Sleep
The EEG and Automated sleep Staging

Centre for Doctoral Training in Healthcare Innovation

Prof. Lionel Tarassenko
Dr Gari Clifford
Overview

- How the electroencephalogram (EEG) is recorded
- How to interpret the EEG
  - Epilepsy
  - Sleep
  - Vigilance
  - Depth of Anesthesia ...
- Feature extraction and event detection in the EEG
- Creating an automated sleep stager
- Making a commercial system
The EEG signal is measured with Ag-AgCl electrodes placed in standard positions on the scalp. The signal is <100μV – Why?

- (Recall ECG is ~1mV)
- Heart: ~3×10⁹
- Brain: ~10¹¹
The EEG signal is measured with Ag-AgCl electrodes

Placed in standard positions on the scalp

Signal is <100μV – Why?
  ▪ due to skull attenuation
The important information is in the frequency domain.

The frequency range from 0.5 to 30 Hz has been arbitrarily divided into 5 bands:

- **Delta** 0.5-4 Hz  Deep Sleep
- **Theta** 4-8 Hz  Drowsiness / light sleep
- **Alpha** 8-13 Hz  Relaxed
- **Beta** 13-22 Hz  Alert
- **Gamma** 22-30 Hz  Short term memory tasks?
Diagnostic uses of the EEG

EEG analysis helps in the diagnosis of brain death, epilepsy and sleep disorders

EEG during an epileptic seizure
Quality of life is heavily dependent on quality of sleep.

Between 5 and 10% of the adult population suffers from some form of sleep disorder (insomnia, heavy snoring, Obstructive Sleep Apnoea (OSA), etc...)

Such people may be referred to a “sleep clinic” by their GP where various signals, including four channels of EEG, the EOG and oxygen saturation, will be recorded throughout the night.

The EEG and the other signals are printed out and reviewed by a trained sleep technician (requiring 2 to 5 hours for each record).
The four channels of sleep EEG are analysed using a rule-based system which assigns consecutive 30-second segments to one of six stages (Wake, Stages 1 to 4, REM sleep).

- 1 = light, 3 & 4 = deep sleep
- Recently stages 3&4 merged
EEG in different sleep stages

Awake

Stage 1 sleep

Stage 2 sleep

Stage 3 sleep

Stage 4 sleep

REM sleep

Alpha activity

Beta activity

Theta activity

K complex

Spindle

Delta activity

Delta activity

Theta activity

Beta activity
The four channels of sleep EEG are analysed using a rule-based system which assigns consecutive 30-second segments to one of six stages (Wake, Stages 1 to 4, REM sleep).

For example, two rules for stage 3:

- an EEG record in which at least 20% but not more than 50% of the epoch consists of waves of frequency 2 Hz or lower which have amplitudes greater than 75 μV peak to peak.
- sleep spindles may or may not be present in stage 3.
Conventional sleep scoring
The important information is in the *frequency* domain.

- Use the Short-term Fourier Transform or an Auto-Regressive (AR) model to extract the frequency-domain information.
The notation AR(\(p\)) refers to the autoregressive model of order \(p\). The AR(\(p\)) model is written as follows:

\[
X_t = \sum a_i X_{t-i} + \varepsilon_t \quad (1 \leq i \leq p)
\]

where the \(a_i\)'s are the parameters of the model and \(\varepsilon_t\) is a white-noise process with zero mean.

An autoregressive model is essentially an infinite impulse response filter which shapes the white-noise input. The poles are the resonances of the filter and correspond to the spectral peaks in the signal.
AR-model vs FFT spectra (for EEG)
Sleep EEG analysis using neural networks
Conventional computing

- A set of programmed instructions
  - IF A = B THEN ADD 3 TO RESULT
  - ELSE SUBTRACT 5

Neural networks

- The solution to a problem is learnt from a set of examples using error feedback
By analogy with the brain, artificial neural networks consist of large numbers of small units (“neurons”) with modifiable connections (“synapses”), ordered in feedforward layers.
Some definitions

- **Neural networks**: A computational system which learns from examples how to recognise complex patterns in data, signals or images.

- **Learning**: The process of modifying the neural network’s internal connections (the synaptic weights) until desired output responses are associated with the input patterns in the training set.

- **Generalisation**: The ability to generate the correct output response for a test pattern, an input pattern not previously seen (i.e. not in the training set).
The signal recorded from one EEG channel is sampled at 128 Hz and segmented into one-second epochs.

The input data are the ten AR coefficients for each consecutive one-second epoch.

The multi-layer perceptron (MLP) neural network is trained to classify the input EEG data into three output classes: awake, light sleep or deep sleep. This involves the gradual modification of the synaptic weights in the hidden-output and input-hidden layers (error minimisation using gradient descent).
The training data are collected from human-scored sleep, selecting only “consensus-scored” Wake, REM or stage 1 and stage 4 data (independently scored by three experts).

Once the network is trained, the intermediate stages for test EEG data are obtained by interpolation.
The neural network is *trained* to classify the input EEG data into three output classes: wakefulness, light sleep or deep sleep.

The trained neural network is used for the automated analysis of the EEG recorded from new patients (*test data*).
Sleep analysis using neural networks

8.75 Hours

W

R

S

human-scored hypnogram
Study of arousals in OSA

- Seven 20-minute recordings from patients with different levels of OSA used as test data
- EEG scored by one expert according to the American Sleep Disorders Association (ASDA) rules
- $P(\text{Wake}) - P(\text{Deep Sleep})$ used to represent the sleep-wake continuum
- Transients shorter than 3 s discarded using median filtering
Sleep analysis using neural networks (2 mins of data)
Sleep analysis using neural networks (20 mins of data)
Continuous tracking of sleep-wake continuum using single channel of EEG

Events on a 2 to 5-second timescale are clearly detected

This type of analysis is *not* possible with the traditional sleep scoring methods, which require several channels and only have 30-sec resolution

Oxford Medical incorporated neural analysis as an option within their Sleep Analysis software
Why start a new company?

- A change in management in Oxford Instruments (parent company of Oxford Medical)
<table>
<thead>
<tr>
<th>Code</th>
<th>Company</th>
<th>Share Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>1005</td>
<td>ARM Hldgs</td>
<td>549</td>
</tr>
<tr>
<td>1225</td>
<td>AEC</td>
<td>547</td>
</tr>
<tr>
<td>631</td>
<td>Anadigm</td>
<td>173</td>
</tr>
<tr>
<td>457</td>
<td>ARC Int</td>
<td>267</td>
</tr>
<tr>
<td>31</td>
<td>Amortech</td>
<td>202</td>
</tr>
<tr>
<td>2568</td>
<td>Artisan</td>
<td>172</td>
</tr>
<tr>
<td>394</td>
<td>BATM Adv Cms</td>
<td>194</td>
</tr>
<tr>
<td>892</td>
<td>CML Micro</td>
<td>737</td>
</tr>
<tr>
<td>2265</td>
<td>Chloride</td>
<td>188</td>
</tr>
<tr>
<td>760</td>
<td>Cirkitelk#</td>
<td>742</td>
</tr>
<tr>
<td>155</td>
<td>Delta</td>
<td>157</td>
</tr>
<tr>
<td>539</td>
<td>Dennisron</td>
<td>152</td>
</tr>
<tr>
<td>240</td>
<td>Domino</td>
<td>223</td>
</tr>
<tr>
<td>45</td>
<td>Dowling Mills</td>
<td>38</td>
</tr>
<tr>
<td>245</td>
<td>Duck</td>
<td>210</td>
</tr>
<tr>
<td>1455</td>
<td>Electronix B</td>
<td>857</td>
</tr>
<tr>
<td>377</td>
<td>Emiss</td>
<td>29</td>
</tr>
<tr>
<td>1643</td>
<td>Ericsson B</td>
<td>816</td>
</tr>
<tr>
<td>594</td>
<td>Fairey Group</td>
<td>582</td>
</tr>
<tr>
<td>2332</td>
<td>Filtronics</td>
<td>245</td>
</tr>
<tr>
<td>703</td>
<td>First Tech</td>
<td>519</td>
</tr>
<tr>
<td>724</td>
<td>Fortress</td>
<td>261</td>
</tr>
<tr>
<td>3525</td>
<td>Geco Int Media</td>
<td>585</td>
</tr>
<tr>
<td>1185</td>
<td>IFC Tower</td>
<td>862</td>
</tr>
<tr>
<td>632</td>
<td>Integration Tec</td>
<td>197</td>
</tr>
<tr>
<td>619</td>
<td>Induja Vision</td>
<td>370</td>
</tr>
<tr>
<td>475</td>
<td>Insetek</td>
<td>55</td>
</tr>
<tr>
<td>355</td>
<td>Intevysyst</td>
<td>173</td>
</tr>
<tr>
<td>845</td>
<td>IPE</td>
<td>205</td>
</tr>
<tr>
<td>219</td>
<td>Isotrim</td>
<td>119</td>
</tr>
<tr>
<td>275</td>
<td>Linsys</td>
<td>372</td>
</tr>
<tr>
<td>175</td>
<td>LPA</td>
<td>70</td>
</tr>
<tr>
<td>1921</td>
<td>Mitek</td>
<td>354</td>
</tr>
<tr>
<td>2530</td>
<td>MXT</td>
<td>901</td>
</tr>
<tr>
<td>535</td>
<td>Network Tech</td>
<td>180</td>
</tr>
<tr>
<td>38</td>
<td>Ommegro</td>
<td>365</td>
</tr>
<tr>
<td>2490</td>
<td>Oxford Inst</td>
<td>185</td>
</tr>
<tr>
<td>1314</td>
<td>Pace Micro</td>
<td>635</td>
</tr>
<tr>
<td>46</td>
<td>Pathos</td>
<td>178</td>
</tr>
<tr>
<td>3946</td>
<td>Philips Imp nv</td>
<td>2771</td>
</tr>
<tr>
<td>470</td>
<td>Paxman</td>
<td>116</td>
</tr>
<tr>
<td>305</td>
<td>Pncos</td>
<td>118</td>
</tr>
<tr>
<td>1151</td>
<td>Post</td>
<td>278</td>
</tr>
<tr>
<td>485</td>
<td>Radnetec</td>
<td>35</td>
</tr>
<tr>
<td>767</td>
<td>Renishaw</td>
<td>762</td>
</tr>
<tr>
<td>389</td>
<td>Rendler</td>
<td>334</td>
</tr>
<tr>
<td>952</td>
<td>Sibber</td>
<td>940</td>
</tr>
<tr>
<td>56</td>
<td>Spirent</td>
<td>560</td>
</tr>
<tr>
<td>325</td>
<td>Spiretech</td>
<td>24</td>
</tr>
<tr>
<td>710</td>
<td>DJC</td>
<td>699</td>
</tr>
<tr>
<td>334</td>
<td>TFT Comms</td>
<td>222</td>
</tr>
<tr>
<td>88</td>
<td>Tadpole Tech</td>
<td>542</td>
</tr>
<tr>
<td>565</td>
<td>Telemetric</td>
<td>322</td>
</tr>
<tr>
<td>1332</td>
<td>Telecom</td>
<td>672</td>
</tr>
<tr>
<td>128</td>
<td>Interpace Fw</td>
<td>114</td>
</tr>
<tr>
<td>45</td>
<td>Total Systemtech</td>
<td>84</td>
</tr>
<tr>
<td>156</td>
<td>Utopia Networks</td>
<td>5</td>
</tr>
<tr>
<td>795</td>
<td>Ultrasound</td>
<td>15</td>
</tr>
<tr>
<td>1444</td>
<td>Vistrek</td>
<td>59</td>
</tr>
<tr>
<td>2170</td>
<td>Volutec</td>
<td>1907</td>
</tr>
</tbody>
</table>

Oxford Instruments’ share price
A change in management in Oxford Instruments

Developing a product from the original concept to (successful) commercial exploitation was and is still the main motivation

Creating new jobs

Financial reward?
July 1999:
Preliminary discussions with Dr Tim Cook of Isis Innovation

July 1999:
Isis Project Manager appointed (Dr Herb Askew)

August 1999:
Meeting with Oxford Instruments CEO who gives green light
August 1999: Potential CEO becomes involved in drafting Business Plan

September 1999: Business Plan is put together with the help of Deloitte & Touche

October 1999: Initial version of Business Plan is discussed with Oxford Instruments
December 1999: Final version of Business Plan is approved and sent to potential investors

December 1999: Heads of Agreement document drawn up by Isis Project Manager is signed by University and Oxford Instruments
January 2000:
Following a presentation at Isis Innovation, Venture Capital Fund agrees to invest in Oxford BioSignals

February 2000:
Investment from University Challenge Fund

May 2000:
Oxford BioSignals is set up, with all relevant IP assigned or licensed to the company
PORTFOLIO OF DOCUMENTS

RELATING TO
THE INVESTMENT BY COMVEST LIMITED,
THE UNIVERSITY OF OXFORD AND OXFORD INSTRUMENTS PLC
IN

OXFORD BIOSIGNALS LIMITED

MAY 2000

Oxford BioSignals
Investment Agreement
The requirements for success?

- Protected intellectual property

British Patent Specification

Filed on: 8 November 1995
In respect of Application No.: 9522872.2
Applicant: Oxford Medical Limited
Inventor(s): Mark LAISTER
Michael DADSWELL
James PARDO
Lionel TARASSENKO
Priority claimed from: NONE
No: ---
Dated: ---
Title: IMPROVEMENTS RELATING TO PHYSIOLOGICAL MONITORING
Client’s reference: Insomnia Monitor

Gill Jennings & Every
European Patent Attorneys
Trade Mark Attorneys
Broadgate House • 7 Bishop Street • London • EC2M 7BH
Dr Paul Brankin  
Oxford Instruments  
Medical Systems Division  
Manor Way  
Old Moking  
Surrey  
GU22 5JU  

7 June 1999

Dear Paul,

US Patent Application No. 08/745,780  
Our Ref: RAJ04697US  
Your Ref: Insomnia Monitor

Further to your letter of 1 June 1999 and to discussions between myself and Professor Tarassenko on the telephone, I have now instructed our US agents to respond to the outstanding Office Action and accordingly I enclose a copy of these instructions herewith.

In addition to accepting the allowed claims and cancelling those rejected by the US Examiner, I have added a further two dependent claims to specifically detail the use of neural networks in connection with both of the independent claims 2 and 20.

I will write to you again when I have received confirmation of a filed response from our US agents.

Yours sincerely,

B E Skope James

enc.

cc: Professor L. Tarassenko


Primary Examiner—Robert L. Maser
Attorney, Agent, or Firm—Hoffmann & Barze, LLP

ABSTRACT

An insomnia or vigilance monitor comprising one or more electronics (14,16) for obtaining an electrical signal from a subject over a period of epochs, the electrical signal being related to sleep or wakefulness stage type being experienced by the subject, and a processor (3) adapted to analyze the electrical signal and assign a sleep or wakefulness stage type to each epoch to generate a hypogram. Methods of monitoring sleep or vigilance using the disclosed system are also disclosed. Further disclosures relates to a method of training and testing a first neural network for use in a physiological monitor, and a method of assigning a class to an epoch of a physiological signal obtained from a subject in a set of samples.

13 Claims, 11 Drawing Sheets
The requirements for success?

- Protected intellectual property
- On-going research for the medium to long-term
- A first-class management team
- A willingness to be flexible – jack of all trades

- Continuous tracking of sleep-wake continuum from a single-channel of EEG
- Automated analysis makes it possible to quantify severity of OSA (and other sleep disorders) before and after treatment.
Questions?
Autonomic Regulation

Rest & Digest

- Constricts pupil
- Stimulates salivation
- Inhibits heart
- Constricts bronchi
- Stimulates digestive activity
- Stimulates gallbladder
- Contracts bladder
- Relaxes rectum

Fight & Flight

- Dilates pupil
- Inhibits salivation
- Relaxes bronchi
- Accelerates heart
- Inhibits digestive activity
- Stimulates glucose release by liver
- Secretion of epinephrine and norepinephrine from kidney
- Relaxes bladder
- Contracts rectum

http://www.becomehealthynow.com/images/organs/nervous/sympth_parasymth.gif
The diurnal rhythm & sleep

Sleep Stage

Awake
REM

Children

Time [hr]

1 2 3 4 5 6 7 8

Young Adults

Time [hr]

1 2 3 4 5 6 7 8

Elderly

Time [hr]

1 2 3 4 5 6 7 8

RR

(a)

(b)

(c)

time [hours]

Non-dipping

Systolic blood pressure (mmHg)

0 120 140 150

Waking

24h
Recall the LF/HF ratio

- Only short segments of data required
- Unit-free - no scaling issues
- Thought to reflect the sympathovagal balance
HRV changes significantly in different sleep cycles and for different conditions:

- **Wakefulness**
- **Deep Sleep**
- **Light Sleep**
- **REM (Dream) Sleep**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake</td>
<td>N/A</td>
<td>3.9</td>
<td>4.0 ± 1.4</td>
<td>N/A</td>
<td>2.4 ± 0.7</td>
</tr>
<tr>
<td>REM Sleep</td>
<td>2→2.5</td>
<td>2.7</td>
<td>3.1 ± 0.7</td>
<td>3.5→5.5</td>
<td>8.9 ± 1.6</td>
</tr>
<tr>
<td>NREM Sleep</td>
<td>0.5→1</td>
<td>1.7</td>
<td>1.2 ± 0.4</td>
<td>2→3.5</td>
<td>5.1 ± 1.4</td>
</tr>
</tbody>
</table>
The statistics of sleep & waking periods

Diagram a shows the time course of sleep and wake periods over 6 hours, with REM and non-REM stages indicated. Diagram b illustrates the duration of wake and sleep periods.

Graph a plots cumulative probability against time for wake periods, with the data divided into First 2 hr, Middle 2 hr, and Last 2 hr categories. The fitted line has an exponent \( \alpha = 1.3 \).

Graph b plots cumulative probability against time for sleep periods, with the data divided into three groups as in graph a, along with fitted lines for different time constants \( \tau \). The time constants are \( \tau = 27 \), \( \tau = 18 \), and \( \tau = 22 \).
Complex example - OSA

- SNA: Sympathetic Nerve Activity (recorded from peroneal nerve)