Status of the Geant4-DNA chemistry

2015 GEANT4 COLLABORATION MEETING – EM SESSION

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Water radiolysis

PHYSICO-CHEMICAL STAGE
**Physico-chemical stage**

<table>
<thead>
<tr>
<th>Electronic state of water molecule</th>
<th>Dissociation channels</th>
<th>Fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All single ionization states: H₂O⁺</td>
<td>H₂O⁺ + 'OH</td>
<td>100</td>
</tr>
<tr>
<td>Excitation state A1B1:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1b1) → (4a1/3s)</td>
<td>'OH + H⁺</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>H₂O + ΔE</td>
<td>35</td>
</tr>
<tr>
<td>Excitation state B1A1:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3a1) → (4a1/3s)</td>
<td>H₃O⁺ + 'OH + e⁻aq (AI)</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>'OH + 'OH + H₂</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>H₂O + ΔE</td>
<td>30</td>
</tr>
<tr>
<td>Excitation state:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rydberg, diffusion bands</td>
<td>H₃O⁺ + 'OH + e⁻aq (AI)</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>H₂O + ΔE</td>
<td>50</td>
</tr>
<tr>
<td>Dissociative attachment: H₂O⁻</td>
<td>'OH + OH⁻ + H₂</td>
<td>100</td>
</tr>
</tbody>
</table>

- Situation 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

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

<table>
<thead>
<tr>
<th>Hole hopping</th>
<th>Product 1</th>
<th>Product 2</th>
<th>Product 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{H}_3\text{O}^+ + \cdot\text{OH})</td>
<td>(\vec{R} (2 \text{ nm}))</td>
<td>0*</td>
<td>(\vec{R} (0.8 \text{ nm})^*)</td>
</tr>
<tr>
<td>(\text{H}<em>3\text{O}^+ + \cdot\text{OH} + e^-</em>{\text{aq}}) (AI)</td>
<td>(\vec{R} (2 \text{ nm}))</td>
<td>0*</td>
<td>(\vec{R} (0.8 \text{ nm})^*)</td>
</tr>
<tr>
<td>(\cdot\text{OH} + \cdot\text{H})</td>
<td>0</td>
<td>(-1/18 \times)</td>
<td>(17/18 \times)</td>
</tr>
<tr>
<td>(\text{H}_2^+ \cdot\text{OH} + \cdot\text{OH})</td>
<td>0</td>
<td>(-2/18 \times)</td>
<td>(16/18 \times \vec{R} (0.8 \text{ nm}) +1/2 \times)</td>
</tr>
<tr>
<td>(\text{H}_2^+ \cdot\text{OH} + \cdot\text{OH})</td>
<td>0</td>
<td>(-2/18 \times \vec{R} (0.8 \text{ nm}))</td>
<td>(16/18 \times \vec{R} (0.8 \text{ nm}))</td>
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</table>

Kreipl et al, 2009
Physico-chemical stage

Electron – water anion recombination

\[ e^- + H_2O^+ \rightarrow \text{channel 1/2/3} \]

15-25% of water anions recombine with electrons at room temperature \( \rightarrow \) non negligible

Decrease the number of solvated electrons

Form \( H_2 \) product, stable species

This reaction might be strongly temperature dependent
Physico-chemical stage

Models for e- + H2O+ $\rightarrow$ channel 1 / 2 / 3

**Model 1: Onsager model** and derivatives ...
Escape probability (when the external field is zero)

- $\phi = \exp \left( -\frac{r_C}{r_0} \right)$ $\leftarrow$ original Onsager’s formula for $F_{ext} = 0$ (derived from swarm particles models)

- $r_C = \frac{e^2}{4\pi \varepsilon \varepsilon_0 k_B T}$ 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
Physico-chemical stage

Models for e- + H2O+ $\rightarrow$ 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 deceleration of the electrons, and the effect of « crowded » 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

\[ \text{H}_3\text{O}^+ , e^{-}_\text{aq} , \text{OH}^- \]
Chemical stage
« Full atomistic » approach

Molecules = balls
Solvant = continuum

Time evolution of concentrations in voxellized geometry

Chemical stage: representation?

Computational complexity

Well adapted for few molecules and heterogenously distributed

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

« Full atomistic » approach
Molecules = balls
Solvant = continuum
Time evolution of concentrations in voxellized geometry

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Time evolution of concentrations in voxellized geometry

Kinetic constants

Well adapted for few molecules and heterogeneously distributed

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Diffusion

SMOLUCHOWSKI DYNAMICS
Smoluchowski-Debye Equation

Stochastic differential equation

\[ \dot{x} = \frac{F_{\text{ext}}(x)}{m \gamma} + \frac{\Gamma(t)}{\gamma} \]

The position is described by a density probability function \( p \) described by a Fokker-Planck equation

\[
\frac{\partial p(x, t \mid x_0, t_0)}{\partial t} = \left( \frac{\partial}{\partial x^2} (D \cdot p) - \frac{\partial}{\partial x} \left( \frac{F_{\text{ext}}(x)}{m \gamma} \cdot p \right) \right)
\]

where \( D = \frac{q^2}{2\gamma} \) with \( \langle \Gamma(t_1) \cdot \Gamma(t_2) \rangle = q \cdot \delta(t_1 - t_2) \)
Illustration in Geant4-DNA

Diffusion-controlled reactions in Geant4-DNA, J Comp Phys (2014), 274, 841-882
# Standard Geant4 transport VS Brownian motion

<table>
<thead>
<tr>
<th></th>
<th>Standard transport of Geant4</th>
<th>Brownian motion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Position and velocity</strong></td>
<td>Deterministic (between two interactions points)</td>
<td>Stochastic</td>
</tr>
<tr>
<td><strong>Path-volume Intersection</strong></td>
<td>« Exact » intersection computable</td>
<td>Is expressed in terms of probability</td>
</tr>
<tr>
<td><strong>Equation of motion</strong></td>
<td>Newton</td>
<td>Fokker-Planck (stochastic equation of motion)</td>
</tr>
</tbody>
</table>
| Time-driven stepping | Given initial positions at time $t=0$  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\rightarrow$ sample positions at time $t = t_0 + \Delta t$</td>
</tr>
</tbody>
</table>
|                      | Given initial position & distance to a boundary  
|                      | $\rightarrow$ sample a time at which the particle can cross the boundary |
|                      | Given a time step $\Delta t$, initial and final distances of a Brownian particle from a boundary  
|                      | $\rightarrow$ what is the probability that the Brownian crossed a boundary during the step |
|                      | Given initial positions at time $t=0$ and $\Delta t$, and knowing distances from reflective boundaries  
|                      | $\rightarrow$ sample probable positions for a selected time step knowing that the particle will be reflected by the surface |
Reactions

SMOLUCHOWSKI REACTION MODEL – DIFFUSION CONTROLLED
Solvation Cage

\[ A + B \overset{k_C}{\underset{k_D}{\rightleftharpoons}} (A:B) \overset{k_R}{\rightarrow} P \]
Smoluchowski definition of reaction rate constant

Link between microscopic description and reaction rate constant:

\[ k = \text{flow of particles in solvation cage} \]

\[ k_C = \mathcal{N}_A \cdot V \cdot \int ds \cdot \vec{j} \cdot d\vec{s} \]

In the absence of external field:

\[ k_C = 4\pi\mathcal{N}_A DR_0 \]

Where \( D \) is the sum of diffusion coefficients and \( R_0 \) the sum of the radius of the cages.

In case of Coulombic field

\[ k_C = \frac{4\pi\mathcal{N}_A DR_C}{\exp \left( \frac{R_C}{R_0} \right) - 1} \]

With \( R_C = \frac{q_1q_2}{\epsilon_\epsilon_0k_B T} \) is the so-called Onsager radius.

Using Smoluchowski theory, we can linked observed reaction rate constantss with reaction radius.
Step-by-step 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 species, return to 1)

![Diagram showing the step-by-step method with interaction and diffusion steps, and a reaction radius criterion.](image-url)
The step-by-step method: reaction

Smoluchowski model:

\[ R_0 = \frac{k}{4\pi N_A D} \]

Reaction rate constant

Reaction radius

Sum of the diffusion coefficients of the reactants

Reaction calculated after each step $\Delta t$ ...

$r < \text{Reaction radius } R$ ?

NO

YES
Step-by-step: method: How to choose $\Delta t$?

Two solutions have been implemented in Geant4-DNA

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

   Step $\Delta t$ are predefined and evolved along the simulation

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

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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 ...

Brute-force method

Compare all distances between N reactants
  ◦ Number of elementary operations $\approx N^2/2$
  ◦ Drawback: CPU

Solution: k-d tree
$d_0$ known
$\Delta t$ ?

If $d_0 < R_0$

Compute $\Delta t_{\text{max}}$

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

$\Delta x_0$ known
$\Delta t = \Delta t_{\text{max}}$

Diffusion

$\Delta x_0$ known
$\Delta t = \Delta t_{\text{lim}}$

Check reactivity via Brownian bridge

Can not react

Can react
Independent reaction times method

DIFFUSION AND PARTIALLY DIFFUSION CONTROLLED MODELS
Independent reaction times method

**Principle**
- Break the N-body problem down smaller 2-body problems

**Model – spherical symmetry**
- One object A at the center of the system of coordinates
- One Brownian B diffusing around the object A
- A reaction radius $R$

**Master equation**
- Smoluchowski diffusion

$$\frac{\partial p_B}{\partial t} = \frac{1}{r^2} \partial_r \left( r^2 \cdot j_B (r, t) \right) \text{ with } j_B (r, t) = D \cdot e^{-\beta U(r)} \left[ \partial_r (e^{\beta U(r)} \cdot p_B (r, t)) \right]$$

- With the following boundary conditions $j_B (R_0, t) = w \cdot p_B (R_0)$
Reaction times

Green functions (Brownian propagators)
- Written as $p(r, t|r_0, t_0, R)$
- Can be used to sample new positions after time steps $\Delta t = t - t_0$

Reaction probability
- Got from integration of Green functions over $r$
- $Y(t|r_0, R) = 1 - \int_R^{\infty} p(r, t|r_0, t_0, R) \, dr$
- Inverse the above equation of $Y$ in respect to time to sample random reaction times

Event table
- Build a table of reaction events for each pair of reactants
- Process the table from the soonest event to the latest and update the table after each reaction by withdrawing reactions that cannot happen because of the disappearance of the corresponding reactants
Inverse a probability function

1D probability $P(x)$
- is defined on range $[x_{min}, x_{max}]$
- is monotonic on $[x_{min}, x_{max}]$

Method
- Sample probability $P_x$
- Sample at $m_1 = \frac{x_{min} + x_{max}}{2}$
- According to the value of $P(m_1)$ value in respect to $P_x$ and knowing the sign of the derivative (increasing/decreasing), redefine $[x_{min}, x_{max}]$ and sample $m_2 = \frac{x_{min} + x_{max}}{2}$
- Arbitrary accuracy, range can be selected for a given interval of interest
Testing IRT vs analytical solution

Reflective box
- Compare analytical solution with MC results
- Use this box to monitor kinetics of bimolecular reactions for a well stirred system and compare the results to analytical ones
Testing IRT vs analytical solution

Tested partially diffusion controlled reactions
- OH+OH
- H+H

Diffusion controlled reactions
- OH+OH
- H+H

Taking into probability encounter (partially diffusion controlled reaction) matters at short distance

Example of kinetics:
Red curve – analytical solution
Histogram – MC result

Box of 100 µm side
Merging representations
Computational complexity

« Full atomistic » approach

Molecules = balls
Solvant = continuum

Time evolution of concentrations in voxellized geometry

Well adapted for few molecules and heterogenously distributed

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

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.
Principle

Modelling consists of
  ◦ Environment
  ◦ Phenomenon/process

Environment
  ◦ Gather all dynamical entities of interest such as chemical species defined as either tracks or concentrations
  ◦ Notify phenomenon/process when watched entities change

Phenomenon
  ◦ Decide next actions to take either after every time step or after being notify of changes by the environment
Gillespie method

Principle

- Monte Carlo method for the compartment based representation
- Each unimolecular and bimolecular reactions are computed randomly using observed reaction rate constant
- Spatial considerations can be taken into account
- The method can be adapted to deal with dense systems where fast reactions happen

Example of kinetics
- Red curve: analytical results
- Histogram: MC results
Conclusions
Conclusions

Particle-based representation
- Alternatives models to the step-by-step method have been implemented for both diffusion controlled and partially diffusion controlled reactions
- Comparison of kinetics in a well stirred environment with analytical solutions satisfactory both for low and high density of reactants
- (On-fly switch from the step-by-step to the IRT method is possible)

Compartment-based representation
- A spatial Gillespie method has been implemented and can work in parallel (same time frame) with the particle-based representation to simulate reactions between species of high concentration
Acknowledgments

Marie Davidkova
Jay Laverne
Vladimir Ivanchenko
Michel Maire
David Bartels
Gabriele Cosmo
Vaclav Stepan
Hoang Tran
John Allison
Joseph Perl
Laurent Garnier
Ivana Hrivnacova
Andrea Dotti
Makoto Asai
John Apostolakis

And all other Geant4 and Geant4-DNA collaborators for the regular technical discussions

Thank you ©