Adhesion dynamics of Circulating Tumor Cells: data analysis through mathematical modeling

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Résumé

The spread of metastases is a phenomenon responsible for about 90% of deaths in cancer patients. A crucial step is the invasion of tumor cells from the primary tumor into the bloodstream and their dissemination in the body. These cells are called circulating tumor cells (CTCs). A small proportion of CTCs may survive and extravasate from a blood vessel and then form secondary colonies or metastases. Prior to extravasation, we can observe a decrease in the speed of CTCs and the arrest on the vessel wall due to the presence of two glycoproteins that establish adhesion bonds (CD44 helps create the early adhesion and ITGB1 stabilizes the bonds created). In collaboration with a team of biologists from Strasbourg, we aim to characterize the behavior of CTCs in the blood circulation under the influence of hemodynamic forces and adhesion forces using in vitro measurements obtained with a microfluidic device.
Using a CSRT tracker, the trajectories and velocities of 137 individual cells were extracted from the videos. They were divided into cohorts with respect to fluid velocity and adhesion protein expression. In a first part, thanks to a statistical analysis of the extracted cell velocities, a significant general slowing behavior over time was found for most cohorts, showing that adhesion is a continuous phenomenon in time.

In the second part, we develop a mathematical model to better quantify these initial observations. Despite the lack of information about the fluid velocity and the device pump, we showed that a Poiseuille profile combined with an oscillatory behavior induced by the pump can be used to model the fluid velocity. This oscillatory Poiseuille flow was weakly coupled to an ODE system modeling cell adhesion. Three different models for cell velocity, drawn from the literature, were explored. Ultimately, we described it as the fluid velocity affected by the formation and disruption of elastic bonds whose strain is proportional to the cell velocity itself.
To overcome difficulties such as data noise and parameter identification, a suitable and carefully designed approach to parameter estimation was developed. It is based on a mixed effects

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model that allows each parameter to be described as the result of a double contribution: the first part corresponds to the fixed effect, which is the same for all cells, while the second random part represents the individual variability. Examining the differences between the estimated parameters in each cohort, we found a greater decrease in cell velocity when fluid velocity was low. In addition, we recovered the importance of the protein CD44 over the protein ITGB1, highlighting the importance of early adhesion rather than its stabilization (previously observed only in vivo). We believe that this work represents an important step in bridging the gap between experimental measurements of CTC dynamics and theoretical frameworks.

Mots-Clés: Ordinary differential equation, Parameter estimation, Circulating tumor cells, Data analysis, Fluid modeling