

# Molecular Seismology: An Inverse Problem in Nanobiology

Peter Hinow<sup>1</sup>, Erik M. Boczko<sup>2</sup>

<sup>1</sup>Department of Mathematics

<sup>2</sup>Department of Biomedical Informatics

Vanderbilt University

Nashville, TN 37240

USA

[peter.hinow@vanderbilt.edu](mailto:peter.hinow@vanderbilt.edu)

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# Overview of the talk

- ▶ Introduction to the biological background
- ▶ Formulation of the inverse problem
- ▶ Numerical simulation results
- ▶ Outlook



# Dynamics of fiber–ligand interaction

It is of great interest to understand the spatio–temporal dynamics of interactions between a biopolymer fiber (such as dsDNA) and a ligand.

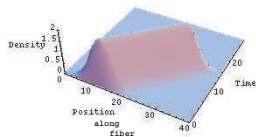
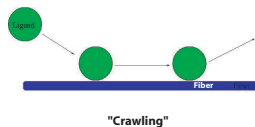
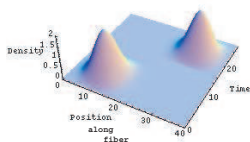
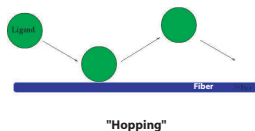
For instance, one would like to investigate

- ▶ binding of transcription factors to their target sites,
- ▶ competition between two or more transcription factors at a promoter site.



# Example: transcription factors bind to DNA

How do transcription factors find their target binding site in the genome?

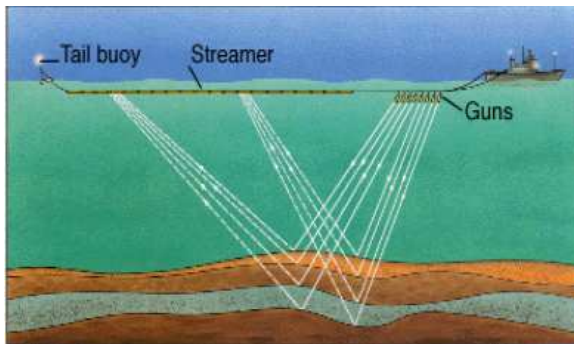


Consider the fiber as an elastic string with linear mass density profile  $\rho(x, t)$ .



# The use of waves for density determination

The problem of mass density or sound velocity profile determination with the help of waves has a long history.



<http://www.trip.caam.rice.edu>

# Statement of the inverse problem

Let  $x \in [0, \ell]$  denote the position along the centerline of the fiber and  $u(x, t)$  the transverse displacement of the centerline.

We consider the non-homogeneous wave equation with damping and external force

$$\begin{aligned}\varrho(x)u_{tt}(x, t) + \nu u_t(x, t) - u_{xx}(x, t) &= F(x, t), \\ u(x, 0) = u_t(x, 0) &= 0\end{aligned}$$

with boundary conditions of Dirichlet or Neumann type.



# Example of a reflection inverse problem

Given a certain fixed excitation profile (Neumann data)

$$u_x(0, t) = \varphi(t),$$

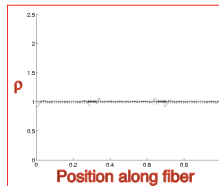
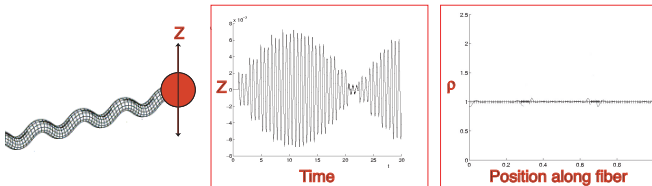
we measure the corresponding Dirichlet response

$$\psi(t) = u(0, t).$$

This problem is called a *reflection* problem, since excitation source and measurement are taken at the same position. Is it possible to obtain the density profile  $\rho(x)$  from the map  $\rho \mapsto \psi$ ?

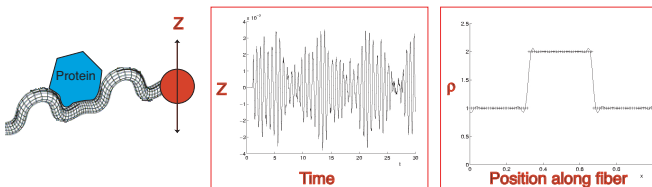


# Molecular seismology – General Principle



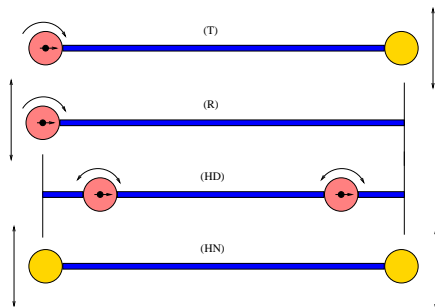
1. Measurement

2. Density Reconstruction





# Potential experimental setups



- ▶ Neumann-to-Dirichlet transmission problem
- ▶ Neumann-to-Dirichlet reflection problem
- ▶ problem with homogeneous Dirichlet conditions, Neumann data are measured
- ▶ problem with homogeneous Neumann conditions, Dirichlet data are measured



# Well-posedness results

The *travel time transformation*

$$z(x) = \int_0^x \rho^{\frac{1}{2}}(\xi) d\xi$$

gives the wave equation in impedance form

$$\eta(z)u_{tt}(z, t) - (\eta(z)u_z(z, t))_z = 0.$$

with the *acoustic impedance*

$$\eta(z) = \sqrt{\rho(z)}.$$

For this equation, Symes (1983) and Rakesh and Sacks (1996) have proved the well-posedness of the inverse problem (reflection and transmission cases).



## Theorem

(Symes, 1983) Let  $u_z(0, t) = \delta(t)$ . Then the Dirichlet response  $\psi(t) = u(0, t)$  on  $[0, 2T]$  determines uniquely the impedance  $\eta(z)$  on  $[0, T]$ , provided  $\eta \in H^1[0, T]$ . Moreover, a local Lipschitz estimate

$$\|\eta_1 - \eta_2\|_{H^1[0, T]} \leq C \|\psi_1(0, \cdot) - \psi_2(0, \cdot)\|_{H^1[0, 2T]}$$

holds.



# A practical inversion algorithm 1

An algorithm to solve the inverse problem in the standard form has been proposed by Tadi (1997). The density  $\varrho$  is allowed to be time dependent. Given a measurement  $\psi$  on  $[0, T]$  one defines a least-square type cost functional

$$J(u, \varrho) = \frac{1}{2} \int_0^T (\psi(t) - u(0, t))^2 dt + \frac{\alpha}{2} \int_0^T \int_0^\ell \varrho_t^2(x, t) dx dt.$$

that is to be minimized subject to the condition

$$\varrho(x, t) u_{tt}(x, t) + \nu u_t(x, t) - u_{xx}(x, t) - F(x, t) = 0.$$



## A practical inversion algorithm 2

The Euler–Lagrange equations that result from the cost functional give rise to an iterative algorithm

$$\varrho^{n+1} = \Phi(\varrho^n),$$

starting from an initial guess  $\varrho^0$ .

Notice that the algorithm returns the density  $\varrho$  as a function of depth  $x$  (other methods exist for the reconstruction of impedance as a function of travel time).



# The frictional heat bath 1

We imagine a fiber immersed in an aqueous solution. Therefore, damping will occur and a random external force is present, of which we assume

$$\begin{aligned}E[F(x, t)] &= 0, \\E[F(x, t)F(y, s)] &= \sigma^2 \delta(t - s) \delta(x - y)\end{aligned}$$

(Gaussian white noise in space and time).



# The frictional heat bath 2

The iterative algorithm allows for an external force. As the particular realization of the random force  $F$  that gave rise to the observed measurement is unknown, we propose two strategies for solving the inverse problem in presence of noise.



# Average over realizations (AOR)

- ▶ With a random realization of the force  $F_i$  perform a reconstruction to obtain the density  $\varrho_i$ ,  $i = 1, \dots, m$ .
- ▶ Take the pointwise average

$$\bar{\varrho} = \frac{1}{m} \sum_{i=1}^m \varrho_i.$$





# Average over signals (AOS)

- ▶ Based on the assumption that the average of the random force is zero.
- ▶ Several recorded signals are averaged

$$\bar{\psi} = \frac{1}{m} \sum_{i=1}^m \psi_i.$$

- ▶ The reconstruction algorithm is applied with mean force equal to zero.



# Neumann-to-Dirichlet setup

We attempt to reconstruct the density profile

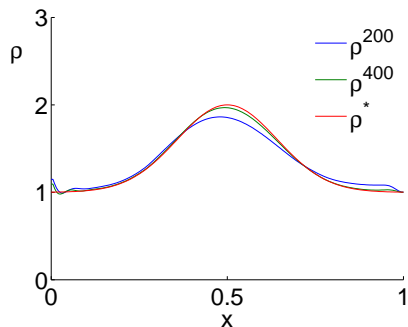
$$\varrho(x) = 1 + \exp\left(-\frac{(x - 1/2)^2}{(1/5)^2}\right), \quad x \in [0, 1].$$

The generic forcing term  $u_x(0, t) = \phi(t)$  is a smooth approximation of the  $\delta$ -pulse. The Neumann-to-Dirichlet setup is

$$u_x(0, t) = \varphi(t), \quad u(1, t) = 0, \quad \psi(t) = u(0, t).$$



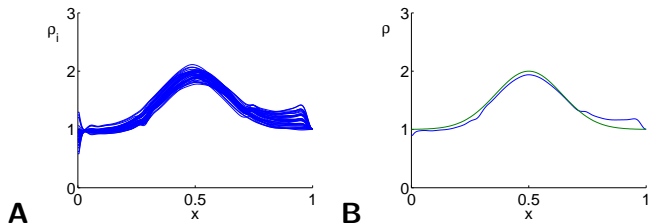
# Results



Rapid convergence of the algorithm (with damping  $\nu = 1$ , but without random forcing).



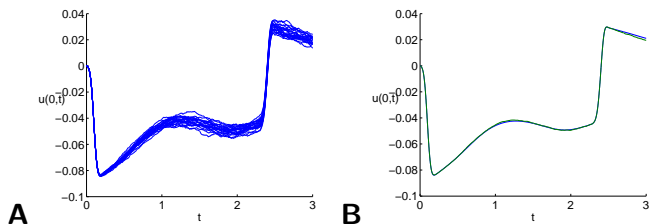
# Results of AOR procedure



**A** 40 reconstructions from a randomly forced damped string each using a different realization of the random force. **B** The average of these reconstructions.



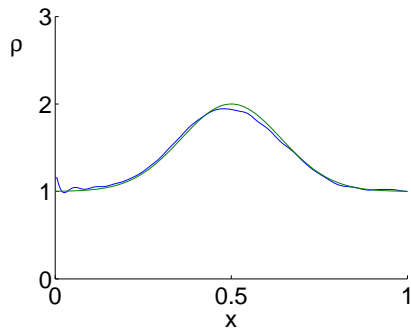
# Results of AOS procedure



**A** 20 signals from forced strings with different realizations of the random force. **B** The averaged signal and signal corresponding to an unperturbed string.



# Results of AOS procedure



The averaged signal is used in the reconstruction algorithm.



# Summary and Outlook

- ▶ We have investigated the density reconstruction problem for elastic fibers in a viscous heath bath.
- ▶ Different boundary setups (reflection and transmission problems, homogeneous boundary conditions) allow robust density reconstructions.
- ▶ Preliminary experiments with DNA fibers suspended in solutions are under way in the laboratory of Dr. Charles Brau, Department of Physics and Astronomy, Vanderbilt University.





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Thank you for your attention.

