

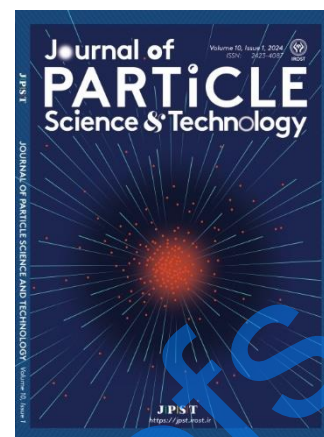
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Optimization of coated microbubble parameters for maximum subharmonic response in ultrasound imaging

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Abstract

Coated microbubbles have become important ultrasound contrast agents because of their nonlinear oscillatory behavior, particularly their ability to generate subharmonic signals. These signals can improve the contrast-to-tissue ratio and enhance imaging quality through deeper penetration and lower attenuation. However, the strength of the subharmonic response is highly dependent on several parameters, including the initial bubble radius, excitation frequency, and acoustic pressure amplitude. Inappropriate parameter selection may reduce signal quality or even lead to microbubble destruction. In this study, a genetic algorithm was used as a metaheuristic optimization method to determine the optimal excitation conditions for maximizing subharmonic response intensity. The dynamic behavior of coated microbubbles was modeled using the modified Rayleigh-Plesset equation combined with the Marmottant shell model. The optimization objective was defined as the maximization of subharmonic scattering power by varying key parameters such as initial radius, excitation frequency, and pressure amplitude. The results showed that optimal performance was achieved for initial radii of 3–4 μm , excitation frequencies around 2 MHz, and pressure amplitudes between 1500 and 1800 kPa. Moreover, simultaneous multi-parameter optimization proved more efficient than single-parameter optimization, enabling more stable and effective operating conditions for enhanced ultrasound imaging. Unlike traditional studies that primarily focus on single-parameter sensitivity analysis, this research introduces a robust multi-parameter optimization framework. By leveraging Genetic Algorithms (GA), we address the intricate, nonlinear coupling between bubble radius, driving pressure, and excitation frequency. This approach moves beyond simple parameter sweeps to identify global optimal conditions for subharmonic response, offering a more comprehensive understanding of the acoustic-bubble interaction.

Keywords: coated microbubbles, ultrasound imaging, subharmonic response, genetic algorithm, excitation parameter optimization

1. Introduction

Cardiovascular diseases and cancer remain among the leading causes of mortality worldwide and impose a substantial economic burden on healthcare systems each year. In this context, the development of accurate, efficient, and safe diagnostic techniques plays a fundamental role in improving clinical outcomes and guiding effective treatment strategies [1]. Among the available imaging modalities, medical ultrasound has become one of the most important diagnostic tools because of its real-time imaging capability, favorable safety profile, noninvasiveness, and potential for functional assessment. These advantages provide ultrasound imaging with distinct practical benefits over other modalities such as magnetic resonance imaging (MRI) and computed tomography (CT), making it one of the most widely used techniques in clinical practice [2].

Ultrasound contrast agents (UCAs) are generally composed of gas-filled microbubbles with diameters in the range of approximately 2 to 10 μm , encapsulated by stabilizing shells made of lipids, proteins, or polymers [3]. Owing to their high compressibility and strong acoustic backscattering properties, these microbubbles can significantly enhance image contrast and improve the visualization of vascular structures and tissue perfusion. Beyond diagnostic imaging, UCAs have also found important applications in targeted drug delivery, molecular imaging, localized pressure estimation, and ultrasound-mediated therapeutic interventions, including selective destruction of malignant cells [4], [5]. Consequently, understanding and optimizing the dynamic behavior of coated microbubbles under acoustic excitation has become a major area of interest in biomedical ultrasound research.

A distinctive feature of encapsulated microbubbles is their nonlinear oscillatory response to ultrasound excitation. In addition to the fundamental response, these agents are capable of generating higher-order harmonics, subharmonics, and ultra-harmonics. Among these components, the subharmonic response is of particular importance because it can markedly improve the contrast-to-tissue ratio and

reduce interference from surrounding tissues, thereby enhancing imaging performance. The generation of subharmonic and ultra-harmonic components, however, requires sufficiently strong nonlinear oscillations and therefore occurs only when the excitation amplitude exceeds a specific threshold. This threshold is influenced by several factors, including bubble size, excitation frequency, and shell rheological properties such as viscosity and elasticity [6].

The mechanical behavior of UCAs is strongly governed by the properties of their encapsulating shell. Early generations of contrast agents were characterized by relatively stiff coatings and are often referred to as hard-shell agents [7]. Their structural characteristics motivated the first theoretical efforts aimed at modeling coated-bubble dynamics under ultrasound exposure. One of the earliest models was introduced by [8] for Albunex microbubbles, in which the shell was assumed to behave as a perfectly elastic material obeying Hooke's law and contributing no additional damping. This framework was later refined by [9] and [10], who incorporated shell shear viscosity into a modified Rayleigh–Plesset equation while assuming an incompressible shell. In 2000, Morgan et al. [11] further developed the theoretical description by proposing a modified Herring equation that included an elastic membrane term based on [12], allowing improved comparison with experimental observations over a range of bubble sizes. Subsequently, Khismatullin and Nadim [13] extended Church's model by considering the viscoelasticity and compressibility of the surrounding liquid and showed that these effects are generally of secondary importance in bubble dynamics.

Despite these developments, early shell models were still limited in their ability to capture important nonlinear mechanical features such as buckling and rupture. To address this limitation, Allen and Rashid [14] introduced nonlinear elasticity into shell modeling through nonlinear Hookean and neo-Hookean formulations. A major advance was achieved by Marmottant et al. [15], who developed the Marmottant model, now widely regarded as one of the most successful frameworks for describing the nonlinear

dynamics of coated microbubbles. This model explicitly accounts for key shell phenomena such as buckling, elastic expansion, and rupture, and predicts that after rupture the microbubble behaves similarly to a free gas bubble. A subsequent extension by [16] further broadened the model's applicability to bubbles with more solid-like shells.

In addition to accurately describing radial oscillations, the Marmottant model has proven particularly effective in predicting subharmonic generation. Sijl et al. [17] demonstrated that subharmonic emissions are strongly associated with rapid variations in shell stiffness caused by relatively small changes in bubble surface area. Katiyar and Sarkar [18] further showed that the subharmonic response depends sensitively on both excitation frequency and pressure amplitude, and introduced the concept of the subharmonic threshold as the minimum pressure required for the first appearance of subharmonic emissions.

More recent studies have continued to investigate the influence of shell properties and acoustic conditions on coated-bubble dynamics. Hosseini and Mahdi [19] examined the radial behavior of a coated bubble near a rigid wall using the Marmottant model and evaluated the corresponding scattered pressure. Their results demonstrated that shell viscosity, initial bubble radius, and bubble-wall distance all significantly affect both bubble oscillations and acoustic scattering. Mahdi, Khalili, and Rahimi [20] refined the Marmottant model by incorporating gradual post-rupture viscosity decay, providing a more precise description of microbubble dynamics. This approach reveals enhanced nonlinearity at high pressures, resulting in a significantly lower subharmonic threshold compared to conventional models. In a later study, Barkand and Mahdi [21] analyzed the shell shedding mechanism in phospholipid microbubbles through a mathematical model based on the modified Rayleigh–Plesset equation coupled with a shell shedding formulation, emphasizing the critical roles of excitation frequency and pressure amplitude in this process.

Experimental investigations have also highlighted the importance of bubble size distribution and acoustic excitation conditions. Gorce, Arditi, and Schneider [22] studied the acoustic response of SonoVue microbubbles and reported that a narrower size distribution produces a stronger and more uniform response around the resonance frequency. Similarly, [23] explored the effects of excitation frequency, pressure amplitude, and waveform on the subharmonic response of SonoVue microbubbles under controlled laboratory conditions. Their findings indicated that excitation frequencies close to the natural resonance frequency of the bubble, together with moderate acoustic pressures in the range of approximately 1–2 MPa, provide the highest efficiency for subharmonic generation.

Recent advances have underscored the significance of subharmonic microbubble emissions in modern ultrasound imaging and diagnostic monitoring. The subharmonic amplitude of single coated microbubbles was demonstrated to exhibit high ambient pressure sensitivity when driven near twice their resonance frequency, establishing that pressure-induced shifts in shell elasticity dictate nonlinear behavior [24]. Building upon this mechanism, Spiekhout et al. [25] introduced a dual-frequency subharmonic imaging modality utilizing a low-frequency bias field for non-invasive blood pressure estimation, achieving a high sensitivity of 0.5 dB/kPa in vitro. Furthermore, Chen et al. [26] reported that manipulating the initial shell state toward the elastic–buckling transition—via tailored multi-gas cores—reduces the subharmonic generation threshold by 12% and enhances scattered amplitude by up to 11 dB. While these studies demonstrate the critical role of shell mechanics and acoustic driving conditions, they primarily focus on fixed single-parameter adjustments or composition tuning, leaving the systematic, multi-parametric acoustic optimization of coated microbubbles unaddressed.

Given the broad and growing use of coated microbubbles in diagnostic and therapeutic ultrasound applications, the optimization of their excitation conditions has become an increasingly important research challenge. Because the subharmonic response depends on the complex interaction among

multiple parameters, conventional one-factor-at-a-time approaches may not be sufficient to identify the most effective operating conditions. In this regard, optimization techniques capable of exploring multidimensional parameter spaces with reduced computational cost and improved reliability are of considerable interest. Therefore, in the present study, a genetic algorithm is employed as a metaheuristic optimization tool to determine the optimal excitation parameters of coated microbubbles, including acoustic pressure amplitude, initial radius, and excitation frequency, with the aim of maximizing the subharmonic response. By combining a robust optimization framework with a physically realistic bubble-dynamics model, this study seeks to identify excitation conditions that can enhance ultrasound imaging performance and potentially support the development of more efficient microbubble-based therapeutic strategies.

Despite extensive studies on subharmonic emissions, a significant gap remains in understanding the multidimensional coupling between microbubble shell mechanics and external excitation parameters. Existing literature predominantly relies on one-factor-at-a-time (OFAT) approaches or grid-based searches, which fail to capture the nonlinear interactions in the parameter space and are computationally prohibitive for polydisperse populations typical of clinical environments. Furthermore, current optimization models often overlook the trade-off between maximizing subharmonic response and maintaining bubble stability under varying acoustic pressures. To address these limitations, this study proposes a robust framework utilizing a Genetic Algorithm (GA) coupled with the Marmottant model. Unlike conventional methods, the GA-based approach efficiently explores the complex, nonlinear landscape of excitation frequency and pressure, providing a computationally efficient solution for identifying optimal conditions that balance signal strength with physical stability.

2. Methods

2.1. Coated bubble dynamics

If a liquid containing a microbubble is exposed to an ultrasound field in which ambient pressure changes frequently and the amplitude of excitation pressure is significant enough, the microbubble starts to oscillate. In the simplest case, the microbubble is spherical during pressure fluctuations. The microbubble oscillations cause radial changes, which the mathematical equation can simulate. Most of the defined models for the encapsulated microbubbles are based on a modified RP equation. Added terms represent the contributions caused by viscoelastic stresses produced in the encapsulation. In these models, viscoelastic terms can be shown as two terms as $\gamma(R)$ and $\kappa^s(R)$, which are the effective surface tension and effective dilatational viscosity, respectively:

$$\rho \left(R\ddot{R} + \frac{3}{2}\dot{R}^2 \right) = P_{G0} \left(\frac{R_0}{R} \right)^{3k} \left(1 - \frac{3k\dot{R}}{c} \right) - \frac{2\gamma(R)}{R} - \frac{4\dot{R}}{R^2} \kappa^s(R, \dot{R}) - 4\mu \frac{\dot{R}}{R} - P_0 + p_A(t) \quad (1)$$

Where P_0 is the hydrostatic pressure, c is the speed of sound, and $p_A(t)$ is the excitation pressure considered sinusoidal in our investigations. Also, the initial conditions are $(t = 0) = R_0$ and $\dot{R}(t = 0) = 0$.

At high excitation pressure, Marmottant et al. [16] provided a model which considers three different states for the surface tension: the buckling state in which the surface tension of a coated bubble is supposed to be zero ($R \leq R_{buckling}$), the elastic state ($\sigma(R) = \chi(R/R_{buckling} - 1)$), and the rupture state in which the bubble is considered to be free (without shell), and in this state the radius of the bubble is larger than the efficient surface tension and dilatational interfacial viscosity are considered as:

$$\sigma(R) = \begin{cases} 0 & \text{if } R \leq R_{\text{buckling}} \\ \chi \left(\frac{R^2}{R_{\text{buckling}}^2} - 1 \right) & \text{if } R_{\text{buckling}} \leq R \leq R_{\text{break-up}} \\ \sigma_{\text{water}} & \text{if } R \geq R_{\text{ruptured}} \end{cases} \quad (2)$$

$$\kappa^S(R) = \text{constant}$$

$$R_{\text{break-up}} = R_{\text{buckling}} (1 + \sigma_{\text{break-up}} / \chi)^{1/2} \quad (3)$$

$$R_{\text{ruptured}} = R_{\text{buckling}} (1 + \sigma_{\text{water}} / \chi)^{1/2} \quad (4)$$

Where χ represents the shell elasticity modulus, R_{buckling} denotes the buckling radius (lower limit), $R_{\text{break-up}}$ signifies the radius at the onset of shell rupture, R_{ruptured} indicates the bubble radius post-rupture, and σ_{water} corresponds to the surface tension of the surrounding water. In this framework, the resonance frequency of the encapsulated microbubble is defined as:

$$f_0 = \frac{1}{2\pi R_0} \sqrt{\frac{1}{\rho} \left(3\gamma p_0 + \frac{2(3\gamma - 1)\sigma_w}{R_0} + \frac{4\chi}{R_0} \right)} \quad (5)$$

The modified RP equation for this model is defined as below.

$$\rho \left(R\ddot{R} + \frac{3}{2}\dot{R}^2 \right) = \left[P_0 + \frac{2\gamma(R_0)}{R_0} \right] \left(\frac{R_0}{R} \right)^{3\gamma} \left(1 - \frac{3\gamma\dot{R}}{c} \right) \quad (6)$$

$$, -\frac{2\gamma(R)}{R} - \frac{4\dot{R}}{R^2} \kappa^S - 4\mu \frac{\dot{R}}{R} - P_0 + P_A(t)$$

The mathematical model for the scattered pressure field is given by [1]:

$$p_{scat}(r, t) = \frac{\rho(R^2\ddot{R} + 2R\dot{R}^2)}{r} \quad (7)$$

Where p_{scat} denotes the scattered acoustic pressure, and r represents the radial distance from the bubble center.

2.1. Numerical procedure and optimization algorithm of microbubbles

The simulation and optimization process of the radial behavior of coated microbubbles based on the Marmottant model is structured as follows. In the first step, the input system parameters, including the physical and mechanical properties of the shell and the surrounding fluid (such as surface tension, density, viscosity, ambient hydrostatic pressure, and shell elasticity modulus), are loaded from the input dataset. Utilizing this information, the microbubble response matrix is initialized to facilitate subsequent dynamic analysis.

In the second step, the initial conditions of the system, comprising the initial radius and acoustic excitation parameters, are defined. Following the definition of these initial conditions, the genetic algorithm (GA) configurations are established, and an initial population of random values is generated for the decision variable(s)—such as the initial radius, excitation frequency, or acoustic pressure amplitude. Genetic operators, including crossover and mutation, are applied to the population members to generate new candidate solutions for evaluation in the objective function. In each iteration, the candidate parameter sets from the population are passed as inputs to the cost function. Within this function, the dynamic Marmottant model is executed, and the time-domain response of the bubble radius under acoustic excitation is simulated. The numerical solution of the nonlinear Marmottant differential equation is performed using the ODE45 solver in MATLAB. During this process, the ultrasound

excitation signal is generated as a time-domain pulse and applied to the model.

At the output of this stage, the temporal variations of the bubble radius and its derivative are calculated. Based on these data, the scattered pressure from the bubble surface is extracted as a function of time and stored in a matrix. Upon the completion of each excitation pulse, the obtained final radius is substituted as the new initial condition, and the simulation loop is repeated for the subsequent pulse. This procedure continues until the final pulse is processed, capturing the complete transient behavior of the bubble in the acoustic field. At the end of the simulation, the time-domain scattered pressure response is transformed into the frequency domain. For this purpose, the Fast Fourier Transform (FFT) is utilized to compute the frequency spectrum. From the resulting spectrum, the response amplitudes at the harmonic and subharmonic components are extracted, and their ratios relative to a reference value are calculated. These values serve as performance indicators for the cost function.

Subsequently, the genetic algorithm generates a new population of parameters based on the cost function evaluations, and the process is repeated. This evolutionary loop continues until the convergence criteria are met or the maximum number of generations is reached. Finally, the optimal combination of the influential parameters, including the initial radius, excitation frequency, and acoustic pressure amplitude, is extracted as the optimal solution, and the final plots, including the frequency response and scattering power, are generated. This step-by-step structure enables a detailed investigation of the excitation parameters' effects on the nonlinear and subharmonic response of microbubbles, providing a robust numerical framework for fitting the model to experimental data and optimizing excitation conditions in ultrasound imaging applications.

The primary objective of the optimization process is to maximize the subharmonic scattering efficiency of the coated microbubble, which is critical for enhancing contrast-to-tissue ratios in medical ultrasound imaging. The objective function, Φ , is mathematically defined as the peak amplitude of the

subharmonic component ($f_{ex}/2$) extracted from the frequency spectrum of the scattered pressure signal evaluated at a focal distance of 75 mm.

The optimization problem is formulated as follows:

$$\Phi(f_{ex}, P_a, R_0) = \max(|\mathcal{F}\{p_{scat}(t) \cdot w(t)\}|_{f_{ex}/2})$$

where:

- $p_{scat}(t)$ is the time-domain scattered pressure signal obtained by solving the nonlinear Marmottant model using the 4th-order Runge–Kutta method (ode45 in MATLAB);
- $w(t)$ is the Hanning window function, applied to the temporal signal (a five-cycle windowed-Hanning sinusoidal pulse) to suppress spectral leakage in the FFT;
- $\mathcal{F}$ denotes the Fast Fourier Transform (FFT) operator;
- f_{ex} , P_a , and R_0 are the decision variables, representing the excitation frequency, the acoustic pressure amplitude, and the initial bubble radius, respectively, with R_0 constrained to the search range of 2–10 μm .

The shell behavior in the Marmottant model is governed by the radius-dependent surface tension:

$$\sigma(R) = \begin{cases} 0 & R \leq R_{buckling} \\ \chi \left(\frac{R^2}{R_{buckling}^2} - 1 \right) & R_{buckling} \leq R \leq R_{break-up} \\ \sigma_{water} & R \geq R_{ruptured} \end{cases}$$

with the shell elasticity modulus $\chi = 0.54$ N/m, shell surface viscosity $\kappa_s = 7.2 \times 10^{-8}$ kg/s, water surface tension $\sigma_{water} = 0.072$ N/m, and polytropic exponent $\gamma = 1.07$. Note that the shell surface tension dynamically varies with radius across three states—buckling, elastic deformation, and rupture—

rather than remaining constant, which dominates the nonlinear subharmonic response under diagnostic acoustic pressures.

To ensure physical validity and structural integrity of the encapsulated bubble, a constraint is integrated into the optimization through a penalty formulation:

Maximize Φ subject to $R_{max} < R_{ruptured}$

where R_{max} is the maximum instantaneous bubble radius during the oscillation cycle. Any candidate solution yielding $R_{max} \geq R_{ruptured}$ is discarded by the Genetic Algorithm (GA), thereby restricting the search space to the region of stable, non-ruptured bubble oscillations. GA was selected because it handles the non-convex, multi-modal search landscape induced by the discontinuities of the Marmottant surface-tension law more robustly than gradient-based methods. This formulation reflects the signal-processing chain implemented in the underlying study — numerical solution of the Marmottant equation, Hanning windowing, spectral analysis via FFT, and extraction of the $f/2$ amplitude — and therefore renders the optimization procedure fully reproducible.

3. Validation

To assess the accuracy of the bubble dynamics simulation results, the reference data reported in [24] were used. For a direct comparison between the experimental and simulated values, all FFT amplitude values were normalized with respect to a reference value. This reference value corresponded to the maximum scattered power from a microbubble with an initial radius of $R_0 = 4.9 \mu\text{m}$ under a pressure amplitude of 100 kPa at the same focal distance. The excitation signal was a five-cycle Hanning-windowed sinusoidal burst with a frequency of 2 MHz and a maximum negative pressure amplitude of 100 kPa. The receiver transducer for the bubble response signal was located at a focal distance of 75mm. In modeling the effects of the shell, a shell elasticity of $\chi = 0.54 \text{ N/m}$ and a shell viscosity of $\kappa_s =$

$2 \times 10^{-8} \text{ kg s}^{-1}$ were considered for this microbubble. The radial variations induced by excitation and the scattered pressure of this single bubble, as a representative of the bubbles investigated within this radial range, are shown in Figures 1 and 2, respectively.

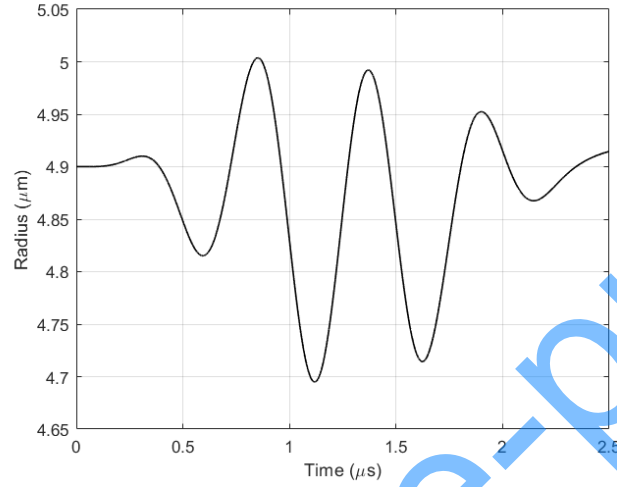


Figure 1. Radial variations of a single BR14 microbubble with an initial radius of $R_0 = 4.9 \text{ μm}$ excited by a five-cycle Hanning-windowed sinusoidal burst with a frequency of 2 MHz and a maximum negative pressure amplitude of 100 kPa.

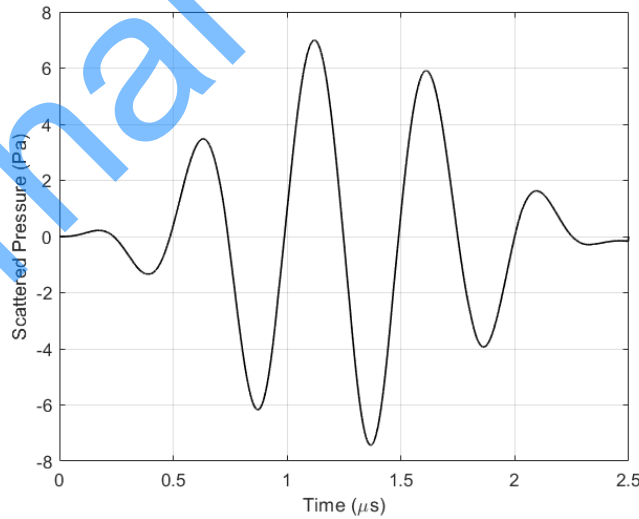


Figure 2. Scattered pressure from a single BR14 microbubble with an initial radius of $R_0 = 4.9 \text{ μm}$, excited by a five-cycle Hanning-windowed sinusoidal burst with a frequency of 2 MHz and a maximum negative pressure amplitude of 100 kPa, at a focal distance of 75 mm.

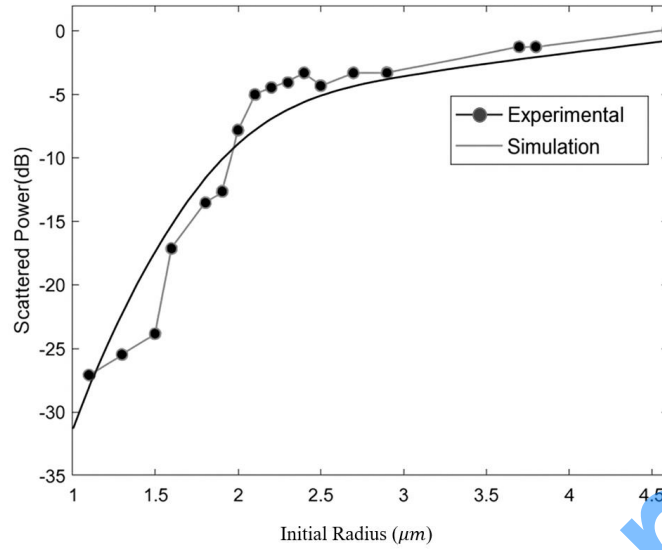


Figure 3. Comparison between the measured fundamental response reported in (Van der Meer et al., 2007)[27] and the simulated response as a function of bubble radius at a pressure amplitude of 100 kPa and a frequency of 2 MHz.

These metrics quantitatively confirm that the simulated response is in strong agreement with the experimental behavior under the tested acoustic excitation (100 kPa, 2 MHz).

To verify the numerical scheme and the optimization framework, the computer program was subjected to internal validation. First, the subharmonic response of a microbubble with the physical properties listed in Table 1 was calculated manually across discrete excitation frequencies. The discrete scattering power points were then compiled to reconstruct the continuous frequency response curve. The Marmottant model was solved using the fourth-order Runge–Kutta method (ode45 in MATLAB) over five acoustic cycles to ensure steady-state conditions. Next, the same optimization problem was solved using the proposed genetic algorithm (GA). The genetic algorithm was executed using MATLAB's Global Optimization Toolbox with a population size of 40, a maximum of 60 generations, a crossover fraction of 0.8, an adaptive mutation rate of 0.05, and an elite count of 2, while retaining default configurations for the remaining internal operators.

Table 1. Parameter Values Considered for Validation.

Symbol	Parameter	Value	SI Unit
R_0	Initial radius	4.9	μm
χ	Shell elasticity	0.54	Nm^{-1}
σ_0	Surface tension of water	0.072	Nm^{-1}
P_0	Atmospheric pressure	100	kPa
κ_s	Surface dilatational viscosity of the shell	2×10^{-8}	kg s^{-1}
c_L	Speed of sound	1500	m s^{-1}
γ	Polytropic exponent	1.07	Dimensionless
μ_L	Viscosity	0.0015	$\text{kg m}^{-1}\text{s}^{-1}$
ρ_L	Density of the surrounding fluid	1000	kg m^3
r	Focal distance	75	mm
fs	Sampling frequency	1000	MHz

The excellent agreement between the manually reconstructed response (Figure 4) and the GA-optimized curve (Figure 5) confirms the accuracy of the numerical solver and demonstrates the robustness of the GA in identifying the peak subharmonic scattering power.

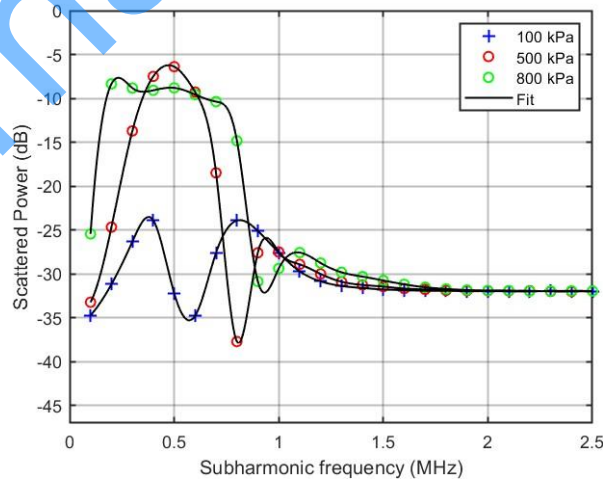


Figure 4. Comparison of the subharmonic scattering power as a function of excitation frequency for three acoustic pressure levels of 100, 500, and 800 kPa.

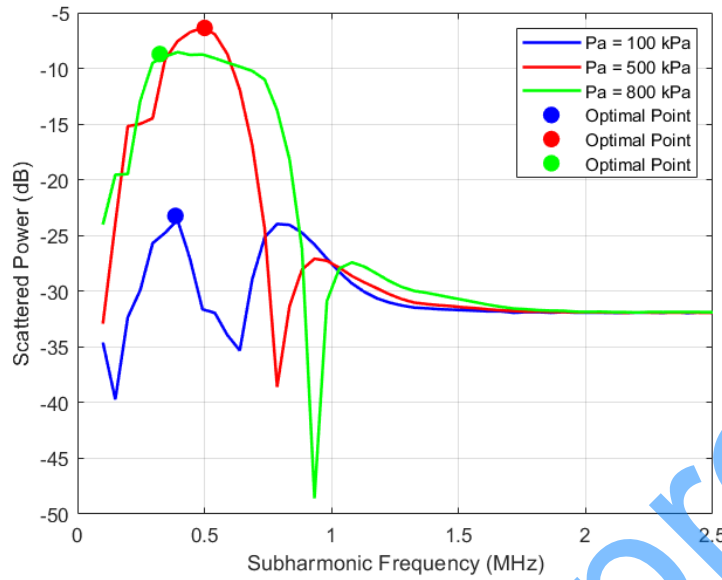


Figure 5. Comparison of the subharmonic scattering power as a function of excitation frequency for three acoustic pressure levels of 100, 500, and 800 kPa using the genetic algorithm. The solid circular points represent the location of the maximum scattering power for each pressure level.

The GA simulations were executed under three acoustic pressure levels (100, 500, and 800 kPa) with an initial bubble radius of $R = 4.9 \mu\text{m}$. The fitness function was defined to maximize the subharmonic scattering component. The results revealed that increasing the excitation pressure shifted the optimal frequency toward higher ranges. Specifically, the GA identified optimal excitation frequencies in the range of 2.0–5.0 MHz (corresponding to subharmonic frequencies of 1.0–2.5 MHz), which maximized the subharmonic power at all three pressure levels. This indicates that excitation intensity governs not only the amplitude of the subharmonic signal but also shifts the frequency matching condition. Consequently, coupling the modified Marmottant model with a GA optimization scheme provides a powerful tool for designing optimal ultrasound contrast imaging protocols.

4. Results and discussion

Following validation, simulations were performed using parameter ranges typical of clinical

diagnostic ultrasound. To determine the optimal initial radius (R_0) yielding maximum subharmonic scattering, a MATLAB code integrating the Marmottant model with a GA was implemented. The Genetic Algorithm (GA) was chosen as the global optimization framework primarily due to the severe nonlinearity, non-convexity, and non-differentiability of the underlying objective function. Because evaluating the subharmonic emission requires numerical integration of the piecewise Marmottant equation followed by Fourier spectral decomposition, the resulting parameter landscape exhibits non-smooth thresholds and multiple local extrema corresponding to harmonic and superharmonic resonances. Deterministic gradient-based methods are inapplicable in the absence of analytical derivatives, while local direct searches (such as pattern search) are prone to entrapment in sub-optimal local basins. GA effectively circumvents these limitations by maintaining population diversity via stochastic crossover and adaptive mutation operators, providing robust global exploration across the threshold-driven acoustic domain without requiring smoothness or differentiability assumptions.

The system parameters were kept consistent with Table 1. The excitation parameters were fixed at a center frequency of 2 MHz and a pressure amplitude of 100 kPa. To emulate a clinically realistic polydisperse agent, the GA (population size = 50) searched a size range of 2–10 μm , assuming a Gaussian distribution of bubble radii.

To optimize the initial bubble radius (R_0) for maximizing subharmonic response, a Genetic Algorithm (GA) was implemented in the MATLAB environment. The optimization search space was constrained between 2 μm and 10 μm , utilizing a population size of 50 and 5 generations to ensure convergence. The bubble dynamics were modeled using the Marmottant formulation, with shell elasticity $\chi=0.54\text{N/m}$, polytropic index $k=1.07$, and shell dilatational viscosity $\kappa_s=2 \times 10^{-8}\text{kg/s}$. The objective function targeted the subharmonic amplitude at $f/2$, computed through a 100,000-point Fast Fourier Transform (FFT) of the scattered acoustic pressure. The simulation employed a 5-cycle sinusoidal burst

windowed by a Hann function, solved via the ode45 numerical solver with relative and absolute tolerances set to 10^{-9} to maintain high computational precision and ensure reproducibility.

The GA utilized 300 function evaluations (Population Size=50×5 Generations + 50 initial) to converge to the optimal radius of 4.13 μm . In contrast, to achieve an equivalent resolution of 0.01 μm over the entire search domain (2–10 μm), an exhaustive grid search would require 800 function evaluations. This indicates that our GA approach achieves the global optimum with approximately 60% fewer computational resources. Furthermore, to verify the robustness of the GA, we performed 10 independent optimization runs with randomized initial populations. The algorithm consistently converged to the same optimal radius ($R \approx 4.13\mu\text{m}$), demonstrating high repeatability and robustness compared to parameter sweeps that may overlook local features if the grid density is insufficient.

Figure 6 shows the subharmonic scattering power as a function of the initial microbubble radius. The response exhibits a distinct resonance peak. The scattering power rises with increasing radius until it reaches a maximum of -24.52 dB at an optimal radius of $R \approx 4.13\text{ }\mu\text{m}$. Beyond this optimal size, the scattering power rapidly decreases and plateaus. These findings indicate that contrast agent suspensions with narrow size distributions centered around 4 μm can significantly maximize backscattered subharmonic signals under these excitation conditions. Increasing acoustic pressure amplitude beyond the threshold ($P_a > P_{\text{thresh}}$) does not merely elevate the acoustic energy; it triggers a period-doubling bifurcation in the radial oscillation. According to the Marmottant model, higher excitation pressures force the lipid monolayer into the nonlinear buckled state, producing asymmetrical radial excursion. This sharp nonlinearity breaks the symmetric energy distribution and funnels scattered energy directly into the subharmonic frequency component ($f/2$).

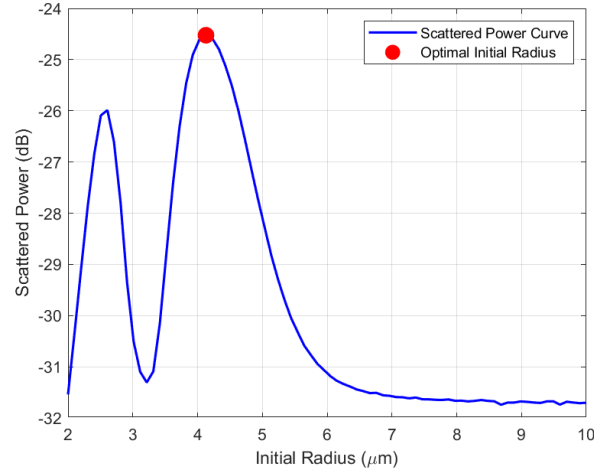


Figure 6. Variations of the scattering power as a function of the initial microbubble radius at an excitation frequency of 2 MHz and an acoustic pressure amplitude of 100 kPa.

To evaluate the convergence characteristics of the optimization process, the generation history is shown in Figure 7. The GA framework demonstrated rapid improvement during the first 15 generations, steadily progressing from an initial mean scattered power of approximately -35.5 dB to the global optimal response. Full asymptotic convergence was achieved around Generation 25, consistently stabilizing at the maximum subharmonic scattered power of -24.52 dB ($R_0 = 4.13 \mu\text{m}$), confirming the computational efficiency and stability of the algorithm.

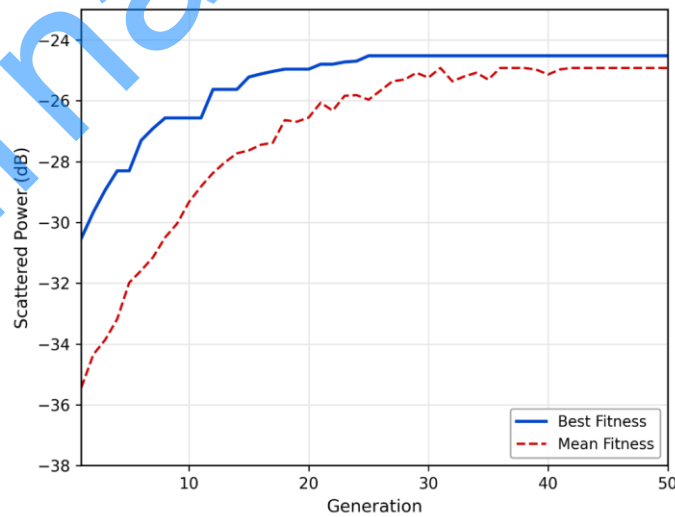


Figure 7. Convergence history of the GA for RO optimization, showing best (solid blue) and mean (dashed red) fitness across 50 generations.

To account for the stochastic nature of the genetic operators, several independent runs with varying random seeds were conducted. The optimization consistently converged to $R_0 \approx 4.13 \mu m$ (peak response $\approx -24.52 \text{ dB}$) with minimal variance ($<0.5\%$), confirming the repeatability and robust convergence of the GA to the true physical resonance. While this study focused on maximizing the subharmonic scattered power to improve contrast-enhanced ultrasound imaging, it is important to acknowledge that clinical image quality is a multifactorial construct. Parameters such as Contrast-to-Tissue Ratio, signal-to-noise ratio, beamforming techniques, and frequency-dependent attenuation also play critical roles. Our optimization framework specifically targets the maximization of the ‘acoustic source strength’ (the microbubble response), which serves as the fundamental physical driver for enhanced contrast.

Next, the acoustic driving pressure was optimized while fixing the initial bubble radius at $R = 4.9 \mu m$ and the frequency at 2 MHz. The GA searched a pressure range of 500–2500 kPa with a population size of 50. The fitness function was defined as the subharmonic component of the scattered acoustic pressure spectrum. As shown in Figure 8, the subharmonic scattering power initially increases with rising pressure amplitude. The GA identified an optimal excitation pressure of 1792.63 kPa $\approx 1800 \text{ kPa}$, yielding a maximum subharmonic power of -9.52 dB .

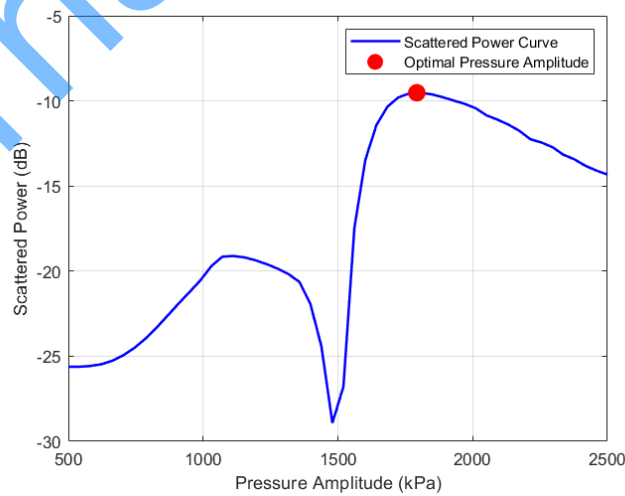


Figure 8. Variations in the scattering power as a function of the excitation pressure amplitude of the microbubbles at an excitation frequency of 2 MHz and an initial radius of $R_0 = 4.9 \mu m$.

Increasing the pressure beyond this threshold leads to a decline in subharmonic emission, approaching a plateau. This decline is attributed to shell saturation effects and potential shell rupture, suggesting that excessively high pressures are counterproductive for subharmonic imaging.

To capture parameter interactions, a dual-parameter optimization framework was executed. The GA optimized both the initial radius ($R \in [1, 10] \mu\text{m}$) and the acoustic pressure amplitude ($P \in [500, 2000] \text{ kPa}$) simultaneously at a fixed frequency of 2 MHz. The GA was configured with a population size of 250 over 30 generations. Figure 9 displays the optimization results. The left panel shows the subharmonic power versus the initial radius for three pressure amplitudes (500, 1000, and 1500 kPa). The nonlinear resonance of the shell-gas system peaks within a narrow size range of 3–4 μm . The right panel illustrates the subharmonic power versus the pressure amplitude for four bubble sizes (2.5, 3.5, 4.5, and 5.5 μm). While higher pressures generally enhance subharmonic emissions, saturation occurs at elevated pressures due to viscoelastic shell damping and highly nonlinear energy dissipation. The GA converged to an optimal initial radius of $R \approx 3.5 \mu\text{m}$ and an excitation pressure in the range of 1500–1800 kPa, achieving a maximum subharmonic scattering power of approximately 7 dB.

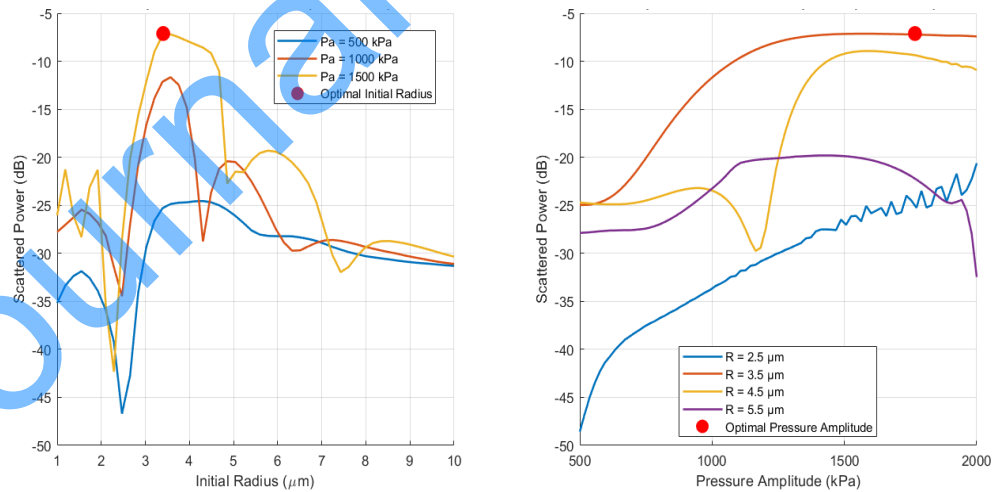


Figure 9. Left: Subharmonic scattering power versus initial radius for three distinct excitation pressure amplitudes (the red dot highlights the optimal initial radius of $\sim 3.5 \mu\text{m}$ under a 1500 kPa excitation pressure). Right: Subharmonic scattering power versus excitation pressure amplitude for three distinct initial radii (the red dot denotes the optimal excitation pressure of $\sim 1800 \text{ kPa}$ for an initial bubble radius of 3.5 μm).

Lastly, the excitation frequency ($f \in [2, 6]$ MHz) and pressure amplitude ($P \in [800, 2800]$ kPa) were simultaneously optimized for a fixed microbubble size of $R = 4 \mu\text{m}$. The GA utilized a population of 250 over 30 generations. Figure 10 presents the two-dimensional parameter sweeps. In the left panel (power vs. frequency at 800, 1800, and 2800 kPa), increasing the pressure shifts the subharmonic peak frequency. In the right panel (power vs. pressure at 2, 4, and 6 MHz), the subharmonic response saturates beyond a critical pressure threshold. The GA identified the global optimum at a center frequency of approximately 2 MHz and an acoustic pressure of 1500–1800 kPa, producing a peak subharmonic power of approximately 8 dB. These results highlight the necessity of multi-parameter co-optimization. Unlike conventional single-parameter sweeps, this simultaneous approach identifies synergistic parameter combinations that maximize subharmonic scattering efficiency, providing a design basis for advanced subharmonic ultrasound imaging protocols.

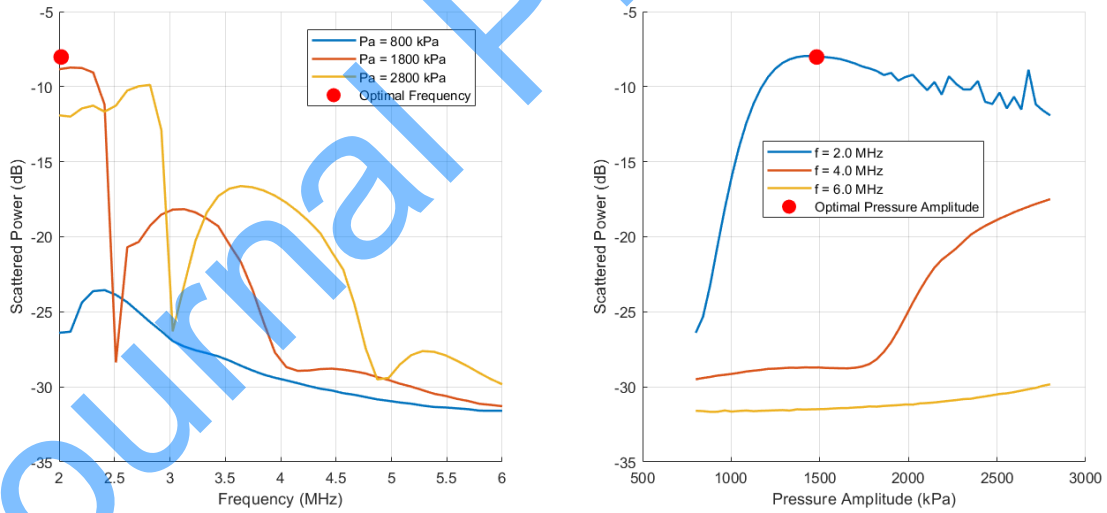


Figure 10. Scattering power as a function of excitation frequency for three different excitation pressure amplitudes, where the red dot indicates the optimal frequency of approximately 2 MHz for a pressure amplitude of 1800 kPa (left). Scattering power as a function of excitation pressure amplitude for three different excitation frequencies, where the red dot indicates the optimal excitation pressure amplitude of approximately 1500 kPa for a frequency of 2 MHz (right).

The frequency dependence reflects the shift in the nonlinear threshold and shell damping. Optimal subharmonic generation occurs when the drive frequency operates in the second harmonic regime of the bubble's eigenfrequency ($f \approx 2f_0$). Excitations below this band fail to achieve the nonlinear threshold needed for bifurcation, whereas higher frequencies substantially increase viscous and acoustic radiation damping, which suppress shell excursions and diminish the subharmonic amplitude.

A notable distinction exists between the validation range (100–800 kPa) and the theoretical optimization results (1800 kPa). The validation phase was strictly bounded by established experimental protocols and clinical safety limits to ensure model fidelity against verified benchmarks. Conversely, the optimization analysis explored the extended parameter space of the Marmottant model to identify the theoretical global maximum of subharmonic scattering. While the model predicts a peak response at 1800 kPa, this regime likely represents a highly nonlinear, non-clinical threshold where bubble dynamics exhibit extreme sensitivity. Future iterations of this model should integrate a 'Clinical Safety Constraint'—specifically an upper bound on the Mechanical Index (MI)—to ensure that the optimized parameters remain within the scope of practical medical imaging and patient safety.

It is noteworthy that the scattering power values exhibit significant sensitivity to the acoustic pressure amplitude (Pa). Our analysis reveals two distinct regimes: a low-pressure linear regime ($P_a \approx 100$ kPa), yielding a subharmonic response of approximately -24.5 dB, and a high-pressure nonlinear regime ($P_a = 1.5$ – 1.8 MPa), where the subharmonic component is enhanced to -7 dB. This observed increase confirms that nonlinear oscillation regimes effectively trigger superior subharmonic scattering, justifying the search within the 1.8 MPa range.

In this study, the optimization framework focused specifically on operational imaging parameters (f , P , and R_0) for a pre-characterized lipid-shelled agent, with shell properties (such as elasticity χ) held constant based on established literature. While minor variations in shell elasticity may slightly shift the

acoustic resonance frequency, the core nonlinear mechanisms governing subharmonic emission remain robust. However, conducting a comprehensive multi-parametric sensitivity analysis encompassing batch-to-batch shell viscoelastic variations represents a valuable direction for future studies focused on microbubble synthesis and customized contrast agent design.

5. Conclusion

In this study, the excitation parameters of coated microbubbles, including the initial radius, acoustic pressure amplitude, and excitation frequency, were numerically optimized using a genetic algorithm to maximize the subharmonic response. The results demonstrated that subharmonic emission strongly depends on the simultaneous selection of these parameters, proving that multi-parameter optimization provides superior insight compared to single-parameter tuning. Specifically, the optimal initial radius was identified around 3–4 μm , the optimal acoustic pressure in the range of 1500–1800 kPa (beyond which response saturation and shell rupture risks increase), and the optimal excitation frequency around 2 MHz (exhibiting pressure-dependent shifts). Under these optimal conditions, the subharmonic scattering power reached approximately –7 to –8 dB.

These findings confirm that the genetic algorithm serves as an efficient *in silico* framework for multivariable optimization of microbubble dynamics. While these theoretical predictions offer a robust benchmark for contrast-enhanced ultrasound tuning, future experimental validations using tissue-mimicking phantoms and *in vitro* setups are essential to confirm their practical applicability under clinical conditions. Ultimately, this approach establishes a solid foundation for guiding contrast agent design and optimizing ultrasound imaging protocols.

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