Molecular biology meets microelectronics

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The marriage of living cells and silicon devices is not without practical difficulties. Technical problems and the characteristics of cell–substrate interactions have, so far, prevented the routine integration of biology and microelectronics for the design of biosensors and medical technology. Now in this issue, a paper by Straub et al.[1] suggests that molecular engineering may provide a means of solving such problems. Careful analysis of the nature of the cell–silicon coupling problem has guided the way.

Cells are equipped with a host of receptors that can transduce chemical signals into electrical ones. If efficiently coupled to an electronic readout device, cells could thus function as versatile biosensors in a variety of applications. Furthermore, intelligent prosthetic devices could be designed that allow two-way communication between their control circuits and the nervous system.

The idea for achieving the "iono-electronic" coupling is simple: Grow the cells of interest on a silicon chip, which is made up of an array of field-effect transistors (FETs), and find a way to couple the bioelectric signals into the circuit. It was shown almost 10 years ago that the "open gates" of FETs can be made to sense the electrical potential of an electrolyte covering the chip[2]. If cells attach to such gate regions and develop bioelectric signals, these should be measurable in the chip as changes in source drain currents. However, to date, two types of problems have hampered progress.

First, bioelectrical circuits often encounter technical problems, such as background noise of the FET and corrosion of the semiconductor substrate, when covered by an electrolyte over extended periods of time. Although the latter can be solved by proper design of the device[3], the former requires more progress in semiconductor technology[4].

Second, the specific way in which cells interact with the substrate can also be problematic. In biological tissues, individual cells are typically separated from one another by gaps of 10–20 nm. It seems that, when growing on artificial substrates, cells continue such habits; in any case, nobody has succeeded in makign cells approach to less than 40 nm, while simultaneously growing functioning ion channels in regions of such close contact[5]. Thus, a cell and a chip are separated by an electrolyte layer, the specific conductance of which is relatively high. By Ohm's law, the voltage drops that bioelectric currents generate along the relatively small distances involved are only in the range of millivolts or smaller.

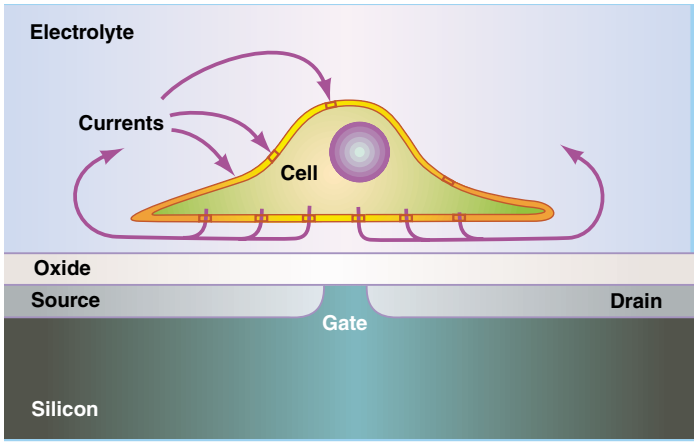

Figure 1. Keeping their distance. The major problem of iono-electrical interfacing is that cells growing on semiconductor devices preferentially remain around 40 nm apart (as in living tissue). Thus, there is a layer of conductive fluid (electrolyte) that shunts the signals mediated by ion channels. Coupling can be improved by optimizing the geometry or by increasing current density (e.g., see ref. 1). Ionic curents are shown as arrows, neglecting contributions by capacitive currents.

Another complication is symmetry and homogeneity: If cell membranes were completely homogeneous, with equal density of ion channels everywhere, a small symmetrical cell would not create large current densities in its surroundings. Currents generated by channels would rather be locally short-circuited to charge up the membrane capacitance. Thus, only intracellular potential gradients and/or gradients in channel density lead to net currents in the cleft[6].

To optimize the signal measured by the transistor, one can try to improve the geometry (which will certainly help) or else increase current density in the cleft. The latter is the route that Straub et al. chose in the present paper. They start with HEK293 cells, which have only very few intrinsic ion channels and consequently cannot readily couple an electrical signal, which they might carry to a substrate. However, when these cells have been transfected with K^+-specific channels, a depolarization applied to their interior opens such channels and creates a considerable current flow in the cleft between cells and the semiconductor. This leads to a sizable change in source drain current, when a cell happens to be appropriately positioned above one of the gate regions of the device.

Straub et al. have used so-called maxi-K^+ channels, which have the property of mediating particularly large currents (and are thus suitable for proof-of-principle experiments). There are straightforward ways for improving the signals in their system, however. One would be to improve the noise performance of the semiconductor device. Another would be to increase channel density. Very intriguing in this regard is the finding that heterologously expressed channels seem to be concentrated on that portion of the cell that is in contact with the substrate. This is exactly where effective iono-electronic interfacing needs them. So it seems that it should not be difficult to "persuade" channels to aggregate even more specifically at such sites.

Molecular biology offers a wealth of tools and reagents to achieve such morphological differentiation. The mechanisms by which ion channels aggregate at postsynaptic densities or at nodes of Ranvier and the molecules that direct such developments are either known already or are in the process of being uncovered[7–9]. This knowledge, combined with the approach taken by Straub et al., suggests that technically satisfying solutions could make the marriage of silicon with cells/neurons less problematic.

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