Solute and cells - aspects of advection-diffusion-reaction phenomena in biochips

The results in this thesis are part of the work carried out during the author's doctoral studies. Funding for the project has been provided by the Programme Commission on Strategic Growth Technologies, the Danish Agency for Science, Technology and Innovation (grant no. 2106-08-0018 'ProCell'), and the overall title of the project is Solutes and cells — aspects of advection-diffusion-reaction phenomena in biochips. The work has consisted of several projects focusing on theory and to some extend analysis of experimental data, with advection-diffusion-reaction phenomena of solutes as the recurring theme. Presented in this thesis is selected parts of the results obtained, which in some cases have also been published in peer-reviewed journals or presented at conferences and meetings, as listed in Sec. 1.2. The studies of the distributions of solutes are motivated by microbiological phenomena in which cells quantitatively interpret the proximal concentration of specific solutes, and integrate this to achieve biological functions. In three specific examples, the author and co-workers have investigated different aspects of the influence of advection, diffusion and reaction on solute distributions, as well as the biological function that is achieved from these varying solute concentration fields. While the basic equations of solute transport have been known for one and a half century, the novelty of cell-controlled high-resolution experimental data on the biological systems obtained from e.g. biochip microfluidics combined with the large variability between different biological systems means that many fundamental effects are yet to be revealed. In the first subproject, we provide the first thorough theoretical description of the Taylor–Aris dispersion of solute concentration from the combined effects of time-dependent advection and diffusion. Combining Aris’s method of statistical moments with Fourier expansion in time and expansion of all spatial dependencies in diffusion eigenmodes, we obtain closed-form expressions for the dispersion that apply to any constant channel crosssection of any initial distribution. These physically transparent expressions are given in terms of the fundamental processes of fluid velocity and solute diffusion causing the dispersion, which allow for both general and specific analyses. We identify a number of novel effects highlighted by different regimes of linear and non-linear response to any driving frequency, possible order-of-magnitude increases of the dispersion in certain regimes, and apparent transient anomalous diffusion, which are all shown to naturally arise from the competing physical processes of solute diffusion, momentum diffusion and local velocity variations. In the second subproject, we study the influence of neighboring cells in shaping the iii Abstract migration of the individual cell by a combined experimental and theoretical approach. Using highly controlled microfluidic cell to obtain culture high-resolution image data with subcellular resolution of migrating cells at various densities, we find strongly fluctuating instantaneous single-cell speeds but similar single-cell speed distributions and directional autocorrelation series among the cells. Furthermore, increasing density only influences the directionality and not the speed. To understand these findings, we analyze the membrane protrusions known as pseudopodia, that the cells use for generating locomotion. The statistics of these pseudopodia show that the cell only controls where these form, but not their behavior after formation. In addition, we find evidence of a cell-secreted chemical that also influences pseudopod formation, and pseudopod formation is therefore a diffusion-reaction process underlying cell migration. We further investigate these dependencies by formulating and using a conceptually simple physics-based model that emphasizes pseudopod-driven motility of the single cell and takes our experimental pseudopod statistics as input. Contrary to previous models aiming at investigating specific traits, ours correctly predict the vast majority of disparate migration features (speed, directionality and sampled space) for each cell in a population, and furthermore also correctly capture the dependencies on density. This shows that the varied single-cell behavior including the overall modulations imposed by density arise as a natural consequence of pseudopod-driven motility in a social context. The final subproject concerns the combined effects of advection, diffusion and reaction of several solutes used by adipose-derived stem cells to make the decision to differentiate into terminal fat storing cells (adipocytes). Details of the signaling underlying the differentiation decision was investigated by combining microfluidic perfusion experiments with several different theoretical approaches. Contrary to current beliefs, we provide strong evidence that single-cell differentiation requires a signal secreted by all cells. Furthermore, a non-trivial secretion rate of this critical signaling species, combined with advection, diffusion and reaction results in complex responses as cell density and flow rate are varied. Since this work calls into question the basics of the differentiation procedure, many open questions have emerged for future studies.

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