Tfy-99.275 Lecture 9

Measuring Depth of Anaesthesia

Solving 'real' Biomedical Signal Interpretation Problems

- In clinical applications it is usually not possible to solve a 'real-world' problem by just applying one single signal processing technique.
- Typically, many different techniques are working together in each application, each one being most suited for processing one type of signal (component) or performing one specific (sub)task

determining level of anaesthesia – not a new problem

- 1500-1000 BC, India and China;
  narcotics extracted from hemp *(Cannabis indica)* and opium *(Papaver somniferum)* for pain relief. There were already then worries about estimating the adequacy and reversibility of their effect in order to prevent disastrous under- or overdosage

- 77 AD, Greece; Dioscorides (*De Materia Medica)* details how to prepare opium in pills for medical use; "a pill the size of a small pea relieves suffering, brings sleep and comfort in the case of abdominal illnesses, but excessive consumption of this drug brings drowsiness and then death "

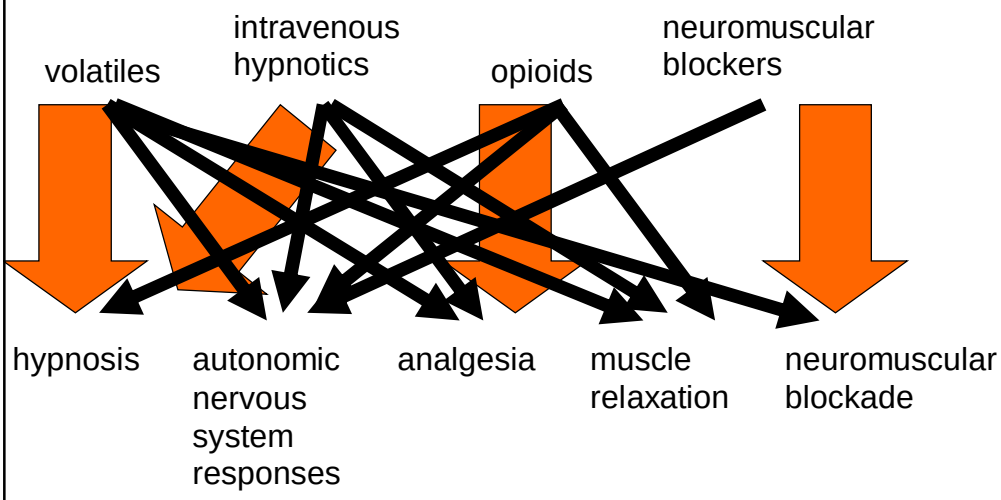
- mid-19th century: anaesthetic properties of nitrous oxide and ether are noted:
  they have effects with respect to amnesia (loss of memory), analgesia (insensibility to pain) and muscular activity, but how to dose them?

controlling 'level' of anaesthesia

- a too 'light level' of anaesthesia is undesirable as the patient may become 'aware' of surgical procedures or (unawarely) experience pain; this can lead to serious physiological and psychological damage.
- a too 'deep level' of anaesthesia is undesirable as it will complicate the patient's recovery, may lead to circulatory and respiratory problems and is inefficient from a hospital resource management point of view.
- there is no such thing as one simple number that describes 'The Level'!

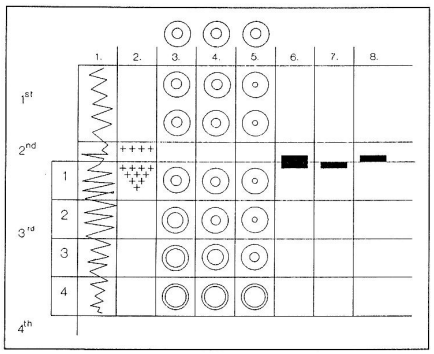
adequacy of anesthesia

- modern anaesthesia aims to keep the patient's state stable, plus
  1. make the patient unaware of the surgical procedure (unconscioussness / hypnosis)
  2. provide insensibility to pain (analgesia)
  3. provide muscle relaxation (to facilitate surgical access)
- typically using a 'cocktail' of drugs (inhalationial and intravenous)
- ! note: there are thus at least 3 'levels' to control



Guedel's Scheme

- based on clinical signs such as respiration, pupil size, eyelid reflexes, swallowing and vomiting reflexes



problematic to use if muscle relaxants/blockers are used (>1942)

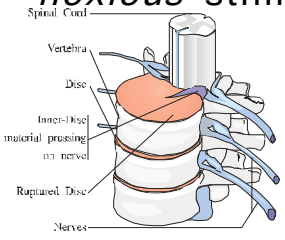
columns
1: breathing pattern
2: eyeball activity
3, 4,5: pupil size for different types of premedication
6: eyelid reflex
7: area of swallowing
8: area of vomiting

rows
1: conscious, some pain suppression
2: unconscious but restless
3: surgical stage
- 1: light anaesthesia, small surgery
- 2: major surgery
- 3: deep anaesthesia
- 4: profound deep anaesthesia (= to be avoided)

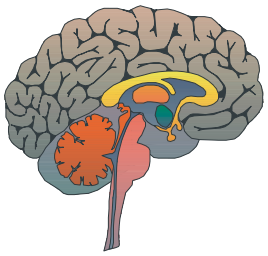
4: toxic stage, lethal

Adequacy of anaesthesia

Unresponsiveness to *noxious* stimuli:



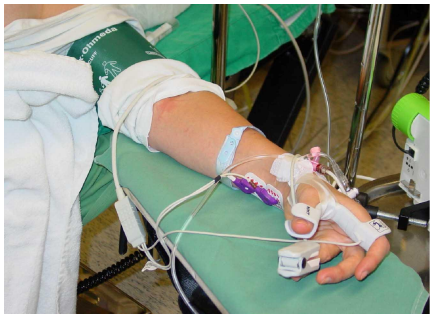
Unresponsiveness to *nonnoxious* stimuli:



Main Entry: **nox·ious**
Pronunciation: 'näk-sh&s
Etymology: Middle English *noxius*, from Latin, from *noxa* harm; akin to Latin *nocEre* to harm
1 a : physically harmful or destructive to living beings

Monitoring muscle blockade

- electrically stimulate a motor nerve and observe reduction in the response (which should be a thumb twitch)
- measure response using pressure/acceleration of thumb movement or muscle activity measurements



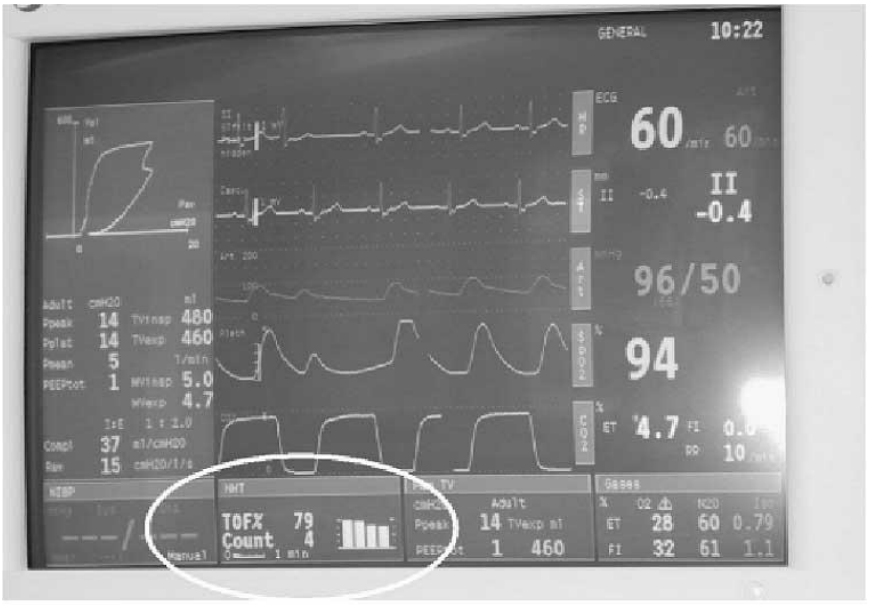
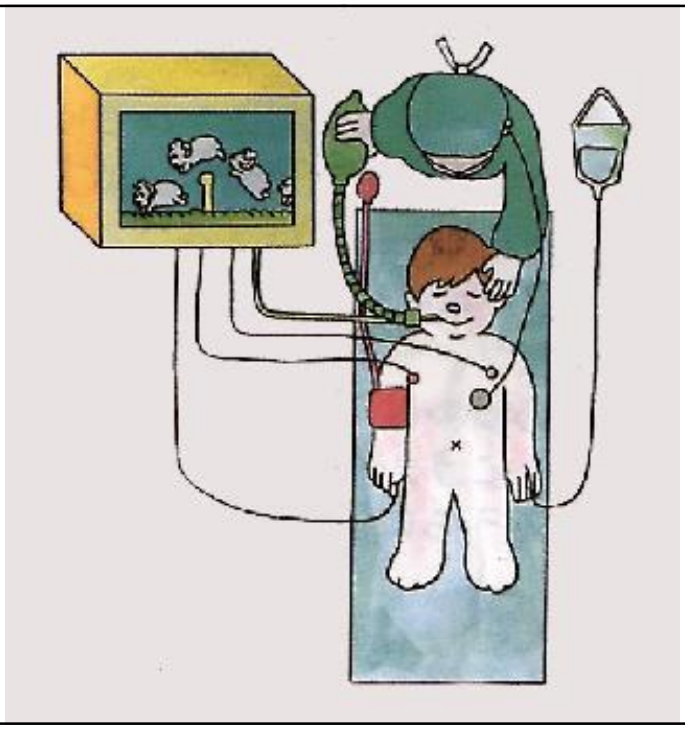


FIGURE 3. Neuromuscular transmission (TOF % and number of counts) is displayed on monitor screen.

Requirements to be fullfilled for an “anaesthetic depth” monitor

- reproducibility and ease of interpretation
- unaffected by neuromuscular blocking drugs
- graded changes with anaesthesia
- speed
- independence from type of anaesthetic drugs used
- sensitive to surgical manipulation
- ease of use



How to measure performance?

- The to be developed monitor output will be some quantitative value(s). How do we relate that to 'level of awareness'?
- There is no golden standard available.
- Anaesthetic drug concentrations are one possible yardstick, (subjective) obseration scales another.

Subjective scales

- Many 'patient states' are assessed by mapping observations to a subjective scale which is ordinal but cannot be used to perform straightforward arithmetic on.

observers assessment of alertness/sedation (OAA/S) (e,g, during operations)
5- Replies to spoken commands, eyes open, awake
4- Sedated, replies to spoken commands, mild hypnosis
3- Ceases to reply to loud commands, eye lid reflex present
2- No reply to spoken commands, no eye lid reflex
1- No reaction to TOF (train-of-four) stimulation (50mA) with movement
0- No reaction to tetanic stimulation with movement

Ramsay scale for level of sedation (e.g in ICU)
Ramsay sedation scale
1- Anxious or restless or both
2- Cooperative, orientated and tranquil
3- Responding to commands
4- Brisk response to stimulus
5- Sluggish response to stimulus
6- No response to stimulus

Alderete scale to assess recovery after operation

	Score
A. Activity	
1. Ability to move all four extremities	2
2. Ability to move two extremities	1
3. Unable to move any extremity	0
B. Respiration	
1. Ability to deep breathe and cough	2
2. Respiratory effort limited and dyspnea present	
3. No spontaneous respiratory effort evident	0
C. Circulation	
1. Systolic arterial pressure +/- 20mm Hg of pre-sedation level	2
2. SAP +/- 20 to 50mm Hg of pre-sedation level	1
3. Systolic arterial pressure +/- 50 or higher of pre-sedation level	0
D. Level of consciousness	
1. Full alertness with ability to answer questions	2
2. Patient can be aroused by verbal stimuli	1
3. Verbal stimuli fails to elicit responses	0
E. Temperature	
between 35.6 and 37.5	2
between 35 and 35.6	1
less than 35 or greater than 37.5.	0

Total score needs to be at least 8 before patient can be discharged

Assessment of performance in case of ordinal scales

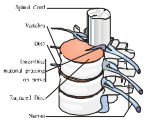
- The only thing we can say that the levels are ordinal, i.e., ordered in some given manner (level N is 'less pain/less sedated/.. 'than level N+1), but we cannot say that a patient with OAA/S level 4 is 'two times more awake 'than one with level 2, or that the difference between level 4 and level 3 is equal to the difference between level 2 and level 1.
- In such cases it is not very useful to examine 'straightforward 'Pearson correlation coefficients, mean squared errors etc as an assessment of practical performance because the appropriate metrics do not apply.
- To measure the practical performance of monitors in such a case we use statistic methods that concentrate on assessing how well the monitor output values follow the *direction* of changes of the patient state on the scale. For example, if a patient is getting more deeply under anesthesia, OAAS level decreases, the monitor output should follow in the same direction (eg, downgoing), if the patient state is stable the monitor output should stay stable, and if the patient wakes up the monitor output should follow with an increasing output value. We can quantify such behaviour by calculating the so-called *prediction probability*.
  The criteria of assessment of performance then become consistent behaviour at all times and speed of following the patient state.

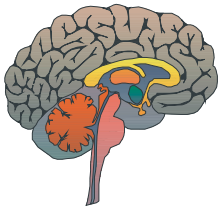
some early suggested techniques

- extension to Guedel's scheme: quantify some of the clinical signs (blood pressure, heart rate, sweating (skin conductance) and tear production) into an overall 'score':
  a very large variability between patients
- isolated forearm technique: an inflatable cuff is used to prevent muscle relaxants from reaching the arm circulation, the patient can be asked to squeeze is hand (indication of conciousness). This can only be used for a short time

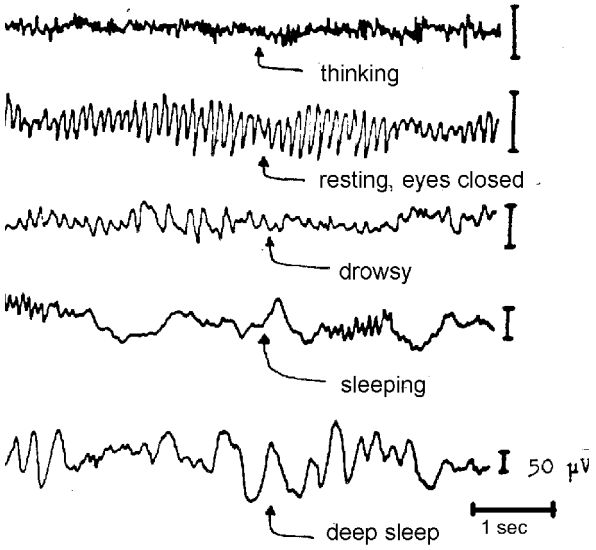
Monitoring Awareness

- awareness is located in the brain > use measurements of brain activity (EEG)





EEG at different levels of awareness



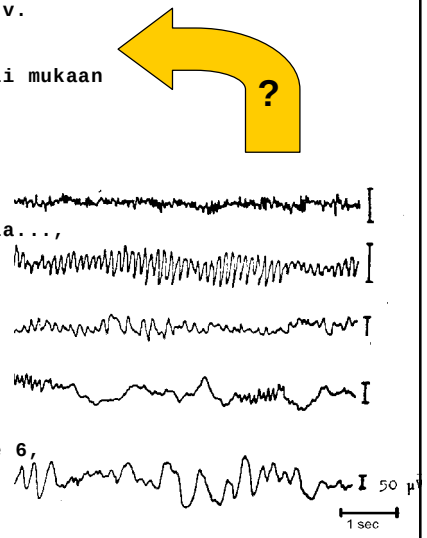
frequency contents and amplitude change with different levels:

HOWEVER:

- inconsistent behaviour during anaesthesia

- different drugs result in different behaviour of the EEG

11:47:03 maanantai 06.10.2003
12:02:32 lapsi saliin
12:06:30 OOAS 5, itkee ja huutaa ja meinaa lähteä karkuun
12:08:03 anestesia alkaa....., lapsi pyörii
12:08:50 OOAS 2
12:09:31 tipan laitto, OOAS 1
12:09:56 Fentanyl 25mikrog i.v., esmeron 6,mg i.v.
12:10:50 intubaatio, OOAS0
12:11:29 putken kiinnitys
12:12:28 potilasta liikutetaan sängyllä, Bis tuli mukaan tässä vaiheessa
12:13:39 potilasta liikutetaan
12:14:41 Pesu
12:23:26 fentanyl 15mikrog i.v.
12:23:48 Toimenpide alkaa
12:24:03 Demographic data : 4v, 13kg,
12:29:40 entropian datan saamisen kanssa ongelmia..., väittää että artefactaa...
12:31:44 Per-dafalgan 250mg i.v.
12:42:15 Zinacef 400 mgi.v.
12:42:48 katetrin laitto
12:42:57 toimenpide loppui
12:43:04 anestesia loppui
12:45:13 extubaatio
12:45:45 ketorin 25mg i.v.
12:47:33 heräämöön
12:47:23 heräämösssä, OOAS 2, Steward1, Alderete 6,
12:51:03 OOAS3, steward1, alderete 6
….
13:47:48 OOAS5, steward 6, alderete 10



EEG processing, time-domain

- one can count the 'zero-crossings' in the EEG; there seems to be an inverse relationship between the zero-crossing frequency and anaesthetic concentrations, but there is a large variability
- moreover, counting zero-crossings is very susceptible to bias in the signal, which makes the method not very practical

EEG processing, frequency domain

- anaesthetics do affect the EEG spectrum, BUT each drug has its own characteristic effect, this makes it impossible to use a 'universal' monitoring system
- to overcome this problem, some derived features can be used like characteristic frequencies: spectral edge freq. (SEF), median power frequency (MPF), peak power frequency (PPF)
- these features change significantly in transition from anaesthesia to recovery, but during anaesthesia inconsistent changes occur

EEG processing, frequency domain

- Frequency bands: anaesthetics affect the distribution of the spectrum across the various bands, but, again, different drugs cause different effects
- Combination of characteristic frequencies and frequency bands (and present them to neural nets): this gives only marginally better results

EEG processing, more

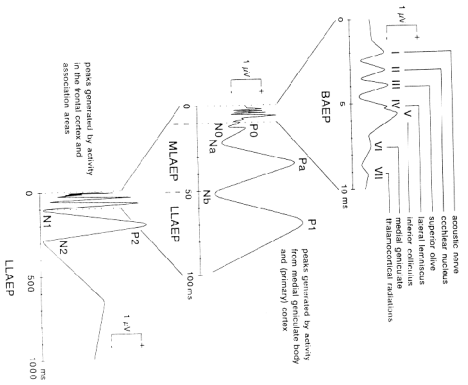
- AR modelling: there is some correlation between changes in the AR coefficients of the EEG with changes in the level of anaesthesia, but again there seems to be a sensitivity with respect to type of drug used
- chaos analysis: describe the amount of predictability of the EEG (EEG = random noise comp. + chaotic comp.). Quantification of the chaotic component shows correlations with concentrations of some types of drugs

Evoked Potentials

- reflect electrical activity elicited in the brain by transmission and processing of a sensory stimulus (visual, auditory, somatosensory). This is typically a very small signal that has to be 'averaged out' from the background EEG by applying many stimuli and adding the recorded activity after each stimulus
- these signals consist of characteristic waves that can be identified as activity originating from specific parts of the (central) nervous system
- auditory evoked potentials (AEPs) have been studied in relation to effects of anaesthetics

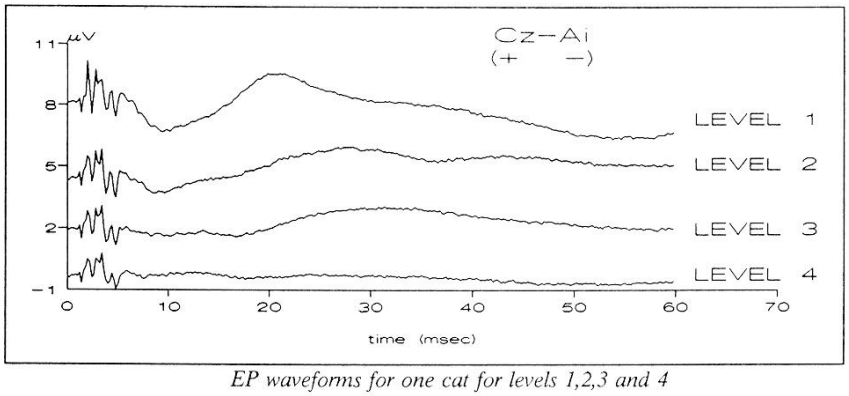
AEP parts

BAEP = Brainstem Auditory Evoked Potential
MLAEP = Middle Latency
LLAEP = Long Latency



A schematic representation of an auditory evoked potential, its various parts and the supposed generators of the peaks. Although not all the generators have been proven, the identifications are clinically useful.

AEPs at different anaesthesia levels



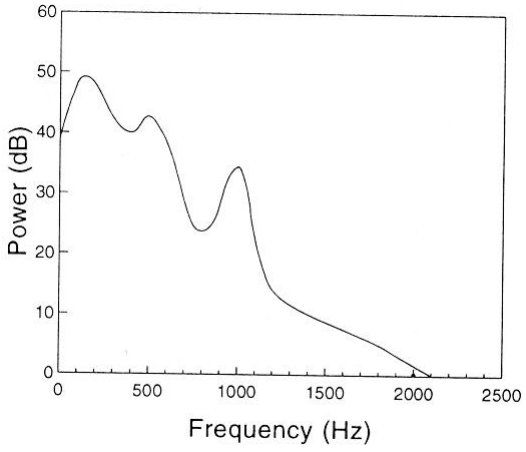
EP waveforms for one cat for levels 1,2,3 and 4

AEP features

- Features like the amplitude and latency of the peaks may be used to assess the effects of anaesthetics.
- Roughly speaking:
  - an increase in latency and decrease in amplitude of some peaks indicates deeper anaesthesia
  - an decrease in latency and increase in amplitude of some peaks indicates lighter anaesthesia (or reaction to surgical actions)
- measurements of these changes seem to be gradual, reproducible, have the same behaviour for different anaesthetics, are not bothered by muscle relaxants, can reflect surgical actions, BUT measurements are complex and require time (averaging)

Recording the EEG / AEPs

- Determination of sampling rate when we want to extract AEPs from the EEG



as can be seen, the frequency contents of an AEP range up to 2 kHz, thus a minimum sampling frequency of 4 kHz is required

Analog Filters

- high-pass 5 Hz (12 dB/octave): to remove very slow components (typically artifacts)
- low-pass 1.5 kHz (12 dB/octave): anti-aliasing filter

- note: analog filters distort time-related properties owing to non-linear phase shifts in the processed signal, especially filters with sharp cut-off characteristics. Therefore only 'shallow' filters (12 dB/octave max.) should be used in this application

- the analog filtered signals are then sampled at 5 kHz (at 12 bits)

- a real-time multi-processing operating system, reads the EEG data, performs the averaging for AEP estimation, and stores data on disk is needed

- evoked potential averaging
  - auditory stimuli, 'clicks ,' are applied (here at a rate of 11.1 Hz)
  - EEG signal parts (here 90 ms, at 5 kHz = 450 samples) that are time-locked to each click are stored, each part is called a sweep (it contains spontaneous EEG activity as well as 'stimulus related brain activity)
  - sweeps are averaged (here 1000 sweeps) to elicit the constant stimulus related activity from the (random) spontaneous EEG

Optimal Filter?

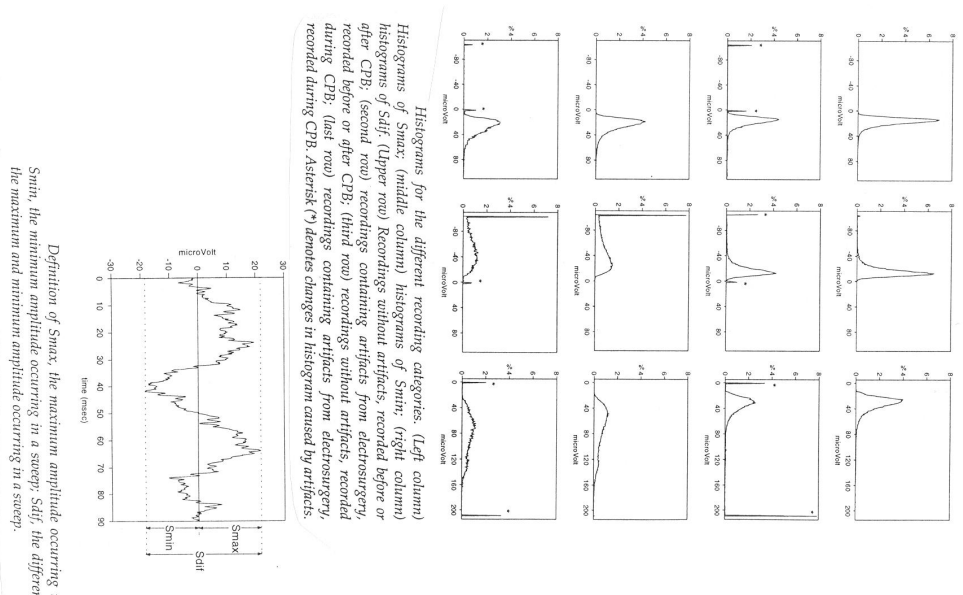
- the averaging process for AEPs is basically applying a moving average filter on all corresponding samples across the sweeps
- better results might theoretically be obtained using a (semi-) optimal filter like the *'a posteriori' Wiener filter*, this is however not used in practice as it is 'too cumbersome' to use and gives only marginally better results.

Averaging is slow

- To average (at least) 1000 sweeps, recorded after clicks that are applied at a rate of 11.1 Hz a recording time of 1000/11.1=90 sec. is needed. This is not so practical (especially during operations).
- Simply increasing the sampling rate does not work, since all kinds of non-linear interactions between the brain's reactions to the stimuli will occur.
- Special techniques that allow for higher average stimulus rates are being developed (recording time 40-50 sec).

Artefact Detection

- each sweep can be checked on its 'validity' before it is to be included in the averaging process. This is done using the 'statistical distribution technique' discussed earlier. Parameters that are examined are maximum and minimum amplitude and slopes.
- Spikes are detected (if possible) and removed using interpolation.
- If there are too many spikes and/or max. and min. deviate much from 'normal' values the sweep is removed from the averaging process.



Definition of Smax, the maximum amplitude occurring in a sweep; Smin, the minimum amplitude occurring in a sweep; Sdif, the difference between the maximum and minimum amplitude occurring in a sweep.

Histograms for the different recording categories. (Left column) Histograms of Smax; (middle column) histograms of Smin; (right column) histograms of Sdif. (Upper row) Recordings without artifacts, recorded before or after CPB; (second row) recordings containing artifacts from electrosurgery, recorded before or after CPB; (third row) recordings without artifacts, recorded during CPB; (last row) recordings containing artifacts from electrosurgery, recorded during CPB. Asterisk (*) denotes changes in histogram caused by artifacts.

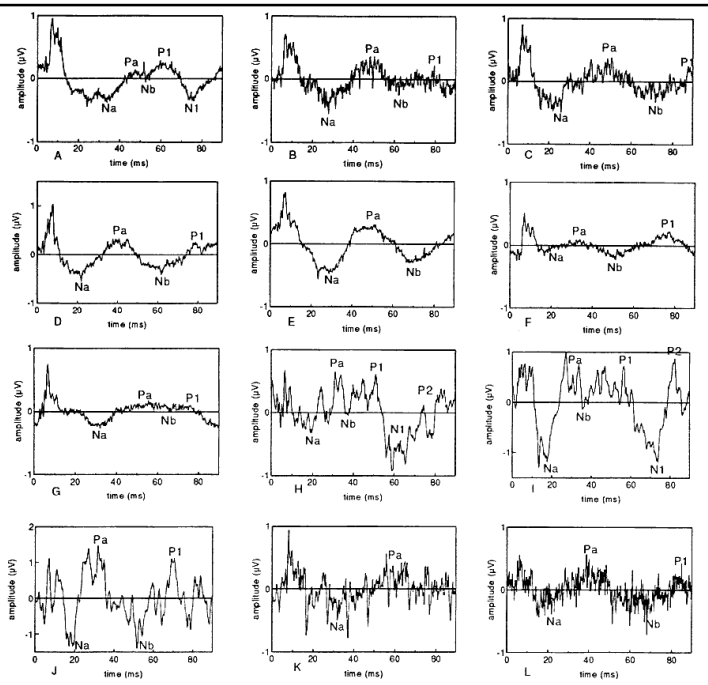
Artefact Histograms

Typical Features Used

- from the EEG: median frequency, spectral edge frequency, peak power frequency and percentages delta (0-4 Hz), theta (4-8 Hz), alpha (8-14 Hz) and beta (above 14 Hz) activity
- from the averaged sweeps (AEPs): latencies and amplitudes of peaks (or other shape descriptors)
- other signals: blood pressure, heart rate, temperatures, inspired/expired gas concentrations, oxygen saturation

Feature Extraction

- Feature extraction from the EEG is fairly straightforward: use the short-term Fourier transform (using 8-second windows, with 2-second overlap and a Blackman time window)
- Features like blood pressure, heart rate etc. can be obtained directly from monitoring equipment
- Extracting features like peak locations from the AEPs is a bit more complicated though. It is a task that is typically performed by experts who use visual association rather than specific rules.



Examples of Auditory Evoked Potentials (AEPs) measured in humans before (figures H, I, and J) and during (all other figures) cardiac surgery. In figures H, I, and J, the effect of muscle artefacts can be seen. Figures F and G show AEPs measured during deeper levels of anaesthesia for the patient whose 'awake' AEP is depicted in figure H; the longer latencies and smaller amplitudes of the peaks are discernible. The effects of interference of equipment can be seen in figures K and L

Techniques for AEP peak identification

- Many methods have been tried out, including
  - maximum detection
  - matched filtering
  - cross correlation with templates
  - expert systems
  - syntactic techniques
  - artificial neural networks

- With use of the peak locations as obtained with the last described method we can make a classifier that perceptual processing and 'awareness ’with about 89% sensitivity and 86% specificity.
- However –this is not a very simple and measurement set-up!

Another Approach: Bispectral Index (BIS)

- developed to assess the hypnotic/sedative component of anaesthesia
- $0 \leq BIS \leq 100$
  BIS = f(Power Spectral vars,Bispectral vars,..)
- use of large (> 2000 patients under different types of anaesthesia) annotated database and statistical analysis

BIS

- hypnosis covered by one figure (=easy)
  - if BIS < 70: probability of awareness is low
  - if BIS ~ 90: consciousness
  - 50 < BIS < 60 for maintenance anaesthesia
- note: this is an indicator for hypnosis, NOT for analgesia (pain suppression)

Hypnotic State/Sedation Level	Score	
Responds readily to name spoken in normal tone	5	
Lethargic response to name spoken in normal tone or says name post-op	4	
Responds only after name is called loudly and/or repeatedly, or opens eyes post-op	3	Conscious
Responds only after mild prodding or shaking	2	
Does not respond to mild prodding or shaking	1	Unconscious
Does not respond to noxious stimulus	0	

Table 2: Hypnotic state/sedation level scoring criteria

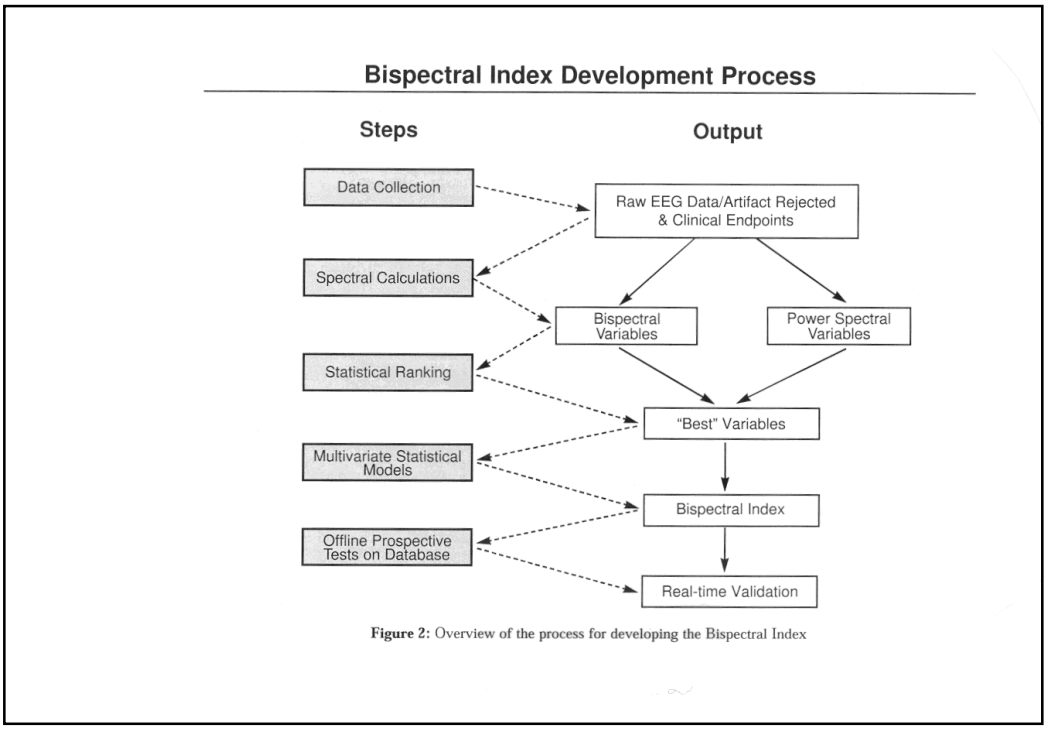


Figure 2: Overview of the process for developing the Bispectral Index

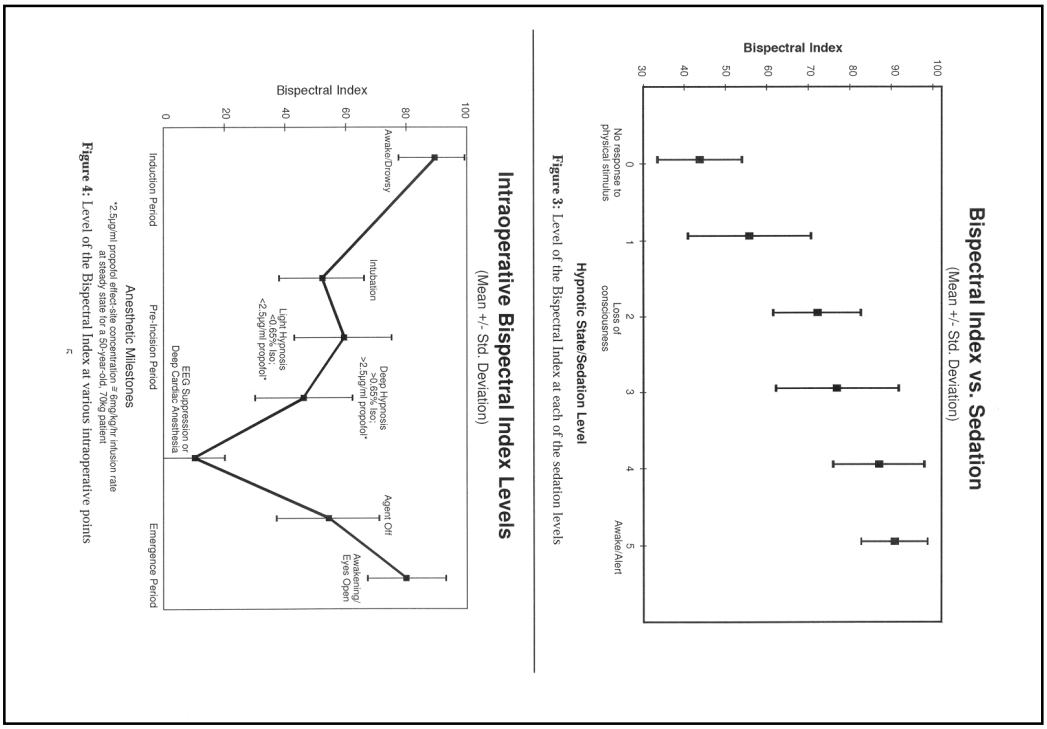


Figure 3: Level of the Bispectral Index at each of the sedation levels

Figure 4: Level of the Bispectral Index at various intraoperative points

BIS index

- purely emperically obtained function that happens to function well under many circumstances.
- 3 components that are weighted and summed in a non-linear fashion to obtain a number between 0 and 100. The weights of the summation change within this range.
  - from the time-domain; Burst Suppression Ratio (BSR), the fraction of time in an epoch when EEG is suppressed, and QUAZI suppression, which allows burst suppression detection in presence of a wandering voltage baseline;
  - from the frequency domain; the relative beta ratio, the log ratio of power in the frequency bands 30-47 Hz and 11-20 Hz (the borders of these bands have been empirically obtained)
  - from the bispectrum; the SynchFastSlow parameter, the log ratio of the sum of all bispectrum peaks in the range 0.5 - 47 Hz over the sum of the bispectrum in the area 40 - 47 Hz.

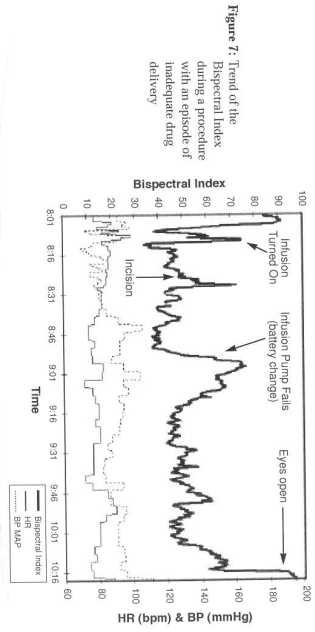


Figure 7: Trend of the Bispectral Index during a procedure with an episode of inadequate drug delivery

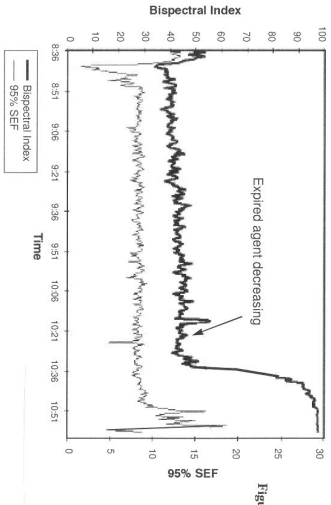


Figure 6: Performance of the Bispectral Index vs. 95% SEF during emergence from an intraopera-tive procedure

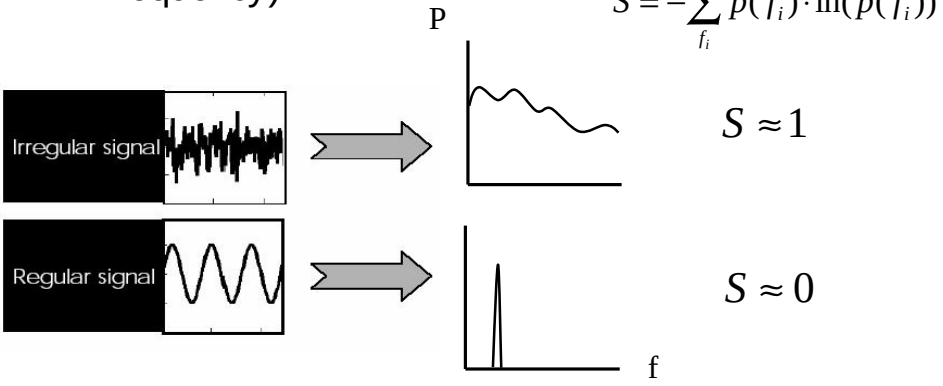
Still more alternative methods exist...

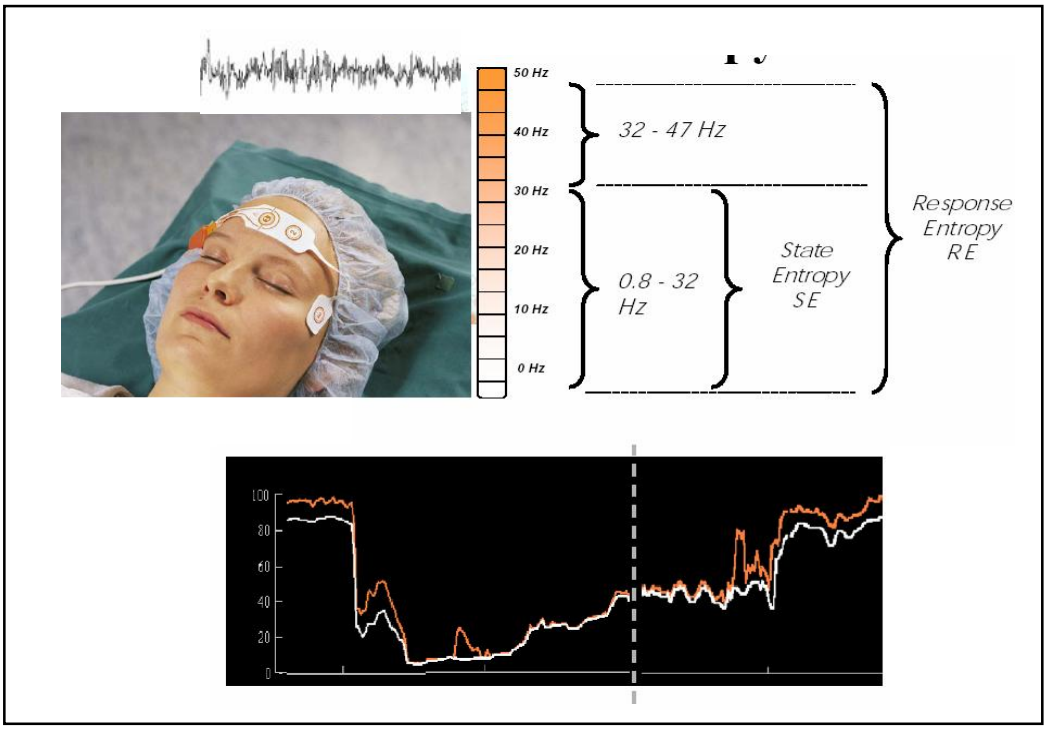
- complexity analysis of the EEG (e.g., using chaos theory, or entropy of the signal) can be used to study how much 'disorder' there is in the signals coming from the brain. A lower level of disorder can then be related to a deeper level of hypnosis.

Spectral Entropy of a signal

- Amount of irregularity/disorder (independent of absolute amplitude or frequency)

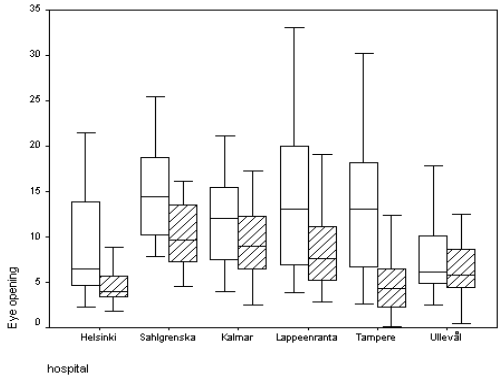
$$S = -\sum_{f_i} p(f_i) \cdot \ln(p(f_i))$$

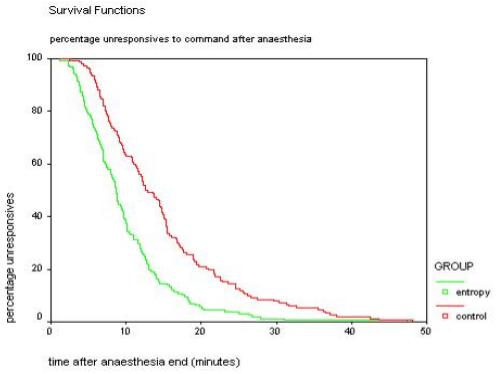




Datex-Ohmeda S/5 Entropy module (2003)

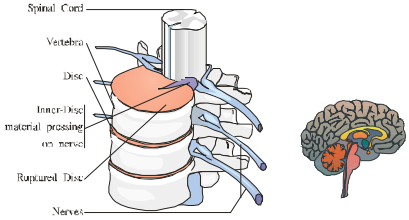
Faster recovery





Monitoring pain and pain suppression (analgesia)

- very difficult to quantify phenomenon
  (and much less studied than hypnosis during anaesthesia)
- depends on many interacting factors
  (individual, stimulus intensity & application, drugs used,...)
- role of brain activity is not as pronounced, autonomic nervous system plays main role

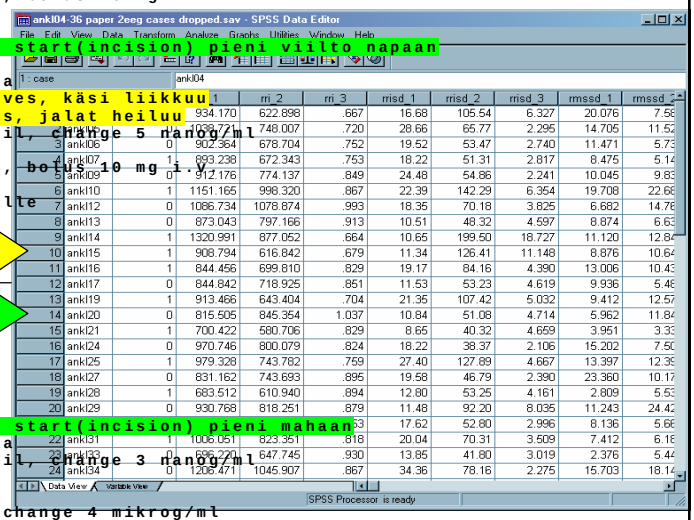


Example of study

- 36 patients without muscle relaxants at start of operation
- idea: in case of pain movement is possible (and highly likely) -> observed movement is indication of pain experience
- minor pain suppression drugs so that a relatively big part of population experiences pain at start of operation

- Record lots of variables - from hemodynamic (blood circulation) data (heart rate variability, photoplethysmogram), forehead muscle activity & EEG
- Select most powerful variables and make classifier that can distinguish movers 'data from non-movers '

```
11:53:20 peittely alkaa
11:54:55 cuffin painelua
11:57:03  10337 Rocuronium, bolus 10 mg i.v.
11:59:28 katetrointi
12:04:30 trendis
12:05:14  00203 Operation, start(incision) pieni viillto napaan
12:05:40 navan levittelyä
12:05:56 kaasu täyttö alkaa
12:06:24  00301 Patient moves, käsi liikkuu
12:07:00 00301 Patien moves, jalat heiluu
12:07:22  10118 Remifentanil, change 5 mikrog/ml
12:08:28 mahan koputtelua
12:08:55  10337 Rocuronium, bolus 10 mg i.v.
12:09:13 troakaari sisään
12:10:52 apuviilto vasemmalle
```



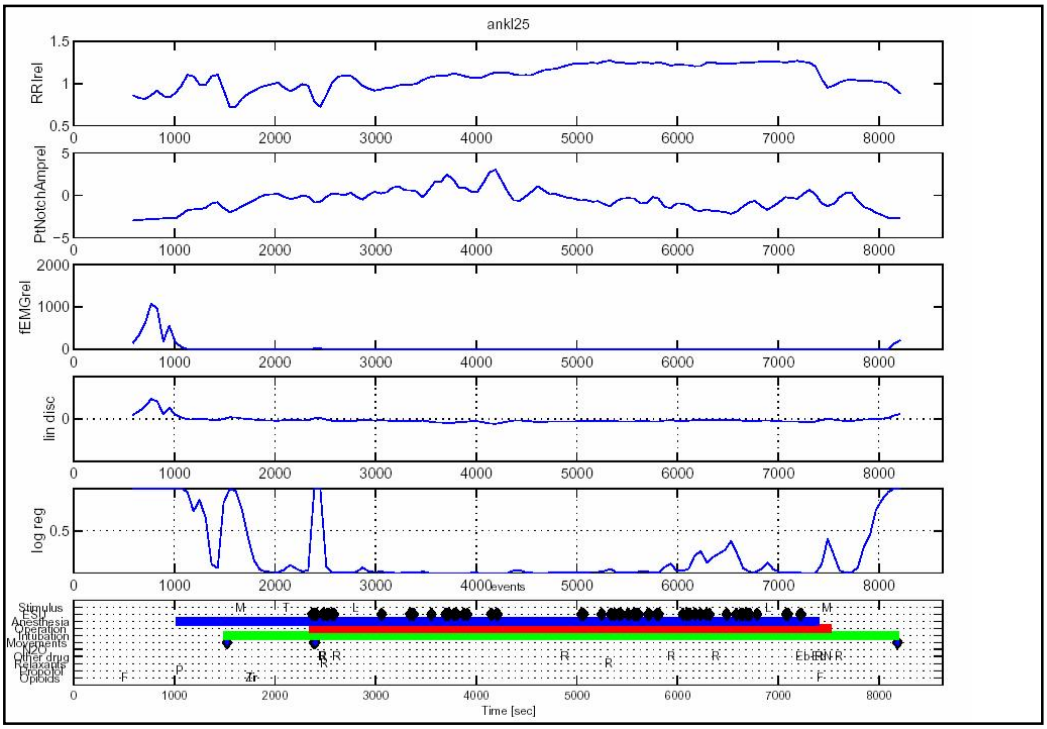

```
11:13:43 sondilla kokeilua
11:17:21 trendis
11:18:44  00203 Operation, start(incision) pieni mahaan
11:18:53 kaasu täyttö alkaa
11:19:43  10118 Remifentanil, change 3 mikrog/ml
11:21:28 viilto mahaan
11:21:38 trokaari mahaan
11:22:08  10214 Propofol, change 4 mikrog/ml
```

Results

- from the original set of 62 variables, some 16-20 are changing differently in response to incision when grouped by movers and non-movers
- a good logistic regression classifier using 3 variables of those;

p(move) = F(heart rate, photoplethysmogram shape,response entropy)

variables used	accuracy	sensitivity	specificity
RE & RRI & PPG notch amplitude	96% (21/22)	90% (9/10)	100% (12/12)
RE & RRI	91% (20/22)	90% (9/10)	92% (11/12)
RE & PPG notch amplitude	91% (20/22)	90% (9/10)	92% (11/12)
RRI & PPG notch amplitude	73% (19/26)	58% (7/12)	86% (12/14)
RE	77% (17/22)	70% (7/10)	86% (12/14)
RRI	73% (19/26)	58% (7/12)	86% (12/14)
PPG notch amplitude	65% (17/26)	50% (6/12)	79% (11/14)



Conclusions

- Depth of Anaesthesia is a very complex issue that has many different components which can all be addressed with different methods, and not all parts of the puzzle are solved yet!
- There is not one golden standard against which performances can easily be measured.

- In this single application, techniques from almost every lecture in this course were used (or at least investigated).
- This is not some special or far-fetched case - in many 'real-life' biomedical signal processing applications (e.g., for cardiologic signals, heart and lung sounds, muscle activity signals) a huge array of techniques is being used to attack problems.
- So, for someone who is doing biosignal processing, there is a continuing need to take notice of all those techniques, and try to assess their potential applicability for the many present and future problems that exist.

Challenges

- understanding the clinical background and problem setting
- understanding the theoretical behaviour of methods that can help to address the problem
- realising that theory is something different than practice, and being able to deal with that
- being able to communicate in several languages