A stochastic model of the cell movement of *Dictyostelium discoideum* in the absence of external cues F. Wegner, Masterarbeit (gemeinsame Betreuung mit Prof. Dr. W. Huisinga), Universität Potsdam (2012).

Moving cells are a major part of many biologically crucial processes. Epidermal cells move towards lesions during wound healing, precursor cells rearrange to form organs and tissues during development, and neutrophils migrate towards sites of bacterial infection as part of the immune response [1], to name only a few examples.

Migration in general is a common process in both pro- and eukaryotes as well as unicellular and multicellular organisms. This has led to the evolution of various forms of movement, including swimming and crawling. This work focuses on crawling amoeboid cells that move on rigid surfaces. What the examples mentioned above have in common is the directed migration in chemical gradients, called chemotaxis, although other kinds of stimuli exist as well. Key properties of the chemotactic process are directional sensing, polarity and the extension of pseudopodia. Directional sensing refers to the ability to detect temporal and spatial stimuli by counting the receptor occupancy over time or across the cell length. The cells then bias their motility toward or away from a signal source. Polarity is the condition when a cell has developed a functionally distinct front and back [2]. Pseudopod formation was initially thought to occur randomly, but was found to be highly ordered [3].

The molecular machinery behind has been studied extensively. Many of the proteins involved in the receptor-ligand interactions, signaling pathways and cytoskeletal rearrangements are known today [1, 21]. Good cellular models exist describing the roles of these mechanisms during chemotaxis. They are bottom-up approaches and try to understand the macroscopic behaviour by means of microscopic characteristics [4].

A prominent model organism for these kind of studies is *Dictyostelium discoideum*, a eukaryotic soil amoebae that uses chemotaxis as a survival mechanism. Starved cells emit cyclic adenosine monophosphate (cAMP) as a chemoattractant for neighbouring cells. This culminates in the formation of multicellular aggregates to outlast adverse conditions [5]. However, *Dictyostelium* also moves in the absence of external signals. But this undirected motility is far less studied, even though it can be understood as a 'ground state' on which the directed movement is built on, and should be of equal interest [4, 6].

It has been found that cells exhibit a correlated random walk without external cues [71. In a normal random walk, the direction of a step is independent of all previous events. In a correlated random walk, the direction of future movements is correlated with the direction of prior movement. In fact, cells bias their motion by oscillating between left and right turns. Through these zig-zag trajectories, they effectively move persistently in one general direction for longer time periods until losing the direction again [8].

Many phenomenological models have been developed to describe the movement of cells in a top-down approach. Most studies applied a generalized Langevin model to account for the deterministic and the stochastic part of the motion, and investigated the statistical characteristics based on velocity such as its auto-correlation function and power spectrum [6, 9, 10]. While these kinds of models succeed in describing the statistics of cell motion, they fail to account for the vast

heterogeneity present in cell populations. On the other hand, models based on the ordered extension of pseudopodia require detailed data on a fine granular time scale [7, 11].

In the present work, time lapse microscopy recordings of vegetative *Dictyostelium discoideum* cells are analysed with regard to two elementary characteristics: the covered distance between two subsequent time steps and the turning angle relative to the prior direction of movement.

To uncover the relation between displacement and turning angle and how they can be used to identify phases of movement is one aim. This is based on the observation that cells have phases of persistent movement and phases of turns. One can imagine, for example, that in phases of persistence, small turning angles are more frequent. Is the extent of directional changes linked with the amount of translocation in a time step? There is also a high statistical dispersion in the behaviour of cells. A question of interest is therefore whether it is possible to identify subpopulations. A final aim is to find out whether one can use these features to develop a stochastic model that describes the cell motility found in the experimental data, especially with respect to cell heterogeneity.

After an introduction to cell migration in general and the model organism, the theoretical background will be presented including a short review of other phenomenological descriptions of cell migration and an introduction to Markov chains, Hidden Markov models and the concept of Granger causality.

The third chapter deals with the descriptive statistics of the experimental data. It presents details about the data sets, the statistics of turning angle and displacement and their relation. It also deals with the problem of heterogeneity of trajectories.

The results of Chapter 3 serve as a reference for Chapter 4. Here, different approaches to describe cell motility are presented. In the first part, cell motility is modelled as a Markov chain, while the second part explains different approaches to use Hidden Markov models. The results of the realisations are compared with the experimental data and shortly discussed.

In Chapter 5, the results are summarised and discussed together with an outlook on possible future work.