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

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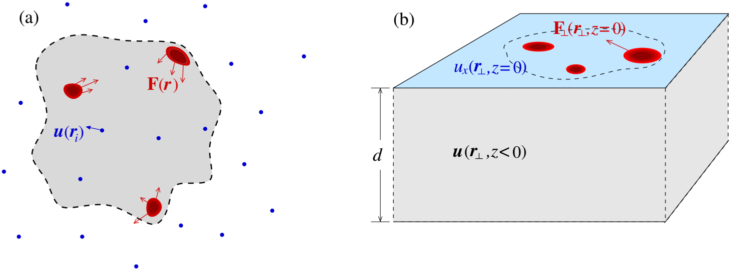
# Traction force microscopy: displacements **u** measured




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

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

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

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

# Discretized forward problem

## Linear algebra system

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

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

- $\{\mathbf{r}_i\}_{i=1}^N$ locations at which measurements are taken
- $\{\mathbf{s}_i\}_{i=1}^M$ locations controlling interpolation of $\boldsymbol{\sigma}$

# Respecting the physics in regularizing the problem

- **Principle:** Coordinate frame should not bias results
- 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

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

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

### Non-invariant functionals

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

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

# 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)

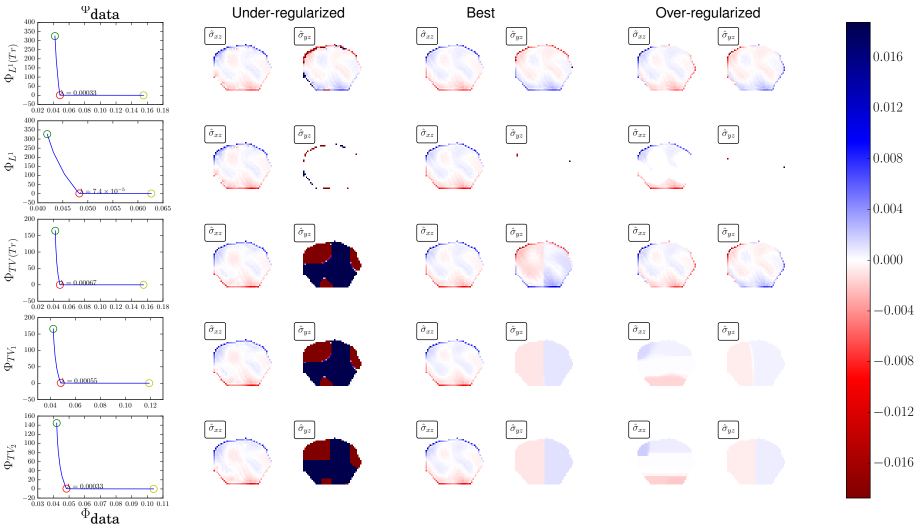
## Advantage gained

1. May restrict the size of the problem
   - Throw away far data points
2. Multiple expansion $\Rightarrow$ decay at rate $r^{-2}$
   - Justifies the use of a cut-off for data to use
   - Sparsify the linear algebra problem

## Regularized inverse problem

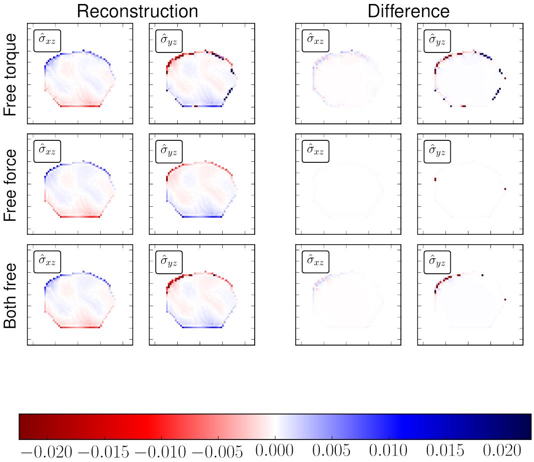
$$\hat{\boldsymbol{\sigma}} = \arg\min_{\boldsymbol{\sigma}} \left[ ||\mathbf{u} - \mathbb{G}\boldsymbol{\sigma}||_2^2 + \lambda \Phi_{\mathrm{reg}}[\boldsymbol{\sigma}] \right]$$

# Rotational invariance matters



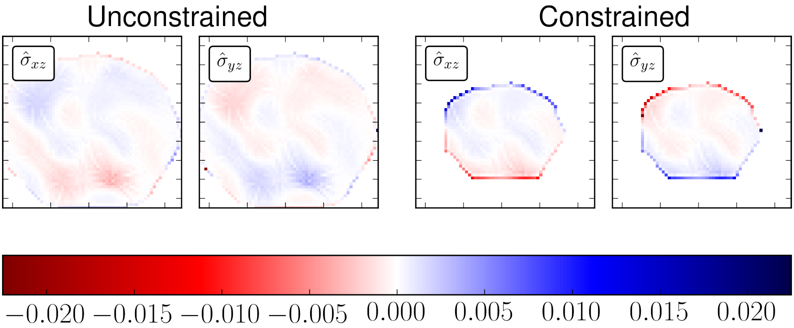

*Units: E(Young's modulus)*

# Force constraint matters




- 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
    - Future idea: Joint force reconstruction and cell boundary determination
    - Future work: May do uncertainty quantification through Bayes