Model-based probability of detection of pathologies in soft tissue

Juan Melchor, Guillermo Rus, Nicolas Bochud, Laura Peralta, Juan Chiachio, and Manuel Chiachio

Dpt. Structural Mechanics, University of Granada, 18071 Granada, Spain.
{jmelchor,grus,nbochud,lperalta,jchiachio,mchiachio}@ugr.es
http://www.ugr.es/~grus/people.htm

Abstract. This contribution is aimed at presenting a computational method for assessment and prediction of mechanical property changes in soft tissue, in order to diagnose certain pathologies.
This diagnostic technology is based on two components: a custom designed piezoelectric transducer that transmits and receives torsion ultrasound, and a model-based inverse problem that simulates using finite elements the ultrasound propagation through the transducer-tissue system and reconstructs the unknown pathology-related mechanical properties using inverse problem-based search algorithms.
As a contribution, this work proposes a semi-analytical estimator of the probability of detection (POD) in the sense of the probability that the pathology effect on the measurement overcomes the measurement noise, based on the finite element model of the ultrasound propagation through the transducer-tissue system. The estimator of the POD can be used as a optimality criterion to optimize the design of the transducer.
This work aims to (i) evaluate the optimal piezoelectric transducer design of the model-based on Probability of detection. A second goal is (ii) a simulated experiment based on the three dimensional model of wave propagation generated by the proposed piezoelectric transducer design. Finally, (iii) a parametric study is carried out to extract practical parameters for final soft tissue applications.
Acknowledgements: Spanish Ministerio de Economia for project DPI2010-17065, Junta de Andalucia for projects P11-CTS-8089 and GGI3000IDIB, and the European Union for program 'Programa Operativo FEDER de Andalucía 2007-2013'.

1 Introduction

The physical principle to mechanically characterize the tissue is the following. A physical magnitude is propagated along the medium to be analyzed, which distorts the wave until it is measured at an accessible surface (see Fig. 1). The mechanical parameters responsible for the modification of the wave can be inferred from the measured one under certain circumstances by means of the inverse problem theory discussed later. Ultrasound is chosen as the physical magnitude for several reasons. First, it is a mechanical wave, controlled by and therefore

most sensitive to the mechanical parameters than any other indirect measurement. Second, the wave is generated at a low strain regime, which has been observed to be more sensitive to variations due to pathology than high strain (Matsumura et al., 2009).

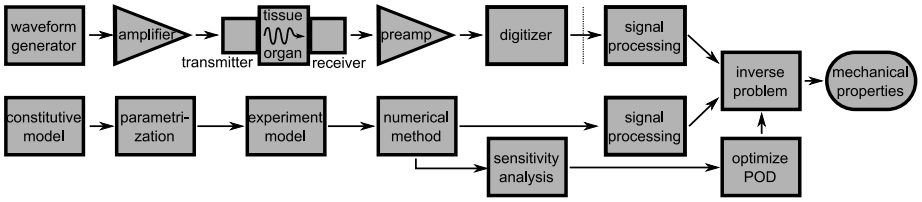

Figure 1. Simplified system for measuring ultrasound wave distortion through tissue and reconstruct mechanical properties.

The application of ultrasonic sensors in the clinical field is mainly covered by compressional waves (Van Kervel and Thijssen, 1983). Recently proposed measurement of ultrasonic attenuation through tissue (McFarlin et al., 2005b,a). These results indicate that a combination of quantitative ultrasonic parameters have the potential for extracting information for characterizing tissue condition (Bader and Bowker, 1983; Ahuja, 1979; Pereira et al., 1991). The combined use of finite element simulation and optimization methods comprise a convenient way to design ultrasonic transducers (Heikkola and Laitinen, 2005; Schröder et al., 2010; Harkness et al., 2011).

One of our first applications will be predicting preterm birth by quantifying shear mechanical properties of the cervix, which is hypothesized to remodel during a the whole gestation in order to prepare for the ripening and dilatation. Very scarce and indirect conclusions about shear mechanical properties analyzed by quantitative ultrasound have been reported specifically for cervical tissue. (Bigelow et al., 2008) recently proposed measurement of ultrasonic attenuation through cervical tissue but concluded that too large variances in their experimental setup did not allow a statistically significant correlation with gestational age. These results indicate that a combination of quantitative ultrasonic parameters have the potential for extracting information for characterizing tissue condition.

In this work, a numerical study of the sensitivity of a custom-designed torsion ultrasonic sensor is provided. A semi-analitical estimate of the probability of detection (POD) is formulated based on a finite element model and an inverse problem framework to reconstruct the relevant properties from experimental measurements.

2 Inverse Procedure

The problem of ultrasonic characterization of mechanical tissue properties is solved by a model-based inverse problem (IP) approach that consists of two steps: (i) to excite the system applying an ultrasonic pulse (displacements), and (ii) to measure the response (displacements). We assume that the dynamic behavior of the tissue in its health and pathologies states is predictable using a well-calibrated model. A finite element method model is used to simulate the sensor-tissue system in the forward procedure that is explained in detail in the last section.

Then, the measured signal is processed to solve the *inverse problem*, i.e., to determine the changes in the tissue from its original state. A genetic algorithm search tool (Rus et al., 2006; Goldberg, 1989) is used to minimize the discrepancy between the experimental readings and the numerically predicted trial response, by means of a cost functional designed to calibrate for coherent uncertainties and noise, and providing maximal robustness and sensitivity.

2.1 Cost functional

The readings from the sensors are denoted by ψ for the theoretical or synthetic case, and ψ^x for the experimental case. A reading ψ^0 in the healthy state of the tissue is defined for calibration and adimensionalization, and the measurement to analyze is defined as,

$$\Phi = \frac{\psi - \psi^0}{\mathrm{RMS}(\psi^0)} \tag{1}$$

where the RMS is the Root Mean Square. A residual γ is defined from the misfit or discrepancy $\Phi^x - \Phi$ between the measurements.

$$\gamma = (\Phi^x - \Phi) \tag{2}$$

The cost functional f or fitness function is defined as the quadratic form,

$$f = \frac{1}{2}|\gamma|^2 = \frac{1}{2}\frac{1}{N_i}\sum_{i=1}^{N_i}\gamma_i^2 \tag{3}$$

2.2 Probability of detection

The POD gives an idea of the probability that a pathology is positively detected, given a specimen, a pathology size and some noise and system uncertainty conditions. The detection and characterization of pathologies is based on the interpretation of the alterations of the measurements due to the presence of the pathology. However, other model uncertainties and system noises also alter these measurements, and are responsible for false positives and negatives. We can estimate the POD by the probability that the alteration of the measurement

caused by the pathology is larger than that caused by the noise. If we label the alteration on the measurement readings caused by the pathology as the SIGNAL component, and the alteration generated by the noise as NOISE, the former definition can be formulated as (Rus et al., 2006),

$$\mathrm{POD} = P\left(\frac{|\mathrm{SIGNAL}|^2}{|\mathrm{NOISE}|^2} > 1\right) \tag{4}$$

Furthermore, three variables are be considered in the problem of maximizing the probability of detection (POD), the level of noise, denoted by σ, the location and extent of the pathologies, denoted by $\mathbf{p}$, and the cost functional that collects the effects of those in a scalar function f, as defined above.

We propose a new criterium of POD associated to multivariable pathologies amount with different references. It is define as follows,

$$\mathrm{RPOD} = \min_{pat_p} \mathrm{POD}(\mathrm{pat_p}) \tag{5}$$

$$\mathrm{POD}(\mathrm{pat_p}) = P\left(\frac{|\mathrm{SIGNAL}(pat_p)|^2}{|\mathrm{NOISE}(pat_p)|^2} > 1\right) \tag{6}$$

where $pat = \{\Delta G^c = G^c - \tilde{G}^c, \Delta G^d = G^d - \tilde{G}^d\}$, G is shear modulus, $\tilde{G}$ is reference measurement of shear modulus, and c and d are parameters relative to connective and dermic tissue respectively, r is range of pathology and p are parameters associated to model design.

From the definition of the simulated noise, the dependency of the variation of the measurement with increasing noise is also linear. These two considerations about linearity support the proposal that the measurements on a specimen with noise and with pathology can be expressed as *Taylor series expansion* centered at the case without noise and without pathology, and neglecting higher order terms (*hot*) than linear,

$$\psi_i(p,\sigma) = \psi_i(0,0) + \underbrace{p\frac{\partial \psi_i}{\partial p}(0,0)}_{\mathrm{SIGNAL}} + \underbrace{\sigma\frac{\partial \psi_i}{\partial \sigma}(0,0)}_{\mathrm{NOISE}} + hot \tag{7}$$

where $i = 1, ..., N_i$ are the measuring points. The first term on the right hand side is the measurement at point i without noise nor pathology. The second term is the alteration of that measurement due to the presence of the pathology only, and is labeled SIGNAL, following the reasoning above. The third term is the alteration of the signal originated by the noise only (NOISE).

The second term of the *Taylor* series (equation 7) depends on the sensitivity of the measurements on the pathology, and can be approximated by finite

differences,

$$\frac{\partial \psi_i}{\partial p}(p_0, 0) = \psi_{i,_p}(p_0, 0) = \frac{\psi_i(p_0 + \Delta p, 0) - \psi_i(p_0 - \Delta p, 0)}{2\Delta p} \tag{8}$$

where $p_0 \to 0$ is a small pathology used to guarantee that the FEM captures the perturbations produced at small Δp (since the case $p = 0$ with no pathology needs to be computed with a topologically different mesh), in order to compute $\psi_{i,_p}(p_0, 0) \approx \psi_{i,_p}(0, 0)$. In addition, a central difference scheme, which yields an error of the order $O(\Delta p^2)$, becomes available. Since the noise component is linear by definition, a forward difference scheme is adopted, whose $O(\Delta\sigma)$ error is sufficient.

Some authors (Saltelli et al., 2000) propose that the parameters Δp and $\Delta\sigma$ should be two orders of magnitude smaller than the values at which the derivative should be computed. However, an estimation of these parameters is studied. It shows $\psi_{i,_p}(0, 0)$ and $\psi_{i,_\sigma}(0, 0)$ versus Δp and $\Delta\sigma$, respectively, for a pathology at the center of the bridge deck. $\Delta p = \Delta\sigma = 10^{-2}$ is shown to produce a stable value of the derivative for the case of the single measurement represented, but the same result is obtained for all 18 measuring points.

The third term of the *Taylor* series (equation 7) can be directly derivated if the equation 4 is assumed,

$$\frac{\partial \psi_i}{\partial \sigma} = \xi_i \mathrm{RMS}(\psi_i^{\mathrm{FEM}}) = \xi_i \mathrm{RMS} \tag{9}$$

Equations (7), (9) and the relationship $|Y_i|^2 = \frac{1}{m}\sum_{i=1}^{m} Y_i^2$, can be combined into (4) to obtain,

$$\mathrm{POD} = P\left(\frac{p^2 \frac{1}{N_i}\sum_{i=1}^{N_i}(\psi_{i,_p}(0,0))^2}{\sigma^2 \mathrm{RMS}^2 \frac{1}{N_i}\sum_{i=1}^{N_i}\xi_i^2} > 1\right) = P\left(p^2 > \frac{\mathrm{RMS}^2\sigma^2\sum_{i=1}^{N_i}\xi_i^2}{\underbrace{\sum_{i=1}^{N_i}(\psi_{i,_p}(0,0))^2}_{S_p}}\right) \tag{10}$$

If the noise generator ξ_i is a random variable, the POD is a probability of the stochastic variable p^2, described by the cumulative probability density function F,

$$\mathrm{POD} = F\left(\frac{\mathrm{RMS}^2\sigma^2\sum_{i=1}^{N_i}\xi_i^2}{S_p}\right) \tag{11}$$

Using Monte Carlo techniques and error propagation theory the noise in the measurement points can be concluded to follow a normal distribution ((Rus

et al., 2006)). Assuming this distribution, the squared sum of the noise ξ_i is known to follow a *Chi-square* distribution, since $\sum_{i=1}^{N_i} \xi_i^2 \longrightarrow \chi^2_{N_i}$ (e.g. (Rade and Westergren, 1999)). The parameter of the *Chi-square* distribution is the number of degrees of freedom N_i, which in this case is the number of measurement points. In the case that $N_i > 10$, the *Chi-square* distribution can be approximated by a Gaussian or normal N distribution $\chi^2(N_i) \approx N(N_i - 2/3, \sqrt{2N_i})$ with mean $N_i - 2/3$ and standard deviation $\sqrt{2N_i}$. This approximation in (11) yields,

$$p^2 \longrightarrow N\left[\frac{\mathrm{RMS}^2\sigma^2(N_i - 2/3)}{S_p}, \frac{\mathrm{RMS}^2\sigma^2\sqrt{2N_i}}{S_p}\right] \tag{12}$$

Since $F(x) = \int_{-\infty}^{x} f(y)\mathrm{d}y$ is the cumulative of the normal probability density function f, whose inverse is $x = G(F(x))$, the useful pathology area to noise ratio p/σ can be expressed from (12) given a POD level as,

$$\frac{p}{\sigma} = \sqrt{\frac{\mathrm{RMS}^2(N_i - 2/3)}{S_p}\left(1 + G[\mathrm{POD}]\frac{\sqrt{2N_i}}{N_i - 2/3}\right)} \tag{13}$$

Note that the analytical expression (12) is only valid for noise with normal distribution at the measurement points.

3 Numerical Results

The purpose of the numerical results is to obtain conclusions about which experimental design is better in characterizing mechanical tissue properties. The scope is to extract some *a priori* thumb rules that allow to select those with a more accessible minimum in the cost function, and guarantee satisfactory results for a minimization algorithm.

3.1 Forward problem

The numerical tool selected for solving the response of the model is the Finite Element Method (FEM). After a convergence test on mesh and time integration, a 8-node quadratic finite element with 4 degrees of freedom per node, with a final discretization consists of 1052 nodes, 186 elements and 32 time increments, has been implemented to solve the model given by the constitutive equations for elastic and piezoelectric materials that the sensor is composed of. The geometry cannot be disclosed in the present document due to intellectual property reasons, but falls beyond of the scope of the POD contribution. The piezoelectric element was developed and implemented in the research academic finite element code FEAP (Taylor, 1987). A sample of resulting measurements is shown in Figure 2.

The results of the simulated signal with a 10% of noise are consistent with the response in the FEM model.

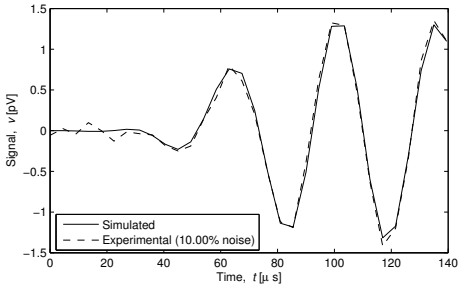

Figure 2. Simulated measurements for model design, noise 0.10%

3.2 Inverse problem

The shape of the cost function provides another subjective way to evaluate the sensitivity of the numerically predicted signals, based on the following criteria:

- The existence of local or global minima affects the convergence of the search algorithm.
- Steep minima are better than those providing soft valleys, due to algorithm convergence performance.
- Valleys that present shapes close to circular are considered as an indicator of uncoupled mechanical properties of soft tissue parameters.

Figure 3 shows a slice of the multidimensional cost function as functions of the parameters G_d and G_c for configuration of the model.

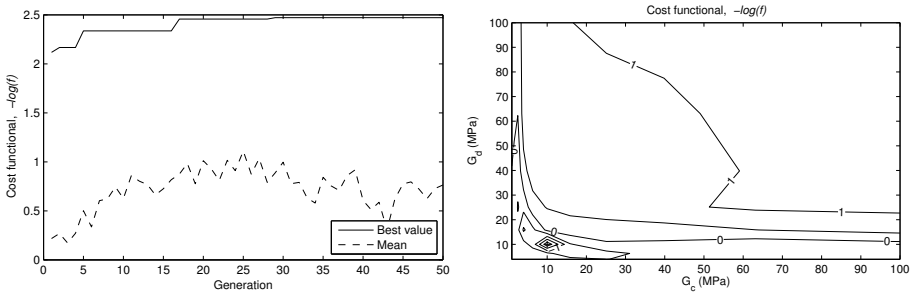

Figure 3. Convergence of the genetic algorithms (top), and cost functional as a function of the parameters with reference G_d and G_c (bottom)

3.3 Probability of detection

The aforementioned criteria is aimed at evaluate the local behavior of the cost functional, regardless of the noise effects. Maximizing the POD enables to find

the smallest pathology given the largest noise levels, independently of the robustness of the convergence of the search. Figure 4 shows an example of the POD estimation for one excitation configuration for increasing pathological values, whereas the dependency of the POD on the pathology extent is illustrated for a fixed noise level that amounts to 0.1%.

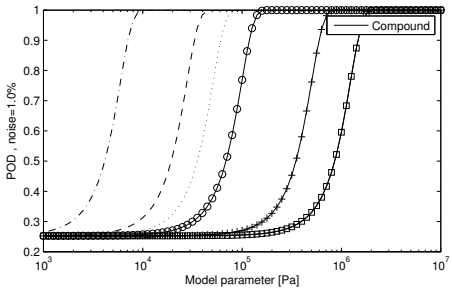

Figure 4. Dependency of the POD on the pathology amount.

From left to right: [G_d 300], [G_c 300], [G_d 3000], [G_c 3000], [G_d 30000] and [G_c 30000], where G_d is compressibility modulus for dermic tissue, G_c is the compressibility modulus for connective tissue and [300, 3000, 30000] are three references of tissue depend on gestational age or other variables, and allows to compute the robust probability of detection RPOD.

3.4 POD optimization

Once identified the effects of the POD, the optimization is calculated to demonstrate if the POD improved by optimal design.

The first four graphs show the regions of maximum POD over the 8 parameters of the model, the fifth graph relates the genetic algorithms search with a population of 20 individuals and 50 mutations and the best value and the last graph shows the optimized parameters for the best POD .

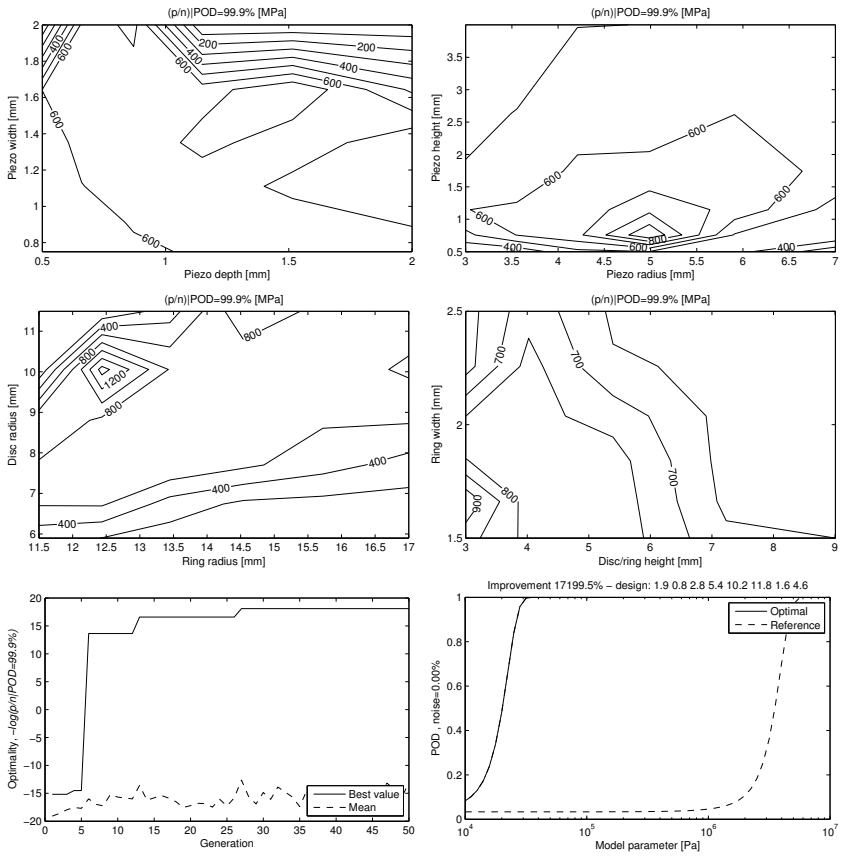

Figure 5. POD optimization

4 Conclusions

A strategy based on the inverse problem to optimize the FEM model have been developed. First we define a cost function as the difference between the experimental and theoretical signals and other statistical tools. Then, we define the POD (Probability of detection) as the probability that the signal is greater than the noise through a Taylor series expansion of the response with respect to noise and pathology-related mechanical properties, which is approximated by a finite differences scheme. After reformulated this concept to the case that concerns us, the better prediction of probability of detection for preterm birth. Through three references in different elastic constants, the RPOD is defined as robust probability of detection with a pessimistic criterion. Finally algorithms are developed to approximate the RPOD from a set of forward simulations of the sensor-tissue system. The RPOD is used for optimizing the sensor design.

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