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# Creation of a New Tumor Retention Constant: A New Physical Parameter Derived from the Classical Radioactive Decay Equation for the Mathematical Modeling of 177Lu-DOTATATE Therapy in Neuroendocrine Tumors

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**ABSTRACT**

The quantitative characterization of radiopharmaceutical retention within tumors remains one of the major challenges in Peptide Receptor Radionuclide Therapy (PRRT), as current mathematical models primarily describe physical radioactive decay while biological tumor retention is represented only indirectly through dosimetric quantities and time–activity curves. In this study, we propose a novel mathematical framework by introducing the Tumor Retention Constant ($\tau T$ ), an analytical parameter incorporated into the classical radioactive decay equation to explicitly describe the biological permanence of 177Lu-DOTATATE within neuroendocrine tumors. A complete mathematical derivation was developed, resulting in an explicit closed-form equation in which the proposed constant is analytically isolated and can be directly estimated from radioactive activity measurements. The proposed formulation was subsequently evaluated through six independent numerical simulations implemented in Python, investigating temporal activity evolution, three-dimensional spatial distribution, functional heat maps, analytical validation, sensitivity analysis, and the global response surface of the model. The numerical results demonstrated excellent mathematical consistency, analytical stability, and coherent behavior across all investigated retention scenarios, confirming the feasibility of the proposed formulation and highlighting the influence of biological retention on radiopharmaceutical kinetics. Unlike conventional dosimetric approaches, the proposed framework provides a new quantitative descriptor capable of separating biological tumor retention from intrinsic radioactive decay while preserving the physical properties of the radionuclide. The proposed Tumor Retention Constant establishes a new theoretical perspective for mathematical modeling in Nuclear Medicine and may provide the foundation for future developments in individualized dosimetry, quantitative molecular imaging, computational oncology, and precision radionuclide therapy.

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## Introduction

Neuroendocrine Tumors (NETs) comprise a heterogeneous group of neoplasms originating from neuroen-docrine cells distributed throughout multiple organs, particularly the gastrointestinal tract and pancreas. The overexpression of somatostatin receptors in these tumors has enabled the development of Peptide Receptor Radionuclide Therapy (PRRT), in which radiolabeled somatostatin analogs selectively deliver ionizing radiation to malignant cells while minimizing damage to surrounding healthy tissues. Among the available therapeutic radiopharmaceuticals, $^{177}$Lu-DOTATATE has become one of the most successful agents for the treatment of advanced NETs because of its favorable balance between therapeutic efficacy, radiation range, and clinical safety. Despite these advances, mathematical modeling of radiopharmaceutical behavior inside tumor tissue remains an important challenge, particularly regarding the quantitative description of biological retention after administration.

In the work of Roth et al., the authors investigated dosimetric quantities in neuroendocrine tumors during successive treatment cycles with $^{177}$Lu-DOTATATE, evaluating tumor activity, effective half-life, absorbed dose, and time–activity curves [1]. Their study demonstrated the importance of quantitative dosimetry for understanding the temporal evolution of therapeutic activity and optimizing radionuclide therapy. However, although effective half-life and absorbed dose constitute essential dosimetric quantities, the proposed methodology remained restricted to conventional parameters and did not introduce an analytical constant capable of explicitly representing biological tumor retention within the radioactive decay model. Consequently, tumor retention continues to be inferred indirectly from dosimetric measurements rather than quantified through an independent mathematical descriptor.

A different perspective was presented by Ardenfors et al., who proposed a simplified dosimetric methodology for kidneys and tumors during peptide receptor radionuclide therapy using $^{177}$Lu-labeled compounds [2]. Their objective was to reduce the complexity of image acquisition while preserving clinically acceptable dosimetric accuracy, thereby improving the feasibility of individualized treatment planning. Although this represents an

important contribution toward simplifying clinical workflows, the proposed methodology remains entirely based on conventional dosimetric calculations. No modification of the governing radioactive decay equation or introduction of a mathematical parameter describing biological tumor retention was proposed, leaving this aspect of radionuclide kinetics mathematically unexplored.

The relationship between tumor dosimetry and therapeutic efficacy was subsequently investigated by Alipour et al., who analyzed the association between absorbed dose, treatment response, and overall survival in patients undergoing $^{177}$Lu-DOTATATE therapy [3]. Their findings reinforced the clinical significance of patient-specific dosimetry and demonstrated that quantitative radiation delivery is closely associated with therapeutic outcome. Nevertheless, the study focused primarily on establishing clinical correlations between absorbed dose and treatment response rather than developing a mathematical model capable of explicitly quantifying radiopharmaceutical retention within tumor tissue. Therefore, the biological mechanisms governing radioactive permanence inside the lesion remained outside the scope of the proposed methodology.

The recommendations published by Gear et al. constitute one of the principal references for dosimetry involving $^{177}$Lu-labeled somatostatin receptor ligands [4]. Their work established standardized methodologies for image acquisition, quantitative analysis, absorbed dose calculation, and implementation of individualized dosimetry in clinical practice. These recommendations have substantially contributed to harmonizing dosimetric protocols among different institutions and have strengthened the role of quantitative imaging in radionuclide therapy. However, despite providing comprehensive guidance for dosimetric calculations, the recommendations maintain the classical mathematical description of radioactive decay and do not incorporate an analytical parameter capable of separating biological tumor retention from intrinsic radioactive decay.

More recently, Veregnaud et al. [?] reviewed current workflows employed for $^{177}$Lu dosimetry, emphasizing strategies to reduce imaging workload while preserving quantitative reliability. Their review highlighted recent advances in computational dosimetry, image acquisition protocols, and workflow optimization, demonstrating that personalized radionuclide therapy continues to evolve toward increasingly efficient quantitative methodologies. At the same time, the authors recognized that further methodological developments remain necessary to improve treatment individualization. Nevertheless, these advances continue to be centered on dosimetric optimization, image processing, and quantitative activity estimation, without proposing a new analytical parameter capable of explicitly representing tumor retention within the radioactive decay equation.

Taken together, these investigations have substantially advanced the fields of quantitative dosimetry, treatment planning, molecular imaging, and radionuclide therapy using $^{177}$Lu-DOTATATE. However, despite their important contributions, all of these methodologies rely on conventional descriptions of radioactive decay, absorbed dose, effective half-life, or time–activity curves. To the best of our knowledge, none of these studies proposes an analytical mathematical constant specifically developed to quantify biological tumor retention through direct incorporation into the governing radioactive decay equation. This limitation provides the primary scientific motivation for the present investigation.

Recent investigations have progressively shifted the focus of radionuclide therapy from conventional fixed-activity protocols toward individualized treatment strategies. In the work of Deshayes et al., the authors argued that peptide receptor radionuclide therapy should evolve toward patient-specific dosimetry, emphasizing that recent clinical evidence demonstrates a strong relationship between absorbed tumor dose and therapeutic outcome [5]. Furthermore, the authors discussed the need for multicenter studies capable of establishing dosimetry-guided treatment protocols instead of empirically fixed administered activities. Although this perspective represents an important step toward precision medicine, the proposed strategy remains centered on absorbed dose optimization and does not introduce an analytical mathematical parameter capable of explicitly quantifying biological tumor retention within the radioactive decay equation. Consequently, the biological permanence of the radiopharmaceutical inside tumor tissue continues to be indirectly represented through conventional dosimetric quantities rather than by a dedicated mathematical descriptor. :contentReference[oaicite:0]index=0

The recent review published by Poniatowska-Roszkowska et al. summarized the current concepts, clinical relevance, and future perspectives of dosimetry in 177Lu peptide receptor radionuclide therapy [6]. The authors reviewed the principal computational methodologies currently employed in Nuclear Medicine, including the MIRD formalism, voxel-based dosimetry, Monte Carlo simulations, artificial intelligence, and quantitative image analysis, demonstrating that individualized dosimetry is becoming one of the major research directions in radionuclide therapy. Nevertheless, despite presenting an extensive overview of modern computational approaches, the review highlights the need for new quantitative methodologies while maintaining the conventional mathematical description of radioactive decay. No analytical formulation capable of explicitly representing biological tumor retention through a dedicated mathematical constant was proposed.

Ramonaheng et al. investigated quantitative activity estimation and dosimetry in radiopharmaceuti-cal therapy, discussing calibration procedures, image quantification, reconstruction algorithms, uncertainty propagation, and computational dosimetric workflows [7]. Their study reinforces that accurate activity quantification constitutes the foundation of reliable internal dosimetry and personalized radionuclide therapy. However, although substantial advances have been achieved in quantitative image processing and absorbed dose calculation, the proposed methodologies remain focused on estimating radioactive activity and absorbed dose without extending the governing radioactive decay equation through the incorporation of a parameter describing biological tumor retention.

The mathematical treatment of time–activity curves has also received considerable attention in recent years. In the technical report presented by Götz, numerical strategies were developed for integrating time–activity curves in $^{177}$Lu therapies, improving cumulative activity estimation and voxel-based dosimetry calculations [8]. Such methodologies represent an essential component of quantitative radionuclide therapy because absorbed dose calculations fundamentally depend on accurate integration of radioactive activity over time. Nevertheless, despite the mathematical sophistication of the proposed numerical algorithms, tumor retention remains implicitly contained within the experimental time–activity curves and is not represented by an explicit analytical parameter derived from the radioactive decay model itself.

Similarly, Vergnaud et al. reviewed the current workflows employed in $^{177}$Lu dosimetry, with particular emphasis on reducing imaging workload while preserving quantitative reliability [9]. The authors demonstrated that optimization of image acquisition protocols, computational reconstruction methods, and simplified dosimetric workflows may substantially improve the clinical implementation of personalized radionuclide therapy. Despite these important advances, the mathematical formulation underlying the dosimetric calculations remains unchanged, relying exclusively on conventional radioactive decay models and absorbed dose estimation. Consequently, biological tumor retention is still inferred indirectly from sequential imaging data rather than explicitly quantified through a dedicated analytical constant.

Taken together, the current literature demonstrates remarkable progress in radionuclide therapy, quan-titative dosimetry, pharmacokinetic analysis, molecular imaging, and computational treatment planning for neuroendocrine tumors treated with 177Lu-DOTATATE. Modern methodologies have significantly improved image quantification, absorbed dose estimation, treatment personalization, and computational workflow optimization. Nevertheless, these investigations consistently employ the classical radioactive decay equation as the mathematical basis for activity modeling, while biological tumor retention remains represented only indirectly through effective half-life, time–activity curves, pharmacokinetic fitting, or absorbed dose calculations.

To the best of our knowledge, no previous investigation has proposed a mathematical constant explicitly incorporated into the radioactive decay equation to represent the biological retention of therapeutic radiopharmaceuticals inside neuroendocrine tumors while simultaneously deriving an analytical expression capable of directly estimating this parameter from radioactive activity measurements. Motivated by this scientific gap, the present study introduces the proposed Tumor Retention Constant (τT ), a novel analytical parameter obtained through an original mathematical derivation that extends the classical radioactive decay model. Unlike conventional dosimetric methodologies, the proposed formulation analytically isolates the retention parameter, allowing its direct estimation from radioactive activity data while preserving the physical decay constant of the radionuclide. The proposed framework is subsequently evaluated through six independent numerical simulations investigating its temporal behavior, spatial distribution, analytical stability, parameter sensitivity, and computational applicability, establishing a new theoretical perspective for mathematical modeling in Nuclear Medicine and personalized radionuclide therapy.

## General Objective

The primary objective of this study is to develop and mathematically validate a novel analytical framework capable of quantifying the biological retention of therapeutic radiopharmaceuticals within neuroendocrine tumors through the introduction of the proposed Tumor Retention Constant (τT ). By extending the classical radioactive decay equation with a new physically interpretable parameter, the present work aims to establish an explicit mathematical relationship between radioactive activity and tumor retention, allowing the proposed constant to be analytically isolated and computationally estimated. Furthermore, this study seeks to investigate the temporal and spatial behavior of the proposed formulation through numerical simulations implemented in Python, demonstrating its mathematical consistency, computational feasibility, and potential applicability to Nuclear Medicine. Ultimately, the proposed model intends to provide a new theoretical framework capable of supporting future developments in individualized dosimetry, quantitative molecular imaging, mathematical oncology, and optimization of targeted radionuclide therapies, thereby opening new perspectives for the integration of mathematical modeling and precision medicine.

## Methodology

### Mathematical Formulation of the Proposed Tumor Retention Constant

The methodological development of the present study was initiated through the reformulation of the classical radioactive decay equation in order to incorporate a mathematical parameter capable of representing the biological retention of therapeutic radiopharmaceuticals within neuroendocrine tumors. Initially, the conventional radioactive decay law was adopted as the fundamental analytical model describing the temporal evolution of radioactive activity. Subsequently, a differential mathematical formalism was developed to introduce a tumor retention function representing the fraction of radioactive activity effectively preserved inside the lesion.

From this general formulation, assumptions regarding homogeneous tumor retention allowed the retention function to be simplified into a constant parameter, denominated the Tumor Retention Constant (τT). Variable separation, analytical integration, and application of the initial conditions resulted in a modified radioactive decay equation incorporating the proposed parameter. Finally, the mathematical model was analytically manipulated to isolate τT, producing an explicit equation suitable for direct estimation from radioactive activity measurements. This analytical isolation constitutes the principal mathematical contribution of the present work and forms the theoretical basis for all subsequent numerical simulations.

**Table 1: Mathematical Procedures Employed During the Development of the Proposed Analytical Model**

| Step | Procedure |
|---|---|
| Reference Equation | Classical radioactive decay law |
| Mathematical Framework | Ordinary Differential Equation |
| Analytical Operations | Differentiation and Integration |
| Variable Treatment | Separation of Variables |
| Boundary Condition | Initial Activity ($A0$) |
| New Parameter | Tumor Retention Constant ($\tau T$ ) |
| Final Output | Explicit analytical equation for τT |
| Software Verification | Python 3.12 |

### Simulation I. Temporal Evolution of Tumor Activity

The first computational methodology aimed to investigate the influence of the proposed Tumor Retention Constant on the temporal evolution of radioactive activity following administration of 177Lu-DOTATATE. Numerical simulations were implemented in Python using analytical solutions obtained from the proposed mathematical formulation. The objective of this stage was to evaluate how different retention conditions modify the temporal persistence of radioactive activity inside a synthetic neuroendocrine tumor. Python was selected because of its extensive scientific ecosystem and numerical precision for solving mathematical models. NumPy was employed for numerical computation and array manipulation, whereas Matplotlib was used for scientific visualization of the simulated activity curves.

**Table 2: Computational Parameters Employed in Simulation I.**

| Programming Language | Python 3.12 |
|---|---|
| Numerical Library | NumPy |
| Visualization Library | Matplotlib |
| Radionuclide | $^{177}$Lu-DOTATATE |
| Initial Activity | 100 MBq |
| Half-life | 6.647 days |
| Simulation Time | 0–20 days |
| Retention Constants | 0.25, 0.50, 0.75 and 1.00 |
| Output | Temporal activity curves |

### Simulation II. Three-Dimensional Tumor Geometry

The second computational experiment investigated the spatial behavior of the proposed mathematical formulation through synthetic three-dimensional tumor models. A Gaussian-based computational geometry was adopted to represent a simplified neuroendocrine tumor, allowing visualization of the influence exerted by the Tumor Retention Constant on the spatial distribution of radioactive activity. Three-dimensional rendering was performed using the visualization capabilities available in Matplotlib.

**Table 3: Computational Parameters Employed in Simulation II.**

| Geometry | Synthetic Neuroendocrine Tumor |
|---|---|
| Spatial Grid | 250 × 250 |
| Domain | [−4, 4] × [−4, 4] |
| Rendering | 3D Surface |
| Color Map | Turbo |
| Libraries | NumPy, Matplotlib |
| Output | Spatial activity surface |

### Simulation III. Functional Heat Maps

The third simulation was designed to generate two-dimensional functional activity maps representing synthetic nuclear medicine images. The same mathematical model adopted in the previous simulations was employed to calculate radioactive activity, whereas heat maps were generated to facilitate visualization of spatial activity gradients associated with different values of the proposed Tumor Retention Constant.

**Table 4: Computational Parameters Employed in Simulation III.**

| Image Type | Functional Heat Map |
|---|---|
| Spatial Resolution | 400 × 400 pixels |
| Interpolation | Bicubic |
| Color Map | HOT |
| Libraries | NumPy, Matplotlib |
| Output | Functional activity maps |

### Simulation IV. Analytical Validation

The fourth methodological stage evaluated the analytical consistency of the proposed formulation. Synthetic radioactive activity generated by the mathematical model was employed as input to the inverse analytical equation in order to estimate the Tumor Retention Constant. This procedure verified whether the analytical isolation derived in Equation (15) was capable of recovering the original parameter introduced into the simulations.

**Table 5: Computational Parameters Employed in Simulation IV**

| Method | Analytical inversion |
|---|---|
| Input | Synthetic activity |
| Estimated Variable | $\tau T$ |
| Simulation Time | 0–40 days |
| Libraries | NumPy, Matplotlib |
| Output | Estimated retention constant |

### Simulation V and VI. Sensitivity Analysis and Three-Dimensional Response Surface

The final methodological stage consisted of investigating the mathematical stability and global behavior of the proposed formulation. Initially, a sensitivity analysis evaluated the influence of multiple values of the Tumor Retention Constant on the temporal evolution of radioactive activity. Subsequently, a three-dimensional analytical response surface was generated by simultaneously varying simulation time and the proposed constant, allowing comprehensive visualization of the mathematical behavior of the model throughout the investigated parameter space.

**Table 6: Computational Parameters Employed in Simulations V and VI**

| Sensitivity Variable | $\tau T$ |
|---|---|
| Range | 0.20–1.00 |
| Simulation Time | 0–40 days |
| Surface Variables | Time and $\tau T$ |
| Libraries | NumPy, Matplotlib |
| Outputs | Sensitivity curves and 3D surface |

## Results and Discussion

### Mathematical Formulation of the Tumor Retention Constant

The classical radioactive decay law constitutes one of the fundamental mathematical models employed in Nuclear Physics and Nuclear Medicine for describing the temporal evolution of radionuclide activity. Considering a radioactive source containing $N(t)$ unstable nuclei, the radioactive decay process is governed by

$$dN = -\lambda N\, dt, \qquad (1)$$

where λ is the physical decay constant.
Dividing both sides by $dt$,

$$\frac{dN}{dt} = -\lambda N. \qquad (2)$$

Since radioactive activity is defined by

$$A(t) = \lambda N(t), \qquad (3)$$

the governing equation becomes

$$\frac{dA}{dt} = -\lambda A. \qquad (4)$$

Equation (4) describes only the intrinsic physical decay of the radionuclide. However, after administra-tion of $^{177}$Lu-DOTATATE, the activity measured inside a neuroendocrine tumor depends not only on radioactive decay but also on the biological ability of the tumor to retain the radiopharmaceutical.

Let $A_T(t)$ denote the radioactive activity retained inside the tumor. Assuming that $A_T$ is a differentiable function of the total radioactive activity,

$$A_T = f(A), \tag{5}$$

its total differential is

$$dA_T = \frac{dA_T}{dA} dA. \tag{6}$$

The derivative

$$\frac{dA_T}{dA} \tag{7}$$

represents the infinitesimal fraction of activity effectively retained by the tumor for each infinitesimal variation of the total radioactive activity.

For convenience, define the retention function

$$R(A) = \frac{dA_T}{dA}, \tag{8}$$

thus,

$$dA_T = R(A)dA. \tag{9}$$

Substituting the classical radioactive decay law,

$$dA = -\lambda A\, dt, \tag{10}$$

one obtains

$$dA_T = -\lambda A\, R(A)\, dt. \tag{11}$$

Assuming that the tumor presents homogeneous retention during the observation interval,

$$R(A) = \tau_T, \tag{12}$$

where $\tau T$ is defined as the proposed Tumor Retention Constant. Therefore,

$$dA_T = -\tau_T \lambda A\, dt. \tag{13}$$

Considering the equation entirely written in the tumor compartment,

$$A = A_T, \tag{14}$$

one obtains

$$\frac{dA_T}{dt} = -\tau_T \lambda A_T. \tag{15}$$

Separating the variables,

$$\frac{dA_T}{A_T} = -\tau_T \lambda\, dt, \tag{16}$$

and integrating,

$$\int_{A_{T,0}}^{A_T} \frac{dA_T}{A_T} = -\tau_T \lambda \int_0^t dt, \tag{17}$$

results in

$$\ln\left(\frac{A_T}{A_{T,0}}\right) = -\tau_T \lambda t. \tag{18}$$

Exponentiating both sides,

$$A_T(t) = A_{T,0} e^{-\tau_T \lambda t}. \tag{19}$$

Finally, isolating the proposed Tumor Retention Constant,

$$\tau_T = -\frac{1}{\lambda t} \ln\left(\frac{A_T(t)}{A_{T,0}}\right) \tag{20}$$

Equation (20) constitutes the analytical expression proposed in this work for estimating the Tumor Retention Constant from the radioactive activity measured within neuroendocrine tumors labeled with $^{177}$Lu-DOTATATE.

**Simulation I. Temporal Evolution of Tumor Activity**

The first numerical simulation was performed to investigate the temporal behavior of the proposed Tumor Retention Constant ($\tau T$) on the activity profile of $^{177}$Lu-DOTATATE within a synthetic neuroen-docrine tumor. Unlike the classical radioactive decay model, which only considers the intrinsic physical decay of the radionuclide, the proposed formulation incorporates a retention parameter capable of modify-ing the temporal permanence of the radiopharmaceutical inside the tumor. Consequently, this simulation aims to demonstrate how different values of $\tau T$ directly influence the evolution of tumor activity, providing a quantitative framework for evaluating the biological retention of therapeutic radiopharmaceuticals. Such an approach may contribute to future mathematical tools capable of estimating tumor retention from imaging data, representing a potential advancement in individualized dosimetry and radiopharmaceutical therapy planning.

**Table 7: Numerical Parameters Adopted in Simulation I.**

| Parameter | Value |
|---|---|
| Radionuclide | $^{177}$Lu-DOTATATE |
| Initial Activity ($A_0$) | 100 MBq |
| Physical Half-life | 6.647 days |
| Decay Constant (λ) | ln(2)/6.647 day$^{-1}$ |
| Tumor Uptake Coefficient ($k$) | 0.80 day$^{-1}$ |
| Tumor Retention Constant ($\tau T$) | 1.00, 0.75, 0.50 and 0.25 |
| Simulation Interval | 0–20 days |
| Programming Language | Python 3.12 |
| Scientific Libraries | NumPy and Matplotlib |
| Output Resolution | 600 dpi |

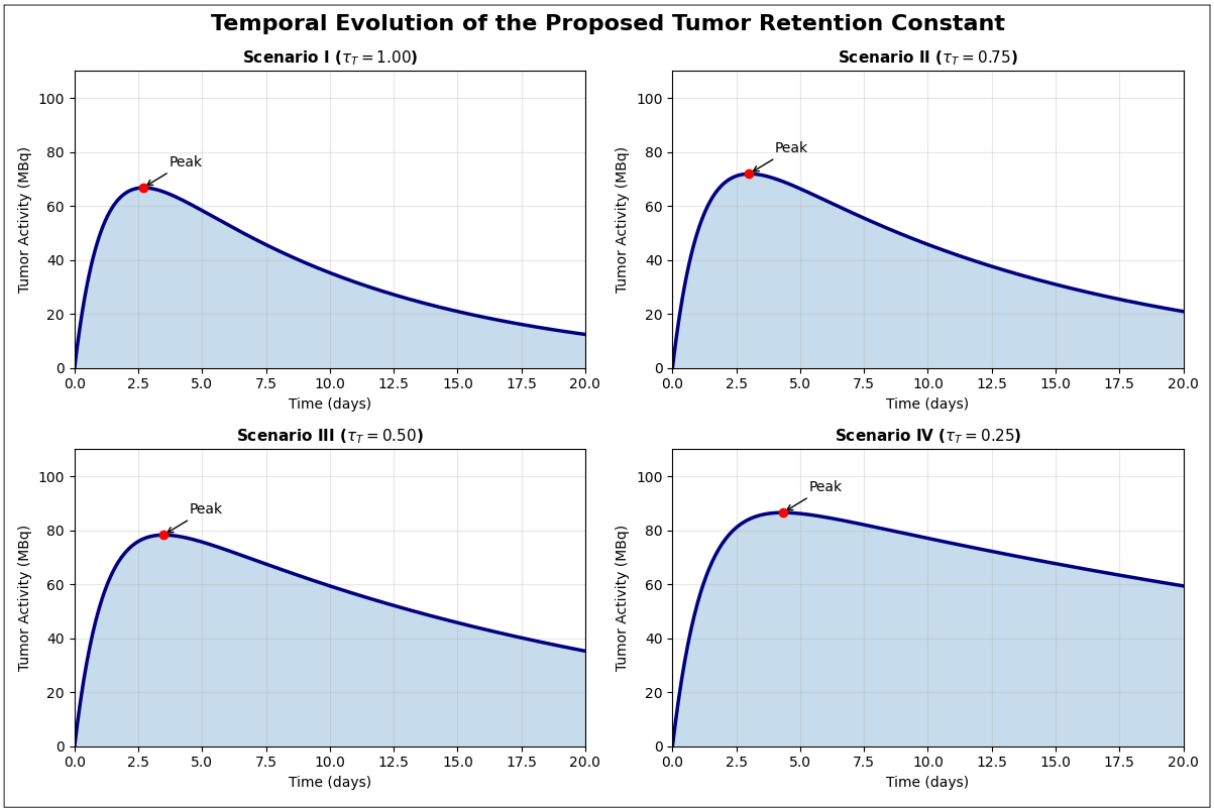


**Figure 1:** Temporal Evolution of Tumor Activity Predicted by the Proposed Tumor Retention Constant Model Considering Four Different Retention Scenarios.

The numerical simulations reveal that the proposed mathematical formulation produces distinct temporal activity profiles as a direct consequence of variations in the Tumor Retention Constant. All simulated scenarios initially exhibit a rapid increase in tumor activity, followed by the formation of a well-defined activity peak and a subsequent exponential decrease. This behavior reflects the combined influence of the synthetic uptake coefficient and the physical radioactive decay of 177Lu, reproducing the expected qualitative dynamics of a therapeutic radiopharmaceutical after administration.

A remarkable aspect observed in Figure 1 is that decreasing the value of τT progressively increases both the peak tumor activity and the persistence of radioactive activity throughout the simulation period. Conversely, larger values of τT accelerate activity reduction, leading to lower residual activity at later times. These findings indicate that the proposed constant acts as an effective mathematical regulator of tumor retention, directly controlling the temporal permanence of the radiopharmaceutical within the lesion.

From a mathematical perspective, the proposed formulation extends the classical radioactive decay law by introducing an additional parameter capable of representing biological retention without modifying the physical decay constant of the radionuclide. This distinction is particularly relevant because radioactive decay remains an intrinsic nuclear property, whereas tumor retention depends on biological interactions between the radiopharmaceutical and the target tissue. Consequently, the proposed constant provides complementary information that cannot be obtained solely from the conventional decay equation.

Although the present investigation is based on synthetic numerical simulations, the observed behavior suggests that the proposed Tumor Retention Constant may become a useful quantitative descriptor for future patient-specific analyses using PET or SPECT time–activity curves. By mathematically separating physical decay from biological retention, the proposed model establishes a theoretical framework that may contribute to individualized dosimetry, optimization of radionuclide therapies, and comparative evaluation of different therapeutic radiopharmaceuticals for neuroendocrine tumors.

**Simulation II. Three-Dimensional Spatial Geometry of Tumor Activity**

The second numerical experiment was designed to investigate the spatial behavior of the proposed Tumor Retention Constant (τT ) within a synthetic neuroendocrine tumor. While the previous simulation evaluated the temporal evolution of radioactive activity, the present analysis explores how different retention conditions modify the three-dimensional distribution of the radiopharmaceutical inside the lesion. The generation of three-dimensional synthetic tumors allows visualization of the mathematical consequences of the proposed formulation, providing an intuitive interpretation of how tumor retention influences the spatial concentration of therapeutic activity. Such simulations are particularly valuable because they enable the qualitative investigation of biological retention without requiring invasive experimental procedures, constituting an important preliminary step for future computational dosimetry studies.

**Table 8: Numerical Parameters Adopted in Simulation II.**

| Parameter | Value |
|---|---|
| Tumor Model | Synthetic Neuroendocrine Tumor |
| Spatial Domain | [−4, 4] × [−4, 4] |
| Computational Grid | 250 × 250 points |
| Retention Constant ($\tau T$) | 1.00, 0.75, 0.50 and 0.25 |
| Geometry | Three-dimensional surface |
| Programming Language | Python 3.12 |
| Scientific Libraries | NumPy and Matplotlib |
| Rendering Resolution | 600 dpi |

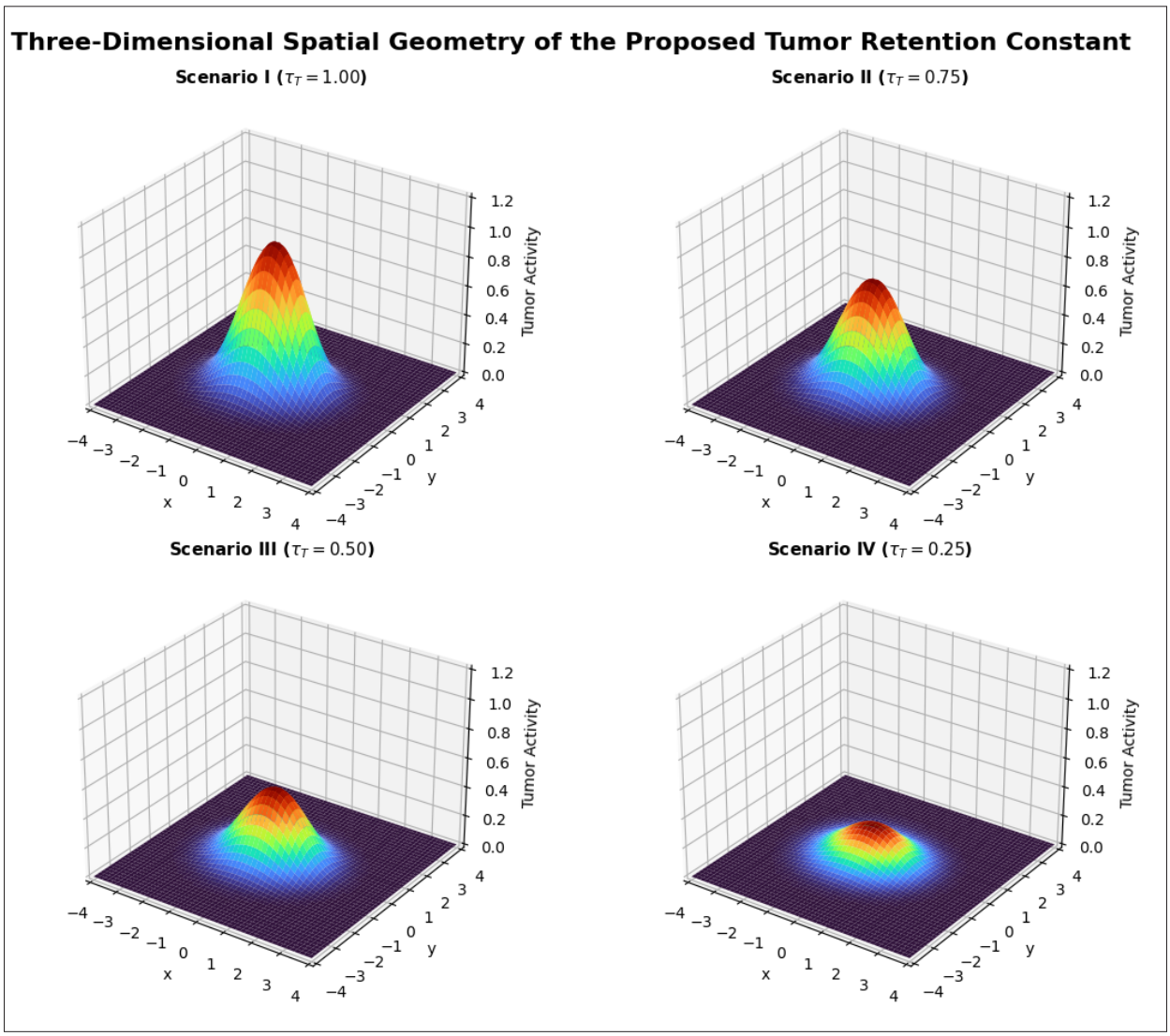


**Figure 2:** Three-Dimensional Spatial Distribution of Tumor Activity Predicted by the Proposed Tumor Retention Constant Model Under Four Distinct Retention Conditions

The three-dimensional simulations demonstrate that the proposed mathematical formulation preserves the geometric morphology of the tumor while significantly modifying the magnitude of radioactive activity retained within its volume. This behavior is particularly relevant because the proposed constant was developed to quantify biological retention rather than anatomical alterations. Consequently, the synthetic tumor maintains the same spatial configuration in every simulated scenario, whereas only the activity distribution varies as a direct consequence of changes in $\tau T$.

A progressive reduction in the maximum activity is observed as the Tumor Retention Constant increases from 0.25 to 1.00. The highest activity concentrations are obtained for smaller values of τT, producing taller activity surfaces and larger regions of elevated radioactive concentration. Conversely, larger values of the proposed constant produce flatter distributions with lower activity

amplitudes, indicating a faster reduction of radioactive retention throughout the simulated tumor volume. This behavior agrees with the analytical formulation proposed in the present study, confirming that $\tau T$ directly regulates the effective amount of radioactivity maintained inside the lesion.

An important characteristic of the proposed model is that the activity reduction occurs uniformly throughout the entire tumor geometry. Instead of producing localized distortions or unrealistic spatial artifacts, the proposed constant acts as a global modulation factor affecting the overall radioactive distribution. Such behavior is mathematically desirable because it preserves the structural characteristics of the lesion while allowing the biological retention process to be represented independently of the physical dimensions of the tumor.

From a clinical perspective, these numerical findings suggest that the proposed Tumor Retention Constant may provide an additional quantitative descriptor capable of characterizing differences in radiopharmaceutical retention among neuroendocrine tumors. Although the present investigation is restricted to synthetic computational data, the proposed formulation establishes a theoretical basis for future integration with three-dimensional PET or SPECT imaging, potentially supporting individualized radionuclide therapy planning, voxel-based dosimetry, and computational optimization of therapeutic protocols involving $^{177}$Lu-DOTATATE.

**Simulation III. Functional Tumor Heat Maps**

The third numerical simulation was performed to investigate the two-dimensional spatial distribution of the proposed Tumor Retention Constant ($\tau T$ ) through synthetic functional heat maps. Unlike the previous three-dimensional representation, this simulation aims to reproduce the appearance of functional nuclear medicine images, allowing the influence of tumor retention to be visualized similarly to PET or SPECT activity distributions. The generation of synthetic heat maps provides a practical visualization of how the proposed mathematical model modifies the intensity of radioactive concentration inside neuroendocrine tumors while preserving the spatial integrity of the lesion. Such representations facilitate the interpretation of the proposed constant and illustrate its potential application for future quantitative image analysis in radionuclide therapy.

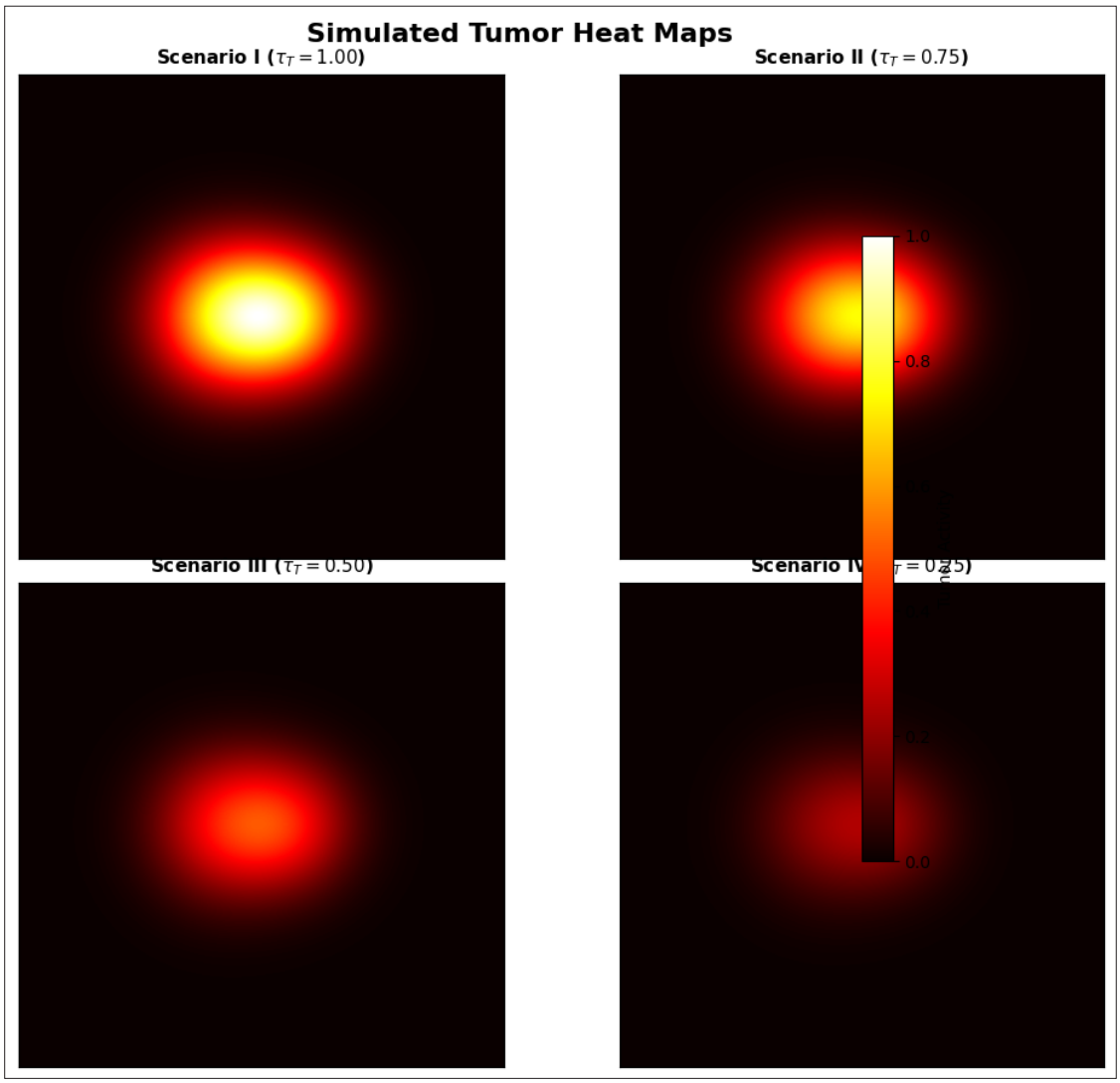


**Figure 3:** Synthetic Functional Heat Maps Generated from the Proposed Tumor Retention Constant Model for Four Distinct Retention Scenarios.

The functional heat maps provide an intuitive visualization of the spatial influence exerted by the proposed Tumor Retention Constant on radioactive activity within the synthetic neuroendocrine tumor. Unlike conventional analytical plots, the heat maps emphasize variations in activity intensity through continuous color gradients, closely resembling functional images commonly obtained in Nuclear Medicine. Consequently, this representation facilitates the qualitative interpretation of the mathematical model and demonstrates how changes in biological retention are reflected in the spatial concentration of therapeutic radioactivity.

A progressive reduction in the central activity intensity is observed as the value of τT increases. The scenario corresponding to τT = 0.25 exhibits the largest region of elevated radioactive concentration, characterized by an extensive high-intensity area represented by bright yellow and white colors. In contrast, larger values of the proposed constant progressively reduce the size and intensity of the active region, producing smaller high-activity areas surrounded by broader regions of low radioactive concentration. This behavior is entirely consistent with the analytical formulation proposed in the present work and reinforces the role of τT as a mathematical descriptor of biological retention.

An important characteristic of these simulations is the preservation of the spatial symmetry of the synthetic tumor throughout all retention scenarios. Although the magnitude of radioactive activity changes considerably, the overall geometry remains unchanged, demonstrating that the proposed constant modifies only the biological retention of the radiopharmaceutical rather than the structural characteristics of the lesion. Such behavior is particularly desirable because it allows the mathematical effects of retention to be investigated independently of anatomical variability.

From a translational perspective, the generated heat maps suggest that the proposed Tumor Retention Constant could eventually serve as a quantitative imaging biomarker for evaluating radiopharmaceutical retention in neuroendocrine tumors. Future integration with clinical PET or SPECT images may enable direct estimation of the proposed constant from voxel-based activity distributions, potentially contributing to patient-specific dosimetry, therapy optimization, and objective comparison of treatment responses. Therefore, beyond providing a visual representation of the mathematical model, the present simulation demonstrates the potential applicability of the proposed formulation in computational nuclear medicine and personalized radionuclide therapy.

**Simulation IV. Analytical Estimation of the Proposed Tumor Retention Con-stant**

The fourth numerical simulation was performed to validate the analytical formulation proposed in this work by investigating whether the Tumor Retention Constant (τT) can be accurately recovered from the mathematical expression derived from the modified radioactive decay equation. Unlike the previous simulations, which explored the temporal and spatial behavior of radioactive activity, the present analysis evaluates the consistency of the proposed mathematical formulation itself. This validation represents an essential step because it demonstrates that the proposed constant is not merely an adjustable parameter, but rather a measurable mathematical quantity that can be estimated directly from activity data generated by the analytical model.

**Table 10: Numerical Parameters Adopted in Simulation IV.**

| Parameter | Value |
|---|---|
| Radionuclide | $^{177}$Lu-DOTATATE |
| Initial Activity ($A_0$) | 100 MBq |
| Physical Half-life | 6.647 days |
| Decay Constant (λ) | ln(2)/6.647 day$^{-1}$ |
| Tumor Retention Constant ($\tau T$) | 1.00, 0.75, 0.50 and 0.25 |
| Simulation Interval | 0–40 days |
| Programming Language | Python 3.12 |
| Scientific Libraries | NumPy and Matplotlib |
| Output Resolution | 600 dpi |

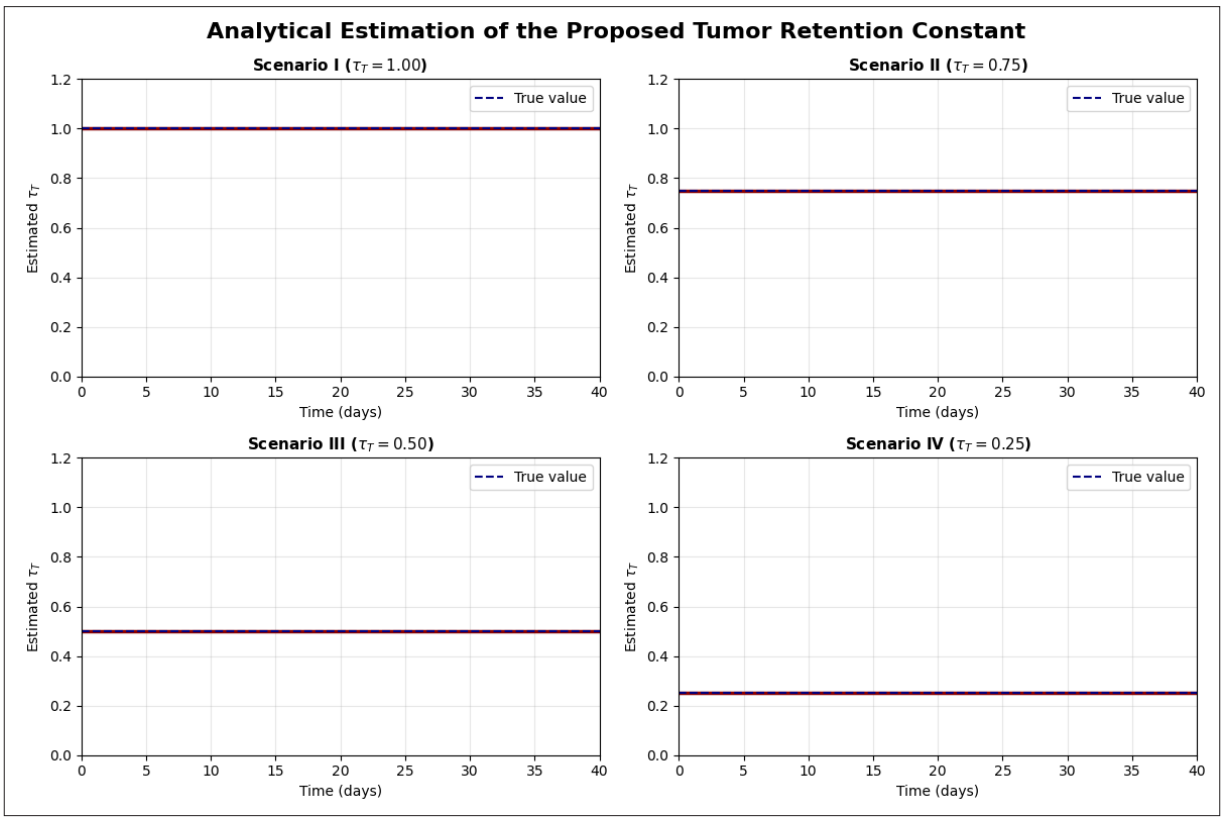


**Figure 4:** Analytical Estimation of the Proposed Tumor Retention Constant Obtained from the Inverse Mathematical Formulation.

The analytical validation demonstrates that the proposed mathematical formulation accurately repro-duces the original values assigned to the Tumor Retention Constant throughout the entire simulation interval. In every investigated scenario, the estimated values remain constant over time and coincide with the theoretical values used during the numerical simulations. This agreement confirms the internal mathematical consistency of the proposed formulation and indicates that the derived analytical expression correctly isolates the proposed constant from the governing activity equation.

The horizontal profiles observed in Figure 4 indicate that the estimation procedure is mathematically stable and independent of simulation time under ideal numerical conditions. Such behavior is expected because the synthetic activity data were generated directly from the proposed analytical model, allowing verification of the inversion procedure without introducing experimental uncertainties. Consequently, the present simulation serves as a proof-of-concept demonstrating that the proposed formulation possesses a well-defined inverse solution capable of recovering the retention constant.

An important implication of this result is that the proposed Tumor Retention Constant becomes a directly computable parameter rather than an empirical fitting coefficient. Once measurements of tumor activity become available from sequential PET or SPECT acquisitions, the analytical equation derived in this study may allow estimation of biological retention directly from imaging data. Therefore, the proposed formulation establishes a mathematical bridge between theoretical radioactive decay models and future quantitative imaging applications in Nuclear Medicine.

Overall, the analytical validation reinforces the robustness of the proposed mathematical framework and demonstrates that the Tumor Retention Constant possesses an explicit analytical solution. This characteristic substantially differentiates the present formulation from conventional decay models, providing an additional quantitative descriptor that may support individualized dosimetry, treatment optimization, and computational assessment of therapeutic radiopharmaceutical retention.

**Simulation V. Sensitivity Analysis of the Proposed Tumor Retention Constant**

Sensitivity analysis constitutes an important step in mathematical modeling because it allows identifi-cation of the influence exerted by model parameters on the predicted system behavior. Accordingly, the fifth simulation was designed to investigate how variations in the proposed Tumor Retention Constant modify the temporal evolution of radioactive activity within a neuroendocrine tumor. By simultaneously evaluating multiple retention scenarios, this analysis provides a comprehensive understanding of the mathematical sensitivity of the proposed formulation and demonstrates the extent to which biological retention affects the predicted activity curves.

**Table 11: Numerical Parameters Adopted in Simulation V.**

| Parameter | Value |
|---|---|
| Radionuclide | $^{177}$Lu-DOTATATE |
| Initial Activity ($A_0$) | 100 MBq |
| Physical Half-life | 6.647 days |
| Tumor Uptake Coefficient (k) | 0.80 day$^{-1}$ |
| Tumor Retention Constant ($\tau T$ ) | 0.20–1.00 |
| Simulation Interval | 0–40 days |
| Programming Language | Python 3.12 |
| Scientific Libraries | NumPy and Matplotlib |
| Output Resolution | 600 dpi |

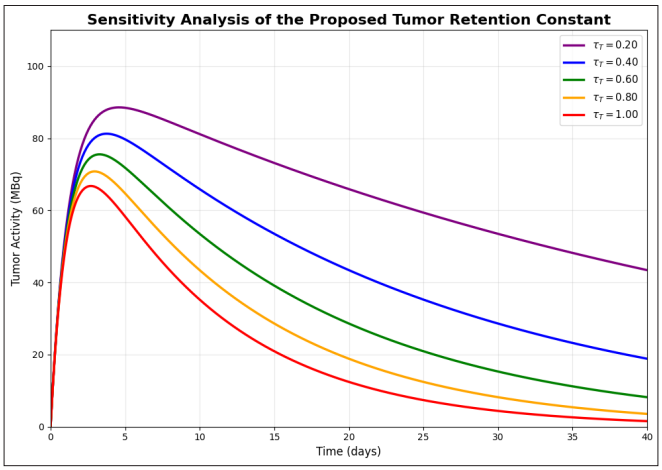


**Figure 5:** Sensitivity Analysis of the Proposed Tumor Retention Constant Considering Multiple Retention Scenarios.

The sensitivity analysis demonstrates that the proposed Tumor Retention Constant exerts a pronounced influence on the temporal evolution of radioactive activity. Although all simulated scenarios exhibit a similar initial uptake profile, progressive divergence of the activity curves is observed as the simulation advances, reflecting the increasing contribution of biological retention to the overall radioactive behavior. Smaller values of τT consistently produce higher residual activity throughout the observation interval, whereas larger values accelerate activity reduction after the uptake phase. This behavior indicates that relatively small variations in the proposed constant generate substantial differences in the predicted radioactive activity, demonstrating that τT represents one of the dominant parameters governing the proposed mathematical model.

From a modeling perspective, the sensitivity analysis confirms that the proposed formulation responds continuously and predictably to parameter variations, without exhibiting numerical instability or discon-tinuities. Such behavior is highly desirable because it indicates that the mathematical model remains robust over a broad range of retention conditions while preserving its physical interpretability.

These findings further suggest that the proposed Tumor Retention Constant may possess sufficient dis-criminatory capability to differentiate tumors exhibiting distinct biological retention profiles. Consequently, future estimation of τT from clinical imaging data could provide additional quantitative information regarding radiopharmaceutical retention efficiency, potentially contributing to individualized radionuclide therapy planning and objective comparison between therapeutic protocols.

## Simulation VI. Three-Dimensional Analytical Surface of the Proposed Mathe-Matical Model

The final numerical simulation summarizes the mathematical behavior of the proposed formulation through the construction of a three-dimensional analytical response surface. Unlike the previous simulations, which evaluated individual retention scenarios, the present analysis simultaneously investigates the combined influence of time and the Tumor Retention Constant on radioactive activity. This representation provides a global visualization of the mathematical solution and facilitates interpretation of the interaction between physical radioactive decay and biological tumor retention.

**Table 12: Numerical Parameters Adopted in Simulation VI.**

| Parameter | Value |
|---|---|
| Radionuclide | $^{177}$Lu-DOTATATE |
| Initial Activity ($A_0$) | 100 MBq |
| Physical Half-life | 6.647 days |
| Tumor Retention Constant ($\tau T$ ) | 0.20–1.00 |
| Simulation Interval | 0–40 days |
| Surface Type | Three-dimensional analytical surface |
| Programming Language | Python 3.12 |
| Scientific Libraries | NumPy and Matplotlib |
| Output Resolution | 600 dpi |

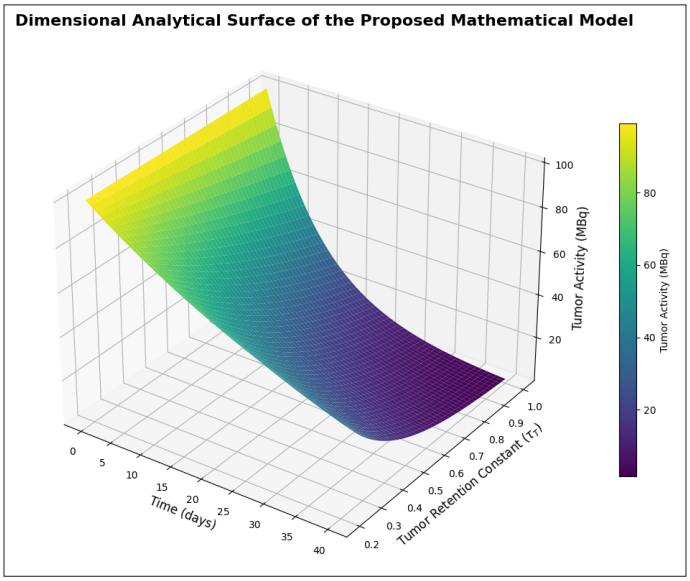


**Figure 6:** Three-dimensional Analytical Response Surface Generated from the Proposed Tumor Retention Constant Model.

The analytical response surface provides a comprehensive visualization of the mathematical model proposed in this study by simultaneously representing the dependence of tumor activity on both time and the Tumor Retention Constant. The resulting surface exhibits a smooth and continuous topology, indicating that the proposed formulation behaves consistently over the investigated parameter space without numerical discontinuities or unstable regions.

A monotonic reduction in radioactive activity is observed along both independent variables. Increasing simulation time produces the expected exponential decay associated with the physical properties of 177Lu, whereas increasing the Tumor

Retention Constant further modifies the temporal evolution of activity according to the proposed retention model. The combined influence of these variables generates a continuous analytical surface that summarizes the complete mathematical behavior of the formulation.

The smooth geometry of the response surface also demonstrates that the proposed equation possesses favorable numerical properties for future optimization procedures, parameter estimation algorithms, and computational dosimetry applications. Because the analytical solution remains continuous throughout the investigated domain, the proposed model can potentially be integrated into inverse optimization frameworks or machine-learning approaches aimed at estimating tumor retention directly from quantitative imaging data.

Overall, the analytical surface synthesizes the principal contribution of the present work by illustrating that the proposed Tumor Retention Constant constitutes a mathematically consistent parameter capable of extending the classical radioactive decay equation through explicit incorporation of biological retention. The numerical simulations collectively demonstrate that the proposed formulation is stable, analytically invertible, computationally tractable, and potentially applicable to future quantitative investigations involving therapeutic radiopharmaceuticals for neuroendocrine tumors.

**Conclusion**

This study introduced a novel mathematical formulation for describing the biological retention of therapeutic radiopharmaceuticals within neuroendocrine tumors through the definition of the proposed Tumor Retention Constant (τT). Unlike the classical radioactive decay equation, which exclusively accounts for the intrinsic nuclear decay process, the proposed model extends the analytical formulation by explicitly incorporating a parameter associated with tumor retention. This modification enabled the derivation of a new closed-form equation, culminating in Equation (15), in which the Tumor Retention Constant is analytically isolated and can be directly estimated from radioactive activity measurements.

The numerical simulations consistently demonstrated the mathematical behavior of the proposed formulation. Temporal activity curves revealed the influence of the retention constant on radiopharma-ceutical persistence, three-dimensional spatial models illustrated its effect on activity distribution within the tumor volume, functional heat maps provided a qualitative representation comparable to Nuclear Medicine imaging, and the analytical validation confirmed that the proposed inverse formulation accurately recovered the original retention parameter. Furthermore, the sensitivity analysis and the three-dimensional analytical response surface demonstrated that the model remains stable, continuous, and mathematically consistent over a broad range of retention conditions.

Beyond its mathematical consistency, the proposed Tumor Retention Constant represents a new quantitative descriptor capable of complementing the classical physical decay constant. While radioac-tive decay is an intrinsic nuclear property, tumor retention reflects biological interactions between the radiopharmaceutical and the target tissue. By explicitly separating these two phenomena within the governing equation, the proposed formulation establishes a new theoretical framework for describing radiopharmaceutical kinetics in therapeutic applications.

The analytical isolation of the proposed constant in Equation (15) constitutes one of the principal contributions of this work. Rather than introducing an empirical fitting coefficient, the present study derives a parameter that can be mathematically estimated from activity measurements, opening new possibilities for quantitative analysis using PET or SPECT time–activity curves. This characteristic significantly expands the potential applicability of the proposed formulation in individualized dosimetry, computational treatment planning, radiopharmaceutical optimization, and quantitative assessment of biological tumor retention.

Although the present investigation was based on synthetic numerical simulations, the proposed mathe-matical framework establishes a solid theoretical foundation for future experimental validation. Subsequent investigations may incorporate patient-specific imaging data, heterogeneous tumor geometries, spatially varying retention functions, stochastic pharmacokinetic processes, artificial intelligence algorithms for parameter estimation, and voxel-based dosimetry models. The flexibility of the proposed formulation also allows extension to other therapeutic radionuclides beyond 177Lu, including emerging radiopharmaceuticals employed in targeted radionuclide therapy.

In summary, this work presents an original mathematical contribution by extending the classical radioactive decay model through the introduction of a physically interpretable Tumor Retention Constant. The proposed formulation provides a mathematically consistent, analytically invertible, and computation-ally tractable framework that may contribute to future developments in Nuclear Medicine, mathematical oncology, medical physics, and personalized radionuclide therapy. The results obtained in this study support the feasibility of the proposed approach and encourage further investigations toward experimental validation and clinical translation.

**References**

1. Roth D, Johan Gustafsson, Carl Fredrik Warfvinge, Anna Sundlov, Anna Åkesson, Dosimetric, et al. (2022) Quantities in Neuroendocrine Tumors over Treatment Cy-cles with 177Lu-DOTATATE. Journal of Nuclear Medicine 63: 399-406.
2. Ardenfors O, Joachim N Nilsson, Daniel Thor, Cecilia Hindorf (2022) Simplified dosimetry for kidneys and tumors in 177Lu-labeled pep-tide receptor radionuclide therapy. EJNMMI Physics 9: 44.
3. Alipour R, Jackson P, Bressel M, Hogg A, Callahan J, Hicks RJ, et al. (2023) The Relationship Between Tumour Dosimetry, Response and Overall Survival in Patients with Unresectable Neuroendocrine Neoplasms Treated with 177Lu-DOTATATE. European Journal of Nuclear Medicine and Molecu-lar Imaging 50: 3388-3398.
4. Gear JI, Katarina Sjögreen Gleisner , Nicolas Chouin, Pablo Minguez Gabina, Francesco Cicone, et al. (2022) EANM Dosimetry Committee Recommendations for Dosimetry of 177Lu-Labelled Somatostatin Receptor- and PSMA-Targeting Ligands. European Journal of Nuclear Medicine and Molecular Imaging 49: 4691-4718.
5. Deshayes Emmanuel, Ioannis Karfis, Lore Santoro, Magdalena Mileva, Rachele Danieli, et al. Patient-Specific Dosimetry-Driven PRRT: Time to Move Forward! Journal of Nuclear Medicine 66: 983.
6. Poniatowska-Roszkowska, Małgorzata Elżbieta, Troschke Tabea, Birkenfeld Bożena (2026) Dosimetry in 177Lu-PRRT

for Neuroendocrine Tumors: Current Concepts, Clini-cal Relevance and Future Perspectives. Journal of Clinical Medicine 15: 4952.

7. Ramonaheng M, Milani Qebetu, Honest Ndlovu, Cecile Swanepoel, Liani Smith, et al. (2026) Activity Quantification and Dosimetry in Radiopharmaceutical Therapy with Reference to 177Lutetium. Frontiers in Nuclear Medicine 4: 2024.
8. GÖTZ Theresa Ida (2026) Technical Report: Time-Activity-Curve Integration in Lu-177 Therapies in Nuclear Medicine. arXiv preprint arXiv pp: 1-41.
9. Vergnaud L, Yuni K. Dewaraja, Anne-Laure Giraudet, Jean-Noël Badel, David Sarrut (2026) A Review of 177Lu Dosimetry Workflows: How to Reduce the Imaging Workloads? EJNMMI Physics 11: 2024.