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Multiscale approach to decohesion in cell-matrix systems

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Abstract. We propose a model for cell-matrix decohesion that highlights the role of elasticity in this process. In doing this, we specialize our previous study of focal adhesion, an integrin mediated structure that oversees and guides the mutual interactions between cells and the extracellular matrix. Specifically, we consider a two-scale asymptotic homogenization technique to study the multi-scale nature of decohesion. Thus, we are able to use micro-structural information available at length scales smaller than those at which focal adhesions are observed. Based on classical two-scale asymptotic techniques the proposed approach allows to define effective elastic coefficients encoding the intrinsic heterogeneous properties of both focal adhesions and extracellular matrix.

Introduction

We focus on integrin-mediated structures of cell attachment, by specializing our study to focal adhesions (FAs) [1-8]. Generally speaking, FAs represent the basic sites by means of cells anchor to ECM and share mechanical forces and biomechanical signals with it [1-8]. It is possible to schematize the structure of a FA in terms of a three-component system, comprising the adhesion plaque, integrin receptors and stress fibers [3, 5, 6].

Experiments show the capability of cells of sensing forces and convert them in biochemical signals, and particular attention has been devoted to the role played by the structural properties of FAs [3, 5, 6, 9-12]. For example, it has been experimentally validated how the ECM's rigidity determines the length and the stability of FAs [3, 5, 6, 9-12]. Conversely, forces originated from cells and transmitted to the ECM via FAs can determine the onset of remodeling, i.e., the rearrangement of the ECM's internal structure and its consequent structural adaptation to cell-induced stimuli [6, 13, 14].

Following all these specific examples, we are interested in studying how the elastic properties of the FAs and of the ECM may influence the dynamics of FA-ECM systems, in the case in which the insurgence and propagation of decohesion is considered. In doing this, based on [5], we develop a multi-scale approach, based on Asymptotic Homogenization [15-18] in order to deduce how the inhomogeneous microstructure of the system comprising a FA and the ECM may affect its overall behavior.

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The model

It is known that FA, ECM and integrins are typically non-homogeneous [19-22]. By considering the ECM at first, we remark that it is a complex medium comprising several species of biological elements, such as proteins and polysaccharides, which present remarkably different biochemical and mechanical properties, as well as topological and geometrical characteristics [19]. Analogous considerations are also valid for the adhesion plaque. In fact, all the protein substructures characterizing the adhesion plaque are quite heterogeneous, since they significantly vary in size, shape, distribution and, in general, in their molecular composition [20]. Several experimental procedures have been developed with the purpose of a comprehensive description of the structure of a FA [20], although the determination of the morphology and of the dynamics of the adhesion plaque represents an important open problem. This aspect results to be clearer if we consider the fact that FA experiences remodeling, which is induced by mechanical actions exchanged with the ECM [6, 13, 14]. The last aspect to mention is the heterogeneity associated with the integrin receptors [21]. In this respect, the integrins' heterogeneity is the result of the formation of interphase regions close to the FA and of the ECM, thereby determining the onset of micro-scale effects. which aims at affecting larger scales phenomena [21]. Furthermore, the attachment of the adhesion plaque to the ECM occurs via different types of integrins, so that, the overall generated forces depend on their composition and non-uniform distribution [21, 22].

Following the discussion reported so far, we can now clarify why we can speak of a multi-scale behavior in the case of FAs and ECM. In fact, the heterogeneity character of both the FA and the ECM are associated with length scales which are smaller than those characterizing the whole adhesion complex. In other words, the system under investigation exhibits at least the co-existence of two main scales: the first one, hereon referred to as *micro-scale*, is typical of the heteregeneities of the components constituting the adhesion plaque, the ECM and the integrins, whereas the *macro-scale* is representative of the system as a whole [15-18]. Such characteristic lengths are well separated. This implies that, by denoting with L_{M} and L_{m} the macro- and the micro-scales, their ratio is much smaller than one, i.e., $\varepsilon = \frac{L_m}{L_M} \ll 1$ [1-8, 15-18]. Such condition, known as *scale separation,* is the starting hypothesis which preludes the application of a multiscale analysis based on a two-scale homogenization technique [15-18].

In this work, we employ a two-scale homogenization procedure to deduce the overall mechanical behavior of a system comprising a FA, the ECM and the integrin receptors and accounting for their inhomogeneities. By referring to the mechanical picture outlined in [5] and by virtue of the scale separation condition discussed above, we re-interpret it in a two-scale fashion. This leads us to formulate constitutive relations that incorporate the information deducible from the micro-structure. In details, we compute *homogenized* or *effective* elastic coefficients, encoding the elastic properties of FAs, ECM and integrins at the scale of the heterogeneities. Moreover, we infer a system of local field equations, describing the point-wise equilibrium of the considered physical system at the micro- and micro-scale, respectively. With reference to [5], we consider a one-dimensional, continuum model, comprising a FA adhesion, the ECM and the integrin receptors.

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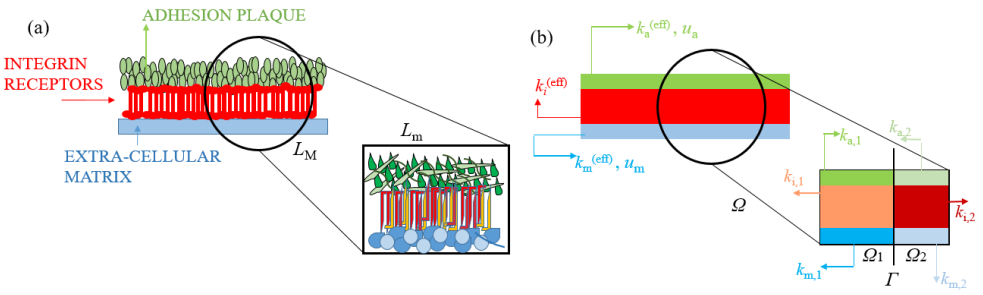

Figure 1: *Schematization of the system comprising FA, ECM and integrins and of its microstructure (a) and mechanical scheme employed in [14] and an example of periodic cell (b).*

The first two components are described as linear elastic fibers, with stiffness k_a and k_m, while the integrins are energetically represented by a linear elastic fragile potential, with stiffness k_i.

We remark that, with the term fragile, we mean that, when the force exerted by the integrins reaches a threshold value, it drops to zero. This way, as shown in [5], we model the onset and propagation of fracture and, in doing this, we illustrate how we adapt and generalize shear lag models to account for decohesion [5, 23, 24].

In this work, we retrace the same steps as in [5], but, instead of considering the elastic properties of the system to be homogeneous, we let them be inhomogeneous, thereby meaning that they vary because of the inhomogeneities arising from the microstructure. Following standard arguments of two-scale asymptotic homogenization, we assume the microstructure to be periodic [15-18]. Although such hypothesis seems to be too restrictive, it has shown to be sufficiently reliable in predicting the development of complex biological structures, e.g., breast cancer and bone remodeling [17, 18]. On the other hand, other biological media, such as spider silks, are known to possess a hierarchical periodic structure [25]. Such a hypothesis leads to the existence of an elementary cell, denoted by Ω, which can be assumed as representative of all elastic properties of the system at the micro-scale. In particular, it can be written as the union of N elements, i.e. $\Omega = \cup_{n=1,\dots,N} \Omega_n$, being Ω_n the portion of the elementary cell in which the elastic properties k_a, k_m and k_i assume the value $k_{a,n}$, $k_{m,n}$, and $k_{i,n}$, jumping across the boundary of Ω_n [15-18].

Results and discussion

We design the mechanical problem at hand in a mono-dimensional framework, and we introduce the scalar-valued functions u_a and u_m to represent the scalar displacements of the adhesion plaque and of the ECM. Moreover, u_a and u_m depend on the variable $x \in [0, L]$, being L the initial length of the system and $[0, L]$ its reference placement [5]. By applying two-scale asymptotic homogenization we obtain the following homogenized equations [26]

$$\frac{d}{dx}\left(k_a^{(eff)}\frac{du_a}{dx}\right) - \frac{k_i^{(eff)}}{d_i l_i}(u_a - u_m) = 0, \qquad x\ in\ ]0, L - L_{det}[, \qquad (1a)$$

$$\frac{d}{dx}\left(k_m^{(eff)}\frac{du_m}{dx}\right) + \frac{k_i^{(eff)}}{d_i l_i}(u_a - u_m) = 0, \qquad x\ in\ ]0, L - L_{det}[, \qquad (1b)$$

$$\frac{d}{dx}\left(k_a^{(eff)}\frac{du_a}{dx}\right) = 0, \qquad x\ in\ ]L - L_{det}, L[, \qquad (1c)$$

$$\frac{d}{dx}\left(k_m^{(eff)}\frac{du_m}{dx}\right) = 0, \qquad x\ in\ ]L - L_{det}, L[, \qquad (1d)$$

where L_{det} is the length of the detached portion of the system, while d_i and l_i are reference lengths associated with the distribution of integrins and their length, respectively [10], and with the effective coefficients $k_a^{(eff)}$, $k_m^{(eff)}$ and $k_i^{(eff)}$ computed as [15-18, 26]

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$$k_a^{(eff)} = \frac{k_{a,1}k_{a,2}}{k_{a,2}\Gamma + k_{a,1}(1-\Gamma)}, \tag{2a}$$

$$k_m^{(eff)} = \frac{k_{m,1}k_{m,2}}{k_{m,2}\Gamma + k_{m,1}(1-\Gamma)}, \tag{2b}$$

$$k_i^{(eff)} = k_{i,1}\Gamma + k_{i,2}(1-\Gamma), \tag{2c}$$

The effective elastic parameters $k_a^{(eff)}$, $k_m^{(eff)}$ and $k_i^{(eff)}$ are, in fact, the solutions of suitable *cell equations*, in the jargon of Asymptotic Homogenization [15-18], obtained by employing standard arguments of two-scale periodic analysis. We emphasize that the functional form of such cell equations depends on the considered mechanical model, describing the macro-scale mechanical interactions exchanged at the scale of the FA-ECM system, and on the way in which inhomogeneities are distributed at the microstructure. In our framework, granted for the linearity of the problem, the obtained cell equations are linear and decoupled from each other, which help us in obtaining their analytical expressions as reported in Equations (2a) – (2c).

As an example, we show the analytical solutions u_a and u_m (Fig. 2, left) computed with the homogenized Equations (1a) – (1d), equipped with the same boundary conditions as in [5]. In particular, we assume that the ECM is clamped at $x = 0$ and traction free at $x = L$, while the FA is traction free at $x = 0$ and subjected to an imposed displacement $\bar{u}$= 2 nm applied at $x = L$. Moreover, we plot the trend of FA's traction, T_a, in the case of ductile rupture [10] (Fig. 2, right). In this case, we fix $k_{a,1}$ = 2 pN/nm, $k_{a,2}$ = 0.7 pN/nm, $k_{m,1}$ = 8.7 pN/nm, $k_{m,2}$ = 11.4 pN/nm, $k_{i,1}$ = 3.9 pN/nm, $k_{i,2}$ = 6.3 pN/nm and Γ = 0.6 (see Fig. 1(b)). The value $L_{det} = 0.336$ μm descends from a minimization analysis of the energy put forward in [5]. Although the micro-scale elastic parameters are chosen to give a proof of concept of our model, they are physically sound and taken within ranges of values experimentally predicted [1-8, 26-28].

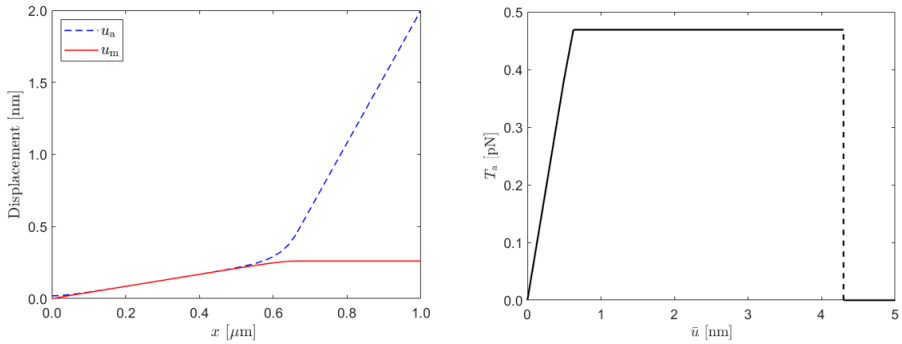

Figure 2: *Left: analytical solutions* $\boldsymbol{u_a}$ *and* $\boldsymbol{u_m}$ *with homogenized coefficients. Right: Trend of FA's traction (*T_a*) in the case of ductile rupture. The values of the constitutive parameters are from [10].*

We can motivate the difference in the trends of u_a and u_m by noticing that, while the adhesion plaque is subjected to the imposed displacement $\bar{u}$, the ECM is not. Moreover, the two components of the FA-ECM system respond differently to the forces exchanged through the integrins because of their diverse elastic properties. This behavior is coherent with that predicted by classical shear lag models [5, 23, 24]. Finally, these results constitute the first step towards a deeper investigation of the decohesive phenomenon and aiming, through a multi-scale approach, at furnishing a more detailed description of the overall nucleation and front advancement [26].

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