

Fully electronic DNA hybridization detection by a standard CMOS biochip

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Abstract

A novel solid-state biosensor for label-free detection of DNA hybridization is presented. The new device is realized in a standard CMOS process, thus allowing the realization of low-cost, portable, fully integrated devices. The detection mechanism is based on the field-effect of the intrinsic negative electric charge of DNA molecules which modulates the threshold voltage of a floating-gate MOS transistor. A fluid cell was developed for delivering DNA samples on the active surface of the chip. The device has an integrated, individual counter-electrode, so dry measurements are possible increasing lifetime of the chip and speeding up the experiment. Successful measurements on a first prototype of the chip, hosting 16 sensors individually addressable, are provided as proof of concept.

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1. Introduction

DNA hybridization detection is a key step in genomics studies and development of diagnostic tools [1]. The standard approach to its detection is based on optic or optic-like methods which make use of a passive substrate for DNA immobilization and indirect detection of labels bound to the target DNA molecule under investigation. A known single strand DNA (probe ssDNA) sequence is immobilized on a substrate (nylon, glass, silicon), the unknown target (target ssDNA) sequence is labelled with a fluorescent or radio label and injected on the substrate. If the two sequences are complementary they hybridize and form the double strand DNA (dsDNA) so the label is immobilized on the substrate as well. The passive substrate is then checked to verify the presence of the label rather than of the DNA molecule. Such technology is mature and established but presents some drawbacks such as the cost of the instrumentation, the necessity of labelling the molecules, the difficulty to integrate the different tools into a single, portable device. For these reasons, several new approaches have been proposed recently, to overcome such problems. These new methods make use of gravimetric mea-

asures based on microbalances (QCM, quartz crystal microbalance) which transduce the change of mass due to hybridization into a change in the resonant frequency of a crystal [2], or based on the use of micromachined cantilevers and their bending due to surface forces [3,4]. Even if they are label-free, these methods are difficult to integrate with standard electronics and require sophisticated technology steps.

Fully electronic detection is the most promising approach to obtain really inexpensive, portable and low-cost devices [4]. Several devices have been proposed in the recent past, either making use of labels such as gold nanoparticles to measure resistance [5,6] or capacitance [7] changes between two electrodes, or making use of electrochemical labels capable of generating a redox current [8,9] detectable by electrodes. These approaches are not fully compatible with a CMOS process, so they cannot easily be integrated with the readout electronics.

In this paper we present a novel, solid-state CMOS device able to detect sequences of DNA by their intrinsic electric charge without the need for external components (counter-electrodes). The sensor is fully compatible with a standard CMOS process. With respect to other sensors for hybridization detection, which make use of capacitors [10], diodes [11] or transistors [12,13,14] implemented in silicon or with nanowires [15], this biosensor is attractive for its extreme simplicity. It allows direct detection of hybridization process, with no need for additional process

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steps. For this reason, it allows the realization of highly integrated arrays with thousands of active sites, direct detection and fully electronic readout capabilities. The electronic readout is also attractive for implementation of portable and/or disposable medical kits.

2. Experimental

2.1. Device structure and working principle

The proposed device mixes the characteristics of the floating-gate MOS transistor and the gate-exposed FET sensors such as the ISFET or CHEMFET [16–18]. A cross-section of the sensor is shown in Fig. 1: it is made-up of a floating-gate transistor (M_0), a control-gate with the role of reference electrode (C_C) and an active area activated by charge induction (A_S).

The single strand probe oligonucleotides are bound on top of the exposed floating-gate surface by an organic/inorganic interface (spacer). The control capacitor and the electric charge, together, determine the actual voltage difference V_F between floating-gate and silicon bulk. The device can be modelled as a transistor with an effective threshold voltage modulated by the DNA charge [22].

A relationship between applied control voltage, molecules charge and effective threshold voltage can be derived from standard electrostatics equations. In particular, if the spacer thickness is several orders of magnitude smaller than the size of active area, the electric field in the spacer is perpendicular to the metal layer and constant since, for every point of the spacer, the surface molecules are seen as an infinite sheet of charge. The same is true in the oxide between metal plates of capacitors, thus we can write:

$$E_C = \frac{V_C - V_F}{t_{PIP2}}, \quad E_F = \frac{V_F}{t_{OX}} \quad (1)$$

$$C_F = \frac{\varepsilon_{OX}(A_C + A_S)}{t_{OX}}, \quad C_C = \frac{\varepsilon_{OX}A_C}{t_{PIP2}} \quad (2)$$

where E_C and E_F are, respectively, electric field in the control capacitor C_C and in the parasitic capacitor C_F , V_C is the control voltage, V_F the floating-gate voltage (both measured with respect to silicon body), t_{PIP2} is the oxide thickness, t_{OX} is the thickness

of field oxide, A_C and A_S are, respectively control capacitor and active area dimensions. Writing Gauss equation for surfaces S1 and S2 of Fig. 1 we obtain:

$$\varepsilon_{SP}E_{SP}A_S = Q_{DNA} \quad (3)$$

$$-\varepsilon_{OX}E_C A_C - \varepsilon_{SP}E_{SP}A_S + \varepsilon_{OX}(A_C + A_S)E_F = Q_0 \quad (4)$$

where E_{SP} is the electric field in the spacer, Q_0 is the electric charge initially trapped in the floating-gate and Q_{DNA} is the total charge of DNA molecules. Substituting (1)–(3) in (4) we obtain the voltage of the floating-gate for a given control bias V_C and charge Q_{DNA} .

$$V_F = \frac{C_C}{C_C + C_F} V_C + \frac{Q_{DNA} + Q_0}{C_C + C_F} \approx V_C + \frac{Q_{DNA} + Q_0}{C_C + C_F} \quad (5)$$

The above equation states that the actual gate voltage of the transistor is modulated by a term which is proportional to the amount of net electric charge immobilized on the active area. Such modulation can be modelled as an opposite shift of the effective threshold voltage (V_{THF}) of the transistor with respect to the native threshold (V_{TH0}):

$$V_{THF} = V_{TH0} - \frac{Q_{DNA} + Q_0}{C_C + C_F} \quad (6)$$

In this way, the hybridization process can be measured as a shift of the threshold voltage of the transistor. In fact, since the DNA macromolecule has an intrinsic electric charge [5], when hybridization takes place the total charge bound on the surface doubles and the left branch of Eq. (6) actually increases. Properly sizing the transistor and the capacitor, this positive shift can be made large enough to raise the threshold above the supply voltage so that a digital ON/OFF signal can be generated.

2.2. Chip design

The test chip was realized in a standard 0.8 μm CMOS process with two metal layers and two polysilicon layers (needed for the realization of a highly linear control capacitor) from austria micro systems (AMS). The device was realized in a multi wafer project (MPW) run, so it makes use of a really standard and commercially available process. A microphotograph of the

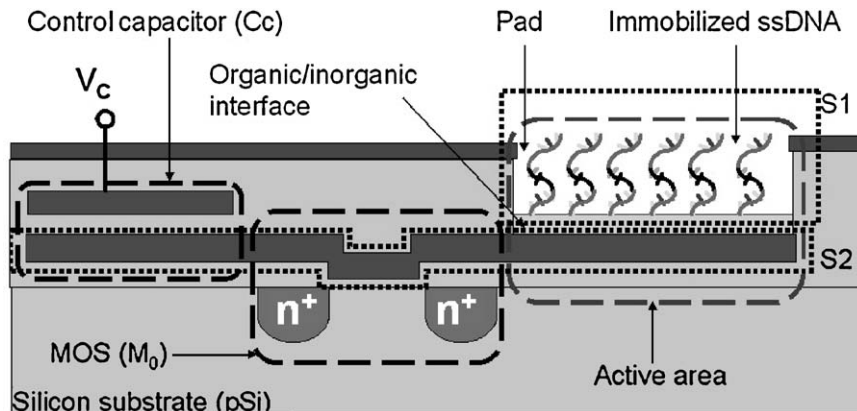


Fig. 1. Structure of the device.

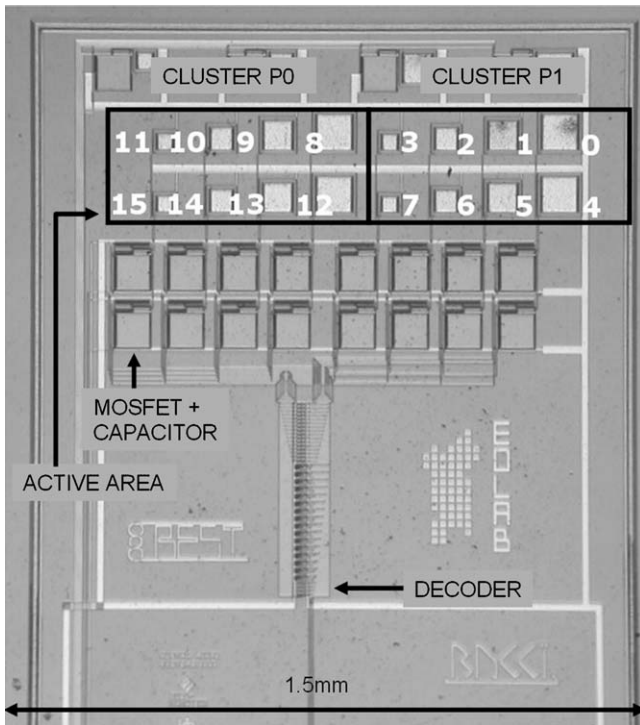


Fig. 2. Microphotograph of the realized chip.

realized chip is shown in Fig. 2. The chip hosts 16 sensors, each of which is made-up of a MOSFET, a control capacitor and an active area. The sizes of active areas range from $40\ \mu\text{m} \times 40\ \mu\text{m}$ to $100\ \mu\text{m} \times 100\ \mu\text{m}$. The active areas are physically separated from the FET and the capacitor; they are obtained opening a test pad over a square shape made in the topmost available metal layer (aluminium). The active area is then connected to the gate of the MOS transistor by a metal path. In this way, the capacitor and the FET are protected from the biological solution by chip passivation. Each sensor can be individually addressed by means of a digital decoder.

The overall size of the chip is $5\ \text{mm}^2$. Such a large space was left around different objects for packaging purposes since a proper microfluidic structure (with a much larger minimum size) had to take place on top of device. The 16 sensors were

subdivided in 2 clusters: an active cluster (T1) and a reference cluster (T0). The reference cluster is needed to test the selectivity of the device, verifying that the biosensor responds only to the proper target sequence and ignores non-complementary sequences.

2.3. Flow cell

Testing of the prototype device required a proper setup, particularly to overcome the problems arisen by the biological processes (hybridization) that had to take place on the surface of the chip. A custom micro-channel structure was realized in order to dispatch probe and target oligonucleotides on the different sensors. Since the 16 sensors were subdivided in 2 clusters, 2 functionalization micro-chambers were realized in order to physically separate the clusters. A separate micro-chamber for hybridization was realized as well. This second chamber, which covers all the 16 sensors, is needed to prevent evaporation of the sample solution containing the target oligonucleotides during the hybridization process. Such process, in fact, takes place at relatively high temperatures ($50\ ^\circ\text{C}$), for a long time (2 h) on very small quantities of liquid (few microliters).

The two chambers, were realized with polydimethylsiloxane (PDMS), an elastomer [19] capable of reproducing complex structures at very high resolution. The microstructures were obtained realizing a negative master of the desired structure. The master was realized patterning, by standard lithography, a photoresist suited to such applications (SU-8), than casting the PDMS in liquid form and baking the structure at proper temperature.

Fig. 3 shows the PDMS microstructure placed on top of the chip by means of a plexiglass holder: different inlet and outlet channels were used to deliver T0 probes on the eight sensors on the left and T1 probes on the eight sensors on the right. The channels have a width of $100\ \mu\text{m}$ and a height of around $200\ \mu\text{m}$.

2.4. Oligonucleotides

Four different sequences of DNA single strands were designed to test the chips: two targets (T0 and T1) to be bound

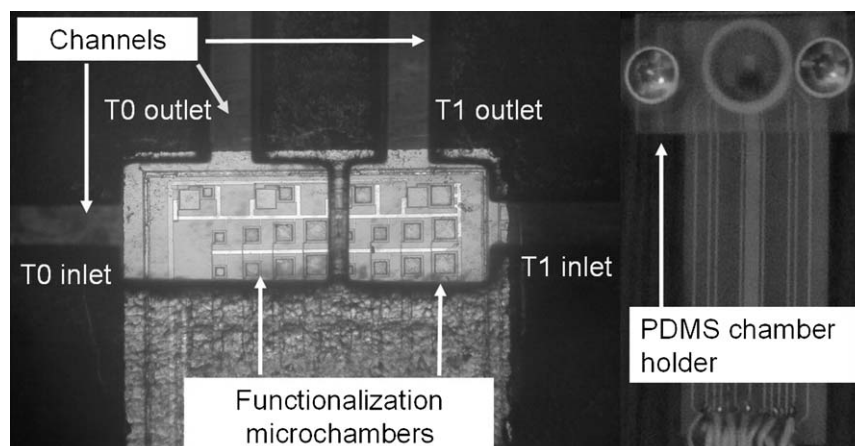


Fig. 3. Chip packaged with the PDMS micro-channel structure (left) and mounted on the board with the microchamber holder (right).

on the surface of the two clusters, and two probes (P0 and P1) to test hybridization. Each of the targets were complementary to its probe but not to the other. The reference probe (T0) was designed with 13-mer poly-dT spacer, followed by a specific sequence from variable region of 16 s rDNA of bacterium *Bacillus subtilis*.

The primer sequence is 5'-TTTTTTTTTTTTTGGTTTCCG-CCCCTTAGTG-3' and was modified by inserting a thiol group in 5' position. The oligonucleotide was purified through oligonucleotide purification cartridge. The complementary strand oligonucleotide, without the spacer region and with sequence 5'-CACTAAGGGCGGAAACC-3' was also synthesized and purified. The oligonucleotide solutions were prepared in distilled water to a final concentration of 0.1 mM. All the solutions were prepared using HPLC grade water (resistivity >18.2 X cm).

2.5. Surface functionalization

A method for covalent immobilization of 5'-thiol-modified single strand DNA probes, onto oxygen exposing surfaces has been developed by exploiting surface derivatization by 3-mercaptopropyltrimethoxysilane and subsequent intermolecular disulfide bond formation [20]. The chosen approach is robust enough to prevent oligonucleotides detachment due to washing procedures connected with device operation but, at the same time, it endows the molecular constructs with enough mobility to retain hybridization capability.

To activate the surface, a layer of properly functionalized spacer molecules must be covalently linked to the underlying surface. The presence of a native oxide layer enables the first step of the immobilization procedure, which consists in the growth of a silane layer by the formation of covalent bonds between the silanol groups and the hydroxyl surface groups (alumosiloxane bond). The aluminum surface was then incubated for 5 min in 0.1 mM 3-MPTS in toluene and subsequently rinsed in abundant pure toluene in order to remove non-chemically bound molecules. Comparative QCM results revealed a silane area per molecule of 0.6 nm², suggesting that we were dealing with monomolecular layer.

The second step consists in anchoring the DNA strands to the spacer layer. This can be done by chemically modifying the DNA strands with a proper side group. As an example, if the spacer molecules (silane-terminated) bear a thiol group, a thiol-modified DNA strand can be linked to this, therefore obtaining a close-packed layer of DNA strands strongly anchored to the sensor surface. Covalent immobilization of such ssDNA should take place via the formation of intermolecular S–S bonds between the thiolate oligonucleotide and the surface SH moieties [21]. To check if the immobilized monolayer still retains hybridization capability for the complementary DNA strand, the hybridization step has been made with a contemporary QCM measurement where the resonance frequency variation of the quartz was measured for detecting if the mass variation due to the hybridization steps. This measurement confirmed that the prepared ssDNA (sub)-monolayer retains hybridization capability [20].

3. Results

3.1. Test strategy

The sequence of steps required to test the hybridization process is given by the following procedure:

- (a) START: activation of the exposed-gate surface by means of 3-MPTS.
- (b) STEP_T1: immobilization of T1 (probe) oligonucleotide on sensors 0–7.
- (c) STEP_T0: immobilization of T0 (probe) oligonucleotide on sensors 8–15.
- (d) STEP_P1: injection, on the entire active surface (sensors 0–15) of P1 (target) oligonucleotide (complementary to T1).
- (e) STEP_P0: injection, on the entire active surface (sensors 0–15) of P0 (target) oligonucleotide (complementary to T0).

After each step, the entire chip was rinsed with a low ionic strength buffer (D-histidine) dried and measured. Measures were done in dry conditions, applying a sweeping voltage to the control-gate and measuring the drain current of each transistor. From the *I/V* characteristics, the threshold voltages were extrapolated. Each sensor in the active cluster (T1) was coupled with its counterpart (same size, symmetric position) in the reference cluster (T0). An output differential voltage was computed, subtracting the threshold of a sensor in the reference cluster (T0) from the threshold of its matched transistor in the active cluster (T1) as follows:

$$V_{OUT}[i] = V_{TH}[i] - V_{TH}[i + 8], \quad 0 \leq i \leq 7 \quad (7)$$

where sensors 0–7 belong to the active cluster (T1) and sensors 8–15 to the reference cluster (T0). This differential approach is needed since each time the chip is rinsed or dried all the thresholds present a collective shift. This phenomenon is due to the floating nature of the gate, which is very sensitive to any variation. When taking the differences between the thresholds, these collective shifts can be cancelled and only specific differences due to the presence of molecules on the surface are highlighted.

3.2. Experimental results

The experimental results are shown in Fig. 4. A fixed pattern noise (FPN) is clearly visible in the starting first datapoints. It is obviously due to the fact the transistors have a floating-gate and they can collect charges during the manufacturing process and during chemical processing (such as the activation of the surfaces with 3-MPTS). For this reason, a very large mismatch is experienced among the initial threshold voltages of each pair. The FPN can be removed simply by subtracting the differential voltage after each step from the initial differential voltage. The outputs after FPN removal are shown in Fig. 5. The detecting capability of the device is self-evident from the resulting graph. In fact: (a) after functionalization with T1 (STEP_T1), the differential responses are positive since the increase of negative charge on cluster T1 increases the thresholds (Eq. (6)) of

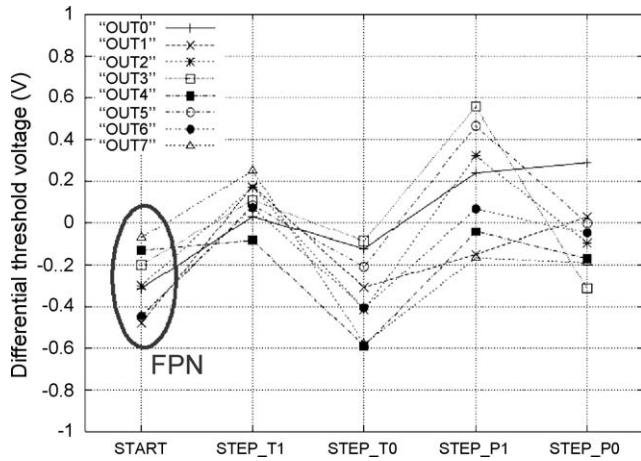


Fig. 4. Differential threshold voltages measured for each pair of active-reference transistors, after each of the following events: (START) functionalization with 3-MPTS, (STEP_T1) immobilization of T1, (STEP_T0) immobilization of T0, (STEP_P1) injection of P1, (STEP_P0) injection of P0. Differential threshold voltage is given by: $OUT[i] = V_{THF}[i] - V_{THF}[i + 8]$.

those transistors (Eq. (7)); (b) in the following step the thresholds of the transistors in cluster T0 increase, so the differential response is negative (Eq. (7)); (c) after hybridization with P1 the net electric charge on the transistor of cluster T1 increase and the differential response is, again, positive; finally (d) after hybridization with P0 the response is negative again.

Averaging the differential responses of each cluster, as done in Fig. 6, makes the detection even more robust. It is remarkable to note that the average peak for STEP_P1 is very similar to the peak of STEP_T1, thus proving that the same amount of charge (so molecules) were immobilized on the surface after hybridization. The same cannot be said for STEP_P0, but this last measure was done 1 week after all the other steps were performed and it is likely that the immobilized molecules partially degenerated so causing an inefficient hybridization. This statistical approach is quite common in DNA chips and could be easily implemented in future versions of the device, making use of smaller sensors. In fact, decreasing at the same time the control capacitor and the active area do not affect the sensitivity of the sensor (Eq. (6)).

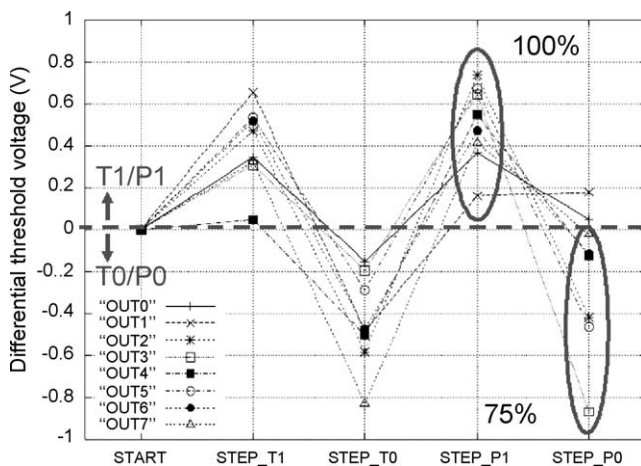


Fig. 5. Differential threshold voltages after fixed pattern noise removal.

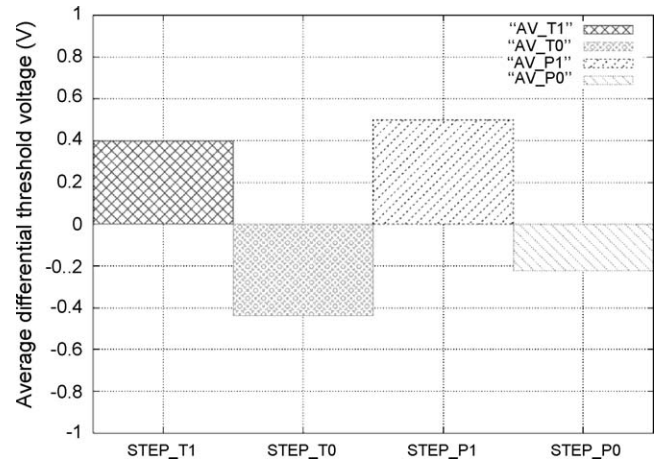


Fig. 6. Average differential threshold voltage calculated on the overall cluster for each event: AV_T1 (STEP_T1), AV_T0 (STEP_T0), AV_P1 (STEP_P1) and AV_P0 (STEP_P0).

Moreover, since the sensor are integrated in a standard CMOS chip, addressing and multiplexing circuitry would be available at no cost.

4. Discussion

The proposed device is able to detect an electric charge bound on the surface of its active area. With respect to many other devices developed to this purpose (such as the ISFET and its derivatives or other sensors for hybridization detection based on field-effect [6,7]), this biosensor has the advantage of being completely integrated in a standard CMOS process. The transistor is a standard, native device of the process and no special manufacturing is needed to prepare the gate-oxide, as happens in many exposed-gate devices. In this way, charge sensitivity is increased because the sensing field-effect is not realized through the gate-oxide, but rather through the organic/inorganic interface (Eq. (3)) which is made-up of a thin and self-assembled molecular layer. Moreover, the electric field generated by the molecules is not needed to turn on the transistor, since the capability of turning on the FET is due to the presence of the integrated control-electrode V_C coupled to the floating-gate of the MOS transistor by control capacitor. In such a way, the detection mechanism is triggered by *differences* in the effective threshold voltage and not by absolute values, so the minimum amount of detectable molecules is not limited by the threshold voltage of the MOS. Moreover, each sensor in the chip has its own integrated counter-electrode which can be individually addressed allowing for the implementation of closed-loop readout circuitry involving only silicon devices and not the bulk of the solution containing the molecules.

The basic operational principle can be further improved at circuit level, adding features for signal processing, filtering, amplification and conditioning. It should be noted that the same approach could be applied to any other bioprocess recognition problem implying a change in electric charge. For these reasons the device allows the realization of highly integrated arrays with thousands of active sites, direct detection and fully electronic

readout capabilities. The electronic readout is also attractive for the possibility of implementing portable and/or disposable medical kits.

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Biographies

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Luigi Raffo received the laurea degree in electronic engineering in 1989, and the PhD degree in electronic engineering and computer science in 1994 from University of Genoa, Italy. In 1994 he has joined the Microelectronic Laboratory of the Electronic Engineering Department of the University of Cagliari as assistant professor. Since 1998 he is professor at the same university. He is teacher of electronic and system design courses. His main research field is the design of digital/analog devices and systems. In this field he is author of more than 70 international publications, and patents. He has been coordinator of EU, Italian Research Ministry, Italian Space Agency, industrial projects.

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Imrich Barák graduated in nuclear chemistry at Comenius University (Bratislava) in 1984 and got his PhD in molecular biology at Institute of Molecular Biology, Slovak Academy of Sciences in 1991. He worked as a postdoctoral fellow at Department of Genetics, University of Georgia, Athens, Georgia, USA. He was a visiting scientist at University of Georgia, Athens. Since 1996 he is a head of Department of Microbial Genetics, Institute of Molecular Biology, Slovak Academy of Sciences in Bratislava. His research domains are in molecular biology of cell differentiation and cell division, microbiology, structural biology and genome wide gene expression. He is author of more than 50 scientific publications and 2 patents. He is coordinator of the Consortium of Central and Eastern European Structural Biology Groups.