GOLDEN BRAIN - Development of novel concepts for communication between living cells and silicon based electronic devices

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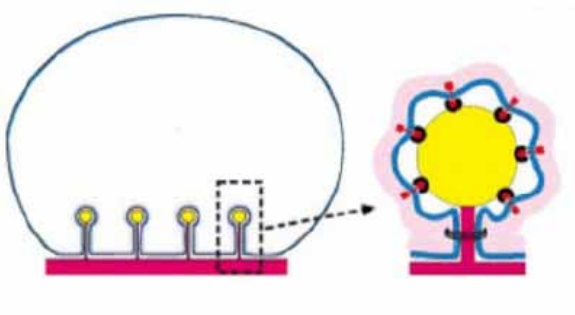
Project goals

The GOLDEN BRAIN project aims at developing and implementing novel generic technologies to form reliable and durable bi-directional electrical and chemical communication between neurons and electronic devices.
The **main hypothesis of the project** was successfully verified: **using a combination of Surface biofunctionalization and three-dimensional nail topologies, various types of neurons and neuron-like cells indeed engulf the nail electrode structures and lead to a high seal resistance**. This enabled recordings with a high signal-to-noise ratio. In addition, **methods to reduce neuronal translocation** have been developed.
Transducer devices for both electrical and chemical stimulation and recording have been designed and processed. In these devices, several of the developed technologies were already successfully integrated. For some not yet integrated results, **appropriate material selection and extensive CMOS process knowledge** made sure that technologies can be easily combined later on.



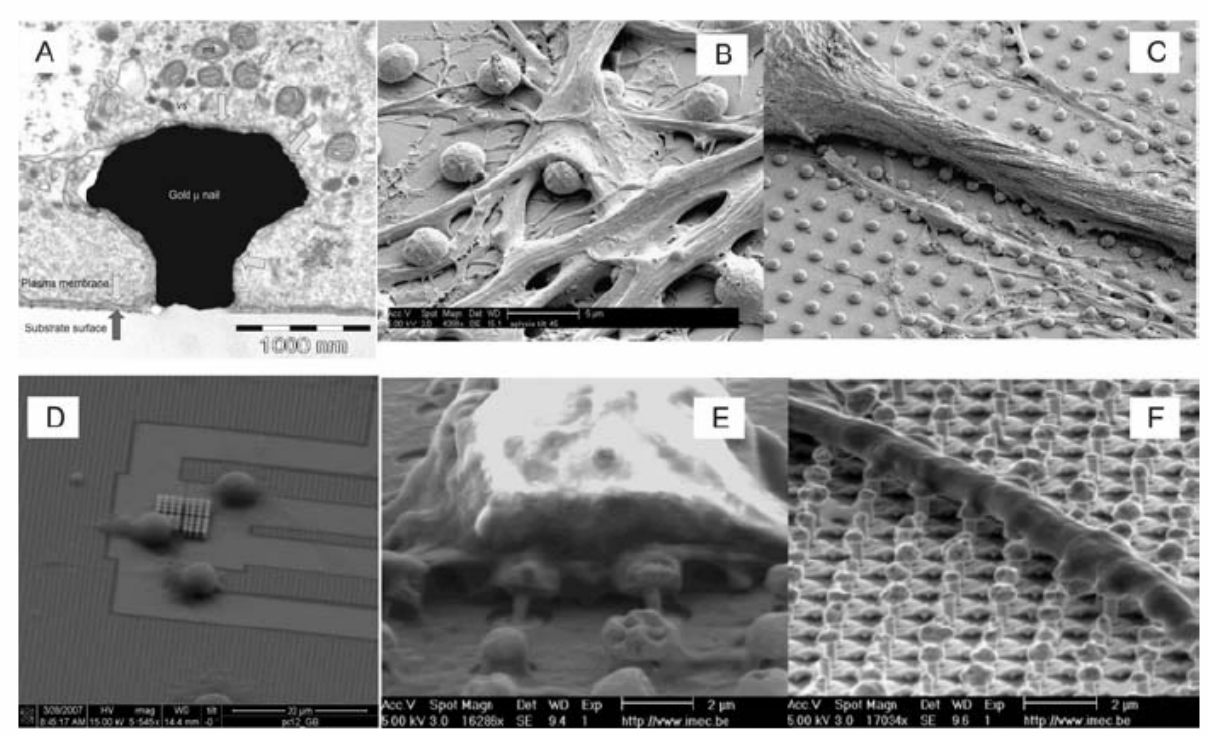
GOLDEN BRAIN centers around the implementation of a nail-based inter-nalization process that provides a significantly better neuron-electronics interface.

The technologies developed within the project are generic to a large extent and they find direct **applicability in the construction of biomedical microstructures** that eventually will **functionally link nerves to robotic prostheses and functionally link damaged neuronal networks, model systems for brain research and biosensors**.

WP1: Several packaged chips containing micronail decorated electrodes were designed: **a 64 MEA with Au micronails-on-silicon**, a **fully CMOS-compatible 15-sensor nail chip**, and a **fully CMOS-compatible 16x16-active sensor chip** with a number of architectural innovations. Extensive screening and biological validation was carried out with respect to nail plating and isolation stacks. **High signal-to-noise ratio recordings were obtained from cardiac cells**.

WP2: Bioactive surfaces were designed in two ways in order to improve adhesion: based on a synthetic route using phagocytosis-inducing peptides and based on a hyaluronidase degrading the extra-cellular matrix. In both cases, **coated beads and Au-nail decorated surfaces were engulfed** by Aplysia neurons and enabled high signal-to-noise recordings.

WP3: Two highly sensitive biosensors for detection of the neurotransmitter ACh were constructed: a **Cn-based ISFET yielding an optical response** (fluorescence) and a **chemically modified floating-gate ISFET based on AChE immobilization**. Large range and high sensitivity (1 mM to 0.1 nM) were observed for the latter where **a novel mechanism** was found that transduces molecular recognition events directly to carrier mobility changes in the FET by the receptor's (protein) induced dipole.



Experimental results: (A) transmission electron micrograph of a micronail engulfed by an Aplysia neuron (HUJI); (B) and (C) scanning electron micrographs of Aplysia neurons cultured on micronails (HUJI); (D) PC12 cells on a multielectrode chip with CMOS compatible (sub)micronails; (E) and (F) scanning electron micrographs of neuroblastoma cells (N2A) cultured on substrates with CMOS compatible (sub)micronails.

WP4: Improved cell adhesion on recording sites with single cell resolution have been developed based on (aligned) microcontact printing and classical lithographic processes. Long-term stability has been achieved through a **combination of chemical functionality patterns with 3D relief structures**. Hippocampal neurons proved to be stable for more than 21 days in culture and with respect to viability, morphology, and electrophysiology, **such grown neuronal networks behaved normally**.

WP5: The original GOLDEN BRAIN hypothesis could be proven that **cultured cells grown on functionalized micro-nail substrates indeed respond by engulfment** (internalization by phagocytosis) of the micronails. Shape, dimensions, and chemical functionalization were extensively optimized to reach this goal. This process was **observed on a large variety of cell types** (Aplysia, hippocampal neurons, PC12, cardiomiocytes). Furthermore, a special culture of large and identifiable cholinergic neurons releasing ACh upon intracellular stimulation has been developed for future validation of chemical synapses.