Sensors and Actuators A 190 (2013) 25–31

Contents lists available at SciVerse ScienceDirect

Sensors and Actuators A: Physical

journal homepage: www.elsevier.com/locate/sna

Towards in vivo differentiation of brain tumor versus normal tissue by means of torsional resonators

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ARTICLE INFO

Article history:
Received 12 July 2012
Received in revised form 29 October 2012
Accepted 31 October 2012
Available online 14 November 2012

Keywords:
Torsional resonators
Piezoelectric sensors
Acoustic sensor
Neurosurgery

ABSTRACT

It was tested to what extend torsional acoustic resonators can serve to in vivo differentiate between healthy and tumorous brain tissue. The resonators employed consist of crystalline quartz. They are cylindrically shaped. The resonance frequency at the fundamental is 78 kHz. The best correlation between the shifts of resonance frequency and resonance bandwidth, on the one hand, and the state of the tissue, on the other, was found when analyzing ratios of the shifts in resonance frequency and resonance bandwidth. These ratios are independent of contact area. Taking data on the fundamental mode as well as the third overtone further improved the efficiency and precision of the technique. These results suggest that torsional resonators can serve as diagnostic tools in neurosurgery.

1. Introduction

Neurosurgery is a surgical discipline, which depends in a particular way on the experienced hand of the surgeon. Two major senses are required to distinguish tumor from normal brain tissue, which are the eyes and the fingertip. Different entities between benign and malignant in brain tumor surgery are first discriminated by visual inspection through a microscope or an endoscope. Second, the surgeon identifies remaining tumor by the way it "feels". Optical technologies have continuously contributed to the advancement of diagnostics and therapy in modern surgery. Other sensor modalities so far do not exist.

Brain tissue is an assembly of billions of glial and neuronal cells in a well defined pattern. It moreover includes vessels, and fibrous material such as elastin, and collagen. Glial cells perform many functions that are essential for the proper functioning of the central nervous system [1]. Tumor tissue is a result of non-oriented diffuse and invasive growth of cells, e.g. cells of glial origin in a glioblastoma tumor, destroying the normal glial and neuronal networks [2,3]. At this point, the palpation of tumor tissue in oncologic brain surgery critically relies on the subjective impression of the surgeon. Also, palpation is only possible on lumps of tumor tissue. It cannot be undertaken on the microscopic level. This situation might be improved with automated – and possibly miniaturized – analytical instrumentation. The goal of this study was to test the usability of torsional resonators as either a replacement or an extension of the surgeons "finger tips". Such a development, if successful, could lead to small sensors attached on the microinstrument's tip.

Given that the surgeon differentiates between healthy and tumorous tissue by manually exerting a gentle pressure and sensing the local stiffness, haptic sensors come to mind as a potential diagnostic tool in microinvasive surgery. Haptic sensors are not widely spread at this time. Spicer et al. have looked into the question of whether haptic devices can be employed for training purposes in the context of a virtual reality-simulated environment [4]. They come to the conclusion that "the realization of ergonomically acceptable haptic interfaces remains elusive". Rosen et al. take a more optimistic view in ref. [5]. They describe an endoscopic surgical grasper employing computerized force-feedback. This device was able to determine the stiffness of different tissues. More recently, Tanaka et al. have constructed a tactile sensing system based on balloon expansion [6]. This instrument targets neurosurgery as the application. It was tested ex vivo on white and gray matter of porcine brain.

Another technique of virtual "palpation" of the brain has recently become available, which is magnetic resonance

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http://dx.doi.org/10.1016/j.sna.2012.10.039

elastography (MRE) [7]. MRE quantifies biomechanical properties of the brain parenchyma by analyzing the propagation of externally elicited shear waves [7]. Altered viscoelastic properties indicate structural alterations in biological tissues at multiple scales with high sensitivity. MRE directly visualizes and quantifies biomechanical tissue properties in vivo [8]. Its routine use for tumor surgery, however, would require an operating room equipped with an intraoperative MRI scanner. For routine neurosurgery it would be desirable to have a smaller and more economic instrument with integrated microsensors.

The use of mechanical resonators to probe a tissue's mechanical properties has been, for instance, explored by Mazza et al. [9] by the Wallaschek group [10,11] and by Scholz et al. [12]. The latter authors combined magnetic resonance elastography with a low-frequency axial vibrator. They tested their instrument on humans. These authors do not find a clear correlation between the stiffness of a tissue and whether or not the tissue is healthy. We come back to this problem in the Section 3.

In this work we study to what extent torsional resonators can take the role of haptic sensors in determining the state of a tissue during brain surgery. It is well known that acoustic sensors can pick up mechanical differences between tissues [9]. Still, it must be emphasized that the parameters sensed by the surgeon are not strictly the same as the ones targeted by torsional sensors. Firstly, haptic inspection occurs at low frequencies (typically 1 Hz), while the torsional resonator operates at many tens of kHz. The stiffness of soft matter depends on frequency because there are relaxation processes with a broad distribution of relaxation rates (including the kHz range). Secondly, there is a difference in amplitude. The strain induced by a torsional resonator is below one percent (usually much less). Linear response is obeyed (as can be checked by searching for an amplitude dependency of the frequency). The surgeon, on the contrary, deforms the tissue by 10% and more. The tissue probably behaves nonlinearly and nonlinear behavior may well be what the surgeon's intuition is based upon. While one might think so, the tangential motion of the resonator (contrasting to normal pressure exerted be the surgeon) does not make a difference. This is so because the sample is incompressible (that is, it deforms much more readily than changing volume). Even if the surgeon exerts a normal force, the tissue's response is still governed by its shear modulus. Tangential and normal stress only make a difference when comparing torsional resonators to conventional ultrasound. Ultrasound is a compressional wave and the response of the material to ultrasound therefore is much different from its response to shear sound.

Torsional resonators are known since the beginning of research on piezoelectric sensors [13]. They have mostly been used to determine the viscosity of complex media at high frequencies. The Pechhold group at Ulm University, in particular, has gathered much experience in their use [14]. Nakken et al. have used torsional rods for rheological measurements on samples which were available in small amounts, only [15]. In the life sciences, torsional oscillators have been employed to measure rheological properties of soft biological tissues [16], and also to measure the viscosity of very small capillary blood samples [17]. The Mazza group [16], in particular, has put forward a detailed quantitative model of the sensor and its response to contact with biological tissue. These authors employed the finite element method (FEM) to construct a full 3D model. They tested the model with tissue extracted from animals post mortem.

In the work reported below, we applied torsional resonators to living animals. The target was to differentiate between brain tumors and healthy tissue. We used commercially available resonators and tested their performance in a surgical environment. Some of the problems discussed below originate from the fact that the specimens (the brains of rats) were comparable in size to the resonator. These problems presumably are less severe in surgery on humans, but in terms of insight into the instrument performance and potential pitfalls, they elucidate what the consequences of limited space and local heterogeneity of the tissue might be. A second important difference was that we contacted the tissue with the piezoelectric resonator itself, rather than a non-piezoelectric rod driven by a separate transducer. The tissue's dielectric constant affects the resonance frequency via a mechanism called piezoelectric stiffening [18]. The stiffness of a piezoelectric rod depends on whether or not the strain-induced polarization is compensated by a corresponding electric charge. This is the case if the active area is covered with electrodes and if these electrodes are well-grounded. However, the active area was not metalized here. The tissue provides for a similar (but ill-controlled) type of electric screening as the electrodes. The fractional frequency shift following from variable electrical screening is of the order of k_c^2 where k_c^2 is square of the electromechanical coupling coefficient. For quartz, k_c^2 is of the order of 1% (depending on the mode of vibration). Importantly, a frequency shift of 1% amounts to $\Delta f \sim 700$ Hz and for that reason even minor changes in the sample's electric properties very noticeably affect the resonance frequency. We come back to the consequences of heterogeneity and ionic conductivity in the discussion.

While one might think that the known dependence of the resonance frequency on temperature would be a severe problem, this is not the case. The thermal mass of the resonator is so large that a temperature change upon touching the sample needs time. Torsional resonators here differ from the more commonly employed thickness shear resonators, which are a few hundred microns thick and quickly adapt their temperature to the environment. The thermal diffusivity of quartz is about $D_T = 1.4 \times 10^{-6}$ m^2/s. With a length of the rod of $L = 2.5$ cm, this translates to a time constant of $\tau = L^2/D_T$ of about 7 min. Temperature effects will produce a drift in the base line, but they will not affect the jump in Δf observed upon touching the animal.

Before describing the experiment, we briefly comment on a key feature of the technique, which is the use of shear waves contrast to the compressional waves employed in conventional ultrasound. Because shear waves decay rapidly in soft materials, shear wave resonators probe the region close to the surface, only. This is an important benefit, since acoustic reflections from bones located nearby would otherwise easily mask the response from the soft tissue. Evidently, the penetration depth of the wave is of prime importance to the measurement and one will always try to adjust the sampling depth to the tissue under investigation. As a rough estimate, the penetration depth amounts to a few wavelengths, that is, to the speed of sound times the period of oscillation. We insert numbers in order to make the estimate quantitative. A typical shear modulus of biological tissue is in the range of a few tens of kPa [19]. Using $G \sim 50$ kPa and $\rho \sim 1$ g/cm^3, one finds a speed of shear sound of $c_S = (G/\rho)^{1/2} \sim 7$ m/s. With a resonance frequency of 78 kHz, one arrives at a penetration depth of 90 μm, which is a reasonable range from a practical perspective. Note that the shear modulus can easily vary over a decade or more. The estimate above therefore necessarily is crude.

The required penetration depth is an important design constraint for miniaturization because small resonators tend do have high resonance frequencies and correspondingly low penetration depths. If miniaturized sensors are to operate at frequencies in the kHz range, these sensors must be intrinsically soft. One way to lower the resonance frequency without making the resonator longer is to apply a constriction at the waist. Since the torsional stiffness of a rod scales as the 4th power of the diameter, most of the twisting deformation will then occur at the waist. There is a second constraint, though: The shifts of frequency and bandwidth scale as the inverse mass of the resonator (cf. Eq. (1) below). If the resonator is too small, it will be easily overdamped upon