Identification of EEG Fingerprints of Simultaneous fMRI in Resting State and Motor Imagery

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Abstract—Over the past few years, simultaneous EEG-fMRI recordings have been largely used to understand the link between EEG and fMRI in multiple conditions. The use of multimodal approaches that combine these two modalities has received recognition as a promising new tool, owing to their highly complementary characteristics. However, such multimodal acquisitions are typically costly, non-portable and overall uncomfortable for patients, mostly due to the use of fMRI. This motivated the search for solutions capable of using only the widely available EEG as a surrogate of the simultaneous BOLD signal. Within this scope, this work investigated an integration strategy whereby relevant EEG-features were extracted and their coefficient estimates learnt so as to predict the simultaneous average BOLD signal measured at a specific distributed network. These network-specific EEG patterns can be referred to as EEG-Fingerprints (EFPs), a concept introduced by Meir-Hasson and their colleagues (Meir-Hasson et al., 2014). The methodology employed relied on a machine learning approach that included linear regression algorithms and cross validation procedures. Independent analyses were performed for data recorded under two experimental conditions: during resting state; and during a motor imagery task.

Index Terms—EEG Fingerprint, Simultaneous EEG-fMRI, Resting State, Default Mode Network, Motor Imagery, Spectral Features, Connectivity Features, Learning, Optimization.

I. INTRODUCTION

Electroencephalography (EEG) measures electrical activity of the brain through a set of electrodes placed on the scalp, which capture transient electrical dipoles generated in the cortex that reflect underlying neuronal processes in real time. By means of these fast dynamics, EEG holds a high temporal resolution (order of the milliseconds), desirable for a wide range of practical applications (Wadman and da Silva, 2017). EEG also benefits from being relatively inexpensive, portable, noninvasive and easy to apply. However, it is very sensitive to noise and lacks specificity because of its low spatial resolution (order of the centimeter) and the fact that source localization from EEG suffers from an ill-posed inverse problem.

On the other hand, functional magnetic resonance imaging (fMRI) reflects the increases in blood flow that accompany neuronal activation. The success of fMRI stems largely from its high spatial resolution (order of the millimeters) and noninvasive nature. However, its temporal resolution (order of the seconds) is limited by the time required to acquire one brain volume and the duration of the hemodynamic response, which acts as a low-pass filter that blurs neural activity (Buxton, 2009). Moreover, fMRI recordings are considerably expensive and time consuming, posing further constraints on the use of this modality for several applications. In this context, the use of multimodal approaches that combine EEG and fMRI has received recognition as a promising novel method for several applications. Yet integrating EEG and fMRI data is not a trivial challenge, in fact multiple multimodal data integration methods have been described and compared in recent years (Perronnet et al., 2018; Abreu et al., 2018).

Notably, multimodal EEG-fMRI acquisitions are of special interest for neurofeedback (NF) based Brain-Computer Interface (BCI) applications, which traditionally rely on either EEG or fMRI recordings. These systems have been exploited as noninvasive techniques to improve neurorehabilitation outcomes in a large spectrum of neurological conditions (Vourvoulos et al., 2019), for example in the context of rehabilitation or several psychiatric disorders (Marzbani et al., 2016). While combining EEG and fMRI for NF training has been demonstrated to provide a more efficient feedback and better regulation results (Perronnet et al., 2017), such multimodal acquisitions enclose several pitfalls: they are costly, non-portable and overall uncomfortable for patients, mostly due to the use of fMRI. Further, integration of EEG and fMRI signals so as to be fed to the feedback loop should be applicable in real-time (Perronnet et al., 2018). Within this framework, significant efforts have been employed to reach solutions that combine the complementary advantages of EEG-fMRI multimodal acquisition, whilst using only the widely available EEG for real-time training. Such solutions rely on the ability to use a set of EEG-derived features to simulate the simultaneous BOLD signal.

This work aims to investigate an integration strategy whereby relevant EEG-features are extracted and their coefficient estimates learnt so as to predict the simultaneous average BOLD signal measured at a specific distributed network. These network-specific EEG patterns can be referred to as EEG Fingerprints (EFPs), a concept introduced by Meir-Hasson and their colleagues (Meir-Hasson et al., 2014) in a related study. The hope is that in the future, the estimated EFPs may be applied during real-time neurofeedback training, in order to attain the quality of the results obtained with a NF EEG-fMRI.
session, without the need to use fMRI.

In this work, independent EFPs are estimated for data recorded under two experimental conditions: during resting state (RS) and during a motor imagery (MI) task. In the former, the BOLD signal considered is extracted from a resting state network, the Default Mode Network (DMN), whereas in the latter the signal is extracted from regions within the motor cortex.

II. RELATED WORK

A. EEG-fMRI in Resting State

Resting state activity comprises the spontaneous fluctuations in human brain activity that occur when subjects are not engaged in a particular task or higher cognitive processes. An important related concept is that of resting state networks (RSNs), which are networks that integrate functionally connected brain regions, i.e., brain regions that share correlated temporal patterns. Since these patterns have first been reported in rsfMRI (resting state fMRI) studies by Biswal et al. (Biswal et al., 1995), several RSNs have been identified. These networks are highly reproducible in multiple resting state conditions and are spatially consistent across different subjects as well. The most widely studied and robustly detected RSN is the Default Mode Network (DMN) (Raichle et al., 2001). This network was first identified by Raichle and colleagues, when stumbling upon a consistent pattern of regions that showed higher activation during control state than during task performance, in positron emission tomography (PET) studies. The DMN includes the anterior cingulate cortex (ACC), the posterior cingulate cortex (PCC), the inferior lateral parietal cortex and the medial prefrontal cortex (mPFC) (Greicius et al., 2002). Although the exact cognitive functions of the DMN are still unclear, there is a growing consensus concerning its involvement in introspection, self-referential cognition and environment monitoring processes (Smith et al., 2018).

The study of RSNs has been proven to be of significant clinical value, providing sensitive markers of disease. Specifically, the DMN has been demonstrated to be altered in a number of conditions such as attention deficit hyperactivity disorder (ADHD) (Rubia et al., 2019) and several chronic pain disorders including migraine and neuropathic pain (Edes et al., 2017; Sağ et al., 2018). Regrettably, only very few studies have been employed to date that try to understand the role of resting state neurofeedback in the treatment of such conditions. Notably, Rubia and colleagues reported a significant increase in the functional connectivity of the DMN, accompanied by improvement of clinical symptoms, following NF therapy with ADHD patients. Moreover, some studies report improvement of pain symptoms in patients with migraine and other types of chronic pain after NF therapy (Marzbani et al., 2016). Altogether, these results indicate that RS patterns may be promising new targets in the field of NF-based therapy.

B. EEG-fMRI in Motor Imagery

The term motor imagery (Jeannerod, 1994) is commonly used in the scientific community to address tasks in which the subject imagines moving a specific body part, without physically executing the movement. Research on motor imagery has identified several similarities between imagined and executed actions, thus supporting the idea that motor imagery is executed via many of the brain structures involved in the programming of movements. Indeed, neuroimaging studies report similar spatiotemporal patterns of neural activation in the two conditions, both engaging a set of frontal motor areas (the supplementary motor area, SMA; the premotor cortex, PMC; the primary cortex, M1) along with posterial parietal regions (the secondary somatosensory cortex, S2) and subcortical structures such as the cerebellum and the basal ganglia (BG) (Pfurtscheller and Neuper, 1997). Over the years, MI has been adopted as a tool for motor rehabilitation (Ramos-Murguialday et al., 2013), improvement of sport performance (Guillot and Collet, 2008), and musical practice (Lotze and Halsband, 2006). For this, the idea of directly training the central nervous system was promoted by establishing an alternative pathway between the user’s brain and a computer system (Wolpaw et al., 2002). This is possible by using EEG-based Brain-Computer Interfaces (BCIs), since they can provide an alternative non-muscular channel for communication with the external world, while providing also a cost-effective solution for training (Vourvopoulos and Badia, 2016). BCIs aim to translate features extracted from recorded brain activity into signals able to communicate with external computer devices, whether for assistance or rehabilitative purposes. In this regard, although EEG is the most popular imaging technique for feature extraction in BCI applications, EEG-based BCIs lack from high accuracy due to poor signal-to-noise ratio, low spatial resolution and non-stationarity of the signals (Lotte, 2014). A way to overcome the current limitations of EEG-based BCIs is to understand the modulation of EEG patterns by capturing user-specific correlates of MI. This can be achieved resorting to fMRI, because of its high spatial resolution. Hence, combining EEG and fMRI in this context may allow the identification of specific EEG correlates that best represent the brain activity associated with the execution of the MI task.

C. EEG-fMRI Integration

Although a great amount of work has been dedicated into formulating a model that expresses the transfer function between the EEG and the BOLD signal, this is still an active area of research. Several transfer functions between EEG and BOLD have been proposed that are based on the time-frequency decomposition of the EEG signal, thus accounting for its temporal and spectral profiles. Hence, these can be referred to as spectral features. Amongst the most well-studied are the root mean square frequency (Kilner et al., 2005), the total power (Wan et al., 2006), the average power across a specific frequency band, and the linear combination of band-specific average power (Goense and Logothetis, 2008). A number of studies exist that compare the performance of these EEG-derived spectral features in the prediction of fMRI data. In particular, studies addressing this question in a visual task with healthy subjects (Rosa et al., 2010) and during
resting state with epileptic patients (Leite et al., 2013) reported that frequency-weighted metrics yield a better performance than power-weighted metrics. However, overall reports in the literature do not provide yet a clear picture regarding the link between EEG and the BOLD signal, and a consensual optimal approach to model such relationship is still lacking.

Concurrently, a growing body of research has been focused on describing the link between the EEG and the simultaneous BOLD in terms of the functional connectivity of the electroencephalogram. Although they are typically more complex and computationally costly, the interest of using such measures lies on the possibility to incorporate in the models the communication patterns across distributed brain regions. Specifically, EEG synchronization measures have been deemed as promising within this context (Abreu et al., 2018), since they reflect aspects of brain activity that are complementary to those captured by spectral power measures. However, the current research on the usage of these measures to predict BOLD activity is rather scarce. As Abreu et al. reviews, both the global field synchronization (GFS) and the phase synchronization index (PSI) have been successfully used to predict simultaneous BOLD changes, and have additionally been found to outperform some of the spectral power measures described above.

Motivated by these promising results, this work explores the potential of another EEG synchronization measure, the imaginary part of coherency (IPC), for the prediction of concurrent BOLD changes. The choice of this measure to assess connectivity was twofold: first, coherency has repeatedly shown to produce more robust results than those obtained by synchronization measures that do not weight in the amplitude of the signals’ complex Fourier spectrum (Nolte et al., 2004); second, to avoid the necessity for source reconstruction, the priority was to use a connectivity measure located on the possibility to incorporate in the models the communication patterns across distributed brain regions. Specifically, EEG synchronization measures have been deemed as promising within this context (Abreu et al., 2018), since they reflect aspects of brain activity that are complementary to those captured by spectral power measures. However, the current research on the usage of these measures to predict BOLD activity is rather scarce. As Abreu et al. reviews, both the global field synchronization (GFS) and the phase synchronization index (PSI) have been successfully used to predict simultaneous BOLD changes, and have additionally been found to outperform some of the spectral power measures described above.

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of neurofeedback scores when EEG is used alone. Their approach was also based on a machine learning mechanism within a linear regression framework. However, in contrast to the approach of Meir-Hasson et al., neurofeedback scores were fed to the learning algorithm, instead of the EEG and fMRI signals alone. Regularization was applied by adding a mixed $L_{1/2}$ penalty along with a $L_1$ penalty to the LSR objective function. The rationale was that because only a few brain regions are expected to be activated by a given cognitive task, it is reasonable to impose spatial sparsity through the use of a $L_1$ penalty. On the contrary, because engagement of brain rhythms is not expected to be sparse across frequencies, and might even be smooth, it would be appropriate to use an additional mixed $L_{12}$ penalty. Here, a mixed norm was used instead of a simple $L_2$ norm to further allow non-relevant frequency bands to hold null coefficients. While the weight of the $L_1$ norm was empirically chosen and fixed, the weight of the $L_{12}$ norm was estimated through an optimization procedure. Both model selection (optimization of the weight parameter) and evaluation were performed using a nested cross-validation procedure (outer 3-fold CV, inner holdout CV with n = 50 number of cycles). Here, the criterion used to assess model performance was the NMSE. Importantly, to select among the many possible models, the method sought to minimize the combined NMSE on the validation and learning set. This was justified on the grounds of whilst using the NMSE from the learning set alone would introduce bias, using the NMSE from the test set alone would introduce variance. Remarkably, Cury et al. showed that only specific channels and frequency bands held high activation, over the several different subjects for whom models were derived. This led them to believe that there may exist a common, more general, model for the population, even if the best possible models are subject-specific.

III. IMPLEMENTATION

A. Characterization of the Resting State Data

The EEG-fMRI data was acquired during rest and eyes open, for a run of 10 minutes. This dataset was acquired and pre-processed in the scope of a previous project (Abreu et al., 2017). The subject was a patient selected from a group of drug-refractory focal epilepsy, undergoing presurgical evaluation from the Program of Surgery for Epilepsy of the Hospital Center of West Lisbon. Epileptic activity was recorded on the EEG for a brief period towards the end of the acquisition. The samples corresponding to the epileptic event were removed from the data analyzed in this work, so as to minimize any confounds of healthy resting state activity. EEG and fMRI data acquisition and pre-processing was as described in Abreu et al (Abreu et al., 2017).

B. Extraction of the Resting State BOLD Signal

The BOLD resting state network of interest, the default mode network (DMN), was mapped through seed-based GLM analysis. The seed selected for the analysis was a well-defined area within the DMN, the PCC. A mask of the seed was created in the FSL’s program FSLeyes, using the Harvard-Oxford Cortical Structural Atlas.. The mask was then binarized and converted from standard to functional space. The average pre-processed BOLD time-series within the PCC was thereby extracted from the functional data and used as an explanatory variable (EV) for GLM analysis. GLM was performed using the FSL’s tool FEAT (Woolrich et al., 2001), and the z-statistic images returned were thresholded. Notice that high z-scores in the z-statistic images belong to brain regions that share strong temporal correlation with the PCC, and therefore are assumed to belong to the DMN. The DMN map was visually confirmed, and its average time-series extracted as the BOLD signal of interest to be further used in the analysis.

The remaining processing steps were implemented in MATLAB. The BOLD signal was first up-sampled to 4 Hz using cubic spline interpolation. The signal was then normalized to have zero mean and one standard deviation. The resulting BOLD time-series was used as the output response $Y(t)$ of the learning algorithms.

C. Characterization of the Motor Imagery Data

The EEG-fMRI data was acquired from a healthy volunteer during a single motor imagery session of 120 seconds. The session consisted of 6 blocks, alternating between rest, eyes open, and motor imagery of the right arm.

Imaging was performed on a Siemens Vida at 3T with a 64-channel head coil. The fMRI data was collected using a 2DEPI sequence, with the following parameters: TR/TE = 1260/30ms, 2.2 mm isotropic, 60 axial slices, with simultaneous multislice acceleration factor 3, and GRAPPA in-plane acceleration factor 2. The EEG data was acquired on a MR-compatible 32-channel BrainAmp MR amplifier (Brain Products, Germany), with a standard montage according to the 10-20 system. Two additional electrodes were used: a reference electrode and an electrode placed on the back for ECG recording. The EEG acquisition was synchronized with the fMRI scanner, and sampled at 5 kHz.

D. Extraction of the Motor Image BOLD Signal

The BOLD signal of interest was obtained through GLM analysis with the FSL’s tool FEAT, using the square waveform of the task paradigm as a EV in the design matrix. The square wave was first convolved with the canonical HRF, as given by a double gamma function with overshoot at 6 seconds relative to onset. Its first temporal derivative was also included as a second regressor in the design matrix. All previous steps were implemented in the FEAT GUI. The z-statistic images returned for the EV were thresholded to obtain the regions that shared high temporal correlation with the input task paradigm. The resulting map was binarized and then multiplied by a binary mask of the motor cortex to remove voxels from non-motor areas. The motor mask was created in the FSL’s program FSLeyes, using the Harvard-Oxford Cortical Structural Atlas (Desikan et al., 2006) and the Juelich Histological Atlas (Eickhoff et al., 2007). The mask was then binarized and converted from standard to functional
space. The average BOLD time-series of the resulting map was extracted to be further used in the analysis. The remaining processing steps, implemented in MATLAB, were the steps already described for the resting state BOLD signal.

E. Extraction of the EEG Features

The following paragraphs describe the post-processing pipeline employed to build the feature space from the EEG data. The input data fed to the pipeline corresponds to the post-processed EEG 2D data matrix, within which each row represents the time-series of one EEG channel. Time-frequency decomposition was accomplished by Morlet wavelet convolution in the time-domain. Accordingly, each of the EEG time-series \(X_j(t)\) was convolved with a Morlet wavelet \(w(t,f)\) with wavelet factor \(R = 7\), to obtain the time-series of the spectral power at frequency \(f\), given by \(P_j(t,f) = |X_j(t) \ast w(t,f)|^2\). This process was repeated for a 100 discrete frequency values, logarithmically distributed from 1 Hz to 30 Hz. The result was a 3D matrix of spectral power values \(X \in \mathbb{R}^{C \times F \times T}\) (\(C\) the number of channels, \(F\) the number of frequency bins, \(T\) the number of time-points).

From the spectrum of the EEG data, both spectral and functional connectivity features were derived. These represent a range of possible ways of modeling the linear relationship between EEG activity and the BOLD response. The spectral features explored in this work were the root mean squared frequency (RMSF), the total power (TP) and the linear combination of band-specific power (LC) (Abreu et al., 2018). The EEG-derived feature matrix, \(X\), built for each of these models, is referred to in this work as \(X_{RMSF}\), \(X_{TP}\), \(X_{LC}\) (respectively). These features were derived through the expressions in equations 3 to 4. Because the latter two rely on the average power across specific ranges of frequencies, the frequency bands of interest had to be defined. Four frequency bands were considered in this work, defined as follows: delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz) and beta (13-30 Hz).

\[
EEG_{RMSF}(t) = \sqrt{\sum_{f_{\min}}^{f_{\max}} f^2 \tilde{P}(f,t)} \tag{1}
\]

\[
\tilde{P}(f,t) = \frac{P(f,t)}{\sum_{f_{\min}}^{f_{\max}} P(f,t)} \tag{2}
\]

\[
EEG_{TP}(t) = \sum_{f_{\min}}^{f_{\max}} P(f,t) \tag{3}
\]

\[
EEG_{LC}(t) = \sum_{k=1}^{N} a_k \left( \frac{1}{|b_k|} \sum_{f_{h_{\min}}}^{f_{h_{\max}}} P(f,t) \right) \tag{4}
\]

with \(EEG_{RMSF}(t)\) the normalized RMSF feature, \(EEG_{TP}(t)\) the TP feature and \(EEG_{LC}(t)\) the LC feature; \(f_{\min}\) and \(f_{\max}\) are the minimum and maximum frequency under analysis, and \(P(f,t)\) the value of the EEG power spectrum at the frequency bin \(f\), at time \(t\). \(\tilde{P}(f,t)\) is then the normalized power spectrum (normalized by the total power).

In equation 4, \(N\) is the total number of frequency bands considered, \(a_k\) the linear combination coefficient associated with the frequency band \(k\), \([f_{h_{\min}}, f_{h_{\max}}]\) its frequency range, and \(|b_k|\) the total number of frequency bins within this range.

Regarding functional connectivity measures, the IPC and the WND of the IPC were used. Similarly to the LC feature matrix, the IPC feature matrix was derived by the linear combination of band-specific IPC, as given by:

\[
EEG_{IPC_{ij}}(t) = \sum_{i=1}^{N} a_k \left( 1 \frac{f_k}{|b_k|} \sum_{f_{h_{\min}}}^{f_{h_{\max}}} IPC_{ij}(f,t) \right) \tag{5}
\]

where

\[
IPC_{ij}(f,t) = Im \left( \frac{\langle P_i(f,t)P_j(f,t)e^{i\Delta \Phi} \rangle}{\langle (P_i(f,t)^2)(P_j(f,t)^2) \rangle^{1/2}} \right) \tag{6}
\]

where \(IPC_{ij}(f,t)\) is the IPC between channel \(i\) and channel \(j\) at frequency \(f\) and instant \(t\), \(\Delta \Phi\) their phase difference at frequency \(f\) and instant \(t\).

However, an important remark must be made regarding the computation of such features for the data under analysis in this work. Coherency (and thus, imaginary part of coherency as well) requires to determine the expected value of the cross-spectrum, \(\langle S_{ij}\rangle\). In theory, this can only be done by averaging the cross-spectrum acquired over a sufficiently large number of trials. However, in this work, a single session was performed for both resting state and motor imagery conditions. Therefore, a different solution was employed, that relied on the Welch overlapped-segment averaging method, commonly used for spectral density estimation (Carter, 1987). Accordingly, to compute the cross-spectrum of two signals \(X_i\) and \(X_j\) throughout time, the following steps were performed: for both \(X_j\) and \(X_i\), time intervals of 2 seconds, centered in time instant \(t\), were divided into \(T\) overlapping segments of 250 ms, and each of the segments was windowed with a Hanning window; at each segment, the complex Fourier spectrum was obtained for both signals, and from the two Fourier spectra the cross-spectrum at that segment was computed; finally, the cross-spectrum obtained for all \(T\) segments was averaged to obtain the expected value of the cross-spectrum, \(\langle S_{ij}\rangle\), at time instant \(t\). However, it is important to emphasize that the procedure described assumes stationarity within each time interval for which coherence is calculated. While this may be a fair assumption for the most part of the motor imagery time-series, it may not be the case for the resting state data, in which the time interval considered may be sufficient for a spurious process to change the connectivity patterns recorded.

The entirety of this procedure was implemented with the MATLAB function \(\text{cpsd}\). From the cross-spectra obtained, coherency was computed, and its imaginary part determined to derive the IPC. Pairwise IPC estimates were averaged across
the four frequency bands of interest (delta, theta, alpha and beta) to obtain the feature matrix $X_{IPC}$. Lastly, from this IPC matrix, the weighted node degree of each channel was estimated (equation 7), to obtain the WND features.

$$EEG_{WND}(t) = \sum_{k=1}^{N} a_k \left( \sum_{j=1}^{C} \left( \frac{f_{bk_{\text{max}}}}{b_k} \sum_{f_{bk_{\text{min}}}} IPC_{ij}(f, t) \right) \right)$$

(7)

where $C$ is the total number of EEG channels considered and $EEG_{WND}$, the WND feature at channel $i$.

To better match the time-series of the simultaneous BOLD signal, each EEG feature $X_i(t)$ was non-linearly transformed through convolution in the temporal-domain with the HRF. This processing step was performed using the MATLAB toolbox SPM12 (Ashburner et al., 2019), designed for the analysis of brain imaging data. The time-series of the HRF was obtained using the function $spm_hrf$, which approximates the to a combination of two gamma functions. Notice that this is in principle the same function as the one used for the the GLM analysis of the MI fMRI data in FSL. The double gamma implemented by $spm_hrf$ is characterized by a set of parameters that dictate its shape and scale, $p_1$ to $p_6$, where: $p_1$ is the delay of the response and $p_2$ the delay of the undershoot (both relative to onset), $p_3$ is the dispersion of the response, $p_4$ is the dispersion of the undershoot and $p_5$ is the ratio of the response to undershoot. More, $spm_hrf$ requires the specification of two additional parameters, $p_6$ and $p_7$, which are the onset and length of the kernel (in seconds). The function $spm_hrf$ considers the canonical (default) HRF to be defined by parameters: $p_1 = 6, p_2 = 16, p_3 = 1, p_4 = 1, p_5 = 6, p_6 = 0, p_7 = 32$. However, since the $X$ is known to vary considerably across subjects, brain regions, and even cognitive tasks, a set of different shapes was considered in this work, characterized by the following range of overshoot delays: 10, 8, 6, 5, 4 and 2 seconds. To maintain a linear relation between the values of the shape parameters ($p_1$ to $p_5$), the canonical values of each of these parameters was multiplied by the scale factor $s = (p_1/6)$.

Convolution between the input feature $X_i(t)$ and the HRF was performed with the function $spm_Volterra$ from the same toolbox. This convolution temporally smooths and gives a BOLD-like shape to the input features of the model, so as to increase their linear relationship with the output response.

The resulting EEG features were down-sampled at 4 Hz, and normalized to have zero mean and one standard deviation, so as to facilitate model computation and the interpretability of coefficient estimates. Because a total of 31 channels, 4 frequency bands and 6 HRF delays was considered, the final feature matrices built contained a total of features $p$ of: $31 \times 4 \times 6 = 744$ (for the $X_{LC}$ and $X_{WND}$ matrices); $31 \times 6 = 186$ (for the $X_{RMSE}$ and $X_{TP}$ matrix); $465 \times 4 \times 6 = 11160$ (for the $X_{IPC}$ matrix). Notice that because the functional connectivity matrix is a diagonal matrix, redundant combinations of channels were removed from the feature matrix, thus only a total of $(31 \times 31 - 31)/2 = 465$ channel pairs remained.

After the computation of the models above, a further analysis was conducted only for the LC features, that aimed to evaluate the cost-effectiveness trade-off of computing models with a reduced feature space. Specifically, new feature matrices were derived for each of the frequency bands, $X_{\delta}$, $X_{\theta}$, $X_{\alpha}$, $X_{\beta}$, and for each of the EEG channels, $X_{Fp1}$, ..., $X_{POz}$. For each dataset, the one-band model and one-channel model that yielded higher performances were used to derive a matrix that only contained features from that frequency band and that channel combined (e.g., $X_{\delta, O2}$). Finally, another matrix was derived for the best band, the best model, and the combination of best band and model, that only contained features convolved with the canonical HRF (overshoot delay at 6 seconds), further reducing the feature space (e.g., $X_{\alpha, can}$, $X_{\delta, can}$, $X_{\alpha, can}$).

IV. Prediction Model

In this work, an independent EFP was learnt for each of the models assessed, here referred to: $X_{RMSE}$, $X_{TP}$, $X_{IPC}$, $X_{WND}$, $X_{IPC}$. All models were fitted by linear regression, using the ENR (elastic net regularization) method for regularization. Hence, ENR was used to fit these models to the training data, so as to predict the BOLD response of interest $Y(t)$, from the set of EEG features $X(t)$. The usage of a regularization strategy such as this one was motivated by the need to reduce model complexity so as to improve model interpretability and control for overfitting effects (and hence improve overall prediction accuracy). The choice of this particular method was supported by the theoretical and empirical knowledge regarding its general characteristics, extensively described elsewhere (Zou and Hastie, 2005). As Zou et al. emphasizes, the ENR combines the better properties of ridge and lasso regression methods, yielding better performance than either of them when used alone. Specifically, it enables to produce sparse models, by setting some of the coefficients to zero, whilst producing a grouping effect, in which highly correlated features are assigned similar weights. ENR incurs a penalty, imposed by a mixed $L_{1/2}$ norm, on the least squares objective function. Hence, it requires the specification of two hyperparameters prior to model estimation: the $\alpha$ parameter, which defines ratio between the weights of the $L_1$ and the $L_2$ norm, and the $\lambda$ parameter, which is the complexity parameter of the model. Instead of optimizing both parameters, the former was set to 0.5 for all the models. This was done in order keep computational cost to a minimum, as well as to create a common ground whereby comparison between different models is easier. The choice of $\alpha = 0.05$ was twofold: first, to impose sufficient sparsity on the models, small values of $\alpha$ were discarded (notice that sparsity increases as $\alpha$ rises from 0 to 1); additionally, a simplistic parameter search was employed, in which model performance, as measured by the BIC, was assessed for a range of $\alpha$ values. The tuning of the $\lambda$ parameter was performed through a nested CV procedure, described in the following section.
V. Model Assessment and Evaluation

For model selection and evaluation, a nested k-fold CV procedure was implemented, with $k = 15$ outer cycles and $n = 20$ inner cycles. For the outer procedure, a few variants of the traditional k-fold CV procedure were explored, whereas for the inner procedure a holdout CV procedure was employed, with learning/validation ratio of $70/30$. The first version of k-fold CV explored, which is also the most simple, is described in this paragraph. The original dataset was split into $k$ roughly equal sized, random partitions. In other words, each sample of the original set $\{1, \ldots, N\}$ was randomly allocated into a specific partition $\{1, \ldots, k\}$. Then, a total of $k$ outer iterations was performed, and at each iteration one partition was retained as the test set, while the remaining $k-1$ partitions were used to fit the model. After all iterations, each partition was used as the test set exactly once. For each of the $k$ training sets, an inner holdout CV procedure with $n$ iterations was performed to estimate the optimal hyperparameter $\lambda$ for that particular set. In each iteration of the inner procedure, training data was randomly assigned to the learning and validation sets, according to a ratio of $70/30$. Data within the learning set was used to compute a family of 20 models, one for each of the 20 $\lambda$ values belonging to a range of interest, $\Lambda = \{\lambda_1, \ldots, \lambda_{20}\}$.

The criterion used for model selection was the BIC value. It was chosen over the AIC criterion because it was deemed as more appropriate for the framework of this work, given that it penalizes more heavily model complexity, and that the size of the penalty grows with the total number of samples. Accordingly, the optimal $\hat{\lambda}$ selected was the one to minimize the combined BIC on the validation and learning set, summed across all $N$ iterations of the inner CV procedure, according to the expression in equation 8). This solution was inspired by the procedure described in Cury et al. (Cury et al., 2019), and sought to avoid the bias that would be introduced if using the BIC from the learning set alone, as well as the variance that would be introduced if using the BIC from the validation set alone.

$$\hat{\lambda} = \arg\min_{\lambda} \left\{ \sum_{n=1}^{N} (BIC_{\lambda})_{n|learn} + \sum_{n=1}^{N} (BIC_{\lambda})_{n|val} \right\}$$ (8)

However, because the data being modeled in this work is time-series data, considerations regarding temporal dependencies should be accounted for. Importantly, samples within the test set are not independent from those of the training set, and thus estimates of model performance may be overoptimistic. Since this is a critical aspect for model assessment and comparison, two modified CV methods to deal with dependent data were also explored in replacement of the outer k-fold CV procedure. These two methods, here referred to as non-dependent k-fold CV and blocked k-fold CV, are described in the following paragraphs.

A nested non-dependent k-fold CV procedure was implemented, with $k = 15$ outer cycles and $n = 20$ inner cycles. The inner CV remained absolutely unchanged. In each iteration of the outer procedure, each of the samples of the original dataset was randomly allocated into one of $k$ equal sized partitions. However, right after allocation, samples within the training set that shared dependencies with any sample within the test set were removed. Importantly, the temporal correlation between two samples was assumed to only depend on their lag, which is to assume that there is a constant $h$ such that samples $x_i$ and $x_j$ are approximately independent, if $|i - j| > h$. For a given time-series, the value of this constant may be determined by analysis of its partial auto-correlation sequence. To obtain an approximate measure of $h$, the partial auto-correlation sequence, out to lag 15, was determined for the output of the model $Y$ and for several representative input features within $X$. The analysis of the partial ACF sequences suggested that the assumption that the auto-correlation of two samples only depends on their lag may be a fair approximation, since the auto-correlation decreased with increasing lag. More, it showed that each sample was significantly correlated with the 3 previous samples and the 3 following samples. However, to minimize data waste, $h = 2$ was chosen, since it should allow to remove almost all of the significant dependencies. Hence, the 2 neighboring samples, in both axis directions, of each test sample were removed from the training set. It was also confirmed that, after removal of dependent data, the size of the training set remained within the acceptable limits in terms of model performance.

Finally, another modified k-fold CV procedure, referred to as blocked CV, was also explored. Similarly to the non-dependent CV, this procedure too works by removing the $h = 2$ neighboring samples of the test samples. The difference relies on the way data is allocated to each partition: instead of randomly allocating samples to one of the $k$ partitions, partitions are created by chronological order, i.e., they consist of uninterrupted blocks of samples. This tremendously minimizes data waste, since only a total of 4 samples need to be removed from the training set in each iteration: the 2 samples before the first sample of the test set, and the 2 samples that follow the last sample of the test set. However, this procedure may be suboptimal for highly non-stationary processes, since the variability of the series throughout time may not be captured at each partition. Hence, if a specific process occurs at a specific moment in time, it is probable that the unique structure that it incurs on the data will not be considered for training and for testing simultaneously. For the particular case of the motor imagery data, a 15-fold blocked CV procedure will certainly not capture resting and task periods on the same subset. As so, $k$ was changed to 5. Indeed, by dividing the data in only 5 blocks, each block is guaranteed to capture one trial of rest and imagery. The same procedure was applied to the resting state dataset, to keep the pipeline the most similar as possible. Additionally, temporal dependencies may also exist between the learning and validation sets of the inner CV procedure, which may be suboptimal for hyperparameter selection. Specifically, simplicity may not be favored enough due to good apparent performance, in terms of the estimated prediction error, of models that are significantly overfitted to the learning
set. However, the data available in this work was insufficient to apply modified CV procedures in the inner CV cycles as well. Removing temporal dependencies from the outer cycles was prioritized, since the first concern was to obtain reliable estimates of the final model’s prediction error. More, notice that despite the inner CV procedure may not promote model simplicity, the BIC is used as a criterion for model selection, and this acts as a safeguard to avoid too complex models that may be prone to overfit.

VI. EXPERIMENTAL RESULTS

A. RESTING STATE RESULTS

The overall results of the elastic net fitting for the resting state data are reported hereafter. Tables I, II and III show the results for 15-fold CV, non-dependent 15-fold CV and blocked 5-fold CV, respectively. The measures reported are the \( \lambda \) parameter and the NMSE and BIC values, estimated by averaging across all folds. The estimated effective DOF of each model is also presented. This was determined from the final EFP of the model, derived by averaging the non-zero values of the coefficient estimates across all folds.

**TABLE I: Cross validated (15-fold CV) \( \lambda \) parameter, NMSE, BIC values and DOF of the elastic net fit of the main models explored. Results respective to the RS data.**

<table>
<thead>
<tr>
<th></th>
<th>Average ( \lambda ) ( (\times 10^{-2}) )</th>
<th>Average DOF ( (\times 10^{-1}) )</th>
<th>Average NMSE ( (\times 10^{-1}) )</th>
<th>Average BIC ( (\times 10^{2}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSF</td>
<td>6.68</td>
<td>26.0</td>
<td>4.56</td>
<td>1.07</td>
</tr>
<tr>
<td>TP</td>
<td>5.02</td>
<td>46.0</td>
<td>6.24</td>
<td>1.71</td>
</tr>
<tr>
<td>LC</td>
<td>8.77</td>
<td>47.0</td>
<td>2.93</td>
<td>2.56</td>
</tr>
<tr>
<td>IPC</td>
<td>7.72</td>
<td>124.0</td>
<td>0.797</td>
<td>8.92</td>
</tr>
<tr>
<td>WND</td>
<td>5.56</td>
<td>80.0</td>
<td>2.26</td>
<td>4.16</td>
</tr>
</tbody>
</table>

**TABLE II: Cross validated (non-dependent 15-fold CV) \( \lambda \) parameter, NMSE, BIC values and DOF of the elastic net fit of the main models explored. Results respective to the RS data.**

<table>
<thead>
<tr>
<th></th>
<th>Average ( \lambda ) ( (\times 10^{-2}) )</th>
<th>Average DOF ( (\times 10^{-1}) )</th>
<th>Average NMSE ( (\times 10^{-1}) )</th>
<th>Average BIC ( (\times 10^{2}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSF</td>
<td>5.07</td>
<td>74.0</td>
<td>4.77</td>
<td>1.49</td>
</tr>
<tr>
<td>TP</td>
<td>8.16</td>
<td>99.0</td>
<td>6.82</td>
<td>2.23</td>
</tr>
<tr>
<td>LC</td>
<td>7.10</td>
<td>125.0</td>
<td>3.49</td>
<td>3.02</td>
</tr>
<tr>
<td>IPC</td>
<td>9.62</td>
<td>234.0</td>
<td>1.80</td>
<td>7.74</td>
</tr>
<tr>
<td>WND</td>
<td>6.60</td>
<td>148.0</td>
<td>3.72</td>
<td>4.01</td>
</tr>
</tbody>
</table>

**TABLE III: Cross validated (blocked 5-fold CV) \( \lambda \) parameter, NMSE, BIC values and DOF of the elastic net fit of the main models explored. Results respective to the RS data.**

<table>
<thead>
<tr>
<th></th>
<th>Average ( \lambda ) ( (\times 10^{-1}) )</th>
<th>Average DOF ( (\times 10^{-1}) )</th>
<th>Average NMSE ( (\times 10^{-1}) )</th>
<th>Average BIC ( (\times 10^{2}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSF</td>
<td>0.350</td>
<td>26.0</td>
<td>5.50</td>
<td>1.22</td>
</tr>
<tr>
<td>TP</td>
<td>0.497</td>
<td>42.0</td>
<td>7.91</td>
<td>1.79</td>
</tr>
<tr>
<td>LC</td>
<td>5.55</td>
<td>41.0</td>
<td>6.35</td>
<td>1.57</td>
</tr>
<tr>
<td>IPC</td>
<td>0.710</td>
<td>104.0</td>
<td>0.743</td>
<td>9.18</td>
</tr>
<tr>
<td>WND</td>
<td>1.61</td>
<td>71.0</td>
<td>3.72</td>
<td>3.58</td>
</tr>
</tbody>
</table>

Figure 1 displays an example of the prediction of the BOLD response from the region of interest. The particular example shown concerns the prediction performed by fitting the \( X_{1,\text{LC}} \) model, using regular 15-fold CV.

**Fig. 1: Example of prediction of the BOLD response. BOLD signal \( (Y, \text{in blue}) \) and respective BOLD estimate \( (\hat{Y}, \text{in green}) \), obtained with the EFP estimated for the \( X_{1,\text{LC}} \) model. Results respective to the RS data.**

In the scope of reducing the feature space of the \( X_{1,\text{LC}} \) model, both one-band and one-channel models were computed for every frequency band considered and for every EEG channel, respectively. This analysis revealed that the \( X_{\alpha} \) model yielded higher predictive performances than the remaining one-band models, both in terms of NMSE and BIC. This result was consistent across all CV procedures employed. Regarding one-channel models, model \( X_{\text{O2}} \) yielded better predictive performance, in terms of NMSE, in all of the CV procedures. However, in terms of model BIC, neither one of the models was consistently better across all CV procedures. The channel selected to perform further analyses was then the channel O2. Hence, features with respect to the alpha frequency band and channel O2 combined were used to build the model \( X_{\alpha,\text{O2}} \). More, the feature space of models \( X_{\alpha}, X_{\text{O2}} \) and \( X_{\alpha,\text{O2}} \) was further reduced by solely integrating features that were convolved with the canonical HRF (overshoot delay at 6 seconds). Results showed that none of these models yielded unacceptably high NMSE. This suggests that modelling resting state BOLD fluctuations within the DMN may be done successfully with a small number of features, and that both activity and the activity from channel O2 may comprise promising features within this scope.

Further insights can be drawn by analyzing the topographic representations of the EFPs obtained. These are shown in figure 2 for the five main models assessed.

B. Motor Imagery Results

The overall results of the elastic net fitting for the motor imagery data are reported hereafter. Tables IV, V and VI show the results for 15-fold CV, non-dependent 15-fold CV and blocked 5-fold CV, respectively.
TABLE IV: Cross validated (15-fold CV) λ parameter, NMSE, BIC values and DOF of the elastic net fit of the main models explored. Results respective to the MI data.

<table>
<thead>
<tr>
<th></th>
<th>Average λ (×10⁻¹)</th>
<th>DOF</th>
<th>Average NMSE (×10⁻¹)</th>
<th>Average BIC (×10²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSF</td>
<td>1.09</td>
<td>39.0</td>
<td>2.25</td>
<td>1.72</td>
</tr>
<tr>
<td>TP</td>
<td>1.04</td>
<td>40.0</td>
<td>2.00</td>
<td>1.84</td>
</tr>
<tr>
<td>LC</td>
<td>1.11</td>
<td>49.0</td>
<td>0.843</td>
<td>2.55</td>
</tr>
<tr>
<td>IPC</td>
<td>1.76</td>
<td>62.0</td>
<td>0.564</td>
<td>4.20</td>
</tr>
<tr>
<td>WND</td>
<td>1.30</td>
<td>57.0</td>
<td>0.925</td>
<td>3.03</td>
</tr>
</tbody>
</table>

TABLE V: Cross validated (non-dependent 15-fold CV) λ parameter, NMSE, BIC values and DOF of the elastic net fit of the main models explored. Results respective to the MI data.

<table>
<thead>
<tr>
<th></th>
<th>Average λ (×10⁻¹)</th>
<th>DOF</th>
<th>Average NMSE (×10⁻¹)</th>
<th>Average BIC (×10²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSF</td>
<td>1.03</td>
<td>54.0</td>
<td>2.65</td>
<td>1.71</td>
</tr>
<tr>
<td>TP</td>
<td>1.44</td>
<td>48.0</td>
<td>3.24</td>
<td>1.58</td>
</tr>
<tr>
<td>LC</td>
<td>1.65</td>
<td>64.0</td>
<td>1.55</td>
<td>2.15</td>
</tr>
<tr>
<td>IPC</td>
<td>2.06</td>
<td>92.0</td>
<td>0.863</td>
<td>4.02</td>
</tr>
<tr>
<td>WND</td>
<td>1.34</td>
<td>69.0</td>
<td>1.33</td>
<td>2.87</td>
</tr>
</tbody>
</table>

TABLE VI: Cross validated (blocked 5-fold CV) λ parameter, NMSE, BIC values and DOF of the elastic net fit of the main models explored. Results respective to the MI data.

<table>
<thead>
<tr>
<th></th>
<th>Average λ (×10⁻¹)</th>
<th>DOF</th>
<th>Average NMSE (×10⁻¹)</th>
<th>Average BIC (×10²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSF</td>
<td>0.719</td>
<td>46.0</td>
<td>1.66</td>
<td>1.94</td>
</tr>
<tr>
<td>TP</td>
<td>0.966</td>
<td>40.0</td>
<td>1.95</td>
<td>1.99</td>
</tr>
<tr>
<td>LC</td>
<td>0.884</td>
<td>45.0</td>
<td>0.713</td>
<td>2.69</td>
</tr>
<tr>
<td>IPC</td>
<td>1.23</td>
<td>54.0</td>
<td>0.420</td>
<td>4.54</td>
</tr>
<tr>
<td>WND</td>
<td>1.28</td>
<td>54.0</td>
<td>0.975</td>
<td>3.09</td>
</tr>
</tbody>
</table>

For this dataset too, one-band and one-channel models were also derived. Results from this analysis show that both X₀α and Xβ models yielded significantly better NMSE than the remaining models, although no significant differences for the BIC values were found. However, between the X₀ and the Xβ model, the NMSE was not deemed as significantly different. Hence, despite the Xβ showing a slightly better NMSE, the X₀ was selected to be used in the subsequent analyses. Regarding the analyses with one-channel models, results show that model XFC1 was the one to yield better predictive performance in terms of NMSE, and thus it was the one selected to perform further analyses. Hence, features with respect to the alpha frequency band and channel FC1 combined were used to build the model X₀,FC1. More, the feature space of models X₀, XFC1 and X₀,FC1 was further reduced by solely integrating features that were convolved with the canonical HRF. Results from this last analysis indicate that the reduced feature models held significantly lower BIC values, XFC1,can, X₀,FC1 and X₀,FC1,can models all yielded unacceptably high NMSE (greater than 1), which indicates that these features alone could not have been used to derive good enough BOLD predictions.

Further insights can be drawn by analyzing the topographic representations of the EFPs obtained. These are shown in figure 3 for the five main models assessed.
estimated for the final models, which was consistently lower than the number of features originally considered. Moreover, the topographic representations of the EFPs suggest that the models obtained were rather sparse across channels, which is in line with the theoretical expectation that only a few brain regions are highly engaged in a specific cognitive process. These results validate not only the choice of elastic net regularization to fit the models, but also the adequacy of the cross validation procedures used for model selection, as well as the criterion adopted to choose amongst competing models, which was the BIC value.

Regarding the performance of the several models tested, as measured by the estimated BIC values, results were also consistent across the two datasets. Specifically, the $X_{RMSF}$ model was deemed to yield the best predictive performance, followed by the $X_{TP}$, the $X_{LC}$, the $X_{WND}$ and finally, the $X_{IPC}$. Regarding the analyses performed in the scope of reducing the feature space of the $X_{LC}$ model, results from both datasets suggest that the BOLD fluctuations of interest may be successfully modelled through a considerably small number of features, particularly features arising from either one single frequency band or one single EEG channel.

Results across the two analysed datasets were also consistent in terms of the evaluation patterns obtained through each of the three cross validation procedures implemented: 15-fold cross validation, 15-fold non-dependent cross validation, and 5-fold blocked cross validation. Specifically, the two modified CV procedures, which attempted to remove temporal dependencies from the time-series data in order to obtain reliable predictions of model performance, estimated overall higher prediction errors than the traditional CV procedure. This may indicate an underestimation of the true NMSE with the regular CV procedure, further validating the need to employ modified CV procedures for model evaluation. Notably, in all the CV methods explored, both the NMSE and the BIC showed to vary similarly amongst the different models. This suggests that the comparison between the models here assessed was not impaired by dependencies within the data.

Finally, for both datasets assessed, the topographic representation of the overall EFPs estimated was in line with previous findings reported for each of the experimental conditions. Specifically, for the resting state data, the topographic representation of the EFPs estimated for the spectral feature models ($X_{RMSF}$, $X_{TP}$ and $X_{LC}$) showed negative coefficients of high absolute value for channels within occipital regions, and in the case of the $X_{LC}$ model these were associated with the alpha frequency band. This suggests a negative correlation between the alpha activity in occipital channels and the BOLD fluctuations within the DMN, a result that has been previously reported. On the other hand, for the motor imagery data, all maps obtained show engagement of regions within the motor cortex (although not exclusively). Specifically, in the EFPs estimated for the $X_{RMSF}$, $X_{LC}$, $X_{IPC}$ models, the highest weights were associated with channels within the secondary sensorimotor cortex. More, for the $X_{LC}$ model, higher coefficient sizes were estimated for features associated with the alpha and beta frequency bands. More, these held negative values, suggesting an ERD of these rhythms with the motor task, which is consistent with the results most frequently reported in the literature. Moreover, by analysing the temporal structure of the coefficient estimates related with the alpha frequency band, it was revealed that the channel C3, located on the primary motor cortex of the contralateral hemisphere to the MI task, was also associated with high coefficient sizes. However, these weights switched between positive and negative values depending on the HRF delay considered. This poses the question of whether it is redundant to consider such a wide range of HRF delays for the purposes of the methodology here studied.

The methodology employed entailed several limitations. An important consideration has to do with the convolution of the EEG-derived features with the family of HRF waveforms, which certainly increased the presumably already high correlation amongst the cluster of features originally fed to the models. This is a concern especially for problems with high number of features and small sample size, which was the case in this work. The redundancy that arises from this phenomenon significantly hinders the interpretation of the models estimated, and thus the identification of the features with the strongest fitting effects. This compromises the search for a clearer view on the relationships being modelled, and thus the future development of more cost-effective solutions. Notably, the elastic net regression algorithm exhibits a grouping effect, whereby similar weights are assigned to highly correlated features. While this effect is often desirable so as to not discard relevant features, it may also be suboptimal when the correlation amongst features is introduced by the processing of the EEG data. In the context of these suppositions, a different pipeline could and should be assessed, in which EEG-derived features were not to be convolved with a family of HRFs, but instead delayed to match the time-frame of the simultaneous BOLD signal.

To improve the predictive performance of the models assessed, increasing the training sample size by using more than one session (of resting state or of motor imagery) could be a possible solution. More, data from separate sessions would not share temporal dependencies, thus being more suitable for evaluating model performance. In another scope, by recording multiple sessions, the motor imagery cross-spectrum could have been averaged across several trials, thus increasing the quality of the functional connectivity estimates. However, this procedure could not be done for the resting state data, which does not yield trial stationarity. To improve the quality of the resting state connectivity estimates, alternative methods for deriving the expected value of the cross-spectrum could have been tested. A possible approach could have been to wavelet-based methods, which are particularly suited to quantifying time varying coherency (Lachaux et al., 2002).

Finally, as a future prospect, the methodology employed could be extended to an EEG-fMRI-NF training framework, in which the NF scores could be directly used to learn the optimal EFPs. This as been recently done on a study that assessed a
similar approach to this one (Cury et al., 2019) and the results were rather promising. More, another future hope would be to apply the pipeline here described on data recorded from multiple subjects, in order to search for a common model, able to account for the differences between subjects.

Acknowledgment: This document was written and made publicly available as an institutional academic requirement and as a part of the evaluation of the MSc thesis in Biomedical Engineering of the author at Instituto Superior Técnico. The work described herein was performed at the Evolutionary Engineering of the author at Instituto Superior Técnico (Lisbon, Portugal), during the period March-October 2019, under the supervision of Prof. Patrícia Figueiredo and Athanasios Vourvopoulos.

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