Methods for Estimation of Hidden Dynamics in Non-Linear Systems for Predicting Sleep-Wake States

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***Abstract*—There is extensive clinical and experimental evidence that links sleep state to seizure generation. Sleep-wake regulation is also altered in epileptic brain. In order to investigate this bi-directional coupling we need to understand the physiology of sleep-wake regulation in normal and epileptic brains. In order to do so we have physiologically-based mathematical models of sleep-wake regulatory system and experimental measurements from this system in chronically implanted normal and epileptic animals. Our objective is to assimilate sparse noisy measurements from the system - such as EEG and behaviorally measured state of vigilance as well as unit recordings from the represented cell groups- into these mathematical models, and thereby both validate or improve the models and detect changes in physiology. Critical to applying this technique to real biological systems is the need to estimate the underlying model parameters. Here, we present an estimation technique capable of simultaneously fitting and tracking multiple model parameters to optimize the reconstructed system state. Performance is gauged by reconstruction and forecasting of state from noisy observations of model-generated data, and compared to other conventional parameter tracking methods. In addition, we have extended our methodology to use state of vigilance as an indirect set of observations relevant to cell-group activities involved in sleep-wake regulation. We can therefore assimilate these indirect observations into the optimized model dynamics to track and predict future state of vigilance in normal and epileptic rats.**

I. Introduction

An epileptic seizure is a transient neurological event due to abnormal brain activity that causes partial or complete loss of control. Persons with epilepsy experience neurological and neurologically sourced pathologies that significantly impact quality of life. One such pathology is sleep disruption. There is a long and established clinical history of the relationship between sleep state and seizure dynamics [1]. Not only is state of vigilance (awake and alert vs. sleep) or more generally brain state affected by epileptic activity, sleep state also confounds any potential pre-seizure signature [2]. Hence it will infinitely complicate any effort towards accurate seizure prediction and detection. To our knowledge, there are no current seizure prediction algorithms that specifically account for the state of vigilance, most likely due to the difficulty of classifying the sleep state based on ElectroEncephalography (EEG).

Sleep state is an emergent phenomenon of the brain network. Changes in sleep state depend on the chemical balance of several crucial neurotransmitters, which in turn are controlled by other factors such as the history of previous sleep states (fatigue) as well as environmental inputs (day vs. night, loud noises). Measurements spanning these elements are often both technically challenging and highly invasive. However, stabilization of sleep-wake cycles is hypothesized to be a means to treat aspects of psychiatric and neurodegenerative diseases such as epilepsy (see for example: [3]). But to do so in a minimally invasive, targeted fashion requires accurate models of the relevant dynamics, and is further constrained by the ability to **observe** the destabilized dynamics. Additionally, if we understand and can observe the dynamics of the brain network that regulate sleep-wake behavior, then we can identify its coupling to the symptoms associated with neurological diseases and develop interventions.

Due to advances in computational neuroscience, physiology, and genetics, several groups have published models of the brain's sleep-wake network [4]. The models are species dependent, high dimensional (10-22 variables) with many parameters, and non-linear. If we could observe or measure all of the physiological activities and interactions represented as variables within these models, we could first validate the models and then utilize them to gain a mechanistic understanding of the brain dynamics throughout transitions. Further, we can ultimately iterate the model forward and predict future sleep states. A major consideration is the cost of particular measurements. In neurophysiological experiments, not only are these measurements financially expensive with high medical risks due to invasive implants, but also they can cause significant and often irreversible damage to the subject of the measurements.

Another major consideration regards the parameters of the model. Although these mathematical models of sleep-wake regulation have the potential to provide mechanistic information about the underlying dynamics, their default parameter sets are often based on simulated conditions and are thus far from the real system. The process of fitting the model parameters to observations of the real system allows potential identification of the root mechanisms of the disease which might not otherwise be known, and therefore opens new avenues for minimally invasive and optimal interventions.

II. METHODS

We have established a rodent model of spontaneous epilepsy which translates well to human temporal lobe epilepsy. Our rodents are continuously cabled for EEG, head acceleration, and single cell recordings. We also perform continuous video monitoring. We have overcome the barriers in obtaining accurate measures of the state of vigilance by combining features extracted from the EEG with head acceleration. The states of vigilance (SOV) are defined as wake and two types of sleep: rapid eye movement (REM) and non-rapid eye movement (NREM). We have also established a robust system to access and chronically record from sleep-regulatory brain structures deeply embedded in brainstem. Our suite of measurements thus offers a platform to study the physiology of sleep-wake regulation both at the cellular and network level.

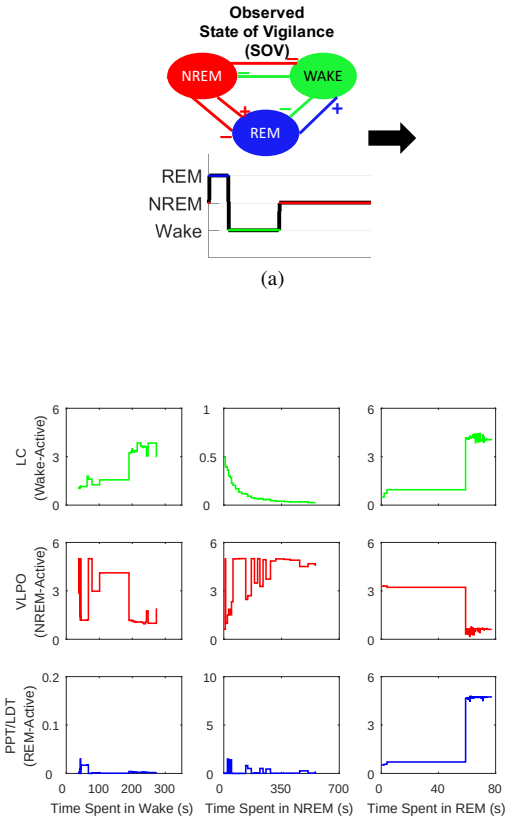
In order to address the challenges involved in using mathematical models we have combined data assimilation with techniques used mainly in control theory to make accurate weather predictions, one of which is Unscented Kalman Filter (UKF). Data assimilation is an iterative prediction-correction scheme that synchronizes a computational model to observed dynamics. In this setting UKF uses the governing equations of the sleep models and any variables in the model that we are able to measure to fully reconstruct model variables, and provides for forecasting of future states [5], [6].

A. Observations from State of Vigilance

The cell groups represented in the mathematical models as variables that regulate sleep-wake behavior are deeply embedded in brainstem. Therefore directly measuring their activity and interactions with invasive probes is technically challenging and sometimes even impossible with current technology. These measurements when possible are often highly damaging to delicate systems that are critical for organism survival. It is therefore advantageous to observe these dynamics through the data assimilation tools using less invasive/less costly measurements.

One approach that we introduced in [7] was to invert the classified SOV time series into estimates of the cell group activity levels. In particular, we utilized the SOV-dependent median activity levels of the corresponding cell groups as the inversion. Although assimilation of the SOV-derived observations into UKF yielded reasonable reconstruction accuracy, the forecast values of the variables did not follow physiological expectations and some of the finer features of the dynamics were not well-reconstructed.

Here we extend this inversion to include information about time since the last state transition. In particular, we use model generated data to create distributions of activity levels of the cell groups as a function of time since transition into each state of vigilance. The means of these distributions over time, shown for three firing rate variables for each SOV in Fig. 1b, along with their variance, are used to translate the state of vigilance as a function of time into probability of activity levels, which is then handed to the UKF as observations.



(a)

(b)

Fig. 1: Observation model from State of Vigilance to cell group activity levels. (a) Measured State of Vigilance (SOV), (b) SOV mean and variance conditioned on time since transition to each state to Probability Distribution Function (PDF) of activity levels of the cell-groups responsible for sleep-wake regulation

B. Multi-Parameter Fitting

The mathematical models we use are based on approximations of the average cell group activities regulating sleep-wake behavior. Therefore, the parameters of these models are inherently estimates of actual physical quantities in real brain. Brains from different species and even brains from individuals from the same species vary. So we expect them to have different representative parameters just as they express different detailed sleep-wake dynamics. These variations introduce the gap between computational models developed using (mostly) simulated conditions, and our real and noisy systems (rodents). Therefore, before we can utilize the UKF to reconstruct the system, we have to first estimate the true parameter set [7]. To address this challenge we look to nonlinear data fitting literature and borrow the Levenberg-Marquardt fitting technique [8]. We couple this algorithm with the UKF to simultaneously estimate multiple parameters of the model while fully reconstructing the dynamics of the real system.

Nonlinear least squares methods involve an iterative im-

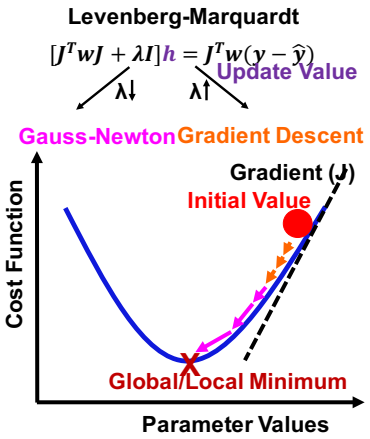


Fig. 2: Levenberg-Marquardt Minimization Routine [8]. For parameter λ small, the approach follows a Gauss-Newton methodology, otherwise it follows a Gradient-Descent approach. This serves to accelerate convergence close to the minimum of the cost function.

provement to parameter values in order to minimize the sum of the squares of the errors between the fitted function and the measured data points. The Levenberg-Marquardt curve-fitting method is a combination of two minimization methods (Fig. 2): the gradient descent method and the Gauss-Newton method. In the gradient descent method, the sum of the squared errors is reduced by updating the parameters such that the system moves in the steepest-descent direction to minimize the squared error. In the Gauss-Newton method, the cost function - the sum of the squared errors - is reduced by assuming the least squares function is locally quadratic, and finding the minimum of the quadratic.

The Levenberg-Marquardt method acts as a gradient-descent method when the parameters are far from their optimal value, and as a Gauss-Newton method when the parameters are close to their optimal value. In detail, it is tuned via the parameter λ, which is adjusted on an iteration by iteration basis based on the total cost function value. When the parameters are too far away from their correct value, the algorithm applies small update values to the parameters to slowly improve the approximation such that the system stays in the stable neighborhood. Once the error function has decreased to the point that there is no danger of divergence, the algorithm switches to the Gauss-Newton method and applies larger update values to the parameters to fully minimize the now locally quadratic squared error function.

III. Results

The performance of our parameter estimation method is illustrated in Fig. 3. Parameter estimation is performed by minimizing the cumulative divergence between short model-generated trajectories and UKF-reconstruction. In practice, the minimization step is applied to UKF-reconstructed trajectories that are at least one sleep-wake cycle long in order to sample the state space. Additionally, the short trajectories are set such that they are long enough for parameter differences to cause significant divergence between model-generated trajectories and UKF-reconstructed dynamics.

Shown in the upper two rows of Fig. 3 are the divergences of model-generated trajectories (cyan trace) from the reconstructed state trajectory (red trace) for two of the model variables. As the fitting progresses in time (latter columns), the dynamics track better. In the lower panels are shown the simultaneous changes in the three parameters being estimated (upper panel), the cost function (second panel), and reconstruction error values for the two variables in the upper panels.

We validated our iterative full-state and multi-parameter estimation methodology against invasive measurements from one of the cell groups represented in the model to be REM active. Rats were implanted with electrodes in brainstem REM active targets, hippocampus, and cortex. After 1-2 weeks recovery, animals were connected to a recording system while we measured EEG, head acceleration and single-cell activities. Recordings were then analyzed as follows: Combinations of hippocampal and cortical field potentials along with head acceleration were used to score state of vigilance [9]. Separately, we analyzed our single-cell recordings from the REM-active cell group to extract activity levels of the group over time. The model parameters were then updated within the data assimilation framework using extracted state of vigilance as observations of the system.

Shown in Fig. 4 are the results from applying the methods described earlier. In particular, the hippocampal and cortical recordings were used to classify the SOV for the animal as shown in upper panel of Fig. 4. We then passed these measurements (Fig. 1a) through our observation model (Fig. 1b) to reconstruct activity levels of the sleep-wake regulatory cell groups represented in the model. The REM-active activity levels from this reconstruction are shown in the lower panel of Fig. 4(red trace), along with the activity levels computed from actual, simultaneously measured single-cell recordings from the REM-active cell group (black trace).

Because the single-cell recording was not used in the original classification of the animal's SOV, we can use it as an actual measurement of the reconstructed state to validate the model reconstruction of the activity of REM-active cell group. The correspondence is reasonably good, and accurately predicts the onset of increases in the activity levels as the animal transitions to the REM state.

It is important to note that the single-cell recording is not independent of the state of vigilance. In particular, the recordings are classified to be measurements from a REM-active cell-group because (1) further histological analysis of the electrode track in the brain, asserts that the electrode was indeed within a known REM-active structure and (2) the periods of higher activity are observed during REM periods. We are currently repeating our experimental measurements across multiple animals to acquire long datasets. We can then apply our modeling analysis to only a fraction of the acquired data to classify state of vigilance and model state reconstruction and prediction. The forecast trajectories can then be validated against the other fraction (test set) of the data to gauge how accurate the model represents the physiological dynamics.

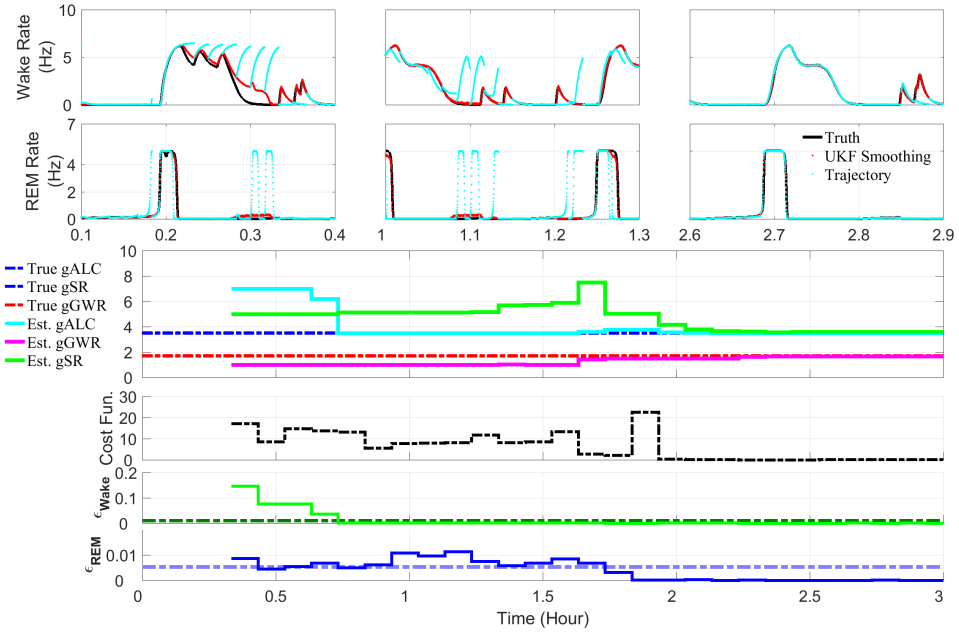


Fig. 3: Simultaneous Parameter Fitting. As the parameters converge to their correct value, the error between model-generated trajectories and actual system dynamics decreases. The error will arrive at its minimum once all the parameters converge to their correct values. The parameter fitting process requires approximately 2hours of model generated data to stabilize while in real-time, it is computationally efficient with run-time of approximately 2-3 minutes.

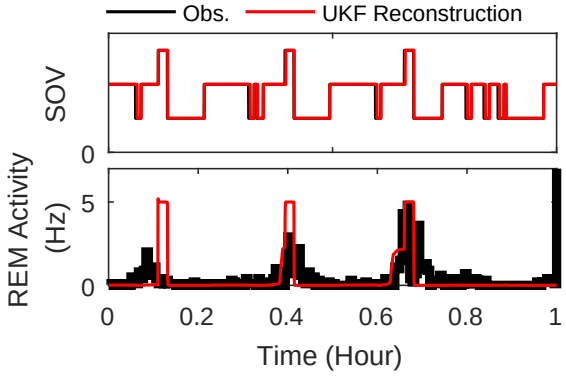


Fig. 4: **Animal SOV to activity levels computed from REM-active cell group.** State of vigilance (SOV) was acquired from animal hippocampal and cortical recordings. It was then passed through our observation model and used to fully reconstruct the model variables represented in the model. The reconstructed activity levels of the REM active cell group (Red trace) were then compared against activity levels computed from invasive, simultaneously measured single-cell recordings from the REM-active cell group. Model reconstruction predicts the original measurements reasonably accurately.

IV. Conclusion

In summary, understanding the role of sleep-wake regulation in epilepsy can drastically improve and even change our approaches in proposing effective treatments. We have established a framework to mechanistically study these dynamics by incorporating experimental measurements into physiologically-based mathematical models. Our efforts will introduce new avenues in model validation, as well as improved understanding of network interactions in epileptic and healthy brain. This has been made possible through the integration of techniques from four different fields. Once we validate the predictive performance of our algorithm, we will move forward to incorporate it into algorithms for seizure prediction.

In a general framework, we assert that data assimilation methods, coupled with dynamical models that embody the governing mechanisms of brain state, will allow for more robust neural prosthetic controllers. We further hypothesize that once such methods are used to validate the models they utilize, which will involve expensive measurements of the variables embodied in the models, that they can be scrutinized to identify the least-costly measures that will allow sufficient observation to achieve the desired levels of control. The elimination of highly-invasive and damaging measurements together with the capability of data assimilation methods to provide a mechanistic explanation of the underlying dynamics can then offer a platform to further identify unstable phenomena in different pathologies and thus propose effective intervention.

Acknowledgment

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