Geant4-DNA chemistry

geant4-dna.org

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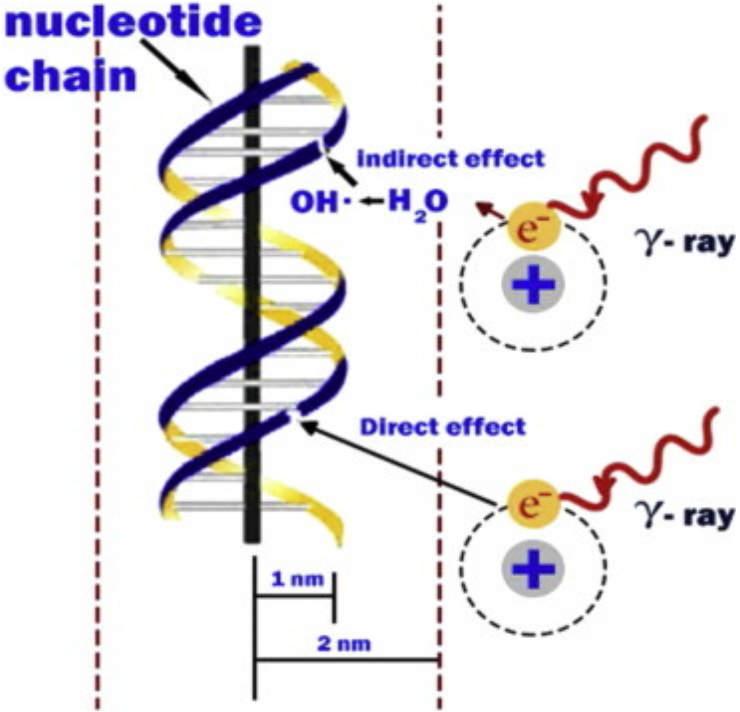
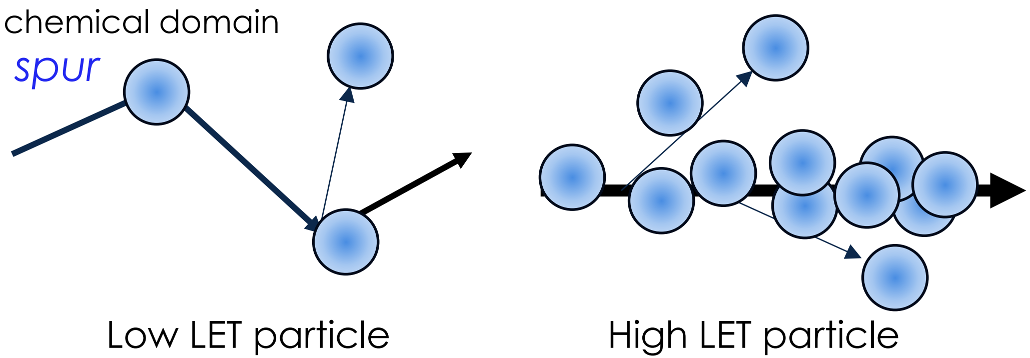
Geant4 version 11.4
Released in December 2025

Indirect Action



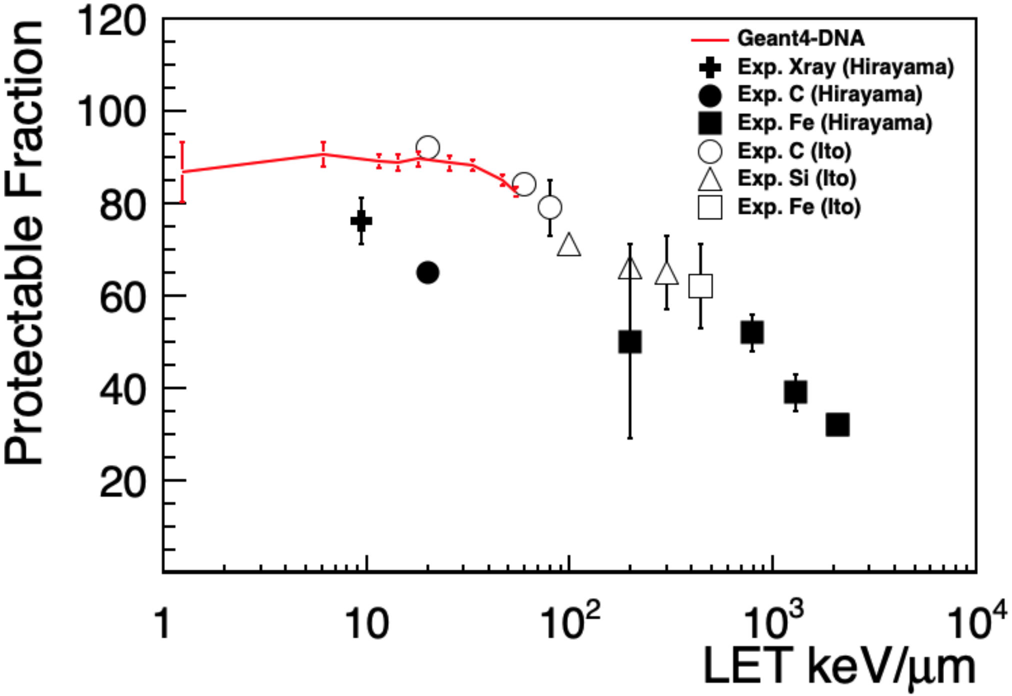
- **Indirect Action**: DNA damage type caused by reactive species such as OH radical which created from radiolysis of water molecule.
  - ☐ **Water radiolysis framework**:
    - — molecule production
    - — molecule diffusion
    - — molecular reaction

This framework must be fully compatible with physical simulation



Ref: J Rad. Res. App. Sci. (2015) 8, 247-254

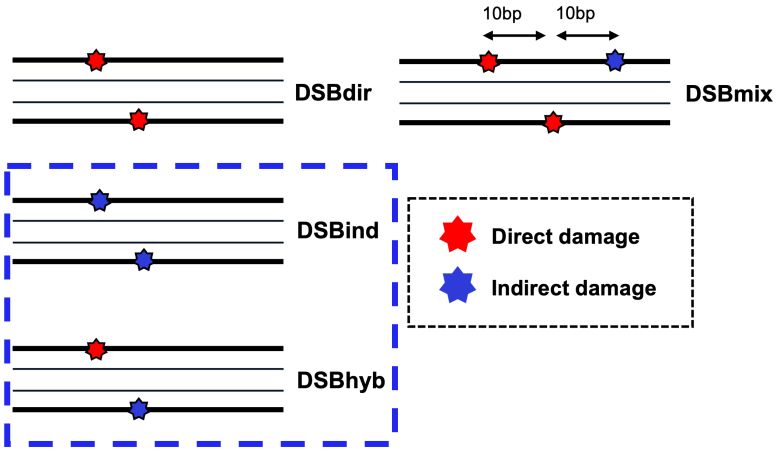
Importance of Indirect Action on DNA damage



It is well known that indirect action is the most dominant process for DNA damage creation at low-LET radiation irradiation!

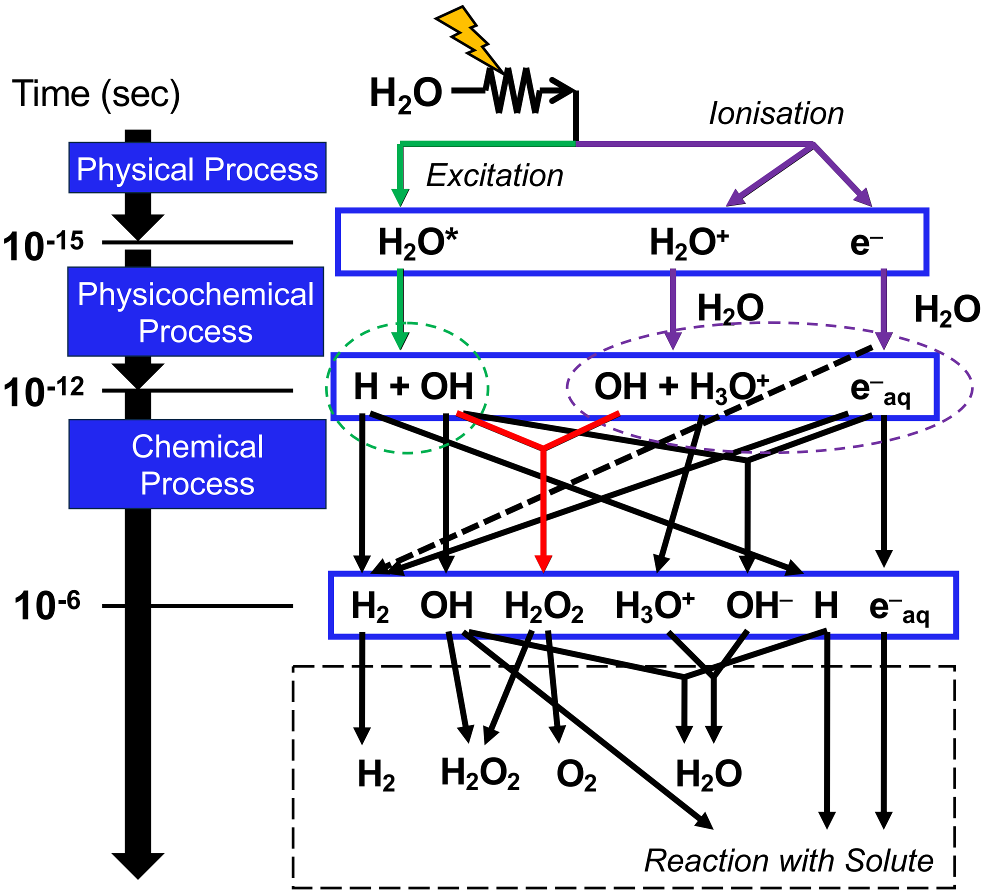
Protectable Fraction (damage type based)

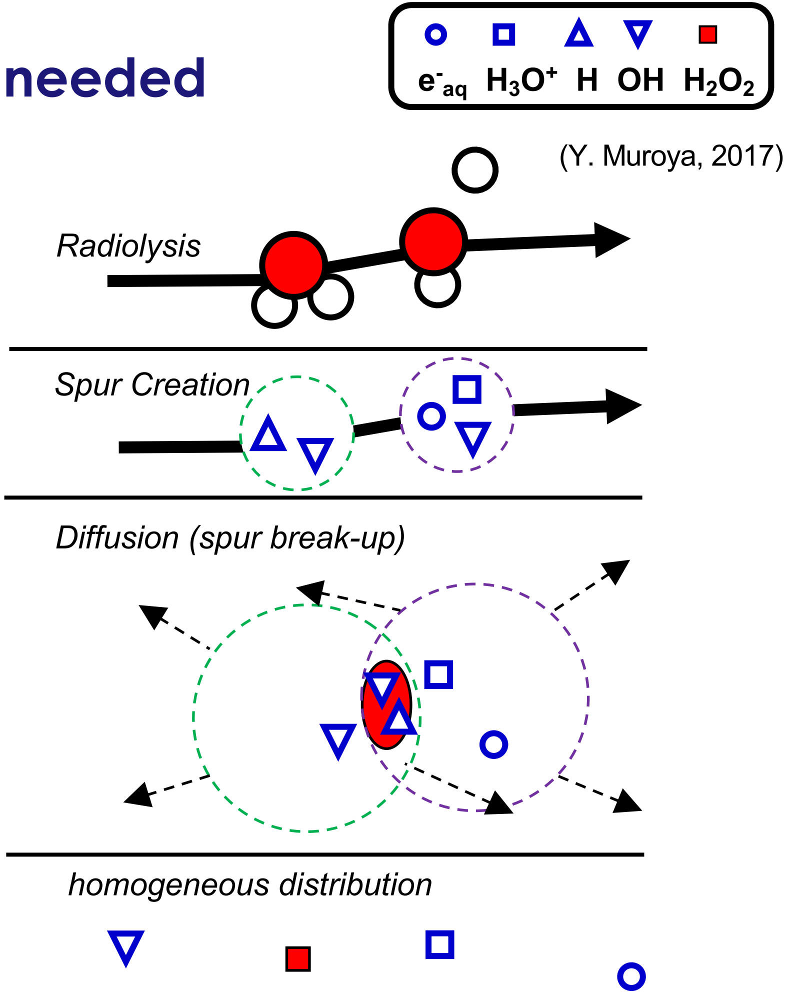
$$\frac{\boxed{N_{DSB_{ind}} + N_{DSB_{hyb}}}}{N_{DSB_{dir}} + N_{DSB_{mix}} + N_{DSB_{ind}} + N_{DSB_{hyb}}}$$



Physica Medica 105 (2023) 102508

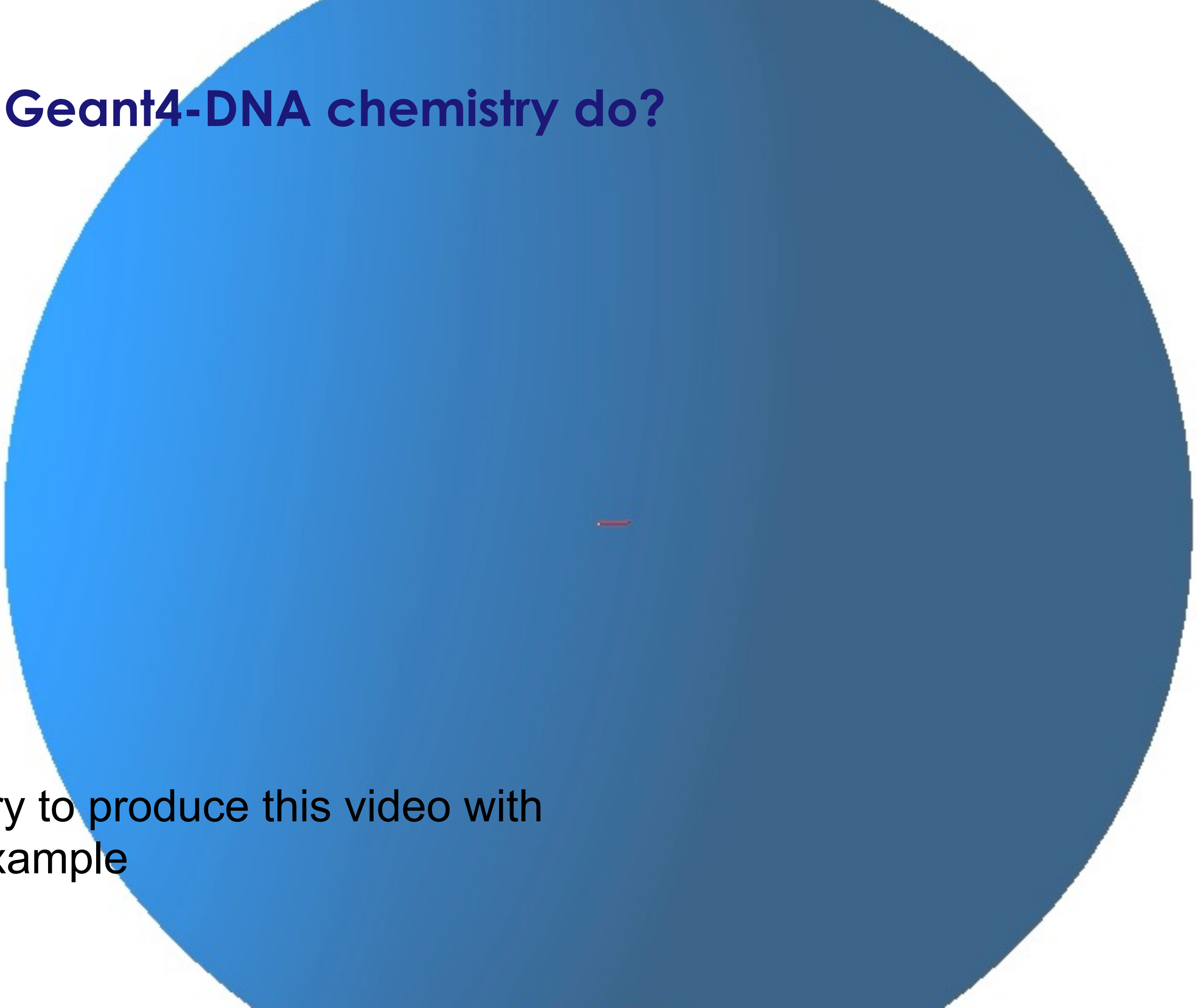
You remember, chemistry module needed





(Y. Muroya, 2017)

What Geant4-DNA chemistry do?



We can try to produce this video with chem3 example

Physico-chemical stage

t=10^{-15}s

t=10^{-12}s

During this stage, water molecules

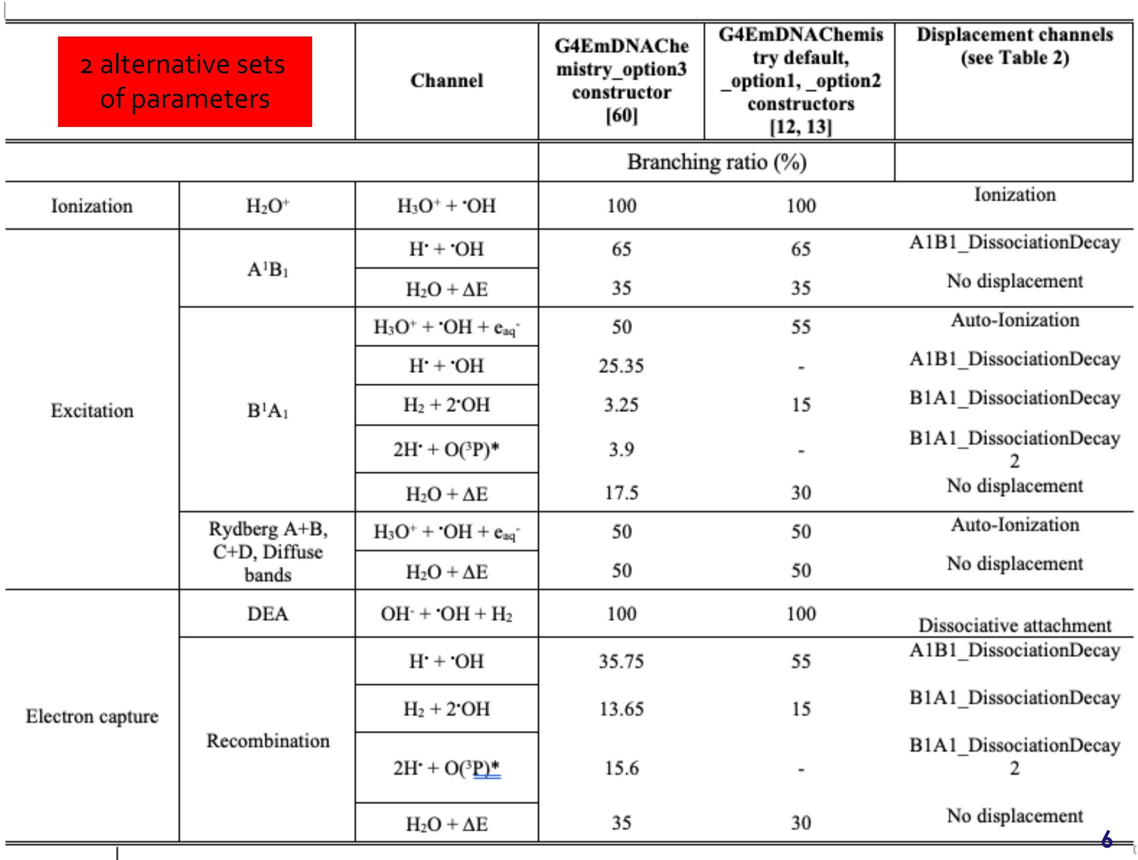
- **Dissociate if**
  - **Ionized**
  - **Electron attachment**
- **Relax or dissociate if**
  - **Excited**
  - **Electron-hole recombination**

From 1 ps, all chemical species are **ready to diffuse and react**

PhD thesis of M. Karamitros (2012)
PhD thesis of W. G. Shin (2020)

J. Comput. Phys. 274 (2014) 841 (link) Phys. Med. 31 (2015) 861-874 (link)
Phys. Med. 88 (2021) 86-90 (link)

Water molecule state



2 alternative sets of parameters

		Channel	G4EmDNAChemistry_option3 constructor [60]	G4EmDNAChemistry default, _option1, _option2 constructors [12, 13]	Displacement channels (see Table 2)
			Branching ratio (%)		
Ionization	H_2O^+	$H_3O^+ + {}^{\bullet}OH$	100	100	Ionization
Excitation	A^1B_1	$H^{\bullet} + {}^{\bullet}OH$	65	65	A1B1_DissociationDecay
		$H_2O + \Delta E$	35	35	No displacement
	B^1A_1	$H_3O^+ + {}^{\bullet}OH + e_{aq}^-$	50	55	Auto-Ionization
		$H^{\bullet} + {}^{\bullet}OH$	25.35	-	A1B1_DissociationDecay
		$H_2 + 2{}^{\bullet}OH$	3.25	15	B1A1_DissociationDecay
		$2H^{\bullet} + O(^3P)^*$	3.9	-	B1A1_DissociationDecay2
		$H_2O + \Delta E$	17.5	30	No displacement
	Rydberg A+B, C+D, Diffuse bands	$H_3O^+ + {}^{\bullet}OH + e_{aq}^-$	50	50	Auto-Ionization
		$H_2O + \Delta E$	50	50	No displacement
Electron capture	DEA	$OH^- + {}^{\bullet}OH + H_2$	100	100	Dissociative attachment
	Recombination	$H^{\bullet} + {}^{\bullet}OH$	35.75	55	A1B1_DissociationDecay
		$H_2 + 2{}^{\bullet}OH$	13.65	15	B1A1_DissociationDecay
		$2H^{\bullet} + O(^3P)^*$	15.6	-	B1A1_DissociationDecay2
		$H_2O + \Delta E$	35	30	No displacement

Chemical stage

J. Comput. Phys. 274 (2014) 841 (link)
Phys. Med. 31 (2015) 861 (link)
J. Appl. Phys. 126 (2019) 114301 (link)
arXiv:2006.14225 (2020) (link)
Med. Phys. 47 (2020) 5920 (link)
Phys. Med. 88 (2021) 86 (link)
Med. Phys. 48 (2021) 890 (link)

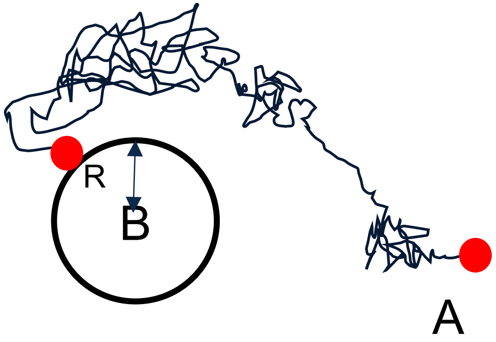
t=10^{-15}s

t=10^{-12}s

t=10^{-6}s

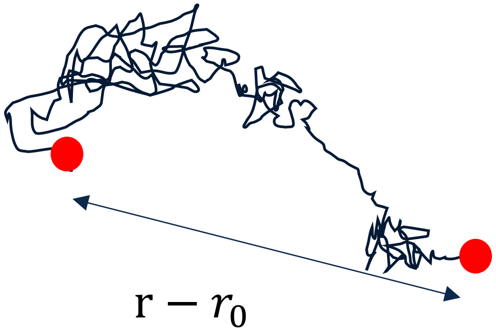
General assumptions:

- Water radiolysis species are **hard spherical particles** (or particle-based),
- **Water (solvent) is considered a continuum**
- Chemical stage starts when **chemical species diffuse through Brownian dynamics** and eventually react.



R : radius reaction

Brownian diffusion



- In simulation, the species are transported in several discrete steps (or time step Δt). The diffusion process corresponds to Smoluchowski equation. Its solution is

$$p(r, \Delta t | r_0) = \frac{4\pi(\mathrm{r} - r_0)^2}{(4\pi \mathrm{D}\Delta \mathrm{t})^{3/2}} \mathrm{e}^{\left\{\frac{-(\mathrm{r} - r_0)^2}{4D\Delta t}\right\}}$$

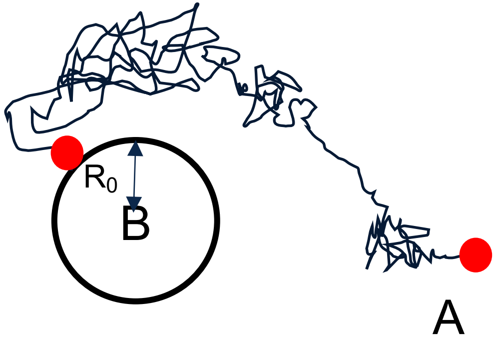
where r_0 is the initial position and r is the next possible position of the species for **the probability $\mathbf{p}(\mathbf{r}, \Delta \boldsymbol{t} | \boldsymbol{r_0})$** in a time interval Δt

- For each Δt, the displacement of species is determined by

$$x(t + \Delta t) = x(t) + R_x\sqrt{2D\Delta t}$$
$$y(t + \Delta t) = y(t) + R_y\sqrt{2D\Delta t}$$
$$z(t + \Delta t) = z(t) + R_z\sqrt{2D\Delta t}$$

(Rx, Ry, Rz) are random numbers

Diffusion-controlled reactions



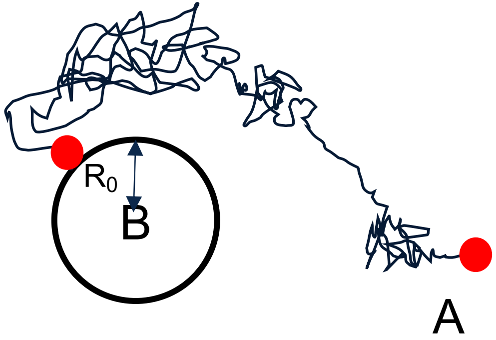
- Reactions are controlled by diffusion.
- Reactions happen when A diffuse close to B within a distance R_0

$$k = 4\pi \mathcal{N}_{\mathcal{A}} \cdot D R_0$$

Reaction radius R_0 can be calculated from reaction constant k (Smoluchowski model)

J. Comput. Phys. 274 (2014) 841 (link)

Diffusion-controlled reactions



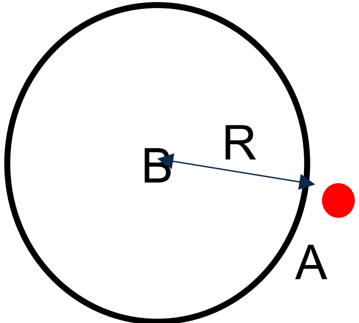
Question: how to know when A will encounter B

1. STEP-BY-STEP (« SBS ») « reference » approach

- Define a time-step Δt to diffuse chemical molecules until to their encounter
- Δt should not too large, we risk missing reactions.
- Δt should not too small, the simulation involves many small-time steps, which is very time-consuming

AN APPROACH CALLED "DYNAMIC TIME STEP" ALLOWS TIME STEPS TO BE CHOSEN ACCORDING TO **THE DISTANCE BETWEEN REACTANTS**

- A probability of reactions that **cannot occur** with at least 95% (default) confidence
- Time steps to take a longer



$$t_D = \frac{(d_0 - R)^2}{64(\sqrt{D_A} + \sqrt{D_B})^2} = \frac{(d_0 - R)^2}{64(D_A + D_B + 2\sqrt{D_A D_B})}$$

Diffusion-controlled reactions

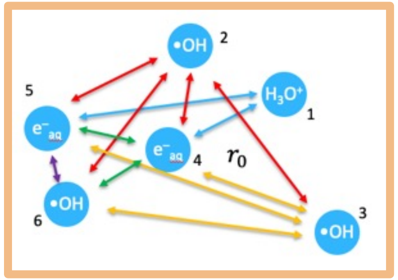
SBS is so slow

2. INDEPENDENT REACTION TIMES (« IRT ») approach
   - assumes that reactions are independent
   - the diffusion of reactants from their initial positions to the reaction site is not influenced by other chemical species

If this condition is met, the solution of the Smoluchowski equation, considering a reaction, is utilized to infer the probability of the reaction.

$$p(t|r_0) = \frac{R}{r_0} erfc\left[\frac{r_0 - R}{\sqrt{4Dt}}\right]$$

R is the reaction radius, r_0 the initial distance of reactants (neutral species).



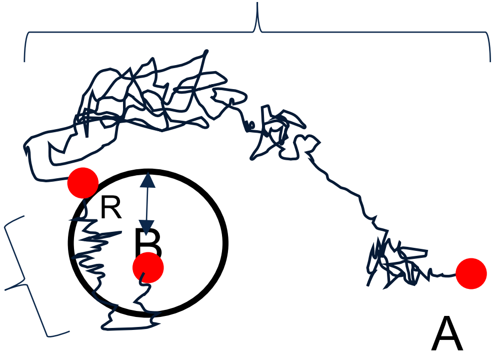
IRT :
1. The reaction times are calculated by all possible reaction probabilities of reactive species.
2. Reactions occur one by one, starting with the pairs having the shortest reaction times. No diffusion is computed

IRT is very fast

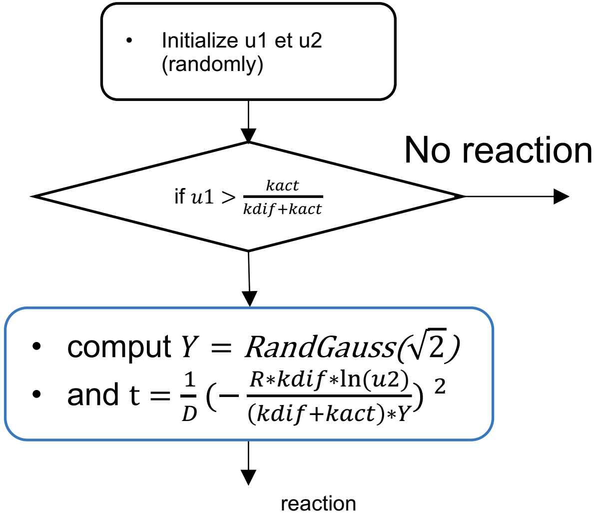
Partially diffusion-controlled reactions

- There are some reactions that are not fully controlled by diffusion when encounter does not mean a reaction.
- This kind of reaction depends on a steady-state rate constant “from encounter” to the reaction which can be defined by the velocity (ν)

$$k_{dif} = 4\pi RD$$



steady-state rate constant : $k_{act} = 4\pi R^2 \nu$



- Initialize u1 et u2 (randomly)

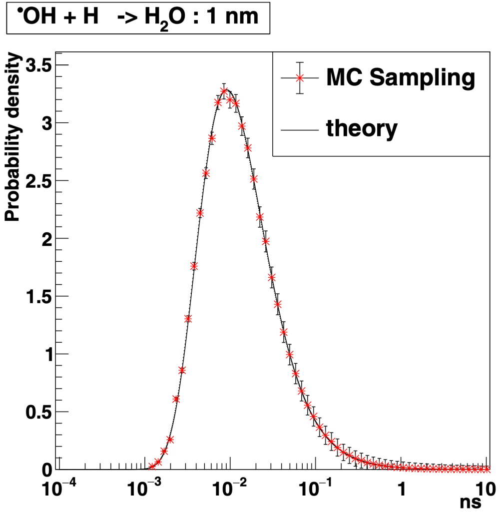
if $u1 > \frac{kact}{kdif+kact}$

No reaction

- comput $Y = RandGauss(\sqrt{2})$
- and t = $\frac{1}{D}\left(-\frac{R*kdif*\ln(u2)}{(kdif+kact)*Y}\right)^2$

reaction

Sampling algorithm



Tran et al. Med. Phys. 48 (2021) 890-901

An example of a reaction list

Reaction	k(1e^{10} M^{-1}s^{-1})	Partially Diffusion-Controlled	Totally Diffusion-Controlled
$H^{\bullet} + e^{-}_{aq} + H_2O \rightarrow OH^- + H_2$	2.5		○
H● + OH● → H2O	1.55	○	
H● + H● → H2	0.503		○
$H_2O_2 + e^{-}_{aq} \rightarrow OH^- + OH^{\bullet}$	1.1	○	
$H_3O^+ + e^{-}_{aq} \rightarrow H\bullet$	2.11	○	
H3O+ + OH- → 2H2O	11.3		○
OH● + e-aq → OH-	2.95	○	
OH● + OH● → H2O2	0.55	○	
$e^{-}_{aq} + e^{-}_{aq} + 2H_2O \rightarrow 2OH^- + H2$	0.636		○

Summarize :

J. Comput. Phys. 274 (2014) 841 (link)
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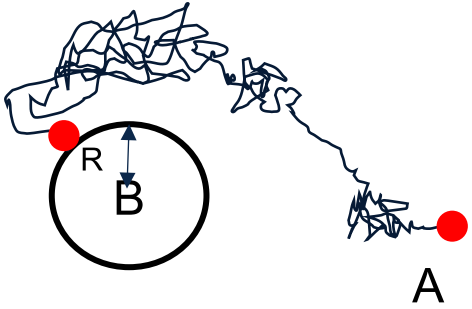
$t=10^{-15}s$ $t=10^{-12}s$ $t=10^{-6}s$

Chemical stage starts when chemical species diffuse through Brownian dynamics and eventually react.

Geant4-DNA adopts :

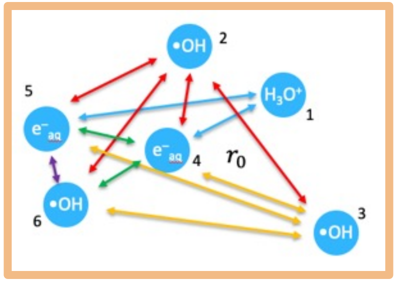
TWO alternative approaches to simulate diffusion – reaction processes:

1. **STEP-BY-STEP (« SBS ») « reference » approach**
   - Brownian transport of molecules from the Smoluchowski model
   - Chemical species are represented by point objects which diffuse in the liquid medium (continuum).



+: Tracking of species
-: Very slow

2. **INDEPENDENT REACTION TIMES (« IRT ») approach**
   - From the 1980's by Clifford, Green et al., widely used today.
   - Iterative process where the approximation of « independent pairs » is assumed: calculates the reaction times between all possible pairs of reactive species, as if they were isolated. Then, reactions occur one by one, starting with the pairs having the shortest reaction times.
   - No longer necessary to diffuse the molecular species and to calculate the possible reactions between the species at each time step.



Clifford et al. (1986)

+: Very fast
-: Tracking of species

Geant4-DNA Chemistry constructors

The chemistry constructors in Geant4-DNA specify the dissociation scheme, chemical actions, and models involved in water radiolysis.

In Geant4.11.3, Geant4-DNA Chemistry constructors :

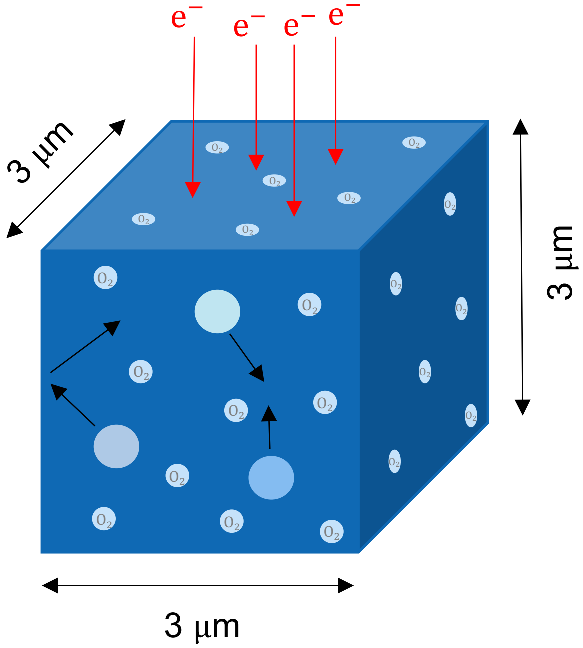
- **G4EmDNAChemistry** : First constructor implemented with parameter values from Karamitros et al.
  – from PARTRAC
- **G4EmDNAChemistry_option1** : Implements a revisited set of chemistry parameters from Shin et al.
  – from TRACs + Burns et al. (1981) + Rowe et al. (1988)
- **G4EmDNAChemistry_option2** : Includes chemistry parameters for reactions with DNA components
  – from Buxton et al. (1988)
- **G4EmDNAChemistry_option3** : Implements the **IRT approach** from Ramos-Mendez et al. (2020)
  – from RITRACKS & Elliot et al. (1994)

Reaction with Scavenging molecule

- the scavenging capacity must be a **continuum**
- the probability of a radiolytic species interacting with scavengers in the target is determined by the following rate equation :

$$\frac{dX}{dt} = -kC_sX$$

where C_s is the scavenger concentration, X is the survival probability of the species and k is the reaction rate. This model is used for both the IRT and SBS

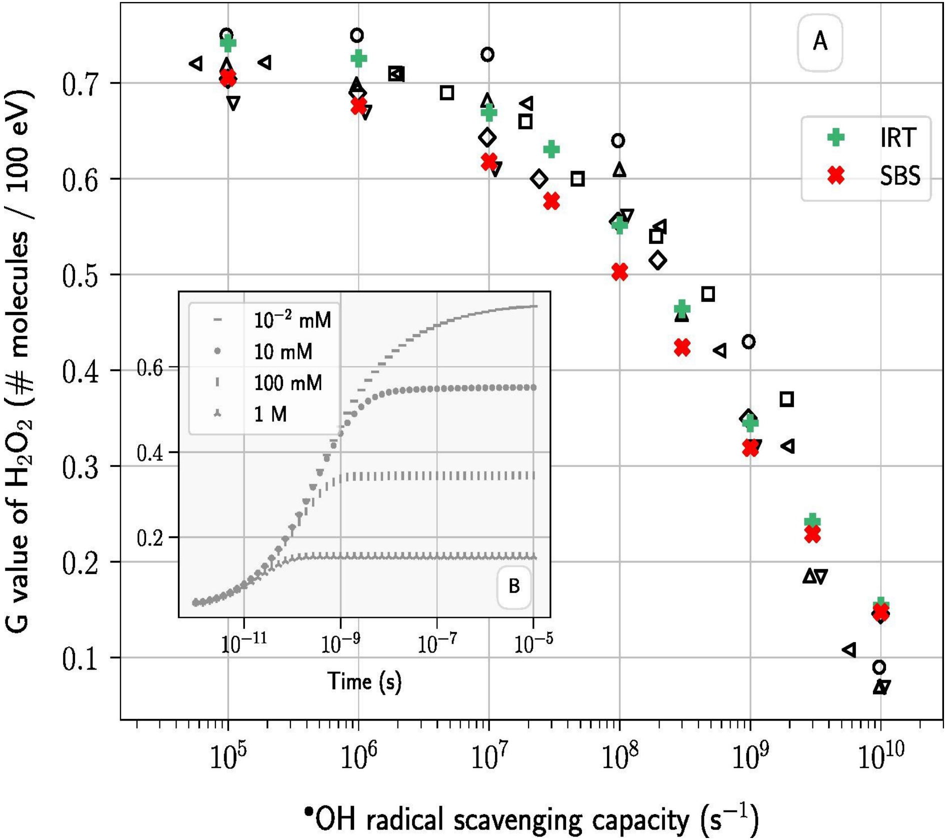


O_2 scavenging molecule (O_2)

● molecule

Reaction with Scavenging molecule

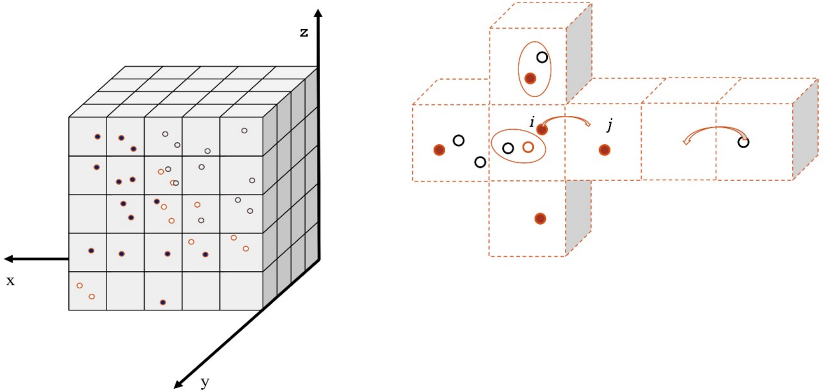
- Impact of scavengers on the production of H2O2 after a ^{60}Co γ-irradiation
- G values of H2O2 as a function of the scavenging capacity for •OH radicals: ( ) NO2- and 25 mM NO3− with the IRT, SBS methods

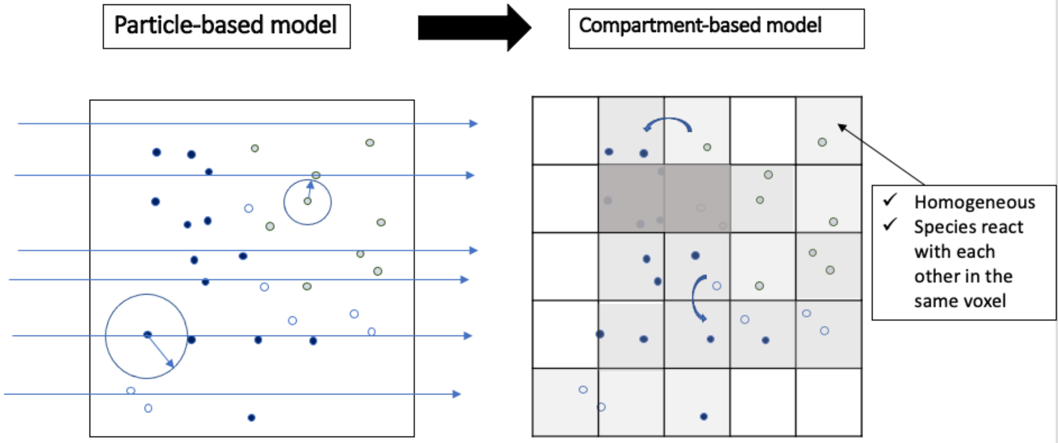


F. Chappuis et al. Physica Medica 108 (2023) 102549

Mesoscopic model

- For SBS, IRT model, computation time remains the main drawback when simulations deal with a **large number of species** or **long-time scales**.
- An alternative approach has recently been implemented in Geant4-DNA using the **compartment-based** representation




Particle-based model

Compartment-based model

✓ Homogeneous
✓ Species react with each other in the same voxel

Using Brownian dynamics and Smoluchowski theory

Using Reaction-Diffusion Master Equation (RDME)

1. Well-mixed species in voxels
2. Species can react with each other in the voxels
3. Diffusion is modelled by jumps between adjacent voxels

Reaction-Diffusion Master Equation

$$\begin{aligned}\frac{\partial}{\partial t}\mathbb{P}(\boldsymbol{u},t) \quad = \quad & \sum_{i=1}^{I}\sum_{r=1}^{R}\left[a_i^r(\mathbf{u}-\boldsymbol{\nu}_{i,r})\,\mathbb{P}(\boldsymbol{u}-\boldsymbol{\nu}_{i,r},t)-a_i^r(\mathbf{u})\,\mathbb{P}(\boldsymbol{u},t)\right] \\ & +\sum_{i=1}^{I}\sum_{\substack{j=1\\ j\neq i}}^{I}\sum_{\ell=1}^{L}\left[\lambda_{i,j}^{\ell}\left(u_i^{\ell}(t)+1\right)\mathbb{P}\left(\boldsymbol{u}-\boldsymbol{e}_{i,j}^{\ell},t\right)-\lambda_{i,j}^{\ell}u_i^{\ell}(t)\mathbb{P}(\boldsymbol{u},t)\right],\end{aligned}$$

Event-driven simulation using the "Next-Subvolume Method" (NSM):

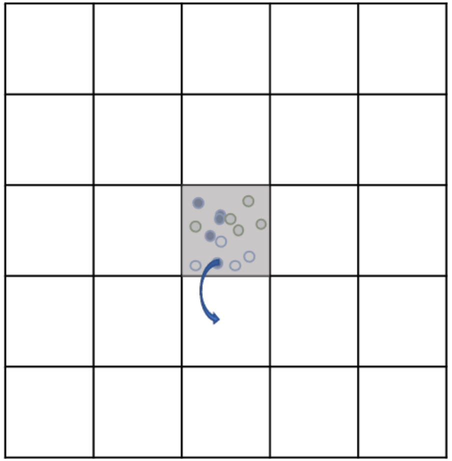
- ➢ Calculation of the propensity functions a_i for all voxels
- ➢ Sampling of the time when the next event occurs

$$\tau_i = \frac{-\ln(\xi)}{a_i}$$

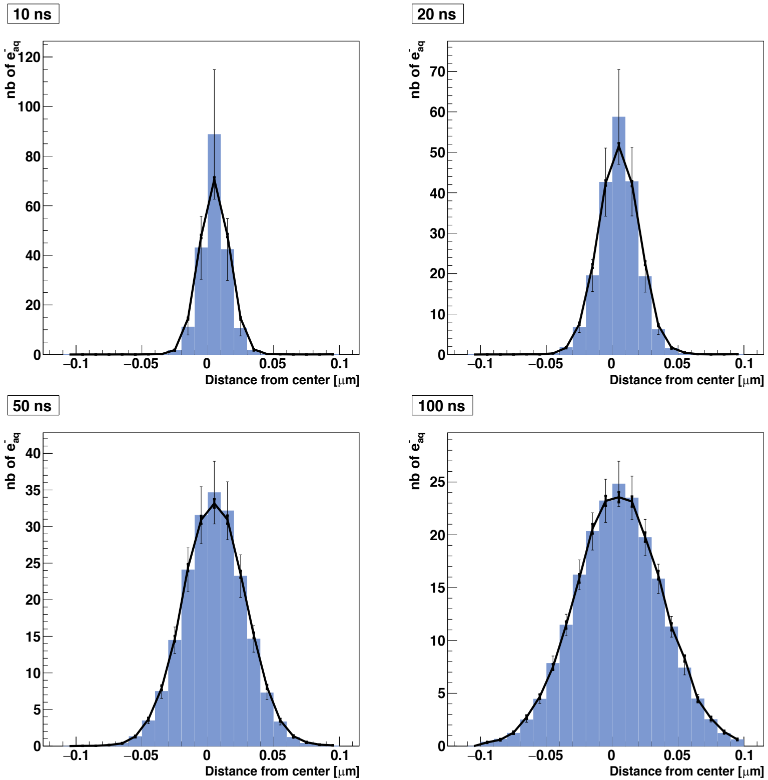
- ➢ Sampling which reaction or diffusion will take place according to the propensity function a_i
- ➢ Processing the first event in the queue and changing the concentrations in the voxels involved in the event
  - ✓ If the event is a reaction, we eliminate reactants and create products.
  - ✓ If the event is a diffusion, we remove the particle in the voxel where it was located and add the particle in the voxel where it goes.

Reaction-Diffusion Master Equation

Diffusion test



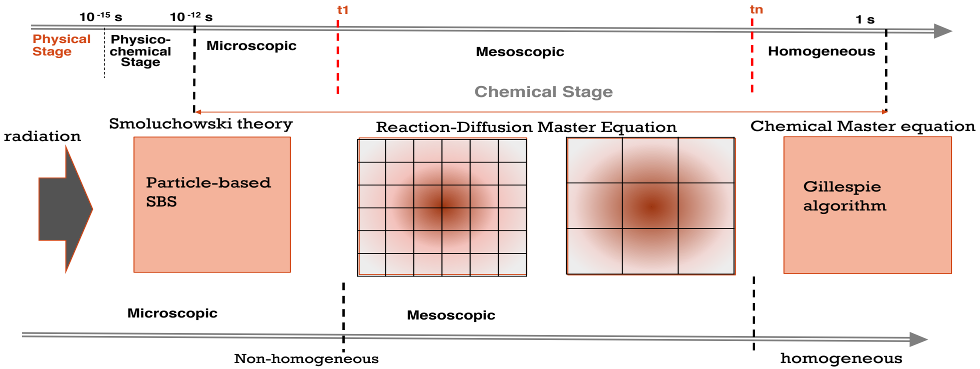
RDME method (blue histogram) and the SBS (line)



Reaction-Diffusion Master Equation

The main idea of this model is the combination of the SBS with the RDME (so-called "SBS-RDME model")

- Since spur sizes are comparable with their reaction radius within a few ns (5 ns as default) after exposure, this period cannot be described by using the "well-mixed" model. Then SBS-RDME model is proposed :
- **Microscopic** stage : particle-based SBS method
- **Mesoscopic** stage : initial mesh resolution should be small. The system used increasingly coarser meshes over time.
- when the **homogeneous** sub-stage started, the CME stochastic process is applied to sample only reactive events



10^{-15} s

10^{-12} s

t1

tn

1 s

Physical Stage

Physico-chemical Stage

Microscopic

Mesoscopic

Homogeneous

Chemical Stage

radiation

Smoluchowski theory

Reaction-Diffusion Master Equation

Chemical Master equation

Particle-based SBS

Gillespie algorithm

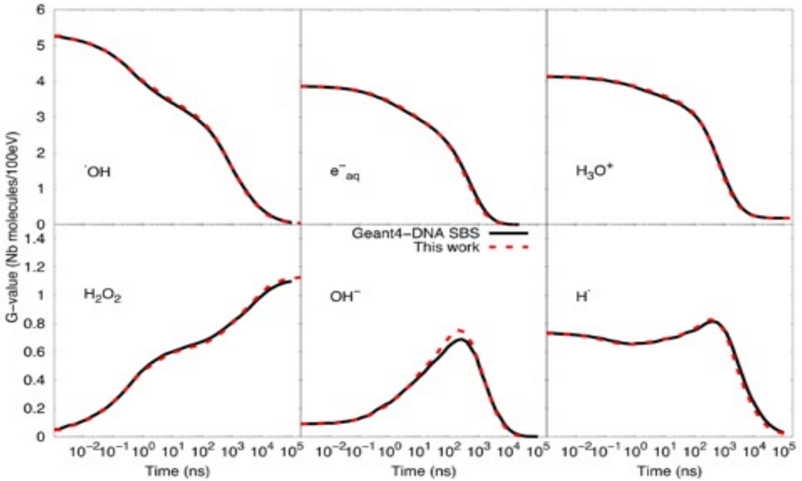
Microscopic

Mesoscopic

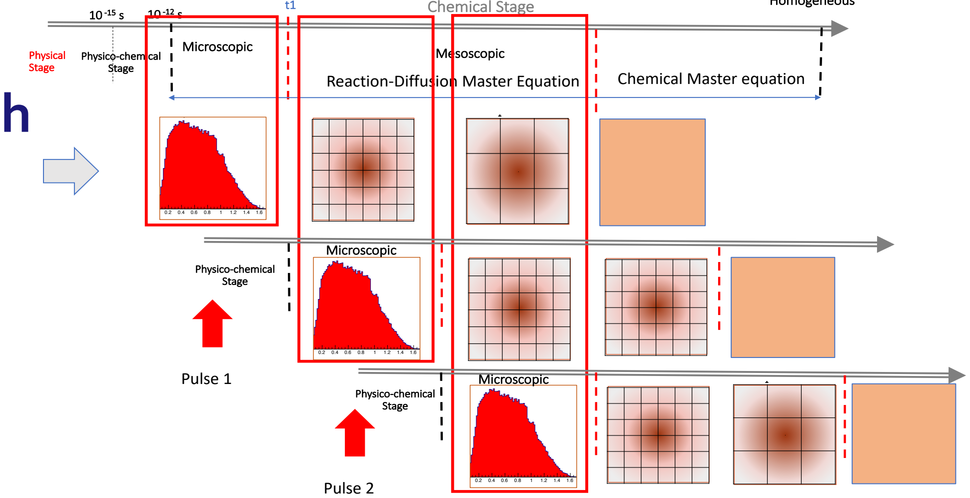
Non-homogeneous

homogeneous

  - Next sub-volume algorithm
  - Hierarchical algorithm for the RDME ("hRDME")
  - Spatial distributions are simulated at voxel level.
  - Coarser meshes over time until we reached the coarsest mesh.

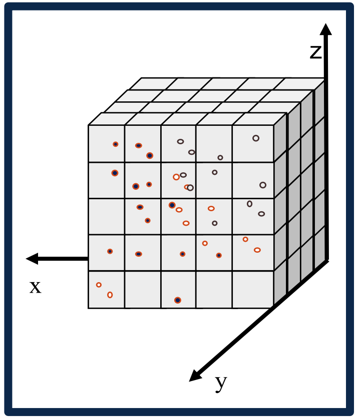


New « mesoscopic » approach



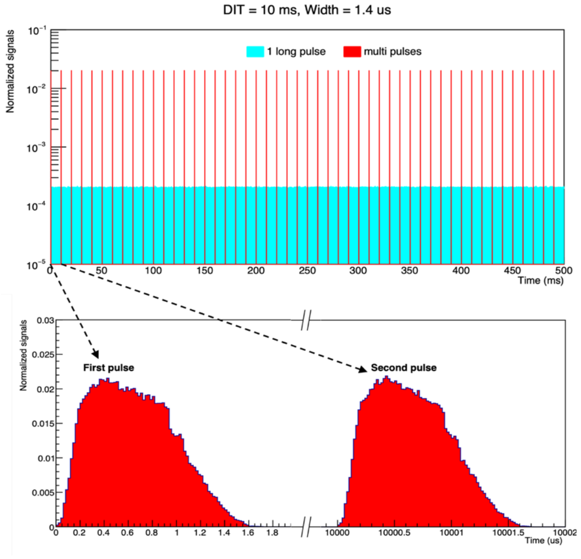
- Use a new « mesoscopic » approach to study the production and evolution of reactive oxygen species generated under irradiation with different dose rate conditions, such as in FLASH RT
- Coarse-grained model: "compartment-based"
- Simulation from heterogeneous (microsecond) to homogeneous states (beyond)
- Multiple pulses simulation

Tran et al., Int. J. Mol. Sci. (2021) 22 (link)



1. Well mixed species in voxels
2. Species can react with each other in the voxels
3. Diffusion is modelled by jumps between adjacent voxels

Voxelization of the simulation volume into smaller sub-volumes. Species are represented by different types of circles

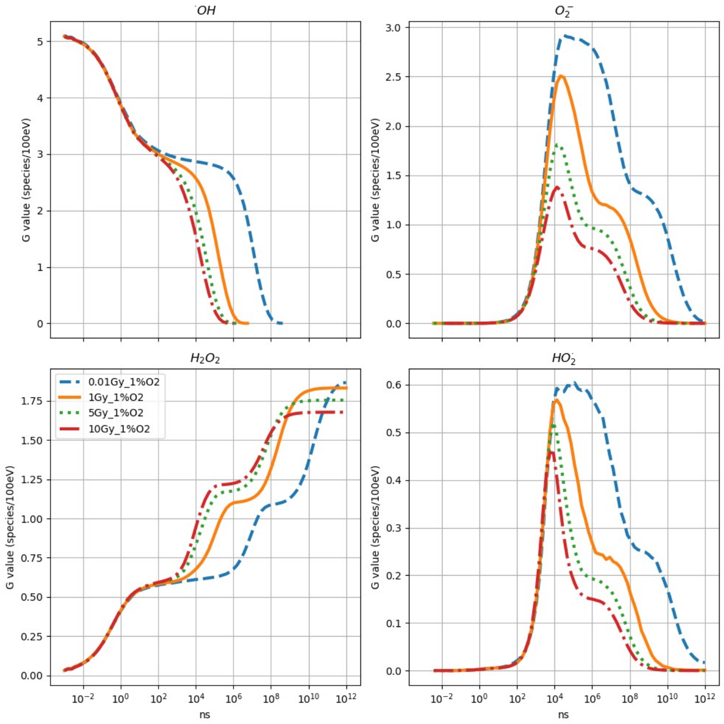


GEANT4-DNA

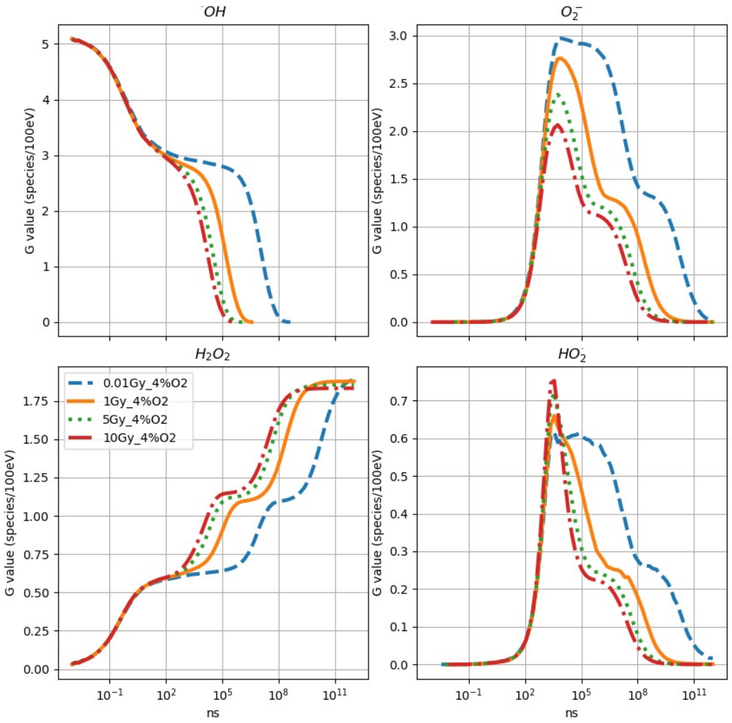
Simulations

Modelling of ultra-high dose rate (UHDR) electron beams 1 MeV

1% O2



4% O2



Geant4-DNA chemistry examples

- The « **chem1** » **extended/medical/dna** example illustrates how to **activate** the simulation of water radiolysis (*step-by-step* method).
- The « **chem2** » **extended/medical/dna** example illustrates how to **set minimum time step** limits on water radiolysis (*step-by-step* method).
- The « **chem3** » **extended/medical/dna** example illustrates how to **implement user actions** in the chemistry module (*step-by-step* method).
- The « **chem4** » **extended/medical/dna** example illustrates how to **compute radiochemical yields ("G") versus time**, including a dedicated ROOT graphical interface (*step-by-step* method).
- The « **chem5** » **extended/medical/dna** example illustrates how to **compute radiochemical yields ("G") versus time**, using alternative physics and chemistry lists (*step-by-step* method).
- The « **chem6** » **extended/medical/dna** example illustrates how to **compute radiochemical yields ("G") versus time and LET** using IRT method.
- The « **scavenger** » **extended/medical/dna** example illustrates how to **simulate scavenging using an easy-to-use interface** and the IRT method.
- The « **UHDR** » **extended/medical/dna** example illustrates how to activate the **chemistry mesoscopic model in combination with the step-by-step model** and allows to simulate chemical reactions beyond 1 µs post-irradiation.

Thank you for your attention!

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