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LIFETIME OF CAVITATION BUBBLES IN HIGH INTENSITY ULTRASONIC BIOPROCESSOR

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Abstract: The interaction between ultrasonic waves and biological tissues is the cause of cavitation phenomena. A primary scope of this paper was to set-up a measurement system for the generation of cavitation by means of forcing a low frequency (20 kHz). From the spectra and power density was evident the presence of the random component associated to the noise of cavitation was evident. For the estimate of this component the technique ARMA spectral was particularly effective. The average lifetime of transient cavitation bubbles estimated from the time constant via the ARMA spectrum, was found to be in agreement with the data in the literature.

Keywords: Acoustic Cavitation, Noise Spectra; ARMA modelling, bubbles lifetime.

1. INTRODUCTION

In recent years, both in esthetic and general medicine the transcutaneous administration of drugs has been promoted instead of the systemic one. The drug delivery through the dermis, or the Transdermal Drug Delivery (TDD), is an alternative advantage compared to common methods, such as injections or oral doses.

However, the biggest and perhaps the only problem for this application, is the function of the skin barrier that limits penetration of many drugs in the body. The first observation of the chemical effects of ultrasound dates back to 1927, while their use in treatment is documented since the 30's.

In 1949, the possibility of increasing the transdermal transport of macromolecules by means of ultrasonic waves was demonstrated experimentally. However, this field of research known as sonochemistry, remained unexplored until the 80's.

More recently (1992), Tachibana [1] noted an increase in the transdermal transport of insulin in diabetic rat skin by the energy associated with the application of ultrasound at low frequency (48 kHz), indicating that the microscopic cavitation bubbles (maximum radius from 10 to 100 μm) (produced on the surface of the skin) can cause a rapid flow of liquid through the trans-and trans-epidermal follicle pathway.

Studies, such as the one cited above, finally lead to the commercial spreading of transdermal systems (Transdermal Drug Delivery Systems, TDDS).

To sum up, the interaction between ultrasound waves and biological tissues is associated with cavitation phenomena that have a dominant role in the delivery of chemical species.

The oscillation of cavitation bubbles is a chaotic phenomenon which is interpreted by applying the equation of single bubble dynamics equation known as the Rayleigh - Plesset [2,3] and those subsequently modified by Gilmor [4], Keller-Miksis [5] Prosperetti [6].

The instants of formation and subsequent implosion of the bubbles can instead be described by a function of several random variables, as suggested by Vokurka [7]. Both trends in time and the power density spectra of signals recorded during the activity of cavitation induced acoustic power delivered by the sonicator; these characteristics that can be justified and classified using the models mentioned above.

In particular, the presence and the extent of harmonic components, subharmonic and superharmonic of the driving [2-6] can get information on oscillation (not linear) of the bubbles. To evaluate the response of an oscillating bubble in a pressure field, it is useful to categorize using the magnitude of fluctuations in the radius of the bubble in response to imposed fluctuating pressure field.

Three regimes can be identified:

1. for small amplitudes of the pressure field, the regime of the response forcing the bubble is linear;
2. as described in reference studies [2-6] the response of a bubble starts to be nonlinear as the amplitude of forcing is increased. Under this system of non-linearity the bubble may continue to fluctuate, led by forcing pressure field. These circumstances are referred to as "acoustic cavitation stable" to distinguish them from those of the third scheme described below;
3. unlikely, the variation in size of a bubble during a single cycle of oscillation can become so large that

the bubble undergoes a cycle of growth and violent collapse. This activity is called cavitation "*Acoustic transient cavitation*" and is distinct from the stable to the fact that the radius of the bubble changes significantly during the growth phase followed by a violent collapse which generates intense pressure pulses.

Transient Cavitation: The distinction between these circumstances in which they system is waiting for a stable acoustic cavitation and those in which there may be transient acoustic cavitation has been drawn from Noltingk Neppiras [8] and was reviewed by Flynn [9] and Young [10].

Consider a bubble subject to a hydrostatic pressure p_0, which overlaps a pressure field oscillating at frequency ω and amplitude p. If $\omega \ll \omega_N$ with ω_N natural frequency of bubble oscillation, the effects of viscosity and inertia of the liquid are relatively insignificant compared to those due to surface tension and can be conducted quasi-static analysis. Under these circumstances, in order to identify the conditions under which the cavitation can be transient, Blake's criterion is considered valid [11] expressing p_B as the minimum acoustic pressure needed for the formation and growth of a bubble:

$$\frac{p_B}{p_0} = 1 + \frac{4}{9} X_B \sqrt{\frac{3X_B}{4(1+X_B)}} \quad (1)$$

where σ is the surface tension of the liquid and X_B is given by:

$$X_B = \frac{2\sigma}{(p_0 \cdot R_B)} \quad (2)$$

Equations (1) and (2) provide a necessary condition but not sufficient for the onset of transient cavitation. To this aim, Apfel [12] derived from Noltingk Neppiras and [8] the condition $R_M/R_0 > 2.3$ as a threshold for transient cavitation bubble radius R_0 initially, reaching a maximum radius equal to R_M. To calculate the maximum range using the following approximate formula valid for $p \gg p_0$.

$$R_M(p,\omega) = \frac{4\beta}{3\omega} \cdot \sqrt{\frac{2{p_0}^2}{\rho p}} \cdot \left[1 + \frac{2\beta}{3}\right]^{\frac{1}{3}} \quad (3)$$

where $\beta = \left(\frac{p}{p_0} - 1\right)$

This relationships shows that the radius does not depend on the initial radius of the bubble but the frequency and the pressure by the driving force. As for the calculation of the pressure p to 20 kHz at a distance z, it is used the relationship on the pressure along the axis of a circular transducer [13]:

$$p(z) = \rho c A \omega \left[e^{-j \cdot \left[\frac{2\cdot\pi}{\lambda} \cdot \left[\sqrt{z^2 + \left(\frac{D}{2}\right)^2} \right] \right]} - e^{-j \cdot \left(\frac{2\cdot\pi}{\lambda} \cdot z \right)} \right] \quad (4)$$

Cavitation noise: In addition to these formulations that set conditions for the establishment of transient cavitation for a single bubble, we clearly deduce from the literature of the field the need to characterize the behavior of an isolated bubble - a situation that never occurs in practice - but a "cloud" of bubbles.

The temporal records of these phenomena produce power density spectra in which spectral lines are related to fundamental frequency that is generated by driving force pressure field, along with a series of harmonics sub harmonics, a result of non-linearity phenomenon in number and intensity dependent on the amplitude of [14].

However, if the presence of many transient cavitation bubbles under the power density spectrum is characterized simultaneously by a similar pattern to that produced by random phenomena such as those generally identified with the term "noise".

A valid theoretical tool for the study of cavitation noise appeared that proposed by Vokurka [7], who modeled the time behaviour of the pulse pressure of each bubble implosion issued by a symmetric exponential function:

$$p(t,\theta) = p_p \cdot e^{\frac{-|t|}{\theta}} \quad (5)$$

where θ is the time constant on the phenomenon of bubble implosion and p_p is the peak pressure. The Power Spectral Density (PSD) of this signal is:

$$s(\omega,\theta) = \left| \frac{2a\omega}{1+\omega^2\theta^2} \right|^2 \quad (6)$$

The Eqs. (5) and (6) therefore provide information concerning both the frequency spectra of each event of implosion and the duration of this phenomenon, apparently represented by θ.

In the case of a "cloud" of transient cavitation bubbles, the phenomenon can be described as the sum of all n individual cavitation events that occur during the negative half-cycle of the drive (during which the threshold is exceeded Blake, Equation (1) that repeat every K-th cycle of the drive itself, as described by the following formula:

$$P(t,\theta,\phi,n) = \sum_{K=-\infty}^{\infty} \sum_{n=1}^{N} P_{Kn} e^{-\frac{|t-KT-\phi_{Kn}|}{\theta_{Kn}}} \quad (7)$$

P_{Kn} is the peak pressure of each implosion, T is the period of forcing (50 μs corresponding to 20 kHz) ϕ represents the temporal instant of the driving pulse within T and N is the number of cavitation bubbles that implode during T.

A further step is made by considering the random components that govern the phenomenon of cavitation. This circumstance is taken into account by the fact that the first three parameters are expressed by many random variables with Gaussian distribution (P_{Kn}, ϕ, θ), while N is considered as an additional random variable with Poisson distribution.

This study stems from the analysis of this "cavitation noise" used to characterize the population of bubbles involved in the transient cavitation means of the model Vokurka.

Specifically, we want to explore the possibility of characterizing the average time constant of the signal generated by the "cloud" of gas bubbles, i.e. the rapidity with which the implosion occurs and therefore an important indicator to population of the bubbles themselves. Therefore, the aim was to perform a fit of the power spectra of signals acquired to estimate the value of this time constant.

2. MATERIALS AND METHODS

Experimental setup for the measurement of the cavitation activity: A first goal of this work consists in setting up an experimental set-up for the generation, measurement and subsequent analysis of cavitation phenomena induced by driving a low frequency equal to 20 kHz.

This frequency is shown [15] as the ideal to produce transient cavitation in water. The experimental bench (Figure 1) comprises a vessel containing the fluid (distilled water) which is induced cavitation, a pulser (VCX-500 Sonicator Vibra CellTM - Sonics & Materials - USA), needle hydrophone with PVDF sensor for the measurement of cavitation (Precision Acoustics, UK - diameter 0.5 mm, PVDF sensitive material, thickness 9 μm, a bandwidth of 15 MHz to -4dB). The temperature signal has been acquired by oscilloscope digital (Yokogawa DL 708E). In addition, the sonicator is support made with a translation stage micrometer (0,2 μm repeatability way, M-CG-405, Physik Instrumente) by a framework and remotely controlled by PC. The signal detected by means the hydrophone was acquired by a digitizer (NI PXI-5122 14-bit, Sampling frequency 100 MHz National Instruments.)

Referring to Figure 2, the tip of the sonicator (b) is positioned at a distance of 9 mm from the hydrophone respectively (a) and 60 mm from the active surface same. This placement has minimized the detection forcing signal and at the same time, it avoided the hydrophone damage. The initial temperature of the distilled water, measured by thermocouple type K during all experiments was between 25 °C and 26 °C. The theoretical amplitude of the field forcing the axis of sonication at a distance of 9 mm, calculated with Equation (4) is approximately 240 kPa for an amplitude of oscillation of the tip of about 45 μm.

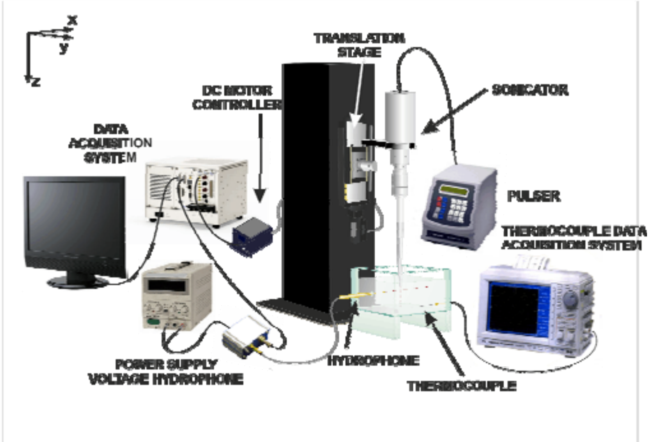

Figure 1. Scheme of experimental set-up.

Analytical tools for the characterization of cavitation noise: First, we developed a simulation program in LabView 8.2 whose aim was to predict the dynamics of bubbles and the pressure they generated during the implosion. This model is based on the aforementioned studies of Rayleigh - Plesset [2,3] Gilmor [4] and Keller-Miksis [5].

The simulations produced were used to analyze the experimental results reported in this study. From the acquired signals and corresponding power spectral density was very clear that the random component related to the presence of cavitation noise. For the estimate of this component has been applied the technique ARMA spectral (Auto Regressive - Moving Average) that, at this preliminary stage, appeared particularly effective for the study and classification of these random components.

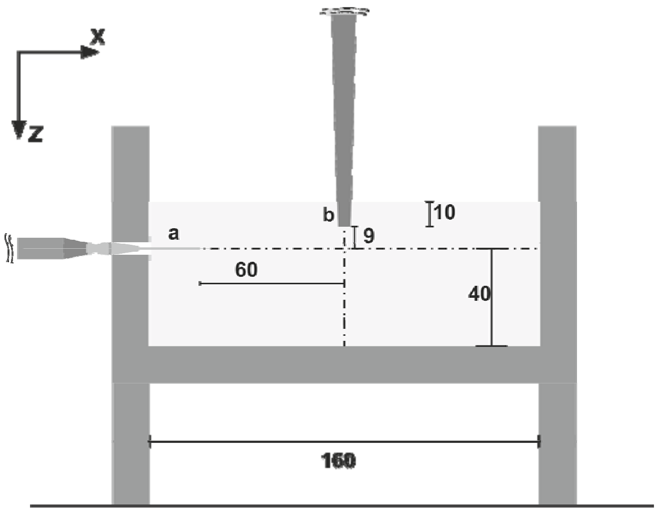

Figure 2. Side view of the measurement system consisting of: (a) needle hydrophone, (b) tip of the sonicator. The dimensions are in millimeters.

Indeed, it is known that these techniques [15] are an alternative to using FFT spectral estimation, when no interest to highlight the presence of harmonic components but rather trends spectrum represented by functions of fractional type Poles/Zeros in which, evidently, poles represent behavior of the type low-pass frequency response and therefore well suited for detecting the presence of components similar to that represented by Equation (6):

$$S(\omega) = \sigma_e^{\ 2} \frac{B(\omega)}{A(\omega)} \quad (8)$$

The PSD is therefore calculated from the ARMA model by the product of the estimated variance of the signal σ_e^2 and estimate a fraction whose numerator and denominator zeros PSD while it estimates the poles.

Measurements and signal processing: Ultrasonic signal behaviour were measured by produced implosion of bubbles transient cavitation generated by sonicator operating at a frequency of 20 kHz. The sampling frequency was set to 50 MHz. The power spectrum of these signals was calculated by using FFT and ARMA. Immediately before the acquisition of any signal on the cavitation, the signal has been acquired (the same time) with the sonicator off.

This signal was therefore considered only on the noise produced by the hydrophone amplifier channel, even when this signal was calculated on the basis of the power spectrum by using FFT and ARMA. Subsequently, each spectrum (FFT and ARMA) signal on the cavitation has been subtracted to the noise and corrected for hydrophone frequency response. We then carried out simulations based on models of Rayleigh - Plesset, Gilmor, Keller-Miksis [2-5].

Figure 3 shows an example of the results obtained by implementing these simulations.

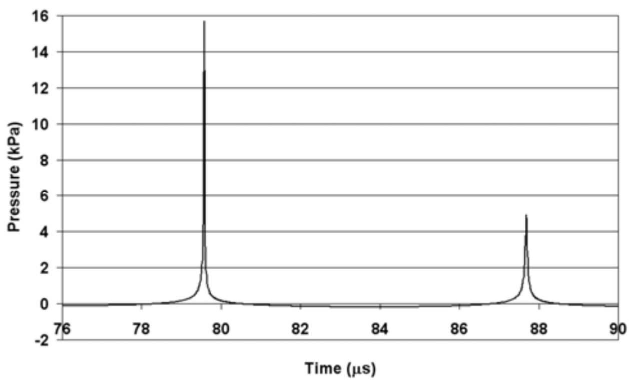

Figure 3. Simulation of the pressure generated by the collapse of one bubble of initial radius of 30 μm and amplitude of the pressure driving p of 100 kPa.

3. RESULTS AND DISCUSSION

Figure 4 shows a typical trace on the registration of the collapse of transient cavitation bubbles.

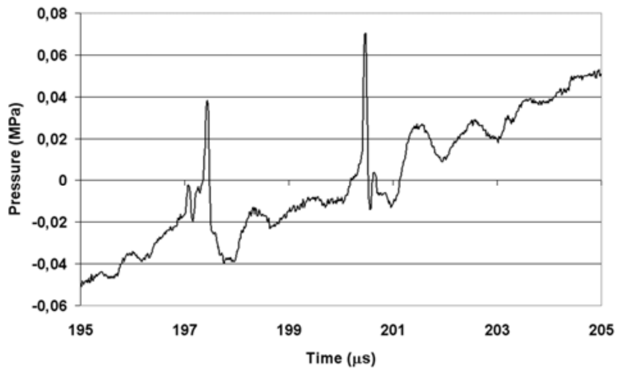

Figure 4. Example of recording events of implosion.

We calculated the spectra of these traces by using FFT spectra and the ARMA technique. A typical result is given in Figure 5.

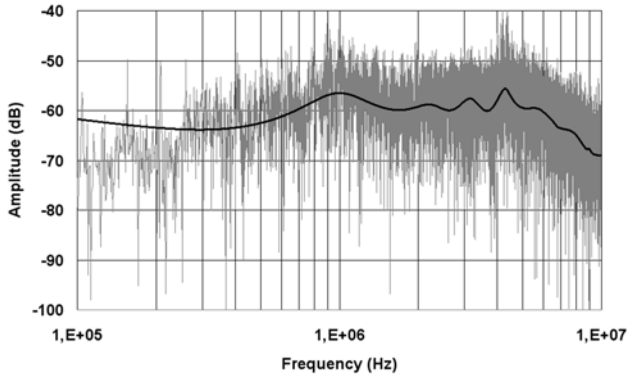

Figure 5. Example of power spectrum density of cavitation noise estimated by means of FFT and ARMA technique (full line, black), subtracted from the noise spectrum.

ARMA spectra was calculated by the time constant θ that characterizes, according to Equations (5) and (7), the rapid implosion of the bubbles. Values θ calculated by ARMA spectra, analyzed by simulations and the Apfel's theory (Equation 3), indicate that the activity is compatible with the recorded cavitation bubbles that reach a maximum radius of the order of 100 μm and a pressure p around 100 kPa. In practice, the duration of pressure pulses recorded from the hydrophone agrees with this "population" of bubbles. Figure 6 shows the values of time constant calculated from the ARMA model to vary amplitude of oscillation of the tip sonicator. Up to the 22 percent there corresponds an amplitude of about 45 μm, while 40 percent (max allowed by the manufacturer with this tip) corresponds to a amplitude of roughly 80 μm. The calculation of the time constant provided by ARMA spectra, was by (137 ± 32) ns on the average value $\bar{\theta}$ and its standard deviation σ_θ for a confidence level of 95 percent calculated by the coverage factor k = 2.26 (Student's distribution).

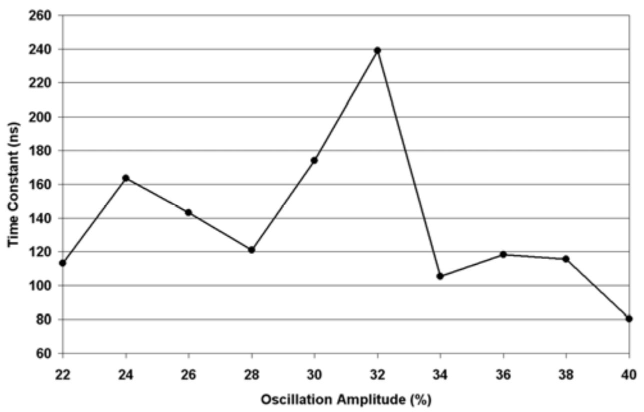

Figure 6. Values of time constant calculated from the ARMA model to vary amplitude of oscillation of the tip sonicator.

4. CONCLUSIONS

Starting from the theory of Apfel, with this work the authors have set themselves the objective of using models that describe the behavior deterministic of individual cavitation bubbles (Rayleigh - Plesset, Gilmour and Keller - Miksis) together with a model on the components random phenomenon of implosion of bubbles (Vokurka) to interpret the results of measurements of transient cavitation in distilled water produced by a generator of low frequency ultrasound (20 kHz). In particular, attention has focused on the analysis of spectra of cavitation with respect to the range representing the so-called "cavitation noise" that is contained in the power supplied by the implosion of bubbles in instants $\bar{\phi} \pm \sigma_{\phi}$ and duration of the order of $\bar{\theta} \pm \sigma_{\theta}$. Given the nature of the spectrum of cavitation noise, characterized by spectral components that are always allocated at the excitation frequency of the sonicator and its sub-harmonics and a range with relatively "flat" which shows a decrease in frequency dependent the time constant $\bar{\theta}$, was chosen to perform the estimation of the latter range by ARMA techniques. The first results are satisfactory as estimates ARMA can develop values of $\bar{\theta}$ compatible with the experimental conditions and in accordance with what has been shown by theoretical models used by [10]. Analysis of time constants calculated and shown in Figure 5, it is not apparent a dependence by oscillation amplitude of the sonicator tip. This circumstance will provide a basis for further investigation.

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