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# Review of electrochemically triggered macromolecular film buildup processes and their biomedical applications

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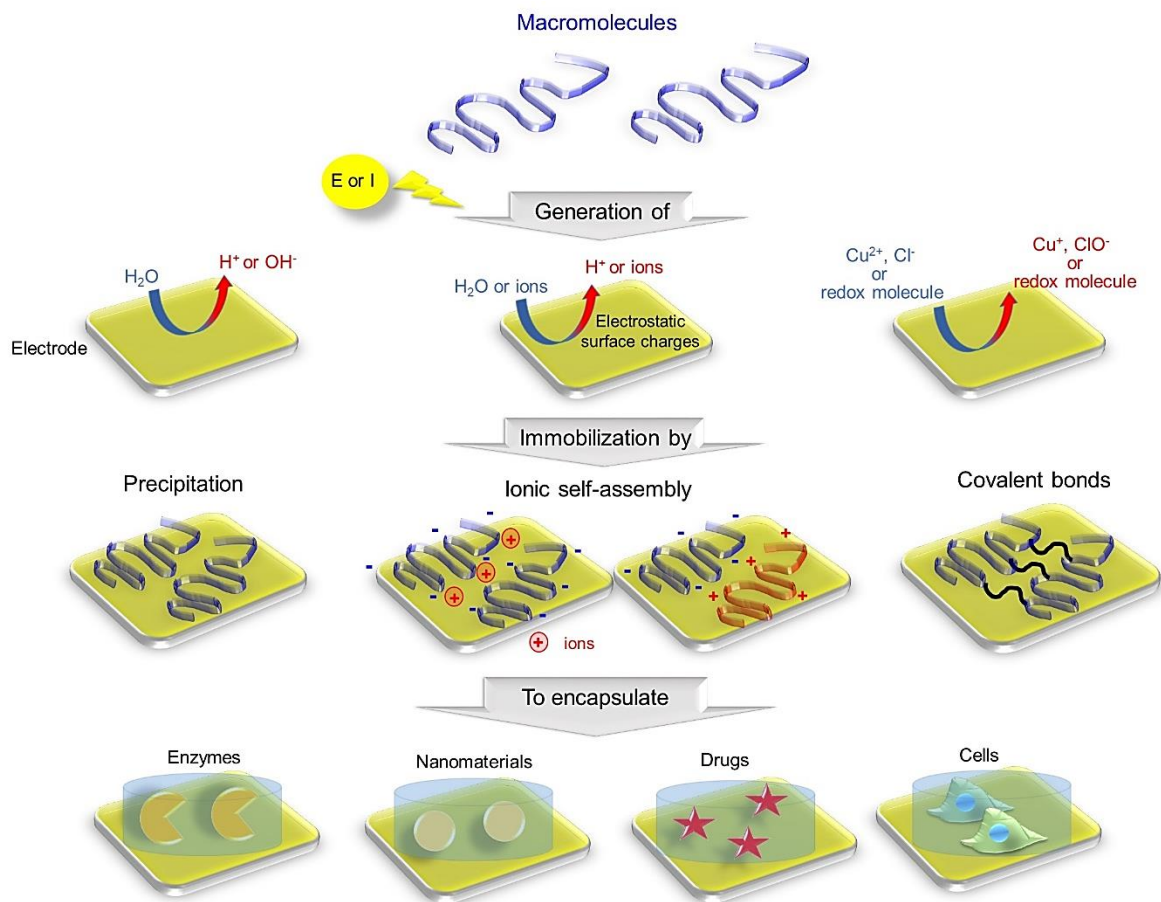
**KEYWORDS:** coatings, polymers, enzymes, electrophoretic, electrodeposition, carbon nanotubes,  
nanoparticles

## ABSTRACT

Macromolecular coatings play an important role in many technological areas, ranging from car industry to biosensors. Among the different coating technologies, electrochemically triggered processes are extremely powerful because they allow in particular spatial confinement of the film buildup up to the micrometer scale on microelectrodes. Here, we review the latest advances in the field of electrochemically triggered macromolecular film buildup processes performed in aqueous solutions. All these processes will be discussed and related to their several applications such as corrosion prevention, biosensors, antimicrobial coatings, drug-release, barrier properties and cell encapsulation. Special emphasis will be put on applications in the rapidly growing field of biosensors. Using polymers or proteins, the electrochemical buildup of the films can result from a local change of macromolecules solubility, self-assembly of polyelectrolytes through electrostatic/ionic interactions or covalent cross-linking between different macromolecules. The assembly process can be in one step or performed step-by-step based on an electrical trigger affecting directly the interacting macromolecules or generating ionic species.

## INTRODUCTION

Functional materials are predicted to have an enormous impact on many aspects of society, including next generation health care and energy-related technologies. Control of the interactions between material surfaces and their environment can be achieved by tailoring their surface properties, especially through the application of coatings. Macromolecular coatings play a major role in many technological areas ranging from the car industry to biosensors, membrane coating or chromatography columns. This has triggered the development of numerous deposition processes,<sup>1-3</sup> the simplest one being macromolecular adsorption. More known methods are for example the Langmuir-Schaefer film transfer<sup>4-5</sup> or the layer-by-layer (LbL) deposition of polyelectrolytes resulting in what is known as "polyelectrolyte multilayers".<sup>6-8</sup> Yet, most of these techniques lead to a uniform deposition and do not allow for spatially resolved film buildups which require the use of spatially localized triggers. To achieve such a spatial buildup, two main triggers are used: light and redox reactions at electrodes. Here, we will review macromolecular film buildup processes triggered by electrochemical means and performed in aqueous solution. Such coating processes are among the first ones which were used industrially at a large scale. In particular, car industry developed the electrodeposition of paint used to prevent corrosion. With the development of miniaturized (bio)sensors, electrochemically triggered buildup processes have found new applications. This review is divided in three sections related to the three categories of electrochemical buildup processes: (1) electrodeposition of macromolecules that result from their change of solubility near the electrode. Such a solubility change is often due to an induced local pH change near the electrode; (2) electrodeposition of polyelectrolytes on electrodes. In this case, polyelectrolytes are deposited through electrostatic or ionic interactions and (3) electrodeposition of polymers through covalent bond formation (Figure 1).



**Figure 1.** Schematic representation of the main processes of macromolecular film buildup triggered by electrochemical means performed in aqueous solution based on precipitation of macromolecules by change of solubility, ionic self-assembly of polyelectrolytes through electrostatic or ionic interactions and covalent bonds formation between macromolecules. Besides a change of the electrostatic surface charge of the electrode, the application of a current (or a potential) induces the generation of a gradient of  $H^+$ ,  $OH^-$ , metal ions or oxidized molecules which interact or react with the macromolecules present in solution. Allowing the encapsulation of enzymes, nanomaterials, drugs or cells, these processes are applied in several applications, such as biosensors, corrosion prevention, antimicrobial coatings, drug-release, barrier properties and cell encapsulation.

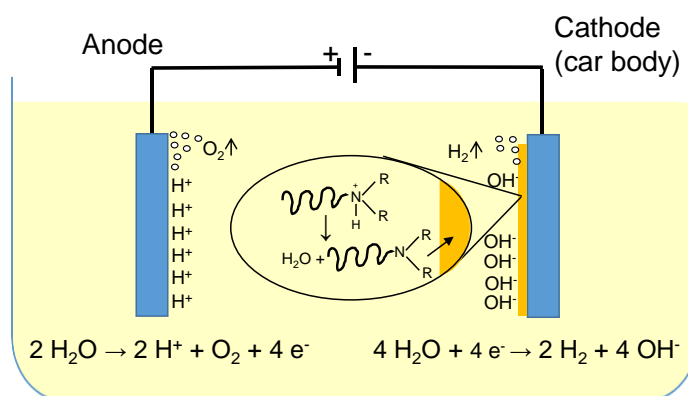
A large number of electrodeposition processes are based on the generation of chemical species (ions or redox molecules) at the electrode that then diffuse towards the solution. The film buildup is thus obtained by reaction or interaction between the electrogenerated species and the macromolecules. In analogy with morphogenic processes, such species can be called morphogens, a concept introduced in 1952 by Alan Turing in biological development.<sup>9</sup> In each section of this review, the numerous applications of each process will be presented such as enzymatic and non-enzymatic biosensors, corrosion prevention, antimicrobial coatings, drug-release, barrier properties and cell encapsulation. Special emphasis will be put on applications in the rapidly growing field of biosensors.

## 1. Electrodeposition through macromolecule precipitation

### 1.1 Electrodeposition of paints and other polyelectrolytes

**Principle.** Electrodeposition of macromolecules through precipitation is a process that has been discovered almost a century ago and is now referenced as electrodeposition of paints. Some patents from the first half of the 20<sup>st</sup> century describe examples of electropainting on conductive surfaces.<sup>10-12</sup> All these processes were based on the deposition of natural resinous materials, such as rubber. Finding no application in the industry, research on this topic was somehow forgotten.<sup>13</sup> During the 1950s with the great development of the car industry, coating processes were greatly needed in order to protect metallic surfaces from rust. Thus between Ford Motor and several paint companies, parallel researches were made to develop water-soluble paints which could be electrodeposited. The electrodeposition of cathodic paints, *i.e.* polycations soluble at acidic pH, is based on their deprotonation at basic pH. A localized precipitation and deposition of the polymers is obtained by the formation of a pH gradient (hydroxide ions gradient) at the electrode due to water electrolysis below a potential of -2 V (Figure 2). Electrodeposition of anodic paints were

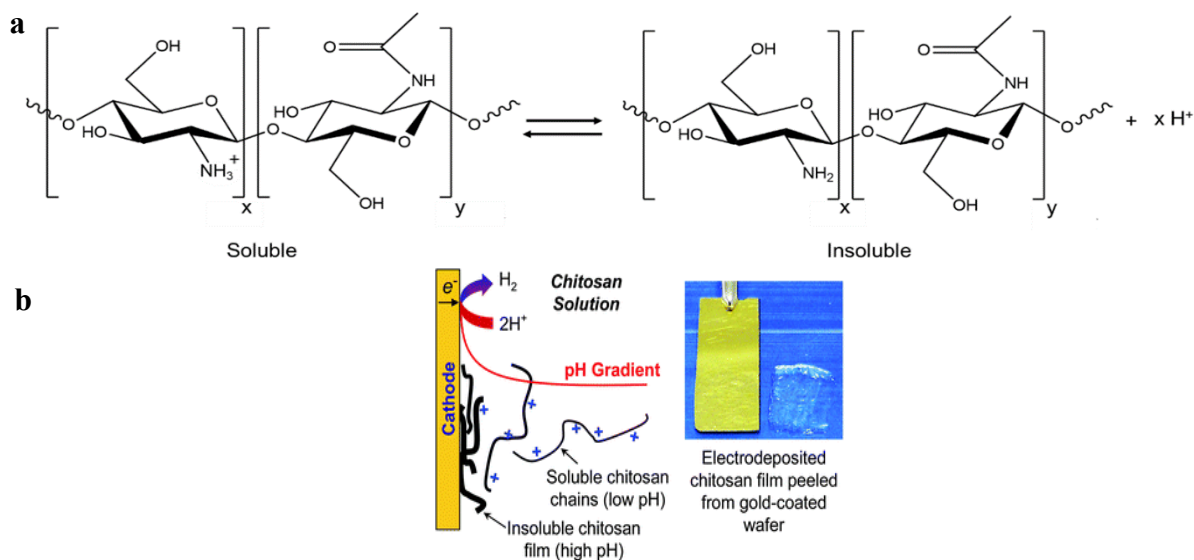
also developed using polyanions soluble at basic pH and insoluble at acidic pH. In this case, a gradient of protons is generated by water electrolysis at 50-400 V. Cathodic paints are mainly used to prevent corrosion in car industry.<sup>14</sup> Numerous papers and reviews, published at the end of the 20<sup>th</sup> century, describe the fundamental aspects of the electrodeposition process<sup>15-19</sup> and the chemistry of the paints and the binders.<sup>20-21</sup>



**Figure 2.** Mechanism of the deposition of a cathodic electrocoating.

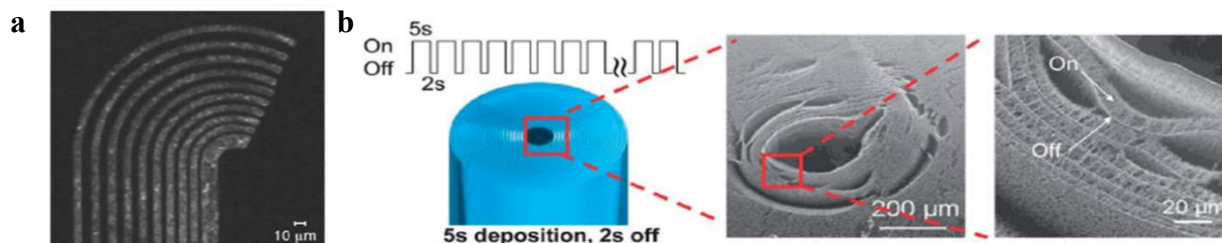
In 2002, Payne and co-workers opened a new page in the field of electrodeposition of polymers by using chitosan, a natural polysaccharide, as cathodic paint.<sup>22</sup> Chitosan is soluble at  $\text{pH} < \text{pKa}$  (about 6.3)<sup>23-24</sup> due to protonation of the primary amino groups and insoluble at  $\text{pH} > \text{pKa}$  (Figure 3a). The precipitation of chitosan in the vicinity of the electrode is obtained typically by generating a basic pH gradient by water electrolysis at -2 V (Figure 3b). The deposition process can be divided in two parts: (i) the electrophoretic motion of charged chitosan chains towards the electrode under the electric field,<sup>25</sup> and (ii) the chitosan precipitation due to pH change in the vicinity of the electrode. Using a microfluidic device under an optical microscope, the presence of a pH gradient<sup>26</sup> has been confirmed near the electrode triggering the formation of a semi-crystalline chitosan gel.<sup>27</sup> Electrochemically inactive, the chitosan gel is permeable to cationic and anionic probes.<sup>28</sup> The

deposited thickness is controlled by different parameters such as the time of deposition or the applied current density.<sup>22, 29</sup> The morphology (pores size and connection) of the gels can be tuned by changing the pH, the salt concentration or the nature of the acidic solution used to solubilize chitosan, *i.e.* acetic acid, malonic acid or citric acid solution.<sup>30-31</sup>



**Figure 3.** (a) Chemical pathway between soluble and insoluble chitosan. (b) Mechanism of cathodic electrodeposition of chitosan and image of the obtained chitosan gel peeled from an electrode. Reproduced with permission from reference 31. Copyright 2013 Royal Society of Chemistry.

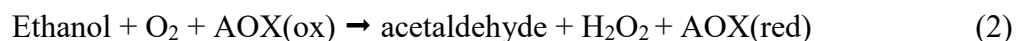
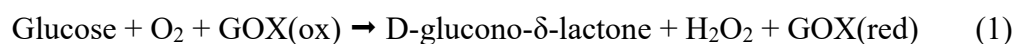
The spatial control of the deposition was shown using wire electrode,<sup>32</sup> patterned template with an edge sharpness of 0.5-1.0  $\mu\text{m}$ <sup>29, 33-34</sup> and confined micropores with a diameter of 3-8  $\mu\text{m}$  (Figure 4).<sup>35</sup> Using photoconductive cathodes to produce hydroxide ions, patterned chitosan depositions were obtained by patterned light illumination.<sup>36</sup> Since 2008, Zhitomirsky and co-workers developed the electrodeposition using other biopolymers (alginate,<sup>37</sup> hyaluronic acid<sup>38</sup>), polypeptides (poly(L-lysine), poly(L-arginine))<sup>39</sup> and synthetic polyelectrolytes.<sup>40-42</sup>



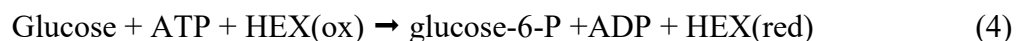
**Figure 4.** Spatially selective electrodeposition of (a) fluorescently labeled chitosan on a curved geometry pattern at a constant current of  $3 \text{ A/m}^2$  for 120 s. Reproduced with permission.<sup>33</sup> Copyright 2009, Royal Society of Chemistry, and (b) of chitosan gel on a wire using on/off application of a current of 0.5 mA. Reproduced with permission from reference 32. Copyright 2014 Royal Society of Chemistry.

**Enzymatic biosensing application.** Enzymatic biosensors are analytical devices that associate a bioreceptor, which is an immobilized enzyme, and a transducer. The transducer converts the (bio)chemical signal resulting from the interaction between the analyte and the enzyme into an electrical signal proportional (or inversely proportional) to the analyte concentration. Oxidoreductases are mainly used due to their ability to catalyze oxidation or reduction reactions by transfer of electrons. In 2002 using commercially available anodic paints, Schuhmann and co-workers found new applications of paint electrodeposition in the field of enzymatic biosensors.<sup>43</sup> Paint electrodeposition processes allowed to co-deposit enzymes by physical entrapment, in copolymer acrylate/acrylate ester (anodic paint)<sup>43-48</sup> or copolymer vinyl imidazole/dimethylaminoethyl methacrylate (cathodic paint) coatings.<sup>49-52</sup> Glucose oxidase (GOX)<sup>43-44, 46-47, 49-51, 53-54</sup> was the first immobilized enzyme for glucose monitoring. The monitoring is based on the detection of  $\text{H}_2\text{O}_2$  generated by the oxidation of glucose by the enzyme (eq 1). This detection is done by measuring the current intensity during the oxidation of  $\text{H}_2\text{O}_2$  at

0.6 V (vs Ag/AgCl). Alcohol oxidase (AOX) was immobilized to titrate ethanol using the same electrochemical detection of H<sub>2</sub>O<sub>2</sub>, produced as secondary product when ethanol is oxidized in acetaldehyde by the enzyme.<sup>55</sup> However due to limited stability of AOX-based sensors at high working potential, AOX and horseradish peroxidase (HRP) bi-enzyme sensors were designed for alcohol sensing at lower working potential.<sup>52, 56</sup> A first layer of HRP was immobilized on the electrode before immobilization of a second layer of AOX using the electrodeposition process. The enzymatic oxidation of ethanol by AOX generates H<sub>2</sub>O<sub>2</sub> which is reduced by HRP (eqs 2-3). The generated current, proportional to the concentration in ethanol, is measured by application of -0.05 V (vs Ag/AgCl).

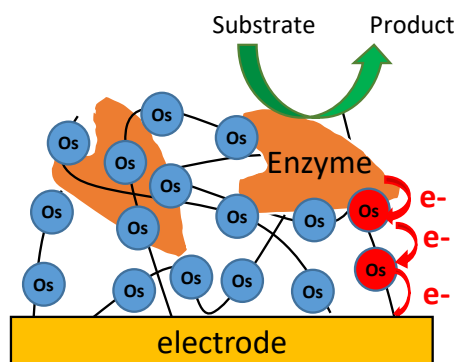


Another bi-enzyme system was developed for ATP sensing by simultaneous immobilization of GOX and hexokinase (HEX).<sup>57</sup> In the presence of a known concentration of glucose, an analytical signal (using H<sub>2</sub>O<sub>2</sub> detection) is measured due to its reduction by GOX (eq 1). When ATP is added to the solution, glucose is also consumed by HEX (eq 4). A competitive consumption of glucose is obtained decreasing the quantity of glucose available for GOX. Thus, the analytical signal due to glucose decreases proportionally to the quantity of ATP present.



In the above studies, the electron transfer between the entrapped redox enzyme and the electrode occurs via free-diffusing redox mediators, *i.e.* the enzymatically generated H<sub>2</sub>O<sub>2</sub>. Generally, direct

electron transfer between the enzyme and the electrode is most of the time prevented due to the deeply buried prosthetic group in the enzyme. In order to improve the electron transfer, osmium functionalized polymers, redox polymers, were co-deposited with several enzymes, such as quinohemoprotein alcohol dehydrogenase,<sup>48</sup> AOX/HRP bi-enzyme system,<sup>52, 56</sup> GOX,<sup>54, 58-59</sup> Laccase,<sup>59-60</sup> cellobiose dehydrogenase,<sup>58</sup> pyrroloquinoline quinone-dependent glucose dehydrogenase.<sup>58, 61-62</sup> In this last case, mediated electron transfer is obtained by electron hopping through consecutive oxidation/reduction reactions of osmium moieties (Figure 5). Recently, Plamper published a review which categorizes the different basic mechanisms for electrochemical switching of redox-active polymers, leading to conformational and solubility changes.<sup>63</sup>



**Figure 5.** Schematic representation of electron hopping mechanism in osmium functionalized polymer deposited by electrodeposition.

The operating stability of electrodeposited redox polymer films was improved by electrochemically induced crosslinking of the deposited films.<sup>59</sup> Epoxy functionalized redox polymers and protected thiol (or amine) bifunctional spacers were co-deposited by application of anodic potential pulse sequence. The generated pH gradient allowed the concomitant electrodeposition of the redox polymer and the deprotection of the spacers leading to the

crosslinking between epoxy and thiol (or amine) moieties. Laccase and GOX were successfully immobilized by this process leading to an improved operation stability of the biosensor over two days. Different types of electrodes were functionalized using the electrodeposition of paints: such as micro-electrodes (*i.e.* four-bands Pt array 1-mm length; 25- $\mu\text{m}$  width; 25- $\mu\text{m}$  distance),<sup>43</sup> tip-like electrodes (*i.e.* home-made platinized pipet tip)<sup>44</sup> or porous electrodes.<sup>47, 54</sup> Porous electrodes were prepared either by electrodeposition of gold on a colloidal crystal template (using silica spheres) followed by its dissolution<sup>47</sup> or by nanoparticle lithography on a layered gold/  $\text{Si}_3\text{N}_4$  insulator/gold structure, nanoparticles being used as a shadow mask.<sup>54</sup> Enzyme loaded electrodeposited films can also be used for biofuel cell applications allowing reproducible and localized enzyme deposition.<sup>64-66</sup>

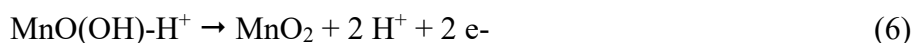
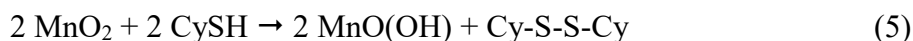
Electrodeposited chitosan films were widely used to develop biosensors by co-deposition with enzymes<sup>67</sup> and various inorganic compounds. The first chitosan based biosensors were based on co-electrodeposition of chitosan with GOX and inorganic nanomaterials such as gold nanoparticles,<sup>68-73</sup> carbon nanotubes,<sup>74-76</sup>  $\text{MnO}_2$  particles<sup>77-78</sup>, nickel nanoparticles<sup>79</sup> and graphene oxide.<sup>80-81</sup> The co-deposition of inorganic nanomaterials improves biosensor properties by promoting electron transfer. The sensitivity and stability of the response of HRP or GOX-based biosensors were also improved by co-incorporation of highly conductive ionic liquids<sup>82-83</sup> and Prussian Blue, an efficient redox mediator for selective reduction of  $\text{H}_2\text{O}_2$ .<sup>84-85</sup> Acetylcholine, choline, polyphenol, superoxide anions and adrenaline biosensors were created by co-deposition of chitosan with acetylcholine esterase,<sup>86-91</sup> choline oxidase,<sup>92</sup> laccase,<sup>93</sup> superoxide dismutase<sup>94</sup> and tyrosinase.<sup>95</sup> GOX-chitosan microspots were designed by generating local pH gradients using scanning electrochemical microscopy.<sup>96</sup> This method may facilitate the construction of a microfabricated biosensor based on spatial segregation of enzymes on a homogeneous support.

Co-electrodeposition of chitosan and two different inorganic components can be done step-by-step to obtain chitosan/Prussian Blue and chitosan/gold nanoparticles double layers before deposition of GOX and  $\beta$ -glucanase mixture solution. The obtained sensor allowed monitoring  $\beta$ -glucan, a natural polymer of D-glucose present in cell walls of yeast or fungi through its oxidation by  $\beta$ -glucanase into glucose which is further oxidized by GOX.<sup>97</sup> To monitor glucose at low working potential, GOX/HRP bi-enzyme sensors were developed by one step co-electrodeposition of chitosan, GOX, HRP and Concanavalin A from a mixed solution.<sup>98</sup> Concanavalin A was used as a linker between the enzymes and chitosan due to its affinity with glycoconjugates. Electrodeposited chitosan can also be used as a platform. Indeed,  $H_2O_2$ <sup>99</sup> and glucose<sup>100</sup> sensors were developed by adsorption of HRP (with gold nanoparticles) and GOX on previously electrodeposited chitosan, respectively. An amperometric  $H_2O_2$  biosensor was designed by co-deposition of alginate with HRP, followed by polyvinyl butyral layer to prevent enzyme leakage.<sup>101</sup>

**Non-enzymatic biosensing applications.** Organic molecules, such as positively charged metalloporphyrins, were co-deposited with negatively charged polymers, using electrodeposition of paints, for nitric oxide (NO) sensing. The detection was based on NO oxidation by metalloporphyrin molecules.<sup>45</sup> Miniaturized potentiometric and voltammetric pH sensors were developed by electrodeposition of two redox polymers, one with covalently linked osmium complexes as pH independent redox species and the other containing a pH-dependent phenothiazine moieties on gold microelectrodes.<sup>102</sup> The peak potentials for both redox immobilized species were determined from the square-wave voltammograms. Using the pH independent polymer as internal reference, the peak potential difference of the pH-dependent redox polymer allowed the determination of the pH in a reproducible manner. It should be noted that Janus particles were obtained by bipolar electrodeposition of paints, where the pH gradient was

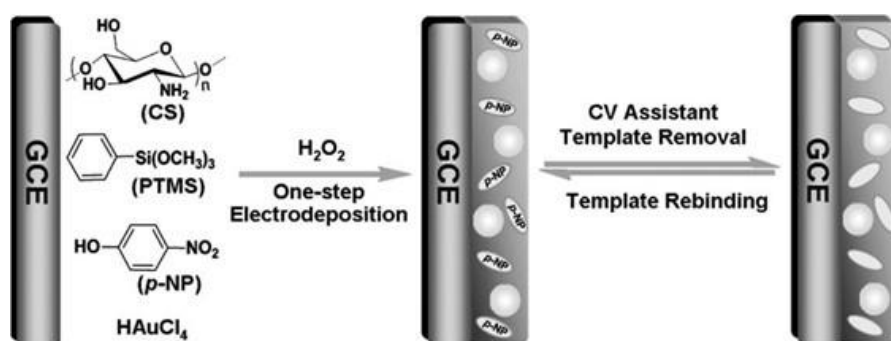
localized at the surface of conducting particles in suspension under an electric field of 71 V/cm.<sup>103</sup> Janus anisotropic particles could be used in applications such as e-paper.<sup>104</sup>

Non-enzymatic biosensors were also developed by co-deposition of chitosan and different inorganic components. Manganese dioxide nanowires were deposited with chitosan for drug<sup>105</sup> and cysteine sensing.<sup>106</sup> Cysteine sensing is based on the redox reaction which takes place between MnO<sub>2</sub> and cysteine to form a disulfide bond between two cysteine molecules and MnO(OH), easily protonated in water (eq 5). Protonated MnO(OH) can be electrooxidized back to MnO<sub>2</sub> by applying a potential of 0.5 V (vs SCE) (eq 6), the measured current being proportional to cysteine concentration.



Trichloroacetic acid (TCAA), a toxic pollutant found in industrial waste, sensor was designed by co-deposition of chitosan and silver nanoparticles. Low detection limit and fast current response of TCAA reduction were obtained due to a good electron hopping in silver nanoparticles and a favorable electrostatic interactions between oppositely charged TCAA and chitosan.<sup>107</sup> NO is a free-radical messenger involved in a wide range of physiological and pathological processes. *In vivo* microsensor for detection of NO in the brain was developed by co-deposition of chitosan, hemin (a metalloporphyrin) and functionalized multi-wall carbon nanotubes.<sup>108</sup> NO was measured by electrochemical reduction at 0.762 V (vs Ag/AgCl) using square wave voltammetry, which offers the advantage of high sensitivity and the chemical resolution needed. Direct electron transfer was ensured by Fe(II)/Fe(III) couple of hemin and carbon nanotubes. Biocompatible carbon nanofiber-chitosan materials were designed for cytosensing. This biosensor is based on the

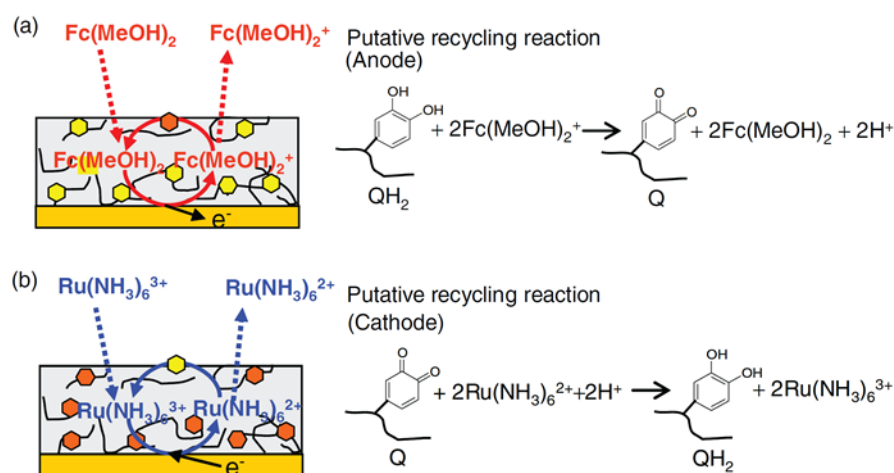
measurement of the impedance signal which depends on the amount of adherent cells.<sup>109</sup> Molecularly imprinted hybrid films were developed to detect p-nitrophenol (p-NP), a toxic substance extensively used in chemical industry.<sup>110</sup> Simultaneous electrodeposition of chitosan, copolymerization of phenyltrimethoxysilane (PTMS) and electroreduction of  $\text{HAuCl}_4$  salt into gold nanoparticles were performed in the presence of p-NP. Thanks to H-bond interactions, p-NP molecules interact with chitosan and are further removed from the electrodeposited coating by cyclic voltammetry (CV) (Figure 6). The applied voltage range of CV causes the cycle of reduction/oxidation of p-NP, disrupting the strong interactions of p-NP with the binding sites and favoring the template removal. After further incubation in different p-NP solutions, differential pulse voltammetry was used to measure the current intensity at the reduction potential of p-NP (0.12 V vs SCE) and to obtain a linear calibration curve versus p-NP concentration. An improved sensorial detection range and detection limit were obtained with p-NP imprinted hybrid films in comparison to non-imprinted film (*i.e.* chitosan/PTMS/gold nanoparticles) thanks to the binding of p-NP.



**Figure 6.** Schematic representation of the fabrication protocol imprinted Chitosan/PTMS/AuNPs on glassy carbon electrode (GCE) for sensing p-NP. Reproduced with permission from reference 110. Copyright 2013 Royal Society of Chemistry.

Different immunosensors were developed by post-functionalization of electrodeposited chitosan with antibodies, oligonucleotides, viruses, phenol/catechol bearing molecules and proteins using physical adsorption or grafting by chemical, electrochemical or enzymatic means. Label free immunosensors for the detection of Hepatitis B surface antigen were designed by physical adsorption of Hepatitis B antibody on 3D porous chitosan membrane<sup>111</sup> and on ferrocene functionalized chitosan films.<sup>112</sup> Antigen concentration was measured through the decrease of amperometric response due to the formation of the antibody/antigen complex layer. This complex layer blocks the transfer of electrons provided by ferrocyanide present in solution<sup>111</sup> or grafted ferrocene<sup>112</sup> under electrochemical stimulation. Glutaraldehyde chemistry applied on electrodeposited chitosan was used to immobilize DNA to obtain biochips<sup>113-115</sup> or sensors able to detect DNA hybridization by the mass change of a microcantilever.<sup>116</sup> Tobacco mosaic virus, genetically modified, was assembled selectively on microelectrodes through nucleic acid hybridization on chitosan for the development of viral templates.<sup>117</sup> By electrodeposition of biotinylated chitosan, streptavidin was immobilized on microelectrodes allowing spatial selectivity of biotinylated protein assemblies, *i.e.* biotinylated Protein A allowing further deposition of fluorescently-labeled antibodies.<sup>118</sup> After its electrodeposition, chitosan can be oxidized using electrochemistry for further grafting of avidin, protein G and green fluorescent protein.<sup>119</sup> Indeed by application of an anodic potential of 0.9 V (vs Ag/AgCl) in the presence of NaCl, reactive mediators, HOCl and OCl<sup>-</sup>, are formed and oxidize chitosan creating aldehyde moieties which can further react with primary amines of proteins. Fluorescently labeled azide tagged bovine serum albumin was covalently fixed on electrodeposited alkyne functionalized chitosan, by Cu(I) catalyzed Huisgen reaction, where Cu(I) was generated at the electrode from reduction of Cu(II).<sup>120</sup> Phenol or catechol moieties have been grafted on electrodeposited chitosan by applying an anodic

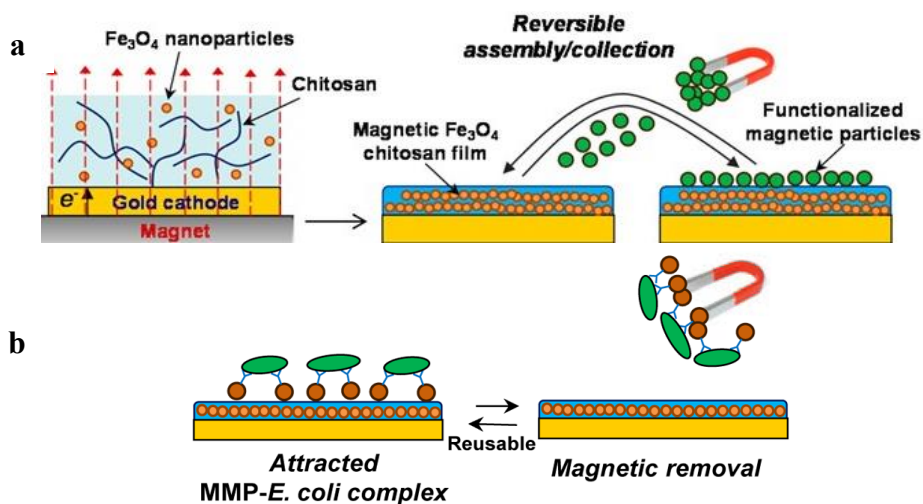
potential by making use of their properties in oxidative state to react with amino groups of chitosan.<sup>121-123</sup> Besides improving the mechanical properties,<sup>124</sup> the presence of catechol moieties amplify the electrochemical signal of redox probes in contact with the chitosan gel (Figure 7).<sup>121,</sup>  
<sup>125</sup> This property was used to detect pyocyanin, a redox active bacterial metabolite<sup>126</sup> and clozapine, an antipsychotic drug.<sup>127-130</sup>



**Figure 7.** Proposed mechanism for amplification of mediator-based electrochemical currents by catechol-modified chitosan films: two mediators, (a) ferrocene dimethanol  $\text{Fc}(\text{MeOH})_2$  and (b) ruthenium hexaamine  $\text{Ru}(\text{NH}_3)_6^{3+}$ , engage oxidative and reductive redox-cycling mechanisms between the phenolic film ( $\text{QH}_2/\text{Q}$ ) and ITO electrode. Reproduced with permission from reference 121. Copyright 2014 John Wiley and Sons.

**Other biomedical applications.** A multi-domain fusion protein, named HLPT, was immobilized covalently on previously electrodeposited chitosan to produce a bacterial signaling molecule in order to electronically induce collective bacterial behavior.<sup>131</sup> This covalent functionalization was obtained enzymatically using tyrosinase and tyrosine containing proteins.<sup>115, 132</sup> The principle is based on an adsorbed tyrosinase layer on the chitosan film which selectively converts tyrosine

residues of proteins into reactive o-quinones. The “activated” proteins can then undergo grafting reactions with the nucleophilic amines of chitosan. Organized magnetic nanoparticles platform was developed for the immobilization of antibody-functionalized magnetic beads to capture specific pathogens and collect them by magnetic removal (Figure 8).



**Figure 8.** Schematic representation of (a) the co-electrodeposition of chitosan (dark blue chains) and magnetic Fe<sub>3</sub>O<sub>4</sub> nanoparticles (orange spheres) in the simultaneous imposition of a magnetic field leading to organized nanoparticles. This magnetic Fe<sub>3</sub>O<sub>4</sub> chitosan film is able to reversibly capture magnetic microparticles (green spheres). (b) This platform can be used to collect and to release *E. Coli* (green ellipsoid) through the reversible immobilization of antibody (anti-*E. Coli*) functionalized magnetic microparticles (MMP-*E. coli*, brown spheres). Reproduced with permission from reference 133. Copyright 2015 American Chemical Society.

This platform was obtained by the electrodeposition of chitosan films in the presence of magnetic nanoparticles by applying both electric and magnetic fields.<sup>133</sup> Microbial fuel cells are devices in which bacteria consume water-soluble waste (such as glucose, ethanol and acetate) to generate electrons. Co-electrodeposited chitosan/alginate/Prussian Blue films offer (i) a biocompatible

matrix for the growth of microorganisms and (ii) a good electron transfer for the development of microbial fuel cell.<sup>134</sup> Nanoparticle platforms were developed by co-deposition of chitosan with fluorescently labeled latex nanoparticles,<sup>135</sup> ZnO particles,<sup>136</sup> ZnS quantum dots,<sup>137</sup> carbon dots<sup>138</sup> to develop fluorescent or photoluminescent coatings with tunable intensity depending on the deposition parameters, such as deposition time. Alternating current electrodeposition was demonstrated to be a suitable technique to deposit uniform poly(acrylic acid)-TiO<sub>2</sub> composite coatings on conductive materials.<sup>139</sup>

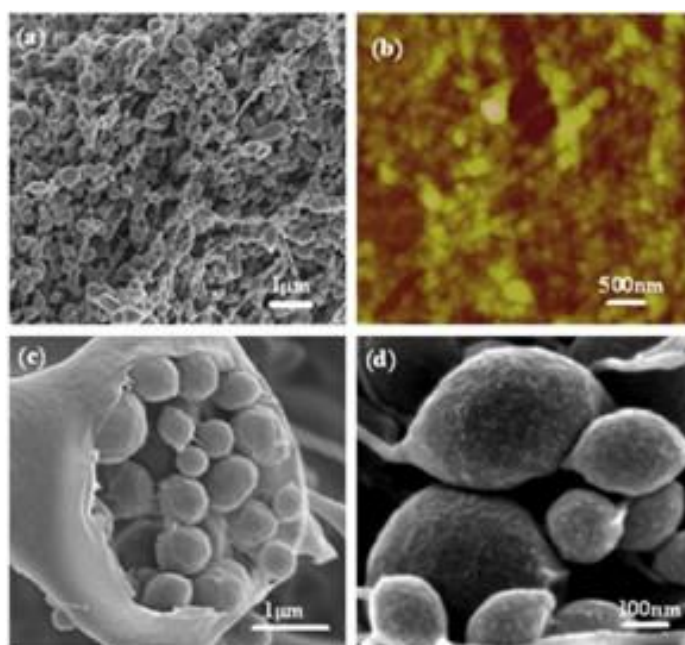
The electrodeposition of natural polymers, such as chitosan or alginate, allows the development of biocompatible coatings for stainless steel or titanium implants. Biocompatibility tests were performed on chitosan/alginate layered coatings, obtained by alternated electrodeposition of chitosan and alginate, showing a suitable cell proliferation.<sup>140</sup> Electrodeposited blends of chitosan and poly(ethylene oxide)<sup>141</sup> or gelatin<sup>142</sup> are promising candidates for implant functionalization with improved mechanical properties compared to chitosan. Co-electrodeposited chitosan/carbon nanotube films enhance cellular adhesion.<sup>143</sup> Biocompatible hybrid coatings were developed by electrodeposition of chitosan with hydroxyapatite (HAp), the major mineral constituent of bones<sup>144-146</sup> and bioactive glass,<sup>147-150</sup> which favor the formation of HAp in contact with physiological fluids. In order to reduce corrosion, chitosan co-deposited with HAp,<sup>151-152</sup> CaSiO<sub>3</sub> particles,<sup>153</sup> carbon nanotubes,<sup>154-155</sup> hexagonal boron nitride/TiO<sub>2</sub><sup>156</sup> and halloysite nanotubes<sup>157</sup> act as protective layers against ion diffusion towards nitinol<sup>154</sup> and stainless steel surfaces.<sup>152, 155-157</sup> Other composite films, obtained by electro-codeposition of carbon nanotubes/alginate,<sup>154</sup> halloysite/HAp/hyaluronic acid,<sup>158</sup> HAp/alginate,<sup>37</sup> TiO<sub>2</sub>/alginate/ bioactive glass<sup>159</sup> and cellulose nano-crystals/alginate,<sup>160</sup> were also developed for corrosion protection of medical implants. Antimicrobial properties of chitosan gels were obtained by incorporation of silver

nanoparticles,<sup>161-164</sup> antibiotics,<sup>165</sup> or antibiotics in combination with graphene oxide<sup>166</sup> or with bioglass.<sup>167</sup> Drug-release surfaces were developed by co-deposition of insulin loaded inorganic nanoplatelets,<sup>168</sup> ibuprofen,<sup>169-170</sup> gelatin/ampicilin<sup>171</sup> and an antiseptic.<sup>172</sup> The release is obtained by application of a potential (typically between  $-5$  and  $+5$  V)<sup>168</sup> or by gel degradation<sup>171</sup> or swelling<sup>172</sup> in PBS. Antibiotic loaded polymeric microspheres/alginate electrodeposited layers can be used as drug-delivery coatings.<sup>173</sup> ZnO/alginate/bioactive glass coatings have both antimicrobial and corrosion protection properties.<sup>174</sup>

## 1.2 Electrogelation of silk

**Principle.** The electrogelation of silk, obtained from silkworm, has been developed using high potentials (up to 30 V).<sup>175-176</sup> By applying a constant electric potential, silk gels were deposited around the positive electrode (anode).<sup>175</sup> The gel, stable when the electrical potential is stopped, can be dissolved by reversing the polarity of the working electrode while a new gel is created on the counter electrode. Silk fibroin is a high molecular weight block copolymer made of heavy and light chains linked by a single disulfide bond.<sup>177</sup> The heavy chain consists of alternating arrays of 12 repetitive hydrophobic peptide domains, rich in alanine and glycine residues, and 11 small hydrophilic charged amorphous domains, rich in acidic groups.<sup>178</sup> For a pH above its pI (4.2), silk protein is negatively charged and intermolecular self-assembly is prevented by electrostatic repulsion. When the pH value decreases by water electrolysis, protonation of acidic groups enables intermolecular self-assembly of silk's macromolecules.<sup>179</sup> These gels exhibit spherical micellar structures obtained from the assembly of 10 nm diameter particles into several hundreds of nm spheres which in turn assemble into large microspheres (Figure 9).<sup>180</sup> Theoretical finite-element electro-diffusion models using classic diffusion and ion migration equations under an electric potential support experimental pH measurement.<sup>181</sup> These models confirm that silk electro-gel

construction is governed by the proton gradient generated from the electrode. Such gels can be deposited on different electrode materials such as copper, aluminum, gold or platinum with various geometries.<sup>175</sup> A thin transparent film with no underlying surface was obtained by using a ring-shaped electrode.<sup>182</sup> This fabrication process allows to confer three dimensionality and crystallinity to the gels. Their mechanical properties can be tuned by varying the time of application or the intensity of the electric potential.<sup>183-184</sup>



**Figure 9.** Morphology of electrodeposited silk gels observed by (a) scanning electron microscopy (SEM) and (b) atomic force microscopy. SEM (c) image of the inside structure of large microspheres and (d) magnified image of its inner part. Reproduced with permission from reference 180. Copyright 2011, Elsevier.

**Applications.** Mainly in random coil conformation, silk fibroin assembled in the gels are lacking thermal and mechanical stability. In order to improve their stability for biomedical applications, cross-linking of the gels was obtained chemically by using glutaraldehyde and physically by

inducing  $\beta$ -sheet cross-links through ethanol dehydration.<sup>185</sup> Very recently, these gels were studied as potential coatings for bone implants.<sup>186</sup> To add an antibacterial activity, silk fibroins were chemically modified by tetracycline, a globally positively charged antibiotic. The obtained positively charged functionalized silk was deposited on a titanium cathode.<sup>187</sup>

### 1.3 Electroprecipitation of enzymes

Electroprecipitation of enzymes is a process based on the application of an electric potential to induce the precipitation of an enzyme on the surface of an electrode. Two different processes are described in the literature: the electrochemical and the electrophoretic depositions. Both are based on the electrolysis of water which generates a proton gradient leading to the aggregation and precipitation of enzymes at a pH close to its isoelectric point (pI). Both processes are summarized in exhaustive reviews<sup>188-189</sup> and will only briefly be presented below.

**Electrochemical deposition of enzymes.** Electrochemical deposition of enzymes is based on the application of relatively low constant voltages (0-2V) in highly conductive solutions. Buffers with high ionic strength are often used to screen the charge of the enzyme which limits its motion in an electric field. Thus, only enzymes present in the vicinity of the electrode are deposited leading to thin coatings (few hundreds of nm). Introduced by Wang *et al.* to create collagen-enzyme biocatalytic membranes,<sup>190</sup> this process was applied for biosensing application by using various enzymes or proteins such as GOX,<sup>191-194</sup> HRP,<sup>195</sup> laccase,<sup>196</sup> or avidin, for further immobilization of biotinylated GOX.<sup>197</sup> To improve the performance of the obtained coatings, enzymes were co-deposited with other compounds such as anionic clay,<sup>198</sup> carbon nanotubes,<sup>93, 199</sup> palladium nanoparticles<sup>200</sup> or redox mediators/polymers.<sup>201-202</sup>

**Electrophoretic deposition of enzymes.** Electrophoretic deposition of enzymes is based on the electrophoretic motion of enzymes. In this process, high voltages (few hundreds of volts) are applied using low ionic strength solutions.<sup>189</sup> To avoid heat and extensive evolution of water electrolysis, pulsed direct current (PDC) or alternating current (AC) are used. Having a high surface charge due to low charge screening, all the enzymes present in solution contribute to the film buildup. The obtained coatings are much thicker (several  $\mu\text{m}$ ) than the ones deposited by electrochemical deposition. Electrophoretic deposition of enzymes was introduced in 2009 by Ammam and coworkers using GOX.<sup>203</sup> Different enzymes, such as  $\beta$ -galactosidase,<sup>204</sup> laccase,<sup>205-206</sup> catalase,<sup>206-207</sup> or glutamate oxidase<sup>208</sup> were immobilized using this process for biosensing and enzymatic biofuel cell applications. Electropolymerization of polypyrrole was performed after the electrophoretic deposition of GOX functionalized carbon nanotubes in order to obtain a stabilization of the assembled coating<sup>205</sup> or before carbon nanotubes and glutamate oxidase deposition to prevent the diffusion of interfering molecules such as ascorbate, urate or acetaminophen.<sup>208</sup>

## 2. Electrochemical deposition through polyelectrolytes self-assembly

### 2.1 Macromolecules deposition under the application of a constant potential

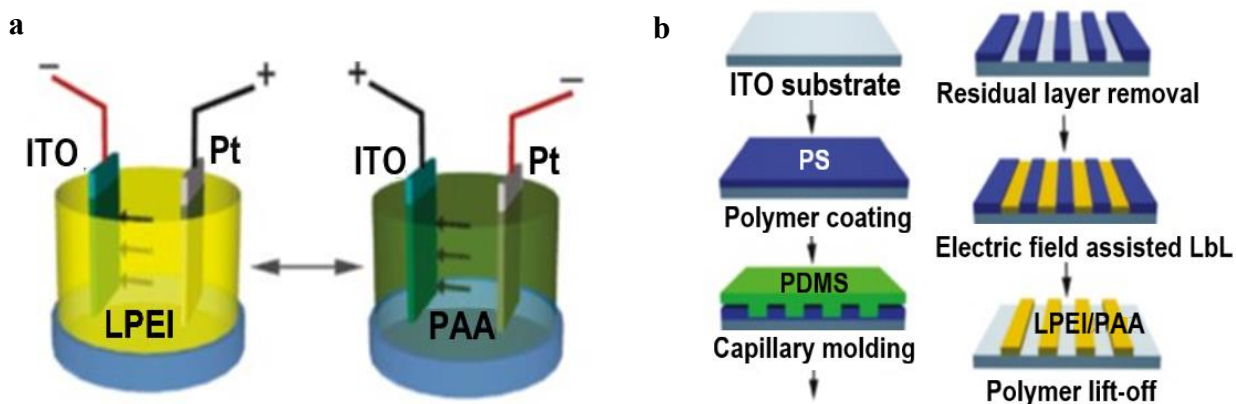
The influence of an electric potential on the adsorption of macromolecules was first studied on proteins<sup>209-214</sup> followed by polycations, such as poly(vinylpyrrolidone)<sup>215-216</sup> and poly(L-lysine)-grafted-poly(ethylene glycol).<sup>217</sup> A surprising phenomenon was observed: positively charged proteins (and polycations) adsorbed on positively charged electrodes by application of an anodic potential. Furthermore, Van Tassel and coworkers highlighted a phenomenon of continuous deposition of different polycations, such as poly(L-Lysine) (PLL), poly(L-ornithine) and poly(allylamine) (PAH) during the application of a potential between 1.2 and 1.5 V (vs Ag/AgCl).

This adsorption of polyelectrolytes on a charged electrode is not only driven by electrostatic interactions but also by weak interactions (van der Waals, close-range) and counterion condensation.<sup>218</sup> Recently, Mergel *et al.* demonstrates the effect of polymer topology and molar mass on the electrodeposition of a quaternized polycation in the presence of hexacyanoferrate(II). In this case, a physically crosslinked polymeric film was obtained upon counterion switching, *i.e.* by oxidation of ferrocyanide into less charged ferricyanide.<sup>219</sup> Polyelectrolyte multilayer films are obtained by the LbL process, based on the alternated deposition of polycations and polyanions on a surface. The application of a constant potential, typically between 1.0 and 2.0 V (vs Ag/AgCl), during the buildup of PAH/poly(styrene sulfonate) (PSS),<sup>220</sup> PLL/dextran sulfate<sup>220</sup> and PLL/DNA<sup>221</sup> multilayers allows to tune their thickness. In 2012, Van Tassel wrote a review to make a summary of the influence of an electrical potential on the assembly and disassembly of polyelectrolyte films.<sup>222</sup> Conductive neutral polymer, used for optoelectronic applications such as polymer light-emitting diodes or photovoltaic devices, can also be deposited under a constant voltage. Conductive multilayer of one component, a conductive polymer poly(3-hexylthiophene), was assembled by several applications of 10 V for 10 min. A controlled thickness and high quality films were obtained with an improved crystallization compared to spin coated macromolecules.<sup>223</sup> High crystallization and ordered arrangement of poly(3-hexylthiophene) allowed to obtain films with high conductance.

## 2.2 Electric-Field Assisted Layer-by-Layer

**Principle.** A derivative technique of the LbL process, the electric-field directed layer-by-layer assembly (EFDLA), was introduced by Gao and co-workers in 2002.<sup>224</sup> Figure 10 shows a schematic illustration of the EFDLA, based on the enhancement of the electrostatic interactions between the polyelectrolytes and the surface by the application of alternated electric potential,

typically between 0.5 and 1.5 V, at each deposition step.<sup>225</sup> When a polycation (linear poly(ethylene imine), LPEI) is brought in contact with the electrode, a negative potential is applied to render the surface negatively charged and to attract the polycation chains to the surface. When the polyanion (poly(acrylic acid), PAA) is in contact with the electrode, the applied potential is reversed to a positive value rendering the surface positively charged and attracting the negatively charged chains. Electroluminescent patterns were obtained by EFDLA of poly(diallyldimethylammonium chloride)/quantum dots on micro-electrodes by application of unfavorable (*i.e.* 0.6 V vs Ag/AgCl) and favorable (*i.e.* 1.4 V vs Ag/AgCl) potentials.<sup>226</sup> EFDLA leads to larger amounts of adsorbed material on the surface than the classic LbL process due to the conformation (in coiled state) of deposited weak polyelectrolytes depending on the assembly pH.<sup>227</sup>



**Figure 10.** Schematic illustrations of (a) electric-field assisted layer-by-layer assembly of LPEI and PAA and (b) pattern formation. Reproduced with permission from reference 225. Copyright 2011 American Chemical Society.

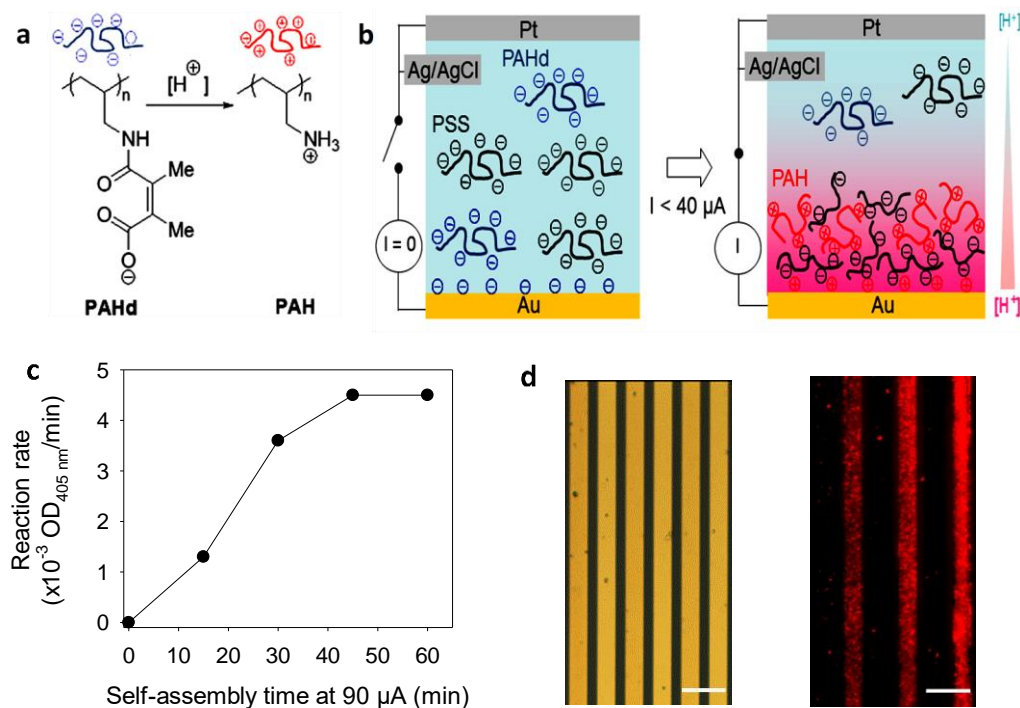
**Applications.** Based on the electrocatalytic activity of quantum dots toward CO<sub>2</sub> reduction, a photo-electrochemical device was developed to build quantum-dots/polycation multilayers on ITO

electrodes.<sup>228</sup> Enzyme and neutral red probe based multilayers were designed for biosensing applications<sup>229-230</sup> and pH measurements,<sup>231</sup> respectively. Polyamide reverse osmosis membranes were functionalized by PEI/PAA multilayers for isopropanol-water separation. In this case, the non-conductive membrane was dipped in the polyelectrolyte solution between two electrodes. A given constant voltage, between 0 and 10 V, was applied to induce polyelectrolytes diffusion towards the membrane.<sup>232-233</sup> Chitosan/lignosulfonate multilayer films with tunable wettability were deposited at an extremely high voltage (4 kV).<sup>234</sup> This high voltage induces the reduction of the surface tension of the polymer solutions during the film buildup. At 0 V, chitosan films deposited on lignosulfate are hydrophilic. The application of the electric field induces structural changes of the deposited chitosan which turns from hydrophilic to hydrophobic.<sup>234</sup> Hydrogen, used as high-energy fuel by aerospace industry, can induce corrosion on stainless steel materials used for their storage. Self-assembled PEI/graphene oxide multilayers appeared to be a practical high barrier H<sub>2</sub> material.<sup>235</sup> When assembled under an electric field, enhanced H<sub>2</sub> barrier properties were obtained due to an increase of the adsorbed amount of graphene oxide.

### 2.3 Electro-self-assembly of polyelectrolytes through electrostatic interactions

Very recently, our team introduced a new way to electrotrigger the assembly of oppositely charged polyelectrolytes in a one pot manner.<sup>236</sup> For this purpose, a charge shifting polyanion, poly(allylamine dimethylmaleic acid) (PAHd), was synthesized by modification of PAH with dimethylmaleic functions. PAHd, negatively charged at basic pH, can be hydrolyzed into positively charged PAH when the pH is decreased (Figure 11a). Mixed with PSS (polyanion) at basic pH in the presence of hydroquinone, PAHd does not form complexes due to electrostatic repulsion. The application of an anodic current (above 40  $\mu$ A) induced the oxidation of hydroquinone leading to an acidic pH gradient in the vicinity of the electrode. This pH decrease

induced the hydrolysis of PAHd into PAH in a confined area and triggered the localized assembly near the electrode of PAH and PSS through attractive electrostatic interactions (Figure 11b).



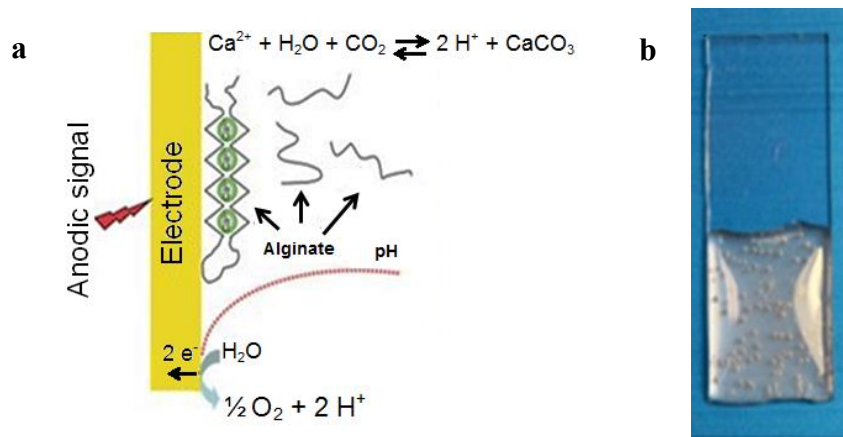
**Figure 11.** (a) Principle of the charge-shifting polyelectrolytes: PAHd (negatively charged) hydrolyzes under acidic conditions into PAH (positively charged). (b) Schematic representation of the one-pot self-assembly of PAH/PSS film (c) Enzymatic reaction rate of PAH/alkaline phosphatase films obtained for different self-assembly times and (d) optical microscope images of microelectrodes, in bright field and in fluorescence mode, where 3 electrodes were addressed to self-assemble PAH/rhodamine labelled alkaline phosphatase. The scale bar represents  $25 \mu m$ . Reproduced with permission from reference 236. Copyright 2015 American Chemical Society.

When using an enzyme instead of PSS, *i.e.* PAHd/alkaline phosphatase/hydroquinone solution, an enzymatically active film was self-assembled whose activity increased with the deposition time (Figure 11c). This process is well suited for the specific functionalization of micro-electrodes

opening the route towards miniaturized biosensors (Figure 11d). Another charge shifting polyanion, poly(allylamine citraconic acid) (PAHc)<sup>237</sup> was used solely in the presence of hydroquinone to self-assemble a one component films by application of an anodic current. The electrogenerated pH gradient induces a partial hydrolysis of PAHc leading to a polyampholyte solution that precipitates on the surface of the electrode.<sup>238</sup>

#### 2.4 Electro-self-assembly of polyelectrolytes through ionic activation

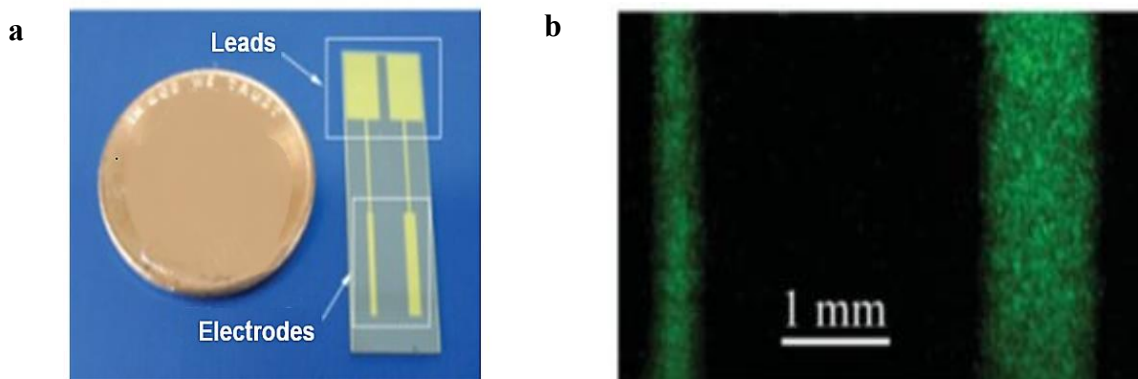
**Principle.** Alginate forms a biocompatible hydrogel in the presence of divalent cations, such as calcium ions, which ionically crosslink its carboxylate groups. Self-assembly of alginate gels can be obtained by ionic activation from an electrode surface using the electrolysis of water (Figure 12a).<sup>239</sup>



**Figure 12.** (a) Mechanism of calcium alginate electro-self-assembly. (b) Electro-self-assembled calcium alginate gel on an ITO-coated glass slide for 5 min at a current density of 3 A/m<sup>2</sup>. Reproduced with permission from reference 239. Copyright 2009 John Wiley and Sons.

Generated in a mixed solution of alginate and insoluble calcium carbonate (CaCO<sub>3</sub>) microparticles, protons partially dissolve CaCO<sub>3</sub> releasing free calcium ions which interact with alginate to form a gel on the surface of the electrode.<sup>240</sup> Figure 12b shows an electro-self-assembly calcium alginate

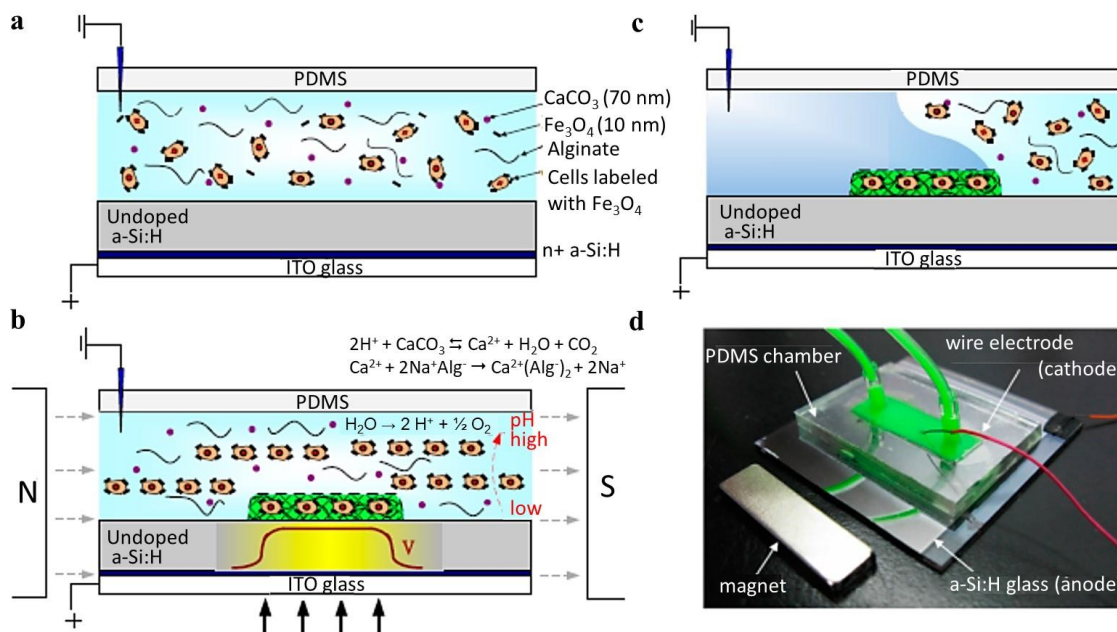
gel with a thickness of 6  $\mu\text{m}$  whose opacity is due to entrapped  $\text{CaCO}_3$  particles. The thickness can be tuned simply by changing the buildup time and the current density.<sup>239-240</sup> Spatial control of the alginate film self-assembly was obtained using patterned electrodes (Figure 13). Confined 3D hydrogels, with a defined shape, were obtained by using an insulating paper with a hole (500  $\mu\text{m}$  in diameter) localized on the working electrode.<sup>241</sup> In 2013,  $\text{CaCO}_3$  particles free alginate gels were developed using electrochemistry.<sup>242</sup> A first layer of electro-self-assembled alginate/ $\text{CaCO}_3$  gel, used as a reservoir of calcium ions, was put into contact with a calcium free alginate solution during the application of a constant potential to form a second layer of alginate gel. Another electrochemical process was described allowing the self-assembly of alginate films based on ionic interactions with iron. Alginate/ $\text{Fe(III)}$  based thin films were obtained by oxidation of  $\text{Fe(II)}$  ions (at 0.8 V vs  $\text{Ag/AgCl}$ ) in the presence of soluble alginate.<sup>243</sup> The deposited thin film could be dissolved upon reduction voltage (-0.4 V) allowing the release of encapsulated proteins. This property is interesting for the development of electrochemically triggered drug release systems. By applying anodic conditions (typically 0.63 V vs SCE) at a chromium working electrode to generate protons, PAH and molybdate ion ( $\text{MoO}_4^{2-}$ ) films were deposited due to PAH protonation and further ion complexation of the polycation.<sup>244</sup>



**Figure 13.** Spatial selectivity of calcium alginate electro-self-assembly on a patterned chip. a) The chip is a silicon wafer with two patterned gold electrodes. b) Fluorescence photomicrograph of electro-self-assembled calcium alginate gels with entrapped fluorescent microparticles. Reproduced with permission from reference 239. Copyright 2009 John Wiley and Sons.

**Applications.** Going further, calcium alginate gels can be co-deposited with cells or bacteria on patterned surfaces in microfluidic devices, allowing in-time visualization of the film growth.<sup>245-246</sup> Different types of bacteria or cells can be entrapped in electro-self-assembled calcium alginate gels, simultaneously or in a step-by-step manner and remain viable.<sup>239, 246-247</sup> By using patterned ITO electrodes, Matsue *et al.* obtained cell-spheroids cultures in alginate gel microwells.<sup>247</sup> It should be noted that vascular-like structures were developed by co-deposition of alginate calcium and cells on a platinum wire electrode.<sup>248</sup> This method of encapsulation allows to develop model bacterial biofilms to study cell signaling<sup>246</sup> or immunoanalysis.<sup>249</sup> Alginate was also co-deposited with hemoglobin onto a porous Co-Ni film to obtain drug delivery platforms.<sup>250</sup> Very recently, magnetically labeled cells were encapsulated in electrodeposited alginate gel. 3D organized assemblies of cells were obtained by coupling with a magnetic field (Figure 14).<sup>251</sup> In a first step, the orientation of the magnetic field allows to arrange specifically the cells. In a second step, a patterned light illumination was projected onto the photoconductive substrate, serving as a photoanode, to electrodeposit the alginate gel, providing a suitable matrix for encapsulation of oriented

cells on the electrode (Figure 14a-b). At the end of the light illumination, the introduction of fresh culture medium into the microchamber allowed to remove the residual deposition solution (Figure 14c).



**Figure 14.** (a–c) Schematic diagrams of a light-addressable electrolytic system used to perform an electrodeposition of magnetically-guided cells encapsulated in alginate hydrogels using a digital micromirror device (DMD). (d) Image of the polydimethylsiloxane (PDMS) microchamber bonded to the photoconductive substrate with a metallic wire inserted into the microchamber as the cathode (green dye was introduced into the microchamber for visibility purposes). Reproduced from reference 251. Open Access 2014 MDPI

### 3. Electrochemical deposition through covalent bond formation

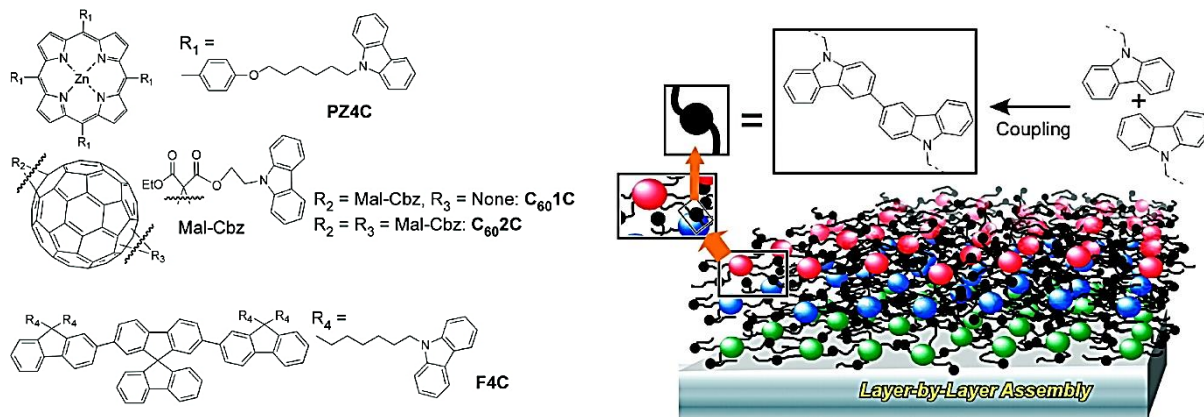
#### 3.1 Electropolymerization

Since 1980's, electropolymerization provides a major route for the synthesis of conducting polymers. Electropolymerization employs electrochemical oxidation of monomers, creating reactive radicals which polymerize and generate an insoluble polymer film. This kind of reaction is limited to monomers that can undergo an oxidation to form a radical. Electropolymerization has been widely used to design enzymatic biosensors<sup>252-254</sup> and biofuel cells.<sup>201</sup> Most electropolymerized films used for biomolecule immobilization are conducting polymers. Indeed, enzyme molecules that are present in the immediate vicinity of the electrode surface can be physically incorporated within the growing polymer network. Electrochemical deposition of enzymes was coupled with electropolymerization to physically entrap enzymes in a conductive matrix.<sup>255</sup> This was done with polyaniline,<sup>256</sup> polypyrrole,<sup>257-259</sup> poly(3,4-ethylenedioxythiophene),<sup>199</sup> poly-o-aminophenol,<sup>196, 260</sup> or poly(o-phenylenediamine).<sup>261</sup> Electropolymerisation is intensively applied for the buildup of molecularly imprinted polymers used for non-enzymatic protein recognition. The concept is based on the polymerization of suitable functional monomers (conductive or not) in the presence of a target protein acting as a template. The subsequent removal of the template creates recognition sites that can, further on, selectively rebind the target such as human serum albumin,<sup>262</sup> myoglobin<sup>263</sup> or hexameric heme protein.<sup>264</sup> Electropolymerization is a field in itself and will not be discussed in further details here as it was already done in several excellent reviews.<sup>265-269</sup>

### 3.2 Electrochemical-coupling layer-by-layer

ElectroChemical-Coupling Layer-by-Layer (ECC-LbL) consists in an enhanced version of LbL assembly, where an electrotriggered cross-linking of the polymer layers is added between each deposition step. In 2010, we introduced the first example based on two polyelectrolytes bearing alkyne or azide functions able to cross-link through Cu(I) catalyzed Sharpless-Huisgens click

reaction.<sup>270</sup> At each adsorption step of alkyne-modified polymer and azide-modified polymer, a reductive potential (-0.35 V vs Ag/AgCl) was applied in the presence of Cu(II) to generate a Cu(I) gradient at the electrode. The presence of Cu(I) triggers the click reaction between alkyne and azide moieties leading to covalent cross-linking of each layer. Using the designation “ECC-LbL” on a system based on the electrochemical triggering of N-alkylcarbazole dimerization,<sup>271</sup> Ariga and co-workers applied the concept to immobilize carbazole functionalized porphyrin, fullerene and fluorine (Figure 15).<sup>272</sup>

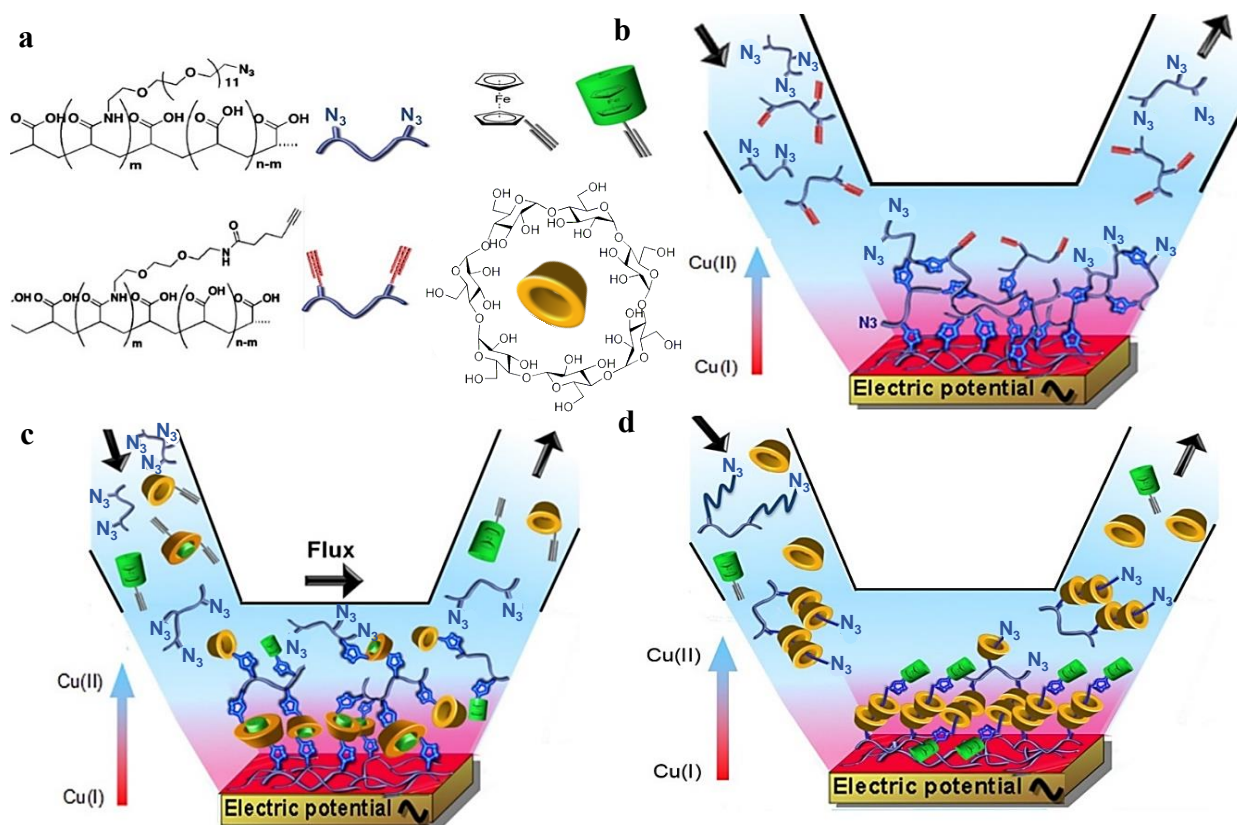


**Figure 15.** Molecules used for electrochemical-coupling layer-by-layer (ECC-LbL) assembly through cross-linking of peripheral N-alkylcarbazole units. Reproduced with permission from reference 272. Copyright 2011 American Chemical Society.

Photovoltaic functions of a prototype p/n hetero-junction device were demonstrated by the alternate deposition of donor (porphyrin) and acceptor (fullerene) molecules. As for other electrochemically triggered systems, ECC-LbL can be performed on patterned electrodes for spatial control of the assembly.<sup>273</sup> Allowing the control of gold nanoparticle distribution in LbL, ECC-LbL offers an economical route to achieve the fabrication of both a gold electrode and a photoactive carbazole rich layer.<sup>274</sup>

### 3.3 Electro-crosslinking of polymers: one pot morphogen self-construction of films

In 2011, our group went one step further and introduced the concept of "one-pot morphogen driven self-assembly".<sup>275</sup> In analogy with developmental biological processes,<sup>276</sup> a morphogen is defined as a molecule or an ion that is produced at an interface and diffuses into the solution, thus creating a concentration gradient, and that locally induces a chemical process. Electrotriggered Cu<sup>I</sup>-catalyzed click reaction between azide and alkyne functionalized polymers was used to illustrate the concept which is schematically represented in Figure 16a-b.<sup>277</sup>

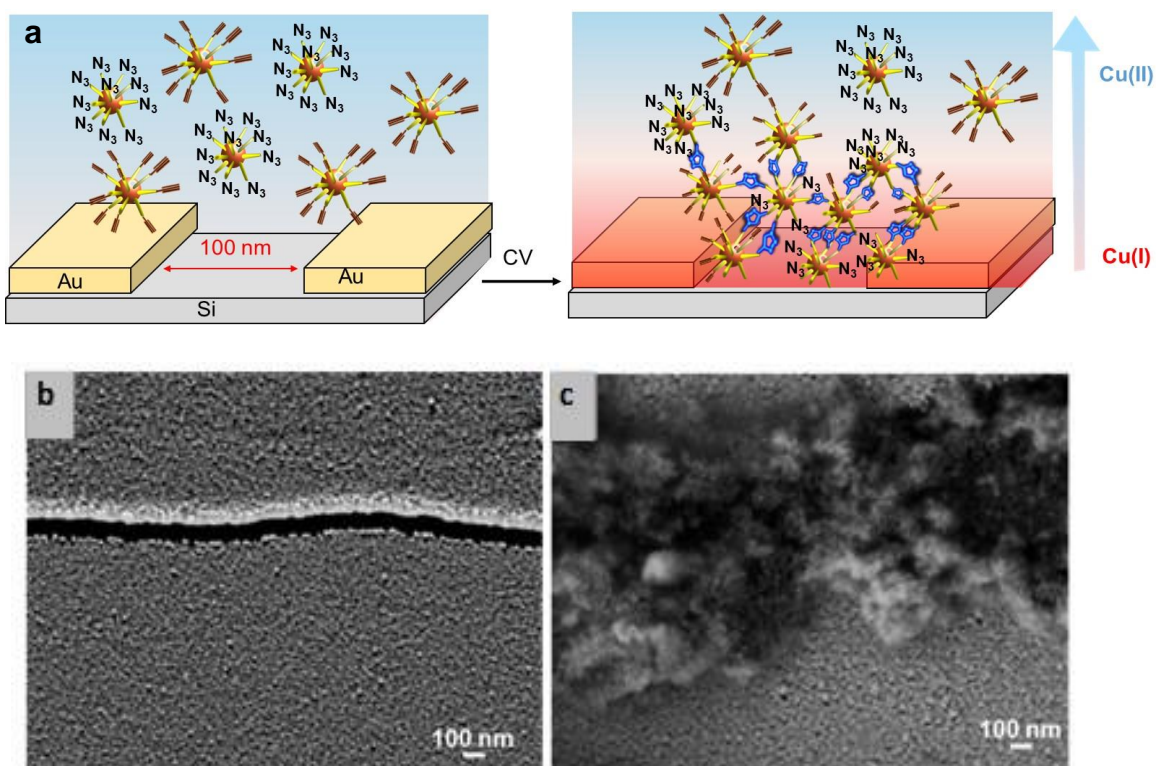


**Figure 16.** One pot morphogen electrochemically driven self-construction of different films by click-chemistry: (a) chemical formulae of the different compounds, (b) PAA-based covalent films, (c) PAA-ferrocene-β-cyclodextrin films based on (c) host-guest interactions and (d) polyrotaxanes. Clickable PAA

(PAA-N<sub>3</sub>, PAA-C≡C), ethynyl-ferrocene and ethynyl-β-cyclodextrin-C≡C react together in the presence of a Cu(I) gradient electrochemically generated from Cu(II) by application of a cyclic voltammetry (CV) at the working electrode.

Two chemically modified poly(acrylic acid), one bearing azide (PAA-N<sub>3</sub>) and one bearing alkyne (PAA-C≡C) functions, were mixed in solution in the presence of Cu(II). These polymers are unable to interact one with each other under these conditions. When an electric potential (cyclic voltammetry from -0.35 V to 0.5 V vs Ag/AgCl) was applied, Cu (II) was reduced generating a Cu(I) gradient which catalyzed the reaction between azide and alkyne functions of the two polymers. Cu(I) was called a morphogen in analogy with biochemical species that diffuse in tissues and modify cell fate.<sup>9, 276</sup> This process leads to the assembly of an electrocrosslinked polymeric film on the electrode surface. Based on the same morphogen and the same reaction, we also generated, in a one-pot manner, films composed of alkyne-grafted polymers and short azide-modified bifunctional ethylene glycol.<sup>279</sup> By using different sizes of homobifunctional ethylene glycol spacers, the thickness and the morphology of the self-assembled films could be tuned. Different types of azide and alkyne functionalized polymers<sup>275</sup> can also be used, among them chitosan to develop antimicrobial coatings.<sup>280</sup> Films based on host-guest interactions were built using a (PAA-N<sub>3</sub>, ethynyl-ferrocene, ethynyl-β-cyclodextrin-C≡C) mixture (Figure 16c).<sup>281</sup> The obtained films allow the further trapping of hydrophobic molecules in free β-cyclodextrin moieties present in the film. Using the same process, coatings based on supramolecular polyrotaxane were obtained from a (PAA-N<sub>3</sub>, ethynyl-ferrocene, β(or α)-cyclodextrin) mixture using electroclick to lock the polyrotaxane geometry (Figure 16d).<sup>282</sup> One step elaboration of inorganic coatings was achieved by applying the electroclick morphogen driven self-construction concept to azide and alkyne functionalized nanoparticles (NPs). The electrodeposition of clickable

iron oxide NPs allows the selective filling of high aspect ratio nanodevices establishing an electrical connection between two gold electrodes separated by a 100 nm-wide nanotrench (Figure 17).<sup>283</sup>

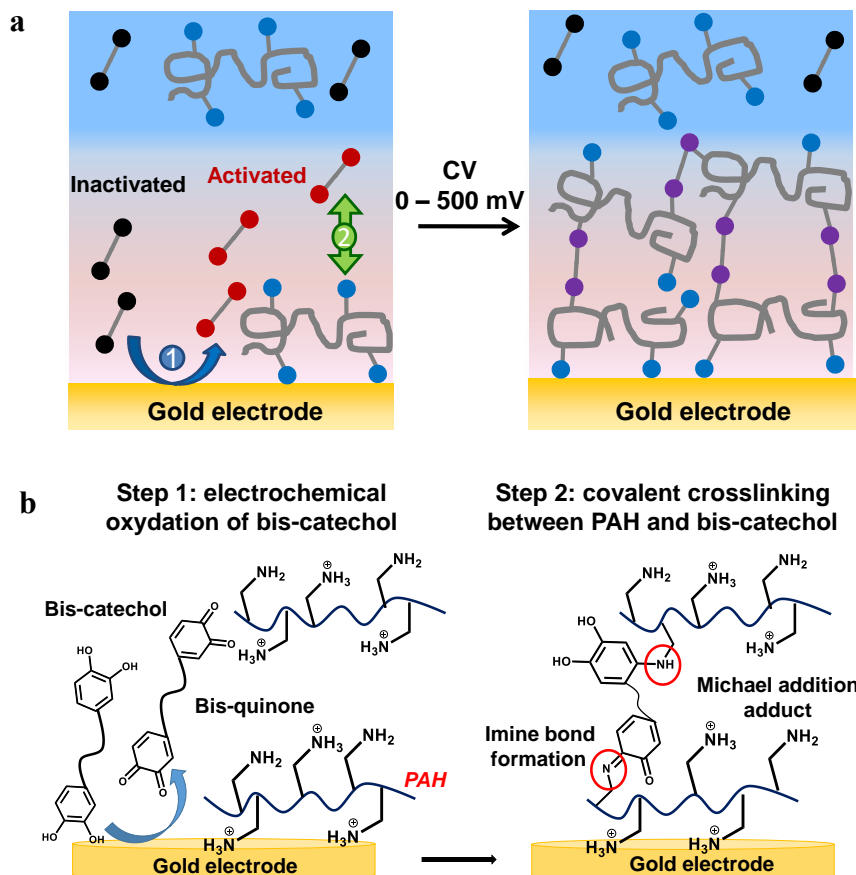


**Figure 17.** One-pot electro-click self-construction of NP films for selective filling of nanotrenches. (a) Schematic representation of the process using alkyne and azide functionalized iron oxide NPs. SEM micrographs of a 100 nm-wide nanotrench (b) before and (c) after filling by iron oxide NPs (20 nm in diameter) after 120 min of CV. Reproduced with permission from reference 283. Copyright 2015 John Wiley and Sons.

Integration of covalent NP films into nanodevices opens the route for biosensing and granular electronic devices. Simultaneous electropolymerization and electroclick functionalization (SEEC) of poly(aniline) was developed using clickable aniline monomers by application of a cyclic

voltammetry (-0.6 V to +0.9 V vs Ag/AgCl).<sup>284</sup> This process allows the control of the film morphology and activity by changing the electropolymerization condition and the electroclicked molecules, respectively.

In 2012 by application of an anodic current, Gray *et al.* generated chlorine species (HOCl) to partially oxidize chitosan forming aldehydes that could further react with amine moieties of the polymer. As the HOCl is generated at the surface of the electrode, the conjugation reaction is localized at the electrode inducing the formation of a biopolymeric hydrogel.<sup>285</sup> Co-deposition of chitosan with GOX<sup>285</sup> or glucose dehydrogenase<sup>286</sup> allows obtaining pH-stable chemical gels with simultaneously conjugating a protein. Very recently, we introduced the electro-crosslinking of polyamines based on mussel-inspired chemistry (Figure 18).<sup>287</sup> Mussels presents unusual adhesion properties under extreme conditions on almost any kind of materials. This ability comes from the secretion of different proteins rich in catechol moieties which have several chemical properties.<sup>288-289</sup> Among them, catechol functions can be oxidized into quinone functions able to react with nucleophilic groups, such as amines or thiols. Using this property, we developed a catechol based electrochemically triggered construction of polymeric films. The principle is based on the application of defined potential cycles on an electrode in contact with a mixture of PAH and bis-catechol spacers, both unable to interact (Figure 18a). During the application of the potential, catechols are oxidized into quinones which then crosslink the polymer chains by reacting with the amine functions through Michael addition and Schiff's base formation (Figure 18b). The buildup kinetic can be tuned by the catechol/amine ratio of PAH/bis-catechol mixture and the scan rate of the CV. This work open the route for biosensing application. Indeed, enzymes could be immobilized trough covalent bonds with this process without any previous functionalization of the protein.

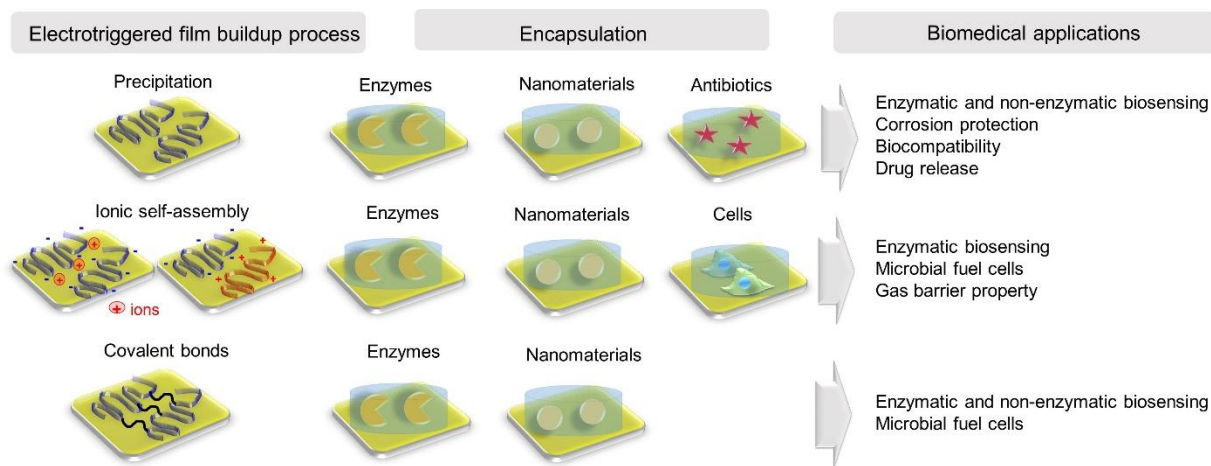


**Figure 18.** (a) Principle of the one pot self-construction of polymeric film based on oxidation of an organic morphogen and (b) schematic representation of the two chemical steps leading to covalent crosslinking between PAH and catechol homobifunctionalized ethylene glycol spacer, named bis-catechol. Reproduced with permission from reference 287. Copyright 2015 American Chemical Society.

## CONCLUSION AND PERSPECTIVES

Different macromolecular film buildup processes triggered by electrochemistry are reviewed. A large variety of such processes exists based on different physico-chemical grounds: precipitation,

polymerization or cross-linking (ionic or covalent). Performed in aqueous solution, a large number of electrodeposition processes are based on the generation of chemical species, which can be called morphogens, at the electrode that then diffuse towards the solution, inducing the film buildup. In general, the different processes are triggered with potentials lying between  $-2$  to  $1.5$  V (rarely up to  $30$  V or kV) and current intensity about few  $A/m^2$ . Thin functionalized films or thick hydrogels are obtained by electroprecipitation of macromolecules to implement enzymatic and non-enzymatic biosensors which need a further crosslinking step to ensure their operating stability. Ionic self-assembly of macromolecules, especially alginate, allows the encapsulation of cells in a suitable environment in mild conditions. Finally, robust functionalized thin films can be designed through covalent cross-linking of macromolecules or inorganic compounds.



**Figure 19.** Summary of the different reviewed electrotriggered film buildup processes and their biomedical applications.

First developed to coat metals in the car industry, electrochemically triggered self-assembly processes are gaining new interests. Their great advantage is to allow the localized deposition of different macromolecules, molecules or inorganic compounds on micro-electrodes. Moreover as the process is controlled by an electrochemical stimulus (current or potential), the trigger can be

switched "on" and "off" allowing the buildup of structured multilayered coatings by finely controlling the application time of the stimulus and by alternating the application of reductive and oxidative potential.<sup>290</sup> Among the reviewed macromolecular film buildup processes, very few are based on coordination bonds. Coordination chemistry, especially metal-ligand, has several advantages due to highly directional interactions, exchangeable components and a multivalent nature.<sup>291</sup> The development of new process which incorporate metal-ions into a supramolecular architecture will give access to rich properties with potential applications for magnetic, electric and optical devices.<sup>292</sup> For example, Metal–Organic Frameworks (MOFs) are a class of materials designed by employing various metal ions and organic linkers. Emerging as an extensive class of crystalline materials with high porosity in nature, MOFs have diverse applications like storage or separation of gases, catalysis, magnetism, luminescence and drug storage and delivery.<sup>292-293</sup> As another perspective using two micro-electrodes, the electrogeneration of two morphogens will allow designing structured coatings at the overlap of two gradients opening the route of the functionalization of non-conductive substrates. Finally, an even further step is to generate the morphogens using adsorbed enzymes which would allow extending the localized buildup processes to non-conductive surfaces with no use of an electrochemical stimulus.

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