Biomedical Ultrasound Fundamentals of Imaging and Micromachined Transducers

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Lecture – 37

Hello and welcome to the lecture on ultrasound contrast agents. I'm Professor Himanshu Shekhar. Ultrasound has several advantages, becoming faster, better, and cheaper with technological advancements, and it has various applications, such as imaging the hand of a fetus and observing heart valve movements in both two-dimensional and three-dimensional formats. However, ultrasound struggles with imaging blood-filled or vascular organs due to weak backscatter from blood, which is mostly liquid and contains few formed elements.

While Doppler ultrasound can provide anatomical and flow information, it relies on frequency shifts proportional to the motion of scatterers like red blood cells. This makes it difficult to detect slow or low-volume flows, such as in microcirculation. This limitation highlights the need for ultrasound contrast agents to enhance scattering from blood-filled organs.

The history of ultrasound contrast agents began with Dr. Raymond Gramiak, who, while injecting indocyanine green dye for X-ray angiography, noticed an unexpected increase in ultrasound signal. He later realized that microbubbles formed at the catheter tip were responsible for the enhancement. Early saline contrast agents were developed by agitating saline to create microbubbles. These are still used today for visualizing conditions like atrial septal defects, where they can reveal abnormal openings between heart chambers. However, saline dissolves quickly and cannot pass through the lung circulation, prompting the development of more stable, commercially available lipid shell contrast agents.

One example of such an agent is SonoVue, filled with sulfur hexafluoride gas, which is dense and sparingly soluble in water, providing better stability than air bubbles. These contrast agents are stabilized by lipid or protein shells and are injected intravenously, remaining within the bloodstream. This is different from contrast agents used in MRI or CT, which can leak into interstitial space.

When ultrasound is applied, these microbubbles undergo volume pulsation, enabling flexible imaging control. Their safety profile is well-established from over 20 years of use. Microbubbles provide strong backscatter due to their low density and speed of sound, enhancing imaging contrast. Creating stable microbubbles requires specific techniques, such as high shear mixing or ultrasonication, to produce bubbles smaller than red blood cells.

Stability is enhanced through surfactants that reduce interfacial tension and gas diffusion, allowing for prolonged storage under specific conditions. In the body, the half-life of microbubbles is a few minutes, after which gases are exhaled and the shell metabolized. Understanding microbubble interaction with ultrasound involves principles like harmonic oscillators, where the bubble's response to applied pressure mirrors the behavior of a mass-spring system, enabling the derivation of formulations for oscillating gas bubbles in response to ultrasound.

The most extensively researched model over several decades is the Rayleigh-Plesset model, along with its various modifications. This model is a nonlinear second-order ordinary differential equation derived from the Navier-Stokes equation, assuming spherical symmetry. It describes the behavior of a bubble in an infinite medium exposed to ultrasound.

$$\rho\left(R(t)\ddot{R}(t) + \frac{3}{2}\dot{R}(t)^2\right) = (P_0 + 2\sigma/R_0 - p_v)\,(R_0/R)^{3\kappa} + p_v - (2\sigma/R(t)) - 4\mu\,(\dot{R}(t)/R(t)) - P_0 - P(t)$$

$$P_s(t) = \rho\,\frac{R(t)}{d}\,(2\dot{R}(t)^2 + R(t)\ddot{R}(t))$$

The Rayleigh-Plesset equation defines the time-dependent radial oscillation, where R(t) is the instantaneous radius of the bubble. The radial oscillations can be solved numerically, with ρ referring to the density. denotes the second derivative and $\dot{R}$ is the first derivative. P_0 is the ambient pressure, which is the sum of atmospheric pressure and hydrostatic pressure if the bubble is submerged. Sigma represents surface tension, p_v is the vapor pressure, R_0 is the initial or equilibrium radius, and κ is the polytropic exponent. P(t) is the excitation pressure of the ultrasound, and μ is the viscosity of the surrounding fluid. This is the Rayleigh-Plesset equation for an unshelled bubble; if a shell is introduced, additional terms are added. By solving this model, the time-dependent radial oscillations of the microbubble can be obtained, and the pressure can be derived from these oscillations using another equation. The pressure radiated at a particular distance can be calculated using a specific expression.

The Rayleigh-Plesset equation is highly nonlinear and complex. However, some intuitive understanding can be gained through simplification. If we assume that the bubble oscillations are small, we can linearize the equation and ignore the contributions of viscosity, vapor pressure, and surface tension, resulting in the Minnaert equation.

$$f = \frac{1}{2\pi R}\sqrt{\frac{3\gamma P}{\rho}}$$

This equation relates the resonant frequency f to the bubble radius, with constants like π, γ (the adiabatic index), P (ambient pressure), and ρ (density). The resonant behavior of microbubbles can be observed through a plot where the x-axis represents the radius in micrometers and the y-axis represents the resonant frequency in megahertz. For instance, a bubble with a resonant frequency of 10 MHz would have a radius of about 0.5 microns, while a bubble resonating at 4 MHz would have a radius close to 0.8 micrometers. The inverse relationship between the radius and resonant frequency is evident. The simplified Minnaert equation shows this, but other factors like shell properties, shell viscosity, shell stiffness, gas properties, and acoustic pressure also influence resonance frequencies when solving the full Rayleigh-Plesset equation.

$$\sigma_{SC} = 4\pi R_0^2 / \left([(\omega/\omega_0)^2 - 1]^2 + \delta^2_{TOT} \right)$$

The scattering cross-section, denoted as σ_{SC}, measures the strength of the bubble scatter and quantifies the total power of the scattered ultrasound relative to the incident ultrasound intensity. The scattering cross-section is given by an expression involving R_0 (initial radius), ω_0 (resonant frequency), ω (frequency), and δ_{TOT} (total damping). Damping occurs due to energy loss from bubble oscillations and can be caused by radiation of sound, viscous damping, or shell friction damping. At resonance, $\omega/\omega_0 = 1$, and the scattering cross-section increases sharply, being limited only by damping. This behavior is analogous to resonance in circuits where only the resistive component remains.

To characterize microbubbles, we need to measure their size distribution experimentally, as the microbubble size significantly influences its acoustic properties. Electro zone or impedance sensing is a gold standard technique for imaging microbubble size. It involves an electrode and a microfluidic channel through which a bubble passes, causing a change in impedance related to the microbubble size. A cuvette containing a dilute bubble suspension is used for this purpose. Measurements typically range from 400 nanometers to 15 micrometers, showing a log-normal type distribution that is somewhat polydisperse.

For characterizing acoustic properties, techniques like measuring scatter or attenuation from bubbles are used. Attenuation spectroscopy involves two confocal broadband PVDF transducers, with the bubble suspension placed in an acoustically transparent chamber between them. By measuring attenuation as a function of frequency, we can observe resonant frequencies. For example, for SonoVue, the resonant frequency is around 3 MHz, where the highest attenuation is observed. Stability of bubbles can be checked over time, as demonstrated by measurements over 1 hour and 30 minutes without significant changes in the attenuation coefficient.