Published in final edited form as:

Eng Appl Artif Intell. 2015 March ; 39: 198–214. doi:10.1016/j.engappai.2014.12.008.

Genetic Programming and Frequent Itemset Mining to Identify Feature Selection Patterns of iEEG and fMRI Epilepsy Data

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Abstract

Pattern classification for intracranial electroencephalogram (iEEG) and functional magnetic resonance imaging (fMRI) signals has furthered epilepsy research toward understanding the origin of epileptic seizures and localizing dysfunctional brain tissue for treatment. Prior research has demonstrated that implicitly selecting features with a genetic programming (GP) algorithm more effectively determined the proper features to discern biomarker and non-biomarker interictal iEEG and fMRI activity than conventional feature selection approaches. However for each the iEEG and fMRI modalities, it is still uncertain whether the stochastic properties of indirect feature selection with a GP yield (a) consistent results within a patient data set and (b) features that are specific or universal across multiple patient data sets. We examined the reproducibility of implicitly selecting features to classify interictal activity using a GP algorithm by performing several selection trials and subsequent frequent itemset mining (FIM) for separate iEEG and fMRI epilepsy patient data. We observed within-subject consistency and across-subject variability with some small similarity for selected features, indicating a clear need for patient-specific features and possible need for patient-specific feature selection or/and classification. For the fMRI, using nearest-neighbor classification and 30 GP generations, we obtained over 60% median sensitivity and over 60% median selectivity. For the iEEG, using nearest-neighbor classification and 30 GP generations, we obtained over 65% median sensitivity and over 65% median selectivity except one patient.

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Key terms

frequent itemset mining; genetic programming; feature selection; pattern classification; iEEG; fMRI; epilepsy

2. Introduction

Epilepsy is a neurological disorder that impairs millions worldwide with recurrent often uncontrollable seizures (World Health Organization, 2012). Physicians at epilepsy centers acquire combinations of various noninvasive or/and invasive brain signal modalities to diagnose the seizure onsets in patients, plan neurosurgical treatment, or fathom ictogenesis mechanisms and epilepsy symptom (Bragin et al., 2010; Donaire et al., 2009a; Donaire et al., 2009b; Engel, 1993; Engel et al., 2010; Fried, 1995; Rosenow and Luders, 2001; Sierra-Marcos et al., 2013; Staba and Bragin, 2011). These modalities include scalp electroencephalography (EEG), intracranial electroencephalography (iEEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), and other neuroimaging data. Traditionally, clinicians resort to subjective manual procedures when screening iEEG or fMRI for epilepsy patient diagnoses. But signal processing techniques in pattern classification and recognition for fMRI and iEEG have become useful tools in epilepsy research to help clinicians more objectively discern differences between functional and dysfunctional brain regions, identifying diseased brain tissue for therapy (Ayoubian et al., 2012; Donaire et al., 2009a; Donaire et al., 2009b; Fernandez-Blanco et al., 2012; Gaspard et al., 2014; Gotman et al., 1995; Grewal and Gotman, 2005; Halford, 2009; Han et al., 2011; Keogh and Cordes, 2007; Lee et al., 2009; Navakatikyan et al., 2006; Osorio et al., 1995; Osorio et al., 1998; Qu and Gotman, 1997; Saab and Gotman, 2005; Tzallas et al., 2009; Tzallas et al., 2012; Wilson and Emerson, 2002; Worrell et al., 2012). With further development, validation, and acceptance across several research groups, such algorithms may translate to practical clinical use as decision-support tools for physicians.

One approach to developing semi-automated pattern classification and decision-support tools for epilepsy data has been in implementing *evolutionary computation* techniques to select, combine, or create measures (extracted features) that quantify the difference between *interictal* biomarkers (e.g., pathological gamma oscillations in iEEG, resting-state blood oxygenation changes in fMRI) and *interictal* background or basal activity (Burrell et al., 2007a; Smart et al., 2007; Smart et al., 2011). Scant research has been published on the application of evolutionary computation to interictal resting-state fMRI signals from epilepsy patients (Burrell et al., 2007b). Instead, pattern detection applications for *ictal* (*seizure*) activity dominate prior research involving evolutionary computation techniques applied to iEEG and EEG, including mostly genetic algorithms (Consul-Pacareu; Haydari et al., 2011; Hsu and Yu, 2010; Ocak, 2008; Patnaik and Manyam, 2008; Rivero et al., 2013; Shen et al., 2013), genetic programming (Sotelo 2013a; Sotelo et al., 2013b), and harmony search optimization (Gandhi et al., 2012; Zainuddin et al., 2013), although some projects have focused on *spike* detection applications (Haydari et al., 2011; Kinnear et al., 1999; Marchesi et al., 1997a; Shen et al., 2013). Additional studies have used evolutionary

computation in other manners for epilepsy data (Bandarabadi et al., 2011; Firpi et al., 2005a; Harikumar et al., 2004; Rivero et al., 2013; Wei et al., 2010). Only a few groups apply evolutionary computation techniques to gamma oscillation pattern detection for encephalography (Firpi et al., 2007; Smart et al., 2007; Smart et al., 2011). We have focused on pattern classification research for *interictal* rather than *ictal* events of interest for the following philosophical positions: (1) certain analyses of interictal brain signals can lead to diagnostic and prognostic information for identifying seizure onset zones equivalent to or complementary to certain analysis of ictal brain signals (Bettus et al., 2011; Crepon et al., 2010; Heers et al., 2014; Korzeniewska et al., 2014; Lu et al., 2014; Matsumoto et al., 2013; Spencer et al., 2008; Thornton et al., 2011; Valentin et al., 2014; Worrell and Gotman, 2011; Zhang et al., 2014); and (2) some patients do not have seizures during epilepsy monitoring, so using brain signals not dependent on seizures provides a means to offer some clinical analysis for patients rather than send them home without any diagnosis. Because it is not a trivial problem to detect interictal biomarkers within iEEG or fMRI signals, especially depending on the signal-to-noise ratio for each brain signal modality, we have used evolutionary computation techniques to search for robust optimal albeit relatively complex and somewhat human-intractable solutions. Commonly referenced alternative approaches for interictal biomarker detectors using iEEG signals still involve a human verification stage to discard numerous false positive detections (Crepon et al., 2010; Gardner et al., 2007; Worrell et al., 2008) despite some algorithm developments (Zelmann et al., 2012). Such human involvement counteracts the main purpose of the semi-automated approach and depending on the false-positive rate of the detection method might be as laborious as marking the actual true-positive events without running the pattern classification. On the other hand, we demonstrated via our prior work on interictal biomarker detection algorithms that—for at least our epilepsy brain signal data—one may gain higher pattern classification performance for features selected using an evolutionary computation method than for features selected by conventional or popular-in-literature methods for iEEG (Firpi et al., 2007; Smart et al., 2007; Smart et al., 2011) and for fMRI (Burrell et al., 2007a).

Evolutionary computation is a discipline comprising the study and development of evolution-based (Darwin, 1978) search optimization algorithms: for instance, an initial search space contains a population of organisms (possible optimal solutions) that stochastically undergoes mutation and recombination before survival selection (i.e., choosing the most fit organisms) and generational (iterative) production of a new population of organisms from the prior population (refining the possible optimal solutions) until no more evolution (optimization convergence). Since its pioneering inception in the 1950s through 1960s (Baeck et al., 1997; Barricelli, 1957, 1962, 1963; De Jong et al.; Fogel, 1998; Fogel et al., 1968; Fraser, 1960; Turing, 1950), evolutionary computation has spawned numerous computer science techniques that today has five classes or dialects of research areas: (1) evolutionary programming (Fogel et al., 1986; Fogel et al., 1968; Sebald and Fogel, 1994), (2) genetic algorithms (Booker et al., 1989; Holland, 1992a, b, 1995), (3) evolution strategy (Schwefel, 1981, 1995), (4) genetic programming (Koza, 1989, 1992, 1994; Koza, 1996, 1997, 1999; Koza et al., 2006), and (5) swarm intelligence (Beni, 2005; Beni and Wang, 1989; Blum and Merkle, 2008; Bonabeau et al., 1999; Dorigo and Gambardella, 1997; Kennedy et al., 2001). In particular, the genetic programming (GP)

methodology is a global search optimization procedure that heuristically develops possible solutions (programs) to a predefined problem statement using biological evolution concepts (i.e., mutation, crossover, and selection) (Koza, 1989, 1992, 1994). The GP algorithm (see Algorithm 1) initializes a set (population) of solutions (individuals) of size P with each element representing a mathematical operation on the input of the GP in the form of a tree structure, uses an objective function to compute an index (fitness) for each individual, and executes the evolutionary processes to create new populations that optimize the fitness to compute best individual. The evolutionary processes have many variations in implementation but the same basic concepts: the selection stage chooses a current population subset (intermediate population) based upon individual fitness; the crossover stage creates new individuals using combinations of paired individuals from the intermediate population, forming a new population; the mutation stage introduces diversity into the new population by randomly altering the makeup of a subset of individuals in the new population; and the survival stage simply selects the fittest individuals from the new population, creating a new initial population of size P for subsequent GP iterations (generations). The algorithm ends upon attaining a predefined number of generations or predefined fitness value. From this final population of solutions, one may select the best (optimal) solution according to the chosen fitness function.

For pattern classification problems to quantitatively discriminate non-biomarker (e.g., basal or baseline activity) and biomarker (e.g., spikes, seizures, PGOs, abnormal CBF activations) brain signals from epilepsy patients, GP has been used for both noninvasive and invasive electroencephalography (Fernández-Blanco et al., 2013; Firpi et al., 2005b, c, 2006; Guo et al., 2011; Lopes, 2007; Marchesi et al., 1997b; Smart et al., 2007; Sotelo et al., 2013a; Sotelo et al., 2013b), MEG (Georgopoulos et al., 2009; Theofilatos et al., 2009), and fMRI (Burrell et al., 2007b). However, GP is *not* a feature selection algorithm. Technically, its use in this way is a mischaracterized application, where algorithmic issues such as bloat, fitness function definition, and choices for the terminals (features) and functions can substantially affect ‘feature selection’ results. Also, GP the algorithm can output practically inelegant solutions since theoretical parsimony is not a guaranteed effect (Kelly, 1995). These limitations accentuate the importance of examining whether GP-based feature-selection solutions demonstrate reproducible results and useful patterns for pattern classification of epilepsy data. Consequently, we investigated GP-based feature selection (i.e., implicit feature selection with GP algorithm) for *interictal* resting-state brain recordings with focus on two main questions regarding the computed feature subsets. Across patients, do selected subsets exhibit the same feature subsets, indicating universal measures, or different subsets, indicating unconventional case-by-case measures? Per patient, are the selected subsets similar if not the same in content, indicating consistency in solutions? Since the confidence interval concept embodies the computation of consistency or reliability in an estimated value or parameter set (Neyman, 1937), we investigated these two questions under the same aim: construct and evaluate confidence intervals for GP-based feature selection. Since a feature subset list is qualitative rather than quantitative data, we considered frequent itemset mining (FIM) as an approach for confidence interval construction.

Frequent itemset mining is the first stage in association rule learning, an established data-mining method to discover highly replicable information within a multitude of data (Agrawal et al., 1993; Agrawal et al., 1996; Agrawal and Srikant, 1994, 1995; Rakesh and Ramakrishnan, 1994, 1995, 1998; Rakesh et al., 1993; Zaki, 2000). As its name implies, an FIM algorithm discovers (i.e., mines) frequently occurring itemsets (i.e., collections of data variables) for pattern observation. An event (item) represents some variable of interest in the data-mining framework. A set of items (itemset), sometimes called a transaction, is an observed combination occurring events. A collection of multiple itemsets (database) is the input for FIM analysis to identify patterns. An itemset percentage (support), s , indicates its regularity or frequency within the database, where an itemset with n events that exceeds a support threshold (or likelihood level), λ , is termed a λ -frequent n -itemset. A maximal (max) λ -frequent n -itemset is an itemset such that any $(n+1)$ -itemset of which it is a subset has $s < \lambda$. Alternatively stated, a max λ -frequent itemset is an itemset that has infrequent ($s < \lambda$) proper supersets. It is important to note that for a given support threshold λ , FIM may output multiple itemsets as max frequent n -itemsets and these max itemsets may range in cardinality (e.g., 2-itemsets and 4-itemsets without 3-itemsets) (Figure 3). As illustrated (Figure 3), given a database (upper left), the FIM algorithm computes frequent itemsets (gray rectangles) and max-frequent itemsets (black rectangles) with the support threshold λ , while the FIM avoids sub-threshold trials within the database (white rectangles) for final output results. The max-frequent itemset with the highest occurrence and largest size in the database represents the final solution (e.g., Figure 1D). Because numerous potentially coincident event combinations must be evaluated to identify at least one pattern in a database, data-mining algorithms such as FIM provide efficient computational execution in terms of memory usage, disk access, and computational burden to search for putative patterns, aiming to avoid spurious results. Among many different FIM implementations (Agrawal et al., 1996; Borgelt, 2005; Zaki, 2000), the APRIORI algorithm (see Algorithm 2) is likely the best known and most often used approach over decades (Bodon, 2003). Yet, there exists few applications of FIM to epilepsy data (Bourien et al., 2005; Bourien et al., 2004; Exarchos et al., 2006; Smart et al., 2012) and none apply FIM in the same manner that we present with this work.

We present a framework to essentially compute confidence intervals for GP-based feature selection that categorize epileptic biomarkers (not seizures but interictal resting-state activity) and brain activity not considered as epileptic biomarkers by implementing the APRIORI FIM algorithm after several GP feature-selection trials. This approach (Figure 1) transforms stochastic results of the GP analysis into more deterministic results via FIM. In Section 3, we explain the approach details: Section 3.1 for the acquisition of each the iEEG and fMRI signals (Figure 1A); Section 3.2 for computation of signal measures via feature extraction process (e.g., Figure 1B); Section 3.3 for selection of a subset of these measures using GP, a process that we repeated in multiple trials for application of FIM (Figures 1C and 2); Section 3.4 for recognition of patterns in repeatedly selected measures (features) via FIM (Figure 1D); and Section 3.5 for our three main computational experiments to apply and validate the framework.

3. Materials and Methods

3.1 Signal Acquisition

We analyzed fMRI collected from one patient group and iEEG collected from another patient group. For each de-identified dataset, the Internal Review Boards at the Georgia Institute of Technology, Emory University, and the University of Pennsylvania approved data analysis. For each dataset, a board-certified clinician annotated “gold standard” epileptic biomarkers, which provided classification labels (i.e., biomarker, non-biomarker) for the *in silico* experiments.

We retrospectively analyzed already acquired interictal iEEG recordings (Figure 1A, left) from seven patients (1 child). Each person had a standard clinical presurgical evaluation for brain resection to treat their seizures: surgical implantation of platinum-iridium brain electrodes (Ad-Tech Medical Instrument Corporation, Racine, WI) before hospitalization in an epilepsy monitoring unit (EMU) to pinpoint a focal seizure-onset zone (SOZ) for neurosurgical resection (Engel, 1987; Luders and Comair, 2000; Rosenow and Luders, 2001). A clinical EMU iEEG system continuously recorded electrophysiology for each patient. For the child, a 128-channel system (Grass-Telefactor, Warwick, RI) with analog anti-aliasing band-pass filtration (−3dB cutoffs at 0.5 and 100 Hz) digitized data at 12 bits per sample and 800 samples per second before digital low-pass filtering (−3dB cutoff at 70 Hz) and down-sampling to 200 samples per second for final storage. For the adults a 64-channel system (Nicolet Biomedical, Madison, WI) with an analog Butterworth band-pass anti-aliasing filter (cutoffs −3dB at 0.5 and 150 Hz) digitized data at 12 bits per sample and 400 samples per second before digital low-pass filtering (−3dB cutoff at 100 Hz) and down-sampling to 200 samples per second for final storage. From the above data for each patient we randomly picked multielectrode iEEG clips with interictal pathological gamma (i.e., 30–100 Hz adults, 30–70 Hz child) oscillations (PGOs) and without any epileptic biomarker activity in clinically marked SOZ electrodes as manually annotated *a priori* by epileptologists. We used interictal PGO data since various types of gamma brain activity offered utility as a potential SOZ biomarker (Bragin et al., 1999; Medvedev et al., 2011; Pan et al., 2009; Smart et al., 2012; Worrell et al., 2004). Our main focus was *not* to discern SOZ electrodes from non-SOZ electrodes (or seizures from non-seizures) but instead indirectly was to discern PGOs from non-PGOs and directly was to find consistently selected measures to discern PGOs and non-PGOs. But the subsequent analyses did include PGOs and non-PGOs across heterogeneous electrodes (i.e., signals inside and outside the SOZ). We normalized signals from each electrode to a -1-to-1 scale before creating two single concatenated time-series signals from all interictal iEEG signals: one with the biomarker activity (i.e., PGOs) and one with the non-biomarker activity (non-PGOs). No chosen signals contained artifacts (e.g., electrical, movement). We applied a zero-phase digital bandpass-filter (i.e., 30–100 Hz) to the scaled artifact-free signals.

We analyzed resting-state ASL (arterial spin labeling) perfusion fMRI scans from five MTLE (mesial temporal lobe epilepsy) patients. Each scan occurred at 3 Tesla with a 3-second repetition time and lasted 40 minutes for four patients and 30 minutes for one patient (P05). We realigned the fMRI images to account for patient motion during scanning and

reduce artifacts, smoothed images with a Gaussian kernel to increase signal-to-noise ratio, performed pairwise subtraction to obtain CBF (cerebral blood flow), and normalized images to the standard MNI (Montreal Neurological Institute) brain template for conformity using SPM (Statistical Parametric Mapping) software (i.e., SPM2) (Frackowiak et al., 2004; Friston et al., 2007). The resulting CBF dataset consisted of 300 or 400 images depending upon scan duration, where each 16-slice (i.e., 64×64 voxels cross-section) image had a $3.44 \times 3.44 \times 7.50 \text{ mm}^3$ voxel resolution. We limited voxel analysis for each patient to left and right hippocampi since prior clinical tests (e.g., positron emission tomography, video-EEG) during their presurgical evaluation in addition to the fMRI revealed a unilateral temporal lobe seizure focus. We computed the time course (i.e. voxel intensity as a function of time) from the voxels in each hippocampus (Figure 1A, right).

3.2 Feature Extraction

For each time-series, whether iEEG concatenation or fMRI voxel, feature extraction involved calculating multiple measures ($n=14$ for iEEG signals and $n=13$ for fMRI signals) from each signal within a moving W -second window using a mathematical expression, or feature, for each measure. We used measures (Table 1) common to both our prior iEEG (Smart et al., 2007) and fMRI (Burrell et al., 2007a) computational epilepsy research for consistency in this work. For the iEEG signals, we computed W by bootstrapping the median PGO duration using the manually annotated timestamps (Smart et al., 2012). We performed feature extraction with an arbitrarily chosen 75 % overlap between consecutive sliding windows to generate 300+ points for each of the two signals (i.e., concatenated PGO events, concatenated non-PGO events). For the fMRI signals, we made W the entire voxel time-course duration to produce a single value per voxel, generating 100+ total observation points from both hippocampi. Ultimately, for each the iEEG and fMRI dataset we computed (1) a measurement matrix, $\mathbf{X}$, with a corresponding measure (representative feature) per column (i.e., $\mathbf{x}_i$ for i -th measure) and observation points per row; and (2) a ground-truth vector, $\mathbf{c}$, with the same number of rows as $\mathbf{X}$ and numeric class labels for non-biomarker (i.e., class 0) and biomarker (i.e., class 1) interictal brain activity in one column. We extracted features such as curve-length (Table 1) and created a statistical sample of measurement values for non-biomarker (Figure 1B, black) and biomarker (Figure 1B, gray) epileptic activity in the iEEG (Figure 1B, left) and fMRI (Figure 1B, right) signals. Both $\mathbf{X}$ and $\mathbf{c}$ became input variables for the feature selection stage (Figure 1C).

3.3 Feature Selection

We used a GP algorithm (Silva and Almeida, 2003a) to indirectly select features and combine measures that optimally classified biomarker and non-biomarker activity according to a filter-based fitness function via Eq. (1), Eq. (2), and Eq. (3) and predefined parameters (Table 2). For each patient and each brain signal modality, we repeated feature selection 500 times using our prior GP-based procedures (Burrell et al., 2007a; Smart et al., 2007): 100 selection trials $\times$ 5 distinct GP generation parameters. We set 0.50 as the initial probabilities for crossover and mutation before the GP adaptively updated both probabilities to improve average population fitness and assist population diversity (Davis, 1989). We utilized total elitism survival to compute the best solution: all the individuals from both parent and children populations are ordered by fitness alone, regardless of being parents or children.

We used lexicographic parsimony pressure to control bloat in GP individuals (Luke and Panait, 2002): a random number of individuals is chosen from the population, choosing individuals with the best fitness, where if two individuals have equal fitness then the individual with less nodes becomes the final solution. We limited the depth of individuals using the dynamic maximum depth parameters to control bloat (Silva and Almeida, 2003b; Silva and Almeida, 2004): a minimum depth of 6 for both data modalities and a maximum depth of 10 for the fMRI and 11 for the iEEG.

For each patient, each GP generation value, and each trial, we inputted the measurement matrix $\mathbf{X}$ and ground-truth vector $\mathbf{c}$ (see Section 3.2) to the GP and outputted two results from the GP: (1) a multiple-input-single-output transformation, f , or alternatively a multivariate function composition using preset expressions (Table 3) and variables (Table 1); and (2) column indices (Figure 1C) for the selected measures from $\mathbf{X}$. Illustrating these two outputs (Figure 2), the gray nodes (rectangles) are GP functions or expressions (Table 3) and the white nodes (rectangles) are GP terminals or variables, which correspond to features (Table 1), for the GP solution. These mock examples correspond to the 99th (Figures 2A and 2B) and 100th (Figures 2C and 2D) trials of computing the best GP solution (Figure 1C) for iEEG (Figures 2A and 2C) and fMRI (Figures 2C and 2D) signals. We ignored the composite functional mappings (e.g., f_{99} and f_{100}) and only compiled the terminals as a database (Figure 1C) for FIM (Figure 1D). We used the same $\mathbf{X}$, $\mathbf{c}$, and GP parameters for the 100 trials. We defined fitness function using the following equations.

$$fitness = (1 - overlap) \cdot (kfactor) \quad (1)$$

$$kfactor = |\mu_1 - \mu_0| / \sqrt{(\sigma_1^2 + \sigma_0^2)/2} \quad (2)$$

$$overlap = \int \min(p(\mathbf{y}|\mathbf{c}=0), p(\mathbf{y}|\mathbf{c}=1)) d\mathbf{y} \quad (3)$$

In Eq. (3), the column vector $\mathbf{y} = f(\mathbf{X})$ had the same number of rows as $\mathbf{X}$ and $p(\mathbf{y}|\mathbf{c} = c)$ equaled the prior distribution $\mathbf{y}$ in class c with mean μ_c and standard deviation σ_c . We used the k-factor in Eq. (2), which paralleled the Fisher discriminant ratio (FDR) and the Cohen's d effect size statistics, to quantify the separation between histograms of measures for the epileptic and non-epileptic classes. The k-factor ranged inclusively between 0 for no separation and infinity for maximum separation. The overlap ranged inclusively between 0 for no overlap and 1 for total overlap. High k-factor values and low overlap values indicated greatly separated histograms. We introduce this overlap parameter since sometimes seemingly good FDR values result from a statistical sample of measures (extracted feature values) with large overlaps in the corresponding histograms for two disjoint classes. The fitness function in (1) penalized GP individuals with large class overlaps by increasing the fitness score in proportion to the amount overlap. More specifically, we multiplied equations (2) and (3) to obtain equation (1) and to account for possible misleading cases of class separation (e.g., probability distributions with distant means but heavy tail skewness proximal means and low variance). Thus, the GP individual with the highest fitness score

was ultimately selected as the best GP solution. Additionally, because we used a filter-based rather than a wrapper-based (e.g., machine learning algorithm) approach for the objective function (Eq. 1), we did not need a cross-validation procedure for the GP. Instead, we developed a framework that not only avoided the consequent high computational complexity and execution duration of a wrapper-based approach but also the dependency on a specific model-fitting method for future pattern classification.

We predefined sixteen GP parameters (Table 2). We arbitrarily chose 100 for the total number of feature selection repetitions (trials), which equaled the total number of FIM database transactions (Figure 1C), for each the iEEG and fMRI data. We used different GP generation values for the iEEG signals (i.e., 5, 10, 20, 30, and 35) versus the fMRI signals (i.e., 10, 20, 30, 40, and 50) after noticing the different GP convergences for the different brain signal modalities. In this work, we did not focus on exploring whether the number of GP trials for the experiments or whether the GP parameters besides number of generations might considerably affect the FIM results for the following reasons: (a) we purposely limited the number of overall framework parameters (e.g., GP, FIM, feature extraction) under investigation for focusing on establishing the overall foundational approach; (b) we considered the GP generations the most important parameter regulating variability in the best GP solution upon conclusion of all iterations; (c) we only considered the best GP solutions (individuals), which when exploiting the procedural robustness of FIM sufficiently determined the most relevant feature subsets for a given GP configuration (even a constrained one as in this work) and served as a methodological archetype for other GP configurations; and (d) we reserved rigorously studying the effects of other GP parameters, especially exhaustively exploring the entire configuration space, for future research.

3.4 Feature Subset Confidence Interval Computation

We considered FIM a very suitable technique to study the consistency (i.e., confidence interval) of GP selected features for quantitatively discerning non-biomarker and biomarker interictal events. We defined a feature subset confidence interval as a list of most frequently co-occurring features (i.e., elements in the subset) after repeating the GP analysis (Figure 1C), where theoretically different GP repeats resulted in different feature subsets and the most frequently selected features represented a type of ‘expected value.’ We compiled the indices (Table 1, 3rd or 4th column) of the selected features (see Section 3.4) to form a database (Figure 1C), **Q**, for the FIM analysis (Figure 1D). For **Q**, each row corresponded to a feature subset. The FIM searched **Q** for frequently co-occurring (co-selected) features.

For each patient and generations parameter, we formed a feature-subset database using the 100 GP feature-selection trials (see Section 3.3). We used FIM support thresholds of $\lambda = 0.10$ (one occurrence in ten trials) for the iEEG feature-subsets and $\lambda = 0.20$ (two occurrence in ten trials) for the fMRI feature-subsets. For both modalities we used a proven high-performance APRIORI FIM implementation (Bodon, 2005) to analyze each database. For instance, if the features entropy and kurtosis comprised a max λ -frequent 2-itemset that occurred 35/100 times in a particular database, then the GP simultaneously selected these two features more than once every three executions, demonstrating some heuristic consistency and pattern in the ability to discern epileptic and non-epileptic activity with

these measures. The FIM avoids an exhaustive search of the total

$$\sum_{k=1}^{14} \binom{14}{k} = 2^{14} - 1 = 16,383$$

possible combinations of creating feature subsets from 14 features (items) by basically first examining the database for 1-itemsets (subsets with only 1 feature) with occurrence greater than or equal to the predefined support threshold λ ; second making 2-itemsets (subsets with only 2 features) using combinations of the 1-itemsets and excluding 2-itemsets that do not suffice the same threshold λ ; third making 3-itemsets (subsets with only 3 features) using combinations of the 2-itemsets and excluding 3-itemsets that do not suffice the threshold λ , and then repeating the same process such that it makes n -itemsets (subsets with n features) using combinations of the $(n-1)$ -itemsets and excluding n -itemsets that do not suffice the threshold λ (Figure 1D). The results of the FIM analysis formed the basis for our main experiments (Figure 1E).

3.5 Main Experiments and Statistical Analyses

We performed three main *in silico* experiments to understand three key complementary aspects regarding the stochastic GP algorithm for selecting the best features that discriminate epileptic biomarkers and disparate events in each the iEEG and fMRI data sets (Figure 1E).

In the first experiment, we observed whether any pattern resulted from mining the GP-selected features across patients and generations to evaluate the reproducibility and subset size of the GP feature-selection for each the iEEG (Table 4) and fMRI (Table 5) data. We revisited these results in the third experiment, which focused on finding possible correlations between measures not frequently identified by the FIM analysis.

In the second experiment, we studied whether the mined GP-selected features had better pattern classification performance than the GP-selected feature-subset with the highest fitness over the 100 trials to evaluate the ultimate utility of using FIM to compute the most appropriate features versus solely using in principle the best GP-selected features. We used sensitivity and selectivity, as defined by equations (4) and (5) respectively, for the pattern classification performance metrics and dependent variables in a three-factor analysis of variance (ANOVA) to test the null hypothesis of no statically significant difference ($p < 0.05$) in performance between mined and not-mined feature subsets. For each the separate fMRI and iEEG data, each patient, each GP generations parameter, and each method (e.g., not mined, mined), we performed leave-M-out cross-validation with a 5-NN (5-nearest-neighbor) classifier and 100 bootstrap samples of disjoint training and testing data with the following percentages of testing points: 92.49 ± 0.54 for iEEG and 49.97 ± 7.44 fMRI. In the ANOVA, we defined as factors (independent variables) the patient, number of GP generations, and method. We presumed a random effects model for the ANOVA for all factors except the method factor. More specifically, the method factor had three levels: (M1) not mined or GP only, (M2) mined, using the max λ -frequent n -itemset with the lowest support (i.e., $s = \lambda$), and (M3) mined, using the max λ -frequent n -itemset with the highest support (i.e., $s > \lambda$). Comparing the performance of the lowest-support and highest-support FIM max λ -frequent n -itemset permitted us to initially test the hypothesis that more frequent and less frequent feature subsets demonstrated equivalent ability to classify biomarker and

non-biomarker events and that any max λ -frequent n-itemset rather than a specific feature subset sufficed pattern classification. We performed a separate ANOVA for each the iEEG (Table 6) and fMRI (Table 7) datasets and each classification metric. To illustrate the ANOVA results, including descriptive statistics such as measures of central tendency and measures of dispersion, we used notched boxplots (Figures 3 and 4) where for each boxplot the width of the notch represented the 95% confidence interval in the median performance metric (e.g., sensitivity, selectivity) with the MATLAB function *boxplot* (McGill, 1978; Nelson, 1989; Velleman and Hoaglin, 1981). Thus, boxplots with non-overlapping notches indicated statistical significance at the 0.05 level (Chambers, 1983).

$$Sensitivity = TP / (TP + FN) \quad (4)$$

$$Selectivity = TP / (TP + FP) \quad (5)$$

In the third experiment, we performed a correlational analysis for each subject and number of GP generations to examine the interchangeability of ‘unshared’ FIM features. We defined an ‘unshared’ FIM feature as a feature not within the intersection of all max λ -frequent itemsets of the same cardinality but within a max λ -frequent itemset. For example (Figure 3), we considered features 3, 4, and 5 but not feature 2 as unshared features. Since λ was a threshold, the FIM algorithm returned multiple non-identical feature subsets all of the same cardinality (Figure 3). We hypothesized that unshared FIM features correlated with each other and that different FIM feature subsets exhibited practical similarity in composition as well as classifier performance. For the correlational analysis, we used the Spearman correlation coefficient test statistic with a null hypothesis of no statistically significant correlation ($r = 0$, $p < 0.05$) between two particular unshared measures. For each subject, we compiled the coefficients of all pairs of unshared measures across generations and computed 95% confidence intervals in the median correlation coefficient for each the iEEG (Figure 6A) and fMRI (Figure 6B) FIM measures. The number of pairs varied across patients even with the same number of GP generations given the cardinality of the patient-specific FIM results (Tables 4 and 5). For each patient, we further visualized the correlation between paired unshared FIM measures as scatterplots for the iEEG data (Figure 7) and the fMRI data (Figure 8). Again, the purpose of these analyses and plots was to quantitatively inspect the practical similarity of different FIM feature subsets.

4. Results

4.1 Observed Patterns with FIM Features

In our first experiment, we observed whether any pattern resulted from mining the GP-selected features across patients and generations to evaluate the reproducibility and subset size of the GP-based feature-selection. We computed the max frequent itemsets, or the most frequently occurring feature subsets among the 100 trials, for each patient, biological data modality, and number of GP iterations (Tables 4 and 5). For each max frequent itemset, the first item occurred most and the last item occurred least. We noticed that GP often picked the same feature subsets within a subject across generations, but that feature subsets differed

across all patients with only 1–2 overlapping features for any given patient pair, and that GP consistently returned subsets with more than one feature for all patients.

For instance, with patient C07 from the iEEG results (Table 4), the GP often selected CL (curve length) and ZC (zero-crossings) for 5 generations, CL and MRV (mean rectified value) for 10, 20, 30, and 35 generations, and RMS (root mean square) along with CL and MRV at 35 generations. For C07, as with four other patients, the number of GP generations marginally affected the FIM feature subset. However, for patients E02 and E11, FIM always clustered the same subsets: PF (peak frequency), MP (mean power spectral density), K (kurtosis), and CL for E02; and PF, MP, and CL for E11. Furthermore, at least one feature (e.g. CL for all, PF for E02, E09, and E11) always recurred in the max frequent itemsets across all generations, implying consistency and patterns in the GP feature-selection.

The fMRI results (Table 5) closely resembled the iEEG results (Table 4). The GP generations only slightly affected the FIM feature subsets. For each subject, at least two of the same features appeared in the max frequent itemset for each number of generations. For example with patient P02, features RE (Renyi entropy) and CL (curve length) occurred in all FIM subsets for all GP generations; also, features NE (nonlinear energy) and RE appeared in all FIM subsets for all GP generations except 30. For instance with patient P05, RE and S appeared in all FIM subsets for all GP generations. But the max itemsets for each patient varied across the number of generations: for P01, sometimes a subset included a fourth feature that was either MF1 (mean frequency) or NE; for P05, sometimes a subset included a third feature that was M, E, or SE1. Additionally, the same subset did not arise for all patients for any given number of generations: for instance with 40 generations, P01 resulted in a confidence interval of features (i.e., RE, V, SE1, and NE) that showed different subset size and contents than the resultant confidence interval of features (i.e., RE, S, and M) for P05.

4.2 Classification Performance with FIM Features

In our second experiment, we studied whether the mined feature subsets had better pattern classification performance than the feature subset with the highest GP fitness of the 100 trials. We were not concerned with achieving high classification performance values but instead we focused on investigating whether (1) changing the number of GP iterations considerably altered performance, which would necessitate parametric care in combining GP with FIM; and (2) using GP alone or in conjunction with FIM yielded similar classification performance. In other words, we conducted another observational study and not an optimization study (deferred as later work).

For the iEEG data, after evaluating both the sensitivity and selectivity metrics, we found (a) statistically significant differences in mean classification performance between patients; (b) statistically significant interactions between patients, methods, and GP generations; and (c) no other statistically significance (Table 6). These results supported the hypothesis that neither the number of GP generations nor the approach to choose the final feature subsets significantly affected classification performance. These results supported the hypothesis that different patients may exhibit different classification performance even when selecting patient-specific features. We hypothesized statistically significant interactions between the

patient and methods, but did not observe this outcome (c.f., Figure 4, Table 6) after computing the classifier sensitivity (e.g., Figure 4A) and selectivity (e.g., Figure 4B), for all patients and methods (i.e., M1: GP alone versus M2: least frequent FIM feature subset versus M3: most frequent FIM feature subset) using the 30 GP generations (Figure 4) and other GP generations (Supplementary Figures). We supposed that we might have seen such an effect with a larger patient sample size, translating to more variability across patient in the ability to quantitatively separate PGO and non-PGO events, or perhaps even with a larger FIM database (e.g., 1000 trials rather than 100 trials). We concluded a need for also patient-specific classifier design and selection (e.g., k-NN for patients like C07, E03, E05, and E11 but architecture such as mixture models for E02, E07, E09) as well as patient-specific feature selection (Table 4) to discern PGO and non-PGO activity given the ANOVA for the patient variable (c.f., Figure 4, Table 6). With 30 GP generations the approach attained over 65% median sensitivity (Figure 4A) and over 65% median selectivity except for E07 (Figure 4B). We found comparable results for other generations (Supplementary Figures).

For the fMRI data, after evaluating both the sensitivity and selectivity metrics, we found (a) statistically significant differences in mean classification performance between patients; (b) statistically significant interactions between patients and methods; (c) statistically significant interactions between patients, methods, and GP generations; and (d) no other statistically significant results (Table 7). These results supported the research hypothesis that the number of GP iterations did not significantly affect classification performance. These results also supported the hypothesis that the approach to choose the final feature subsets (e.g., GP alone, GP and FIM) significantly affected classification performance and depended on each patient. We expected statistically significant interactions between the patient and methods, indeed observing this outcome in some instances (c.f., Figure 5, Table 7), implying that different patients may likely need different approaches to quantitatively assess CBF for biomarker and non-biomarker voxels. We concluded a need for patient-specific approaches to classify fMRI CBF epileptic activity at all three major pattern classification modules: feature extraction; feature selection, which unlike the iEEG findings necessitate a confidence interval analysis such as FIM to identify the best feature subset; and perhaps even the machine learning architecture (like the iEEG conjectures) to computationally decide biomarker and non-biomarker voxels. With 30 GP generations the approach attained over 60% median sensitivity (Figure 5A) and over 60% median selectivity (Figure 5B). We found comparable results for other generations (Supplementary Figures). For one patient (Figure 5B: P05 and M3) we obtained median selectivity of 1.00 (occluded by axes).

4.3 Relationship between Features

The correlational analysis per dataset for each patient to investigate unshared features, or measures computed from features within the to all FIM subsets, or less frequently selected features, revealed (Figure 6) weak to strong nonlinear relationships between certain iEEG measures (median: $0.10 < r < 0.70$, $p < 0.001$) and strong to very strong nonlinear relationships between many fMRI measures (median: $0.50 < r < 0.99$, $p < 0.001$). Likewise, the correlational analysis for each GP generations after compiling all patients per dataset revealed weak to strong nonlinear relationships between certain iEEG measures and strong to very strong

nonlinear relationships between many fMRI measures (results not shown). Thus, while the selected and mined measures exactly differed in some instances, further scrutiny determined that sometimes the algorithms picked somewhat similar (correlated) measures during these discrepancies (Figures 7 and 8), especially for the fMRI signals (Figure 8). For instance, E05 and P02 demonstrated the highest overall correlation coefficients (E05: Figure 6A, P02: Figure 6B) for their corresponding signal modalities. We respectively identified nine and seven distinct unshared FIM measures (i.e., each panel along the row/column of the y-axis/x-axis in figures) with E05 using 35 GP generations (Figure 7) and with P02 using 50 GP generations (Figure 8), where some pairings of measures exhibited nonlinear correlations while others no correlation. We noticed a similar pattern with patients corresponding to relatively lower overall correlation coefficients (e.g., E09: Figure 6A, P01: Figure 6B) (e.g., Supplementary Figures S1 and S2).

5. Discussion

Applying FIM to repeated GP-based feature selection, we found patterns in the cardinality of the selected feature subsets, reproducibility of the subsets, and correlations between infrequently selected measures as well as a validation of patient-specific feature subsets.

5.1 Observed Patterns with FIM Features

Firstly, no analysis resulted in a feature subset with only one feature. More specifically, for each patient and each the fMRI and iEEG signals, the feature selection to discriminate biomarker and non-biomarker interictal brain activity outputted *at least two* features. These results suggest that careful consideration must be taken in the approaches for feature extraction and feature selection, especially if the aim is to reduce false detections. Moreover, these findings partially confirm why the current techniques to detect iEEG gamma oscillations, which typically rely on a single feature (e.g., a measure tantamount to time-series energy or line-length) rather than multiple features, experience relative disadvantages in both classification performance and overall human-free semi-automated implementation (Crepon et al., 2010; Gardner et al., 2007; Worrell et al., 2008). Conversely, the hybrid GP and FIM method used semi-automatic heuristics and an objective class separation statistic via the GP stage to eliminate subjectivity, assumption, and doubt in the proper feature space dimension reduction for pattern classification.

Secondly, the FIM approach verified the reproducibility of the stochastic GP feature selection results. We observed within-patient similarity and across-patient variability for FIM feature subsets per number of GP iterations and each brain signal modality. Thus, we objectively disproved the notion of universal features, or “one feature subset fits all” for different patients since a single specific FIM subset did not frequently reproduce across all patients.

5.2 Classification Performance with FIM Features

We determined for each the iEEG and fMRI data that (a) the FIM features typically showed the same or higher classification performance as the pre-FIM features and (b) the frequent FIM feature subsets demonstrated classification performance equivalent to or higher than the

less-frequent FIM feature subsets (Figures 4A, 4B, 5A, and 5B). We conjectured that GP-based feature selection computed a feature superset to sufficiently discriminate non-biomarker and biomarker events and that the FIM features represented the most indispensable subset, or kernel, of this superset. We recognized the need for patient-specific *feature-selection* methods, as well as patient-specific *feature subsets* (see Section 5.1), certainly for the fMRI signals and possibly for the iEEG signals. We conjectured that perhaps inherent physical differences between the biological and acquisition properties (e.g., spatiotemporal resolution) of the two signal modalities influenced differences in iEEG and fMRI results. But this experiment should be repeated with a larger patient sample, where ideally acquisition of both iEEG and fMRI should occur for each patient, to more clearly study modality distinctions.

5.3 Relationship between Less Frequently Selected FIM Features

We investigated similarities in the different FIM feature subsets. We found correlations between FIM measures unshared to all groups in many cases. This result indicated that although the FIM subsets were technically different combinations of features implicitly selected by the GP, the subsets may have been practically the same as disjoint measures often showed similar quantitative properties per their nonlinear correlation with other measures. Thus, the stochastic nature of the GP may still have a tendency to similarly select features with complementary in a subset despite not replicating exactly the same subset. This tendency needs further study to determine whether it may change depending on the user-chosen fitness function. For instance, an alternative GP objective function to our choice (i.e., Eq. (1)) might result in more or less correlated unshared measures and in turn less or more similar subsets.

5.4 Limitations and Future Research

Firstly, we emphasize that our application of the GP algorithm *implicitly* performed the feature selection. That was, while the GP formed a subset of features during its global optimization process to return the best solution, it was not a necessary outcome that the selected features had any statistically or intrinsically relevant information. One main factor in this limitation was the challenge of bloat (i.e., unreasonably large complex solutions with many introns) in constructing GP individuals. Two additional main factors in this limitation were ostensible bias in the fitness function or the functions (e.g., Table 3): in either case, the mathematics that define the fitness and functions may favor particular features but not others, perhaps erroneously rendering the unfavored measures irrelevant to the problem when in fact they might help achieve a fit solution in combination with the right complementary measures. Furthermore, some features might get selected just to produce a constant. We partially alleviated these concerns by using GP parameters that adaptively controlled bloat and diversity in the search space (Davis, 1989; Silva and Almeida, 2003b; Silva and Almeida, 2004; Luke and Panait, 2002), but we may not have adequately addressed the needed breadth of the function set (Table 3). Moreover, our GP-based feature selection still actually performed feature *transformation* since it not only selected the measurement vectors but also produced a mapping function to obtain an optimized fitness value over the stochastic population of solutions in the search space. By discarding the composite functional mapping information (Section 3.3), which in theory learned a

nonlinear boundary that quantitatively separated non-biomarker and biomarker brain activity, we basically reintroduced the burden of computing an equivalent multi-dimensional boundary to the subsequent classifier.

Secondly, we focused on observations rather than optimizations of the approach. We aimed to observe whether the FIM analysis identified patterns in features selected via GP, establishing a framework for constructing a type of confidence interval for a selected feature subset, and not yet to design the most optimal framework for the same purpose. Thus, we did not exhaustively examine all framework parameters, especially given the large size of the parameter space and the ensuing computational complexity of traversing such a space for each main module (i.e., feature extraction, GP, FIM) let alone the entire approach of combined modules. Future work should explore the effects of changing method parameters (e.g., sliding window duration of feature extraction, the set of GP functions, the set of GP terminals, population size, fitness functions, natural selection operators, crossover and mutation probabilities, FIM support threshold, machine-learning method and its configurations) and even on ‘confidence interval construction’ and pattern classification performance.

6. Conclusions

We developed a method to categorize biomarker and non-biomarker epileptic activity in iEEG and fMRI signals from epilepsy patients by combining GP and FIM techniques. We used FIM to compute qualitative confidence intervals for features selected via a GP algorithm. We observed within-subject consistency and across-subject variability for GP-based feature selection for both fMRI and iEEG signals. We concluded that the problem of detecting interictal biomarkers for each iEEG and fMRI signal modalities necessitates patient-specific feature extraction, feature selection, and likely also machine learning modules in an overall canonical pattern classification framework (Duda et al., 2000). We demonstrated classifier performance comparable to prior state-of-the-art research (Figures 4 and 5).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant funds from the United Negro College Fund Special Programs Corporation NASA Harriett G. Jenkins Pre-doctoral Fellowship Program to Dr. Smart and the National Institute of Neurological Disorders and Stroke (1R01NS048598-01A2) to both Drs. Burrell and Smart provided partial research support for this work. The authors thank the physicians from the Center for Functional Neuroimaging and Department of Neurology at the University of Pennsylvania, the Children’s Hospital of Philadelphia, and the Mayo Clinic in Rochester, Minnesota for providing the separate raw iEEG signals and raw fMRI signals for the signal processing analysis in this work by Drs. Smart and Burrell.

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Highlights

- We created a novel method using FIM to compute qualitative confidence intervals for features selected using a GP algorithm.
- We observed within-subject consistency and across-subject variability in implicit feature selection via GP for both interictal fMRI and interictal iEEG signals.
- We achieved over 60% median sensitivity and over 60% median selectivity for both iEEG and fMRI data except for a single subject.

Figure 1.
Illustration of the feature subset confidence interval framework using GP and FIM.

Figure 2.
Examples of GP individuals in tree format.

Figure 3.
Example of an FIM database and result in lattice format.

Figure 4.
Classification performance for the iEEG data.

Figure 5.
Classification performance for the fMRI data.

6A

6B

Figure 6.
Correlation coefficients for all pairs of unshared FIM measures.

Figure 7.
Scatterplots of paired unshared FIM measures for one iEEG patient and $G = 35$.

Figure 8.
Scatterplots of paired unshared FIM measures for one fMRI patient and $G = 50$.

Table 1

Extracted features for each the iEEG and that fMRI.

Feature	Description	Index (iEEG)	Index (fMRI)
Complexity (C)	Diversity of amplitudes values and sequential values	14	not used
Curve Length (CL)	Arc length and curvature of time series amplitudes	1	2
Energy (E)	Average square amplitude	not used	1
Interquartile Range (IQR)	Nonparametric amplitude value dispersion	7	not used
Kurtosis (K)	Unbiased amplitude peakedness	10	6
Mean (M)	Average amplitude	not used	4
Mean Frequency (MF1)	Frequency at spectral density centroid	not used	12
Mean Periodogram (MP)	Average broadband power spectral density	5	not used
Mean Rectified Value (MRV)	Average absolute value of amplitude	3	not used
Median Frequency (MF2)	Frequency at median spectral density magnitude	not used	11
Nonlinear Energy (NE)	Change in instantaneous amplitude and frequency	not used	3
Peak Frequency (PF)	Frequency at spectral density maximum	6	13
Renyi Entropy (RE)	Diversity of amplitude values	13	10
Root Mean Square (RMS)	Quadratic mean of amplitude values	2	not used
Shannon Entropy (SE1)	Information content of amplitude values	12	9
Skewness (S)	Unbiased amplitude asymmetry	9	7
Spectral Entropy (SE2)	Randomness of frequency content	11	8
Standard Deviation (SD)	Unbiased amplitude standard deviation	8	not used
Variance (V)	Unbiased amplitude standard deviation squared	not used	5
Zero-Crossings (ZC)	Number of intersections at zero-mean line	4	not used

Table 2

GP parameters for each the iEEG and the fMRI.

Parameter	Description	Value (iEEG)	Value (fMRI)
stop condition	rule for algorithm stoppage	max number of generations	max number of generations
number of generations	number of algorithm iterations	5, 10, 20, 30, and 35	10, 20, 30, 40, and 50
number in population	total number of individuals, whether parents or/and offspring, per iteration	500	500
initial population type	method of initializing the population of individuals	ramped half-and-half	ramped half-and-half
sampling percentage of population	percentage of population to sample as parents for generating offspring	0.9	0.9
sampling	method of selecting parent individuals from current population to generate offspring individuals	lexictour	lexictour
operator names	list of evolution-based operations	crossover, mutation	crossover, mutation
initial operator probabilities	values for genetic operator probabilities	crossover: 0.50, mutation: 0.50	crossover: 0.50, mutation: 0.50
operator probabilities type	choice to iteratively update operator probabilities (variable) or to not update the probabilities (fixed)	variable	variable
fitness function	metric for assess surviving individuals from a population	see Equations 1–3	see Equations 1–3
fitness function goal	directionality of the fitness metric (maximizes or minimizes) during the optimization process	maximize	maximize
survival	method of using a fitness function to select individuals from current population to new population	totalitism	totalitism
functions	list of possible functions to create composite function	see Table 3	see Table 3
terminals	list of possible input values for a function	see Table 1	see Table 1
minimum depth	minimum tree depth for an individual	6	6
maximum depth	maximum tree depth for an individual	11	10

Table 3

GP functions.

Function	Symbol
Absolute value	$\parallel$
Addition	$+$
Arctangent	atan
Cosine	cos
Cube	$()^3$
Division	$/$
Maximum	max
Minimum	min
Multiplication	$\cdot$
Natural logarithm	ln
Sine	sin
Square	$()^2$
Square root	
Subtraction	$-$

Table 4

FIM results per patient and number of GP generations for the iEEG signals.

Subject	G = 5	G = 10	G = 20	G = 30	G = 35
C07	CL, ZC	CL, MRV	CL, MRV	CL, MRV	CL, MRV, RMS
E02	CL, K, MP, PF	CL, K, MP, PF	CL, MP, K PF	CL, K, MP, PF	CL, K, MP, PF
E03	CL, SE1	CL, PF	CL, PF	CL, SE1	CL, SE1
E05	RMS, CL	ZC, CL	CL, ZC	RMS, K, PF	RMS, K
E07	ZC, CL	ZC, SD	ZC, RMS	ZC, K	RMS, CL
E09	CL, RMS, PF	CL, PF, RMS	CL, PF, SD	RMS, ZC, PF, SD	CL, PF, RMS
E11	CL, MP, PF	CL, MP, PF	CL, MP, PF	CL, MP, PF	CL, MP, PF

Table 5

FIM results per patient and number of GP generations for the fMRI signals.

Subject	G = 10	G = 20	G = 30	G = 40	G = 50
P01	RE, V, SE1	RE, V, SE1	RE, V, SE1, MF	RE, V, SE1, NE	RE, V, SE1, MF
P02	RE, NE, CL	RE, NE, CL	RE, CL, SE2	NE, RE, CL, V	RE, NE, CL, V
P03	M, NE	M, NE, RE	M, NE, RE	M, NE, RE	M, NE, RE
P04	NE, V, PF	NE, V, PF	NE, V, MF2, SE1	NE, V, MF2, RE	NE, V, RE, MF
P05	RE, S	RE, S, SE1	RE, S, E	RE, S, M	RE, S, SE1, E

Table 6

ANOVA results for the iEEG.

iv	Sensitivity (iEEG)					Selectivity (iEEG)				
	ss	df	ms	F	p	ss	df	ms	F	p
patient	129.38	6	21.56	78.2	0	393.48	6	65.58	105.73	0
generation	0.28	4	0.07	0.05	0.99	0.58	4	0.15	0.04	1
method	2.55	3	0.85	0.76	0.54	7.01	3	2.34	0.71	0.57
patient × generation	5.59	24	0.23	0.89	0.62	11.51	24	0.48	0.71	0.83
patient × method	5.42	18	0.3	1.15	0.33	14.16	18	0.79	1.16	0.32
generation × method	3.24	12	0.27	1.03	0.43	8.73	12	0.73	1.07	0.4
patient × generation × method	18.86	72	0.26	116.6	0	48.85	72	0.68	168.07	0

iv = independent variable; df = degrees of freedom; ss = sum of squares; ms = mean of squares; F = F statistic value; p = F-test p-value

Table 7

ANOVA results for the fMRI.

iv	Sensitivity (fMRI)					Selectivity (fMRI)				
	ss	df	ms	F	p	ss	df	ms	F	p
patient	90.24	4	22.56	21.10	0.00	161.38	4	40.34	38.75	0.00
generation	0.32	4	0.08	0.97	0.55	0.35	4	0.09	1.29	0.40
method	6.32	3	2.11	0.83	0.51	3.36	3	1.12	0.30	0.83
patient × generation	1.83	16	0.11	0.67	0.80	1.17	16	0.07	0.82	0.66
patient × method	13.96	12	1.16	6.85	0.00	11.92	12	0.99	11.13	0.00
generation × method	1.65	12	0.14	0.81	0.64	1.02	12	0.08	0.95	0.51
patient × generation × method	8.16	48	0.17	47.78	0.00	4.28	48	0.09	60.57	0.00

iv = independent variable; df = degrees of freedom; ss = sum of squares; ms = mean of squares; F = F statistic value; p = F-test p-value

Algorithm 1

Pseudocode for GP Algorithm

```

01. R = 100; /* R is number of repeats (i.e., run or trials) of GP algorithm */
02. P = 500; /* P is population size for each GP trial */
03. G = 30; /* G is number of generations or GP iterations */
/* start loop for repeat */
04. FOR rr = 1 to R
/* start loop for generation*/
05. FOR gg = 0 to G;
06. Randomly_Generate_Initial_Population();
07. WHILE NOT (Other_Termination_Criterion_Satisfied_for_Run)
/* start loop for population*/
08. FOR pp = 1 to P
09. Compute_Fitness_for_Population_Individual();
10. END
/* end loop for each population*/
/* start loop for population*/
11. FOR jj = 1 to P
12. my_operator = Select_Genetic_Operator();
13. SWITCH my_operator
14. CASE 'mutation'
15. Select_One_Individual_Based_on_Fitness (fitness_values_population);
16. Perform_Mutation(probability_ mutation);
17. Copy_Offspring_to_New_Population();
18. CASE 'crossover'
19. Select_Two_Individuals_Based_on_Fitness(fitness_values_population);
20. Perform_Crossover(probability_crossover);
21. jj = jj + 1;
22. Insert_Two_Offspring_into_New_Population();
23. END
24. END /* end loop for population */
25. END /* end loop for generation*/
26. Store_Result_of_Current_Trial(rr);
27. END /* end loop for repeat*/

```

Algorithm 2

Pseudocode for APRIORI FIM Algorithm

```

/* C_k is current list of candidate frequent itemsets */
/* F_k is current list of lambda frequent itemsets */
/* S_k is current list of support values for each candidate frequent itemset */
/* F_k_previous is previous list lambda frequent itemsets */
/* num_frequent_itemsets is the cardinality of F_k */
/* database is the input to the FIM algorithm */
/* compute the lambda-frequent 1-itemsets
01. F_1 = Compute_Frequent_Items(database, lambda);
/* start loop for computing frequent n-itemsets */
02. k = 2;
03. WHILE NOT (num_frequent_itemsets == 0)
/* lambda is the minimum support threshold */
/* F_k_previous = F_1 when k = 2 */
04. C_k = Generate_Candidate_Frequent_Itemsets(F_k_previous);
05. S_k = Compute_Support_for_Candidate_Frequent_Itemsets(C_k);
06. F_k = Compute_Frequent_Itemsets(C_k, S_k, lambda);
07. F_k_previous = F_k;
08. k = k+1;
09. num_frequent_itemsets = Compute_Size(F_k);
10. END /* end loop for computing frequent n-itemsets */

```