New Perspectives in Sedation-Analgesia

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New Perspectives in Sedation-Analgesia

- Current situation
- Sedative Effects
  - Defining optimal sedation
  - Use of EEG derived measurements
  - Predicted Concentrations: TCI systems
- Collateral Effects
  - Respiratory Effects
  - Cognitive Effects: Recovery

Sedation-Analgesia: current situation

- **Different Departments: different solutions**
  - Anesthesiologists only
    - Nurses
    - Supervised nurses
  - GI endoscopists by themselves
- **Hospital CLINIC-Barcelona (2014):**
  - 15% of total anesthetic activity in the OR
  - >50% of total anesthetic activity outside the OR (NORA) (~10,000 pat/year)
  - **Significant part in GI Endoscopy practice (>20 patients/day)**
- 25% of all income in Anesthesia Dpt (ASA-USA):
  - Ophtalmologic+Gastroscopy+Colonoscopy

Sedation-Analgesia: current situation

- Increasing **social demand**
- Required by **our colleagues**:
  - GI endoscopists,
  - Invasive Radiology,
  - Cardiology Labs
  - Ophtalmology
  - Psychiatry
  - …
- The majority are **outpatients**:
  - Coming from home (often with very little information)
  - Rapid discharge
- Some (many) are among our **sickest patients**
- Relatively **slow development** of control systems:
  - Infra valued: patient, anesthesiologists, colleagues
  - "Low intensity Anesthesia"
  - Less dosing → less problems

Sedation-Analgesia: control

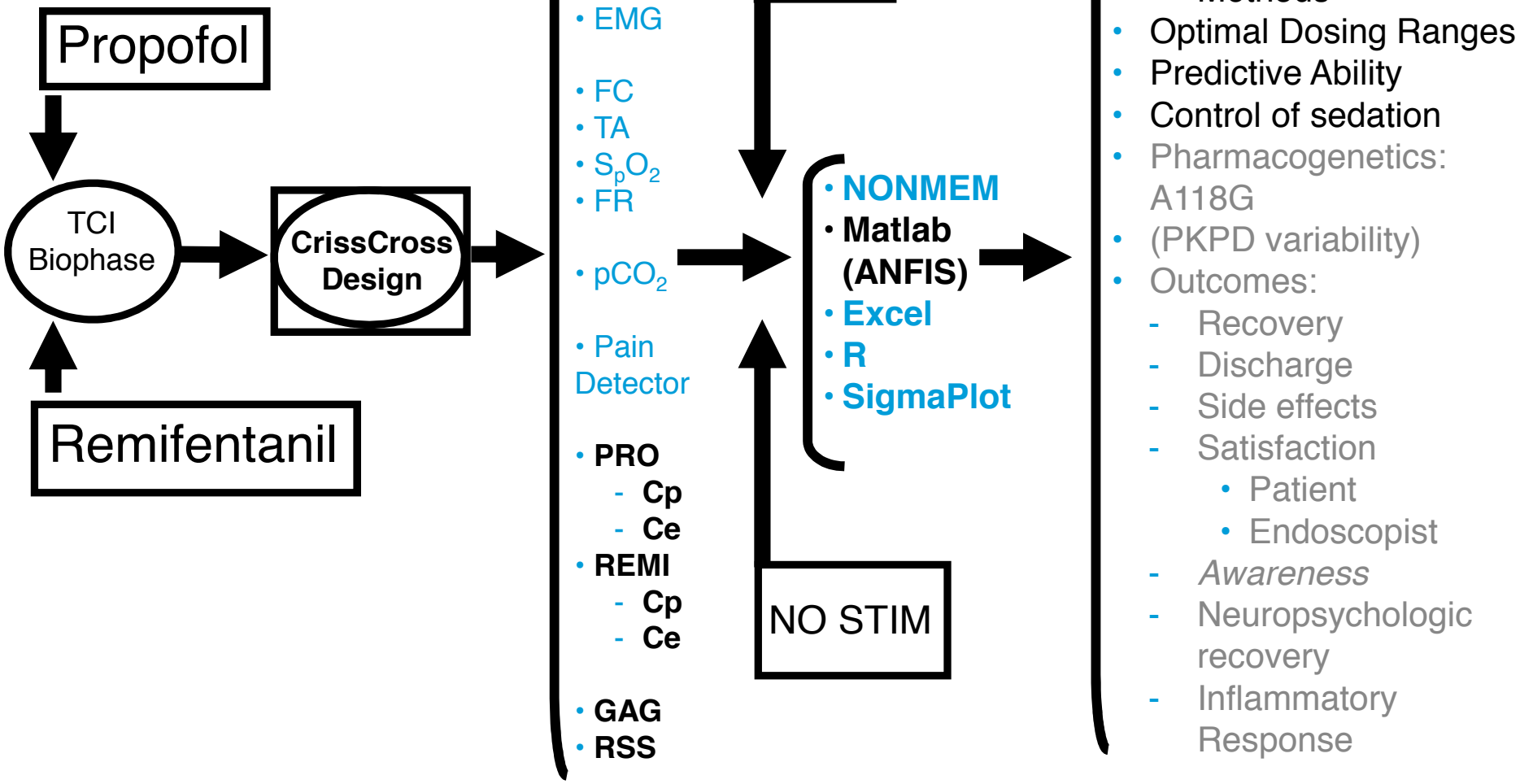
- **Therapeutic effect:** sedation and/or analgesia
  - Poorly controlled:
    - Observing the patient (no objective measure)
    - Endoscopist comments (“he’s moving”, “eyes open”, …)
- **Side effects:**
  - **Potentially serious**
  - Hemodynamics
  - Respiratory: must keep spontaneous respiration
- **Ambulatory context:**
  - Discharge back to normal life
  - Optimal titration of drugs

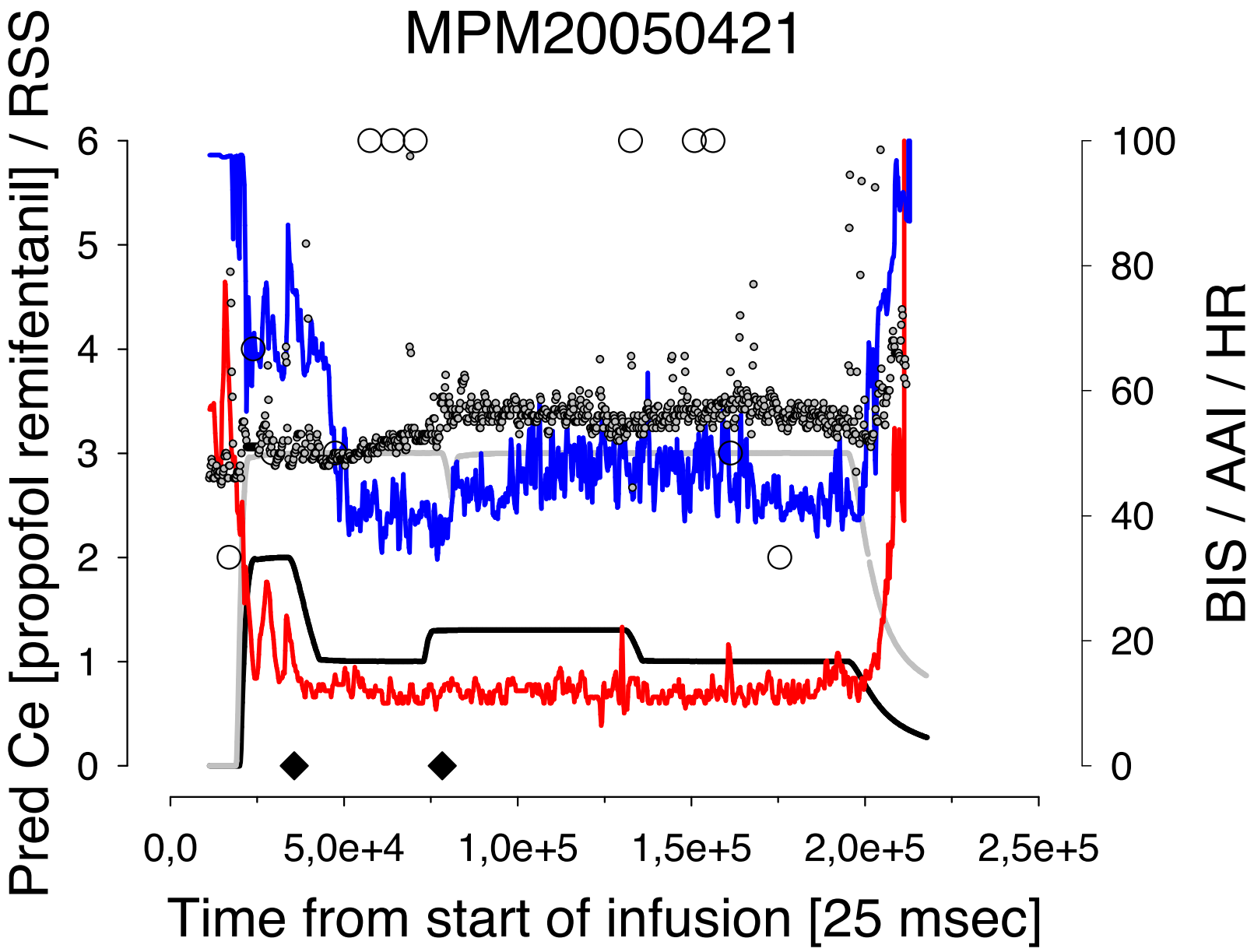
Anesthetic vs Sedative Effects: Control Systems

- Well validated in General Anesthesia:
  - Monitoring hypnotic effect
  - Monitoring hemodynamics
  - Respiratory monitoring
  - Predicted concentrations
    - TCI systems
    - End tidal concentration of inhalation agents
- Sedation-Analgesia:
  - Lower concentrations
  - Inter-patient variability
  - Spontaneous breathing (respiratory depression)
  - No NMBA
    - Presence of artifacts (muscular)

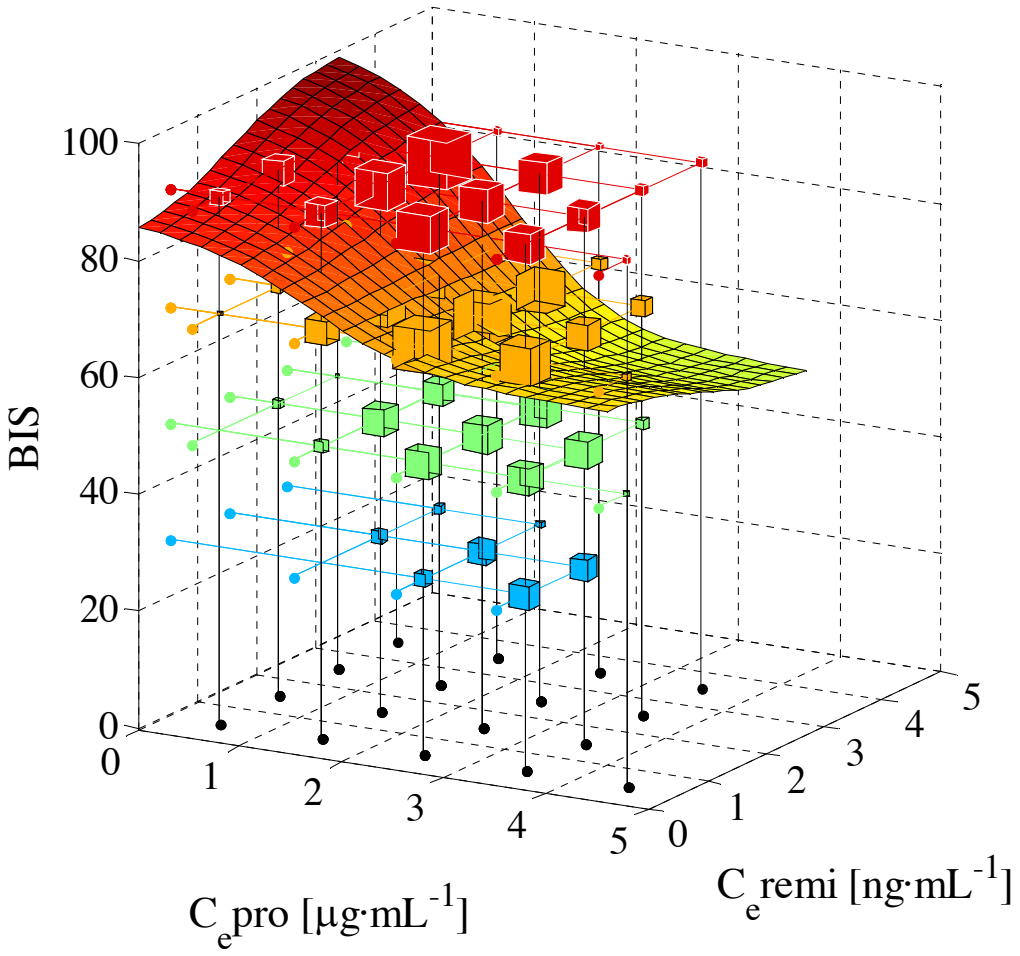
Modeling the effect of Propofol and Remifentanil for Sedation-Analgesia in GI endoscopic procedures

USE patients (n):
- **120 "learning"**
- **68 "prospective validation"**





Propofol-Remifentanil Data→ Effect



- Data from 110 patients
- > 10.000 data points
  - Colored Cubes
- "Estimates" the surface relationship of prop & remi
- Defines (combined) "target concentrations" for propofol and remifentanil
  - For a given BIS effect
- Prospectively validated

Gambús P; Anesth & Analg, 2011

Ramsay Sedation Scale- 4
[Arousable to tactile stimuli]

	Propofol ($\mu g \cdot mL^{-1}$)	**Remifentanil** ($ng \cdot mL^{-1}$)
Target Conc [C_e]	2.7-1.8	0-1.5

	AAI/2	**BIS**
Range	25-30	71-75

These combinations can be used as safe starting points when using TCI systems to provide **MAC-sedation** for GI endoscopy (ultrasonographic endoscopy, ERCP, …)

Gambús P; Anesth & Analg, 2011

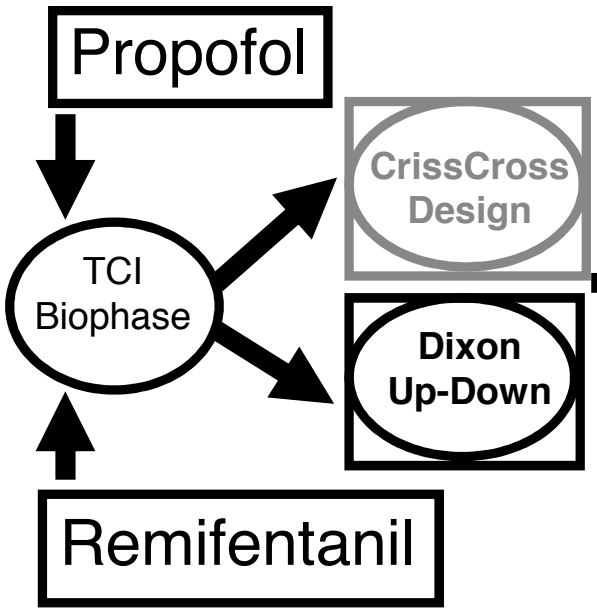
Can we use TCI as a measure of Sedation?

Can we use predicted effect-site concentrations to better adjust sedation?

Optimal Dosing to Avoid a Gag Response

- How many patients gag with placement of endoscope?
  - No problems in 20% pts
  - "Stress Response:" BP, HR, moving
  - Risk of esophageal tear,…
- Best approach:
  - Use Propofol and Remi TCIs
  - TCI Remi and Propofol Bolus
  - Non-TCI Remi infusion plus Propofol bolus
- Patients randomized to 4 groups, all with TCI pumps
  - REMI 1 // REMI 2
  - PROP 2 // PROP 3
- Second drug adjusted per Dixon Up/Down Method
  - Gag (+): increase in next patient
  - Gag (-): decrease in next patient
- Gag evaluated by the same endoscopist
- Endoscopy continued
  - Patients stayed in their assigned TCI group

USE patients (n):
210 “Dixon U-D”



Data collection
(Rugloop II)

- **BIS**
- AAI
- IoC
- EEG
- EMG
- FC
- TA
- S_pO_2
- FR
- **pCO_2**
- **A118G**
- PRO
  - Cp
  - Ce
- REMI
  - Cp
  - Ce
- **GAG**
- RSS

Data analysis
(Software)

STIM

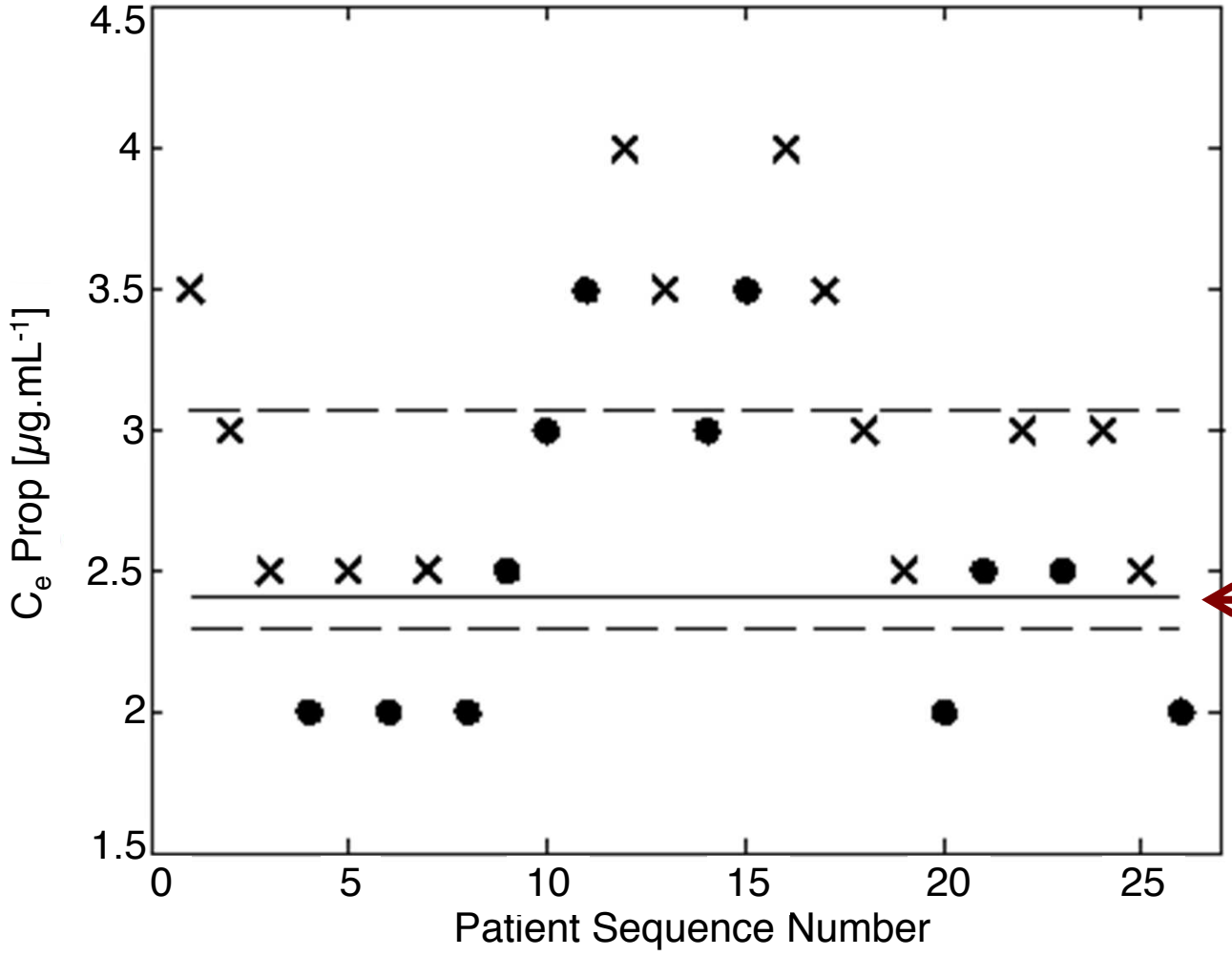
NO STIM

- NONMEM
- **Matlab (ANFIS)**
- **Excel**
- **R**
- **SigmaPlot**

Expected results

- PKPD Models
- Synergy
  - Methods
- Optimal Dosing Ranges
- Predictive Ability
- Control of sedation
- Pharmacogenetics: A118G
- (PKPD variability)
- Outcomes:
  - Recovery
  - Discharge
  - Side effects
  - **Satisfaction**
    - **Patient**
    - **Endoscopist**
  - *Awareness*
  - Neuropsychologic recovery
  - Inflammatory Response

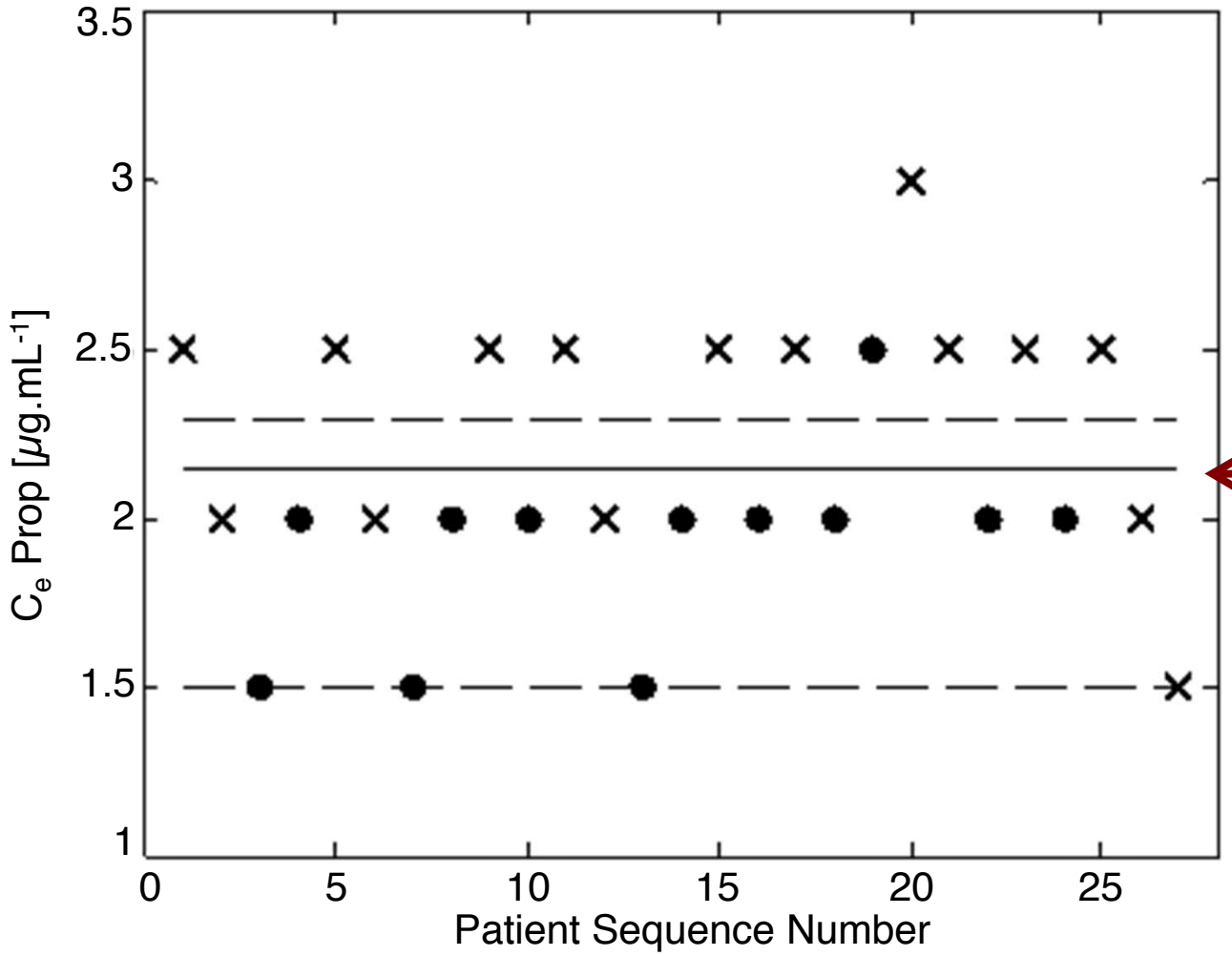
Optimal Dosing to Avoid Gag
Remi 1 ng/mL Group



Propofol
C_{50}: 2.4

Borrat X, Anesth Analg; in press

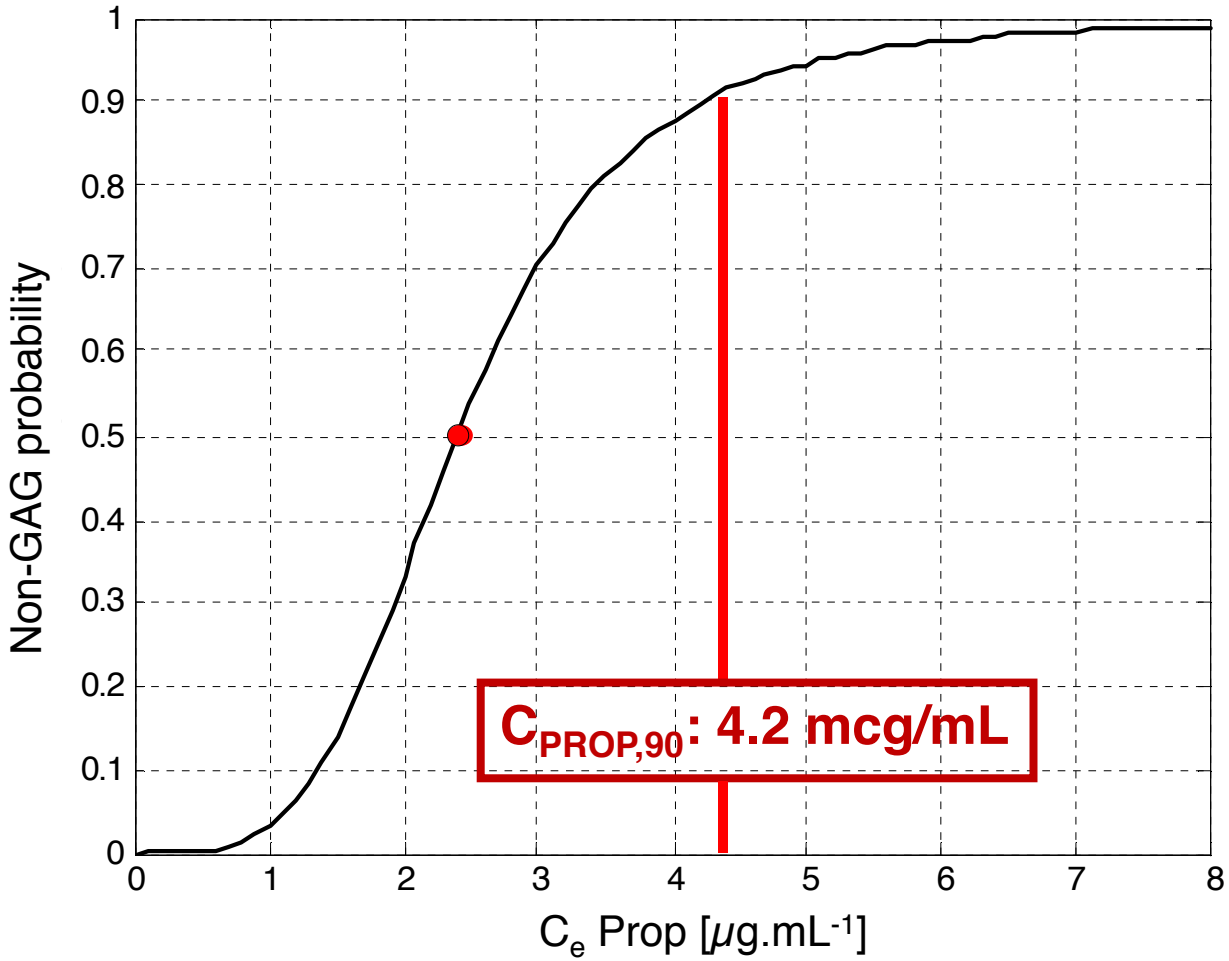
Optimal Dosing to Avoid Gag
Remi 2 ng/mL Group



Propofol C_{50}: 2.1

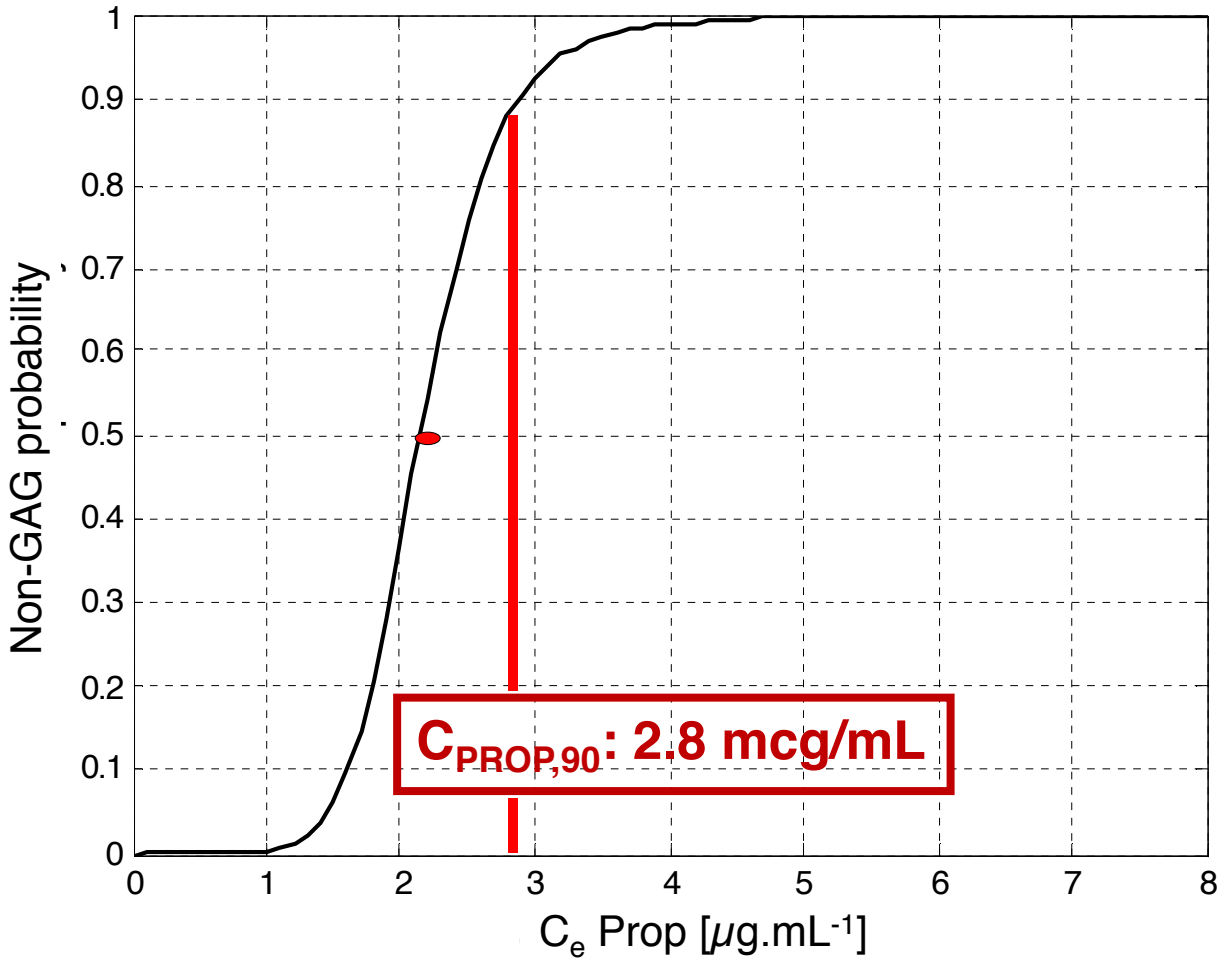
Borrat X, Anesth Analg; in press

Optimal Dosing to Avoid Gag Remi 1 ng/mL Group



Borrat X, Anesth Analg; in press

Optimal Dosing to Avoid Gag Remi 2 ng/mL Group



Borrat X, Anesth Analg; in press

Optimal TCI targets to avoid Gag

	Ce50	Ce90
Remifentanil 1 ng/mL	2.4 mcg/mL	4.2 mcg/mL
Remifentanil 2 ng/mL	2.1 mcg/mL	2.9 mcg/mL
Propofol 2 mcg/mL	1 ng/mL	4.8 ng/mL
Propofol 3 mcg/mL	0.7 ng/mL	3.1 ng/mL

RSS: 4	**Propofol** ($\mu g \cdot mL^{-1}$)	**Remifentanil** ($ng \cdot mL^{-1}$)
Target Conc [C_e]	2.7-1.8	0-1.5

- Agreement with volunteer studies
- Higher than targets for RSS 4
- Bolus and continuous infusion can be estimated

Sedation-Analgesia Side Effects

Respiration

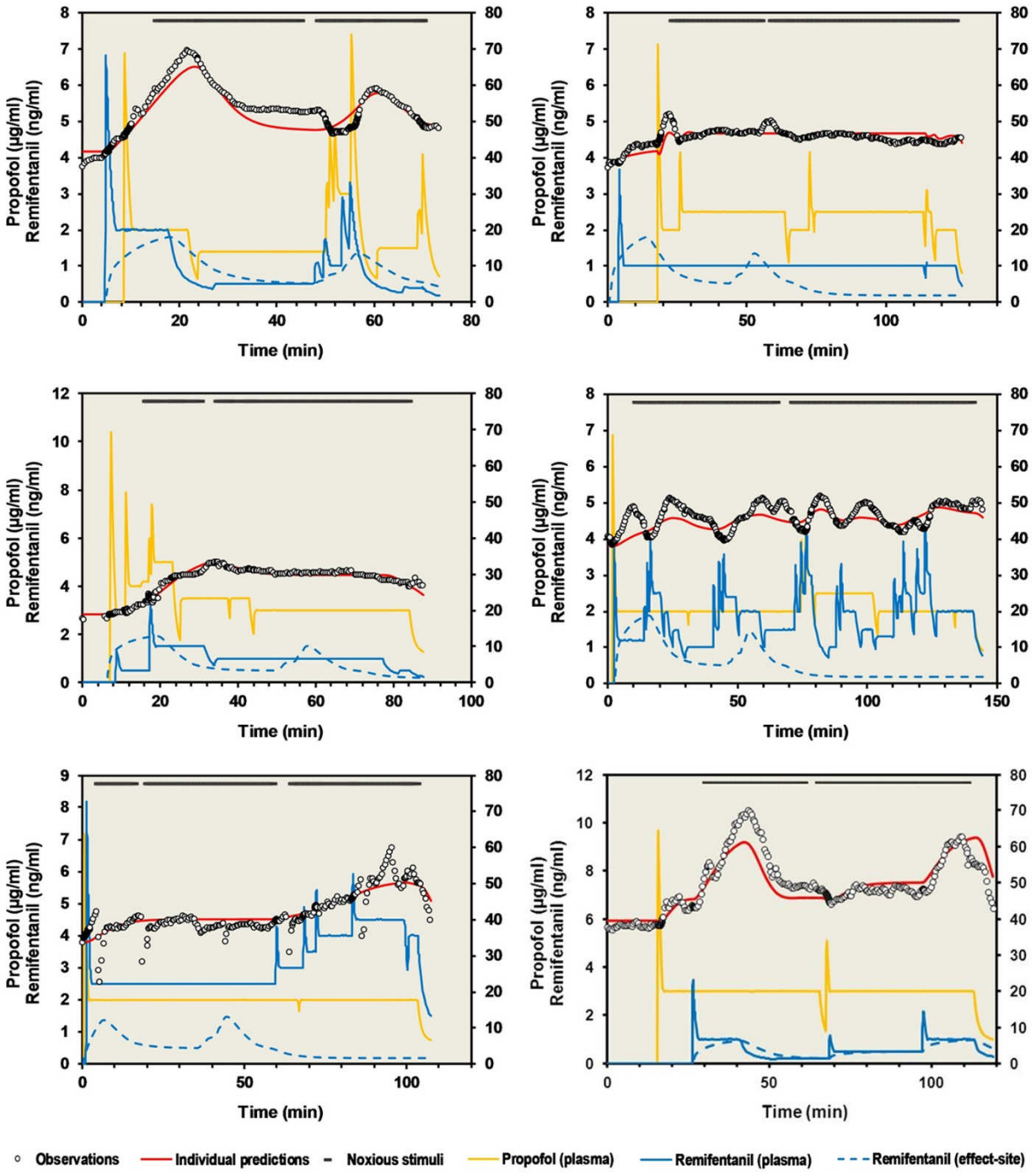
MAC related injury: Closed claim analysis

- 1952 claims in total; 6% were related to MAC
- Respiratory depression, after absolute or relative overdose of sedative or opioid drugs, was the most common (21%, n=25) specific damaging mechanism in MAC claims
- Nearly half of these claims were judged as preventable by better monitoring, including capnography, improved vigilance, or audible alarms.

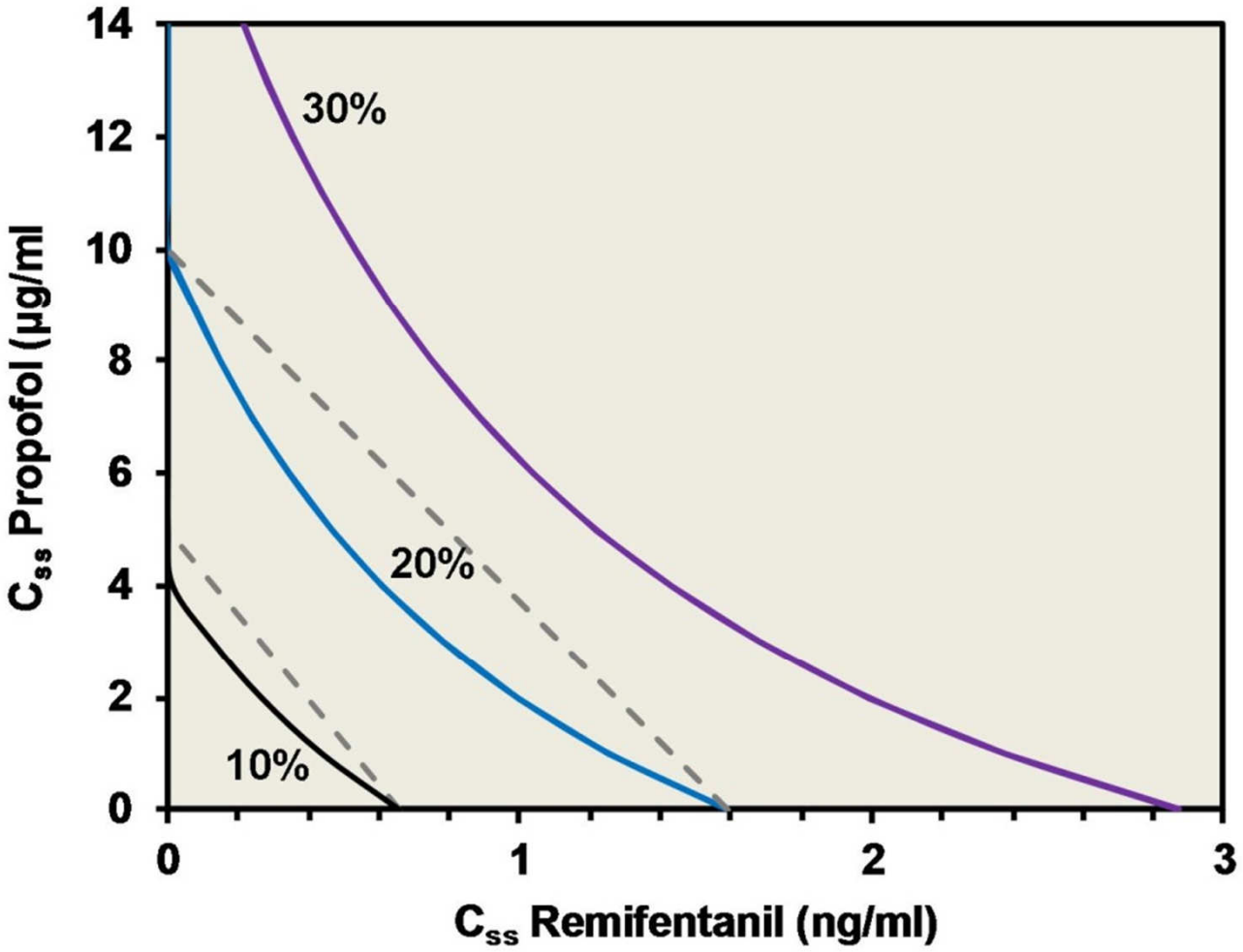
Bhananker, Anesthesiology, 2006

Monitoring: Respiratory Function

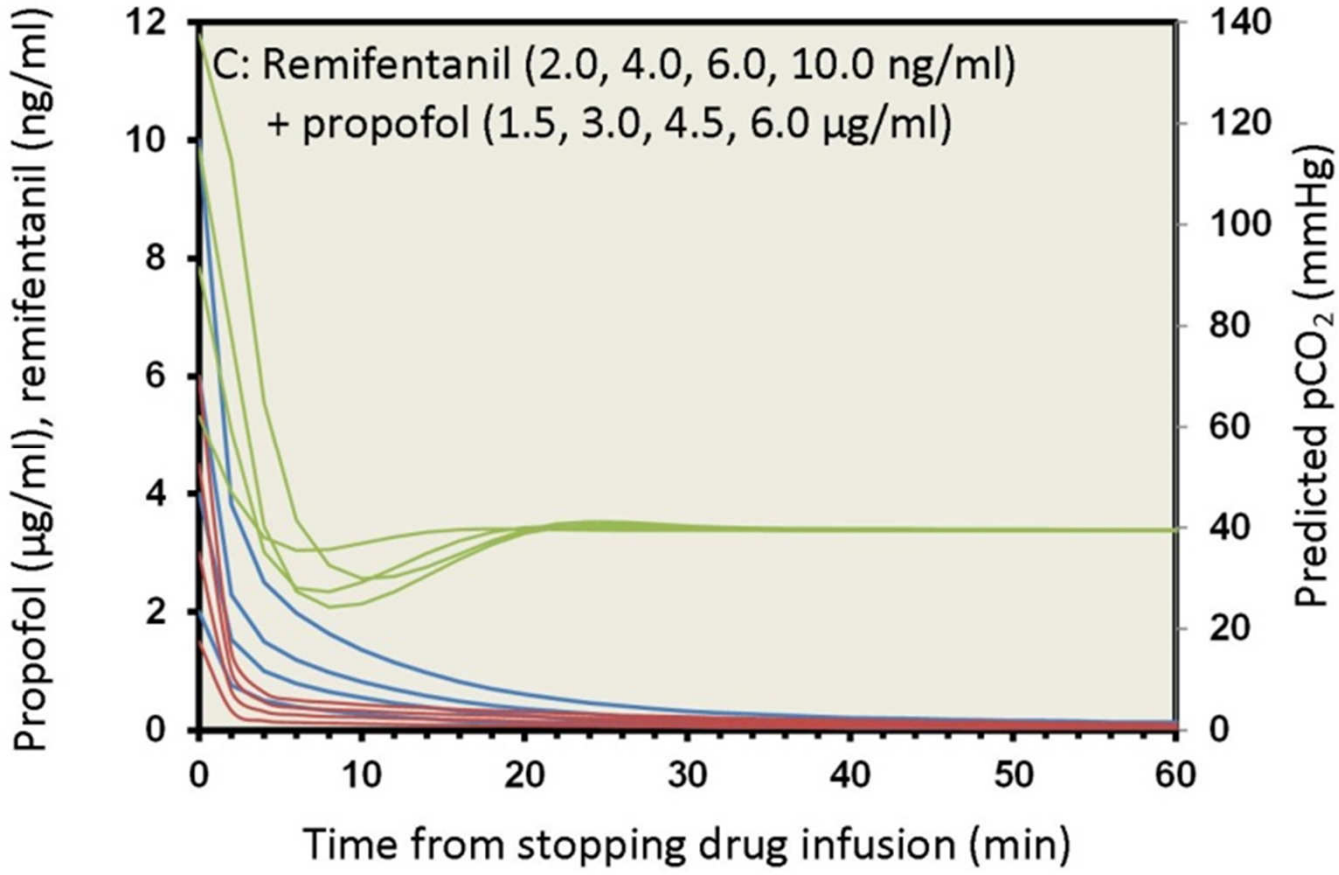
- **Oxygen delivery**
  - **SpO_2**
  - **O_2 Supply**
- **Ventilation**
  - Respiratory Rate: **$ETCO_2$, Impedance, Acoustic, Plethysmogram, exhaled Water Vapor…**
  - Spirometry: TV, minVol
- **CO_2 elimination**
  - **$ETCO_2$**
  - **$PTCO_2$ (transcutaneous sensor)**
  - (Art. Blood gases)



Propofol Remifentanil: Synergy for Respiratory Depression



TCI Propofol-Remifentanil: Recovery of CO2 to normal



Sedation Analgesia and Respiratory Function Summary

- Sedation-Analgesia **is not** General Anesthesia
  - Optimal sedation measures
- Synergistic Respiratory Depression:
  - Measure and Predict
  - Keep control and anticipate
- Integrate influence of noxious stimuli (variability)
  - Noxious stimulus increases 20% for sedation
  - Noxious stimulus has no effect respiratory depression
  - GAG increases 70% requirements pro-remi
- **Always consider the "whole picture"**

Should we measure recovery of cognitive function after Sedation-Analgesia?

Monitoring Cognitive Recovery

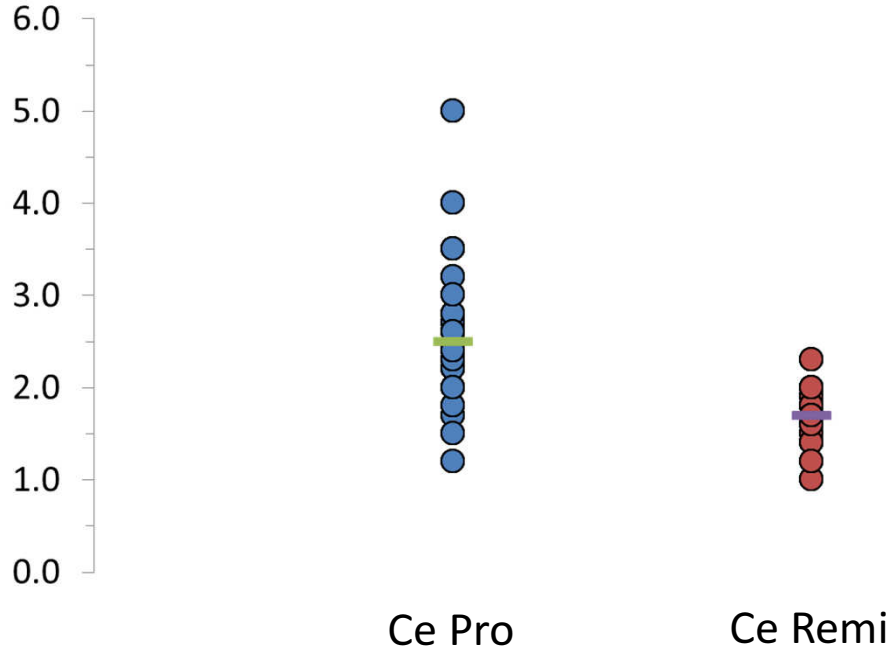
- Outpatients
- Resume normal life
- Conservative approach
  - Discharge criteria from ambulatory surgery
  - Based mostly hemodynamics, side effects
  - Recommend patients taking no responsibility
- Technologic development allows bedside measurement of cognitive function

Monitoring Cognitive Recovery

- 30 patients
- Colonoscopy
- TCI Sedation-Analgesia
  - Propofol
  - Remifentanil
- Cogstate®
  - Pre
  - Basal
  - 10, 40, 120 min after end of colonoscopy
- Cogstate®
  - Attention
    - Detection task
    - Identification task
  - Memory
    - Visual Memory
    - Working Memory
- Presented to the patient with a laptop computer
- Prevent learning effect
  - Prebasal
  - Basal

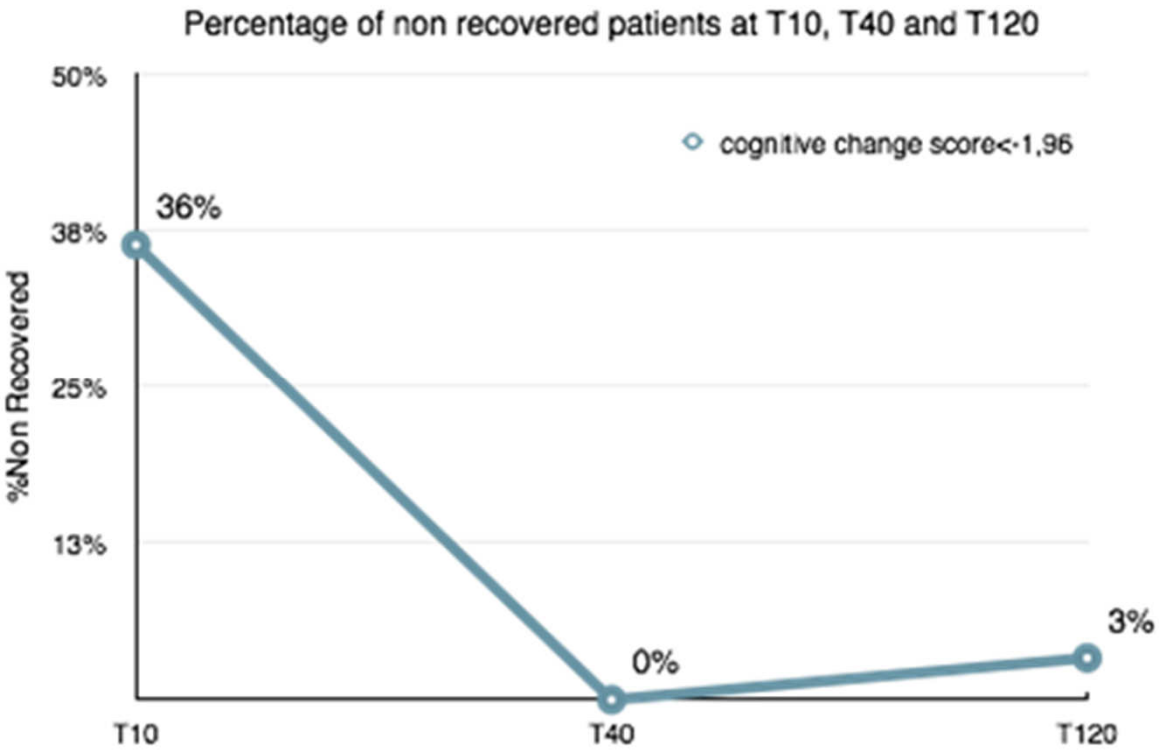
Monitoring Cognitive Recovery

- Median age: 59 years
- ASA 1-2
- Median duration of colonoscopy: 23 min
- Significant changes from baseline, only attention tasks
  - Identification
- Memory (visual or working) not affected



Monitoring Cognitive Recovery

- Further studies required
  - Cognition
  - Ambulatory surgery
- Redefine discharge criteria
- Individualized discharge based on
  - Recovery (side effects, …)
  - **Cognition**



Conclusions

- Expansion of Sedation-Analgesia
- Avoid **serious complications**: improve control
- **Improve control** by
  - **Keep in mind: Sedation** is not general anesthesia
  - Optimal objective monitoring of **sedation**
  - Optimal monitoring **respiratory function**
  - Incorporate factors to **decrease variability in effects**
- **Significant role for TCI systems**
- **Optimize discharge**
  - Evaluate Cognitive Recovery
- **“Personalized Sedation-Analgesia”**