



# A Toolkit for Cellular Level Radiation Dosimetry

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**Abstract** — Investigating the irradiation of cells is essential for elucidating cellular responses to diverse doses and modalities of ionizing radiation. Such radiobiological studies typically involve exposing arrays of cells to radiation beams to analyze the interactions between energetic particles and cellular constituents. To facilitate the computational modeling of these experiments, we introduce *cellmaker*, an open-source toolkit developed to simulate the *in vitro* and *in vivo* irradiation of cell arrays. This toolkit generates both uniform and randomized cell array geometries and features automated spatial randomization of the cell nucleus within the array. The simulated Bragg peak at 1150  $\mu\text{m}$  demonstrated an absolute difference of 78  $\mu\text{m}$  (a 6.35% relative deviation) from the 1228- $\mu\text{m}$  National Institute of Standards and Technology reference 10-MeV proton range, mainly due to coarse scoring thicknesses. Validation of the present model confirms the accurate cellular geometry, seamless integration with the Particle and Heavy Ion Transport code System (PHITS) Monte Carlo package, and good dosimetric agreement with MIRDcell.

**Keywords** — Cellular dosimetry, Monte Carlo method, open source, cell irradiation, nuclear radiation.

## I. INTRODUCTION

Monte Carlo (MC) methods play an essential role in cellular level radiation dosimetry and have become increasingly important in medical physics research [1]. Their importance is evident across a wide range of applications. In radionuclide therapy, cellular-scale S-values [2] are used to quantify the dose delivered not only to radiolabeled cells but also to neighboring cells, allowing the evaluation of cross-fire effects [3–7].

In boron neutron capture therapy, the therapeutic effect depends strongly on the spatial distribution of  $^{10}\text{B}$  at both intercellular and intracellular levels, and many studies have therefore computationally examined the relationship between  $^{10}\text{B}$  heterogeneity and biological response [8–10].

In particle therapy, cellular level dose heterogeneity is also of considerable importance [11–13]. For example, the stochastic microdosimetric kinetic model has shown that stochastic dose deposition and its dispersion at cellular scales can significantly affect the biological effectiveness of heavy-ion therapy [14,15]. In addition, cellular level dose evaluation is increasingly being

explored in radiological protection as a basis for more mechanistic assessment of radiation risks from internal exposure [16,17]. Therefore, accurate simulation tools for describing radiation transport and dose deposition at cellular scales are of considerable importance.

In earlier work, we investigated the irradiation of cellular monolayers using neutron [11] and photon [9] beams, as well as extensive cell arrays for proton boron fusion therapy [12] using the MC methods. Moreover, we modeled a comprehensive nine-cell configuration comprising cytoplasm and nucleus arranged on a uniform grid as described in Ref. [18] and examined its response to proton beams of varying incident energies [8].

Given the large number of variables that influence dosimetric outcomes including sensitivity parameters, irradiation geometry, and cellular organization, it is essential to conduct thorough sensitivity analysis. Consequently, a flexible, user-friendly toolkit is required to enable the construction of detailed cellular arrays while granting complete control over geometric configurations, irradiation conditions, and tally definitions. Such a toolkit would ensure methodological consistency, reproducibility, and equitable comparison across studies, thereby facilitating comprehensive, transparent, and robust assessments of cellular level radiation dosimetry.

In the present work, we introduce `cellmaker`, an open-source toolkit that enables users to generate cell arrays with either uniform or random arrangements with *in vitro* and *in vivo* options. The `cellmaker` toolkit offers complete control over a wide range of parameters, including the number of cells; cellular and nucleus dimensions and flatness; intercellular pitch; thickness of the overlying buffer medium; source particle type; energy and geometry; MC computation settings; and the material composition of the cytoplasm, nucleus, buffer, and surrounding environment. In addition, `cellmaker` automatically generates dose, track, and geometric tallies.

The novelty of `cellmaker` lies in bridging the gap between simplified analytical dosimetry and highly complex MC modeling. While analytical tools like MIRDcell provide rapid dosimetric evaluations, they fundamentally rely on idealized, concentric spherical geometries and precalculated S-values that cannot account for full particle transport physics or morphological variations.

Conversely, advanced MC toolkits such as GATE [19–29] and Geant4-DNA [30] offer exceptional physical accuracy but demand extensive programming expertise, while native Particle and Heavy Ion Transport code System (PHITS) modeling requires labor-intensive and error-prone manual scripting. `cellmaker` removes these technical barriers via a lightweight, open-source, graphical user interface

(GUI)–driven platform that automatically generates complex two-dimensional (2D) *in vitro* and three-dimensional (3D) *in vivo* ellipsoidal cell populations. It introduces automated stochastic placement algorithms for eccentric nuclear positioning while rigorously preventing cell overlap and membrane protrusion. Crucially, `cellmaker` eliminates human error by dynamically computing precise asymmetrical cytoplasm volumes and seamlessly integrating them into ready-to-run PHITS configurations, including the tallies, thereby making accurate cellular dosimetry accessible to a broader range of researchers.

The specific objective of this study is to establish the `cellmaker` framework and systematically evaluate its computational accuracy. In particular, our validation methodology is designed to rigorously verify all core aspects of the generated models, the precision of the geometry generation, the robustness of the stochastic algorithms for random cell and eccentric nucleus placement, and the fidelity of the underlying particle transport and dosimetry. Ultimately, we aim to demonstrate that this fully open-source toolkit provides a highly reliable and flexible resource for researchers conducting radiation dosimetry studies at the cellular level. The toolkit is interfaced with the PHITS MC package [31], thereby exploiting its advanced particle transport and dosimetry capabilities. We believe that this fully open-source toolkit will be a valuable resource for researchers conducting radiation dosimetry studies at the cellular level.

## II. MATERIALS AND METHODS

### II.A. Cellmaker Program Structure

The `cellmaker` program was implemented entirely in C++ programming language using the Qt framework (<https://www.qt.io/>), comprising approximately 1500+ source code lines. It provides a GUI (see Fig. 1) that enables intuitive interaction with the model. The current model provides two primary modes for cellular level dosimetry that are *in vitro* and *in vivo*. In the *in vitro* scenario, individual cells are modeled as half ellipsoids, whereas their nuclei are defined as full ellipsoids. Conversely, for the *in vivo* case, the cells are modeled entirely as full ellipsoids to reflect their placement within the body rather than on a flat petri dish. The system allows users to configure a wide range of geometric parameters, including the cell array dimensions, cell and nucleus diameters, intercell pitch, buffer thickness, and cell and nucleus flatness ratios. Furthermore, activating the *in vivo* option enables the user to specify the number

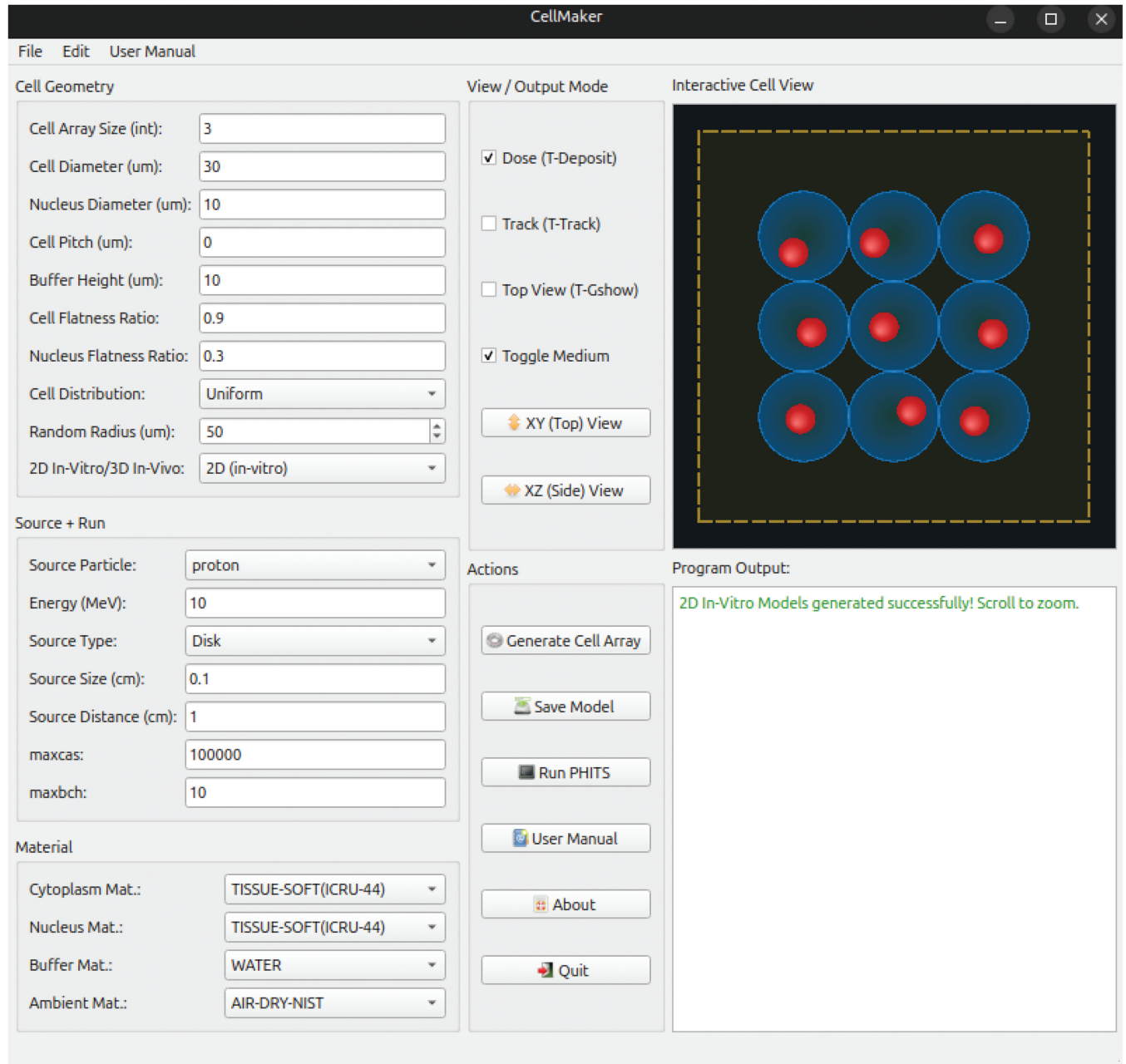


Fig. 1. The cellmaker program GUI in action.

of cell layers along the  $z$ -axis. This generates a 3D cellular structure with customizable interlayer spacing, which directly dictates the spatial configuration of the modeled cells (see Fig. 2). Finally, the program includes the option to employ either uniform or random cell distributions across both the 2D in vitro and 3D in vivo settings.

For the uniform configuration, cells are positioned on a square lattice comprising  $n^2$  elements, where  $n$  denotes the user-defined array size. In the random configuration, cell locations are generated by applying a random spatial

perturbation to points on a standard geometric lattice grid. For the in vitro case, each cell is displaced within a user-defined radius around its respective lattice node via uniform polar angle and radial sampling, while all cells remain on a constant  $Z = 0$  plane (the substrate). Considering the in vivo case, the cells will be placed along the  $Z$  coordinate as defined by the users. Regardless of the overall distribution scheme, the nucleus position within each cell is randomized by default:  $X$ ,  $Y$ , and  $Z$  coordinates are sampled uniformly within the bounds of the corresponding cytoplasmic domain, ensuring that each nucleus resides entirely inside its host cell.

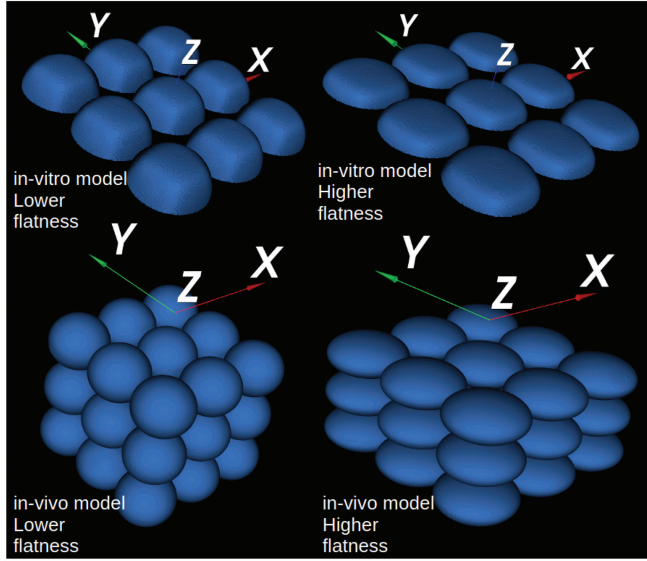


Fig. 2. Variation of cell shape for different flatness ratios and modeling modes.

The present toolkit incorporates comprehensive user-defined parameters for both particle source configuration and MC simulation settings. The source particle specifications include selection from fundamental particle types (proton, neutron, photon, and alpha particle) through a dropdown interface, alongside configurable source characteristics including energy, source geometry (disk or point source), source dimensions, and source-to-target distance. MC simulation parameters are customizable through user-defined controls for maximum histories (maxcas) and batch count (maxbch), enabling precise regulation of computational resources and statistical accuracy. Furthermore, the material specification encompasses four distinct

cellular and environmental components, namely, (1) cytoplasm, (2) nucleus, (3) buffer medium, and (4) ambient material. The model implements precise material definitions for seven distinct tissue types: (1) soft tissue, (2) water, (3) cortical bone, (4) adipose tissue, (5) A-150 plastic, (6) B-100 plastic, and (7) skeletal muscle.

The material composition for each defined material is shown in Table 1. The cellmaker automates material assignment procedures, seamlessly integrating predefined material properties with corresponding density values for each defined component. This comprehensive parameterization enables flexible and accurate modeling of diverse radiobiological scenarios while maintaining computational efficiency through automated material-handling modules. The GUI permits the user to selectively activate or deactivate dose scoring, track scoring, and geometrical view tallies.

## II.B. Visualization and Geometry Implementation

The program automatically produces 2D visualizations of the generated cell array using `QGraphicsEllipseItem` and `QPainterPath`. A top view panel displays the planar arrangement of cells together with the spatial distribution of their nuclei (see Fig. 3), whereas a side view panel depicts the vertical profile of the array. Depending on the selected mode, this side view illustrates either the semi-ellipsoidal cell morphology and curvature of the cellular dome (in vitro) or the full ellipsoidal morphology submerged within the tissue buffer (in vivo). The visualization routine is developed in C++ using the Qt framework.

For the 2D in vitro case, cell centers ( $c_x, c_y$ ) are mapped onto a planar lattice defined by

TABLE 1  
Elemental Composition of Materials (wt%) Implemented in cellmaker Program

| Material                           | Density (g/cm <sup>3</sup> ) | Elemental Composition (wt%)                                                            |
|------------------------------------|------------------------------|----------------------------------------------------------------------------------------|
| Tissue soft (ICRU-44) <sup>a</sup> | 1.06                         | H (10.5), C (25.6), N (2.7), O (60.2), Na (0.1), P (0.2), S (0.3), Cl (0.2), K (0.2)   |
| Water                              | 1.00                         | H (11.1), O (88.9)                                                                     |
| Bone cortical (ICRU-44)            | 1.92                         | H (3.4), C (15.5), N (4.2), O (43.5), Na (0.1), Mg (0.2), P (10.3), S (0.3), Ca (22.5) |
| Adipose tissue (ICRU-44)           | 0.95                         | H (11.4), C (59.8), N (0.7), O (27.8), Na (0.1), S (0.1), Cl (0.1)                     |
| A-150 plastic (ICRU-44)            | 1.127                        | H (10.1), C (77.6), N (3.5), O (5.2), F (1.7), Ca (1.9)                                |
| B-100 plastic (ICRU-44)            | 1.45                         | H (6.6), C (53.7), N (2.1), O (3.2), F (16.7), Ca (17.7)                               |
| Muscle skeletal (ICRU-44)          | 1.05                         | H (10.2), C (14.3), N (3.4), O (71.0), Na (0.1), P (0.2), S (0.3), Cl (0.1), K (0.4)   |
| Dry air (NIST) <sup>b</sup>        | 0.00129                      | C (0.0124), N (75.5267), O (23.1781), Ar (1.2827)                                      |

<sup>a</sup>ICRU: International Commission on Radiation Units and Measurements.

<sup>b</sup>NIST: National Institute of Standards and Technology.



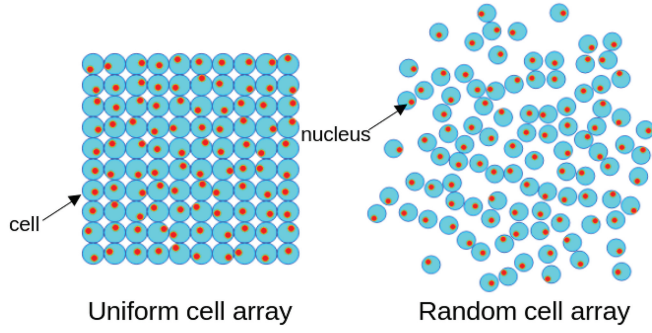


Fig. 3. Schematic diagram showing uniform and random cell array definitions implemented in the present model.

$$\begin{aligned} c_{x,i} &= i \cdot (d + p) - \frac{(N - 1)(d + p)}{2}, \\ c_{y,j} &= j \cdot (d + p) - \frac{(N - 1)(d + p)}{2}, \end{aligned} \quad (1)$$

where  $d$  = cell diameter (cellSize);  $p$  = spacing (CellPitch);  $N$  = number of cells per dimension.

When the 3D in vivo option is activated, the model extends this mathematical grid into a multilayer volumetric array. The vertical position of each cellular layer  $k$  is calculated as

$$c_{z,k} = -D_{depth} - r_z - k \cdot (2r_z + p_z), \quad (2)$$

where  $D_{depth}$  = user-defined tissue depth (depth);  $r_z$  = major vertical axis of the cell (actualCellRz);  $p_z$  = interlayer spacing along the  $z$ -axis (pitchZ);  $k$  = current layer index (from 0 to  $N_z - 1$ ).

To model random distributions, lattice points are perturbed by a displacement vector. In 2D mode, this vector is constrained within a disk of radius  $r_{user}$ . To ensure a uniform area distribution, the radial displacement  $r_{pos}$  is sampled as  $r_{user} \sqrt{U(0,1)}$ ; see Algorithm 1. In 3D mode, the perturbation expands to a spherical volume, where uniform random coordinates  $(u, v, w)$  are continuously sampled within a unit sphere and scaled by  $r_{user}$ . A rejection sampling loop (limit 1000) enforces physical validity in both modes by maintaining a minimum Euclidean distance between all cell centers. In 3D space, this safe collision distance is strictly defined as  $\max(d, 2r_z)$  to prevent overlapping of the fully modeled ellipsoids.

The half-ellipsoidal geometries for in vitro cells is taken from Ref. [18] and were previously utilized in our previous studies [11,32]. For in vivo representations, our full-ellipsoidal model builds upon the foundational spherical geometries established by standardized platforms like MIRDcell. However, our approach provides enhanced

flexibility by allowing users to independently adjust the cellular flatness ratio to better approximate diverse tissue morphologies. While we acknowledge the limitation that these idealized geometries cannot capture the complete structural irregularities of true biological cells, this method provides a necessary and practical balance between computational efficiency and morphological realism.

In order to strictly preserve the integrity of the MC geometry, the cellmaker code is explicitly designed to execute a hard abort. It never permits overlaps nor does it silently truncate the array. As implemented in the source code, if the maximum of 1000 rejection sampling iterations is exhausted without successfully finding a valid coordinate, the algorithm flags a failure state (placementOk = false). The program immediately breaks the generation loops, completely clears the cached cell array from memory [currentCellList.clear()], and outputs a hard error to the GUI (Error: Unable to place cells without overlap.). Because the generation function terminates, the software physically prevents the user from exporting a compromised, overlapping cell.inp file to PHITS. This fail-safe ensures all exported geometries are strictly free of Boolean spatial intersections. While effective for moderately packed environments, simple rejection sampling limits the maximum achievable packing fraction. Future versions targeting ultradense in vivo tissues will benefit from force-directed relaxation or random walk displacement algorithms to achieve higher densities without triggering generation aborts.

## II.C. Nucleus Spatial Constraints

To prevent the nucleus from protruding through the cellular boundary, distinct mathematical constraints are applied based on the selected physical model.

For the 2D in vitro semi-ellipsoidal model, placement is constrained using a bounding cylinder approximation. First, the absolute maximum vertical center position  $z_{max}$  is restricted to ensure that the full width of the nucleus can fit within the narrowing upper dome of the cell. The vertical position  $n_z$  is then sampled between the minimum valid floor height and  $z_{max}$ . To guarantee that the upper portion of the nucleus does not clip the inward curving cell wall, the maximum allowable lateral offset  $L_{max}$  is calculated using the available cell radius at the highest point of the nucleus ( $n_z + h_{nuc}$ ) as

$$L_{max} = \left[ \frac{d}{2} \sqrt{1 - \left( \frac{n_z + h_{nuc}}{h} \right)^2} \right] - r_{nuc}, \quad (3)$$

**Algorithm 1. Lattice-Perturbed Random Cell and Nucleus Placement**

**Require:** Grid  $N_x \times N_y \times (N_z + 1)$ , Cell radii  $(R_{xy}, R_z)$ , Nucleus radii  $(r_{xy}, r_z)$ , Pitch  $P$ , Mode (Uniform/Random), Max perturbation  $R_{rand}$

```

1:  $C_{placed} \leftarrow \emptyset$ 
2: For each base lattice node  $P_{base}$  in the grid do
3:    $placed \leftarrow \text{False}$ ,  $attempts \leftarrow 0$ 
4:   while not placed and attempts < 1000 do
5:     if Mode is Uniform then
6:        $P_{cand} \leftarrow P_{base}$ 
7:        $D_{safe} \leftarrow 0$  ▷ Lattice inherently safe
8:     else if 2D in vitro mode then
9:       Sample  $r \leftarrow R_{rand} \sqrt{U(0, 1)}$ ,  $\theta \leftarrow U(0, 2\pi)$ 
10:       $P_{cand} \leftarrow P_{base} + (r \cos \theta, r \sin \theta, 0)$ 
11:       $D_{safe} \leftarrow 2R_{xy}$  ▷ XY plane collision only
12:    else ▷ 3D in vivo mode
13:      Sample vector  $\vec{v}$  uniformly from within a unit ball
14:       $P_{cand} \leftarrow P_{base} + R_{rand} \vec{v}$ 
15:       $D_{safe} \leftarrow \max(2R_{xy}, 2R_z)$  ▷ 3D bounding collision
16:    end if
17:    if  $\min_{C \in C_{placed}} \text{dist}(P_{cand}, C) \geq D_{safe}$  then
18:       $C_{center} \leftarrow P_{cand}$ ,  $placed \leftarrow \text{True}$ 
19:    else
20:       $attempts \leftarrow attempts + 1$ 
21:    end if
22:  end while
23:  if not placed then return Error: Overlap unresolved
24:  end if ▷ Nucleus Membrane Protrusion Constraints

25:  if 3D in vivo mode then
26:     $S \leftarrow \max\left(\frac{r_{xy}}{R_{xy}}, \frac{r_z}{R_z}\right)$  ▷ Proportional scale factor
27:     $Safe_{rx} \leftarrow R_{xy}(1 - S)$ ,  $Safe_{rz} \leftarrow R_z(1 - S)$ 
28:    Sample  $\vec{u} = (u_x, u_y, u_z)$  uniformly from within a unit ball
29:     $\vec{n}_{offset} \leftarrow (u_x Safe_{rx}, u_y Safe_{rx}, u_z Safe_{rz})$ 
30:  else ▷ 2D in vitro dome mode
31:     $Z_{min} \leftarrow r_z$ 
32:     $Z_{max} \leftarrow R_z \sqrt{1 - (r_{xy}/R_{xy})^2} - r_z$ 
33:    Sample  $Z_{nuc} \sim U(Z_{min}, Z_{max})$ 
34:     $Safe_{rx} \leftarrow R_{xy} \sqrt{1 - ((Z_{nuc} + r_z)/R_z)^2} - r_{xy}$ 
35:    Sample  $r_{nuc} \leftarrow Safe_{rx} \sqrt{U(0, 1)}$ ,  $\theta_{nuc} \leftarrow U(0, 2\pi)$ 
36:     $\vec{n}_{offset} \leftarrow (r_{nuc} \cos \theta_{nuc}, r_{nuc} \sin \theta_{nuc}, Z_{nuc})$ 
37:  end if
38:   $C_{placed} \leftarrow C_{placed} \cup \{(C_{center}, C_{center} + \vec{n}_{offset})\}$ 
39: end for
40: return  $C_{placed}$ 

```

where  $r_{nuc}$  = lateral radius of the nucleus;  $h_{nuc}$  = vertical radius of the nucleus;  $d$  = cell diameter;  $h$  = overall cell height (majorZ). The final lateral position is sampled using polar coordinates within the safety radius  $L_{max}$ . The concept of nucleus spatial constraints is shown schematically for a circular nucleus region in Fig. 4.

Conversely, for the 3D *in vivo* model where both the cell and nucleus are represented as full ellipsoids, the constraint mechanism utilizes a proportional volumetric scaling approach. A maximum bounding ratio  $S$  is computed by evaluating the proportions of the nucleus radii to the cell radii:

$$S = \max\left(\frac{r_{nuc}}{r_{cell}}, \frac{h_{nuc}}{h_{cell}}\right). \quad (4)$$

This ratio establishes an internal safety domain, configured as an inner ellipsoid with radial boundaries  $r_{safe} = r_{cell}(1 - S)$  and  $h_{safe} = h_{cell}(1 - S)$ . The spatial coordinates of the nucleus center ( $n_x, n_y, n_z$ ) are subsequently determined by generating a uniform random vector ( $u, v, w$ ) within a unit sphere and projecting it onto this safe ellipsoidal domain. This methodology mathematically guarantees that the nucleus can be safely positioned anywhere within the 3D cytoplasm without breaching the outer cellular membrane.

The *cellmaker* algorithm employs a rigorous spatial and Boolean boundary checking protocol. First, it prevents cell-to-cell overlap during randomized generation via strict minimum distance rejection sampling. Second, it applies an explicit microscopic buffer margin

( $\epsilon = 10^{-6}$  cm) to eccentrically placed nuclei, guaranteeing they remain entirely within the cytoplasm. This prevents the shared boundary tracking errors common in MC engines. Finally, rather than using a static bounding box, the software dynamically sizes the outer tissue medium with a 20- $\mu$ m margin to prevent peripheral clipping. It then automatically generates mutually exclusive Boolean logic in the PHITS [Cell] section, completely eliminating undefined spatial intersections.

In summary, instead of relying on trial-and-error rejection sampling, our algorithm precalculates a strict internal safe bounding domain, making boundary violations mathematically impossible by design. To numerically verify this, we executed a stand-alone test generating 1 000 000 random cell-nucleus configurations using representative dimensions. The test yielded a 100% acceptance rate with exactly zero boundary violations.

## II.D. Program Output and Execution

The simulation parameters are encapsulated within a custom CompleteCell data structure, which stores the specific spatial coordinates ( $x, y, z$ ), cellular and nuclear semi-axes ( $r_x, r_z, n_{rx}, n_{rz}$ ), and dynamically allocated surface identifiers for every individual cell. A dedicated helper module, *phitsScriptGen*, parses this data array to systematically construct a fully compliant PHITS input file named *cell.inp* within the selected program output directory. The generation routine begins by writing the [Parameters], [Source], and [Material] sections based directly on the user GUI

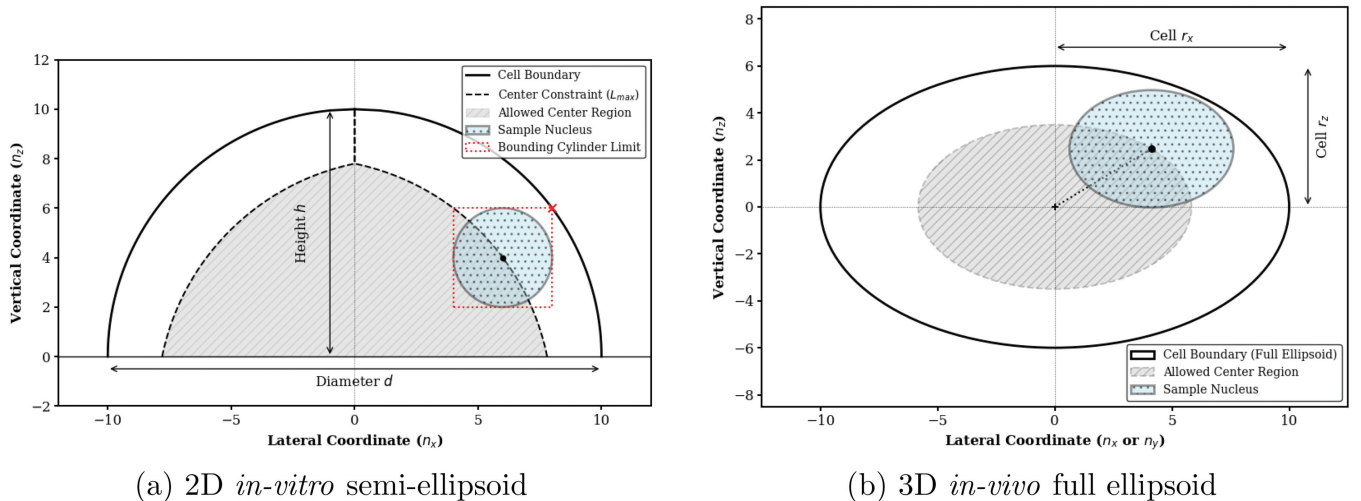


Fig. 4. Schematic diagrams illustrating the mathematical constraints applied to prevent the nucleus from protruding beyond the cellular boundary. (a) The bounding cylinder approximation utilized for the 2D semi-ellipsoidal cell model. (b) The proportional volumetric scaling approach implemented for the 3D full ellipsoidal cell model.

configurations, allowing for variable beam profiles (e.g., point or disk sources), projectile types, and standardized International Commission on Radiation Units and Measurements material assignments.

Within the [Surface] and [Cell] sections, the routine automates the complex mathematical definitions and Boolean logic required for the MC engine. Nucleus and cell boundaries are primarily defined utilizing the ELL (ellipsoid) geometry macro. For the 3D in vivo mode, these are defined as complete volumetric domains. For the 2D in vitro mode, a horizontal macroscopic cutting plane (PZ 0.0) is introduced to mathematically truncate the cellular ellipsoids into basal domes. The module automatically applies Boolean subtractive logic to hollow out the nucleus from the cytoplasm region, ensuring strictly discrete material boundaries without overlapping geometries. The entire cellular array is then submerged within an optimized rectangular parallelepiped buffer container, while the external boundaries are designated as a void space to safely terminate particle transport. Depending on the active user toggles, the script has the ability to append specialized tally cards for visualization and data collection, including [T - Gshow] and [T - Track]. Crucially, for microdosimetric scoring via the [T - Deposit] tally, the program automatically computes the exact analytical volumes of the complex cellular compartments to ensure accurate dose normalization. The nucleus volume is rigorously calculated as  $V_{nuc} = \frac{4}{3}\pi r_{x,nuc}^2 r_{z,nuc}$ . The cellular cytoplasm volume is subsequently derived by subtracting this nuclear volume from the overall cell body volume (utilizing  $\frac{4}{3}\pi$  for full ellipsoids and  $\frac{2}{3}\pi$  for in vitro semi-ellipsoids).

Finally, an integrated execution pipeline leverages the QProcess class to asynchronously launch the local MC engine (via phits.sh on GNU/Linux and phits.bat on Microsoft Windows, respectively) directly from the graphical interface. The routine establishes the working directory and pipes the standard output of the simulation log into the program GUI in the QTextBrowser widget. This provides users with seamless, real-time monitoring of the transport calculation and batch progression without the need to interface with external command line terminals.

The ATIMA database is utilized for continuous energy loss alongside the INCL model for nuclear reactions and cross sections, supplemented by evaluated data libraries for secondary particle transport. The PHITS default energy transport cutoff has been used for all particle types. For scoring, the toolkit simultaneously generates Cartesian grids for spatial visualizations

(normalized to mega-electron-volt per source) and region boundaries for compartment-specific cellular evaluations, with physical dose automatically normalized per primary source particle (gray per source).

## II.E. Computational Scheme

To demonstrate the functional capabilities of the cellmaker program, three distinct case studies for the in vitro mode were conducted involving a 9-cell uniform array, a 25-cell uniform array, and a 100-cell array featuring both uniform and random distributions. Protons were utilized as the primary source particles across all cases due to their precise range, which is instrumental in validating the generated geometry and their ability to secondary particles at high energies.

In the nine-cell-array configuration, two irradiation scenarios were evaluated, namely, (1) the irradiation of the entire array and (2) the targeted irradiation of the central cell using a perpendicular disk source having energy of 10 MeV. These models allowed for the precise determination of the absorbed dose within both the cellular cytoplasm and the nucleus, providing a granular assessment of primary beam energy deposition at the cellular level. Both cases were simulated using a disk source (*s-type* = 1) with maxcas = 100 000 and maxbch = 100, while maintaining PHITS defaults for the random seed and energy cutoffs.

The investigation was further extended to a 25-cell array to analyze the transport of secondary radiation and the resulting scattering effects on neighboring cells. By irradiating only the central cell with 70-MeV protons with a fixed buffer medium with thickness of 2000  $\mu\text{m}$  and varying the cell pitch across 0, 10, 30, and 90  $\mu\text{m}$ , the secondary alpha-particle dose delivered to nontargeted cells was quantified as a function of spatial separation. Finally, the 100-cell model was employed to compare uniform and random cellular distributions under a 30- $\mu\text{m}$  proton beam having 70-MeV energy under a fixed 3000- $\mu\text{m}$  buffer medium thickness. This large-scale simulation facilitated the generation of 3D dose distribution plots for the cellular cytoplasm, demonstrating the proficiency of the program in modeling complex, nonlinear geometries and visualizing energy deposition patterns across dense biological entities. The cases were simulated using a disk source (*s-type* = 1) with maxcas = 1 000 000 and maxbch = 100, while maintaining PHITS defaults for the random seed and energy cutoffs.

Considering the in vivo case, the  $3 \times 3 \times 3$  cell array was constructed for both uniform and random (with 50- $\mu\text{m}$  sampling radius) distribution modes. The



generated cell arrays were irradiated with a 70-MeV proton beam having 10- $\mu\text{m}$  radius [i.e., disk source,  $s\text{-type}=1$ ]. For both cases, the buffer medium thickness (i.e., in vivo depth) was set to 5000  $\mu\text{m}$ . After cell irradiation, the 3D dose distribution plots over the modeled cell domains were obtained. It needs to be noted that all the modeled cells in this computational scheme were considered to have a diameter of 30  $\mu\text{m}$ . Within the scope of this computational scheme, all case studies characterized the cellular cytoplasm and nucleus as soft tissue, utilizing water as the buffer medium. The cases were simulated with PHITS defaults for the random seed and energy cutoffs.

In order to illustrate the practical capabilities of the cellmaker program, a uniform and random  $7 \times 7$  in vitro cell array was modeled to simulate an internal irradiation scenario. For a simplified monoenergetic (incident energy of 5.83 MeV)  $^{225}\text{Ac}$  alpha-particle-emitting point source (it needs to be noted that PHITS requires ion energies in mega-electron-volts per nucleon), the alpha particle (four nucleons) was configured with an input energy of 1.4575 MeV/nucleon, yielding a total energy of 5.83 MeV, which represents the initial alpha-particle emission, and was positioned within a single cell in the array. The resulting alpha-particle dose dispersion in the cytoplasm and nucleus was scored. These results demonstrate the ability of the present model to report subcellular, compartment-specific dosimetric values, which is critical for accurate internal radiation dosimetry in clinically relevant applications. Both cases were simulated using a point source ( $s\text{-type}=9$ ) with  $\text{maxcas}=1\,000\,000$  and  $\text{maxbch}=100$ , while maintaining PHITS defaults for the random seed and energy cutoffs.

The cellmaker toolkit was developed and compiled using the GNU Compiler Collection version 16.1.1 and the cross-platform Qt framework version 5.15.19, specifically linking against the Qt5 Core, GUI, Widgets, and OpenGL libraries. While development and benchmarking were conducted on an Artix GNU/Linux operating system, the underlying Qt architecture natively supports cross-platform compilation. All MC particle transport simulations were executed using PHITS version 3.280 on a workstation equipped with an AMD Ryzen Threadripper 9960  $\times$  24-core processor (48 threads) and 128 GB of RAM.

### III. RESULTS AND DISCUSSION

In order to rigorously validate the compartment-specific dosimetric capabilities and geometric positioning

accuracy of our methodology, we conducted a direct benchmark comparison against the established MIRDcell (V4.17) standard. We defined a simplified two-cell model consisting of a 5- $\mu\text{m}$ -radius nucleus and a 15- $\mu\text{m}$ -radius outer cytoplasm for both cells, set at a center-to-center separation distance of 30  $\mu\text{m}$  in a unit density water medium (1.0 g/cm<sup>3</sup>). To ensure an exact 1:1 parameter match across all platforms, specific configurations were applied. In MIRDcell, we utilized the 1-D Cell Pair geometry, selecting a monoenergetic 5.83-MeV alpha-particle emitter and setting 100% of the activity to be uniformly distributed exclusively within the source cell nucleus. By default, cellmaker models a localized point source (within the nucleus or cytoplasm) and constructs realistic ellipsoidal cell morphologies. Therefore, we modified the cellmaker output script specifically for this benchmark to match the analytical assumptions.

First, we forced the ellipsoidal boundary definitions to perfectly spherical configurations by setting the cell and nucleus flatness ratios to 1.0 (equating the semi-axes). Second, we overrode the default point source configuration in the [Source] section to uniformly and isotropically sample the alpha-particle emissions throughout the entire volume of the primary cell nucleus. This was then evaluated against a manually constructed baseline PHITS script that natively used perfect spherical surfaces (SPH).

As detailed in Table 2, the dosimetric results demonstrated strong agreement across all three models. Both the self-absorbed dose  $D_{\text{self}}$  to the source nucleus and the cross-dose  $D_{\text{cross}}$  to the adjacent target nucleus calculated by the modified cellmaker script closely matched the manually constructed PHITS benchmark and the standard MIRDcell values. The minor dosimetric variances observed between the analytical (MIRDcell) and MC (PHITS) platforms are an expected consequence of their fundamentally different transport physics. By successfully reproducing these compartment-specific standard values, this cross validation directly confirms both the geometric coordinate precision of the cellmaker framework and the physical accuracy of the underlying transport engine.

The results shown in Fig. 5 illustrate the full irradiation of a uniform nine-cell array using 10-MeV protons across varying buffer medium thicknesses. The results indicate that the absorbed dose within the cell array that is placed underneath the buffer medium increases with buffer thickness until reaching the Bragg peak. This observation aligns with the theoretical maximum range of 10-MeV protons in the water medium, which is approximately 1200  $\mu\text{m}$ . The precise alignment between the peak dose deposition and this depth validates the

TABLE 2

Benchmark Comparison of Self-Absorbed Dose,  $D_{\text{self}}$ , and Adjacent Cell Cross Dose,  $D_{\text{cross}}$ , for a 5.83-MeV Alpha-Particle Generated Uniformly Within the Source Nucleus\*

| Dosimetry Platform | Geometry Generation   | $D_{\text{self}}$ (Gy/decay) | $D_{\text{cross}}$ (Gy/decay) |
|--------------------|-----------------------|------------------------------|-------------------------------|
| MIRDcell V4.17     | Analytical Standard   | 0.0931                       | 0.00185                       |
| PHITS (v3.28)      | Manual Spheres Script | 0.0969                       | 0.00197                       |
| PHITS (v3.28)      | cellmaker Script      | 0.0969                       | 0.00165                       |

\*The simplified 1:1 geometry assumes 5- $\mu\text{m}$  nuclei, 15- $\mu\text{m}$  cells, and a 30- $\mu\text{m}$  separation distance.

accuracy and consistency of the computational model. Notably, this trend remains consistent for both the cellular cytoplasm and the nucleus, suggesting a uniform energy deposition profile across different cellular compartments. Considering the dose in the cellular nucleus, the dose deposition curves for different cell nuclei exhibit slight variations for different cells. This could be due to the randomized placement of the cell nucleus within the cell domain that leads to slight variations in the dose deposition in the cell nucleus shown in Fig. 5 under the full uniform irradiation conditions.

The dose deposited by a 10-MeV proton beam in the central cell (cell 5) of the array is shown in Fig. 6 for different buffer thicknesses composed of water. In both the cytoplasm and the nucleus of the targeted cell, the absorbed dose rises with increasing buffer thickness, attains a maximum (the Bragg peak), and then declines to essentially zero at a thickness of roughly 1200  $\mu\text{m}$  corresponding to the range of 10-MeV protons in water. Peripheral cells receive negligible dose, consistent with

the limited lateral scattering of protons in matter and confirming that the beam delivers dose selectively to the intended central cell.

Fig. 7 presents the normalized alpha-particle dose deposited in the cytoplasm and nucleus of a 25-cell array when the central cell (cell 13) is irradiated with 70-MeV protons. The water equivalent buffer thickness is held constant at 2000  $\mu\text{m}$ . The dose profiles are shown for several intercellular pitch values, i.e., the center-to-center spacing between adjacent cells in the array. The layout of the cell array, together with the definition of the pitch distance, is illustrated schematically in Fig. 8. The diagram emphasizes that cell 13 is the sole target of the proton beam while the remaining cells are positioned symmetrically around it, either with a finite pitch (spacing) or in a tightly packed configuration (zero pitch).

Analysis indicates an inverse relationship between the alpha-particle dose and the distance from the primary irradiation site. The highest-dose concentrations are localized to cells in close proximity to the central target,

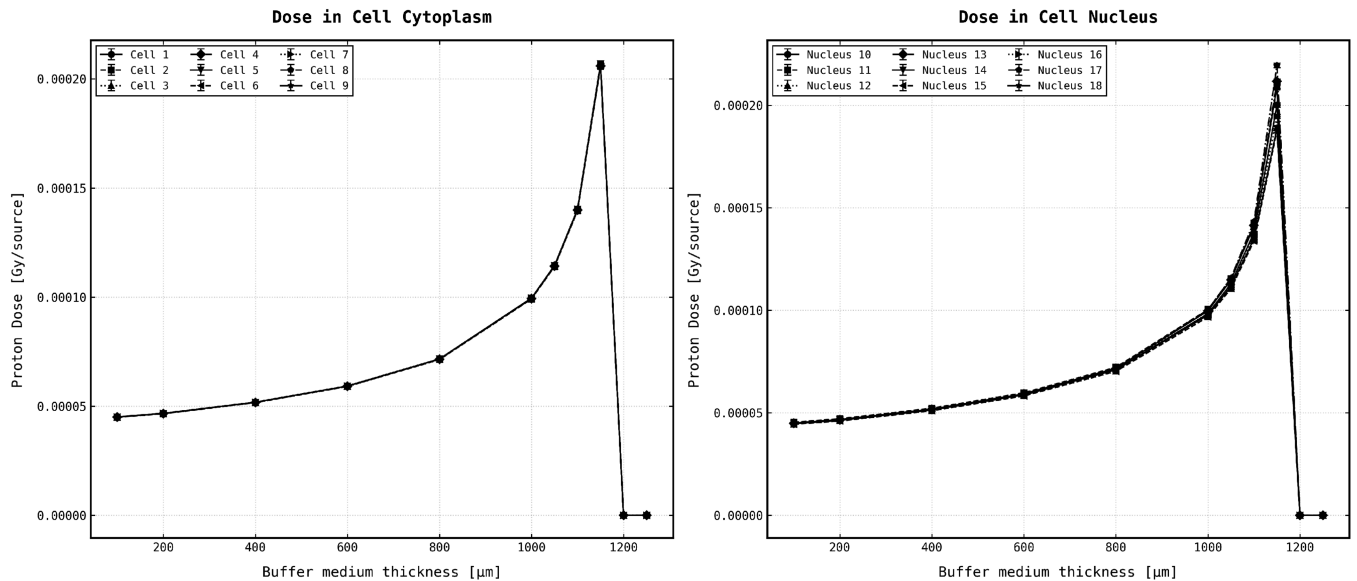


Fig. 5. The proton dose deposition versus buffer medium thickness for full irradiation of a uniform nine-cell array.

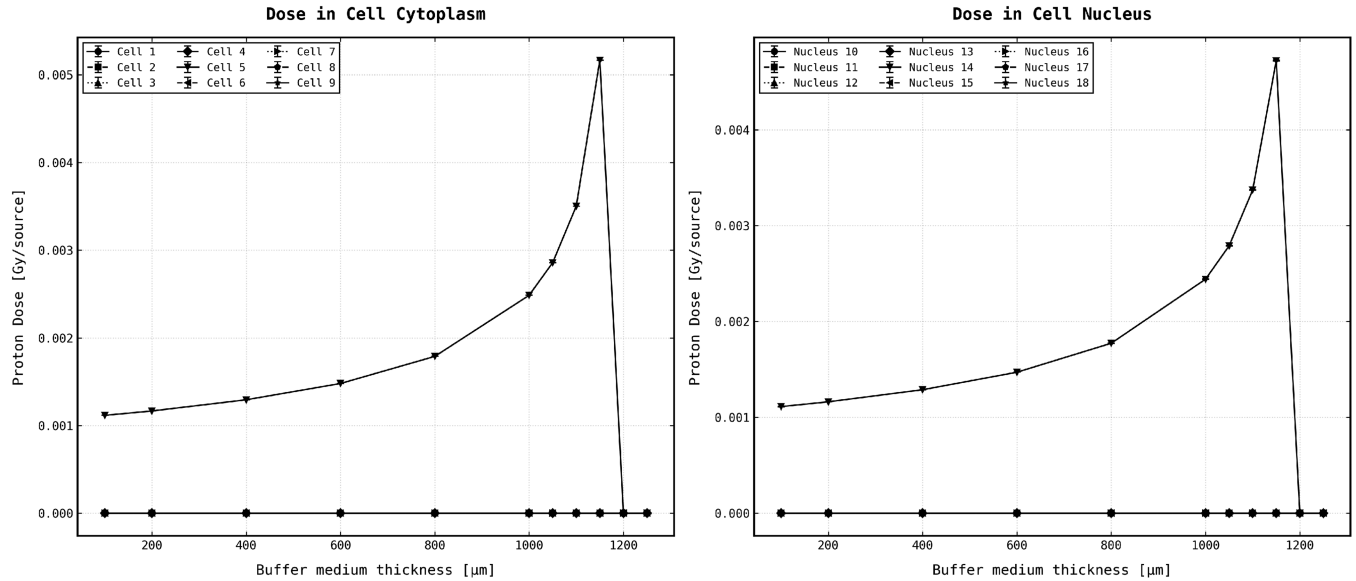


Fig. 6. The proton dose deposition versus buffer medium thickness for central cell irradiation of a uniform nine-cell array.

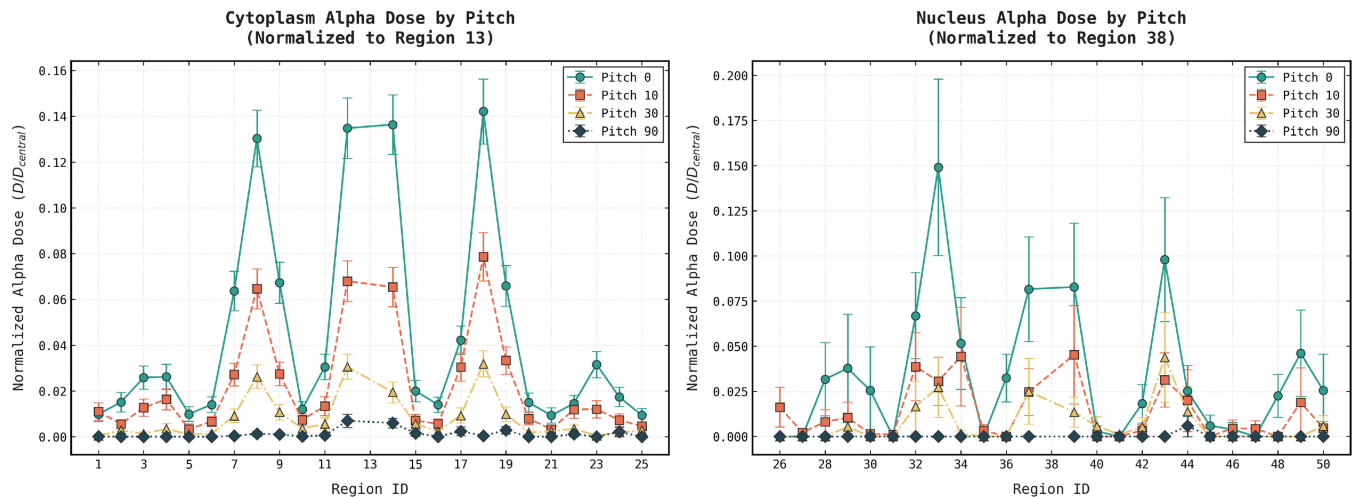


Fig. 7. Variation of normalized alpha-particle dose at different cells (i.e., region identifiers) exposed to proton beams having different pitch distances.

while more distal cells receive a diminished dose due to the inherent short-range nature of alpha particles produced during proton-matter interactions. Moreover, incremental increases in pitch distance specifically at 10, 30, and 90  $\mu\text{m}$  further attenuate the dose in neighboring cells, confirming that the spatial separation eventually surpasses the alpha-particle ionization path. This model effectively characterizes secondary particle scattering and spatial dose distribution, offering a robust framework for investigating the physical factors that may involve the bystander and rescue effect in cellular arrays. Previous studies have utilized the MC method to investigate the spatial characteristics of the bystander effect in sparsely

populated cell environments [33]. The cellmaker package offers this functionality natively, providing enhanced features and greater control.

Figs. 9 and 10 illustrate the 3D dose distributions for  $10 \times 10$  cell arrays (100 cells) in uniform and random arrangements, respectively. Following irradiation with a 30- $\mu\text{m}$ , 70-MeV proton beam, normalized doses were calculated for primary protons as well as secondary photons, neutrons, and alpha particles. In the uniform array configuration, the primary proton dose is highly localized, restricted almost exclusively to the four central cells directly within the path of the incident beam. This confirms a lack of significant lateral scattering for the

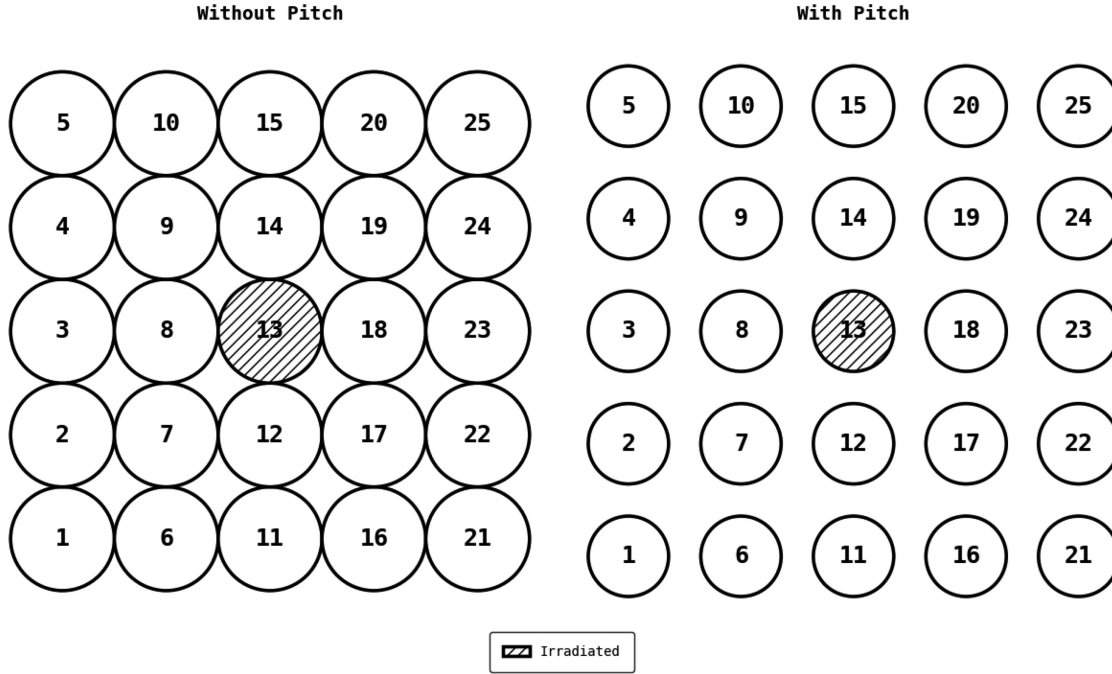


Fig. 8. Schematic diagram showing  $5 \times 5$  cell array without and with pitch distance. The central cell (region identifier 13) was set to be the target of proton beam irradiation.

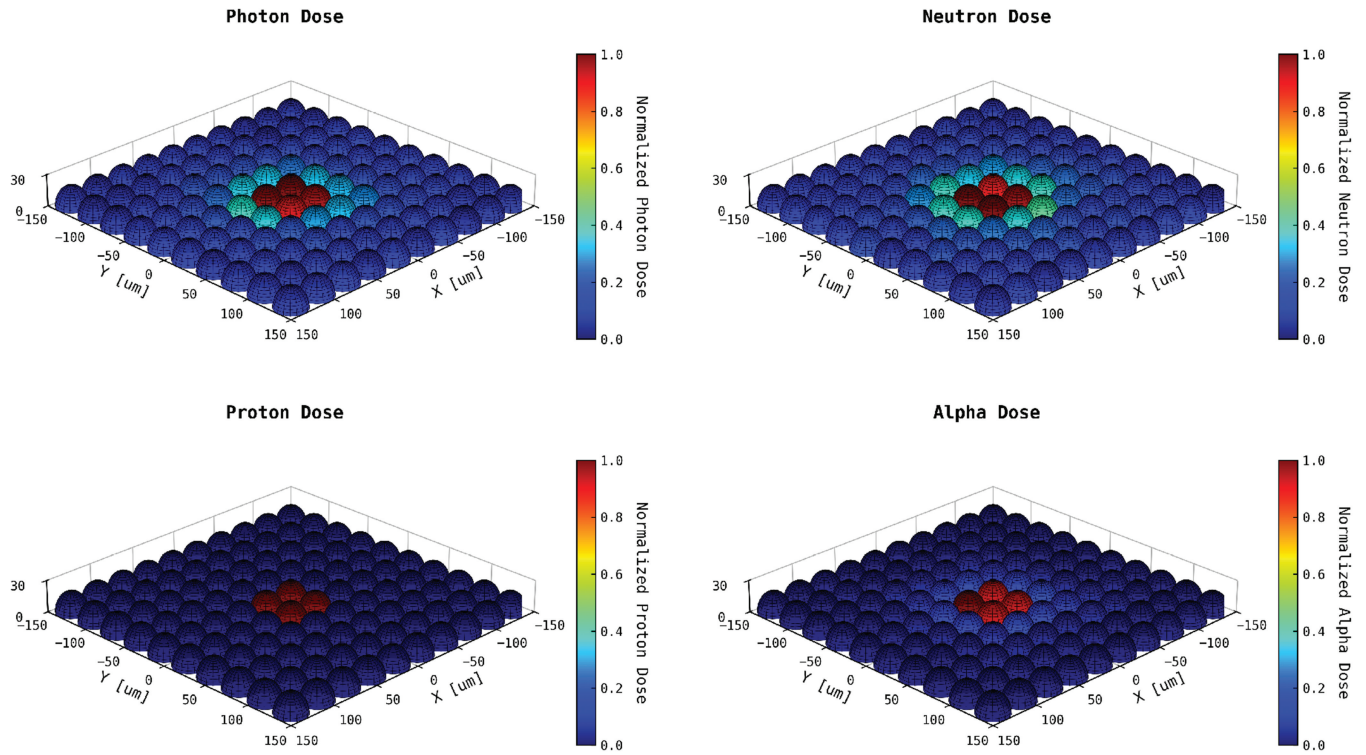


Fig. 9. The 3D dose deposition in  $10 \times 10$  uniform cell array by incident proton beam. Average relative errors for photons, neutrons, protons, and alpha particles are, respectively, 0.4418, 0.5183, 0.1628, and 0.7587 in the nucleus, and 0.1351, 0.1604, 0.0532, and 0.4777 in the cytoplasm.



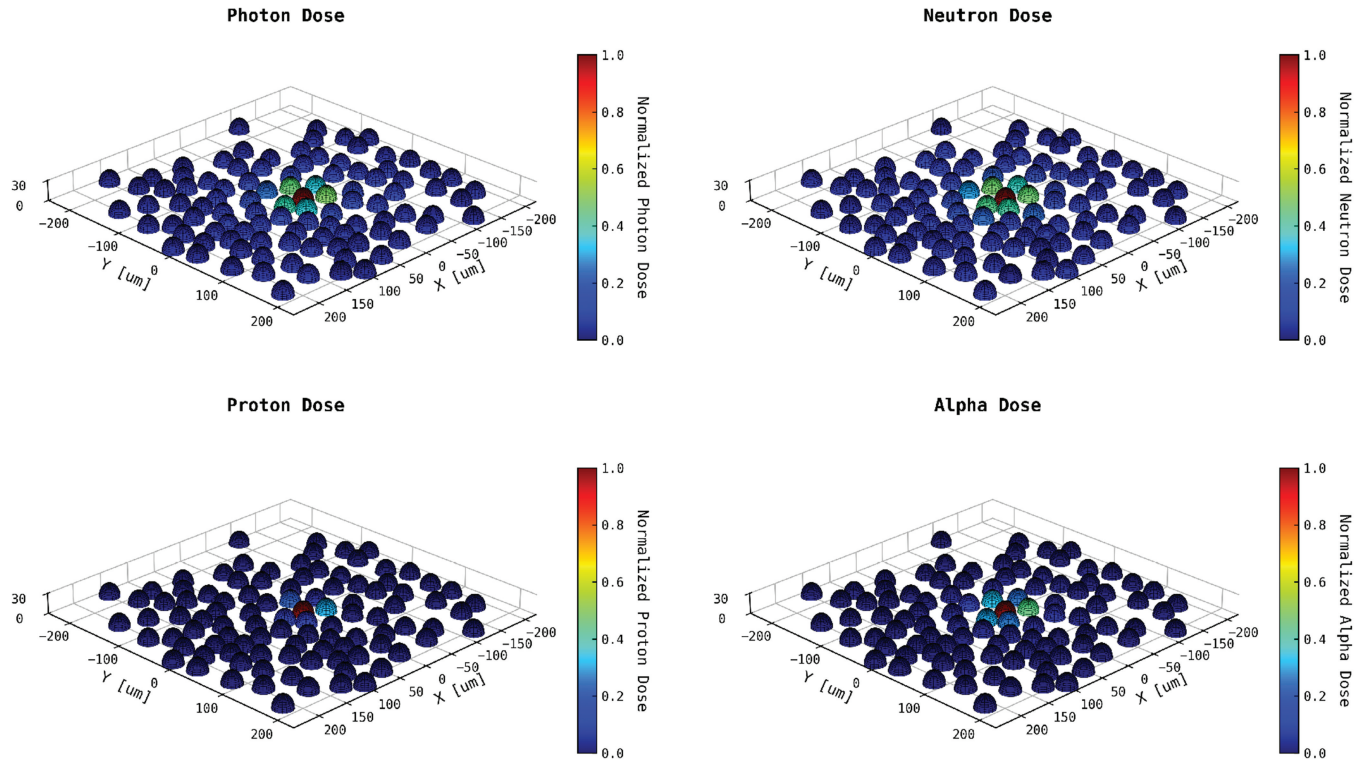


Fig. 10. The 3D dose deposition in  $10 \times 10$  random cell array by incident proton beam. Average relative errors for photons, neutrons, protons, and alpha particles are, respectively, 0.5094, 0.5826, 0.1874, and 0.8088 in the nucleus, and 0.1610, 0.1882, 0.0617, and 0.5962 in the cytoplasm.

primary beam. Conversely, secondary radiations exhibit varying degrees of lateral dispersion. Indirectly ionizing radiations that are photons and neutrons demonstrate nonnegligible dose deposition in distal neighboring cells due to their characteristically long mean free paths. In contrast, the dose distribution from heavily ionizing alpha particles remains concentrated in cells that were near the array center (cells surrounding the central four cells), governed by their well-defined and relatively short ranges in biological media.

The 3D dose deposition within a random cellular array, arising from primary protons and secondary photons, neutrons, and alpha particles, is illustrated in Fig. 10. The dose dispersion patterns for both primary and secondary particles exhibit distinct spatial spreading characteristics, primarily governed by the random distribution of cells within the modeled domain. The cells located in close proximity to the incident proton beam axis receive higher primary and secondary doses, whereas those located in peripheral regions undergo significantly lower dose deposition.

The 3D dose deposition profiles for the uniform and random cell arrays are illustrated in Figs. 11 and 12, respectively. The absorbed doses from primary protons,

as well as secondary photons, neutrons, and alpha particles, are visualized using a continuous color gradient mapped across the 3D geometries. Because the primary proton beam is defined with a 10- $\mu\text{m}$  radius at the center of both arrays, the maximum dose deposition within the uniform array is highly concentrated in the centrally located cells. Correspondingly, in the randomly distributed array, the cells positioned most closely to the central axis of the beam receive the highest primary proton dose.

In contrast to the highly localized energy deposition of the primary proton beam, the dose dispersion profiles for secondary photons and neutrons are substantially broader and more diffuse across both the uniform and random cell arrays. This pronounced scattering effect is primarily attributed to the fundamental physical properties of photons and neutrons. As uncharged and sparsely ionizing particles, they possess extended mean free paths and lower linear energy transfer (LET). Consequently, they penetrate and scatter extensively throughout the surrounding buffer medium and cellular array before depositing their energy.

Within the uniform cell array, this behavior generates a distinct and highly symmetrical radial dose gradient. While the maximum secondary dose remains



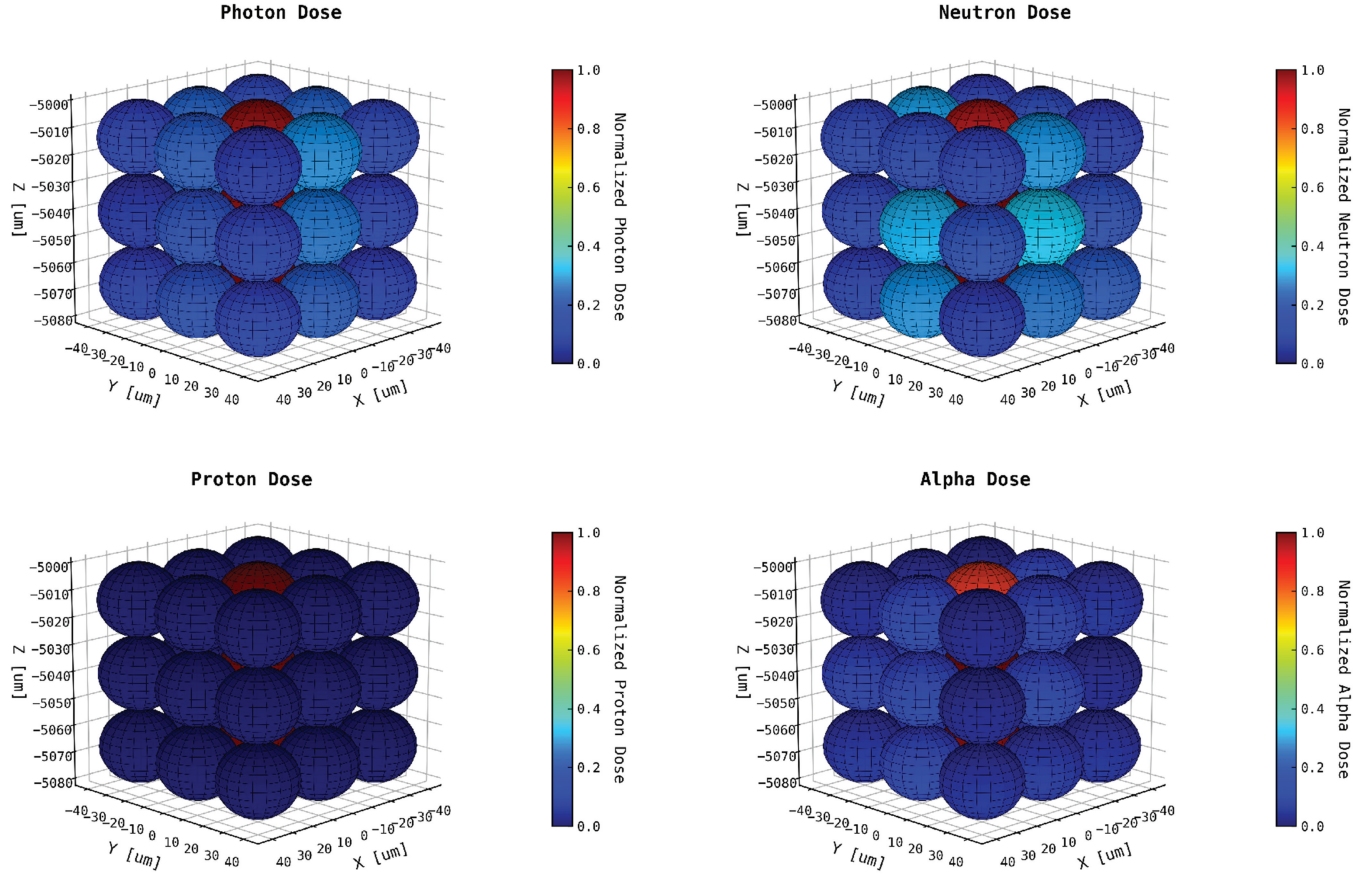


Fig. 11. The 3D dose deposition in  $3 \times 3 \times 3$  uniform cell array by incident proton beam. Average relative errors for photons, neutrons, protons, and alpha particles are, respectively, 0.7166, 0.7884, 0.2590, and 0.8257 in the nucleus, and 0.2150, 0.3041, 0.0999, and 0.4427 in the cytoplasm.

concentrated in the central cells closest to the primary beam axis, the absorbed dose steadily attenuates as a function of radial distance. As a result, the cells positioned at the extreme diagonal corners of the lattice (farthest out from the central interaction zone) receive the lowest secondary dose contributions. A parallel geometric attenuation is observed in the randomly distributed cell array. Despite the absence of a structured lattice, cells situated farther from the central axis of the primary beam still receive progressively lower doses of photons and neutrons. This spatial distribution directly reflects the reduction in secondary particle fluence, which intrinsically diminishes as the radial distance from the primary proton track increases.

Last, the dose deposition profile for secondary alpha particles exhibits a similar macroscopic trend but with a distinctly different spatial signature. Unlike the widespread, diffuse scattering patterns produced by secondary photons and neutrons, the alpha-particle dose is highly localized and sharply confined. This spatial restriction is a direct consequence of the intrinsic physical properties

of alpha particles. Alpha particles are heavy charged particles that are densely ionizing (exhibiting very high LET), and they rapidly deposit their energy over an extremely short range in the modeled domain. Consequently, the secondary alpha dose is almost entirely constrained to the immediate vicinity of the primary proton beam axis, with negligible lateral propagation into the surrounding cells.

The spatial configuration of cellular positions is a critical determinant of the total absorbed dose in cells. This is of particular significance in radiobiological studies, as cells in vivo and in vitro typically lack the uniform fixed lattice structure. By incorporating a randomized spatial distribution, the model would have the ability to model nonuniform large-scale cohorts (considering the stochastic nature of dose scoring in a random spatial distribution). Furthermore, this approach facilitates a deeper understanding of how physical parameters such as primary and secondary radiation components tend to influence cellular level dosimetry, particularly in the clinically sensitive low-dose regime.

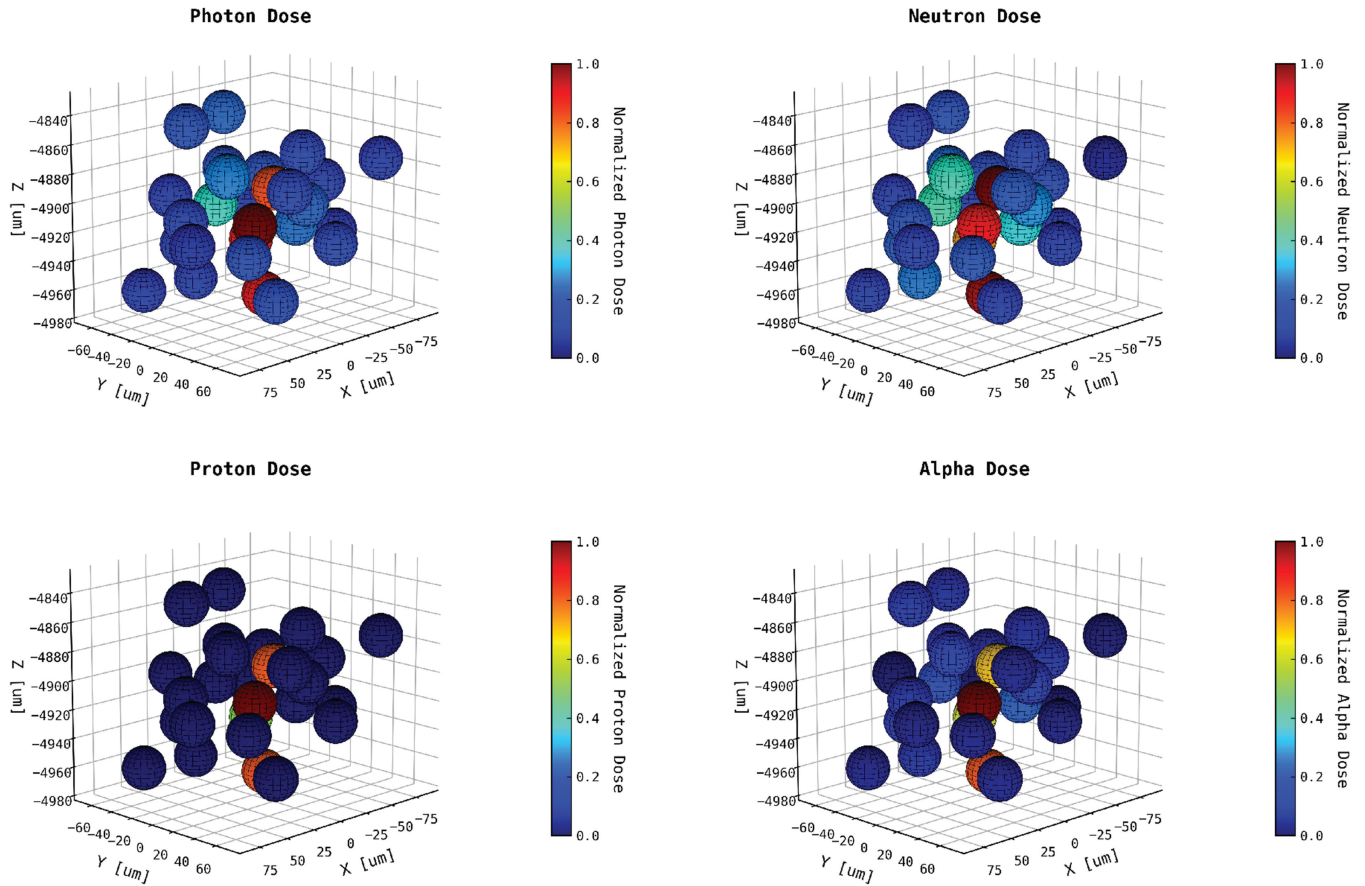


Fig. 12. The 3D dose deposition in  $3 \times 3 \times 3$  random cell array by incident proton beam. Average relative errors for photons, neutrons, protons, and alpha particles are, respectively, 0.6936, 0.7241, 0.2661, and 0.8471 in the nucleus, and 0.2044, 0.2899, 0.0955, and 0.4645 in the cytoplasm.

The results from the  $7 \times 7$  uniform and random cell array distributions from an internal alpha-particle-emitting source are shown in Figs. 13 and 14, respectively. The analysis of alpha-particle dose distributions reveals distinct dosimetric profiles dependent on the spatial geometry of the cell array. As illustrated by the probability density distributions (violin plots), both uniform and random cellular geometries exhibit highly skewed dose distributions. This pronounced skew is primarily due to the localization of the alpha-particle-emitting source strictly within the nucleus of a single cell in the array. Because the internal source is confined to one specific nucleus, it creates an extreme high-dose outlier for that single compartment, driving the long upper tail seen in the plots. While the source nucleus receives an exceptionally high dose, the remaining target nuclei receive less overall dose than their respective, broader cytoplasmic compartments.

Notably, the transition from a uniform array to a random array distribution fundamentally alters the dose dispersion morphology. The uniform model

produces a more stratified dose distribution resulting from the discrete, fixed distances between the single emitting point source and neighboring target cells. Conversely, randomizing the cellular coordinates introduces continuous intercellular distances. This geometric stochasticity smooths the probability density function, eliminates discrete dose tiering, and increases the overall variance within the lower-dose regimes. Consequently, the random distribution model captures a more continuous and realistic representation of energy deposition and dosimetric heterogeneity within complex biological tissues.

#### IV. SUMMARY AND CONCLUSIONS

In this work we have presented *cellmaker*, an open-source, C++/Qt-based toolkit that enables rapid generation of cellular arrays for MC transport simulations with PHITS. The program provides exhaustive user control over geometric parameters (cell and nucleus dimensions,

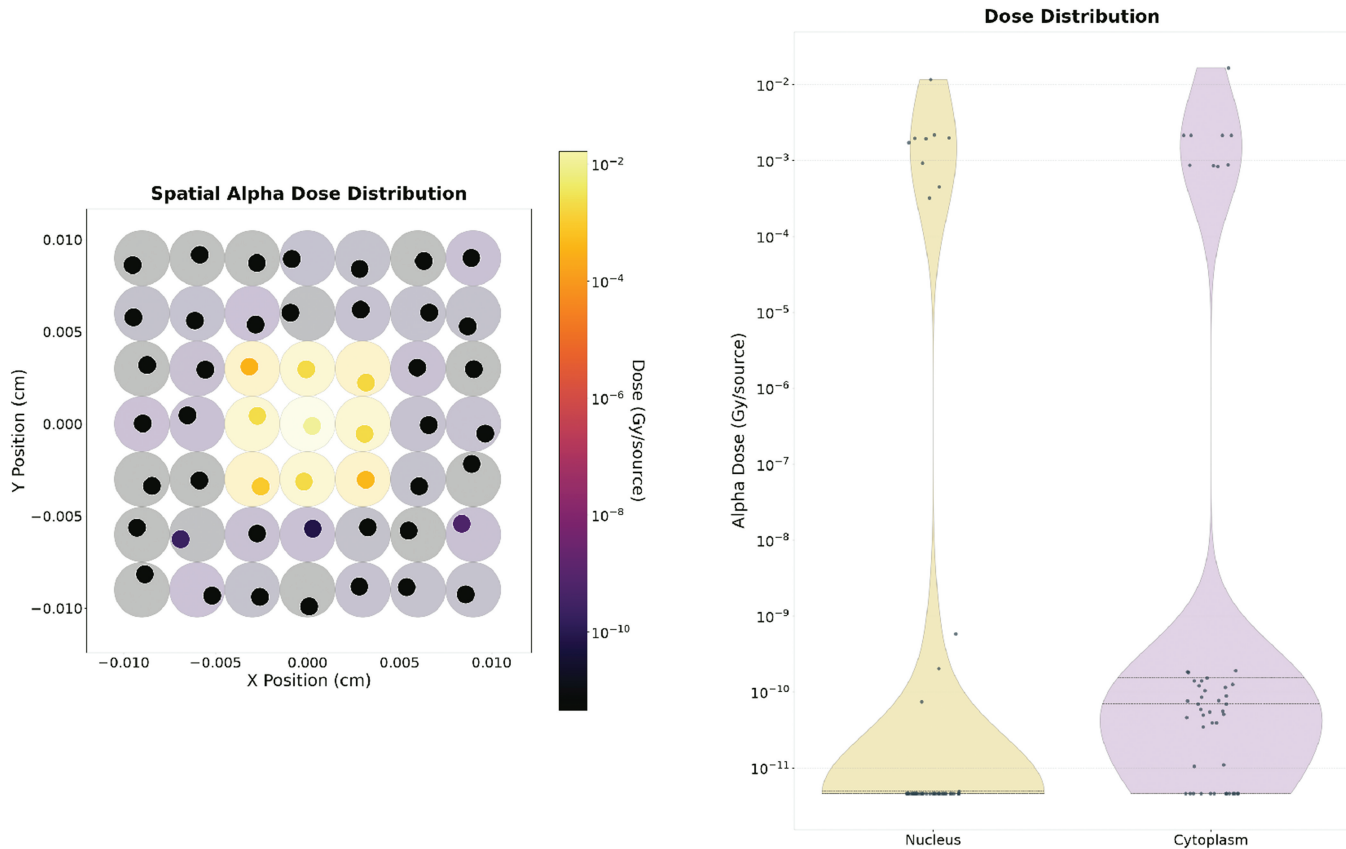


Fig. 13. Internal irradiation of  $7 \times 7$  uniform cell array with alpha-particle-emitting point source.

intercellular pitch distance, cell and nucleus flatness ratio, buffer medium thickness, and spatial distribution), source specifications (particle type, energy, geometry, and source-to-target distance), and material definitions (seven tissue-equivalent media). By automating the creation of dose, track, and geometric tallies, *cellmaker* ensures methodological consistency and reproducibility across a wide spectrum of radiobiological investigations.

The capability of the toolkit for the *in vitro* case was demonstrated through three case studies encompassing 9-cell, 25-cell, and 100-cell configurations. For low-energy (10 MeV) protons, the simulated Bragg peak position in the buffer medium agreed with the analytically expected range, thereby validating the geometric fidelity of the generated models. Targeted irradiation of a single central cell confirmed the high spatial selectivity of the proton beam and the negligible dose to surrounding cells, while the secondary alpha dose exhibited a clear inverse dependence on intercellular pitch, illustrating the importance of cellular spacing in bystander dose assessments. In the larger  $10 \times 10$  arrays, the contrast between uniform and random cell distributions highlighted the pronounced influence of spatial heterogeneity on the deposition

patterns of both primary and secondary radiation components, particularly for photons and neutrons with long mean free paths.

To more accurately represent *in vivo* biological conditions, a 3D  $3 \times 3 \times 3$  cell array was constructed to simulate both uniform and randomly distributed spatial arrangements. By mapping the 3D dose dispersion generated by both primary and secondary particles across this array, the study evaluated the efficacy of the *cellmaker* toolkit. The results confirm that *cellmaker* is highly capable of modeling the complex, multi-layered cellular structures that are essential for precise *in vivo* cellular dosimetry.

In addition, an internal alpha-particle irradiation scenario was modeled using the *cellmaker* platform for a  $7 \times 7$  cell array. The dose distributions in uniform and random cell arrays were modeled. The results show that the present platform can be used in studying internal cellular irradiation for different cell compartments (i.e., cytoplasm and nucleus domains).

Collectively, these results underscore the utility of *cellmaker* as a versatile platform for high-throughput, cellular-level dosimetry. The *cellmaker* program

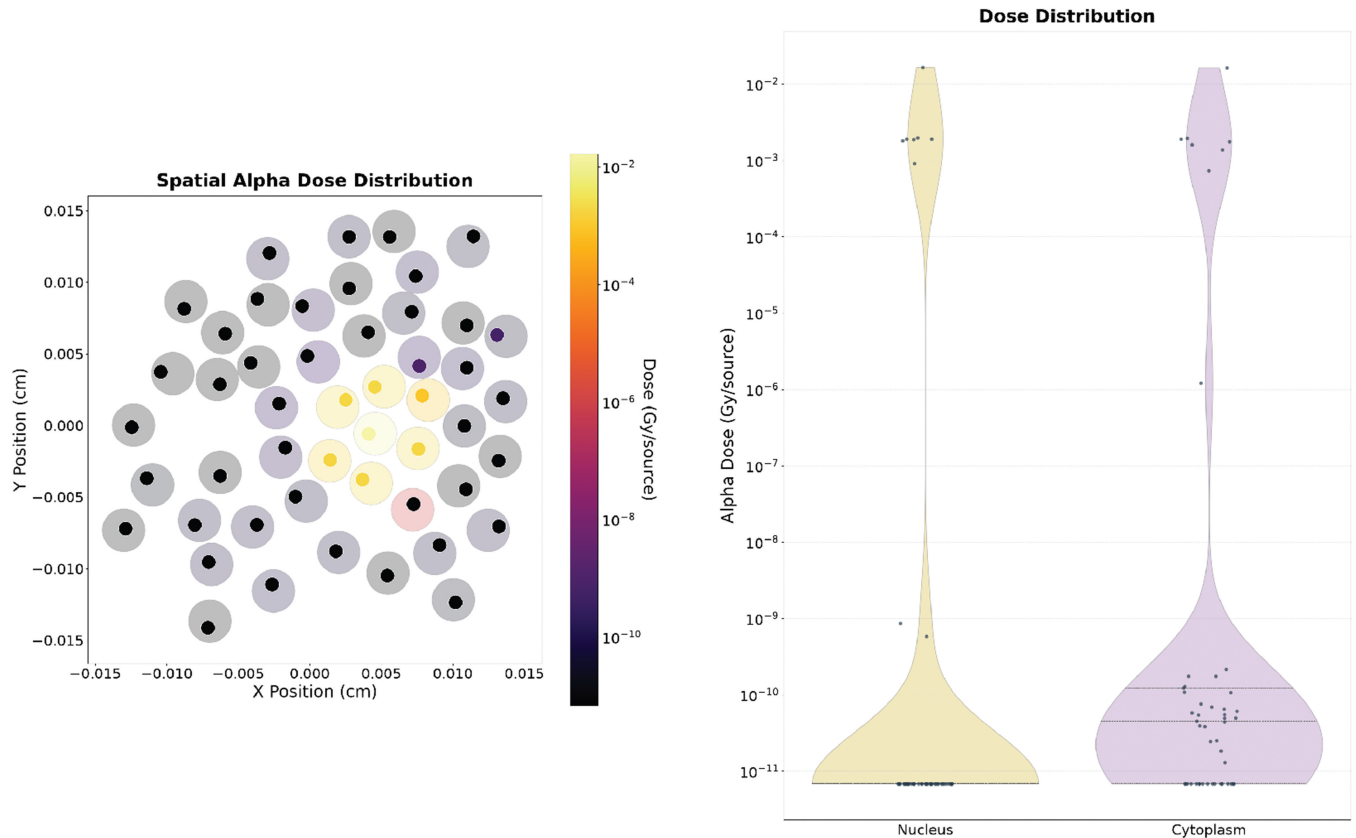


Fig. 14. Internal irradiation of  $7 \times 7$  random cell array with alpha-particle-emitting point source.

provides high-resolution physical dosimetric input, which serves as a foundational tool to support future radiobiological modeling, rather than evaluating biological outcomes directly. By coupling flexible geometry generation with the advanced physics models of PHITS, the toolkit facilitates systematic sensitivity analyses of physical parameters that govern energy deposition at the cellular level. We anticipate that cellmaker will serve as a valuable resource for the radiation biology community, enabling transparent, reproducible, and robust studies of cellular radiation response, secondary particle effects, and spatially dependent radiobiological phenomena.

### Author Contributions

CRedit: **Hiroshi Watabe:** Conceptualization, Funding acquisition, Writing – review & editing; **Tatsuhiko Sato:** Formal analysis, Methodology, Software, Validation; **Peter K. N. Yu:** Funding acquisition, Resources, Writing – review & editing; **Dragana Krstic:** Data curation, Formal analysis, Investigation; **Dragoslav Nikezic:** Investigation, Validation, Writing – review & editing; **Kyeong Min Kim:** Investigation, Visualization; **Taiga Yamaya:** Formal analysis, Methodology; **Naoki Kawachi:** Resources, Validation; **Hiroki Tanaka:** Data

curation, Visualization; **Zoran Jovanovic:** Formal analysis, Software; **A. K. F. Haque:** Software, Visualization; **M. Rafiqul Islam:** Data curation, Validation; **Gary Tse:** Validation, Writing – review & editing; **Mehrdad Shahmohammadi Beni:** Conceptualization, Methodology, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing.

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## Data Availability Statement

All original source code and built executables for the cellmaker toolkit have been made publicly accessible and can be obtained from <https://github.com/msbCyricTohoku/CellMaker> or [https://figshare.com/articles/software/A\\_toolkit\\_for\\_cellular\\_level\\_radiation\\_dosimetry/31427519](https://figshare.com/articles/software/A_toolkit_for_cellular_level_radiation_dosimetry/31427519). The Windows version of the program can be downloaded from <https://github.com/msbCyricTohoku/CellMaker/releases>. The cellmaker is fully open-source and free software; however, the actual MC transport executions inherently depend on PHITS, which requires a separate license and registration through the Japan Atomic Energy Agency. Please visit <https://phits.jaea.go.jp/>.

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