Modeling spatio-temporal receptor/ligand-interaction in living cells

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1. Introduction

Exposure to environmental contaminants can lead to a complex cellular response, including toxic effects that might even be involved in carcinogenesis and immunosuppression. Unraveling the underlying mechanisms is essential not only for a comprehensive understanding of such processes but might help to develop new strategies for therapy and prevention. Since biological experiments are often expensive and the number of different conditions and time points is limited, simulations of such intracellular processes constitute an essential tool. Such simulations not only allow the prediction of a response e.g. at an arbitrary time point, but enable the identification of the primary factors that determine the cellular response to contamination.

2. Geometry reconstruction

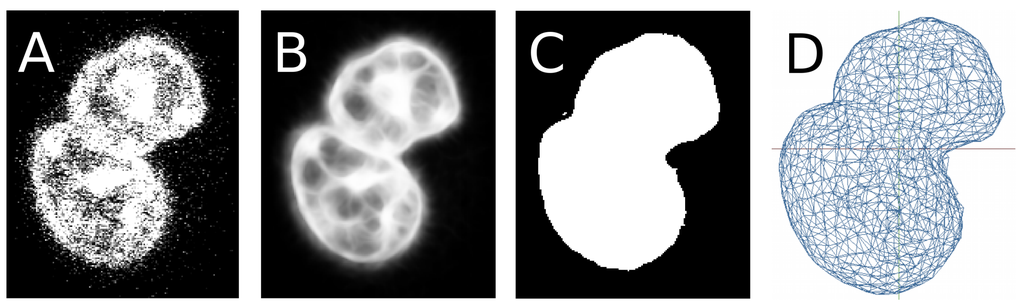

Fig. 1: Steps of geometry reconstruction using NeuRA2. (A) Normalization, (B) Filtering, (C) Segmentation, and (D) Mesh generation.

- 3D stacks imaged by confocal laser scanning microscopy
- Neuron Reconstruction Algorithm (NeuRA2, Fig. 1) used to reconstruct cytoplasm and nucleus (Fig. 2) of various cell lines
- 100 randomly sampled metabolizing units added (Fig. 2)

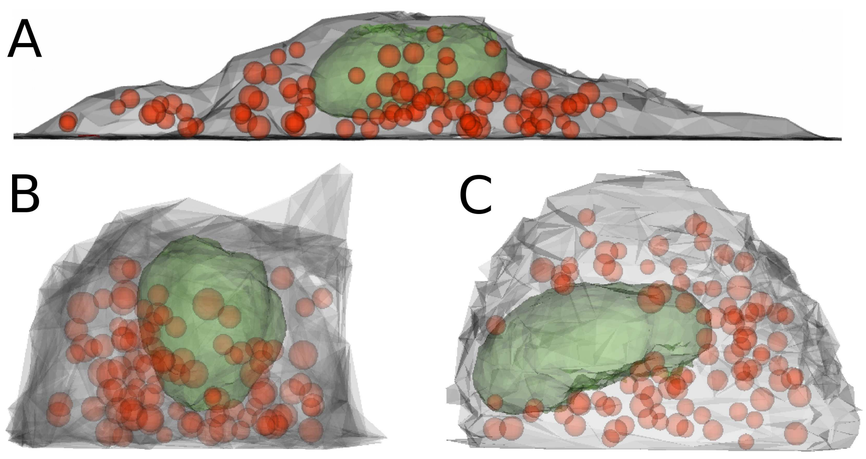

Fig. 2: Reconstructed cell geometries of (A) tao BpRc1, (B) Hepa-1c1c7, and (C) A549 cell line: Plasma membrane (gray), nucleus (green), and randomly sampled metabolizing units (red).

3. Parameter estimation

- diffusion coefficients D and reaction rates k measured by FRAP experiments
- measurements for cytoplasm and nucleus under different conditions (concentration of contamination & time after exposure)
- inversion of parameters using various model types [1, 2]

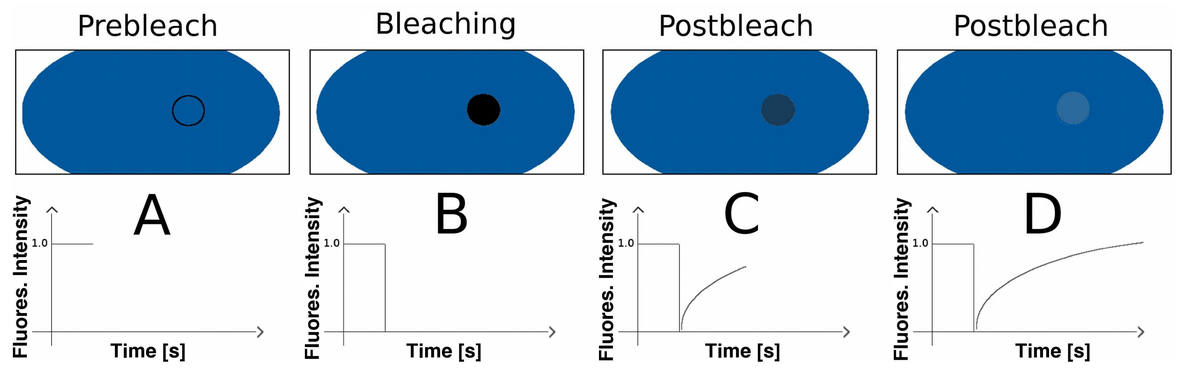

Fig. 3: Concept of FRAP experiments.

Model functions:

n vacant binding sites:

$$F + S_{\mathsf{i}} \underset{k_{\mathsf{off_i}}}{\overset{k_{\mathsf{on_i}}}{\rightleftharpoons}} B_{\mathsf{i}} \quad , \ \mathsf{i} = 1 \ldots n \qquad .$$

where F represents the unbound (free) fraction, S_{i} the vacant binding sites and B_{i} the bound fraction.

- Pure Diffusion Model [2]
- Reaction Dominant Model (n BS)[2]
- Reaction Diffusion Model with Single Diffusion (n BS)[2]
- Reaction Diffusion Model with Multiple Diffusion (n BS)[1]

4. Simulation

- particle based simulation approach using (I) reconstructed geometries and (II) estimated diffusion coefficients and reaction rates
- constant amount of contaminant outside of the cellular domain over time
- no flow from inside to cellular exterior and from nucleus to cytoplasm
- contaminants captured and degraded in metabolizing units

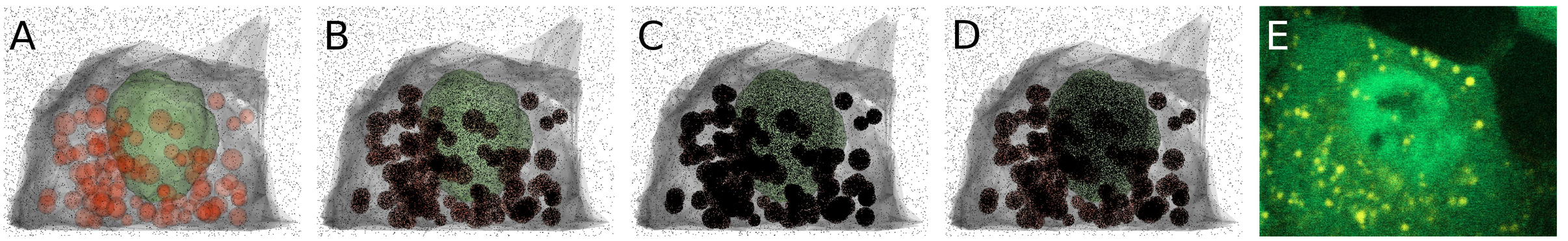

Fig. 4: Contaminants' interaction and distribution using particle based simulation approach with underlying diffusion coefficients and reaction rates estimated by FRAP and reconstructed geometries by NeuRA2. Distribution of contaminants (A) at exposure time, (B) 5 min, (C) 15 min, and (D) 30 min after exposure. (E) Observed contaminant (yellow) and receptor (green) distribution in real Hepa-1c1c7 cell after 30 min.

- simulated distribution patterns (Fig. 4A-D) comparable to contaminant and receptor distribution observed in real cells after 30 min (Fig. 4E)
- study of impact of influencing factors e.g. amount of metabolizing units, degradation scheme, and cell geometry on cellular response to contamination

[1] J. Mai, S. Trump, R. Ali, R. L. Schiltz, G. Hager, T. Hanke, I. Lehmann, and S. Attinger, "Are assumptions about the model type necessary in reaction diffusion modeling?- a frap application," *Biophys. J.*, vol. 100, no. 5, pp. 1178–1188, March 2011.

[2] B. L. Sprague, R. L. Pego, D. A. Stavreva, and J. G. McNally, "Analysis of binding reaction by fluorescence recovery after photobleaching," *Biophys. J.*, vol. 86, pp. 3473–3495, June 2004.

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