GCR Event-Based Risk Model (GERMcode)

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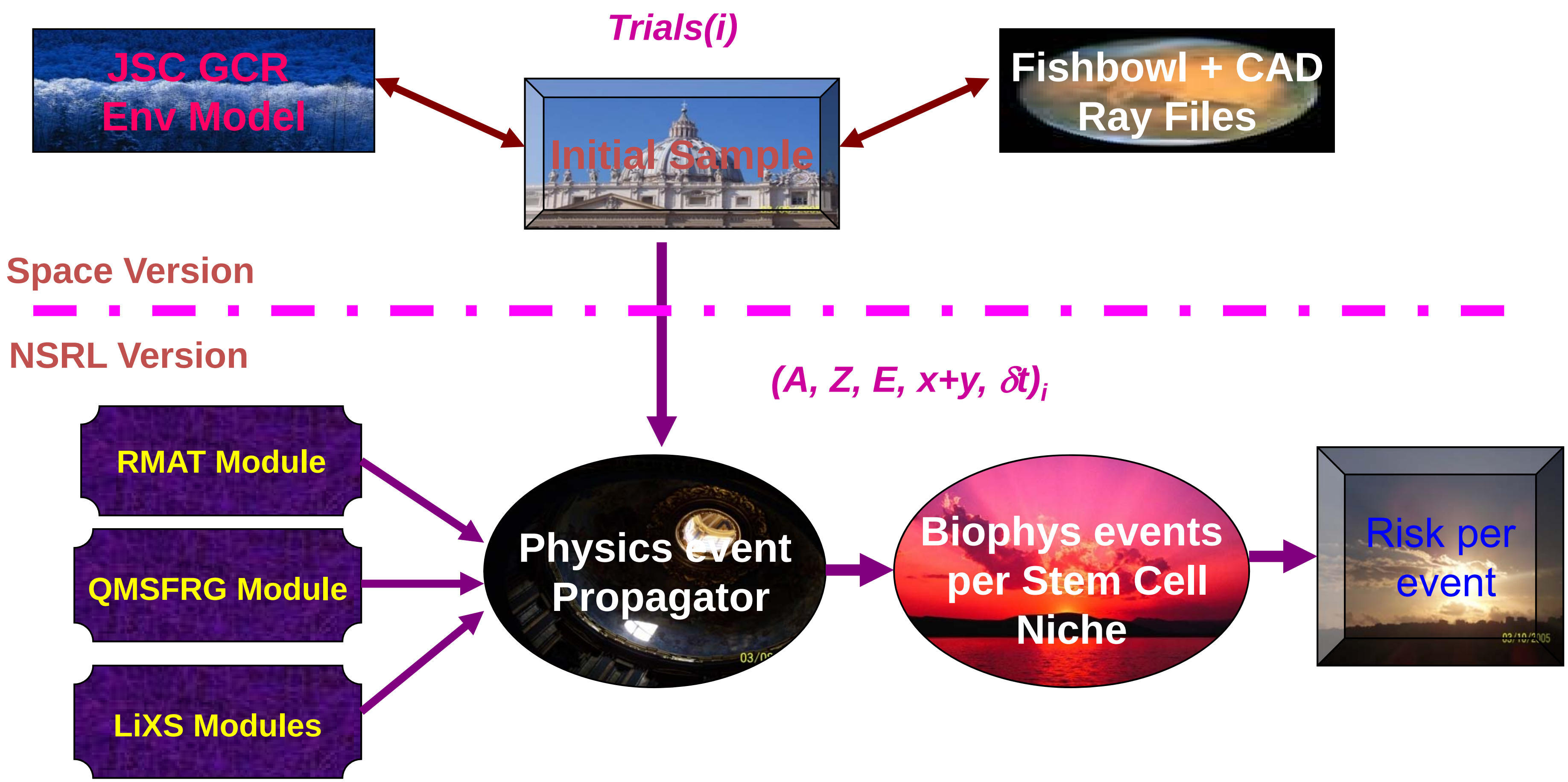


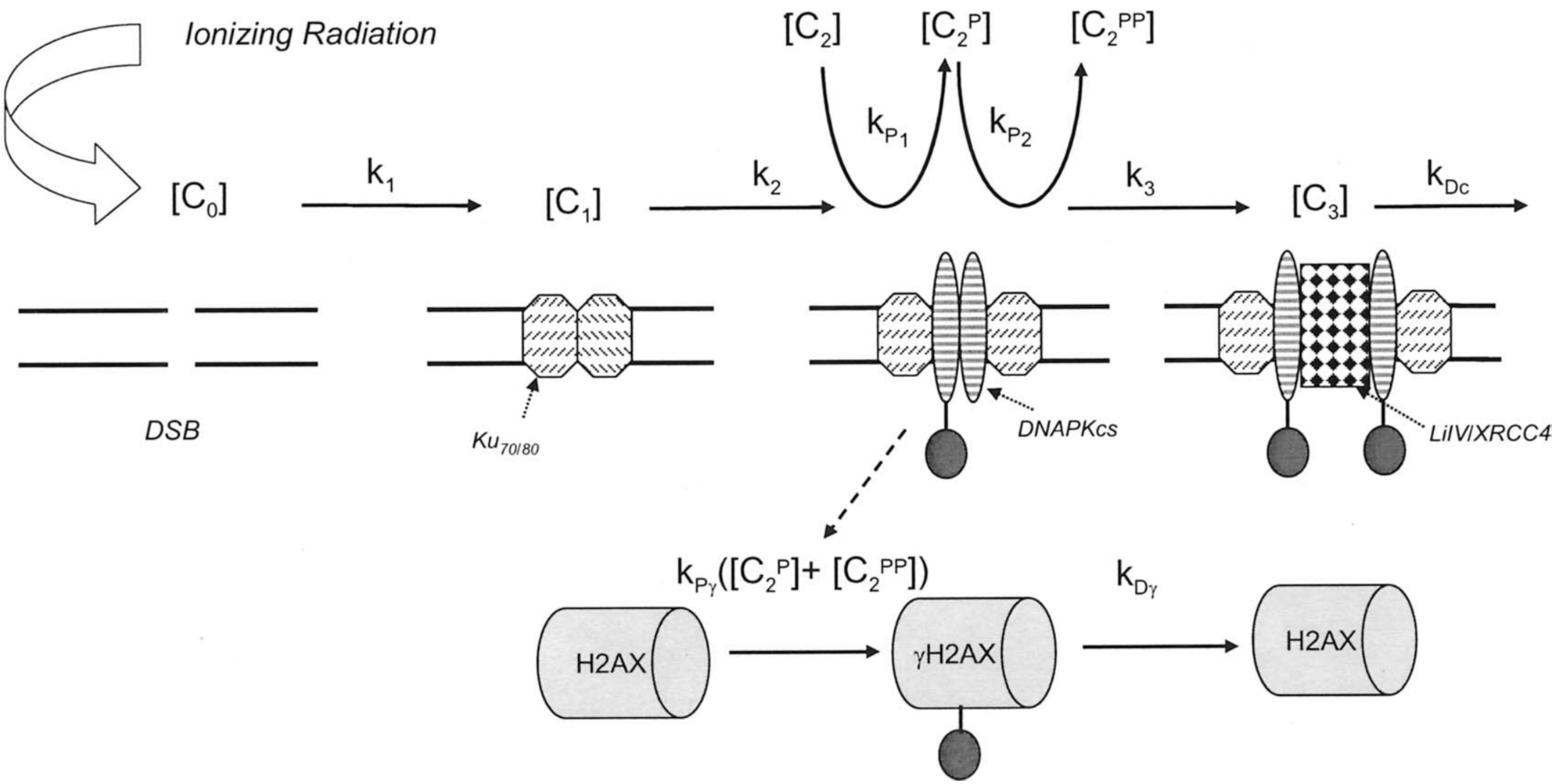
Events vs Flux/Dose

- 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



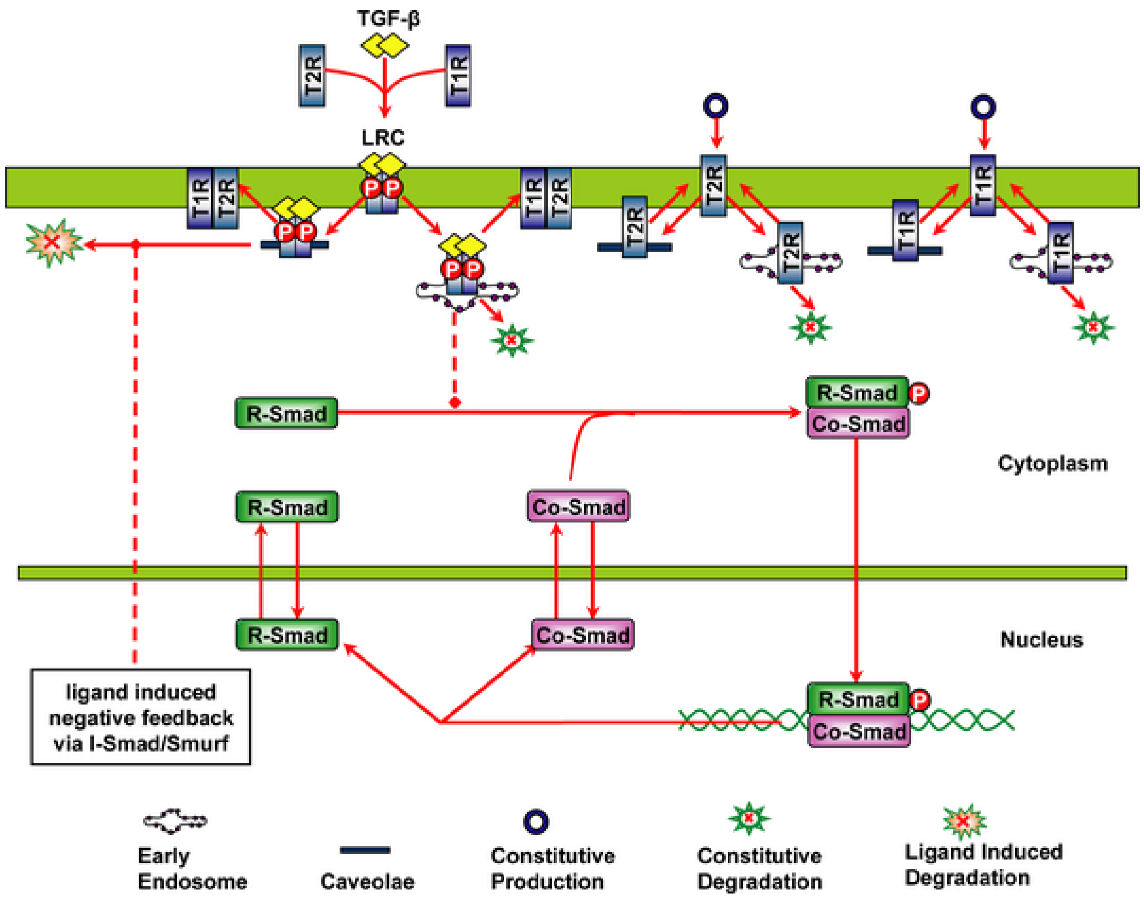
Cucinotta et al., Biochemical Kinetics of DSB Repair and Induction of γ-H2AX Foci by Non-homologous End Joining, Rad. Res., 169, 214-222, 2008

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.

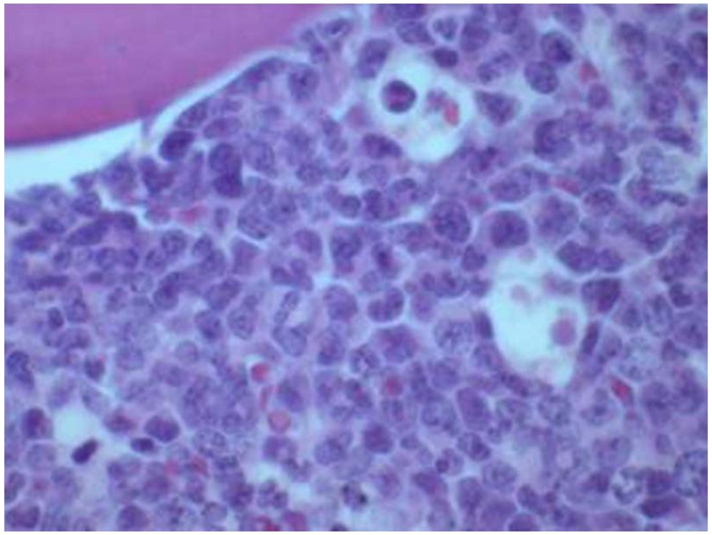


Zi Z, Klipp E (2007) Constraint-Based Modeling and Kinetic Analysis of the Smad Dependent TGF-β Signaling Pathway. PLoS ONE 2(9): e936. doi:10.1371/journal.pone.0000936
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0000936

Biological Process Relaxation Time

- Multiple events by GCR and SPEs for given process -

Repopulation Differentiation Senescence	***Relaxation Times***	1-30 days



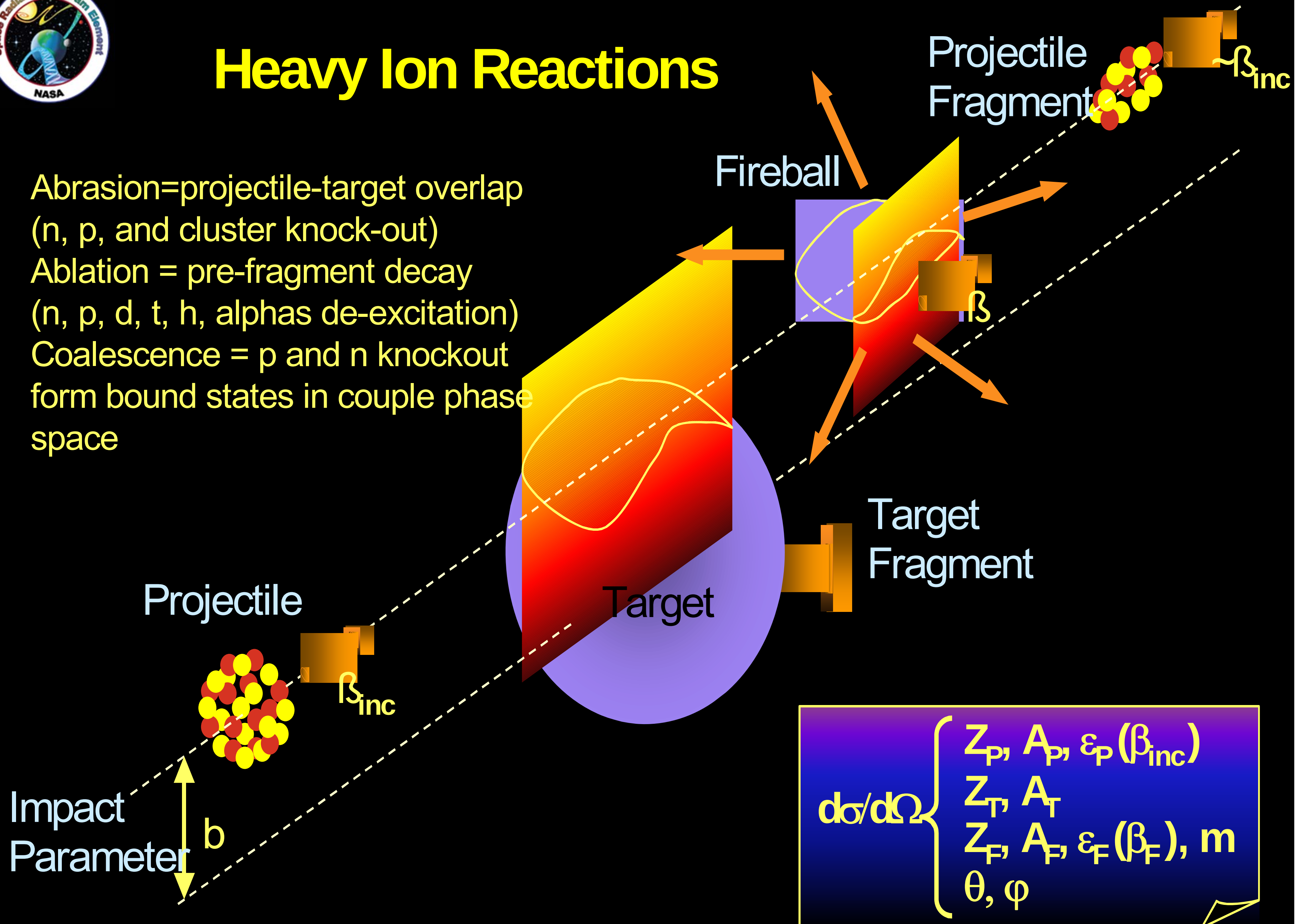
Cucinotta and Dicello, On the Development of Biophysical Models for Space Radiation Risk Assessment, NTRS 20000083882, 1999

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

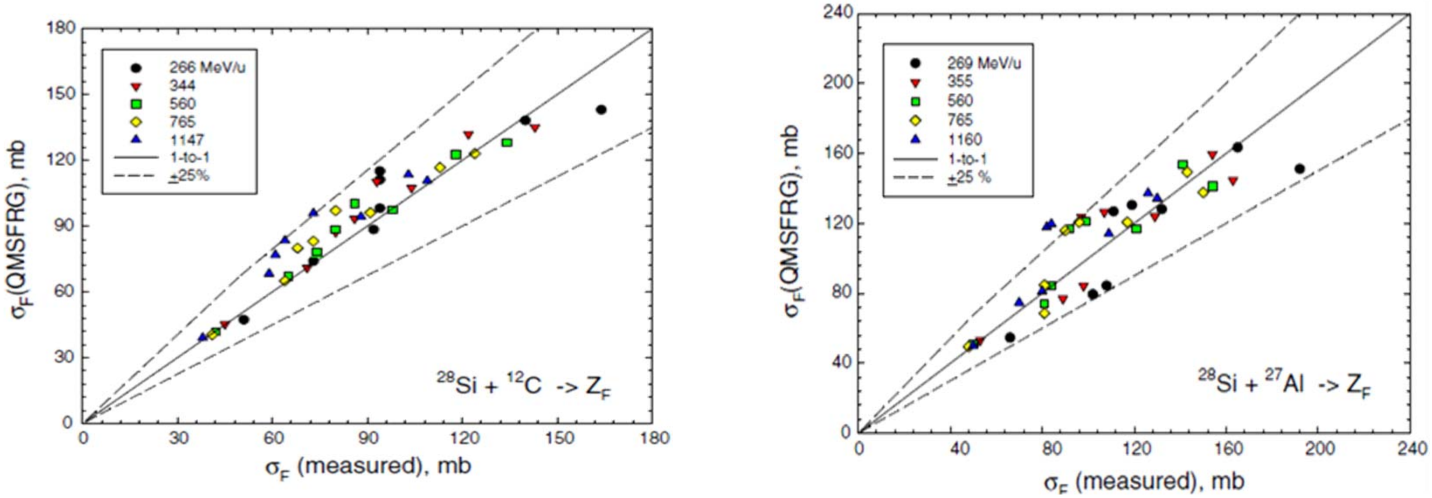
Heavy Ion Reactions

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

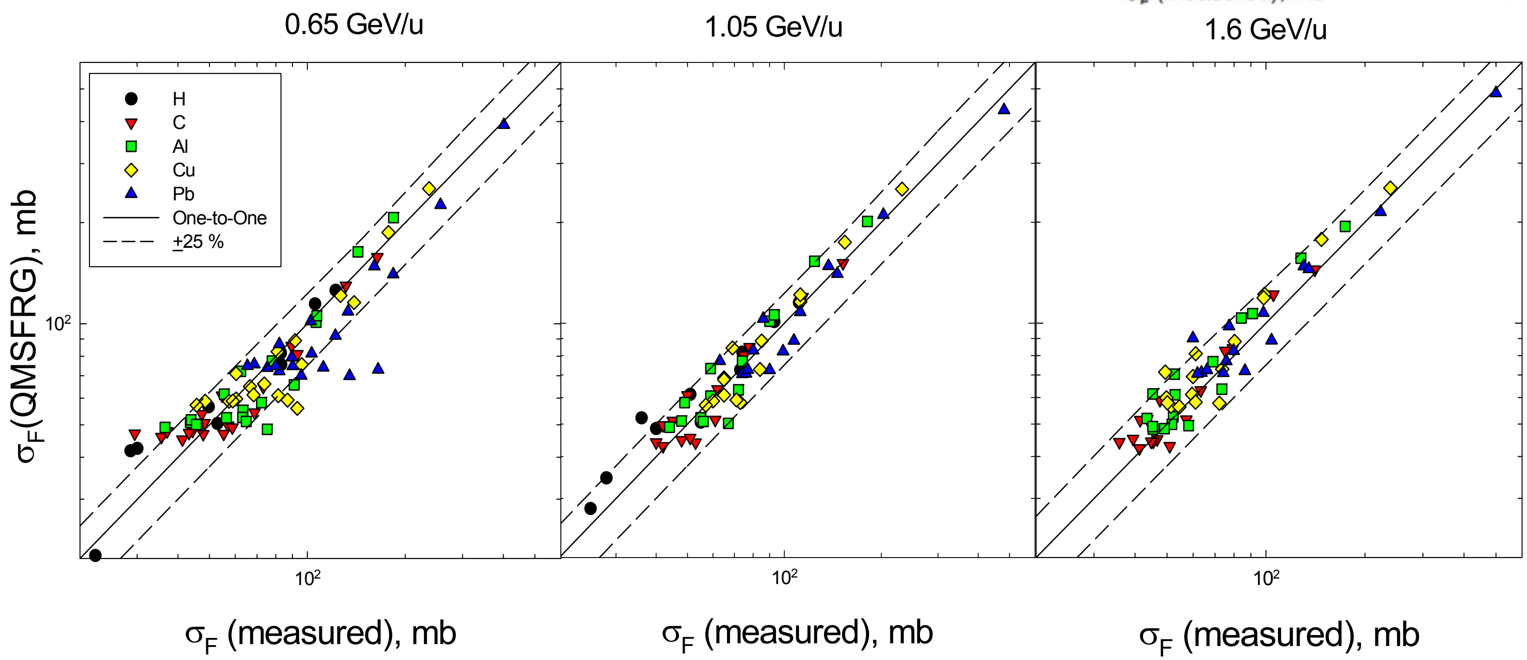


Fragmentation Cross Sections: Comparison of QMSFRG to Si and Fe Beams

Si



Fe



QMSFRG to data of Zeitlin et al., Radiat. Meas. 43, 1242-1253 (2008)

NSRL for Biophysics Applications

Approximate Composition

$N_{101.7}O_{33.1}Al_{36}$

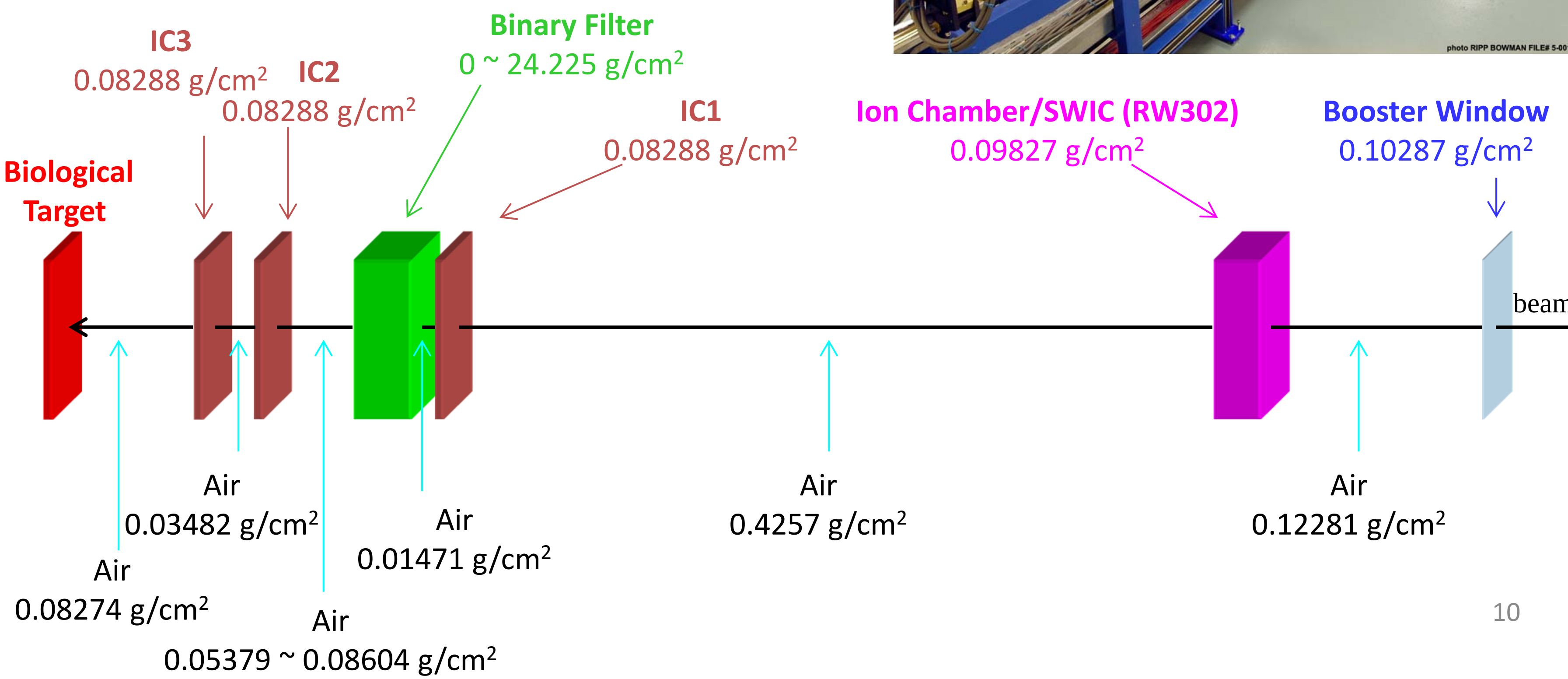
Density: 0.00194 g/cm^3

Thickness: 1.2166 g/cm^2

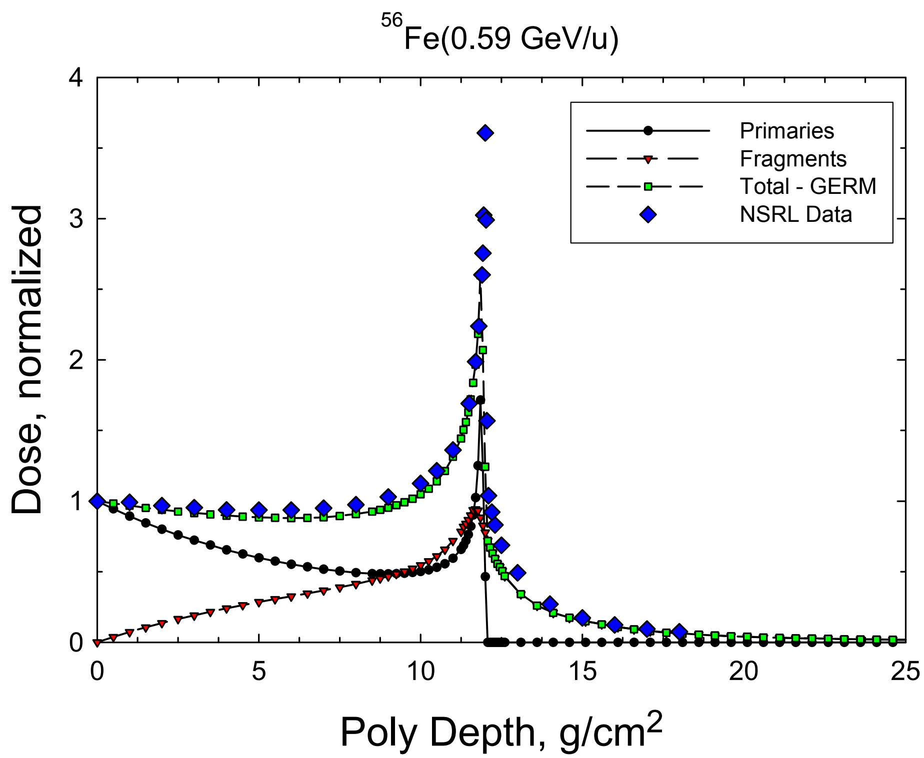
N: 2.09×10^{22} atoms/g

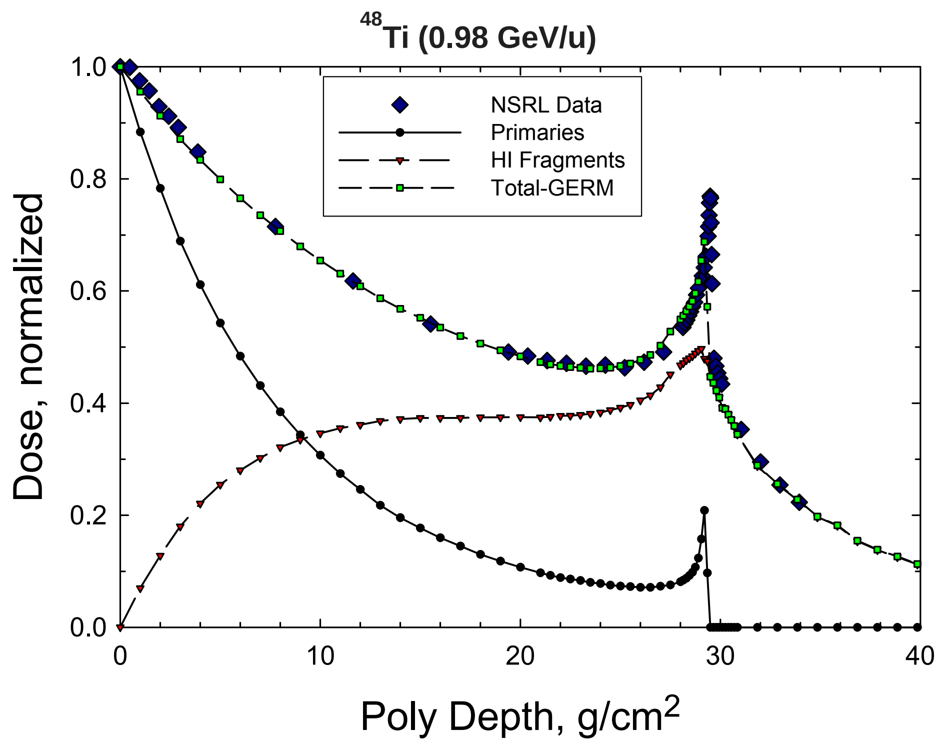
O: 6.81×10^{21} atoms/g

Al: 7.41×10^{21} atoms/g



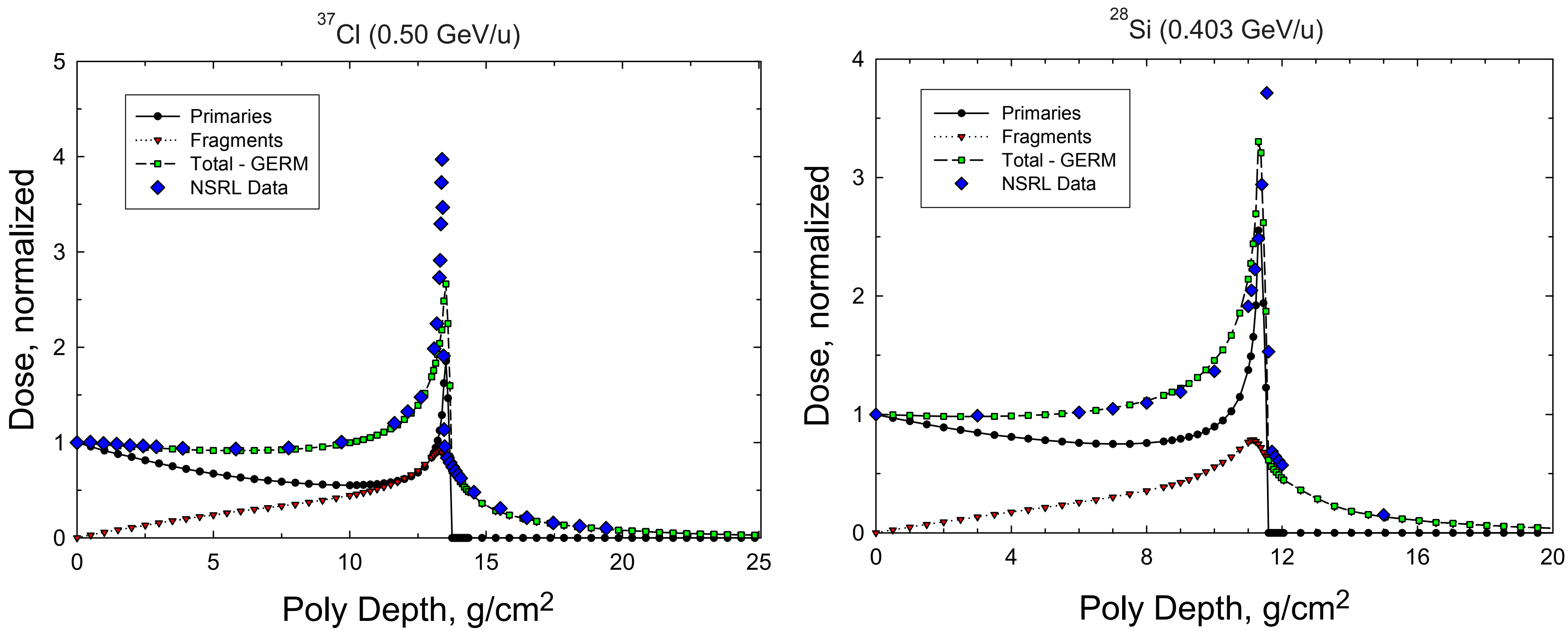
NSRL Bragg Curve Comparison to GCR Event-based Risk Model (GERMcode)





Cucinotta FA et al., Radiation Protection Dosimetry, 143, 384-390, 2011,

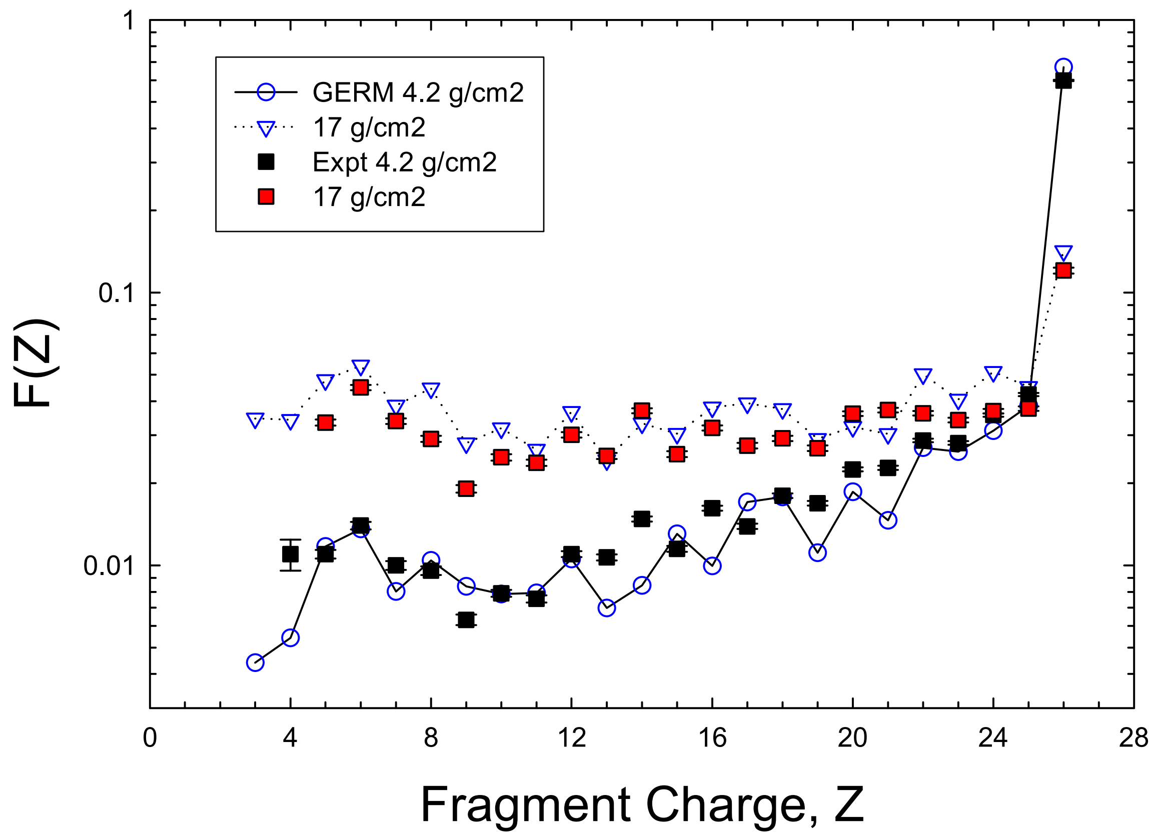
NSRL Bragg Curve Comparison to GCR Event-based Risk Model (GERMcode)



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/GERMcode; 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

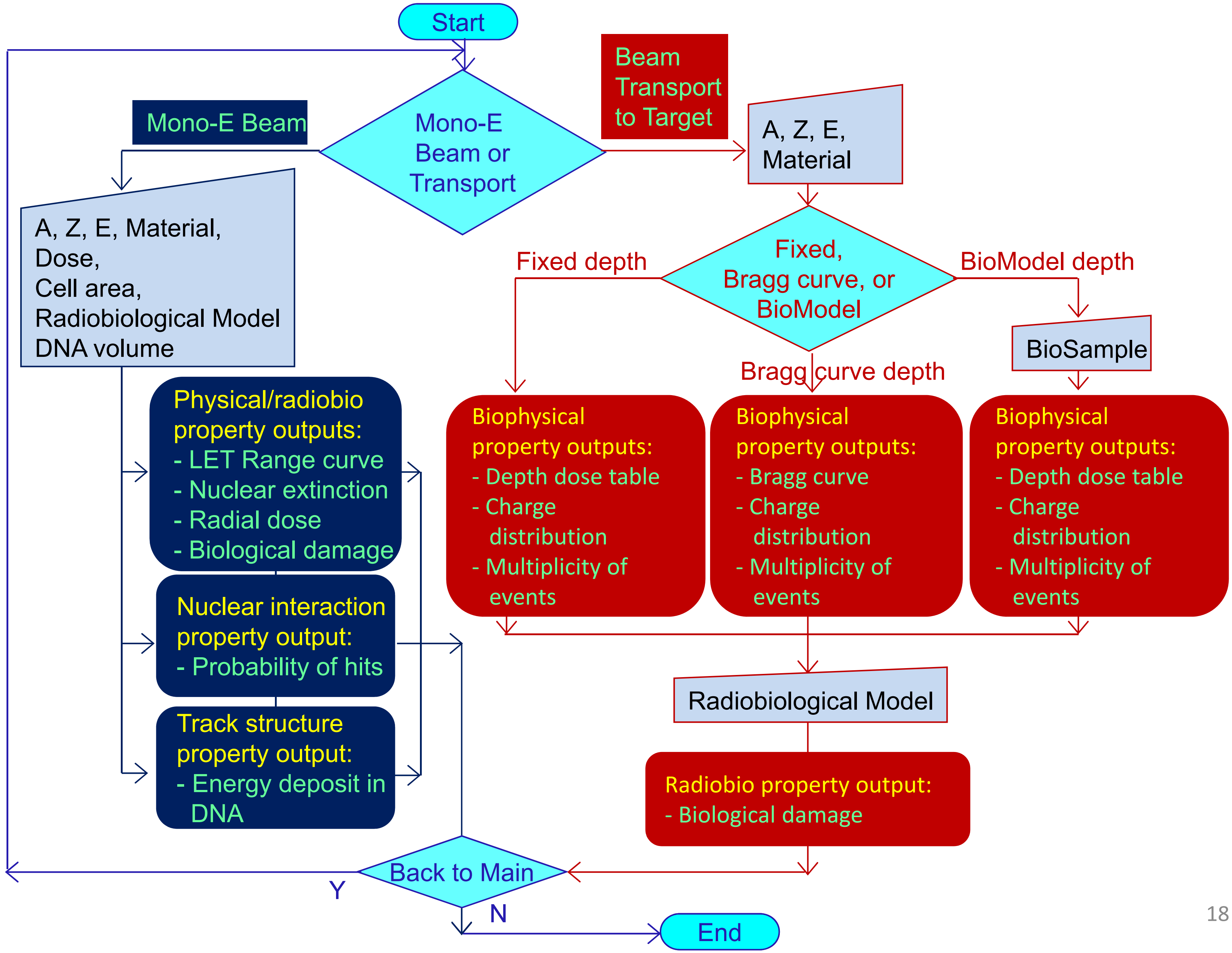
- GCR Event-based Risk Model (GERM) wraps the existing physics code developed on the span of decades into a user-friendly graphics interface based on a fast Monte-Carlo algorithm
- Radiation transport in GERMcode is based on Monte Carlo method to solve the transport problem for a distribution of particles 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

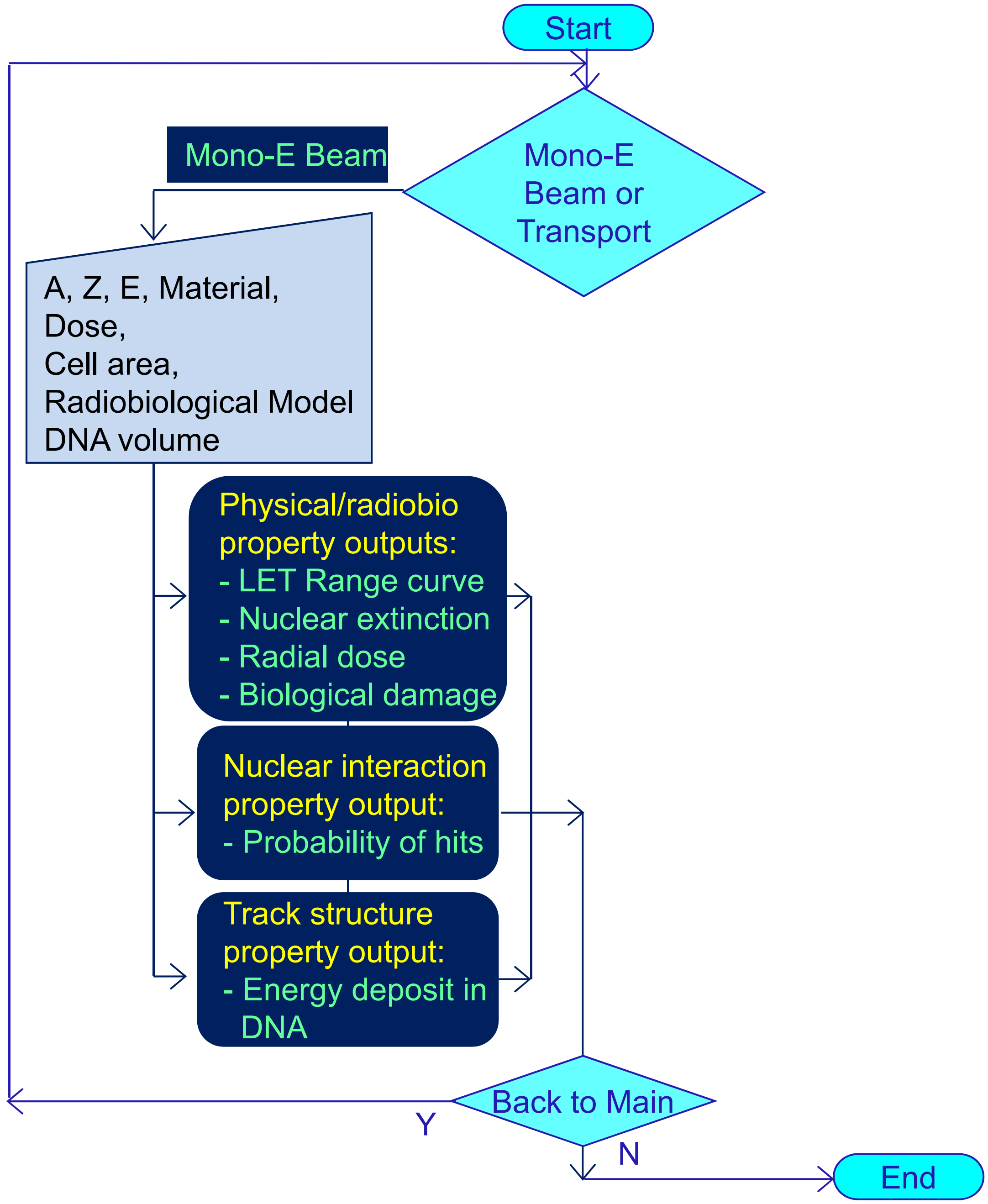
NSRL GERMcode GUI Overview

- 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

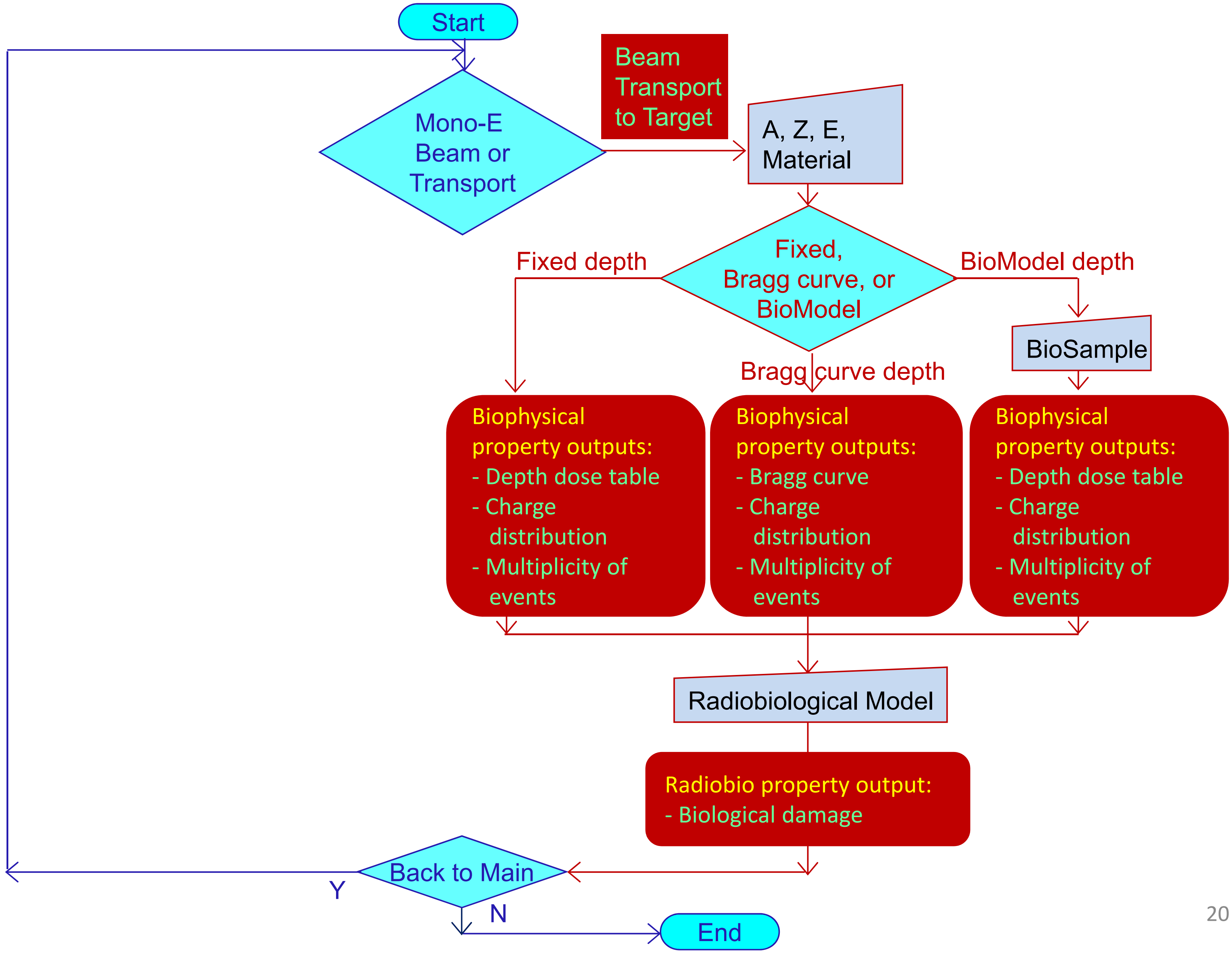
GUI for the NSRL GERMcode



Mono-Energetic Beam



Mono-Energetic Beam Transport



User Input Control Parameters

Parameter	Mono-energetic beam	Radiation transport in thick target
Charge number, Z	1 – 28	1 – 28
Mass number, A	1 – 58	1 – 58
Beam energy, MeV/u	50 – 1500 MeV/u	50 – 1500 MeV/u
Material	Water Aluminum Polyethylene CO_2 Graphite Carbon	Water Aluminum Polyethylene CO_2 Graphite Carbon
Dose, Gy	0.0 - 5.0 Gy	
Cell area, μm^2	0.1 – 1000 μm^2	
DNA volume (*d* x *l* of cylinder volume, unit in *nm*)	DNA segment (2 x 2) Nucleosome (10 x 5) DNA fiber (25 x 25)	
Transport Depth		• Fixed Depth • Bragg Curve • Biological Models
Radiobiological model	• No Katz model • Cell survival • Chrom. aberration • Cell mutation • Mouse tumor model	• No radiobio model • Cell survival • Chrom. aberration • Cell mutation • Mouse tumor model

• Beam transport for fixed depth	
• Beam transport for Bragg curve depth	
• Beam transport in bio-logical sample	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 along the beam
	T-25 flask
	T-75 flask
	Flaskette
	Chamber slide
	6-well plate

Ion Types in GERMcode with Default Nuclei Highlighted

Z	A
H	**1**
	2
	3
He	3
	4
	6
Li	6
	7
	8
	9
Be	7
	9
	10
	11
B	8
	9
	10
	11
	12
	13

Z	A
C	9
	10
	11
	12
	13
	14
	15
	16
N	12
	13
	14
	15
	16
	17
	18
O	14
	15
	16
	17
	18
	19
	20

Z	A
F	17
	18
	19
	20
	21
	22
Ne	18
	19
	20
	21
	22
	23
	24
Na	20
	21
	22
	23
	24
	25
	26
	27

Z	A
Mg	22
	23
	24
	25
	26
	27
	28
	29
Al	24
	25
	26
	27
	28
	29
	30
	31
Si	26
	27
	28
	29
	30
	31
	32
	33
	34

Z	A
P	28
	29
	30
	31
	32
	33
	34
	35
S	30
	31
	32
	33
	34
	35
	36
	37
	38

Z	A
Cl	32
	33
	34
	35
	36
	37
	38
	39
	40
Ar	34
	35
	36
	37
	38
	39
	40
	41
	42
K	36
	37
	38
	39
	40
	41
	42
	43
	44

Z	A
Ca	38
	39
	40
	41
	42
	43
	44
	45
	46
Sc	41
	42
	43
	44
	45
	46
	47
	48
Ti	43
	44
	45
	46
	47
	48
	49
	50

Z	A
V	46
	47
	48
	49
	50
	51
	52
Cr	48
	49
	50
	51
	52
	53
	54
Mn	50
	51
	52
	53
	54
	55

Z	A
Fe	52
	53
	54
	55
	56
	57
Co	55
	56
	57
Ni	56
	57
	58

Physical and Biophysical Properties of Mono-energetic Beams

Input Parameter	Mono-energetic beam
Charge number , Z	1 – 28
Mass number, A	1 – 58
Beam energy, E(MeV/u)	50 – 1500 MeV/u
Material	Water Aluminum Polyethylene CO_2 Graphite Carbon
Dose, Gy	0.0 - 5.0 Gy
Cell area, μm^2	0.1 – 1000 μm^2
DNA volume (*d* x *l* of cylinder volume, unit in *nm*)	DNA segment (2 x 2) Nucleosome (10 x 5) DNA fiber (25 x 25)
Radiobiological model (Katz model[1])	• No Katz model • Cell survival • Chrom. aberration • Cell mutation • Mouse tumor model

	Output	Input Parameter
Physical property	LET and Range curve	$(Z, A, E)_{Material}$
	Nuclear extinction	$(Z, A, E)_{Material}$
Radiobiological property	Radial dose	$(Z, A, E)_{Tissue}$
	Biological damage of Katz model[1]	$(Z, A, E)_{Tissue}$
Nuclear interaction property	Probability of hits[2]	$(Dose, Cell Area, Z, A, E)_{Tissue}$
Track structure property	Energy deposition in DNA volume[3]	$(Z, A, E)_{Tissue}$

[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* x *l* cylinder volume in *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)

Input Parameter	Radiation transport in thick target
Charge number, Z	1 – 28
Mass number, A	1 – 58
Beam energy, E(MeV/u)	50 – 1500 MeV/u
Material	Water Aluminum Polyethylene CO_2 Graphite Carbon
Transport depth	• Fixed depth • Bragg curve depth • Biological models
Radiobiological model	• No Katz model • Cell survival • Chrom. aberration • Cell mutation • Mouse tumor model

	Output	Input parameter		
		Fixed depth	Bragg curve depth	Biology model depth
Bio-physical property	Depth-dose	$(Z,A,E)_{Material}$	$(Z,A,E)_{Material}$	$(Z,A,E)_{Tissue}$
	Charge distribution	$(Z,A,E)_{Material}$	$(Z,A,E)_{Material}$	$(Z,A,E)_{Tissue}$
	Multiplicity of events of HI, Neutron, Proton, or α	$(Z,A,E)_{Material}$	$(Z,A,E)_{Material}$	$(Z,A,E)_{Tissue}$
Radio-biological property	Biological damage of Katz model[1]	$(Z,A,E)_{Tissue}$	$(Z,A,E)_{Tissue}$	$(Z,A,E)_{Tissue}$

[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.

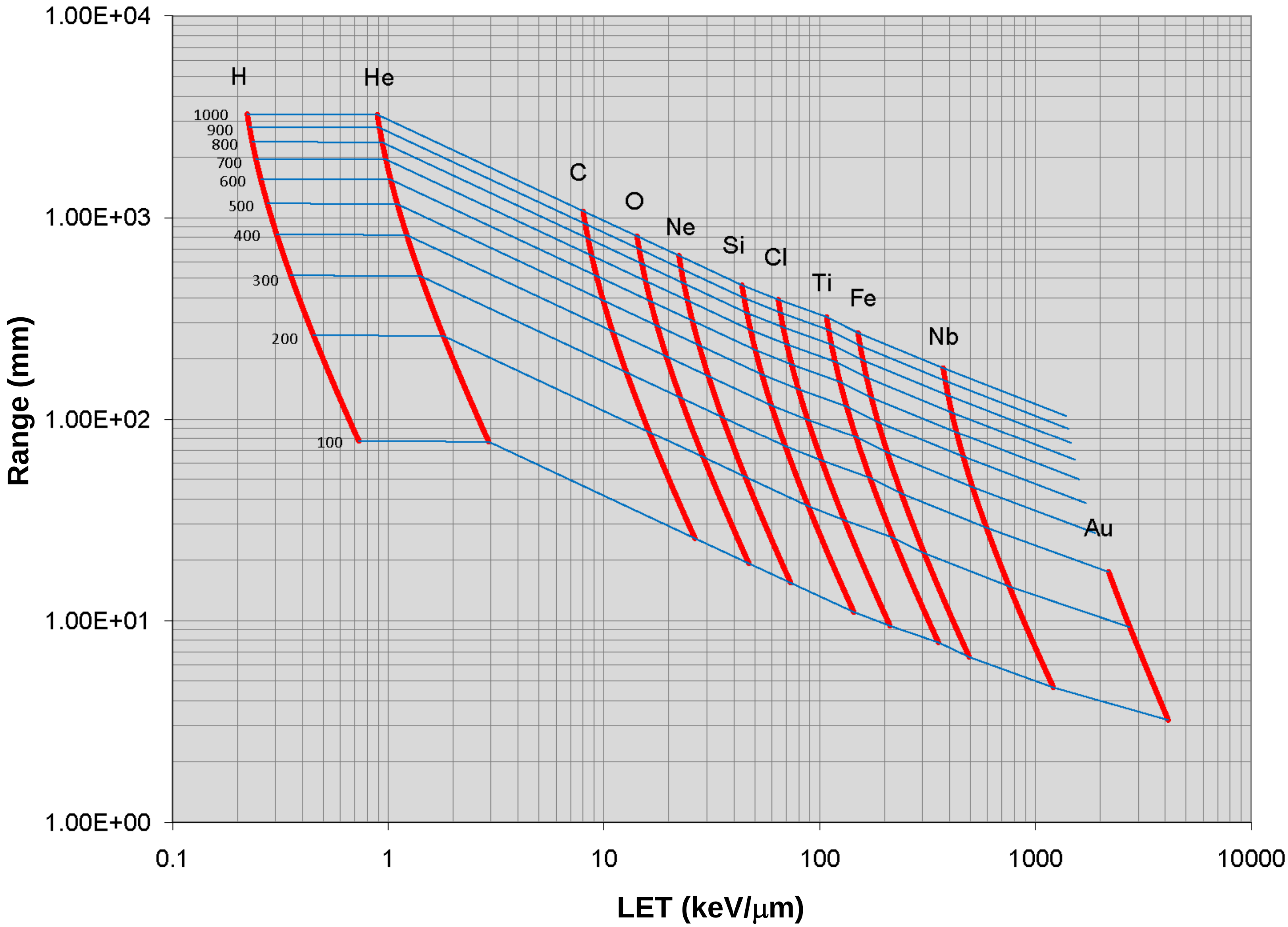
Homework

Beam Ion Species and Energies Used Previously at NSRL

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

http://www.bnl.gov/medical/NASA/CAD/Beam_Ion_Species_and_Energy.asp

LET-Range Distribution for Water



http://www.bnl.gov/medical/NASA/CAD/LET-Range.pdf

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.

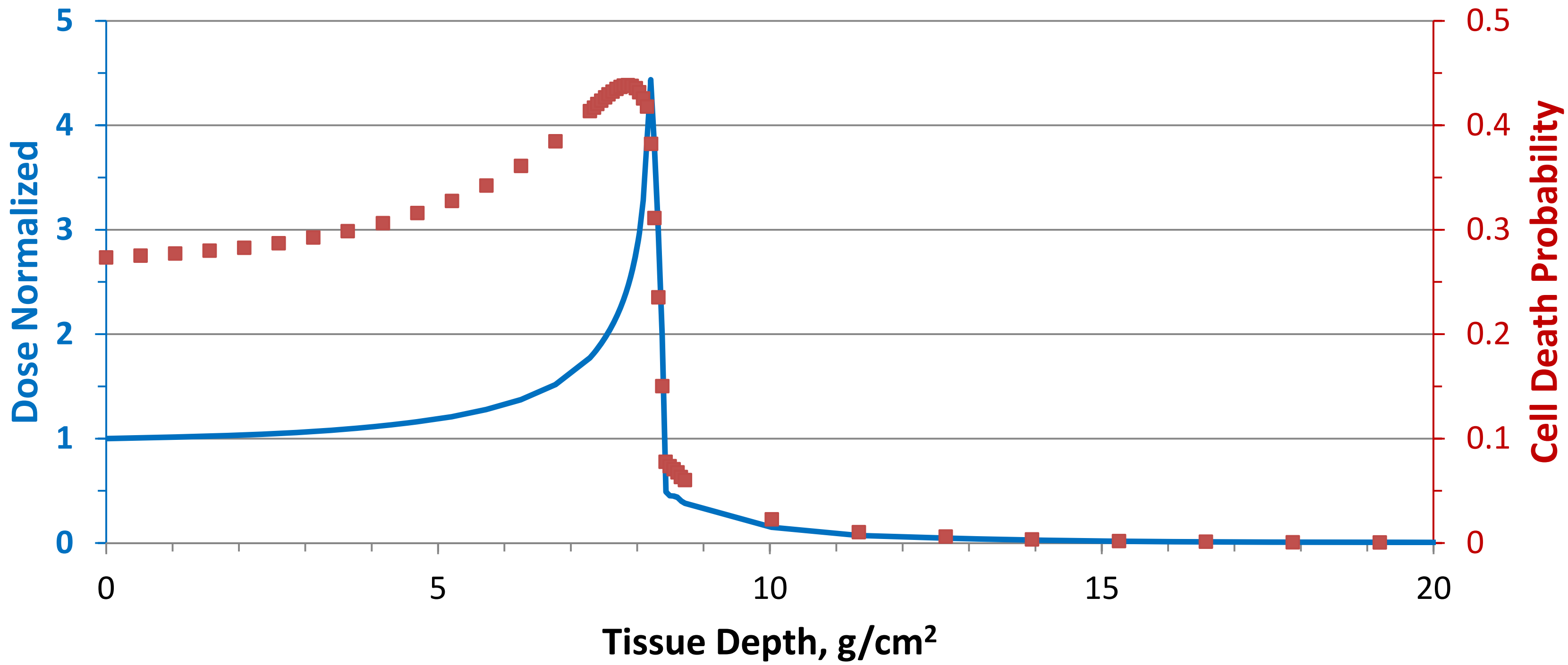
- Calculate values of LET and range for a water, and compare them to the Range vs. LET graph (slide 28). Generate the same graph for another material.
- Calculate mean free path, probability to suffer a nuclear interaction after 1 or 5 g/cm^2 of a material for specified beams and energies.
- By applying 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 (δ-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 γ-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?

Cell Death for Entrance Dose of 1 Gy by ^{28}Si 300 MeV/u



- 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

1. Cucinotta, F. A., Plante, I., Ponomarev, A. L., and Kim, M. Y., Nuclear Interactions in Heavy Ion Transport and Event-Based Risk Models, *Radiation Protection Dosimetry,* 143, 384-390, 2011.
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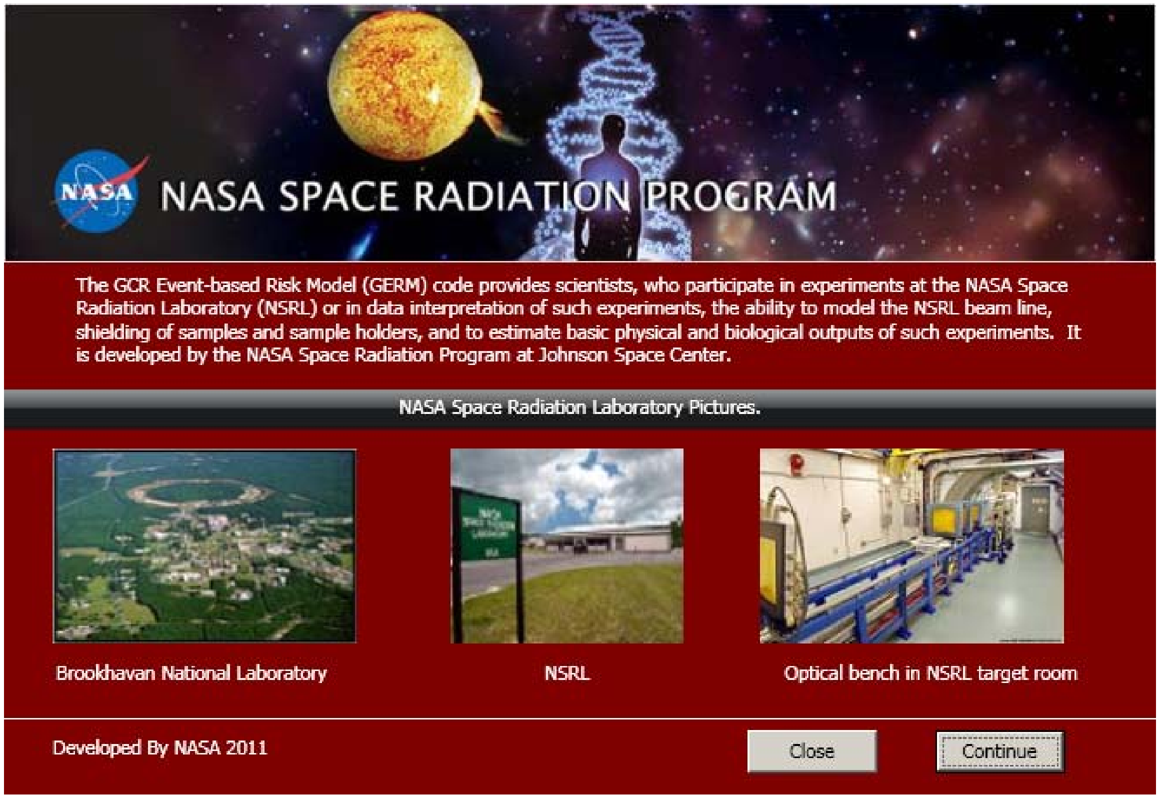
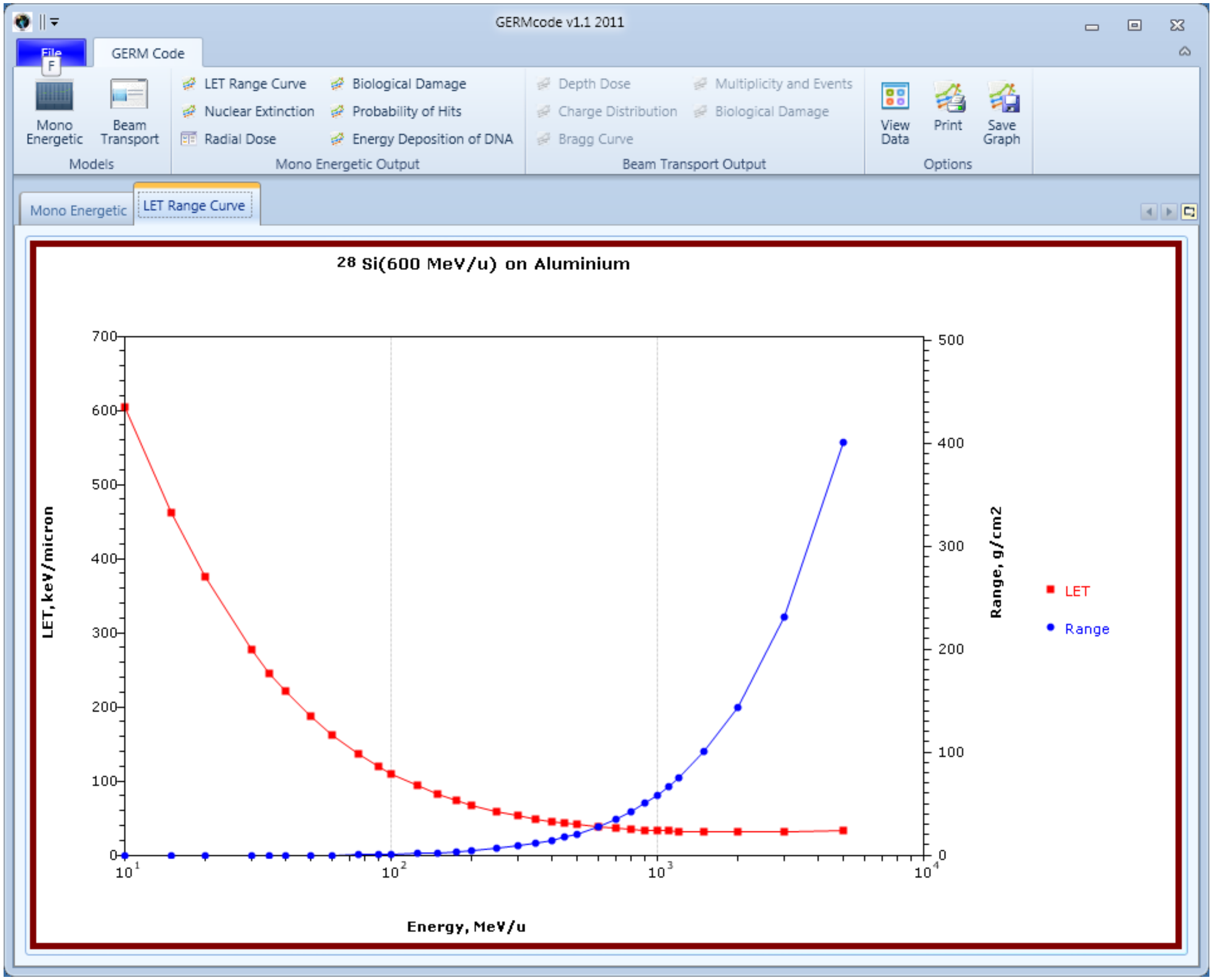
NSRL GERMcode GUI Outputs

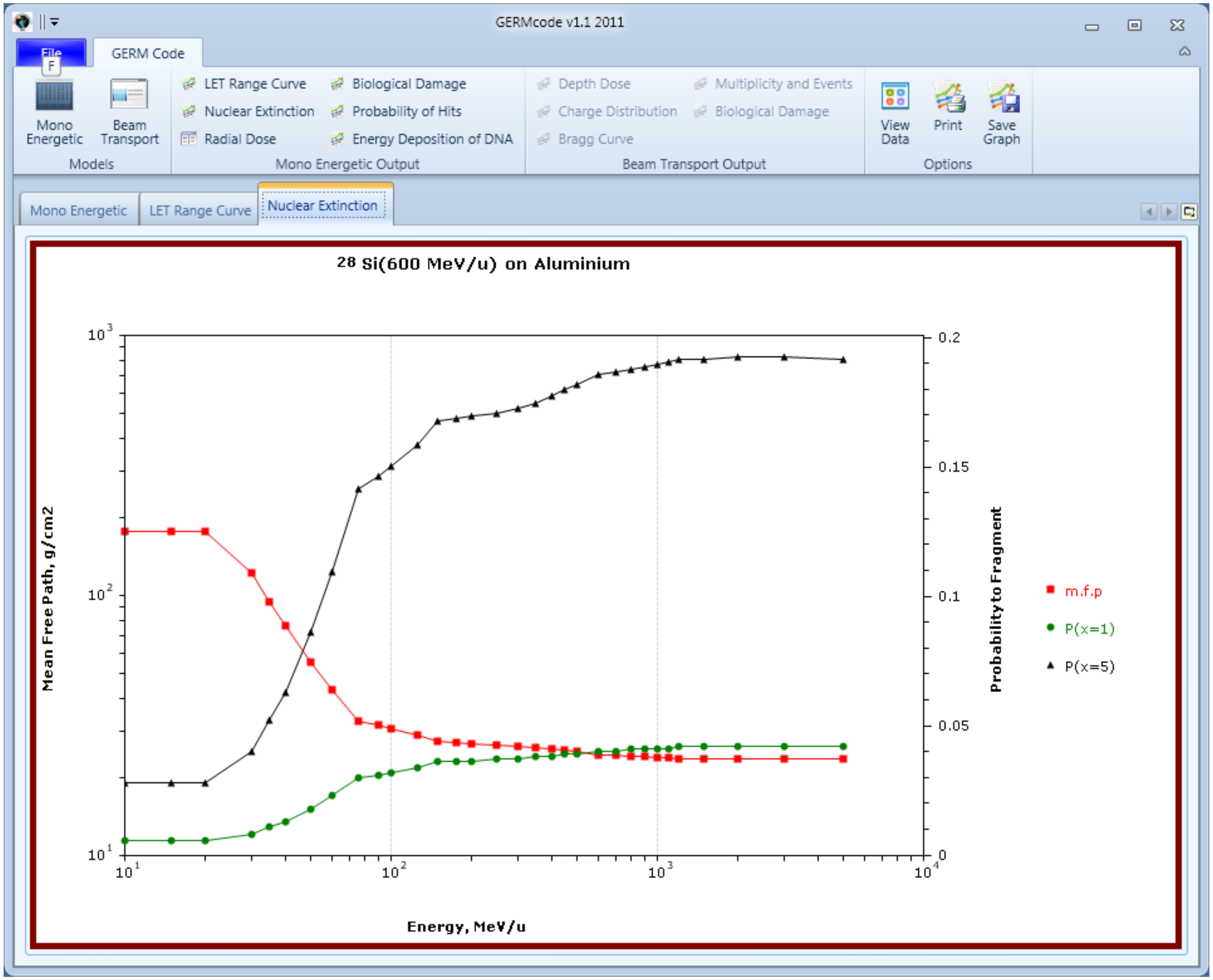


Option for Mono Energetic Beam



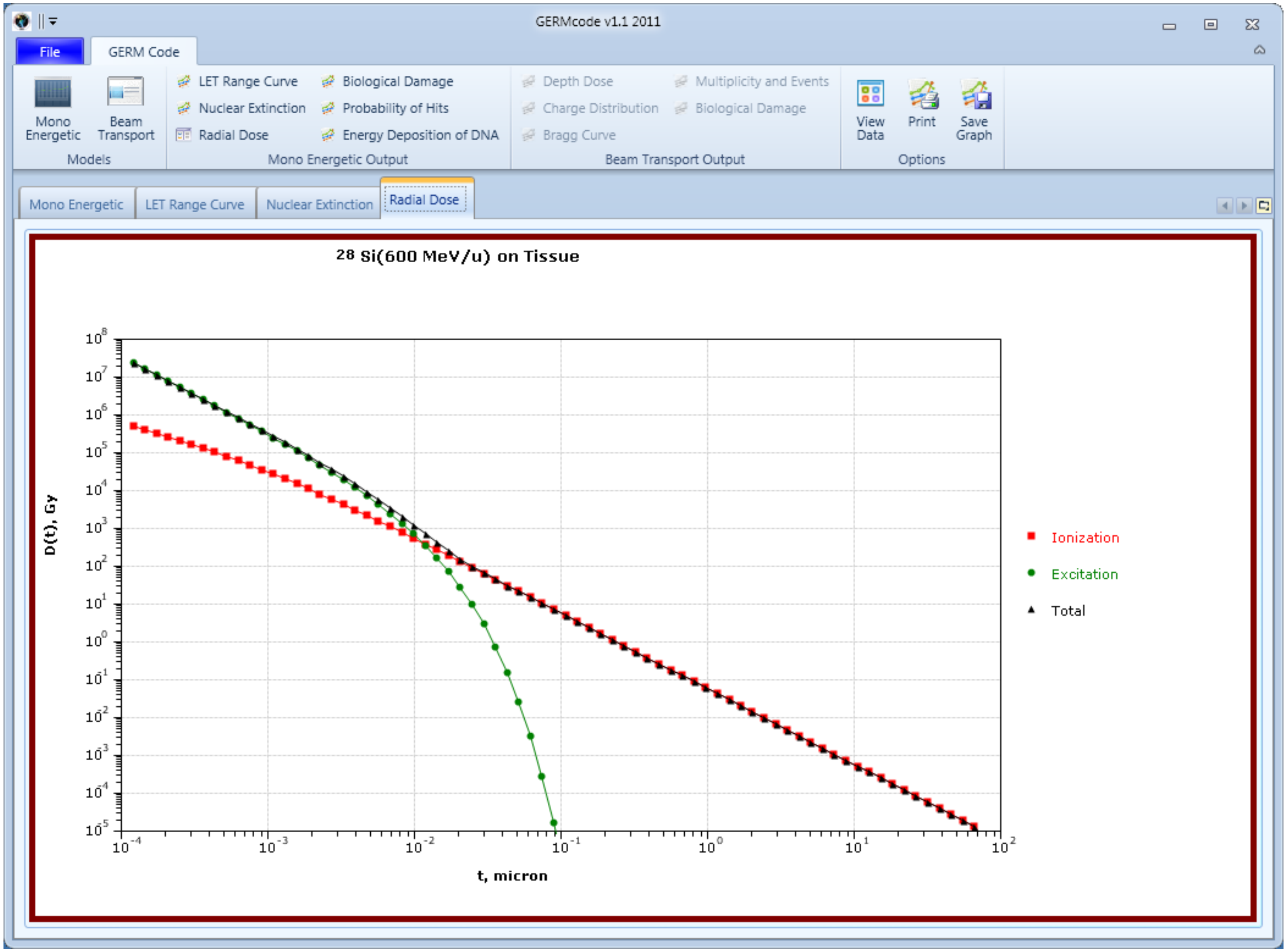
LET and **Range** curves of ^{28}Si beam on aluminum shielding as a function of kinetic energy of the beam.

Option for Mono Energetic Beam



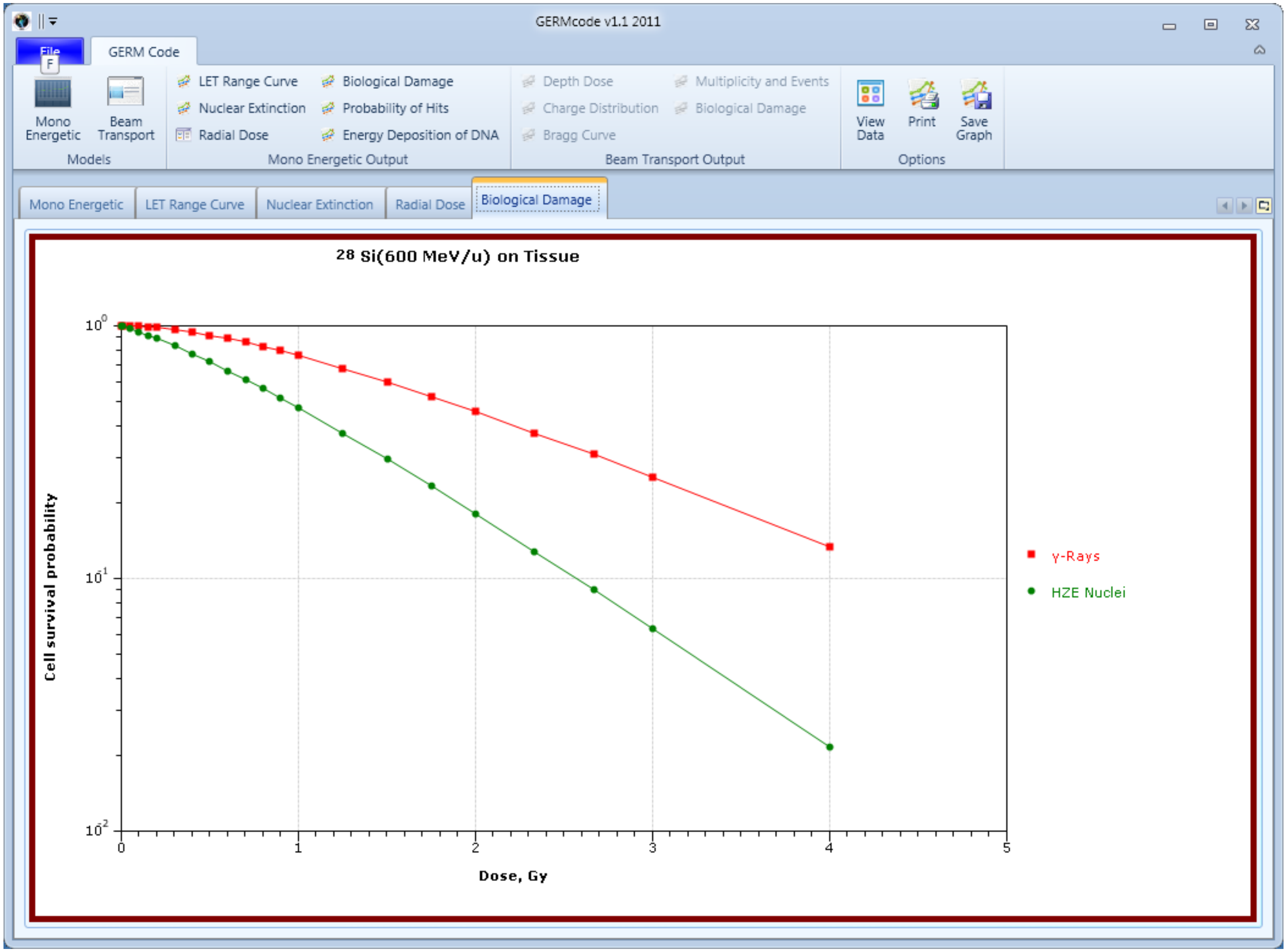
Nuclear Extinction: The **mean free path** and the probability of nuclear interaction at **1 g/cm²** and **5 g/cm²** of ^{28}Si beam on aluminum shielding as a function of kinetic energy of the beam.

Option for Mono Energetic Beam



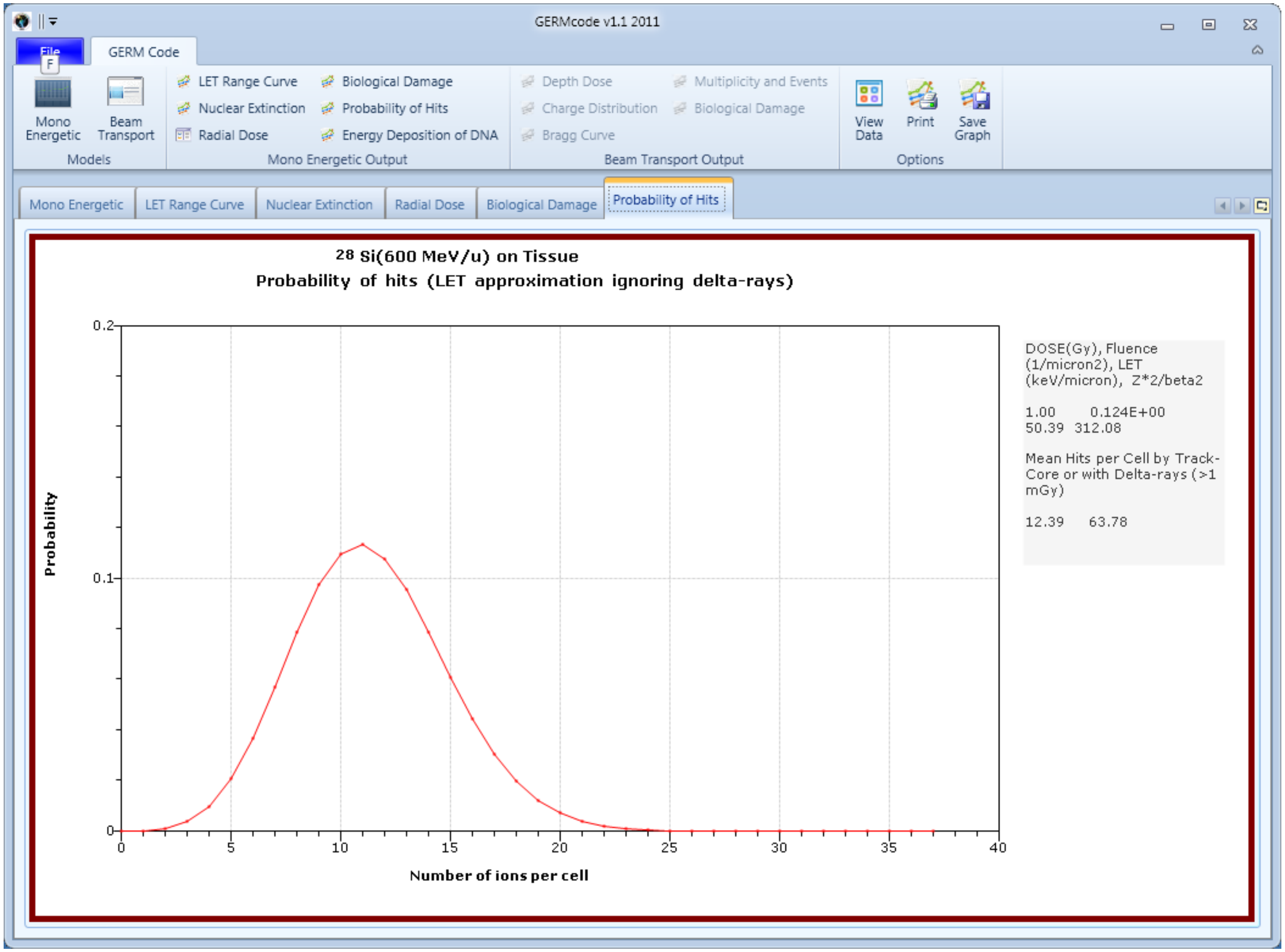
Radial Dose: The evaluation of radial dose of **ionization**, **excitation** and **total** as a function of radial distance from the exposure to **600 MeV/u ^{28}Si beam** on the **tissue** equivalent material.

Option for Mono Energetic Beam



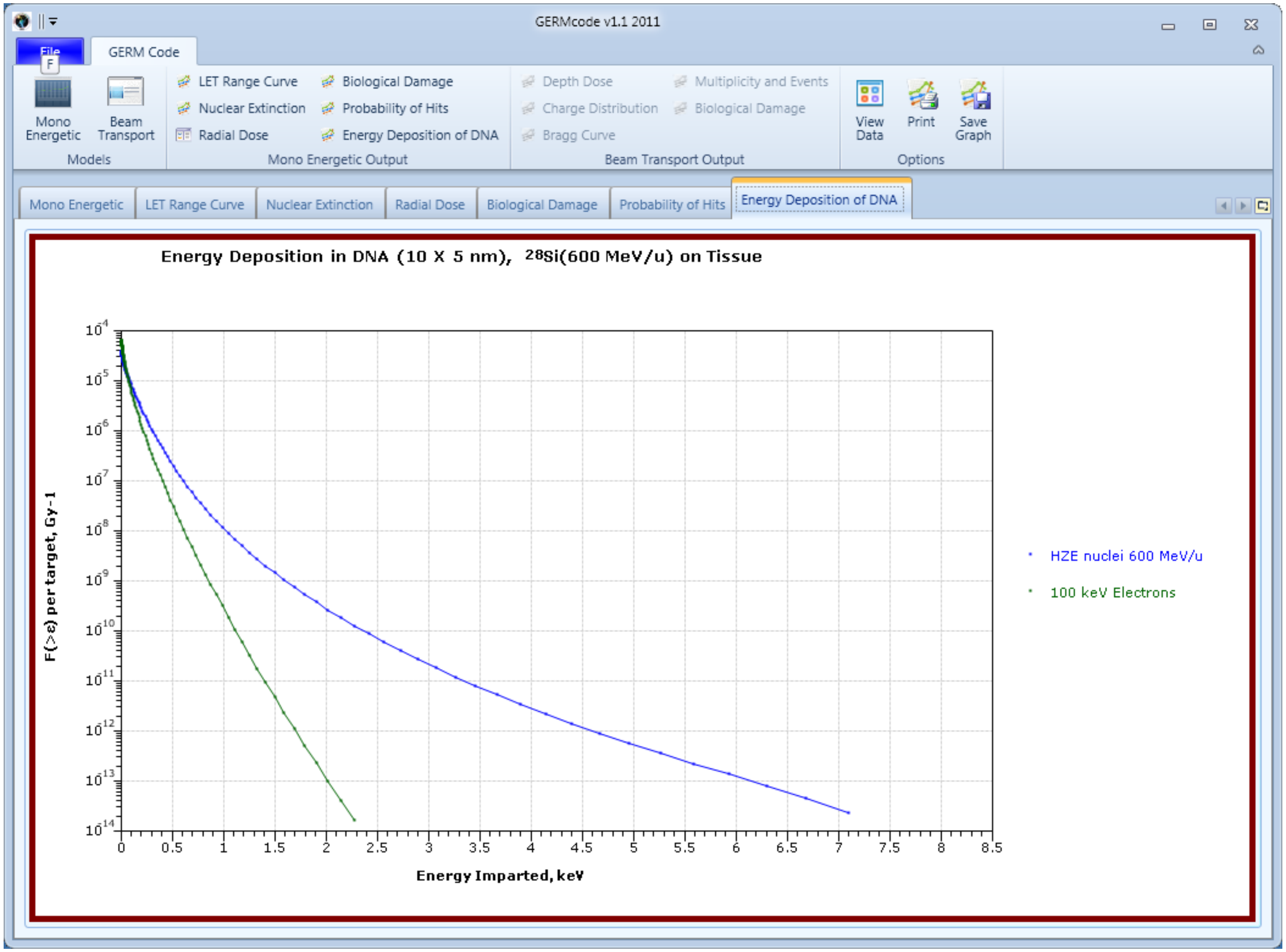
Biological Damage: Cell survival responses as a function of the dose using **600 MeV/u ^{28}Si beam** or **γ-rays** on the **tissue** equivalent material.

Option for Mono Energetic Beam



Probability of Hits: The Poisson distribution of probability of hits from the exposure to **1 Gy** using **600 MeV/u ^{28}Si beam** in the cell area of **100 μm^2**. Displayed figure is the probability of hits per cell in the **track core** only, ignoring δ-rays. The mean hits per cell for LET approximations **with and without** δ-rays are stated in the text of the output window.

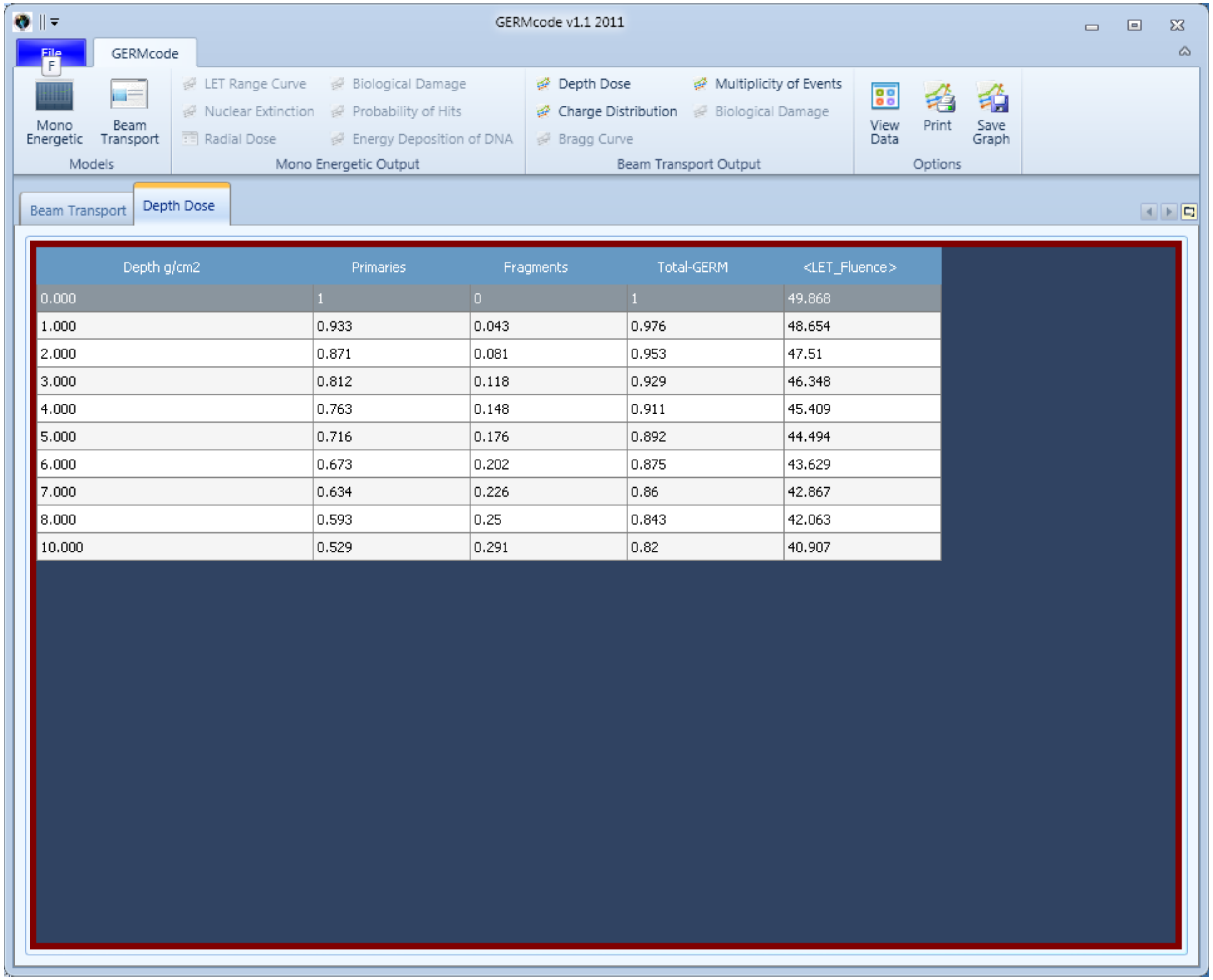
Option for Mono Energetic Beam



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** (δ-ray events) produced about an ion's path

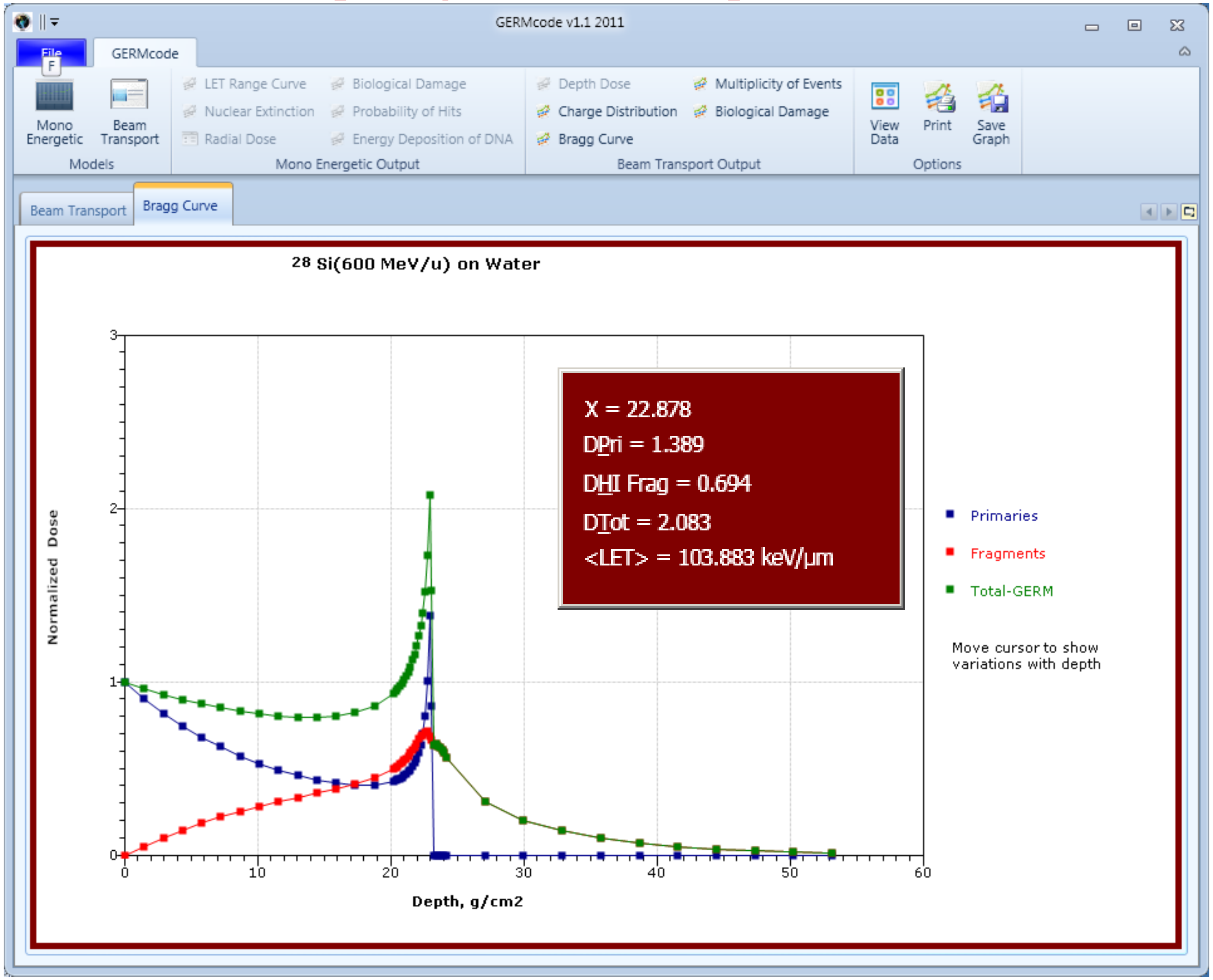
Option for Beam Transport



Depth g/cm2	Primaries	Fragments	Total-GERM	<LET_Fluence>
0.000	1	0	1	49.868
1.000	0.933	0.043	0.976	48.654
2.000	0.871	0.081	0.953	47.51
3.000	0.812	0.118	0.929	46.348
4.000	0.763	0.148	0.911	45.409
5.000	0.716	0.176	0.892	44.494
6.000	0.673	0.202	0.875	43.629
7.000	0.634	0.226	0.86	42.867
8.000	0.593	0.25	0.843	42.063
10.000	0.529	0.291	0.82	40.907

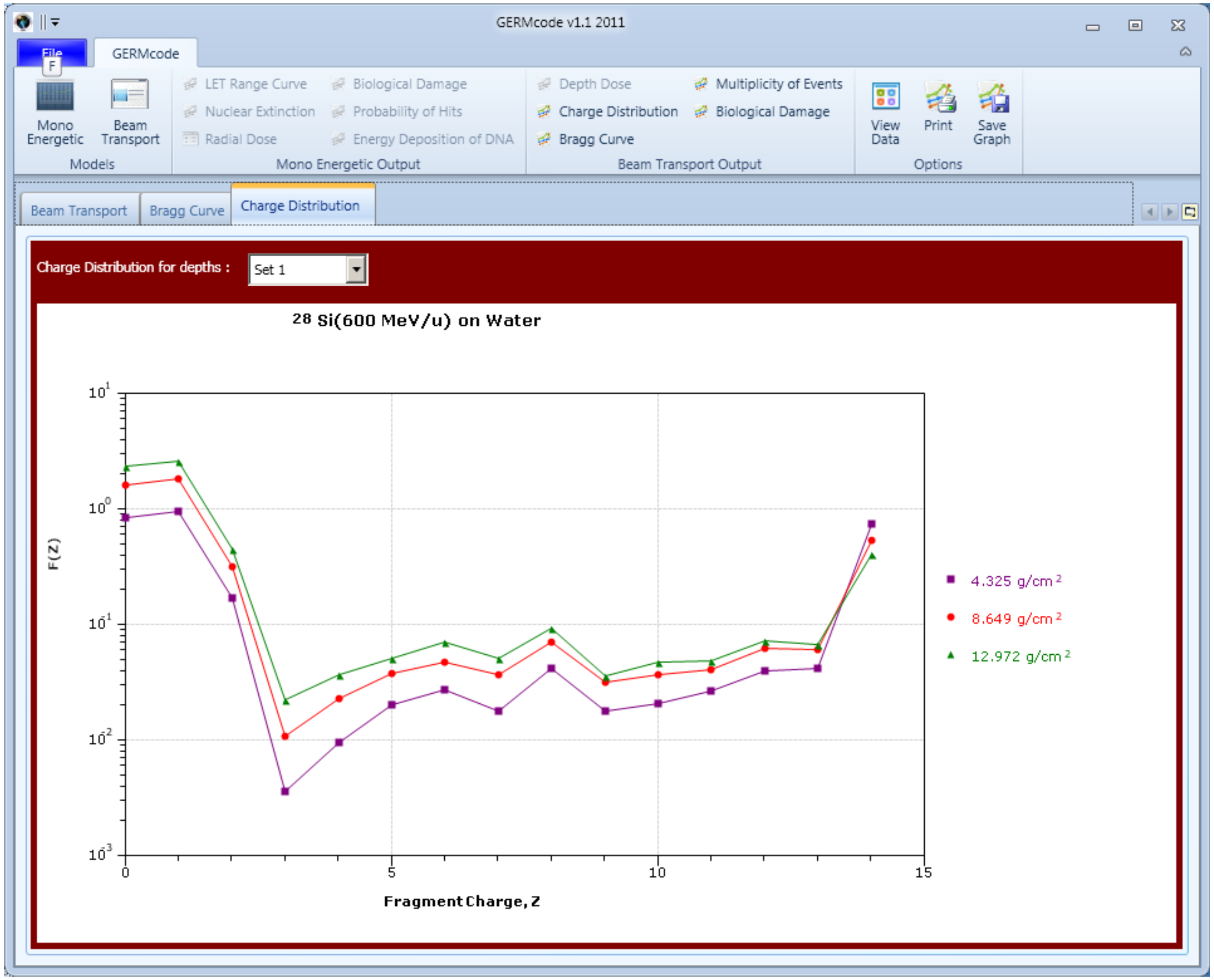
Depth Dose for Fixed Depth: Normalized depth-dose evaluation using 600 MeV/u ^{28}Si beam on water for primaries, fragments, and total at 10 depths of water in the NSRL beam line. The last column shows the fluence-based average LET at each depths.

Option for Beam Transport



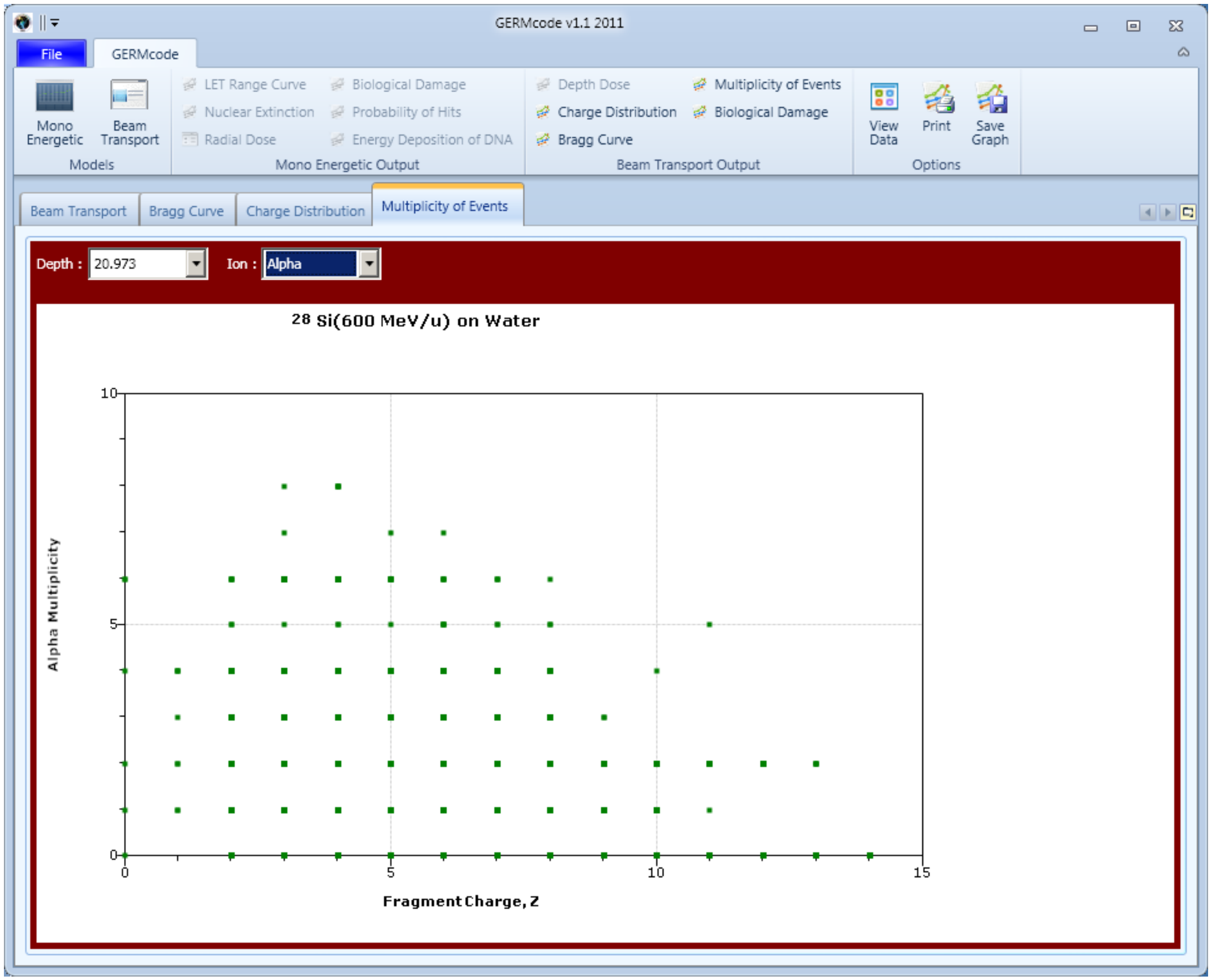
Bragg Curve: Normalized dose of 600 MeV/u ^{28}Si beam for **primaries**, **fragments**, and the **total** as a function of depth of water in the NSRL beam line. Variations of the normalized doses and the fluence-based average LET with water depths are displayed in the inset, as cursor moves along the graph.

Option for Beam Transport



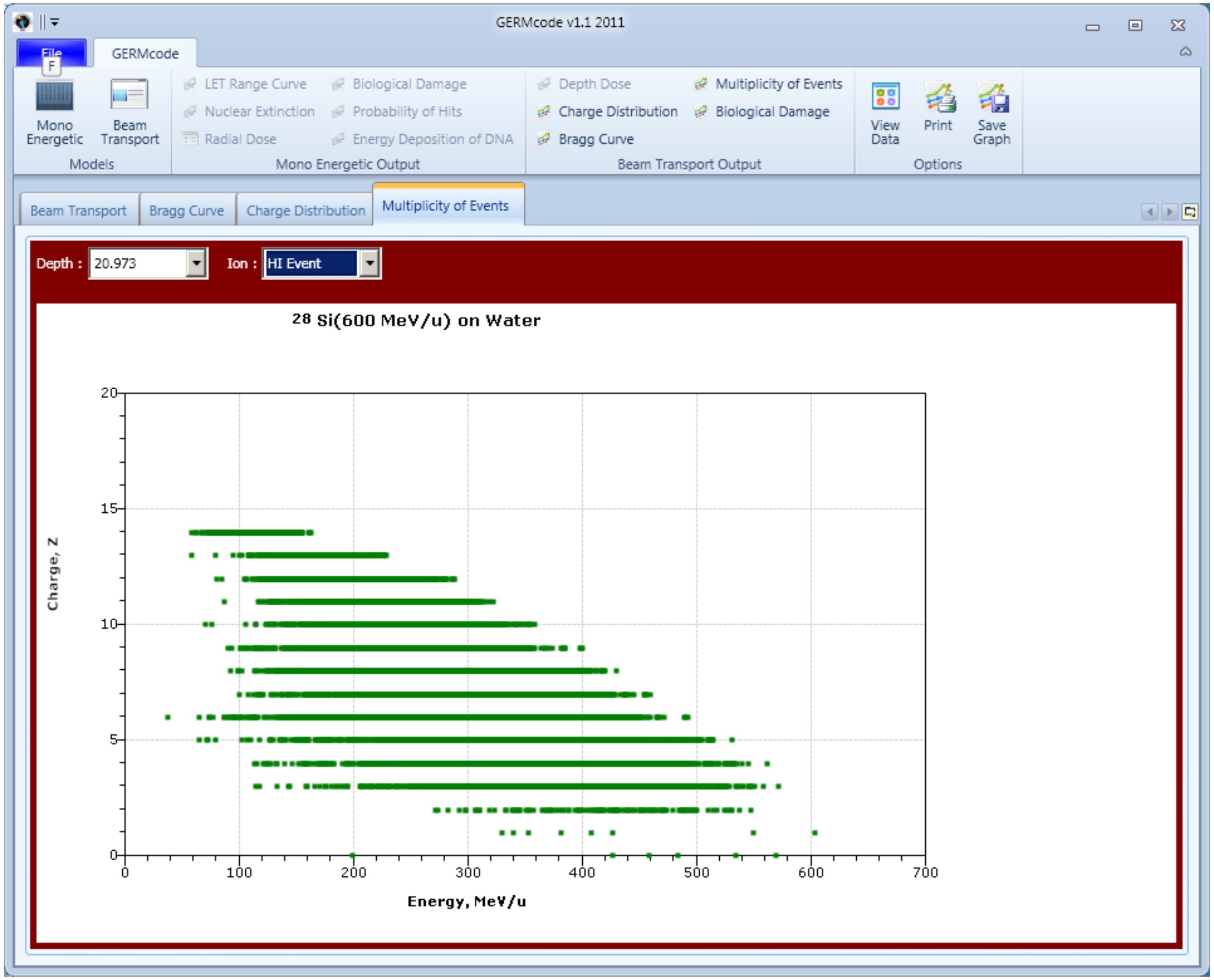
Charge Distribution: Cumulative spectrum of fragments from exposure to **600 MeV/u ^{28}Si beam** transported through the **water**.
Various number of sets are available in the drop-down menu for the shielding depths by selecting “For Fixed Depth”, “For Bragg Curve”, or “For Biological Model” .

Option for Beam Transport



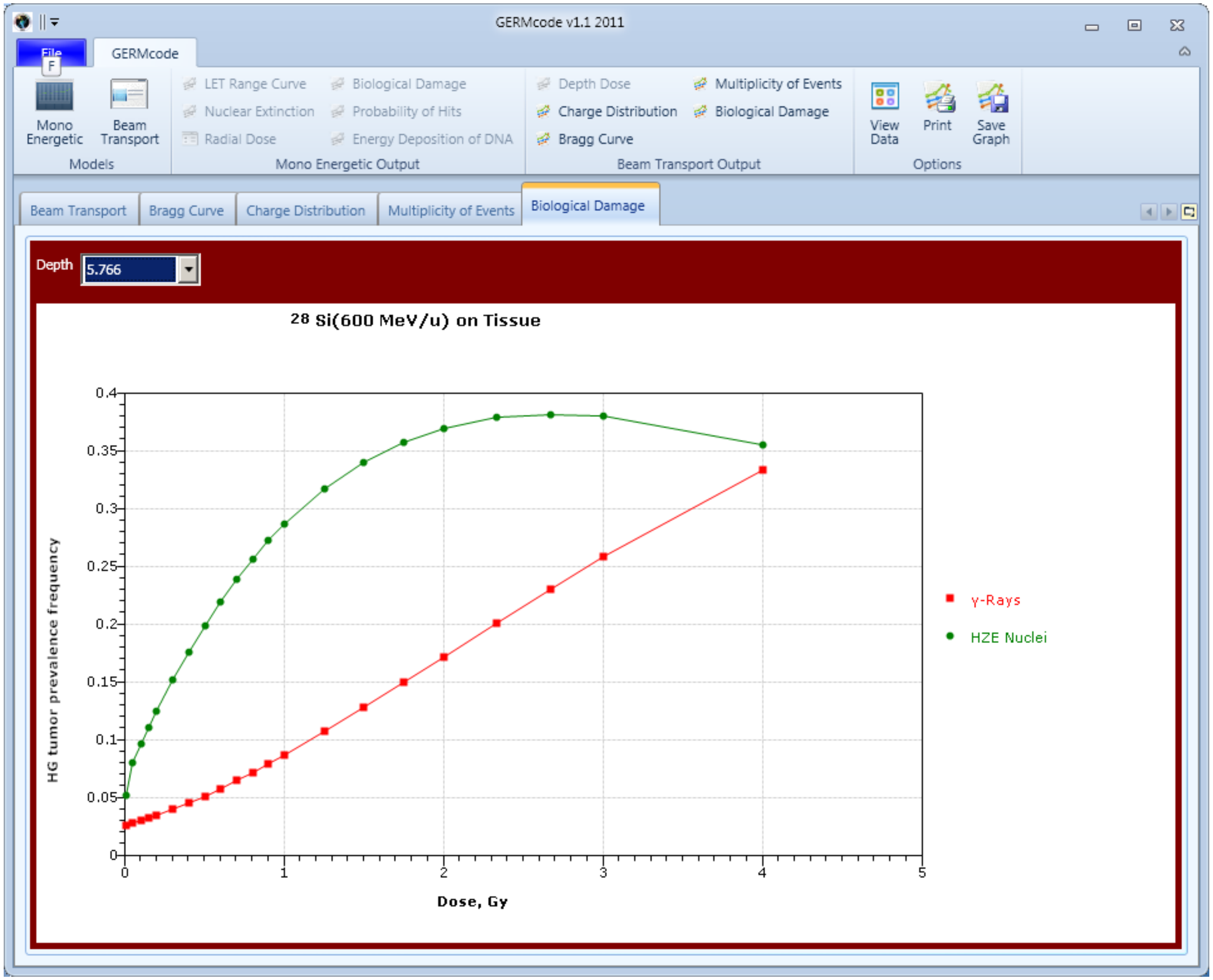
Multiplicity of Events: Multiplicity of α-**particles** in heavy ion fragmentation event at the **depth** of ~21 g/cm^2 of water from exposure to 600 MeV/u ^{28}Si beam. Drop-down menus of "Depth" and "Ion" are available for the selection of depth and the particle type of neutron, proton, or α. Also, energy distribution of heavy ion event is displayed by selecting "HI Event" from the drop-down menu of "Ion".

Option for Beam Transport



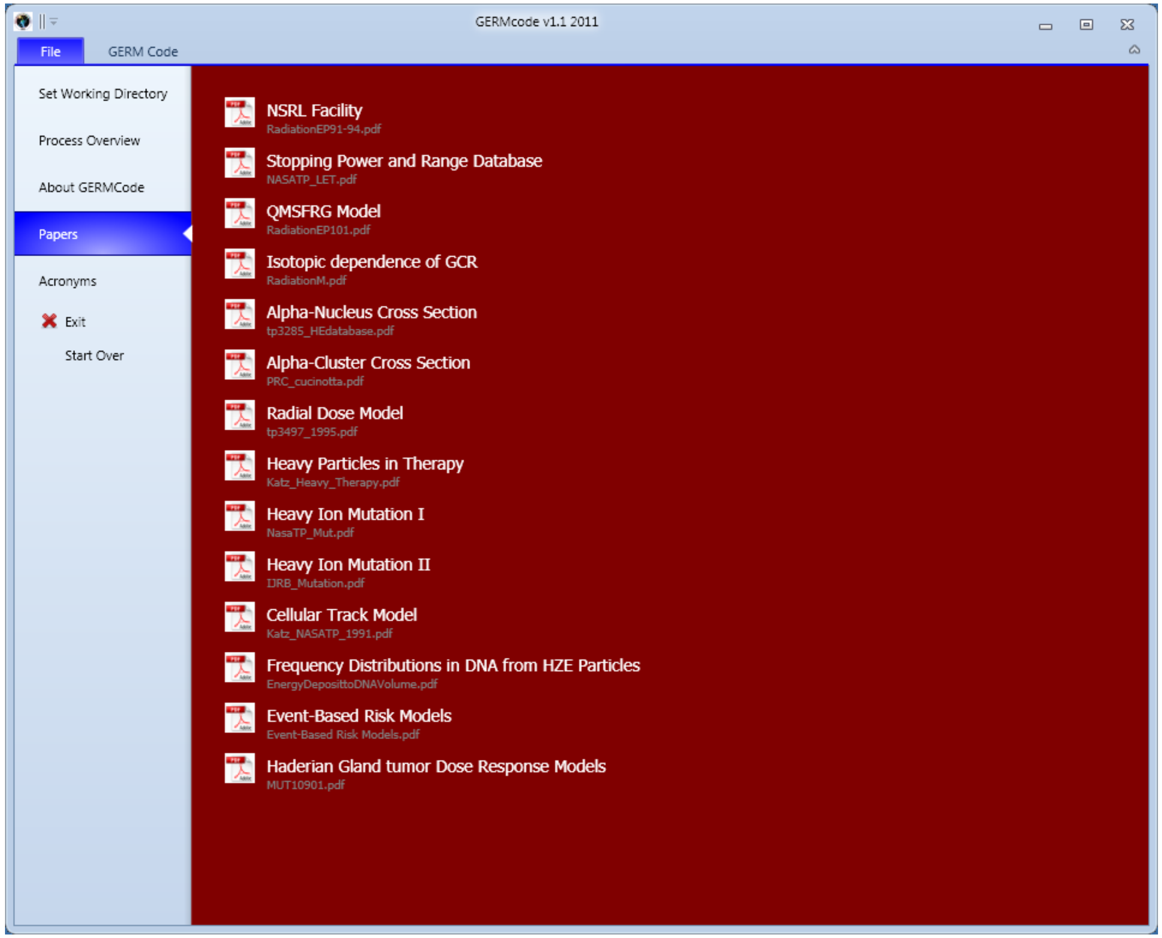
Multiplicity of Events: Downgraded energy distribution of particles produced from heavy ion events at the **depth** of ~21 g/cm^2 of water from exposure to 600 MeV/u ^{28}Si beam is displayed by selecting “**HI Event**” from the drop-down menu of “Ion”.

Option for Beam Transport



Biological Damage: Harderian gland tumor prevalence curve at the depth of ~6 g/cm^2 of tissue equivalent material as a function of the dose using **600 MeV/u ^{28}Si beam** or **γ-rays**.

Reference Papers from File Menu in the Main Tool Bar



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.