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document title/ *titre du document*

SIMULATION OF INTERACTIONS OF RADIATION WITH BIOLOGICAL SYSTEMS AT THE CELLULAR AND DNA LEVEL

STATEMENT OF WORK

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reference/*réference* EMA/99-144/PN
issue/*édition* 1
revision/*révision* 1
date of issue/*date d'édition* 9 December 1999
status/*état* N/A
Document type/*type de document*

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CHANGE LOG

reason for change */raison du changement*	issue/*issue*	revision/*revision*	date/*date*
	1	1	9 December 1999

CHANGE RECORD

ISSUE: 1 REVISION: 1

reason for change/*raison du changement*	page(s)/*page(s)*	paragraph(s)/*paragraph(s)*

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1 INTRODUCTION

DNA is the unique "assembly instruction code" for all life on Earth. One of the several causes for DNA mutations, eventually leading e.g. to human cancer, is cellular radiation damage. Practically all forms of life are unavoidably exposed to a certain degree of radiation. On Earth, the radiation environment consists of cosmic rays and their secondary particles, of primordial radiation background from heavy elements in the Earth's crust, and of the additional man-made radiation sources. In space, one is additionally unprotected by the atmosphere and faced with the biologically adverse environments of trapped particles, solar particle events and galactic heavy ions.

Traditionally, the biological effects of radiation are analysed in the top-bottom order, i.e. evaluation of the absorbed macroscopic radiation "dose" at a given location in the biological tissue is translated to the degree of danger it presents, and dose limits are consequently set that are considered to be acceptable. The present activity proceeds in a reverse order, from bottom to top, by analysing the nano-scale effects of energetic particles at the cellular and DNA molecule level by using a particle transport simulation code. The new-generation object-oriented GEANT4 Monte Carlo software toolkit [Ref. 1], the work of more than 100 scientists in over 40 institutes world-wide, is chosen as the platform for this study.

2 OBJECTIVE

There is currently significant U.S. activity in the field of DNA radiation damage simulation and tests, both for space and other applications, e.g. at Lawrence Berkeley National Laboratory [Ref. 2], at the NASA-sponsored National Space Biomedical Research Institute [Ref. 3], and in other groups. It is the intention of this work to establish a strong European presence in the field based on the existing collaboration framework between ESA and CERN, one part of which is the GEANT4-based Shielding Tools TRP activity with DERA and the University of Southampton [Ref. 4, 5]. Programmatically, the objective is therefore to form a world-class network of European experts covering the various aspects of the problem. Collaboration of professionals working in particle, space and cosmic ray physics, in medical and biological fields, and in radiation dosimetry shall be established.

The technical aim of the study is to establish a rigorous programme focusing on the simulation requirements for the interaction between the DNA molecule and the particles traversing the cellular structures in its vicinity. The problem entails physical, chemical and biological aspects alike, and is a difficult one. Processes taking place both outside and within the target molecule shall be considered, not forgetting the additional complexity brought by the variety of damage types, and by the cellular DNA repair mechanisms. Human, animal, and plant DNAs shall be considered. The different radiation environments on Earth, in the oceans, in the atmosphere, and in space shall also be taken into account. The technical outcome of the work shall be a set of User Requirements for the GEANT4-based DNA analysis tool. Validation programme, using experimental DNA testing and /or existing databases, or interfacing to macromolecular Monte Carlo codes, is also to be proposed.

3 BRIEF DESCRIPTION

The study is divided into the following three Work Packages. The suggested share of each WP of the overall study effort is given in parentheses. These percentages are, however, for indication only, and the Contractor may propose a different division of effort.

WP 1) Systematic study of the problem area, including terrestrial and space radiation environments, cellular and DNA radiation damage types, cellular repair mechanisms, free radicals and other chemical or biological factors (including shielding), and relevant Geant4 capabilities. In the course of this the collaboration structure shall be outlined, and the various European experts identified (~20%).

WP 2) Detailed interviews and collaboration with the various experts focusing on the user requirements for the Geant4-based cellular and DNA radiation damage simulation tool. A rigorous and thorough set of such requirements shall be produced, also indicating possible areas where knowledge on the cellular functions, or on other biological or physics aspects, is currently insufficient (~70%).

WP 3) Proposal for a combined simulation and experimental validation programme, and investigation of applicability of the work to wider European medical, biological, space and Geant4 communities (~10%).

These Work Packages are discussed in more detail in Sections 5-7.

4 CONSTRAINTS

Inclusion of any institutes or experts in the collaboration network shall be subject to the prior approval of the programme co-ordinators:

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5 WORK PACKAGE 1: SYSTEMATIC STUDY OF THE PROBLEM AREA

The Contractor shall perform a thorough study of the various fields relevant for the work. This shall culminate in a detailed review of the physical, chemical and biological aspects to be taken into account in the tool. The network of European expertise shall be formed at this stage. Work Package 1 is composed as follows.

A) Assessment of radiation environments on Earth and in Space

- Cosmic rays and their secondary particles on Earth (at sea level and in air space)
- Primordial radiation sources on Earth
- Man-made radiation sources on Earth

- Cosmic rays in space, with particular focus on heavy ions
- Trapped particles in the magnetosphere
- Solar protons and ions
- Other relevant radiation sources in space

B) Biological aspects; radiation-induced cellular and DNA damage

- Types of DNA damage (e.g. single-strand vs. double-strand)
- The effectiveness of heavy ions vs. singly charged particles
- The role and efficiency of cellular DNA repair mechanisms
- Radiation vs. free radicals and other sources of DNA damage
- The influence of other surrounding cellular structures, both on Earth and in microgravity
- Relative importance, where known, of the various genes in the DNA from mutation point of view (e.g. the gene *p*-53 that controls the programmed cell death is a long and delicate molecule, and as such prone to radiation damage).
- Other relevant biological factors

Based on this Work Package and on input from the experts, the Contractor may propose an extension of the collaboration network. The deliverable from the WP 1 is a Work Package Report in Word 7 and pdf formats, resulting from the documentation and input provided by the collaborating experts. Following acceptance of WP 1 by the programme co-ordinators, the Contractor can proceed to WP 2.

6 WORK PACKAGE 2: COLLECTION OF USER REQUIREMENTS

User requirements for the Geant4-based cellular and DNA radiation damage simulation tool shall be gathered in this Work Package. This shall be based on detailed interviews and collaboration with the various experts identified in the course of WP 1. The user requirements provided by the experts shall be assembled into a User Requirements Document (URD). The URD shall comply with the ESA PPS-05 standard for small software projects [6].

Work Package 2 is composed as follows.

A) Physics and processes requirements

- Heavy ion interactions with molecular structures
- Low-energy electromagnetic interactions
- Low-energy hadronic interactions
- Step size and energy loss requirements; secondary particle production
- Other physics and processes required in biological targets in general, and in the vicinity of cells and DNA molecules in particular
- Consideration of biological processes (such as DNA repair mechanisms, apoptosis) vs. physical processes

B) Geometry requirements

- Implementation of the structure of the DNA
- Implementation of the composition of the DNA
- Other cellular structures
- Shielding provided by the biological tissue

C) Visualisation requirements

- DNA and cellular structures visualisation; particle tracks
- Visualisation of biological and chemical processes; visualisation of DNA ruptures
- Scaling and zooming

D) General simulation and data analysis requirements

- Hierarchy and scalability of the simulation
- Combination of DNA and cellular simulation results ultimately to macroscopic biological predictions
- Run-time requirements

E) Identification of areas where biological information, data or theories are currently missing.

F) Identification of areas where new physics data or models are required.

Based on input and documentation provided by the collaboration experts, the deliverables from the WP2 are a User Requirements Document and a Work Package Report, delivered in Word 7 and pdf formats. Following acceptance of WP 2 by the programme co-ordinators, the Contractor can proceed to WP 3.

7 WORK PACKAGE 3: PROPOSAL FOR VALIDATION PROGRAMME AND INVESTIGATION OF WIDER APPLICATIONS

The Contractor shall propose a validation programme of the eventual cellular and DNA radiation damage simulation tool together with a proposal for verification by experimental measurements, biological data or theories. Possible use of the tool, or its derivatives, shall be outlined based on evaluations in wider medical, pharmaceutical and radiation protection areas. A preliminary proposal for the continuation of the present work shall also be outlined.

Work Package 3 is composed as follows.

A) Validation and verification programme:

- Proposal for test case simulation scheme for validation purposes
- Based on WP1, collection of references on experimental DNA radiation damage data
- Comparison to biological theories on the cellular processes
- Proposal for DNA and cellular (and possibly pure physics) experiments where data is missing

B) Pre-assessment of possibilities in wider medical etc. fields and proposal for continuation of work

- Interviews
- Preliminary analysis of wider applications
- Proposal for continuation

Based on input and documentation from the collaboration experts, the deliverable from the WP 3 is a Work Package Report in Word 7 and pdf formats.

8 MANAGEMENT AND SCHEDULE

The time scale foreseen for this study is 12 months with start in the first quarter of 2000. The ESA Standard Requirements for Management, Reporting, Meetings and Deliverables (Appendix 2 to the contract) shall apply to the present activity with the following modifications, which shall prevail. For convenience, the paragraph numbering given here below follows that of Appendix 2:

- Section 3 on Meetings (an electronic version of the final presentation shall be delivered to the Agency in PowerPoint format),
- Section 4.1.2 is not applicable,
- It is sufficient to deliver the Final Report referred to in Section 4.1.1 in electronic (Word 7 and HTML) formats only.

The contractor shall further deliver, in Word 7 and HTML formats, an article suitable for publication in the Agency's "Preparing for the Future" brochure, of approximately 1000 words length.

The following is an outline of the Work Programme. The Contractor may propose different timeframes for the individual Milestones.

Milestone 1, Systematic study of the problem area, formation of the expert network

Start Event: Kick-off
End Event: WP 1 Report, KO + 2 months

Milestone 2, Collection of user requirements

Start Event: WP 1 Report
End Event: WP 2 Report, KO + 9 months

Milestone 3, Proposal for simulation and experimental validation programme; study of wider applications; proposal for continuation

Start Event: WP 2 Report
End Event: WP 3 Report and Final Report, KO + 12 months

9 LIST OF COLLABORATORS

The following is a list of Collaborators that have agreed to provide their expertise to this study at the start of the contract in the form of interviews, discussions or meetings. The Contractor may propose new Collaborators in the course of the work, with the constraint indicated in Chapter 4.

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