# PhD in Electrical, Electronics and Communications Engineering

## Research Title: Continuous Monitoring of Anaesthetics Concentration to Control Anaesthesia Delivery

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| **Funded by** | Politecnico di Torino with funding by Compagnia di Sanpaolo |

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| **Context of the research activity** | **Motivation**: every year, 30,000 people undergo anaesthesia and remain awake, still feeling pain while not being able to move, due faulty drug administration. Many more are put into uselessly deep or prolonged chemical coma. Proper anaesthesia requires the achievement of a certain target plasma concentration of the drugs (e.g. propofol, fentanyl or midazolam, etc.). Today, such drugs are regularly injected by Target Controlled Infusion (TCI) systems, while the usual magnitude of prediction errors in control models reaches 20-30% due to the patients' diversity. Therefore, continuous monitoring of anaesthetic agents circulating in body fluids would contribute to better individualization of patients' management.<br><br>**Project Focus**: to propose the realization of a system with a semi-closed-loop control for anaesthesia delivery based on the anaesthetics monitoring in human fluids. Core of the system will include several electrochemical sensors for the real-time monitoring of anaesthetics and sedatives, and complementary intelligent decision- making algorithms able to adjust dosages and delivery rates according to the sensor measurements, under the ultimate control of anaesthesiologists.<br><br>**Expected outcome**: to produce a prototype of a device implementing semi-closed-loop anaesthesia delivery based on real-time measurements of anaesthetics concentration. The prototype will be ready for clinical development, after appropriate animal testing. |

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| | The Project will be developed in cooperation with the EPFL in Lausanne, Switzerland, and the attempted program for the PhD period is:<br>• M1-6, study at Politecnico di Torino of the project and of basic knowledge. State of the Art studies. Design of the platform;<br>• M7-12, EPFL mobility for preliminary studies for the realization of the system for simulating the extraction of a sampling amount of anaesthetics from patient's blood and of a miniaturized nano-bio-chip system for on-line monitoring of the anaesthetic concentration. A nano-bio-chip will be designed and fabricated at EPFL for real-time and continuous monitoring of several anaesthetics;<br>• M13-18, development at Politecnico di Torino of electronic interfaces;<br>• M19-30, EPFL mobility for integration of electronics and testing;<br>• M31-36, at Politecnico di Torino, final setup, result elaboration and PhD Thesis discussion preparation (with Thesis writing). Support of Swiss partners in final testing (some temporary travels to EPFL for final tests). |

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| **Objectives** | The clinical use of Anaesthetics requires a thorough titration of dosage to ensure the achievement and maintenance of the proper effect intensity. The PharmacoKinetic (PK) parameters that characterize drug disposition are also depending on various patient characteristics and are not fully predictable. Therefore, anaesthesiologists need to continuously adjust the delivered dosages in order to keep drug concentrations at a certain level to assure appropriate sedation and to avoid patient's intoxication and/or awareness.<br><br>Anaesthesia is a process of a balanced delivery of several compounds, including anaesthetics, analgesics and muscle relaxants. The continuous adjustment of the drug delivery rate can be based on two types of strategies, which tend generally to be used by the anaesthetists:<br><br>1. The first strategy is an "a priori" predictive approach. This strategy is based on the prediction of drug concentration profiles using PK concepts and known parameters characterizing drugs' Absorption, Distribution, Metabolism and Elimination (ADME). This approach is typically implemented in programmable infusion pumps [1]. However, the probability of inaccuracies and prediction |

errors is high (20-30%) due to the inter-patient variability.

2. The second strategy relies on feedback loops “a posteriori”. This strategy is based on monitoring patient’s physiological variables, e.g. blood pressure, heart rate or reactivity to pain. The bispectral index (BIS - recorded by EEG) is also able to provide an indication of hypnotic levels [2] and can be used to derive the PK parameters of propofol too [3]. However, these variables are not specific and the BIS signal may leads to misjudgement of the level of sedation.

Therefore, both methods are not perfectly efficient and safe enough while inattention and inexperience of medical personal are causes of incidents during anaesthesia [4].

The project has the goal of realising a continuous Therapeutic Drug Monitoring (TDM) [5] system that

1. monitors concentration levels of anaesthetics during anaesthesia;
2. assists in patient specific injection/infusion dosage and rate decisions.

In one hand, the measurement of the drug concentration in blood is usually performed using techniques such as liquid or gas chromatography [6], mass spectrometry [7] or radioimmunoassay that are technically demanding and do not allow on-line continuous monitoring. On the other hand, a tremendous breakthrough in drug detection has been more recently proposed by using electrochemical biochips [8-11]. In these chips, specificity is ensured by proper probes [10] or specific coatings [12], while sensitivity is improved by nano- structured surfaces [9,11]. These developments open to continuous monitoring of anaesthesia cocktails (e.g. propofol, fentanyl, midazolam etc.), as proven by the case of propofol [13]. However, the drug concentration profile in body fluids has a complicated dependency on the delivered drug dosage.

The combination of a set of electrochemical sensors and an intelligent semi-closed-loop algorithm and their integration onto an existing programmable pump will improve and personalize the provision anaesthesia delivery.

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[2] Kramer et al. J Am Osteopath Assoc. 98(1998):385-6

[3] Sartori et al. IEEE EMBS 2005 Vol. 1, pp 74-77
[4] Pham et al. Annual Review of Medicine 63(1), 2012, 447–463
[5] Varvel et al., J Pharmacokinet Biopharm. 20(1992) 63-9
[6] Nikolin et al. Basic Med Sci. 2004 May;4(2):5-9
[7] James et al. Biochem. J. (1952) Biochem. J. 50: 679–680
[8] Carrara et al. CCME conf., 9-11 April 2009, pp.1-6
[9] Carrara et al. Biosensors and Bioelectronics 26(2011) 3914–3919
[10] Carrara et al. Sensors 2012, 12(5), 6520-6537
[11] Carrara et al. Biosensors and Bioelectronics, 53(2014) 283-287
[12] Lindner et al., US patent, US 2012/0116195 A1
[13] Takita et al. Anaesthesiology. 106(2007) 659-664

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| **Skills and competencies for the development of the activity** | Requested Skills and Competences are:<br>• Basic knowledge of Electronic Design and Embedded Systems<br>• Basic Knowledge of Biosensing and Biomedical Applications<br>• Basic Knowledge in Micro&Nano Systems Technologies<br>• Experience in Circuit Design and PCB realisation |