THEORETICAL EVALUATION TO ASSIST TARGETED DRUG DELIVERY WITH ULTRASOUND-SUPPORTED SONOPORATION FOR FUTURE LASER-DRIVEN STUDIES AT ELI-NP

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Abstract. Inaugural studies of medicine-supporting research foreseen to be implemented at the High-Power Laser Systems (HPLS) at ELI-NP will benefit substantially from achieving a fast and localized delivery of radiological substances. Microbubbles driven by an ultrasonic transducer have been used successfully as delivery agents for pharmaceuticals for several decades. They can support future oncology programs facilitating high-dose rate therapies (e.g., flash therapy) at ELI-NP, since a very localized and swift delivery of drugs and nanoparticles is achievable using the bubbles. We herein depict a theoretical evaluation to control the critical microbubble explosion that creates the high-pressure gradients of need for in-vitro and in-vivo sonoporation of drugs and nanoparticles based on the Rayleigh-Plesset equation. Suitable bubble sizes \( R_0 \) and corresponding resonance frequencies \( f_{\text{res}} \) are derived for which an ultrasonic-driven explosion can be achieved assuming an externally applied pressure \( P_\infty(t) \) of sinusoidal nature. With \( R_0 \) in the \( \mu \text{m} \) and \( f_{\text{res}} \) in the MHz regime, the crucial explosion times \( T_{\text{expl}} \) can be short (\(< 2 \mu\text{s}\)) allowing the sought-after fast delivery of the pharmaceutical payload.

Key words: Sonoporation, microbubbles, nuclear medicine.

1. INTRODUCTION

The Extreme Light Infrastructure for Nuclear Physics (ELI-NP) foresees the implementation of innovative programs to support the medical field. The highest human-made intensities provided by the High-Power Lasers Systems (HPLS) at ELI-NP lead to ion and photon beam peak intensities of hitherto unknown magnitude. Controlling those beams, ELI-NP research will potentially open up, among others, an avenue for blue-sky research of novel concepts in radiology. Herein, oncology matters are of paramount interest. Recent successes in preclinical laser-driven Proton Neutron Capture Therapy (PNCT) at ELI-Beamlines in Prague [1], show that...
even \textit{in-vivo} cancer treatments at HPLS facilities can be envisaged in the not-that-distant future. This circumstance, in conjunction with the advances in flash therapy [2], fuelled the authors’ engagement in the laser-induced medical application field. Naturally, with the high precision achievable with an HPLS for spatial and temporal beam delivery, the ultrasound-driven targeted delivery of pharmaceuticals by microspheres emerged as a promising concept that coheres with the aforementioned unique HPLS benchmarks.

In clinical practice, microbubbles have been used as contrast agents [3] as well as for a wide portfolio of therapeutic applications, as they optimize sound reflection and support cavitation. The latter is based on the fact that they oscillate and even resonate with applied pressure, depending on the oscillation frequency $f$ and acoustic power $P_{acq}$. For optimized conditions, they will be made to burst by the ultrasound energy, producing a very localized shock wave that enlarges pressure gradients of substances attached to or embedded into them [4]. Hence, over the last two decades, focused ultrasound-supported sonoporation has become a method supporting the noninvasive delivery of pharmaceuticals to different cell types. The drugs and nanoparticles, as well as genes, can be attached to microspheres in a manifold of different ways. The pharmaceutics can be bound noncovalently to a microbubble’s outer shell \textit{via} specific chemical ligands or attached to an oily layer if the drug is hydrophobic in nature. Other possibilities include a direct embedding into the cell membrane itself or the encapsulation of the pharmaceutics within a liposome inside the microsphere [5, 6].

Since perfluorocarbon- and SF$_6$-filled microspheres are sufficiently stable for circulating in the blood vessels as agents, they can act as the agent’s porters to the therapeutical destination inside the body. Ultrasound applied by a transducer over the outer skin can then be focused accordingly to burst the microbubbles at the destination volume, causing a very localized release of the drug or nanoparticle [7, 8]. The possibility to attain a targeted on-target/off-tumor release of the delivery of pharmaceutics is exciting with respect to the reduction of side effects related to standard chemotherapy procedures while, at the same time, increasing the procedure’s effectiveness as selective pharmaceutical porters. As such, it is envisaged that microbubbles support future medical treatments, allowing the fast and efficient delivery of the minimal pharmaceutical dose in need. This ability is of particular importance if cytotoxic agents are used. Furthermore, microbubble-driven precision delivery may rise to prominence in conjunction with the recent successes in immunotherapy. A PED-project centering around this unique idea was rewarded to the ELI-NP team in 2020 PN-III-P2.1-PED-2019-2325 (540/PED/2020) by the Romanian Government.

As for the sonoporation process, typical benchmarks for the ultrasonic transducers comprise hundreds of kPa of peak pressure provided by a periodic sinusoidal waveform allowing the \textit{in-situ} delivery of the pharmaceutical agent. Modern ultra-
sound transducers can deliver those high pressures to an extended volume of a few hundreds of mm$^3$. Therefore, ultrasound-mediated microsphere destruction by steering their explosion via sonoporation seems to be a very efficient way for localized payload delivery to the small volumes to be irradiated by the laser-induced beams which is the inherent favorable characteristic of an HPLS, such as ELI-NP. The theoretical work depicted herein has to be seen as a prima facie step to support the instigation of sonoporation-mediated HPLS-driven oncology.

2. THE PHYSICS AND RATIONALE OF MICROBUBBLE CAVITATION

Processes relating to the cavitation of microspheres in fluid media must be evaluated before an in-vivo application of the medical procedure in order to allow and optimize the spatial and temporal delivery of the pharmaceutical product. This coincides with the quest to minimize stress on the patient’s healthy cells, which are collaterally exposed to the procedure. Forcing the microbubble to burst by externally applied pressure allows a momentary amplification of the pressure gradient applied to the pharmaceutical load to be delivered. Driven by this pressure gradient enables the drugs or nanoparticles then to penetrate the selected cell tissue. The rationale of the simulations depicted herein is firstly to find the resonance frequency $f_{\text{res}}$ at which the microbubble with a certain radius $R_0$ bursts. It will be shown that $f_{\text{res}}$ lies within a rather narrow bandwidth. The value of $R_0$ was varied according to the products supplied by acknowledged providers. Typically radial mean values for $R_0$ span from 0.75 $\mu$m to 1.30 $\mu$m. The simulations also encompass the determination of the time-scale $T_{\text{exp}}$ at which the bubble’s eruption appears. Herein, $T_{\text{exp}}$ should be minimized to allow for the fastest pharmaceutical payload delivery using multi-cycles in quick succession. According to literature, $T_{\text{exp}}$ will be in the order of a $\mu$s, which is confirmed by the simulations as displayed in the following chapters.

2.1. MODELING OF THE MICROBUBBLE EXPLOSION IN WATER WITH THE RAYLEIGH-PLESSET EQUATION

Cellular responses such as membrane permeability and cytoskeleton disassembly guided by the work of Wang et al. [9] have been researched regarding their dependence on the core parameters such as the acoustic driving pressure $P(t)$ and distances between the delivering microbubble, of a diameter of $\sim 1.5 \mu$m to around 2.6 $\mu$m. The bubble’s diameter is somewhat smaller than the dimension of the typical human cell. A two-dimensional boundary element model best describes the theoretical behavior between the two entities based on the Rayleigh-Plesset equation given as

$$R(t) \frac{d^2 R(t)}{dt^2} + \frac{3}{2} \left( \frac{dR(t)}{dt} \right)^2 + \frac{4 \nu_L}{R(t)} \frac{dR(t)}{dt} + \frac{2 \gamma}{\rho_L R} + \frac{\Delta P(t)}{\rho_L} = 0,$$  \hspace{1cm} (1)
where \( R(t) \) is the radius of the bubble, \( \rho_L \) and \( \nu_L \) are the liquid’s density, and viscosity, \( \gamma \) is the surface tension of the bubble-liquid interface, \( \Delta P(t) = P_\infty(t) - P_B(t) \), in which, \( P_B(t) \) is the uniform pressure within the bubble, and \( P_\infty(t) \) is the external pressure infinitely far away from the bubble. As the Rayleigh-Plesset equation is of non-linear differential nature, the time-evolution \( R(t) \) can be quite intricate. Figure 1 sketches the microsphere’s shape evolution following the appliance of a varying external pressure \( P_\infty(t) \) till its explosion in a simplified manner. At the starting time, \( T_0 \), the bubble radius is \( R_0 \), and the bubble holds an internal pressure \( P_B(T_0) \) surrounded by normal ambient pressure in a liquid carrier which, in clinical practice (in-vivo), will be normal blood plasma that has an almost identical specific weight compared to water. At the time \( T_1 \), after the ultrasound transducer is switched on, the bubble is compressed by the external pressure to its first relative temporal minimum \( R_{\text{min},rel}(T_1) \). Thereafter, relaxation allows the \( R(t) \) to rebounce by expansion due to the negative pressure gradient associated with \( p_2 \). Typical values of the temporal relative maximum \( R_{\text{max},rel}(T_2) \) are in the order of \( \sim 1.2R_0 \). In case an explosion is achieved after a few cycles, the maximum relative value of \( R_{\text{max},rel}(t) \) will gradually grow while the minimum value will gradually decline. Due to the intricate nature of the Rayleigh-Plesset (Equation 1), the minima and maxima do not correspond in general to the minimum and maximum amplitudes of \( P_\infty \), as the viscosity and the surface-tension lead to a complex response in the bubble’s temporal \( R(t) \) function. A sign of the onset of explosion for \( f_{\text{res}} \) is that, after several cycles of compression and expansion, the bubble is eventually compressed down to 1% of its original radius. The subsequent large stretching extends the bubble to almost twice its original volume at a critical time \( T_4 \). Since the expansion continues above the maximum bubble volume, the bubble bursts at \( T_{\text{expl}} \), with a delay of only a few tens of ns after the time for the critical expansion at \( T_4 \). When it then reaches the relative maximum radius \( R_{\text{max},rel}(T_4) \), it collapses during compression; an event called inertial cavitation in which the bubble’s potential energy is partly converted into chemical reactions, heat, light, and sound emissions [10]. The latter will allow the pharmaceuticals to obtain a high enough pressure gradient \( p_{\text{max}} \) to penetrate through the cancerous cell membrane and to be delivered at target. The remnants of the original microbubble form a conglomerate of smaller ‘waste’-microspheres, as indicated in Figure 1.

In the clinical praxis, the pressure \( P_\infty(t) \) will be provided by a Wavefront Generator and amplified by a Broadband Amplifier operating over a wide range between, e.g., 10 kHz to 12 MHz. Output levels of up to 200 W are achievable for a variety of waveforms. For the calculation of the in-vitro water-model, to be used for sonoporation of substances into populations of cultivated cells, a sinusoidal pressure with a peak-to-peak difference of \( \Delta P_\infty(t) = 400 \text{kPa} \) with high frequencies in between 1 MHz to 10 MHz was simulated. In practice, the focal spot of standard transducers can be maximized to a diameter of several tens of mm in which \( P_\infty(t) \) in
Evaluation for drug delivery with sonoporation in future studies at ELI-NP

Fig. 1 – Model of the sonoporation process leading to the explosion of a microbubble in time sequence (left-to-right, & up-to-down) containing pharmaceutical load represented by the black dots. The process starts at normal surrounding pressure at $T_0$ and ends with the explosion $T_{\text{expl}}$ at which the original bubble disintegrates, giving maximum pressure $p_{\text{max}}$ to the payload. In between the bubble undergoes compression at the times $T_1$ and $T_3$ and expansion at $T_2$ and $T_4$.

In accordance with Equation 1 applies. The cross-section area supported by ultrasound-mediated sonoporation, therefore, spans well over the range that would be covered by laser-induced particle- and $\gamma$—radiation supplied by an HPLS facility.

3. NUMERICAL RESULTS OF THE RAYLEIGH-PLESSET SIMULATION IN WATER

The aim of these simulations was to find $f_{\text{res}}$ for a given radius $R_0$ in the quest to minimize sonoporation-induced side effects and to deduce the ideal microbubble size for future treatments. E.g. the onset of unwanted sonoporation of healthy cell membranes caused by high negative pressure gradients is a known complication [11] that can be avoided by minimizing the ultrasound cycles to a few periods. Hence a determination of $f_{\text{res}}$ and the related widths as well as $T_{\text{expl}}$ for a specific $R_0$ is paramount. The Rayleigh-Plesset equation was transcribed into a Fortran90 program to assure numerical accuracy of the highest precision. The source code is made available for the public with the corresponding link shown in the ‘Code and data Availability’ Chapter at the end.
For the parameters of Equation 1 we assumed the standard values as given in literature for water, namely, \( \nu_L = 0.89 \, \text{mPa} \cdot \text{s} \), \( \varrho_L = 1.00 \times 10^3 \, \text{kg} \cdot \text{m}^{-3} \), and \( \gamma = 70 \, \text{kPa} \cdot \mu \text{m} \). The modeling in water as the medium has to be seen as the first approach for \textit{in-vitro} studies. The value of \( R_0 \) is aligned with the standard mean radius of commercially available microsphere products as quoted by their providers. The analysis shows that the actual explosion process only sets in the MHz regime for a rather small frequency window around \( f_{\text{res}} \) which the latter differing substantially for varying values of \( R_0 \). Figure 1 displays three selected simulations for \( R_0 = 0.79 \, \mu \text{m} \), 1.00 \( \mu \text{m} \), and 1.30 \( \mu \text{m} \), which exhibit different resonance values for \( f_{\text{res}} \). The simulated values for \( R_0 \) were given by standard microsphere sizes, which are available commercially. The crucial explosion times, \( T_{\text{expl}} \), in the examples chosen were calculated to be 0.63 \( \mu \text{s} \) for the largest bubble of \( R_0 = 1.30 \, \mu \text{m} \) and 0.60 \( \mu \text{s} \) for \( R_0 = 1.00 \, \mu \text{m} \) as well as 0.86 \( \mu \text{s} \) for \( R_0 = 0.79 \, \mu \text{m} \).

Figure 3 underlines the importance of the resonance condition for the resonant frequency \( f_{\text{res}} \) for a certain bubble size. If one defines \( R_{0\text{min}} \) as the minimal radius at which for a given frequency \( f_{\text{res}} \) the explosion of the microsphere can no longer be achieved, and \( R_{0\text{max}} \) is the corresponding maximal radius, one sees that for higher frequencies, both values are quickly converging, leaving a very small radius parameter-regime for which sonoporation can be achieved in the frequency domain. In clinical practice this narrow frequency window can however be overcome by a suitable tuned variation of \( f_{\text{res}} \) guided by Equation 1. In any case, the optimization of this circumstance inhibits unwanted cavitation around healthy cells. Figure 3 shows this effect for \( f_{\text{res}} = 3 \, \text{MHz} \), \( f_{\text{res}} = 5 \, \text{MHz} \), and \( f_{\text{res}} = 7 \, \text{MHz} \) aligning with the results shown in Figure 1. One sees that for frequencies \( f_{\text{res}} \geq 5 \, \text{MHz} \) the actual size of the bubble to be forced to explosion is rather narrow. This tendency gets emphasized for 7 MHz, where even for a slightly smaller or larger radial size than \( R_0 = 0.79 \, \mu \text{m} \) the bubble cannot be forced into an eruption. This narrow resonant bandwidth with respect to \( R_0 \) can be seen as an utmost remarkable effect due to the non-linear nature of the Rayleigh-Plesset equation. Note that the depicted radial values in Figure 3 do not correspond exactly to the previously defined \( R_{0\text{min}} \) and \( R_{0\text{max}} \) as they were purely chosen to sketch the resonance condition. Precise values for \( R_{0\text{min}} \) and \( R_{0\text{max}} \) are given in Table 1.

It can therefore be concluded that for ultrasonic-supported sonoporation cycles, a small value for the standard deviation of the radii is paramount. The results from the manifold of parameters are summarized in Table 1, which allowed us to draw a conclusion on the microbubbles to be considered for experimental campaigns. In Table 1 \( R_{0\text{opt}} \) defines the radius in the range of \( R_{0\text{min}} \leq R_{0\text{opt}} \leq R_{0\text{max}} \) for which \( T_{\text{expl}} \) is minimized, allowing the fastest, hence optimal delivery time of the pharmaceutical payload. Interestingly, \( R_{0\text{opt}} \) declines steadily with a higher \( f_{\text{res}} \).
Evaluation for drug delivery with sonoporation in future studies at ELI-NP

A first glance would suggest that the lowest frequency at 3 MHz would be a good choice as it caters to a rather large range of bubble sizes between $R_0^{\text{min}} = 0.87 \mu m$ to $R_0^{\text{max}} = 1.29 \mu m$ which spans almost over the full palette of commercially available products. However, a closer look at $f_{\text{res}} = 5$ MHz delivers a better result, if one uses the SONOVUE® (sulfur hexafluoride microbubbles, Bracco Imaging, SpA, Colleretto Giacosa, Italy) with $R_0 = 0.96 \mu m \pm 0.04 \mu m$ (mean radius and its deviation) [12] are used, as $T_{\text{expl}}$ is minimized to only 0.59 $\mu s$. These quality parameters sets them apart from other commercially available contrast agents available: DEFINITY™ (perflutren lipid microspheres; Lantheus Medical Imaging, North Billerica, MA, USA) with $R_0 = 0.61 \mu m$; OPTISON™ (perflutren protein type A microspheres, GE Healthcare AS, Oslo, Norway) with $R_0 = 1.54 \mu m$;
The preparation of in-vivo research would foresee applying Equation 1 to the conditions inside a body. First and foremost, that would lead to the inclusion of the parameters applying to blood. For mice, the fluid density of blood is \( \rho = 1.057 \times 10^3 \) kg \( \cdot \) m\(^{-3} \) [14], which is close to that of water. However, the liquid viscosity is \( \nu_L = 5.996 \text{ mPa} \cdot \text{s} \) [15], which is almost 7-times higher than of water, shifting the results

and SONAZOID\textsuperscript{TM} (perfluorbutan microbubbles, GE Healthcare, Little Chalfont, England) which have hugely different diameters such as 1.22 \( \mu \text{m} \) (DEFINITY) or 3.08 \( \mu \text{m} \) (OPTISON). This conclusion was only most recently supported by a combined theoretical and in-vivo study depicted in [13].

3.2. NUMERICAL RESULTS OF THE RAYLEIGH-PLESSET SIMULATION FOR BLOOD

Fig. 3 – Simulation of the microbubble contraction and expansion for a sinusoidal pressure of \( P(t) = 101 \text{kPa} - 200 \text{kPa} \times \sin(2\pi f \cdot t) \) according to the Rayleigh-Plesset equation in water for (a) \( f_{\text{res}} = 3 \text{MHz} \), (b) \( f_{\text{res}} = 5 \text{MHz} \), and (c) \( f_{\text{res}} = 7 \text{MHz} \). The temporal behaviour is given for two different \( R_0 \), namely for (a): \( R_{0 \text{min}} = 0.86 \mu\text{m} \), and \( R_{0 \text{max}} = 2.3 \mu\text{m} \), (b): \( R_{0 \text{min}} = 0.90 \mu\text{m} \), \( R_{0 \text{max}} = 1.1 \mu\text{m} \), and (c): \( R_{0 \text{min}} = 0.76 \mu\text{m} \) and \( R_{0 \text{max}} = 0.81 \mu\text{m} \). The red oval striped markers indicate the explosion times for \( R_0 \)–values that fulfill the resonance conditions in Figure 1 from which also the x–axis legend is taken.

Most important is to note that no bubble explosion sets in as in Figure 1. Also note the different time scales between subplot a) versus subplots b) and c).

Most important is to note that no bubble explosion sets in as in Figure 1. Also note the different time scales between subplot a) versus subplots b) and c).
Table 1

$R_{0}^{\text{min}}$ and $R_{0}^{\text{max}}$ denote the minimum and maximum values of $R_{0}$ for which a burst can be achieved for a given frequency $f_{\text{res}}$. $R_{0}^{\text{opt}}$ gives the optimal bubble radius for which the explosion time $T_{\text{exp}}$ is minimal at a given $f_{\text{res}}$. The external pressure is given by $P_{\infty} = 101\, \text{kPa} - 200\, \text{kPa} \times \sin(2\pi f_{\text{res}} \cdot t)$ in the simulations with $f_{\text{res}}$ varying between 3 MHz to 8 MHz.

<table>
<thead>
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<th>$f_{\text{res}}$ / MHz</th>
<th>$R_{0}^{\text{min}}$ / µm</th>
<th>$R_{0}^{\text{max}}$ / µm</th>
<th>$R_{0}^{\text{opt}}$ / µm</th>
<th>$T_{\text{exp}}$ / µs</th>
</tr>
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<td>2.28</td>
<td>1.29</td>
<td>0.63</td>
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<tr>
<td>4</td>
<td>1.02</td>
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<td>1.08</td>
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<td>0.90</td>
<td>1.04</td>
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<td>0.80</td>
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<tr>
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<td>0.719</td>
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of the water model substantially. Figure 4 depicts a simulation with $R_{0} = 1.0\, \mu\text{m}$ for SonoVue® microspheres for the mouse model.

![Simulation of microbubble contraction and expansion](image)

Fig. 4 – Simulation of the microbubble contraction and expansion for a sinusoidal pressure of $P(t) = 101\, \text{kPa} - 400\, \text{kPa} \times \sin(2\pi f_{\text{res}} \cdot t)$ according to the Rayleigh-Plesset equation in mouse blood for $f_{\text{res}} = 1.9\, \text{MHz}$. The legend is taken from Figure 1. Most important is to note that the bubble explosion sets in quickly after $T_{\text{exp}} = 0.44\, \mu\text{s}$. Due to the increased $\nu_{L}$, the maximum $f_{\text{res}}$ to achieve explosion for SonoVue® bubbles was calculated to be as low as 1.9 MHz for a peak-to-peak pressure of 800 kPa.
A resonant frequency of $f_{\text{res}} = 1.9\,\text{MHz}$ was deduced which allowed the burst to set in after $T_{\text{expl}} = 0.44\,\mu\text{s}$. The significant changes in the mouse model compared to water are due to the increased $\nu_L$. To achieve this fast bubble disintegration, the maximum frequency had to be decreased to 1.9 MHz, while the peak-to-peak pressure to be supplied in-vitro had to be enlarged to 800 kPa. Although the in-vitro application leads to very different parameters, the underlying physics phenomena governed by the Rayleigh-Plesset equation are well simulated by the developed code and will inform future studies at ELI-NP.

4. CONCLUSION

In this work, we depicted a theoretical approach to assist targeted drug delivery in-vitro with ultrasound-supported sonoporation into cell probes for potential future laser-driven studies at ELI-NP based on the Rayleigh-Plesset equation in water. It was found that for standard ultrasound parameters in a rather low to moderated pressure regime with a peak-to-peak amplitude difference of 400 kPa, SonoVue® microspheres with $\varphi = 1.92\,\mu\text{m}$ would be best suited to bring on the fastest possible bubble explosion ($T_{\text{expl}} = 0.59\,\mu\text{m}$) at a resonance frequency around $f_{\text{res}} = 5\,\text{MHz}$ thus minimizing side effects such as unwanted cavitation in the vicinity of the cell probes. Simulations using the parameter for mouse blood in preparation for in-vivo studies show the same physical behaviour, but for rather different parameters, which entails the need to double the peak-to-peak pressure values to 800 kPa to achieve the bubble’s disintegration albeit at a much lower $f_{\text{res}}$ at 1.9 MHz. The differences in frequency and peak-to-peak pressure are mainly due to the huge discrepancy in viscosity between water and blood plasma. In-vivo applications will allow faster explosion times of $T_{\text{expl}} = 0.44\,\mu\text{m}$. In any case, the application of the Rayleigh-Plesset equation will guide future in-vitro and in-vivo work.

5. CODE AND DATA AVAILABILITY

The Fortran90 code of the Rayleigh-Plesset equation and the data are available to the public and can be found at: https://github.com/chiehjen/bubble.

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