

Technical Proposal for the Geant4-DNA Project

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1 Introduction and outline

Estimating the cancer risk for human exposure to space radiation is a challenge, which requires a wide range of knowledge involving physics, chemistry, biology, medicine and software engineering.

Traditionally the biological effects of radiation are analysed in top-bottom order, for example the evaluation of the absorbed macroscopic radiation dose at a given location in the biological tissue is translated into the degree of danger it implies, and dose limits are consequently set in a way that are considered to be acceptable.

As a consequence, the cited top-bottom order dosimetry fails when the biological effects of radiation on cellular and DNA molecule level are object of study.

In this context, a General Study was performed, as part of ESA/ESTEC Contract No 14402/00/NL/MV in order to evaluate the requirements for a simulation tool, based on the Geant4¹ Toolkit, to study the radiation interactions with cells and DNA molecules, with the aim of gaining a knowledge of radiation effects on biological structures at all levels (macroscopic and microscopic).

This proposal aims to bring the requirements resulting from this General Study into an operative phase, developing a software system to fulfil them.

The Geant4-DNA Project is meant to provide a simulation tool, useful in space applications in terms of radioprotection of astronauts and airlines pilots, and, in particular, in the context of ESA programmes and projects which involve the human presence in the space, such as Aurora, Humex, Desire. The outcome of the project would be relevant also for biological experiments, and it can have applications both in radiotherapy and in radiobiology; therefore, the project has a potential for the transfer of technologies from the space environment to the society at large. The physics developments to model physics interactions down to a small scale would be also useful in studies of micro- and nano-dosimetry, of interest in various experimental applications, such as the study of radiation damage to detectors and electronics.

Because of its intrinsic multidisciplinary nature, this project is meant to foster the construction of a scientific network of experts in various related disciplines, where the proposed contractor would play a role of central coordination.

Geant4 has been chosen as the ideal simulation framework for this project, because of its object oriented architecture, allowing further extension and evolution, and its powerful physics extensions at low energies.

¹ <http://cern.ch/geant4/>

2 Technical Proposal

2.1 Planned Activities

We plan to perform the following activities as part of this proposal:

- To build a scientific network of researchers in biochemistry, genetic and medicine, who can support the activities with their expertise, complementary to the physics and software engineering expertise provided directly by INFN key personnel.
- In depth study of background scientific knowledge, from physics, biochemistry and medicine point of view.
- Collection of information about the most modern model approaches about radiation interactions with biological structures at different levels, from physics, biochemistry and medicine point of view.
- Review of the User Requirements resulting from the Geant4-DNA General Study.

Development of Geant4 components and a Geant4-based application whose goal is the modelisation of radiation interactions and effects at cellular and DNA level.

2.2 Study Plan

We intend to articulate the study plan through three phases, in the process to obtain the final goal of the proposal:

1. In depth study of the project environment in terms of scientific knowledge, presenting the most advanced instruments with the aim of modelizing the radiation interactions at cellular and DNA level with accuracy.

2. Creation of a Geant4-DNA application prototype

3. Development of the prototype and related Geant4 components into an articulated Geant4 application, whose goal is the modelisation of radiation effects at cellular and DNA level.

Our group adopts a rigorous software process, which is both iterative and incremental, modelled on top of the United Software Development processes (USDP). We plan to develop the software described in the proposal through a series of iterations, each one visiting all the main software disciplines (Requirements, Analysis and Design, Implementation, Testing, Deployment).

The software process includes peer reviews of architecture, design and code.

The organisation of the activities associated to the three sub-projects into Work Packages, as well as the corresponding milestones, is described in detail in the following sections.

The Geant4-DNA Project is meant to produce toolkit components or applications, also to be released as part of the toolkit (advanced application examples).

2.3 Work Packages and Milestones

- PHASE 1 -

2.3.1 Work Package 1: study of the space radiation environment

1. Perform analysis of domain

2. Study of cosmic radiation
3. Study of solar radiation
4. Study of Jovian electrons
5. Study of trapped radiation
6. Study of secondary radiation environments

2.3.2 Work Package 2: work team definition

The **DNA project** involves various scientific domains; for this reason it is essential to gather together scientific researchers belonging to the following fields:

1. High and low energy physics
2. Space physics
3. Medical physics
4. Software engineering
5. Biology
6. Genetics
7. Chemistry
8. Medicine

2.3.3 Work Package 3: study of ESA space projects

The **DNA project** has got relevant implications in ESA space missions; as a consequence it is important to study particular ESA programmes and projects in order to harmonise the DNA project with ESA's ones, in particular:

1. Aurora
2. Humex
3. Desire

2.3.4 Work Package 4: study of existing physics models

Study of interactions of particles involved in the space environment with matter:

1. Electromagnetic interactions
2. Hadronic interactions
3. Heavy ion interactions

2.3.5 Work Package 5: study of radiation effects on macroscopic biological structures

1. Study of dosimetric quantities of interest under a macroscopic point of view
2. Study of radiation damage on human tissues
3. Study of high doses of radiation on human tissues
4. Study of low doses of radiation on human tissues

2.3.6 Work Package 6: study of radiation effects on microscopic biological structures

1. Study of biological structures of interest as cells and DNA
2. Study of dosimetric quantities of interest from a microscopic point of view
3. Study of radiation effects on cells and DNA

2.3.7 Work Package 7: study of existing bio-chemical models

1. Study of DNA damage due to radiation exposure (base alteration, base deletion, sugar alteration, strand break, mismatched base)
2. Study of reaction to DNA damage (cell cycle arrest, apoptosis, repair)

2.3.8 Work Package 8: study of existing Monte Carlo codes

This study reviews the present situation of Monte Carlo codes in order to perform simulations required by the Geant4-DNA Project, for example based on the following models:

1. Continuous-slowng-down (CSD) scheme
2. Condensed-random-walk scheme
3. Event-by-event scheme

This phase will be performed in 6 months.

► MILESTONE 1: SCIENTIFIC BACKGROUND

In Milestone 1 the scientific background knowledge in physics, bio-chemistry and medicine will be accurately known, in order to set up appropriate scientific instruments to achieve the final goal of the proposal. The corresponding deliverables and the time of delivery are listed in Appendix A.

- PHASE 2 -

2.3.9 Work Package 9: review of Geant4 functionality

This study is meant to verify the capabilities of Geant4 to perform simulations required by the DNA project in terms of:

- Geometry
- Materials
- Physics models

2.3.10 Work Package 10: review and update of the User Requirements

Review of the User Requirements established the 21st February 2001 in the context of the **Geant4-DNA** General Study.

This phase will be performed in 1 month. The User Requirements Document will be continuously updated throughout the duration of the project.

► MILESTONE 2: USER REQUIREMENTS DOCUMENT

In Milestone 2 the User Requirements will be specified and analysed. The corresponding deliverables and the time of delivery are listed in Appendix A.

- PHASE 3 -

2.3.11 Work Package 11: 1st iteration - explorative prototype

Creation of a Geant4 prototype in order to verify Geant4 capabilities to satisfy the User Requirements; the prototype will be developed in the following steps:

1. Update of the User Requirements
This element consists in a review of the sources of user requirements (scientific literature, other software codes, direct elicitation from stakeholders) to verify if the user

requirements have changed with respect to the previous version of the User Requirements Document, and in the modification of the User Requirements Document accordingly, to accommodate the necessary evolutions.

2. Study of the User Requirements

This element consists in an application of the mental faculties to the acquisition of knowledge about the topic of each user requirement, consisting in a careful examination and critical analysis of the scientific literature pertinent to that topic; in the first iteration the study privileges the breadth, rather than the depth, of acquisition of knowledge pertinent to the scope of the project.

3. Design

This element consists in identifying a candidate architecture for the system and in creating an object model, focusing on how functional and non-functional requirements may be realized. Design features are envisaged based on the User Requirements Document. The Analysis & Design discipline of the Unified Software Development Process is followed as a guideline for this element (see I. Jacobson, G. Booch and J. Rumbaugh, The Unified Software Development Process, Addison-Wesley, 1999).

4. Implementation

This element consists in the development of source code and scripts according to the design model blueprint, in unit testing the components and integrating them.

5. Test

This element consists in verifying the result from implementation; it includes planning an initial set of system and acceptance (validation) tests broadly covering the main features of the system, designing and implementing the tests, performing the tests and analysing the test results. The Test discipline of the Unified Software Development Process is followed as a guideline for this element (see I. Jacobson, G. Booch and J. Rumbaugh, The Unified Software Development Process, Addison-Wesley, 1999).

6. Documentation

This element consists in the creation of documents illustrating the main features of the system and how to use it. The documentation includes a Software Architecture Document, a Design Model, a Test Plan, a Traceability Map of user requirements, a Software User Manual, a web page with background information on the project, plots and tables with results from this iteration, and links to the deliverables and documents.

The prototype is meant to be the first of a series of iterations in the context of an iterative-incremental software process model.

2.3.12 Work Package 12: review of the 1st iteration

This phase consists in a review of the prototype in terms of:

- Results
- Problems encountered
- Comments for the future

This phase will be performed in 17 months.

► MILESTONE 3: PROTOTYPE

Milestone 3 includes to realisation of the prototype with benchmarks in terms of software processes, development, tests and results. The corresponding deliverables and the time of delivery are listed in Appendix A.

- PHASE 4 -

2.3.13 Work Package 13: 2nd iteration - modelisation of radiation interactions with macroscopic biological structures

1. Update of the User Requirements
This element consists in a review of the sources of user requirements, in particular those specific to radiation interactions with macroscopic biological structures, (scientific literature, other software codes, direct elicitation from stakeholders) to verify if the user requirements have changed with respect to the previous version of the User Requirements Document, and in the modification of the User Requirements Document accordingly, to accommodate the necessary evolutions.
2. Study of the User Requirements
This element consists in an application of the mental faculties to the acquisition of knowledge about the topic of user requirements specific to radiation interactions with macroscopic biological structures, consisting in a careful examination and critical analysis of the scientific literature pertinent to that topic; in this iteration the study increases the depth of acquisition of knowledge with respect to the previous iteration.
3. Design
This element consists in refining the architecture for the system and the object model, focusing on how requirements specific to radiation interactions with macroscopic biological structures may be realized. Design features are envisaged based on the User Requirements Document. The Analysis & Design discipline of the Unified Software Development Process is followed as a guideline for this element (see I. Jacobson, G. Booch and J. Rumbaugh, The Unified Software Development Process, Addison-Wesley, 1999).
4. Implementation
This element consists in the development of source code and scripts according to the design model blueprint, in unit testing the components and integrating them, with focus on radiation interactions with macroscopic biological structures; with respect to the previous iteration, more refined models and algorithms are implemented, based on available scientific literature.
5. Test
This element consists in verifying the result from implementation, with focus on radiation interactions with macroscopic biological structures; it includes refining the initial set of system and acceptance (validation) tests, with focus on radiation interactions with macroscopic biological structures, designing and implementing the tests, performing the tests and analysing the test results. The Test discipline of the Unified Software Development Process is followed as a guideline for this element (see I. Jacobson, G. Booch and J. Rumbaugh, The Unified Software Development Process, Addison-Wesley, 1999).
6. Documentation
This element consists in the update of documents illustrating the main features of the system according to the progress in the current iteration, and how to use the system at the current stage. The Software Architecture Document, Design Model, the Test Plan, the Traceability Map of user requirements, the Software User Manual, the web page with background information on the project, plots and tables with results from this iteration, and links to the deliverables and documents are updated.

2.3.14 Work Package 14: 2nd iteration - modelisation of radiation interactions with cellular structures

7. Update of the User Requirements
This element consists in a review of the sources of user requirements, in particular those specific to radiation interactions with cellular structures, (scientific literature, other software codes, direct elicitation from stakeholders) to verify if the user requirements have changed with respect to the previous version of the User Requirements Document, and in the modification of the User Requirements Document accordingly, to accommodate the necessary evolutions.
8. Study of the User Requirements
This element consists in an application of the mental faculties to the acquisition of knowledge about the topic of user requirements specific to radiation interactions with cellular structures, consisting in a careful examination and critical analysis of the scientific literature pertinent to that topic; in this iteration the study increases the depth of acquisition of knowledge with respect to the previous iteration.
9. Design
This element consists in refining the architecture for the system and the object model, focusing on how requirements specific to radiation interactions with cellular structures may be realized. Design features are envisaged based on the User Requirements Document. The Analysis & Design discipline of the Unified Software Development Process is followed as a guideline for this element (see I. Jacobson, G. Booch and J. Rumbaugh, The Unified Software Development Process, Addison-Wesley, 1999).
10. Implementation
This element consists in the development of source code and scripts according to the design model blueprint, in unit testing the components and integrating them, with focus on radiation interactions with cellular structures; with respect to the previous iteration, more refined models and algorithms are implemented, based on available scientific literature.
11. Test
This element consists in verifying the result from implementation, with focus on radiation interactions with cellular structures; it includes refining the initial set of system and acceptance (validation) tests, with focus on radiation interactions with cellular structures, designing and implementing the tests, performing the tests and analysing the test results. The Test discipline of the Unified Software Development Process is followed as a guideline for this element (see I. Jacobson, G. Booch and J. Rumbaugh, The Unified Software Development Process, Addison-Wesley, 1999).
12. Documentation
This element consists in the update of documents illustrating the main features of the system according to the progress in the current iteration, and how to use the system at the current stage. The Software Architecture Document, Design Model, the Test Plan, the Traceability Map of user requirements, the Software User Manual, the web page with background information on the project, plots and tables with results from this iteration, and links to the deliverables and documents are updated.

2.3.15 Work Package 15: 2nd iteration - modelisation of radiation interactions with microscopic biological structures

13. Update of the User Requirements
This element consists in a review of the sources of user requirements, in particular

those specific to radiation interactions with microscopic biological structures, (scientific literature, other software codes, direct elicitation from stakeholders) to verify if the user requirements have changed with respect to the previous version of the User Requirements Document, and in the modification of the User Requirements Document accordingly, to accommodate the necessary evolutions.

14. Study of the User Requirements

This element consists in an application of the mental faculties to the acquisition of knowledge about the topic of user requirements specific to radiation interactions with microscopic biological structures, consisting in a careful examination and critical analysis of the scientific literature pertinent to that topic; in this iteration the study increases the depth of acquisition of knowledge with respect to the previous iteration.

15. Design

This element consists in refining the architecture for the system and the object model, focusing on how requirements specific to radiation interactions with microscopic biological structures may be realized. Design features are envisaged based on the User Requirements Document. The Analysis & Design discipline of the Unified Software Development Process is followed as a guideline for this element (see I. Jacobson, G. Booch and J. Rumbaugh, *The Unified Software Development Process*, Addison-Wesley, 1999).

16. Implementation

This element consists in the development of source code and scripts according to the design model blueprint, in unit testing the components and integrating them, with focus on radiation interactions with microscopic biological structures; with respect to the previous iteration, more refined models and algorithms are implemented, based on available scientific literature.

17. Test

This element consists in verifying the result from implementation, with focus on radiation interactions with microscopic biological structures; it includes refining the initial set of system and acceptance (validation) tests, with focus on radiation interactions with microscopic biological structures, designing and implementing the tests, performing the tests and analysing the test results. The Test discipline of the Unified Software Development Process is followed as a guideline for this element (see I. Jacobson, G. Booch and J. Rumbaugh, *The Unified Software Development Process*, Addison-Wesley, 1999).

18. Documentation

This element consists in the update of documents illustrating the main features of the system according to the progress in the current iteration, and how to use the system at the current stage. The Software Architecture Document, Design Model, the Test Plan, the Traceability Map of user requirements, the Software User Manual, the web page with background information on the project, plots and tables with results from this iteration, and links to the deliverables and documents are updated.

2.3.16 Work Package 16: review of the 2nd iteration

- Results
- Problems encountered
- Comments for the future

This phase will be performed in one year.

► MILESTONE 4: SECOND ITERATION

Milestone 4 includes the realisation of the second iteration with benchmarks in terms of software processes, development, tests and results. The corresponding deliverables and the time of delivery are listed in Appendix A.

- PHASE 5 -

2.3.17 Work Package 17: 3rd iteration - modelisation of radiation interactions with macroscopic biological structures

1. Update of the User Requirements
This element consists in a review of the sources of user requirements, in particular those specific to radiation interactions with macroscopic biological structures, (scientific literature, other software codes, direct elicitation from stakeholders) to verify if the user requirements have changed with respect to the previous version of the User Requirements Document, and in the modification of the User Requirements Document accordingly, to accommodate the necessary evolutions.
2. Study of the User Requirements
This element consists in an application of the mental faculties to the acquisition of knowledge about the topic of user requirements specific to radiation interactions with macroscopic biological structures, consisting in a careful examination and critical analysis of the scientific literature pertinent to that topic; in this iteration the study increases the depth of acquisition of knowledge with respect to the previous iteration.
3. Design
This element consists in further refining the architecture for the system and the object model, focusing on how requirements specific to radiation interactions with macroscopic biological structures may be realized. Design features are envisaged based on the User Requirements Document. The Analysis & Design discipline of the Unified Software Development Process is followed as a guideline for this element (see I. Jacobson, G. Booch and J. Rumbaugh, The Unified Software Development Process, Addison-Wesley, 1999).
4. Implementation
This element consists in the development of source code and scripts according to the design model blueprint, in unit testing the components and integrating them, with focus on radiation interactions with macroscopic biological structures; with respect to the previous iteration, more refined models and algorithms are implemented, based on available scientific literature.
5. Test
This element consists in verifying the result from implementation, with focus on radiation interactions with macroscopic biological structures; it includes further refining the set of system and acceptance (validation) tests, with focus on radiation interactions with macroscopic biological structures, designing and implementing the tests, performing the tests and analysing the test results. The Test discipline of the Unified Software Development Process is followed as a guideline for this element (see I. Jacobson, G. Booch and J. Rumbaugh, The Unified Software Development Process, Addison-Wesley, 1999).
6. Documentation
This element consists in the update of documents illustrating the main features of the system according to the progress in the current iteration, and how to use the system at

the current stage. The Software Architecture Document, Design Model, the Test Plan, the Traceability Map of user requirements, the Software User Manual, the web page with background information on the project, plots and tables with results from this iteration, and links to the deliverables and documents are updated.

2.3.18 Work Package 18: 3rd iteration - modelisation of radiation interactions with cellular structures

1. Update of the User Requirements

This element consists in a review of the sources of user requirements, in particular those specific to radiation interactions with cellular structures, (scientific literature, other software codes, direct elicitation from stakeholders) to verify if the user requirements have changed with respect to the previous version of the User Requirements Document, and in the modification of the User Requirements Document accordingly, to accommodate the necessary evolutions.

2. Study of the User Requirements

This element consists in an application of the mental faculties to the acquisition of knowledge about the topic of user requirements specific to radiation interactions with cellular structures, consisting in a careful examination and critical analysis of the scientific literature pertinent to that topic; in this iteration the study increases the depth of acquisition of knowledge with respect to the previous iteration.

3. Design

This element consists in further refining the architecture for the system and the object model, focusing on how requirements specific to radiation interactions with cellular structures may be realized. Design features are envisaged based on the User Requirements Document. The Analysis & Design discipline of the Unified Software Development Process is followed as a guideline for this element (see I. Jacobson, G. Booch and J. Rumbaugh, The Unified Software Development Process, Addison-Wesley, 1999).

4. Implementation

This element consists in the development of source code and scripts according to the design model blueprint, in unit testing the components and integrating them, with focus on radiation interactions with cellular structures; with respect to the previous iteration, more refined models and algorithms are implemented, based on available scientific literature.

5. Test

This element consists in verifying the result from implementation, with focus on radiation interactions with cellular structures; it includes further refining the set of system and acceptance (validation) tests, with focus on radiation interactions with cellular structures, designing and implementing the tests, performing the tests and analysing the test results. The Test discipline of the Unified Software Development Process is followed as a guideline for this element (see I. Jacobson, G. Booch and J. Rumbaugh, The Unified Software Development Process, Addison-Wesley, 1999).

6. Documentation

This element consists in the update of documents illustrating the main features of the system according to the progress in the current iteration, and how to use the system at the current stage. The Software Architecture Document, Design Model, the Test Plan, the Traceability Map of user requirements, the Software User Manual, the web page with background information on the project, plots and tables with results from this iteration, and links to the deliverables and documents are updated.

2.3.19 Work Package 19: 3rd iteration - modelisation of radiation interactions with microscopic biological structures

7. Update of the User Requirements

This element consists in a review of the sources of user requirements, in particular those specific to radiation interactions with microscopic biological structures, (scientific literature, other software codes, direct elicitation from stakeholders) to verify if the user requirements have changed with respect to the previous version of the User Requirements Document, and in the modification of the User Requirements Document accordingly, to accommodate the necessary evolutions.

8. Study of the User Requirements

This element consists in an application of the mental faculties to the acquisition of knowledge about the topic of user requirements specific to radiation interactions with microscopic biological structures, consisting in a careful examination and critical analysis of the scientific literature pertinent to that topic; in this iteration the study increases the depth of acquisition of knowledge with respect to the previous iteration.

9. Design

This element consists in further refining the architecture for the system and the object model, focusing on how requirements specific to radiation interactions with microscopic biological structures may be realized. Design features are envisaged based on the User Requirements Document. The Analysis & Design discipline of the Unified Software Development Process is followed as a guideline for this element (see I. Jacobson, G. Booch and J. Rumbaugh, The Unified Software Development Process, Addison-Wesley, 1999).

10. Implementation

This element consists in the development of source code and scripts according to the design model blueprint, in unit testing the components and integrating them, with focus on radiation interactions with microscopic biological structures; with respect to the previous iteration, more refined models and algorithms are implemented, based on available scientific literature.

11. Test

This element consists in verifying the result from implementation, with focus on radiation interactions with microscopic biological structures; it includes further refining the set of system and acceptance (validation) tests, with focus on radiation interactions with microscopic biological structures, designing and implementing the tests, performing the tests and analysing the test results. The Test discipline of the Unified Software Development Process is followed as a guideline for this element (see I. Jacobson, G. Booch and J. Rumbaugh, The Unified Software Development Process, Addison-Wesley, 1999).

12. Documentation

This element consists in the update of documents illustrating the main features of the system according to the progress in the current iteration, and how to use the system at the current stage. The Software Architecture Document, Design Model, the Test Plan, the Traceability Map of user requirements, the Software User Manual, the web page with background information on the project, plots and tables with results from this iteration, and links to the deliverables and documents are updated.

2.3.20 Work Package 20: review of the 3rd iteration

- Results

- Problems encountered
- Comments for the future

This phase will be performed in one year.

► **MILESTONE 5: THIRD ITERATION**

Milestone 5 includes the realisation of the third iteration with benchmarks in terms of software processes, development, tests and results. The corresponding deliverables and the time of delivery are listed in Appendix A.

2.4 Scholarship

A dedicated post-doctoral fellow is foreseen, to work full-time on the project for the duration of 4 years. The funds associated to the contract would be entirely devoted to the fellowship payment.

2.5 Cost Price Data

The research work performed as part of this contract will utilize the existing research facilities at INFN Genova. No cost will be charged for such facilities. The funds associated to the contract will be utilized for a post-doctoral fellowship supporting key personnel.

2.6 Profit

Being a public research institute, all the funds acquired through a contract would be utilized to perform the scientific research described in this proposal, with no profit.

2.7 Type of Price

The price (50 K euro) is firm fixed.

2.8 Milestone Payments Plan

We propose the following payments plan:

- 20% at the start of the contract
- 20% at milestone 1
- 30% at milestone 3
- 20% at milestone 4
- 10% at milestone 5

