Modeling Motion of Contaminant BaP in Cytoplasm

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1. Introduction

The response of cells to contaminant stressors like nicotine is of great importance for human health. The focus of the project is to model the whole pathway of contaminants until the entrance into the nucleus. The long term goal of the project is to understand the influence of contaminant molecules on biological cell functions. Our first step is to model the motion of the contaminant Benzo[a]pyrene BaP within the cytoplasm. To achieve this goal, the cell culture surrounded by the fluorescent contaminant is imaged by a laser microscope. Filters and contour extracting algorithms are used to extract the cell geometry. Finally the movement of the contaminant is modeled using reaction-diffusion-equations and random-walk-processes.

2. Methods & Materials

Motion of unbound and bound particles

motion of receptor-bounded complex more directed towards cell nucleus than motion of free molecules

- unbounded as Random-Walk-Process[3]: probability of all jump directions are the same

$$P\left[(x_{t+1}, y_{t+1}) = (x_t \pm 1, y_t \pm 1)\right] = \frac{1}{4}$$

- bounded as Random-Walk-Process with drift[3], [1]: step in preferred direction is more probable than a step in the opposite

$$P[x_{t+1} = x_t + s_t] = p$$
$$P[x_{t+1} = x_t - s_t] = 1 - p$$
$$\text{whereas:} \quad s_t = \text{Sign}[x_{Dir} - x_t] = \begin{cases} 1 & , x_{Dir} > x_t \\ 0 & , x_{Dir} = x_t \\ -1 & , x_{Dir} < x_t \end{cases}$$

Association and Dissociation

compounds can unbind and free particles can be bind[2], [4]

- $B_t = const.\ \forall t$: fraction of bounded particles at time t
- BT: mean binding time
- k_{on}: rate of binding molecules per timestep (association)
- k_{off}: rate of unbinding molecules per timestep (dissociation)

$$k_{on} = \frac{B_t}{BT \cdot (1 - B_t)} \qquad \text{and} \qquad k_{off} = \frac{1}{BT}$$

Simulation of FRAP experiments

- Fluorescence Recovery After Photobleaching (FRAP) experiments as application of motion-model
- FRAP is a method of confocal laser scanning microscopy (cLSM)
- assignment of diffusion and binding parameters by these experiments[5]

4. Discussion & Future work

The influences on the recovery of FRAP experiments of directed particle movement and the possibility of particle capture in cell membranes are rarely described in the literature. In contrast to the standard figures of FRAP data found in the literature, particle capture by the cell nucleus causes a zero limit in the recovery as displayed in Fig. (6) (solid lines).
Further, the recovery is fastened and shifted to smaller values

- by definition of a higher probability value for steps towards the sink
- by definition of a higher mean binding time
- by definition of a higher fraction of bounded particles

In the future we plan to derive an analytical solution for the FRAP data to change this qualitive conclusions into quantitive. This solution will allow to infer all parameters which describe the diffusion and binding processes from real FRAP data. Therefor different diffusion coefficients have to be modeled in a next step.

3. Results

Motion of unbound and bound particles

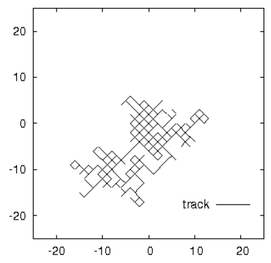

Fig. 1: free particle

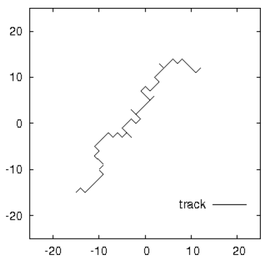

Fig. 2: bounded particle

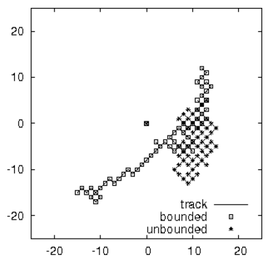

Fig. 3: free and bounded particle

Association and Dissociation

- implementation of the fact that unbounded contaminants can be bounded and the other way around
- track is combination of directed and undirected walk (see Fig. 3)

Simulation of FRAP experiments

1. Simulation with particles which are unbounded, walk undirected and can not enter the nucleus (see Fig. 4)
2. Simulation with particles which are bounded, walk with a drift and captured by nucleus (see Fig. 5)

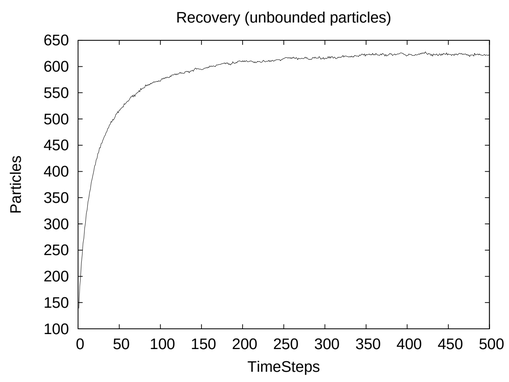

Fig. 4: only unbounded particles

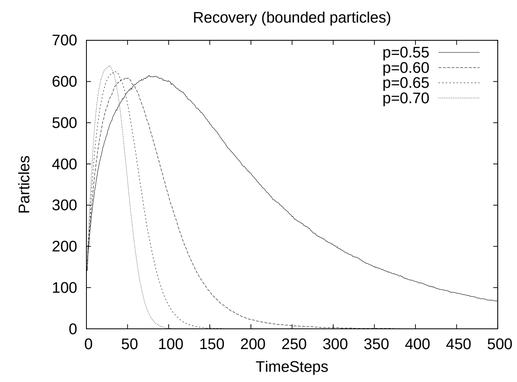

Fig. 5: only bounded particles

3. Simulation with particles which can bind and unbind by varying some parameters (first only the bounded fraction can be captured, second all particles can be capured by the nucleus) (see Fig. 6)

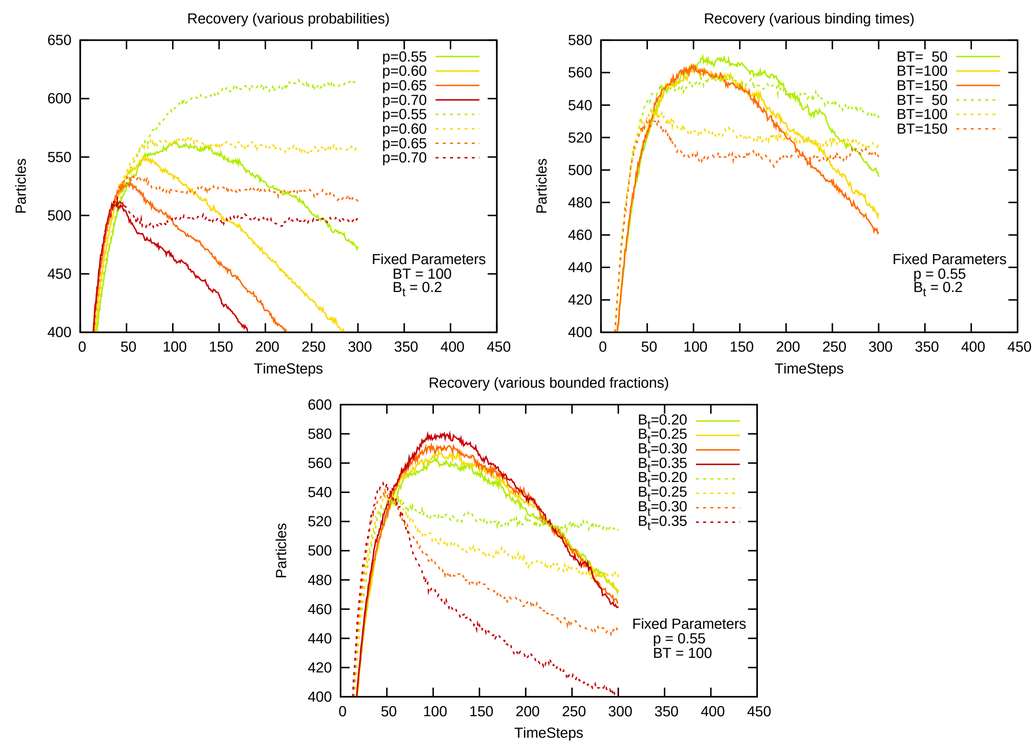

Fig. 6: FRAP simulations: capture of all particles (solid line) and capture of bounded particles (dotted line)

References

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[3] C. P. Fall, E. S. Marland, J. J. Tyson, and J. M. Wagner, *Computational Cell Biology*. Springer Verlag, 2005.

[4] R. D. Phair, S. A. Gorski, and T. Misteli, "Measurement of dynamic protein binding to chromatin in vivo, using photobleaching microscopy," *Methods in Enzymology*, vol. 375, pp. 393 – 414, 2004.

[5] M. J. Saxton, "Anomalous subdiffusion in fluorescence photobleaching recovery: A monte carlo study," *Biophysical Journal*, vol. 81, pp. 2226 – 2240, October 2001.

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