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Dynamic Nanoplatforms in Biosensor and Membrane Constitutional Systems

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Abstract Molecular recognition in biological systems occurs mainly at interfacial environments such as membrane surfaces, enzyme active sites, or the interior of the DNA double helix. At the cell membrane surface, carbohydrate–protein recognition principles apply to a range of specific non-covalent interactions including immune response, cell proliferation, adhesion and death, cell–cell interaction and communication. Protein–protein recognition meanwhile accounts for signalling processes and ion channel structure. In this chapter we aim to describe such constitutional dynamic interfaces for biosensing and membrane transport applications. Constitutionally adaptive interfaces may mimic the recognition capabilities intrinsic to natural recognition processes. We present some recent examples of 2D and 3D constructed sensors and membranes of this type and describe their sensing and transport capabilities.

Keywords Bilayers · Biosensor · Constitutional dynamic chemistry · Dynamic interfaces · Nanoparticles · Quartz crystal microgravimetry · Surface plasmon resonance

Contents

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Abbreviations

Con A	Concanavalin A
Gb3	Globotriaosylceramide
GM1	Monosialotetrahexosylganglioside
HBM	Hybrid bilayer membrane
MIP	Molecularly imprinted polymer
NP	Nanoparticle
QCM	Quartz crystal microbalance
SAM	Self assembled monolayer
SERS	Surface Enhanced Raman Spectroscopy
SPR	Surface plasmon resonance

1 Introduction

Constitutional dynamic chemistry (CDC) and its application dynamic combinatorial chemistry (DCC) are new evolutional approaches to produce *chemical diversity* [1]. Basically, CDC implements a dynamic reversible interface between interacting components. It might mediate the structural self-correlation of different domains of the system by virtue of their basic constitutional behaviours. On the other hand, the self-assembly of the components controlled by mastering molecular/supramolecular interactions may embody the flow of structural information from molecular level toward nanoscale dimensions. Understanding and controlling such up-scale propagation of structural information might offer the potential to impose further precise order at the mesoscale and new routes to obtain highly ordered ultradense arrays over macroscopic distances.

Herein we describe forays to date in the field of adaptive interfaces to investigate biointeractions as well as discussing some emerging possibilities. In recent times, ideas from the fields of synthetic chemistry, nanochemistry and biochemistry have confluenced around the biosensor field (Fig. 1). Nanoplatforms possessing the intrinsic optical, electronic and magnetic properties of nanomaterials when combined with synthetic surface chemistry and an understanding of biomolecules can create opportunities for the transduction of biological interactions.

A biosensor can be described as a complex device for the detection of analytes that combines a biological component with a physicochemical detector component [2, 3]. This device, depending on how it functions, may take up a variety of forms from 2D surface based approaches to 3D micro and nanoplatforms. Examples of 3D

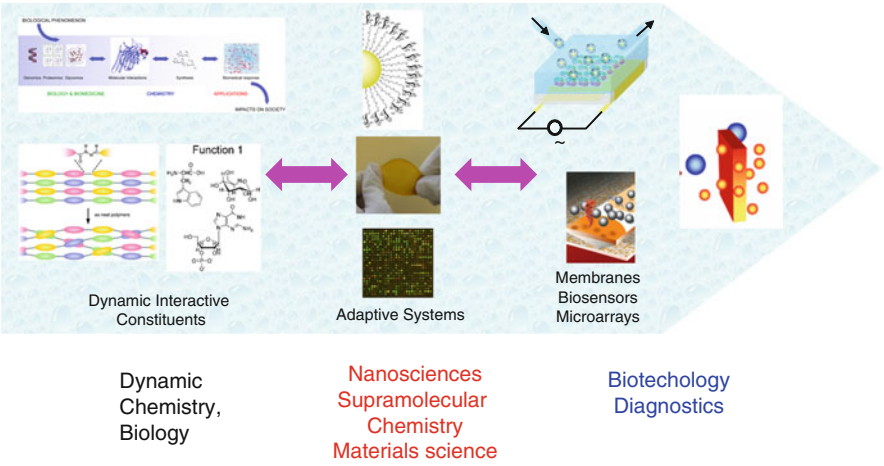

Fig. 1 Dynamic chemistry and biology toward dynamic interactive nanosystems for biotechnological and diagnostics applications

platforms include plasmonic silver or gold nanoparticles which can be applied based on their optical response (SPR); these structures have also been used to augment 2D platform sensitivity by increasing surface area by assembly or taking advantage of nanospecific amplifications (e.g. SERS).The transduction element, converting the biological interaction to a quantifiable signal, can be formed from a variety of materials such as quartz, gold, silicon, etc.

In order to interact with biological components in a specific and readable manner, an interface structure containing the biological recognition element should be bound to the transduction material. Ideally this interface will inhibit non-specific interaction maximizing response to biospecific interaction. A somewhat "bioinspired" feature to introduce to the interface architecture is that of dynamic constitutionality (Fig. 2). This essentially represents a layer in which the components may themselves reorganize within the layer under the influence of a variety of changing parameters such as molecular recognition event, temperature, pH, etc.

For an example of such a layer we only have to look to the biological model of the cell membrane, a structure which is inherently dynamic composed as it is of fluid hydrophobic material, throughout which are distributed the biological transduction elements. The cell membrane interface at which *biological signal transduction* occurs is intrinsically dynamic where a combination of *fluidity* or *mosaicism* contributes to the complexity of the recognition processes [4]. If we are then aiming to understand the nature and energy dynamics of such interactions better through biophysical study, incorporating the thermodynamically controlled dynamic behaviours of the in vivo interface in sensor design represents an important advance.

Understanding biological processes at a molecular level bridges biology and CDC [5, 6]. As "dynamic chemistry" it is underpinned by the labile, reversible yet

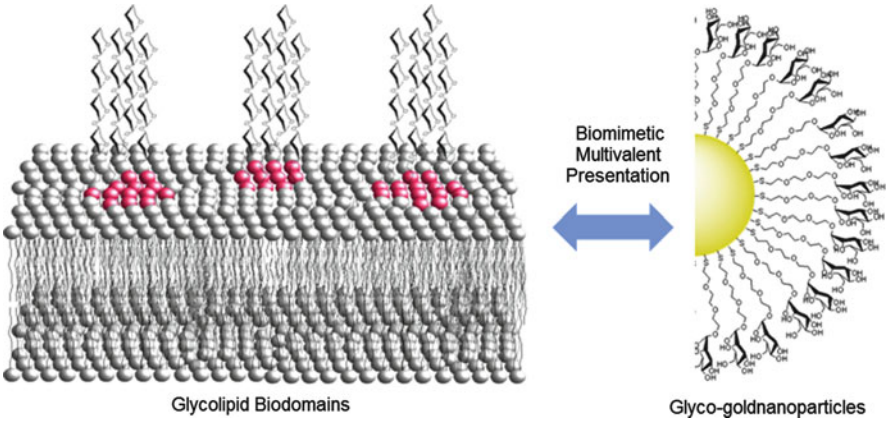

Fig. 2 Glyco-gold nanoparticles as biomimetic multivalent systems

highly specific interactions which exist throughout nature defining structures, mediating information transfer, etc. As an area of research it has been developed over the past 10 years incorporating interactions observed in nature such as hydrophobic interaction, hydrogen bonding, metal ion coordination, electrostatic interactions and π-stacking. Complementary to the novel science based around supramolecular interactions, synthetic bioinspired supramolecular designs can in turn provide a greater depth of understanding of biological mechanisms. Through the principles of self-assembly and molecular recognition allied to synthetic chemistry, we can access a range of self-organized materials which can interact on a biological scale and in a biological manner with the present and growing capability to incorporate built-in nanomaterial signal transmitters from the nanoscale. Molecular recognition events such as carbohydrate–protein or protein–protein interactions occurring at the cell surface can be understood within this concept of chemical collectivism [7–9]; indeed this collective self-assembly can be considered as a basis for the structural evolution of the biosphere [10]. Within this context, during the last decade the CDC is expressing more interest for dynamic constitutional systems, undergoing continual change in constitution, through dissociation/reconstitution of different components during complex processes. This concept can be related to a sort of "*Chemical collectivism*" or of "*Chemical Darwinism*" The reversibility of interactions between components of a system is a crucial factor and, accordingly, the dynamic interfaces might render the emergence system states self-adaptive, which mutually (synergistically) may adapt their spatial/temporal distribution based on their own structural constitution during the simultaneous formation of self-organized domains. The extension of the constitutional chemistry approach to nanoplatforms would be able to compete at multiple length scales within nanoscopic networks and to display variations in their sizes and functionality. Furthermore, we can relate this behaviour to purely synthetic compositions such as the "*Dynamic interactive systems*" [11–13] characterized by their aptitude to

organize (self-control) macroscopically their distribution in response to external stimuli in coupled equilibria.

This growing multidisciplinary field of nanobiotechnology could have important contributions to make to the future of medicine [14], part of which, the consideration of molecular recognition events at the cell membrane surface as information transfer, could have important implications when applied to pharmaceutical development [15, 16]. Dynamic interfaces may provide a means to reach greater sensitivities and novel unpredicted behaviours in terms of biological interaction both for in vitro measurement and in vivo applications.

2 Biosensing Methods/Techniques

2.1 Quartz Crystal Microgravimetry

Quartz Crystal Microgravimetry (QCM) sensors work on the phenomenon of piezoelectricity. This mechanical-electrical effect was first reported in 1880 by the Curie brothers describing the generation of electrical charges on the surface of solids caused by pulling, pushing or torsion [17]. Initially it was demonstrated that there exists a linear relationship between mass adsorbed to crystal surfaces and the crystals resonant frequency in air or a vacuum [18]. Extension of this observation to study biological interactions was realized with the design of solution based systems and combination of these with microfluidics and controlled surface chemistry. Consequently, QCM has become a highly relevant analytical technique due to it sensitive solution-surface interface measurement capability. It possesses a wide detection range which at the low end can detect monolayer coverage by small molecules.

Sauerbrey provided the first treatment of the effect of mass loading on quartz resonators (Eq. (1) in [18]). He showed that an ideal layer of foreign mass results in a frequency decrease that is proportional to the deposited mass where the resonator was operated in air or vacuum. Assuming the density of the crystal and the adsorbed layer were equal, then the above-mentioned equation held valid. This equation is valid for a thin, uniform, rigidly attached mass. Application of QCM to biological samples became possible when suitable oscillator circuits for operation in liquids were developed [19]. As the Sauerbrey relationship was formulated for thin rigid films in air or vacuum, questions arose as to the validity of the Sauerbrey relationship in liquid media. For a long time it was postulated that a direct quantification of protein adsorption at functionalized surfaces was possible based on this relationship. However, frequency shifts larger than those observed in air were frequently observed in aqueous media for equivalent proteins. When used in liquid media other important frequency determining factors have to be taken into account. When in contact with a liquid, the frequency depends on the liquid density and also on its viscosity. This modified resonant frequency shift was treated theoretically by

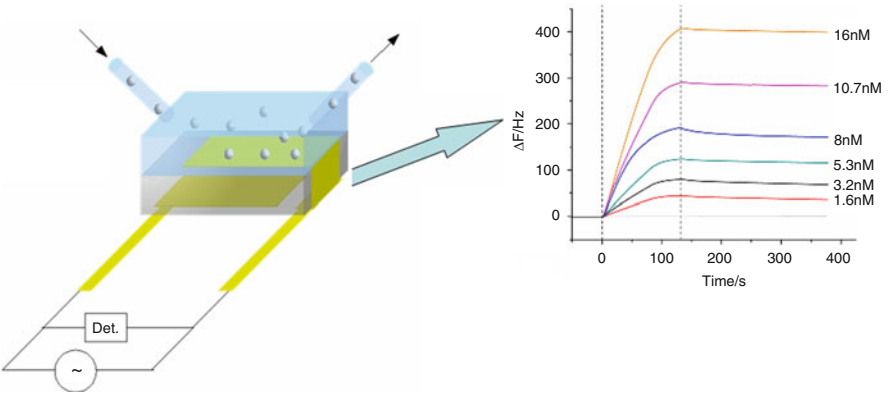

Fig. 3 Representation of QCM experimental setup and concentration assay for gold sugar nanoparticles binding on immobilized lectin layer

Kanazawa et al. [20] and their calculations are valid for rigid films immersed in liquid. However, this work is not valid for non-rigid "soft" materials. For soft material layers it was even noticed that in applying Sauerbrey's equation the mass of the viscoelastic layer is underestimated and the result is a "missing mass" which was elucidated in calculations by Voinova et al. [21].

Alongside viscoelastic properties, electrolyte contributions, surface roughness and surface energy changes may have to be considered. For example, changes in hydrophilicity can cause very large response changes in QCM as a function of surface roughness [22, 23]. Rough and hydrophilic surfaces entrap liquids in small cavities contributing to the overall mass detected. Hydrophobic surface cavities may be unwetted and so contain air or vacuum cavities resulting in an artificially large frequency change on hydrophilization of the surface. These problems can be kept to a minimum by optimizing surface smoothness. Although on analysing soft material adsorption in liquid environments the frequency shift cannot be translated directly to mass load according to the Sauerbrey relationship, the quartz crystal microbalance can be used for label free analysis of binding events. Concentration dependant measurements of the frequency shift together with the assumption of a linear relationship between ΔF and Δm allow thermodynamic and kinetic parameters of binding events to be determined as has been demonstrated in numerous examples described in the following section (Fig. 3).

2.1.1 Quartz Crystal Microgravimetry in Biosensing

QCM has been used extensively in the areas of DNA hybridization, protein adsorption studies, immunological systems and also in the areas of protein–protein and protein–carbohydrate interaction [24]. Examples prepared using carbohydrate SAMs to function as lectin biosensors are known since initially it was shown

through investigation by quartz crystal microbalance that self-assembled monolayers (SAMs) of Gb3 mimics having different lengths of alkyl chains prepared on gold surfaces could interact with galactose-specific lectin *ricinus communis agglutin* (RCA_{120}) and Shiga toxins (Stxs) [25]. Later it was shown that the α-Gal carbohydrate antigen interacted in a specific manner with tri-Gal presenting SAMs [26]. "Click chemistry" was introduced in later work for the preparation of carbohydrate functionalized crystal surfaces which then showed selective lectin recognition [27, 28]. There are far more examples if one looks to oligonucleotide interactions with the first direct DNA detection using QCM back in 1988 [29]. Following this there were many more studies carried out using immobilized oligonucleotide surfaces. These immobilizations were generally performed using biotin–avidin [30], or gold–thiol interactions [31, 32] with varying surface performances ensuing.

Polymer adsorption has also been adapted to QCM sensing whereby biofunctional thin films are adsorbed on the crystal surface with non-specific binding controlled by tuning of polymer composition. This approach proved successful as applied to carbohydrate–protein interaction by Matsuura et al. through adsorption of lactose bearing amphiphilic polymers on hydrophobic surfaces which then showed RCA_{120} and peanut lectin (PNA) affinity [33]. Carbohydrate surfaces prepared by photo insertion into an adsorbed polymer were tested by QCM and showed the predicted affinities [34] while in another example a covalently bound glycopolymer demonstrated Concanavalin A detection ability [35].

A general limitation on QCM sensitivity is the mass of the analyte which is to be adsorbed from solution. At present QCM does not have single small molecule sensitivity. The most common procedure for QCM detection of protein–carbohydrate interaction is immobilization of the small molecule as the surface bound receptor in SAMs [26–28] or polymer films [34, 36] followed by monitoring of the binding of the relatively large protein, antibody, etc. Amplification methods may thus be employed in order to study certain biorecognition processes. Two previously demonstrated ways in which to achieve amplification are mass increase, i.e. the introduction of nanoplatforms such as nanoparticles (NPs), vesicles [37] and micelles to carry the recognizing small molecule element, and also by increasing recognizing surface area, e.g. porous films, MIP multilayers, etc. [38]. Nanoparticles as frequency change enhancement probes have already been demonstrated for the biotin–streptavidin interaction [39] and also for enhanced DNA detection by QCM. DNA-conjugated nanoparticles can be used to enhance the signal produced upon hybridization to a surface bound single-stranded template [40]. The carbohydrate–lectin interaction was also recently investigated by Barboiu et al. using this NPs–QCM approach (Fig. 4) [41] It can be concluded that NPs act as efficient QCM signal enhancers. The amplification is considerable, which is to be expected given an estimated increase in the region of ~6,000 mass%. NPs and QCM can go hand in hand in order to expand the applicability of the QCM technique to investigate small molecule interactions in real-time. Frequency changes of 1,600 Hz were observed for complete NP saturation while typical protein layers would show changes in the region of 100 Hz. GlycoNPs have been described as being biomimetic in their multivalent sugar presentation and the results presented concur. Large avidity increases with

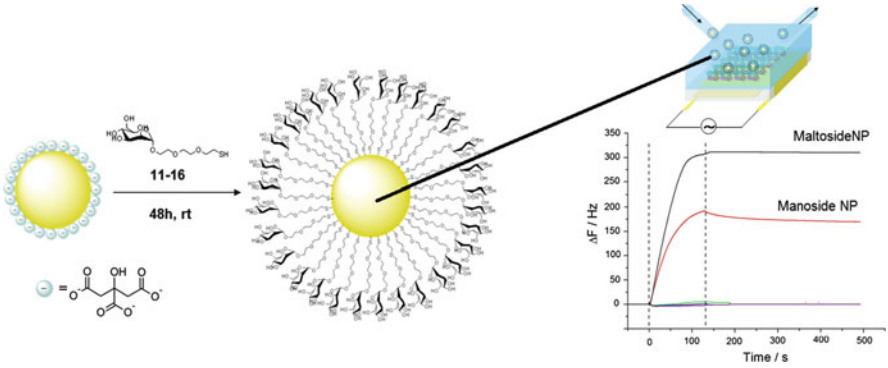

Fig. 4 Glyconanoparticles recognition by ConA functionalized QCM electrode surfaces

enhancement factors (β) of 2,000 and 25,000 for Mannoside and Maltoside nanoparticles respectively were shown, relative to the corresponding monomer [41].

2.2 Surface Plasmon Resonance

SPR is one of the most commonly employed surface sensing techniques today [42]. Like QCM it is a surface analytical technique capable of in situ monitoring of interfacial processes. Whereas QCM is an acoustic wave device where the QCM oscillation frequency and quality are related to the mass loading and the viscoelastic properties of the adsorbed materials, Surface Plasmon Resonance (SPR), another label-free detection technique, is based on the resonance coupling between incident light and a gold surface plasmon wave. In a classical SPR instrument, this occurs at a typical incident angle, causing a minimum in the reflectivity of the p-polarized light beam. The value of this critical angle depends on the thickness and refraction index of any layer adsorbed on the gold surface. The measured signals are thus proportional to the molecular weight of the adsorbed materials, and can be used to quantify the number density of different types of adsorption [43]. SPR measures "dry mass" meaning that the signal measured is not sensitive to water associated with macromolecules. This is not the case for QCM where the response may also contain an associated water contribution. Adsorbed molecular mass may thus be more directly discerned from SPR data.

It appears that in most cases the techniques are comparable in terms of resulting sensitivity. Whereas the SPR has the advantage in terms of real sensitivity, the fact the QCM technique also measures entrapped water amplifies the gravimetric response and may render it sensitivity comparable in macromolecular binding experiments [44, 45]. An added advantage of QCM over SPR is the availability of the QCM-D technique which is a measurement of the dissipation energy. A film that is viscoelastic or "soft" will not fully couple with the quartz crystal's oscillation

and in doing so will dampen it. This damping thus contains information as to the film's viscoelastic properties [46].

2.2.1 Surface Plasmon Resonance in Biosensing

SPR has been applied in the study of a range of biological interactions including carbohydrate–protein, protein–protein, DNA hybridization and DNA–protein interaction [47]. Recent developments in interface engineering have allowed the technique to approach small molecule sensitivity further [48]. Binding and cross reactivity studies are becoming possible by using glyconanoparticles and lectins layers. Ramstrom et al. [49] showed that glyconanoparticles exhibit affinity ranking consistent with that of free ligands in solution. Like QCM, a major advantage of this technique is that it allows label free analysis, thus avoiding problems such as structural interference caused by fluorescent labelling techniques. It is also amenable to amplification techniques to increase sensitivity such as those using plasmonic particles [50–54].

2.3 Electrochemical Sensing Platforms

The electrochemical based biosensors are the most widely used format in biosensing. Typically the reaction under investigation would either generate a measurable current (amperometric), a measurable potential or charge accumulation (potentiometric) or measurably alter the conductive properties of a medium (conductometric) between electrodes [55].

The coupling of biomimetic dynamic interfaces with electrochemical impedance spectroscopy has shown value in the study of ion transport studies across tethered bilayers [56]. Electrochemical impedance spectroscopy may prove valuable used in conjunction with the previously described techniques [57, 58]. Again electrode construction with readily chemically adaptable surface materials such as gold, silver and glass/silica amongst others make this a promising approach for introducing functional interfaces.

3 Nanoplatforms for Biosensing and Membranes

Multivalent interactions represent multiple copies of a specific recognition element connected in some way to a central scaffold. Resultant affinity can be highly dependent on the nature of the scaffold as multivalent interactions have been shown to be influenced by such factors as shape, valency, orientation and flexibility. In this context, adaptive scaffolds can exhibit a large range of *dynamic valencies*. Lower valency categories are supramolecules such as crown ethers, cryptands,

calixarenes and porphyrins and higher valency scaffolds include dendritic structures, nanoparticles or confined pores. The self-assembly of the system components controlled by mastering molecular/supramolecular interactions may embody the flow of structural information from molecular level toward nanoscale dimensions. Resultant spatio/temporal affinity is highly dependent on the nature of the scaffold as multivalent interactions have been shown to be influenced by such factors as shape, valency, orientation and flexibility. The possibility of designing and engineering nanometric multivalent platforms is at the forefront of cross-disciplinary oriented research. Natural systems have evolved for billions of years to accept complex evolutive structures. Using this model, the synthetic systems could be extended to the vast field of scientific challenges, for example, resulting in the property (function)-driven generation of new adjustable (adaptive) system structures. Various 2D platform types for such sensing have be applied, adapted to SPR, QCM and electrical methods, as well as 3D surface approaches utilizing the intrinsic physical properties. Dynamic self assembled *monolayers*, *supported bilayers* and *dynameric films* can represent platforms for studying multivalent interactions. Such evolutive dynamic devices at the nanoscale may possess novel properties not present in the bulk material. The integration of dynamic systems might give great potential in applications.

3.1 Nanoparticles

Nanoparticles display large surface to volume ratios and can report on biological interaction directly from nanodispersions in biological media [59]. The intrinsic nanoscale property of the material can enable highly sensitive transduction of biointeractions.

This is the case for gold and silver nanoparticles which have sensing capability based on the sensitivity of their surface plasmon absorbance band to the surrounding environment. This absorption band shows an interparticle distance dependency which is very useful in terms of selective particle aggregation studies as a means of sensing [60]. Aggregation causes a coupling of the gold nanoparticle's plasma modes, which results in a red shift and broadening of the longitudinal plasma resonance in the optical spectrum [61]. It has been observed in theoretical and experimental studies that when the individual spherical gold particles come into close proximity to one another, electromagnetic coupling of clusters becomes effective for cluster–cluster distances smaller than five times the cluster radius ($d < 5R$, where d is the centre-to-centre distance and R is the radius of the particles) and may lead to complicated extinction depending on the size and shape of the formed cluster aggregate. This effect is negligible if $d > 5R$ but becomes increasingly important at smaller distances [62]. The wavelength at which absorption due to dipole–dipole interactions occurs may vary from 520 nm (effectively isolated particles) through 750 nm (particles that are separated by only 0.5 nm), and the resulting spectra are a composite of the conventional plasmon resonance due to single spherical particles and the new peaks

resulting from particle–particle interactions [63]. This interparticle plasmon coupling during biointeraction induced aggregation has been exploited for DNA and antibody detection and colorimetric detection of lectin-carbohydrate interactions using functionalized particles [64–66] among others. Non-specific adsorption of biomacromolecules can be minimized by using ethylene glycol based linkers to protect the gold core [67].

Other nanomaterials can also be employed in the fabrication of nanoparticles. The intrinsic photoluminescence of quantum dots has been utilized for specific protein sensing [68, 69]. Composites of the aforementioned gold NP, silver NP and quantum dots usually with silica or polymeric materials have also been employed as described in a recent review [70] The multivalent presentation of carbohydrate ligands significantly enhances the binding affinity toward lectins by several orders of magnitude in comparison to the free ligands in solution and strongly depends on the type and length of the spacer linkage and ligand density [71].

The final goal is subsequently to apply the nanodevices directly in vivo, using the powerful detection abilities of NPs to localize and image static and tumour cells efficiently. Interestingly, the strong binding of gold glyconanoparticles on bacterial cell surfaces gives rise to the high potential of labelling proteins on in vivo biological surfaces using carbohydrate nanoplatforms [72].

3.2 Dynamic Interfaces

Different interfaces are known to show constitutionally dynamic behaviours:

1. Biomimetic interfaces including lipid bilayers, hybrid bilayers, tethered bilayers as well as other interdigitated layers are composed of naturally existing constituents based mainly on the hydrophobic interaction.
2. Non-biomimetic interfaces which are constructed as they are from supramolecular associations or reversible covalent linkages. An approach to such an interface can be envisaged through the application of supramolecular chemistry and dynamic constitutional chemistry which are both conducive to adaptive structures.

3.2.1 Supported Bilayers

Supported bilayers represent biomimetic layers which can be supported on a range of materials and adapted for the study of biointeractions (protein–protein, lipid–lipid) including molecular recognition, ion-channel transport and intramembrane interactions. This interface type can be separated into the so-called SLBs (supported lipid bilayers), HBMs (hybrid bilayer membranes) and t-BLMs (tethered bilayer membranes).

The SLB is conventionally formed on silica surfaces and stabilized by interactions between the hydrophilic hydroxyl surface and the phospholipid headgroups. It is purely a phospholipid bilayer stabilized only by electrostatics and the hydrophobic

effect, which, through incorporation of bioactive structures such as membrane proteins, glycolipids and glycoproteins, can give a biomimetic response with interacting species in solution.

A range of molecular recognition based interactions have been studied using this layer type. The carbohydrate–protein interaction was investigated by Liebau et al. who, using QCM and glycolipid as the dynamic recognition element, showed some specific lectin adhesion to a supported lipid bilayer [73].

SPR imaging was also employed to look at the same cholera toxin–GM1 interaction on a supported bilayer by Philips et al. in array experiments [74]. Another investigative technique applied to the model ganglioside–cholera toxin system was total internal reflection fluorescence microscopy applied to spatially addressable supported bilayer membranes [75]. The recognition by HIV-1 surface glycoprotein gp120 of glycosphingolipids partitioned within an SBM has also been looked at by total internal reflection fluorescence [76].

Other types of cell membrane interaction have also been examined. For example Wang et al. have used an electrochemical SPR sensor to monitor peroxidase enzyme activity within the plasma membrane [77]. As a means of improving stability and creating a closer approximation of a true cell membrane, interlayer structures between the lower phospholipid leaf and the solid supports have been tested. Cushion layers based on PEG to enable transmembrane protein insertion were tested by Munro et al. [78], while Schuster et al. have reviewed the use of S-layer proteins as a construction element [79, 80].

Solid supported bilayers of other composition have also been reported such as lipopolysaccharide bilayers which can mimic the outer bacterial membrane with this example used to monitor bacteriophage interaction by AFM [81].

3.2.2 Hybrid Bilayers

The HBM consists of two differing leaves normally generated on a gold or silica surface. The lower leaf is a fixed long chain alkyl self-assembled monolayer covalently bound to a solid support while the upper leaf is a phospholipid monolayer [82, 83]. This type of bilayer may show increased stability due to the covalent nature of the lower leaf fixation; however it would present a system further removed in structure from the biological condition given this fixed nature and more limited fluidity [84].

In terms of biosensing applications using such layers, again cholera toxin detection on a porous silicon substrate [85] has been reported. Also biotin–avidin interaction by QCM [86], glutamate detection [87], as well as protein membrane interactions [88, 89] have been studied.

3.2.3 Tethered Bilayers

The tethered bilayer offer improvements in both stability and in terms of its approximation of the true cell membrane through incorporation of tethering links

between the bilayer and solid support which allows both inner and outer phospholipid leaf to interface with an aqueous domain [90–92]. The result is a self-assembled bilayer which exhibits a closer approximation of true cell membrane fluidity [93]. Such a construction also allows for the accommodation of proteins [94], incorporated synthetic ion-channels [95] and sugar lectin systems [96]. Taylor et al. has reported on SPR detection of cholera toxin using a tethered bilayer [97]. Cornell et al. investigated ion channel based sensors with tethered bilayers [98].

3.2.4 Vesicular Systems

Vesicles have demonstrated their dynamic behaviour in studies showing evidence of rapid domain formation in response to external stimuli [9]. The binding of glycosidic domains to cholera toxin has been demonstrated using vesicles as biomimetic sensors [99]. Protein–carbohydrate interaction has also been studied using synthetic glycolipids recently by Barboiu et al. [100] (Fig. 5).

They demonstrated an affinity enhancement of mannoside vesicles when compared with the Me-α-glucose monosaccharide in solution. The 40-fold increase can be attributed to multivalent glycoside presentation, allied to their fluidity within bilayers. The dynamic hydrophobic interface between carbohydrate molecules and bilayers may mediate the structural self-correlation of supramolecular sugar clusters by virtue of their basic constitutional behaviours. The resultant dynamic system can undergo continual change in its constitution through dissociation/reconstitution of different mesophases during the vesicle recognition process. Artificial glycocalix bilayer vesicles decorated with sugars reversibly agglutinate, depending on the

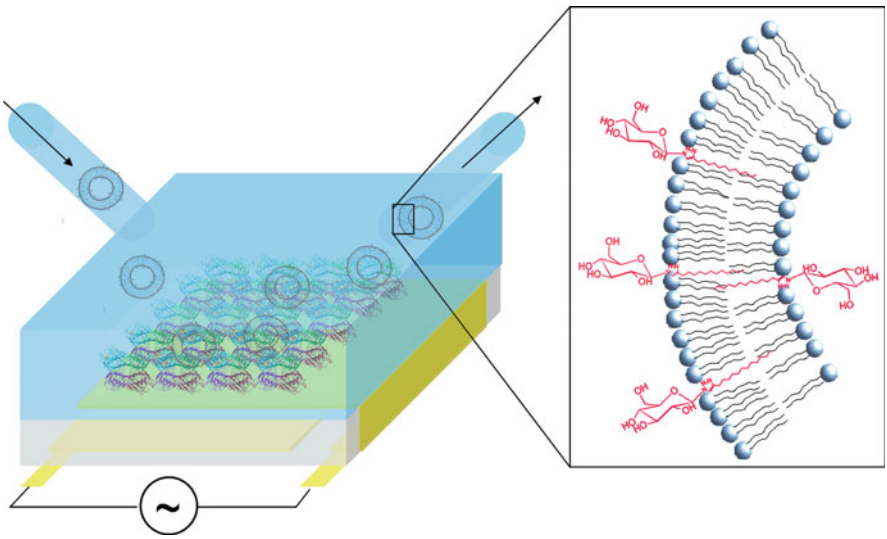

Fig. 5 Con A layers exposed to functionalized vesicle solutions within a QCM system

surface coverage of sugars. These dynamic constitutional vesicles operating via multivalent orthogonal interactions operating simultaneously are nice examples for further understanding molecular recognition at cell surfaces [101].

3.2.5 Supported Self-Assembled Monolayers and Bilayers on Surfaces

As an intermediate between solid supported layers and the inherent dynamic and nanostructured properties of phospholipid vesicle supports, silica and especially mesoporous silica nanoparticles may provide interesting platforms for dynamic bilayers. Previous studies have shown that stable bilayers can form on both amorphous [102] or functional silica [103, 104] and mesoporous nanoparticles [105] or membranes [106]. This type of biomimetic carrier has great potential as a type of trackable stabilized membrane capable of displaying cellular targeting elements in a close to natural configuration.

Besides the bilayer type dynamic interfaces there also exist dynamic interfaces involving SAMs. The cooperative dynamic nature of SAMs on gold has been confirmed previously [107]. On 2D surfaces the level of mobility in gold–thiol SAMs has been looked at and is considered quite slow ranging from 10^{-18} to 10^{-14} cm^2 s^{-1} (~1 nm/h) [109, 108] when compared to phospholipid and membrane protein, lateral mobilities of around 10^{-8} cm^2 s^{-1}.

A few different studies have shown evidence for thiol mobility in the presence of supramolecular driving forces. Mixed monolayer mobility has been studied by Rotello and co-workers and has been shown to be influenced by intramonolayer hydrogen bonding [110–112]. They noticed a surface adaptation towards increased binding affinity over time for their system based on a mixed monolayer protected cluster interacting with flavin. This shows that functional gold nanoparticles possess an adaptive quality which could be exploited for high affinity recognition of biomacromolecules. The ligands can reorganize on the particle surface during interactions to the most energetically favourable configuration. Hypothetically speaking this may allow a preconditioning step to optimal multivalent affinity monomer organization using such particles which, given the slow mobility previously cited within such a layer, could remain intact over a useful timescale or could be locked in place using, for example, a monomer–monomer bridging photoreaction. Supramolecular peptide–peptide interactions have also been shown to cause layer reorganization [113]. Another example of this dynamic behaviour was demonstrated by X-ray diffraction and reflectivity on particles immobilized at the air–water interface by Nørgaard et al. [114]. These mixed monolayer protected particles (hydrophobic/hydrophilic) were deemed environmentally responsive to the hydrophobic effect as their ligand groups were shown to reorganize to give a more stable equilibrium interface. This type of dynamic behaviour is also in evidence by the formation of functional islands due to phase separation on particle surfaces [115, 116]. In the case of gold NPs perhaps a more dynamic

interface layer would result by employing a more labile anchoring group than thiol, such as an amino, phosphine or carboxylate.

3.2.6 Supramolecular Networks and Constitutionally Dynamic Polymers

Materials based on reversibly covalently bound constituents could also be applied in the construction of constitutionally dynamic systems [117]. For example, the "glycodynamers" could be exploited as adaptive layers for selective protein sensing [118] or adaptive nucleic acid [119, 120] displays could be exploited for DNA sensing applications. These sensing interfaces could be "pre-conditioned" and fixed for optimal sensing of the choice analyte using the principles already established in DCC [1].

Supramolecular networks film deposited on 2D surfaces provides an interesting route to adaptive functional surfaces [121, 122]. Such films can take the form of metallo-organic frameworks [123], hydrogen bonded networks, Van der Waals etc. or combinations of the above. There are very few examples in the literature of the employment of such a film although it has been demonstrated for hydrogen peroxide sensing [124]. An elegant use of reversible covalently structured architecture for a condition dependent detachable shell nanodelivery vehicle was demonstrated by Oishi et al. Through incorporation of disulfide bridges as a structuring element in their transmembrane delivery studies they showed that exposure to disulfide reducing cytosolic glutathione increased the efficiency of load delivery [125]. This type of layer can be imagined as a constitutionally dynamic framework which, through the incorporation of biorecognition elements, can open new avenues in adaptive biosensing [126].

Fullerene–sugar conjugates with a specific multivalent presentation have recently been used for achieving high affinity interactions with lectins and enzymes [127–129]. These nanoplatforms have been used as inhibitors for *Escherichia coli FimH*, showing interesting antiadhesive bacterial properties [128] or as strong inhibitors of glycosidase bearing an important multivalent effect [129].

3.2.7 Systems Membranes

Besides the bilayer type dynamic interfaces there also exists dynamic interfaces which can be constructed based on the principles of supramolecular and dynamic covalent chemistry and which can be applied toward sensing and targeting at the molecular level. New routes toward self-preparation of highly ordered ultradense nanoarrays over macroscopic distances led to membrane systems where the concept of self-organization and a specific function (i.e. generation of specific translocation pathways in a hybrid solid) might in principle be associated [130–134]. The resulting hybrid materials are composed from functional domains self-organized at the nanometric level, randomly ordered in the hybrid matrix. These oriented nanodomains result from the controlled self-assembly of simple molecular

components which are then fixed by sol-gel transcription. These results provide new insights into the basic features that control the convergence of *supramolecular self-organization* with the conduction *supramolecular function* and suggest tools for developing the next generation of highly conductive materials. This is reminiscent of the supramolecular organization of binding sites in channel-type proteins collectively contributing to the selective translocation of solutes along the hydrophilic pathways. On the other hand, the weak supramolecular interactions' (H-bonds, van der Waals, etc.) positioning of the molecular components are typically less robust than the cross-linked covalent bonds formed in a polymerization process, like the sol-gel. Accordingly, a sole solution to overcome these difficulties is to improve the binding (association) efficiency of molecular components generating supra-molecular assemblies. At least in theory, an increased number of interactions between molecular components and the right selection of the solvent might improve the stability of the templating supramolecular systems, communicating with the inorganic siloxane network. Among these systems the nucleobases and nucleosides are well known fascinating compounds with a great ability to form directionally controlled multiple H-bonding, hydrophobic and stacking interactions [135, 136]. Their remarkable self-association properties play a critical role in the stabilization of higher-order RNA hairpins loops, double or triple helix DNA and G-quartets or G-quadruplexes [137, 138].

Many fundamental biological processes appear to depend on unique properties of inner hydrophilic domains of the membrane proteins in which ions or water molecules diffuse along the directional pathways. In the membrane protein systems simple *inner functional moieties* (i.e. carbonyl, hydroxyl, amide, etc.) are pointing toward the protein core, surrounded by the *outer scaffolding protein wall* orienting the transport direction. Bilayer or nanotube artificial membranes were developed with the hope of mimicking the natural ion-channels, which can directly benefit the fields of separations, sensors or storage-delivery devices.

Supramolecular columnar ion-channel architectures confined within scaffolding hydrophobic silica mesopores can be structurally determined and morphologically tuned by alkali salts templating [130, 131]. The dynamic character allied to reversible interactions between the continually interchanging components make them respond to external ionic stimuli and adjust to form the most efficient transporting superstructure, in the presence of the fittest cation, selected from a set of diverse less-selective possible architectures which can form by their self-assembly. Evidence has been presented that such a membrane adapts and evolves its internal structure so as to improve its ion-transport properties: the dynamic non-covalent bonded macrocyclic ion-channel-type architectures can be morphologically tuned by alkali salts templating during the transport experiments or the conditioning steps [95].

From the conceptual point of view these membranes express a synergistic adaptive behaviour: the addition of the fittest alkali ion drives a constitutional evolution of the membrane toward the selection and amplification of the specific transporting superstructures within the membrane in the presence of the cation that promoted its generation in the first place. This is a nice example of dynamic self-instructed ("trained") membranes where a solute induces the upregulation of its

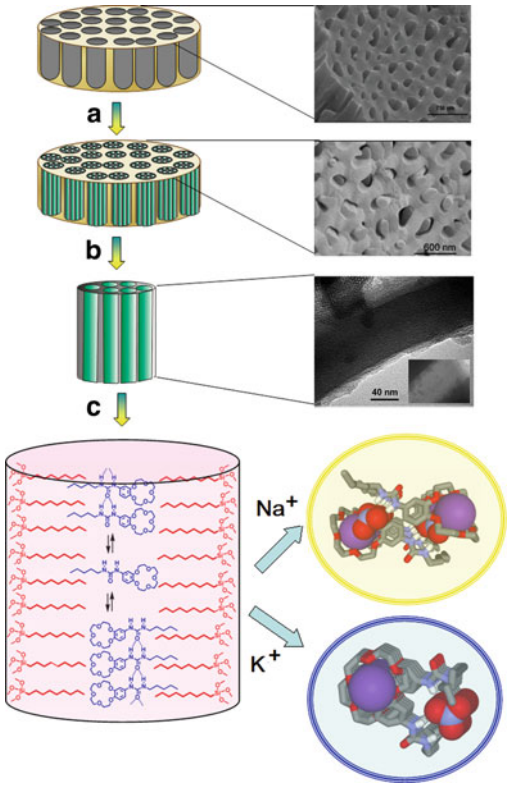

Fig. 6 Schematic representation of the synthetic route to obtain constitutional silica mesoporous membranes is (**a**) filled with mesostructured silica-CTAB, (**b**) then calcinated, (**c**) reacted with hydrophobic ODS and finally filled with the hydrophobic carriers. Generation of directional ion-conduction pathways which can be morphologically tuned by alkali salts templating within *dynamic hybrid materials* by the hydrophobic confinement of ureido-macrocyclic receptors within silica mesopores [130]

own selective membrane. This led to the discovery of the functional supramolecular architecture evolving from a mixture of reversibly insidepore exchanging devices via ionic stimuli so as to improve membrane ion transport properties. These phenomena might be considered as an upregulation of the most adapted 3D "*insidepore*" superstructure, enhancing the membrane efficiency and the selectivity by the binding of the ion-effectors (Fig. 6).

Finally these results extend the application of *CDC* from materials science to *functional Dynamic Interactive Membranes- Systems-Membranes*, using *dynamic intrapore resolution* towards *dynamic hybrid materials and membranes*. Such systems evolve to form the fittest insidepore architecture, demonstrating flexible functionality and adaptation in confined conditions.

4 Conclusions

Looking through the literature to date it is apparent that the use of constitutionally dynamic interfaces for biorecognition and membrane transport represents an emerging field. There are quite a few examples where biomimetic type supported

membranes are employed due to the continual improvements in their structural approximation of the true cell membrane. Allied to in vitro cell work these studies should yield some interesting insights into membrane recognition processes and could readily be employed, for example, in the characterization of novel "targeting and delivery" nanomaterials.

Supramolecular and constitutional dynamic interfaces and layers have evidently not been consciously much employed to date in biosensing and transport applications. They may provide some initial chemical synthetic difficulties when compared to using naturally derived substances such as phospholipid and cholesterol based components but they may provide a route to nanostructured surfaces and particles demonstrating unknown specificities and behaviours.

The benefits of the constitutionally dynamic approach are many, including nanomedicines of unprecedented avidity through optimal multivalent adaptation which can apply not only in biosensing but also in nanotargetting therapies, reciprocating an improved understanding at the molecular level of biological processes, e.g. multivalent phenomena, while at the same time enhancing our capability in influencing deliberately biological processes.

Finally, the results obtained extend the application of *CDC* [1, 139] from materials science [8] to *functional constitutional devices* [95, 140]. This feature offers to chemical sciences perspectives towards self-designed systems evolving their own functional superstructure so as to improve their performances. Prospects for the future include the development of these original methodologies towards dynamic materials, presenting a greater degree of structural complexity. They might provide new insights into the basic features that control the design of new materials, mimicking the constitutional biosystems with applications in chemical separations, sensors or as storage-delivery devices.

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