

Chapter 24

Status and Perspectives of Ion Track Electronics for Advanced Biosensing

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Abstract New *multifunctional* ion irradiation-based three-dimensional electronic structures are developed for biotechnological applications, specifically for sensing of biomaterials, bacteria and mammalian cells. This is accomplished by combined micrometric surface and nanometric bulk microstructuring of insulators (specifically of polymer foils and SiO₂/Si hybride structures) by adequate ion beams.

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Our main goal is the production of a cheap small universal generic working platform with multifunctional properties for biomedical analysis. Surface engineering of this platform enables cell bonding and its bulk engineering enables the extraction of *cell secrets*, for the sake of intercepting and analyzing the biomolecules used in cell communication. The exact knowledge of the spectrum of these cell-secreted signalling molecules should enable one to identify unambiguously the cell type. This knowledge will help developing strategies for preventive quorum sensing of bacteria, with the aim of fighting bacterial infections in an ecologically secure way.

Keywords Ion tracks • Microbeams • Polymers • Etching • Cells • Bacteria • Biosensors • Biomolecules • Signalling molecules • Quorum sensing

24.1 Ion Irradiation of Thin Polymer Foils

24.1.1 *Ion Tracks in Thin Polymer Foils*

Since the 1960s of the last century it has been known that energetic (with tens of MeV or more) heavy (with atomic masses being usually larger than that of Ar) ion irradiation (“swift heavy ions”, SHI) of polymers introduces very narrow (some nm in diameter) but long (with ranges R of typically 10–100 μm) parallel trails of damage, the so-called latent ion tracks. In foils with thickness $d < R$ the latent tracks penetrate throughout the whole foil.

The radiation damage of polymers {such as polyethylene terephthalate (PTE, mylar) or polycarbonate (PT, makrofol)} stems from the formation of radio-chemical reaction products. Smaller ones readily escape thus adding new free volume to the intrinsic one along the irradiated zones. This enables electrolytes to penetrate into the polymer along the latent tracks, thus forming parallel liquid conducting nanowires between the foil’s front and back sides. Irradiated polymer

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foils mimic bioelectronic functionalities, as they resemble somewhat biological membranes which also contain a number of parallel electrolyte-filled nanopores.

Larger reaction products tend to aggregate towards carbonaceous clusters [7] which might behave as obstacles for the smooth ionic current passage along the tracks, upon application of a voltage across the foil. As a result, charges may pile up in front of them until the electric field across them exceeds their breakthrough field strength. At that moment current spikes emerge [15] which eventually are associated with negative differential resistances [10]. As the spike height is decreased by eventually adsorbed surface layers of biomaterials, pulsating tracks can also be exploited for biosensing [16].

Foils with current spike emitting tracks are thought to mimic neurons. In a multitude of such tracks, the individual randomly emitted spikes synchronize themselves towards phase-locked oscillations within domains of typically 20–30 mm² size (determined by the mean free pathlength of the charge carriers within one AC half period) [11, 12] – similarly as they occur for neurons in the human brain, where their interaction results in the formation of brain waves. The frequency of these collective track pulsations is around 0.1–30 Hz [15, 16], hence in the order of magnitude which is similar to brain waves. The presently available neural network theory describes the behavior of pulsating tracks at least qualitatively well.

The radiochemical changes along ion tracks, preferentially chain scissioning, make the ion track region vulnerable to being dissolved (‘etched’) by aggressive chemicals (such as NaOH in the case of PET as polymeric substrate) [8], thus, transforming the original ‘latent tracks’ into nanopores, the so-called “etched tracks”. Whereas etching of a track from both sides for a sufficient time leads to cylindrical tracks, etching from one side only for a sufficient time leads to conical tracks [26]. Compensation of this etching process on one foil side by an in-diffusing neutralizer solution from the other side leads to much shorter etched tracks, the so-called “funnel-type” tracks [13].

Surfaces of polymers charge up negatively if in contact with electrolytes. Hence, in the case of electrolyte-filled conically etched tracks where the electric field gradients are non-zero, an unidirectional force acts upon the ions. Macroscopically, such tracks exhibit current rectification [25]. Tunnel-type tracks combine both the rectifying and spike-emitting properties [13]. Any material of interest for electronics or biotechnology (such as (semi)conductors or enzymes) deposited within the etched tracks or on their walls may transform the pore-containing polymer foils into either nanoelectronic devices or biosensors, respectively.

24.1.2 Microbeam-Induced Surface Structures in Polymer Foils

In the past decades, ion-beam based surface microstructuring techniques (by microbeams, focused ion beams and irradiation through masks) gained an increasing importance. They allow one to deposit well-defined quantities of radiation damage at precisely defined locations into adequate substrates which upon etching can

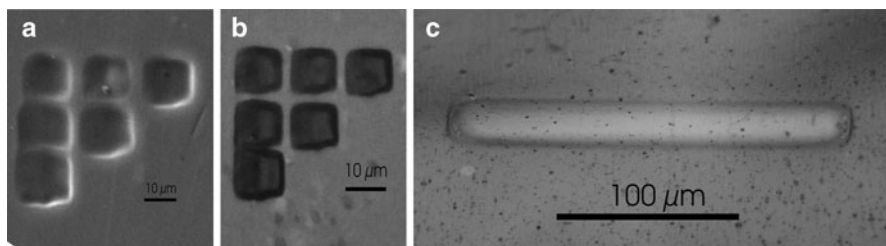


Fig. 24.1 First test experiments at the Porto Alegre microbeam facility. Shown are (a, b) $10\ \mu\text{m} \times 10\ \mu\text{m}$ and (c) $200\ \mu\text{m} \times 20\ \mu\text{m}$ large patterns as obtained after irradiation with 3 MeV H^+ at fluences of 2×10^{17} , 4×10^{17} and $8 \times 10^{17}\text{cm}^{-2}$ for the three, two and one spots in the *upper*, *central* and *lower lines* of (a) and (b), respectively, and $2 \times 10^{17}\text{cm}^{-2}$ for the long pattern of (c); (a) without etching (i.e., influence of sputtering only) and (b, c) subsequently etched with 6 M NaOH at 60°C for 30 min. Images taken with optical microscope under tilted illumination

be transformed into 3D-surface microstructures. Depending on the choice of the ion impact and on the duration of etching, three-dimensional topological surface structures of any desired shape (such as craters, holes, trenches, grids etc.) and depth can be created. Figure 24.1 shows a first test example for the Porto Alegre microbeam with 3 MeV protons and a lateral resolution of $\sim 1\ \mu\text{m}$.

These surface depressions are characterized by chemical material's modifications (due to the irradiation-induced enrichment of carbon and the formation of radicals, unsaturated and double bonds, etc. [7] and/or due to the etching that removes surface contaminants and also exposes unsaturated bonds) that make them more biocompatible than unirradiated polymer surface regions. Furthermore, it is the altered surface topology that favors the bonding of living cells (topologically-selected cell bonding). Surface structures with horizontal dimensions of at least $\sim 10\ \mu\text{m}$ and perpendicular dimensions of $\sim 1\ \mu\text{m}$ are required in this case.

24.2 Present State-of-the-Art Ion-Irradiation-Based Devices

24.2.1 Ion Track Technology

A large experience in swift heavy ion track technology has already been accumulated. On the one hand, this concerns especially the creation and investigation of ion-track/Si hybride nanostructures which form a principally new foundation for the interfacing of conventional electronics with ion-track based electronic devices. Following this approach, novel multifunctional electronic devices with unique parameters have been created that were hitherto unknown in electronics [5, 6, 20, 24]. On the other hand, ion track technology has been directed towards biosensing applications, by functionalizing the ion tracks directly by attaching bioactive compounds (such as enzymes) to their walls (e.g., for glucose and urea sensing [9, 17]).

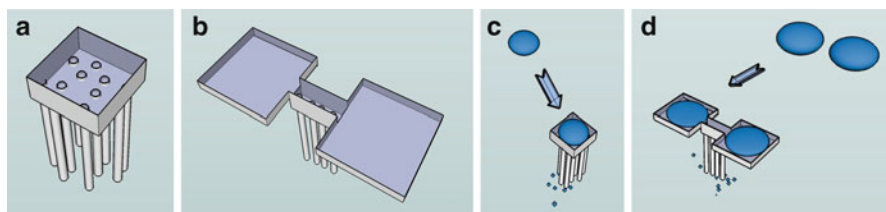


Fig. 24.2 Principle sketch of the structures used (a) to extract secrets from cells, (b) to intercept quorum sensing. In both cases, microbeam-created surface depressions exist that are connected by etched ion tracks with the foil backside. In (b), an additional narrow and deep trench connects the surface depressions, and only the trench itself is connected with the foil backside via etched ion tracks. (c, d) Cells arriving at the platform are bond inside the depressions at the foil surface. Their secrets are extracted via some (chemical or physical) potential gradient applied through the etched ion tracks towards the foil backside (c) either directly or (d) during the cell's (biochemical) information exchange

24.2.1.1 TEMPOS Structures

In former experiments, SiO_2/Si and SiON/Si bilayer structures were ion-irradiated, etched and filled with (semi)conducting matter (such as Ag, Au or TiO_2 nanoparticles, or C_{60} , carbon nanotubes, phthalocyanines, etc.) to produce novel electronic devices with peculiar properties such as tunable rectification and tunable switching (flip-flops), negative differential resistances (NDR) accompanied by light emission, high resistivity against electromagnetic pulses (EMP), the capabilities for current amplification, self-oscillations if exposed to energetic irradiation, intrinsic capability for making logic AND and OR decisions, and sensing of physical (such as light, temperature, magnetic fields, etc.) and chemical (such as H_2O , NH_3 , etc.) parameters [5, 6, 20, 24]. These structures were denoted by the acronym “TEMPOS” which stands for “tunable electronic material with pores in oxide on semiconductor”. Later on this group was expanded towards bilayer structures made of irradiated polymers such as kapton and Si.

24.2.1.2 Electronics with Electrolytes in Etched Tracks (E^3T)

Self-carrying ion track-containing thin polymer foils immersed in suitable electrolytes can be used as substrates for the construction of biosensors that exploit the principle bioreaction: $\text{X} + \text{Y} \rightarrow \text{Z}$ where X is the analyte, Y – the agent, and Z – the reaction product. The ion tracks can either be used as-prepared or after etching. Two approaches must be distinguished (see also Fig. 2 in Ref. [1]).

Historically, the first strategy developed for track-based biosensing was the blocking of the transmission through a polymer foil containing a *single etched* track clad with an appropriate bio-agent, by a specific biomolecule, which increased the foil resistance [22, 27]. Whereas the advantage of this strategy is its extreme

sensitivity by making single biomolecules detectable, its disadvantages include the need for highly precise pore preparation and very low currents to be detected.

Therefore a more robust approach has been developed which requires much less effort for sensor preparation and yields larger currents for biosensing. The worse detection sensitivity of that approach does not signify any drawback for practical applications as the minimum detectable concentrations C_{\min} are still far below medical requirements C_{med} (for example, for glucose sensors [9], $C_{\min} \sim 10^{-5} \dots 10^{-6}$ M whereas $C_{\text{med}} \sim 5 \times 10^{-4} \dots 10^{-3}$ M). This could be accomplished by using a *multitude* (typically $10^6 \dots 10^9 \text{ cm}^{-2}$) of *parallel etched* tracks (each of them clad with an appropriate bio-agent, e.g. an enzyme) within a thin polymer foil, and by the simultaneous enrichment of ionic products of suitable (such as enzymatic) bio-reactions within these tracks due to their high confinement [9, 14, 17, 18].

A modification of the second technique is given by the adsorption of bio-reaction products onto the surface of foils containing *many latent* SHI tracks, which leads to a decrease of the foil conductivity [14, 16, 23]. For more sophisticated systems, two or more such foils can be arranged sequentially. These systems have been denoted as “Electronics with Electrolytes in Etched Tracks” (E³T) as they form a new field of biomimicking electronics. Such systems have an inherent capability for logic AND or OR decisions.

24.2.2 Ion-Beam Based Surface Microstructuring

24.2.2.1 Cell Bonding to Polymer Films

In spite of a great variety of individual results, there exist some general rules-of-the-thumb on how cell adhesion and proliferation on polymeric substrates can be influenced positively. These are:

- chemical factors such as the choice of adequate biocompatible deposits, hydrophilicity, surface charges and chemical surface etching;
- energetic irradiations such as laser treatment, plasma treatment, low energy or high energy ion irradiation;
- topological 3D structuring of the substrate surface by mechanical techniques such as molding, casting, evaporation, electrospin-coating of preferentially carbonaceous materials (such as nanofibers, etc.), or by irradiation (e.g. by ion microbeams or laser irradiation), or by subsequent etching. Both nano- and microstructuring of the substrate influence the cell adhesitivity and other cell properties positively.

The first possibility is the most widespread in literature (~50%), followed by the second (~30%) and the third one (~20%), but the majority of authors agree that a combination of all three approaches yields the best results. Topological bonding (e.g. in microbeam-created large-scale (~ μm) surface depressions with a nm-sized

surface fine structure (as given by e.g., etched swift heavy ion tracks)) combined with either energetic surface treatment or deposition of surface adhesive extracellular matrix proteins (such as fibronectin, vitronectin, collagen and laminin) in the depressions and, eventually, cell-rejecting deposits elsewhere (e.g., by a thin Teflon coating) appear most favorable for the production of predetermined cell patterns on polymeric surfaces. Therefore we have overtaken this concept for our studies.

24.2.2.2 A New Working Platform for Biotechnology and Biosensing

Thin SHI-irradiated polymer foils (e.g., PET or PC) are covered by thin teflon-like films (produced by teflon sputtering) that change the contact angle from $\sim 69^\circ$ (for PET) towards $\sim 150^\circ$. Microbeam irradiation removes that protective layer and introduces radiation damage throughout the foil. Whereas the highly hydrophobic Teflon-like surface coating prevents the attack of etchants such as NaOH; the foil etching of both the microbeam-induced radiation damage and the ion tracks is possible within the microbeam-irradiated zones. As the microbeam-created radiation damage density is much lower than that of the SHI tracks, only a shallow depth is etched in the microbeam-irradiated zones, whereas the ion tracks are already etched throughout their whole lengths, thus, yielding transparent connections between the microbeam-irradiated structures and the foil backside (Fig. 24.1a). Please note that the etched ion tracks connect *exclusively* these depressions with the foil backside. If necessary, the interior of the depressions can still be clad with the above-mentioned EMPs whereas they do not stick to the Teflon-covered regions.

In accordance with e.g., Bačáková et al. [2, 3], the depressions are optimized for preferential bonding of the selected cells to them. Whereas for depressions of typically $10\ \mu\text{m} \times 10\ \mu\text{m}$ size and $>0.5\ \mu\text{m}$ depth, individual cells can be accommodated comfortably; larger sizes enable the accumulation of cell clusters of predetermined size. The fixation of cells and/or cell clusters at well-defined sites on a biocompatible substrate enables one to have these cells easily accessible for more detailed examinations and to perform experiments of greater accuracy and unambiguity than usually obtained by conventional large-size biological experiments in petri shell cultures. In this way, it is also possible to connect each individual cell by (e.g., evaporated) contact stripes for electrophysiological experiments, if required.

Due to their large ($\gg 1\ \mu\text{m}$) size, non-helical cells (including mammalian cells and bacteria) do not have any chance to penetrate through the tracks, however, their secretion products do. As the cells tend to fill out all the space within the depressions (especially if these depressions have circular shapes), they thus shield the underlying ion tracks largely from the solution within which they are embedded, so that there is little chance for this medium to leak towards the other foil side. The cell-rejecting Teflon coating on the unirradiated polymer surface restricts the cell population to the depressions only.

In case of need, HPLC and mass spectrometry are applied for the analysis of the cell-secreted and transmitted biomolecules. They can also be visualized by

immunofluorescence staining and quantified by an enzyme-linked immunosorbent assay (ELISA), protein electrophoresis and immunoblotting, and flow cytometry. The gene expression, i.e. the presence of mRNA encoding specific protein molecules secreted by the cells, can be determined by a real-time polymerase chain reaction (real-time PCR).

The etched tracks are expected to serve as channels for extracting the cell secrets to be analyzed towards the foil back side. Their accumulation there in a clean solution (buffer or water) enables their background-free examination. The efficiency of the connection between the cells and the other foil side is determined by the overall track cross section, i.e. by the number of etched tracks and their diameter. For a track density of $\sim 4 \times 10^6$ tracks cm^{-2} and for cell-containing microstructures of ~ 10 μm diameter, in average 4 ± 2 tracks are expected to end up in each microstructure. For the etched track diameters of ~ 100 nm, the overall cross-sectional area of all these etched tracks is in the order of 3×10^{-10} cm^2 , hence amounts to 0.03% of the whole microstructure area. For higher track densities in the order of $\sim 1 \times 10^9$ tracks cm^{-2} , each microstructure will be hit by about $1,000 \pm 30$ tracks which occupy 0.75% of the whole microstructure area.

The concept of extracting secrets from cells within microstructures on polymeric surfaces through a number of etched ion tracks should yield some enrichment of these secrets within the tracks. First, secrets emitted from the cell towards the foil direction cannot escape into the opposite direction (and be diluted there in the ambient solution) as they are blocked by the cell itself. Also, the cross sectional area of all etched tracks being in contact with the microstructure is only a tenth or so of the microstructure area itself so that all secreted molecules will be enriched within the tracks by this order of magnitude. On the other hand, the diffusion coefficient of the secreted molecules within the confined etched tracks will be lower than their bulk diffusivity, hence their concentration will be further enhanced due to their smaller migration speed. Further, as the potential energy of the secreted molecules within the tracks is reduced as compared with that of the molecules within the microstructure (due to the smaller track dimensions), there exists a potential gradient from the cell within the microstructure towards the etched tracks which also favors the molecule's enrichment within the tracks. Also, deionized water or a buffer solution on the opposite foil side will reduce the background in detection of the extracted signal molecules. Last not least, putting a suitable chemical or physical potential gradient across the membrane towards the foil backside enables an efficient extraction of the biomolecules.

In principle, the basic concept to separate two compartments of a vessel from each other by a porous membrane from each other has been realized already much earlier [4]. However, their aims and objectives were quite different. They used microchannel plates of $\frac{1}{2}$ mm thickness and ~ 1 cm^2 area with pores of diameters as large as 10 or 50 μm to separate the two compartments from each other, for the study of cell diffusion effects.

Furthermore, the work of Giselsbrecht et al. [19], who applied microthermoforming of ion-irradiated and etched polymer films, is not comparable with the

approach presented here. The disadvantage of the above mentioned work is that the porous compartments created and described by these authors were in the order of a few 100 μm size, hence more than the order of magnitude and larger than our microbeam-created structures. In this way, bonding of single cells or of assemblies of only a few cells (specifically bacteria) at well-defined places is impossible. Further, this approach leaves the foils transparent everywhere, whereas in our concept the foils are transparent only at the place of the microbeam-created surface microstructures and hence are selective to the cell-emitted secrets only. In other words, our approach allows for a much better definition of the origin of the biomaterials being detected on the cell-free foil side.

24.2.2.3 Cell Communication, Quorum Sensing

Cells that are bound to surface depressions at some distance to each other (to prevent direct cell-to-cell contact) may be connected with each other by narrow microbeam-produced trenches (so narrow that blocking by another bacterium settling is prevented there) on the same foil side (Fig. 24.2b). Due to three surfaces in close vicinity, these trenches are regions of strongly lowered surface potential energy which hence will attract many (neutral or charged) of the molecules secreted from the cells.

Etched ion tracks connecting (only!) these trenches with the opposite foil side can then serve as channels to either intercept the cell-borne signalling molecules of the cell conversation by pumping them to the opposite foil side or to introduce other molecules such as inhibitors. This can be enabled by applying a small pressure gradient across the substrate foil. The enhancement of both the signal and the signal/noise ratio obtained in this way are favorite conditions for performing the usual biochemical analytic techniques (such as high-performance liquid chromatography (HPLC), mass spectrometry, (cyclic- or differential pulse-) voltammetry, luminescence, Fourier transform infrared spectroscopy or combinations of these techniques [21]) right behind the tracks.

For the foils with $R > d$ the microbeam-induced radiation damage extends throughout the whole foils, and rather symmetric microstructures emerge upon etching of the irradiated foils from both sides. Even if $R \gg d$ holds, the projectile's stopping power (hence also the etching rate) does not change remarkably and the beam scattering is negligible. Then both etched microstructures are virtually identical, which enables one to construct working platforms with a 1:1 relation of both front and back sides. After connecting these microstructures by etched ion tracks with each other and after depositing identical cells into the depressions on both sides, one has thus obtained an experimental platform for the direct and unambiguous check in how far is a cell beneath, e.g. environmental stress may influence the behavior of the other one via information exchange through the etched tracks.

24.3 Conclusions and Outlook

Ion irradiation-based structures can be usefully applied to biotechnology and biosensing. The present project is devoted to the creation of a platform for cell analysis which should be used especially for the study of bacterial intercommunication and for bacteria sensing, for the sake of fighting diseases without the use of antibiotics. Furthermore, this enables one to tackle quite a number of new problems, some of which being listed subsequently.

Mobility studies: determination of diffusion coefficients of biomolecules and helical bacteria in the closely confined environment; track-based sensors for helical bacteria; synchronization of bioreactions in a multitude of etched tracks.

Advanced ion track-based biosensors: TEMPOS-type biosensors; biosensors with self-enhancing response; sequential and parallel biosensing; sensing of enzymatic reaction chains; biosensors with inherent AND/OR logics; time-integrating biosensors; pulsating biosensor networks.

Research on cell conversation: novel sensors for bacteria detection; metal sensors with anaerob bacteria; cell-interaction studies; charged signal molecules; interception of quorum sensing molecules upon subjecting cells (especially bacteria) to physical or chemical stress factors such as antibiotics or toxins.

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