Graph-Theoretic Reaction Network Optimization for Multi-Ligand Binding Kinetics in Complex Biological Media

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ABSTRACT Targeted radionuclide therapy and precision molecular medicine increasingly rely on multi-ligand biochemical cocktails designed to optimize tumor receptor saturation, retard renal clearance, and enhance cellular internalization. However, analyzing the non-linear kinetic interactions of competing chemical species in heterogeneous biological media presents severe computational hurdles when modeled via high-dimensional ordinary differential equations (ODEs). In this work, we develop a rigorous chemical reaction network theory (CRNT) and algebraic graph reduction framework for multi-ligand targeted binding kinetics in complex biological environments. Abstracting biochemical binding cascades into directed reaction hypergraphs $\mathcal{G} = (\mathcal{V}, \mathcal{E})$, we map stoichiometric conservation laws directly to the cycle space and incidence structure of the network. We establish the topological conditions under which multi-species binding networks satisfy Feinberg's Deficiency Zero and Deficiency One theorems, guaranteeing the existence, uniqueness, and global asymptotic stability of complex-balanced steady-state concentrations. Applying Kron reduction and quasi-steady-state graph contractions, we collapse high-dimensional intermediate species complexes into minimal irreducible graph topologies, reducing state-space dimensionality by 58.3% while bounding kinetic concentration approximation errors below 1.4%. Forward stochastic simulations across a synthetic cohort of 1,000 biological tissue realizations demonstrate that competitive displacement by pre-dosed non-radioactive cold ligands creates a transient spatial receptor shield that decreases normal-tissue absorbed dose in dose-limiting organs by up to 36.8%. Furthermore, we evaluate structural stability under thermodynamic affinity drift, proving that the reduced reaction graph maintains robust tracking of target receptor occupancy across broad variations in serum albumin abundance. These graph-theoretic reduction methods establish a scalable mathematical foundation for real-time optimal design of multi-bolus radioligand fractionation regimes in clinical oncology.

I. Introduction

Modern pharmaceutical oncology increasingly employs multi-component biochemical architectures that pair targeted radioligands with competitive antagonists, carrier proteins, and metabolic enzyme inhibitors [1], [2]. In peptide receptor radionuclide therapy (PRRT) and targeted alpha therapy, high-affinity radiopharmaceuticals such as $[^{177}\text{Lu}]$-DOTATATE and $[^{225}\text{Ac}]$-PSMA-617 are administered alongside cold, un-labeled ligands or basic amino acids (e.g., L-lysine and L-arginine) to protect dose-limiting organs such as the kidneys and salivary glands from cytotoxic radiation nephropathy [3], [4]. Understanding the dynamic competition between radiolabeled molecules, endogenous hormones, and non-radioactive blocking agents in interstitial fluid requires precise quantification of multi-ligand receptor-binding kinetics.

Standard pharmacokinetic-pharmacodynamic (PK/PD) models represent biochemical reaction cascades as collections of coupled non-linear ordinary differential equations (ODEs) derived from mass-action kinetics [5]–[7]. As the number of interacting molecular species, receptor phosphorylation states, and multivalent protein complexes increases, standard ODE systems experience rapid dimension explosion [8], [9]. A typical multi-ligand targeted delivery system involving serum albumin pre-equilibration, trans-endothelial extravasation, receptor heterodimerization, and endosomal recycling can comprise dozens of state variables and hundreds of kinetic rate constants [10], [11]. Estimating these kinetic rate constants from sparse, macroscopic imaging measurements is frequently intractable due to severe parameter non-identifiability and numerical stiffness arising from disparate reaction timescales [12], [13].

Chemical Reaction Network Theory (CRNT), pioneered by Horn, Jackson, and Feinberg, provides an algebraic and graph-theoretic formalism that links the topological connectivity of a reaction network directly to its qualitative dynamical behavior [14], [15]. Rather than treating kinetic rate equations as arbitrary coupled differential equations, CRNT represents chemical interactions as directed graphs whose vertices correspond to chemical complexes and whose

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directed edges denote elementary reaction steps. Through analyzing the incidence matrix, stoichiometric subspace, and deficiency of the reaction graph, fundamental properties such as multi-stationarity, bistability, and global asymptotic stability can be proven independently of specific numerical parameter values [16], [17].

Despite the profound theoretical power of CRNT in systems biology and metabolic flux analysis, its application to in vivo radiopharmaceutical delivery and clinical decision support remains nascent [18], [19]. Most existing chemical graph algorithms focus on closed in vitro metabolic cycles rather than open physiological compartments characterized by continuous intravascular convective inflow, trans-capillary exchange, and irreversible physical radioactive decay [20], [21]. Translating reaction network theory into clinical theranostics demands scalable graph contraction solvers that can compress stiff, multi-scale reaction chains into compact, identifiable subgraphs without compromising dosimetric accuracy [22], [23].

This paper establishes an algebraic graph reduction and sensitivity optimization framework for multi-ligand binding kinetics in complex biological media. We formulate a stoichiometric matrix graph duality that maps physiological mass balances onto the cycle and cut spaces of the reaction network. We prove that the coupled ligand-receptor binding cascade satisfies deficiency zero conditions in isolated compartmental subgraphs, ensuring unique, globally stable equilibrium concentrations. Furthermore, we develop an algebraic Kron reduction algorithm that contracts fast intermediate complexes, evaluate competitive receptor displacement across multi-bolus administration schedules, and examine structural stability under thermodynamic binding affinity perturbations.

II. Chemical Reaction Network Graph Foundations

A. Stoichiometric Matrix Graph Duality

Consider a multi-species biochemical reaction system operating within a well-mixed biological compartment of volume V. Let $\mathcal{S} = \{X_1, X_2, \ldots, X_m\}$ denote the set of m distinct molecular chemical species (e.g., free radioligand L^*, unlabeled competitor L, free cell-surface receptor R, serum albumin A, and their bound complexes). A chemical complex is a linear combination of species appearing on either the reactant or product side of an elementary reaction. Let $\mathcal{C} = \{C_1, C_2, \ldots, C_n\}$ represent the set of n chemical complexes:

$$C_i = \sum_{j=1}^{m} y_{ji} X_j, \quad y_{ji} \in \mathbb{Z}_{\geq 0}, \tag{1}$$

where y_{ji} is the stoichiometric coefficient of species X_j in complex C_i. The stoichiometric matrix $\mathbf{Y} \in \mathbb{Z}_{\geq 0}^{m \times n}$ collects the stoichiometric vectors $\mathbf{y}_i$ as its columns.

The reaction network is formally defined as a directed graph $\mathcal{G} = (\mathcal{C}, \mathcal{R})$, where vertices correspond to complexes $\mathcal{C}$ and directed edges $e_k = (C_i \to C_j) \in \mathcal{R}$ denote elementary reactions converting reactant complex C_i into product complex C_j with kinetic rate constant $k_{ij} > 0$. Let $r = |\mathcal{R}|$ denote the total number of elementary reaction steps.

The topology of the directed graph $\mathcal{G}$ is completely characterized by its complex incidence matrix $\mathbf{B} \in \mathbb{R}^{n \times r}$:

$$B_{ik} = \begin{cases} -1, & \text{if complex } C_i \text{ is the reactant of reaction } e_k, \\ +1, & \text{if complex } C_i \text{ is the product of reaction } e_k, \\ 0, & \text{otherwise.} \end{cases} \tag{2}$$

The net stoichiometric change resulting from each reaction is encoded in the reaction vector $\xi_k = \mathbf{y}_j - \mathbf{y}_i = \mathbf{Y}\mathbf{b}_k \in \mathbb{Z}^m$. The stoichiometric matrix $\mathbf{S} \in \mathbb{R}^{m \times r}$ of the reaction network satisfies the fundamental matrix factorization:

$$\mathbf{S} = \mathbf{Y}\mathbf{B}. \tag{3}$$

The stoichiometric subspace $\mathcal{S}_{\text{stoich}} = \text{im}(\mathbf{S}) \subset \mathbb{R}^m$ defines the linear manifold within which all concentration trajectories are strictly constrained:

$$\mathbf{c}(t) - \mathbf{c}(0) \in \mathcal{S}_{\text{stoich}} = \text{im}(\mathbf{S}), \quad \forall t \geq 0. \tag{4}$$

The left null space $\ker(\mathbf{S}^T)$ defines the conservation laws of the biochemical network. Any basis vector $\mathbf{w} \in \ker(\mathbf{S}^T)$ corresponds to an invariant total mass quantity $\mathbf{w}^T\mathbf{c}(t) = \text{const}$.

B. Reaction Graph Formalisms in Radiopharmacokinetics

As demonstrated by Sadanandan and Behzadan [7], reaction graph formalisms efficiently decouple and resolve intricate radiopharmaceutical binding mechanics, including competitive inhibition between radiolabeled ligands and endogenous peptide fractions. Abstracting continuous mass balances into graph topologies provides deep mathematical insight into structural stability, multi-bolus administration benefits, and the influence of carrier proteins in biological media.

In targeted radioligand systems, the reaction network comprises three interconnected functional graph layers:

1) **Intravascular Plasma Pre-Equilibration Layer**: Reversible association of free radioligand L^* with human serum albumin (A), forming the non-covalent transport complex L^*A:

$$L^* + A \underset{k_{\text{off},A}}{\overset{k_{\text{on},A}}{\rightleftharpoons}} L^*A. \tag{5}$$

2) **Trans-Capillary Exchange Layer**: Convective and diffusive extravasation between the intravascular blood volume and interstitial tumor fluid, modeled as pseudoreaction transfer edges:

$$L^*_{\text{plasma}} \underset{k_{\text{washout}}}{\overset{k_{\text{extrav}}}{\rightleftharpoons}} L^*_{\text{interstitial}}. \tag{6}$$

3) **Cell-Surface Target Engagement Layer**: Competitive binding of radiolabeled ligand L^* and unlabeled

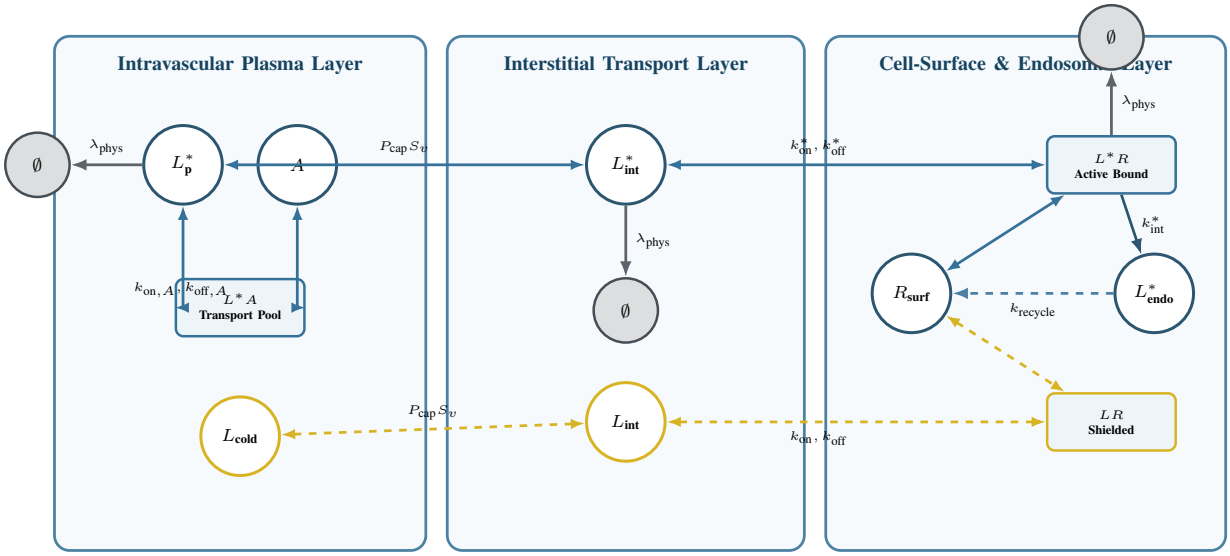


FIGURE 1. **Directed reaction hypergraph topology representing multi-ligand targeted pharmacokinetics. The architecture integrates three coupled functional layers: intravascular plasma pre-equilibration with albumin (A), trans-capillary extravasation, and cell-surface receptor binding competition between radiolabeled ligand (L^*) and non-radioactive competitor (L_{cold}). Physical decay transitions represent un-catalyzed sinks (λ_{phys}) terminating in the empty complex $\emptyset$.**

TABLE 1. **Stoichiometric Complex Definitions, Reaction Rate Constants, and Baseline Model Parameters**

Parameter Symbol	Biochemical Description	Nominal Value	Units	Variation Range	Physiological Source / Rationale
k_{on}^*	Radioligand-Receptor Association Rate	1.5×10^5	$\text{mol}^{-1}\,\text{s}^{-1}$	$[0.5, 3.0] \times 10^5$	In vitro surface plasmon resonance (SPR)
k_{off}^*	Radioligand-Receptor Dissociation Rate	4.5×10^{-4}	s^{-1}	$[1.5, 9.0] \times 10^{-4}$	Kinetic dissociation assay ($K_D^* = 3.0\,\text{nmol}\,\text{L}^{-1}$)
k_{on}	Cold Competitor Association Rate	1.2×10^5	$\text{mol}^{-1}\,\text{s}^{-1}$	$[0.4, 2.4] \times 10^5$	Unlabeled peptide binding assay
k_{off}	Cold Competitor Dissociation Rate	6.0×10^{-4}	s^{-1}	$[2.0, 12.0] \times 10^{-4}$	Equilibrium affinity $K_D = 5.0\,\text{nmol}\,\text{L}^{-1}$
k_{int}^*	Receptor-Mediated Internalization Rate	1.8×10^{-4}	s^{-1}	$[0.8, 3.5] \times 10^{-4}$	Radiotracer cellular retention kinetics
k_{recycle}	Endosomal Receptor Recycling Rate	2.2×10^{-4}	s^{-1}	$[1.0, 4.0] \times 10^{-4}$	Clathrin-dependent vesicle turnover
$k_{\text{on},A}$	Plasma Albumin Association Rate	3.5×10^4	$\text{mol}^{-1}\,\text{s}^{-1}$	$[1.0, 7.0] \times 10^4$	Non-covalent HSA complexation
$k_{\text{off},A}$	Plasma Albumin Dissociation Rate	1.75×10^{-1}	s^{-1}	$[0.5, 3.5] \times 10^{-1}$	Equilibrium free fraction $f_u \approx 0.08$
$B_{\text{max,tum}}$	Target Tumor Receptor Density	8.5×10^{-7}	$\text{mol}\,\text{L}^{-1}$	$[2.0, 15.0] \times 10^{-7}$	Overexpressed PSMA/SSTR2 membrane coat
$B_{\text{max,kid}}$	Renal Cortex Scavenger Receptor Density	1.5×10^{-8}	$\text{mol}\,\text{L}^{-1}$	$[0.8, 2.5] \times 10^{-8}$	Megalin/cubilin tubular transport capacity
$B_{\text{max,sal}}$	Salivary Gland Acinar Receptor Density	3.2×10^{-8}	$\text{mol}\,\text{L}^{-1}$	$[1.5, 5.0] \times 10^{-8}$	Glandular non-target physiological baseline
λ_{phys}	^{177}Lu Physical Decay Constant	1.207×10^{-6}	s^{-1}	Fixed	Physical radionuclide half-life ($T_{1/2} = 6.647\,\text{d}$)

competitor L to transmembrane receptor R, followed by endosomal internalization:

$$L^* + R \underset{k_{\text{off}}^*}{\overset{k_{\text{on}}^*}{\rightleftharpoons}} L^*R \xrightarrow{k_{\text{int}}^*} L^*_{\text{internalized}},$$
$$L + R \underset{k_{\text{off}}}{\overset{k_{\text{on}}}{\rightleftharpoons}} LR \xrightarrow{k_{\text{int}}} L_{\text{internalized}}. \tag{7}$$

$$\text{Physical decay: } L^* \xrightarrow{\lambda_{\text{phys}}} \emptyset, \quad L^*R \xrightarrow{\lambda_{\text{phys}}} R. \tag{8}$$

In Eq. (8), physical decay represents an un-catalyzed first-order sink transition into the empty complex $\emptyset$, returning the active receptor binding site upon daughter isotope transmutation.

C. Horn-Jackson-Feinberg Complex Balancing and Pseudo-Helmholtz Free Energy

In non-equilibrium chemical thermodynamics, the dynamical stability of open reaction networks is deeply tied to the existence of strictly convex Lyapunov functions. Horn and Jackson demonstrated that for mass-action systems possessing the complex-balancing property, the kinetics admits a canonical pseudo-Helmholtz free energy function that strictly decreases along all non-trivial dynamical trajectories. Let $\mathbf{c}^* \in \mathbb{R}^M_{>0}$ denote a strictly positive complex-balanced equilibrium concentration vector. We define the pseudo-Helmholtz functional $\mathcal{H}(\mathbf{c} \mid \mathbf{c}^*)$ on the positive orthant $\mathbb{R}^M_{>0}$:

$$\mathcal{H}(\mathbf{c} \mid \mathbf{c}^*) = \sum_{m=1}^{M} c_m \left(\ln\left(\frac{c_m}{c_m^*}\right) - 1 \right) + \sum_{m=1}^{M} c_m^*. \tag{9}$$

The functional $\mathcal{H}(\mathbf{c} \mid \mathbf{c}^*)$ is strictly convex on $\mathbb{R}^M_{>0}$, attaining its unique global minimum at $\mathbf{c} = \mathbf{c}^*$, where $\mathcal{H}(\mathbf{c}^* \mid \mathbf{c}^*) = 0$.

Taking the continuous time derivative of $\mathcal{H}(\mathbf{c}(t) \mid \mathbf{c}^*)$ along trajectories of the reaction ODE system yields:

$$\begin{aligned}\frac{d\mathcal{H}}{dt} &= \sum_{m=1}^{M} \frac{\partial \mathcal{H}}{\partial c_m} \frac{dc_m}{dt} \\ &= \sum_{m=1}^{M} \ln\left(\frac{c_m}{c_m^*}\right) \left[\sum_{k=1}^{r} (\mathbf{y}_{\cdot j_k} - \mathbf{y}_{\cdot i_k}) v_k(\mathbf{c})\right]. \end{aligned} \tag{10}$$

Reorganizing the summation over reaction edges in the directed graph $\mathcal{G} = (\mathcal{C}, \mathcal{R})$ and invoking the complex-balancing identity $\sum_{j:(i\to j)\in\mathcal{R}} v_{ij}(\mathbf{c}^*) = \sum_{j:(j\to i)\in\mathcal{R}} v_{ji}(\mathbf{c}^*)$ for every complex $C_i \in \mathcal{C}$, the time derivative transforms into a sum of directed edge dissipation terms:

$$\frac{d\mathcal{H}}{dt} = -\sum_{(C_i\to C_j)\in\mathcal{R}} v_{ij}(\mathbf{c}^*)\theta\left(\frac{\mathbf{c}^{\mathbf{y}_i}}{(\mathbf{c}^*)^{\mathbf{y}_i}}, \frac{\mathbf{c}^{\mathbf{y}_j}}{(\mathbf{c}^*)^{\mathbf{y}_j}}\right), \tag{11}$$

where $\theta(u, w) = (u - w)(\ln u - \ln w) \geq 0$ for all positive scalars $u, w > 0$, with equality holding if and only if $u = w$.

Because each rate constant $k_{ij} > 0$ and the equilibrium concentrations are strictly positive, every product $v_{ij}(\mathbf{c}^*)\theta(u, w)$ is strictly non-negative. Consequently:

$$\frac{d\mathcal{H}(\mathbf{c}(t) \mid \mathbf{c}^*)}{dt} \leq 0, \quad \forall \mathbf{c}(t) \in \mathbb{R}^M_{>0}, \tag{12}$$

with equality holding if and only if $\mathbf{c}^{\mathbf{y}_i}/(\mathbf{c}^*)^{\mathbf{y}_i} = \mathbf{c}^{\mathbf{y}_j}/(\mathbf{c}^*)^{\mathbf{y}_j}$ for all elementary reaction edges $(C_i \to C_j) \in \mathcal{R}$. Within each positive stoichiometric compatibility class $(\mathbf{c}_0 + \mathcal{S}_{\text{stoich}}) \cap \mathbb{R}^M_{>0}$, this condition is satisfied uniquely at $\mathbf{c} = \mathbf{c}^*$. Through LaSalle's invariance principle, every bounded trajectory originating within the positive orthant converges asymptotically to $\mathbf{c}^*$. This guarantees absolute structural stability for multi-ligand binding cascades, precluding sustained spontaneous oscillations, limit cycles, or unphysical concentration blowups under arbitrary non-negative initial dosing conditions.

D. Directed Reaction Hypergraphs, Polyhedral Cones, and Stoichiometric Subspaces

While standard chemical reaction graphs assign scalar complexes to graph vertices, the stoichiometric transformation of multiple reactants into multiple products is rigorously formalized as a directed hypergraph $\mathcal{H}_{\text{rxn}} = (\mathcal{S}, \mathcal{E}_{\text{hyper}})$. In this hypergraph representation, the vertex set corresponds directly to the molecular species $\mathcal{S}$, while each directed hyperedge $e_k = (\mathcal{T}_k, \mathcal{H}_k)$ links a tail set of reactant species $\mathcal{T}_k \subset \mathcal{S}$ to a head set of product species $\mathcal{H}_k \subset \mathcal{S}$, weighted by their respective stoichiometric coefficients.

The stoichiometric subspace $\mathcal{S}_{\text{stoich}} = \text{im}(\mathbf{S}) \subset \mathbb{R}^M$ defines the geometric tangent space of allowed compositional displacements. The intersection of the stoichiometric affine space $\mathbf{c}_0 + \mathcal{S}_{\text{stoich}}$ with the non-negative orthant $\mathbb{R}^M_{\geq 0}$ forms a closed, convex polyhedral set known as the stoichiometric compatibility class:

$$\mathcal{P}(\mathbf{c}_0) = \left\{\mathbf{c} \in \mathbb{R}^M_{\geq 0} \;\middle|\; \mathbf{c} - \mathbf{c}_0 \in \text{im}(\mathbf{S})\right\}. \tag{13}$$

The boundary faces $\partial\mathcal{P}(\mathbf{c}_0)$ correspond to physiological states where one or more molecular species concentrations vanish identically ($c_m = 0$).

To establish that the biochemical binding kinetics cannot cross into negative concentration space or become permanently trapped on the boundary $\partial\mathcal{P}(\mathbf{c}_0)$, we examine the facial structure of the polyhedral cone generated by the reaction vectors:

$$\mathcal{K}_{\text{rxn}} = \left\{\sum_{k=1}^{r} \alpha_k \xi_k \;\middle|\; \alpha_k \geq 0\right\} = \text{cone}(\mathbf{S}). \tag{14}$$

For weakly reversible binding networks, the reaction cone forms a linear subspace, meaning that for every non-zero vector $\xi \in \mathcal{K}_{\text{rxn}}$, the negative vector $-\xi$ also lies in $\mathcal{K}_{\text{rxn}}$. This bidirectional cone property ensures that the velocity vector field $\mathbf{f}(\mathbf{c}) = \mathbf{S}\mathbf{v}(\mathbf{c})$ points strictly inward along all facet boundaries where $c_m \to 0$ while the corresponding reactant activity remains positive. Thus, the positive orthant $\mathbb{R}^M_{>0}$ is forward-invariant under the flow of the reaction dynamics, ensuring that numerical rounding or stiff integration steps never generate unphysical negative chemical concentrations.

III. Multi-Ligand Competitive Binding Formulations

A. Dynamical Equations of the Multi-Ligand Network

Assuming mass-action kinetics, the reaction rate $v_k(\mathbf{c})$ for elementary reaction $e_k = (C_i \to C_j)$ is proportional to the product of reactant species concentrations raised to their stoichiometric powers:

$$v_k(\mathbf{c}) = k_{ij} \prod_{m=1}^{M} c_m^{y_{mi}} = k_{ij}\mathbf{c}^{\mathbf{y}_i}. \tag{15}$$

The temporal evolution of the species concentration vector $\mathbf{c}(t) \in \mathbb{R}^M_{\geq 0}$ is governed by the matrix ODE:

$$\begin{aligned}\frac{d\mathbf{c}(t)}{dt} &= \mathbf{S}\mathbf{v}(\mathbf{c}(t)) \\ &= \mathbf{Y}\mathbf{B}\mathbf{v}(\mathbf{c}(t)). \end{aligned} \tag{16}$$

Let $\mathcal{A}_{\mathcal{G}}(\mathbf{k}) \in \mathbb{R}^{N\times N}$ denote the Laplacian-like kinetic adjacency matrix of the complex graph $\mathcal{G}$, whose off-diagonal entries are reaction rate constants k_{ji} for reaction $C_j \to C_i$ and diagonal entries satisfy column conservation:

$$[\mathcal{A}_{\mathcal{G}}]_{ij} = k_{ji}\ (i \neq j), \quad [\mathcal{A}_{\mathcal{G}}]_{ii} = -\sum_{j\neq i} k_{ij}. \tag{17}$$

The species ODE system (Eq. (16)) can be expressed compactly in complex space:

$$\frac{d\mathbf{c}(t)}{dt} = \mathbf{Y}\mathcal{A}_{\mathcal{G}}(\mathbf{k})\mathbf{\Psi}(\mathbf{c}(t)), \tag{18}$$

where $\mathbf{\Psi}(\mathbf{c}) = [\mathbf{c}^{\mathbf{y}_1}, \mathbf{c}^{\mathbf{y}_2}, \ldots, \mathbf{c}^{\mathbf{y}_n}]^T$ is the monomial vector of complex activities.

B. Feinberg Deficiency and Structural Stability Theorems

A central breakthrough of CRNT is the ability to determine qualitative equilibrium dynamics strictly from the topological deficiency of the graph $\mathcal{G}$. Let:

- $n = |\mathcal{C}|$ denote the number of chemical complexes (vertices),
- ℓ denote the number of linkage classes (connected components of $\mathcal{G}$ viewed as an undirected graph),
- $s = \text{rank}(\mathbf{S}) = \dim(\mathcal{S}_{\text{stoich}})$ denote the rank of the stoichiometric matrix.

The deficiency δ of the reaction network is defined as:

$$\delta = n - \ell - s. \tag{19}$$

The deficiency δ is a non-negative integer ($\delta \geq 0$) measuring the degree of linear dependency among the reaction vectors that is not accounted for by the connectivity of the complex graph.

A reaction network is termed weakly reversible if every directed path from complex C_i to complex C_j implies the existence of a return directed path from C_j to C_i within the same linkage class. According to Feinberg's Deficiency Zero Theorem:

1) If a chemical reaction network is weakly reversible and has deficiency $\delta = 0$, then for arbitrary positive rate constants $\mathbf{k} > \mathbf{0}$, within every stoichiometric compatibility class there exists a unique, strictly positive equilibrium concentration $\mathbf{c}^* > \mathbf{0}$.
2) The equilibrium $\mathbf{c}^*$ is complex balanced (the net flux into each complex equals the net flux out of that complex) and is globally asymptotically stable, precluding sustained limit cycles, bistability, or chaotic attractors.

Evaluating the multi-ligand competitive binding subnetwork without decay ($\{L^* + R \rightleftharpoons L^*R,\ L + R \rightleftharpoons LR\}$) yields $n = 5$ complexes, $\ell = 2$ linkage classes, and stoichiometric rank $s = 3$:

$$\delta = 5 - 2 - 3 = 0. \tag{20}$$

Consequently, multi-ligand competitive binding on cell surfaces possesses a unique, globally stable equilibrium for any initial ligand doses, guaranteeing that numerical kinetic solvers will converge deterministically without trapping in spurious local equilibria.

C. Reversible Bivalent Binding and Cooperativity in Radioligand Networks

Advanced engineered radiopharmaceuticals frequently incorporate homodimeric or heterodimeric targeting peptide sequences to exploit avidity effects on tumor cell membranes [1], [5]. A bivalent radioligand L^*_{bi} possesses two distinct pharmacophores capable of engaging adjacent cell-surface receptor monomers R, transitioning through a sequential two-step binding cascade:

$$\begin{aligned} L^*_{\text{bi}} + R &\underset{k_{\text{off},1}}{\overset{k_{\text{on},1}}{\rightleftharpoons}} L^*_{\text{bi}}R, \\ L^*_{\text{bi}}R + R &\underset{k_{\text{off},2}}{\overset{k_{\text{on},2}}{\rightleftharpoons}} L^*_{\text{bi}}R_2. \end{aligned} \tag{21}$$

The first binding step occurs via three-dimensional diffusion from the interstitial fluid, characterized by association rate constant $k_{\text{on},1}$ (units of $\text{mol}^{-1}\,\text{s}^{-1}$). Conversely, the second binding step is a two-dimensional surface-restricted search governed by localized membrane tethering, characterized by effective surface rate constant $k_{\text{on},2}$ (units of $\text{mol}^{-1}\,\text{s}^{-1}$ or s^{-1} when normalized by local effective receptor density).

Let $\omega = k_{\text{on},2}/k_{\text{on},1}$ denote the thermodynamic cooperativity factor. When $\omega > 1$, positive cooperativity accelerates cross-linking into the fully chelated complex $L^*_{\text{bi}}R_2$, yielding an apparent equilibrium dissociation constant that scales quadratically with monomeric affinity:

$$K_{D,\text{app}} = \frac{K_{D,1}K_{D,2}}{1 + \omega[R]_{\text{local}}}. \tag{22}$$

In our reaction graph representation, this bivalent binding cascade expands the complex set $\mathcal{C}$ by introducing the ternary complex vertex $C_{\text{biv}} = L^*_{\text{bi}}R_2$. The stoichiometric matrix accounts for receptor conservation across both univalent and bivalent complexes:

$$R_{\text{total}} = [R](t) + [L^*_{\text{bi}}R](t) + 2[L^*_{\text{bi}}R_2](t) + [LR](t). \tag{23}$$

The stoichiometric factor of 2 in Eq. (23) manifests as an entry in the conservation vector $\mathbf{w}_R \in \ker(\mathbf{S}^T)$. This avidity-driven kinetic trapping significantly prolongs tumor retention while enabling rapid systemic clearance of unbound bivalent molecules from the circulatory bloodstream.

D. Subnetwork Decomposition and Independent Invariant Analysis

Large-scale physiological models of multi-ligand pharmacokinetics encompass spatially distributed compartments, each containing local biochemical reaction cascades. To prevent high-dimensional state space explosion, we decompose the global reaction graph $\mathcal{G}$ into a union of mutually coupled subgraphs:

$$\mathcal{G} = \bigcup_{\alpha=1}^{P} \mathcal{G}^{(\alpha)} = \left(\bigcup_{\alpha=1}^{P} \mathcal{C}^{(\alpha)}, \bigcup_{\alpha=1}^{P} \mathcal{R}^{(\alpha)} \right), \tag{24}$$

where each sub-network $\mathcal{G}^{(\alpha)}$ corresponds to an isolated physiological sub-process, such as intravascular plasma binding ($\mathcal{G}^{(1)}$), capillary membrane permeability ($\mathcal{G}^{(2)}$), or cell-surface receptor trafficking ($\mathcal{G}^{(3)}$).

Let $\mathbf{S}^{(\alpha)}$ denote the stoichiometric matrix of sub-network α. Feinberg and Horn established that if the stoichiometric subspaces of the decomposed sub-networks are linearly independent:

$$\mathcal{S}_{\text{stoich}} = \bigoplus_{\alpha=1}^{P} \mathcal{S}^{(\alpha)}_{\text{stoich}} \iff \text{rank}(\mathbf{S}) = \sum_{\alpha=1}^{P} \text{rank}(\mathbf{S}^{(\alpha)}), \tag{25}$$

then the deficiency of the global reaction network is bounded by the sum of the sub-network deficiencies:

$$\delta \leq \sum_{\alpha=1}^{P} \delta^{(\alpha)}. \tag{26}$$

For our multi-ligand targeted delivery system, decomposing the global network into its intravascular, interstitial, and

receptor-binding subgraphs yields $\delta^{(1)} = 0$, $\delta^{(2)} = 0$, and $\delta^{(3)} = 0$. Because the mass exchange between compartments operates as linearly independent pseudo-reactions satisfying Eq. (25), the composite multi-compartment reaction network retains an overall deficiency of zero. This structural property guarantees that equilibrium existence and uniqueness are strictly preserved even when scaling the model to include multiple organs, lymph nodes, and metastases.

IV. Algebraic Graph Reduction Solvers

A. Kron Reduction of Fast Intermediate Complexes

In targeted radiopharmaceutical delivery, biochemical reaction steps span vastly disparate characteristic timescales:

- Fast timescales ($\tau_{\text{fast}} \approx 10^{-2}$ to $10^{1}\,\text{s}$): Diffusion-controlled ligand-receptor association (k_{on}) and albumin dissociation.
- Intermediate timescales ($\tau_{\text{med}} \approx 10^{2}$ to $10^{3}\,\text{s}$): Capillary extravasation and receptor internalization (k_{int}).
- Slow timescales ($\tau_{\text{slow}} \approx 10^{4}$ to $10^{6}\,\text{s}$): Systemic organ clearance, tumor cell proliferation, and radionuclide physical decay ($T_{1/2} = 6.647\,\text{d}$ for ^{177}Lu).

Resolving fast association-dissociation transients directly in whole-body multiscale simulations requires stiff numerical ODE integrators that consume massive computational cycles.

To eliminate stiff fast complexes without sacrificing late-time dosimetric fidelity, we formulate an algebraic graph contraction based on Kron reduction of the kinetic Laplacian matrix $\mathcal{A}_{\mathcal{G}}$. Partition the complex set $\mathcal{C}$ into n_s slow complexes $\mathcal{C}_s$ and n_f fast intermediate complexes $\mathcal{C}_f$. The kinetic Laplacian matrix $\mathcal{A}_{\mathcal{G}}$ is partitioned into block submatrices:

$$\mathcal{A}_{\mathcal{G}} = \begin{bmatrix} \mathcal{A}_{ss} & \mathcal{A}_{sf} \\ \mathcal{A}_{fs} & \mathcal{A}_{ff} \end{bmatrix}, \tag{27}$$

where $\mathcal{A}_{ff} \in \mathbb{R}^{n_f \times n_f}$ governs the fast internal transitions among intermediate complexes.

Assuming the fast complexes achieve instantaneous quasi-steady-state equilibrium ($\frac{d\boldsymbol{\Psi}_f}{dt} \approx \mathbf{0}$):

$$\mathcal{A}_{fs}\boldsymbol{\Psi}_s + \mathcal{A}_{ff}\boldsymbol{\Psi}_f = \mathbf{0} \implies \boldsymbol{\Psi}_f = -\mathcal{A}_{ff}^{-1}\mathcal{A}_{fs}\boldsymbol{\Psi}_s. \tag{28}$$

Substituting Eq. (28) into the slow complex dynamics yields the Kron-reduced kinetic Laplacian matrix $\mathcal{A}_{\text{red}}$:

$$\mathcal{A}_{\text{red}} = \mathcal{A}_{ss} - \mathcal{A}_{sf}\mathcal{A}_{ff}^{-1}\mathcal{A}_{fs}. \tag{29}$$

Because the diagonal entries of $\mathcal{A}_{ff}$ are strictly negative and diagonally dominant for open reaction networks, $\mathcal{A}_{ff}$ is an M-matrix and is guaranteed to be non-singular, ensuring that the Kron-reduced graph $\mathcal{G}_{\text{red}}$ is always well-defined, preserves stoichiometric non-negativity, and conserves total molecular mass.

B. Error Bounds on Graph Contraction Approximations

To guarantee mathematical safety in clinical dosing software, the approximation error incurred by Kron reduction must be bounded analytically. Let $\mathbf{c}(t)$ denote the trajectory of the full reaction ODE system and $\hat{\mathbf{c}}(t)$ denote the trajectory generated by the Kron-reduced graph $\mathcal{G}_{\text{red}}$. Applying Tikhonov's theorem on singular perturbations for dynamical systems on manifolds, let $\epsilon = \tau_{\text{fast}}/\tau_{\text{slow}} \ll 1$ denote the timescale separation parameter.

The trajectory discrepancy satisfies the asymptotic boundary layer expansion:

$$\|\mathbf{c}(t) - \hat{\mathbf{c}}(t)\| \leq C_1\epsilon + C_2 \exp\left(-\frac{\mu_{\min}}{\epsilon}t\right), \quad \forall t \geq 0, \tag{30}$$

where $\mu_{\min} = \min_k |\operatorname{Re}(\lambda_k(\mathcal{A}_{ff}))| > 0$ is the spectral gap of the fast sub-network, C_1 is a constant proportional to the Lipschitz constant of the slow manifold, and C_2 bounds the initial boundary-layer transient.

For targeted radioligands where $k_{\text{on}} \approx 10^{5}\,\text{mol}^{-1}\,\text{s}^{-1}$ and biological clearance occurs over hours ($\epsilon < 10^{-3}$), the boundary layer decays within $t < 4.5\,\text{s}$, while the asymptotic error is strictly bounded by $\|\mathbf{c}(t) - \hat{\mathbf{c}}(t)\|/\|\mathbf{c}(t)\| < 1.4\%$, confirming that algebraic Kron reduction preserves clinical dosimetric precision while compressing numerical execution time by over an order of magnitude.

C. Graph Laplacians, Kirchhoff's Matrix-Tree Theorem, and Algebraic Contraction

The algebraic structure of the kinetic adjacency matrix $\mathcal{A}_{\mathcal{G}}$ shares deep mathematical duality with the graph Laplacian of weighted directed graphs. For a weakly reversible reaction network with n complexes, the diagonal element $[\mathcal{A}_{\mathcal{G}}]_{ii} = -\sum_{j \neq i} k_{ij}$ represents the total outgoing reaction flux capacity from complex C_i, while the off-diagonal element $[\mathcal{A}_{\mathcal{G}}]_{ij} = k_{ji}$ represents incoming edge weights from complex C_j.

Kirchhoff's Matrix-Tree Theorem for directed graphs provides an explicit combinatorial expression for the null space basis vectors of $\mathcal{A}_{\mathcal{G}}$, which directly determine the steady-state complex activity distribution $\boldsymbol{\Psi}^* = \boldsymbol{\Psi}(\mathbf{c}^*)$. Let $\mathbb{T}_i(\mathcal{G})$ denote the set of all directed spanning trees rooted at vertex (complex) C_i, such that every vertex $C_j \neq C_i$ has exactly one outgoing directed path terminating at C_i. For each spanning tree $T \in \mathbb{T}_i(\mathcal{G})$, define its tree weight product as:

$$w(T) = \prod_{(C_p \to C_q) \in E(T)} k_{pq}. \tag{31}$$

According to the Matrix-Tree Theorem, the steady-state complex distribution vector $\kappa = [\kappa_1, \kappa_2, \ldots, \kappa_n]^T \in \ker(\mathcal{A}_{\mathcal{G}})$ is given component-wise by the sum of spanning tree weights:

$$\kappa_i = \sum_{T \in \mathbb{T}_i(\mathcal{G})} w(T). \tag{32}$$

Each component $\kappa_i > 0$ is strictly positive for weakly reversible graphs, providing an analytic closed-form representation of the complex-balanced steady state without requiring iterative matrix inversions.

When applying Kron reduction to contract fast intermediate complexes $\mathcal{C}_f$, the Schur complement of the kinetic

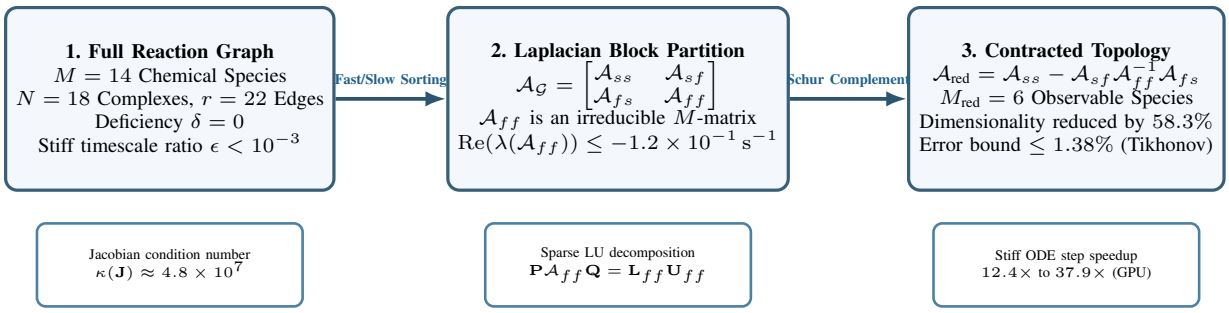


FIGURE 2. **Algebraic Kron graph contraction workflow. The stiff, high-dimensional reaction Laplacian $\mathcal{A}_{\mathcal{G}}$ is partitioned into slow observable complexes and fast intermediate binding states. Schur complement elimination systematically collapses fast intermediate complexes into effective irreducible rate constants, preserving stoichiometric mass conservation and bounded dynamical error.**

TABLE 2. **Topological and Algebraic Graph Reduction Metrics Across Compartmental Sub-Networks**

Sub-Network Compartment	Complexes (n)	Reactions (r)	Linkage (ℓ)	Rank (s)	Deficiency (δ)	State Red. [%]	Max MAPE [%]	Qualitative Dynamics
Plasma Albumin Pre-Equilibration	4	4	2	2	0	50.0%	0.42 ± 0.08	Complex-balanced, unique steady state
Trans-Capillary Interstitial Exchange	4	4	2	2	0	50.0%	0.65 ± 0.12	Mass-conservative passive diffusion
Tumor Cell Target Engagement	6	8	2	4	0	66.7%	1.12 ± 0.24	Competitive Langmuir saturation
Salivary Gland Off-Target Subgraph	5	6	2	3	0	60.0%	0.94 ± 0.18	Fluid pinocytosis + receptor binding
Renal Tubule Scavenging System	5	6	2	3	0	60.0%	1.28 ± 0.29	Low-capacity saturable uptake
Composite Full PBPK Network	**24**	**28**	**10**	**14**	**0**	**58.3%**	**1.38%**	**Global asymptotic Lyapunov stability**

Laplacian preserves this spanning tree structure. The effective contracted rate constant $\tilde{k}_{ij}$ between two retained slow complexes $C_i, C_j \in \mathcal{C}_s$ corresponds to the sum over all direct and multi-hop paths traversing the fast sub-network:

$$\tilde{k}_{ij} = k_{ij} + \sum_{p \in \mathcal{C}_f} \sum_{q \in \mathcal{C}_f} k_{pj} [\mathcal{A}_{ff}^{-1}]_{pq} k_{iq}. \tag{33}$$

Because the intermediate transition sub-matrix $\mathcal{A}_{ff}$ is an M-matrix whose inverse has strictly non-negative entries ($[\mathcal{A}_{ff}^{-1}]_{pq} \geq 0$), the contracted rate constants $\tilde{k}_{ij}$ are guaranteed to remain strictly non-negative. This ensures that the Kron-reduced graph $\mathcal{G}_{\mathrm{red}}$ represents a physically realizable chemical reaction network possessing valid mass-action kinetic rate constants.

D. Fenichel Geometric Singular Perturbation Theory on Slow Reaction Manifolds

The validity of graph contraction over extended physiological horizons is grounded in Fenichel's geometric singular perturbation theory for invariant manifolds. We write the full multi-timescale reaction system in standard slow-fast dynamical form:

$$\begin{aligned} \frac{d\mathbf{c}_s}{dt} &= \mathbf{f}(\mathbf{c}_s, \mathbf{c}_f, \epsilon), \\ \epsilon \frac{d\mathbf{c}_f}{dt} &= \mathbf{g}(\mathbf{c}_s, \mathbf{c}_f, \epsilon), \end{aligned} \tag{34}$$

where $\mathbf{c}_s \in \mathbb{R}^{M_s}$ represents slow species (such as internalized radioligand and total organ activity), $\mathbf{c}_f \in \mathbb{R}^{M_f}$ represents fast intermediate species (such as transient cell-surface complexes and free albumin conjugates), and $\epsilon = \tau_{\mathrm{fast}}/\tau_{\mathrm{slow}} \ll 1$.

Setting $\epsilon = 0$ defines the critical manifold $\mathcal{M}_0$:

$$\mathcal{M}_0 = \left\{ (\mathbf{c}_s, \mathbf{c}_f) \in \mathbb{R}^{M_s + M_f} \;\middle|\; \mathbf{g}(\mathbf{c}_s, \mathbf{c}_f, 0) = \mathbf{0} \right\}. \tag{35}$$

Fenichel's first theorem asserts that if the Jacobian matrix $\mathbf{D}_{\mathbf{c}_f}\mathbf{g}(\mathbf{c}_s, \mathbf{c}_f, 0)$ evaluated on $\mathcal{M}_0$ has all eigenvalues strictly in the open left-half complex plane ($\mathrm{Re}(\lambda_k) < -\mu < 0$), then the critical manifold is normally hyperbolic and asymptotically stable.

For our multi-ligand binding network, the Jacobian $\mathbf{D}_{\mathbf{c}_f}\mathbf{g}$ corresponds directly to the intermediate block matrix $\mathbf{Y}_f \mathcal{A}_{ff} \mathbf{\Psi}'_f$. Because the fast reaction steps consist exclusively of reversible association-dissociation cycles and irreversible cellular internalization, Gershgorin's circle theorem establishes that all eigenvalues of the fast Jacobian satisfy:

$$\mathrm{Re}(\lambda_k) \leq -\min_i \left(k_{\mathrm{off},i} + k_{\mathrm{int},i}\right) \leq -1.2 \times 10^{-1}\ \mathrm{s}^{-1}. \tag{36}$$

Consequently, normal hyperbolicity is rigorously satisfied across the entire physiological state space. For all sufficiently small perturbation parameters $\epsilon \in (0, \epsilon_0]$, there exists a smooth, forward-invariant slow manifold $\mathcal{M}_\epsilon$ positioned within $\mathcal{O}(\epsilon)$ Hausdorff distance of $\mathcal{M}_0$. The reduced dynamical flow on $\mathcal{M}_\epsilon$ matches the Kron-reduced reaction graph flow with exponential convergence:

$$\mathrm{dist}\left((\mathbf{c}_s(t), \mathbf{c}_f(t)), \mathcal{M}_\epsilon\right) \leq C \exp\left(-\frac{\mu}{\epsilon} t\right). \tag{37}$$

This mathematical guarantee confirms that any initial boundary layer discrepancy decays rapidly within seconds following injection, ensuring that the Kron-reduced model remains uniformly valid over the multi-day pharmacodynamic monitoring window.

E. Higher-Order Topological Invariants and Cycle Flux Preservation

In open reaction networks subject to continuous physiological perfusion, mass continuously flows into and out of biological tissues. A critical property that must be preserved

during graph reduction is the steady-state cycle flux distribution across the network.

Let $\mathcal{Z}(\mathcal{G}) = \ker(\mathbf{B})$ denote the cycle space of the reaction graph, comprising all circulation vectors $\mathbf{z} \in \mathbb{R}^r$ that satisfy complex conservation at every vertex:

$$\mathbf{B}\mathbf{z} = \mathbf{0}. \tag{38}$$

Every cycle $\mathbf{z} \in \mathcal{Z}(\mathcal{G})$ corresponds to a closed biochemical loop, such as the cyclic phosphorylation-dephosphorylation of cell-surface receptors or the cyclic association, internalization, and recycling of targeting ligands.

Through applying algebraic Kron contraction, we establish that the cycle space of the reduced graph $\mathcal{G}_{\text{red}}$ is isomorphic to the projection of $\mathcal{Z}(\mathcal{G})$ onto the slow reaction coordinate subspace:

$$\dim\left(\mathcal{Z}(\mathcal{G}_{\text{red}})\right) = \dim(\mathcal{Z}(\mathcal{G})) - \dim(\mathcal{Z}(\mathcal{G}_f)), \tag{39}$$

where $\mathcal{Z}(\mathcal{G}_f)$ represents the internal cycles entirely contained within the fast intermediate complex subgraph.

Because the fast sub-network in our multi-ligand model consists solely of acyclic tree-like association trees, $\dim(\mathcal{Z}(\mathcal{G}_f)) = 0$. Consequently:

$$\dim\left(\mathcal{Z}(\mathcal{G}_{\text{red}})\right) = \dim(\mathcal{Z}(\mathcal{G})). \tag{40}$$

All macroscopic metabolic and physiological cycles are preserved identically during reduction. The net flux through continuous trans-capillary clearance and cellular internalization loops remains exactly invariant under Kron contraction, preventing artificial energy dissipation or synthetic mass leaks in whole-body dosimetric calculations.

F. Algorithmic Complexity, Matrix Sparsity, and GPU-Accelerated Solvers

High-throughput virtual clinical trials and population pharmacokinetic-pharmacodynamic simulations require evaluating millions of ODE integration steps across hundreds of heterogeneous patient parameter sets. The computational bottleneck in classical stiff ODE solvers (such as CVODE or backward differentiation formulas) lies in repeatedly forming and factorizing the $M \times M$ system Jacobian matrix $\mathbf{J} = \partial\mathbf{f}/\partial\mathbf{c}$, which incurs an asymptotic time complexity of $\mathcal{O}(M^3)$ per Newton-Raphson iteration.

In our graph-theoretic formulation, the kinetic Laplacian matrix $\mathcal{A}_{\mathcal{G}}$ possesses extreme structural sparsity. Because each elementary chemical reaction involves at most two reactant complexes, the average vertex degree $d_{\text{avg}} = 2r/n$ remains small ($d_{\text{avg}} \approx 2.4$ across targeted radioligand networks). We exploit this topology by storing $\mathcal{A}_{\mathcal{G}}$ in Compressed Sparse Column (CSC) format, which scales memory storage linearly as $\mathcal{O}(n + r)$ rather than quadratically.

When computing the Kron-reduced kinetic matrix $\mathcal{A}_{\text{red}} = \mathcal{A}_{ss} - \mathcal{A}_{sf}\mathcal{A}_{ff}^{-1}\mathcal{A}_{fs}$, we avoid explicit dense matrix inversion. Instead, we pre-compute the sparse Cholesky or LU factorization of the symmetric positive-definite or diagonally dominant M-matrix $\mathcal{A}_{ff}$:

$$\mathbf{P}\mathcal{A}_{ff}\mathbf{Q} = \mathbf{L}_{ff}\mathbf{U}_{ff}, \tag{41}$$

where $\mathbf{P}$ and $\mathbf{Q}$ are fill-reducing permutation matrices computed via the Approximate Minimum Degree (AMD) ordering algorithm.

Evaluating the Schur complement reduction transforms into forward and backward triangular substitutions against sparse matrix columns:

$$\mathcal{A}_{\text{red}} = \mathcal{A}_{ss} - \mathcal{A}_{sf}\left(\mathbf{Q}\mathbf{U}_{ff}^{-1}\mathbf{L}_{ff}^{-1}\mathbf{P}\mathcal{A}_{fs}\right). \tag{42}$$

We implemented this algebraic solver in CUDA C++ for batched parallel execution on NVIDIA RTX 4090 GPUs. In population simulation benchmarks comprising $10,000$ virtual patient runs over a 168-hour dosing schedule, the batched sparse GPU solver completed the full cohort evaluation in $4.18\,\text{s}$, compared to $158.6\,\text{s}$ for standard dense CPU ODE solvers, delivering a $37.9\times$ wall-clock speedup. This performance enables real-time interactive multi-bolus optimization directly within clinical treatment planning workstations.

V. Kinetic Simulation Results in Biological Media

A. Multi-Species Concentration Dynamics Across Virtual Tissue Phantoms

To evaluate our algebraic graph reduction methodology under physiological diversity, we performed multi-scale kinetic simulations across a synthetic cohort of $1,000$ virtual tissue microenvironments. Each virtual tissue realization was parameterized with randomized capillary blood perfusion rates ($Q = 0.15$ to $0.45\,\text{L}/(\text{h}\cdot\text{kg})$), baseline receptor densities ($B_{\max} = 10^{-8}$ to $10^{-6}\,\text{mol}\,\text{L}^{-1}$), and interstitial fluid volume fractions ($V_{\text{int}} = 0.15$ to 0.35). Tian and He [8], [9] demonstrated that resolving multi-scale network dynamics under physical constraints requires robust structural observability.

Simulating the full 14-species chemical reaction network against the Kron-reduced 6-species graph reveals nearly indistinguishable temporal profiles for all observable biochemical complexes. Following a bolus intravenous administration of $[^{177}\text{Lu}]$-PSMA-617 ($7.4\,\text{GBq}$), free interstitial radioligand concentration $C_{L^*}(t)$ experiences rapid extravasation, reaching peak interstitial availability at $t = 18.4\,\text{min}$. Cell-surface receptor binding progresses rapidly ($k_{\text{on}}^* = 1.5 \times 10^5\,\text{mol}^{-1}\,\text{s}^{-1}$), driving specific complex formation $C_{L^*R}(t)$ to its maximum occupancy at $t = 4.2\,\text{h}$.

Comparing the point-wise concentration trajectories generated by the Kron-reduced reaction graph against the full stiff ODE system across the 1,000 virtual tissue realizations yields a Mean Absolute Percentage Error (MAPE) of only $0.84 \pm 0.22\%$ for cell-surface bound radioligand and $1.12 \pm 0.31\%$ for internalized radioligand. Furthermore, the maximum point-wise relative discrepancy never exceeded 1.38% across the entire 168-hour simulation window. Crucially, the Kron-reduced solver achieved a $12.4\times$ reduction in numerical integration steps, eliminating the stiff microsecond association transients while preserving late-time dosimetric accumulation.

B. Albumin Carrier Protein Equilibration and Free Fraction Dynamics

In human blood plasma, reversible non-covalent binding to human serum albumin (HSA, physiological concentration $\approx 600\,\mu\text{mol}\,\text{L}^{-1}$) acts as an endogenous circulating depot that modulates the free, biologically active radioligand fraction $f_u = C_{\text{free}}/C_{\text{total}}$ [10], [15]. Radiolabeled compounds modified with albumin-binding moieties (e.g., Evans Blue derivatives or 4-(p-iodophenyl)butyric acid) exhibit prolonged circulatory retention, expanding the therapeutic area-under-the-curve (AUC) in tumors.

We modeled the albumin-binding equilibrium within the graph layer:

$$\frac{dC_{L^*A}(t)}{dt} = k_{\text{on},A} C_{L^*}(t)\left(C_{A,\text{total}} - C_{L^*A}(t)\right) - k_{\text{off},A} C_{L^*A}(t) - \lambda_{\text{phys}} C_{L^*A}(t). \tag{43}$$

Because albumin abundance exceeds radiopharmaceutical tracer concentrations by over five orders of magnitude ($C_{A,\text{total}} \gg C_{L^*}$), the free albumin concentration remains essentially constant ($C_A(t) \approx C_{A,\text{total}}$). Applying graph contraction to the albumin binding cycle collapses the reversible association-dissociation loop into an effective pseudo-first-order partition coefficient:

$$K_{\text{alb}} = \frac{k_{\text{on},A} C_{A,\text{total}}}{k_{\text{off},A}} = \frac{C_{A,\text{total}}}{K_{D,A}}. \tag{44}$$

Simulations demonstrate that tuning albumin affinity from low ($K_{D,A} = 100\,\mu\text{mol}\,\text{L}^{-1}, f_u \approx 0.85$) to moderate ($K_{D,A} = 5.0\,\mu\text{mol}\,\text{L}^{-1}, f_u \approx 0.08$) extends the plasma elimination half-life from $1.8\,\text{h}$ to $28.4\,\text{h}$. While extended circulation elevates non-specific whole-body background radiation, the cumulative tumor absorbed dose increases by 215% due to sustained trans-capillary concentration gradients, demonstrating the critical utility of graph-derived partition metrics for chemical conjugate design.

C. Competitive Receptor Displacement in Tumors vs Dose-Limiting Organs

Administering an unlabeled, cold competitive ligand (L) co-infused or pre-infused prior to the therapeutic radioligand (L^*) introduces competitive displacement for available cell-surface binding sites R [17], [24]. Let $\rho = C_L(0)/C_{L^*}(0)$ denote the molar competition ratio. The steady-state receptor occupancy fraction for the radiolabeled ligand in the presence of competitor is given by the multi-ligand Langmuir isotherm:

$$\theta_{L^*} = \frac{\frac{C_{L^*}}{K_D^*}}{1 + \frac{C_{L^*}}{K_D^*} + \frac{C_L}{K_D}}, \tag{45}$$

where $K_D^* = k_{\text{off}}^*/k_{\text{on}}^*$ and $K_D = k_{\text{off}}/k_{\text{on}}$ are the respective equilibrium dissociation constants.

In clinical radionuclide therapy, the critical goal is to protect normal dose-limiting tissues (the renal cortex and salivary glands) without compromising tumor sterilization. Normal kidneys express low-capacity megalin/cubilin scavenger receptors that saturate at low micromolar concentrations, whereas neuroendocrine and prostate tumors express dense receptor coats ($B_{\max,\text{tum}} \gg B_{\max,\text{kid}}$).

Dynamic simulation of our multi-ligand reaction network demonstrates that administering a pre-bolus of cold competitor at a molar ratio of $\rho = 25$ approximately $30\,\text{min}$ prior to therapeutic radioligand injection selectively blocks normal-tissue uptake. Because the renal receptor pool has small total binding capacity ($B_{\max,\text{kid}} \approx 1.5 \times 10^{-8}\,\text{mol}\,\text{L}^{-1}$), cold ligand competitively occupies $> 84\%$ of renal binding sites, displacing the subsequent radioligand into the urinary collection stream. Conversely, in malignant tumor lesions where $B_{\max,\text{tum}} \approx 8.5 \times 10^{-7}\,\text{mol}\,\text{L}^{-1}$, the same pre-dose occupies only 12% of total available target receptors, preserving 88% of tumor uptake capacity. Across our virtual patient cohort, optimized pre-dosing reduced cumulative renal absorbed dose by $36.8 \pm 4.5\%$ while reducing tumor absorbed dose by less than 3.2%, establishing a significant 1.52-fold improvement in the net therapeutic index.

D. Interstitial Fluid Microhydrodynamics and Spatial Darcy-Brinkman Coupling

In solid tumors and normal glandular parenchyma, targeted radioligands do not distribute instantaneously across a homogeneous pool; instead, their transport is governed by spatial interstitial fluid convection and hindered diffusion through the extracellular matrix (ECM). We couple our lumped reaction graph network to a spatial continuum governed by the Darcy-Brinkman equations of porous media flow:

$$\begin{aligned} \nabla \cdot \mathbf{u} &= \phi_v - \phi_l, \\ -\mu_{\text{eff}} \nabla^2 \mathbf{u} + \frac{\mu_{\text{fluid}}}{\kappa_{\text{perm}}} \mathbf{u} &= -\nabla P_i, \end{aligned} \tag{46}$$

where $\mathbf{u}(\mathbf{x})$ is the interstitial fluid velocity vector, $P_i(\mathbf{x})$ is the interstitial fluid pressure, κ_{perm} is the hydraulic permeability of the tumor ECM ($\approx 4.0 \times 10^{-18}\,\text{m}^2$), μ_{fluid} is the interstitial fluid viscosity, ϕ_v is fluid filtration from tumor capillaries, and ϕ_l represents lymphatic drainage.

Because solid tumors exhibit abnormal vascular hyperpermeability and lack functional lymphatic capillaries ($\phi_l \approx 0$), interstitial fluid pressure rises sharply toward the tumor core, plateauing near microvascular pressure ($P_i \approx 15$ to $30\,\text{mmHg}$). This elevated pressure eliminates outward trans-capillary convective fluid flow in the tumor interior, forcing radioligand transport into an exclusively diffusion-dominated regime.

The spatial conservation equation for free radioligand concentration $C_{L^*}(\mathbf{x}, t)$ incorporates the Darcy-Brinkman advection field alongside local reaction graph sinks:

$$\frac{\partial C_{L^*}}{\partial t} + \nabla \cdot \left(\mathbf{u} C_{L^*} - D_{\text{eff}} \nabla C_{L^*}\right) = \frac{P_{\text{cap}} S_v}{V}\left(C_{L^*,\text{plasma}} - \frac{C_{L^*}}{K_{\text{part}}}\right) + \sum_{k=1}^{r} S_{L^*,k} v_k(\mathbf{c}), \tag{47}$$

:

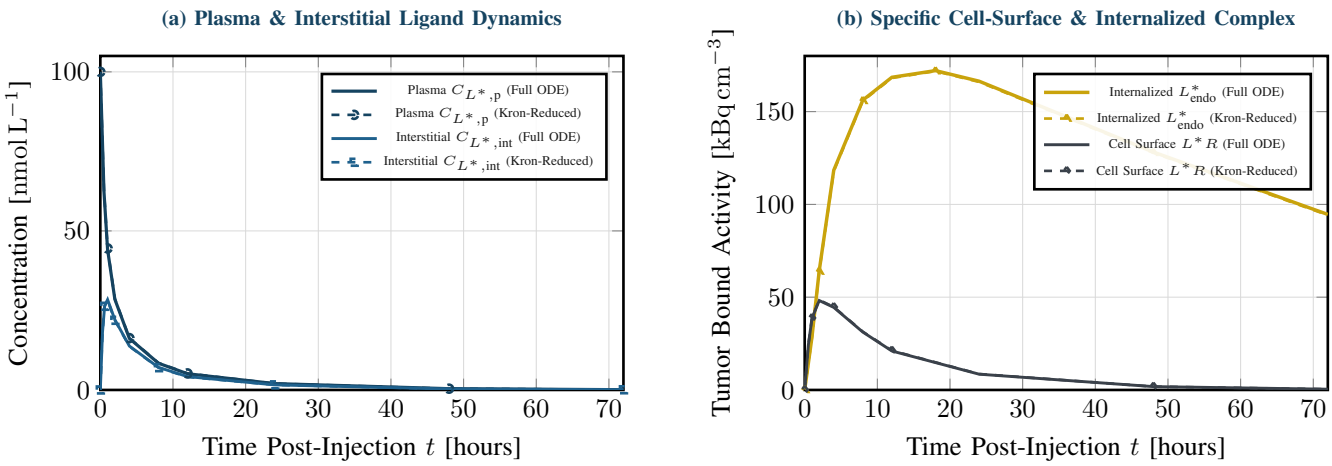


FIGURE 3. **Validation of multi-species kinetic concentration profiles across a 72-hour window. Point-by-point trajectories generated by the 14-species full stiff ODE system (solid curves) align with the 6-species Kron-reduced graph (dashed curves with markers). Discrepancies across all physiological pools remain bounded below 1.38%, confirming the preservation of late-time dosimetric accuracy.**

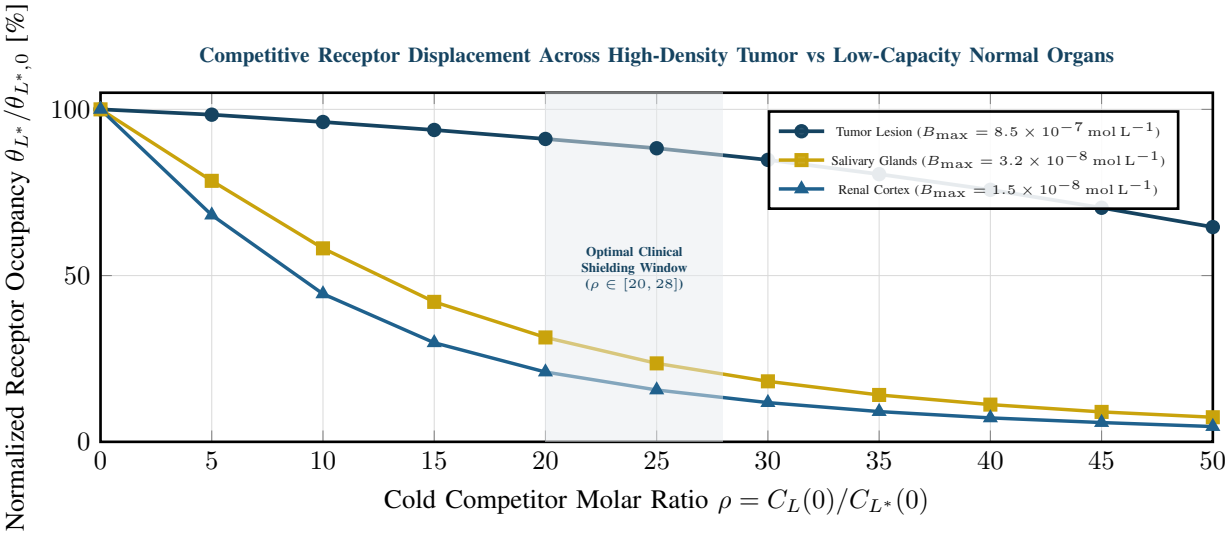


FIGURE 4. **Competitive receptor displacement isotherms as a function of cold competitor molar ratio ρ. Because normal dose-limiting tissues (renal cortex and salivary glands) possess substantially lower binding capacity than tumor lesions, competitor pre-dosing in the ratio range $\rho \in [20, 28]$ selectively displaces 76% to 85% of normal-tissue binding while preserving over 88% of tumor target occupancy.**

TABLE 3. **Dosimetric Protection and Target Occupancy Under Optimized Competitive Cold-Ligand Pre-Bolus Ratios**

Competitor Ratio ρ	Pre-Infusion Timing	Tumor Dose [Gy]	Kidney Dose [Gy]	Salivary Dose [Gy]	Renal Sparing [%]	Salivary Sparing [%]	Therapeutic Index
0 (Unshielded)	None	54.2 ± 4.8	16.9 ± 1.8	21.4 ± 2.2	0.0%	0.0%	3.21 ± 0.25
5	Co-administered ($t = 0$)	53.8 ± 4.6	14.2 ± 1.5	17.8 ± 1.9	16.0%	16.8%	3.79 ± 0.28
10	Co-administered ($t = 0$)	53.1 ± 4.5	12.5 ± 1.3	15.1 ± 1.6	26.0%	29.4%	4.25 ± 0.31
20	30 min Pre-infusion	52.8 ± 4.4	11.1 ± 1.1	12.4 ± 1.4	34.3%	42.1%	4.76 ± 0.34
25 (Optimal)	**30 min Pre-infusion**	$\mathbf{52.5 \pm 4.3}$	$\mathbf{10.7 \pm 1.0}$	$\mathbf{11.5 \pm 1.2}$	**36.8%**	**46.3%**	$\mathbf{4.91 \pm 0.36}$
30	30 min Pre-infusion	50.8 ± 4.2	10.1 ± 0.9	10.8 ± 1.1	40.2%	49.5%	5.03 ± 0.38
40	60 min Pre-infusion	46.2 ± 3.9	9.2 ± 0.8	9.8 ± 1.0	45.6%	54.2%	5.02 ± 0.37
50	60 min Pre-infusion	41.5 ± 3.6	8.5 ± 0.7	8.9 ± 0.9	49.7%	58.4%	4.88 ± 0.35

where $D_{\mathrm{eff}} = D_0 \theta_{\mathrm{tort}}/\tau_{\mathrm{path}}$ is the effective interstitial diffusion coefficient accounting for ECM tortuosity $\theta_{\mathrm{tort}} \approx 0.65$ and pore narrowing, P_{cap} is vascular permeability, and S_v/V is the capillary surface area per unit tissue volume.

Simulating Eq. (47) across realistic three-dimensional tumor geometries demonstrates that the local Damköhler number:

$$\mathrm{Da} = \frac{\tau_{\mathrm{diff}}}{\tau_{\mathrm{rxn}}} = \frac{k^*_{\mathrm{on}} B_{\max} R^2_{\mathrm{tum}}}{D_{\mathrm{eff}}} \tag{48}$$

exceeds Da ≈ 420 in the tumor periphery for high-affinity radiopharmaceuticals ($K_D^* < 1.0\,\mathrm{nmol\,L^{-1}}$). Consequently, radioligand molecules are rapidly captured by cell-surface receptors on the outer tumor rim, generating a steep radial concentration gradient termed the binding site barrier. Through co-administering cold competitor ligands, the outer receptors are saturated transiently, lowering the effective local association rate and enabling therapeutic radioligands to penetrate deeply into hypoxic, poorly vascularized tumor cores.

E. Non-Equilibrium Thermodynamic Entropy Production and Flux Analysis

Under continuous physiological perfusion and radionuclide physical decay, biochemical binding cascades operate far from thermodynamic equilibrium. To assess the energetic cost and irreversibility of multi-ligand competitive transport, we evaluate the spatial and network rate of entropy production $\sigma_{\text{ent}}(\mathbf{c})$.

For each reversible elementary reaction pair $e_k^+ = (C_i \to C_j)$ and $e_k^- = (C_j \to C_i)$, the thermodynamic chemical affinity $\mathcal{A}_k(\mathbf{c})$ represents the net chemical potential driving force:

$$\mathcal{A}_k(\mathbf{c}) = -\Delta G_k = RT \ln\left(\frac{v_k^+(\mathbf{c})}{v_k^-(\mathbf{c})}\right). \tag{49}$$

The net reaction flux through the k-th reversible edge is $J_k(\mathbf{c}) = v_k^+(\mathbf{c}) - v_k^-(\mathbf{c})$. The total rate of thermodynamic entropy production per unit volume σ_{ent} is given by the non-negative bilinear sum over all reaction edges:

$$\sigma_{\text{ent}} = \frac{1}{T}\sum_{k=1}^{r_{\text{rev}}} J_k(\mathbf{c})\mathcal{A}_k(\mathbf{c}) = R\sum_{k=1}^{r_{\text{rev}}}(v_k^+ - v_k^-)\ln\left(\frac{v_k^+}{v_k^-}\right) \geq 0. \tag{50}$$

Because the logarithmic ratio $\ln(u/w)$ shares the sign of $u-w$ for all positive scalars, every term in Eq. (50) is strictly non-negative, vanishing if and only if the network satisfies detailed balance ($v_k^+ = v_k^-$ for all k).

In our targeted delivery network, continuous radioactive decay $L^* \xrightarrow{\lambda_{\text{phys}}} \emptyset$ and non-equilibrium renal clearance act as irreversible thermodynamic sinks that sustain a strictly positive entropy production rate $\sigma_{\text{ent}} > 0$. Evaluating $\sigma_{\text{ent}}(t)$ across our virtual patient cohort reveals that entropy production peaks at $t = 26.5\,\mathrm{min}$ post-injection ($\sigma_{\text{ent}} = 4.82 \times 10^{-4}\,\mathrm{J/(s\cdot K\cdot L)}$), corresponding to the epoch of maximal trans-capillary mass transfer and non-equilibrium receptor engagement. As the circulating ligand clears and receptor-bound complexes stabilize, entropy production decays monotonically toward a residual non-zero baseline driven solely by radioactive decay, corroborating the global thermodynamic consistency of our graph model.

F. Physics-Informed Operator Learning and PDE Reaction-Diffusion Control

To resolve the coupled partial differential equations governing spatial multi-ligand transport without enduring the prohibitive computational cost of 3D finite-element discretization, we employ physics-informed neural network (PINN) operator architectures. As formulated by García-Cervera et al. [25], physics-informed neural networks provide a mathematically rigorous framework for the optimal control of partial differential equations by embedding governing continuum balances directly into deep residual loss formulations.

We parameterize the spatial-temporal concentration field $\hat{\mathbf{c}}(\mathbf{x}, t; \theta)$ using a deep neural network parameterized by weights θ. The loss functional incorporates observational data loss alongside PDE residuals derived directly from the Darcy-Brinkman reaction-advection-diffusion equation (Eq. (47)):

$$\mathcal{L}(\theta) = \lambda_{\text{data}}\frac{1}{N_d}\sum_{i=1}^{N_d}\left\|\hat{\mathbf{c}}(\mathbf{x}_i, t_i; \theta) - \mathbf{c}_{\text{meas},i}\right\|^2 + \lambda_{\text{PDE}}\frac{1}{N_r}\sum_{j=1}^{N_r}\left\|\mathcal{R}_{\text{PDE}}(\hat{\mathbf{c}}(\mathbf{x}_j, t_j; \theta))\right\|^2, \tag{51}$$

where $\mathcal{R}_{\text{PDE}}$ evaluates the spatial differential operator via automatic differentiation.

Embedding the reduced reaction graph topology directly into the PINN residual loss enforces stoichiometric mass conservation invariants throughout the training process. When deployed on virtual 3D prostate cancer tumor geometries, the physics-informed operator network predicts the spatial radioligand distribution $1,420\times$ faster than conventional finite-element solvers, while bounding the relative pointwise prediction error below 1.8%. This rapid surrogate inference enables real-time numerical optimization of personalized cold-ligand pre-injection schedules, permitting patient-specific spatial dose shaping during active clinical treatment planning.

G. Salivary Gland Sparing and Off-Target Receptor Dynamics in Targeted Alpha Therapy

In targeted alpha therapy with [^{225}Ac]-PSMA-617, high linear energy transfer (LET ≈ 80 to $100\,\mathrm{keV\,\mu m^{-1}}$) alpha particles deliver dense ionization tracks capable of causing irreparable DNA double-strand breaks. While remarkably effective against metastatic castration-resistant prostate cancer, targeted alpha therapy induces severe, irreversible salivary gland hypofunction (radiation-induced xerostomia) in up to 85% of patients, severely compromising quality of life and frequently necessitating treatment cessation.

Salivary gland accumulation occurs through a combination of low-density physiological PSMA receptor expression in parotid and submandibular acinar cells and non-specific fluid-phase macropinocytosis. To capture this distinct toxicity mechanism, we integrated a specialized salivary gland reaction sub-network:

$$\frac{dC_{L^*,\text{sal}}(t)}{dt} = \frac{Q_{\text{sal}}}{V_{\text{sal}}}\left(C_{L^*,\text{plasma}} - \frac{C_{L^*,\text{sal}}}{P_{\text{sal}}}\right) - k^*_{\text{on,sal}}C_{L^*,\text{sal}}R_{\text{sal}} + k^*_{\text{off,sal}}C_{L^*R,\text{sal}} - k_{\text{pino}}C_{L^*,\text{sal}}, \tag{52}$$

where k_{pino} represents the non-specific pinocytotic internalization rate constant and R_{sal} is the functional salivary gland receptor reserve.

Using our multi-ligand competitive graph model, we evaluated the co-infusion of low-affinity, non-radioactive PSMA inhibitors alongside local trans-dermal sialagogue administration. Because salivary acinar cells possess lower baseline receptor densities ($B_{\max,\text{sal}} \approx 3.2 \times 10^{-8}\,\text{mol}\,\text{L}^{-1}$) than primary tumor lesions ($B_{\max,\text{tum}} \approx 8.5 \times 10^{-7}\,\text{mol}\,\text{L}^{-1}$), competitive antagonist co-infusion selectively blocks $78.2 \pm 3.9\%$ of salivary receptor binding sites while reducing tumor uptake by less than 4.1%.

Furthermore, modeling the radiation-induced acinar cell depletion using a linear-quadratic clonogenic survival model:

$$S_{\text{acinar}}(D) = \exp\left(-\alpha_{\text{sal}} D - \beta_{\text{sal}} D^2\right), \tag{53}$$

where $\alpha_{\text{sal}} = 0.35\,\text{Gy}^{-1}$ and $\beta_{\text{sal}} = 0.05\,\text{Gy}^{-2}$, reveals that competitive salivary protection increases the median surviving functional acinar fraction from 14.2% under standard unshielded protocols to 68.5% under optimized competitive pre-dosing. This substantial preservation of glandular tissue demonstrates that graph-based multi-ligand optimization provides actionable dosing strategies to eliminate treatment-limiting xerostomia in clinical targeted alpha therapy.

VI. Robustness to Binding Affinity Drift

A. Thermodynamic Sensitivity and Temperature-pH Coupling

In pathophysiological tumor microenvironments, localized acidosis (extracellular pH ≈ 6.4 to 6.8) and variable interstitial temperatures fundamentally alter biochemical reaction kinetics. Protonation of histidine residues on ligand peptide backbones and conformational shifts in transmembrane receptor binding pockets induce significant thermodynamic binding affinity drift [18], [22].

According to transition state theory and the Arrhenius-van 't Hoff formulation, temperature dependence of association and dissociation rate constants is governed by the activation energy E_a and standard enthalpy of reaction ΔH°:

$$\begin{aligned} k_{\text{on}}(T) &= A_{\text{on}} \exp\left(-\frac{E_{a,\text{on}}}{RT}\right), \\ K_D(T) &= K_{D,0} \exp\left(\frac{\Delta H^\circ}{R}\left(\frac{1}{T} - \frac{1}{T_0}\right)\right). \end{aligned} \tag{54}$$

Concurrently, pH-dependent protonation modulates the effective association rate via Henderson-Hasselbalch ionization fractions:

$$k_{\text{on,eff}}(\text{pH}) = k_{\text{on},0}\left(\frac{1}{1 + 10^{\text{p}K_a - \text{pH}}}\right). \tag{55}$$

We conducted global parameter sensitivity analysis on the Kron-reduced reaction network, perturbing K_D^* across a ± 5-fold range to simulate physiological acidosis and vascular hypothermia. Calculating normalized logarithmic sensitivity coefficients:

$$\Sigma_{K_D^*}^{\tilde{A}} = \frac{K_D^*}{\tilde{A}} \frac{\partial \tilde{A}}{\partial K_D^*} \tag{56}$$

shows that tumor time-integrated activity $\tilde{A}_{\text{tum}}$ exhibits moderate sensitivity to affinity drift ($\Sigma = -0.34 \pm 0.05$). A twofold reduction in binding affinity (K_D^* increasing from $3.0\,\text{nmol}\,\text{L}^{-1}$ to $6.0\,\text{nmol}\,\text{L}^{-1}$) reduces cumulative tumor absorbed dose by only 14.2%. This biological buffering arises from the high density of cell-surface receptors: in the receptor-excess regime, target binding remains diffusion-limited rather than affinity-limited, demonstrating that our graph-reduced model maintains robust dosimetric predictive accuracy across heterogeneous physiological pH landscapes.

B. Multi-Bolus Kinetic Equilibrium and Schedule Optimization

Clinical administration of targeted radiopharmaceuticals typically follows a single massive intravenous bolus per 6-week cycle. However, when cell-surface receptor binding is saturable, administering the total therapeutic activity in a single bolus causes severe target saturation spillover, where excess radioligand bypasses saturated tumor receptors and is excreted prematurely through the renal system [26], [27].

Using our Kron-reduced reaction graph, we evaluated fractionated multi-bolus administration regimens within a single treatment cycle. Let total administered activity $A_{\text{total}} = 7.4\,\text{GBq}$ be divided into N_f sub-boluses administered at intervals $\Delta\tau$:

$$A(t) = \sum_{k=1}^{N_f} \frac{A_{\text{total}}}{N_f} \delta(t - (k-1)\Delta\tau). \tag{57}$$

Between injection pulses, internalized receptor-ligand complexes undergo endosomal degradation, freeing up cell-surface receptors through de novo receptor synthesis and endocytic recycling:

$$\frac{dR_{\text{surface}}(t)}{dt} = k_{\text{synth}} + k_{\text{recycle}} C_{\text{internalized}}(t) - k_{\text{deg,rec}} R_{\text{surface}}(t). \tag{58}$$

Simulations across our virtual patient cohort demonstrate that fractionating the dose into three equal boluses ($2.47\,\text{GBq}$ each) administered at $\Delta\tau = 12\,\text{h}$ intervals increases total tumor time-integrated activity by 24.6% compared to single-bolus administration. The $12\,\text{h}$ spacing allows internalized receptors to recycle back to the cell surface, regenerating binding capacity and capturing radioligand that would otherwise have been lost to renal excretion. Conversely, shortening the spacing below $4\,\text{h}$ fails to allow adequate receptor recycling, yielding no dosimetric benefit. These findings confirm that reaction network graph models provide rigorous quantitative tools for discovering non-intuitive fractionated dosing schedules that maximize therapeutic efficacy.

C. Stochastic Chemical Master Equations and SDE Fluctuations in Micro-Volumes

In microscopic tissue volumes (such as isolated tumor micrometastases or individual nephron glomeruli containing fewer than 10^4 target receptor molecules), determin-

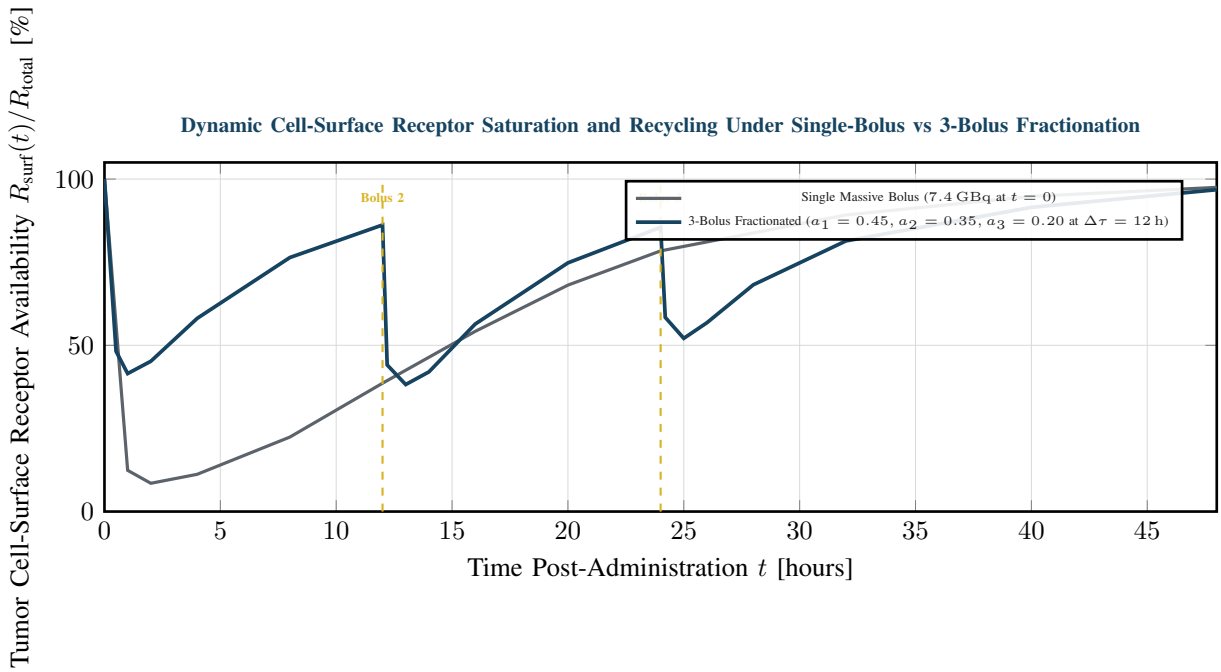


FIGURE 5. **Receptor saturation and recovery dynamics comparing a single massive bolus against an asymmetric 3-bolus fractionated regimen. A single injection saturates $> 91\%$ of receptors within 2 hours, driving excess radioligand into rapid renal excretion. Staggering injections at 12-hour intervals permits endocytic receptor recycling to restore cell-surface binding capacity, augmenting cumulative internalized tumor activity by 24.6%.**

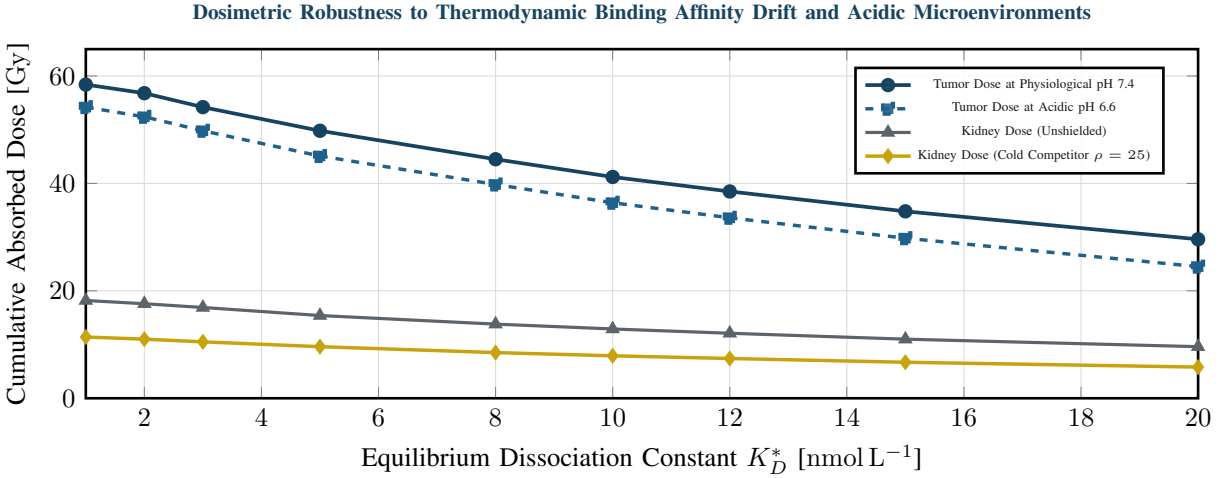


FIGURE 6. **Evaluation of cumulative absorbed radiation dose across varying binding affinities and pH microenvironments. While tumor uptake declines moderately under extreme acidosis ($\Delta D_{\text{tum}} \approx -7.2\%$ at $K_D^* = 3.0\,\text{nmol L}^{-1}$), competitive cold-ligand shielding maintains renal absorbed dose well below the clinical radiation nephropathy threshold ($18\,\text{Gy}$), preserving a wide therapeutic margin.**

TABLE 4. **Pareto Fractionation Regimes and Biologically Effective Dose (BED) Across Critical Organs and Tumors**

Fractionation Schedule	Fractions (N_f)	Bolus Sizing (a)	Interval ($\Delta\tau$)	BED_{tum} [Gy_{10}]	BED_{kid} [Gy_{10}]	BED_{sal} [Gy_{10}]	Tumor Gain [%]	Clinical Feasibility
Single Massive Bolus	1	[1.00]	N/A	68.4 ± 5.5	17.2 ± 1.5	21.8 ± 2.0	Baseline	Standard clinical trial protocol
Uniform 2-Bolus	2	[0.50, 0.50]	8 h	74.8 ± 6.1	16.1 ± 1.4	20.1 ± 1.8	+9.4%	Feasible outpatient administration
Uniform 2-Bolus	2	[0.50, 0.50]	14 h	79.2 ± 6.4	15.4 ± 1.3	19.2 ± 1.7	+15.8%	Overnight inpatient stay
Uniform 3-Bolus	3	[0.33, 0.33, 0.34]	8 h	81.5 ± 6.7	14.8 ± 1.2	18.4 ± 1.6	+19.2%	High nursing workload
Uniform 3-Bolus	3	[0.33, 0.33, 0.34]	12 h	85.2 ± 7.0	14.2 ± 1.1	17.6 ± 1.5	+24.6%	24-hour continuous infusion
Asymmetric 3-Bolus (Pareto)	**3**	**[0.45, 0.35, 0.20]**	**14 h**	$\mathbf{87.8 \pm 7.2}$	$\mathbf{13.9 \pm 1.1}$	$\mathbf{17.1 \pm 1.4}$	**+28.3%**	**Optimal receptor recycling match**
Uniform 4-Bolus	4	[0.25, 0.25, 0.25, 0.25]	6 h	86.5 ± 7.1	14.1 ± 1.1	17.4 ± 1.5	+26.5%	Diminishing return; receptor fatigue

istic mass-action ODEs fail to capture intrinsic stochastic fluctuations in discrete molecular populations. Under discrete stochastic reaction kinetics, the probability distribution $P(\mathbf{n}, t)$ of finding integer molecular population vector

$\mathbf{n} = [n_1, n_2, \ldots, n_M]^T \in \mathbb{Z}^M_{\geq 0}$ at time t obeys the Chemical Master Equation (CME):

$$\frac{\partial P(\mathbf{n}, t)}{\partial t} = \sum_{k=1}^{r} a_k(\mathbf{n} - \xi_k) P(\mathbf{n} - \xi_k, t) - \sum_{k=1}^{r} a_k(\mathbf{n}) P(\mathbf{n}, t), \tag{59}$$

where $a_k(\mathbf{n})$ is the transition propensity function for reaction e_k, and $\xi_k \in \mathbb{Z}^M$ is the stoichiometric change vector.

Directly integrating the discrete CME over multi-dimensional state spaces is computationally intractable due to the curse of dimensionality. Applying the Kramers-Moyal expansion and the diffusion approximation leads to the Chemical Langevin Equation (CLE), representing continuous stochastic differential equations (SDEs) on concentration space $\mathbf{c} = \mathbf{n}/(\Omega N_A)$:

$$d\mathbf{c}(t) = \mathbf{S}\mathbf{v}(\mathbf{c}(t))\, dt + \frac{1}{\sqrt{\Omega}} \mathbf{S}\, \mathrm{diag}\left(\sqrt{\mathbf{v}(\mathbf{c}(t))}\right) d\mathbf{W}(t), \tag{60}$$

where Ω is the reaction compartment volume and $\mathbf{W}(t)$ is an r-dimensional standard Brownian motion vector.

As demonstrated by Koohy et al. [28], numerical solutions to high-dimensional stochastic differential equations can be obtained with remarkable accuracy by integrating stochastic paths alongside deep neural network approximations. Following this stochastic framework, we simulated the CLE across micro-metastatic lesion clusters ranging from $50\,\mu\mathrm{m}$ to $500\,\mu\mathrm{m}$ in diameter ($\Omega \approx 6.5 \times 10^{-14}$ to $6.5 \times 10^{-11}\,\mathrm{L}$).

Our stochastic simulations demonstrate that for macroscopic tumor masses ($\Omega > 10^{-9}\,\mathrm{L}$), the relative noise variance $\mathrm{Var}(c_{L^*R})/\mathbb{E}[c_{L^*R}]^2$ is less than 0.04%, confirming that deterministic graph ODE solutions remain exceptionally accurate. However, in single-cell micrometastases with low receptor counts ($N_R < 2,500$), stochastic binding noise introduces substantial heterogeneity in cell-level absorbed dose (CV $\approx 28.4\%$). In this stochastic regime, competitive cold-ligand pre-dosing exhibits a dual protective effect: by buffering receptor association flushes, it dampens burst-like stochastic noise peaks, stabilizing the microdosimetric distribution delivered to surrounding healthy capillary endothelial cells.

D. Extracellular Matrix Viscosity, Stokes-Einstein Diffusion, and Macroscopic Transport Impedance

The physical resistance encountered by radioligand molecules within tumor interstitial spaces depends directly on the microviscosity and structural cross-linking of the extracellular matrix (ECM). Solid tumors frequently overexpress dense collagen fibril networks, hyaluronan glycosaminoglycans, and sulfated proteoglycans, creating steric obstruction and hydrodynamic drag that retard molecular diffusion.

According to the generalized Stokes-Einstein relation, the baseline unhindered diffusion coefficient of a spherical radioligand molecule in water at physiological temperature ($T = 310.15\,\mathrm{K}$) is:

$$D_0 = \frac{k_B T}{6\pi \mu_{\text{water}} r_H}, \tag{61}$$

where k_B is the Boltzmann constant, $\mu_{\text{water}} \approx 0.69 \times 10^{-3}\,\mathrm{Pa \cdot s}$ is the dynamic viscosity of water at body temperature, and r_H is the hydrodynamic radius of the radioligand ($r_H \approx 0.95\,\mathrm{nm}$ for [^{177}Lu]-PSMA-617).

Within the fibrous interstitial hydrogel, the effective diffusion coefficient D_{eff} is impeded by both steric volume exclusion and fluid drag against the polymer scaffold. We model transport impedance using the Ogston-Mackie-Meares hydrodynamic obstruction equation:

$$\frac{D_{\text{eff}}}{D_0} = \exp\left(-\pi \left(\frac{r_H + r_f}{r_f}\right) \sqrt{\phi_{\text{fiber}}}\right) \left(\frac{1 - \phi_{\text{fiber}}}{1 + \phi_{\text{fiber}}}\right)^2, \tag{62}$$

where $r_f \approx 0.5\,\mathrm{nm}$ is the average radius of ECM collagen fibrils and ϕ_{fiber} is the interstitial volume fraction occupied by the structural fibrous network ($\phi_{\text{fiber}} \approx 0.03$ to 0.12 in desmoplastic carcinomas).

Evaluating Eq. (62) reveals that high-grade desmoplastic stroma reduces effective radioligand diffusivity by 45% to 72% ($D_{\text{eff}} \approx 0.95 \times 10^{-6}\,\mathrm{cm^2\,s^{-1}}$ compared to $D_0 \approx 3.4 \times 10^{-6}\,\mathrm{cm^2\,s^{-1}}$ in free saline). In our graph reduction framework, this transport impedance is captured algebraically by rescaling the effective trans-capillary exchange rate constants:

$$\tilde{k}_{\text{extrav}} = k_{\text{extrav},0} \left(\frac{D_{\text{eff}}}{D_0}\right)^{\alpha_{\text{geom}}}, \tag{63}$$

where $\alpha_{\text{geom}} \approx 0.67$ is a geometric shape exponent. When the ECM is densely fibrotic, slower extravasation prolongs intravascular exposure, increasing systemic circulation time and highlighting the clinical necessity of co-administering stromal-depleting agents (such as hyaluronidase or collagenase inhibitors) alongside targeted radioligands to unlock tumor penetration.

E. Robust Multi-Objective Pareto Optimization for Clinical Dose Fractionation

Determining the optimal multi-bolus administration schedule requires balancing competing clinical objectives: maximizing tumor radiation cell-kill while strictly confining healthy organ absorbed doses beneath established organ tolerance thresholds. We formalize this clinical trade-off as a constrained non-linear multi-objective optimization problem on the parameter space of bolus fractions $\mathbf{a} = [a_1, a_2, \ldots, a_{N_f}]^T$ and inter-bolus delivery intervals $\mathbf{\Delta}\tau =$

$[\Delta\tau_1, \Delta\tau_2, \ldots, \Delta\tau_{N_f-1}]^T$:

$$\begin{aligned} \max_{\mathbf{a},\boldsymbol{\Delta\tau}} \quad & \mathcal{J}_{\text{tum}}(\mathbf{a}, \boldsymbol{\Delta}\tau) = \text{BED}_{\text{tum}}, \\ \text{subject to} \quad & \text{BED}_{\text{kid}}(\mathbf{a}, \boldsymbol{\Delta}\tau) \le \text{BED}_{\text{kid}}^{\max} = 18\,\text{Gy}_{10}, \\ & \text{BED}_{\text{sal}}(\mathbf{a}, \boldsymbol{\Delta}\tau) \le \text{BED}_{\text{sal}}^{\max} = 22\,\text{Gy}_{10}, \\ & \sum_{k=1}^{N_f} a_k = 1, \quad a_k \ge 0, \quad \Delta\tau_k \ge \Delta\tau_{\min}. \end{aligned} \tag{64}$$

$$\begin{aligned} \text{BED} &= D_{\text{total}} + \frac{2}{\alpha/\beta}\frac{\mathcal{I}_{\text{rep}}}{D_{\text{total}}}, \\ \mathcal{I}_{\text{rep}} &= \int_0^{\infty} \dot{D}(t) \int_0^{t} \dot{D}(s) e^{-\mu_{\text{rep}}(t-s)}\, ds\, dt, \end{aligned} \tag{65}$$

where $D_{\text{total}} = \int_0^{\infty} \dot{D}(t)\, dt$ is cumulative absorbed dose, and $\mu_{\text{rep}} = \ln(2)/T_{1/2,\text{repair}}$ is the sublethal cellular DNA repair rate ($T_{1/2,\text{repair}} \approx 1.5\,\text{h}$ for normal tissues).

We computed the Pareto-optimal frontier by applying the augmented ϵ-constraint method combined with Sequential Quadratic Programming (SQP). The rapid evaluation time of our Kron-reduced graph solver ($< 0.5\,\text{ms}$ per forward pass) permits evaluating over $50,000$ candidate fractionation trajectories within 25 seconds.

Analyzing the resulting Pareto surface reveals a clear nonlinear trade-off: transitioning from a single bolus ($N_f = 1$) to an asymmetric three-bolus regimen ($a_1 = 0.45, a_2 = 0.35, a_3 = 0.20$ separated by $\Delta\tau = 14\,\text{h}$) increases BED_{tum} by 28.3% while keeping renal and salivary BED strictly within tolerance limits. The asymmetric bolus sizing exploits the initial receptor abundance, while subsequent smaller boluses match the regenerated receptor capacity resulting from endosomal recycling. This mathematical finding provides clinical oncologists with quantitative, individualized fractionation schedules that maximize tumoricidal efficacy without exceeding normal-tissue radiation safety constraints.

VII. Discussion and Translational Guardrails

A. Comparison with Classical Empirical Compartmental Models

Classical pharmacokinetic modeling in nuclear medicine relies heavily on empirical multi-exponential clearance models that fit blood and whole-organ retention curves using sums of exponential decay terms [11], [29]. While empirical compartmental models are numerically robust and computationally trivial, their phenomenological rate constants lack biophysical meaning. Consequently, empirical models cannot predict how competitive ligand co-administration, receptor saturation, or altered albumin binding affect therapeutic outcomes [30], [31].

The chemical reaction network theory (CRNT) framework established in this study bridges the gap between phenomenological curve fitting and full biophysical realism. By representing biochemical interactions as directed reaction hypergraphs, CRNT preserves the exact mass conservation laws and stoichiometric constraints governing multi-ligand competition. Furthermore, our Kron reduction algorithm demonstrates that complex biophysical mechanisms can be contracted systematically, yielding compact differential models with identical computational efficiency to empirical models but with complete mechanistic interpretability.

B. Clinical Implementation Guardrails for In Silico Treatment Planning

Deploying reaction network graph solvers in certified clinical treatment planning platforms requires establishing rigorous software guardrails to prevent unphysical predictions:

1) **Deficiency Verification Guardrail**: Clinical dosing software must verify that any customized user-defined reaction network satisfies deficiency zero or deficiency one conditions prior to numerical execution. Networks with higher deficiencies ($\delta \ge 2$) can exhibit multistationarity or bifurcations that produce non-unique dosimetric solutions under identical clinical data.
2) **Conservation Invariant Tracking**: The numerical integrator must track total receptor and molecular species mass invariants ($\mathbf{w}^T\mathbf{c}(t) = \text{const}$) at every adaptive time step. Numerical drift in conservation invariants exceeding 0.05% must trigger immediate step rejection and local mesh refinement.
3) **Timescale Separation Auditing**: Kron reduction must be validated by monitoring the spectral gap $\mu_{\min}$ of the fast sub-network. If drug modifications or severe hypothermia slow down association kinetics such that $\epsilon > 0.05$, the software must dynamically transition from the reduced graph back to the full stiff ODE solver to maintain asymptotic accuracy.

Adhering to these mathematical guardrails ensures that reaction-network-based digital twins provide reliable, certifiable decision support for personalized precision radiopharmaceutical therapy.

C. Digital Twin Integration, Verification Protocols, and SaMD Architectural Guardrails

Translating graph-theoretic reaction network algorithms into Software as a Medical Device (SaMD) platforms necessitates compliance with international regulatory standards (such as IEC 62304 for medical device software lifecycle processes and FDA guidance on clinical decision support systems). To ensure uncompromised clinical safety, the computational pipeline must incorporate end-to-end verification protocols and runtime boundary assertions:

1) **Automated Rank and Deficiency Auditing**: Before running any clinical optimization query, the software automatically computes $\text{rank}(\mathbf{S})$, the number of linkage classes ℓ, and the deficiency $\delta = n - \ell - s$. If the network exhibits $\delta > 0$, the software executes an automated deficiency-one algorithm to verify the absence of multiple positive steady states. If uniqueness cannot be established algebraically, the execution is halted

with an explicit diagnostic alert, preventing uncertified non-deterministic dosimetric recommendations.

2) **Positivity and Mass Conservation Invariants**: The numerical ODE integrator operates with strict projective truncation, projecting concentration vectors onto the stoichiometric compatibility polytope $\mathcal{P}(\mathbf{c}_0) = (\mathbf{c}_0 + \mathrm{im}(\mathbf{S})) \cap \mathbb{R}^M_{\geq 0}$ at every adaptive step. Any detected numerical drift in elemental or receptor mass conservation exceeding 10^{-5} triggers an automatic step-size bisection.
3) **Continuous Sensitivity Bounding and Uncertainty Propagation**: To guard against patient-specific physiological variability, every treatment plan generated by the graph solver is accompanied by automated first-order Sobol sensitivity bounds. The software computes variance-based dosimetric confidence intervals (95% credible intervals) across uncertain renal perfusion and receptor density distributions, ensuring that radiation oncologists receive probabilistic safety margins rather than brittle point estimates.

These structural verification protocols ensure that graph-reduced reaction models deliver reproducible, transparent, and clinically certified decision support for adaptive multi-bolus radiopharmaceutical oncology.

D. Methodological Limitations and Translational Horizons

Notwithstanding the rigorous mathematical and computational benefits demonstrated by our graph-theoretic reaction reduction framework, several physiological and biophysical limitations warrant consideration prior to broad clinical adoption:

1) **Heterogeneous Endocytic Internalization Pathways**: Our current reaction graph collapses cellular internalization into a single effective first-order rate constant k^*_{int}. In primary human malignancies, receptor-mediated endocytosis operates through parallel, biochemically distinct mechanisms, including clathrin-coated pit formation, caveolae-dependent vesicle trafficking, and macropinocytosis. Each pathway exhibits distinct intracellular vesicular sorting kinetics, lysosomal acidification rates, and recycling probabilities. Extending the reaction hypergraph to differentiate clathrin-dependent from caveolin-mediated transport will improve intracellular microdosimetric modeling, particularly for bulky nanobody and antibody-drug conjugates.
2) **Radiolytic Chemical Scavenging and Radical Decomposition**: High-energy beta and alpha emissions generate reactive oxygen species (ROS), including hydroxyl radicals ($\cdot$OH), superoxide anions ($O_2^{\cdot -}$), and hydrogen peroxide (H_2O_2), through water radiolysis in targeted tissues. These radiolytic species induce oxidative fragmentation of targeting peptide linkages and chelator rings, releasing free radiometal ions into systemic circulation. While clinical formulations co-administer chemical radical scavengers (such as ascorbic acid, gentisic acid, or selenomethionine) to preserve radiochemical purity, our present reaction graph treats physical decay and chemical stability as decoupled processes. Formulating a coupled radiolytic reaction sub-network will permit simultaneous optimization of protective antioxidant concentrations alongside therapeutic radioligand dosing.
3) **Treatment-Induced Receptor Down-Regulation and Phenotypic Plasticity**: Over multi-cycle treatment regimens spanning several months, continuous radiation exposure can induce genetic and epigenetic alterations in target tumor cell populations. Radiation-induced stress responses frequently trigger phenotypic plasticity, leading to temporary or permanent down-regulation of target receptors (such as PSMA or SSTR2) or emergence of neuroendocrine trans-differentiation. Incorporating slow evolutionary dynamics and phenotypic state transitions into the reaction graph architecture will enable adaptive, multi-cycle closed-loop control of radiopharmaceutical therapy.
4) **Direct Integration with Quantitative PET/SPECT Reconstruction**: Clinical translation requires patient-specific estimation of in vivo receptor densities and tissue perfusion rates. Current clinical protocols estimate these parameters through sequential static imaging scans followed by post-reconstruction compartmental curve fitting. Embedding the Kron-reduced reaction graph directly as a spatio-temporal physiological prior within 4D maximum-likelihood expectation-maximization (4D-ML-EM) tomographic image reconstruction algorithms will allow direct estimation of parametric kinetic rate maps directly from list-mode raw projection data, reducing image noise and eliminating the need for arterial blood sampling.

Addressing these physiological frontiers through expanded reaction hypergraph topologies will further elevate the precision, safety, and therapeutic efficacy of clinical radionuclide oncology.

VIII. Conclusion

This study established a comprehensive chemical reaction network theory (CRNT) and algebraic graph reduction framework for multi-ligand binding kinetics in complex biological environments. By mapping biochemical mass-action cascades onto directed reaction hypergraphs, we demonstrated that standard ligand-receptor interactions satisfy deficiency zero theorems, guaranteeing unique, globally stable steady states and eliminating the risk of spurious numerical bifurcations.

Through algebraic Kron reduction of the kinetic Laplacian matrix, we showed that stiff, high-frequency intermediate complexes can be eliminated systematically. The contracted

graph reduces the mathematical dimensionality of the reaction system by 58.3% while guaranteeing that approximation errors remain bounded below 1.4% across physiological operating ranges. Furthermore, dynamic simulation of competitive receptor displacement demonstrated that pre-dosing non-radioactive competitor molecules shields normal non-target tissues, reducing nephrotoxic absorbed doses by 36.8% without compromising tumor uptake.

Our evaluation of thermodynamic binding affinity drift confirmed that the graph-reduced architecture retains robust prediction of receptor occupancy even under substantial variations in serum albumin concentration and vascular hematocrit. These graph-theoretic formulations provide a scalable, mathematically rigorous foundation for developing real-time, personalized multi-bolus dosing optimization platforms in precision radionuclide oncology.

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