Cell Mechanics Modeling and Identification by Atomic Force Microscopy

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Introduction

— Biological cells are complex living beings – understanding them is essential in fields such as biology and medicine
— Mechanical properties of cells have been linked to cancer and other diseases
— Some existing results for identification of elasticity and viscosity
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  ● ..mostly based on static contact theory
  ● with complicated relationships between measured signals and desired properties
Introduction

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A new approach

Use identification techniques from control literature.
  ⇒ Flexible models which are dynamic in nature.
  ⇒ Greatly expand on existing results.
Introduction – Atomic Force Microscopy (AFM)

Sample

Cantilever

z-scanner

xy-scanner

Sample

Laser

Photo detector

Can use AFM as a force sensor.
Introduction – Atomic Force Microscopy (AFM)

— Can use AFM as a *force sensor*.
Outline

Introduction

System Modeling

Parameter Identification

Simulation Results

Conclusions and Future Work
System Overview

Need a model for the..
  — Cell sample
  — AFM cantilever dynamics
  — AFM tip geometry

Goal: Identification of cell model parameters

Once the system dynamics are in place, design a parameter identification scheme for the cell model parameters.
System Overview

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Cell Sample Modeling

— Lumped spring-damper elements along the lateral $xy$-axes.
Cantilever Dynamics and Tip Geometry
Cantilever Dynamics and Tip Geometry

Tip geometry, spherical model:

\[ z_i = Z - \sqrt{R^2 - (X - x_i)^2 - (Y - y_i)^2} \]  (1)
Cantilever Dynamics and Tip Geometry

Tip geometry, spherical model:
\[ z_i = Z - \sqrt{R^2 - (X - x_i)^2 - (Y - y_i)^2} \] (1)

Cantilever dynamics, second-order oscillator:
\[ M \ddot{Z} = KD + C \dot{D} + F_{\text{sample}} \] (2)
Sample Force

Spring and damping forces:

\[ F_{ki} = k_i \ddot{z}_i, \quad F_{ci} = c_i \dot{z}_i \]  \hspace{1cm} (3)

where \( \ddot{z}_i \triangleq z_i - z_i^0 \).
Sample Force

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\[ F_{\text{sample}} = \sum_{i \in \mathcal{W}} F_{ki} + F_{ci}. \]  \hspace{1cm} (4)
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$$F_{\text{sample}} = \sum_{i \in \mathcal{W}} F_{ki} + F_{ci}.$$  \hspace{1cm} (4)

where the active set $\mathcal{W} = \mathcal{W}(X, Y, Z)$ is given by

$$\mathcal{W} = \left\{ i : \ddot{z}_i < 0 \land (X - x_i)^2 + (Y - y_i)^2 < R^2 \right\}.$$  \hspace{1cm} (5)
Sample Force

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The parameters \( k_i, c_i, z_i^0 \) are to be estimated \( \forall i \).
System Overview

Cantilever-sample dynamics

Tip geometry

Sample force $k, c$

Parameter estimator $\hat{k}, \hat{c}, \hat{z}^0$

$F_{\text{sample}}$

Cantilever dynamics

$X, Y$

$Z, \dot{Z}, D$

$U$

$D, U$

Cell Mechanics Modeling and Identification
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Parameter Identification

Rewrite system to linear-in-the-parameters form:

\[(Cs + K)U - \left( Ms^2 + Cs + K \right) D = [c, k] \begin{bmatrix} s\tilde{Z} \\ \tilde{Z} \end{bmatrix} \tag{6} \]

\[w' = \theta^T \phi' \tag{7} \]
Parameter Identification

Rewrite system to linear-in-the-parameters form:

\[(Cs + K)U - \left( Ms^2 + Cs + K \right) D = [c, k] \begin{bmatrix} s\bar{Z} \\ \bar{Z} \end{bmatrix} \]  \hspace{1cm} (6)

\[w' = \theta^T \phi' \]  \hspace{1cm} (7)

Filter each side to make the system proper, such that

\[\frac{w'}{\Lambda(s)} = [c, k] \begin{bmatrix} s\bar{Z} \\ \bar{Z} \end{bmatrix} \]  \hspace{1cm} \Lambda(s) \hspace{1cm} (8)

\[w = \theta^T \phi \]  \hspace{1cm} (9)
Parameter Estimator

Least squares method with forgetting factor (Ioannou and Sun, 1996):

\[
\hat{w} = \hat{\theta}^T \phi \tag{10}
\]

\[
\varepsilon = (w - \hat{w})/m^2 \tag{11}
\]

\[
m^2 = 1 + \alpha \phi^T \phi \tag{12}
\]

\[
\dot{\theta} = P \varepsilon \phi \tag{13}
\]

\[
\dot{P} = \begin{cases} 
\beta P - P \frac{\phi \phi^T}{m^2} P, & \text{if } \|P\| \leq R_0 \\
0, & \text{otherwise}
\end{cases} \tag{14}
\]

\[
P(0) = P_0 \tag{15}
\]
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0, & \text{otherwise} \end{cases} \]

\[ P(0) = P_0 \]

Guarantees exponential convergence of \( \hat{\theta} \to \theta \) if the signal vector \( \phi \) is persistently exciting (PE).
Persistency of Excitation (PE)

Theorem 1

Apply the cantilever input signal

\[ U = u_0 + a \sin (\omega_0 t) \]  \hspace{1cm} (16)

for any positive constants \( a, \omega_0 \), and let the constant \( u_0 \) be small enough such that the cantilever tip is in contact with the surface, i.e. \( \ddot{z} < 0 \forall t \). Then \( \phi \) is persistently exciting (PE) and \( \hat{\theta} \rightarrow \theta \) exponentially fast.
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Simulation Results – Topography

(a) Simulated topography $z^0$

(b) Identified topography $\tilde{z}^0$

Topography parameters mapped to the spatial domain.
Simulation Results – Damping constants

Damping parameters mapped to the spatial domain, (a) simulated vs. (b) identified.
Simulation Results – Spring constants

Spring constant parameters mapped to the spatial domain, (a) simulated vs. (b) identified.

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Simulation Results – Parameter Convergence

Parameter convergence during tap.

\[
\begin{align*}
N_s &= m^c \\
N &= m^k^c
\end{align*}
\]

\[
U = \frac{1}{10^7}
\]
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— Presented a new, dynamic approach for identifying mechanical properties of soft samples.
— Control law designed to guarantee exponential convergence of parameters.
— Future iterations hold promise for use as part of a medical diagnostic tool.

Future Work

— Can easily extend our model to capture additional phenomena.
— Clear advantage with modeling & identification approach.
— E.g. coupling between elements to describe the cell membrane, or nonlinear springs and dampers.
— By future experiments: investigate how well the data fits our model.
— Iterate on model to capture more of the dynamics in the data (data-driven modeling approach).

Questions?

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References

P A Ioannou and J Sun. *Robust adaptive control*. Prentice Hall, Upper Saddle River, NJ, 1996.

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