Overview on “dsbandrepair” example

geant4-dna.org

“dsbandrepair” advanced example

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Geant4-DNA tutorial
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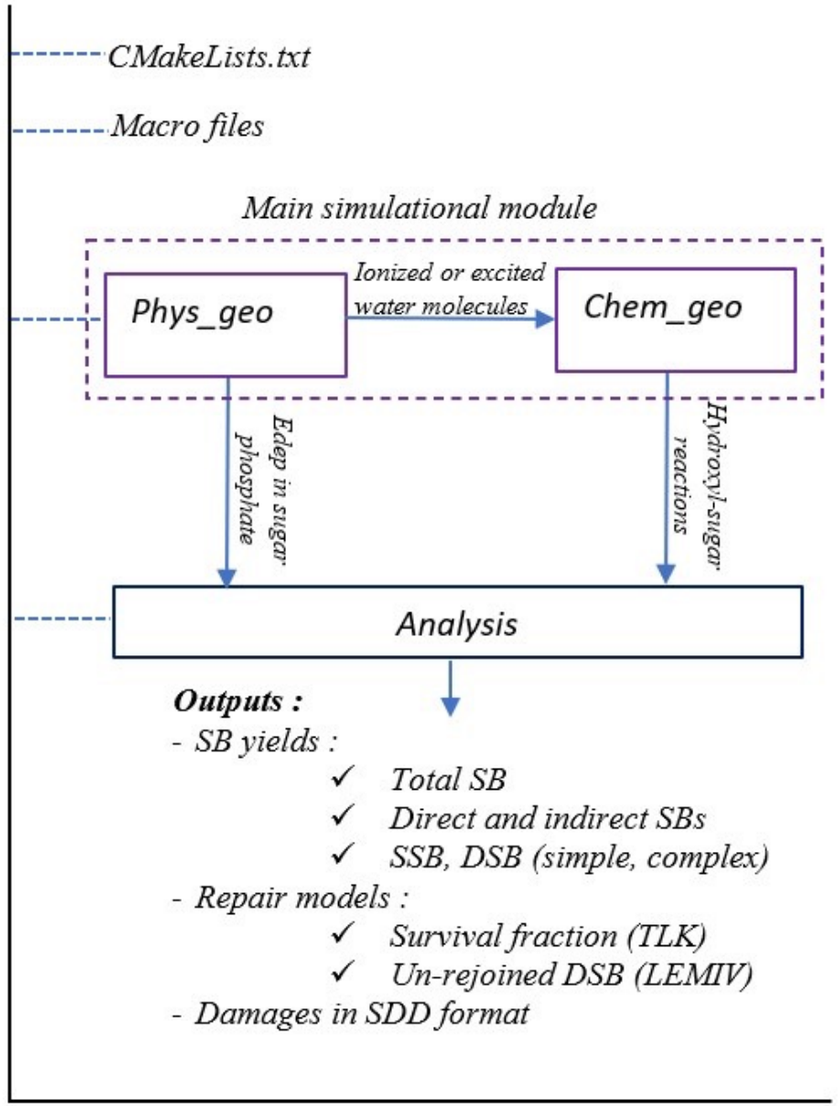
"dsbandrepair" advanced example

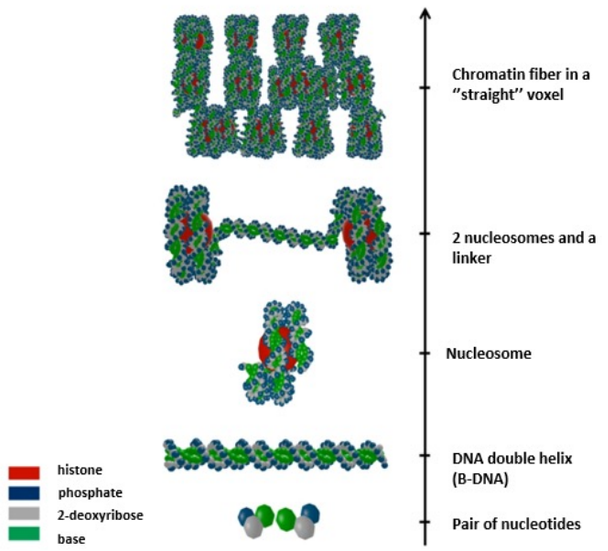
- The example aims to evaluate the **early** radiation-induced DNA damage
- It combines:
  - **Geometrical models** of nuclei with full genome content constructed with DnaFabric (Comput. Phys. Comm. 2016 204:159-169)
  - **Physics** for direct strand breaks (SB) and initialisation of the physico-chemical stage
  - **Chemistry** for indirect SB
  - **Repair models**: Two Lesion Kinetic (TLK) for Survival fraction, Local Effect Model (LEM-IV) for Un-rejoined DSB, Belov's model for repair proteins kinetics
- This is an advanced example located in **$G4EXAMPLES/advanced/dna/dsbandrepair**
- An alternative example for DNA damage calculation: **$G4EXAMPLES/advanced/dna/moleculardna**
- Support MPI parallelism

Structure of "dsbandrepair"

- Three modules: Phys_geo, Chem_geo, & Analysis.
  - **Can be run separately**
  - **Phys_geo module:**
    - Physical stage
    - G4EmDNAPhys_opt2, G4EmDNAPhys_opt4 or G4EmDNAPhys_opt6.
    - **Direct damages**
  - **Chem_geo module:**
    - Physico-chemical stage
    - Chemical stage
    - SBS (G4DNAChem_opt2), IRT_syn (G4DNAChem_opt3_extended)
    - **Indirect damages**
  - **Analysis module:**
    - Score and classify DNA damages
    - Repair models: TLK, LEMIV, Belov's model



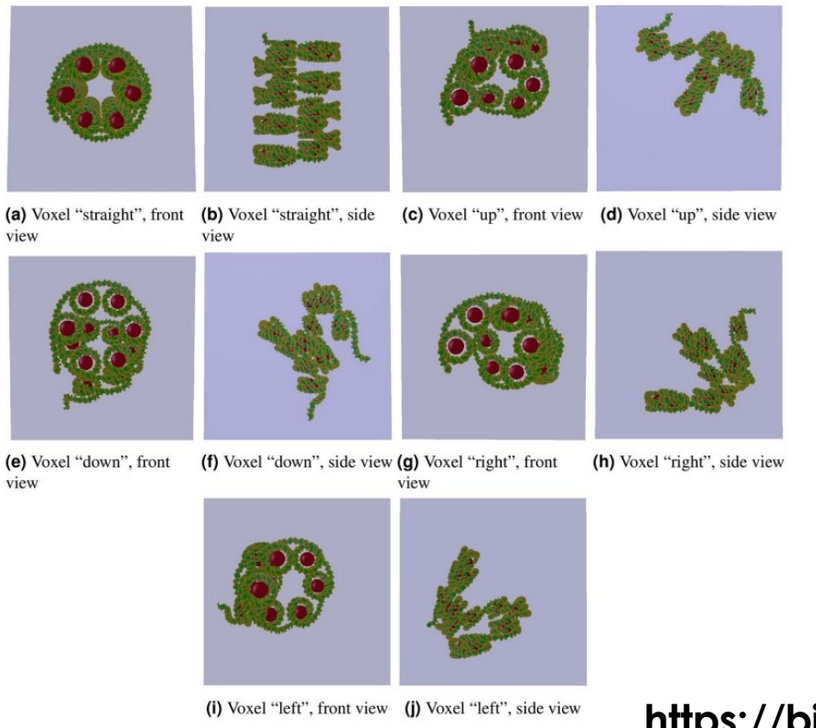
DnaFabric geometry

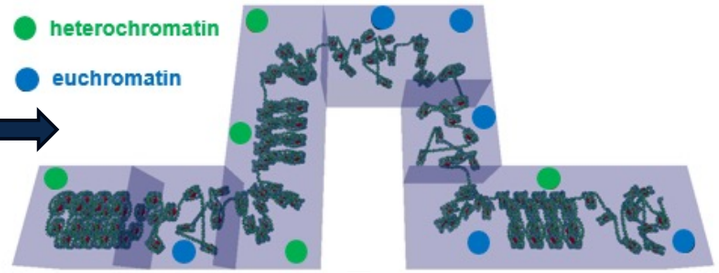


DnaFabric generates, edits, displays and exports complex DNA geometrical models
https://doi.org/10.1016/j.cpc.2016.02.019

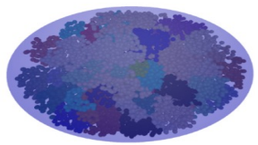
Shape and orientation
- Voxel "Straight"
- Voxel "Up"
- Voxel "Down"
- Voxel "Right"
- Voxel "Left"

Chromatin compaction
- Heterochromatin
- Euchromatin

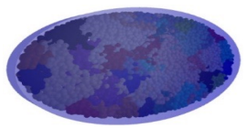




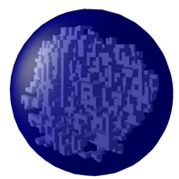
yeast, bacteria, human cell nuclei



Human fibroblast (6 Gbp)



Human endothelium (6Gbp)



S. Cerevisiae (12 Mbp)

https://bitbucket.org/sylMeylan/opendnafabric

Geometry files - voxels

VoxelDown.fab2g4dna

```
# This a fab2g4 file generated by the Fabric software in order for it to be imported within a Geant4 simulation.

_Version 1

# General informations

_Name   VoxelDown
_Size   40
_Number voxelNucleosome 12
_Number voxelLinker 13
_Number voxelBasePair   2415

# Molecule radius
# molecule name, molecule radius (nm), water radius (nm) if any

_Radius phosphate1  0.27    0.459
_Radius deoxyribose1    0.29    0.493
_Radius base_adenine    0.3 0.51
_Radius base_thymine    0.3 0.51
_Radius base_guanine    0.3 0.51
_Radius base_cytosine   0.3 0.51
_Radius deoxyribose2    0.29    0.493
_Radius phosphate2  0.27    0.459
_Radius histone 2.4 0
# Volume placements
# placement name, material, strand, copy number, x (nm), y (nm), z (nm)

# Start linker placements
_pl phosphate1  homogeneous_dna 1   0   10.76873589 -5.684747219    -20.02845001
_pl deoxyribose1    homogeneous_dna 1   0   10.43498039 -5.487388611    -19.91998672
_pl base_adenine    homogeneous_dna 1   0   10.33613682 -5.912311554    -19.75789261
_pl base_thymine    homogeneous_dna 2   0   9.783616066 -6.140942574    -19.58668137
_pl deoxyribose2    homogeneous_dna 2   0   9.282407761 -6.162928104    -19.43764877
_pl phosphate2  homogeneous_dna 2   0   9.296749115 -6.529817104    -19.26100349
```

Voxel characteristics

Molecules characteristics

Molecules placement

Heterochromatin

- VoxelStraight
- VoxelDown
- VoxelUp
- VoxelLeft
- VoxelRight

Euchromatin

- VoxelStraight2
- VoxelDown2
- VoxelUp2
- VoxelLeft2
- VoxelRight2

Geometry files - nucleus

human_fibroblast.fab2g4dna

```
# This a fab2g4 file generated by the Fabric software in order for it to be imported within a Geant4 simulation.

_Version 1

# World description

# Voxel placements
# name, x (nm), y (nm), z (nm)
_Type Ellipsoid 9850 7100 2500

_pl VoxelLeft       0  0  -5080  -3600  120  1  0  0  0  1  0  0  0  1
_pl VoxelStraight   0  0  -5040  -3600  120  0  0  -1 0  1  0  1  0  0
_pl VoxelStraight   0  0  -5000  -3600  120  0  0  -1 0  1  0  1  0  0
_pl VoxelStraight   0  0  -4960  -3600  120  0  0  -1 0  1  0  1  0  0
_pl VoxelStraight   0  0  -4920  -3600  120  0  0  -1 0  1  0  1  0  0
_pl VoxelStraight   0  0  -4880  -3600  120  0  0  -1 0  1  0  1  0  0
_pl VoxelStraight   0  0  -4840  -3600  120  0  0  -1 0  1  0  1  0  0
_pl VoxelDown2      0  0  -4800  -3600  120  0  0  -1 0  1  0  1  0  0
_pl VoxelRight      0  0  -4800  -3640  120  0  0  -1 1  0  0  0  -1 0
_pl VoxelStraight   0  0  -4800  -3640  160  0  -1 0  1  0  0  0  0  1
_pl VoxelUp         0  0  -4800  -3640  200  0  -1 0  1  0  0  0  0  1
```

Nucleus geometry

Voxel type | **Chrom. ID** | **Dom. ID** | **Position** | **Rotation**

Available geometries: Human fibroblast, human endothelium (HUVEC), yeast (S. Cerevisiae)

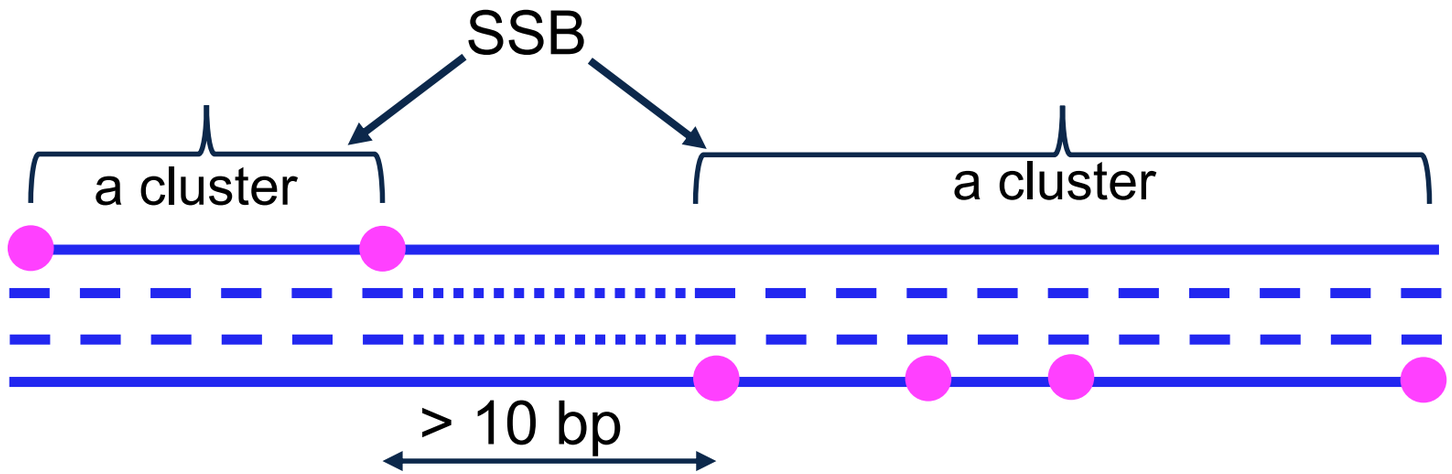
Analysis

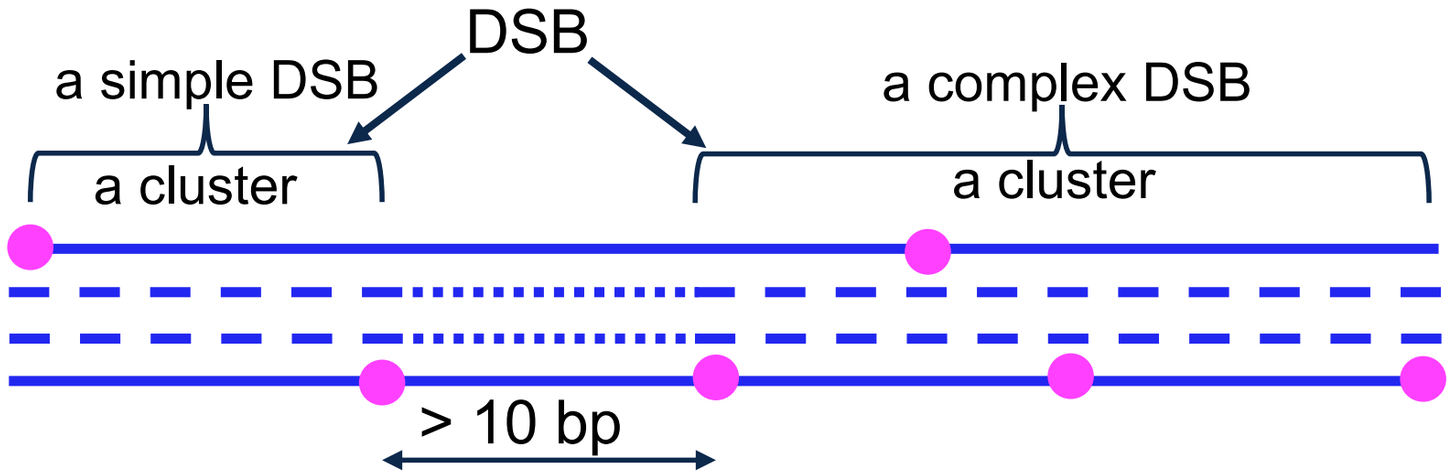
- Independent C++ code requiring ROOT
- Parameters of analysis are defined in macro file
- Workflow of the process:
  - Direct SB calculation for physical stage output
  - Indirect SB calculation for chemical stage output
  - Clustering and classification
  - Repair models

- **Direct DNA damage assessment:** using E threshold of 17.5 eV *(Sci. Rep., vol. 7:11923, 2017)* in the nucleotide backbone volume
- **Indirect DNA damage assessment:** P = 40% uniform random among chemical reactions between °OH and 2-Deoxyribose DNA component (Sci. Rep., vol. 7:11923, 2017)
- E and P can be changed in macro file.

Clustering algorithm and classification

- Clustering algorithm is applied to both direct and indirect SBs
- A new cluster is registered if the location of its first SB is more than d = 10 bp (default) far away from the location of the last SB of the previous cluster
- d can be changed in macro file





Example of macro for physical stage (dsbandrepair.in)

- Run dsbandrepair with simple cell nucleus defined in "dsbandrepair.in" macro file
- Open dsbandrepair.in, you will see
  - /dsbandrepair/det/celldefinitionfile dnafabric_geometries/lightGeometryForTest.fab2g4dna
  - /dsbandrepair/det/voxeldefinitionfile dnafabric_geometries/VoxelDown2.fab2g4dna
  - /dsbandrepair/det/voxeldefinitionfile dnafabric_geometries/VoxelLeft2.fab2g4dna
  - /dsbandrepair/det/voxeldefinitionfile dnafabric_geometries/VoxelRight2.fab2g4dna
  - /dsbandrepair/det/voxeldefinitionfile dnafabric_geometries/VoxelStraight2.fab2g4dna
  - /dsbandrepair/det/voxeldefinitionfile dnafabric_geometries/VoxelUp2.fab2g4dna

Define DNA content of 5 voxel types of eurochomatin

```
# Voxel placements
# name, x (nm), y (nm), z (nm)
_Type Spherical 520

_pl VoxelDown2  0 0 -80 240 -80 1 0 0 0 1 0 0 0 1
_pl VoxelStraight2  0 0 -80 200 -80 1 0 0 0 0 1 0 -1  0
_pl VoxelStraight2  0 0 -80 160 -80 1 0 0 0 0 1 0 -1  0
_pl VoxelStraight2  0 0 -80 120 -80 1 0 0 0 0 1 0 -1  0
_pl VoxelStraight2  0 0 -80 80  -80 1 0 0 0 0 1 0 -1  0
_pl VoxelStraight2  0 0 -80 40  -80 1 0 0 0 0 1 0 -1  0
_pl VoxelStraight2  0 0 -80 0 -80 1 0 0 0 0 1 0 -1  0
_pl VoxelStraight2  0 0 -80 -40 -80 1 0 0 0 0 1 0 -1  0
_pl VoxelLeft2  0 0 -80 -80 -80 1 0 0 0 0 1 0 -1  0
```

Describe cell nucleus and voxel filling info

Example of macro for chemical stage (chem.in)

```
########################## Macro file for Chem_geo ##########################
#
/process/had/verbose 0
/process/em/verbose 0
/control/verbose 0
/run/verbose 0
/event/verbose 0
/tracking/verbose 0
/process/verbose 0
#
#========================  CHOOSING CHEMYSTRYLIST   ======================
# 02 options for chemList: G4EmDNAChemistry_option2 (default), G4EmDNAChemistry_option3
/dsbandrepair/chem/chemList G4EmDNAChemistry_option2
#
#
#========================  Set ENDTIME for Chemical reactions   ======================
#
/scheduler/endTime 5 nanosecond
#
```

Example of macro for analysis (analysis.in)

```
#============================================   PARAMETERS FOR DAMAGES   ============================================
#" **Note: "#" is used for comments. Thereby, remove the "#" at the beginning of folowing commands to use them.
#/ana/cellNucleusName Fibroblast             # Optional;
#/ana/ouputName  Output0.dat                 #Set name for output file, default is Output.dat
#/ana/thresholdFordirectSBSelection 17.5     # eV; Threshold for selecting direct damages; default value is 17.5 eV
#/ana/probForIndirectSBSelection 40          # %; Propability for selecting indirect damages; default value is 40 %
#/ana/skipIndirectDamages                    # Use it if users want to skip analyzing indirect damages
#
#=====================================  PARAMETERS FOR CLASSIFYING DAMAGES  ====================================
#
## **Note: For classifying damages, repair models (TLK, LEMIV..), user can load damages from an existing SDD file.
#/ana/loadDamagesFromSDD SDDformat_Output.dat   #load damages from existing SDD file. It'll skip analyzing root files.
#/ana/BpForDSB  10                           # The minimum distance between two clusters, default value is 10
#/ana/unitOfNormalization 2                  #unit type for normization: 1: [Gy-1 * Gbp-1]; 2 : [Gy-1]; default is 1
```

SBs calculation

Clustering: SBs => DSBs

Output files: SDD and ASCII file with yields of SSBs, DSBs (simple and complex), DSB type (direct, indirect, hybrid)

Hands-on practice on “dsbandrepair” advanced example

Build and run “dsbandrepair” advanced example

- **Build** and **compile** dsbandrepair. Open a terminal, run the following commands:
  - cd
  - cp –R $G4EXAMPLES/advanced/dna/dsbandrepair .
  - mkdir build-dsbandrepair
  - cd build-dsbandrepair
  - cmake ../dsbandrepair
  - make ← make –jN if you have N cores
- Next, build “analysis” module (need ROOT package):
  - mkdir myAna
  - cd myAna
  - cmake ../../dsbandrepair/analysis
  - make
  - cd ../

Build and run “dsbandrepair” advanced example

- **Build** and **compile** dsbandrepair with **MPI**:
  - Install G4mpi library (*require openmpi-1.8 installed*):
  - cd
  - mkdir g4mpi && cd g4mpi/
  - mkdir build && cd build
  - cmake $G4EXAMPLES/extended/parallel/MPI/source -DCMAKE_INSTALL_PREFIX=../
  - make && make install
  - **Build** and **compile** dsbandrepair:
  - cd
  - cp –R $G4EXAMPLES/advanced/dsbandrepair .
  - mkdir build-dsbandrepair && cd build-dsbandrepair
  - cmake -DUSE_MPI=TRUE -DG4mpi_DIR=<g4mpi-path>/lib[64]/G4mpi-V.m.n ../dsbandrepair
  - make

Running with MPI is not covered in this hands-on

- See README for more details on using dsbandrepair with MPI.

Hands-on practice on “dsbandrepair” advanced example

- Edit dsbandrepair.in to run for 1500 e- of 5 keV:
  - /gps/particle e-
  - /gps/energy 5. keV
  - /run/beamOn 1500
- Save the changes.
- **Run physical stage:**
  - ./dsbandrepair dsbandrepair.in
- Try to analyze:
  - Open file analysis.in, change the name of output file
    - /ana/ouputName Output1.dat
    - Note: If there is a « #» at the beginning of a command, remove it for invoking.
  - Save and run in Terminal: ./myAna/runAna analysis.in

Hands-on practice on “dsbandrepair” advanced example

- See results in Output1.dat :
  - Do you see direct SBs? indirect SBs?
- **Run chemical stage:**
  - Open file chem.in, change chemistry list:
    - /dsbandrepair/chem/chemList G4EmDNAChemistry_option3
  - Save file and run in Terminal:
    - ./dsbandrepair chem.in chem
    - Note: check the build directory if there is a folder ‘chem_output’, then delete it before executing the above command. To delete, use: rm –rf chem_output
- Try to analyze:
  - Open file analysis.in, change the name of output file
    - /ana/ouputName Output2.dat
  - Save and run in Terminal: ./myAna/runAna analysis.in
  - Do you see indirect SBs? Why?

Hands-on practice on “dsbandrepair” advanced example

- Play with other parameters in analysis.in to see how they affect the DNA damage results:
  - Change the break-energy for direct SB:
    - /ana/thresholdFordirectSBSelection 5
    - Save and run : ./myAna/runAna analysis.in
  - Or change the Propability for selecting indirect damages:
    - /ana/probForIndirectSBSelection 60
    - Save and run : ./myAna/runAna analysis.in
  - Or change the the minimum distance between two clusters:
    - /ana/BpForDSB 5
    - Save and run: ./myAna/runAna analysis.in

  Note: For more details of these parameters, see the lecture on Biology

- Try to re-run the chemical stage with G4EmDNAChemistry_option2

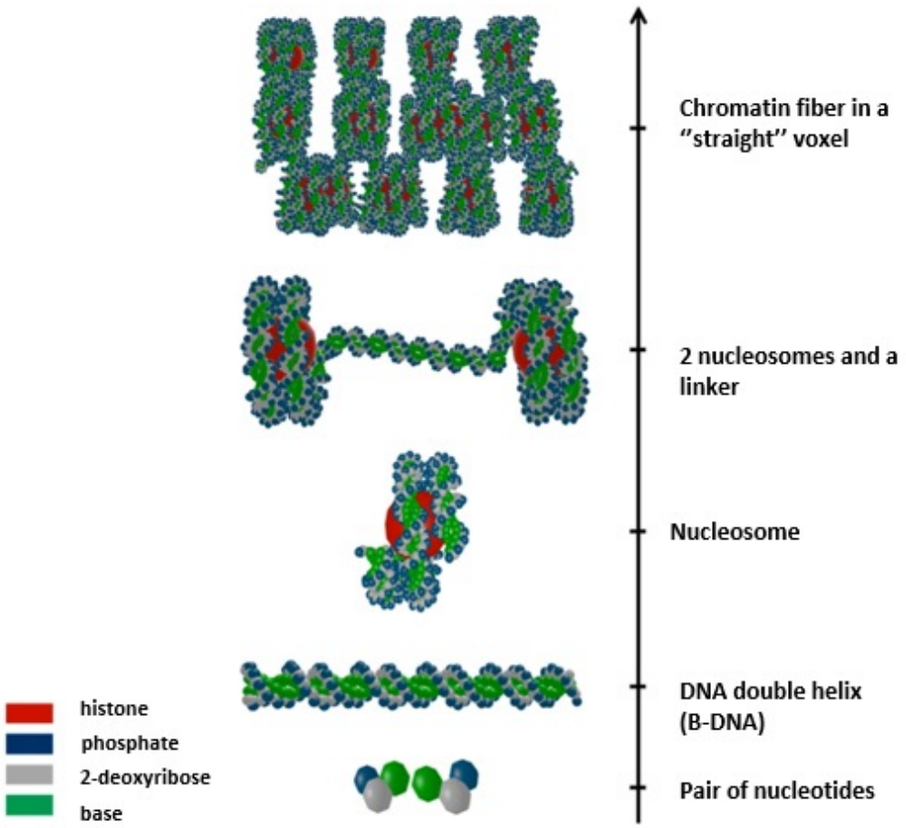
Homework

- Repair models:
  - Increase the number of primary electrons and run:
  - Invoke TLK and LEM-IV model in analysis.in
  - Plot the Survival fraction curve from the data contained in TLK_Ouput.dat
  - Plot the un-rejoined DSB from the data contained in LEMIV_Ouput.dat
- Read README.txt, play with human cell nuclei:

E-mail me if you need help: anhlt_inst@mst.gov.vn

Back-up slides

Simulation of direct damage



- **DNA geometrical description** using voxels of 40 nm side :
  - build with the DNAFabric software
  - Exported to Geant4-DNA application: PhysGeoImport.cc, DetectorConstruction.cc
- Physics: **Geant4-DNA constructor** (easily changed by the user)
- Score energy deposits in sugar-phospahte backbone (including hydration shell)

Example of macro for physical stage (dsbandrepair/macros/fibroblast.in)

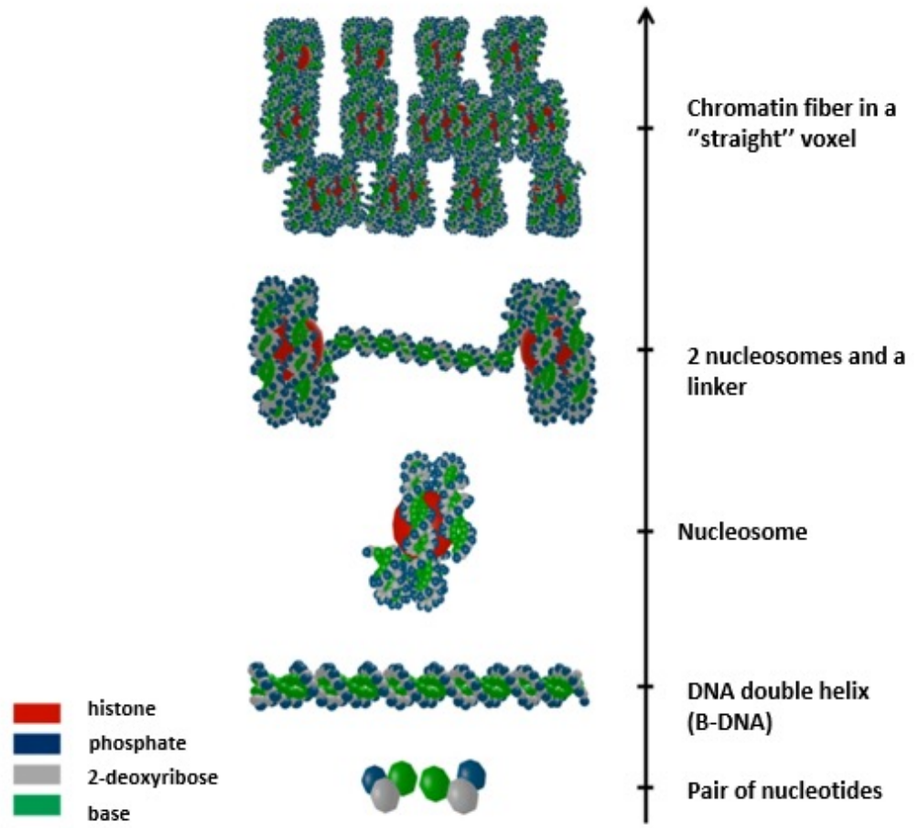
fibroblast.in

```
########################## Macro file for Phys_geo ##########################
#
#======================  PATHS FOR INPUTS          ======================
#
## if don't set semi-lengths for world Box, code will use the sizes
## of cell nucleus for calculating: WorldSemiXY = 2*SemiXY, WorldSemiZ = SemiZ.
/dsbandrepair/det/worldBoxSizes 100 100 5 um  # Set SemiX, SemiY, SemiZ for world box;

/dsbandrepair/det/celldefinitionfile        ../dnafabric_geometries/human_fibroblast.fab2g4dna

/dsbandrepair/det/voxeldefinitionfile       ../dnafabric_geometries/VoxelDown.fab2g4dna
/dsbandrepair/det/voxeldefinitionfile       ../dnafabric_geometries/VoxelLeft.fab2g4dna
/dsbandrepair/det/voxeldefinitionfile       ../dnafabric_geometries/VoxelRight.fab2g4dna
/dsbandrepair/det/voxeldefinitionfile       ../dnafabric_geometries/VoxelStraight.fab2g4dna
/dsbandrepair/det/voxeldefinitionfile       ../dnafabric_geometries/VoxelUp.fab2g4dna

/dsbandrepair/det/voxeldefinitionfile       ../dnafabric_geometries/VoxelDown2.fab2g4dna
/dsbandrepair/det/voxeldefinitionfile       ../dnafabric_geometries/VoxelLeft2.fab2g4dna
/dsbandrepair/det/voxeldefinitionfile       ../dnafabric_geometries/VoxelRight2.fab2g4dna
/dsbandrepair/det/voxeldefinitionfile       ../dnafabric_geometries/VoxelStraight2.fab2g4dna
/dsbandrepair/det/voxeldefinitionfile       ../dnafabric_geometries/VoxelUp2.fab2g4dna
#
#======================  CHOOSING DNA PHYSICSLIST  ======================
#
/dsbandrepair/phys/physicsList G4EmDNAPhysics_option2
#
#======================  INITIALIZE   RUNMANAGER   ======================
#
/run/initialize
#
```

Example of macro for physical stage – continued (dsbandrepair/macros/fibroblast.in)

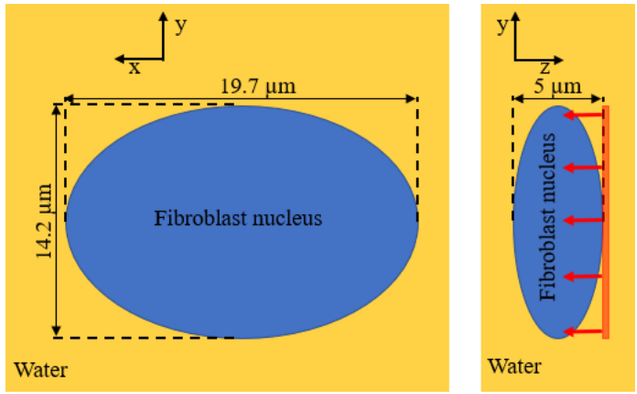
```
#========================  BEAM SPATIAL DISTRIBUTION ======================
# beam profile: Parallel, Ellipse;
# See cell-definition file for setting dimensions below:
/gps/pos/type Plane
/gps/pos/shape Ellipse
/gps/pos/halfx 9850 nm
/gps/pos/halfy 7100 nm
/gps/pos/centre 0. 0. 2500. nm
/gps/direction 0 0 -1

#
#========================  SET PARTICLE'S INFO       ======================
#
/gps/particle proton
/gps/energy 1. MeV
#
#========================  SET EVENTS and START A RUN  ====================
#
/run/printProgress 10  # Print progress for each mpi process
/run/beamOn 2
```

Simulation of indirect damage



- Chemical stage simulation:
  - The DNA geometry is translated in terms of **"static chemical molecules"** in the Chemical stage
  - **G4EmDNAChemistry_option2** (SBS) or **G4EmDNAChemistry_option3_extended** (IRT-sync: G4EmDNAChemistry_option3 + radicals/DNA reactions) is then used for simulating the diffusion of radicals and their reactions with each other or with DNA constituents in an Step by Step mode
  - **Scavenging not explicitly simulate**d: the absorption of radicals by the histones and a chemical step duration of 5 ns account for scavenging effects.
- Score all the reactions between hydroxyl radical and 2-Deoxyribose DNA component

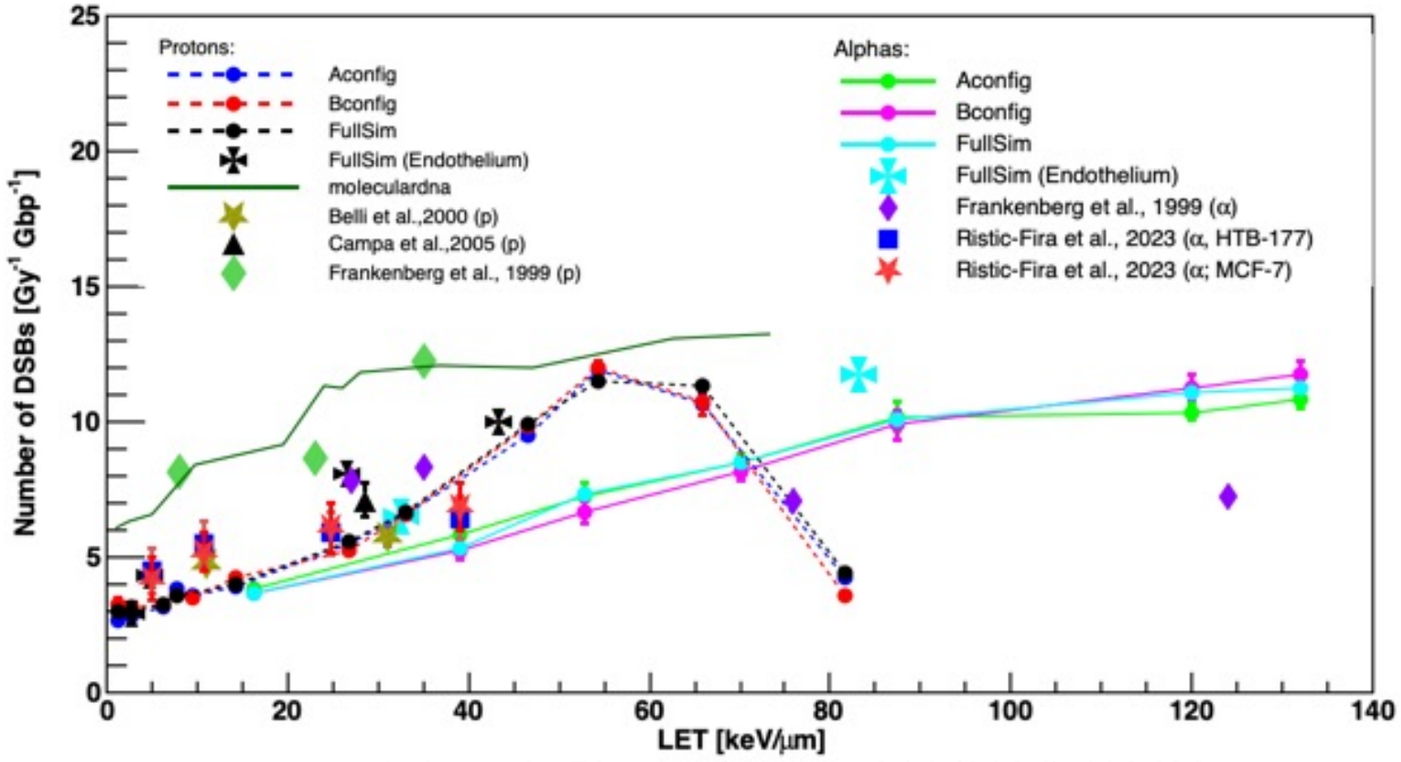
Benchmarking results – DSB yields



- Fibroblast
- euchromatin (34%), heterochromatin (66%)

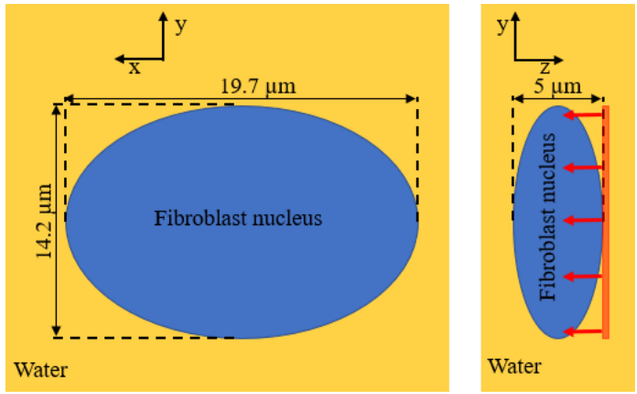
Aconfig:
- **G4DNAPhys_opt2 + G4DNAChem_opt2**
- **Using SBS**
- **End-time: 5 ns**

Bconfig:
- **G4DNAPhys_opt2 + G4DNAChem_opt3**
- **Using IRT_syn**
- **End-time: 5 ns**



Anh et al., Physica Medica, 214 (2024),103422

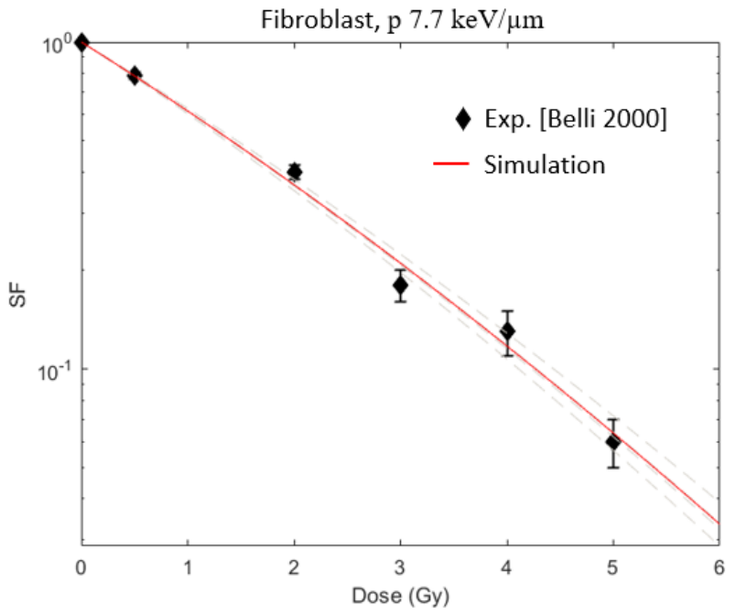
Benchmarking results – biological endpoints

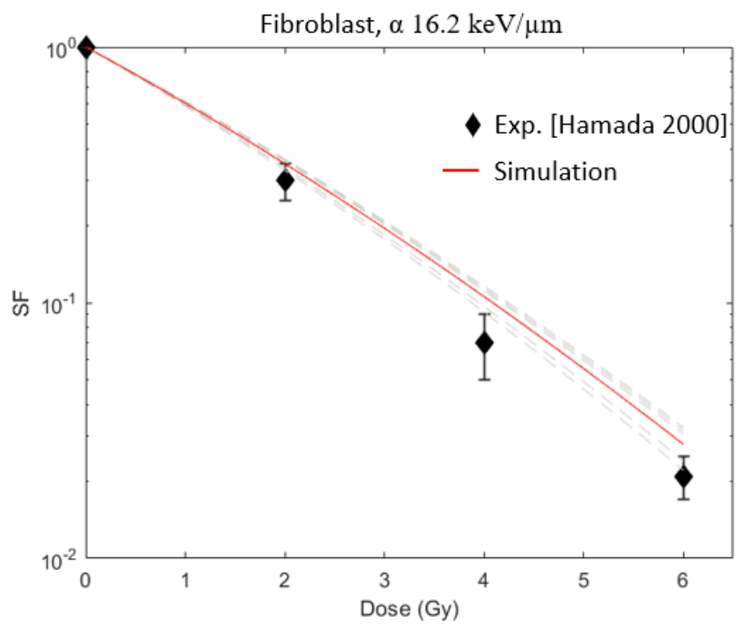


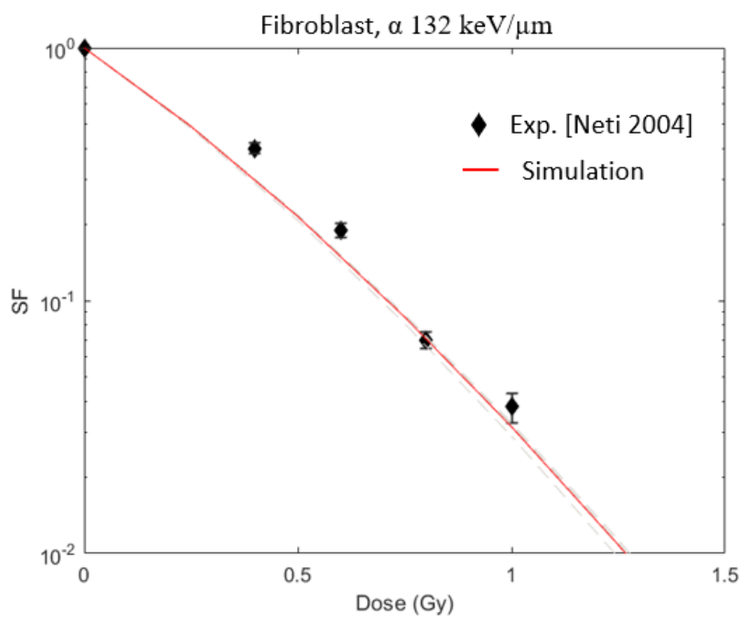
TLK model

Fibroblast, Survival fraction

Parameters of the model kept identic to the original ones published for fibroblast cells

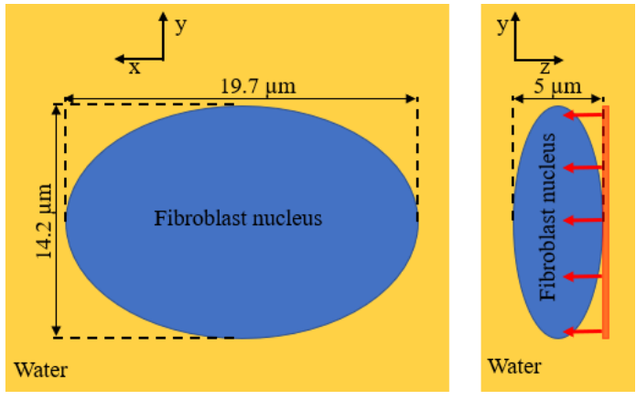




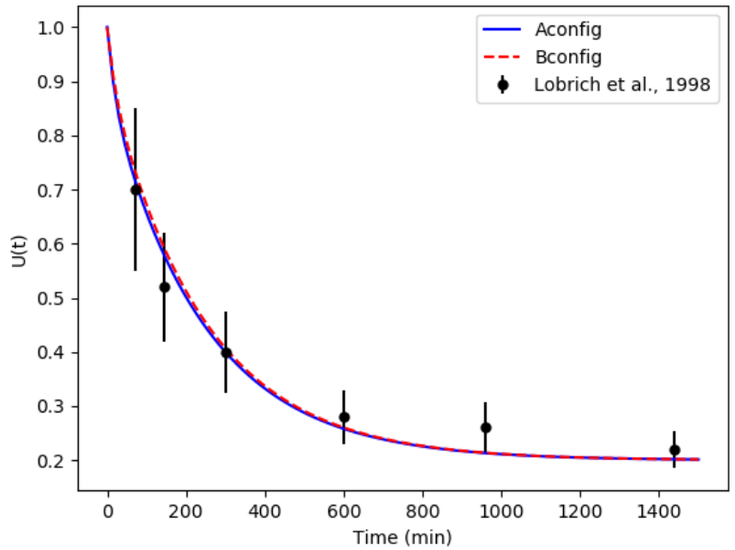


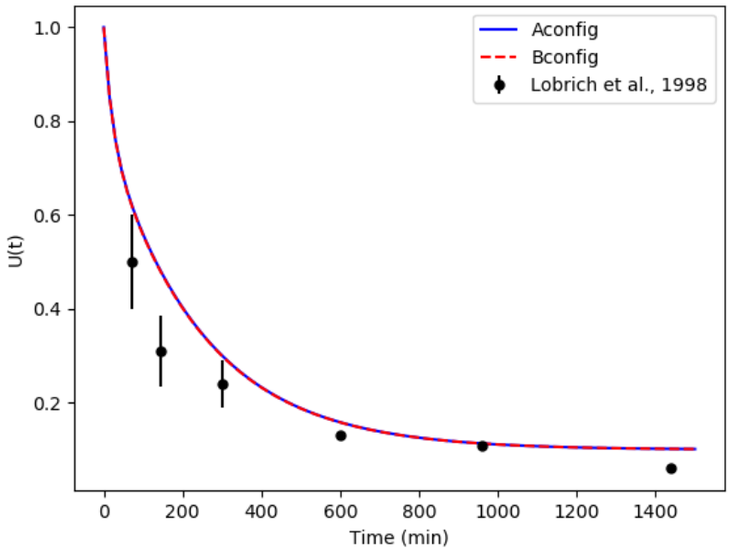
Anh et al., Physica Medica, 214 (2024),103422

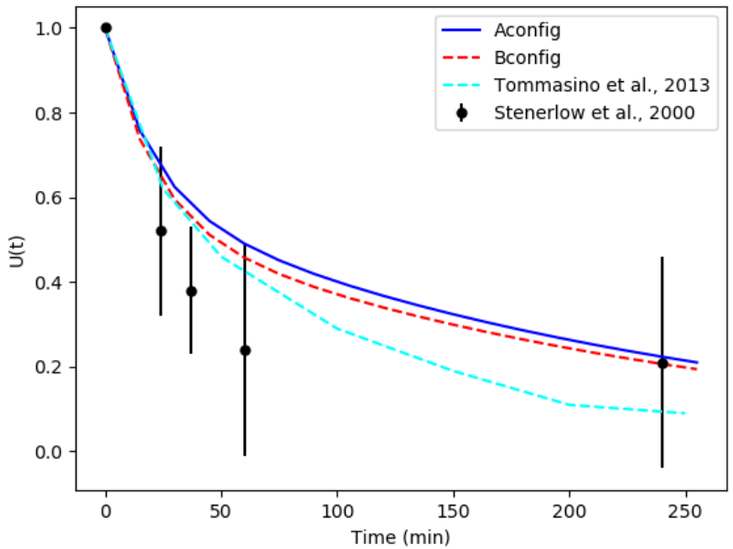
Benchmarking results – biological endpoints



LEM IV model
Fibroblast, Unrejoined DSBs

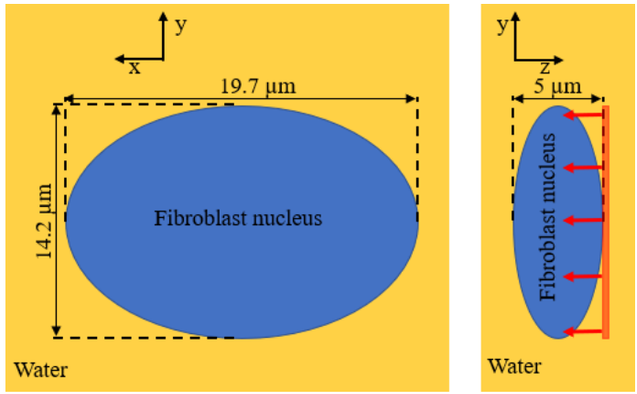






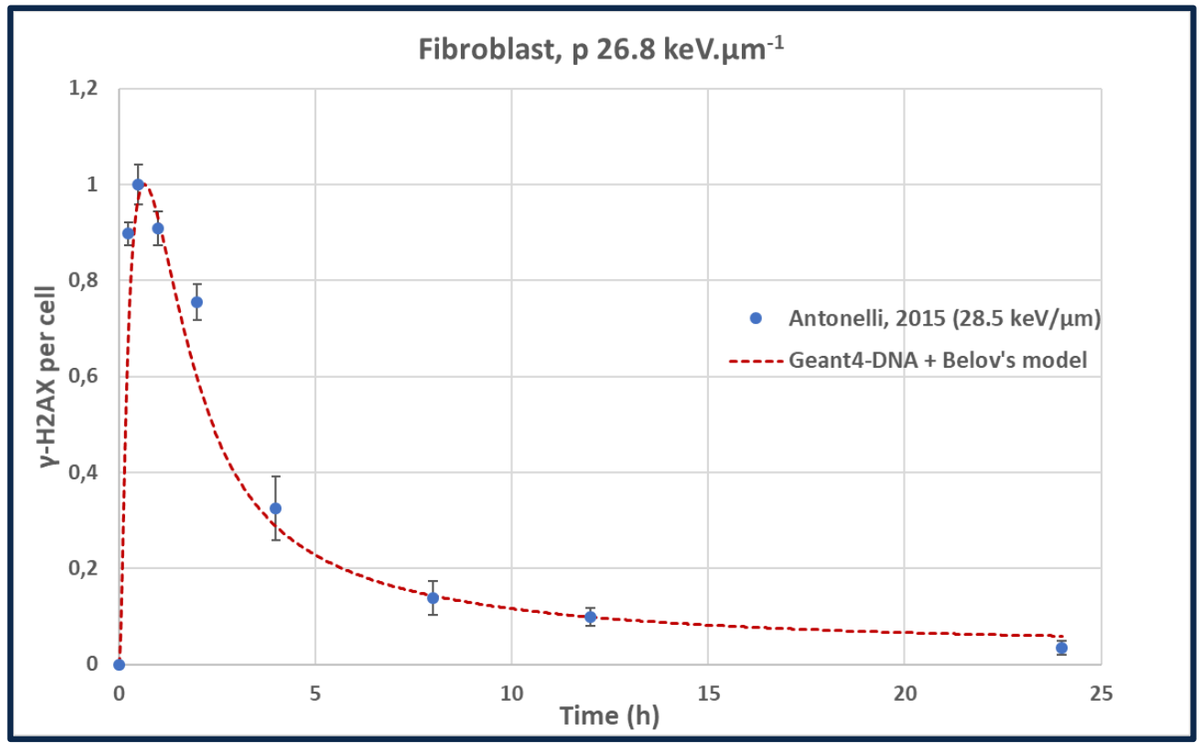
Anh et al., Physica Medica, 214 (2024),103422

Benchmarking results – biological endpoints



Belov's model

Fibroblast, γ-H2AX foci



Example of macro for analysis continued (dsbandrepair/macros/analysis.in)

```
#
#==========================================  PARAMETERS FOR TLK MODEL  ==========================================
#
/ana/TLK/used                   true    #flag to enable/disable TLK model. Enabled if: true
/ana/TLK/lambda1                3.0     #λ1 and λ2 are respectively simple DSB and complex repair probability
/ana/TLK/lambda2                0.03    #λ1 and λ2 are respectively simple DSB and complex repair probability
/ana/TLK/beta1                  0.01    #β1 and β2 are respectively simple DSB and complex misrepair probability
/ana/TLK/beta2                  0.06    #β1 and β2 are respectively simple DSB and complex misrepair probability
/ana/TLK/eta                    0.0002  # h-1;a binary misrepair probability ; 0.0011 for DNAFabric fibroblast
#/ana/TLK/eta                    0.0011  # h-1;a binary misrepair probability; 0.0011 for DNAFabric fibroblast
/ana/TLK/doseMax                6.0     #Compute SF up to doseMax Gy and with step deltaDose
/ana/TLK/deltaDose              0.25    #Compute SF up to doseMax Gy and with step deltaDose

#
#==========================================  PARAMETERS FOR LEMIV MODEL  ==========================================
#
/ana/LEMIV/used                 true   #flag to enable/disable LEMIV model. Enabled if: true
#/ana/LEMIV/loopLength           2E6     #length of the loop in bp, default 2Mbp
/ana/LEMIV/Funrej               0       #Funrej is the fraction of DSBs that are not repaired even for late times
/ana/LEMIV/Tfast                0.24    #constant time in h-1
/ana/LEMIV/Tslow                2.81    #constant time in h-1
/ana/LEMIV/timeMax              25      # compute fraction of unrejoined DSB up to timeMax h at deltaT step
/ana/LEMIV/deltaTime            0.25    # compute fraction of unrejoined DSB up to timeMax h at deltaT step
#
#==========================================  PARAMETERS FOR BELOV MODEL  ==========================================
# **Note: The implementation of BELOV model in dsbandrepair is still in development
/ana/BELOV/used                 false    #flag to enable/disable BELOV model. Enabled if: true
/ana/BELOV/Nirrep               0.035   #Nirrep fraction, if it's not be set, fraction of complex DSB will be used
/ana/BELOV/Dz                   1.0     #Dz
```

Output files: ASCII files for each repair model