TOPAS-nBio Documentation

Release 2.0

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GETTING STARTED

Note: We plan a new release within the month. The new release will be built on the new TOPAS version available at the OpenTOPAS GitHub. Version 4.0 of OpenTOPAS is available at: https://opentopas.github.io/index.html. Version numbers continue in sequence from previous versions of TOPAS. For more information, see below.

Note: TOPAS-nBio's current version is v2.0 and works with TOPAS release 3.8 and newer release.

The code is available at: https://github.com/topas-nbio/TOPAS-nBio/releases/tag/v2.0 Please use the code as much as possible and report any issues to the TOPAS-nBio forum.

Note: The forum is currently moving and will soon be available at a different site. No posts on the old TOPAS and TOPAS-nBio forums will be answered by the TOPAS team anymore.

This is an important announcement for our users on the release of OpenTOPAS.

The TOPAS team has moved to a full open-source approach with major upgrades. This new version of OpenTOPAS is a continuation of the TOPAS development. The past principal investigators, Drs. Harald Paganetti and Bruce Faddegon, and the new principal investigators, Drs. José Ramos and Jan Schuemann are committed to continuing TOPAS's development and long-term sustainment through OpenTOPAS.

1. Version 4,0 of OpenTOPAS is available through a new GitHub at https://opentopas.github.io/index.html. Version numbers continue in sequence from previous versions of TOPAS.

2. **Major improvements include:**

     - Update to Geant4.11.1.3 - rigorous testing completed

     - A wholly new, doubly diverging MLC to replace the past defective one

     - A new second cancer model

     - A new mesh phantom model for mice

     - The first imaging extension to allow modeling of basic CT, SPECT, and PET imaging detectors (to be expanded)

     - A new module for photo-neutron simulation in X-ray therapy

     - Support for all optical material properties provided by Geant4

3. For the TOPAS-nBio extension, all new releases of TOPAS-nBio will be tested exclusively for compatibility with OpenTOPAS. A new OpenTOPAS-nBio release is planned for the end of May.

4. A new user guide with improved search capabilities and all new features will soon be available at the OpenTOPAS GitHub and https://opentopas.readthedocs.io/en/latest/.

5. A quick start procedure for installing OpenTOPAS may be found on GitHub (OpenTOPAS_quickstart_Debian.md or OpenTOPAS_quickstart_forMacOS.md)

6. Our development team will address all questions on OpenTOPAS through the OpenTOPAS user forum, which can be accessed through GitHub at https://github.com/OpenTOPAS/OpenTOPAS/discussions.

7. Various other improvements are listed on our GitHub website. We are already working on the next release, which will include Geant4 version 11.2, a new interface compatible with DICOM-RT for x-ray and electron therapy, and a new example for multi-scale SARRP simulations.

8. The OpenTOPAS team is working on long-term sustainment plans with the help of NIH/NCI.

We can't wait to see our users advancing medical uses of ionizing radiation with OpenTOPAS. Please take advantage of the OpenTOPAS user forum and its refined capabilities.

We look forward to seeing you there.

José Ramos, Jan Schuemann, Harald Paganetti, Bruce Faddegon, and the entire OpenTOPAS team

WELCOME TO THE DOCUMENTATION OF TOPAS-NBIO!

The TOPAS Monte Carlo (MC) system has played a significant role in making Monte Carlo simulations widely available for proton therapy related research and is further used in radiation therapy and medical imaging research. While TOPAS provides detailed simulations of patient scale properties, the fundamental unit of the biological response to radiation is a cell. Thus, we developed TOPAS-nBio, an extension of TOPAS dedicated to advance understanding of radiobiological effects at the (sub-)cellular (i.e., the cellular and sub-cellular) scale. TOPAS-nBio is designed as a set of open source classes that extends TOPAS to model radiobiological experiments. TOPAS-nBio is based on and extends Geant4-DNA, which extends the Geant4 toolkit, the basis of TOPAS, to include very low-energy interactions of particles down to vibrational energies. TOPAS-nBio explicitly simulates every particle interaction (i.e., without using condensed histories) and propagates radiolysis products. To further facilitate the use of TOPAS-nBio, a graphical user interface was developed. TOPAS-nBio offers full track-structure Monte Carlo simulations, integration of chemical reactions within the first millisecond, an extensive catalogue of specialized cell geometries as well as sub-cellular structures such as DNA and mitochondria. TOPAS-nBio provides the initially induced damage patterns and interfaces to mechanistic models of DNA repair kinetics. Thus, together with TOPAS, this extension offers access to accurate and detailed multiscale simulations, from a macroscopic description of the radiation field to microscopic description of biological outcome.

The TOPAS-nBio package was described in Radiation Research, 2019, 191(2), p.125 (also see *Citations*). By releasing TOPAS-nBio as an open source extension to TOPAS, we intend to encourage active involvement of the research community to continuously extend and improve the features of TOPAS-nBio.

1.1 Introduction to TOPAS-nBio

1.1.1 The TOPAS-nBio extension

TOPAS-nBio is an extension to the Monte Carlo toolkit OpenTOPAS which wraps and extends the Geant4 Simulation Toolkit. TOPAS was designed to make Geant4 more readily available to both research and clinical medical physicists as well as to extend its functionality. TOPAS-nBio further extends the functionality of the toolkit for radiobiology applications.

Motivation for TOPAS-nBio

TOPAS has been successfully applied to research in radiation therapy physics and macroscopic organ or cellular biology. However, more fundamental research is needed to understand the underlying mechanisms of radiation action, describe effects of oxygenation, intracellular signaling, drug-induced radiation sensitization or resistance and many other effects. Variations at the cellular and sub-cellular level, both for tumors and surrounding normal tissues, need to be considered. Such research is ideally supported by detailed *in silico* simulations at the sub-cellular level.

The goal of this work was to lay the foundation to a deeper understanding of the biological effects of radiation in order to facilitate new research at the boundary between physics, chemistry and biology. By providing detailed physics and chemistry simulations in combination with detailed representations of biological systems, such as cells and their nuclei, we aim to promote a mechanistic description connecting sub-cellular energy deposition phenomena to observable

biological outcomes. We have thus developed TOPAS-nBio, an extension to TOPAS specifically aimed at the simulation of radiobiological experiments by modeling detailed biological effects at the nanometer scale. By taking advantage of the simplicity and reliability engineered into TOPAS while providing nanometer-scale Monte Carlo simulations, we have made complex code accessible to researchers who may consider using Monte Carlo simulations to improve the physical, chemical and biological description of their experimental design or data analysis.

1.2 How to Install TOPAS-nBio

1.2.1 Installing OpenTOPAS

TOPAS-nBio is an extension to the TOPAS toolkit, using the OpenTOPAS version. In order to install TOPAS-nBio, users must first install OpenTOPAS.

TOPAS-nBio (starting with version 3.0) requires OpenTOPAS version 4.0 or newer.

OpenTOPAS can be downloaded from OpenTOPAS. Installation instructions for OpenTOPAS can be found on the OpenTOPAS GitHub in the "quickStart" files.

1.2.2 Installing TOPAS-nBio

Download the TOPAS-nBio extension and put in a separate directory (e.g. /PathToWorkDirectory/TOPAS-nBio). This path should not be inside the main TOPAS installation directory to avoid accidental loss of your extensions and parameter files when updating to a new TOPAS version. After building TOPAS link the TOPAS-nBio extension and rebuild the code:

```
cmake -DTOPAS_EXTENSIONS_DIR=/PathToWorkDirectory/TOPAS-nBio
make -j8
```

1.3 Parameter File System

TOPAS-nBio is an extension to OpenTOPAS, which follows a consistent set of design paradigms. OpenTOPAS (from here on simply TOPAS) is controlled by a simple text file which is used to specify the all the simulation parameters.

Detailed documentation is provided on the TOPAS Parameter System. Here we provide a brief summary of the parameter syntax.

The system takes a set of "Parameters Files," simple text files made up of lines of key/value pairs:

```
Parameter_Type : Parameter_Name = Parameter_Value # Optional comment
```

The order of lines within a parameter file does not matter.

A Parameter_Name can be almost any string, but we have prefix conventions to keep things clear:

- `Ma/` for Materials
- `El/` for Elements
- `Is/` for Isotopes
- `Ge/` for Geometry Components
- `So/` for Particle Sources
- `Ph/` for Physics

- `Ch/` for Chemistry (introduced for TOPAS-nBio)
- `Mo/` for Chemical Molecules (introduced for TOPAS-nBio IRT)
- `Vr/` for Variance Reduction
- `Sc/` for Scoring
- `Gr/` for Graphics
- `Tf/` for Time Features
- `Ts/` for TOPAS overall control

The Parameter_Type tells TOPAS what type of data will be in this parameter:

- `d` for Dimensioned Double
- `u` for Unitless Double
- `i` for Integer
- `b` for Boolean
- `s` for String
- `dv` for Dimensioned Double Vector
- similarly for `uv`, `iv`, `bv` and `sv`

The Parameter_Name and Parameter_Value define what the line does. There are certain key parameters that will initiate the construction of, for example, a scorer or a geometry, which then causes TOPAS to look for necessary connected parameters, e.g. the size of the object.

Within TOPAS-nBio, many new components and options have been developed, the implementation and the required parameters are described on this site. For all other parameters covered by TOPAS, please refer to the OpenTOPAS documentation: TOPAS Parameter System.

1.4 Members of the TOPAS-nBio Collaboration

1.4.1 Members of TOPAS-nBio

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CENBG

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1.4.3 Previous Contributors

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1.5 Citations

1.5.1 Main TOPAS-nBio publication

When using TOPAS-nBio, please be sure to cite the following paper (Featured on the Cover of Radiation Research)

Schuemann, J., McNamara, A. L., Ramos-Méndez, J., Perl, J., Held, K. D., Paganetti, H., Incerti, S., Faddegon, B. (2019). TOPAS-nBio: An Extension to the TOPAS Simulation Toolkit for Cellular and Sub-cellular Radiobiology. Radiation Research, 191(2), 125–138. PMID: 30609382. PMCID: PMC6377808. http://doi.org/10.1667/RR15226.1 , PubMed

1.5.2 Other relevant TOPAS-nBio publications

Underwood, T. S. A., Sung, W., McFadden, C. H., McMahon, S. J., Hall, D. C., McNamara, A. L., Paganetti H., Sawakuchi G. O., Schuemann J. (2017). Comparing stochastic proton interactions simulated using TOPAS-nBio to experimental data from fluorescent nuclear track detectors. Physics in Medicine and Biology, 62(8), 3237–3249. PMID: 28350546. http://doi.org/10.1088/1361-6560/aa6429

Ramos-Méndez, J., Schuemann, J., Incerti, S., Paganetti, H., Schulte, R., & Faddegon, B. (2017). Flagged uniform particle splitting for variance reduction in proton and carbon ion track-structure simulations. Physics in Medicine and Biology, 62(15), 5908–5925. PMID: 28594336. PMCID: PMC5785278. http://doi.org/10.1088/1361-6560/aa7831

McNamara, A., Geng, C., Turner, R., Ramos-Méndez, J., Perl, J., Held, K., Faddegon B., Paganetti H., Schuemann J. (2017). Validation of the radiobiology toolkit TOPAS-nBio in simple DNA geometries. Physica Medica, 33, 207–215. PMID: 28017738. PMCID: PMC529229. http://doi.org/10.1016/j.ejmp.2016.12.010

McNamara, A. L., Ramos-Méndez, J., Perl, J., Held, K., Dominguez, N., Moreno, E., Henthorn, N., Kirkby, K. J., Meylan, S., Villagrasa, C., Incerti, S., Faddegon, B., Paganetti, H., Schuemann, J. (2018). Geometrical structures for radiation biology research as implemented in the TOPAS-nBio toolkit. Physics in Medicine and Biology, 63(17), 175018. http://doi.org/10.1088/1361-6560/aad8eb

Ramos-Méndez, J., Perl, J., Schuemann, J., McNamara, A., Paganetti, H., & Faddegon, B. (2018). Monte Carlo simulation of chemistry following radiolysis with TOPAS-nBio. Physics in Medicine and Biology, 63(10), 105014. PMID: 29697057. PMCID: PMC6027650. http://doi.org/10.1088/1361-6560/aac04c

Ramos-Méndez, J., Burigo, L. N., Schulte, R., Chuang, C, & Faddegon, B. (2018). Fast calculation of nanodosimetric quantities in treatment planning of proton and ion therapy. Physics in Medicine and Biology 63(23), 235015-14 pp. PMID: 30484432. http://iopscience.iop.org/article/10.1088/1361-6560/aaeeee

Zhu H., Chen Y., Sung W., McNamara A. L., Linh T. T., Burigo L. N., Rosenfeld A. B., Li J., Faddegon B., Schuemann J., Paganetti H. (2019). The microdosimetric extension in TOPAS: Development and comparison with published data. Physics in Medicine and Biology; 64(14):145004. PMID: 31117056. http://doi.org/10.1088/1361-6560/ab23a3

Hahn, M.B. (2023). Accessing radiation damage to biomolecules on the nanoscale by particle-scattering simulations. Journal of Physics Communications; 7(4):042001. http://doi.org/10.1088/2399-6528/accb3f

1.5.3 The Standard for DNA Damage (SDD)

Schuemann J., McNamara A. L., Warmenhoven J., et al. (55 authors). (2019). A new Standard DNA Damage (SDD) data format. Radiation Research; 191(1):76. PMID: 30407901. PMCID: PMC6407706. https://doi.org/10.1667/RR15209.1

1.5.4 Cell models with organelles and targeted nanoparticles

Hahn, M.B., Zutta Villate, J.M. (2021). Combined cell and nanoparticle models for TOPAS to study radiation dose enhancement in cell organelles. Sci Rep 11(1): 6721. PMID: 33762596. PMCID: PMC7990972. https://doi.org/10.1038/s41598-021-85964-2

1.5.5 A few publications where TOPAS-nBio was used

McNamara A. L., Kam W. W., Scales N., McMahon S. J., Bennett J. W., Byrne H. L., Schuemann J., Paganetti H., Banati R., Kuncic Z. (2016). Dose enhancement effects to the nucleus and mitochondria from gold nanoparticles in the cytosol. Physics in Medicine and Biology 61(16):5993-6010. PMID: 27435339; PMCID: PMC4993038. https://doi.org/10.1088/0031-9155/61/16/5993

Sung W., Ye S. J., McNamara A. L., McMahon S., Hainfeld J., Shin J., Smilowitz H., Paganetti H., Schuemann J. (2017). Dependence of gold nanoparticle radiosensitization on cell geometry. Nanoscale; 9(18):5843-5853. PMID: 28429022. PMCID: PMC5526329. https://doi.org/10.1039/c7nr01024a

Yang C., Bromma K., Sung W., Schuemann J., Chithrani D. (2018). Determining the Radiation Enhancement Effects of Gold Nanoparticles in Cells in a Combined Treatment with Cisplatin and Radiation at Therapeutic Megavoltage Energies. Cancers (Basel). 2018; 10(5). pii: E150. PMID: 29786642. PMCID: PMC5977123. https://doi.org/10.3390/cancers10050150

Sung W., Schuemann J. (2018). Energy Optimization in Gold Nanoparticle Enhanced Radiation Therapy. Physics in Medicine and Biology; 63(13): 135001. PMID: 29873303. PMCID: PMC6040581. https://doi.org/10.1088/1361-6560/aacab6

Sung W., Jeong Y., Kim H., Jeong H., Grassberger C., Jung S., Ahn G. O., Kim I. H., Schuemann J., Lee K., Ye S. J. (2018). Computational Modeling and Clonogenic Assay for Radioenhancement of Gold Nanoparticles using 3D live cell images. Radiation Research; 190(5): 558-564. PMID: 30142031. PMCID: PMC6258025. https://doi.org/10.1667/RR15134.1

1.5.6 Original TOPAS paper

Perl, J., Shin, J., Schuemann, J., Faddegon, B., & Paganetti, H. (2012). TOPAS: an innovative proton Monte Carlo platform for research and clinical applications. Medical Physics, 39(11), 6818–6837. PMID: 23127075. PMCID: PMC3493036. http://doi.org/10.1118/1.4758060 |

OpenTOPAS

OpenTOPAS can be downloaded from https://opentopas.github.io/index.html and the OpenTOPAS documentation can be found at: https://opentopas.readthedocs.io

The Geant4-DNA project

TOPAS-nBio is based on and extends Geant4-DNA. Information on the Geant4-DNA project can be found at: http://geant4-dna.org/

1.6 License

TOPAS-nBio is an open-source extension to OpenTOPAS that is layered on top of Geant4 and Geant4-DNA (for references see *Citations*). TOPAS-nBio follows the same licensing as Geant4:

TOPAS-nBio Software License Version 1.0, 28 May 2019

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1.7 Introduction

Geometries and Set-Up in TOPAS-nBio

To cover a wide range of geometries, TOPAS-nBio offers the user a vast catalogue of biological targets. On the micrometer scale, users can select cells by shape or differentiation, choosing to model a single cell or multiple cells (e.g., neuron network or cells *in vitro*). Other micrometer (sub-cellular) scale targets, such as the cell nucleus or mitochondria are also offered as geometries. A single organelle structure may be simulated or multiple organelles can be included in the full cell geometry.

On the nanometer scale, biologically significant molecules (e.g., DNA, RNA, membrane lipids) are offered as geometries. Since DNA is the primary target of radiation in the cell, realistic DNA models are important for track structure simulations. For this reason, TOPAS-nBio has developed numerous models of DNA in different stages of hierarchal folding within the cell. This includes models of the cell nucleus incorporating the DNA structure from chromatin territories and chromatin fibre models down to the double strand DNA helix. Other potential radiation targets are also considered, for example mitochondrial DNA, membranes and other molecules essential to healthy cell function (RNA, proteins).

Geometries are designed as custom geometry components in TOPAS. Users have the option of modifying the geometry extension class itself to customize a specific component for their own application or users can interact with the component using the parameter file exclusively. For more information on how to modify geometry components or write your own, see the OpenTOPAS documentation on custom geometry components.

1.8 Cell Models

A common end point of measurement for cells cultured *in vitro* in radiobiology is clonogenic cell survival. Single cell Monte Carlo simulations can provide insight into the total dose received by the cell or the distribution of dose within sub-regions of the cell (e.g., dose to the cell nucleus). This may be correlated with experimental measurements of the loss of a specific function or cell death. Single cell models can also form the geometric boundary for more complex studies, for example, calculating the energy deposited in other sub-cellular components (e.g., organelles, cell membranes) or investigating DNA damage in the nucleus.

TOPAS-nBio provides users with a unique framework for simulating multiple cell types and the option of including organelle sub-components in the model.

1.8.1 Spherical Cell

The TsSphericalCell component is a model of a spherical cell with the option of including organelles. To create the model specify the component name as well as the cell radius required:

```
s:Ge/MyCell/Type="TsSphericalCell"
d:Ge/MyCell/CellRadius=20 um
```

Users have the option of including a nucleus. Specify the radius to add the nucleus to the cell:

```
d:Ge/MyCell/Nucleus/NucleusRadius=5. um
```

The nucleus position within the cell can be edited using:

```
d:Ge/MyCell/Nucleus/translateX = 0.2 um
d:Ge/MyCell/Nucleus/translateY = 0.0 um
d:Ge/MyCell/Nucleus/translateZ = 0.1 um
```
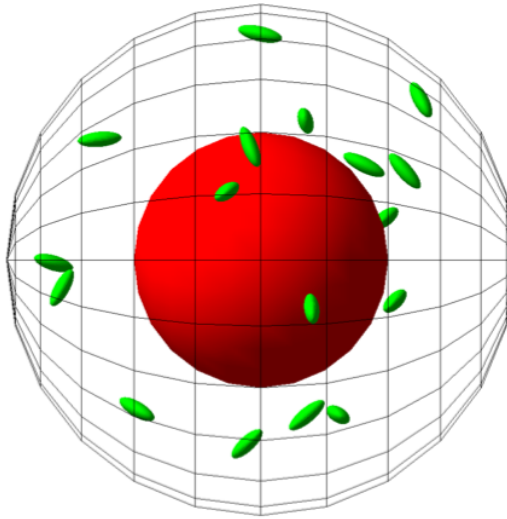
Mitochondria can also be placed randomly in the cell, the size and the number of mitochondria are specified in the parameter file:

```
i:Ge/MyCell/Mitochondria/NumberbOfMitochondria=20
d:Ge/MyCell/Mitochondria/a=0.5 um
d:Ge/MyCell/Mitochondria/b=0.3 um
d:Ge/MyCell/Mitochondria/c=0.9 um
```

A nucleus and mitochondria may be added to any of the cell models listed in a similar manner.

1.8.2 Ellipsoid Cell
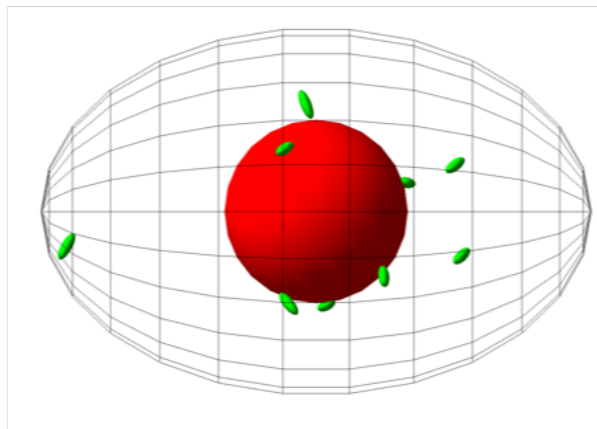
The TsEllipsoidCell component is a model of an ellipsoid cell with the option of including organelles. To use the cell model, specify the component name as well as the semi-axis lengths of the ellipsoid:

```
s:Ge/MyCell/Type="TsEllipsoidCell"
d:Ge/MyCell/xSemiAxis=20 um
d:Ge/MyCell/ySemiAxis=10 um
d:Ge/MyCell/zSemiAxis=15 um
```

1.8.3 Cuboidal Cells
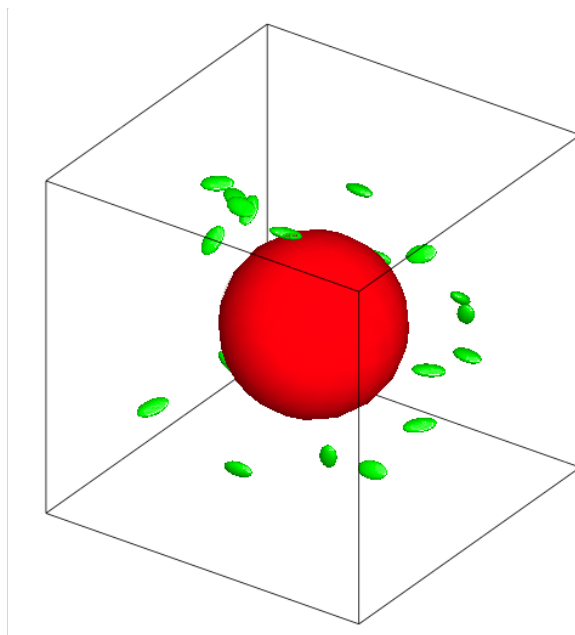
The TsCuboidalCell component is a model of a cuboidal or rectangular cell with the option of including organelles. To use the model specify the component name as well as the half-lengths of each side of the cube/rectangle required:

```
s:Ge/MyCell/Type="TsCuboidalCell"
d:Ge/MyCell/Cell_HLX=10 um
d:Ge/MyCell/Cell_HLY=20 um
d:Ge/MyCell/Cell_HLZ=10 um
```

1.8.4 Irregular-shaped cells

Cells with irregular-shapes are also available. This includes 3 fibroblast cell models and a 3D hexagonal cell.

Three models of Fibroblasts are provided in TOPAS-nBio:

```
s:Ge/MyCell/Type="TsFibroblastCell1"

s:Ge/MyCell/Type="TsFibroblastCell2"

s:Ge/MyCell/Type="TsFibroblastCell3"
```

An irregular-shaped cell using a hexagon is also available with optional organelles:

```
s:Ge/MyCell/Type="TsHexagonCell"
```
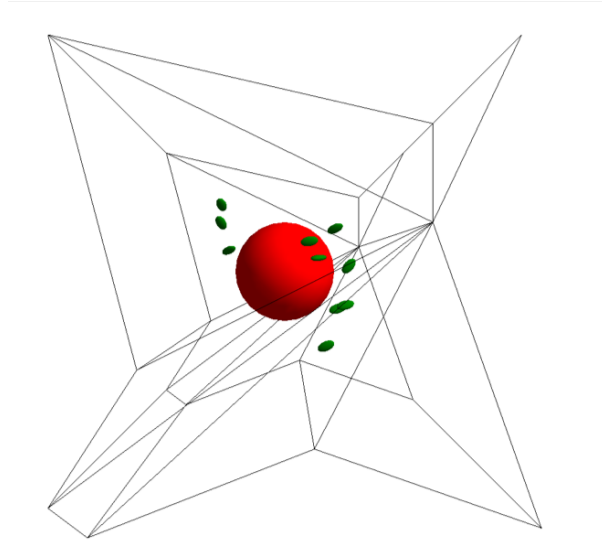
1.8.5 Bone Cells

Three different bone cell geometries are available in TOPAS-nBio: osteoblasts, osteoclasts and osteocytes.

Osteocytes and osteoblasts have the option of including a single nucleus and/or mitochondria.

Osteoblasts are cubical, users should specify the half-lengths of the cell:

```
s:Ge/MyCell/Type="TsOsteoblast"
d:Ge/MyCell/Cell_HLX=10 um
d:Ge/MyCell/Cell_HLY=10 um
d:Ge/MyCell/Cell_HLZ=10 um
```

Osteocytes are irregular shaped cells:

```
s:Ge/MyCell/Type="TsOsteocyte"
```

Osteoclasts are large cells (50 - 120 um) with multiple nuclei. Users should specify the size of the cell, the number of nuclei and the size of the nuclei:

```
s:Ge/MyCell/Type="TsOsteoclast"
d:Ge/MyCell/CellRadius=50. um

#Nuclei
d:Ge/MyCell/Nucleus/NucleusRadius=5. um
i:Ge/MyCell/Nucleus/NumberOfNuclei=5
```
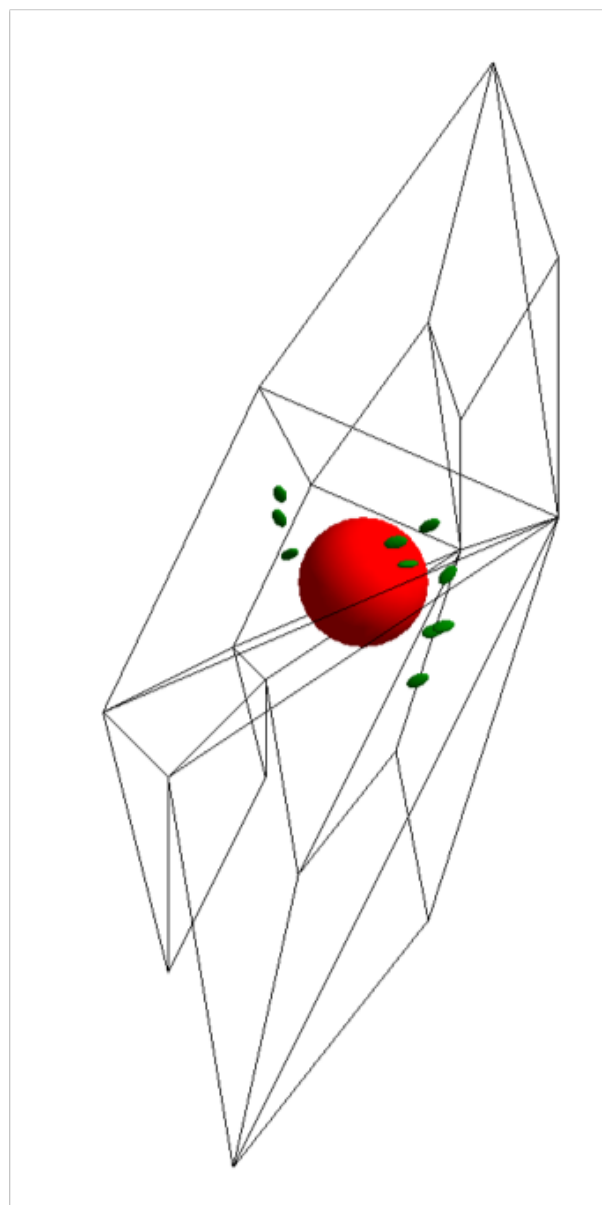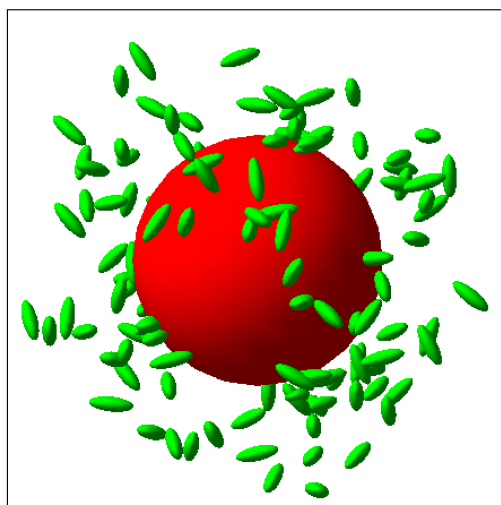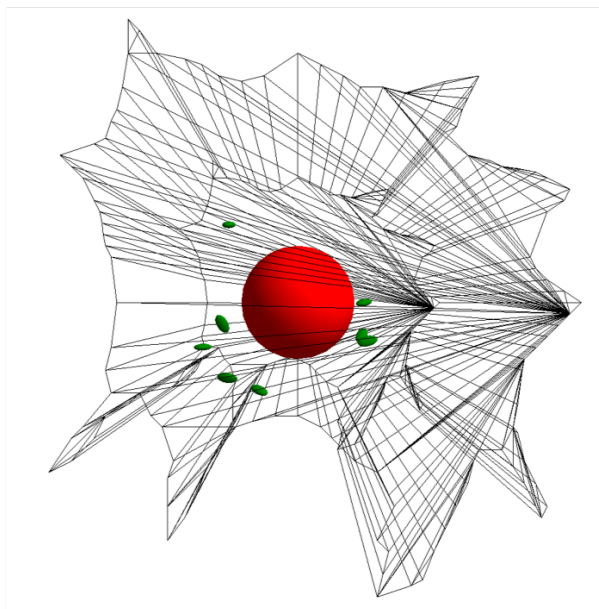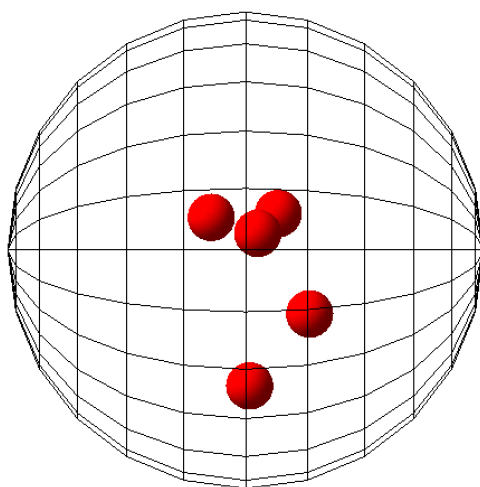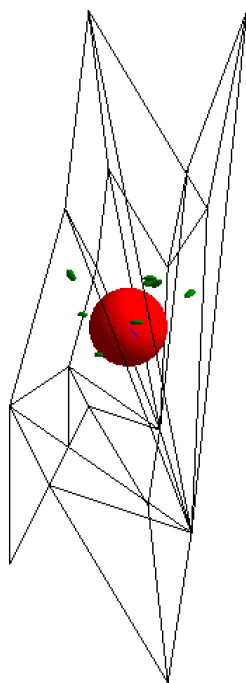
1.8.6 Blood Cells

Red blood cell (RBC) and lymphocyte geometry extensions are available in TOPAS-nBio.
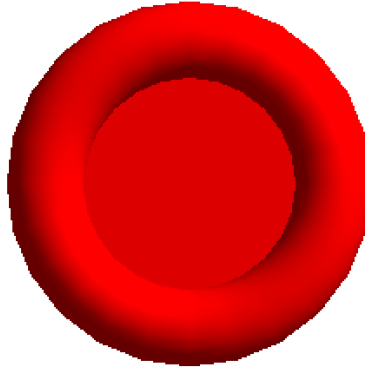
The red blood cell requires users to specify its radius and width (of the thickest section). The cell is modeled as a torus. Generally the radius of these cells are 6-8 um and the thickness of the torus is 1-3 um. Red blood cells do not contain any organelles:

```
s:Ge/MyCell/Type="TsRedBloodCell"
d:Ge/MyCell/RBCRadius=6 um
d:Ge/MyCell/RBCWidth=2 um
```
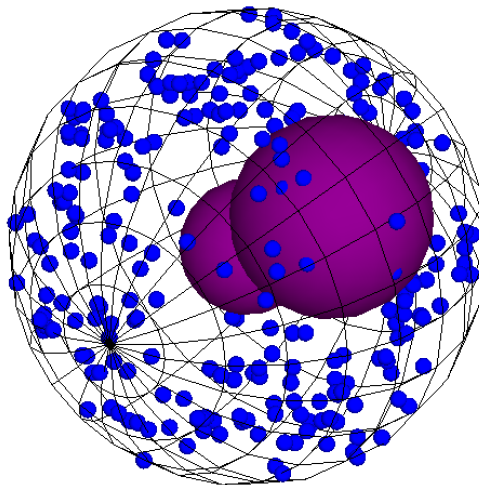
Basophils are white blood cells that have 2-3 lobed nucleus and contain many granules. Since the nucleus is generally bilobed, the model nucleus has two lobes and users need to specify the radius of the cell. The model also has the option of including granules throughout the cytoplasm with a default radius of 0.25 um, users should specify the number of granules:

```
s:Ge/MyCell/Type="TsBasophil"
d:Ge/MyCell/BasophilRadius=7.0 um

#Optional: include granules
i:Ge/MyCell/Granule/NumberOfGranules = 200
```
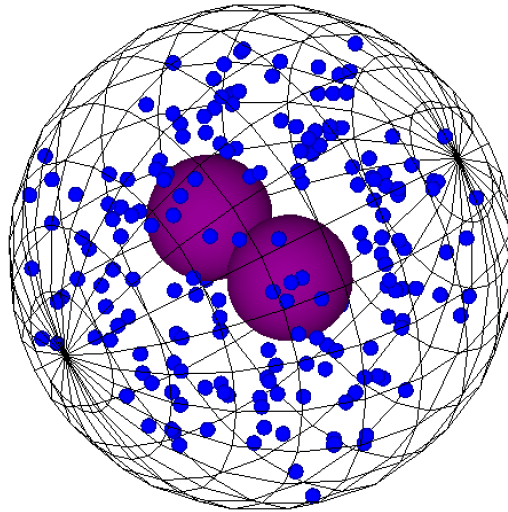
Eosinophils are white blood cells that are bi-lobed, also containing granules. The model also has the option of including granules throughout the cytoplasm with a default radius of 0.25 um, users should specify the number of granules:

```
s:Ge/MyCell/Type="TsEosinophil"
d:Ge/MyCell/EosinophilRadius=8.0 um

#Optional: include granules
i:Ge/MyCell/Granule/NumberOfGranules = 200
```
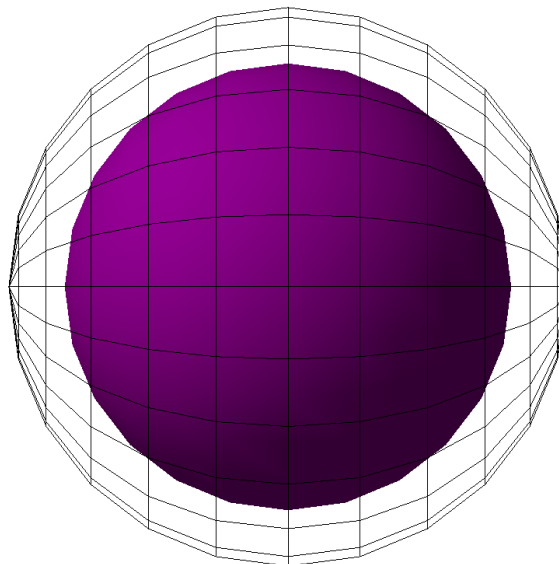
Lymphocytes are small white blood cells (leukocyte) with a single large nucleus. Users have to specify the cell radius.

Nucleus radius may also be set, if not set by the user, the default radius is 4 um:

```
s:Ge/MyCell/Type="TsLymphocyte"
d:Ge/MyCell/LymphocyteRadius=5.0 um

s:Ge/MyCell/Nucleus/NucleusRadius=4.5 um
```
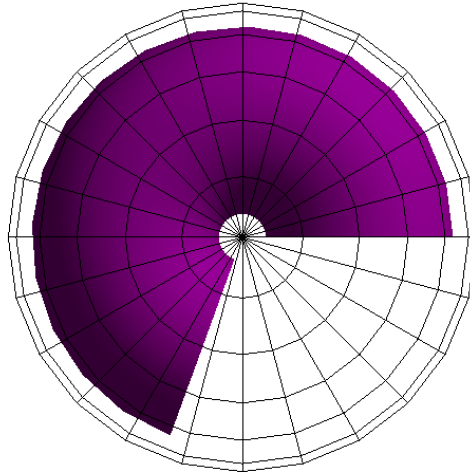
Monocytes are also white blood cells with a kidney-shaped nucleus. Users need to specify the cell radius:

```
s:Ge/MyCell/Type="TsMonocyte"
d:Ge/MyCell/MonocyteRadius=10.0 um
```
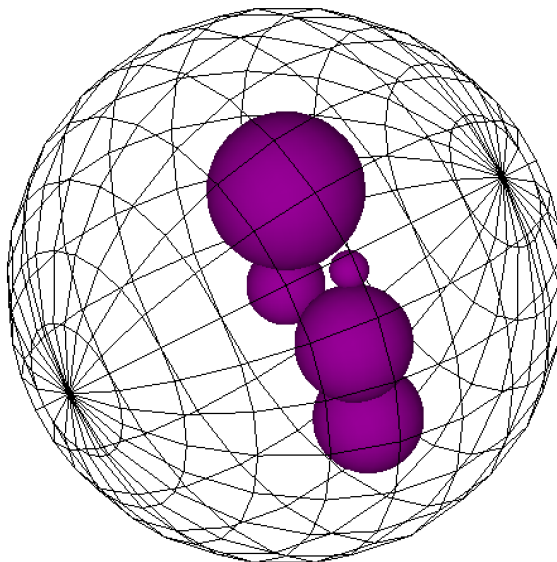
Neutrophil are white bloods cells with a multi-lobed nucleus (3-5 lobes). Users need to specify the cell radius. The model contains a 5 lobed nucleus:

```
s:Ge/MyCell/Type="TsNeutrophil"
d:Ge/MyCell/NeutrophilRadius=7.0 um
```

1.8.7 Neurons
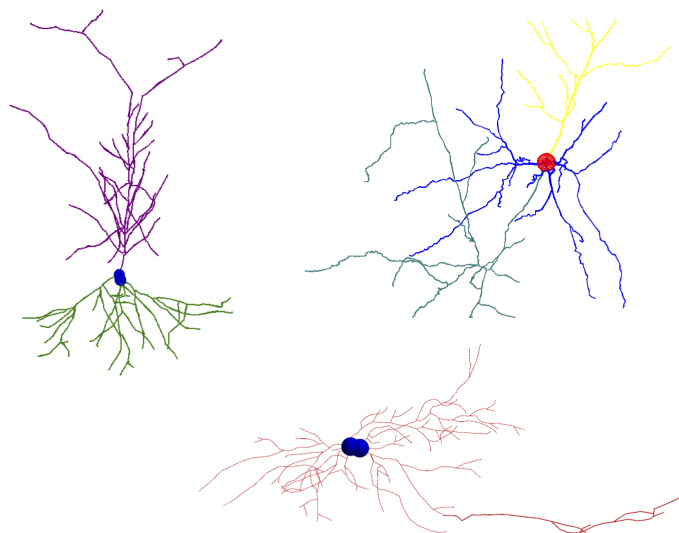
In order to model realistic representations of the numerous types of neurons and supporting glial cells in the central nervous system, TOPAS-nBio has an interface to the NeuroMorpho neuron database. The database contains over 100,000 neuron and glial geometries in 40 different brain regions for several different species, including rodent and human. To model a cell structure from the database, users need to download the standardized ASCII data file (in the SWC open source format for storing neuron morphologies) of the specific neuron or glial cell they wish to simulate. The standard SWC format is a text file starting with a free-text header section (denoted by the symbol #) and contains a matrix of 7 columns below the header. The standard format defines four neuron components with an integer value (1 – soma, 2 – axon, 3 – basal dendrite and 4 – apical dendrite) while values of 5+ are used for custom parameters. Note some formats extend on the standard format (SWC++) and include fork and end points as values 5 and 6, respectively.

To simulate the neuron, specify the name of the SWC file, for example:

```
s:Ge/Neuron/Type="TsNeuroMorpo"
s:Ge/Neuron/NeuroMorpoFileName="NMO_00943_prc.txt"
```

A ntuple scorer specifically for neuron structures is also available:

```
s:Sc/NeuronScorer/Quantity    = "NtupleForNeuron"
```

1.8.8 Cell Culture
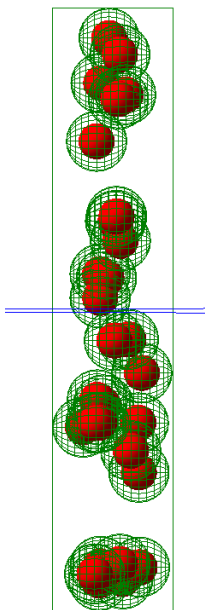
TsCellCulture is a geometry extension for filling a rectangular volume with spherical cells, with a central nucleus. Users should specify the size of the container volume, the radius of the spherical cell and the radius of the spherical nucleus. The total number of cells also has to be specified:

```
s:Ge/MyCulture/Type="TsCellCulture"
s:Ge/MyCulture/Material="G4_WATER"
s:Ge/MyCulture/Parent="World"
d:Ge/MyCulture/Container_HLX= 100 um
d:Ge/MyCulture/Container_HLY= 100 um
d:Ge/MyCulture/Container_HLZ= 20 um
i:Ge/MyCulture/NumberOfCells = 20
d:Ge/MyCulture/CellRadius=10 um
d:Ge/MyCulture/NucleusRadius= 6 um
```

An example scoring extension is also provided:

```
s:Sc/CultureScorer/Quantity = "NtupleForCulture"
```

1.9 Cell Models with Organelles and targeted Nanoparticles

The TsSphericalCellSphericalNP model allows to simulate nanoparticles within cells together with their nucleus, mitochondria, and the cell membrane. The nanoparticles can be distributed randomly within the cytosol, or being additionally located at the surface of different cell organelles.

1.9.1 Background

The dose enhancement by metallic nanoparticles can increase the biological effectiveness of radiation damage in biomolecules and tissue. To apply them effectively as radiosensitizer during cancer therapy their influence on the locally delivered dose has to be determined. Hereby, the locations of the nanoparticles within an irradiated cell influence the energy deposit in the different cell organelles, e.g. the nucleus, mitochondria, membrane and the cytosol. TOPAS-nBio provides users with a framework for simulating cells including their organelle together with nanoparticles. Further details can be found in the related publication https://doi.org/10.1038/s41598-021-85964-2

1.9.2 Spherical Cell

The TsSphericalCellSphericalNP component is a model of a spherical cell with the option of including organelles and nanoparticles.
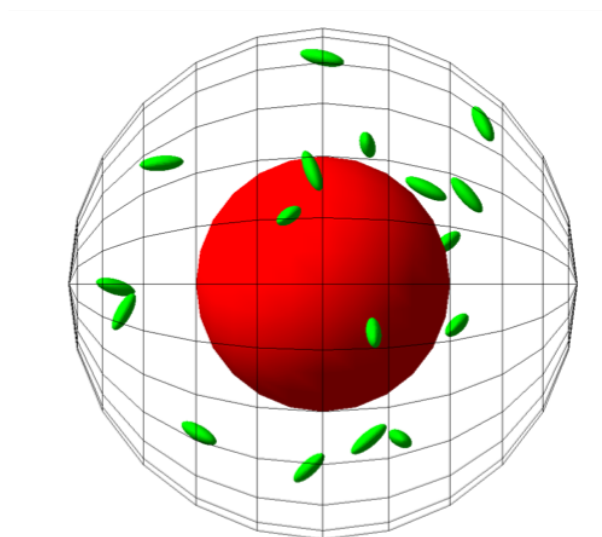
To create the cell model specify the component name as well as the radius of the cell by defining:

```
s:Ge/MyCell/Type="TsSphericalCellSphericalNP"
s:Ge/MyCell/Parent="World"
d:Ge/MyCell/CellRadius=6.0 um
```

1.9.3 Nucleus

Users have the option to include a nucleus. Specify the radius to add the nucleus to the cell:

```
d:Ge/MyCell/Nucleus/NucleusRadius= 3.3 um
s:Ge/MyCell/Nucleus/Color="red"
s:Ge/MyCell/Nucleus/DrawingStyle="solid"
```

The nucleus position within the cell can be edited using:

```
d:Ge/MyCell/Nucleus/translateX = 0.2 um
d:Ge/MyCell/Nucleus/translateY = 0.0 um
d:Ge/MyCell/Nucleus/translateZ = 0.1 um
```

1.9.4 Mitochondria

Mitochondria can also be placed randomly in the cell, the radius and the number of mitochondria are specified in the parameter file:

```
i:Ge/MyCell/Mitochondria/NumberbOfMitochondria=20
d:Ge/MyCell/Mitochondria/r=0.5 um
```

1.9.5 Membrane

A membrane can be added to the cell by defining the thickness:

```
d:Ge/MyCell/Membrane/Thickness = 10.0 nm
```

1.9.6 Randomly distributed Nanoparticles
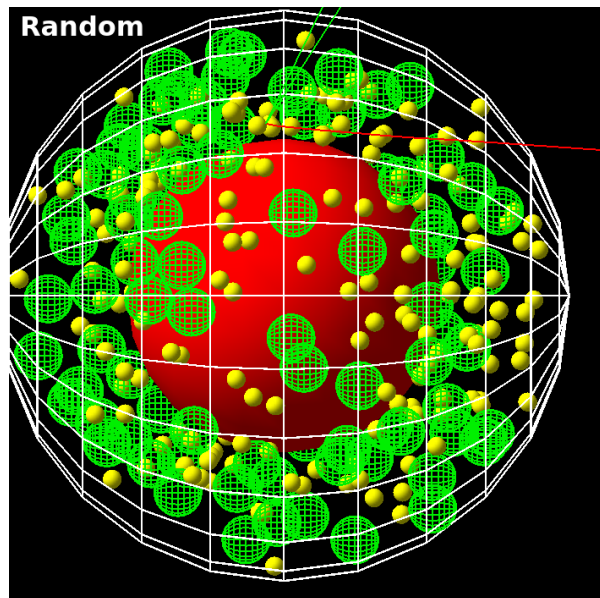
Nanoparticles can be distributed randomly within the cytosol by the following commands:

```
i:Ge/MyCell/Nanoparticle/NumberOfNanoparticles = 1000000
d:Ge/MyCell/Nanoparticle/r = 5 nm
s:Ge/MyCell/Nanoparticle/Material = "Gold"
s:Ge/MyCell/Nanoparticle/Color = "yellow"
s:Ge/MyCell/Nanoparticle/DrawingStyle = "solid"
```

These nanoparticles are not overlapping and always placed outside of the nucleus, mitochondria and cell membrane.

1.9.7 Nanoparticles targeting the Nucleus
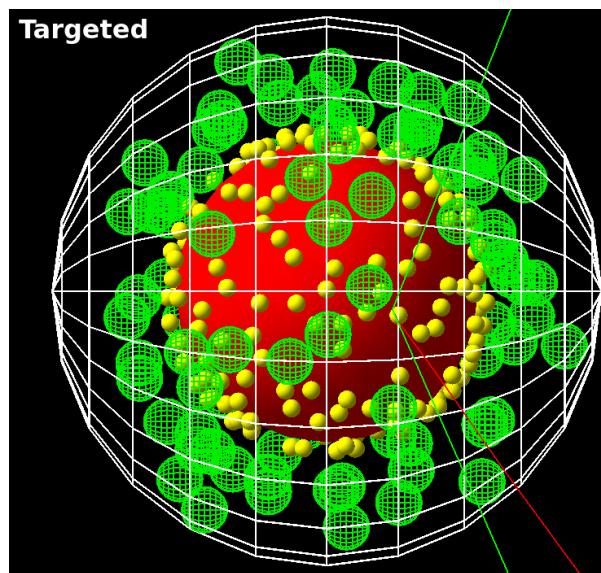
Nanoparticles located at the surface of the nucleus can be added by:

```
i:Ge/MyCell/Nanoparticle/NumberOfNanoparticlesAtNucleus = 10000
```

1.9.8 Nanoparticles targeting the Mitochondria

Nanoparticles located at the surface of different mitochondria can be added by:

```
i:Ge/MyCell/Nanoparticle/NumberOfNanoparticlesAtMitochondria = 20000
```

1.9.9 Combination of different Nanoparticle locations

The amount nanoparticles within the cytosol, the nucleus and at the mitochondria can be defined independently. The following example would create 1000 nanoparticles randomly distributed within the cytosol, 2000 at the surface of the nucleus, and 5000 at the surfaces randomly distributed over all mitochondria:

```
i:Ge/MyCell/Nanoparticle/NumberOfNanoparticles = 1000
i:Ge/MyCell/Nanoparticle/NumberOfNanoparticlesAtNucleus = 2000
i:Ge/MyCell/Nanoparticle/NumberOfNanoparticlesAtMitochondria = 5000
```

1.9.10 Simulation speed

When many nanoparticles are simulated standard overlap checking can become very slow. Since the TsSphericalCell-SphericalNP model performs an analytical overlap check which is much faster than the standard Topas overlap check, the latter one can be deactivated to increase the speed of geometry construction substantially. This can be achieved by:

```
b:Ge/CheckForOverlaps = "False"
b:Ge/CheckInsideEnvelopesForOverlaps = "False"
```

For details of this parameters please compare section 7.3 of the Topas documentation.

1.9.11 Scoring

An example scoring extension is provided which scores individual energy deposit events in all subcomponents of the cell:

```
s:Sc/OrganelleScorer/Quantity = "OrganelleScorer"
s:Sc/OrganelleScorer/Component = "MyCell"
```

1.9.12 Literature

If you use this extension please cite the following article which provides additional details:

> Hahn, M.B., Zutta Villate, J.M. (2021). Combined cell and nanoparticle models for TOPAS to study radiation dose enhancement in cell organelles. Sci Rep 11(1): 6721. PMID: 33762596. PMCID: PMC7990972. https://doi.org/10.1038/s41598-021-85964-2

1.10 DNA Models

Undeniably the nucleus and the genome it contains is the primary radiation target in the cell and of vital importance in most radiobiology studies. Accurate models of the spatial and temporal distribution of radiation induced damage, in the form of DSBs or lesions, on the full DNA structure and its successive evolution is essential for formulating a full understanding of the biological effects of radiation.

1.10.1 Simple Cylindrical Targets
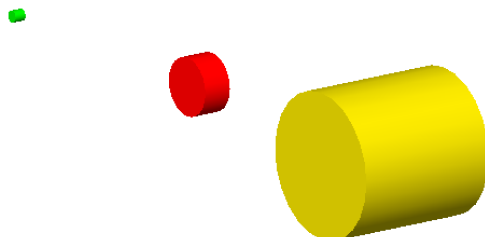
DNA has been modeled with Monte Carlo simulations for the last three decades. Originally, energy depositions were modeled within simple cylindrical targets representing DNA stands, nucleosomes or chromatin fibers in order to compare to the experimental microdosimetry data [Nikjoo1989] [Nikjoo1991].

Three simple cylindrical target geometries are available, these represent a chromatin fiber (yellow), nucleosome (red) and DNA strand (green), respectively:

```
s:Ge/MyChromatin/Type="TsCylindericalChromatin"
s:Ge/MyNucleosome/Type="TsCylindericalNucleosome"
s:Ge/MyDNA/Type="TsCylindericalDNA"
```

The size of the cylinders are set to fixed sizes of the representative geometry. For the DNA strand this is a length of 2 nm with a diameter of 2 nm, the nucleosome has a length of 10 nm and diameter of 5 nm while the chromatin fiber has a length of 25 nm and diameter of 25 nm. However, users do have the option of specifying new dimensions for each component with the following parameters:

```
d:Ge/MyChromatin/ChromatinHalfLength=12.5 nm
d:Ge/MyChromatin/ChromatinRadius=12.5 nm

d:Ge/MyNucleosome/NucleosomeHalfLength=5 nm
d:Ge/MyNucleosome/NucleosomeRadius=2.5 nm

d:Ge/MyDNA/DNAHalfLength=1 nm
d:Ge/MyDNA/DNARadius=1 nm
```

1.10.2 Charlton DNA Model
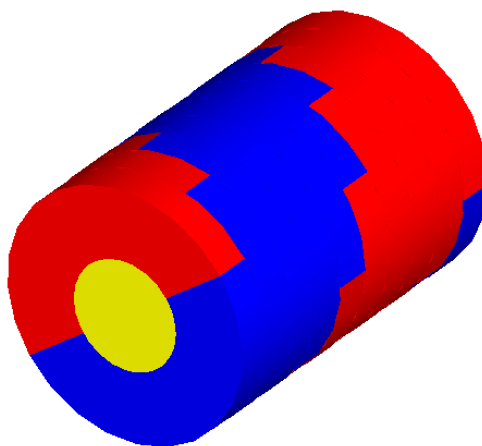
The TsCharltonDNA model is based on a simple combination of cylinders. More details can be found in Charlton et al. (1989) [Charlton1989]. The inner cylinder has a diameter of 1 nm and length of 0.34 nm, representing the basepair of the DNA strand. Two surrounding half-cylinders represent the sugar phosphate backbone of the DNA; these are each rotated by 36 degrees on adjacent base-pairs. Users have to specify the number of base pairs to be simulated:

```
s:Ge/MyDNA/Type="TsCharltonDNA"
i:Ge/MyDNA/NumberOfBasePairs=10
```

1.10.3 Linear DNA Model

A similar model to the above Charlton DNA model is called TsLinearDNA which also models the DNA basepair as a cylinder of diameter 1 nm and length 0.34 nm, but models the sugar phosphate backbone as two quarter cylinders opposite each other with an outer diameter of 2.37 nm, rotated by 36 degrees on each subsequent basepair:

```
s:Ge/MyDNA/Type="TsLinearDNA"
i:Ge/MyDNA/NumberOfBasePairs=10
```
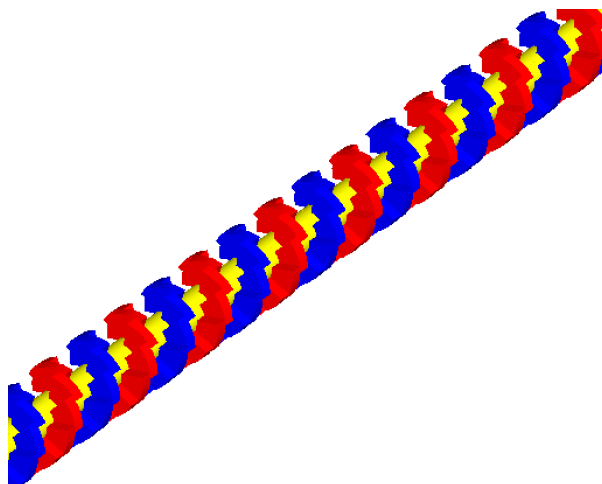
1.10.4 Circular Plasmid
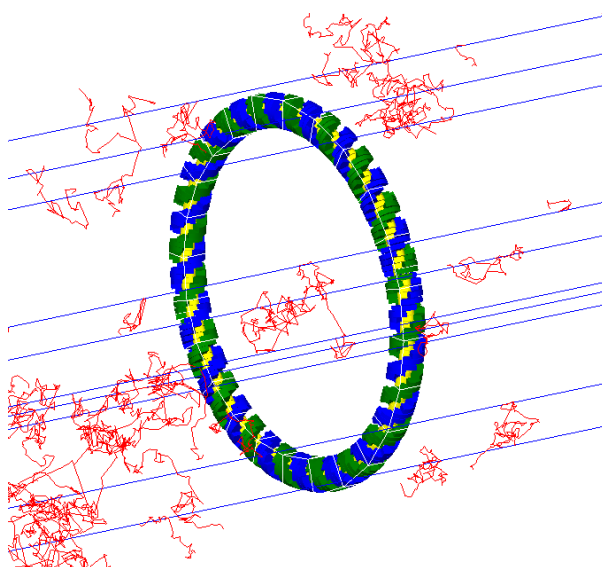
TsPlasmid is a simple circular plasmid. The DNA has the same structure as the linear DNA model but arranged in a ring. Each DNA segment consists of a central cylindrical basepair (diameter 1 nm and length 0.34 nm) surrounded by two quarter cylinders (diameter 2.37 nm) for the sugar phosphate backbone. Users have to specify the number of basepairs:

```
s:Ge/CircularPlasmid/Type      = "TsPlasmid"
#Define the number of base pairs in the ring
i:Ge/CircularPlasmid/NumberOfBasePairs = 2000
```

1.10.5 Supercoiled Plasmid
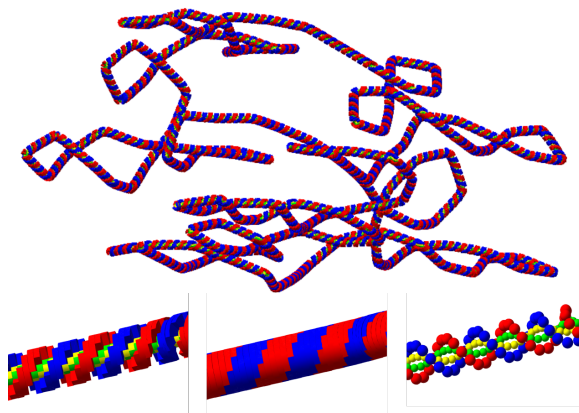
TsSupercoiledPlasmid is a supercoiled plasmid defined from an ascii file that contains the vertex position (in nm) of a deformed polygon that forms the supercoiled path. Different configurations of DNA can be chosen: half cylinders (HalfCylinder), quarter cylinders - similar to the circular plasmid (QuarterCylinder) or spheres (Sphere). The DNA consists of the sugar phosphate backbone and base. Users have to specify the file name of the ascii file that contains the vertex of the deformed polygon forming the supercoiled plasmid. We provide two files pBR322_a.xyz and pBR322_b.xyz. For these files, supercoiling is achieved using the Vologodskii methodology [Vologodskii1994]:

```
s:Ge/SupercoiledPlasmid/Type      = "TsPlasmidSupercoiled"
#Define the file name
i:Ge/SupercoiledPlasmid/FileName = "pBR322_a.xyz"
# Define the DNA model
s:Ge/SupercoiledPlamid/DNA_Model = "QuarterCylinder" # HalfCylinder or Sphere
```

If each coordinate in the ascii file belongs to a single basepair of the plasmid, then the following must be set:

```
b:Ge/SupercoiledPlamid/SegmentPlasmidPath = "False" # Default False
```

Otherwise, the deformed polygon is segmented using units of 0.34 nm and smoothed.

1.10.6 IRT Supercoiled Plasmid
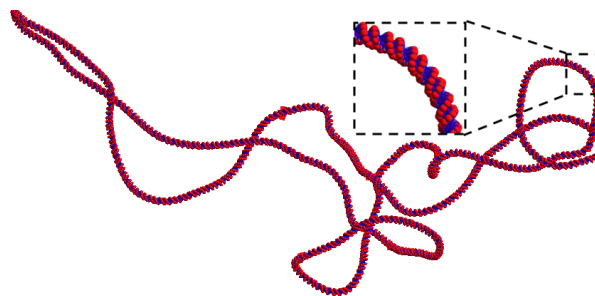
TsIRTSupercoiledPlasmid is a supercoiled plasmid geometry defined from a DnaFabric [Meylan2016] file (.fab2g4dna) that contains the plasmid information in a volume by volume manner. This geometry can be used for regular energy deposit simulations to account for DNA Strand Breaks due to physical interactions and for indirect DNA Strand Breaks using the IRT scorers. The geometry is made using six cut spheres using the solid Booleans method from Geant4 which increases the geometry initialization time but gives a smooth plasmid. The following parameters are necessary for the use of this geometry, the enclosure radius, the DnaFabric input file and a plasmid location and rotation:

```
s:Ge/IRTSupercoiledPlasmid/Type = "TsIRTPlasmidSupercoiled"
d:Ge/IRTSupercoiledPlasmid/R = 0.5 um
s:Ge/IRTSupercoiledPlasmid/InputFile = "pUC19.fab2g4dna"
s:Ge/IRTSupercoiledPlasmid/EnvelopeFile = "Plasmid_Envelope.xyz"
i:Ge/IRTSUpercoiledPlasmid/NumberOfPlasmids = 5
```

The `Plasmid_Envelope.xyz` file can be done by hand by a user, it is a file containing the position x, y and z and the rotations of a set of plasmids. However, we recommend the use of a pre simulation setup tool called TsIRTSupercoiled-PlasmidSetup to aid in this task. This tool is further explained in *IRT Supercoiled Plasmid Setup*. The number of lines in the `Plasmid_Envelope.xyz` file must be greater or equal to the `NumberOfPlasmids` parameter.

We provide one pUC19 plasmid in DnaFabric format called "pUC19_20C_3Sigma_ALP_Corrected.fab2g4dna" generated using Brownian Dynamics [Ermak1978] with a temperature of 20 degrees Celsius and -0.03 super helix density. This plasmid is the one shown at the start of this section.

1.10.7 Solenoid Chromatin Fiber Model

TsSolenoidFiber is a chromatin fiber model, based on a solenoid geometry, described in Henthorn et al. (2017) [Henthorn2017].
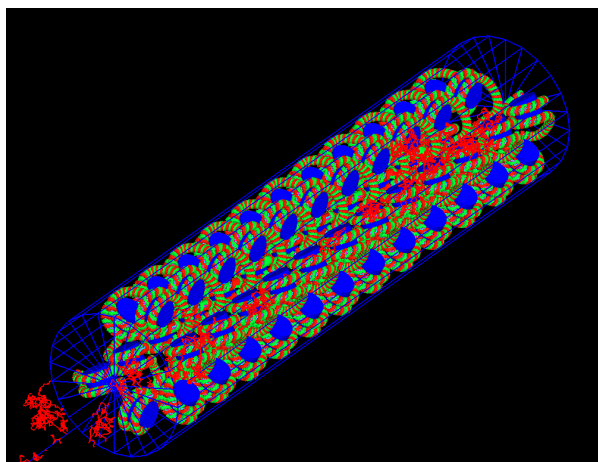
By default the model of the double helix has backbones and bases modeled as spheres wrapped around a cylindrical histone protein. The radius of the base sphere is 0.208 nm, while the backbone sphere had a radius of 0.240 nm. Users can also specify to build the DNA backbone and base volumes as half cylinders, described by Charlton, Nikjoo and Humm (1989) [Charlton1989], or as quarter cylinders, as described by Bernal and Liendo (Med. Phys. 2009) [Bernal2009]. The histone radius is 3.3 nm with a length of 5.7 nm. The double helix structure is wrapped around cylindrical histones in 1.65 left-handed turns to form the nucleosome. These are arranged in a solenoid chromatin conformation, with 6 histones per turn of the fiber. Each fiber contains 61 histones and ~10.8 kbp of DNA.

Users can set the fiber radius and length:

```
d:Ge/Fiber/FiberHalfLength = 80.0 nm
d:Ge/Fiber/FiberRadius = 18.5 nm
```

Users can change the number of histones per turn:

```
i:Ge/Fiber/NumberOfHistonesPerTurn = 6
```

Users can change the DNA volume geometry, by including one of the below:

```
s:Ge/Fiber/DNA_Model = Sphere            #Described by Bertolet et al. (2022)
s:Ge/Fiber/DNA_Model = HalfCylinder      #Described by Charlton, Nikjoo and Humm (1989)
s:Ge/Fiber/DNA_Model = QuarterCylinder   #Described by Bernal and Liendo (2009)
```

Note that as of v1.1, the sphere model is slightly different from the one in v1.0. Also, different models for the hydration shell around these three DNA models have been added. See Bertolet et al. 2022 [Bertolet2022] for more details. Also,

Two different scorers are provided for the TsSolenoidFiber; NtupleForBasePair and NtupleForSpatial. Both of these are described in more detail here.

1.10.8 Geant4-DNA Full Nuclear Model
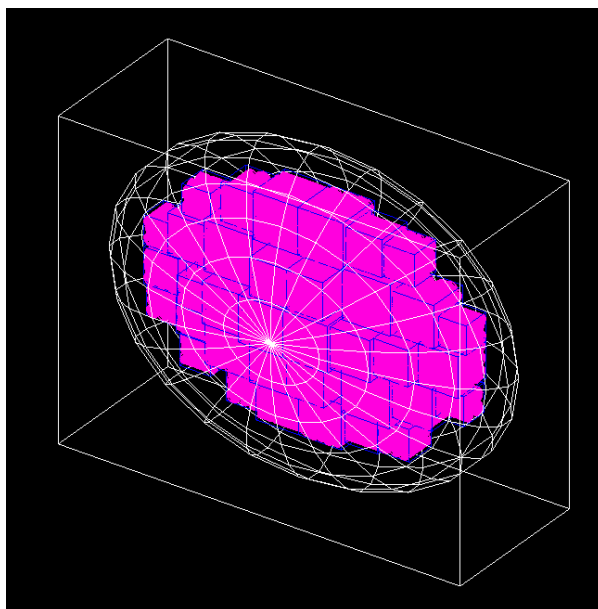
The Geant4-DNA model represents the whole genome (6 x 10^9 bps) within an ellipsoid nucleus for a cell in the G0/G1 phase and is further described in Dos Santos M et al. (2014) [DosSantos2014].

The DNA double helix strands are composed of two separate strands built from the union of spheres. The sugar-phosphate backbone of the DNA has a total diameter of 2.16 nm and the DNA base, within the backbone structure, has a diameter of 0.34 nm. The double helix is used to form a nucleosome which consists of a core histone protein (cylinder with diameter 6.5 nm and length of 5.7 nm) wrapped by two turns of the DNA double helix (a total of 200 bps). The chromatin fiber is represented by a cylinder of diameter 30.8 nm and length 161 nm. Each fiber contains 90 nucleosomes which are placed on a helix. To represent the chromatin loops, 7 chromatin fibers are arranged in a "flower" shape. The flower has 7 "petals", with each composed of 4 fibers arranged in a diamond. The flower substructures fill 23 chromosome territories, each represented by a box of varying size.

Users need to include the files of data specifying the position of the chromosome territories within the nucleus. These files are named chromo*.dat (24 files total).

To build the full DNA hierarchy, the flags to specify the building of the chromatin fibers and the basepairs should be set to true:

```
s:Ge/MyCell/Type="tsdna"
b:Ge/MyCell/BuildChromatinFiber="true"
b:Ge/MyCell/BuildBases="true"
```

1.10.9 References

1.11 Nucleus Model

The last release of TOPAS-nBio provides a model of a cell nucleus as a sphere uniformly filled with DNA. The nucleus is created and dimensionated by the parameter:

```
s:Ge/Nucleus/Type                   = "TsNucleus"
s:Ge/Nucleus/Parent                 = "World"
d:Ge/Nucleus/NucleusRadius          = 4.65 um
```

The built DNA is structured in fibers as shown in DNAModels readthedocs.
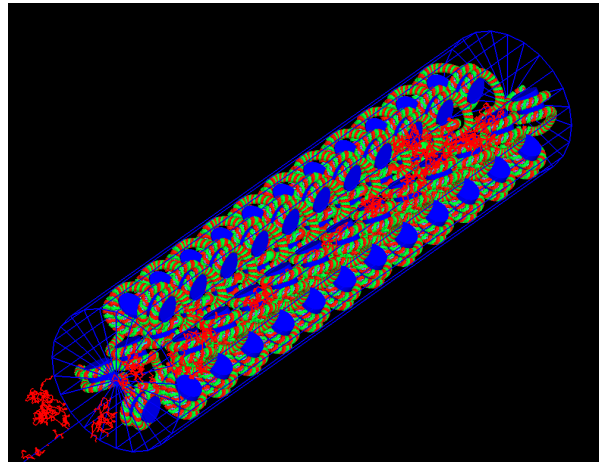
1.11.1 DNA models

Fibers are composed of linked double helix with backbones and bases that can be modeled as quarter cylinders, half cylinders or spheres (see DNAModels readthedocs). This can be specified by the user using the parameter:

```
s:Ge/Nucleus/DNAModel = "QuarterCylinder"
```

and the options "HalfCylinder" and "Sphere", respectively. Besides bases and backbones, hydration shells around double helices can be added to account for close ionizations that may be translated into backbone breaks (see Nucleus Scorer readthedocs). The thickness of the hydration shell can be controlled using:

d:Ge/Nucleus/HydrationShellThickness = 0.16 nm

DNA is wrapped around cylindrical histones (length of 3.3 nm and length of 5.7 nm), which in turn form a solenoid chromatin using 6 histones per turn of the fiber. The length and the radius of a fiber can be specified by users:

```
d:Ge/Nucleus/FiberRadius = 18.5 nm
d:Ge/Nucleus/FiberLength = 120.0 nm
```

1.11.2 Hilbert curve and geometry information

These cylindrical fibers are linked using the Hilbert curve to fill the space with linked DNA structures. The files 'supportFiles/HilbertPoints_iteration*.dat' are provided, containing the position of the vertices of several iterations of the Hilbert curve to connect different fibers. For example, the first iteration is represented by

The Hilbert curve can be fractally repeated through different layers, generating a voxel like the following one:

Then, this voxel can be repeated into the 3D space to fill the whole nucleus. Users can control these features through the parameters:

```
s:Ge/Nucleus/HilbertCurveFileName      = "supportFiles/HilbertPoints_iteration1.dat"
i:Ge/Nucleus/HilbertCurveLayer         = 4
i:Ge/Nucleus/HilbertCurve3DRepeat      = 30
```

where 'HilbertCurve3DRepeat' represents the number of repetitions in a single direction, so if 30 is specified, a total of 30x30x30 = 27000 voxels is obtained. The size of these voxels is indirectly controlled by the previous 5 parameters, considering that the distance between points of a Hilbert curve is given by the fiber length plus 40 nm. The spherical nucleus intersect then this rectangular strucutre of voxels, and the geometrical information about which parts of the DNA is contained within the nucleus and the assignation of each base pair to different chromosomes needs to be specified in separated files ('supportFiles/Geoinfo.txt', 'supportFiles/CopyNoTable.txt' and 'supportFiles/signedCHVoxel.txt') when scoring damage to the nucleus (see Nucleus Scorer readthedocs). Therefore, to modify any of the previous parameters is not recommended, and should be only performed if users can make sure that the geometrical information in those files is updated.

The provided configuration gives a nucleus with 6.078 Gbp, as each fiber contains 15,150 bp, each voxel 4.242 Mbp. 14328 of the voxels are contained within the nucleus.

1.11.3 Optional building of substructures and materials for the scorer

Users can control whether they want to include bases, backbones, hydration shells and histones working as scavengers of chemical reactive species using the parameters:

```
b:Ge/Nucleus/AddBases                  = "true"
b:Ge/Nucleus/AddBackbones              = "true"
b:Ge/Nucleus/AddHydrationShell         = "true"
```

In order for the scorer to account hits in the desired structures of the DNA, the materials for bases, backbones, hydration shells of both strands and for the histones to work as scavengers need to be different from 'G4_WATER' used for the rest of the nucleus, even though if they are just copies, as specified in Nucleus Scorer readthedocs. In the provided example, we use the following configuration:

```
s:Ma/G4_HistoneMaterial/CloneFromMaterial    = "G4_WATER"
d:Ma/G4_HistoneMaterial/CloneWithDensity     = 1.407 g/cm3
s:Ge/Nucleus/Histone/Material                = "G4_HistoneMaterial"

s:Ma/G4_BaseMaterial/CloneFromMaterial       = "G4_WATER"
d:Ma/G4_BaseMaterial/CloneWithDensity        = 1.0 g/cm3
s:Ge/Nucleus/Base1/Material                  = "G4_BaseMaterial"
s:Ge/Nucleus/Base2/Material                  = "G4_BaseMaterial"
```

(continues on next page)

```
s:Ma/G4_BackboneMaterial/CloneFromMaterial  = "G4_WATER"
d:Ma/G4_BackboneMaterial/CloneWithDensity   = 1.0 g/cm3
s:Ge/Nucleus/Backbone1/Material        = "G4_BackboneMaterial"
s:Ge/Nucleus/Backbone2/Material        = "G4_BackboneMaterial"

s:Ma/G4_WATER_MODIFIED/CloneFromMaterial    = "G4_WATER"
d:Ma/G4_WATER_MODIFIED/CloneWithDensity     = 1.0 g/cm3
s:Ge/Nucleus/HydrationShell1/Material  = "G4_WATER_MODIFIED"
s:Ge/Nucleus/HydrationShell2/Material  = "G4_WATER_MODIFIED"
```

1.11.4 Rotating nucleus

As of v1.1, users can rotate the nucleus arbitrarily for different runs. This can be controlled by the parameter:

```
b:Ge/Nucleus/RotateNucleusForEachRun        = "false"
```

Note that nucleus will keep the same position for all the events in the same run.

1.12 Other Models

Recent experimental evidence is challenging the DNA-centric model of radiobiology and suggesting the full effect of radiation may not be initiated from DNA damage exclusively. Experiments in which the cytoplasm is irradiated, while the nucleus is spared, suggest that radiation induced damage in extra-nuclear cell structures may also be of importance for developing a comprehensive model of the cellular response to radiation. Some targets, other than DNA, are also included in TOPAS-nBio.

1.12.1 Membranes
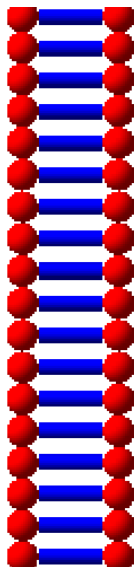
A lipid bilayer is created in TOPAS-nBio consisting of two hydrophilic heads, each a sphere of radius ~2 nm, and a tail region consisting of a cylinder of radius ~1 nm and length of ~2 nm. The total thickness of the membrane is between

7 - 10 nm. All dimensions are changeable parameters:

```
d:Ge/MyCell/LipidHeadRadius=1. nm
d:Ge/MyCell/LipidTailHalfLength=3. nm
d:Ge/MyCell/LipidTailRadius=0.5 nm
```

The membrane can be formed as a ring or a layer generated by the base elements i.e. the lipid unit:

```
s:Ge/MyCell/Type="TsMembraneLayer"

//or

s:Ge/MyCell/Type="TsMembraneRing"
```

For the ring geometry the number of lipids forming the ring should be specified:

```
i:Ge/MyCell/NumberOfLipids=50
```
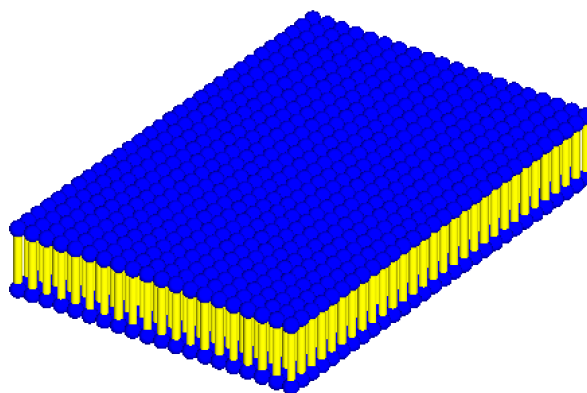

A membrane layer configuration is also available using the TsMembraneLayer extension geometry. This forms a grid of the lipid unit and the number of rows and columns should be specified:

```
i:Ge/MyCell/NumberOfRows=20
i:Ge/MyCell/NumberOfColumns=30
```

Transmembrane proteins, which represent ion channels or communication proteins can also be included in the membrane layers.

Ion channels are generally formed by three or more protein subunits. The TsIonChannel extension models a complex ion channel consisting of 5 protein sub-units of length 40 nm (modeled as cylinders, each with a 5 nm radius) arranged in a circle within the membrane layer. Users need to specify the bilayer parameters as well as the number of rows and columns in the membrane layer:

```
s:Ge/MyCell/Type="TsIonChannel"

i:Ge/MyCell/NumberOfRows=50
i:Ge/MyCell/NumberOfColumns=50
```

Communication proteins consist of a single protein structure and are modeled as a single cylinder with the TsChannel extension. The number of rows and columns in the membrane should be specified, as well as the inner and outer radii of the membrane channel (Rmin and RMax, respectively) and the half-length of the protein channel:
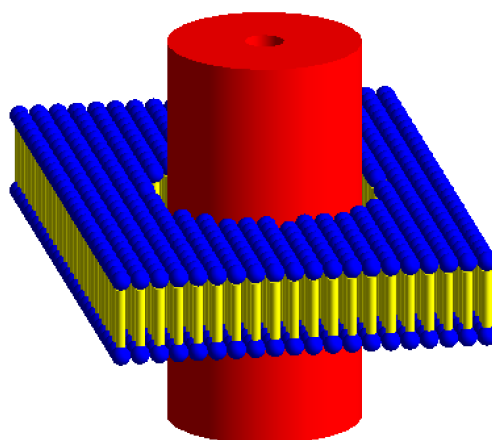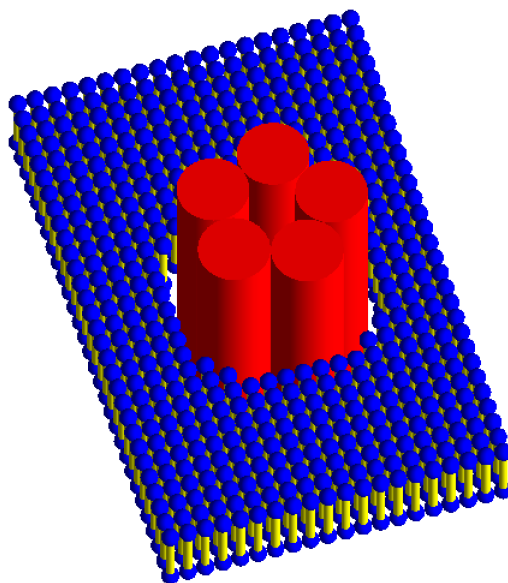
```
s:Ge/MyCellType="TsChannel"

i:Ge/MyCell/NumberOfRows=100
i:Ge/MyCell/NumberOfCols=50

d:Ge/MyCell/ChannelRmax = 10 nm
d:Ge/MyCell/ChannelRmin = 2 nm
d:Ge/MyCell/ChannelHalfLength = 20 nm
```

1.12.2 Mitochondria
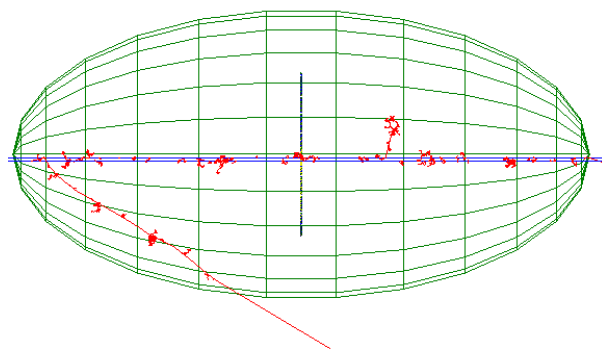
Mitochondria are the only sites of extra-nuclear DNA in eukaryotic cells. Mitochondrial DNA (mt-DNA) in humans contains ~ 16569 bps encoding 37 genes and unlike nuclear DNA, which is linear, mt-DNA is circular.

Mitochondria are generally ellipsoid shaped and can be modeled using the G4Ellipsoid geometry type. The semi-axis lengths (HLX, HLY and HLZ) of the ellipsoid must be specified. mt-DNA may be included in the model, modeled as either a circular or non-circular plasmid using the TsPlasmid extensions, for example:

```
# Mitochondria
s:Ge/MyMito/Type              = "G4Ellipsoid"
d:Ge/MyMito/HLX               = 0.5 um
d:Ge/MyMito/HLY               = 1 um
d:Ge/MyMito/HLZ               = 0.4 um

s:Ge/mDNA/Type     = "tsplasmid"
#Define the number of base pairs in the ring
i:Ge/mDNA/NumberOfBasePairs = 200
s:Ge/mDNA/Parent = "MyMito"
```

1.12.3 Proteins

The protein data bank (PDB) contains over 130,000 biological macromolecular 3D structures, including proteins and nucleic acids. Many of these proteins are essential to normal cellular function, and precise modeling of the spatial distribution in a realistic molecular model can aid in extending our understanding of the effect of radiation.

1.12.4 IRT Supercoiled Plasmid Setup

IRT plasmid Strand Break simulations need the information of the chemical species within the DNA that react in order to properly simulate indirect Strand Breaks. Such information is provided using a `Plasmid.xyz` file. The physical information for direct Strand Breaks is handled by Geant4, which only needs the location and rotation of the plasmid geometries in the form of an `Envelope.xyz` file. The user can create both files by hand or by using an external tool. TOPAS-nBio provides a tool to automatize this process in a pre-simulation using the TsIRTPlasmidSupercoiledSetup geometry. The example `TsDNAPlasmidSetup.txt` illustrates the use this tool. The following parameters must be given to the TsIRTPlasmidSupercoiledSetup component:

```
# Water Envelope Size
d:Ge/plasmid/R = 0.5 um

# Number of Plasmids
i:Ge/plasmid/NumberOfPlasmids = 5

# The DnaFabric file with the plasmid information
s:Ge/plasmid/InputFile  = "pUC19_20C_3Sigma_ALP_Corrected.fab2g4dna"

# The output file
s:Ge/plasmid/OutputFile = "Plasmid_50ugg_Sphere_1um_diameter"
```

The TsPlasmidSupercoiledSetup component will generate two files: `Output_plasmids.xyz` and `Output_envelopes.xyz` which can be used in a TsIRTSupercoiledPlasmid geometry and TsIRTStrandBreaks scorer. It is recomended that when using the TsPlasmidSupercoiledSetup tool, the following parameters should be set as follows:

```
i:So/Demo/NumberOfHistoriesInRun = 0
Ts/NumberOfThreads = 1
```

1.13 Introduction

TOPAS-nBio facilitates the use of the physical and chemical processes available in the Geant4-DNA Toolkit.

TOPAS-nBio further provides additional capabilities:

1. New physics and chemistry lists designed to match experimental G-values as described in our publications *Citations*

2. The possibility to customize physical models using modules involved in the pre-defined physics list.

3. Definition of regions to activate different physics lists, e.g. Geant4-DNA.

4. The use of a variance reduction techniques.

5. Reconfiguration of parameters for the physico-chemical stages.

6. Explicit transport and visualization of the chemical species in the chemical stage.

Here we provide a list of available options for the physics and chemistry settings as well as several examples to retrieve the spatio-temporal information of the physical and chemical tracks in different geometrical components, e.g. via particle tuple or single and double strand breaks.

1.14 Physics Processes

The physical processes of the Geant4-DNA toolkit [Incerti2010] [Bernal2015] [Incerti2018] can be used in TOPAS-nBio to perform track-structure simulations via the modules `g4em-dna` and `g4em-dna_optN` with N = 1,...,8. To use any of these lists, users need to include one of these modules in the modular physics list, e.g.:

```
sv:Ph/Default/Modules = 1 "g4em-dna_opt2"
```

1.14.1 List of Available Modules

It is not trivial to set a default physics list for track-structure Monte Carlo simulations. The lack of experimental measurements at nanoscopic scales makes it difficult to validate of the existing physics models. Typically, experiments are performed in water-gas, allowing detectors to be 1000 times larger than for liquid water, however, with potentially different interaction between the water molecules. New measurements for liquid water at nanoscales as well as a for few other materials are now available and implemented in Geant4-DNA.

Geant-DNA provides several constructors which contain a variety of physics models for scattering processes. Hence, the selection of a suitable physics list is delegated to the users judgment according to the problem they want to tackle. A detailed description of each process and associated model available in Geant4-DNA is shown here. These models are condensed into several Geant4 constructors as shown here The correspondence between the Geant4-DNA physics constructors and the TOPAS modules is shown in the table below. Users who are advanced experts in Geant4 physics can also write their own Geant4 physics modules and plug these into TOPAS through the extensions interface, see OpenTOPAS physics list.

TOPAS Module Name	Geant4 Class Name	Notes
TsEmDNAPhysics	N/A	Allows to customize physics models per process
TsEmDNAChemistry	N/A	Includes revised chemistry parameters
TsEmDNAChemistryExtended	N/A	Includes revised chemistry parameters and an extended set of reactions
g4em-dna	G4EmDNAPhysics	Default Geant4-DNA constructor
g4em-dna_opt1	G4EmDNAPhysics_option1	
g4em-dna_opt2	G4EmDNAPhysics_option2	Accelerated default Geant4-DNA constructor
g4em-dna_opt3	G4EmDNAPhysics_option3	
g4em-dna_opt4	G4EmDNAPhysics_option4	See Kyriakou et al., (2016)
g4em-dna_opt5	G4EmDNAPhysics_option5	
g4em-dna_opt6	G4EmDNAPhysics_option6	See Bordage et al., (2016)
g4em-dna_opt7	G4EmDNAPhysics_option7	
g4em-dna_opt8	G4EmDNAPhysics_option8	
g4em-dna-stationary	G4EmDNAPhysics_stationary	The kinetic energy of the particle is set to its incident value in inelastic processes
g4em-dna-stationary_opt2	G4EmDNAPhysics_stationary_opt2	The kinetic energy of the particle is set to its incident value in inelastic processes
g4em-dna-stationary_opt4	G4EmDNAPhysics_stationary_opt4	The kinetic energy of the particle is set to its incident value in inelastic processes
g4em-dna-stationary_opt6	G4EmDNAPhysics_stationary_opt6	The kinetic energy of the particle is set to its incident value in inelastic processes
g4em-dna-chemistry	G4EmDNAChemistry	Default Geant4-DNA constructor
g4em-dna-chemistry_opt1	G4EmDNAChemistry_opt1	Includes revised chemistry parameters

1.14.2 Physics models per region

A region is a Geant4 concept that allows the use of different production cuts of secondary particles in different parts of the simulated geometry/world. Geant4-DNA extended that capability to use different physical models in different geometry components [Ivanchenko2011]. This allows to delegate the more computationally expensive tracking of detailed particle interactions to specific components while using the condensed-history approach elsewhere. In this way, the simulation can be sped up without compromising accuracy, if the setup is carefully designed. This feature is also available in TOPAS-nBio. In order to use this capability, the first step is to assign all the components where simulations using the Geant4-DNA physics processes are wanted, to a region, e.g.:

```
s:Ge/MyComponent1/AssignToRegionNamed     = "DetailedTransport"
s:Ge/AnotherComponent/AssignToRegionNamed = "DetailedTransport"
```

Subsequently, an electromagnetic standard physics list is defined in a modular way and the Geant4-DNA physics is activated in the region of interest (*DetailedTransport* in this example) by the following parameter:

```
sv:Ph/Default/Modules = 1 "g4em-penelope"
s:Ph/Default/ForRegion/DetailedTransport/ActiveG4EmModelFromModule = "g4em-dna"
```

The example G4DNAModelPerRegion.txt shows a complete implementation of this capability.

1.14.3 Customizable Physics models

TOPAS-nBio provides the flexibility to control the model type involved in each process provided by Geant4-DNA through the module `TsEmDNAPhysics`. To accomplish this task, the energy cut for applying electron capture or electron solvation is automatically readjusted according to the lower energy limit of the physical models. In this way, it is possible, for example, to combine the elastic models from the CPA100 implementation available in `g4em-dna_opt6` with the inelastic models from the Emfietzoglou-based implementation available in `g4em-dna_opt4`:

```
sv:Ph/Default/Modules = 1 "TsEmDNAPhysics"

s:Ph/Default/Electron/SetElasticScatteringModel    = "CPA100"
s:Ph/Default/Electron/SetExcitationModel           = "Emfietzoglou"
s:Ph/Default/Electron/SetIonisationModel           = "Emfietzoglou"
b:Ph/Default/Electron/ActiveVibExcitation          = "True"
b:Ph/Default/Electron/ActiveAttachment             = "True"
```

This feature is supported for mainly for electrons and in a restricted way for protons (only the elastic scattering model WentzelVI can be chosen instead of the default one). The example `ActiveCustomizablePhysics.txt` shows a complete implementation of this capability.

1.14.4 Variance reduction for e- ionization events

Another capability included in the module `TsEmDNAPhysics` is a variance reduction named flagged uniform particle split. This technique performs uniform splitting to secondary electrons produced in ionization events at strategically located regions (defined by the user) within the geometry and assigns a unique flag number, which is inherited by their progeny. The flag permits reclassification of each split event as if they were produced by independent histories. This method reduces the variance by improving the statistics of secondary electrons, while keeping the time increase small compared to the generation of additional particles, by only producing additional electrons in strategically selected regions [RamosMendez2017]. To use this technique, as a first step, the volumes of interest (where the split will occur) must be assigned to a common region:

```
s:Ge/MySplitRegion/AssignToRegionNamed = "SplitRegion"
```

Then, the variance reduction has to be activated and the region and the number of particle splits must be defined, in the example below, 100 electrons will be propagated for every 1 electron entering the region:

```
b:Vr/UseG4DNAVarianceReduction = "True"
s:Vr/ParticleSplit/SplitElectronsInRegionNamed = "SplitRegion"
i:Vr/ParticleSplit/NumberOfSplit = 100
```

The scorers used with this technique must be modified to register the contribution of each split particle independent from other particles using a flag. Two concrete scorers that show how to use this option are `TsScoreDBSCAN.cc` and `TsScorePDB4DNA.cc`. The associated examples are `DBSCAN_VRT.txt` and `PDB4DNA_VRT.txt`. These examples show the implementation of this technique for the calculation of DNA strand breaks.

1.14.5 References

1.15 Chemistry

1.15.1 TOPAS-nBio Default chemistry list

We recommend the following chemistry parameters which include changes that allowed to reconcile the experimental and simulated yields of chemical species at the picosecond level as shown in [RamosMendez2021].

The default chemistry list for TOPAS-nBio can be found at `topas-nBio/examples/processes/TOPASDefaultReactions.txt`.

To use the default chemistry parameters from TOPAS-nBio, users had to use the topas chemistry modules, either `TsEmDNAChemistry` or `TsEmDNAChemistryExtended`. In addition, add the following parameter:

```
includeFile = TOPASDefaultReactions.txt
```

The example `topas-nBio/examples/scorers/IRTGetGValue/TsIRTGvalue.txt` shows how to properly use this chemistry list and recreate the validation results from [RamosMendez2021].

1.15.2 Geant4 Default chemistry list

TOPAS-nBio can inherit the parameters (reactions, reaction rates, etc.) provided by the Geant4-DNA toolkit to perform radiolysis simulations via the modules g4em-dna-chemistry and g4em-dna-chemistry_opt1. The chemistry parameters provided in the first module are reported in [Karamitros2012] [Incerti2016]. The chemistry parameters provided in the second module are reported in [RamosMendez2018].

The activation of the chemical stage is performed by including a chemistry model in the modular physics list, for example using the following parameter:

```
sv:Ph/Default/Modules = 2 "g4em-dna" "g4em-dna-chemistry"
```

The order of these modules must be consistent with the occurrence of the physical and chemical processes. Thus, the module for the physical process must be followed by the module for the chemical process. By default, the pre-chemical and chemical stages are activated, but no explicit step-by-step transport is performed. This is useful only for the scoring of the G-value (the yield of chemical species per 100 eV of energy deposit) as a function of time. A scorer that retrieves this quantity is the `GValue` scorer. The example `topas-nBio/examples/scorers/SBSGetGValue/GvalueG4DNADefault.txt` shows a complete implementation of this scorer.

1.15.3 Actvating the Chemistry of TOPAS-nBio

Simulation of chemical species reactions can be activated by using a set of parameters associated with a chemistry name (analogous to the physics list `Ph/ListName`). Different sets of parameters can be associated to different chemistry names, and only those assigned to the chemistry name defined by the following parameter will be used (e.g. `TOPASChemistry`:

```
s:Ch/ChemistryName = "TOPASChemistry"
```

The configuration of parameters for the chemistry stage requires the user to define an end time and (in the case of the Step-By-Step method) a time resolution. The end time must be larger than 1 ps (i.e. the time where the chemical stage begins). The time resolution can be defined piecewise. For example, to set the transport of chemical species up to 15 ns with time step resolution of 1 ns from 1 ps to 10 ns and 10 ps from 10 ns to 15 ns, the following parameters must be set (assuming the chemistry name `TOPASChemistry`):

```
# Activate Chemistry and Set Chemistry End Time
b:Ch/TOPASChemistry/ChemicalStageTransportActive      = "True"
d:Ch/TOPASChemistry/ChemicalStageTimeEnd              = 15.0 ns

# Only for Step-By-Step Chemistry
dv:Ch/TOPASChemistry/ChemicalStageTimeStepsHighEdges   = 2 10.0  15.0 ns
dv:Ch/TOPASChemistry/ChemicalStageTimeStepsResolutions = 2  1.0  10.0 ps
```

After these parameters have been set, the spatio-temporal information of the chemical species is available and can be visualized using the TOPAS graphics for Step-By-Step chemistry only. A scorer example to retrieve the track information (physical and chemical) is `particleTuple.txt`. A graphics example to visualize the transport of chemical species is `ActiveChemistryDefault.txt`.

1.15.4 Configurable chemistry list

Simulation of the water radiolysis process requires the setup of a large set of parameters: branching ratios, dissociation schemes, reaction rates, types of chemical species and diffusion coefficients. Advanced users that require to activate or deactivate reactions, change the reaction rates or diffusion coefficients, etc., have that flexibility provided by TOPAS-nBio. For that, one of the specialized modules `TsEmDNAChemistry` and `TsEmDNAChemistryExtended` must be included instead of the Geant4DNA chemistry module as follows:

```
sv:Ph/Default/Modules = 2 "TsEmDNAPhysics" "TsEmDNAChemistry"
```

or:

```
sv:Ph/Default/Modules = 2 "TsEmDNAPhysics" "TsEmDNAChemistryExtended"
```

Instead of the `TsEmDNAPhysics` physics module, one of the other options described in the *Physics Processes* can be used.

In this way, a whole set of parameters can be customized by using the following conventions. Chemical species are named using full names without separation spaces, for example, H_2O_2 is HydrogenPeroxide (case insensitive). The list of available molecules and diffusion coefficients customizable via `TsEmDNAChemistry` and `TsEmDNAChemistryExtended` are shown in the following table:

Molecule	TOPAS name	D ($10^{-9} m^2/s$) at 25ºC
e^-_{aq}	SolvatedElectron	4.9
$^{\bullet}OH$	Hydroxyl	2.2
$H^{\bullet}$	Hydrogen	7.0
H_3O^+	Hydronium	9.46
H_2	Dyhydrogen	4.8
OH^-	Hydroxide	5.3
H_2O_2	HydrogenPeroxide	2.3
O_2	Oxygen	2.4 (only in TsEmDNAChemistryExtended for SBS)
O_{2-}	SuperoxideAnion	1.75 (only in TsEmDNAChemistryExtended for SBS)
HO_2	HydroPeroxy	2.3 (only in TsEmDNAChemistryExtended for SBS)
HO_{-2}	Dioxidanide	1.4 (only in TsEmDNAChemistryExtended for SBS)
O_3P	AtomicOxygen	2.0 (only for IRT)
O^-	Oxyde	2.0 (only for IRT)
$O_3^{\;-}$	Trioxide	2.0 (only for IRT)
O_3	Ozone	2.0 (only for IRT)

Prechemical stage

The dissociation schemes and branching ratios are inherited from Geant4-DNA. In general, users do not need to change or set these values. If for any reason the users require customization of these parameters, the following parameters available in TOPAS-nBio will facilitate this task (assuming `s:Ch/ChemistryName = "TOPASChemistry"`):

```
u:Ch/TOPASChemistry/IonizationState/DissociativeDecay = 1.00
u:Ch/TOPASChemistry/A1B1/DissociativeDecay = 0.65
u:Ch/TOPASChemistry/A1B1/Relaxation = 0.35
u:Ch/TOPASChemistry/B1A1/AutoIonization = 0.55
u:Ch/TOPASChemistry/B1A1/DissociativeDecay = 0.15
u:Ch/TOPASChemistry/B1A1/Relaxation = 0.30
u:Ch/TOPASChemistry/RydbergStatesAndDiffuseBands/AutoIoinization = 0.5
u:Ch/TOPASChemistry/RydbergStatesAndDiffuseBands/Relaxation = 0.5
```

Chemical stage

For the chemical stage, the number of reactions and reaction rates are also inherited from Geant4-DNA. Additional reactions can be defined using the molecules from the previous table, and the reaction rates can also be overwritten for the existing reactions. The way the reactions are defined is the following, let us assume we have two molecules named `SolvatedElectron` and `Oxygen`. After their reaction, they produce the product `SuperoxideAnion`. Then, two parameters are required to define that reaction: one parameter to associate the pair of molecules and define the products, one parameter to assigns the reaction rate (with units of /M/s), e.g:

```
# Define the products:
sv:Ch/TOPASChemistry/Reaction/SolvatedElectron/Oxygen/Products    = 1 "SuperoxideAnion"

# Assign a reaction rate value:
d:Ch/TOPASChemistry/Reaction/SolvatedElectron/Oxygen/ReactionRate = 1.9e10  /M/s

# Assign the Reaction Type
i:Ch/TOPASChemistry/Reaction/SolvatedElectron/Oxygen/ReactionRate = 2

# SBS Compatible Reactions
b:Ch/TOPASChemistry/Reaction/SolvatedElectron/Oxygen/CompatibleWithStepByStep = "True"
```

Reaction types can be 1, 2, 3, 4 or 5 depending on the reactants charge and mode of reaction (totally diffusion controlled or partially diffusion controlled) [Plante2017]. Background reactions (type 6) are threated separetedly for either Step-By-Step or IRT simulations, as it will be discussed in a following section.

If the reaction does not produce any product or the product won't react further, for example, the product from $^\bullet$OH + H$^\bullet$ –> H$_2$O, then the name `None` must be used, e.g:

```
# Define the reaction without products:
sv:Ch/TOPASChemistry/Reaction/Hydroxyl/Hydrogen/Products = 1 "None"
```

TOPAS-nBio provides two sets of chemical parameters in the files `TOPASChemistry.txt` and `TOPASChemistry_Extended.txt` to be used with `TsEmDNAChemistry` and `TsEmDNAChemistryExtended`, respectively. These files (available in examples/processes) should be included in the usual way with `includeFile = "TOPASChemistry.txt"`. The first set of reactions and reaction rates reproduces experimental data from the literature, as reported in [RamosMendez2018]. The examples `ActiveChemistryRevised.txt` and `ActiveChemistryExtended.txt` show how to define the new reaction capability.

Truncation transport for chemical stage

An additional feature is the capability to terminate the transport of chemical species in volumes having a user defined material. In that case, the species are terminated once they come in contact with the volume (at the boundary or the first step within the volume). To use that capability, a new material must be cloned from the G4_WATER material:

```
s:Ma/G4_WATER_MODIFIED/CloneFromMaterial = "G4_WATER"
d:Ma/G4_WATER_MODIFIED/CloneWithDensity  = 1.0 g/cm3
```

Then call the following parameters (also, see example `RemoveChemicalSpeciesInVolume.txt`):

```
s:Ch/TOPASChemistry/RemoveInMaterial = "G4_WATER_MODIFIED"
sv:Ch/TOPASChemistry/RemoveInMaterialTheseMolecules = 2 "SolvatedElectron" "Hydrogen"
```

1.15.5 Chemical Diffusion-Reaction Algorithms

TOPAS-nBio incorporates two different methods for the diffusion and reaction of chemical species, the Step-By-Step (SBS) [Turner1983] and Independent Reaction Times (IRT) [Clifford1986] methods. Either method can be invoked by means of specific scorers. Main differences between both methods are the following:

- SBS simulates the spatial and temporal evolution of the chemical species and thus is slower than IRT.
- SBS allows to visualize chemical evolution.
- IRT can reach up to two or three orders of magnitude shorter times than SBS.
- Further chemical species can be defined only in IRT using parameters starting with ''Mo'', see below.
- Reactions between chemical species and background are defined in a different way between both methods.
- Products from background reactions can be simulated only with IRT.

Step-By-Step

For the SBS method, TOPAS-nBio inherits the reactions and molecules from Geant4-DNA. To incorporate reactions with the background (scavenging) in TOPAS-nBio, the following structure must be used:

```
# The Reactant: Scavenged Molecules
sv:Sc/SBSGValue/Scavenger/Molecules = 2 "SolvatedElectron" "Hydroxyl"

# The Scavenger concentrations
dv:Sc/SBSGValue/Scavenger/Concentrations = 2 1e-2 1e-2 M

# The Scavenger reaction rate
dv:Sc/SBSGValue/Scavenger/ReactionRates = 2 5e10 2.7e9 /M/s

# Confirm if there are products: Must be set to False.
bv:Sc/SBSGValue/Scavenger/HasProducts = 2 "False" "False"
```

where M = 1 mol/dm3.

In the previous example solvated electrons and Hydroxyl radicals will be scavenged at a rate (scavenging capacity) of $5 \times 10^8 s^{-1}$ for the solvated electrons and $2.7 \times 10^7 s^{-1}$ for the hydroxyl radical, respectively. Current version of TOPAS-nBio does not produces any product from background reaction. This capability will be added in a future release of TOPAS-nBio.

Independent Reaction Times

For IRT we provide a revisited reaction kinetics model (reaction and reaction rates) reported in [RamosMendez2021] which reconciliated simulated and measured G values at the picosecond range. This model is provided in the example TOPAS-nBio/examples/scorers/GetIRTGvalues.

The user can define new molecules by using the parameter system by using the `Mo` prefix as follows:

```
# Define the internal Symbol of the Molecule
s:Mo/DMSO/Symbol = "DMSO^0"

# Define the Diffussion Coefficient
d:Mo/DMSO/DiffusionCoefficient = 0 nm2/s

# Define the Charge of the Molecule
u:Mo/DMSO/Charge = 0

# Define the reaction radius
d:Mo/DMSO/Radius = 0.3 nm
```

New molecules defined with the previous method are not compatible with the StepByStep method. In IRT, the declaration of background reactions follows the same convention from the regular reactions:

```
sv:Ch/TOPASChemistry/BackgroundReaction/hydroxyl/DMSO/Products = 1 "OHDMSOProduct^0"
d:Ch/TOPASChemistry/BackgroundReaction/hydroxyl/DMSO/ReactionRate = 7.1e9 /M/s
d:Ch/TOPASChemistry/BackgroundReaction/hydroxyl/DMSO/Concentration = 1e-1 M
```

Two models for simulating background reactions are provided, and can be selected as follows:

> # Either ExponentialSingleFactor or ExponentialDoubleFactor s:Ch/TOPASChemistry/BackgroundReaction/hydroxyl/DMSO/Scav
> = "ExponentialSingleFactor"

Where `ExponentialSingleFactor` refers to method described in [Plante2017] and `ExponentialDoubleFactor` is the method described in [Pimblott1991].

TOPAS-nBio IRT allows for the activation and deactivation of reactions. This allows users to define a list of chemical reactions and pick and choose which ones of them will be active during the simulation without the need to introduce or delete the whole reaction:

```
# Deactivate an already existing Chemical Reaction
b:Ch/TOPASChemistry/Reaction/hydrogen/hydroxyl/Active = "False"

# Deactivate an already existing Background Reaction
b:Ch/TOPASChemistry/BackgroundReaction/hydroxyl/DMSO/Active = "False"
```

1.15.6 Simulations considering pH

The IRT method of TOPAS-nBio allows the user to scale the pH value of the medium. This can be usefull to model the physical conditions of experimental setups in more detail. The pH scalling was developed following the work of [Autsavapromporn2007] and [Plante2011]. To change the pH of the medium the following parameters are used:

```
# Modeling acid properties can be set to "H2SO4" or "Generic"
# "Generic" is an artifical PH scalling in which no acid is present
s:Ch/TOPASChemistry/ModelAcidPropertiesFromSubstance = "H2SO4"
```

```
# Use acid concentration to change pH, not available with "Generic" solvent
s:Ch/TOPASChemistry/ModelAcidPropertiesWithConcentration = 0.4 M

# Use a specific pH and calculate acid concentration
s:Ch/TOPASChemistry/ModelAcidPropertiesWithpH = 4.6
```

The last two parameters; `ModelAcidPropertiesWithConcentration` and `ModelAcidPropertiesWithpH` canot be used at the same time, if the user attemps to do so TOPAS will exit and an error message displayed. TOPAS-nBio will automatically scale reaction rates for reactions between two charged chemical species based on the ionic strength of the medium. An example is provide shown this capability throught the Fricke dosimeter, see example TOPAS-nBio/example/scorers/FrickeIRT

1.15.7 IRT Automatic Temperature Scalling

TOPAS-nBio provides its users with a built-in temperature scalling algorithm compatible with IRT. It is based on the work of [Elliot1994] and [DuPenhoat200]. Specif details regarding the implementation can be found in [RamosMendez2022]. To use the temperature scaling of reaction rates and diffusion coefficients, the users must the parameter `u:Ch/TOPASChemistry/Temperature` and setting it to the temperature in Celsius.

For the best results, it is recommended to also change the water density to the value that corresponds with the desired temperature. We provide users with two examples that showcase this TOPAS-nBio IRT feature in the folder `/examples/scorers/Temperatures`: `TemperatureExample_20C.txt` and `TemperatureExample_90C.txt`.

We remind users that this specific implementation is only valid between 0 and 90 degrees Celsius.

1.15.8 References

1.16 Introduction

Biological modeling descibes the response of cells to the initial damage. Overall, the goal is to develop a comprehensive and inclusive modeling from the initial physics events to the final observed biological outcome. In many cases, the development of biological models and track structure Monte Carlo simulations is performed by different groups. TOPAS-nBio supports the Standard for DNA Damage (SDD) [Schuemann2019], which offers a connection between the simulation of DNA damage induction in the physical and chemical stage, and the modeling of DNA repair kinetics. The strengh of the SDD is that it allows cross-comparison of the results of damage induction codes, cross-comparison of predicted outcome from biological models using the same DNA damage distribution, and a link between the two modeling realms.

1.17 Mechanistic Models of DNA Repair

The biological modeling within TOPAS-nBio has been developed by our external collaborators at Manchester University and Queens University Belfast (see *Members of the TOPAS-nBio Collaboration*). Two models have been used together with TOPAS-nBio that are described in more detail in this section.

1.17.1 DaMaRiS

DaMaRiS (DNA Mechanistic Repair Simulator) has been developed at the University of Manchester. DaMaRiS uses a distribution of DNA damage as input to model Non-Homologous End Joining (NHEJ) DNA repair kinetics. The input can be supplied via the SDD standard ([Schuemann2019]). In addition, DaMaRiS has been integrated into the TOPAS-nBio framework, thus a single TOPAS-nBio simulation can include the entire process from initial cell irradiation to final outcome. The SDD-compatible DaMaRiS framework can be downloaded from https://gitlab.com/PRECISE-RT/releases/damaris_topas-nbio.

The methodology behind DaMaRiS has been published in [Warmenhoven2020], [Ingram2019], [Henthorn2019], [Henthorn2018], [Henthorn2017].

1.17.2 MEDRAS

The MEDRAS (Mechanistic DNA Repair And Survival) model has been developed at Queen's University, Belfast. Beginning from an initial distribution of DNA damage, it probabilistically models the interaction of free DSB ends, based on a spatially-dependent interaction probability. This is used to calculate rates of both correct rejoining and misrepair. This process models the kinetics of repair through each of the three major repair processes (NHEM, Homologous Recombination (HR) and Backup/Microhomologoy Mediated End Joining (MMEJ)), allowing the simulation of cells with different repair capacities. MEDRAS can generate predictions of a range of biological endpoints, including DSB repair kinetics as well as rates of double strand break misrepair, mutation, and chromosome aberrations. Survival can also be modelled for a range of different cell backgrounds.

The model has been described in [McMahon2016] and [McMahon2017]. MEDRAS takes DSB damage distributions as input, but is (currently) an external Python-based program that can be linked to TOPAS-nBio via the SDD. The SDD-compatible MEDRAS model can be downloaded from https://github.com/sjmcmahon/Medras-MC.

1.17.3 References

1.18 The TOPAS-nBio Graphical User Interface

TOPAS-nBio includes an optional Graphical User Interface (GUI). The GUI allows the user to easily manipulate graphics (rotate, zoom and click on graphical elements to get more information about the selected geometry element or particle track) and inspect and adjust TOPAS parameters.

The GUI is intended as a rapid prototyping extension of TOPAS-nBio. It allows you to easily see and adjust geometry and review the behavior of a small set of particle histories. The GUI then gives you the ability to save the new parameters, such that these saved values can later be loaded back in to a new TOPAS-nBio session, with or without the GUI.

For larger, high precision runs, with larger numbers of histories, the user will generally run on a batch system (cluster or cloud) without the GUI.

Future developments will extend the system such that users will be able to directly launch cluster or cloud jobs from the GUI, with the GUI serving to monitor the progress of those jobs and display their results.

The GUI is based on the Qt Toolkit. To activate the GUI, include the following parameter in your TOPAS Parameter Control File:

```
Ts/UseQt = "True"
```

TOPAS will then bring up the GUI.
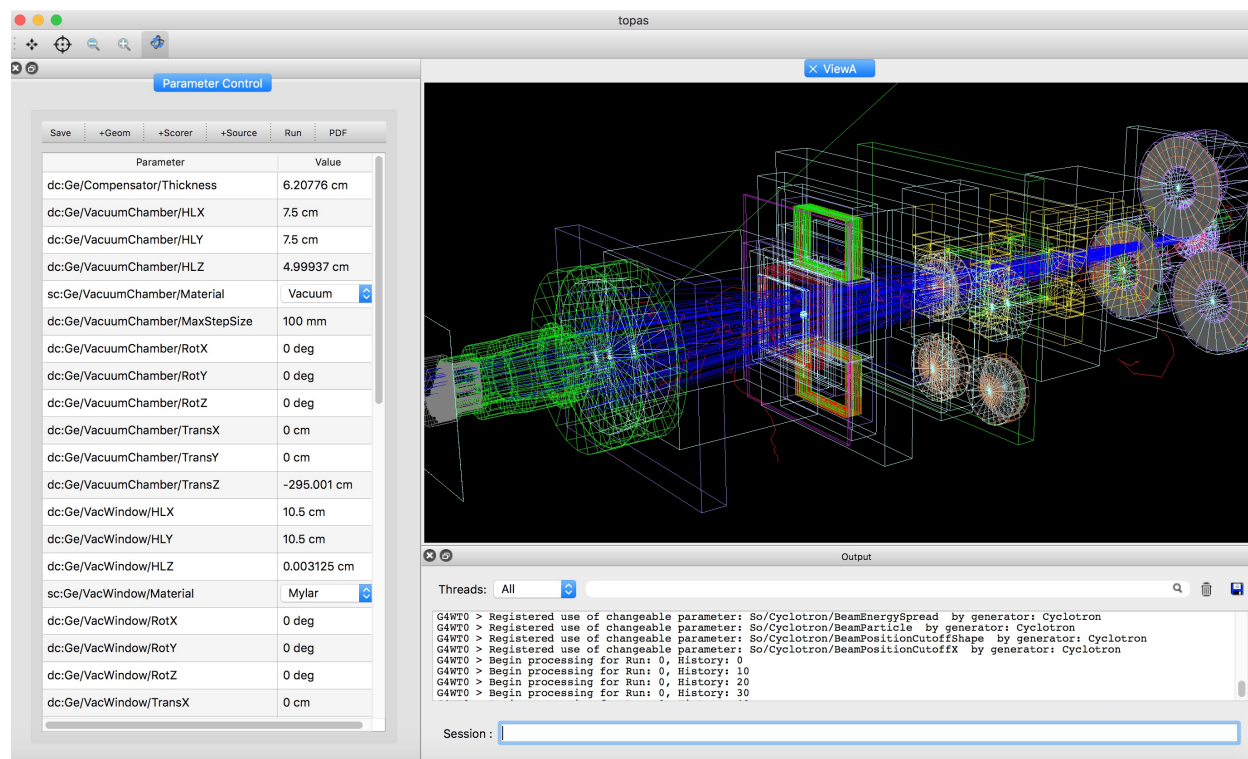
1.18.1 Mouse Control

The top row of icons determine the behavior of the mouse when one clicks in the graphics window. Going from left to right:

- Pick to Translate the Image. Moving the mouse will move the image left right up or down

- Pick to Inquire. A pop-up window will give details about the selected object within the image (name of geometry, material, density etc., or type of particle track, partile energy, etc.).

- Pick to Zoom out

- Pick to Zoom in

- Pick to Rotate. Moving the mouse will rotate the image.

1.18.2 The Parameter Control Table

The Parameter Control Table includes one row for each of the parameters that you can adjust. Click on the given value to adjust. There may be a slider or a text input box, depending on the parameter type. If you type an invalid entry, a warning message will appear in the session console area on the lower right, and the previous value will be restored.

You choose which of your TOPAS parameters will be displayed here by adding the prefix character "c" (for "changeable") to the parameter type. So, for example, to have the Z Half Length of a component named MyBox be included in this control area, specify it in the parameter control file as:

```
ic:Ge/MyBox/HLX = 2
```

Or to have this NOT be present in the control area:

```
i:Ge/MyBox/HLX = 2
```

1.18.3 Additional Functions

A set of buttons above the parameter control table support additional functions:

- Save: saves the current set of parameters to a new file in your current directory. The file name will be displayed in the session console area on the lower right. The new file will NOT overwrite your original parameter file. Rather, it will create a new parameter file that includes only your changes, and that then uses the TOPAS inclueFile mechanism to bring in your original parameter file for the other, unchanged values.

- +Geom: Brings up a window to let you add a new Geometry Component

- +Scorer: Brings up a window to let you add a new Scorer. Note that due to constraints in the way Geant4 initializes various functions, you can only add scorers Before the first run.

- +Source: Brings up a window to let you add a new Particle Source. Note that due to constraints in the way Geant4 initializes various functions, you can only add scorers Before the first run.

- Run: Runs your simulation. You can issue this as many times as you wish, changing parameters and re-running to see new results.

- PDF: Saved the current graphics window to a PDF file in your current directory.

1.19 Introduction

Scorers in TOPAS-nBio

TOPAS-nBio offers the user a few generic scorers for some geometries as well as specialized scorers for select geometry components. Users also have the option of using the TOPAS scorers.

Many of our scorers are based on the ntuple scorer of TOPAS, which allows quantities for each event to be scored in columns. This gives you the flexibility to also edit the extension to score any additional information required by the simulation. More information on custom extension components is available here.

> **Warning:** Note: The DoseToWater and DoseToMaterial scorers do not work with the Geant4-DNA physics processes. Please use the DoseToMedium scorer.

1.20 Cell Scorer

1.20.1 Organelle Cell Scorer

A generic ntuple cell scorer is provided. This scorer allows the user to do scoring in the organelles of the cell:

```
#Score energy deposited in Cell components
s:Sc/OrganelleScorer/Quantity = "NtupleForCell"
```

The scorer is compatible with all the cell models and outputs the following data:

```
Columns of data are as follows:
 1: Position X [cm]
 2: Position Y [cm]
 3: Position Z [cm]
 4: Energy [MeV]
 5: Energy Deposited [MeV]
 6: Particle Type (in PDG Format)
 7: Track ID
 8: Run ID
 9: Event ID
10: Volume Name
```

Users may edit the NtupleForCell extension to edit or add additional output parameters. More information on how to design custom scorers and the n-tuple format can be found on the OpenTOPAS custom scorers readthedocs.

1.20.2 Neuron Scorer

A ntuple scorer specifically for neuron structures is also available:

```
s:Sc/NeuronScorer/Quantity    = "NtupleForNeuron"
```

This ntuple scorer is an extension that can be edited by the user to add additional output parameters, depending on the application. More information on how to design custom scorers and the n-tuple format can be found on the OpenTOPAS custom scorers readthedocs. The default output of the scorer is:

```
Columns of data are as follows:
 1: Position X [cm]
 2: Position Y [cm]
 3: Position Z [cm]
 4: Energy [MeV]
 5: Energy Deposited [MeV]
 6: Particle Type (in PDG Format)
 7: Track ID
 8: Run ID
 9: Event ID
10: Volume Name
11: Replica Number
```

Here, replica number applies to the components comprising the dendrites and axons.

1.21 DNA Scorers

TOPAS-nBio provides a scorer for the damage induced to several DNA structures using the step-by-step method to simulate molecule diffusion and chemical reactions. This scorer can be used to simple DNA structures, such as the Charlton DNA model, circular and linear plasmids, simple DNA cylinders. To use this scorer, the following parameter is required:

```
s:Sc/DNADamageScorer/Quantity = "DNADamageStepByStep"
```

We provide another parameter file with all the options for the scorer and explanations about these. This file is located at the path: 'examples/scorers/DNAScorerStepByStep.txt'. To use it, please include this file in your parameter file

with the adequate path reference. For example, in the example 'FullDNADamageInPlasmid.txt' at the path 'examples/scorers/SBSDamageToDNAPlasmid/', the following parameter is included:

```
includeFile = ../DNAScorerStepByStep.txt
```

1.21.1 Damage scoring

A strand break (SB) is considered whenever one of the following conditions is met:

- The total energy deposited in a backbone exceeds the specified threshold (direct damage)

- A hydroxil interacts with a backbone, with a given probability to induce damage (indirect damage)

- An ionization is produced in the surrounding hydration shell, which damage is propagated to the backbone (direct damage)

The threshold for direct damage to the backbone can be specified by the user using the parameter:

```
d:Sc/DNADamageScorer/DirectDamageThreshold = 11.75 eV     # For half-cylindrical DNA
→model, the recommended value is 17.5 eV
```

Another option is to consider a probability for direct damage linearly increasing with the deposited energy instead of a single threshold. To do so, the following three parameters need to be specified:

```
b:Sc/DNADamageScorer/UseLinearProbabilityForDirectDamage = "true"
d:Sc/DNADamageScorer/LowerLimitForLinearProbabilityFunction = 5 eV
d:Sc/DNADamageScorer/UpperLimitForLinearProbabilityFunction = 37.5 eV
```

where the probability of damage is set to 0 for energies lower than or equal to the "LinearProbability_lower_limit"; to 1 for energies greater than or equal to "LinearProbability_upper_limit" and increases linearly between those two values.

Since v1.1, there are two methods available to score indirect damage, either (a) specifying a single probability for a hydroxyl radical to cause damage once they encounter a backbone or a base; or (b) specifying a distinct probability for the hydroxyl radical to interact once they encounter backbones or bases, and then another distinct probability to produce a break only if the radical interacts with the DNA component. In the first option, radicals are always removed scavenged when they face a DNA component, whereas in the second option radicals are allowed to continue on their way if they happen not to interact. Details and the reasoning behind these two methods can be found in[1]. Users can select one method or the other with the boolean parameter:

```
b:Sc/DNADamageScorer/AlwaysScavengeSpeciesInDNAComponents = "false"
```

If it is set to "false", the probability for an hydroxyl to cause damage once interacting with a backbone is controlled by the parameter:

```
u:Sc/DNAScorer/ProbabilityForOHToCauseDamage = 0.4
```

If it is set to "true", the probability for a radical to interact with (being scavenged by) a backbone, and the probabilities for a radical to cause damage once it interacts with backbone and bases are controlled by:

```
u:Sc/DNADamageScorer/ProbabilityOfScavengingInBackbone = 0.25 # For half-cylindrical DNA
→model, the recommended value is 0.0585
u:Sc/DNADamageScorer/ProbabilityOfScavengingInBase = 1.0
```

---

[1] Bertolet, A., Ramos-Mendez, J., McNamara, A., Yoo, D., Ingram, S., Henthorn, N., Warmenhoven, J. W., Faddegon, B., Merchant, M., McMahon S. J. (2022). Impact of DNA geometry and scoring on Monte Carlo track-structure simulations of initial radiation induced damage. Radiation Research, Submitted.

```
u:Sc/DNADamageScorer/ProbabilityOfIndirectDamageToBackbone = 0.55 # If always scavenging␣
↪in DNA components, the recommended value is 0.4
u:Sc/DNADamageScorer/ProbabilityOfIndirectDamageToBase = 1.0 # If always scavenging in␣
↪DNA components, the recommended value is 0.4
```

Note that these parameters should be adapted to the DNA geometry model employed (see[Page 52, 1]).

Since v1.1, a new parameter to handle quasi-direct damage (i.e., damage as a consequence of charge transfer from the solvated water shell to the backbone) can be controlled by the parameter:

```
u:Sc/DNADamageScorer/ProbabilityOfChargeTransferFromHydrationShellToBackbone = 0.3333333
```

Finally, one can exclude direct, quasi-direct and/or indirect damages from the results with the parameters:

```
b:Sc/DNADamageScorer/ScoreDirectDamages = "true"
b:Sc/DNADamageScorer/ScoreIndirectDamages = "true"
b:Sc/DNADamageScorer/ScoreQuasiDirectDamages = "true"
```

A double strand break (DSB) is defined as two SB in complementary strands separated by less than a given number of base pairs. This separation is set to 10 by default but can be controlled by the parameter:

```
i:Sc/DNADamageScorer/MaximumBasePairDistanceToConsiderDSB = 10
```

All SB not included in DSB are scored as single strand breaks (SSB). Complex damages in the same number of base pairs as specified by "DSBSeparation" are also counted. In particular, we differentiate among two SSBs (SSB+), two DSBs (DSB+) or any other combination of more complex damages. These tallies are independent of the SSB and DSB tallies, i.e., the DSBs in a DSB+ damage still are counted as two DSBs.

Besides scoring within a stretch of DNA (10 base pairs or the specified length), 'foci' of DSB separated within a given spatial distance can be also counted. This can be managed by the parameters:

```
b:Sc/DNADamageScorer/ScoreNumberOfFoci = "true"
dv:Sc/DNADamageScorer/FociSizes = 2 150 500 nm # Maximum of 5 sizes
```

Each focus is created by the boolean union of spheres with radius equal to those given by the "FociSizes" parameter around each DSB. Up to 5 sizes can be used in a single simulation to calculate the correspondent number of foci. These numbers are also included in the default output of this scorer.

1.21.2 Preparing the proper output

As several subcomponents are created as children of the primary geometry component, the scorer needs to locate at which logical level base pairs (base, backbones and hydration shells) are generated. This is specified by the parameter:

```
i:Sc/DNADamageScorer/BasePairPositionAtGeometricHierarchy = 0
```

where 0 means that base pairs are the last subcomponent created, i.e., there are no further children.

1.21.3 Stopping scoring at a given dose

An additional parameter has been added to score only the damage resulting after a given dose is delivered. This can be specified by means of:

```
d:Sc/DNADamageScorer/StopTrackingAtDose = 0.5 gray
```

Please note that this parameter does not stop the simulation and the remaining histories will go on whenever this dose to the scoring component is achieved. However, all particles in these remaining histories will be stopped at their first interaction within the scoring component.

1.21.4 Outputs

Our scorer offers four different outputs.

1. The regular output for nTuple scorers in TOPAS is produced, including an event-by-event description of the energy and dose imparted to the nucleus; the track-averaged LET computed as the energy divided by the track length of the primary particle inside the nucleus; and a complete list of damages (SSB, DSB, SSB+, DSB+, more complex and foci), classified by either direct, indirect or hybrid (in the case of DSB). However, one can decide whether to include damages classified by their origin by means of:

```
b:Sc/DNADamageScorer/BreakDownOutputPerDamageOrigin = "true"
```

2. The Standard for DNA Damage (SDD) can be produced[2]. All the fields included in the SDD format is on the SDD ReadtheDocs. Whether to use the minimal SDD output or the complete specification is controlled by the parameter:

```
b:Sc/DNADamageScorer/MinimalSDDOutput = "false"
```

Also, the user can only include those damages including a DSB using the parameter:

```
b:Sc/DNADamageScorer/IncludeDSBDamageSitesOnlyinSDD = "true"
```

3. An exhaustive list of the damage produced in each backbone and base can be obtained in CSV format by setting:

```
b:Sc/DNADamageScorer/WriteCSVOutputWithAllDamageSpecification = "true"
```

This list includes all the base pairs affected in each chromosome, with 'D' meaning direct damage; 'I' indirect damage; 'M' multiple damage (direct+indirect); and '*' meaning that some energy has been imparted to that element but not enough to consider a direct damage.

4. A visual output of 3D and 2D fluorescence focus assay-like images can be provided. These images are obtained by locating all the DSBs and convolving them with a Point Spread Function (PSF), which blurs each one of the DSBs in all directions. In v2.0, only an isotropic Gaussian function can be used as PSF, although the width (sigma parameter) of the Gaussian function can be specified. Users can select what 2D planes to obtain, and the spatial resolution for the calculated images. For the 2D images, several images with different resolutions can be obtained after a single simulation. This is controlled by the following set of parameters (by default at the DNAScorerStepByStep.txt auxiliary file):

```
b:Sc/DNADamageScorer/Get3DFociImage = "true"
b:Sc/DNADamageScorer/Get2DFociImages = "true"
sv:Sc/DNADamageScorer/2DFociImagePlanes = 3 "X" "Y" "Z"
```

(continues on next page)

---

[2] Schuemann, J., McNamara, A. L., Warmenhoven, J. W., Henthorn, N. T., Kirkby, K. J., Merchant, M. J., et al. (2019). A New Standard DNA Damage (SDD) Data Format. Radiation Research, 191(1), 76

```
s:Sc/DNADamageScorer/MicroscopePSFShape = "Gaussian"
d:Sc/DNADamageScorer/MicroscopePSFWidth = 400 nm
dv:Sc/DNADamageScorer/Foci2DImageResolutions = 2 25 100 nm
d:Sc/DNADamageScorer/Foci3DImageResolution = 400 nm
```

Images are given in csv files, in which the first columns indicate the indexes of the image matrix (i, j, k for 3D images; i, j for 2D images) and the last column provides the pixel value for the correspondent indexes. The extent of the 2D images on each plane can be specified by the parameters:

```
d:Sc/DNADamageScorer/ImageXMinPosition = 0 um - Ge/Nucleus/NucleusRadius
d:Sc/DNADamageScorer/ImageXMaxPosition = Ge/Nucleus/NucleusRadius um
d:Sc/DNADamageScorer/ImageYMinPosition = 0 um - Ge/Nucleus/NucleusRadius
d:Sc/DNADamageScorer/ImageYMaxPosition = Ge/Nucleus/NucleusRadius um
d:Sc/DNADamageScorer/ImageZMinPosition = 0 um - Ge/Nucleus/NucleusRadius
d:Sc/DNADamageScorer/ImageZMaxPosition = Ge/Nucleus/NucleusRadius um
```

A python-based script is accompanying the example at 'examples/scorers/SBSDamageToDNANucleus' to visualize the 3D and 2D images generated.

1.21.5 Excluding fragments

Finally, an additional feature consists of excluding damages produced in those fragments of DNA (i.e., the DNA between two DSBs) that are shorter than a given threshold. This is controlled by the set of parametes:

```
b:Sc/DNADamageScorer/ExcludeShortFragment = "true"
i:Sc/DNADamageScorer/LowerThresholdForFragmentDetection = 250
i:Sc/DNADamageScorer/UpperThresholdForFragmentDetection = 300000000
```

where the thresholds refer to the number of base pairs in each fragment.

1.21.6 Deciding in which structures to score

A single element of a DNA strand is composed of three different components: base, sugar-phosphate backbone and hydration shell. Also, the double helixes are coiled around proteins called histones that confer structural support to the DNA arrangement. Histones can be used as scavengers for chemical species (via the boolean parameter "HistoneAsScavenger"). One can include physical and chemical interactions with any of these four types of structures. To specify which interactions to include, the lists of considered materials for each strand are specified using the parameters:

```
sv:Sc/DNADamageScorer/Strand1MaterialNames = 4 "G4_WATER_MODIFIED" "G4_BackboneMaterial"
↪"G4_BaseMaterial" "G4_HistoneMaterial"
sv:Sc/DNADamageScorer/Strand2MaterialNames = 4 "G4_WATER_MODIFIED" "G4_BackboneMaterial"
↪"G4_BaseMaterial" "G4_HistoneMaterial"
```

where these materials need to be defined and assigned to each subcomponent in the Nucleus parameter section. Note that "G4_WATER_MODIFIED" is assigned to the hydration shell in our example.

1.21.7 Scoring in the Nucleus

Damage to the fractal DNA in a nucleus can be scored using the geometry component TsNucleus. This scorer is a sub-version of the more general DNADamageStepByStep component, and it still uses the same auxiliary parameter file, 'DNAScorerStepByStep.txt'. Check example on 'examples/scorers/SBSDamageToDNANucleus'. The quantity and the component for the scorer need to be specified as follows (assuming that TsNucleus class is named as "Nucleus"):

```
s:Sc/DNADamageScorer/Quantity = "DNADamageNucleusStepByStep"
s:Sc/DNADamageScorer/Component = "Nucleus"
```

Also, to correctly consider all the hits produced in all geometric subcomponents, it is necessary to propagate the scorer to the children components via:

```
b:Sc/DNADamageScorer/PropagateToChildren = "true"
```

The parameter 'ScoringRadius' filters the considered hits to be scored, and it is set to the nucleus radius using, for example:

```
d:Sc/DNADamageScorer/ScoringRadius = Ge/Nucleus/NucleusRadius um
```

Geometrical information about the nucleus is also needed to correctly locate the damages along the chromosomes of the nucleus. This information for our nucleus model is provided in the "supportFiles" folder and is passed to the scorer through the parameters:

```
s:Sc/DNADamageScorer/GeometryInfo = "supportFiles/Geoinfo.txt"
s:Sc/DNADamageScorer/CopyNoTable = "supportFiles/CopyNoTable.txt"
s:Sc/DNADamageScorer/signedCHVoxel = "supportFiles/signedCHVoxel.txt"
```

1.21.8 References

1.22 Chemical Scorers

Chemical scorers are those that utilize either the *Step-By-Step* (SBS) or the *Independent Reaction Times* (IRT) algorithms to simulate the diffusion and reaction of chemical species. TOPAS-nBio provides six chemical scorers, two for SBS and four for IRT. These scorers are:

Scorer Type	Scorer Quantity
SBS	TsSBSGValue
	TsSBSMoleculesAtTime
IRT	TsIRTGvalue
	TsIRTInterTrack
	TsIRTInterPulse
	TsIRTStrandBreaks

Chemical scorers provide a way to terminate the tracks based on total primary energy loss, total primary track length or number of primary particle steps. This is implemented as both, a way to control the particle track size for more control of the G-values, and as a way to reduce the total number of chemical species produced by a certain particle track.

1.22.1 Step-By-Step Scorers

SBS GValues

The Step-By-Step G-Values scorer was the first chemical scorer available since the first release of TOPAS-nBio. It remained the same from its previous versions, however the naming convention was changed in order to fall in line with the rest of the chemical scorers. The TOPAS-nBio parameter name for this scorer component changed from `GValue` to `TsSBSGValue`. An example of the usage of this scorer can be found at `/examples/scorers/TsSBSGValues/` with TOPAS-nBio defined reactions `GvalueRevisedPhysicsChemistry.txt` and Geant4-DNA default reactions `GvalueG4DNADefault.txt`. The parameters to setup this scorer are:

```
# The times at which to report the GValues
dv:Sc/SSBGvalue/TimeToRecord = 7 1 10 100 1e3 1e4 1e5 1e6 ps
```

And the following particle track kill options:

```
# Total Energy Loss to Kill the primary track
d:Sc/SSBGvalue/KillPrimaryIfEnergyLossExceeds = 10 eV

# Total energy loss by the primary particle after which the track will be aborted
# and no chemistry will be conducted
d:Sc/SSBGvalue/AbortEventIfPrimaryEnergyLossExceeds = 100 eV

# Total track length to kill the primary track
d:Sc/SSBGvalue/KillPrimaryBasedOnTrackLength = 1 um
```

The rest of the parameters will be handled by the Ch chemistry parameters. Most of the chemical scorers share the same particle track kill options. This scorer has been used to calculate G-values with relatively good agreement as published in [Ramos-Méndez2018].

Number of Molecules At Time

The `TsSBSMoleculesAtTime` scorer is a way to obtain the total number of a chemical species instead of its G-value (species per 100 eV of energy deposit). It shares the same particle track kill options from the `TsSBSGValue` scorer. An example of such scorer can be found in the folder `examples/scorers/TsSBSMoleculesAtTime/`, with the file name `TsSpeciesAtTime.txt`. Instead of providing the explicit time values to report G-values from the `TsSBSGValue` scorer, an automatic binning is provided by using the following four parameters:

```
# Number of time bins
d:Sc/MoleculesAtTime/TimeBins = 100

# The lower time limit
d:Sc/MoleculesAtTime/TimeBinMin = 1 ps

# The upper time limit
d:Sc/MoleculesAtTime/TimeBinMax = 1e6 ps

# True for logarithmic binning, false for linear binning
b:Sc/MoleculesAtTime/TimeBinLog = "True"
```

1.22.2 Independent Reaction Times Scorers

IRT GValues

The `TsIRTGValue` scorer is the IRT version of `TsSBSGValue`. The necessary parameters to setup the scorer are similar to those from the `TsSBSMoleculesAtTime` scorer. Alongside the particle track kill options the parameters are:

```
# Scorer Cutoff time
d:Sc/IRTGValue/CutoffTime = 1 us

# Optional: if it exists the regular track kill options are ignored: Defaults to 0
i:Sc/IRTGValue/MaximumNumberOfSteps = 1e6

# Report DeltaG Values: Defaults to false
b:Sc/IRTGValue/ReportDeltaGValues = "True"
```

DeltaG values are an optional part of this scorer, they report the number of times a certain reaction is performed during the simulation per 100 eV of energy deposit (same units as the G-values). The output file of the DeltaG values will have the same name from the `OutputFile` parameter from the scorer with a `_DeltaG.phsp` added at the end.

Apart from this parameters, all IRT scorers take additional parameters from the `/procesess/TsIRT.cc` file in order to create the time bins to report the G-values:

```
# The lower bin limit
d:Sc/IRTGValue/TimeLower = 1 ps

# The upper bin limit
d:Sc/IRTGValue/TimeUpper = 1 us

# The number of Logarithmic bins
i:Sc/IRTGValue/TimeBins = 100

# Use High Time Scavenger: Defaults to False
b:Sc/IRTGValue/HighTimeScavenger = "False"
```

The `TimeLower`, `TimeUpper` and `TimeBins` are optional and defaults to the values shown here. The `HighTimeScavenger` parameter is used to limit the scavenging reaction to 1 micro second, this is done to avoid long simulation times between cycling reactions of the form:

```
ReactantA + ScavengerA = ReactantB
ReactantB + ScavengerB = ReactantA
```

By having this limiter, no type VI reaction will be performed after 1 micro second. However some applications may depend on higher simulations times with the need of special scavengers like the Fricke dosimeter in which case users can opt to remove this limiter.

An example of the usage of this scorer can be found at `/examples/scorers/TsIRTGvalue/TsIRTGvalue.txt`. TOPAS-nBio IRT simulations accuracy has been reported in [Ramos-Méndez2021]. The Fricke dosimeter has been implemented alongside a way to automatically change reaction times by pH as explained in *Independent Reaction Times*, the `/examples/scorers/TsFricke/FrickeIRT.txt` example shows the implementation of the results published in [Ramos-Méndez2020].

IRT GValues Inter-Track

TOPAS-nBio allows users to quantify the effect of multiple particle tracks on chemical yields, in what is known as inter track effects. These effects don't appear unless two or more tracks happen to interact with the medium in close proximity considering both the space and the time of ionization and excitation of the medium. Specifically speaking, two particle tracks must happen with a time separation of at least 1 micro second and a separation of a few tens of nano meters apart.

The `TsIRTInterTrack` scorer was made to quantify this effect on a track-by-track basis. It allows the use of as many tracks as the user specifies distributed in the space and time which the user can manually specify with:

```
# Set to True to allow multiple tracks per IRT run: Defaults to False
b:Sc/IRTGValuesIT/UseMultipleTracks = "True"

# Set the individual time at which each track hits the scorer
dv:Sc/IRTGValuesIT/TimeDelay = 5 1 2 2 5 1e3 ps

# Set the spatial offset of each track per IRT run.
dv:Sc/IRTGValuesIT/SpatialOffsetX = 0 1 0   5 10 nm
dv:Sc/IRTGValuesIT/SpatialOffsetY = 0 1 1 50 20 nm
dv:Sc/IRTGValuesIT/SpatialOffsetZ = 0 1 1   0 10 nm
```

An example of this scorer can be found at `/examples/scorers/TsInterTrack/TsIRTInterTrack.txt`. Using this scorer it is possible to recreate the results reported in [Kreipl2009].

IRT GValues Inter-Pulse

Experimentally, determining a track-by-track inter-track effect is not available, instead we rely on the use of a pulsed irradiation. By using pulsed irradiation, high radiation dose rates can be achieved in what is called FLASH irradiation. TOPAS-nBio includes a scorer that allows to simulate inter track effects called `TsIRTInterPulse`. This scorer was used in the paper [Ramos-Méndez2020]. It completely removes the particle track kill options while providing additional options for the pulse distributions with the parameters:

```
# Total Dose used per IRT run
d:Sc/IRTCummulative/PrescribedDose = 5 Gy

# The Pulse Distribution can be:
# "Gaussian", "Uniform", "None", "Discrete" and "Exponential"
s:Sc/IRTCummulative/PulseDistribution = "Gaussian"

# Pulses to use, dose will be distributed among them: Defaults to 1
i:Sc/IRTCummulative/NumberOfPulses = 5

# Number of Pulses per unit time
d:Sc/IRTCummulative/PulsesFrequency = 1e6 /s
```

If the pulses are "Gaussian" or "Uniform" the following parameters must be set:

```
# The mean time of the pulse
d:Sc/IRTCummulative/PulseTimeMean = 1 us

# The average duration of the pulse by using the FWHM
d:Sc/IRTCummulative/PulseFWHM = 2 us
```

If the pulses are "Discrete", the following parameters are needed:

```
dv:Sc/IRTCummulative/TimeValues  = 5   1  1.5    2  2.5    5 us
uv:Sc/IRTCummulative/TimeWeights = 5 0.1 0.25 0.05 0.25 0.35
```

If the pulses are "Exponential" only the mean time of the pulse is needed with:

```
d:Sc/IRTCummulative/PulseTimeMean = 1 us
```

Chemical simulations always start at 1 pico second, taking into account the physical and pre-chemical stages. Due to the behaviour of the time sampling when using pulse distributions it is possible to have chemical species created and diffusing before the chemical stage. To avoid this, users can use the following parameter:

```
b:Sc/IRTCummulative/ForceLowTimeCutTo1ps = True
```

The default value of this parameter is `False`.

TOPAS-nBio provides an example of this scorer in `/examples/scorers/TsIRTCummulative/TsIRTCummulative.txt`. The effect of FLASH radiation on chemical yields using this scorer in TOPAS-nBio was published [Ramos-Méndez2020], for more information regarding the expected results and details about FLASH please refer to this paper.

Note: The user must take care to not overload the IRT of TOPAS-nBio by sending either a high number of pulses or a high dose, otherwise this scorer may consume all the memory available, causing the computer to freeze or crash, user discretion is advised.

IRT DNA Strand Breaks

Both the SBS and IRT scorers can be used for DNA strand break simulations. The specific implementation of such simulations can be very complex depending on the reaction-diffusion algorithm. TOPAS-nBio provides a way to simulate DNA strand breaks in plasmid DNA using the IRT method. In order to properly run plasmid DNA strand break simulations, the user must perform some pre-simulation setup either by hand or by using the *IRT Supercoiled Plasmid Setup* provided in the TOPAS-nBio code. The `TsIRTStrandBreaks` scorer assumes the user has already performed the necessary steps and has the necessary files to properly score de DNA strand breaks by using:

```
d:Sc/DNAStrandBreak/PrescribedDose = 50 Gy
s:Sc/DNAStrandBreak/InputFile = "pUC19_Plasmids.xyz"
iv:Sc/DNAStrandBreak/OnlyUseDNAMoleculesWithID = 1 104
```

Where the `InputFile` refers to the file containing the position of the DNA molecules. `OnlyUseDNAMoleculesWithID` allows to filter DNA molecules prior to entering the IRT simulation and save time. An example of this scorer can be found at `/examples/scorers/TsScoreDNADamage/PlasmidIrradiation/TsScoreDNADamage.txt`. For more information regarding the performance and setup of this example, see [Ramos-Méndez2021].

This scorer will produce three different files, a `phsp` file with the number of molecules at a given time of the simulation, a header file for this file and a `.dnadamage` file. The `.dnadamage` file contains the `Base Pair ID` and `Strand ID` of each break. It is up to the user to work around this information to obtain the number of Single Strand Breaks and Double Strand Breaks. The `Base Pair ID` will be a number between 1 and the number of plasmids multiplied by the number of base pair per plasmid. The user will need to obtain the `Plasmid ID` by dividing the `Base Pair ID` by the number of base pairs of the specific plasmid used.

Note: It is important to mention that this scorer is not `Multithread` compatible and must be used with a thread

---

number of 1. Future releases may address this limitation.

Note: Other DNA damage scorers are available and are compatible with the SBS method, see the appropriate sections in this documentation for more detail.

1.22.3 References

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