Chapter 1

Examining the dynamics of a vector representing neurophysiological state during intensive care

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Several monitors are used to monitor vital physiological variables in stroke patients in the neurointensive care unit. Decisions which ultimately affect the patient's outcome must be made on the basis of these and other data such as medical images. A continuous bedside neurological monitor could give a timely indication of changes in the patient's neurological condition. This research represents the development of such a monitoring system. The system combines several physiological and electroneurophysiological parameters into a neurophysiological state vector. Such a state vector representing physiological condition was first described by John Siegel et al. [5]. Goldberger demonstrated that a loss of heart rate variability over time corresponds with a state of pathology and in general that a loss of complexity of the dynamics of the associated physiological parameters typifies several diverse disease states [3]. In this work, the dynamics of a time-varying neurophysiological state vector representing the condition of stroke patients in the neurointensive care unit are examined. The neurophysiological state vector consists of parameters derived from the latencies and amplitudes of significant peaks in the brainstem auditory and somatosensory evoked potentials recorded at regular intervals together with spectral information derived from the electroencephalogram and parameters routinely monitored in the intensive care unit, including heart rate and oxygen saturation.

1.1 Introduction

When a stroke patient is transferred to the neurointensive care unit, various bedside monitors are used to keep track of the patient's condition. A comprehensive cardiac monitor tracks the condition of the circulatory system in terms of parameters such as heart rate, blood pressure and blood oxygen saturation. Renal output, respiration and the functioning of other systems are also routinely monitored. Regular neurological examinations give an idea of the neurological condition, but there is no single continuous monitor of brain function.

CT scans and MR images give an excellent idea of large structural changes in the brain. Although these imaging techniques provide a wealth of information, they reflect only structural changes at a particular instant in time, and there is some risk associated with moving a critically ill patient to the scanning division of the hospital.

Electrophysiological techniques, such as EEG and evoked potentials, are not typically employed on a continuous basis in the intensive care unit. These tests may be ordered if changes are noticed in the neurological examination results. The techniques are valuable in that they directly reflect the functioning of the central nervous system, are non-invasive and can be applied continuously.

The purpose of this work is to provide a prototype for a continuous monitor of neurophysiological function for use at the bedside in the intensive care unit. Such a monitor could potentially give an early indication of changes in a patient's neurological condition.

1.2 State space representations in physiology

In this work, the brain's condition is represented as a vector of time-varying scalar parameters related to various aspects of brain function. Together these parameters make up a neurophysiological state vector.

In general the state of an object may be described by a number of variables x_1 to x_N. The range of possible values that the variables may take describes the extent of the state space of the system. Although the state space may be higher-dimensional, it can usually only be represented graphically in two or three dimensions. Siegel et al. represented an 11-dimensional vector on a circular chart [5].

The trajectory that a system's state follows in state space relates to the complexity of the system. If the system's state is fixed and constant, or if it is entirely random, the effective complexity of the system is very low. Alternatively, the dynamics of the state may describe an attractor of some sort in state space. The state of a complex system may describe a simple limit cycle or a more complicated strange attractor in state space.

Claude Bernard, the father of modern physiology, wrote [1]:

> "...all of the vital mechanisms [in an organism], varied as they are, have only one object: that of preserving *constant* the conditions of

> life in the [internal environment]."

In the wake of the success of this view, Walter Cannon coined the term homeostasis to describe:

> "...the coordinated physiological process which maintains most of the *steady states* in the organism."

In terms of state space representations, the concept of homeostasis as it was originally defined implies that the dynamics of the physiological state of a healthy organism describe a fixed point in state space, and that the pathological states are unstable. In the last 25 years, it has been shown that this is not true.

Siegel and his colleagues showed in 1979 [5] that under pathological conditions, the physiological state may repeateably and stably occupy the same abnormal region of state space. For example, Siegel constructed a vector of 11 parameters, such as partial pressure of carbon dioxide, cardiac output and mean arterial pressure, and represented these radially on a circular chart. The normal average value of a parameter was represented as a point at unit distance from the circle's origin. A complete set of normal values would result in a unit circle if the points were joined. Any deviation from normal was represented by the displacement of a point from the unit circle, scaled in terms of the normal standard deviation of the parameter. Siegel found that under pathological conditions, different constellations were formed, but that certain constellations were persistent and common to particular pathologies. They were able to use these charts to characterize such states as normal stress after trauma and primary myocardial infarction.

Goldberger and others [3], [2] have shown that the dynamics of the physiological state in a healthy person describe a complicated attractor and not a fixed point in state space. For example the heart rate should necessarily vary in a fractal manner in a healthy individual. It has been reliably shown that a decrease in heart rate variability accompanies certain pathological conditions.

1.3 State space dynamics in electroencephalography

The electroencephalogram (EEG) is a record of the electrical activity of the brain. The dynamics of the EEG display the property that they lose complexity under unhealthy conditions. For example, it has been shown that the complexity of the EEG is higher in a normal awake subject than when the subject is asleep, comatose or in a state of epileptic seizure. This is if complexity is quantified in terms of the embedding dimension of the EEG whch is normally very high. Arguably it is not meaningful to specify the embedding dimension under these conditions. Under abnormal conditions, the embedding dimension has been reported to fall as low as 4 to 6 [4]. This relates to the underlying number of degrees of freedom of the mechanism which gives rise to the dynamics of the

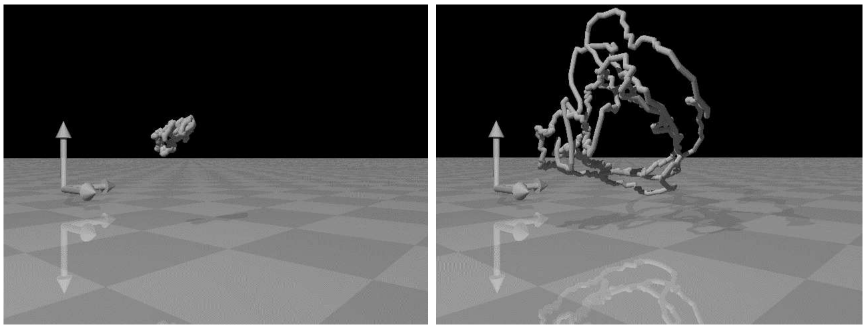

Figure 1.1: Phase portraits of EEG burst-suppression activity during induced coma.

observed variable. This corresponds to the dimensionality of the phase space needed to fully describe the variable's dynamics. For a single variable, the vector in phase space consists of that variable and the appropriate number of its derivatives.

Apart from embedding dimension, phase space portraits and Lyapunov exponents are used to study system dynamics. The Lyapunov exponents describe the rate at which two points which are initially close in phase space diverge in time. Positive Lyapunov exponents denote an unstable system and negative exponents denote a stable system. Under conditions of visual stimulation, it appears that the alpha activity generated in the occipital cortex becomes entrained and simpler, with an accompanying increase in negativity of the Lyapunov exponents [6]. This suggests that the system is stabilized by the entraining effect of the visual stimulation.

Figure 1.1 shows phase space portraits for the EEG exhibiting burst-suppression in a person in pentobarbital-induced coma. The left panel shows the phase portrait during 2 seconds of suppression and the right panel shows the phase portrait during 2 seconds of burst activity. The EEG amplitude is represented on the three axes with lags of 0, 0.1 and 0.2 seconds. Whilst activity is minimal during the period of suppression, the portrait from the burst period shows an attractor which suggests low-dimensional periodic activity. This is consistent with the observation that pathological conditions result in a decrease in complexity of the dynamics of functional measures such as heart rate and EEG. In further analogy with heart rate variability, it has been shown that under healthy conditions, the EEG alpha band energy must be variable.

1.4 Neurophysiological state

The neuromonitoring system developed for this study combines various parameters into a vector representing the state of the central nervous system. These parameters fall into two main groups: electrophysiological and other physiological parameters. The emphasis of the study is on continual electrophysiological monitoring, since this is not done routinely in the intensive care unit. To address in part the requirement for a comprehensive representation of the state of the central nervous system, it was decided to include other parameters in the neurophysiological state vector.

The parameters cover a range of functions of the brain. The electroencephalogram recorded from scalp electrodes reflects cortical activity. In the wakeful state, cortical electrical activity has a higher average frequency than during sleep or coma. In barbiturate-induced or severe coma, cortical electrical burst-suppression patterns are observed. This information is included in the state vector as the energy in the delta, alpha and beta energy bands at each electrode and the presence or absence of burst-suppression activity.

The more basic life-supporting functions of the brain are performed by its deeper structures - the midbrain and the brainstem. The function of these areas is evaluated by means of evoked potentials. In the somatosensory evoked potential (SEP), the response of the brain to electrical stimulation of a peripheral nerve is tested. For our purposes we stimulate at the median nerve at the wrist and measure the response of different areas of the brain along the sensory pathways. The latencies of particular peaks in the response are observed and included in the state vector as a means of assessing the integrity of the sensory pathways. The peaks originate at certain points along the sensory pathways, in the brainstem, diencephalon and cortex and are measured on the left and the right sides. In the brainstem auditory evoked potential (BAEP), the response of the brain to auditory stimulation is tested. The latencies and amplitudes of three particular peaks of interest (waves I, III and V) are recorded in the state vector, and these correspond to the time it takes the signal to get from the cochlea to the cochlear nerve, pons and inferior colliculus respectively. In brain-injured patients the absence of the SEP may indicate a poor prognosis but the bilateral absence of the SEP almost always indicates a bad outcome. The brainstem is a primitive part of the brain, responsible for many basic life-supporting functions such as regulating blood pressure, heart rate and breathing. Absent waves III and V in the BAEP may therefore indicate serious damage to the basic functioning of the brain. Of course, the BAEP only reflects damage to the brainstem along the auditory pathways, and this is one of the reasons that a comprehensive neurophysiological state vector should include some other parameters such as heart rate, blood pressure and breathing rate which indicate whether the brainstem is performing its regulatory function. Also included in the vector are the intracranial pressure and cerebral blood flow velocities obtained by transcranial doppler if they are available.

Figure 1.2 shows a stack of SEPs recorded from a patient who suffered a large hemispheric infarction. The recordings were made every 15 minutes over a period of 18 hours. The values in the neurophysiological state vector correspond to the peak latencies marked on these raw traces. The complete state vector consists of more than a hundred parameters, and the exact number depends on the data which are available from the patient. A meaningful subset which omits redundant parameters may be selected for representation. Such an 8-parameter

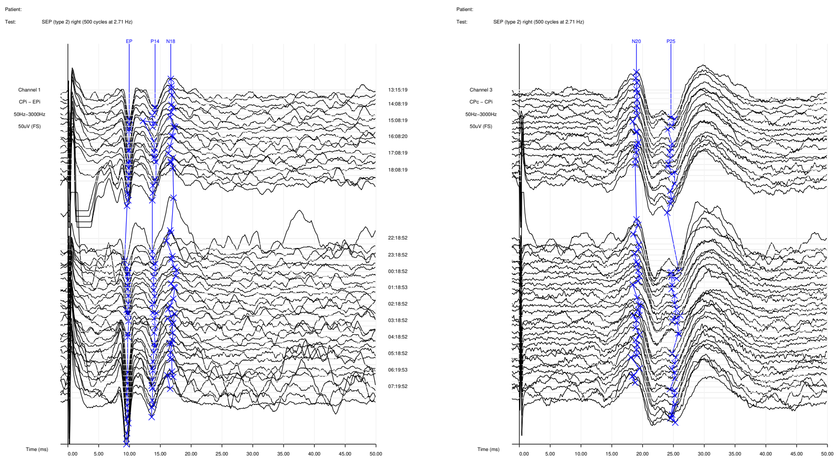

Figure 1.2: A stack of SEPs recorded in a patient with a large hemisphere infarction over a period of 18 hours. The traces on the left were recorded from CP-EPi and those on the right from CPc-CPi.

subset is shown in Figure 1.3. Some artifacts due to noise are evident in these traces. These data are from the same subject as Figure 1.2.

1.5 Regions of state space

Further work in this study is concerned with characterizing the dynamics of the neurophysiological state vector. Consistent with the discussion above, it is expected that the neurophysiological state vector should undergo a predictable pattern of changes as a a patient's condition changes. In the case of a patient for whom illness results in death, it is expected that cortical functioning should be lost first with an associated decrease in the average frequency and energy of the cortical EEG energy. Next the SEP is expected to exhibit shifts in latencies of the significant peaks, and finally the BAEP is expected to show latency shifts and loss of amplitude. A definite and predictable trajectory of the state through its space is anticipated. It is of course not possible to represent the entire space graphically, but some subspace could be represented. Figure 1.4 shows the 3-dimensional subspace of the state vector consisting of the wave I, III and V latencies of the BAEP. The values for a normal subject are located closer to the origin, within the boxed-off area, and the values for a patient who has suffered a posterior subarachnoid hemorrhage are shown beyond the boxed area. Work is currently underway to collect data to observe shifts from one region of the space to another. Such a shift occured in the patient of Figure 1.2, but the shift is not evident in the subspace diagram due to noise and the limited amount of data.

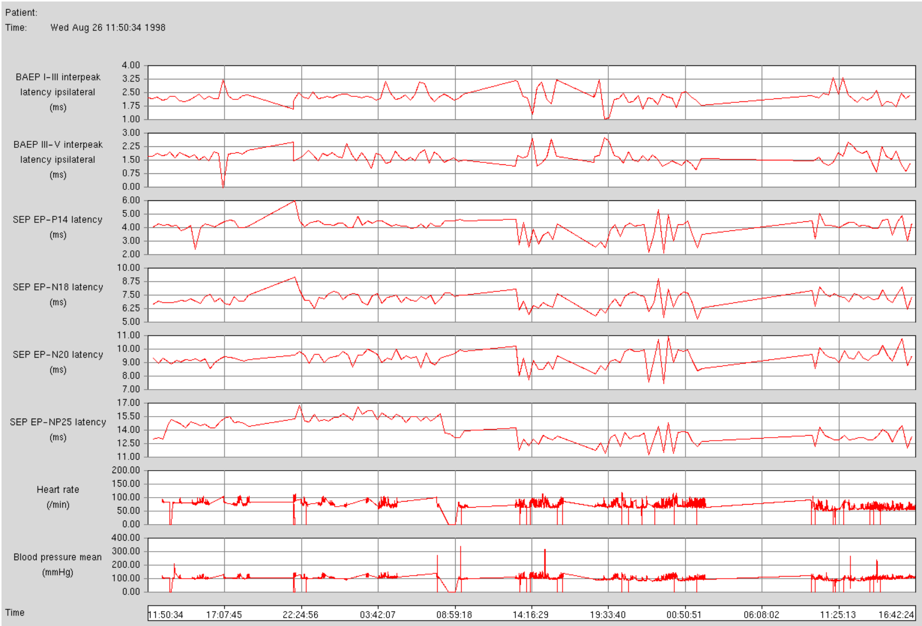

Figure 1.3: A subset of the parameters in the neurophysiological state vector, recorded in a patient with a large hemisphere infarction over a period of 18 hours. The parameters are BAEP wave I-III interpeak latency, BAEP wave III-V interpeak latency, SEP EP-P14 latency, SEP EP-N20 latency, SEP EP-P25 latency, heart rate and mean arterial blood pressure.

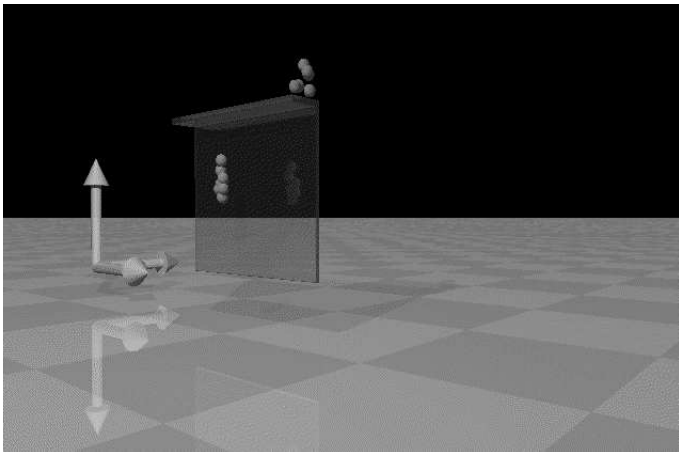

Figure 1.4: Diagram of subspace showing BAEP waves I, III and V latencies for a patient with and without subarachnoid hemorrhage (right and left clusters respectively).

1.6 Conclusion

Automatic analysis facilitates interpretation of electrophysiological data by clinicians unskilled in neurophysiology. With state space trajectory representations, it may be possible to have a computer identify normal and abnormal regions of the space and indicate the region of the space that the patient vector occupies. It may be possible by extrapolation to make a prediction of how the vector values may change in future with the purpose of triggering intervention if necessary. By combining the parameters, early subtle changes reflected across a number of parameters may be detected which would otherwise go unnoticed if the parameters were observed individually.

In ongoing work, neurointensive care patients are being monitored for an extended period during their stay in the intensive care unit. Patients are included in the study if they are suffering a large hemispheric or cerebellar infarction with edema or intracerebral hemorrhage with CT evidence of mass effect. It is expected that these patients may exhibit tissue shifts with associated changes in the BAEP and SEP results. The state space representation of the data will be examined to identify regions of the state space associated with different disorders or stages of illness. The dynamics will be examined to determine whether it is possible to identify trends with predictive value in the data.

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