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## EFFECTS OF FRICTION COEFFICIENT AND RECEPTOR NUMBER ON CELL-SUBSTRATE INTERACTIONS DURING MIGRATION

Henry C. Wong and William C. Tang

Department of Biomedical Engineering University of California, Irvine Irvine, CA 92697 USA

#### INTRODUCTION

Biological tissues are composed of cells that adhere to the extracellular matrix (ECM) via cell-surface integrin receptors that bind to specific proteins, such as fibronectin, embedded in the matrix. In this manner, the ECM functions as a structural support for the attached cells, and mechanical forces are able to be transmitted from the cell to the ECM and vice versa [1]. Cell migration, a process that is highly dependent on these mechanical interactions, is important for many normal biological processes and diseases that occur in the human body, which include embryonic development, immune response, would healing, and cancer invasion [2]. Though many continuum models of cell migration have been proposed, there is still a need for a model that can be used to quantitatively understand the mechanical factors that can influence the movement of a cell on a substrate. This would be invaluable to the research areas of tissue engineering as well as cancer metastasis. We utilized a finite element model to elucidate the mechanism of cell-substrate interactions for a cell that consistently migrates in a single direction. Our model follows the approach taken by Gracheva and Othmer [2], but we extended their model to describe two-dimensional plane strain behavior.

#### **METHODS**

The initial shape of the cell was modeled as a circular disk with a radius of 25  $\mu$ m and a thickness of 10  $\mu$ m. To describe the passive elastic mechanical properties of the cell, a neo-Hookean strain energy function was used. We used an initial Young's modulus of 1 kPa and an initial bulk modulus that was twenty times the initial shear modulus to obtain a Poisson ratio of about 0.475. This was done to mimic the nearly incompressible nature of the cell. In addition to passive stresses, the cell was able to actively generate stresses due to the contraction of the actomyosin cytoskeleton. The chemical reaction in which

inorganic phosphate detaches from the actin-myosin-ADP complex (AM-ADP) is the step in which intracellular stress is generated. Thus, we assumed that the active stress was proportional to the amount of AM-ADP. The transient concentration of this complex was obtained by solving the system of equations using the kinetic data for non-muscle myosin II obtained by Kovacs, *et al* [3]. The total stress tensor was a sum of the passive and active stress tensors.

As the cell generates active stresses in order to move forward, a drag force per area is exerted by the substrate on the ventral surface of the cell. In our model, we assumed that this cell-substrate traction was equal to but opposite in direction to the product of the concentration of bound integrin receptors ( $C_b$ ), the cell velocity, and the friction (or drag) coefficient for one bound receptor ( $\beta_0$ ) [2]. The range of the drag coefficient  $\beta = \beta_0 C_0$ , which represents the ratio of traction to speed in our model, was estimated to be from 10<sup>3</sup> to 10<sup>5</sup> pN-s/µm<sup>3</sup> [4, 5], where  $C_0$  is the concentration of total (free and bound) receptors on the cell's ventral surface. Since the total number of receptors (N) varies from 10<sup>4</sup> to 10<sup>7</sup> [6], the values of the parameter  $\beta_0$  were also estimated.

In order to consider the force-sensitivity of the focal adhesions, the sites of cell-ECM contact, the reverse rate coefficient for the receptor-substrates reactions was assumed to be a function of the applied force according to the Bell model. The parameters we used for the low affinity  $\alpha_5\beta_1$  integrin-fibronectin interactions at lower loading rates were obtained by Li, *et al* [7]. Moreover, the anterior of cells are more strongly attached than the posterior of the cell. We modeled this by assuming that the reverse rate coefficient with zero applied force increased linearly from the anterior to the posterior [2], which reduced the amount of bound integrin receptors at the cell rear. In our model, the ratio of the reverse rate coefficient from the rear to the front was 100 [6]. Finite element algorithms written in MATLAB were used to conduct the numerical simulations.

### RESULTS

Figure 1 shows plots of the average cell speed and maximum cellsubstrate tractions as functions of the friction coefficient for one bound receptor ( $\beta_0$ ) for different levels of the normalized friction coefficient ( $\beta/10^3$  pN-s/µm<sup>3</sup>) and the normalized receptor number ( $N/10^5$ ).



Figure 1. Plot of average speed (a, c) and maximum tractions (b, d) for different levels of  $\beta/10^3$  pN-s/µm<sup>3</sup> (a, b) and *N*/10<sup>5</sup> and (c, d)

#### DISCUSSION

The upper two plots in Fig. 1 show how the average cell speed and cell-substrate traction varies with the drag coefficient. For each curve, the concentration of total receptors and the drag coefficient for each bound receptor vary simultaneously such that their product, the drag coefficient, is a constant. For each of the curves, as  $\beta_0$  increases the total receptor number varies from  $10^7$  to  $10^5$ . As shown in Fig. 1 a, the drop in the cell speed is more significant as the friction coefficient varies from  $10^3$  to  $10^4$  pN-s/µm<sup>3</sup>. According to the results, an order of magnitude of increase in  $\beta$  is associated with an order of magnitude decrease in the average speed. The dependence of the cell speed with  $\beta_0$  is more evident at greater values of  $\beta_0$  and lower values of  $\beta$ . Maximum and minimum cell-substrate tractions were observed at the anterior and posterior of the cell, respectively. This was expected in our model since tractions were directly proportional to the concentration of bound receptors, which were lower at the rear of the cell. Figure 1 b shows that maximum tractions are more sensitive to the friction coefficient in the range of  $10^4$  to  $10^5$  pN-s/ $\mu$ m<sup>3</sup>, which differs from the behavior of the average cell speed. Furthermore, the average and minimum tractions exerted on the cell's ventral surface did not vary as significantly with either  $\beta$  or  $\beta_0$  (not shown).

In contrast, the lower two plots in Fig. 1 show how the average cell speed and cell-substrate traction vary independently with the drag coefficient for each bound receptor and the total number of receptors. In particular, increases in both of these quantities can independently cause the cell to reduce its speed and to exert less traction on the substrate. However, for a given total receptor number, greater changes in the speed and traction occur within different ranges of  $\beta_0$ . For instance, for a receptor number of 400,000, the average cell speed declines by 90.1% as  $\beta_0$  varies from about 4.9 to 49 pN-s/µm, whereas traction only changes by 3.1%. On the other hand, as  $\beta_0$  is increased further, from 49 to 490 pN-s/µm, the maximum tractions show a more significant decline from about 316 Pa to 208 Pa.

In this study, we have investigated the individual and combined effects of the receptor number and the drag coefficient for each bound receptor in order to further our understanding of the mechanism of cell-substrate interactions in the context of cell motility.

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