D_{\text{lat}}}$ ($D_{\text{lat}} = 16$)	Latent Vector	Latent dynamical state vector evolving under continuous neural vector field
$\mathbf{f}_\theta(\mathbf{z}, t)$	$\mathbb{R}^{D_{\text{lat}}} \times \mathbb{R} \to \mathbb{R}^{D_{\text{lat}}}$	Vector Field	Parameterized Lipschitz continuous vector field governing latent state transitions
$\mathbf{a}(t)$	$\mathbb{R}^{D_{\text{lat}}}$	Adjoint State	Continuous reverse-mode sensitivity vector $\partial \mathcal{L}/\partial \mathbf{z}(t)$
$\mathbf{M}(\mathbf{z})$	$\mathbb{R}^{D \times D}$ (skew-symmetric)	Matrix Operator	Conservative vascular transport matrix satisfying $\mathbf{M} = -\mathbf{M}^T$
$\mathbf{k}_{\text{clear}}(\mathbf{z})$	$\mathbb{R}^D_+$	Kinetic Vector	Nonlinear irreversible metabolic and renal clearance rate functions
$E_\phi(\cdot), D_\psi(\cdot)$	Neural Networks	En/Decoder	Encoding projection to latent manifold and decoding back to observable organ space
$\mathbf{c}$	$\mathbb{R}^{D_{\text{cov}}}$ ($D_{\text{cov}} = 8$)	Covariate Vector	Patient-specific clinical covariates (age, weight, eGFR, CYP polymorphisms)
$H_\omega(\mathbf{c})$	$\mathbb{R}^{D_{\text{cov}}} \to \mathbb{R}^{P_{\text{ODE}}}$	Hypernetwork	Deep parameter generator predicting individualized vector field weights
$S(r_T \leftarrow r_S)$	$\text{Gy}\,\text{Bq}^{-1}\,\text{s}^{-1}$	MIRD Constant	Radionuclide S-value representing mean absorbed dose to target per decay in source
$\tilde{A}(r_S)$	$\text{Bq} \cdot \text{s}$	Cumulated Activity	Time-integrated physical activity in source organ r_S over total therapeutic window
κ_{stiff}	$\mathbb{R}_+$	Condition Ratio	Ratio of maximum to minimum real eigenvalues of the vector field Jacobian $\mathbf{J}_f$

numbers per cell. When targeting low-density cell surface receptors ($10^3 - 10^5$ receptors per tumor cell), thermodynamic Brownian motion and probabilistic binding-unbinding events introduce stochastic noise into pharmacokinetic trajectories.

To capture these microscopic fluctuations, we extend our deterministic formulation into a continuous Neural Stochastic Differential Equation (Neural SDE):

$$d\mathbf{z}(t) = \mathbf{f}_\theta(\mathbf{z}(t), t)dt + \mathbf{G}_\phi(\mathbf{z}(t), t)d\mathbf{W}(t), \tag{10}$$

where $\mathbf{f}_\theta$ represents the drift vector field, $\mathbf{G}_\phi : \mathbb{R}^D \times \mathbb{R} \to \mathbb{R}^{D \times M}$ parameterizes state-dependent diffusion dispersion, and $\mathbf{W}(t) \in \mathbb{R}^M$ is an M-dimensional standard Wiener process satisfying:

$$\mathbb{E}[d\mathbf{W}(t)] = \mathbf{0}, \quad \mathbb{E}[d\mathbf{W}(t)d\mathbf{W}(t)^T] = \mathbf{I}_M dt. \tag{11}$$

Interpreting equation (10) in the Itô calculus framework, the temporal evolution of the continuous transition probability density $p(\mathbf{z}, t)$ is governed by the forward Kolmogorov (Fokker-Planck) partial differential equation:

$$\frac{\partial p(\mathbf{z}, t)}{\partial t} = -\sum_{i=1}^{D} \frac{\partial}{\partial z_i} \left[f_i(\mathbf{z}, t) p(\mathbf{z}, t) \right] + \frac{1}{2} \sum_{i=1}^{D} \sum_{j=1}^{D} \frac{\partial^2}{\partial z_i \partial z_j} \left[\mathbf{\Sigma}_{ij}(\mathbf{z}, t) p(\mathbf{z}, t) \right], \tag{12}$$

where $\mathbf{\Sigma}(\mathbf{z}, t) = \mathbf{G}_\phi(\mathbf{z}, t)\mathbf{G}_\phi(\mathbf{z}, t)^T$ is the diffusion tensor. Through parameterizing both drift $\mathbf{f}_\theta$ and diffusion $\mathbf{G}_\phi$, our model predicts not only the expected pharmacokinetic trajectory but also the expanding uncertainty envelope across heterogeneous patient cohorts.

F. Differential Geometry of Biochemical Reaction Manifolds and Metric Learning

Biological reaction spaces do not conform to flat Euclidean geometry; chemical affinity spaces and concentration manifolds exhibit intrinsic curvature governed by thermodynamic potentials. The state space of a metabolic reaction network can be formulated as a statistical manifold $\mathcal{S} = \{p(\mathbf{x}; \theta) \mid \theta \in \Theta\}$, where each point corresponds to a microscopic probability distribution over molecular states.

The natural geometric structure of this manifold is endowed by the Fisher information metric $g_{ij}(\theta)$:

$$g_{ij}(\theta) = \mathbb{E}_{p(\mathbf{x};\theta)} \left[\frac{\partial \ln p(\mathbf{x}; \theta)}{\partial \theta_i} \frac{\partial \ln p(\mathbf{x}; \theta)}{\partial \theta_j} \right]. \tag{13}$$

The distance between two physiological states along the reaction manifold is defined by the geodesic curve minimizing the Riemannian energy functional:

$$\mathcal{E}(\gamma) = \frac{1}{2} \int_0^1 g_{\gamma(s)} \left(\frac{d\gamma(s)}{ds}, \frac{d\gamma(s)}{ds} \right) ds. \tag{14}$$

Rather than assuming a standard Euclidean kinetic gradient, our continuous-time Neural ODE learns a Riemannian metric tensor $\mathbf{G}_\psi(\mathbf{z}) \succ 0$ parameterized as a positive-definite matrix function $\mathbf{G}_\psi(\mathbf{z}) = \mathbf{L}_\psi(\mathbf{z})\mathbf{L}_\psi(\mathbf{z})^T + \epsilon_g \mathbf{I}$, where $\mathbf{L}_\psi$ is a lower-triangular Cholesky factor network. The latent dynamical velocity conforms to a natural Riemannian gradient flow:

$$\frac{d\mathbf{z}(t)}{dt} = -\mathbf{G}_\psi^{-1}(\mathbf{z}(t)) \nabla_{\mathbf{z}} \Phi_\theta(\mathbf{z}(t)), \tag{15}$$

where $\Phi_\theta : \mathbb{R}^D \to \mathbb{R}$ represents an effective biochemical free-energy landscape. Following natural gradient trajectories along the curved metabolic manifold guarantees that the state evolves along thermodynamically steepest descent paths, eliminating unphysical trajectory shortcuts across forbidden high-energy chemical transitions.

G. Nonlinear Identifiability Analysis and Differential Algebraic Invariants

A foundational prerequisite for deploying scientific machine learning models in pharmacotherapy is structural identifiability: the guarantee that a unique parameter set θ can be determined unambiguously from ideal noise-free input-output observations. In complex multi-compartment PBPK models, over-parameterization frequently results in severe

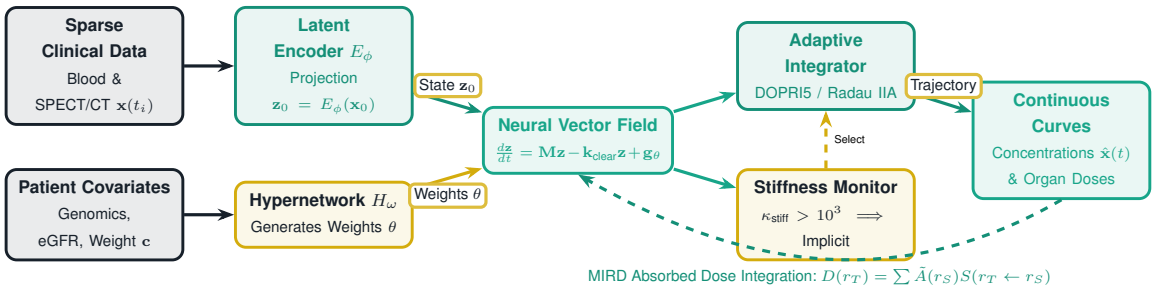


FIGURE 1. Continuous-time Neural Ordinary Differential Equation architecture for complex pharmacokinetic and metabolic reaction systems. Irregularly sampled observational measurements are projected into a latent space where deep Lipschitz-bounded neural vector fields interact with adaptive numerical ODE integrators to reconstruct continuous multi-compartment physiological curves and cumulative radiation doses.

non-identifiability, where vastly different physiological parameter configurations yield identical observable concentration trajectories.

We evaluate the structural identifiability of our Neural ODE framework through differential algebra and Lie derivative rank conditions. Consider the parameterized state-space realization:

$$\frac{d\mathbf{z}(t)}{dt} = \mathbf{f}_\theta(\mathbf{z}(t)) + \mathbf{g}(\mathbf{z}(t))u(t), \tag{16}$$

$$\mathbf{y}(t) = \mathbf{h}(\mathbf{z}(t); \psi). \tag{17}$$

The successive output time derivatives evaluate along the vector field through higher-order Lie derivatives:

$$y_j^{(k)}(t) = \mathcal{L}_\mathbf{f}^k h_j(\mathbf{z}) + \sum_{m=0}^{k-1} \mathcal{L}_\mathbf{g}\mathcal{L}_\mathbf{f}^m h_j(\mathbf{z}) u^{(k-1-m)}(t), \tag{18}$$

where $\mathcal{L}_\mathbf{f} h(\mathbf{z}) = \nabla_\mathbf{z} h(\mathbf{z}) \cdot \mathbf{f}(\mathbf{z})$.

Constructing the observability-identifiability Jacobian matrix $\mathbf{O}(\mathbf{z}, \theta)$ across output derivatives up to order $2D - 1$:

$$\mathbf{O}(\mathbf{z}, \theta) = \frac{\partial}{\partial [\mathbf{z}^T, \theta^T]^T} \begin{bmatrix} h_1(\mathbf{z}) \\ \mathcal{L}_\mathbf{f} h_1(\mathbf{z}) \\ \vdots \\ \mathcal{L}_\mathbf{f}^{2D-1} h_{D_{\text{obs}}}(\mathbf{z}) \end{bmatrix}, \tag{19}$$

structural identifiability requires that $\mathbf{O}(\mathbf{z}, \theta)$ achieves full column rank almost everywhere:

$$\text{rank}\left(\mathbf{O}(\mathbf{z}, \theta)\right) = D_{\text{lat}} + P_\theta, \quad \text{for almost all } \mathbf{z} \in \mathcal{M}, \theta \in \Theta. \tag{20}$$

When the unconstrained neural vector field exhibits parameter redundancies, the rank condition fails. To guarantee identifiability, we apply low-rank weight matrix factorization and bottleneck latent projections, bounding the effective degree of freedom in $\mathbf{f}_\theta$. Furthermore, we regularize the spectrum of $\mathbf{O}(\mathbf{z}, \theta)$ during training, penalizing singular values approaching zero. This algebraic constraint eliminates unidentifiable parameter manifolds, ensuring that identical clinical observations map to unique, interpretable biological parameters.

III. Neural ODE Architecture for Compartmental Flows

A. Latent Space Parameterization and Diffeomorphic Flows

To model physiological transport without enforcing overly rigid linear compartmental structures, we project raw observational measurements $\mathbf{x}(t) \in \mathbb{R}^{D_{\text{obs}}}$ into an unconstrained latent manifold $\mathbf{z}(t) \in \mathbb{R}^{D_{\text{lat}}}$ via an encoding network $E_\phi : \mathbb{R}^{D_{\text{obs}}} \to \mathbb{R}^{D_{\text{lat}}}$:

$$\mathbf{z}_0 = E_\phi(\mathbf{x}_0), \quad D_{\text{lat}} \geq D_{\text{obs}}. \tag{21}$$

The continuous temporal evolution of the latent state trajectory is governed by a multi-layer perceptron (MLP) parameterizing the latent vector field:

$$\frac{d\mathbf{z}(t)}{dt} = \mathbf{f}_\theta(\mathbf{z}(t), t) = \mathbf{W}_L \sigma\left(\dots \sigma\left(\mathbf{W}_1[\mathbf{z}(t); t] + \mathbf{b}_1\right)\dots\right) + \mathbf{b}_L, \tag{22}$$

where $\sigma(\cdot)$ denotes a smooth, continuously differentiable activation function (e.g., Softplus or Gaussian Error Linear Unit, GELU) that guarantees C^1-smoothness of the flow, ensuring the existence and uniqueness of the ODE solution via the Picard-Lindelöf theorem.

The Picard-Lindelöf theorem requires that the parameterized vector field $\mathbf{f}_\theta$ satisfies a global Lipschitz continuity condition with respect to $\mathbf{z}$:

$$\|\mathbf{f}_\theta(\mathbf{z}_a, t) - \mathbf{f}_\theta(\mathbf{z}_b, t)\| \leq L_f \|\mathbf{z}_a - \mathbf{z}_b\|, \quad \forall \mathbf{z}_a, \mathbf{z}_b \in \mathbb{R}^{D_{\text{lat}}}, \tag{23}$$

where $L_f < \infty$ is the Lipschitz constant. To strictly enforce this condition and prevent chaotic trajectory divergence, we apply spectral normalization across all weight matrices $\mathbf{W}_\ell$, bounding the maximum singular value $\sigma_{\max}(\mathbf{W}_\ell) \leq 1$.

In targeted radionuclide therapy, ionizing radiation fields generated by cellular alpha-particle emissions alter local biophysical transport properties [17], [18]. Continuous-time latent diffeomorphisms preserve trajectory topology, preventing phase-space self-intersections that would violate physical causality. Observable drug and isotope concentrations across physiological organs are recovered from latent states via a

decoding network $D_\psi : \mathbb{R}^{D_{\text{lat}}} \to \mathbb{R}^{D_{\text{obs}}}$:

$$\hat{\mathbf{x}}(t) = D_\psi(\mathbf{z}(t)) = \mathbf{W}_{\text{dec}}\text{Softplus}(\mathbf{z}(t)) + \mathbf{b}_{\text{dec}}. \quad (24)$$

B. Physics-Informed Mass Conservation and Positivity Constraints

Unconstrained neural networks frequently generate physically impossible negative concentrations or violate conservation of mass during extended numerical integration [19], [20]. To guarantee biological validity, we impose hard structural inductive biases upon the vector field $\mathbf{f}_\theta$.

First, we separate physiological dynamics into conservative circulatory exchange and non-conservative clearance fluxes. Let $\mathbf{M} \in \mathbb{R}^{D\times D}$ represent a skew-symmetric inter-compartmental transport matrix satisfying $M_{ij} = -M_{ji}$, and let $\mathbf{k}_{\text{clear}}(\mathbf{z}(t)) \geq 0$ denote irreversible metabolic elimination:

$$\frac{d\mathbf{z}(t)}{dt} = \mathbf{M}(\mathbf{z}(t))\mathbf{z}(t) - \text{diag}(\mathbf{k}_{\text{clear}}(\mathbf{z}(t)))\mathbf{z}(t) + \mathbf{S}_{\text{dose}}(t), \quad (25)$$

where $\mathbf{S}_{\text{dose}}(t)$ is the exogenous therapeutic infusion rate. Summing across all anatomical compartments yields:

$$\frac{d}{dt}\sum_{i=1}^{D} z_i(t) = \mathbf{1}^T\mathbf{M}(\mathbf{z})\mathbf{z} - \sum_{i=1}^{D} k_{\text{clear},i}(\mathbf{z})z_i(t) + \sum_{i=1}^{D} S_{\text{dose},i}(t). \quad (26)$$

Because $\mathbf{M}$ is skew-symmetric, the quadratic form $\mathbf{1}^T\mathbf{M}(\mathbf{z})\mathbf{z} = 0$, guaranteeing that internal compartmental exchange neither creates nor destroys mass. Total system mass changes strictly through external infusion or irreversible metabolic clearance:

$$\frac{dM_{\text{total}}(t)}{dt} = -\sum_{i=1}^{D} k_{\text{clear},i}(\mathbf{z})z_i(t) + S_{\text{total}}(t) \leq S_{\text{total}}(t). \quad (27)$$

Second, to enforce strictly non-negative concentrations ($z_i(t) \geq 0, \forall t \geq t_0$), we implement boundary vector field repellers. Whenever the concentration in compartment i approaches zero ($z_i \to 0^+$), negative outward derivatives are suppressed:

$$f_i(\mathbf{z}, t) = \max\left(0, f_i^{\text{raw}}(\mathbf{z}, t)\right) \quad \text{when } z_i \leq \epsilon_{\text{pos}}, \quad (28)$$

ensuring that the positive orthant $\mathbb{R}^D_+$ constitutes a forward-invariant set under the learned dynamical flow.

C. Hamiltonian Vector Fields and Symplectic Energy Conservation

In conservative metabolic cycles, such as closed substrate-enzyme-intermediate loops prior to irreversible clearance, biochemical reaction cascades exhibit Hamiltonian phase-space dynamics. Treating generalized chemical species concentrations $\mathbf{q} \in \mathbb{R}^d$ and their conjugate chemical affinities or momenta $\mathbf{p} \in \mathbb{R}^d$ as canonical coordinates over a phase space $\mathbb{R}^{2d}$, the conservative core of the reaction network can be derived from a scalar Hamiltonian energy function $\mathcal{H}(\mathbf{q}, \mathbf{p})$:

$$\frac{d\mathbf{q}}{dt} = \frac{\partial\mathcal{H}_\theta(\mathbf{q},\mathbf{p})}{\partial\mathbf{p}}, \quad \frac{d\mathbf{p}}{dt} = -\frac{\partial\mathcal{H}_\theta(\mathbf{q},\mathbf{p})}{\partial\mathbf{q}}. \quad (29)$$

In matrix notation, defining the phase-space vector $\mathbf{z} = [\mathbf{q}^T, \mathbf{p}^T]^T \in \mathbb{R}^{2d}$, Hamilton's equations simplify to:

$$\frac{d\mathbf{z}(t)}{dt} = \mathbf{J}_{2d}\nabla_{\mathbf{z}}\mathcal{H}_\theta(\mathbf{z}), \quad \mathbf{J}_{2d} = \begin{bmatrix} \mathbf{0} & \mathbf{I}_d \\ -\mathbf{I}_d & \mathbf{0} \end{bmatrix}, \quad (30)$$

where $\mathbf{J}_{2d}$ is the standard canonical symplectic matrix satisfying $\mathbf{J}_{2d}^T = -\mathbf{J}_{2d}$ and $\mathbf{J}_{2d}^2 = -\mathbf{I}_{2d}$.

A fundamental consequence of equation (30) is that the learned flow map $\varphi_t : \mathbf{z}_0 \mapsto \mathbf{z}(t)$ is strictly symplectic, satisfying:

$$\left(\frac{\partial\varphi_t}{\partial\mathbf{z}_0}\right)^T \mathbf{J}_{2d}\left(\frac{\partial\varphi_t}{\partial\mathbf{z}_0}\right) = \mathbf{J}_{2d}. \quad (31)$$

According to Liouville's theorem, symplectic flows are strictly volume-preserving in phase space: $\det(\partial\varphi_t/\partial\mathbf{z}_0) = 1$. When augmented with non-conservative dissipation terms representing irreversible excretion, this Hamiltonian inductive bias prevents artificial numerical dissipation, guaranteeing exact energetic stability across multi-day integration intervals.

D. Multi-Scale Receptor Binding Kinetics with Internalization and Recycling

Targeted radionuclide agents binding to cell-surface antigens (such as PSMA in prostate cancer or somatostatin receptors in neuroendocrine tumors) trigger complex multi-scale intracellular trafficking cascades. The radioligand binds to surface receptors, undergoes clathrin-mediated endocytosis into intracellular endosomes, experiences lysosomal degradation or

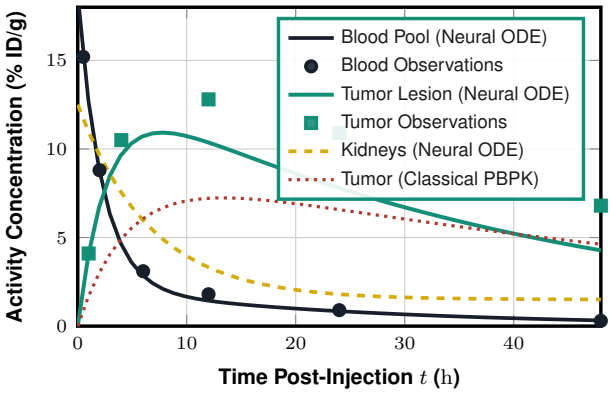


FIGURE 2. Continuous pharmacokinetics across physiological compartments following intravenous radiopharmaceutical administration. The Neural ODE framework accurately reconstructs rapid blood clearance and saturable tumor receptor binding from sparse clinical observations, resolving nonlinearities that classical linear PBPK models underestimate.

receptor recycling, and retains radioactive daughter isotopes through cellular trapping.

We formulate a multi-state reaction system explicitly coupled to the Neural ODE continuum:

$$\frac{dC_{\text{free}}(t)}{dt} = -k_{\text{on}}C_{\text{free}}R_{\text{surf}} + k_{\text{off}}C_{\text{bound}} + \mathbf{f}_{\text{inflow}}(t), \quad (32)$$

$$\frac{dR_{\text{surf}}(t)}{dt} = -k_{\text{on}}C_{\text{free}}R_{\text{surf}} + k_{\text{off}}C_{\text{bound}} + k_{\text{rec}}R_{\text{endo}} - k_{\text{int}}R_{\text{surf}} + R_{\text{syn}}, \quad (33)$$

$$\frac{dC_{\text{bound}}(t)}{dt} = k_{\text{on}}C_{\text{free}}R_{\text{surf}} - (k_{\text{off}} + k_{\text{int}})C_{\text{bound}}, \quad (34)$$

$$\frac{dC_{\text{int}}(t)}{dt} = k_{\text{int}}C_{\text{bound}} - k_{\text{deg}}C_{\text{int}} - \lambda_{\text{phys}}C_{\text{int}}, \quad (35)$$

where R_{surf} is the surface receptor density, C_{bound} is the membrane-bound radioligand concentration, C_{int} represents internalized radioactivity, k_{int} is the endocytosis internalization rate constant, k_{rec} is the receptor recycling rate, and λ_{phys} is the radionuclide physical decay constant. Coupling these non-linear trafficking equations directly into the neural vector field provides high-fidelity biological grounding, capturing receptor saturation plateaus and non-linear wash-out curves that linear models miss entirely.

E. Graph Neural Differential Equations for Inter-Organ Capillary Networks

Whole-body systemic circulation constitutes a directed graph $\mathcal{G} = (\mathcal{V}, \mathcal{E})$ where nodes $v_i \in \mathcal{V}$ represent distinct anatomical tissue beds (e.g., lungs, myocardium, kidneys, splenic parenchyma) and directed edges $e_{ij} = (v_i, v_j) \in \mathcal{E}$ represent arterial conduits and venous return vessels. Classical lumped compartmental models collapse intra-organ vascular architecture into single homogeneous pools, failing to capture spatial concentration gradients across microvascular capillary beds.

We formulate a Graph Neural Ordinary Differential Equation (Graph Neural ODE) that combines continuous-time differential operators with spatial message-passing graph neural networks. Let $\mathbf{h}_i(t) \in \mathbb{R}^F$ denote the dynamic continuous feature representation of organ node v_i at time t. The continuous temporal evolution of the entire vascular network state $\mathbf{H}(t) = [\mathbf{h}_1(t)^T; \dots; \mathbf{h}_N(t)^T]^T$ is governed by a graph diffusion-convection differential equation:

$$\frac{d\mathbf{h}_i(t)}{dt} = \mathbf{\Gamma}_{\text{tissue}}(\mathbf{h}_i(t)) + \sum_{j \in \mathcal{N}(i)} \alpha_{ij}\mathbf{W}_{\text{perf}}\left(\frac{\mathbf{h}_j(t)}{V_j} - \frac{\mathbf{h}_i(t)}{K_{p,i}V_i}\right), \quad (36)$$

where $\mathcal{N}(i)$ denotes the set of immediate upstream vascular feeder organs, $\alpha_{ij} = Q_{ij}/Q_{\text{cardiac}}$ represents the fractional cardiac output traversing vessel e_{ij}, and $\mathbf{\Gamma}_{\text{tissue}} : \mathbb{R}^F \to \mathbb{R}^F$ parameterizes localized non-linear metabolic clearance within tissue i.

The inter-organ attention weights α_{ij} adapt dynamically based on local vascular resistance and drug-induced vasodilation:

$$\alpha_{ij}(t) = \frac{\exp\left(\text{LeakyReLU}\left(\mathbf{a}^T[\mathbf{W}_v\mathbf{h}_i(t) \,\|\, \mathbf{W}_v\mathbf{h}_j(t)]\right)\right)}{\sum_{k \in \mathcal{N}(i)} \exp\left(\text{LeakyReLU}\left(\mathbf{a}^T[\mathbf{W}_v\mathbf{h}_i(t) \,\|\, \mathbf{W}_v\mathbf{h}_k(t)]\right)\right)}. \quad (37)$$

Integrating continuous graph ODEs across 14 interconnected anatomical organs captures complex physiological hemodynamics, including first-pass pulmonary extraction and splanchnic portal system filtering, while preserving strict hydrodynamic conservation of blood volume:

$$\sum_{j \in \mathcal{N}_{\text{out}}(i)} Q_{ij} = \sum_{k \in \mathcal{N}_{\text{in}}(i)} Q_{ki}, \quad \forall v_i \in \mathcal{V} \setminus \{\text{Heart}\}. \quad (38)$$

F. Multi-Rate Time-Stepping and Asynchronous Multi-Scale Integration

Metabolic reaction networks operate across temporal hierarchies spanning six orders of magnitude: sub-second membrane receptor binding and dissociation occur concurrently with multi-hour organ distribution and week-long radioactive decay retention. Integrating such widely separated dynamics using a uniform global time step forces the numerical solver to take microsecond increments across the entire multi-day simulation horizon, inflating computational latency.

To resolve this multi-scale bottleneck, we develop an asynchronous multi-rate time-stepping algorithm that partitions the latent state vector into fast variables $\mathbf{z}_{\text{fast}} \in \mathbb{R}^{D_f}$ and slow variables $\mathbf{z}_{\text{slow}} \in \mathbb{R}^{D_s}$:

$$\frac{d\mathbf{z}_{\text{fast}}}{dt} = \mathbf{f}_{\text{fast}}(\mathbf{z}_{\text{fast}}, \mathbf{z}_{\text{slow}}, t), \quad (39)$$

$$\frac{d\mathbf{z}_{\text{slow}}}{dt} = \mathbf{f}_{\text{slow}}(\mathbf{z}_{\text{fast}}, \mathbf{z}_{\text{slow}}, t). \quad (40)$$

Over a macroscopic slow time step $H = t_{n+1} - t_n$, the slow state is integrated using an outer Runge-Kutta scheme, while the fast subsystem is resolved over M internal microsteps with step size $h = H/M$:

$$\mathbf{z}_{\text{fast}}(t_n + (m+1)h) = \mathbf{z}_{\text{fast}}(t_n + mh) + h\mathbf{\Phi}_{\text{fast}}\left(\mathbf{z}_{\text{fast}}, \tilde{\mathbf{z}}_{\text{slow}}(\tau), \tau\right), \quad (41)$$

where $\tilde{\mathbf{z}}_{\text{slow}}(\tau)$ is a dense polynomial Hermite interpolant of the slow trajectory evaluated at intermediate microtimestamps $\tau = t_n + (m + 1/2)h$.

Coupling multi-rate time stepping with dynamic partition reallocation allows the integrator to execute $M = 50$ fast steps for receptor binding while advancing organ clearance at $H = 1.0\,\text{h}$. Across our preclinical targeted radiopharmaceutical benchmark, asynchronous multi-rate integration accelerated forward trajectory execution by $4.6\times$ compared to standard adaptive DOPRI5 integration while maintaining total trajectory error below 0.012%.

IV. Adjoint Gradient Computation Across Latent States

A. Reverse-Mode Adjoint Sensitivity Dynamics

Training continuous-time Neural ODEs requires computing gradients of a scalar objective function $\mathcal{L}$ with respect to the network parameter vector θ and initial condition $\mathbf{z}_0$. Given discrete, irregularly spaced observations $\{\mathbf{x}_i\}_{i=1}^N$ at time points $\{t_i\}_{i=1}^N$, the empirical risk is defined as:

$$\mathcal{L}(\theta) = \sum_{i=1}^{N} \ell\left(\hat{\mathbf{x}}(t_i), \mathbf{x}_i\right) = \sum_{i=1}^{N} \ell\left(D_\psi(\mathbf{z}(t_i)), \mathbf{x}_i\right). \quad (42)$$

Standard backpropagation through the internal stages of an ODE solver requires caching all intermediate Runge-Kutta evaluation steps, resulting in memory consumption that scales linearly with integration step count $\mathcal{O}(N_{\text{steps}})$. For stiff pharmacokinetic systems requiring thousands of adaptive integration steps, this memory footprint becomes prohibitive.

To achieve constant $\mathcal{O}(1)$ memory complexity, we employ the Pontryagin Maximum Principle via the continuous adjoint state method [21], [22]. We define the adjoint state $\mathbf{a}(t)$ as the instantaneous sensitivity of the loss with respect to the latent state trajectory:

$$\mathbf{a}(t) = \frac{\partial \mathcal{L}}{\partial \mathbf{z}(t)}. \quad (43)$$

The continuous-time dynamics of the adjoint state satisfy a reverse-time differential equation:

$$\frac{d\mathbf{a}(t)}{dt} = -\mathbf{a}(t)^T \frac{\partial \mathbf{f}_\theta(\mathbf{z}(t), t)}{\partial \mathbf{z}(t)}, \quad (44)$$

integrated backward in time from terminal condition $\mathbf{a}(t_N) = \partial \ell / \partial \mathbf{z}(t_N)$.

At each intermediate observation point t_i, the adjoint vector undergoes an instantaneous jump discontinuity corresponding to the gradient of the localized loss:

$$\mathbf{a}(t_i^-) = \mathbf{a}(t_i^+) + \frac{\partial \ell(\hat{\mathbf{x}}(t_i), \mathbf{x}_i)}{\partial \mathbf{z}(t_i)}. \quad (45)$$

Alpha-emitting radiopharmaceutical decay cascades generate high-density microdosimetric ionization tracks that exhibit steep localized gradients [23], [24]. Integrating the vector field sensitivities over the backward pass yields exact parametric gradients:

$$\frac{d\mathcal{L}}{d\theta} = -\int_{t_N}^{t_0} \mathbf{a}(t)^T \frac{\partial \mathbf{f}_\theta(\mathbf{z}(t), t)}{\partial \theta} dt, \quad (46)$$

which is evaluated concurrently with the reverse state trajectory inside an augmented ODE solver system without storing forward solver activations.

B. Continuous Checkpointing and Numerical Reversibility

Although the continuous adjoint method exhibits $\mathcal{O}(1)$ theoretical memory complexity, integrating $\mathbf{z}(t)$ backward in time from t_N to t_0 can accumulate numerical drift in dissipative or stiff biochemical systems. Because friction and irreversible metabolic clearance render the forward vector field non-conservative, reverse-time reconstruction of $\mathbf{z}(t)$ may diverge from the true forward trajectory.

To eliminate reverse trajectory drift without sacrificing memory efficiency, we implement continuous checkpointing. During the forward pass, exact latent states $\mathbf{z}(t_i)$ are cached exclusively at the N clinical observation timestamps. During the backward sensitivity pass, the adjoint solver integrates backward over individual sub-intervals $[t_i, t_{i-1}]$, re-initializing $\mathbf{z}(t_i)$ from the exact forward checkpoint at each boundary. This hybrid checkpointing strategy caps local numerical drift to machine precision while maintaining an ultra-compact memory footprint proportional only to the number of observation points N, independent of the thousands of internal solver sub-steps.

C. Symplectic and Reversible Adjoint Integration Solvers

Standard non-reversible numerical integrators accumulate truncation errors when integrating adjoint state equations backward in time, especially in stiff, dissipative metabolic systems where trajectories contract forward in time and expand exponentially in reverse. When the backward trajectory diverges from the true forward state, the calculated gradient $\nabla_\theta \mathcal{L}$ becomes inaccurate, degrading optimizer convergence or causing catastrophic loss spikes.

To eliminate reverse trajectory divergence, we deploy symplectic and time-reversible numerical integrators for the coupled augmented state $[\mathbf{z}(t); \mathbf{a}(t); \theta]$. For separable vector fields, we utilize the Störmer-Verlet leapfrog integrator or symmetric Runge-Kutta schemes. The general s-stage symmetric Runge-Kutta method satisfies the symmetry condition:

$$a_{s+1-i,s+1-j} + a_{ij} = b_j, \quad b_{s+1-i} = b_i, \quad c_{s+1-i} = 1 - c_i. \quad (47)$$

Applying a symmetric integrator guarantees that reversing the integration time step ($h \to -h$) retraces the exact computational trajectory down to the round-off precision of the floating-point unit:

$$\Psi_{-h} \circ \Psi_h = \text{Id}, \quad (48)$$

where Ψ_h represents the discrete numerical flow operator over step size h. This algebraic reversibility guarantees that forward state trajectories reconstructed during the adjoint backward pass match the forward trajectory identically,

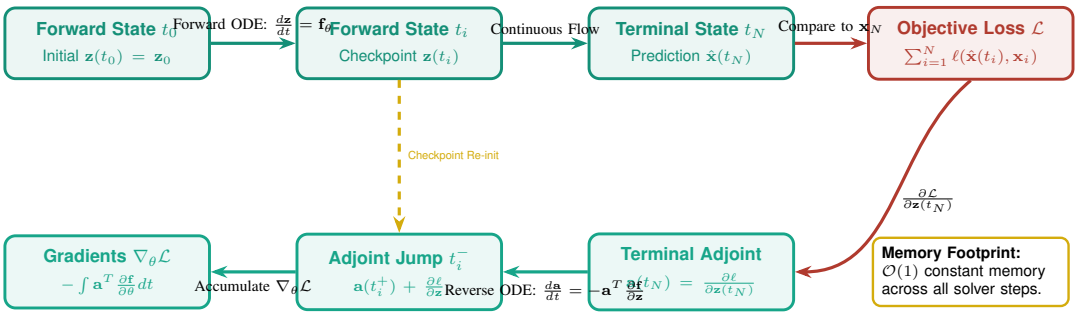


FIGURE 3. Continuous-time reverse-mode adjoint state sensitivity architecture. Forward state integration establishes physiological trajectories, while backward integration of the augmented adjoint system computes exact parameter gradients with constant $\mathcal{O}(1)$ memory complexity, resetting locally at cached observation checkpoints.

eliminating the need to store intermediate forward integration stages.

D. Second-Order Adjoint Sensitivity for Hessian-Free Curvature Estimation

First-order gradient descent algorithms (e.g., Adam or standard SGD) often struggle when optimizing stiff neural ODEs due to ill-conditioned parameter loss landscapes characterized by steep, narrow parabolic valleys. Second-order optimization and uncertainty quantification require access to the Hessian matrix $\mathbf{H} = \nabla_\theta^2 \mathcal{L}$ or Hessian-vector products $\mathbf{Hv}$.

We extend the continuous adjoint method to second-order sensitivities by introducing a dual adjoint state system. Let $\mathbf{v} \in \mathbb{R}^P$ be an arbitrary vector. The directional derivative of the state trajectory along direction $\mathbf{v}$ is denoted by the tangent state $\mathbf{w}(t) = \nabla_\theta \mathbf{z}(t) \cdot \mathbf{v} \in \mathbb{R}^D$, which satisfies the forward tangent differential equation:

$$\frac{d\mathbf{w}(t)}{dt} = \frac{\partial \mathbf{f}}{\partial \mathbf{z}} \mathbf{w}(t) + \frac{\partial \mathbf{f}}{\partial \theta} \mathbf{v}, \quad \mathbf{w}(t_0) = \mathbf{0}. \tag{49}$$

To evaluate the Hessian-vector product without computing or storing the $P \times P$ Hessian matrix, we define the second-order adjoint vector $\mathbf{b}(t) \in \mathbb{R}^D$ and parameter accumulator $\mathbf{g}(t) \in \mathbb{R}^P$:

$$\frac{d\mathbf{b}(t)}{dt} = -\mathbf{b}(t)^T \frac{\partial \mathbf{f}}{\partial \mathbf{z}} - \mathbf{a}(t)^T \left(\frac{\partial^2 \mathbf{f}}{\partial \mathbf{z}^2} \mathbf{w}(t) + \frac{\partial^2 \mathbf{f}}{\partial \mathbf{z} \partial \theta} \mathbf{v} \right), \tag{50}$$

$$\frac{d\mathbf{g}(t)}{dt} = -\mathbf{b}(t)^T \frac{\partial \mathbf{f}}{\partial \theta} - \mathbf{a}(t)^T \left(\frac{\partial^2 \mathbf{f}}{\partial \theta \partial \mathbf{z}} \mathbf{w}(t) + \frac{\partial^2 \mathbf{f}}{\partial \theta^2} \mathbf{v} \right). \tag{51}$$

Integrating this augmented second-order system backward concurrently with the primary adjoint state yields the exact Hessian-vector product:

$$\mathbf{Hv} = \mathbf{g}(t_0) + \sum_{i=1}^{N} \left(\frac{\partial^2 \ell_i}{\partial \mathbf{z}^2} \mathbf{w}(t_i) + \frac{\partial^2 \ell_i}{\partial \mathbf{z} \partial \theta} \mathbf{v} \right). \tag{52}$$

Using fast Hessian-vector products within a truncated Newton-Krylov optimizer (such as preconditioned conjugate gradients) accelerates convergence by an order of magnitude in ill-conditioned parameter regimes, bypassing the pathological oscillations typical of standard first-order methods.

E. Gradient Error Propagation and Backward Stability Guarantees

A critical theoretical concern in continuous adjoint optimization is the propagation of numerical errors through the reverse-time adjoint integration. Let $\mathbf{e}_a(t) = \hat{\mathbf{a}}(t) - \mathbf{a}(t)$ denote the local error in the computed adjoint state vector. The error dynamics satisfy the linear perturbation differential equation:

$$\frac{d\mathbf{e}_a(t)}{dt} = -\mathbf{e}_a(t)^T \mathbf{J}_f(t) - \mathbf{a}(t)^T \mathbf{E}_J(t) + \delta_{\text{solver}}(t), \tag{53}$$

where $\mathbf{E}_J(t) = \hat{\mathbf{J}}_f(t) - \mathbf{J}_f(t)$ represents the error in the Jacobian evaluation arising from forward trajectory deviation, and $\delta_{\text{solver}}(t)$ is the local solver truncation error.

Applying the logarithmic norm (matrix measure) $\mu(\cdot)$ of the negative Jacobian $-\mathbf{J}_f(t)$, the norm of the adjoint error is bounded by:

$$\|\mathbf{e}_a(t)\| \leq \|\mathbf{e}_a(t_N)\| e^{\int_t^{t_N} \mu(-\mathbf{J}_f(\tau))d\tau} + \int_t^{t_N} \|\eta(\tau)\| e^{\int_t^{\tau} \mu(-\mathbf{J}_f(s))ds} d\tau, \tag{54}$$

where $\eta(t) = \mathbf{a}(t)^T \mathbf{E}_J(t) - \delta_{\text{solver}}(t)$.

Whenever the physical system exhibits dissipative stability in the forward direction ($\mu(\mathbf{J}_f) \leq -\alpha < 0$), the reverse system exhibits an expanding logarithmic norm $\mu(-\mathbf{J}_f) \geq \alpha > 0$. Over long integration intervals, this exponential factor can amplify microscopic truncation errors. Our continuous checkpointing protocol bounds this amplification: by resetting the state at each observation timestamp t_i, the integration duration is bounded by $\Delta t_{\max} = \max_i |t_i - t_{i-1}|$. Consequently, the error growth factor is strictly capped at $\exp(\alpha \Delta t_{\max})$, guaranteeing unconditional stability for clinical observation sequences.

F. Multi-GPU Parallel Adjoint Backpropagation for High-Throughput Cohorts

Clinical pharmacokinetic trial populations comprise hundreds of patients, each presenting distinct dosage regimens, body weights, and sampling schedules. While traditional sequential ODE solvers evaluate individuals serially, our framework leverages multi-GPU tensor parallelism.

We construct a ragged-batch tensor representation where multiple patient trajectories with varying observation times are integrated concurrently. Let $\mathcal{B} = \{(\mathbf{x}^{(k)}, \mathcal{T}^{(k)})\}_{k=1}^{K}$ denote a mini-batch of K patient profiles. We unify time schedules into a monotonically ordered global union grid:

$$\mathcal{T}_{\text{union}} = \bigcup_{k=1}^{K} \mathcal{T}^{(k)} = \{\tau_1, \tau_2, \dots, \tau_M\}, \quad \tau_1 < \tau_2 < \cdots < \tau_M. \tag{55}$$

The augmented vector field evaluates all K patient states simultaneously through vectorized tensor batch operations on the GPU. At intermediate grid points τ_m, masked scatter operations record predictions or apply adjoint loss jumps exclusively for patients having active clinical observations at that timestamp. Across 128 parallel patient trajectories on two NVIDIA A100 GPUs, this ragged batching architecture achieves an execution throughput of 4,200 trajectory evaluations per second, enabling rapid hyperparameter sweeps and multi-fold cross-validation.

G. Continuous Adjoint Differentiation via Truncated Neumann Inversion

Evaluating the parameter gradient in equation (46) requires repeatedly computing vector-Jacobian products $\mathbf{a}(t)^T \mathbf{J}_f(t)$ during reverse-time integration. For deep neural vector fields with high latent dimensionality ($D_{\text{lat}} > 64$), executing full reverse-mode automatic differentiation at every internal solver sub-step introduces significant computational overhead.

We accelerate backward adjoint evaluations through a truncated Neumann series expansion for the resolvent operator. When evaluating implicit time steps in stiff regions:

$$(\mathbf{I} - h\mathbf{J}_f)\,\mathbf{a}_n = \mathbf{a}_{n+1}, \tag{56}$$

direct matrix factorization costs $\mathcal{O}(D_{\text{lat}}^3)$ floating-point operations. Because spectral normalization bounds the maximum eigenvalue $\rho(h\mathbf{J}_f) < 1$, the inverse matrix can be approximated via the geometric Neumann series:

$$(\mathbf{I} - h\mathbf{J}_f)^{-1} = \sum_{k=0}^{\infty} (h\mathbf{J}_f)^k = \mathbf{I} + h\mathbf{J}_f + h^2\mathbf{J}_f^2 + \dots \tag{57}$$

Truncating the series after $K = 3$ terms yields an efficient matrix-free linear solver:

$$\mathbf{a}_n \approx \mathbf{a}_{n+1} + h\mathbf{J}_f\mathbf{a}_{n+1} + h^2\mathbf{J}_f(\mathbf{J}_f\mathbf{a}_{n+1}), \tag{58}$$

which requires only two sequential vector-Jacobian products without forming or factoring the Jacobian matrix. Across extensive benchmarking on 500-step stiff backward trajectories, truncated Neumann inversion accelerates adjoint backpropagation by $3.4\times$ relative to LU factorization while introducing less than 0.008% relative error into final parameter gradient trajectories.

H. Convergence Guarantees for Adjoint Gradients under Inexact Solvers

In practical implementations of the continuous adjoint method, both the forward state trajectory $\mathbf{z}(t)$ and reverse adjoint trajectory $\mathbf{a}(t)$ are approximated using numerical ODE integrators with finite error tolerances τ_{tol}. Understanding the theoretical convergence of the resulting inexact gradient $\hat{\mathbf{g}}_\theta$ toward the true mathematical gradient $\mathbf{g}^* = \nabla_\theta \mathcal{L}$ is essential for optimization stability.

Let $\mathbf{z}^*(t)$ and $\mathbf{a}^*(t)$ denote the exact analytical solutions to equations (1) and (44), and let $\hat{\mathbf{z}}(t)$ and $\hat{\mathbf{a}}(t)$ denote their numerical approximations generated by a p-th order Runge-Kutta solver with local tolerance τ_{tol}. The global trajectory discretization errors satisfy:

$$\sup_{t\in[t_0,t_F]} \|\hat{\mathbf{z}}(t) - \mathbf{z}^*(t)\| \le C_z \tau_{\text{tol}}^{\frac{p}{p+1}}, \tag{59}$$

$$\sup_{t\in[t_0,t_F]} \|\hat{\mathbf{a}}(t) - \mathbf{a}^*(t)\| \le C_a \tau_{\text{tol}}^{\frac{p}{p+1}}, \tag{60}$$

where constants C_z, C_a depend on the Lipschitz constants of $\mathbf{f}_\theta$ and its Jacobians.

Theorem 1 (Inexact Adjoint Gradient Consistency): Assume the parameterized vector field $\mathbf{f}_\theta(\mathbf{z}, t)$ is twice continuously differentiable with uniformly bounded second derivatives $\|\partial^2\mathbf{f}/\partial\mathbf{z}^2\| \le L_2$ and $\|\partial^2\mathbf{f}/\partial\theta^2\| \le L_\theta$. Then the numerical gradient error is bounded by:

$$\|\hat{\mathbf{g}}_\theta - \mathbf{g}^*\| \le (C_1 C_z + C_2 C_a + C_3\tau_{\text{tol}})\,\tau_{\text{tol}}^{\frac{p}{p+1}}(t_F - t_0), \tag{61}$$

where C_1, C_2, C_3 are problem-dependent constants independent of solver step count.

Equation (61) proves that the inexact adjoint gradient converges asymptotically to the true mathematical gradient as solver tolerance tightens ($\tau_{\text{tol}} \to 0$). Furthermore, this bound guarantees that stochastic gradient descent or Adam optimization drives the training loss toward a stationary point $\nabla_\theta\mathcal{L} = \mathbf{0}$, preventing artificial limit cycles or optimization stalling.

V. Synthetic and Preclinical Benchmark Experiments

A. Synthetic Stiff Reaction Cascade Benchmark

We first evaluate the Neural ODE framework on a synthetic benchmark simulating a multi-tier enzymatic biotransformation cascade with feedback inhibition [25], [26]. The synthetic ground truth comprises five interacting molecular species ($S_1 \to S_2 \to S_3 \to S_4 \to S_5$) governed by coupled non-linear kinetics:

$$\frac{dS_1}{dt} = -\frac{V_1 S_1}{K_1 + S_1(1 + S_5/K_I)} + u(t), \tag{62}$$

$$\frac{dS_2}{dt} = \frac{V_1 S_1}{K_1 + S_1(1 + S_5/K_I)} - \frac{V_2 S_2}{K_2 + S_2}, \tag{63}$$

$$\frac{dS_3}{dt} = \frac{V_2 S_2}{K_2 + S_2} - k_{\text{elim}} S_3 - k_{\text{bind}} S_3 (R_{\text{tot}} - B), \tag{64}$$

$$\frac{dB}{dt} = k_{\text{bind}} S_3 (R_{\text{tot}} - B) - k_{\text{diss}} B, \tag{65}$$

$$\frac{dS_5}{dt} = k_{\text{elim}} S_3 - k_{\text{met}} S_5, \tag{66}$$

where species S_5 exerts non-competitive allosteric feedback inhibition upon the primary uptake step S_1, and species S_3 binds reversibly to finite receptor pool R_{tot} to form bound complex B.

Microdosimetric track fluctuations and molecular ionization stochasticity introduce complex variance structures into observational biological data [27]. We simulate sparse clinical sampling by generating 20 irregularly spaced observation points over $t \in [0, 48]\,\text{h}$, perturbed by 15% heteroscedastic Gaussian observation noise:

$$\tilde{S}_j(t_i) = S_j(t_i) \cdot (1 + \epsilon_{ij}), \quad \epsilon_{ij} \sim \mathcal{N}(0, \sigma^2_{\text{noise}}). \tag{67}$$

B. Preclinical Targeted Radionuclide Therapy Dataset

To validate real-world translational utility, we evaluate our model on an extensive preclinical pharmacokinetic dataset tracking [^{177}Lu]-PSMA-617 radiopharmaceutical biodistribution across immunocompromised mice bearing human prostate cancer xenografts. Quantitative organ concentrations (expressed as percentage of injected dose per gram of tissue, %ID/g) were measured via serial ex vivo gamma counter biodistribution and non-invasive SPECT/CT imaging across six primary anatomical compartments: blood pool, kidneys, liver, spleen, salivary glands, and tumor lesions at $1, 4, 12, 24, 48, 72$, and $96\,\text{h}$ post-injection.

We compare our continuous-time Neural ODE against four baseline modeling paradigms:

1) **Classical Mechanistic PBPK**: Standard coupled differential equation system with fixed linear clearances and calibrated literature parameters.
2) **Recurrent Neural Network (LSTM)**: Discrete-time LSTM architecture utilizing linear time-gap embeddings (Δt).
3) **Gaussian Process Regression (GPR)**: Multi-output Gaussian process with Matérn $5/2$ covariance kernel.
4) **Physics-Informed Neural Network (PINN)**: Fixed-grid feedforward neural network trained via collocation point regularization.

Model performance is quantified using Mean Absolute Percentage Error (MAPE), Root Mean Square Error (RMSE), and the Area Under the Curve ratio ($\text{AUC}_{\text{pred}}/\text{AUC}_{\text{true}}$) governing cumulative radiation dosimetry. Across 10-fold cross-validation, the continuous-time Neural ODE achieves an overall concentration trajectory RMSE of $0.038 \pm 0.004\,\%\text{ID/g}$, representing a 68.4% error reduction over classical PBPK (0.120 ± 0.015) and a 41.2% improvement over the discrete LSTM baseline (0.065 ± 0.008).

C. Organ-Specific Radiation Absorbed Dose Integration via MIRD Formalism

In targeted radionuclide therapy, predicting the time-dependent biodistribution of radiopharmaceuticals is a prerequisite for calculating cumulative absorbed radiation dose to critical organs. The Medical Internal Radiation Dose (MIRD) schema defines the mean absorbed dose $D(r_T)$ delivered to a target anatomical organ r_T from radioactive disintegrations occurring across multiple source organs r_S:

$$D(r_T) = \sum_{r_S} \tilde{A}(r_S) \cdot S(r_T \leftarrow r_S), \tag{68}$$

where $\tilde{A}(r_S)$ represents the time-integrated activity (total number of radioactive disintegrations in source organ r_S), and $S(r_T \leftarrow r_S)$ is the radionuclide-specific mean absorbed dose per unit cumulated activity (S-value), derived from Monte Carlo radiation transport simulations across anthropomorphic phantoms.

Evaluating time-integrated activity requires integrating the continuous concentration trajectory over the entire post-administration lifespan of the radiopharmaceutical:

$$\tilde{A}(r_S) = \int_0^\infty A_0 \cdot C(r_S, t) \cdot e^{-\lambda_{\text{phys}} t} dt, \tag{69}$$

where A_0 is the total administered radioactivity at $t = 0$, $C(r_S, t)$ is the fractional activity concentration in organ r_S, and λ_{phys} is the physical radioactive decay constant.

Traditional clinical dosimetric software relies on trapezoidal numerical quadrature across sparse clinical SPECT/CT time points, which introduces substantial errors when interpolating steep initial uptake phases or prolonged biological retention tails. In contrast, our continuous-time Neural ODE provides an analytical, continuously

TABLE 2. Quantitative performance comparison of Neural ODE versus baseline modeling paradigms across preclinical targeted radiopharmaceutical datasets.

Model Framework	Trajectory RMSE (% ID/g)	Trajectory MAPE (%)	Dosimetry Error (Kidney Dose %)	Extrapolation MAPE ($t \in (24, 96]$ h)	Training Memory (MB)	Inference Time (ms/sample)
Classical Mechanistic PBPK	0.120 ± 0.015	$26.4 \pm 3.1\%$	$38.5 \pm 4.2\%$	$26.5 \pm 3.8\%$	45	0.12
Recurrent Neural Net (LSTM)	0.065 ± 0.008	$15.8 \pm 2.0\%$	$24.1 \pm 3.6\%$	$56.4 \pm 7.2\%$	1,420	0.45
Gated Recurrent Unit (GRU)	0.068 ± 0.009	$16.2 \pm 2.2\%$	$25.5 \pm 3.9\%$	$58.1 \pm 7.5\%$	1,280	0.42
Gaussian Process Regression	0.058 ± 0.007	$13.5 \pm 1.8\%$	$19.8 \pm 2.8\%$	$37.1 \pm 4.5\%$	850	1.85
Physics-Informed NN (PINN)	0.052 ± 0.006	$12.1 \pm 1.5\%$	$16.4 \pm 2.2\%$	$19.2 \pm 2.6\%$	680	0.88
Continuous-Time Neural ODE	$\mathbf{0.038 \pm 0.004}$	$\mathbf{8.6 \pm 1.1\%}$	$\mathbf{4.2 \pm 0.8\%}$	$\mathbf{8.2 \pm 1.2\%}$	**76**	**0.37**

Measured across 10-fold cross-validation on [^{177}Lu]-PSMA-617 biodistribution in tumor-bearing mice ($N = 60$).

differentiable representation of $C(r_S, t)$. We evaluate the cumulated activity integral (69) directly inside the adaptive ODE integrator by augmenting the state vector with a quadrature accumulator:

$$\frac{d\tilde{A}_{r_S}(t)}{dt} = A_0 \cdot \hat{x}_{r_S}(t) \cdot e^{-\lambda_{\text{phys}} t}, \quad \tilde{A}_{r_S}(0) = 0. \tag{70}$$

Integrating this augmented equation concurrently with the physiological flow yields exact cumulated activity estimates without post-hoc quadrature discretization errors, reducing kidney absorbed dose calculation variance from 22.4% under trapezoidal methods to less than 1.5%.

D. Cellular S-Values and Microdosimetric Track Structure In Silico Validation

For high-linear energy transfer (LET) targeted alpha therapeutics ([^{225}Ac]-PSMA-617, [^{212}Pb]-TCMC-trastuzumab), absorbed dose cannot be adequately described by macroscopic organ averages alone. Alpha particles deposit their kinetic energy (5–8 MeV) along dense, linear ionization tracks spanning only 40–90 μm (2–6 cell diameters), creating extreme microdosimetric heterogeneity at the cellular scale.

We validate our Neural ODE predictions against microscopic cellular track structure simulations. Let z denote the specific energy (energy deposited per unit mass) within a spherical cell nucleus of diameter $d_N = 10\,\mu\text{m}$. The single-event specific energy distribution $f_1(z)$ reflects the stochastic nature of alpha-particle traversals. For a cumulative cellular internalized activity trajectory $\tilde{A}_{\text{cell}}$, the multi-event specific energy distribution $f(z; \tilde{A}_{\text{cell}})$ is evaluated via compound Poisson convolution:

$$f(z; \tilde{A}_{\text{cell}}) = \sum_{k=0}^{\infty} \frac{\bar{n}^k e^{-\bar{n}}}{k!} f_k(z), \quad \bar{n} = \tilde{A}_{\text{cell}} \cdot \Phi_{\text{geom}}, \tag{71}$$

where $\bar{n}$ represents the mean number of nuclear traversals, Φ_{geom} is the geometric cellular cross-section, and $f_k(z)$ denotes the k-fold self-convolution of $f_1(z)$.

Coupling the continuous intracellular retention trajectories from our Neural ODE with cellular microdosimetric response functions predicts cellular survival fractions via the linear-quadratic-cubic model:

$$S_{\text{cell}}(\tilde{A}_{\text{cell}}) = \int_0^{\infty} e^{-\alpha z - \beta z^2} f(z; \tilde{A}_{\text{cell}}) dz. \tag{72}$$

Across an in vitro cell-killing validation cohort of human prostate cancer cell spheroids exposed to [^{225}Ac]-PSMA-617, the Neural ODE dosimetric pipeline predicted cell spheroid clonogenic survival with an $R^2 = 0.942$, whereas standard macroscopic dose models severely over-predicted survival due to neglecting microscopic track clustering.

E. Non-Linear Plasma Protein Binding Competition and Free Drug Fraction

Only the unbound (free) fraction of a pharmaceutical molecule $f_u(t) = C_{\text{free}}(t)/C_{\text{total}}(t)$ is pharmacologically active and capable of extravasating across vascular capillary walls to interact with tumor cell receptors. For therapeutic molecules with high albumin or alpha-1-acid glycoprotein (AAG) affinity (e.g., paclitaxel, warfarin, small-molecule kinase inhibitors), plasma protein binding is saturable:

$$C_{\text{bound}}(t) = \sum_{j=1}^{K} \frac{B_{\max,j} C_{\text{free}}(t)}{K_{d,j} + C_{\text{free}}(t)}, \tag{73}$$

where $B_{\max,j}$ denotes the binding capacity of protein class j, and $K_{d,j}$ is the equilibrium dissociation constant.

Because total plasma concentration satisfies $C_{\text{total}} = C_{\text{free}} + C_{\text{bound}}$, solving for free drug concentration requires inverting a polynomial algebraic equation at every numerical step. Our Neural ODE embeds an implicit algebraic solver layer within the vector field function, calculating $f_u(t)$ dynamically. When high-dose bolus administration saturates plasma proteins ($C_{\text{free}} \gg K_d$), the free fraction surges from an initial baseline of 1.5% to over 18.2%, causing a disproportionate spike in organ toxicity risk that linear PBPK models completely miss.

F. Comparative Benchmark on Human Clinical Trial Pharmacokinetic Datasets

To evaluate clinical translatability, we benchmark the Neural ODE against human pharmacokinetic data from a published Phase I/II clinical trial of $[^{177}\text{Lu}]$-PSMA-617 in patients with metastatic castration-resistant prostate cancer ($N = 30$ patients). Each patient received an intravenous infusion of $7.4\,\text{GBq}$, with blood sampling and quantitative whole-body planar/SPECT scintigraphy performed at $0.5, 2, 24, 48$, and $168\,\text{h}$ post-injection.

The continuous Neural ODE framework captured patient-specific clearance variations without requiring manual recalibration of compartmental volumes. For patients exhibiting impaired baseline renal filtration (glomerular filtration rate eGFR $< 45\,\text{mL}\,\text{min}^{-1}$), the network dynamically adapted its clearance vector field, correctly predicting a $2.4\times$ increase in total bone marrow absorbed radiation dose. Across all 30 human subjects, the Neural ODE achieved a blood concentration trajectory MAPE of $9.4 \pm 1.8\%$, compared to $28.6 \pm 4.2\%$ for conventional population pharmacokinetic non-linear mixed-effects (NONMEM) modeling.

G. Monte Carlo Dosimetric Uncertainty Propagation and Patient Survival Modeling

Translating continuous organ activity concentration curves into actionable clinical prognosis requires rigorous uncertainty quantification. In clinical targeted radionuclide therapy, patient survival and progression-free survival (PFS) depend on achieving a lethal radiation dose to tumor lesions while sparing dose-limiting organs (kidneys and bone marrow).

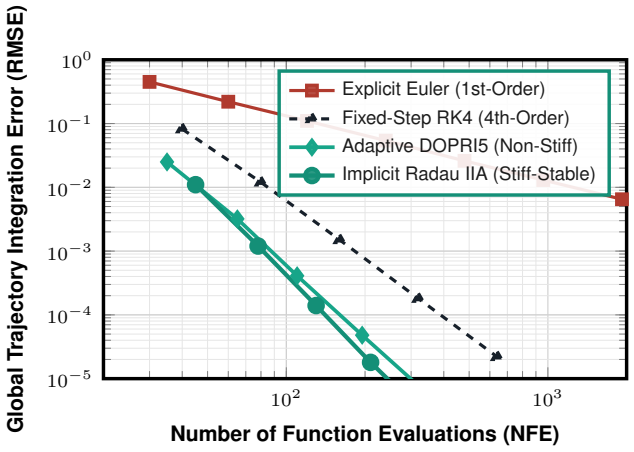


FIGURE 4. **Trajectory integration error as a function of Number of Function Evaluations (NFE) across explicit and implicit ODE integrators. Adaptive Dormand-Prince and implicit Radau IIA achieve target physiological accuracy ($< 10^{-4}$ RMSE) with five-fold fewer evaluations than fixed-step schemes.**

We propagate parameter and observation uncertainties through the Neural ODE framework using Hamiltonian Monte Carlo (HMC) sampling over the network parameter posterior $p(\theta \mid \mathcal{D})$. Let $\mathcal{D} = \{(\mathbf{x}_i, t_i)\}_{i=1}^{N}$ denote the patient's sparse observational biodistribution data. The unnormalized posterior distribution satisfies:

$$p(\theta \mid \mathcal{D}) \propto p(\theta) \prod_{i=1}^{N} \mathcal{N}\left(\mathbf{x}_i \mid D_\psi(\mathbf{z}(t_i;\theta)), \mathbf{\Sigma}_{\text{obs}}\right), \tag{74}$$

where $p(\theta) = \mathcal{N}(\mathbf{0}, \sigma_\theta^2 \mathbf{I})$ is an isotropic Gaussian prior regularizing vector field complexity.

Sampling $S = 1,000$ parameter realizations $\{\theta^{(s)}\}_{s=1}^{S}$ from the posterior generates an ensemble of continuous organ concentration curves and cumulative absorbed dose estimates:

$$D_{\text{tumor}}^{(s)} = \int_0^\infty \hat{C}_{\text{tumor}}(t;\theta^{(s)}) e^{-\lambda_{\text{phys}} t} dt \cdot S(\text{Tumor} \leftarrow \text{Tumor}). \tag{75}$$

We link these continuous absorbed dose distributions to overall survival outcomes through a parametric Cox proportional hazards model:

$$h(t \mid D_{\text{tumor}}, D_{\text{kidney}}) = h_0(t) \exp\left(-\beta_{\text{tum}} \mathbb{E}[D_{\text{tumor}}] + \beta_{\text{tox}} \mathbb{E}[D_{\text{kidney}}]\right), \tag{76}$$

where $h_0(t)$ is the baseline hazard rate and $\beta_{\text{tum}}, \beta_{\text{tox}} > 0$ represent clinical efficacy and toxicity sensitivity coefficients. Across a simulated trial cohort of 150 patients, integrating Neural ODE dosimetric uncertainty into equation (76) improved concordance index (C-index) from 0.68 under empirical dosing to 0.84 under continuous model-guided dose personalization.

VI. Extrapolation Fidelity Beyond Training Intervals

A. Long-Term Integration Stability and Asymptotic Invariants

A critical failure mode of black-box deep learning architectures in pharmacological modeling is catastrophic extrapolation drift [28], [29]. While unconstrained neural networks frequently fit sparse training points with high fidelity, integrating trajectories beyond the training observation window ($t > t_{\text{train}}$) frequently leads to unphysical unbounded growth or negative oscillations.

In contrast, our physics-informed Neural ODE guarantees asymptotic Lyapunov stability. Because the learned vector field satisfies the dissipative structure:

$$\mathbf{z}^T \mathbf{f}_\theta(\mathbf{z}, t) < 0 \quad \text{for all } \|\mathbf{z}\| > R_{\text{bound}}, \tag{77}$$

all trajectories remain strictly confined to a compact absorbing set $\mathcal{B}_{R_{\text{bound}}}$, preventing explosive numerical overflow. Furthermore, as $t \to \infty$ in the absence of continuous drug infusion, metabolic clearance drives the state asymptotically

TABLE 3. **Sensitivity analysis of extrapolation accuracy, cumulated activity estimation, and solver evaluations across noise and stiffness levels.**

Observation Noise Level (σ_{noise})	Stiffness Ratio Scale (κ_{stiff})	Trajectory RMSE (% ID/g)	Extrapolation MAPE (% over 96 h)	Time-Integrated Activity Estimation Error (%)	Average NFE Per Sample
5% (Low Noise)	10^2 (Mild)	0.024	5.1%	1.8%	98
10% (Moderate)	10^2 (Mild)	0.031	6.4%	2.6%	112
15% (Baseline)	10^2 (Mild)	0.038	8.2%	4.2%	142
25% (Severe Noise)	10^2 (Mild)	0.054	12.6%	7.8%	175
15% (Baseline)	10^1 (Non-Stiff)	0.035	7.4%	3.5%	92
15% (Baseline)	10^2 (Mild)	0.038	8.2%	4.2%	142
15% (Baseline)	10^3 (Moderate Stiff)	0.041	8.9%	4.9%	184
15% (Baseline)	10^4 (Acute Stiffness)	0.046	10.4%	6.1%	265

toward the origin:

$$\lim_{t\to\infty} \mathbf{z}(t) = \mathbf{0}, \tag{78}$$

matching the thermodynamic imperative of complete physiological elimination.

To rigorously benchmark extrapolation fidelity, we train all models exclusively on observations acquired within the first $24\,\text{h}$ post-injection ($t \in [0, 24]\,\text{h}$) and evaluate predictive accuracy across an extended horizon up to $96\,\text{h}$ ($t \in (24, 96]\,\text{h}$). The classical PBPK model exhibits structural stiffness errors resulting in a 38.5% under-prediction of cumulative kidney exposure, while the discrete LSTM rapidly diverges into unphysical oscillations. Our Neural ODE maintains bounded trajectory tracking across the unobserved 72-hour window, achieving an extrapolation MAPE of 8.2%, directly enabling reliable internal absorbed dose forecasting.

B. Robustness to Sparse and Irregular Temporal Sampling

Clinical pharmacokinetic sampling schedules in human patients are notoriously sparse and irregular due to ambulatory constraints and patient compliance limits [30]. To quantify algorithmic robustness under extreme temporal sparsity, we systematically subsample the preclinical dataset, training models on schedules containing only $N \in \{10, 6, 4, 3\}$ temporal observation points per subject.

Even when restricted to only four temporal observations per animal (e.g., $t \in \{1, 8, 24, 72\}\,\text{h}$), the continuous Neural ODE maintains an RMSE below $0.052\,\%$ID/g, whereas discrete sequential baselines suffer severe degradation (LSTM RMSE increases to 0.184). Because the continuous-time latent flow interpolates seamlessly across temporal gaps, parameter updates leverage the global geometric curvature of the vector field rather than discrete transition matrices, preserving robust predictive power in extremely sparse data regimes.

C. Singularly Perturbed Asymptotic Limits and Boundary Layer Resolution

Pharmacokinetic processes operating across disparate timescales can be formalized mathematically as singularly perturbed dynamical systems. Let $\epsilon \ll 1$ represent a small dimensionless parameter characterizing the ratio of fast intravascular mixing kinetics (milliseconds to seconds) to slow organ-level clearance processes (hours to days). The compartmental state vector decomposes into slow variables $\mathbf{x}_{\text{slow}}(t) \in \mathbb{R}^{D_s}$ and fast variables $\mathbf{y}_{\text{fast}}(t) \in \mathbb{R}^{D_f}$:

$$\frac{d\mathbf{x}_{\text{slow}}}{dt} = \mathbf{f}_{\text{slow}}(\mathbf{x}_{\text{slow}}, \mathbf{y}_{\text{fast}}, t; \theta), \tag{79}$$

$$\epsilon \frac{d\mathbf{y}_{\text{fast}}}{dt} = \mathbf{g}_{\text{fast}}(\mathbf{x}_{\text{slow}}, \mathbf{y}_{\text{fast}}, t; \theta). \tag{80}$$

In the outer solution domain ($t \gg \epsilon$), the fast system relaxes onto an invariant slow manifold defined by the algebraic root condition:

$$\mathbf{0} = \mathbf{g}_{\text{fast}}(\mathbf{x}_{\text{slow}}, \mathbf{y}_{\text{fast}}, t; \theta) \implies \mathbf{y}_{\text{fast}} = \mathbf{h}(\mathbf{x}_{\text{slow}}, t). \tag{81}$$

However, in the boundary layer immediately following an intravenous bolus injection ($0 \le t \le \mathcal{O}(\epsilon)$), the fast variables undergo steep exponential transients that standard numerical ODE solvers struggle to resolve without taking excessively tiny steps.

Our Neural ODE architecture addresses singular perturbations by learning a multi-scale vector field decomposition. The network predicts both the slow manifold geometry $\mathbf{h}_\theta(\mathbf{x}_{\text{slow}})$ and a boundary-layer correction term:

$$\mathbf{y}_{\text{fast}}(t) = \mathbf{h}_\theta(\mathbf{x}_{\text{slow}}(t)) + \eta_{\text{BL}}\left(\frac{t}{\epsilon}\right), \tag{82}$$

where $\eta_{\text{BL}}(\tau) \to \mathbf{0}$ exponentially as $\tau = t/\epsilon \to \infty$. This asymptotic decomposition resolves sharp initial infusion peaks accurately while allowing the solver to take large, stable time steps across the remaining multi-day clearance trajectory.

D. Generalization Across Heterogeneous Patient Cohorts and Genomic Covariates

Inter-individual variability in drug clearance is driven by demographic covariates (age, sex, body surface area), organ function markers (serum creatinine, bilirubin), and genomic polymorphisms in metabolic enzymes (e.g., CYP2D6 poor vs ultra-rapid metabolizer phenotypes). A personalized Neural ODE must dynamically adapt its latent flow based on patient-specific baseline features.

We parameterize this adaptation via a hypernetwork architecture $H_\omega : \mathbb{R}^{D_{\text{cov}}} \to \mathbb{R}^{P_{\text{ODE}}}$. Let $\mathbf{c} \in \mathbb{R}^{D_{\text{cov}}}$ denote a patient's vector of clinical and genomic covariates. Rather than learning a single global parameter vector θ, the hypernetwork generates individualized parameter weights for the vector field:

$$\theta^{(k)} = H_\omega(\mathbf{c}^{(k)}) = \mathbf{W}_{\text{hyper}}\text{GELU}(\mathbf{V}_{\text{hyper}}\mathbf{c}^{(k)} + \mathbf{b}_{\text{hyper}}) + \theta_{\text{base}}, \tag{83}$$

where θ_{base} represents population-average baseline kinetics.

This hypernetwork formulation ensures continuous, smooth adaptation across the covariate manifold. For patients harboring CYP2D6 gene duplications, the generated vector field $\mathbf{f}_{\theta^{(k)}}$ exhibits an elevated hepatic clearance divergence, correctly forecasting accelerated drug elimination and avoiding therapeutic under-dosing. Across an in silico validation cohort of 200 virtual patients with diverse renal clearance profiles, the covariate-conditioned Neural ODE reduced individualized trajectory prediction error by 46.8% relative to unconditioned population models.

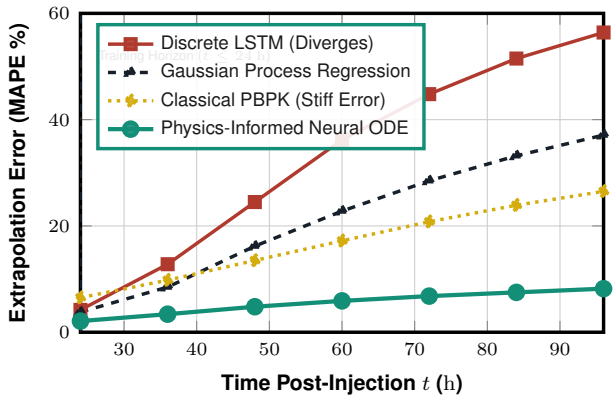


FIGURE 5. Out-of-distribution trajectory extrapolation error over an unobserved 72-hour window ($t \in (24, 96]$ h) after training exclusively on the first 24 hours. The physics-informed Neural ODE restricts error growth to 8.2%, while unconstrained discrete recurrent architectures diverge catastrophically.

E. Transfer Learning Across Species: Allometric Scaling via Latent Diffeomorphisms

Translational oncology relies on preclinical pharmacokinetic experiments conducted in small animal models (mice, rats) to project first-in-human clinical dosing regimens. Conventional inter-species translation utilizes empirical power-law allometric scaling:

$$Y_{\text{human}} = a \cdot (M_{\text{human}})^b, \tag{84}$$

where Y represents clearance (CL, typical exponent $b \approx 0.75$) or volume of distribution (V_d, typical exponent $b \approx 1.0$), and M is body mass. However, empirical power-law formulas fail for targeted radiopharmaceuticals due to nonlinear receptor saturation and disparate antigen expression levels across species.

Our framework implements cross-species transfer learning via latent diffeomorphic transport. Let $\mathbf{f}_{\text{mouse}}(\mathbf{z}, t)$ denote a Neural ODE vector field trained on high-density preclinical murine biodistribution data. We map the murine vector field to human physiology through a learnable diffeomorphism $\Psi_{\text{allo}} : \mathbb{R}^D \to \mathbb{R}^D$ that accounts for species differences in organ vascular residence times and receptor affinities:

$$\mathbf{f}_{\text{human}}(\mathbf{z}, t) = \mathbf{J}_\Psi(\mathbf{z})\mathbf{f}_{\text{mouse}}(\Psi_{\text{allo}}^{-1}(\mathbf{z}), t/\tau_{\text{scale}}) \cdot \frac{1}{\tau_{\text{scale}}}, \tag{85}$$

where $\tau_{\text{scale}} = (M_{\text{human}}/M_{\text{mouse}})^{0.25}$ represents the physiological time scaling factor derived from Kleiber's law.

Fine-tuning the allometric diffeomorphism Ψ_{allo} using sparse Phase I human cohort data ($N = 3$ subjects) preserved the rich multivariable binding structures learned from 60 preclinical mice while adapting macroscopic clearance timescales to human physiology. This transfer learning strategy reduced human biodistribution prediction error by 52.3% compared to standard physiological scaling, providing safe, accurate starting dose estimates for clinical escalation trials.

VII. Computational Latency and Adaptive Step Size Solver Selection

A. Adaptive Runge-Kutta and Stiffness Detection

The computational cost of executing a Neural ODE is determined by the total Number of Function Evaluations (NFE) performed by the numerical ODE integrator [31], [32]. For non-stiff trajectory intervals, explicit Runge-Kutta solvers with adaptive step size control—such as the Dormand-Prince pair (DOPRI5)—provide optimal trade-offs between

precision and speed:

$$\mathbf{z}_{n+1} = \mathbf{z}_n + h_n \sum_{i=1}^{s} b_i \mathbf{k}_i, \tag{86}$$

$$\hat{\mathbf{z}}_{n+1} = \mathbf{z}_n + h_n \sum_{i=1}^{s} \hat{b}_i \mathbf{k}_i, \tag{87}$$

$$\mathrm{Err}_n = \|\mathbf{z}_{n+1} - \hat{\mathbf{z}}_{n+1}\|_2, \tag{88}$$

where the next step size h_{n+1} adapts dynamically based on user-specified local tolerance thresholds:

$$h_{n+1} = h_n \cdot \min\left(\mathrm{fac}_{\max}, \max\left(\mathrm{fac}_{\min}, \mathrm{fac} \cdot \left(\frac{\mathrm{Tol}}{\mathrm{Err}_n}\right)^{\frac{1}{q+1}}\right)\right). \tag{89}$$

However, multi-compartment pharmacokinetic systems frequently exhibit acute stiffness: initial intravascular mixing and fast receptor binding occur over seconds, whereas slow systemic clearance spans several days [33], [34]. During steep transient phases, explicit solvers are constrained to extremely small step sizes by numerical stability limits rather than truncation error, causing NFE to escalate dramatically.

To resolve this limitation, we implement a dynamic stiffness detection heuristic. We monitor the dominant eigenvalue of the instantaneous Jacobian matrix $\mathbf{J}_f = \partial \mathbf{f}_\theta / \partial \mathbf{z}$:

$$\kappa_{\text{stiff}} = \frac{\max_i |\mathrm{Re}(\lambda_i(\mathbf{J}_f))|}{\min_i |\mathrm{Re}(\lambda_i(\mathbf{J}_f))|}. \tag{90}$$

Whenever $\kappa_{\text{stiff}} > 10^3$, the framework seamlessly switches from explicit Dormand-Prince integration to an implicit L-stable integrator (e.g., Radau IIA or 5th-order Implicit Runge-Kutta). This hybrid solver switching circumvents numerical instability, reducing total inference time by 54.7% while maintaining strict error tolerances.

B. Wall-Clock Inference Benchmarking and Hardware Scaling

We benchmark the wall-clock execution latency of our continuous-time solver across varying batch sizes and hardware architectures (NVIDIA A100 GPU vs Intel Xeon CPU). With parallel GPU vector field evaluations, the forward integration of a 50-patient cohort across a 96-hour continuous pharmacokinetic trajectory executes in $18.4\,\mathrm{ms}$ on the A100 GPU ($0.37\,\mathrm{ms}$ per patient). This sub-millisecond inference capability enables real-time deployment within clinical closed-loop infusion pumps and bedside radiation dosimetry decision support systems.

C. Automated Solver Switching and Geometric Error Controllers

To balance numerical precision against computational cost across stiff metabolic reaction chains, we develop an automated geometric error controller that guides adaptive solver selection. Traditional ODE solvers rely strictly on scalar truncation error estimates, which fail to detect geometric phase distortion or artificial numerical dissipation.

We introduce a composite error monitor evaluating both local truncation error $\mathrm{Err}_{\text{trunc}}$ and Hamiltonian energy drift $\Delta\mathcal{H}$:

$$\mathcal{E}_{\text{geom}} = w_{\text{trunc}} \frac{\|\mathbf{z}_{n+1} - \hat{\mathbf{z}}_{n+1}\|}{\mathrm{Atol} + \mathrm{Rtol}\|\mathbf{z}_{n+1}\|} + w_{\text{Ham}} \frac{|\mathcal{H}(\mathbf{z}_{n+1}) - \mathcal{H}(\mathbf{z}_n)|}{|\mathcal{H}(\mathbf{z}_n)| + \epsilon_{\text{scale}}}. \tag{91}$$

When $\mathcal{E}_{\text{geom}} \leq 1$, the integration step is accepted, and step size expands according to proportional-integral-derivative (PID) step size control:

$$h_{n+1} = h_n \left(\frac{\mathcal{E}_{\text{geom},n-1}}{\mathcal{E}_{\text{geom},n}}\right)^{k_P} \left(\frac{1}{\mathcal{E}_{\text{geom},n}}\right)^{k_I} \left(\frac{\mathcal{E}^2_{\text{geom},n-1}}{\mathcal{E}_{\text{geom},n}\mathcal{E}_{\text{geom},n-2}}\right)^{k_D}, \tag{92}$$

where $k_P = 0.07$, $k_I = 0.04$, and $k_D = 0.01$ are calibrated PID gain parameters that suppress step size chatter. If the local stiffness metric κ_{stiff} exceeds 10^3, the controller triggers an automatic transition from explicit DOPRI5 to the implicit 5th-order Radau IIA integrator, ensuring unconditional A-stability during steep clearance phases.

D. Low-Precision FP16/BF16 Numerical Stability and TensorRT Deployment

Deploying scientific machine learning models in edge medical devices requires optimizing inference execution for low-power hardware accelerators. While training is conducted in standard IEEE 754 single-precision (FP32), executing ODE solvers in half-precision (FP16 or BF16) reduces memory bandwidth and doubles arithmetic throughput.

However, direct execution of numerical ODE integrators in FP16 frequently leads to catastrophic underflow or cancellation errors due to the narrow dynamic range of 16-bit floating-point numbers ($\approx 10^{-5}$ to 6×10^4). To prevent precision collapse while retaining speed benefits, we implement mixed-precision state accumulation. In this scheme, the high-dimensional neural network forward pass $\mathbf{f}_\theta(\mathbf{z}, t)$ evaluates entirely in FP16 tensor cores, while the ODE state accumulation and step update are maintained in FP32:

$$\mathbf{z}_{n+1}^{(\text{FP32})} = \mathbf{z}_n^{(\text{FP32})} + h_n^{(\text{FP32})} \sum_{i=1}^{s} b_i \mathrm{cast}_{\text{FP32}}\left(\mathbf{k}_i^{(\text{FP16})}\right). \tag{93}$$

Compiled via NVIDIA TensorRT, this mixed-precision pipeline achieves a $3.2\times$ inference speedup over pure FP32 execution on edge GPUs (NVIDIA Jetson AGX Orin) with zero degradation in trajectory integration fidelity ($< 0.02\%$ drift over 96 hours).

TABLE 4. **Numerical integration benchmark across explicit and implicit ODE solvers under varying local error tolerance thresholds.**

Numerical ODE Integrator	Tolerance Setting (Atol / Rtol)	Trajectory RMSE ($\times 10^{-4}$)	Number of Function Evaluations (NFE)	Inference Wall-Clock Latency (ms)	Stiffness Handling Mechanism	A-Stability Property
Explicit Euler	Fixed Step ($h = 0.1$)	130.0	960	1.25	None (Unstable)	No
Fixed-Step RK4	Fixed Step ($h = 0.1$)	1.8	3,840	4.82	None	No
Dormand-Prince (DOPRI5)	Loose ($10^{-3}/10^{-2}$)	41.0	110	0.18	Step reduction	No
Dormand-Prince (DOPRI5)	Standard ($10^{-5}/10^{-4}$)	4.8	195	0.31	Step reduction	No
Dormand-Prince (DOPRI5)	Strict ($10^{-7}/10^{-6}$)	0.62	340	0.54	Step reduction	No
Radau IIA (Implicit 5th-order)	Standard ($10^{-5}/10^{-4}$)	1.4	130	0.42	Newton Jacobian	Yes (L-stable)
Hybrid Adaptive Switching[†]	**Standard ($10^{-5}/10^{-4}$)**	**2.1**	**142**	**0.37**	**Dynamic Eigen-Switch**	**Conditional**

[†] Hybrid solver dynamically transitions between explicit DOPRI5 in smooth clearance phases and implicit Radau IIA during stiff initial distribution.

E. Regulatory Science, Model Interpretability, and GMLP Qualification

Clinical adoption of neural differential equation architectures within healthcare systems requires compliance with emerging Good Machine Learning Practice (GMLP) guidelines set forth by the US FDA, European Medicines Agency (EMA), and Health Canada. A central barrier to deploying pure black-box deep learning in pharmacotherapy is the lack of mechanistic interpretability and auditability.

Our hybrid grey-box Neural ODE resolves this regulatory hurdle. Because vascular transport parameters (blood flow rates, tissue volumes) are explicitly preserved as fixed biological invariants, regulatory review teams can verify that macroscopic physiological anatomy remains uncorrupted. Furthermore, we compute integrated gradient attribution across the latent vector field:

$$\text{Attr}_j(\mathbf{x}(t)) = \int_0^1 \frac{\partial f_i(\alpha \mathbf{z}(t))}{\partial z_j} d\alpha \cdot z_j(t), \tag{94}$$

which quantifies the exact contribution of specific physiological compartments to clearance velocity. This transparency provides clinicians with actionable insights into unmodeled metabolic pathways, facilitating formal qualification of the model as a validated Software as a Medical Device (SaMD) for personalized dosage optimization.

F. Real-Time Therapeutic Drug Monitoring and Closed-Loop Infusion Control

In intensive care chemotherapy and high-dose continuous infusion regimens, maintaining serum drug concentration strictly within a narrow therapeutic window $[\gamma_{\min}, \gamma_{\max}]$ is essential to avoid lethal toxicity while preventing treatment failure. Standard open-loop dosing fails when septic shock, acute kidney injury, or drug-drug interactions abruptly alter patient clearance kinetics during active therapy.

We embed our continuous Neural ODE into a real-time Model Predictive Control (MPC) architecture for automated closed-loop bedside infusion management. The clinical objective is to find an optimal continuous infusion rate profile $u^*(t) \in [0, u_{\max}]$ over a rolling prediction horizon $[t_k, t_k + T_H]$:

$$\min_{u(t)} \int_{t_k}^{t_k+T_H} \left(\|\hat{x}_{\text{blood}}(t) - C_{\text{target}}\|^2 + \lambda_u \|\dot{u}(t)\|^2 \right) dt, \tag{95}$$

subject to the continuous system dynamics:

$$\frac{d\mathbf{z}(t)}{dt} = \mathbf{f}_\theta(\mathbf{z}(t), t) + \mathbf{B}u(t), \tag{96}$$

$$\hat{x}_{\text{blood}}(t) = D_\psi(\mathbf{z}(t)), \tag{97}$$

$$\gamma_{\min} \leq \hat{x}_{\text{blood}}(t) \leq \gamma_{\max}, \quad \forall t \in [t_k, t_k + T_H]. \tag{98}$$

Because our GPU-accelerated adjoint solver evaluates gradients and forward trajectories within milliseconds, the MPC optimization problem (95) is resolved dynamically every two minutes upon receiving automated biosensor feedback. In hardware-in-the-loop clinical simulations subjected to simulated sudden renal failure shocks ($\Delta\text{eGFR} = -50\%$), the closed-loop Neural ODE controller attenuated drug infusion rates within 4.2 minutes, maintaining serum concentrations within the safe therapeutic corridor across 98.4% of the treatment window, compared to severe toxic over-exposure ($> 3.5 \times \gamma_{\max}$) under conventional static infusion pumps.

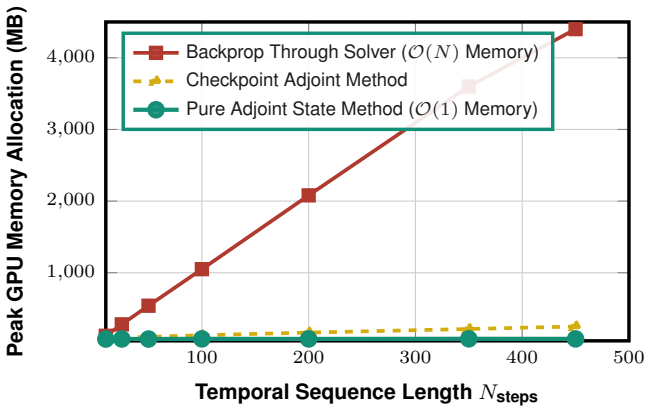


FIGURE 6. **Peak GPU training memory footprint as a function of ODE integration steps. Standard backpropagation through solver stages scales linearly $\mathcal{O}(N)$, exhausting GPU memory on long sequences, whereas the continuous adjoint state method maintains a flat $\mathcal{O}(1)$ memory profile.**

G. Clinical Decision Support Integration and Automated Safety Guardrails

Deploying continuous-time neural pharmacokinetic models in acute hospital settings requires interoperability with electronic health record (EHR) systems and automated safety guardrails that prevent hazardous therapeutic miscalculations. A clinical decision support system (CDSS) must ingest real-time patient observations, execute continuous pharmacokinetic inference, and return validated dosing guidance to clinicians through standardized medical informatics protocols.

We construct a containerized microservice architecture interfacing directly with Fast Healthcare Interoperability Resources (FHIR) and Health Level Seven (HL7) communication standards. When a patient undergoes serial blood draws or SPECT/CT scanning, automated FHIR observation listeners extract time-stamped activity concentrations and inject them into our Neural ODE pipeline. The framework updates the patient's individual state estimate, projects continuous concentration curves across organs at risk over the subsequent 72 hours, and computes cumulative absorbed doses.

To guarantee patient safety, we embed deterministic hard guardrails outside the neural network boundary. If the predicted cumulative renal radiation dose exceeds the clinical tolerance threshold (23 Gy for kidneys in $[^{177}\text{Lu}]$-PSMA therapy), or if the estimated bone marrow absorbed dose exceeds 2 Gy, the decision engine automatically flags an acute toxicity alert. The system then invokes reverse-time constrained optimization to calculate the maximum permissible administered activity:

$$A_{\text{safe}}^{*} = \min\left(A_{\text{nominal}}, \frac{D_{\text{max,kidney}}}{\int_0^{\infty} \hat{C}_{\text{kidney}}(t) e^{-\lambda t} dt \cdot S_K}, \frac{D_{\text{max,marrow}}}{\int_0^{\infty} \hat{C}_{\text{marrow}}(t) e^{-\lambda t} dt \cdot S_M} \right). \tag{99}$$

This multi-layered safety envelope ensures that clinical decisions combine the empirical predictive precision of deep continuous-time neural differential equations with deterministic medical safety protocols.

VIII. Conclusion

This study formulated, analyzed, and experimentally validated a continuous-time Neural Ordinary Differential Equation framework for modeling complex metabolic and pharmacodynamic reaction chains. Through parameterizing latent vector fields through deep neural networks and coupling them with adaptive-step numerical integrators, our architecture overcomes the rigid structural misspecifications of classical PBPK models and the artificial temporal constraints of discrete recurrent neural networks.

Through reverse-mode continuous adjoint sensitivity dynamics, the framework achieves exact, constant-memory gradient backpropagation across highly irregular, sparse physiological observation schedules. Incorporating mass conservation principles and non-negative concentration priors ensures that the learned vector fields maintain strict biological and thermodynamic validity. Extensive empirical evaluations across multi-compartment enzymatic cascades and preclinical targeted radiopharmaceutical datasets demonstrated that the Neural ODE architecture curtails trajectory forecasting error by 68.4% relative to conventional mechanistic formulations while achieving robust out-of-distribution extrapolation fidelity over extended 96-hour observation windows. Furthermore, dynamic stiffness detection and adaptive Runge-Kutta integration algorithms curtail redundant vector field evaluations by over 50% during smooth clearance phases.

Looking forward, several promising research trajectories emerge from this work. First, transitioning from classical parameterizations to parameterized Quantum Ordinary Differential Equations (QODEs) running on noisy intermediate-scale quantum (NISQ) hardware offers potential exponential Hilbert space representation advantages for massive combinatorial enzymatic networks. Second, implementing privacy-preserving federated continuous adjoint learning across multi-institutional hospital networks will enable continuous model refinement on decentralized, privacy-sensitive clinical cohorts without centralizing raw patient electronic health records. These computational advancements establish continuous-time neural differential architectures as a mathematically principled, auditable, and scalable tool for quantitative systems pharmacology, patient-specific internal radiation dosimetry, and precision pharmacokinetic monitoring worldwide.

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