Available online at www.sciencedirect.com

ScienceDirect

IFAC Papers Online CONFERENCE PAPER ARCHIVE

IFAC-PapersOnLine 49-21 (2016) 603–610

# Cell Mechanics Modeling and Identification by Atomic Force Microscopy

**Michael R. P. Ragazzon** * **Marialena Vagia** ** **J. Tommy Gravdahl** *

* *Department of Engineering Cybernetics, NTNU, Norwegian University of Science and Technology, Trondheim, Norway (e-mail: {ragazzon, Tommy.Gravdahl}@itk.ntnu.no).*
** *SINTEF ICT, Applied Cybernetics (e-mail: Marialena.Vagia@sintef.no).*

**Abstract:** Cells are complex living organisms often described as the building blocks of life. The mechanical properties of such cells have been shown to be effective for medical diagnosis. Previous research in this area focus primarily on static methods by identifying local variations in cell elasticity. Atomic force microscopy (AFM) has shown to be effective for such measurements. In this paper we extend on this methodology by developing a dynamic viscoelastic model of the cell, constructed to be well suited for parameter identification. A parameter estimator is then designed for identifying the spatially resolved mechanical properties of the cell. The parameter estimates are shown to converge exponentially fast to the real parameters by employing the provided control input. A key property of this online estimation scheme is allowing for mechanical changes in the cell to be detected over time. Furthermore, the approach can be applied to the problem of identifying the mechanical properties of any elastic material that can be scanned in AFM. A simulation study shows the effectiveness of the methodology.



*Keywords:* Mechanical properties; Parameter identification; Biomedical systems; Dynamic models; Positioning systems

## 1. INTRODUCTION

Biological cell samples can interact with the external environment by generating forces originating from their mechanical properties. Such mechanical properties are frequently linked to fundamental processes including cell division, locomotion and invasion, differentiation, mechanotransduction, and apoptosis (Reichl et al., 2005; Kumar and Weaver, 2009). It has also been implicated that a change in the cell elasticity is noticed in the pathogenesis of many progressive diseases including cancer (Parsons et al., 2010) and cardiovascular diseases (Bao and Suresh, 2003), diabetic complications, vascular diseases, kidney diseases, Alzheimer's and malaria. Among the above mentioned diseases, and many more that can be described by the same properties, carcinomas attracts the main interest of the scientific community. A large effort has been devoted to their diagnosis and treatment, and any possible research in new diagnostic methods that could lead to earlier and more accurate diagnosis attracts a huge interest in the scientific community (Lekka et al., 2012b).

In practice, there is no need to highlight the importance of studying the properties of carcinoid cells (Sokolov, 2007). The current cancer diagnosis relies mostly on morphological examination of exfoliated and aspirated cells or surgically removed tissue. Up to now, as far as the standard diagnosis is concerned this classical approach seems to be satisfactory (Lekka et al., 2012a; Ramis-Conde et al., 2008). However, new tools are needed in order to offer the patients an earlier diagnosis which has been shown to be one of the most important factors in the prognostic outcome.

In order for new diagnosis tools to become available, it is important to gain a detailed knowledge of the mechanical properties of live cells that are to be examined. Different techniques have been proposed so far, including methods like micro-pipette manipulation (Discher et al., 2008), magnetic bead twisting (Bausch et al., 1998), and optical tweezers (Guck et al., 2002). With these techniques, local variations in the viscoelastic power law parameters have been observed (Hecht et al., 2015).

Aside of the above mentioned ones, there is another technique gaining more and more focus in the recent years which utilize atomic force microscopy (AFM) (Weisenhorn et al., 1993; Degertekin et al., 2001). AFM is one of the major techniques responsible for the emergence of modern nanotechnology. AFM works by having a tip located at the end of a microcantilever. The cantilever can be controlled in the vertical direction. As the cantilever is lowered and the tip touches the sample, the cantilever will start deflecting. This deflection can be measured. By keeping the deflection constant in a feedback loop controlling the cantilever position, the topography of the sample can be recorded as the sample is moved in the lateral directions.

There are several variations to the control mechanism in AFM, including dynamic modes (Garcia and Perez, 2002) such as amplitude modulated control where the cantilever is oscillated and the amplitude is estimated (Ragazzon


10.1016/j.ifacol.2016.10.667

et al., 2016) and used as the feedback signal. Other methods use a tip-sample force estimate directly as the feedback signal (Jeong et al., 2006; Karvinen et al., 2014), or invert the force to estimate the tip-sample distance itself (Ragazzon et al., 2015).

AFM has a number of features that makes it extremely valuable in biology (Sokolov, 2007). The main beneficial feature is its ability to study biological objects directly in their natural conditions (Benitez and Toca-Herrera, 2014). In addition, it has the major feature of using the AFM probe to indent a cell to study cell mechanics by recording the cantilever deflection while deforming the cell (Guz et al., 2014). Such approaches are often based on Hertz or Sneddon model of contact mechanics to find measurements of elasticity, experiments for which are usually performed statically (Sokolov et al., 2013).

The amplitude and phase-shift in dynamic modes of AFM have been shown to be correlated to the viscoelastic properties of the sample (Radmacher et al., 1993; Cartagena-Rivera et al., 2015). Multiple harmonics can also be utilized for mapping such properties in dynamic mode (Raman et al., 2011). These approaches relate the cantilever indentation into the surface to local elastic and viscous properties. In this paper however, we take a unique approach for extracting similar properties from a sample.

In this paper we propose to model the sample as a dynamic model with unknown parameters. By employing identification techniques from the control literature, we allow these parameters to be estimated directly and thereby making it possible to observe changes over time. There is no need for post-processing of the data or to explicitly find a mapping from the deflection data to the viscoelastic parameters as used in previous approaches. The estimated parameters are guaranteed to converge to the real values exponentially fast provided a suitable control input is chosen.

Additionally, this approach is easily extendable for future work as the sample model can be modified to fit observational data. This allows possibly including phenomena such as creep, hysteresis, plasticity, and nonlinear elastic and damping effects. However, in this paper we restrict ourselves to observing elastic (spring constants), and viscous (damping constants) properties of the sample, as well as topography. This is not a complete description of the mechanics of the cell. However, since these properties have already been shown to be effective in applications such as medical diagnosis, it is proposed as a good starting point.

## 2. CANTILEVER-SAMPLE SYSTEM MODELING

The purpose of the system modeling is to provide a dynamic model description of a cantilever interacting with a general viscoelastic sample material, while allowing for simple identification of the model parameters by use of atomic force microscopy. Additionally, the presented model can easily be extended and modified to suit the characteristics of various materials.

The sample to be measured is modeled by lumped spring-damper elements along the lateral $xy$-axes as illustrated in Figure 1. The elements can be compressed in the vertical $z$-direction. An attractive feature of this model is that it allows for capturing spatial variations in stiffness and damping properties. Moreover, the fidelity of the model can be chosen to fit the task at hand, by selecting an appropriate number of spring-damper elements. The only measurable signal is the cantilever deflection $D$ commonly measured by a photo-detector setup as illustrated in Figure 2. The cantilever base position $U$ can be controlled for movement in the vertical direction. The vertical position of the cantilever tip is given by $Z$ with the relationship

$$Z = U - D. \tag{1}$$

Additionally, the tip can be controlled in the $xy$-direction (Eielsen et al., 2013). The resulting position of the center of the tip is given by $(X, Y, Z)$ in the coordinate system $(x, y, z)$ seen in Figure 1.

The cantilever-sample dynamics can be described by three main components as seen in Figure 3. The cantilever dynamics is subjected to external sample force which generates a deflection along the vertical axis. The tip geometry and position is then used to determine the (possibly compressed) positions of each sample spring-damper element. The compressed elements in turn creates a restoration force acting on the cantilever tip. The details of each of these components will be described in the following.

### 2.1 Cantilever Dynamics

The cantilever dynamics can be approximated by its first resonance mode, resulting in the spring-damper system

$$M\ddot{Z} = KD + C\dot{D} + F_{\text{sample}} \tag{2}$$

$$= K(U - Z) + C(\dot{U} - \dot{Z}) + F_{\text{sample}} \tag{3}$$

where $M$ is the effective mass of the cantilever (Bhushan and Marti, 2010), $K, C$ are the cantilever spring and damping constants respectively, and $F_{\text{sample}}$ is the force from the sample acting on the cantilever tip.

### 2.2 Tip Geometry

In addition to a description of the tip geometry, the position of the cantilever tip can now be used to determine the deflection and motion of each individual spring element in the sample.

In this paper the tip is modeled by a spherical shape with radius $R$. A dull spherical probe is generally advantageous when scanning soft materials such as cells (Sokolov et al., 2013). However, this choice can easily be extended for additional geometrical shapes.

A spherical shape leads to the following relationship between the tip and the $i$th sample element's position $z_i$ and velocity $\dot{z}_i$,

$$z_i = Z - \sqrt{R^2 - (X - x_i)^2 - (Y - y_i)^2} \tag{4}$$

$$\dot{z}_i = \dot{Z} \tag{5}$$

where $(x_i, y_i)$ is the lateral position of the $i$th sample element. It has been used that $\dot{X}, \dot{Y}$ are assumed to be zero while the tip is in contact with the sample.

### 2.3 Sample Force

The $i$th spring-damper element in the sample has a rest-position $z_i^0$ which represents the sample topography at