



EDEE Doctoral Programs in Electrical Engineering

EE-600: Usability Engineering

Lecture #11 Full System for Personalized Anaesthesiology In Precision Medicine

What we really mean for Usability?

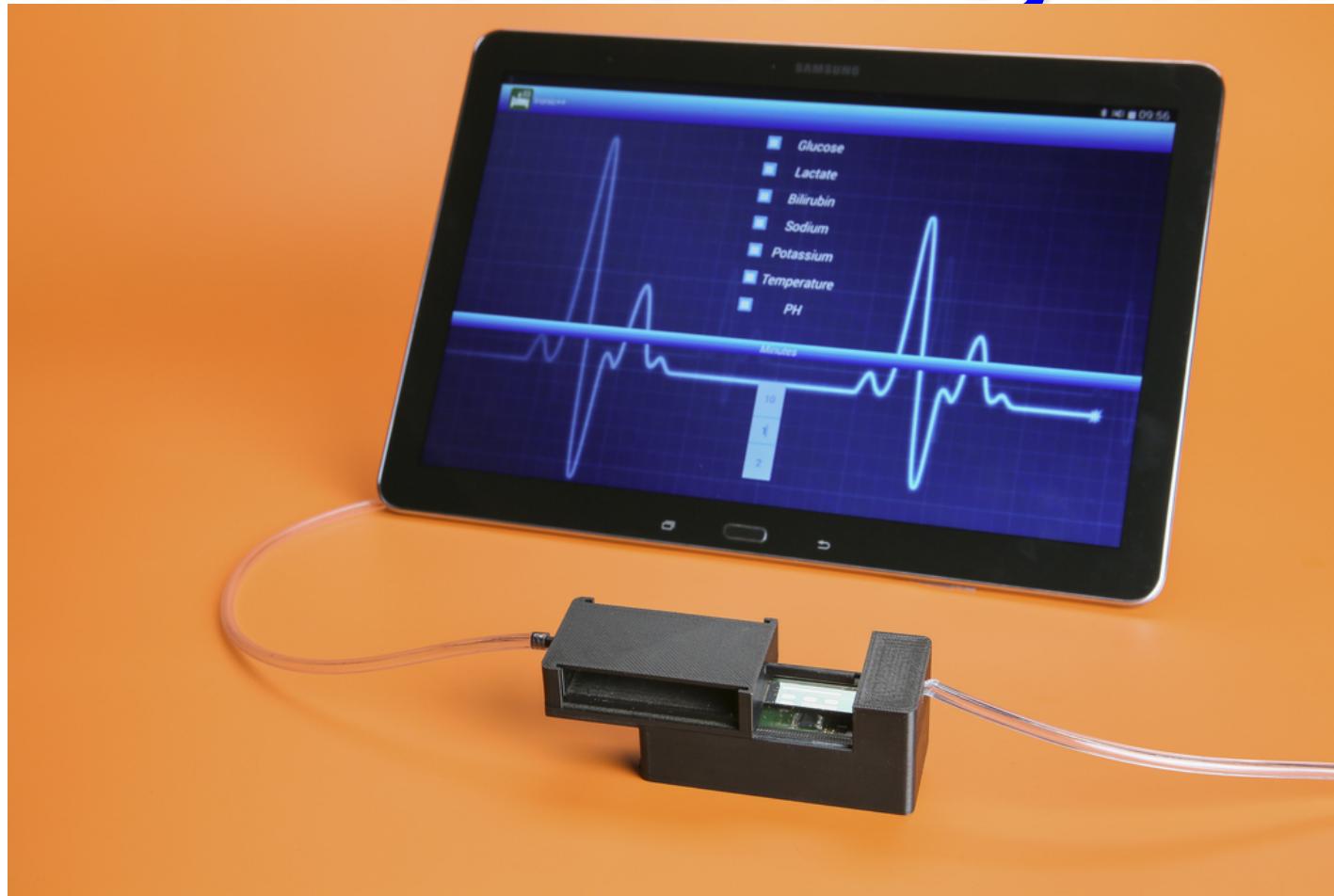
In the context of this course,
“Usability”
is the

“*the evaluation of the
effectiveness use of products
and its safety*”

What then is “Usability Engineering”?

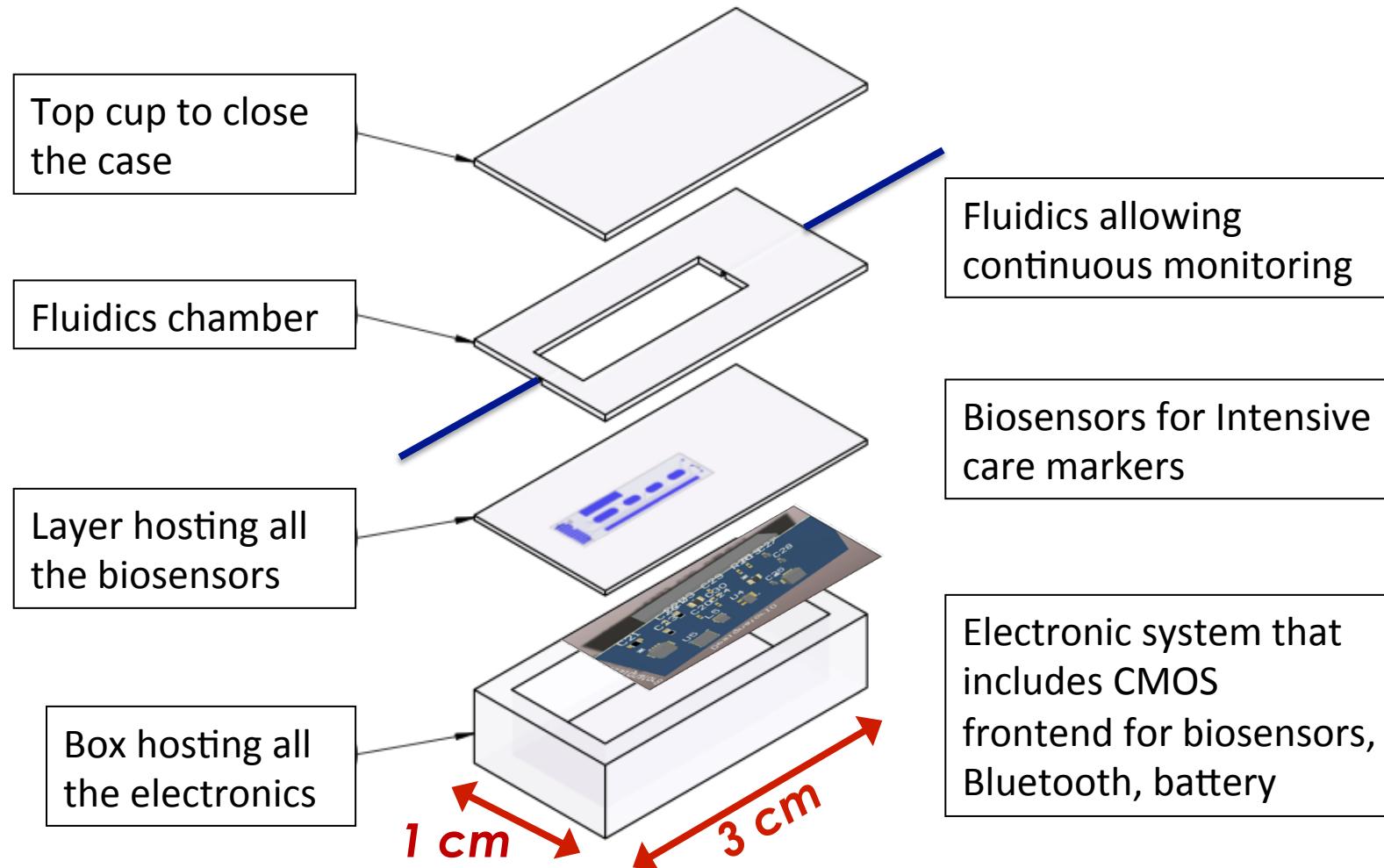
In the context of this course,
“Usability Engineering”
is
“*obtaining the usability
by design*”

The full connected system



The whole system with the AndroidTM interface that allows connectivity too

First Fully-Autonomous system for Continuous monitoring in ICUs

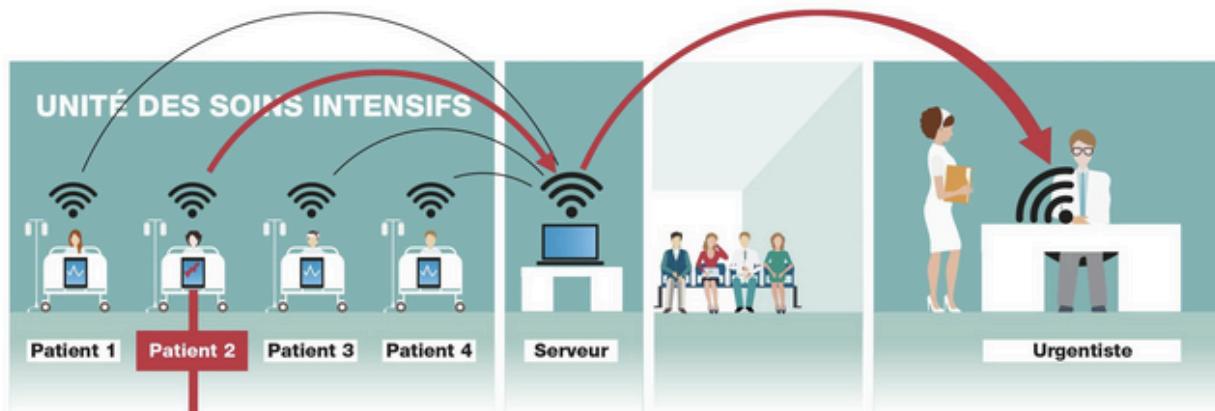


(c) S.Carrara

Remote Patients' monitoring from Smartwatches

Des smartwatch pour alerter les médecins aux soins intensifs

Les patients admis en soins intensifs doivent être sous surveillance constante. Un dispositif de biocapteurs collecte en temps réel les données vitales du malade. Si une anomalie est détectée, une alerte prévient le médecin de garde.



La smartwatch de l'urgentiste est connectée via le wifi au serveur central de l'unité des soins intensifs. Il renseigne en continu le médecin sur l'état de santé de ses patients et l'alerte en cas de problèmes.

(c) S.Carrara

EPFL Infographic: Pascal Coderay

...from Tablet to Smartwatches...



(c) S.Carrara

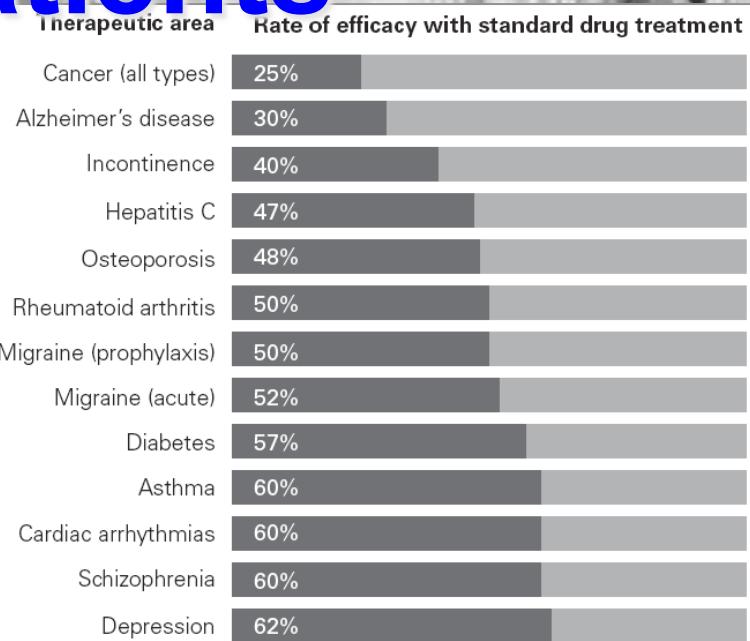
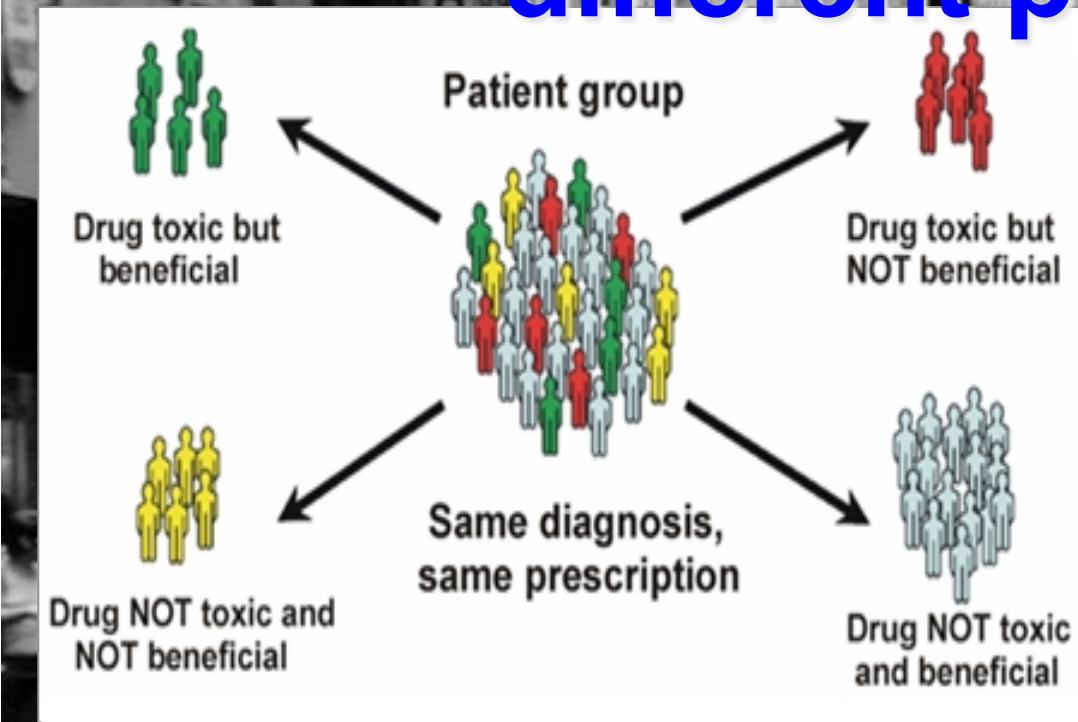
One Interface for Remote Monitoring of Patients in Intensive Care Units



Image | Bam Labs

The whole system with the AndroidTM interface that allows connectivity too

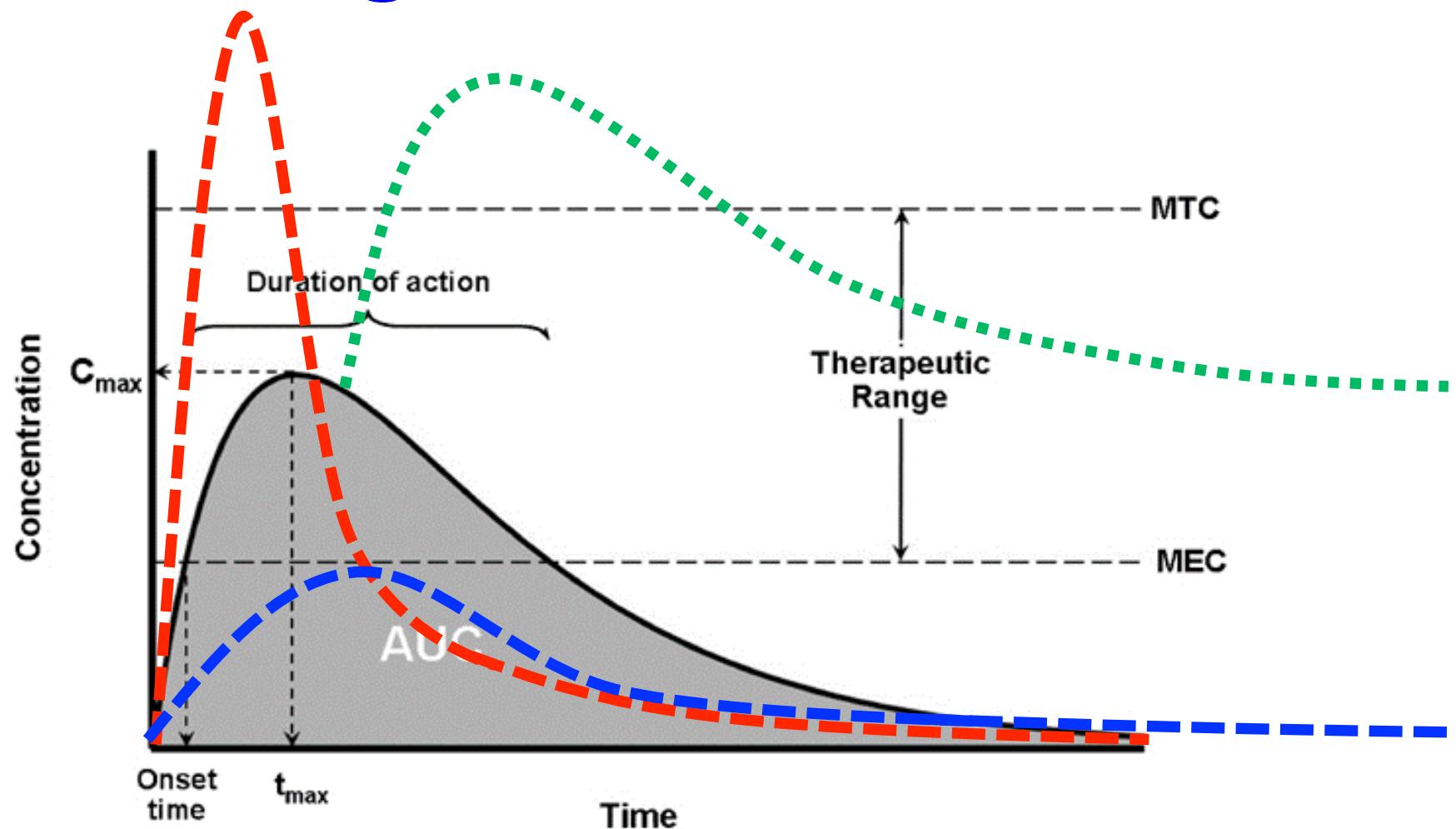
Different outcomes for different patients



For depression, the data apply specifically to the drug class known as selective serotonin reuptake inhibitors.

Source: Brian B. Spear, Margo Heath-Chiozzi, and Jeffrey Huff, "Clinical Application of Pharmacogenetics," *Trends in Molecular Medicine* (May 2001).

Patients' metabolism drive the Drugs effect in time!



(c) S.Carrara

What “TDM” Stands for?

In the context of this course,

“TDM”

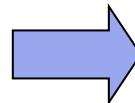
stands for

“*Therapeutic Drug Monitoring*”

TDM : Classical procedures



Information
+ Treatment



Blood imatinib measurement request
 This form serves for case report form in the Imatinib Concentration Monitoring Evaluation study

CHUV Centre hospitalier universitaire de lausanne
 DEPARTEMENT DE PATHOLOGIE ET DE MEDICINE DE LABORATOIRE

PATIENT:
 Last name: _____
 First name: _____
 Gender: female male
 Full certificate: _____

APPLICANT:
 First name: _____
 Last name: _____
 Address: _____
 Phone: _____

Conditions required: stable treatment over at least 1 week
 (minimum 3 ml of EDTA or whole blood)

ESSENTIAL INFORMATION

IMATINIB TREATMENT START: (date) **IMATINIB TREATMENT STOP:** (date)
ACTUAL DATE AND TIME OF DAMPING: **ACTUAL DATE AND TIME OF LAST DOSE:**
GIMe® (imatinib): mg (date) **HEIGHT:** cm **BODY WEIGHT:** kg

OTHER CONCOMITANT DRUGS (taken during last week): **REASON:**

DIAGNOSIS: (possibility of attaching raw data as appendix)
 CML: chronic accelerated blastic initial diagnosis:
 Hematological response: complete partial absent Date of evaluation:
 Cytogenetic response: % Ph+ cells Date of evaluation:
 Molecular response: % BCR-ABL transcript (international scale) Date of evaluation:

TOXICITY SIGNS AND SYMPTOMS:
 no yes (please check and source the adverse events reported by the patient MDCT-CAE 3.0, see verso)
 Neutropenia Thrombocytopenia Anemia
 Increased transaminases Hemorrhages Nausea/vomiting/dyspepsia
 Increased creatinine Skin rash/itching Diarrhea
 Fluid retention/edema Dizziness/vertigo Headache
 Other: _____

OTHER CLINICAL INFORMATION OF INTEREST: (inpatient admission, other diseases, etc.) _____

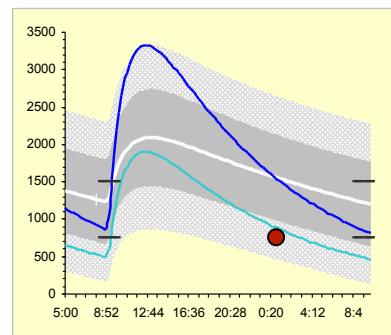
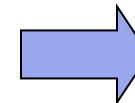
CLINICAL INVESTIGATION:
 In vitro (baseline/both arms) Study visit (both arms) Routine TDM (only for intervention arms)
 Therapeutic failure/progression Suspicion of toxicity Other: _____

ATTACHMENTS: Blood counts Biochemistry lab results Cytogenetic response Molecular response

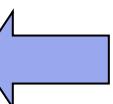
Received at PCL laboratory on: _____ Visit: _____ (to be filled by the laboratory) Period: _____



Blood sampling



Interpretation
+ Recommendations



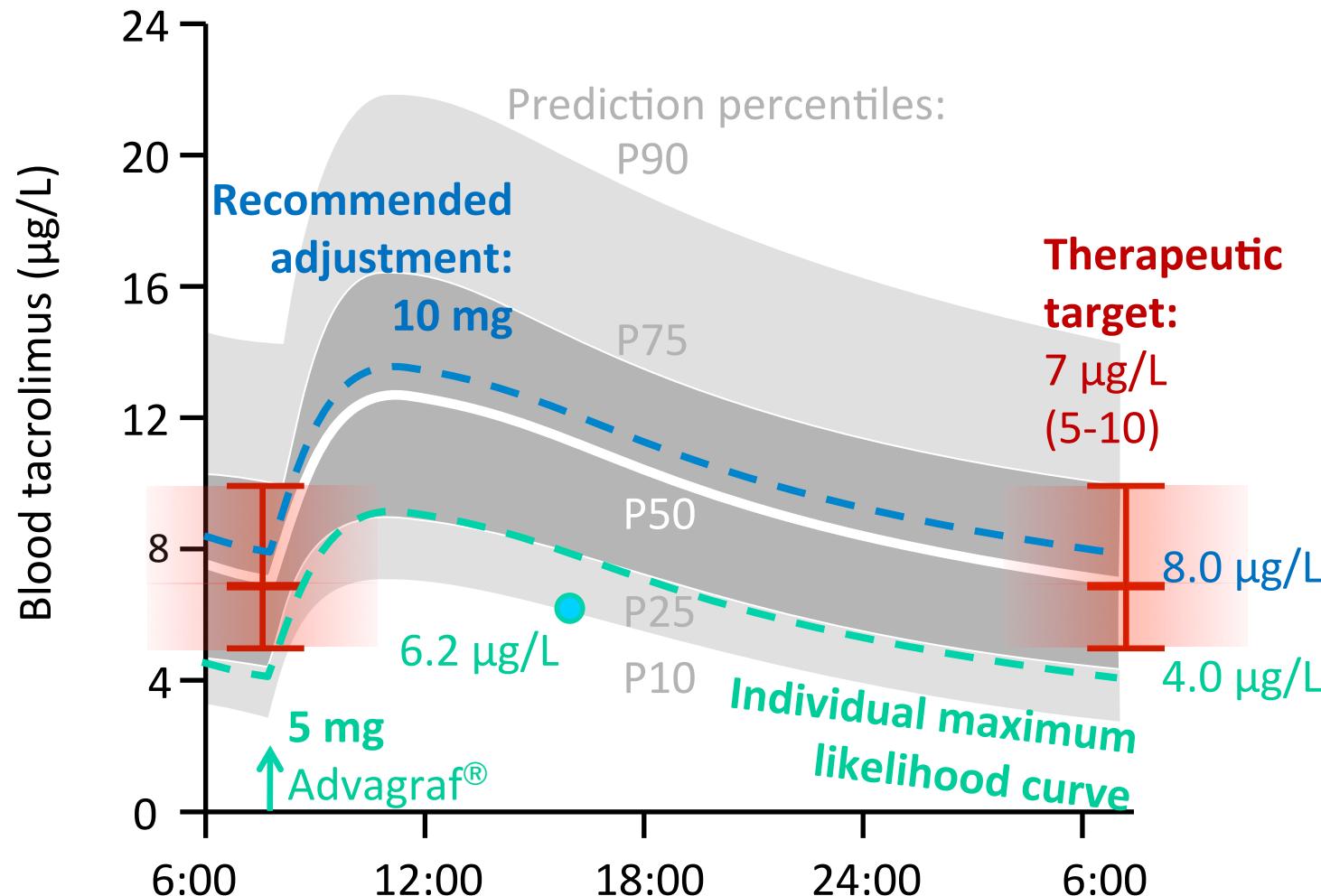
Concentration measurement



Sample postage

Bayesian TDM interpretation

Example: Tacrolimus, extended release formulation (Advagraf®)



Intravenous anaesthesia: Traditional approach

- Propofol first choice
- The anaesthetist must start the infusion at high rate, then slow it down progressively to reach and maintain a plateau

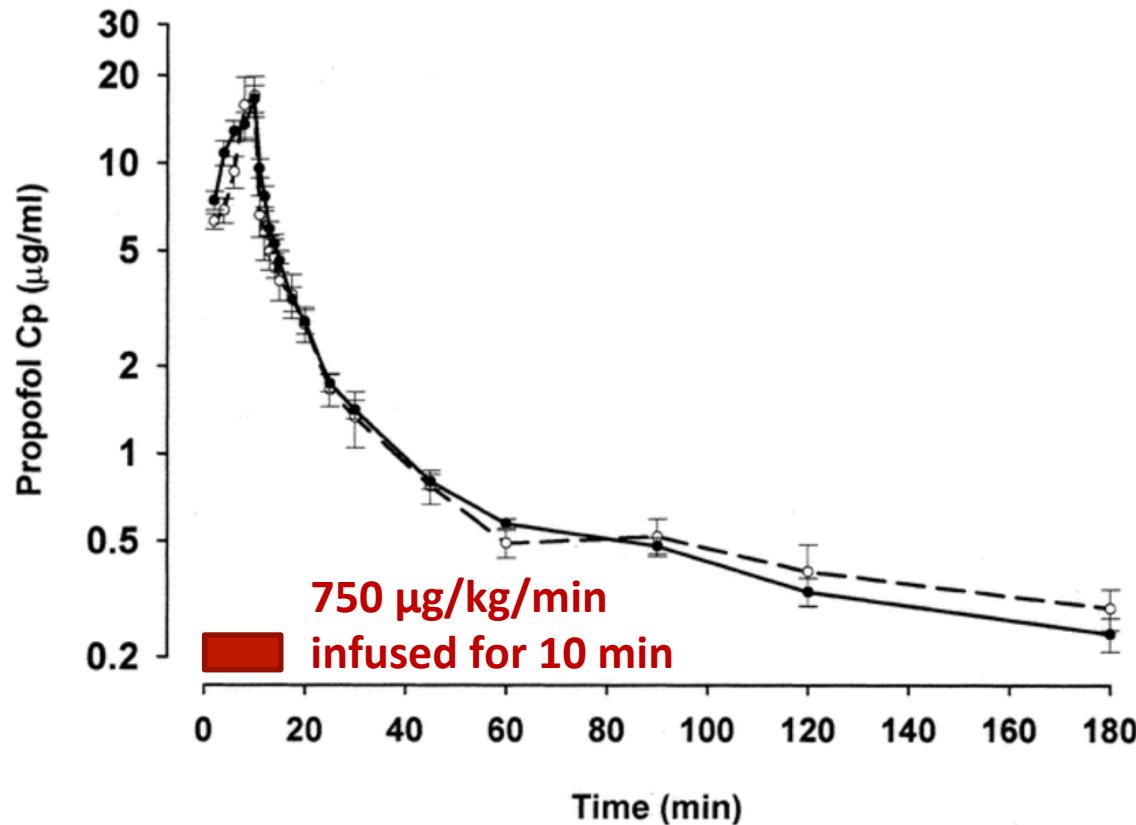


Manual infusion scheme for a target concentration of 3 mg/l :

- loading dose of 1 mg/kg*
- followed immediately by an infusion of 10 mg/kg/h for 10 min*
- 8 mg/kg/hour for the next 10 min*
- and 6 mg/kg/hour thereafter.*

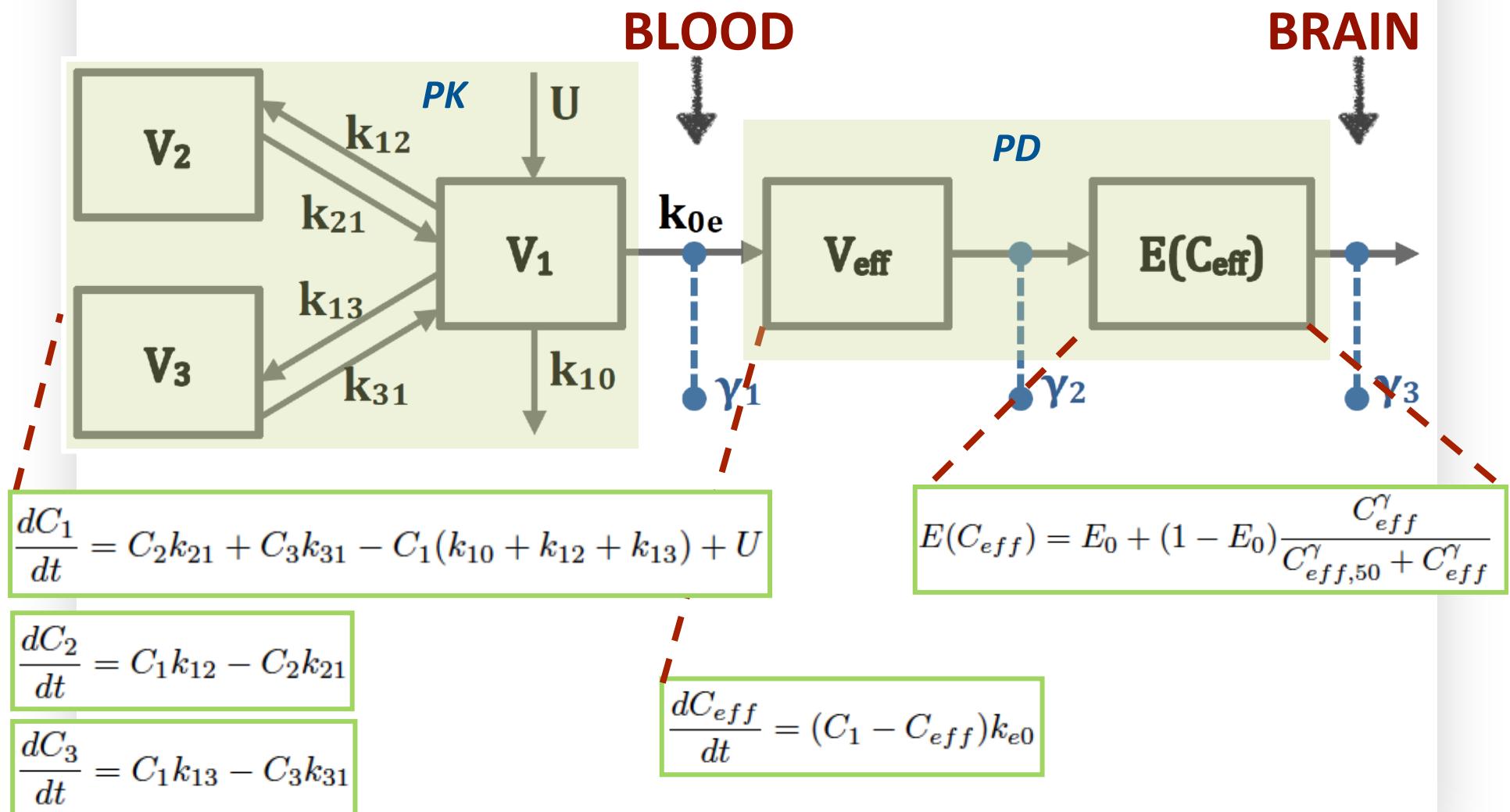
Roberts FL & al. Induction and maintenance of propofol anaesthesia. A manual infusion scheme. Anaesthesia. 1988;43 S:14-7

Propofol : Multiexponential Pharmacokinetics



Johnson KB & al. Influence of Hemorrhagic Shock Followed by Crystalloid Resuscitation on Propofol. Anesthesiology 2004;101:647-59

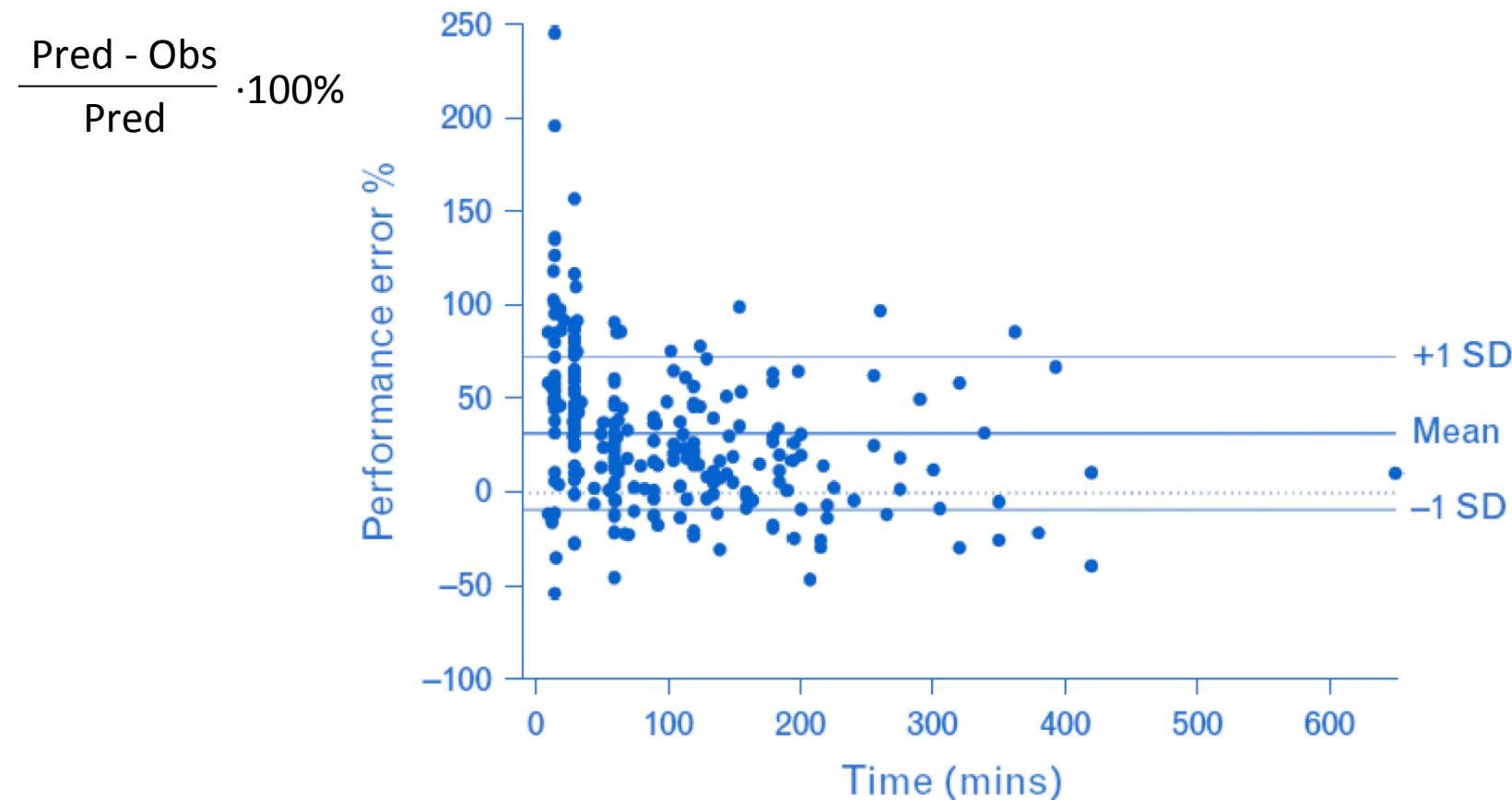
Propofol PK-PD model



Courtesy, Alena Simalatsar

Known inaccuracies and bias

254 measurements in 50 TCI patients (Marsh model)



Cowley NJ & al. Eur J Anaesthesiol 2013;30:627-32

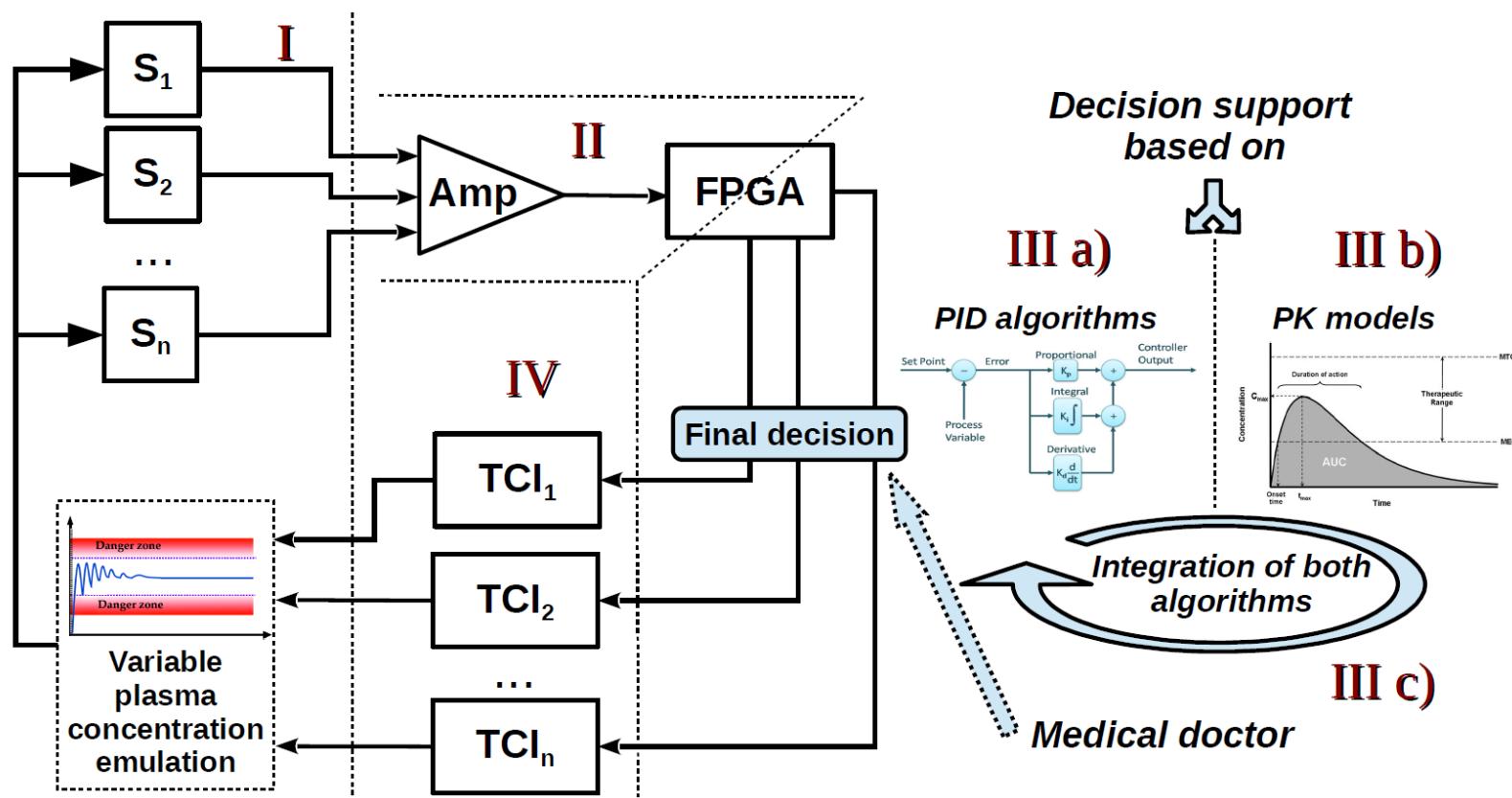
Intravenous anaesthesia: Target Controlled Infusion (TCI)

- The anaesthetist chooses a target concentration exposure (blood or brain)
- A computer-driven pump calculates the suitable infusion regimen to reach this exposure, based on an internal PK model
- The same model is applied to all patients:
 - no personalization for individual characteristics influencing PK
 - no account for the large between patient PK variability
 - open-loop algorithm, without feedback from patient response

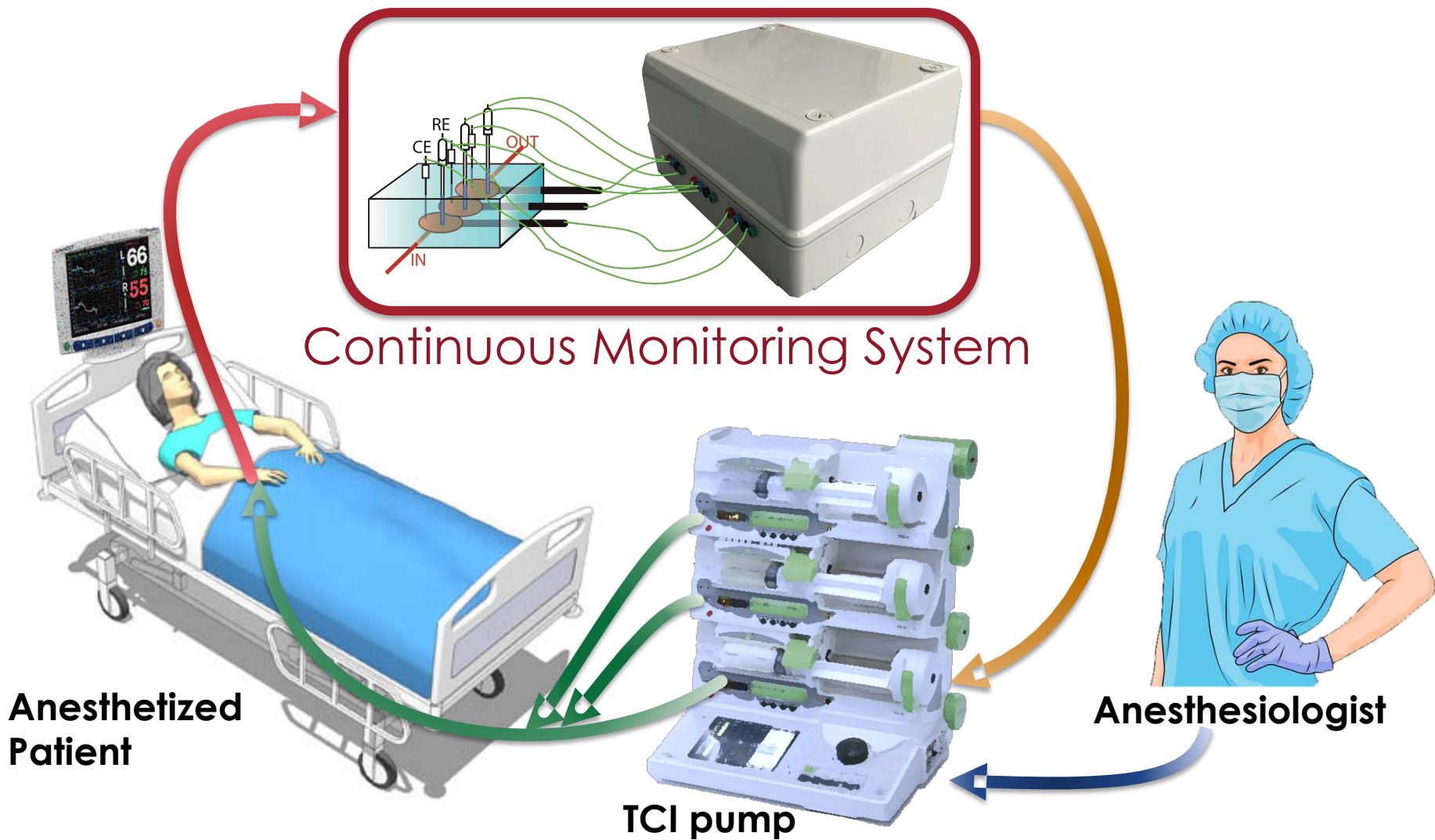


Fresenius Kabi Orchestra® Base Primea

The solution: Monitoring integrated in the Pump

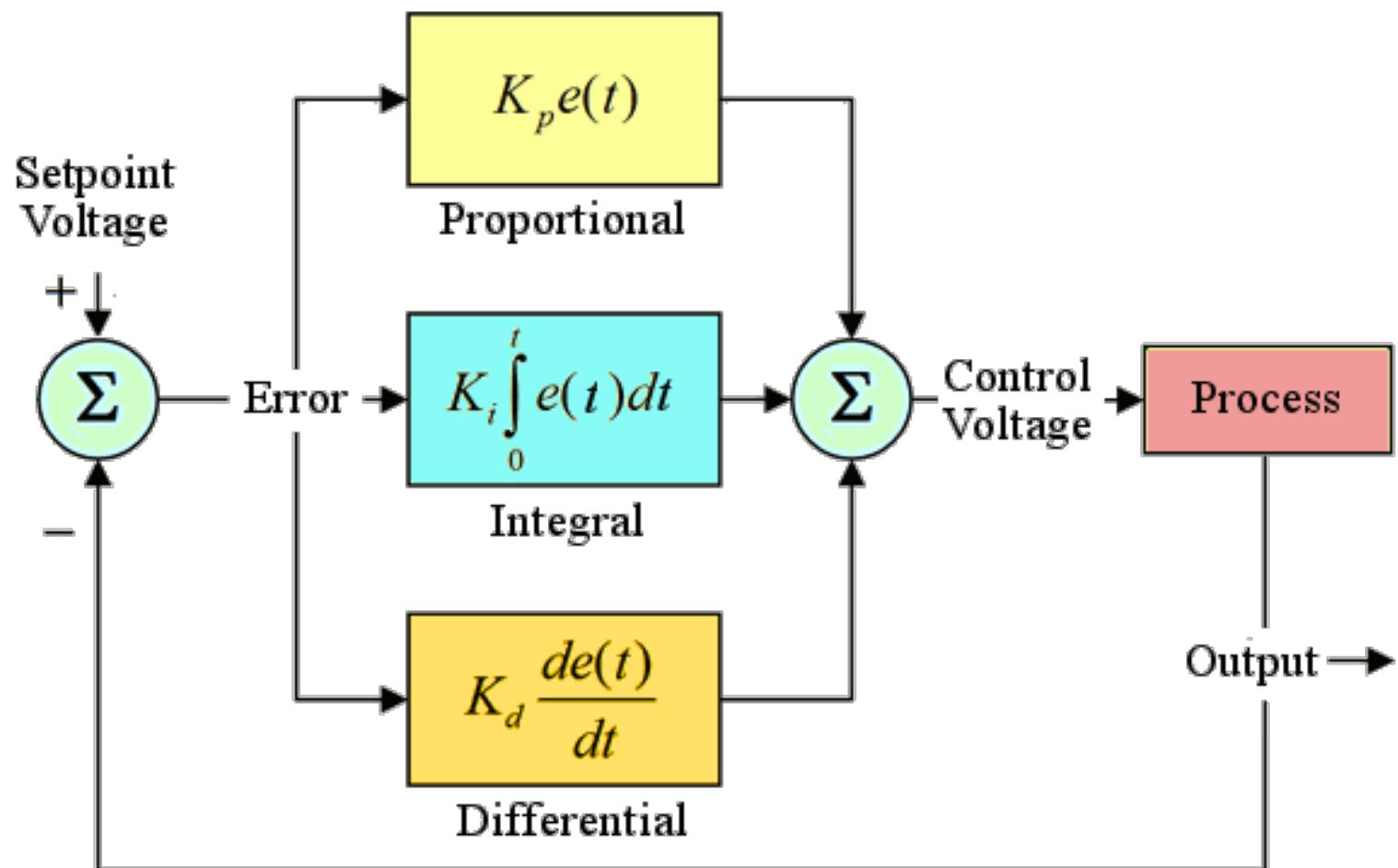


Monitoring during Anesthesia



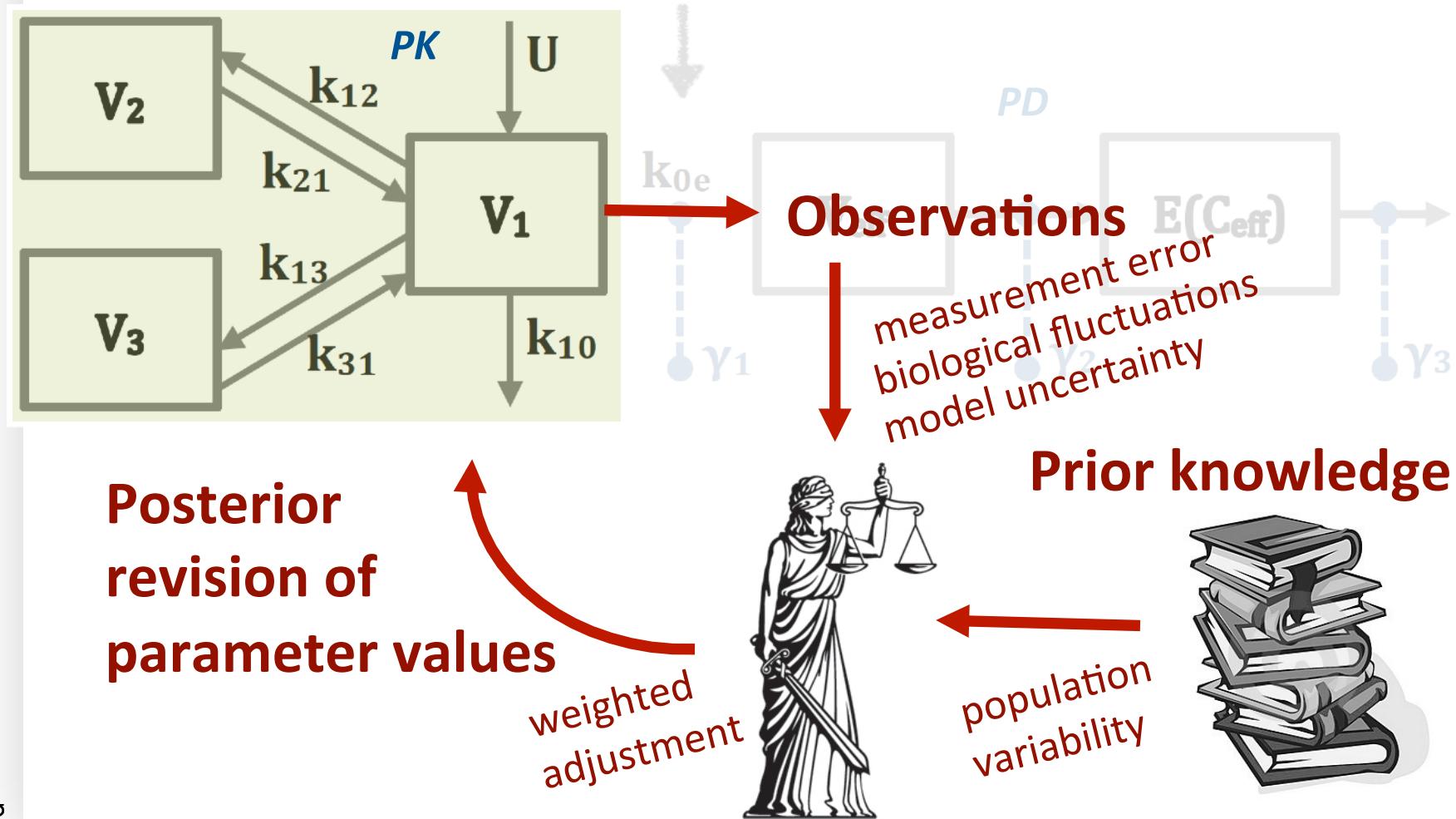
Feed-back: PID Controller

(PK-unaware!)

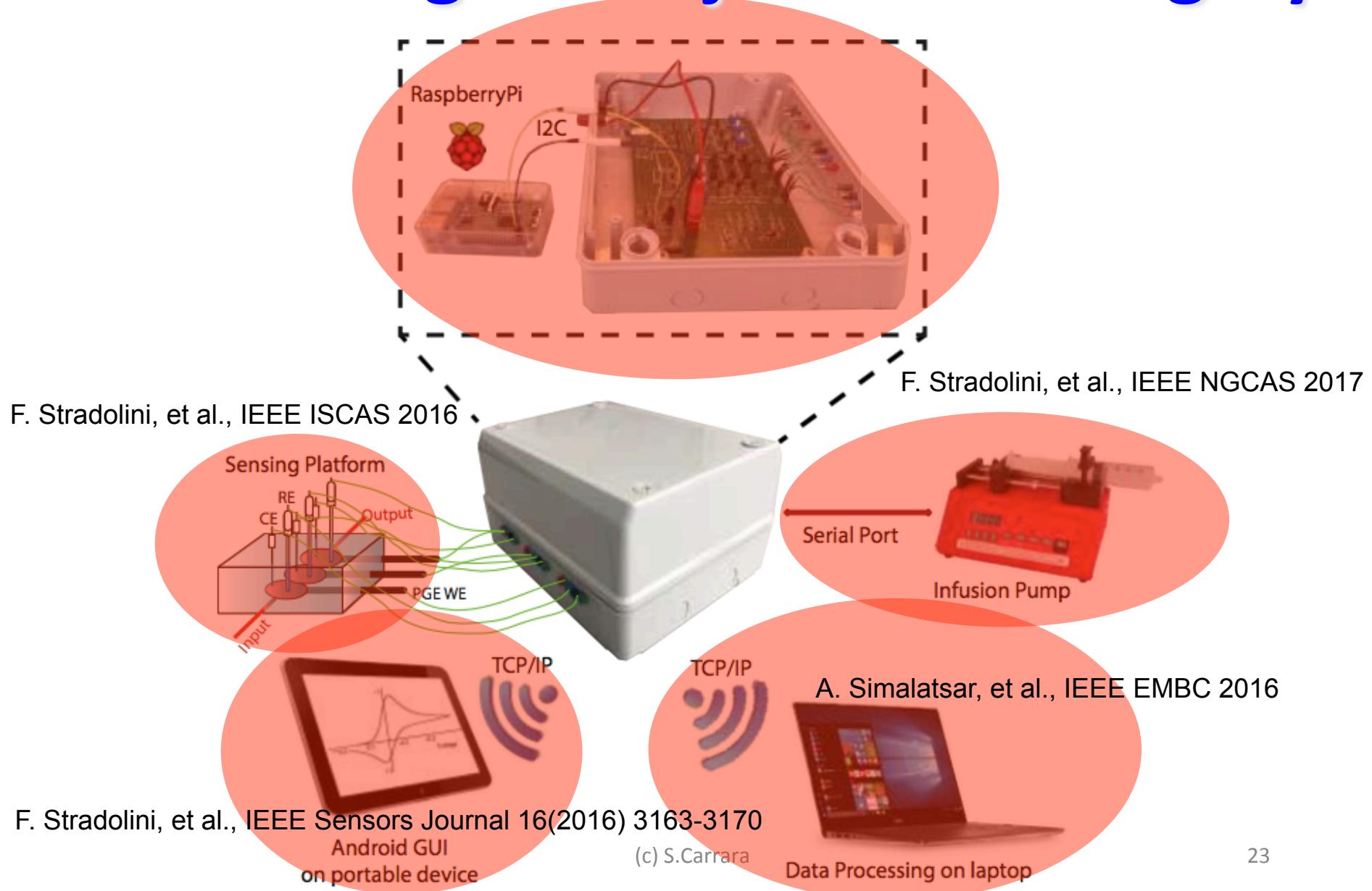


Feed-back: Bayesian adjustment

Prediction



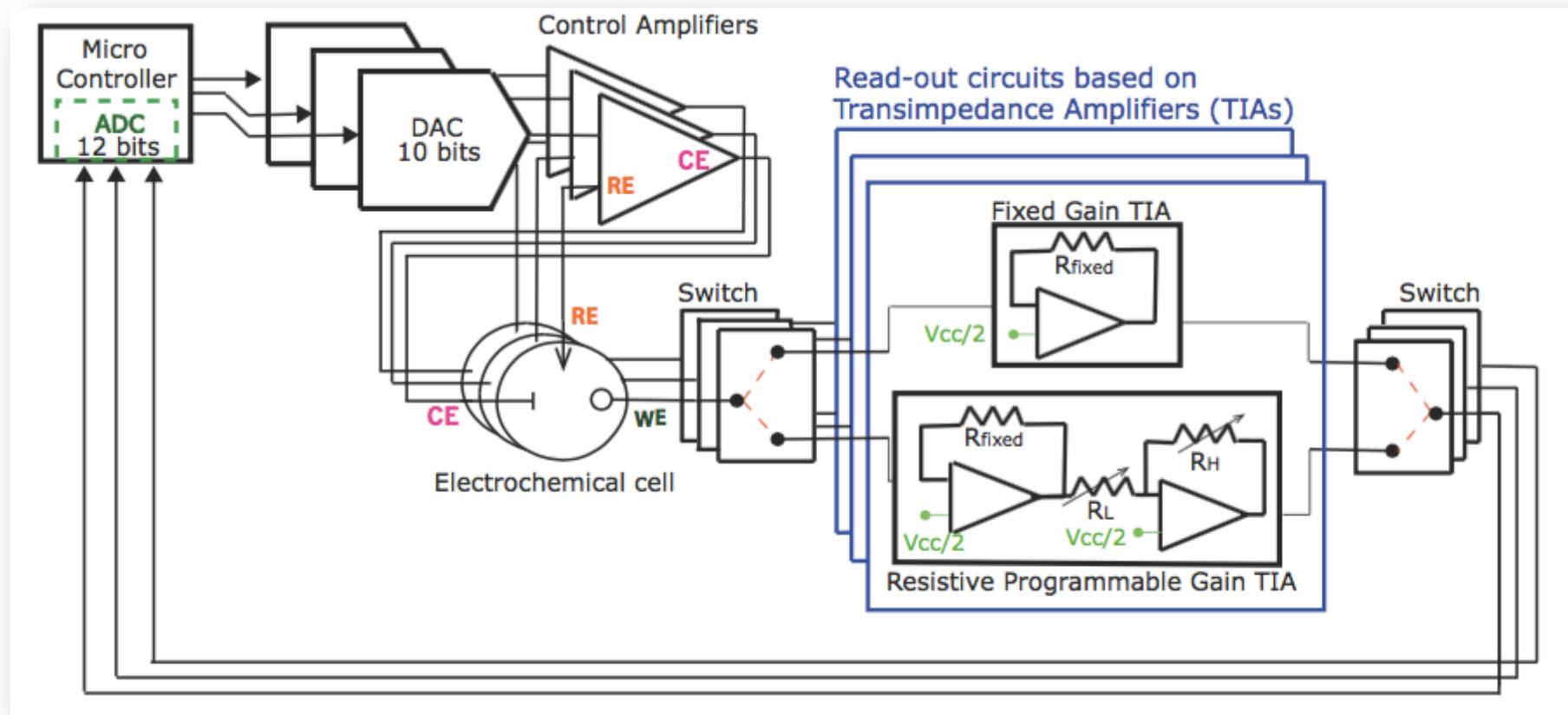
Monitoring and Injection in Surgery



Drug Cocktails usually used in Anaesthesiology

- Propofol (an anaesthetics)
- ~~Fentanyl~~ (an analgesic) **Paracetamol**
- Midazolam (a muscle relaxant)

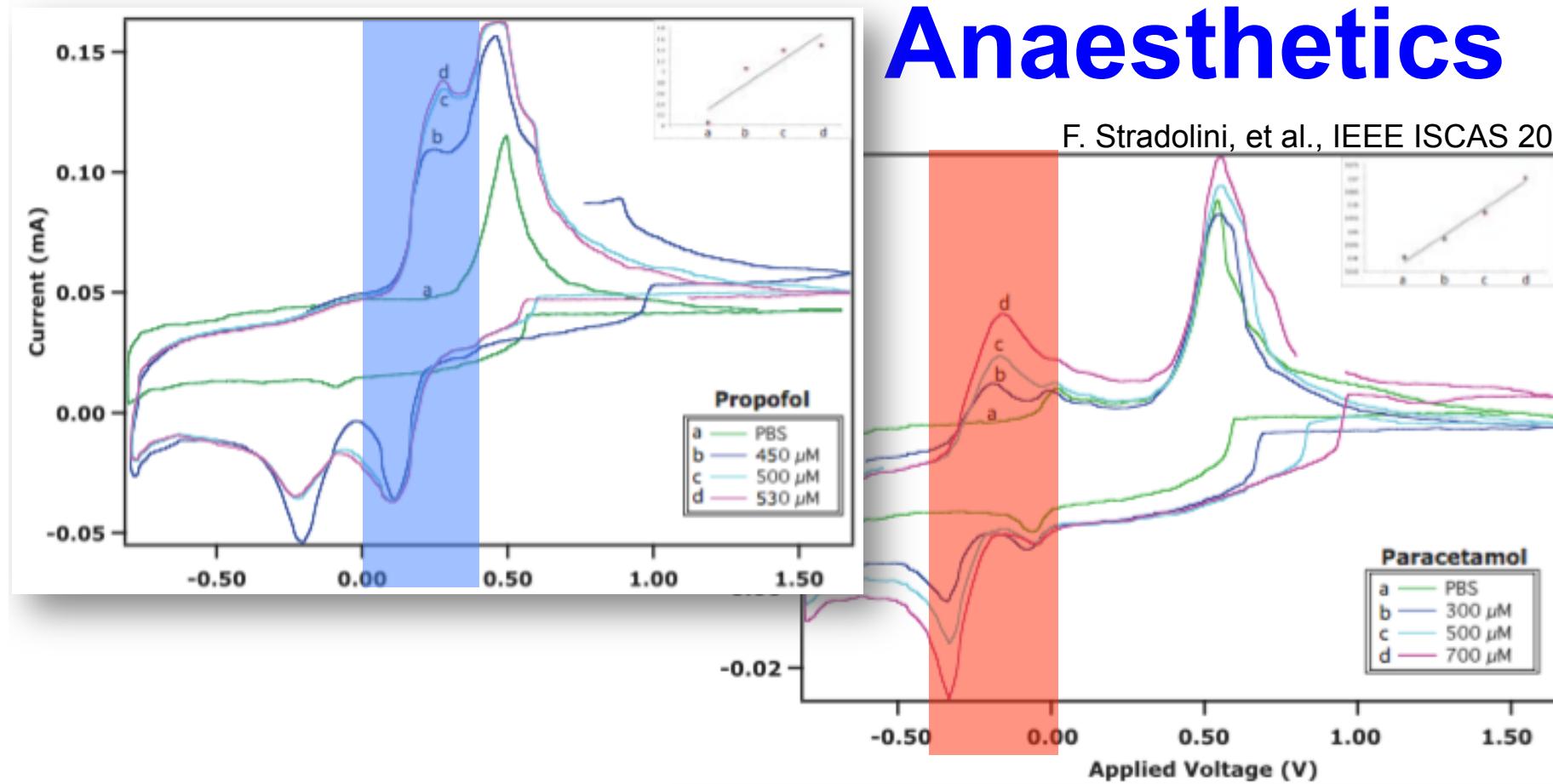
Detection of Anaesthetics



F. Stradolini, et al., IEEE ISCAS 2016

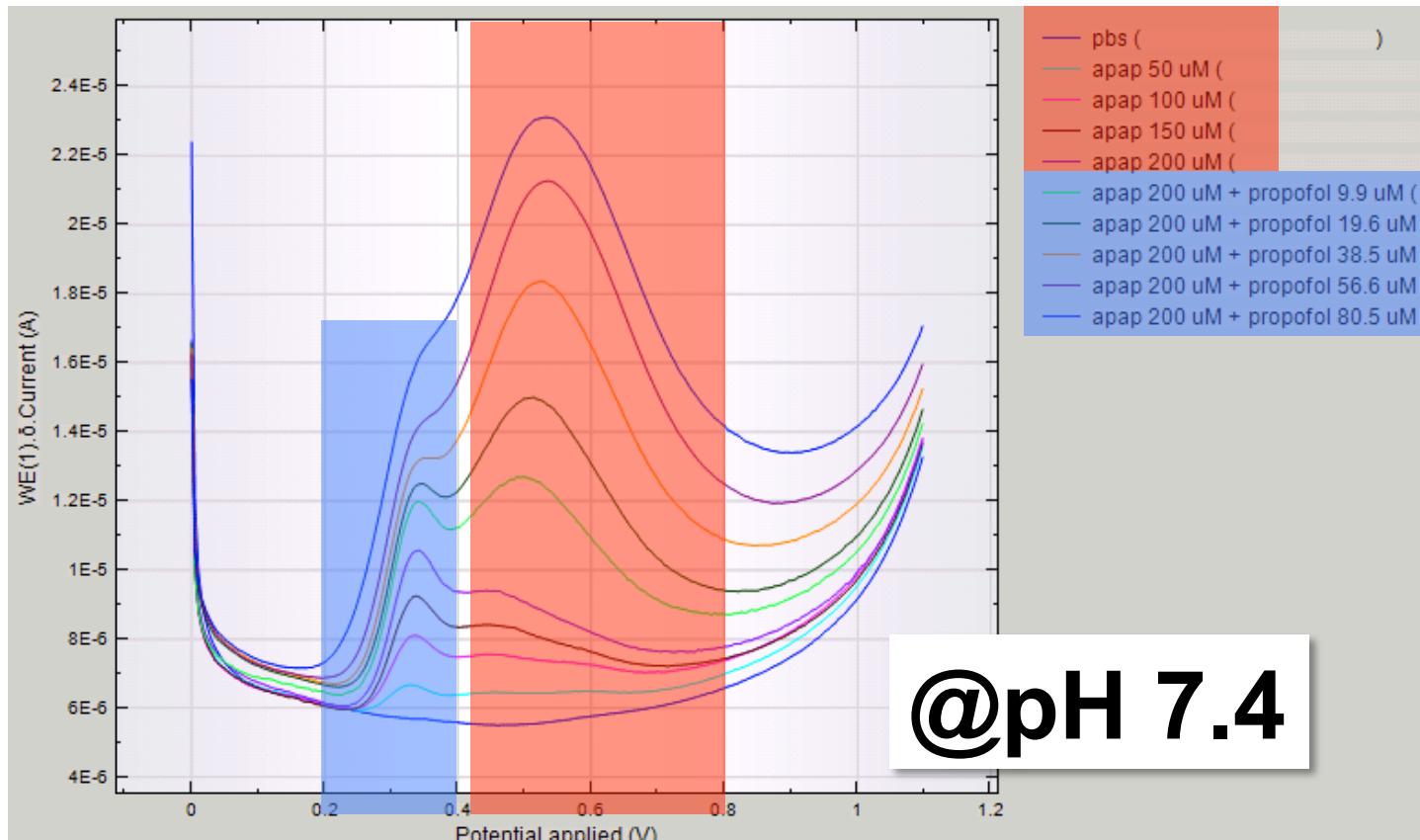
Multiplexed reading of the the different sensors for the anaesthetics in grounded-working configuration

Electrochemical detection of Anaesthetics



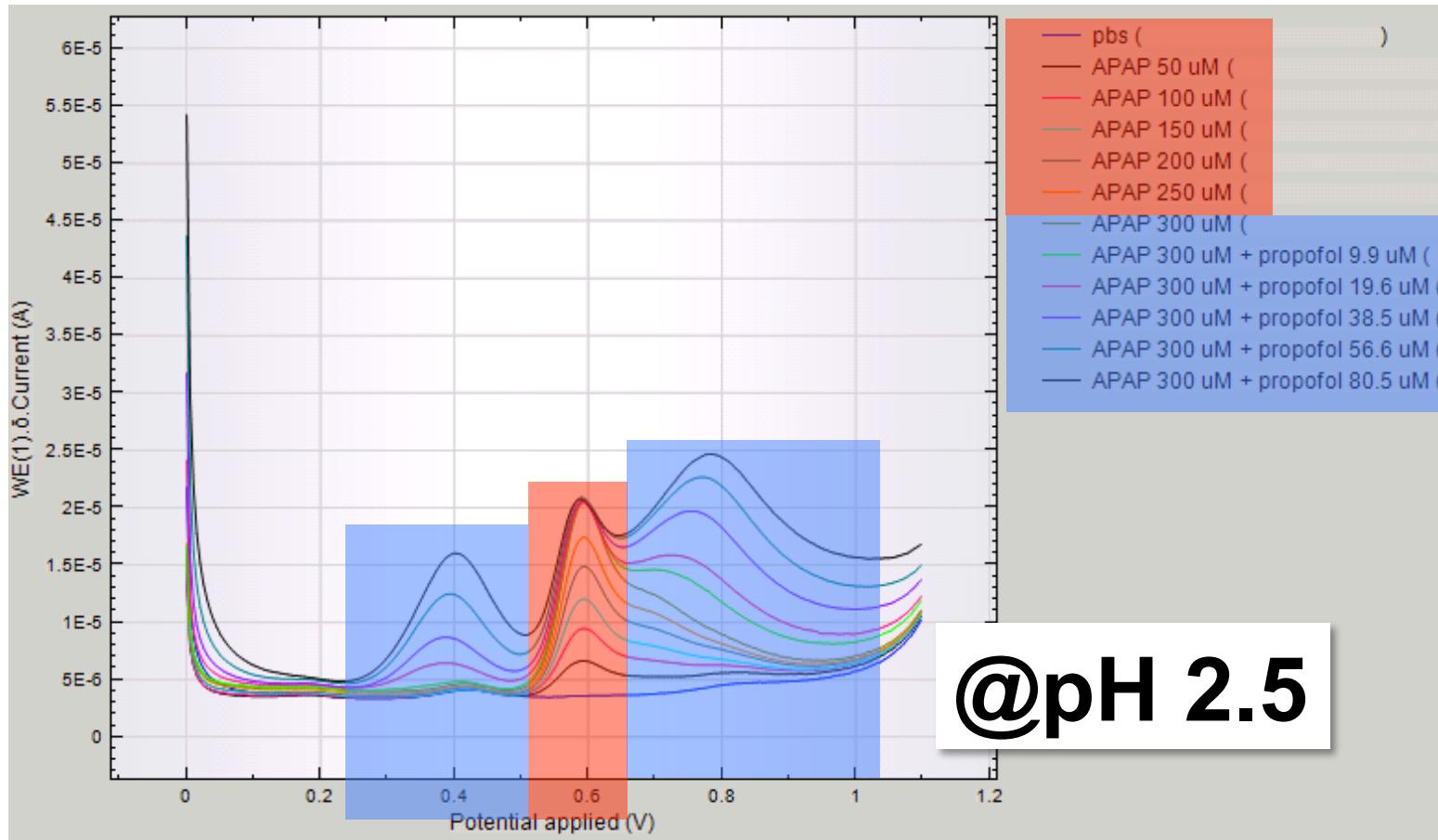
Cyclic Voltammograms measured for propofol and paracetamol with carbon electrodes

Multiplex of Anaesthetics



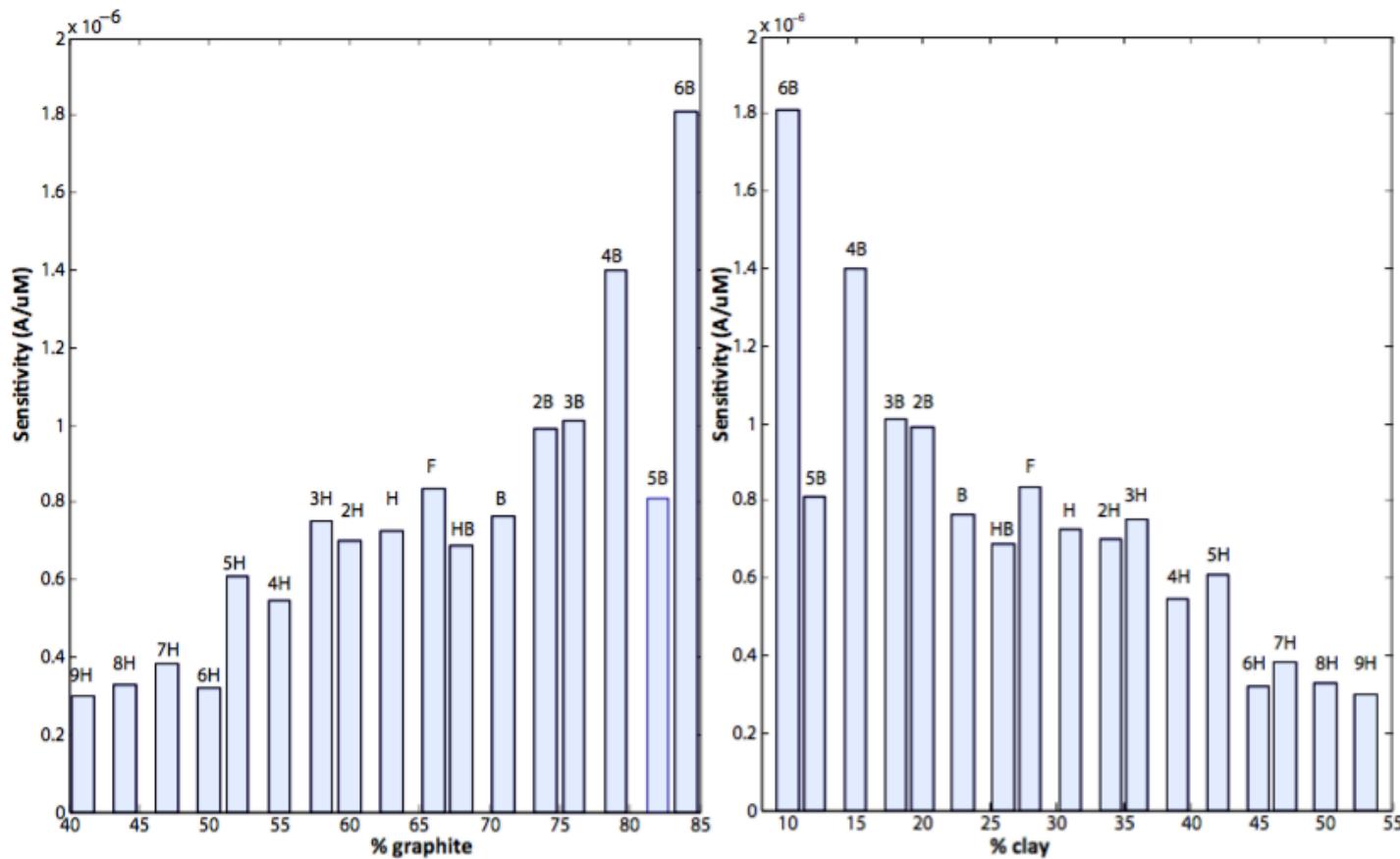
Cyclic Voltammograms measured for propofol and paracetamol (APAP) with Pencil Graphite Electrodes

Multiplex of Anaesthetics



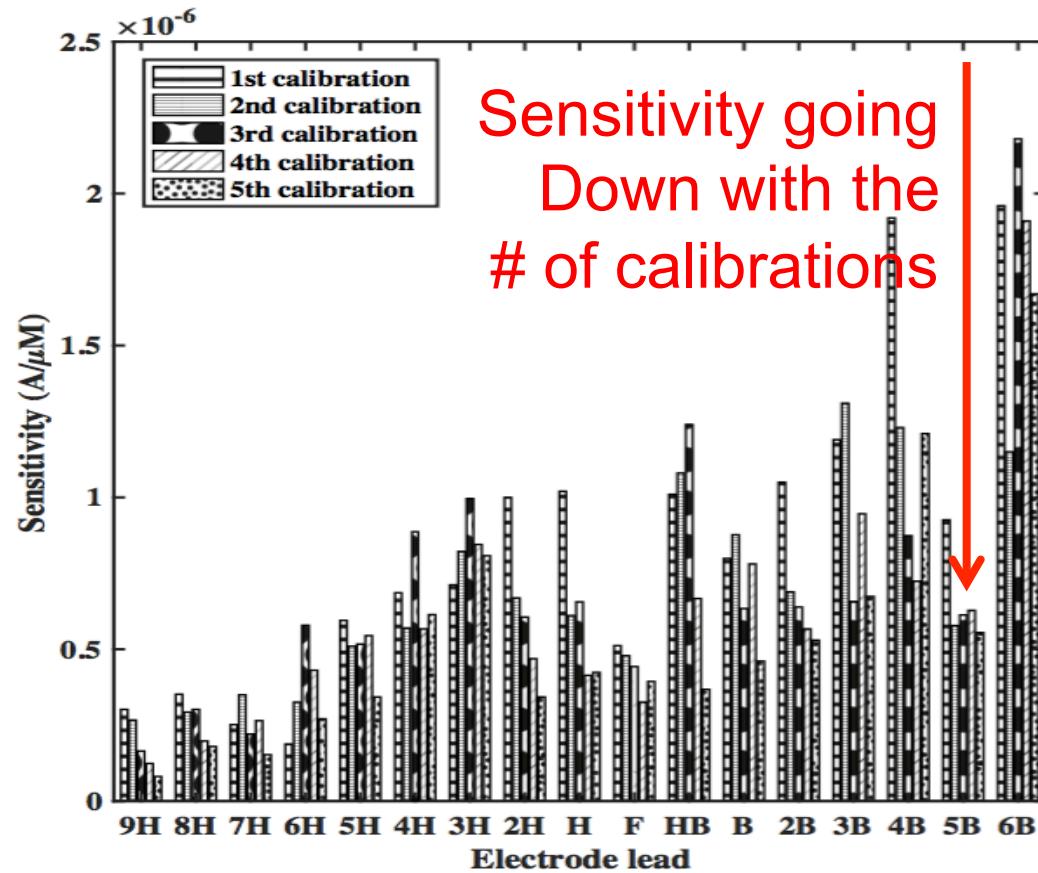
Cyclic Voltammograms measured for propofol and paracetamol (APAP) with Pencil Graphite Electrodes

Detection of Anaesthetics



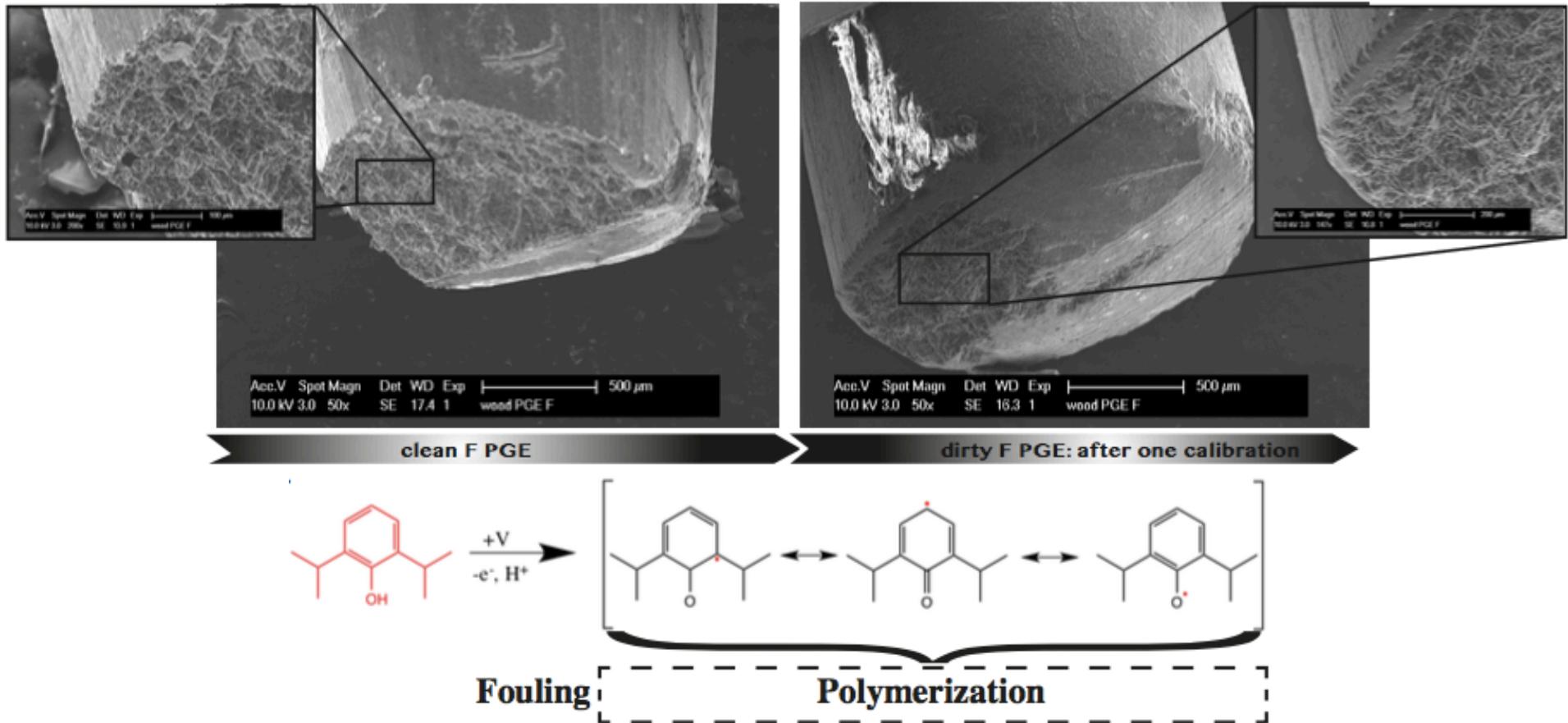
Comparison in sensitivity for different % of graphite and clay in lead compositions

Detection of Anaesthetics



Shows the intra-electrode sensitivities obtained by five subsequent propofol calibrations performed on each PGE. Trend for all the different graphite lead compositions are reported

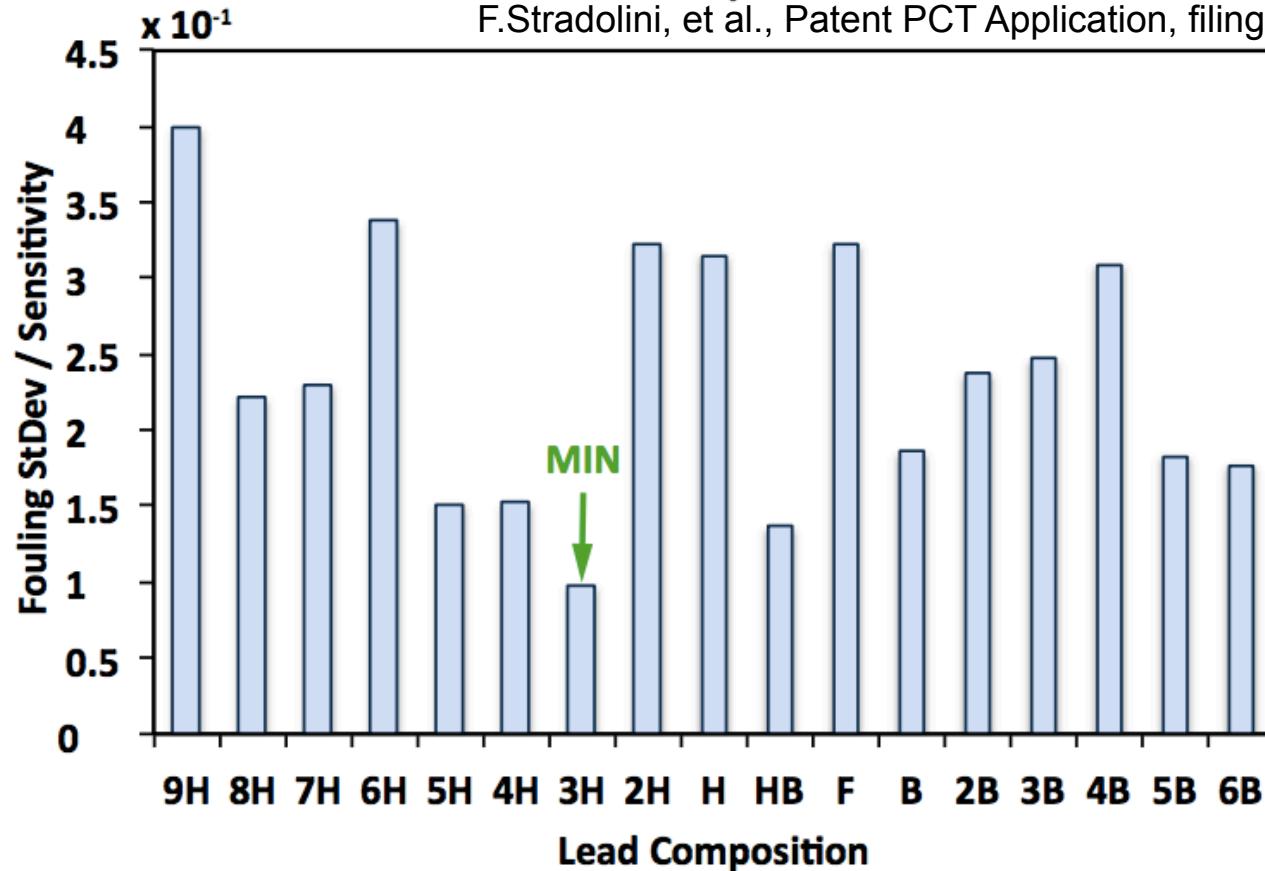
Detection of Anaesthetics



Sensitivity is going down due to issues related to Fouling of Propofol onto the graphite electrode: SEM images and suggested mechanism of propofol electro-oxidation reaction

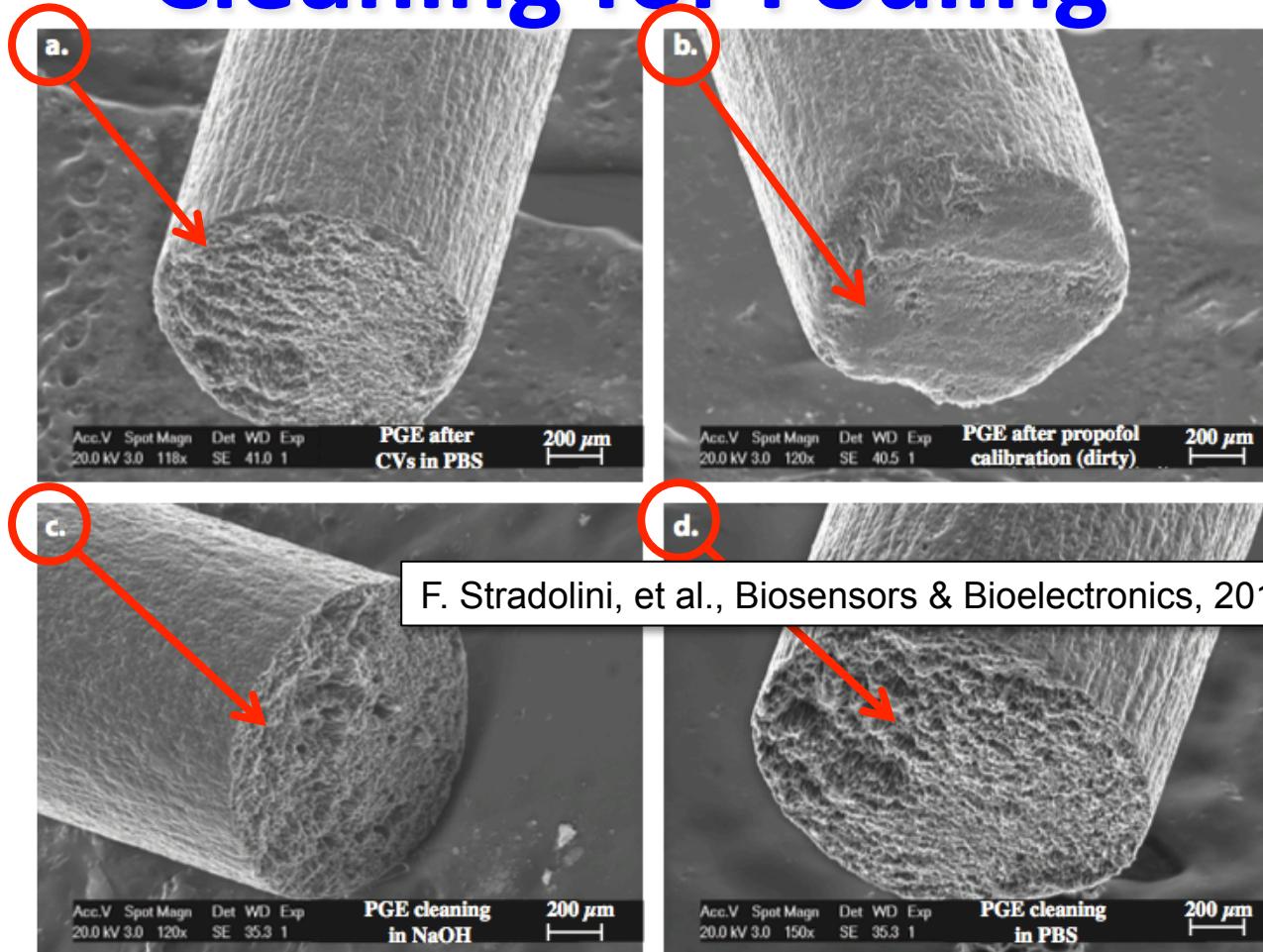
Detection of Anaesthetics

F.Stradolini, et al., Patent PCT Application, filing date May 30, 2017



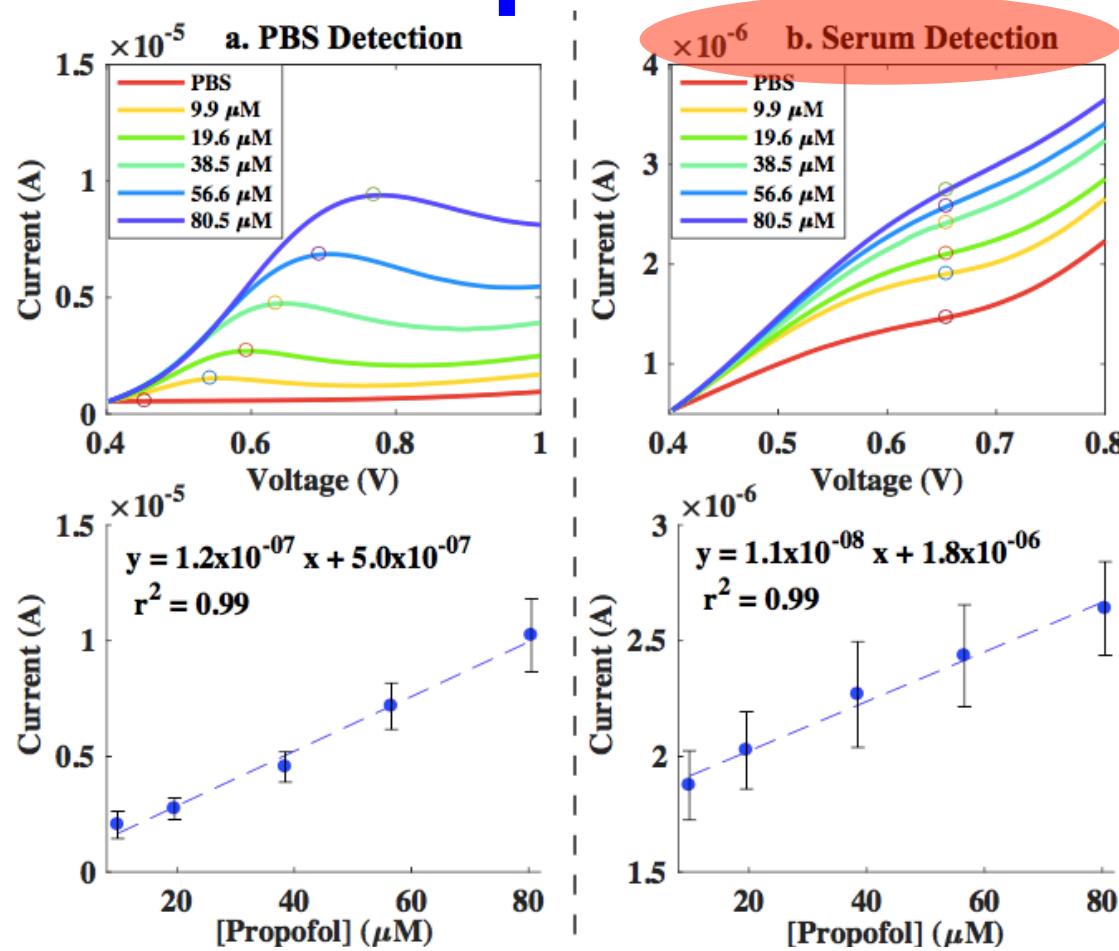
Variability in S for subsequent propofol calibrations on the same electrode respect to the average S of the electrode itself
(Fouling StDev/Sensitivity)

Cleaning for Fouling



SEM images: a.) bare electrode after 5 cycles of CV in only PBS (background electrolyte), b.) after one propofol calibration, c.) after NaOH cleaning and d.) after PBS cleaning

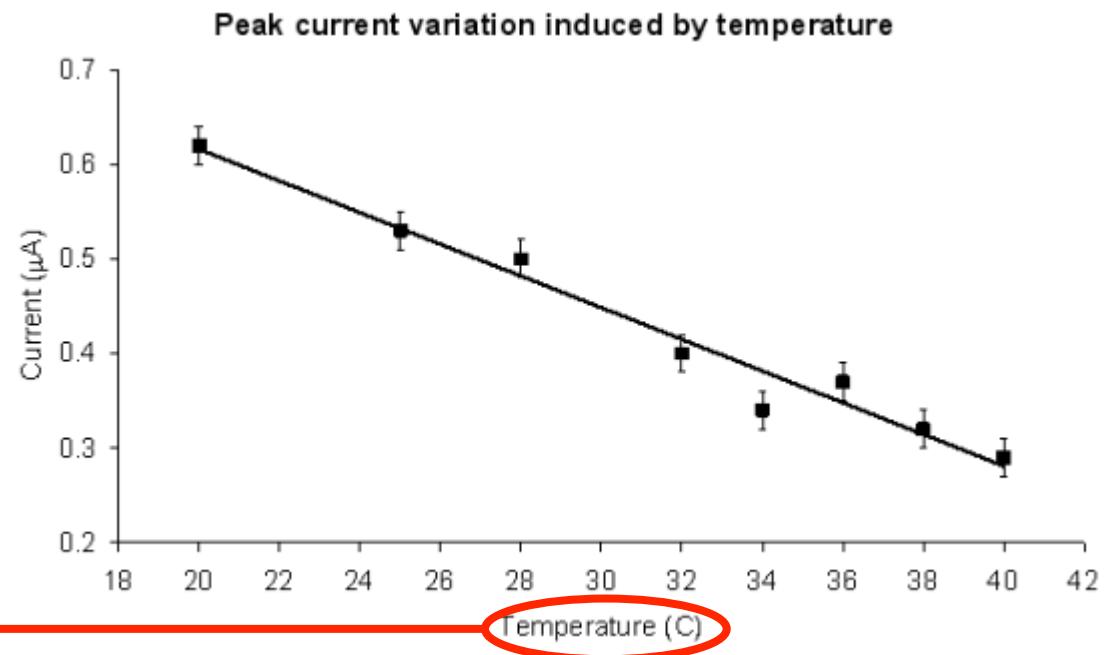
Long-term Propofol Monitoring



Best detection characteristics so far for long-term propofol monitoring, being able to measure the drug up to 4 hours

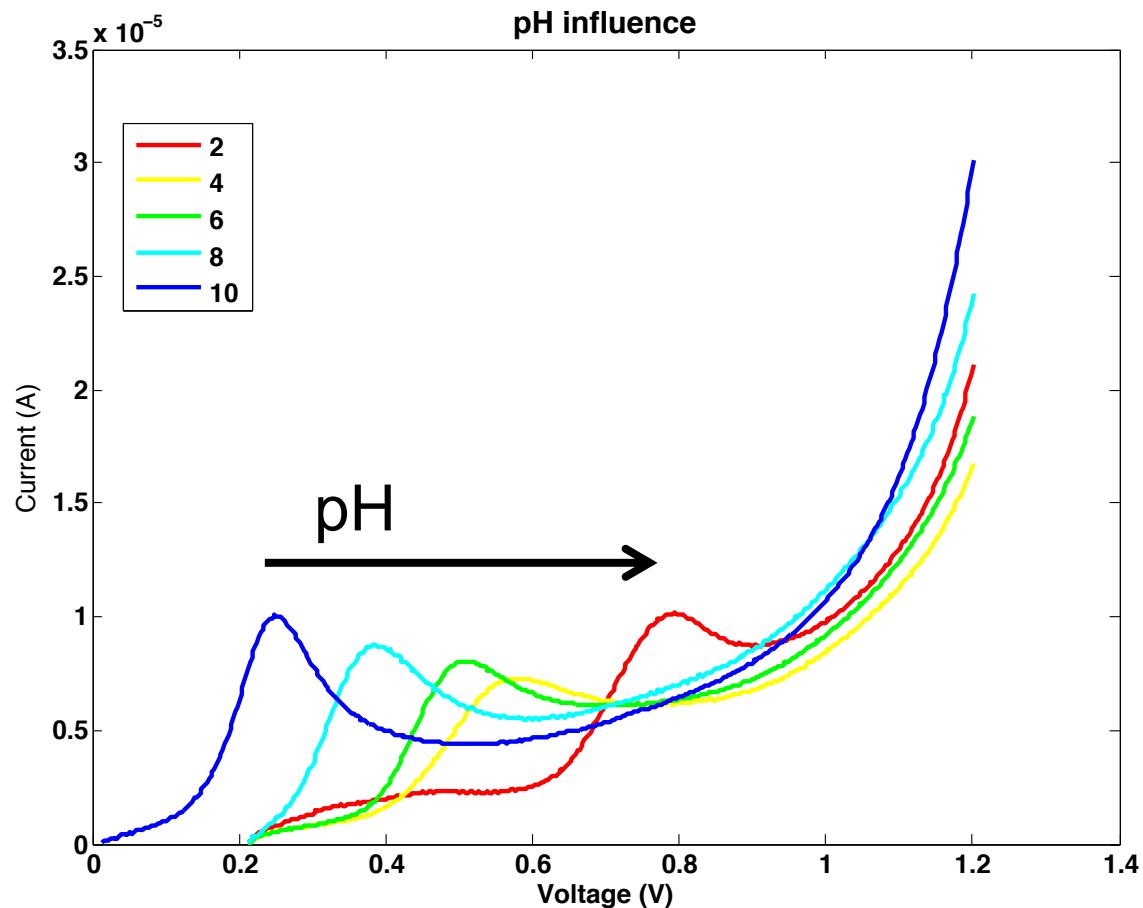
Reliability in Temperature

$$i \propto nFvD \left(\frac{nFvD}{RT} \right)^{1/2} C_r$$



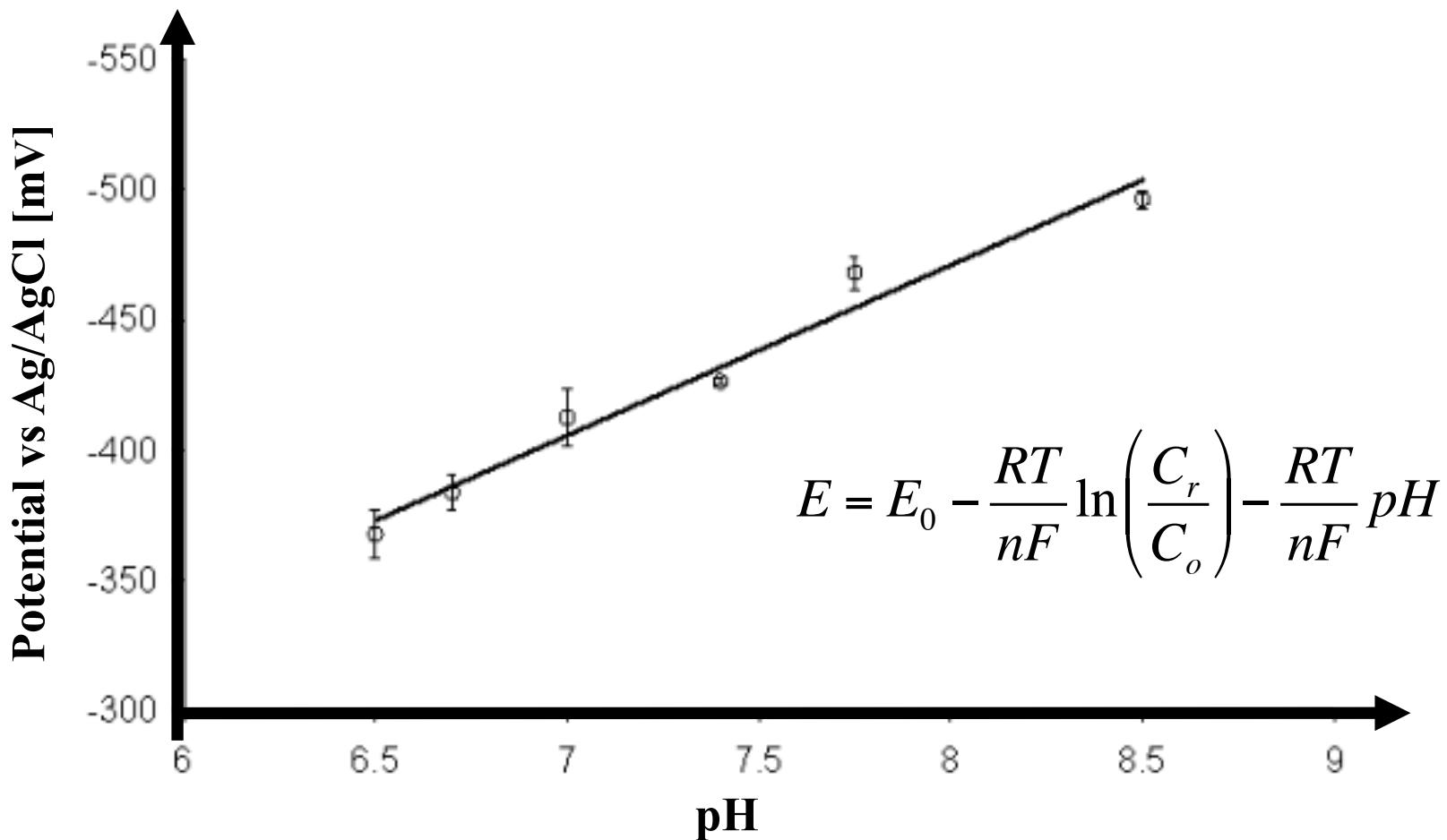
Biosensors response requires temperature compensation

Reliability in pH



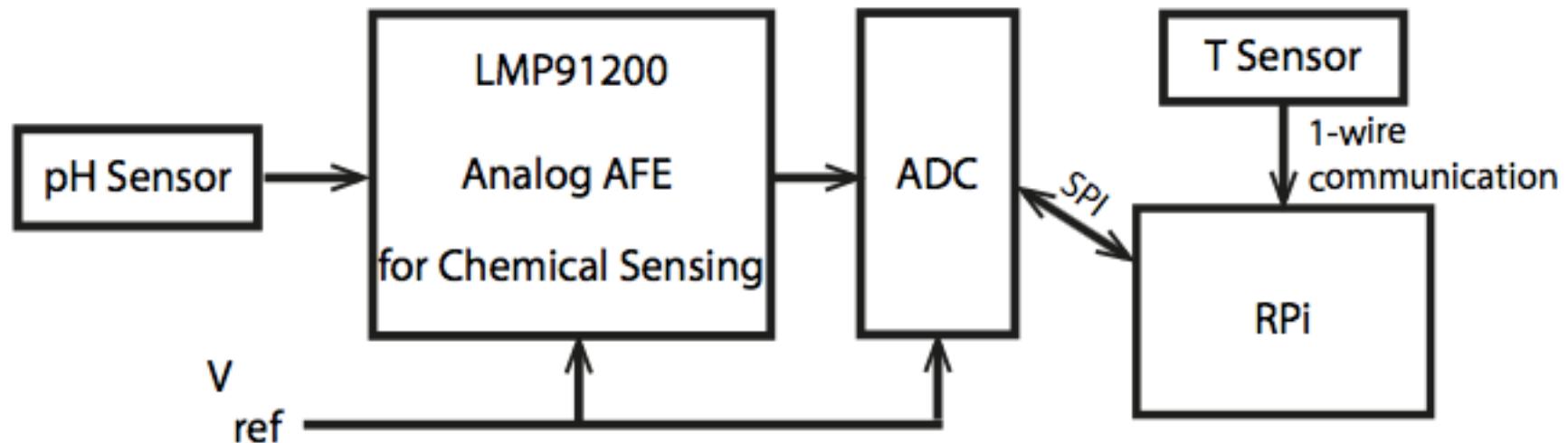
The pH changes the voltage position of the Faradaic Peak of the Propofol

Reliability in pH



The pH changes the voltage position of the Faradaic current due to Nernst equation

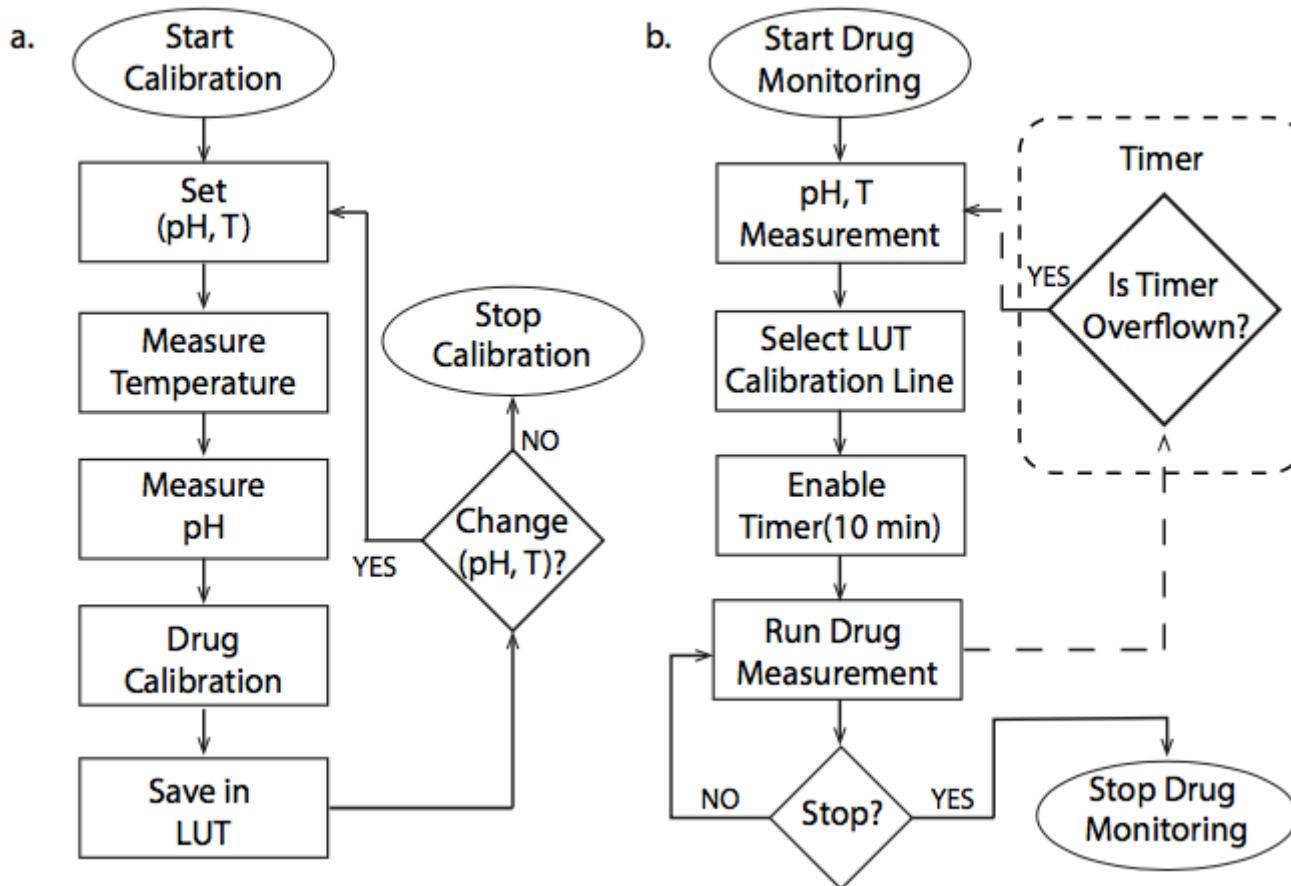
Interface for T & pH



S.L.Ntella 'n' F.Stradolini, et al., IEEE Sensors Conference 2017

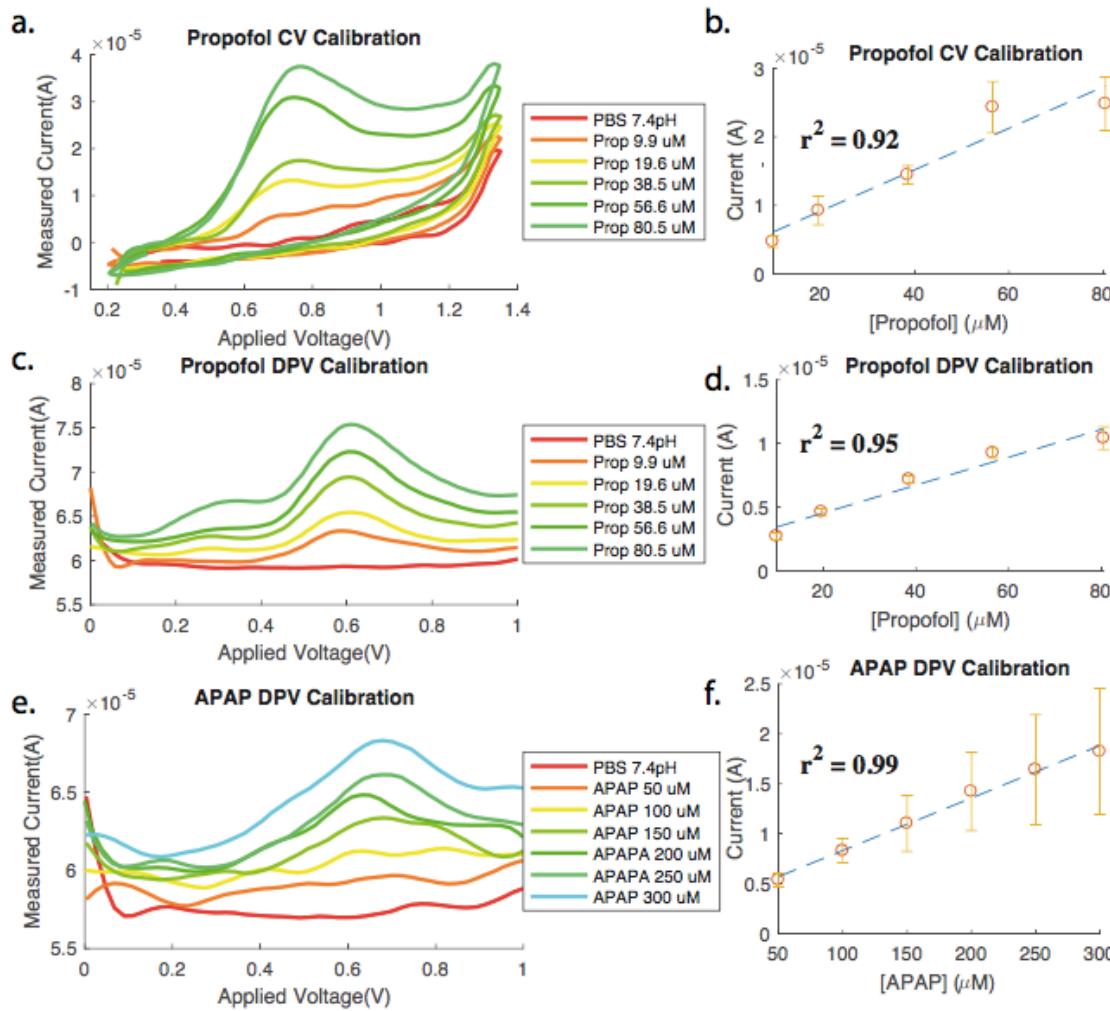
Schematic of the portable mixed signal circuit
for pH and T sensing

Calibration Procedures



Main procedures for calibrating the pH-T system (a) and for monitoring a drug (b)

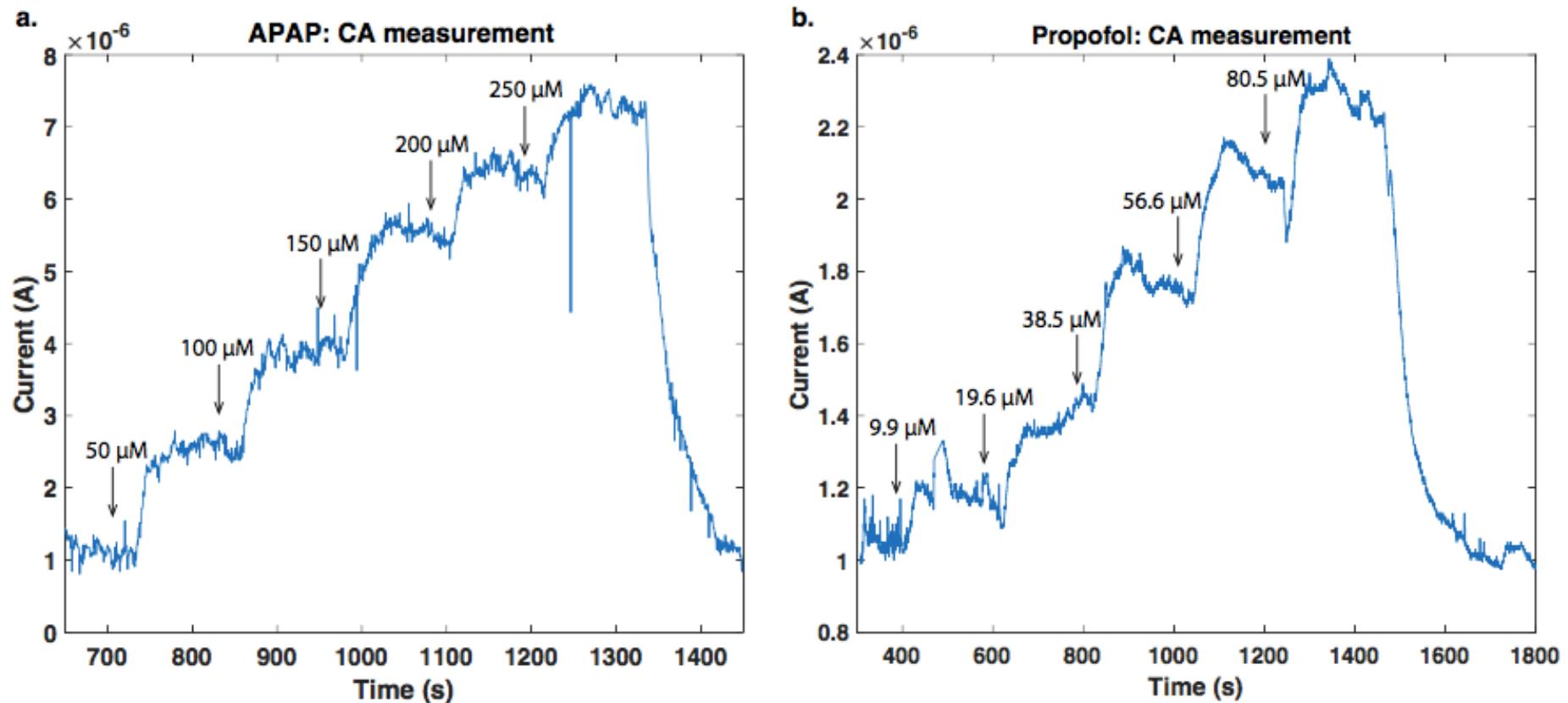
Calibration of Anaesthetics



Sensors for Propofol, Paracetamol, and Midazolam have been already successfully developed and tested

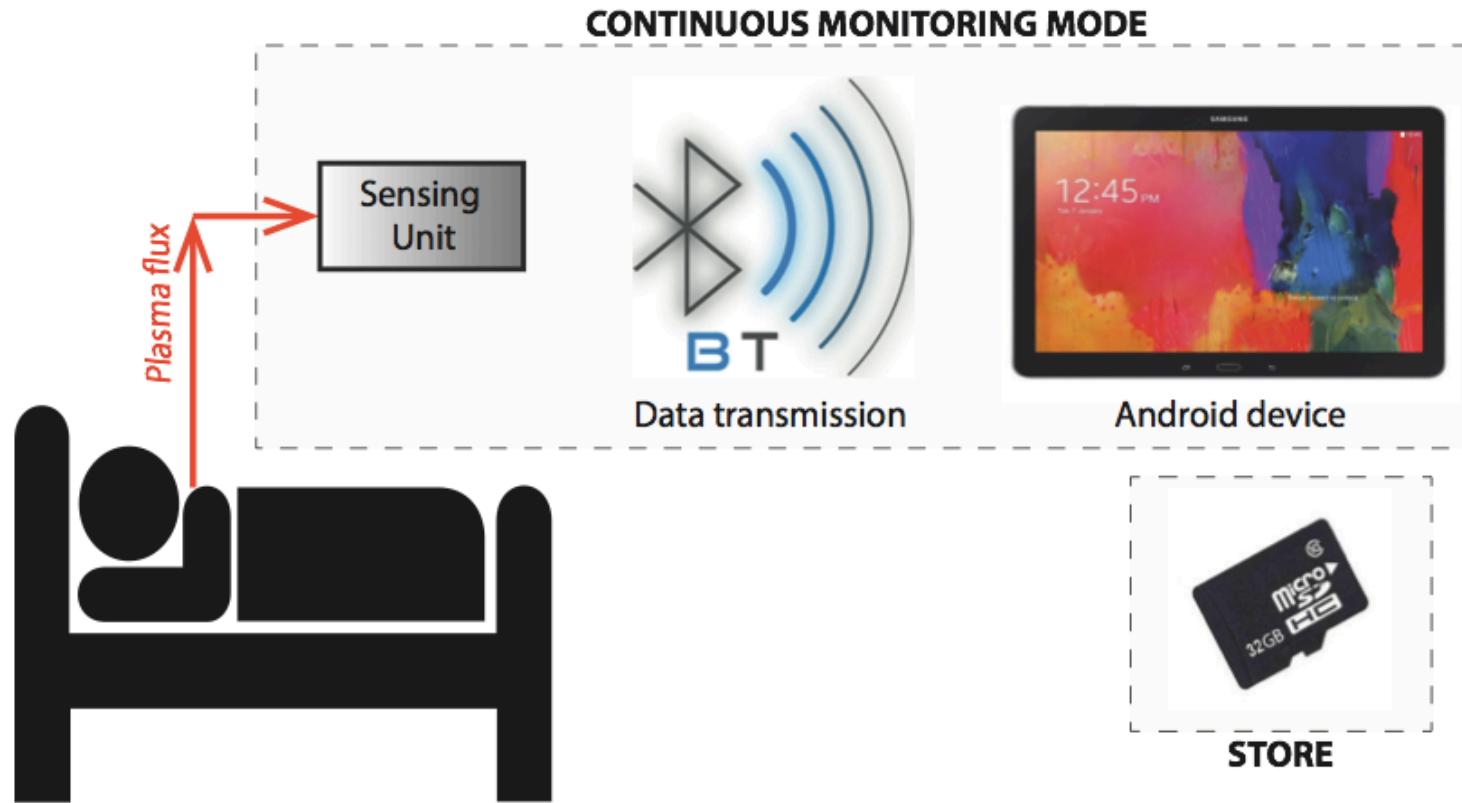
Monitoring of Anaesthetics

F. Stradolini, et al., IEEE TBCAS 12 (2018) 1056-1964



Sensors for Propofol, Paracetamol, and Midazolam have been already successfully developed and tested

Monitoring in intensive Care Units

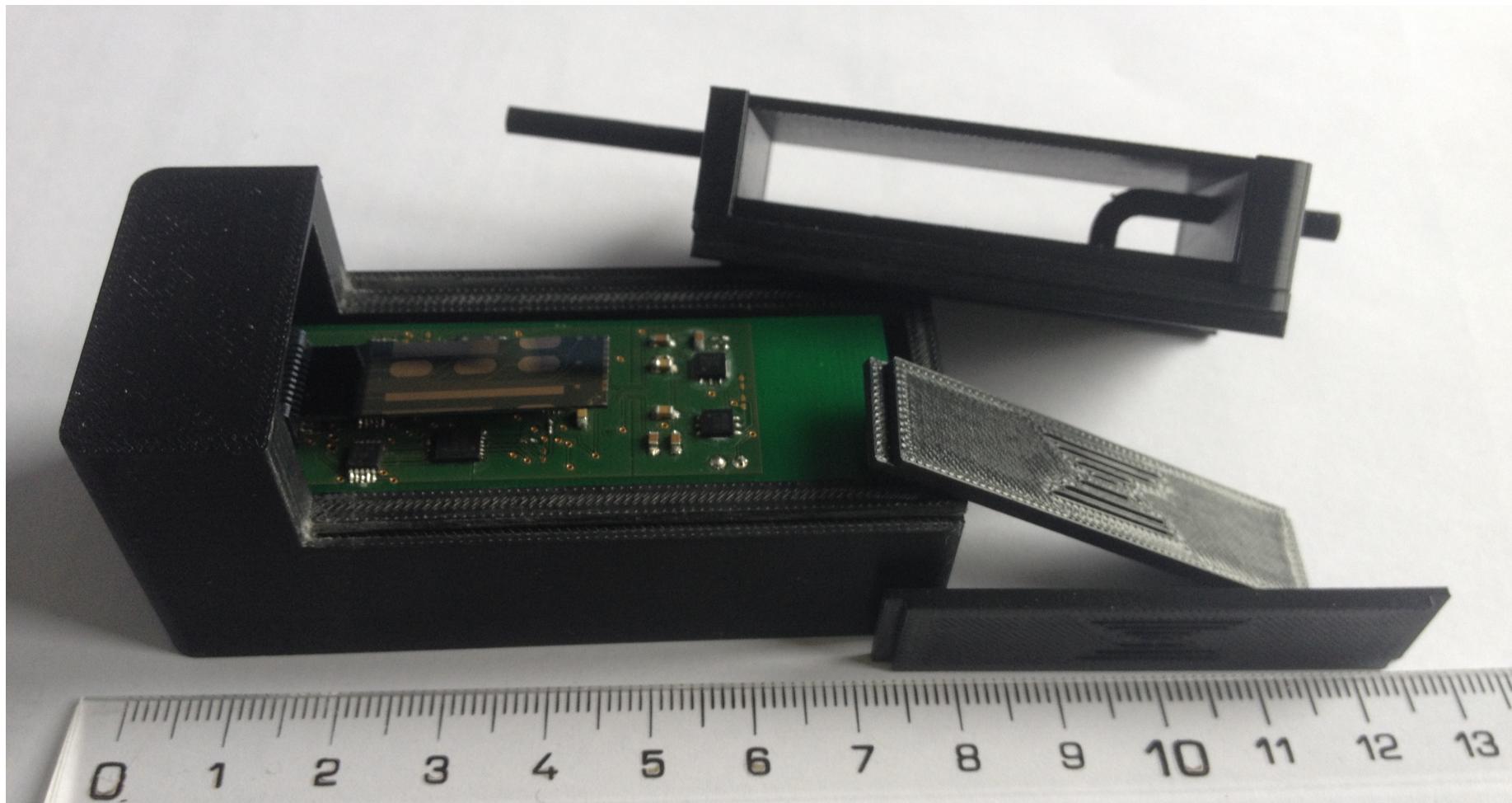


F. Stradolini, et al., IEEE Sensors Journal 16(2016) 3163 - 3170

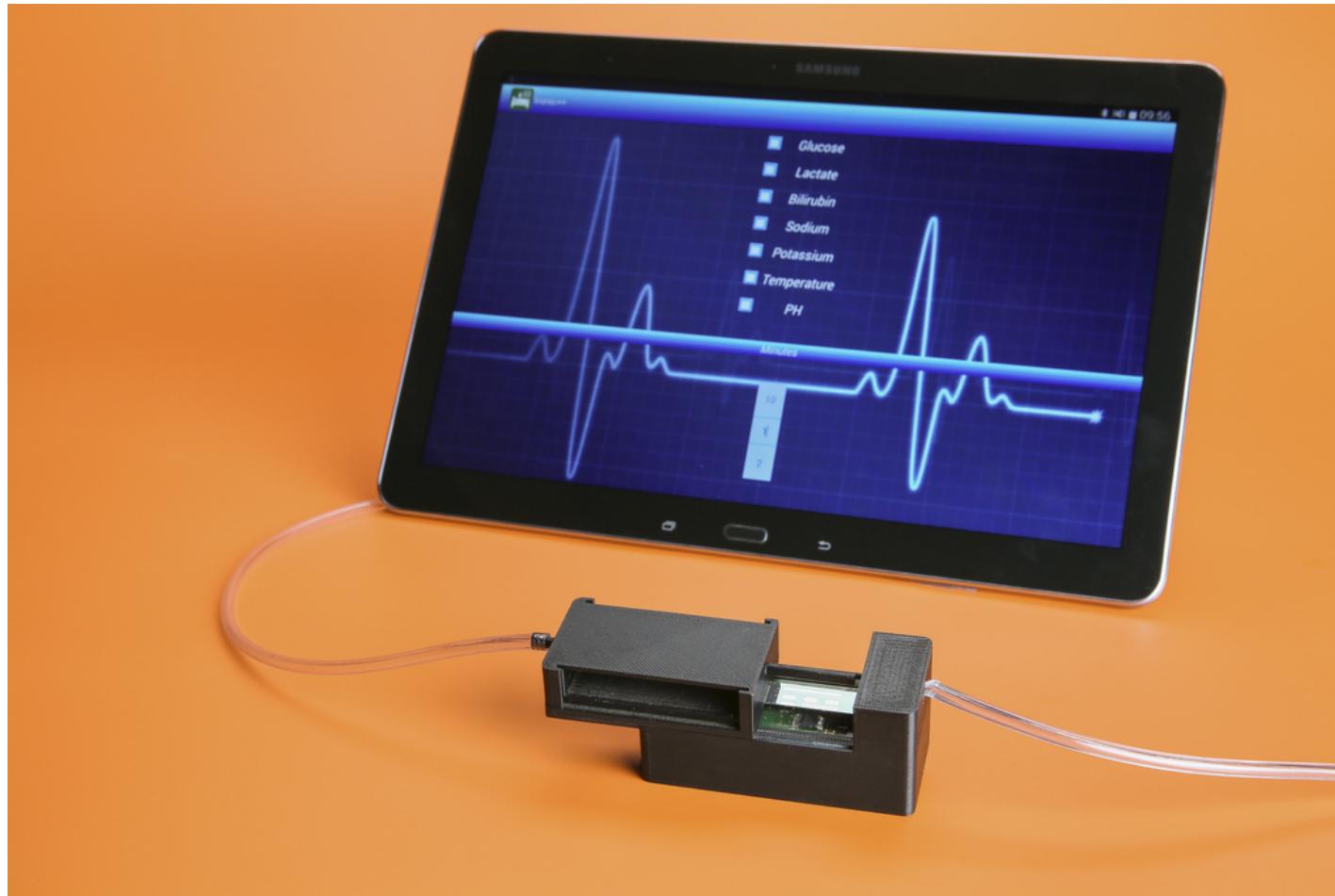
Monitoring scenario where the main parameters of the patient are continuously displayed on an Android mobile device

Monitoring in intensive Care Units

F. Basilotta, et al., IEEE BioCAS 2015

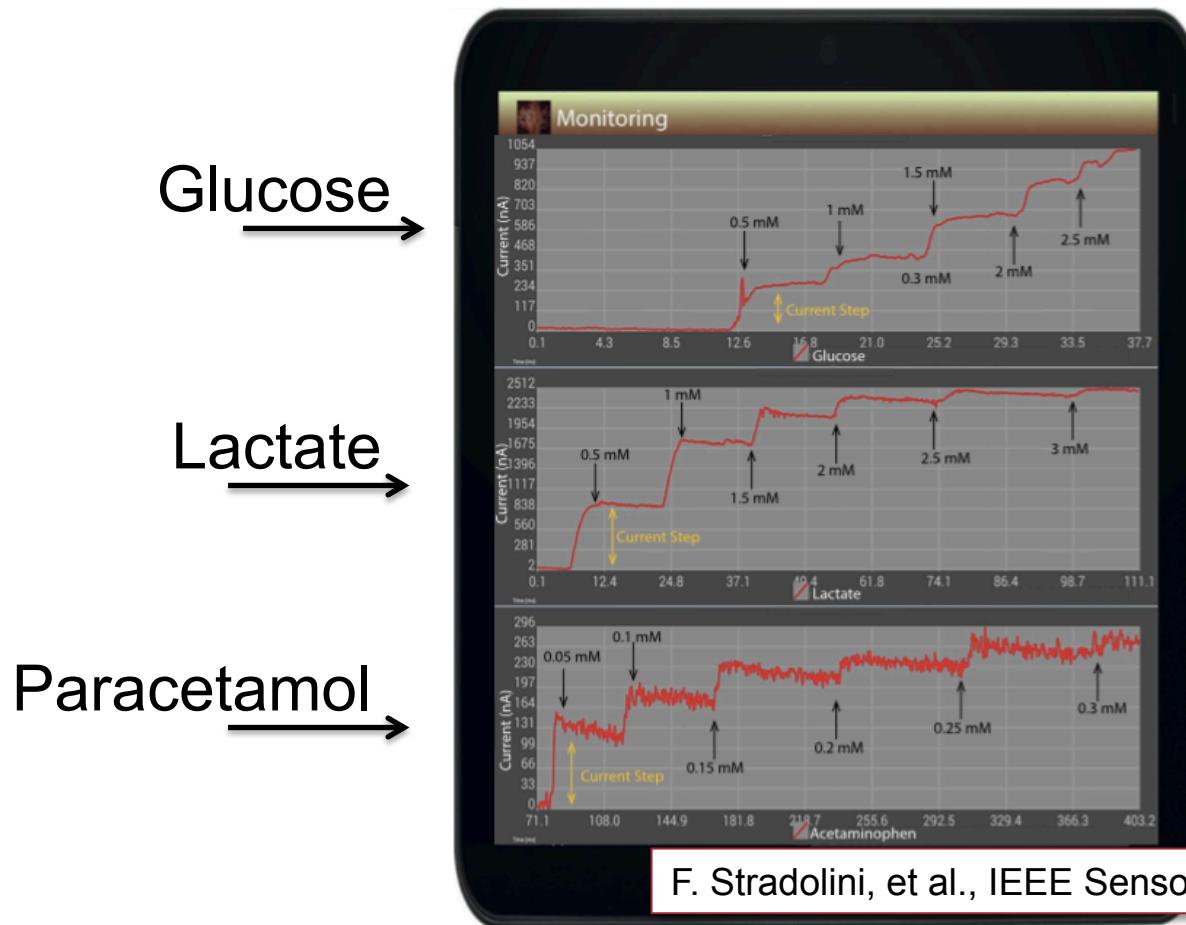


Android Interface



The whole system with the AndroidTM interface that allows connectivity too

Android Interface



The whole system with the AndroidTM interface that allows connectivity too

Connectivity with Smart-Watch

Smartwatches deliver alerts to intensive care doctors

Patients in intensive care must be constantly monitored. Their vital signs are recorded in real time by a series of biosensors. If an anomaly is detected, an alert is sent to the doctor on duty.



Live Demo @ BioCAS17

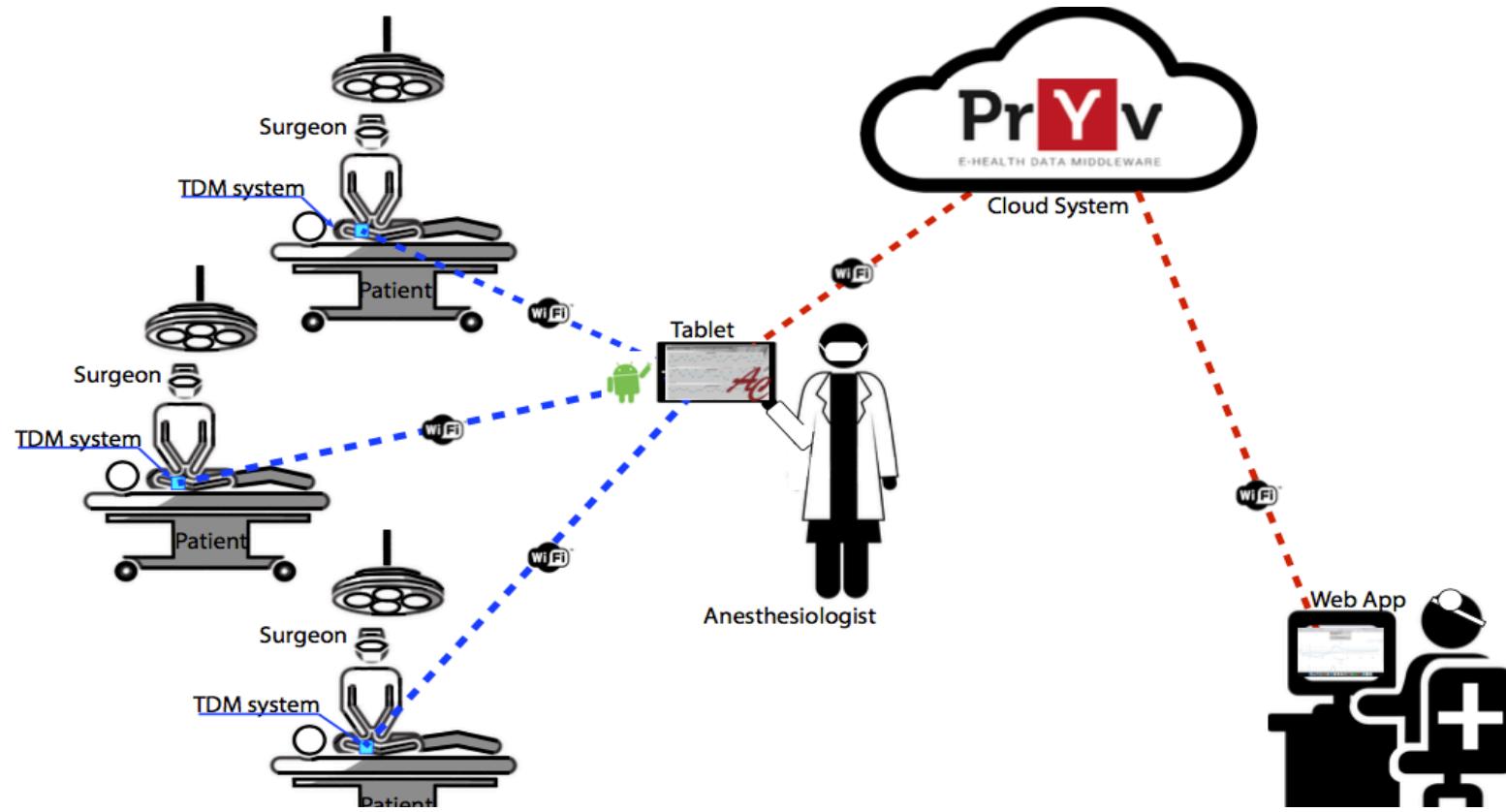


F. Stradolini, et al., MOBILHEALTH 2016



Connectivity till the smart-watch by the WiFi network has been successfully investigated as well

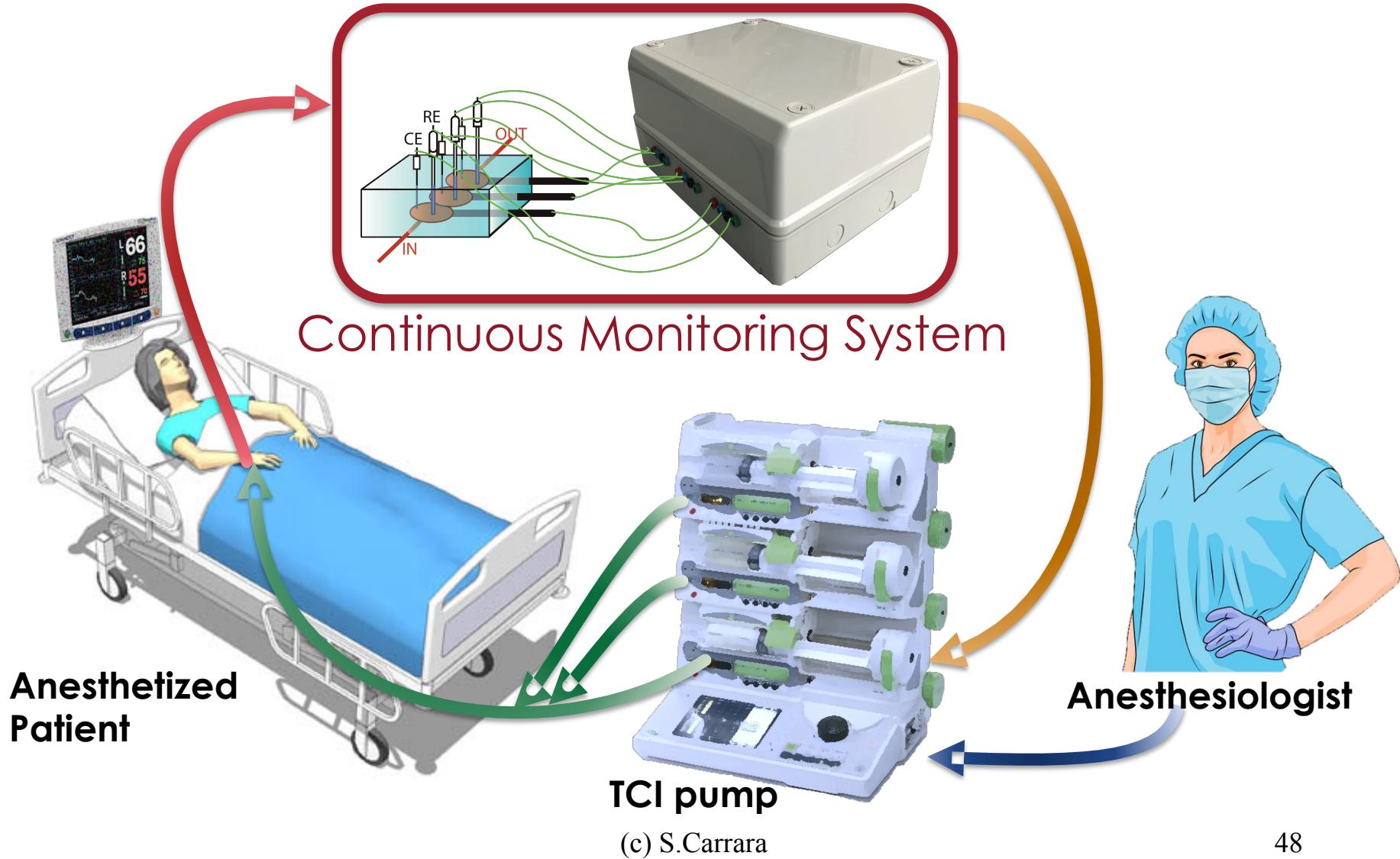
Connectivity through Cloud



N.Tamburrano 'n' F. Stradolini, et al., IEEE ISCAS 2018, invited paper

Connectivity by through the cloud has been successfully investigated too

Do we have already all we need for Precision Anesthesiology?



Well, ...let us ask Francesca!



(c) S.Carrara