Master's thesis: Mathematical modeling and simulation of the chemotactic movement of neutrophils in inflammatory environments
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The human immune system is essential in protecting the body against harmful agents. If a pathogen enters the body, the immune system relies primarily on particular white blood cells called **neutrophils**. They play a fundamental role after tissue inflammation due to their ability to imprison and degrade pathogens.
Neutrophils identify the correct path toward the inflammatory site while they follow increasing concentrations of inflammatory cytokines; this phenomenon is called **chemotaxis**. To accomplish their defensive task, neutrophils produce high amounts of cytotoxic molecules that require oxygen consumption, called **reactive oxygen species (ROS)**. This process was denoted as the **respiration burst**, and it was described about ninety years ago. Later research on neutrophil activity has confirmed that ROS production is required in various intracellular processes that trigger significant functional responses in neutrophils, such as cell motility.
Mathematical models for chemotaxis have been developed since the 1970s, starting with E. Keller and L. Segel. From that year on, several chemotactic processes were described using this model. Furthermore, mathematical analysis of biochemical processes started at the beginning of the 20th century, when L. Michaelis and M. Menten suggested a mathematical model describing enzyme kinetics in 1913. Their model is still used to describe various biochemical processes due to their dependence on enzymatic activity, as the respiration burst also does.
In this thesis, we derive a mathematical model describing the chemotactic movement of neutrophils in inflammatory environments under the chemoattractant's influence. This was elaborated in collaboration with Dr. Michael Gruber's group (University Medical Center Regensburg), which performed experimental investigations on neutrophil activity. The model includes both the respiratory burst and ROS influence on neutrophil motility; the novel aspect of it consists of the fact that it contains an additional variable in comparison to the Keller-Segel model, namely the concentration of ROS. Thus, the chemotactic sensitivity is not constant as in their model but a function depending on ROS. This aligns with other mathematical models from previous research that include a non-constant chemotactic sensitivity, usually depending on the cells or the chemoattractant.
The resulting model is a fully non-linearly coupled PDE system. Using numerical tools, we performed computational simulations to determine those variables' evolution in time and space. Finally, with the help of the model, we can recover qualitatively the experimental features, particularly that ROS play an essential role in neutrophil motility.
Further upgrades of the resulting model might be to consider additional processes to obtain a more realistic, complete model, for example, the presence of the different priming phases within a cell population or neutrophil death induced by ROS-mediated suicidal NETosis. Besides these mentioned processes, even more pathways and mechanisms occur simultaneously. With the help of such a mathematical model, we can describe that complex interplay more precisely and, therefore, clarify how neutrophils behave when bacterial infection takes place. That knowledge is relevant, e.g., for developing therapeutic strategies to prevent autoimmune activity resulting from persistent neutrophil functionality.