A Pathway to Simulate Radiation Chemistry of FLASH Radiation using TOPAS-nBio:

Combining Heterogeneous and Homogeneous Chemistry in a general Cellular Environment Model

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Introduction

- Pulse radiolysis irradiation has been the primary tool for exploring radiation chemistry on the past decades.

- Nowadays, the so-called FLASH irradiation has been proposed to be used for oncological applications since there are evidence that normal tissue is spared with ultra-high dose rates irradiation: the flash effect.*

- However, the underlying mechanism of the FLASH effect that cause this effect (e.g., as oxygen depletion) are yet to be fully understood.

- The radiation chemistry perspective could offer a fundamental explanation from first principles.

*Montay-Grue P., Petersson K., et al. (2017), Vozenin M-C., De Fornel P. (2018)

Background

- Pure water has been used as an approximation for the cellular environment
- From physical perspective water seems like a reasonable approach for the ionizations in the medium since water is ~80% of the cell constituent*.
- However, for the chemical reactions between biomolecules and radiolysis chemical species inside the cell this model is insufficient.

* Zhang J. et al, (2017)

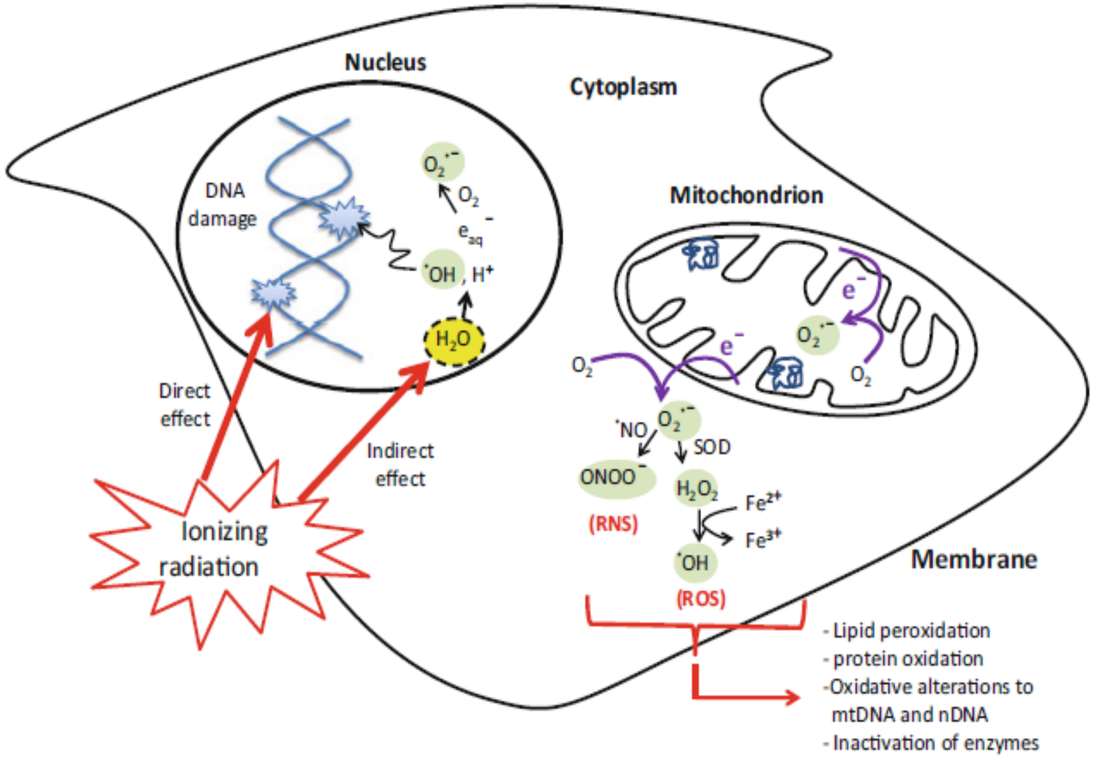


Imagen taken from: Zhang J.et al (2017) The Translationally Controlled Tumor Protein and the Cellular Response to Ionizing Radiation-Induced DNA Damage.

Current Models

Time log-scale

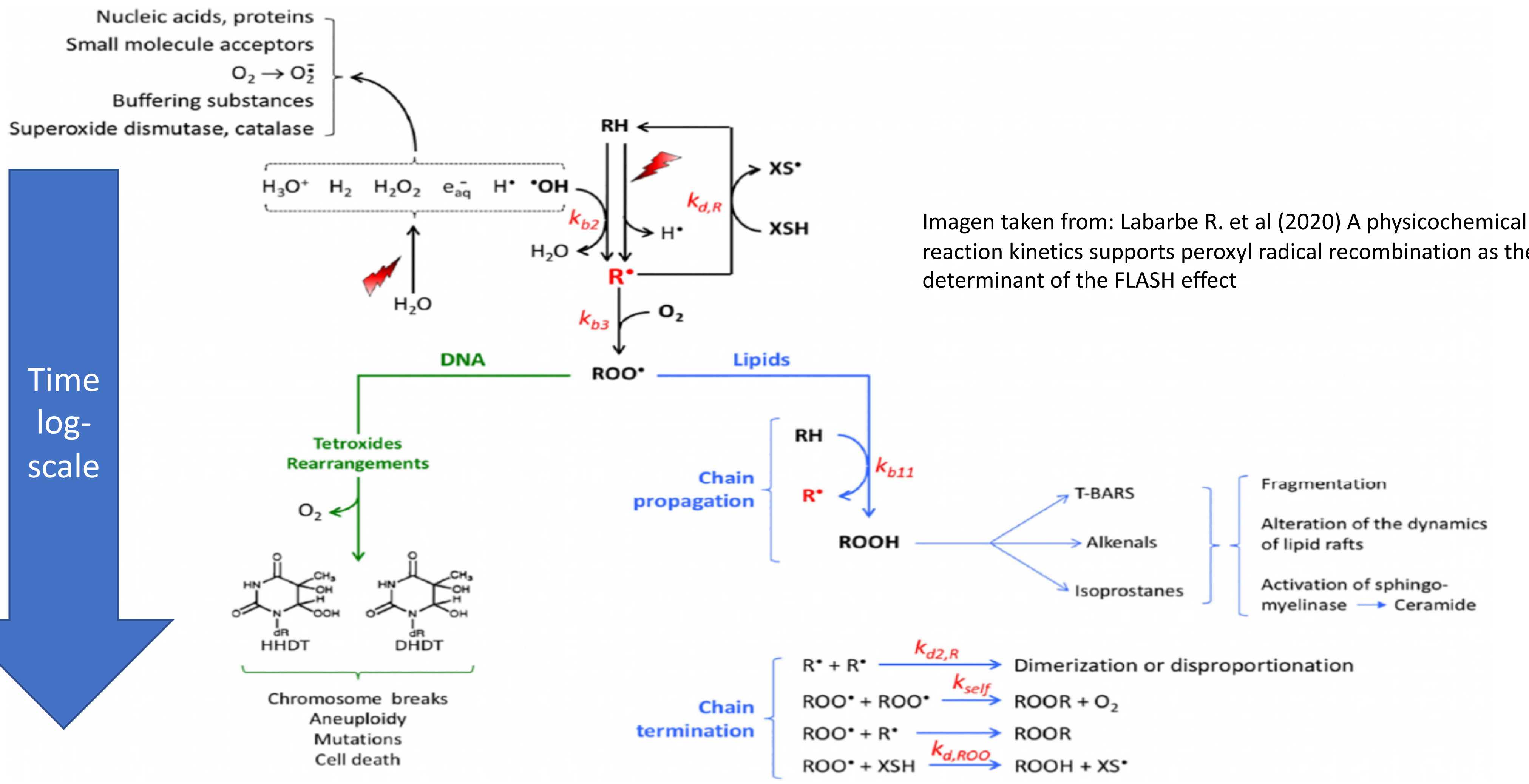


Imagen taken from: Labarbe R. et al (2020) A physicochemical model of reaction kinetics supports peroxyl radical recombination as the main determinant of the FLASH effect

Current Models

Reaction	Reaction Rate
$RH + H \rightarrow R$	$K_{dH} = 1{\times}10^8/Ms$
$RH + e^-_{aq} \rightarrow Rd$	$K_{de^-_{aq}} = 1.4{\times}10^8/Ms$
$OH + GSH \rightarrow H2O + GS$	$K_{dOH} = 1{\times}10^8/Ms$
$OH + RH \rightarrow R$	$K_{b2} = 1{\times}10^9/Ms$
$R + GSH \rightarrow RH + GS$	$K_{dR} = 300/s$
$R + R \rightarrow 2R$	$K_{d2R} = 5{\times}10^7/Ms$
$R + O_2 \rightarrow ROO$	$K_{b3} = 5{\times}10^7/Ms$
$ROO + XSH \rightarrow ROOH + XS$	$K_{dROO} = 0.0408/s$
$2ROO \rightarrow O_2 + ROH + RO$	$K_{self} = 1{\times}10^4/Ms$
$ROO + RH \rightarrow ROOH + R$	$K_{b11} = 20/Ms$

Models have been proposed on the past: Spitz D. R., Buettner G. R. et al (2019) LaBarbe R., Hotoiu L. et al (2020)

We can take them as a starting point to explore further aspects.

Data taken from: Labarbe R. et al (2020) A physicochemical model of reaction kinetics supports peroxyl radical recombination as the main determinant of the FLASH effect

Propose a multiscale model

A model for the cellular environment should contemplate some general milestones*:

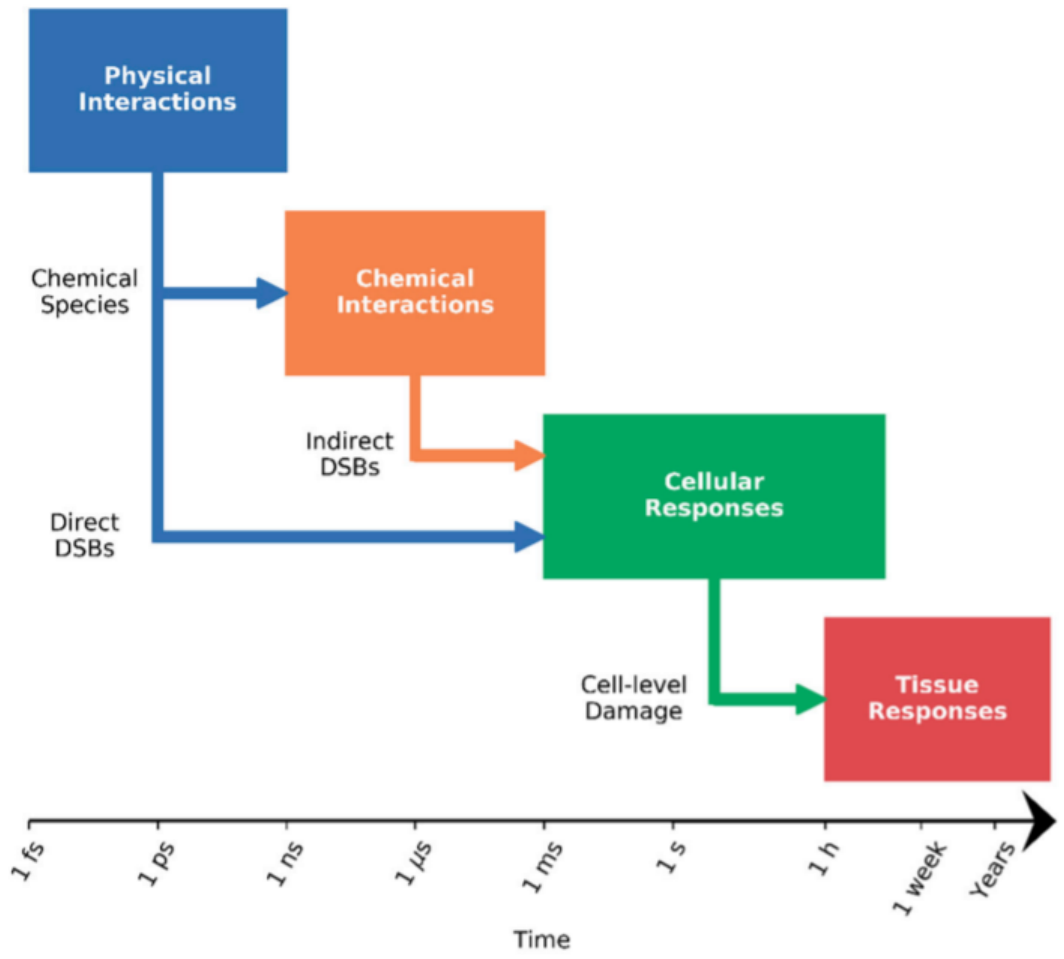
- Intertrack reactions and heterogeneous chemistry.
- Specific for time scales of interest.
- Consider the oxygen concentration and consumption.
- Scavenging capacity of the environment .
- Follow relevant products of scavenged species.

Koch C. J. (2019), Wardman P. (2020)*

Time scale of interest

- "In irradiated cells or tissue, oxygen is therefore likely to be consumed largely via the formation of transient peroxyl radicals ($ROO^{\bullet}$) formed in diverse secondary reactions"*
- "$R^{\bullet}$ fades away in complete absence of O_2 with a half-reaction time of 500μs in bacteria and less than 5 ms in mammalian cells."*
- The mean survival time of relevant radicals may indicate a good time-span for a model

* Labarbe R. et al (2020)



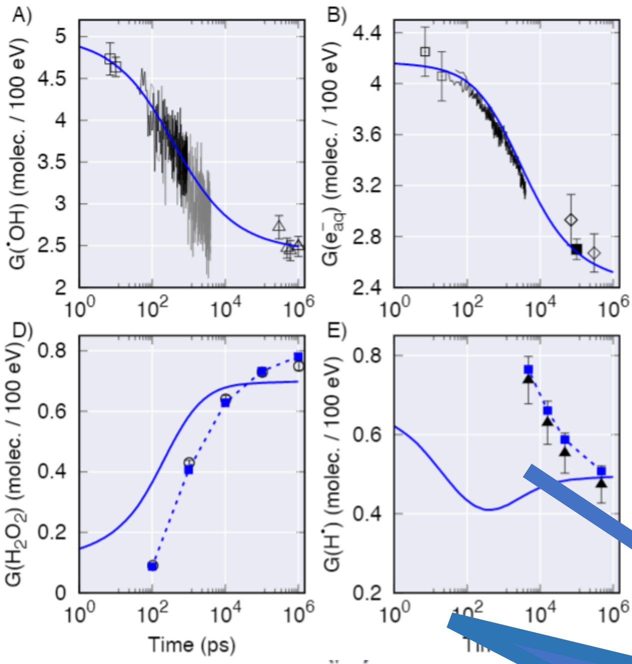
Time stages for living tissue irradiation response. Image obtained from: McMahon S. & Prise K. (2019).

Heterogeneous and homogeneous stages

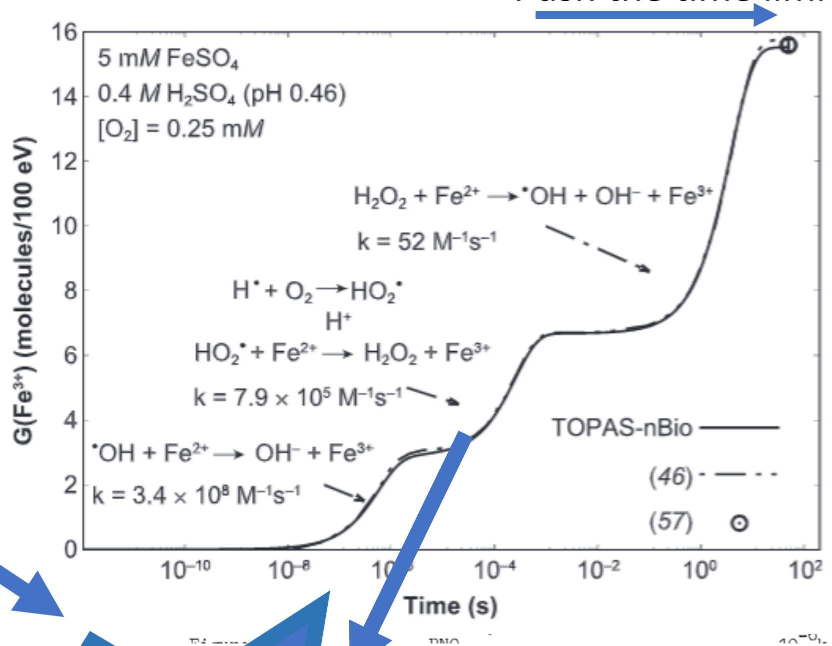
Reaction	Reaction rate
$e^-_{aq} + e^-_{aq} \rightarrow H_2 + 2OH^-$	$5.5\times10^9/Ms$
$H^+ + e^-_{aq} \rightarrow H$	$2.3\times10^{10}/Ms$
$H + e^-_{aq} \rightarrow H_2 + OH^-$	$2.5\times10^{10}/Ms$
$OH + e^-_{aq} \rightarrow OH^-$	$3.0\times10^{10}/Ms$
$H_2O_2 + e^-_{aq} \rightarrow OH + OH^-$	$1.1\times10^{10}/Ms$
$H^+ + OH^- \rightarrow H_2O$	$1.4\times10^{11}/Ms$
$H + H \rightarrow H_2$	$7.8\times10^9/Ms$
$H + OH \rightarrow H_2O$	$2.0\times10^{10}/Ms$
$H_2O_2 + H \rightarrow H_2O + OH$	$9.0\times10^7/Ms$
$OH + OH \rightarrow H_2O_2$	$5.5\times10^9/Ms$

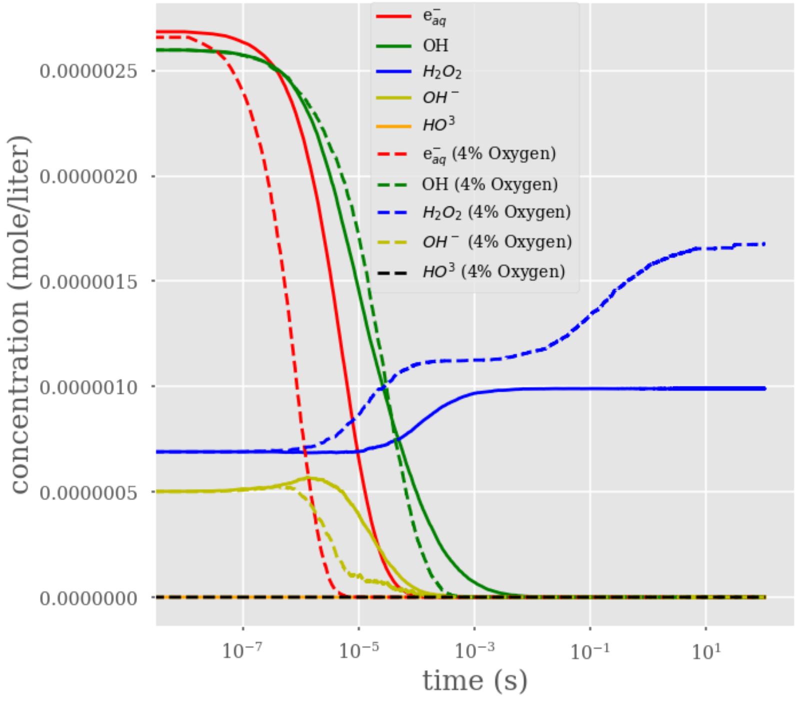
Data taken from: LaVerne J. A. & Pimblott S. M. (1993) Yields of Hydroxyl Radical and Hydrated Electron Scavenging Reactions in Aqueous Solutions of Biological Interest

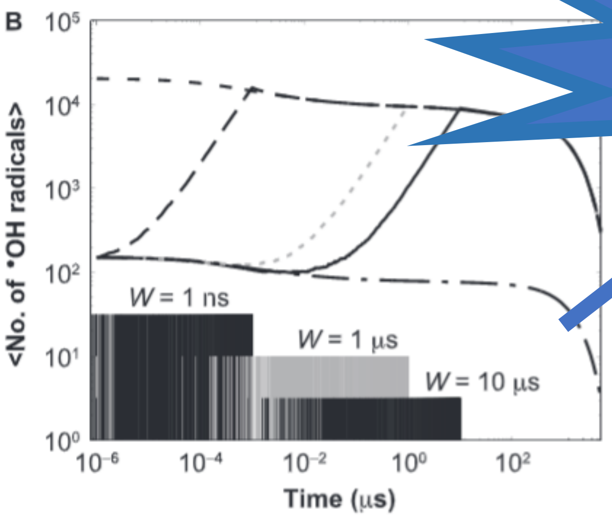
- The complete scheme of reactions for the radiolysis of water is ~80 reactions long [Pastina B. & LaVerne J. A. (2001)]
- However, at the early stages of the irradiation we can use a reduced scheme that describes all the early reactions
- We can apply this logic to the proposed model in order to obtain a more compact one

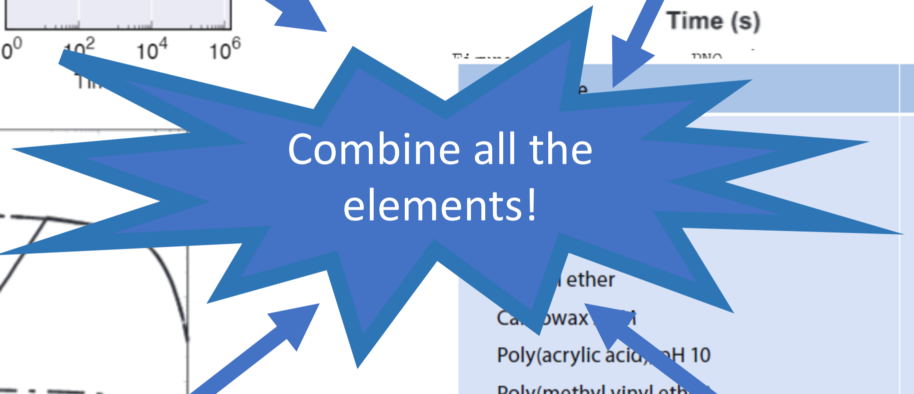


Push the time limit further









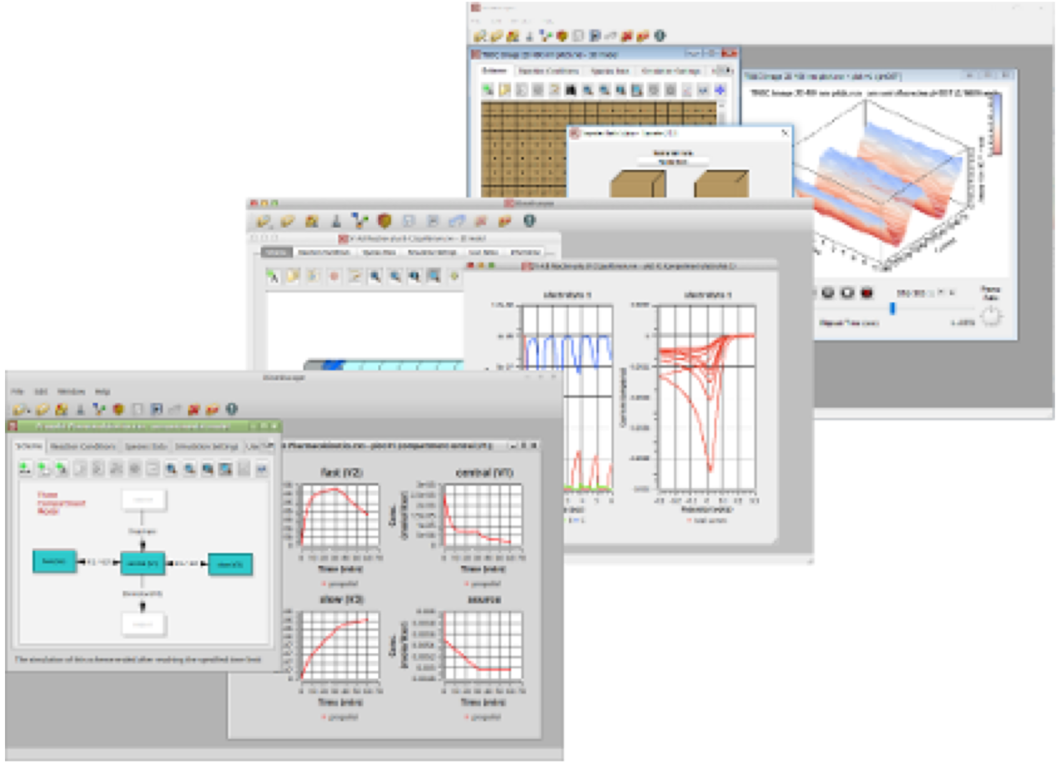
...e	•OH	Tl(II)
	3.1	
	3.1	
	3.1	
	4.5	
...ether	4.7	
Ca...owax...	10.6	
Poly(acrylic acid), pH 10	100	
Poly(methyl vinyl ethe...	110	
2-Deoxyribose	3.1	
	3.1	0.77
Thy	4.2	
Cyt	4.6	
Ura	5.2	
Thd	5.0	
dAdo	1.4	0.72

Add detailed reactions schemes

We can use specialized software to handle it

KINETISCOPE
a stochastic kinetics simulator

- We can coupe results from TOPAS at the end of the heterogeneous stage (~1μs) and then use software capable of solving concentration differential equations (such as Kinetiscope) so it can give us longer time scales considering the homogeneous chemical stage (>100 s)



Future Work

- We Will follow the present strategy to develop a robust cellular environment model.

- At the same time we will need to take a deep look on the experimental data compiled for decades in order to obtain the chemical parameters required.

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