# Force Traction Microscopy: an inverse problem with pointwise observations

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**Abstract**

Force Traction Microscopy is an inversion method that allows to obtain the stress field applied by a living cell on the environment on the basis of a pointwise knowledge of the displacement produced by the cell itself. This classical biophysical problem, usually addressed in terms of Green functions, can be alternatively tackled using a variational framework and then a finite elements discretization. In such a case, a variation of the error functional under suitable regularization is operated in view of its minimization. This setting naturally suggests the introduction of a new equation, based on the adjoint operator of the elasticity problem. In this paper we illustrate the rigorous theory of the two–dimensional and three dimensional problem, involving in the former case a distributed control and in the latter case a surface control. The pointwise observations require to exploit the theory of elasticity extended to forcing terms that are Borel measures.

## Introduction

Many living cells have the ability to migrate, both in physiological and pathological conditions; examples include wound healing, embryonic morphogenesis and the formation of new vessels in tumours. The motility of a cell is driven by the reorganization of its inner structure, the cytoskeleton, according to a complex machinery. The net effect of this process is that a cell is able to apply a stress on the environment, pulling the surrounding material and produce its own movement. The biophysical details of the internal engine of a cell are far from being fully understood or rephrased in terms of a mathematical model; nevertheless its inverse counterpart, that is the determination of forces on the basis of measured displacement, is quite a popular problem in the biophysical community.

The early idea to study the force applied by cells in their migration as an inverse problem dates back to the work of Harris and coworkers in the eighties [13]. They consider the action of fibroblasts (cells with a high degree of contractility) laying on a flat poliethylene sheet. They argue that the wrinkles produced by the cells on the substrate are a good indicator of the stress exerted by the cells on the surface itself: direction, height and length of the buckles correlate with the direction and intensity of the force, respectively.

After several efforts, the correct methodology to translate the qualitative argument above into a quantitative procedure was formulated by Dembo and Wang in a seminal paper about twenty years later [10, 9]. Their technique was new, both in a technological and in a methodological sense. The use of a soft poliacrilamide substrate avoids the emergence of wrinkles, that are typically produced in a nonlinear elasticity range. Thus restricting to a linear elastic regime, the displacement of fluorescent beads dispersed in the elastic material is evaluated from different images. Finally, they solve the direct problem in terms of Green elasticity functions and then minimize the error under regularization by a discrete Tichonov method. This method has become a standard in biophysics and has been applied to a variety of cell types in a number of experimental settings to investigate cell adhesion, contractility, variability of the dynamics of stiffer and softer substrates, response to chemotactic stimula and many others.

An alternative approach to address the same issue can be stated in a continuous variational framework [2]. Again, the starting point is a Tichonov functional defined as the error norm plus a penalization of the magnitude of the force. If a variation of the cost functional is operated at a continuous level, the definition of an adjoint problem for the unknown force naturally arises. This way, two elliptic partial differential equations coupled by the (linear) source terms are obtained and their approximate solution can be addressed, for instance, by a finite element discretization. The adjoint method has been applied to evaluate the surface tension generated by different cell lines, solving a two–dimensional depth–averaged elasticity set of equations.

Although the optimal control approach is less popular than the standard inverse method based on Green functions, it has some attractive features that make it worth to investigate further. The first reason is of numerical type: a variational formulation, based on forward and adjoint problem to be solved jointly, can be addressed by a finite element code where local approximating polinomials might be computationally more efficient than convolution of global Green functions plus a decoupled minimizing algorithm. The second, more relevant, issue is that Green functions of the elasticity problem are known explicitly only in few simple geometrical configurations, including the infinite half–plane. The typical biological domain where cells apply stress in their three dimensional migration is geometrically complex and Green functions are not known a priori. Last but not least, the optimum control theory offers a framework for a natural generalization of the forward model to a number of important biological characterizations, in particular nonlinear elastic materials, possibly including non–homogeneities and anisotropy due to fibres embedded in the material itself.

The aim of this paper is state a firm theoretical ground for the formal derivation and the rigorous theory of the force traction microscopy in three dimensions. Such a theory is, at our knowledge, still lacking and this paper aims to fill this gap. The availability of pointwise observations makes it impossible to state the well posedness of the problem using Hilbert spaces only and we resort to the theory developed by Casas [6, 5, 7]. Existence and uniqueness of the solution is proved in a general context that encompasses distributed boundary control in two and three dimensions. The differential system determined and analyzed in this work are the intermediate mathematical step in view of its numerical discretization and applications to applied biophysical questions in cell motility.

# 1 Background

In this section we resume a number of classical results of functional analysis and partial differential equations that will be used in this paper.

## 1.1 Functional spaces

The theory of linear elliptic equations is classically based on the definition of some suitable functional spaces. We sketch here below the main definitions and properties; more details can be found, for instance, in [1] and [19] [1].

**Definition 1** *Given $\Omega$ an open set in $\mathbb{R}^n$, we set the following Sobolev spaces:*

- $L^p(\Omega) := \{\mathbf{u} : \Omega \to \mathbb{R}^m \mid \int_\Omega |\mathbf{u}|^p < \infty\}$;
- $W^{k,p}(\Omega) := \{\mathbf{u} \in L^p(\Omega) \mid \nabla^i \mathbf{u} \in L^p(\Omega),\ \forall i \in \{1, \dots, k\}\}$.

*where $\nabla^i$ is the i-th gradient and $\nabla^0 := \mathbf{1}$ is the identity tensor.*

Non integer indexed Sobolev space (i.e. when $k \in \mathbb{R}$) can be also defined, see [4], and they will turn useful in the following. Relevant examples of Sobolev spaces are the following Hilbert spaces:

- $L^2(\Omega)$ with the scalar product $(\mathbf{u}|\mathbf{v})_{L^2(\Omega)} := \int_\Omega \mathbf{u} \cdot \mathbf{v}$;
- $H^k(\Omega) := W^{k,2}(\Omega)$ with the scalar product $(\mathbf{u}|\mathbf{v})_{H^k(\Omega)} := \sum_{i=0}^k \int_\Omega \nabla^i \mathbf{u} \cdot \nabla^i \mathbf{v}$.

The trace operator $\tau_{\partial\Omega}$ is defined as the restriction of a function defined on $\Omega \subset \mathbb{R}^n$ over its boundary $\partial\Omega$, having dimension $n-1$. Traces are characterized by [1, 4]:

**Theorem 2** *(Trace Theorem) Let $\Omega \in \mathbb{R}^n$ an open bounded set with boundary $\partial\Omega$. The trace $\tau_{\partial\Omega}$ is a linear and continuous functional such that:*

- *injects $W^{1,p}(\Omega)$ in $L^p(\partial\Omega)$ if $p < n$;*
- *if $\mathbf{u} \in H^k(\Omega)$ then $\tau(\nabla^i \mathbf{u}) \in H^{k-1/2}(\partial\Omega)$.*

Using traces, we can define subspaces of Sobolev spaces that allow us to treat boundary conditions. Let us define the space of fields in $H^1(\Omega)$ satisfying homogeneous Dirichlet boundary condition on $\Gamma_D$:

$$H^1_{0,\Gamma_D}(\Omega) := H^1(\Omega) \cap \mathsf{ker}(\tau_{\Gamma_D}).$$

A similar construction allows us to define, more generally, the space $W^{1,s}_{0,\Gamma_D}$ $(s > 0)$, see [1, 19]. It is worth noting that (thanks to Poincare Lemma [22]) $H^1_{0,\Gamma_D}(\Omega)$ can be equipped with the scalar product: $(\mathbf{u}|\mathbf{v})_{H^1_{0,\Gamma_D}(\Omega)} := \int_\Omega \nabla\mathbf{u} \cdot \nabla\mathbf{v}$ equivalent to the one given above. The following special case of Sobolev Embedding theorem [19] holds:

**Theorem 3** *Let $\Omega \subset \mathbb{R}^n$ an open bounded domain $n = 2, 3$. Then:*

- $W^{1,p}(\Omega) \hookrightarrow C^0(\mathsf{cl}\Omega)$, $p > n$;
- $H^2(\Omega) \hookrightarrow W^{1,p}(\Omega)$, $p \in [1, \frac{2n}{n-2}]$;
- $W^{1,p}(\Omega) \hookrightarrow L^2(\Omega)$, $p \geq \frac{2n}{n+2}$;

*where $\hookrightarrow$ means that the inclusion is continuous and the symbol $\mathsf{cl}$ denote the closure of a set.*

## 1.2 Linear Elasticity

In a spatial description of continuum mechanics the force balance equations on a bounded domain $\Omega \subset \mathbb{R}^n$ $(n \leq 3)$ read: [2]

$$\begin{cases} -\nabla \cdot \mathbf{T} & = \mathbf{b}, \qquad \text{in } \Omega, \\ \mathbf{Tn} & = \mathbf{c}, \qquad \text{on } \Gamma_N, \\ \mathbf{u} & = 0, \qquad \text{on } \Gamma_D. \end{cases} \tag{1}$$

[1] In this work we tacitly assume that we are dealing with domains enjoying some special properties. The interested reader may find in [1, 19] the hypothesis needed to develop the theory. In the following, sections, we will stick us with a bounded $C^2-$regular boundary, which is enough to prove the results shown here.

[2] Vectors (here elements of $\mathbb{R}^n$) are indicated with boldface latin letter, second order tensor (here elements of $\mathsf{Lin}(\mathbb{R}^n)$) with capitol boldface and fourth order tensor (here elements of $\mathsf{Lin}(\mathsf{Lin}(\mathbb{R}^n))$) with capitol blackboard boldface. Scalar products in these spaces are indicated with the same symbol "$\cdot$", the context clarifying the meaning.

where $\Gamma_D, \Gamma_N \subset \partial\Omega$ are open sets such that $\mathsf{cl}(\Gamma_N \cap \Gamma_D) = \emptyset$ and $\Gamma_N \cup \Gamma_D = \partial\Omega$. In our framework the domain $\Omega$ is the portion of the space occupied by the elastic gel. Its boundary $\partial\Omega$ can be be constrained not to move (zero displacement on $\Gamma_D$) or can be loaded by the action of the cell on $\Gamma_N$. The vector fields $\mathbf{b}$ and $\mathbf{c}$ are the given applied load per unit volume and surface, respectively; they represent the traction exerted by the cell on the gel.
The symbol $\mathbf{T} : \mathbf{x} \in \Omega \mapsto \mathbf{T}(\mathbf{x}) \in \mathsf{Sym}(\mathbb{R}^n)$ denotes the Cauchy stress tensor field of the material contained in $\Omega$. The internal forces in an elastic body depend on the strain of the material with respect to a reference relaxed configuration. If we denote by $\mathbf{u} : \mathbf{x} \in \Omega \mapsto \mathbf{u}(\mathbf{x}) \in \mathbb{R}^n$ the displacement field due to the traction of the cell, it must be $\mathbf{T} = \hat{\mathbf{T}}(\nabla\mathbf{u})$ being $\hat{\mathbf{T}}$ the constitutive map for $\mathbf{T}$. For objectivity reasons, such a constitutive map must be non-linear [8]. For small deformations, the stress tensor $\mathbf{T}$ can be approximated by its first order derivative evaluated in the relaxed configuration: $\mathbf{T} = \hat{\mathbf{T}}(\nabla\mathbf{u}) \approx \hat{\mathbf{T}}'(0)[\nabla\mathbf{u}]$. Here $\hat{\mathbf{T}}'(0) := \mathbb{C}$ is a fourth–order constant tensor: in indicial form $T_{ij} = C_{ijmn}\,\partial_n u_m$.
Therefore $\mathbb{C} \in \mathsf{Lin}(\mathsf{Lin}(\mathbb{R}^n))$ and it satisfies the following conditions [8]:

$$\mathbb{C}[\mathbf{S}] = \mathbb{C}[\mathbf{S}^T], \quad \forall \mathbf{S} \in \mathsf{Lin}(\mathbb{R}^n), \tag{2}$$

$$\mathbf{S} \cdot \mathbb{C}[\mathbf{S}] \geq \alpha \mathbf{S} \cdot \mathbf{S}, \quad \alpha > 0, \forall \mathbf{S} \in \mathsf{Sym}(\mathbb{R}^n), \tag{3}$$

$$\mathbf{S} \cdot \mathbb{C}[\mathbf{H}] = \mathbf{H} \cdot \mathbb{C}[\mathbf{S}], \quad \forall \mathbf{H}, \mathbf{S} \in \mathsf{Sym}(\mathbb{R}^n). \tag{4}$$

The condition (2) accounts for objectivity in the linearized case, the symmetry property (4) reflects torque balance while the inequality (3) is a requirement of "stability", namely strong ellipticity in the partial differential equation's literature.
The variational form of (1) in the case of linear(ized) elasticity is, formally,

$$\int_\Omega \mathbb{C}[\nabla\mathbf{u}] \cdot \nabla\mathbf{v} = \int_\Omega \mathbf{b} \cdot \mathbf{v} + \int_{\Gamma_N} \mathbf{c} \cdot \mathbf{v}, \tag{5}$$

for all suitable $\mathbf{v}$. The problem (1) has been studied in great detail, [8], [17]. Several results of well posedness and regularity are known and we resume here only those strictly needed for our purposes.
First of all, it holds:

**Theorem 4** *(Lax–Milgram Lemma) Given the problem in* (5) *with* $\mathbf{b} \in L^2(\Omega)$, $\mathbf{c} \in L^2(\Gamma_N)$, $\Omega$ *a bounded open set with Lipschitz boundary and* $\Gamma_D \neq \emptyset$. *Let the coefficient* $\mathbb{C}$ *satisfy conditions* (3) *and* (4)*; then, problem* (5) *admits a unique solution in* $H^1_{0,\Gamma_D}(\Omega)$ *which depends continuously on the data.*

In the following we assume to deal with a bounded, open domain $\Omega$ with smooth enough boundary $\partial\Omega$ ($C^2-$regularity is enough). The weak solution of an elliptic problem possesses remarkable regularity properties [8], [18]:

**Theorem 5** *Let the problem (5) be given with* $\mathbf{b} \in L^2(\Omega)$, $\mathbf{c} \in H^{\frac{1}{2}}(\Gamma_N)$ *and* $\Omega$ *a bounded open set such that its boundary* $\partial\Omega$ *is* $C^2-$*regular. If* $\Gamma_D \neq \emptyset$ *and* $\Gamma_N = \emptyset$ *or* $\mathsf{cl}(\Gamma_N \cap \Gamma_D) = \emptyset$ *then the solution* $\mathbf{u}$ *of* (5) *belongs to* $H^1_{0,\Gamma_D}(\Omega) \cap H^2(\Omega)$ *and depends continuously on the data.*

According to Theorems 3 and 5, the solution of an elliptic problem is continuous when the above hypothesis holds.
For reasons that will be clear in the following, we need to extend the above theory to the case of forcing terms of the linear elasticity operator that are are Borel measures (i.e. elements of the dual space of $C^0$, see [21]). Following Casas [7, 5] the following theorem holds for the pure Dirichlet and pure Neumann case, although a generalization to the mixed case is straightforward when $\Omega$ is sufficiently regular:

**Theorem 6** *Let $\Omega$ a bounded open set such that its boundary $\partial\Omega$ is $C^2-$regular. Set $s \in [1, \frac{n}{n-1})$ and $s'$ such that $\dfrac{1}{s} + \dfrac{1}{s'} = 1$. Then, the variational problem: find $\mathbf{u} \in W^{1,s}(\Omega)$ such that $\forall \mathbf{v} \in W^{1,s'}(\Omega)$ equation (5) holds, given $\mathbf{b}$ and $\mathbf{c}$ regular Borel measure, admits a unique solution which depends continuously on the data.*

## 1.3 Optimal Control

In this work, the term at the right hand side of equation (5) is to be interpreted as a control, so that the traction at the boundary $\mathbf{c}$ or the volume force $\mathbf{b}$ are formally an unknown of the problem. In the following, such a control will be generically indicated as $\mathbf{f} \in \mathsf{F}$, where $\mathsf{F}$ is a suitable Hilbert space. We also denote by $\mathsf{U}$ the Hilbert space that the displacement $\mathbf{u}$ belongs to.
We introduce below two operators that will turn useful for the applications to be discussed in the following.

**Solution Operator:** We define solution operator $\mathcal{S} : \mathsf{F} \to \mathsf{U}$, the map that, for a given control $\mathbf{f}$ on the right hand side of (1) or (5), assigns the displacement field $\mathbf{u}$ that solves the problem. More specifically, we study the following two cases [3] :

- Distributed control: $\mathcal{S}\mathbf{b} = \mathbf{u}$ iff (1) or (5) hold, with $\mathbf{c} = 0$ ;
- Boundary Control: $\mathcal{S}\mathbf{c} = \mathbf{u}$ iff (1) or (5) hold, with $\mathbf{b} = 0$.

In this section we assume that $\mathsf{F}$ and $\mathsf{U}$ are tuned in such a way that:

$$\mathcal{S} \in \mathsf{Lin}(\mathsf{F}, \mathsf{U}). \tag{6}$$

The rigorous proof of this fact in the specific cases of interest herein is given in Sections 2 and 3.

**Observation Operator:** In this work we are interested in pointwise observation of the state. Typically, in cellular traction microscopy some beads are seeded into the elastic matrigel and their displacement is recorded during the motion of the cell. Mathematically, the observation operator is therefore a list of Dirac delta distributions i.e. $\mathcal{O} := (\delta_{\mathbf{x}_1}, \dots, \delta_{\mathbf{x}_N})$. It can be easily shown that this operator is continuous in the functional spaces of our interest if $\Omega \subset \mathbb{R}^n$, $n \leq 3$. In fact (see [21]):

**Proposition 7** *$\mathcal{O}$ is a linear and continuous form on $C^0(\mathsf{cl}\Omega)$ if $\Omega \subset \mathbb{R}^n$ ($n = 1, 2, 3$).*

Under suitable regularity of the control $\mathbf{f}$, in the following section we will prove that

$$\mathcal{O} \in \mathsf{Lin}(\mathsf{U}, \mathbb{R}^{Nn}). \tag{7}$$

### 1.3.1 Penalty Functional

The information experimentally provided to solve the inverse problem, i.e. the pointwise measurements of the state $\mathbf{u} \in \mathsf{U}$ are usually not sufficient to ensure the well posedness of Problem (1). The problem is therefore underdetermined and, as customary, we state a suitable minimization problem to circumvent this drawback. Let:

- $\mathbf{f} \in \mathsf{F}_{\text{adm}}$, where $\mathsf{F}_{\text{adm}}$ is a closed subspace of $\mathsf{F}$;
- $\mathsf{X} := \mathbb{R}^{Nn}$, where $N$ is the number of beads and $n = 1, 2, 3$ as before (we denote with the circle $\circ$ the scalar product in $\mathsf{X}$);

[3] For simplicity, we restrict ourselves in the case where only the control appears as a forcing term. The more general case in which the forces in (1) or in (5) are sum of known fields and the control is analogous but technically more cumbersome, since the solution operator $\mathcal{S}$ is affine (see [16]).

- $\mathcal{S} \in \mathsf{Lin}(\mathsf{F}, \mathsf{U})$ is the solution control–to–state map defined previously, satisfying (6);
- $\mathcal{O} \in \mathsf{Lin}(\mathsf{U}, \mathsf{X})$ is the observation operator defined above, satisfying (7);
- $u_0 = (\mathbf{u}_0^1, \ldots, \mathbf{u}_0^N) \in \mathsf{X}$ is the list of the measured displacements, supposed to be known;
- $\varepsilon > 0$ is the penalization parameter, to be fixed.

**Definition 8** *The penalty functional $\mathcal{J} : \mathsf{F} \to \mathbb{R}^+$ is defined as:*

$$\mathcal{J}(\mathbf{g}) = \frac{1}{2}\|\mathcal{O}\mathcal{S}\mathbf{g} - u_0\|_{\mathsf{X}}^2 + \frac{\varepsilon}{2}\|\mathbf{g}\|_{\mathsf{F}}^2. \tag{8}$$

Our goal is to minimize the functional $\mathcal{J}$ on $\mathsf{F}_{\text{adm}}$. If the forward problem (1) has the properties stated in the previous section, the existence and uniqueness of a global minimum for the functional $\mathcal{J}$ above can be readily obtained. We first state (see [16]):

**Proposition 9** *The penalty functional $\mathcal{J}$ in (8) is coercive and strictly convex. Moreover, if* (6) *and* (7) *hold, it is also continuous.*

Then, we recall a classical theorem [16]:

**Theorem 10** *Let $\mathcal{J} : \mathsf{F}_{\text{adm}} \subset \mathsf{F} \to \mathbb{R}^+$ be a continuous, coercive and strictly convex functional. If $\mathsf{F}_{\text{adm}}$ is a closed subspace of $\mathsf{F}$ then a unique minimum point of $\mathcal{J}$ exists.*

After proving that $\mathcal{J}$ admits a unique minimum point, say $\mathbf{f}$, we can characterize it using the Euler equation associated to $\mathcal{J}$. It is easy to show that:

**Proposition 11** *If* (6) *and* (7) *hold, then $\mathcal{J}$ is differentiable.*

The following statement resumes the results obtained in this section:

**Theorem 12** *Let $\mathsf{F}$ an Hilbert space, $\mathcal{J} : \mathsf{F}_{\text{adm}} \subset \mathsf{F} \to \mathbb{R}^+$ defined as in* (8) *and $\mathsf{F}_{\text{adm}}$ being a closed subspace of $\mathsf{F}$. Let the hypothesis (6), (7) on $\mathcal{S}$ and $\mathcal{O}$ hold.*
*Then, a unique minimum point of $\mathcal{J}$ exists, say $\mathbf{f} \in \mathsf{F}_{\text{adm}}$ and it solves:*

$$\mathcal{P}\mathcal{J}'(\mathbf{g}) = 0. \tag{9}$$

*where the prime ($'$) means differentiation and $\mathcal{P} \in \mathsf{Lin}(\mathsf{F})$ is the projection onto $\mathsf{F}_{\text{adm}}$.*

### 1.3.2 Adjoint State

Since the functional $\mathcal{J}$ admits a unique global minimum in a closed subspace $\mathsf{F}_{\text{adm}} \subset \mathsf{F}$ and it is differentiable, from (9) it follows that the optimal control $\mathbf{f} \in \mathsf{F}_{\text{adm}}$ satisfies

$$\mathcal{P}\mathcal{J}'(\mathbf{f}) = 0 \;\Leftrightarrow\; \varepsilon\mathbf{f} + \mathcal{P}(\mathcal{O}\mathcal{S})^T(\mathcal{O}\mathcal{S}\mathbf{f} - u_0) = 0, \tag{10}$$

To avoid the evaluation of the operator $\mathcal{S}$ in equation (10), we introduce the so called adjoint state [16]. The proof of well posedness of the following problem will be given in the following sections for the specific contexts. Let $\mathbf{p} \in \mathsf{P}$ be formally defined as:

$$\mathcal{A}^T\mathbf{p} = \mathcal{O}^T(\mathcal{O}\mathbf{u} - u_0), \tag{11}$$

where $\mathsf{P}$ is a suitable functional space and $\mathcal{A}^T : \mathsf{P} \to \mathsf{U}^*$ an operator to be assigned. Roughly speaking, $\mathcal{A}$ should be taken such that the operator $\mathcal{S}\mathcal{A}$ will be easy to deal with. For example, in Section 2, we will find that $\mathcal{S}\mathcal{A}$ is the identity map. Differently to most of the literature on the subject (e.g. [16]), we strictly need to make a distinction between $\mathcal{A}$ and $\mathcal{S}^{-1}$ as we shall see in Section 3. Now, plugging Equation (11) into (10) we obtain:

$$\varepsilon\mathbf{f} + \mathcal{P}(\mathcal{A}\mathcal{S})^T\mathbf{p} = 0. \tag{12}$$

The choice of the operator $\mathcal{A}$ and the analysis of its continuity property is the main goal of the paper. We deal with this issue in the following section, discussing the control of Dirichlet and Mixed problems.

### 1.4 Optimal Control and Inverse Problems

Since we want to use the tool presented above as an Inverse method rather than an Optimal Control one, it is worthwhile to recall some basic definitions and properties of Inverse and Ill–Posed problems and their regularization. As a basic reference for this theory we refer to [12]. Here the discussion is kept at a minimum degree of complexity and, hence, of rigour. Let us focus on our basic problem, i.e. find the force producing exactly the displacement measured which writes in formulas:

$$\text{find } \mathbf{f} \in \mathsf{F}_{\text{adm}} \text{ such that } \mathcal{OS}\mathbf{f} = u_0. \tag{13}$$

Since the problem above can in principle fail one or more among the three Hadamard condition of well posedness (and actually does, in practice), it is convenient to introduce a mollified notion of solution. We call $\mathbf{f}_{BAS} \in \mathsf{F}_{\text{adm}}$ the *Best Approximation Solution* of (13) if:

$$\mathbf{f}_{BAS} = \arg\min_{\mathsf{F}_{\text{adm}}}\{\|\mathbf{g}\|_{\mathsf{F}} \text{ such that } \mathbf{g} = \arg\min_{\mathsf{F}_{\text{adm}}}\left(\mathbf{h} \mapsto |\mathcal{OS}\mathbf{h} - u_0|\right)\} \tag{14}$$

This definition naturally induces a weakened concept of the inverse map of $\mathcal{OS}$, namely the *Moore Penrose Generalized Inverse*, $(\mathcal{OS})^\dagger$. Apart of technical definitions, we can recall its most interesting properties:

$$\mathsf{dom}(\mathcal{OS})^\dagger := \mathsf{ran}(\mathcal{OS}) + (\mathsf{ran}(\mathcal{OS}))^\perp \tag{15}$$

$$(\mathcal{OS})^\dagger : u_0 \in \mathbb{R}^n \mapsto \mathbf{f}_{BAS} \in \mathsf{F}_{\text{adm}} \tag{16}$$

Since the range of the operator $\mathcal{OS}$ ($\mathsf{ran}(\mathcal{OS})$) is a subspace of $\mathbb{R}^{3N}$, we can apply the Proposition 2.4 and the Theorem 2.5 of [12] saying that the above defined $\mathbf{f}_{BAS}$ exists unique and the operator $(\mathcal{OS})^\dagger$ is continuous.
Applying the Tichonov regularization procedure to the operator $(\mathcal{OS})^\dagger$, we end up with the minimum problem for the family, with respect to the parameter $\varepsilon$, of penalty functional in (8). Actually, the Theorem 5.2 in [12] confirms that the sequence of minimum of $\mathcal{J}$ converges strongly to $\mathbf{f}_{BAS}$ provided the regularization parameter $\varepsilon$ and the noise level on the data $u_0$ tend to 0 in a suitable way.

## 2 The Dirichlet Problem with Distributed Control

In this section we introduce and analyse an inverse problem which arises in cellular traction microscopy on flat substrates. We provide well posedness results for the problem formally stated in [2, 3] in the plane. Results still hold for a Dirichlet problem in $\mathbb{R}^3$ with almost no modifications.

### 2.1 Forward Problem

Let $\Omega \subset \mathbb{R}^2$ be an open bounded domain with $C^2-$regular border, where the Dirichlet problem of Linear Elasticity applies. For this section we consider $\Gamma_D = \partial\Omega$, $\mathsf{F} = L^2(\Omega)$, $\mathsf{U} = H^2(\Omega) \cap H^1_0(\Omega)$, $\mathbf{c} = 0$ and $\mathbf{b} := \mathbf{f}$. The problem (1) or (5) with the above hypothesis reads:

$$\text{given } \mathbf{f} \in L^2(\Omega), \text{ find } \mathbf{u} \in H^2 \cap H^1_0(\Omega) \text{ s.t. } \forall \mathbf{v} \in H^1_0(\Omega):$$

$$\int_\Omega \nabla\mathbf{u} \cdot \mathbb{C}[\nabla\mathbf{v}] = \int_\Omega \mathbf{f} \cdot \mathbf{v}. \tag{17}$$

According to the notation introduced in the previous section, if $\mathbf{u}$ and $\mathbf{f}$ satisfy (17), then we say that $\mathcal{S}\mathbf{f} = \mathbf{u}$. If $\mathbf{f} \in L^2(\Omega)$ is known, the problem (17) is well posed from Theorem 4 and its solution satisfies, thanks to Theorem 5:

$$\|\mathcal{S}\mathbf{f}\|_{H^2(\Omega)} \leq k\|\mathbf{f}\|_{L^2(\Omega)}, \quad k > 0, \tag{18}$$

which is the continuity estimate requested in (6) for the solution operator.

### 2.1.1 Admissible Force Space

Let $\Omega_c \subset \Omega$ be the Lebesgue–measurable set where the cell lays and $\mathbf{f} \in \mathsf{F} = L^2(\Omega)$ the force density per unit surface exerted by the cell. Since neither external forces nor constraints apply on the cell and inertia is negligible, we can argue that its force field $\mathbf{f}$ must have null average and null average momentum, so that it belongs to [4]:

$$\mathsf{F}_{\mathrm{adm}} := \{\mathbf{g} \in \mathsf{F} = L^2(\Omega) | \int_{\Omega_c} \mathbf{f} = 0, \int_{\Omega_c} \mathbf{r} \times \mathbf{f} = 0, \ \mathbf{f} = 0 \text{ a.e. on } \Omega \setminus \Omega_c\}. \tag{19}$$

We can easily prove the following characterization of $\mathsf{F}_{\mathrm{adm}}$.

**Proposition 13** $\mathsf{F}_{\mathrm{adm}}$*, as defined in* (19)*, is a closed subspace of* $\mathsf{F}$*.*

## 2.2 Optimal Control

### 2.2.1 Penalty Functional

Our goal is to determine $\mathbf{f}$ which minimizes the penalty functional in (8) and belongs to a closed subspace $\mathsf{F}_{\mathrm{adm}} \subset \mathsf{F}$. In the previous sections, we have proved (see inequality (18)) that the suitable choice of $\mathsf{U}$ and $\mathsf{F}$ done at the beginning of this section yields a continuous solution operator $\mathcal{S}$ (i.e. satisfying (6)). Since the solution $\mathbf{u}$ belongs to $H^2(\Omega)$, also the observation map $\mathcal{O}$ is continuous. In fact, by the Sobolev Theorem 3, $H^2(\Omega) \hookrightarrow C^0(\mathsf{cl}\Omega)$ when $n = 2, 3$ and, thanks to Proposition 7, the condition (7) is clearly satisfied. We can then apply Theorem 12 and find that, in this case, our functional $\mathcal{J}$ admits a unique minimum point and it is differentiable therein.

### 2.2.2 Adjoint State

In this section we explicitly assign the operator $\mathcal{A}$ appearing, in abstract form, in equation (11) and we prove some of its properties. Taking $\mathcal{A} = \mathcal{S}^{-1}$, we argue that Problem (11) rewrites as follows (cfr. with [6]): [5]:

$$\text{find } \mathbf{p} \in W_0^{1,s}(\Omega) \text{ s.t. } \forall \mathbf{q} \in W_0^{1,s'}(\Omega):$$

$$\int_\Omega \nabla\mathbf{p} \cdot \mathbb{C}[\nabla\mathbf{q}] = (\mathcal{O}\mathbf{u} - u_0) \circ \mathcal{O}\mathbf{q}. \tag{20}$$

The next step is to prove the well posedness of the above equation.

**Proposition 14** *The problem in* (20) *is well posed when* $s \in [1, \frac{n}{n-1})$*,* $s'$ *is conjugate to* $s$*,* $\Omega$ *is a bounded domain with* $C^2-$*boundary and* $n = 2, 3$*.*

[4]To define the wedge product in $\mathbb{R}^2$, we proceed in this way. Fix $\mathbf{J} \in \mathsf{Skw}(\mathbb{R}^2) \cap \mathsf{Ort}(\mathbb{R}^2)$ one among the two perpendicular turn in $\mathbb{R}^2$ [20]. Define: $\mathbf{h} \times \mathbf{g} = \mathbf{J}\mathbf{h} \cdot \mathbf{g}$ for all vectors $\mathbf{g}$,$\mathbf{h}$ of $\mathbb{R}^2$.
Moreover we have defined $\mathbf{r}(\mathbf{x}) := \mathbf{x} - \mathbf{o}$ where $\mathbf{o} \in \mathbb{R}^3$ is a given point.

[5]$W_0^{1,s}(\Omega)$ is the subspace of $W^{1,s}(\Omega)$ of functions having zero trace on $\partial\Omega$, see [19] and [1].

*Proof:*
As a consequence of the Prop. 7, $\mathcal{O}^T(\mathcal{O}\mathbf{u}-u_0)$ is a Borel measure (having fixed $\mathbf{u}\in H^1_{0,\Gamma_D}(\Omega)\cap H^2(\Omega)\hookrightarrow C^0(\mathsf{cl}\Omega)$ as noted before).
We also observe that, by Sobolev embedding Theorem:

$$\mathbf{q}\in W^{1,s'}(\Omega)\hookrightarrow C^0(\mathsf{cl}\Omega) \text{ if } s'>n \Leftrightarrow s\in[1,\frac{n}{n-1}).$$

Then, we can apply Theorem 6 with $s\in[1,\frac{n}{n-1})$ and $n=2,3$ to prove the thesis.

□

Using Sobolev embedding Theorem 3 it can be proved that:

$$\mathbf{p}\in W^{1,s}(\Omega)\hookrightarrow L^2(\Omega) \text{ if } s\geq\frac{2n}{n+2}\Leftrightarrow s'\in[1,\frac{2n}{n-2}).$$

Moreover, let $\mathbf{q}=\mathcal{S}\mathbf{h}$ ($\mathbf{h}\in L^2(\Omega)$): one has from (18) that $\mathbf{q}\in H^2(\Omega)\cap H^1_0$.
Using again the Sobolev embedding Theorem 3, one has:

$$H^2(\Omega)\hookrightarrow W^{1,s'}(\Omega) \text{ if } s'\in[1,\frac{2n}{n-2}]\Leftrightarrow s\geq\frac{2n}{n+2}.$$

Collecting the latter results, the following equation is thus well defined granted $s\in[\frac{2n}{n+2},\frac{n}{n-1})$:

$$\int_\Omega\nabla\mathbf{p}\cdot\mathbb{C}[\nabla\mathcal{S}\mathbf{h}]=\int_\Omega\mathbf{h}\cdot\mathbf{p}.$$

We observe that the equality above follows from the definition of $\mathcal{S}$ (as in the forward problem (17)) and the symmetry of $\mathbb{C}$ (see Eq. (4)).

### 2.2.3 Characterization of the optimal control

The optimal control $\mathbf{f}$ satisfies, as stated in (12), $\mathbf{f}=-\frac{1}{\varepsilon}\mathcal{P}\mathbf{p}$. We now wish to characterize the projection operator $\mathcal{P}:\mathsf{F}\to\mathsf{F}_{\text{adm}}\subset\mathsf{F}$. Equation (12) here takes the following meaning:

$$(\varepsilon\mathbf{f}+\mathbf{p}|\mathbf{h})_{L^2(\Omega)}=0,\qquad\forall\mathbf{h}\in\mathsf{F}_{\text{adm}}. \tag{21}$$

Since any test function $\mathbf{h}$ is equal to zero in measure on $\Omega\setminus\Omega_c$, equation (21) reduces to:

$$\varepsilon(\mathbf{f}|\mathbf{h})_{L^2(\Omega_c)}+(\mathbf{p}|\mathbf{h})_{L^2(\Omega_c)}=0,\qquad\forall\mathbf{h}\in\mathsf{F}_{\text{adm}c}, \tag{22}$$

where $\mathsf{F}_{\text{adm}c}:=\{L^2(\Omega_c)|\int_{\Omega_c}\mathbf{f}=0,\int_{\Omega_c}\mathbf{r}\times\mathbf{f}=0\}$.
Then $\mathbf{f}=-\frac{1}{\varepsilon}\chi_c\mathbf{p}+\mathbf{f}^\perp$, where $\mathbf{f}^\perp\in\mathsf{F}_{\text{adm}c}^\perp$ and $\chi_c$ is the characteristic function of $\Omega_c$. To determine $\mathbf{f}^\perp$ we note that (from the Theorem on the dimension of range and kernel [20]):

**Theorem 15** *Let $\mathcal{H}\in\mathsf{Lin}(\mathsf{Y},\mathbb{R}^n)$, $\mathsf{Y}$ a (possibly infinite dimensional) Hilbert space, $n\in\mathbb{N}$. Then $\mathsf{dim}(\mathsf{ker}\mathcal{H})^\perp\leq n$.*

In $\mathbb{R}^2$, if we set $\mathcal{H}=\left[\mathbf{f}\in L^2(\Omega_c)\mapsto\left(\int_{\Omega_c}\mathbf{f},\int_{\Omega_c}\mathbf{r}\times\mathbf{f}\right)\in\mathbb{R}^3\right]$, then we have $\mathsf{dim}\mathsf{F}_{\text{adm}c}^\perp\leq 3$. Moreover one can readily find a 3–dimensional basis, say $\{\mathbf{e}_i\}_{i=1}^3$ for this space. Set $\{\mathbf{e}_1,\mathbf{e}_2\}$ as two constant, linearly independent–valued mappings. Obviously, if $\mathbf{h}\in\mathsf{F}_{\text{adm}c}$:

$$(\mathbf{e}_i|\mathbf{h})_{L^2(\Omega_c)}=\int_{\Omega_c}\mathbf{e}_i\cdot\mathbf{h}=\mathbf{e}_i\cdot\int_{\Omega_c}\mathbf{h}=0,$$

for $i=1,2$. Evidently $\{\mathbf{e}_1,\mathbf{e}_2\}\subset\mathsf{F}_{\text{adm}c}^\perp$. Next, let $\mathbf{J}\in\mathsf{Skw}(\mathbb{R}^2)\cap\mathsf{Ort}(\mathbb{R}^2)$ the chosen perpendicular turn in $\mathbb{R}^2$, as in footnote 4 (the same calculation in $\mathbb{R}^3$ would require a slightly different technique). Choose $\mathbf{e}_3(\mathbf{x})=\mathbf{J}\mathbf{x}$, then:

$$(\mathbf{e}_3|\mathbf{h})_{L^2(\Omega_c)}=(\mathbf{J}\mathbf{r}|\mathbf{h})_{L^2(\Omega_c)}=\int_{\Omega_c}\mathbf{J}\mathbf{r}\cdot\mathbf{h}=\int_{\Omega_c}\mathbf{r}\times\mathbf{h}=0.$$

Eventually, given $\{\mathbf{e}_i\}_{i=1}^3$ as above, $\mathbf{f} \in \mathsf{F}_{\mathrm{adm}}$ turns out to be:

$$\mathbf{f} = -\frac{1}{\varepsilon}\chi_c \mathbf{p} + \sum_{i=1}^{3} l_i \mathbf{e}_i, \tag{23}$$

where $(l_i)_{i=1}^3 \in \mathbb{R}^3$ are the Lagrangian multiplier associated to the constraint of null net force and torque (see the definition of $\mathsf{F}_{\mathrm{adm}c}$ above) and so they are unknowns of the problems.

## 2.3 System of equations

Here below we resume the results of the present section, pointing out the system of differential equations, in weak form, that one may want to solve in practice.

find $\mathbf{u} \in H^2(\Omega) \cap H_0^1(\Omega)$, $\mathbf{p} \in W_0^{1,s}(\Omega)$, $(l_i)_{i=1}^3 \in \mathbb{R}^3$, $s \in [\frac{2n}{n+2}, \frac{n}{n-1})$
such that $\forall \mathbf{q} \in W_0^{1,s'}(\Omega)$, $\forall \mathbf{v} \in H_0^1(\Omega)$:

$$\begin{cases} \displaystyle\int_\Omega \mathbb{C}\nabla\mathbf{u}\cdot\nabla\mathbf{v} + \int_\Omega \mathbf{f}\cdot\mathbf{v} & = 0, \\ \displaystyle\int_\Omega \mathbb{C}\nabla\mathbf{p}\cdot\nabla\mathbf{q} + \sum_{j=1}^{N} \delta_{\mathbf{x}_j}\mathbf{u}\cdot\delta_{\mathbf{x}_j}\mathbf{q} & = \displaystyle\sum_{j=1}^{N} u_{0_j}\cdot\delta_{\mathbf{x}_j}\mathbf{q}, \\ \displaystyle\mathbf{f} + \frac{1}{\varepsilon}\mathbf{p} - \sum_{i=1}^{3} l_i\mathbf{e}_i & = 0, \\ \displaystyle\int_\Omega \mathbf{f} & = 0, \\ \displaystyle\int_\Omega \mathbf{r}\times\mathbf{f} & = 0. \end{cases} \tag{24}$$

# 3 Boundary Control with Neumann or Mixed Conditions

While traction force microscopy on flat surfaces is nowadays a well established technique for cells moving on flat surfaces, the challenging goal is currently to obtain a good reconstruction of the stress exerted by a cell in its physiological three dimensional migration environment. In a typical experimental setup, a cell is immersed in a matrigel box as in Fig. 1 and exerts a stress on the inner boundary of the gel, the traction at the inner surface plays here the role of the unknown of the problem. Homogeneous Dirichlet or Neumann condition can be considered for the outer boundary, i.e. the walls of the box..

## 3.1 Forward Problem

Let $\Omega \subset \mathbb{R}^3$ be an open bounded domain with $C^2-$regular border, as in fig.1. The boundary conditions characterize a mixed problem in Linear Elasticity and, in this section, we consider $\mathsf{U} = H^1_{0,\Gamma_D}(\Omega) \cap H^2(\Omega)$, $\mathsf{F} = H^{\frac{1}{2}}(\Gamma_N)$, $\mathbf{c} := \mathbf{f}$ and $\mathbf{b} = \mathbf{0}$. The forward problem (1) or (5) now reads:

given $\mathbf{f} \in H^{\frac{1}{2}}(\Gamma_N)$, find $\mathbf{u} \in H^1_{0,\Gamma_D}(\Omega) \cap H^2(\Omega)$ such that for all $\mathbf{v} \in H^1_{0,\Gamma_D}(\Omega)$:

$$\int_\Omega \nabla\mathbf{u}\cdot\mathbb{C}[\nabla\mathbf{v}] = \int_{\Gamma_N} \mathbf{f}\cdot\mathbf{v}. \tag{25}$$

The above problem admits a unique solution in $H^1(\Omega)$ thanks to the Lax–Milgram lemma (Theorem 4). If we consider the setup as in fig.1, where $\Gamma_D \neq \emptyset$ and $\mathsf{cl}(\Gamma_N \cup \Gamma_D) = \emptyset$, we can apply the Theorem 5 to obtain the estimate:

$$\|\mathcal{S}\mathbf{f}\|_{H^2(\Omega)} \leq k\|\mathbf{f}\|_{H^{\frac{1}{2}}(\Gamma_N)}, \qquad k > 0, \tag{26}$$

where $\mathcal{S}\mathbf{f} = \mathbf{u}$ iff (25) is satisfied. For a pure Neumann problem ($\Gamma_N = \partial\Omega$), the same results hold, but the solution $\mathbf{u}$ is unique up to a rigid motion (see [8]).

### 3.1.1 Admissible Force Space

As in the case of distributed control of the previous section, since neither force nor constraint act on the cell, we define the admissible force space as:

$$\mathsf{F}_{\mathrm{adm}} := \{\mathbf{g} \in \mathsf{F} = H^{\frac{1}{2}}(\Gamma_N) | \int_{\Gamma_N} \mathbf{f} = 0, \int_{\Gamma_N} \mathbf{r} \times \mathbf{f} = 0\}. \tag{27}$$

This is a closed subspace of $L^2(\Gamma_N)$ and therefore also of $\mathsf{F} = H^{\frac{1}{2}}(\Gamma_N)$ since $H^{\frac{1}{2}}(\Gamma_N) \hookrightarrow L^2(\Gamma_N)$, the proof being the same as the one given in the previous section (it is sufficient to exchange $\Omega$ with $\Gamma_N$, noting that also $\Gamma_N$ has finite measure).

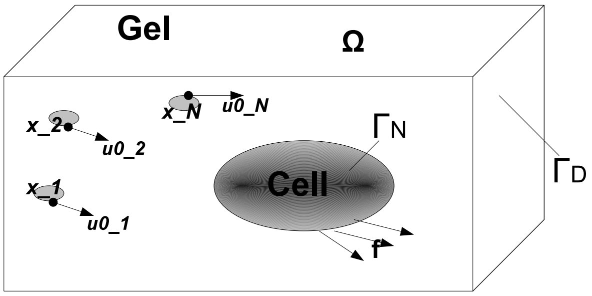


Figure 1: Three Dimensional Setup

## 3.2 Optimal Control

### 3.2.1 Penalty Functional

We search for $\mathbf{f} \in \mathsf{F}_{\mathrm{adm}}$ which minimizes the functional in (8). The discussion below is very similar to the one in the previous Section and some details are omitted.
We have proved in (26) that the choice of $\mathsf{U}$, $\mathsf{F}$ done in this section provides a continuous solution operator $\mathcal{S}$. Since the solution $\mathbf{u}$ belongs to $H^2(\Omega)$ also the observation map $\mathcal{O}$ is continuous. In fact, by Sobolev Theorem 3, $H^2(\Omega) \hookrightarrow C^0(\mathsf{cl}\Omega)$ when $n = 2, 3$ and, thanks to Proposition 7, (7) is clearly satisfied. We can then apply Theorem 12 to see that in this case our functional $\mathcal{J}$ admits a unique minimum point and it is differentiable therein.

### 3.2.2 Adjoint State

In the following, we explicitly characterize the operator $\mathcal{A}$ that appears in (11) and prove some of its properties. In this case $\mathcal{A} \neq \mathcal{S}^{-1}$, in fact we state the following counterpart of (11) (cfr. with [7]):

find $\mathbf{p} \in W^{1,s}_{0,\Gamma_D}(\Omega)$ s.t. $\forall \mathbf{q} \in W^{1,s'}_{0,\Gamma_D}(\Omega)$:

$$\int_\Omega \nabla \mathbf{p} \cdot \mathbb{C}[\nabla \mathbf{q}] = (\mathcal{O}\mathbf{u} - u_0) \circ \mathcal{O}\mathbf{q}. \tag{28}$$

We now state the well posedness of the above equation, the proof being identical to the one of the Prop. 14.

**Proposition 16** *The problem in* (28) *is well posed when* $s \in [1, \frac{n}{n-1})$, $s'$ *is conjugate to* $s$, $\Omega$ *is a bounded domain with* $C^2-$*boundary and* $n \leq 3$.

It happens that $\mathbf{p} \in L^s(\Gamma_N)$ because from Trace Theorem 2 :

$$W^{1,s}(\Omega) \hookrightarrow L^s(\partial\Omega) \text{ if } s < n.$$

Moreover, let $\mathbf{q} = \mathcal{S}\mathbf{h}$ ($\mathbf{h} \in H^{\frac{1}{2}}(\Gamma_N)$); one has, according to (18), that $\mathbf{q} \in H^1_{0,\Gamma_D}(\Omega) \cap H^2(\Omega)$. Using again the Sobolev embedding Theorem 3, we find that:

$$H^2(\Omega) \hookrightarrow W^{1,s'}(\Omega) \text{ if } s' \in [1, \frac{2n}{n-2}] \Leftrightarrow s \geq \frac{2n}{n+2}.$$

Since, by virtue of Trace Theorem 2 one has $H^1(\Omega) \hookrightarrow H^{\frac{1}{2}}(\Gamma_N)$; then it is worth to point out the following embedding:

$$H^1(\Omega) \hookrightarrow L^{s'}(\partial\Omega) \text{ if } s' \in [1, \frac{2n-2}{n-2}] \Leftrightarrow s \geq \frac{2n-2}{n}.$$

that guarantees $\mathbf{h} \in L^{s'}(\partial\Omega)$.
According to the results above, the following equation is thus well defined, granted $s \in [\frac{2n-2}{n}, \frac{n}{n-1}]$:

$$\int_\Omega \nabla \mathbf{p} \cdot \mathbb{C}[\nabla \mathcal{S}\mathbf{h}] = \int_{\Gamma_N} \tau_{\Gamma_N} \mathbf{p} \cdot \mathbf{h}, \tag{29}$$

We observe that the equality above follows from the definition of $\mathcal{S}$ (as in the forward problem (25)) and the symmetry of $\mathbb{C}$ (see Eq. (4)).

**Remark 17** *Similar arguments hold for a pure Neumann problem, excepts for minor details.*

**Remark 18** *A proof of the well posedness for a pure Neumann problem when* $\mathsf{supp}\mathcal{O} \subset \partial\Omega$ *is given in [11] using the potential theory (suitable for the boundary elements numerical method). Here we do not constrain the support of the observation operator.*

### 3.2.3 Characterization of the optimal control

The optimal $\mathbf{f}$, as stated in (12), satisfies $\mathbf{f} = -\frac{1}{\varepsilon}\mathcal{P}\mathcal{S}^T\mathcal{A}\mathbf{p}$. It can be useful to recall that Equation (12) here takes the following meaning (see (29)):

$$\varepsilon(\mathbf{f}|\mathbf{h})_{H^{\frac{1}{2}}(\Gamma_N)} + \int_{\Gamma_N} \mathbf{p} \cdot \mathbf{h} = 0, \qquad \forall \mathbf{h} \in \mathsf{F}_{\text{adm}}. \tag{30}$$

Given $\mathbf{p} \in W^{1,s}(\Omega)$, thanks to Riesz theorem (see [4]), a unique solution $\mathbf{f} \in H^{\frac{1}{2}}(\Gamma_N)$ of this problem exists since $\mathbf{h} \in H^{\frac{1}{2}}(\Gamma_N) \mapsto \int_{\Gamma_N} \mathbf{p} \cdot \mathbf{h}$ is a linear and continuous functional on $H^{\frac{1}{2}}(\Gamma_N)$. Unfortunately, Equation (30) cannot be approximated by standard FEM tools, even when $\mathsf{F}_{\text{adm}} = \mathsf{F}$, since they usually not deal with non integer Sobolev spaces. A reasonable and computationally cheap way to overcome these difficulties is addressed in the next paragraph.

### 3.2.4 An hypothesis on the Observation Operator and consequences

We note that, according to Theorem 2, the trace of an element of $W^{1,s}(\Omega)$ ($s$ as before) does not necessarily belongs to $H^{\frac{1}{2}}(\Gamma_N)$. Nevertheless, if we add an additional hypothesis, we can achieve more regularity for the adjoint state.

**Hypothesis 19** *The support of the observation operator $\mathcal{O}$ is an open set contained in $\Omega'$ which is such that $\mathsf{cl}\Omega' \subsetneqq \Omega$.*

Using the hypothesis 19, we are able to state (see [14] for the proof):

**Proposition 20** *Let $\Omega" \subset \Omega \setminus \Omega'$ strictly. Then $\mathbf{p}|_{\Omega"}$ belongs to $H^1(\Omega")$.*

Since, by the above hypothesis 19, $\mathsf{dist}(\Gamma_N, \Omega') > 0$ we can surely choose a set $\Omega" \subset \Omega \setminus \Omega'$ such that $\Gamma_N \subset \Omega"$. Then, by (20), $\mathbf{p}|_{\Omega"}$ belongs to $H^1(\Omega")$ and, by the trace Theorem 2, $\tau_{\Gamma_N}\mathbf{p}$ belongs to $H^{\frac{1}{2}}(\Gamma_N)$. According to [7], the adjoint variable $\mathbf{p}$, solution of (28), actually solves:

$$\int_\Omega \mathbf{p} \cdot (\nabla \cdot (\mathbb{C}\nabla \mathbf{q})) + (\mathbf{p}|(\mathbb{C}\nabla \mathbf{q})\mathbf{n})_{H^{\frac{1}{2}}(\Gamma_N)} = (\mathcal{O}\mathbf{u} - u_0) \circ \mathcal{O}\mathbf{q}. \tag{31}$$

If we put the last equation inside Eq. (12) with $\mathbf{q} = \mathcal{S}\mathbf{h}$ ($\mathbf{h}$ is any function in $H^{\frac{1}{2}}(\Gamma_N)$, as before), we find that:

$$\mathbf{f} = -\frac{1}{\varepsilon}\mathcal{P}\mathbf{p},$$

which is a purely algebraic equation in the non constrained case (i.e., when $\mathcal{P}$ is the identity). The constrained case can be treated as above, as we shall see during the next paragraph. Before going on, we shall note that, thanks to the hypothesis 19, the problem is well posed choosing $\mathsf{F} = L^2(\Gamma_N)$.

### 3.2.5 The Space ${\mathsf{F}_{\text{adm}}}^\perp$

In the constrained case the latter equation can be exploited as in Section 2, and

$$\mathbf{f} = -\frac{1}{\varepsilon}\tau\mathbf{p} + \mathbf{f}^\perp$$

with $\mathbf{f}^\perp \in {\mathsf{F}_{\text{adm}}}^\perp$. As said before we consider $\mathsf{F}_{\text{adm}}$ as in the definition (27) but with $\mathsf{F} = L^2(\Gamma_N)$. The actual calculation of a basis for its orthogonal ${\mathsf{F}_{\text{adm}}}^\perp$ can be performed exactly in the same way we have done in Section 2 (the little difference is due to the fact that we are working in three dimension). Actually, by the theorem of range and kernel (Theorem 15 of Section 2) we argue that $\mathsf{dim}({\mathsf{F}_{\text{adm}}}^\perp) \leq 6$, since we are now in $\mathbb{R}^3$. But one can readily find a 6−dimensional basis for ${\mathsf{F}_{\text{adm}}}^\perp$ letting $(\mathbf{e}_i)_{i=1}^3$ be three constant–linear independent–valued mappings and $\mathbf{e}_{i+3} = \mathbf{r} \times \mathbf{e}_i$, $i = 1, 2, 3$. The conclusion of the proof follows exactly the same calculations and reasoning of the discussions done for the analogous problem faced in Section 2.

Another observation that is worth to be done is the following: the null total moment of force constraint can be a little tricky to implement. For this reason, and only in this paragraph, we deal with the following admissible force space:

$$\mathsf{F}_{\text{adm}} := \{\mathbf{g} \in \mathsf{F} = L^2(\Gamma_N) | \int_{\Gamma_N} \mathbf{f} = 0\}.$$

Loosely speaking, we do not enforce the equilibrium of momentum and we just constraint the force field to have null resultant only. This choice of $\mathsf{F}_{\text{adm}}$, as the reader may easily verify, does not affect the well posedness results previously found. In such a case, we find that the set of equations (where $(l_i)_{i=1}^3$ is the set of Lagrangian multiplier associated with the constraint):

$$
\begin{aligned}
\mathbf{f} &= -\frac{1}{\varepsilon}\tau\mathbf{p} + \sum_{i=1}^{3} l_i \mathbf{e}_i \\
\int_{\Gamma_N} \mathbf{f} &= 0
\end{aligned}
$$

can be solved explicitly thanks to the fact that the basis $(\mathbf{e}_i)_{i=1}^3$ assume constant values. The above equation is thus equivalent to:

$$
\mathbf{f} = \frac{1}{\varepsilon}\left(\frac{1}{|\Gamma_N|}\int_{\Gamma_N} \tau\mathbf{p} \; - \tau\mathbf{p}\right)
$$

being $|\Gamma_N|$ the $(n-1)$-measure of $\Gamma_N$. Of course, this kind of reasoning can be repeated when treating the problem discussed in Section 2.

### 3.2.6 System of equations

Here below we resume the results of the Section, pointing out the system of differential equations in weak form that one may want to solve in practice. Here we consider the assumption made in section 3.2.5, i.e. we only consider the null total force constraint, that give us a considerably simpler set of equations.

$$
\text{find } \mathbf{u} \in H^1_{0,\Gamma_D}(\Omega) \cap H^2(\Omega),\ \mathbf{p} \in W^{1,s}_{0,\Gamma_D}(\Omega),\ s \in [\tfrac{2n-2}{n}, \tfrac{n}{n-1}]
$$
$$
\text{such that } \forall \mathbf{q} \in W^{1,s'}_{0,\Gamma_D}(\Omega),\ \forall \mathbf{v} \in H^1_{0,\Gamma_D}(\Omega):
$$

$$
\begin{cases}
\displaystyle\int_\Omega \mathbb{C}\nabla\mathbf{u}\cdot\nabla\mathbf{v} + \int_{\Gamma_N} \mathbf{f}\cdot\mathbf{v} & = 0, \\
\displaystyle\int_\Omega \mathbb{C}\nabla\mathbf{p}\cdot\nabla\mathbf{q} + \sum_{j=1}^{N} \delta_{\mathbf{x}_j}\mathbf{u}\cdot\delta_{\mathbf{x}_j}\mathbf{q} & = \displaystyle\sum_{j=1}^{N} u_{0_j}\cdot\delta_{\mathbf{x}_j}\mathbf{q}, \\
\displaystyle\mathbf{f} = \frac{1}{\varepsilon}\left(\frac{1}{|\Gamma_N|}\int_{\Gamma_N}\tau\mathbf{p} \; - \tau\mathbf{p}\right), &
\end{cases}
\tag{32}
$$

We are now in the position to step back to the original biological problem and recover the physical interpretation of equations (32). This reintepretation may become more apparent when assuming that the elastic gel is isotropic, so that the elasticity tensor takes a particularly simple form, depending just on two material parameters ($\mu$ and $\lambda$, the usual Lamé moduli). In this case equations (32) rewrite

$$
\begin{cases}
\displaystyle\int_\Omega (\mu\nabla\mathbf{u}\cdot\nabla\mathbf{v} + \lambda(\nabla\cdot\mathbf{u})(\nabla\cdot\mathbf{v})) - \frac{1}{\varepsilon}\left(\int_{\Gamma_N}\mathbf{p}\cdot\mathbf{v} + \frac{1}{|\Gamma_N|}\int_{\Gamma_N}\mathbf{p}\cdot\int_{\Gamma_N}\mathbf{v}\right) & = 0, \\
\displaystyle\int_\Omega (\mu\nabla\mathbf{p}\cdot\nabla\mathbf{q} + \lambda(\nabla\cdot\mathbf{p})(\nabla\cdot\mathbf{q})) + \sum_{j=1}^{N}\delta_{\mathbf{x}_j}\mathbf{u}\cdot\delta_{\mathbf{x}_j}\mathbf{q} & = \displaystyle\sum_{j=1}^{N} u_{0_j}\cdot\delta_{\mathbf{x}_j}\mathbf{q},
\end{cases}
\tag{33}
$$

The differential system in weak form (33) eventually answers the following question. Given an isotropic elastic material (like polyacrilamide), with known elastic moduli $\lambda$ and $\mu$, deformed by a living cell embedded in it, we have experimentally measured pointwise displacements $\mathbf{u}$ in the positions $\mathbf{x}_j$. The force field that produces such a displacement, in the sense of the one minimizing the penalty functional (8), is the traction field $\mathbf{f}$ solution of the system (33), defined on the boundary $\Gamma_N$ where the gel and the cell are in contact.

The traction $\mathbf{f}$ is simply proportional to the solution of the adjoint equation $\mathbf{p}$, up to a correction due to the null–average constrain. The two differential equations are coupled by linear non–differential terms, of surface or volumetric type. In this respect, one can pictorially say that the discrepancy between the measured and the calculated displacement the right hand side of equation (33.b) is the volumetric source for the adjoint field $\mathbf{p}$, its value at the interface being basically the cell traction we are looking for.

### 3.2.7 An analytical example

Consider a spherical cell of radius $r_1$ immersed in an infinite elastic medium with observed displacement $u_2$ in every point of a spherical surface located in $r = r_2$. When substituting the elasticity operator by the Laplacian, the system of equations can be easily integrated. The symmetry of the problem allows to rewrite the system of equations (33) in strong form as follows

$$\frac{\mu}{r^2}\left(r^2 u'\right)' = 0, \qquad \mu u'(r_1) = -p(r_1)/\epsilon \tag{34}$$

$$\frac{\mu}{r^2}\left(r^2 p'\right)' = \delta(r - r_2)(u(r) - u_2), \qquad p'(r_1) = 0, \qquad p(0) = 0. \tag{35}$$

where $u(r)$ is the radial component of the displacement, that depends on the radial coordinate only and the prime $'$ denotes differentiation with respect to $r$. Notice that the null force condition in the origin accounts, in this symmetric problem, for the null-average requirement on the $p$ field.
For given $u(r_2)$, the second equation has solution

$$p(r) = \frac{\Delta u}{\mu}\frac{1}{r - r_2} + br + c \tag{36}$$

where

$$\Delta u = -(u(r_2) - u_2) \tag{37}$$

and the boundary and symmetry conditions fix the integration constants, thus giving:

$$p(r) = \frac{\Delta u}{\mu}\left(\frac{1}{r - r_2} + \frac{r}{(r_2 - r_1)^2} + \frac{1}{r_2}\right). \tag{38}$$

It follows that

$$p(r_1) = \frac{\Delta u}{\mu}\frac{r_1^2}{r_2(r_2 - r_1)^2}. \tag{39}$$

We are now in the condition to integrate equation (34):

$$\mu r^2 u' = \mu r_1^2 u'(r_1) = r_1^2(-p(r_1)/\epsilon) = -\frac{\Delta u}{\epsilon\mu}\frac{r_1^4}{r_2(r_2 - r_1)^2}. \tag{40}$$

Further integration yields

$$u(r) = \frac{\Delta u}{\epsilon\mu^2}\frac{r_1^4}{r_2(r_2 - r_1)^2}\frac{1}{r} \tag{41}$$

which is an implicit expression of the displacement $u(r)$ depending on its own value in $r_2$. It is particularly useful to evaluate the expression (41) in such a point, where the explicit value can be calculated

$$u(r_2) = u_2\left(1 + \epsilon\mu^2\frac{r_2^2(r_2 - r_1)^2}{r_1^4}\right)^{-1} \tag{42}$$

The expression (42) points out the role of the stabilization parameter and of the geometric ratio in the inversion procedure. The inverted datum is always damped with respect to the measured one. Assuming that $u_2$ is exactly known, as expected the exact datum is recovered as $\epsilon \to 0$. More remarkably, for fixed $\epsilon$, we obtain the convergence rate of the inverted to the exact solution depending on the mutual radius of the cell and the measurement surface. The error vanishes quadratically for $\rho = \frac{r_2}{r_1} \to 1$, that is when the two surfaces approach each other. Conversely, for given $r_1$, the data are damped by the inversion procedure as the fourth power of $\rho$, so that in the applications it is to be expected that the inverted force field is underestimated when the measurement points are not located sufficiently near to the cell surface.

# Final remarks

A inverse problem inspired by biophysical practice has been address in terms of formal and rigorous statements. The specific characteristics of this problem is to assume pointwise observations: they call for a generalization of the classical elasticity theory to forcing terms (for the adjoint problem) that are Borel measures.

Our main aim here is the correct statement of the set of equations that can be adopted to address traction force microscopy in a three dimensional environment, a challenging question in cell biology. The mathematical theory largely stands on known results, while the novelty of this contribution is in the specific form system of equations (32) and their well posedness for the application at hand. Now, on this basis, the reader interested in biological applications can step forward to the numerical approximation of these two elliptic partial differential equations, coupled by the boundary conditions. The integration of the reduced symmetric problem of section 3.2.7 provides a concrete example of the method that can be helpful in view of its numerical integration and application to real data.

It may be worth to recall that force traction microscopy in three dimensions is still in its infancy; just in very recent years imaging techniques have revealed detail of the patterns of the mechanical strain produced by the cells in their movement. Early attempt of quantitative inversion have been carried out [15], but a precise analysis of the methods seems to be still missing. The content of this paper provides now the basis for a mathematically precise application of the inversion method to real biophysical questions.

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