



Numerical dosimetric analysis of low-energy positrons in living biological samples[☆]

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ABSTRACT

Positron Annihilation Spectroscopy (PAS) probes the nanoscale free volume and electronic environment of cells and tissues through the formation and decay of positronium, and is potentially non destructive when operated at sufficiently low dose rates. Extending PAS from a bulk, drop-casted and contact-based technique to a depth-resolved intravital setting for living tissues requires moderated, monoenergetic positron beams in the 5–20 keV range. In this case, the absorbed dose that such beams deliver to living matter has never been quantified. We present a numerical framework that couples positron transport to a time-resolved radiobiological model to provide the first estimate of cellular viability during PAS. The mass stopping power of a Liver Endothelial Cell monolayer is herein computed and cell survival is then evaluated with a Linear-Quadratic model extended in time to include sub-lethal damage repair and ultra-high dose rate (FLASH) sparing. Three delivery regimes, continuous, pulsed and trap-based bunched, are compared over implantation energies of 5–100 keV. As a case study, we explore the action of a continuous positron beam utilizing a ²²Na source, operating near the highest performance currently achieved with this technology and modeled at its maximum potential. Naturally, to perform true non-destructive spectroscopy, the beam intensity must be deliberately scaled down to avoid damaging the cells. We confirmed that biological sample viability is governed not by the temporal structure of the beam but by the time-averaged flux delivered to the sample. In order to collect 10⁶ annihilation events for a positron lifetime spectrum before the radiation reduces the surviving fraction below 90% in the 5–20 keV window required for depth-resolved analysis, a 30–50 mCi ²²Na is required, along with a digital system for the detection of at least 10⁵ counts/sec. These results define the dose-driven viability limits of future intravital PAS and frame depth-resolved spectroscopy of living cells as an instrumental challenge for next-generation positron beam systems.

1. Introduction

While the universe exhibits a profound matter–antimatter asymmetry, the precise interactions between fundamental particles and their antimatter counterparts provide a powerful tool for investigating human biology. To detect the physiological disparities caused by pathophysiological phenomena, new precise medical imaging techniques are needed. Positron annihilation spectroscopy (PAS) has gained increased attention in recent years in the biomedical scenario due to its ability to probe structural and chemical variations in cells and tissues, successfully identifying conditions such as skin cancer or hypoxia in spheroids (Moskal et al., 2023; Karimi et al., 2023). By monitoring the formation

and lifetime of Positronium (Ps), a meta-stable bound state between a positron and an electron, PAS provides a unique nanoscale probe into the free volume and electronic environment of biological systems (Bass et al., 2023). However, the vast majority of PAS studies are currently performed with drop-casted ²²Na sources directly in contact with tissues, leaving the specific interaction between positrons and living matter largely unknown.

The use of these drop-casted sources present a significant limitation: they emit positrons with a broad energy spectrum (up to 545 keV), resulting in uncontrolled penetration depths that can span hundreds of micrometers depending on sample density (Dryzek and

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Singleton, 2006). This lack of axial resolution prevents the selective interrogation of specific cellular layers or the microvascular endothelial wall. Consequently, to transition PAS from a bulk assessment tool to a precise diagnostic probe, it is necessary to employ moderated, monoenergetic positron beams. Such beams allow the control of implantation energy, typically in the range of 1–20 keV, enabling depth-resolved spectroscopic analysis of hydrated thin biological tissues in wet chambers.

Although PAS utilizes ionizing radiation, a critical advantage of this technique lies in its potential for non-destructive monitoring of samples when operating at low dose rates. In the literature, it has been observed that exposure to low doses of ionizing radiation can lead to an adaptive response in cells, leading to DNA damage repair, antioxidant response and cell cycle regulation (Guéguen et al., 2018). Furthermore, low-dose radiotherapy (LDRT) can also be used to increase metastatic cancer susceptibility to the immune system of the patient and immunotherapy, while reducing absorbed dose (Herrera et al., 2022). To this day, the effect of positrons injected in biological samples from positron beams has not been investigated. However, a computational model in the electron radiotherapy energy range (6–24 MeV) showed that the absorbed dose of positrons in tissues is higher than electrons (Arêas and Ballester, 2025). Furthermore, studies of positron dosimetry in the typical monoenergetic positron beam energy range used for PAS are completely absent.

In this work, building on our earlier feasibility analysis (Vicini et al., 2025), we develop a numerical framework that derives the absorbed dose rate in living cellular monolayer from the positron mass stopping power and beam fluence, and couples it to a time-resolved radiobiological model to predict cell survival. The mass collision stopping power is computed for a single-layer endothelial liver tissue model, whose elemental composition is built from ICRU-44 data (White et al., 1989), using the Berger and Seltzer formulation. Three beam delivery modes are considered, continuous, pulsed and trap-based (Murtagh et al., 2023) over implantation energies ranging from 5 to 100 keV, with emphasis on the 5–20 keV window required for depth-resolved analysis of thin biological layers. By combining the absorbed dose with a Linear-Quadratic survival model that incorporates sub-lethal damage repair and ultra-high-dose-rate (FLASH) sparing, we provide the first estimate of the cellular viability achievable during PAS analyses, and identify the conditions under which a non-destructive measurement is, and is not, possible. This framework is intended as a starting point for the dosimetric calibration of PAS with monoenergetic positron beams to probe living cells while preserving their viability.

2. Materials and methods

For the dose estimation in a biological sample, a computational model using Python 3.12 has been developed. The code takes as inputs the parameters of a variable energy positron beam, the atomic composition and the radiobiological parameters typical of the liver tissue.

2.1. Target tissue physics and mass stopping power formulation

The numerical framework has been based on a human tissue made of Liver Sinusoidal Endothelial Cells, which are already used in radiobiological studies (Chen et al., 2015). To replace generic water phantoms with a high-fidelity biological targets, the elemental composition of human liver tissue was explicitly modeled using the elemental datasets and mass fractions (w_i) compiled in ICRU Report 44 (White et al., 1989). The cells were modeled as consisting of 75% water (Berger and Seltzer, 1983; Coskun and Simons, 2011), 15% nucleus, 10% cellular membrane (Coskun and Simons, 2011; Harayama and Riezman, 2018; Zimmerberg, 2006), consisting of the main molecules that form the lipid bilayer (Bär et al., 2018; Sarin, 2010; Bonfiglio et al., 2010).

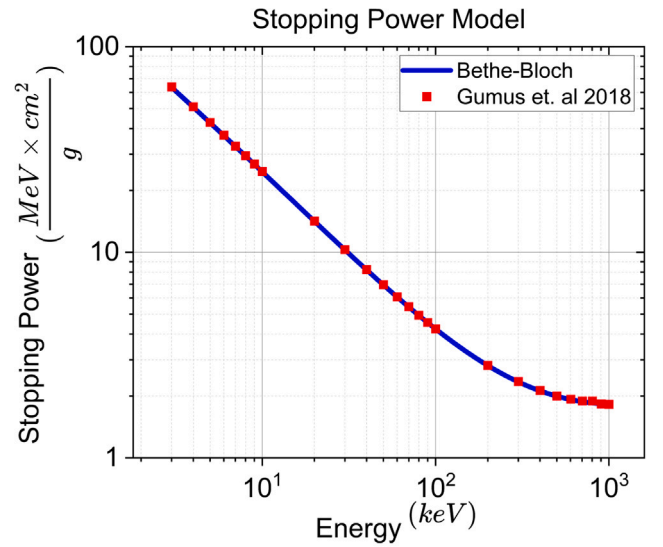


Fig. 1. Bethe-Bloch stopping power model between 3 keV and 1 MeV, compared with the model implemented by Gumus et al. for water-based biological compounds (Gumus et al., 2018).

The effective macroscopic charge-to-mass ratio $\langle Z/A \rangle$ and the mean excitation energy $\langle I \rangle$ of the composite liver medium were derived via the implementation of Bragg's additivity rule (Berger and Seltzer, 1964):

$$\langle Z/A \rangle = \sum_i w_i \left(\frac{Z_i}{A_i} \right) \quad (1)$$

$$\ln \langle I \rangle = \frac{\sum_i w_i \left(\frac{Z_i}{A_i} \right) \ln(I_i)}{\langle Z/A \rangle} \quad (2)$$

The primary transport simulation calculates the mass collision stopping power $S(E)/\rho$ (MeV cm²/g) within the relativistic and intermediate energy regimes using the classical Berger and Seltzer formulation, officially ratified in ICRU Report 37 (Berger and Seltzer, 1983):

$$\frac{S(E)}{\rho} = \frac{2\pi r_e^2 m_e c^2 N_A \langle Z/A \rangle}{\beta^2} \left[2 \ln \left(\frac{E}{\langle I \rangle} \right) + \ln \left(1 + \frac{\tau}{2} \right) + F^+(\tau) \right] \quad (3)$$

where $\tau = E/(m_e c^2)$ represents the rate between the positron kinetic energy and the electron energy at rest, $\beta = v/c$ is the relativistic velocity parameter expressed as the ratio between positron velocity and c , N_A is Avogadro's number, and $F^+(\tau)$ is the quantum electrodynamics kinematic and particle-specific correction function derived from the Bhabha scattering cross-section in the Rohrlich and Carlson formulation (Rohrlich and Carlson, 1954):

$$F^+(\tau) = 2 \ln(2) - \frac{\beta^2}{12} \left[23 + \frac{14}{\tau + 2} + \frac{10}{(\tau + 2)^2} + \frac{4}{(\tau + 2)^3} \right] \quad (4)$$

We compared the output of this model represented with a blue line in Fig. 1 with the one implemented by Gumus et al. for biological compounds such as nucleotides and water (Gumus et al., 2018). This formulation models positron transport by taking into account the quantum mechanical distinguishability of the incident antiparticle from target orbital electrons, while treating positron–electron annihilation as an active, open interaction channel (Singh et al., 2016).

2.2. Positron source architecture and macroscopic dosimetry

In this model, we defined a static beam geometry for three different particle transport modalities (continuous, pulsed and bunched) treating the spatial profile of the beam as a Gaussian distribution with a full-width at half-maximum (FWHM) of 2.0 mm, which restricts the

effective target exposure surface to an area of $Area = \pi(FWHM/2)^2 = \pi mm^2$. In the code, we implemented a ^{22}Na radioactive β^+ decay source characterized by a nominal activity $A_{Na22} = 1.85$ GBq.

2.2.1. Continuous source regime

The continuous working regime simulates the Variable Energy Positron Beam currently used in our lab. The net useful positron emission rate reaching the biological matrix (R_{sample}) is calculated by considering the nuclear decay function with the strict β^+ branching ratio ($BR_{pos} = 0.9034$, correcting for the 9.66% electron capture decay branch) (National Nuclear Data Center, 2023), the low energy moderation efficiency of an optimized multiple-layer tungsten mesh ($\eta_{mod} = 1.2 \times 10^{-3}$), and the electrostatic transport efficiency of the focal beamline optics ($\eta_{trans} = 0.50$) (Williams et al., 2015):

$$R_{sample} = A_{Na22} \cdot BR_{pos} \cdot \eta_{mod} \cdot \eta_{trans} \quad [e^+/s] \quad (5)$$

The resulting time-invariant continuous fluence rate $\Phi_{cont} = R_{sample}/Area$ establishes the macroscopic steady-state continuous dose rate:

$$\dot{D}_{cont} = \frac{S(E)}{\rho} \cdot \Phi_{cont} \cdot K \quad [Gy/s] \quad (6)$$

where $K = 1.602e^{-8}$ is the conversion factor for units of measurement consistency.

2.2.2. Pulsed source regime

Then, we modeled a pulsed positron regime, introducing a periodic time structure. This configuration is particularly useful to perform PALS, by tagging the injected positron time of arrival. This is possible by using a chopper stage to tag the positrons, and a buncher to reduce the pulse width at the sample (Suzuki et al., 1991). Frequency of the pulses is greater than the positron source fluency to effectively provide the “start” signal for lifetime measurements. In our model, we used a frequency of 50 MHz as reported by Sperr et al. for the PLEPS setup in Munich (Sperr et al., 2008). We modeled the chopper with an open-window (ON) duration of $\tau_{ON} = 2.0$ ns. Because f_{chop} is greater than the sample arrival rate ($f_{chop} \gg R_{sample}$), the system is governed by a Poisson arrival statistics where the average number of particles per period is defined as $N_{per\ period} = R_{sample}/f_{chop} \ll 1$. Multi-particle arrival events have been supposed statistically negligible, and the transmission probability simplifies to the geometric transmission fraction:

$$\mu_{trans} = \tau_{ON} \cdot f_{chop} = 0.10 \quad (7)$$

Crucially, because an active chopper behaves purely as a geometric shutter and cannot compress the continuous stream, the instantaneous particle flux during the active window remains identical to the underlying continuous beam. Thus, the instantaneous peak dose rate and the time-averaged dose rate are mathematically decoupled:

$$\dot{D}_{PULSED_{peak}} = \dot{D}_{cont} \quad (8)$$

$$\dot{D}_{PULSED_{avg}} = \mu_{trans} \cdot \dot{D}_{PULSED_{peak}} \quad (9)$$

2.2.3. Bunched source regime

The bunched regime models a particle accelerator setup with a positron trap for positron storage and controlled release (Greaves and Surko, 2002; Natisin et al., 2016). This positron bunching will decouple the final positron fluency in this configuration from source activity. The beam is buffer-gas cooled, actively compressed into high-density packets of positrons. We suppose here realistic parameters achieved in this type of device, i.e. Murtagh et al. (2023), Antonello et al. (2020) and Krasnický et al. (2013), containing $N_b = 1.0 \times 10^7$ positrons per bunch, with a compressed bunch duration, in our case supposed as $\tau_b = 10.0$ ns, and a repetition frequency $f_{rep} = 1 \times 10^{-2}$ Hz. We considered a positron trap overall efficiency of $\eta_{bunch} = 0.10$. The time-averaged fluence rate (Φ_{avg}) and the instantaneous intra-bunch fluence

rate (Φ_{inst}) are derived from the fraction η of the source rate R_{sample} captured per trap cycle, and formalized as follows:

$$N_b = 10^7 \text{ positrons} \quad (10)$$

$$\Phi_{avg} = \frac{f_{rep} \cdot N_b}{Area} \quad (11)$$

$$\Phi_{inst} = \frac{N_b}{\tau_b \cdot Area} \quad (12)$$

The corresponding time-averaged ($\dot{D}_{avg}$) and peak instantaneous ($\dot{D}_{peak}$) dose rates are evaluated through:

$$\dot{D}_{avg} = \frac{S(E)}{\rho} \cdot \Phi_{avg} \cdot K \quad (13)$$

$$\dot{D}_{peak} = \frac{S(E)}{\rho} \cdot \Phi_{inst} \cdot K \quad (14)$$

where $K = 1.602e^{-8}$ is the conversion factor for units of measurement consistency.

The effective temporal compression ratio $\dot{D}_{peak}/\dot{D}_{avg} = 1/(\tau_b \cdot f_{rep}) = 1 \times 10^{10}$ forces the instantaneous dose delivery to exceed ultra-high dose rate boundaries (≥ 40 Gy/s), entering in an equivalent paradigm of the FLASH therapy radiobiological paradigm (Favaudon et al., 2014) with the intent to enlarge the observation time of the sample.

2.3. Approximate radiobiological modeling and tissue repair kinetics

To determine cellular endpoints, the classic radiobiological Linear-Quadratic (LQ) equation for the computation of the cellular survival fraction (SF) is expanded into the time domain to incorporate the dual phenomena of sub-lethal damage repair protraction ($G(\mu, t)$) and ultra-high dose rate tissue sparing ($h(\dot{D}_{peak})$) (Brenner, 2008):

$$SF(D) = \exp(-\alpha D - \beta \cdot h(\dot{D}_{peak}) \cdot G(\mu, t) \cdot D^2) \quad (15)$$

where the total accumulated physical dose is explicitly tracked as a function of elapsed wall-clock time: $D(t) = \dot{D}_{avg} \cdot t$, $h(\dot{D}_{peak})$ is the FLASH sparing factor as a function of the instantaneous dose rate, and $G(\mu, t)$ is the Lea-Catcheside Protraction factor. The radiobiological sensitivity parameters assigned to the hepatic endothelial lineage are defined by a linear coefficient $\alpha = 0.10$ Gy $^{-1}$ and a quadratic coefficient $\beta = 0.05$ Gy $^{-2}$, establishing a low tissue-specific α/β ratio of 2.0 Gy characteristic of late-responding normal organs (Son et al., 2013; Franken et al., 2013).

The survival fraction (SF) presented in Eq. (15) is a foundational concept in radiobiology used to estimate cellular sensitivity to ionizing radiation. It represents the percentage or ratio of living cells that remain functional and capable of reproducing after being exposed to a specific absorbing dose.

2.3.1. The Lea-Catcheside protraction factor

The temporal mitigation of the quadratic indirect damage component due to continuous enzymatic repair during extended exposures is quantified by the dimensionless Lea-Catcheside protraction factor $G(\mu, t)$ (Lea and Catcheside, 1942). Sourcing the *in vitro* molecular repair half-life for liver cells as $T_{1/2} = 0.5$ h (1800 s), the monoexponential, first-order biological repair rate constant is established as $\mu = \ln(2)/T_{1/2} \approx 3.8508 \times 10^{-4}$ s $^{-1}$ (Brenner, 2008). The analytical G -factor is evaluated as a function of total irradiation duration ($t = D/\dot{D}_{avg}$) using the Dale formulation (Dale, 1985):

$$G(t) = \frac{2[\mu t - 1 + \exp(-\mu t)]}{(\mu t)^2} \quad (16)$$

Because biological reactions happen much slower than the initial physical radiation events, the average dose rate over time ($\dot{D}_{avg}$) is the most relevant metric for determining biological effects.

For the pulsed regime, the inter-pulse periods (< 1 ms) are several orders of magnitude shorter than the enzymatic repair half-life ($T_{1/2} = 30$ min), thus the intracellular molecular repair machinery remains

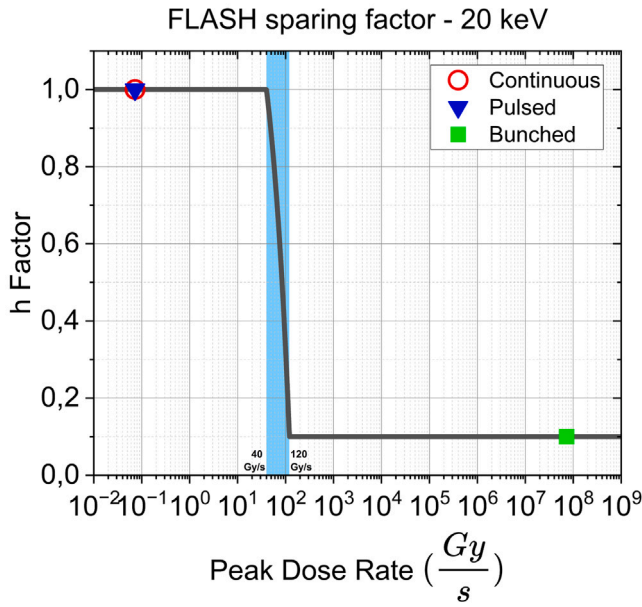


Fig. 2. Phenomenological FLASH sparing factor h as a function of instantaneous peak dose rate. The operating points of the continuous, pulsed and bunched regimes at 20 keV are highlighted; the bunched configuration sits beyond the 120 Gy/s saturation threshold, achieving the maximum sparing $h_{\min} = 0.10$.

entirely insensitive to discrete micro-structures, experiencing the beam as a continuous stream. This is not entirely true for the bunched regime: in this case positrons reach the sample every 100 s, giving the tissue some time for initiating repair mechanisms between bunches. Dale (1999) and Hyland et al. (2014). We found that when the product μt is smaller than 10^{-8} , the direct numerical evaluation of Eq. (16) in our Python code becomes unstable because the expression approaches an indeterminate form. To avoid this numerical issue, we use the second order Taylor expansion of Eq. (16), given in Eq. (17), which is an accurate approximation in this regime.

$$G(t) = 1.0 - \frac{\mu t}{3.0} \quad \text{for } \mu t < 10^{-8} \quad (17)$$

2.3.2. Phenomenological FLASH sparing factor

The transient normal tissue protection triggered under ultra-high dose rate conditions is governed by the chemical hypothesis of Radiolytic Oxygen Depletion (Pratx and Kapp, 2019). Under FLASH dose rate delivery regime (>40 Gy/s), local dissolved oxygen is consumed via radiolytic radical interactions significantly faster than capillary blood flow can replenish it via passive diffusion, establishing a protective state of transient hypoxia that suppresses the fixation of indirect DNA lesions (Montay-Gruel et al., 2019). This behavior is modeled phenomenologically by applying the scaling modifier $h(\dot{D}_{\text{peak}})$ directly to the quadratic component. Based on validated preclinical thresholds (Montay-Gruel et al., 2017; Vozenin et al., 2019), $h(\dot{D}_{\text{peak}})$ is mathematically implemented as a continuous, vectorized piecewise linear ramp function (2) triggered strictly by the instantaneous peak dose rate:

$$h(\dot{D}_{\text{peak}}) = \begin{cases} 1.0 & \text{if } \dot{D}_{\text{peak}} \leq 40 \text{ Gy/s} \\ 1.0 - (1.0 - h_{\min}) \frac{\dot{D}_{\text{peak}} - 40.0}{120.0 - 40.0} & \text{if } 40 < \dot{D}_{\text{peak}} \leq 120 \text{ Gy/s} \\ h_{\min} = 0.10 & \text{if } \dot{D}_{\text{peak}} > 120 \text{ Gy/s} \end{cases} \quad (18)$$

Specifically, the value $h_{\min} = 0.10$ reflects a maximum 90% suppression of indirect radical damage, consistent with reported *in vivo* oxygen depletion thresholds (Vozenin et al., 2019; Bourhis et al., 2019).

3. Results

3.1. From positron flux to cellular dose

The central biological question motivating this work is whether variable energy positron beams in the 5–100 keV range, required for depth-resolved PAS analysis of *in vitro* biological layers, can be used without compromising the viability of inspected living samples. To assess this, we adopt literature derived viability thresholds based on hepatic sinusoidal cells from which we can estimate the optimal dose values (Park et al., 2012; Jirtle et al., 1982). Specifically we highlighted three ranges of survival fractions (SF): 99%, 95% and 90%. In the first, the cell population retains essentially full viability. The accumulated dose in this case is within an adaptive response range ($< \sim 100$ mGy) (Vaiserman, 2010; Feinendegen, 2005) where ionizing radiation has been shown to activate antioxidant defences, DNA damage surveillance, and cell cycle checkpointing rather than causing net biological injury (Feinendegen, 2005; Vaiserman, 2010). Then, when the threshold of 5% cell death is reached, there is a moderate sub-lethal damage, compatible with structural measurements if surviving cells remain representative of intact tissue. In the last case, by approaching the limit of what can be called physically non-destructive, a significant committed cell death and early structural alterations (membrane leaking, organelle fragmentation) may be distorting the nanoscale structural landscape probed by positronium. These thresholds provide the biological criterion against which all dosimetric results below are evaluated. A PAS measurement that keeps $SF \geq 99\%$ throughout its duration is considered non-destructive by any reasonable definition and therefore a preferable functioning regime. Consequently, one that drives SF below 90% yields a o-Ps lifetime altered by annihilation events happening from dying and structurally compromised cells, undermining the nanoscale structural and chemical information that the technique can provide. The dose rate $\dot{D}$ delivered to a cell culture depends on two physically distinct quantities: the positron fluence rate ϕ [$e^+ \text{ mm}^{-2} \text{ s}^{-1}$], determined by the beam configuration and source activity, and the mass stopping power S/ρ [$\text{MeV} \times \text{cm}^2 \times \text{g}^{-1}$], determined by the beam energy and tissue composition. Considering the cellular constituent of the hepatic sinusoidal cells that PAS would be used to probe, the stopping power spans from $S/\rho = 42.7 \text{ MeV} \times \text{cm}^2 \times \text{g}^{-1}$ at 5 keV to $S/\rho = 4.24 \text{ MeV} \times \text{cm}^2 \times \text{g}^{-1}$ at 100 keV, which means that in the investigated energy span the stopping power experience a ten-fold decrease according to the Bethe-Bloch model. Then, positron energy determines the implantation depth in the sample (and whether the cellular compartment is probed by positron annihilation), and the rate at which radiation is absorbed in the sample (dose rate). The two contributions cannot be decoupled: the energy determines both the biological sample depth profiling with PAS, and how quickly cells are damaged. Table 1 reports the computed average and peak dose rates for the tested beam configurations and energies. The continuous ^{22}Na slow positron beam delivers average dose rates spanning from 0.1 Gy/s at 5 keV to 0.01 Gy/s at 100 keV. The pulsed configuration reduces the average by one decade for each energy due to inherent positron transport inefficiencies, while leaving the instantaneous dose rate unchanged ($\dot{D}_{\text{peak}} = \dot{D}_{\text{cont}}$). The bunched working regime presents instead a different scenario: the average dose rates are one order of magnitude below the ^{22}Na continuous source, identical to the pulsed regime. Differently, the instantaneous dose rates can reach values in the range of 10^7 to 10^8 Gy/s during each 10 ns bunch, therefore exceeding the FLASH saturation threshold of 120 Gy/s (Vozenin et al., 2019).

3.2. The survival Fraction–Dose relationship. How much radiation can an *in vitro* tissue tolerate under a slow positrons beam?

Before asking how long an intravital PAS experiment can safely last, it is worth establishing the dose at which each viability threshold is crossed. In the continuous and pulsed working regimes, the 99%

Table 1
Computed stopping powers and dose rates in the three positron beam configurations.

Energy [keV]	Stopping power [MeV cm ² /g]	Continuous beam		Pulsed beam		Bunched beam	
		$\dot{D}_{\text{avg}}$ [Gy/s]	$\dot{D}_{\text{peak}}$ [Gy/s]	$\dot{D}_{\text{avg}}$ [Gy/s]	$\dot{D}_{\text{peak}}$ [Gy/s]	$\dot{D}_{\text{avg}}$ [Gy/s]	$\dot{D}_{\text{peak}}$ [Gy/s]
5	42.67	2.2×10^{-1}	2.2×10^{-1}	2.2×10^{-2}	2.2×10^{-1}	2.2×10^{-2}	2.2×10^8
10	24.62	1.3×10^{-1}	1.3×10^{-1}	1.3×10^{-2}	1.3×10^{-1}	1.3×10^{-2}	1.3×10^8
15	17.80	9.1×10^{-2}	9.1×10^{-2}	9.1×10^{-3}	9.1×10^{-2}	9.1×10^{-3}	9.1×10^7
20	14.15	7.2×10^{-2}	7.2×10^{-2}	7.2×10^{-3}	7.2×10^{-2}	7.2×10^{-3}	7.2×10^7
50	6.94	3.5×10^{-2}	3.5×10^{-2}	3.5×10^{-3}	3.5×10^{-2}	3.5×10^{-3}	3.5×10^7
100	4.24	2.2×10^{-2}	2.2×10^{-2}	2.2×10^{-3}	2.2×10^{-2}	2.2×10^{-3}	2.2×10^7

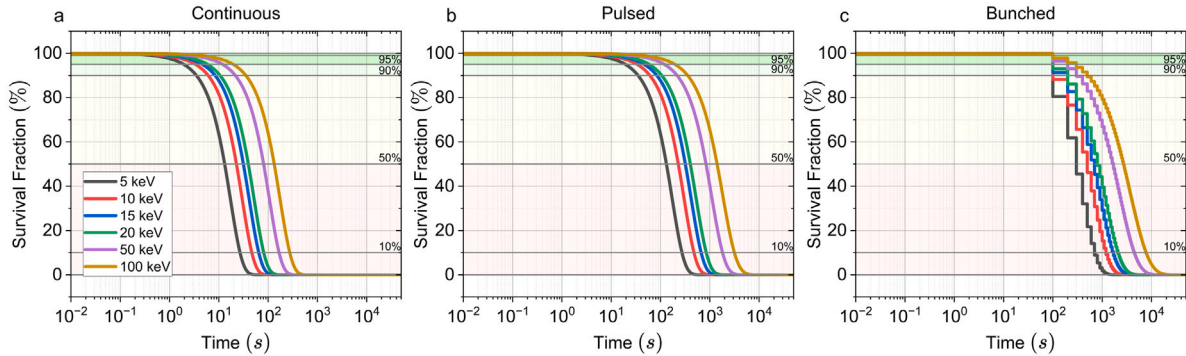


Fig. 3. Survival fraction (SF) as a function of wall-clock irradiation time for the continuous (left), pulsed (center), and bunched (right) beam configurations, at six implantation energies (5–10–15–20–50–100 keV). Horizontal bands mark the 95%, 90%, 50% and 10% viability thresholds.

viability boundary, falls at a dose value of $D \approx 100$ mGy at almost all energies. Then, the cells are in the linear region of the LQ model, where $\beta \cdot D^2 \ll \alpha \cdot D$. The threshold is determined almost entirely by α , and the 99% boundary is nearly the same regardless of β , G , or h . In the bunched source case, the situation is completely different since the bunched source delivers dose only in discrete quantity, one bunch of positrons at a time. Therefore, $SF = 99\%$ is not achievable at any energy in the bunched regime. Even at 100 keV, the first bunch already delivers 216 mGy and reduces SF to 97.8%. The adaptive threshold of $D = 100$ mGy is smaller than a single bunch at every energy, making the 99% viability level unattainable in the bunched regime. A 95% threshold is reachable only at 100 keV (equal to 2 “bunches”, with a dose of ≈ 432 mGy) and at 50 keV (1 bunch, dose of ≈ 354 mGy), while a 90% survival fraction is accessible at 100 keV with 4 “bunches” and 864 mGy, requiring between 38% and 41% more dose than the continuous source, reflecting FLASH and repair protection (Table 2). This drives the cells SF toward the pure exponential Eq. (15) and shift the median lethal dose LD_{50} from ≈ 2.8 Gy to ≈ 5.8 Gy, under the assumption that bunch peak dose rate governs FLASH sparing. Therefore, looking at the SF panels of Fig. 3, one notices that the bunched source produces a visible energy spread. Specifically, at $t \approx 40$ min the SF spans from effectively 0% (5 keV) to $\sim 64\%$ (100 keV). This spread reflects the energy dependence of the stopping power, since higher-energy positrons have a lower S/ρ , therefore depositing less energy to these cells at any given time. In the bunched regime $G \approx 0.5$ – 0.7 and $h = 0.1$ across all energies, so $G \times h \approx 0.05$ – 0.07 , which is 90 times lower the value for the continuous and pulsed regime. This means that the β term contributes negligibly to the LQ model.

3.3. How long can a positrons-based measurement last?

The biological utility of any PAS experiment on living tissue ultimately reduces to a single question: before the cellular viability degrades beyond an acceptable threshold, how many annihilation events can be recorded? A statistically robust positron lifetime spectrum typically requires $\sim 10^6$ – 10^7 counts (Wagner et al., 2018), demanding acquisition windows of tens of minutes to hours depending on the source configuration and detector efficiency.

Continuous beam

For the continuous regime, the 99% viability boundary ($D \approx 100$ mGy) is crossed in 0.44 s at 5 keV and 4.4 s at 100 keV. While, the 90% threshold requires only 3.5 s at 5 keV and 35 s at 100 keV (Table 2). Within one minute of continuous irradiation at 5 keV, the delivered dose already exceeds 13 Gy and the surviving fraction collapses to $< 0.01\%$. At 20 keV, the same 60 s window delivers 4.3 Gy and leaves $SF \approx 25\%$ (Fig. 4). Even at the most favorable energy of 100 keV, 5 min of continuous exposure accumulates 6.5 Gy ($SF \approx 7\%$), and 30 min delivers ~ 39 Gy. These figures correspond to a ^{22}Na source operated at its maximum potential, i.e. at the highest activity commercially available for beam-grade sources, $A_{22\text{Na}} = 50$ mCi (1.85 GBq), together with the moderation and transport efficiencies of Eq. (5) ($\eta_{\text{mod}} = 1.2 \times 10^{-3}$, $\eta_{\text{trans}} = 0.50$). Coupled to a digital acquisition system with a high efficiency detection system reaching 10^4 – 10^5 counts/s (Hirschmann et al., 2021; Yu et al., 2026), such a configuration allows a structurally meaningful lifetime spectrum to be collected in theory in few seconds, before the surviving fraction drops below the 90% structural-integrity limit in the 10–20 keV range relevant for depth-resolved biological spectroscopy (Dryzek and Singleton, 2006). We stress, however, that this represents an *upper-bound* (worst-case) dose: the 90% window already lies below the strict non-destructive criterion ($SF \geq 95\%$), so a genuinely non-destructive acquisition would require deliberately scaling the source flux down, at the price of proportionally longer integration times to reach the same counting statistics (see for instance Ref. Vicini et al. (2025)).

Pulsed beam

The pulsed configuration extends the time window for measurements by exactly one decade across all energies, since $\dot{D}_{\text{avg}}^{\text{pulsed}} = \mu_{\text{trans}} \dot{D}_{\text{cont}} = 0.10 \dot{D}_{\text{cont}}$. The 99% boundary is now reached in 4.4 s (5 keV) to 44 s (100 keV), and the 90% boundary in 35 s to 355 s. While this modest improvement shifts the time to reach the LD_{50} from 13 s–133 s (continuous) to 132 s–23 min (pulsed), it is still far removed from the measurement durations needed for a long term robust spectroscopy measure. Crucially, because the instantaneous peak dose rate during each 2 ns open window equals $\dot{D}_{\text{cont}}$ (0.02–0.22 Gy/s

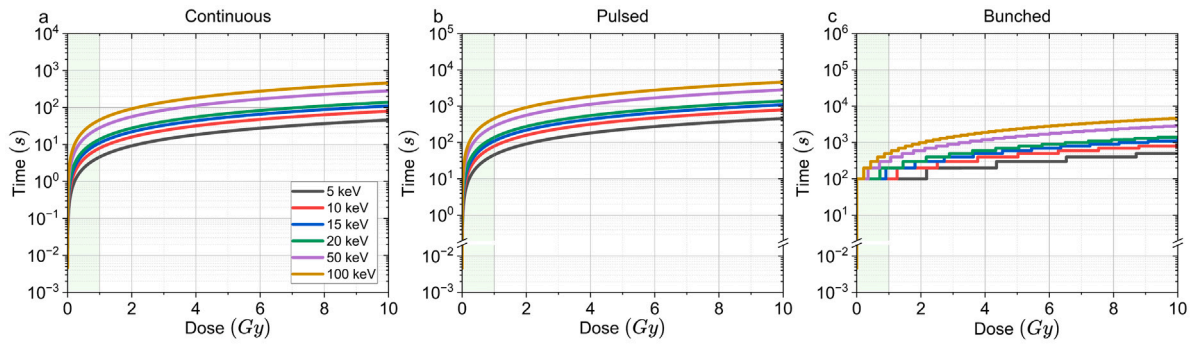


Fig. 4. Wall-clock time required to accumulate a given absorbed dose, for the three beam configurations at six implantation energies. The shaded region indicates doses below the 1 Gy of deposited dose.

Table 2

% Cell surviving fraction (SF) for the three beam regimes, evaluated simultaneously at the discrete wall-clock times $t = n_b \times T_{\text{rep}}$ ($T_{\text{rep}} = 100$ s) imposed by the bunched source. Each row represents the state of the irradiated sample after exactly n_b bunch-delivery events; all three regimes share the same elapsed time t , making the comparison physically meaningful.

E [keV]	n_b	t [s]	Surviving fraction SF [%]		
			Continuous	Pulsed	Bunched
5	0	5	84.45	98.86	nb
	0	10	63.38	97.61	nb
	0	30	6.14	91.68	nb
	1	100	≈ 0	63.55	80.44
10	0	5	92.06	>99	nb
	0	10	81.46	98.67	nb
	0	30	33.67	95.61	nb
	1	100	≈ 0	81.53	88.20
15	0	5	94.57	>99	nb
	0	10	88.60	>99	nb
	0	30	52.49	96.95	nb
	1	100	≈ 0	87.64	91.32
20	0	5	95.82	>99	nb
	0	10	90.62	>99	nb
	0	30	63.65	97.62	nb
	1	100	3.66	90.64	93.04
50	0	10	95.91	>99	nb
	0	30	84.98	98.88	nb
	1	100	37.69	95.92	96.52
	2	200	4.23	90.89	93.06
100	0	30	91.75	>99	nb
	1	100	63.86	97.63	97.86
	2	200	25.95	94.89	95.73
	3	300	6.83	91.82	93.60

Continuous: $\dot{D}_{\text{avg}} \in [0.022, 0.218]$ Gy/s (100–5 keV); no FLASH ($h = 1$); dose $D_c = \dot{D}_c \cdot t$.
Pulsed: $\dot{D}_{\text{avg}} = 0.10 \dot{D}_c$, $\dot{D}_{\text{peak}} = \dot{D}_c$; no FLASH ($h = 1$); dose $D_p = 0.10 \dot{D}_c \cdot t$.
Bunched: $\dot{D}_{\text{peak}} \sim 10^7\text{--}10^8$ Gy/s; FLASH active ($h = 0.10$); inter-bunch repair $\mu T_{\text{rep}} = 0.038$.

across the energy range), no FLASH protection is activated ($\dot{D}_{\text{peak}} \ll 40$ Gy/s) and the quadratic damage term of the modified LQ model is active, with $h(\dot{D}_{\text{peak}}) = 1.0$ at all energies. The pulsed regime thus provides no radiobiological advantage, but it acts as a time-tagging method for PALS (Sperr et al., 2008).

Bunched beam

The bunched regime presents a qualitatively different scenario driven by two concurrent mechanisms. In fact, the instantaneous peak dose rate during each bunch ($\dot{D}_{\text{peak}} \sim 10^7\text{--}10^8$ Gy/s) strongly exceeds the FLASH saturation threshold by five to six orders of magnitude, activating a probable oxygen-depletion protection with $h = h_{\text{min}} = 0.10$ (Favaudon et al., 2014; Vozenin et al., 2019). Additionally, the 100 s inter-bunch interval permits significant sub-lethal damage repair: $\mu T_{\text{rep}} = 0.038$, corresponding to $\sim 3.8\%$ repair per cycle, which drives

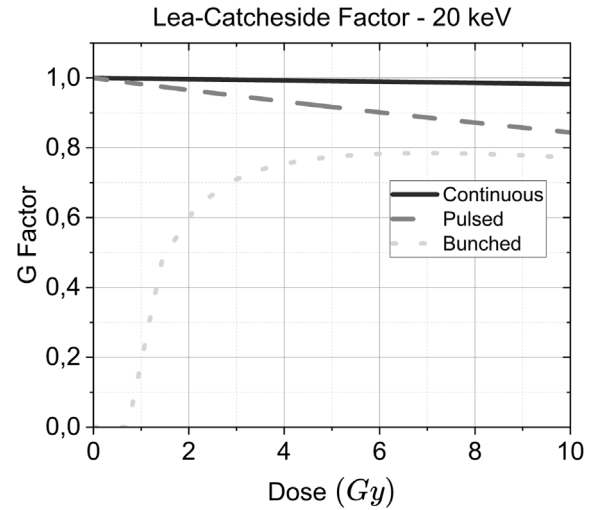


Fig. 5. Lea-Catcheside protraction factor $G(\mu, t)$ as a function of accumulated dose at 20 keV, for the three beam regimes. G remains close to unity in the continuous regime, decreases mildly under pulsed delivery, and collapses toward 0.5–0.7 in the bunched regime as the 100 s inter-bunch interval permits significant enzymatic repair.

the G factor toward a value of 0.5–0.7 (Dale, 1985) (Fig. 5), shifting the survival curve from exponential behavior toward the linear $SF \approx e^{-aD}$. Together, these effects raise the mathematical LD_{50} from ≈ 2.86 Gy (continuous) to $\approx 5.7\text{--}5.98$ Gy (bunched), and increase the dose required for 90% cell killing by 33–38% depending on beam energy.

However, the discrete nature of dose delivery imposes a hard quantization constraint. Each bunch delivers a minimum dose $\Delta D_b = \dot{D}_{b,\text{avg}}/f_{\text{rep}}$, spanning from 216 mGy (100 keV) to 2176 mGy (5 keV). At 100 keV, the most favorable configuration, the viability thresholds are crossed as follows: after the first bunch ($t = 2.0$ min), $D = 216$ mGy and $SF = 97.9\%$; after two bunches ($t = 4.0$ min), $D = 432$ mGy and $SF = 95.7\%$; after four bunches ($t = 8.0$ min), $D = 864$ mGy and $SF = 91.4\%$. The 90% viability threshold is therefore crossed within ten minutes at 100 keV. For the PAS-critical range of 5–20 keV, even the first bunch delivers 720–2170 mGy, immediately driving SF below 95% (at 20 keV) or 80% (at 5 keV), making no $SF \geq 99\%$ measurement achievable at any energy in the bunched regime. Table 2 summarizes these operational windows across all configurations.

The energy–time–damage trade-off

Integrating our dosimetric and radiobiological computational hypothesis, the following operational guidelines emerge for hepatic endothelial tissue: a **continuous beam** can be used only for intravital measurements at 20 keV lasting < 1.3 s ($SF > 99\%$) or < 11 s (SF

>90%). Recently, efficient digital spectrometers coupled to positron beam reached 10^4 – 10^5 counts/s (Hirschmann et al., 2021; Yu et al., 2026), meaning that in our considered scenario, it would be possible to collect between 10^5 – 10^6 events before $SF < 90\%$. Therefore, despite we estimate unreasonable to obtain meaningful events with $SF < 99\%$, statically spectroscopic acquisition can be acquired before the tissue experience strong structural damages. The usage of a **pulsed beam** can extend these operational windows to <13 s ($SF > 99\%$) and <1.8 min ($SF > 90\%$) at 20 keV. These working regimes are still below practical acquisition thresholds, however theoretically they could allow the collection of at least 10^7 annihilation event to compute a full lifetime spectrum. Unlike the conditions available at higher energies, the pulsed regime at 20 keV barely allows studies targeting moderate cell-survival criteria (~ 80 – 85% SF) over exposures of 2–3 min, critically limiting the time available for assessing early radiation-induced structural changes via Ps lifetime shifts (Moskal et al., 2023; Karimi et al., 2023).

The **bunched beam** at 20 keV imposes severe constraints due to the highly localized energy deposition, yielding a massive minimum discrete increment of ~ 720 mGy per bunch ($t = 2.0$ min, $E = 20$ keV). A single-bunch protocol ($t = 100$ s, $D \approx 720$ mGy, $SF = 93\%$) already fails to satisfy strict non-destructive criteria ($SF > 99\%$), while a two-bunch sequence ($t = 200$ s, $D \approx 1.44$ Gy, $SF = 86.1\%$) further compromises viability. The large dose per bunch and absence of fine dose control preclude $SF > 95\%$ operation entirely. Although an adaptive dose-fractionation strategy by delivering one bunch, acquiring data during the subsequent repair interval, and repeating, could exploit the inter-bunch repair window to partially restore sublethal damage, this approach is rigidly bounded by the $e^{-\alpha D}$ irreversible component, which dominates the rapid killing at this energy.

These results indicate that, among the three regimes, the bunched configuration at 20 keV maintains SF above the 90% threshold for a single bunch (2 min); however, since no regime satisfies the strict $SF \geq 95\%$ non-destructive criterion in the 5–20 keV window, this establishes as an instrumental challenge for new intravital positrons' spectrometers.

4. Discussion

Our dosimetric numerical framework presents the evolution of Vicini et al. (2025) and a preliminary quantitative estimate of absorbed dose and cellular survival for monoenergetic positron beams in the 5–100 keV range relevant to depth-resolved PAS of *in vitro* biological samples.

Across all the three considered beam regimes, the possible measurement duration scales as $1/S(E)$, varying by the full Bethe-Bloch stopping-power ratio $S(5 \text{ keV})/S(100 \text{ keV}) \approx 10$ over the modeled energy range. Because low implantation energies, which are those required to probe cellular monolayers and thin cultures (Bass et al., 2023; Karimi et al., 2023), also produce the highest stopping powers, the two quantities demanded by intravital PAS (fine axial resolution and low damage rate) are physically anti-correlated. These evidences, in our opinion, highlight that both continuous and pulsed regimes may provide potential destructive measurements in living wet materials.

Specifically, our finding that positrons deposit dose efficiently in soft tissue is consistent with the computational comparison of Arêas and Ballester (2025) at MeV energies, extended here for the first time into the keV regime relevant to slow-positron beams. The viability thresholds adopted (99/95/90% SF) are grounded in the low-dose adaptive-response literature (Feinendegen, 2005; Vaiserman, 2010; Guéguen et al., 2018), where sub-100 mGy exposures activate antioxidant and DNA-repair pathways rather than net injury, supporting our identification of the 99% boundary (≈ 100 mGy) with the upper limit of the hormetic regime.

In our calculations, the bunched regime was modeled providing the maximal FLASH sparing ($h = h_{\min} = 0.10$) for the provided instantaneous dose rates 10^7 – 10^8 Gy/s, values that are comparable with

the one obtained by Kroll et al. (2022). Therefore, characterizing the FLASH effect by the intra-bunch peak dose rate represents the least conservative metric and worst case scenario for the biological tissue, to our knowledge. The physical conditions under which radiolytic oxygen depletion can provide tissue sparing are far more constrained than implied by the instantaneous peak alone. Therefore, the effect is conventionally defined by the mean dose rate over the entire exposure, which must exceed ~ 40 Gy/s and be delivered in less than 200 ms (Montay-Gruel et al., 2017; Vozenin et al., 2019).

In our computed bunched regime, the dose accumulates across bunches separated by 100 s. Consequently, the overall mean dose rate drops to the order of 10^{-2} Gy/s, leaving only the isolated 10 ns pulses to satisfy the instantaneous dose-rate criterion. Moreover, the tissue-sparing mechanism depends heavily on delivery timing where the sparing only occurs if consecutive pulses strike before dissolved oxygen can re-equilibrate, which requires intervals below 50 ms (Zhu et al., 2021). This required interval is vastly shorter than our actual inter-bunch spacing. Ultimately, this separation of timescales mirrors the conditions in our model that allow for sub-lethal damage repair between individual bunches (Dale, 1985; Prax and Kapp, 2019).

The trap-based accumulation of positrons allows to modulate the delivery time structure from the 10 ns short bunch to what it is called slow extraction: by slowly ramping the electric potential barrier of the trap, the release of positrons is smeared across a wider time window. This mode of operation could reduce the instantaneous dose rate, while producing bunches with the required inter-bunch intervals to avoid oxygen re-equilibration in the tissue. A range of different function modes is available that will open the possibility to optimize the positrons per bunch and repetition rate, increasing the admissible time of acquisition and reducing the absorbed dose in living tissues.

Irrespective of the sparing factor, the bunched regime is strictly constrained by the discrete nature of its dose delivery. A single bunch deposits between ≈ 216 mGy (100 keV) and ≈ 2176 mGy (5 keV). These values of dose per bunch are compatible with ranges present in literature of 0.3–3 Gy/s (Ashraf et al., 2022; Giuliano et al., 2023). Thus, the 99% viability level, corresponding to ≈ 100 mGy, lies below the dose delivered by a single bunch at any incident energy, rendering it mathematically unreachable. Even the 95% viability threshold is met only marginally at the 100 keV limit. Ultimately, it is dose quantization, rather than the total accumulated dose, that precludes fine control over the survival fraction, a systemic limitation specific to trap-based bunching and absent in continuous or pulsed beams.

The practical conclusion for intravital PAS is that sample viability is governed not by the choice of time structure of the working regime (continuous, pulsed, or bunched) but by the time-averaged flux delivered to the sample. Operating a continuous or pulsed beam at the deliberately attenuated flux of the state-of-the-art apparatus ($\sim 10^{-4}$ Gy/s) keeps a multi-hour acquisition within a sub-gray total dose, whereas the bunched regime offers FLASH and repair protection at the cost of coarse, sub-gray dose quantization unsuitable for the strict non-destructive threshold.

5. Conclusions

We have presented the first quantitative dosimetric framework for low-energy (5–100 keV) monoenergetic positron beams applied to *in vitro* biological samples, with explicit reference to depth-resolved positron annihilation spectroscopy of hepatic endothelium. By coupling the Berger-Seltzer mass collision stopping power for positrons in a multi-elemental liver target with three realistic beam architectures (continuous ^{22}Na , pulsed, and bunched), each evaluated at the maximum positron flux attainable from a ^{22}Na source, we computed both the time-averaged and the instantaneous absorbed dose rates, and propagated them through a time-resolved Linear-Quadratic survival model accounting for sub-lethal damage repair (Lea-Catcheside G factor) and ultra-high dose rate tissue sparing (phenomenological FLASH

h-factor). Three findings emerge from this analysis. First, the average dose rate delivered to a sample is governed by the time-averaged positron flux reaching the target, and is essentially decoupled from the temporal microstructure of the beam: the continuous, pulsed, and bunched configurations differ by at most one order of magnitude in delivered dose, with the bunched and pulsed regimes both ≈ 10 times below the continuous one. Second, the bunched regime activates two protective mechanisms simultaneously, the FLASH oxygen depletion sparing within each 10 ns burst (peak dose rate 10^7 – 10^8 Gy/s, far exceeding the 120 Gy/s saturation threshold) and partial sub-lethal damage repair across the inter-bunch interval, yielding an effective LD_{50} that is approximately twice that of the continuous source. Third, since all dose figures are computed at this maximum attainable ^{22}Na flux, they represent the upper-limit (worst-case) doses deliverable by a system of this kind; under these conditions none of the three regimes is compatible with strict non-destructive operation ($SF \geq 95\%$) over the acquisition windows required for statistically robust positronium lifetime spectroscopy in the 5–20 keV range, most relevant to depth-resolved cellular probing. The necessary time to complete the acquisition of a statistically relevant lifetime spectrum is between 2–6 s for the continuous regime, 4–13 s for the pulsed, and a single pulse for the bunched, requiring a detection system with a high count rate. This makes it essential to quantify, for each regime, by how much the flux — and therefore the delivered dose — must be reduced to stay below the $SF \geq 95\%$ limit, while still collecting the counts needed for a statistically meaningful spectrum over the correspondingly longer acquisition time. It is far more feasible to acquire a useful spectrum before crossing the 90% viability limit (threshold for drastic changes in tissue structure) for all the three regimes. These results identify dose quantization in the bunched regime, and time-averaged flux attenuation in the continuous and pulsed regimes, as the two practical levers available to push intravital PAS toward the non-destructive limit. They also frame a clear set of open questions, namely (i) the experimental measurement of the LQ parameters and repair kinetics on the specific cell line of interest, (ii) the cross-validation of the predicted survival fractions against Live&Dead assays developed for this apparatus, and (iii) the extension of the present transport model with Monte Carlo depth-dose profiling, so that dose and implantation depth, and hence damage and spatial resolution, can be jointly optimized. Bridging these gaps will determine whether monoenergetic positron beams can ultimately deliver on the promise of nanoscale, depth-resolved, non-destructive spectroscopy of living matter.

CRediT authorship contribution statement

Matteo Vicini: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Paola Folegati:** Writing – review & editing, Formal analysis, Conceptualization. **Giancarlo Maero:** Writing – review & editing, Supervision. **Leonardo Resciniti:** Writing – review & editing, Investigation, Formal analysis. **Rafael Ferragut:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Formal analysis, Conceptualization. **Claudio Conci:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The code supporting the findings of this study is publicly available on GitHub at <https://github.com/clod91s/ALFRED>.

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