Overview of the Geant4-DNA chemistry

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1st Geant4-DNA tutorial
ESA/ESTEC – 07/11/2014

H₃O⁺

°OH

e⁻aq

2
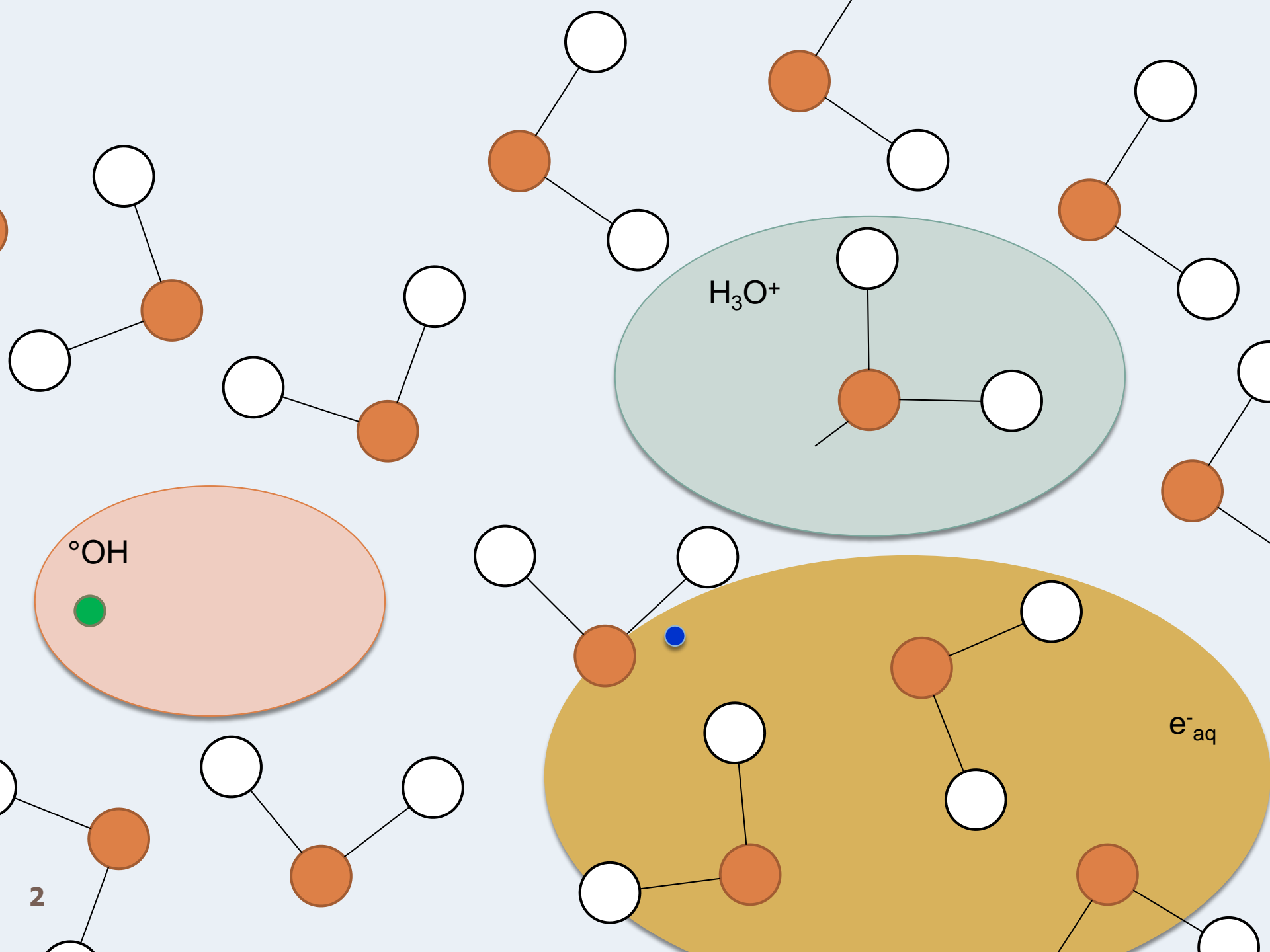
Contribution of indirect effects

Survival vs Dose with different DMSO concentrations

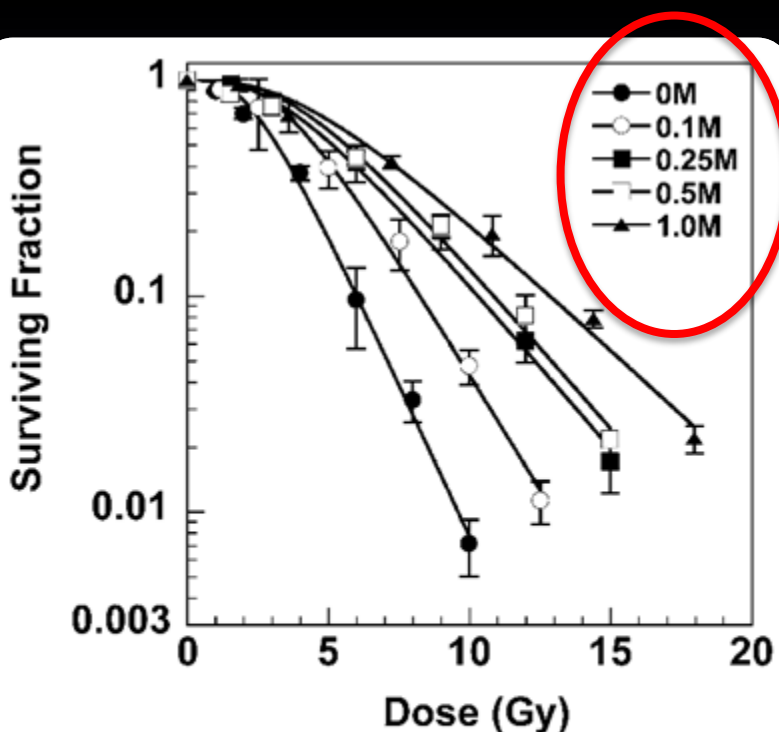**Contribution of indirect effects VS LET**

FIG. 1. X-ray survival of V79 cells in the presence of DMSO. Error bars represent the standard deviations ($n = 2$–3). These curves were fitted by the single-hit multitarget equation as described in the Materials and Methods.
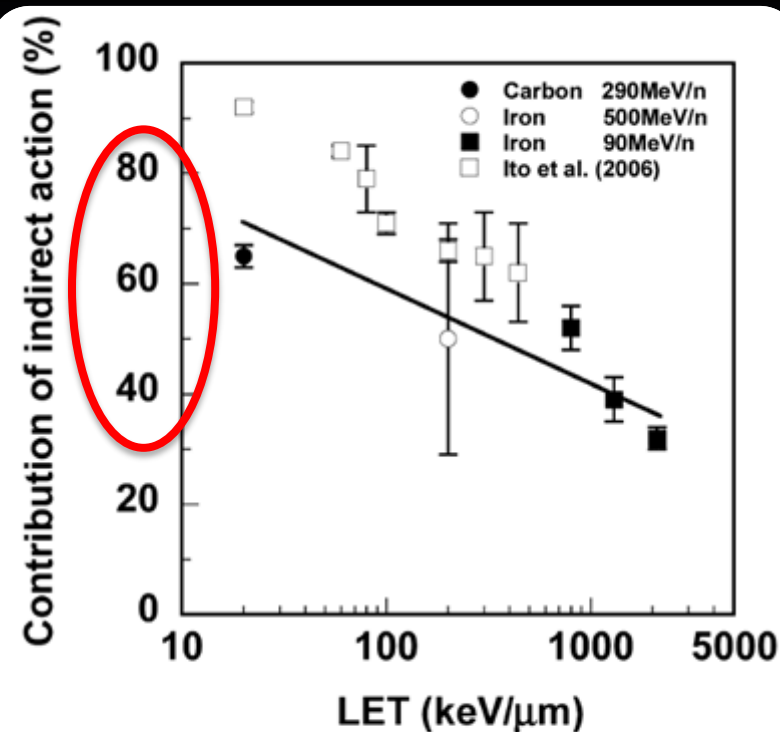

FIG. 4. LET dependence of the contribution of indirect action in cell killing. The error bars are standard errors for a protectable fraction calculated from a regression line. Data from Ito *et al*. for HL-60 cells (6) are plotted in the figure.

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Why using Geant4?

Geant4's features

- Rather reliable toolkit, system testing, constant evolution

- Multiple physics models available

- Geometry and visualization capabilities

- Modern architecture

Benefits

- Software coherence & **Unified simulation platform**
  - No need to separate the different stages (physics, chemistry…)
  - Only one simulation setup needed

- **Modelling compatible with Geant4's …**

Physico-chemical stage

- During this stage, water molecules
  - Dissociate if ionized
  - Relax or dissociate if excited

Electronic state of water molecule	Dissociation channels	Fraction (%)
All ionization states	$H_3O^+ + \bullet OH$	100
Excitation state A1B1: $(1b1) \rightarrow (4a1/3s)$	$\bullet OH + H\bullet$	65
	$H_2O + \Delta E$	35
Excitation state B1A1: $(3a1) \rightarrow (4a1/3s)$	$H_3O^+ + \bullet OH + e^-_{aq}$	55
	$\bullet OH + \bullet OH + H_2$	15
	$H_2O + \Delta E$	30
Excitation state: Rydberg, diffusion bands	$H_3O^+ + \bullet OH + e^-_{aq}$	50
	$H_2O + \Delta E$	50

ConstructDissociationChannels()

- Dissociative attachment: $H_2O^- \rightarrow H_2 + OH^- + \bullet OH$
- Situtation at 1 picosecond? Are the dissociation channels dependent on the LET?
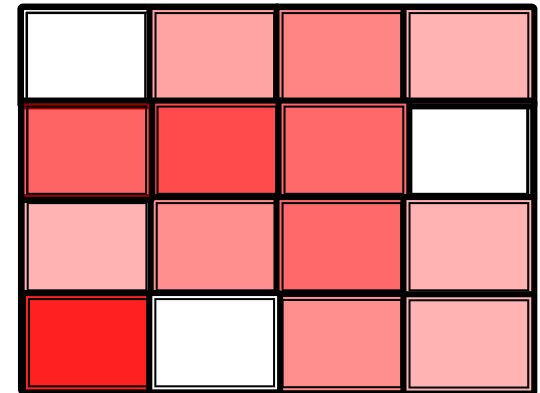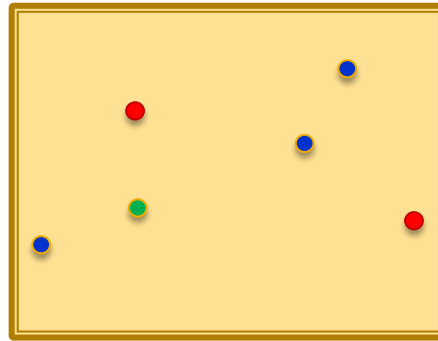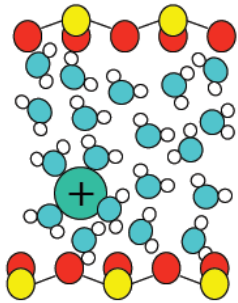- Can be tuned by the user

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Chemical stage: representation?

« **Full atomistic** » approach

Molecules = balls
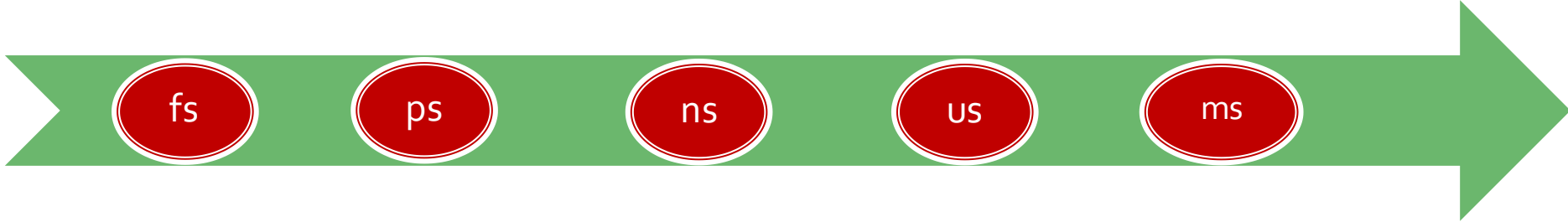**Solvant** = continuum

Time evolution of **concentrations** in **voxellized** geometry

Computational complexity

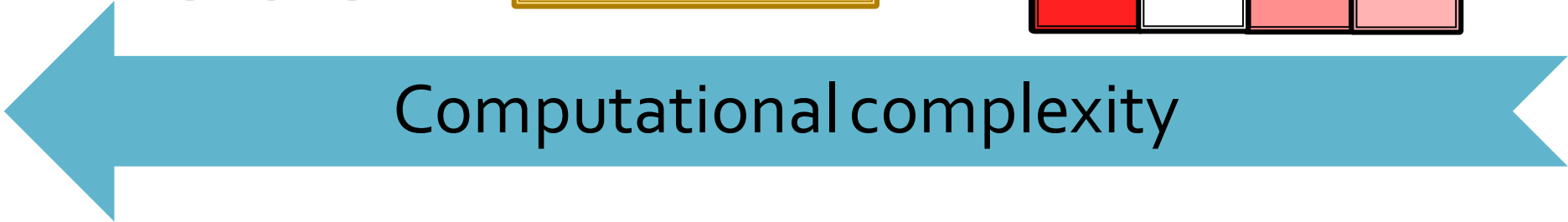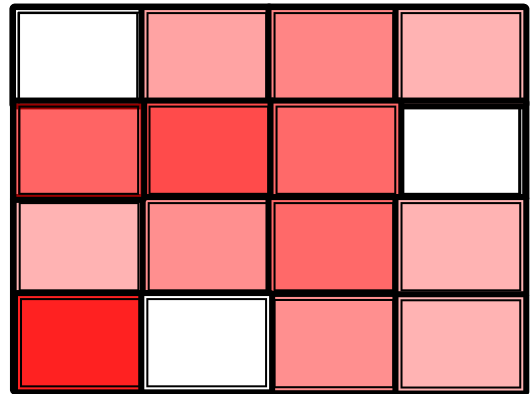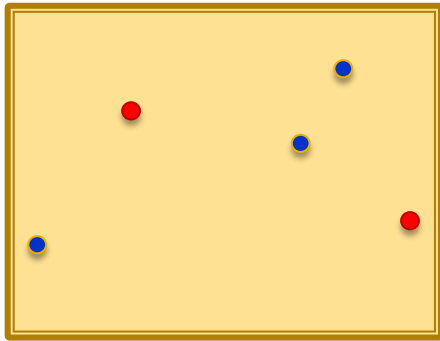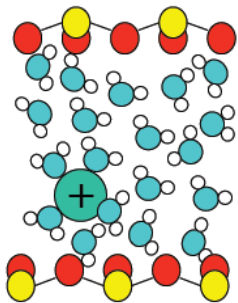Well adapted for few molecules and heterogenously distributed

Assumption : molecules are homogenously distributed into one voxel. More adapted for large N

fs | ps | ns | us | ms

« **Full atomistic** » approach

Molecules = balls
Solvant = continuum

Time evolution of **concentrations** in **voxellized** geometry

Computational complexity

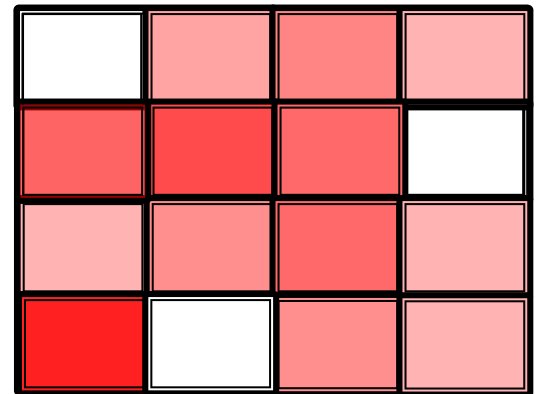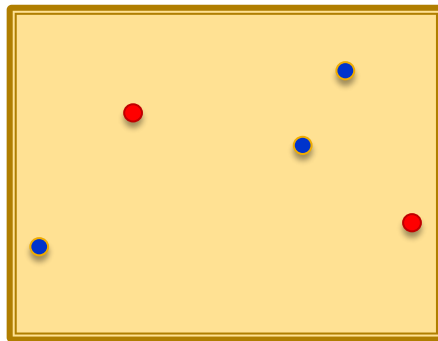Kinetic constants

« **Full atomistic** » approach

Molecules = balls
Solvant = continuum

Time evolution of **concentrations** in **voxellized** geometry
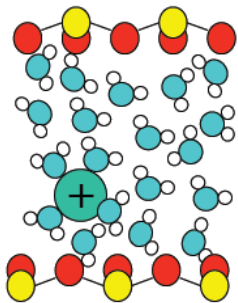
Computational complexity

Chemical stage: model

- Diffusion-limited reactions
  - no reversible reactions

- Step-by-step approach combining dynamical time steps and Brownian bridge

- Method splits into two stages:
  - **Decision** stage: which reaction will happen? When?
  - **Action** stage:
    - Diffusion
    - Can the selected reactants can indeed react?

Brownian motion: the Langevin equation

- A particle in a fluid is slowed down by a friction force:

$$m\ddot{\vec{r}} = \underbrace{-\gamma\dot{\vec{r}}}_{} + \overrightarrow{\mathbf{F}_{ext}}(\vec{r})$$

Friction force

- If its mass is weak→ the particle undergoes multiple collisions with the medium :

$$m\ddot{\vec{r}} = -\gamma\dot{\vec{r}} + \overrightarrow{\mathbf{F}_{ext}}(\vec{r}) + \overrightarrow{\vec{\psi}(t)}$$

Random force

- This is the so-called Langevin equation → stochastic

The Langevin equation

$$\ddot{\vec{\mathbf{r}}} = -\frac{\gamma}{m}\dot{\vec{\mathbf{r}}} + \frac{\overrightarrow{\mathbf{F}_{ext}}(\vec{\mathbf{r}})}{m} + \frac{\vec{\psi}(t)}{m}$$

$$\ddot{\vec{\mathbf{r}}} = -\alpha\dot{\vec{\mathbf{r}}} + \frac{\overrightarrow{\mathbf{F}_{ext}}(\vec{\mathbf{r}})}{m} + \vec{\Gamma}(t)$$

Langevin force

- Hypothesis:

$$\left\langle \vec{\Gamma}(t) \right\rangle = \vec{0} \qquad \left\langle \vec{\Gamma}(t_1) \cdot \vec{\Gamma}(t_2) \right\rangle = q \cdot \delta(t_1 - t_2)$$

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- Langevin Equation

$$\ddot{\vec{\mathbf{r}}} = -{\color{red}\alpha}\dot{\vec{\mathbf{r}}} + \frac{\overrightarrow{\mathbf{F}_{ext}}(\vec{\mathbf{r}})}{m} + {\color{blue}\vec{\Gamma}(t)}$$

- Hypothesis

Very weak mass + thermal equilibrium

$${\color{red}\alpha}\dot{\vec{\mathbf{r}}} = \frac{\overrightarrow{\mathbf{F}_{ext}}(\vec{\mathbf{r}})}{m} + {\color{blue}\vec{\Gamma}(t)}$$

Smoluchowski-Debye Equation

- Equation

$$\alpha \dot{\vec{\mathbf{r}}} = \frac{\overrightarrow{\mathbf{F}_{ext}}(\vec{\mathbf{r}})}{m} + \vec{\Gamma}(t)$$

- Random differential equation

➔ $\vec{\mathbf{r}}$ is described by a density probability function p

$$p(\vec{\mathbf{r}},t \,|\, \vec{\mathbf{r}}_0, t_0) = \frac{4\pi \cdot \vec{\mathbf{r}}^2}{\left(4\pi D\left(t - t_0\right)\right)^{\frac{3}{2}}} \exp\left(-\frac{\left(\vec{\mathbf{r}} - \vec{\mathbf{r}}_0\right)^2}{4D\left(t - t_0\right)}\right)$$

➔ The simulation may be taken as a succession of time steps Δt wher $\Delta t = t - t_o$

où $D = \dfrac{q^2}{2\gamma^2}$ with $\left\langle \vec{\Gamma}(t_1) \cdot \vec{\Gamma}(t_2) \right\rangle = q \cdot \delta(t_1 - t_2)$

Observed step r(t-t_0)

Point 2

Point 1

Reel diffusion step
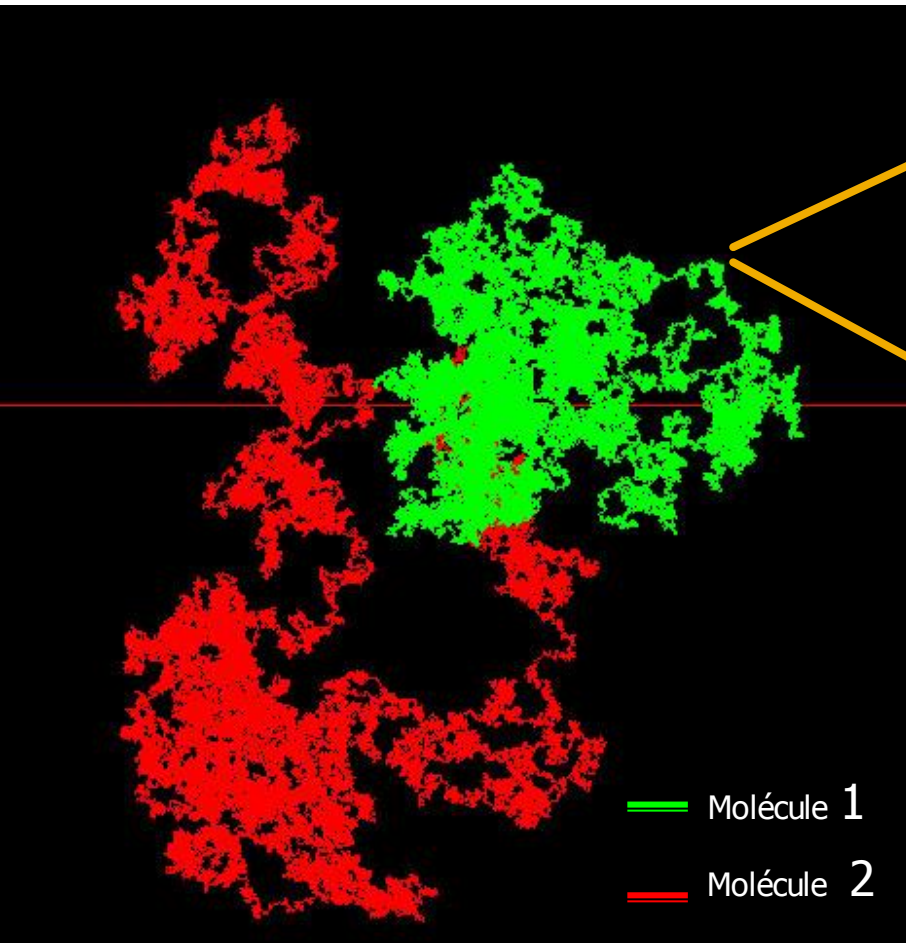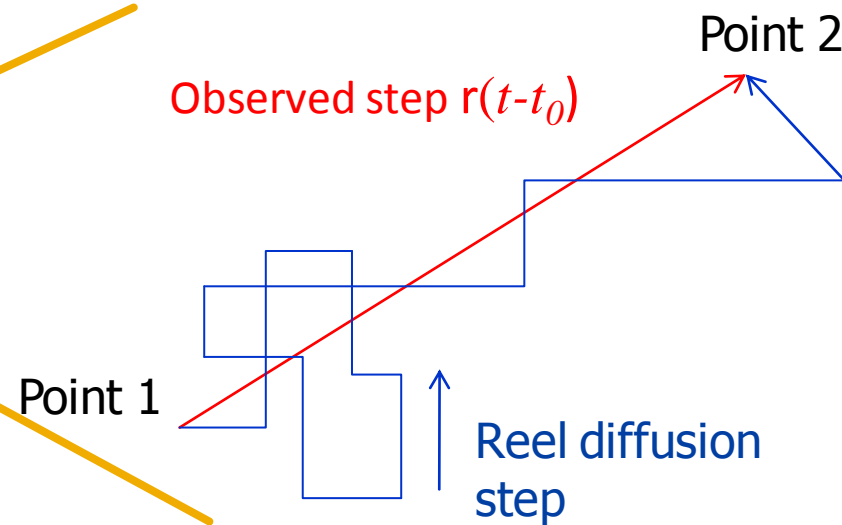
$$p(r,t|t_0) = \frac{4\pi \cdot r^2}{\left(4\pi D\left(t-t_0\right)\right)^{\frac{3}{2}}} \exp\left(-\frac{r^2}{4D\left(t-t_0\right)}\right)$$

Molécule 1

Molécule 2

Standard transport in Geant4 VS Brownian motion

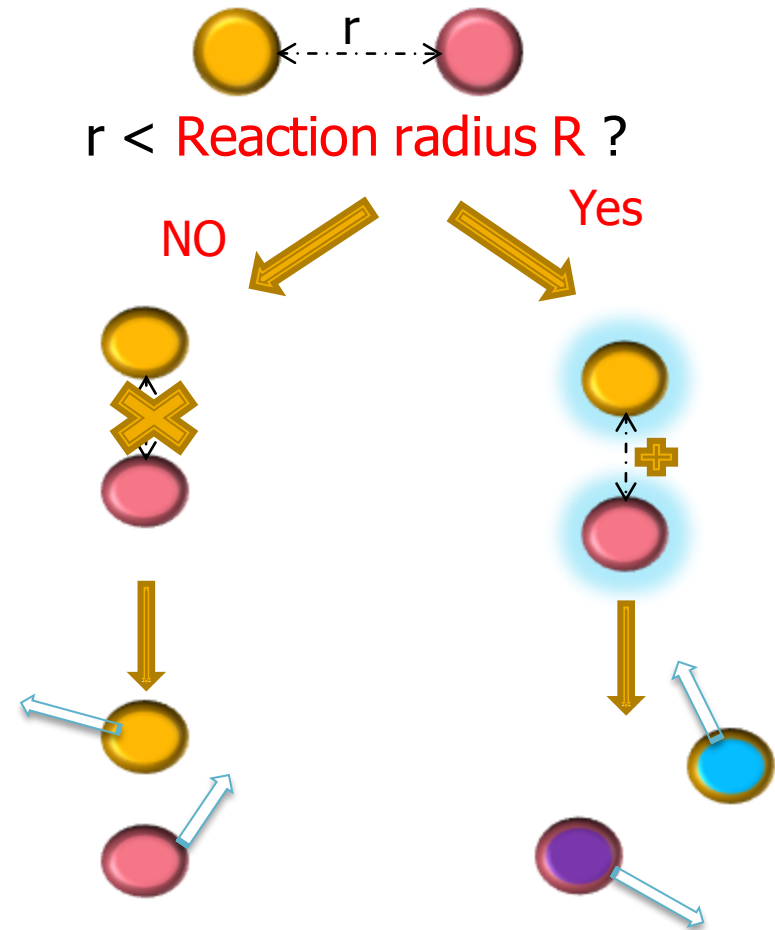|	STANDARD TRANSPORT OF GEANT4	BROWNIAN MOTION
Position and velocity	**Deterministic** (between two interactions points)	**Stochastic**
Path-volume Intersection	« Exact » intersection computable	Can be expressed in terms of **probability**
Equation of motion	Newton	Fokker-Planck (stochastic equation of motion)

The step –by-step method: principle

Etape chimique

Step-by-step method

1. **Interaction**
   Can the molecules react ?
   Criterium: separation distance

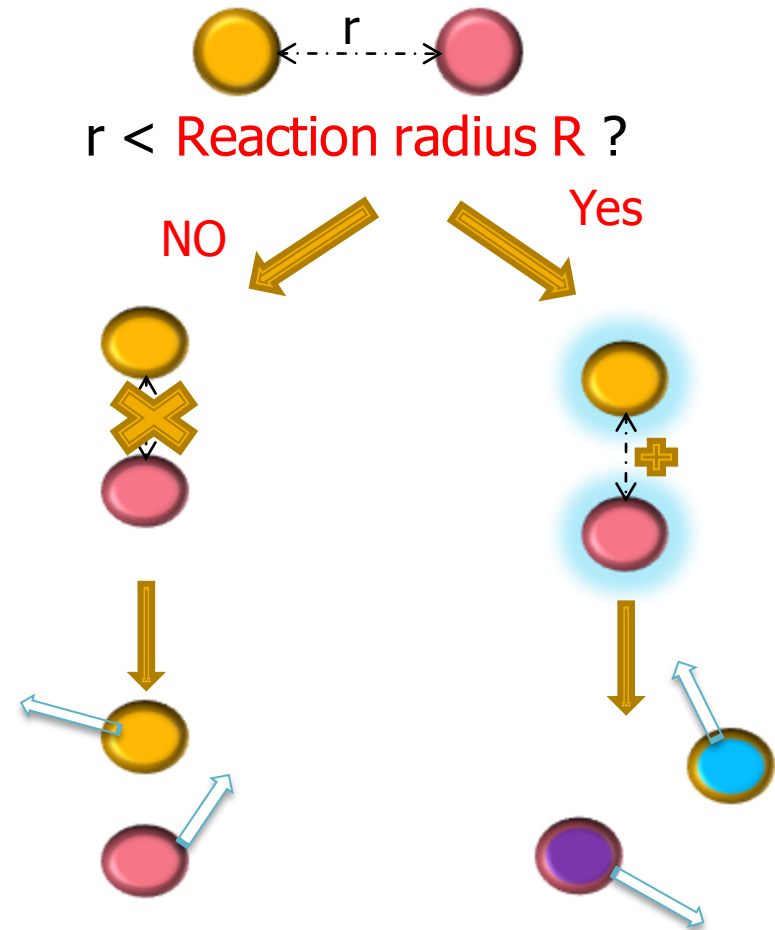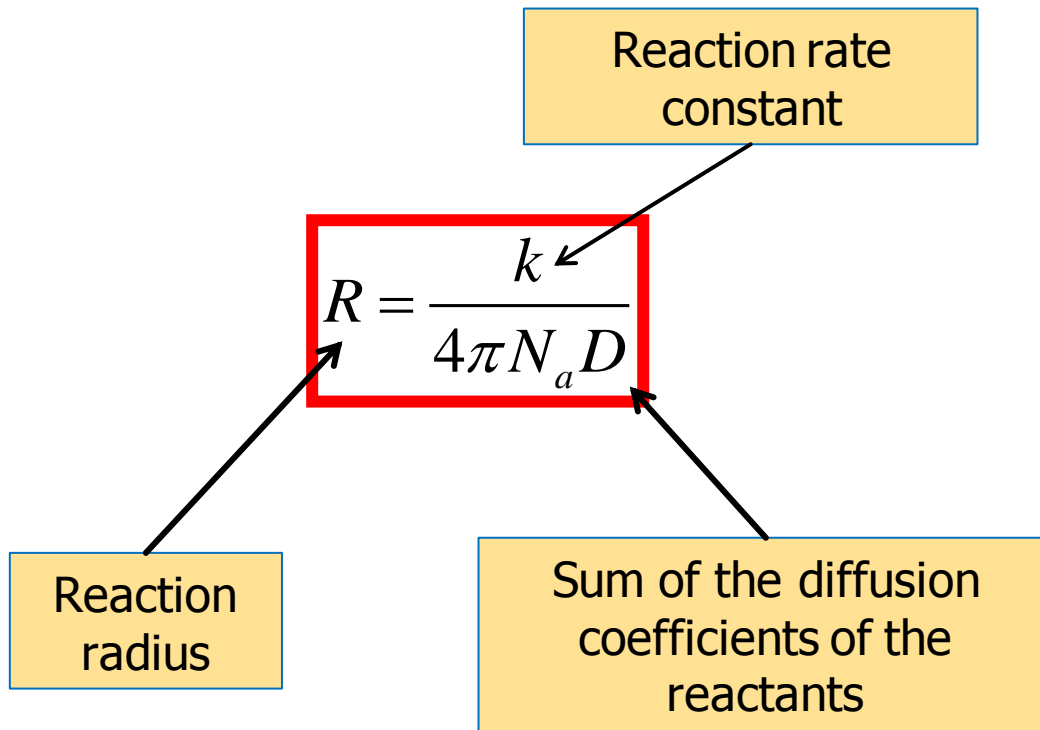2. Take one **diffusion** step for all molécules, return to **1)**

r < Reaction radius R ?

NO   Yes

$t=10^{-12}s$ $t=10^{-6}s$

The step –by-step method: reaction

Smoluchowski model:

Reaction rate constant

$$R = \frac{k}{4\pi N_a D}$$

Reaction radius

Sum of the diffusion coefficients of the reactants

r

r < Reaction radius R ?

NO

Yes

Reaction calculated after each step Δt ...

Step-by-step: method: How to choose Δt ?

- Two solutions have been implémented in Geant4-DNA

1) Select an arbitrary time step
   - Example : A la **PARTRAC***

     Step Δt are predefined and evolved along the simulation

Time interval (s)	Δt (ps)
Until 1.0×10^{-11}	0.1
$1.0 \times 10^{-11} - 1.0 \times 10^{-10}$	1
$1.0 \times 10^{-10} - 1.0 \times 10^{-9}$	3
$1.0 \times 10^{-9} - 1.0 \times 10^{-8}$	10
Above 1.0×10^{-8}	100

*Kreipl et al, Radiat Environ Biophys, **48**, 11-20 (2009)
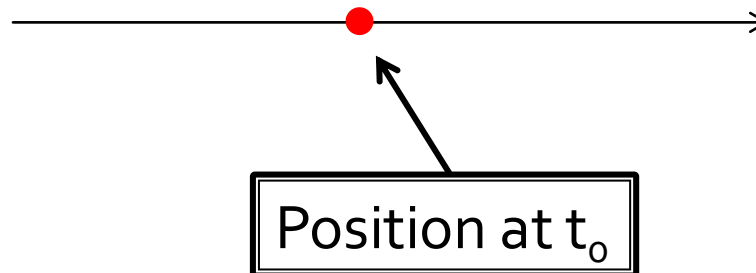
2) Compute it in respect to the next reaction*
   - Explanation ...

*Michalik et al., Radiation Research **149**, 224-236 (1998)
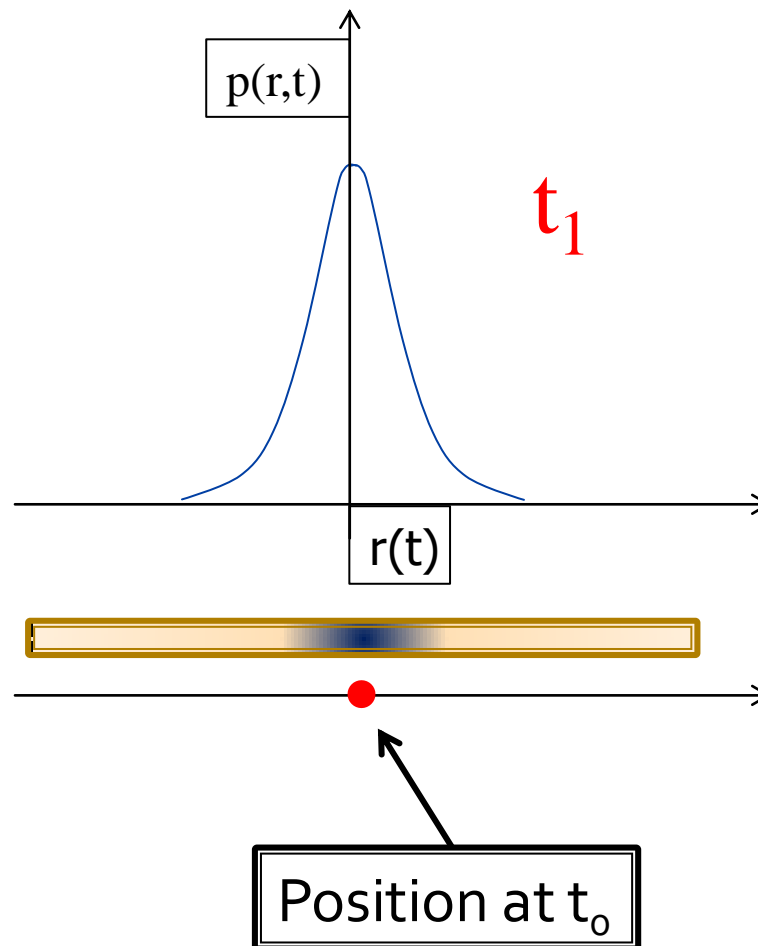
Step-by-step method: diffusion process

- How to compute a Δt in order to avoid missing reactions?

Position at t_o

Step-by-step method: diffusion process

- How to compute a Δt in order to avoid missing reactions?
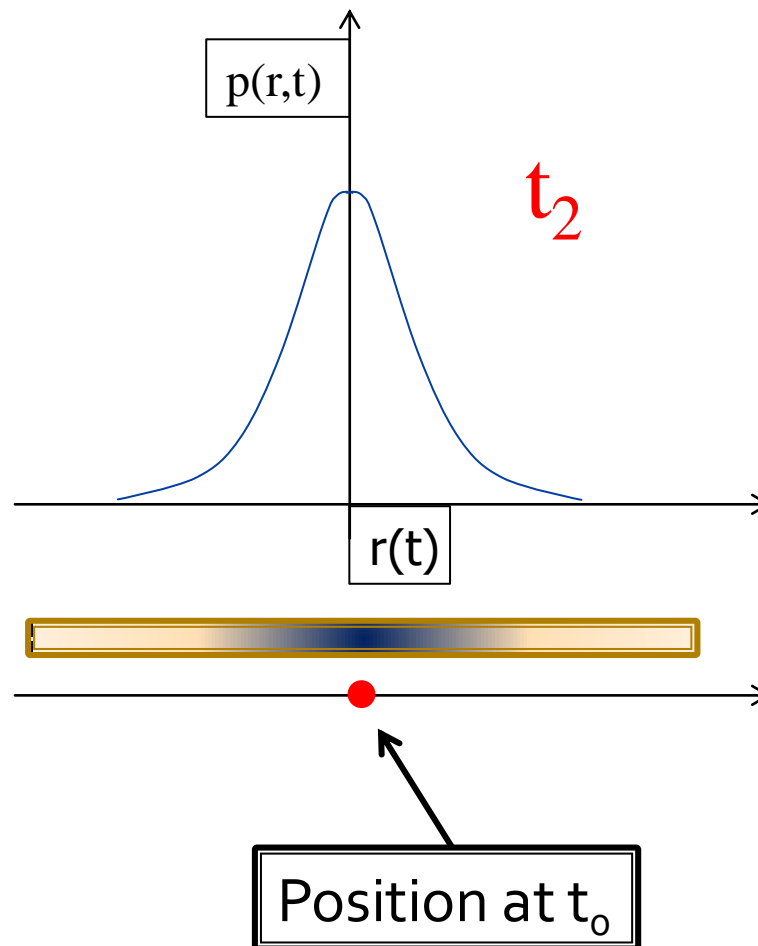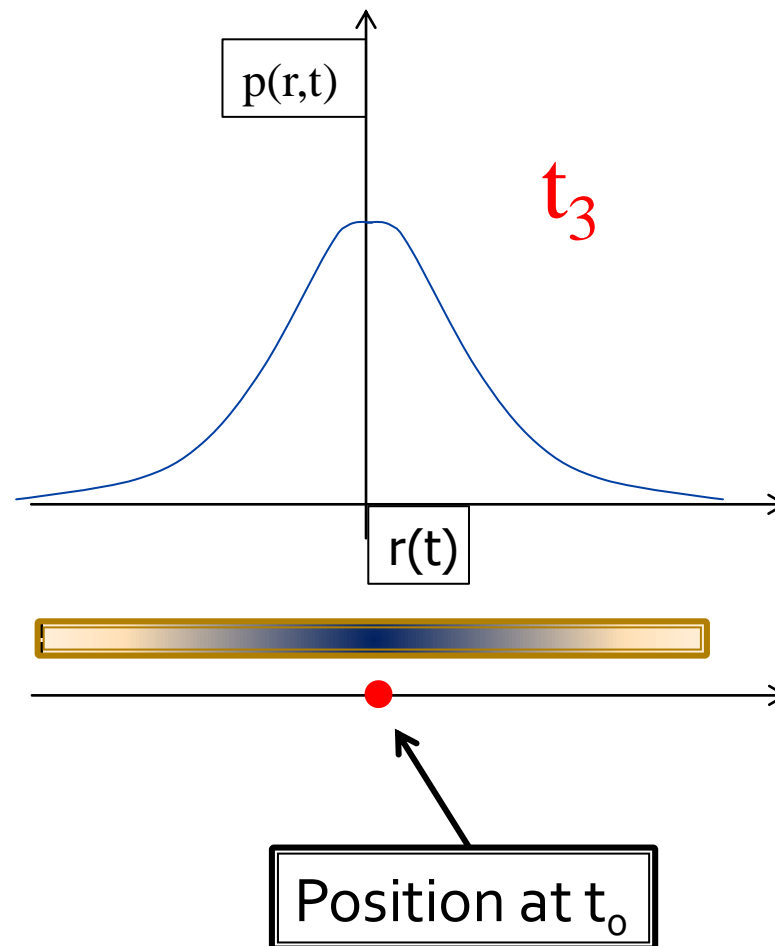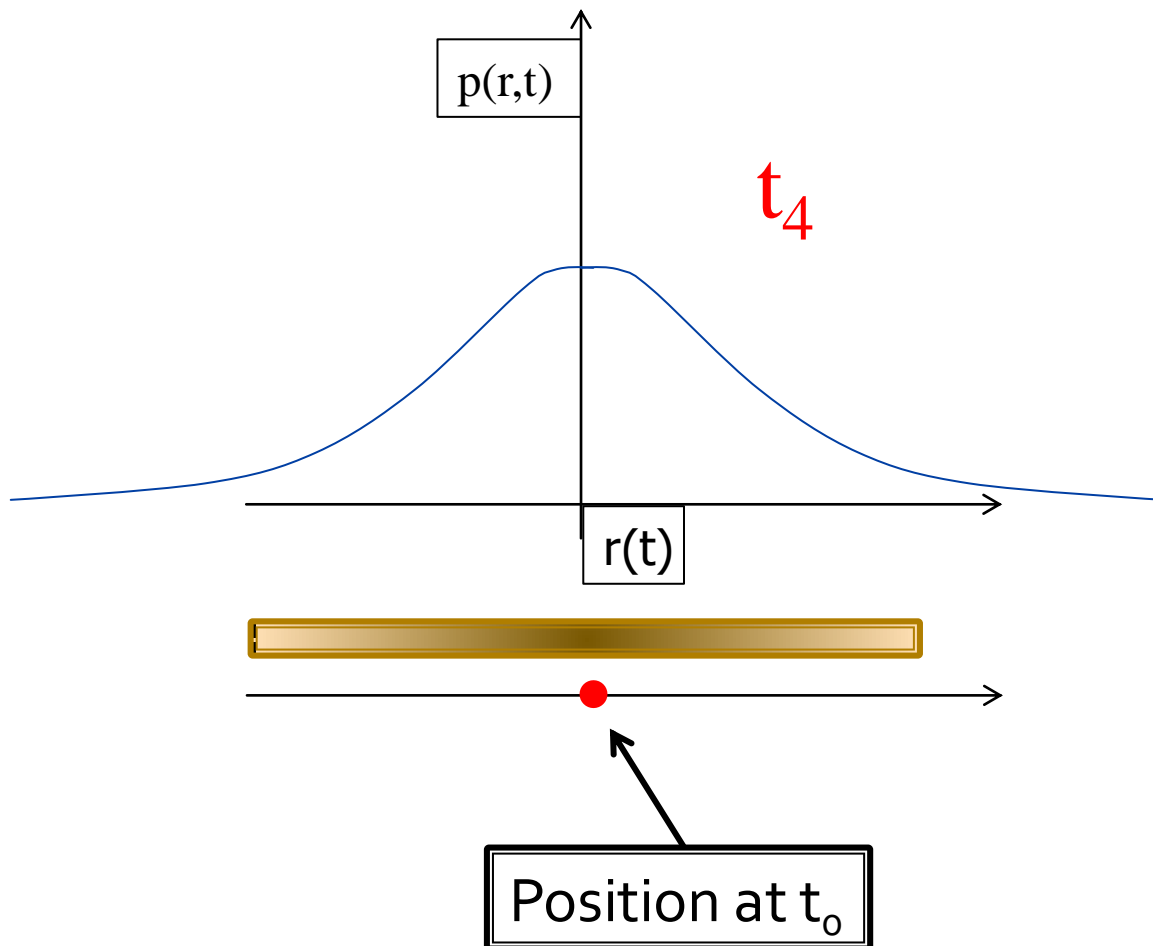
Step-by-step method: diffusion process

- □ How to compute a Δt in order to avoid missing reactions?

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Step-by-step method: diffusion process

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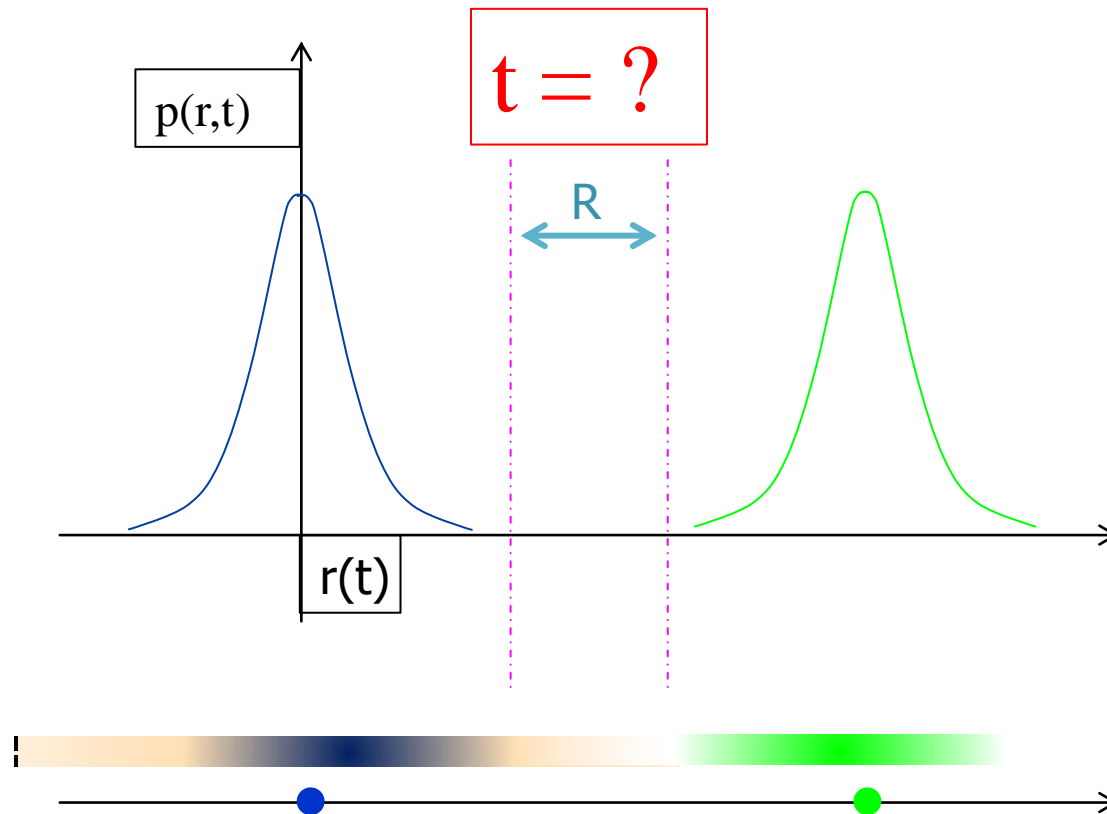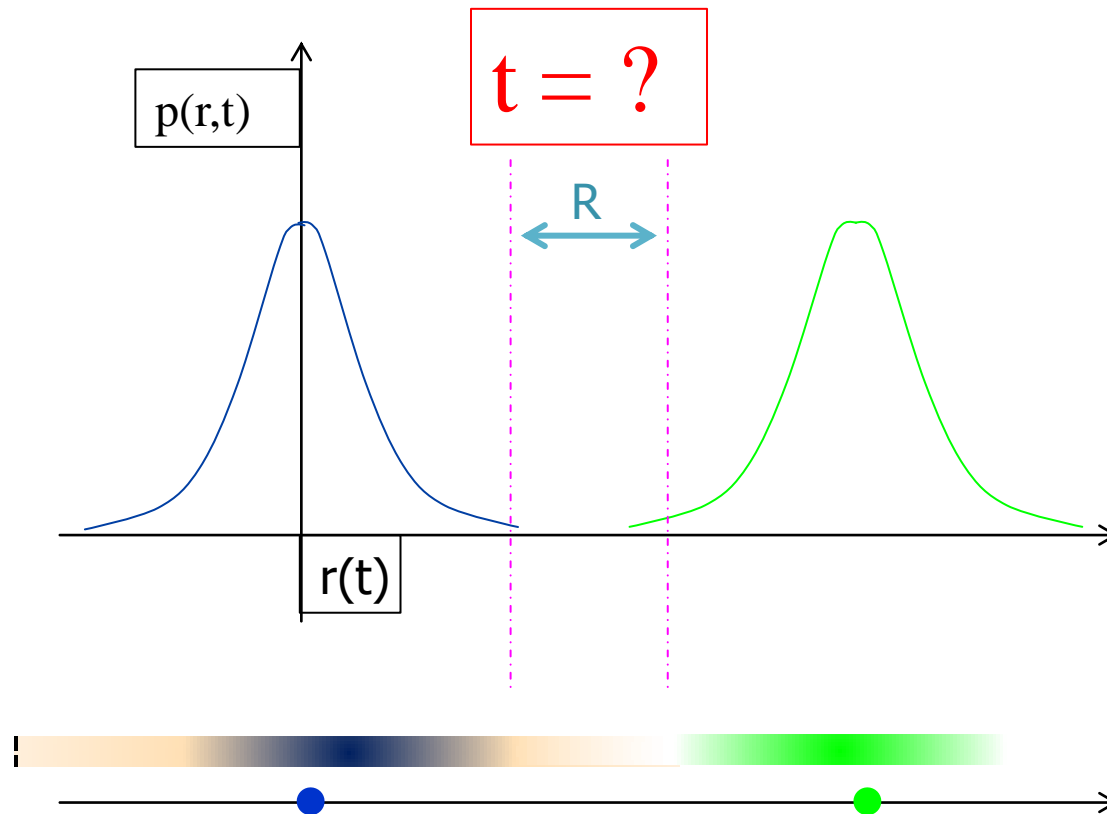
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□ How to compute a Δt in order to avoid missing reactions?

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Step-by-step method: diffusion process
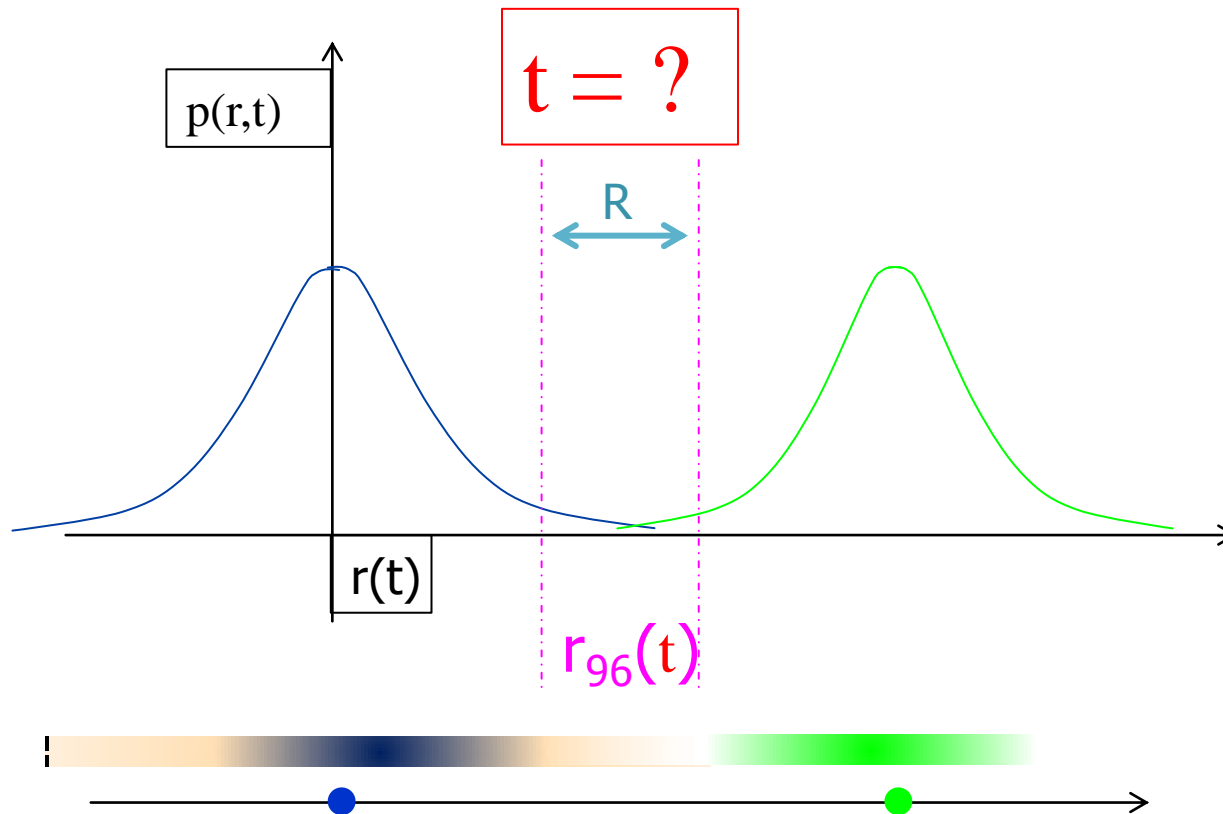
☐ How to compute a Δt in order to avoid missing reactions?

« Dynamical time step » technique*

*Michalik et al., Radiation Research **149,** 224-236 (1998)
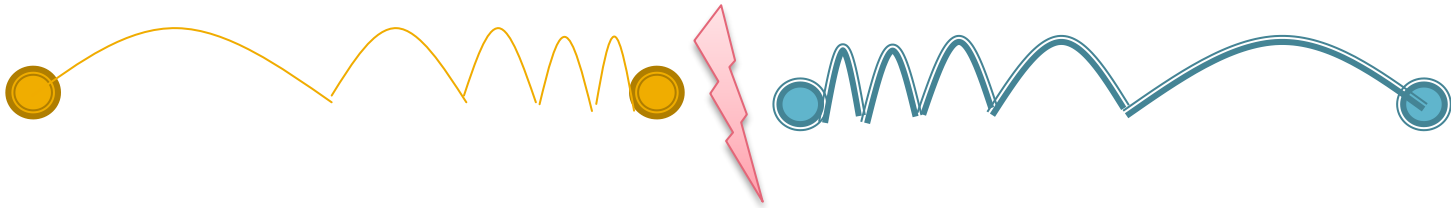
Drawback of the dynamical time steps

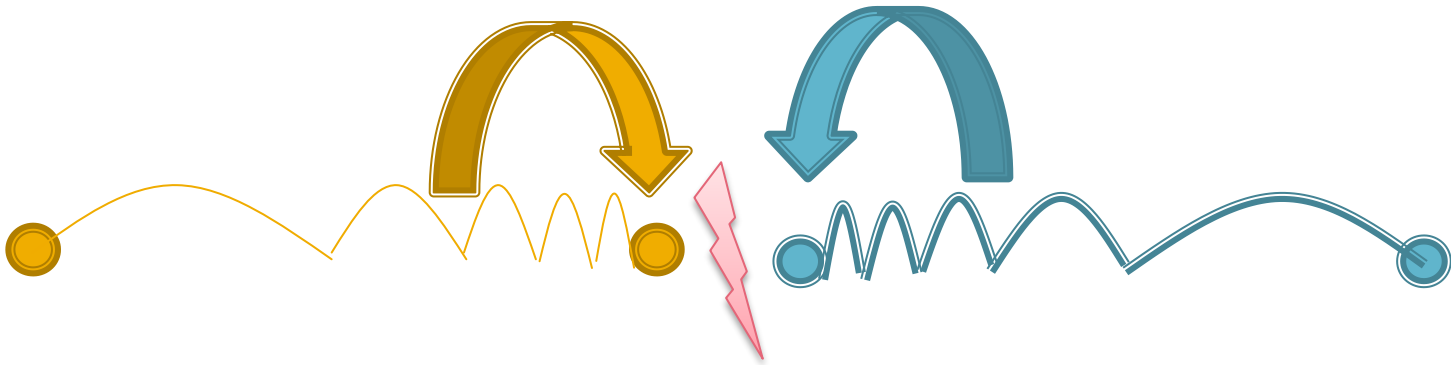- Multiple smaller and smaller steps

Drawback of the dynamical time steps

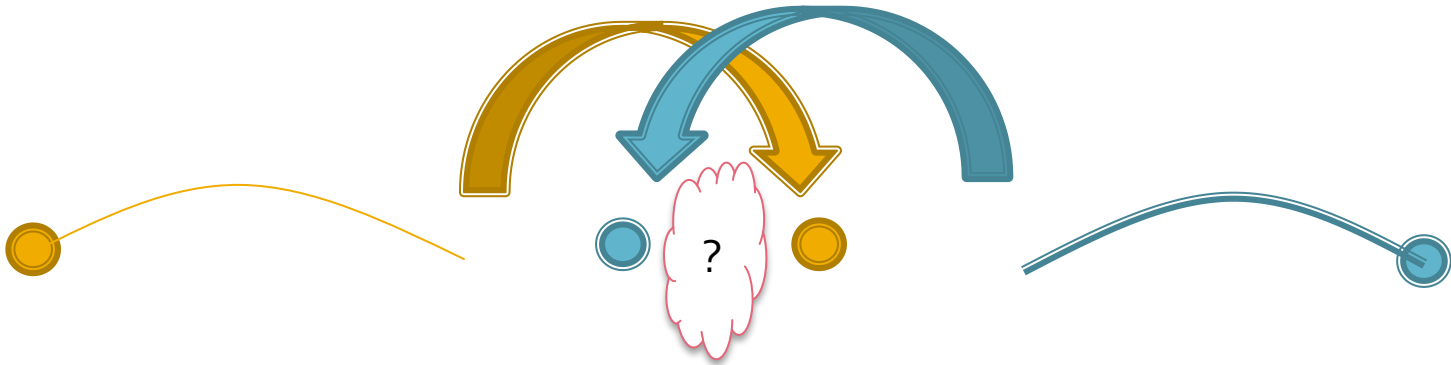- Multiple smaller and smaller steps

Drawback of the dynamical time steps

- Multiple smaller and smaller steps
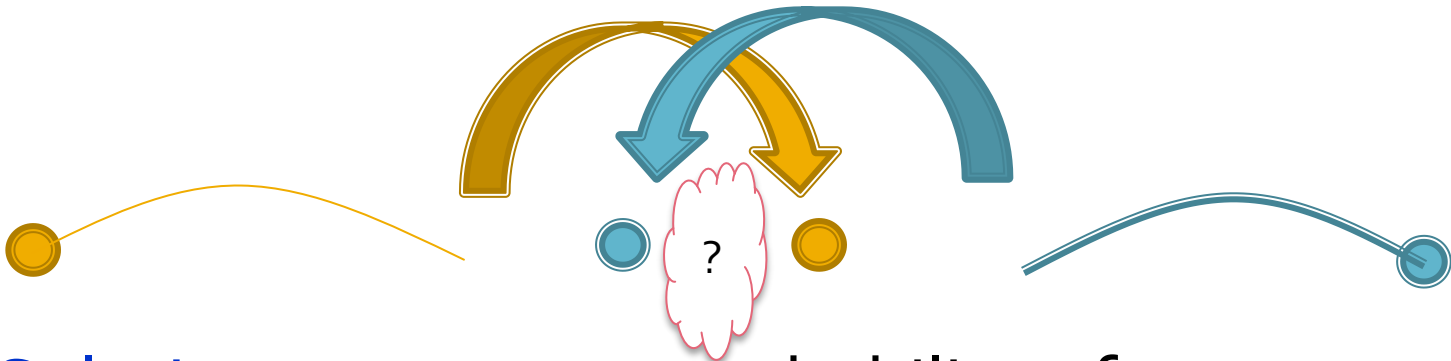- Solution: impose a minimum time step

Drawback of the dynamical time steps

- Multiple smaller and smaller steps
- Solution: impose a minimum time step
- Problem : may miss reactions

Drawback of the dynamical time steps

- Multiple smaller and smaller steps
- Solution: impose a minimum time step
- Problem : may miss reactions

- Solution: compute a probability of encounter during a time step
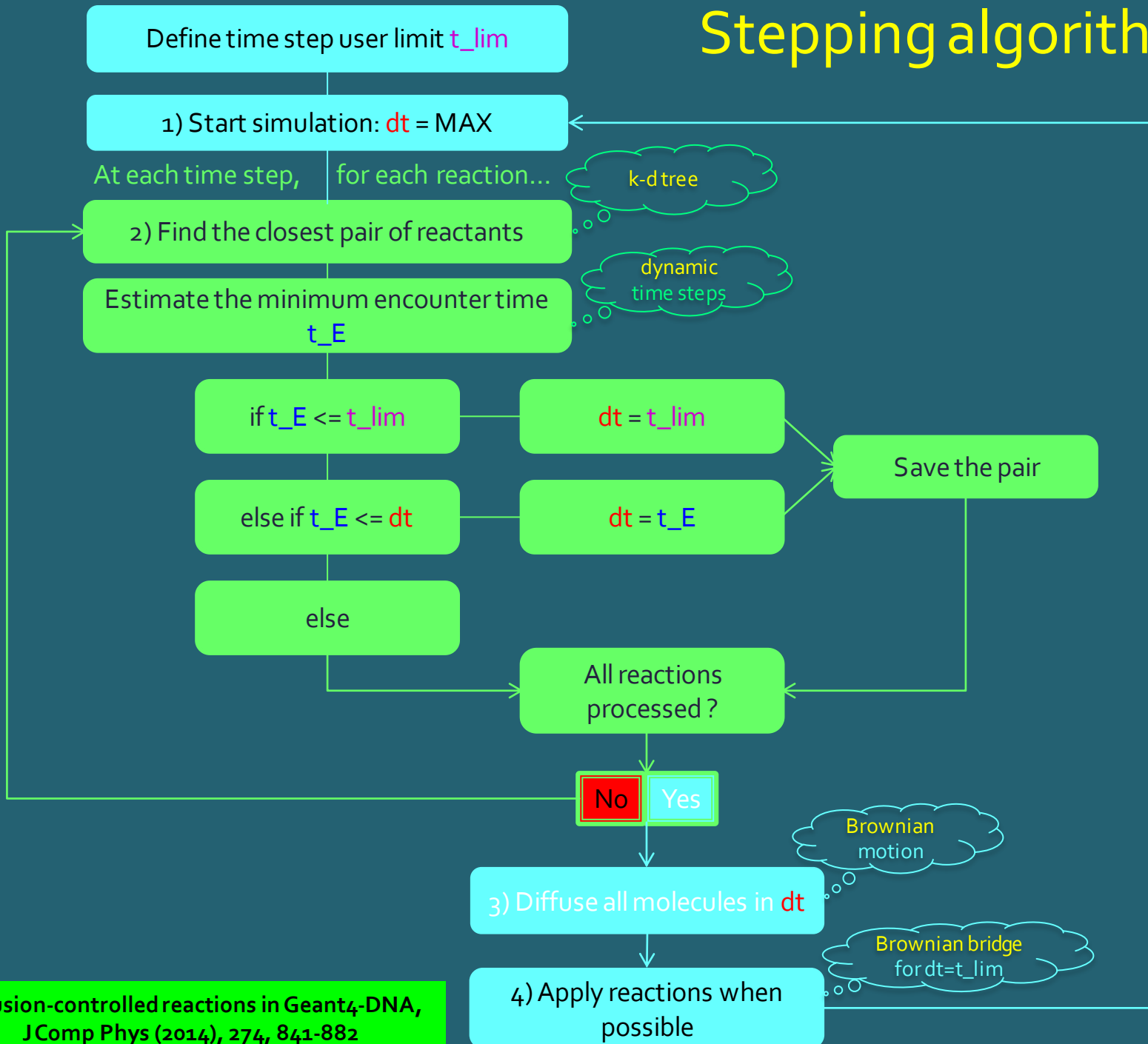 - Brownian bridge

Speed up the step by step method ...

Reaction ➔ search for the closest neighbor

- **Brute-force method**
  Compare all distances between N reactants

  - Number of elementary operations ≈ $N^2/2$

  - Drawback: CPU

- **Solution** : **k-d tree**

Stepping algorithm*

Define time step user limit t_lim

1) Start simulation: dt = MAX

At each time step, for each reaction...

k-d tree

2) Find the closest pair of reactants

dynamic time steps

Estimate the minimum encounter time t_E

if t_E <= t_lim → dt = t_lim

else if t_E <= dt → dt = t_E

Save the pair

else

All reactions processed ?

No   Yes

Brownian motion

3) Diffuse all molecules in dt

Brownian bridge for dt=t_lim

4) Apply reactions when possible

Diffusion-controlled reactions in Geant4-DNA, J Comp Phys (2014), 274, 841-882

* simplified

Chemical stage: parameters

Species	Diffusion coefficient D (10^{-9} m² s⁻¹)
H_3O^+	9.0
$H\bullet$	7.0
OH^-	5.0
e^-_{aq}	4.9
H_2	4.8
$\bullet OH$	2.8
H_2O_2	2.3

In ConstructMolecules()

Reaction	Reaction rate (10^{10} M⁻¹ s⁻¹)
$H_3O^+ + OH^- \rightarrow 2\ H_2O$	14.3
$\bullet OH + e^-_{aq} \rightarrow OH^-$	2.95
$H\bullet + e^-_{aq} + H_2O \rightarrow OH^- + H_2$	2.65
$H_3O^+ + e^-_{aq} \rightarrow H\bullet + H_2O$	2.11
$H\bullet + \bullet OH \rightarrow H_2O$	1.44
$H_2O_2 + e^-_{aq} \rightarrow OH^- + \bullet OH$	1.41
$H\bullet + H\bullet \rightarrow H_2$	1.20
$e^-_{aq} + e^-_{aq} + 2\ H_2O \rightarrow 2\ OH^- + H_2$	0.50
$\bullet OH + \bullet OH \rightarrow H_2O_2$	0.44

In ConstructReactionTable()

We followed the set of parameters published by the authors of the PARTRAC software (Kreipl et al., REB 2009). However, these parameters can be modified by the user.
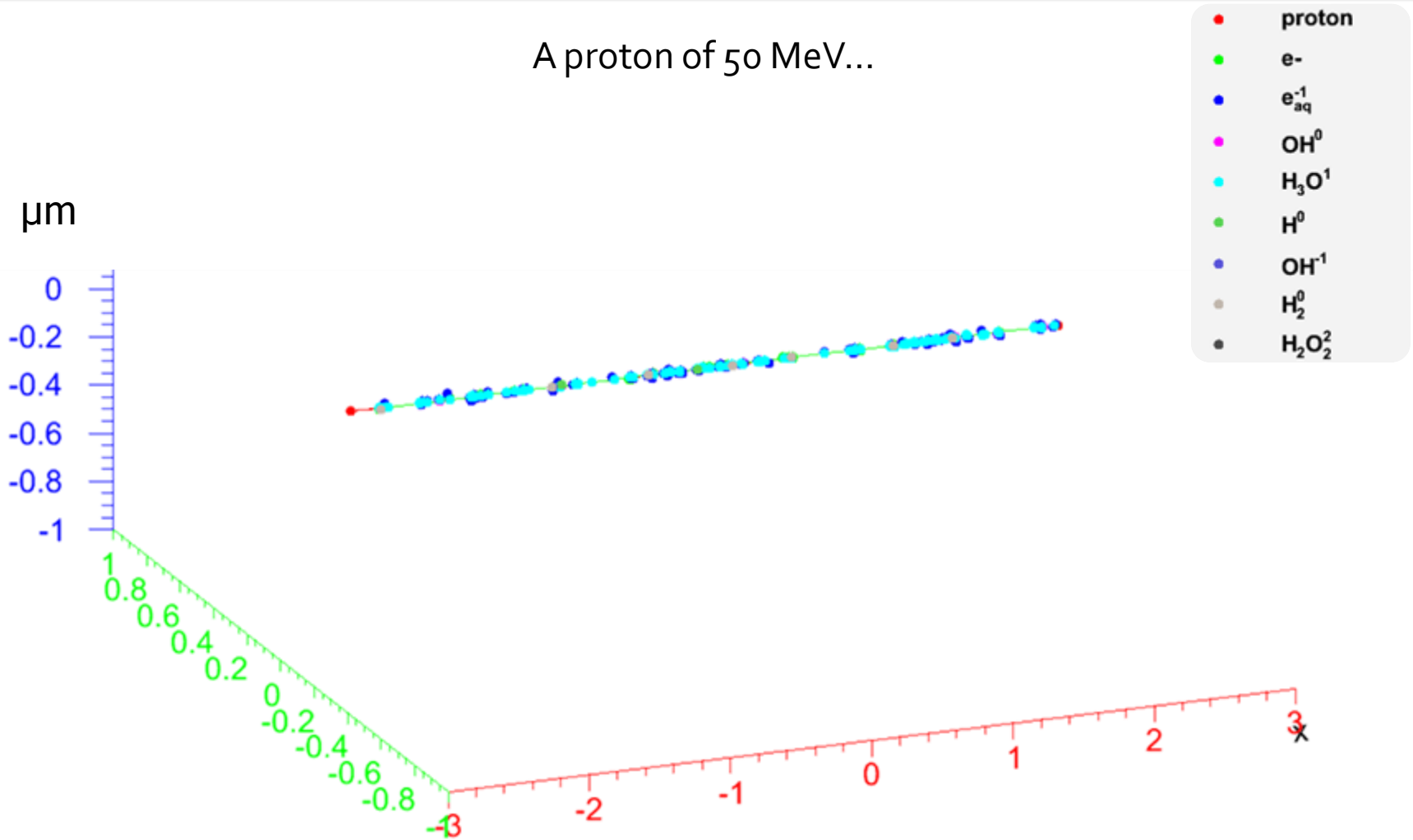
Kreipl *et al*, 2009

Simulation setup

- Protons in 5 μm finite cube of liquid water

- When a particle leaves the cube, it is taken out from the simulation
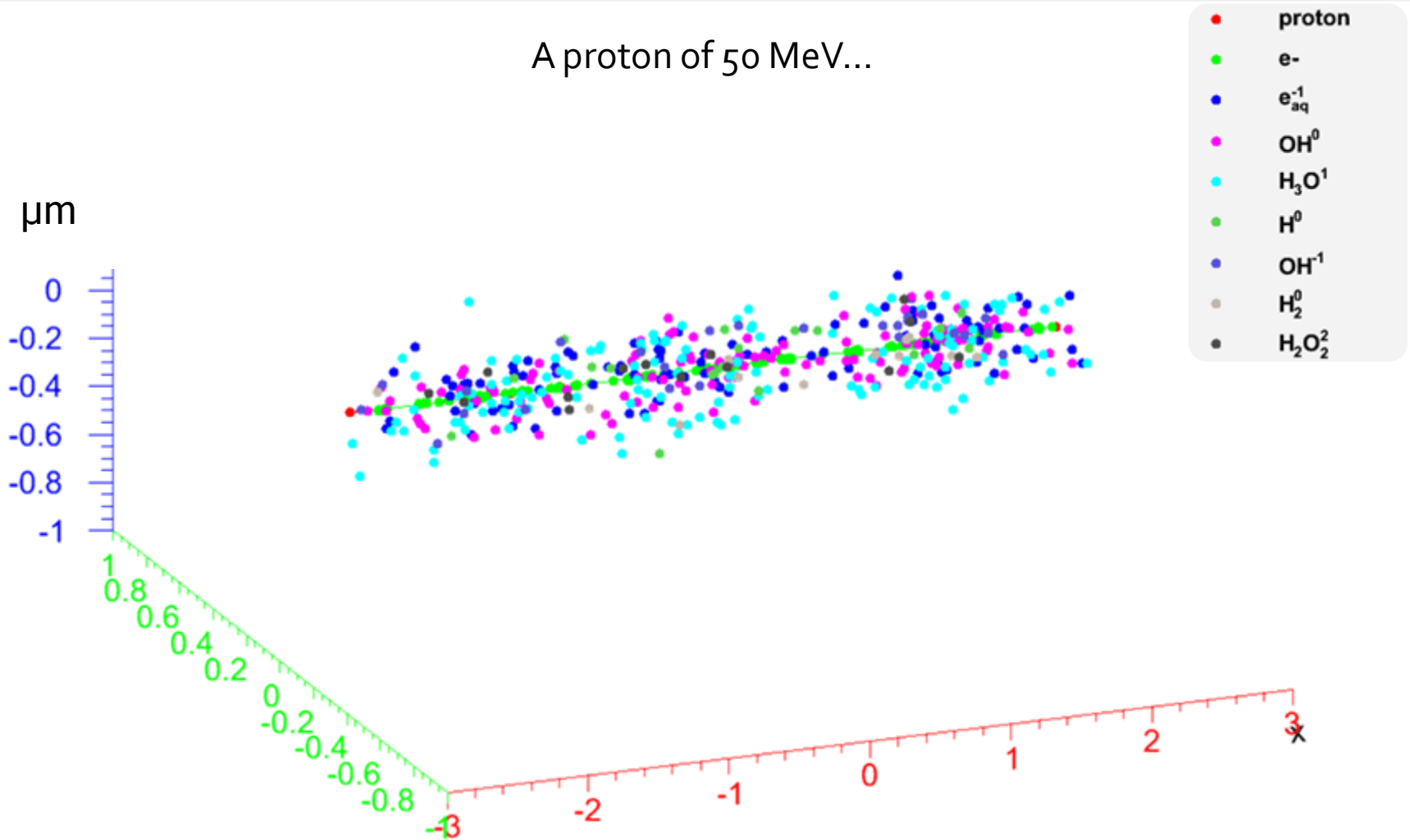

5 μm

——— Proton
——— Electron

Secondaries
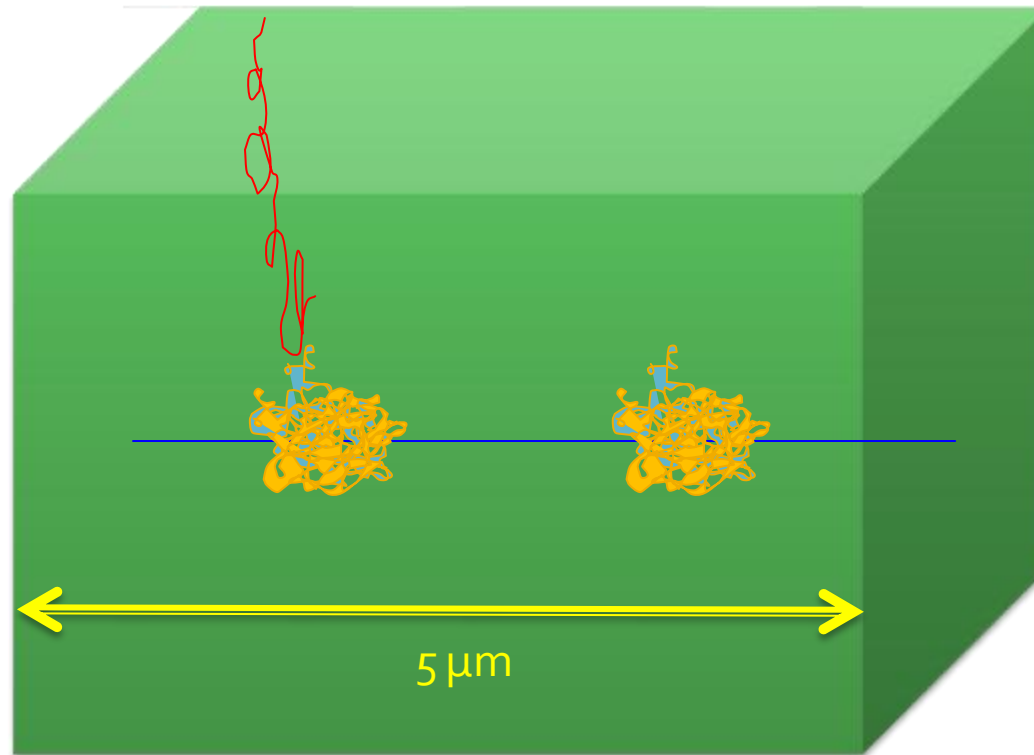
Situation at 1 picosecond

A proton of 50 MeV...

Situation at 1 microsecond
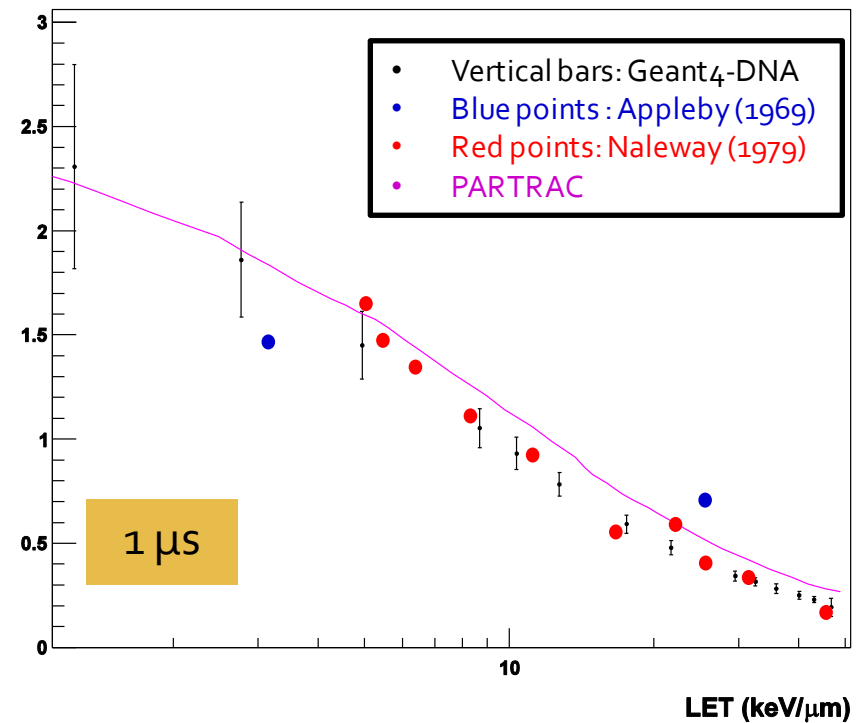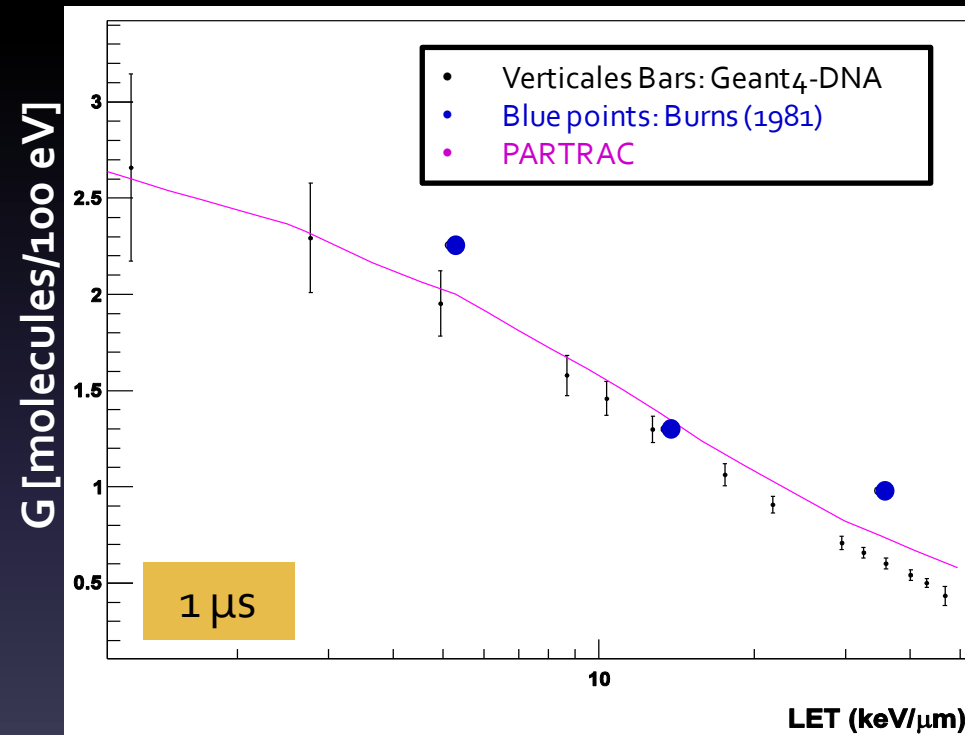

A proton of 50 MeV...

Radiochemical yields VS LET

OH radicals

Solvated e-

➔ General trend reproduced

DNA chemistry limitations

Usage

- Add reactions → **data needed**
- Prototype
  → Bad interface, bugs etc …
  → Don't hesitate to contact us

Models

- Particle-continuum representation
  → CPU and memory consuming
  → Run on a cluster
- Diffusion-controlled reactions

Indirect effects

- Ongoing developments

Thank you for coming

Questions?

Diffusion-controlled reactions in Geant4-DNA, J Comp Phys (2014), 274, 841-882