Inference in biophysical models

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Outline

- Path integral-based Bayesian inference

  examples: functional interpolation
  source recovery
  dielectric reconstruction

- Dynamic Force Spectroscopy: inferring potentials and diffusivities

- Reconstructing cellular focal adhesions

Chang, Savage, Chou, J. Stat. Phys., **157**, 582, (2014)

Chang, Fok, Chou, Biophys. J., **109**, 966, (2015)

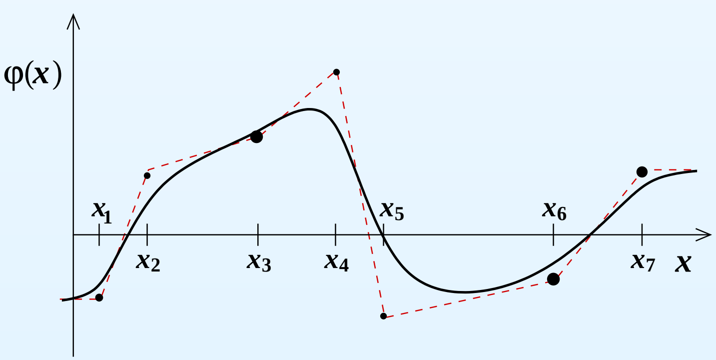
Path integral-based interpolation

inverse problems typically ill-posed: Tikhonov L^2-regularization

Example: constructing a nonparametric function $\varphi(\mathbf{x})$ from point-wise measurements φ_{obs} at positions $\{\mathbf{x}_m\}$ by seeking minima of

$$H[\varphi] = \underbrace{\frac{1}{2}\sum_{m=1}^{M}\frac{1}{s_m^2}\left(\varphi(\mathbf{x}_m) - \varphi_{\text{obs}}(\mathbf{x}_m)\right)^2}_{H_{\text{obs}}[\varphi]} + \underbrace{\frac{1}{2}\sum_{\alpha}\gamma_\alpha\int |D^\alpha\varphi|^2 \mathrm{d}\mathbf{x}}_{H_{\text{reg}}[\varphi]},$$

s_m :measurement weights
γ_α :regularization strength



C. Farmer, Algorithms for Approximation (Springer, 2007)

Path integral-based interpolation

integrate by parts to write $H[\varphi]$ as

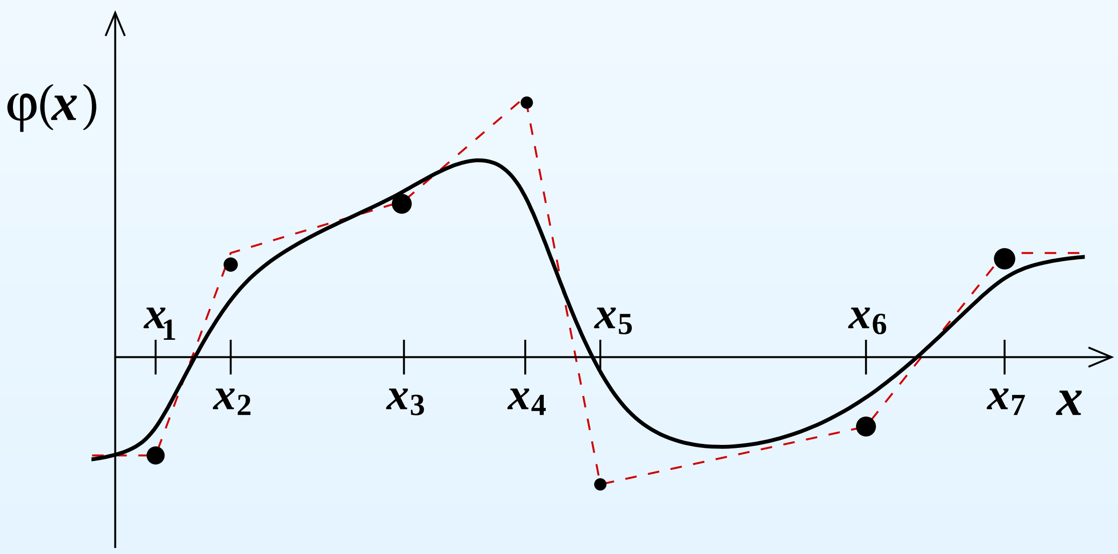
$$H[\varphi] = \underbrace{\frac{1}{2}\sum_{m=1}^{M}\frac{1}{s_m^2}\left(\varphi(\mathbf{x}_m) - \varphi_{\mathrm{obs}}(\mathbf{x}_m)\right)^2}_{H_{\text{obs}}} + \underbrace{\frac{1}{2}\int \varphi(\mathbf{x})P(-\Delta)\varphi(\mathbf{x})\mathrm{d}\mathbf{x}}_{H_{\text{reg}}[\varphi]},$$

- selects smooth solutions with smoothness controlled by $H_{\text{reg}}(\varphi;\gamma_\alpha)$
- transforms the original inverse problem into a convex optimization problem that possesses an unique solution
- choice of γ_α and order of P is related to “‘prior” knowledge on φ.

Probability over reconstructed functions

convert $$H[\varphi] = \underbrace{\frac{1}{2}\sum_{m=1}^{M}\frac{1}{s_m^2}\left(\varphi(\mathbf{x}_m) - \varphi_{\mathrm{obs}}(\mathbf{x}_m)\right)^2}_{H_{\mathrm{obs}}[\varphi]} + \underbrace{\frac{1}{2}\int \varphi(\mathbf{x})P(-\Delta)\varphi(\mathbf{x})\mathrm{d}\mathbf{x}}_{H_{\mathrm{reg}}[\varphi]},$$

into a probability over the different reconstructed functions



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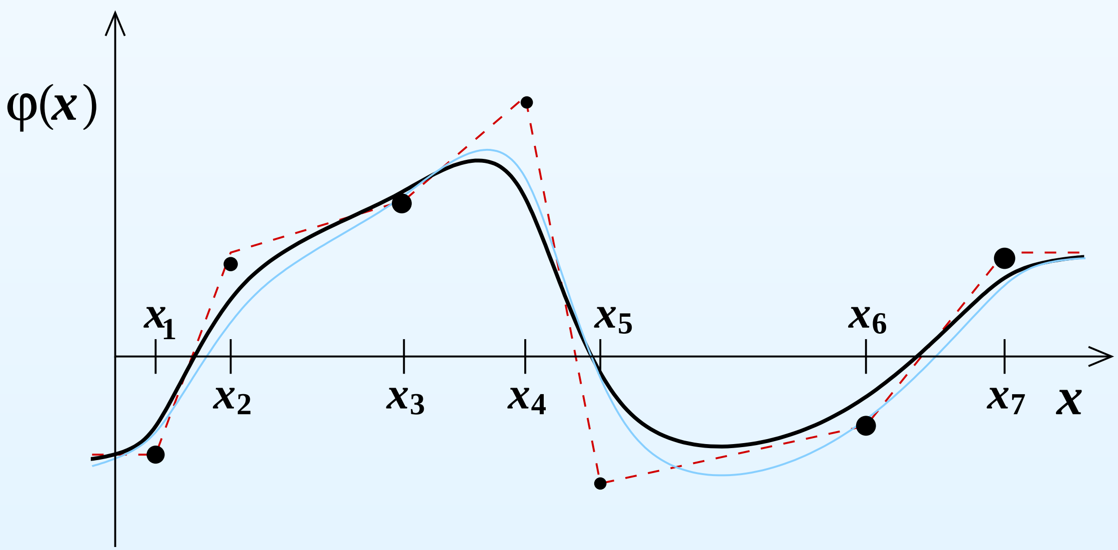

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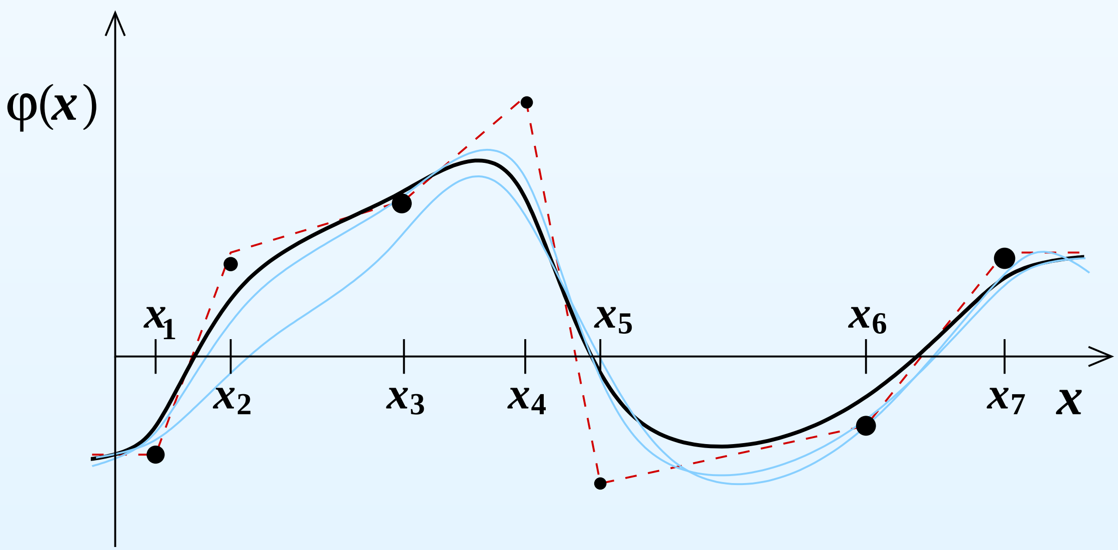

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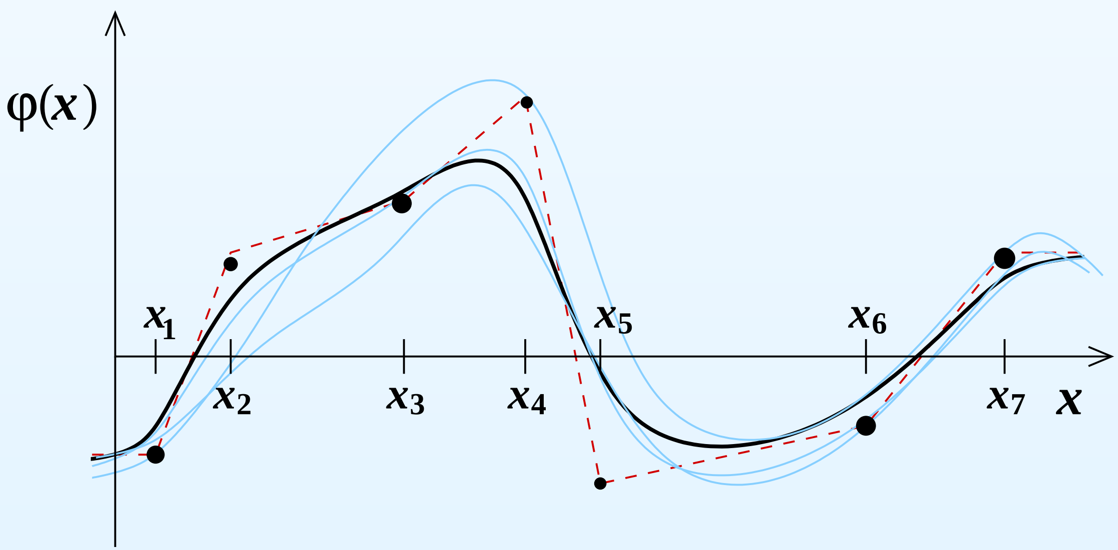


C. Farmer, Algorithms for Approximation (Springer, 2007)

Path integral-based Bayesian inference

Bayesian inference on φ, given $\varphi_{\rm obs}$, involves construction of a *posterior probability distribution* $\pi(\varphi|\varphi_{\rm obs})$ which obeys

$$\pi(\varphi|\varphi_{\rm obs}) = \frac{\overbrace{\Pr(\varphi_{\rm obs}|\varphi)}^{\text{likelihood}}\,\overbrace{\Pr(\varphi)}^{\text{prior}}}{\underbrace{Z[0]}_{\text{normalization}}}$$

- $Z[0]$ =integral over all functions (normalization)
- posterior π is a density in the space of functions
- *mean-field* inverse problem maximizes $\pi(\varphi|\varphi_{\rm obs})$ and finds most probable $\varphi(\mathbf{x})$ subject to prior $\Pr(\varphi)$
- uncertainty is related to variance of posterior from mean-field

Path integral-based inference

interpret Tikhonov regularization as a Gaussian prior and data term as a likelihood:

$$\pi(\varphi|\varphi_{\mathrm{obs}}) = \frac{1}{Z[0]} e^{-H[\varphi]} = \frac{1}{Z[0]} \underbrace{\exp\left\{-\frac{1}{2}\sum_{m=1}^{M}\frac{1}{s_m^2}\left(\varphi(\mathbf{x}_m) - \varphi_{\mathrm{obs}}(\mathbf{x}_m)\right)^2\right\}}_{\text{likelihood } (\exp\{-H_{\text{obs}}\})}$$

$$\times \underbrace{\exp\left\{-\frac{1}{2}\int \varphi(\mathbf{x}) P(-\Delta)\varphi(\mathbf{x})\mathrm{d}\mathbf{x}\right\}}_{\text{prior } (\exp\{-H_{\text{reg}}\})}$$

where $Z[0] = \int \mathcal{D}\varphi e^{-H[\varphi]} = \int \mathcal{D}\varphi e^{-H_{\text{reg}}[\varphi]} e^{-H_{\text{obs}}[\varphi]}$

choose regularization $P(-\Delta)$ based on prior knowledge of correlations

Gaussian functional integration

quadratic forms for $H[\varphi]$:

$$Z[0] = \int \mathcal{D}\varphi e^{-H[\varphi]}$$
$$= \int \mathcal{D}\varphi \exp\left\{-\frac{1}{2}\iint \varphi(\mathbf{x})A(\mathbf{x},\mathbf{x}')\varphi(\mathbf{x}')\mathrm{d}\mathbf{x}\mathrm{d}\mathbf{x}' + \int b(\mathbf{x})\varphi(\mathbf{x})\mathrm{d}\mathbf{x}\right\},$$

$\Rightarrow$ probability density is Gaussian in function-space and

$$Z[0] = \exp\left\{\frac{1}{2}\iint b(\mathbf{x})A^{-1}(\mathbf{x},\mathbf{x}')b(\mathbf{x}')\mathrm{d}\mathbf{x}\mathrm{d}\mathbf{x}' - \frac{1}{2}\ln\det A\right\}.$$

where $A(\mathbf{x},\mathbf{x}') = A_{\text{reg}} + A_{\text{obs}}$ and

$$\int A(\mathbf{x},\mathbf{x}')A^{-1}(\mathbf{x}',\mathbf{x}'')\mathrm{d}\mathbf{x}' = \delta(\mathbf{x}-\mathbf{x}'')$$

Path integral-based inference

- from H_{reg} term, $A_{\text{reg}}(\mathbf{x}, \mathbf{x}') = P(-\Delta)\delta(\mathbf{x} - \mathbf{x}')$ encodes *a priori* spatial correlation of φ through the Green's function $A_{\text{reg}}^{-1}(\mathbf{x}, \mathbf{y}) = G(\mathbf{x}, \mathbf{y})$

- from H_{obs} term, $A_{\text{obs}}(\mathbf{x}, \mathbf{x}') = \delta(\mathbf{x} - \mathbf{x}') \sum_{m=1}^{M} s_m^{-2} \delta(\mathbf{x}' - \mathbf{x}_m)$ and $b(\mathbf{x}) = \sum_{m=1}^{M} s_m^{-2} \delta(\mathbf{x} - \mathbf{x}_m) \varphi_{\text{obs}}(\mathbf{x}_m)$ encodes the data terms

- theory is Gaussian and exactly solvable

What if we wish to recover a function $\xi(\mathbf{x})$ given measurements of another coupled function $\varphi(\mathbf{x}_m)$?

Path integral recovery of a parameter function

general one-to-one relationship between $\xi(\mathbf{x})$ and $\varphi(\mathbf{x})$:

$$F(\varphi(\mathbf{x}), \xi(\mathbf{x})) = 0 \qquad \mathbf{x} \in \Omega \setminus \partial\Omega.$$

$F(\varphi(\mathbf{x}), \xi(\mathbf{x})) = 0$ constrains φ to ξ via *e.g.*, a PDE

now, regularize $\xi(\mathbf{x})$ using knowledge of its spatial correlations via the posterior probability density

$$\pi(\varphi, \xi | \varphi_{\mathrm{obs}}) = \frac{1}{Z[0]} \exp\left\{ -\frac{1}{2} \int \sum_{m=1}^{M} \delta(\mathbf{x} - \mathbf{x}_m) \frac{(\varphi(\mathbf{x}) - \varphi_{\mathrm{obs}}(\mathbf{x}))^2}{s_m^2} \mathrm{d}\mathbf{x} \right\}$$
$$\times \exp\left\{ -\frac{1}{2} \int \xi(\mathbf{x}) P(-\Delta) \xi(\mathbf{x}) \mathrm{d}\mathbf{x} \right\} \boldsymbol{\delta}\left(F(\varphi, \xi)\right),$$

impose $F = 0$ via functional “Donsker’s” $\delta-$function

Path integral-based inference

exponentiating the δ-function, $\boldsymbol{\delta}\left(F(\varphi,\xi)\right) = \int \mathcal{D}\lambda e^{-i\int \lambda(\mathbf{x})F(\varphi(\mathbf{x}),\xi(\mathbf{x}))\mathrm{d}\mathbf{x}}$ (where $\lambda(\mathbf{x})$ is the Fourier wavevector function), posterior depends on three functions φ, ξ, λ:

$$\pi(\varphi,\xi,\lambda|\varphi_{\mathrm{obs}}) = \frac{1}{Z[0]}\exp\left\{-H[\varphi,\xi,\lambda|\varphi_{\textsf{obs}}]\right\},$$

where $Z[0] = \iiint \mathcal{D}\xi\mathcal{D}\varphi\mathcal{D}\lambda \exp\left\{-H[\varphi,\xi,\lambda|\varphi_{\textsf{obs}}]\right\}$ and

$$\begin{aligned} H[\varphi,\xi,\lambda|\varphi_{\mathrm{obs}}] =& \frac{1}{2}\int\sum_{m=1}^{M}\delta(\mathbf{x}-\mathbf{x}_m)\frac{(\varphi(\mathbf{x})-\varphi_{\mathrm{obs}}(\mathbf{x}))^2}{s_m^2}\mathrm{d}\mathbf{x} \\ &+ \frac{1}{2}\int \xi(\mathbf{x})P(-\Delta)\xi(\mathbf{x})\mathrm{d}\mathbf{x} + i\int\lambda(\mathbf{x})F(\varphi,\xi)\mathrm{d}\mathbf{x}, \end{aligned}$$

is a functional of φ, ξ, and the Fourier wave vector $\lambda(\mathbf{x})$.

Path integral-based inference: extremal solution

maximum a posteriori estimation (MAP) inference: minimize energy functional wrt $\varphi(\mathbf{x}), \xi(\mathbf{x})$, and $\lambda(\mathbf{x})$. E-L eqns:

$$F(\varphi,\xi) = 0, \quad P(-\Delta)\xi + \frac{\delta}{\delta\xi(\mathbf{x})}\int \lambda(\mathbf{x})F(\varphi,\xi)\mathrm{d}\mathbf{x} = 0,$$

$$\sum_{n=1}^{M}\delta(\mathbf{x}-\mathbf{x}_n)(\varphi(\mathbf{x})-\varphi_{\mathrm{obs}}(\mathbf{x})) + \frac{\delta}{\delta\varphi(\mathbf{x})}\int \lambda(\mathbf{x})F(\varphi,\xi)\mathrm{d}\mathbf{x} = 0$$

integrating over $\lambda(\mathbf{x})$ and $\varphi(\mathbf{x})$, *effective* $H[\xi|\varphi_{\text{obs}}]$ may not be Gaussian

semiclassical perturbation near extremal solution:

$$H[\xi] \approx H[\xi^*] + \frac{1}{2}\int \mathrm{d}\mathbf{x}\int \mathrm{d}\mathbf{x}'\delta\xi(\mathbf{x})\left(\frac{\delta^2 H}{\delta\xi(x)\delta\xi(\mathbf{x}')}\right)\delta\xi(\mathbf{x}') + O(\delta\xi^3)$$

Applications: deterministic models

- interpolating membrane deformations: Canham-Helfrich model
- source recovery: $F(\varphi(\mathbf{x}), \xi(\mathbf{x})) \Rightarrow \Delta\varphi(\mathbf{x}) = \rho(\mathbf{x})$
- dielectric recovery: $F(\varphi(\mathbf{x}), \xi(\mathbf{x})) \Rightarrow \nabla \cdot (\epsilon(\mathbf{x})\nabla\varphi(\mathbf{x})) = \rho(\mathbf{x})$

Membrane interpolation

$$H[\varphi|\varphi_{\text{obs}}] = \frac{1}{2}\int \sum_{m=1}^{M} \frac{\delta(\mathbf{x}-\mathbf{x}_m)}{s_m^2}(\varphi(\mathbf{x})-\varphi_{\text{obs}}(\mathbf{x}))^2 \mathrm{d}\mathbf{x} + \frac{1}{2}\int \varphi(\mathbf{x}) P(-\Delta)\varphi(\mathbf{x})\mathrm{d}\mathbf{x},$$

Use Canham-Helfrich model $P(-\Delta) = \beta(\kappa\Delta^2 - \sigma\Delta)$ in E-L Eq:

$$\frac{\delta H}{\delta\varphi} = \sum_{m=1}^{M} \frac{\delta(\mathbf{x}-\mathbf{x}_m)}{s_m^2}(\varphi(\mathbf{x}) - \varphi_{\text{obs}}(\mathbf{x})) + P(-\Delta)\varphi(\mathbf{x}) = 0.$$

for fluctuations, consider

$$Z[J] \propto \exp\left\{ \frac{1}{2}\iint J(\mathbf{x})A^{-1}(\mathbf{x},\mathbf{x}')J(\mathbf{x}')\mathrm{d}\mathbf{x}'\mathrm{d}\mathbf{x} \right.$$
$$\left. + \int J(\mathbf{x}) \sum_{m=1}^{M} \frac{\varphi_{\text{obs}}(\mathbf{x}_m)A^{-1}(\mathbf{x},\mathbf{x}_m)}{s_m^2}\mathrm{d}\mathbf{x} \right\}$$

Path integral-based inference

through functional differentiation of $Z[J]$, mean-field solution is

$$\frac{1}{Z[0]}\frac{\delta Z[J]}{\delta J(\mathbf{x})}\bigg|_{J=0} \equiv \langle \varphi(\mathbf{x})\rangle = \sum_{m=1}^{M} \frac{\varphi_{\mathrm{obs}}(\mathbf{x}_m)A^{-1}(\mathbf{x},\mathbf{x}_m)}{s_m^2},$$

and variance in the solution is

$$\frac{1}{Z[0]}\frac{\delta^2 Z[J]}{\delta J(\mathbf{x})\delta J(\mathbf{x}')}\bigg|_{J=0} \equiv \Big\langle \varphi(\mathbf{x}) - \langle\varphi(\mathbf{x})\rangle\,, \varphi(\mathbf{x}') - \langle\varphi(\mathbf{x}')\rangle\Big\rangle = A^{-1}(\mathbf{x},\mathbf{x}'),$$

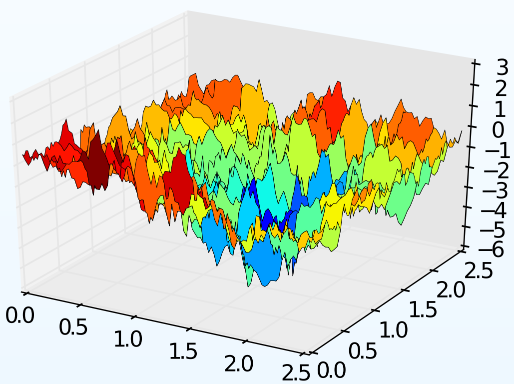
$$A^{-1}(\mathbf{x},\mathbf{x}') = G(\mathbf{x},\mathbf{x}') - \bar{\mathbf{G}}^T(\mathbf{x})\left(\mathbf{I}+\mathbf{\Lambda}\right)^{-1}\mathbf{G}(\mathbf{x}'),$$

where, $\bar{G}_j(\mathbf{x}) \equiv s_j^{-2}G(\mathbf{x},\mathbf{x}_j)$, $G_i(\mathbf{x}) \equiv G(\mathbf{x},\mathbf{x}_i)$, $\Lambda_{ij} \equiv s_i^{-2}G(\mathbf{x}_i,\mathbf{x}_j)$, and, in 2D,

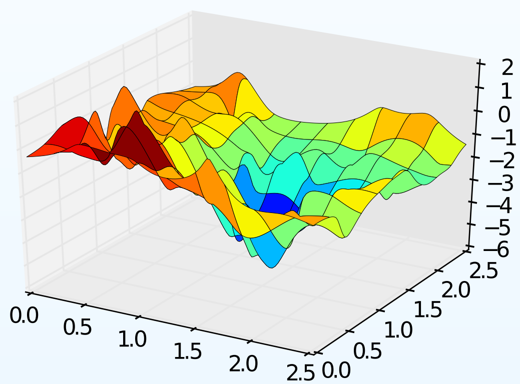
$$G(\mathbf{x},\mathbf{x}') = -\frac{1}{2\pi\beta\sigma}\left[\log\left(|\mathbf{x}-\mathbf{x}'|\right) + K_0\left(\sqrt{\frac{\sigma}{\kappa}}|\mathbf{x}-\mathbf{x}'|\right)\right]$$

Path integral-based inference

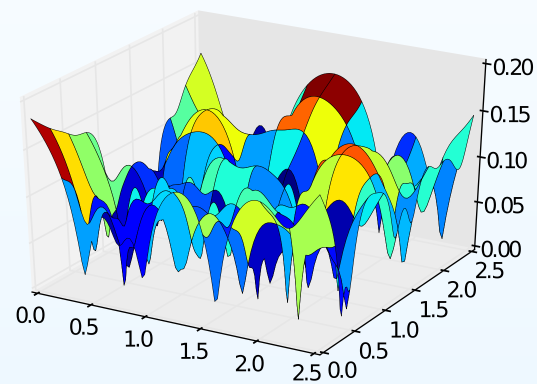
interpolating membrane height fluctuations:



simulated $\varphi(\mathbf{x})$



$\langle\varphi(\mathbf{x})\rangle$ from 100 points



$\sqrt{\langle(\varphi(\mathbf{x}) - \langle\varphi(\mathbf{x})\rangle)^2\rangle}$

Source recovery: $\Delta\varphi(\mathbf{x}) = \rho(\mathbf{x})$

recover the source function $\rho(\mathbf{x})$ from measurements of $\varphi(\mathbf{x}_i)$

$$
\begin{aligned}
H[\varphi,\rho,\lambda|\varphi_{\mathrm{obs}}] =& \frac{1}{2}\int\sum_{m=1}^{M}\frac{\delta(\mathbf{x}-\mathbf{x}_m)}{s_m^2}(\varphi(\mathbf{x})-\varphi_{\mathrm{obs}}(\mathbf{x}))^2\mathrm{d}\mathbf{x} \\
&+\frac{1}{2}\int\rho(\mathbf{x})P(-\Delta)\rho(\mathbf{x})\mathrm{d}\mathbf{x}+i\int\lambda(\mathbf{x})\left(\Delta\varphi(\mathbf{x})-\rho(\mathbf{x})\right)\mathrm{d}\mathbf{x}
\end{aligned}
$$

Euler-Lagrange equations $\left(\frac{\delta H}{\delta\varphi}=\frac{\delta H}{\delta\rho}=\frac{\delta H}{i\delta\lambda}=0\right)$:

$$
\begin{aligned}
\Delta\varphi^\star(\mathbf{x}) &= \rho^\star(\mathbf{x}), \\
P(-\Delta)\Delta^2\varphi^\star(\mathbf{x}) &= -\sum_{m=1}^{M}\frac{\delta(\mathbf{x}-\mathbf{x}_m)}{s_m^2}(\varphi^\star(\mathbf{x})-\varphi_{\mathrm{obs}}(\mathbf{x}))
\end{aligned}
$$

Uncertainty of source recovery

posterior takes the form

$$\pi(\rho(\mathbf{x}) = \Delta\varphi | \varphi_{\mathrm{obs}}(\mathbf{x}_i)) = \frac{1}{Z[0]} \exp\left\{ -\frac{1}{2} \int \sum_{m=1}^{M} \frac{\delta(\mathbf{x} - \mathbf{x}_m)}{s_m^2} (\varphi(\mathbf{x}) - \varphi_{\mathrm{obs}}(\mathbf{x}))^2 \mathrm{d}\mathbf{x} \right\}$$

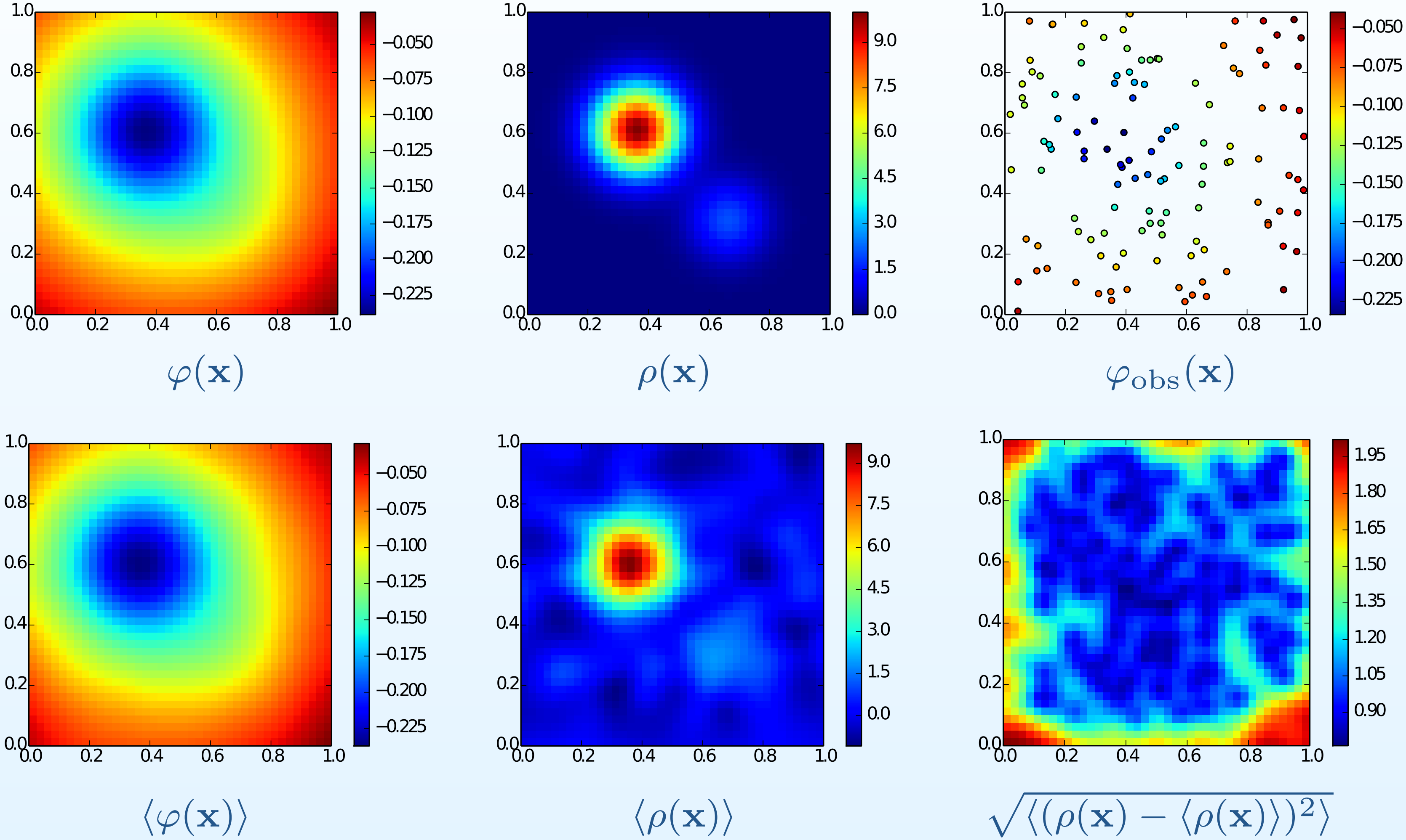
$$\times \exp\left\{ -\frac{1}{2} \int \underbrace{\Delta\varphi(\mathbf{x})}_{``\rho(\mathbf{x})''} P(-\Delta)\Delta\varphi(\mathbf{x}) \mathrm{d}\mathbf{x} \right\},$$

$$Z[J] \propto \exp\left\{ \frac{1}{2} \iint \Delta J(\mathbf{x}) A^{-1}(\mathbf{x}, \mathbf{x}')\Delta' J(\mathbf{x}')\mathrm{d}\mathbf{x}'\mathrm{d}\mathbf{x} + \int J(\mathbf{x})\Delta \sum_{m=1}^{M} \frac{\varphi_{\mathrm{obs}}(\mathbf{x}_m) A^{-1}(\mathbf{x}, \mathbf{x}_m)}{s_m^2} \mathrm{d}\mathbf{x} \right\}$$

where first two moments are found from $\left.\frac{\delta Z[J]}{\delta J(\mathbf{x})}\right|_{J=0}$ and $\left.\frac{\delta^2 Z[J]}{\delta J(\mathbf{x})\delta J(\mathbf{x}')}\right|_{J=0}$, *e.g.*,

$$\frac{1}{Z[0]} \left.\frac{\delta Z[J]}{\delta J(\mathbf{x})}\right|_{J=0} = \left(\sum_{m=1}^{M} \frac{\varphi_{\mathrm{obs}}(\mathbf{x}_m)\Delta A^{-1}(\mathbf{x}, \mathbf{x}_m)}{s_m^2} \right) = \langle \rho(x) \rangle$$

Path integral-based inference



Dielectric reconstruction

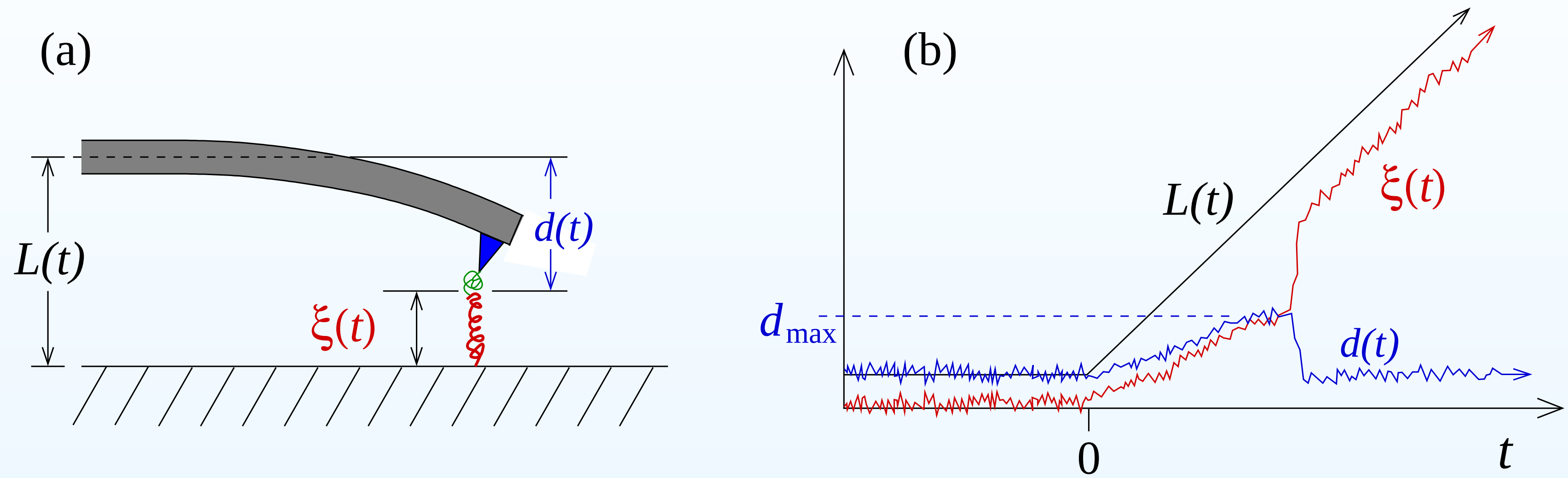
$$H[\varphi, \epsilon, \lambda|\rho, \varphi_{\mathrm{obs}}] = \frac{1}{2}\sum_{m=1}^{M}\int \frac{\delta(\mathbf{x}-\mathbf{x}_m)}{s_m^2}|\varphi(\mathbf{x}) - \varphi_{\mathrm{obs}}(\mathbf{x})|^2 \mathrm{d}\mathbf{x}$$
$$-\frac{1}{2}\int \epsilon(\mathbf{x})\Delta P(-\Delta)\epsilon(\mathbf{x})\mathrm{d}\mathbf{x} + i\int \lambda(\mathbf{x})\left[\nabla\cdot(\epsilon\nabla\varphi) - \rho\right]\mathrm{d}\mathbf{x},$$

which yields the Euler-Lagrange equations

$$\nabla\cdot(\epsilon\nabla\varphi) = \rho,$$
$$\Delta P(-\Delta)\epsilon = -\nabla\lambda\cdot\nabla\varphi,$$
$$\nabla\cdot(\epsilon\nabla\lambda) = -\sum_{j=1}^{M}\frac{\delta(\mathbf{x}-\mathbf{x}_j)}{s_j^2}(\varphi(\mathbf{x}) - \varphi_{\mathrm{obs}}(\mathbf{x}))$$

integrating out φ and $\lambda \Rightarrow$ nonquadratic $H_{\mathrm{eff}}[\epsilon] \Rightarrow$ perturbation

Dynamic Force Spectroscopy (DFS)

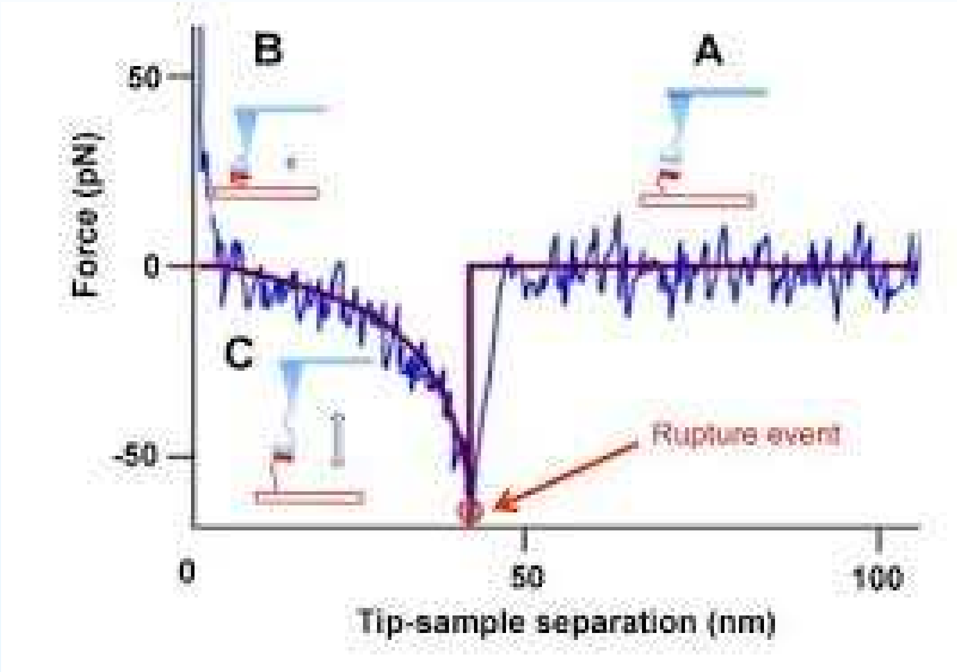


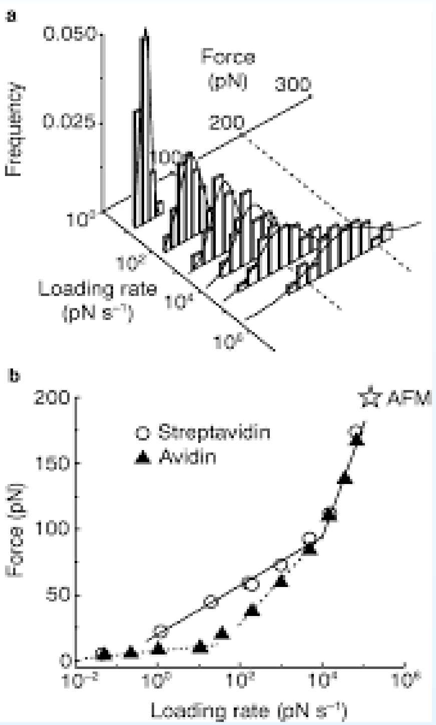
- pull on bond using device with intrinsic spring constant K.
- puller position $L(t)$ and deflection $d(t)$, or force f_a are measured.
- bond displacement $\xi(t) = L(t) - d(t)$.

What can we say about the bond from measurements of $\xi(t)$?

DFS: expts & theory

DFS experiments:





force−displacement curves rupture force distributions

theory for rupture forces involves parametric bond energy

Evans, Hummer, Szabo, Dudko, 1999+

DFS: Work/Fluctuation Thms

Cohen, Jarzynski, Crooks

$$e^{-\Delta U/k_B T} = \langle e^{-W/k_B T} \rangle$$

Implication: One can characterize the free-energy surface by systematically perturbing system.

Limitations:

- Requires initial equilibrium distribution
- No natural likelihood function for maximum likelihood inference
- No handle on variable diffusivity

Hummer and Szabo, PNAS, **98**, 3658, (2001)

DFS: overdamped limit

- neglect inertia and impose fluctuation-dissipation:

$$\mathrm{d}\xi = A(\xi, t)\mathrm{d}t + \sqrt{2D(\xi)}\mathrm{d}W,$$

- drift: $A(x,t) = D(x)\left[f(x) + \underbrace{K(L(t) - x)}_{f_a}\right] + D'(x)$

- associated Fokker-Planck Eq:

$$\frac{\partial P(x,t)}{\partial t} - \frac{\partial}{\partial x}\left(PD(x)\frac{\partial \Phi}{\partial x}\right) = \frac{\partial}{\partial x}\left(D(x)\frac{\partial P}{\partial x}\right).$$

- total potential: $\Phi(x,t) = \underbrace{U(x)}_{\text{bond}} + \underbrace{\frac{K}{2}(x - L(t))^2}_{\text{harmonic}}$

DFS: inverse problem

- molecular force $f(x) = -\frac{\mathrm{d}U}{\mathrm{d}x}$, bond mobility $D(x)$
- assume pulling device is moved at constant V: $L(t) = L_0 + Vt$
- applied force $f_a(t) = K\,[L(t) - d(t)]$ equivalent to measuring $\xi(t)$
- avoid parametric model for $U(x)$ or $D(x)$

Goal: reconstruct $f(x) = -\frac{\mathrm{d}U}{\mathrm{d}x}$, $D(x)$ from trajectories $\xi(t)$ measured @ times t_i

DFS: Bayes formulation

- prior probability density on bond force $f(x)$:

$$\pi(f|\boldsymbol{\theta}) = \mathcal{Z}_f^{-1} \exp\left\{-\frac{1}{2}\int_0^\infty f(y)R_f(-\Delta)f(y)\mathrm{d}y\right\}$$

to enforce $D(x) > 0$, define log-diffusivity $g(y) = \ln(D(y)/D_0)$ where $D_0 > 0$ is a uniform background diffusivity

- prior probability density on the log-diffusivity $g(y)$:

$$\pi(g|\boldsymbol{\theta}) = \mathcal{Z}_g^{-1} \exp\left\{-\frac{1}{2}\int_0^\infty g(y)R_g(-\Delta)g(y)\mathrm{d}y\right\}.$$

$\boldsymbol{\theta}$: parameters in R_f, R_g.

DFS: Bayes formulation

- prior distributions on $f(x)$ and $g(x)$ enforce Gaussian spatial auto-correlations on the target functions.

- auto-correlations are determined by the Green's functions of R_f and R_g, which encode magnitude and scale information on the spatial variability of f and g.

- trajectory is composed of measurements of bond displacements, $\boldsymbol{\xi} \equiv (\xi_1, \xi_2, \ldots, \xi_N)$, taken at times $t_1, t_2, \ldots t_N$.

DFS: data

forward problem: given $f(x)$ and $D(x) = D_0 e^{g(x)}$ *likelihood* of the trajectory $\xi_{0\le j\le N}$ is $\pi(\boldsymbol{\xi}|f,g) = \prod_j \Pr(\xi_{j+1}|\xi_j, f, g)$.

total likelihood for observing entire ensemble of M trajectories $\mathbf{X} = \{\boldsymbol{\xi}^{(\alpha)}\}, (1 \le \alpha \le M)$, is the product of individual likelihoods:

$$
\begin{aligned}
\pi(\mathbf{X}|f,g) &= \prod_\alpha \pi(\boldsymbol{\xi}^{(\alpha)}|f,g) \\
&= \exp\left\{ -\sum_{\alpha,j} \left[\frac{(\xi_{j+1}^{(\alpha)} - \xi_j^{(\alpha)} - A(\xi_j^{(\alpha)}, t_j)\delta t)^2}{4D(\xi_j^{(\alpha)})\delta t} \right] \right\} \prod_{\alpha,j} \sqrt{\frac{1}{4\pi D(\xi_j^{(\alpha)})\delta t}}
\end{aligned}
$$

DFS: posterior distribution

$$\pi(f,g|\mathbf{X},\boldsymbol{\theta}) = \frac{\pi(\mathbf{X}|f,g)\pi(f|\boldsymbol{\theta})\pi(g|\boldsymbol{\theta})}{\pi(\mathbf{X})} \equiv \frac{e^{-H[f,g|\mathbf{X},\boldsymbol{\theta}]}}{\mathcal{Z}},$$

where $\mathcal{Z}$ is a normalization and H is the information Hamiltonian:

$$\begin{aligned} H\left[f,g \mid \mathbf{X},\boldsymbol{\theta}\right] =& \frac{1}{2}\int_0^\infty f(y)R_f(-\Delta)f(y)dy + \frac{1}{2}\int_0^\infty g(y)R_g(-\Delta)g(y)\mathrm{d}y \\ &+ \frac{1}{2}\sum_{\alpha,j}\ln D(\xi_j^{(\alpha)}) + \sum_{\alpha,j}\frac{\left(\xi_{j+1}^{(\alpha)} - \xi_j^{(\alpha)} - A(\xi_j^{(\alpha)},t_j)\delta t\right)^2}{4D(\xi_j^{(\alpha)})\delta t}, \end{aligned}$$

Extremal solution $f^*(x), g^*(x)$ from E-L eqs:

$$\left.\frac{\delta H}{\delta f}\right|_{f=f^*} = \left.\frac{\delta H}{\delta g}\right|_{g=g^*} = 0$$

DFS: E-L equations

Extremal solution $f^*(x), g^*(x)$ from solutions to E-L Eqs:

$$\frac{\delta H}{\delta f(y)} = R_f(-\Delta) f(y) - \frac{1}{2}\sum_{\alpha,j} \delta(y-\xi_j^\alpha)\left[\xi_{j+1}^{(\alpha)} - \xi_j^{(\alpha)} - A(y,t)\delta t\right]$$

$$\frac{\delta H}{\delta g(y)} = R_g(-\Delta) g(y) + \frac{1}{2}\sum_{\alpha,j} \frac{\partial}{\partial y}\left[\delta(y-\xi_j^{(\alpha)})(\xi_{j+1}^{(\alpha)} - \xi_j^{(\alpha)} - A(y,t_j)\delta t)\right]$$

$$+ \frac{1}{2}\sum_{\alpha,j} \delta(y-\xi_j^{(\alpha)})\left\{1 - \frac{(\xi_{j+1}^{(\alpha)} - \xi_j^{(\alpha)})^2 - A^2(y,t_j)(\delta t)^2}{2D(y)\delta t}\right\}.$$

$D \Leftrightarrow g$ and $A[f,g]$: eqns are coupled nonlinear PDEs

now choose $R_{f,g}(-\Delta)$...

DFS: choose regularization

If $R_f = R_g = 1$ Green's function is $\delta-$distribution. Solution is unregularized piecewise constant recovery of force and diffusivity. For smoother recoveries, assume f and g are infinitely-differentiable

$$R_f(-\Delta) = \frac{e^{-\gamma_f \Delta/2}}{\beta_f \sqrt{2\pi\gamma_f}}, \qquad R_g(-\Delta) = \frac{e^{-\gamma_g \Delta/2}}{\beta_g \sqrt{2\pi\gamma_g}}.$$

γ=spatial scale; $1/\beta$=temperature

determine $\boldsymbol{\theta} = (\beta_f, \beta_g, \gamma_f, \gamma_g)$ by maximizing marginal likelihood

$$\pi(\mathbf{X}|\boldsymbol{\theta}) = \iint \mathcal{D}f\mathcal{D}g\, \pi(\mathbf{X}|f,g)\pi(f|\boldsymbol{\theta})\pi(g|\boldsymbol{\theta})$$

with respect to $\boldsymbol{\theta}$. Nonlinear $\Rightarrow$ perturbation...

DFS: Expansion about extremals, $f^\star$, $g^\star$

expand about extremal points $f^\star, g^\star$ to quadratic order

$$H[f, g|\mathbf{X}, \boldsymbol{\theta}] \approx H[f^\star, g^\star|\mathbf{X}, \boldsymbol{\theta}] + \frac{1}{2}\iint \boldsymbol{\varphi}(y)^t \boldsymbol{\Sigma}^{-1} \boldsymbol{\varphi}(z) \mathrm{d}y \mathrm{d}z$$

difference of functions from their classical solution is defined by

$$\boldsymbol{\varphi}(x) = \begin{bmatrix} f(x) - f^\star(x) \\ g(x) - g^\star(x) \end{bmatrix}$$

and the semiclassical Hessian $\boldsymbol{\Sigma}^{-1}$ matrix is

$$\boldsymbol{\Sigma}^{-1} = \begin{bmatrix} \frac{\delta^2 H}{\delta f(y) \delta f(z)} & \frac{\delta^2 H}{\delta f(y) \delta g(z)} \\ \frac{\delta^2 H}{\delta g(y) \delta f(z)} & \frac{\delta^2 H}{\delta g(y) \delta g(z)} \end{bmatrix}_{f^\star, g^\star}$$

DFS: Maximum marginal likelihood for $\boldsymbol{\theta}$

perform Gaussian integrals to evaluate $\pi(\mathbf{X}|\boldsymbol{\theta})$ and maximize wrt $\boldsymbol{\theta}$
equivalent to minimizing

$$-\ln \pi(\mathbf{X}|\boldsymbol{\theta}) = H[f^\star, g^\star|\mathbf{X}, \boldsymbol{\theta}] + \mathrm{Tr}\ln \boldsymbol{\Sigma} - \mathrm{Tr}\ln G_f(x,y) - \mathrm{Tr}\ln G_g(x,y),$$

$$\begin{aligned} H[f^*, g^*|\mathbf{X}, \boldsymbol{\theta}] = & \frac{1}{4}\sum_{\alpha,j} f^*(\xi_j^{(\alpha)})\left[\xi_{j+1}^{(\alpha)} - \xi_j^{(\alpha)} - A(\xi_j^{(\alpha)}, t)\delta t\right] \\ & + \frac{1}{4}\sum_{\alpha,j}\left[g^{*\prime}(\xi_j^{(\alpha)})(\xi_{j+1}^{(\alpha)} - \xi_j^{(\alpha)} - A(\xi_j^{(\alpha)}, t_j)\delta t)\right] \\ & - \frac{1}{4}\sum_{\alpha,j} g^*(\xi_j^{(\alpha)})\left[1 - \frac{(\xi_{j+1}^{(\alpha)} - \xi_j^{(\alpha)})^2 - A^2(\xi_j^{(\alpha)}, t_j)(\delta t)^2}{2D^*(\xi_j^{(\alpha)})\delta t}\right] + \frac{1}{2}\sum_{\alpha,j}\ln D^*(\xi_j^{(\alpha)}) \\ & + \sum_{\alpha,j}\frac{\left(\xi_{j+1}^{(\alpha)} - \xi_j^{(\alpha)} - A(\xi_j^{(\alpha)}, t_j)\delta t\right)^2}{4D^*(\xi_j^{(\alpha)})\delta t} \end{aligned}$$

also depends on $\boldsymbol{\theta}$ also through f^* and g^* $\Rightarrow$ self-consistent calculation

Dynamic Force Spectroscopy

Reconstruction Procedure

1. If unknown, estimate the background diffusivity D_0 and spring constant K by maximizing probability of observed large distance trajectory data

2. For each choice of regularization parameters $\beta_{f,g}, \gamma_{f,g}$:

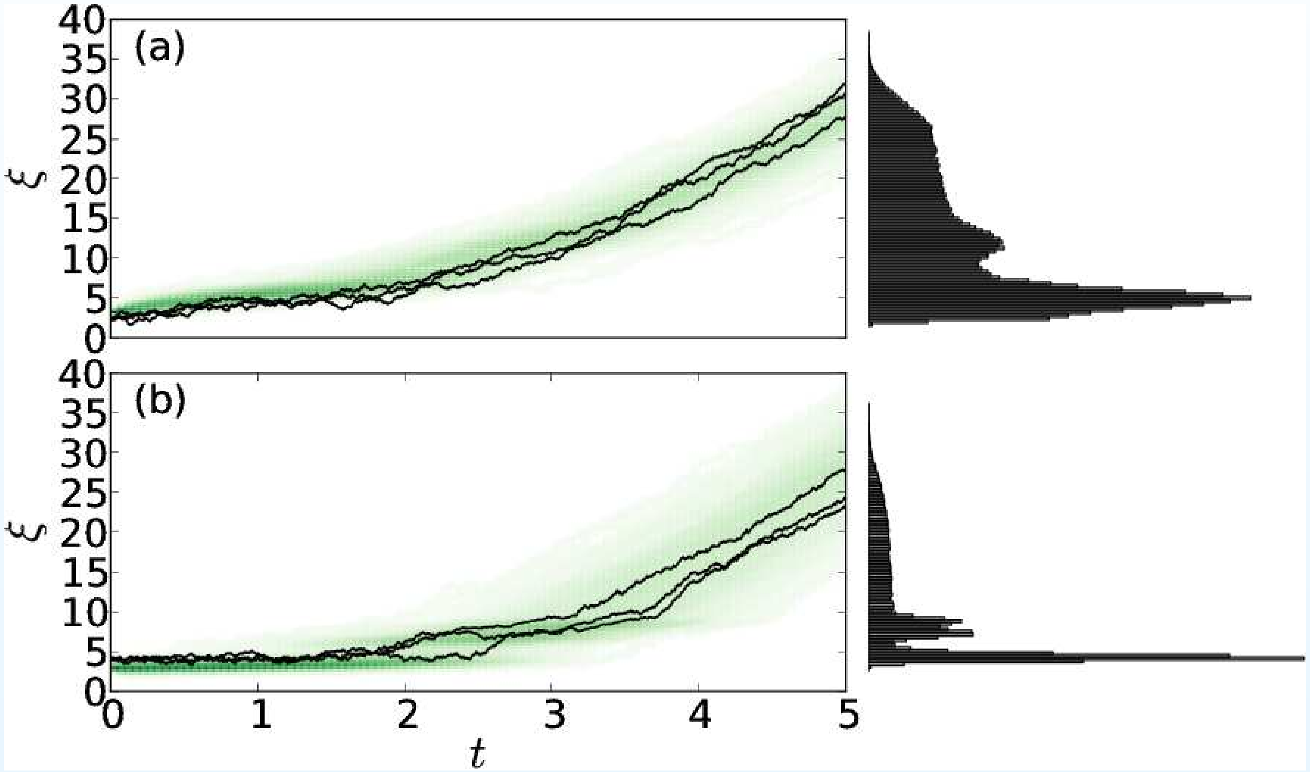
   (a) Solve for the maximum *a posteriori* solution $f^\star, g^\star$

   (b) Compute the semiclassical variance matrix $\mathbf{\Sigma}$

3. Choose regularization parameters that maximize $\ln \pi(\mathbf{X}|\boldsymbol{\theta})$

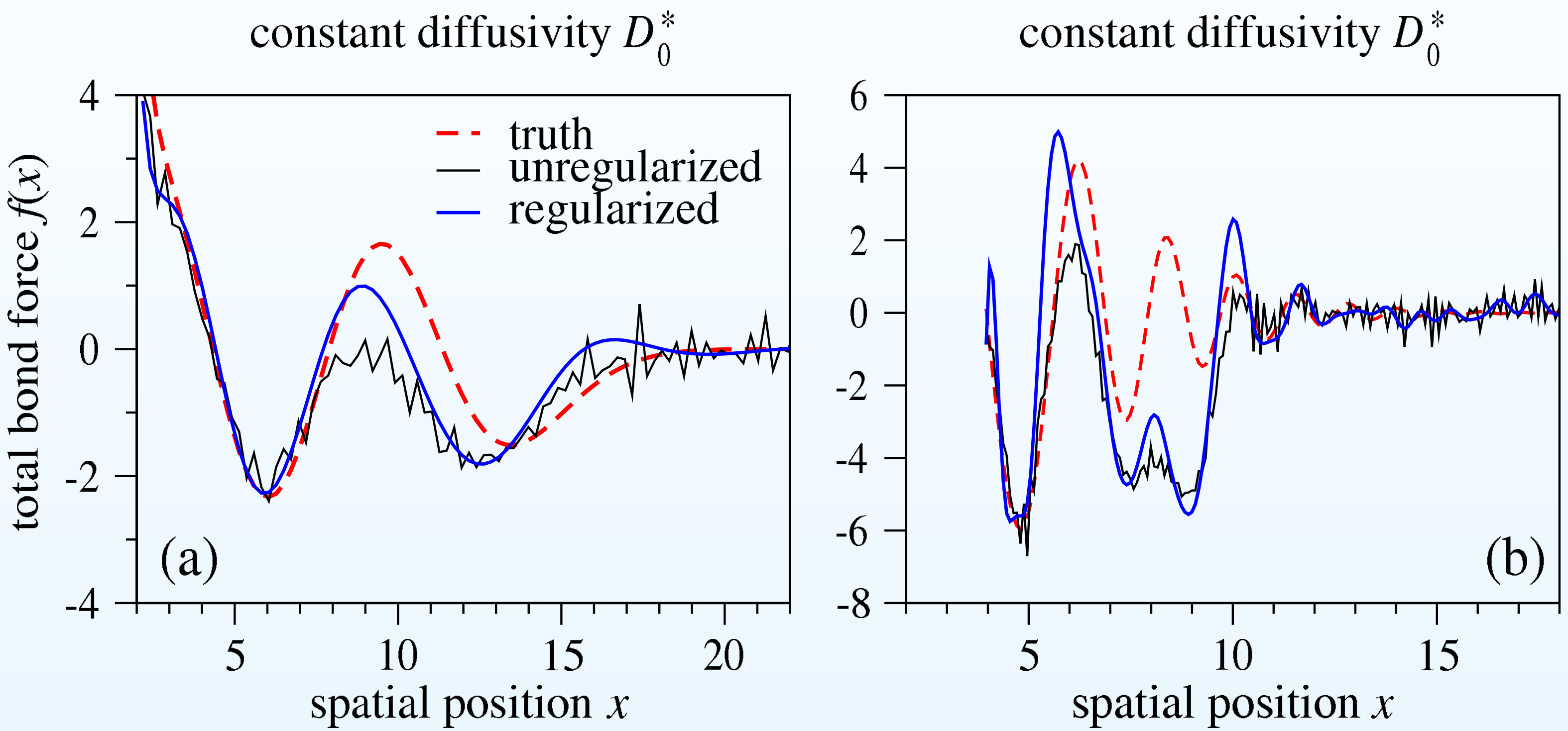
4. repeatedly iterate to find updated $f^\star, g^\star$

Dynamic Force Spectroscopy



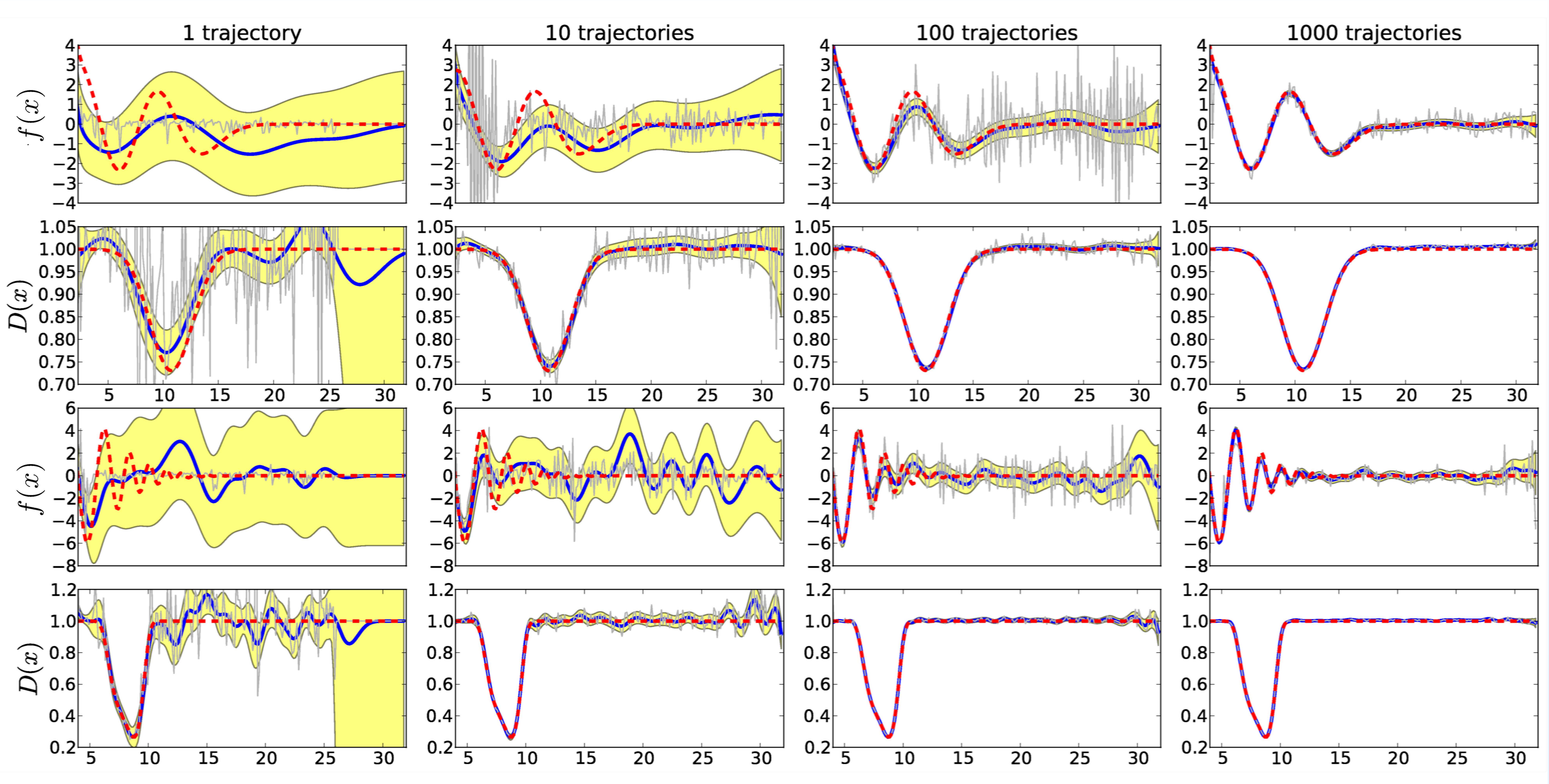
simulated trajectories and event density across time

Dynamic Force Spectroscopy



mean-field potentials using wrong (constant) diffusivity D_0^*

Dynamic Force Spectroscopy

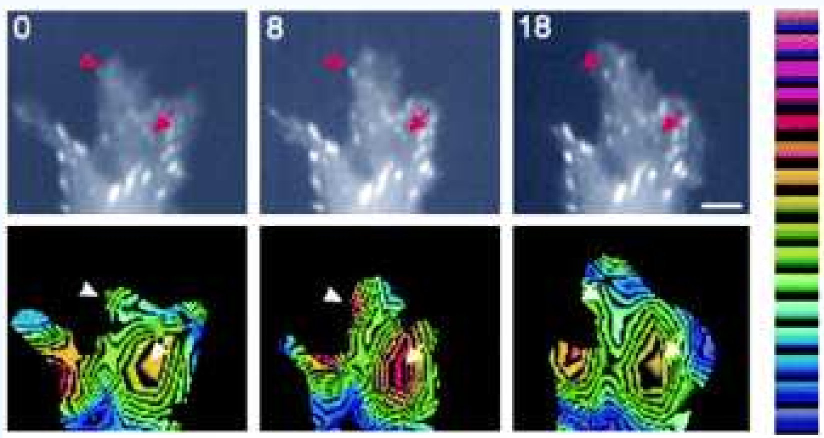


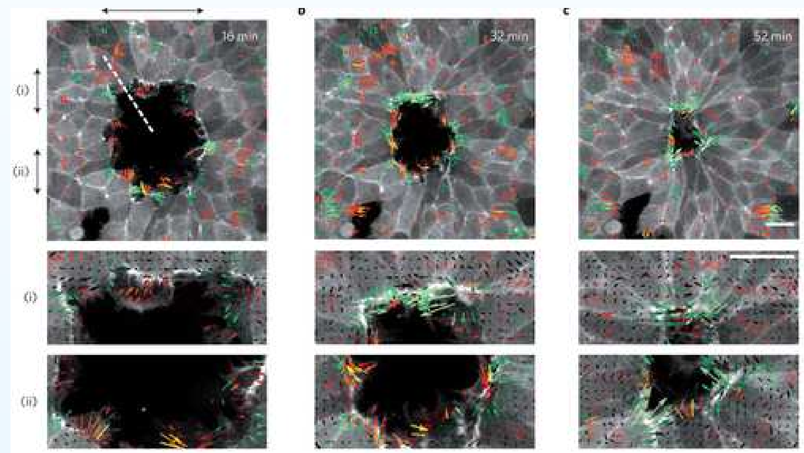
simultaneous reconstruction of $f(x)$ and $g(x)$ works well

yellow: 95% confidence bands

Cell motion through focal adhesions

cells bind to and move along substrates via “focal adhesions” (localized sources of surface stress)





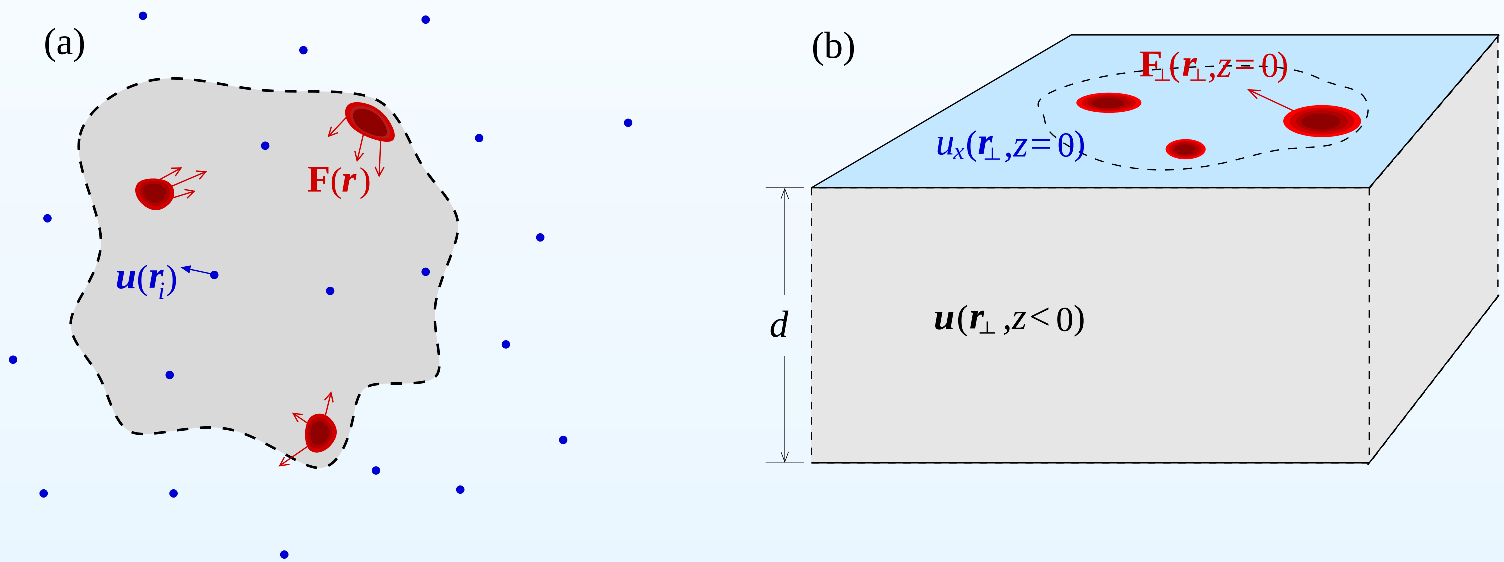
single cell stress

surface stresses in cell sheets

stresses often measured from deformations on elastic substrate

Inferring adhesion stresses

inverse problem: infer surface stress profiles from displacements of fiduciary markers (“surface stress recovery”)



model the (well-characterized) elastic substrate

Green's function

Green's function for elastic half-space $(d \to \infty)$ problem:

$$G_{ss} = \frac{1+\nu}{2\pi E}\left[\frac{2(1-\nu)R_\perp - z}{R_\perp(R_\perp - z)} + \frac{[2R_\perp(\nu R_\perp - z) + z^2]s^2}{R_\perp^3(R_\perp - z)^2}\right],$$

$$G_{zz} = \frac{1+\nu}{2\pi E}\left(\frac{2(1-\nu)}{R_\perp} + \frac{z^2}{R_\perp^3}\right),$$

where $s = x, y$ are distances from point force and $R_\perp \equiv \sqrt{x^2 + y^2}$.

assume substrate with Young's modulus E and Poisson ratio ν

Locating focal adhesions

- restrict to surface stresses $\sigma_{x,y}$ acting on plane normal to $\hat{z}$ axis.
- define in-plane stress distribution as $\boldsymbol{\sigma}(\mathbf{r}_\perp) = \sigma_x \hat{x} + \sigma_y \hat{y} + 0\hat{z}$.
- resulting displacement field

$$u_j(\mathbf{r}_\perp, z) = \int \mathrm{d}\mathbf{r}'_\perp \mathrm{d}z' G_{js}(\mathbf{r}_\perp - \mathbf{r}'_\perp, z)\sigma_{sz}(\mathbf{r}'_\perp),$$

where $s = (x, y)$ and $j = (x, y, z)$

- tangential stresses can lead to normal displacement

Objective function (log likelihood)

$$\Phi_{\mathrm{data}}[\boldsymbol{\sigma}] = \sum_{i}^{N} |\mathbf{u}_{\mathrm{data}}(\mathbf{r}_i) - \mathbf{u}_{\mathrm{model}}(\mathbf{r}_i)|^2.$$

since $\mathbf{u}_{\mathrm{data}}(\mathbf{r}_i)$ is given and $\mathbf{u}_{\mathrm{model}}(\mathbf{r}_i) = \int \mathrm{d}\mathbf{r}'_\perp \mathbf{G}(\mathbf{r}_\perp - \mathbf{r}'_\perp, z)\boldsymbol{\sigma}(\mathbf{r}'_\perp)$,
$\Phi_{\mathrm{data}}[\boldsymbol{\sigma}]$ is a functional over dimensionless surface-stress $\boldsymbol{\sigma}(\mathbf{r}_\perp)$

regularization terms with rotational invariance in $M_{jk}(\mathbf{r}_\perp) = \partial_j \sigma_k(\mathbf{r}_\perp)$:
Trace($\mathbf{M}$) = $\nabla_\perp \cdot \boldsymbol{\sigma}(\mathbf{r}_\perp)$ and Det($\mathbf{M}$)

adding L_p-norm regularization terms,

$$\Phi[\boldsymbol{\sigma}] = \Phi_{\mathrm{data}}[\boldsymbol{\sigma}] + \frac{\gamma_1}{2}\int_\Omega |\nabla_\perp \cdot \boldsymbol{\sigma}(\mathbf{r}_\perp)|^{p_1} \mathrm{d}\mathbf{r}_\perp + \frac{\gamma_2}{2}\int_\Omega |\mathrm{Det}(\mathbf{M}[\boldsymbol{\sigma}])|^{p_2} \mathrm{d}\mathbf{r}_\perp$$

Force- and torque-free constraints

"overdamped" limit: zero net force and net torque

$$\mathbf{F}_\perp = \int_\Omega \boldsymbol{\sigma}(\mathbf{r}_\perp)\mathrm{d}\mathbf{r}_\perp = 0, \quad \mathbf{T} = \int_\Omega \mathbf{r}_\perp \times \boldsymbol{\sigma}(\mathbf{r}_\perp)\mathrm{d}\mathbf{r}_\perp = 0,$$

to "enforce" these constraints, add $|\mathbf{F}_\perp|^2$ and $|\mathbf{T}|^2$

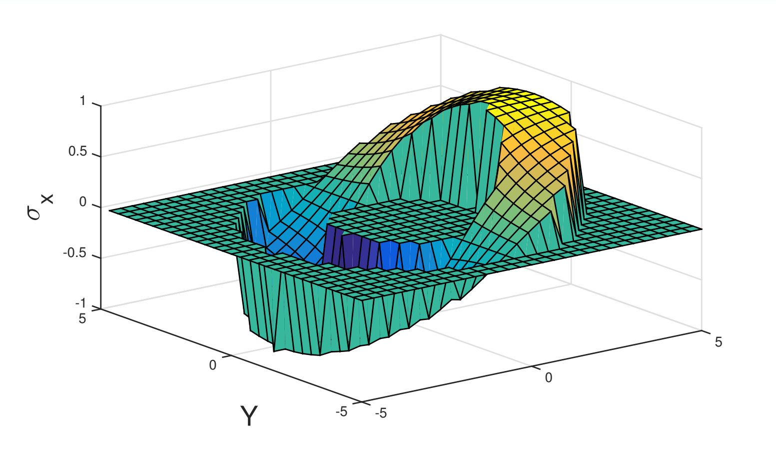
$$\Phi[\boldsymbol{\sigma};\theta] = \Phi_{\mathrm{data}}[\boldsymbol{\sigma}] + \frac{\gamma_1}{2}\int_\Omega |\nabla_\perp \cdot \boldsymbol{\sigma}(\mathbf{r}_\perp)|\mathrm{d}\mathbf{r}_\perp + \frac{\gamma_2}{2}\int_\Omega |\mathrm{Det}(\mathbf{M}[\boldsymbol{\sigma}])|\mathrm{d}\mathbf{r}_\perp \\ + \lambda_{\mathrm{F}}|\mathbf{F}_\perp|^2 + \lambda_{\mathrm{T}}|\mathbf{T}|^2,$$

implicit constraint: $\boldsymbol{\sigma}(\mathbf{x}) = 0$ for $\mathbf{x} \in \mathbb{R}^2 \setminus \Omega$

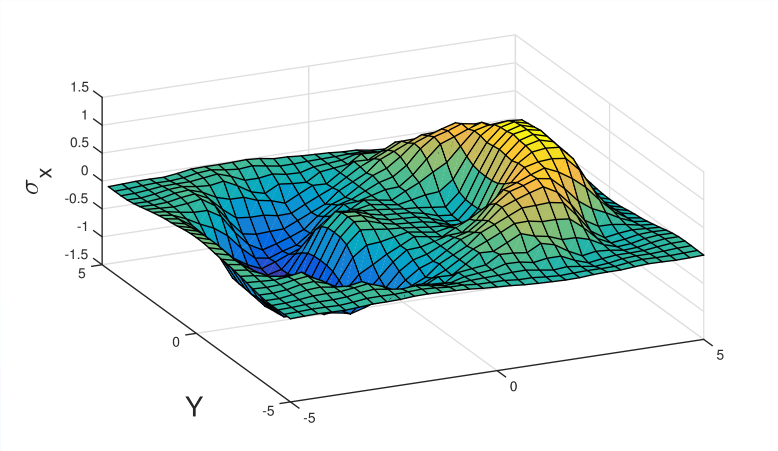
for compactly supported focal adhesions, try $p_1 = p_2 = 1$?

Preliminary L_2 (Tr^2) reconstruction

simple annulus, *without* Ω constraint, $\sim 15\%$ data points



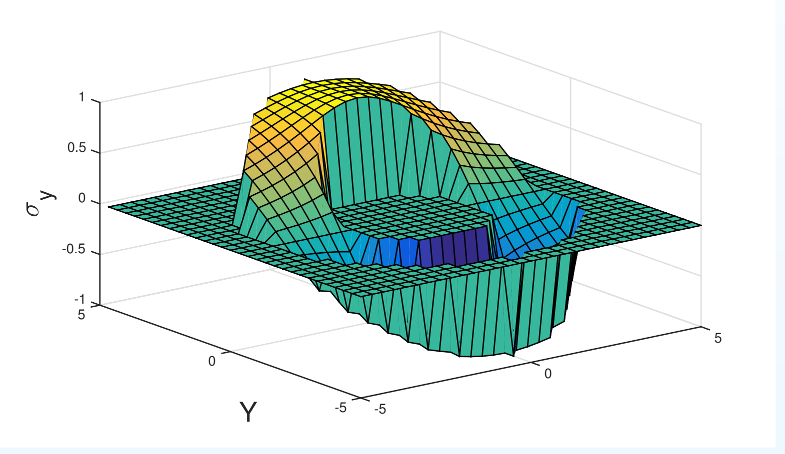
$\sigma_x(\mathbf{r}_\perp)$ input



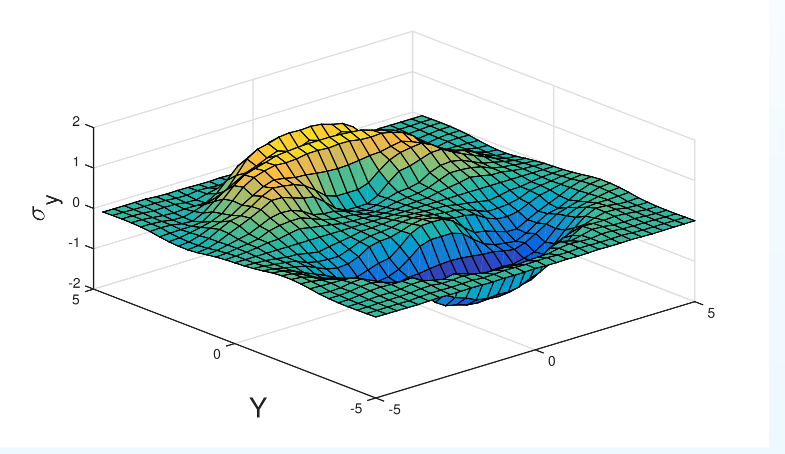
$\sigma_x(\mathbf{r}_\perp)$ reconstructed

Preliminary L_2 (Tr^2) reconstruction

simple annulus, *without* Ω constraint, $\sim 15\%$ data points



$\sigma_y(\mathbf{r}_\perp)$ input



$\sigma_y(\mathbf{r}_\perp)$ reconstructed

Optimization

apply a split-Bregman method by defining

$$s(\mathbf{r}_\perp) \equiv \nabla_\perp \cdot \boldsymbol{\sigma}, \quad m(\mathbf{r}_\perp) \equiv \mathrm{Det}[\mathbf{M}(\mathbf{r}_\perp)],$$

and minimize in stages the split objective function

$$\begin{aligned} H[\boldsymbol{\sigma}|\mathbf{u}_{\text{data}}(\mathbf{r}_i),\theta] =& \Phi_{\mathrm{data}}[\boldsymbol{\sigma}] + \frac{\gamma_1}{2}\int_\Omega |\varphi_1(\mathbf{r}_\perp)|\mathrm{d}\mathbf{r}_\perp + \frac{\gamma_2}{2}\int_\Omega |\varphi_2(\mathbf{r}_\perp)|\mathrm{d}\mathbf{r}_\perp \\ &+ \lambda_{\mathrm{s}}\int_\Omega |\varphi_1(\mathbf{r}_\perp) - s(\mathbf{r}_\perp)|^2\mathrm{d}\mathbf{r}_\perp + \lambda_{\mathrm{m}}\int_\Omega |\varphi_2(\mathbf{r}_\perp) - m(\mathbf{r}_\perp))|^2\mathrm{d}\mathbf{r}_\perp \\ &+ \lambda_{\mathrm{F}}|\mathbf{F}_\perp|^2 + \lambda_{\mathrm{T}}|\mathbf{T}|^2. \end{aligned}$$

$\varphi_1(\mathbf{r}_\perp)$ and $\varphi_2(\mathbf{r}_\perp)$ "replace" $s(\mathbf{r}_\perp)$ and $m(\mathbf{r}_\perp)$, while $\lambda_{\mathrm{s}}\int_\Omega |\varphi_1(\mathbf{r}_\perp) - s(\mathbf{r}_\perp)|^2\mathrm{d}\mathbf{r}_\perp$ and $\lambda_{\mathrm{m}}\int_\Omega |\varphi_2(\mathbf{r}_\perp) - m(\mathbf{r}_\perp)|^2\mathrm{d}\mathbf{r}_\perp$ enforce $\varphi_1(\mathbf{r}_\perp) = s(\mathbf{r}_\perp)$ and $\varphi_2(\mathbf{r}_\perp) = m(\mathbf{r}_\perp)$

Locating focal adhesions

$$\begin{aligned}\Phi[\boldsymbol{\sigma}, s; \theta] = \quad & \Phi_{\mathrm{data}}[\boldsymbol{\sigma}] + \frac{\gamma_1}{2}\int_\Omega |s(\mathbf{r}_\perp)|\mathrm{d}\mathbf{r}_\perp + \lambda_{\mathrm{s}}\int_\Omega |s - \nabla_\perp\cdot\boldsymbol{\sigma} - b^{(k)}|^2\mathrm{d}\mathbf{r}_\perp \\ & + \lambda_{\mathrm{F}}|\mathbf{F}_\perp[\boldsymbol{\sigma}]|^2 + \lambda_{\mathrm{T}}|\mathbf{T}[\boldsymbol{\sigma}]|^2,\end{aligned}$$

where the k^{th} iterate of the increment $b^{(k)}(\mathbf{r}_\perp)$ is found through

$$b^{(k+1)} = b^{(k)} + \nabla_\perp\cdot\boldsymbol{\sigma}^{(k+1)} - s^{(k+1)},$$

and the determination of $\boldsymbol{\sigma}^{(k+1)}$ and $s^{(k+1)}$ are found through the two-step iteration

$$\boldsymbol{\sigma}^{(k+1)} = \arg\min_{\boldsymbol{\sigma}}\left\{\Phi_{\mathrm{data}}[\boldsymbol{\sigma}] + \lambda_{\mathrm{s}}\int_\Omega |s^{(k)} - \nabla_\perp\cdot\boldsymbol{\sigma} - b^{(k)}|^2\mathrm{d}\mathbf{r}_\perp + \lambda_{\mathrm{F}}|\mathbf{F}_\perp[\boldsymbol{\sigma}]|^2 + \lambda_{\mathrm{T}}|\mathbf{T}[\boldsymbol{\sigma}]|^2\right\},$$

$$s^{(k+1)} = \arg\min_{s}\left\{\frac{\gamma_1}{2}\int_\Omega |s(\mathbf{r}_\perp)|\mathrm{d}\mathbf{r}_\perp + \lambda_{\mathrm{s}}\int_\Omega |s - \nabla_\perp\cdot\boldsymbol{\sigma}^{(k+1)} - b^{(k)}|^2\mathrm{d}\mathbf{r}_\perp\right\}.$$

The second optimization step can be implemented using the shrink operator