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Spatial-Temporal Analysis of Fetal Bio-Magnetic Signals

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Abstract

Non-invasive technique such as Magneto-encephalography (MEG), initially pioneered to study human brain signals, has found many other applications in medicine. SQUID2 Array for Reproductive Assessment (SARA) is a unique noninvasive scanning-device developed at the University of Arkansas for Medical Sciences (UAMS) that can detect fetal brain and other signals. The fetal magneto-encephalography (fMEG) signals often have many bio-magnetic signals mixed in. Examples include the movement of the fetus or muscle contraction of the mother. As a result, the recorded signals may show unexpected patterns, other than the target signal of interest. These “interventions” make it difficult for a physician to assess the exact fetal condition, including its response to various stimuli. We propose using *intervention analysis* and *spatial-temporal autoregressive moving-average* (STARMA) modeling to address the problem. STARMA is a statistical method that examines the relationship between the current observations as a linear combination of past observations as well as observations at neighboring sensors. Through intervention analysis, the change in a pattern due to “interfering” signals can be accounted for. When these interferences are “removed,” the end product is a “template” time series, or a typical signal from the target of interest. In this research, a “universal” template is obtained. The template is then used to detect intervention in other datasets by the method of template matching. By this method, it is possible to detect if there is an intervention in any dataset. It will assist physicians in monitoring the actual signal generated by fetal brain and other organs of interest.

Keywords

Magneto-encephalography (MEG); Fetal magneto-encephalography (fMEG); spatial time series; spatial-temporal analysis; non-stationarity; non-homogeneity; intervention analysis; template matching

2. INTRODUCTION

Aside from a sensor placed over a target, MEG signals are often collected by more than one sensor placed on the vicinity of the target. The signals from the target sensor and its neighboring sensors are related to one another spatially. In other words, these signals are correlated across sensors as well as over time. We call this set of information spatial time-series. A spatial time-

²Superconducting Quantum Interference Device

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series of MEG signals can sometimes be affected by unknown interferences, commonly called *interventions*. Interventions can convert an otherwise stationary and homogeneous series to non-stationary and non-homogeneous series, which are difficult to analyze (Fitzgerald et al. 2000, Mäkinen et al. 2005). By way of a definition, homogeneity is a spatial effect analogous to stationarity in the time dimension (Cressie 1991).

To obtain the most accurate information from MEG signals, it is desirable to be aware of an existence of an intervention, so that it can be identified and accounted for. The conventional procedure to eliminate the interfering-signal components include visually inspecting the data. Then a spatial filter is applied based on orthogonal projection operators. This was accomplished by the combination of Woody filtering and orthogonal projection method (Ussitalo and Ilmoniemi 1997, Vrba et al 2002). While this is widely practiced, it is subject to some well known shortcomings. First, not all interventions can be detected by inspection. Second, signals in the specified frequency range are arbitrarily removed or attenuated. This often results in useful signals being discarded (Akay 1996).

An alternative method, *Intervention analysis*, is a classical method of dealing with external events that affect a time series (Pankratz 1991, Chan 2005). The standard procedure to detect an intervention involves “template matching,” where a template of a typical signal without intervention is derived. The correlation between the template and a non-stationary and/or non-homogeneous series is then computed. The correlation (or rather the lack of a correlation) will indicate whether there is an intervention.

Typically, a signal judged to be devoid of an intervention is used as a template. However, a scientific method to obtain such a template—aside from a qualitative judgment—has yet to be found. Potentially, we offer such a method in this paper. First, a non-stationary and/or non-homogeneous series is modeled using a Spatial-Temporal Auto-regressive Moving-Average (STARMA) model. Second, a *transfer function* is calibrated to capture the known intervention. From these techniques, a universal template is derived. A template-matching procedure is then proposed to detect interventions in any unknown dataset.

SARA is a unique non-invasive fMEG measurement device developed at the University of Arkansas for Medical Sciences (UAMS). It was designed to detect weak biomagnetic activity of the fetal brain (Robinson et al. 2000). The 151 sensor array of SQUID is intended to read signals from all biologically active sources inside a fetal body. The SARA instrument is illustrated in Figure 1. Aside from the hardware, the manufacturer provided software for regular signal processing, formally called the CTF Data Editor.

The data collected from the abdomen of any pregnant patient include these signals:

- Maternal heart and fetal heart
- Signals generated by fetal brain
- Smooth uterine-muscle signals and maternal gastro intestinal signals
- Other bio-magnetic signals, modulated by fetus movement
- Bio-magnetic signals from unknown sources

Numerous interventions can be present in these data, including the following

- Fetal heart signals
- Fetal breathing
- Maternal heart signals

- Maternal breathing
- Movement of the fetus
- Movement of the mother
- Other unknown interferences

Figure 2 shows a typical session recording for SARA. The signal is measured in Femto-tesla, suggesting a rather weak signal. Shown in the Figure is the recording for a single sensor (channel). Six samples are collected in a session, each 60-second in length, consisting of 18,750 data points each (or a large amount of information). Even with the untrained eyes, it is obvious that sinusoidal patterns are present in the raw data. Those who have examined these signals previously would recognize that the sinusoidal patterns are probably due to the infant's breathing. Such breathing constitutes an intervention; it makes the signal non-stationary.

3. METHODOLOGY

Rather than arbitrarily removing intervention signals within a frequency range, as is performed by filters, an alternative is to explicitly analyze the stationarity and homogeneity of a time series. While there is a plethora of information on stationarity, literature on homogeneity is relatively sparse. Spatial heterogeneity is a kind of spatial effect that suggests the lack of stability over space in the underlying behavioral or other relationships (Chan 2005). To confirm non-homogeneity in a dataset, space-time autocorrelations of different target sensors and its first- and second-order neighbors are calculated. The process of producing the “template” and detecting an intervention can be broadly divided in two phases. The first phase models the data with the spatial-temporal method and the second phase accounts for the intervention using *intervention analysis*.

Prior to any modeling procedure, however, the raw data have to be pre-screened as follows.

Step 1. Removal of Maternal and fetal magneto-cardiogram (MCG):

A raw dataset is usually contaminated by maternal and fetal MCG artifacts. These artifacts are eliminated by applying projection operators on the data to obtain “clean” fMEG signals (Vrba et al 2002). This is done on the Data Editor that comes with the SARA instrument.

Step 2. Apply a viewing filter of 0.5 to 10Hz:

A SARA dataset is collected at a sampling rate of 312.5 Hz and in a bandwidth of 0–100 Hz. For the purpose of this study, we apply a viewing filter of 0.5 to 10Hz, as fetal brain activity is in this range (Eswaran et al. 2002). This is also done in Data Editor.

Step 3. Visually inspect the data for channels affected:

In the datasets with known breathing interventions, channels near the fetal heart and channels affected by the maternal heart are inspected by looking at the filtered data and its frequency spectrum. For unknown datasets this is not required. Again, this is done in the Data Editor.

Step 4. Select the channels:

Once the channels have been inspected, the channel most affected with an intervention(s) is selected as the target sensor.

3.1. Spatial-temporal analysis

For a spatial time series consisting of T observations over time and involving N sensors (channels), the spatial-lag operator $L^{(l)}$ for the signal at the i th sensor, $z_i(t)$, is defined as

$$L^{(l)} z_i(t) = \sum_{j=1}^N w_{ij}^{(l)} z_j(t) \quad \text{Equation 1}$$

Here $w_{ij}^{(l)}$ is a set of weights assigned to every l th spatial order, within which contain the neighboring sensors j . As will be explained in more detail, the weights reflect the strength of the signal emanating from i to j . When $l = 1$, we are referring to the most immediate neighbors. When $l = 2$, we are referring to the next neighbor over and so on. Figure 3, which is a detailed plot of the sensor map of Figure 1, shows the target sensor LI1 and its first-order second-order and third-order neighbors as concentric contours or “onion rings.” Oftentimes, they are called the rook and bishop contiguity relationships respectively.

Based on this spatial lag operator $L^{(l)}$, space-time autocorrelation for time-lag s and spatial-lag l is defined by the following equation:

$$\rho_{llk}(s) = \frac{\sum_{i=1}^N \sum_{t=1}^{T-s} L^{(l)} z_i(t) L^{(k)} z_i(t+s)}{\sqrt{\sum_{i=1}^N \sum_{t=1}^T (L^{(l)} z_i(t))^2 \cdot \sum_{i=1}^N \sum_{t=1}^T (L^{(k)} z_i(t))^2}} \quad \text{Equation 2}$$

Alternatively, Moran’s I is also a viable way to check homogeneity in a dataset. Recall Pearson’s correlation is simply defined as

$$\sum_{ij} [(z_i - \bar{z}_i)(z_j - \bar{z}_j)] / s(z_i) s(z_j) \quad \text{Equation 3}$$

where $s(z_i)$ is the standard deviation of observations z_i . Let us modify this to consider a related, but similar denominator. Suppose we consider the effect of a spatial weight-matrix, $\mathbf{W} = [w_{ij}]$, we have the Moran’s I statistics:

$$n \sum_i \sum_j w_{ij} [(z_i - \bar{z}_i)(z_j - \bar{z}_j)] / w \sum_i (z_i - \bar{z})^2 \quad \text{Equation 4}$$

In other words, Moran’s I is simply the Pearson correlation taking into account a given spatial contiguity as defined by the $\mathbf{W}$ matrix.

In Equation 4, $w = \sum_{i=1}^N \sum_{j=1}^N w_{ij}$. In general, $w = 2(2\bar{R}C' - \bar{R} - C')$ in the *rook*’s definition of contiguity (or for first-order neighbors), $w = 4(\bar{R} - 1)(C' - 1)$ in the *bishop*’s definition (second-order neighbors), and $w = 2(4\bar{R}C' - 3\bar{R} - 3C' + 2)$ in the *queen*’s definition (first- and second-order neighbors combined). Here $\bar{R}$ is the number of rows and C' the number of columns in an array, typically organized in a grid or lattice pattern. In a square $C' \times C'$ grid, these formulas become $4C'(C' - 1)$, $4(C' - 1)$ and $4(2C' - 1)(C' - 1)$ respectively. While the definition is

introduced in a typical grid tessellation, the same concepts apply toward other tessellations, including “Chinese checker” patterns, as is the case for the SARA instrument.

Following this definition, a frequency plot of Moran’s I values is calculated based on a large enough Monte-Carlo sampling of observations z_i over the given spatial contiguity pattern. Based on this frequency plot, a hypothesis is formulated to check the homogeneity of a given dataset. For example, a hypothesis can be generated for a 95% confidence level as follows. A *cumulative* distribution of Moran’s I is constructed, as shown in Figure 4, where the cumulative distribution is the frequency with which the threshold value I' is *exceeded*.

Based on Figure 4, these hypotheses can be formulated for the upper tail of this distribution:

A null hypothesis H_0 : When (the number of Moran’s I values which is greater than 0.5) ≥ 200 , The region will be considered homogenous.

An alternate hypothesis H_A : When (the number of Moran’s I values which is greater than 0.5) < 200 , The region will be considered non-homogenous.

In this case, a threshold of 200—presumably a small fraction of the data points in Figure 4—is picked from the randomization frequency plot, serving as a datum for comparison with a given dataset. We wish to test whether the dataset is correlated or not correlated, where a correlated dataset *suggests* non-homogeneity and an uncorrelated one suggests homogeneity. Notice that Moran’s I tests the spatial heterogeneity of the data at an instant of time. To check the homogeneity over time, we revert to Space-Time Autocorrelation, as defined in Equation 2.

Notice that Moran’s I complements space-time autocorrelation in spatial analysis, inasmuch as it takes spatial contiguity into account *a priori*. In such a way, geometric patterns in the data are acknowledged and do not need to be accounted for by a statistical correlation. Because of the complementarity between the two statistics, we use both correlation measures in our analysis.

3.2. Target sensor, neighbors and spatial weights

If there is a single target to monitor, one wishes to construct a *univariate* space-time model around the target, consisting of the target sensor and its neighboring sensors. In a classical univariate STARMA model, first-order neighbors are closer in distance than second-order neighbors and the second-order neighbors are closer in distance than third-order neighbors. Spatial weights are determined to represent the *a priori* correlation or relationship between the target sensor and each of its neighbors. Spatial weights are a function of distance between the target and the respective neighbors. Generally speaking, weights decline with distance. These

weights are normalized, or $\sum_{j=1}^N w_{ij}^{(l)} = 1$ for up to N neighbors in the l^{th} order neighborhood.

In the case there is more than one target, or the “focal area of interest” consists of a large area, more than one univariate STARMA model is constructed, or $i = 1, 2, \dots, N$. For all i , $w_{ij}^{(l)}$ are nonzero only if sites i and j are l^{th} order neighbors of interest. As mentioned, this can be represented in a form of a matrix. The matrix representation of the set of weights $w_{ij}^{(l)}$ is $\mathbf{W}^{(l)}$, an $N \times N$ matrix with each row summing to one. Weights are calculated using forward solution of a Maxwell equation, as given by de Munck (1992) and Vrba et al (2004a). The computer program by Vrba et al (2004a) takes input as the locations of a current dipole at the target and a bank of neighboring sensors, and produces the intensities of magnetic field on the sensors due to the current dipole.

According to Moran’s I and space-time autocorrelation, suppose the dataset is non-homogeneous. For example, suppose the space-time autocorrelation values are significant for

first two lags in the space dimension, it supports the hypothesis of a non-homogeneous dataset. When corroborated with Moran's I , we wish to induce homogeneity in the dataset. Analogous to inducing stationarity, differencing is done in the space dimension similar to the time dimension. This means the zeroth-order series is subtracted from first-order neighbors and first-order neighbors by second-order and so on. Figure 5 gives an idea of spatial differencing, where the number of sensors—shown as ellipses—in each spatial neighbor is different. As illustrated in Figure 3, a single target is involved here as the zeroth order neighbor. Each target and its first-order and second-order neighbors are shown as a swath, and each swath is repeated over the time axis. Naturally the contour (“onion ring”) of first-order neighbors includes more sensors than the target zeroth-order neighbor. And the “onion ring” of second-order neighbors includes even more sensors than the first-order neighbors.

In this Figure, we show that the differencing is performed across neighbors, in addition to across time. Differencing between t and $t-1$ time-periods now translates to differencing between a target-sensor reading and the *average* of its first-order neighbors. This means the zero order reading is subtracted from the average of first order neighbors and first order neighbors by second order and so on. Similar to such operation in the time dimension, one degree of freedom is lost as a result of each spatial differencing.

Once homogeneity is obtained, the choice of a target sensor (or sensors) becomes less important. The reason is that all the neighboring sensors are now homogeneous. In other words, a univariate STARMA model constructed for target sensor i is theoretically the same as one for sensor i' .

3.3. STARMA Modeling

As described by Pfeifer and Deutsch (1980), a family of space-time models called STARMA can be synthesized for modeling a wide variety of space-time processes. These models are characterized by auto-regressive and moving-average terms lagged both in space and time. As Giacomini and Granger (2002) pointed out, STARMA can be derived through a (nontrivial) transformation of the Vector Auto-Regressive Moving-Average model, a model that tracks a vector of several data points simultaneously. Since each spatial neighborhood has its special characteristics, the transformation is in fact a restriction related to the neighborhood structure as revealed by a set of weight matrices. Kamarianakis (2003) has researched on three alternate modeling techniques that apply to multiple time-series data corresponding to different spatial locations. We believe that a similar approach can be carried out for MEG signals. Aside from the time dimension, STARMA describes spatial autocorrelation, or time cross-correlation between the signals at pairs of sensors. As mentioned, this is accomplished based on space-time autocorrelation between the l th and k th order neighbors using a set of weights $w_{ij}^{(l)}$.

In many ways, we can relate a time series with ordinary least-squares regression, where the dependent variable is z_t , and the independent variables are the one- and two-period lagged-data z_{t-1} , z_{t-2} and so on. While regression mainly entertains the relationship between the dependent and independent variables, autoregressive moving-average (ARMA) models take into explicit account the relationship between the dependent variable and the error (moving average) terms a_t as well. The STARMA model is given by the equation

$$z_t = \sum_{k=1}^p \sum_{l=0}^{\lambda_k} \varphi_{kl} L^{(l)} z_{t-k} - \sum_{k=1}^q \sum_{l=0}^{m_k} \theta_{kl} L^{(l)} a_{t-k} + a_t$$

Equation 5

where z_t is the stationary and homogeneous time series of interest, a_t is the residual series, and ϕ_{kt} and θ_{kt} are calibration constants. In addition to time shifts, L works as the backshift operator on the spatial component. Hence, $L^{(l)}z_t$ is the calculation performed on the l th-order neighbor of z_t . λ_k is the spatial order of the k th auto-regressive term and m_k is the spatial order of the k th moving-average term. The common designation of STARMA model is STARMA $(p, q, d)^r(m, n, D)$. Here p and q are the orders of auto-regressive parameters and moving-average parameters respectively in the time dimension, m and n are the order of auto-regressive and moving-average parameters in the spatial dimension, d and D represent differencing in time and space dimension correspondingly to induce stationarity and homogeneity. Tracing back to the database, r gives the order numbers of neighbors modeled.

Realization of a STARMA model starts with an extensive examination of the dataset and its statistical parameters such as autocorrelation and partial autocorrelation. This is performed from different perspectives. The dataset is checked for non-stationarity and non-homogeneity in time and space respectively. After “sanitization” of the data, i.e., after the dataset has been made stationary and homogeneous, the temporal and spatial autocorrelations decide the order of the STARMA model. STARMA parameters are then estimated and a tentative model is formed. Model is passed through various diagnostic checks to determine whether the model represents the data accurately. If not the whole process is repeated and another tentative model is tested. One of the important parameters is the spatial weight assigned to each order of neighbor, whether it be the first-, second-, third-order neighbors. Also, individual weights are assigned to each sensor to reflect its contribution toward the target sensor under consideration.

3.4. Intervention Analysis

As mentioned, a time series of observations can sometimes be affected by external events, commonly called interventions. An intervention is described as an event which affects the statistical properties such as the mean and standard deviation of the series. Such events change a regular stationary/homogeneous time series into a non-stationary/non-homogeneous one. Built upon on STARMA, Greene (1992) removes an intervention using an exogenously derived screen. Instead of such a template, Wright (1995) models interventions with a transfer function. Chan (2005) provides a comprehensive discussion of stationarity, homogeneity, STARMA, and intervention analysis. To model an intervention, let us consider an output or endogenous variable Y_t that is related to a single input or exogenous X_t variable through the dynamic model

$$Y_t = v(B)X_t + n_t \quad \text{Equation 6}$$

Here Y_t is the time series of interest, $v(B)$ is the transfer function, with individual coefficients representing *impulse response weights*, and n_t is noise.

Several tasks are associated with the modeling of intervention analysis.

- Deciding if and when an intervention occurs.
- Finding the transfer function, $v(B)$, to represent the intervention(s).
- Identifying precisely what external events are interventions to the time series.

Following Equation 6, the identification of the transfer function model will be much simpler if the input series is white noise. When the original input follows some other stochastic process, simplification is possible by *pre-whitening* (Mills 1990, Chan 2005). The input series that is differenced to induce stationarity and homogeneity is capable of being represented by some member of the general linear class of STARMA models. Once the autoregressive and moving-

average operators have been calibrated, the input series X_t can be transformed into white noise by the following equation:

$$\theta_x^{-1}(B) \varphi_x(B) X_t = \alpha_t$$

which, to a close approximation, transforms the correlated input series X_t to the uncorrelated white noise series α_t .

At the same time, we can apply the same transformation to the output series Y_t to obtain

$$\beta_t = \theta_x^{-1}(B) \varphi_x(B) Y_t$$

Then the transfer-function model can be written as

$$\beta_t = v(B) \alpha_t + \varepsilon_t$$

where, ε_t is the transformed noise series defined by

$$\varepsilon_t = \theta_x^{-1}(B) \varphi_x(B) n_t$$

Interventions are then modeled by adding a transfer function model to the STARMA model. The analog of the bivariate model described in Equation 6 can now be written as

$$\beta_t = v(B) \alpha_t + \varphi_z(B) \frac{\vartheta_t}{\theta_z(B)} = v(B) \alpha_t + \varepsilon_t$$

Equation 7

where β_t is the estimated output from the pre-whitened input-series α_t , $\varphi_z(B)$ is the STARMA auto-regressive operator, $\theta_z(B)$ is the STARMA moving-average operator, ϑ_t is the combined effects of all other factors, and ε_t is the transformed noise-series. Here, the transformed noise series ε_t is defined as the *Template*, since it is devoid of interventions and other patterns in the time series. It represents the “un-tampered” signal of interest. *When other pre-whitened signals are compared to it, this template will help detect the existence of an intervention.*

Notice the calibration of the transfer function is iterative. It comes after the calibration of the STARMA model, since the results of the STARMA calibration are used in the pre-whitening procedure. If the calibration of the transfer function is not satisfactory, one may need to go back to the STARMA calibration. This is repeated until both the STARMA and transfer function calibrations are complete.

3.5. Modeling steps of the algorithm

We have seen the four “data pre-screening” steps previously, labeled Steps 1 through 4. The following are the remaining modeling steps, Steps 5 through 12. They are used to derive templates from different datasets, including the “universal” template. These eight computational steps capture the discussions in methodological sections 3.1 through 3.4, or from “Spatial-temporal analysis” to “Intervention Analysis.”

Step 5. Identify first-, second- and third-order neighbors:

In this step the neighbors are identified. The closest neighbors or adjacent neighbors are considered to be the first-order neighbors and the next closest to be second-order neighbors, and so on for the third and fourth.

Step 6. Induce stationarity in the dataset:

Differencing in the time dimension of the first- and second-lag is done to achieve a level of stationarity in the signals.

Step 7. Induce homogeneity in the dataset:

Differencing in the spatial dimension of first-order (and higher-order) neighbors is achieved to make the non-homogenous data homogenous.

Step 8. Calculate weights and consolidating series:

Using the software package for forward solution of dipole-fit, weights for neighbors are calculated and applied. Then the first-, second-, and third-order neighbors are consolidated into one series.

Step 9. Remove known interventions:

In case of fetal breathing, a series without intervention is produced by passing through a stop band filter of 0.9 – 1.1 Hz. The band filter of 0.25 to 0.5 Hz is used in the case of maternal breathing. Both are used when maternal and fetal breathing are present simultaneously. For maternal breathing artifacts, this filter is applied in the data editor before data is tested for stationarity and homogeneity. For datasets with unknown intervention the above two filters are not applied.

Step 10. Run model:

The STARMA model is run on the resulting dataset to find the best-fit model.

Step 11. Calibrate transfer function. (Iterative):

In this iterative step, impulse-response weights are calculated and applied to pre-whitened input series.

Step 12. Saving the template:

At the end of the STARMA and transfer-function modeling, the user is asked to save the template in TXT file for future use.

4. CURRENT STUDY

Prior to Step 10, a consolidated time series is created consisting of a weighted sum of the observations that are the l^{th} order neighbors. In effect, the time series of the l^{th} order neighbors are converted into a single time series using $w_{ij}^{(l)}$.

4.1. Data sets with maternal and fetal breathing

Three datasets with interventions of maternal and/or fetal breathing are used in this study to derive the aforementioned template. As mentioned, the recording sessions consist of 6 trials

each, 2 minutes in a continuous mode at a sampling rate of 312.5 Hz and an anti-aliasing filter of 100 Hz (Preißl et al. 2001).

Pat 2011 dataset—The data collected from this patient, labeled as PAT 2011, had interventions caused by maternal and fetal breathing. Maternal breathing is usually present in the whole dataset. As can be seen, there are peaks around 0.2 to 0.5 Hz. This can be easily seen in the frequency spectrum shown in Figure 6. Fetal breathing can be understood as a process in which fetus exercises his/her lungs by pumping it. It is something that an adult does when s/he gets hiccups. This dataset has fetal breathing in its sixth trial. Fetal breathing is more prominent in a fetus late in their gestational age. This type of intervention is intermittent and very irregular. A fetus might breathe for a small period of time in a trial and then stop, or it might continue during the whole trial. Although this is a very small activity, the MEG signals produced by fetal breathing interfere with fetal brain signals. A spectrogram with fetal breathing will show peaks in 0.9 to 1.1 Hz frequency which is also the range where we see fetal brain activity. Using just a band-stop filter of 0.9 to 1.1 Hz might take off some of the fetal brain activity signals, in addition to the breathing. By contrast, STARMA and transfer function modeling can retain the fetal brain signals while removing its breathing artifact.

The frequency spectrum shown in Figure 6 is plotted after fetal and maternal heart beats (or MCG) have been eliminated by the method of orthogonal projection operator—at a frequency that is distinct from other signals of interest. Now it is known that the data has intervention due to fetal breathing, further processing has to be done. This is to remove the breathing intervention, and at the same time without eliminating the fetal brain signals. The target sensor is selected by inspecting the individual sensors that are close to the fetal heart. The sensor with peak at 1 Hz was selected, suggesting the “center” of the fetal breathing artifact. Its first-order, second-order and third order neighbors are identified based on the distance from the target sensor.

Once the target sensor and its neighbors are identified, the data from the sensors are de-trended and differenced in time and space dimensions to induce stationarity and homogeneity. To de-trend the data, the dataset is shifted by 350 data points, corresponding to the periodicity inherent in the SARA datasets. After de-trending, the dataset is differenced in time dimension to remove additional “trend,” and second-order differencing is used to achieve stationarity. Now weights are identified using the forward model for dipole fit. Here the dipole location is close to the target sensor; weights are subsequently calculated for each sensor. Table 1 below gives the different weights for first-, second- and third-order neighbors.

Once the temporal data is “sanitized,” the signals of first-order second-order and third-order neighbors are consolidated into one series, as suggested previously. Now all the weights are multiplied against their corresponding sensor series and the series are consolidated into one. Three series will be obtained, each for an order of neighbors. Then first-order differencing is done in the spatial dimension to induce homogeneity. In doing so one degree of freedom is lost.

Now the data are all set for input to the STARMA algorithm. In spite of the removal of maternal breathing and maternal and fetal heartbeats, this dataset is still left with fetal breathing intervention. Since we need data without intervention, we process the same data except that before any further differencing is done it is passed through a band stop of filter of 0.9 to 1.1 Hz. This will give us a dataset with fetal breathing filtered.

Now these two datasets—before and after fetal breathing removal—are fed to the STARMA and transfer function calibration program. The IMSL³ program asks for the number of observations (starting at $t = 1$) in the time series. This occurs prior to any intervention dataset

is required as input. Since the start of intervention is not known, some randomly chosen numbers are to be tested. After many trials, 1000 number of usable observations was decided. IMSL then calculates the sample autocorrelation and sample partial autocorrelation.

Next the first tentative model is established. Since the estimate is not likely to reflect the final, selected model, and in the spirit of parsimony, the preliminary estimate should contain as few parameters as possible. Since both the autocorrelation and partial autocorrelation have significant values in the first lag, an AR(1) or a MA(1) model can be selected. The model STARMA (p, q, d)³(m, n, D) assumes the following dimensions: STARMA (1,0,2)³(0,0,1). In other words, only one spatial auto-regressive parameter $p = 1$ is warranted. Up to three orders of neighbors—zeroth, first and second—were modeled. Parameter coefficients for the selected model are then calibrated. These estimates are then used as pre-whitening parameters in the transfer-function computation, as shown in Equation 7.

The impulse-response weights were calculated and displayed, along with the auto-regressive and moving-average parameter coefficients. The spatial-temporal model calibrated six impulse response weights for the combined series, which equates to the three immediate responses, and three responses for one lag in the zeroth, first and second order neighbors. Then the STARMA program asks whether the user would like to perform the next iteration. If the user agrees to perform the next iteration then the same process repeats. If not, it will ask the user to save the residual series. This residual series is our *template*. The best model identified for this data set was STARMA (3,1,2)³(2,1,1). The SSE and R^2 values for the best model are 0.325 and 0.5237 respectively. This STARMA model can be written out long hand as:

$$y_t^0 = c + p_1 y_t^1 + p_2 y_t^2 + p_3 y_{t-1}^0 + v_t^0 x_t^0 + v_{t-1}^0 x_{t-1}^0 + v_t^1 x_t^1 + v_{t-1}^1 x_{t-1}^1 + v_t^2 x_t^2 + v_{t-1}^2 x_{t-1}^2 + q_1 a_t$$

To show the values of the transfer function weights, the following table consists of three rows ($r=3$) and two columns ($m=2$), where the impulse-response weights were calibrated for t and for $t-1$.

v_t^0	0.7432	v_{t-1}^0	-0.2202
v_t^1	0.0522	v_{t-1}^1	0.0143
v_t^2	0.0182	v_{t-1}^2	0.0003

When all the parameter coefficients and constant, including impulse-response weights, are included, the model looks like this:

$$y_t^0 = 0.673 - 0.20y_t^1 + 0.17y_t^2 + 52.88y_{t-1}^0 + 0.7432x_t^0 - 0.2202x_{t-1}^0 + 0.0522x_t^1 + 0.0143x_{t-1}^1 + 0.0182x_t^2 + 0.0003x_{t-1}^2 + 0.1686a_t$$

The residual series is saved and will be used for template matching.

Pat 006 dataset—After maternal and fetal cardiograms have been removed by the CTF Data Editor, the frequency spectrum of all the sensors is plotted in Figure 7. Not surprisingly, this dataset has maternal breathing as intervention. It can be visually detected by examining the frequency spectrum. As can be seen, there are peaks around 0.2 to 0.5 Hz.

³IMSL stands for International Mathematical and Statistical Library

Maternal breathing affects channels in the upper part of the SARA sensor array, which are close to maternal heart (see Figure 1). They are inspected individually to find a target sensor. After careful observation, sensor MCO0 was selected as our target sensor. Similar data analysis was performed as with the previous dataset. When all the parameter coefficients, impulse response and constant are identified, the model looks like this:

$$y_t^0 = -0.3568 + 1.276y_t^1 + 0.570y_{t-1}^2 + 0.0137x_t^0 + 0.0171x_{t-1}^0 \\ + 0.00961x_t^1 + 0.0111x_{t-1}^1 + 0.0171x_t^2 + 0.0133x_{t-1}^2 + 0.5701a_t$$

The residual series is again saved as template to be used for template matching.

Pat 2014 dataset—As with the Pat 2011, this dataset has both maternal and fetal breathing artifacts. From the raw data, fetal and maternal cardiograms were first removed by using the orthogonal projection operator in the CTF Data editor. A viewing filter of 0.5 to 10 Hz was applied, which effectively focuses upon the fetal brain signals. Then the frequency spectrum of this data set was inspected. Figure 8 shows the frequency spectrum of the dataset, in which the peaks around 0.3 to 0.5 and 0.9 to 1.1 Hz are highlighted, confirming maternal and fetal breathing respectively.

Now for further processing, the target sensor (at MLH2) and its neighbors are identified by inspecting the sensor data individually for the peaks of interest. When all the parameter coefficients, impulse response weights and constant are identified, the model looks like this:

$$y_t^0 = 0.3087 + 0.2012y_t^1 + 0.1749y_t^2 + 0.7820x_t^0 - 0.2134x_{t-1}^0 \\ - 0.1624x_t^1 + 0.0739x_{t-1}^1 - 0.0314x_t^2 + 0.0663x_{t-1}^2 + a_t$$

Once again, the residual series is saved as template to be used for template matching

4.2. Datasets with unspecified interventions

Two datasets with *unspecified* interventions were analyzed. The data may include maternal or fetal breathing or both, but the exact interventions are unknown. They were tested and the corresponding templates were found.

Pat 526 and Pat 531—The two datasets were processed in the same manner as Pat 2011, Pat 006, and Pat 2014. Filters for both maternal and fetal breathing were applied to obtain series without intervention. The best model identified for the Pat 526 dataset is STARMA (3,1,2)³(2,1,1). The SSE and R^2 values for the best model are 0.244 and 0.6219 respectively. When all the parameter coefficients, impulse response weights and constant were identified, the model looks like this:

$$y_t^0 = 0.0817 + 1.3y_t^1 + 0.5y_t^2 + 264.9y_{t-1}^0 + 0.07004x_t^0 - 0.01038x_{t-1}^0 \\ + 0.0518x_t^1 - 0.0312x_{t-1}^1 + 0.0286x_t^2 - 0.03896x_{t-1}^2 + 0.4718a_t$$

The residual series is saved as a template to be used for template matching.

The best model identified for the Pat 531 dataset is STARMA (2,0,2)³(2,0,1). The SSE and R^2 values for the best model are 0.562 and 0.4091 respectively. When all the parameter coefficients, impulse response weights and constant were identified, the model looks like this:

$$y_t^0 = 0.3087 + 0.2012y_t^1 + 0.1749y_t^2 + 0.7820x_t^0 - 0.2134x_{t-1}^0 \\ - 0.1624x_t^1 + 0.0739x_{t-1}^1 - 0.0314x_t^2 + 0.0663x_{t-1}^2 + a_t$$

The residual series is again saved as a template to be used for template matching.

4.3. Unknown Datasets

The datasets used in this section are completely different from rest of the datasets. The time, type or any other information about the intervention is unknown. It is not even known if there is any intervention present.

Pat 25 and Pat 31 datasets—The data acquisition in these patients was done for some other study and dataset is unknown to us. On inspecting the datasets by frequency spectrum it did not peak around 0.9 to 1 Hz, nor did it show any peaks around 0.25 to 0.5 Hz. This suggests that the data do not have maternal or fetal breathing in it. A template was obtained for this data using the same procedure as for other datasets, except that, in the absence of fetal-breathing intervention, it was not passed through a 0.9–1.1 Hz filter.

The best model identified for the Pat 25 dataset is STARMA (2,1,2)³(2,1,1). The SSE and R^2 values for the model are 0.595 and 0.6103 respectively. After all the parameter coefficients, impulse response weights and constant were estimated, the model looks like this:

$$y_t^0 = -0.161472 - 0.1y_t^1 + 168.0y_{t-1}^2 + 0.00307x_t^0 + 0.018822x_{t-1}^0 \\ - 0.00275x_t^1 - 0.0002x_{t-1}^1 + 0.0061x_t^2 + 0.0019x_{t-1}^2 + 0.0323a_t$$

As with other datasets, the residual series is saved for template matching

The best model identified for Pat 31 data set is STARMA (2,1,2)³(2,1,1). When expanded, the model looks like

$$y_t^0 = -0.219964 + 9.201y_t^1 + 0.104y_t^2 + 0.8605x_t^0 - 0.06421x_{t-1}^0 \\ + 0.009755x_t^1 - 0.1771x_{t-1}^1 + 0.0467x_t^2 + 0.0039x_{t-1}^2 + 0.1036a_t$$

Once again, the residual series is saved for template matching.

4.4. Template Matching

At the end of the above work, all templates are to be checked whether they are similar to each other statistically. Our hypothesis is that, after removing all interventions, all templates should be similar (but not before then). Anyone of these can serve as a “universal” template for detection of unknown interventions. The Kolmogorov-Smirnov (K–S) test is typically used to check whether two series are significantly different in a statistical sense. This test is performed by computing the maximum distance between the cumulative distributions of the two samples. The two samples are tested for a pre determined (threshold) p -value. In our case, the p -value is taken as 0.05 which means the K–S test will test the null hypothesis of similarity between two series at a 95% confidence level. If the null hypothesis is not rejected, we conclude that the differences between two series could have occurred by chance.

Table 2 through Table 6 are some sample results from K–S tests among different pairs of templates. This test was performed on all the templates paired with other templates, to check whether they are significantly different from each other.

The K–S tests show that the templates obtained from datasets with interventions—Pat 006, Pat 2014, Pat 2011, Pat 526 and Pat 531—are not significantly different from each other at a 95% confidence interval. However, templates from unknown datasets, Pat 25 or Pat 31, are significantly different from the rest of the templates.

4.5. Test for Intervention

The flow chart shown in Figure 9 explains the step-by-step process to test an *unknown dataset* for the presence of an intervention—the subject of this paper. The data obtained from the SARA device is the raw data which is input to the “Remove MCG” tool for eliminating the two dominating signals: maternal and fetal cardiograms. In the next step the data is tested for stationarity and homogeneity. If the data is found to be non-stationary and non-homogenous, this step would induce stationarity and homogeneity in the dataset by differencing in time and space dimensions. Now two copies of the dataset are made. One of them is passed through the filters and other is used as it is. As we know, the interventions have been filtered out in one of the datasets. We take the difference between the two datasets to obtain the effect of intervention. Now the series with the intervention effect and the filtered dataset is pre-whitened and are fed to the transfer-function model. The impulse response weights are calculated and are applied to the pre-whitened input series. The residual series obtained after the application of transfer function model is now tested against the “universal” template for the presence of any unknown intervention.

The K–S test is performed to find whether the universal template and residual series are significantly different statistically. If the two are not significantly different, it is concluded that either there is no intervention or the interventions present in the dataset are not significant. Otherwise, it is concluded that large interventions are present.

5. CONCLUSION AND RECOMMENDATIONS

For an accurate analysis of fMEG data, we outlined a spatial-temporal procedure to discern if any intervention—such as movement, breathing or others—has occurred in the recorded signals. A “universal” template is obtained from datasets that are known to contain interventions. Suppose the frequency spectrum of the MCG-filtered fMEG signals from a 37-week fetus shows a peak at around 1 Hz, which matches the observed fetal breathing pattern in the raw data. We hypothesized that the data had interventions caused by fetal breathing. Steps have been outlined in this paper to remove these interventions temporally and spatially. This results in a residual series devoid of any intervention. This can be used subsequently as a “universal” template, or a “gold standard” against which unknown datasets can be compared.

From our experiments, templates from patient data known to have intervention are derived: Pat 006, Pat 2011, Pat 2014, Pat 526, and Pat 531. They are not significantly different statistically from each other according to the Kolmogorov-Smirnov test. They are used to form a “universal” template—despite the undoubted presence of moderate differences. The resulting residual template is subsequently used to cross match other “templates” from unknown datasets, with the intent of detecting the presence of an intervention.

Identifying a universal template is contingent upon removing interventions from the signal. The resulting series will be a “signature” series that will closely resemble a target signal when non-stationary activities are absent. Such a signatory series will be used as a template for comparison with other recorded fMEG signals. Through its correlation with a subject signal,

this template can be used to account for any interventions in the subject series. Templates from patients with unknown datasets—for example, Pat 25, Pat31—do not match with the “universal” template derived from other datasets known to have interventions. One word of qualification is in order here. The template obtained here is based on datasets representing mid-range gestation periods. Whether the template would be different for fetuses of early or late gestation periods is still unknown. Additional work is ongoing to answer this question.

When there are different types of fetal or maternal activities interfering with the subject signals, it is hypothesized that this modeling procedure can be extended to identify them one at a time. For accurate hypothesis testing and easy interpretation of the biomagnetic signals by physicians, a high-end visualization tool is being implemented to supplement our current modeling procedure.

Once it is known that an intervention is present in the dataset, the next step in this research would be to identify what type of intervention is present and how to remove it? This would be a challenging step since very little is known about the dataset. Research is underway to tackle this problem.

An important feature of the SARA instrument is that it records fetal brain’s evoked response due to both auditory and visual stimulation. As the fetal evoked response is dependent on the fetal position and sleep status, multiple recordings have to be performed on different days and different time. Fetal evoked response, being very low in magnitude compared to other prominent signals, makes it difficult to identify the precise experiment in which a fetus has shown evoked response activity. Presently, only 60% of fetuses show evoked response activity. To assess the accuracy of this measurement, applying the current technique to detect intervention on these datasets could be a worthy next step in this research. In other words, this methodology can be applied to detect fetus evoked responses in various patients. It would be of great help if it can be told which fetus has responded to various stimuli and which has not.

Also another step in this research is to automate the whole process, where interventions can be detected in datasets by the click of a button. There are three different software packages that have been used to achieve the goal. The Data Editor displays the dataset and is used to eliminate the two dominating MCG signals generated by maternal and fetal heart. Then the data set is checked for stationarity and homogeneity by using MATLAB. If required, known interventions can be removed. The processed dataset from MATLAB is then fed to a FORTRAN program to apply the transfer-function modeling procedure. This program uses various routines from IMSL. The outputs from different sets of software are manually fed from one to other. The identification of first, second and third order neighbor of a target sensor is also manual.

Our goal would be automating the whole process. A matrix of all the sensors as target sensor and its neighbors can be made and accessed according to the user input of target sensors. Various routines can be written to export/import the datasets from one software to another. Routines to display the data or intermediate data or different figures as per user instructions would make the whole process more transparent. The last step would be to provide a user-friendly interface to this complex procedure of detecting intervention.

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7. APPENDIX

In Section 3.4, we suggested that residual series obtained from every dataset is white noise. As described by Chan (2005), Equation 7 uses an output series estimated from a pre-whitened input series. This equation has transformed our error terms a_t into noise series ε_t . The pre-whitening procedure does not necessarily convert the output series to white noise, however, since the whitening procedure is specifically geared for the input series.

If a stochastic linear process has an input that is white noise, it consists of a sequence of uncorrelated random variables with mean zero and constant variance (Box and Jenkins 1997). Also, it has the autocorrelation function in the simple form of

$$\rho_k = \begin{cases} 1 & (k=0) \\ 0 & (k \neq 0) \end{cases}$$

We are pleased to report that this is confirmed by the autocorrelation and partial autocorrelation plots of residuals in all our experiments.

A complementary test for testing verifying white noise can be performed on the residual series. In order to test the whiteness of residuals, Portmanteau test was introduced by Box and Jenkins for auto-regressive moving-average models, where the test statistic (Q) is defined as:

$$Q = n \sum_{k=1}^K \widehat{\gamma}_k^2 \sim \chi_{K-p-q}^2$$

where n is the number of observations, $\widehat{\gamma}_k^2$ is the estimated autocorrelation value for the sequence of residuals with lag k , K is an integer, the exact choice of which is arbitrary, and p and q are the numbers of auto-regressive and moving-average coefficients respectively. This test statistic has to be computed for all the fitted models. All the residual series obtained from different datasets would be tested to find out which model produces the whitest residual series among them. This could be an alternate method to select the most suitable model for a particular dataset.

Should the auto-regressive and moving-average operators fail to whiten the output series, it would indicate that the transfer function has not picked up all the remaining interventions in the data. This suggests that closer examination is necessary to discern the adequacy of the model and the accuracy of the data analysis. For example, the data can be further screened for discernable interventions. It can also be further examined for stationarity and homogeneity. Likewise, the postulated STARMA model can be further scrutinized for its goodness-of-fit.

Figure 1. SARA instrument with 151 Channels
(Robinson et al. 2001)

Figure 2.
A typical data set recorded by SARA

Figure 3.
Target sensor and its first second and third order neighbors.

Figure 4.
Moran *I* statistics

Figure 5.
Spatial Differencing

Figure 6.
Frequency spectrum of Pat 2011 dataset

Figure 7.
Frequency spectrum of Pat 006 dataset

Figure 8.
Frequency spectrum of Pat 2014 dataset

Figure 9.
Test for intervention

Table 1

Weights for each sensor

Target Sensor MLI1				
First Order Neighbor	Second Order Neighbor		Third Order Neighbor	
0.1406	0.0736	0.0240	0.0316	0.0429
0.1974	0.0897	0.0052	0.0568	0.0451
0.1084	0.0359	0.1344	0.0420	0.0285
0.1277	0.1075	0.0240	0.1218	0.0549
0.2510	0.1729	0.1419	0.1274	0.1939
0.1748	0.1044	0.0864	0.0809	0.0799
			0.0414	0.0108
			0.0112	0.0308

Table 2

Template matching (Patients 006 & 2014) – not significantly different

Comparison of Population Distributions			
	Sample Size	Sample Median	
t1(pat006)	100	1.33188115	
t3(pat2014)	100	-1.2154325	
Difference		2.54731365	
Kolmogorov-Smirnov Test			
Null Hyp.	Alt. Hyp.	Test Statistic	P-Value
Identical	Different	0.17	0.1112
Do not reject the null hypothesis at the 5.0% significance level.			

Table 3

Template matching (Patients 006 & 2011) – not significantly different

Comparison of Population Distributions			
	Sample Size	Sample Median	
t1(pat006	100	1.33188115	
t2(pat2011)	100	−0.876825	
Difference		2.20870615	
Kolmogorov-Smirnov Test			
Null Hyp.	Alt. Hyp.	Test Statistic	P-Value
Identical	Different	0.10	0.6994
Do not reject the null hypothesis at the 5.0% significance level.			

Table 4

Template matching (Patients 006 & 526) - not significantly different

Comparison of Population Distributions			
	Sample Size	Sample Median	
t1(pat006	100	1.33188115	
t4(pat526)	100	−0.6454628	
Difference		1.97734395	
Kolmogorov-Smirnov Test			
Null Hyp.	Alt. Hyp.	Test Statistic	P-Value
Identical	Different	0.16	0.1546
Do not reject the null hypothesis at the 5.0% significance level.			

Table 5

Template matching (Patients 006 & 25) - Significantly Different

Comparison of Population Distributions			
	Sample Size	Sample Median	
t1(pat006	100	1.33188115	
t6(hr25)	100	−2.30305155	
Difference		2.54731365	
Kolmogorov-Smirnov Test			
Null Hyp.	Alt. Hyp.	Test Statistic	P-Value
Identical	Different	0.28	0.0008
Do not reject the null hypothesis at the 5.0% significance level.			

Table 6

Template matching (Patients 006 & 31) - Significantly Different

Comparison of Population Distributions			
	Sample Size	Sample Median	
t1(pat006	100	1.33188115	
t7(hr31)	100	-1.20443207	
Difference		2.53631322	
Kolmogorov-Smirnov Test			
Null Hyp.	Alt. Hyp.	Test Statistic	P-Value
Identical	Different	0.22	0.0158
Do not reject the null hypothesis at the 5.0% significance level.			