Ultrasound can help small particles penetrate into biofilms using a new oscillatory diffusion mechanism

Biofilms form when microorganisms, such as bacteria or algae, attach to a surface and surround themselves with a matrix of extracellular polymeric substance (or EPS). Biofilms are ubiquitous in nature and in a vast array of industrial and biological processes, playing a key role in applications as diverse as tooth decay, food digestion, water reclamation, and the aquatic food chain, to name only a few. Researchers have found that biofilms are involved in nearly 80% of infectious diseases. The microorganisms within a biofilm cluster into colonies, sometimes consisting of only one type of organism and at other times consisting of a mixture of organism types. These organisms interact and communicate extensively with each other, in ways that researchers are only just beginning to understand. They compete for minerals and nutrients, they emit and sense a wide variety of chemicals in a process called quorum sensing to identify numbers and characteristics of neighboring organisms, and they sometimes emit toxins to kill off competitors.

Fig. 1. A slice of an alginate hydrogel film showing penetration of fluorescent liposomes into the film (a) with ultrasound exposure and (b) without ultrasound. The film thickness is approximately 120 micrometers, and the film is covered by a liposome suspension. (From Ma et al., J. Acoust. Soc. Am., Aug 2015).

All of these microorganism interactions are controlled by the diffusive transport of chemicals within the biofilm. Diffusion within a biofilm is generally slowed by the gel-like structure of the film, which is one reason why biofilms offer microorganisms partial protection to antimicrobial chemicals and responses of the human immune system. A diffusive process is one in which a substance, such as a chemical or heat, spreads gradually outward by the random thermal motion of the molecules making up the substance. The rate of diffusion of a substance is proportional to the product of the gradient of the substance concentration and a coefficient (called the diffusion coefficient), which is a function of temperature of the diffused substance and the transport medium through which the diffusion occurs.

A group of scientists at the University of Vermont have recently discovered that exposure of a biofilm to moderate-intensity ultrasound can dramatically increase the rate of diffusion of certain substances into the biofilm. The initial discovery was reported by Ma et al. (*J. Acoust. Soc. Am*., Aug 2015), who showed experimentally that a suspension of small (~400nm diameter) protein capsules containing a fluorescent liquid, called *liposomes*, exhibit dramatically greater penetration into an alginate hydrogel, which was used as a synthetic biofilm structure, than occurs with molecular diffusion alone (Fig. 1).

The publication cited below provides an explanation for how ultrasound can enhance the diffusion rate of nanoparticles in a hydrogel, such as a biofilm. Ultrasound, like any acoustic signal, causes the fluid elements within the biofilm to oscillate back and forth over a distance that depends on the frequency and amplitude of the ultrasound. When the fluid contains nanoparticles, these particles pass repeatedly through the pore spaces within the entangled proteins that make up the biofilm. However, sometimes the small particles will become temporarily trapped in the hydrogel protein network or otherwise impeded in their oscillatory motion. When this occurs, the ultrasonic forcing leads the particles to exhibit a behavior that appears similar to molecular diffusion, but at a much faster rate. To demonstrate this proposed diffusion mechanism, we developed a simple one-dimensional stochastic model of oscillatory particle motion with random particle hold-up. In the limit of small time step, we showed that this stochastic model reduces to the standard diffusion equation, and we derived an expression for the effective diffusion coefficient induced by the ultrasonic forcing.

The discovery that ultrasound can enhance penetration of nanoparticles into biofilms has a wide range of potential applications, enabling an ability to selectively inject matter into biofilms either for mitigation purposes or to modify or control the biofilm process.

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Publication

A model of ultrasound-enhanced diffusion in a biofilm.
Marshall JS
J Acoust Soc Am. 2016 Jun