Reconstruction of localized force distributions in cells and tissues from substrate displacements using physically-consistent regularization

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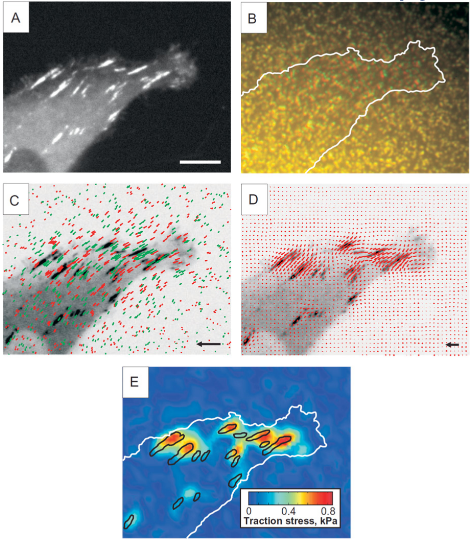
Traction force microscopy



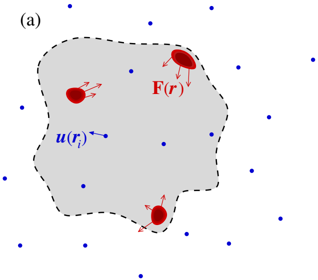
Plotnikov et. al. Methods Cell Biol. 2014

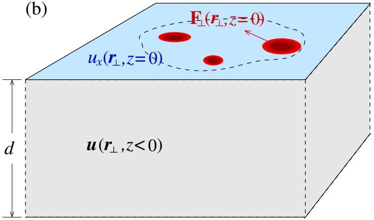
Imaging focal cell adhesions by tracking the displacement of fluorescent markers placed within a medium

- A Confocal image of human breast adenocarcinoma cell
- B Position of fluorescent beads
- C Displacement field for beads
- D Stress field
- E Stress magnitude

Goal: Determine tangential traction stress at the surface of medium

Linear elasticity theory for displacements **u**





- $\boldsymbol{\sigma}$ is tangential surface stress tensor, proportional to the $\mathbf{F}_\perp$
- **u** found "exactly" in closed-form for any fixed piecewise-polynomial approximation of $\boldsymbol{\sigma}$

In-plane surface displacements, as $d \to \infty$,s where $G \propto (Er)^{-1}$

$$u_x(x,y) = \int_\Omega \mathrm{d}x'\mathrm{d}y'\, G_{xx}(x-x', y-y')\sigma_{xz}(x',y') + \int_\Omega \mathrm{d}x'\mathrm{d}y'\, G_{xy}(x-x', y-y')\sigma_{yz}(x',y')$$

$$u_y(x,y) = \int_\Omega \mathrm{d}x'\mathrm{d}y'\, G_{yx}(x-x', y-y')\sigma_{xz}(x',y') + \int_\Omega \mathrm{d}x'\mathrm{d}y'\, G_{yy}(x-x', y-y')\sigma_{yz}(x',y')$$

Discretized forward problem

Linear algebra system

- $\boldsymbol{\sigma}$ interpolated about points $\mathbf{s}_i$ (using polynomials)
- Solution exact up to order of interpolation of $\boldsymbol{\sigma}_i$

$$\underbrace{\begin{pmatrix} u_x(\mathbf{r}_1) \\ u_x(\mathbf{r}_2) \\ \vdots \\ u_x(\mathbf{r}_N) \\ u_y(\mathbf{r}_1) \\ u_y(\mathbf{r}_2) \\ \vdots \\ u_y(\mathbf{r}_N) \end{pmatrix}}_{2N\times 1} = \overbrace{\begin{pmatrix} \mathbb{G}_{xx} & \mathbb{G}_{xy} \\ \mathbb{G}_{yx} & \mathbb{G}_{yy} \end{pmatrix}}^{\mathbb{G}} \underbrace{\begin{pmatrix} \sigma_{xz}(\mathbf{s}_1) \\ \sigma_{xz}(\mathbf{s}_2) \\ \vdots \\ \sigma_{xz}(\mathbf{s}_M) \\ \sigma_{yz}(\mathbf{s}_1) \\ \sigma_{yz}(\mathbf{s}_2) \\ \vdots \\ \sigma_{yz}(\mathbf{s}_M) \end{pmatrix}}_{2M\times 1}$$

- $\{\mathbf{r}_i\}_{i=1}^N$ locations at which measurements are taken
- $\{\mathbf{s}_i\}_{i=1}^M$ locations controlling interpolation of $\boldsymbol{\sigma}$
- $\mathbb{G}$ composed of grid-cell moments of the Greens function
- $\mathbb{G}$ depends on the interpolation order of $\boldsymbol{\sigma}$

Using the physics to help constrain the inverse problem

Reasonable physical assumptions

1. No force outside the cell footprint
2. No inertia (forces and torques each sum to zero)

Advantage gained

1. Reduction in problem size
   - Throw away far data points
2. Multipole expansion $\Rightarrow$ decay at rate r^{-2}
   - Cutoff data by distance
   - Sparsify the matrix $\mathbb{G}$

Still need to regularize the inverse problem

Criteria for a well-posed problem

- Solution exists
- Solution unique
- Solution continuous w.r.t. data

$$\hat{\boldsymbol{\sigma}} = \arg\min_{\boldsymbol{\sigma}} \left[\underbrace{||\mathbf{u} - \mathbb{G}\boldsymbol{\sigma}||_2^2}_{\Phi_{\text{data}}} + \lambda \Phi_{\text{reg}}[\boldsymbol{\sigma}] \right]$$

Respecting the physics in regularizing the inverse problem

- **Principle:** Coordinate system should not bias results
- **Solution:** Regularize using functionals of the tensor invariants

Tensor invariants

$$\mathrm{Tr}(\boldsymbol{\sigma}) = \sigma_{xz} + \sigma_{yz}$$

$$\mathrm{Det}(\boldsymbol{\sigma}) = \sigma_{xz}\sigma_{yz}$$

Invariant regularization functionals Φ_{reg}

$$\Phi_{L^1(Tr)} = \int_\Omega |\sigma_{xz}(x,y) + \sigma_{yz}(x,y)| \mathrm{d}x\mathrm{d}y$$

$$\Phi_{TV(Tr)} = \int_\Omega |\nabla(\sigma_{xz}(x,y) + \sigma_{yz}(x,y))| \mathrm{d}x\mathrm{d}y.$$

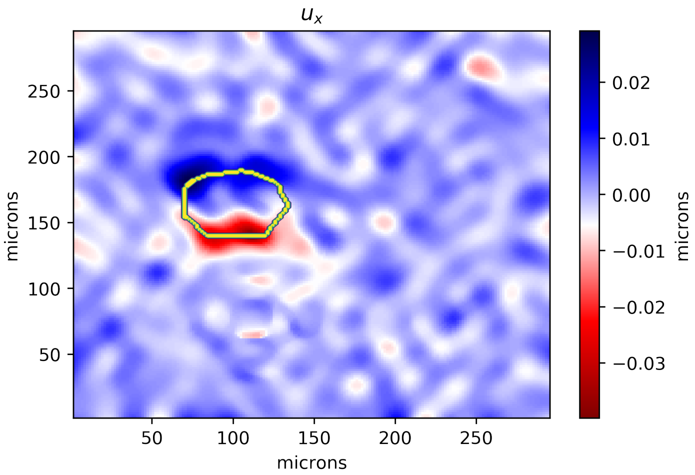
Non-invariant functionals Φ_{reg}

$$\Phi_{L1} = \int_\Omega \left(|\sigma_{xz}(x,y)| + |\sigma_{yz}(x,y)|\right) \mathrm{d}\mathbf{x},$$

$$\Phi_{TV_1} = \int_\Omega \left(|\nabla\sigma_{xz}(x,y)| + |\nabla\sigma_{yz}(x,y)|\right) \mathrm{d}\mathbf{x} \qquad \Phi_{TV_2} = \int_\Omega \left(|\partial_x\sigma_{xz}| + |\partial_y\sigma_{xz}| + |\partial_x\sigma_{yz}| + |\partial_y\sigma_{yz}|\right) \mathrm{d}\mathbf{x}$$

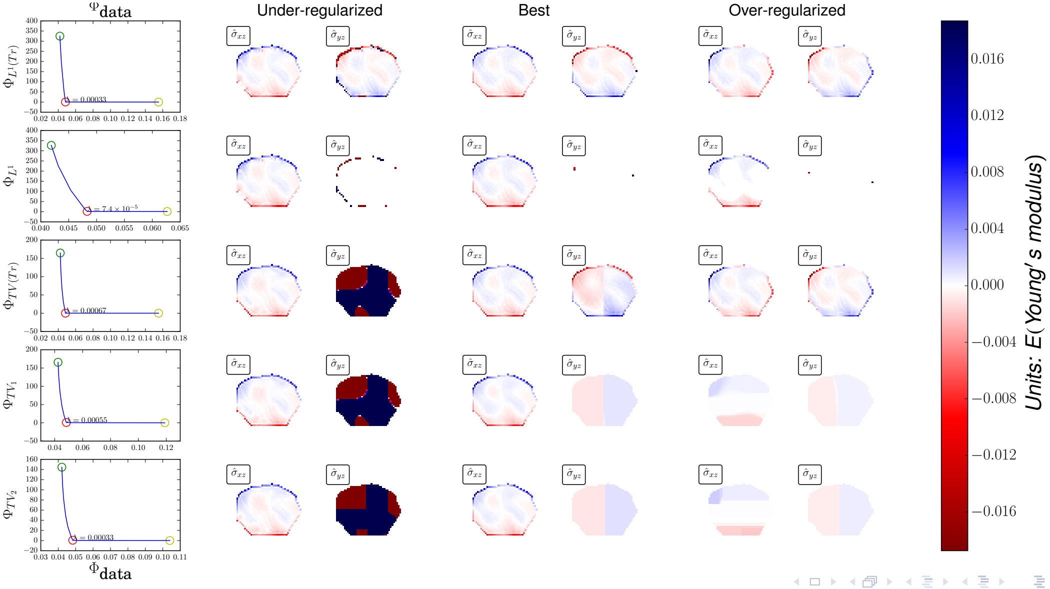
High-resolution data

- Mesenchymal stem cell
- Polyacrylamide hydrogels
- Fluorescent beads in a regular grid
- High-resolution measurement of displacement field
- Cell boundary estimated from raw bright-field image (superimposed)

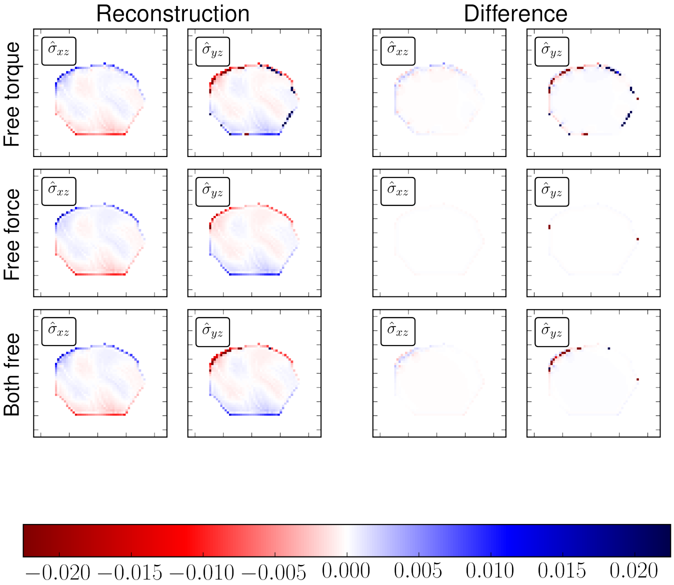


Courtesy of Gabriel Popescu, UIUC

Rotational invariance matters

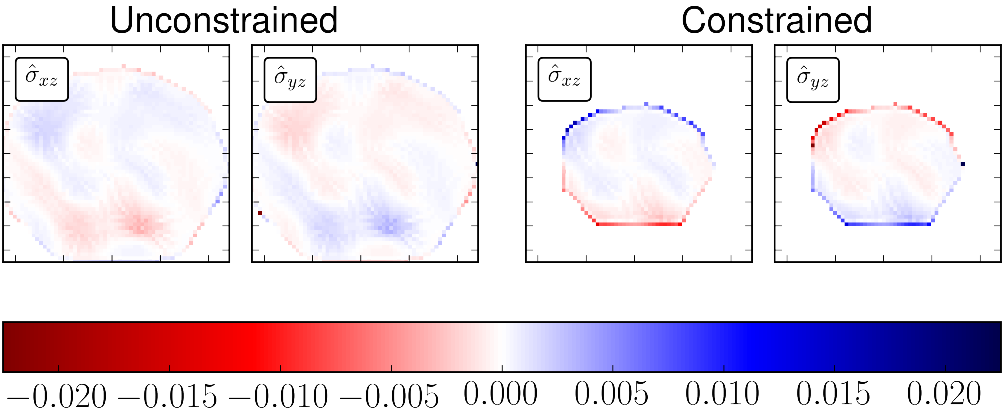


Force constraints matter



- Reconstructions performed using $L_1(Tr)$
- Difference compared to fully-constrained reconstruction
- Neither force nor torque cancel unless enforced explicitly

The footprint constraint matters



- Force concentrated near edges of the cell
- Location of edges is important

Summary and Future directions

- The regularization should be consistent with the known physics (as in a Bayesian prior)
- The numerical solution of the forward problem should be consistent with the regularization
- Localization of the cell footprint is important in determining traction
  - Extension: Joint force reconstruction and cell boundary determination
  - Extension: Uncertainty quantification through Bayes