Virtual Resection for Predicting the Outcome of Epilepsy Surgery

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Summary

The identification of effective targets for resection is a crucial requirement for the surgical treatment of epilepsy. Quantitative methods have the potential to provide beneficial information in this regard and might in the future reduce the necessary time and effort for physicians.

The approach described here uses a distributional clustering framework for the modeling of multivariate time series to predict the efficacy of arbitrary resections. This novel approach allows simulating the resection of any combination of channels and assigns them a collective value indicating the likelihood of the model's ictal state. When simulated, the majority of resections that rendered patients seizure free in reality (Engel class I) considerably decrease the probability of the ictal state compared to the situation of no resection. The same is not the case for most actually performed but ineffective resections (Engel class IV) and most random simulated resections.

The presented method enables physicians to test planned resections in silico for their efficacy before surgery. Further validation could help to establish this method in the clinical routine and thereby not only disburden physicians from a cumbersome and error prone task but also introduce objectivity into it and eventually increase the success rate in epilepsy surgery.

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Keywords: Epilepsy, quantitative EEG, resective surgery, predictive modeling

Computerbasierte Vorhersage der Wirkung von Epilepsiechirurgie

Bei der chirurgischen Behandlung von Epilepsie ist es entscheidend, Gewebe zu identifizieren, dessen Resektion einen positiven Effekt für den Patienten hat. Quantitative Methoden können diesbezüglich hilfreiche Informationen bereitstellen und somit den Arbeits- und Zeitaufwand für Ärzte verringern. Bis heute werden quantitative Methoden im routinemässigen Arbeitsablauf jedoch kaum verwendet und die zu resezierenden Hirnareale werden nach wie vor fast ausschliesslich von Experten durch visuelle Analyse bestimmt.

Die hier beschriebene Methode modelliert die zeitliche Entwicklung von intrakraniellen EEG-Ableitungen, um die Wirksamkeit hypothetischer Resektionen vorherzusagen. Das Modell berechnet dazu die Wahrscheinlichkeit iktaler Zustände für die simulierte Resektion beliebiger Kombinationen von EEG-Kanälen. Verglichen mit dem Ausgangszustand führt die Simulation von tatsächlich durchgeführten Resektionen, unter welchen die Patienten anfallsfrei wurden (Engel-Klasse I) im Modell mehrheitlich zu einer erheblich tieferen Wahrscheinlichkeit iktaler Zustände. Bei den meisten Resektionen, die keinen vorteilhaften Effekt für den Patienten hatten (Engel-Klasse IV) und den meisten zufälligen simulierten Resektionen ist keine vergleichbare Wahrscheinlichkeitsabnahme zu beobachten.

Dieser neuartige Ansatz ermöglicht es Ärzten, geplante Resektionen zuerst am Computer auf ihre vermutliche Wirksamkeit zu prüfen. Eine umfangreichere Validierung könnte diese Methode im klinischen Alltag etablieren und dadurch Ärzte von mühsamen und fehleranfälligen Arbeiten entlasten, ein erhöhtes Mass an Objektivität in den prächirurgischen Arbeitsprozess

bringen und voraussichtlich die Erfolgsrate in der Epilepsiechirurgie erhöhen.

Schlüsselwörter: Epilepsie, quantitative EEG-Analyse, Epilepsiechirurgie, prädiktive Simulation

Résection virtuelle pour simuler la chirurgie de l'épilepsie

Dans la chirurgie de l'épilepsie, il est crucial d'identifier avec précision la zone à réséquer. Les méthodes quantitatives peuvent y contribuer, et vont potentiellement faciliter les investigations pré-chirurgicales. A ce jour les approches quantitatives n'ont cependant pas encore été intégrées dans la décision clinique, et l'identification des cibles de la chirurgie est faite par examen visuel. L'approche que nous décrivons ici utilise des méthodes de partitionnement de données («clustering» en anglais) appliquées aux séries temporelles pour prédire l'effet de différentes résections. Cette nouvelle approche nous permet de simuler la résection d'un groupe de canaux, et d'attribuer à la configuration restante une probabilité d'entrer ou non dans un état ictal. Lorsque nous simulons la résection effectuée chez les patients sans crises après l'intervention (Engel 1), notre model prédit une probabilité plus faible pour la résurgence d'un état ictal. Par contre, si nous simulons la résection effectuée chez des patients avec persistance de crises après l'opération, ou des résections au hasard, on note que cette probabilité n'est pas diminuée.

La méthode que nous présentons permet donc aux cliniciens de tester des résections in silico avant de les réaliser. La validation clinique de notre méthode pourrait aider le clinicien, en introduisant une méthode objective dans la bilan pré-chirurgical de l'épilepsie.

Mots-clés : épilepsie, EEG quantitatif, chirurgie résective, prédiction

Introduction

Epileptic seizures heavily decrease patients' quality of life. To render patients seizure free is thus the main goal of epilepsy treatment. Using pharmaceuticals, this is not achieved in around one third of all epilepsy patients [1-4]. For those suffering from pharmacoresistant focal onset epilepsies, surgical treatment can be considered. Surgical treatment aims to remove the tissue that is necessary and sufficient for the generation of epileptic seizures, termed the epileptogenic zone (EZ) [5, 6]. Since this zone is a theoretical concept, there is no technique to directly identify it by any current imaging or electrophysiological technique and clinicians are forced to use approximations.

One proxy that is often used in practice is the seizure onset zone (SOZ) which is defined by the channels of an EEG recording first showing continuous epileptiform activity. The SOZ is thought to overlap with the EZ but its exact boundaries and the actual extent of overlap with the EZ remain unknown [5]. Nowadays, the determination of the SOZ is still mainly done visually by human experts, as no automated method has found its way into clinical routine. However, the visual analysis has several disadvantages: It requires time and lacks objectivity. Also the success rate of the current practice leaves room for improvement – long-term seizure freedom is achieved in up to 2/3 of patients [7-10].

Computational analysis of intracranial EEG (iEEG) data could help to improve on all these issues and thus has evoked large interest and extensive research. A variety of techniques based on different mathematical and physical concepts has been applied to iEEG to identify tissue for surgical resection. Signals can be analyzed individually (univariate) or by their interrelations with other signals (bivariate and multivariate), whereas the latter can be further divided into symmetric relations (undirected) and causal relations (directed). Furthermore, such techniques can be linear or non-linear and they can be applied in signal space or in frequency space. For a comprehensive survey the interested reader may refer, for example, to [11].

Functional network analysis has been used to identify critical channels as potential targets for surgical removal. Typically, each channel constitutes a node and connections between nodes are determined by some pairwise dependency measure. Using graph theory nodes can be characterized and selected by their position or influence in the network regarding connectivity, centrality or similar. Several studies have shown relations between such salient nodes and the resected brain tissue and its related post-surgical outcome [12-16]. A limitation of these approaches is their descriptive nature, i.e. they cannot make predictions about the system under modifications; also, the pairwise construction of node relations does not capture statistical dependencies of higher order.

Few studies presented computational models to simulate and assess resective surgery targets in silico. Hutchings et al. combined a nonlinear computational model with subject-specific diffusion tensor imaging data [17]. Sinha et al. set up patient-specific dynamical network models using network connectivity derived from interictal ECoG data [18, 19]. Goodfellow et al. used the first half of seizures from iEEG data to derive patient-specific functional networks of neural mass models which then allow to test alternative resection strategies [20]. Using various periictal segments of the same patients' data, Lopes et al. set up a mathematical model to examine the contribution of brain regions

to seizure generation and thereby make recommendations for resection [21]. All these models have shown to capture crucial features of the data and to provide additional clinically relevant information.

Here we present some illustrative examples of a further method recently developed at the Inselspital [22] that sets up a probabilistic model that, after a learning procedure, can be used to simulate the effects of the removal of tissue beneath the electrodes of the EEG. In particular, it allows making predictions about seizure likelihood after selective elimination of input signals (EEG channels). The method has been shown to predict a clear decrease in seizure likelihood when resections are simulated that rendered the corresponding patients seizure free in reality. Vice versa, resections which did not have any beneficial effect for the patients in reality do generally not decrease the predicted seizure likelihood when simulated [22].

A soft clustering method

In the following, a brief description is provided how a model is derived from an iEEG recording (left half of **Fig. 1**) and how this model is used to make predictions about the efficacy of resections (right half of **Fig. 1**). For a detailed mathematical description and an in-depth understanding of the process please refer to the method's original publication [22].

At the beginning a model is generated using the data of all channels of a periictal segment, containing the complete seizure and the immediately preceding 180 second (s) preictal period. This allows the model to learn both, ictal and non-ictal activity. Afterwards the model is used with the data of all channels, but only from the preictal segment. This constitutes the situation when no resection is simulated. Then, the data of an arbitrary set of channels is removed for the entire recording which simulates the resection of this set. The difference between this situation and the situation where no resection was simulated yields the model's prediction about the efficacy of the specific resection. The actual set of channels recording from tissue that

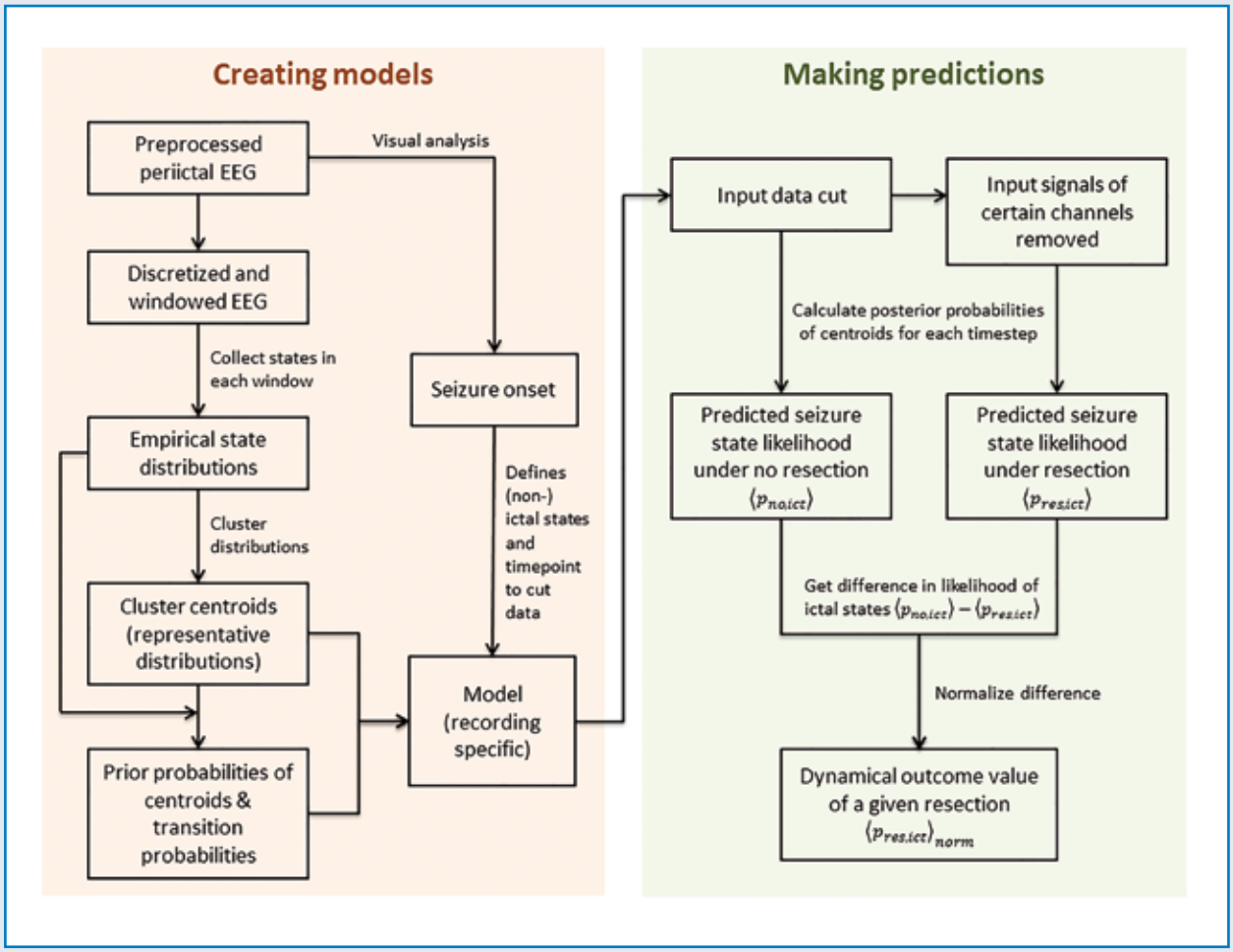

Figure 1: The course of actions to generate a model from an intracranial EEG recording (left half) and to make a prediction for an arbitrary resection using the model (right half). Further explanations can be found in the text.

was later resected is subsequently referred to as the *actual resection* (determined using coregistered pre- and post-operative MR images and post-implantation CT images [15]).

Initially the periictal iEEG data of a recording (panel 1 in **figures 2-4**) is preprocessed (filtered and normalized channel-wise), discretized to 7 values and time windowed (window length = 1.25s). The discretized values of all channels inside a window constitute a distribution and all these empirical distributions are clustered to get 6 representative distributions (the cluster centroids, in the following called the model's states). It can now be determined for each time step which state best represents the data in that window (panel 2 in **figures 2-4**). This is the model's description of the full data. Using this description one can define the probabilities of all states when no further information is provided (prior probabilities) and the transition probabilities between states. The time point of seizure onset (visually identified by an experienced epileptologist) separates the recording into a preictal phase and an ictal phase. If a state is occurring mainly during the preictal phase it is considered a non-ictal state, by contrast states mainly occurring in the ictal phase are considered ictal states.

The seizure onset also determines the time point after which no iEEG data is provided to the model when making predictions (following referred to as cutting the data). In these simulations, the probability distribution of the states before seizure onset and the transition probabilities induce the states' temporal dynamics in the ictal phase. When the data is cut (panel 3 in **figures 2-4**) one calculates the probabilities of each state at each time step (posterior probabilities). The summed probability of all ictal states in the ictal phase determines the predicted likelihood of a seizure occurring.

Repeating this process, but with the input data of some channels removed over the whole recording (panel 4 and 5 in **figures 2-4**), simulates the resection. The resulting likelihood of a seizure occurring in contrast to the situation where no resection is simulated determines the predicted efficacy of this resection to hinder the development of seizures. We call this predicted efficacy dynamical outcome which is 1 for complete seizure abatement, between 0 and 1 for lower predicted benefit or below 0 if the resection is even expected to worsen the situation.

Example cases

We now show three examples of the procedure described above. In all cases the periictal iEEG time series is shown in the first panel with the clinically determined seizure onset at 180s. The second panel shows the corresponding temporal evolution of the state probabilities when the full iEEG data is fed to the model. This determines the ictal states (the states predominantly active after 180s) and the time point to cut the input data for the subsequent simulations. If the input data is cut, the state probabilities develop according to the model afterwards which is shown in the third panel. The fourth and the fifth panel show situations when additionally the input data of certain channels is removed completely, for the actual resection (panel 4) and an equally sized random set of channels (panel 5).

The first case is of a patient with Engel class I (i.e. the patient was seizure free after resection). After the seizure onset, different states become probable that have not been probable before. In both cases where the full data is provided (panel 2 of **Fig. 2**) and with the data cut after seizure onset (panel 3 of **Fig. 2**), the transitions to state 4 and then to states 2 and 5 remain similar. According to the second panel, the states 1-2 and 4-5 are classified as the ictal states. When simulating the patient's actual resection, the probabilities of the ictal states largely vanish and the non-ictal state 6 becomes highly probable. This indicates that the removal of these channels is expected to prevent the development of seizures (panel 4 of **Fig. 2**).

Since this patient became seizure free after surgery, this is what one would expect from the corresponding simulation. A majority of tested random resections containing the same number of channels as the actual resection have no such effect. This indicates they would not help to reduce seizure occurrence as one would expect from arbitrary resections (one example shown in panel 5 of **Fig. 2**). Accordingly, this patient counts as a true positive case in the summary statistics (see below).

The second case is from an Engel class IV patient (i.e. no improvement at all after surgery). The succession of states in the ictal part of the recording does not change when no input data is provided in this part (panel 2 and 3 of **Fig. 3**). In patients without any reduction of seizure occurrence in reality, one would obviously want the model to predict the same. However, in this case the simulation of the actual resection extensively lowers the probability of the ictal states (2-6) (panel 4 of **Fig. 3**). This can typically not be observed for random resections (panel 5 of **Fig. 3**). The patient thus counts as a false positive.

The third case is again from a class IV patient. The initial order of states becoming active in the ictal part (panel 2 of **Fig. 4**) is not observable after the data is cut at seizure onset (panel 3 of **Fig. 4**). This time the simulation of the actual resection correctly predicts it to have no beneficial effect for the patient (no decrease of the probabilities of the ictal states 2-5) (panel 4 of **Fig. 4**). The same is the case for most random resections and some, as the one displayed in panel 5, are also predicted to be more beneficial for the patient than the actual resection (lower probability of the ictal states). This patient counts as a true negative.

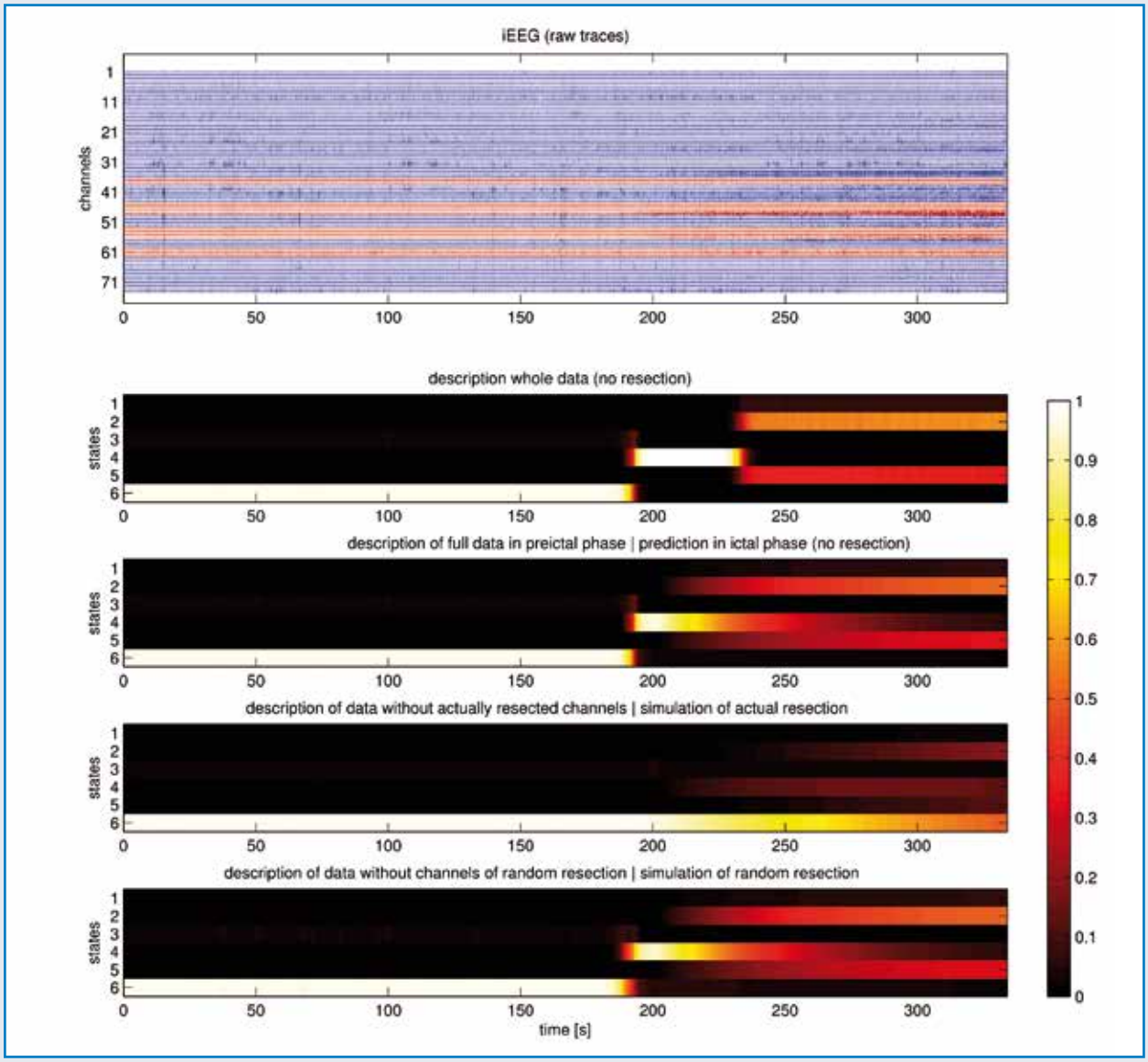

Figure 2: Panel 1 shows the segment of the intracranial EEG recording of a class I patient (4) that was used to create the model which then correctly predicts the efficacy of the actual resection (dynamical outcome = 0.955). The clinically determined seizure onset is at 180s and channels recording from brain tissue that was subsequently resected are in red. Panels 2-5 show for different situations the probabilities (color coded) of the model's states (y-axis) over time (x-axis). Panel 2: full iEEG data is provided to the model for the preictal and the ictal phase. Based on this analysis states 1-2 and 4-5 are defined as ictal states because they are mainly probable during the seizure. Panel 3: iEEG data of all channels until the seizure onset is provided whereas the dynamics in the ictal phase are determined by the model only. Still, they strongly resemble the dynamics in panel 2. Panel 4: iEEG data of all but the actually resected channels until the seizure onset is provided. The model predicts a high probability of a non-ictal state (state 6) throughout. Panel 5: iEEG data of all but a random selection of channels until the seizure onset is provided. The model predicts an ictal dynamic.

Summary statistics

In former publications this method was applied to groups of pharmacoresistant epilepsy patients that had resective surgery with known outcome and a follow-up of at least one year [22, 23]. We here show the summary results for 20 patients (see [23] for details on the patients). Only patients free from seizures and auras after surgery (Engel class I) and patients for whom the surgery had no beneficial effect (Engel class IV) were included.

We generated a model for the first artifact-free recording of each patient and assessed the effectiveness of different simulated resections to prevent a developing seizure. For each model we simulated the resection of the channels that recorded from tissue that got afterwards resected during surgery (the actual resection). In addition, we tested for each patient's model a set of

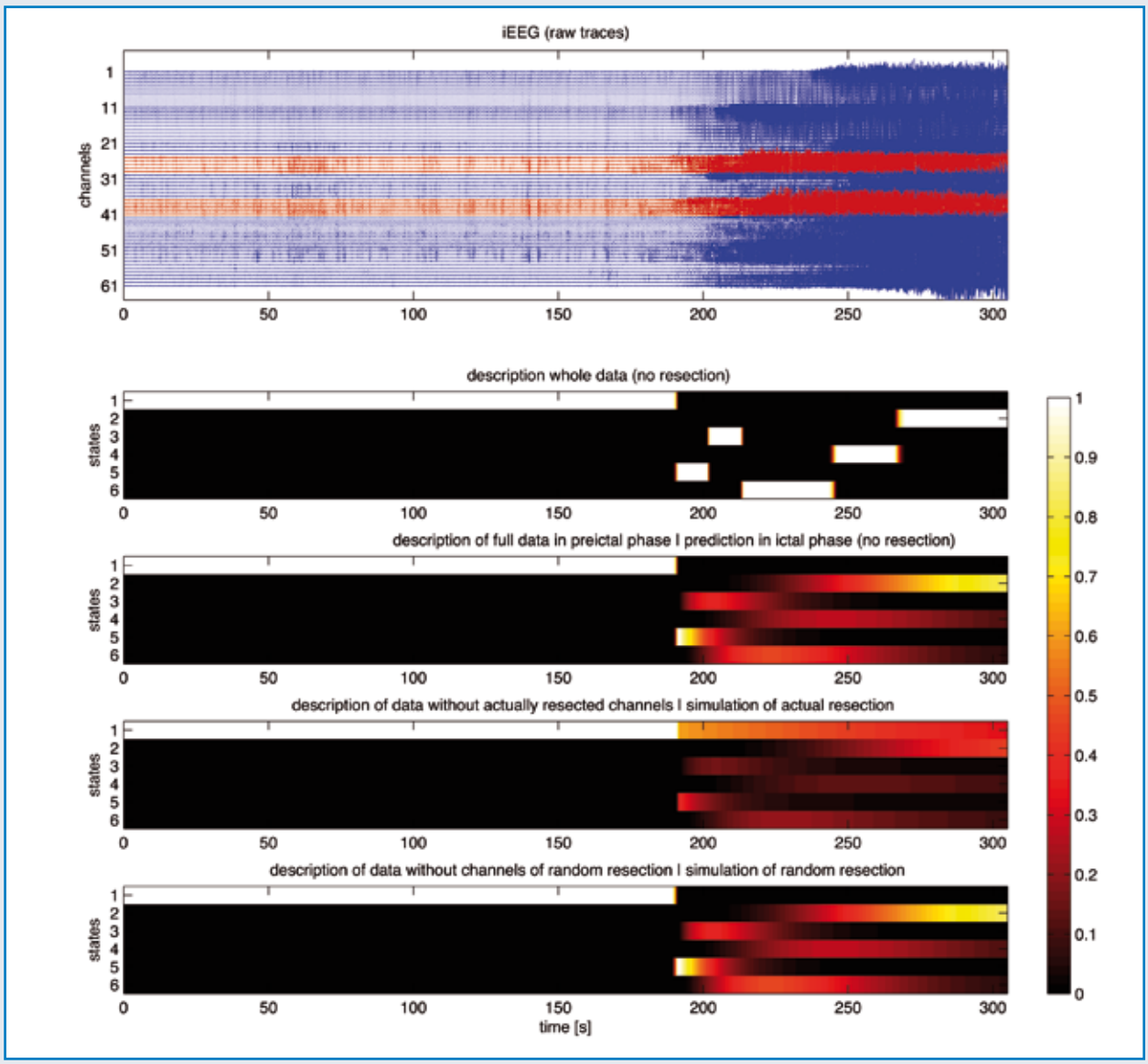

Figure 3: The same displays and depictions as in Fig. 2 for a class IV patient (15) where the model falsely predicts considerable benefit for the patient from the actual resection (dynamical outcome = 0.896). The ictal states are in this case states 2-6.

3000 random resections. The number of channels in these random resections was constrained to the number of actually resected channels of the respective patient, and the channels of the actual resection were excluded from becoming part of the random resections.

This procedure was performed for all models and the results are collected in Figure 5. The sorted dynamical outcomes of all simulated resections are shown as the cumulative distribution by the black line. From all random resections (~60'000) a large portion has a very low dynamical outcome indicating their inefficiency.

Discussion

We applied a dynamic soft clustering approach for multivariate time series to intracranial EEG data of epilepsy patients to predict the effectiveness of (virtual) resections to prohibit seizures. The probability of automatically determined ictal model states was used as an outcome performance measure, called the dynamical outcome.

When simulating the resections actually performed in the patients, we found a considerable decrease in dynamical outcome in most Engel class I patients correctly predicting the benefit of the actual resection. Given the vast numbers of possible models and channel resection protocols, it is extremely unlikely to get these results by chance. In the Engel class IV patients, we found in most cases no considerable decrease of dynamical outcome

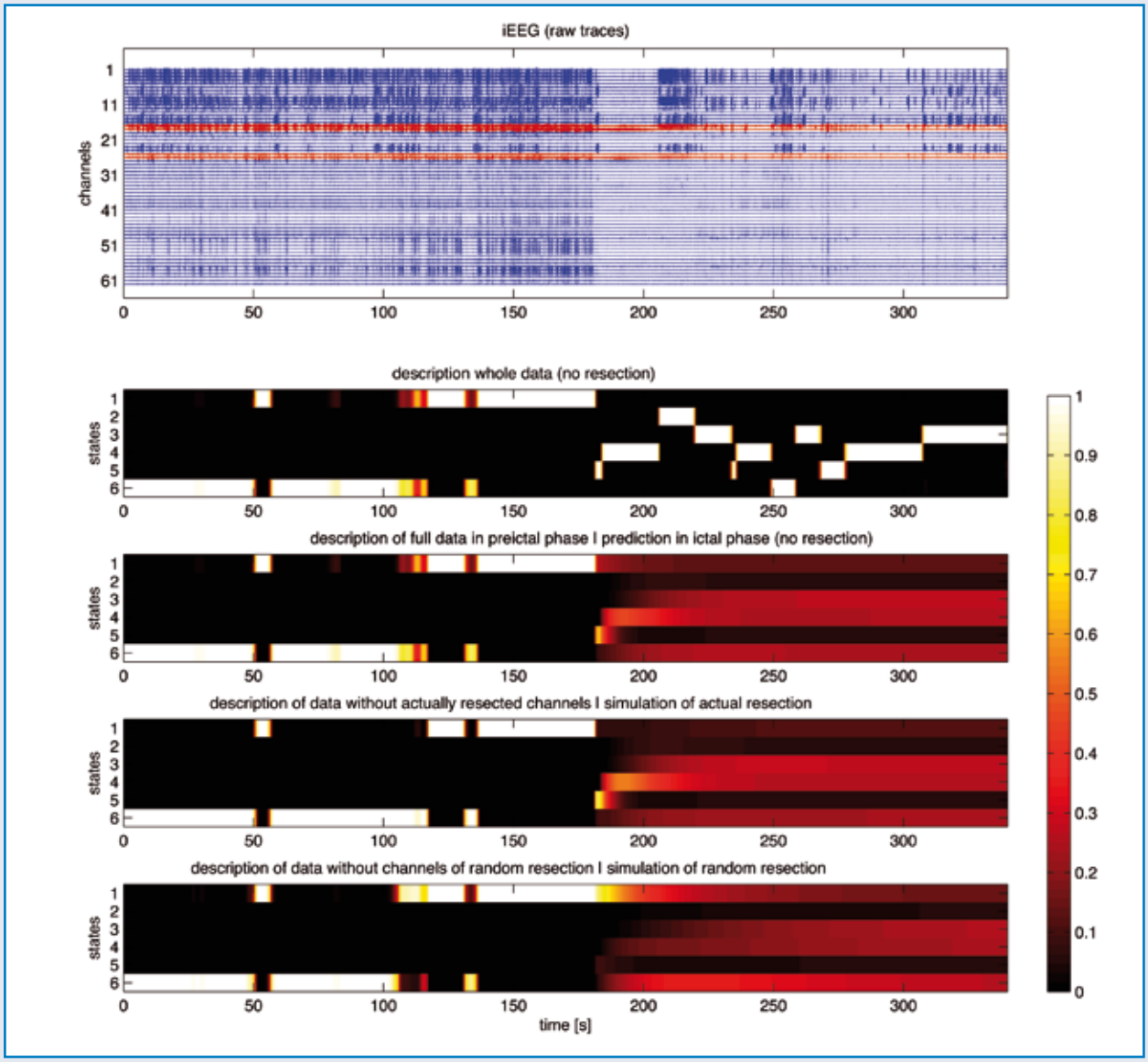

Figure 4: The same displays and depictions as in Fig. 2 for a class IV patient (17) where the model correctly predicts no improvement by the actual resection (dynamical outcome = 0.0). The ictal states are in this case states 2-5.

when simulating the actual resections. In this case the interpretation of the results is ambiguous as the negative prediction may also be caused by the model's failure to capture crucial features of the time series. When simulating arbitrary resections, in all cases the majority of resections are predicted to have no considerable beneficial effect. This verifies that the method is specific and does not predict high benefit for a disproportional number of resections.

These results suggest that the presented approach is capable of extracting key features of epileptic iEEG time series and, based on that, predicting the seizure-preventing efficacy of different resection protocols. Visual analysis typically focuses on searching suspicious patterns as spike-waves or low-amplitude, fast oscillations. This univariate view may be too simplistic for some forms of epileptic activity. Multivariate measures including complex interactions of multiple subparts of the epileptic brain could provide new and helpful information. It will be the object of future work to identify these crucial features.

So far, most of these approaches share the limitation that they can currently only make assessments of previously selected resections and are not able to provide the resection(s) predicted to be most beneficial. To find the best resection in the huge number of possible resections is a combinatorial optimization problem. In the case of nonlinear methods, there is (currently) no algorithm to solve this problem exactly in feasible time. Approximate algorithms like e.g. metaheuristic procedures would be a possibility to extend such approaches to include that capability in the future.

To bring these technologies closer to clinical understanding and finally acceptance, one needs to inves-

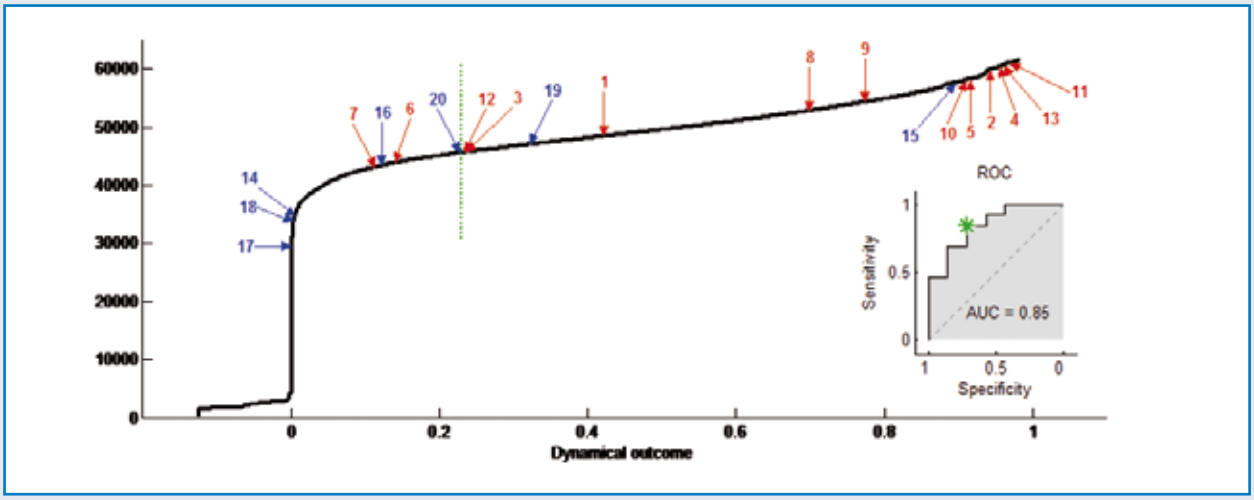

Figure 5: Conjoint dynamical outcomes of 20 patients. All simulated resections of all patients are depicted as cumulative distribution by the black line. The actual resections are denoted by the colored arrows and patient identifiers, red for Engel class I patients (1-13) and blue for Engel class IV patients (14-20). The ROC-curve displays the method's performance as binary classifier with the green asterisk as the point with minimal distance to perfect performance. The green dotted line is the corresponding optimal threshold.

tigate the meaning of the cluster centers displayed in Figures 2-4. Are these clusters indicating the appearance of certain wave-forms or wave-form distributions among iEEG channels?

Numerous approaches including the one presented here can be used to assess the efficacy of distinct and clinically preselected channel resections. In their visual analyses epileptologists focus on suspicious patterns such as spike-waves or low amplitude, fast oscillations, thus univariate signal characteristics. Suboptimal outcomes suggest that at least some cases require more elaborated considerations like multivariate techniques incorporating complex interactions of different subparts. This assumption is supported by the growing perception of epilepsy as a network phenomenon [13, 15, 16, 24-30]. Computational models such as the clustering procedure presented in this study could provide assistance to grasp such complex interactions and thus have the potential to improve the surgical treatment of epilepsy.

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