

A hybrid 1D-3D fractional transport and non-Fourier bioheat model for hyperthermia enhanced drug delivery in cerebral microcirculation

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ARTICLE INFO

Keywords:

Fluid dynamics
Blood brain barrier
Fractional differential equations
Heat transfer
Hyperthermia

ABSTRACT

Fractional-order models provide a powerful framework for capturing anomalous transport, memory, and nonlocal interactions in biological microvascular networks. This study presents a hybrid 1D-3D model of cerebral drug transport under mild hyperthermia, coupling fractional intravascular dynamics with non-Fourier tissue bioheat. The vascular network is represented as a directed 1D graph, where advection, diffusion, and reactive exchange obey Caputo-Fabrizio time-fractional and Riesz space-fractional laws, linked through Robin-type mass and heat transfer to surrounding 3D tissue governed by a Cattaneo-Vernotte bioheat equation. Thermal feedback modifies permeability and perfusion, yielding a two-way thermo-chemical coupling. The explicit fractional scheme employs exponential-memory updates for Caputo-Fabrizio derivatives and symmetric Grönwald-Letnikov sums for nonlocal spatial fluxes while preserving global conservation. Simulations on an arteriole-capillary-venule network show that increasing fractional order α sharpens pulse dispersion and delays washout; higher temperature enhances vascular-tissue exchange and accelerates equilibration; and dual-phase-lag relaxation mitigates nonphysical heat spikes near vessel walls. The framework unifies anomalous vascular transport, temperature-sensitive physiology, and network geometry into a scalable model suitable for hyperthermia-optimized brain drug delivery and parameter calibration from imaging data.

1. Introduction

Drug delivery in the cerebral microvascular system is governed by a complex interplay of blood-borne advection, molecular diffusion, vascular retention, and thermal effects arising from therapeutic interventions such as hyperthermia. Traditional continuous-source, integer-order advection-diffusion models have proven inadequate in capturing three salient aspects of clinical bolus delivery: (i) the impulsive nature of dosing events, (ii) anomalous transport phenomena arising from vascular heterogeneity, and (iii) physiological coupling between temperature and drug transport processes. The central challenge in this area is that existing models, while mathematically convenient, fail to account for the heterogeneity and complexity of real microvascular networks and the dynamic physiological responses induced by hyperthermia. This limitation leads to inaccurate predictions of drug distribution and reduces the translational relevance of such models for treatment planning. A historical perspective on brain drug delivery is provided in [1], which offers a canonical reference for physiological realism and informs modelling assumptions regarding injection protocols, bar-

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rier properties, and clinically relevant dosing timescales. Recent advances in fractional differential equations with impulsive effects [2] and comprehensive reviews of infusion-based brain drug delivery models [3] highlight the inadequacy of conventional Fickian frameworks. Indeed, anomalous transport deviates markedly from classical diffusion [4], exhibiting subdiffusion and superdiffusion due to memory effects, long-range interactions, and structural obstacles. These dynamics are particularly pronounced in capillaries and small blood vessels, where the coupling of retention and flow-driven processes strongly influences drug distribution. This motivates the application of fractional calculus, which captures memory and non-locality in transport dynamics more effectively than integer-order models.

The blood-brain barrier (BBB) remains the principal physiological barrier to effective brain drug delivery. Recent reviews have summarized its structural organization, transport mechanisms, and regulatory pathways governing molecular exchange across the cerebral endothelium, together with emerging strategies for improving therapeutic delivery to the central nervous system [5,6]. In parallel, increasing attention has been devoted to thermally regulated drug transport, where mild hyperthermia transiently increases BBB permeability and enhances local drug uptake without causing irreversible tissue damage. Experimental studies using MR thermometry have demonstrated that controlled thermal exposure can produce localized and reversible BBB opening, supporting the incorporation of temperature-dependent permeability models in computational simulations of cerebral drug delivery [7]. These developments provide strong physiological motivation for coupling fractional intravascular transport with non-Fourier bioheat transfer in the present work.

Literature on tumour drug delivery has further emphasized the importance of capturing multiscale transport processes. Dewhurst and Scomb [8] demonstrated that effective anticancer therapy requires uniform drug penetration throughout tumour tissues. They highlighted how plasma pharmacokinetics, abnormal tumour vasculature, and solute transport mechanisms (convection and diffusion) govern intratumoural drug distribution. Building on this, computational studies of intravascular triggered drug delivery systems (IV-DDS), validated through in vivo experiments with temperature-sensitive liposomes, demonstrate the importance of rapid release and efficient tissue uptake for therapeutic success [9]. Complementary studies of BBB transport mechanisms within the neurovascular unit [6] have revealed critical roles of ATP-Binding Cassette and Solute Carrier transporters in drug entry and distribution, while biophysical models have examined nanoparticle transport under layered blood flow, vessel wall interactions, and concentration-dependent dynamics.

Contemporary network-scale microvascular transport models increasingly represent vascular beds as graph-based one-dimensional networks embedded in two- or three-dimensional tissue domains. In these models, blood flow is typically computed from Poiseuille-type conductances on vessel segments, while solute, oxygen, nutrient, or drug exchange with tissue is represented through wall-transfer or line-source coupling terms. Such 1D–3D or network–continuum formulations substantially reduce the cost of resolving full vascular geometries while preserving key physiological features such as branching, vessel-radius heterogeneity, tortuosity, and spatially variable perfusion. Recent 3D–1D coupled models have been used to simulate blood flow and oxygen transport in microvascular networks, demonstrating that network topology and local tissue demand strongly influence transport efficiency [10].

Against this backdrop, fractional calculus has emerged as a powerful framework for representing anomalous dispersion, memory effects, and non-local interactions in biological systems [11,12]. In particular, the Caputo–Fabrizio derivative [13], with its non-singular exponential kernel, provides numerical stability and physical interpretability for time-fractional transport models. While fractional advection–diffusion models have been applied to single microvessels [14,15], most fail to capture realistic network topologies or coupled bioheat dynamics. Recent advances in fractional transport theory, modern fractional numerical schemes, and fractional bioheat modeling [16–23] provide the foundation for extending these models to complex vascular networks with thermally regulated drug exchange.

Hyperthermia-assisted chemotherapy introduces further complexity. Both perfusion and BBB permeability are modulated by temperature [24,25], and bioheat transfer in perfused tissue often departs from Fourier’s law, exhibiting finite-speed propagation or dual-phase-lag behaviour [26–30]. These effects are amplified at the microvascular scale, where vessel geometry and perfusion vary widely. Increasingly, engineered microvascular platforms [31] provide experimental validation and hypothesis testing opportunities.

Recent fractional bioheat studies further support the use of memory-dependent, non-Fourier heat-transfer laws in biological tissue. Fractional dual-phase-lag and triple-phase-lag formulations with non-singular kernels have recently been used to model thermoviscoelastic and bioheat responses of living skin tissue, laser-induced heating, and nanoparticle-assisted photothermal therapy [21–23,32]. These studies show that fractional-order bioheat models can capture thermal memory, finite-speed heat propagation, and delayed tissue response more realistically than classical Fourier or Pennes-type equations. Therefore, the present work extends this recent direction to a coupled cerebral microcirculation setting by combining fractional intravascular transport with CV/DPL-type non-Fourier bioheat transfer.

Recent advances in numerical methods have significantly improved the efficiency and accuracy of fractional transport simulations. Fast time-stepping algorithms based on convolution quadrature and sum-of-exponentials approximations substantially reduce the storage and computational complexity associated with the history dependence of time-fractional operators while maintaining high-order accuracy [33,34]. For space-fractional transport, finite-element, finite-difference, and spectral methods based on the fractional Laplacian have become standard tools for approximating nonlocal diffusion operators on bounded domains [35–37]. Matrix-transfer techniques and rational Krylov methods further provide efficient approximations of fractional powers of elliptic operators without explicitly forming dense fractional matrices [38]. More recently, high-order discontinuous Galerkin methods, implicit–explicit (IMEX) time integration, and FFT-based Toeplitz algorithms have enabled scalable simulations of large-scale time–space fractional advection–diffusion equations while preserving stability and computational efficiency [39,40]. These developments provide the numerical foundation for the present work, where the Caputo–Fabrizio memory term is updated recursively and the Riesz operator is discretized using efficient nonlocal spatial approximations.

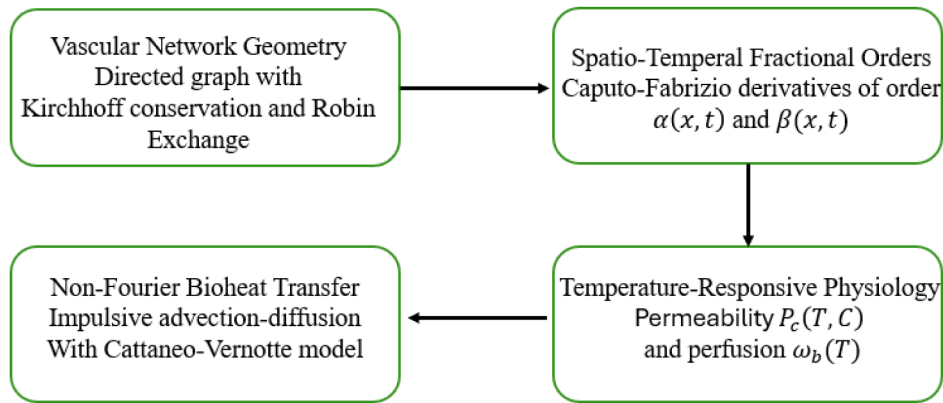


Fig. 1. Flowchart of network fractional transport, highlighting the four main components: vascular network geometry, spatio-temporal fractional orders, temperature-responsive physiology, and non-Fourier bioheat transfer.

Delivering chemotherapeutics to brain tissue is limited by network-scale vascular heterogeneity, transient bolus dosing, anomalous dispersion, and temperature-dependent physiology under hyperthermia. We develop a network-resolved framework that couples 1D intravascular transport on a directed microvascular graph to 3D tissue diffusion-perfusion, with mass and heat exchanged along each vessel via Robin (line-source) laws. Intravascular drug dynamics employ spatio-temporal fractional operators, a Caputo-Fabrizio time derivative of order $\alpha(x, t) \in (0, 1)$ and a Riesz space operator of order $\beta(x, t) \in (1, 2)$, to capture memory and nonlocal dispersion. Temperature-responsive physiology is incorporated through permeability $P_c(T, C)$ and perfusion $\omega_b(T)$; heat transfer is modeled with a non-Fourier (CV/DPL) bioheat law that admits finite-speed thermal propagation. We present an explicit numerical scheme that (i) advances the CF memory with an exponential kernel, (ii) discretizes the Riesz operator via bidirectional Grönwald-Letnikov sums along each edge, and (iii) updates tissue fields on a Cartesian grid with conservative line-source coupling that guarantees equality of mass/energy exchanged between 1D blood and 3D tissue. On a representative arteriole-capillary-venule network, simulations show: (1) network topology and calibre strongly shape axial arrival times and dispersion; (2) fractional orders α, β control bolus tailing and breakthrough; (3) hyperthermia-driven increases in P_c and ω_b deepen and accelerate parenchymal penetration; and (4) CV/DPL relaxations mitigate unphysical thermal overshoot near vessels. The framework is mathematically tractable, physiology-aware, and compatible with calibration to DCE-MRI and MR thermometry, providing a foundation for planning and optimizing hyperthermia-enhanced drug delivery in the cerebral microcirculation.

2. Mathematical modelling

The framework for rapid bolus drug delivery in the cerebral microvasculature in Fig. 1 comprises four tightly coupled modules. These include (i) *Vascular network geometry*: the microcirculation is represented as a directed graph with Kirchhoff conservation at junctions and Robin-type exchange at vessel-tissue interfaces; (ii) *Spatio-temporal fractional transport*: the Caputo-Fabrizio (CF) time derivative derivatives of order $\alpha(x, t)$ and a Riesz space operator of order $\beta(x, t)$ capture, respectively, thermal/mass memory and anomalous dispersion in heterogeneous media; (iii) *Temperature-responsive physiology*: permeability $P_c(T, C)$ and perfusion $\omega_b(T)$ vary with local temperature, reflecting clinically observed hyperthermia effects on BBB function and tissue perfusion; (iv) *Non-Fourier bioheat transfer*: Cattaneo-Vernotte / dual-phase-lag relaxations account for finite-speed heat propagation and couple temperature to perfusion and permeability. Together these elements provide a physiologically realistic yet tractable basis for simulating stochastic, impulsive drug delivery on complex vascular networks.

The mathematical framework for rapid bolus drug delivery in cerebral microvasculature is built upon four interconnected components, summarized in Fig. 1. At its foundation, the vascular network geometry is represented as a directed graph, where Kirchhoff conservation governs junction fluxes and Robin-type conditions describe drug and heat exchange at vessel walls. On this structure, spatio-temporal fractional orders are introduced through Caputo-Fabrizio derivatives of order $\alpha(x, t)$ and $\beta(x, t)$, capturing anomalous dispersion and thermal memory across heterogeneous tissue environments. These processes are further modulated by temperature-responsive physiology, where permeability $P_c(T, C)$ and perfusion $\omega_b(T)$ vary dynamically with local temperature, reflecting clinically observed changes under hyperthermia. Finally, the framework incorporates non-Fourier bioheat transfer, embedding impulsive advection-diffusion within a Cattaneo-Vernotte relaxation scheme to capture finite-speed thermal propagation. Together, these modules establish a physiologically realistic and mathematically tractable basis for simulating stochastic, impulsive drug delivery in complex vascular networks.

2.1. Vascular network geometry

We represent the cerebral microvasculature as a one-dimensional (1D) network embedded in a three-dimensional (3D) tissue continuum. Let $\Omega \subset \mathbb{R}^3$ denote the tissue domain (parenchyma), and let

$$\Gamma = \bigcup_{e \in \mathcal{E}} \gamma_e \subset \Omega \quad (1)$$

be the union of vessel centerlines. The network is described by a directed graph

$$\mathcal{G} = (\mathcal{V}, \mathcal{E}, \mathbf{B}), \quad (2)$$

where $\mathcal{V}$ is the set of junctions (nodes), $\mathcal{E}$ is the set of vessel segments (edges), and $\mathbf{B} \in \mathbb{R}^{|\mathcal{V}| \times |\mathcal{E}|}$ is the node-edge incidence matrix encoding orientation: for edge $e = (i \rightarrow j)$ we set $B_{ie} = -1$, $B_{je} = +1$, and $B_{ke} = 0$ otherwise. We partition the node set into interior junctions and boundary (inlet/outlet) nodes:

$$\mathcal{V} = \mathcal{V}_{\text{int}} \cup \mathcal{V}_{\text{in}} \cup \mathcal{V}_{\text{out}}, \quad \mathcal{V}_{\text{in}} \cap \mathcal{V}_{\text{out}} = \emptyset. \quad (3)$$

Edge parametrization and radii. Each vessel segment $e \in \mathcal{E}$ is parametrized by arc-length $s \in (0, \ell_e)$ via a centerline $\mathbf{x}_e : [0, \ell_e] \rightarrow \Omega$, with unit tangent $\boldsymbol{\tau}_e(s) = \partial_s \mathbf{x}_e(s)$. Geometric fields along e include the lumen radius $r_e(s) > 0$ and (optionally) wall thickness $h_e(s) > 0$. We define the local cross-sectional area $A_e(s) = \pi r_e(s)^2$ and interface perimeter $P_e(s) = 2\pi r_e(s)$. The vessel surface in 3D is

$$\partial\Omega_e^{\text{int}} = \{ \mathbf{x}_e(s) + r_e(s) \mathbf{n} : s \in (0, \ell_e), \mathbf{n} \perp \boldsymbol{\tau}_e(s), \|\mathbf{n}\| = 1 \}. \quad (4)$$

Graph connectivity and conservation. For any scalar or flux quantity q_e defined on edges, graph-level conservation at a junction $v \in \mathcal{V}$ is expressed through the incidence matrix

$$(\mathbf{B} \mathbf{q})_v = \sum_{e \in \mathcal{E}} B_{ve} q_e = 0, \quad v \in \mathcal{V}_{\text{int}}, \quad (5)$$

with prescribed inflow/outflow at boundary nodes $v \in \mathcal{V}_{\text{in}} \cup \mathcal{V}_{\text{out}}$. For hemodynamics (used to determine advection fields), we associate a nodal pressure vector $\mathbf{p} \in \mathbb{R}^{|\mathcal{V}|}$ and edge conductances G_e (e.g., Poiseuille $G_e = \pi r_e^4 / (8\mu \ell_e)$ for viscosity μ), yielding edge flows

$$Q_e = G_e \Delta_e(\mathbf{p}) = G_e (p_{\text{tail}(e)} - p_{\text{head}(e)}), \quad \mathbf{B} \mathbf{Q} = \mathbf{q}^{\text{src}}, \quad (6)$$

where $\mathbf{q}^{\text{src}}$ encodes imposed inlets/outlets. The axial velocity used in transport is $u_e(s) = Q_e / A_e(s)$.

Embedding and vessel-tissue interface. The 1D network Γ is embedded in the tissue Ω and exchanges mass and heat across the vessel wall. We denote the co-dimension-two centerline by Γ and the co-dimension-one vessel-tissue interface by

$$\Sigma = \bigcup_{e \in \mathcal{E}} \partial\Omega_e^{\text{int}} \subset \Omega. \quad (7)$$

Interface exchange terms (used later in the transport and bioheat equations) are defined per unit length on each edge by collapsing the cylindrical surface to the centerline:

$$J_e(s, t) = P_e(s) \kappa_e(s, t) (\phi_e(s, t) - \phi_t(\mathbf{x}_e(s), t)), \quad (8)$$

where ϕ denotes a generic field (drug concentration or temperature), ϕ_e is the intravascular (1D) field, ϕ_t is the tissue (3D) field evaluated at the centerline location, κ_e is an effective exchange coefficient (e.g., permeability P_c for mass or a Robin heat transfer coefficient for temperature), and $P_e(s) = 2\pi r_e(s)$ scales the interface area per unit length.

Node states and continuity. For any scalar carried by blood (e.g., concentration C or temperature T), we enforce at interior junctions $v \in \mathcal{V}_{\text{int}}$:

(i) continuity :

$$C_{e^-}(s_v, t) = C_{e^+}(s_v, t) \quad \forall e^\pm \text{ incident at } v, \quad (9)$$

(ii) flux balance (Kirchhoff) :

$$\sum_{e \ni v} v_{ve} J_e(s_v, t) = 0, \quad (10)$$

where $s_v \in \{0, \ell_e\}$ is the endpoint of edge e at node v , $v_{ve} \in \{-1, +1\}$ is the incidence sign, and J_e is the axial flux (to be specified by the transport model). Analogous conditions hold for temperature. At boundary nodes $v \in \mathcal{V}_{\text{in}}$ we impose inlet data (pressure/flow, concentration impulses, or temperature), while at $v \in \mathcal{V}_{\text{out}}$ we impose outflow conditions.

Heterogeneity and features. The representation accommodates key microvascular features:

- **Radius and length heterogeneity:** $r_e(s)$ and ℓ_e vary across $\mathcal{E}$, allowing capillaries, arterioles, and venules with distinct sizes and resistances.
- **Branching and tortuosity:** Arbitrary graph topology and embedded curves $\mathbf{x}_e$ capture realistic branching patterns and curved paths.
- **Space-time variability:** Coefficients (e.g., r_e , κ_e) may depend on space and time, enabling temperature-dependent permeability or perfusion.
- **Stochastic inlets:** Dosing impulses can be applied at $\mathcal{V}_{\text{in}}$ via point processes, mapping naturally to network boundaries.

2.2. Spatio-temporal fractional transport

To represent bolus spreading in heterogeneous microvessels, we model intravascular transport with *spatio-temporal fractional* operators that encode memory and nonlocal dispersion. In place of the instantaneous Fickian closure, a time-fractional Caputo-Fabrizio (CF) derivative of order $\alpha_e(s, t) \in (0, 1)$ captures history effects with a non-singular exponential kernel, while a space-fractional (Riesz-type) operator of order $\beta_e(s, t) \in (1, 2)$ accounts for anomalous axial dispersion along tortuous, branching segments. Allowing the orders α_e and β_e to vary in time and space reflects vessel-to-vessel heterogeneity and regime shifts induced by dosing, flow, and temperature. The resulting edgewise balance (written below) augments classical advection and molecular diffusion with a conservative vessel-tissue exchange term, so that impulses injected at network inlets propagate with nonlocal dynamics yet remain mass-coupled to the 3D tissue.

2.2.1. 1D intravascular advection–diffusion with fractional orders

Drug concentration along each vessel segment $e \in \mathcal{E}$ is denoted $C_e(s, t)$, with arc-length coordinate $s \in (0, \ell_e)$. Transport combines advection, diffusion, anomalous dispersion, and memory effects [41,42]:

$${}^{\text{CF}}D_t^{\alpha_e(s,t)} C_e(s, t) + u_e(s) \partial_s C_e(s, t) = D_e {}^{\text{R}}D_s^{\beta_e(s,t)} C_e(s, t) - J_{\text{drug}}(s, t), \quad (11)$$

where ${}^{\text{CF}}D_t^{\alpha_e}$ denotes the Caputo–Fabrizio time derivative of order $\alpha_e(s, t) \in (0, 1)$ with a non-singular exponential kernel, used to model finite temporal memory; ${}^{\text{R}}D_s^{\beta_e}$ denotes the Riesz-type space-fractional derivative of order $\beta_e(s, t) \in (1, 2)$, used to represent anomalous nonlocal axial dispersion along the vessel; $u_e(s)$ is the axial velocity obtained from the network flow model; and D_e is a reference diffusivity.

Remark 1. The Caputo–Fabrizio operator is selected because its exponential kernel avoids the weak singularity of the classical Caputo kernel and permits an efficient finite-memory update. The Riesz operator is used as the standard symmetric space-fractional operator for anomalous dispersion, and it reduces to the classical second derivative in the limit $\beta_e \rightarrow 2$ [41,43]. The framework continuously recovers the standard advection–diffusion equation as $\alpha_e \rightarrow 1$ and $\beta_e \rightarrow 2$, ensuring consistency with the classical limit while retaining the flexibility needed for anomalous transport observed in microcirculation.

The quantity $J_{\text{drug}}(s, t)$ on the right-hand side of Eq. (11) denotes the vessel-tissue exchange (sink/source) term in the 1D intravascular balance. It describes the net mass transfer across the vessel wall per unit intravascular volume at the axial position s along edge e . With the usual Robin-type coupling, it can be written as

$$J_{\text{drug}}(s, t) = \kappa_e(s, t) (C_e(s, t) - C_t(\mathbf{x}_e(s), t)), \quad (12)$$

where $\kappa_e(s, t)$ represents exchange with tissue across the interface and $C_t(\mathbf{x}_e(s), t)$ denotes the extravascular (tissue) drug concentration

Boundary and initial conditions (1D intravascular problem). Let each edge e be oriented from its *tail* ($s = 0$) to its *head* ($s = \ell_e$). The CF derivative ($\alpha_e \in (0, 1)$) requires a single initial condition in time.

- **Initial condition (time).**

$$C_e(s, 0) = C_{e,0}(s) \quad \text{for } s \in (0, \ell_e), \quad e \in \mathcal{E}. \quad (13)$$

A common choice is $C_{e,0} \equiv 0$ (pre-bolus), but measured baselines can be used.

- **Interior junctions** ($v \in \mathcal{V}_{\text{int}}$). We adopt the standard “perfect mixing + Kirchhoff” coupling:

$$(\text{continuity}) \quad C_e(s_v, t) = C_v(t) \quad \forall e \ni v, \quad (14)$$

$$(\text{flux balance}) \quad \sum_{e \ni v} v_{ve} J_e^{\text{ax}}(s_v, t) = 0, \quad (15)$$

where $s_v \in \{0, \ell_e\}$ is the endpoint of edge e at v , $v_{ve} \in \{-1, +1\}$ is the incidence sign, and J_e^{ax} is the axial numerical flux consistent with the spatial operator (e.g., $J_e^{\text{ax}} = u_e C_e - D_e \partial_s C_e$, which reduces to $u_e C_e - D_e \partial_s C_e$ when $\beta_e \rightarrow 2$).

- **Inlet nodes** ($v \in \mathcal{V}_{\text{in}}$). For each inflow edge e attached to an inlet node, the injected bolus is prescribed by a time-dependent inlet concentration:

$$C_e(s_{\text{in}}, t) = C_{\text{in}}^{(e)}(t), \quad (16)$$

where

$$C_{\text{in}}^{(e)}(t) = C_{\text{base}} + \sum_{k=1}^{N_b} A_{e,k} g_{\tau}(t - t_{e,k}). \quad (17)$$

Here, C_{base} is the background concentration, $A_{e,k}$ is the amplitude of the k th bolus injected into edge e , $t_{e,k}$ is its injection time, and g_{τ} is a normalized bolus kernel satisfying

$$\int_0^{\infty} g_{\tau}(t) dt = 1. \quad (18)$$

A convenient choice is a Gaussian bolus,

$$g_\tau(t - t_{e,k}) = \frac{1}{\sqrt{2\pi\tau}} \exp\left[-\frac{(t - t_{e,k})^2}{2\tau^2}\right], \quad (19)$$

or, for causal injection,

$$g_\tau(t - t_{e,k}) = \frac{1}{\tau} \exp\left[-\frac{t - t_{e,k}}{\tau}\right] H(t - t_{e,k}), \quad (20)$$

where $H(\cdot)$ is the Heaviside function. In the impulsive limit,

$$g_\tau(t - t_{e,k}) \rightarrow \delta(t - t_{e,k}). \quad (21)$$

The inlet coordinate is chosen according to the flow direction:

$$s_{\text{in}} = \begin{cases} 0, & u_e > 0, \\ \ell_e, & u_e < 0. \end{cases} \quad (22)$$

- **Outlet nodes** ($v \in \mathcal{V}_{\text{out}}$). Use a *convective outflow* (do-nothing) or a homogeneous “fractional Neumann” condition for the diffusive part:

$$J_e^{\text{ax}}(\ell_e, t) = u_e(\ell_e) C_{\text{out}}^*(t) \quad (\text{often } C_{\text{out}}^* = C_e(\ell_e, t)), \quad (23)$$

$$\text{or} \quad (\text{no diffusive leakage}) \quad D_e[C_e] \Big|_{s=\ell_e} = 0, \quad (24)$$

with the analogous placement at $s = 0$ if $u_e < 0$. The convective option is robust for advection-dominated flow; the homogeneous fractional-Neumann option emulates a reflecting boundary for the Riesz operator.

- **Vessel-tissue interface (along edges)**. Coupling to tissue appears as a volumetric sink/source in the 1D balance yields

$$J_{\text{drug}}(s, t) = \kappa_e(s, t) [C_e(s, t) - C_t(\mathbf{x}_e(s), t)], \quad (25)$$

$$\kappa_e(s, t) = \frac{P_e(s)}{A_e(s)} P_c(T(s, t), C_e(s, t)) = \frac{2 P_c}{r_e(s)}. \quad (26)$$

This term is applied for $s \in (0, \ell_e)$ and appears with opposite sign as a line source in the 3D tissue equation to ensure mass conservation.

The 1D vascular network is embedded as centerlines $\Gamma = \bigcup_{e \in \mathcal{E}} \gamma_e$ with parameter $s \in (0, \ell_e)$ and mapping $\mathbf{x}_e(s) \in \Omega$. Exchange across each vessel wall is represented per unit length by the perimeter $P_e(s) = 2\pi r_e(s)$ and an effective permeability (or mass transfer coefficient) $\kappa_e(s, t)$.

2.2.2. 3D extravascular transport with vessel-tissue exchange

The drug concentration $C_t : \Omega \times [0, T] \rightarrow \mathbb{R}_{\geq 0}$ in the brain tissue (parenchyma) surrounding the vessels (tissue domain $\Omega \subset \mathbb{R}^3$), with porosity $\phi_t(\mathbf{x}) \in (0, 1]$ and (possibly anisotropic) effective diffusivity tensor $\mathbf{D}_t(\mathbf{x}, T)$ typically satisfies a diffusion-perfusion balance in the tissue,

$$\phi_t \partial_t C_t - \nabla \cdot (\mathbf{D}_t \nabla C_t) = S_{\text{ves}}(\mathbf{x}, t) - k_{\text{el}} C_t - R_{\text{bind}}(C_t), \quad (27)$$

with k_{el} is a linear elimination rate (lymphatic/biochemical), and R_{bind} is a reversible/irreversible uptake term (e.g., $R_{\text{bind}} = k_{\text{on}} C_t$ or Michaelis–Menten). The vessel-to-tissue line source is

$$S_{\text{ves}}(\mathbf{x}, t) = \sum_{e \in \mathcal{E}} \int_0^{\ell_e} P_e(s) \kappa_e(s, t) (C_e(s, t) - C_t(\mathbf{x}_e(s), t)) \delta(\mathbf{x} - \mathbf{x}_e(s)) ds, \quad (28)$$

with intravascular concentration C_e provided by the 1D edge Eq. (11).

If some microvasculature is subgrid, a volumetric perfusion term can be used instead of the explicit line source to avoid double counting, i.e.,

$$\phi_t \partial_t C_t - \nabla \cdot (\mathbf{D}_t \nabla C_t) = \underbrace{\omega_b(T) (C_b - C_t)}_{\text{well-mixed blood exchange}} - k_{\text{el}} C_t - R_{\text{bind}}(C_t), \quad (29)$$

where $\omega_b(T)$ is the temperature-responsive perfusion rate and C_b is the local blood (or arterial) concentration. In hybrid settings, apply (28) to resolved edges and (29) only to unresolved regions.

Boundary and initial conditions.

• **Initial condition.**

$$C_t(\mathbf{x}, 0) = C_t^0(\mathbf{x}) \quad \text{in } \Omega. \quad (30)$$

• **Boundary conditions.** Partition the external boundary into mutually disjoint sets $\partial\Omega = \partial\Omega_D \cup \partial\Omega_N \cup \partial\Omega_R$ (with outward unit normal $\mathbf{n}$). Impose

– Dirichlet (prescribed concentration):

$$C_t(\mathbf{x}, t) = C_{\text{ext}}(\mathbf{x}, t) \quad \text{on } \partial\Omega_D. \quad (31)$$

– Neumann (prescribed flux):

$$-\mathbf{n} \cdot \mathbf{D}_t(\mathbf{x}, T) \nabla C_t(\mathbf{x}, t) = q_t(\mathbf{x}, t) \quad \text{on } \partial\Omega_N, \quad (32)$$

with $q_t \equiv 0$ giving a no-flux boundary.

– Robin (convective exchange):

$$-\mathbf{n} \cdot \mathbf{D}_t(\mathbf{x}, T) \nabla C_t(\mathbf{x}, t) = h_t(\mathbf{x}) (C_t(\mathbf{x}, t) - C_{\text{ext}}(\mathbf{x}, t)) \quad \text{on } \partial\Omega_R, \quad (33)$$

with $h_t(\mathbf{x}) \geq 0$.

Remark 2.

- For unbounded/large domains approximated by a finite Ω , a small- h_t Robin condition on the outer boundary (or periodic boundaries, where appropriate) can emulate far-field decay $C_t \rightarrow C_{\text{ext}}$.
- The fractional order $\alpha_e < 1$ represents temporal memory in intravascular transport. Biologically, this memory may arise from reversible drug–wall interactions, transient binding to plasma or endothelial surfaces, delayed release from vascular reservoirs, and heterogeneous residence times in branching microvessels. Smaller α_e produces stronger memory, broader breakthrough curves, and delayed washout.
- The Riesz order $\beta_e < 2$ represents nonlocal axial dispersion. In a homogeneous straight vessel, the classical limit $\beta_e = 2$ recovers Gaussian/Fickian spreading. Values $\beta_e < 2$ account for anomalous spreading induced by vessel-radius variability, branching, tortuosity, uneven velocities, recirculation at junctions, and heterogeneous exchange with tissue. Thus, decreasing β_e increases long-range spatial coupling and broadens the bolus profile along the network.

2.3. Non-Fourier bioheat transfer

Classical Fourier/Pennes bioheat models assume an instantaneous constitutive relation

$$\mathbf{q} = -k \nabla T, \quad (34)$$

which can overpredict thermal penetration and smear sharp temperature fronts during hyperthermia at the microvascular scale. To capture finite heat-propagation speeds and rapid transients, we adopt a non-Fourier framework based on the Cattaneo-Vernotte / dual-phase-lag (CV/DPL) law, introducing a flux relaxation time $\tau_q > 0$ and, optionally, a gradient phase lag $\tau_T \geq 0$, so that

$$\tau_q \partial_t \mathbf{q} + \mathbf{q} = -k \nabla T_t - \tau_T \partial_t (\nabla T_t). \quad (35)$$

This renders the thermal problem weakly hyperbolic, enforces causality, and recovers the Fourier/Pennes limit when $\tau_q = \tau_T = 0$. Within our network-resolved setting, CV/DPL dynamics are applied to both the 3D tissue temperature $T_t(\mathbf{x}, t)$ and the 1D intravascular temperature $T_e(s, t)$, coupled by conservative Robin-type exchange along each vessel with perimeter-scaled coefficient

$$H_e = P_e h_{\text{th}}. \quad (36)$$

Temperature feeds back on physiology via perfusion $\omega_b(T)$ and permeability $P_c(T, C)$, while metabolic and external sources (Q_m, Q_{ext}) drive heating. This formulation is consistent with the fractional transport and interface laws introduced earlier, and improves fidelity for fast heating/cooling protocols and treatment planning (e.g., MR thermometry).

2.3.1. Tissue (3D) CV/DPL bioheat

Let $T_t(\mathbf{x}, t)$ be tissue temperature and $\mathbf{q}(\mathbf{x}, t)$ the tissue heat flux (in $\Omega \subset \mathbb{R}^3$). The DPL constitutive law and energy balance are

$$\text{(flux)} \quad \tau_q \partial_t \mathbf{q} + \mathbf{q} = -k \nabla T_t - \tau_T \partial_t (\nabla T_t), \quad (37)$$

$$\text{(energy)} \quad \rho c \partial_t T_t = -\nabla \cdot \mathbf{q} + \omega_b(T_t) c_b (T_a - T_t) + Q_{m,t} + Q_{\text{ext}} + S_{\text{ves}}(\mathbf{x}, t), \quad (38)$$

where $\mathbf{q}$ is the heat flux, k is tissue conductivity, ρc volumetric heat capacity, $\omega_b(T) c_b (T_a - T_t)$ is perfusion heat exchange with arterial blood, τ_q the flux relaxation time, and τ_T the temperature-gradient lag ($\tau_T = 0$ reduces (37) to CV, and further $\tau_q = 0$ to Fourier/Pennes), $Q_{m,t}$ is metabolic heat generation, and Q_{ext} represents external heating (e.g. hyperthermia source). The vessel-tissue exchange appears as a line source

$$S_{\text{ves}}(\mathbf{x}, t) = \sum_{e \in \mathcal{E}} \int_0^{\ell_e} H_e(s, t) [T_e(s, t) - T_t(\mathbf{x}_e(s), t)] \delta(\mathbf{x} - \mathbf{x}_e(s)) \, ds, \quad H_e = P_e h_{\text{th}}, \quad (39)$$

with perimeter $P_e = 2\pi r_e$, wall heat transfer coefficient h_{th} , and centerline $\mathbf{x}_e(s)$.

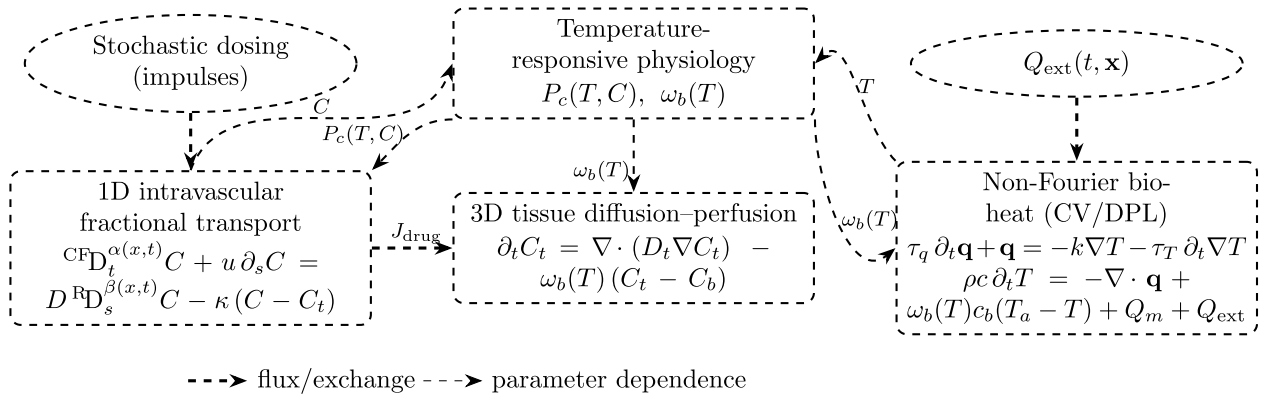


Fig. 2. Coupling of spatio-temporal fractional transport, temperature-responsive physiology, and non-Fourier bioheat transfer. Solid arrows: material/energy fluxes; dashed arrows: parameter dependences.

Temperature-responsive physiology. At each vessel-tissue interface, permeability P_c and perfusion ω_b depend on local blood or tissue temperature T :

$$J_{\text{drug}}(s, t) = P_c(T_i(s, t), C(s, t)) (C_e(s, t) - C_t(x_e(s), t)), \quad (40)$$

$$\omega_b(T_i) = \omega_{b,0} (1 + \eta_T (T_i - T_0)), \quad (41)$$

where T_0 is baseline physiological temperature, η_T is a sensitivity coefficient, and $\omega_{b,0}$ is resting perfusion. BBB permeability is similarly enhanced at elevated T , with sigmoidal or exponential response laws fitted to experimental data. This coupling allows hyperthermia to directly modulate mass transfer rates between blood and tissue.

2.3.2. Blood (1D along each edge) CV/DPL bioheat

On edge e with arc-length $s \in (0, \ell_e)$, cross-section $A_e(s) = \pi r_e^2(s)$, perimeter $P_e(s) = 2\pi r_e(s)$, axial velocity $u_e(s)$, and axial heat flux $q_e(s, t)$, the constitutive law and cross-section -averaged energy balance read

$$(\text{flux}) \quad \tau_{q,e} \partial_t q_e + q_e = -k_e \partial_s T_e - \tau_{T,e} \partial_t (\partial_s T_e), \quad (42)$$

$$(\text{energy}) \quad \rho_b c_b A_e \partial_t T_e + \rho_b c_b A_e u_e \partial_s T_e = -\partial_s q_e - H_e(s, t) [T_e - T_t(x_e(s), t)] + A_e Q_{m,e}(s, t) + A_e Q_{\text{ext},e}(s, t). \quad (43)$$

Here k_e is the effective axial thermal conductivity/dispersion of blood, $\rho_b c_b$ its volumetric heat capacity, and $Q_{m,e}/Q_{\text{ext},e}$ denote intraluminal metabolic/external heating per unit volume.

Conservation. The wall exchange terms in (39) and (43) are equal and opposite (via $+H_e(T_e - T_t)$ in tissue and $-H_e(T_e - T_t)$ in blood), ensuring net energy conservation of the coupled 1D-3D system.

Remark 3. The CV/DPL parameters τ_q and τ_T describe finite-rate thermal relaxation. Here, τ_q is the heat-flux relaxation time, measuring the delay between an imposed temperature gradient and the resulting heat flux. The parameter τ_T is the temperature-gradient phase lag, describing the delay in the establishment of the thermal gradient itself. When $\tau_q = \tau_T = 0$, the model reduces to the classical Fourier/Pennes bioheat equation. Nonzero values are used to represent finite-speed thermal propagation, microvascular thermal inertia, and delayed tissue response during short-time hyperthermia. In practical simulations, these parameters should be selected from experimentally measured or literature-reported tissue relaxation times, and their effect should be examined through sensitivity analysis.

3. Method of solution

We solve the coupled network-tissue fractional transport and non-Fourier bioheat system with a stable *partitioned IMEX* scheme in time, graph/FEM discretizations in space, and conservative 1D–3D interface assembly. The diagram as shown in Fig. 2 provides the minimal structure required to couple (i) 1D intravascular advection-diffusion-reaction on edges, (ii) 3D tissue diffusion-perfusion in Ω , and (iii) bidirectional mass/heat exchange across Σ via line-source terms concentrated along Γ .

The key ingredients are: (i) graph-based flow and advection on the 1D network, (ii) Caputo-Fabrizio (CF) time memory updated by an auxiliary ODE with $O(1)$ storage, (iii) a Riesz space-fractional operator along vessel centerlines via symmetric shifted Grünwald (SGL) or matrix-fractional techniques, (iv) CV/DPL bioheat in tissue and blood with implicit relaxation, and (v) Robin-type line couplings that enforce equal-and-opposite exchange.

3.1. Preprocessing: flow and geometry

1. Solve the network Poiseuille problem for nodal pressures $\mathbf{p}$ and edge flows

$$Q_e = G_e \Delta_e(\mathbf{p}) \quad (44)$$

under imposed inlet/outlet conditions.

2. Set $u_e(s) = Q_e / A_e(s)$.
3. Build the graph incidence $\mathbf{B}$ and per-edge 1D grids $s_j = j h_e$, $j = 0, \dots, N_e$, with $h_e = \ell_e / N_e$ (nonuniform h_e acceptable).
4. Generate a tetrahedral (or voxel) mesh of Ω for the tissue variables (T_i, C_i) with standard H^1 elements.

3.2. Temporal discretization (global time grid)

Let $t^n = n\Delta t$, $n = 0, \dots, N_T$. At each step we iterate

(heat) $\Rightarrow$ physiology $\Rightarrow$ intravascular $\Rightarrow$ tissue,

until convergence of (T_i, T_e, C_e, C_i) at t^{n+1} . Implicit parts use backward Euler; advective and explicit source parts are treated by upwind/IMEX.

3.3. Caputo–Fabrizio (time) memory with $\mathbf{O}(1)$ storage

For each edge location (e, s) define the memory variable

$$m_e(t) = \int_0^t \partial_\tau C_e(\tau) \exp(-\lambda_e(t)[t - \tau]) d\tau, \quad \lambda_e(t) = \frac{\alpha_e(s, t)}{1 - \alpha_e(s, t)}. \quad (45)$$

The CF derivative is ${}^{\text{CF}}D_t^{\alpha_e} C_e = \frac{m_e}{1 - \alpha_e}$ (with the standard normalization). The memory obeys

$$\partial_t m_e = \partial_t C_e - \lambda_e m_e, \quad m_e(0) = 0,$$

discretized implicitly as

$$m_e^{n+1} = \frac{m_e^n + C_e^{n+1} - C_e^n}{1 + \lambda_e^{n+1} \Delta t}, \quad {}^{\text{CF}}D_t^{\alpha_e} C_e|_{t^{n+1}} = \frac{m_e^{n+1}}{1 - \alpha_e^{n+1}}. \quad (46)$$

Thus the CF term adds neither a long-history convolution nor storage growth.

3.4. Riesz (space) fractional operator along edges

The one-dimensional Riesz fractional derivative can be interpreted as the negative fractional Laplacian under appropriate boundary conditions. More precisely, for sufficiently smooth functions defined on a bounded interval,

$${}^{\text{R}}D_s^\beta C(s) \approx -(-\partial_{ss})^{\beta/2} C(s), \quad 1 < \beta < 2, \quad (47)$$

where $(-\partial_{ss})^{\beta/2}$ denotes the spectral fractional Laplacian. This representation is widely adopted because it provides a mathematically rigorous definition of the Riesz operator on bounded domains while naturally incorporating boundary conditions through the spectrum of the classical Laplace operator. It also enables efficient numerical discretizations based either on finite-difference approximations or on matrix-function techniques, where the fractional operator is obtained by applying a fractional power to the discrete Laplacian. A comprehensive treatment of the equivalence between the Riesz fractional derivative and the fractional Laplacian, together with their numerical approximation, can be found in Podlubny (1999) [43] and Acosta and Borthagaray (2017) [35]. Motivated by these results, we approximate the Riesz derivative on each network edge by the corresponding fractional Laplacian, i.e., ${}^{\text{R}}D_s^{\beta_e} C_e \approx -(-\partial_{ss})^{\beta_e/2} C_e$ by either:

1. **SGL finite differences (Toeplitz convolution):**

$$\left[{}^{\text{R}}D_s^{\beta_e} C_e \right]_j = \frac{1}{h_e^{\beta_e}} \sum_{k=-K}^K g_k^{(\beta_e)} C_{e, j-k}, \quad g_k^{(\beta)} = (-1)^k \binom{\beta}{|k|}, \quad (48)$$

with symmetric weights and one-sided corrections at endpoints (compatible with junction conditions). The convolution is applied in $\mathcal{O}(N_e \log N_e)$ using FFT.

2. **Matrix-fractional (MTT/eigensolve):** Assemble the standard 1D stiffness matrix K_e and mass matrix M_e with Dirichlet traces at the nodes, and then define $L_e = M_e^{-1} K_e$. The fractional derivative is approximated by

$${}^{\text{R}}D_s^{\beta_e} C_e \approx -\Phi_e \Lambda_e^{\beta_e/2} \Phi_e^\top \mathbf{c}_e,$$

where $L_e = \Phi_e \Lambda_e \Phi_e^\top$, and $\mathbf{c}_e$ collects the nodal values of C_e . For spatially or temporally variable $\beta_e(s, t)$, a rational Krylov or Padé approximation of $L_e^{\beta/2}$ is employed.

3.5. Discrete intravascular update (IMEX on each edge)

With (46) and upwind for advection, the edgewise balance

$${}^{\text{CF}}D_t^{\alpha_e} C_e + u_e \partial_s C_e = D_e {}^{\text{R}}D_s^{\beta_e} C_e - \kappa_e (C_e - C_t^\Gamma) \quad (49)$$

is advanced from $t^n \rightarrow t^{n+1}$ by

$$\frac{m_e^{n+1}}{1 - \alpha_e^{n+1}} + \underbrace{U_e C_e^{n+1}}_{\text{upwind}} = D_e \mathcal{R}_e^{(\beta, n+1)} C_e^{n+1} - \kappa_e^{n+1} (C_e^{n+1} - C_t^{\Gamma, n+1}) + \underbrace{U_e C_e^n}_{\text{IMEX}}, \quad (50)$$

where U_e is the discrete upwind operator, $\mathcal{R}_e^{(\beta, n+1)}$ the Riesz matrix at t^{n+1} , and C_t^Γ the tissue trace evaluated on the centerline. Junction conditions (continuity + Kirchhoff flux) are enforced by small interface blocks.

Stochastic dosing. Inlet values are imposed as

$$C_e(0, t) = C_{\text{base}} + \sum_k A_{e,k} g_\tau(t - t_{e,k}), \quad (51)$$

with $\{t_{e,k}\}$ from a point process and narrow kernel g_τ (impulsive limit $\tau \rightarrow 0$).

3.6. Non-Fourier bioheat step (tissue and blood)

We use the CV/DPL formulation with implicit relaxation. In tissue,

$$\tau_q \frac{\mathbf{q}^{n+1} - \mathbf{q}^n}{\Delta t} + \mathbf{q}^{n+1} = -k_t \nabla T_t^{n+1} - \tau_T \nabla \left(\frac{T_t^{n+1} - T_t^n}{\Delta t} \right), \quad (52)$$

$$\rho_t c_t \frac{T_t^{n+1} - T_t^n}{\Delta t} = -\nabla \cdot \mathbf{q}^{n+1} + \omega_b(T_t^n) c_b (T_a - T_t^{n+1}) + Q_{m,t}^{n+1} + Q_{\text{ext}}^{n+1} + S_{\text{ves}}^n, \quad (53)$$

where the perfusion is lagged (Picard) for robustness and the line source S_{ves}^n uses the previous iterate (T_e^n, T_t^n) .

Along each edge, with axial flux q_e ,

$$\tau_{q,e} \frac{q_e^{n+1} - q_e^n}{\Delta t} + q_e^{n+1} = -k_e \partial_s T_e^{n+1} - \tau_{T,e} \partial_s \left(\frac{T_e^{n+1} - T_e^n}{\Delta t} \right), \quad (54)$$

$$\rho_b c_b A_e \frac{T_e^{n+1} - T_e^n}{\Delta t} + \rho_b c_b A_e u_e \partial_s T_e^{n+1} = -\partial_s q_e^{n+1} - H_e^n (T_e^{n+1} - T_t^{\Gamma, n+1}) + A_e (Q_{m,e}^{n+1} + Q_{\text{ext},e}^{n+1}). \quad (55)$$

Inlet/outlet and junction mixing conditions are enforced as in the mass problem.

3.7. Physiology update and coupling

With (T_t^{n+1}, T_e^{n+1}) available, update

$$\omega_b^{n+1} = \omega_b(T_t^{n+1}), \quad P_c^{n+1} = P_c(T_t^{\Gamma, n+1}, C_e^n), \quad \kappa_e^{n+1} = \frac{P_e}{A_e} P_c^{n+1},$$

then reassemble the exchange terms for the next transport solve. Equal-and-opposite signs are used in the 1D and 3D balances to preserve conservation.

3.8. Tissue concentration step

Given κ_e^{n+1} and C_e^{n+1} , assemble the line source

$$S_{\text{ves}}^{n+1}(\mathbf{x}) = \sum_e \int_0^{\ell_e} P_e \kappa_e^{n+1} (C_e^{n+1} - C_t^{\Gamma, n}) \delta(\mathbf{x} - \mathbf{x}_e(s)) ds, \quad (56)$$

and advance

$$\phi_t \frac{C_t^{n+1} - C_t^n}{\Delta t} - \nabla \cdot (\mathbf{D}_t \nabla C_t^{n+1}) = S_{\text{ves}}^{n+1} - k_{\text{el}} C_t^{n+1} - R_{\text{bind}}(C_t^{n+1}) \quad \text{in } \Omega, \quad (57)$$

with the boundary conditions in Section 2.2.

3.9. 1D–3D interface assembly

The line sources/sinks are evaluated by projecting centerline quadrature onto the FEM basis:

$$\int_{\Omega} S_{\text{ves}} w \, dx = \sum_e \sum_q (P_e \kappa_e (C_e - C_t^\Gamma) w^\Gamma)_{(e,q)} \omega_q, \quad (58)$$

with w^Γ the test function traced to Γ and ω_q quadrature weights. This “embedded 1D–3D” assembly guarantees that the integral of exchange in tissue equals the negative of the sum of edge sinks.

3.10. Nonlinearity, iteration, and stopping

Inside each global time step we perform $k = 0, 1, \dots$ Picard (or Newton) iterations:

$$(T_t^k, T_e^k) \Rightarrow (\omega_b^k, P_c^k, \kappa^k) \Rightarrow C_e^{k+1} \Rightarrow C_t^{k+1} \Rightarrow (T_t^{k+1}, T_e^{k+1}), \quad (59)$$

terminating when the composite residual

$$\frac{\|C_e^{k+1} - C_e^k\|}{\|C_e^{k+1}\|} + \frac{\|C_t^{k+1} - C_t^k\|}{\|C_t^{k+1}\|} + \frac{\|T_e^{k+1} - T_e^k\|}{\|T_e^{k+1}\|} + \frac{\|T_t^{k+1} - T_t^k\|}{\|T_t^{k+1}\|} < \varepsilon \quad (60)$$

falls below a tolerance ε (e.g., 10^{-6}).

3.11. Linear algebra and stability

All subproblems lead to sparse linear systems. We use:

- AMG-preconditioned CG/GMRES for symmetric/unsymmetric FEM blocks in tissue.
- Edge-local banded/Toeplitz solvers (SGL) or small dense eigensolves (MTT) per edge.
- Small coupling blocks to enforce junction continuity/Kirchhoff constraints.

The scheme is unconditionally stable for the implicit CF-Riesz-exchange core; advection CFL can be relaxed by upwinding or semi-Lagrangian transport on edges. In the limit $\alpha \rightarrow 1$, $\beta \rightarrow 2$, $\tau_q, \tau_T \rightarrow 0$, the method reduces to a standard advection-diffusion-Pennes solver.

3.12. Algorithm summary

1. **Precompute** network flows Q_e , velocities u_e , and spatial matrices.
2. For $n = 0, \dots, N_T - 1$:
 - Outer loop** (Picard/Newton): until convergence
 - i. **Bioheat**: advance $(T_t, \mathbf{q})$ and (T_e, q_e) with CV/DPL (implicit).
 - ii. **Update physiology**: $\omega_b(T_t)$, $P_c(T_t^\Gamma, C_e)$, κ_e .
 - iii. **Intravascular**: advance C_e with CF memory (46), Riesz operator, upwind advection, and exchange (50).
 - iv. **Tissue**: assemble S_{ves} and advance C_t (implicit diffusion, implicit uptake).
3. **Postprocess** observables (bolus arrival, AUC, peak T , dose maps).

4. Numerical study

We assess the network-resolved 1D–2D framework on a synthetic arteriole–capillary–venule (ACV) graph embedded in a 2D tissue sheet. Baseline parameters are physiologically plausible and consistent with the governing equations (Caputo–Fabrizio/Riesz intravascular transport, diffusion–elimination in tissue, Fourier bioheat with wall relaxation, and conservative line-source coupling). Unless stated otherwise, inlet dosing is a single Gaussian bolus and the tissue domain is chosen sufficiently large that periodic numerics do not influence the solution over the simulated horizon.

4.1. Network of the cerebral microvasculature

We constructed a synthetic microvascular network as a directed graph $\mathcal{G} = (\mathcal{V}, \mathcal{E}, \mathbf{B})$, embedded in a 2D plane for visualization and in $\Omega \subset \mathbb{R}^2$ for modelling, similar to graph-based microvascular transport modelling in [14,15]. The network has one arteriole inlet, a small capillary bed, and two venular outlets. Edges are oriented from inlets to outlets. Fig. 3 demonstrates structure and patterns of the synthetic microvascular network which branches symmetrically from an arteriole inlet (v_0) into two daughter paths and drains to two outlets (v_7, v_8).

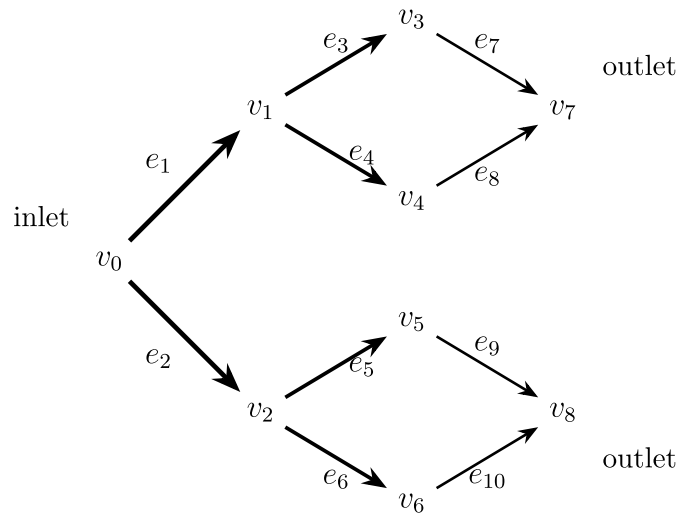


Fig. 3. Constructed microvascular graph with one arteriole inlet (v_0), bifurcating into a capillary bed and draining to two venular outlets (v_7, v_8). Edge thickness denotes calibre tiers (arteriole > pre-capillary > capillary/terminal).

Table 1

Vascular network segments (Fig. 2). Parent-segment radii/lengths; conductance $G = \pi r^4 / (8\mu L)$. Flows shown are illustrative with $Q = G\Delta p$, $\mu = 3$ mPa s, and $\Delta p = 100$ Pa.

From	To	Radius (μm)	Length (μm)	G ($\text{m}^3 \text{Pa}^{-1} \text{s}^{-1}$)	Q ($\text{m}^3 \text{s}^{-1}$)
v_0	v_1	10.00	200	6.545e-15	6.545e-13
v_0	v_2	10.00	200	6.545e-15	6.545e-13
v_1	v_3	8.00	150	3.574e-15	3.574e-13
v_1	v_4	8.00	150	3.574e-15	3.574e-13
v_2	v_5	8.00	150	3.574e-15	3.574e-13
v_2	v_6	8.00	150	3.574e-15	3.574e-13
v_3	v_7	6.35	120	1.774e-15	1.774e-13
v_4	v_7	6.35	120	1.774e-15	1.774e-13
v_5	v_8	6.35	120	1.774e-15	1.774e-13
v_6	v_8	6.35	120	1.774e-15	1.774e-13

Nodes (with coordinates for plotting). $\mathcal{V} = \{v_0, \dots, v_8\}$ with positions

$$\mathbf{x}_{v_0} = (0, 0), \mathbf{x}_{v_1} = (1, 1), \mathbf{x}_{v_2} = (1, -1), \mathbf{x}_{v_3} = (2, 1.6), \mathbf{x}_{v_4} = (2, 0.4),$$

$$\mathbf{x}_{v_5} = (2, -0.4), \mathbf{x}_{v_6} = (2, -1.6), \mathbf{x}_{v_7} = (3, 1.0), \mathbf{x}_{v_8} = (3, -1.0).$$

Inlet: $\mathcal{V}_{\text{in}} = \{v_0\}$; Outlets: $\mathcal{V}_{\text{out}} = \{v_7, v_8\}$; Interior junctions: $\mathcal{V}_{\text{int}} = \mathcal{V} \setminus (\mathcal{V}_{\text{in}} \cup \mathcal{V}_{\text{out}})$.

Edges (orientation tail $\rightarrow$ head).

$$\mathcal{E} = \{e_1 : v_0 \rightarrow v_1, e_2 : v_0 \rightarrow v_2, e_3 : v_1 \rightarrow v_3, e_4 : v_1 \rightarrow v_4, e_5 : v_2 \rightarrow v_5, e_6 : v_2 \rightarrow v_6, \\ e_7 : v_3 \rightarrow v_7, e_8 : v_4 \rightarrow v_7, e_9 : v_5 \rightarrow v_8, e_{10} : v_6 \rightarrow v_8\}.$$

Incidence matrix. With node order $(v_0, \dots, v_8)$ and edge order $(e_1, \dots, e_{10})$, the incidence matrix $\mathbf{B} \in \mathbb{R}^{9 \times 10}$ (tail -1 , head $+1$) is

$$\mathbf{B} = \begin{bmatrix} -1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ +1 & 0 & -1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & +1 & 0 & 0 & -1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & +1 & 0 & 0 & 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & +1 & 0 & 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 & +1 & 0 & 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & +1 & 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & 0 & 0 & 0 & +1 & +1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & +1 & +1 \end{bmatrix}.$$

Table 2

Baseline parameters. Symbols and units match the model equations; r_e , $A_e = \pi r_e^2$ and $P_e = 2\pi r_e$ vary by calibre (arteriole $\rightarrow$ precapillary $\rightarrow$ capillary).

Block	Quantity	Symbol	Value	Unit / note
Tissue (mass)	Diffusivity	D_t	1.0×10^{-9}	$\text{m}^2 \text{s}^{-1}$
Tissue (mass)	Elimination rate	k_{el}	1.0×10^{-4}	s^{-1}
Tissue (mass)	Porosity (void fraction)	ϕ_t	0.2	–
Tissue (mass)	Initial concentration	$C_i(\cdot, 0)$	0	drug units
Tissue (heat)	Baseline temperature	T_0	310.15	K
Tissue (heat)	Conductivity	k_t	0.5	$\text{W m}^{-1} \text{K}^{-1}$
Tissue (heat)	Vol. heat capacity	ρc_t	3.6×10^6	$\text{J m}^{-3} \text{K}^{-1}$
Tissue (heat)	Thermal diffusivity	α_t	1.39×10^{-7}	$\text{m}^2 \text{s}^{-1}$
Tissue (heat)	Hyperthermia peak	Q_0	5.0×10^4	W m^{-3} (Gaussian)
Tissue (heat)	Heating width (std.)	σ_Q	0.25	mm
Blood (1D)	Viscosity	μ	3.0	mPa s
Blood (1D)	Pressure drop (per edge)	Δp	100	Pa (illustrative)
Blood (1D)	Axial velocity	u_e	computed	Q_e/A_e (Poiseuille)
Blood (1D)	Axial dispersion	D_{ax}	5.0×10^{-10}	$\text{m}^2 \text{s}^{-1}$
Blood (1D)	Vol. heat capacity	ρc_b	3.9×10^6	$\text{J m}^{-3} \text{K}^{-1}$
Blood (1D)	Inlet temperature	$T_e(0, t)$	T_0	K
Interface	Permeability (drug)	P_e	1.0×10^{-6}	m s^{-1}
Interface	Volumetric exchange	κ_e	$2P_e/r_e$	s^{-1}
Interface	Heat transfer coeff.	h_h	800	$\text{W m}^{-2} \text{K}^{-1}$
Interface	Line heat coeff.	H_e	$h_h P_e$	$\text{W m}^{-1} \text{K}^{-1}$

Table 1 summarizes the geometry and hydraulic properties of the top-level segments in the constructed cerebral microvascular graph. Hydraulic conductance is computed by Poiseuille's law $G = \pi r^4 / (8\mu L)$. Flows shown are illustrative with $Q = G\Delta p$, $\mu = 3 \text{ mPa} \cdot \text{s}$, and $\Delta p = 100 \text{ Pa}$.

4.2. Numerical setup and baseline parameters

Tissue (2D). Forward-Euler time stepping with a 5-point Laplacian for both C_t and T_t . Vessel-to-tissue exchange is applied as conservative line sources along each polyline:

$$\Delta C_t = \Delta t \frac{P_e P_e [C_e - C_t]}{\Delta A} \Delta s, \quad \Delta T_t = \Delta t \frac{H_e [T_e - T_t]}{\rho c_t \Delta A} \Delta s,$$

where $\Delta A = \Delta x \Delta y$ and Δs is the local edge arc-length increment.

Blood (1D along edges). Upwind advection for C_e and T_e ; second-order central diffusion for C_e ; Riesz operator via bidirectional Grünwald-Letnikov sums; explicit Caputo-Fabrizio memory update. For T_e , after advection we apply exact wall relaxation over Δt with rate $H_e / (\rho c_b A_e)$.

Stability guidance. Choose Δt to satisfy

$$\Delta t \lesssim \min \left(\frac{\Delta x^2}{4D_t}, \frac{\Delta s}{\max_e u_e}, \frac{\Delta s^2}{2D_{ax}} \right),$$

and reduce Δt if strong fractional dispersion or wall exchange induces overshoot.

Flows/velocities Q_e , u_e are obtained from Poiseuille with the illustrative Δp . 1D intravascular transport on edges with advection $u_e = Q_e / A_e$, and other baseline parameters are given in **Tables 2** and **3**.

4.3. Numerical results

The 10-edge network consisting of a single inlet node (v_0), six interior nodes (v_1 – v_6), and two outlet nodes (v_7 and v_8) is used in this study (see **Fig. 4**). We evaluated the proposed hybrid 1D–2D fractional transport and bioheat model on a representative cerebral microvascular network embedded in a $3.0 \times 2.5 \text{ mm}^2$ tissue domain with baseline temperature $T_0 = 310.15 \text{ K}$. Blood flow in the vascular network was computed using the Poiseuille model, while intravascular drug transport was solved using the fractional advection–diffusion formulation coupled to the surrounding tissue through conservative line-source exchange. The lumen equations were advanced using an implicit–explicit (IMEX) time integration scheme with upwind discretization for advection and implicit treatment of the fractional diffusion and exchange terms. The tissue equations were solved on a Cartesian grid with conservative vessel–tissue coupling and an unconditionally stable update of the CV/DPL bioheat model. The following numerical experiments are presented to illustrate the behaviour of the proposed model under physiological and hyperthermic conditions.

Table 3

Baseline parameters used in the numerical study. Symbols and units match the model equations; r_e and $P_e = 2\pi r_e$ vary by calibre (arteriole $\rightarrow$ precapillary $\rightarrow$ capillary).

Frac. transport (1D)	CF time order	α	0.80	–
Frac. transport (1D)	CF kernel time	τ	2.0	s
Frac. transport (1D)	Riesz order	β	1.60	–
Frac. transport (1D)	Riesz coeff.	K_β	5.0×10^{-10}	$\text{m}^\beta \text{s}^{-1}$
Injection	Baseline level	C_{base}	0	drug units
Injection	Bolus amplitude	A	1.0	drug units
Injection	Bolus peak time	t_0	3.0	s
Injection	Bolus width (std.)	σ	0.6	s
Discretization	Tissue domain	Ω	$[0, 3] \times [0, 2.5]$	$\text{mm} \times \text{mm}$
Discretization	Grid	$N_x \times N_y$	240×180	$\Delta x = \Delta y \approx 16.7 \mu\text{m}$
Discretization	Edge spacing	Δs	5–10	μm
Discretization	Time step	Δt	10^{-3}	s (explicit)
Discretization	Final time	T_{end}	10	s

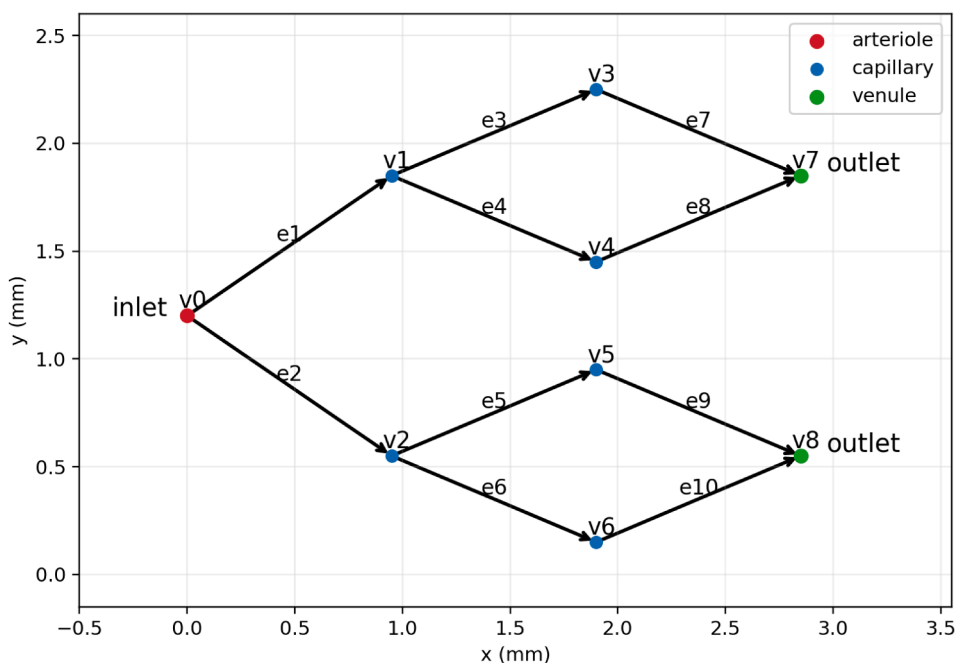


Fig. 4. The 10-edge vessel network with arteriole (red), capillary (blue) and venule (green) nodes.

The computational efficiency of the proposed model was evaluated using a time step of $dt = 2.271 \times 10^{-4}$ s, corresponding to a total of $N_t = 2374$ time steps. All simulations were performed on a standard CPU, requiring a total execution time of 29.42, s. The peak memory consumption during the simulation was 171.11, MB, demonstrating that the proposed numerical framework is computationally efficient and memory economical. These results indicate that the method can accurately resolve the transient transport dynamics while maintaining a modest computational cost, making it suitable for large-scale vascular network simulations.

Fig. 5 compares the final tissue drug concentration distributions predicted by the classical-order model (left) and the proposed fractional-order model (right). In both cases, the drug remains localized around the vascular network, forming narrow perivascular concentration halos that closely follow the vessel geometry. The highest concentrations occur along the distal branches, where the injected bolus reaches the downstream vessels and exchanges with the surrounding tissue. The absence of spurious long-range spreading in both simulations demonstrates that the conservative vessel–tissue coupling accurately confines drug transport to the vicinity of the vasculature.

Although the overall spatial distributions are qualitatively similar, the fractional-order model exhibits slightly smoother concentration gradients and a more gradual redistribution of the drug along the vascular branches as shown in Fig. 6. These differences arise from the combined effects of the Caputo–Fabrizio time-fractional derivative and the Riesz space-fractional operator, which introduce temporal memory and nonlocal spatial transport into the governing equations. Consequently, the fractional formulation predicts a more realistic representation of anomalous transport processes, including prolonged residence and enhanced redistribution within the vascular–tissue system. In contrast, the classical model corresponds to purely local transport and produces slightly sharper

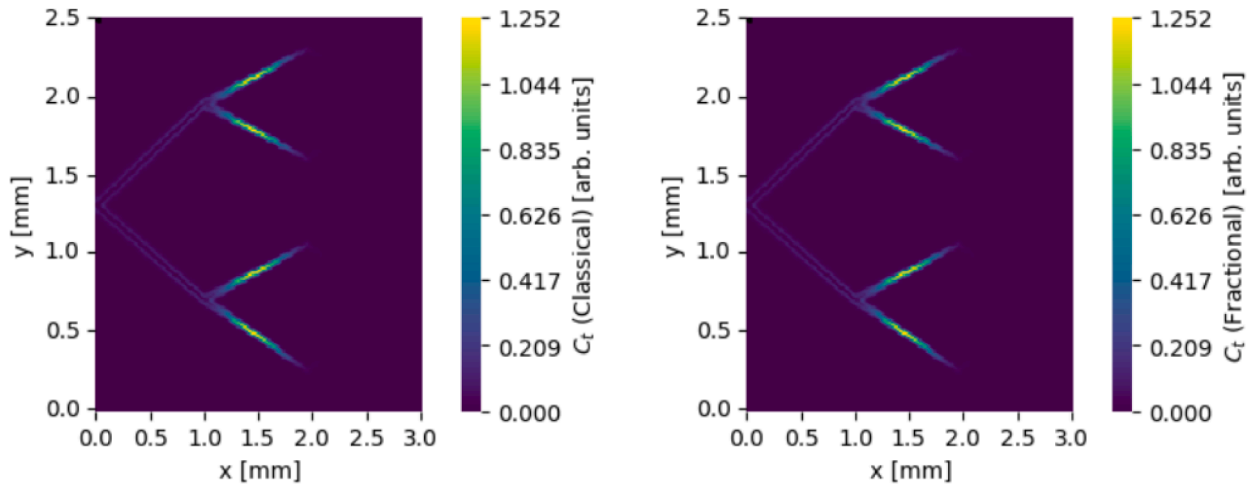


Fig. 5. Side-by-side heatmaps compare tissue drug concentration for (left) the classical-order model with $\alpha = 1, \beta = 2$ and (right) the fractional-order model with right: $\alpha = 0.8, \beta = 1.6$ model, highlighting the influence of fractional transport on drug distribution.assumptions.

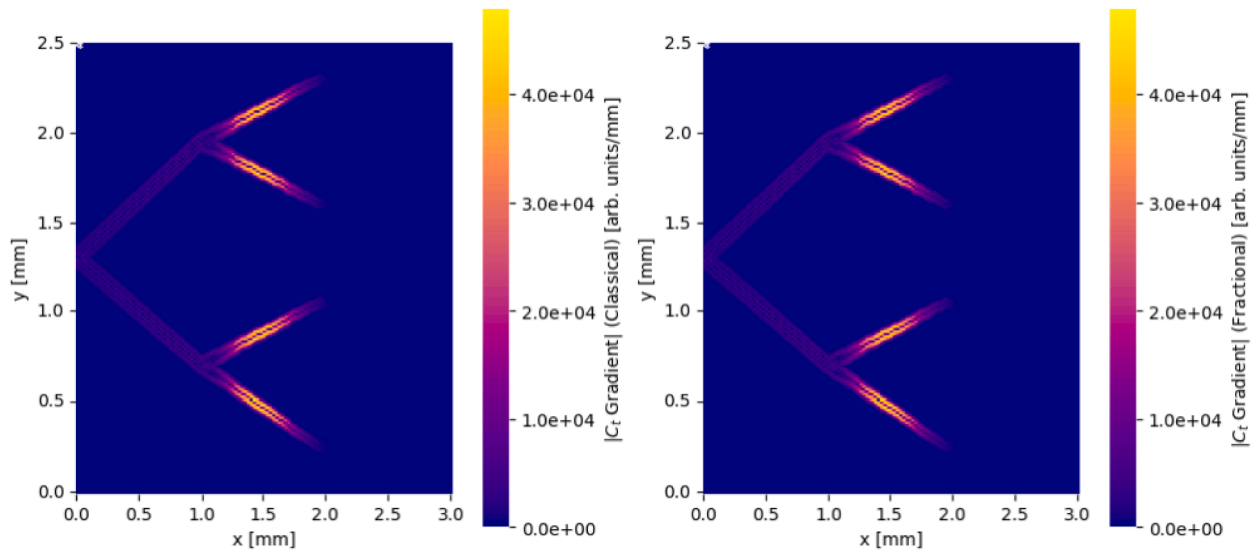


Fig. 6. Comparison of tissue concentration gradient heatmaps for (left) the classical-order model with $\alpha = 1, \beta = 2$ and (right) the fractional-order model with $\alpha = 0.8, \beta = 1.6$ models.

concentration profiles. The close agreement between the two models confirms that the proposed fractional formulation recovers the classical behavior while providing additional flexibility for modeling non-Fickian drug transport in heterogeneous cerebral microvascular networks.

Fig. 7 presents the corresponding intravascular distributions of concentration C_e and temperature T_e within the directed vascular network. The injected bolus enters through the inlet and is transported into both branches by blood flow. At the final simulation time, the concentration front has propagated toward the outlet vessels, producing relatively higher concentrations near the exit boundaries while upstream segments exhibit lower concentrations because of axial dispersion and continuous transvascular leakage. The intravascular temperature exhibits a modest increase in vessels adjacent to the heated region, whereas axial convection smooths the thermal gradients along the network, resulting in continuous and physically realistic temperature profiles.

Fig. 8 presents the final tissue distributions of drug concentration $C_t(x, y, t_{\text{end}})$ (left) and temperature, $T_t(x, y, t_{\text{end}})$ (right), obtained from the coupled vascular–tissue transport model at $t_{\text{end}} = 1.0$ s. The drug concentration remains highly localized around the vascular network, forming narrow perivascular concentration halos that closely follow the vessel geometry. This behavior indicates that mass transfer occurs predominantly through transvascular exchange, with only limited diffusion into the surrounding tissue. The highest tissue concentrations are observed adjacent to the distal branches of the network, where the transported bolus reaches the outlet

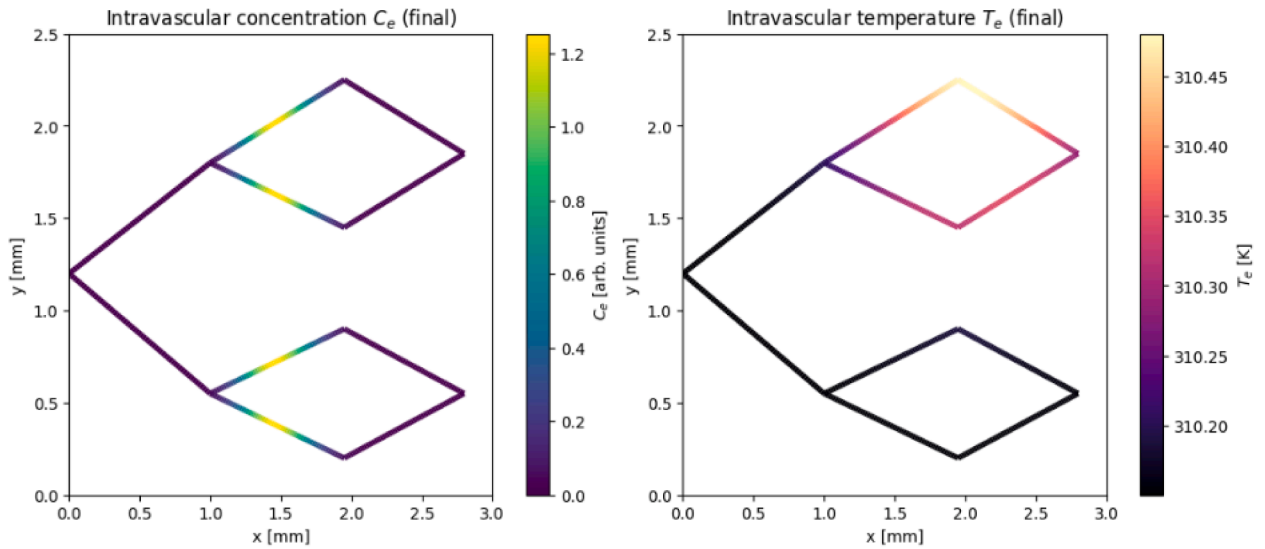


Fig. 7. Final distributions of intravascular concentration C_e on the left column and the intravascular temperature T_e on the right column in the directed vascular network at $t = 1$ s., constructed by projecting edge-wise vessel concentrations to the 2D tissue coordinate frame.

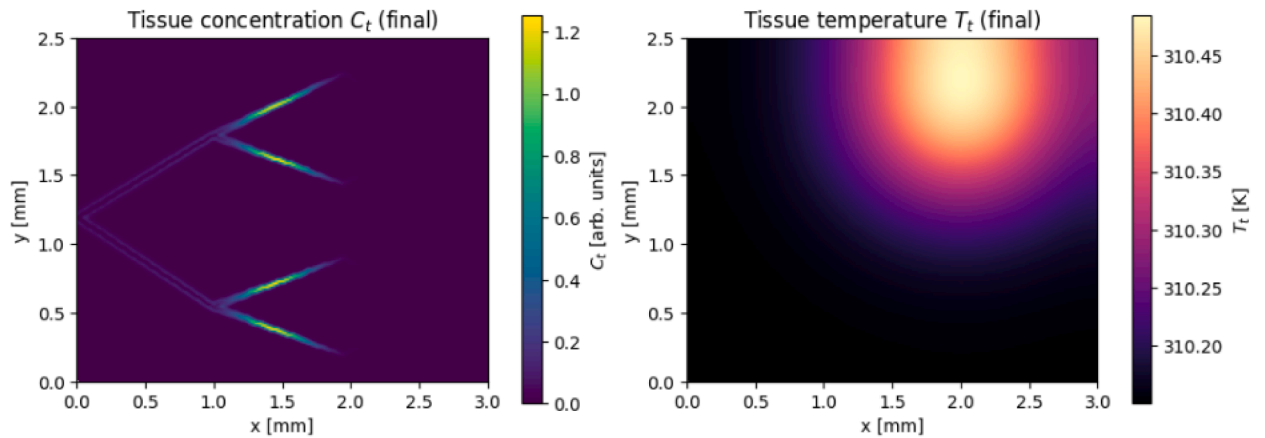


Fig. 8. Final tissue drug concentration heatmap, $C_t(x, y, t_{end})$ on the left column, obtained from the coupled vascular-tissue simulation and the final tissue temperature heatmap, $T_t(x, y, t_{end})$ on the right column, from the coupled thermal solver including perfusion and external heating terms.

vessels and exchanges with the surrounding parenchyma. The absence of spurious long-range spreading confirms that the proposed coupling strategy conserves mass while maintaining physically realistic localization of drug transport.

The corresponding tissue temperature distribution generated by the prescribed Gaussian heat source centered at $(x_Q, y_Q) = (2.0, 2.1)$ mm. A smooth, localized hotspot develops near the upper central region of the tissue domain and decays gradually with increasing distance from the heat source. The maximum tissue temperature reaches approximately 310.45 K, corresponding to a modest temperature increase of about 0.3 K above the physiological baseline ($T_0 = 310.15$, K). This mild and spatially confined heating produces continuous thermal gradients without numerical oscillations, consistent with the non-Fourier Cattaneo–Vernotte/Dual-Phase-Lag bioheat formulation. The localized elevation in temperature enhances vessel-wall permeability in the heated region, thereby promoting greater drug transfer from the vasculature into the surrounding tissue while maintaining physiologically safe thermal conditions.

The vascular concentration patterns demonstrate the coupled influence of advection, anomalous axial dispersion, transvascular exchange, and fractional memory on drug transport. The Caputo–Fabrizio–Riesz formulation captures these nonlocal transport mechanisms, yielding smooth concentration profiles that represent physiologically realistic residence times within the vascular–tissue system. The downstream accumulation of the bolus has important physiological significance, indicating that the concentration front is transported efficiently through the vascular network while remaining affected by heterogeneous residence times and wall exchange. Regions exposed to elevated temperatures exhibit enhanced permeability, allowing increased drug transfer into the surrounding tissue, whereas other regions undergo progressive dilution during downstream transport. Consequently, the predicted concentration

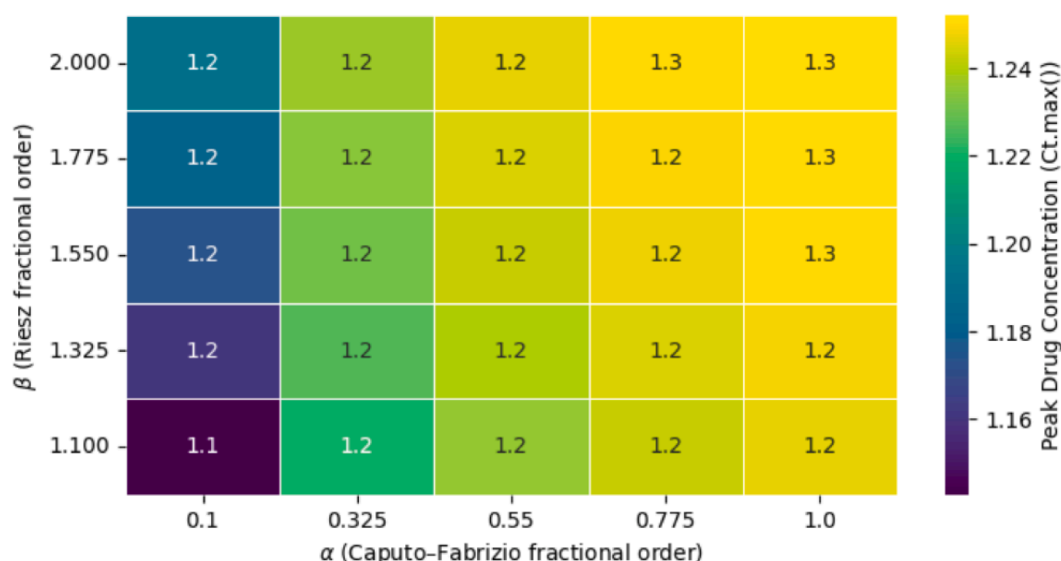


Fig. 9. Heatmaps of peak tissue concentration for the fractional-order parameter grid, with $1.1 \leq \alpha \leq 1$ and $1.1 \leq \beta \leq 2$. Higher values of both alpha and beta generally lead to slightly higher peak drug concentrations in this sensitivity range.

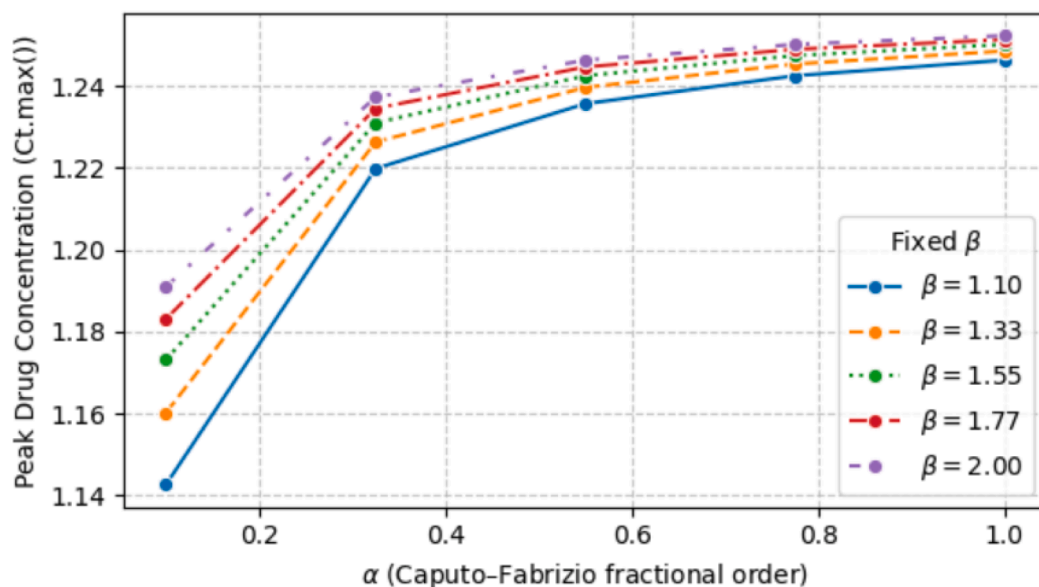


Fig. 10. Peak drug concentration vs. α for Various Fixed β Values.

distributions reflect genuine non-Fickian transport arising from vascular heterogeneity and memory-dependent mass transfer rather than numerical artifacts.

A sensitivity analysis was also performed to investigate the influence of the fractional transport parameters on drug delivery. Fig. 9 presents a heatmap of the peak tissue drug concentration as a function of the Caputo–Fabrizio time-fractional order (α) and the Riesz space-fractional order (β). The results demonstrate that both fractional parameters influence the extent of drug accumulation within the tissue, although the sensitivity remains moderate over the investigated parameter range. The lowest peak concentration is obtained for the combination of $\alpha = 0.1$ and $\beta = 1.1$, where strong temporal memory and enhanced nonlocal spatial transport produce greater spreading of the injected bolus, thereby reducing the local maximum concentration. For a fixed value of β , increasing α from 0.1 toward 1.0 results in a gradual increase in the peak tissue concentration as shown in Fig. 10. This trend indicates that weaker temporal memory allows the drug to remain more concentrated, leading to higher local accumulation. Likewise, for a fixed value of α , increasing the Riesz fractional order β also produces a slight increase in the peak concentration. As β approaches the classical diffusion limit, anomalous spatial spreading is reduced, resulting in a more localized concentration distribution and consequently a larger peak value.

Table 4Peak tissue concentration ($C_{t,\max}$) for different combinations of α and β .

β	α				
	0.100	0.325	0.550	0.775	1.000
1.100	1.1427	1.2198	1.2356	1.2425	1.2463
1.325	1.1602	1.2263	1.2396	1.2453	1.2485
1.550	1.1732	1.2310	1.2425	1.2474	1.2501
1.775	1.1831	1.2345	1.2446	1.2489	1.2513
2.000	1.1910	1.2373	1.2463	1.2501	1.2522

The highest peak concentrations are observed in the upper-right region of the heatmap, corresponding to $\alpha \approx 1.0$ and $\beta \approx 2.0$, while the lowest values occur in the lower-left corner. Although the overall variation is relatively small (approximately 10% across the parameter space), the results confirm that both temporal memory and nonlocal spatial transport play complementary roles in regulating drug delivery. Table 4 shows peak tissue concentration ($C_{t,\max}$) for different combinations of the Caputo–Fabrizio fractional order (α) and the Riesz fractional order (β). Rows correspond to β values and columns correspond to α values. These findings demonstrate that the proposed fractional-order model provides a flexible framework for controlling drug transport characteristics and reproducing anomalous transport behavior in heterogeneous cerebral microvascular networks.

Overall, the coupled simulations demonstrate that the proposed network-fractional framework provides a stable and physically consistent description of heat and mass transport within the cerebral microvasculature. The model successfully reproduces localized tissue drug uptake, clinically relevant mild hyperthermia, finite-speed thermal propagation, and anomalous intravascular transport governed by fractional memory effects. These results highlight the capability of the proposed approach to capture the complex interactions among vascular flow, tissue heating, and transvascular drug delivery, making it a promising computational framework for investigating hyperthermia-enhanced therapeutic transport.

5. Conclusion and discussion

This work presented a coupled hybrid 1D–3D fractional framework for modeling hyperthermia-enhanced drug delivery in the cerebral microcirculation. The proposed formulation integrates Poiseuille-based blood flow in a vascular network, Caputo–Fabrizio time-fractional intravascular transport, Riesz space-fractional axial dispersion, conservative vessel–tissue coupling, and non-Fourier Cattaneo–Vernotte/Dual-Phase-Lag bioheat transfer within a unified computational framework. By combining fractional transport with thermal regulation, the model captures the complex interactions among blood flow, heat transfer, vascular permeability, and drug exchange that govern therapeutic delivery in brain tissue.

The numerical simulations demonstrate that the proposed framework reproduces physiologically realistic coupled transport phenomena. The fractional orders α and β play a key role in controlling drug dynamics: decreasing α strengthens temporal memory and prolongs intravascular residence, whereas decreasing β enhances nonlocal axial dispersion associated with vascular heterogeneity. The predicted tissue concentration remains localized around the vascular network, while the intravascular concentration propagates smoothly toward the outlet under the combined influence of advection, transvascular exchange, and fractional memory. Furthermore, localized heating produces a moderate temperature rise of approximately 0.3 K above the physiological baseline, corresponding to mild hyperthermia that enhances vessel permeability and tissue drug uptake without exceeding clinically safe temperature limits. These findings are consistent with reported therapeutic hyperthermia ranges and demonstrate the capability of the model to capture the coupled effects of heat and mass transport in cerebral microvascular networks.

From a computational perspective, the proposed formulation is conservative by construction, with vessel loss terms balanced exactly by tissue source terms for both mass and energy. The Caputo–Fabrizio derivative requires only $\mathcal{O}(1)$ memory storage per time step, avoiding the large history requirements associated with classical fractional derivatives, while the Riesz fractional operator can be efficiently evaluated using Toeplitz–FFT convolution or matrix-fractional techniques. These properties provide a scalable foundation for simulations on larger vascular networks.

The present study nevertheless has several limitations. The numerical examples were performed on a hybrid 1D–2D configuration rather than a fully coupled 1D–3D geometry and employed a synthetic cerebral vascular network with simplified constitutive models for blood viscosity, perfusion, and temperature-dependent permeability. In addition, the model has not yet been calibrated or validated against experimental measurements of blood–brain barrier permeability, dynamic contrast-enhanced MRI, or MR thermometry.

Future work will focus on extending the framework to patient-specific three-dimensional vascular networks, incorporating more realistic hemodynamic and thermophysical properties, and validating the model against experimental and clinical datasets. Additional investigations will include breakthrough-curve analysis, optimization of hyperthermia protocols, repeated and multiple-bolus drug administration, and high-performance parallel implementations for large-scale simulations. These developments will further establish the proposed fractional network framework as a predictive computational tool for designing and optimizing hyperthermia-assisted drug delivery strategies for neurological disorders.

CRediT authorship contribution statement

Parul Tiwari: Formal analysis, Investigation, Validation, Writing – original draft, Writing – review & editing; **B. Wiwatanapataphee:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing, Validation, Resources.

Declaration of competing interest

The authors declare no competing of interest.

Acknowledgement

The authors would like to thanks the anonymous reviewers for providing meaningful suggestions and improving the quality of the research.

Data availability

Data will be made available on request.

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