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Diversity of biomedical applications of acoustic radiation force

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ABSTRACT

This manuscript is a summary of the paper presented at the ICU'2009 on biomedical applications of acoustic radiation force with emphasis on emerging applications in microfluidics, biotechnology, biosensors and assessment of the skeletal system. In this brief overview of current and projected applications of radiation force, no detailed description of the experiments illustrating particular applications are given as this would result in a far different and longer paper. Various mechanisms of acoustic radiation force generations and their biomedical applications are considered. These mechanisms include: (a) change in the density of energy of the propagating wave due to absorption and scattering; (b) spatial variations of energy density in standing acoustic waves; (c) reflection from inclusions, walls or other interfaces; and (d) spatial variations in propagation velocity. The widest area of biomedical applications of radiation force is related to medical diagnostics, to assessing viscoelastic properties of biological tissues and fluids, and specifically to elasticity imaging. Another actively explored area is related to manipulation of biological cells and particles in standing ultrasonic wave fields.

There are several poorly explored areas of potential biomedical applications of ultrasound radiation force. A promising area of biomedical application of ultrasound radiation force is stirring and mixing of microvolumes of liquids in microfluidics and in various biotechnological application where diffusion rate is the main factor limiting the efficiency of the process of interest. A new technique, called "swept frequency method", based on the use of radiation force in the standing acoustic wave for microstirring of liquids is described. The potential applications of the ultrasound radiation force for assessment of skeletal system, where conventional bone ultrasonometry are inapplicable are considered.

Contents

1. Introduction

The range of biomedical applications of acoustic radiation force is broad, including elasticity imaging [1–4], monitoring therapy [5–7], targeted drug and gene delivery [8,9], molecular imaging [10], acoustical tweezers [11–13], and increasing the sensitivity of biosensors and immunochemical tests [14,15].

The manipulation of particles and cells in suspensions by the radiation force of the standing acoustic wave has the oldest history. This effect has been known since 1874, after the experiments of August Kundt demonstrated that fine particles are collected at the nodes of the standing acoustic wave [16]. The biomedical significance of this effect was first demonstrated in 1971 by Pond, Woodward and Dyson, who discovered that red blood cells in the blood vessels *in vivo* can be collected in standing acoustic waves in bands half a wavelength apart [17].

Another application of radiation force with a long history is the measurement of ultrasound intensity in liquids using the radiation

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force balance. The concept of the radiation force balance was proposed and experimentally demonstrated by Wood and Loomis in 1927 [18]. The first paper presenting this important practical application was published in 1929 [19]. The system described in that paper became the prototype for the most common instrument for calibration of therapeutic transducers.

Detailed analysis of the physical basis of biomedical applications of ultrasound radiation force was made in numerous reviews and the original articles of Nyborg published since the mid-sixties [20–22].

A major surge in various biomedical applications of acoustic radiation force started in the 1980s and continues today.

2. A brief overview of current fields of biomedical applications of acoustic radiation force

The widest area of current biomedical applications of radiation force is related to medical diagnostics, to assessing viscoelastic properties of biological tissues and fluids, and specifically to elasticity imaging. Radiation force of a focused ultrasound beam acts as a virtual finger for remote probing of internal anatomical structures and obtaining diagnostic information. Elasticity imaging is one of the most rapidly developing areas of medical ultrasound. Approaches to elasticity imaging techniques based on the use of radiation force include vibro-acoustography (VA) [1], Acoustic Radiation Force Impulse (ARFI) imaging [2], and Shear Wave Elasticity Imaging (SWEI) [3]. Probably the most efficient elasticity imaging method based on radiation force is Supersonic Shear Imaging (SSI), which is a branch of SWEI developed by Fink and coworkers during the last decade [4]. SSI demonstrated excellent results in elasticity imaging of breast, liver and muscles [23–25].

Other applications of radiation force include assessing the viscoelastic properties of fluids and biological tissue [26–28], targeted drug and gene delivery [8,9], molecular imaging [10], and monitoring lesions during therapy [5–7].

Biological effects of radiation force and their potential applications are among the oldest subjects of interest in medical ultrasound. The possibility of using radiation force of focused ultrasound for stimulation of neural structures has been extensively explored since the early 1970s by Gavrilov et al. [29–31] and later by Dalecki et al. [32]. The use of ultrasound radiation force for the development of robotics systems and automated control systems based on the use of tactile sensations in the human–machine interface has been proposed [33].

Numerous biomedical applications of radiation force are related to manipulating particles and cells in the standing acoustic wave. There exists a wide range of literature on acoustic radiation force in standing wave used for manipulating biological cells in a solution, separating different types of particles from a liquid or from each other, increasing the sensitivity of biosensors, immunochemical tests and acoustical tweezers [11–13,34–37].

3. Types of radiation force

The acoustic radiation force is a period-averaged force exerted on the medium by a sound wave. Radiation force can be produced due to various physical effects:

1. Change in the density of energy of the propagating wave due to absorption and scattering.
2. Spatial variations of energy density in standing acoustic waves.
3. Reflection from inclusions, walls or other interfaces.
4. Spatial variations in propagation velocity.

The first of the listed mechanisms of radiation force generation was most thoroughly studied by Eckart, who derived equations for the average force and motion in a homogeneous viscous fluid [38]. This mechanism is the basis of ultrasonic elasticity imaging methods using the radiation force of focused ultrasound for remotely generating shear stress in tissues [1–4].

The second mechanism of radiation force generation in the standing acoustic waves, which was first demonstrated in the experiments of Kundt, is currently widely used for applications related to manipulation of particles [34–37,39–41].

A classical example of the third mechanism is one of the oldest applications of radiation force – ultrasound radiation force balance, proposed by Wood and Loomis in 1927 [3,4]. This mechanism is the basis of many applications employing vibro-acoustography principles developed in the last decade by Greenleaf, Fatemi and their coworkers [1,42–45].

The fourth mechanism provides generation of radiation force in a medium without attenuation or reflection of ultrasound [46]. Variations in the sound wave velocity in a medium result in spatial variations of the energy density of the propagating wave. Depending on the sign of the gradient of the energy density, the generated radiation force can be directed both outward and toward the source of the propagating wave. As a result, a harder inclusion in a medium will be compressed while a softer inclusion will be stretched along the axis of ultrasonic beam.

The fourth type of radiation force currently has no biomedical applications. Theoretical estimates showed that such a non-dissipative radiation force can be comparable to the classical unidirectional dissipative radiation force [46] and potentially can find applications in tissue characterization. There are numerous other poorly explored areas of potential biomedical applications of ultrasound radiation force. A few examples of such applications explored by Artann Laboratories are presented in the following section.

4. Examples of yet-to-be explored applications of acoustic radiation force

4.1. Ultrasound radiation force for assessment of the skeletal system

Ultrasonic devices for assessment of bones are divided into two groups: heel ultrasonometers, based on ultrasound through-transmission measurements of a heel bone, and axial ultrasonometers, which use surface transmission measurements in long bones such as the tibia and radius [47–49]. Bone ultrasonometers are considered a simple, safe, and cost-effective technique sensitive to both mechanical and structural features of the bone. However, the application of these devices is greatly limited by the fact that there are very few anatomical sites where the measurements can be made. Such an important site like the pelvic bone (from the point of view of osteoporosis and fracture risk assessments) cannot be tested by conventional ultrasonometers because of the limited accessibility of this bone. The possibility of remotely generating and measuring the propagation parameters of acoustic waves in the pelvic bone would greatly increase the potential of bone ultrasonometry for osteoporosis assessment. Another important potential application of bone ultrasonometers capable of remote measurements is in neonatology, for the assessment of the skeletal system in newborns and infants, where conventional bone ultrasonometry is inapplicable and X-ray densitometry is restricted in its application. The problem of assessment of the neonatal skeletal system became especially vital during recent decades: with the growing incidence of osteopenia of prematurity – decreased bone