How to measure pain in the unconscious patient?

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Lecture Series in Biomedical Signal and Image Processing
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centro hospitalar
do Porto

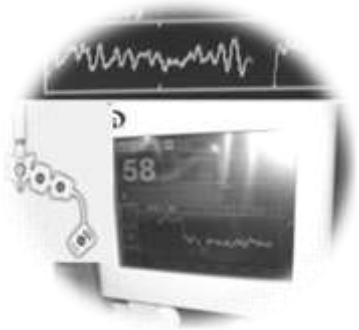
Introduction

Some Pain-related concepts

"pain can be defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"
International Association for the Study of Pain

INTRODUCTION:

General Anaesthesia Triade



Hypnosis

Electroencepl

Rate

Blood Pressure

Tears

Sweat

Muscle Paralysis

Movement

Electromiogram

How to measure nociception?

General Anaesthesia

INTRODUCTION:

General Anaesthesia Triade

Awareness and Pain

General Anaesthesia Triade

Michael Jackson Trial

Monitor and Titrate

INTRODUCTION:

Sensing and Pain

Fiber Type	Function	Fiber Diameter (μm)	Conduction Velocity (m/s)	Spike Duration (ms)	Absolute Refractory Period
A				0.4-0.5	0.4-1
α	Proprioception; somatic motor	12-20	70-120		
β	Touch, pressure, motor	5-12	30-70		
γ	Motor to muscle spindles	3-6	15-30		
δ	Pain, cold, touch	2-5	12-30		
B	Preganglionic autonomic	<3	3-15	1.2	1.2
C					
Dorsal root	Pain, temperature, some mechanoreception, reflex responses	0.4-1.2	0.5-2	2	2
Sympathetic	Postganglionic sympathetic	0.3-1.3	0.7-2.3	2	2

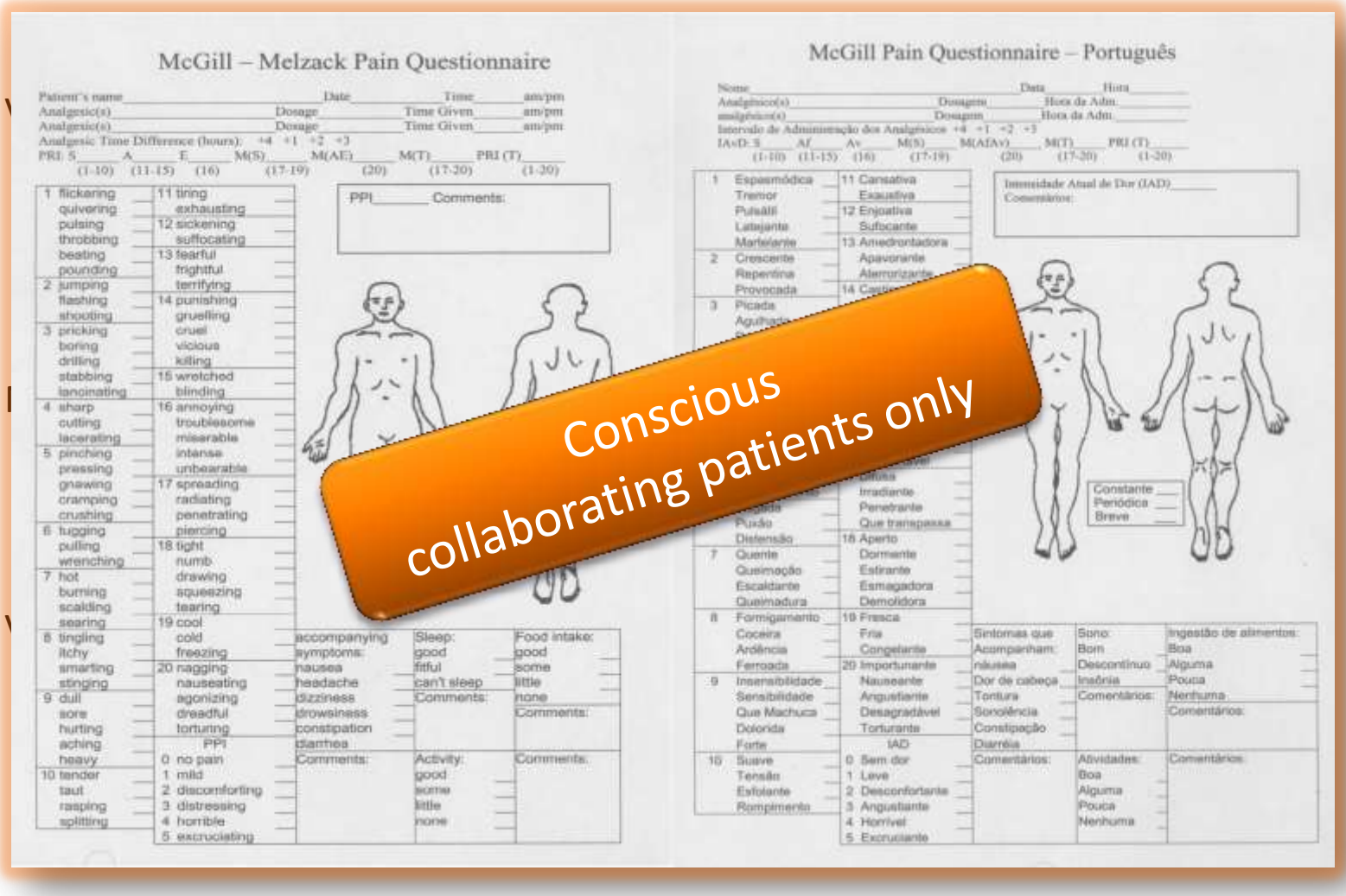
Pain Induction

Experimental Methods of Pain Induction

Cutaneous	Muscular	Visceral
Electrical Thermal Mec Ch	Isch	cal l al nical

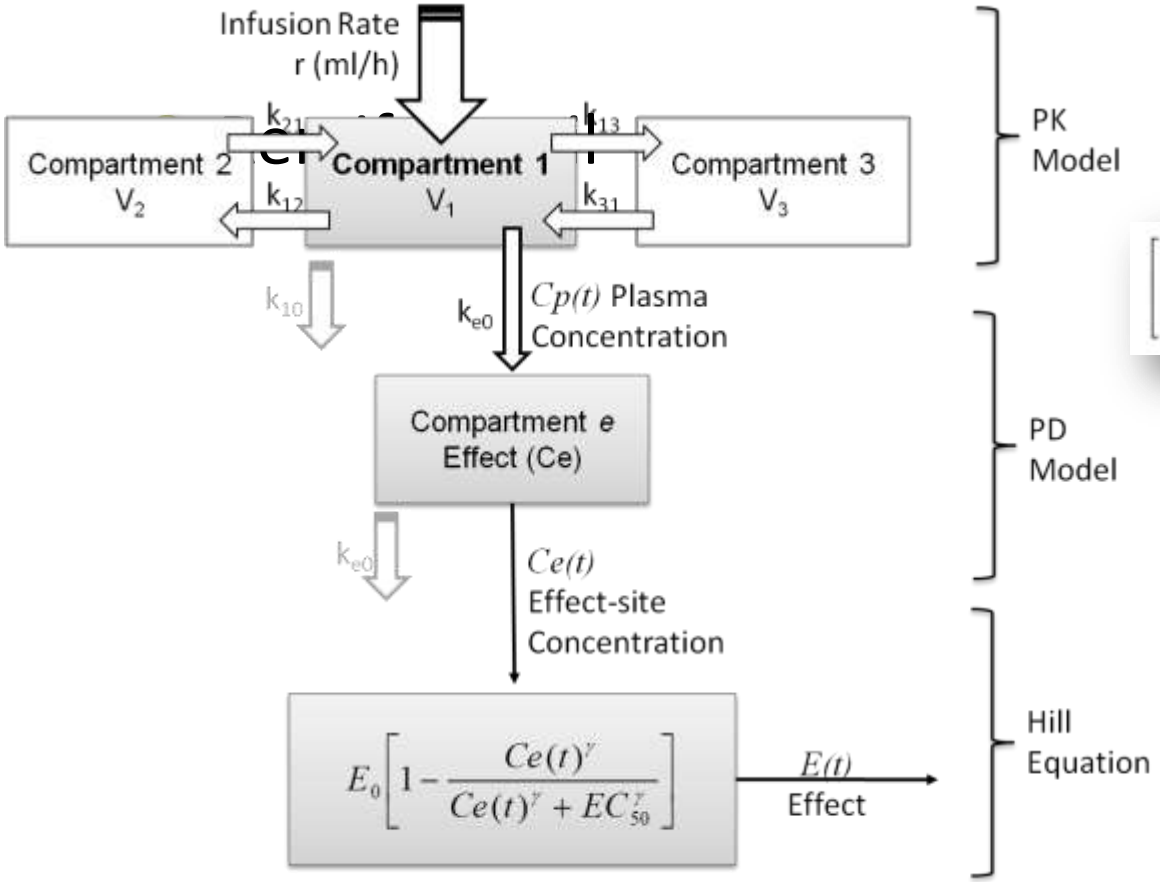
Objective Pain Induction
↓
Objective Pain Assessment

Pain Assessment



R. Melzack and W. S. Torgerson. On the language of pain. Anesthesiology, 34(1): 50-59, 1971.
F. Varoli and V. Pedrazzi. Adapted version of the McGill pain questionnaire to brazilian portuguese. Brazilian Dental Journal, 17(4):328-335, 2006.

Anaesthetic Drugs



$$\begin{bmatrix} \dot{m}_1(t) \\ \dot{m}_2(t) \\ \dot{m}_3(t) \\ \dot{Ce}(t) \end{bmatrix} = \begin{bmatrix} -k_{12}-k_{13}-k_{10} & k_{21} & k_{31} & 0 \\ k_{12} & -k_{21} & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 \\ \frac{k_{e0}}{V_1} & 0 & 0 & -k_{e0} \end{bmatrix} \begin{bmatrix} m_1(t) \\ m_2(t) \\ m_3(t) \\ Ce(t) \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} r(t)$$

$$E(t) = E_0 \left[1 - \frac{Ce(t)^{\gamma}}{Ce(t)^{\gamma} + EC_{50}^{\gamma}} \right]$$

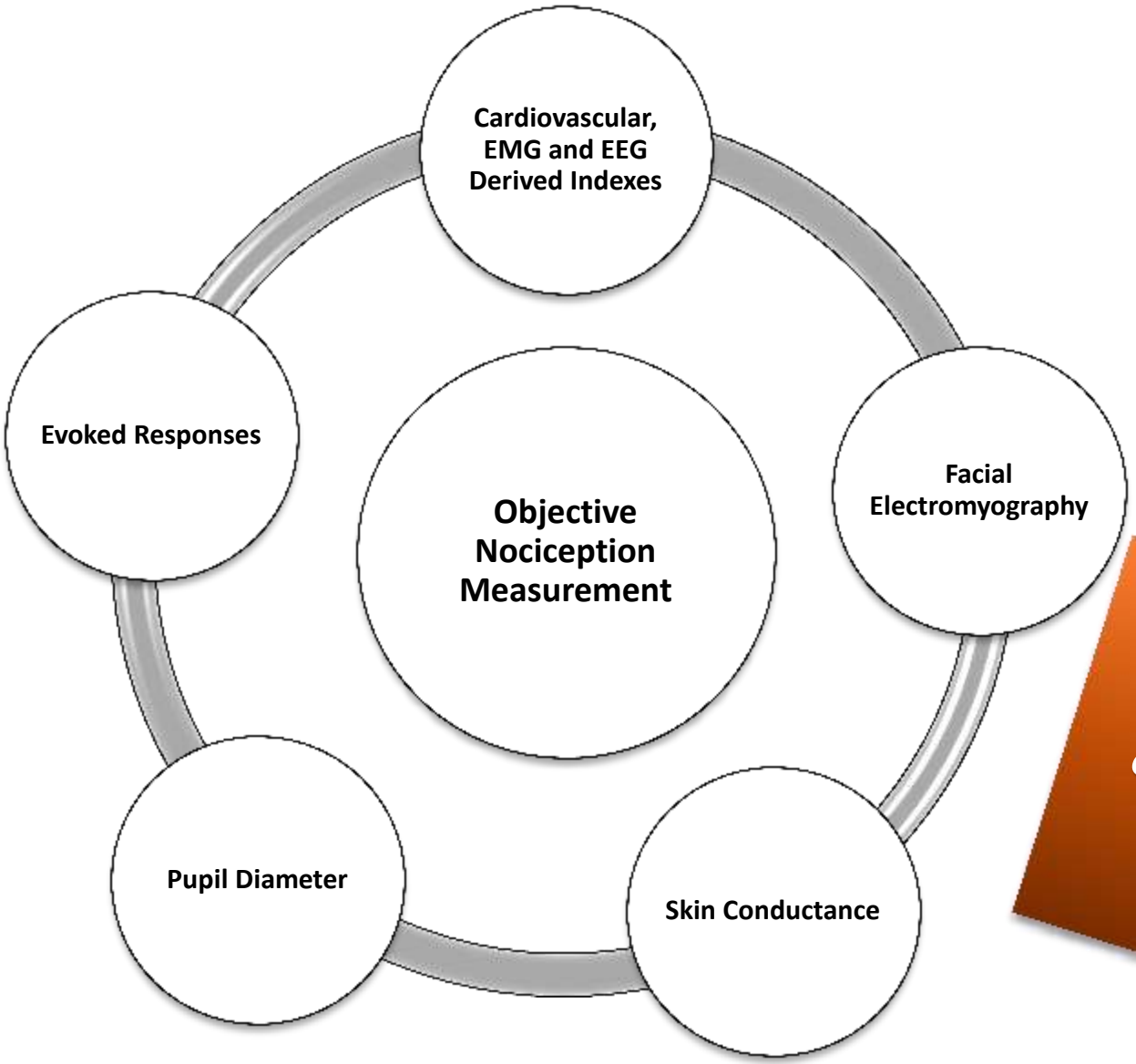
$$U_A(t) = \frac{Ce_A(t)}{EC_{50A}} \qquad U_H(t) = \frac{Ce_H(t)}{EC_{50H}}$$

$$\theta(t) = \frac{U_H(t)}{U_H(t) + U_A(t)}$$

$$E(t) = E_0 \left(1 - \frac{\left((U_H(t) + U_A(t)) / U_{50\theta}(t) \right)^{\gamma}}{1 + \left((U_H(t) + U_A(t)) / U_{50\theta}(t) \right)^{\gamma}} \right)$$

C. F. Minto, T. W. Schnider, T. G. Short, K. M. Gregg, A. Gentilini, and S. L.Shafer. Response surface model for anesthetic drug interactions. Anesthesiology, 92(6):980-1002, 2000.

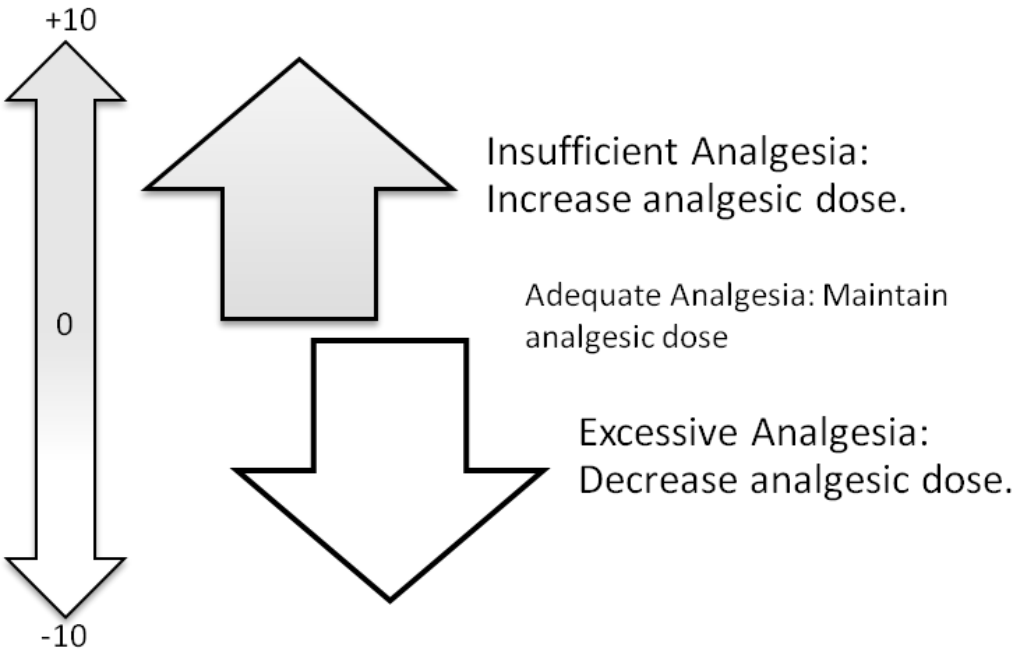
State of the Art

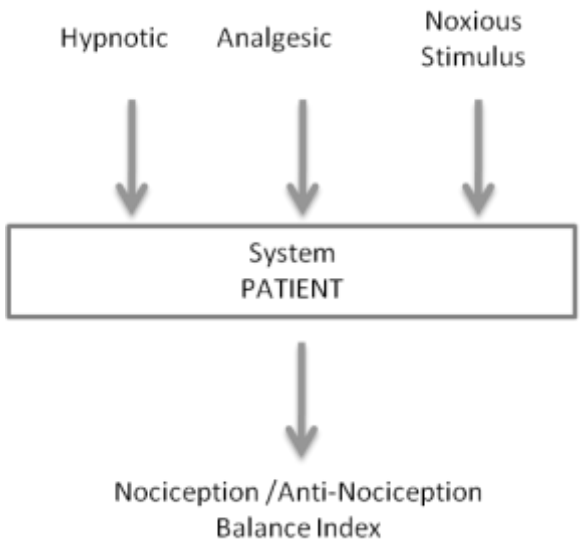


None broadly accepted and disseminated

INTRODUCTION:

Nociception / Anti-Nociception Indicators

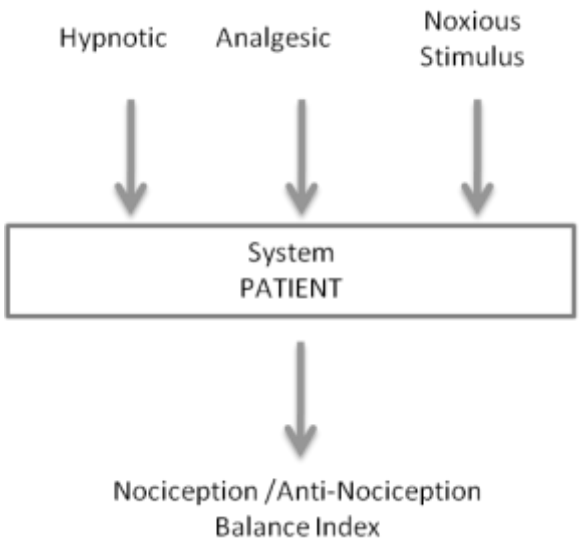




Nociception Studies

Collecting and Preparing the data

Nociception Studies in Anesthesia



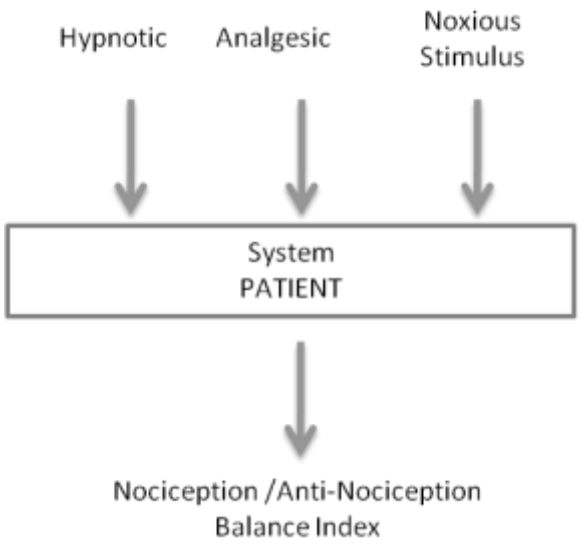
Interpatient Variability

+

Intrapatient Variability

- Design adequate clinical protocol
  - Inclusion criteria
  - Data to collect
- Submit to the institution's Ethics Committee
- Written informed consent

Nociception Studies in Anesthesia



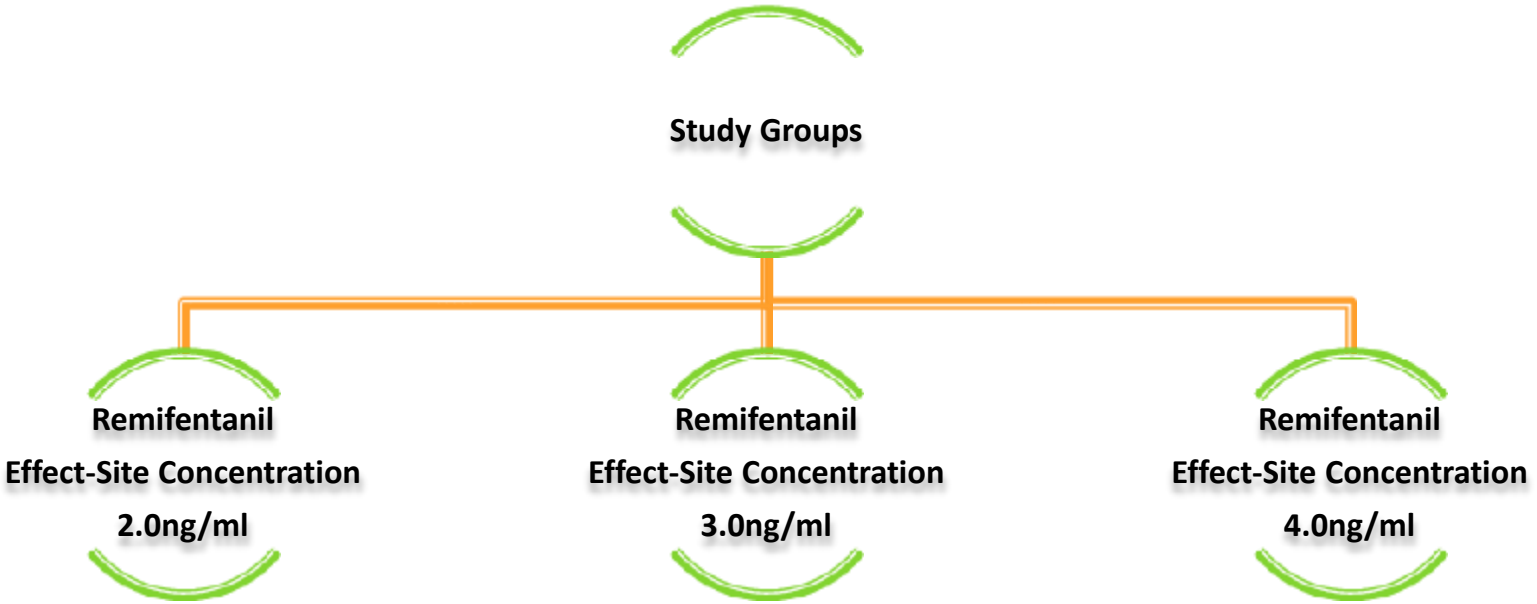
Interpatient Variability

+

Intrapatient Variability

- Passive nociception assessment
- Active nociception assessment

Clinical Protocol Design



- Phase I
  - Response to precise noxious stimuli:
    - laringoscopy/intubation;
    - tetanic stimulus;
    - incision.
- Phase II
  - Response of physiological variables to different combinations of stimulus intensity and drug doses:
    - Remifentanil ascending/descending steps.

Clinical Protocol Design

Clinical Setup

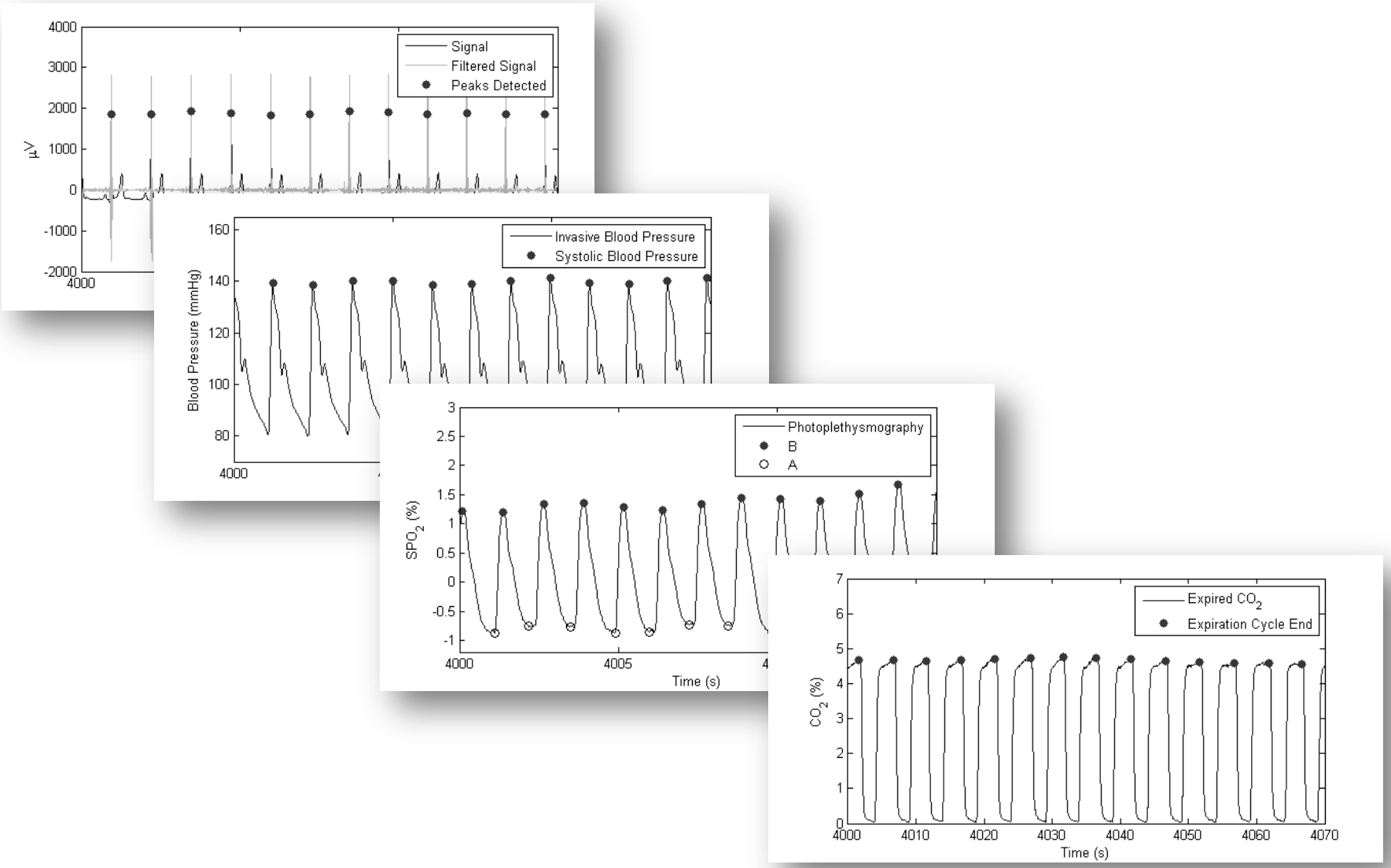
A – BIS Monitor; B – Orchestra pumps C – Datex monitor; D – Ruglopp II Waves

Data Overview

Signal	Number of Channels	Unit	Sampling Rate (Hz)
EEG	4 (eeg0, eeg1, eeg2, eeg3)	μV	128
ECG	1 (ecg)	μV	300
PPG	1 (pleth)	%	100
IBP	1 (invp)	mmHg	100
CO_2	1 (co2)	%	25

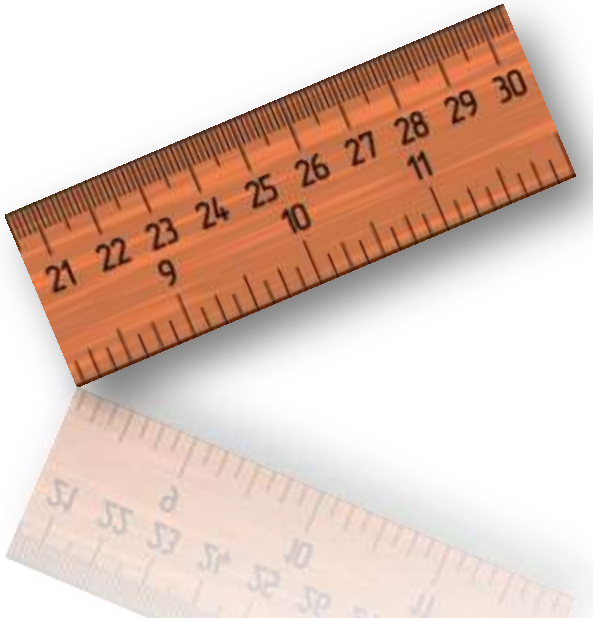
Datex	BIS Bilateral and CVI	TCI Data
1. Time	16. Suppression Rate L (%)	37. Infused Volume (ml)
2. ECG Heart Rate (beats/min^{-1})	17. Spectral Edge Frequency L (Hz)	38. Remifentanil Cp (ng/ml)
3. BP Systolic (mmHg)	18. BIS L	39. Remifentanil Ce (ng/ml)
4. BP Diastolic (mmHg)	19. Total Power L (dB)	40. Remifentanil Ct (ng/ml)
5. BP Mean (mmHg)	20. EMG L (dB)	41. Infusion Rate (ml/h)
6. BP Heart Rate (beats/min^{-1})	21. SQI L (%)	42. Infused Volume (ml)
7. Non-Invasive BP Systolic (mmHg)	22. ASYM (rw)	43. Propofol Cp (μg/ml)
8. Non-Invasive BP Diastolic (mmHg)	23. SD BIS L	44. Propofol Ce (μg/ml)
9. Non-Invasive BP Mean	24. SD EMG L	45. Propofol Ct (μg/ml)
10. Temperature (°C)	25. CVI L	46. Infusion Rate (ml/h)
11. SPO2 (%)	26. Impedance L (Ω)	47. SPO2 Amplitude (%)
12. SPO2 Pulse Rate (beats/min^{-1})	27. Supression Rate R (%)	
13. CO2 Et (%)	28. Spectral Edge Frequency R (Hz)	
14. CO2 Fi (%)	29. BIS R	
15. CO2 Respiration Rate (cycles/min^{-1})	30. Total Power R (dB)	
	31. EMG R (dB)	
	32. SQI R (%)	
	33. SD BIS R	
	34. SD EMG R	
	35. CVI R	
	36. Impedance R (Ω)	

Waves Pre-Processing

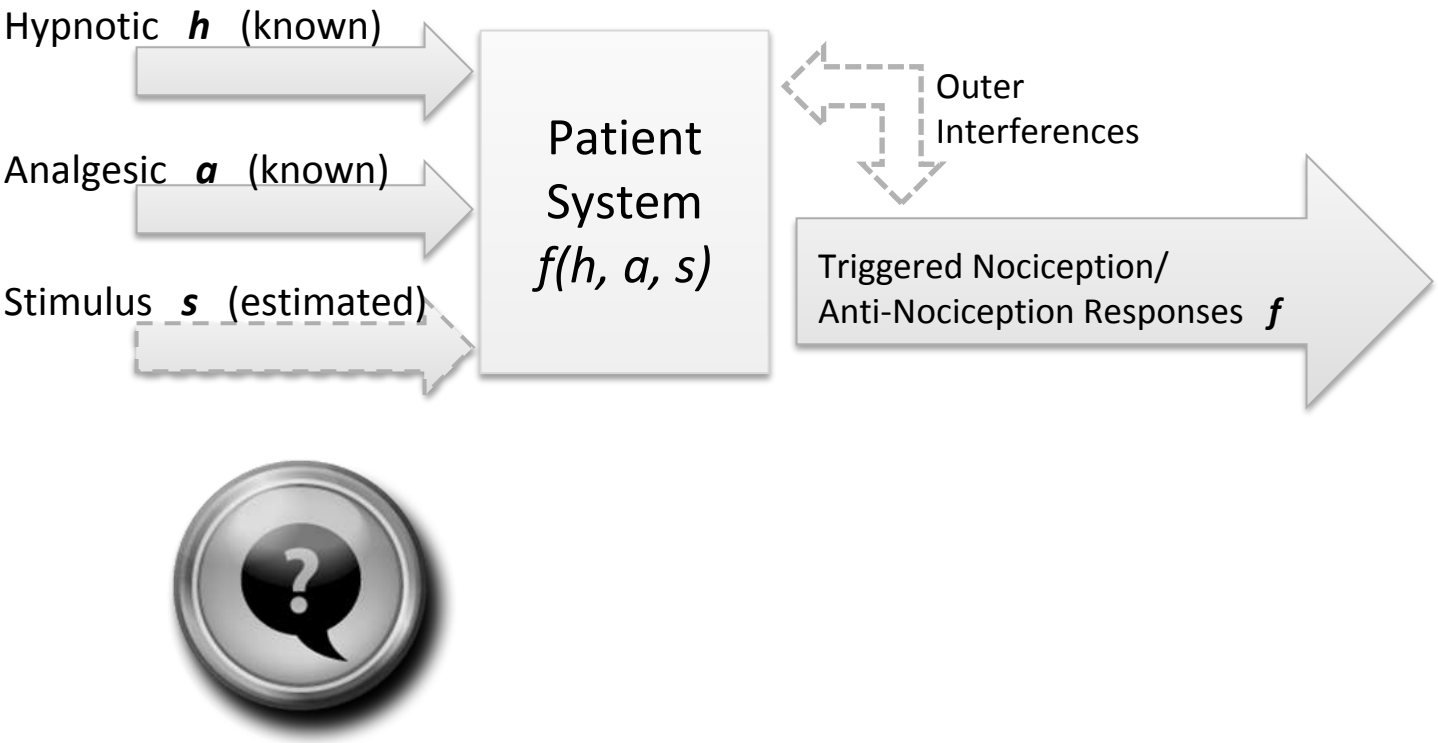


Stimulus Intensity Analysis

Collecting and Preparing the data



Stimulus Intensity Estimation



Methods

- A total of 35 stimuli have been evaluated
- Target: Sociedade Portuguesa de Anestesia (SPA) and Anaesthesiologists from Centro Hospitalar do Porto

$$\pi_{nix} = \frac{exp \sum_{j=0}^{x} [\beta_n - (\delta_i + \tau_k)]}{\sum_{k=0}^{m} exp \sum_{j=0}^{k} [\beta_n - (\delta_i + \tau_k)]} \quad x = 0, ..., 10$$

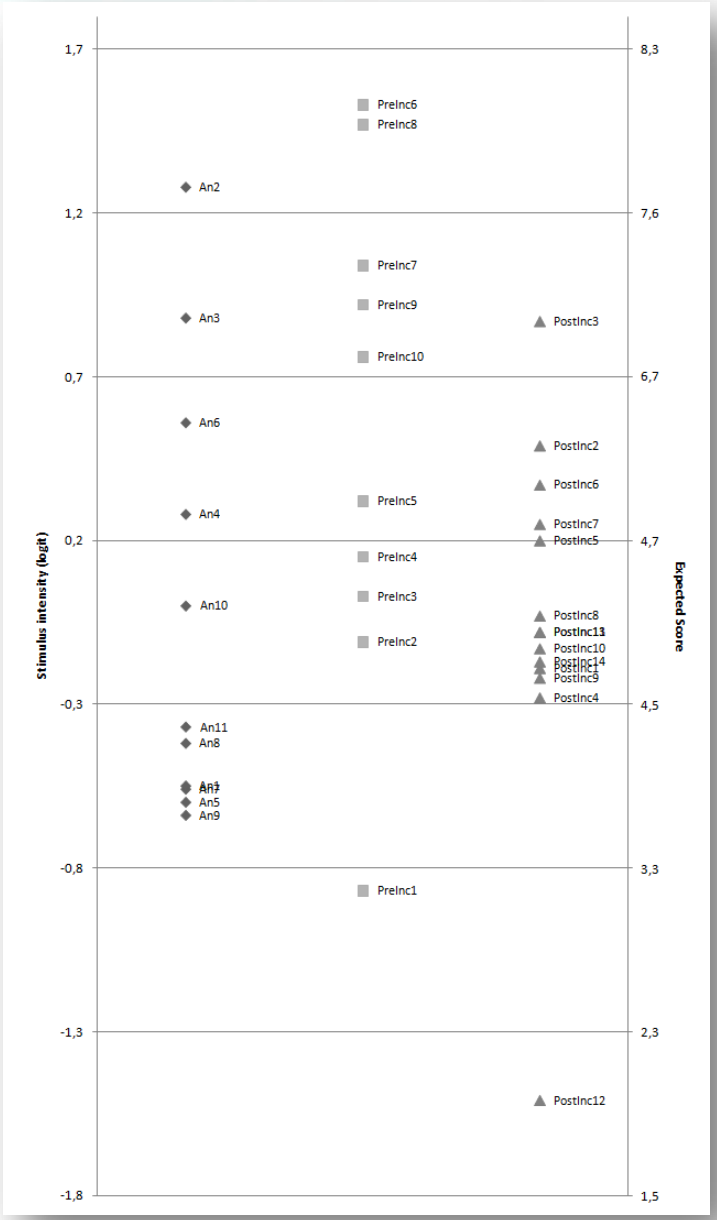
where $\tau_0 \equiv 0$ so that $\sum_{j=0}^{k} [\beta_n - (\delta_i + \tau_k)] = 1.$

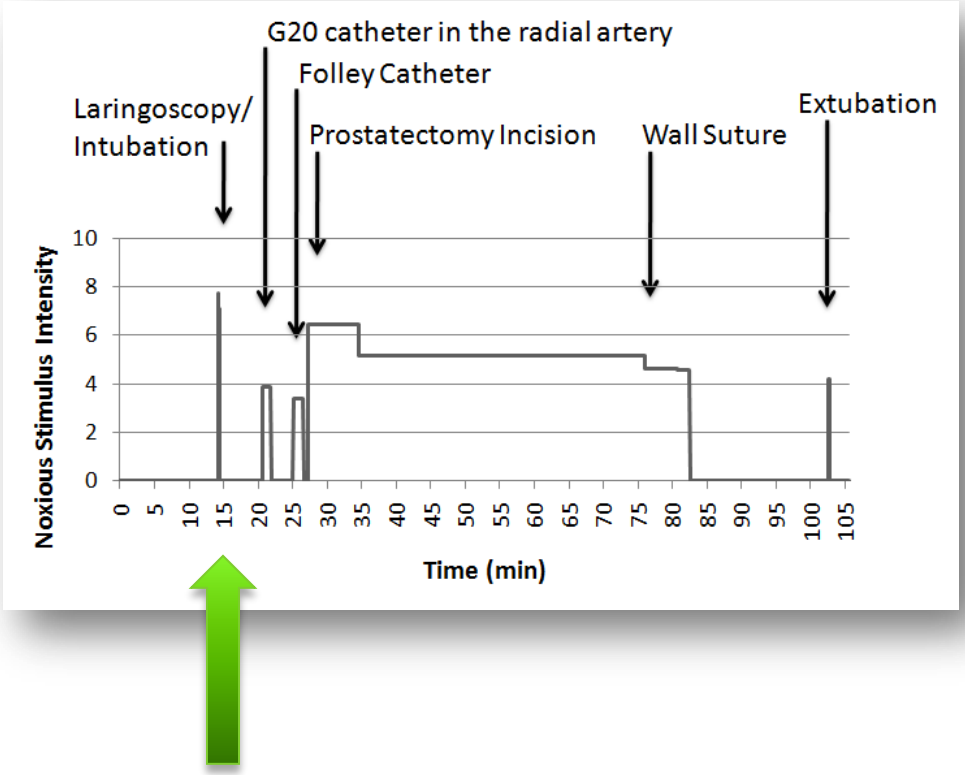
Rasch Model

G. Rasch. Probabilistic Models for Some Intelligence and Attainment Tests. Danish Institute for Educational Research, Copenhagen, 1960. Expanded edition, Chicago: Mesa Press, 1992.
J. M. Linacre. Many-facet Rasch measurement. Mesa Press, Chicago, 2nd edition, 1994.

STIMULUS INTENSITY ANALYSIS:

Results and Discussion





Data Analysis

Passive Nociception Measures

Introduction

- Study physiological responses to precise noxious stimuli
  - Phase I

HR, SBP, PPGA, ANSSI, BIS, EMG and EMG SD

- Analyze maintenance phase of general anaesthesia, and the impact of different anaesthetic drugs' combinations
  - Phase II
    - Steady-State Detection
    - Physiological Modelling

Phase II. Maintenance Analysis – Steady-State Detection

$$T_1 = 3\lambda_1 w, \quad T_2 = w$$

$$|W_f(p_1)| \text{ and } |W_f(p_2)| \geq T_1$$

$$sign(W_f(p_1)).sign(W_f(p_2)) < 0,\ p_2 - p_1 \leq t_p$$

$$|W_f(t_a)| \text{ and } |W_f(t_b)| \geq T_2$$

$$|W_f(t_a - 1)| \text{ and } |W_f(t_b + 1)| < T_2$$

Abnormalities Detection

$$= \sum_{i \in I_j} c_{j,i}$$

$$=$$

Low Fr
Compon

where $\varphi_{j,i}$ and $\psi_{j,k}$

Wavelet Tra

Steady-Sate Index

$$T_s = \sigma_{W_f}, \quad T_u = 3\lambda_2 \sigma_{W_f}, \quad T_w = \sigma_{WW_f}$$

SS index is defined according to the following rules:

- if $|W_S f(t)| > T_u$ then $\beta(t) = 0$, where T_u is the identification WT modulus threshold for unsteady status;
- if $|W_S f(t - \Delta t)| < T_s$ then $\beta(t) = 1$, where T_s is the identification WT modulus threshold for steady status, and Δt a long enough time interval to identify SS;
- to detect zero-crossing points, the second order WT is used. If $|W_S f(t)| < T_s$ and $|WW_S f(t)| < T_w$ then $\beta(t) = 1$ where T_w is the second-order WT modulus threshold to identify zero-crossing point in the WT.

$$\beta(t) = \xi[\theta(t)]$$

$$\theta(t) = |W_S f(t)| + \gamma |WW_S f(t)|$$

$$\gamma = \begin{cases} 0 & |WW_S f| \leq T_w \\ (|WW_S f| - T_w)/2T_w & |WW_S f| \in]T_w, 3T_w[\\ 1 & |WW_S f| \geq 3T_w \end{cases}$$

$$\beta(t) = \begin{cases} 0 & \theta(t) \geq T_u \\ \xi[\theta(t)] & T_s < \theta(t) < T_u \\ 1 & \theta(t) \leq T_s \end{cases}$$

$$\xi(x) = \frac{1}{2}\left[cos\left(\frac{x - T_s}{T_u - T_s}\pi\right) + 1\right]$$

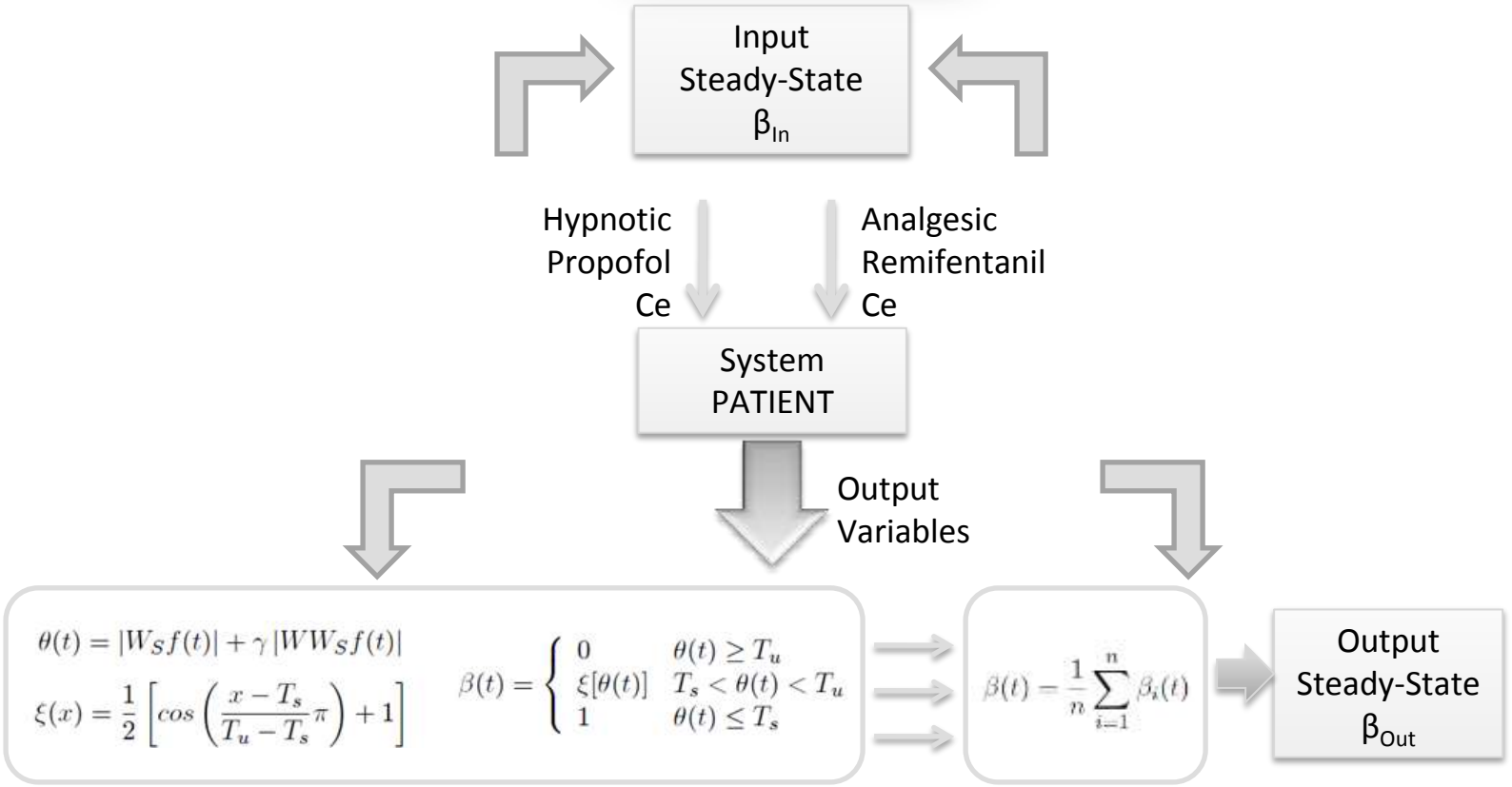
S. Mallat and S. Zhong. Characterization of signals from multiscale edges. Pattern Analysis and Machine Intelligence, IEEE Transactions on Signal Processing, 14(7):710-732, 1992.

T. Jiang, B. Chen, X. He, and P. Stuart. Application of steady-state detection method based on wavelet transform. Computers and Chemical Engineering, 27 (4):569-578, 2003.

Phase II. Maintenance Analysis – Steady-State Detection

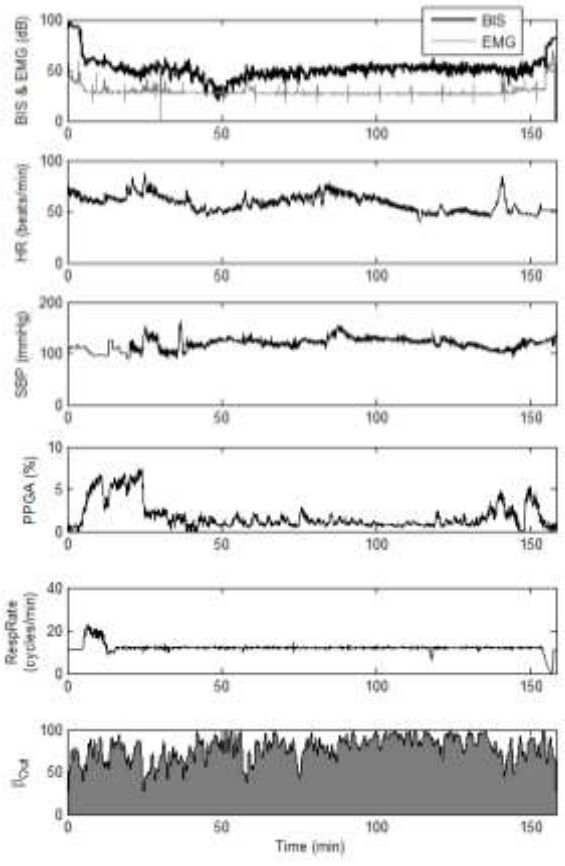
$$\beta_{In}(t) = \frac{1}{n}\sum_{i=1}^{n}\beta_{Signal_i}(t)$$

$$\beta_{Out}(t) = \frac{1}{m}\sum_{i=1}^{m}\beta_{Signal_i}(t)$$



Phase II. Maintenance Analysis – Steady-State Detection

Time Percentage in SS (N=31)	
Remifentanil Ce	74,1±7,8
Propofol Ce	79,5±6,6
Stimulus	90,4±3,1
β_{In}	59,5±8,5
BIS	75,0±9,7
EMG	67,0±7,6
HR	32,6±17,1
SBP	40,3±19,3
PPGA	59,4±28,6
RespR	88,4±9,6)
β_{Out}	24,3±14,2

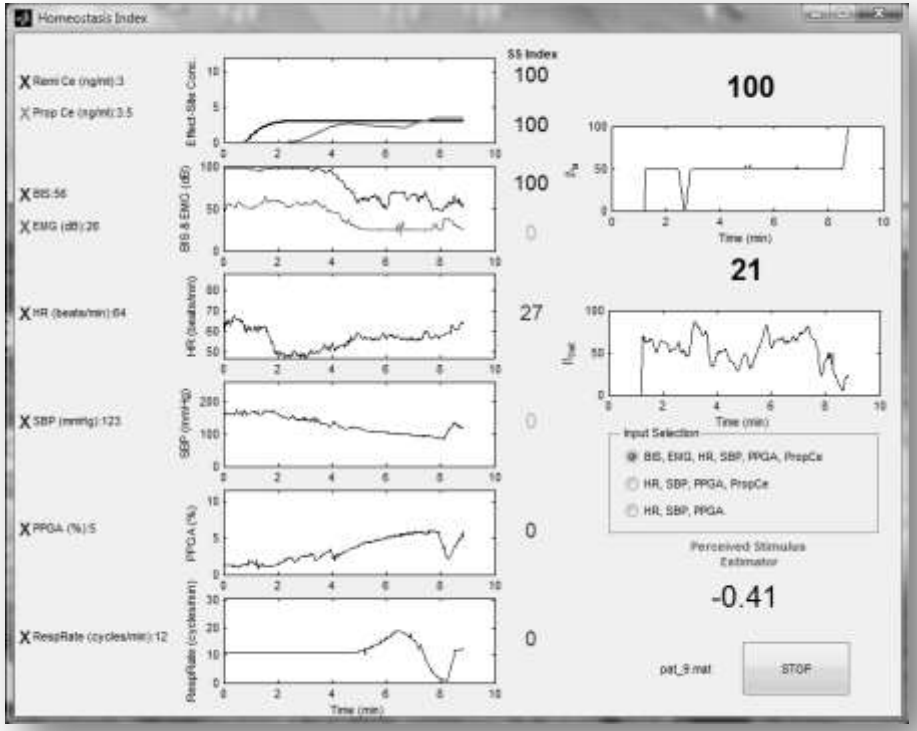


Outputs

	Original			
	Baseline/Pre-Laringo	Laringoscopy	Tetanic	Incision
HI				
RemiCe=2.0	23,7	-24,64	10,22	-3,68
RemiCe=3.0	26,6	-12,22	-4,02	-3,84
RemiCe=4.0	22,0	-10,05	-4,91	5,53

DATA ANALYSIS:

Monitoring System – Homeostasis Index and Perceived Stimulus Estimator



Evoked Potentials

Active Nociception Measures

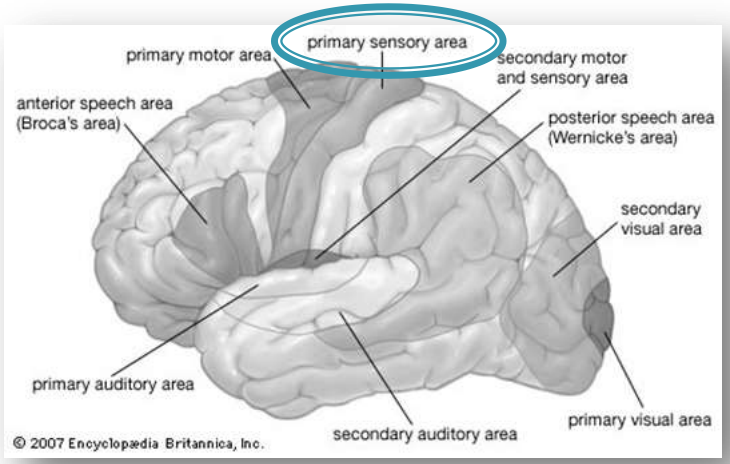
Introduction

The nociceptive signal is transmitted over small diameter A-δ and C-fibers in the dorsal horn, via the dorsal root ganglion.

Second order neurons relay the signal to the thalamus via the spinothalamic tra

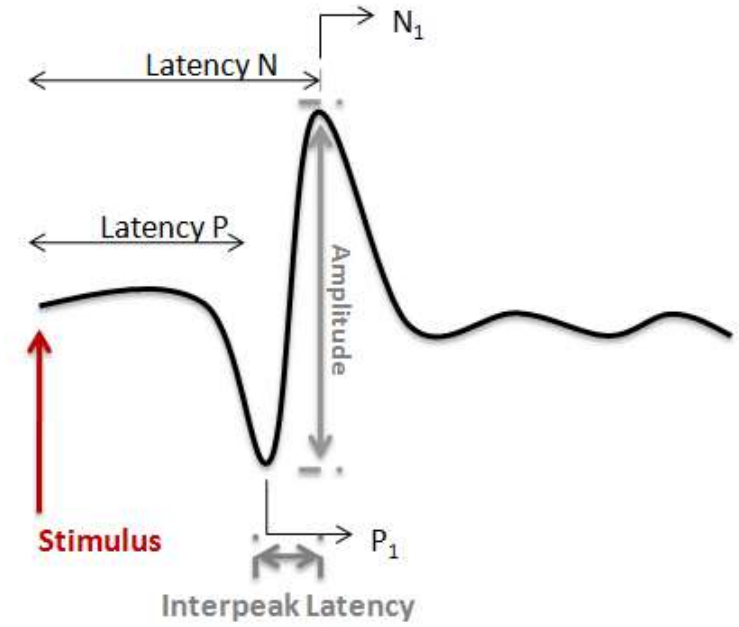
Third order neurons project from the thalamus to the primary sensor cortex
conscious perception of pain occurs.

Grünenthal Award 2011

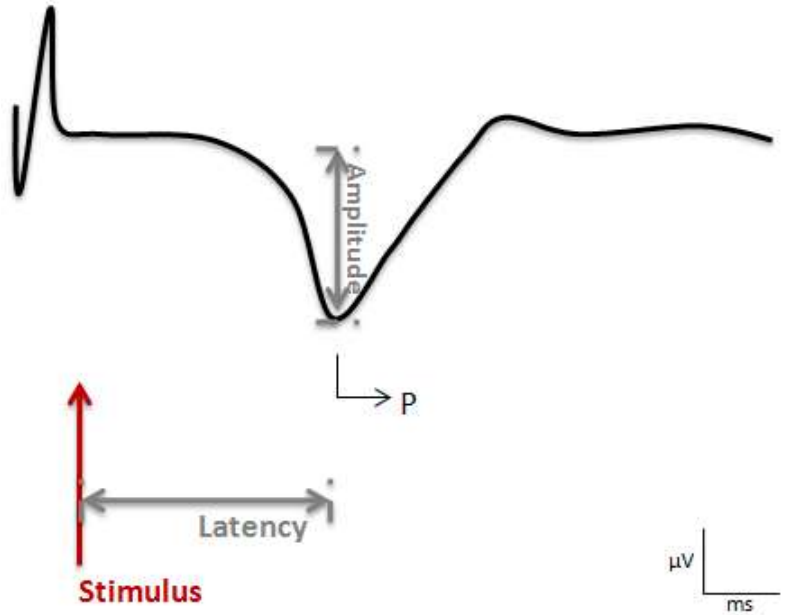


C. Thornton and R. M. Sharpe. Evoked responses in anaesthesia. British Journal of Anaesthesia, 81(5):771781, 1998.
A. Kumar, A. Bhattacharya, and N. Makhija. Evoked potential monitoring in anaesthesia and analgesia. Anaesthesia, 55(3):225241, 2000.

Introduction



Cortical Site



Cervical Site

Clinical Protocol Design

Sensitive (ST), Motor (MT) and Painful Threshold (PT)

Remifentanil Only		Remifentanil and Propofol		Propofol and Remifentanil	
Propofol Ce (μg/ml)	Remifentanil Ce (ng/ml)	Propofol Ce (μg/ml)	Remifentanil Ce (ng/ml)	Propofol Ce (μg/ml)	Remifentanil Ce (ng/ml)
0	0	0	1	1.2	1
0	1	1.2	1	1.2	2
0	2	2	1	1.2	2.5
0	2.5	2.5	1	1.2	3
Remifentanil 0.5 ng/ml increasing steps		Propofol 0.5 μg/ml increasing steps		Remifentanil 0.5 ng/ml increasing steps	

STOP increasing drugs' concentrations when BP or HR decrease below 20% baseline values, by clinical indication, or on OAAS=2 (loss of response to verbal command)

A –

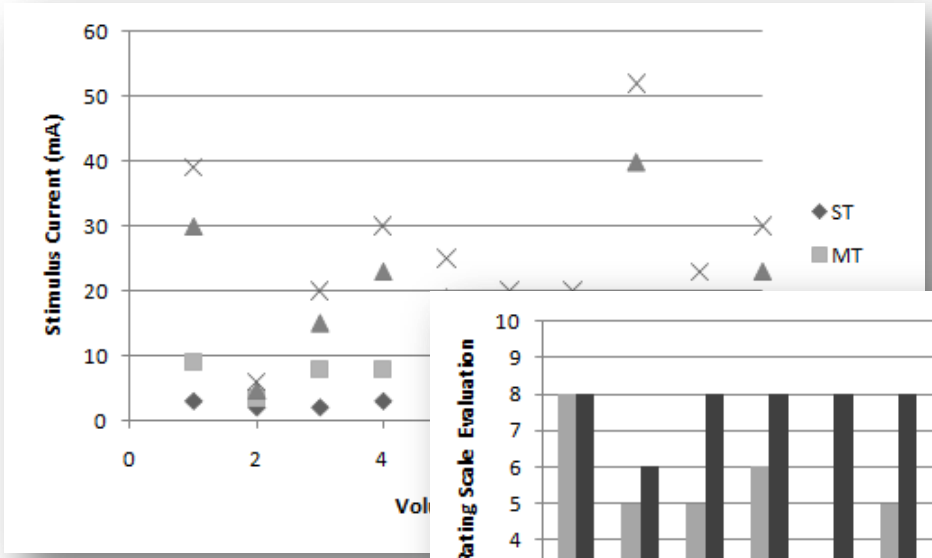
C –

electrodes

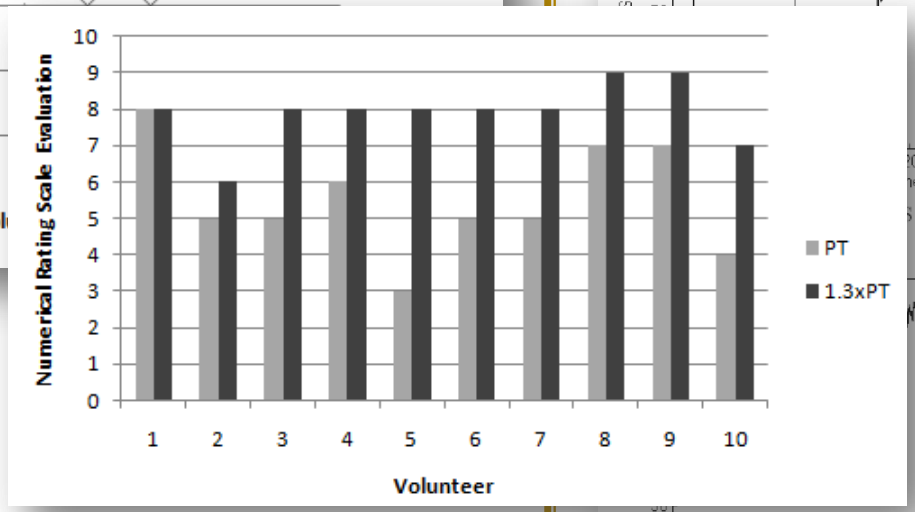
Institutional Approval

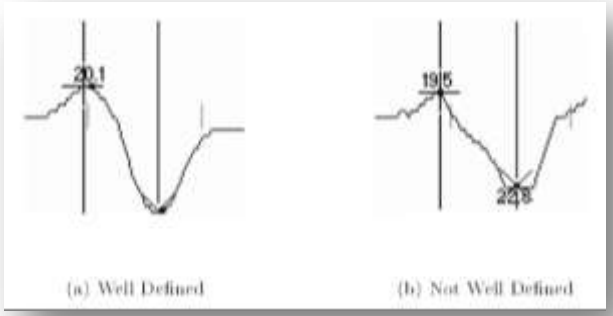
Financial Department Appreciation

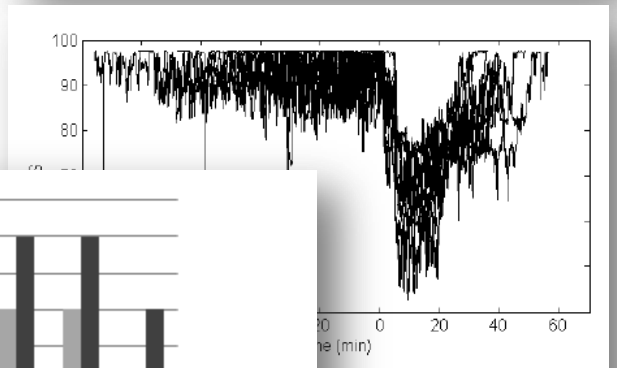
Results and Discussion

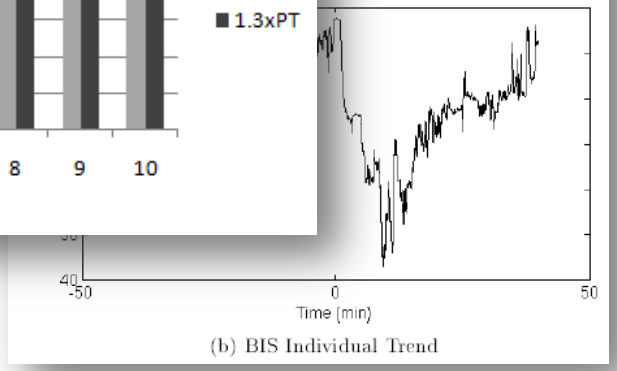


ST – Sensitive Threshold
MT – Motor Threshold
PT – Painful Threshold

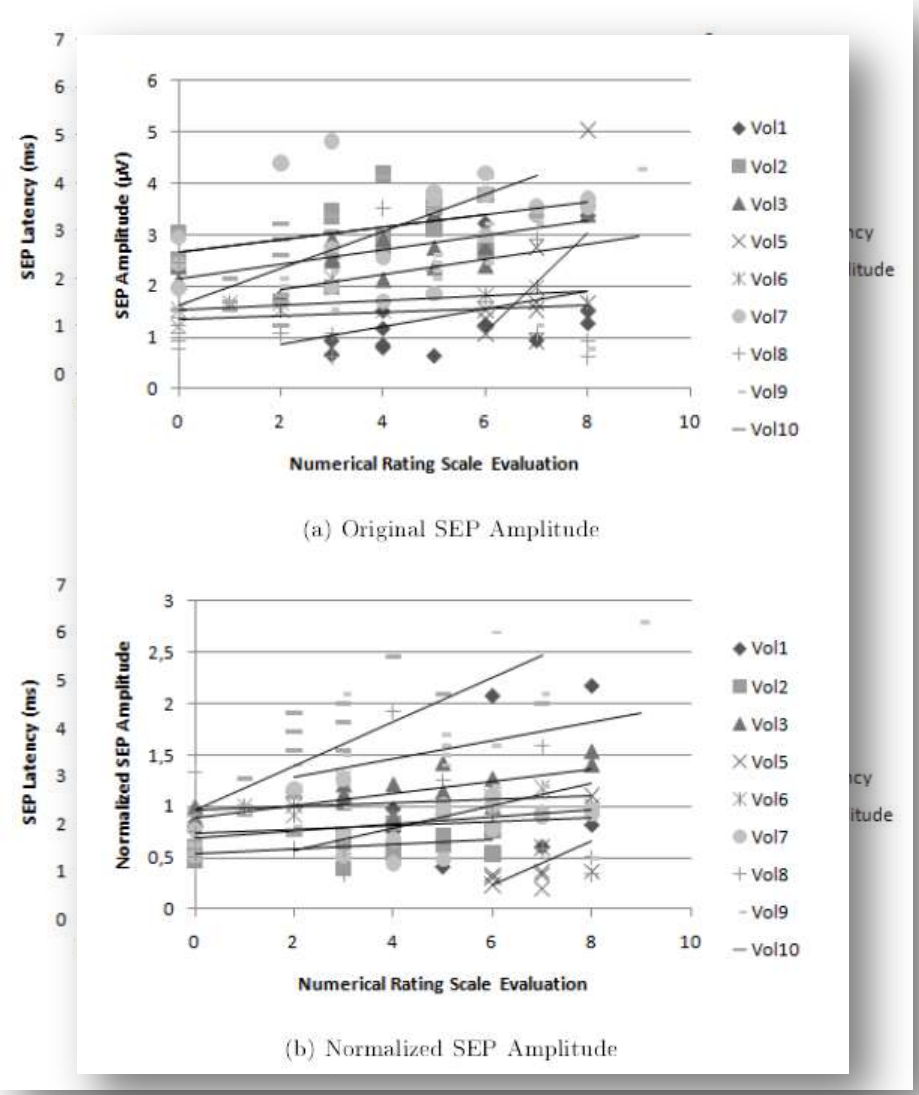








Results and Discussion



Baseline Normalization

$$SEPAmp_{Norm} = \frac{SEPAmp}{SEPAmp_0}$$

where $SEPAmp$ is the observed SEP amplitude and $SEPAmp_0$ is the SEP amplitude for the PT stimulus without drugs in the system.

$$R = \frac{SEPAmp}{SEPLat}$$

where $SEPLat$ is the SEP latency, and

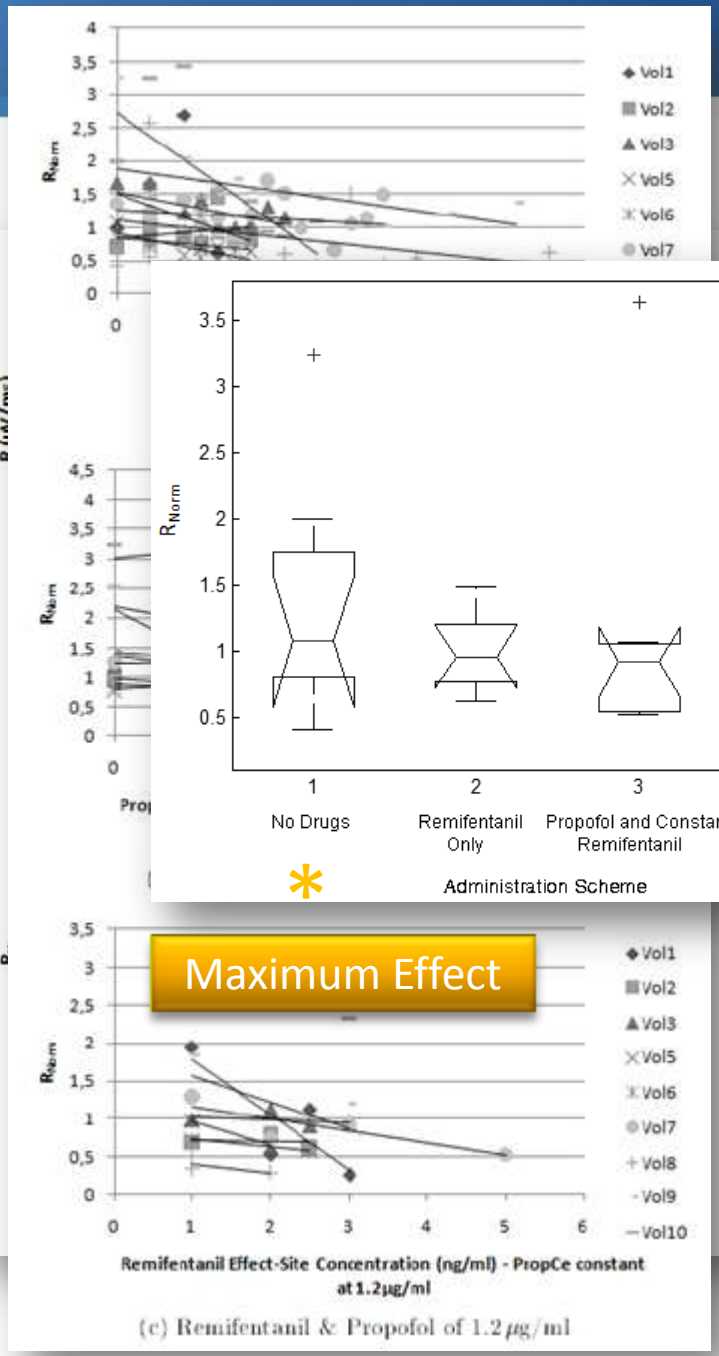
$$R_{Norm} = \frac{SEPAmp_{Norm}}{SEPLat_{Norm}}$$

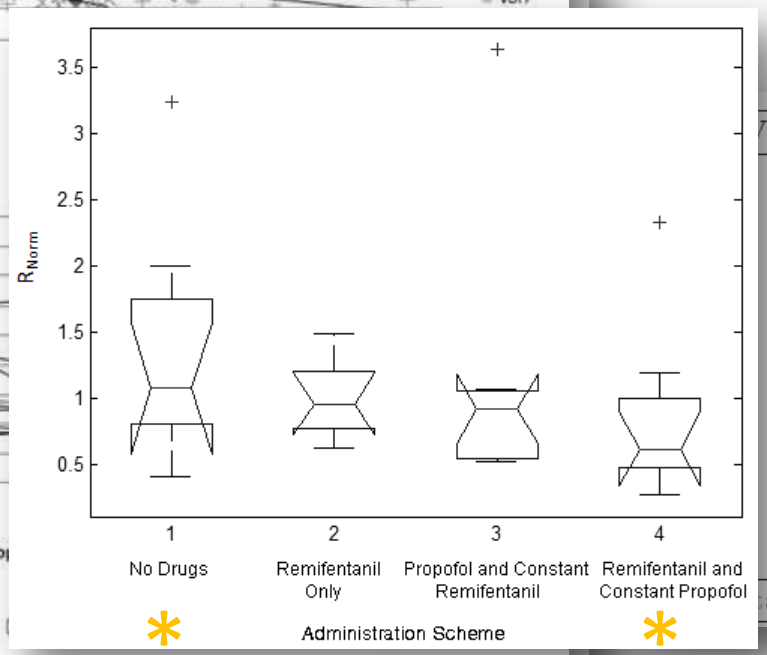
where $SEPLat_{Norm}$ is the normalized latency by the observed latency to the PT prior drug administration ($SEPLat_0$)

$$SEPLat_{Norm} = \frac{SEPLat}{SEPLat_0}$$

Painful Threshold as Reference

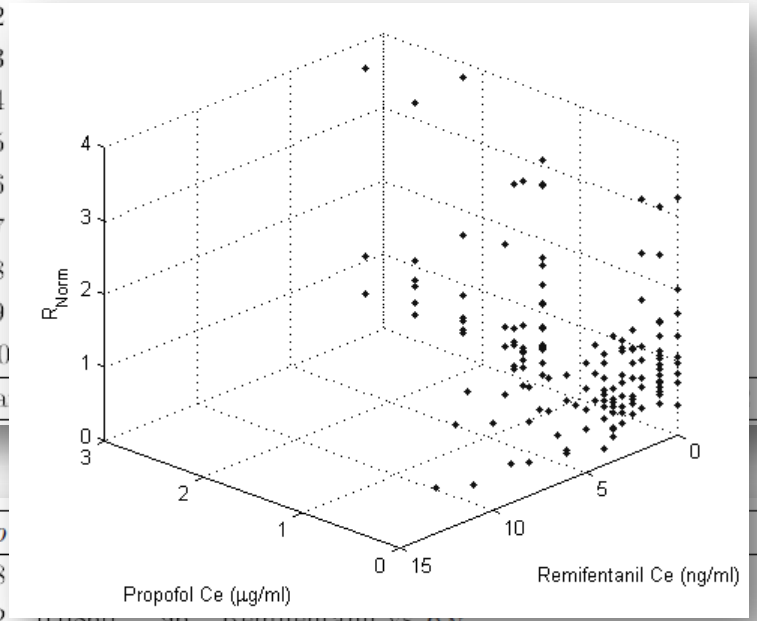
EVOKED POTENTIALS:





Maximum Effect

Volunteer	NRS vs R_{Norm}	N	Remifentanil vs R_{Norm}	N
1	0,4564	14	-0,6347	8
2				8
3				10
4				
5				8
6				8
7				16
8				15
9				13
10				10



Pharmacodynamic Model

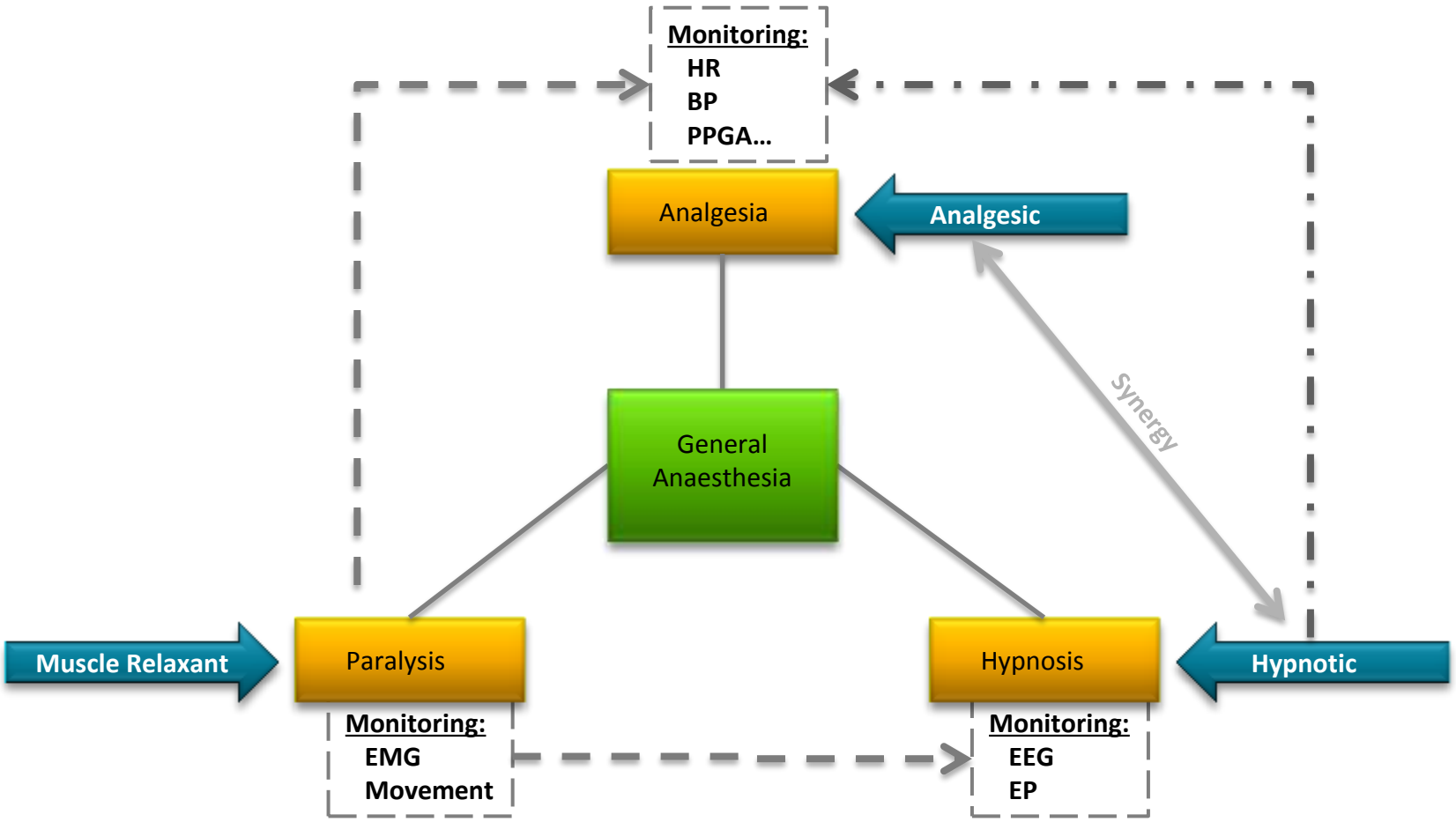
ρ		
0,1678		
-0,1762		
-0,1251		1.0 ng/ml vs R_{Norm}
-0,0231		1.2 µg/ml vs R_{Norm}

On Nociception Control

Thinking beyond the measurements

ON NOCICEPTION CONTROL:

General Anaesthesia Triad Control



A Parallel Problem to Nociception Control

- Hypnosis Control
  - Validated consciousness monitors
  - Pharmacodynamic models
  - Fast acting/excreted hypnotic drug

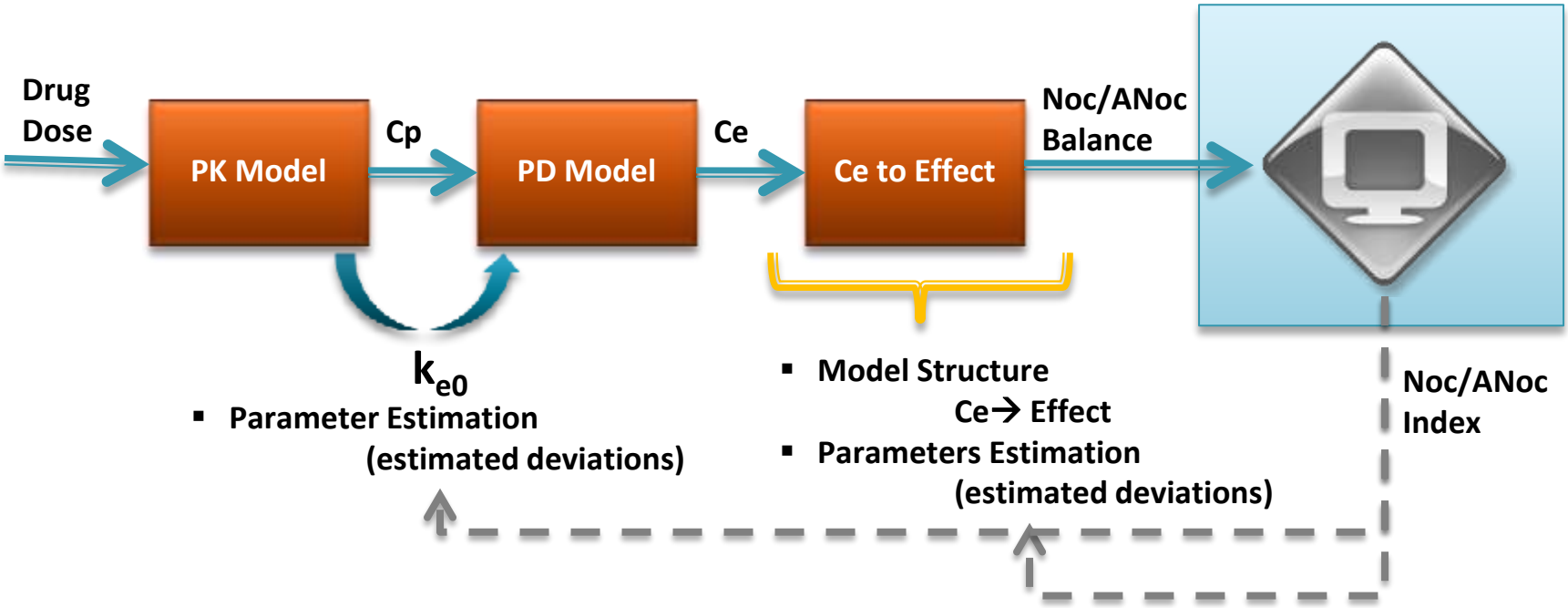
$$\begin{bmatrix} \dot{m}_1(t) \\ \dot{m}_2(t) \\ \dot{m}_3(t) \\ \dot{Ce}(t) \end{bmatrix} = \begin{bmatrix} -k_{12}-k_{13}-k_{10} & k_{21} & k_{31} & 0 \\ k_{12} & -k_{21} & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 \\ \frac{k_{e0}}{V_1} & 0 & 0 & -k_{e0} \end{bmatrix} \begin{bmatrix} m_1(t) \\ m_2(t) \\ m_3(t) \\ Ce(t) \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} r(t)$$

$$E(t) = E_0 \left[1 - \frac{Ce(t)^\gamma}{Ce(t)^\gamma + EC_{50}^\gamma} \right]$$

	State Entropy	
Hill Equation	Average	Standard-Deviation
E_0	86.89	1.5
EC_{50} $(\mu g/ml)$	1.9	1.5
γ	4.5	3
Pharmacodynamics (Ellerkmann et al)		
k_{e0} (min^{-1})	0.48	0.37

R. K. Ellerkmann, M. Soehle, T. M. Alves, V. M. Liermann, I. Wenningmann, H. Roepcke, S. Kreuer, A. Hoeft, and J. Bruhn. Spectral entropy and bispectral index as measures of the electroencephalographic eects of propofol. Anesthesia and Analgesia, 102(5):1456-1462, 2006.

Nociception Control



Conclusions

Conclusions

- Why is nociception monitoring important?
  - Patient wellbeing
  - Unable to communicate patients
  - Post-operative persistent/chronic pain
  - Long-term effects of anesthetics
  - Titrate the anesthesia triad
  - Automatic control of anesthesia

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- Instituto de Telecomunicações

Thank you

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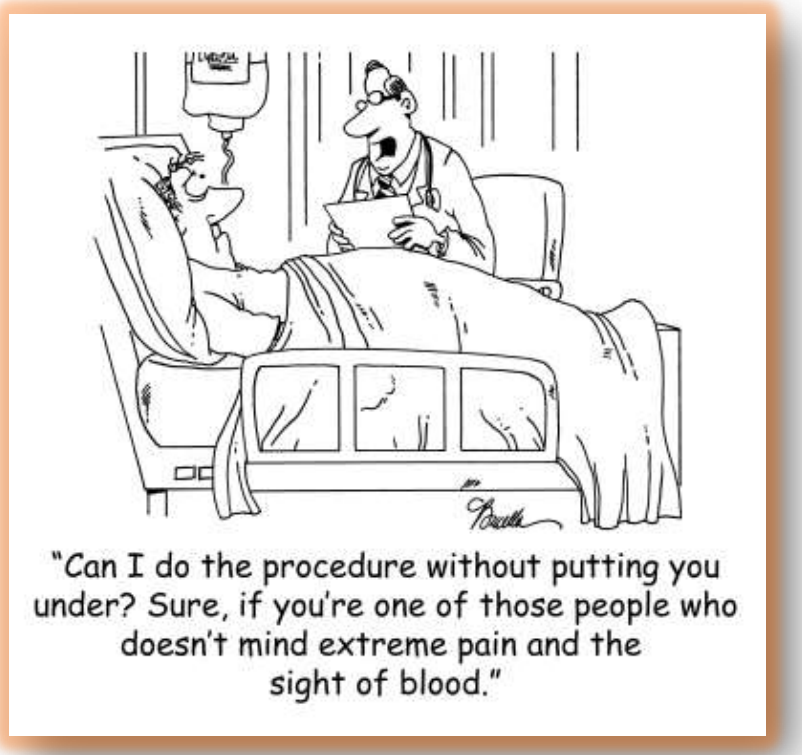

"Can I do the procedure without putting you under? Sure, if you're one of those people who doesn't mind extreme pain and the sight of blood."