

# Flow Sensing in Cancer at High Cell Density

Louis Gonzalez<sup>1</sup>, Michael Vennetilli<sup>2</sup>, Nicholas Hilgert<sup>3</sup> and Andrew Mugler<sup>1</sup>

**Abstract**—Autologous chemotaxis, in which cells secrete and detect molecules to determine the direction of fluid flow, is thwarted at high cell density because molecules from other cells interfere with a given cell’s signal. Using a minimal model of autologous chemotaxis, we determine the cell density at which sensing fails and find that it agrees with experimental observations of metastatic cancer cells. To understand this agreement, we derive a physical limit to autologous chemotaxis in terms of the cell density, the Péclet number, and the length scales of the cell and its environment. Surprisingly, in an environment that is uniformly oversaturated in the signaling molecule, we find that sensing not only can fail, but can be reversed, causing backwards cell motion. Our results get to the heart of the competition between chemical and mechanical cellular sensing and shed light on a sensory strategy employed by cancer cells in dense tumor environments.

## I. BACKGROUND AND MOTIVATION

The first stage of cancer metastasis is invasion, where tumor cells migrate toward vessels in the body. Migration is guided by various environmental cues, including fluid flow. Some cells detect the flow direction by autologous chemotaxis, in which molecules are secreted, biased by the flow, and detected again by the cell [1]. In tumor environments, high cell density poses a challenge to autologous chemotaxis: in addition to detecting its own secreted molecules, a cell will detect molecules secreted by nearby cells. The disruption of autologous chemotaxis at high cell density has been demonstrated experimentally with metastatic cancer cells [2]. However, the physical mechanisms of autologous chemotaxis and its disruption at high cell density are still poorly understood.

## II. RESULTS

We used COMSOL to numerically solve the fluid-flow and advection-diffusion equations describing autologous chemotaxis (Figure 1 inset). For a given cell density, in a confined environment with dimensions consistent with the experimental microfluidic device [2], our numerical solution provides the anisotropy in the molecule concentration surrounding a given cell. We found that the anisotropy falls off at a characteristic cell density that is consistent with the experimentally observed densities at which cells do and do not migrate with the flow [2] (Figure 1, low and high, respectively).

To explain this agreement, we derived a physical limit to autologous chemotaxis using a mean field approximation.

<sup>1</sup>Department of Physics and Astronomy, University of Pittsburgh, Pittsburgh, PA. Emails: gonzalez@pitt.edu, andrew.mugler@pitt.edu

<sup>2</sup>AMOLF, Amsterdam, Netherlands. Email: m.vennetilli@amolf.nl

<sup>3</sup>Department of Systems Biology, Harvard Medical School, Boston, MA. Email: nhilgert@g.harvard.edu

The limit predicts the falloff density as a function of the Péclet number and the cell and confinement length scales. The predicted scaling of anisotropy with cell density matches the numerics, and the falloff density agrees within a factor of two (Figure 1).

Finally, we predict that in the presence of an oversaturated amount of background ligand, the anisotropy detected by a cell can actually reverse directions, causing backwards migration. This reversal is distinct from a second reversal mechanism that relies on direct mechanosensing of the fluid flow [2]. Both mechanisms may contribute to invasion *in vivo*.

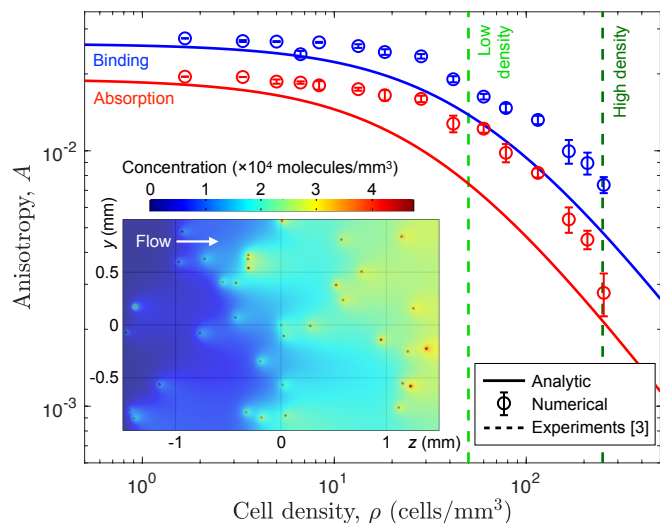


Fig. 1. Anisotropy in concentration surrounding the center cell as a function of cell density, for our numerical solution (see inset) and analytic approximation. Experimental densities at which cells do (low) or do not (high) migrate with the flow [2] are consistent with high and low anisotropy values from the theory, respectively.

## III. CONCLUSION

We elucidate the physical mechanisms underlying a remarkable form of flow detection in cancer metastasis and how this detection process breaks down at high cell densities, which is critical for the crowded tumor environment.

## REFERENCES

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