THE UNIVERSITY OF BRITISH COLUMBIA
*Department of Electrical & Computer Engineering*
*Division of Control Systems in Pharmacology & Therapeutics*

# Embedding Aerospace Control Knowledge in Automatic Drug Delivery

**M. Huzmezan**

# Division of Control Systems in Pharmacology and Therapeutics

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## Anesthesia
## B.C. Children's Hospital

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# On going research projects

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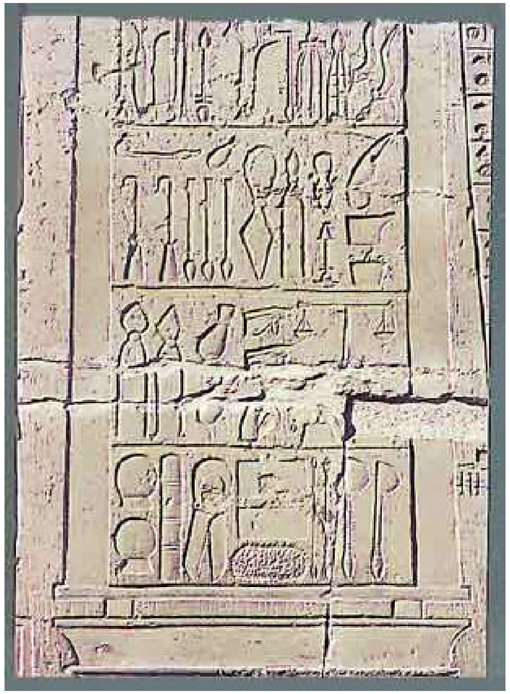
# CLINICAL ANESTHESIA

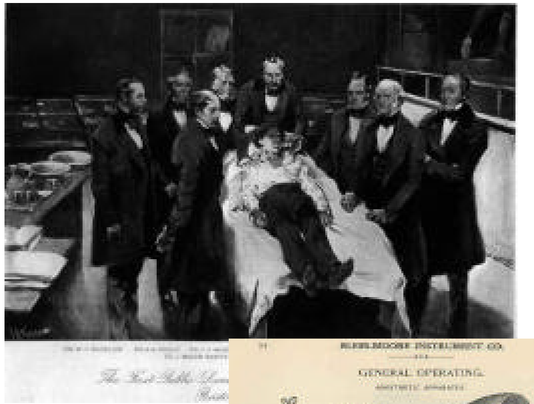
## PERSPECTIVES FOR CONTROL

# Anesthesia – A Historical Perspective



Ca. 300-80 b.c.

Opioid Sponge



Ca. 1846

Ether, Opium

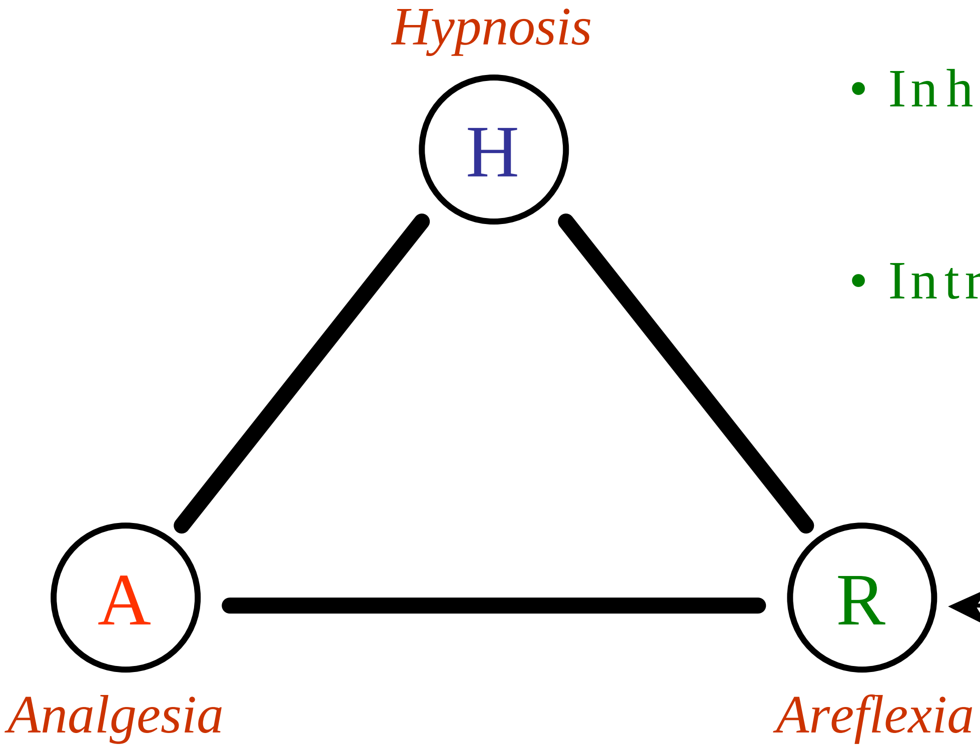
A hastily rigged apparatus

Ca. 1900

Chloroform, Morphine

Anesthetic apparatus

# Modern Practice: Balanced Anesthesia




**Anesthetics:**

- Inhalation
  - Ether, Nitrous Oxide
  - Isoflurane, Sevoflurane, Desflurane,etc…
- Intravenous
  - Barbiturates (thiopental)
  - Benzodiazepines
  - Isopropylphenol (**propofol**)

**NMBs:**
- Curare
- Succinylcholine

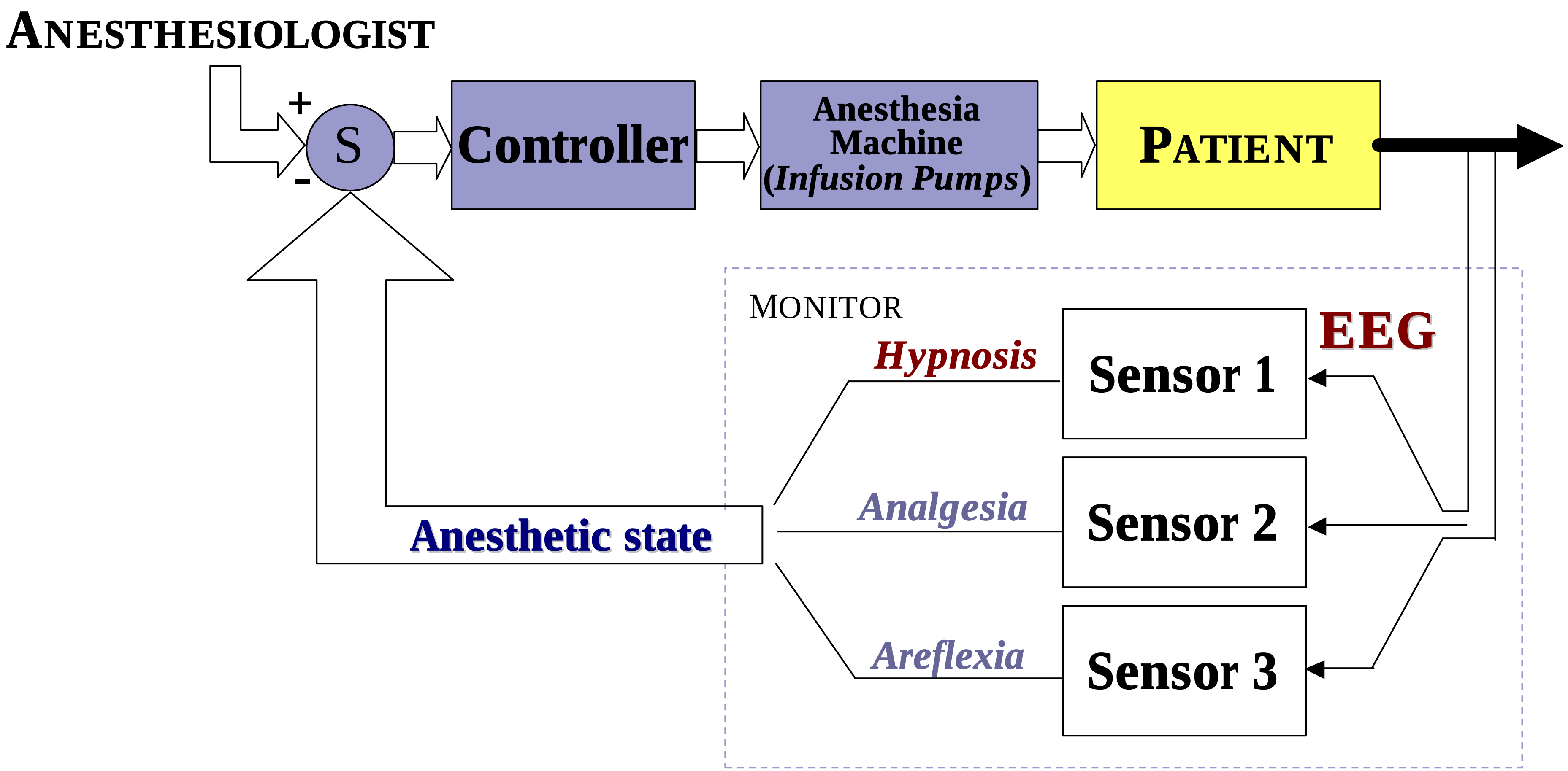
**Opioids:**
- Morphine
- Fentanyl, **Remifentanil**
- Naloxone

# MODERN PRACTICE: ANESTHESIA TIME COURSE

- Induction

  Secure patient's airway (endotracheal tube, LMA)
  - Premedicant (benzodiazepine and opioids)
  - Large bolus of anesthetic (propofol)
  - Muscle relaxant
- Maintenance
  - Constant background level of inhalational anesthetic
  - Intravenous infusion (propofol)
  - Boluses of anesthetic/opioid
- Emergence
  - All anesthetic are off
  - Bolus of opioid for post-operative pain

# Context



ANESTHESIOLOGIST
+
S
-
Controller
Anesthesia Machine (Infusion Pumps)
PATIENT
MONITOR
Hypnosis
Sensor 1
EEG
Analgesia
Sensor 2
Areflexia
Sensor 3
Anesthetic state

# TOWARDS AN ANESTHESIA 'AUTOPILOT'

- **Analogies:**

  - –Maintaining a level of Hypnosis/Analgesia = Maintaining a trajectory
  - –Induction, Maintenance, Emergence = Take off, Cruising, Landing
  - –Surgery stimuli= Gusts, Wind shear
  - –Damping oscillatory responses using drugs = Stability Augmentation
  - –Multiple drugs = Elevator, Ailerons, Rudder, Canards

**The "autopilot' acts at the regulatory level reducing the pilot's workload**

- ✓ Anesthetists, like pilots, have the final authority
- ✓ Anesthetists, like pilots, define the setpoints
- ✓ Human intervention is expected during emergency

# TOWARDS AN ANESTHESIA 'AUTOPILOT'

- Significant variability and uncertainty
- Lack of first principles models
- Only few states are measurable
- Partly unknown state parameters are defining the system behavior
- Highly coupled systems

- Relatively reduced variability and uncertainty
- Modeled using first principles
- The system behavior is given by known state parameters
- Most states are measurable
- Slightly coupled systems
- The system has been designed with a control systems' approach in mind

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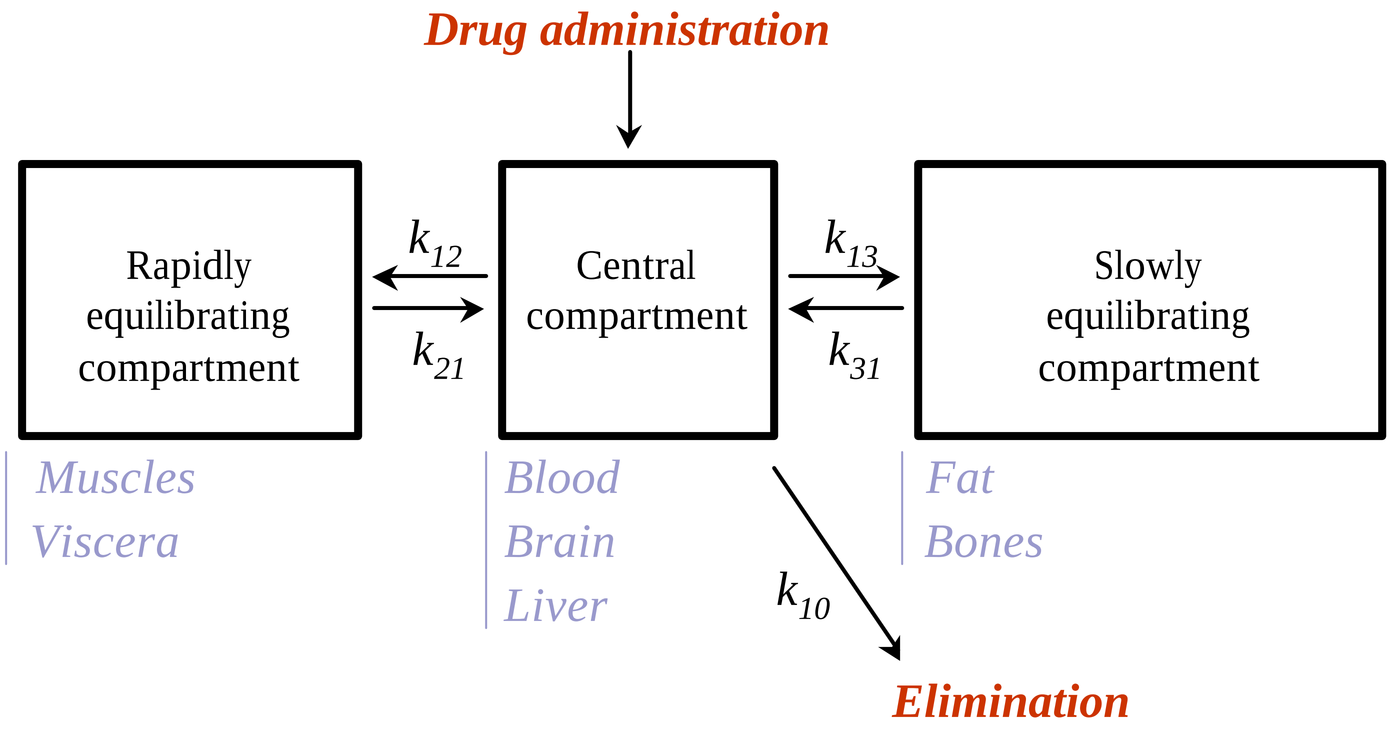
# AUTOMATION IN CLINICAL ANESTHESIA

**S. Bibian (Ph.D.)**




$$[c]_p = \sum_{i=1}^{3} A_i \cdot e^{-\alpha_i \cdot t}$$

$$PK(s) = e^{-t_d \cdot s} \cdot \frac{1}{V_1} \cdot \frac{(s+k_{21}) \cdot (s+k_{31})}{(s+\pi) \cdot (s+\alpha) \cdot (s+\beta)}$$

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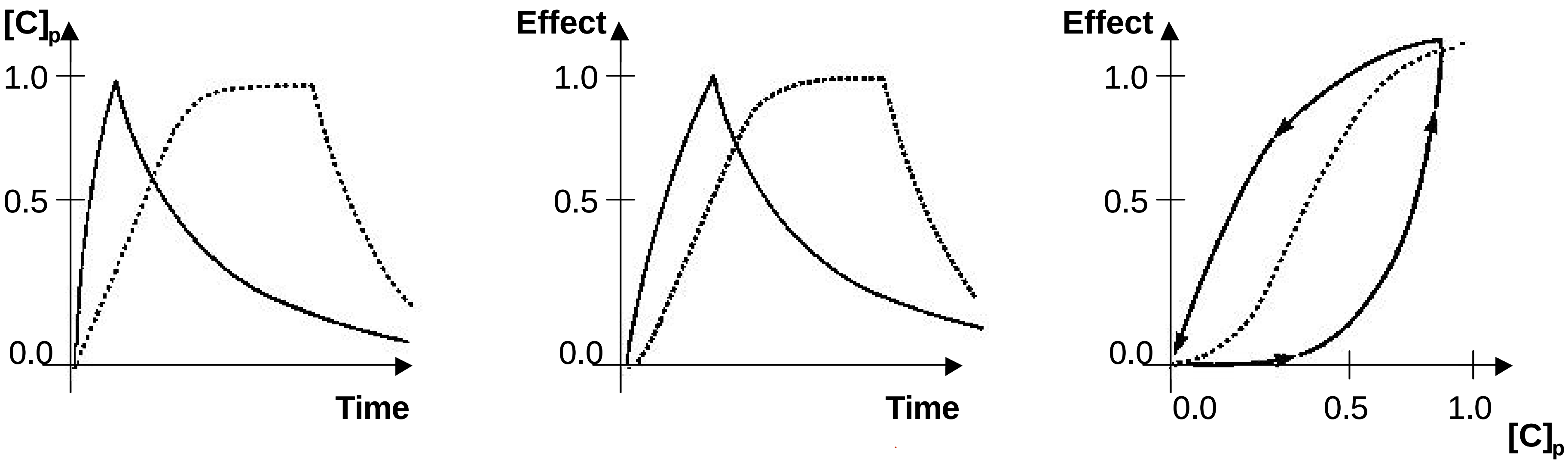
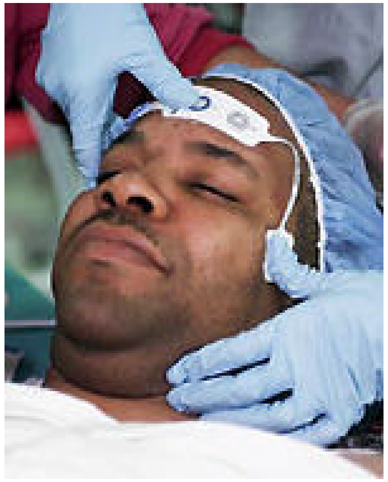
# PHARMACODYNAMICS

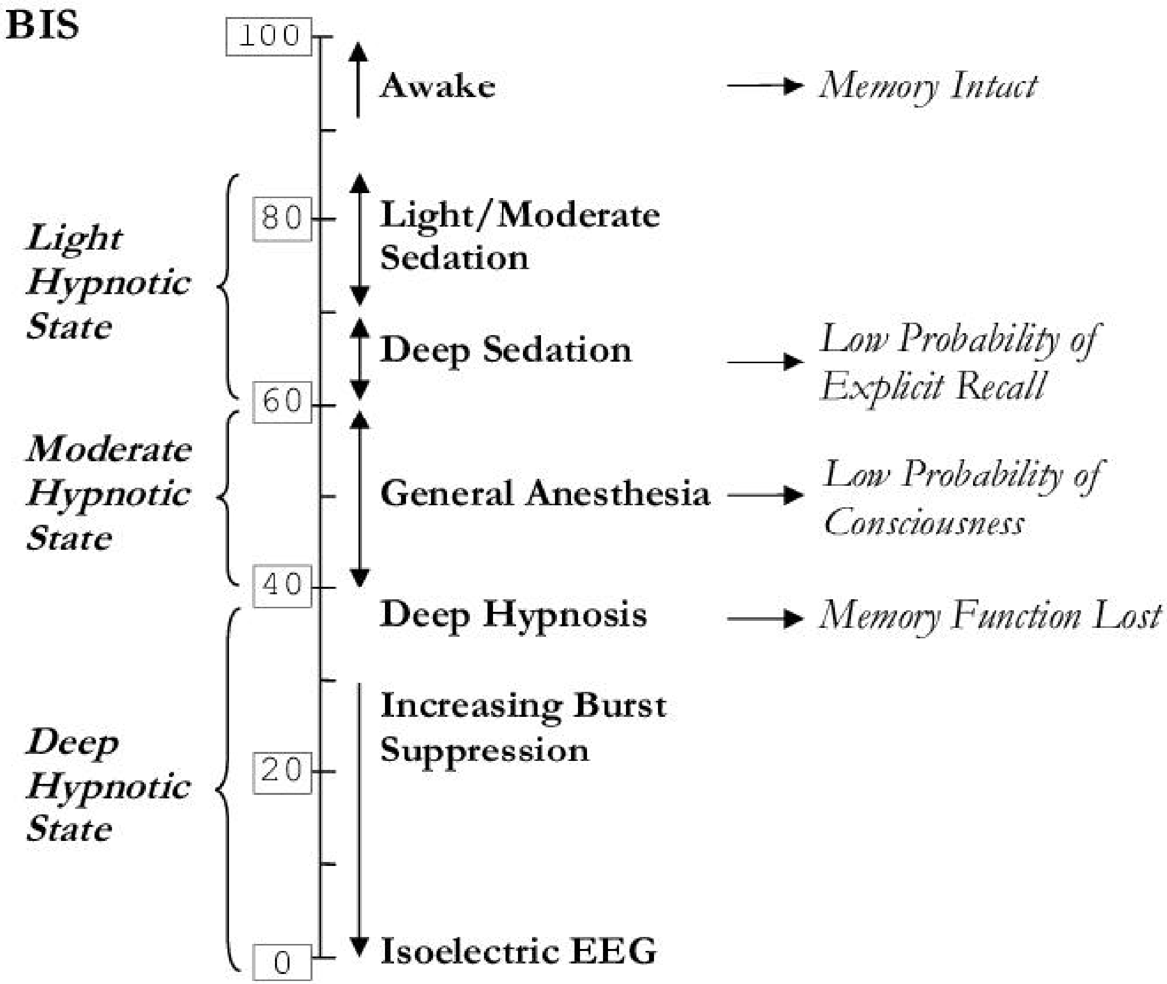
*describe the dose/response relationship*




$$PD_{C_{pn}}(s) = \frac{\widehat{E}(s)}{C_p(s)} = K_e(C_{pn}) \cdot \frac{k_{e0}}{s + k_{e0}}$$

# QUANTIFYING DRUG EFFECT: HYPNOSIS

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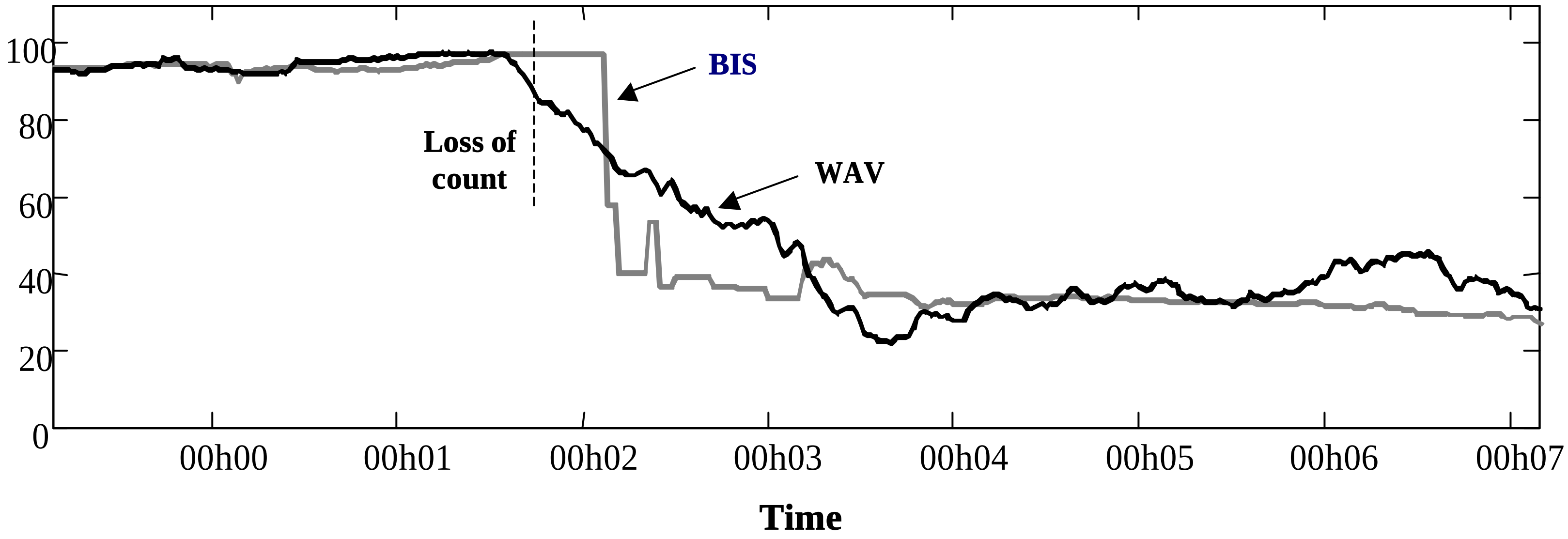
# QUANTIFYING DRUG EFFECT: HYPNOSIS

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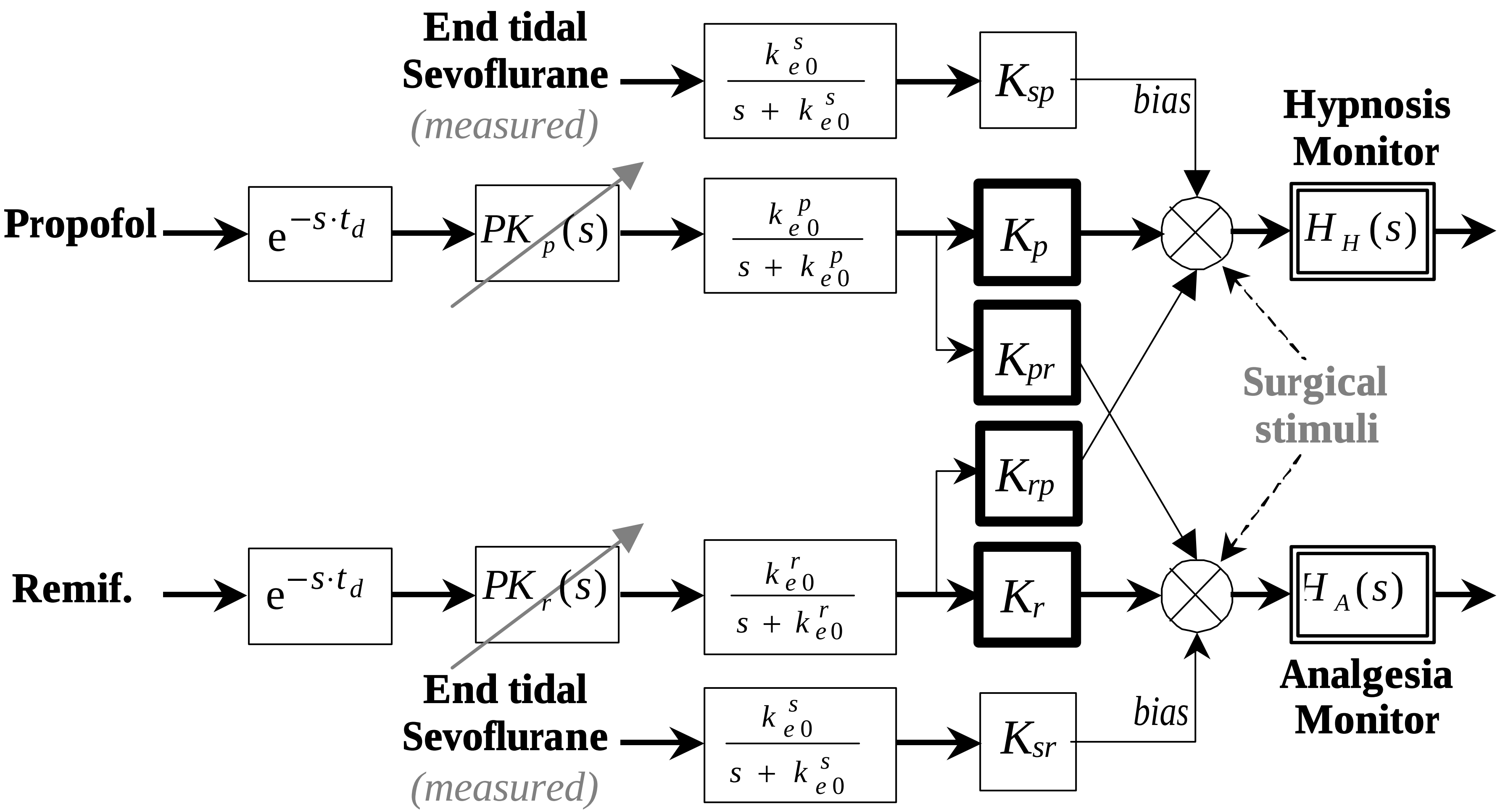
# Quantifying Drug Effect: Analgesia

- End-tidal $CO_2$
  - Measures of opioid effect
  - Easily measured (capnograph)
  - Almost no coupling with propofol
- Heart Rate Variability
  - Measures sinus arrhythmia (early indication of pain)
  - **Needs to be investigated**
- EEG activity
  - Limited therapeutic window

# CONTROL PROBLEM FORMULATION: MIMO

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# Control Endpoints

**Performance specification:**

- **Minimum overshoot and fast settling time**
- **ACCOUNT FOR UNCERTAINTIES**
- **Account for constraints (i.e. maximum plasma concentration, infusion rate, etc…)**
- **Optimization of drug use (minimization of cost functions, plasma concentration, etc…)**

**A glimpse at the solution:**

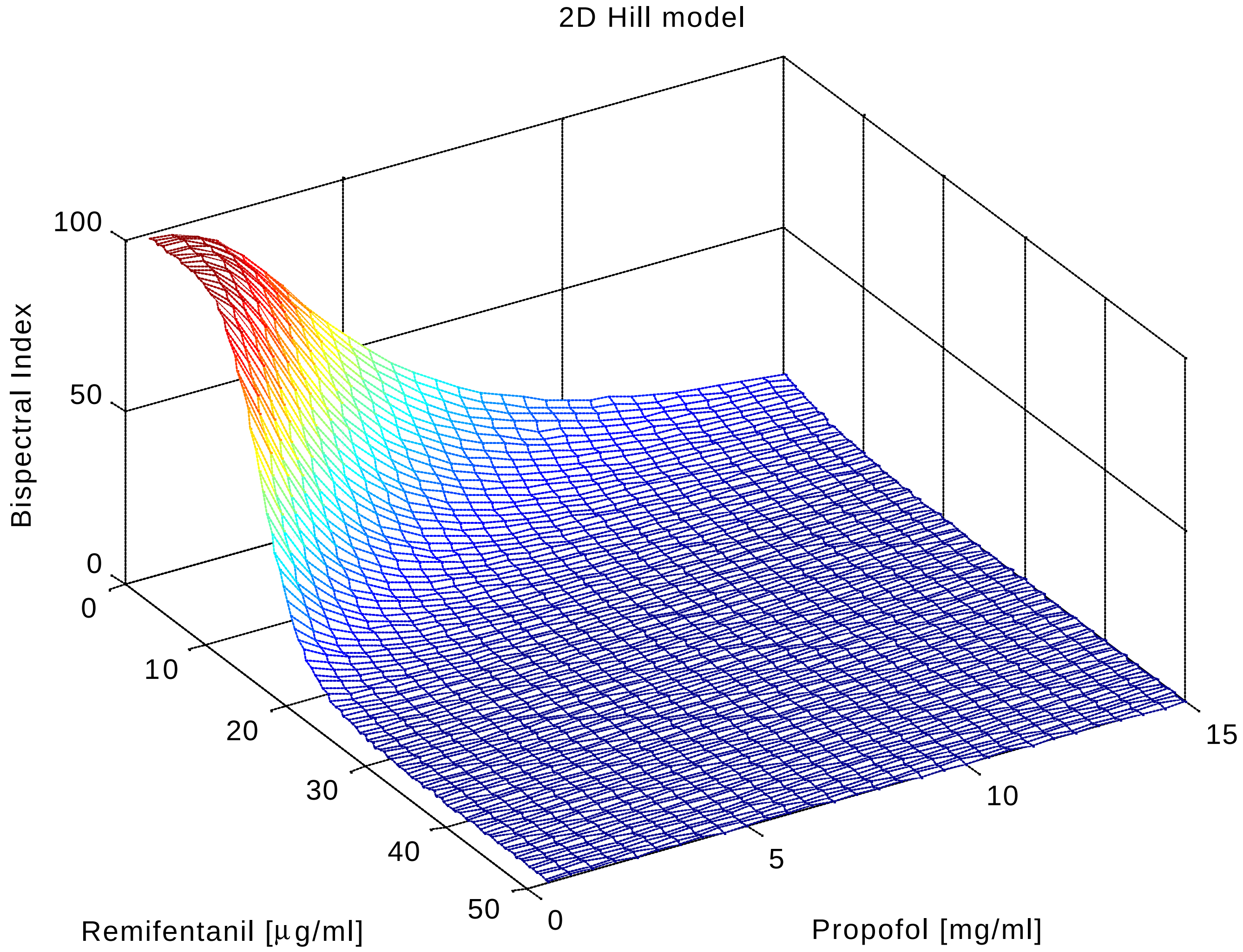
- **Multivariate robust controller** (fast control of Remifentanyl, while sluggish control of Propofol)
- **Model Predictive Control to account for constraints**
- **Slow adaptation of the gains** (the controller may have to choose between few models in a library)

→ How will we integrate all these aspects?

**First step:**

- **IDENTIFICATION!**

# IDENTIFICATION

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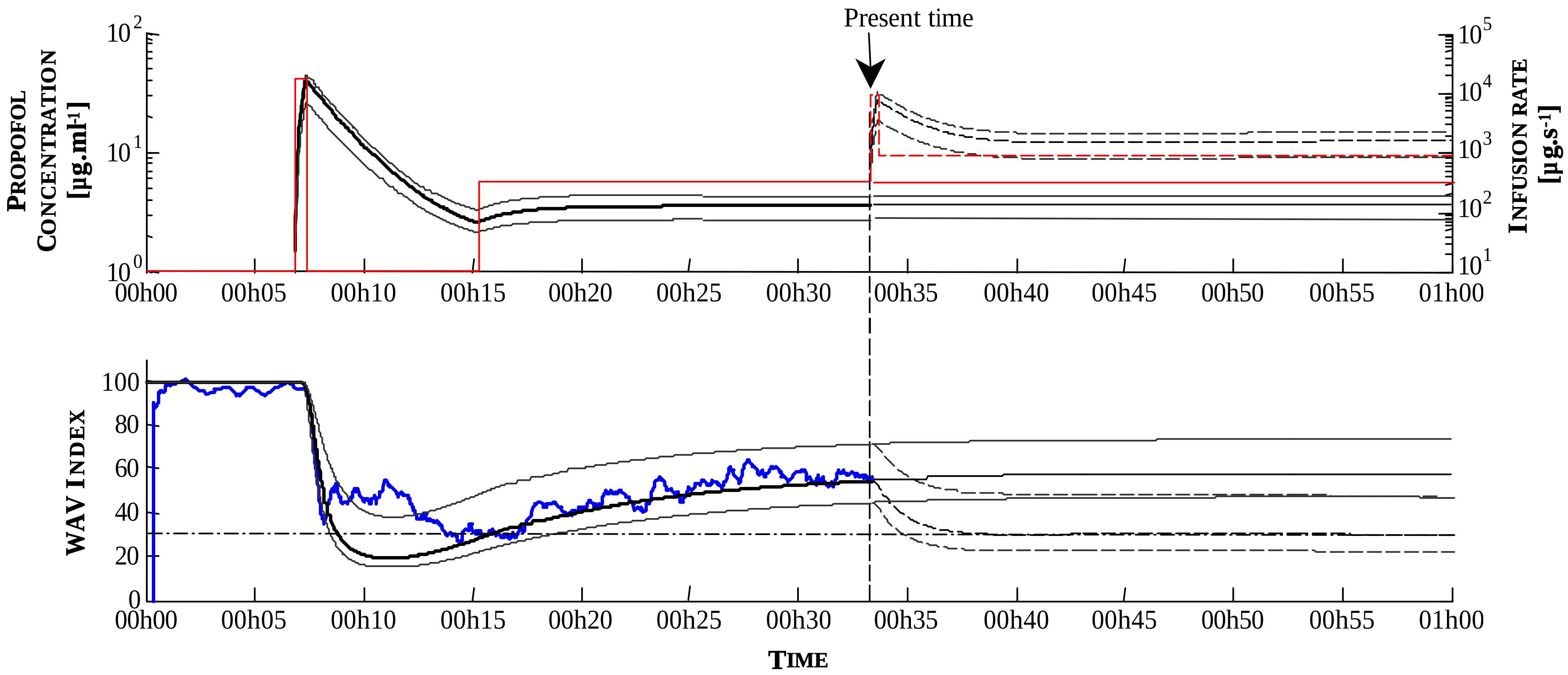
# ADVISORY SYSTEM

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# DISCUSSION

- Optimizes drug usage
- Improves patients' safety and comfort
- Reduces the anesthetist workload

- Anesthetists will need to monitor the controller as well!
- Based on surrogate measures of Hypnosis and Analgesia

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# Monitoring the Anesthetic-Induced Unconsciousness (Hypnosis) Using Wavelet Analysis of Electroencephalogram

**T. Zikov (MA.Sc.)**

# What Are We Trying to Do?

- Aim:
  - To extract a particular feature from the EEG
  - To establish its correlation to the hypnotic state of the patient – **index of hypnosis**
- Tool:
  - Wavelet analysis

# Stationary Wavelet Transform (SWT)

No downsampling:

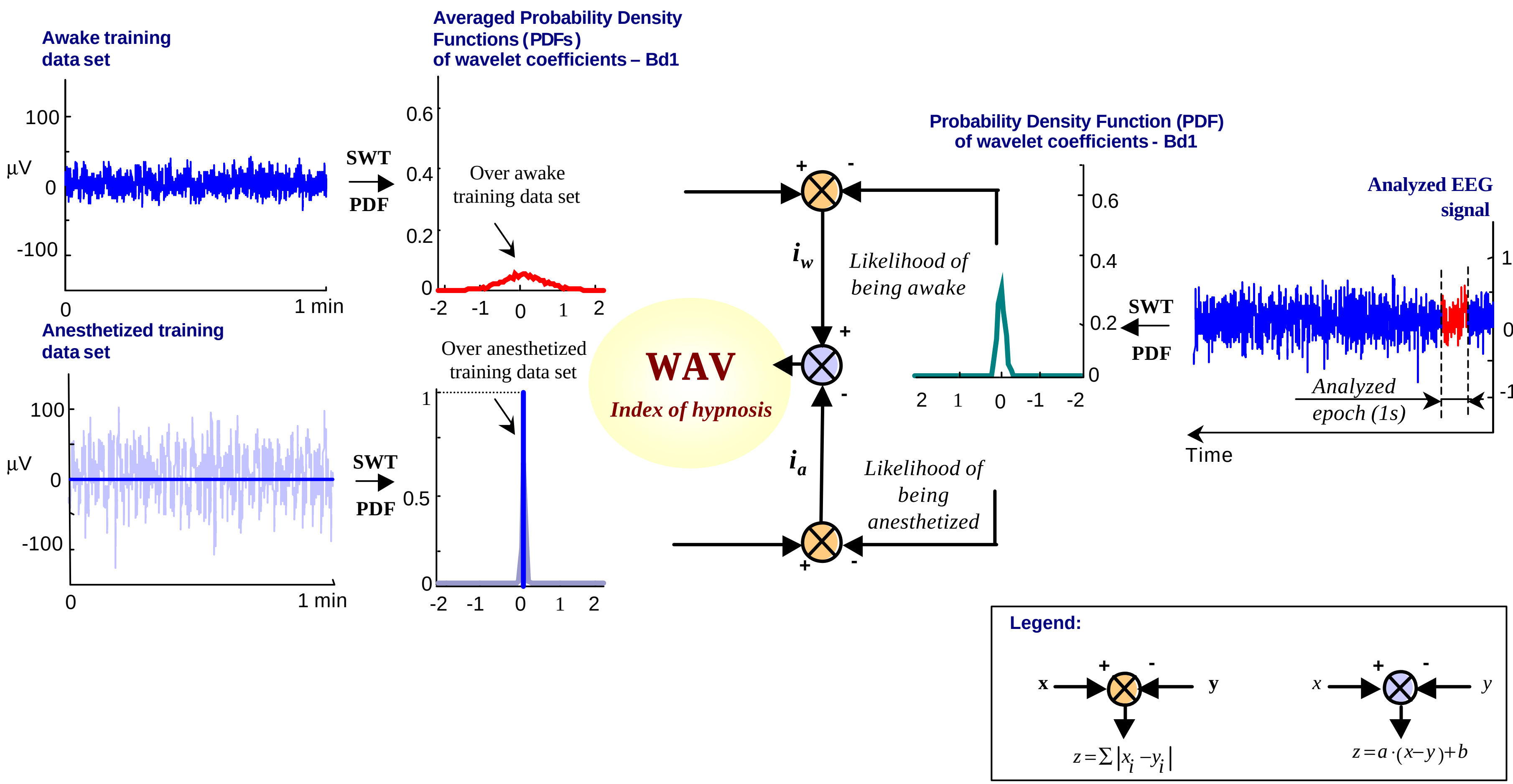
- same # of coefficients in each frequency band equal to the signal length

$\Rightarrow$

- **Better for statistical analysis**
- Better time localization **(for artifact removal)**
- Price: redundancy $\Rightarrow$ increased calculation complexity

- Practically realized by filter banks:
  - The low- and high-pass filters fulfill special requirements
  - Different filters $\Rightarrow$ different wavelet families

# Methodology

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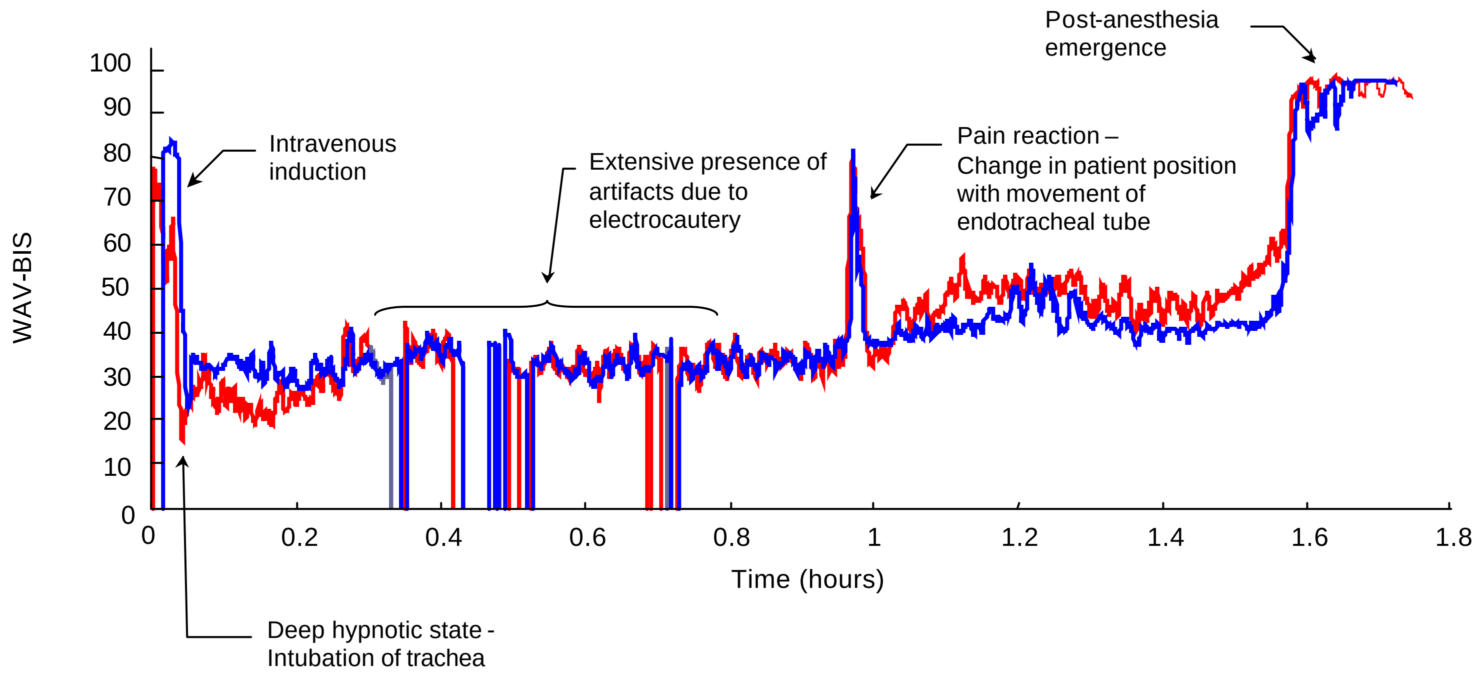
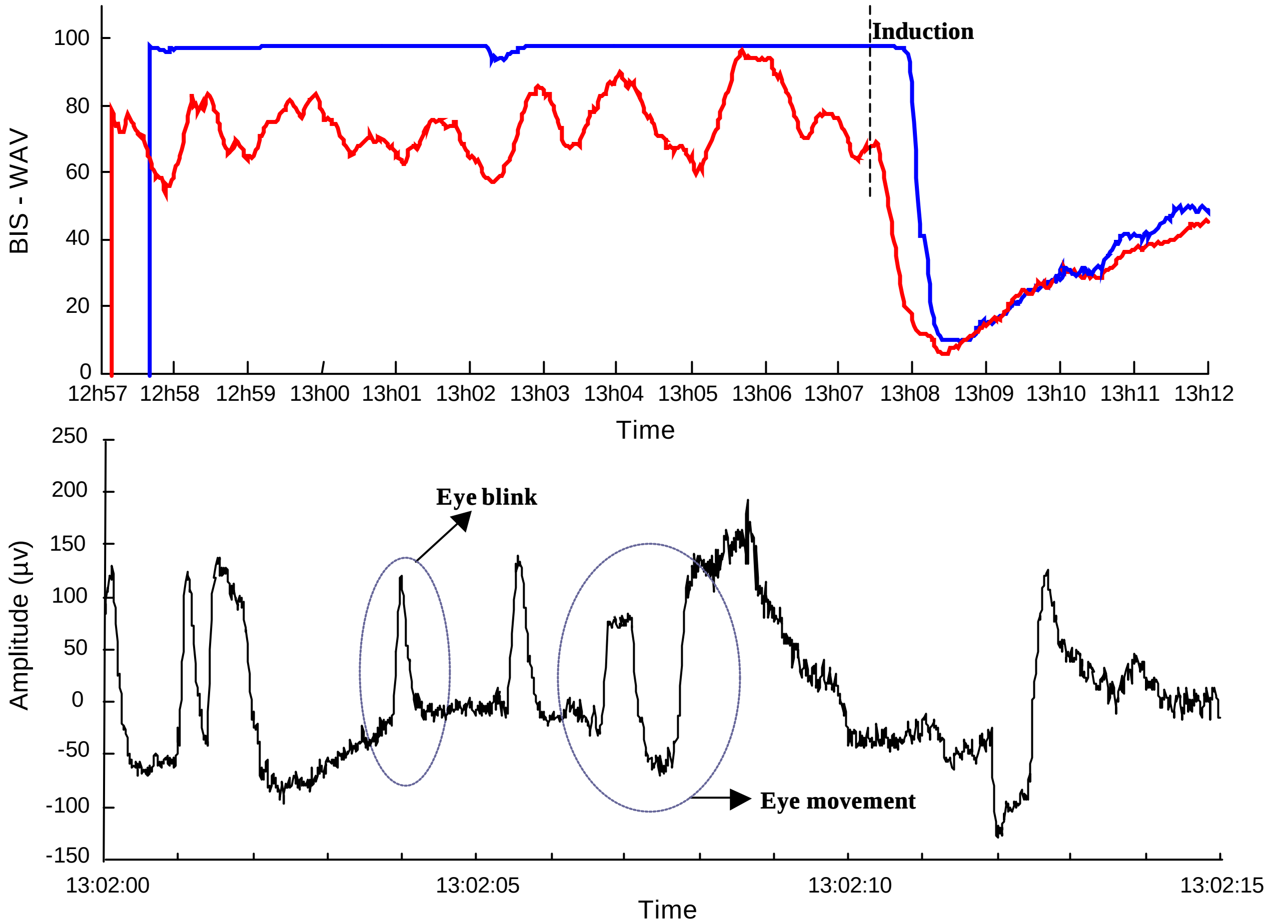
# A Clinical Case



# Influence of Ocular Artifacts (OAs)

## OAs:

- Spikes or square-like waveforms
- Occupy low frequencies
  =16 Hz



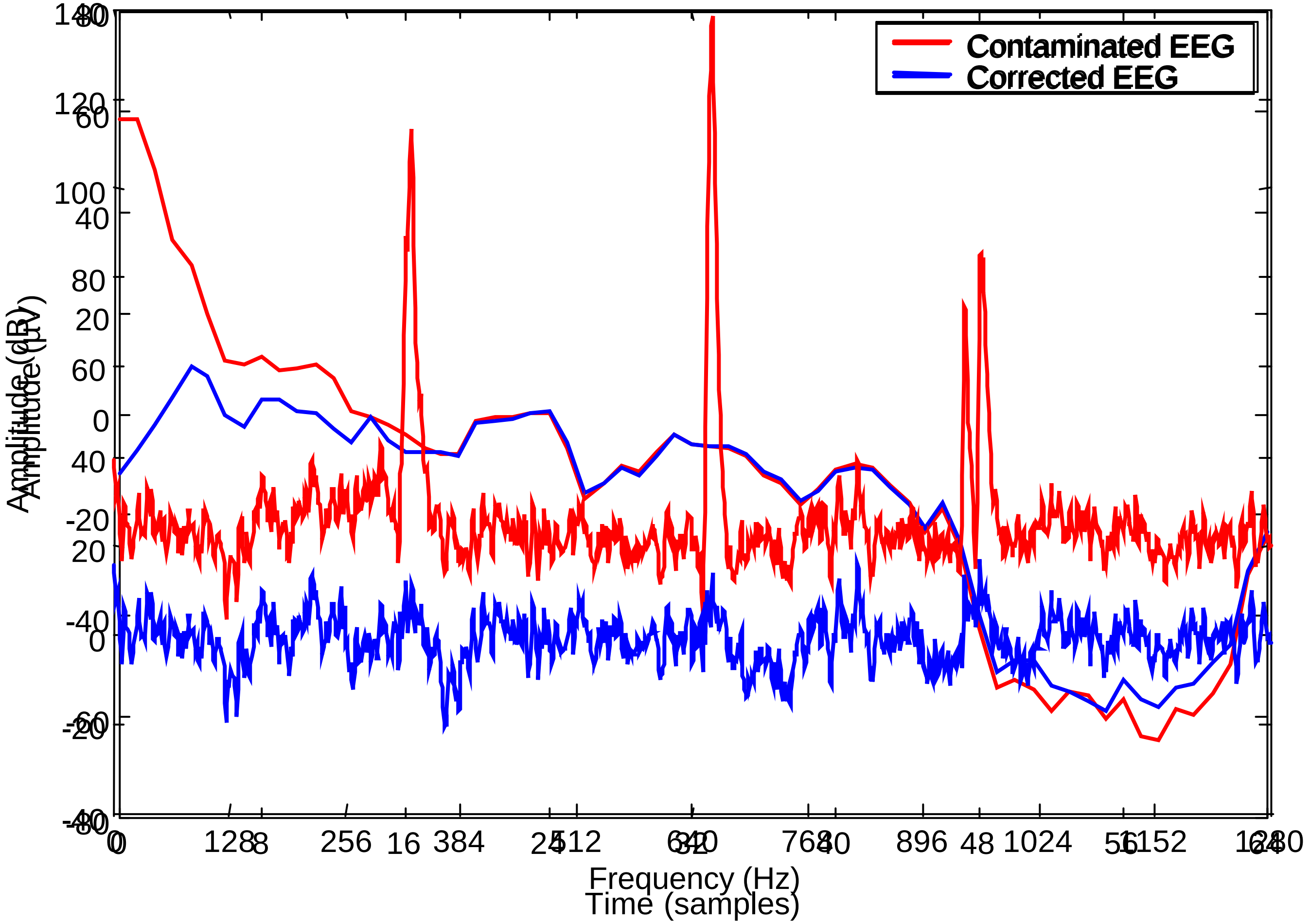
# More details

- **Wavelet filter: Coiflet 3**
  - **Resembles eye blink**

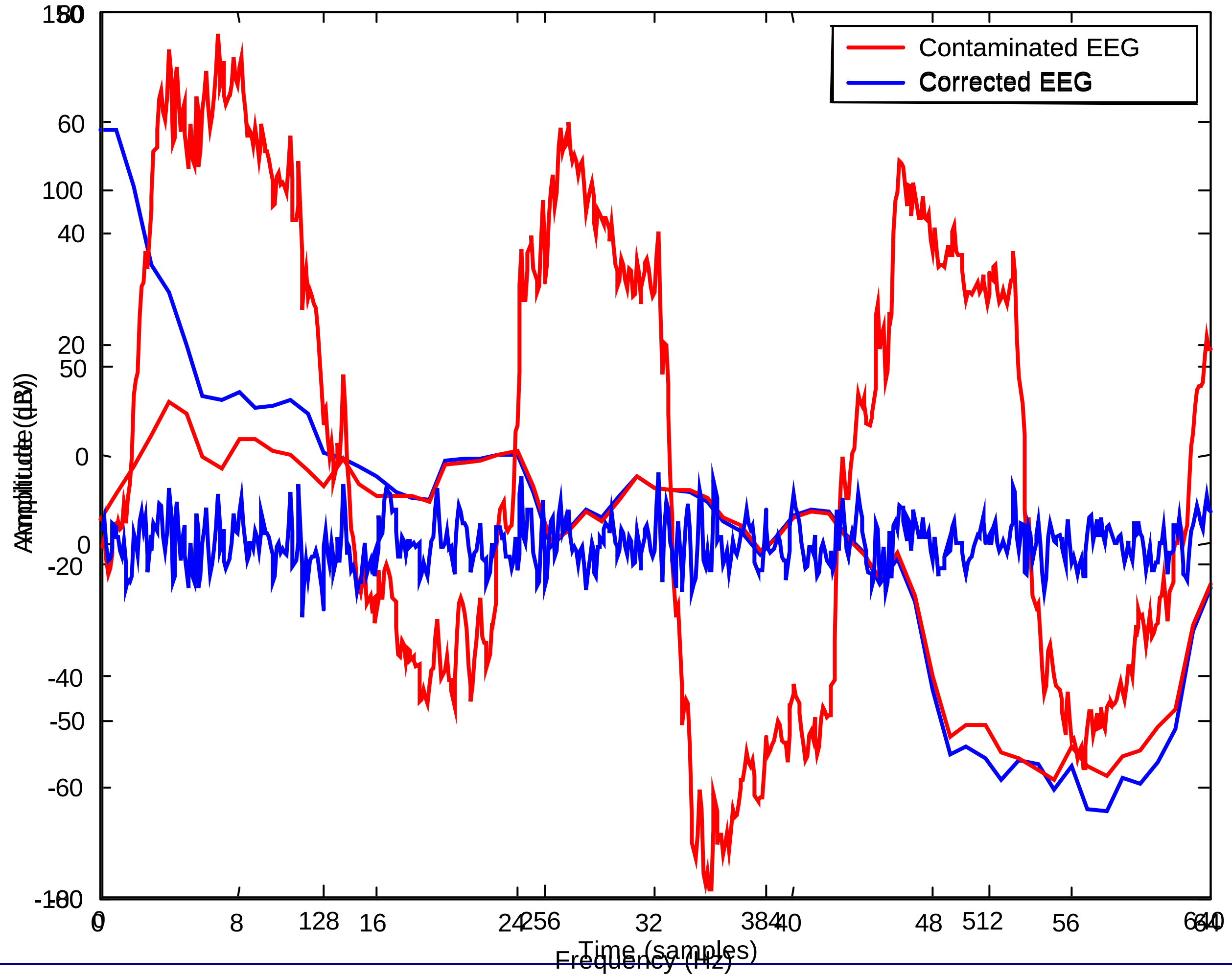
  **Þ artifacts well-localized in wavelet domain**
- **5-level SWT with thresholding up to 16 Hz**
  - **For bands $Ba_5$, $Bd_5$ - $Bd_3$:**

  **Þ ( coefficients = $T_k$) ? 0**
- **Equivalent to estimating the OA based on large coefficients, and then subtracting it from the corrupted EEG epoch.**

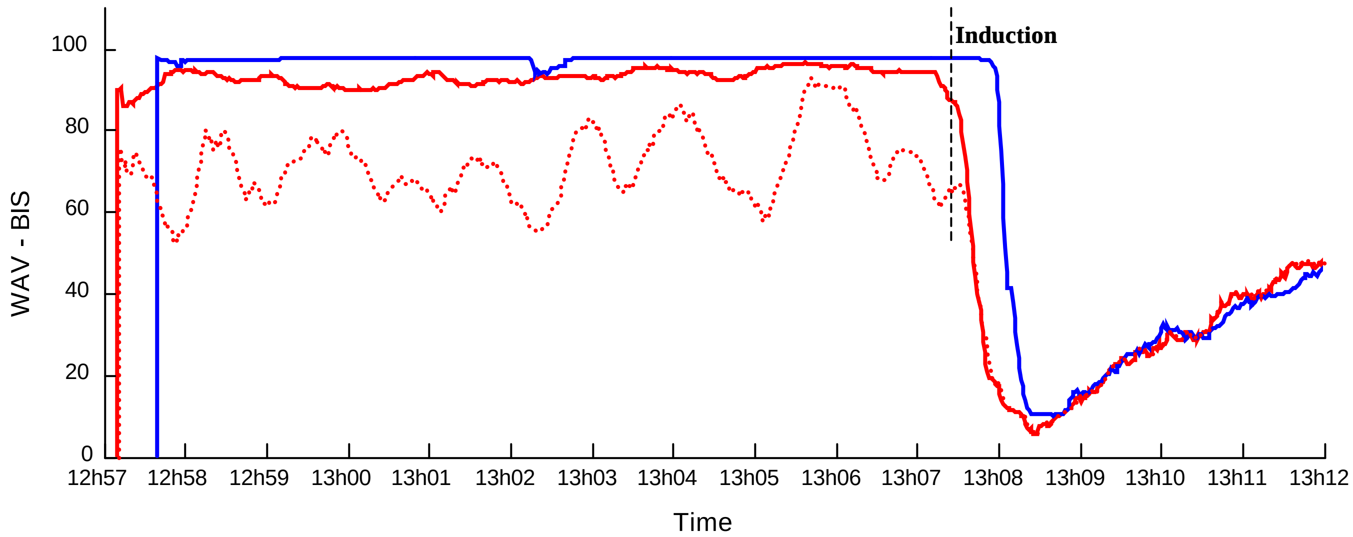
# Results: Slow Blinks (10 s)



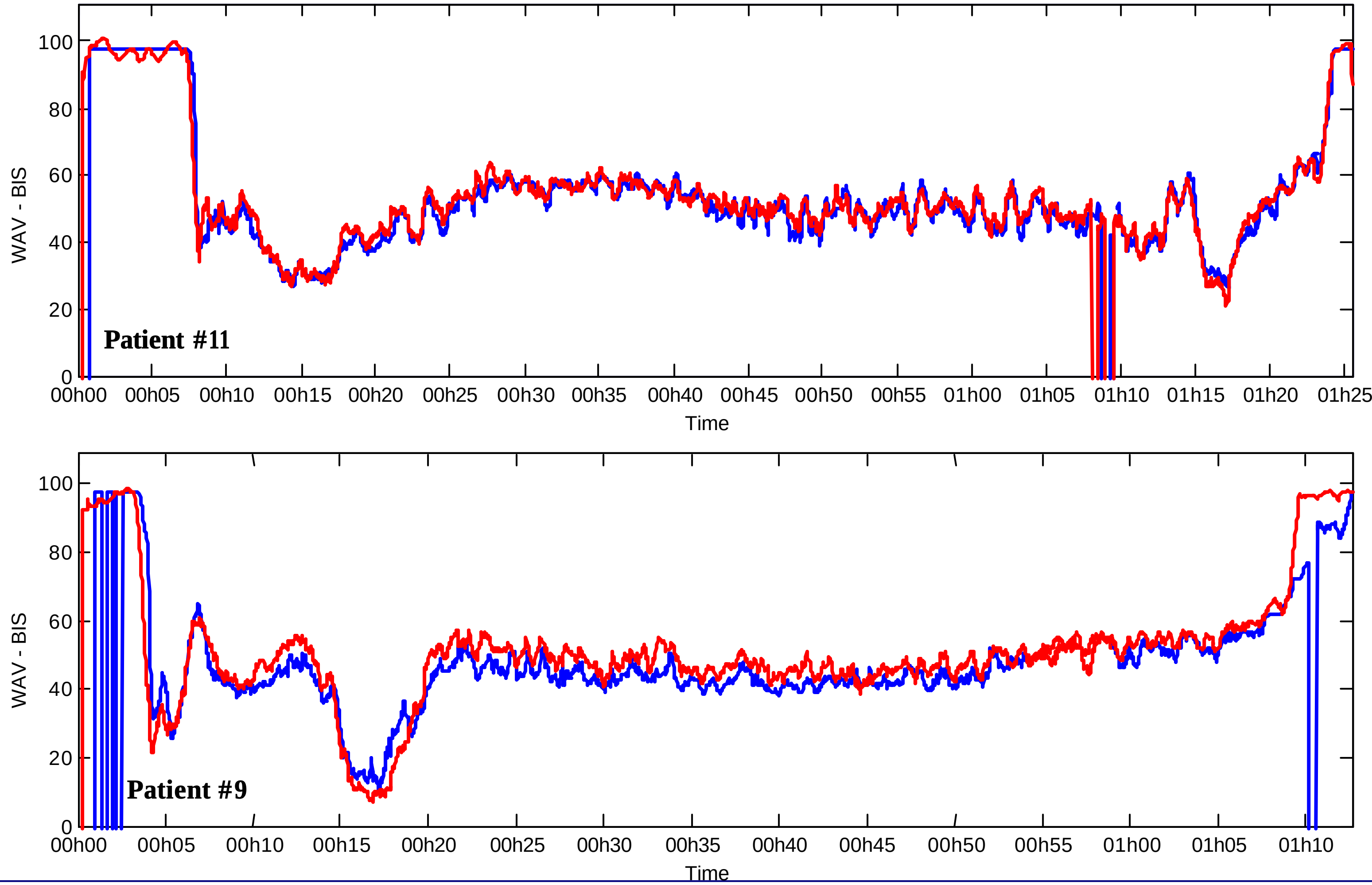
# Results: Vertical Eye Movements (5 s)



# De-noised WAV Index



# Time Courses: WAV Index and BIS

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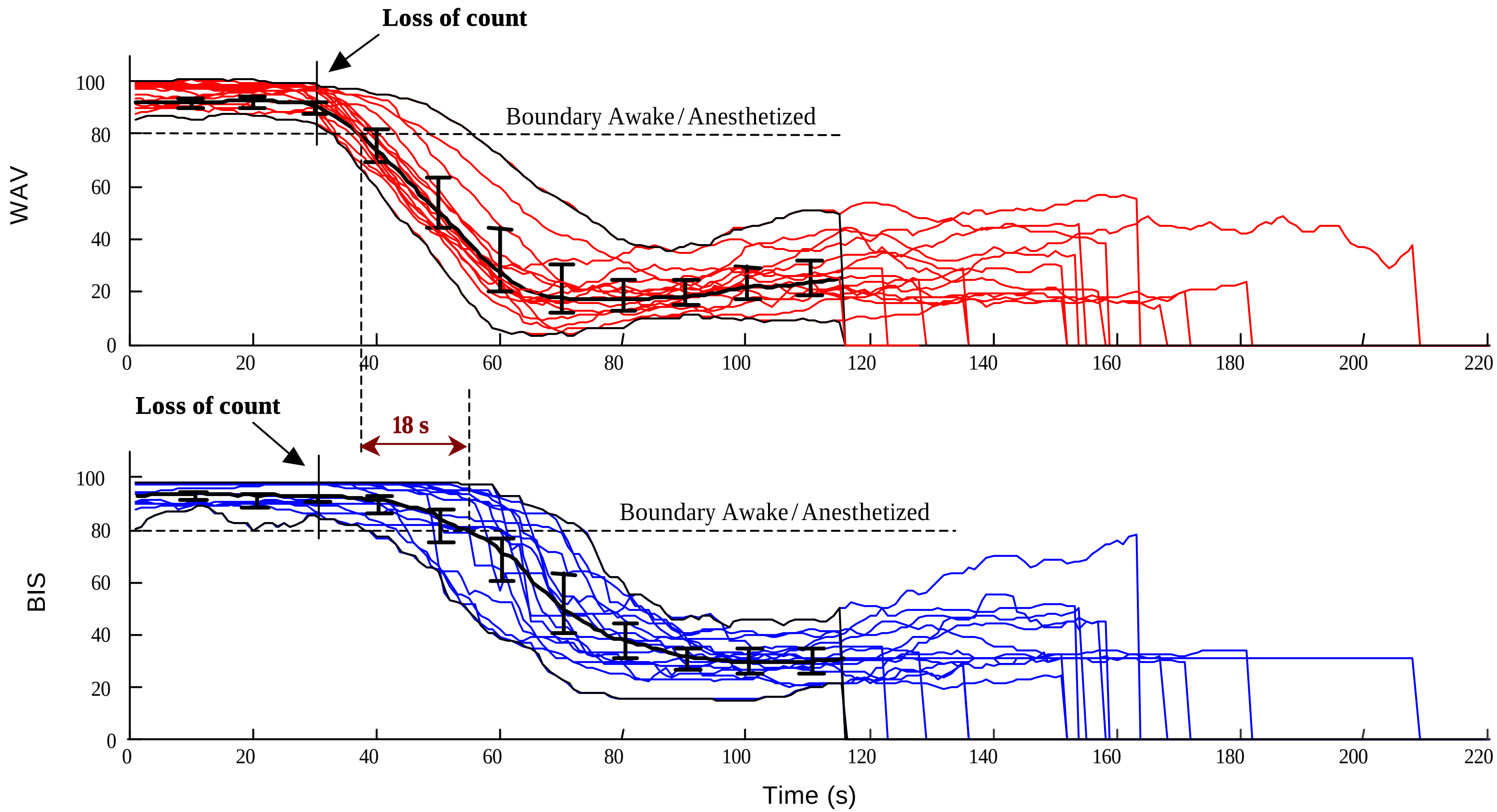
# Induction: WAV Index vs. BIS

- Arthroscopy study: 16 cases synchronized at LOC

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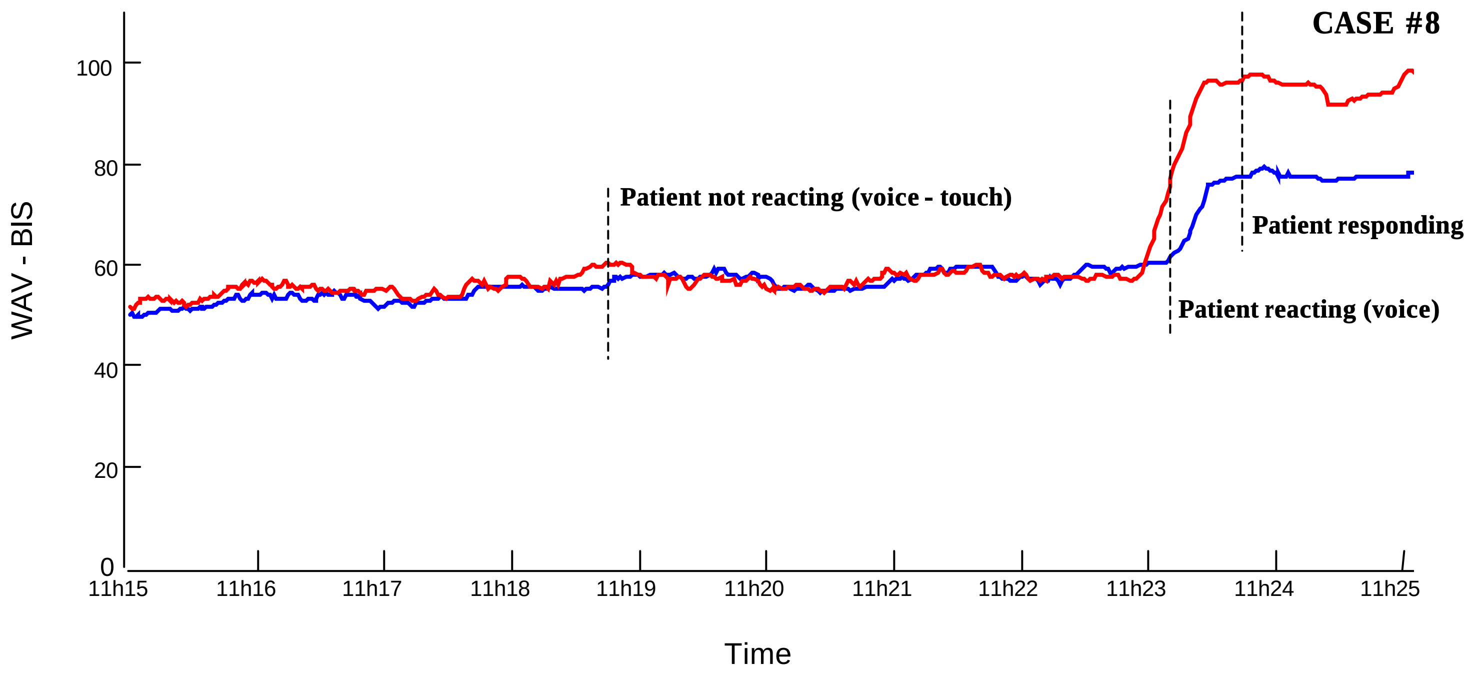
# Emergence: WAV Index vs. BIS

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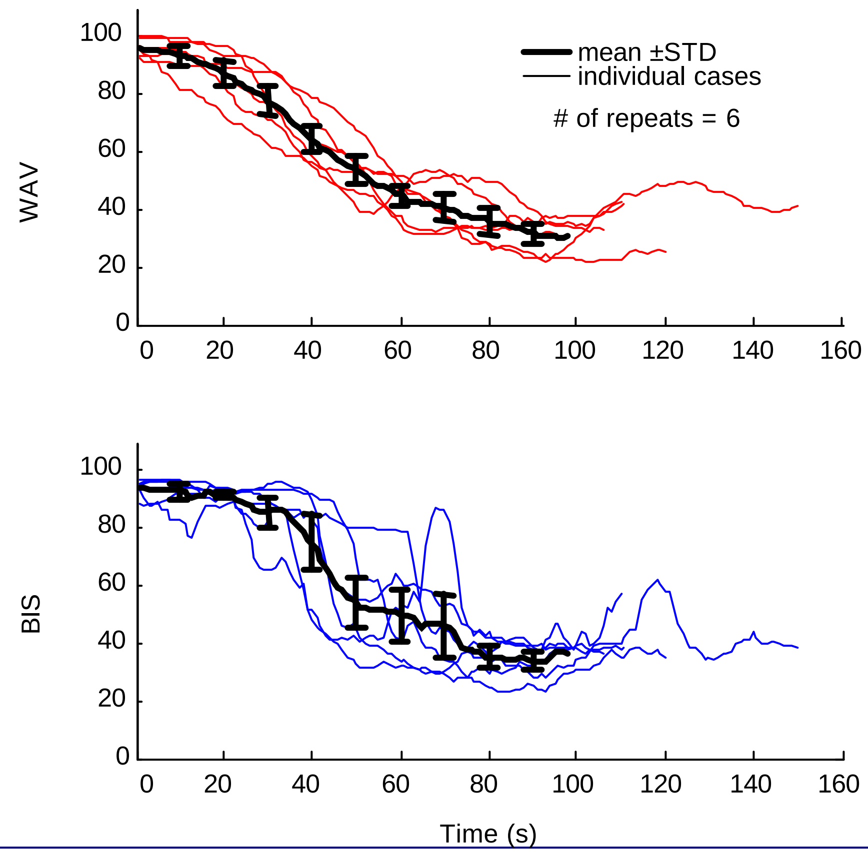
# Intra-patient Variability

- ECT Study: Patient #3



# Conclusion

- The WAV Index correlates closely to the BIS® index.
- The WAV Index provides a lead time of ~ 18 s.
- The WAV Index is more consistent.
- The WAV Index has a very low algorithmic complexity.
- Neither large subject pool nor extensive training data sets are needed for the tuning of WAV Index.
- WAV Index exibits less intra-patient variability.

- Current work: Automation of artifact removal

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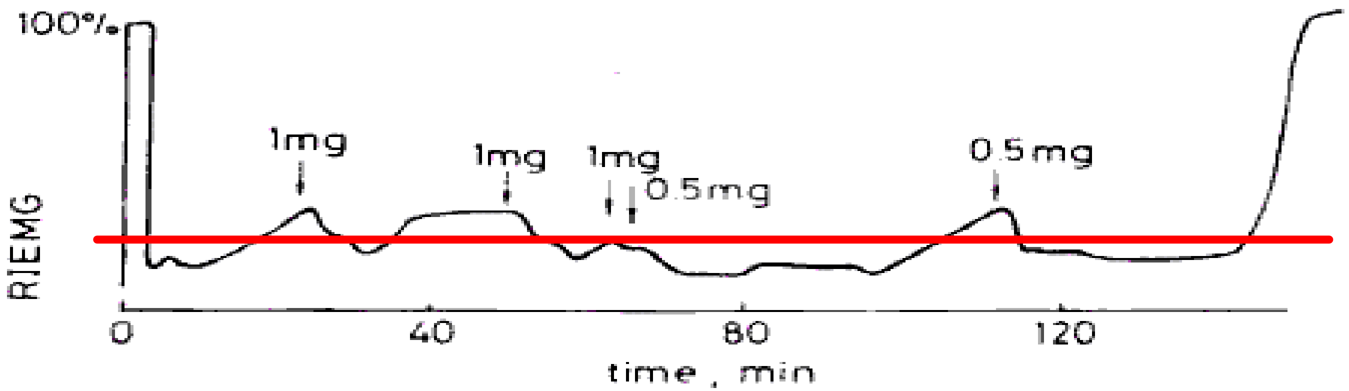
# Improvement of Neuromuscular Block through Computer Control

**T. Gilhuly (Ph.D.)**

# Background and justification

- In general, control improves care:
  - Less drug, time and cost
  - Use of faster/less toxic drugs,
  - Maintenance of drug in the therapeutic range
- For NMB:
  - Avoids the situation of non-reversal
  - Allows quick interruption during surgery



# Neuromuscular blocking agents

- Produce paralysis for surgery
- Rocuronium: competitive inhibitor of neurotransmitter at muscarinic acetylcholine receptors
- Safe drugs → a good starting point

# Difficulties for control: Interpatient variance

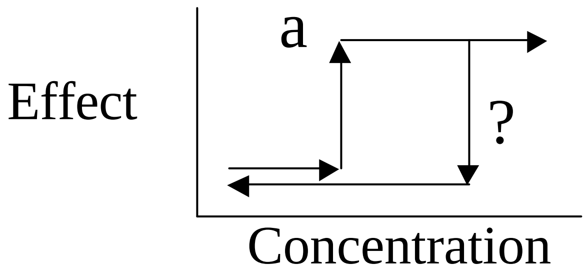
- Interpatient variance is manifested by drug interactions, age and health related differences

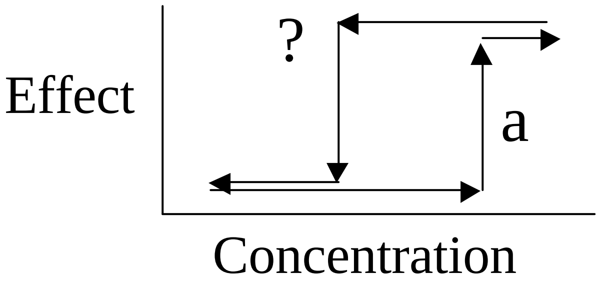
| Group | Time to $\geq$ 80% Block (min) | Time to Maximum Block (min) | Clinical Duration (min) |
|---|---|---|---|
| Infant (3mo-1yr) | | 0.8 (0.3-3.0) | 41 (24-68) |
| Pediatric (1-12yr) | 0.8 (0.4-2.0) | 1.0 (0.5-3.3) | 26 (17-39) |
| Adults (18-64yr) | 1.0 (0.4-6.0) | 1.8 (0.6-13.0) | 31 (15-85) |
| Geriatric ($\geq$65yr) | 2.3 (1.0-8.3) | 3.7(1.3-11.3) | 46 (22-73) |

| Parameter | †Adults | †Geriatric | ‡Adults | ‡Renal Transplant | ‡Hepatic Dysfunction | *Pediatric |
|---|---|---|---|---|---|---|
| $Cl$(L/kg/hr) | $0.25 \pm 0.08$ | $0.21 \pm 0.06$ | $0.16 \pm 0.05$ | $0.13 \pm 0.04$ | $0.13 \pm 0.06$ | 0.44 |
| $V_d^{ss}$ (L/kg) | $0.25 \pm 0.04$ | $0.22 \pm 0.03$ | $0.26 \pm 0.03$ | $0.34 \pm 0.11$ | $0.53 \pm 0.14$ | 0.298 |
| $T_{1/2}\ \beta$ (hr) | $1.4 \pm 0.4$ | $1.5 \pm 0.04$ | $2.4 \pm 0.8$ | $2.4 \pm 1.1$ | $4.3 \pm 2.6$ | 0.8 |
| MRT (min) | | | $\{44 \ldots 68\}$ | $\{80 \ldots 100\}$ | $\{80 \ldots 100\}$ | 31 |

# Intrapatient variance

- Blood/Drug loss
- Tolerance: reduction in drug effect despite constant drug concentrations at effect site

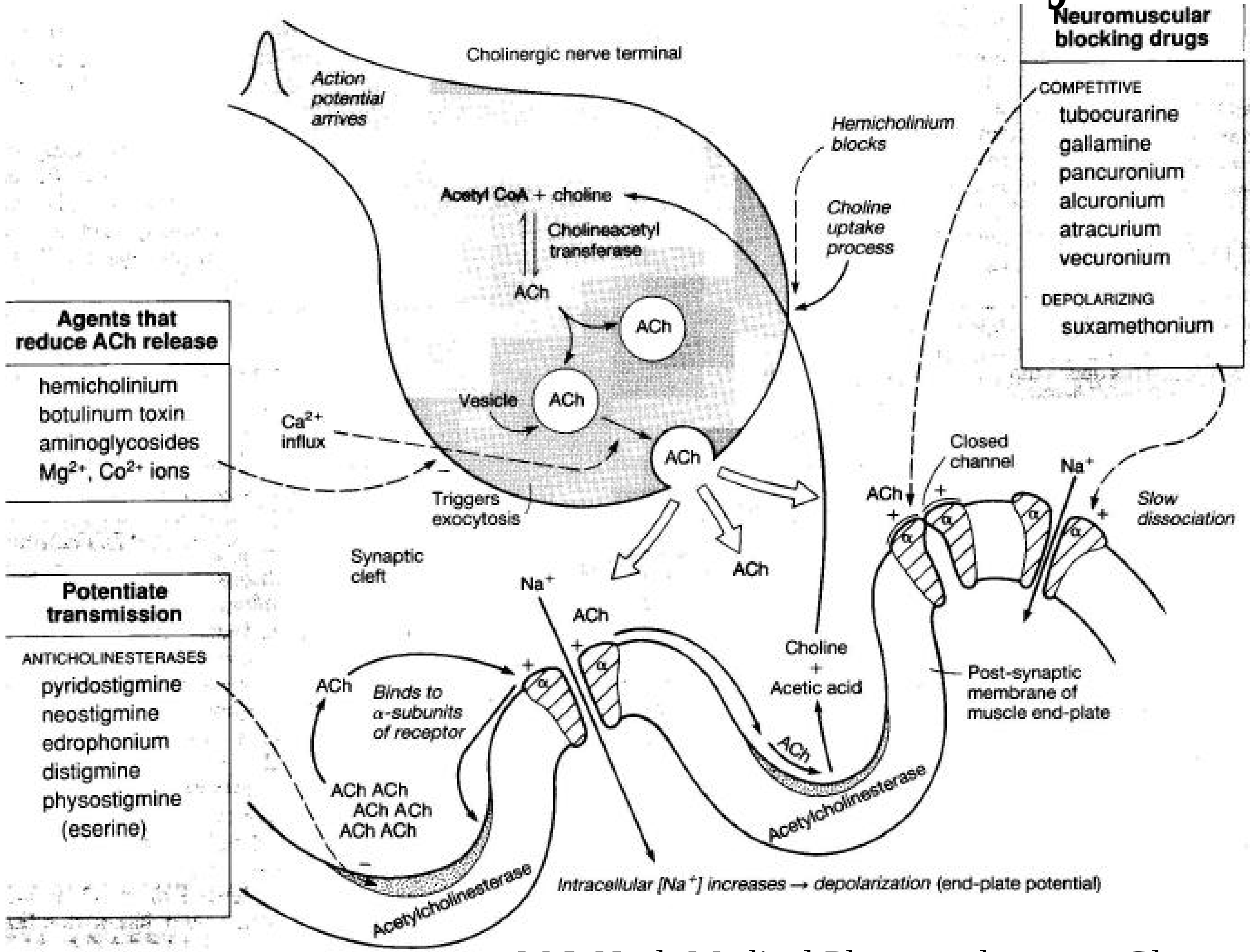



•Sensitization: intensification in drug effect despite constant drug concentrations at biophase

a: procedure beginning, ? : end

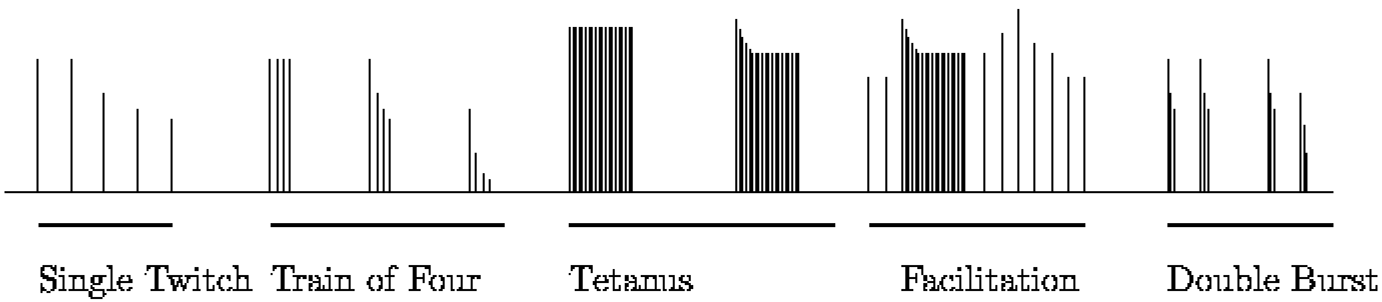
# PMD IV: The neuromuscular junction




M.J. Neal, Medical Pharmacology at a Glance, 1992

# Neuromuscular stimulus effects

- Stimuli are needed to evoke response →depletion→change in response
- Commercial stimuli:  ST/TOF/Tetanus/DBS/PTC
- Sensitivity is proportional to exhaustion of immediately releasable stores:  Tetanus, PTC > TOF, DBS > ST

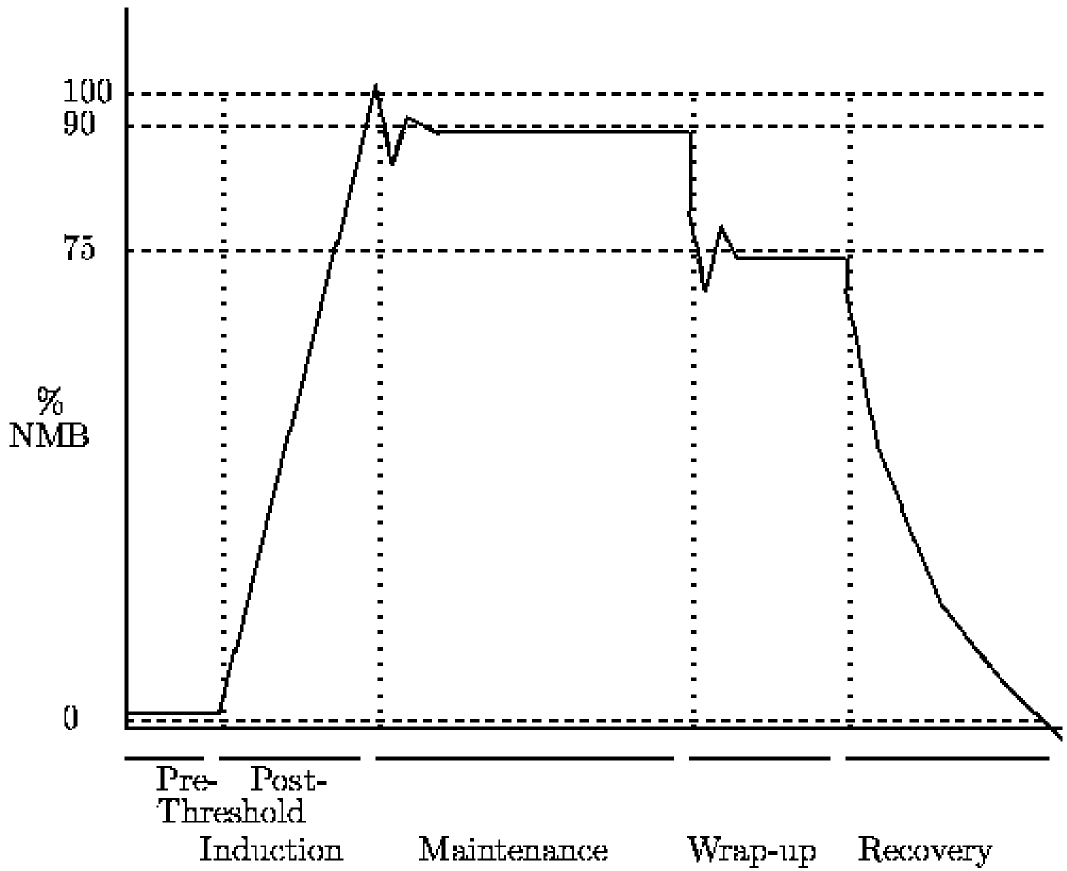


# Changing surgical demands and conditions

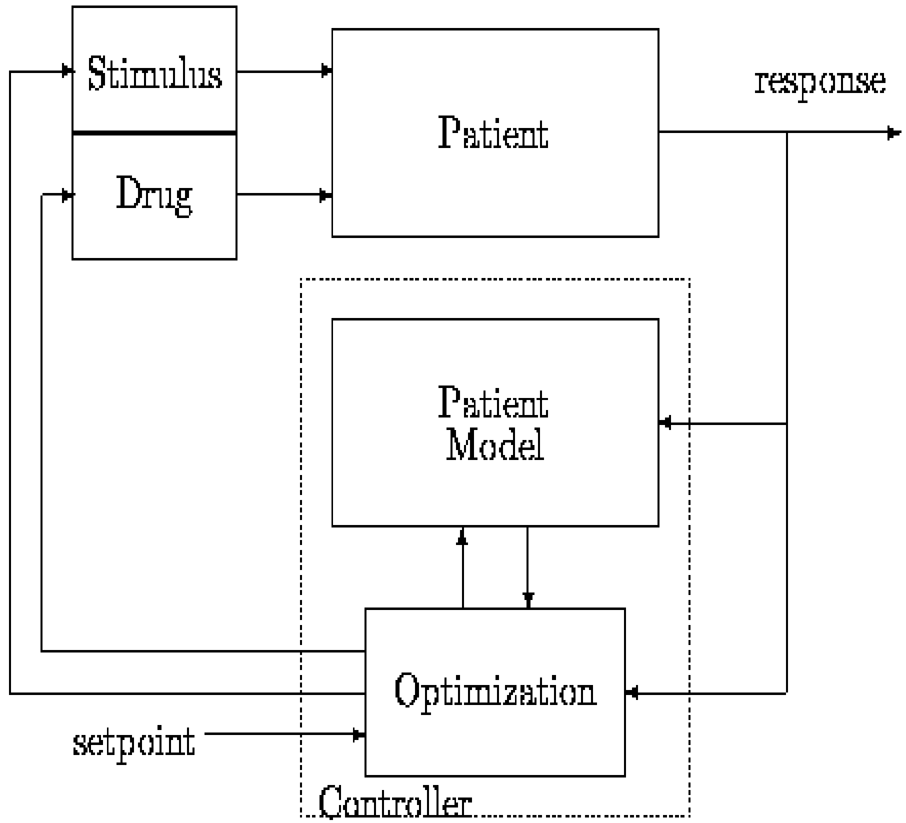
- Staged surgery:

  Induction,
  maintenance,
  wrap-up, recovery

- Different stages require different stimuli



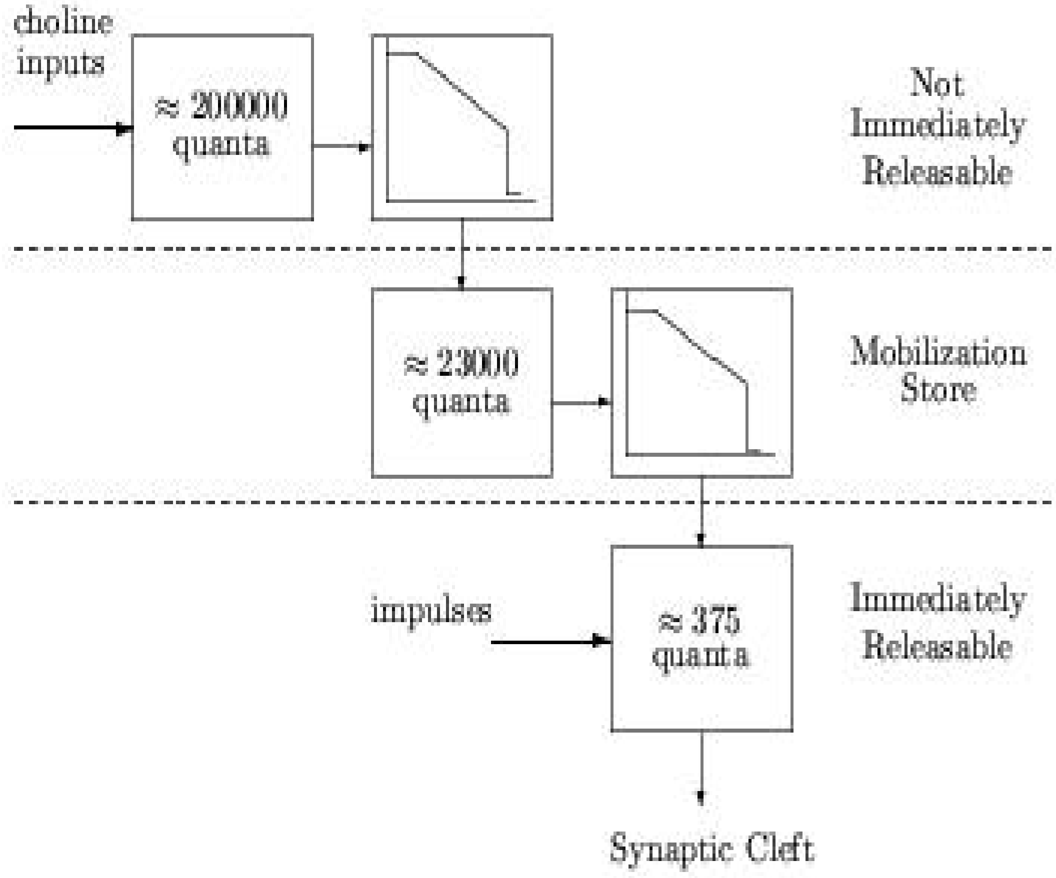
# PMD III: Better modeling: From SISO to MISO




- Why? Stimulation influences response
- Update patient model to include sensor

# PMD V: Muscle/quantal ACh model and Optimal stimulator

- Synaptic model as three tanks, flows between tanks dictated by demand
- Use to find "optimal stimulation" at time applied
- Tune according to literature results

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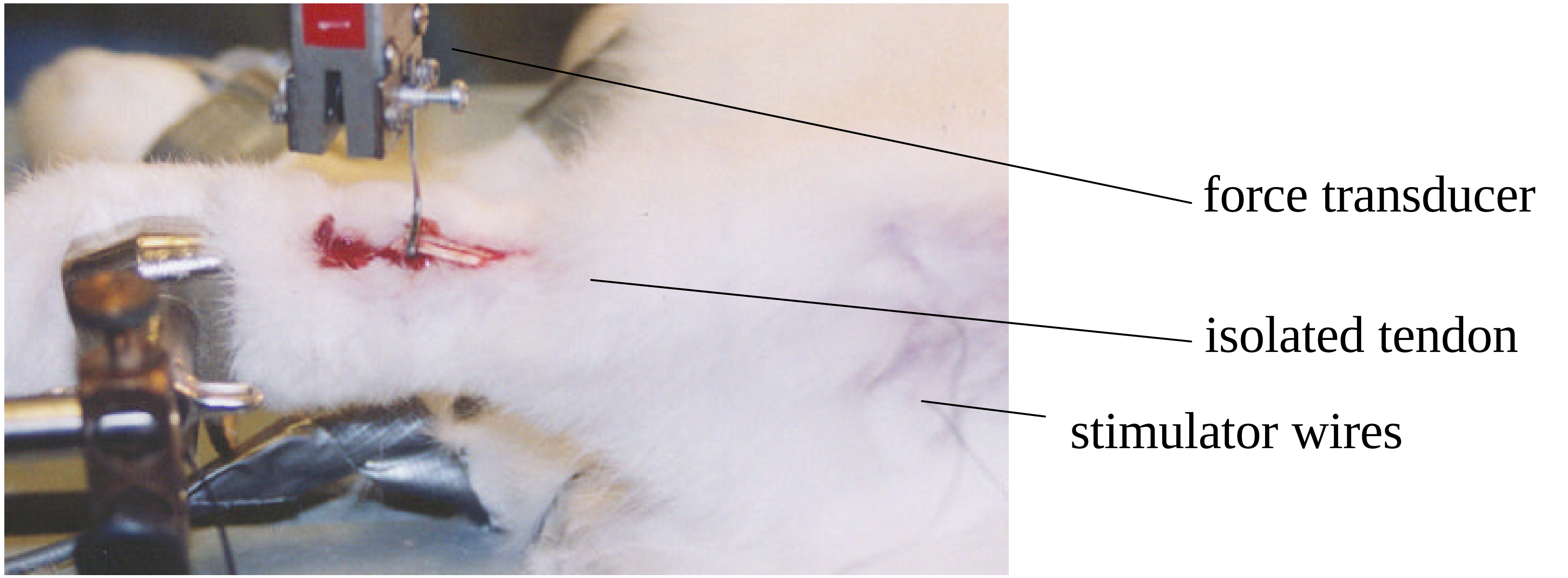
# Initial experiments I: Motivation, methods, equipment

- Motivation: identify basic model, establish lab technique
- Methods: adductor polis force measurement with ulnar nerve TOF stimulation



# IE II: Experimental setup

Computer controlled pump

Anaesthesia monitor

Response monitor

Vitals

Software/ Brainwave controller

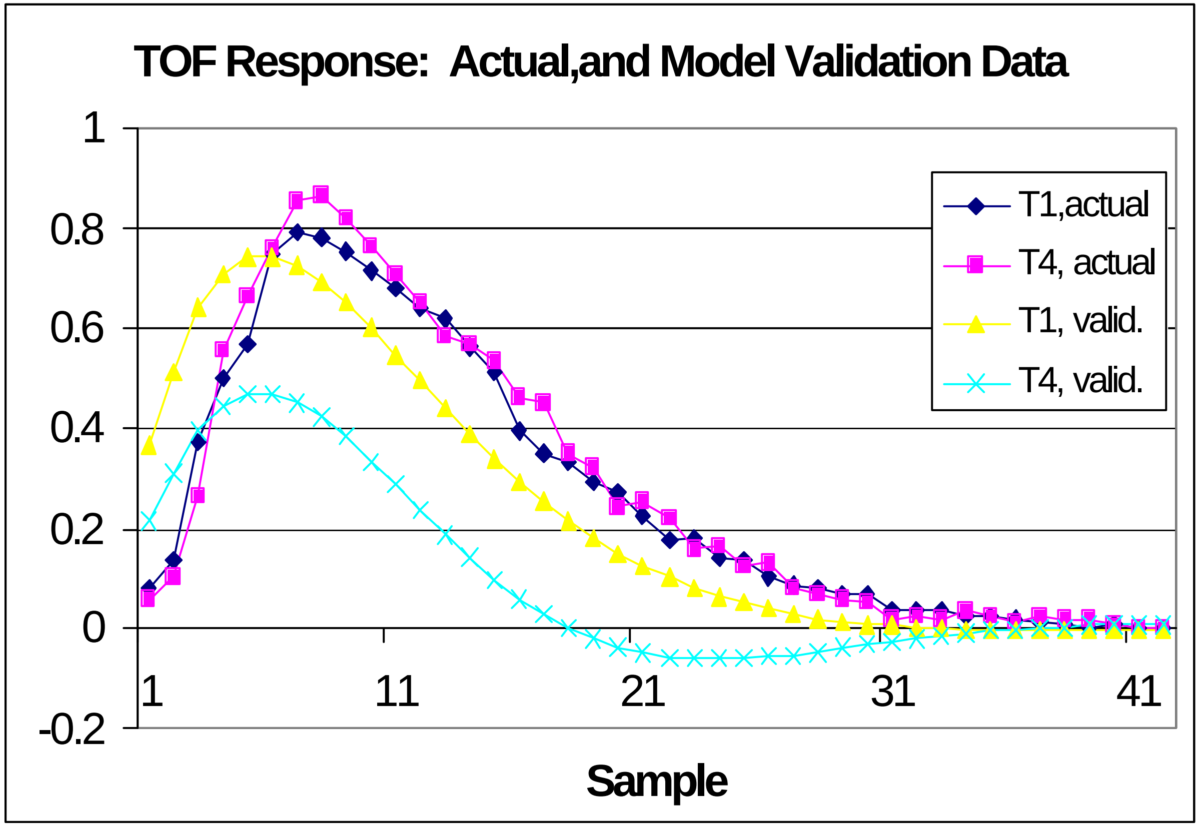
Surgical bench, tools

# IE IV: results

$$A(q)y(t) = B(q)u(t) + e(t)$$

T1: $A(q) = 1 - 1.392\, q^{-1} + 0.1907\, q^{-2} + 0.2374\, q^{-3}$,
$B(q) = 0.366$

T4: $A(q) = 1 - 1.423\, q^{-1} + 0.1994\, q^{-2} + 0.2736\, q^{-3}$
$B(q) = 0.2171$



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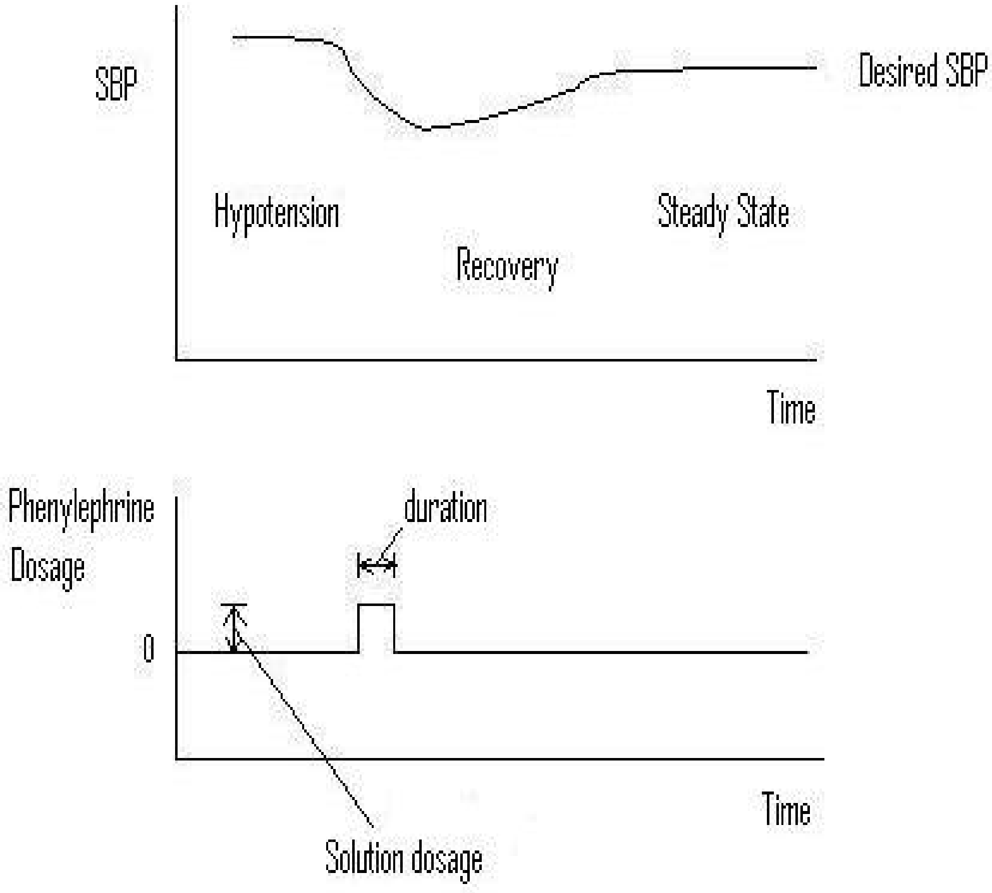
# The Determination of Correct Dosage of Phenylephrine

**P.Fung (MA.Sc.)**
**R. Desjardins (Fellow)**

# The Problem

- Phenylephrine is administered to restore the maternal blood pressure at the BC Women's Hospital

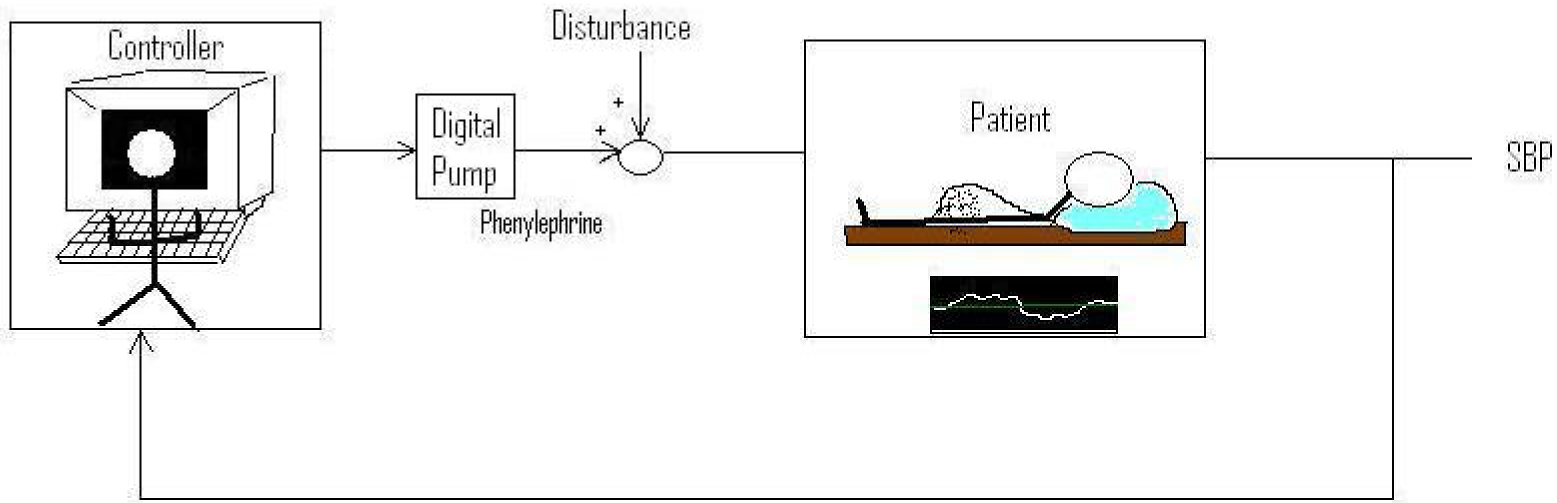
- Phenylephrine patient's response is not fully understood.



# Objective

- To identify the relationship between Systolic Blood Pressure and Phenylephrine
- To design an advisory feedback control system which regulates a patient’s SBP by means of Phenylephrine with the anesthetist in the loop

# System Identification



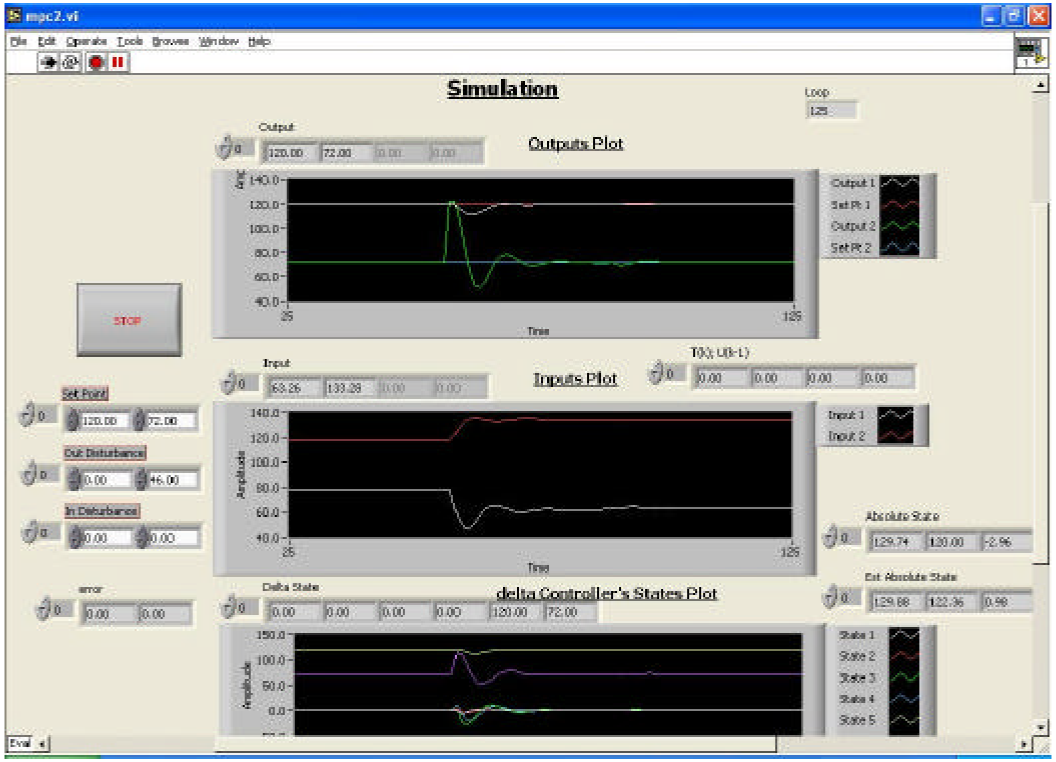

The above block diagram represents the feedback loop. The patient is the plant and the PC based advisory system is the controller supervized by the anesthetist.

First, both the Phenylephrine and the disturbance models have to be identified. Clinical data is collected from the BC Women's Hospital.

# Controller and Actuator

- Design of the controller / advisory system :
  - The system receives the desired SBP set point from the doctor
  - The doctor can opt to impose feedback as suggested by the system (closed loop), or to administer some other dosage (open loop).
  - The system continues to monitor the patient even when it is offline always displaying a suggested dosage.
  - A digital pump serves as actuator.

# The LabVIEW Controller




- The discrete state space predictive controller is implemented in LabVIEW. Shown above is a simulator in current development stage.

# Values of the Project

- Prevent overuse of Phenylephrine, which may cause hypertension response with reflex bradycardia
- Improve consistency of the drug administration with computerized system
- Increase efficiency of the process so that the doctor has more time for patient care

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# Delivery & Outcome of Epidural Anesthesia

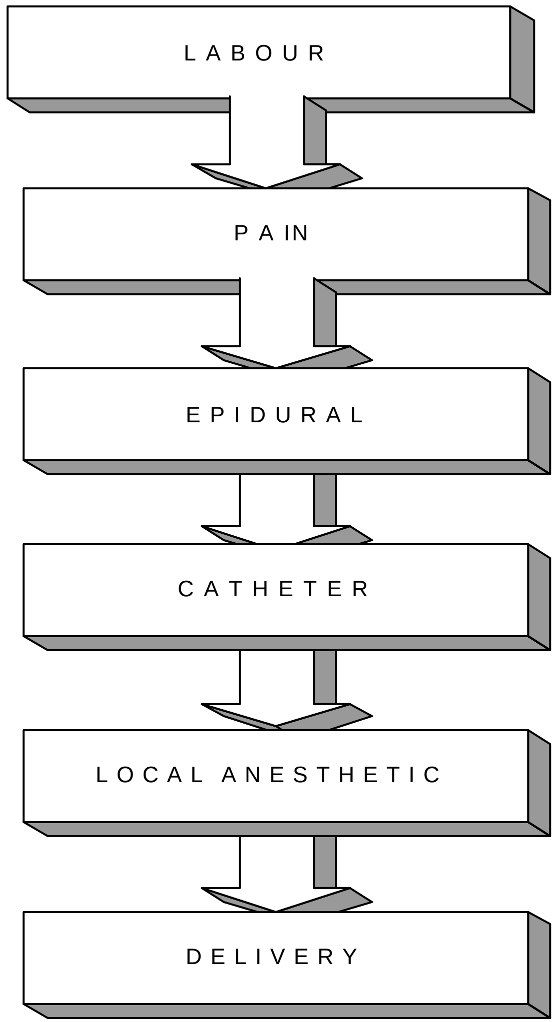
**TBA**

# Objective

- Reduced pain
- Reduced workload allowing for:
  - A broad patient basis
  - Time for other critical cases
- Increased safety features
- Nurse autonomy
- Increased time for indirect care

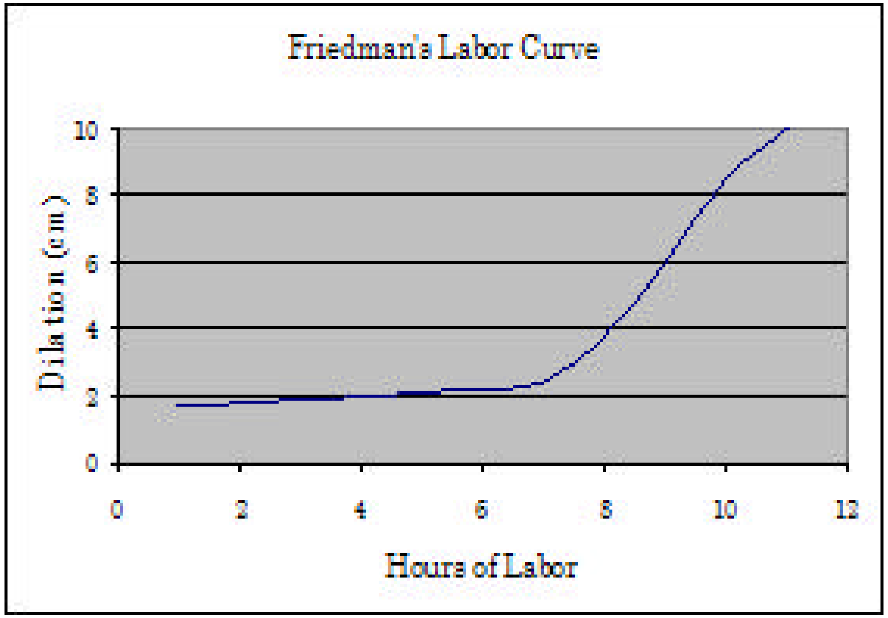
# The Delivery Flowchart and Key Factors

- Block
  - Goal T10 – L2
  - Bounds T8 – L4
- Cervical dilation ~0 – 10 cm
- VAS pain levels 0 – 10 mirroring the Freedman cervical dilation curve with some lag
- Constraints of BF for fetus and mother
- Constraints on levels of block



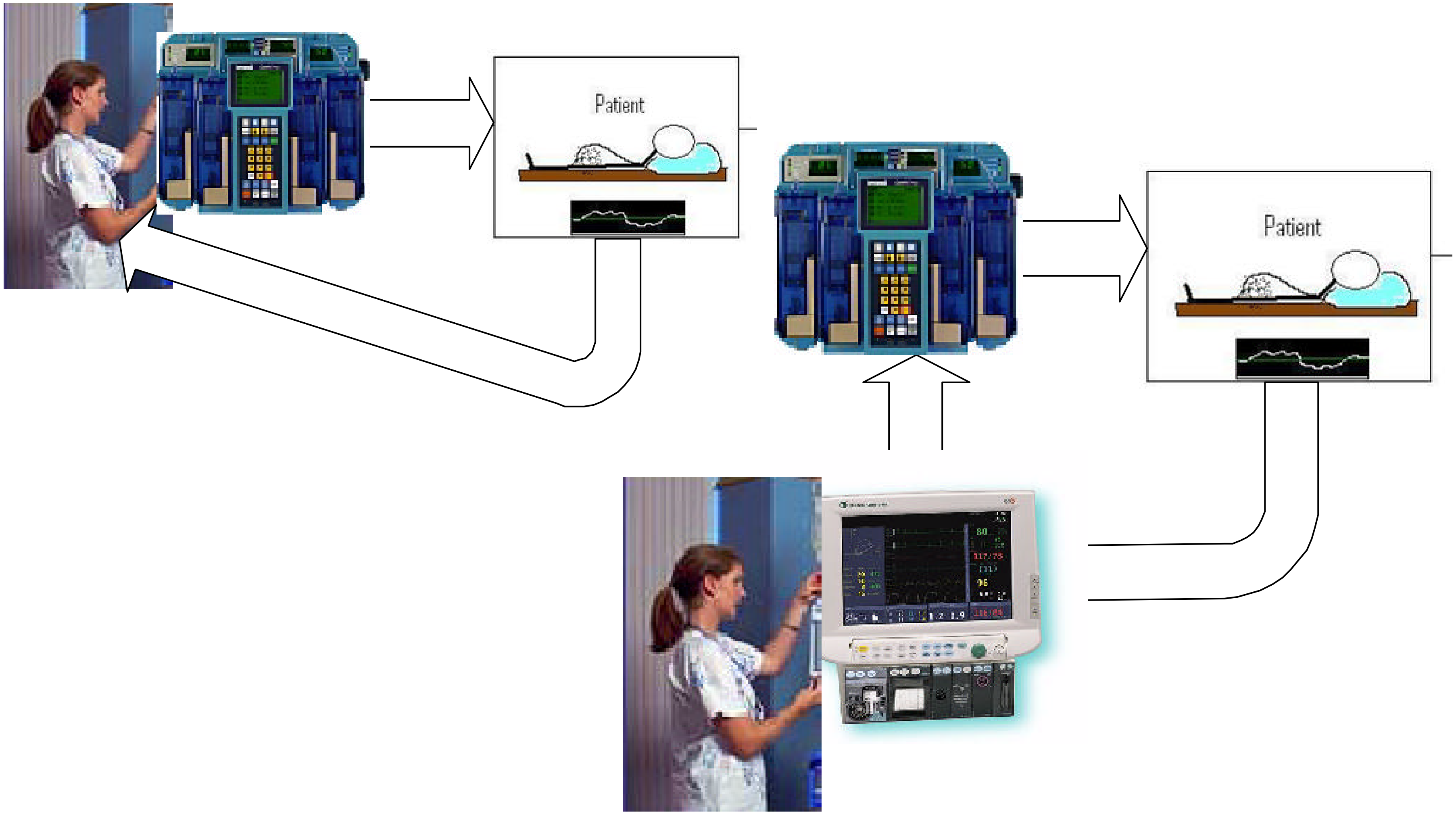
# Current Practice

- At the BC Women's Hospital:
  - Cervical dilation measured every 2 hours
  - M+F BP measured every ½ hour
- Measuring these parameters and recording them is part of current practice
- Drug delivery:
  - Bupivicaine: 0.0625 – 0.125 %
  - Fentanyl 2 – 3 micro g /cc with infusion rates from 15 – 45 cc/hour




Cervical dilation = Level of Pain

# Open vs. Closed Loop System



# Proposed Solution

A controller / advisory system is designed to:

- Maintain minimal pain levels while minimizing drug infusion
- Monitor the mother and fetus safety
- Accept sensor and nurse measurements
- Allow the use of feedback or manual override.
- Continuously monitor the patient and display a suggested drug dosage.
- Adapt its outputs to a multi-channel digital pump which serves as actuator with the ability to continuously modify the drug concentration while maintaining the solution infusion rates within tight bounds