Analysis of the Heart Sounds and Murmurs of Fetuses and Preterm Infants

Theses of the PhD dissertation

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Introduction

Phonocardiography (PCG) deals with processing of the acoustic signals produced by the mechanical actions of the heart resulting in the vibration of the valves, heart muscle tissues and great vessels [13]. One of the central issues is to extract the different heart sounds from a noisy recording and relate them to the corresponding cardiac event. Moreover, heart sounds can be further analysed and certain features can be extracted for estimating the underlying cardiac parameters.

The importance of the heart was already realized in the fourth century B.C., although with some misconceptions: Aristotle argued that it was the seat of intelligence, motion and sensation [14]. From the medical perspective, Hippocrates noted already an early form of auscultation by holding an ear against the chest, but in his works he described only breathing sounds. Blood circulation was first described by William Harvey, an English Physician in 1628. In the same century, the polymath Robert Hooke (1635-1703) described the diagnostic potential of heart sounds [15]:

> *"I have been able to hear very plainly the beating of a Man's Heart... Who knows, I say, but that it may be possible to discover the Motions of the hemal Parts of Bodies... by the sound they make, that one may*

> *discover the Works performed in the several Offices and Shops of a Man's Body, and thereby discover what Instrument or Engine is out of order."*

These investigations lead to the invention of the stethoscope in 1816 by R. T. H. Laennec, and a century later the fetoscope for fetal heart sound examination. Nowadays, because of new advances in cardiac imaging, cardiac auscultation has become a preliminary test in the primary health care. On the other hand, due to the limited financial and human expert resources and the development of modern low cost computational devices in information technology, phonocardiography emerges also as a topic of current research and a possible tool aiding clinical decision making.

That phonocardiography offers unexplored possibilities is especially valid for the examination of fetuses because of their hidden position enabling the usage of only a limited number of monitoring techniques. Furthermore, due to its passive nature causing no irradiation at all, fetal phonocardiography can be applied for long-term monitoring. The development of adequate methods, which are certainly needed because of the great amount of data, could enable nearly continuous monitoring of the wellbeing of the fetus. Furthermore, the detection of abnormal heart sounds could contribute to the early diagnosis of cardiac anomalies.

Computerized phonocardiography is also a tool for quantitative and objective analysis which is missing in classical auscultation. This can be exploited, for instance for the monitoring of certain cardiac diseases by assessing the underlying cardiac dynamics. Nonetheless, for achievements in PCG the knowledge of the cardiologists, electric, computer and mechanical engineer has to be combined, making it an exciting and difficult multidisciplinary field of science.

Methods

All fetal phonocardiographic (fPCG) data was recorded with a phonocardiographic cardiotocographic (CTG) device (Fetaphon-2000$^{\text{TM}}$, Pentavox Ltd.) domiciliary or in clinical environment, in the case of the latter one mostly at the Hungarian Institute of Cardiology, Budapest. The length of these recordings was usually 20 minutes corresponding to the length of conventional CTG examinations. The fPCG device uses a sampling frequency of 333 Hz and a resolution of 8 bits. The recorded data was transferred via a mobile network and stored on an evaluation centre.

Phonocardiographic data of preterm infants was recorded using a self-made electronic stethoscope at the 1st Department of Paediatrics, Semmelweis University of Medicine, Budapest. After preprocessing, the data was archived for further analysis with a sampling frequency of 3000 Hz and a resolution of 16 bits. The length of the measurements was usually 30 seconds long. Informed consent was obtained in all cases.

The difficulty in phonocardiographic signal processing arises from the nonstationarity of the signals, often resulting in very short transients, and a low signal-to-noise ratio. Some of the noise can be filtered out using traditional linear filters, but noise components often overlap with heart sound components not only in the time, but also in the frequency domain. I applied a wide variety of tools for biomedical signal processing, not all of them producing acceptable outcomes. In this work I present the results of the following approaches:

- **Time domain methods**: linear filtering, improved ensemble averaging [16], heuristic methods
- **Time-frequency domain methods**: short time Fourier transform [17], wavelet transform [18], Wigner-Ville distribution [19]
- **Signal modelling and model fitting**: linear and nonlinear chirp models [20, 21], time-frequency domain based parameter estimations [22], Monte Carlo method [23]

There are several important phonocardiographic features which have to be assessed. In the case of fetal CTG measurements the fetal heart rate (FHR) is one of the most important ones, which can be calculated based on the cyclostationary period of the fPCG signal. Moreover, recent studies suggest that based on the variability of the beat-to-beat times the development of the fetal nervous system can be assessed [24] and further details of the fetal wellbeing (e.g. detection of IUGR) can be monitored [25], emphasizing the importance of exact FHR determination.

Splitting, that is the temporal separation of different heart sound components, is often one symptom of cardiac anomalies [26]. Quantitative analysis is very difficult because of the overlapping components. Approaches based on models of the heart sounds show a possibility of estimating not only the splitting but also other parameters of the heart sounds.

The detection of murmurs is crucial for early diagnosis of cardiac diseases, but it is also a difficult task due to the presence of noise, especially in the case of the PCG signals of fetuses and preterm infants. Nevertheless the detection is only the first step in clinical applications because based on extracted parameters of the underlying cardiovascular phenomena can be monitored or classification of the heart diseases is possible in some cases.

In this dissertation I present novel results for investigating these aspects based on the methodology mentioned above.

For processing and analysis of the data and visualisation of the results I implemented all algorithms in different versions of Matlab (The MathWorks Inc., Natick, MA, USA).

New Scientific Results

The results of this dissertation can be summarized in two main parts: the first one dealing with the results on fetal phonocardiography and the second one describing achievements in investigating preterm neonates with patent ductus arteriosus.

Thesis I: *Analysis of fetal heart sounds and murmurs*

I.1. Based on the analysis of fetal phonocardiographic records I have found that different levels of accuracy are needed for the determination of T_{bb} beat-to-beat times in the case of conventional obstetrician fetal heart rate (FHR) analysis (e.g. NST) than in the case of profound FHR analysis for the assessment of fetal wellbeing (IUGR, fetal breathing, . . .), where the starting point is the variability of the T_{bb}, thus, by introducing NL, as a metric for the level of noise, and HiR, as a metric for the rate of beat detection, I have shown that the HiR of FHR calculation based on conventional time-domain autocorrelation can be improved by applying a wavelet transform based, time-frequency domain autocor-

relation, where prediction based on preceding beat-to-beat times further improves the reliability.

Related publications: [1]

In the case of conventional FHR calculation of CTG data often the autocorrelation of the time-domain signal or envelogram is used. However, with noisy signals, such as fPCG, noise bursts and in some cases even murmur corrupts the determination of the cyclostationary period, i.e. the heart rate. I introduced a method which exploits the specific time-frequency signature of the heart sounds, thus not only the periodicity of high intensity pulses, that is heart sounds, is taken into account for determining the heart rate, but also the time varying spectra of the heart sounds.

For comparison with conventional time-domain autocorrelation more than 500 fetal phonocardiographic records with different amounts of disturbances were processed. Although the wavelet transform based method yields only a modest improvement on average, more precisely less than 5 %, the distribution of improvement values is very encouraging because improvement up to 18 % could be achieved and the amount of decrement is rarely greater than 5 %.

Further analysis revealed that for noise levels less than 20 % both methods perform fairly well. As the noise level increases the range of possible HiR values widens because in some cases the different methods achieve only lower HiR-s. However, for NL in the range of 20-35 %, the time domain based method has a lower limit of possible worst HiR values than the wavelet transform based approach. In other words, the worst HiR that the wavelet transform based method can achieve for increased level of noise is always better than the worst performance of the time domain based correlation, at least in the case of these records. In the case of higher NL the performance of both methods degrades similarly.

> **I.2. I have shown that by modifying the amplitude and frequency characteristics of an existing heart sound model – which assumes the heart sounds as the superposition of two components, one from each side of the heart – it can be applied for modelling fetal first heart sounds; furthermore, the nine parameters of this model can be in general estimated using Monte Carlo simulation.**
>
> Related publications: [1]

Based mainly on the work of Xu *et al.* on S2 sound modelling of adults [21, 22], the following chirp model has been adapted for fetal heart sound modelling, presented here for the S1 sound:

$$s_M(t) = A_M \sin(\varphi_M(t)) \cdot e^{-t/\tau_M}, \quad (1)$$

$$s_T(t) = A_T \sin(\varphi_T(t - t_d)) \cdot e^{-(t-t_d)/\tau_T}, \quad (2)$$

$$s_{S1}(t) = s_M(t) + s_T(t), \quad (3)$$

where A_M and A_T are the initial amplitudes, φ_M and φ_T the phase functions, and τ_M and τ_T are the time constants of the damping of the sinusoidal mitral and tricuspid components, respectively. Finally, t_d is the delay between the above two components, that is the splitting interval.

A linear frequency decrease often proved to be sufficient, meaning that the phase functions can be defined as follows:

$$\varphi_M(t) = 2\pi \int_{-\infty}^{t} f_M(\tau) \mathrm{d}\tau = 2\pi \int_{-\infty}^{t} F_M - \Delta f_M \cdot \tau \, \mathrm{d}\tau, \quad (4)$$

$$\varphi_T(t) = 2\pi \int_{-\infty}^{t} f_T(\tau)\mathrm{d}\tau = 2\pi \int_{-\infty}^{t} F_T - \Delta f_T \cdot \tau \,\mathrm{d}\tau, \quad (5)$$

where $f_T(t)$ and $f_M(t)$ are the instantaneous frequency functions with an initial frequency of F_M and F_T and a negative slope of Δf_M and Δf_T for the mitral and tricuspid components, respectively.

This two-component model contains altogether nine parameters. The estimation of these parameters can be performed by using the Monte Carlo method [23]. In the case of this analysis the number of random simulated heart sounds was in the order of 10^6. Although the error surface of this optimization contains a great number of local minima, which may result in false parameter values, in the case of increased splitting – which may be a symptom of a cardiac anomaly – the method becomes more reliable. Furthermore, preliminary results achieved with an implementation on manycore computing architectures, namely GPUs, show a running time improvement of more than two orders of magnitude. This makes an increased number of simulations possible, resulting in increased reliability.

As an example, one fetal S1 sound and the corresponding synthesized signal is presented in Fig. 1 together with the time-frequency representations of both signals.

I.3. Based on the analysis of a great number of fetal PCG recordings I have revealed that certain congenital heart diseases can be suspected based on the presence of fetal heart murmur, and that five parameters characterising fetal heart murmur are the length, the intensity, the timing, the dominant frequency and the shape of the envelope. Furthermore,

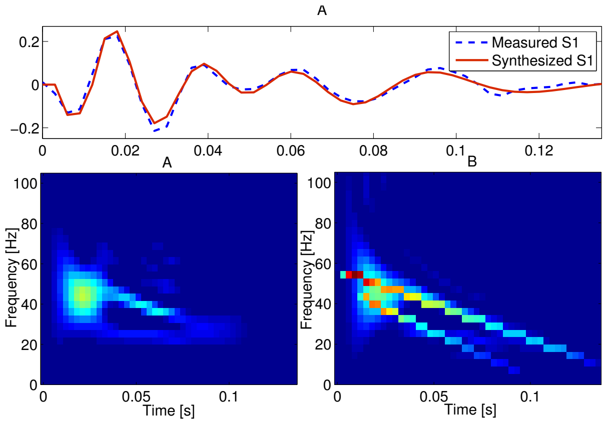

Figure 1: (A) A fetal S1 sound (dashed) and the result of the Monte Carlo based model fitting (solid). The normalized root mean square error between the measured and synthesized S1 sound is 24 %. The time-frequency distribution of (B) the the measured fetal S1 sound and (C) the corresponding synthesized heart sound superimposed by the instantaneous frequency function of the model (the color of the line corresponds to the instantaneous amplitude). Note the linear frequency decrease, especially observable of the component with higher frequencies. The time-frequency representations were calculated using the Wigner-Ville distribution.

the determination of these parameters is crucial for finding a possible relationship between heart murmurs and different heart defects.

Related publications: [2, 8, 12]

The detection of fetal murmurs is extremely difficult due to the attenuation caused by the maternal tissues and the low signal-to-noise ratio with many sources of noise (for example maternal heart and digestive sounds). There is also an important empirical observation, namely dominant low-frequency components of fetal heart murmur can be recorded on the maternal abdomen. In contrast, the murmur of children and adults has usually higher dominant frequency components than the main heart sounds. In addition, the recorded fetal heart murmurs exhibit in some cases a rather cyclostationary property despite the certainly turbulent origin of the murmur signal.

The suggested method tries to exploit these differences and applies an improved version of ensemble averaging for heart sound signal enhancement and heart cycle comparison.

In order to be be consistent with medical murmur parameters, and in this way facilitate the acceptance of fetal murmur analysis in the medical community we defined the following aforementioned five parameters. It is important to note that during the investigations it has been found that these five parameters can be calculated in an automatic way and have possible high discriminative value. For demonstrating the clinical significance of fetal murmur detection a case of congenital heart disease is presented hereunder where fetal phonocardiographic records revealed fetal heart murmur (Fig. 2). Although this is not a verified clinical trial these results support the feasibility of this new method, which could contribute to the prenatal detection of CHDs, as a pre-screening method for a comprehensive echocardiographic examination, especially in the low risk population.

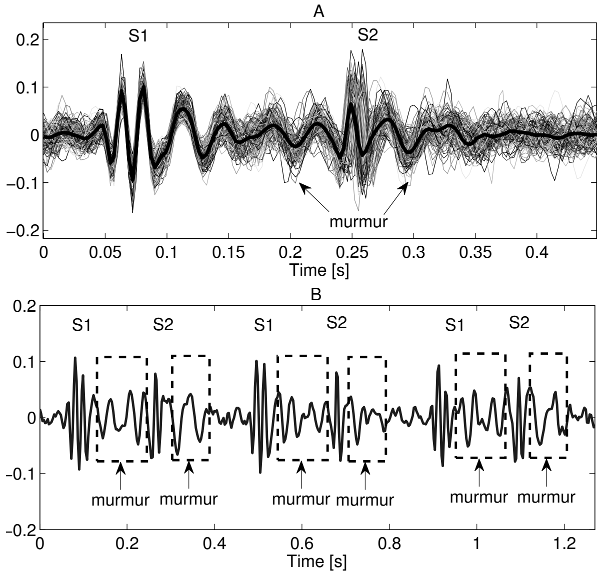

Figure 2: (A) The characteristic heart cycle (thick line) and the corresponding heart cycles (thin lines) of the fetus with Tetralogy of Fallot, pulmonary insufficiency and and aorta-pulmonary vessels producing fetal heart murmur. (B) Three consecutive heart cycles from the same record.

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Thesis II: *Phonocardiographic analysis of preterm neonates with patent ductus arteriosus (PDA) with special attention on the detection of heart murmur related to PDA and the relationship between parameters of the heart sounds and murmur and clinical parameters.*

II.1. I have worked out a method for the detection of murmur originating from the turbulent blood flow through the ductus arteriosus that achieves 90 % reliability, hereby opening possibilities for monitoring the disease through murmur analysis. This was confirmed by preliminary results from the correlation of certain murmur parameters with important medical parameters, in particular the diameter of the PDA and the maximal blood flow velocity through the PDA.

Related publications: [3, 6, 7]

The first step towards a PCG based PDA monitoring framework is the detection of the murmur related to the turbulent blood flow through the ductus arteriosus. Although methods have been suggested for murmur detection [27, 28], it is an especially difficult task for preterm neonates due to the high level of noise (e.g. breathing machine) and the low intensity of the murmur.

The introduced characteristic heart sound calculation method provides a way for observing typical heart cycle dynamics. Furthermore, the set of heart cycles used for the characteristic sound calculation can be used for automated processing, applied also for murmur detection. Due to the presence of wide band noise

I introduced a signal envelope based detection algorithm using baseline correction, which can be regarded as a form of adaptive thresholding. Heuristic rules based on *a priori* knowledge are also incorporated in the method for increased robustness.

When classifying preterms with and without PDA based on the length of detected late systolic sound components, and using a threshold of 7 % of the length of the systole, 90 % sensitivity and 60 % specificity could be achieved. Although the specificity is quite low, these are promising results, since the major goal is not a diagnosing but a monitoring application.

A second step of the development of a possible PDA monitor is to select appropriate parameters and find the relationship with important medical parameters. This is an even more challenging problem because the generation of murmur in such a complex scenario is still not completely understood. Nonetheless results exist on the relationship between frequency parameters of the murmur and important parameters of a stenosis producing heart murmur [29,30]. During my investigations I also performed measurements analysing this aspect. I found a weak relationship between the frequency parameters of the murmur and the diameter of the PDA (D_{PDA}) and the maximal blood flow though the PDA (v_{max}), shown in Fig. 3. Unfortunately, due to the lack of reference data with sufficient accuracy, these results are of a preliminary nature.

II.2. I have observed the temporal separation (split) of the aortic and pulmonary components of the second heart sound (S2) of preterm neonates with PDA, and I have introduced a heuristic method for estimating the splitting interval (SI) making the quantitative analysis possible and finding a 30 % average

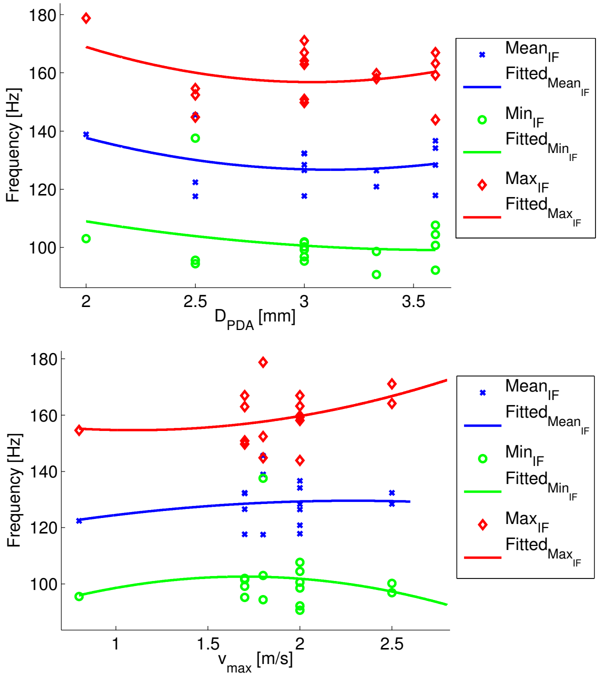

Figure 3: Extracted murmur parameters vs. medical parameters of the PDA: diameter of the PDA (top) and maximal blood flow velocity through the PDA (bottom). The frequency parameters are calculated from the instantaneous frequency of the murmur. The fitted regression curves are quadratic functions. As observable the frequency parameters of the murmur decrease substantially with D_{PDA} and increase with v_{max}.

increase of the SI around the time of the closure of the PDA in the case of preterms under pharmacological treatment.

Related publications: [3]

The closure of the patent ductus arteriosus is a dynamic process that is still not completely understood. Clearly, this process also affects the pressure ratios between the left and right side of the heart which can be assessed based on the splitting of the S2 sound. This phenomenon was also visually observed in the case of some of the recordings. Unfortunately the two components of the S2 sound usually overlap even in the time-frequency domain in a great manner, making separation very difficult. I introduced a solution for estimating the SI by applying a heuristic method which exploits the fact that the aortic and pulmonary components have an exponentially decreasing instantaneous frequency function resulting in high frequency oscillations only at the beginning of the components.

Since the exact accuracy of this method could not be verified because invasive measurements would have been needed, I applied a model-based approach. I adapted an existing heart sound model [21] to the characteristics of S2 sounds of preterm neonates, and verified the suggested SI estimation method on synthesised S2 sounds. This analysis revealed that reliable splitting interval estimation can be performed in the case of SI $>$ 7 ms.

I applied the introduced algorithm on the PCG data from preterm infants with PDA and found that in the case of pharmacologically treated infants the SI increased significantly around the time of the closure of the ductus arteriosus with respect to the period before the closure (Fig. 4). This result could also contribute to a possible PDA monitor although long term measurements on more patients are needed for better investigation of the SI dynamics.

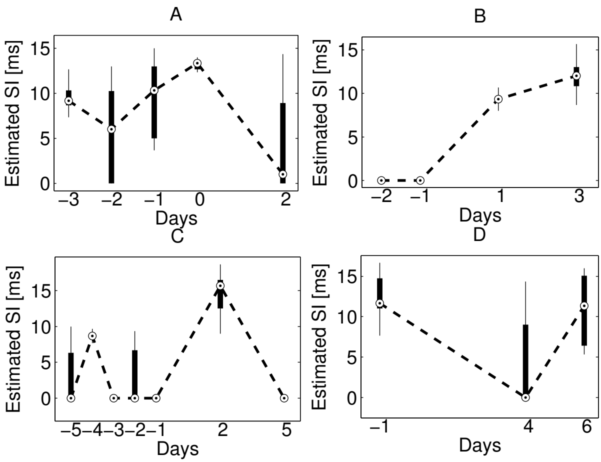

Figure 4: Box plot of the estimated SI over several days of four preterm infant with PDA treated pharmacologically. All four figures are drawn in a way that the closure of the PDA lies on Day 0. The dashed line shows the change of the median. An increase of the estimated SI around the time of the closure is observable.

Possible Applications

Most of the application possibilities of the presented results are rather evident because in most of the cases practical motivations were behind the investigations. The results of Thesis I are mostly specific to the analysis of fetal heart sounds, however the improved ensemble averaging could be utilized also for the heart sound analysis of preterm neonates, because a low signal to noise ratio was present also in that scenario. Improved fetal heart rate determination is an important step towards extending monitoring capabilities of the fetal wellbeing, namely based on heart rate variability analysis. This would be especially beneficial in the case of the telemetric system where surveillance is possible on a daily basis. Regarding the fetal heart sound model there is a possibility for further parameter extraction. For instance, it might be possible to track the blood pressure changes of the fetus in a throughout the pregnancy because some heart sound parameters correlate with certain blood pressure values. This is not possible with any other present technology. One of the most important findings is the observation of fetal heart murmurs in the case of certain congenital heart diseases (CHD). Although the significance of this result depends on the incidence of innocent murmurs and “silent” CHDs, having obtained the preliminary results it may be established that murmur detection and analysis can contribute to the widespread screening of cardiac abnormalities, especially in the low risk population. Furthermore, all these findings could assist in the development of a fetal expert system for automated surveillance or clinical decision support (Fig. 5).

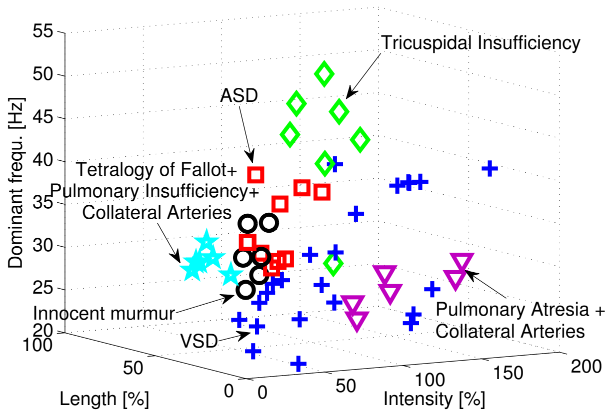

Figure 5: The distribution of three murmur parameters (length, intensity, dominant frequency). Each data point represents a murmur extracted from fPCG records of fetuses with different CHDs. The different symbols represent the related CHD to the murmur. Although there is some overlap, different domains that correspond to different CHDs can be defined.

The major motivation behind the analysis of the heart sounds of preterm infants with patent ductus arteriosus (PDA) was the investigation of a possible PCG-based PDA monitor, which is also the most important possible application. It should be mentioned that continuous monitoring of important medical parameters of the PDA is not possible at present. Although a difficult step is still ahead, namely to relate extracted heart murmur parameters reliably with medical parameters, the presented results support this concept. The method for splitting interval estimation serves the same issue, but it could be also applied in other fields of phonocardiography because the separation of the heart sound components is an important symptom in the case of other cardiovascular diseases as well. It should be noted, however, that in order to achieve the accurate and reliable tracking of important parameters of the ductus arteriosus, a multimodal approach is needed, since the hemodynamic significance of the PDA also depends on several parameters. These multimodal measurements could consist of the analysis of the murmur, estimation of the SI, analysis of the pulse wave, and monitoring of the blood oxygen level as well as some further parameters. The above envisaged system would improve the monitoring of patients with heart diseases such as PDA as well as lead to an increased understanding of the process of the PDA closing and its response to medication.

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And, although it cannot be formulated in words, thank you, my lovely Ramó.

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