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Inverse problems for the determination of traction forces by cells on a substrate: a comparison of two methods

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1 Introduction

Traction forces exerted by cells on soft elastic substrates are important for characterizing the types of mechanisms used for cell migration. Classical tools for the determination of traction forces include the knowledge of the displacement field thanks to fluorescent beads embedded into the substrate [1]. Then, from the discrete beads displacements, an inverse problem is solved to obtain the stress field. Two currently used methods in the literature are the well-known Fourier Transform Traction Cytometry (FTTC) method [2] and the adjoint method (AM) [3-4], which are compared here.

A real case is presented where the displacement field is known from cancer cell migration study [5]. The two methods allow the recovery of the traction stresses and their results are compared. Similar results are seen as long as an adequate projection technique is used (zero force imposed outside the cell). It is found that the AM allows a finer resolution of the traction forces, in particular at the cell edge. This is a strong incentive to use this method for the investigation of cancer cell migration on soft substrates [5].

2 Methods

Experiments

The experimental methods have been described previously [1,4]: substrates are gels, made of Polyacrylamide and bis-acrylamide in water possessing known elastic properties (E=10 kPa, as measured by indentation with an Atomic Force Microscope, using ν=0.5) which give the Lamé coefficients. Gels are functionalized using sulfo-sanpah and collagen, following a classical protocol [1]. Fluorescent beads (0.2 µm) are embedded into the gel. Cells (cancer cell line, RT112 from invasive bladder cancer) are seeded on the gels and left overnight to spread. Experiments require images from cells (green fluorescence using actin-GFP transfected RT112 cells) and red fluorescent images of beads at the same time. Finally the initial position of beads is determined by detaching cells at the end of the experiment (using distilled water). Displacements are obtained by taking the difference between the present and initial position.

Adjoint method (AM)

The AM [3-4] formulates the inverse problem as a constrained minimization of the distance $\|\mathbf{u}-\mathbf{u}_0\|$ between the measured displacements $\mathbf{u}_0$ and predicted ones $\mathbf{u}$ under penalization of traction stress magnitude $\|\mathbf{T}\|$ (Tikhonov regularization). The optimal solution gives the displacement and the stress field $\mathbf{T}$ simultaneously and is characterized as the solution of a coupled system of two Lamé's Partial Differential Equations (PDEs) [3-5]. The first one is the direct problem and the second is the adjoint problem. The PDEs are solved using finite elements method with piecewise linear basis functions (P_1) on an unstructured triangular mesh ('Triangle' software) to compute $\mathbf{u}$ and $\mathbf{T}$. The AM does not need any approximations of the experimental displacement field since bead positions coincide with meshpoints; furthermore it insures zero traction forces outside the cell (mathematical constraint). The control of the stability of solutions is done by minimizing the Tikhonov functional $\|\mathbf{u}-\mathbf{u}_0\|^2+\varepsilon\|\mathbf{T}\|^2$ where ε is the regularization parameter. This parameter is determined using the L-curve technique [5], as well as a simultaneous inspection of the stress vector field (see Figure 1). Handling of the AM is not difficult and computations are fast.

Fourier Transform Traction Cytometry (FTTC)

The FTTC method [2,6] defines the inverse problem as the expression in Fourier space of the

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integral form of the Boussinesq-Cerruti solution of the elastic half-space. This method is easy to implement and leads to fast computations. It needs interpolating the experimental displacements on a given structured rectangular grid (piecewise constant functions P_0). This step introduces an additional error which increases the difficulties because of the inverse nature of the problem. Another problematic aspect of the FTTC method is that it does not insure that the stress field is zero around the cell. Therefore we include a projection technique insuring this condition. Finally we also use a Tikhonov regularization technique [5,6].

3 Results and Discussion

The results are presented below, for a cell migrating on a gel, during the phase where it pulls at the front to move to the lower left part in Fig. 1. Stress vectors are shown in Fig. 1, whereas stress iso-contours are depicted in Fig. 2, using AM and FTTC method.

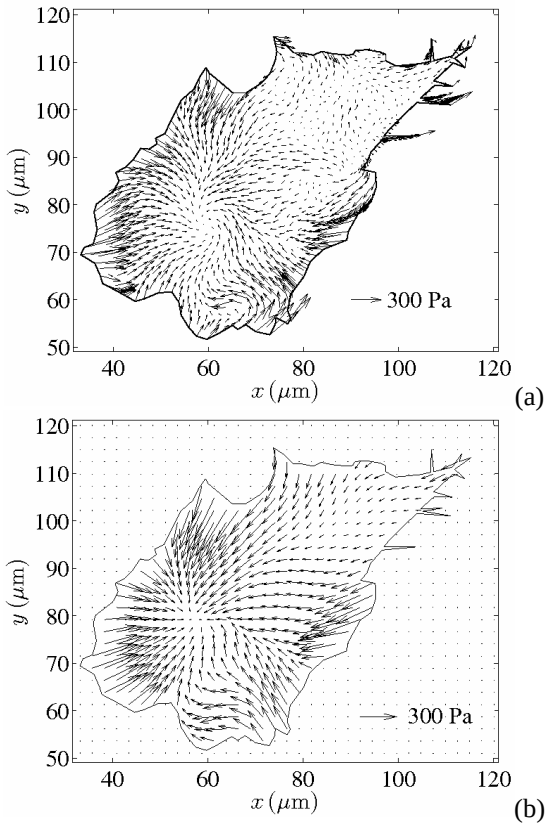

Figure 1 Comparison of stress vectors obtained using (a) AM (b) FTTC method

Clearly there is a qualitative agreement between the two methods; however we note discrepancies in finer details:

- slightly different locations of maximum stresses (Fig. 2, cell lower right part),
- different vector directions (Fig. 1, cell lower right),
- better resolution of AM method (filopods, Fig. 1a).

Thus the AM seems to provide better results due to more accurate mesh and contour descriptions. Indeed, P_1 approximation used with AM (as compared to P_0 for FTTC) improves the accuracy, as seen with filopods or cell edges in Fig. 1. This is important since adhesion sites are precisely located at cell borders [5].

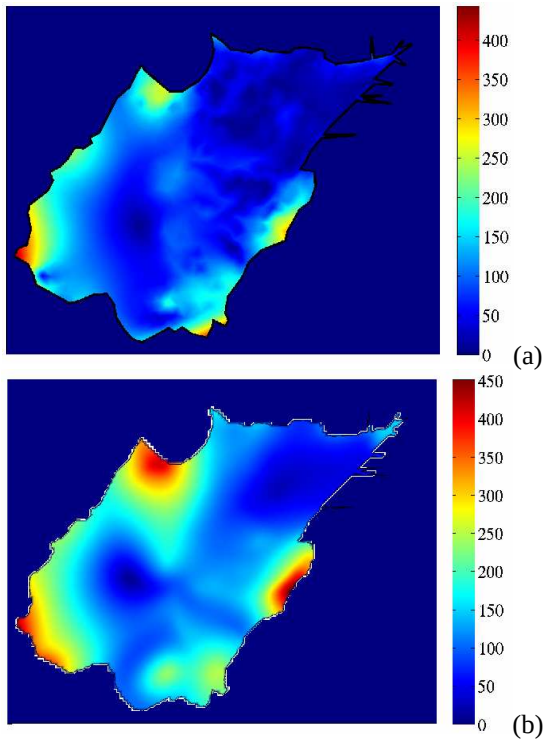

Figure 2 Stress iso-contours obtained using (a) AM (b) FTTC method

4 Conclusions

The results show the advantage of the AM, although the FTTC method, with the improvement of a projection technique, yields acceptable results. The AM provides a better resolution, and is fast to simulate. In this respect it provides a suitable framework for the calculation of cell tractions.

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