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Galactic cosmic ray simulation at the NASA Space Radiation Laboratory

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Abstract

Most accelerator-based space radiation experiments have been performed with single ion beams at fixed energies. However, the space radiation environment consists of a wide variety of ion species with a continuous range of energies. Due to recent developments in beam switching technology implemented at the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory (BNL), it is now possible to rapidly switch ion species and energies, allowing for the possibility to more realistically simulate the actual radiation environment found in space. The present paper discusses a variety of issues related to implementation of galactic cosmic ray (GCR) simulation at NSRL, especially for experiments in radiobiology. Advantages and disadvantages of different approaches to developing a GCR simulator are presented. In addition, issues common to both GCR simulation and single beam experiments are compared to issues unique to GCR simulation studies. A set of conclusions is presented as well as a discussion of the technical implementation of GCR simulation.

Keywords

Space radiation; Galactic cosmic ray simulation

1. Introduction

The health effects of space radiation on astronauts represent a major limiting factor for long-duration human space missions beyond Low Earth Orbit (LEO) (Durante, 2014). Beyond LEO, the most important sources of space radiation consist of galactic cosmic rays and Solar Particle Events (SPE). GCR nuclei of average energy can penetrate a substantial thickness of materials, on the order of 10s to 100s of centimeters of water or aluminum. If a nuclear

interaction between a primary GCR ion and a target nucleus occurs, the lighter secondary products will lose energy at a lower rate, and therefore will be able to penetrate even further. For this reason, it is not possible to provide sufficient shielding material to fully absorb all types of radiation in space. In addition, the relative biological effectiveness of nuclei will change as a function of depth of penetration, because the composition and energy of the nuclei changes due to atomic and nuclear interactions. The Linear Energy Transfer (LET) of each nucleus also changes as it loses energy and slows down inside the material being penetrated.

The major GCR particle types include hydrogen (H), helium (He), carbon (C), oxygen (O), neon (Ne), silicon (Si), calcium (Ca), and iron (Fe). The energy spectra of all GCR particles are very broad with the region extending from approximately 10 MeV/n to 50 GeV/n being of primary importance to space applications (Grahn, 1973; Slaba and Blattnig, 2014; Durante and Cucinotta, 2011). GCR exposures occur at low fluence rate, with each cell in an astronaut's body being "traversed by a proton about every three days, helium nuclei once every few weeks, and high atomic number (Z) and energy (HZE) nuclei about once every few months" (NASA, 2015a). The cells are not traversed at random and the traversals are not statistically independent. The traversal of a cell nucleus usually correlates with the simultaneous traversal of very large numbers of additional cell nuclei (on the order of 10^9) in the tissue along the track of the same particle. These fluence rates correspond to tissue doses or effective dose-rates of about 0.3–0.6 mGy/day and 1–1.8 mSv/day, respectively. However, the use of absorbed dose (or dose-rate) is misleading, because the energy lost by each incident particle is deposited in a highly non-uniform way, both physically and temporally. Dose-rate effects may best be understood in terms of particle fluence rate (commonly referred to as particle flux); any such effects will be dependent on the end-point considered, and the time constants of the chemical kinetics involved.

SPEs consist primarily of protons and, much like GCR, have a broad energy spectrum with the energy region of most importance to human space flight extending out to a few hundred MeV. The SPE spectra include much smaller components of helium and heavy nuclei. The shapes of the energy spectra, as well as the total fluence, vary considerably from event to event. Over the course of an SPE, dose-rates can fluctuate between 0–100 mGy/hr inside the protection of a vehicle. SPE dose-rates can also differ by several-fold between tissue sites because of the variable energy spectra of the protons or other nuclei. Similar to the case for GCR, the use of dose or dose-rate to characterize protons in space can be misleading from a biological point of view, except in cases where the proton fluence is high enough to ensure that the target organism has been irradiated uniformly. Note, however, that statements concerning dose and dose-rate for SPE are also dependent on the space vehicle or space habitat analyzed and the SPE spectrum chosen. There are large variations across both of those variables.

Energy deposition in biomolecules, cells, and tissues is distinct when comparing protons and HZE nuclei to common forms of terrestrial radiation. For the particles comprising space radiation, energy deposition is highly localized along the trajectory of each particle with lateral transport of energetic electrons (delta-rays) away from the nuclei's path. The rate of energy deposition per unit length of a particle trajectory is described as LET. The unit

generally used in radiobiology for LET is the kilo-electron volt per micrometer, or keV/μm. The LET of charged particles changes as a function of particle velocity, β, or kinetic energy, and its charge, Z, approximately in proportion to Z^2/β^2. As the velocity (or energy) of a particle increases, the LET decreases to a minimum near a velocity of approximately 90% of the speed of light; at higher energies the LET increases very slowly due to relativistic effects. High-energy charged particles lose energy when they traverse any material. As they slow down, the LET increases to a maximum and then very rapidly decreases to zero. The low-energy maximum in the LET occurs very close to the point where the charged particle loses its remaining energy and stops. Nuclear fragmentation and other nuclear interactions, including projectile fragmentation of the primary ion and target fragmentation of tissue constituents, occur as ions traverse tissue. For proton and HZE nuclei irradiation, target fragmentation, including secondary neutron production, introduces an additional high LET component into the radiation field.

Space radiation risks of concern to NASA are carcinogenesis (increased risk to fatal cancers), acute (in-flight) and late (i.e. after a mission) risks to the central nervous system (CNS), degenerative tissue risks such as cardiovascular disease, and acute radiation syndromes. For cancer and acute risk estimates, human epidemiology data with gamma-ray and X-ray exposures play a key role in risk estimation models. Acute risks are a concern for SPE, while cancer, CNS, and cardiovascular risks, etc., are a concern for both GCR and SPE. The current model of cancer risks used by NASA, NSCR 2012 (Cucinotta et al., 2013) scales cancer incidence or mortality rates estimated from epidemiology data to the effects for the low dose-rates and radiation types in space using a dose- and dose-rate effectiveness factor (DDREF) and radiation quality factor, respectively. There are large uncertainties in this model, which, in order of decreasing importance are as follows: the radiation quality factors, dose and dose-rate dependencies, the transfer of risk across populations, the determination of space radiation organ exposures, and the various errors in human data sources. In addition, there are uncertainties related to the underlying assumptions of the model due to possible qualitative differences between high- and low-LET radiations, the validity of the assumptions of linearity and additivity of effects for different radiation components, and the possible synergistic risks from other flight factors on radiation risks. Because solar protons are largely low LET, and the proton fluences during SPE's can be highly variable, the predominant uncertainty for acute risk estimates is related to the understanding of dose-rate effects.

Of greatest concern are the effects of GCR from hydrogen to nickel in the approximate energy range from 10 MeV/n to 50 GeV/n (Slaba and Blattnig, 2014; Durante and Cucinotta, 2011). Space-based studies to investigate the physics, biology, and clinically evident health consequences of space radiation suffer from severe limitations. Among them are the necessary choice of minimal radiation exposure to spacecraft crews; the small number of humans with space experience; restrictions on mass, volume and power available for equipment and maintenance of laboratory animals; and the lack of real-time access to experiments by investigators. For these and similar reasons, NASA recognized early in the development of space radiation research that statistically significant data with the accuracy required for proper risk management could only be obtained by the use of high-energy, ion beams at ground-based accelerators. Consequently, there have been research programs

concentrating on understanding the effects of heavy ions conducted at several particle accelerators around the world (Sihver, 2008). The first acceleration of relativistic heavy ion beams occurred at Princeton in 1971 (White et al., 1971; Isaila et al., 1972), followed by the BEVALAC at Lawrence Berkeley National Laboratory (LBNL), the Helmholtzzentrum für Schwerionenforschung (Helmholtz Center for Heavy Ion Research, formerly Gesellschaft für Schwerionenforschung, GSI), the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory (BNL), the Heavy Ion Medical Accelerator (HIMAC) at the National Institute of Radiological Sciences (NIRS) in Chiba, Japan, and additional accelerator facilities in Europe and Asia. An active program is currently underway at NSRL, and a future program at higher energy, above 10 GeV/n, is planned at the Facility for Antiproton and Ion Research (FAIR) at the Helmholtzzentrum für Schwerionenforschung (Durante et al., 2007; Stohlker et al., 2015; Sihver, 2008; Chattopadhyay, 2014; Heuser, 2013).

To date, typical ground-based experiments have involved the use of single ion beams, with or without degraders, at fixed energies. However, accelerator technology has developed to the stage where it has now become feasible to accelerate a variety of beams with differing energies, with beam switching times sufficiently small (less than two minutes) that allow approximate reproduction of parts of the GCR spectrum in ground-based facilities (Slaba et al., 2015a, 2016) compressed into a high dose-rate exposure, or beams consisting of various ions simultaneously. This will allow researchers to simulate a mixed field in tissue to investigate the combined biological effect of different LET irradiations. This new experimental capability better simulates the space environment and allows for ground based experiments to replicate the important biological effects of a mixed radiation spectrum, e.g. the field of light ions (defined as isotopes of hydrogen and helium), that are major contributors to space radiation dose equivalent along with representative heavy ions (Norbury and Slaba, 2014; Walker et al., 2013).

It is useful to identify the main reasons for considering GCR simulation. In preparation for sending astronauts on long duration missions into space, it is necessary to simulate the same overall environment in ground-based facilities. Of course, the practical implementation of GCR simulation will be different from the real space environment in terms of the particle spectrum, dose and dose-rate. While the implementation of GCR simulation will only be an approximation to the true situation in space, it is a great improvement over the single ion exposure now widely in use. Therefore, current approaches would be complemented with single beams to develop radiobiological mechanistic understanding and phenomenological relationships. Knowing what harmful health effects occur leads to the development of appropriate countermeasures. This reasoning is a biological end point phenomenological approach and does not rely entirely on standard radiobiological issues such as cancer mechanisms, predictive models or risk analysis. However, if extrapolated to its full extent, this approach will impose a set of experimental conditions that will be needed in order to eliminate or isolate the risks from GCR alone as well as in combination with other space “toxicities”, such as microgravity or a restrictive diet. Nonetheless, determining risk from the space environment is necessary if GCR exposure alone leads to such risks as increased carcinogenesis, cognitive dysfunction, and cardiovascular problems, since efforts can then be targeted towards risk reduction. Indeed, the recent NASA Research Announcement (NRA)

(NASA, 2015a) gives an indication of what are expected of the results of GCR simulation: “Ultimately mixed field studies must inform risk model predictions, biomarker discovery and validation, and countermeasure identification and validation across all risk areas” (NASA, 2015a; Appendix D, p. 16). Thus, results from mixed field studies must ultimately find their way into risk models. The mechanisms and repair or recovery pathways seen after exposure to single ions may be quite different, particularly with dose-rate. It is important to know how relevant space radiation doses and dose-rates of mixed field exposure damage cells, and GCR simulation will make that feasible. It can be challenging, however, to design experiments with adequate statistical power for very low dose, low dose-rate studies.

Finally, GCR simulation can benefit from studies from the particle physics community, such as better measurements of nuclear cross sections at different energies, a precise knowledge of the GCR flux for different species at all energies throughout the solar cycle, and developing more effective solutions to reproduce a particle dose more similar to the one of GCR. For example, the Alpha Magnetic Spectrometer AMS-02 (Aguilar et al., 2015) on the International Space Station (ISS) is providing precision flux measurements of all cosmic rays species during the ascending and descending phase of the solar cycle that can further constrain the GCR simulation model and improve the final results.

The outline of the rest of this paper is as follows: Section 2 presents a discussion of previous studies of GCR simulation after introducing the two concepts of external field versus local tissue field approaches to GCR simulation. Section 3 discusses GCR simulation from the NASA perspective. This is followed by Section 4 which highlights the importance of continuing single beam experiments to complement GCR simulation experiments. Sections 5 and 6 are devoted to some on-going important issues that arise when implementing a GCR simulator at an accelerator laboratory, such as NSRL: Section 5 specifically addresses issues common to both single beam experiments and GCR simulation experiments, and Section 6 addresses issues that are unique to GCR simulation alone. Section 7 branches out to other applications of GCR simulation, followed by Section 8 which delves into the actual plans for constructing a GCR simulator at NSRL. Finally, Section 9 presents a summary and some conclusions.

2. Previous studies

Before proceeding to the full discussion of GCR simulation, it is worthwhile to summarize previous studies of this subject. This section starts with a background discussion of the external field versus local tissue field methods, prior to delving into the previous studies, which include several workshops and two journal papers.

2.1. External field approach versus local tissue field approach to GCR simulation

A topic that sometimes causes confusion comes when specifying the actual ions and energies that should be provided by an accelerator laboratory GCR simulator. The answer is not as simple as providing the same ions and energies seen in space, because it would be almost impossible for an accelerator to provide a continuous energy spectrum for each ion. There are two approaches to GCR simulation called the “external field” approach and the “local tissue field” approach that have been studied thus far (Slaba et al., 2015a, 2016; Kim

et al., 2015). The external field approach to GCR simulation aims to directly simulate the GCR spectrum which is external to a spacecraft shield. This external spectrum is significantly modified upon passage through the spacecraft, with many more neutrons and light ions of reduced energy present in the interior of the spacecraft. It is this modified interior spectrum to which an astronaut is actually exposed. Simulating the external GCR spectrum is called the external field approach, while simulating the spectrum occurring within an astronaut is called the local tissue field approach. In implementing GCR simulation at a ground-based accelerator, the required particle energies are much lower for the local tissue field approach. Because of the relatively low energy of NSRL, the local tissue field approach may provide a more flexible and feasible solution at this time. Both methods have their own set of limitations. The external field approach might be more suitable at higher energy machines, such as FAIR (Durante et al., 2007). All of these issues are discussed extensively in the accompanying article by Slaba et al. (2016) and the paper by Kim et al. (2015).

2.2. Workshops

Several workshops have recently focused on GCR simulation at NSRL. The first workshop was held at NASA Langley Research Center in Hampton, Virginia in October, 2014. Participants included fifteen physicists and radiobiologists from a variety of institutions including NSRL, and all participants are coauthors of this paper. The second workshop was held in January, 2015 as part of the NASA Space Radiation Investigators' Workshop in Galveston, Texas. This second workshop included about fifty participants from a much broader variety of institutions, and again many of these participants are also coauthors of this paper. A third workshop was held at the Radiation Research Society meeting in Weston, Florida in September, 2015. In order to promote a broad international discussion, a collaboration was developed, including the many coauthors of this paper. This broad input from the international community was also the subject of several presentations at international conferences (Slaba et al., 2015b; Norbury et al., 2015a, 2015b, 2015c).

A list of issues and questions about the necessity and implementation of GCR simulation were raised at the various workshops mentioned above. For example, is GCR simulation really needed or wanted by space radiobiologists? If so, what scientific questions would GCR simulation help address? What knowledge gaps would GCR simulation help close? And how in particular would GCR simulation be useful? In answer to these questions, space radiobiologists were generally very enthusiastic about the availability of ground-based GCR simulation, although there were numerous concerns about the practicality of its implementation in regards to animal housing, personnel, financial costs, and duplicative efforts across laboratories. To this end, a call was made for more unified standards in radiation parameters, and for more aggressive tissue/organ sharing from current and future NSRL experiments, an effort that is already underway (NASA, 2015b). Dosimetry questions were also raised. How would dosimetry on a GCR simulation combination of beams be performed, and how would one measure the exposure dose of individual beams in the mixed field? In answer to these questions, the NSRL staff stated that scintillators would be used for low dose experiments and there would be no serious dosimetry issues in changing from high to low dose. Questions about the external vs. local tissue field issues were also raised,

including: Would a combination of both the local tissue field approach and the external field approach be possible, with perhaps a shield or water phantom positioned downstream? It was discussed that from a biological perspective, this dual field approach may be better. Numerous other ideas and issues were also generated. For example, it was pointed out that the idea of GCR simulation is not new and the idea has been around for about twenty years. The hope of microgravity simulations was raised, as was the potential for delivery of sequential beams (i.e. delivery of one beam after another) versus a full mixed beam field, with a mixture of beams delivered at the same time (perhaps all at the same rigidity).

2.3. Study of Slaba et al

A detailed implementation study of GCR simulation has recently been completed by Slaba et al. (2015a, 2016), which focused on specifying the reference field and spelling out strategies for selecting the beams at NSRL. A detailed GCR simulation reference field in terms of ion species, beam energies and dose can be found in Tables A1, A2, A3 of that paper. The study appears as a companion paper in the present journal volume and is divided into three main areas.

First, the issue was considered of whether to simulate the free space GCR environment (external to a spacecraft) versus simulating the GCR field induced at local tissue sites, given current accelerator facility constraints. The latter option – simulation of local tissue GCR field – was chosen as being the most feasible implementation for GCR simulation at NSRL due to the maximum energy available, which at the upgraded NSRL will be 1. 5 GeV/nucleon for heavy ions and 4.0 GeV for protons, versus the currently available energies of 1. 0 GeV/nucleon and 2.5 GeV, respectively. (Note that issues of the beam traversing mouse and cell containers etc. do not significantly alter these two basic approaches to GCR simulation.)

Second, the question was addressed concerning the need for multiple GCR simulation reference fields versus a single reference field. Obviously, a single field would be preferred from a cost and convenience perspective. It was found that variations in shielding configurations, variable GCR fluence due to solar activity, and tissue location within the body are smaller than or approximately equal to uncertainties associated with modeling the free space GCR environment, transport models and experimental designs. This allowed for the selection of a single GCR simulation field which was chosen to represent the spectrum induced in female blood forming organs (BFO) behind 20 g/cm^2 of aluminum shielding during solar minimum. (Note that it is this GCR simulation reference field that will be seen directly by astronauts in a typical space vehicle and therefore it is this field that is being proposed for GCR simulation lab experiments at NSRL.)

Third, a preliminary beam selection strategy was considered. As emphasized in previous work (Norbury and Slaba, 2014; Walker et al., 2013), isotopes of hydrogen and helium, collectively called light ions, make a significant (sometimes dominant) contribution to dose equivalent for realistic thick shielding used in current and future vehicle designs. Therefore, hydrogen and helium needed to be considered separately from heavy ions in the GCR simulation beam selection strategy and the hydrogen and helium energy spectra are represented directly. For heavy ions, a selection strategy based on reproducing the LET

spectra was used. This method also was shown to very well predict track structure spectra, based on the track structure parameter, Z^{*2}/β^2.

In addition to those three main sections, Slaba et al. (2015a, 2016) briefly discussed some of the disadvantages of the proposed method, such as the lack of inclusion of neutrons, pions, and associated electromagnetic (EM) cascades. Neutrons are not present in the external GCR spectrum, but are produced copiously when GCR particles undergo nuclear reactions with spacecraft shielding material. These secondary neutrons impinge on astronauts' bodies. If one were using the external field approach to GCR simulation, then external beams would hit aluminum targets with secondary neutrons produced on the other side of the target. The local tissue field approach, which simulates the beams directly hitting tissue, is unable to include the neutron-induced charged particle field because neutron beams are unavailable in conjunction with ion beams of sufficient energy. Pions and electromagnetic cascades (electrons, muons, photons) are also secondary particles that are not present in the local tissue field approach.

Slaba et al. (2015a, 2016) further considered avoidance of Bragg peaks in animal experiments, providing a clear example of how biological constraints can be included in the simulator design process. Specifically, they propose that lower energy (stopping particles) should be represented but hot spots (Bragg peaks) should be avoided. If Bragg peaks are present in different places in animals in different experiments, experimental reproducibility will be difficult, if not impossible. This was later addressed in a revised strategy for hydrogen and helium ions (Slaba et al., 2015a, 2016), which specifically avoided Bragg peaks in experiments with mice. A modified approach would be needed for any larger species. This strategy could be extended to heavy ions, but would greatly increase the burden on the facility for fast ion and energy switching. The idea would be to test all (or maybe partial) implementation of the GCR simulator at NSRL and also answer some of the major radiobiology and logistical questions related to the simulator (assuming they can be clearly identified). It is reasonable to note that avoidance of Bragg peaks in the experimental designs (leading to better reproducibility) produces a difference to the actual situation in space, where GCR particles are always stopping in tissue and target materials. However, because the space environment involves a large variety of nuclei at a large variety of energies, these hot spots gradually coalesce into a spread out Bragg peak, exactly as implemented in the local tissue field approach (Slaba et al., 2015a, 2016). In the local tissue field approach, each beam will later transform into a variety of particles at different energies after interacting with tissue material.

2.4. Study of Kim et al

Recently, Kim et al. (2015) published the results of an extensive simulation using the stochastic transport code, GERM (GCR Event Risk Model), to define a GCR reference field using 9 HZE particle beam–energy combinations, each with a unique absorber thickness to provide fragmentation and 10 or more energies of proton and He beams. Their kinetics model of HZE particle hit probabilities suggests that experimental exposures of several weeks will be needed to avoid high fluence rate artifacts, which places limitations on the experiments that may be feasible.

Nuclear reactions in absorbers or tissue equivalent materials, as well as in tissues of rodents and holders, may also emit neutrons. Kim et al. (2015) make four important points: (1) neutrons may be more important on Mars than in transit; (2) high energy neutrons will not be very effective; (3) the number of neutrons produced in heavy ion fragmentation is about the same as the number of protons, so it should be relatively straightforward to multiply the proton flux by a factor to account for neutron-induced nuclear reactions; (4) neutrons are produced by incident GCR particles – there is not a significant number of free neutrons in space, so there is no need to generate extra neutrons in a GCR simulator which uses the external field approach.

Kim et al. (2015) also provided a detailed discussion of the importance of biological relaxation times in planning fluence-rate and length of exposure. These included the turnover times of different tissue types and the distinct mechanisms for targeted and non-targeted effects in cancer risk. In addition, slowly and rapidly dividing tissues, as well as abscopal effects, could require different optimal chronic exposure times. The authors also conclude that, for CNS risks, changes in cognition and behavior, may be through multiple mechanisms that can culminate in acute and late outcomes, including synaptic changes. They specifically pointed out that “synapse formation, stabilization, and decay have a fast actin-dependent component (less than one day) and a slow plasticity-dependent component (days to years)”. Importantly, the average lifetime of synapses varies not only in different regions of the brain, but also in comparison between mice or rats and humans.

The authors go on to consider practical aspects of setting up experiments that require long-term or split irradiations to take advantage of a GCR simulation facility. They conclude that it is essential to base its use on a solid scientific basis, and suggest several areas of interest, including the possibility that synergistic interactions of particles of different radiation qualities may lead to differences in biological responses for a mixed-field of particles of varying track structure.

3. NASA requirements

This section examines GCR simulation from the NASA perspective, including GCR simulation study requests in recent research calls. In March, 2015, NASA issued an NRA (NASA, 2015a) that set forth the requirements for development of GCR simulation. These requirements are quoted here:

“Study formulations should consider that optimized combinations of particle types and energies may differ across risk areas (e.g., cancer vs. CNS) and across model validation testing.

- How many different particles (including particle types and energies) are sufficient to adequately simulate the biological and health consequences of GCR across risk areas? What is the time scale (dose-rate and duration) and order of delivery of particle types?
- What mixed radiation field, including protons, helium and heavier nuclei, provides the most stringent tests of model predictions?

- Is there an intermediate capability that may provide a similar statistical power for determining the validation of radiation models?

In addressing the above questions, the design and implementation of critical experiments are needed to support the definition of end user capabilities. Topics may include, but are not limited to, the following:

- Studies that implement LET-sensitive experiments that test hypotheses, based on existing experimental data with single ion exposures, about how experimental endpoints may change in response to a mixed field chronic exposure.
- Studies that implement geometry/time-sensitive experiments to scale cell and animal model results to humans at very low doses, supporting the extrapolation of simulator experimental exposure schemes to space relevant particle fluxes.
- Studies to determine whether the effects of different particles, or particles delivered at different times, depend on the order in which they are delivered. Studies should consider the effects of the order of heavier ions (high LET) on cells/animals previously exposed to protons (low LET).
- Studies that implement time-scale-sensitive experiments that consider the different lifetime scale of animals and humans. At low doses, these effects may not be easily separated from the effects of geometry (e.g., number of cells, or fraction of tissue or organ responding to the radiation).”

The need to address issues related to effective simulation of the space radiation environment and knowledge gaps identified in order to provide accurate risk assessment are outlined in the NASA Human Research Program’s strategic research plan (NASA, 2015c). This document covers the four major risk areas of radiation carcinogenesis, acute and late CNS effects, cardiovascular/degenerative tissue effects and acute radiation syndromes due to SPEs. For example, the degenerative tissue (non-cancer or non-CNS) effects such as cardiovascular disease, cataracts, and others including digestive and respiratory diseases, are documented in epidemiology as well as in experimental studies following exposures to terrestrial sources of ionizing radiation (e.g., gamma rays and X-rays) (Little et al., 2012). However, low dose thresholds, dose-rate and radiation quality effects, as well as mechanisms and major risk pathways, are not well-characterized. Likewise, for cancer risk assessment, the effect of protracted exposures simulating the dose-rates found in the space environment on cancer incidence and tumor spectrum is a major open question. GCR simulation studies at NSRL will contribute to the body of evidence required to close these knowledge gaps and provide critical data for accurate modeling of these risks.

4. Single beam experiments

While there is interest in pursuing GCR simulation studies, it should be understood that such a program would never completely replace single beam experiments. Also, single beam experiments will be needed as a reference to the multiple beams used in GCR simulation. A healthy balance of both GCR simulation and single beam studies should be pursued. The original idea behind doing experiments at NSRL was to elucidate cancer and other disease mechanisms. With the multiple beam studies in GCR simulation, it becomes unclear as to

which beam causes a specific outcome. Comparison to single beam experiments is therefore considered to still be very important, and may remain necessary for the understanding of the basic interaction mechanisms between radiation and biological models, from cells to tissues to whole organisms. It is evident that single beam studies are needed as a reference to observe additive or even synergistic effects of simultaneously acting different LET irradiations. They are also useful in deciphering the extent of any mitigating effects that a chronic low LET radiation exposure may exert against damaging biochemical changes induced by a subsequent exposure to high LET radiation. Conversely, it is possible that in some instances a chronic low LET exposure may exert potentiating effects that will alter the effect of a subsequent traversal by a heavy ion. At high doses in charged particle therapy, non-linear additive models are used to predict tumor cell killing in mixed radiation fields generated by projectile fragmentation (Loeffler and Durante, 2013). Exposures of biological systems to energetic heavy ions behind thick shields, such as might realistically exist in spacecraft or in a habitat on a planetary surface, also generally produce data compatible with additive functions, and the beam quality can be represented by the dose-averaged LET (Herr et al., 2015) or associated microdosimetric quantities (ICRP, 2013).

The GCR simulator fills an important gap in NASA's approach to understanding space radiation risk, since NASA wants to establish risk in general, not just for individual ions or protons. In addition, countermeasure testing and biomarker validation in a mixed field will be an important capability in the near future. It is important that validation of countermeasures and biomarkers be performed in a mixed field more closely representing the true space environment. Studies have shown that countermeasures that are efficacious in a gamma or neutron field do not exhibit the same efficacy under similar conditions in a mixed gamma/neutron field suggesting the mechanisms may be quite different for single field exposure compared to a mixed field, particularly when radiation quality is considered (Cary et al., 2012). It is also important to remember that experiments at NSRL are intended to place risk assessment on a solid basis of fundamental science, and are therefore focused on establishing the biological mechanisms underlying the health effects of space radiation. Single beam studies, in addition to GCR simulation, will therefore always be needed. In addition, the selected particle types and energies chosen in the mixed field studies (e.g., 1 GeV protons, 600 MeV/n Fe) should be relatable back to the vast amount of existing radiobiological experimental data collected over the past several decades. Likewise, future single beam experiments should consider using particle types, energies, and exposures consistent with GCR simulator species to enhance interpretation of experimental results.

5. Issues common to both GCR simulation and single beam experiments

Some of the issues raised at the workshops mentioned previously and subsequently discussed by the broader community will now be considered in more detail. Many issues were raised about space radiation experiments in general, as opposed to problems particular to GCR simulation. It is therefore worthwhile to break the further discussion into two main areas. The first discusses issues that apply to all space radiation experiments, including both GCR simulation experiments as well as the current paradigm of single beam experiments discussed in the previous section, and the second discusses issues that apply to implementation of GCR simulation alone.

5.1. Low dose-rate

According to the recent NRA (NASA, 2015a), each cell in an astronaut's body in deep space is traversed by a proton every three days, by a He nucleus every few weeks, and by a heavy ion every few months. NASA states that "these fluence rates correspond to tissue doses or effective dose-rates of about 0.3–0.6 mGy/day and 1–1.8 mSv/day". Dose-rates available at NSRL are up to 15 Gy/min for the 20 × 20 cm^2 beam configuration and about 0.5 Gy/min for the 60 × 60 cm^2 configuration (NASA, 2015a). As an example of lower dose rates available, one investigator regularly uses 0.2 cGy/min for 10–50 cGy total dose. Due to facility and running time constraints, the majority of ground-based radiobiology beam experiments have used much higher dose-rates than those that occur in space. However, as is well documented, biological mechanisms are profoundly different following high versus low and very low doses, at least for sparsely ionizing X- or gamma-rays, and there is no reason to believe that this may not also be true at equivalent dose-rates for sparsely ionizing high energy protons and alpha particles (Hall and Giaccia, 2012). Therefore, low dose-rate experiments, such as extended fractionations, need to be performed. This will, of course, require greater cooperation between experimental teams. For example, the medical facility staff at Brookhaven National Lab could perform animal irradiations at fractionated intervals over a long period of time without requiring the presence of principal investigators on site. A program of extended low dose-rate experiments will require a larger commitment for beam time and NASA fiscal support. Efforts to facilitate tissue sharing across multiple principal investigators and experimental endpoints will greatly enhance the scientific return on investment.

Specifically, three critical issues – feasibility of low dose-rate, availability, and cost of beam time – are important challenges to be solved, particularly since the latter two are critical. The following possibilities should be considered to address these challenges: 1) using a controlled large angle irradiation as a piggy-back experiment; 2) creating multiple, switchable beam output in the same experimental room (in order to "multiplex" irradiation, to decrease costs and increase availability); and 3) creating multiple simple experimental rooms, each using one of the above multiplexed beams. Each of these possibilities are accompanied by additional challenges and costs, emphasizing the importance of identifying more long-term, feasible approaches to practically implementing ground-based GCR simulation. Cancer is a disease that progresses over a long period of time; therefore, one might measure the effect of radiation after the initiating event in order to look at variations in tumor progression. One has to consider progression as well as initiation. The risk for carcinogenesis when oncogenically progressed cells are irradiated is much higher when given acutely. It is unclear whether this is the case at low dose-rate and is likely very specific to the -omic alteration that renders a cell as oncogenically progressed.

Experiments at NSRL are not necessarily designed to input directly into risk models, but rather to study the basic biological pathways of carcinogenesis. These limitations are not isolated to cancer research; the bones, eyes, CNS, cardiovascular, and other systems may incur substantial and short timeframe damage and functional degradation in the compressed timeframe of current lab experiments which may or may not be accurate for space. Data from human exposures for cardiovascular effects note varying results with fractionated

exposures in humans (low-LET) and the inverse dose rate effect seen with high LET ^{252}Cf neutron exposures for lung and mammary carcinogenesis (Ullrich et al., 1977) suggest that effects of dose-rate for high-LET radiation must be considered (Delgado et al., 2014).

5.2. Overlapping tracks

One effect of delivering beams at high dose-rate is that heavy ion tracks can overlap (Curtis, 1994) when passing through cellular material. In contrast, with the actual low dose-rates experienced in space, tracks will not overlap, except with respect to large target volumes and/or long biological relaxation times. Note that overlaps depend on the volume of interest (e.g. DNA versus the full range of delta rays even out to ~cm for 1 GeV/n) and the time of interest, such as physico-chemical times of 10^{-9} sec versus years for some long-term biological effects. Therefore, a possible concern is that GCR simulation won't help to improve NASA risk models. In order for biological experiments to avoid the overlap effect, experiments at low dose-rate would minimize multi-track hits per cell nucleus per exposure, and thus bring these experiments closer to the space radiation environment.

5.3. Dose

The concept of "dose-response" is a fundamental concept in radiobiology, where one wishes to determine a certain type of biological or other response of the system to the amount of dose delivered. Often this is represented graphically with the dose plotted on the horizontal axis and the response plotted on the vertical axis. It is important that a GCR simulator is able to represent the dose experienced in space, so that the response that one observes corresponds to the response that would occur on a particular mission such as a trip to Mars. Recent measurements (Zeitlin et al., 2013) of the space radiation environment in transit to Mars yield a dose equivalent rate of 1.84 ± 0.33 mSv/day using ICRP60 quality factors (0.48 ± 0.08 mGy/day). For a 180-day cruise to Mars, this corresponds to a dose of 86 mGy and 172 mGy for the roundtrip journey. Adding a 500-day Mars surface exposure of about 105 mGy (Hassler et al., 2014; Kerr, 2013) yields a total dose of about 277 mGy, which is roughly 1 Sv for a 3-year Mars mission. The recent NRA (NASA, 2015a) requires experiments with doses below 1 Gy for protons and below 0.5 Gy for heavy ions. While low dose-rate experiments are extraordinarily laborious, the challenge is worthwhile, as replicating dose-rates and total dose consistent with the space environment may be worthwhile to help inform future Mars missions.

5.4. Neutrons

Neutron contributions have been considered a primary issue in all workshops and many discussion sessions. Neutrons are secondary particles produced by space radiation interactions with shielding, tissue and other target materials, and there have been only limited radiobiology studies focused on neutron energies of primary importance to space applications, i.e., in the range 1 MeV to 1 GeV. Current radiobiology studies using charged particle beams lack neutron contributions. (The secondary neutrons produced in laboratory exposure rooms make very small contributions to dose.) However, it needs to be clarified that a significant portion of the neutron-induced charged particle field is explicitly represented in the local field approach; namely, the proton elastic recoil and all other nuclear reaction products with $Z \leq 2$. The lacking component is the higher LET, short-ranged,

charged tissue target fragments with $Z > 2$. A neutron spectrum similar to the neutron environment behind shielding in space can be directly produced by stopping a mixed beam of protons and He in an aluminum (or other) target.

Neutron issues include their biological effects, their relevant fluence and energy, and the availability of sources at other facilities. Most of the neutron data are in the few MeV region, whereas space radiation requires studies at the hundreds of MeV up to GeV. Cyclotrons can produce neutrons in the several hundred MeV range and they might provide a useful tool for a limited number of studies to address outstanding biological questions regarding high energy neutrons. An interesting approach to simulating neutrons is to use a mixed, weighted spectrum of hydrogen and helium ions, as such an approach can simulate the effective dose produced by neutrons to within a few percent. On the other hand, experimental biologists are eager to know the direct biological effects of neutrons before replacing with other sources. Neutron measurements are inherently more difficult than charged particles, with the contribution to the dose being less than 10%. (Kohler et al., 2014).

It would be useful to study the differences in biological response between the external field versus local approach. The lack of a complete neutron-induced charged particle field in the local field approach can be a serious issue for biological responses, considering that historically the relative biological effectiveness (RBE) values for neutrons are much higher (up to 50×). To disregard that effect on the biology may end up skewing the data obtained from GCR simulation. More studies of the biological effects of neutrons as a function of their energies (especially in the energy region of several hundreds of MeV) are also needed.

5.5. End points

The end points to be studied for cell and animal experiments are crucial. Which end points give the most relevant information for determining oncogenesis, cardiovascular disease, cognitive deficits, etc.? One approach to answering this question is to consider the severity of clustered and persistent DNA damage as a marker for biological response. This severity can be correlated to the measured ionization densities created by the charged particles when traversing biological material. Another approach is to consider cell-to-cell communication in the spread of oxidative damage from targeted cells to neighboring bystander cells.

It may be useful if GCR simulation addresses both cell and animal studies and it may be feasible to design some experiments that allow direct comparison of the *in vitro* and *in vivo* (Kronenberg et al., 2009, 2013) systems. In some cases, the less expensive cell culture experiments may mimic what happens in the body. Validation of cell culture systems with *in vivo* models to confirm or refute the reliability of studies with surrogate systems might increase the number of experimental approaches that can be included in the suite of GCR simulation studies. For studies of cancer incidence, staging, and progression, *in vivo* models remain critical.

5.6. CNS effects

CNS effects pose a particular challenge for space radiobiologists. For example, while quality factor estimates exist for cancer, and RBE estimates are available for degenerative tissue effects, such as cataracts and cardiovascular disease, this information is generally absent for

CNS effects. While quality factors have been considered extensively, and dose equivalent was considered a useful guide for choosing beams for other experiments, such information is not available or useful for CNS studies. Another challenge for CNS studies is that the relevant reference field for CNS may well be different from the Slaba et al. (2015a) field using the local tissue field approach. Time issues are also likely important for CNS effects, as cell repair will occur during non-exposure times. If a cell is hit twice with a year interval between hits, and the damage is sufficient, the cell may die/be removed. However, if the cell survives, some types of cellular damage will likely be repaired, while others will persist depending upon particle type and LET. For example, DNA damage caused by a high-LET Fe ion will be more complex and more difficult to repair than that caused by a low-LET proton. Moreover, epigenetic changes in neurons and glia that alter gene expression and function as a result of ion exposure can persist for long periods of time, and could also be dependent upon particle type. Although there may be one hit per cell every few months for heavy ions, there may be one hit every three days for protons. So, repair molecules will be in use continuously that may result in a sparing effect since they are readily mobilized. Conversely, this scenario, might result in an “inverse” dose-rate effect, i.e. more damage than observed at a high dose-rate, because those repair molecules are already in use repairing damage from a light ion and there is only a limited supply. It is also critical to point out that the geometric cross section of neurons including their many processes is quite large compared to their nuclei and it is currently unknown whether the thin processes and synaptic structures themselves function as the relevant targets. Thus, the “hit per cell” estimates may be systematically underestimated. Finally, there may be spatial coupling between cylindrical particle tracks and three dimensional arrangements of neurons comprising microcircuits leading to simultaneous stimulation/damage of multiple “circuit elements” with enhanced consequences.

5.7. Neurocognitive issues

The move towards a multi-ion beam that covers the spectrum of LETs is a significant step towards modeling the effect of GCR on neurocognitive function. While it will never be possible to deliver a GCR simulation beam in a manner that will reflect the protracted exposure in space, the GCR simulation beam will provide a means to develop a risk assessment model for neurocognitive impairment for a multi-ion exposure. Additional studies will need to be conducted to include the neurocognitive decline that will occur as a result of co-incident neutron exposure. However, given the challenges noted above for ground-based neutron exposure, such effects will have to be treated as additional weighting factors, using co-incident neutron and HZE exposure (achieved via aluminum shielding) to determine the exact weighting factor for neutron exposure. The ability to model the intra-cranial dose and LET distribution to which astronauts will be subjected – and in particular the likelihood of hot-spots from attenuated particles – should allow for more realistic rodent dose risk assessment studies. Specific GCR simulation beams can be designed that will reproduce similar dose and LET distributions within rats or mice to that observed in humans.

Regardless of GCR simulation or single ion beam exposure, animal age at the time of exposure is an important issue. In its recent NRA (NASA, 2015a), NASA established that rodents for space radiation experiments should be of astronaut-age equivalent at the time of

space radiation exposure (e.g. 5–7 month old mouse is roughly equivalent to a 35 year old human). This issue is expanded in the next section. Also, given the demonstrated dynamic response of the brain and neurocognitive performance to single ion beam exposures, short and long time points after exposure should be evaluated. Finally, given that neurocognitive testing in rodents falls short of mimicking human cognition and behavioral performance, a battery of tests should be employed to gain a full picture of space radiation influence on brain and behavior. Ideally, such tests would have human testing counterparts, such as psychomotor vigilance.

5.8. Extrapolation to humans

There are many open issues, common to both GCR simulation and single beam experiments, in extrapolating animal studies to humans. These include the time scale and the geometry discussed in the next two paragraphs.

The *time scale* of the model systems used needs to be considered. A 3-yr Mars mission lasts about 5% of a human lifetime, but exceeds a mouse lifetime. Scaling the exposure to occur over 5% of a mouse lifetime leads to a dose-rate that is about 20–25 times that experienced by a human on the way to Mars. However, although the biology of aging of the mouse will need to be scaled across its lifetime, the chemistry in the mouse signaling pathways may or may not be the same as in a human, and the reaction rates, at least for initial events, also may be similar to that in humans, leading to an additional modifier to the dose-rate effects. Tissue turnover rates may not scale with lifespan, introducing additional confounding variables. Furthermore, care should be taken in age selection of experimental animals to account for the impact of biochemical or physiological changes at different life stages (e.g. puberty, senescence) on the outcome of radiation effects.

The *geometry* of a mouse irradiation is also affected by the time scale:

- Dose-rate effects that may be caused by interactions between particle signals are not likely to be equally probable in humans and mice.
- The fraction of tissues and organs affected by irradiation at a given fluence will be different in a mouse and a human; the number of cells in 10% of a human brain is equivalent to a much larger percentage of the cells in a mouse brain. To allow as much extrapolation as possible across species, studies should be based on organ doses to be expected in humans, as available from MATROSHKA studies on the ISS (Berger et al., 2013; Reitz et al., 2009). This will help account for the different shielding effect of the tissue surrounding the organs in humans and experimental animals, such as rodents.
- In order to properly interpret the results of experiments intended to simulate space travel, the number of cells responding to the incident particles (i.e., traversed by a track or its delta rays, or receiving chemical signals from other affected cells and tissues) needs to be known or estimated in order to properly scale the experiment.
- At low fluences, the cells responding to an initial incident track are not likely to be the same cells that respond to subsequent tracks, and therefore split low doses

or fractionated low doses are not likely to be an accurate measure of dose-rate effects.

Cancer induction by heavy ions in laboratory animals reveals a relative pattern and can help to understand the mechanisms and the general mode of action. However, absolute extrapolation concerning dose-effect relationships, latency of cancer appearance, time effects and maybe even LET-effect relationships are difficult. Epidemiological studies as proposed for other carcinogens to achieve a more rational risk assessment (Goldsmith et al., 1995) are limited by the very small astronaut population size. Furthermore, the judgment of cancer induction that differs between different animal species with respect to human cancer risk is an unanswered issue. For drugs or chemicals, the distribution in the body and the metabolism (e.g. in the liver) may play a significant role in interspecies differences of cancer induction (Lock and Smith, 2003). For radiation exposure, interspecies differences in the cellular radiation response and in the radiosensitivity of different organs might exist. Studies of both mouse and human cells, especially when performed in environments that mimic the *in vivo* situation (e.g., oxygen tension, co-culture with other cells typically present in the same microenvironment), may better enable extrapolation from mice to humans. A comparison of rodent and human cellular responses to GCR simulation might support extrapolation of rodent data to humans. This could be achieved through the previously suggested increase in investigator collaboration. Studies with stem cells from tissues as targets for malignant transformation (Trosko et al., 2005) could also help to understand heavy ion induced carcinogenesis.

While rodents have their drawbacks in regards to cancer, they continue to prove an excellent model to study the CNS effects of space radiation, particularly for whole body exposure in the awake and behaving animal. Neurocognitive studies in rodents also provide excellent translational applicability to humans, particularly as many tests in rodents mimic those in humans. Furthermore, given the neuroanatomical, physiological, and biochemical similarities between the rodent and human brain, extrapolations from *in vivo* exposure in rodents has great potential to be extrapolated to humans.

5.9. Beam delivery geometry

GCR incidence in space is isotropic, whereas beam irradiations are axial, thus the geometric distribution of detected radiation events in space may be different from that in a beam. Also, a straight-ahead approximation is not perfectly accurate and one needs to take into account that nuclear reaction products scatter into a relatively large solid angle, thus affecting the distribution of overlapping tracks. Therefore, while GCR simulation studies are worth pursuing, additional 3-dimensional calculations are needed to optimize beam composition.

6. Issues unique to GCR simulation

The issues unique to GCR simulation can be further divided into two groups, namely those issues that arise with the external field approach, versus issues that arise only with the local tissue field approach.

6.1. Multiplicity effects

When a GCR or heavy ion beam strikes an atomic nucleus in a target material, several light particles – including protons or neutrons – can be emitted at the same time (Demoulins et al., 1990; Bastid et al., 1990). These fragments can originate both from projectiles – GCR ions – and targets, which in turn might be the nuclei of the shielding material and/or those of the biological material itself. The number of particles of each kind is called the *multiplicity* of that particle for that reaction.

When the emission of multiple particles (not just protons, but alphas and carbons and others, depending on the mass of the incident projectile) occurs inside a cell (either by a projectile fragmenting on some of the atomic nuclei in the cell, or by multiple pieces coming off an atomic nucleus in the cell that has served as the target of a nuclear reaction), then the simultaneous energy deposition by multiple particles will have a different effect than the same energy deposition occurring over a longer period of time, during which the cell chemistry would have had a chance to return to its equilibrium state. The multiple pieces of a projectile will come out in a narrow angle, and will traverse a large number of neighboring cells at the same time, so that any effects will be correlated. Finally, to the extent that any dose rate effects depend on overlap of tracks, the probability that fragment tracks overlap will be different for fluence randomized over the entire target tissue volume, on the one hand, and for the overlapping of spatially correlated tracks on the other. It is not clear how large such effects may be, but in the stopping region of an incident beam and beyond, the radiation field consists almost entirely of projectile fragments (Schimmerling et al., 1989), most of which will be correlated products of heavy ion reactions.

Multiplicity effects are not included explicitly in current modeling calculations, which are based on the use of inclusive cross sections (this accounts for the correct number of particles, but not for any correlations between them). However, the contribution of multiple correlated particles will distort estimates of dose rate (or flux). Multiplicity effects may also influence radiobiological consequences of energy deposition in correlated numbers of cells. The contribution of multiplicity effects would likely seem to be minor, but the magnitude of such effects needs to be estimated with theoretical calculations and Monte-Carlo simulations; if such calculations predict any significant effects, appropriate experiments to test such estimates need to be designed.

6.2. Biological mechanisms

There may exist fundamental differences between the biological mechanisms observed in single beam experiments compared to mixed field experiments of a GCR simulator. As discussed above, synergistic effects may occur, such as a sparing effect due to previously active repair mechanisms, or an inverse dose-rate effect due to resource scarcity from the constant DNA damage and repair cycle, or other physiological changes including transmission of key signaling molecules (or lack thereof), may be especially important for non-cancer effects. A mixed field approach may allow for the validation of existing radiobiological models developed from beam experiments applied to a mixed field environment.

Studies using both single beams and mixed fields would be beneficial, and the body of literature on single beam studies will be useful in interpreting GCR simulation experiments. However, physiological effects in an integrated host environment are more complex and challenging to study, yet are critical to risk estimation. While the issue of biological mechanism applies to both the local tissue field method and the external field method of GCR simulation, there remains the question of difference in biological mechanisms when neglecting high LET tissue target fragments with $Z > 2$ produced from neutrons or lack of multiplicity in the local field approach compared to the mixed field approach.

If exposures from a GCR simulation are delivered over extended periods of time, another biological phenomenon will need to be considered in the interpretation of the resulting data, namely effects on the cell cycle. It has been established that exposure to both low and high LET radiation can induce cell cycle delay or arrest in some normal cell types (Fournier and Taucher-Scholz, 2004; Pouget and Mather, 2001). For actively dividing cell types with different radio-sensitivity whose cell cycle profiles are altered by radiation exposure to different extents, newly emerging cells over the course of the irradiations will not receive the same number of “hits” over time as others in the population. In contrast, for post-mitotic cells like neurons, multiple doses of ions would be delivered to the same number of cells over time. Because astronauts traveling in space have cell types that would respond in differing manners, both of these phenomena are important. Therefore, comparison of single beams versus mixed fields will be advantageous when interpreting GCR simulation results in terms of cell cycle effects, as well as for cancer mechanisms.

6.3. DNA repair considerations

The complex DNA lesions created after exposure to GCR require various DNA repair processes, and the interplay between the processes remains unknown. This is particularly true for low dose-rate exposures. Likely damage caused by a single GCR particle track includes DNA double- and single-strand breaks, DNA base damage at apyrimidinic/apurinic sites, and DNA-protein crosslinks (Ciccia and Elledge, 2010; Iyama and Wilson, 2013; Asaithamby et al., 2011). Other mutagenic processes will include replication and transcription fork stalling and the emergence of highly persistent RNA:DNA:RNA hybrids (R-loops) (Aguilera and García-Muse, 2012). Repair of these multiple-damaged sites will require simultaneous functioning DNA repair systems, including DNA nucleotide excision repair, base excision repair, single-strand annealing, homologous recombination (HR), non-homologous end joining (NHEJ), alternative-NHEJ, and newly identified RNA transcription termination factors (RTTFs), including RPRD1B (Kub5/Hera), RPRD1A (p15RS), PSF, XRN2, and SETX (Aguilera and García-Muse, 2012; Helmrich et al., 2013; Morales et al., 2014; Richard et al., 2013). Currently, facility constraints limit our knowledge of: (i) the exact nature of the complex DNA damage created by GCRs; (ii) how such complex lesions are repaired; and most importantly, (iii) what role GCRs play in carcinogenic risk, particularly in gender-specific manners (Morales et al., 2015). Availability of a user-friendly facility for access to GCR exposure is warranted for increased fundamental understanding of DNA damage and repair. In terms of studies using GCR simulation versus single ion beams, the best procedure would be a comparison between the two. This would allow comparison and contrast between the different damages created. For DNA that has undergone repair,

cells can be used that have defects (and then corrections) in any of the repair pathways mentioned above.

6.4. Ordering of beams

Evidence exists (Durand and Olive, 1976; Ngo et al., 1981; McNally et al., 1984; Zhou et al., 2006) that the order in which different beams are delivered may produce different biological outcomes. For example, if one delivers a beam of protons followed by a Si beam, then the biological effect might be different than for a Si beam delivered first, followed by a beam of protons. There are two broad outcomes from multi-beam exposures. Either the beams act independently, which results in an additive effect or the beams interact, which results in an effect that is synergistic. Evidence for both of these outcomes is observed. Synergism is demonstrated with a variety of beam combinations (Durand and Olive, 1976; Ngo et al., 1981; McNally et al., 1984; Yusuke et al., 2004; Zhou et al., 2006). The favored hypotheses is that high-LET radiation damage inhibits or interferes with some aspect of the low-LET repair. Low-LET damage is not repaired as efficiently when combined with higher-LET radiation compared with low-LET radiation alone. Hence, it is not the initial damage which induces differential outcomes but the damage repair response. However, synergy has been shown to depend on the beam order in some cases (Durand and Olive, 1976; Ngo et al., 1981; Zhou et al., 2006), but not in others (McNally et al., 1984). Ngo et al. observe that these differential effects only occur at doses greater than about 8 Gy of neon or X-rays, while Zhou et al. find differences at 40 cGy of iron or titanium combined with protons. Differences in dose-rates (Suzuki, 1993) or interval times as well as radiation or cell type may account for these discrepancies.

Conversely, additivity can be observed with a variety of beam combinations regardless of beam order (Barendsen and Beusker, 1960; Higgins et al., 1983, 1984; Demizu et al., 2004). Interestingly, Higgins et al. demonstrated that it was simultaneous exposure to both photons and neutrons which showed synergistic effects on cell survival, whereas no such effect was observed when beams were delivered sequentially in either order (Higgins et al., 1983). Similar additivity for simultaneous exposures is seen when photons are combined with argon or silicon (Furusawa et al., 2002).

The time interval between exposures is also an important factor to consider when assessing the effects of mixed radiation fields especially in the context of space radiation where dose-rates for individual ions are very low. There appears to be a window in which beam order dependent effects occur and after which the effects are similar to those calculated from simple additivity of the individual beam effects. (Ngo et al., 1981; McNally et al., 1984; Sutherland et al., 2005; Zhou et al., 2006; Hada et al., 2007). Thus, the risk of a synergistic effect may be substantially lower in a realistic space radiation environment and any radiation scheme which simulates the GCR spectrum should attempt to mimic similar numbers of events which coincide within the window of opportunity for these effects.

If beam order affects biological outcomes, then this phenomenon will not be present in space and one might take steps to avoid it in GCR simulation. A pseudo-random (but repeatable) beam order delivery has been suggested, however, this may not be suitable. In order to obtain a generalization (i.e. probability of some biological outcome or risk), one would have

to repeat the identical experiment many times, with no other changes. This method is not practical or a good use of resources, especially for animals. Comparison of different biological parameters, or with other experiments, end-points, etc. could only be made with many repetitions of each set of conditions. If beam order affects outcomes, this can best be discovered with defined sequences and will be useful information for future aims of low dose-rate experiments. If the order does not matter, there is of course no need for randomization.

7. Applications

One of the aims of the present paper is to list a variety of applications of GCR simulation that may lead to future studies or would benefit from GCR simulation data. Some of these broader applications are now discussed.

7.1. Implementation of a pilot GCR simulation campaign

Initiating a research program devoted to GCR simulation at NSRL is a complicated process. A suggestion is to invite several biologists to submit a realistic research hypothesis. The objective is not to evaluate the merits of each proposed study, but to assume that each has been approved. Each researcher would prepare a submission to NSRL documenting the geometry of the specimen, dose points, and number of specimens or replicates, etc. The NSRL staff would present a menu of ions and energies that represent the GCR reference field, and then assemble a protocol for executing the experiment taking into account the time to physically set up the experiment in the cave, time to switch ions, time to tune energies and duration of exposure for each beam. This would be repeated for each required replicate. The idea is to get a sense of the demands on time and effort and ultimately the cost of establishing a meaningful GCR campaign. An example might be to perform one experimental campaign for carcinogenesis using mice, one study for cardiovascular effects, one study for neurological effects and one study for *in vitro* endpoints of interest. These should be condensed proposals that only emphasize the hypothesis to be tested and irradiation protocols required to test that hypothesis. Emphasis would also be placed on tissue sharing to ensure that the most information is gained from each specimen or animal. This would be an iterative procedure that might require modifications to experiments and compromises for the GCR reference field before hardware and software become finalized at NSRL. Such an approach could also provide guidelines for optimization of experimental design as well as help determine appropriate ions and energies for the GCR reference field.

Rather than immediately implementing the full set of GCR simulation beams and energies, one might start with H, He, O, and Ar. All of these ions share a similar production method at NSRL, which might simplify the ion source configuration. ^{4}He and ^{16}O have essentially the same charge to mass (Q/M) ratio, and it might be possible to produce a mixture of these four ions for simultaneous acceleration and extraction in NSRL. H and He must be included, and the intermediate Z and high Z ions could be selected for other operational reasons.

Another possible consideration that could limit the complexity of the GCR simulator is the question of to what extent experiments can survive a major interruption of a challenging simulation protocol that might take hours or days to fix, such as unanticipated and

unavoidable beam downtime. While this could happen (and has happened) during a single ion campaign at NSRL, the probability of such an occurrence would increase with the complexity of the GCR simulation.

A possible mitigation strategy for the complexity issue would be to initially limit the number of different beams used in the GCR simulator. Concentrating on a limited number of beams and energies would allow the physics and radiobiology to be carefully understood. One advantage of the local field approach in this regard is that it allows for systematic and quantifiable tuning of the simulator complexity while still maintaining a direct connection to the reference field fluence. For the external field approach, it will be important to understand in detail how the radiation field will change after shielding with the most common shielding materials, e.g., Al, polyethylene. For both versions of the GCR simulator, more data are needed for light ion beams, i.e., protons and He. To benchmark and improve the particle and ion transport codes, there is a need to measure differential and double differential cross sections, along with multiplicities. A detailed study using a few beams might also enable more detailed and consistent tests of biological and risk models. Since dose and dose equivalent are not the best risk coefficients, one needs to know the ionization densities created by the charged particles in tissue equivalent materials, and so micro-/nano-dosimetric measurements are needed using tissue equivalent proportional counters (TEPC) or compact track structure imaging detectors (Casiraghi et al., 2015).

7.2. GCR simulation using the external field approach

Due to energy limitations at NSRL, much of the present paper has discussed GCR simulation using the local tissue field approach (Slaba et al., 2015a, 2016) instead of the external field approach. However, as previously mentioned, the external field approach may be suitable at higher energy machines such as FAIR (Durante et al., 2007). The present subsection discusses some possible applications of the external field approach.

Using multiple beams designed to simulate the GCR environment in space will provide benchmark data on secondary particle fluences behind shielding materials of varying thicknesses and composition. One example of a possible measurement would be to measure both the fluence and contribution to the total dose and equivalent dose from secondary neutrons. Because of the limitations of neutron instrumentation used in space, space-based measurements of the fluence and dose from neutrons only cover a small range of neutron energies, and as a result the estimates of the total dose from neutrons carry a large degree of uncertainty. Accelerator-based measurements of neutrons can cover a much wider range of neutron energies with a much higher degree of fidelity than can be done in space. With a simulated GCR beam, the production of neutrons and other secondary particles can be sampled simultaneously over a wide range of particle species and energies. When the measurements are conducted under highly controlled and well-defined conditions, as in an accelerator environment, these data can then be used as benchmarks in shielding calculations.

Exposure of materials and electronics to a simulated GCR beam will test the effects of damage due to multiple hits that cannot be performed using a single ion and single ion energy. For example, effects from multiple hits in a material or electronic circuit could be

different depending on whether the multiple hits were due to two protons striking the target area, or a proton and a heavy ion striking the target area. Experiments investigating multiple hits from different ion species would be possible with a GCR simulator. Experiments conducted on shielding materials and electronics are less susceptible to dose-rate effects than biological experiments. Thus, GCR simulator experiments that expose materials to the total dose or fluence expected in a mission should lead to results very close to the same exposures protracted over a longer period of time.

7.3. Biophysical modeling

The GCR simulator will provide data to improve, test, and verify theoretical radiation action and transport models, especially for the track structure and radiation damage modeling community. There are several aspects to consider: theoretical studies should favor a single beam experiment, as it is a pure beam and easier to simulate and to interpret. However, the external field approach introduces radiation contamination to the experimental setup, which is difficult to match in simulations. Local field mixed beams are better characterized for simulation and interpretation, as the contamination is better known. This includes the above-mentioned discussion about multiplicities. Furthermore, experiments with a biological endpoint may profit from mixed beam (multiple ions at multiple energies) experiments, as outcomes may be clearer to see and to evaluate as for single beam and energy experiments. This will help refine models and outcome predictions. Another intriguing topic is the possibility to use the GCR simulator as a neutron source. While neutron contribution to the physical dose is mostly understood, their contribution to biological endpoints is still to be examined. Again, experimental data will provide valuable input for the modeling community.

7.4. Simulation of experiments on the International Space Station

The preceding discussion has centered on issues and comparisons between single beam experiments versus GCR simulation experiments conducted at ground-based accelerators. However, space-based radiobiology experiments could benefit significantly from comparisons to ground-based measurements which simulate space conditions. This is possibly an ideal application of GCR simulation. Several radiobiological experiments have been aboard the ISS for some time (Yoshida et al., 2010) and GCR simulation experiments would give valuable information to compare to ISS experiments. However, the best comparisons would need to use the dose and dose-rate found in the ISS, which brings back the issues discussed in previous sections.

8. Current plans for GCR simulator implementation at NSRL

The discussion so far has broadly addressed a range of issues and uses of a GCR simulator, including applications and ideas for implementation. The present section focuses on the actual construction timetable at NSRL, which is of interest to those actually planning to conduct GCR simulation experiments in the near future. Developments are currently underway to provide a GCR simulation beam at NSRL. The GCR Simulator Project at NSRL will generate an accelerator-based spectrum of ions and energies that closely approximate those that are known to make up the shielded GCR environment in space.

These upgrades will enhance the ability to simulate the primary and secondary environment with a mixed field, high-energy capability planned for completion in late 2016. The energy of the final beam line will be upgraded to deliver beams at 1.5 GeV/n, to better represent the energies in the natural GCR. Reference fields will be defined to include the rapid switching of ions such as, protons, He, O, Si and Fe over multiple energies with the possible usage of well-designed absorbers. This will allow GCR species to be simulated with high precision in major energy (or LET) bins. Energy is expected to range from 50–1500 MeV/n with LET ranging between 0.25–1000 keV/μm. To simulate organ exposures within a shielded spacecraft geometry, emphasis will be placed on delivering the majority of the dose from protons (50–60%) and alpha particles (10–20%) with heavier ions (Z >3) and secondary particles contributing the remainder of the total dose. Validation studies are needed to determine the number of different particles (including particle types and energies) that are sufficient to adequately simulate the biological and health consequences of GCR across major risk areas. An intermediate field capability will be developed to validate final beam selection, including number of species and energies, as well as operational parameters. More detailed descriptions of the field characteristics will be made available on the NSRL website as the upgrades progress.

The plan for implementing GCR simulation at NSRL is to spend 2016 refining the control tools, integrating the various components of the system to deliver a uniform beam of any one of a list of many ions, including protons. The intent is to do so rapidly, reliably and without intervention from machine experts and operators, a feat which will no doubt take more than one iteration. In late 2015 and early 2016, the high energy capability will be tested. The needed upgrades for this were successfully installed during the 2015 summer shutdown. The full GCR capability is expected to be offered in 2017, in both normal and large beam configuration.

The rapid energy changing has been developed at NSRL about eight years ago, and has been undergoing refinements from year to year. It is used routinely for energy changing, taking on the order of 2 minutes to complete in most cases. It is achieved either by scaling the various beam component settings from those used for the current energy to those required for the next, or by restoring archived values, if the desired energy has been already prepared in the past. The advancements which lead to this capability were mostly in the magnet current management software. As for rapid ion changing, it has been under development for the past three years, and required both hardware and software advances. The ion source for the booster is a combination of a Laser Ion Source (LIS) capable of producing a singly charged ion beam from any solid target, a pair of hollow cathode sources, used to do mostly the same with gases, all feeding an Electron Beam Ion Source (EBIS). The EBIS traps the ions and subjects them to bombardment by an intense electron stream which strips them of their own electrons. The time in the trap determines the stripping level. From the EBIS the beam is accelerated through two small LINACs into the booster where it is injected, captured, accelerated and extracted into the NSRL beam line. All the elements mentioned here must be changed in one way or another to affect an ion change. Software tools have been developed that enable this change of settings to take place in an instant. The actual change-over takes between one and two minutes, as certain operations must take place in sequence,

and some active components take time to change setting. Both ion and energy changes are proving to be reliable and repeatable.

This leaves the question of beam quality at the target room. Rapid changes will be of limited use if the beam in the target room requires reshaping every time ions or energies are changed. Some hardware is being added to the extraction magnet, namely a variable-thickness foil-changer, which ensures good control over the spatial distribution of the beam entering the extraction magnet. This, in turn, gives good control over the beam shape in the target room, which is a major factor in the quality of the dose measurement by the ion chamber just upstream from the target stand. When installation is complete, it is expected that both ion and energy changes will be made without affecting the beam shape, and hence calibration, by more than 2–3%, so that these switches should take 1–2 minutes each.

9. Summary and conclusions

A mixed field GCR simulator is an important step toward an understanding of the risks due to space radiation. It is recognized that the GCR simulator will not replace single ion beam investigations, but will serve as a complementary investigation with important implications for the understanding of space radiation risk. The local tissue field approach and the external field approach to the GCR simulator were introduced. Differences and issues, both distinct to each approach to GCR simulation and common to them both, were discussed. A set of conclusions can now be presented.

- In addition to simulating mixed fields, the developments under way to support the GCR simulation beam at BNL are likely to lead to valuable improvements in NSRL usefulness:
  - Fast switching has already been shown to improve throughput of experiments.
  - Generating proton beams independently of the tandem and linear accelerator setup is likely to result in significant operational savings and additional flexibility.
  - Increasing the NSRL ability to handle 1.5 GeV/n Fe will allow more alternatives to obtain mixed fields as well as higher energies for testing and validation of shielding concepts.
  - A second beam line, including modification of the switching magnet so that beams could be switched between beam lines from pulse to pulse would add an important capability, useful for all experiments, with significant cost/benefit improvements.
- GCR simulation studies are worth continuing, but require 3-dimensional calculations to optimize beam composition.
- The local tissue field approach, instead of the external field approach, is most appropriate for NSRL because, due to energy limitations, the external field approach captures only 60% of the effective dose contribution, compared to 90%

for the local tissue field approach for the upgraded NSRL (Slaba et al., 2015a, 2016).

- Hybrid approaches that combine the external field and local tissue field approaches should be pursued to arrive at an optimal beam delivery system that more broadly covers the range of particles, energies, and other factors than either approach independently.
- The effects of neutrons are important and need further study both theoretically and experimentally.
- Experiments at low dose-rate are needed in order to understand the geometry and time scales involved in low fluence exposures.
- Experimental approaches need to be developed to allow identification and counting of cellular targets affected by particle tracks.
- Beam delivery order may be important.
- GCR simulation studies cannot replace single beam experimental programs. Continued single beam experiments are an important approach to understand the biological mechanisms involved in radiation risk and need to be pursued. GCR simulation studies offer an important approach to test and validate mechanistic predictions, as well as provide a possibility of generating new hypotheses.
- Validation studies will be important to determine the number of different particles (including particle types and energies) that are sufficient to adequately simulate the biological and health consequences of GCR across the major risk areas of carcinogenesis, in-flight and late central nervous system effects, as well as cardiovascular and other degenerative tissue diseases from exposure to space radiation.
- Countermeasure testing and validation in a mixed field (high and low LET particles) environment will be a high priority of the GCR simulator.
- The opinions of this paper should be condensed into specified acceptance criteria for a GCR simulator that need to be satisfied by both the prescribed menu of beams and ability of NSRL to implement the protocol.
- A full GCR simulation capability is expected to be available at NSRL in 2017.
- The selected particle types and energies chosen in the mixed field studies should be relatable back to the vast amount of existing radiobiological experimental data collected over the past several decades.

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