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Ultrasound, cavitation bubbles and their interaction with cells ☆

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Abstract

This article reviews the basic physics of ultrasound generation, acoustic field, and both inertial and non-inertial acoustic cavitation in the context of localized gene and drug delivery as well as non-linear oscillation of an encapsulated microbubble and its associated microstreaming and radiation force generated by ultrasound. The ultrasound thermal and mechanical bioeffects and relevant safety issues for *in vivo* applications are also discussed.

Keywords: Ultrasound; Bioeffects; Acoustic cavitation; Non-linear acoustics; Microstreaming; Acoustic radiation force; Shear stress

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1. Introduction

Due to the limitations of non-specificity and side-effects (viral toxicity and immune rejection) associated with drug delivery or viral-mediated gene delivery means, non-viral technologies which include chemical and physical approaches have

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attracted scientists' attention and are being rapidly developed [1]. Accompanying the newly emerging biotechnologies in drug delivery, moderate intensity ultrasound (US) assisted by encapsulated microbubbles (EMB) has been used in *in vitro* and *in vivo* targeting drug delivery *via* a process called "sonoporation" [2–9]. Very much like its counterpart "electroporation" [10], sonoporation is believed to generate transient pores in cell membranes allowing drug, DNA, and antibody delivery into the cell [11]. Unlike electroporation, sonoporation has a unique advantage; it can propagate into deep tissue and also can be focused specifically into the target because US is a mechanical wave. Although the physical mechanisms of sonoporation are not fully understood, the consensus of the ultrasound community seems to be that some form of acoustic cavitation is involved. This chapter reviews the basic physical principles of ultrasound, non-linear oscillations of a free and an encapsulated bubble, acoustic cavitation and its associated physical phenomena such as acoustic microstreaming, shear stress and radiation forces.

2. Review of fundamental physics of ultrasonic waves

2.1. Non-focused ultrasonic plane-traveling waves

Let us consider a half-space ($x>0$) filled with a liquid or soft-tissue. For most cases, the soft-tissue may be considered as a liquid-like medium. At $x=0$, there is a thin solid-plane as shown in Fig. 1 with lateral dimensions (perpendicular to x direction) much greater than the wavelength (λ) of the sound wave. This plane, a sound source, is vibrating sinusoidally with time and back and forth in space around its initial position at $x=0$; its vibration leads to the production of a sound wave in the region $x>0$. The displacement of this source plane with respect to $x=0$ can be written as

$$x(t) = A \cos(2\pi ft + \phi_0), \tag{1}$$

where f is frequency of the vibration, $A(>0)$ is the amplitude, ϕ_0 is the initial phase which determines the initial ($t=0$) conditions of the source plane. For example, if $\phi_0=0$, the displacement and velocity of the source plane are $x=A$ and $v=dx/dt=0$, respectively, when $t=0$. In the regime of linear acoustics (we will consider non-linear acoustics in later sections), a traveling pressure wave propagating along x direction in a medium is generated by the vibrating sound

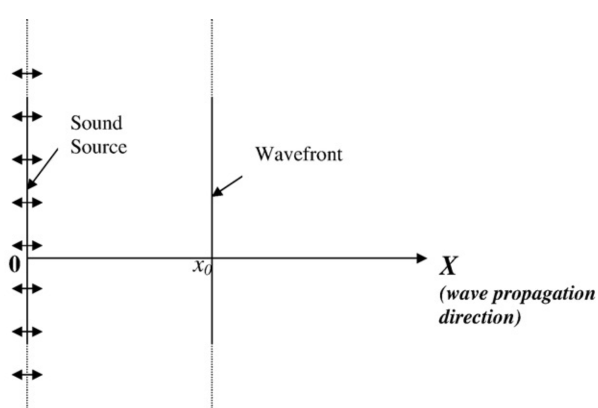

Fig. 1. A plane-wave sound source and its wavefront.

source. That is to say, the pressure in the medium is a function of x and t and fluctuates around the atmospheric pressure. If we define the acoustic pressure $p(x, t)$ as the excess of the total pressure to the atmospheric pressure, it can be written as

$$p(x,t) = P_0(x) \cos(kx - \omega t) = p_0 e^{-\alpha x} \cos(kx - \omega t). \tag{2}$$

Here $P_0(x)$ is the acoustic pressure amplitude which is a function of position x and is equal to $p_0 e^{-\alpha x}$, where $p_0=P_0(0)$, the pressure amplitude at $x=0$. Other parameters include the angular frequency $\omega=2\pi f$, the propagation constant (or wave number) $k=2\pi/\lambda$ and the attenuation coefficient of the medium α. For a soft-tissue, α is approximately a linear increasing function of frequency in the megahertz range. The attenuation coefficient α describes the energy transfer from the sound wave to the medium mainly through absorption and scattering processes. Absorption converts acoustic energy irreversibly into heat mainly *via* viscous friction. Inside the tissue or in aqueous suspensions of cells, inhomogeneities exist. Scattering is a process whereby the inhomogeneities re-direct some sonic energy to regions outside the original wave-propagation path. If the density of the inhomogeneity is high, multiple-scattering may occur. In other words, in such instances sonic energy may scatter among several inhomogeneities back and forth for several times before it is diminished by absorption. In water, the attenuation coefficient α is often negligible and the multiplying factor $e^{-\alpha x}$ may be considered to be unity in Eq. (2). Frequency and wavelength are not independent for a sound wave; they are related by the relationship of $f\lambda=c$, where c is called the phase velocity. In water or soft-tissue, the phase velocity at 20 °C is approximately equal to 1500 m/s.

Noting that if $x=x_0$, $p(x, t)$ in Eq. (2) becomes

$$p(x_0,t) = P_0(x)\cos(kx_0 - \omega t) = p_0 e^{-\alpha x_0}\cos(kx_0 - \omega t); \tag{3}$$

thus the acoustic pressure at any point on the plane $x=x_0$ changes sinusoidally in time, the phase being equal to $kx_0-\omega t$. A plane or a surface where every point has the same phase is called a wavefront. An acoustic wave which has a set of planes as its wavefronts and can be represented by Eq. (2) is often called a non-focused plane-traveling wave. When the frequency f is above the typical human audible range ($f \geq 20$ kHz), this type of sound wave is called ultrasound (US). In principle, the plane wavefront of a traveling wave described by Eq. (2) has infinite dimensions. In practice, however, a simple sound source is often a circular ceramic disk that exhibits a piezoelectric effect and has a radius a of a finite dimension; it is also called a "piston" sound source. The nature of the US generated by the piston source is quite different from a plane-traveling wave; it depends on the ratio a/λ. However, under the condition $a \gg \lambda$, the sound wave in the far-field region (which we will define later) behaves like an ultrasonic beam with a circular cross section. Within the beam, particularly close to the beam axis, the acoustic pressure may be approximately described by Eq. (2).

In general, the sound field generated by a piston source has a main beam, which contains most of the acoustic energy, and several side-lobes [12]. Due to the circular symmetry of a piston source, we may use coordinates of x (the wave-propagation direction) and $\sigma = \sqrt{y^2 + z^2}$ to describe the acoustic intensity of