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Identifying Nonlinear Characteristics for the Bulk Response of Ultrasound Contrast Agents

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***Abstract*— Ultrasound contrast agents consist of gas-filled microbubbles stabilized by a shell. Under ultrasound insonification, these bubbles oscillate nonlinearly with resonance frequencies being well within the diagnostic range. Currently, different detection methods are proposed, often with a heuristic reasoning based on the bubble nonlinearity being modeled by a time-invariant polynomial characteristic. However, it has been demonstrated [1] that microbubbles exhibit the behavior of a nonlinearity with memory. To optimize detection schemes, we propose to take this into account by ultrasound contrast agent modeling with a Wiener series. With these models, which can be identified from acoustic measurements, nonlinear system theory can be applied to improve detection methods. The feasibility of contrast agent modeling by Wiener series was evaluated on a contrast agent simulation, implemented by a modified Rayleigh-Plesset differential equation. For a sinusoidal input, the Wiener series approximated contrast agent behavior with a mean square error of 7.6% of the power of the contrast agent signal. The Wiener series approach was subsequently validated in an experimental setup where the nonlinear characteristics of a commercially available contrast agent were identified. The model obtained allowed for a mean square prediction error of 2.6% of the power of the measured signal for a pseudo-random multilevel sequence. With these experiments, it has been shown that the modeling of the oscillation behavior of ultrasound contrast agents with a Wiener series is feasible.**

I. Introduction

Ultrasound Contrast Agents consist of gas microbubbles with diameters ranging from 1–10 μm. They are filled with a low-solubility gas and encapsulated by a shell to prevent them from dissolving. These microbubbles oscillate under ultrasound insonification, with resonance frequencies being well within the diagnostic range.

To optimize detection schemes, thorough modeling of bubble oscillation behavior is required. It has already been found in [1] that contrast agent microbubbles exhibit the behavior of a nonlinear system with memory. Currently employed detection schemes such as phase inversion imaging, however, follow heuristic approaches which do not take this phenomenon into account.

Different models for the oscillation behavior of contrast agent microbubbles have been developed. These are implemented by nonlinear differential equations like modified Rayleigh-Plesset or Herring equations [2] which are derived from the physical model of an oscillating gas bubble suspended in liquid with additional parameters accounting for the shell encapsulating the gas. These models allow a representation of microbubble behavior under specific assumptions such as, for example, radial oscillation. As the differential equations in question can only be solved numerically, their use in the development of detection schemes is limited to verification of detection performance.

Nonlinear system theory, on the other hand, offers well-established model identification and signal processing methods which can be used for the development of new detection methods for contrast agents. In this paper we apply models based on the Wiener- and Volterra nonlinear system theory to ultrasound contrast agents and identify model parameters by acoustic measurements.

II. Nonlinear Modeling

Discrete-time linear causal time-invariant systems can be fully described by their impulse response $h[n]$. The output is given by the convolution of input $x[n]$ and impulse response:

$$y[n] = \sum_{k=0}^{\infty} h[k]x[n-k]. \quad (1)$$

The above system may be extended with nonlinear terms to allow modeling of nonlinear systems, yielding the Volterra series [7]:

$$y[n] = \sum_{i=0}^{\infty} \mathbf{H}_i \left[h_i[k_1, \ldots, k_i]; x[n]\right]. \quad (2)$$

The Volterra functionals $\mathbf{H}_i$ are implemented by the i-dimensional convolution of the kernel h_i and the input $x[n]$:

$$\mathbf{H}_i = \sum_{k_1=0}^{\infty} \cdots \sum_{k_i=0}^{\infty} h_i[k_1, \ldots, k_i]x[n-k_1] \cdots x[n-k_i]. \quad (3)$$

With these functionals, the system output can be written as:

$$\begin{aligned} y[n] = h_0 &+ \sum_{k_1=0}^{\infty} h_1[k_1]x[n-k_1] \\ &+ \sum_{k_1=0}^{\infty}\sum_{k_2=0}^{\infty} h_2[k_1,k_2]x[n-k_1]x[n-k_2] \\ &+ \sum_{k_1=0}^{\infty}\sum_{k_2=0}^{\infty}\sum_{k_3=0}^{\infty} h_3[k_1,k_2,k_3]x[n-k_1]\times \\ &\qquad x[n-k_2]x[n-k_3] \\ &+ \ldots. \end{aligned} \quad (4)$$

The characteristics of the nonlinear system in question may be determined by the identification of the kernels h_i. The identification of the kernels, however, is only feasible, if the contribution of every functional can be considered separately. It is therefore necessary to conduct an orthogonalization with respect to the input signal which yields a Wiener series [8]. Such a series is characterized by orthogonality of all functionals $\mathbf{H}_i$:

$$\overline{\mathbf{H}_i \mathbf{H}_j} = \begin{cases} c, & i = j \\ 0, & i \neq j \end{cases}, \tag{5}$$

with $c \in \mathbb{R}^+$ and the overbar denoting a time average.

III. Identification of Kernels

The kernels can be determined by a least squares estimation. Equation (4) can be rewritten as

$$y[n] = \sum_i a_i q_i[n], \tag{6}$$

or in matrix form as

$$\mathbf{y} = \mathbf{Q}\mathbf{a}. \tag{7}$$

The matrix $\mathbf{Q}$ contains all distinct monomials $q_i[n]$, that is all possible combinations of the input contained in (4):

$$q_i[n] = 1 \cdot 1 \cdots x[n - k_1] \cdots x[n - k_m]. \tag{8}$$

With this method all monomials such as 1, $x[n]$, $x[n-1]$ as well as higher order monomials such as $x[n]x[n-1]$ can be constructed.

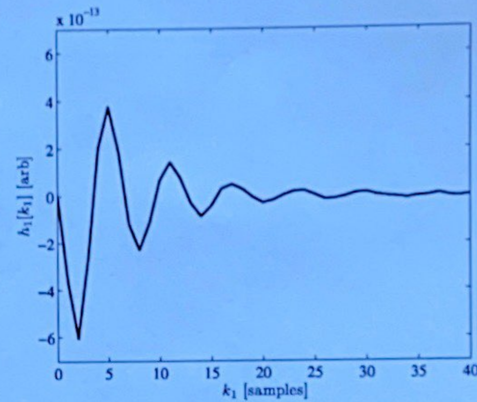
Equation (7) can be solved by numerically stable linear least squares methods based on Cholesky factorization. For this paper, an identification algorithm as proposed in [4] was used to determine the kernels.

To obtain numeric stability, it is important that the excitation signal is chosen so that all identified terms contribute to the overall output. It has been shown in [5] that pseudorandom multilevel maximum-sequences are suitable excitation signals. For N-th order models, an $N+1$ level sequence is necessary.

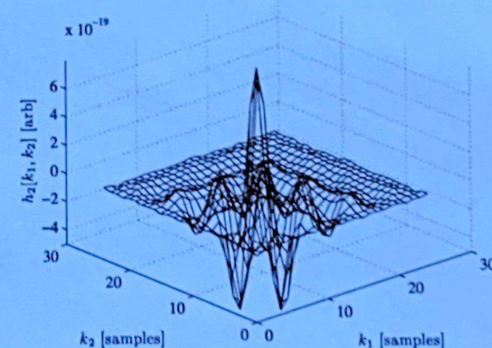
IV. Contrast Agent Simulation

To validate the model obtained from the Wiener series, the kernels h_i were determined for a contrast agent simulation. For this, a contrast agent microbubble with a resting diameter $r_0 = 0.75\,\mu$m was simulated by means of the modified Rayleigh-Plesset equation as given in [6] (parameters used for the simulation, the notation corresponding to [6]: $c = 1480\ \mathrm{m\,s^{-1}}$, $\mu = 10^{-3}$ Pa s, $\rho = 998\ \mathrm{kg\,m^{-3}}$, $\sigma = 0.072\ \mathrm{N\,m^{-1}}$, $\delta_t = 0$, $S_f = 0\ \mathrm{kg\,s^{-1}}$, $\chi = 0\ \mathrm{kg\,s^{-2}}$). Normally distributed white noise was used as excitation signal, and input and output signals were used to identify a third order Wiener series with a memory length of 40 samples. A total of 12481 coefficients was determined. The identification results are shown in Fig. 1.

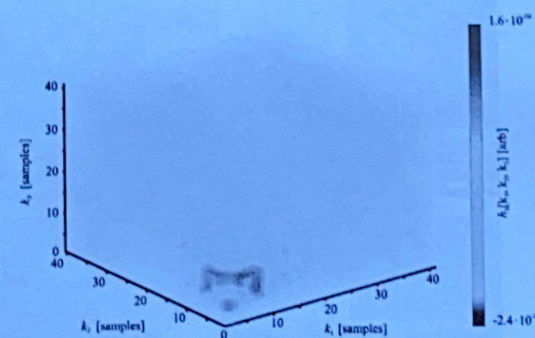
It can be seen that the constant kernel corresponds to the bubble's resting radius. The linear kernel, shown in Fig. 1(a), exhibits the behavior of a damped oscillator. If all other



(a) Linear kernel h_1 identified from contrast agent simulation.



(b) Quadratic kernel h_2 identified from contrast agent simulation.



(c) Cubic kernel h_3 identified from contrast agent simulation.

Fig. 1. Kernels identified from contrast agent simulation. Constant kernel $h_0 = 0.75 \cdot 10^{-6}$. The linear kernel 1(a) represents the impulse response of the system. It exhibits the behaviour of a damped oscillator. Similarly, the second and third order kernels, 1(b) and 1(c), show the quadratic and cubic components of the system. Since these contain nonzero components at lags larger than zero, the system under investigation is a nonlinear system with memory.

components were disregarded, then the first order component would represent the impulse response of the system. The second order kernel, shown in Fig. 1(b), models the quadratic response of the system. Constant and second harmonic frequency components are generated. Similarly, the third order kernel, shown in Fig. 1(c), models the cubic components, with contributions at the third harmonic and fundamental. Since the quadratic and cubic kernels contain coefficients at lags greater zero, the system identified from the contrast agent simulation features nonlinearity with memory.

To implement a nonlinear system with memory, a linear system with memory may be connected in series with a static nonlinearity. The Wiener kernels of such a system are factorizable. However, the kernels obtained from the contrast agent simulation are not factorizable which demonstrates that microbubbles cannot be modeled by a cascade of linear system and a static nonlinearity.

V. Simulation Results

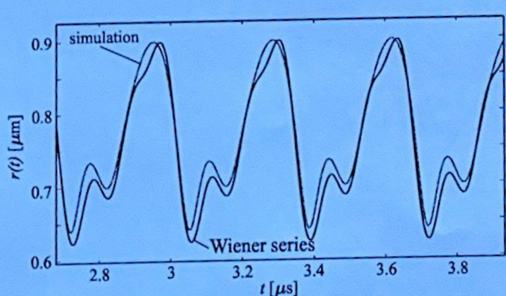


Fig. 2. Comparison of Wiener series model with contrast agent simulation for a sinusoidal input ($f_0 = 3\,\text{MHz}$, $\hat{p} = 100\,\text{kPa}$, $r_0 = 0.75\,\mu\text{m}$).

Model accuracy can be evaluated by comparing simulation output with Wiener series output for a sinusoidal input. The response of both can be seen in Fig. 2. Except for small deviations, the curves match with a mean square error of 7.6% of the power of the simulation signal. These deviations, however, can be explained by comparing the spectrum of both signals, shown in Fig. 3. Although the constant component, the fundamental, as well as the second and third harmonics are modeled perfectly, higher harmonics and subharmonics are not taken into account. Thus, an ideal representation of the contrast agent simulation cannot be achieved with a third order Wiener series. Ultrasonic waves generated by a contrast agent microbubble, however, are subject to damping through tissue, which increases with frequency. Furthermore, the ultrasound transducers used for characterization of contrast agents feature bandpass behavior. Therefore, when characterizing actual contrast agents, higher frequency components than the third harmonic cannot be measured, and the limitation of the Wiener series as described above will be less pronounced.

VI. Experimental Apparatus

The feasibility of ultrasound contrast agent modeling by Wiener series was evaluated by determining the kernels h_i by

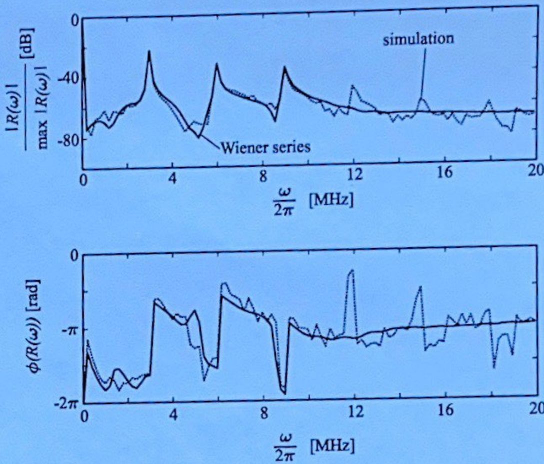


Fig. 3. Comparison of spectra of Wiener series model with contrast agent simulation for a sinusoidal input ($f_0 = 3\,\text{MHz}$, $\hat{p} = 100\,\text{kPa}$, $r_0 = 0.75\,\mu\text{m}$). The upper plot shows the magnitude of the microbubble's response to a sinusoid excitation. The output of the Wiener series consists of four components, constant component, fundamental and the second and third harmonics. The second and third harmonics are generated by the second and third order kernel which enables the modeling of quadratic and cubic terms respectively. The Wiener series cannot model components higher than third order, as it features at most cubic terms of the input. Furthermore, subharmonics cannot be modeled.

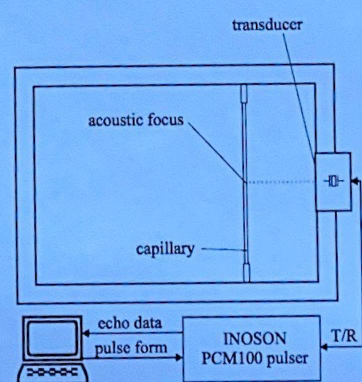


Fig. 4. Experimental setup (top view).

acoustic measurement.

The experimental setup for this evaluation consisted of a single capillary tube (Cuprophan RC55 8/200, inner diameter 200 μm, Membrana GmbH, Wuppertal, Germany) immersed in a water bath. It was filled with a monolayer lipid, undiluted contrast agent (SonoVue™, kindly supplied by Bracco Research SA, Geneva, Switzerland, mean diameter 2.5 μm, size distribution shown in [3]). The capillary tube was located in the focal point of a spherically focused single element transducer (Panametrics V395, Panametrics-NDT, Waltham, MA) with a center frequency of 2.25 MHz. The contrast agent, contained in the capillary, was insonified by a fully programmable ultrasound pulser/receiver (PCM100, Inoson

GmbH, St. Ingbert, Germany) in pulse-echo mode. The presence of contrast agent in the capillary was ascertained by optical inspection with a 60x magnification microscope. A schematic of the acoustic setup is given in Fig. 4.

For the actual identification, the contrast agent was insonified by a three level (+1, 0, -1) pseudo-random maximum sequence with a peak amplitude of 10 V, and the echo was recorded. This experiment was repeated 250 times to increase signal-to-noise ratio. After averaging and downsampling to a sampling frequency of 12.5 MHz, input and output data were used for identification of a second order Wiener series model.

VII. Experiment Identification Results

Determination of the second order Wiener model for the contrast agent was numerically stable. Model performance was evaluated by comparing the Wiener series output for a pseudo-random sequence with measurement data obtained from the experiment. The results are shown in Fig. 5. It can be seen that the curves match almost perfectly. The mean square error is 2.7% of the power of the reference signal.

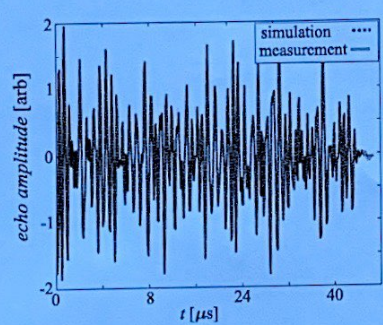


Fig. 5. Comparison of measurement and simulation.

VIII. Conclusion and Outlook

In this paper, a novel method for the modeling of ultrasound contrast agent based on nonlinear system theory has been proposed: the behavior of contrast agents under insonification is described by a Wiener series, which allows simple parameter identification without model fitting. Additionally, based on these models, nonlinear filters for increased contrast-to-tissue-ratio can be designed in the future. The approach was first tested on a simulation of the response of microbubbles. Comparison of the results showed a good approximation of bubble behavior by the Wiener series. These results were confirmed by experiments: it was possible to determine the Wiener kernels of a contrast agent by acoustic measurement and the model allowed approximation of contrast agent behavior with high accuracy.

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