NMP4-CT-2005-017114

"RECEPTRONICS"

LABEL-FREE BIOMOLECULAR DETECTORS: AT THE CONVERGENCE OF BIOENGINEERED RECEPTORS AND MICROELECTRONICS

Instrument: STREP

Thematic Priority: NMP

PUBLISHABLE EXECUTIVE SUMMARY

1st Oct 2006 – 30th Sep 2007

Start date of project: Oct. 1st 2005 Duration: 3 years

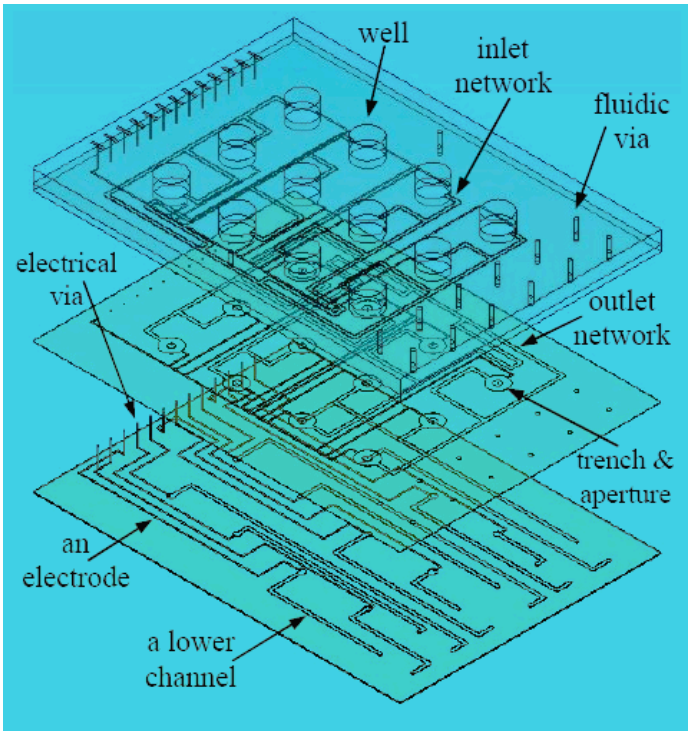
Publishable executive summary

Introduction

RECEPTRONICS, is a project financed by the VIth European Research WorkProgram involving 9 partners from European Institutions, namely: University of Bologna (Coordinator), Centre National de la Recherche Scientifique - CNRS Grenoble (FR), DSV and LETI laboratories at Commissariat à l'Energie Atomique - CEA Grenoble (FR), National and Kapodistrian University of Athens - NKUA (GR), EE and Chemistry Departments of University of Southampton (UK), Silicon Biosystems, S.p.A. (IT), and SPI-BIO (FR).
The total cost of the RECEPTRONICS project is 3.5M€ with a grant of 2M€ from EC. The goal is to develop low-cost, label-free biomolecular sensors by integrating concepts and methods from bio-nanotechnology and microelectronics. The RECEPTRONICS project is based on a strong multi-disciplinary platform where integration of knowledge from Biology, Physics, and Information Technologies is required.

Counting molecular events one-by-one

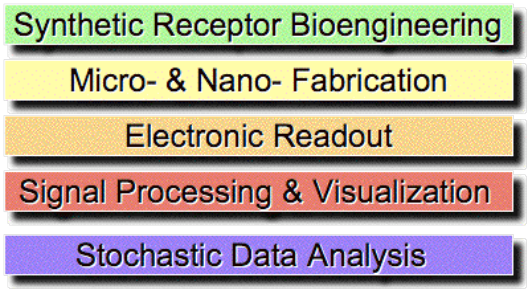
The project is aimed to achieve the goal of estimating target concentrations by counting singular molecular events. Due to technical limitations and sometimes convenience, biological analyses traditionally take averages over group of cells or molecules. However, averaging is sometimes problematic as it may mask important individual variations in structural and dynamics properties at both the cellular and molecular levels. Single molecule approaches have the advantage of avoiding averaging, enabling observation of transient intermediates and heterogeneity. Hence they might revolutionize the way many biological questions are addressed. This approach is true especially in sensing techniques. Unlike sensors aimed at detecting macroscopic quantities such as weight, pressure or acceleration, the input in biosensing is by definition a discrete quantity: the molecule. For this reason, by identifying single molecules in a sample might lead to the maximum resolution physically achievable. In other words, since concentration is made of a finite number of elements, the best sensitivity can be achieved by counting molecular events of the same nature one-by-one. This is the reason why the single molecule detection challenge plays a fundamental role for implementing highly sensitive devices for both applications in diagnostics and drug discovery. Unlike conventional biosensors where concentration sensitivity is in the milli-molar range, the granularity of the input becomes apparent below the pico-molar order of magnitude.



In molecular recognition, state-of-the-art artificial systems cannot compete with living organisms. As an example, the sensitivity of chemical senses in insects is much greater than conventional electronic systems such as the electronic nose.

State-of-the-art nose technology is currently based on electrical conducting polymers - materials which are similar to plastics but can conduct electricity. These materials can be primed to absorb and respond to different odour molecules, and a typical artificial nose will feature an array of polymer sensors, each of which is responsive to a particular substance. However, odours affect many of the sensors in different ways, and the resulting pattern of responses needs to be analysed. Furthermore, their sensitivity is still relatively low. The RECEPTRONICS project has picked up the problem from a different angle. The project plan to replicate what goes on in biology. In the nose are cells with molecules embedded in the cell membrane. When these bind with an odour molecule, a hole opens in the molecule and an electrical current flows, creating a stimulus, which is transmitted to the brain.

The Project proponents are strongly convinced that the goal of molecular recognition could only be achieved using several strategies belonging to both Nanotechnology and Information Technology. This is the reason why RECEPTRONICS is organized in a stack of technology objective layers (see figure below) where each task is integrated and developed in a strong synergy with others. The way followed by the project to boost the sensor sensitivity is based on using affinity-binding paradigm employed by receptors. Receptors are proteins that are usually sitting on the cell membrane that are employing an extremely efficient molecular machinery for detecting specific molecules. The goal of the project is to combine efficiency of this bio-molecule with powerful flexibility of integrated electronics in a unique device called Receptron. The researchers will use molecular engineering techniques to create customized receptors that are sensitive to different substances. These receptors will be embedded in membranes in an array, with each receptor linked to an electronic interface, which can detect electronic signals transmitted when the receptor binds with its target molecule. The system will be mounted on a credit-card sized chip. The three-year project will focus on designing a system, which could be used in medicine to detect hormones, and so help doctors to diagnose a wide range of diseases. This could be done since molecular recognition is one of the most important steps required for a deep understanding of mechanisms in living beings. Every active cell interacts each other and with the environment by means of a complex network of molecular messengers at very low concentration. There are perhaps thousands or millions of regulatory substances in the human body and any imbalance between them may have dramatic consequences for well-being and health.



Being able to detect specific biological molecules at very low concentrations is a new promising area of Medicine that aims to identify the onset or prediction of disease before the patient shows any symptoms. If the technology can be made cheap and simple enough for widespread use, it will enable the rapid identification and monitoring of proteins and pathogens. As a result, it will be possible not only to give appropriate treatment much more quickly but also to make treatment patient specific, leading to fewer side-effects and faster patient recovery. RECEPTRONICS could provide a breakthrough technology for sophisticated diagnostic tools in the field of early cancer diagnosis and hormone balance monitoring. Furthermore, the same technology could be employed for detecting contaminants at very low concentration for environmental safety in Agriculture and industrial processes.

The expected project outputs are:

* The exploitation of hybrid technologies for the study and the implementation of an integrated sensor aimed at achieving extremely high sensitivity for portable and low-cost devices.
* The final device should ultimately be developed by embedding a platform consisting of:
  - A biomorphic front-end, dedicated to highly specific affinity interaction with the target molecules.
  - Advanced microelectronic systems dedicated to the detection, amplification and conditioning of the signals.
* The development of a method to customize the device for specific target molecules. For this purpose, validation exercises will be undertaken within the program, using different kinds of receptors for several applications.

Main results of the first year of the project

- Validation of synthetic fusion protein design principle. Natural ion channels are artificially coupled with specific receptors. The resulting protein is not existing in living beings, but it can be used to naturally detect target substances at molecular level;
- Design and test of several approaches to electrically address arrays of artificial lipid bilayers and methods for delivering fusion proteins into them. The design has been driven by the requirements to achieve high reliability and reproducibility for industrial applications; Structures with an yield of about 90% have been preliminary demonstrated in the Project.
- Design and test of an extremely compact electronic system for single molecule event detection. The system, as large as a credit card, is the first step for designing efficient and integrated electronics for interfacing bionanosystems;
- Data acquisition and statistical elaboration of molecular signals. This is needed since molecular signalling is intrinsically stochastic and it should be treated with proper tools. Precision below 1% of accuracy for ion channel open probability could be achieved with developed algorithms.

Main results of the second year of the project

- Single molecule events recorded on arrays of electrically addressable micro- and nano-spots;
- Consolidation of the above technologies for achieving more robust testing data and yield;
- New generation of synthetic receptors based on the tandem principle to new target molecules and constructs;
- Consolidation of the reading out architecture based on Sigma-Delta amplifiers interfaced to DSP processing;

Ongoing status of the project can be found in the website: www.receptronics.org.