DNA Diagnostics: Optical or by Electronics?

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Abstract

In this paper, we very briefly review DNA biosensors based on optical and electrical detection principles, referring mainly to our past work applying both techniques but here using nearly identical sensor chip surface architectures, i.e., capture probe layers that were prepared based on a pulsed plasma deposition protocol for maleic anhydride and subsequent wet-chemical attachment of the amine-functionalized peptide nucleic acid (PNA) probe oligonucleotides. 15 mer DNA target strands, labeled with Cy5-chromophores that were attached at the 5’ end were used for surface plasmon optical detection and the same target DNA but without label was used in OTFT sensor-based detection where the mere charge density of the bound (hybridized) DNA molecules modulate the source-drain current. The sensing mechanisms and the detection limits of the devices are described in some detail. Both techniques allow for the monitoring of surface hybridization reactions, and offer the capacity to quantitatively discriminate between targets with different degrees of mismatched sequences.

Introduction

The race in DNA diagnostics between optical detection principles (absorption/transmission, fluorescence, surface plasmon spectroscopy, etc.) and electrical/electrochemical/electronic concepts is not decided yet. Both approaches continue to offer solutions for fast, multiplexed, simple and cheap detection of oligonucleotides, PCR amplicons, genomic DNA (fragments), etc. [1]. Most likely, the competition will never see a single winner that meets all needs because the different practical formats and boundary conditions for applications, as well as, market requirements may ask for specific and unique solutions that could be better achieved in one case by optics and in another situation by electronics.

Along these lines, we will briefly review our contributions in both categories of DNA diagnostics and will then present a number of examples of what we could demonstrate for the sensitive detection of DNA in (from) solution by monitoring surface hybridization reactions of target strands binding from the analyte solution to surface-attached capture oligonucleotides. A particular emphasis will be put on the physico-chemical principles of these surface recognition and binding (or dissociation) reactions in order to be able to develop criteria of how to optimize sensitivity, selectivity, e.g., for the detection of single nucleotide polymorphisms (SNPs), etc. in DNA diagnostics.

Surface Plasma Field-enhanced Fluorescence Spectroscopic (SPFS) Detection of Surface Hybridization Reactions

The schematics of the set-up used for the surface-plasmon optical recording of DNA association/binding (surface hybridization) and dissociation reactions between surface-attached capture probe strands and target strands from solution is shown in Figure 1A classical surface plasmon spectrometer in the Kretschmann configuration [2] is modified by a module consisting of a collection lens, a spectral filter to differentiate the emitted fluorescence light against elastically scattered surface plasmon modes, (an attenuator when needed to not run the photomultiplier near saturation) and a monitoring unit, a photomultiplier in our case here, operated in the photon counting mode. This attachment allows for the application of fluorescence detection principles to be implemented as surface plasmon field enhanced fluorescence spectroscopy for the detection of hybridization kinetics as well as for the determination of affinity constants by titration experiments [3].

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The use of SPFS in our optical experiments is absolutely necessary and essential because for a capture probe density at the transducer surface typical for our sample preparations the mere binding of target sites of 15 bases alone does not lead to a significant modification of the (optical) interfacial architecture, which would be the basis for a label-free detection concept. This is demonstrated in Figure 2 which compares the results for the angular scan mode and the kinetic mode of classical SPR experiments, i.e., the (attempt for) label-free detection of the target binding, with that of employing SPFS for the identical experiment. In both cases, i.e., in the angular scan mode and during the kinetic recording, no change of the reflectivity signal in SPR spectroscopy can be seen: the reflected intensity scans taken as a function of the angle of incidence, \( \theta \) before and after the hybridization reaction, respectively, are virtually superimposable. Alternatively, the reflected intensity, taken as a function of time after injection of the target solution (1 \( \mu \)M of T2-MM0/Cy5) remained constant; hence, there is no label-free optical monitoring and quantification of these surface hybridization events possible.

However, if the fluorescence intensity emitted by the Cy5-chromophores attached to the targets is monitored by SPFS either as a function of time after injection of the solution or as a function of the incident angle, \( \theta \) after the completion of the binding reaction, respectively, a strong signal with an excellent signal-to-noise (S/N) ratio can be recorded: the fluorescence data taken as a function of the angle of incidence before the injection of the target solution into the flow cell just show a fluorescence background with no distinct features; however, after hybridization of the chromophore-labeled target strands a strong fluorescence signal follows the excitation profile of the SPR mode (as seen in the dip of the reflectivity curves) with the well-known shift of the angular position of the peak intensity of the fluorescence spectrum relative to the minimum position of the reflectivity scan [4].

The kinetic recording of both, the reflected intensity, \( R \), and the fluorescence intensity, \( F \), taken simultaneously at a constant angle of incidence, \( \theta =56 \text{ deg}, R \sim 0.3 \) shown in the right panel (b) of Figure 2 also demonstrates convincingly the need for a label in the monitoring and quantification of this surface binding reaction: while the reflectivity remains constant over the time of the binding event, the fluorescence performs a moderate jump in intensity upon the injection of the target solution and then shows an exponential increase to an equilibrium intensity level which, for a given affinity constant, is strictly determined in a unique way by the bulk concentration of the target solution.

The initial intensity jump originates from chromophores excited in the bulk solution by the exponentially decaying evanescent field of the surface plasmon mode, “looking” some 170 nm away from the interface into the solution, and resulting in a contribution to the overall fluorescence signal, which increases linearly with the bulk concentration, but disappears upon rinsing the flow cell with pure buffer (Figure 2b, “buffer rinsing”). The exponential fluorescence intensity increase which follows the initial jump reflects the surface association reaction, the hybridization, of the targets from the bulk solution to the capture probes and can be analyzed to give the \( k_a \) reaction rate constant of the process. After the saturation of the intensity increase indicates the completion of the association reaction rinsing the cell with pure buffer results in the aforementioned sudden decrease of the fluorescence intensity to a level that represents the occupancy of binding sites on the sensor surface. As can be seen from Figure 2 the kinetic signal shows an excellent S/N ratio and, in general, can be easily analyzed in order to yield the individual kinetic rate constants, \( k_a \) and \( k_{off} \) as well as the affinity constant \( K_A = k_a / k_{off} \) (or the half-saturation-concentration \( c_{1/2} = K_A / k_{off} \)), respectively. The latter can then be compared to the result of a titration experiment (cf. below). Since the target of the experiment in Figure 2 is fully complementary to the capture nucleotide sequence the dissociation process for the limited time window that it was observed in this experiment does not lead to a decrease in fluorescence because \( k_{off} \) is simply too small (Table 1).

### An Interfacial Architecture for Monitoring Oligonucleotide Hybridization Reactions Suitable for both Detection Principles

In order to make sure that the results obtained by optical detection-in our case by surface-plasmon field enhanced fluorescence spectroscopy (SPFS) of interface binding reactions between surface-attached oligonucleotide capture probe strands and complementary target strands from solution-can be directly compared to the data derived from an electronic transducer device—the ones presented and discussed here from an organic thin film transistor (OTFT)—we designed an interfacial architecture that could be used for both transducer platforms because it took into account the technical needs of both experiments [5].

For the OTFT detection of hybridization reactions, monitored online in a flow cell with buffer, this requires a protective layer that shields the organic semi-conducting material against the in-diffusion of ions from the buffer solution. Otherwise, this would destructively interfere with the electronic performance of the transistor with its source-drain-current that is modified by the gate (surface and/or bulk) electrical charges [6]. This was achieved by the appropriate design of the layered architecture as shown in Figure 3 (also Figure 4): Onto the solid (but possibly flexible) substrate a thin layer (22 nm) of poly(4-vinylphenol) was deposited. The use of this prepolymer provides for a useful but not fully protective layer against the in-diffusion of ions from the buffer solution.

The kinetic recordings of both, the reflected intensity and the fluorescence intensity, respectively, measured at a fixed angle of incidence, \( \theta =56 \text{ deg}, R \sim 3 \), as a function of time, respectively, as well as the affinity constants \( K_A = k_a / k_{off} \), as derived from kinetic measurements like the one shown in Figure 5, for target strands that are fully matched to the probe sequence (T2-MM0/Cy5), or display a single (T1-MM1/Cy5) or two mismatches (T3-MM2/Cy5), respectively.

![Figure 2](image)

**Figure 2:** (a) Angular scans of the reflectivity, \( R \), (reflected SPR intensity scaled to the incoming intensity) as a function of the angle of incidence \( \theta \) before (full dots) and after hybridization (continuous curve), respectively, (b) Kinetic experiments, i.e., reflectivity \( R \) (full squares) and fluorescence intensity \( F \) (open circles), respectively, measured at a fixed angle of incidence (\( \theta =56 \text{ deg}, R =3 \)) as a function of time, \( t \). The arrows indicate the injection of the target solution and of pure buffer, respectively.

| Rate constants, \( k_a \) and \( k_{off} \), respectively, as well as the affinity constants \( K_A = k_a / k_{off} \), as derived from kinetic measurements like the one shown in Figure 5, for target strands that are fully matched to the probe sequence (T2-MM0/Cy5), or display a single (T1-MM1/Cy5) or two mismatches (T3-MM2/Cy5), respectively. |
|---------------------------------|-----------------|-----------------|-----------------|
| \( k_a / M\text{m}^2\text{s}^{-1} \) | \( k_{off} / s^{-1} \) | \( K_A / M^{-1} \) |
| T2-MM0/Cy5 | 3.3 10^{10} | 1.6 10^{6} | 3.4 10^{1} |
| T1-MM1/Cy5 | 1.3 10^{10} | 4.0 10^{5} | 1.5 10^{6} |
| T3-MM2/Cy5 | 3.9 10^{10} | 4.0 10^{5} | 2.2 10^{6} |

**Table 1:** Rate constants, \( k_a \) and \( k_{off} \), respectively, as well as the affinity constants \( K_A = k_a / k_{off} \), as derived from kinetic measurements like the one shown in Figure 5, for target strands that are fully matched to the probe sequence (T2-MM0/Cy5), or display a single (T1-MM1/Cy5) or two mismatches (T3-MM2/Cy5), respectively.
(PVP) (MW 20,000 g/mol), blended with the cross linker 4,4’-(hexafluoroisopropylidene) diphthalic anhydride (HDA), was spin-coated as the ultra-thin dielectric layer that allows for operation at very low voltages, which is necessary for stable operation in air and water [7]. Then a thin layer (15 nm) of a semiconducting molecule (5,5’-bis-(7-dodecyl-9-H-fluoren-2-yl)-2,2’-bithiophene (DDFTTF) was deposited by thermal evaporation. Onto this, the Au electrodes were evaporated through a shadow mask with a separation gap of 50 µm, sealed by a thin layer of SiOx, acting as an insulating coating to reduce the influence of charge screening effect during the sensor operation in buffer media. Additionally, a protective coating was prepared by a (pulsed) plasma-polymerization step [8] in a reactor that polymerizes fluorine-rich monomers (perfluoro (1,3-dimethylcyclohexane), cf. the molecular structure given in Figure 4) to a Teflon-like polymeric barrier layer, the thickness of which could be as low as 5 nm. This was enough to protect the semiconducting channel material yet allowed for a capacitive coupling of any bio-affinity reaction at the surface of the device in contact with the analyte solution to the conducting channel between source and drain electrode of the transistor [8].

For the optical detection by surface plasmon fluorescence spectroscopy, the same pulsed plasma modifications were applied to the Au-substrates in order to have (nearly) identical architectures for the functionalization of the transducer via the same concepts.

The important surface bio-functionalization step in both transducer cases was a plasma-polymerization coating of maleic anhydride as the monomer feed into the reactor, which results in a thin polymer coating that further protects the device and by means of its anhydride (surface-) functionalities allows for a wet-chemical functionalization of the transducers for the specific affinity reaction between proteins like antigen-antibody reactions or for a hybridization reactions, e.g., for SNPs detection. Here we used amine-terminated PNA oligonucleotides that couple directly to the anhydride groups to form stable and robust amid bonds between the transducer surface and the capture probe oligonucleotides [9,10]. This is schematically shown in Figure 4. Nominally, PNAs are neutral; hence, upon the binding of the charged target DNA strands from solution such a hybridization event has a maximum change in the surface charge density at the device surface resulting in a significant change of the source-drain current, $\Delta I_{DS}$. The nucleotide sequences of the PNA probe strands and the corresponding DNA target strands with sequences being either fully complementary to the probe sequence (MM0) or carrying one (MM1) or two (MM2) mismatches, respectively, are shown in Table 2. The target sequences used for the optical detection (and in some test cases also for the electronic recordings) carried in addition a chromophore, Cy5, at their 5’ end [11].

**Optical Detection of Single Nucleotide Polymorphism By SPFS**

A typical kinetic experiment of a hybridization reaction between the surface-attached PNA capture probe P2-15mer and a target strand is shown in Figure 5. After recording for a few minutes the fluorescence baseline with its negligible background signal the injection of a 50 nM buffer solution of the fully complementary DNA target strand T2-MM0/Cy5 induces the association reaction, which can be easily fitted by a single exponential fluorescence increase (red curve in Figure 5).

Upon switching to pure PBS buffer solution running through the flow cell a moderate desorption reaction sets in which again can be easily fitted to a single exponential. When quantified according to a Langmuir model that does fit the data quite well, these T2-MM0/Cy5 hybridization kinetics experiments as well as the ones recorded with the other targets, i.e., T1-MM1/Cy5 and T3-MM2/Cy5 strands, respectively, then lead to the kinetic rate constants as summarized in Table 2.

As expected, the association rate constants, $k_{as}$, decreased...
immobilized via the plasma-polymerized maleic anhydride layer and the fully complementary DNA target T2-MM0/Cy5 binding from bulk solutions of different concentrations. The intensities are presented on a logarithmic scale in order to emphasize the excellent signal-to-noise ratio observed also for the lower concentrations. Note that even bulk concentrations as low as 10 pM lead to an easily measurable signal that can be fitted to a single exponential increase (red full curve).

By plotting the obtained saturation values of the fluorescence intensity (on a linear scale as % of the maximum intensity which corresponds to full coverage) as a function of the bulk concentration (on a logarithmic scale) at which these values were reached (Figure 7) one obtains an S-shaped curve that can be well-fitted by a Langmuir adsorption isotherm with a half-saturation value, $c_{1/2}=K_d$, which amounts to $c_{1/2}=3.3$ nM for the MM0 targets. For the MM1 target this $K_d$ value decreased to $K_d=6$ µM and for the MM2 target to $K_d=50$ µM, respectively. These values are well within the experimental range of the

significantly with the introduction of one or two mismatches in the sequences of the duplexes. Additionally, the dissociation rate constants, $k_{off}$, increased. As a consequence, the affinity constants $K_A=k_{on}/k_{off}$ decreased by two orders of magnitude in going from a fully matched to a singly mismatched target sequence. This has been seen before with other interfacial architectures, e.g., based on biotinylated probe strands surface-immobilized via a streptavidin matrix [12]. Within the Langmuir adsorption model, these affinity constants and the resulting $K_A$ values can then be compared with those obtained by titration experiments. The corresponding series of kinetic titration recordings are documented in Figure 6. The data shown are the fluorescence intensities measured during the hybridization- and dissociation reactions between the capture PNA-probe P2-15mer DNA (T2-MM0/Cy5) hybridization reactions. The solid arrows indicate the injection of the target solution with a flow rate of 300 µL/min. The fluorescence was recorded until saturation was reached at each concentration. After the recording of the 1 nM and the 50 nM solution, respectively, the dissociation process was initiated by and monitored during rinsing the flow cell with pure buffer (open arrow).

Figure 6: Kinetic titration curves measured by SPFS for PNA (P2-15 mer)/DNA (T2-MM0/Cy5) hybridization reactions. The solid arrows indicate the injection of the target solution with a flow rate of 300 µL/min. The fluorescence was recorded until saturation was reached at each concentration. After the recording of the 1 nM and the 50 nM solution, respectively, the dissociation process was initiated by and monitored during rinsing the flow cell with pure buffer (open arrow).
results obtained by the kinetic analysis and confirm the applicability of the Langmuir model [12,13]. These values are also close to the results obtained by SPFS for an interfacial architecture in which the capture probe layer was surface attached via a biotin–moiety attaching the probe sequence to a streptavidin matrix [14].

The slight differences might indicate that details of the supramolecular interfacial architecture, indeed, influences the hybridization kinetics as well as the affinities through the influence of the matrix-dependent probe density which for a finite ionic strength leads to minor cross-talk between the hybridization events at different binding sites [15].

The most important finding, however, i.e., the discrimination between different mismatches – the detection of SNPs—does not depend on the supramolecular details of the binding matrix. One should keep in mind, however, that SPFS despite its enormous sensitivity and superb Limit of Detection (LOD) does require a chromophore label, at least for the monitoring of hybridization reaction in DNA sensing. In these cases the (sandwich) ELISA approach, i.e., the use of a capture molecule and a fluorophore–labeled detection molecule that sandwich the label-free analyte [16] typically is not an option. It has been demonstrated only in special cases of the detection of PCR amplicons in which surface binding by hybridization to the surface probe and the subsequent monitoring of the event by the decoration of the bound but unlabeled amplicon by a second chromophore-labeled short DNA stand was documented. Hence, a technique that is label free is highly desirable.

**Electronic Recording of Surface Hybridization Reactions**

A typical electronic signal obtained during the binding of T1-MM1 target strands to the OFET immobilized PNA capture probe P2-15mer is given in Figure 8. Shown is firstly the source-drain current, $I_{DS}$, as a short record of the baseline current while pure PBS buffer was running through the flow cell at an average flow rate of 300 μL/min. Upon the injection of a 1 μM buffer solution of the target strand the increase in $I_{DS}$ measured during 6 min nearly reached the saturation value and could be fitted by a single exponential increase, cf. the red curve in Figure 8, from which the electronic $k_{on}$ rate constant could be determined [5].

Upon switching back to pure buffer, cf. “PBS rinse” in Figure 8, the current returns to its original background value, here monitored for several minutes and again fitted by a single exponential (red curve) that yields the $k_{on}$ rate constant. It should be noted that the increase and decrease in $I_{DS}$ can be easily monitored with an excellent signal-to-noise ratio, originating from the fact that each and every single target strand binding to the (nominally) uncharged PNA matrix at the OFET gate surface introduces 15 negative charges from its phosphate groups to the interface. This leads to a rapidly increasing surface charge density which couples to the conducting channel of the transistor reversibly modifying (increasing and decreasing) the source-drain current. However, another factor that can affect the signal intensity is the mismatch in the target DNA; as the mismatch increases in base-pair, less or no change in current occurs [17].

If one performs kinetic titration experiments, i.e., if one monitors the current increase (or decrease) upon changing (increasing or decreasing) the bulk target concentration, $c_0$, of T2-MM0, until saturation at the new equilibrium current is reached one can analyze the kinetics by quantifying the association as well as the dissociation process as it is demonstrated in Figure 9A. Note that already at a bulk target concentration of $c_0=1$ nM a current increase with a very good signal-to-noise ration can be monitored. This is, however, not so surprising because for the expected affinity constant of $K_{d}=4 \cdot 10^8$ M$^{-1}$ a bulk concentration of 1 nM leads to a surface coverage at equilibrium $\theta=0.99$. However, another factor that can affect the signal intensity is the mismatch in the target DNA; as the mismatch increases in base-pair, less or no change in current occurs [15].

More surprising is the dissociation rate constant $k_{off}$ which decreases for increasing mismatch at least for the monitoring of hybridization reaction in DNA sensing.
of about 10% of the full coverage which can be easily detected by its influence on the source-drain-current. In fact, the current at 10 nM bulk concentration leads to an equilibrium current that is already above the 50% half-saturation level (Figure 9A).

If one plots the saturation currents in a linearized Langmuir isotherm, i.e., \( c_0/I_{DS} \) as a function of the bulk concentration, \( c_0 \), one obtains a linear fit line with the affinity constant as the fit parameter as demonstrated in Figure 9B. For this T2-MM0 hybridization reaction monitored label free by the OFET one obtains \( K_d = 8 \times 10^8 \text{ M}^{-1} \) in good agreement to the kinetic analysis and to earlier data reported for the biotin/streptavidin binding matrix by SPFS measurements [3].

Plotting again the saturation currents in % of the maximum change of the source-drain-current, \( \Delta I_{DS} \), taken as 100% coverage, as a function of the \((\log) \) bulk concentration, \( c_0 \), one obtains the well-known Langmuir adsorption isotherms. This is documented in Figure 10 for the T2-MM0 and the T1-MM1 hybridization reactions, respectively. Although the experimental error of the individual coverage determination is considerable the obtained half-saturation-concentrations correspond quite well to the ones obtained by the SPFS-optical determination (within a factor of 3).

Comparison between (Surface Plasmon) Optical and Electronic Monitoring of DNA Hybridization Events

A direct comparison of kinetic measurements recorded either electronically with the transistor sensor or optically by surface plasmon fluorescence spectroscopy is presented in Figure 11. The left panel (A) shows the association and dissociation kinetic traces for hybridization reactions between the surface probes and targets with MM0 (T2, black data), MM1 (T1, blue data), and MM2 (T3, orange data) injected as 100 nM solution (full arrow) after recording the baseline for several 10 secs.

After saturation was reached, switching to pure buffer running through the flow cell (“PBS rinse”, open arrows in Figure 11) induced the dissociation process. The full red curves are fits based on a Langmuir model for this surface reaction. The right panel (B) shows the identical experiment recorded with Cy5 labeled targets and monitored optically by SPFS. Again, the arrows indicate the injection of the target solutions and pure buffer, respectively, and the full red curves are Langmuir fits.

A first comparison indicates that both techniques allow for the monitoring of surface hybridization reactions, both are able to discriminate between targets with different degrees of mismatched sequences (SNPs detection), however, SPFS needs a label while the electronic detection does not. Slight differences in the relative signal amplitude probably reflect minor differences in the respective \( K_d \) values: the targets for the SPFS measurements are chromophore-labeled, the corresponding \( K_d \) values can be seen in Figure 7; targets for the OFET measurements are unlabeled, \( K_d \) values are shown in Figure 10.

An obvious difference of the two sets of data is the very different time scale for the association and dissociation kinetics, which results in a much shorter time needed to reach saturation in the case of OFET detection. A tentative explanation is the enormous charge density that builds up upon the association/binding of the analyte molecules to the interface, each bringing 15 net negative charges to the transistor surface. Further experiments, e.g., by means of (uncharged) PNA probe strands are under way to confirm this working hypothesis.
Another recent development that we should mention in this context is the use of reduced graphene oxide as the gate material for the construction of a FET device [18]. The high conductivity of the graphene allows for an unprotected exposure of the graphene and even of the two Au electrodes to the electrolyte solution if the device is operated as a biosensor in a flow cell: the current through the graphene channel is so much higher than that through the electrolyte as a “short-cut” which amounts to only 5-10% of the total current. The majority current through the graphene, however, is the one that is modified by the bio-recognition reaction between a receptor immobilized on the gate and the analyte molecule binding to it from solution [19].

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