

## Introduction

Mechanobiology examines the input and output of mechanical forces by cells. Contractile forces generated by the actin-myosin cytoskeleton are transmitted to the exterior environment via associated trans-membrane proteins such as integrins (1). Referred to as traction forces, these forces are detected predominantly near cell periphery or front in an orientation towards cell center (2). Active forces are located at nascent or maturing focal adhesions near the front while resistive forces are located at mature focal adhesions near the rear (3, 4).

In addition to propelling cell migration, traction forces are believed to perform important functions such as organizing the extracellular matrix (5), probing mechanical properties of the environment (6), and sensing the state of the cell itself such as shape and size (7). Adhesive cells are also keenly sensitive to mechanical forces transmitted via the surrounding matrix (8), fluid shear (9), or cell-cell contact (10). These mechanical signals elicit many profound responses to affect cell migration (11), growth (12), and differentiation (13).

Methods for mapping cellular traction forces, referred to in general as traction force microscopy (TFM; 2, 14, 15, 16), represent a fundamental tool for mechanobiology. TFM is commonly performed by culturing cells on a substrate of elastic material such as polyacrylamide, embedded with particle markers for mapping force-induced strains, which are then used for calculating the distribution of cell-imposed stresses. However, while the calculation of strain from stress is straightforward, the inverse calculation essential for understanding traction force generation is much more challenging. Known mathematically as an ill-posed problem, simple approaches may fail to yield a unique solution and the results are prone to artifacts from measurement noise (17). To mitigate these problems, most conventional approaches include a regularization term to balance the accuracy of fitting against noise-induced artifacts and complexity of the solution (2, 17). However, in addition to the compromise in accuracy and resolution, it is difficult to define the weight factor for regularization that sets the balance between accuracy and artifacts (18).

Neural network-based deep learning has been deployed as a powerful method for solving ill-posed problems (19). Using a large dataset of known relationships between stress and strain for training, the approach optimizes a cascade of convolutional operations with the goal of transforming the distribution of strains into the distribution of stresses (20). Due to its fundamental difference from conventional methods, such neural networks avoid the use of regularization and associated compromises.

In the present implementation, a large training set of stress and strain that mimic cell-substrate mechanical interactions is generated by computer simulation. The approach, as evaluated by comparing the results with those generated by a conventional implementation of TFM, proves capable of mapping traction stress at a high speed, accuracy, and resolution.

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