Soft Materials-Based Biosensing Medical Applications

Edited by Deepak Gupta, Milan Singh, Rishabha Malyiya and Sonali Sundram





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Foreword

The field of biosensing has seen remarkable advancements in recent years. This book is a timely contribution, offering an in-depth understanding of the latest developments in soft material-based biosensors.

The book is divided into sixteen chapters, each authored by experts in the field, covering topics such as synthesizing soft materials, liquid crystals, ionic hydrogel strain sensors, natural product-based soft materials, nanotechnology-enhanced soft materials, and graphene oxide-based biosensors, among others. Each chapter explores the potential applications of these biosensors across various fields, including biomedicine, environmental monitoring, and drug delivery.

One of the key strengths of this book is its comprehensive coverage of soft material-based biosensors. The authors have done an excellent job of summarizing the current state-of-theart and offering insights into future research directions and opportunities in the field. It is also an excellent resource for graduate students and researchers new to soft material-based biosensors.

I am confident that this book will be a valuable resource for the scientific community, particularly for those involved in developing biosensors for various applications. I congratulate the editors and authors for their contributions in producing such an important work. I highly recommend this book to anyone interested in the field of soft material-based biosensors.

Dr. Shyamal Kumar Kundu Professor, Galgotias University, Greater Noida, India

Preface

Soft materials have gained significant attention in biosensing due to their unique properties, such as flexibility, biocompatibility, and responsiveness to external stimuli. This book highlights recent advancements in soft material-based biosensors and their applications across various fields, including biomedicine, environmental monitoring, and drug delivery. The book is divided into sixteen chapters, beginning with an introduction to soft materials and their unique properties. The following chapters explore various aspects of soft materialbased biosensors, including synthesizing soft materials, the use of liquid crystals as potential biosensors, ionic hydrogel strain sensors, natural product-based soft materials in electrochemical biosensors, nanotechnology-enhanced soft materials, and soft and flexible material-based affinity sensors.

Furthermore, the book delves into specific applications of soft material-based biosensors, such as detecting cancer biomarkers, drug delivery, and the detection and treatment of oral cancer. It also examines the use of functionalized biomaterials in treating diabetic patients and recent advancements in 3D printable biosensors. The final chapter focuses on the environmental implications of soft materials, highlighting their journey from the lab to industry, with a discussion on sustainable and cost-effective biosensors and their potential applications in environmental monitoring.

This book is designed for researchers, scientists, and graduate students interested in soft material-based biosensors and their applications. It offers a comprehensive overview of recent advancements in the field and their potential applications, from the lab to industry. We hope this book will inspire further research and development in soft material-based biosensors. We extend our gratitude to everyone who contributed to this important work, and to Martin Scrivener and Scrivener Publishing for making its publication possible.

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Abstract

Soft materials are a class of materials having properties intermediate between fluids and crystals. Colloids, liquid crystals, foams, gels, and polymer solutions are some examples of soft materials. The study of soft materials began with Alberts Einstein's work on Brownian motion. Pierre-Gilles de Gennes has been referred to as the "father of soft matter." The most important characteristics of soft materials include Brownian motion due to thermal fluctuation, short-range order of intermo-lecular forces, and its self-assembling tendency due to reaction-limited aggregation (RLA) and diffusion-limited aggregation (DLA). Soft materials experience a repulsive force because all the particles obey the Pauli-exclusion principle.

Keywords: Soft materials, Brownian motion, colloids, liquid crystals, polymers

List of Abbreviations

- DLA Diffusion-Limited Aggregation
- LCs Liquid Crystals
- LCD Liquid Crystal Display
- PVC Poly Vinyl Chloride
- RLA Reaction-Limited Aggregation
- SEM Scanning Electron Microscopy
- TBDA terephthalylidene-bis-[4-n-decylaniline]
- TEM Transmission Electron Microscopy

1.1 Introduction

Soft materials are a class of materials that include liquid crystals (LCs), colloids, foams, gels, and polymer solutions. Soft materials have complex properties intermediate between those of fluids and crystals, and they resemble naturally occurring systems like membranes and tissue systems. Pierre-Gilles de Gennes has been referred to as the "father of soft matter."

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Figure 1.1 Different types of molecular architecture. (a) Flexible coil, (b) rigid rod, (c) polyrotaxane, (d) cyclic, (e) branched, (f) comb-branched, (g) star-branched, (h) loosely cross-linked, (i) tightly crosslinked, (j) interpenetrating network, (k) random hyperbranched, (l) dendrigrafts, and (m) dendrons.

In 1991, Pierre-Gilles de Gennes was awarded the Nobel Prize in Physics for his groundbreaking work demonstrating that the methods used to understand order phenomena in basic systems can be extended to the more complex field of soft matter. Specifically, de Gennes's research focused on the properties of LCs and polymers, two important classes of soft materials [1, 2]. Because of their huge molecular scale and entangled structure, soft materials such as polymers display distinctive dynamic behavior. The idea of reptation scaling theory provides a framework for understanding and describing the motion of entangled polymer chains. de Gennes and Edward's reptation model describes the dynamics of polymer chains in a melt by imagining them flowing within a tube. Entanglements and topological limitations imposed by interactions with other chains are shown by the tube. This model has proven significant in understanding polymer dynamics and rheology by providing insights into the behavior and mobility of polymer chains in melts. According to this hypothesis, the relaxation period in entangled systems is proportional to the cube of molecule mass. It was Pierre de Gennes who developed the concept of polymer reptation and derived scaling relationships. Later, another scientist from Cambridge, Sir Sam Edwards, devised tube models and predictions of the shear relaxation modulus. Based on the architecture, there are different kinds of molecular structures such as flexible coil, rigid rod, cyclic polymers, and polyrotaxane structures as shown in Figure 1.1. There are certain cross-linked structures such as loosely cross-linked polymers, densely cross-linked polymers, and interpenetrating networks. At the same time, there are branched structures such as random-short, random-long, regular comb, regular short-branched, and star-branched structures. Another class of soft materials is called dendritic, which consists of random hyperbranched, dendrigrafts, dendrons, and dendrimers [3].

1.2 Brief Introduction to Theories of Soft Matter

Soft matter systems have micrometer-scale diameters, resulting in their typical short-range order. By simplifying the system and focusing on essential elements, coarse-grained models

successfully reflect the behavior of soft matter. Brownian motion, which is caused by continual random motion, is a significant characteristic of soft matter, particularly colloidal particles. The ability of soft matter to self-assemble is an important trait that drives the development of complex structures. The Lennard–Jones potential, which accounts for van der Waals attractions and hard-sphere repulsion, is frequently used to explain interactions in soft materials. These theories will be discussed in detail in subsequent sections, providing further insights into soft matter phenomena.

1.3 Classification of Soft Materials

Soft materials can be classified into colloids, polymers, foams, gels, LCs, and biological membranes based on the structures and properties that they exhibit.

1.3.1 Colloids

A colloid has sub- μ m particles (but not single molecules) of one phase dispersed in a continuous phase. The size scale of the dispersed phase is between 1 nm and 1 μ m [4, 5]. The dispersed phase and the continuous phase can consist of either a solid (S), liquid (L), or gas (G). In a combination of any two of these phases, however, there is no gas-in-gas colloid because there is no interfacial tension between gases [6]. Figure 1.2 shows an example of a colloidal structure made by an element of gold [22]. The classification of colloids is shown in Table 1.1.

There are several ways for the preparation of colloids such as physical, chemical, as well as some dispersion methods, among which the given two methods are the most important:

- Physical method: Large-size particles can be dispersed into the colloidal dimensions by spraying, milling, or shaking and mixing.
- Chemical method: Using redox reactions, condensation, and precipitation, small, dissolved molecules can be condensed into larger colloidal particles.



Figure 1.2 TEM image of a colloid aggregate of gold showing DLA structure [22].

Dispersed phase	Continuous phase	Name	Examples
Liquid/Solid	Gas	Aerosol	Fog, hair spray, and smoke
Gas	Liquid/Solid	Foam	Beer froth, shaving foam, and poly(urethane) foam
Liquid	Liquid/Solid	Emulsion	Mayonnaise and salad dressing
Solid	Liquid	Sol	Latex paint and toothpaste
Solid	Solid	Solid suspension	Pearl and mineral rocks

Table 1.1 Classification of colloids.

The wettability of colloidal particles and the interactions that occur at the particlesurface contact are critical in determining the structure and equilibrium characteristics of interfaces that include colloidal particles [29]. The interactions of colloidal particles trapped at a fluid interface differ from those found in three-dimensional systems. This is because the fluid interface serves as a constrained habitat for the colloidal particles. A colloidal particle is thought to be linked to a fluctuating surface that divides two distinct phases with differing physicochemical properties, such as density, dielectric permittivity, and ionic strength. The properties of colloidal particle surfaces can be impacted by a variety of parameters, including the assembled size, shape, charge, wettability, and surface chemistry of the object. These characteristics influence the behavior of the interface, making it challenging to develop an analytical account of the interactions that occur in systems where colloids are confined at fluid interfaces. There are certain forces that influence the assembly of colloidal particles. These forces are divided mainly into two categories: direct interactions and external interactions.

Direct interactions are naturally tied to colloidal object properties such as size, shape, the chemical composition of the surface, the charge carried by the colloidal particles, and their roughness. These parameters regulate the attractive or repulsive forces experienced by the particles and impact their arrangement at the contact as shown in Figure 1.3. External interactions, on the other hand, are connected with the presence of external fields operating on single objects or groups of particles. These fields can impose forces such as electric, magnetic, or gravitational forces on colloidal particles, affecting their placement and alignment [7].

The interfacial area of the colloid is an important factor that affects the behavior of colloids. For a spherical particle having radius r, the ratio of surface area to volume is

$$\frac{A}{V} = \frac{4\pi r^2}{\frac{4}{3}\pi r^3} \approx \frac{1}{r}$$
(1.1)

The interface becomes more significant when the size of the particles is small. Consider a 1-cm³ phase dispersed in a continuous medium. If it is made up of a single particle, then the surface area is 0.0006 m². In case the particle is broken into smaller fragments, then the surface area increases drastically as shown in Table 1.2.



Figure 1.3 (a) Colloidal particle interactions at a fluid interface include total electrostatic repulsions caused by combining dipolar and coulomb interactions, which are balanced by van der Waals and capillary attractive forces, (b) solvation-mediated interactions that occur when the environment (temperature, pH, or ionic strength) changes in the case of colloidal microgel particles, (c) interactions mediated by ligands include both attractive hydrophobic forces and steric repulsions [22].

Number of particles	Particle volume (m ³)	Edge length (m)	Total surface area (m ²)
1	10 ⁻⁶	10 ⁻²	0.0006
10 ³	10 ⁻⁹	10 ⁻³	0.006
10 ⁶	10 ⁻¹²	10 ⁻⁴	0.06
109	10 ⁻¹⁵	10 ⁻⁵	0.6
1012	10 ⁻¹⁸	10 ⁻⁶	6.0
1015	10 ⁻²²	10 ⁻⁷	60
10 ¹⁸	10 ⁻²⁴	10 ⁻⁸	600

 Table 1.2 Significance of change in total surface area with respect to the number of particles.

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Colloids are present in various food items we consume, including dairy products like milk. Milk is a colloidal system in which lipid oil is dispersed in water. The protein component of milk consists of caseins, which are held together by calcium phosphate units, forming a complex micellar structure. Ice cream is another example of a colloid. It comprises an emulsion, which is a mixture of fat and water, a semi-solid foam, and a gel. These components give ice cream its characteristic texture and stability. Paints and ink are also examples of colloids. In the past, paints were made by dissolving natural polymers such as resins in oil. The resulting mixture formed a colloidal suspension, where the solid particles were dispersed in the liquid medium. Soil is a natural colloid that contains four major constituents: organic matter, mineral sediments, air, and water. These components interact to form a complex structure, with the colloidal nature of soil playing a crucial role in its fertility and ability to retain water.

Another phenomenon involving colloids is shear thickening, which is defined as a rise in viscosity as the shear rate increases. It is a reversible phenomenon in stable dense colloidal suspensions. There is no hysteresis in the flow curve measurements in such systems, indicating that the behavior during increasing and decreasing shear rates is constant. However, when colloidal stability is decreased, resulting in particle aggregation, the rheological reaction becomes time-dependent. This means that the behavior of colloidal suspension under shear is affected by the duration of shear as well as the history of past shear circumstances. As a result, the presence of particle aggregation in colloidal suspensions brings complexity and time-dependent rheological features [8]. The shear thickening behavior of polymer colloids (200-nm particles of polymers dispersed in water) shows that, at a low shear rate, it flows like a liquid, and, at a high shear rate, it behaves like a solid.

1.3.2 Polymers

The acronym "polymer" is derived from the Greek words polus, which means "many" and meros, which means "part." Joons Jacob Berzelius used the term polymer for the first time in 1833 [9]. A polymer is a large molecule, typically with 50 or more repeat units. In the case of a polymer, a unit is a monomer. A polymer made up of the same group of monomers is known as a homopolymer and with a different group of monomers is known as a copolymer. Examples of a polymer include everyday plastics (polystyrene and polyethylene), rubbers, and biomolecules such as proteins and starch. According to physicists, a polymer can be described as a string of pearls in which each pearl represents a repeat unit of atoms linked together by strong covalent bonds as shown in Figure 1.4. Figure 1.4a-a shows the transmission electron microscopy (TEM) image of a necklace kind of structure formed by cobalt oxide nanoparticles coated with polystyrene. These nanoparticles have a diameter of 20 nm. The image was taken after a 3-h oxidation process. After 1 week of storage, the necklaces are still visible but may have undergone some changes, as shown in the image Figure 1.4a-b. Similarly, Figure 1.4a-c shows a high-magnification field-effect scanning electron microscopy (SEM) image of an indium tin oxide surface having discrete chains of nanoparticles. Figure 1.4a-d shows a low-resolution SEM image, which provides a less detailed view of the necklaces formed by indium tin oxide particles after they have been calcined [30]. Proteins are also polymer in nature. In the case of a protein molecule, the repeat units are amino acids. It is possible to predict the size and shape of the polymer molecules, in which the most important parameter is the number of repeat units, N. Figure 1.4b-a shows the X-ray tomography picture of a "granular polymer" made up of several equal-length segments of a chain of spheres. The close-up of the darkened (red) area in Figure 1.4b-a



Figure 1.4 (a) A transmission electron microscopy (TEM) image showing the structure of a necklace formed by cobalt oxide nanoparticles coated with polystyrene [30]. (b) X-ray tomography picture of a "granular polymer" made up of several equal-length segments of a chain of spheres [22].

is shown in Figure 1.4b-b. The connecting connections are visible, allowing us to discern which spheres are linked together in each chain [22]. Addition and condensation polymerization are the two main methods of polymer formation. In the case of addition polymerization, a monomer reacts with an initiator or catalyst, forming a chain where one bond remains unsatisfied. This unsatisfied bond can then react with another monomer, leading to the continuous growth of the polymer chain. The process repeats until two chains combine or an initiator terminates the chain. On the other hand, condensation polymerization involves the combination of a monomer with exposed hydrogen (H) atoms and a monomer with exposed oxygen-hydrogen (OH) atoms. This reaction results in the release of water as the H and OH groups combine to form H_2O . This water release allows the monomers to link together and form a polymer.

Polymers can be classified into three main types: naturally occurring polymers, semisynthetic, and synthetic polymers.

- Natural polymers are polymers found in nature, which are generally extracted from plants and animal sources. Some common examples of natural polymers include resins, proteins, starch, and cellulose.
- Semi-synthetic polymers are polymers that are synthesized from natural polymers but are subjected to certain chemical treatments such that they can change their physical properties. Vulcanized rubber, gun cotton, and rayon are examples of semi-synthetic polymers.
- Synthetic polymers are man-made polymers synthesized artificially by a method called polymerization. Nylon, synthetic rubber, poly vinyl chlorid (PVC), polyethylene, polystyrene, and Teflon are a few examples of synthetic polymers [10].

1.3.3 Liquid Crystals

Liquid crystals (LC) are soft materials having the properties intermediate between crystalline solids and isotropic liquids. They have molecules having both orientational and positional ordering like that of crystalline solids and some groups of LCs have orientational

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order, and they behave like isotropic liquids as they exhibit fluidity. Based on the transformation to mesophase (mesophase is another name for the LC phase), LC can be classified as thermotropic LCs and lyotropic LCs. Thermotropic LC achieves mesophases with the help of thermal processes and lyotropic LC achieves mesophase by adding certain chemical solvents or by changing concentration. Thermotropic LC can be further divided into fields of calamitic (rod-shaped), discotic (disc-shaped), and cholesteric as shown in Figure 1.5. Among these, calamitic LC is more common in the field of application. Calamitic LCs can be further classified into nematic, smectic, and cholesteric LCs [11, 12]. A given liquid LC may exhibit a single phase or a sequence of phases. For a calamitic LC, when the temperature changes, phase transitions are observed.

During any phase transition, there is a certain symmetry breaking happening in the materials. Because it is difficult to describe two different phases using a single analytical function, a term known as order parameter has been introduced, which measures the breaking of symmetry. In the case of LCs, the order parameter lies between 0.3 and 0.7. LCs exhibit characteristic textures for every phase due to their birefringent nature. These textures can be studied with the help of polarizing optical microscope. The visible characteristic structures include schlieren, focal conic, and fan-like, which arise due to the point defect and line defects as shown in Figure 1.6. A point defect can be seen at the centre of this schlieren textures due to certain topological defects. A point defect is a disclination in a LC that is marked by a localized region of broken molecular alignment. It appears as a single



Figure 1.5 Classification of liquid crystal and applications [13].