# The Role of Directional Persistence in Neutrophil Chemotaxis: Navigation in Multiple Gradients

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***Abstract* – To combat invading pathogens, neutrophils must efficiently migrate from the vasculature to specific sites within infected tissues. In particular, these cells must be capable of sensing and accurately interpreting a complex mixture of multiple chemotactic signals as they navigate towards their end targets. This coordinated movement may be explained via the combined effect of directional persistence and the spatial integration of local directional signals. Here we demonstrate a stochastic model for neutrophil chemotaxis that captures these characteristics explicitly through an orientation state-keeping variable and a chemotactic bias defined in terms of sensitivities to different chemoattractant species.**

***Keywords* – neutrophil, motility, chemotaxis, chemokinesis, chemoattractant, persistence, sensitivity, chemotactic bias, discontinuous galerkin.**

NEUTROPHILS recruited by infected tissue are likely to encounter complex chemoattractant landscapes consisting of many different chemical signals. To successfully navigate through such environments, cells must integrate and prioritize the signals they receive. Typically, neutrophils prioritize end target chemoattractants over their intermediate (endogenous) counterparts as dictated by an intracellular signaling hierarchy[1], most likely achieved via heterologous receptor desensitization by the dominant agonists. This allows them to find their phagocytic targets efficiently even in the presence of endogenous chemoattractants.

In most settings, however, these end target agonists are quite scarce relative to the endogenous type. Moreover, unlike the former, endogenous agonists are known to signal simultaneously within the cell to produce an integrated response. This allows cells to migrate away from one chemoattractant source towards another against a local gradient, as observed experimentally[2]. By preferentially seeking distant sources, neutrophils may thus respond in stepwise fashion towards sequentially encountered gradients as a means to locate end target sources[3].

While mathematical models of neutrophil chemotaxis in multiple chemoattractant gradients have been proposed[4,5], none have provided a comprehensive rationalization of the observed behaviors in the context of directional persistence and adaptation to proximal sources. We demonstrate that multistep navigation can be recovered by a memory mechanism to track cell orientation if used in conjunction with spatial signal integration scaled by time-independent sensitivity functions derived using kinetic arguments.

## I. SUMMARY

The model consists of two-dimensional position variables that update according to an orientation variable. Orientation is in turn affected by the vector sum of chemoattractant gradients scaled by concentration-dependent sensitivities to each chemoattractant. These deterministic equations are converted to a system of stochastic differential equations (SDEs) to describe the time-dependent state of a single neutrophil. Finally, a macroscopic model is derived by a Fokker-Planck equation corresponding to the SDEs. The resultant partial differential equation is solved using a discontinuous galerkin approach that is suitable for convection-dominated problems.

## II. CONCLUSION

We present a stochastic model for neutrophil chemotaxis in multiple chemoattractant gradients to demonstrate that multistep navigation can be explained simply by time-independent signal processing and memory of past orientation. The model may help elucidate the mechanisms that direct the process of chemotaxis *in vivo*.

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