How to use stimuli-responsive soft materials for detection?

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How to use stimuli-responsive soft materials for detection?

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The growing demand for rapid, cost-effective, and user-friendly detection methods has driven advancements in "stimuli-responsive soft materials" for sensor development. Many examples of complex and liquid crystals emulsions can be found demonstrating their application for the detection of bacteria, virus, enzyme, or specific molecules. However, despite frequent comparisons between emulsions and foams, the exploration of liquid foams for sensor applications remains limited. Paradoxically, foam-based sensors for fetal lung maturity were developed in the 1970s, before the emergence of more sophisticated detection methods. Here, we describe some examples of soft interfaces used as sensor to detect biomarkers, enzymes, and bacteria, with a strong emphasis on foam. We demonstrate how to use the foamability and foam stability as read-out mechanism. We discuss approaches developed for complex emulsions and liquid crystals, highlighting their potential adaptation to liquid foams.

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Introduction

A chemical sensor is often described as a system that utilizes chemical species or chemical reactions, in combination with a transducer to detect and quantify specific biological analytes or substances [1]. These systems convert a chemical response into a measurable signal, often with high specificity and sensitivity, enabling the detection of various compounds or biological processes in a wide range of applications, including medical diagnostics, environmental monitoring, and food safety [2]. These chemical sensors have been developed as alternatives to conventional testing methods, which are typically complex, requiring specialized equipment and skills, and they are expensive and time consuming [3]. For instance, bioassays are widely employed in healthcare to identify and measure biochemical markers like metabolites or enzymes, being crucial diagnostic indicators for tracking diseases and health conditions. However, the high costs associated with commercial equipment and reagents required for these bioassays have restricted their utilization to professional laboratories in developed countries [3]. Another example concerns the detection of foodborne bacteria, which is also a growing global public health concern due to illnesses and deaths occurring from consuming contaminated food [4]. The traditional approach to bacterial detection involves cell culture, which takes several days, making it too slow to prevent health crises. While methods using polymerase chain reaction (PCR) offer faster results (within a few hours), they necessitate costly equipment operated by skilled personnnel. The limitations of current conventional methods hinder the ability to rapidly test large quantities of food and water prior to consumption. For these reasons, food industries are looking for sensors which enable the rapid and reliable detection of food bacteria [4]. Another important category of substances of concern are harmful pesticides and environmental pollutants [5]. In environmental monitoring, chemosensors, highly sensitive, easy-to-use, label-free, and lead to ultrafast detection of analyte molecules are in great demand [5]. Reducing the cost of analyzing samples using faster screening methods and less sophisticated equipment would also allow for more extensive monitoring [5]. Facile contaminant detection on the field before samples are sent to specialized laboratories

would offer significant benefits. Therefore, the need for on-site detection method, that is rapid, low-cost, and user-friendly, especially for developing countries, has led to the increased activity in sensor development based on new conceptual approaches [3, 6].

One recent answer to this scientific challenge is the development of sensors based on "stimuli-responsive smart materials" [3]. Many examples of complex emulsions and liquid crystals (LC), etc. used to detect bacteria, enzymes, or pesticides can be found in the literature [7−11]. In contrast, very few studies related to the use of liquid foams as sensors are available, whereas plenty of "stimuli-responsive" foams have been described over the last decade [12]. Interestingly, the first utilization of foams for detection purposes like fetal lung maturation was described in the 1970s, before the emergence of other more precise techniques [13].

Liquid foams are known to be very sensitive systems, which can amplify small changes occurring at the molecular scale into drastic changes in terms of foamability (the ability to produce foam) and foam stability with time. Foams have been qualified of "molecular magnifying glasses", allowing phenomena that occur at the molecular level to be distinguished at the spatial scale of the naked eye (and far-field optics) without the need for additional instrumentation. For example, even nonscientist people know that the foam obtained by the egg white is very sensitive and easily destabilized by a trace of residual egg yolk [14]. Similarly, sea foam is a good example of the foam sensitivity. When the sea undergoes significant agitation, it can incorporate air and form foams, albeit weak and short-lived. However, the presence of stabilizing agents, such as dissolved organic carbon from decomposed organisms like plankton, leads to the production of more durable foams that can be observed drifting along coastlines. Sea foam is therefore a good indicator of the presence of industrial or natural surfactants [15]. The prerequisite to use liquid foam as sensor is the necessity to find suitable conditions to obtain foams with two distinct behaviors in the presence and absence of the targeted analyte: high/low foamability or high/low foam stability.

Given that the utilization of liquid foams as sensors remains limited, and despite the distinct differences between emulsions and foams, they are frequently compared in the literature [16]. Thus, in this review, we focus on the use of soft interfaces for detection. We first explain the recent examples described in the literature regarding the application of complex and LC emulsions for detection purposes. The approaches developed for these emulsions may provide the readers with insights into the possibilities offered by these systems, which could potentially be extended to foams as well in terms of surfactant design and chemical sensing mechanisms approaches. Then, the key information on liquid foams in terms of foamability and foam stability are summarized.

We describe in detail all the examples of liquid foams used as sensor in the literature to detect biomarkers, enzymes, and bacteria. Finally, potential opportunities and challenges toward further development of liquid foams as sensors are outlined.

Complex emulsions and LC emulsions as sensors: Design, properties, and current limitations

Emulsions are a great example of soft interfaces sensors. Many examples of emulsions used for sensing are described in the literature mainly from the group of Pr. T.M. Swager [7−11]. The sensing principles used in these examples could be a good starting point to develop further the sensors based on liquid foam. Hence, this review focuses on the most notable examples to illustrate their potential. For additional examples, readers are encouraged to refer to recent reviews on the topic [7, 8, and 17].

Complex emulsions

Complex emulsions are defined as emulsions, in which the droplets contain two or more phase-separated liquids [18]. The peculiarity of these complex droplets is that they can have different morphologies. Typical examples are multiple emulsions such as oil-in-water-in-oil but also more unusual structures such as Janus droplets. These complex emulsions can change their morphology due to changes in the balance of interfacial tensions leading to changes in the ordering and curvature of the droplets' fluid interface triggered by chemical or physical stimuli (Figure 1a). These changes in emulsion droplets morphology have been used to detect a wide range of biomarkers, bacteria, virus, or analytes [3, 7, 19−21].

Complex droplets are created by combining two immiscible liquids: a fluorinated liquid (FC) and a hydrocarbon or organic liquid (HC), dispersed within an outer aqueous phase containing surfactants (W). The interplay of low interfacial tensions between the hydrocarbon and fluorocarbon phases ($\gamma_{FC/HC}$) leads to dynamic complex droplet morphologies, sensitive to slight changes in interfacial tensions at the water−fluorocarbon interface ($\gamma_{FC/W}$) and the water−hydrocarbon interface ($\gamma_{HC/W}$). These droplets can exhibit different morphologies: a double-emulsion hydrocarbon-in-fluorocarbon-in-water (HC/FC/W) structure when ($\gamma_{HC} \gg \gamma_{FC}$), a Janus morphology when ($\gamma_{HC} \sim \gamma_{FC}$), and a double-emulsion FC/HC/W morphology when ($\gamma_{HC} \ll \gamma_{FC}$) (Figure 1a) [18]. Altering surfactant concentrations or their effectiveness at the interfaces triggers changes in droplet morphology due to changes in interfacial tensions, influencing also their optical refractory properties (Figure 1b). Optical variations caused by changes in droplet morphology are visible to the naked eye, providing a direct optical read-out mechanism for droplet shape. For example, layers of double emulsions appear opaque, whereas Janus droplets are transmissive, influenced by both droplet shape and the liquids' index of

Figure 1
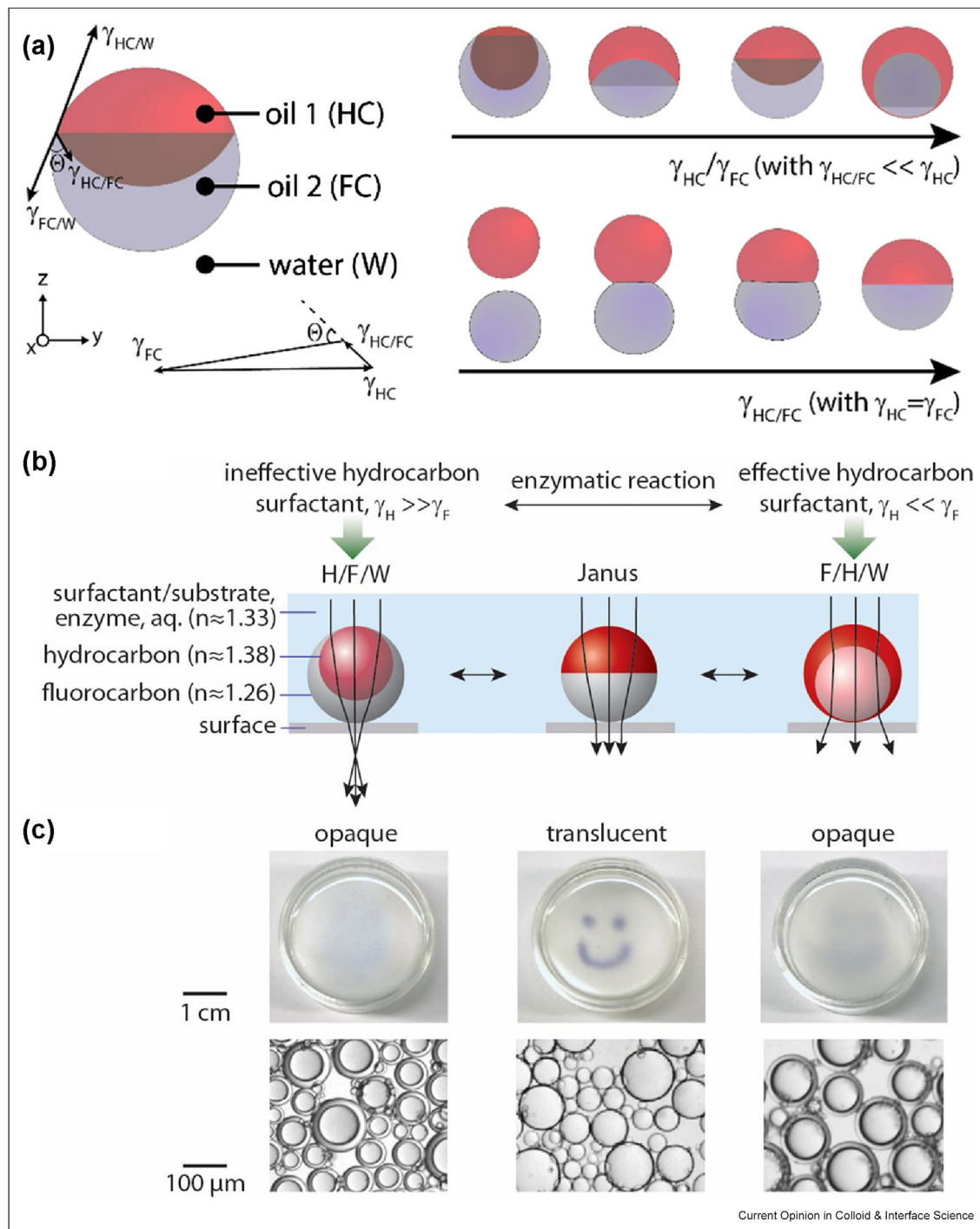
(a) The morphology of complex multiple and Janus emulsion droplets is governed by the equilibrium of interfacial tensions acting at different interfaces, as depicted in the schematic. This equilibrium exclusively dictates the droplet shape, in accordance with Neumann's triangle. These physical relationships establish the conditions that shape the close-to-spherical Janus droplets and also define the equilibrium shapes of nonspherical droplets. HC corresponds to hydrocarbon oil and FC to fluorocarbon oil. Reproduced with permission from Ref. [8].Copyright 2023, Springer. **(b)** Schematic of the reconfigurable droplets acting as tunable lenses since the optical transmission of an emulsion film depends on the droplet morphology and can be tuned due to specific enzymatic reaction leading to detection of enzymes. n corresponds to the approximate refractive indices of the different liquid phases. Depending on the surfactant conditions and the interfacial tensions at the fluorocarbon–water and hydrocarbon–water interfaces, these droplets dynamically change their morphology and can adopt three general configurations: H/F/W, Janus, or F/H/W. It is important to point out that because fluorinated liquids have a greater density, the droplets orient itself gravity when placed on a surface, which is important to achieving the desired optical response. **(c)** Photographs of polydisperse emulsions in a Petri dish placed over an image of a smiley face to demonstrate changes in the optical transmission used for enzymatic detection. (Scale, 1 cm) Pictured below are optical micrographs of representative droplets. (Scale, 100 μm) Reproduced with permission from Ref. [19]. Copyright 2017, PNAS.

refraction. The read-out mechanism is the change in the optical transmission of the droplets. The change in transmission can be collected with a spectrometer or with a smartphone as illustrated by L.D. Zarzar et al. (Figure 1b-c) [19]. The key parameter to design such emulsions is to use a surfactant system responsive to the molecules, bacteria, enzyme, proteins, etc. that should be detected (Figure 2).

Based on this change of optical transmission, different enzymes have been successfully detected by these complex emulsions such as lipase (detection limit around 50LU/L) and sulfatase (detection limit around 40U/L) (Figure 2a) [19]. The activity of lipase and sulfatase are measured by optical changes induced by the use of cleavable surfactants initially stabilizing the biphasic hydrocarbon-fluorocarbon droplets, which are

Figure 2
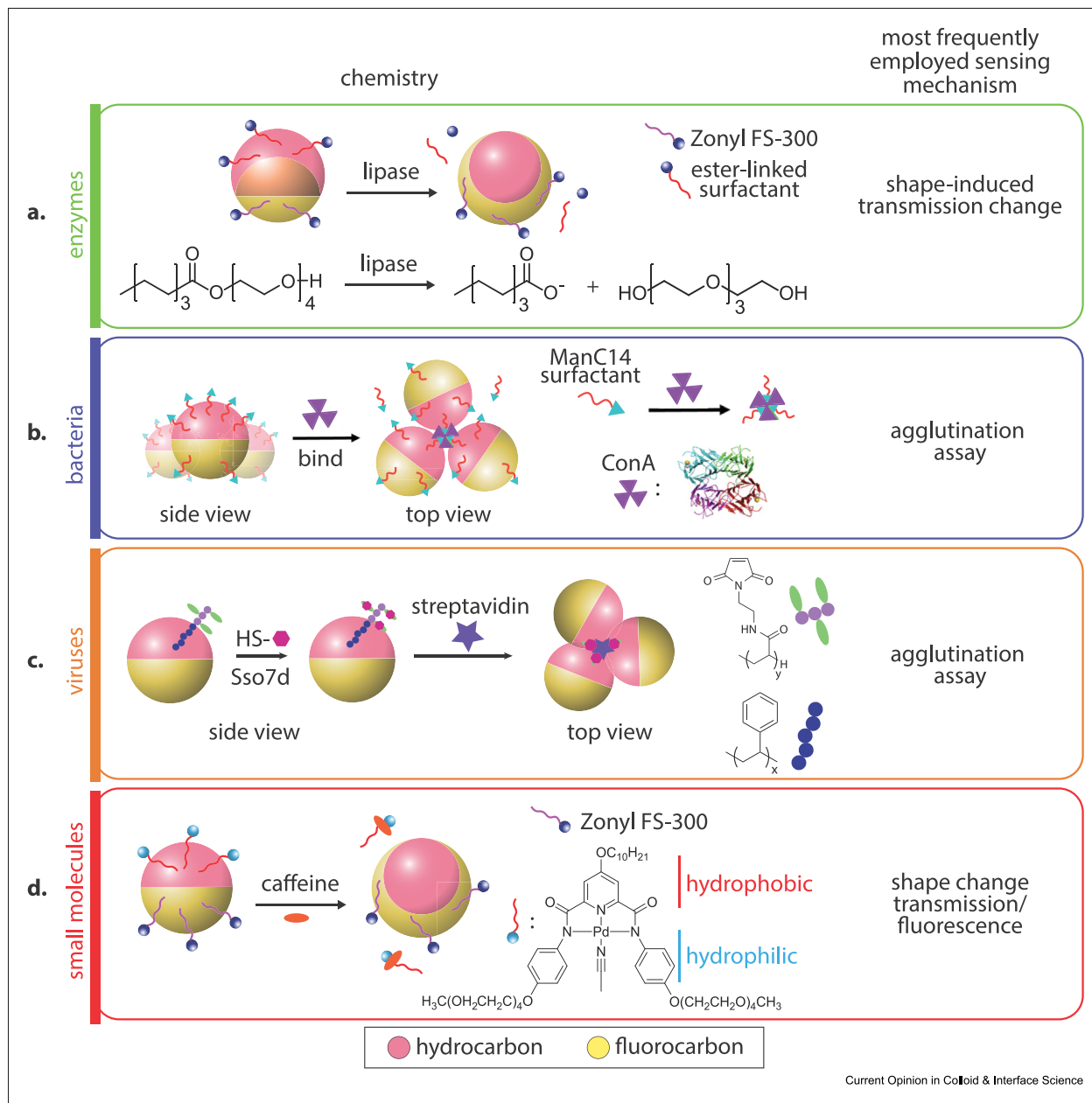
Schematic of the various sensing principles used in the literature with complex emulsions. **(a)** Lipase is detected by using cleavable surfactant inducing a change of the droplets morphology leading to a change of optical transmission of the samples in the presence of lipase. **(b)** Bacteria detection due to the use of a surfactant sensitive to binding with the bacterial lectin giving rise to droplets agglutination and change of optical transmission. **(c)** Virus detection in the same way than for (b) by using antigen binding protein for agglutination. **(d)** Specific surfactant is used to form a complex in the presence of caffeine leading to a change of droplets morphology and optical transmission due to change in interfacial tension. Reproduced with permission from Ref. [7]. Copyright 2020, AIP Publishing.

cleaved in the presence of the enzymes leading to a change of interfacial tensions and ultimately to a change of droplets morphology [19]. The cleavage of the surfactants leads to a change of the droplet shape to a double emulsion morphology with a hydrocarbon oil core and fluorocarbon oil shell resulting in optically detectable droplet morphological reconfiguration (Figure 2a).

Similarly, by designing Janus emulsions stabilized with mannose-base surfactants, it is possible to detect *Escherichia coli* bacteria due to the presence of a mannose-specific lectin (Figure 2b) [21]. The Janus droplets stabilized with mannose-based surfactants orient naturally in a vertical direction as a result of the difference in densities between the hydrocarbon and fluorocarbon solvents used for their production. In the presence of the bacteria, the binding of the bacterial lectin to the mannose units of the surfactant causes the Janus droplets agglutination leading to a tilted geometry. The optical difference between the naturally aligned Janus droplets and the agglutinated Janus droplets is the read-out mechanism to detect the presence of *E. coli* with a limit of detection around 10^4 CFU mL^{-1}. By using a similar sensing strategy, the Janus droplets agglutination has also been used for sensing of the virus Zika (Figure 2c) [22]. In this case, the Janus droplets are first functionalized with an antigen binding protein rcSso7d variant (rcSso7d-ZNS1) to detect the Zika NS1 protein. The addition of tetravalent streptavidin to the rcSso7d-SA functionalized droplets triggered agglutination by linking rcSso7d from different droplets together leading to a change of optical transmission. The detection limit is around 100 nM Zika NS1 protein [22].

These complex emulsions have also been shown to detect analytes easily such as for example caffeine (Figure 2d) [23]. The Janus droplets are stabilized with a specific caffeine-sensitive surfactant. This specific surfactant can bind caffeine at the droplet interface, resulting in both an increase in hydrophobicity as well as a decrease in its surfactant strength [23]. Thus, in the presence of small amount of caffeine in the water phase surrounding the droplets, there is a change in the balance of interfacial tensions leading to morphological droplets change from Janus droplets to a double emulsion morphology with a hydrocarbon oil core and fluorocarbon oil shell in water. Again, an optical transmission modification is observed.

In all the complex emulsions used for sensing, the challenging task is the initial formulation of the complex emulsions with the right choice of solvents and surfactants to reach different emulsions droplets morphology. As illustrated here, most of the time, specific surfactants need to be synthetized.
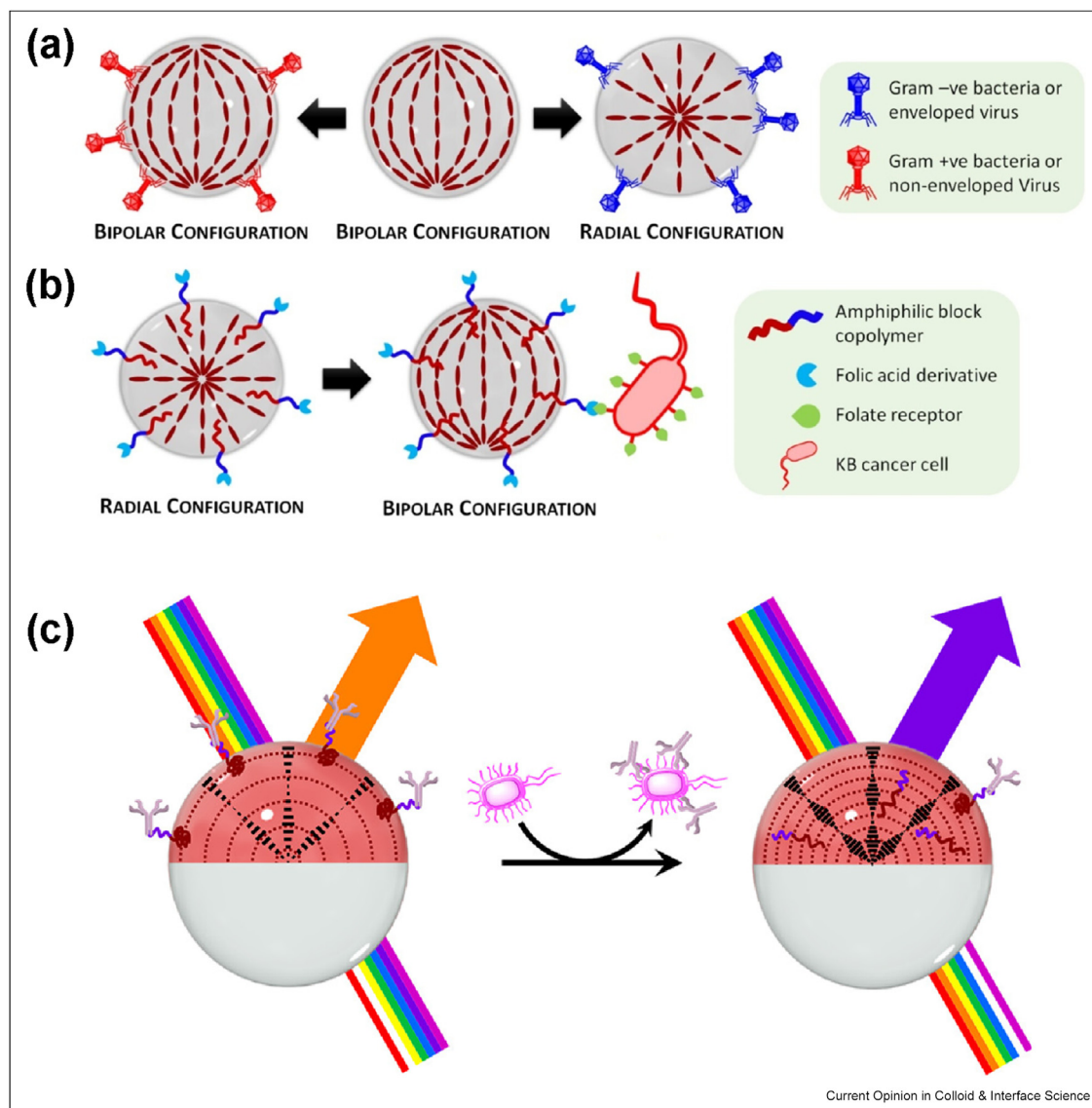
LC emulsions

Another type of emulsions has been recently described in the literature with strong potential as sensor; it is the LC emulsions from the group of Pr. F. Caruso and Pr. T. Swager [9, 17, 24]. LC are soft materials responsive to external stimuli, combining the fluid characteristics of liquids with the anisotropic properties of crystals. LC molecules maintain orientational and positional order while retaining their liquid nature. In the presence of external stimuli, molecular-level changes are triggered leading to a modification of the order and orientation of the molecules, which then is translated to macroscopic modifications, thereby modifying the properties of the LC materials. Many LC-based sensors have been traditionally used in thin film, but the main advantages of using LC emulsions droplets is their larger specific area and their very rich configurations of optical textures [11]. LC emulsions hold immense potential for chemical and biological sensing due to the exquisite sensitivity of their liquid crystal organization to interactions occurring at the molecular level within the droplet's interfaces. Thus, modifications occurring at the molecular level can then be easily detected through an optical texture change. LC emulsions have already been used for the detection of biomolecules, bacteria, virus, and environmental pollutants (Figure 3) [17]. As for complex emulsions described above, the key component is the use of a specific responsive surfactant capable of inducing interfacial changes in the presence of the components to be detected.

For example, cholesteric LC emulsions have been used as optical sensor applied to detect various analytes, including metabolites (e.g., glucose and cholesterol) and carbon dioxide [25, 26]. The selective reflection of cholesteric LC depends directly on the pitch of their helical structure, which can be altered in response to an external stimulus (such as the analytic in this case), resulting in a change in reflection wavelength (color). The changes in reflection wavelength are induced by the analytic-triggered physical swelling of the cholesteric helix, leading to a red-shift in reflection. The detection limit is good with limit of glucose detection of 0.5 µM for example [26].

Another approach is based on the integration of side-chain LC polymer surfactants functionalized with recognition elements to facilitate ligand−receptor interactions and induce a change in LC configuration within the droplets. Thus, several LC emulsion-based sensors have been designed for detecting cholic acid, enzymatic reactions, DNA, proteins, antibodies, or bacteria (Figure 3a−b) [17]. For example, LC droplets decorated with poly(l-lysine) have been used for the detection of DNA [27]. Indeed, Poly(l-lysine) induce a radial configuration within the droplets, while the adsorption of double-stranded DNA results in a bipolar configuration. The detection limit is 50 nM ssDNA [27].

Figure 3

Schematic representation of the mechanisms of LC emulsion-based sensors: **(a)** Enveloped viruses or Gram negative bacteria induce ordering transitions from bipolar to radial upon interaction with LC emulsions. **(b)** Radial-to-bipolar ordering transition induced by the interaction of an amphiphilic block copolymer bearing a terminal folic acid derivative and folate receptors present in KB cancer cells. **(c)** Schematic representation of the mechanism for the detection of *Salmonella enterica* using chiral nematic (N*) complex emulsions. Reproduced with permission from Ref. [17]. Copyright 2023, Wiley. Changes in the reflected light are produced through changes in the interfacial activity of boronic acid polymeric surfactants induced by a competitive binding/unbinding of IgG antibodies at the LC/W interface. Reproduced with permission from Ref. [9]. Copyright 2021, ACS.

Recently, the detection of *Salmonella enterica* has been demonstrated using complex LC emulsions [17]. These emulsions are based on cholesteric LC and FC oils and were employed for the detection of *S. enterica*. This method relied on the reversible interactions of boronic acid polymeric surfactants with anti-*Salmonella* IgG antibodies at the LC/water interface (Figure 3c). Biomolecular recognition events involving the foodborne pathogen *S. enterica* alter the pitch of the cholesteric structure, resulting in changes to its reflection wavelength [9]. Thus, such biomolecular recognition events can vary the pitch length of LC organization due to the presence of binaphthyl units in the polymeric structure, which are known to be powerful chiral dopants. The optical readout for the detection of bacteria is the interface-triggered

reflection changes. The detection limit was calculated to be 10^3-10^4 cells/mL [9].

For LC emulsions, the challenging task is the emulsion preparation step to control the organization at interfaces to obtain the distinct optical signatures needed as read-out mechanisms for sensing under polarized-light optical microscopy [28]. Moreover, such as for complex emulsions, the use and design of specific responsive surfactant system are key for using LC emulsions as sensor.

Foam stability and foamability: Two main parameters used for detection

Liquid foams are based on the dispersion of a gas inside a liquid phase, typically exhibiting gas volume fractions ranging between 0.65 and 0.95. The gas bubbles with average diameters spanning from 0.1 to a few mm are uniformly dispersed within a continuous liquid phase. Foams do not form spontaneously; some stirring and agitation must be done to disperse the gas into the liquid and create the bubble interfacial area. Thus, foams are metastable systems. Due to the unavoidable influence of gravity-driven aging processes (drainage), which synergize with disproportionation and bubble coalescence phenomena, foams evolution is a clear possible readout. Liquid foams and emulsions are frequently compared due to their similarities, but their behavior is quite different in practice since several parameters differ significantly in magnitude [29]. Notably distinct from emulsions, foams are characterized by larger bubble sizes (from few microns to millimeters), contrasting with the smaller droplet sizes (from few hundred nanometers to few micrometers). Another main difference is the surface tension, which is very high for pure air–water surface (72 mN m^{-1} at 25 °C), and much lower for pure oil-water interface (around 20–40 mN m^{-1} at 25 °C). The density difference between air and oil is also a key difference between foams and emulsions. As described previously, many examples of the use of complex and LC emulsions as sensor systems (see previous sections) are described in the literature. However, due to their differences and sensitivity, liquid foams also could be used as sensor for many applications. Liquid foams can amplify small changes occurring at the nanometer scale of the interface into drastic foam changes in terms of foamability and foam stability with time (lifetime of the foam under static conditions). A key advantage of liquid foams as sensors over emulsions lies in their ability to translate molecular scale events at the interface into visually detectable changes in foam characteristics, observable directly without complex instrumentation. Many reviews and book chapters are available on the two topics: foam stability and foamability [30–35]. Here, we summarize the main information useful for the readers to understand how liquid foams can be used as sensor by using changes in foamability or foam/bubbles stability before describing the examples of liquid foams as sensor available in the literature.

Foam stability: Definition and quantification for detection

The distinction between transient and metastable foams is linked to their respective lifetimes [32]. Transient foams exhibit short durations, typically lasting only a few seconds while metastable foams can last from minutes to years. The formation of metastable foams is based upon the alteration of surface properties through the utilization of foam stabilizing agents, including surfactants, polymers, proteins, or particles [36]. These foam stabilizing agents play a crucial role in enhancing foam stability by counteracting the destabilization mechanisms. Since all the liquid foam sensors described in the literature until now are based on the use of surfactants, we only describe here the main role of surfactants as foaming agent in sensor systems.

Surfactants accumulate at the air/water surface and reduce the surface tension and, notably in the context of foams, stabilize the thin films between bubbles against rupture. The manifestation of surface tension comes from an imbalance of attractive intermolecular interactions at the liquid's surface, necessitating additional energy to create an interface between a liquid and a gas, attributed to the surface tension. The reduction in surface tension is mandatory for the transformation of liquid from its bulk state, characterized by minimal surface area, into foam with high surface area [34]. Due to their amphiphilic nature, surfactant molecules spontaneously adsorb at the air/water interface. For foam, in the case of anionic surfactants, this process leads to the formation of two double layer distributions of charges, comprising a plane of negative heads and an adjacent diffuse cloud of positive counterions. Consequently, the two adjacent air/water surfaces in foam are enveloped by charged monolayers that repel each other, thereby stabilizing the foam films at a thickness where electrostatic attractions and Van der Waals interactions are balanced. The opposing electrostatic and Van der Waals forces typically equilibrate for film thicknesses ranging from 10 to 1000 nm. In the case of nonionic surfactant, the thin films are stabilized *via* steric repulsion [34]. The foam stability is linked to different parameters. The bulk viscosity of the foamed solutions is important to control the foam stability and it depends on the concentration and the self-assembly formed by the surfactants, among other parameters [37]. Another crucial parameter is the interfacial viscoelasticity controlling the drainage, but also affecting coalescence and coarsening [38]. An increase of surface viscoelasticity for foams based on surfactants leads to an increase of the whole foam stability [38]. The readers can find all the information on coarsening in foams with various surfactants and gases in

the review from Briceño-Ahmuda and Langevin [39], and also on coalescence in foams [38, 40]. It is important to keep in mind also that foams are also very sensitive to changes in environmental conditions (temperature, pH, etc.) due to possible changes of surfactant self-assembled structures inside the foam liquid channels and at the air/water surface [12].

The foam stability can be measured using various methods depending on the specific characteristics of the foam and the desired outcomes. Some of the methods are very simple, and other methods are more sophisticated (foam rheology, bubbles coalescence, etc.) [41]. Yet, visual observation is one of the most common techniques and very useful for the use of foam as sensor. It consists in following the evolution of the foam height over time. This method provides quantitative data on foam stability. Another method is based on the determination of the liquid drainage rate by measuring the liquid drained over time by visual observation or by conductimetry. The determination of the bubble size distribution with time is also a good method to follow the foam stability, and it can be done by simple techniques such as optical microscopy or image analysis. All these simple methods could be utilized to leverage foam stability as a means of detecting contaminants, biomarkers, bacteria, and so on.

Foamability: Definition and quantification for detection

In the literature, it is commonly described that foamability is linked to the surfactant concentration. However, it is important to keep in mind that when foamability as a detection method will be used, the correlation between foamability of the surfactant solution and the surfactant concentration is not straightforward [34]. Many studies have shown that the foamability is linked to the rate of surfactant adsorption, and with the surface concentration of surfactant [34]. However, the foamability is also closely linked to the dynamic surface properties such as for example surface elasticity, as demonstrated recently for various surfactants by Petkova et al. [34]. The foamability of surfactant solutions is further influenced by the chosen foam production method. This method dictates the efficiency of air entrapment and the extent of bubble coalescence during foam generation [33]. The air process entrapment leads to an increase of foam volume, whereas the bubbles coalescence leads to a decrease of foam volume [34]. Thus, to obtain an increase of foam volume during foam production, coalescence must be limited. The bubbles coalescence depends on the competition between the rate of surfactant adsorption on the bubbles surface and the drainage time of the thin film between the bubbles. Various foaming methods exist and they have all been described and compared in the review by Drenckhan and Saint-Jalmes [33]. In brief, the methods

for foam production can be sorted according to the way in which the energy to create the interfaces is provided; there are physical (mechanical or phase transitions), chemical, or biological methods. The physical methods include amongst the most known methods: whipping, shaking, double-syringe, and gas bubbling [33]. The chemical methods are based on the bubble's creation by a gas-releasing chemical or electrochemical (electrolysis) reaction. The biological methods rely on gas produced by specific species, for example in baking. The examples of liquid foams as sensor used in both physical and chemical methods as described in detail in the next sections.

In practice, foamability can be easily determined by measuring visually or with a camera, the volume of foam generated with a specific foam production method after a given time. When measuring foamability and foam stability for detection, it is essential to standardize the conditions such as temperature, humidity, and foam production method to ensure accuracy. Additionally, various instruments are commercially available for measuring foam stability and foamability based on the methods explained above.

Liquid foams for biomarkers detection

The "foam" test, also known as the "shake" test, was a method used in the past to assess fetal lung maturity during pregnancy. Developed around 50 years ago, this test was of paramount importance in obstetrics as it provided valuable information about the readiness of a fetus's lungs for breathing outside the womb [13]. The principle behind the foam/shake test relies on the ability of lung surfactants, particularly phospholipids, to reduce surface tension in the amniotic fluid. These surfactants are essential for maintaining the stability of the alveoli, the tiny air sacs in the lungs, by preventing them from collapsing during exhalation. During the test, a sample of amniotic fluid was mixed with ethanol, which acts as an antifoaming agent for most biological compounds (Figure 4) [13]. If the amniotic fluid contained sufficient phospholipids, stable bubbles would form upon vigorous shaking due to the reduced surface tension. Indeed, phospholipid surfactants can generate a surface tension lower than that of an ethanol—water mixture containing 47.5% ethanol and 52.5% water (vol/vol), which aids in maintaining stable bubble structures. Based on these principles, the shake/foam test for assessing fetal lung maturity was developed. This test involves vigorously shaking of ethanol and amniotic fluid, followed by observation for the presence of stable bubbles, indicative of sufficient surfactant phospholipid for predicting mature lungs at birth. The presence of stable bubbles indicates mature fetal lungs capable of producing surfactants necessary for proper lung function after birth (Figure 4). The read-out mechanism is the bubbles stability.

Figure 4
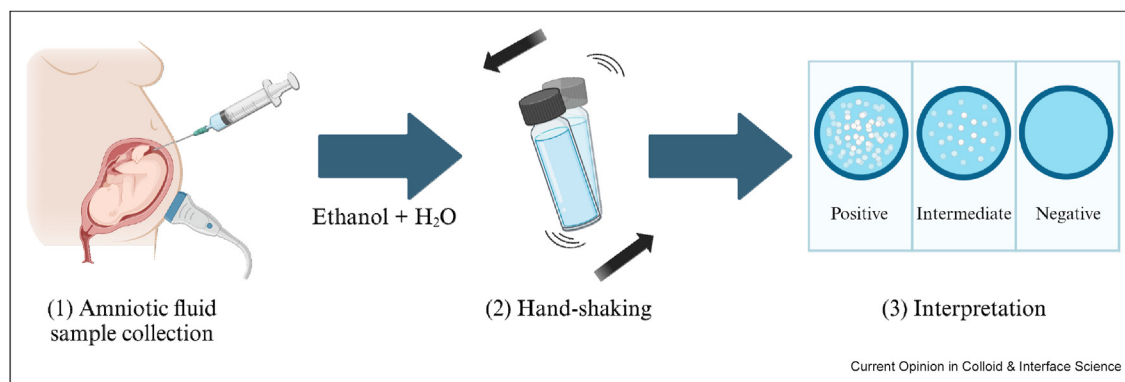
Schematic of the foam/shake test method to detect fetal lung maturity during pregnancy. **(a)** Amniotic liquid is collected. **(b)** Amniotic liquid is mixed with ethanol and water and foam/bubbles are produced by vigorous hand-shaking of the mixture. **(c)** Interpretation of the result by looking from the top at the air/water surface after shaking. If no bubbles are present, the test is negative. If many bubbles are present, the test is positive. Created in BioRender. Fameau, A. (2024) BioRender.com/d25k931.

This test was particularly important in the past because it offered a simple and relatively quick way to assess fetal lung maturity, which was crucial to determine the timing and method of delivery. In cases where the fetus's lungs were deemed immature, it might prompt healthcare providers to delay delivery or consider interventions to accelerate lung development, such as administering corticosteroids to the mother. Conversely, if the test indicated mature lungs, it could provide reassurance and support the decision for the fetus to be delivered without delay, reducing the risk of respiratory distress syndrome and associated complications after birth. Few years after the development of the shake/foam test, a commercially available kit (Lumadex-FSI test) was available based on the same principle. Utilizing the commercial kit Lumadex-FSI *versus* the manual test was a good way to eliminate the need for manual ethanol pipetting and preparation of lecithin standards, saving significant time and greatly reducing the risk of pipetting errors. Despite its historical significance, the foam/shake test has largely been replaced by more accurate and sophisticated methods for assessing fetal lung maturity. However, its development represented a milestone in obstetric care, providing valuable insights into fetal lung development and helping to improve outcomes for newborns at risk of respiratory problems. It is important to notice that still today, this method (with slight adaptation) is used for specific detection in developed countries. For example, early identification of hyaline membrane disease (HMD) in newborns is crucial for their prompt transfer to a neonatal intensive care unit, thereby improving their outcomes. This underscores the need for a rapid, simple, and reliable test for assessing pulmonary maturity in at-risk infants [42]. The biochemical tests or immunoassays to detect HMD require technical skill and are expensive. Therefore, developed countries still rely on the simple and cheap shake/foam test to detect HMD. It is a common bedside test used to determine surfactant lung deficiency in newborns [42].

Recently, the possible use of liquid foams for the detection of various biomarkers has regained interests [43]. The foam detection concept is based on the utilization of a host-guest system containing a foaming surfactant (Figure 5a). The host-guest system is based on tetradecyltrimethyl ammonium bromide ($C_{14}TAB$) as guest and β-cylodextrin (β-CD) as host in water. The effectiveness of a foaming surfactant can be hindered by its encapsulation within a β-cyclodextrin molecule (host). This hydrophobic cavity in the host molecule traps the surfactant's hydrophobic tail (guest), preventing it from participating in foam generation. The presence of a specific biomarker disrupts this host-guest interaction. This disruption can occur through two mechanisms: competition with the biomarker for the host cavity or degradation of the host molecule itself. When the targeted biomarker is present (Figure 5a), it displaces the surfactant from the host-guest complex. This liberates the surfactant, allowing it to participate in foam formation. The resulting foam volume (foamability) is directly proportional to the biomarker concentration. This makes the detection process visually quantifiable by the naked eye or measurable with a simple ruler.

This approach was illustrated with two important models' biomarkers: cholic acid and cholesterol. Bile acids, such as cholic acid, are crucial metabolites playing a key role in digestion and are monitored in individuals with liver and intestinal diseases [44]. Cholesterol and its metabolites are vital components of the plasma membrane and various cellular organelles, holding

Figure 5
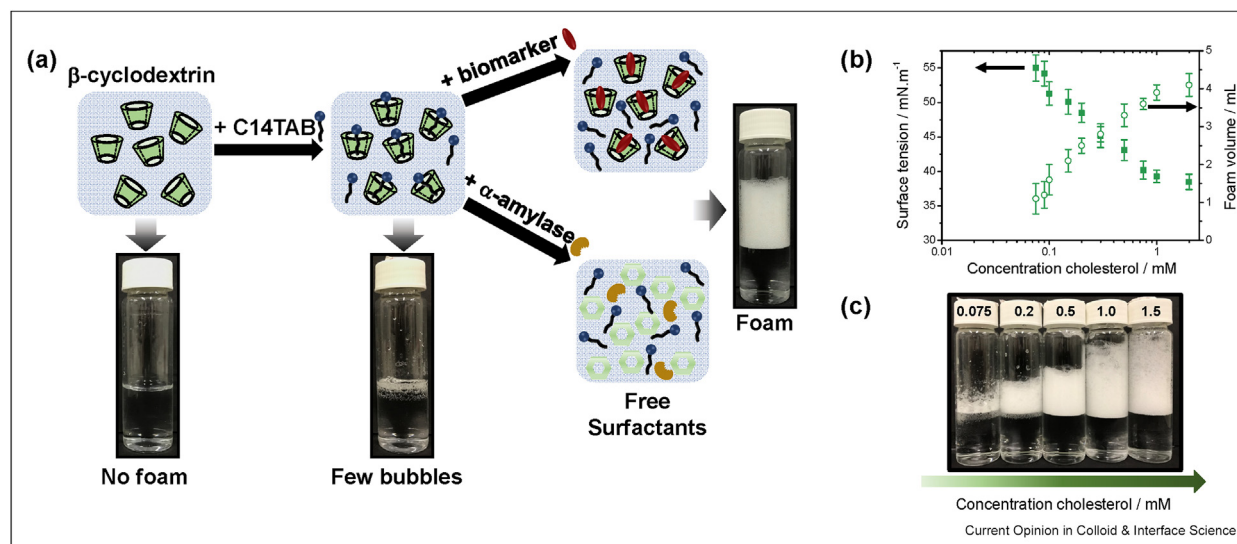
(a) Schematic illustration of the foam detection principle based on a host-guest complex of β-cyclodextrin with the cationic foaming surfactant C$_{14}$TAB. The biomarker (cholic acid or cholesterol) or the enzyme (α-amylase) disrupt the complex of β-cyclodextrin/C$_{14}$TAB in aqueous solution by either competitive substitution with β-cyclodextrin or by its degradation. It results in a change of the foam volume after hand-shaking. **(b)** Evolution of surface tension (■) and foam volume (○) with the concentration of cholesterol. The arrows are drawn to guide the eye. **(c)** Pictures of the samples right after hand-shaking with different concentrations of cholesterol. An increase of the foam volume with increasing concentration of cholesterol is observed. Adapted with permission from Ref. [43]. Copyright 2023, Elsevier.

significance in the detection of cardiovascular diseases [44]. The cholic acid and cholesterol assay are based on a competition between analyte and surfactant for the host. In the presence of cholic acid or cholesterol, the C$_{14}$TAB is replaced by the biomarker inside the host (β-cyclodextrin). Cholic acid and cholesterol are known to have a higher binding constant for β-CD than C$_{14}$TAB. C$_{14}$TAB monomers are released from the β-CD, adsorb at the air—water interface, and decrease the surface tension (Figure 5b—c). Thus, foam can be produced. The foamability is linked to the quantity of the biomarkers detected (Figure 5b—c).

Liquid foams for enzyme detection

Enzymes play essential roles in catalyzing biological reactions and maintaining metabolic systems [45]. The approach of using liquid foams to detect enzymes has been shown for three enzymes in the literature: α-amylase, catalase, and lipase [46—49]. The role of lipases is to saponify triglycerides and other esterified substrates into fatty acids and glycerol. Lipase serves as a significant diagnostic enzyme and biomarker for pancreas-related conditions like pancreatitis [50]. α-amylase, is associated with gastrointestinal tract conditions [51]. Identifying atypical enzyme activity, such as elevated lipase levels, in conjunction with a physical examination, serves as diagnostic indicators for various diseases. Catalase is an oxidoreductase that degrades hydrogen peroxide into

water and oxygen. Catalase is employed by various pathogens to protect themselves from hydrogen peroxide, a weapon frequently deployed by the host immune system in addition to oxidative stress [52].

To detect α-amylase activity, the host-guest system described previously (Section Liquid foams for biomarkers detection) was used (Figure 5) [43]. In this case, the foaming surfactant was not released because of competitive interactions but due to the degradation of the host molecules (β-CD) *via* the enzyme: α-amylase catalyses the hydrolytic cleavage of the internal α-1,4-glycosidic bridge in cyclodextrin, which resulted in the release of the foaming C$_{14}$TAB surfactant, a decrease of the surface tension and the corresponding foaming. Thus, the more active the enzyme, the more C$_{14}$TAB was released and the more foam could be produced. The foamability increased almost linearly as a function of the α-amylase activity, i.e., the enzyme activity could be deduced from simply measuring the foam volume with the naked eye (Figure 5).

The detection and quantification of enzymes such as lipases and catalases are very important for the food industry, as the detection of foodborne pathogens is a growing global public health concern due to the illnesses and deaths resulting from consuming contaminated food [53,54]. Despite rigorous cleaning and disinfection

procedures in the food industry, surfaces in processing equipment can still be contaminated by microorganisms [53]. These bacteria often persist on surfaces, forming biofilms composed of polysaccharides, proteins, and enzymes. Removing these biofilms using standard cleaning procedures is challenging, and raises concerns for food safety as pathogenic microorganisms can be involved in biofilm formation [53]. Many pathogens are known to readily produce biofilms, aiding their survival in food production plants. Therefore, food contact surfaces in processing equipment are considered major factors in the risk of cross-contamination to food products and quality deterioration in the products [53]. Rapid and reliable detection of biofilms and bacterial enzymes is thus a significant concern in the food industry [54]. Obtaining rapid microbiological analysis results of food-contact surfaces is crucial for making informed decisions and ensuring food safety. Developing products capable of detecting biofilms quickly is imperative for safeguarding food products. The traditional methods for identifying contaminating microorganisms and quantifying biofilm contamination have several drawbacks. For example, the conventional method for bacterial detection requires cell culturing, which involves labor-intensive steps such as enrichment, bacterial culture, and identification. This method is time-consuming, requiring 3−5 days to yield results, and demands specialized laboratory equipment, which is ineffective in preventing health crisis or to overcome product's blockages [54]. Methods based on the PCR are more rapid (few hours) but require expensive

equipment operated by trained technicians. These drawbacks of the current methods surrender the possibility of testing quickly the efficiency of the hygiene procedures [55]. The food industry is still actively looking for new ways of detection, which can be an easy on-site detection method for the operators working in the food chain production with potential advantages in terms of speed and cost. In this context, liquid foams as sensor have demonstrated a strong potential.

One way to detect the presence of biofilm on a surface is to determine the presence of catalase produced from bacteria. The foam detection principle is based on the production of oxygen bubbles generated from the decomposition of hydrogen peroxide by the catalase, and the boosted stabilization of these bubbles by the presence of surfactants. The oxygen bubble stabilized by the surfactants are then visualized as a foam by naked eyes (Figure 6) [48,49]. The read-out mechanism is the production of foam. This method provides the tested surface with a substrate for the enzyme hydrogen peroxide (H_2O_2), along with a foam stabilizer (surfactant) that is not sensitive to oxidation. It is important to notice also that the same approach has been used to measure the catalase activity in human cells [47].

In the study, catalase-positive bacteria known to produce biofilms and seen as threat of the food industry, were evaluated: *Staphylococcus aureus*, *Escherichia coli*, *Listeria monocytogenes*, *Pseudomonas aeruginosa*, *Salmonella enterica ser. Typhimurium* and *Cronobacter sakazakii* [48].

Figure 6
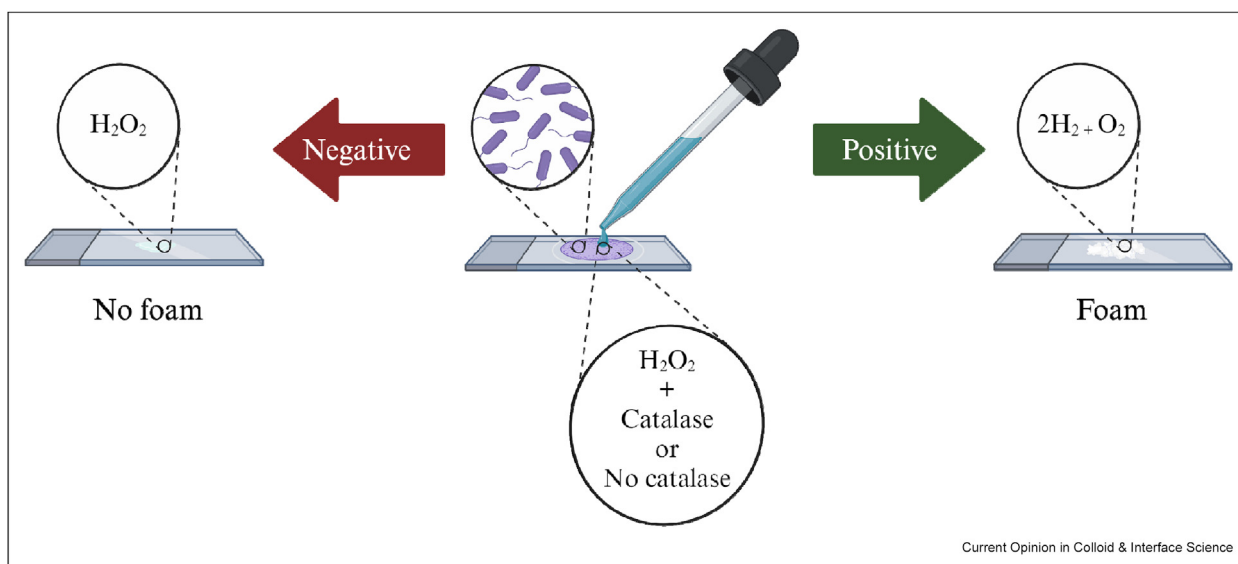
Schematic showing the foam detection test for bacteria producing catalase embed in a biofilm in a surface. A formulation containing water, surfactants, hydrogen peroxide, and bleaching agents is deposited on the surface to test. If catalase is absent, no foam is formed. If catalase is present, foam is formed in few minutes due to the production of oxygenbubbles which are stabilized by the surfactants. The formation of foam indicates the presence of biofilm containing bacteria producing catalase. Created in BioRender. Fameau, A. (2024) BioRender.com/k34s597.

Two different surfaces were also tested (stainless steel and propylene surfaces) to show the robustness of the detection method. The formulation used for detection was based on anionic foaming surfactants, hydrogen peroxide and bleaching agents. The formulation was sprayed onto the surface being tested, and the results were observed after 10 min of exposure to the formulation. Foam was produced and detected by the naked eye for all bacteria and surfaces when biofilms were present (Figure 6). However, no foam was produced and detected in the absence of biofilm or in the absence of bacteria producing catalase. The minimum detection limit was around 10^4 CFU cm^{-2}, which is a good result since no sampling by swabbing, etc. was needed [48]. Based on these promising results, a formulation containing hydrogen peroxide, ethoxylated fatty alcohols, anionic and nonionic surfactants, and bleaching agents have been commercialized under the name "BIOFINDER" [49]. Thanks to the rapid foam production, the test is fast and easy for operators to perform. They simply need to apply the liquid formulation to the surfaces and wait a few minutes to determine whether foam is produced or not. This example illustrates that liquid foams display many advantages for the detection in food industry: simplicity to perform the test, produce rapid visual readout, and require no specific equipment [6]. Moreover, the formulation is simple and based on only few components at low price.

To detect the presence of lipase by using liquid foams, another approach was used for enzyme detection which is based on changes in the foaming properties of enzyme cleavable surfactants (Figure 7). Cleavable surfactants have a hydrolytic bond in their structure that can be broken in a controllable and predictable way [56]. Upon cleavage, the surface activity of these surfactants can either increase or decrease [57]. The cleavable surfactant used to detect lipase is an ester-based surfactant, (tetra(ethylene glycol)mono-*n*-octanoate (TEO)) [46]. TEO is a good foaming agent. Upon addition of the lipase, the ester-linkage in the TEO surfactant is cleaved into the corresponding carboxylic acid (octanoic acid) and tetra(ethylene glycol) (Figure 2b) [58]. These resulting reaction products are ineffective foaming agents, which is why no foam can be produced anymore [46]. The read-out mechanism for the detection of lipase is the inability of foam production by mechanical agitation, contrary to catalase detection for which the production of foam was the read-out mechanism. The potential of liquid foams as sensors for detecting lipase was illustrated by producing foams with a milk frother for 10 s as a function of the lipase action time. The height of the generated foam corresponding to the so-called foamability was measured immediately with a ruler (Figure 7a). Before adding the lipase, high quantity of foam was produced due to the high foamability of the TEO surfactant. In the presence of the lipase, a decrease of the foam height with lipase action time for all lipase activities was observed (Figure 7b). The increase of the lipase activity results in a decrease of the foam height at shorter lipase action times. Thus, by plotting the foam height against the lipase activity, it is

Figure 7
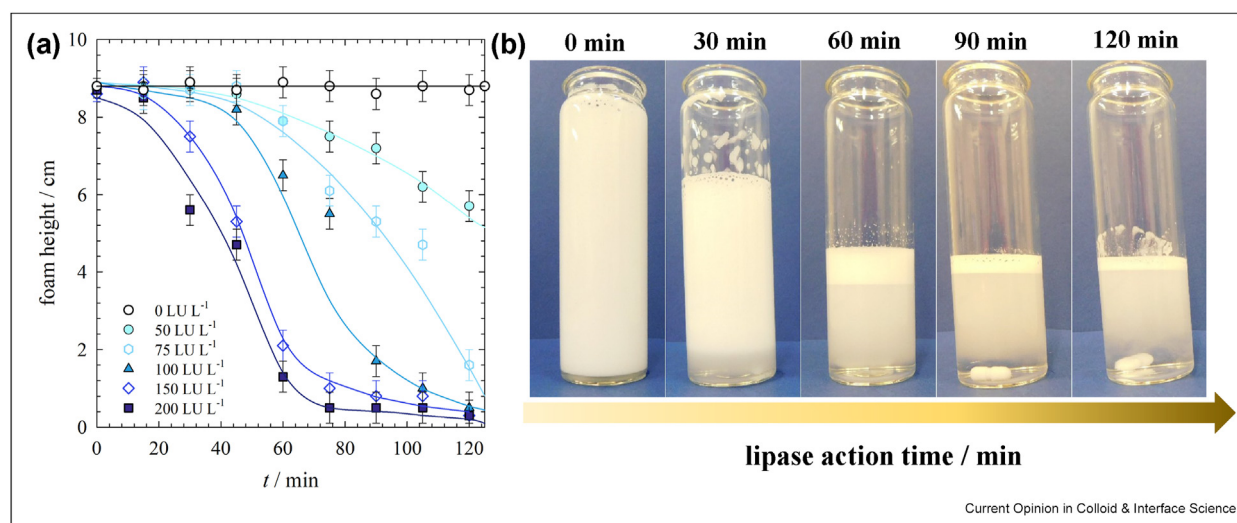
(a) Foam height produced after stirring as a function of lipase action time for various lipase activities at T = 17 °C. The solid lines are drawn to guide the eye. **(b)** Pictures of samples with a lipase activity of 200 LU L^{-1} just after generating the foam as function of lipase action time. Note that a high foam quantity is produced before adding the lipase (0 min). Once the lipase is added the foam height decreases with lipase action time. The foams decay quickly and must therefore be re-produced for each lipase action time. Reproduced with permission from Ref. [46]. Copyright 2024, Elsevier.

possible to obtain a calibration curve for the detection of enzyme activity. Moreover, by comparing this foam detection method with the complex emulsions approach to detect lipase activity (Figure 2b), the foam detection method is faster with similar sensitivity [19]. This study demonstrates that the changes of foaming properties for the surfactants are also a way to detect and quantify enzyme activity such as lipase [46].

Liquid foams for bacteria detection

The only example in the literature showing the use of liquid foam for the direct detection of bacteria and not for bacterial enzyme detection has been designed to detect specifically *E. coli* O157:H7 (*E. coli* O157:H7) [59]. Foodborne illness, commonly known as food poisoning, is a significant global concern, leading to symptoms like diarrhea, nausea, hospitalization, and even fatalities [4]. Among the various pathogens causing these illnesses, *E. coli* O157:H7 stands out as a particularly menacing threat to the public health worldwide [60]. This strain of *E. coli* is notorious for causing severe diseases such as hemorrhagic colitis and hemolytic uremic syndrome, especially affecting vulnerable demographics like the elderly, young children, and immunocompromised individuals [60]. This is why an early detection of harmful food pathogens like *E. coli* O157:H7 is paramount for effective prevention strategies. Traditionally, the gold standard for detecting this food pathogen in food samples has been the culture method. Several alternative detection methods, including enzyme-linked immunosorbent assay, PCR, and electrochemical sensors, have been developed to detect *E. coli* O157:H7 with high sensitivity. However, these methods often have the traditional shortcomings, i.e., price, equipment, rendering them unsuitable for on-site detection, particularly in resource-limited settings [4]. A detection method for *E. coli* O157:H7 has been developed by Liu et al. based on the foam height produced in the presence of *E. coli* O157:H7 [59]. This quantitative immunoassay for *E. coli* O157:H7 detection was developed by integrating a catalyzed foam-generation reaction with a specific pathogen recognition component. Different components and steps are required to produce the final foam test. First, *E. coli* O157:H7 need to be enriched and captured using monoclonal antibody to *E. coli* O157:H7 (mAb1) modified Fe_3O_4 magnetic nanoparticles. Then, the gold and platinum nanoparticles (Au@Pt NP) are loaded onto the silica nanoparticles (SiO_2) to form Au@Pt/SiO_2 nanoparticles. These Au@Pt/SiO_2 nanoparticles are then functionalized with antibodies against *E. coli* O157:H7 (mAb2-Au@Pt/SiO_2 nanoparticles). These antibody-labeled mAb2-Au@Pt/SiO_2 nanoparticles are crucial in catalyzing the decomposition of H_2O_2 into water and oxygen. Specifically, the Au@Pt nanoparticles exhibit remarkable catalytic efficiency, ensuring the rapid generation of oxygen bubbles from H_2O_2 in the presence of the target pathogen, *E. coli*

O157:H7. In the presence of *E. coli* O157:H7, the oxygen bubbles produced by the catalytic reaction are trapped by the foaming surfactant, which is sodium dodecyl sulfate, resulting in the stabilization of the gas bubbles and the accumulation of foam. In spite of a much more elaborated system being needed for gas production, the foam remains the main read-out method. The authors demonstrated that the height of the foam directly correlates with the concentration of *E. coli* O157:H7, enabling quantitative measurement by naked eyes with a ruler. The detection limit was determined to be around 10^2CFU mL^{-1}. The practical application potential of this method was demonstrated through its successful detection of *E. coli* O157:H7 in milk samples. The reason foam method to detect *E. coli* developed by Liu et al. is better compared to the conventional methods is its simplicity and cost-effectiveness. However, there are several chemical synthesis steps to produce the antibodies catalytic nanoparticles, and the detection limit is still high in comparison to conventional methods [59].

Conclusions and perspectives

Many recent studies have emerged in the literature, demonstrating the potential of utilizing soft-interfaces as sensors for detecting bacteria, enzymes, biomarkers, etc. [7–9,17]. Emulsion and LC have been described in many studies, showing the strong potential of such approaches. Liquid foams, which have been much less explored as sensors, can also be utilized for numerous targeted applications as sensors due to their high sensitivity linked to their high surface area and impact of the variation in surface tension upon detection events. The primary advantage of liquid foams over emulsions as sensors lies in their ability to allow observation of events taking place at the molecular level at a spatial scale visible to the naked eye. This can be achieved without the necessity of additional instrumentation; one can simply observe the foam directly.

It is quite surprising that the first example of using liquid foams as sensors to detect lung maturity in fetus, which occurred 50 years ago and led to the development of a commercial foam-based detection kit, was not followed by further applications [13]. It took almost 40 years for the use of liquid foams as sensors to resurface, this time for detecting bacterial contamination in food industries [48]. Once again, a commercial product was developed and is now available for purchase, clearly demonstrating the vast potential of liquid foams for detection applications due to their ease of use, rapid detection, and low cost. The main point in evaluating sensory materials is to move beyond the laboratory and test in real-world conditions, which is already the case for liquid foams in contrary to many examples in the literature based on responsive materials. Liquid foams hold significant promise for point-of-care testing due to several compelling advantages: low cost, ease of use, rapid visual

results, and minimal equipment requirements [6]. These tests often only require a few components to create a stable foaming solution, and the stability can be further optimized by tailoring the composition for different temperature ranges. As highlighted in this review, liquid foams offer a versatile sensing platform applicable in diverse settings, particularly in resource-limited regions where rapid and simple bioassays are crucial for health monitoring, like assessing newborn pulmonary maturity [42,61]. Foam sensors have the potential to revolutionize on-site detection by offering speed, affordability, and user-friendliness [3]. Importantly, the immediate feedback provided by foams can serve as a real-time screening method. If necessary, more precise conventional methods can be employed for confirmation and quantification of biomarkers, bacteria, viruses, etc., at lower concentrations.

A key challenge lies in identifying suitable conditions to create foams that exhibit distinct behaviors in the presence and absence of the target analyte. Ideally, we seek a significant difference in either foamability (high *vs.* low foam formation) or foam stability (stable *vs.* rapidly collapsing foam). Building upon the success of complex emulsions, the principle suggests that any desired analyte could potentially be detected using liquid foams, provided the foaming surfactant can be tailored to become responsive to the target. This opens doors for exploring various host-guest systems based on foaming surfactants, extending the potential applications far beyond the ones presented in this review [62]. Various responsive systems based on foaming surfactants can also be easily designed based on the abundant literature in this field to detect various analytes [12,63,64]. Here, we only presented examples based on foams produced from surfactants, but liquid foam sensors could also be produced based on polymers, particles, etc. by taking advantages of the huge literature on aqueous foams produced and stabilized by these other foam stabilizing agents [12,37,65–67]. Another future direction to consider in this field could be drawing inspiration from developments in the field of gas-propelled sensors [68]. Gas-propelled sensors are based on a simple gas-based signal transduction for detection. In such sensors, the target recognition events can be converted to gas propulsion, which can be displayed as a read-out signal [68].

It is important to recognize that while liquid foam is a valuable tool for detection, it also has significant limitations, particularly when dealing with samples that contain multiple foaming agents or antifoam components. For instance, in the use of liquid foams as sensors to detect fetal lung maturity, ethanol is mixed with water to prevent foam formation from other biological compounds present in amniotic fluid. Additionally, foam production is influenced by factors such as temperature, humidity, and agitation rates. Automated systems that maintain consistent test conditions can help reduce variability in results. By carefully controlling these conditions and selecting appropriate solvents and foaming systems, the limitations of using liquid foam as sensors can be mitigated.

In conclusion, unlocking the full potential of liquid foams as versatile sensors relies on a multidisciplinary approach to overcome remaining challenges such as specificity, sensitivity, signal amplification, and read-out accuracy. This review serves as a springboard for future research, aiming to refine existing concepts for detection using soft interfaces.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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   * * of outstanding interest

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