CELLULAR TRACTION AS AN INVERSE PROBLEM

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Abstract. The evaluation of the traction exerted by a cell on a planar substrate is here considered as an inverse problem: shear stress is calculated on the basis of the measurement of the deformation of the underlying gel layer. The adjoint problem of the direct two-dimensional plain stress operator is derived by a suitable minimization requirement. The resulting coupled systems of elliptic partial differential equations (the direct and the adjoint problem) are solved by a finite element method and tested vs. experimental measures of displacement induced by a fibroblast cell traction.

Introduction. The study of the basic mechanisms of cell migration has received a tremendous increment in the last few years. Cell locomotion occurs through a very complex interaction that involves, among others, actin polymerization, matrix degradation, chemical signaling, adhesion and pulling on substrate and fibers [12]. All these ingredients concur not only in single cell migration but also in collective morphogenetic behaviors [15].

When focusing on mechanical aspects only, a major issue is the determination of the dynamical action of the cells on the environment during migration: the cells adhere, pull the surrounding matrix and move. As a cell can have more than one hundred of focal adhesion sites, each one with thousand of integrins, it is quite difficult to obtain a pointwise description of the forces exerted by moving cells on a direct basis. Nevertheless, the striking improvement of nanotechnology has very recently lead to *direct* measurements of the cell traction: cells are deposed on a bed of microneedles and, on the basis of the Young modulus, the moment of inertia, length and displacement of the microneedles, one can directly obtain the exerted deflective force [4,14]. However, these very recent experimental achievements still provide partial information on a very special configuration only: the resolution of the displacement field is at most the distance between two microneedles (2 microns) and, more important, this setting is far from being a natural migration environment.

This kind of considerations suggests that the dynamics of cell locomotion can be fruitfully studied as an *inverse* problem, an idea that dates back to the seminal paper of Harris and coworkers [8]. A thin elastic film over a fluid is deformed under cell traction in a wrinkled pattern and the size of the crimps is correlated to the shear load. Unfortunately, buckling of thin film is an essentially nonlinear phenomena and a quantitative reconstruction of the exerted traction would call for a non–trivial stability analysis in nonlinear elasticity.

A quantitative methodology has been proposed in 1996 by Dembo *et al* [3], using prestressed silicone rubber, an approach further improved by Dembo & Wang in 1999 [2]. They deduce the traction exerted by a fibroblast on a polyacrilamide substrate from the measured displacement of several fluorescent beads merged in the upper layer of the gel. The gel is soft enough to remain in a linear elasticity regime and no wrinkles form. The cellular traction is then computed by maximizing the total Bayesian likelihood of the markers displacement predicted on the basis of the Boussinesq solution for the linear elastic half–plane with pointwise traction.

The same approach (in two spatial dimensions) is followed by Schwarz and others [11] who invert numerically the Boussinesq integral operator, thus expressing the displace-

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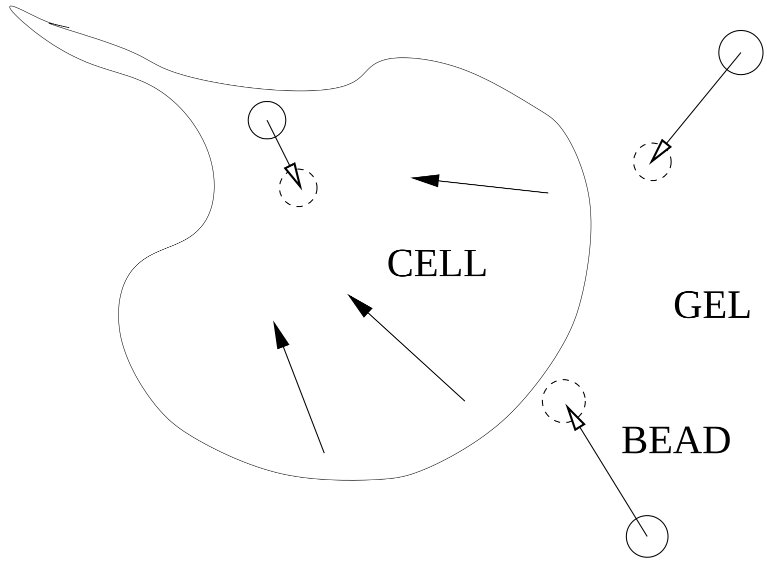

FIG. 0.1. *The experiment by Dembo & Wang. The cell exerts a traction (filled-hat arrows) on the gel. The beads, solidal with the substrate, move from the former position (continuous-line circle) to the new one (dashed circles). The difference in these positions gives the displacement of the gel (empty-head arrows).*

ment in terms of the traction. They point out the strong dependence of the solution on small variations in the data, in particular those depending on experimental uncertainty. They therefore propose a regularization of the original problem according to the Tichonov method [7].

In this paper the same biomechanical issue studied by Dembo and Wang is addressed by a different mathematical approach, based on the classical functional analysis framework due to Lions [10]. On the basis of dimensional arguments, the three–dimensional elasticity system of equations is first reduced to a two–dimensional one. The inverse problem is then stated as minimization of the distance between the measured and the computed displacement under penalization of the force magnitude [13]. Standard derivation of the cost function leads to two sets of elastic–type problems: the direct and the adjoint one. The unknown of the adjoint equation is just the shear force exerted by the cells we are looking for. The two systems of equations are then numerically solved by a coupled finite element discretization.

The paper is organized as follows. In Section 1 the abstract formulation of the minimization of a cost functional is stated. The resulting adjoint problem is specified to the case of linear elasticity with an unknown body force in Section 2. The methods and results of the numerical approximation of the system of equations are illustrated in Section 3, where the specific force field exerted by a fibroblast on a flat surface is calculated and qualitatively compared with the numerical results obtained by different approaches. The Appendix details the assumptions that yield a two dimensional *plain stress* system of equations in linear elasticity. Analogies and differences between the present approach and the ones reported in the relevant literature are discussed in the Concluding Remarks.

1. Abstract formulation. Let V be a Hilbert space equipped with the internal product $(\cdot,\cdot)$. Let $U \subset V$ and let $U = U_0 \otimes U_1$ be an orthogonal (non trivial) decomposition of U in V. Consider the linear operator linear operator $A : U \to V$ and the problem

$$A\mathbf{u} = \mathbf{f}, \tag{1.1}$$

where $\mathbf{u} \in U$. We call direct problem the determination of $\mathbf{u} \in U$ for a given $\mathbf{f} \in V$. If $\mathbf{u} \in U$ is given, by straightforward application of the operator A we get a $\mathbf{f} \in V$ and, in this sense, we denote $\mathbf{u} = \mathbf{u}(\mathbf{f})$. This is the inverse problem. Often only a partial knowledge of $\mathbf{u}$ is available. As a member of V, any $\mathbf{u} \in U$ can be orthogonally decomposed in two components $\mathbf{u} = \mathbf{u}_0 + \mathbf{u}_1$, where $\mathbf{u}_0 \in U_0$ and $\mathbf{u}_1 \in U_1$. If only the component $\mathbf{u}_0$ is known, the association $\mathbf{u} \to \mathbf{f}$ illustrated above cannot be carried out. Even worse, in general $\mathbf{u}_0$ and $\mathbf{u}_1$ are not in U, the domain of the operator A. These reasons make the problem ill–posed and call for a suitably supplementary condition to determine an optimal $\mathbf{f}$ on the basis of a partial knowledge of $\mathbf{u}$.
Let $\mathbf{u}_0 \in U_0$ and define P the projector $P : U \to U_0$. We introduce the functional $J : V \to \mathbb{R}$

$$J(\mathbf{f}) = (P\mathbf{u}(\mathbf{f}) - \mathbf{u}_0, \mathbf{u}(\mathbf{f}) - \mathbf{u}_0) + \varepsilon(\mathbf{f}, \mathbf{f}), \tag{1.2}$$

where $\varepsilon > 0$ is a penalty parameter.
We look for $\mathbf{g} \in V_c$ such that

$$J(\mathbf{g}) \leq J(\mathbf{f}), \qquad \forall \mathbf{f} \in V_c, \tag{1.3}$$

where V_c is a convex and closed subset of V. In other words, we look for a value of $\mathbf{f}$ minimizing the distance between $\mathbf{u}$ and $\mathbf{u}_0$ under penalty of the norm of $\mathbf{f}$.
Taking the Gateaux derivative of J evaluated in $\mathbf{g}$, we obtain the equivalent condition,

$$J'[\mathbf{g}](\mathbf{f} - \mathbf{g}) \geq 0, \qquad \forall \mathbf{f} \in V_c, \tag{1.4}$$

that is

$$(P\mathbf{u}(\mathbf{g}) - \mathbf{u}_0, \mathbf{u}(\mathbf{f}) - \mathbf{u}(\mathbf{g})) + \varepsilon(\mathbf{g}, \mathbf{f} - \mathbf{g}) \geq 0, \qquad \forall \mathbf{f} \in V_c. \tag{1.5}$$

Introduce the adjoint problem

$$A^*\mathbf{p} = P\mathbf{u}(\mathbf{g}) - \mathbf{u}_0, \tag{1.6}$$

where $A^* : V \to U_0$. Using the adjoint problem, equation (1.5) rewrites

$$(\mathbf{p}, A\left(\mathbf{u}(\mathbf{f}) - \mathbf{u}(\mathbf{g})\right)) + \varepsilon(\mathbf{g}, \mathbf{f} - \mathbf{g}) \geq 0, \qquad \forall \mathbf{f} \in V_c, \tag{1.7}$$

or

$$(\mathbf{p}, \mathbf{f} - \mathbf{g}) + \varepsilon(\mathbf{g}, \mathbf{f} - \mathbf{g}) \geq 0, \qquad \forall \mathbf{f} \in V_c. \tag{1.8}$$

Therefore we obtain

$$\mathbf{g} = -\frac{1}{\varepsilon}\mathbf{p}, \tag{1.9}$$

where $\mathbf{g} \in V_c$.

2. Linear elasticity. In this section we apply the general theory illustrated above to the specific problem of the small deformation of a homogeneous elastic body subject to body forces only. Let $\mathbf{u}(\mathbf{x})$ be the displacement vector field, $\mathbf{x} \in \Omega \subset \mathbb{R}^3$. Suppose that the displacement is known in a subset $\Omega_0 \subset \Omega$; the target function $\mathbf{u}_0(\mathbf{x})$ has support in Ω_0. In the problem at hand the force is exerted just on the portion of the domain where the cell lies; let us call this subdomain $\Omega_c \subset \Omega$ (see figure 2.1). The cell actually adheres to the substrate just in specific small regions called focal adhesion sites, that can be experimentally localized [1]. No reason prevents restricting the force support to these areas; this assumption is not applied here just because the information is missing for the experiment numerically reproduced in the final section.
The linear elasticity operator in strong form is

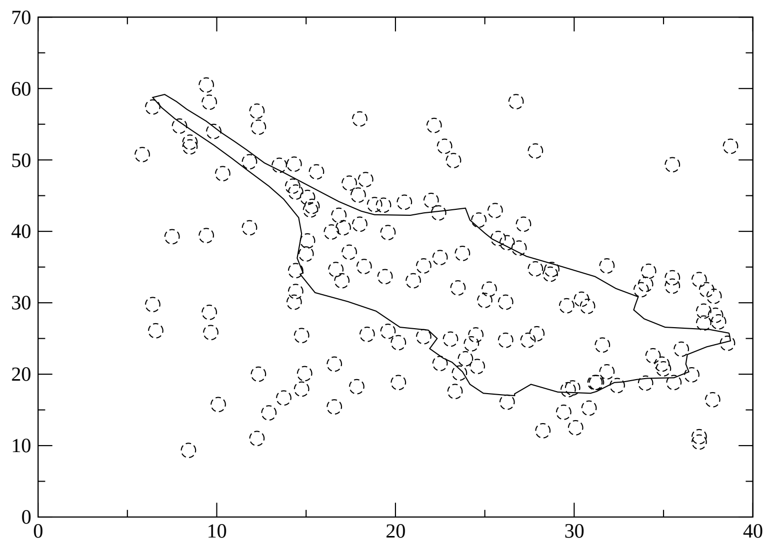

FIG. 2.1. *The domain Ω of the elasticity equation contains the subdomain Ω_c, the area covered by the cell and where the force applies: in the figure it is enclosed by the continuous line. The dashed circles are centered in the beads location and their collection represent the Ω_0 subdomain where the displacement is known.*

$$A\mathbf{u} = -\mu\Delta\mathbf{u} - (\mu + \lambda)\nabla\left(\nabla \cdot \mathbf{u}\right), \tag{2.1}$$

where μ and λ are the Lamè constants that characterize the material.
The elasticity problem reads

$$A\mathbf{u} = \mathbf{f}, \qquad \mathbf{u}|_{\partial\Omega} = 0. \tag{2.2}$$

The direct problem consists in solving Equation (2.2) for a given force field $\mathbf{f}$; the inverse problem is to determine the force that produces a known displacement. Here, as in all cases of practical interest, the displacement is not known in all the domain Ω, but just in Ω_0. In this case the inverse problem is ill-posed and uniqueness of the solution has to be recovered supplementing one more condition. Note that no issue of regularization in the sense of smooth dependence on initial data is addressed here

directly: regularity will follow *a posteriori*.
After definition of the bilinear form

$$\sigma(\mathbf{u},\mathbf{v}) = \mu \int_\Omega \nabla\mathbf{u} : \nabla\mathbf{v}\, d\Omega + (\mu+\lambda) \int_\Omega (\nabla\cdot\mathbf{u})\,(\nabla\cdot\mathbf{v})\, d\Omega, \qquad \mathbf{u},\mathbf{v} \in H_0^1(\Omega), \quad (2.3)$$

the weak form of the problem (2.1) can be stated as follows: for a given function $\mathbf{f} \in L^2(\Omega)$, find the solution $\mathbf{u} \in H_0^1(\Omega)$ such that

$$\sigma(\mathbf{u},\mathbf{v}) = (\mathbf{f},\mathbf{v}), \qquad \forall\mathbf{v} \in H_0^1(\Omega). \quad (2.4)$$

The unique solution for the given $\mathbf{f}$ will be denoted by $\mathbf{u}(\mathbf{f})$ [5].
We note that any $\mathbf{u} \in H_0^1(\Omega)$ can be trivially rewritten $\mathbf{u} = \chi_0\mathbf{u} + (1-\chi_0)\mathbf{u}$, where χ_o is the characteristic function of the Ω_0 set. This form provides an orthogonal decomposition of $\mathbf{u}$ as a member of $L^2(\Omega)$. Therefore we can define the projector P as follows:

$$P\mathbf{u} = \chi_o\mathbf{u}. \quad (2.5)$$

The mere knowledge of $\mathbf{u}_0$ does not allow to obtain $\mathbf{f}$ straightforwardly. We therefore define the functional J as

$$\begin{aligned} J(\mathbf{f}) &= \int_{\Omega_0} |\mathbf{u}-\mathbf{u}_0|^2\, dV + \varepsilon \int_\Omega |\mathbf{f}|^2 dV \quad (2.6)\\ &= \int_\Omega (P\mathbf{u}-\mathbf{u}_0)\cdot(\mathbf{u}-\mathbf{u}_0)\, dV + \varepsilon \int_\Omega |\mathbf{f}|^2 dV, \end{aligned}$$

where ε is a real positive number. We look for $\mathbf{g}$ minimizing J:

$$J(\mathbf{g}) \le J(\mathbf{f}), \qquad \forall\mathbf{f} \in V_c, \quad (2.7)$$

where $V_c \subset L^2(\Omega)$ is the space of the finite energy functions with support in Ω_c. The minimization of J accomplishes the minimization of the distance of the solution from the measured value $\mathbf{u}_0$ under penalization of the magnitude of the associated force field $\mathbf{f}$. The penalty parameter ε balances the two requirements.
The minimum of J occurs in $\mathbf{g}$, where the Gateaux derivative satisfies

$$J'[\mathbf{g}](\mathbf{f}-\mathbf{g}) \ge 0, \qquad \forall\mathbf{f} \in V_c, \quad (2.8)$$

that is

$$\int_\Omega (P\mathbf{u}(\mathbf{g})-\mathbf{u}_0)\cdot(\mathbf{u}(\mathbf{f})-\mathbf{u}(\mathbf{g}))\, dV + \varepsilon \int_\Omega \mathbf{g}\cdot(\mathbf{f}-\mathbf{g})\, dV \ge 0, \qquad \forall\mathbf{f} \in V_c, \quad (2.9)$$

Introduce the adjoint problem

$$\begin{aligned} A^*\mathbf{p} &= P\mathbf{u} - \mathbf{u}_0, \quad (2.10)\\ \mathbf{p}|_{\partial\Omega} &= 0. \end{aligned}$$

Because here A is self–adjoint, back substitution into Equation (2.8) gives

$$\int_\Omega A^*\mathbf{p}\cdot(\mathbf{u}(\mathbf{f})-\mathbf{u}(\mathbf{g}))\, dV + \varepsilon \int_\Omega \mathbf{g}\cdot(\mathbf{f}-\mathbf{g})\, dV \ge 0, \qquad \forall\mathbf{f} \in V_c, \quad (2.11)$$

or

$$\int_{\Omega} \mathbf{p} \cdot (\mathbf{f} - \mathbf{g})\, dV + \varepsilon \int_{\Omega} \mathbf{g} \cdot (\mathbf{f} - \mathbf{g})\, dV \geq 0, \qquad \forall \mathbf{f} \in V_c, \tag{2.12}$$

and, finally, one finds the optimal body force in the sense of (2.7):

$$\mathbf{g} = -\frac{\chi_c}{\varepsilon}\mathbf{p}, \tag{2.13}$$

where χ_c is the characteristic function of the Ω_c set. The function $\mathbf{g}$ vanishes outside Ω_c because of our characterization of the set of admissible force fields V_c.

3. Numerical methods and results. For the specific application addressed in the present paper, the general three–dimensional theory illustrated above is restricted to 2D. The three–dimensional elasticity system of equations is approximated to a two–dimensional plain–stress one by vertical average along an *effective thickness* (see Appendix). The direct and inverse systems of partial differential equations deduced in Section 2 now rewrite

$$-\hat{\mu}\Delta\mathbf{u} - (\hat{\mu} + \hat{\lambda})\nabla(\nabla \cdot \mathbf{u}) = -\frac{\chi_c}{\varepsilon}\mathbf{p}, \qquad \mathbf{u}|_{\partial\Omega} = 0, \tag{3.1}$$

$$-\hat{\mu}\Delta\mathbf{p} - (\hat{\mu} + \hat{\lambda})\nabla(\nabla \cdot \mathbf{p}) = \chi_o\mathbf{u} - \mathbf{u}_0, \qquad \mathbf{p}|_{\partial\Omega} = 0. \tag{3.2}$$

Equations (3.1) and (3.2) have been discretized by a finite element method using linear basis functions on an unstructured mesh. The two resulting linear systems are solved by a global conjugate gradient method, thus avoiding any unnecessary iterative coupling [13].

The computational domain is a square with side of 100 microns. The effective Lamè constants are taken from [2], thus resulting in $\hat{\mu} = 2100$ and $\hat{\lambda} = 4150$ PicoNewton per micrometer. The measured displacement $\mathbf{u}_0$ and the cell contour are obtained from the same paper.

The value of the penalty parameter ε can be suitably chosen when reinterpreting the system of Equations (3.1)-(3.2) as a filter. In fact, suppose for a moment that $\Omega_0 = \Omega$ under periodic boundary conditions. The amplitude of the Fourier components of of the solution u_k, p_k satisfy

$$\hat{\mu}k^2 u_k \simeq -\frac{1}{\varepsilon}p_k, \tag{3.3}$$

$$\hat{\mu}k^2 p_k \simeq u_k - u_{0,_k}, \tag{3.4}$$

that is

$$u_k = \frac{u_{0,k}}{1 + \varepsilon\hat{\mu}^2 k^4}. \tag{3.5}$$

Equation (3.5) points out that the system of Equations (3.1)–(3.2) acts as a filter damping the modes corresponding to wavenumbers $\gtrsim \varepsilon^{-1/4}\hat{\mu}^{-1/2}$. The penalty parameter used the calculations illustrated below is $\varepsilon = 10^{-6}$, thus damping algebraically wavelenghts larger than 9 μm.

In Figure 3.1 a portion of the computational domain is shown: the cell contour, the displacement of the beads and the computational mesh are plotted. The cell contour represents a boundary between internal and external elements. Note that some nodes of the mesh correspond to the original beads location while others do not: they have been created for the sake of regularity of the computational grid. The present approach ensures a full flexibility in this respect. According to the notation introduced in the preceding sections, the cell contour defines Ω_c while the collection of the elements that have at least one node with measured displacement defines Ω_0.

The computed displacement is shown in Figure 3.2. The mean difference between

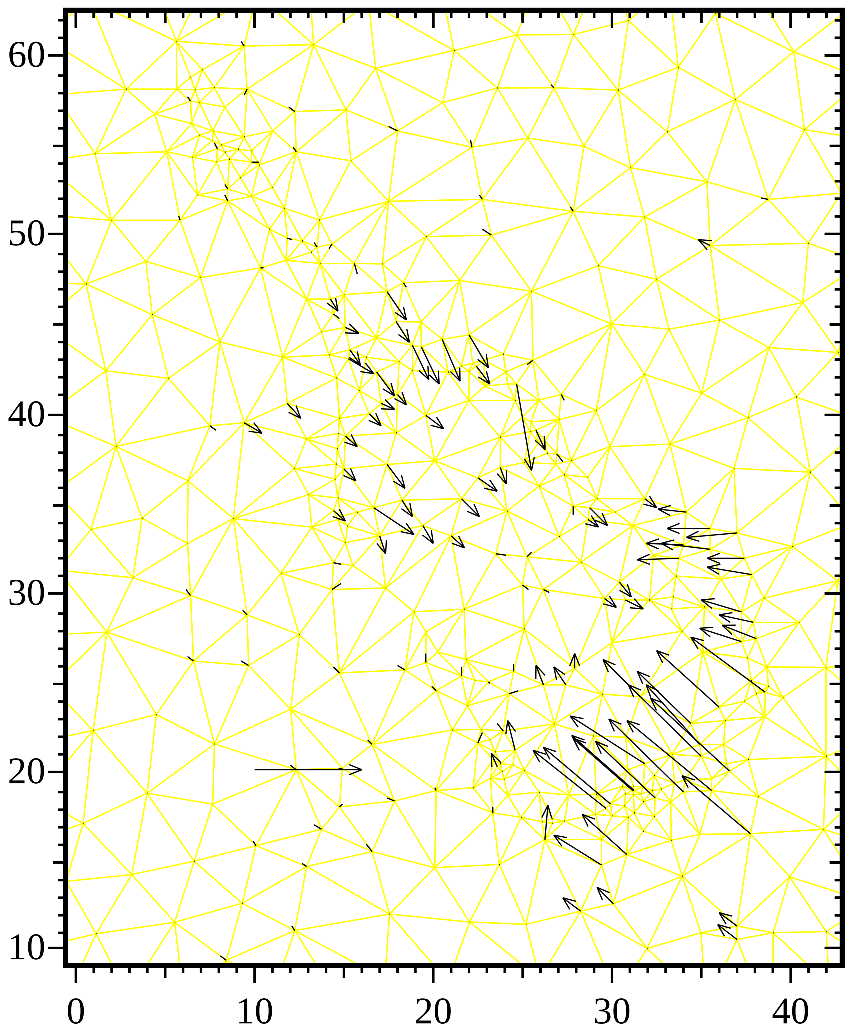

Fig. 3.1. *Experimental displacement of the beads merged in the upper layer of the gel, as taken from [2]. The computational mesh is represented in grey. The mesh satisfies two constraints: is has a node in every point where displacement has been measured and a sequence of element sides coincides with the boundary of the cell. The reference vector at the bottom left corner is 6 microns long.*

the calculated and the measured solution is

$$\frac{1}{n}\sum_{i=1}^{n}\sqrt{(\mathbf{u}_i-\mathbf{u}_{0,i})^2}=8.8\ 10^{-2}\,\mu\mathrm{m} \tag{3.6}$$

where the sum runs over all the nodes where $\mathbf{u}_0$ is known.

The displacement of the gel matrix essentially occurs around the cell edge and,

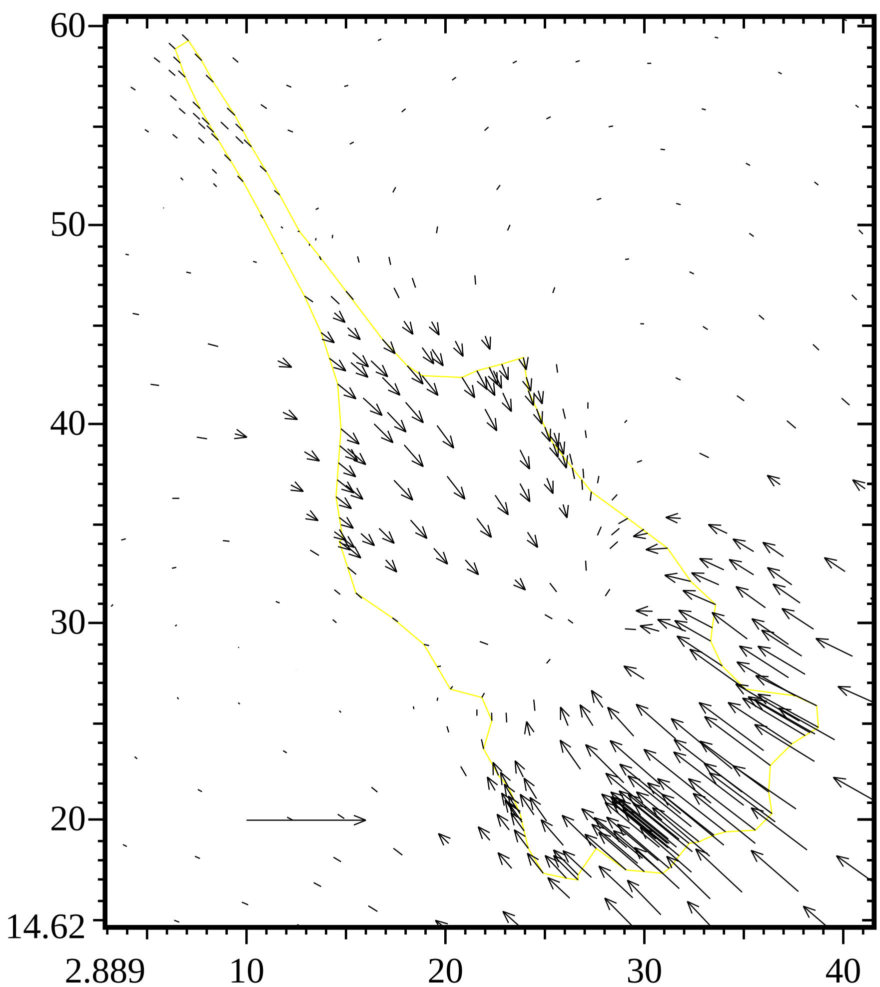

FIG. 3.2. *Computed displacement of the gel layer. The reference vector at the bottom left corner is 6 microns long.*

secondly, at the tail, as can be observed also in Figure 3.3, where the magnitude of the displacement field is represented.

The computed force field is plotted in Figure 3.4. The qualitative behavior is very

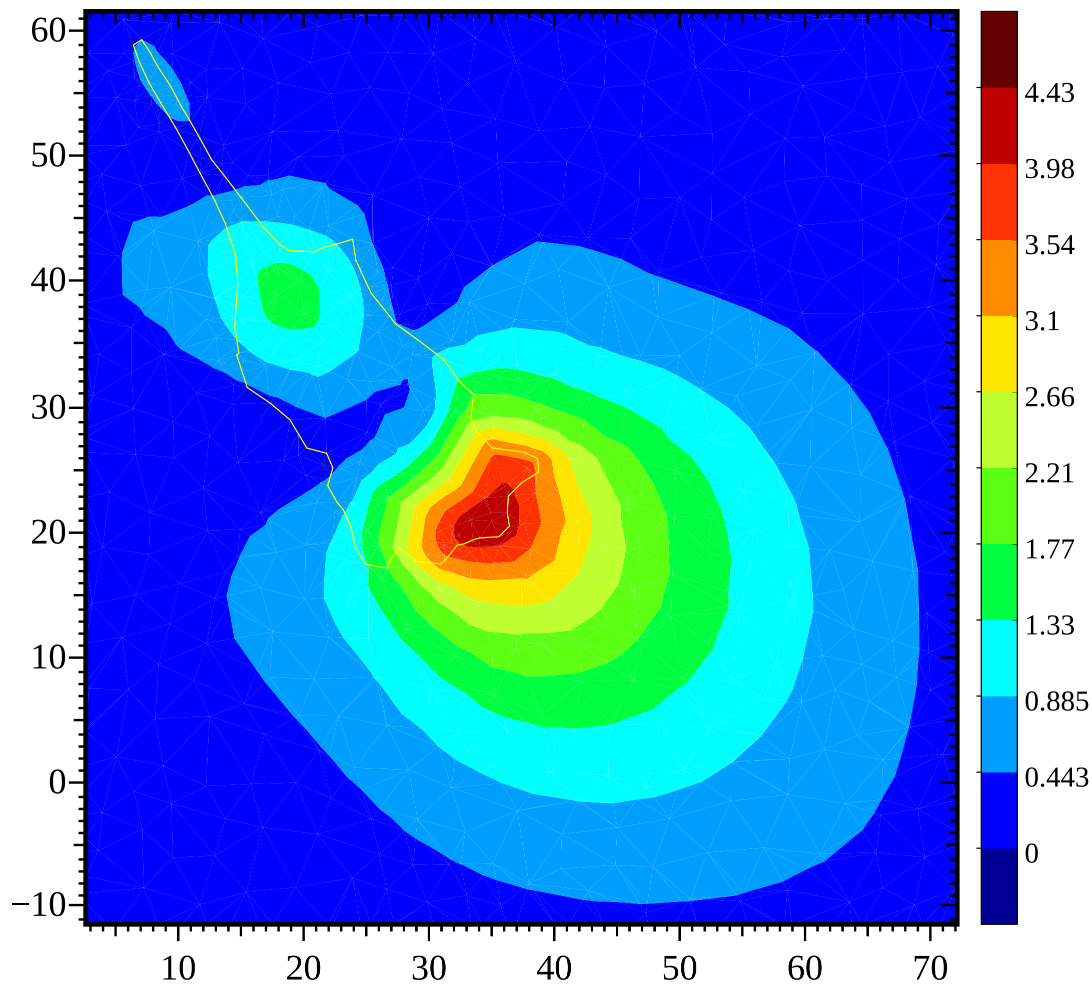

FIG. 3.3. *Color map of the magnitude of the computed displacement of the gel layer. The color scale is in microns.*

near to results shown by Dembo and Wang. The exerted force reaches the maximum value of some thousands of PicoNewtons, corresponding to the remarkable stress of thousands of Pascal. A striking feature of the plot is that the cell is pulling both at the edge and at the tail, although the latter by less intensity. This result is in agreement with [2].

Final Remarks. In this paper a novel method has been proposed for solving the inverse problem to obtain forces from displacement of an elastic body. The statement and functional derivation of a cost function yields two coupled systems of partial dif-

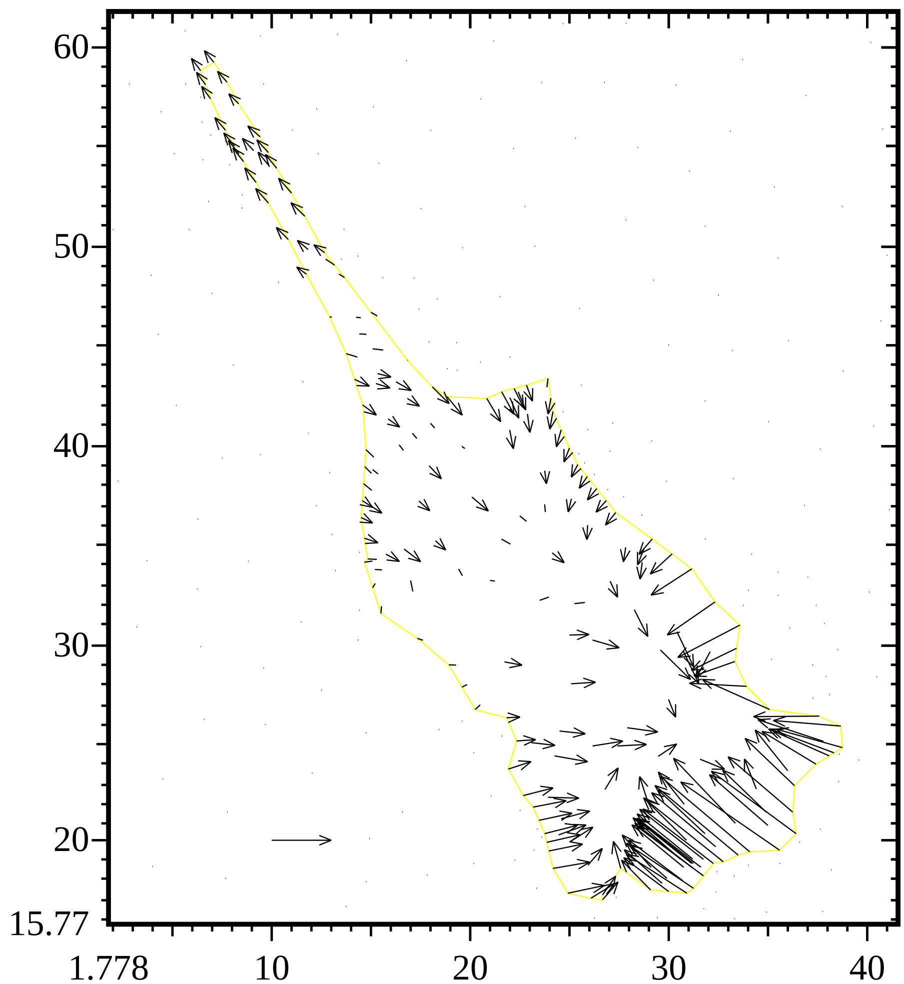

Fig. 3.4. *Computed force field exerted by the fibroblast on the gel layer. The magnitude of the reference vector at the bottom left corner corresponds to* 10^3 *PicoNewton.*

ferential equations. The numerical solution of the inverse problem deduces the force acting on a surface on the basis of a partial knowledge of the deformation. As a specific application, the method has been applied to obtain a quantitative plot of the forces exerted by a fibroblast cell on a gel substratum.

The proposed approach is quite general in not assuming a pointwise nature of the surface force. The direct solution of the elasticity equations makes possible, in principle, to apply the proposed methodology to a variety of situations for which the Boussinesq solution does not apply: for instance non-homogeneous substrate or non isotropic pre-stress of the gel.

The deduction of the system of equations from a minimum principle provides a clear meaning to the regularization procedure, while the statement of the equations in precise functional spaces ensures the well posedness of the direct and inverse problem. Finally, the numerical integration of the equations by a finite element discretization ensures full geometrical flexibility to account for the complicated contour of a cell or to operate local mesh refinements suggested by accuracy arguments.

Appendix A. Two dimensional modeling. The Extracellular Matrix is deformed by the traction exerted by the cell and, in principle, the strain of the gel can be predicted solving the force balance equation for an elastic three–dimensional body with suitable boundary conditions. However, an *a priori* consideration of the characteristics of the displacement field in the elastic substrate suggests some suitable simplification of the full three dimensional model.
As a matter of fact, the substrate layer is very shallow: its horizontal extension ($\sim$ mm) is much larger than the vertical one ($\sim 10-100\mu$m). However this geometrical scale ratio by itself does not allow any estimate of the behavior of the solution along the vertical direction, a consideration that could be helpful in addressing a suitable approximate model.
The useful observation is instead that the vertical displacement is very small when compared to the horizontal one. Let us denote by X and Z the typical scale lengths of the horizontal and vertical displacement, respectively. The length X is of the order of the diameter of a cell ($\sim 20\mu$m), while Z is to be determined. In the following we indicate by U and W the typical horizontal and vertical displacement.
The boundary conditions of the three dimensional force balance equation at the cell–gel interface read

$$\mu(u_z + w_x) = \tau \qquad \text{at} \qquad z = 0, \tag{A.1}$$

$$(\mu+\lambda)w_z + \lambda u_x = 0 \qquad \text{at} \qquad z = 0. \tag{A.2}$$

As $\mu \sim \lambda$, inspection of Equation (A.2) yield that it must be $W/Z \sim U/X$. According to the experimental evidence, the vertical displacement is much smaller than the horizontal one: $U \gg W$. Using this observation into Equation (A.1) one deduces that $|w_x| \ll |u_z|$ and therefore the horizontal derivative of the vertical displacement can be neglected therein.
It follows that to first order the horizontal displacement vanishes in the layer at the depth $Z \sim \mu U/\tau$. In the mentioned experiments

$$U_{max} = 6\,\mu\text{m}, \qquad \mu = \frac{E}{2(1+\nu)} = \frac{E}{3} = 2000\,pN/\mu m^2 \qquad \tau_{max} = 10^4\,pN/\mu m^2$$

thus yielding $Z_{max} \sim 1\mu$m, much smaller than the height of the matrigel layer (70μm). According to the observations above, we adopt a two dimensional "plain stress" model, obtained by vertical integration of the three dimensional equation of the linearized elasticity along the effective thickness Z_{max}. Therefore one gets

$$-\hat{\mu}\Delta\mathbf{u} - (\hat{\mu}+\hat{\lambda})\nabla(\nabla\cdot\mathbf{u}) = \boldsymbol{\tau}, \tag{A.3}$$

where $\boldsymbol{\tau}$ is the shear stress at the surface. The quantities

$$\hat{\mu} = Z_{max}\frac{E}{2(1+\nu)} \qquad \hat{\lambda} = Z_{max}\frac{E\nu}{1-\nu^2} \tag{A.4}$$

are the effective Lamè constants of the two-dimensional model and have the dimension of force per unit length [3, 9]. It is to be remarked that the above determination of Z_{max} is based on dimensional arguments only.

Acknowledgments. The author is indebted with Pierluigi Rozza, Enrico Serra and Luigi Preziosi for fruitful discussions about the content of this paper. This research has been partially supported by the FIRB 2001 Project "Metodi dell'Analisi Matematica in Biologia, Medicina e Ambiente".

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