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Metal-responsive interdigitated bilayer for selective quantification of mercury(II) traces by surface plasmon resonance

Elizaveta Ermakova,^a Oleg Raitman,^a Alexander Shokurov,^a Maria Kalinina,^a Sofiya Selector,^a Aslan Tsivadze,^a Vladimir Arslanov,^{*a} Michel Meyer,^b Alla Bessmertnykh-Lemeune,^{*b} Roger Guillard^b

Reusable surface plasmon resonance chips allowing the quantitative and selective detection of mercury(II) ions in water at the 0.01 nM level is reported. The surface-modified gold sensor consists of a rarefied self-assembled monolayer of octanethiol topped by a Langmuir-Blodgett monolayer of an amphiphilic and highly-specific chelator. The interdigitated architecture confers to the bilayer a high packing density, surface coverage, and binding-group accessibility.

Intensive research activities are currently devoted to the development of sensitive and selective sensors for toxic metal ions owing to the essential impact of these species on the environment and human health. Among them, mercury is one of the main targets considering its rapid bioaccumulation and high neurotoxicity. Accordingly, the maximal allowed concentration in drinking water is 10 nM.¹ Although a plethora of colorimetric and fluorescent chemosensors for Hg²⁺ are currently available,² efficient, cost-effective, and rapidly-responding solid-state sensors operating at sub-micromolar concentration levels are still rare.³

Sensors based on the surface plasmon resonance (SPR) effect are particularly attractive because of their ultra-high sensitivity with detection limits in the nanomolar range. The signal transduction mechanism based on the change of the refractive index is therefore one of the most effective for investigating the interactions between

a receptor (ligand) deposited as a film on a metallic surface and an analyte (substrate) injected into the contact solution.⁴ Besides, SPR detectors possess many other advantages, such as the absence of any label, the compatibility with aqueous media, the possibility to miniaturize the sensing device and to equip it with other analytical probes (e.g. fiber optics,⁵ electrochemical setup,⁶ or amplifying effect of gold nanoparticles).⁷ Moreover, it is a quantitative method despite the extremely small amount of materials (sensitive layer and analyte) required for the analysis. It is also worth to mention that SPR devices can be fitted with a microflow cell. In the continuous flow mode, the concentration of the analyte during the measurement remains constant, which is of particular interest from both a practical and theoretical point of view.

The design of selective SPR devices relies on the adequate functionalization of a gold layer, a task that can be easily achieved by attaching specific receptors endowed with a high affinity and selectivity for the targeted analyte. As host-guest recognition processes are ubiquitous in life-sciences (base-pairing, antibody-antigen interactions etc.), it is not wondering that SPR sensors have been applied overwhelmingly for monitoring the interactions between biological substrates (proteins, enzymes, nucleic acids etc.).^{4a,8} Works on the detection of metal ions in aqueous media are more seldom and challenging. These SPR sensors often obtained by covering the gold surface with a layer of polymer incorporating molecular receptors (ligand or biomolecules) adapted to the target.¹³ Likewise, gold-coated electrodes are commonly used in the most popular electrochemical detection of mercury.⁹¹⁰¹¹ However, the efficiency of both types of detectors is limited by the slow diffusion of the analyte into the polymeric matrix and the restricted accessibility of the recognition sites. Additional issues might be low film adhesion, high film resistivity, and low chemical stability especially in case of biomolecules.

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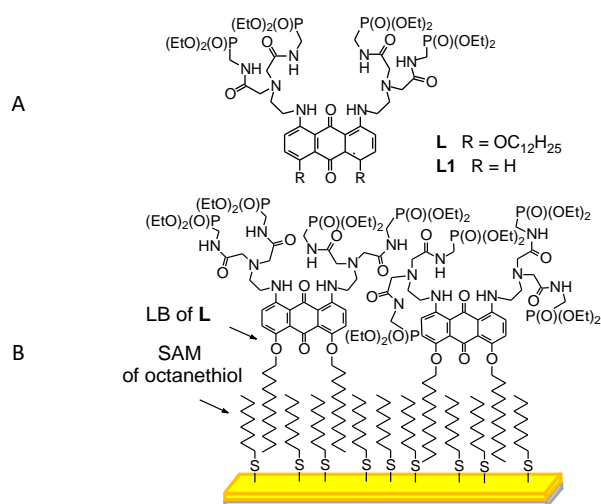


Figure 1. Structure of chemosensors L and L1 based on the 1,8-diaminoanthraquinone chromophore (A). Schematic representation of the interdigitated Au/SAM/LB(L) bilayer architecture (B).

In that respect, deposition of self-assembled monolayers (SAM) is emerging as a promising alternative.^{13b,14} Covalently-bonded SAMs incorporating molecular receptors or appropriate biomolecules located close to the interface and in proximity of the gold layer give rise to stable and selective responses upon analyte binding. However, the design of such films is challenging and major improvements are still sought to overcome the limitations intrinsic to SPR technology. Among them, the most important ones are (i) the low chemical stability of self-assembled monolayers (SAM) (cf. oxidation of thiol groups) and (ii) the non-selective interaction with impurities or analytes diffusing directly to the gold substrate as a consequence of the incomplete coverage of the surface¹⁵ that leads to the presence of defects (pinholes) in the SAM.^{14f,16} In addition, thiolated chelators inevitably contain, unlike alkythiols, bulky functional groups which might perturb the alignment of the molecular chains, a prerequisite for achieving a highly-ordered coverage of the surface.^{16a,17}

Beside SAMs, Langmuir-Blodgett (LB) films can also be used as SPR sensors. However, multilayer LB films of voluminous or branched amphiphilic chelators exhibit usually a lower stability as they are washed away from the gold surface in the course of the analysis.¹⁸ LB monolayers can be used instead, provided that they remain firmly fixed onto the solid support and that the ligand bears hydrophilic binding sites pointing away from the surface in direction to the analyzed solution. However, stable LB monolayers can only be obtained by the "bottom up" methodology, which supposes that some functional groups from the chelator are oriented towards the surface interacting with the gold atoms and are no longer available for metal binding, thus lowering the uptake efficiency.

Herein, an alternative approach for constructing the sensing film on the gold surface is described. We demonstrate that the immobilization of the chemosensor by combining both SAM and LB techniques¹⁹ affords sensitive and selective metal-responsive SPR chips with enhanced stability and uniform orientation of the binding units towards the solution. This bilayer methodology is applied for the direct quantification of Hg²⁺ cations at the trace level (ppt to ppb). To that aim, an interdigitated bilayer is constructed stepwise on a gold substrate by self-assembling first octanethiol into a

rarefied monolayer.¹⁹ Next, a second monolayer consisting of the amphiphilic and highly mercury-selective ligand L (Fig. 1A, B),²⁰ is deposited on the top of the SAM by means of the LB technique. The resulting interpenetrated architecture of the SAM/LB bilayer film differs from that of lipid membrane bilayers or Y-type multilayers (LB films and SAM/LB-films). Indeed, in the three latter cases the films consist of closely-packed hydrocarbon chains, but hydrophobic interactions between adjacent monolayers cannot provide the same high level of interlayer adhesion as the second LB-layer tends to be anchored on the first one by hydrogen bonds or electrostatic interactions.²¹ In our approach, the weak van-der-Waals interactions between the hydrocarbon chains of the adjacent layers compete with the Au–S bonds. As a consequence, the alkanethiol molecules move laterally over the surface,^{3b} producing a beneficial reduction of pinholes in the film.

As a proof of concept, we report hereafter on the elaboration of a highly-sensitive and selective, but also reusable, mercury(II) sensor with a quantification limit close to 10⁻¹¹ M in aqueous media and a linear response spanning up to 5 orders of magnitude. Our rational design of the SPR chip rests on the use of the amphiphilic chemosensor L derived from 1,8-diamino-9,10-anthraquinone (Fig. 1A) as the solution-exposed component of the rarefied SAM/LB bilayer architecture. The choice of the chelator is based on the following criteria. We have recently shown that polyamino-9,10-anthraquinones endowed with diethoxyphosphoryl-substituted carbamoyl fragments allow for cheap, fast, sensitive, and highly selective colorimetric detection of various metal ions in aqueous solutions at the ppm levels.^{20,22} High affinity and selectivity towards Hg²⁺ was found for chemosensor L and its water-soluble analogue L1 that lacks the lipophilic alkoxy substituents (Fig. 1A). Spectrophotometric, pH-metric, and NMR studies evidenced both the formation of mono- and dinuclear [Hg(L1)] (log K₁₁ = 5.3) and [Hg₂(L1)] complexes (log K₂₁ = 4.0) and the involvement of the aminoanthraquinoyl moiety in the Hg²⁺ binding scheme.²⁰ High-resolution ESI-MS measurements in methanol/water mixtures confirmed the [Hg(L1)] and [Hg₂(L1)] stoichiometries deduced from UV-vis titrations. Structural information on these species was tentatively gained by ¹H and ³¹P NMR spectroscopy in D₂O.²⁰ Accordingly, the tertiary amines, one anthraquinone oxygen atom, the carbamoyl, and phosphoryl groups are most likely involved in coordination, in such a way that each polyamine branch binds a single metal ion. However, in the absence of a crystal structure, the exact binding mode of the amide moieties (Hg–O or Hg–N coordination) cannot be definitively ascertained. Ligation of the deprotonated amidic nitrogen atoms, as described for mercury complexes formed with cyclic amides,²³ would result in stable 5-membered cycles and seems the most probable coordination mode in agreement with the pH-metric studies.

Noteworthy, chemosensor L retains its high affinity and selectivity towards Hg²⁺ once incorporated in a Langmuir monolayer or LB multilayers.²⁴ Moreover, the strongly light-absorbing anthraquinone scaffold of L might also contribute to increase the sensitivity of the SPR system.²⁵

Bilayer films were prepared on freshly cleaned gold-coated glass slides by formation of an octanethiol SAM followed by the deposition of a monolayer of L by the vertical top-down LB method (ESI†). After each deposition step, the films were characterized by

cyclic voltammetry (CV), electrochemical impedance spectroscopy (EIS), and contact angle (θ) measurements.

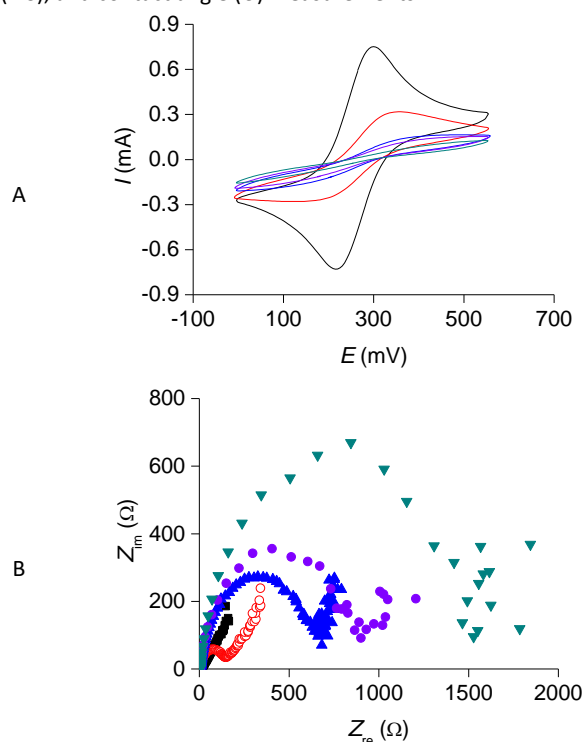


Figure 2. Characterization of Au/SAM/L bilayer by EIS. Cyclic voltammograms (A) and Nyquist plots (B) of the $[\text{Fe}(\text{CN})_6]^{3-}/[\text{Fe}(\text{CN})_6]^{4-}$ redox couple (1 mM each in 0.5 M KCl) recorded for a bare gold surface (black), octanethiol Au/SAM (2 min exposure in 1 mM ethanol solution of octanethiol; red), Au/SAM/LB(L) (blue), and Au/SAM/LB(C) electrodes (3 min exposure of Au/SAM/LB(L) to 10^{-11} M (violet) and 10^{-6} M (green) aqueous solution of $\text{Hg}(\text{ClO}_4)_2$).

Cyclic voltammograms obtained for the $[\text{Fe}(\text{CN})_6]^{3-}/[\text{Fe}(\text{CN})_6]^{4-}$ redox couple (Fig. 2A, Fig. S2 ESI[†]) at bare (Au) and modified electrodes (Au/SAM and Au/SAM/LB(L)) are shown in Fig. 2A. Upon covering the pure gold surface by a SAM of octanethiol, a significant decrease of the current together with a concomitant increase of the anodic and cathodic peak separation point out the existence of an array of pinhole defects in the microelectrode assembly.²⁶ For the Au/SAM/LB(L) electrode, only the non-faradic current is observed, indicating the formation of a compact and robust interdigitated bilayer (Fig. 2A, Fig. S2, ESI[†]). After its exposure to an aqueous 10^{-11} M and 10^{-6} M $\text{Hg}(\text{ClO}_4)_2$ solution, an additional decrease of the current intensity was observed, reflecting an even more regular and dense coverage of the metallic conductor by the insulating bilayer. It can be concluded that the lower current is a direct consequence of the structural changes undergone by the flexible receptor upon Hg^{2+} binding. Becoming more rigid, the metal-bound ligands give rise to a denser packing, thus affording a more organized and protective layer. Noteworthy, the voltammograms for Au/SAM/LB(C) ($\text{C} = \text{Hg}^{2+}$ complex of L) were insensitive to exposure times ranging from 2 min to 1 h, revealing the high stability of the Au/SAM/LB(L) bilayer in water towards leaching.

To gain a deeper insight into the structure of Au/SAM and Au/SAM/LB(L) systems, they were also examined by electrochemical impedance spectroscopy (EIS) under the

experimental conditions used for the CV studies. The Nyquist diagrams for bare and modified Au/SAM electrodes are shown in Fig. 2B and compared to those recorded for an Au/SAM/LB(L) chip before and after contact with an aqueous 10^{-11} M and 10^{-6} M $\text{Hg}(\text{ClO}_4)_2$ solution. They were analyzed according to the Randles equivalent circuit approach (Fig. S3, ESI[†]),²⁷ the fitted parameters being reported in Table 1. It should be stressed that in case of naked gold, the frequency window was limited by the too high electron-transfer rate. As expected, the film thickness exerts a strong influence: the double-layer capacitance (C_{dl}) decreases whereas the charge-transfer resistance (R_{ct}) increases, as evidenced by the larger left-sided Nyquist half-circles. Concomitantly, the Warburg impedance (W), which describes the diffusional impedance to/from a flat electrode, rises as the coating becomes thicker. The higher R_{ct} value obtained for the Au/SAM/LB(L) bilayer supports the idea that interdigitation of both monolayers is accompanied with a defect-healing process that restricts the accessibility of the $[\text{Fe}(\text{CN})_6]^{3-}/[\text{Fe}(\text{CN})_6]^{4-}$ anions to the surface. Moreover, exposure of Au/SAM/LB(L) to mercury(II) produces a two-fold increase of R_{ct} , reflecting the robustness and rather high level of organization of the Au/SAM/LB(C) bilayer, as already evidenced by CV measurements. Assuming that the electron transfer between the redox couple and gold occurs only at pinholes, the electrode coverage (θ) could be estimated (Eq. S1, ESI[†]). Data reported in Table 1 evidence a significantly higher coverage level of the surface upon formation of the bilayer, which almost totally insulates the gold electrode.

Contact angle measurements clearly pointed out the higher hydrophobicity of Au/SAM ($\theta = 71^\circ$) and Au/SAM/LB(L) ($\theta = 74^\circ$) in comparison to bare gold ($\theta = 57^\circ$). Interestingly, Hg^{2+} uptake by the Au/SAM/LB(L) bilayer does not affect the wetting properties of the film ($\theta = 74.2^\circ$ and 75°), in accordance with the formation of neutral complexes at the surface and the reorientation of the binding units upon complexation, as previously observed at the air/water interface.^{24,28}

Analytical performances of Au/SAM/LB(L) chips were studied by using a commercial SPR spectrophotometer equipped with a microflow cell. In preliminary experiments, the stability of Au/SAM and Au/SAM/LB(L) was ascertained by observing a constant SPR signal when deionized water was pumped through the cell for up to 40 min at a constant flow rate of $100 \mu\text{L}/\text{min}$. A second control experiment involving an Au and Au/SAM chip ruled out Hg/Au amalgam formation on the gold surface, as well as unspecific adsorption of either Hg^{2+} or ClO_4^- ions when an aqueous $\text{Hg}(\text{ClO}_4)_2$ solution ($c = 10^{-11}$ – 10^{-6} M) flowed through the cell (Fig. S4–S5, ESI[†]).

Table 1 Parameters obtained for different film systems on a gold electrode from impedance plots

Electrode	Hg^{2+} (M)	R_s (Ω)	R_{ct} (Ω/cm^2)	C_{dl} ($\mu\text{F}/\text{cm}^2$)	W (Ω)	θ (%)
Au		4.58	7.25	21.16	72.75	0
Au/SAM		6.55	131.19	11.02	107.58	94.5
Au/SAM/LB(L)		7.63	578.43	8.63	129.48	98.7
Au/SAM/LB(C)	10^{-11}	6.78	707.40	8.43	408.80	99.0
Au/SAM/LB(C)	10^{-6}	6.58	1761.10	6.58	799.50	99.4

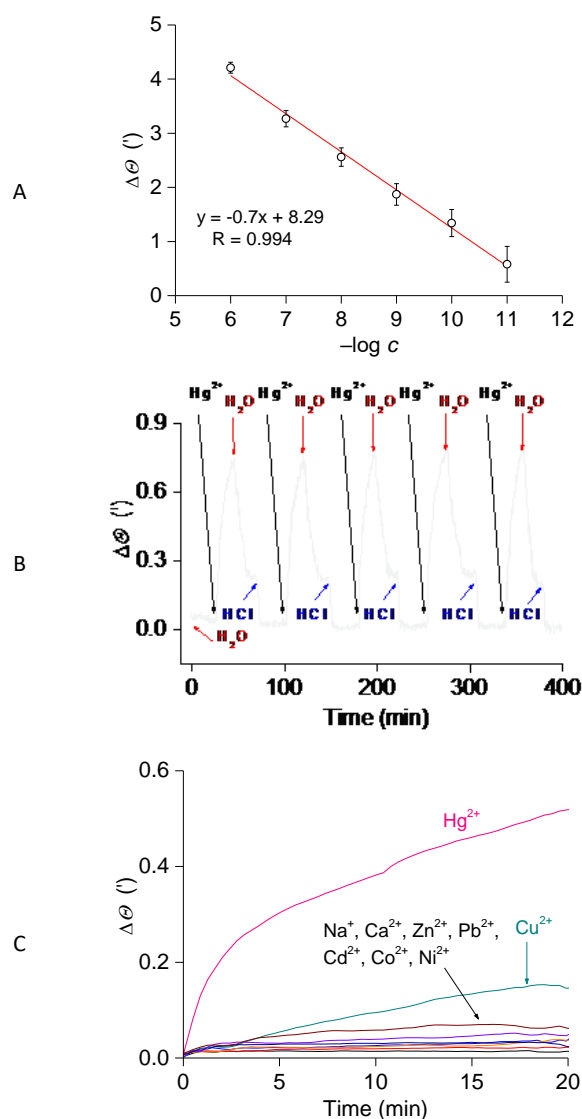


Figure 3. Semi-log calibration curve of the SPR response recorded for the Au/SAM/LB(L) chip in the presence of Hg^{2+} in deionized water (A). Time-dependent SPR signal change after the sequential exposure of the Au/SAM/LB(L) sensor to a 10^{-5} M $\text{Hg}(\text{ClO}_4)_2$ solution in deionized water (rising curve), pure water (first stage of decline), and 0.01 M HCl (second stage of the decline) (B). Time-dependent SPR signal changes upon sequential addition of 8 metal ions and Hg^{2+} ($c = 10^{-5}$ M) (C).

A typical SPR sensogram recorded for a Au/SAM/LB(L) chip for mercury(II) concentrations in the range 10^{-11} – 10^{-6} M is reproduced in Fig. S6 (ESI†). It shows a regular signal growth with increasing mercury concentration. The sensor is sensitive enough to reliably determine mercury concentrations as low as 10^{-11} M (2 ppt) in spiked solutions. The semi-log calibration function displayed in Fig. 3A evidences a linearity range spanning 5 decades.

The Hg^{2+} binding kinetics by the Au/SAM/LB(L) chip was investigated by analyzing the sensogram data (Fig. S6, ESI†) with the classical pseudo-first-order Langmuir adsorption kinetic model (FLM) (Eq. S2, ESI†) that commonly applies to various types of analytes.^{14f} However, the nonlinear semi-log plot displayed in Fig. S8 (ESI†) definitively rules out this model. This mismatch can be related to one or several of the following factors: diffusion

limitations, presence of more than one type of binding centers, or steric hindrance between immobilized receptors.^{14c,29} In contrast, the pseudo-first-order Langmuir adsorption kinetic model with diffusion limitations (DLM) (Eq. S4, ESI†) fits properly the experimental data (Fig. S9, ESI†). To the best of our knowledge, this is the first time that a metal ion adsorption process on a thin film built in a microflow cell is found to follow the DLM model, although the adsorption of various alkanedithiols on gold were rationalized by this rate law too.^{29b} However, the reported value of the apparent rate constant (k_m) is about one order of magnitude higher ($k_m = 0.13 \text{ s}^{-1/2}$ at $c = 5 \times 10^{-6}$ M)^{29b} than the one found herein ($k_m = 0.018 \text{ s}^{-1/2}$ at $c = 10^{-6}$ M). Interestingly, the k_m values summarized in Table S2 (ESI†), which approximately double when the Hg^{2+} concentration increases from 10^{-11} M to 10^{-6} M, evidence no direct proportionality with the total metal concentration. This non-linear dependence of k_m vs. c has already been observed at several instances, for example in the case of various thiols adsorption.³⁰

As a matter of facts, the mercury uptake kinetics by the immobilized ligand L can be adequately described by the model that takes into account both adsorption and diffusion processes. Experimentally, the stationary regime is reached after some tens of minutes (Fig. S6, ESI†). Considering the diffusion coefficient of Hg^{2+} in aqueous solution ($D = 9.1 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$), the mass-transfer should only take a few seconds and should not strongly depend on the metal-ion concentration.³¹ Accordingly, the diffusion of Hg^{2+} in the receptor sublayer with a thickness of about 1 nm cannot account on its own for the observed time-dependence of the SPR signal. Hence, the mass transfer is likely limited by the binding process, although it can also be argued that Hg^{2+} is a very labile cation which was found to react extremely rapidly with a water-soluble analog of L that lacks both aliphatic chains.²⁰ However, so-called "surface effects" related to local changes in viscosity, permittivity, and desolvation rates at the interface, as well as molecular rearrangements within the bilayer may significantly contribute to slowdown the metal-ion uptake kinetics by the film. It turns out that the mercury sorption process is significantly slower than the adsorption of alkanethiols under similar experimental conditions.^{29b}

To evaluate the reusability of the sensor and check for possible losses in sensitivity, regeneration tests were carried out in two steps after exposing the Au/SAM/LB(L) bilayer to a 10^{-6} M $\text{Hg}(\text{ClO}_4)_2$ aqueous solution for 25 min. The chip was first washed by pumping for 25 min deionized water while monitoring the SPR signal. Then, the microflow cell was flushed for 5 min with 10^{-2} M HCl. As shown in Fig. 3B, about 70% of the bound metal is washed away by the water flow with a pseudo-first-order dissociation rate constant of $k_{\text{dis}} = 8.2 \times 10^{-4} \text{ s}^{-1}$ (Eq. S7, ESI†). This value, which is about eleven times lower than the one obtained for the dissociation of Cd^{2+} /metallothionein surface complexes in similar SPR-experiments ($k_{\text{dis}} = 10^{-2} \text{ s}^{-1}$),^{29d} reflects the multidentate character of the receptor and the structural reorganization undergone by the top sublayer upon decomplexation. The partial elution of mercury by water, while complete desorption requires a wash with a dilute acid stream, suggests the occurrence of both weak and strong binding

sites within the bilayer. Accordingly, the structural parameters of immobilized complexes are different from those observed in solution studies of ligand L1. It means that a significant fraction of Hg²⁺ cations is only loosely bound, most likely to carbamoyl and/or phosphoryl oxygen atoms. A second fraction is more tightly entrapped by the polydentate N,O-receptor, as found in solution.²⁰ The acid-promoted dissociation of the chelate enables to fully recover the uptake capacity of the sensor and its sensitivity towards Hg²⁺. Furthermore, Fig. 3B highlights the excellent chemical stability and resistance towards leaching, as the analytical performances remain unaltered even after five adsorption/desorption cycles.

Finally, interference studies involving eight environmentally relevant cations, including toxic metals, were carried out (Fig. 3C). In these cross-selectivity experiments, equimolar amounts of perchlorate salts ($c = 10^{-5}$ M) were injected into the analyzed solution in the following sequence: Na⁺, Ca²⁺, Zn²⁺, Ni²⁺, Pb²⁺, Cd²⁺, Co²⁺, Cu²⁺, and Hg²⁺. Among them, only Cu²⁺ produced a noticeable SPR signal. However, when Hg²⁺ was spiked at the same concentration into the cocktail of the 8 other tested cations, a reliable response could be recorded, demonstrating an excellent selectivity of the Au/SAM/LB(L) chips.

In conclusion, a novel approach for preparing metal-responsive SPR chips is proposed, which takes advantage of the chemical diversity and stability provided by the interdigital arrangement of a SAM/LB bilayer deposited on a gold surface. This strategy has several advantages over the classical Au/SAM or Au/LB approaches, including the less-demanding synthesis of molecular receptors (i.e. no need of anchoring SH groups) as well as the formation of a denser, and thus more stable, film. The bilayer technology enabled to selectively quantify mercury(II) in aqueous solutions at the sub-nanomolar level (0.01 nM or 2 ppt) thanks to the outstanding coordination properties of the amphiphilic chemosensor L. The performances of this chip withstand the comparison with those of ICP-MS and are superior to any other optical sensor. Processing of the time-dependent SPR signals allows one to solve not only a purely analytical problem, but provides also some insights into the molecular interactions occurring in planar organized systems. It can also be emphasized that the efficient fabrication method described herein for obtaining SPR sensors might be also useful for elaboration of ion-selective electrodes, as evidenced by our impedance spectroscopic data.

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