Bubble dynamics involved in ultrasonic imaging

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In clinical ultrasound, blood cells cannot be differentiated from surrounding tissue, due to the low acoustic impedance difference between blood cells and their surroundings. Resonant gas bubbles introduced in the bloodstream are ideal markers, if rapid dissolution can be prevented. Ultrasound contrast agents consist of microscopically small bubbles encapsulated by an elastic shell. These microbubbles oscillate upon ultrasound insonification. Microbubbles with thin lipid shells have demonstrated highly nonlinear behavior. To enhance diagnostic ultrasound imaging techniques and to explore therapeutic applications, these medical microbubbles have been modeled. Several detection techniques have been proposed to improve the detectability of the microbubbles. A new generation of contrast agents, with special targeting ligands attached to the shells, may assist the imaging of nonphysical properties of target tissue. Owing to microbubble-based contrast agents, ultrasound is becoming an even more important technique in clinical diagnostics.

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Ultrasonic imaging is a relatively cheap, reliable diagnostic technique. Typical diagnostic ultrasonic frequencies range from 1 MHz (heart and liver) to 100 MHz (eye and skin). A signal generated by an ultrasonic transducer typically consists of a pulse of a few microseconds with an angular center frequency ω. Part of this signal propagates through target tissue, part is reflected by macroscopic tissue structures, part is absorbed by tissue, and part is scattered by structures in the tissue that are smaller than the acoustic wavelength. A small portion of the transmitted acoustic energy is received by the transducer, which is used to build an ultrasonic image. The received signal is the superposition of specular reflections at tissue boundaries and echoes from tissue backscattering. The quantity of signal specularly reflected from a boundary that separates tissues 1 and 2 depends on the acoustic impedance change in the tissue:

$$R_I = \frac{(Z_2 - Z_1)^2}{(Z_2 + Z_1)^2}$$ (1)

where $R_I$ is the intensity reflection coefficient. The acoustic impedance of a medium is defined by:

$$Z = \frac{\rho c}{\kappa}$$ (2)

where $c$ is the speed of sound in the medium, $\kappa$ is the compressibility and $\rho$ is the density.

Scattering

Scattering is far more complicated [1]; an inhomogeneity in the path of a soundwave causes it to spread out in a variety of directions [2]. The quotient representing the power scattered per unit solid angle and per unit incident intensity, is referred to as the differential scattering cross-section [2]. When the direction toward the receiver extends back to the source, such as in pulse-echo systems, it is termed backscattering. Under this condition, the backscattering cross-section $= 4\pi \times$ differential scattering cross-section [2]. When multiplying the differential scattering cross-section and the backscattering cross-section with the density of the scatterers per unit volume, the scattering and backscattering coefficients are obtained,
respectively. The backscattering coefficient of a medium containing a small concentration of fluid spheres with radii \( r \) is given by [3]:

\[
\eta(\omega) = 3k^2 \eta_0^2 r^2 \left( \frac{J_1(2kr)}{2kr} \right)^2
\]

where \( k \) is the acoustic wave number, \( J_1 \) is the first-order Bessel function of the first kind, and \( \eta_0 \) is the variance of the density/compressibility fluctuation:

\[
\eta_0^2 = N_0 \left( \frac{\kappa_1 - \kappa_0}{\kappa_0} \right) \rho_1 \rho_0 \left( \frac{\rho_1 - \rho_0}{\rho_0} \right)^2
\]

where \( N_0 \) is the number of scatterers per unit volume, \( \kappa_1 \) is the compressibility of the scatterer, \( \kappa_0 \) is the compressibility of the surrounding medium, \( \rho_1 \) is the density of the scatterer, and \( \rho_0 \) is the density of the surrounding medium.

From EQUATIONS 1 & 4, it can be seen that blood cells are poor scatterers in the clinical diagnostic frequency range. Since imaging blood flow and measuring organ perfusion are desirable for diagnostic purposes, a marker must be added to the blood. The marker helps to differentiate between blood and other tissue types, by providing additional and desirably characteristic backscatter [4]. Gas bubbles are suitable markers, not only because they have a high compressibility (gaseous microbubbles are 10,000-times more compressible than red blood cells [5]) and low density compared with the surrounding medium, but also because they resonate. For example, De Jong computed the scattering cross-section in water of a rigid iron sphere and a gas sphere, both with a 1-µm radius [6]. At a driving frequency of 3 MHz, the scattering cross-section of the gas sphere is 160 dB higher than that of the rigid sphere.

**Ultrasound contrast agents**

Microbubbles that are used for ultrasonic imaging purposes are termed ultrasound contrast agents. The development of these agents has gone through several generations [7]. TABLE 1 provides an overview of the ultrasound contrast agents that are most commonly used in imaging research. Free microbubbles represent generation 0. These bubbles rapidly dissolve owing to diffusion.

The change of gas bubble radius as a function of time, due to diffusion, is given by [8]:

\[
\frac{dr}{dt} = DL \left( \frac{C_1}{C_0} \left( 1 - \frac{2\sigma}{rp} \right) \rho_s^+ \left( \frac{1}{r} + \frac{1}{\sqrt{\piDt}} \right) \left( \frac{1}{r} \right) \right)
\]

where \( C_1/C_0 \) is the ratio of the dissolved gas concentration to the saturation concentration (saturation ratio), \( D \) is the diffusion constant, \( L \) is the Ostwald coefficient, \( p_0 \) is the ambient pressure, \( p_0^+ \) is the applied static overpressure, \( r \) is the instantaneous bubble radius, \( t \) is the time starting (\( t = 0 \)) when the bubble surface is exposed to the liquid surface, and \( \sigma \) is the surface tension. EQUATION 5 illustrates that the disappearance of gas

| Table 1. Overview of the most commonly used ultrasound contrast agents in diagnostic imaging research. |
| --- |
| **Agent** | **Manufacturer** | **Shell** | **Gas/vapor** | **Mean diameter (µm)** |
| --- | --- | --- | --- | --- |
| **First-generation: encapsulated air bubbles** | | | | |
| Albunex | Molecular Biosystems, Inc. | Albumin | Air | 4.3 |
| Levovist® | Schering AG | Lipid/galactose | Air | 2–3 |
| Sonovist® | Schering AG | Cyanoacrylate | Air | 1–2 |
| **Second-generation: encapsulated, low-solubility gas bubbles** | | | | |
| BR14 | Bracco Diagnostics Inc. | Lipid | C\(_3\)F\(_{10}\) | 2.5–3.0 |
| Definity® | Bristol-Myers Squibb | Lipid/surfactant | C\(_3\)F\(_{8}\) | 1.1–3.3 |
| EchoGen® | Sonus Pharmaceuticals, Inc. | Surfactant | C\(_3\)F\(_{12}\) | 2–5 |
| Imagent® | Alliance Pharmaceutical Corp. | Lipid/surfactant | N\(_2/C_6\)F\(_{14}\) | 6.0 |
| Optison™ | GE Healthcare | Albumin | C\(_3\)F\(_{8}\) | 2.0–4.5 |
| Quantison™ | Upperton Ltd | Albumin | Air | 3.2 |
| SonoVue® | Bracco Diagnostics Inc. | Lipid | SF\(_6\) | 2.5 |
| **Third-generation: particulated gas bubbles with controlled acoustic properties [31]** | | | | |
| AI-700 | Acusphere, Inc. | Polyactide co-glycolide | C\(_3\)F\(_{10}\) | 2 |
| CARDIOsphere® | POINT Biomedical Corp. | Polyactide | N\(_2\) | 4.0 |
| Sonazoid | GE Healthcare | Lipid/surfactant | C\(_3\)F\(_{10}\) | 2.4–3.6 |

**Note:** These classifications are approximate, since not all agents fit neatly into the generation categories. Adapted from [7,21–30].
bubbles in a liquid medium is highly influenced by gas diffusion parameters and applied overpressure, and that the disappearance time of gas bubbles is shorter when the liquid medium is under pressure. However, the difference is of a much smaller order than the half-size time of the bubbles (the time it takes for a bubble to dissolve until it has reached half its initial size [9]), as illustrated in Figure 1.

To prevent rapid dissolution, generation 0 microbubbles could have diameters of 80 µm, which would prevent them from passing the lung capillaries. First-generation ultrasound contrast agents consist of air bubbles encapsulated by a stabilizing shell. With mean diameters below 6 µm, these bubbles are small enough to pass through capillaries.

For encapsulated microbubbles, shell stiffness parameters $\chi$ and $S_{sh}$ have been introduced [6,10]:

$$\chi = \frac{S_{sh}}{8 \pi} \left(\frac{E}{1 - \nu}\right)$$

(6)

where $E$ is Young’s modulus, $\nu$ is the shell thickness, and $\nu$ is the Poisson ratio. For albumin and lipid nanoshells, it is assumed that $0.499 < \nu < 0.500$ [11]. The shell properties of an ultrasound contrast agent must be derived from experimental data. Second-generation agents consist of encapsulated gas microbubbles with an elastic shell. The linear angular resonance of microbubbles with a viscoelastic shell can be approximated by a Newtonian model [12,13]:

$$\omega_0^2 = \frac{3}{2} \left( \frac{\Gamma}{r_0} + \frac{2 \sigma \rho \Gamma}{r_0} \right) - \frac{2 \sigma \rho + 6 \chi}{r_0^3 \rho}$$

(7)

or by a viscoelastic model [14,15]:

$$\omega_0^2 = \frac{1}{r_0^2 \rho} \left( 3 \Gamma p_0 + \frac{4 \sigma_0 + 4 E}{r_0} \right)$$

(8)

Here, $r_0$ is the equilibrium bubble radius, $\Gamma$ is the polytropic exponent of the gas, $\rho$ is the density of the host medium, and $\omega_0$ is the angular resonance frequency. Clearly, if the size distribution of the microbubbles is wide, the agent will respond to a wide ultrasonic frequency band. If the size distribution of the microbubbles is narrow, the agent will be selective to a narrow frequency band.

When using perfluorocarbon gases rather than air, the microbubbles will first swell, due to the diffusion of dissolved gases into the bubbles, and then dissolve. The low diffusion rate of high-molecular-weight perfluorocarbons prolongs microbubble presence from seconds to minutes [4]. Often, the surface of the bubble shell has a negative charge, in order to prolong its presence in target tissue [16].

Agents can be designed to specifically target a receptor system [17], thus facilitating ultrasonic molecular imaging [18]. Third-generation ultrasound contrast agents consist of bubbles with these special targeting shell properties. Owing to primary radiation forces, microbubbles can be forced to translate away from the transducer, to vessel walls, thereby increasing the success rate of targeting [18,19]. Submicron contrast agents have also been of interest, because they can travel through the lymphatic system and are small enough to be extravasated from tumor neovascularity [5,20].

Ultrasound contrast agents have also been involved in therapeutic applications. Since any drug might, in some form, be attached to a bubble, the number of potential therapeutic applications of bubbles is virtually unlimited. This review’s scope is limited to diagnostic applications; hence, the physical mechanisms involved in bubble-imaging techniques are described.

Originally, ultrasound contrast studies were performed for left ventricular function and myocardial perfusion [31]. Currently, ultrasound contrast agents have, among others, been implicated in the following diagnostic techniques: imaging the heart [27], vasculature including vasa vasorum, liver, spleen [7], kidneys [32] and brain [33,34], measuring tissue perfusion [4] and ejection fractions [35], detecting focal lesions in the liver [36], angiogenesis assessment [37], characterizing tumors, and detecting sites of inflammation [26].

Contrast bubble models

The prediction of the dynamic behavior of ultrasound-insonified encapsulated microbubbles, in order to enhance detection techniques, has been of much interest. Their behavior has been studied with acoustic methods, such as the measurement of backscattering under different conditions [38], (high-speed) photography [9,39–41], and other optical methods, such as the dynamic measurement of light scattering [13].

The oscillating behavior of ultrasound contrast agent microbubbles in Newtonian fluids has been frequently described by a Rayleigh–Plesset–Noltingk–Nappiras–Poritsky (RPNP) equation, which is modified for the stiffness of a shell [6,42,43], and by a Herring equation, which is modified for a viscous shell [13,18,40].
Other models include a RPNP equation modified for the mechanical properties of the shell [44], a zero-thickness interface model [14], and a model accounting for variations in surface tension [45]. In general, the presence of blood has a relatively small effect on bubble dynamics [46]. The RPNP equation has been modified to include the shell properties stiffness and friction [47]:

\[ \rho r \ddot{r} + \frac{3}{2} \rho r^2 = \left( p_0 + \frac{2 \sigma}{r_0} \right) \left( \frac{r_0}{r} \right)^3 - \frac{4 \mu r}{r} - \frac{2 \sigma}{r} \]

(9)

where \( c \) is the speed of sound in the medium, \( p_g(t) \) is the driving acoustic pressure in time, \( S_0 \) is the shell friction, \( \mu \) is the shear viscosity of the medium, \( \omega \) is the angular driving frequency and \( \delta \) is the damping coefficient due to heat conduction [48]:

\[ \delta = \frac{\sinh z + \sin z}{3(\Gamma - 1) + \sinh z + \sin z} \]

(10)

where \( z = r_0/l_0 \), in which \( l_0 \) is the thermal boundary layer thickness:

\[ l_0 = \frac{K_g}{\chi^2 \rho_g C_p} \]

(11)

Here, \( C_p \) is specific heat of the gas, \( K_g \) is the thermal conductivity of the gas and \( \rho_0 \) is the density of the gas. Note that the vapor pressure of the liquid has been neglected, which is valid in the authors’ situation [49]. The modified RPNP equation is used for simulating bubble response to sonication at moderate acoustic pressures (i.e., mechanical index \([MI] \leq 0.6\) [9]). On clinical ultrasound devices, the intensity of the ultrasonic field is generally adjusted with a switch for the MI, rather than the acoustic amplitude. The MI is defined as \( MI = p^*/(f f_{0}) \), where \( p^* \) is the peak rarefractional acoustic pressure normalized by 1 MPa, and \( f \) is the center frequency of the ultrasound normalized by 1 MHz.

An example of simulated oscillating behavior of a microbubble is illustrated in Figure 2. The microbubble with half resonance size oscillates exactly \( \phi = \pi \) rad out of phase with the driving pressure \( p_0 = p^* \sin \omega t \), in which \( p^* \) is the peak-positive acoustic pressure. At resonance, \( \phi = (3/2)\pi \) rad, and at double resonance \( \phi = 2\pi \) rad. As the damping decreases, the transition in offset becomes more abrupt [48]. For microbubbles with thin elastic shells, the modified RPNP equation produces a slightly conservative estimate of the radial excursion, as opposed to the modified Herring equation [9]. The modified Herring equation is given by [13,40]:

\[ \rho r \ddot{r} + \frac{3}{2} \rho r^2 = \left( p_0 + \frac{2 \sigma}{r_0} + \frac{2 \kappa}{r_0} \right) \left( \frac{r_0}{r} \right)^3 - \frac{4 \mu r}{r} - \frac{2 \sigma}{r} \]

(12)

where \( \mu_s \) is the shell shear viscosity.

Equations 9 & 12 can only be solved numerically. Figure 3 illustrates solutions of the modified Herring equation, and Fourier-spectra thereof, at different acoustic amplitudes, for a bubble with a negligible shell. At 10 kPa, the bubble oscillates linearly, but at higher acoustic amplitudes, the bubble has a longer expansion than a contraction phase, and a higher outward than inward excursion. At 391 kPa, a slow expansion is followed by a rapid collapse, which is followed by a number of rebounds. Furthermore, the maximal bubble excursion is more than 12-times the equilibrium radius. The nonlinear behavior described here generates harmonics. Examples of the acoustic emission from ultrasound contrast agent bubbles can be appreciated in [20]. Figure 4 demonstrates the spectra of the ultrasound contrast agent Levovist®. The modified Herring equation used for simulating bubble response to sonication at moderate acoustic pressures (i.e., mechanical index \([MI] \leq 0.6\) [9]).
response to the highest driving amplitude has been attributed to microbubble disruption, which is discussed in a following section.

**Figure 5** illustrates $r-t$ curves computed with both models, for a free gas microbubble and for an encapsulated microbubble insonified at a relatively high acoustic pressure of 210 kPa. The curves are very similar for the free gas bubble and for the encapsulated bubble.

**Harmonic imaging**

At lower driving pressures, microbubbles produce linear backscatter enhancement, which only results in an augmentation of the echo from blood [31]. The nonlinear behavior of the microbubbles, which results in harmonic backscatter, can be used to discriminate blood from the surrounding tissue. The increase of nonlinear behavior with acoustic driving pressure is demonstrated in **Figures 3-5**. To suppress signals from tissue, a band pass filter around the second harmonic frequency component of the echo can be used to produce the ultrasound image [51]. This imaging technique is ineffective, due to the wide overlap of the base band and the second harmonic in broadband systems. Furthermore, this technique is not effective at high driving pressures, since tissue harmonics may interfere with the signals from the perfused areas. Therefore, nondestructive imaging is preferably performed at moderate acoustic pressures.

Given the lack of subharmonic generation in tissue, subharmonic imaging is an alternative [52]. However, subharmonic generation occurs only when the acoustic amplitude exceeds a certain threshold level. Goertz and coworkers recently demonstrated that microvessels can be successfully detected in vivo using subharmonic imaging with a transmit frequency of 20 MHz [53].
Multipulse techniques have been developed to enable the separation of contrast agent signals from tissue signals [51]. In these techniques, multiple pulses with modifications in amplitude (power modulation) [54,55], phase (pulse inversion) [55–57], or pulse length (pulse subtraction) [58] are transmitted rapidly after one another, after which the linear contribution in the echo signal is canceled out by summation or subtraction, leaving a residual signal containing harmonics (Figure 6). Overviews of multipulse imaging methods have been given in [57–59]. With the introduction of affordable broadband transducers, far more complicated pulse schemes have become possible, such as multifrequency excitation [58,60]. Since the bubble oscillation amplitude depends on the ambient pressure, a relatively low frequency can be used to modulate the ambient pressure, whereas a frequency close to bubble resonance is used to excite the bubble. Two-frequency excitation may be sufficient to induce nonlinear behavior of the microbubbles at moderate incident pressures [58]. Coded excitation, another technique, operates by transmitting a relatively long pulse (high energy) with a low amplitude (low destruction rate), which is decoded (compressed) to obtain sufficient axial resolution. The use of chirps (long bursts with increasing or decreasing instantaneous frequency) has been proposed for coded excitation [58].

**Microbubble disruption**

During the collapse phase, when the kinetic energy of the bubble surpasses its surface energy, a bubble may fragment into a number of smaller bubbles [41,61,62]. Fragmentation has been exclusively observed with contrast agents with thin, elastic shells. Fragmentation is the dominant disruption mechanism for these bubbles [61]. Thick-shelled bubbles have demonstrated gas release during a high-amplitude ultrasonic cycle [9,63,64]. The increased pressure difference between the inside and outside of the bubble during the ultrasonic wave causes the shell to be stretched across a critical deformation, resulting in its mechanical cracking. The released bubble has an oscillation amplitude much higher than an encapsulated bubble of the same size. Therefore, the acoustic signal from a contrast agent after gas release differs from that of the same contrast agent before gas release, until the released gas has dissolved.

The coalescence (merge) of ultrasound contrast agent microbubbles has been observed in vitro. However, long, low-amplitude bursts are needed for the forced approach of microbubbles, resulting in coalescence [9]. Therefore, this phenomenon is negligible in vivo.

Ultrasound-induced disruption of the microbubbles will result in strong, transient, harmonic echoes [65]. These strong echoes instantly reveal which areas on the resulting image represent perfused regions. After a disruptive ultrasonic burst, the disappearance of microbubble fragments or released gas may be traced with low-amplitude ultrasound, as well as the wash-in rate of fresh contrast agent [66]. Hydrostatic overpressures may be determined using the pressure-dependant changes in the echo signal. Making use of the subharmonic response leads to more precise sizing [9,67] and pressure measurements [43,68].

**Expert commentary**

According to the WHO, clinical considerations alone are not sufficient for a correct diagnosis in 20–30% of cases worldwide [101]. Of these cases, 80–90% can be diagnosed using common x-ray or ultrasound examinations [101]. The most commonly performed diagnostic imaging technology is x-ray, followed at a distance by ultrasound. For example, in Ontario, Canada, 63% of the diagnostic imaging examinations in hospitals are performed with x-ray, 16% with ultrasound, 9% with computed tomography, 7% with nuclear medicine, 4% with magnetic resonance imaging and 1% with catheterization [69]. When the absolute hospital operating expenses are considered, x-ray and ultrasound have approximately the same price per examination [69]. Other imaging techniques are roughly three-times as expensive, except...
for catheterization, which is 20-times as expensive. However, x-ray is a less desirable imaging technique than ultrasound, due to the negative radiation effects. Therefore, novel ultrasound-based imaging techniques are being developed that may compete with other imaging techniques.

The main disadvantage of ultrasonography has been that only physical properties of the tissue are imaged. A new generation of ultrasound contrast agents may help to overcome this limitation, where ligands with specific targeting properties are attached to the shell of the microbubbles. Such agents would certainly be more expensive than the current second-generation agents. However, by providing accurate and reliable early diagnosis, contrast sonography could reduce downstream resource use, and thus reduce overall healthcare costs, thereby justifying incremental examination costs [4].

Five-year view

Ultrasonic contrast-enhanced imaging applications depend on the detectability of microbubbles. In turn, the detectability depends on the ultrasonic pulsing scheme. Initiatives have been undertaken to find the optimal pulse sequence for a maximal contrast-to-tissue ratio in combination with an imaging resolution that is as high as possible. Enhancement in image quality owing to coded excitation has been anticipated in the near future. It should be noted that, if the bubble populations have a narrower size distribution and uniform shell thicknesses, ultrasound contrast agent bubble responses will be more accurately predicted.

Figure 6. Multipulse contrast-specific imaging by phase modulation (A) and amplitude modulation (B). (A) Two incident pulses are used with the same amplitude, but opposite phases. (Aii) After summation, signal echoes from linear scatterers cancel out. (Aiii) Signal echoes from nonlinear scatterers do not fully cancel out after summation, leaving a residual signal containing even harmonics. (B) Two incident pulses are used with the same phase, but amplitudes differing by a factor of two. (Bii) After subtraction, signal echoes from linear scatterers cancel out. (Biii) Signal echoes from nonlinear scatterers do not fully cancel out after subtraction, leaving a residual signal containing harmonics. Reproduced with kind permission from [51] ©2005 Springer Science and Business Media.

Figure 5. Computed solutions of the modified Rayleigh–Plesset–Noltingk–Neppiras–Poritsky equation (dotted line) and the modified Herring equation (solid line). The following values were used for these equations: \( c = 1480 \text{ m s}^{-1} \), \( \omega \pi / 2 \approx 0.5 \text{ MHz} \), \( p_0 = 1 \text{ atm} \), \( \rho = 210 \text{ kPa} \), \( r_0 = 0.75 \mu \text{m} \), \( \varepsilon = 20 \text{ nm} \), \( \mu = 10^{-3} \text{ Pa s} \), \( \rho = 998 \text{ kg m}^{-3} \) and \( \sigma = 0.072 \text{ N m}^{-2} \). (A) \( r-t \) curves of a free gas bubble, with \( \dot{S} = 0 \text{ kg s}^{-1} \), \( \dot{\delta} = 0 \text{ kg s}^{-1} \), \( \mu = 10^{-1} \text{ Pa s} \) and \( \chi = 1.1/8 \pi \text{ kg s}^{-2} \). The shell stiffness, \( \chi \), has been determined in [10].

\[ P_1 (\text{positive}) \quad P_2 = -P_1 (\text{negative}) \]

\[ \begin{align*}
  &\text{i) Incident pulse} \\
  &\text{ii) Linear scatterers} \\
  &\text{iii) Nonlinear scatterers} \\
  &\text{Sum} \\
\end{align*} \]

\[ \begin{align*}
  &\text{i) Incident pulse} \\
  &\text{ii) Linear scatterers} \\
  &\text{iii) Nonlinear scatterers} \\
\end{align*} \]

\[ P_1 - 2 \times P_2 \]

P1: Pulse 1; P2: Pulse 2.
Ultrasound images acquired using lipid-shelled microbubbles targeted to leukocytes were presented in [70]. The high resolution of these in vivo images in comparison with the ex vivo gamma camera images of the same tissue samples is striking. The potential of targeted ultrasonic imaging is clearly demonstrated.

Ultrasonically-induced release of therapeutic substances from microbubbles has been proposed in numerous papers [71–73]. The combination of diagnostic, targeted microbubbles with therapeutic substances may lead to a simple method to instantly cure upon diagnosis. Both diagnosis (through ultrasonic imaging) and therapy (through ultrasound-induced release) could be performed with one device.

Contrast agents for magnetic resonance imaging have been designed to accumulate in specific cells [1,74]. As opposed to ultrasound contrast agents, whose microbubbles are limited to flowing through vessels, magnetic resonance contrast agents consist of nanoparticles that are small enough to access cells. Therefore, undesirable accumulation of magnetic resonance contrast agent takes place in organs other than the imaged organ. To overcome this, nanometer-sized magnetic resonance markers may be coupled to microbubbles. In the organ to be imaged, these markers are released with a high-MI ultrasonic burst. This will result in an increase of the uptake of magnetic resonance contrast agent by the targeted organ. Radionuclides used for positron emission tomography might also be encapsulated by microbubbles, in order to reduce unspecific binding.

Increasing concern has been shown for ultrasound safety issues when using ultrasound contrast agents [75]. Although no side effects have been officially reported [4], the current acoustic amplitudes permitted are based on tissue without cavitation nuclei, such as microbubbles. Since the use of ultrasound contrast agents has become increasingly popular, and their applications have been multiplied, a new safety standard in ultrasonic imaging should be defined in the near future.

In conclusion, ultrasound is becoming an even more important technique in clinical diagnostics.

**Key issues**

- Predicting the transient behavior of microbubbles has been of much interest.
- The detection of the presence of bubbles can be enhanced by:
  - improving pulsing schemes
  - improving processing methods
  - improving bubble properties
- Ultrasonic imaging could be combined with other techniques, such as magnetic resonance imaging and positron emission tomography.
- A new safety standard in ultrasonic imaging should be defined in the future.

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