GCR Event-Based Risk Model (GERMcode)

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GCR Event-based Risk Model (GERMcode)

Trials(i)

Initial Sample

Fishbowl + CAD Ray Files

Space Version

NSRL Version

(A, Z, E, x+y, \( \delta t \))_i

Physics Event Propagator

Biophys events per Stem Cell Niche

Risk per event

JSC GCR Env Model

RMAT Module

QMSFRG Module

LiXS Modules

LiXS Modules
Events vs Flux/Dose

- NASA High-Z and E Transport (HZETRN) code calculates the average flux and dose of particles behind spacecraft and tissue shielding.
- Monte-Carlo transport codes (GEANT, FLUKA, etc.) are cumbersome and not used for biophysics applications.
- An event refers to the correlated energy depositions in time and space of cosmic ray interactions with cells controlled by the tissue matrix (environment).
  - Time-dependent transport codes are needed due to cell & tissue signaling activation and relaxation times:
    - Biological steady-state is altered by proton hits pre-, during, or post- HZE events.
  - Transport code must describe temporal and micro-spatial density of functions to correlate DNA and oxidative damage with non-targeted effects (signals, bystander, or other).
Biological Process Relaxation Time
- Multiple events by GCR and SPEs for given process -

DNA repair/ATM  **Relaxation Times**  3-24 hrs

Biological Process Relaxation Time
- Multiple events by GCR and SPEs for given process -

**TGFβ-SMAD**

*Relaxation Times* 1-5 days

*Figure 1. Schematic representation of Smad dependent TGF-β signaling pathway.*


http://www.plosone.org/article/info:doi/10.1371/journal.pone.0000936
Biological Process Relaxation Time
- Multiple events by GCR and SPEs for given process -

Repopulation
Differentiation
Senescence

Relaxation Times 1-30 days

Transport Codes for Stochastic Models of Radiation Risks

• New approaches to risk assessment will require event based models of particle transport that track time and spatial dependent interactions of particles in tissue structures

• The GCR Event Based Risk Model (GERMcode) is a Monte-Carlo based approach for this purpose that builds on the success of HZETRN/BRYNTRN codes using QMSFRG

• The GERMCode will incorporate stochastic distribution of incident particles
  ✓ Bi-directional transport allows to use FISHbowl spacecraft and organ geometry ray tracing
  ✓ Angular corrections can be added for small tissue samples where risk models are formulated using the stochastic approach
  ✓ The GERMcode will tally time-dependent events in support of new approaches to biological response models
Heavy Ion Reactions

Abrasion = projectile-target overlap
(n, p, and cluster knock-out)
Ablation = pre-fragment decay
(n, p, d, t, h, alphas de-excitation)
Coalescence = p and n knockout
form bound states in couple phase space
Fragmentation Cross Sections: Comparison of QMSFRG to Si and Fe Beams

Approximate Composition

\[ N_{101.7}O_{33.1}Al_{36} \]

Density: 0.00194 g/cm³

Thickness: 1.2166 g/cm²

N: \( 2.09 \times 10^{22} \) atoms/g

O: \( 6.81 \times 10^{21} \) atoms/g

Al: \( 7.41 \times 10^{21} \) atoms/g

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**NSRL for Biophysics Applications**

**Biological Target**

- IC3: 0.08288 g/cm²
- IC2: 0.08288 g/cm²

**Binary Filter**

- IC1: 0.08288 g/cm²

**Ion Chamber/SWIC (RW302)**

- 0.09827 g/cm²

**Booster Window**

- 0.10287 g/cm²

**Air**

- 0.03482 g/cm²
- 0.01471 g/cm²
- 0.4257 g/cm²
- 0.12281 g/cm²

**Air**

- 0.08274 g/cm²
- 0.05379 ~ 0.08604 g/cm²

**Beam**
NSRL Bragg Curve Comparison to GCR Event-based Risk Model (GERMcode)

Cucinotta FA et al., Radiation Protection Dosimetry, 143, 384-390, 2011,
NSRL Bragg Curve Comparison to GCR Event-based Risk Model (GERMcode)

Cucinotta FA et al., Radiation Protection Dosimetry, 143, 384-390, 2011
Thick Target Comparison with NASA’s GERMcode

Iron (1 GeV/u) on Polyethylene

Cucinotta FA et al., Radiation Protection Dosimetry, 143, 384-390, 2011
Summary of GERMcode Accuracy for Physics

- Atomic variables agree with experiments to within ±5%
  - LET, Range, Straggling parameters
- Absorption X-section within ± 5%
- Elemental fragment X-section within ± 25% to H.I. experiment
  - Errors are local in Z and E minimizing their impact
- Comparison to NSRL Data: Excellent agreement at all depths
- QMSFRG X-sections in HZETRN/GERM code; classical X-sections in GEANT4, FLUKA and PHITS models
- Focus of future work to add mesons and photons/electrons and to improve accuracy of event generator for light particles
- Systems biology approach to risk prediction requires event based physical/biological models to account for stochastic transition rates
Future Plans

• GCR Event-based Risk Model (GERM) wraps the existing physics code developed on the span of decades into a user-friendly graphics interface based on a fast Monte-Carlo algorithm

• Radiation transport in GERM code is based on Monte Carlo method to solve the transport problem for a distribution of particles present in space and track the evolution of individual particles within a material
  – The Monte Carlo approach will work together with the bi-directional ray-tracing technique following approach of HZETRN/BRYNTRN codes

• From radiation transport in matter we advance the model to the cell and tissue effects that can address risk models that go beyond dose and dose equivalent

• New technology (GPU) will enable the model to address full GCR simulations
NSRL GERMcode GUI v1.1
NSRL GERMcode GUI Overview

• A stochastic simulation tool using track structure and nuclear interactions provides the description and integration of physical and biophysical events from mono-energetic ions.

• A stochastic Monte-Carlo based model of radiation transport in spacecraft shielding and tissue is developed with the quantum multiple scattering model of heavy ion fragmentation (QMSFRG) and the energy loss processes.

• For the scientists who participate in NSRL experiments or in data interpretation of such experiments, GERMcode provides the ability to:
  ✓ Model the beam line, shielding of samples and sample holders
  ✓ Estimate basic physical and biological outputs of the designed experiments
GUI for the NSRL GERMcode

Start

Mono-E Beam or Transport

Mono-E Beam

A, Z, E, Material, Dose, Cell area, Radiobiological Model DNA volume

Physical/radiobio property outputs:
- LET Range curve
- Nuclear extinction
- Radial dose
- Biological damage

Nuclear interaction property output:
- Probability of hits

Track structure property output:
- Energy deposit in DNA

Biophysical property outputs:
- Depth dose table
- Charge distribution
- Multiplicity of events

Radiobiological Model

Radiobio property output:
- Biological damage

BioSample

Fixed depth

Fixed, Bragg curve, or BioModel

Bragg curve depth

BioModel depth

Back to Main

Y

A, Z, E, Material

Beam Transport to Target

End
Mono-Energetic Beam

Start

Mono-E Beam or Transport

Mono-E Beam

A, Z, E, Material, Dose, Cell area, Radiobiological Model DNA volume

Physical/radiobiological property outputs:
- LET Range curve
- Nuclear extinction
- Radial dose
- Biological damage

Nuclear interaction property output:
- Probability of hits

Track structure property output:
- Energy deposit in DNA

Back to Main

Y

N

End
Mono-Energetic Beam Transport

Start

Mono-E Beam or Transport

Beam Transport to Target

A, Z, E, Material

Fixed depth

Fixed, Bragg curve, or BioModel

BioModel depth

Bragg curve depth

Biophysical property outputs:
- Depth dose table
- Charge distribution
-Multiplicity of events

Biophysical property outputs:
- Bragg curve
- Charge distribution
-Multiplicity of events

Biophysical property outputs:
- Depth dose table
- Charge distribution
-Multiplicity of events

Radiobiological Model

Radiobio property output: Biological damage

Back to Main

Y

BioSample

N

End
## User Input Control Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mono-energetic beam</th>
<th>Radiation transport in thick target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charge number, Z</td>
<td>1 – 28</td>
<td>1 – 28</td>
</tr>
<tr>
<td>Mass number, A</td>
<td>1 – 58</td>
<td>1 – 58</td>
</tr>
<tr>
<td>Beam energy, MeV/u</td>
<td>50 – 1500 MeV/u</td>
<td>50 – 1500 MeV/u</td>
</tr>
<tr>
<td>Material</td>
<td>Water, Aluminum, Polyethylene, CO₂, Graphite, Carbon</td>
<td>Water, Aluminum, Polyethylene, CO₂, Graphite, Carbon</td>
</tr>
<tr>
<td>Dose, Gy</td>
<td>0.0 – 5.0 Gy</td>
<td></td>
</tr>
<tr>
<td>Cell area, μm²</td>
<td>0.1 – 1000 μm²</td>
<td></td>
</tr>
<tr>
<td>DNA volume (d x l of cylinder volume, unit in nm)</td>
<td>DNA segment (2 x 2), Nucleosome (10 x 5), DNA fiber (25 x 25)</td>
<td></td>
</tr>
<tr>
<td>Transport Depth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiobiological model</td>
<td>No Katz model, Cell survival, Chrom. aberration, Cell mutation, Mouse tumor model</td>
<td>No radiobio model, Cell survival, Chrom. aberration, Cell mutation, Mouse tumor model</td>
</tr>
</tbody>
</table>

- **Beam transport for fixed depth**
  - Mouse: Longitudinal placement along the beam
  - Mouse: Transverse placement to the beam
  - Rat: Longitudinal placement along the beam
  - Rat: Transverse placement to the beam
  - Ferret: Longitudinal placement along the beam
  - Ferret: Transverse placement to the beam

- **Beam transport for Bragg curve depth**
  - Mouse: Longitudinal placement along the beam
  - Mouse: Transverse placement to the beam
  - Rat: Longitudinal placement along the beam
  - Rat: Transverse placement to the beam
  - Ferret: Longitudinal placement along the beam
  - Ferret: Transverse placement to the beam

- **Beam transport in biological sample**
  - T-25 flask
  - T-75 flask
  - Flaskette
  - Chamber slide
  - 6-well plate
Ion Types in GERMcode with Default Nuclei Highlighted
# Physical and Biophysical Properties of Mono-energetic Beams

<table>
<thead>
<tr>
<th>Input Parameter</th>
<th>Mono-energetic beam</th>
<th>Output</th>
<th>Input Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charge number, Z</td>
<td>1 – 28</td>
<td>LET and Range curve</td>
<td>((Z, A, E)_{\text{Material}})</td>
</tr>
<tr>
<td>Mass number, A</td>
<td>1 – 58</td>
<td>Nuclear extinction</td>
<td>((Z, A, E)_{\text{Material}})</td>
</tr>
<tr>
<td>Beam energy, (E(\text{MeV/u}))</td>
<td>50 – 1500 MeV/u</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Material</td>
<td>Water, Aluminum, Polyethylene, CO₂, Graphite Carbon</td>
<td>Radiobiological property</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radial dose</td>
<td>((Z, A, E)_{\text{Tissue}})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biological damage of Katz model(^1)</td>
<td>((Z, A, E)_{\text{Tissue}})</td>
</tr>
<tr>
<td>Dose, Gy</td>
<td>0.0 - 5.0 Gy</td>
<td>Nuclear interaction property</td>
<td>Probability of hits(^2) ((Z, A, E)<em>{\text{Tissue}}), ((Dose, Cell Area, Z, A, E)</em>{\text{Tissue}})</td>
</tr>
<tr>
<td>Cell area, (\mu m^2)</td>
<td>0.1 – 1000 (\mu m^2)</td>
<td>Probability of hits(^2)</td>
<td></td>
</tr>
<tr>
<td>DNA volume ((d \times l) of cylinder volume, unit in \text{nm})</td>
<td>DNA segment (2 x 2), Nucleosome (10 x 5), DNA fiber (25 x 25)</td>
<td>Track structure property</td>
<td>Energy deposition in DNA volume(^3) ((Z, A, E)_{\text{Tissue}})</td>
</tr>
<tr>
<td>Radiobiological model (Katz model(^1))</td>
<td>No Katz model, Cell survival, Chrom. aberration, Cell mutation, Mouse tumor model</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Biological damage using Katz model: Cell survival; Chromosomal aberration; Cell mutation; Mouse tumor model

\(^2\)Probability of hits for Poisson distribution of ion hits

\(^3\)DNA volume of \(d \times l\) of cylinder volume in \text{nm}: DNA segment (2 x 2); Nucleosome (10 x 5 for 160 BP); Chromosome fiber (25 x 25)
# Biophysical and Radiobiology Properties of NSRL Beam Transport
(Monte-Carlo trials along path of primary ion)

<table>
<thead>
<tr>
<th>Input Parameter</th>
<th>Radiation transport in thick target</th>
<th>Output</th>
<th>Input parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charge number, Z</td>
<td>1 – 28</td>
<td>Fixed depth</td>
<td>(Z,A,E) Material</td>
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<tr>
<td>Mass number, A</td>
<td>1 – 58</td>
<td>Bragg curve depth</td>
<td>(Z,A,E) Material</td>
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<tr>
<td>Beam energy, E(MeV/u)</td>
<td>50 – 1500 MeV/u</td>
<td>Biology model depth</td>
<td>(Z,A,E) Tissue</td>
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<tr>
<td>Material</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
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<tr>
<td>Aluminum</td>
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<tr>
<td>Polyethylene</td>
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<td></td>
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<tr>
<td>CO₂</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Graphite</td>
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<td></td>
<td></td>
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<tr>
<td>Carbon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charge number, Z</td>
<td></td>
<td>Depth-dose</td>
<td>(Z,A,E) Material</td>
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<tr>
<td>Beam energy, E(MeV/u)</td>
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<td>Biology model depth</td>
<td>(Z,A,E) Tissue</td>
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<tr>
<td>Material</td>
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<tr>
<td>Water</td>
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<td>Aluminum</td>
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<tr>
<td>Bragg curve depth</td>
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<tr>
<td>Biological models</td>
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<tr>
<td>No Katz model</td>
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<tr>
<td>Cell survival</td>
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<tr>
<td>Chrom. aberration</td>
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<td>Cell mutation</td>
<td></td>
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<tr>
<td>Mouse tumor model</td>
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<tr>
<td>Radiobiological model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biological damage of Katz model(^1)</td>
<td>(Z,A,E) Tissue</td>
<td>(Z,A,E) Tissue</td>
<td>(Z,A,E) Tissue</td>
</tr>
</tbody>
</table>

\(^1\)Biological damage using Katz model:
- Cell survival;
- Chromosomal aberration;
- Cell mutation;
- Mouse tumor model
From Radiation Transport in Materials To Radiation Effects in Astronauts

- GERMcode results are applicable to biological events on the cell/tissue level.
- Energy imparted from a particle at certain material depth can be scored per pixel within a cell and per cell in a tissue matrix.
- Radiation transport in matter is applied to study tissue radiation effects within a human body.
- The scored stochastic biological effects can be DNA double strand breaks, apoptotic cells, or other processes.
- To speed up Monte Carlo simulations, a new technology refereed as General-Purpose Graphic Processor Unit (GPGPU) will be implemented.
Homework
# Beam Ion Species and Energies Used Previously at NSRL

<table>
<thead>
<tr>
<th>Ion Species</th>
<th>Energy, MeV/u</th>
<th>Maximum Intensity, ions per spill</th>
<th>LET for a Water, KeV/μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H</td>
<td>50 - 2500</td>
<td>$6.4 \times 10^{11}$</td>
<td>1.26 - 0.21</td>
</tr>
<tr>
<td>$^4$He</td>
<td>50 - 1000</td>
<td>$0.88 \times 10^{10}$</td>
<td>5.01 - 0.89</td>
</tr>
<tr>
<td>$^{12}$C</td>
<td>65 - 1000</td>
<td>$1.2 \times 10^{10}$</td>
<td>36.79 - 8.01</td>
</tr>
<tr>
<td>$^{16}$O</td>
<td>50 - 1000</td>
<td>$0.4 \times 10^{10}$</td>
<td>80.5 - 14.24</td>
</tr>
<tr>
<td>$^{20}$Ne</td>
<td>70 - 1000</td>
<td>$0.1 \times 10^{10}$</td>
<td>96.42 - 22.25</td>
</tr>
<tr>
<td>$^{28}$Si</td>
<td>93 - 1000</td>
<td>$0.3 \times 10^{10}$</td>
<td>151 - 44</td>
</tr>
<tr>
<td>$^{35}$Cl</td>
<td>500 - 1000</td>
<td>$0.2 \times 10^{10}$</td>
<td>80 - 64</td>
</tr>
<tr>
<td>$^{40}$Ar</td>
<td>350</td>
<td>$0.02 \times 10^{1}$</td>
<td>105.8</td>
</tr>
<tr>
<td>$^{48}$Ti</td>
<td>150 - 1000</td>
<td>$0.08 \times 10^{10}$</td>
<td>265 - 108</td>
</tr>
<tr>
<td>$^{56}$Fe</td>
<td>50 - 1000</td>
<td>$0.2 \times 10^{10}$</td>
<td>832 - 150</td>
</tr>
<tr>
<td>$^{84}$Kr</td>
<td>383</td>
<td></td>
<td>403</td>
</tr>
<tr>
<td>$^{131}$Xe</td>
<td>228</td>
<td></td>
<td>1204</td>
</tr>
<tr>
<td>$^{181}$Ta</td>
<td>292 - 313</td>
<td></td>
<td>1827 - 1896</td>
</tr>
<tr>
<td>$^{197}$Au</td>
<td>76 - 165</td>
<td>$1 \times 10^7$</td>
<td>4828 - 3066</td>
</tr>
<tr>
<td>Sequential Field (Fe/H)</td>
<td>1000</td>
<td>Various</td>
<td>150/0.2</td>
</tr>
<tr>
<td>SPE</td>
<td>30-180</td>
<td>Various</td>
<td>1.26 - 0.21</td>
</tr>
</tbody>
</table>

LET-Range Distribution for Water

HW1: Mono-energetic Beam

The variety of ion beams with various energies are used at the NSRL, which are relevant to the dominant ion species in space. Exercise physical, radiobiological, and nuclear interaction properties of various ion beams for materials.

- Calculate values of LET and range for a water, and compare them to the Range vs. LET graph (slide 28). Generate the same graph for another material.
- Calculate mean free path, probability to suffer a nuclear interaction after 1 or 5 g/cm² of a material for specified beams and energies.
- By applying cellular track model of Katz, calculate cell survival probability, translocation frequency, HPRT mutation frequency, or HG tumor prevalence frequency from exposure to a selected beam.
- Evaluate radial dose of ionization and excitation for the tissue equivalent material.
- Calculate the Poisson distribution of ion hits for a given cell size and dose.
- Evaluate the frequency distributions of energy imparted per DNA target from the direct interactions of primary ions (ion events) with the target and the 100 keV electrons (delta-ray events) produced about an ion’s path.
HW2: Transport in Thick Target

The beam delivered to radiobiology samples at NSRL can have many components in addition to the nominal beam particles due to the NSRL beam transport after beam line shift. Biological effects are determined by both the physical beam transport though the targets and the biological effectiveness of the mixed charged-particle radiation field. Therefore, biological end points can not be described by LET alone. Using the cellular track model of Katz for the mixed-radiation fields:

1) Compare the biological effects as a function of the exposed dose by a given ion beam or $\gamma$-rays after transported through the various depths of tissue equivalent material.

2) Compare the biological Bragg curve of cell death of a given ion beam to the physical Bragg curve for a tissue equivalent material.

   - Before the particles reach the Bragg peak region, does the biological Bragg curves follow the physical Bragg curve?
   - At the physical Bragg peak location, may not the same peak be observed from the biological response curves?
Radiation damage to the DNA is usually the *initial* event for many radiation induced biological effects observed in cells. Most biological end points are usually observed in *lightly* damaged cells, and the cells heavily damaged and unable to replicate will be excluded from analysis for end points. Before reaching the physical Bragg peak, the cells are more likely to be *lightly* damaged by long-range δ-rays.

At the Bragg peak region: The particles lose energy sharply and produce δ-rays that have shorter ranges. The cells in the physical Bragg peak region are then either heavily damaged when they are directly hit by the charged particle or experience less damage by the δ-rays when they are not traversed directly.

Cell death curve shows that the severely damaged cells at the Bragg peak are more likely to go through reproductive death, the so called “overkill”. → Not the same peak observed.
References


NSRL GERMcode GUI Outputs
LET and Range curves of $^{28}$Si beam on aluminum shielding as a function of kinetic energy of the beam.
Nuclear Extinction: The mean free path and the probability of nuclear interaction at 1 g/cm² and 5 g/cm² of ²⁸Si beam on aluminum shielding as a function of kinetic energy of the beam.
Radial Dose: The evaluation of radial dose of ionization, excitation and total as a function of radial distance from the exposure to 600 MeV/u $^{28}$Si beam on the tissue equivalent material.
Biological Damage: Cell survival responses as a function of the dose using 600 MeV/u $^{28}$Si beam or $\gamma$-rays on the tissue equivalent material.
Probability of Hits: The Poisson distribution of probability of hits from the exposure to 1 Gy using 600 MeV/u $^{28}\text{Si}$ beam in the cell area of 100 $\mu$m$^2$. Displayed figure is the probability of hits per cell in the track core only, ignoring $\delta$-rays. The mean hits per cell for LET approximations with and without $\delta$-rays are stated in the text of the output window.
Energy Deposition in DNA Volume: The frequency distributions of energy imparted per DNA volume of nucleosome from the exposure to 1 Gy using 600 MeV/u $^{28}$Si beam. The nucleosome (160 Base-pairs) volume is assumed as a cylinder in the dimension of 10 nm (diameter) $\times$ 5 nm (length).

- the direct interactions of primary ions (ion events) with the target
- the 100 keV electrons ($\delta$-ray events) produced about an ion’s path
Depth Dose for Fixed Depth: Normalized depth-dose evaluation using 600 MeV/u \(^{28}\text{Si}\) beam on water for primaries, fragments, and total at 10 depths of water in the NSRL beam line. The last column shows the fluence-based average LET at each depths.
Bragg Curve: Normalized dose of 600 MeV/u $^{28}$Si beam for **primaries**, **fragments**, and the **total** as a function of depth of water in the NSRL beam line. Variations of the normalized doses and the fluence-based average LET with water depths are displayed in the inset, as cursor moves along the graph.
Charge Distribution: Cumulative spectrum of fragments from exposure to 600 MeV/u $^{28}$Si beam transported through the water.
Various number of sets are available in the drop-down menu for the shielding depths by selecting “For Fixed Depth”, “For Bragg Curve”, or “For Biological Model”.
Multiplicity of Events: Multiplicity of $\alpha$-particles in heavy ion fragmentation event at the depth of $\sim 21 \text{ g/cm}^2$ of water from exposure to 600 MeV/u $^{28}\text{Si}$ beam. Drop-down menus of “Depth” and “Ion” are available for the selection of depth and the particle type of neutron, proton, or $\alpha$. Also, energy distribution of heavy ion event is displayed by selecting “HI Event” from the drop-down menu of “Ion”.

Option for Beam Transport
Multiplicity of Events: Downgraded energy distribution of particles produced from heavy ion events at the depth of ~21 g/cm² of water from exposure to 600 MeV/u $^{28}$Si beam is displayed by selecting “HI Event” from the drop-down menu of “Ion”.

Option for Beam Transport
Biological Damage: Harderian gland tumor prevalence curve at the depth of ~6 g/cm² of tissue equivalent material as a function of the dose using 600 MeV/u $^{28}$Si beam or $\gamma$-rays.
Opening of “File” tab in the main toolbar. Detailed information about GERMcode can be accessed from the menu listed in the left panel of the window. From the menu of “Papers”, the published papers can be accessed for the reference to GERMcode.