Recent developments in the TOPAS-nBio radiobiology toolkit

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Background: TOPAS and TOPAS-nBio are Monte Carlo simulation toolkits based on Geant4/Geant4-DNA, aimed at reducing the programming burden of the user. The radiobiology toolkit TOPAS-nBio [1] is an extension to TOPAS [2] and was designed as a set of open-source classes to model biological damage induced by ionizing radiation at the molecular scale. TOPAS-nBio provides users with a tool to model the track structure of particles as well as the chemistry processes of water radiolysis within comprehensive biological geometries, simulating radiation induced biological damage. Furthermore, DNA repair kinetics can be modeled by DAMARIS [3]. We present an update on recent developments in the toolkit.

Material and Methods: TOPAS-nBio is based on and extends the models of Geant4-DNA [4], to include very low-energy interactions of particles and explicitly simulates every particle interaction (i.e., without using condensed histories) as well as propagates radiolysis products. In our first release, we included a full nuclear DNA model based on a model of a fractal globule using a 3D space-filling Hilbert curve. Although this geometry is a good representation of chromosome territories on the microscale level, the DNA density is constant throughout the nucleus, this does not accurately capture specific collocated DNA regions or genes. Furthermore, our original model did not give users the ability to add both heterochromatin and euchromatin geometries in the same nucleus simulation. Currently, we are working towards developing a more advanced nuclear DNA model utilizing genomic data from Hi-C.

The chemical reactions and species provided in Geant4-DNA has also been expanded and a new method based on independent reaction times (IRT) has been implemented into the code. IRT is a stochastic technique consisting of sampling of reaction times and chemical reactions of pairs of species, independent from the surrounding neighbors.

Preliminary results: Using Hi-C data, we are working towards implementing a new representation of nuclear DNA into TOPAS-nBio. This model will include a geometric representation of topologically associating domains (TADs) as spherical volumes (see figure 1A). TADs are self-interacting genomic regions and are specific to each cell line. Each TAD volume will be further voxelized and filled with accurate DNA nucleosome volumes, including a full double helix DNA structure wrapped around histones. Users can specify the geometries of these DNA regions as either heterochromatin or euchromatin (see Figure 1B), this feature is already available in TOPAS-nBio. This new nucleus model will allow for a more accurate geometric representation of specific cell lines to be modeled and eventually can lead to estimations of radiation damage to chromosomes or even specific genes within the cell.

Chemical stage simulations using IRT was successfully implemented into TOPAS-nBio and it was found that they were a factor of 145 faster than with step-by-step tracking.

These new developments will allow users to more accurately estimate initial radiation damage to DNA and predict endpoints relevant to *in vitro* experiments by using DAMARIS. Additionally, visualization of damage is also available to represent 3D and 2D images of DNA foci.

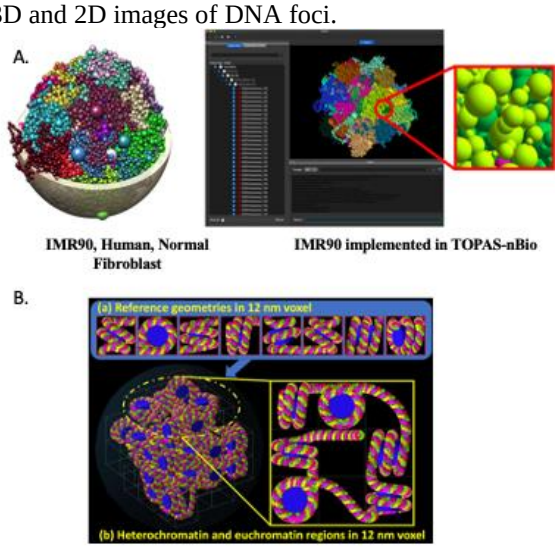

Figure 1: A. An illustration of the nucleus of a human fibroblast (IMR90) represented with Hi-C data showing the location of the TADs and this implementation in TOPAS-nBio. B. Voxel representation of heterochromatin and euchromatin geometries in the nucleus model of TOPAS-nBio.

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