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On the Effect of Substrate Compliance on Cellular Motility

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Abstract

Recent *in vitro* studies have highlighted the importance of substrate stiffness in governing a range of cellular functions. Motility of adherent cells, in particular, is found to be regulated by the substrate rigidity. Many cell types exhibit a subtle biphasic migration-velocity response to increasing substrate rigidity, with fast migration occurring at intermediate stiffness and slower migration on very compliant or highly rigid substrates. This study aims at improving the understanding of mechanisms responsible for cell sensitivity to the mechanical stiffness of extracellular environment during migration. We use the "two-spring model" as a mechanistic paradigm for rigidity sensing ability of cells at the scale of a single adhesion site. This will be implemented in a simple physical model of cell motility to elucidate how the local autonomy at the scale of adhesion sites may spatially and temporally regulate the cell motility. The model predicts a bell-shaped dependence between the speed of locomotion and substrate rigidity, similar to the experimental observations. This behavior is demonstrated to be rooted in the different effect of substrate rigidity on the magnitude of anterior and posterior actomyosin contractile forces which leads to the variation of net traction in a biphasic fashion.

Keywords: Cell motility; Adhesion; Substrate stiffness; Cytoskeleton; Modeling

Introduction

Cell-substrate interaction is the central player in regulation of multiple cellular functions including migration, growth, proliferation, and differentiation. These interactions typically occur between heterodimeric transmembrane integrins (mainly $\alpha_5\beta_1$ and $\alpha_v\beta_3$) present on the cell surface and ligands attached to the components of extracellular matrix (ECM). Ligands are specific functional domains of ECM proteins, such as fibronectin, laminin, vitronectin, and collagen, with binding affinity towards the integrin receptors. In addition to integrin-ligand adhesion specificity, the physical features of the ECM such as its roughness, rigidity and distribution pattern of ligands can regulate the cellular behavior. Mechanical stiffness of ECM, in particular, is found to be a major regulator for multiple aspects of cellular function, ranging from cell viability to the lineage commitment and differentiation [1]. Cells in general, exhibit an apparent adhesion preference for stiffer substrates with more organized cytoskeleton (CSK) and larger projected spread area [2,3]. Contractile cells become more proliferative and less apoptotic in response to the increasing substrate stiffness [4]. Other studies have indicated a strong influence of substrate elasticity on the lineage commitment of naive stem cells and driving their differentiation to variety of mature cells [5,6].

In this paper, we focus on motility as a cellular function which depends on the flexibility of substrate [7,8]. Pelham and Wang [2] in a seminal study reported that the rate of motility and lamellipodial activity of rat kidney epithelial and 3T3 fibroblastic cells are regulated by the rigidity of the underlying collagen coated polyacrylamide substrates. Sensitivity of cellular motility to the rigidity of the adhesive substrates is used as a directional cue to induce biased cell motility. The term "durotaxis" is coined to refer to the tendency of cells to migrate from softer to stiffer region of a substrate with gradient of rigidity, a phenomenon analogous to haptotaxis in which cells preferentially migrate towards areas with stronger adhesivity [7]. A striking aspect of rigidity dependent motility of cells is the biphasic dependence between the substrate stiffness and the migration velocity in some cell types. Namely, the speed of migration of vascular smooth muscle cells, neutrophils, epithelial, and osteoblastic cells show a biphasic dependence on the substrate compliance, suggesting the existence of an optimal stiffness capable of supporting a maximal speed of migration [9-13].

How cells actively sense and react to the rigidity of their environment is elusive. It has been postulated that the cell-substrate adhesion sites act as the local mechanosensors and convert the mechanical forces into biochemical signaling [14]. But how does such local autonomy lead to a biphasic migration-velocity response to increased substrate rigidity? To address this question, in this study we propose a force-based dynamic model of cell locomotion on compliant bio-adhesive substrates. In this model, the motility of contractile cells is assumed to be driven by the difference in contractile leverage between the cell posterior and interior, exerted by actomyosin filaments [15]. This difference provides a net traction which enables cell to migrate forward and overcome the frictional resistance due to repetitive attachment/detachment to/from the substrate. The magnitude of actomyosin contractile forces, exerted at each cell-substrate adhesion site, depends on the local rigidity of the substrate and is estimated in a phenomenological manner using Schwarz's two-spring model [16]. We find that the rigidity dependent contractile force developed at each actomyosin filament leads to a net traction and consequently a translocation velocity which both could change with substrate rigidity in a biphasic fashion.

Molecular and Physical Models of Rigidity Sensing

The adhesion machinery of cells consists of specialized subcellular adhesion sites formed between the ECM ligands and integrin receptors which are associated with contractile bundles of actin filaments at their proximal ends. These sites serve not only as local anchors, linking cells to the ECM or to their neighbors, but also provide a platform for the interplay between the ECM properties and the intracellular signals. The complex and versatile organization of adhesion sites renders them as cell mechanosensors; they act as pathways to transmit actin

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filament forces to the substrate as well as transduction of ECM forces to intracellular signals. The underlying basis regulating this signaling is not clarified yet; however, several compelling lines of evidences suggest that the substrate stiffness is capable of mediating the myosin activation by forming a positive feedback loop [1]. Different assumptions are made regarding the molecular repertoire of this feedback loop between the adhesion sites and CSK. For example, it is proposed that the increase in tension of actin filaments may induce an influx of extracellular calcium ions through the stress activated channels [7]. On stiff substrates, strong mechanical feedback from the substrate occurs after a small integrin displacement. Because elastic energy is the integration of forces along the distance, with the same amount of energy consumption soft substrates can generate only a weaker mechanical feedback but a longer displacement. The stronger mechanical feedback on stiff substrates then leads to the activation of stress-sensitive ion channels [17]. This response in turn may regulate the extent of protein tyrosine phosphorylation which leads to an increased energy consumption and a further increase in tension. Another proposed scenario suggests an intracellular feedback loop by activation of GTPase Rho upon formation of cell-substrate adhesion sites [14]. Integrin clustering in the plasma membrane is accompanied by the assembly of the cytoplasmic plaque and might lead to Rho-activation. Rho in turn activates myosin II molecular motor activity (through ROCK) and F-actin polymerization (through mDia1), leading to increased tension in the actin filaments. This tension is transmitted back to the focal adhesion, where it leads to anisotropic cluster growth in the direction of force by an unknown mechanotransductory mechanism. Until the positive feedback loop is terminated, it can be modulated by both internal and external factors, including substrate rigidity.

Even such seemingly simple schemes of sensory mechanism are often dauntingly complex to be verified experimentally. Schwarz et al. [16] have shown that rigidity sensing at adhesion sites can be understood on the basis of a simple physical ansatz that idealizes the cell-substrate adhesion site as assemblies of active mechanical springs, often referred to as two-spring model. Here, we briefly describe this paradigm model and will show later that, in combination with a force based dynamic model, it can provide a mechanistic description for the biphasic dependence between the substrate stiffness and the migration velocity. Consider an adhesion site between the integrins and surface ligands of a compliant substrate (Figure 1). The cytoplasmic face of adhered integrins is bound to the actin microfilaments which are under tensile stress due to the motor activity of myosin molecules. This way, the tensile force F generated in actomyosin filaments is transferred to the substrate through integrin-ligand anchorage points. In the two-spring model, the mechanical contributions of CSK and ECM are represented

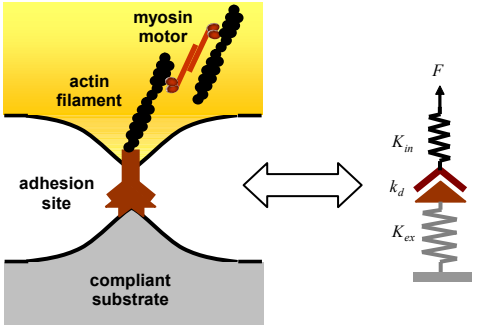

Figure 1: Schematic representation of an adhesion site on a compliant substrate and its equivalent "two spring model".

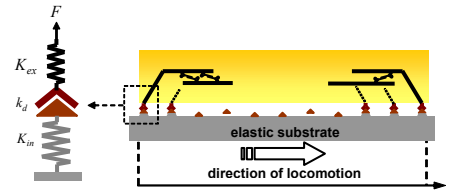

Figure 2: Schematic representation of a cell on a compliant substrate. Cell is modeled as a 1D object. The actomyosin contractile forces are assumed to be exerted only at cell posterior and anterior compartments.

by two linear springs with spring constants of K_{in} and K_{ex}, respectively (Figure 1). As an approximation, the force exerted by a motor, F, can be assumed to linearly change with the velocity of myosin v, as

$$F(v) = F_S\left(1 - \frac{v}{v_0}\right), \tag{1}$$

where v_0 is the zero-load velocity and F_S is the stall force of the motor; that is, the maximal force allowing motor movement. Putting the rate of the energy generated by the motion of motors equal to the rate of energy storage in the deformed CSK and substrate, it can be shown that the force F by which an actomyosin filament pulls on the compliant substrate changes with time as [16]

$$F = F_S\left(1 - \exp\left(\frac{-t}{t_K}\right)\right), \tag{2}$$

where $t_K = F_S / v_0 K$ and $K = \left(K_{in}^{-1} + K_{ex}^{-1}\right)^{-1}$.

Since the contractile forces are transduced through the integrin-ligand bonds, the pulling force $F(t)$ vanishes once the bond ruptures. The probability of bond dissociation itself depends on the applied force $F(t)$. We model the breaking of the bond by a Poisson process and define a bond survival probability $p(t)$ that obeys $dp(t)/dt = -k_d(t)p(t)$. We assume that k_d takes a simple Arrhenius form $k_d(t) = k_{do}\exp(F(t)\,\delta / k_BT)$ where k_{do} is the disruption rate in the absence of CSK force, δ is an activation length, and k_BT is the thermal energy. This way, the average contractile force exerted on each bond is given by

$$\bar{F} = \int_0^\infty k_d(t)F(t)\,p(t)\,dt, \tag{3}$$

where $p(t) = \exp\left[-\int_0^t k_d(t')\,dt'\right]$. Calculation the value of $\bar{F}$ for different substrate rigidities K_{ex} indicates that the average actomyosin force increases and reaches an asymptote upon increasing the substrate rigidity. Note that, if the dissociation rate was taken to be constant, then the average actomyosin force $\bar{F}$ could be evaluated analytically, as shown by Schwarz et al. [16]. In this paper, however, we consider the more general case of force dependent K_d and calculate $\bar{F}$ through the integral representation (3).

A Physical Model for Motility

Now let us implement this sensory mechanism in a simple physical model of cell locomotion. Consider a cell adhered on a linear elastic substrate which is coated with immobilized bio-adhesive ligands with areal density of N_L. The total force acting on a cell can be divided into the traction force F_{trac} due to the adhesion to the substrate and the resistive friction force F_{fric} of the substrate, due to repetitive attachment-detachment between the integrins and surface ligands; i.e.,

$$F_{trac} - F_{fric} = 0. \tag{4}$$

Parameter	Value	Source
N_L	10^3 μm^{-2} (10^{-2}-10^4 μm^{-2})	22
$N_{R,tot}$	10^5	23
δ	0.5 nm	24
k_{eq}	10 μm^2 (10^{-3}-10^3 μm^2)	25
ξ_0	0.04 pN.s/μm	assumed
k_{d0}	0.2 s^{-1} (10^{-5}-10 s^{-1})	25

Table 1: Estimated values for model parameters. Parentheses show biological range of the variables.

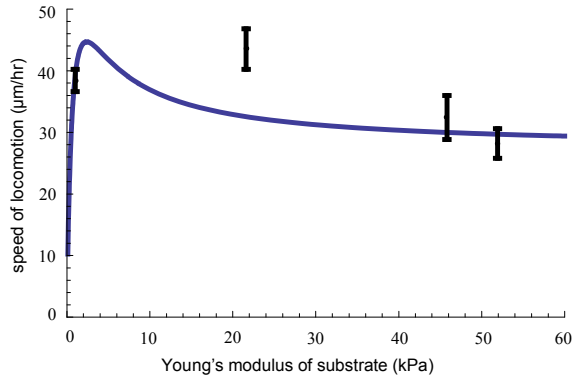

Figure 3: Predicted biphasic relationship between the speed of locomotion and the rigidity of underlying substrate. Model predictions are also compared with experimental data of Peyton and Putnam [9].

We assume that the actomyosin filaments form a dipole and the contractile forces are only exerted on the adhesion bonds in the front and rear parts of the crawling cell (Figure 2). Hence, the total traction force acting on the call can be written as

$$F_{trac} = F_{trac}(f) - F_{trac}(r), \tag{5}$$

where $F_{trac}(f)$ and $F_{trac}(r)$ are the front and rear components of the traction. The difference between these traction components is caused by the asymmetric concentration and/or trafficking of the intracellular proteins along the cell. This asymmetry leads to polarization and translocation of cell body as opposed to random searching of the environment [18]. Taking $N_B(f)$ and $N_B(r)$ to be the number of integrin-ligand bonds located at the cell anterior and posterior, respectively, the corresponding traction forces can be estimated as $F_{trac}(f) = N_B(f)\,\bar{F}(f)$ and $F_{trac}(f) = N_B(r)\,\bar{F}(r)$. Here $\bar{F}(f)$ and $\bar{F}(r)$ represent the average contractile forces developed at the each actomyosin filament at front and rear compartments of the cells, respectively (estimated by Eq. (3)). Note that here we have also assumed an asymmetry in spatial distribution of tensile force $\bar{F}$ acting on each integrin-ligand bond. The stall force of each filament is expected to change with the number of bound myosin motors [19] and hence the asymmetric distribution of myosins is assumed to cause an asymmetry in F_S. Similarly, the velocity histogram of actins can change with the number of the bound myosins [20].

Taking $N_{R,tot}$ as the total number of free integrins on the cell membrane, we have $N_{R,tot} = N_R(f) + N_R(r)$ where $N_R(f)$ and $N_R(r)$ are the number of free integrins at the front and rear compartments, respectively. At steady state conditions, we have ($i = f,r$)

$$N_B(i) = \frac{k(i)\,N_R(i)\,N_L}{1 + k(i)\,N_L}, \tag{6}$$

where $k(i)$ is the integrin-ligand affinity. Following Bell [21], we assume that the affinity depends on the actomyosin force as ($i = f,r$)

$$k(i) = k_{eq}\exp\left(-\bar{F}(i)\delta / k_B T\right), \tag{7}$$

where k_{eq} is the equilibrium affinity in absence of CSK force. The friction force F_{fric} is directly proportional to the number of adsorbed integrins. This is

$$F_{fric} = v_{cell}\left(\xi_0 N_B(f) + \xi_0 N_B(r)\right), \tag{8}$$

where ξ_0 is the average drag created by a single integrin-ligand bond and v_{cell} is the average cell velocity. The cell velocity v_{cell} can be calculated after substitution of Eqs. (5) and (8) into (4).

Table 1 shows the values of the model parameters. Unless otherwise specified, the stall forces at the cell posterior and anterior ($F_S(r)$ and $F_S(f)$) are taken to be 20 pN and 10 pN, respectively. Similarly, the values of $v_0(r)$ and $v_0(f)$ are assumed to be 20 μm/sec and 10 μm/sec, respectively. Considering the Young's modulus of E_{in}~10 kPa for the CSK [26], the intracellular spring constant K_{in} scales as $K_{in} \sim \alpha K_{in} / (1 - \nu^2)$ with α being the protein length scale (on the order of 1 nm) and ν the CSK Poisson's ratio (~0.5). A similar dependency is assumed to hold between the extracellular spring constant K_{ex} and the substrate elastic modulus K_{ex}. Figure 3 represents the variation of predicted cell velocity with the stiffness of the substrate. The results show a subtle biphasic dependence between the migration speed and the substrate stiffness. That is, the maximum velocity occurs within a narrow range of stiffness,

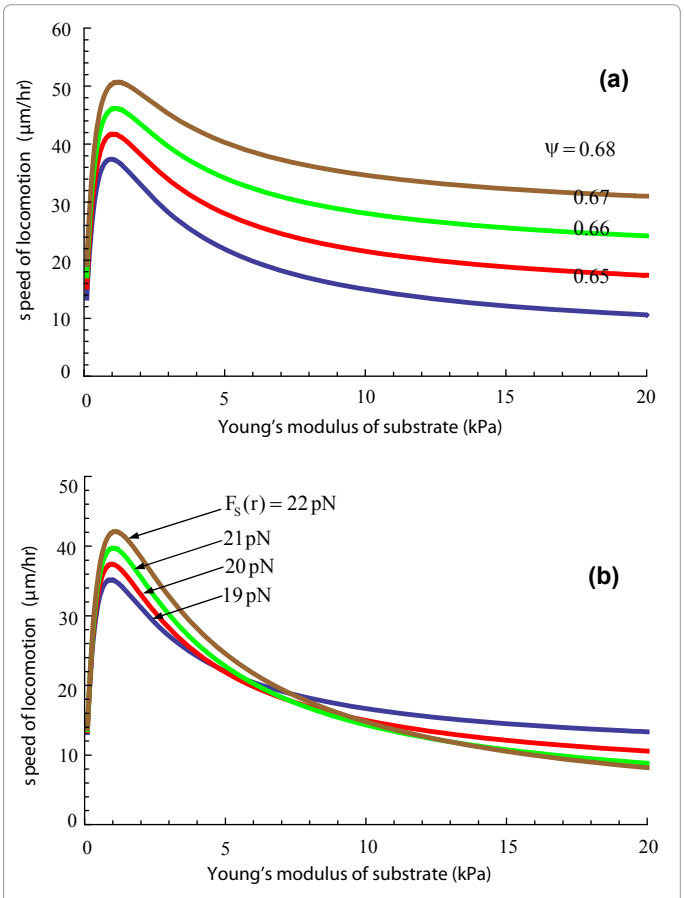

Figure 4: (a) Effect of asymmetry in distribution of free integrin density represented by ratio $\psi = N_R(f) / N_{R,tot}$ on the speed of locomotion on compliant substrates. **(b)** Effect of posterior stall forces on the rigidity dependent speed of locomotion. The stall force at the front edge is kept constant at $F_S(f) = 10$ pN.

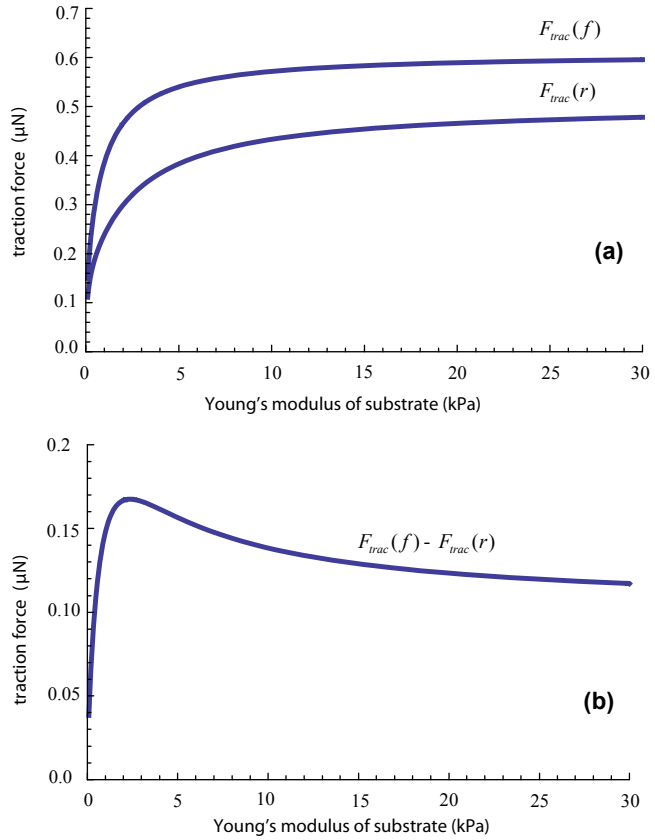

Figure 5: (a) Variation of anterior and posterior traction forces at the cell-substrate interface with the rigidity of the substrate. **(b)** The difference between the anterior and posterior tractions shows a bell-shaped dependence on the substrate rigidity.

beyond which the velocity decreases with increasing the rigidity of underlying substrate. The model predictions are also compared with the experimental data of Peyton and Putnam who quantified the migration of smooth muscle cells on acrylamide gels coated with fibronectin [9]. Similar biphasic response has been also reported for the migration of neutrophils, osteoblasts, tumor, and epithelial cells [10-13].

Correlated with cell polarity, the cellular motility is strongly coupled with front-back asymmetric distribution of intracellular proteins, due to protein trafficking and/or polarized endocytosis. Figure 4 (a) shows the effect of asymmetry in distribution of free integrins, represented by ratio $\psi = N_R(f) / N_{R,tot}$, on the overall cell velocity. While the velocity maintains its biphasic dependence on the substrate rigidity, its magnitude decreases as the degree of integrin asymmetry decreases. The effect of asymmetry in stall force on the overall velocity is studied by changing the stall force at the rear filaments while the stall force of the front filaments is kept constant at 10 pN, as shown by Figure 4 (b). The larger stall force indicates a larger number of myosin motors bound to the actin microfilaments. The maximum attainable velocity as well as the asymptotic velocity on increasingly stiffer substrates changes as the posterior stall force varies.

An attractive feature of the proposed model is its ability to describe how local rigidity sensing at the scale of adhesion sites may regulate the cell translocation as a whole. The model suggests that the rigidity dependent motility of contractile cells is due to the different effect that changing substrate rigidity may have on CSK contractile forces at the front and rear compartments of the cell. This affects the magnitude of net tractions required for translocation of cell mass. To show this, let us consider the change of traction forces at the rear and front points of the cell ($F_{trac}(r)$ and $F_{trac}(f)$, respectively) in response to the change in substrate rigidity, as shown by Figure 5(a). While tractions at both points increase and reach an asymptotic value as substrate rigidity increases, the retractive posterior traction enhances at slower rate compared to the frontal point. This is due to the larger stall force (F_S) and stepping velocity (v_0) assumed for the calculation of the contractile force at cell posterior, using the two-spring model. Such subtle asymmetry in traction forces leads to a net mechanical leverage which enables cells to migrate forward. The difference between the values of anterior and posterior tractions is shown by Figure (5b). This difference exhibits a similar dependence as shown to exist between the cell velocity and substrate rigidity by Figure 3. This is quite expected as the net traction provides the driving force for cell translocation. The biphasic variation of net traction with the underlying stiffness is what we infer to be the underlying reason of rigidity dependent motility in many types of contractile cells.

Conclusion

Numerous aspects of the anchorage dependent cell functions, including survival, proliferation, differentiation and migration can be regulated by the rigidity of ECM. Adhesions guide these diverse processes both by mediating force transmission from the cell to the flexible substrate and by controlling biochemical signaling pathways. While the adhesion-mediated mechanosensitivity has been described and validated in many experimental systems, and its phenotypic manifestations are well-documented; yet the underlying molecular mechanisms are still elusive. The development of theoretical models of adhesion-mediated mechanosensitivity, coupled with a deeper understanding of the underlying physical principles, is essential pre-requisites for the design of effective experimental strategies aimed at deciphering the molecular underpinnings of this intriguing phenomenon. In long run, such an understanding may have a powerful impact on rational design of tissue engineering scaffolds and also contribute to our general understanding of cell function and help to gain a deeper insight into etiology of diseases and improving therapeutic strategies. In this paper, we proposed a simple physical model of cell motility on compliant substrates. The goal was to quantify the mechanism of rigidity sensing by motile cells and understand the underlying physics which leads to rigidity dependent velocity of cells crawling on soft bio-adhesive substrates. The model demonstrates that the rigidity dependent motility of cells is rooted in the different effect that changing substrate rigidity may have on CSK contractile forces at the cell posterior and anterior. As a result, the net traction force exerted on the cell varies with the rigidity of the underlying substrate.

It is obvious that the proposed model is built upon a number of simplifying assumptions that are acceptable only as a first order approximation. Perhaps the most important feature of cellular adhesion/migration which is overlooked in our model is the assembly of bound integrins to form a heterogeneous distribution of focal adhesion sites. Due to integrin clustering, the contractile forces are distributed within a number of integrin-ligand bonds under a focal adhesion and hence, the disruption kinetics of bonds will be different from what our simplistic model predicts. A more realistic estimation of the traction forces transmitted to the substrate warrants an analysis of the decay and stability of these focal adhesions under rigidity dependent CSK forces [27]. Being exclusively focused on the effect of substrate compliance, the model cannot elucidate how cells probe other substrate properties (such as substrate adhesivity) and how these properties couple with substrate

compliance to mediate the cellular motility. For example, it is shown that the value of optimal substrate stiffness (supporting the maximum speed of locomotion) depends on the density of immobilized ligands and decreases upon increasing the ligand density [9,13]. Despite these shortcomings, we believe that the proposed model captures the physical mechanism by which the motile cells perceive the substrate rigidity and can be used to develop more sophisticated models of cellular motility on compliant bio-adhesive substrates.

Acknowledgments

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