EPFL

EDEE Doctoral Programs in Electrical Engineering

EE-600: Usability Engineering

Lecture #11
Full System for Personalized Anaesthesiology In Precision Medicine

(c) S.Carrara

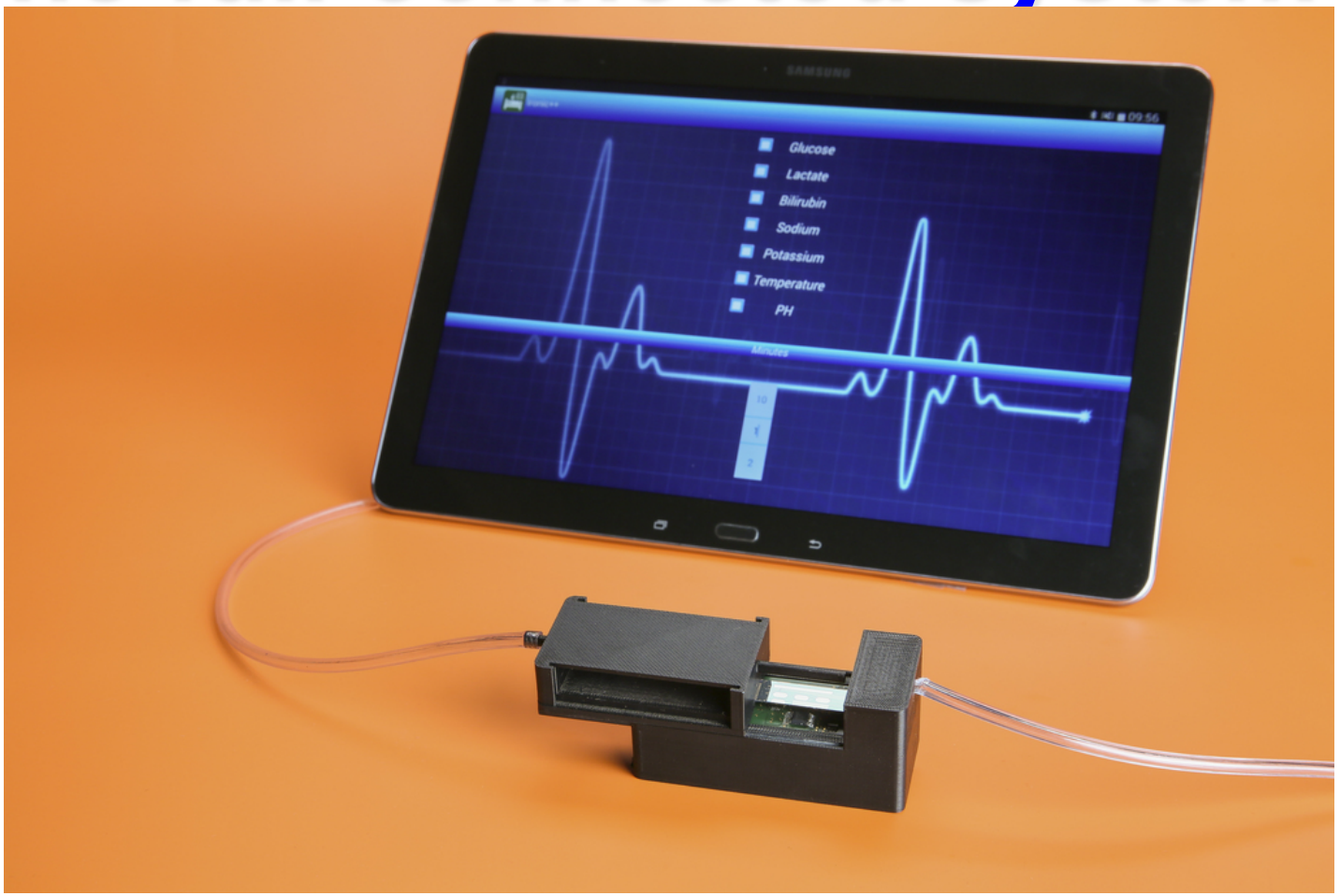
What we really mean for Usability?

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"?

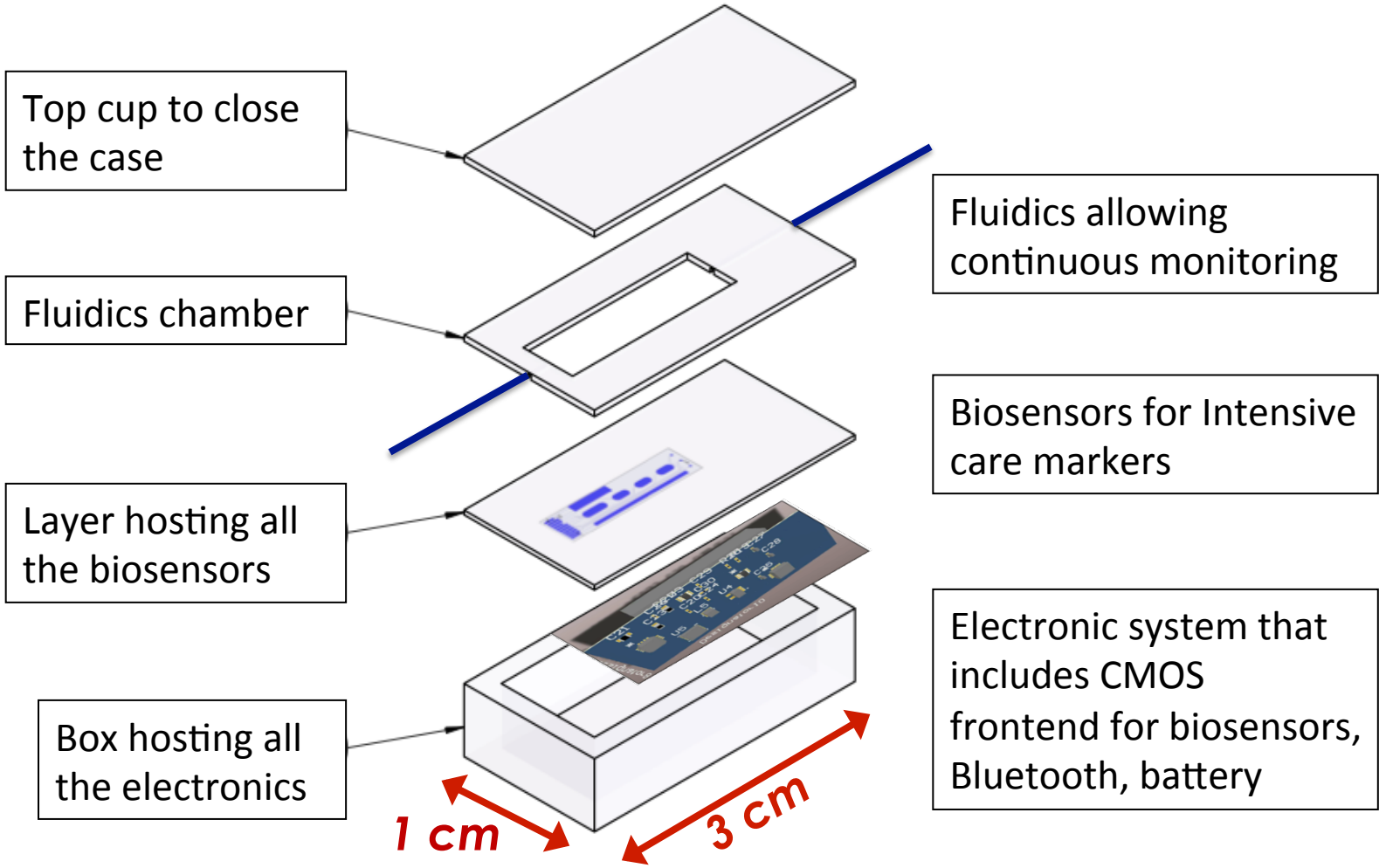
In the context of this course,
"**Usability Engineering**"
is
"***obtaining the usability by design***"

The full connected system

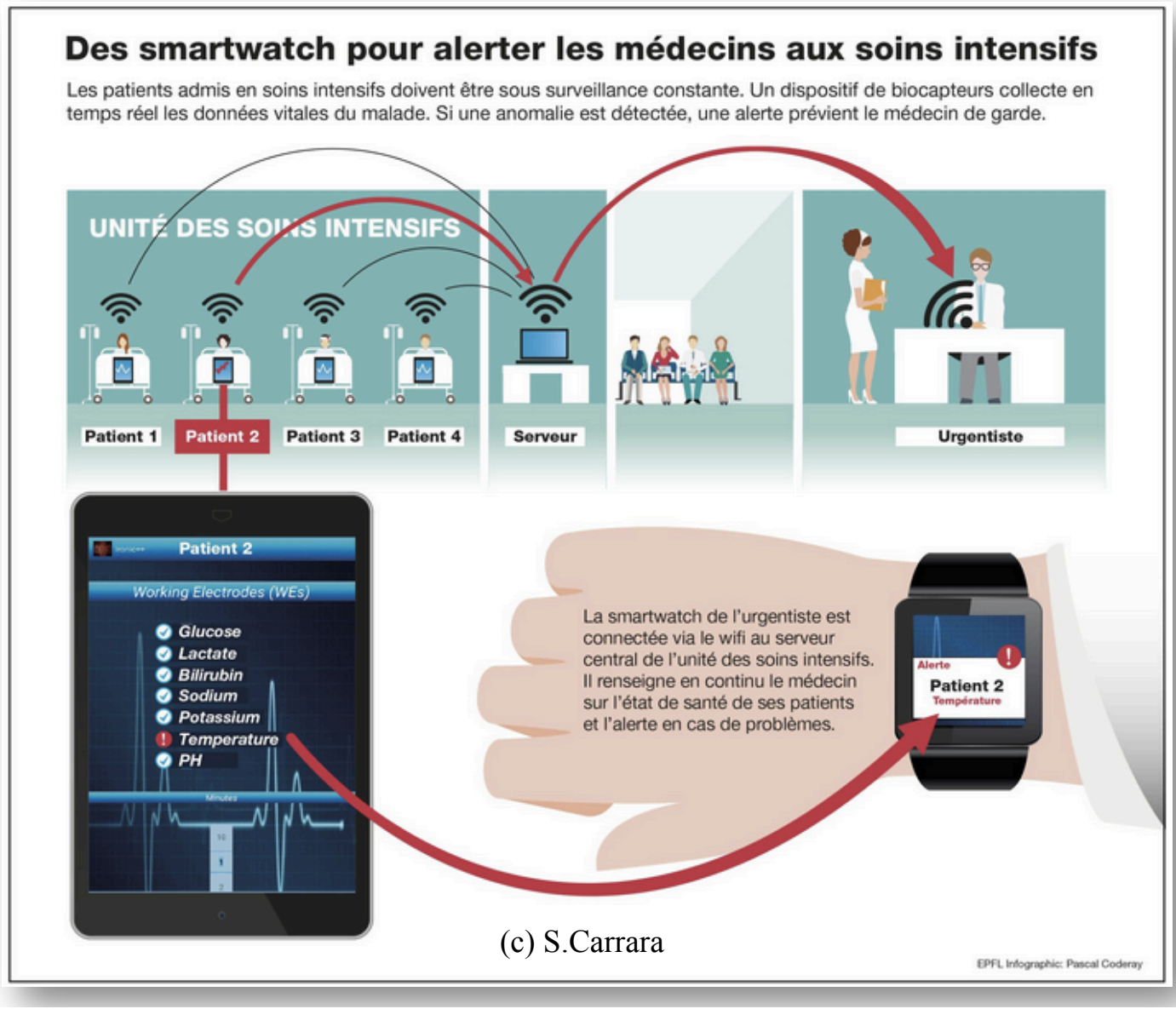


The whole system with the Android™ interface that allows connectivity too

First Fully-Autonomous system for Continuous monitoring in ICUs



Remote Patients' monitoring from Smartwatches



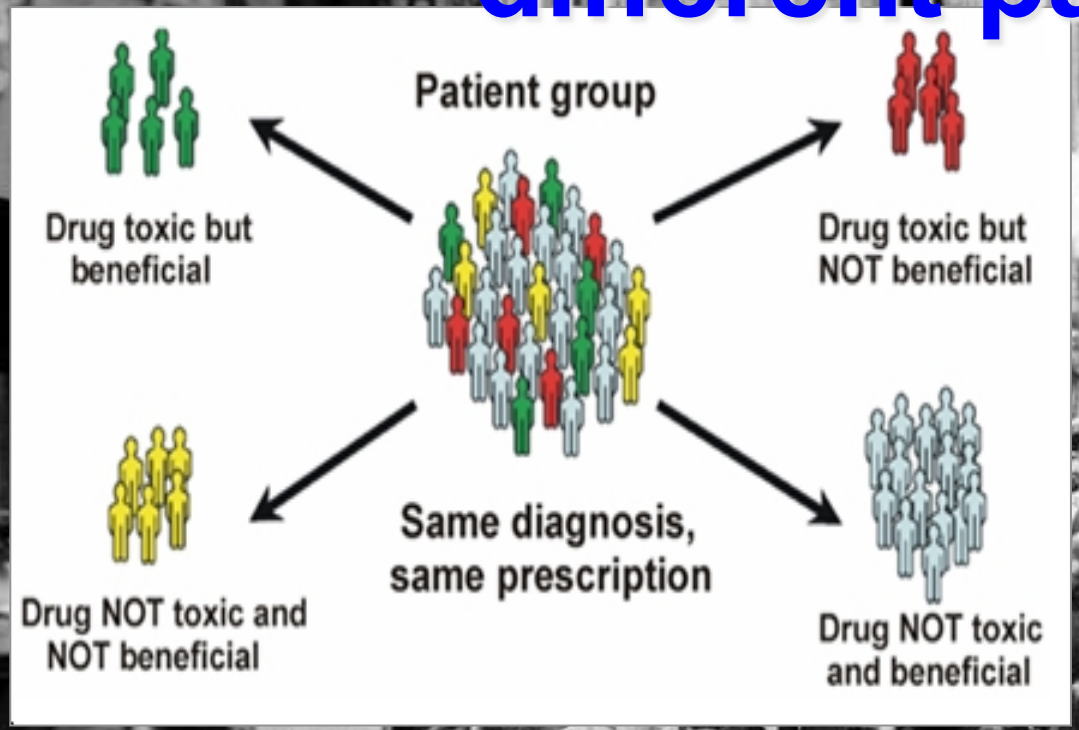
…from Tablet to Smartwatches…

One Interface for Remote Monitoring of Patients in Intensive Care Units

Image | Bam Labs

The whole system with the Android™ interface that allows connectivity too

Different outcomes for different patients

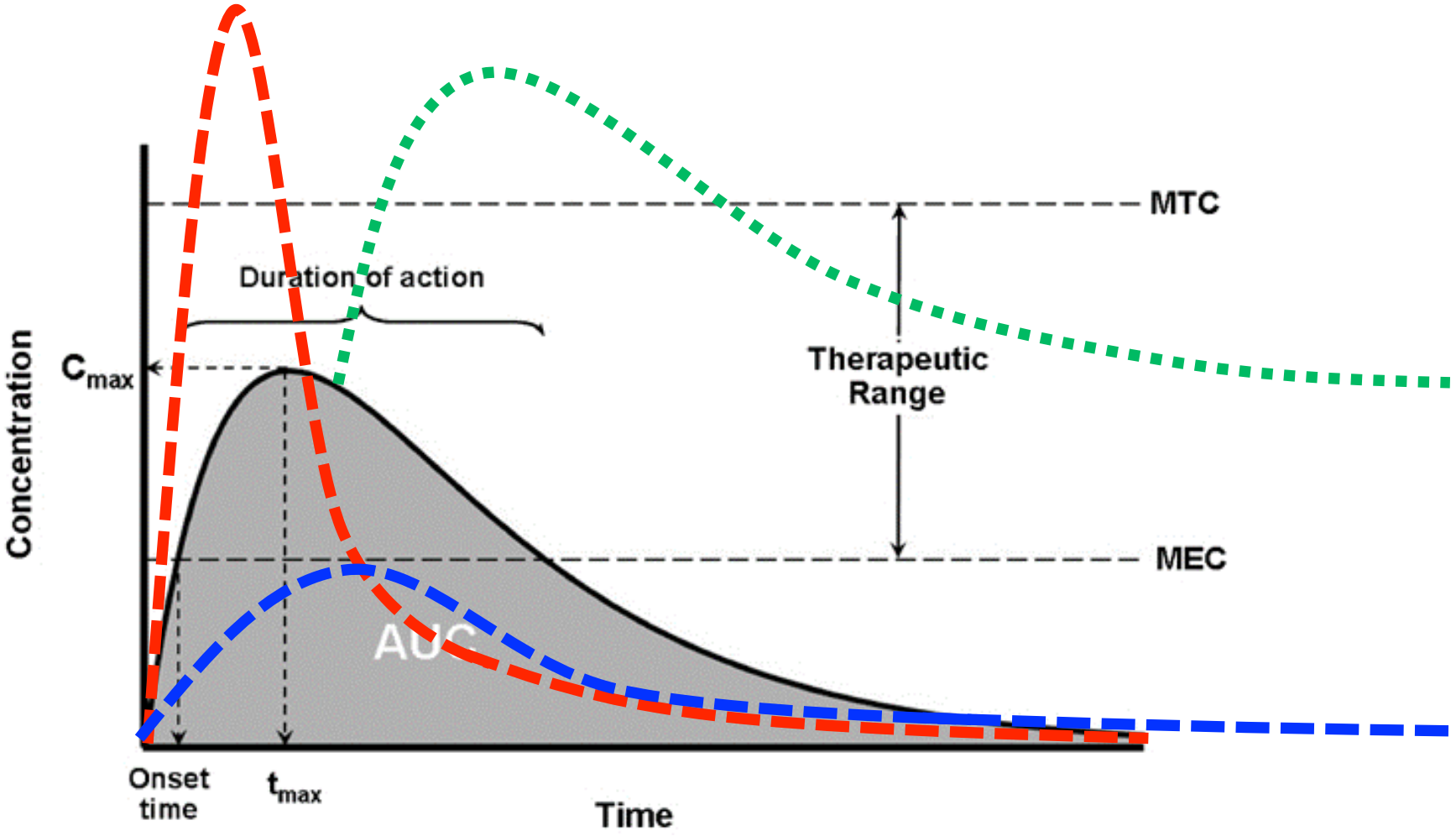


Therapeutic area	Rate of efficacy with standard drug treatment
Cancer (all types)	25%
Alzheimer's disease	30%
Incontinence	40%
Hepatitis C	47%
Osteoporosis	48%
Rheumatoid arthritis	50%
Migraine (prophylaxis)	50%
Migraine (acute)	52%
Diabetes	57%
Asthma	60%
Cardiac arrhythmias	60%
Schizophrenia	60%
Depression	62%

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).

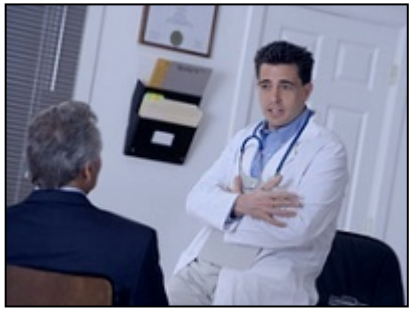
Patients' metabolism drive the Drugs effect in time!



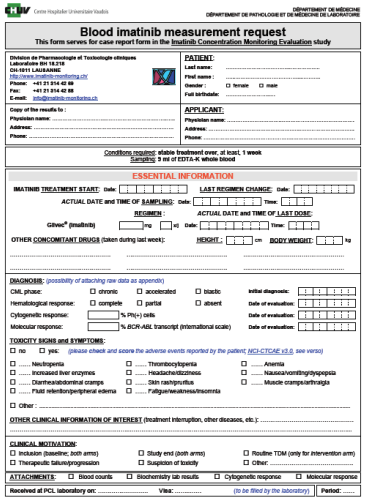
What "TDM" Stands for?

In the context of this course,
"**TDM**"
stands for
"***Therapeutic Drug Monitoring***"

TDM : Classical procedures



Information
+ Treatement

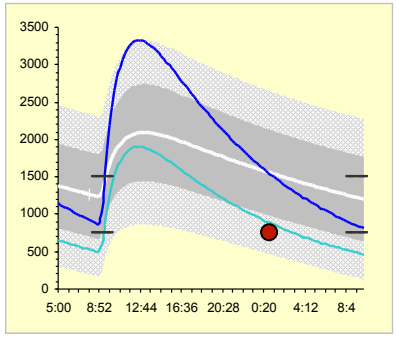


TDM request
+ Clinical data

Blood sampling

Sample postage

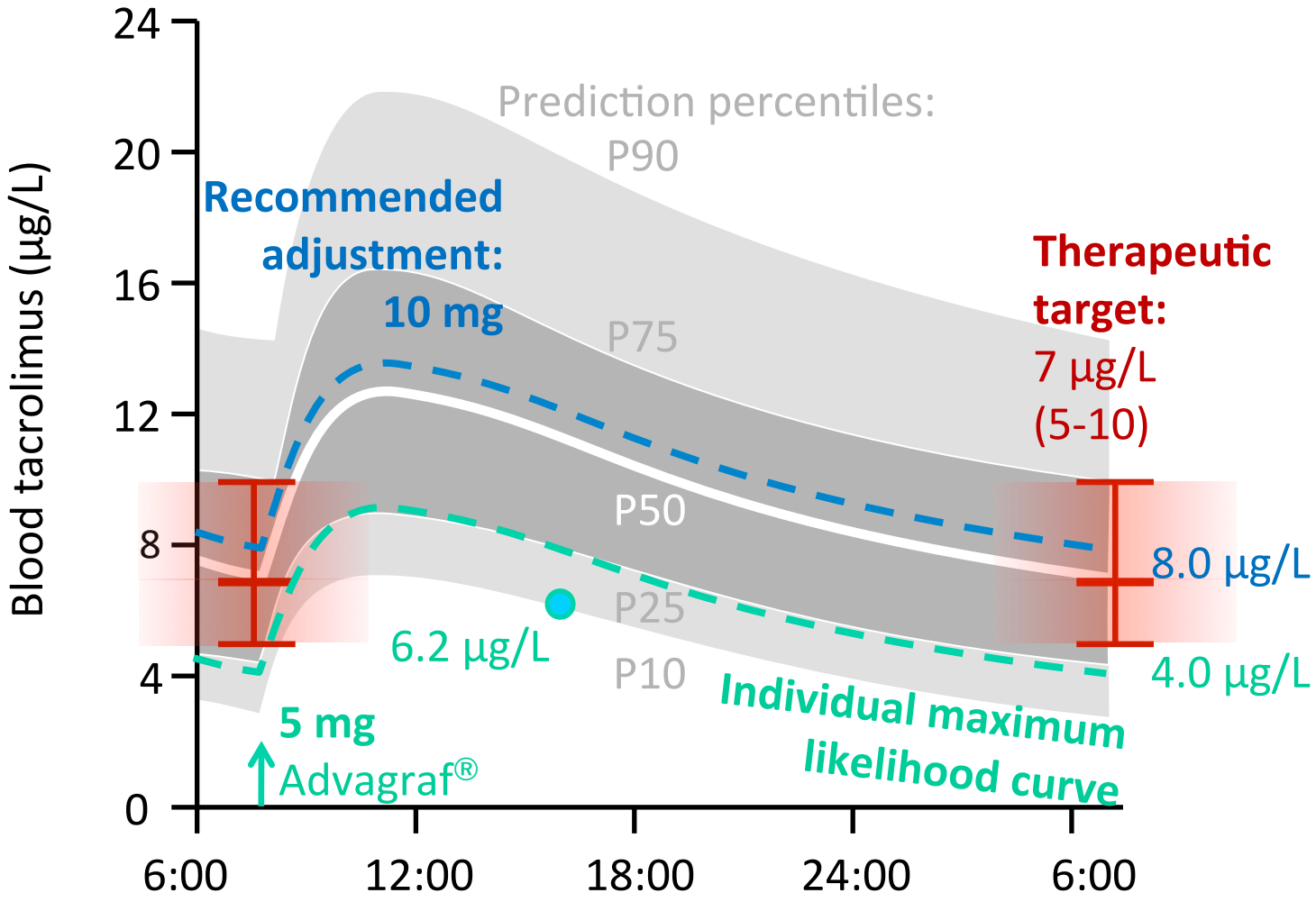
Concentration measurement



Interpretation
+ Recommendations

Bayesian TDM interpretation

Example: Tacrolimus, extended release formulation (Advagraf ®)



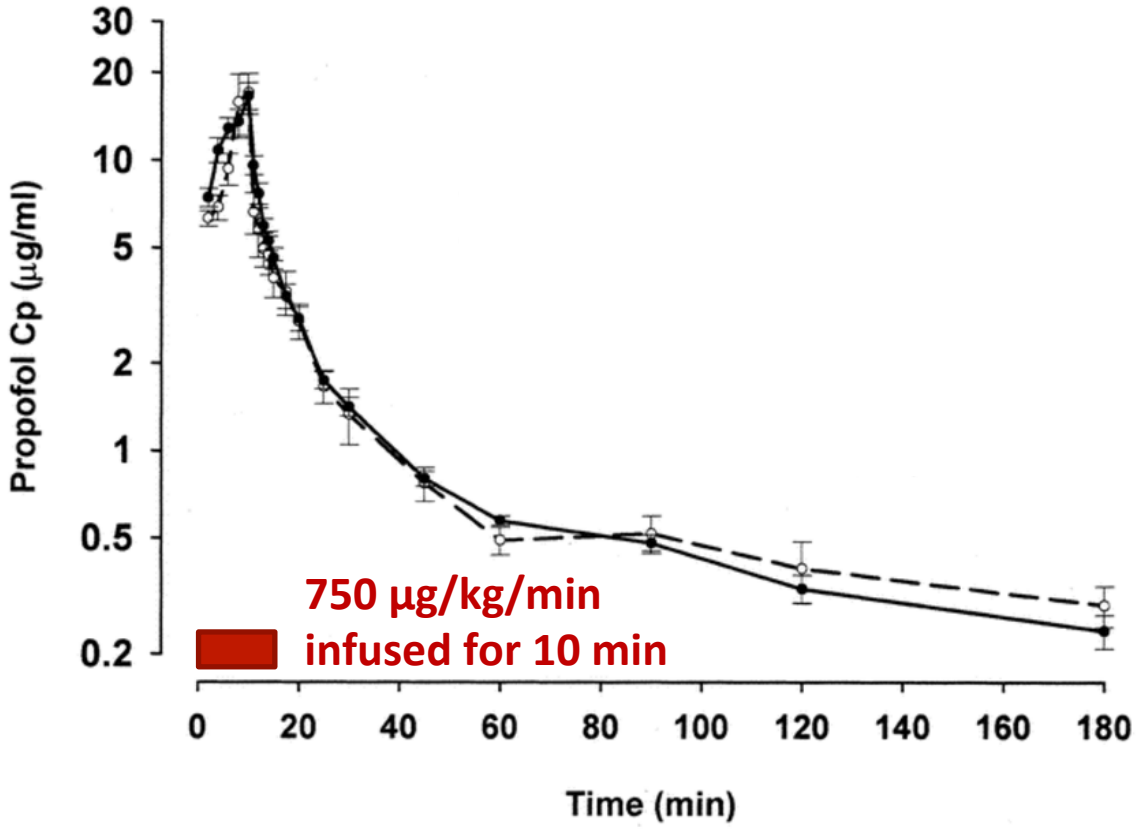
Intravenous anaesthesia: Traditional approach

- 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.

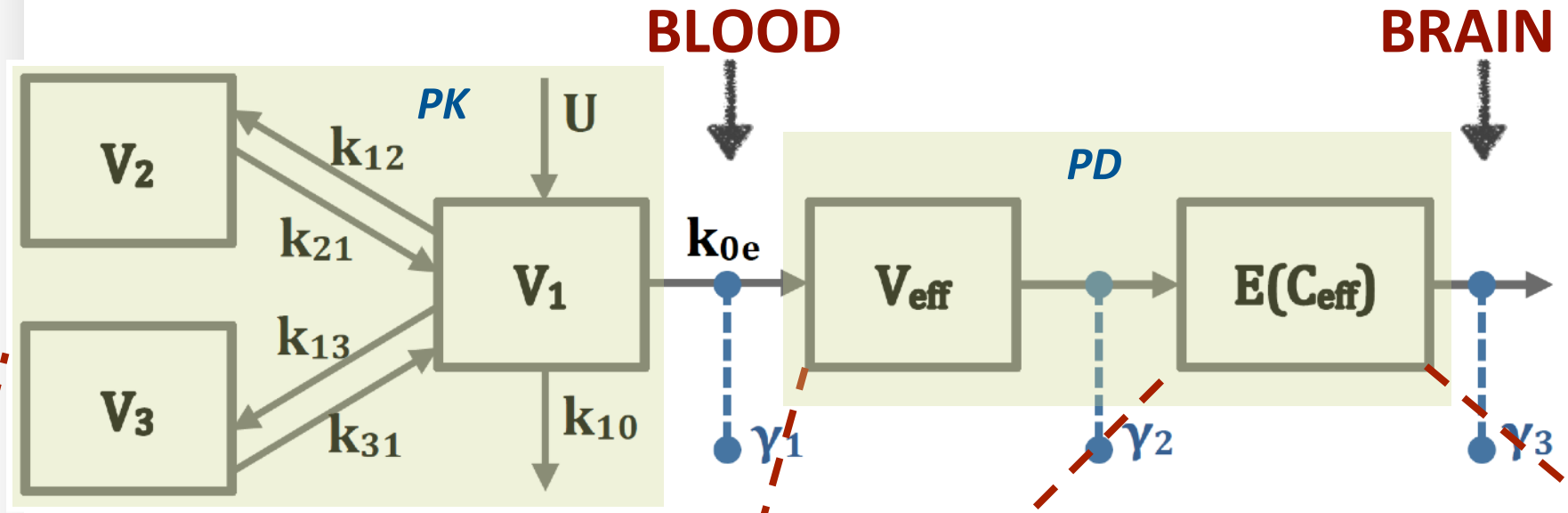
Roberts FL & al. Induction and maintenance of propofol anaesthesia. A manual infusion scheme. Anaesthesia. 1988;43 S:14-7

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



$$\frac{dC_1}{dt} = C_2k_{21} + C_3k_{31} - C_1(k_{10} + k_{12} + k_{13}) + U$$

$$\frac{dC_2}{dt} = C_1k_{12} - C_2k_{21}$$

$$\frac{dC_3}{dt} = C_1k_{13} - C_3k_{31}$$

$$\frac{dC_{eff}}{dt} = (C_1 - C_{eff})k_{e0}$$

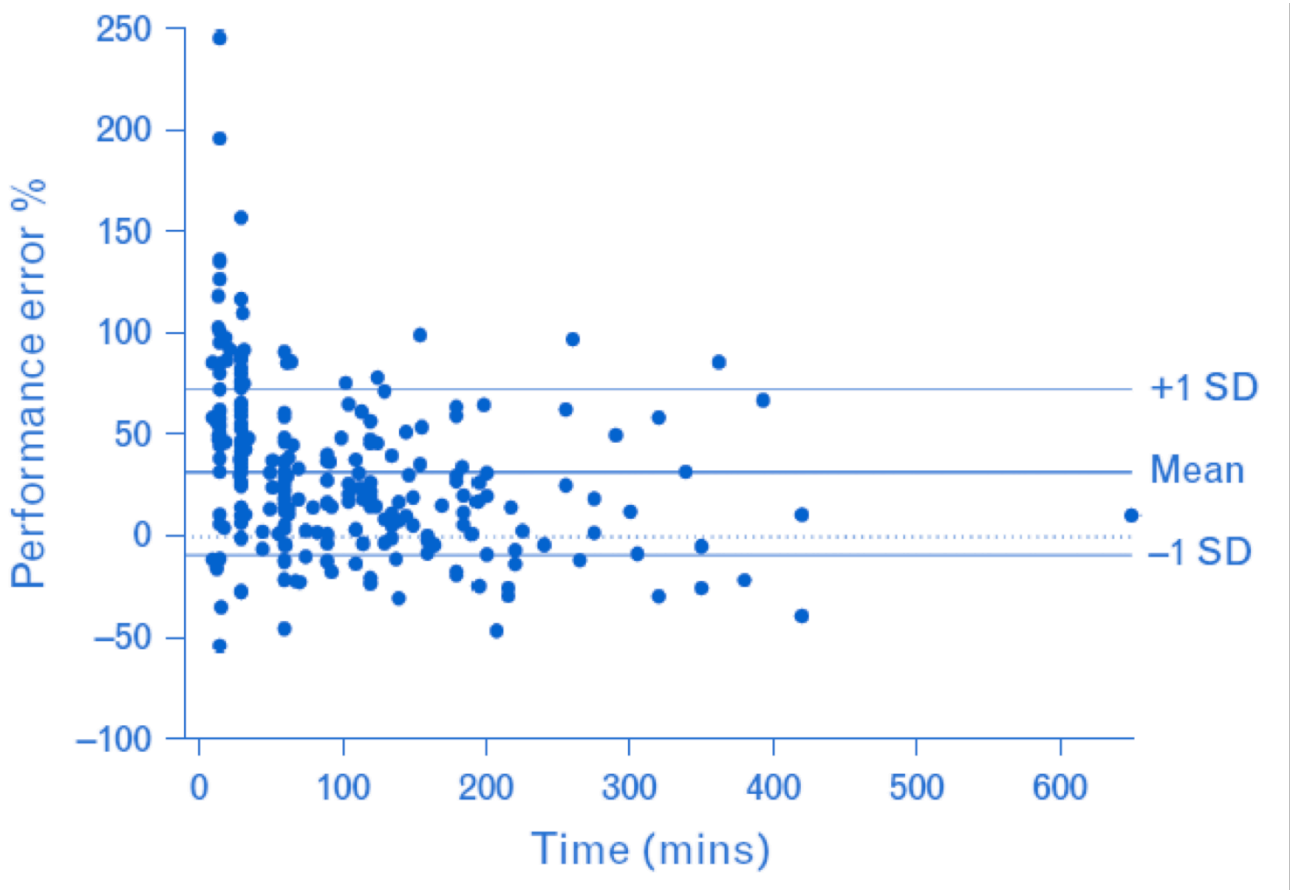
$$E(C_{eff}) = E_0 + (1 - E_0)\frac{C_{eff}^{\gamma}}{C_{eff,50}^{\gamma} + C_{eff}^{\gamma}}$$

Courtesy, Alena Simalatsar

Known inaccuracies and bias

254 measurements in 50 TCI patients (Marsh model)

$$\frac{\text{Pred - Obs}}{\text{Pred}} \cdot 100\%$$



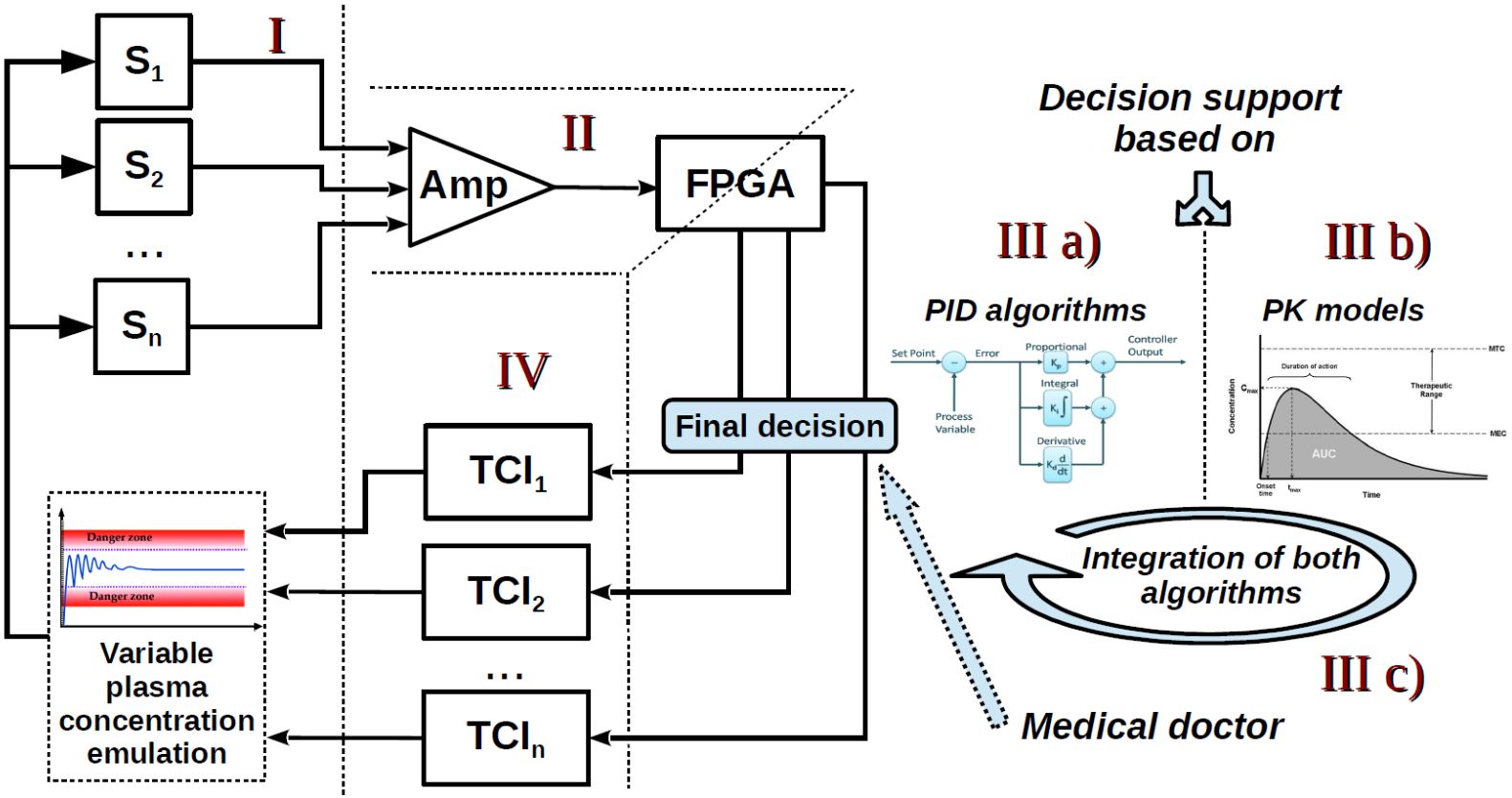
Cowley NJ & al. Eur J Anaesthesiol 2013;30:627-32

Intravenous anaesthesia: Target Controlled Infusion (TCI)

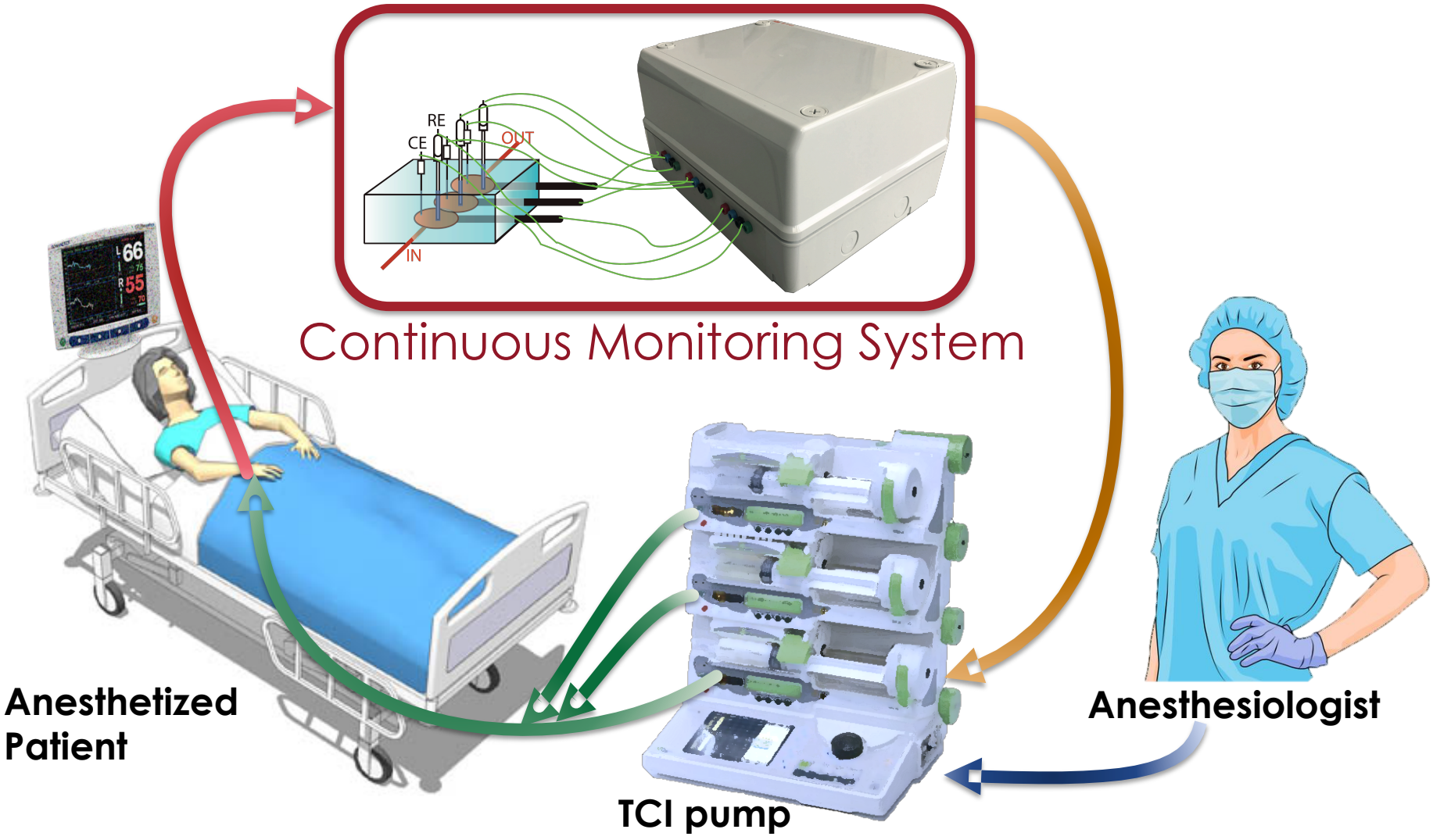
- The anaesthetist choses a target concentration exposure (blood or brain)
- A computer-driven pump calculates the suitable infusion regimen to reach this exposure, based on an internal PK model
- The same model is applied to all patients:
  - no personalization for individual characteristics influencing 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

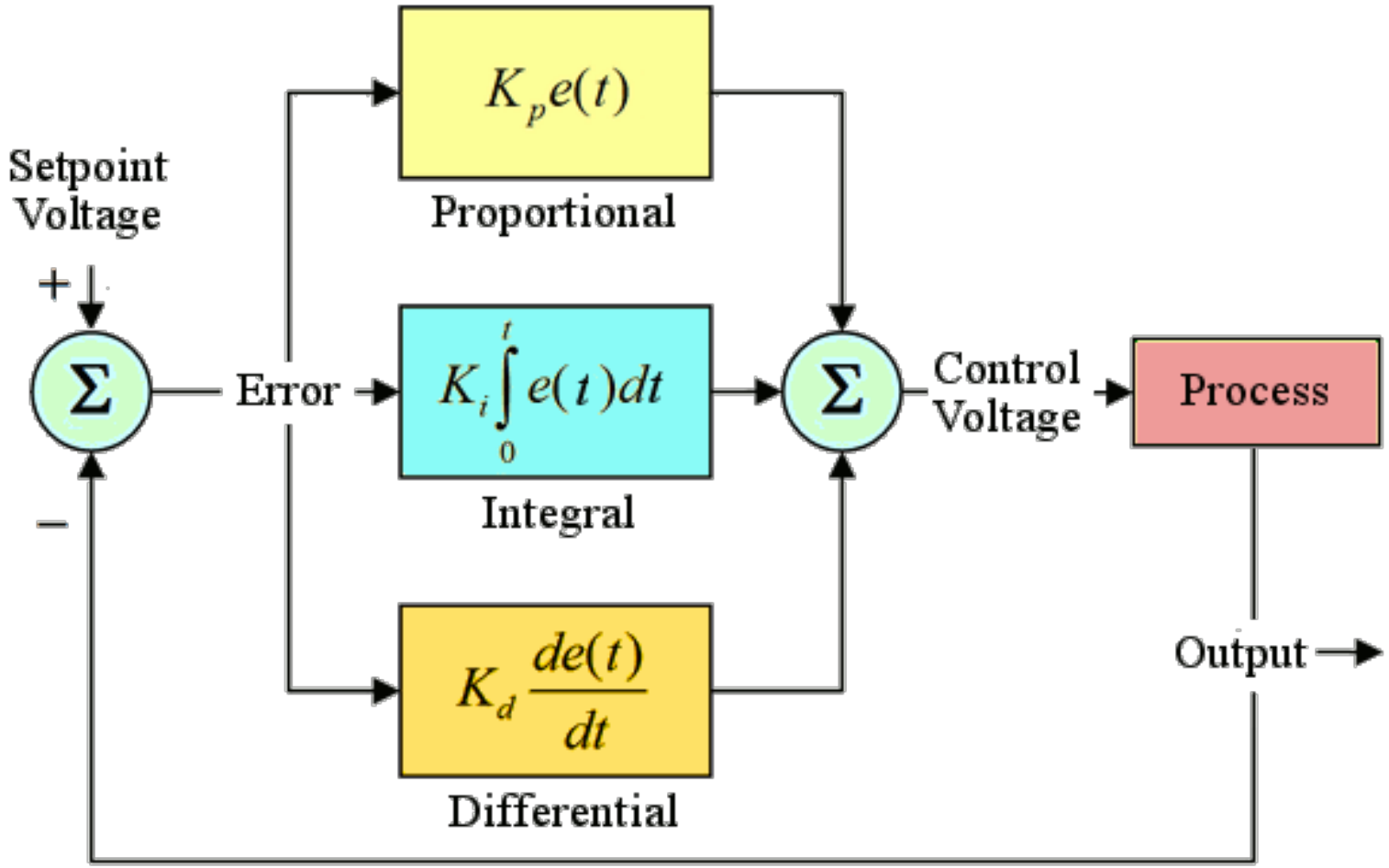


Monitoring during Anesthesia



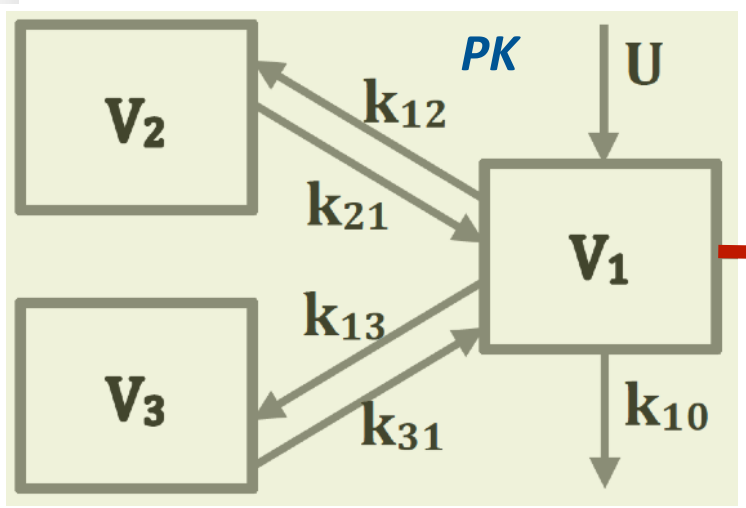
Feed-back: PID Controller

(PK-unaware!)



Feed-back: Bayesian adjustment

Prediction



Observations

measurement error
biological fluctuations
model uncertainty

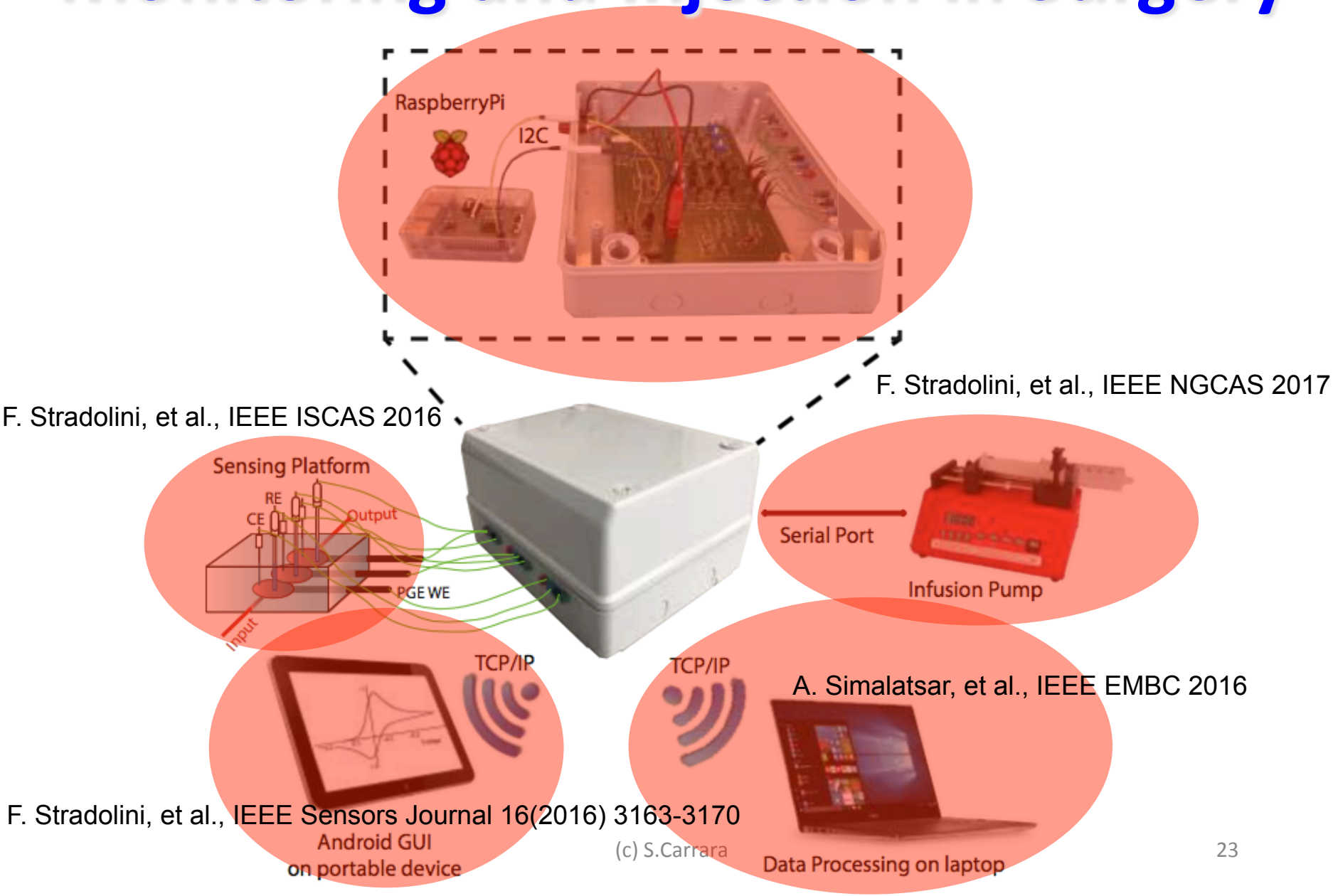
Prior knowledge

population variability

weighted adjustment

Posterior revision of parameter values

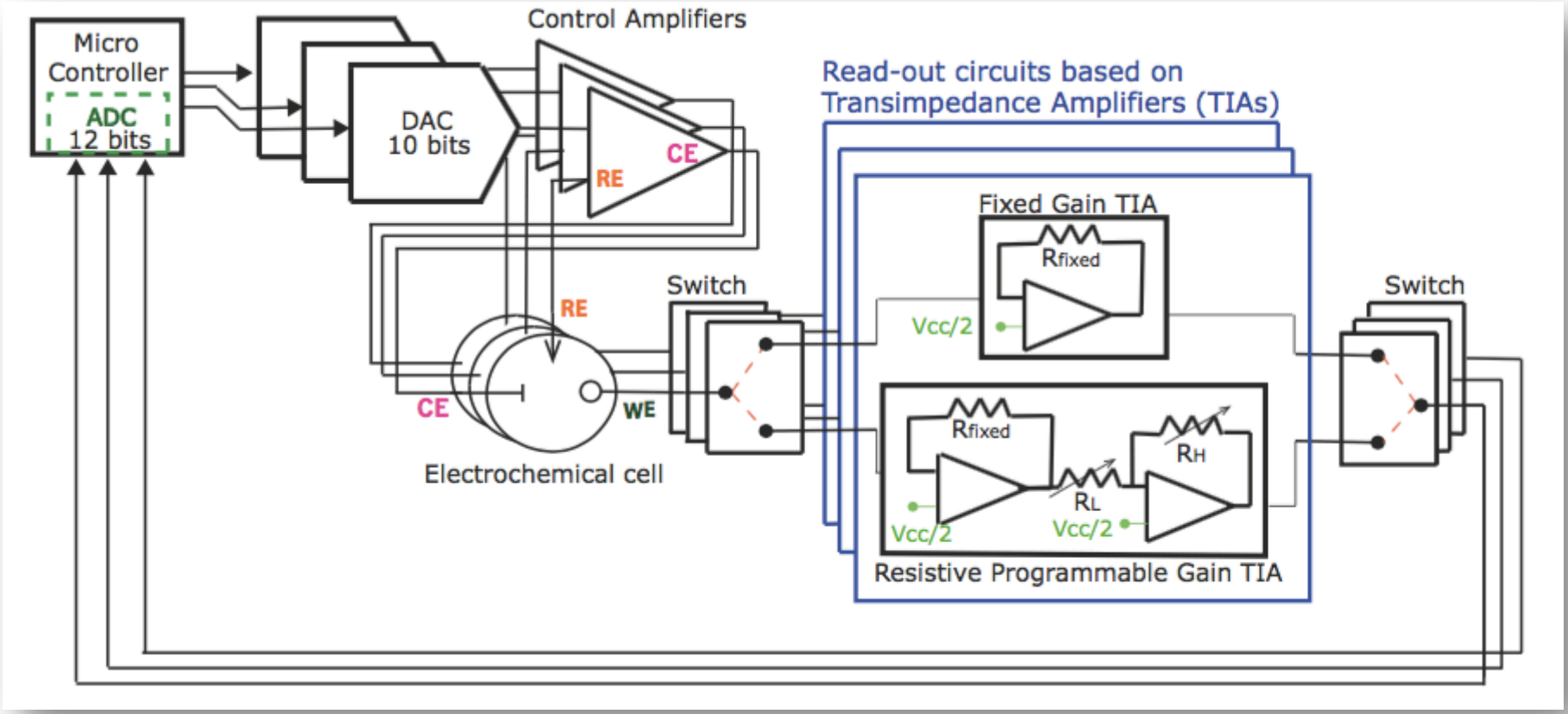
Monitoring and Injection in Surgery



Drug Cocktails
usually used in Anaesthesiology

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

Detection of Anaesthetics

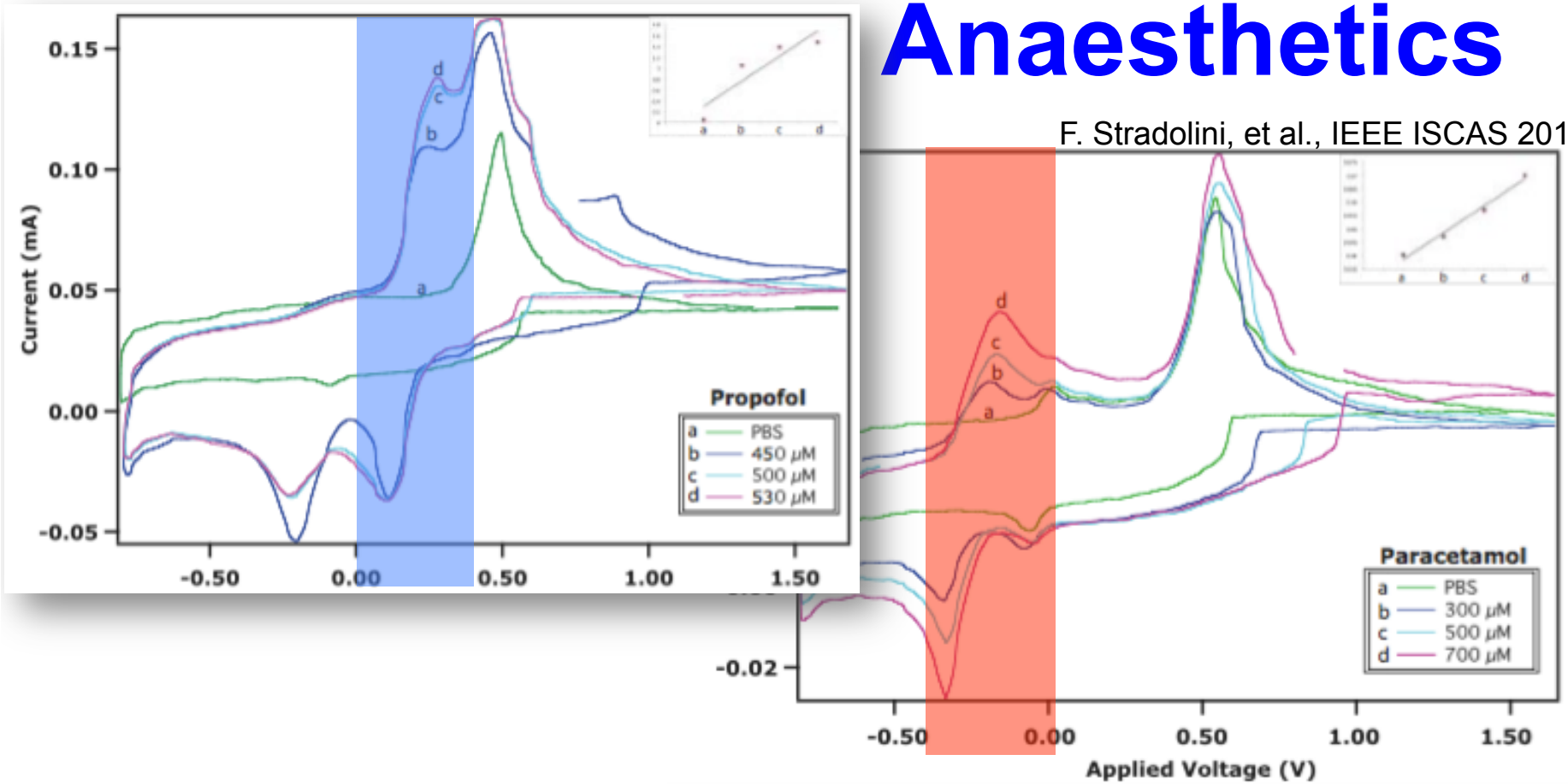


F. Stradolini, et al., IEEE ISCAS 2016

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

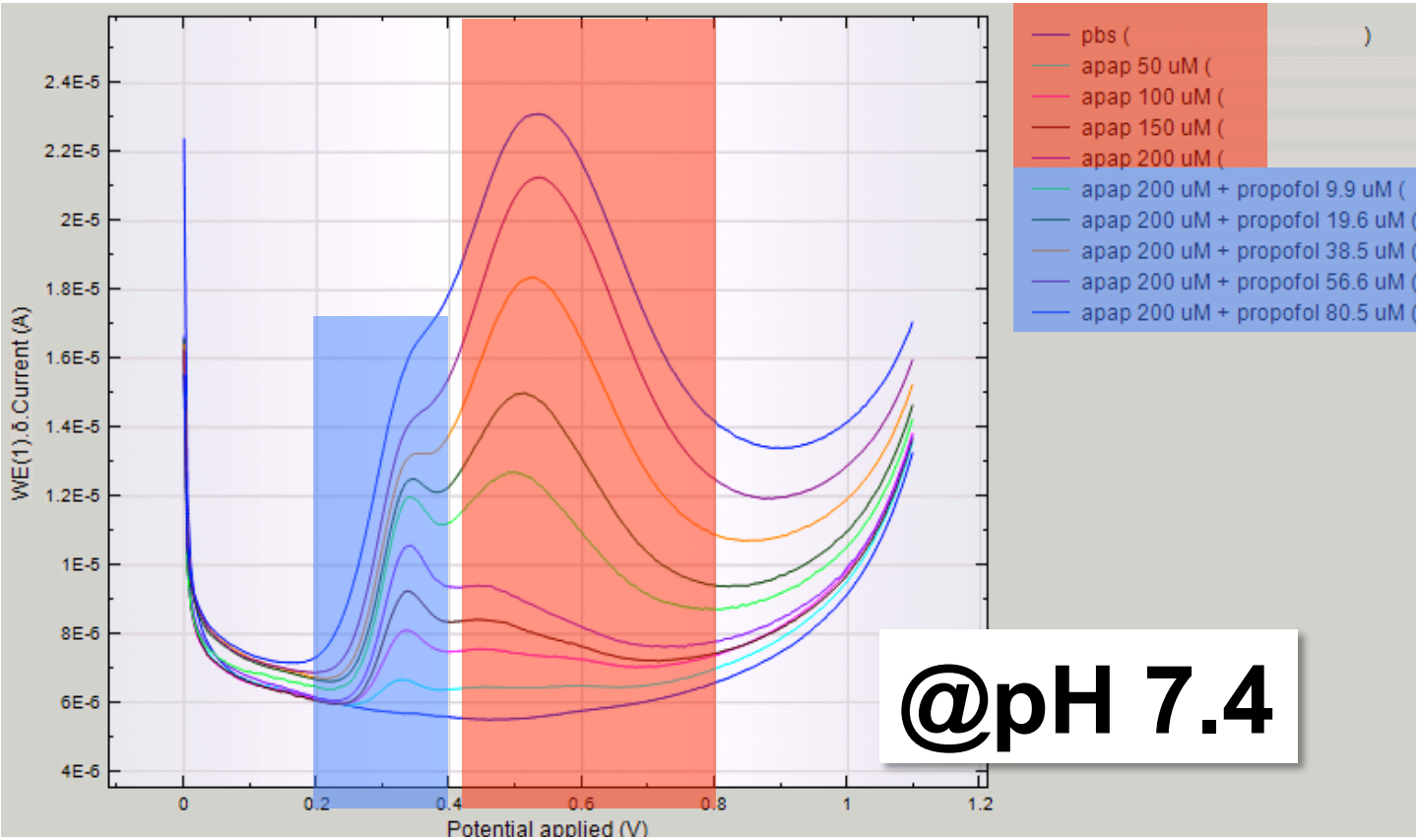
Electrochemical detection of Anaesthetics

F. Stradolini, et al., IEEE ISCAS 2016



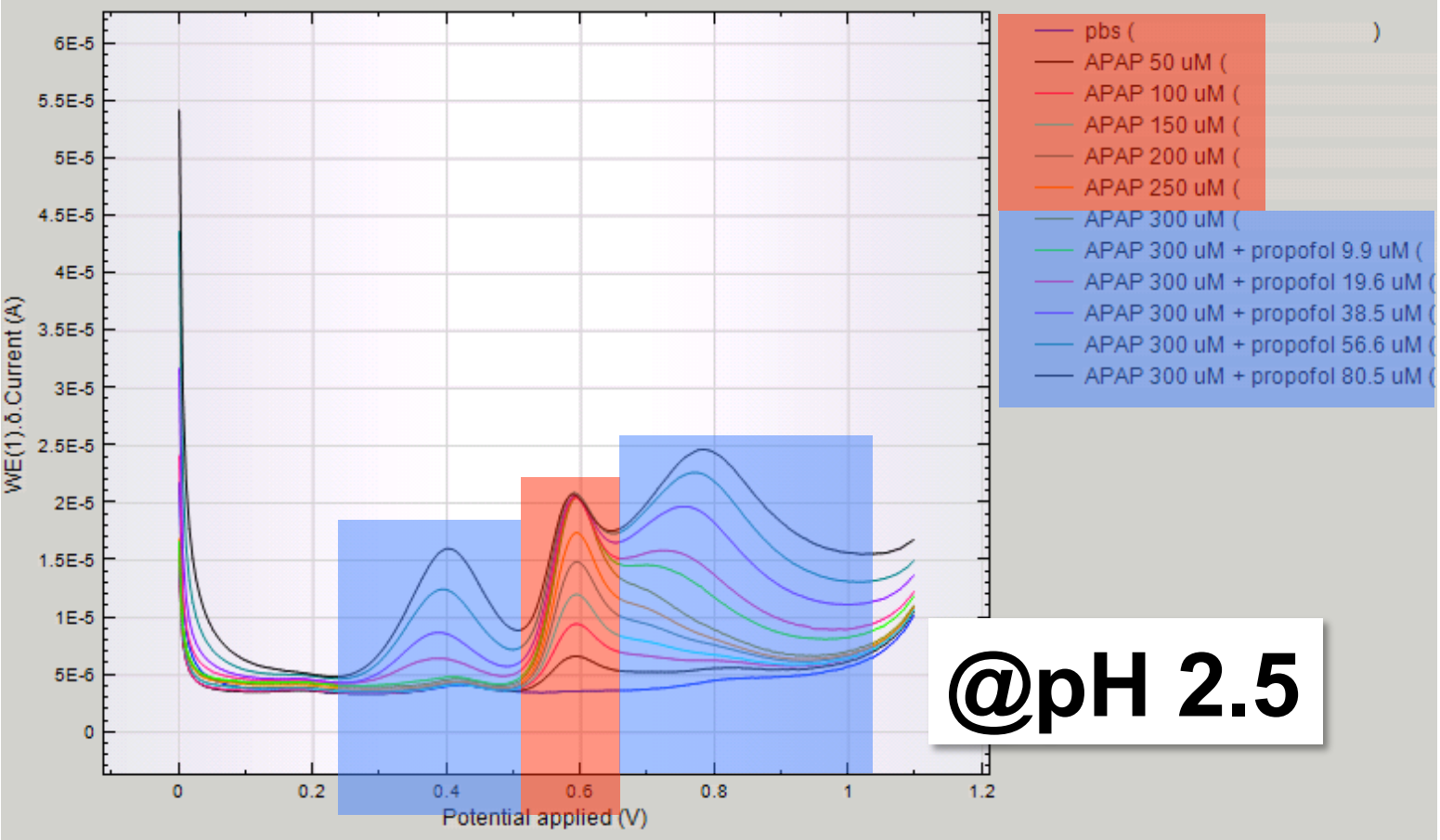
Cyclic Voltammograms measured for propofol and paracetamol with carbon electrodes

Multiplex of Anaesthetics



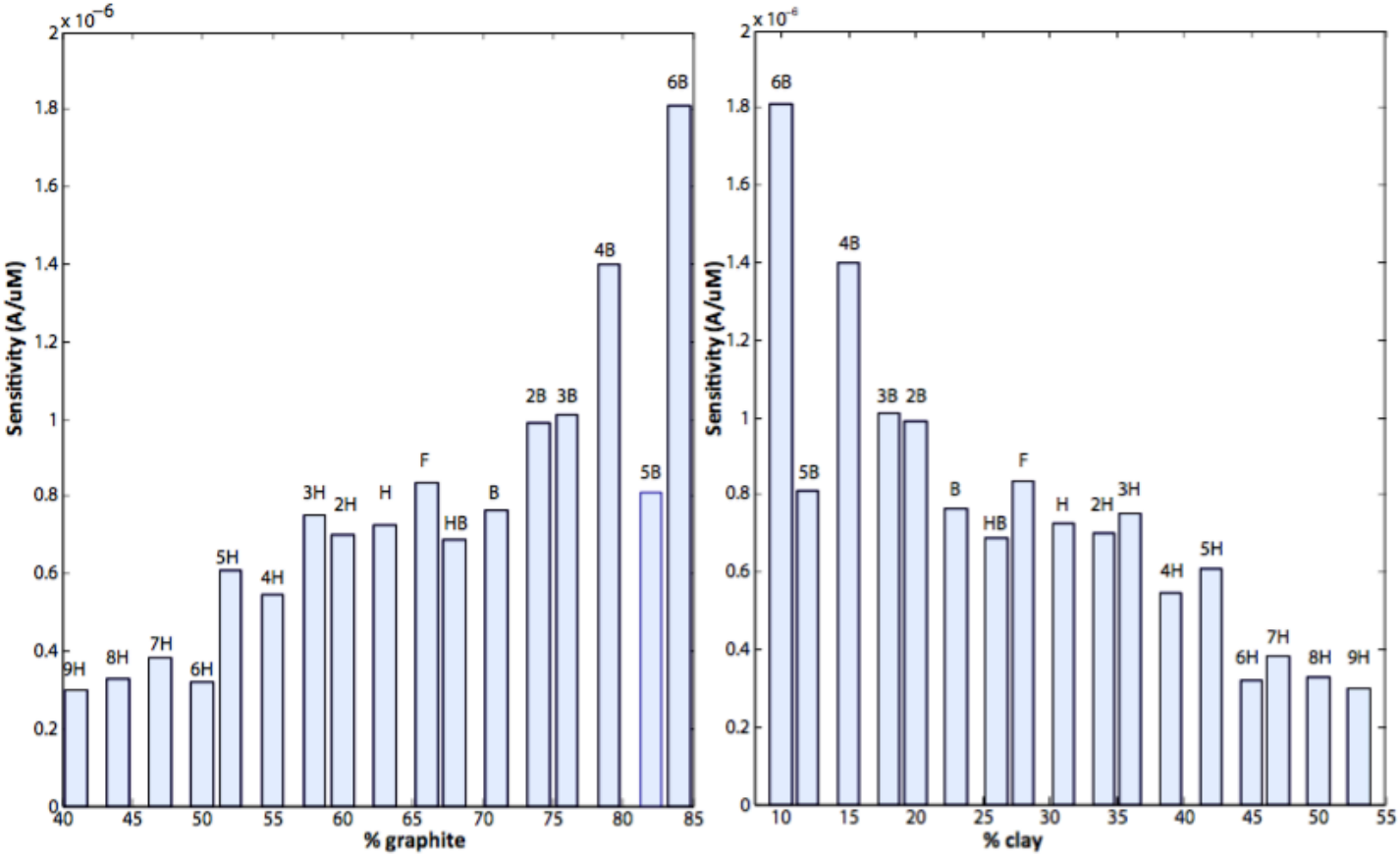
Cyclic Voltammograms measured for propofol and paracetamol (APAP) with Pencil Graphite Electrodes

Multiplex of Anaesthetics



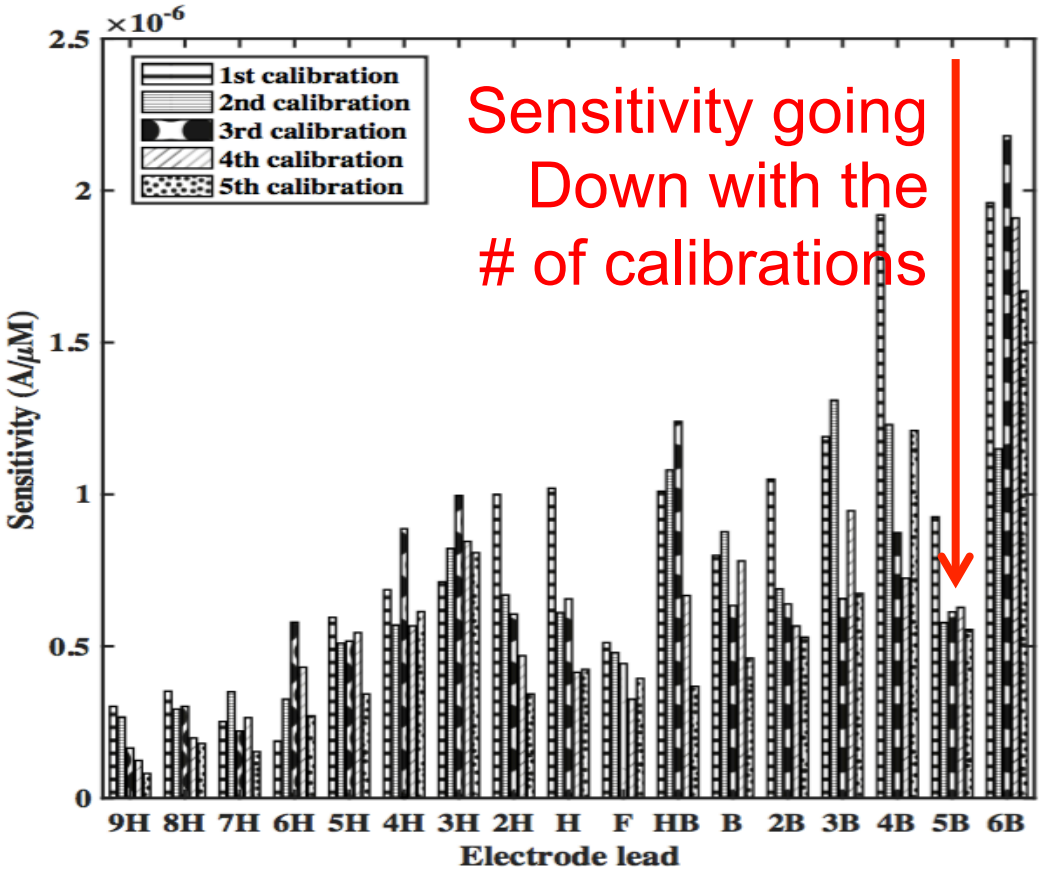
Cyclic Voltammograms measured for propofol and paracetamol (APAP) with Pencil Graphite Electrodes

Detection of Anaesthetics



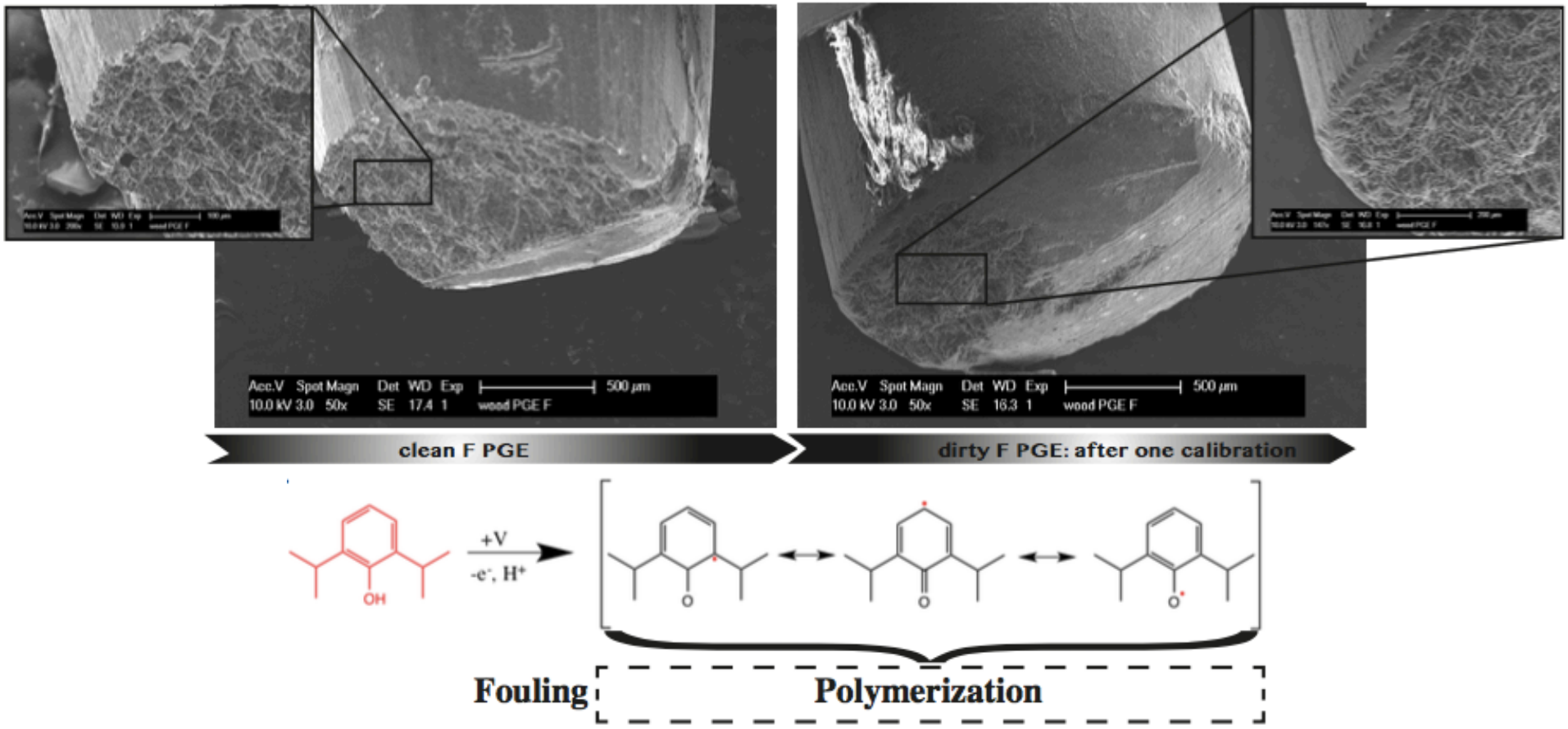
Comparison in sensitivity for different % of graphite and clay in lead compositions

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

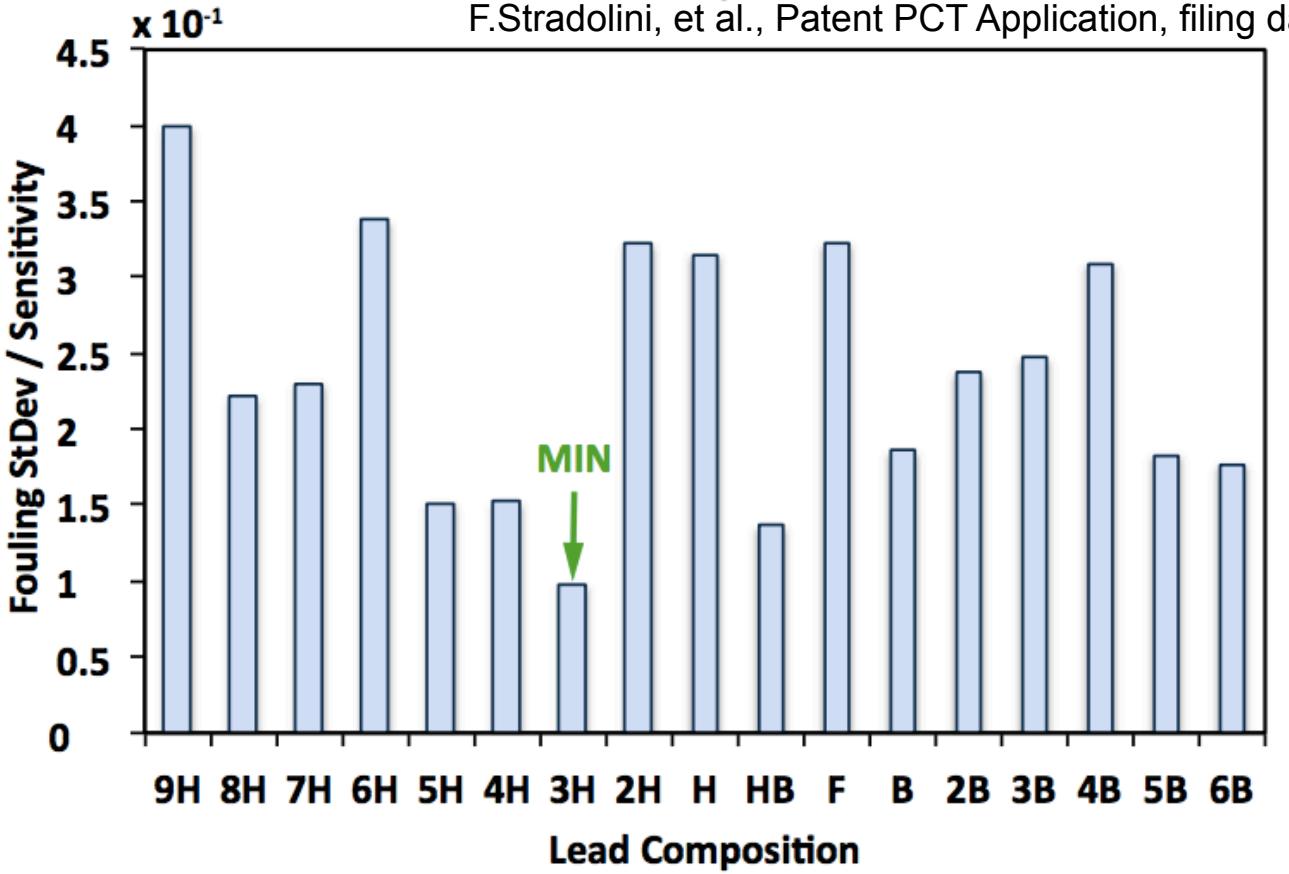
Detection of Anaesthetics



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

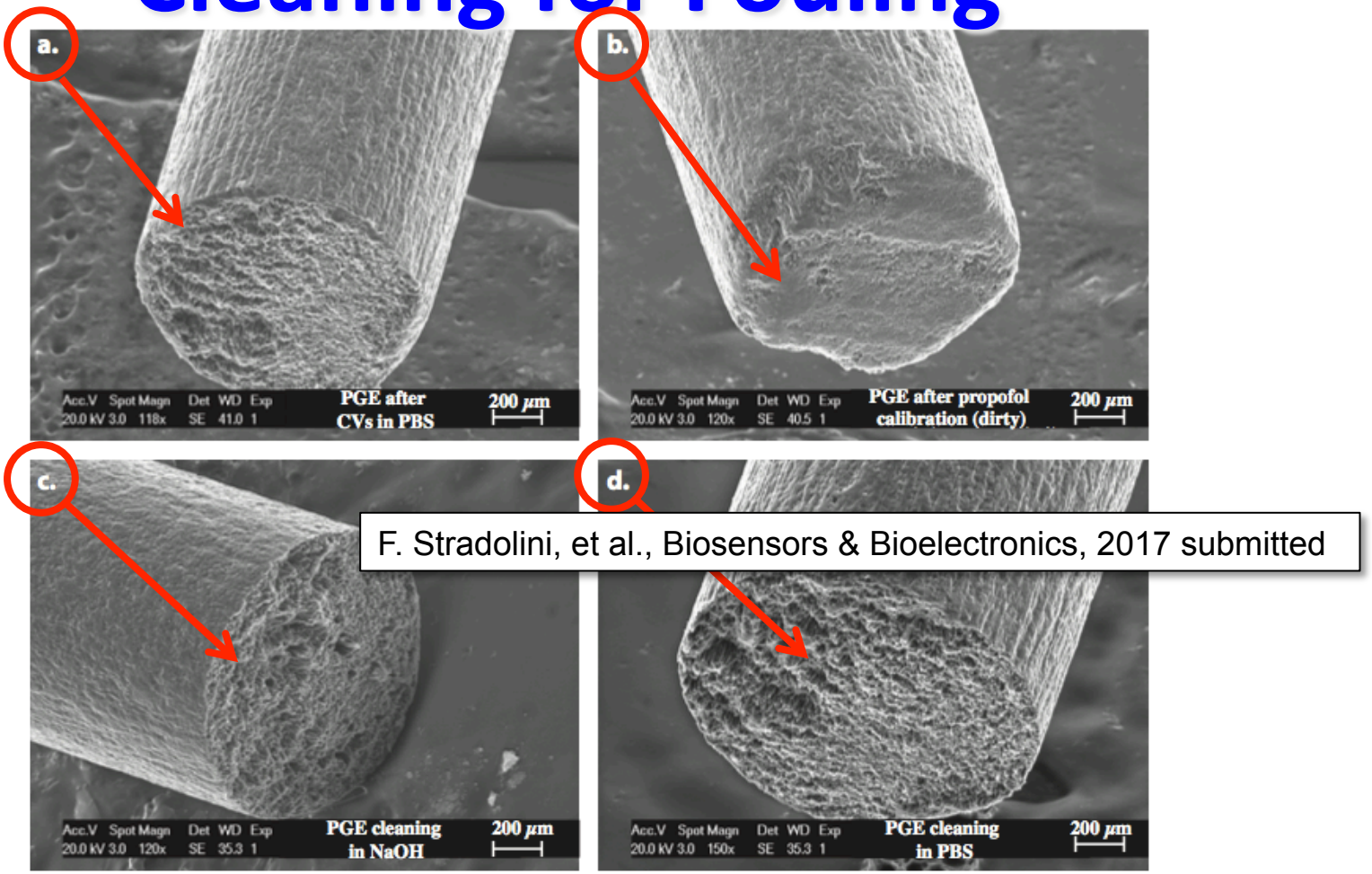
F.Stradolini, et al., Patent PCT Application, filing date May 30, 2017



Variability in S for subsequent propofol calibrations on the same electrode respect to the average S of the electrode itself

(Fouling StDev/Sensitivity)

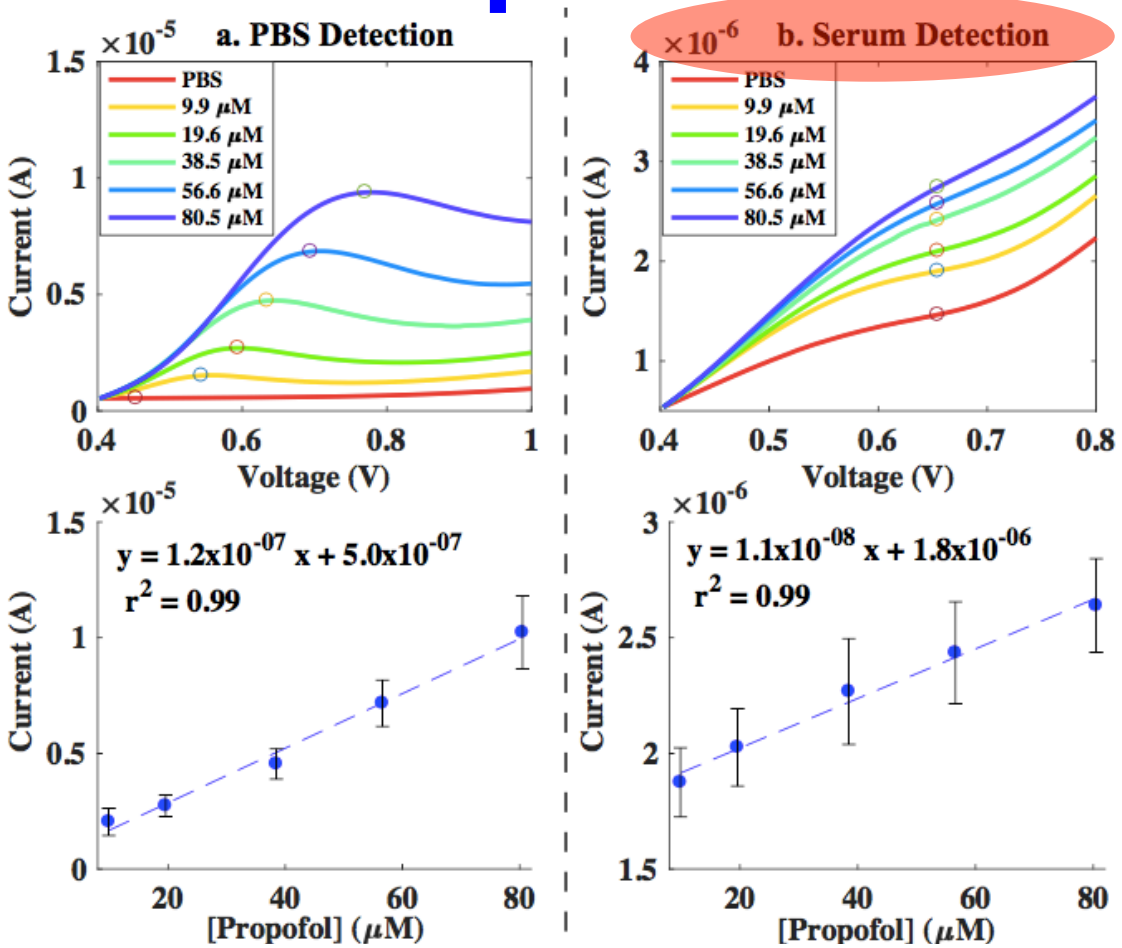
Cleaning for Fouling



F. Stradolini, et al., Biosensors & Bioelectronics, 2017 submitted

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

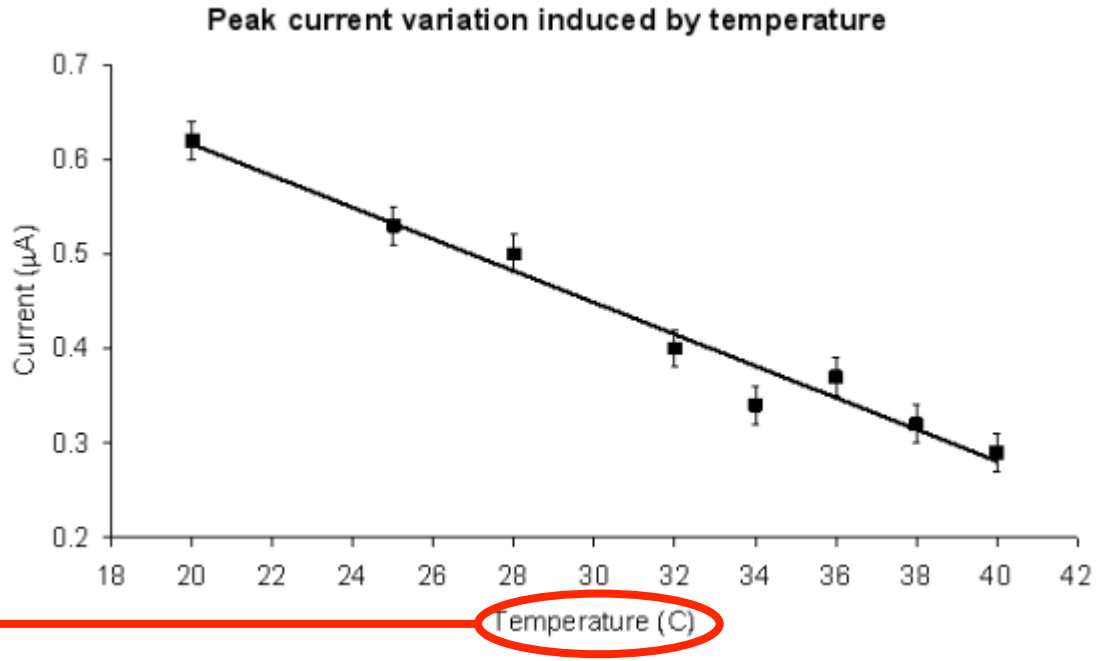
Long-term Propofol Monitoring



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

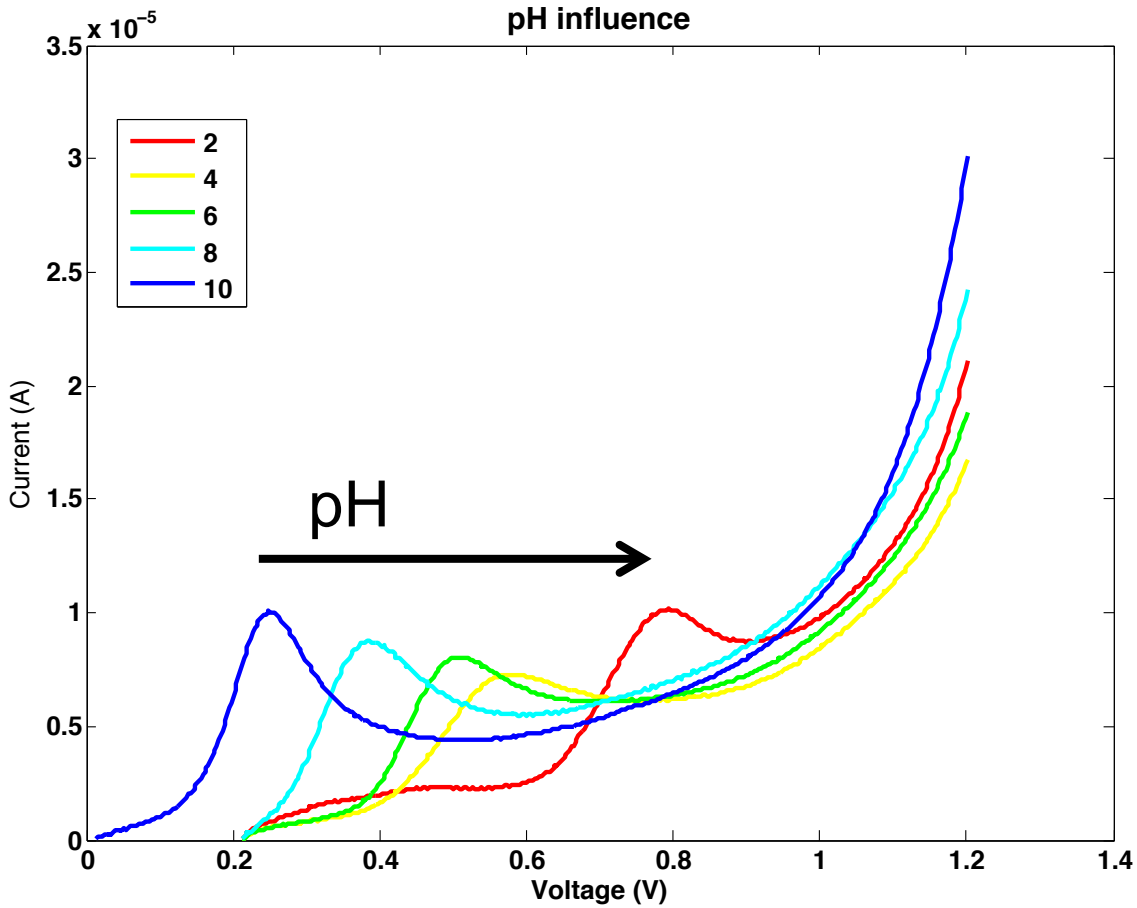
Reliability in Temperature

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



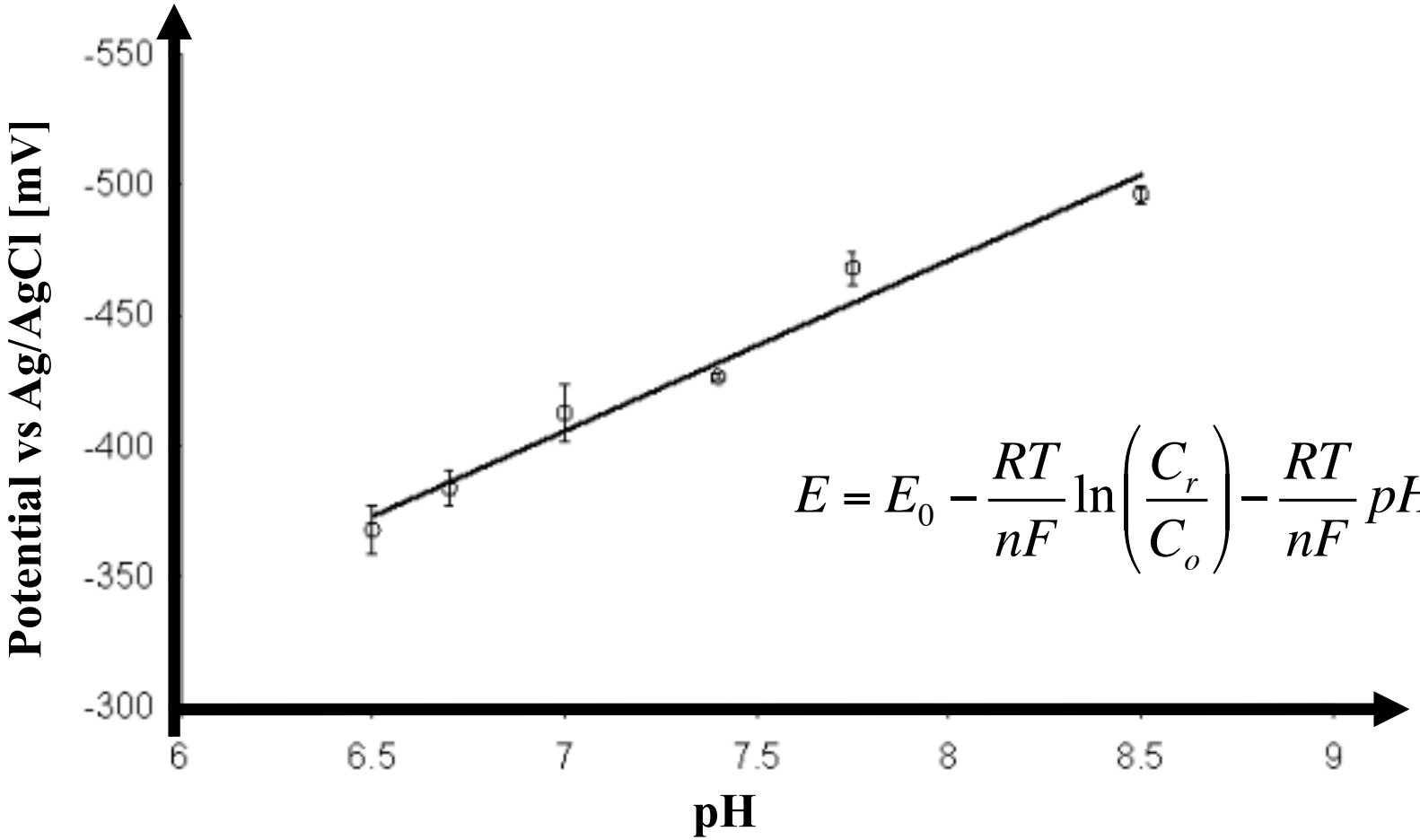
Biosensors response requires temperature compensation

Reliability in pH



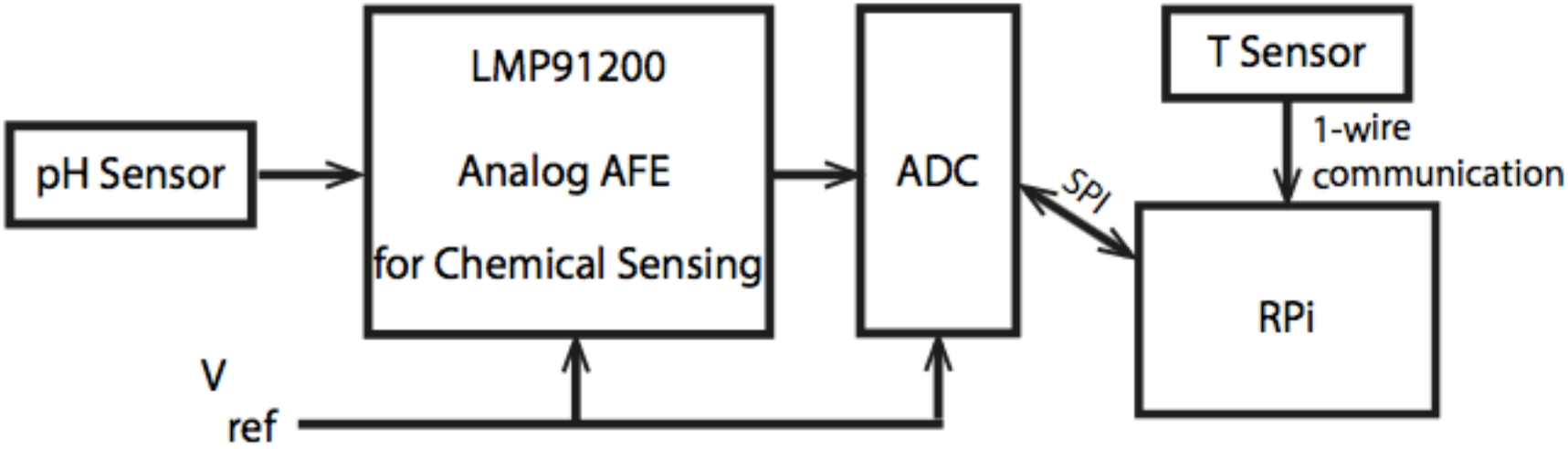
The pH changes the voltage position of the Faradaic Peak of the Propofol

Reliability in pH



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

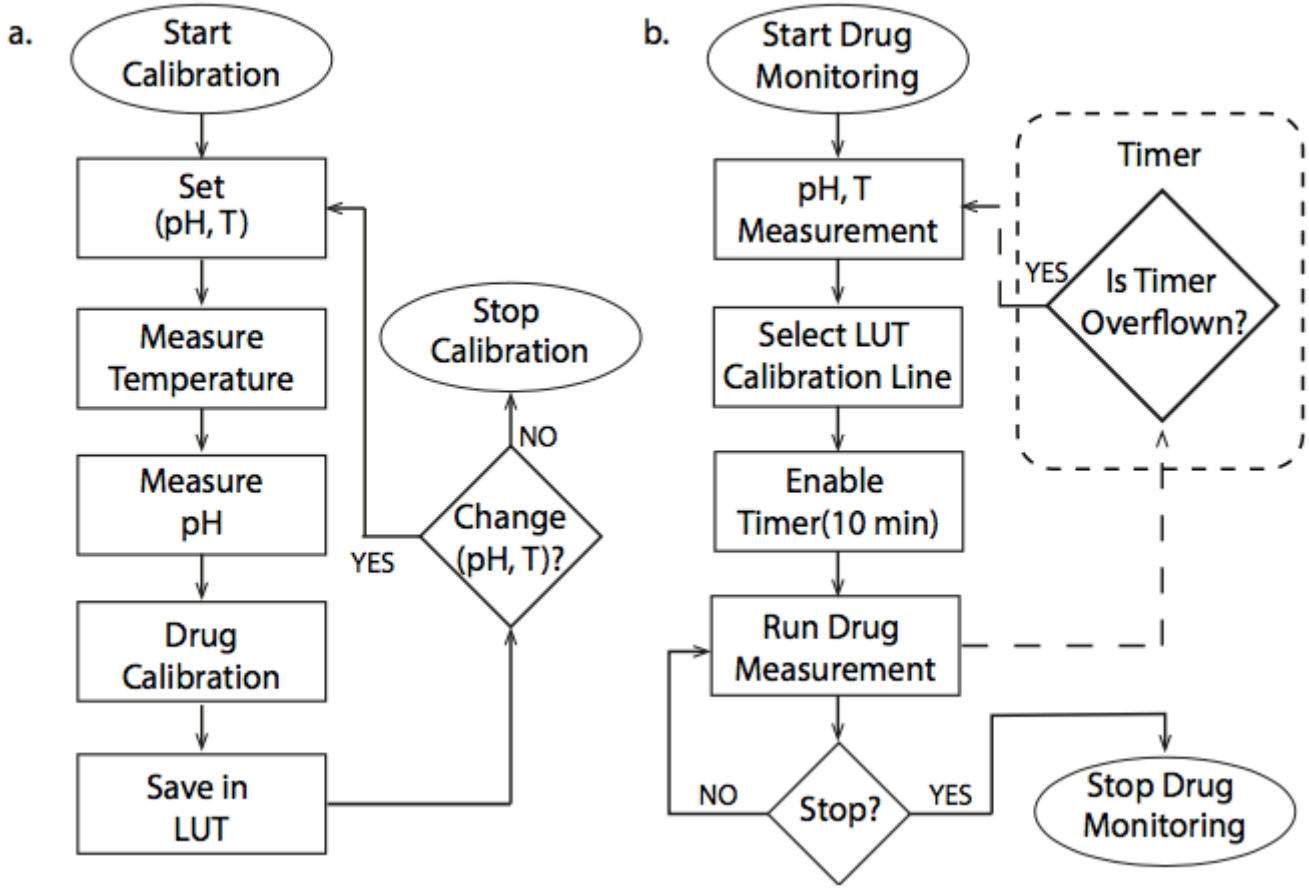
Interface for T & pH



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

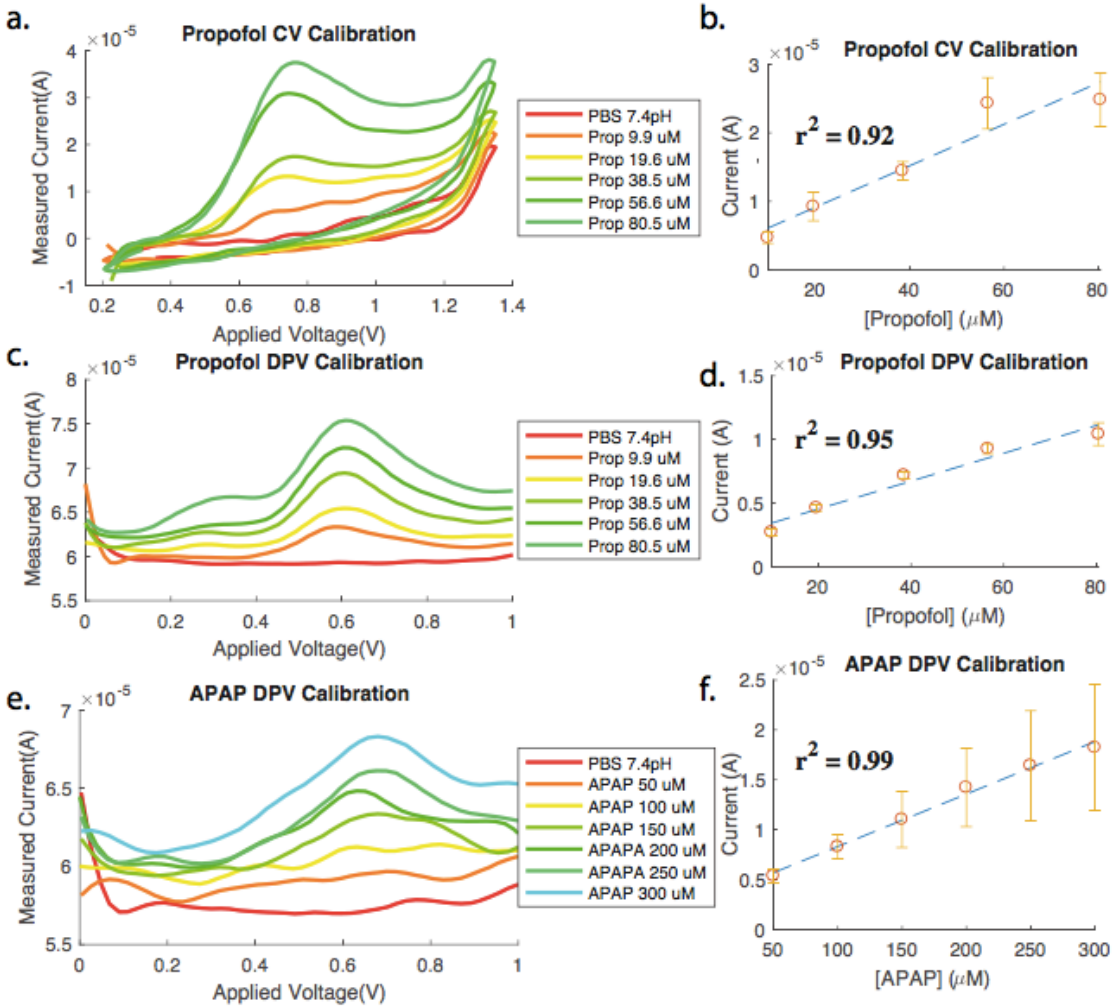
Schematic of the portable mixed signal circuit for pH and T sensing

Calibration Procedures



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

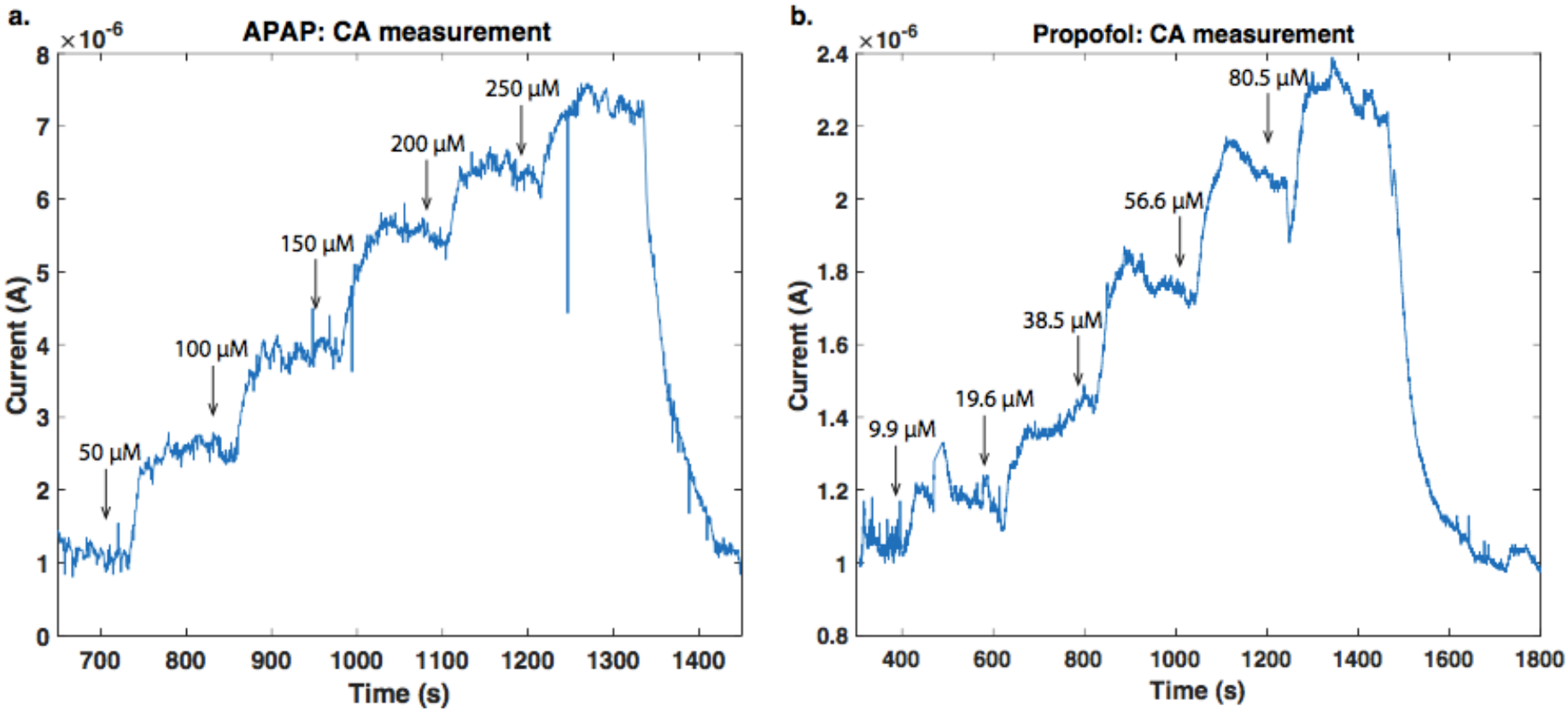
Calibration of Anaesthetics



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

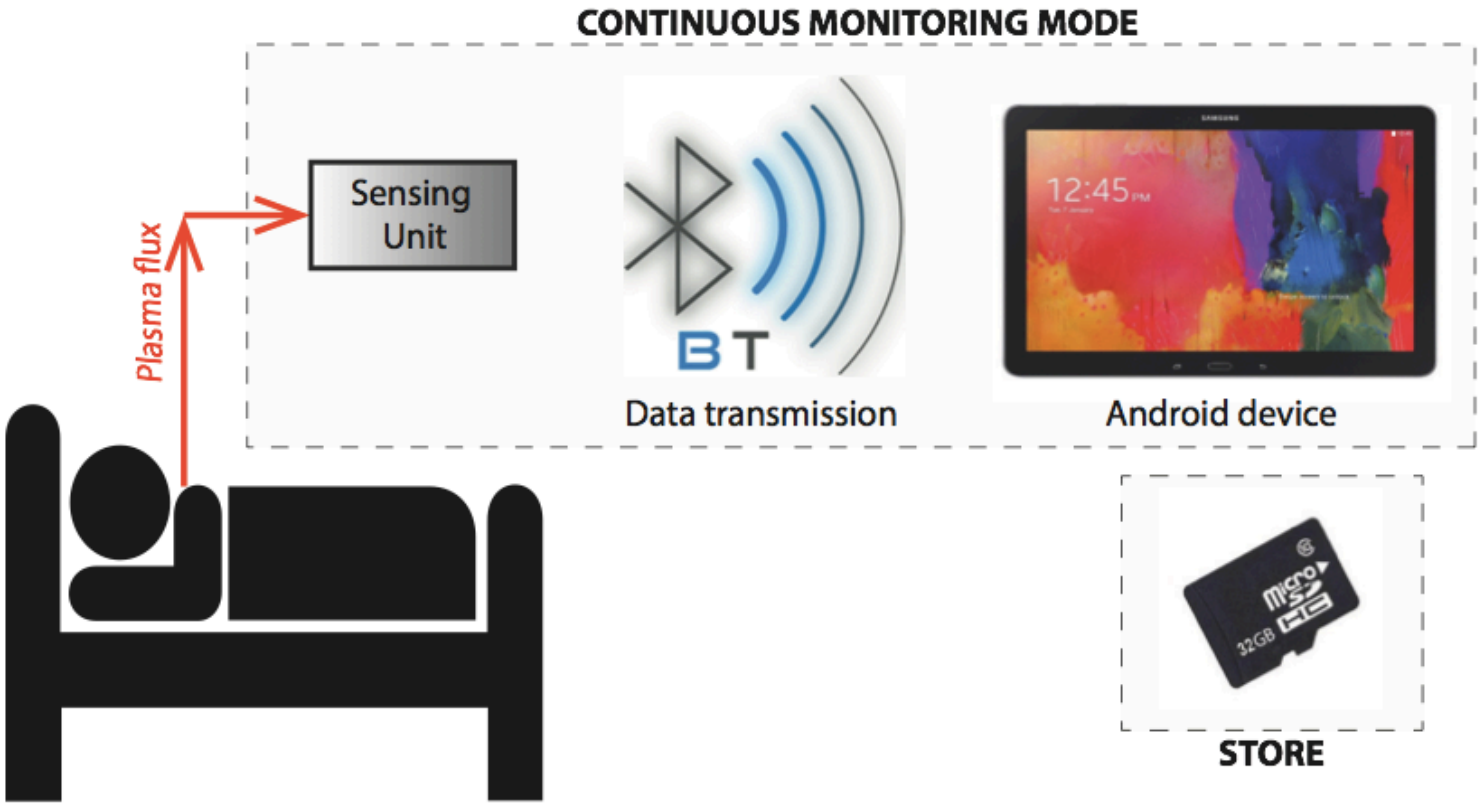
Monitoring of Anaesthetics

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

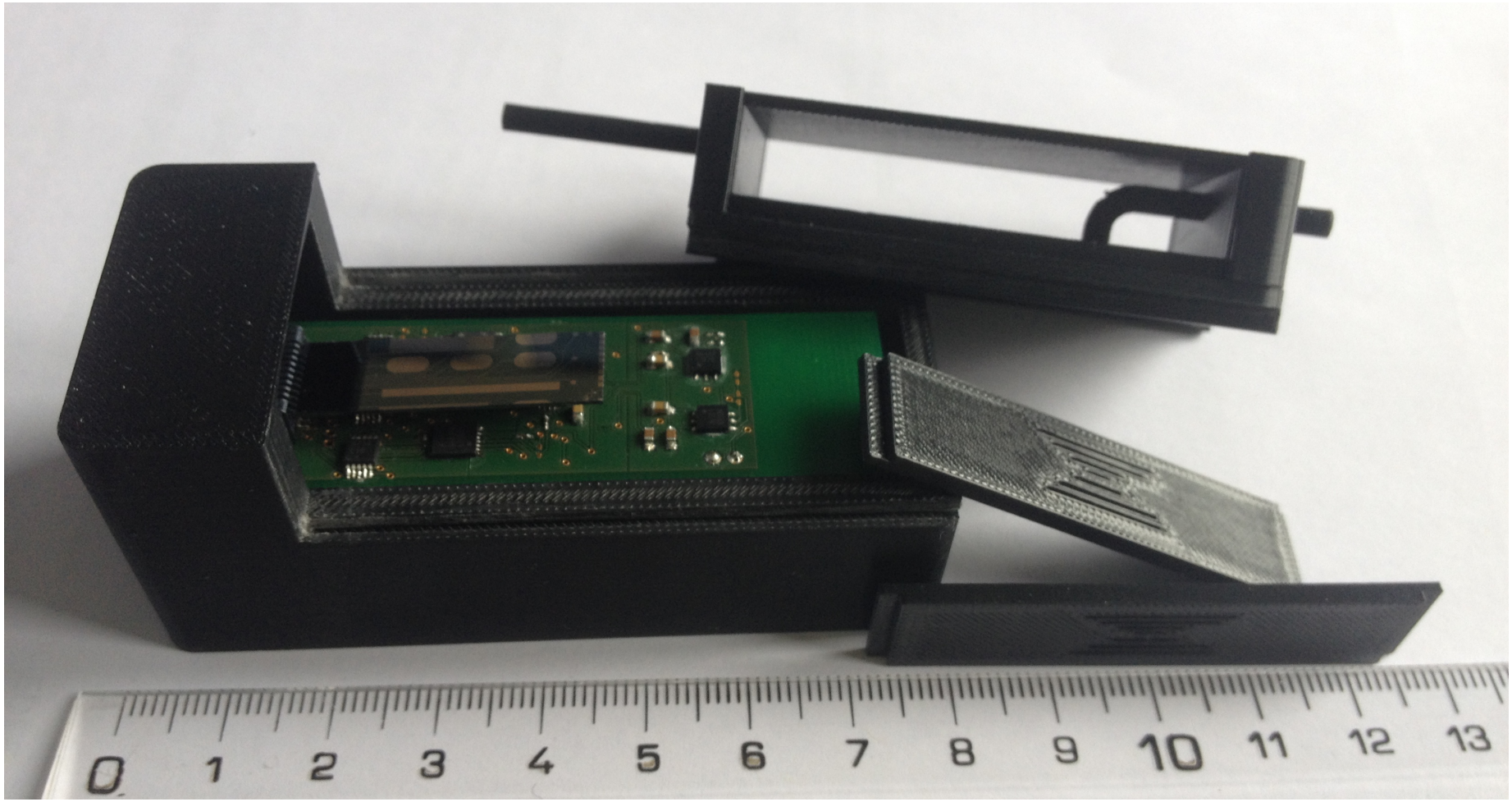


F. Stradolini, et al., IEEE Sensors Journal 16(2016) 3163 - 3170

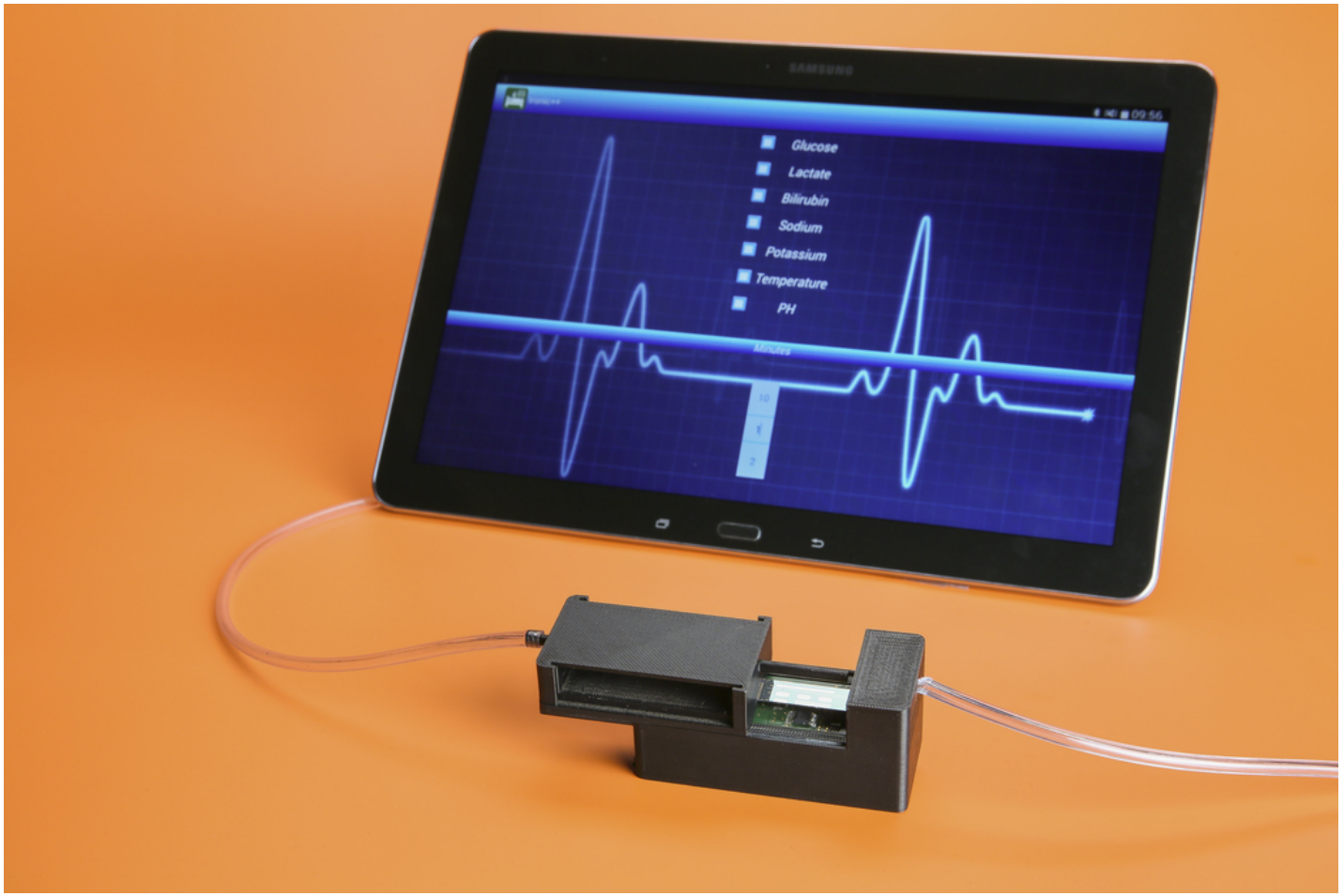
Monitoring scenario where the main parameters of the patient are continuously displayed on an Android mobile device

Monitoring in intensive Care Units

F. Basilotta, et al., IEEE BioCAS 2015



Android Interface



The whole system with the Android™ interface that allows connectivity too

Android Interface

Glucose

Lactate

Paracetamol

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

The whole system with the Android™ interface that allows connectivity too

Connectivity with Smart-Watch

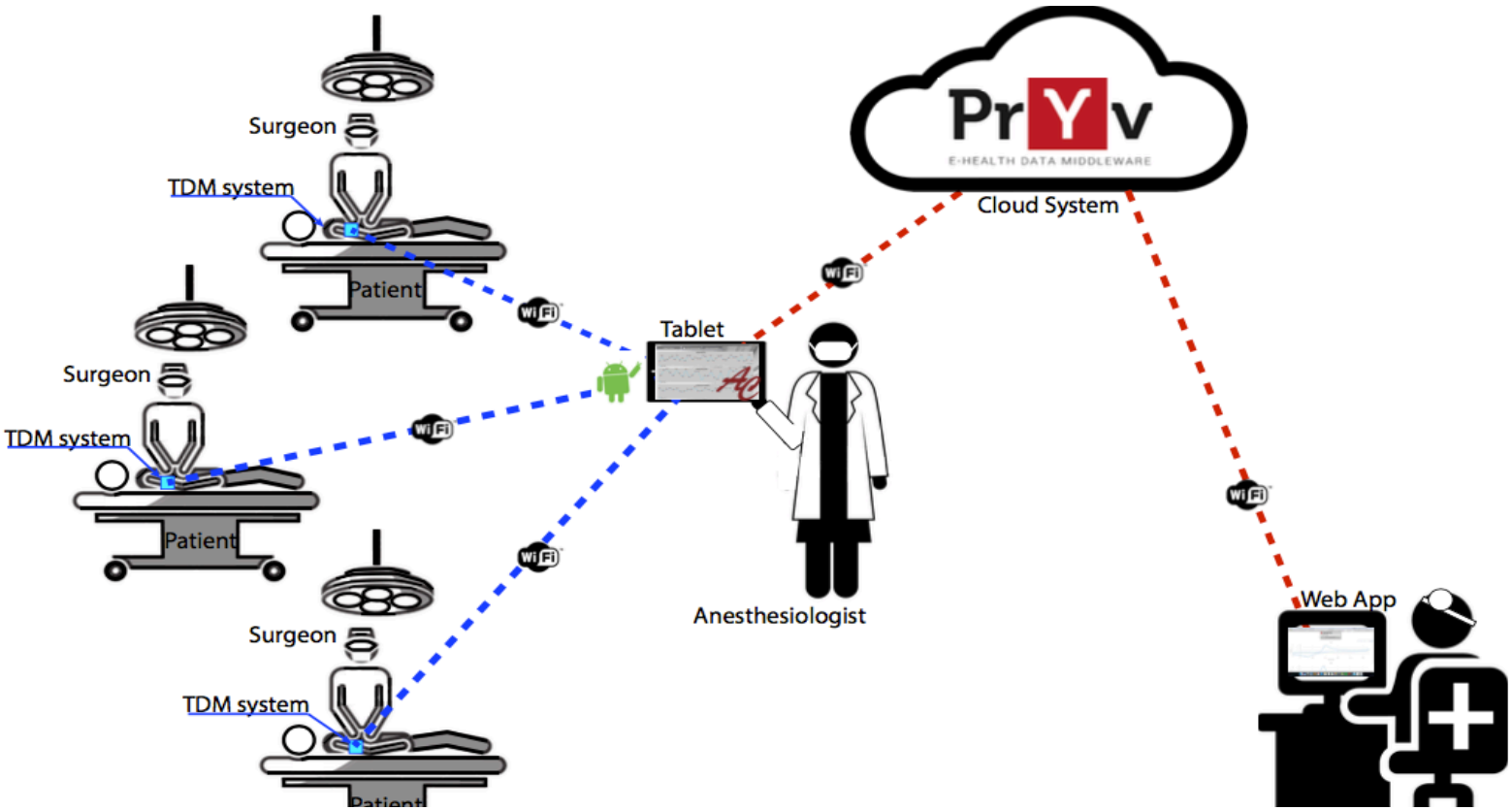
Live Demo @ BioCAS17

YouTube

F. Stradolini, et al., MOBILHEALTH 2016

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

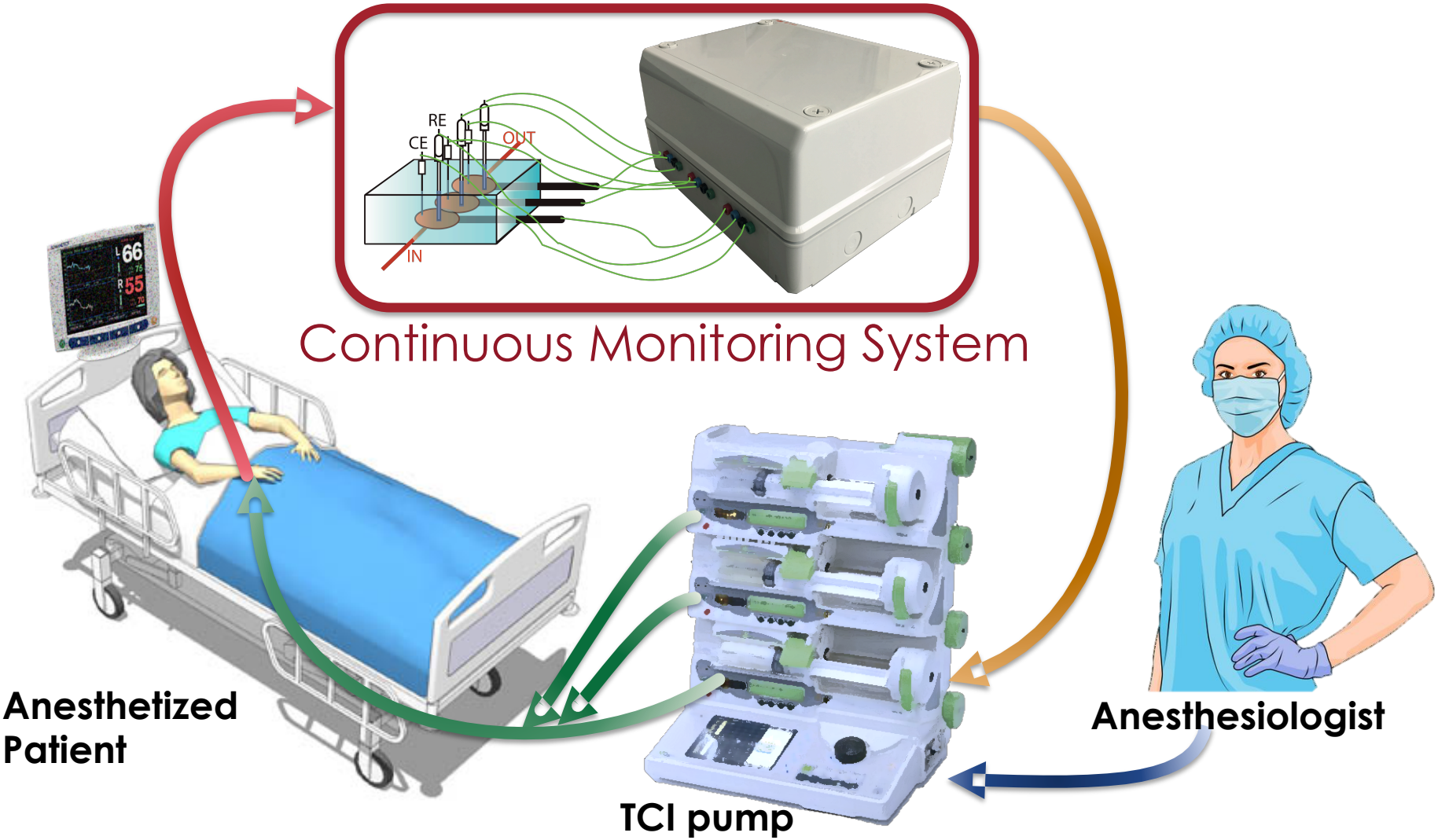
Connectivity through Cloud



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!