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Abstract. In this chapter we present a model framework for multi-cellular simulations which is built on conceptual analogies to colloidal particles. Cells are approximated as homogeneous isotropic elastic sticky objects, capable of migrating, growing, dividing and changing orientation. A cell is parameterized by biomechanical, cell-kinetic and cell-biological parameters. Each model parameter can in principle be determined experimentally. We show some simulation results for in-vitro systems and discuss the effect of model variants on simulated multi-cellular growth phenomena. The aim of this chapter is to provide an introduction and overview of the algorithms, technical concepts and the framework necessary to perform equivalent computational simulations with different model variants.

1. Introduction

Many experimental observations and their analysis by mathematical models indicate that many aspects of cell behavior, in particular in a culture medium, may well be approximated if one assumes that cells behave as colloidal particles. Isolated cells in suspension and in the absence of stimuli such as morphogens perform a random movement [1, 2]. This movement can perfectly be approximated by the same Fokker-Planck, or Langevin equation that is used to model the dynamics of colloidal particles. As a response on a chemoattractant cells perform a directed movement (e.g., [3, 4]). The collective moment of cells can be shown to follow Keller-Segel-type equations if one assumes that the movement of each individual cell follows a Langevin-equation of motion consisting of a random contribution and a term triggered by chemotaxis [5]. The adhesion forces of S180 cells have recently been shown to be well fitted by the Johnson-Kendall-Roberts-model (JKR) as long as no rupture of the cytoskeleton occurs [6]. The JKR-model describes the forces between homogeneous isotropic elastic adhesive spheres ([7] and refs.
therein). Based on the interpretation of cells as physical particles Beysens et. al. [8] derived a fluctuation-dissipation-like relation for cells, in analogy to Brownian particles. However, cells are not Brownian particles. For example, on a solid surface they perform an active movement rather than being passively pushed by random collisions with particles of a liquid suspension. So already for those observations that indicate a formal analogy between cells and colloids, the interpretation of the model parameters cannot be the same in both systems. Cells can also grow and divide in a way that colloidal particles cannot, and, more importantly, they can control and modify their properties, shape and their state of action by a complex intracellular machinery, which also colloidal particles cannot do. Moreover, cells may be committed to a strict genetic program which precisely determines the change of their parameters. Such a strict genetic program is found for example in early animal development.

However, many observations in unstructured cell populations and even in some intermediate phases in development can be explained by models that rely basically on the colloidal particle concept with only modest extensions i.e. they do not need complex differentiation or regulation processes. Here we present the basic framework and a number of model variations that underly models of multi-cellular phenomena in experimental in-vitro settings and selected in-vivo observations. We have used the different model variants to model aspects of monolayer cultures (e.g. [9, 10, 11, 12, 13, 14, 15, 16]), multi-cellular spheroids [17, 14, 16], epithelium such as intestinal crypts [18, 19] and systems in early development [20, 21, 16].

The chapter is organized as follows. Next we introduce a set of basic model assumptions and a number of variants designed to model the growth of monolayer populations in-vitro. We directly introduce some model variants. As the next step we turn the model assumptions into a computer algorithm and after this into a mathematical framework. Subsequently we present selected simulation results and finally close the article by a discussion. The discussion refers briefly to other methods described in this book, but this article focuses almost solely on center-based off-lattice models since other methods are explained in the other chapters of this book. The article is largely based on refs. [14, 13, 16] where further results may be found.

2. The model framework

2.1. Biological background

We demonstrate the modeling framework for cells growing in tissue cultures on a flat substrate. The cultures are used to study multi-cellular systems under well-defined conditions. In monolayer cultures cells usually grow on a flat surface covered by proteins, growth factors etc. [22, 23, 24, 25]. After cells have been seeded in culture they attach to the surface and subsequently migrate, grow and divide. Normal cells stop dividing at confluence that is, once they cover the floor of the culture dish. This is called contact inhibition of growth [26]. Different from normal