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Modeling Actin Filament Reorganization in Endothelial Cells Subjected to Cyclic Stretch

G. CIVELEKOGLU, Y. TARDY AND J.-J. MEISTER†
Biomedical Engineering Laboratory,
Swiss Federal Institute of Technology,
PSE-Ecublens,
1015 Lausanne,
Switzerland

Hemodynamic forces affect endothelial cell morphology and function. In particular, circumferential cyclic stretch of blood vessels, due to pressure changes during the cardiac cycle, is known to affect the endothelial cell shape, mediating the alignment of the cells in the direction perpendicular to stretch. This change in cell shape proceeds a drastic reorganization at the internal level. The cellular scaffolding, mainly composed of actin filaments, reorganize in the direction which later becomes the cell's long axis. How this external mechanical stimulus is 'sensed' and transduced into the cell is still unknown. Here, we develop a mathematical model depicting the dynamics of actin filaments, and the influence of the cyclic stretch of the substratum based on the experimental evidence that external stimuli may be transduced inside the cell via transmembrane proteins which are coupled with actin filaments on the cytoplasmic side. Based on this view, we investigate two approaches describing the formulation of the transduction mechanisms involving the coupling between filaments and the membrane proteins. As a result, we find that the mechanical stimulus could cause the experimentally observed reorganization of the entire cytoskeleton simply by altering the dynamics of the filaments connected with the integral membrane proteins, as described in our model. Comparison of our results with previous studies of cytoskeletal dynamics reveals that the cytoskeleton, which, in the absence of the effect of stretch would maintain its isotropic distribution, slowly aligns with the precise direction set by the external stimulus. It is found that even a feeble stimulus, coupled with a strong internal dynamics, is sufficient to align actin filaments perpendicular to the direction of stretch.

1. INTRODUCTION

Vascular endothelium is a monolayer of cells lining the inner wall of blood vessels, and serves as the interface between the flowing blood and the vessel wall. As blood flows through an artery, it imparts a force on the endothelial cells and the vessel wall. This force can be decomposed into two components: one tangent to the surface of the artery, in the direction of blood flow, and the other normal to the arterial surface. The

†To whom correspondence should be addressed.

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tangential component, fluid shear stress, results from the flow of blood and is exerted on the apical surface of endothelial cells. The normal component results from the blood pressure causing a radial expansion of the artery wall during the cardiac cycle, and therefore subjecting the endothelial cells to a cyclic circumferential hoop stretch as the artery diameter increases during systole and decreases during diastole, as a result of changes in blood pressure. Thus, this latter mechanical stimulus is exerted on the basal surface of endothelial cells by cyclic stretching of the extracellular matrix. Under the effect of these dynamic forces, the endothelial cells undergo a number of morphological and structural changes, both in their physiological environment and *in vitro* experiments (Fry, 1968; Dewey *et al.*, 1981; Levesque *et al.*, 1986; Kim *et al.*, 1989; Davies, 1989). The cells respond to changes in their physical environment, such as flow patterns and pressure variations, by active adaptation. Today, the importance of hemodynamic forces in the development of various cardiovascular diseases, such as atherosclerosis, is well recognized (Zarins *et al.*, 1983; Ku *et al.*, 1985). However, the detailed mechanism(s) by which the endothelial cells sense the changes in their environment and respond to them is still poorly understood.

In vitro studies indicate that endothelial cells elongate and align *in the direction of flow* when they are subjected to shear stress [see, Zhao *et al.*, 1995, Fig. 1(b)] and *in the direction perpendicular to stretch* when they are subjected to uniaxial substrate stretch [see, Zhao *et al.*, 1995, Fig. 1(c)]. These changes in cell morphology *reflects* a profound reorganization at the intracellular level. Changes in intracellular ionic fluxes, gene regulation and a drastic alteration of the cytoskeletal structure accompany and/or produce this metamorphosis (Shen *et al.*, 1992; Resnick *et al.*, 1993; Davies and Tripathi, 1993; Girard and Nerem, 1995). The endothelial cytoskeleton mainly consists of two different types of dynamic actin structures: the bundles of actin filaments, referred to as *stress fibers*, grouped together by actin binding proteins, and the *distributed isotropic network* of filaments that fills the cytoplasm (Satcher, 1993). There are many attachment points between the F-actin cytoskeleton and the cell membrane, and, in the endothelial cells, this structural backbone is directly attached to the luminal and basal membranes without an additional distinct submembraneous network (Satcher and Dewey, 1996; Satcher, 1993). Under the effect of these hemodynamic forces the two components of the actin cytoskeleton undergo a drastic change: the bundles of filaments become longer and orient in the flow direction, and the distributed network of filaments reorient preferentially *in the direction of flow* converting to more acute angles, when subjected to shear stress, and similarly, the filament bundles orient in the *direction perpendicular to stretch* when subjected to uniaxial substrate stretch [see, Zhao *et al.*, 1995, Fig. 3(b,c); Satcher and Dewey, 1996; Moore *et al.*, 1994; Dewey *et al.*, 1981].

Despite the strong relationship that exists between the mechanical stimuli and the shape change and internal reorganization of the cell, the mechanism(s) of force transduction still remains unknown. Mechanosensitivity of membranes through stress-sensitive ion channels, or receptors, activation of second messenger systems,

or mechanically induced gene regulation, are potential force transduction mechanisms which are currently under investigation (Harrigan, 1990; Sachs, 1988; Resnick *et al.*, 1993). Intuitively, the cytoskeleton connected to the membrane and extending throughout the cell seems the most likely candidate for force transmission to the interior of the cell (Davies and Barbee, 1994; Davies and Tripathi, 1993; Osol, 1995; Satcher and Dewey, 1996).

The effect of shear stress on cell morphology and structure has been extensively investigated experimentally (Dewey *et al.*, 1981; Davies, 1989; Girard and Nerem, 1995) and to lesser extent in a theoretical framework (Suciu *et al.*, 1997). However, the effect of substrate stretch has received attention only recently, and has not yet been studied from a theoretical point of view (Ives *et al.*, 1986; Iba and Sumpio, 1991; Moore *et al.*, 1994; Zhao *et al.*, 1995). Although the shear stress and the substrate stretch are *sensed* through different parts of the cell (the apical and the basal surface, respectively), the resemblance of their effects on the internal reorganization [compare Zhao *et al.*, 1995, Fig. 3(b) and (c)] suggests that the mechanism(s) by which these physical stimuli are transduced throughout the cell may be similar. In particular, transmembrane proteins, such as integrins, which spread throughout the plasma membrane, both at the apical and the basal surfaces, may play a key role in these mechano-transduction mechanisms (Wang *et al.*, 1993; Ingber, 1991). These proteins provide the link between the actin cytoskeleton and the external environment of the cell, directly or via a chain of actin-associated proteins, and their dynamics is coupled with cytoskeletal dynamics (Schmidt *et al.*, 1994). In this paper, we investigate the reorganization of the endothelial actin cytoskeleton as a response to uniaxial substrate stretch in a theoretical framework.

The model presented here should be viewed as a sequel of two previous theoretical studies of actin filament organization, described in Civelekoglu and Edelstein-Keshet (1994) and in Suciu *et al.* (1997). In Civelekoglu and Edelstein-Keshet (1994), the spontaneous organization of actin filaments into bundles and/or orthogonal networks, and the transition between these structures was studied. It was shown that, under certain conditions, a minute change in the parameters representing the details of biochemical interactions, such as the binding affinities or the rate of association or dissociation, is sufficient to break the stability of the isotropic distribution, leading to a rapid formation of bundles or orthogonal networks. Furthermore, the transition between these two structures was found to be highly sensitive to certain parameters. In Suciu *et al.* (1997), the above model was modified to account for the effect of an external force, the fluid shear stress, in endothelial cytoskeleton. It was found that the effect of shear stress, altering the dynamics of a small fraction of the cytoskeletal filaments, namely those attached to transmembrane proteins, is sufficient to break the stability of the isotropic network and to favor the formation of bundles of filaments.

This paper concerns the effect of a different mechanical stimulus, namely the substrate stretch, on the dynamics and organization of the cell's actin cytoskeleton. As the mechanism(s) by which this extracellular stimulus is translated into the cell

is not clear, we propose two different scenarios by which a uniaxial stretch of the substratum may alter the dynamics and the organization of endothelial actin filaments. The model presented in this paper involves a description of actin dynamics closely resembling the ones in Civelekoglu and Edelstein-Keshet (1994) and Suciu *et al.* (1997). In addition to the internal dynamics of the cytoskeleton described in these papers, we consider two different approaches accounting for the effect of substrate stretch on the actin filament organization. The linear analysis and numerical simulations of the model equations confirm that the proposed mechanisms are sufficient for the initiation and the development of the observed response of endothelial cytoskeleton to stretch. We further compare the results of the two different hypotheses proposed to describe the transduction of the external stimulus.

In the following section, we describe the features and the structure of the model, and present the two mechano-transduction hypotheses which lead to two different formulations of the effect of substrate stretch. Then, we proceed with the formulation of the model equations, corresponding to the two hypotheses given in the previous section. The results include linear analysis of the equations and numerical simulations. The final section comprises an overall discussion and comparison of the results obtained from the two different approaches, and with previous work.

2. The Modeling Strategy and Hypotheses

As in previous theoretical considerations of actin filament organizations, here too we focus on the orientation of actin filaments on a plane representing the quasi two-dimensional cytoskeletal network (Civelekoglu and Edelstein-Keshet, 1994; Suciu *et al.*, 1997). Therefore, we assume that all the variables represented in the present model are spatially homogeneously distributed. The angle θ represents an angle on the plane, with respect to a fixed orientation and the plane is the projection of the cell(s) on the substratum (see Fig. 1).

In incorporating the effect of substrate stretch on the cytoskeletal reorganization into the model, we base our hypothesis on the experimental evidence that transmembrane proteins play a key role in the transduction of this external mechanical stimulus into the cell (Ingber, 1991; Wang *et al.*, 1993; Petrov and Usherwood, 1994). The radial expansion of the artery causes a uniaxial stretch (in the circumferential direction) of the extracellular matrix which is in the order of 10% in a normal aorta. Along with this stretch/relaxation cycle, the integral membrane proteins embedded in the plasma membrane, traversing the bilayer and anchoring the cell to the extracellular matrix, move away from or towards each other, as shown in Fig. 2, along the rim of each circular cross section of the cylindrical surface. Note that this displacement, being a uniaxial one, does not affect the relative position of these proteins along the longitudinal axis of the cylinder (the vertical axis of the cylinder), that is the axis perpendicular to stretch. The actin filaments which are attached to these integral membrane proteins, directly or indirectly via a chain of actin associated proteins,

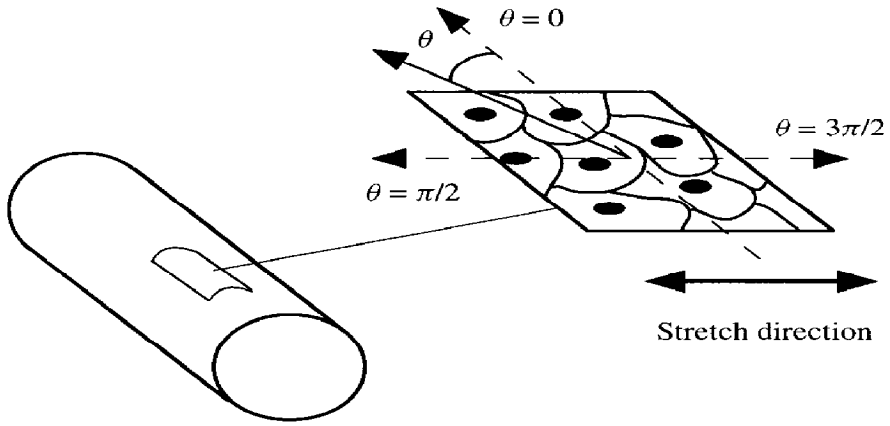

Figure 1. The quasi-two-dimensional flat piece cut from the artery wall, the plane of projection of the cells and their cytoskeleton, the angle θ on the plane, and the direction of stretch.

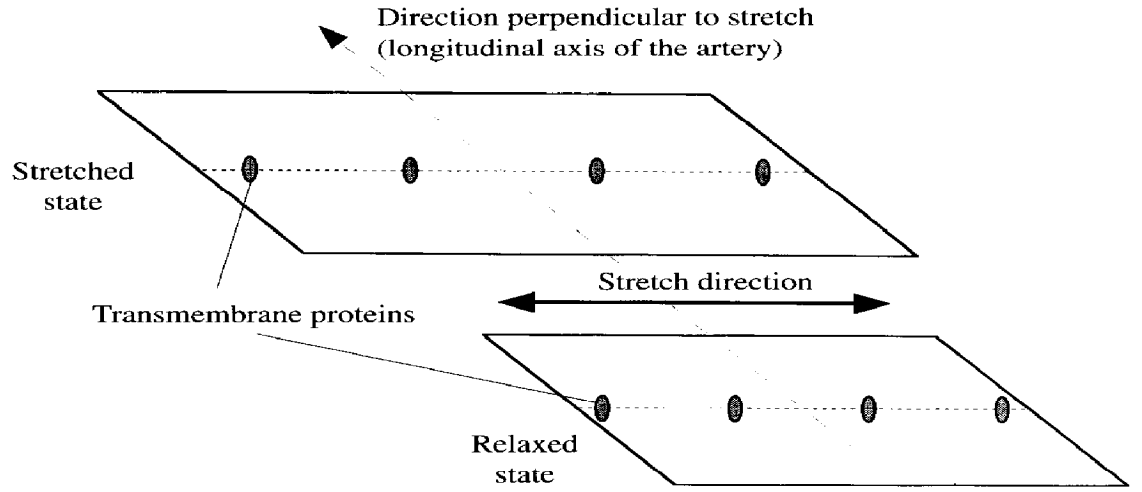

Figure 2. The uniaxial stretch of the substratum and the displacement of the integral membrane proteins away from each other along the circumference, and the direction perpendicular to stretch.

are in turn influenced by this displacement. We assume that this effect has either one of the following implications on the cytoskeletal dynamics.

HYPOTHESIS I. *The displacement of the proteins away from each other influences the dynamics of actin filaments attached to them by* breaking *the bonds between the filaments (via actin binding proteins), and/or the connection between the filaments and the transmembrane proteins. We base the formulation of this effect on the following experimental results. Numerous studies indicate that actin filaments are flexible to bending yet extremely rigid to extension (Kishino and Yanagida, 1988; Ookawa* et al., *1993; Kojima* et al., *1994; Ben-Avraham and Tirion, 1995). That is, there is substantial difference in the flexibility of filaments to bending and extensibility. When the anchoring points of the filaments, the transmembrane proteins, are displaced under the effect of substrate stretch, whether the filaments are exposed to bending or extension is determined by their angle of orientation with respect to the stretch direction. In particular, those which are parallel to the stretch direction are exposed to extension, whereas those perpendicular are exposed to bending. Therefore, in the view of the experimental findings on filament flexibility,* the bonds between filaments which are perpendicular to stretch direction, or simply the filaments perpendicular to that direction, are less likely to break than those oriented in the direction of stretch. *This means that the dissociation coefficients of the binding proteins anchoring the filaments to the membrane, or holding the filaments together, assume an angle-dependent form when the substratum is stretched.*

HYPOTHESIS II. *The cyclic translocation of the proteins influences the dynamics of actin filaments by inducing a cyclic turn,* a rotational motion, *of the microfilaments attached to them. Due to the viscous nature of the intracellular milieu, the amplitude of this motion depends on the angle of orientation of the filament with respect to the direction of stretch. In particular, the filaments which are perpendicular to stretch direction undergo the widest turn, whereas the filaments along the direction of stretch remain still. That is, the angular flux velocity is a function of the angle of orientation. It is also a function of time since the stretch is cyclic and fully elastic, hence the filaments* swing, *sweeping an angular section defined by their angle of orientation. Therefore, in this view,* filaments which are perpendicular to stretch direction are more motile than those which are parallel to it, and hence are more likely to meet other filaments and to form bonds. *Here, note that the physiological stretch cycle is 1 s (assuming 60 heart beats per min), whereas the chemical interactions involved in binding of filaments is in the millisecond range. This permits numerous binding between filaments within each cycle.*

The dynamics of the actin cytoskeleton, as described in Suciu *et al.* (1997), together with the formulation of the effect of the substrate stretch, based on the hypotheses above, result in two different descriptions of the cytoskeletal dynamics under the influence of uniaxial substrate stretch.

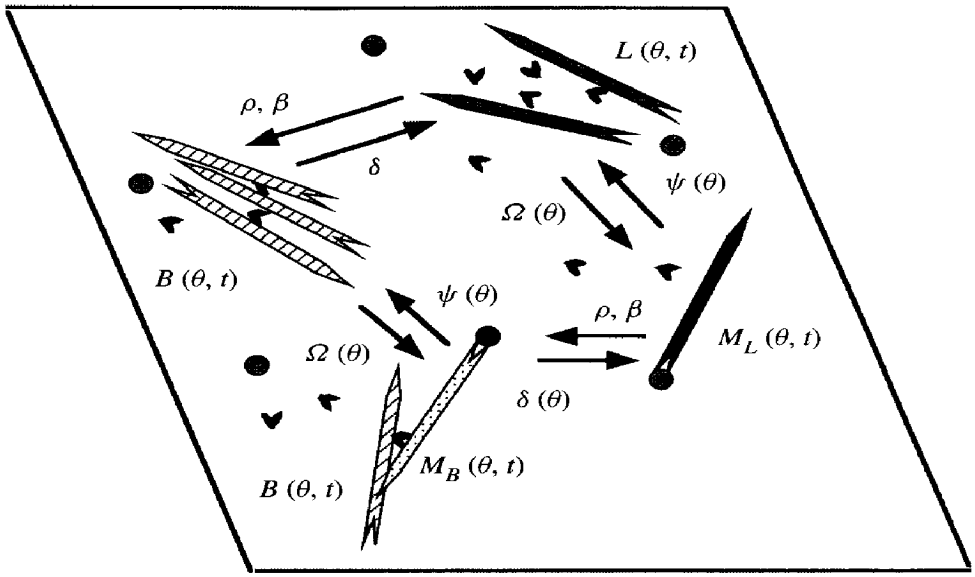

Figure 3. Schematic diagram showing the four populations of filaments: free filaments, in gray; bound filaments, hatched; free filaments anchored to the membrane, in black; bound filaments anchored to the membrane, dotted. The gray circles denote the transmembrane proteins through which the filaments are anchored to the membrane, and the solid heart-shaped figures denote the actin bundling proteins. The exchange rates between different populations of filaments are indicated with arrows.

3. Model Equations

The dynamics of actin filaments described in this paper is in close resemblance with the model considered in Suciu *et al.* (1997). We first focus on the internal dynamics of the actin filaments and introduce the necessary variables and parameters. In order to describe the interactions between actin filaments via actin binding proteins and their coupling with the transmembrane proteins we have four states of actin filaments. That is, a given filament belongs to either one of the following four populations of filaments at a given time. The 'free' filaments, L, are those which are neither attached to other filaments nor anchored to the membrane. The 'bound' filaments, B, are those which are attached to other filaments via actin bundling proteins but not anchored to the membrane. The 'membrane-free' filaments, M_L, are those directly anchored to the membrane but not attached to other filaments. Finally, the 'membrane-bound' filaments, M_B, are those which are directly anchored to the membrane and attached to other filaments via acting bundling proteins (see Fig. 3). In our model equations, the free filaments are the analogue of the *distributed isotropic cytoskeletal network* and the bound ones are the analogue of the *stress fibres*. The repertoire of each four type of filaments include interactions with all other types of filaments, binding and dissociation via actin binding proteins, and coupling and uncoupling with integral membrane proteins. These interactions are accounted for by simple rate constants and/or functions describing their stere-

ospecific characteristics, and result in exchange of filaments between populations. The ratio of G and F-actin is assumed to be constant throughout this reorganization process (Satcher, 1993). However, the randomizing effect of the filament turnover, breaking, annealing and such, is accounted for by a slow diffusion term for the filaments L and M_L, which represent the distributed isotropic actin network (Suciu *et al.*, 1997). For a more detailed description of the terms concerning the actin dynamics the reader is referred to Civelekoglu and Edelstein-Keshet (1994), and/or Suciu *et al.* (1997).

Both systems of equations include the following variables and parameters which represent the cytoskeletal dynamics:

L, B, M_L, M_B four types of filament populations, distinguished by their connections with other filaments and transmembrane proteins

$K(\theta)$ the kernal representing the angular dependence of the rate constant for binding of filaments via parallel actin binding proteins

β the binding affinity of filaments via actin binding proteins

ρ the concentration of free actin binding protein

δ the dissociation rate of acting binding proteins

μ_L the rotational diffusion constant for free filaments connected with the transmembrane proteins

μ_{ML} the rotational diffusion constant for free filaments connected to the transmembrane proteins

ψ the dissociation rate of filament connections with the transmembrane proteins

ω the rate of attachment of filaments to transmembrane proteins.

3.1. ***System I.*** Under Hypothesis I, the effect of translocation of the integral membrane proteins directly influences the dynamics of the crosslinks between filaments as well as the dynamics of filaments anchorage points to the membrane. That is, the external effect can be accounted for directly in the dissociation constants δ and ψ. We proceed with a description of the four populations of actin filaments as a function of their angle of orientation, θ and t. This leads to four state variables $L(\theta, t)$, $B(\theta, t)$, $M_L(\theta, t)$, $M_B(\theta, t)$. All other variables and parameters are as described in the beginning of this section. We only modify the constants δ and ψ, accounting for the rate of dissociation of the bonds between filaments and the transmembrane proteins, respectively, to be functions of θ. We choose the following functions to reflect the angular dependence of these dissociation rates:

$$\begin{aligned} \delta &= \delta_1 + \delta_2 |\sin\theta| \\ \psi &= \psi_1 + \psi_2 |\sin\theta| \end{aligned} \tag{1}$$

where δ_1 and ψ_1 are the constant dissociation rates, independent of stretch, and δ_2 and ψ_2 are the maximal contribution rates to the dissociation due to the effect of substrate stretch. The exact form of the above functions are unimportant for the

results of the model, any other function f bearing the following main characteristics leads to similar conclusions: f must attain its maximum at $\theta = \pi/2$ and $\theta = 3\pi/2$; f must be 0 at $\theta = 0$ and π; $f \geq 0$ for $\theta \in [0, 2\pi]$.

These properties are based on the variability of the resistance of bonds between filaments oriented at various directions, due to the bending and extensibility properties of the microfilaments, as discussed in Section 2.

The following system of equations describe the dynamics of actin filaments and the influence of stretch on the dissociation of bonds between crosslinked filaments and the filaments' anchorage points to the membrane.

$$\begin{aligned}
\frac{\partial}{\partial t}B(\theta,t) &= \rho\beta L(K^*L) + \rho\beta B(K^*L) + \rho\beta M_L(K^*L) + \rho\beta M_B(K^*L) \\
&\quad -\delta(\theta)B + \psi(\theta)M_B - \omega B \\
\frac{\partial}{\partial t}L(\theta,t) &= -\rho\beta L(K^*B) - \rho\beta L(K^*L) - \rho\beta L(K^*M_L) - \rho\beta L(K^*M_B) \\
&\quad +\delta(\theta)B + \psi(\theta)M_L - \omega L + \mu_L\frac{\partial^2 L}{\partial\theta^2} \\
\frac{\partial}{\partial t}M_B(\theta,t) &= \rho\beta L(K^*M_L) + \rho\beta B(K^*M_L) + \rho\beta M_L(K^*M_L) + \rho\beta M_B\langle K^*M_L\rangle \\
&\quad -\delta(\theta)M_B - \psi(\theta)M_B + \omega B \\
\frac{\partial}{\partial t}M_L(\theta,t) &= -\beta\rho M_L(K^*L) - \rho\beta M_L(K^*B) - \rho\beta M_L(K^*M_L) \\
&\quad -\rho\beta M_L(K^*M_B) + \delta(\theta)M_B - \psi(\theta)M_L + \omega L + \mu_{ML}\frac{\partial^2 M_L}{\partial\theta^2}. \qquad (2)
\end{aligned}$$

The terms such as $\rho\beta M_L(K^*B)$ include a convolution integral where:

$$K^*B = \int_{2\pi}^{0} K(\theta - \theta')B(\theta', t)\,d\theta',$$

and describe, in this case, the rate at which the bound filaments, B, in any orientation interact, bind and align with membrane-free filaments, M_L, in direction θ in the presence of actin binding proteins, ρ [for a more detailed explanation of such terms the reader is referred to Civelekoglu and Edelstein-Keshet (1994)]. Terms such as $\delta(\theta)B$ denote, for example, the rate at which bound filaments become free as the bonds between crosslinked filaments dissociate and similarly $\psi(\theta)M_L$ denotes the rate at which the membrane-free filaments become free filaments as filaments detach from the membrane. For the terms $\delta(\theta)B$ in the first and second equations, and $\psi(\theta)M_L$ in the second and fourth equations, the rate constants $\delta(\theta)$ and $\psi(\theta)$ are considered to be constant. That is, $\delta_2 = \psi_2 = 0$, since the effect of stretch is not exerted on these types of filaments directly. For the membrane-bound filaments such dissociation terms, $\delta(\theta)M_B$ and $\psi(\theta)M_B$, are functions of

stretch. The terms such as ωL or ωB denote the rate at which the free or bound filaments anchor to the membrane, and become membrane-free or membrane-bound filaments, respectively. Finally the $\mu_L \frac{\partial^2 L}{\partial \theta^2}$, $\mu_{ML} \frac{\partial^2 M_L}{\partial \theta^2}$ terms describe the random reorientation of filaments of type L and M_L, respectively, due to the randomizing effect of breaking and annealing of filaments and the filament turnover rate [for a more detailed explanation of these terms the reader is referred to Suciu *et al.* (1997)]. All the above terms describe a dynamic exchange between four populations of filaments and/or alteration in their orientation. For example, as a result of a filament–filament type interaction, say $\rho\beta M_L(K^*B)$, the bound filaments, B, bind and align with membrane-free filaments and remain as bound filaments as they are still only attached to other filaments and not directly anchored to the membrane; however, the corresponding membrane-free filaments, M_L, become membrane-bound types. Thus there is a corresponding loss term, the second term, in the rate equation for M_L, and a corresponding increase in the equation for M_B, the second term.

The mathematical form of these equations is similar to the ones given in Suciu *et al.* (1997), however, here, there are some additional terms and all functions are periodic in θ, with period 2π. The additional terms appear in the last two equations and are all interaction terms allowing the binding of membrane attached filaments with all other populations. The period of all state variables being 2π, as opposed to π in Suciu *et al.* (1997), results from the plane of projection being the top view of the cell rather than a cross section as in Suciu *et al.* (1997). Therefore, here, all four types of filaments can be oriented from 0 to 2π. These differences render the equations in a suitable form for linear analysis and allow us to compare the analytical results with numerical simulations and to draw important conclusions.

3.2. ***System II.*** In order to describe the cylic rotational motion of the filaments on the two-dimensional surface in consideration, it is most desirable to describe the distribution of all four populations of actin filaments, including their position, r, and orientation, θ. However, a model based on such a description is far from being amenable to analytical or numerical treatment. Therefore, we proceed with the following arguments leading to a description of a simplified geometry, fully capturing the desired dynamics.

Due to the cyclic circumferential stretch of the substratum, the anchorage points of the filaments, the transmembrane proteins, move *only* along the direction of stretch, and *not* in the direction perpendicular to stretch. Moreover, all points along the line of the circumference move away from or towards each other with the effect of stretch or relaxation (see Fig. 2). Therefore, lumping the continuum of filament anchorage points simply in two discrete points in the stretch direction, moving away from or towards each other captures the essential aspects of the dynamics (see Fig. 4). Hence, to describe the geometry for the reorientation of filaments due to the translocation of the transmembrane proteins on the surface, we consider an angle θ, indicating the orientation of the filaments,

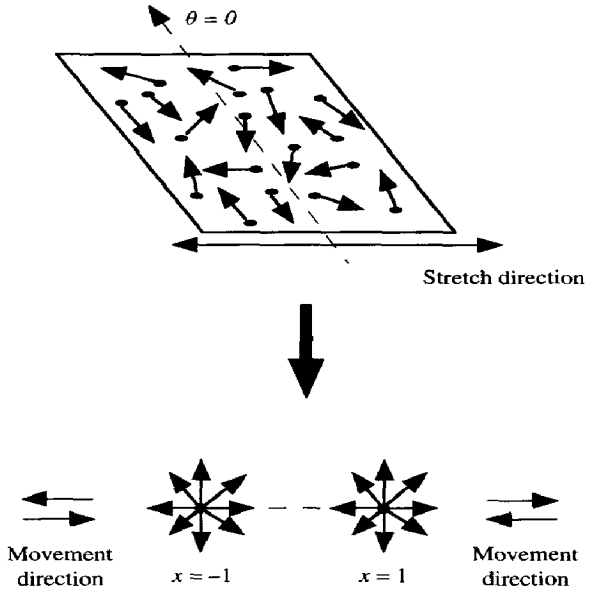

Figure 4. The surface in consideration and the simplified geometry. The angle θ and the variable $x = -1, 1$ indicate the orientation and the two anchorage positions of the filaments moving away from each other.

and $x = -1$ and 1, indicating the positions of the filaments' anchorage points along the stretch direction. Note that the introduction of the variable x at two discrete points does not mean we study a fully two-dimensional problem. We consider a one-dimensional problem as before; however, at two discrete points in this case. This allows us to capture the movement of the anchorage points of the filaments on the membrane away from or towards each other as a result of the stretching of the membrane caused by the swelling of a cylindrical surface.

In the present case, all variables, L, B, M_L, M_B are functions of θ, x and t. θ varies from 0 to 2π, and represents an angle of orientation, with respect to the axis perpendicular to the stretch direction. $x = -1, 1$ are the two positions of the transmembrane proteins, moving away from or towards each other, and the distance between these two points represents the maximal distance within which two filaments anchored to the membrane can *feel* each other, and bind to each other, during a stretch cycle.

The rate of change of the density of the membrane-bound filaments due to the rotational motion of the filaments, caused by the displacement of the transmembrane proteins away from or towards each other, can then be described by an angular flux term, similar to the one in Suciu *et al.* (1997) formulated for shear stress:

$$\frac{\partial}{\partial\theta} V_{ML} M_L \qquad \frac{\partial}{\partial\theta} V_{MB} M_B. \tag{3}$$

In this case, the flux velocities, V_{ML}, V_{MB}, depend on both θ and x, and are of the form:

$$\begin{aligned} V_{ML}(\theta, x) &= v_{ML} \cos\theta \operatorname{sgn}(x) \sin\lambda t \\ V_{MB}(\theta, x) &= v_{MB} \cos\theta \operatorname{sgn}(x) \sin\lambda t \end{aligned} \tag{4}$$

where v_{ML} and v_{MB} are the maximal reorientation rates for the free and bound filaments attached to integral membrane proteins, and the constant λ defines the period of oscillations. We assume different maximal turning rates for the free and bound types of filament, $v_{MB} < v_{ML}$, due to restriction of motion of large molecules in the viscous cytoplasm. Note that both of these angular velocity terms depend on the variable x through $\operatorname{sgn}(x)$ which captures the reorientation movement of filaments away from or towards each other. For a detailed description and derivation of the values of these velocities the reader is referred to Suciu *et al.* (1997).

As discussed in the previous subsection, here too, the exact form of these functions are unimportant for the results, and any other function g, satisfying the following properties, results in similar conclusions: g must attain its maximum at $\theta = 0$ and π; g must be 0 at $\theta = \pi/2$ and $3\pi/2$; $g(\theta, 1)$ must be positive in the first and second quadrants, and negative in the third and fourth quandrants; g must be odd in x, that is $g(-1) = -g(1)$. These properties are based on the physical description of the angular displacement of filaments due to translocation of their anchorage points.

The following system of equations describe the dynamics of actin filaments and the effect of the translocation of the transmembrane proteins due to cyclic stretch of the substratum.

$$\begin{aligned}
\frac{\partial}{\partial t}B(\theta, x, t) &= \rho\beta L(K^*L) + \rho\beta B(K^*L) + \rho\beta M_L(K^*L) + \rho\beta M_B(K^*L) \\
&\quad -\delta B + \psi M_B - \omega B \\
\frac{\partial}{\partial t}L(\theta, x, t) &= -\rho\beta L(K^*B) - \rho\beta L(K^*L) - \rho\beta L(K^*M_L) - \rho\beta L(K^*M_B) \\
&\quad +\delta B + \psi M_L - \omega L + \mu_L \frac{\partial^2 L}{\partial\theta^2} \\
\frac{\partial}{\partial t}M_B(\theta, x, t) &= \rho\beta L(K^*M_L) + \rho\beta B(K^*M_L) + \rho\beta M_L(K^*M_L) \\
&\quad +\rho\beta M_B(K^*M_L) - \delta M_B - \psi M_B + \omega B - \frac{\partial}{\partial\theta}V_{MB}M_B \\
\frac{\partial}{\partial t}M_L(\theta, x, t) &= -\beta\rho M_L(K^*L) - \rho\beta M_L(K^*B) - \rho\beta M_L(K^*M_L) \\
&\quad -\rho\beta M_L(K^*B_B) + \delta M_B - \psi M_L + \omega L \\
&\quad -\frac{\partial}{\partial\theta}V_{ML}M_L + \mu_{ML}\frac{\partial^2 M_L}{\partial\theta^2}.
\end{aligned} \tag{5}$$

The mathematical form of these equations is, as in System I, similar to the ones given in Suciu *et al.* (1997); however, here there is an additional variable x. Also, as in System I, here too all functions are periodic in θ with period 2π and the flux velocity function has a different form than the one given in Suciu *et al.* (1997).

Note that in the systems of equations (2) and (5), the total density of actin filaments:

$$M = \int_{-\pi}^{\pi} \{L(\theta, t) + B(\theta, t) + M_L(\theta, t) + M_B(\theta, t)\}\, d\theta \tag{6}$$

remains constant over time. [For system (5), the actual total mass is indeed $M = M_{-1} + M_1$, where M_{-1} is the mass at $x = -1$, and M_1 is the mass at $x = 1$, each calculated as in equation (6)]. That is, there is no change in the total amount of actin filaments in the system. This represents the treadmilling case where there is no net increase or decrease in total F-actin in the cytoskeleton.

4. Results

4.1. ***Analysis.*** First, note that in the absence of the external stimulus, the actin dynamics is similar in the systems of equations (2) and (5). That is, equations (2) with constant dissociation rates, δ and ψ, and equations (5) with null angular flux velocities, V_{ML} and V_{MB}, are identical except an additional discrete positional representation in equations (5). For the linear analysis of the systems (2) and (5), we therefore use the common description of the actin dynamics alone, where the effect of the external stimulus is neglected. Thus, the following analysis concerns the 'truncated' equations where δ and ψ are constant in case of equations (2) and the angular flux velocities, V_{ML} and V_{MB}, are null in case of equations (5).

We begin by discussing the properties of a uniform steady state of the 'truncated' systems (2) and (5), $\bar{L}$, $\bar{B}$, $\bar{M}_L$, $\bar{M}_B$, that is systems (2) and (5) in the absence of the external effect. That is, a time independent steady state in which every orientation (and position, in the case of System II) is equally probable. Setting the time, angle and positional derivatives to zero, we obtain the following equations in terms of the homogeneous steady states ($\bar{L}$, $\bar{B}$, $\bar{M}_L$, $\bar{M}_B$):

$$\begin{aligned} \frac{\bar{L} + \bar{M}_L}{\bar{B} + \bar{M}_B} &= \frac{\delta}{\beta\rho M} \\ \frac{\bar{B} + \bar{L}}{\bar{M}_B + \bar{M}_L} &= \frac{\psi}{\omega}. \end{aligned} \tag{7}$$

These are the ratio of the sum of filaments of type L, and M_L, the analogue of the distributed isotropic network of filaments, to the sum of filaments of type B and M_B, the analogue of stress fibers, and the ratio of the cytoskeletal filaments anchored to the membrane to those which are not, in terms of the binding and dissociation rate constants, the actin binding concentration and the total actin mass. Thus, we have

explicit descriptions of how the cytoskeleton is divided into its different components in a homogenous equilibrium state, in the absence of external stimulus.

We further wish to test the stability of the homogeneous steady state of these truncated equations to small perturbations, as was done in Civelekoglu and Edelstein-Keshet (1994). Defining new variables, B' and L' as:

$$\begin{aligned} B' &= B + M_B \\ L' &= L + M_L \end{aligned} \tag{8}$$

and assuming $\mu_L \cong \mu_{ML}$, our 'truncated' equations reduce to the system of equations (1) in Civelekoglu and Edelstein-Keshet (1994). Hence, in the absence of the external stimulus, the results of the linear stability analysis presented in their paper apply to our equations, assuming that the diffusion coefficients μ_{ML} and μ_L are the same. The coefficient C, given in the dispersion relation in Civelekoglu and Edelstein-Keshet (1994), is a combination of the parameters in the equations, and its value determines the stability properties of the homogeneous steady state. Namely, if $C < 0.04$ [see Civelekoglu and Edelstein-Keshet, 1994, Fig. 3(b)] the linear analysis predicts that there will be a spontaneous self-organization of actin filaments in parallel bundles. The results of their numerical simulations of the nonlinear system confirm these predictions. Based on their results, we conlcude that our system is at a stable equilibrium in the absence of the external stimulus, provided that the parameters do not satisfy the dispersion relation (Civelekoglu and Edelstein-Keshet, 1994, equation (4)). And, we wish to analyze the effect of the external stimulus on this stable system, and study its dynamics.

Table 1. The range of values for the parameters used in the numerical simulations. Most parameters were found in raw form in the literature and were adapted to correspond to the geometry and their representation in the model.

Symbol	Standard value	References
α	20–30°	Civelekoglu and Edelstein-Keshet (1994)
β	0.1–5 μM^{-1} s^{-1}	Burridge *et al.* (1990), Dufort and Lumsden (1993)
ρ	0.1–2 μM	Pollard and Cooper (1986)
δ	0.1–2 s^{-1}	Burridge *et al.* (1990), Dufort and Lumsden (1993)
μ_L	0.01–1 rad^2 s^{-1}	Civelekoglu and Edelstein-Keshet (1994)
μ_{ML}	0.001–0.2 rad^2 s^{-1}	adapted from the value of μ_L
ψ	0.5–2 s^{-1}	Meyer and Aebi (1990), Dufort and Lumsden (1993), coupling rate in Schmidt *et al.* (1994)
ω	0.01–0.5 μM^{-1} s^{-1}	Meyer and Aebi (1990), Dufort and Lumsden (1993), uncoupling rate in Schmidt *et al.* (1994)

4.2. ***Numerical simulations.*** Equations (2) and (5) were simulated with methods identical to the ones described in Suciu *et al.* (1997) and Civelekoglu and Edelstein-Keshet (1994). The parameters used for the computations were gathered from biological literature and/or from previous theoretical models where similar rate constants were used. A list of the parameters and the corresponding references is given in Table 1. The discretization was done on a grid with $\Delta\theta = 10°$ and

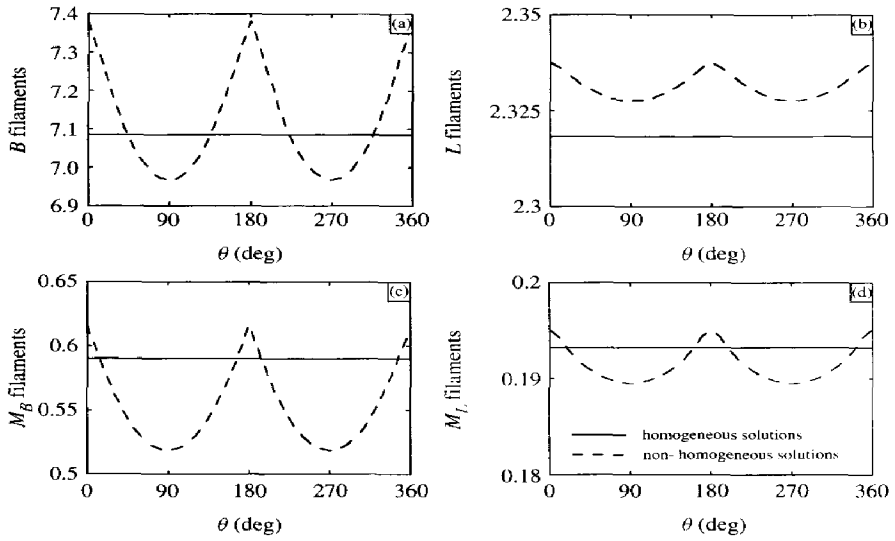

Figure 5. The homogeneous and non-homogeneous solutions of the system of equations (2) in the absence (solid lines), and in the presence (dashed lines) of the external stimulus, respectively. The plots (a)–(d) correspond to the final stationary densities of the bound $B(\theta, t)$, free $L(\theta, t)$, membrane-bound $M_B(\theta, t)$, and the membrane-free $M_L(\theta, t)$ filament types, respectively. In the case where the external force is absent, the rate of detachment of the filaments from the membrane and the dissociation rate between filaments is constant for all populations $\delta = \delta_1$ and $\psi = \psi_1$. It is seen that the initial homogeneous state is stable in this case and all filaments remain equally distributed over all orientations. In the case where the external stimulus is present (dashed lines) the rate of detachment of the filaments from the membrane and the dissociation rate between filaments are angle dependent for the filaments coupled with the membrane δ_2, $\psi \neq 0$. The solution is non-homogeneous in this case, and two peaks, centered at $\theta = 0$ and 180°, are seen in the distribution of all four types of filaments. For the solutions shown a discretization with $\Delta\theta = 36$, $\Delta t = 0.001$ was used and the total number of iterations was 12×10^6 in the case where the external stimulus is absent, and 40×10^6 in its presence. The parameters used were: $\rho = 0.5, \beta = 0.3, \alpha = 21°, \delta_1 = 0.5, \omega = 0.1, \psi_1 = 1.2, \mu_{ML} = 0.6, \mu_L = 0.6$, and in the absence and the presence of the external stimulus the following values of δ_2 and ψ_2 were used, respectively $\delta_2 = 0$, $\psi_2 = 0$ and $\delta_2 = 0.1$, $\psi_2 = 0.2$.

$\Delta t = 0.001$, and Courant–Friedrichs–Lewy stability conditions were verified for the stability of the numerical scheme. The time step Δt corresponds to a minimal time required for interaction between molecules, in the order of milliseconds. In the figures shown here, the initial densities were small random deviations, of magnitude 10%, superposed on a uniform distribution. The resuls of all simulations were in total agreement with the linear analysis results, that is, in the absence of the external stimulus, the system remained at a stable homogeneous state for the parameters which did not satisfy the dispersion relation adapted from Civelekoglu and Edelstein-Keshet (1994).

Figures 5(a)–(d) shows the numerical solutions of the system of equations (2) in the absence of the external stimulus (solid lines), and including the effect of stretch as described in Section 3.1 (dashed lines). That is, the solid lines indicate the numerical

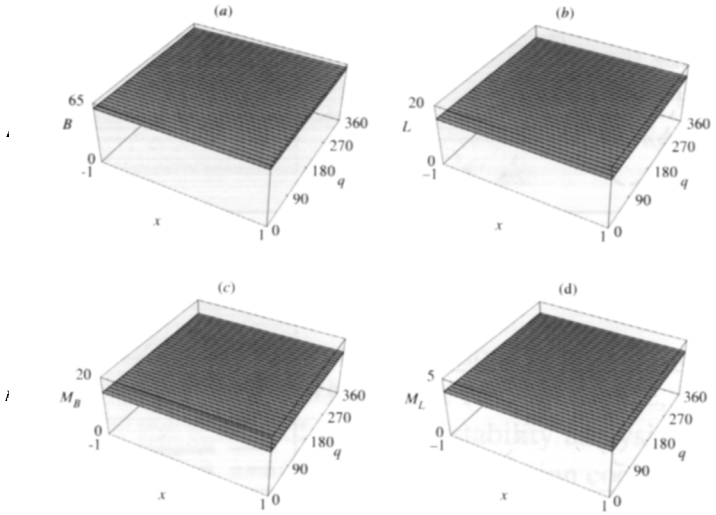

Figure 6. The homogeneous solution of equations (5) in the absence of the external stimulus. That is, the rate of angular flux rate of filaments coupled with the membrane $(\nu_{ML}, \nu_{MB}) = 0$. The plots (a)–(d) correspond to the stationary homogeneous densities of the bound $B(\theta, x, t)$, free $L(\theta, x, t)$, membrane-bound $M_B(\theta, x, t)$, and the membrane-free $M_L(\theta, x, t)$ filament types, respectively. The discretization was as in Fig. 5, the total number of iterations was 6×10^6. The parameters used were $\rho = 0.2$, $\beta = 0.1$, $\alpha = 40°$, $\delta = 0.5$, $\omega = 0.025$, $\psi = 0.1$, $\mu_{ML} = 0.2$, $\mu_L = 0.5$, and the values of $\nu_{MB} = \nu_{ML} = 0$. It is seen that the initial homogeneous state is stable in this case and all filaments remain equally distributed over all orientations.

solution of the system (2) where the functions $\delta(\theta)$ and $\psi(\theta)$ are constant, thus do not depend on θ. This corresponds to a system where the external stimulus is absent. We wish to compare the solution of this system with one where the external effect is taken into account while all other conditions remain the same. These results are shown with dashed lines, thus, the dashed lines indicate the solution of the system (2) with parameters and initial conditions identical to the ones employed to obtain the solid line solutions, except that the functions $\delta(\theta)$ and $\psi(\theta)$ here depend on θ as described in Section 3.1. Each set of four plots correspond to angular densities of the four types of filaments, L, B, M_B and M_L in the equations. In the absence of the external force, the densities of all four populations remain homogeneous, at the levels predicted by the linear stability analysis [Fig. 5(a–d), solid lines]. When the effect of stretch is added to the system (meaning that the functions $\delta(\theta)$ and $\psi(\theta)$ are made to be θ dependent), two small peaks in the distributions of the filaments anchored to the membrane appear in early stages, then are transmitted into the other two types of filaments, and become amplified with time. Only the final state of the system, obtained through numerical simulations, is shown is Fig. 5(a)–(d) (dashed lines). Note that the peaks in all populations are centered at $\theta = 0, 180°$, the direction perpendicular to the stretch direction, indicating the alignment of filaments along the direction perpendicular to stretch, as observed experimentally. Also the total number of iterations 60×10^6 correspond to a time scale in the order of 16 h.

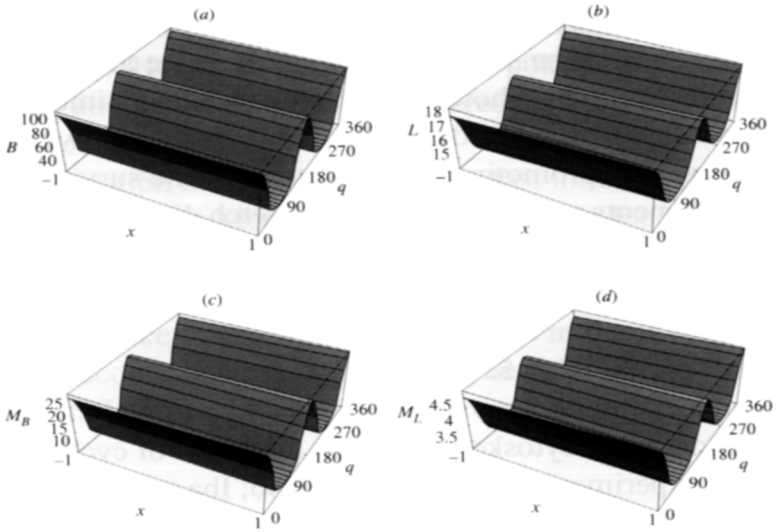

Figure 7. The non-homogeneous solution of equations (5) in the presence of the external stimulus. That is, the rate of angular flux rate of filaments coupled with the membrane $(\nu_{ML}, \nu_{MB}) \neq 0$. The plots (a)–(d) correspond to the final stationary densities of the bound $B(\theta, x, t)$, free $L(\theta, x, t)$, membrane-bound $M_B(\theta, x, t)$, and membrane-free $M_L(\theta, x, t)$ filament types, respectively. The discretization and the parameters given in Fig. 6 were used, only the total number of iterations was 12×10^6 in order to reach a stable solution, and the values of $\nu_{ML} = 0.1$ and $\nu_{MB} = 0.1$. Two peaks, centered at $x = -1, 1$ and $\theta = 0$ and 180°, are seen in the distribution of all four types of filaments.

Figure 6(a)–(d) shows the numerical simulations of the system of equations (5) in the absence of the external stimulus, and the Fig. 7(a)–(d) shows the solution of the system, with the same parameters and initial conditions, but including the effect of stretch as described in Section 3.2. Each set of four plots correspond to angular densities of four types of filaments L, B, M_B and M_L, at positions $x = -1$ and 1. For an easier visualization, the plots at $x = -1$ and 1 were connected to form a smooth surface. In Fig. 6(a)–(d), all four densities remain homogeneous in orientation and position, whereas with the addition of the effect of stretch (Fig. 7(a)–(d)) two peaks at $\theta = 0, 180°$ appear at both $x = -1, 1$. Again, the orientations which become accentuated are those perpendicular to stretch direction, as observed experimentally. As in the previous case, the peaks which first appear in the densities of the filaments coupled with the membrane, are then transmitted into the other two densities, and are magnified with time.

In all simulations of the systems of equations (2) and (5), two peaks in the filament densities in the direction perpendicular to stretch were observed in the presence of the effect of this external stimulus. These results are in total agreement with the experimental observations. For the parameter set for which spontaneous parallel alignment was predicted in Civelekoglu and Edelstein-Keshet (1994), the two peaks in the filament densities formed rapidly, in the presence, as well as in the absence of the external stimulus (result not shown). In the presence of the stretch effect, the

two peaks that formed were always in the direction perpendicular to stretch, but in its absence, the position of the 180° apart two peaks were arbitrary and depended on the initial conditions. This shows that this mechanical stimulus may have the following effect on the cytoskeletal dynamics. Stretching directly alters the internal cytoskeletal dynamics by promoting the formation, or the survival, and/or turning and alignment of filaments perpendicular to the stretch direction, and hence sets the direction of alignment regardless of the initial polarity of the cytoskeleton.

5. DISCUSSION

Alignment of endothelial cytoskeleton under the effect of cyclic stretch has been previously studied experimentally (Ives *et al.*, 1986; Iba and Sumpio, 1991; Moore *et al.*, 1994; Zhao *et al.*, 1995). To our knowledge, this is the first attempt to describe this phenomenon in a theoretical framework. Previous theoretical studies of cytoskeletal remodeling are based on either a mechanical approach, where the dynamics at the molecular level is not included (Sherratt and Lewis, 1993; Satcher and Dewey, 1996; Dembo, 1989; Alt, 1987; Oster and Odell, 1984), or a biochemical approach where the cytoskeleton is viewed as a pool of interacting molecules, separated from its mechanical environment (Civelekoglu and Edelstein-Keshet, 1994; Dufort and Lumsden, 1993). In Suciu *et al.* (1997) the effect of an external mechanical force, namely that of shear stress, was incorporated into a model based on biochemical interactions.

In this paper, we present a theoretical model of the endothelial cytoskeletal remodeling under the effect of cyclic stretch. Our model includes a description of the cytoskeletal dynamics, and a direct effect of the external stimulus, in a simplified geometry. In System I, the uniaxial stretch of the substrate induces a directional preference on the breaking of bonds between filaments and their coupling with the membrane. In System II, the stretch causes a cyclic swing of filaments which are connected with the membrane. Both of the hypothetical mechanisms considered in this paper are based on the experimental evidence that the cytoskeleton directly detects the external stimulus exerted on the membrane, through coupling with integral transmembrane proteins (Schmidt *et al.*, 1993; Kusumi *et al.*, 1993; Wang *et al.*, 1993). With this work, we do not imply that other force transduction systems based on stretch sensitive ion channels or second messenger systems are unimportant, rather, we suggest a complementary mechanism which can explain the precise choice in the direction of cytoskeletal reorientation. Intuitively, with other mechanisms based soley on biochemical events, it is indeed difficult to explain this precise direction of reorganization.

Our results indicate that the time course of the cytoskeletal reorganization based on the effect of an external mechanical stimulus, is orders of magnitude slower than a cytoskeletal reorganization based on the intrinsic biochemical mechanisms. Here, the response is feeble and slow, as opposed to the strong and spontaneous

reorganization as described in (Civelekoglu and Edelstein-Keshet, 1994; Dufort and Lumsden, 1993). However, the cytoskeletal polarity is firmly dictated by the external stimulus, already in early stages, whereas it is arbitrary in a model based solely on activation/inactivation of molecules.

Actin depolymerization has been reported as a fast initial response to mechanical stimuli such as shear stress Morita *et al.* (1994). On a longer time scale (24 h), exposure to fluid shear stress shows no significant change in the F/G-actin ratio in endothelial cells (Satcher, 1993). Incorporating an initial transient decrease in F/G-actin ratio, or other force transduction mechanisms into our model which already comprises a microscopic description of the cytoskeleton may be achieved quite easily once the details of the biochemical pathways underlying these mechanisms become clear.

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