Molecular Seismology: An Inverse Problem in Nanobiology

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Overview of the talk

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

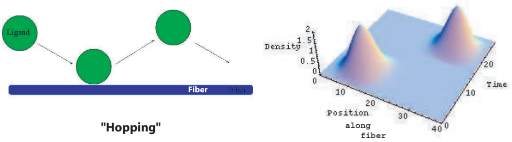
Dynamics of fiber–ligand interaction

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

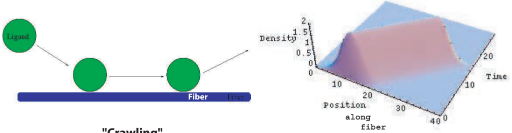
For instance, one would like to investigate

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

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



"Hopping"

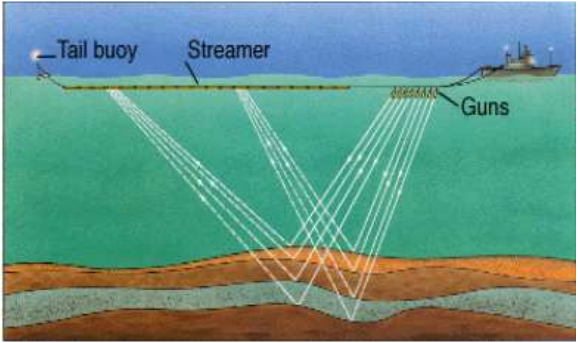


"Crawling"

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

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

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

with boundary conditions of Dirichlet or Neumann type.

Example of a reflection inverse problem

Given a certain fixed excitation profile (Neumann data)

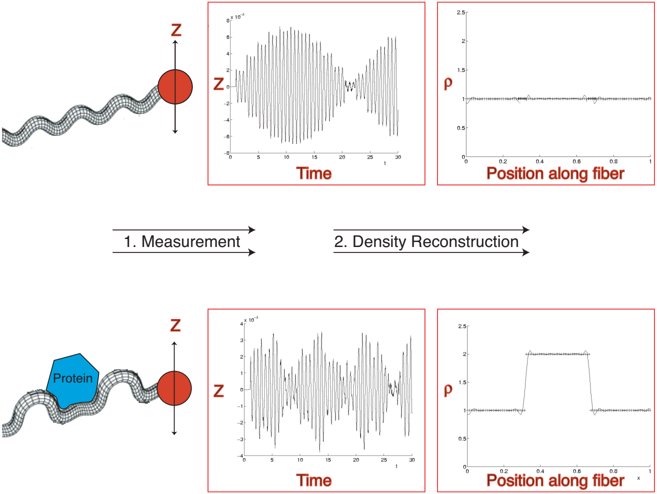
$$u_x(0, t) = \varphi(t),$$

we measure the corresponding Dirichlet response

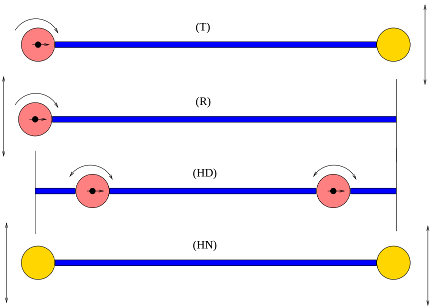
$$\psi(t) = u(0, t).$$

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 $\varrho(x)$ from the map $\varrho \mapsto \psi$?

Molecular seismology – General Principle



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

The *travel time transformation*

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

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*

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

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

Well–posedness of the Neumann–to–Dirichlet problem

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.

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

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

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 ϱ^0.

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

The frictive 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

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

(Gaussian white noise in space and time).

The frictive 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 ϱ_i, $i = 1, \ldots, m$.
- 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.

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Neumann–to–Dirichlet setup

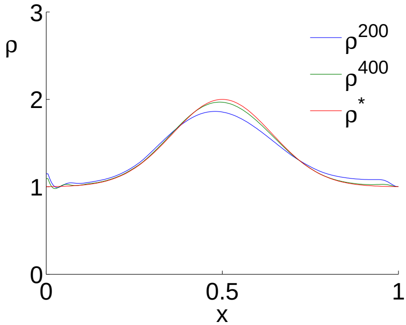
We attempt to reconstruct the density profile

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

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

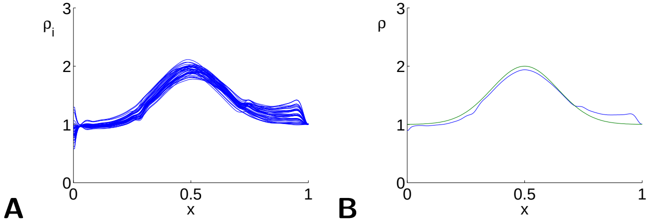
$$u_x(0,t) = \varphi(t), \quad u(1,t) = 0, \quad \psi(t) = u(0,t).$$

Results



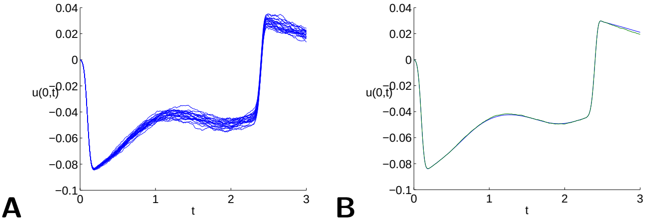
Rapid convergence of the algorithm (with damping $\nu = 1$, but without random forcing).

Results of AOR procedure



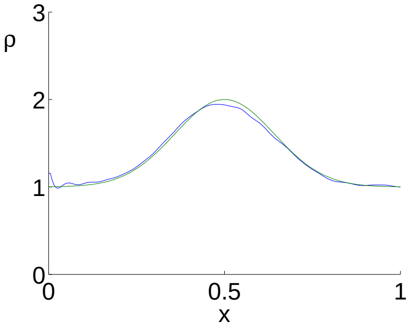
A 40 reconstructions from a randomly forced damped string each using a different realization of the random force. **B** The average of these reconstructions.

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.

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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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References

P. Hinow and E. M. Boczko. Molecular seismology: An inverse problem in nanobiology. J. Theor. Biol. **246**:145–158

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Thank you for your attention.