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NON-REGULARISED INVERSE FINITE ELEMENT ANALYSIS FOR 3D TRACTION FORCE MICROSCOPY

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Abstract. The tractions that cells exert on a gel substrate from the observed displacements is an increasingly attractive and valuable information in biomedical experiments. The computation of these tractions requires in general the solution of an inverse problem. Here, we resort to the discretisation with finite elements of the associated direct variational formulation, and solve the inverse analysis using a least square approach. This strategy requires the minimisation of an error functional, which is usually regularised in order to obtain a stable system of equations with a unique solution. In this paper we show that for many common three-dimensional geometries, meshes and loading conditions, this regularisation is unnecessary. In these cases, the computational cost of the inverse problem becomes equivalent to a direct finite element problem. For the non-regularised functional, we deduce the necessary and sufficient conditions that the dimensions of the interpolated displacement and traction fields must preserve in order to exactly satisfy or yield a unique solution of the discrete equilibrium equations. We apply the theoretical results to some illustrative examples and to real experimental data. Due to the relevance of the results for biologists and modellers, the article concludes with some practical rules that the finite element discretisation must satisfy.

Key words. Inverse analysis, linear elasticity, finite elements, three-dimensional traction force microscopy.

1. Introduction

The development of computational methods that allow scientists to accurately quantify the forces that cells exert on their surrounding has attracted a large amount of research [6, 14, 29, 31, 9], which can be also found in recent review articles [30]. These methods are currently being used to elucidate the proteins that control the mechanical response of cells when undergoing embryo morphogenesis, wound closure or cancer growth, to name a few [5, 32].

Some of the experimental techniques that were originally developed to measure the cellular tractions used micromachined substrates [15], microneedles, or micro-pilars [13]. Nowadays, the most popular methodology is to compute the cell tractions from the measured cell velocities and displacements on a polyacrylamide gel substrate. In some cases, this gel is partially covered by a membrane of polydimethylsiloxane (PDMS) that surrounds the cell monolayer in order to control the initial conditions of the cell migration. The idea of indirectly retrieving the cell tractions from the substrate deformations is founded on the seminal work of Harris et al. [18], and was later experimentally implemented in two [10] and three dimensions [11]. These techniques have been experimentally improved by Toyjanova et al. [31] in order to increase the accuracy of the measurements. Figure 1 illustrates the set-up considered in the present paper, where the deformation $\boldsymbol{u}_0$ at the top surface of an assumed elastic gel is measured, and the traction field $\boldsymbol{t}$ obtained indirectly.

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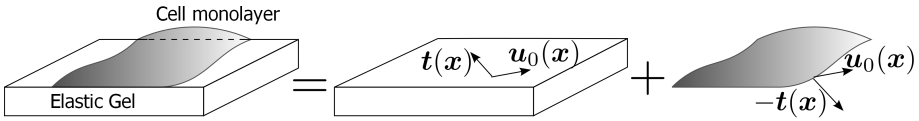

FIGURE 1. General set-up in Traction Force Microscopy (TFM). A displacement field $\boldsymbol{u}_0$ is imposed by the cell monolayer on the top of an assumed elastic gel is measured, and the traction field $\boldsymbol{t}$ computed by solving an inverse elasticity problem.

Computationally, retrieving the tractions $\boldsymbol{t}$ exerted by the cells from the measured displacements $\boldsymbol{u}_0$ requires the solution of an inverse elasticity problem. In the present paper we analyse the finite element discretisation of this inverse problem. The use of finite elements in inverse analysis is a common practice in scattering problems [4], localisation of pollutant sources [12], estimation of Robin coefficients [21], or in elasticity problems [2, 34]. So far, the construction of well-posed inverse problems is ensured by resorting to Tikhonov regularisation [2, 27, 29, 34], which depends on a penalty parameter. The optimal value of this parameter, which compromises the accuracy of the equilibrium conditions and the condition number of the system of equations has been studied for instance in [17]. We here determine the conditions that give rise to a well-posed discretised inverse elasticity problem in the absence of regularisation. We focus our attention on finite element (FE) discretisations of some commonly employed configurations in Traction Force Microscopy (TFM), also known as Cell Traction Microscopy [33]. We show that the regularisation process is in fact unnecessary, or it can be circumvented by modifying the domain discretisation.

The paper is organised as follows. In Section 2 we present the continuous direct and inverse problems. Section 3 describes the discrete versions of these two problems, and analyses the uniqueness of the solution in the inverse problem according to the dimensions of the discrete traction and displacement fields. Section 4 applies the methodology to a toy problem that illustrates the main theoretical results, and to a problem with real experimental data.

2. Continuous problem in linear elasticity

2.1. Continuous direct problem. We consider an open connected domain $\Omega \subset \mathbb{R}^3$ subjected to homogeneous displacement conditions at a Dirichlet boundary $\Gamma_d \neq \emptyset$ and to surface loads $\boldsymbol{t}$ on a Neumann boundary Γ_n, with $\bar{\Gamma}_d \cap \bar{\Gamma}_n = \emptyset$ and with the boundary $\partial\Omega = \overline{\Gamma_d \cup \Gamma_n}$ which is Lipschitz-continuous. The material in Ω is assumed to obey a linear elastic constitutive law with Lamé coefficients $\lambda > 0$ and $\mu > 0$, which are not necessarily constant in the domain Ω. After neglecting the volumetric forces, the strong form of linear elasticity may be stated as the following boundary value problem [7]:

$$\boldsymbol{\nabla} \cdot \boldsymbol{\sigma}(\boldsymbol{u}) = \boldsymbol{0}, \quad \forall \boldsymbol{x} \in \text{int}(\Omega), \tag{1}$$

$$\boldsymbol{\sigma}(\boldsymbol{u})\boldsymbol{n} = \boldsymbol{t}, \quad \forall \boldsymbol{x} \in \Gamma_n, \tag{2}$$

$$\boldsymbol{u} = \boldsymbol{0}, \quad \forall \boldsymbol{x} \in \Gamma_d, \tag{3}$$

with $\boldsymbol{\sigma}(\boldsymbol{u}) = \lambda(\nabla \cdot \boldsymbol{u})\mathbf{I} + \mu(\boldsymbol{\nabla}\boldsymbol{u} + \boldsymbol{\nabla}\boldsymbol{u}^T)$ denoting the stress tensor. The traction field may contain discontinuities, but it is assumed that $\boldsymbol{t} \in T \subseteq L^2(\Gamma_n)$. We point out that the strong form (1)-(3) and the subsequent results are valid for