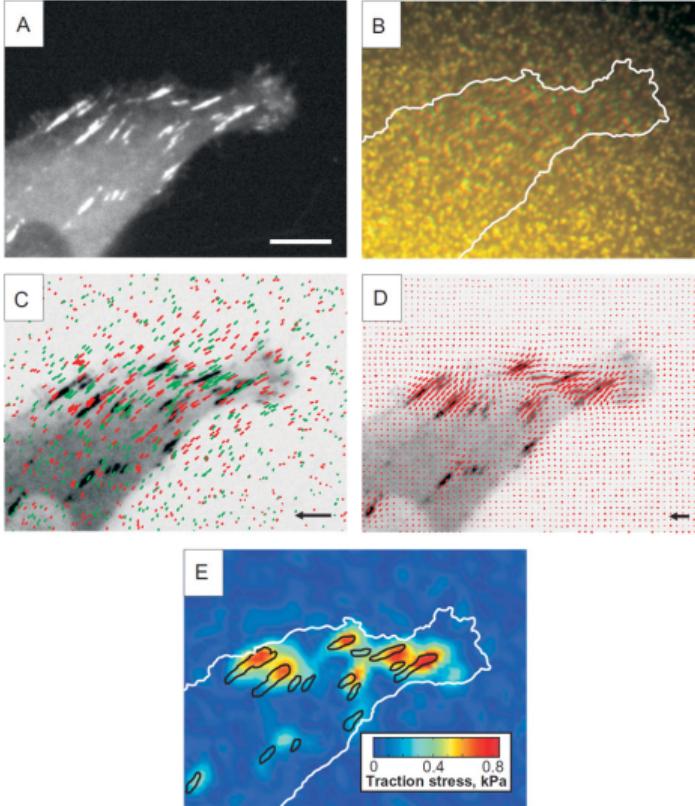


Reconstruction of localized force distributions in cells and tissues from substrate displacements using physically-consistent regularization

Joshua C. Chang (NIH), Yanli Liu (UCLA), Tom Chou (UCLA)

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Traction force microscopy



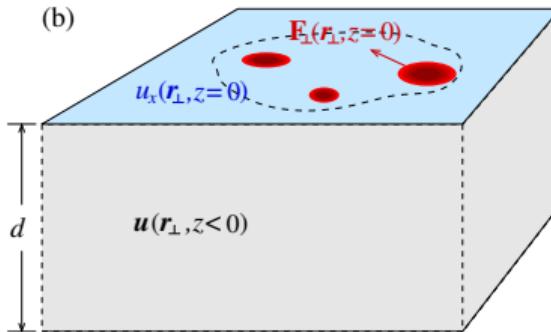
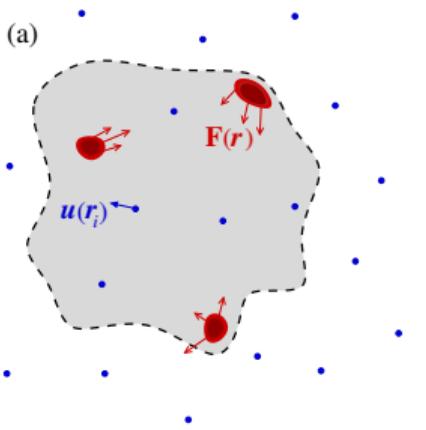
Imaging focal cell adhesions by tracking the displacement of fluorescent markers placed within a medium

- 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

Plotnikov et. al. Methods Cell Biol. 2014

Linear elasticity theory for displacements \mathbf{u}



- σ is tangential surface stress tensor, proportional to the \mathbf{F}_\perp
- \mathbf{u} found “exactly” in closed-form for any fixed piecewise-polynomial approximation of σ

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

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

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

Discretized forward problem

Linear algebra system

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

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

- $\{\mathbf{r}_i\}_{i=1}^N$ locations at which measurements are taken
- $\{\mathbf{s}_i\}_{i=1}^M$ locations controlling interpolation of σ
- Origins of \mathbb{G} depend on the interpolation order of σ

Using the physics to help constrain the problem

Reasonable physical assumptions

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

Advantage gained

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

Still need to regularize the problem

Criteria for a well-posed problem

- Solution exists
- Solution unique
- Solution continuous wrt 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 problem

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

Tensor invariants

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

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

Invariant regularization functionals Φ_{reg}

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

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

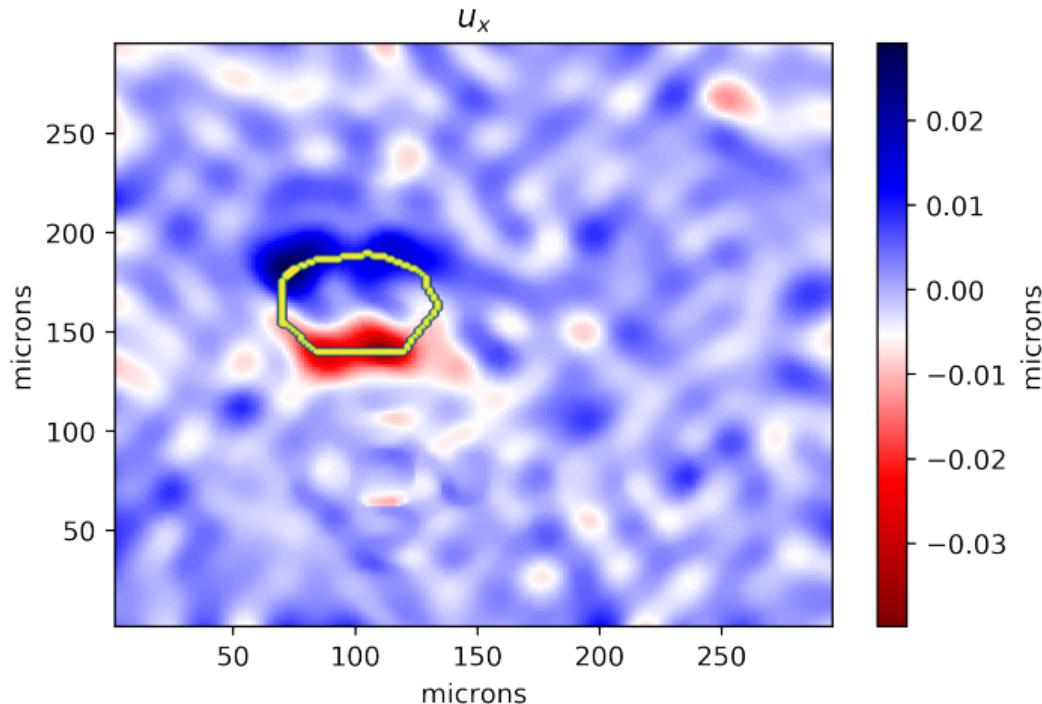
Non-invariant functionals Φ_{reg}

$$\Phi_{TV_1} = \int_{\Omega} (|\nabla \sigma_{xz}(x, y)| + |\nabla \sigma_{yz}(x, y)|) d\mathbf{x}$$

$$\Phi_{TV_2} = \int_{\Omega} (|\partial_x \sigma_{xz}| + |\partial_y \sigma_{xz}| + |\partial_x \sigma_{yz}| + |\partial_y \sigma_{yz}|) d\mathbf{x}.$$

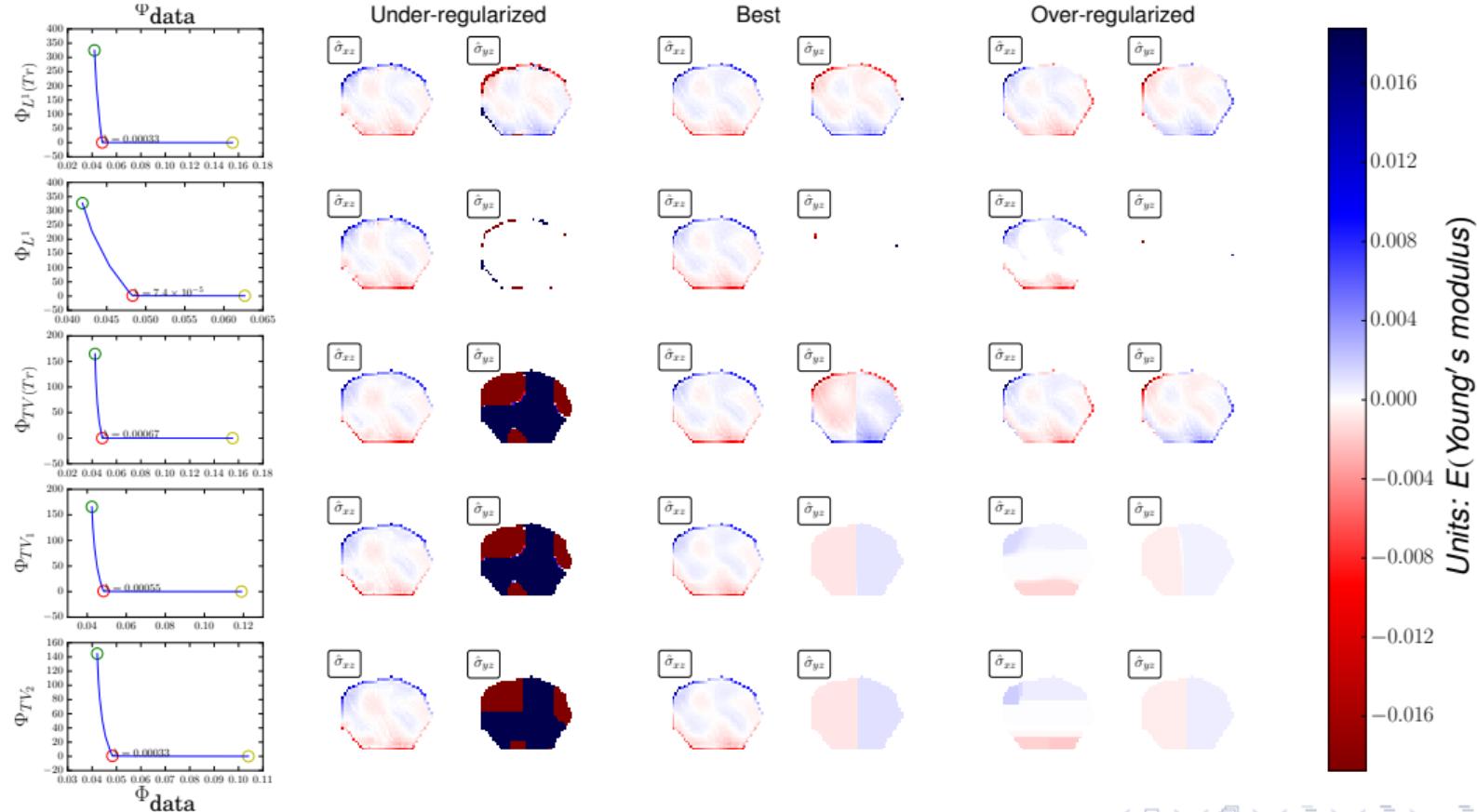
High-resolution data

- Polyacrylamide hydrogels with fluorescent grid
- High-resolution measurement of displacement field
- Hand-drawn cell boundary superimposed

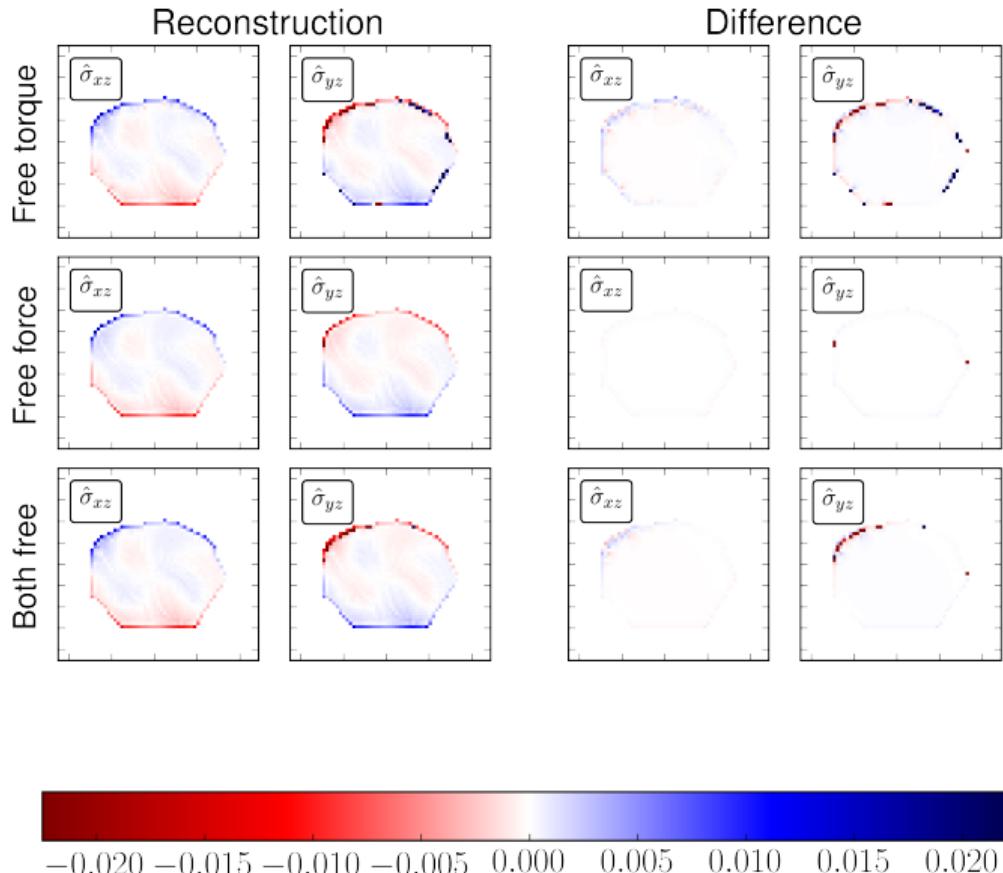


Courtesy of Gabriel Popescu, UIUC

Rotational invariance matters

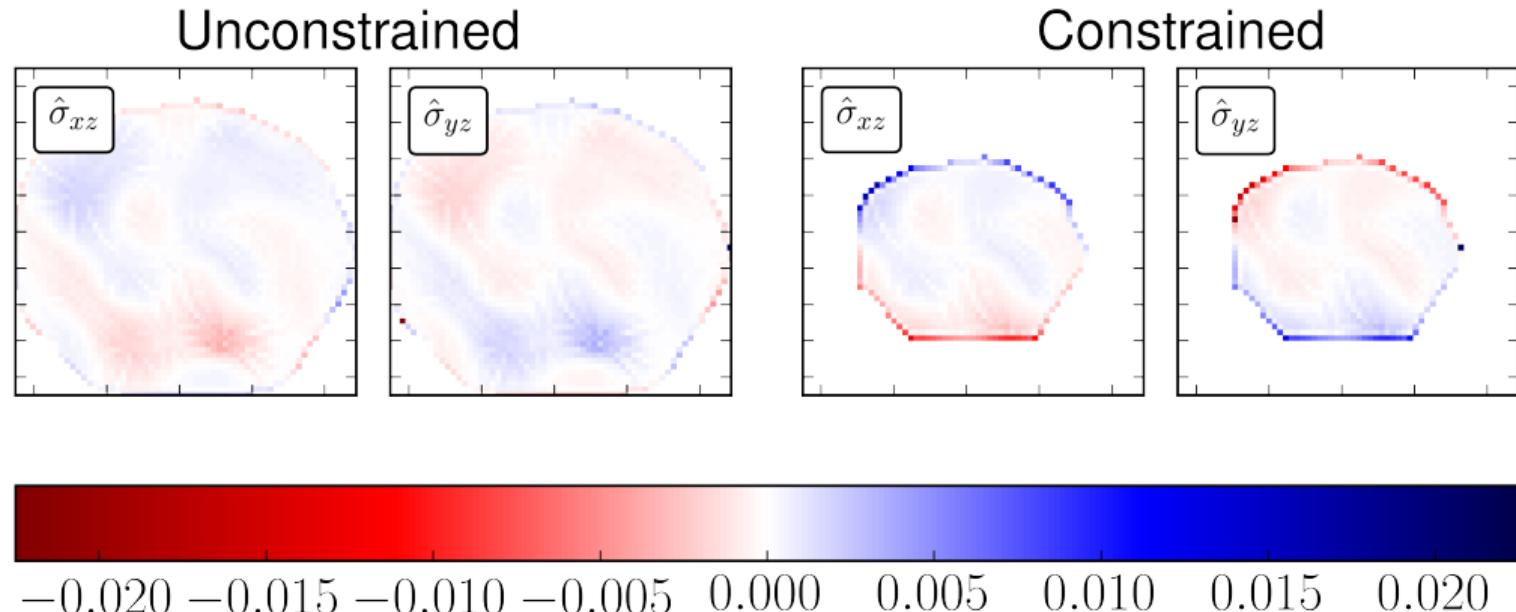


Force constraints matter



- 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