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Modelling the Bystander Effect in Proton SFRT

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Bystander Effect in Spatially Fractionated Radiotherapy

- Bystander effect (RIBE): "Ionising **radiation induced non-targeted effects in non-irradiated cells** within or nearby an irradiated volume" [Wang et al., 2018]

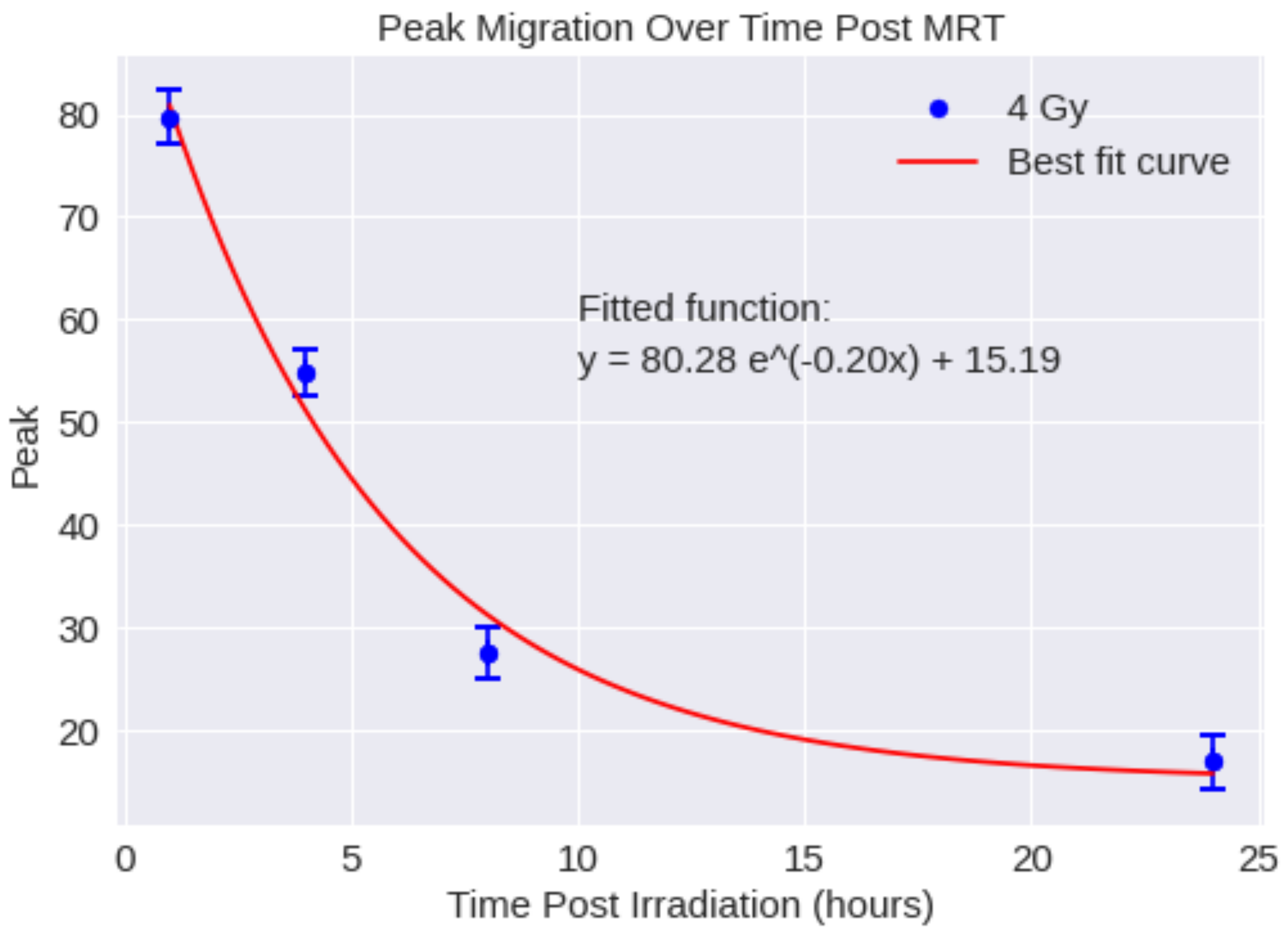
- Evidence of RIBE in **proton** irradiation [Mukherjee and Chakraborty, 2019; Pouget et al., 2018]

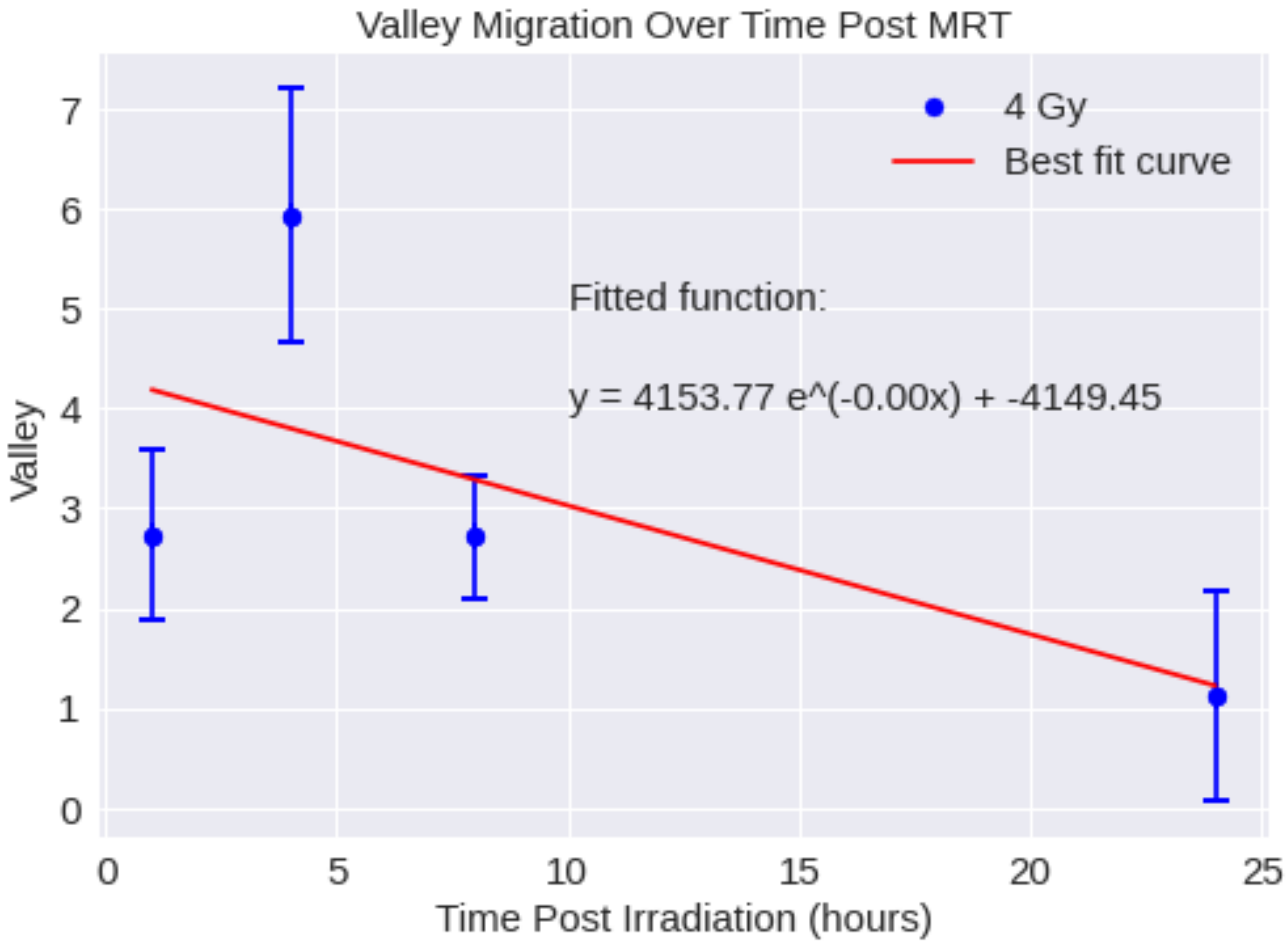
- Evidence of RIBE in **partial** particle irradiation [Shao et al., 2006]

- There is evidence of RIBE in **proton SFRT** in some cell lines (A549) [Autsavapromporn et al., 2023].

Preliminary Experimental Results

- J. McGarrigle —> FaDu cells





Possible Signalling Agents

- RIBE due to communication between irradiated and non-irradiated cells through signalling agents [Klammer et al., 2015].

- Examples of candidates [Marín et al., 2015]:
  - **Small species**: free radicals, reactive oxygen species (ROS), Ca^{2+} and nitrogen oxide (NO).
  - Large species: cytokines, exosomes and other proteins.

ROS in Water Radiolysis

- Radiolysis is a fast channel of chemical production.
- Used TOPAS and TOPAS-nBio.
- Focus on H_2O_2 .

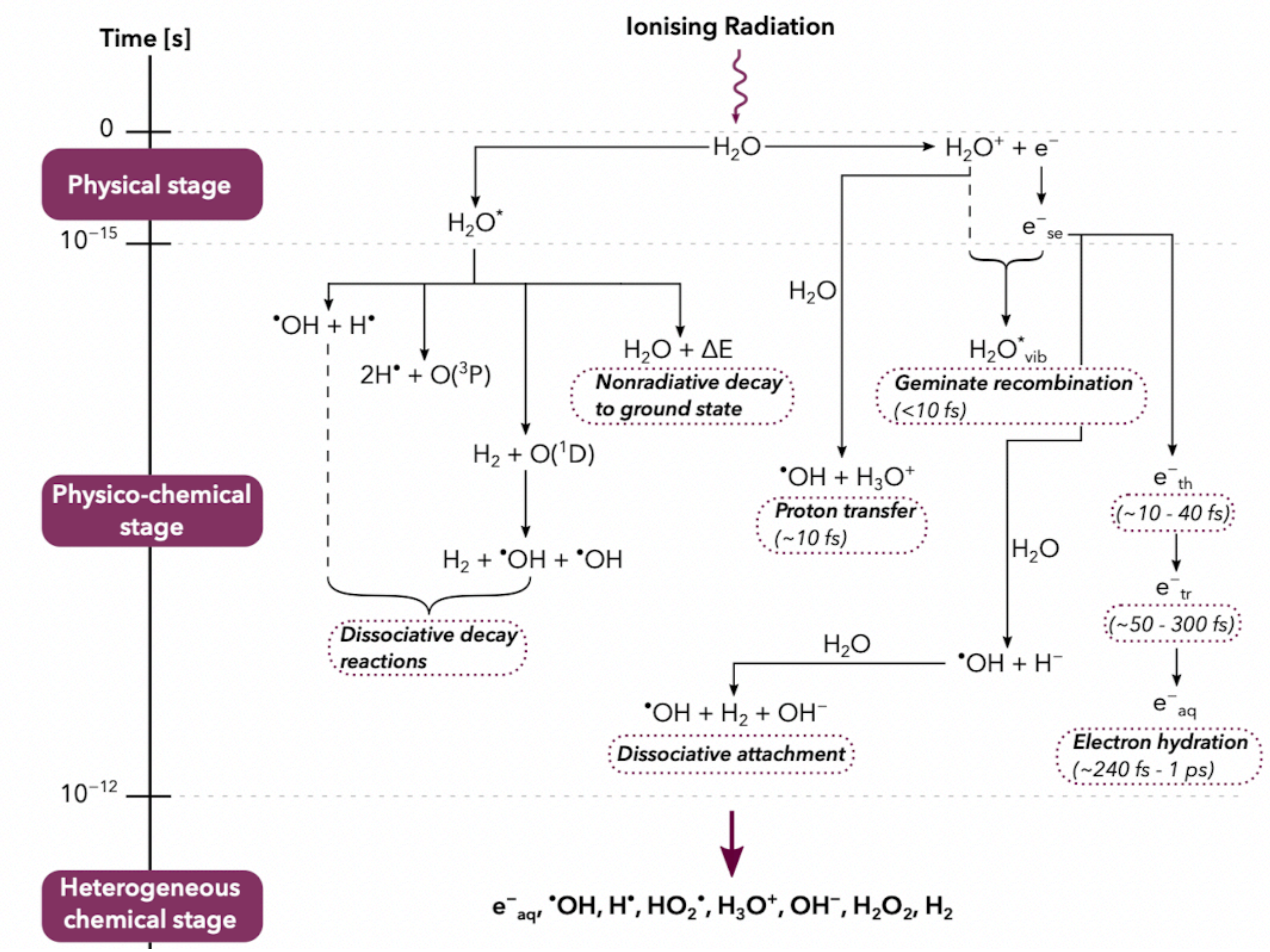


Image: Masilela 2023, PhD thesis.

Simulation Details

- Based on T. Masilela's set-up. Beams: 0.4 x 6 mm^2; ctc: 3.2 mm

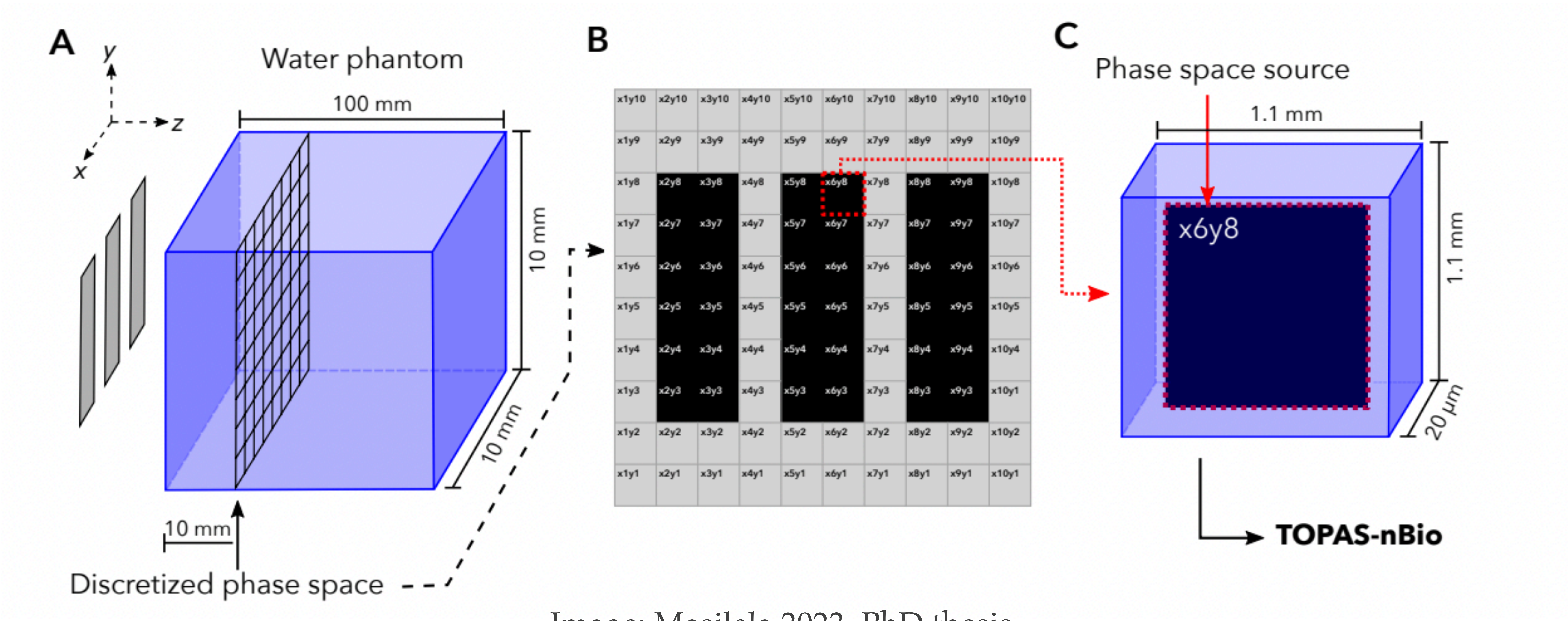
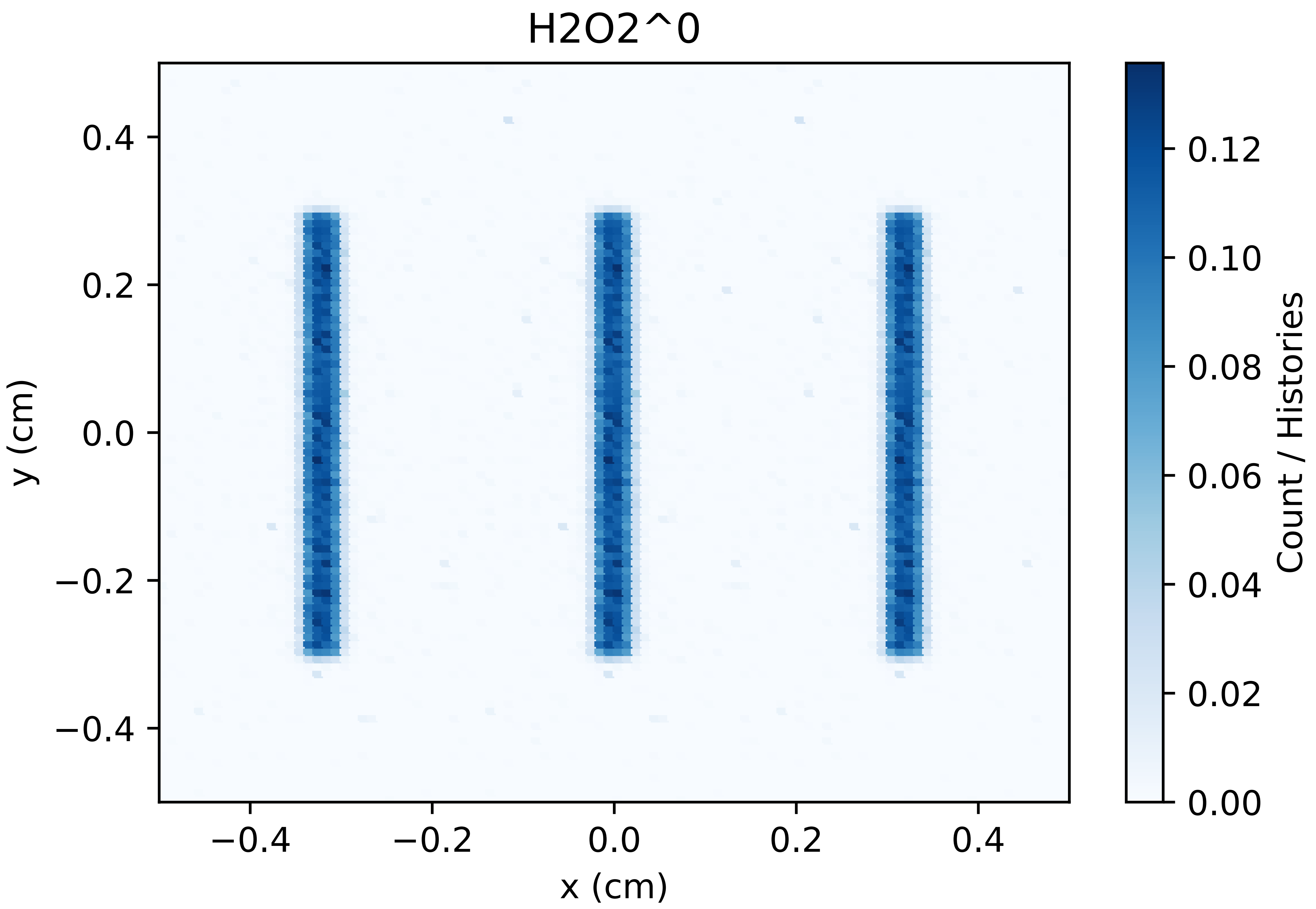
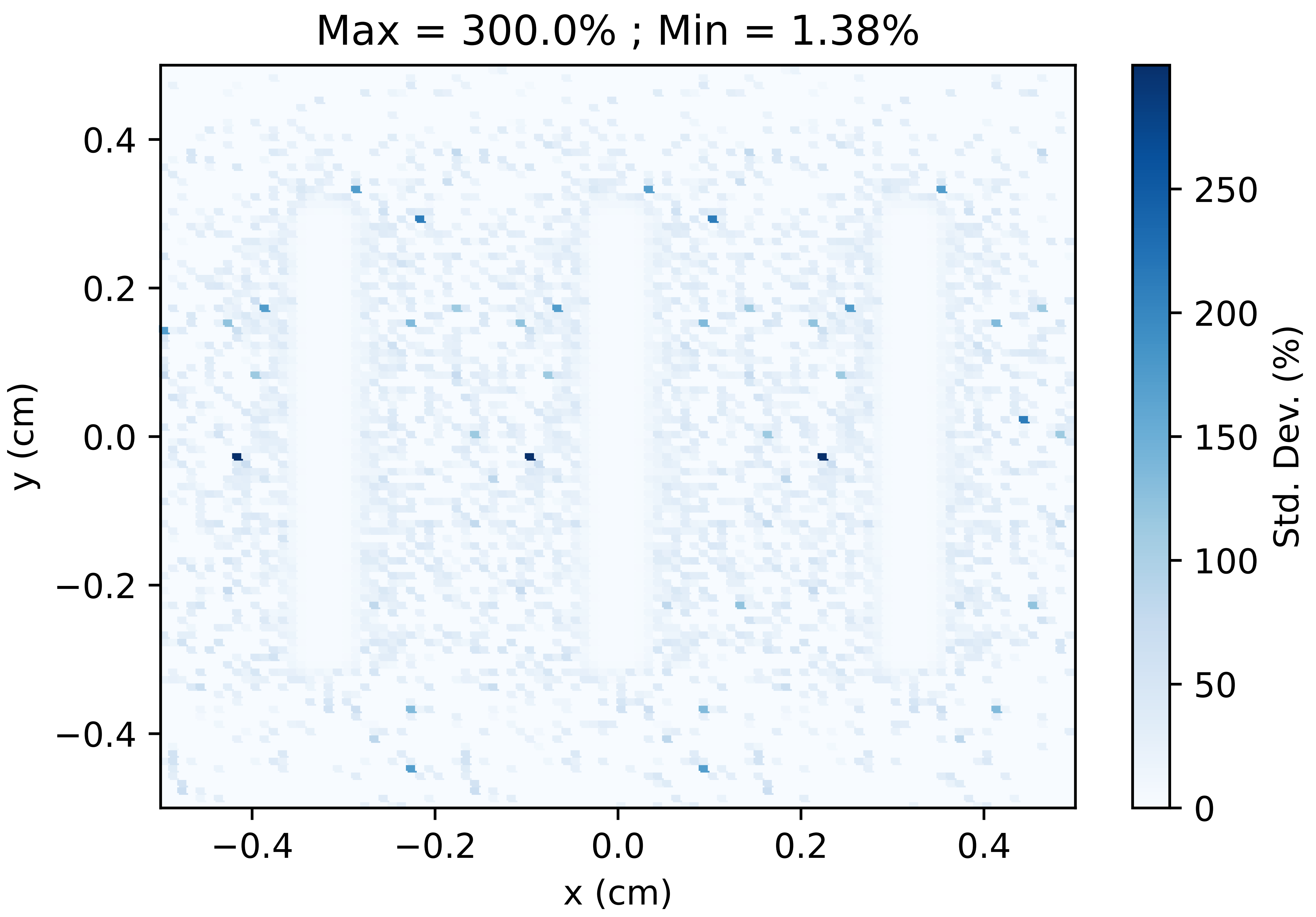


Image: Masilela 2023, PhD thesis.

Simulation Results

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





Transport of H_2O_2 After Generation

- Biological stage is late.
- Will consider spatial evolution of H_2O_2 as a function of time.

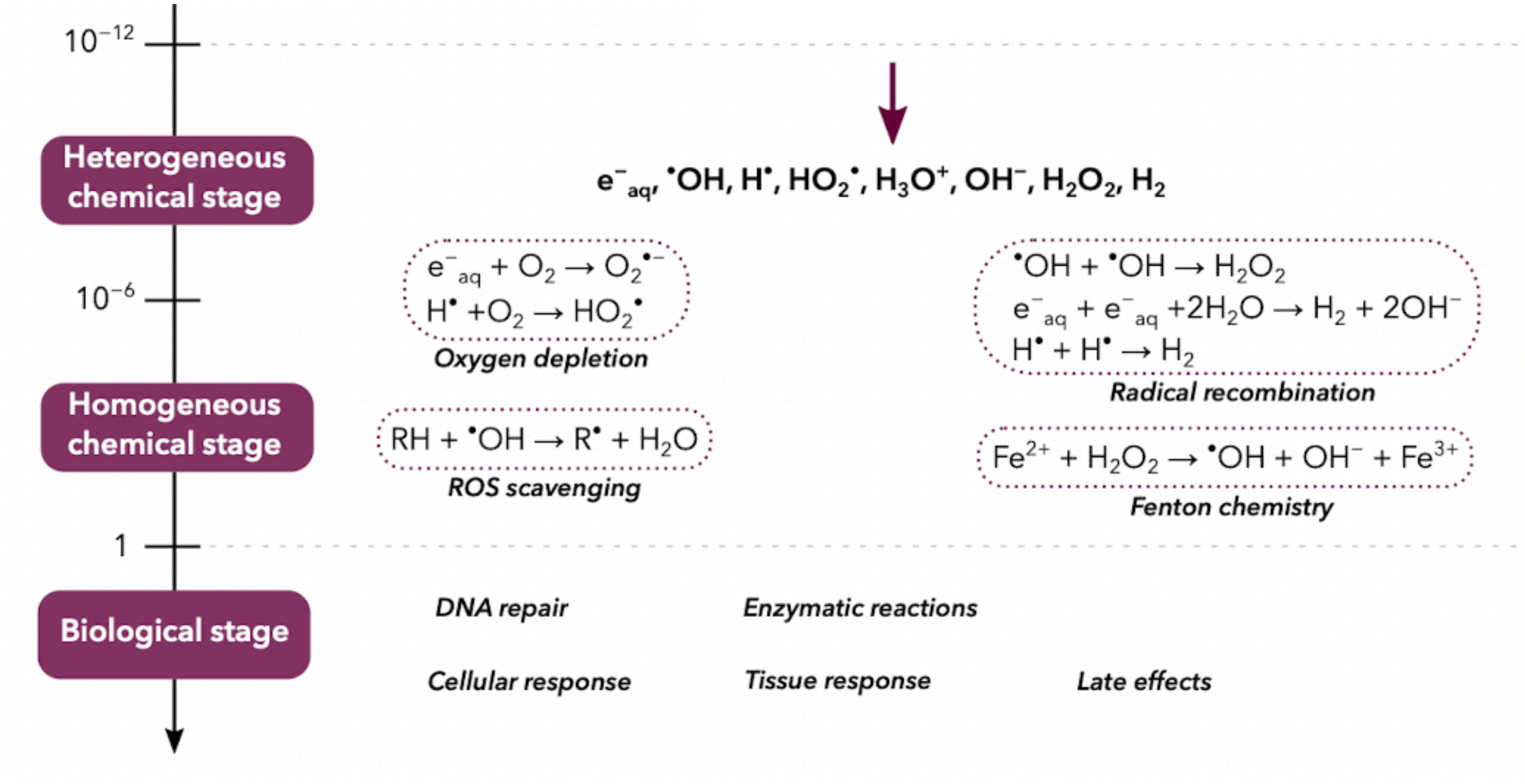


Image: Masilela 2023, PhD thesis.

Neglecting Homogenous Chemical Stage

- TOPAS-nBio cannot consider the homogenous chemical stage.
- Free diffusion shows that the spatial distribution doesn't change in < 1s.

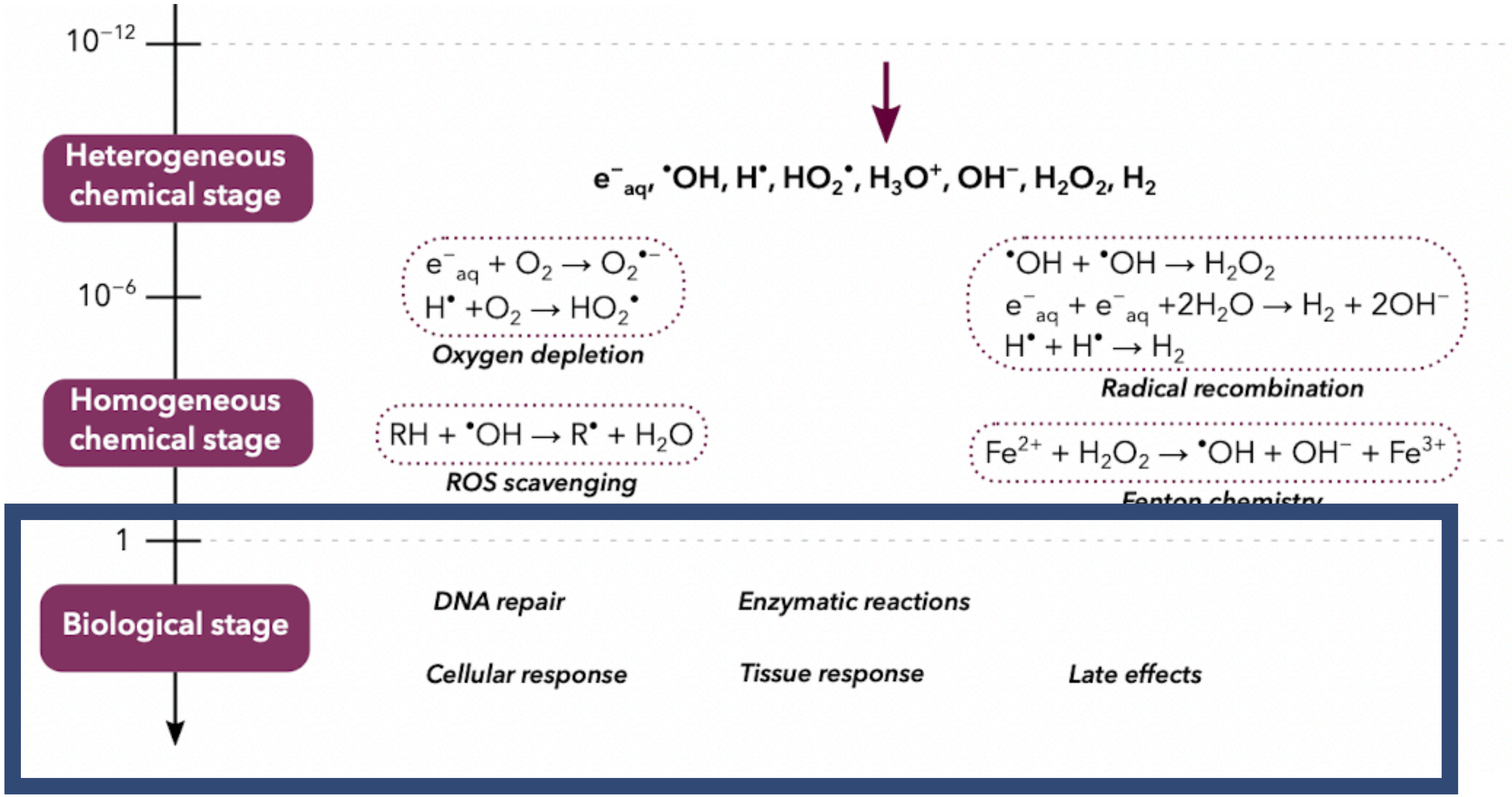


Image: Masilela 2023, PhD thesis.

Neglecting Homogenous Chemical Stage

- Free diffusion is implemented using Smoluchowski diffusion theory [Karamitros et al., 2014].
- Each molecule generated during the simulation will be transported using these equations.

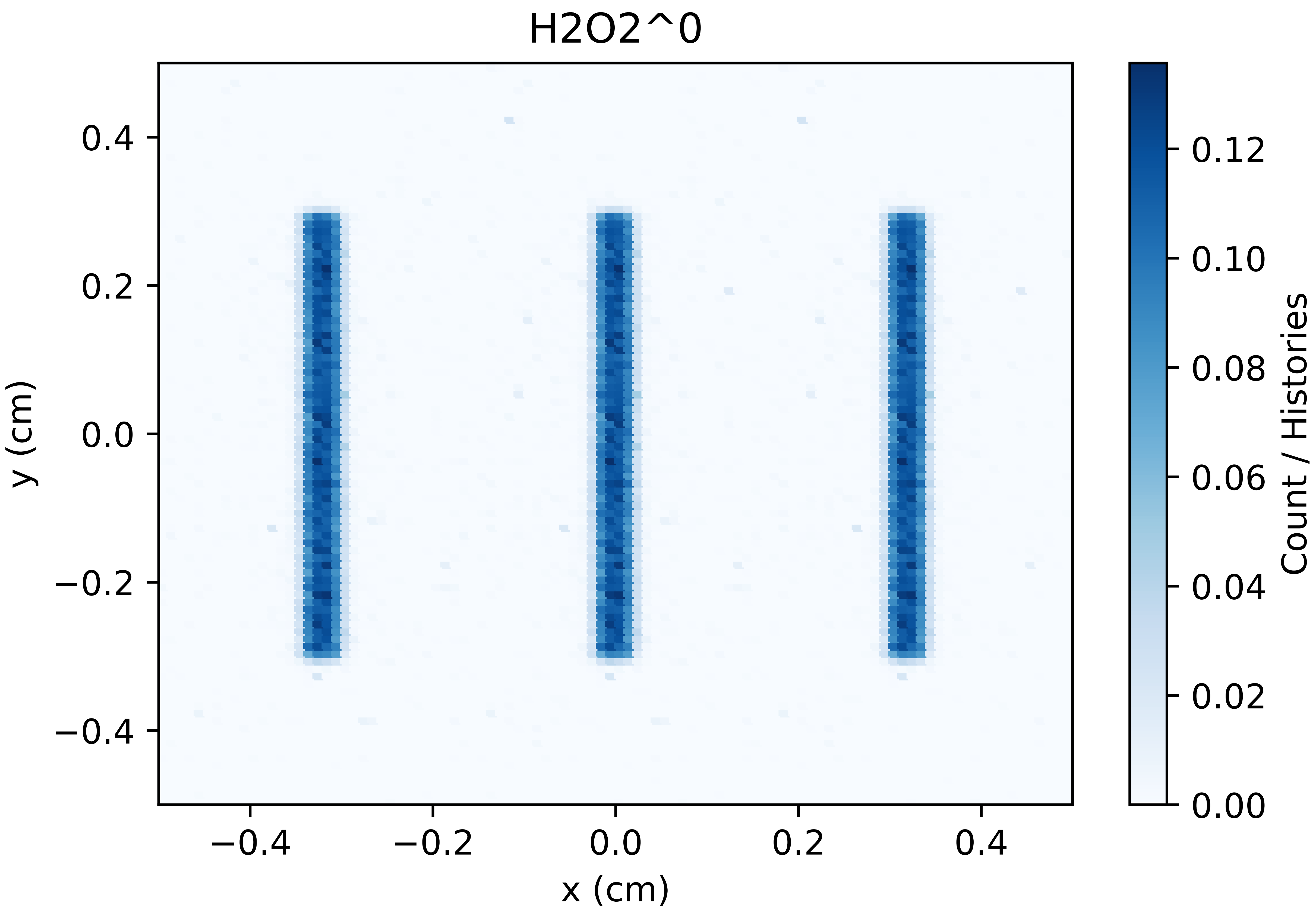
$$\hat{x}(\tau) = x_0 + \sqrt{2D \cdot \tau} \cdot \hat{\xi}_x$$

$$\hat{y}(\tau) = y_0 + \sqrt{2D \cdot \tau} \cdot \hat{\xi}_y$$

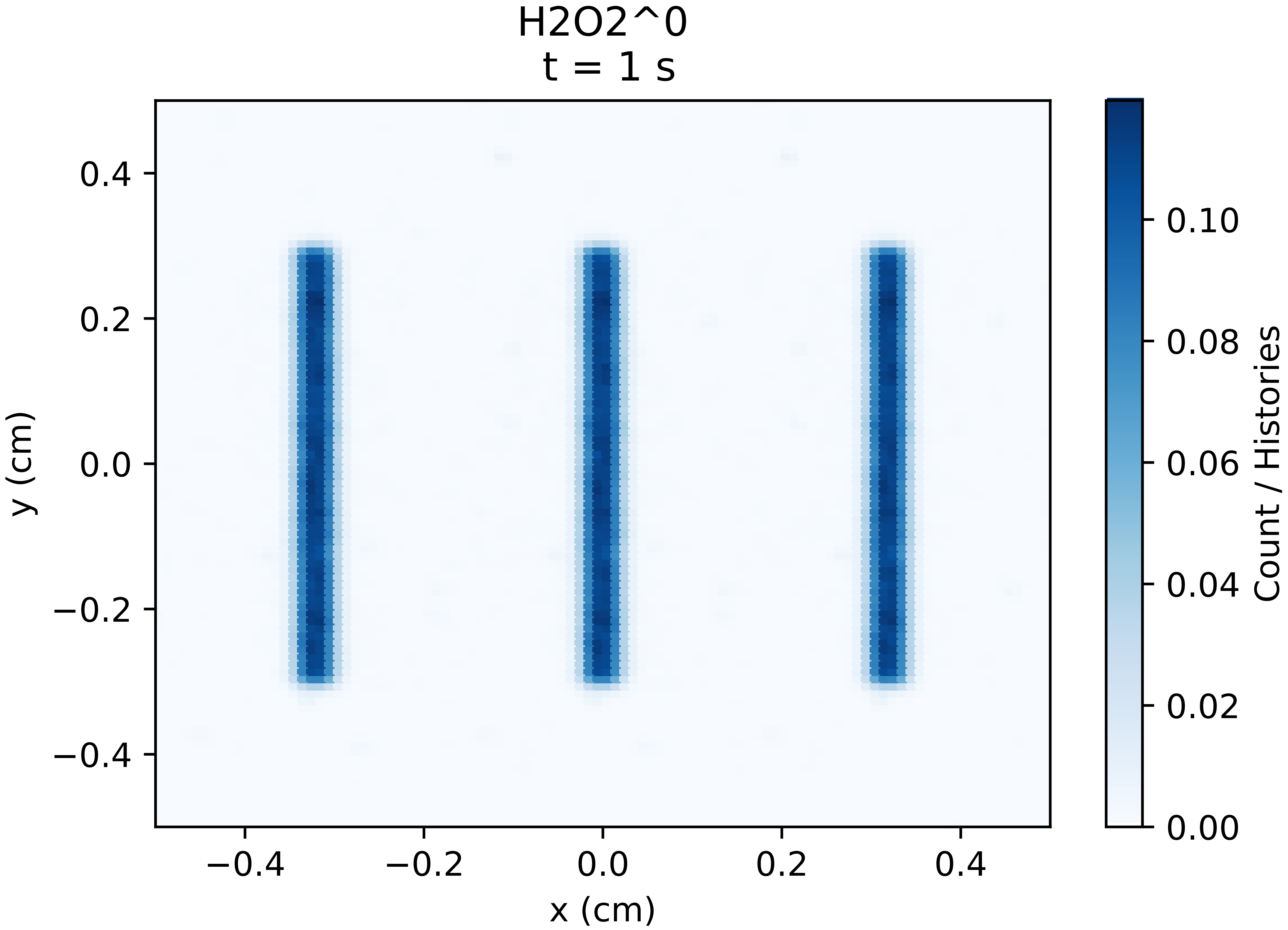
$$\hat{z}(\tau) = z_0 + \sqrt{2D \cdot \tau} \cdot \hat{\xi}_z$$

Neglecting Homogeneous Chemical Stage

t =1 μs



t =1 s



Neglecting Homogeneous Chemical Stage

- We assume that the stage takes place because free diffusion is slow enough.
- We assume that H_2O_2 concentration's evolution is homogeneous in space because the material is homogeneous.
- We assume that some H_2O_2 survives the stage and remains stable.

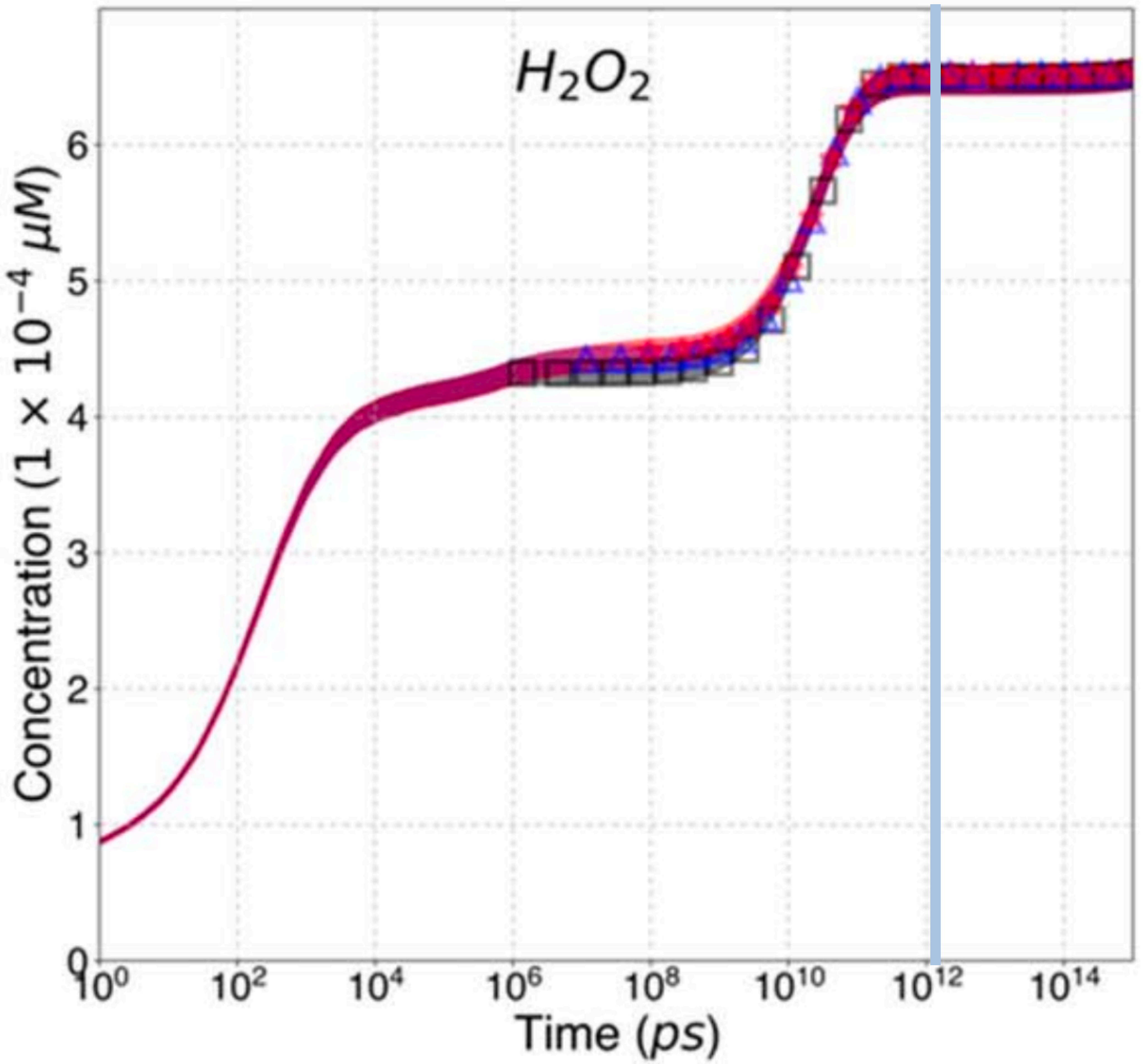
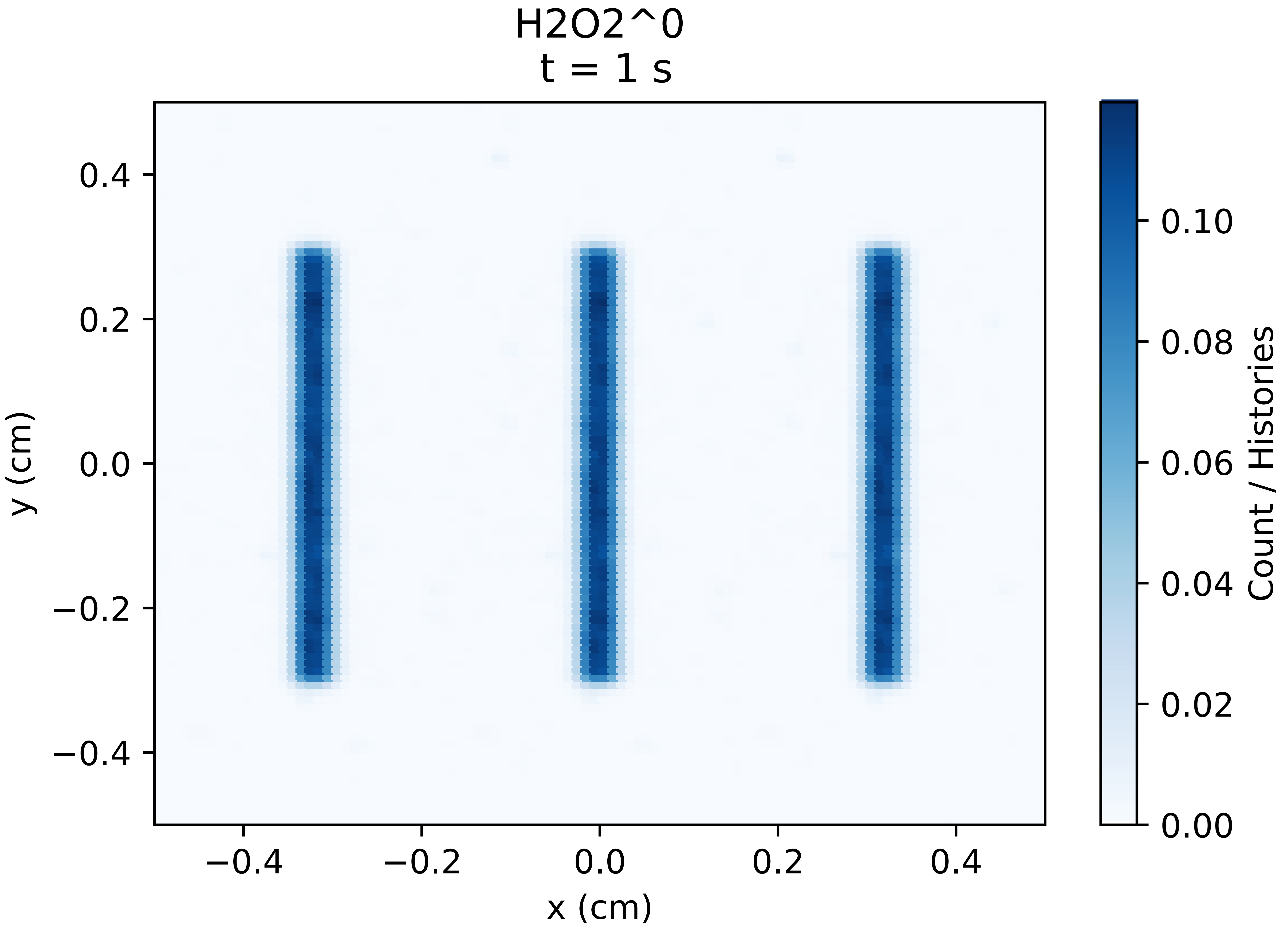


Image: D-Kondo 2023

Neglecting Homogeneous Chemical Stage

- i.e.: We assume this spatial distribution is valid.
- Most likely with different absolute values but (sort of) the same proportion.



Transport of H_2O_2 After Generation

- Add a probability for survival to molecules transported using Smoluchowski free diffusion theory.

$$\hat{x}(\tau) = x_0 + \sqrt{2D \cdot \tau} \cdot \hat{\xi}_x$$
$$\hat{y}(\tau) = y_0 + \sqrt{2D \cdot \tau} \cdot \hat{\xi}_y$$
$$\hat{z}(\tau) = z_0 + \sqrt{2D \cdot \tau} \cdot \hat{\xi}_z$$

- Probability of survival = $e^{-k\tau}$

- Will consider the **time** when the **concentration is spatially homogenous**.

Transport of H_2O_2 After Generation

- Based on background pseudo first-order reactions, for concentration of H_2O_2, $\phi(x, y)$, add exponential decay:

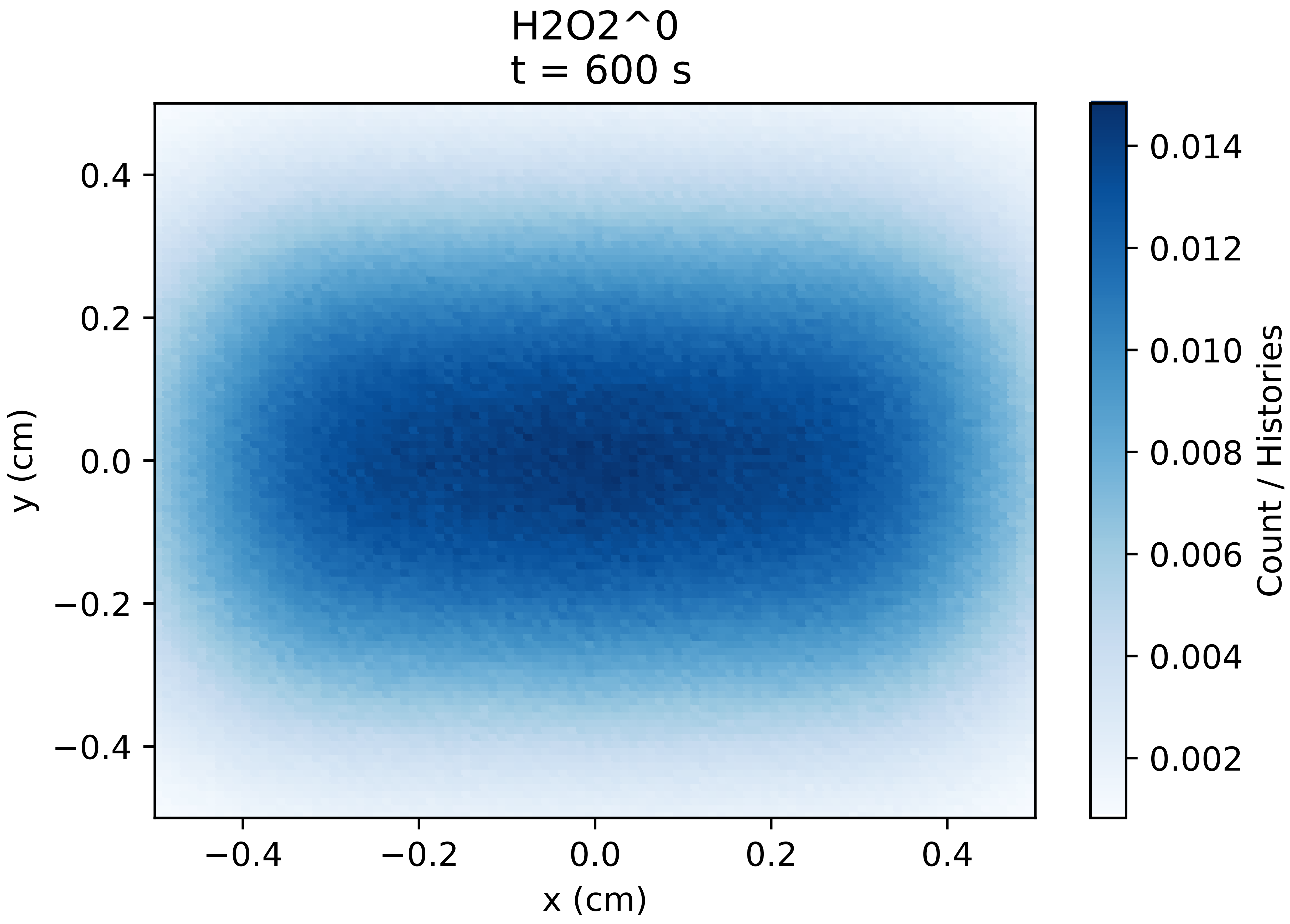
$$\frac{d\Phi(x,y,\tau)}{d\tau} = -k\Phi(x,y,\tau) \qquad \text{->} \qquad \Phi = \phi\, e^{-k\tau}$$

- k is the (pseudo) first order **rate constant**.

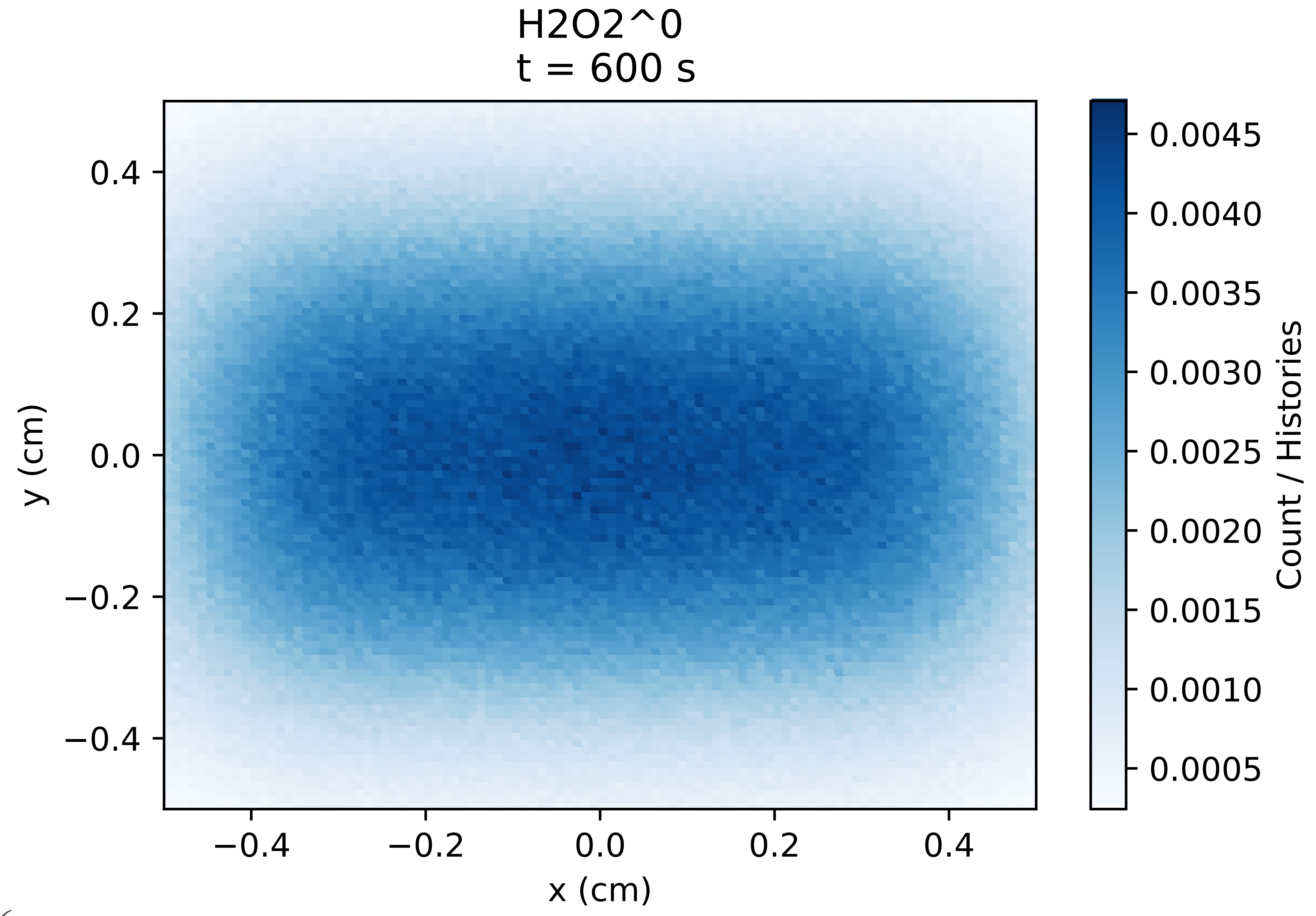
- In Zhang et al. 2023, $k = 2 \cdot 10^{-1}, 2 \cdot 10^{-2}, 2 \cdot 10^{-3}\ s^{-1}$ based on cell absorption.

Model for Transport - $k = 2.3 \cdot 10^{-3}$

- Free diffusion

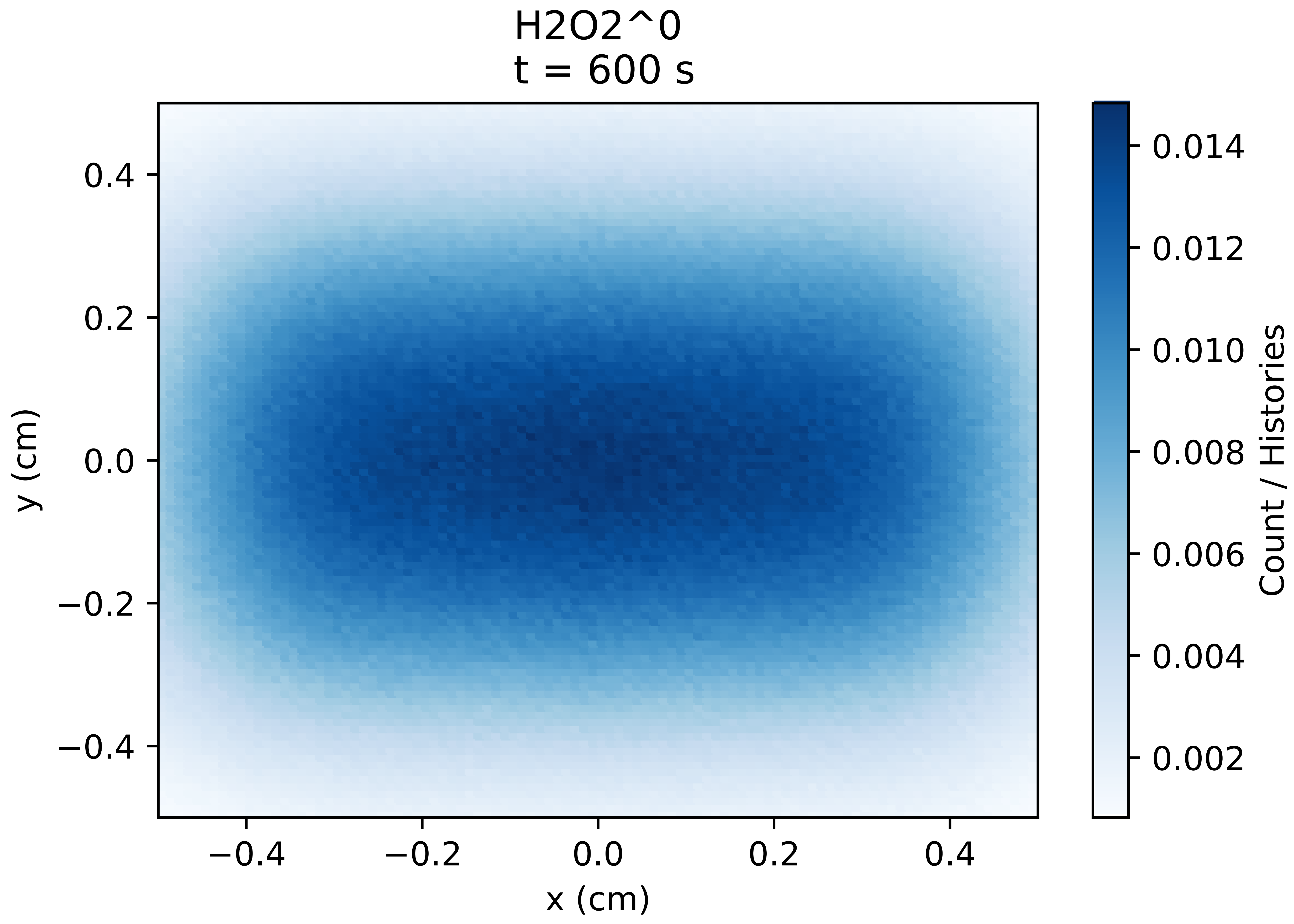


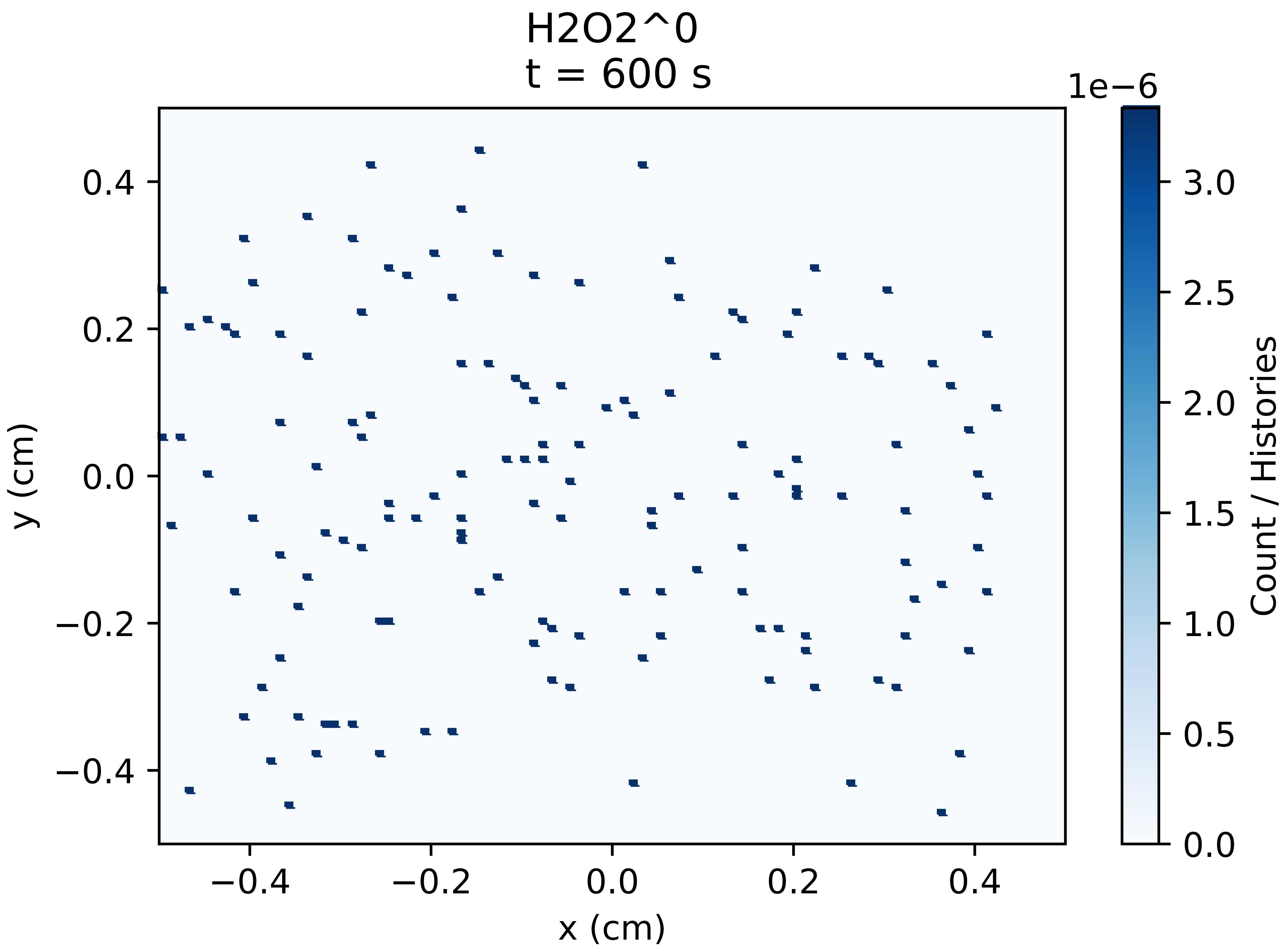
- Free diffusion + exponential decay



Model for Transport - $k = 2.3 \cdot 10^{-2}$

- Free diffusion
- Free diffusion + exponential decay



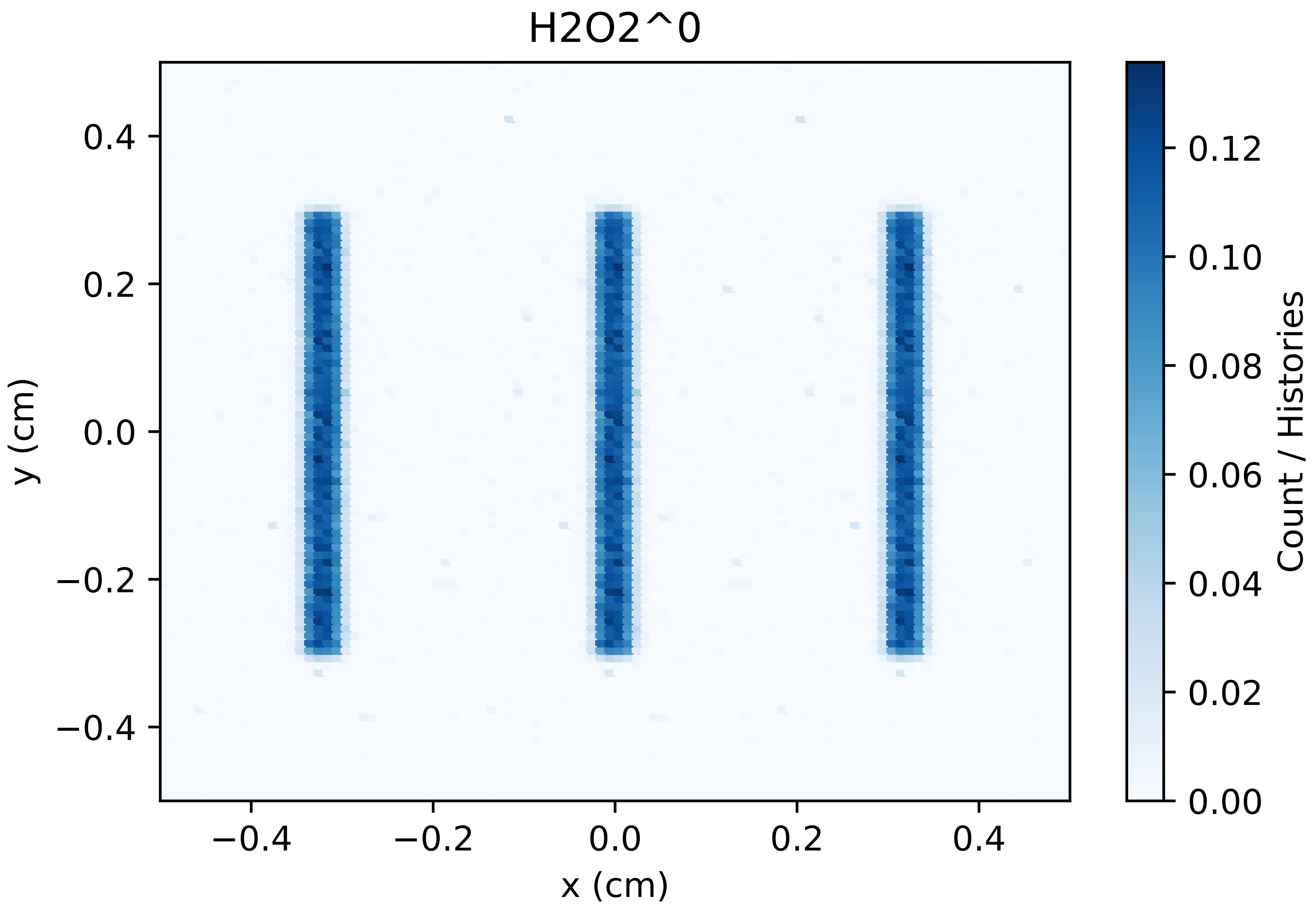


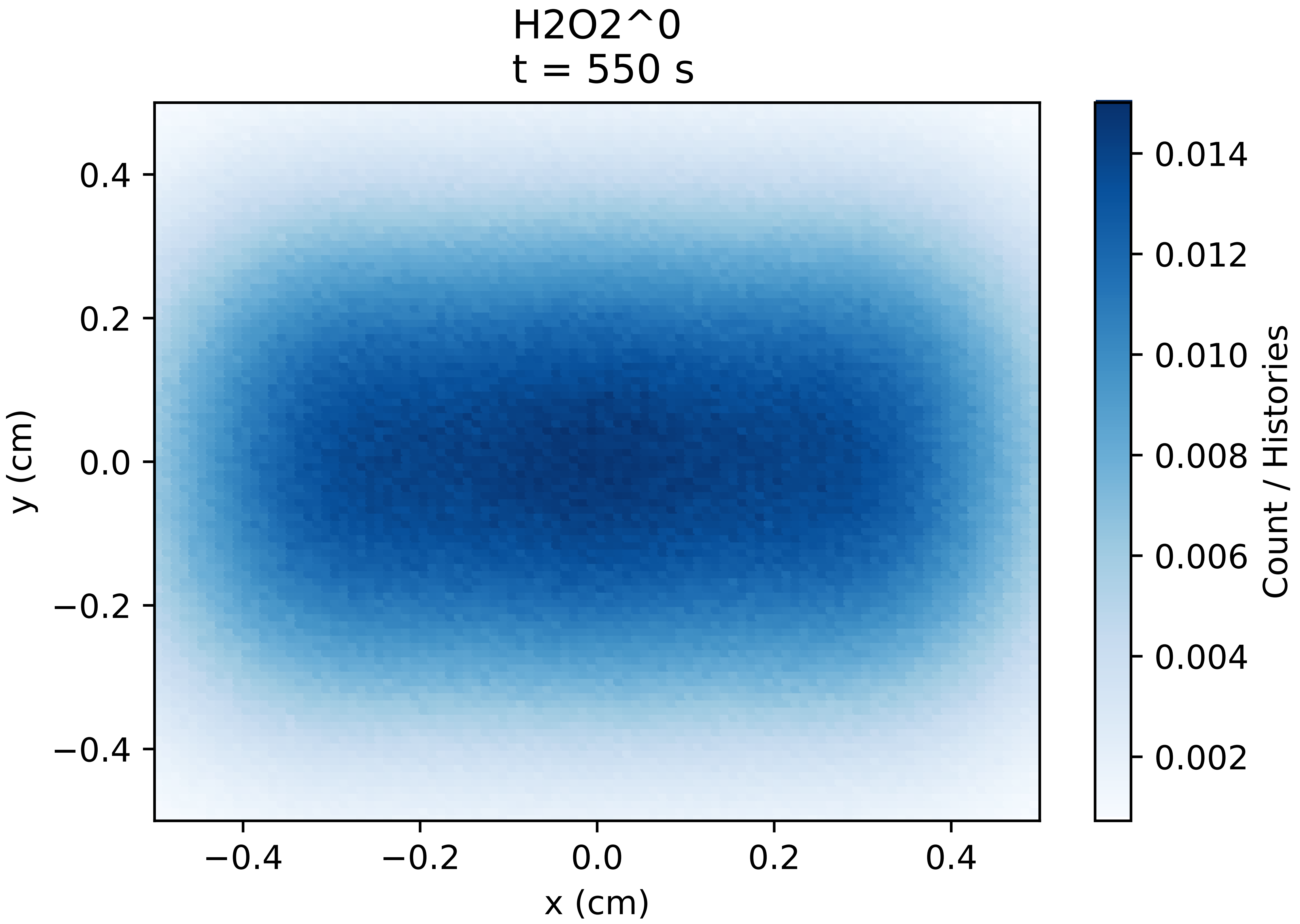
Physical Limits of H_2O_2 range

- Time to achieve homogenous concentration will depend on **valley width**.
- Type of SFRT may influence the impact that H_2O_2 has.

Physical Limit of H_2O_2 range

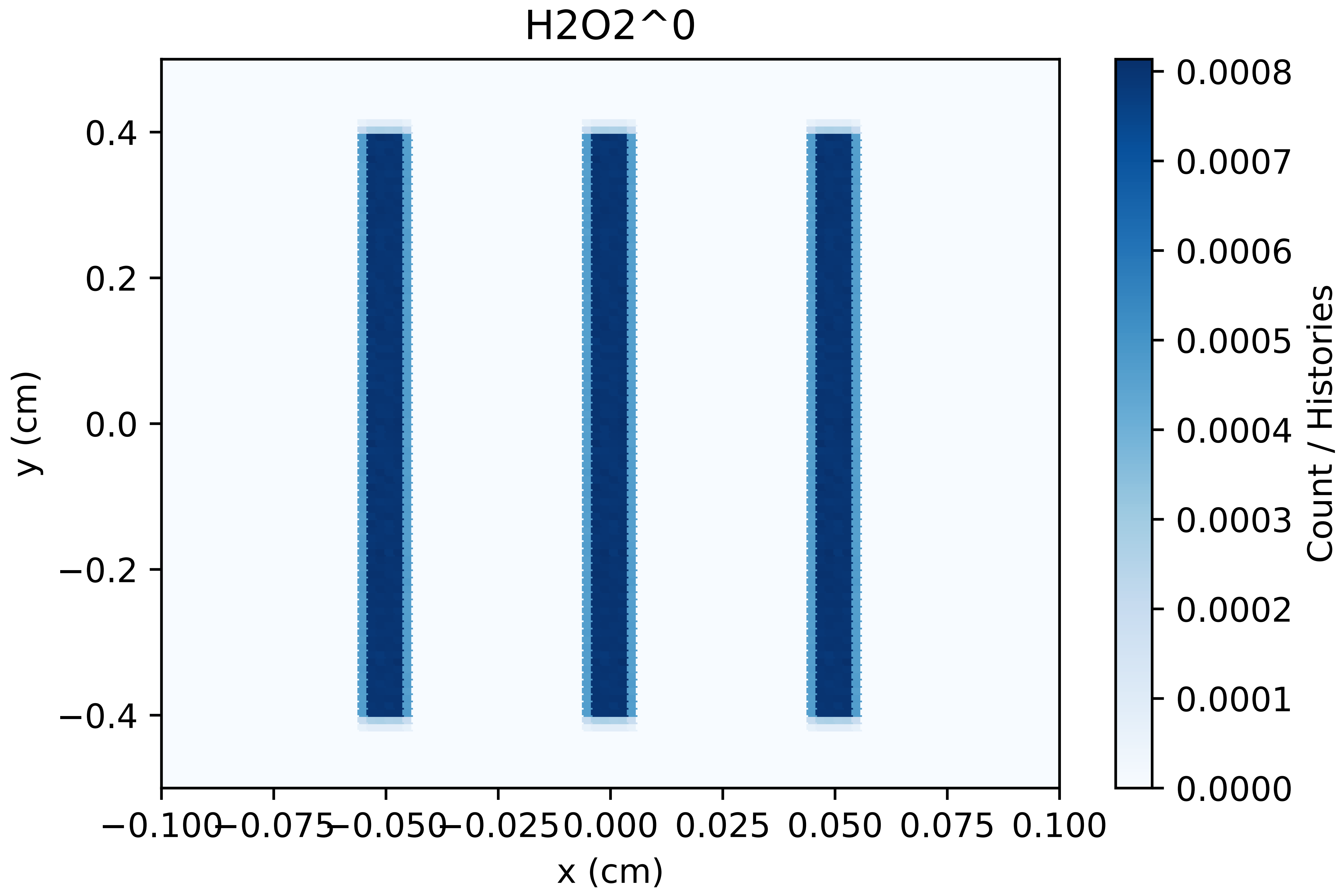
- T. Masilela —> **Minibeam -** size: 0.4 x 6 mm^2 ; ctc: 3.2 mm

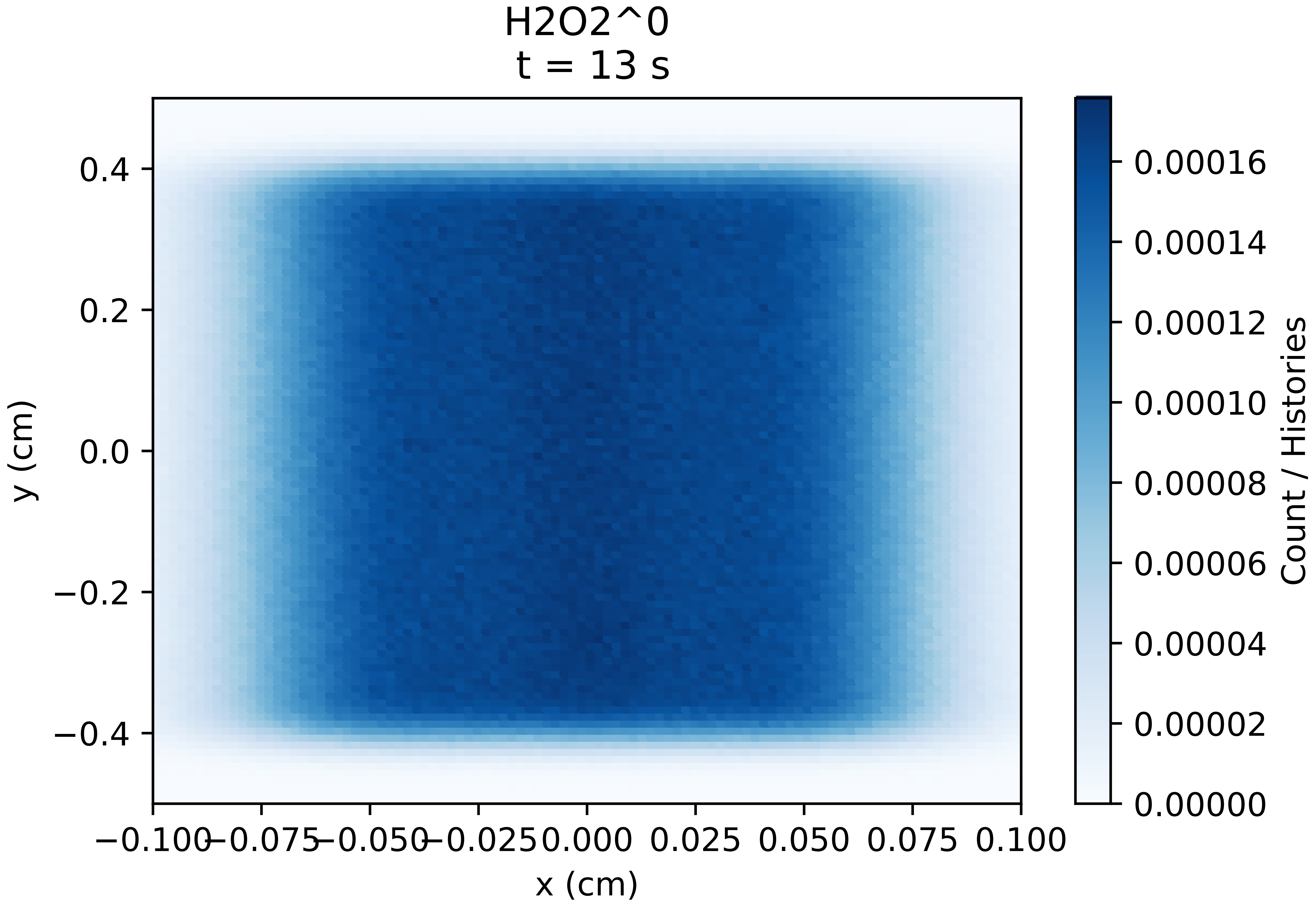




Physical Limit of H_2O_2 range

- J. McGarrigle —> **Microbeam -** size: 0.1 x 8 mm^2 ; ctc: 0.5 mm





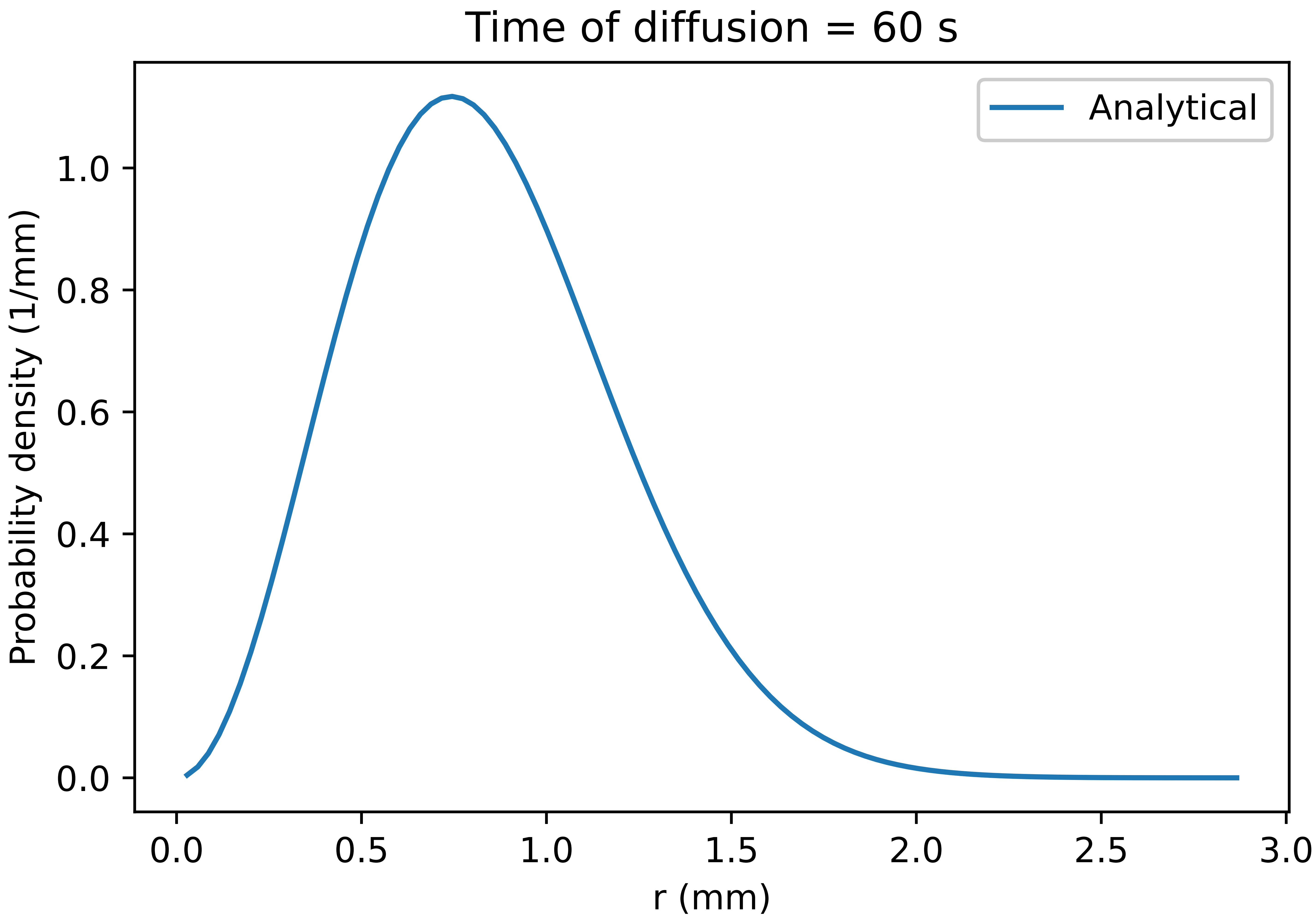
Physical Limit of H_2O_2 range

- Pdf for distance travelled by H_2O_2 after some time.

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

- For homogeneous valley coverage: $\bar{r} \sim VW$

- Condition satisfied for several cases.



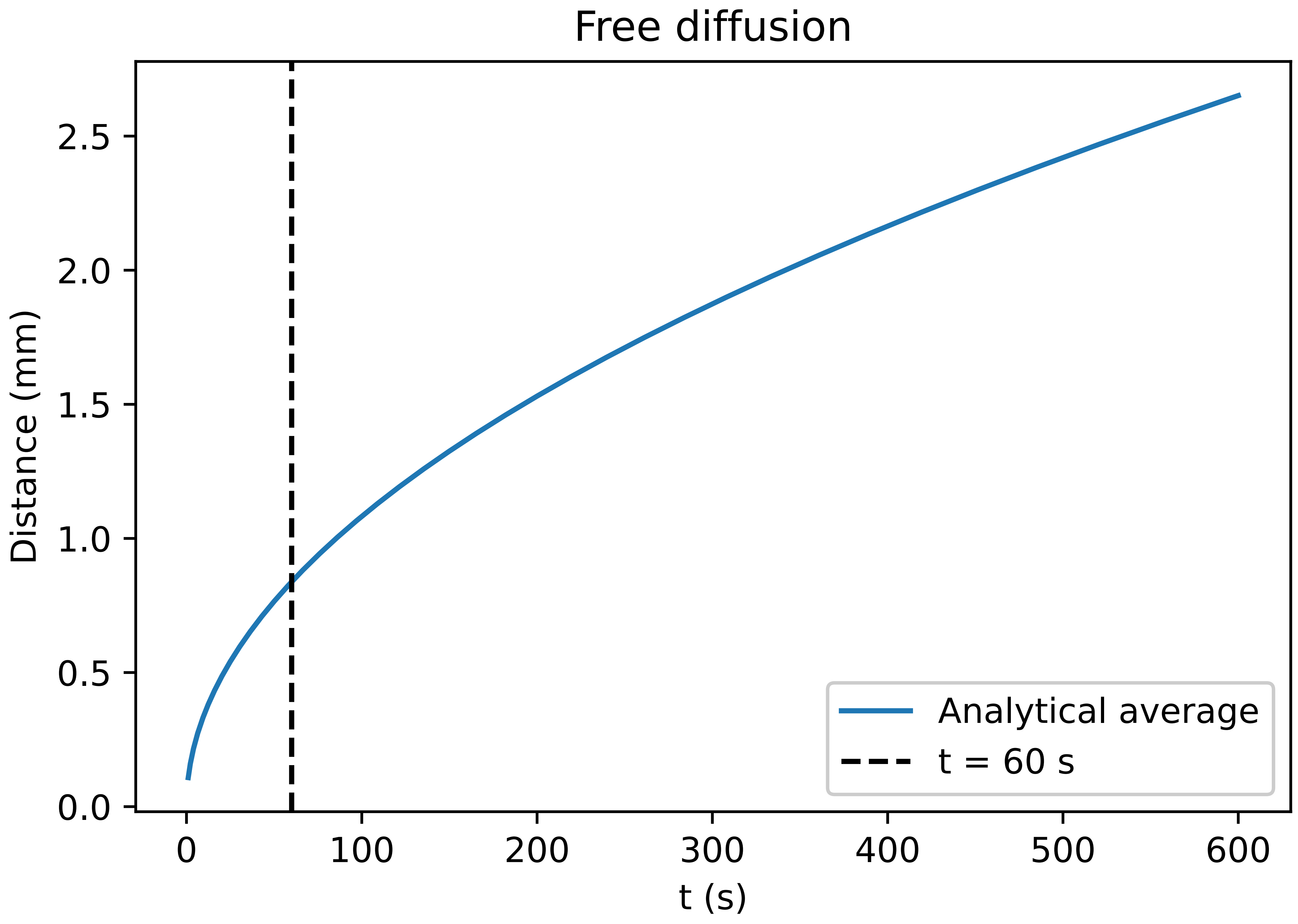
Physical Limit of H_2O_2 range

- Analytical probability density function:

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

- Average can be calculated analytically.

$$\bar{r}(t) = 4\sqrt{\frac{Dt}{\pi}}$$



H_2O_2 as RIBE Signalling Agent

- Short half-life: ~50 ms [Orrico et al., 2022], 2.2 s [Ledo et al., 2022]

- "May give rise to long-lived radicals that have half-lives of minutes to hours" [Deckrock et al., 2017].

- We studied a possible mechanism for this phenomenon involving Ca^{2+}.

Cell Models for the Bystander Effect

- There is a lack of experimental quantitative data on RIBE agent production.

- Reviewed models for cell experiments involving RIBE which do not require specific concentrations as input:
    1. Matsuya et al. 2018
    2. McMahon et al. 2013

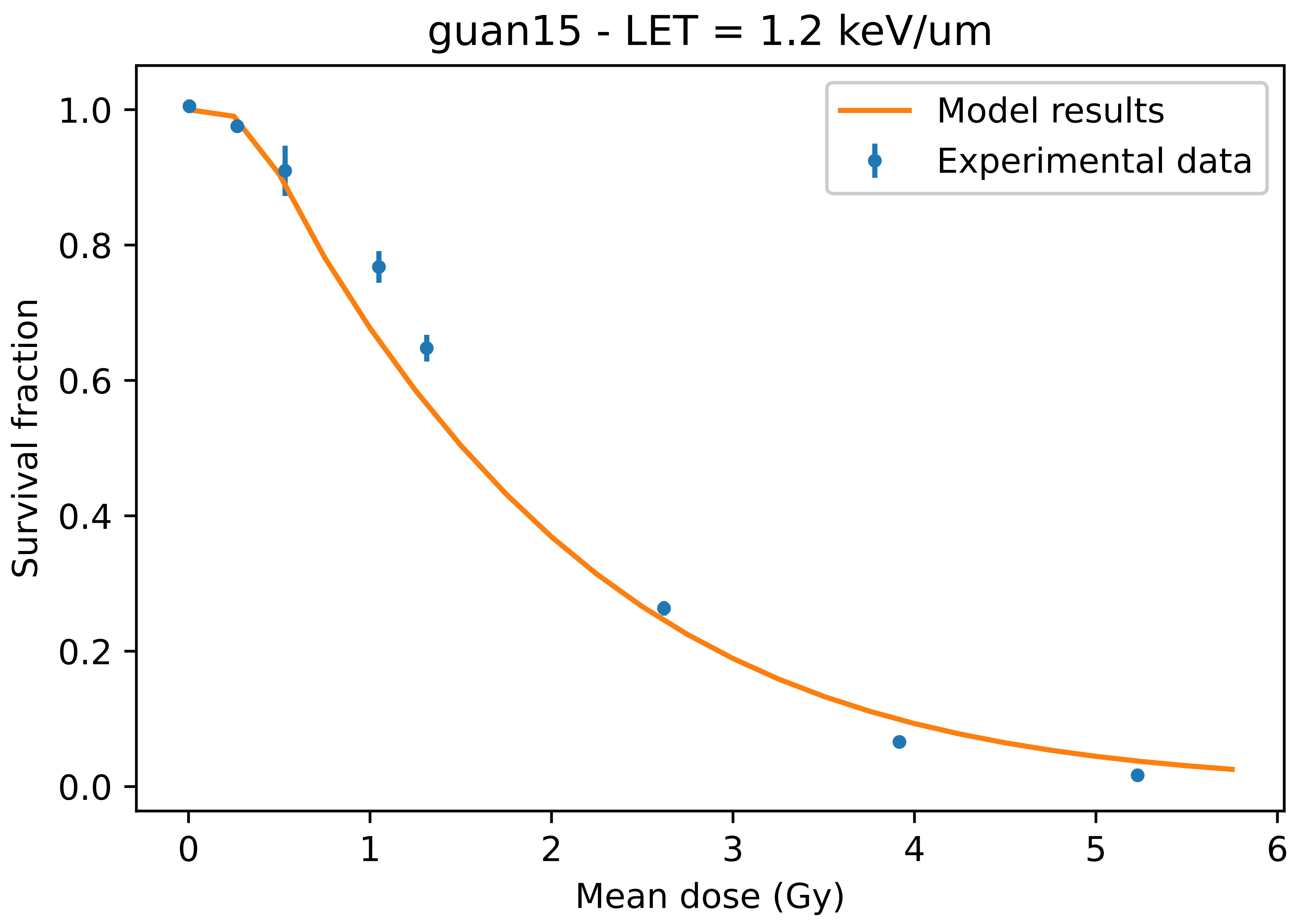
Results McMahon et al. 2013

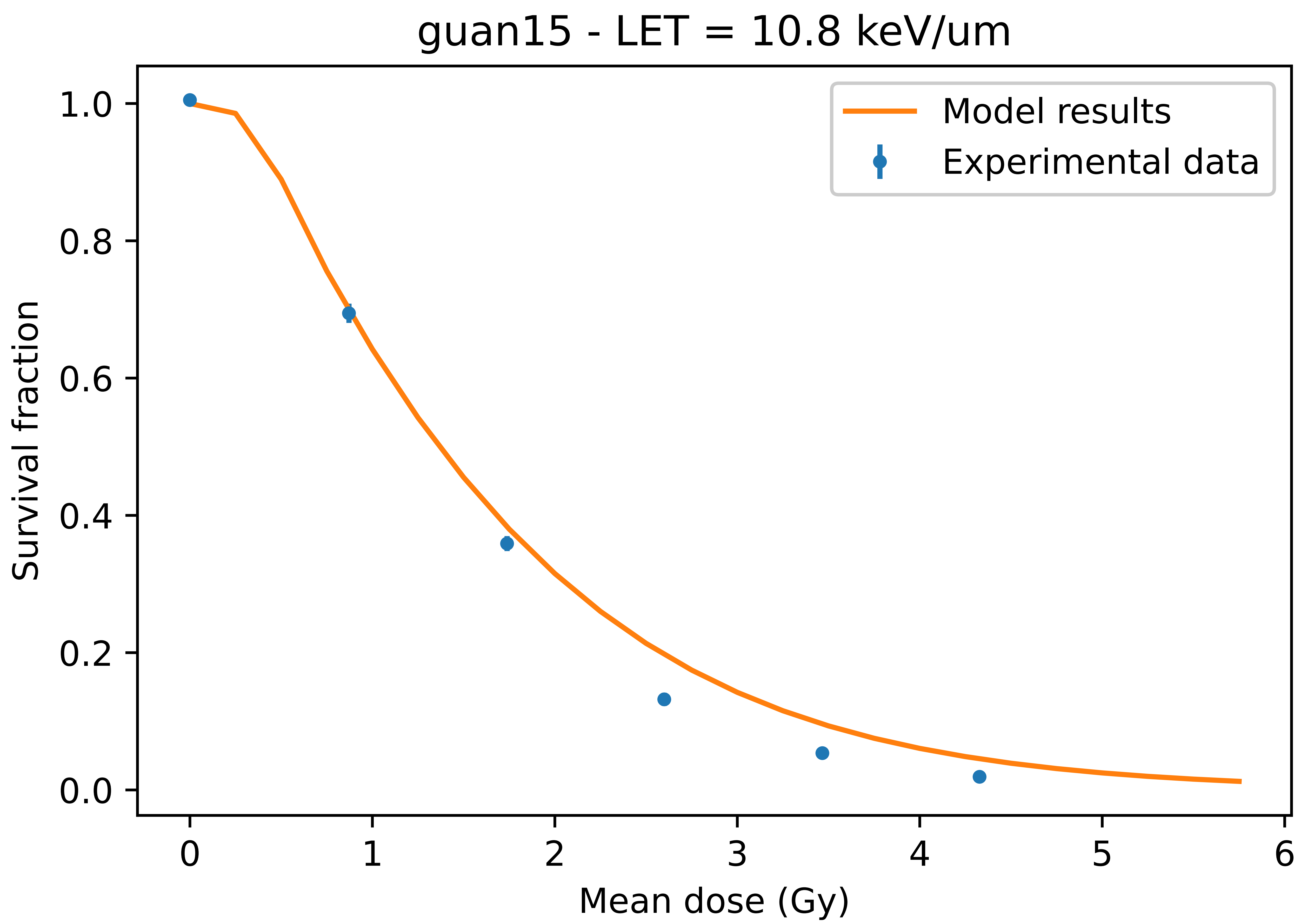
- Model is originally applied to 3 examples: uniform irradiation, media transfer experiments, partial irradiation.

- Originally developed for photons, adapted it to protons.

- Managed to use this model for proton cell **uniform irradiation** experiments [Guan et al. 2015].

Results McMahon et al. 2013





Prospects

- Use McMahon 2013 for other proton irradiation settings.

- Try to include our studies on signal transport in this model and remove fitting parameters.

- Research experimental data on FaDu RIBE (signals and their production).

Summary

- Simulated ROS generated after irradiation.
- Analysed the behaviour of H_2O_2 after $t > 10^{-6}$ s including removal.
- Compared how beam arrangement can influence H_2O_2's impact.
- Found model for cells survival including RIBE, suitable for our experiments.

Extra Slides

References

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- [Orrico et al., 2022] The permeability of human red blood cell membranes to hydrogen peroxide is independent of aquaporins. Journal of Biological Chemistry, 298(1):101503.
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- [Zhang et al., 2023] A theoretical study of h2o2 as the surrogate of dose in minibeam radiotherapy, with a diffusion model considering radical removal process. Medical Physics, 50(8):5262–5272.

Ca^{2+} Signalling in RIBE

- Important signalling species.
- Generated during all sorts of irradiation.
- Positive feedback loop with ROS.
- Ca^{2+} -waves phenomenon [Deckrock et al., 2017].

- ➡ Quantity generated by direct radiation or by ROS?
- ➡ Removal?
- ➡ Half-life?

Other Research Not Included

- Study of Model for Transport I done for other radiolysis products.
- Other Model for Transport studied, has advantages over Model I.
- Found k values from experimental data.
- Study of homogenous coverage done for several beam arrays.
- Reviewed several Ca^{2+} transport models and its impact on RIBE.

Cell Models for the Bystander Effect

- **Matsuya, Y.**, Sasaki, K., Yoshii, Y. et al. Integrated Modelling of Cell Responses after Irradiation for DNA-Targeted Effects and Non-Targeted Effects. Sci Rep 8, 4849 (2018). https://doi.org/10.1038/s41598-018-23202-y

- **McMahon, S. J.**, Butterworth, K. T., Trainor, C., McGarry, C. K., O'Sullivan, J. M., Schettino, G., Hounsell, A. R., & Prise, K. M. (2013). A kinetic-based model of radiation-induced intercellular signalling. PloS one, 8(1), e54526. https://doi.org/10.1371/journal.pone.0054526