Silicon in vivo

Architectural solutions to the problem of linking the world of microelectronics to that of living systems

G. F. Cerofolini

August 11, 2009

Summary

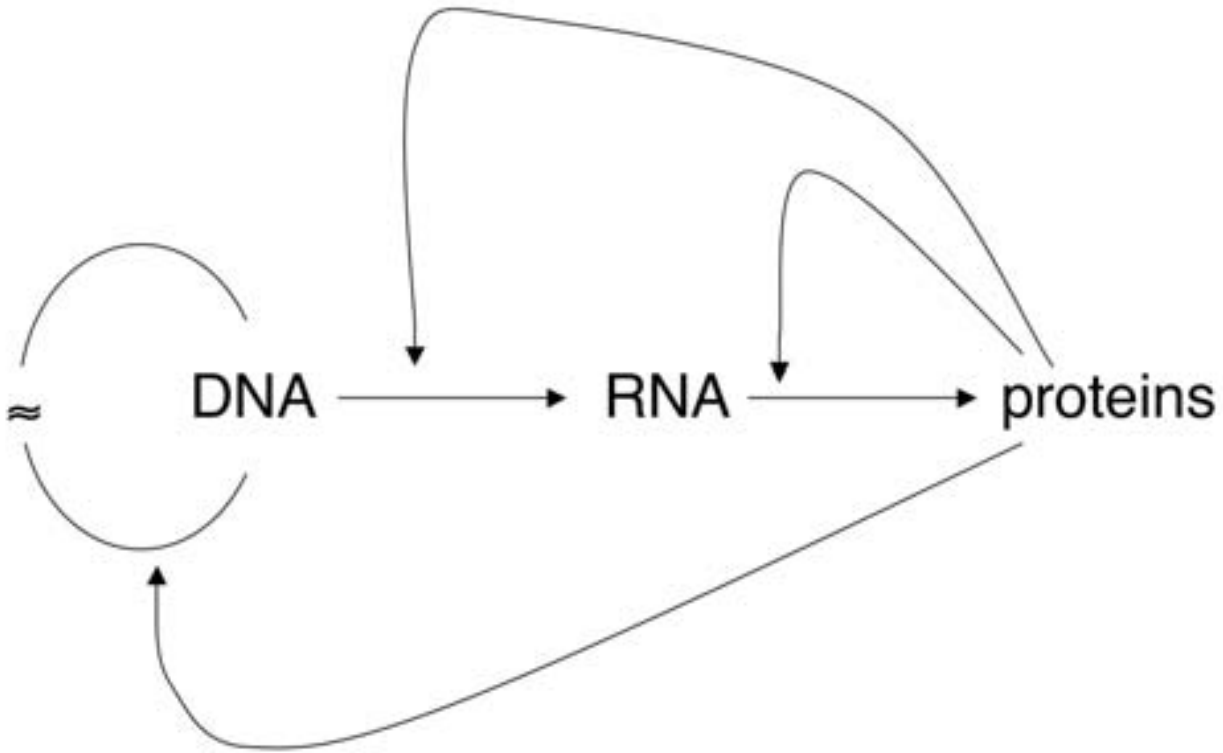
The worlds of microelectronics and biosystems have had very few, if any, common points. They, indeed, differ in use of materials (based on silicon rather than on carbon), information carriers (electron and holes rather than ions), length scales (0.1 μm vs. 10 μm), and time scales (10^{-8} s vs. 10^{-3} s). It is, thus, not strange that for many years microelectronics has ignored biology, typically considering biosystems as a source of contamination for rinsing water in device processing.
The exponential growth of microelectronics has however allowed the construction of complex electronic systems with comparable size to that of the biological unit—the cell. This occurrence permits, at least in principle, the exploration of living system at the sub-cellular level. The exploitation of silicon devices for that purpose, however, is made difficult by the fact that the CMOS technology was developed to decouple as far as possible the electronic device from the external world, and that this effort has continued even with the most recent developments.

This lecture is addressed identify the combinations of architectures, materials, and processes that allow the sensing of the electrical and chemical properties of cells on the 10 nm length scale. The availability of such systems is expected to be able to produce a shift of paradigm in medicine.

Outline

The Central Dogma of Biology

genome expressome



Metabolic pattern

Dominated by complexity:

Metabolic pattern

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- temporal domain: cyclic behaviour

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- spatial domain: cellular morphology and subcellular structure

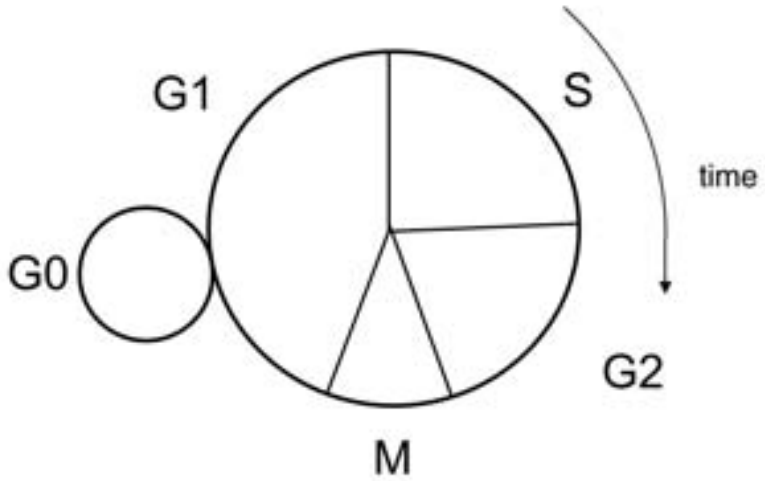
Metabolic pattern

Dominated by complexity:

- temporal domain: cyclic behaviour
- spatial domain: cellular morphology and subcellular structure
- chemical domain: heterogeneity at all levels

Temporal domain

The biological clock



Cellular structure and morphology

Cellular structure and morphology

Cell structure

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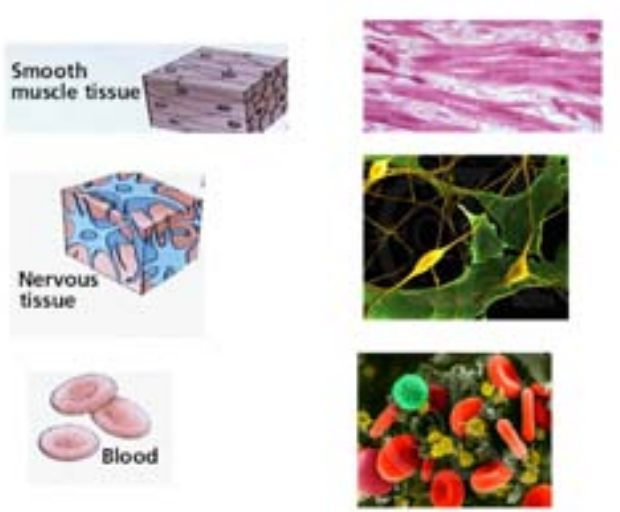
Cell structure

Cell morphology



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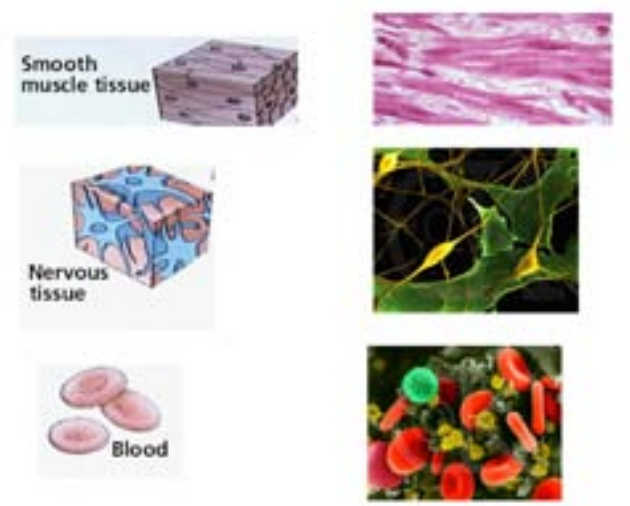
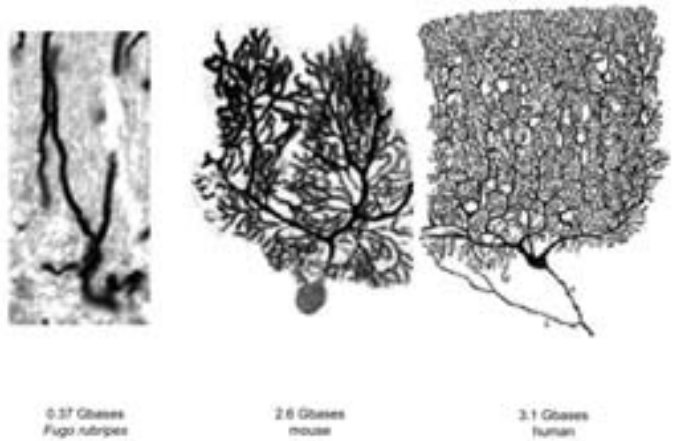




Chemical heterogeneity

Chemical heterogeneity

- Many elements

Chemical heterogeneity

- Many elements

Atomic concentration in sea water of selected elements and their biological relevance

element	concentration [cm^{-3}]	relevance	element	concentration [cm^{-3}]	relevance
H	6.6×10^{22}	++	F	4.1×10^{16}	–
O	3.3×10^{22}	++	N	2.1×10^{16}	++
Cl	3.2×10^{20}	++	Li	1.5×10^{16}	–
Na	2.7×10^{20}	++	P	1.4×10^{15}	++
Mg	3.3×10^{19}	++	Rb	8.4×10^{14}	–
S	1.7×10^{19}	++	I	2.8×10^{14}	*
Ca	6.0×10^{18}	++	Al	2.2×10^{14}	*
K	5.8×10^{18}	++	Fe	1.1×10^{14}	++
C	1.4×10^{18}	++	Mn		+
Br	4.9×10^{17}	–	Zn		+
B	2.6×10^{17}	*	Cu		+
Si	6.4×10^{16}	*	Co		*
Sr	5.5×10^{16}	*	V		*

Symbols:

++ ubiquitous and abundant,

\+ necessary for all living systems, but only as traces,

* necessary only for some living living,

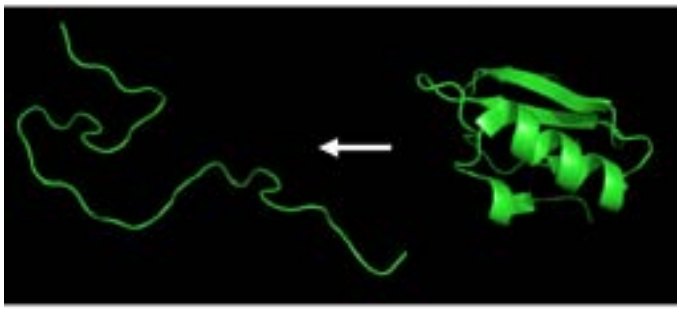
– unnecessary

Chemical heterogeneity

- Many elements
- Much more different molecules

Chemical heterogeneity

- Many elements
- Much more different molecules
- Different configurations within the same molecule



H. Frauenfelder, P. G. Wolynes, R. H. Austin; *Rev. Mod. Phys.* **71** , S419 (1999)

The amount of information required to model metabolism

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L. Hood, J. R. Heath, M. E. Phelps, B. Lin; *Science* **306**, 640–643 (2004)

The need of sensing single cells

"In the prostate, there are neuroepithelial cells, various stromal cells, endothelial cells, and epithelial cells (from which 95% of cancers arise), each of which exhibits a continuous developmental cycle. One cannot reliably generate information for networks from mixed populations of cells. Various investigators have used cell sorting, manual dissection, or laser capture microdissection (LCM) to obtain relatively homogeneous populations of cells. However, cell sorting and LCM themselves may cause processing-induced changes in gene expression, and manual microdissection rarely provides completely homogeneous cell types. Furthermore, even cells of one type typically represent different stages of a developmental or physiological process.

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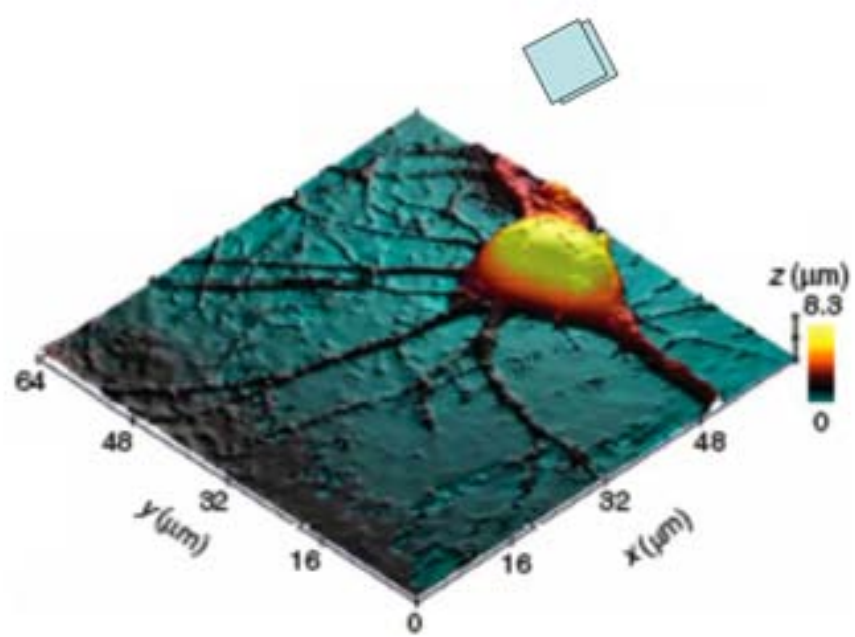
Nanorobots



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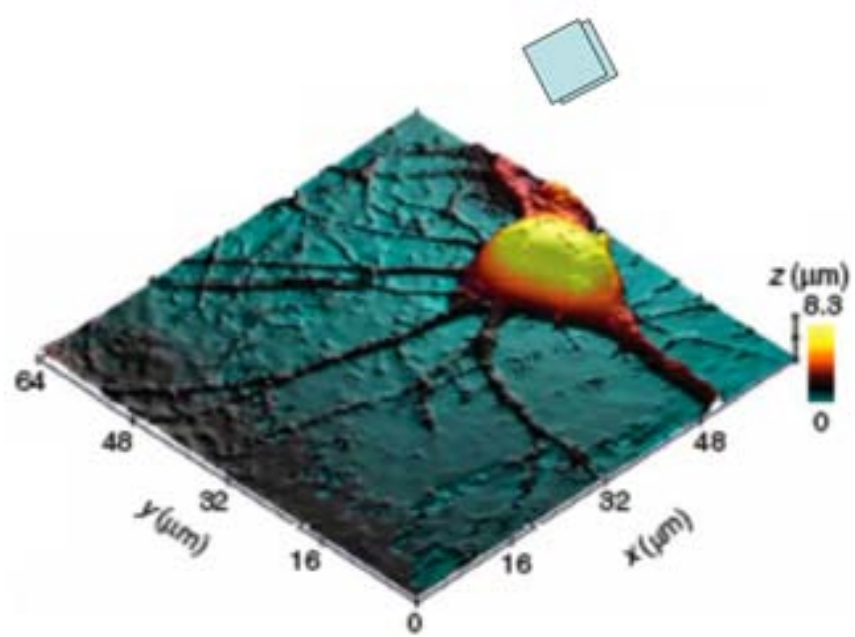

Technology will allow—but a models for the various cells are required.

Genome, expressome, metabolome

It is a common place in the description of cells to consider (in addition with the *genome*) the *expressome* (i.e., the set of functional and structural molecule that are the final result of the Central Dogma of Biology) and the *metabolome* (i.e., the set of substances destroyed or produced in the cell metabolism) as separate entities, the first one acting as a regulatory agent of the second one. Since both functional and structural molecules are produced or degraded during the cellular metabolism the distinction is mainly quantitative, being related to the lifetime of the considered species—high for 'expressites', low for metabolites. It is thus convenient to consider metabolites M_i (with concentration C_i) and expressites E_k (with concentration $\mathcal{E}_k$) separately.

Life functionals. Metabolites

The concentration $C_i(\mathbf{x}', t)$ at time t of any metabolite M_i outside the cell is expected to depend on the concentrations $C_j(\mathbf{x}, t)(j = 1, \cdots, N)$ of all the species M_j inside the cell, and $C_j(\mathbf{x}', t)$ $(j \neq i)$ of all the other species M_j:

$$C_i(\mathbf{x}', t) = F_i \left[C_j(\mathbf{x}, t), C_j(\mathbf{x}', t)_{j \neq i} | \mathcal{E}_k(\mathbf{x}, t) \right], \tag{1}$$

where $\mathbf{x}$ and $\mathbf{x}'$ denote internal and external points, and $\mathcal{E}_k(\mathbf{x}, t)$ $(k = 1, \cdots, K)$ denotes the local concentration of the k-th of the K internal substances (nucleic acids or expressites) interacting with the metabolites. It is noted that the above partition between metabolites and expressites implies that from the topological point of view the cell must be considered as a closed set (with its boundary, the membrane, belonging to the set).

Each functional $F_i\left[\cdot|\cdot\right]$ is extremely complex, although in ultimate analysis it is nothing but the solution of the coupled diffusion-reaction equations, where diffusion coefficients, reaction rates and orders, etc. contain the internal degrees of freedom $\mathcal{E}_k(\mathbf{x},t)$ as parameters. In turn, these concentrations may similarly be written in terms of other K functionals $\mathcal{F}_k\left[\cdot|\cdot\right]$:

$$\mathcal{E}_k(\mathbf{x},t) = \mathcal{F}_k\left[\mathcal{E}_l(\mathbf{x},t)_{l\neq k}|\, C_j(\mathbf{x},t)\right]. \tag{2}$$

Needless to say, functionals $\mathcal{F}_k\left[\cdot|\cdot\right]$ are extremely complex too.
The major goal of systems biology is the determination of $F_i\left[\cdot|\cdot\right]$ and $\mathcal{F}_k\left[\cdot|\cdot\right]$ specifying in detail the reaction-diffusion equations for all species in the cell.

Determining the life functionals

Imagine that one is able to map all metabolic species and to monitor their time variation outside the cell; assume in other words that $\forall i \left(C_i(\mathbf{x}', t) \right)$ is known. If one may formulate a reasonable guess of $\mathcal{E}_k(\mathbf{x}, t)$ (through the accumulated knowledge on cell structure and function), Eq. (1) for known $F_i \left[\cdot | \cdot \right]$ may thus be viewed as an equation for $\forall i \left(C_i(\mathbf{x}, t) \right)$. Although most likely this problem is improperly posed, its solution is expected to allow *the recognition of the inner cellular state from the outer chemical-physical state*.

Early attempts at subcellular sensing

Exploiting the sensitivity of existing devices to α particles:

$$^{7}\mathrm{Li} + {}^{1}\mathrm{n} \longrightarrow 2\alpha, \tag{3}$$

$$^{10}\mathrm{B} + {}^{1}\mathrm{n} \longrightarrow {}^{7}\mathrm{Li} + \alpha. \tag{4}$$

G. F. Cerofolini, G. Ferla, A. Foglio Para; *Giornale di Fisica* **23**, 201 (1982)

G. F. Cerofolini, E. Romano; *Appl. Phys. A* **91**, 181 (2008)

Scaling down device size offers new possibilities

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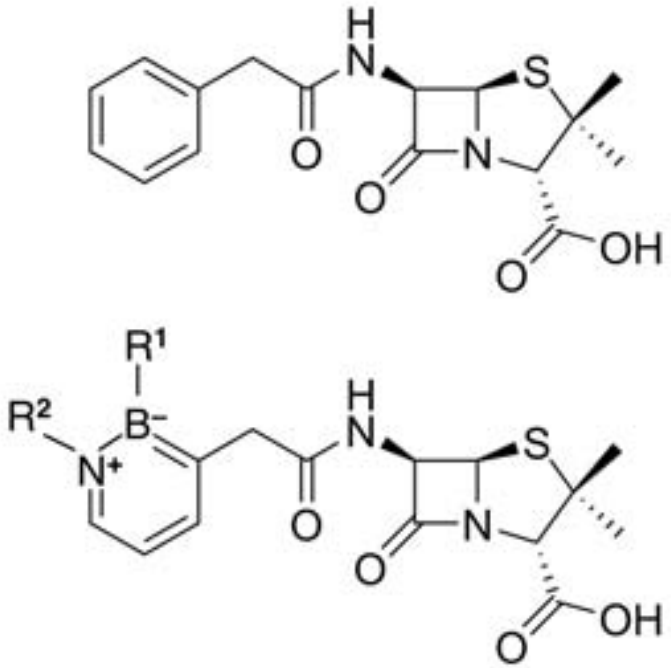
- pharmaceutical drugs may be modified via the insertion of boron in their structure without modification of their activity
- there are substances, with assured biological activity but of uncertain mechanism, that can likely be modified with the insertion of boron in their structure without loss of biological activity

An example

Modifying penicillin G with the substitution of a $B(R^1)\overset{\cdots}{-}N(R^2)$ group for one $C(H)\overset{\cdots}{-}C(H)$, with R^1 and R^2 two sidechain groups sufficiently bulky to protect the $B\overset{\cdots}{-}N$ bond from hydrolysis:



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This pathway has the advantage of exploiting existing circuits, leaving to bioinformatics the task of reconstructing the space distribution of biomolecules from the distribution of cells crossed by the alphas, and to chemistry the task of designing and synthesizing the molecules with the wanted behaviour.

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- Other possibilities are offered by boron-containing drugs: a lot of potential boron carriers (such as boron-containing porphyrins, aminoacids, carbohydrates, nucleic-acid bases, etc.) have been synthesized and tested especially having in mind cancer therapy based on neutron capture by boron.

  Z. Leśnikowski, E. Paradowska, A. B. Olejniczak, M. Studzińska, P. Seekamp, U. Schüßler, D. Gabel, R. F. Schinazi, J. Plešek; *Bioorg. Med. Chem.* **13**, 4168 (2005)

Another roadmap—exploiting the increase of complexity of integrated circuits

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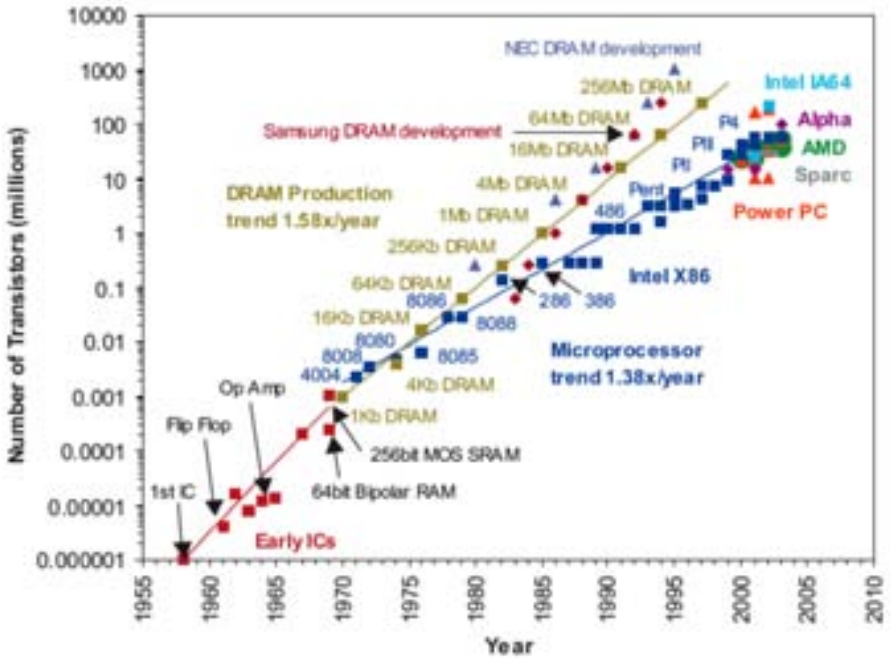
- Moore



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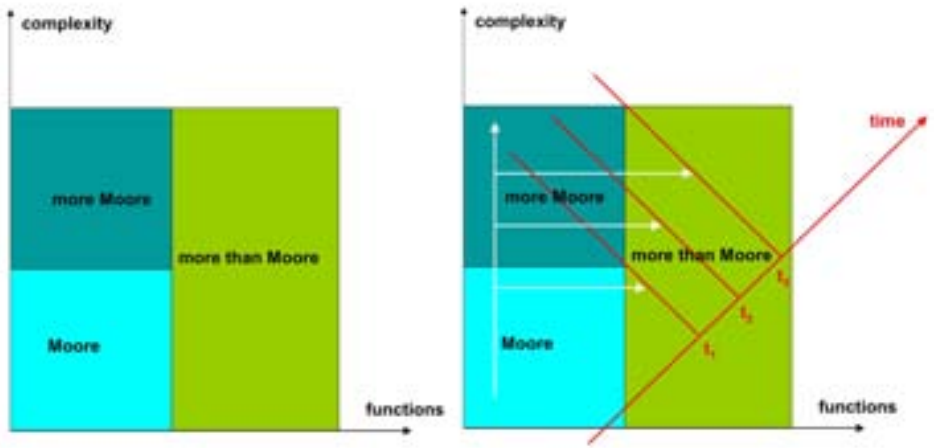
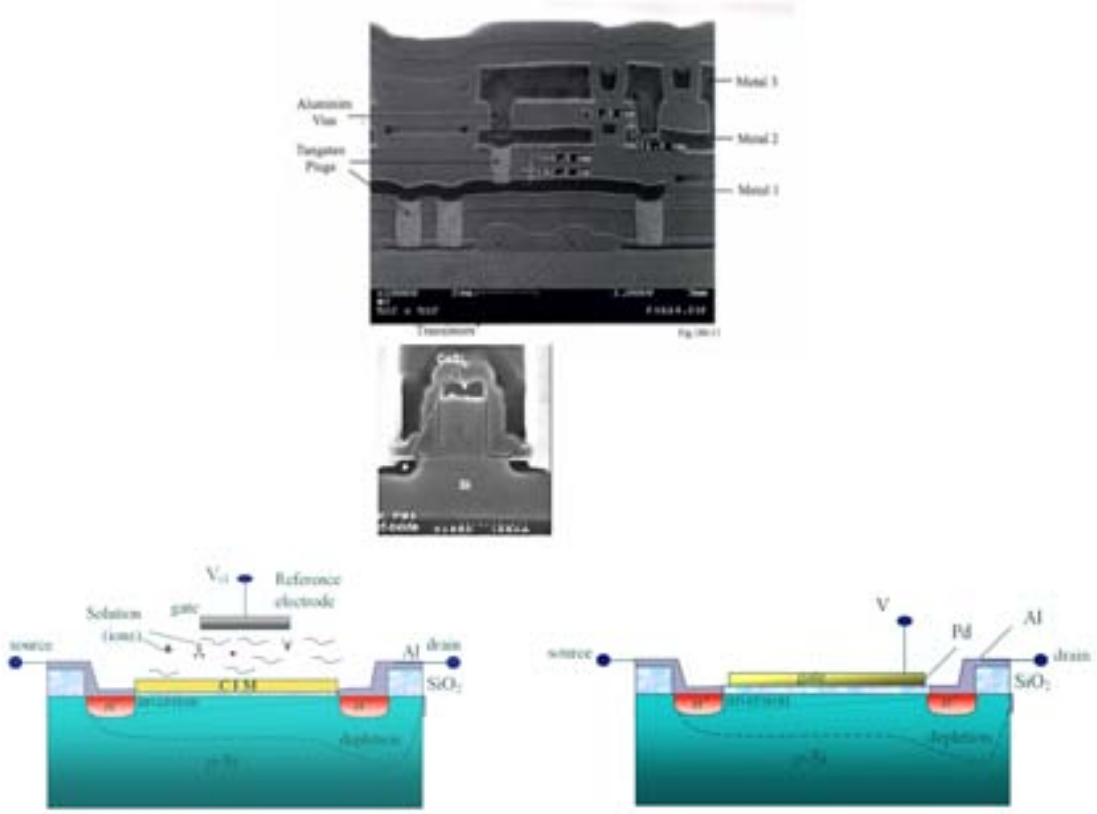


Reasons for the delay

Comparing the structure of a real integrated circuit (*top*) with those of ion-sensitive (*bottom and left*) and gas-sensitive (*bottom and right*) FETs of interest as sensors:



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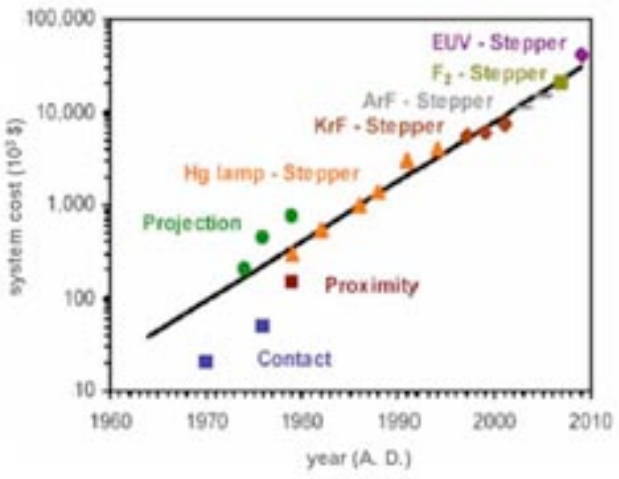

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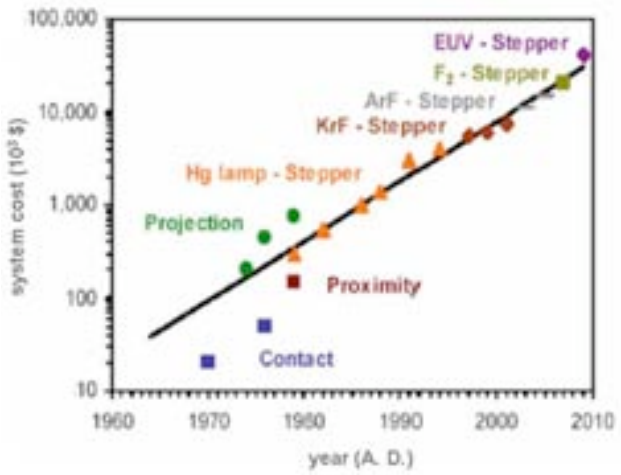

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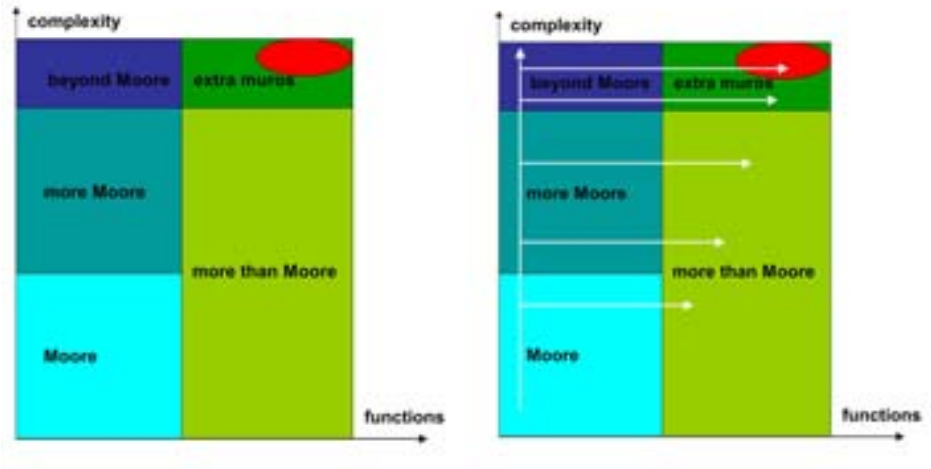
- Extra muros

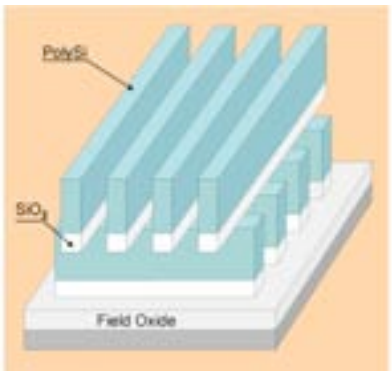


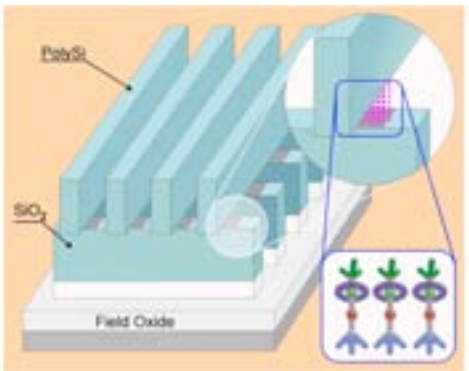
Nanobiosensing

Nanobiosensing is expected to be the final step of a gradual evolution eventually leading from current ICs to circuits of TSI complexity with many functions and spatial resolution sufficient to sense living systems with deep sub-cellular resolution, embedded in silicon-based logic circuit.

The crossbar structure

A crossbar is nothing but the superposition of an array of n parallel conductive wires on an array of m parallel wires; the arrays are oriented perpendicularly (within a non-critical accuracy) to one another. The $m \times n$ overlapping regions are referred to as cross-points and are usually filled with material with desired electrical properties. If this material displays suitable electrical properties (like hysteresis in electrical conductance) the crossbar may open a new paradigm for the design and production of electronic devices.





Producing crossbars with sublithographic methods

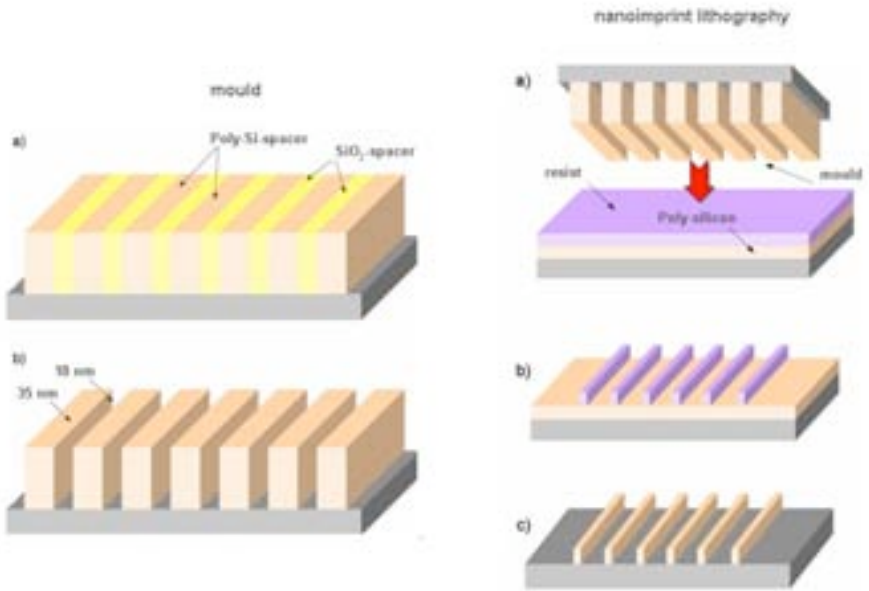
The crossbar structure may be prepared with wire width on the nanoscale with nonlithographic techniques (NLTs). Each NLT exploits the following features:

- (V) it is possible to prepare highly homogeneous film and to control 'vertically' their thickness t down to the sub-nanometre length scale; and
- (V-to-H) it is possible to transform the 'vertical' thickness t into patterns with 'horizontal' width w:

$$t \xrightarrow{\text{NLT}} w.$$

Imprint lithography

Imprint lithography is a contact lithography where (V) and (V-to-H) are exploited for the preparation of a contact mask. The process is based on the sequential alternate deposition of two films, A and B, characterized by a preferential etching for one (say A) of them. After cutting at 90°, polishing, and controlled etching of A, one eventually gets a mask formed by trenches running parallel to one another at a distance fixed by the thickness of B.



Sidewall patterning techniques

A totally different approach for the preparation of wire arrays with pitch on the 10 nm length scale is based on the multi-sidewall patterning technique (S^{n}PT). The S^{n}PT is essentially based on the repetition of the sidewall patterning technique (SPT), an age-old technology.

Sidewall patterning techniques

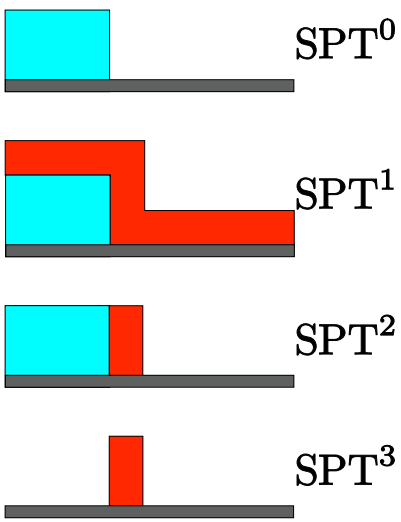
The SPT involves the following steps:

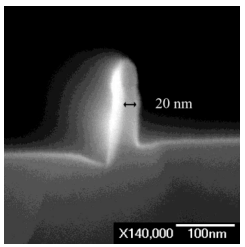
- SPT^0, the *lithographic definition* of a seed with sharp edge and high aspect ratio;
- SPT^1, the *conformal deposition* on this feature of a film of uniform thickness; and
- SPT^2, the *directional etching* of the film until the original seed surface is exposed.

If the process is stopped at this stage, it results in the formation of side walls of the original seed; otherwise, if

- SPT^3, the original seed is removed via a *selective etching*,

what remains at the end of this sequence is constituted only by the walls of the seed edges.





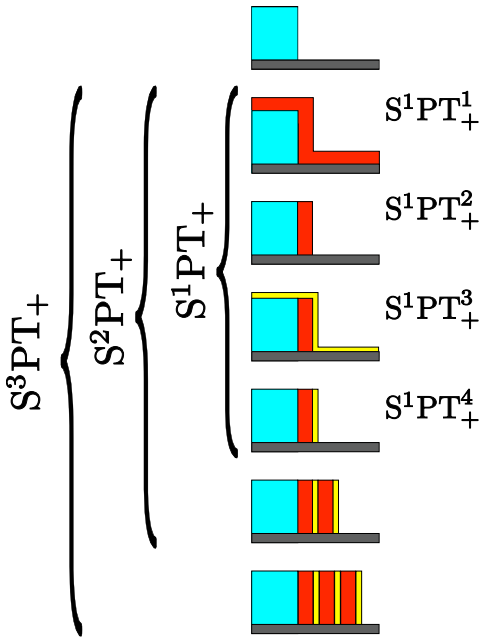
S^nPT routes

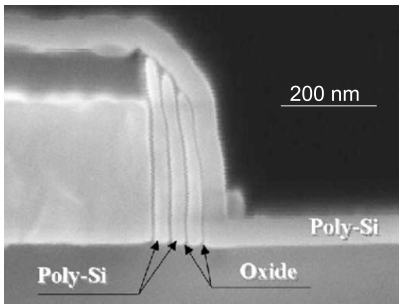
Two S^nPT routes have been considered: the additive (S^nPT_+) and multiplicative ($S^nPT_\times$) routes. The S^nPT_+ is recent and was proposed having in mind the preparation of crossbars for molecular electronics. The $S^nPT_\times$ is instead much older: The first demonstrators were developed for the generation of gratings with sub-lithographic period; recently, however, this technique has been used for the preparation of wire arrays in biochips too.

Additive route—S^nPT_+

The S^nPT_+ is substantially based on *n* SPT repetitions where *the original seed is not removed and each free wall of newly grown bars is used as a seed for the subsequent SPT*.
Each SPT_+ cycle starts from an assigned seed and proceeds with the following steps:

- $S^nPT^1_+$, conformal deposition of a conductive material,
- $S^nPT^2_+$, directional etching of this material up to the exposure of the original seed,
- $S^nPT^3_+$, conformal deposition of an insulating material, and
- $S^nPT^4_+$, directional etching of this material up to the exposure of the original seed.

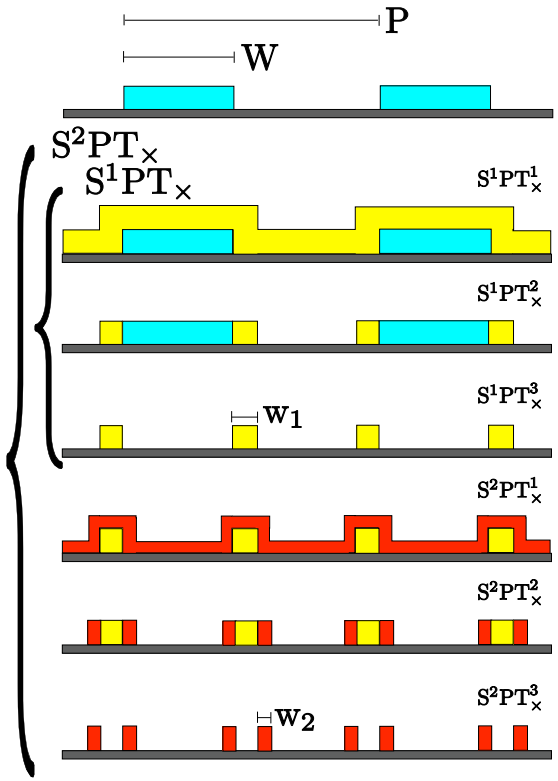




Multiplicative route—$S^nPT_\times$

The multiplicative generation requires that both sides of each newly grown spacer are used as seeds for the subsequent growth—that is possible only if the original seed is etched away at the end of any cycle. In $S^nPT_\times$ each multiplicative $SPT_\times$ cycle involves therefore the following steps:

- $S^nPT^1_\times$, conformal deposition of a film on the seed,
- $S^nPT^2_\times$, directional etching of the newly deposited film up to the exposure of the seed, and
- $S^nPT^3_\times$, selective etching of the original seed.



Addressing

Each line defining the crossbar extends beyond the crossing region and in this zone it is used for addressing. This region is then covered with cross-points protecting cap, that is etched away along a narrow (sublithographic) line misoriented with respect to the array by a small angle θ. In this way the zones where the bars are not covered are separated by a distance that diverges for $\theta \longrightarrow 0$; thus, if θ is sufficiently small, the separation between the zones no longer protected makes them accessible to conventional lithography and suitable for contacting the external circuitry. In this method each line is linked separately from the others to the external circuitry.

Area consumption in addressing

Although addressing n^2 cross-points requires therefore $2n$ contacts, demultiplexing is area consuming:

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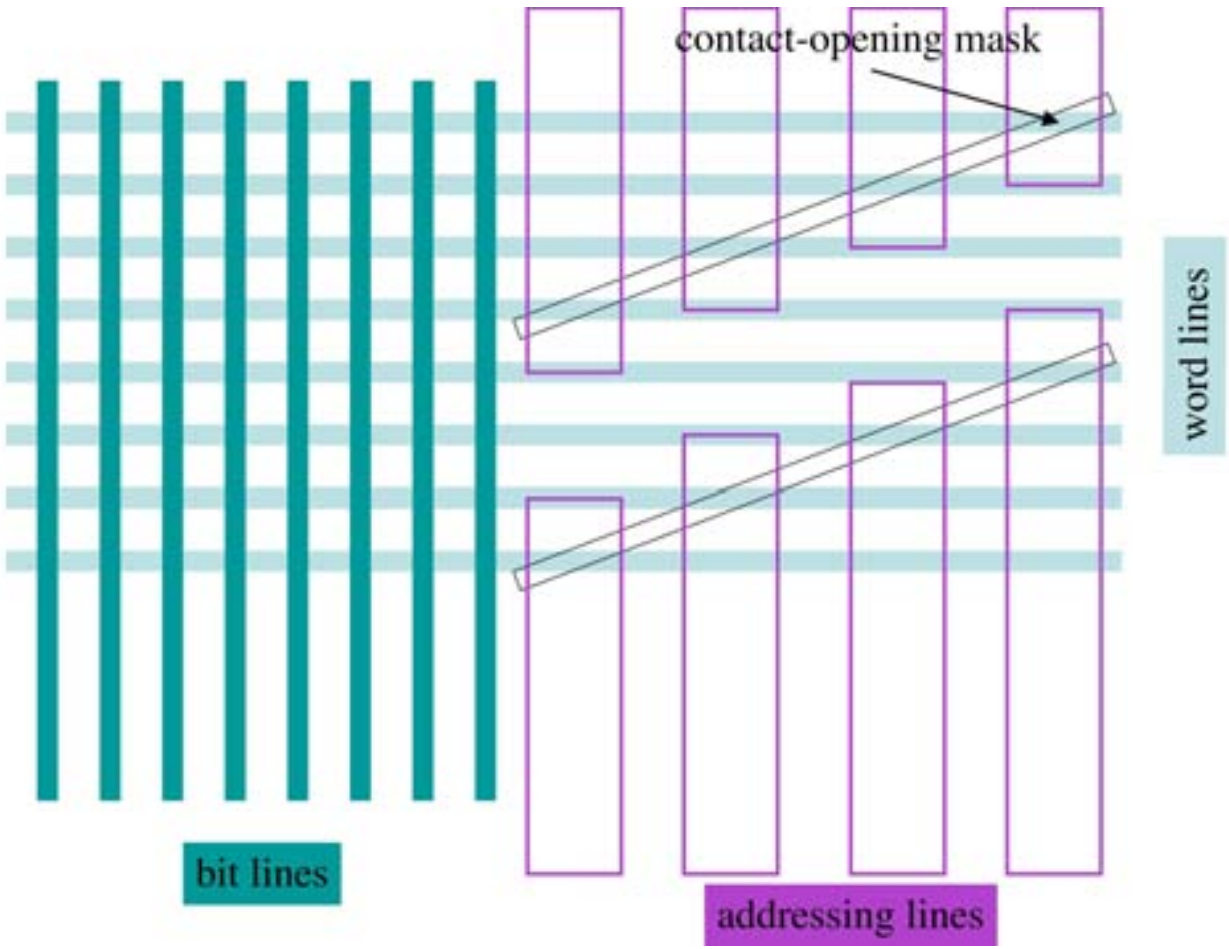
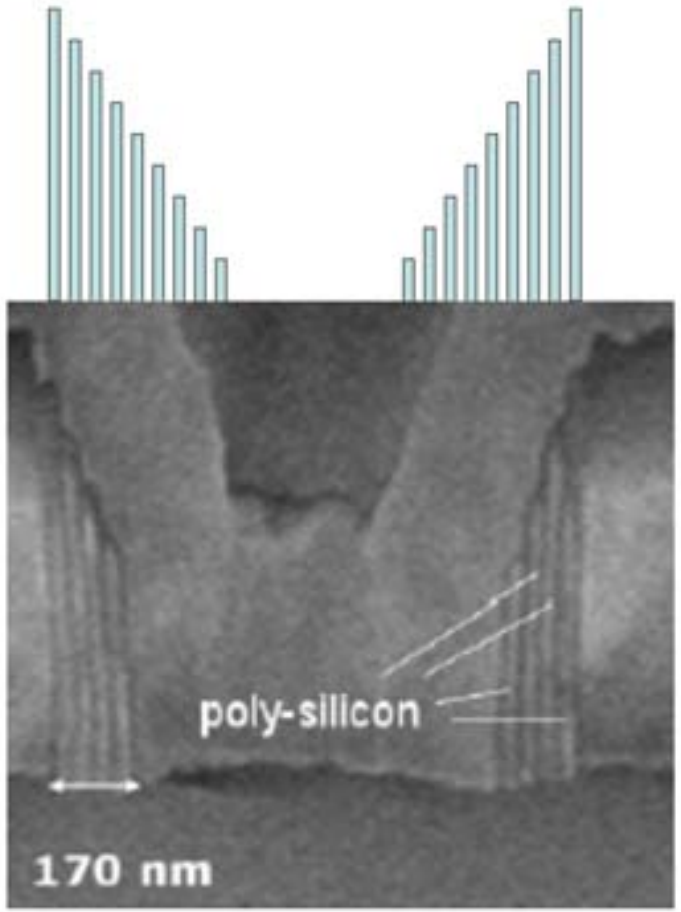


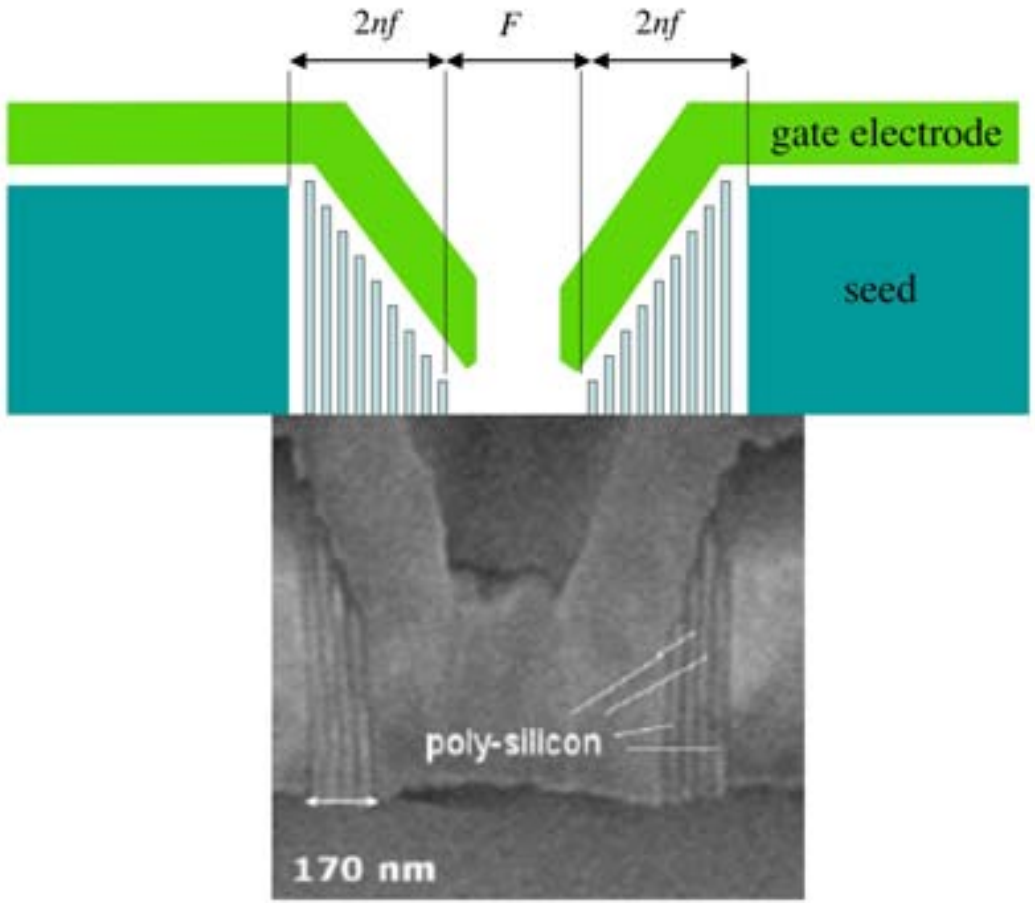
Saving area with S^{n}PT

S^{n}PT results in wires with height decreasing progressively with n:

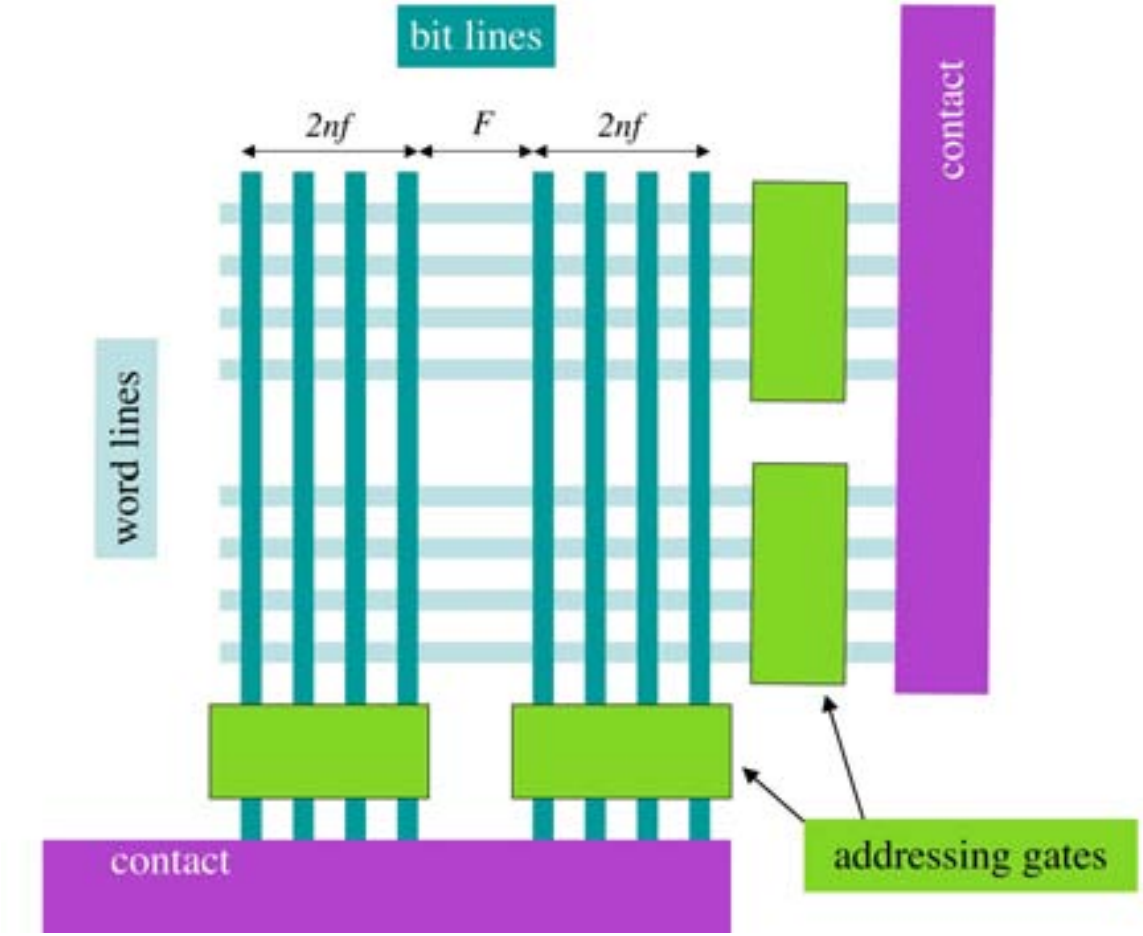


Exploiting the disadvantage. I

This seeming disadvantage can be exploited for an extremely efficient demutiplexing



Exploiting the disadvantage.II

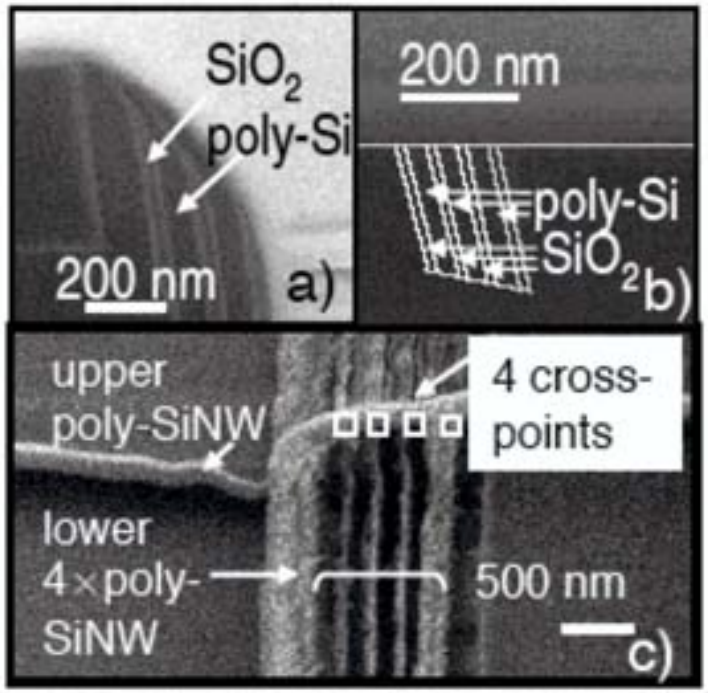


An example

Top-Down Poly-Si Nanowire Crossbars Fabricated with Sub-Photolithographic Pitch

M. Haykel Ben Jamaa[1], Gianfranco Cerofolini[2], Giovanni De Micheli[1], and Yusuf Leblebici[3]

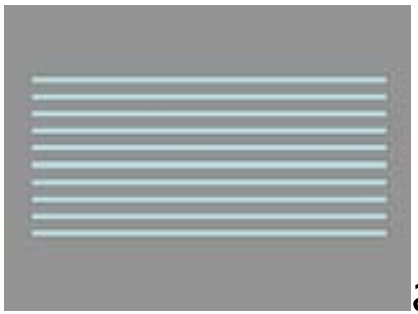
[1]Integrated Systems Laboratory, EPFL (Swiss Federal Institute of Technology), 1015 Lausanne, Switzerland
[2]Department of Material Sciences, University of Milano - Bicocca, 20126 Milan, Italy
[3]Microelectronic Systems Laboratory, EPFL (Swiss Federal Institute of Technology), 1015 Lausanne, Switzerland

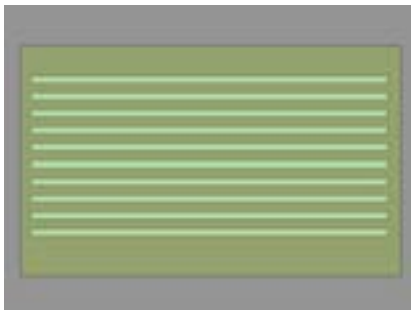


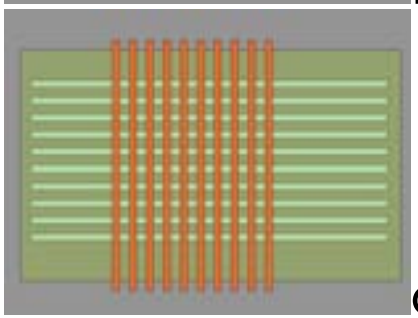
Another roadmap—The crossbar route

Crossbar preparation

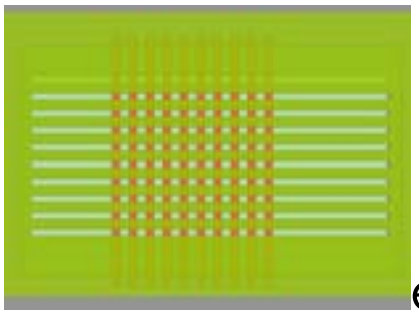
Nanobiosensors for the sub-cellular analysis are possible exploiting the crossbar structure.


a


b


c

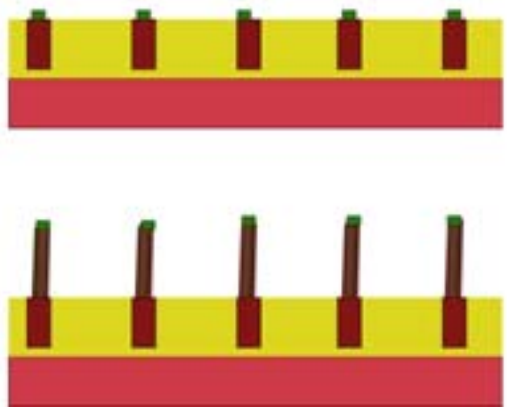

d


e

Another roadmap—The crossbar route

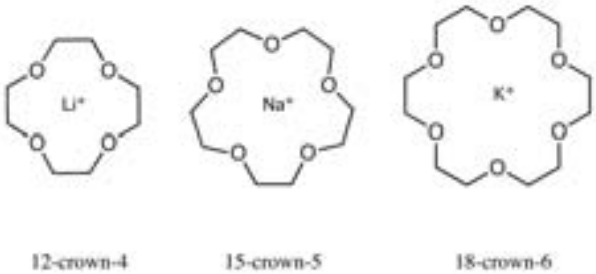
Adding probes to the crossbar

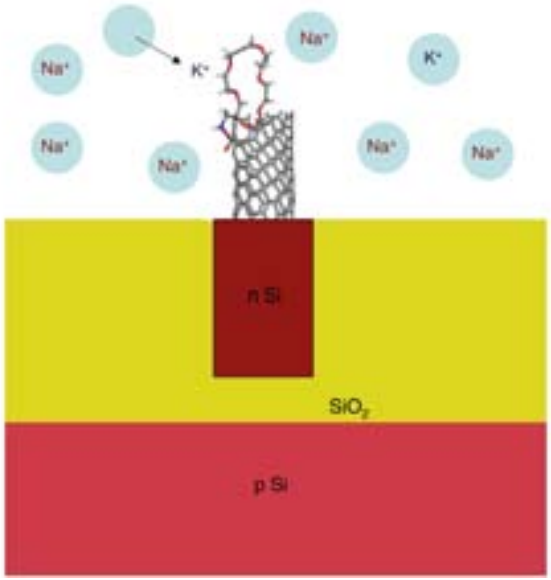
The immersion of the resulting structure in a solution of a salt of a reducible metal (like nickel, copper, etc.) will result in its electroless deposition in elemental form onto the exposed silicon. The deposited film may be thermodynamically or kinetically controlled to have an assigned thickness. A thermal treatment of the structure will result in the formation of one or more islands on the silicon with size controlled by surface and interfacial tension. After that, if the system is exposed to an ethylene or acethylene atmosphere at high temperature (say in the interval $700 - 1000\,^{\circ}\mathrm{C}$); in this environment the metal islands catalize the formation of carbon nanotubes (CNTs) whose diameter is assigned by the diameter of the metal catalyst.



Applications. I

- Selective determination of alkaline ions with crown ethers

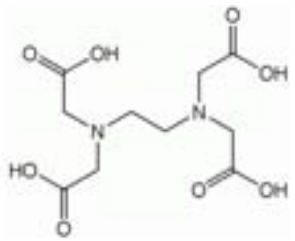




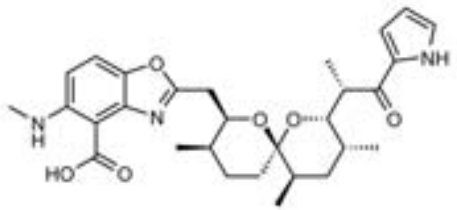
Applications. II

- Determination of calcium with EDTA or A23187

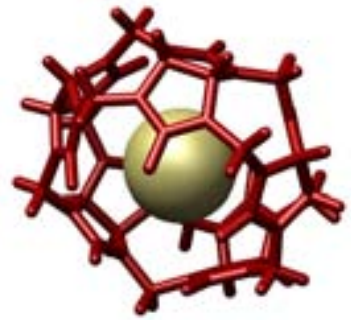
EDTA



A23187



- Determination of anions with with carcerands



Applications. III

- Determination of neutral species, derivatizing the CNT with suitable receptors reacting redox with the target species donating an electron to it (or *vice versa*). To allow the continuous operation of the electrode, however, the receptor must contain a sacrificial region that restores its pristine redox state with a longer time constant than the time required for the detection of the signal.

Conclusions

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- When a pixel matrix has been prepared, there is the need of putting the active elements (the cross-points) in electrical contact with the cell. This step is not trivial; the selective growth of CNTs has been identified as a key tool for that.
- At last, the preparation is completed with the functionalization of the CNTs, finalized to allow them to feel the assigned species.