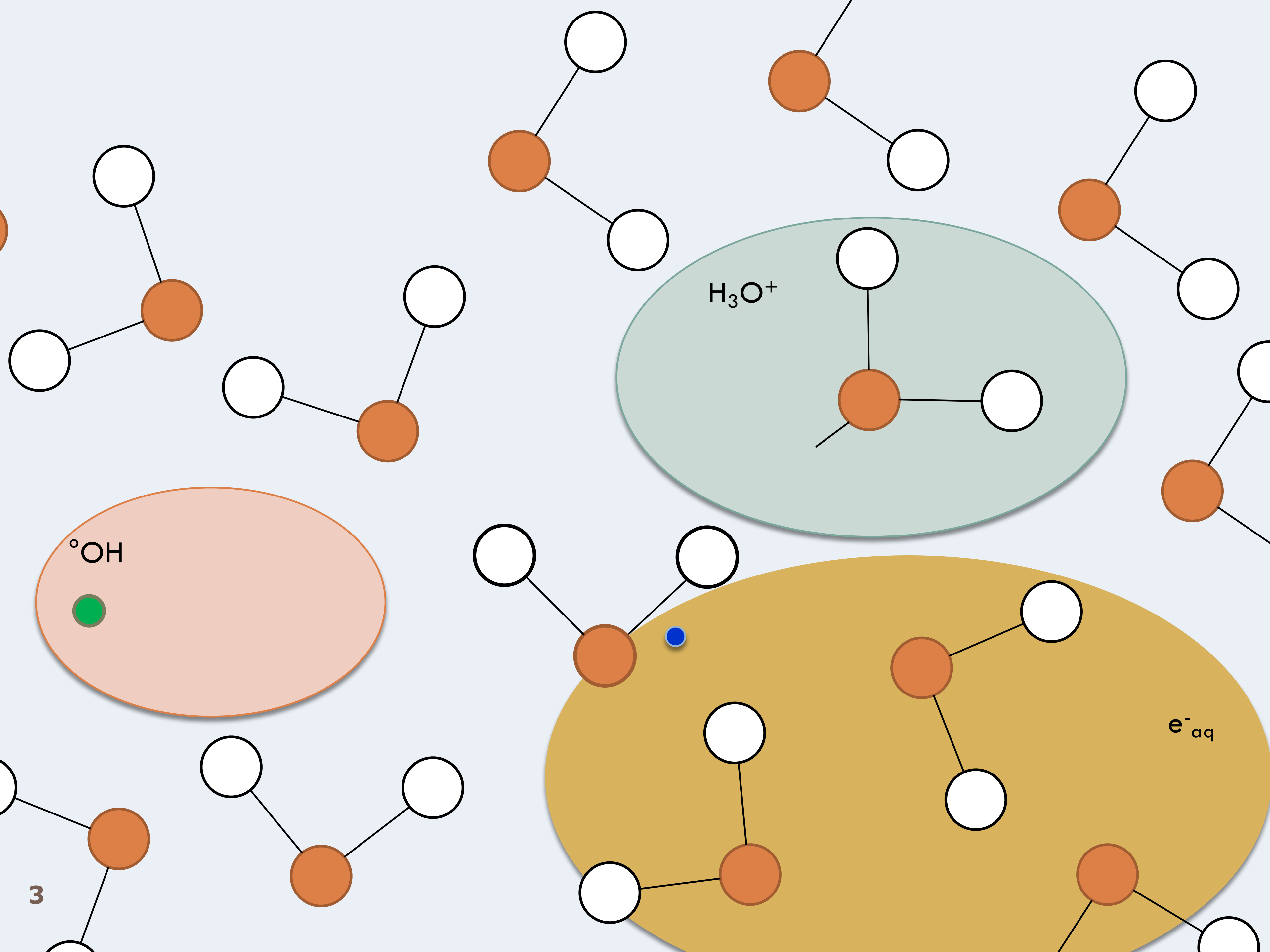
Chemical module of Geant4-DNA

NEWS AND PERSPECTIVES

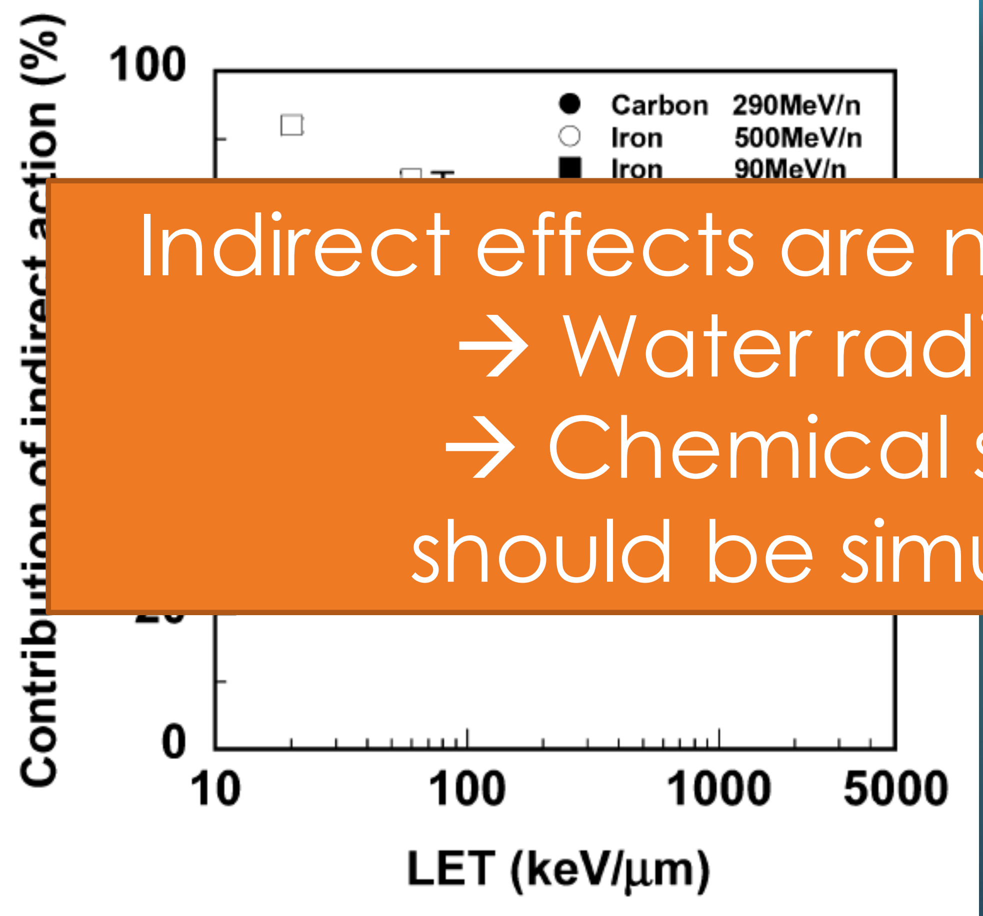
HIROSHIMA - 2015 GEANT4-DNA TUTORIAL

Water radiolysis …

A REMINDER


H_3O^+
°OH
e^-_{aq}

Contribution to cell death of indirect effects VS LET



Why modelling

s?

direct

n **up to**

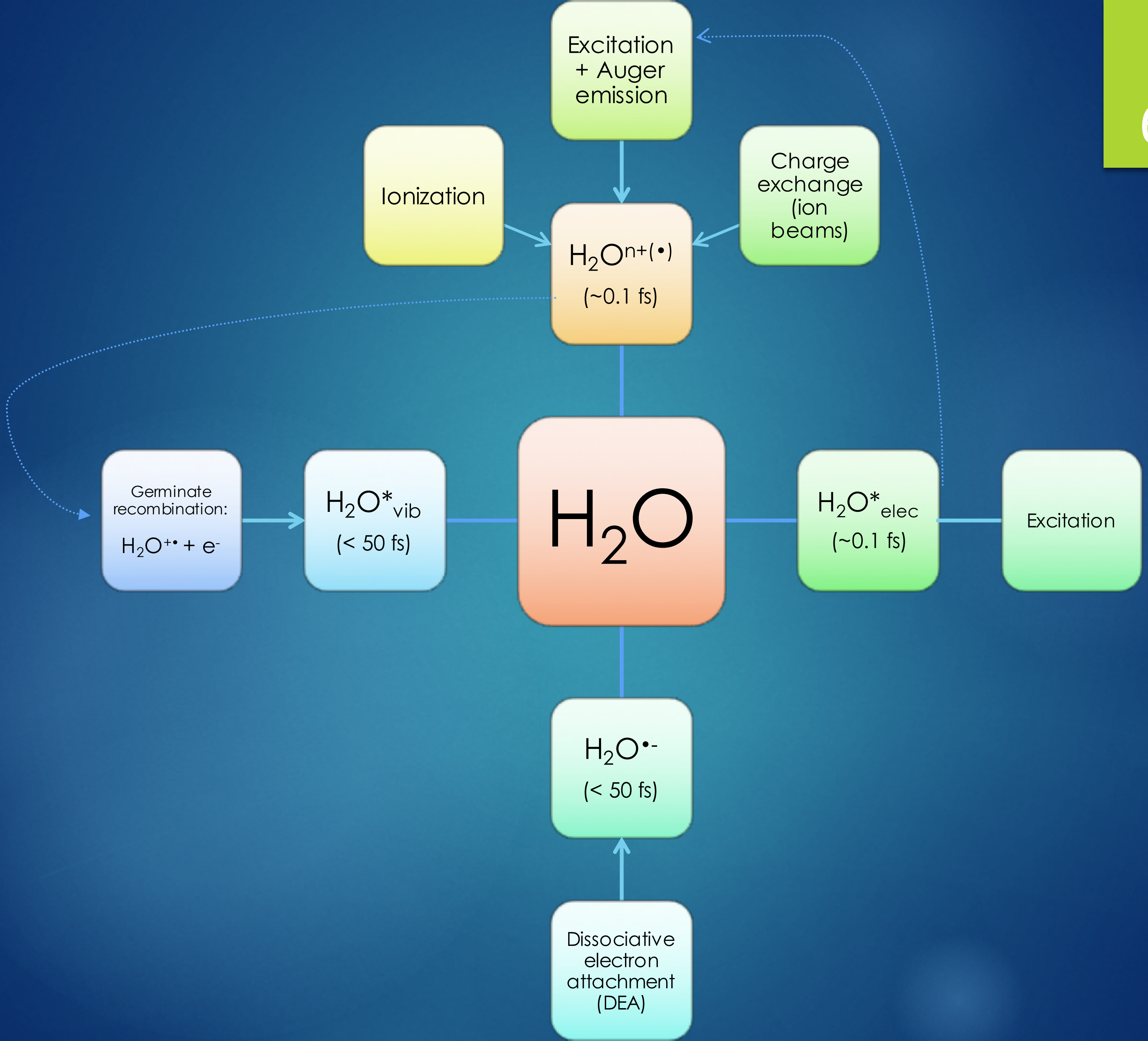
on

Indirect effects are not negligible
→ Water radiolysis
→ Chemical stage
should be simulated

Hirayama et al, Rad Res **171**, 212-218 (2009)

Modelling chemistry in Geant4 ?

PHYSICO-CHEMICAL & CHEMICAL STAGES



Excitation + Auger emission

Ionization

Charge exchange (ion beams)

$H_2O^{n+(\bullet)}$ (~0.1 fs)

Germinate recombination: $H_2O^{+\bullet} + e^-$

$H_2O^*_{vib}$ (< 50 fs)

H_2O

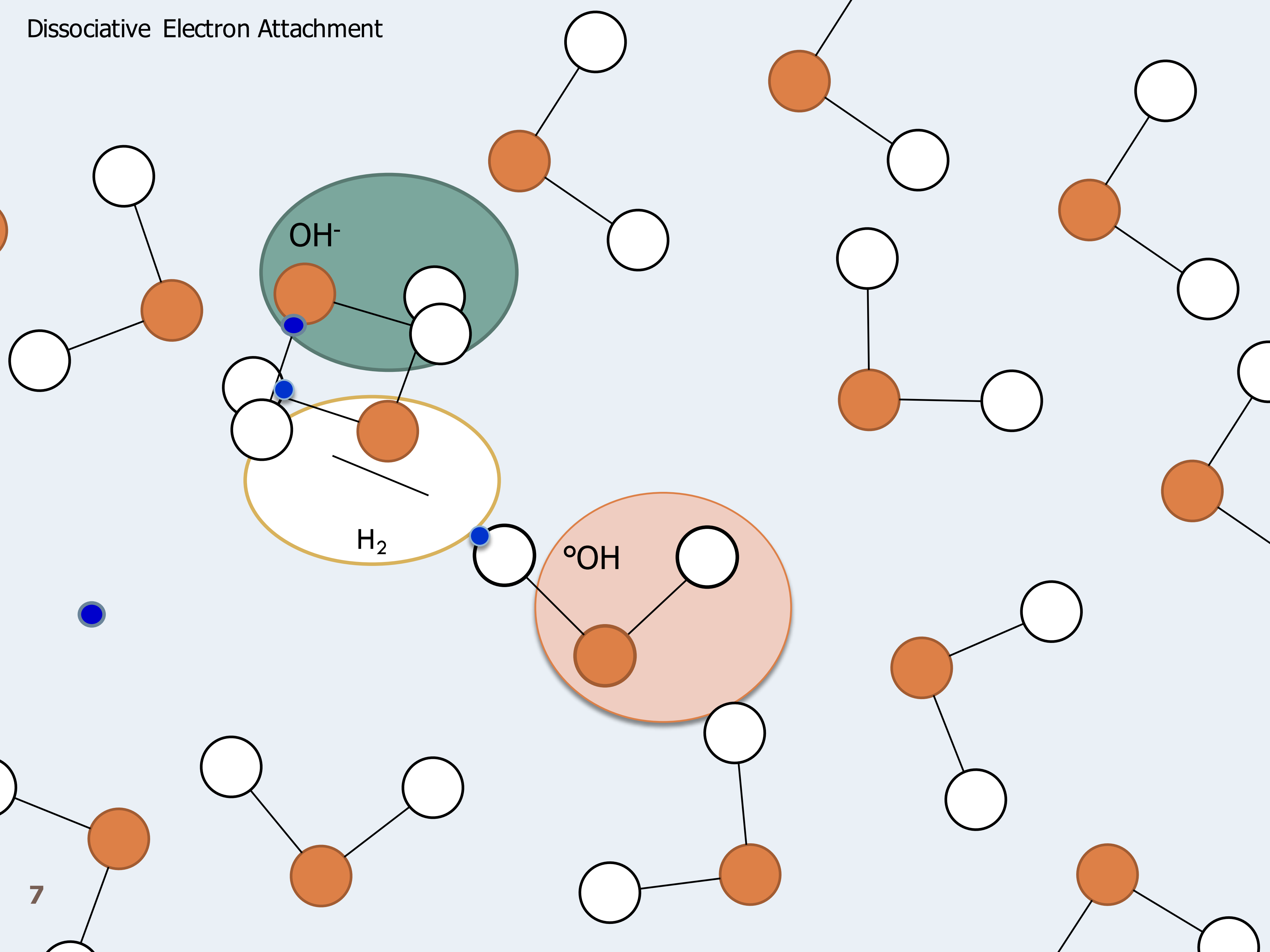
$H_2O^*_{elec}$ (~0.1 fs)

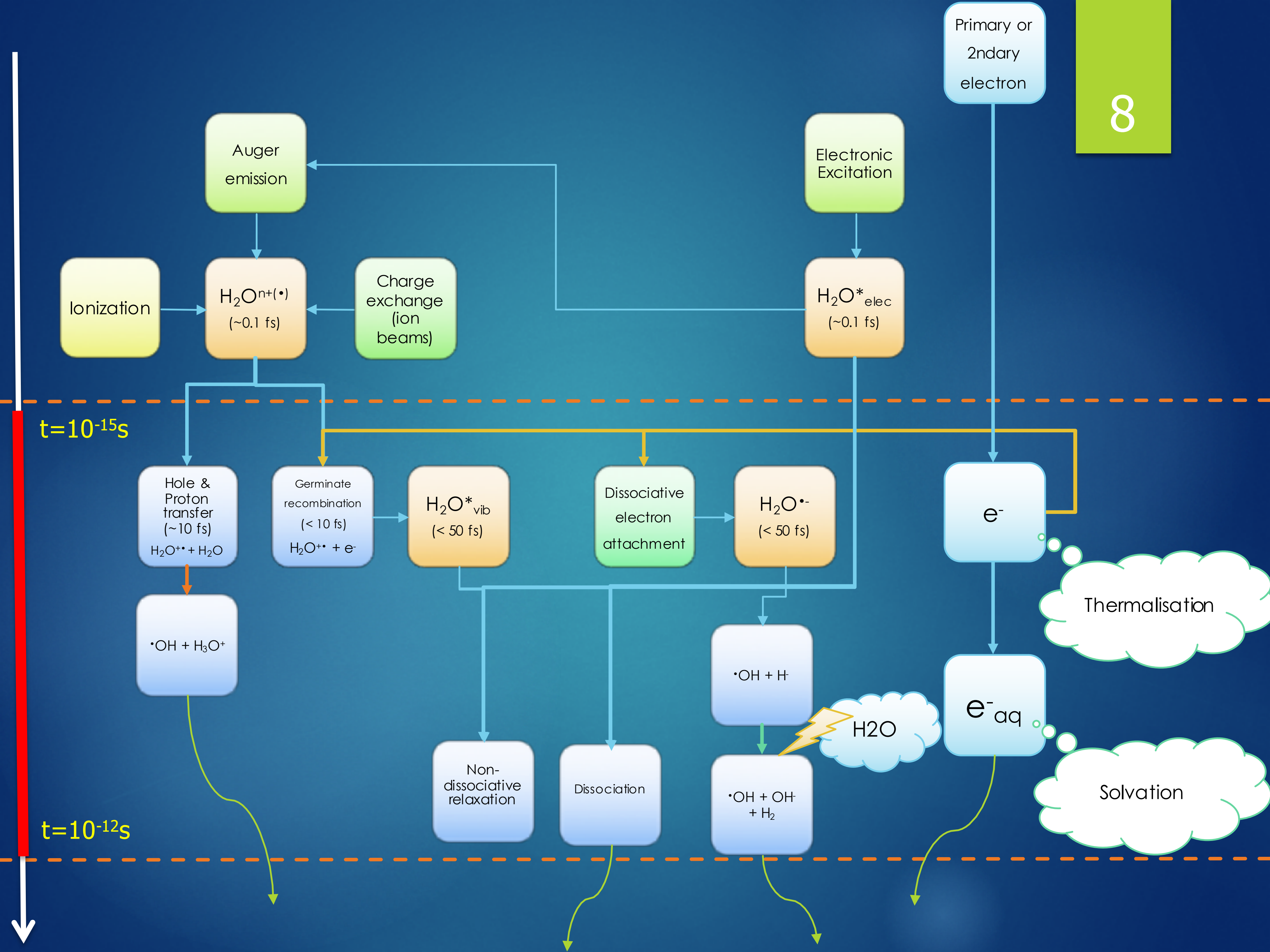
Excitation

$H_2O^{\bullet-}$ (< 50 fs)

Dissociative electron attachment (DEA)

Dissociative Electron Attachment





Primary or 2ndary electron

Auger emission

Electronic Excitation

Ionization

$H_2O^{n+(\bullet)}$ (~0.1 fs)

Charge exchange (ion beams)

$H_2O^*_{elec}$ (~0.1 fs)

$t=10^{-15}s$

Hole & Proton transfer (~10 fs) $H_2O^{+\bullet} + H_2O$

Germinate recombination (< 10 fs) $H_2O^{+\bullet} + e^-$

$H_2O^*_{vib}$ (< 50 fs)

Dissociative electron attachment

$H_2O^{\bullet-}$ (< 50 fs)

e^-

Thermalisation

$^{\bullet}OH + H_3O^+$

$^{\bullet}OH + H^-$

H2O

e^-_{aq}

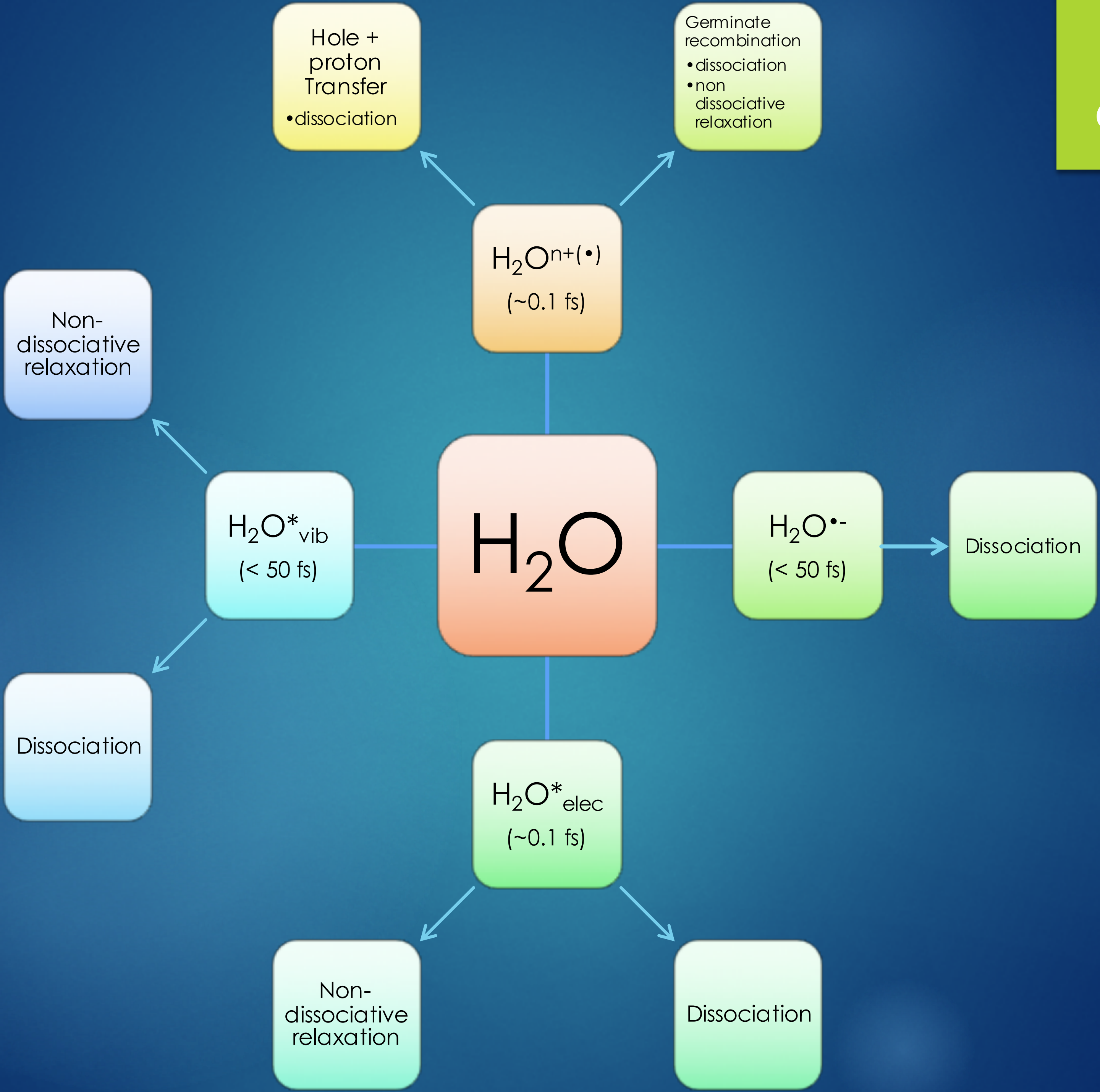
Solvation

Non-dissociative relaxation

Dissociation

$^{\bullet}OH + OH^- + H_2$

$t=10^{-12}s$



Hole + proton Transfer
- dissociation

Germinate recombination
- dissociation
- non dissociative relaxation

$H_2O^{n+(\bullet)}$
(~0.1 fs)

Non-dissociative relaxation

$H_2O^*_{vib}$
(< 50 fs)

H_2O

$H_2O^{\bullet-}$
(< 50 fs)

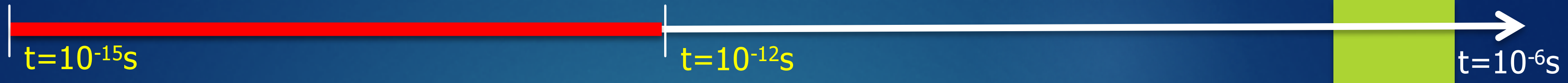
Dissociation

Dissociation

$H_2O^*_{elec}$
(~0.1 fs)

Non-dissociative relaxation

Dissociation



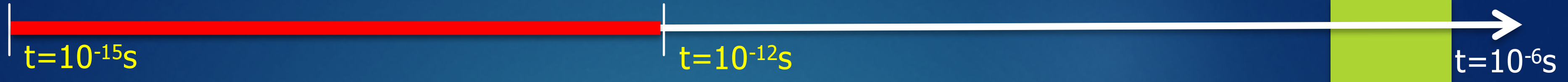
Physico-chemical stage

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

- Situtation at 1 picosecond?
- Can be tuned by the user

- Note: the current version of the physico-chemistry is not compatible with the atomic deexcitation theory available in Geant4

Kreipl *et al*, 2009

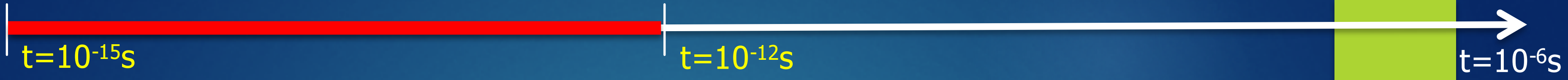


Physico-chemical stage

	Hole hopping	Product 1	Product 2	Product 3
$H_3O^+ + {}^{\bullet}OH$	$\vec{R}\ (2\ nm)$ (charge transfer)	0*	$\vec{R}(0.8\ nm)$*	—
$H_3O^+ + {}^{\bullet}OH + e^-_{aq}$ (AI)	$\vec{R}(2\ nm)$ (charge transfer)	0*	$\vec{R}(0.8\ nm)$*	
${}^{\bullet}OH + H^{\bullet}$	0	$-1/18 \times \vec{R}(2.4\ nm)$	$17/18 \times \vec{R}(2.4\ nm)$	—
$H_2 + {}^{\bullet}OH + {}^{\bullet}OH$	0	$-2/18 \times \vec{R}\ (0.8\ nm)$	$16/18 \times \vec{R}(0.8\ nm)\ + 1/2 \times \vec{R}(1.1\ nm)$	$16/18 \times \vec{R}(0.8\ nm)\ - 1/2 \times \vec{R}(1.1\ nm)$
$H_2 + {}^{\bullet}OH + OH^-$	0	$-2/18 \times \vec{R}(0.8\ nm)$	$16/18 \times \vec{R}(0.8\ nm) + 1/2 \times \vec{R}(1.1\ nm)$	$16/18 \times \vec{R}(0.8\ nm)\ - 1/2 \times \vec{R}(1.1\ nm)$

- Where to place the radiolytic products?
- Defined in G4DNAWaterDissociationDisplacer

Kreipl *et al*, 2009



Physico-chemical stage

Electron – water anion recombination

$e^- + H_2O^+ \rightarrow$ channel 1 / 2 / 3

- 15-25 % of water anions recombine with electrons at room temperature → non negligeable
- Decrease the number of solvated electrons
- Form H_2 product, stable species
- This reaction might be strongly temperature dependent

t=10^{-15}s t=10^{-12}s t=10^{-6}s

Physico-chemical stage

Models for e- + H2O+ → channel 1 / 2 / 3

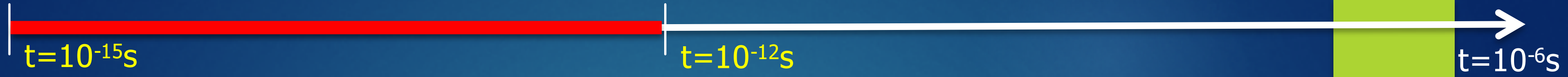
- **Model 1: Onsager model** and derivatives …
  Escape probability (when the external field is zero)
  - $\phi = \exp\left(-\frac{r_C}{r_0}\right)$ ← original Onsager's formula for $F_{ext} = 0$ (derived from swarm particles models)
  - $r_C = \frac{e^2}{4\pi\epsilon\,\epsilon_0 k_B T}$ is called the Onsager radius and corresponds to the distance at which the potential energy of the pair equals the thermal energy
  - r_0 is the initial separation distance
- **Model 1** being tested

t=10^{-15}s t=10^{-12}s t=10^{-6}s

Physico-chemical stage

Models for e- + H2O+ → channel 1 / 2 / 3

- **Model 2: « Molecular dynamics »-like** treatment :
  - The electron is still **tracked using the cross sections** of DEA & vibrational/rotational excitation
  - But the sub excitation electrons also **migrate in the potential** generated by all the nearby holes and electrons in diffusion
  - Accounts for the **decceleration** of the electrons, and the effect of **« crowdy » regions**
- ***Note to G4 developers***
  Model 2 would **require the physics models to work in the chemistry framework**, feasible, but G4VEmProcess should not store locally « track-dependent attributes »
  (e.g. theNumberOfInteractionLengthLeft)



Physico-chemical stage

- Dominant species at the end of the physico-chemical stage

H_3O^+ , e^-_{aq} , °OH

Chemical stage

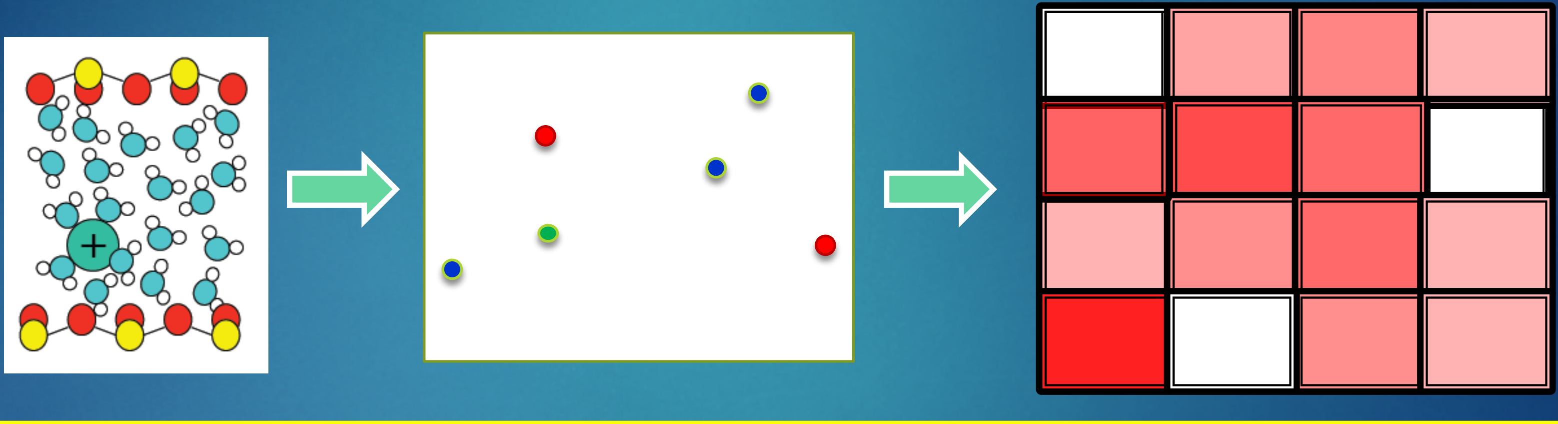
t=10^{-15}s t=10^{-12}s t=10^{-6}s

Chemical stage: representation?

« **Full atomistic** » approach

Molecules = balls
Solvant = continuum

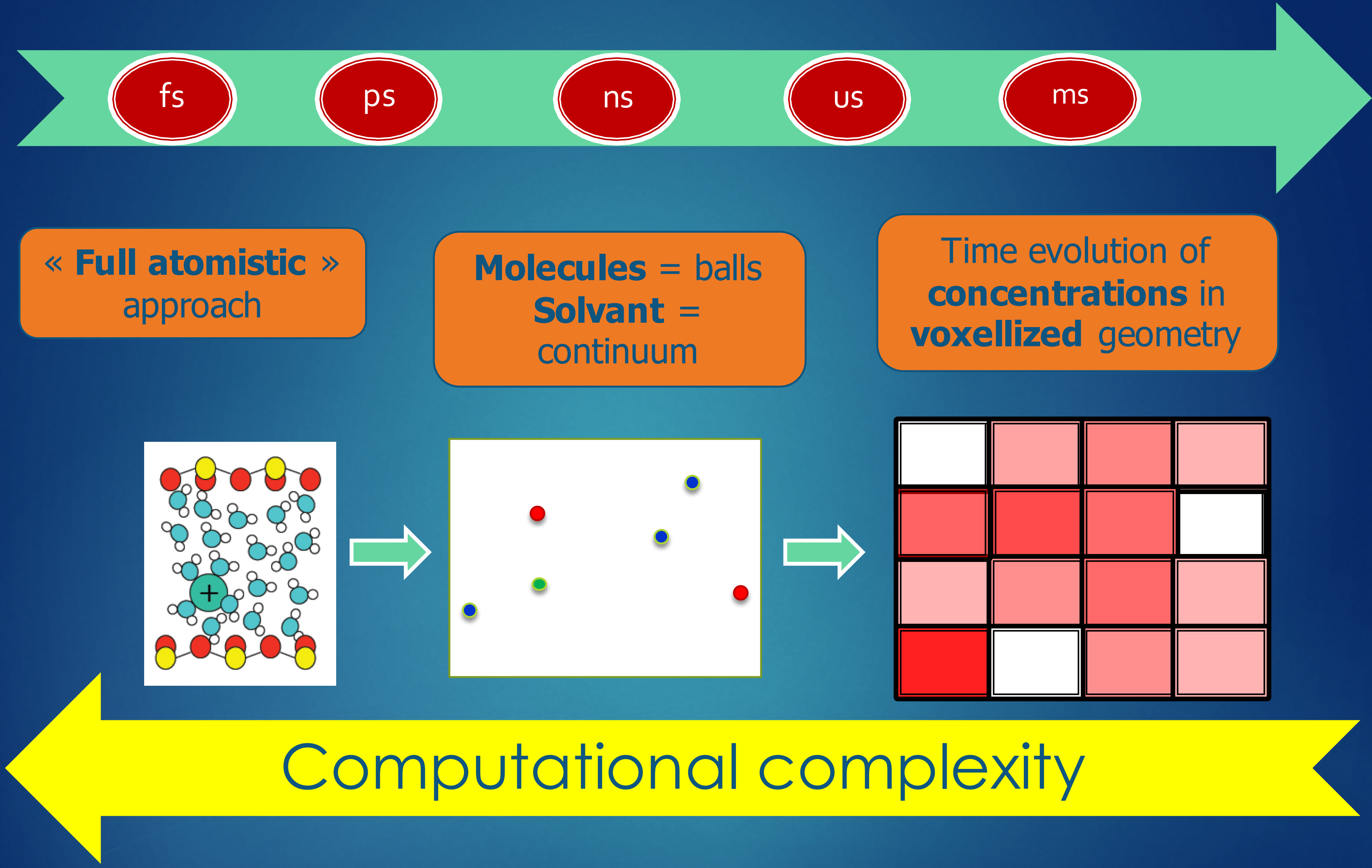
Time evolution of **concentrations** in **voxellized** geometry



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

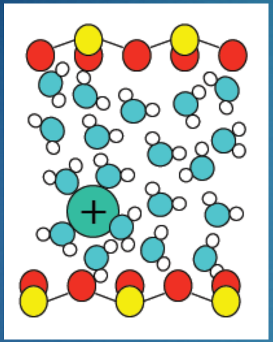
Computational complexity

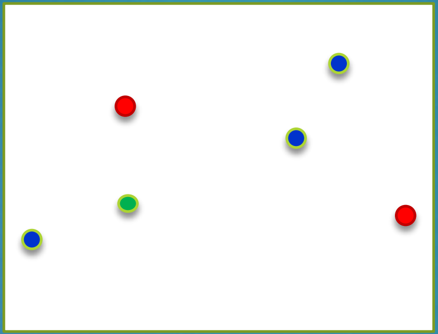
Kinetic constants

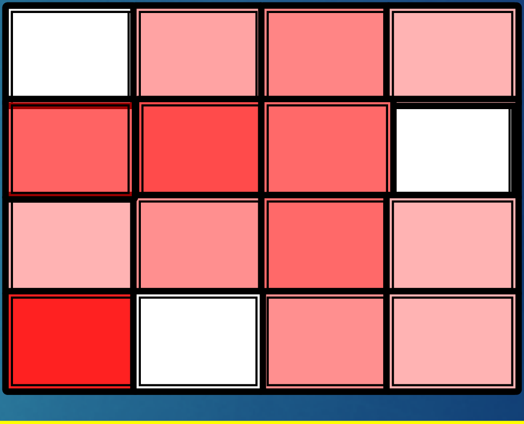
« **Full atomistic** » approach

Molecules = balls
Solvant = continuum

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







Computational complexity

Diffusion

SMOLUCHOWSKI DYNAMICS

Brownian motion – the Langevin equation

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

$$m\ddot{x} = \underbrace{-\alpha\dot{x}}_{\text{Friction force}} + F_{ext}(x)$$

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

$$m\ddot{x} = -\alpha\dot{x} + F_{ext}(x) + \underbrace{\psi(t)}_{\text{Random force}}$$

- This is the so-called Langevin equation → stochastic

Towards the Smoluchowski-Debye equation

- Langevin Equation

$$\ddot{x} = -\frac{\alpha}{m}\dot{x} + \frac{F_{ext}(x)}{m} + \frac{\psi(t)}{m}$$

$$\ddot{x} = -\gamma\dot{x} + \frac{F_{ext}(x)}{m} + \underbrace{\Gamma(t)}_{\text{Langevin force}}$$

Where $\gamma = \frac{\alpha}{m}$

- Hypothesis

$$\langle\Gamma(t)\rangle = 0$$
$$\langle\Gamma(t_1)\cdot\Gamma(t_2)\rangle = q\cdot\delta(t_1 - t_2)$$

Very weak mass + thermal equilibrium ⇒ $\gamma\dot{x} \gg \ddot{x}$

$$\gamma\dot{x} = \frac{F_{ext}(x)}{m} + \underbrace{\Gamma(t)}_{\text{Langevin force}}$$

Smoluchowski-Debye Equation

- Stochastic differential equation

$$\dot{x} = \frac{F_{ext}(x)}{m\,\gamma} + \frac{\Gamma(t)}{\gamma}$$

- The position is described by a density probability function p described by a *Fokker-Planck equation*

$$\boxed{\frac{\partial p(x,t|x_0,t_0)}{\partial t} = \left(\frac{\partial}{\partial x^2}(D\cdot p) - \frac{\partial}{\partial x}\cdot\left(\frac{F_{ext}(x)}{m\gamma}\cdot p\right)\right)}$$

where $D = \frac{q^2}{2\gamma}$ with $\langle\Gamma(t_1)\cdot\Gamma(t_2)\rangle = q\cdot\delta(t_1 - t_2)$

Smoluchowski-Debye Equation

- Solutions of the SDE in absence of external field

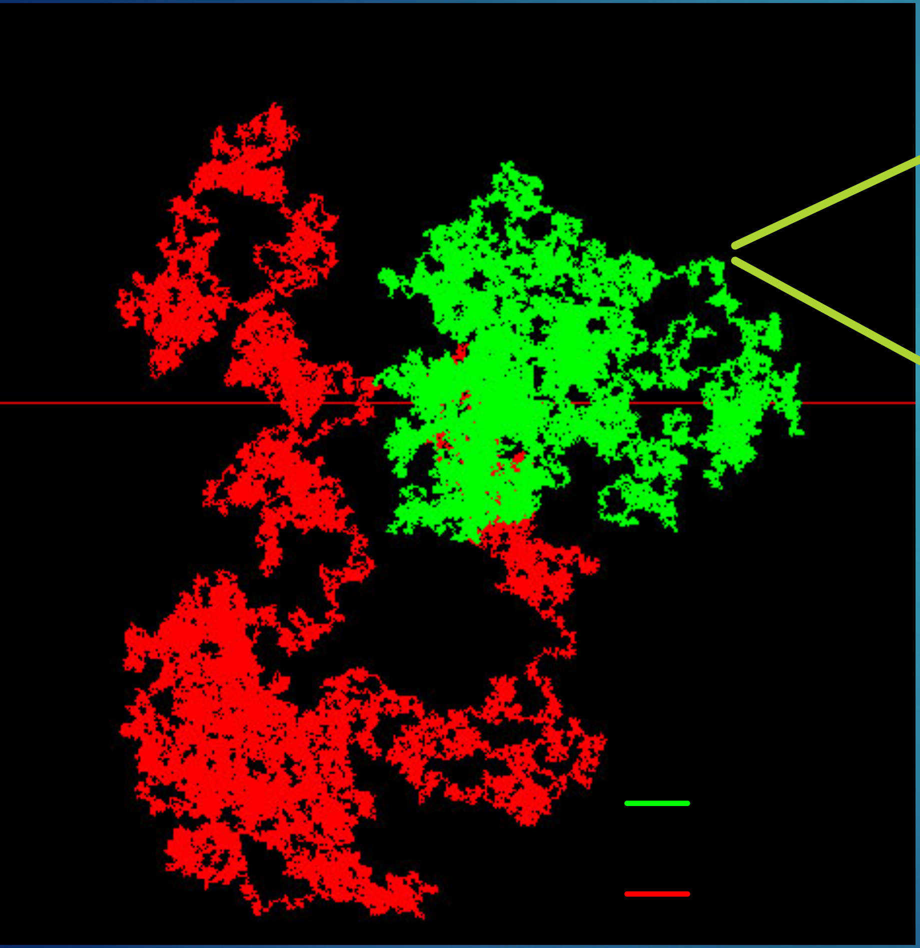
$$p(x,t|x_0,t_0) = \frac{1}{\left(4\pi D(t-t_0)\right)^{\frac{1}{2}}} \exp\left(-\frac{(x-x_0)^2}{4D(t-t_0)}\right) \quad \text{in 1D}$$

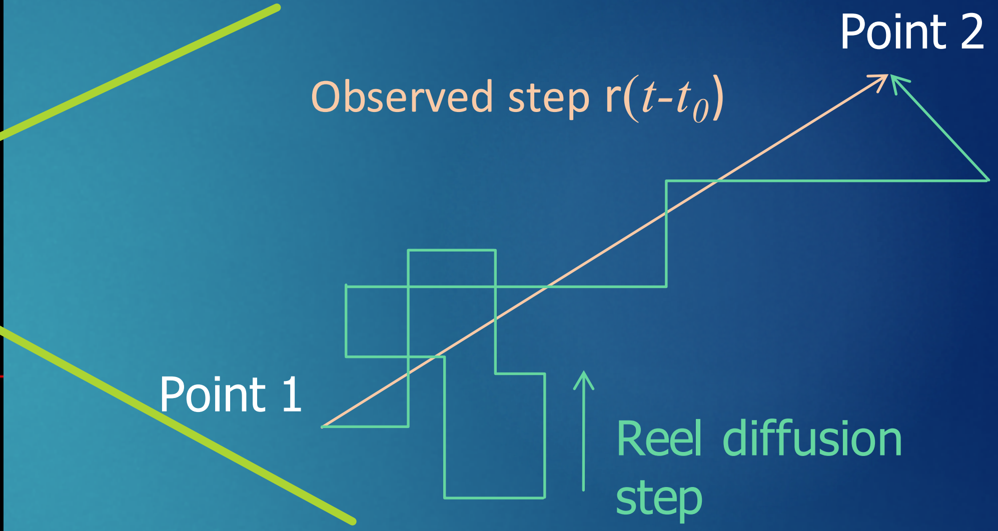
$$p(r,t|r_0,t_0) = \frac{4\pi r^2}{\left(4\pi D(t-t_0)\right)^{\frac{3}{2}}} \exp\left(-\frac{(r-r_0)^2}{4D(t-t_0)}\right) \quad \text{in 3D integrated over the angles}$$

where $D = \frac{q^2}{2\gamma}$ with $\langle \Gamma(t_1) \cdot \Gamma(t_2) \rangle = q \cdot \delta(t_1 - t_2)$

➔ The simulation is a succession of time steps Δt where $\Delta t = t - t_0$

Illustration in Geant4-DNA





Point 2

Observed step r(t-t_0)

Point 1

Reel diffusion step

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

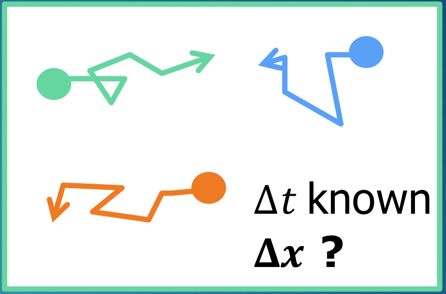
Diffusion-controlled reactions in Geant4-DNA, J Comp Phys (2014), 274, 841-882

Standard Geant4 transport VS Brownian motion

	Standard transport of Geant4	Brownian motion
Position and velocity	Deterministic (between two interactions points)	Stochastic
Path-volume Intersection	« Exact » intersection computable	Is expressed in terms of probability
Equation of motion	Newton	Fokker-Planck (stochastic equation of motion)

(Some) requirements for Brownian dynamics simulations

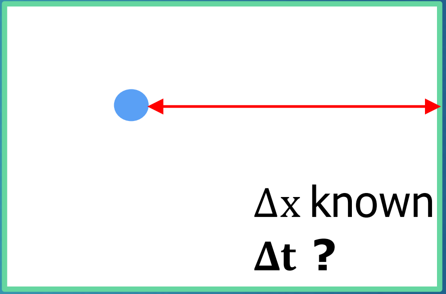
- Given initial positions at time $t=0$ and Δt
  → sample probable positions



Δt known
Δx ?

Time-driven stepping

- Given initial position, distance to a boundary
  → sample a time at which the particle can cross the boundary

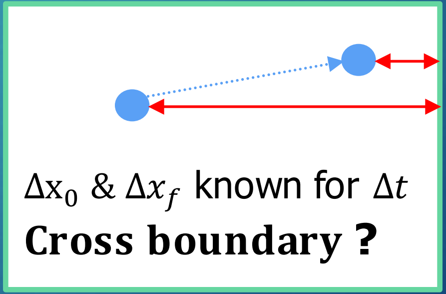


Δx known
Δt ?

Problem known as the « first passage time »

Space-driven stepping

- Given a time step Δt, initial and final distances of a Brownian particle from a boundary
  → what is the probability that the Brownian crossed a boundary during the step



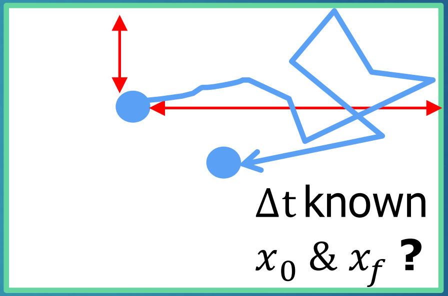
Δx_0 & Δx_f known for Δt
Cross boundary ?

Problem known as the «Brownian bridge»

(Some) requirements for Brownian dynamics simulations

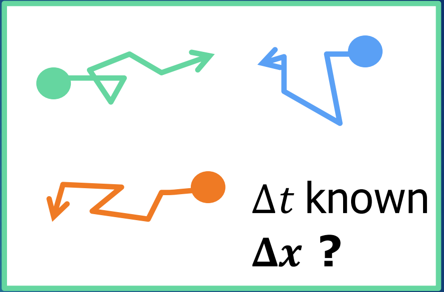
Not yet used in the current version

- Given initial positions at time t=0 and Δt and knowing distances from reflective boundaries → sample probable positions for a selected time step knowing that the particle will be reflected by the surface



Time-driven stepping with reflective boundaries

1/ Time-driven stepping



Time steps are fixed
Space steps are computed

- Two methods
  - Step-by-step method – the Ermack McCammon algorithm

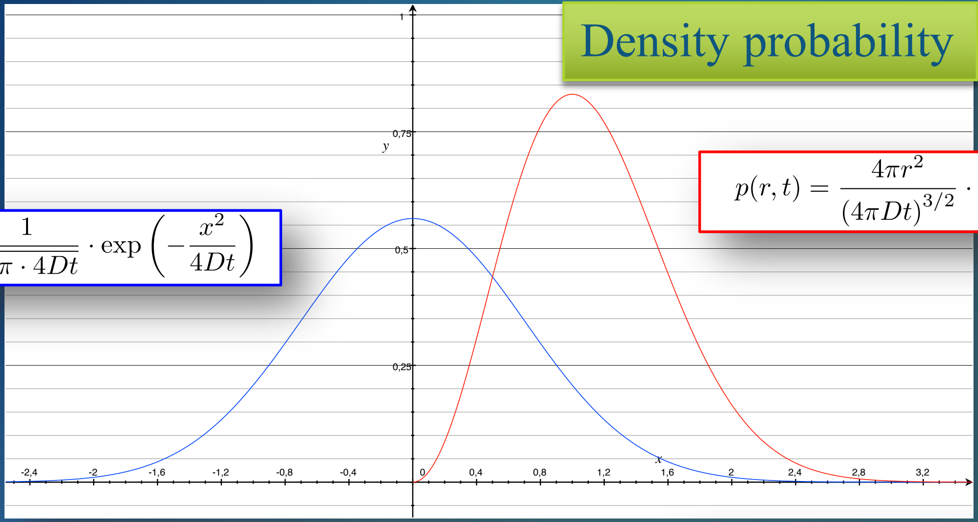
$$\Delta x_i = \sqrt{2D\Delta t} \cdot N(0,1) + \frac{D \cdot \Delta t}{k_B T} \cdot F_i(x_i^0)$$

with $\Delta t \gg \frac{mD}{k_B T}$, $N(0,1)$ is a random number sample from a Gaussian distribution of mean 0 and standard deviation 1

Equivalent to the Smoluchowski dynamics

  - Sampling probability functions

1/ Time-driven stepping – Probability functions



Density probability

1D

$$p_1(x,t) = \frac{1}{\sqrt{\pi \cdot 4Dt}} \cdot \exp\left(-\frac{x^2}{4Dt}\right)$$

$$p(r,t) = \frac{4\pi r^2}{(4\pi Dt)^{3/2}} \cdot \exp\left(\frac{-r^2}{4Dt}\right)$$

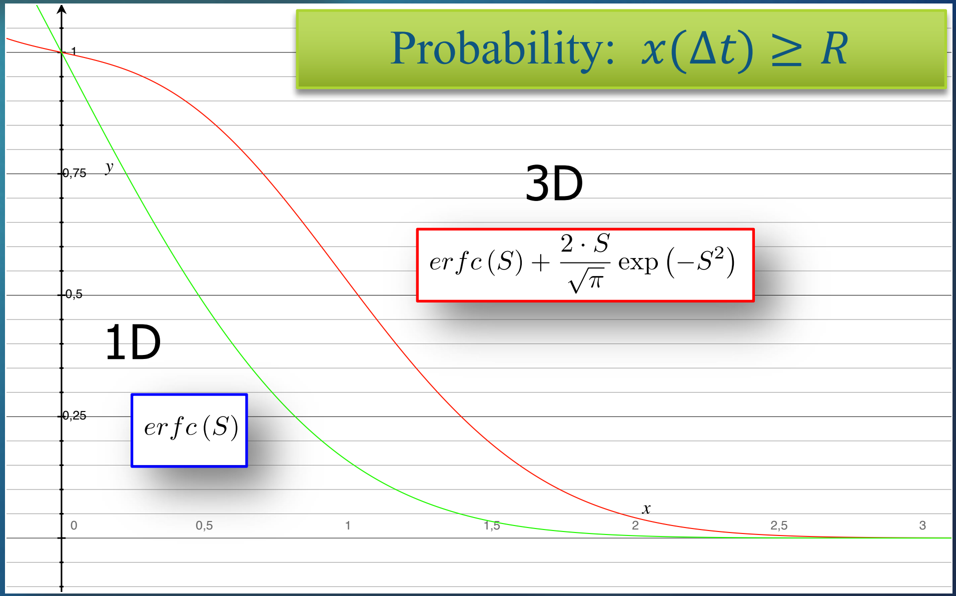
3D

Initial position
x = 0
or r= 0

Time steps are fixed
Space steps are computed

$$P(r \in [R;+\infty[\,,t) = \int_R^{+\infty} p(r,t)\cdot dr$$

$$S = \frac{r}{2\sqrt{Dt}}$$



Probability: $x(\Delta t) \geq R$

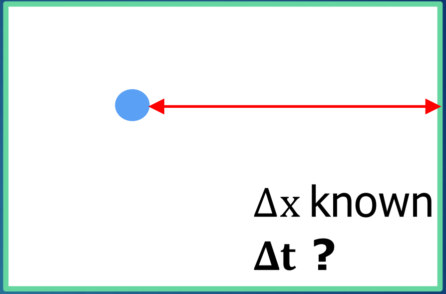
3D

$$erfc\,(S) + \frac{2\cdot S}{\sqrt{\pi}}\exp\left(-S^2\right)$$

1D

$$erfc\,(S)$$

2/ First passage time (First-hitting-time)



1) Follow the trajectories step-by-step

- To avoid small time steps Δt → select Δt_{max} , the biggest time steps possible during which it is guaranteed the boundary is not crossed
- For instance : select Δt_{max} such as

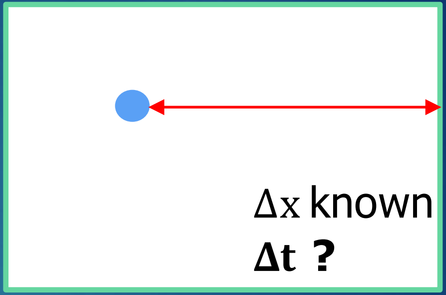
$$P\ (\Delta \mathrm{x}, \Delta t_{max}) = 95\%$$

- Δt_{max} are dynamical computed
- Space steps are sampled using Δt_{max}

One can use minimum allowed time steps Δt_{min} to guarantee that the time steps don't become too small

- When the particle gets close to the boundary by a certain threshold (could be time or space based) use tricks to either
  - Adjust the final time step
  - Take the full time step Δt_{min} and use Brownian bridge to determine if the particle has crossed the boundary during Δt_{min}

2/ First passage time (First-hitting-time)



2) Sample the probability function to predict a first passage time

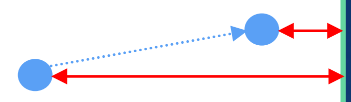
- For instance, in 1D, invert in respect to time

$$P = \mathrm{erfc}\left(\frac{\Delta x}{2\sqrt{Dt}}\right)$$

In 3D, the direct inversion technique does not work because the probability is more complicated

- Advantage compared to the step-by-step stepping : only one step taken (event-driven simulation)

3/ Brownian bridge



d_0 & d_f known for Δt

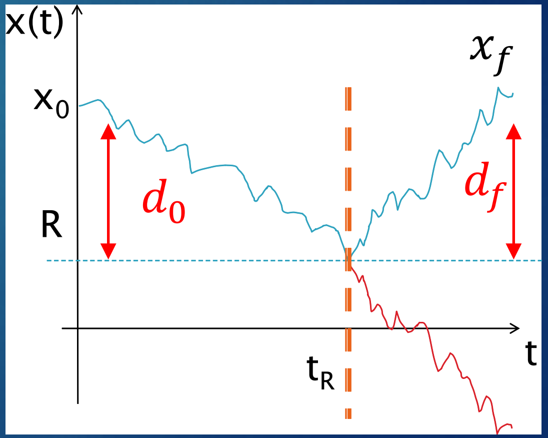
Cross boundary ?

- Given a time step Δt, initial and final distances of a Brownian particle from a boundary → what is the probability that the Brownian crossed a boundary during the step

$$P = exp\left(-\frac{d_0 d_f}{D \cdot \Delta t}\right)$$

Where d_0 is the initial distance from the boundary and d_f is the final distance from the boundary

- Note: The current implementation is a 1D approximation



Reactions

SMOLUCHOWSKI REACTION MODEL –

DIFFUSION CONTROLLED

Reaction rate constant 1/2

- Chemical master equation (*reaction level – well mixed chemical system*)

Number of species : $\vec{N}(t) = \left(N_1(t), N_2(t), \dots, N_n(t)\right)$
Time evolution of $\vec{N}(t)$ is stochastic and defined by the density probability p

$$\frac{\partial p\left(\vec{N}(t), t\right)}{\partial t} = \sum_{r=\text{bimolecular reactions}} a_r\left(\vec{N}(t) - \vec{v_r}\right) \cdot p\left(\vec{N}(t) - \vec{v_r}, t\right) - \sum_{r=\text{unimolecular reactions}} a_r\left(\vec{N}(t)\right) \cdot p\left(\vec{N}(t), t\right)$$

- Ordinary differential equations

$$\frac{d\langle N_k\rangle}{dt} = \sum_{i,j=\text{bimolecular reactions}} \pm k_{ij} \cdot \langle N_i\rangle \cdot \langle N_j\rangle + \sum_{i=\text{unimolecular reactions}} \pm k_i \cdot \langle N_i\rangle$$

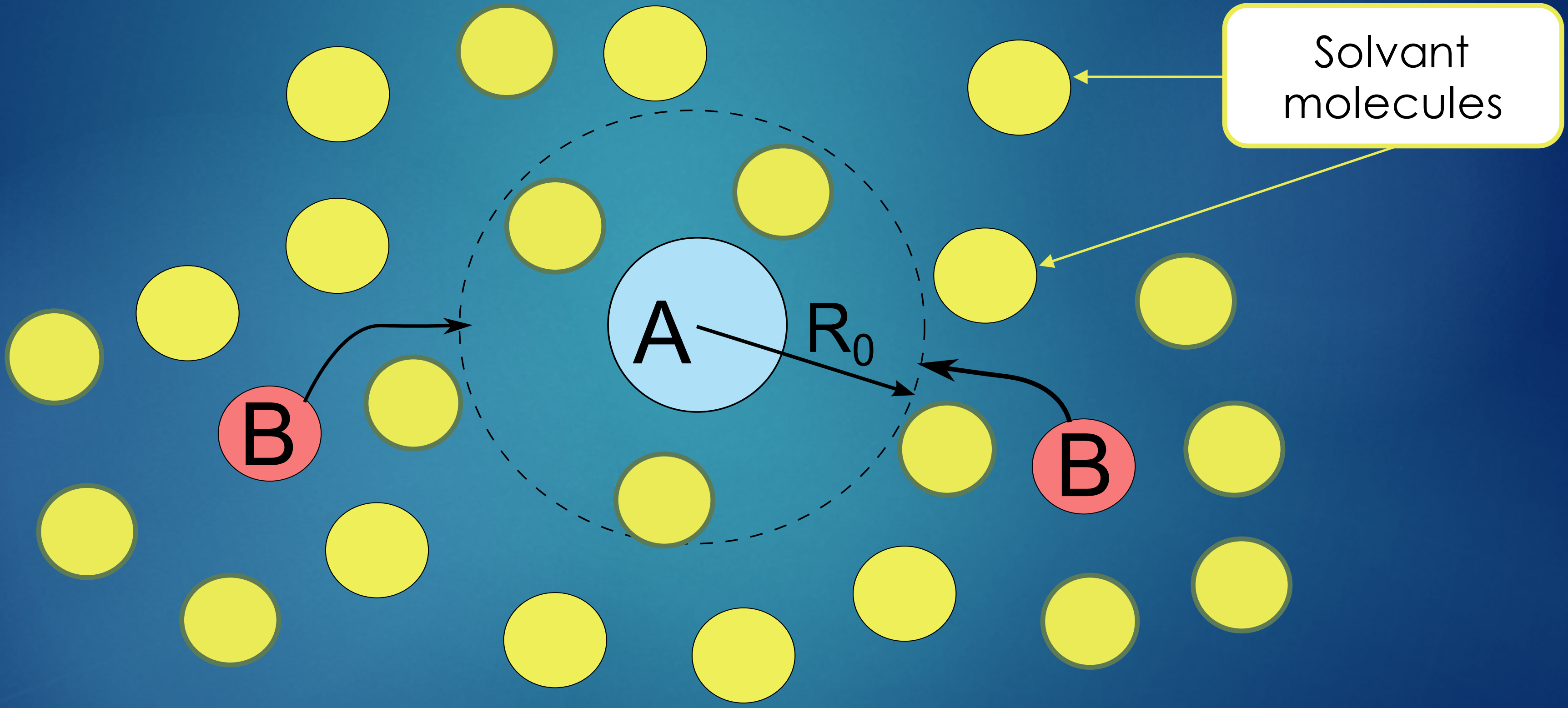
- Observed reaction rate constant

$$A + B \xrightarrow{k_{obs}} P$$

$$\frac{d\langle P\rangle}{dt} = k_{obs}\langle A\rangle\langle B\rangle$$

Solvation Cage

$$A + B \underset{k_D}{\overset{k_C}{\rightleftarrows}} (A{:}B) \xrightarrow{k_R} P$$



Reaction rate constant 2/2

- Reaction rate constant when complex life time very short

$$A + B \underset{k_D}{\overset{k_C}{\rightleftarrows}} (A{:}B) \xrightarrow{k_R} P$$

$$\frac{d\langle P\rangle}{dt} = \frac{k_R}{k_D + k_R}\left(k_C \cdot \langle A\rangle\langle B\rangle - \frac{d\langle C\rangle}{dt}\right)$$

If $\frac{d\langle C\rangle}{dt} \to 0$ since $\frac{d\langle P\rangle}{dt} = k_{obs}\langle A\rangle\langle B\rangle$

$$k_{obs} = \frac{k_R k_C}{k_D + k_R}$$

NB: this steady-state approximation will be removed with next versions of the chemistry

- Reaction rate constant in case of diffusion-controlled reaction (also called diffusion-limited reaction)

$$\lim_{k_R \to \infty} k_{obs} = \lim_{k_R \to \infty} \frac{k_C}{\frac{k_D}{k_R} + 1} = k_C \to k_{obs} \approx k_C$$

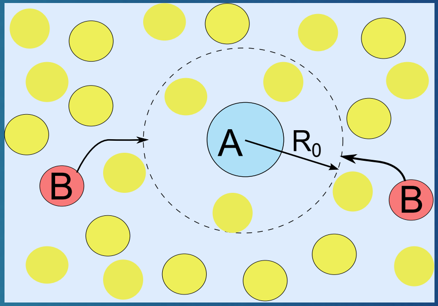
Note: when k_R is finite, we fall in the case of the so-called partially diffusion-controlled reactions for which models are being considered for next versions of Geant4-DNA chemistry

Smoluchowski definition of reaction rate constant

- Link between microscopic description and reaction rate constant :

k = flow of particles in solvation cage

$$k_C = \mathcal{N}_A \cdot V \cdot \int_{dS} \vec{j} \cdot \overrightarrow{dS}$$



In the absence of external field:

$$\boxed{k_C = 4\pi \mathcal{N}_A D R_0}$$

Where D is the sum of diffusion coefficients and R_0 the sum of the radius of the cages

In case of Coulombic field

$$\boxed{k_C = \frac{4\pi \mathcal{N}_A D R_C}{\exp\left(\frac{R_C}{R_0}\right) - 1}}$$

With $R_C = \frac{q_1 q_2}{\epsilon_r \epsilon_0 k_B T}$ is the so-called Onsager radius

Using Smoluchowski theory, we can linked observed reaction rate constantss with reaction radius

The implemented method

- STEP-BY-STEP WITH DYNAMICS TIME STEPS AND BROWNIAN BRIDGE
- DIFFUSION-CONTROLLED REACTIONS

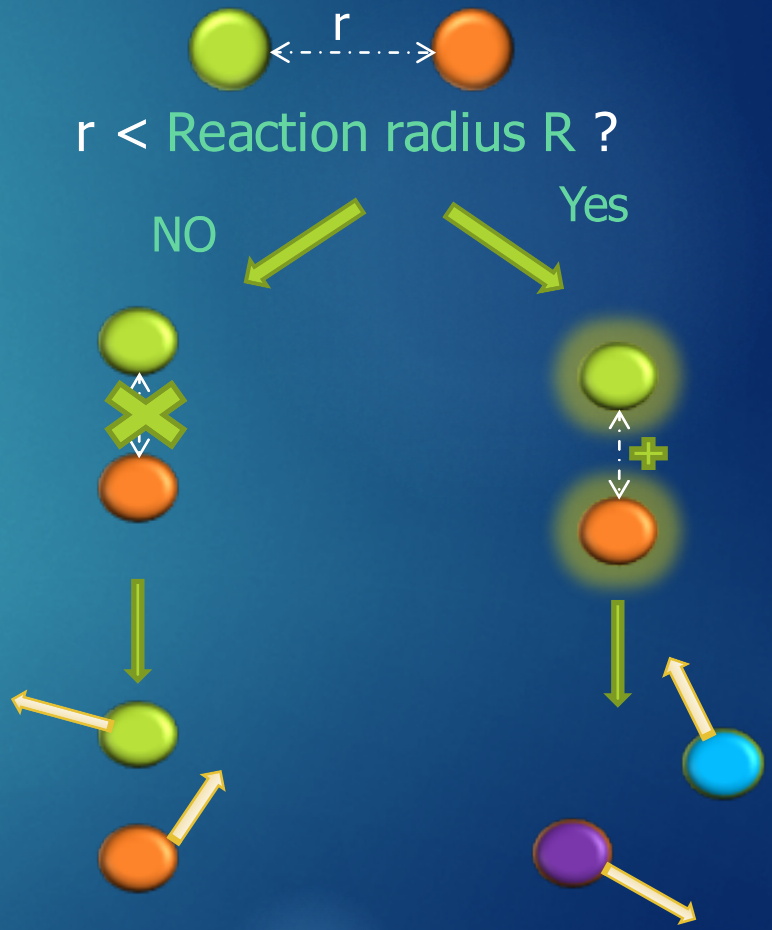
The step –by-step method: principle

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)**



t=10^{-12}s

t=10^{-6}s

The step –by-step method: reaction

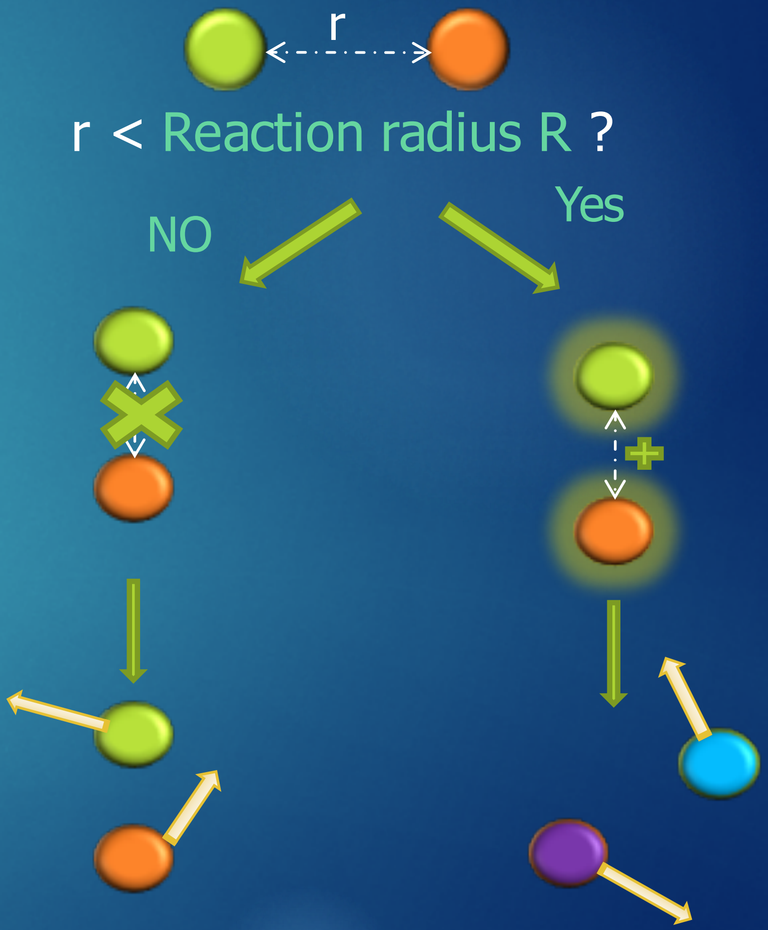
Smoluchowski model:

Reaction rate constant

$$\boxed{R_0 = \frac{k}{4\pi N_A D}}$$

Reaction radius

Sum of the diffusion coefficients of the reactants



Reaction calculated after each step Δt …

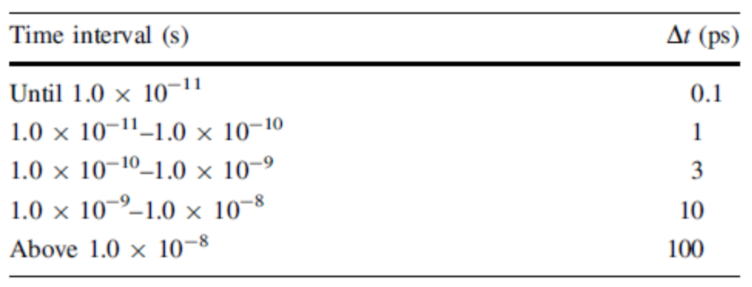
Step-by-step: method: How to choose Δt ?

- Two solutions have been implemented in Geant4-DNA

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

     Step Δt are predefined and evolved along the simulation

*Kreipl et al, Radiat Environ Biophys, **48**, 11-20 (2009)



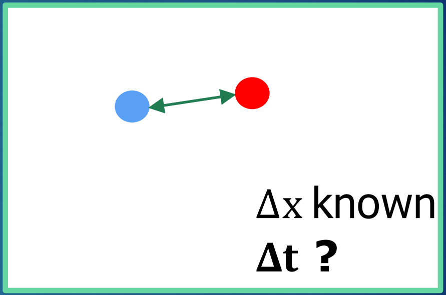
Time interval (s)	Δt (ps)
Until 1.0×10^{-11}	0.1
1.0×10^{-11}–1.0×10^{-10}	1
1.0×10^{-10}–1.0×10^{-9}	3
1.0×10^{-9}–1.0×10^{-8}	10
Above 1.0×10^{-8}	100

2) Compute it in respect to the next reaction*
   - Explanation …

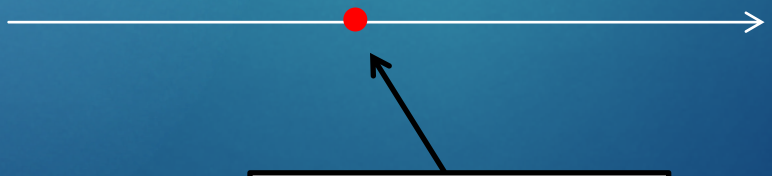
*Michalik et al., Radiation Research **149**, 224-236 (1998)

Step-by-step method: diffusion process

- How to compute a Δt in order not to miss reactions?



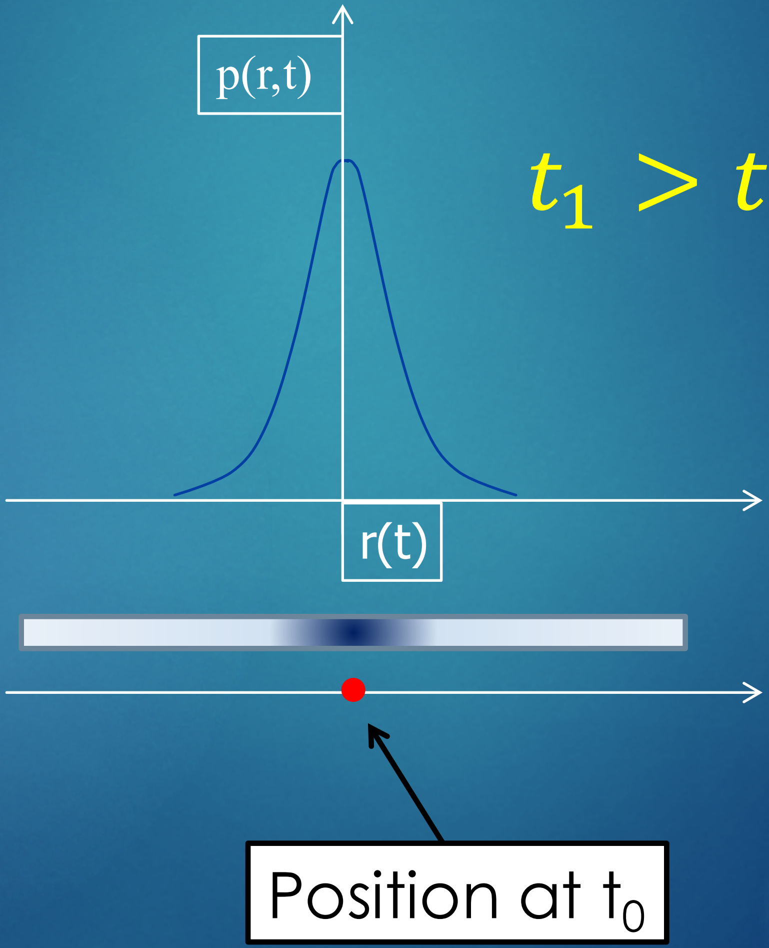
Same problem as the first passage time



Position at t_0

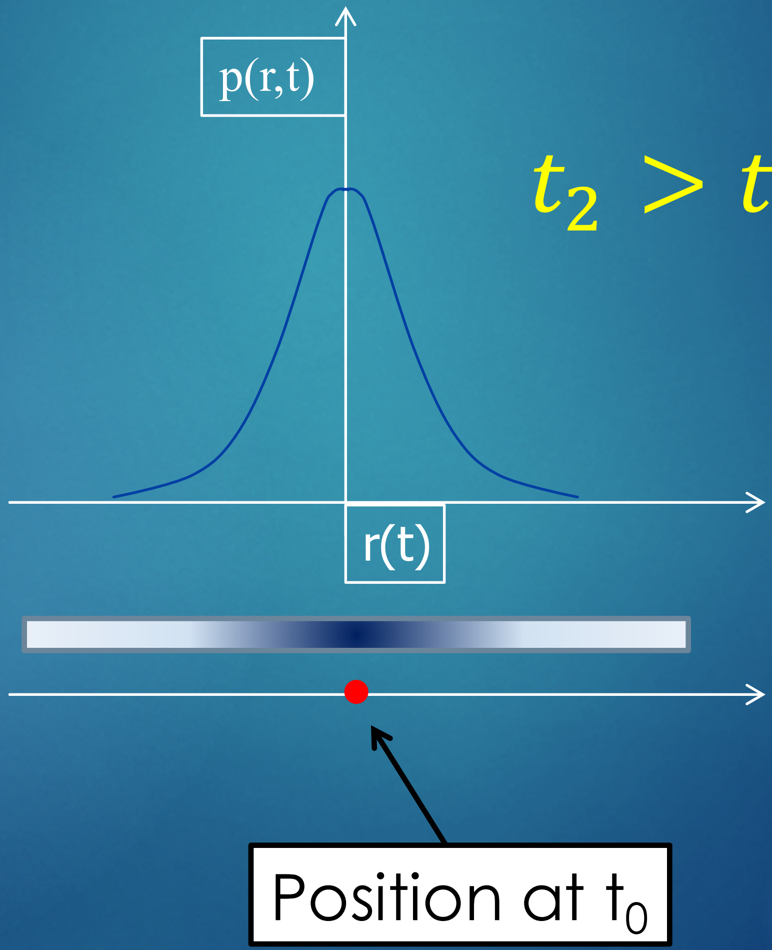
Step-by-stepmethod: diffusion process

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



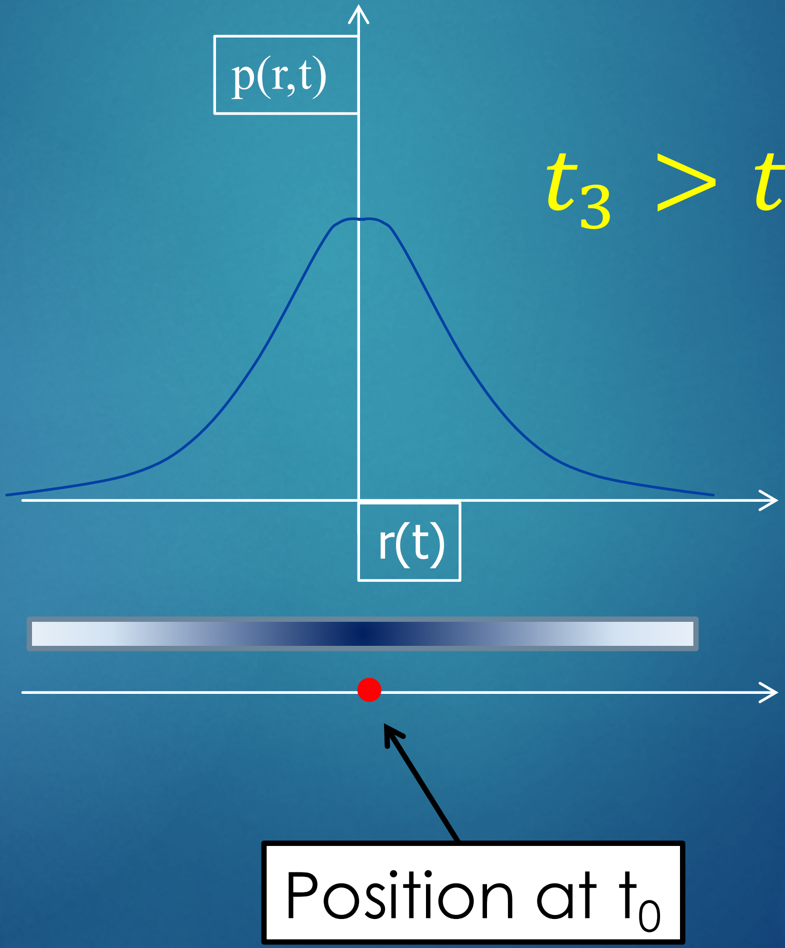
Step-by-stepmethod: diffusion process

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



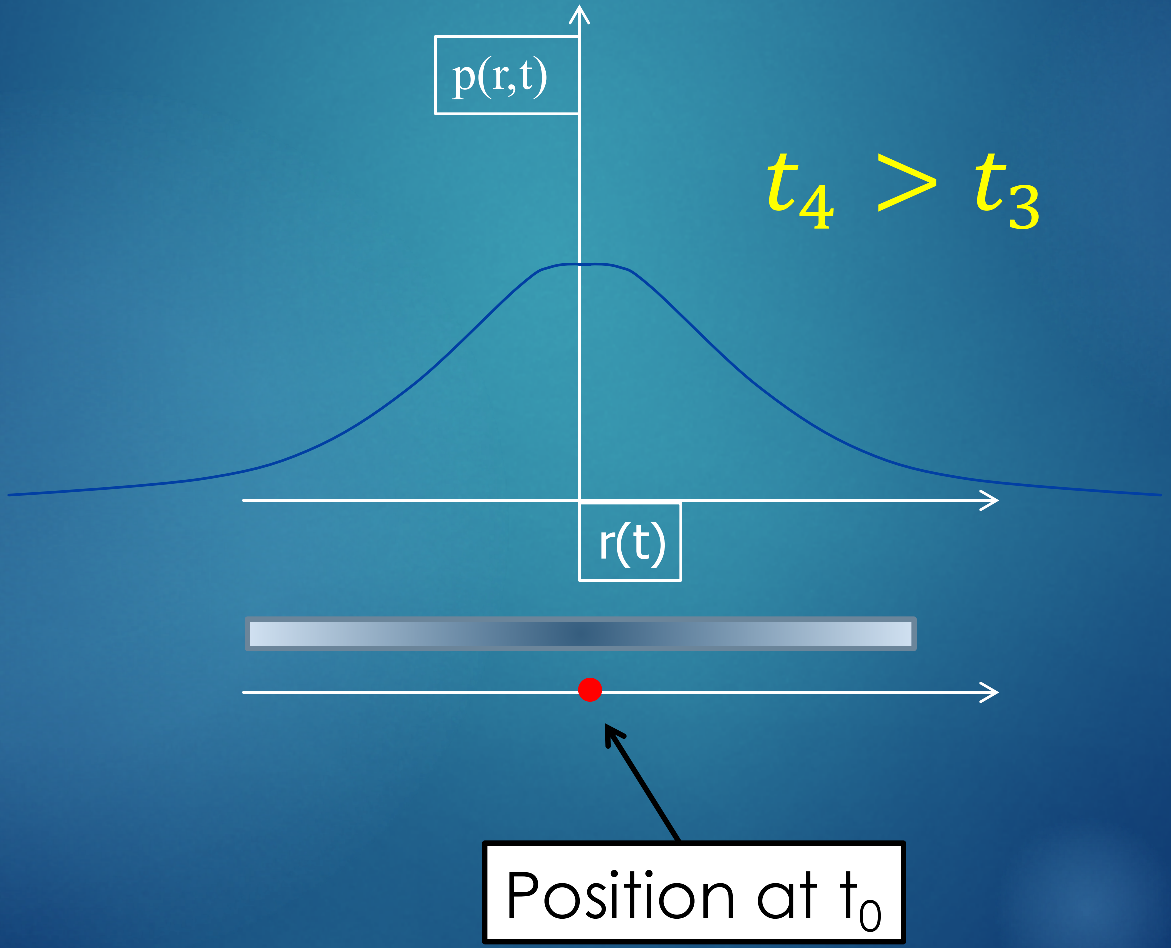
Step-by-stepmethod: diffusion process

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



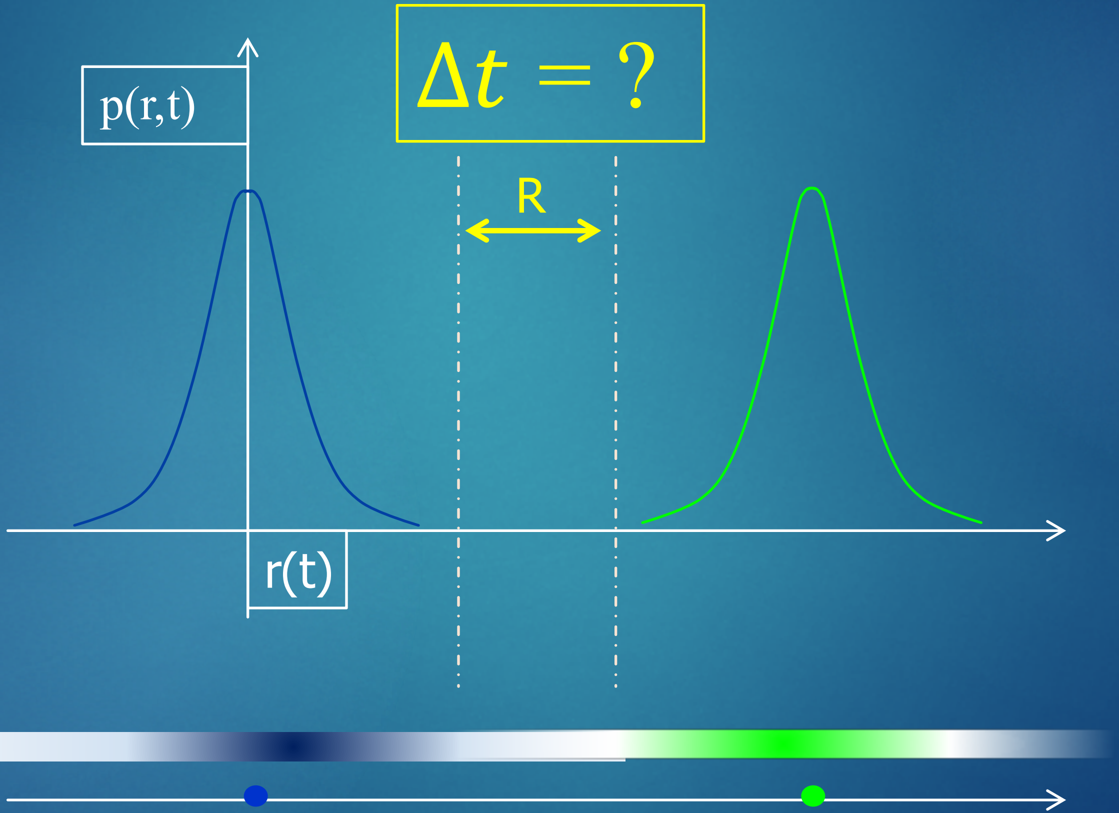
Step-by-stepmethod: diffusion process

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



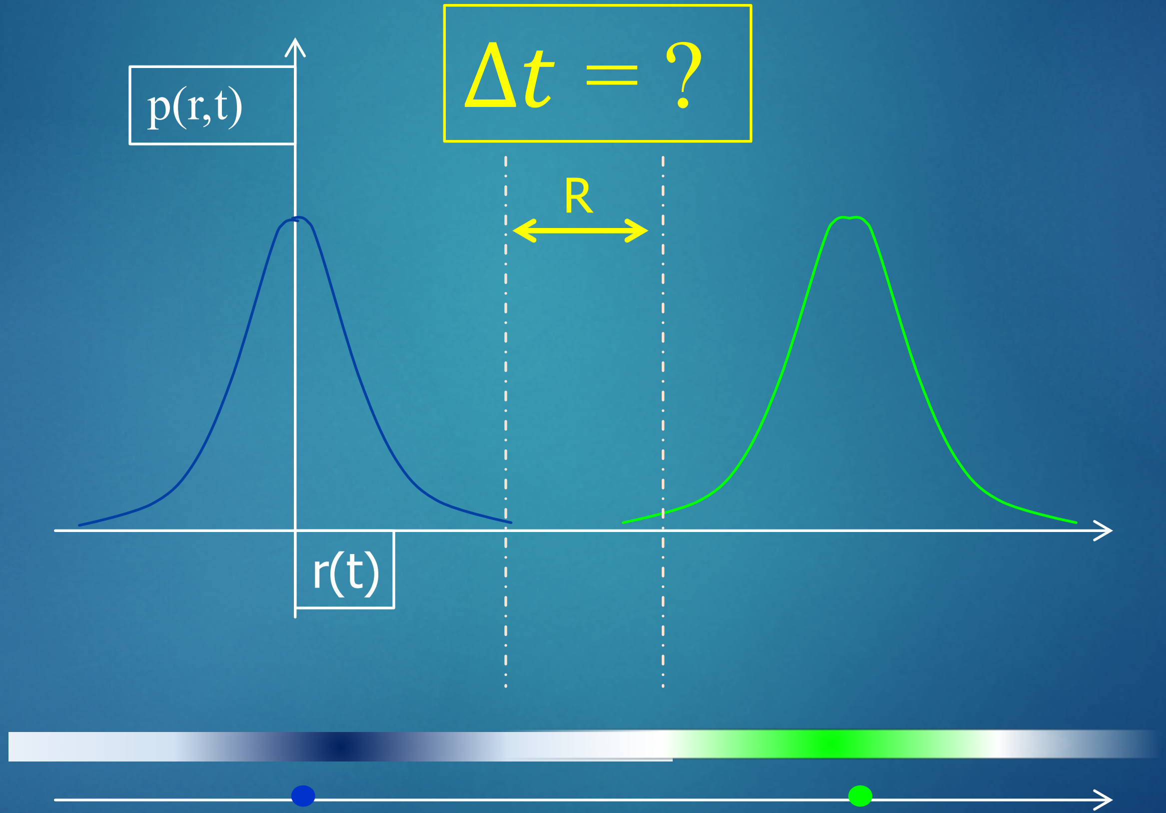
Step-by-stepmethod: diffusion process

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



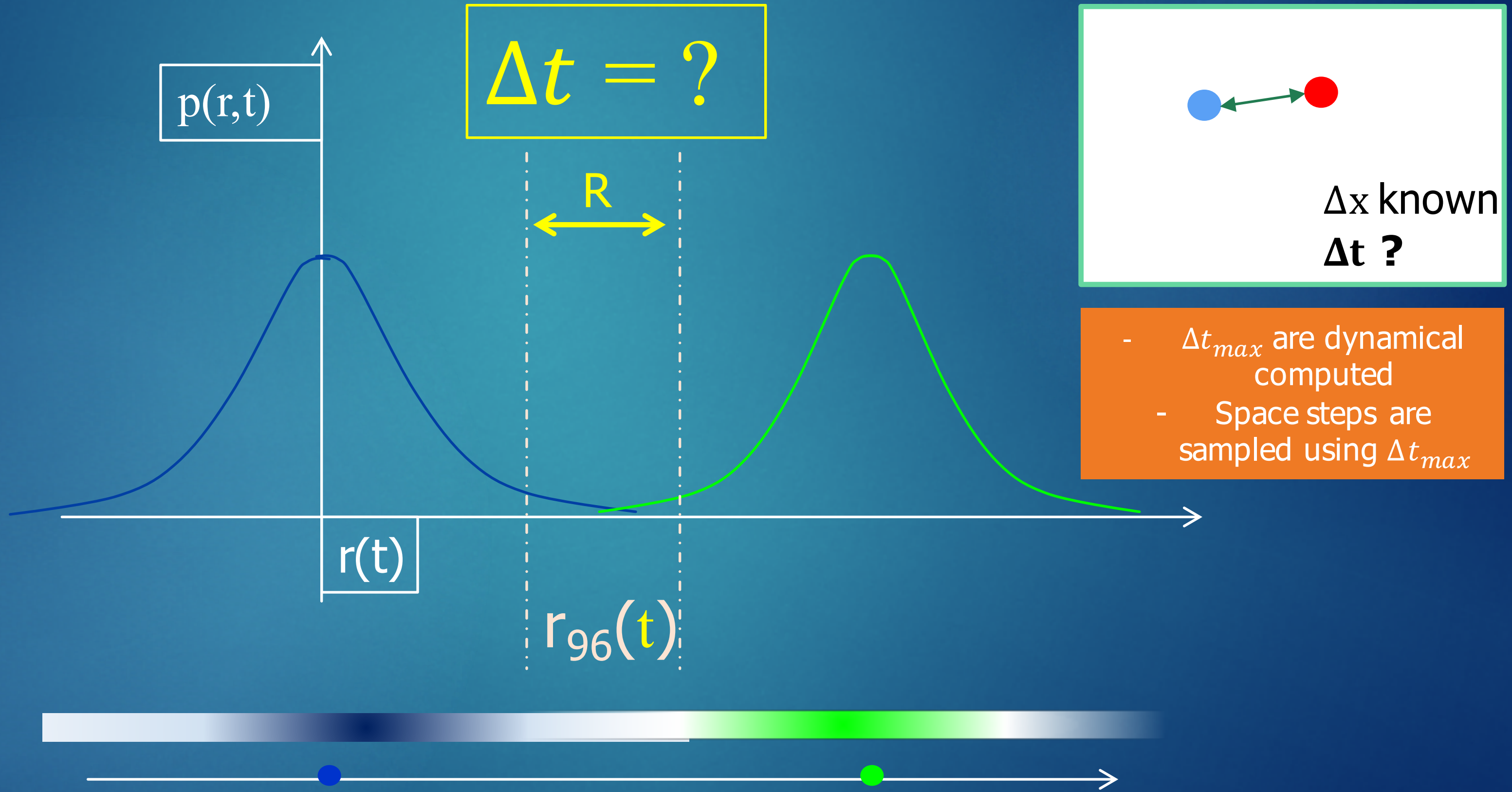
Step-by-stepmethod: diffusion process

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



Step-by-stepmethod: diffusion process

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

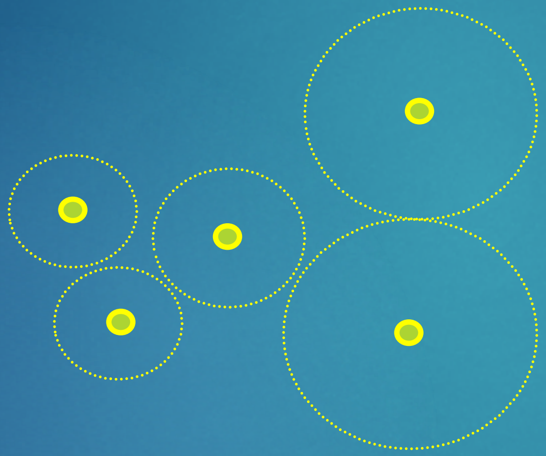


- Δt_{max} are dynamical computed
- Space steps are sampled using Δt_{max}

« Dynamical time step » technique*

*Michalik et al., Radiation Research **149**, 224-236 (1998)

Dynamical time-step – Protective time-space spheres



The dynamical time steps method can be seen as defining « protective time-space spheres »* where diffusion steps can be taken safely without reaction

**This is just an illustration*

Drawback of the dynamical time steps

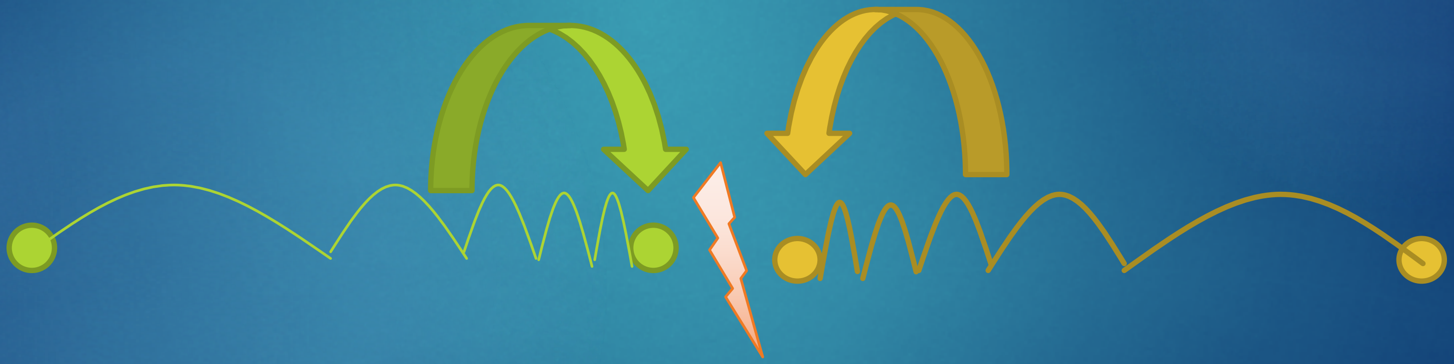
- Multiple smaller and smaller steps

Drawback of the dynamical time steps

- Multiple smaller and smaller steps before reacting (or not)

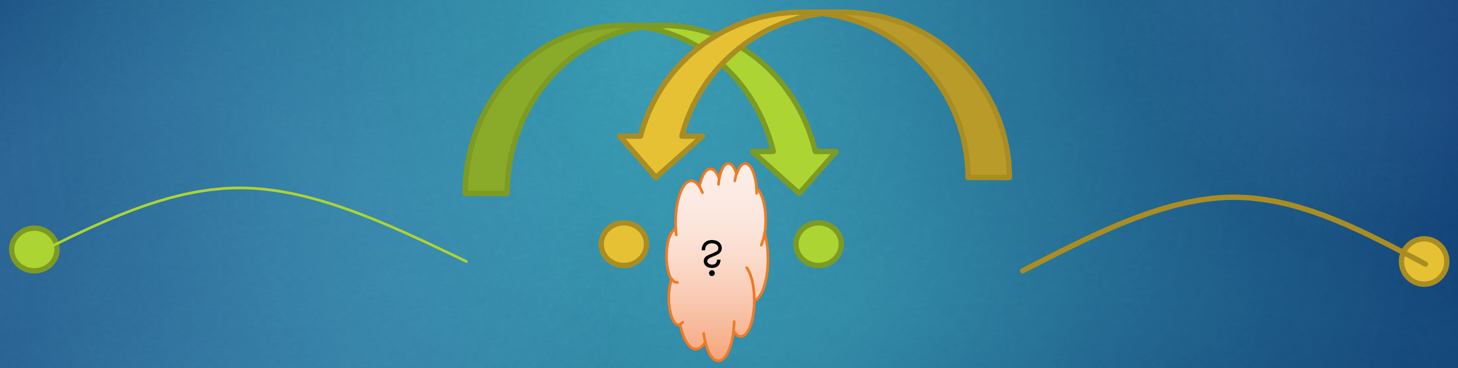
Drawback of the dynamical time steps

- 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 when threshold time steps are used
  - Brownian bridge (1D approximation)

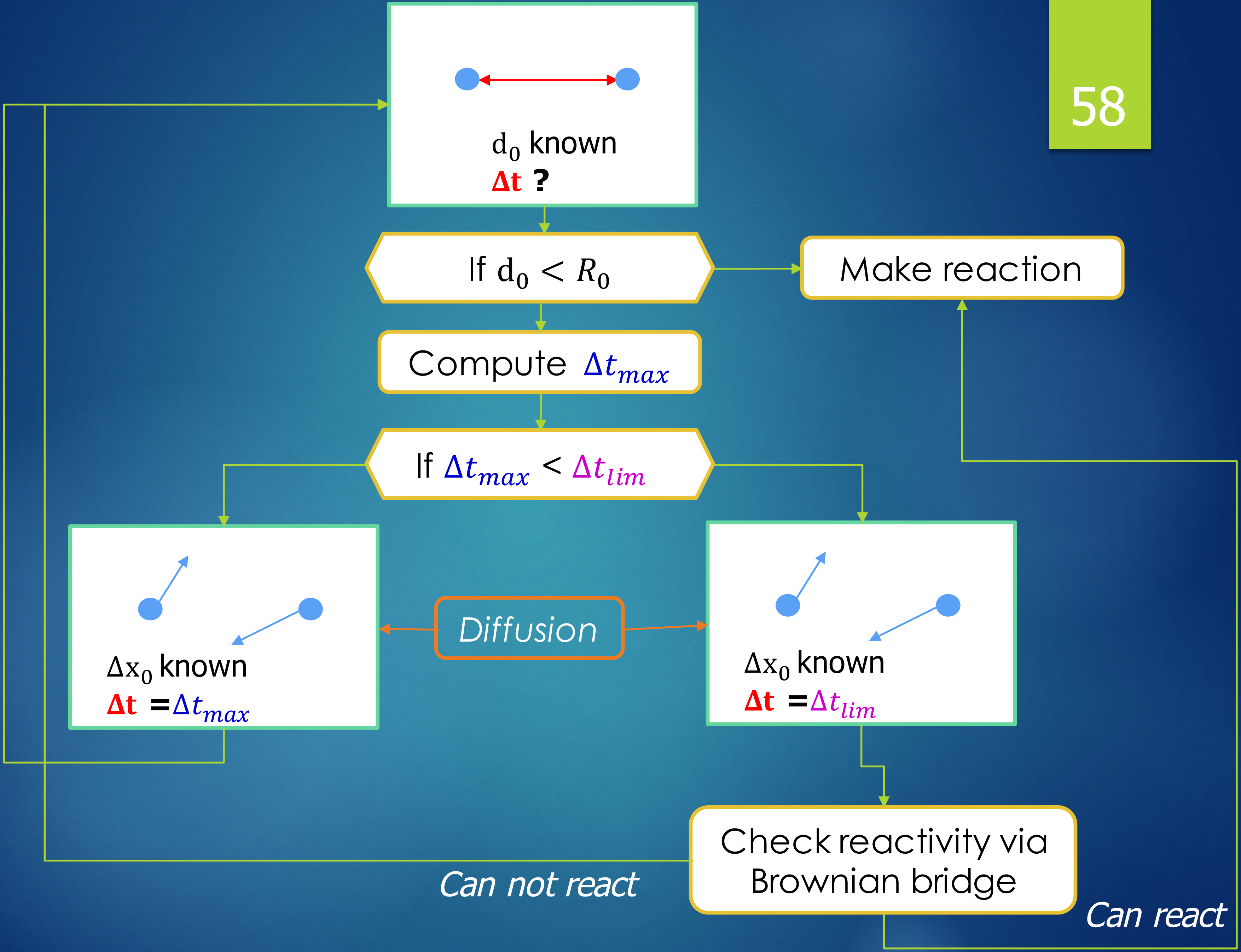
Speed up the step by step method …

Reaction → search for the closest neighbor

- **Brute-force method**

  Compare all distances between N reactants
  - Number of elementary operations ≈ $\mathbf{N^2/2}$
  - Drawback: CPU

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



d_0 known

Δt ?

If $d_0 < R_0$

Make reaction

Compute Δt_{max}

If $\Delta t_{max} < \Delta t_{lim}$

Diffusion

Δx_0 known

Δt = Δt_{max}

Δx_0 known

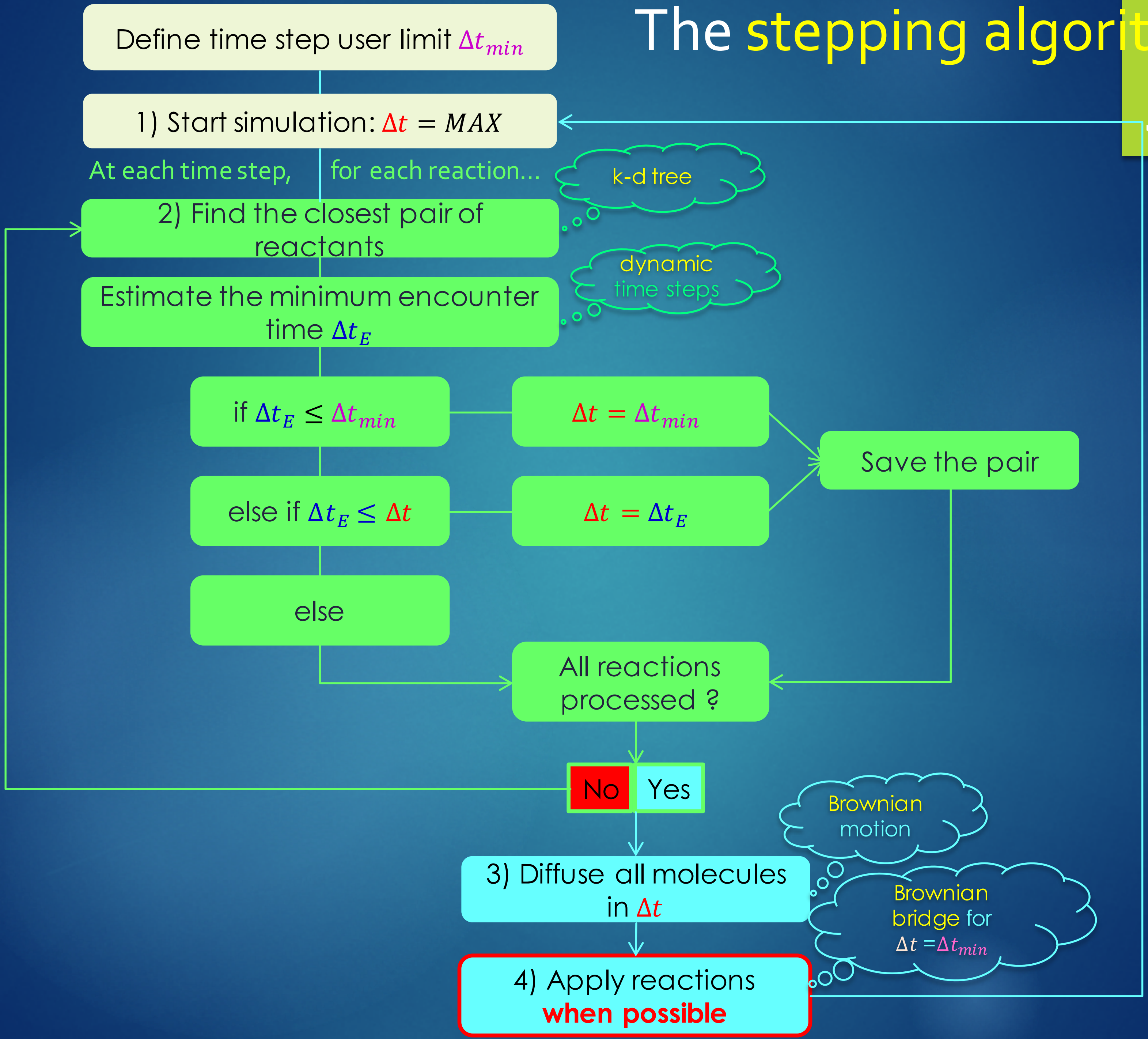
Δt = Δt_{lim}

Check reactivity via Brownian bridge

Can not react

Can react

The stepping algorithm*



Define time step user limit Δt_{min}

1) Start simulation: $\Delta t = MAX$

At each time step, for each reaction…

2) Find the closest pair of reactants

k-d tree

Estimate the minimum encounter time Δt_E

dynamic time steps

if $\Delta t_E \leq \Delta t_{min}$

$\Delta t = \Delta t_{min}$

else if $\Delta t_E \leq \Delta t$

$\Delta t = \Delta t_E$

Save the pair

else

All reactions processed ?

No

Yes

3) Diffuse all molecules in Δt

Brownian motion

4) Apply reactions **when possible**

Brownian bridge for $\Delta t = \Delta t_{min}$

* simplified

$t=10^{-15}s$ → $t=10^{-12}s$ → $t=10^{-6}s$

Chemical stage: parameters

Species	Diffusion coefficient D (10^{-9} m² s^{-1})
H_3O^+	9.0
H•	7.0
OH^-	5.0
e^-_{aq}	4.9
H_2	4.8
•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

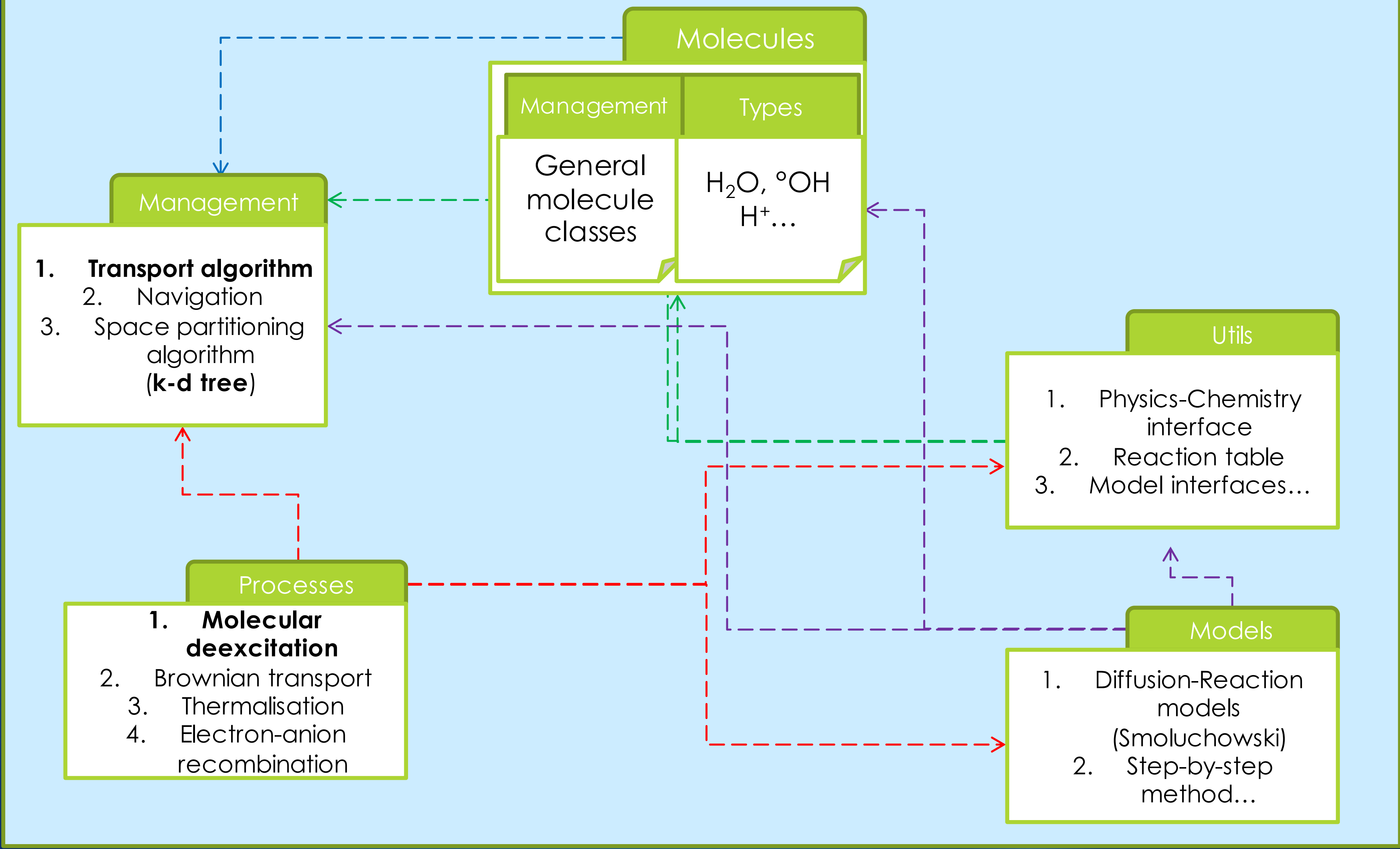
In ConstructReactionTable()

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

Class hierarchy

$G4INSTALL/source/processes/electromagnetic/dna



Molecules

Management

General molecule classes

Types

H_2O, °OH H^+…

Management

1. **Transport algorithm**
2. Navigation
3. Space partitioning algorithm (**k-d tree**)

Utils

1. Physics-Chemistry interface
2. Reaction table
3. Model interfaces…

Processes

1. **Molecular deexcitation**
2. Brownian transport
3. Thermalisation
4. Electron-anion recombination

Models

1. Diffusion-Reaction models (Smoluchowski)
2. Step-by-step method…

G4DNA chemistry limitations

Usage

- Add reactions → **data needed**
- **Limited number of simulated molecules (simulation limited to small volumes)**
- **Still a prototype**, refactoring needed
  → Bad interface, bugs etc …
  → Don't hesitate to report to us any bug

Models

- Particle-continuum representation
  → CPU and memory consuming
  → Run on a cluster
- No reversible reactions
- Diffusion controlled reactions only
- **Real dissociation scheme of water molecule?**
- **Working on new models to handle partially diffused-controlled reactions with reversible intermediate state**

Notes related to the delivered code

- The code which is delivered to you today is a beta release
  - Known bugs
    - When beaming protons, solvated electrons may get solvated out of the volume of the electron originate, you'll see warnings thrown by G4Navigator
    - Radiolytic products could also be generated out of the original volume for similar reasons
  - Don't use this code for production!
  - With final 10.2 release, minor interface change will occur (definition of species, UI commands …)

Perspectives

Remarks

Heterogenous to homogeneous phase
(radiolytic products orignally located close to the deposited energy then diffuse)

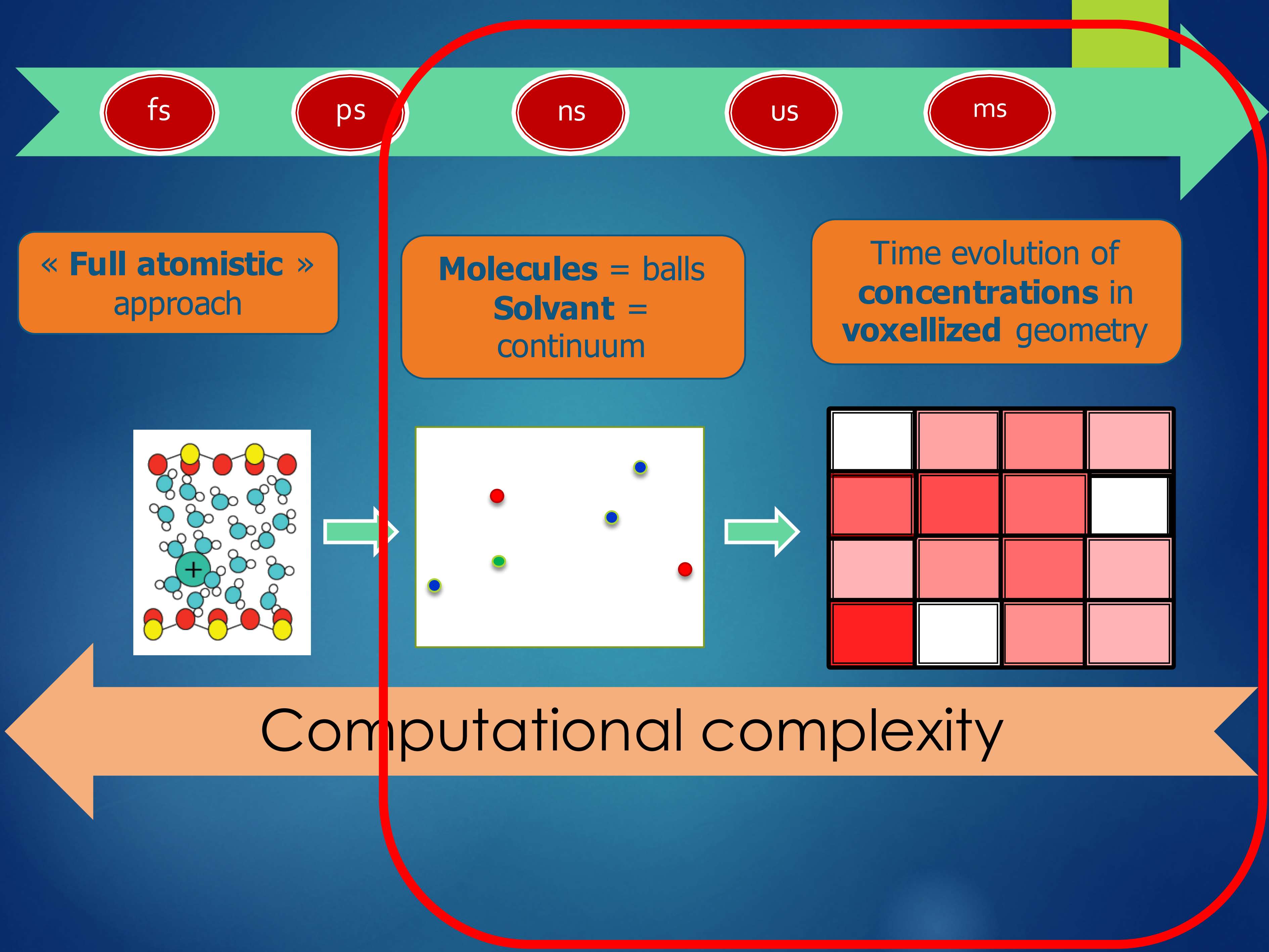
As LET increases
➔ deterministic

Biochemical processes
➔ high N molecules
➔ often used compartment approaches

Radical-biomolecules reactions (such as proteins, lipids …)?

Need to go to higher time
(DNA repair – protein recruitment)

➔ Develop a hybrid method combining **particle-based** and **compartment** representations



fs ps ns us ms

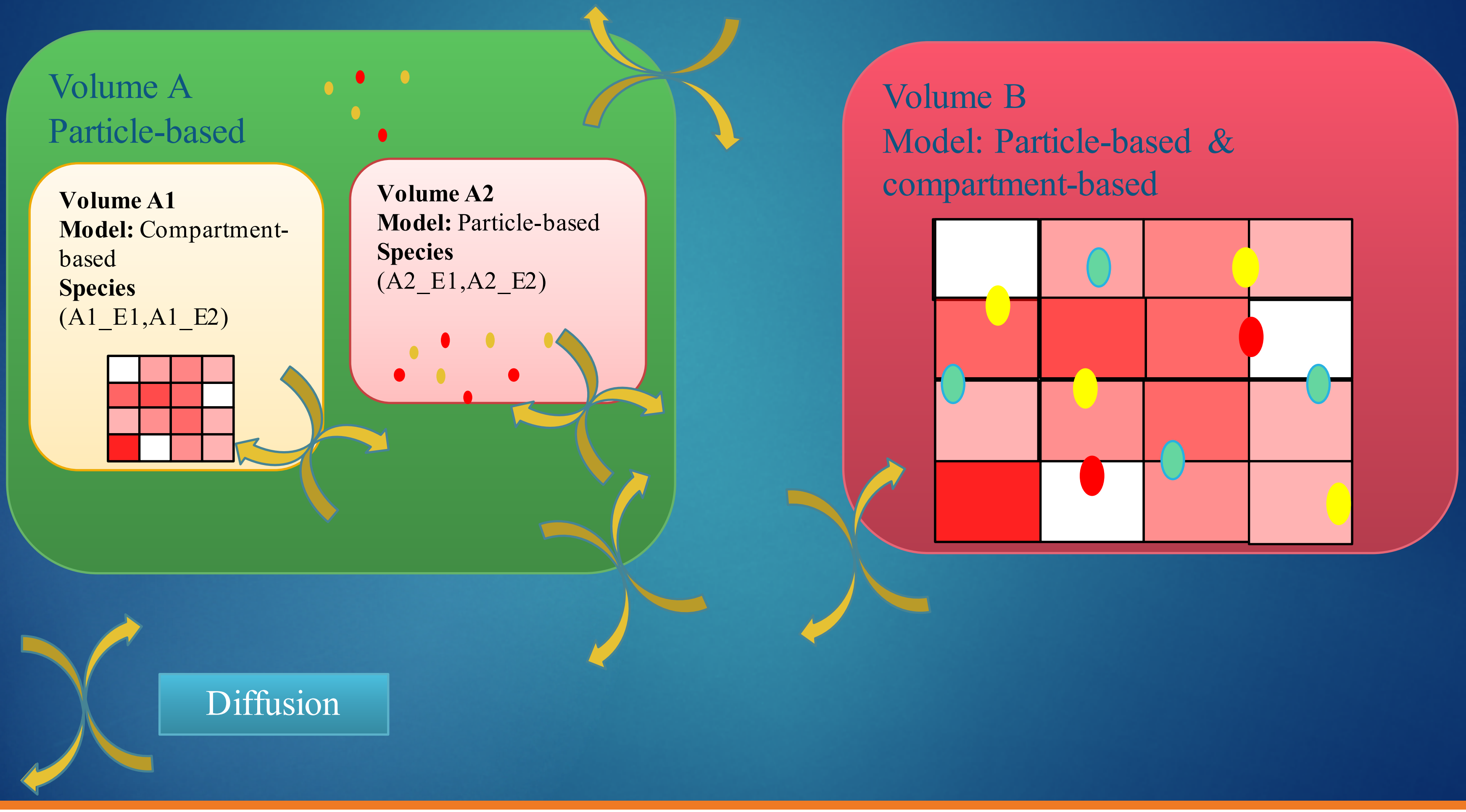
« **Full atomistic** » approach

Molecules = balls
Solvant = continuum

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

Computational complexity

Merging representations



Volume A
Particle-based

Volume A1
Model: Compartment-based
Species
(A1_E1,A1_E2)

Volume A2
Model: Particle-based
Species
(A2_E1,A2_E2)

Volume B
Model: Particle-based & compartment-based

Diffusion

One volume may have both **particle-based** (to handle low number of species) and **compartment-based/well-stirred** (to handle high number of species) representations

Alpha testers

- Major developments will not be released in official Geant4 releases before 2017/2018 – The code delivered to you today is been largely rewritten → we need to test it
- Alpha testers should be **experimented Geant4 Users/Developers only**
- Role
  - Suggest new features / propose new developments
  - Report bugs, test the code for your use case
- Drawbacks
  - Unstable versions
  - You'll not be allowed to published any results coming out the alpha releases, neither the methods being developed
- Alpha testing starting in 2016

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esa

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http://geant4-dna.org

Thank you ☺

Questions?

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