Characterizing Fetal Sympatho-Vagal Balance through Multivariate Time-Varying Autoregressive Modeling of Magnetocardiographic Data

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Abstract— **We propose a method to analyze fetal beat-to-beat heart rate variability (HRV) obtained from magnetocardiographic (MCG) measurements at different times of gestation using a multivariate time-varying autoregressive (MTVAR) model. Our approach is based on treating a group of HRV signals from a single fetus and measured at different gestational periods as a dynamical system, from which a suitable MTVAR model is obtained. Then, changes in the values of the coefficients of the MTVAR model are associated to changes in fetal sympatho-vagal balance. Such association is made by comparing the dynamics of the MTVAR coefficients to the SDNN/RMSSD ratio, which is known to be a potential marker for sympatho-vagal balance. Furthermore, an overall behavior of the sympatho-vagal balance during the gestation is estimated from the average values of the MTVAR coefficients and compared to the tendencies previously reported in the literature. In order to demonstrate the applicability of the proposed modeling approach, real magnetocardiographic data from a healthy fetus is analyzed. Preliminary results show that the MTVAR model provides good insight into the sympatho-vagal dynamics with greater specificity compared to traditional measures.**

Keywords— **Fetal magnetocardiography, sympatho-vagal balance, heart rate variability, time-varying autoregressive modeling.**

I. INTRODUCTION

Fetal heart rate (fHR) monitoring is one of the most useful techniques for clinical fetal evaluation and neurodevelopmental research [1]. Doppler ultrasound-based cardiotocography (CTG) systems are widely used for assessing fHR and many other parameters of fetal development. However, CTG systems lack the precision required to accurately assess beat-to-beat variations, especially in early stages of gestation. In comparison to CTG, fetal magnetocardiography (fMCG) provides a precise signal that can be detected throughout the last half of pregnancy and often earlier [2]. Furthermore, fMCG allows for the temporal resolution of the QRS complex detection to be greatly enhanced [3], then enabling precise fetal beat-to-beat heart rate variability (HRV) analysis.

Although heart rate is affected by many factors, the utility of fHR monitoring is based on the increasing influence of the autonomic nervous system (ANS) during gestation. The separate rhythmic contributions from the sympathetic and parasympathetic (or vagal) branches of the ANS are mainly responsible of modulating fHR. Vagal tone causes fHR to fall, while sympathetic tone causes it to rise. Thus, fHR is regulated primarily by balancing sympathetic and vagal tone [4]. For this reason, much effort has been placed in the development of different methods to accurately quantify the sympatho-vagal balance by means of HRV analysis. In previous studies, linear HRV analyses, both in the time and frequency domains, have proved to be viable in the fetus [5,6]. Classical parameters of the time domain such as the standard deviation of the normal to normal beat intervals (SDNN) and the root mean square of successive differences of the normal beats (RMSSD) have been commonly used in earlier studies on fetal HRV [7], but they are not accurate enough and require a more extensive physiological validation to become an standard in the quantification of the sympatho-vagal balance. On the other hand, the representation of the frequency spectrum in the human fetus is currently a matter of debate [8].

In this paper, we propose a modeling approach for the characterization of the sympatho-vagal balance which is based on a multivariate time-varying autoregressive (MTVAR) model of the fetal HRV. The MTVAR modeling approach has been previously found useful in characterizing the dynamics of electroencephalographic (EEG) data from epileptic seizures [9]. In our case, the goal is to correlate the dynamics of the coefficients associated to the MTVAR model to (i) changes in the vagal components of the HRV when analyzing measurements corresponding to a single gestational period, and (ii) overall changes of the sympahto-vagal balance during different gestational periods when analyzing a group of measurements. In the first case, the correlation is investigated by comparing the dynamics of the MTVAR model's coefficients to the mean heart rate (mHR), the SDNN/RMSSD ratio, and to the fetal HR pattern (fHRP) index [10]. For the case when a group of fetal HRV measurements acquired at different gestational periods is analyzed as a dynamic system, we propose to use the mean value of the time-varying coefficients as an indicator of the overall development of the sympatho-vagal balance through gestation. The trend of such indicator is expected to

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follow the tendency reported in the literature, where the sympatho-vagal balance has been reported to decrease towards term due to an increased vagal influence [11].

Therefore, in Section II we describe the proposed MTVAR modeling approach. In Section III we show the applicability of our method through numerical examples using real fMCG data, and in Section IV we discuss the results and future work.

II. METHODS

Let us denote the HRV signal at a given gestational period as vector $\boldsymbol{x}_k = [x_{k,1}\ x_{k,2}\ \ldots\ x_{k,N}]^T$, where k corresponds to the gestational variable such that $k = 1, 2, \ldots, K$ equally spaced gestational periods, and N is the number of samples. Furthermore, let us define the following autoregressive model for the measurements [12]:

$$\boldsymbol{x}_\nu = \boldsymbol{\omega} + \sum_{l=1}^{p} A_l \boldsymbol{x}_{\nu-l} + \boldsymbol{\varepsilon}_\nu \qquad (1)$$

where ν is the dynamic variable, p is the order of the model, A_l are the coefficients of the model, $\boldsymbol{\omega}$ is a vector of intercept terms that allows to model nonzero mean time series, and $\boldsymbol{\varepsilon}_\nu$ is a vector of uncorrelated random noise.

For the case when ν corresponds to equally spaced gestational periods, i.e. $\nu = k$, then (1) becomes a multivariate model for a time series of K-dimensional state vectors, where $A_1, A_2, \ldots, A_p \in \mathcal{R}^{K\times K}$ are the coefficient matrices of the model. Hence, the problem of computing a model from the measured data corresponds to find the values of the p coefficients such that (1) best fits the data according to a selection criterion [13]. Finally, the MTVAR modeling problem corresponds to the case when the values of the coefficient matrices are updated every τ samples, which results in a group of time-varying coefficients.

The MTVAR models have been used to study the dynamics of different types of multivariate time series. For example, this modeling approach was used in [9] to study EEG data of generalized seizures for the identification of changes in frequency structure over time, which may suggest that seizures are product of multiple processes. In [14], the coefficients of a MTVAR model are used as unique identifiers of EEG data from different mental tasks, so they can be used in brain-computer interface as control commands. In our case, a similar approach is proposed: the dynamics of the MTVAR coefficients will be associated to the dynamics of the sympatho-vagal balance. In order to validate such association, we compare the dynamics of the computed MTVAR coefficients to the mHR, the SDNN/RMSSD ratio, and the fHRP index, as all them are currently used as reference parameters in clinical applications and have shown good potential as markers to reflect sympatho-vagal balance [15].

III. NUMERICAL EXAMPLES

We conducted a series of experiments in which we applied the MTVAR model described in Section II to real fMCG data from a healthy patient at the 24, 26 and 28 week of gestation. The data were collected at the MEG-Center in Tübingen, Germany. The sample rate was 1250 Hz and recordings were performed during 30 minutes intervals. Then, the algorithm described in [3] was applied for the detection of the R peaks, and from them the HRV signal was constructed. An example of the resulting signal for the recordings at week 26 is shown in Figure 1. The HRV signals corresponding to weeks 24 and 28 are shown as supplementary material in [16].

We performed two different kind of analysis to the HRV signals. Firstly, we analyzed each gestational period individually to evaluate changes in the vagal components of the HRV during the time of the recordings. Secondly, we took all available measurements and obtained the MTVAR model. From the dynamics of the corresponding coefficients, we characterized the overall tendency of the sympatho-vagal balance relative to the measurement period. In both cases, the autoregressive models were obtained using the computer implementation proposed in [17], and the optimal order for the models was selected according to Schwarz's Bayesian Criterion [18] in every case.

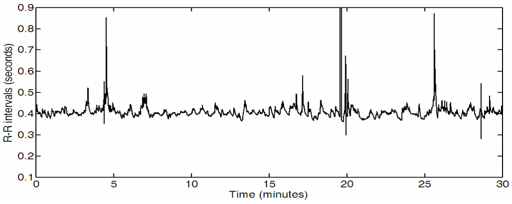

Fig. 1 HRV signal corresponding to the recordings at the 26 week of gestation

A. *Univariate Analysis*

In this case, we computed the autoregressive model for the gestational periods individually. In each case, the model was computed using a window with a fixed size τ = 256 heart beats [19]. The window was shifted every sample to cover the complete HRV signal, which allowed to update the coefficients of the model. Given that the modeling process not necessarily chooses the same order for each

HRV signal, the number of coefficients might differ. Since we are interested in the dynamics of the coefficients and not in their values themselves, we computed the compound variability of the coefficients by means of the multivariate Length Transform [20] given by

$$\lambda_i = \sum_{j=i}^{\tau+i-1} \sum_{l=1}^{p} |A_{l,j} - A_{l,j-1}|, \ i = 1, 2, \ldots \qquad (2)$$

where the index i stands for the coefficients' update time. Figure 2 shows the result of this process for the case of the HRV data previously shown in Figure 1. The results corresponding to the data of weeks 24 and 28 are shown in [16].

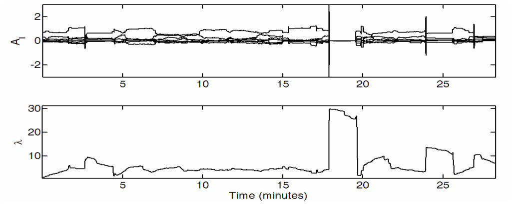

Fig. 2 Dynamics of the autoregressive model's coefficients for the HRV signal corresponding to the recordings in Figure 1 (top) and their multivariate Length Transform (bottom)

The variability information of the autoregressive coefficients given by λ is then compared to the mHR, the SDNN/RMSSD ratio, and the fHRP index, which are computed as described in [7, 10]. In order to make a more accurate comparison, two additional measures are proposed:

- SDNN/λ ratio, which is motivated by the similirarities between the RMSSD and λ. However, we expect λ to provide an enhanced quantification of the short-term variability;
- State detection index (SDI) which is based in the SDNN/λ ratio and uses an statistical criterion to classify fHR rate accelerations within the lenght of the study in three levels: (1) above SDNN/λ ratio's mean, (2) above the mean plus one standard deviation, and (3) above the mean plus two times the standard deviation.

Therefore, we computed all the previously described measures for the HRV signals. The results are shown in Figure 3 for the data corresponding to week 26, and in [16] for weeks 24, and 28. Note that the mHR is given in heart beats per minute, the SDNN/RMSSD and SDNN/λ ratios are adimensional, and the fHRP and SDI indexes indicate different discrete levels related to the sympatho-vagal balance of the fetus [15]. Our results show a strong correlation between sustained accelerations in fHR and the SDNN/λ ratio, while providing greater specificity in comparison to the SDNN/RMSSD ratio. This fact is more clearly shown by comparing the fHRP against the SDI: they both correspond to discrete versions of the SDNN/RMSSD and SDNN/λ ratios, respectively. However, the fHRP is not capable to determine the activity state of the fetus most of the time (which is indicated by a zero-value in the fHRP graph in Figure 3). On the other hand, the SDI index is directly linked to fHR accelerations, specially in terms of the duration and magnitude of the events within the processing window, then it provides a better insight on the activity state of the fetus.

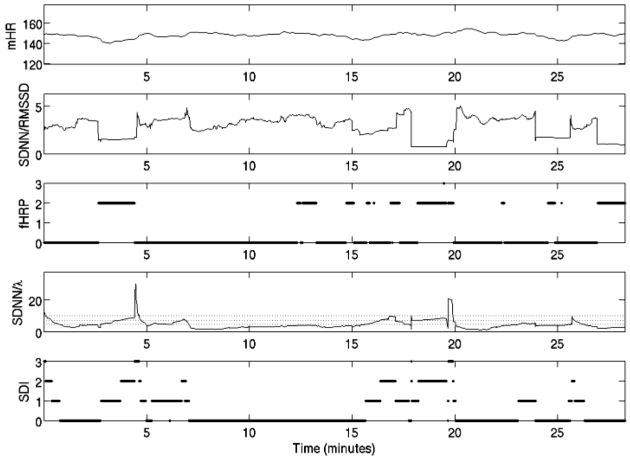

Fig. 3 HRV univariate analysis of the data corresponding to the 26 week of gestation. The dotted-lines in the SDNN/λ ratio (fourth row) indicate, from lower to higher magnitude, the mean value, the mean plus one standard deviation, and the mean plus two standard deviations, respectively. Then, the SDI (fifth row) corresponds to a three-level categorization of the SDNN/λ ratio

B. *MTVAR Modeling*

We computed the MTVAR model of the measurements for the case when they are analyzed together as a dynamical system. Since the coefficients A_l are now matrices, we studied the dynamics of the diagonal components only, as it is assumed that the measurements at each gestational period are independent between each other. Therefore, we calculated λ of the diagonal elements at each gestational period and compared their dynamics. Figure 4 shows the variations in time of the diagonal elements in matrix A_1 (figures corresponding to matrices $A_2, \ldots, A_p$ are shown in [16]), as well as their length transforms. In comparison to the univariate analysis, the MVTAR modeling approach also shows the relative dynamics of the system as function of the gestational period. However, note that the short-term characteristics are kept, as shown around the 18 minutes of the recording of week 26, where an increase in the variability is clearly noted as probable result of increased fetal activity.

Finally, we computed the mean value of λ over time for each gestational period and normalized it to the total energy for the dynamical system. As result, we obtained the mean energy content (in percent) at each gestational period, which turned out to be of 28%, 55%, and 17%, for week 24, 26, and 28 respectively. These percentages could be used as an overall indicator of the relative changes of the sympatho-vagal balance at the analyzed gestational periods.

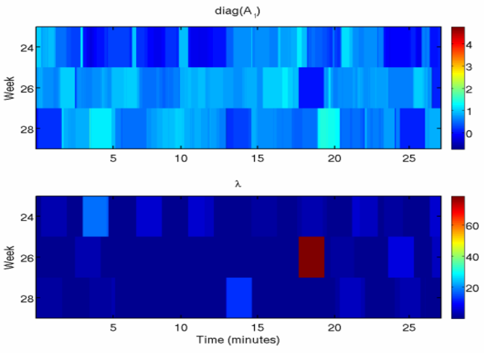

Fig. 4 MTVAR analysis. Figures show the dynamics of the diagonal elements of A_1 (top) and the corresponding length transform (bottom)

IV. CONCLUSIONS

We presented a method to characterize the sympatho-vagal balance by using the dynamics of the coefficients of an MTVAR model as indicator, where the variability content of the coefficients was enhanced through the length transform. Our characterization is in agreement with traditional measures, but seems to provide a higher level of specificity. Still, further physiological validation of the proposed measures is required.

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REFERENCES

[1] Martin CB (1982) Physiology and clinical use of fetal heart rate variability. Clin Perinatol 9:339-352
[2] Peters M, Crowe J, Pieri JF, Quartero H, Hayes-Hill B, James D, et al. (2001) Monitoring te fetal heart non-invasively: a review of methods. J Perinat Med 29:408-416
[3] Wilson JD, Govindan RB, Hatton JO, Lowery CL, Preissl H (2008) Integrated approach for fetal QRS detection. IEEE Trans Biomed Eng 9:2190-2197
[4] Malliani A, Pagani M, Montano N, Mela GS (1998) Sympathovagal balance: a reappraisal. Circulation 23:2640-2643
[5] Van Leeuwen P, Geue D, Lange S, Hatzmann W, Groenemeyer D (2003) Changes in the frequency power spectrum of fetal heart rate in the course of pregnancy. Prenat Diagn 23:909-916
[6] Schneider U, Frank B, Fiedler A, Kaehler C, Hoyer D, Liehr M, Haueisen J, Schleussner E (2008) Human fetal rate variability-characteristics of autonomic regulation in the third trimester of gestation. J Perinat Med 36.433-441
[7] Grimm B, Haueisen J, Huotilainen M, Lange S, Van Leeuwen P, Menendez T, et al. (1997) Recommended standards for fetal magnetocardiography. Pacing Clin Electrophysiol 26.2121-2126
[8] David M, Hirsch M, Karin J, Toledo E, Akselrod S (2007) An estimate of fetal autonomic state by time-frequency analysis of fetal heart rate variability. J Appl Physiol 102:1057-1069
[9] Krystal AD, Prado R, West M (1999) New methods of time series analysis of non-stationary EEG data: eigenstructure decompositions oftime varying autoregressions. Clin Neurophysiol 110:2197-2206
[10] Nijhuis JG, Prechtl HFR, Martin CB, Bots RSG (1982) Are there behavioral states in the human fetus? Early Hum Dev 6:177-195
[11] Zhuravlev Y, Rassi D, Mishoin AA, Emery SJ (2002) Dynamic analysis of beat-to-beat fetal heart rate variability recorded by SQUID magnetometer: quantification of sympatho-vagal balance. Early Hum Dev 66:1-10
[12] Neumaier A, Schneider T (2001) Estimation of parameters and eigenmodes of multivariate autoregressive models. ACM Trans Math Softw 27:27-57
[13] Lütkepohl H (1993) Introduction to multiple time series analysis. Springer-Verlag, Berlin
[14] Anderson CW, Stolz EA, Shamsunder S (1998) Multivariate autoregressive models for classification of spontaneous electroencephalographic signals during mental tasks. IEEE Trans Biomed Eng 45(3):277-286
[15] Task Force (1996) Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task force of the European society of cardiology and the north American society of pacing end electrophysiology. Eur Heart J 17:354-381
[16] Available at http://biomag2010.gutierrezruiz.com
[17] Schneider T, Neumaier (2001) Algorithm 808: ARfit – A Matlab package for the estimation of parameters and eigenmodes of multivariate autoregressive models. ACM Trans Math Softw 27:58-65
[18] Schwarz G (1978) Estimating the dimension of a model. Ann Statist 6:461-464
[19] Ronneburger A, Kähler C, Hoyer D, Schleussner E, Schneider U, Hauisen J, et al. (2004) Influence of fetal state of activity and duration of recording time on linear and non-linear parameters of fetal heart rate variability investigated by fetal magnetocardiography. Biomed Eng 48(Suppl):143
[20] Gutiérrez D, Preissl H, Eswaran H, Lowery CL (2007) A study of fetal sympatho-vagal balance at various gestational periods using the length transform on magnetocardiographic data. Comp Cardiol 34:685-688

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