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A Model of Ultrasound Contrast Agent for Blood Flow Investigation at Higher Harmonics

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Introduction

Harmonic imaging techniques involve ultrasound detection at higher harmonics. In combination with ultrasound contrast agents this allows to easier distinguish among tissue and blood, especially at lower flow velocities. However radiation forces [1] are an important factor at common diagnostic intensities. The primary radiation force may cause significant bubble movement along ultrasound beam, thereby distorting results of measurement of slower flows.

In this work a model by Tortoli *et al.* [2] is extended by adding the transient bubble response. This allows to simulate the full spectrum of bubble response, including higher harmonics. Results for a single bubble driven by continuous acoustic signal are presented.

Model

For planar and parallel acoustic waves which isotropically change size of a microbubble, the primary ultrasound force is defined by [2]

$$F_u(\omega)=\frac{\pi P_a^2 D}{\rho_0 c\omega}\cdot\frac{2\beta_t/\omega}{\left[\left(\frac{\omega_0}{\omega}\right)^2-1\right]^2+\left(\frac{2\beta_t}{\omega}\right)^2}, \quad (1)$$

where P_a — acoustic pressure at bubble surface, D — bubble diameter, ρ_0 — medium density, c — sound velocity, β_t — total damping, ω_0 — bubble eigenfrequency, ω — angular velocity of waves.

This force is in balance with the fluid drag force

$$F_D=C_D\,\mathrm{Re}\cdot\frac{\pi D\upsilon\rho_0}{8}\left\|V_f-V_b\right\|; \quad (2)$$

$$\mathrm{Re}=\frac{\left\|V_f-V_b\right\|}{\upsilon}D; \quad (3)$$

$$C_D=\frac{24}{\mathrm{Re}}+\frac{6}{1+\sqrt{\mathrm{Re}}}+0{,}4; \quad (4)$$

where υ — medium kinematic viscosity, V_f — flow velocity, V_b — bubble velocity, Re — Reynolds number, C_D — drag coefficient. This is valid in a Newtonian fluid [2].

The balance defines bubble trajectory which can be rather complex. Both forces have longitudinal (z) and radial (r) components (Fig. 1).

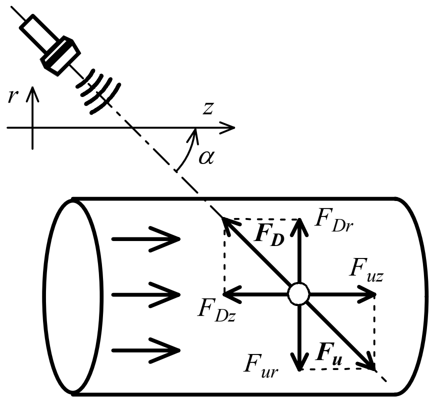

Fig. 1. Forces acting on a microbubble. α is Doppler angle

It is convenient to represent vectors by complex numbers $z + \mathrm{i}r$ and write the balance equation as follows:

$$\mathbf{F_{us}}-\mathbf{F_D}=m\frac{\mathrm{d}\,\mathbf{V_b}}{\mathrm{d}\,t}, \quad (5)$$

where m is the effective bubble mass which accounts for surrounding fluid.

A particular beam pressure profile [2] which modulates P_a is also important. It was approximated by

$$K(z,r)=\exp\left(-2\left[(z-z_i)\sin\alpha-r\cos\alpha\right]/w\right), \quad (6)$$

where z_i = 1 mm is a constant point of intersection with ray axis (the transducer is always 20 mm from this point), w = 5 mm is a profile width parameter that determines focus sharpness.

The transient bubble response [3] is described by

$$\rho R\ddot{R}+\frac{3}{2}\rho\dot{R}^2=\left(\frac{2\sigma}{R_0}+p_0-p_v\right)\left(\frac{R_0}{R}\right)^{3b\gamma}+p_v-$$
$$-p_0-\frac{2\sigma}{R}-2S_p\left(\frac{1}{R_0}-\frac{1}{R}\right)-\delta\omega\rho R\dot{R}-p_{ac}(t), \quad (7)$$

where R — instantaneous bubble radius, $\dot{R}$ — its first time derivative, $\ddot{R}$ — its second time derivative, σ — fluid surface tension, $R_0 = D/2$, p_0 — external pressure, p_v — vapor pressure, b — adiabaticity factor, γ — specific ratio of bubble gas, δ — attenuation factor, $p_{ac}(t)$, ω — time function and angular frequency of driving signal, S_p — bubble shell stiffness. The parameters b and δ are calculated using complex expressions omitted here. Besides assumptions for (1) and (2), elastic bubble deformation is assumed.

After the equation has been solved numerically, the spectrum of $\dot{R}$ can be converted [3] to the spectrum of p_s; the latter yields scattering cross–section which is commonly used to describe intensity of the received signal.

The inverse of $F_D(\|V_b - V_f\|)$ can be used to predict steady–state velocity of the bubble by substituting F_D with F_u (1). It has a form of a 5th degree polynomial in $u = V^2$:

$$\begin{cases} P(u)=\sqrt{\dfrac{1.28R^3\rho}{\eta}}u^5+12.8Ru^4+\sqrt{\dfrac{1152R\eta}{\rho}}u^3+ \\ \quad +24\dfrac{\eta}{\rho}u^2-\dfrac{F_D}{\pi\sqrt{R\rho\eta/32}}u-\dfrac{4F_D}{\pi R\rho}, \\ F_D^{-1}(\bullet)=u^2\ \forall u: P(u)=0, u\in\Re, u\geq 0 \end{cases} \quad (8)$$

(η is fluid dynamic viscosity). Real and non–negative polynomial roots yield relative velocity squared. However this approach is unidimensional thus for any value of α polynomial roots must be found separately for longitudinal and radial components.

Techniques

Both equations of motion are solved numerically with the standard Matlab solver *ode113*. The trajectory can be simulated even using simple constant–step methods, but a variable–step method consumes memory more efficiently.

The Doppler shift is taken into account by introducing the concept of *local time*

$$t_L = t - \Delta t(z, r), \quad (9)$$

where Δt is location–dependent propagation delay in the signal path. In reality, two arbitrary instants of wave phase at the receiver are separated by different amount of time than originally, at the transmitter. Removing these propagation delays yields "original" time values which can be used as time base for $p_{ac}(t)$ and its envelope, $P_a(t)$. Additionally the pressure is zeroed while $t_L < 0$. More specifically, using t_L to generate $P_a(t)$ inside the differential equation problem of (5) yields t at the solver output; to simulate bubble oscillation with (7) later, $p_{ac}(t)$ is generated on basis of t_L but is used together with t.

A similar approach implements Doppler shift for the second time to reflect distortions in the return path:

$$t_R = t' + \Delta t(z', r'). \quad (10)$$

Here t_R are time instants at the receiver and t' are part of bubble response solution. The latter no more correspond to t because of arbitrary time step used by solver. Corresponding bubble locations $z' + \mathrm{i}r'$ must be calculated in order to obtain the propagation delay; spline interpolation has proved adequate but this is not a critical requirement.

In turn, interpolation is also required when solving equation (7) since the driving signal, $p_{ac}(t)$, is specified at t, not t'. Because of quick changes in pressure, crude models like linear interpolation are now completely unsuitable.

Some tricks are needed because of large amounts of data involved — for example, a typical $p_{ac}(t)$ comprises about $3\cdot 10^6$ elements.

It is impractical to use a reference this big, especially inside the differential equation problem: *interp1* generates some internal data to approximate the entire reference with a spline and this task is very memory–intensive (some hundred MB might be required). Besides, sometimes Matlab 5.3 has problems utilizing virtual memory for that and as a result 1 GB of physical memory is not enough any more.

It may be difficult to keep a personal computer running a few days continuously. Power outages and software glitches will destroy the entire work as ODE solvers themselves can not back up results from time to time.

To overcome these problems, the response simulation is done piecewise. The entire $p_{ac}(t)$ is divided into 90000–element chunks, each chunk is solved separately and the last value is used as initial conditions for the next chunk. The differential equation problem, in turn, loads no more than 10000 elements, with an overlap of 4 to assure spline continuity. Bubble locations $z' + \mathrm{i}r'$ mentioned above are obtained by similar technique.

Results and discussion

Trajectory and response of a single resonant Levovist® bubble (R_0 = 0.99 µm) in water driven by a 4 MHz continuous wave were simulated. Flow rate was 10 cm/s. The pressure at beam focus was 46 kPa; it roughly corresponds to 300 kPa in pulsed mode at PRF = 16 kHz and t_p = 1.5 µs (what is currently being simulated). 300 kPa, in turn, were chosen because of limitations of RPNNP equation and its problematic convergence at higher pressures. As Levovist properties required by the equation were not known, they have been chosen ($S_p = 10^{-3}$, $S_f = 0$) to yield close value of total damping δ and similar appearance of $F_u(D)$ plot with respect to those given by Tortoli *et al.* [2].

It is evident that even moderate ultrasound intensities result in significant bubble displacement. As can be seen in Fig. 3, bubbles have almost stopped; corresponding velocities projected onto the ultrasound beam range from –7 cm/s to +2 cm/s, that is, negative Doppler shift still dominates in the spectrum solely because of gradual velocity change. Consequently with CW techniques, or even with PW at higher duty cycles and especially longer bursts, the cost of using contrast agents may be too high.

The radiation force always induces negative Doppler shift. Any positive shifts that may appear in spectra are due to the original flow direction. The amount of shift is twice as high with respect to the first harmonic — in excellent agreement with prediction by Chang *et al*. [4].

The peak intensity of the second harmonic is lower by 8.9 and 8.7 dB, accordingly. This depends on acoustic pressure: a separate response simulation shows higher harmonics clearly dominating at 75 kPa but not yet at 50 kPa.

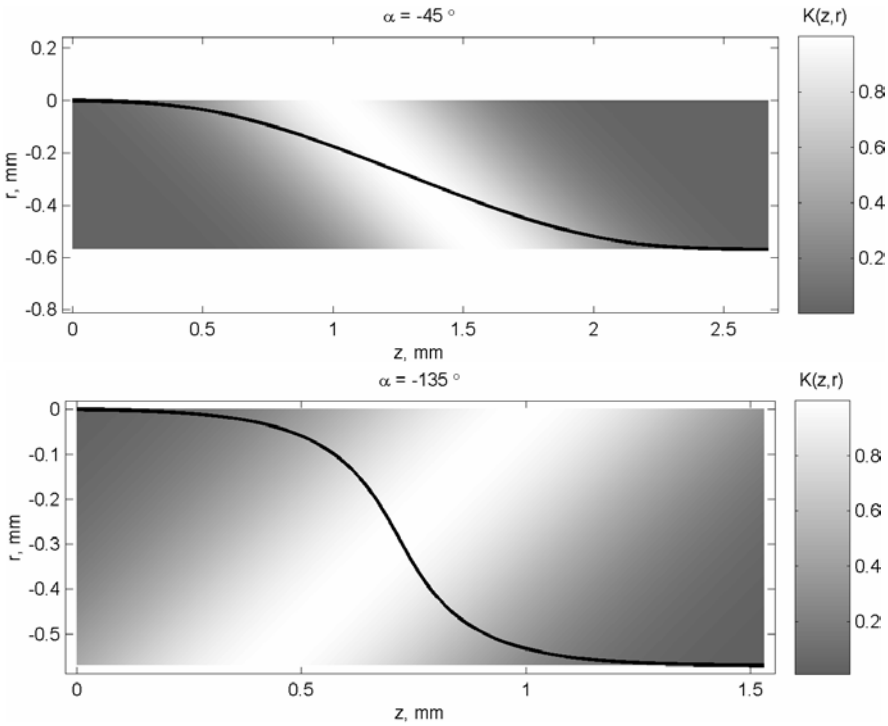

Fig. 2. Trajectories in case of different Doppler angle

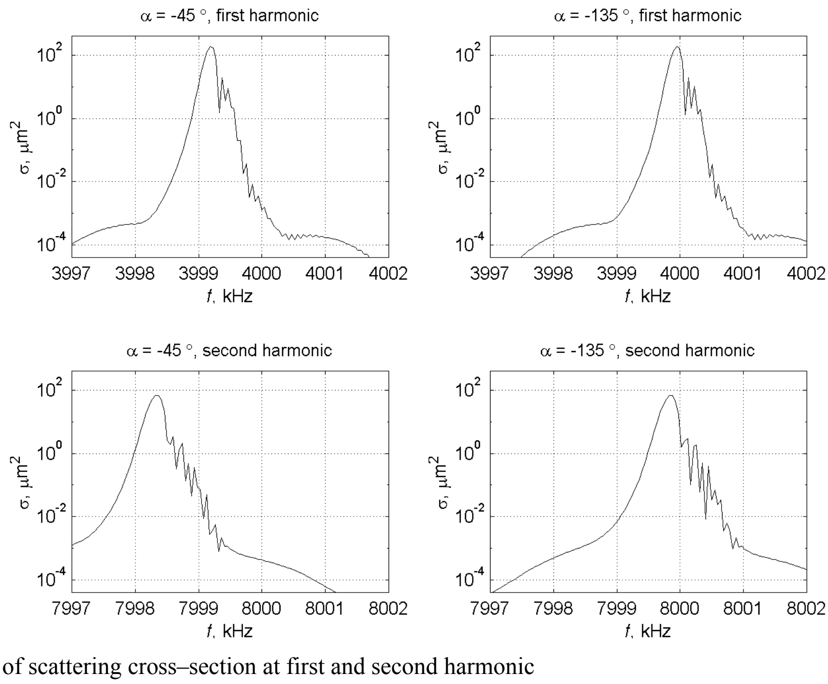

Fig. 3. Resulting spectra of scattering cross–section at first and second harmonic

Resource requirements for the simulation are another issue. Chosen tasks are barely adequate for a contemporary personal computer (Pentium 2.4 GHz, 1 GB RAM). Trajectory simulation lasts more than 7 hours almost independently upon Doppler angle, whereas response simulation needs **more than 5 days** for a single bubble despite of significant improvement (a few times faster) due to short chunks of $p_{ac}(t)$. This can be seen in Fig. 4. Additionally it shows that the progress rate is not constant: the solver assures constant accuracy by decreasing time step in case of higher ultrasound pressure, which reaches 46 kPa only in the beam center.

This is the reason why a more realistic case, an ensemble of different–sized bubbles, is not affordable so far. For example, Tortoli [2] used 25 bubbles covering entire size distribution of Levovist. Implementation of the solver algorithm in a language with less overhead (C for example) would significantly speed up simulations and hence provide means for a more thorough investigation. Parallel computing would also help because different bubbles can be simulated independently.

Another possible improvement is to include frequency–dependent attenuation in medium. The only requirement is a method which allows to simulate corresponding distortions of an arbitrary signal in time domain.

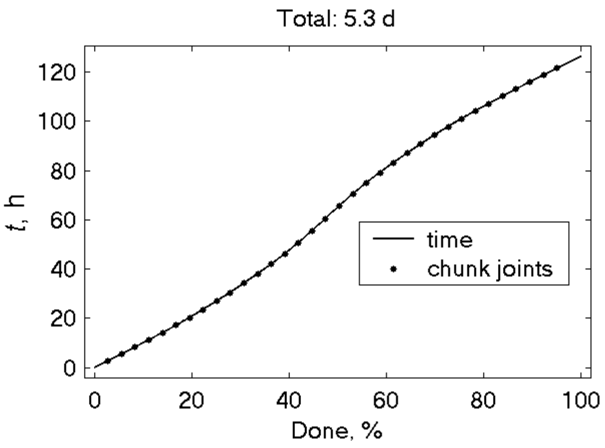

Fig. 4. Cumulative simulation time

Conclusions

An improvement of a known model was given that allows to estimate displacements of contrast agent particles due to acoustic pressure and predict the full harmonic spectrum of their frequency response.

A more recent model of contrast microbubble has been used, thus enabling simulations with rigid–shell contrast agents. Results show that in a typical setup, Levovist® bubble of a certain size moving among with 10 cm/s water flow is almost stopped even by 46 kPa of continuous ultrasound wave.

The main drawback is extremely long simulation time due to numeric solution approach. Implementation in a language of level lower than Matlab might change that.

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T. Burba. A Model of Ultrasound Contrast Agent for Blood Flow Investigation at Higher Harmonics // Electronics and Electrical Engineering. – Kaunas: Technologija, 2006. – No. 8(72). – P. 79–82.

Primary radiation force subjects contrast agent particles to movement which can yield wrong Doppler shift. A known model of this movement is extended to include bubble oscillations. This allows to predict full spectrum of the returned signal, hence the model is useful for second–harmonic imaging. Analytical method to calculate steady–state velocity from parameters like bubble diameter, ultrasound pressure and frequency is provided; some simulation peculiarities are explained. Trajectory and response of a single bubble for two different Doppler angles were simulated using Matlab. A resonant bubble carried by 10 cm/s water flow exhibits almost no Doppler shift if irradiated forward flow by 46 kPa CW ultrasound. A drawback of the model – very long simulation time. Il. 4, bibl. 4 (in English; summaries in English, Russian and Lithuanian).

Т. Бурба. Модель ультразвукового контрастного вещества для исследований потока крови на высших гармониках // Электроника и электротехника. – Каунас: Технология, 2006. – № 8(72). – С. 79–82.

Первичная сила излучения вызывает перемещение частиц контрастного вещества и может исказить доплеровское смещение. Известная модель этого перемещения дополнена колебаниями микропузырька. Это позволяет прогнозировать весь спектр принятого сигнала, поэтому модель полезна для гармонической визуализации. Представлен аналитический метод вычисления установившегося значения скорости из таких параметров, как диаметр пузырька, давление и частота ультразвука. Объяснены некоторые особенности моделирования. В системе Matlab были смоделированы траектория и спектр отклика единичного пузырька при двух значениях доплеровского угла. Доплеровский сдвиг почти элиминируется в случае пузырька, резонирующего в потоке воды скоростью 10 см/с и облучаемого против течения непрерывной акустической волной давлением 46 кПа. Недостаток модели — очень долгое моделирование. Ил. 4, библ. 4 (на английском языке; рефераты на английском, русском и литовском яз.).

T. Burba. Ultragarsinės kontrastinės medžiagos modelis kraujo srauto tyrimams aukštesnėse harmonikose // Elektronika ir elektrotechnika. – Kaunas: Technologija, 2006. – Nr. 8(72). – P. 79–82.

Pirminė spinduliavimo jėga sukelia kontrastinės medžiagos dalelių judėjimą ir gali iškreipti doplerinį poslinkį. Žinomas šio judėjimo modelis papildytas mikroburbuliuko matmenų svyravimais. Tai leidžia prognozuoti visą grįžusio signalo spektrą, todėl modelis naudingas harmoniniam vizualizavimui. Pateiktas analitinis metodas nusistovėjusiam greičiui apskaičiuoti iš tokių parametrų, kaip burbuliuko skersmuo, akustinės bangos slėgis ir dažnis. Paaiškintos kai kurios modeliavimo ypatybės. Sistemoje Matlab buvo sumodeliuota pavienio burbuliuko trajektorija ir atsako spektras. Veikiant rezonuojantį burbuliuką, nešamą 10 cm/s vandens tėkmės, tolydine 46 kPa akustine banga prieš srovę, doplerinis poslinkis beveik panaikinamas. Modelio trūkumas – labai ilgas modeliavimas. Il. 4, bibl. 4 (anglų k.; santraukos anglų, rusų ir lietuvių k.).