

# Collagen Density Regulates Tumour Spheroid Growth Through Cell Motility: A Computational Study

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## Abstract

We aim to define the role of matrix density on tumour growth through a discrete computational framework. We integrate experimental data to characterize the dynamics of individual cellular movement, accounting for the mechanical properties of the ECM, and we evaluate how the emerging trends modulate the growth of multicellular structures.

## Introduction

Recently, several studies have revealed an interplay between the mechanical properties of the cellular microenvironment and the emergent cell behaviour. For instance, experimental studies conducted with 3D scaffolds, such as hydrogels composed of collagen, have been helpful to improve the understanding of the role of the extracellular matrix (ECM) on cellular processes [1]. However, it is still unclear how matrix density regulates tumour growth.

On the one hand, it is well established that matrices of higher density may suppress growth by exerting compressive forces on cells [2]. On the other hand, experimental studies have also shown that matrices with higher density tend to limit cell movement due to steric hindrance [3, 4]. In turn, this situation promotes individual cell migration in matrices composed of lower collagen concentrations, which can subsequently affect the tumour's size.

In order to overcome some of the intrinsic disadvantages of experimental studies, such as increased costs and long time scales, advances have been made in computational modelling to create models and simulation frameworks to further study these biological questions. Multiple computer-based frameworks have been implemented to study tumour systems, as reviewed in more detail in [5]. Computational implementation can rely on continuum, discrete or hybrid approaches.

Nonetheless, the adequacy highly depends on the subject of study.

Here, we present a discrete model extension to PhysiCell (an open-source modelling framework) [6] in which the effect of the ECM density on cell motility and, consequently, on tumour growth is introduced [7]. We aimed to build a model that was able to capture the general tendencies presented in previous experimental works [4], while still having a low computational cost and flexibility to adapt to other experimental setups. Accordingly, we also integrated previously published rheology results [8] to characterize how the collagen density of the matrix restrains cell motility.

## Methods and Materials

In this study, we aimed to replicate the experimental results found in [4]. The premise of this previous work was to seed individual cancer cells in collagen matrices of varying concentrations and to assess how the collagen density modulates cell behaviour. To simulate these experiments, we extended the open-source PhysiCell modelling framework (version 1.7.1) [6, 7].

Specifically, we introduced the effect of drag forces imposed by the ECM by taking into account the dynamic viscosity of the collagen matrices, as previously characterized in [8]. Moreover, we defined cell-generated forces using the data in [4], which enabled us to better capture the heterogeneity in cell movement.

## Results

We simulated the individual motility of cells in three different collagen concentrations (2.5 mg/mL, 4.0 mg/mL and 6.0 mg/mL). Overall, our results show that we are able to qualitatively describe how an increase in matrix density leads to smaller cell velocity values (Fig 1) and how this, in turn, suppresses the invasion of single cells, producing

cell clusters of larger areas (Fig 2). In contrast, lower density values enable cell migration, resulting in sparser and smaller tumours.

## Conclusions

Our results show that our model successfully replicates the experimental results. In fact, we have been able to qualitatively describe how an increase in matrix density leads to smaller cell velocity values and how this, in turn, suppresses the invasion of single cells, producing cell clusters of larger areas. In contrast, lower density values enable cell migration, resulting in sparser and smaller tumours.

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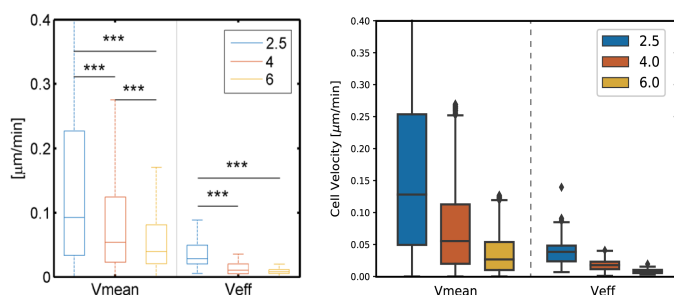


Fig. 1. Experimental (left) and computational (right) results for the mean and effective velocities of cells seeded in different collagen densities, tracked for 24 hours. Results suggest that collagen density hinders individual cell motility.

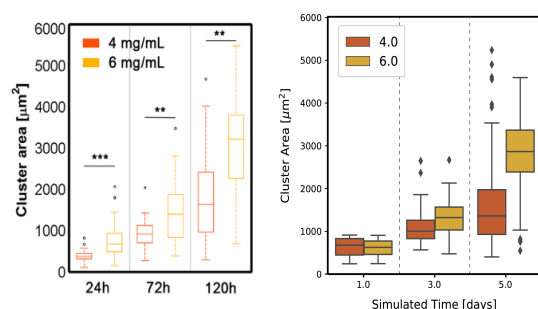


Fig. 2. Cluster area evolution over time for experimental (left) and computational (right) configurations. As the density of the matrix increases, cluster area also increases, as cells become unable to migrate and start forming large structures.