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REVIEW

Analysis of the evolution of the detection limits of electrochemical DNA biosensors

Mathieu Lazerges · Fethi Bedioui

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Abstract In this paper we critically review detection limits of electrochemical DNA biosensors enabling DNA detection without target labelling. The review includes transduction principles and latest breakthroughs. To compare the efficiency of each type of electrochemical DNA biosensor, a simple DNA biosensors classification is established on the basis of the nature of the bio-electrochemical transduction.

Keywords Biosensor · DNA · Electrochemical · Label-free

Introduction

DNA biosensing is a major challenge in gene diagnosis. Electrochemical DNA biosensors designed during the last three decades have two major advantages over fluorimetric analysis—they are label-free and the transduction is more direct than for other techniques, because the biochemical process is transduced in an electrical response. The most severe limitation of electrochemical DNA biosensors is the detection limit, which is far below that of fluorimetric assays. Nevertheless, recent work focusing on enhancing the detection limit of electrochemical biosensors has reported analysis of DNA at femtomolar and attomolar levels. This review focuses on the evolution of label-free electrochemical biosensors comprising DNA or PNA (peptide nucleic acid) probes grafted on to a solid substrate and direct hybridization with an unlabelled DNA target, with electrochemical transduction during hybridization matched with, or without, a redox indicator. Biosensors using redox enzymes are not reported herein, because proteins are less resilient than chemical redox probes. The classification of biosensors presented herein is based on the nature of the bio-electrochemical transduction. Only biosensors involved in detection limit breakthroughs, with the two lowest detection limits obtained, are reported in the main text of the manuscript. The detection limits are estimated as the standard deviation, σ, of the blank: for most of the articles reviewed herein, the detection limit is reached when the signal is equal to 3σ. A full listing of biosensor detection limits is given in the electronic supplementary material.

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M. Lazerges (✉) · F. Bedioui (✉)
Unité de Pharmacologie Chimique et Génétique et Imagerie, Chimie ParisTech, Ecole Nationale Supérieure de Chimie de Paris, Paris, France
e-mail: mathieu.lazerges@parisdescartes.fr
e-mail: fethi-bedioui@chimie-paristech.fr

M. Lazerges · F. Bedioui
Unité de Pharmacologie Chimique et Génétique et Imagerie UMR 8151, CNRS, Paris, France

M. Lazerges · F. Bedioui
Unité de Pharmacologie Chimique et Génétique et Imagerie, Université Paris Descartes, Paris, France

M. Lazerges · F. Bedioui
Unité de Pharmacologie Chimique et Génétique et Imagerie (N° 1022), INSERM, Paris, France

Biosensors based on direct DNA oxidation

Direct electrochemical oxidation of guanine can be used to prepare DNA biosensors [1–10], because the faradic charge required for guanine oxidation is higher after hybridization. These biosensors are classically prepared by electrochemical adsorption of the DNA probe (i.e. stripping) on to electrode surface. Such biosensors can be prepared with

Table 1 Evolution of the detection limit of DNA oxidation-based biosensors. Breakthroughs are indicated with bold characters and the two lowest detection limits are indicated with italic characters (φ = diameter; A = area)

Technique	Electrode (size)	Immobilization	Probe and target	Detection limit (mismatch detection)	Year and Ref.
Differential pulse voltammetry	Carbon paste (φ=3.5 mm)	Stripping	20 b poly(G) 20 b poly(C)	**10^{-6} molL^{-1}**	1997 [1]
Differential pulse voltammetry	Carbon paste (φ=3.5 mm)	Stripping	Inosine-substituted 29 b DNA 29 b DNA	**10^{-8} molL^{-1}**	1998 [2]
Differential pulse voltammetry	Carbon paste (φ=3 mm)	Stripping	23 b DNA 23 b DNA	**3×10^{-9} molL^{-1}** (single mismatch)	2002 [4]
Differential pulse voltammetry	Carbon paste (φ=5 mm)	Stripping	20 b DNA 20 b DNA	**5×10^{-10} molL^{-1}** (single mismatch)	2005 [6]
Differential pulse voltammetry	Platinum polypyrrole polyvinyl sulfonate (A=0.03 cm^2)	Covalent	30 b poly(C) 30 b poly(G)	***10^{-17} molL^{-1}***	2007 [8]
Differential pulse voltammetry	Graphite pencil (φ=2 mm)	Stripping	20 b DNA probe fragmentized genomic DNA	***10^{-15} molL^{-1}***	2011 [10]

inosine-substituted guanine-free probes to silence the probe signal. A 10^{-6}molL^{-1} detection limit was reported in 1997 for a strip-based biosensor [1]: DNA probes were adsorbed on carbon paste by application of 0.5 V vs Ag/AgCl. Later, from 1998 to 2005, similar designs involving stripping on carbon paste electrodes enabled detection limits as low as 10^{-8}molL^{-1}, 3×10^{-9}molL^{-1}, and 5×10^{-10}molL^{-1} to be obtained [2, 4, 6]. A biosensor designed by grafting a DNA probe on to a conducting polymer surface with a detection limit of 10^{-17}molL^{-1} was reported few years later [8]. Evolution of the detection limits of this type of biosensor is summarized in Table 1.

Ten biosensors reported in this review are based on this technology, and only two have a detection limit in the femto and attomolar range [8, 10]. It is interesting to note that these two sensitive devices are not based on carbon-paste electrodes. The 10^{-17}molL^{-1} detection limit was achieved for a polydeoxycytidine target, which is not a classic target [8]. The 10^{-15}molL^{-1} detection limit was reached for a genomic DNA target [10]. Such a large target enhances the signal because oxidation charge depends directly on the number of target bases. The lowest detection limits enabling single mismatch detection for this kind of biosensor is within the nanomolar range [4, 6]. It should also be noted that these biosensors cannot be regenerated to perform further hybridization, because oxidation of the probe guanine bases is irreversible.

Non-faradic biosensors

When a solid electrode is immersed in an electrolyte, diffusion of charge occurs in a layer in the vicinity of the interface, leading to formation of a capacitor. Interfacial models, taking into account electrostatic interactions and charge diffusion effects, enable calculation of the electric potential within the length of the layer on the electrode side (space charge layer) and on the electrolyte side (electrolyte double layer), and therefore the capacitance. For a metallic electrode, the capacitance is located in the double layer (l_{dl}), where potential variation occurs (Fig. 1a). In contrast, for a semi-conductor electrode, the capacitance is located in the space charge layer (l_{sc}) (Fig. 1b). The charges of the charge layer and the double layer are opposite, because of charge conservation, meaning that modification of the double layer after the adsorption process results in modification of the space charge, and thus to the creation of interfacial capacitance.

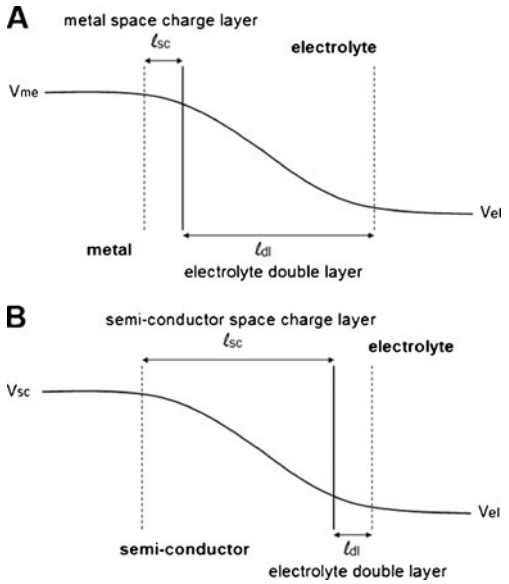

Fig. 1 Electrode–electrolyte space-charge layer for a metal (**A**) and a semiconductor (**B**)

Table 2 Evolution of the detection limit of non-faradaic DNA biosensors. Breakthroughs are indicated with bold characters and the two lowest detection limits are indicated with italic characters (*A* = area)

Technique	Electrode (size)	Immobilization	Probe and target	Detection limit (mismatch discrimination)	Year and Ref.
Impedance	Si_3N_4 (A=0.05 cm^2)	Covalent	30 b poly(C) 30 b poly(G)	**10^{-10} molL^{-1}**	2000 [11]
Impedance	Polyethylenimine screen-printed (A=3 mm^2)	Electrostatic	Insert PCR DNA amplicon complementary insert PCR DNA	**5×10^{-17} molL^{-1}**	2007 [18]
Impedance	Boron-doped diamond-coated with polyethylenimine	Electrostatic	30 b DNA 30 b DNA	***10^{-20} molL^{-1}*** (single mismatch)	2009 [30]
Impedance	GaN nanowire	Covalent	15 b DNA 15 b DNA	*10^{-19} molL^{-1}* (single mismatch)	2011 [33]

The interface charge density changes during hybridization on to the surface of a biosensor, because of the increased concentration of negatively charged DNA target and sodium counter ions within the double layer. This leads to variation of the interfacial capacitance. Elsewhere, the surface shielding effect of the DNA layer after hybridization leads to an increase of the charge-transfer resistance of the interface. Electrochemical impedance measurements are classically used to monitor both capacitance and resistance changes. The major advantage of impedance analysis over voltamperometric techniques is accurate monitoring of DNA hybridization by measurement of the double layer interfacial capacitance. If no faradic reaction occurs, the equivalent electrical circuit of the electrochemical cell consists of serial resistance and capacitance. The order of magnitude of the resonance frequency can be deduced from RC, where R is the electrolyte resistance and C the interfacial capacitance. For classical hybridization conditions (0.5 molL^{-1} NaCl; 10^3 Ω m), metallic electrodes (50 μF m^{-2}), and classical electrochemical cells (1 cm between working and counter electrode), the RC time constant is in the ms range, corresponding to a 1 kHz frequency range. Single frequency impedance measurements in this frequency range enable monitoring of DNA hybridization, but a preliminary study of impedance response over a large range of frequency enables choice of the optimum frequency for optimization of signal response. The 25 non-faradic DNA biosensors reviewed herein show that this approach enables DNA detection in a large concentration range, from 10^{-4} to 10^{-20} molL^{-1} [11–35]. A 10^{-10} mol L^{-1} detection limit was reached with a DNA biosensor comprising 30-base poly(C) (polycytosine) probes grafted on to the surface of a silicon device [11]. A 5×10^{-17} molL^{-1} detection limit has been reported for a biosensor based on electrostatic immobilization of DNA probes in a polymer layer including positive charges [18]. A 10^{-20} molL^{-1} detection limit with a similar biosensor design was reported two years later [30]. Detection limit evolution of non-faradic biosensors is summarized in Table 2.

It is interesting to point out that electrochemical impedance can increase or decrease after hybridization, depending on the interface structure. Two designs of biosensors enable a detection limit in the attomolar range to be obtained for a biosensor designed by electrostatic immobilization of DNA probes on to a polyethylene imine positively charged surface [18, 30] and for a biosensor designed using a nanowire semi-conducting electrode [33]. The change of the relative capacitance after to hybridization (negative charge), which is more important for a biolayer with a positive charge than for a biolayer with a negative charge, explains the low detection limit obtained with the polyethylene imine-based biosensors [18, 30]. Use of semiconductors is also of interest [30, 33], because variation of the potential is more important (Fig. 1a) than for metal (Fig. 1a). Indeed, the interfacial mirror charge effect induces an important change of the potential of the charge layer located on the semiconductor, and thus to an important change of capacitance. Both effects explain why there is a detection limit gap of three decades between these three biosensors [18, 30, 33] and the other twenty. Regeneration of the biosensors based on this principle is possible.

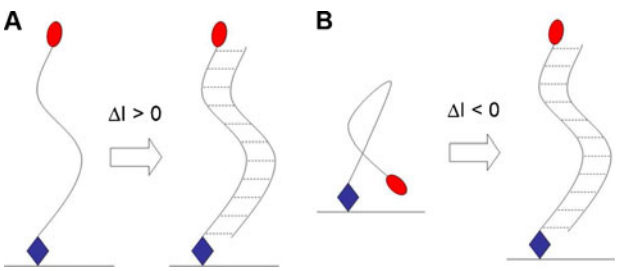

Fig. 2 Biosensors based on redox probe labelling with a classic probe (**A**) and an hairpin probe (**B**). *Blue*, anchoring group; *red*, electroactive group

Table 3 Evolution of the detection limit of redox probe-labelled DNA biosensors. Breakthroughs are indicated with bold characters and the two lowest detection limits are indicated with italic characters (φ = diameter)

Technique	Electrode (size)	Immobilization	Probe and target	Detection limit (mismatch detection)	Year and Ref.
Cyclic voltammetry	Gold (φ=1.6 mm)	Chemical adsorption	28 b hairpin DNA 27 b DNA	**10^{-8}molL^{-1}** (single mismatch)	2003 [36]
Cyclic voltammetry	Gold (φ=1 mm)	Chemical adsorption	44 b hairpin DNA 20 b DNA	***10^{-13}molL^{-1}***	2006 [38]
Differential pulse voltammetry	Gold (φ=0.2 mm)	Chemical adsorption	27 b hairpin DNA 27 b DNA	***10^{-9}molL^{-1}*** (single mismatch)	2011 [42]

Biosensors based on redox probe labelling

Two kinds of biosensor are based on redox probe labelling. A classical DNA probe (Fig. 2a) is labelled with a grafting group (blue) and a redox probe (red). The redox current of the probe increases after hybridization because the DNA duplex is able to enhance long range electron transfer from the redox probe to the electrode, because of base π-stacking in a DNA duplex. For a hairpin probe (Fig. 2b), the redox group is in the vicinity of the electrode for the non-hybridized probe. Indeed, redox current decreases after hybridization as transfer electron distance between the redox group and the surface increases.

The seven DNA biosensors based on probe labelling and reviewed herein enable DNA detection limits in the nano to the picomolar range [36–42] (Table 3). A 10^{-8} molL^{-1} detection limit has been reported for biosensors comprising a 28-base hairpin DNA probe monolayer chemically adsorbed on to a gold surface [36]. A 10^{-13}mol L^{-1} detection limit was achieved a few years later by use of a similar procedure [38].

Few biosensors using this transduction principle have a detection limit in the picomolar range (which is high by comparison with other techniques). The lowest detection limits are obtained for DNA biosensors using hairpin DNA probes [38, 42]. This high detection limit is because of the feeble redox faradic charge of the labelled probe. Indeed, this charge is feeble by comparison with guanine oxidation-based biosensors, because each DNA target includes several guanine bases, and more feeble than the redox charge involved in charge-transfer-based biosensors, because the amount of redox probe in bulk solution is very high by comparison with the amount adsorbed. No micro or nanodevices have been developed, because the signal will drastically decrease with decreasing surface area, because the amount of redox probe depends directly on electrode surface area. Regeneration is possible with these biosensors.

Biosensors based on long-range electron transfer toward a redox indicator

The principle of this type of DNA biosensor is based on use of the redox signal of an electroactive compound via long-range electron transfer through double-stranded DNA resulting from π-stacking of bases along the double helix. Three kinds of DNA biosensor use this phenomenon. The simplest is the direct redox signal of an intercalated electroactive compound (Fig. 3a). The second kind is based on the redox signal of an electroactive compound diffusing in solution via long-range electron transfer along double-stranded DNA (Fig. 3b). The last type is a combination of the two: the redox signal of an electroactive compound diffusing in solution is catalyzed by an intercalated electroactive compound which enhances long-range electron transfer via double-stranded DNA (Fig. 3c).

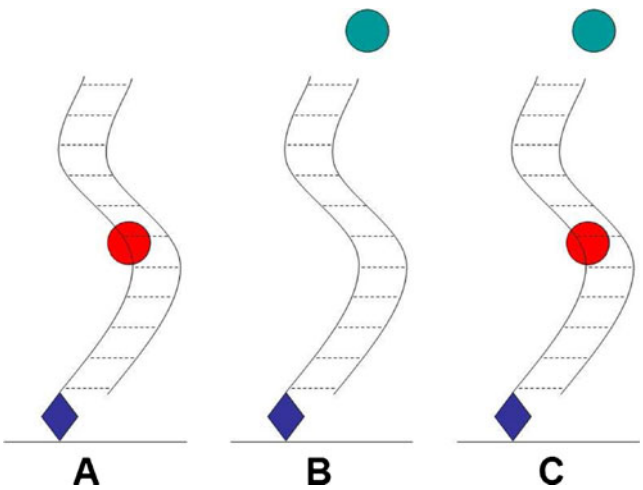

Fig. 3 DNA biosensors involving long-range electron transfer via double-stranded DNA. (**A**) Intercalated electroactive compound. (**B**) Electoactive compound diffusing in solution. (**C**) Electroactive compound diffusing in solution and redox signal catalyzed by intercalated electroactive compound. *Blue*, anchoring group; *red*, intercalated electroactive compound; *blue–green*, electroactive compound diffusing in solution

Table 4 Evolution of the detection limit of long-range electron-transfer-based DNA biosensors. Breakthroughs are indicated with bold characters and the two lowest detection limits are indicated with italic characters (φ = diameter)

Technique	Electrode (size)	Immobilization	Probe and target	Detection limit (mismatch detection)	Year and Ref.
Cyclic voltammetry	Glassy carbon	Covalent	20 b poly(T) 20 b poly(A)	$\mathbf{2\times10^{-4}molL^{-1}}$	1993 [43]
Cyclic voltammetry	Gold	Covalent	20 b DNA 20 b DNA	$\mathbf{2\times10^{-13}molL^{-1}}$	1994 [44]
Cyclic voltammetry	Gold (φ=1.6 mm)	Covalent	20 b DNA 20 b DNA	$\mathbf{2\times10^{-14}molL^{-1}}$ (single mismatch)	2002 [55]
Differential pulse voltammetry	Nano-structured conducting polymer	Covalent	21 b DNA 21 b DNA	$\boldsymbol{10^{-15}molL^{-1}}$ (single mismatch)	2007 [77]
Linear sweep voltammetry	Gold microband structure	Covalent	21 b DNA 18 b poly(T) mRNA	$\boldsymbol{10^{-16}molL^{-1}}$ (single mismatch)	2010 [106]

DNA-biosensors based on long-range electron transfer are numerous; approximately 100 examples are cited herein [43–133]. They enable detection of DNA in the micro to femtomolar range (Table 4). In 1993 a $2\times10^{-4}molL^{-1}$ detection limit was reported for a biosensor designed by grafting a DNA probe on to a glassy carbon electrode [43]. A detection limit of $2\times10^{-13}molL^{-1}$ was achieved one year later by grafting a DNA probe on to a gold substrate [44] and a $2\times10^{-14}molL^{-1}$ detection limit was achieved with a similar set up approximately ten years later [55]. A $10^{-15}molL^{-1}$ detection limit was achieved five years ago by use of a nano-structured conducting polymer electrode to increase the roughness of the biosensitive surface [77]. A $10^{-16}molL^{-1}$ detection limit for messenger RNA (mRNA), by use of nano-gap architecture, was recently reported [106]: RNA messenger was hybridized on both extremities by use of two different probes separated by a nano-gap. Hybridization enables measurement of current flow across the nano-gap, resulting in a very low detection limit.

Recent designs of biosensor based on nanostructured materials enable detection limits in the femtomolar range to be achieved. Mismatch discrimination is easy using this class of biosensor. Indeed, π-stacking of DNA bases along the helix is breaks in a mismatching duplex, resulting in a decrease of long-range electron transfer efficiency (i.e. redox current decrease). It is important to note that this effect do not depend on temperature, enabling mismatch detection at temperatures below the duplex fusion temperature. Biosensor regeneration is possible in this case.

Biosensors based on conducting polymers

Organic conducting polymers can be reversibly oxidized and each polymer has specific electrochemical behaviour depending mainly on its chemical structure. for polypyrole, reversible oxidation to a bipolaron (i.e. di-cation charge carrier) occurs as relatively low potentials (Fig. 4).

DNA probes can be grafted (i.e. covalent bonding) or doped (i.e. non-covalent bonding) on to organic conducting polymers and the faradic charge required to switch from the reduced to oxidized state is modified during hybridization, enabling DNA detection, as depicted in Fig. 4 for polypyrrole. The hybridization signal is based on measurement of the faradic charge difference before (Q_0) and after (Q_1) hybridization. It is important to point out that some DNA biosensors are designed by using a conducting polymer as immobilizing layer for the DNA probes, but these use another kind of electrochemical transduction. These latter

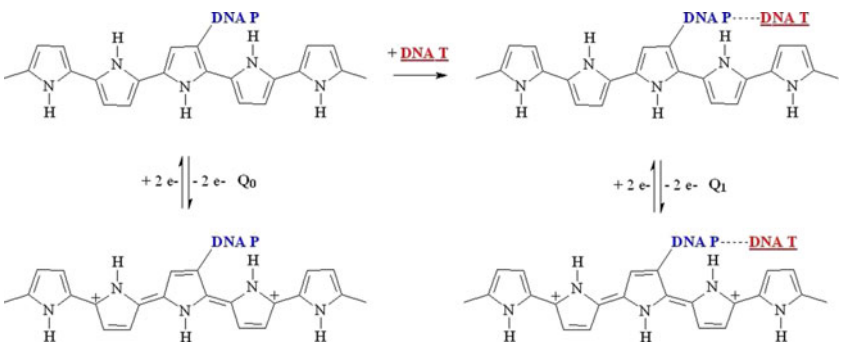

Fig. 4 Reversible oxidation of polypyrrole labelled with a DNA probe, *P*, before (charge Q_0) and after (charge Q_1) hybridization with a DNA-target, *T*

Table 5 Evolution of the detection limit of conducting polymer-based DNA biosensors. Breakthroughs are indicated with bold characters and the two lowest detection limits are indicated with italic characters (φ = diameter; A = area)

Technique	Electrode (size)	Immobilization	Probe and target	Detection limit (mismatch detection)	Year and Ref.
Cyclic voltammetry	Platinum polypyrrole (A=0.7 cm^2)	Covalent	25 b DNA 25 b DNA	**2×10^{-9} molL^{-1}**	1997 [134]
Cyclic voltammetry	Platinum polypyrrole (A=0.7 cm^2)	Covalent	25 b DNA 25 b DNA	**2×10^{-12} molL^{-1}**	2002 [138]
Cyclic voltammetry	Gold polypyrrole (φ=25 μm)	Electrostatic	27 b DNA 27 b DNA	***2×10^{-16} molL^{-1}*** (single mismatch)	2006 [145]
Cyclic voltammetry	Platinum polypyrrole (φ=10 μm)	Electrostatic	18 b DNA 244 b DNA PCR amplicon	***2×10^{-21} molL^{-1}*** (single mismatch)	2008 [153]

biosensors are not classified in this section but in the one relevant to the nature of transduction—direct DNA oxidation [8] or long-range electron transfer [77]. A classical conducting polymer results in a decrease of the switch faradic charge after hybridization. The 17 DNA-biosensors based on this technology reported herein enable micro to zetto (10^{-21}) molar detection limits to be obtained [134–163] (Table 5). A 2×10^{-9}molL^{-1} detection limit was first reported in 1997 for a DNA biosensor based on covalent immobilization of a DNA probe on a polypyrrole film [134]. A similar biosensor design yielded to 2×10^{-12}molL^{-1} detection limit a few years later [138]. More sensitive DNA biosensors based on conducting polymer technology have been prepared by electrostatic DNA probe immobilization on to a polypyrrole microelectrode, yielding a 2×10^{-16}molL^{-1} detection limit for a 27-base DNA-target [145] and 2×10^{-21}molL^{-1} for a 244-base PCR amplicon DNA [153].

As was reported for DNA biosensors based on long-range electron transfer, the detection limit is enhanced when micro-devices are used. Regeneration is possible for these biosensors. It is interesting to note that use of polypyrrole material was a breakthrough enabling manufacture of DNA biosensors with the lowest detection limits. This material is convenient for design of biosensors; it enables use of chemical groups to graft DNA probes in the β position of the pyrrole ring [134, 138]. Moreover, the positive charge of the polypyrrole network enables direct electrostatic immobilization of DNA probes [145, 153]. It is interesting to note that the low detection limits of non-faradic biosensors designed using polyethylenimine (10^{-19} and 10^{-20}molL^{-1}) [30, 33] are in the same range as detection limits of the two biosensors designed with polypyrrole (10^{-16} and 10^{-21}molL^{-1}) [145, 153]. In the non-faradic biosensor the charge is capacitive. In the conducting polymer, although the charge is faradic, because the polypyrrole chain

Table 6 Evolution of the detection of limit of faradic resistance variation-based DNA biosensors. Breakthroughs are indicated with bold characters and the two lowest detection limits are indicated with italic characters (φ = diameter)

Technique	Electrode (size)	Immobilization	Probe and target	Detection limit (mismatch detection)	Year and ref.
Differential pulse voltammetry	Carbon paste (φ=3 mm)	Stripping	21 b DNA 21 b DNA	**2×10^{-9} molL^{-1}** (single mismatch)	2000 [164]
Differential pulse voltammetry	Carbon paste (φ=3 mm)	Stripping	24 b DNA 595 b DNA PCR amplicon	**10^{-9} molL^{-1}**	2002 [165]
Differential pulse voltammetry	ZrO_2 (φ=3 mm)	Chemical adsorption	24 b DNA 24 b DNA	**10^{-10} molL^{-1}**	2004 [167]
Differential pulse voltammetry	Polyaniline nanowire	Covalent	24 b DNA 24 b DNA	**10^{-12} molL^{-1}** (3-base mismatch)	2006 [170]
Differential pulse voltammetry	Poly-calcon carboxylic acid (φ=3 mm)	Covalent	18 b DNA 18 b DNA	**7×10^{-13} molL^{-1}** (single mismatch)	2009 [181]
Differential pulse voltammetry	Nanostructured polyeriochrome black T (φ=3 mm)	Covalent	26 b hairpin DNA 18 b DNA	***10^{-13} molL^{-1}*** (single mismatch)	2010 [184]
Differential pulse voltammetry	Nanostructured chitosan–CeO_2–ZrO_2	Chemical adsorption	20 b DNA 20 b DNA	*10^{-13} molL^{-1}* (3-base mismatch)	2012 [192]

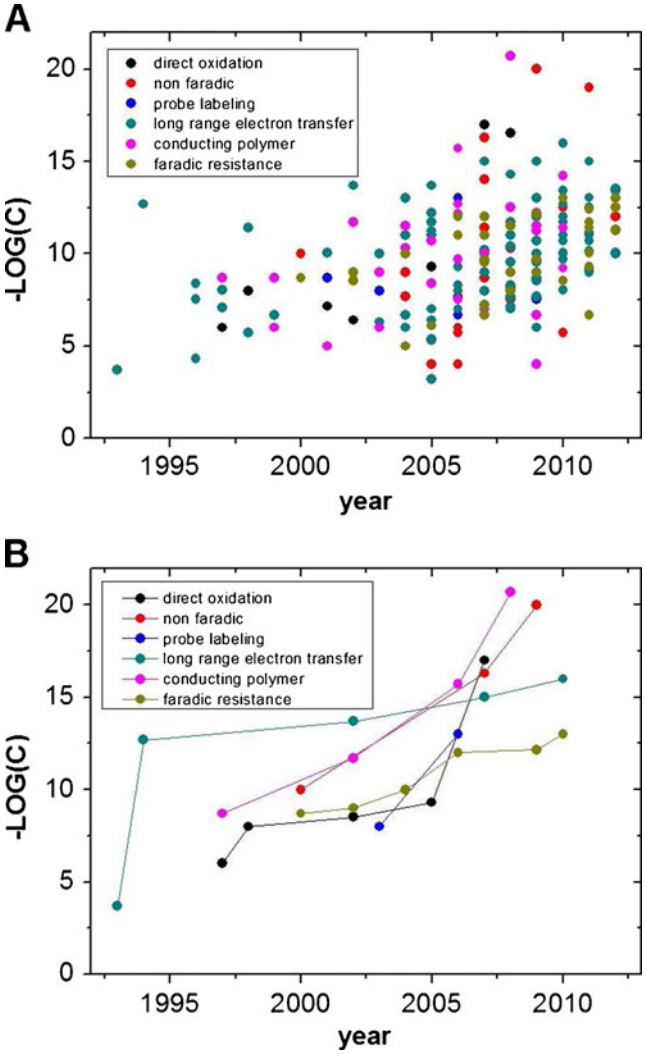

Fig. 5 **A**. Overall evolution of the detection limit of DNA biosensors based on different technology during the last three decades. **B**. General evolution type by type

is reversibly oxidized, there is large component of capacitive charge, as can be observed from the, mainly imaginary, impedance behaviour of the conducting polymer. Thus it can be stated that DNA hybridization transduction using polyethylenimine and conducting polymer is similar and both enable low detection limits.

Biosensors based on variation of faradic resistance

The method of transduction of these biosensors is based on a decrease of the faradic redox current of an electroactive compound after hybridization. Methylene blue is currently used for this purpose because it has greater affinity for single-stranded DNA than double-stranded DNA. Thirty-two DNA-biosensors using such detection scheme are reported herein, and enable detection limits that vary from micro to picomolar [164–195]. A biosensor designed by stripping DNA probes on to carbon paste electrode achieved a 10^{-5}molL^{-1} detection limit in 2000 [164] and a 10^{-9}molL^{-1} detection limit two years later. Further progress has been achieved by using coated millimetric electrodes: detection limits for ZrO_2 [167], polyaniline [170], polycalcon carboxylic acid [181], polyeriochrome black T [184], and chitosan–CeO_2–ZrO_2 [192] are, respectively, 10^{-10}, 10^{-12}, 7×10^{-13}, 10^{-13}, and 10^{-13}molL^{-1}.

The detection limit of these biosensors is within the picomolar range and it is high compared with other biosensors. It is interesting to point out that biosensors based on increasing the faradic current of a solvated redox probe (charge-transfer biosensors) have lower detection limits than biosensors based on reducing the faradic current. No micro or nanometric devices have been prepared by variation of faradic resistance (Table 6), meaning that the detection limit may be improved for this type of biosensor. Regeneration of this type of biosensor is also possible.

Overall DNA-biosensor detection limit evolution

This review on direct DNA detection with electrochemical biosensors, without target labelling and without using enzymes, gives insight into modern technology available for gene diagnosis. The general evolution of the detection limit of DNA-biosensors over the past three decades is presented in Figs. 5a (overall) and 5b (evolution).

This overall evolution shows that a major breakthrough was achieved in DNA biosensing during the three last decades by use of electrochemical devices. DNA biosensors based on probe labelling with a redox probe and on increasing faradic resistance do not enable high sensitivity, in the nanomolar range, because of the feeble hybridization transduction signal. Biosensors based on guanine oxidation enable detection in the femtomolar range but regeneration of the biosensor is not possible. Biosensors based on long-range electron transfer enable detection in the femtomolar range. Biosensors based on non-faradic measurement and use of conducting polymers, involving both capacitive and redox processes, enable detection in the femto to attomolar range.

Conclusion

It should be noted that the detection limits of the numerous biosensors reported herein were investigated under ideal hybridization conditions, and numerous DNA biosensor targets are oligonucleotide or PCR amplicons. As detection

limit requirements seem to be fulfilled, it will be interesting in a near future to evaluate these biosensors for the detection in biological matrix, to challenge fluorimetric assays.

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