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Introduction on Foam and its Impact in Bioreactors

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Abstract

Foam formation in bioreactors (fermenters) and other types of reactors is a highly interesting topic that touches several disciplines. All of the phenomena involved in foam formation have been the subject of many studies, but their relationships are still not obvious to newcomers. This review aimed to give the reader a good background for understanding the various phenomena involved in foam formation, especially in bioreactors. Hopefully, this would give the reader the tools necessary to access any needed information about foaming, a task that can be difficult without such basic knowledge.

Keywords: bioreactor, foam, foaming, froth, bioprocess

Introduction

Foam formation is observed in many processes associated with numerous disciplines. Foam can be observed in most fermentation processes, where its presence can greatly reduce product yield and overall process performance. Foam has sparked the interest of many researchers, and its formation implies many phenomena touching a wide array of disciplines. Since foam formation and its destruction exploit those phenomena, it's sometimes hard to solve foaming problems in bioreactors without reading literature from other disciplines. This difficulty is too often reflected in the literature where many empirical findings on foam in biotechnology lack a physical description of the mechanism behind its formation or its destruction. The present review aimed at giving the resources needed to understand the principles governing those phenomena and their impact on fermentation processes performed in bioreactors. Each section of this review offers an accessible explanation for any given basic aspect, supported by references of both important publications as well as reports on very recent work.

The first section offers an introduction to the interesting physics of foam. It deals with the structure, the behavior, and a few simple concepts that can be helpful to handle the subject. The second section is focused on foam formation in bioreactors, on the consequences of foaming, on foam mitigation or destruction, and, also, on how the foam can be used positively.

Physics of Foam

Definition

Foam can be defined as a complex structure composed of gas pockets separated by liquid membranes [1–3]. Foam is subjected to strict physics rules and, when observed closely, it reveals a well-defined substructure. Its structure is influenced by the liquid fraction, which is the proportion of fluid in the foam. The physics involved in the foam is easier to observe in a foam with a low liquid fraction, also called dry foam. Therefore, the structure of dry foam has been described first.

Structure of Foam

With a low liquid fraction, the foam is well-defined, and the structure is easily visible [4–6]. It is by observing dry foam that Plateau, in 1873, was able to define its structure in simple terms [5–8]. He noticed that the thin membranes and the dense liquid channels form a network of nodes connected in intersections following a specific set of constraints [8–10]. He observed that a three-channel intersection joins at a specific angle of 120° and that a four-channel intersection joins at a specific angle of 109.4°. The name, "Plateau borders" is given to the set of nodes and channels. The four-channel configuration is reminiscent of the methane steric configuration (Figure 1). Such a configuration is the result of an energetic equilibrium [6,8,10].

As the bubbles are pushing one against another, the forces at the interfaces push the channels to adopt Plateau border strict angles [5,11]. These shape the bubble edges into polygons. As naturally formed foam can have a large variety of shapes and sizes, no specific shape can be found. Nonetheless, the polygon shape with a small number of corners seems to be unfavorable in aging foam. With two dimensional foam, bubbles with fewer

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*Corresponding author: Email: Gabriel.St-Pierre-Lemieux@usherbrooke.ca than six edges will slowly collapse, as described by Von Neumann in 1952 [12,13]. With three dimensional foam, a simulation seems to fix this number to sixteen edges [13].

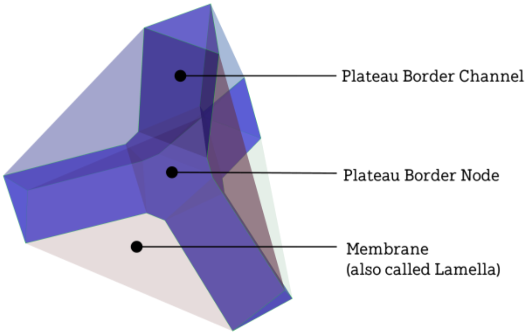

Figure 1: Four-channel Plateau border junction.

Foam exhibits a variety of size distributions. It can have a broad range of sizes, in which case the foam is defined as polydispersed, or a narrow range, which is defined as mono-dispersed [6,7]. Because of various phenomena, which have been described later, foam is commonly polydispersed. A truly mono-dispersed foam is theoretical, but it may also be produced on purpose, mainly, because it offers an easier structure for investigation [6].

The final layout of the foam structure is an intriguing topic that has been well-studied and is still being investigated by numerous scientists. Based on the mathematical work of Green and Fresnel, Lord Kelvin proposed a foam structure that minimizes interface areas and respects the Plateau border [14]. This "ideal" foam is mono-dispersed and is formed of rhombic dodecahedrons. Later, in 1992, using a computer program developed by Brakke [15], Weaire and Phelan identified another configuration that uses two different shapes of the same volume. Those shapes are the pyritohedron and the truncated hexagonal trapezohedron (Figure 2). Interestingly, foam with the Weaire–Phelan configuration was produced experimentally in 2011 [16]. Those mono-dispersed and "ideal" foams are used to understand foam energy balance and to develop analytical equations on diverse foam characteristics [11].

An increase of the liquid fraction will relax the strict and well-defined angle of the Plateau border present in dry foam. The presence of a larger space in the channels puts less strain on the surfaces, allowing them to adopt a spherical configuration. At the extreme limit, in wet foam, nearly no interactions occur between the surfaces, and the structure behaves like a suspension with nearly undeformed bubbles. The liquid fraction at which the surface of the bubble is not deformed by its interactions is called the critical liquid fraction (Φ_{crit}). As it may be suspected, at this point, there is no more strain applied to the surfaces. A detailed article about foam structure, the energy computation inside different foams, and the transitioning between dry and wet foam was published by Drenckhan and Hutzler in 2015 [11]. A more accessible introduction to the same subject was produced by Garrett in 2016 [7].

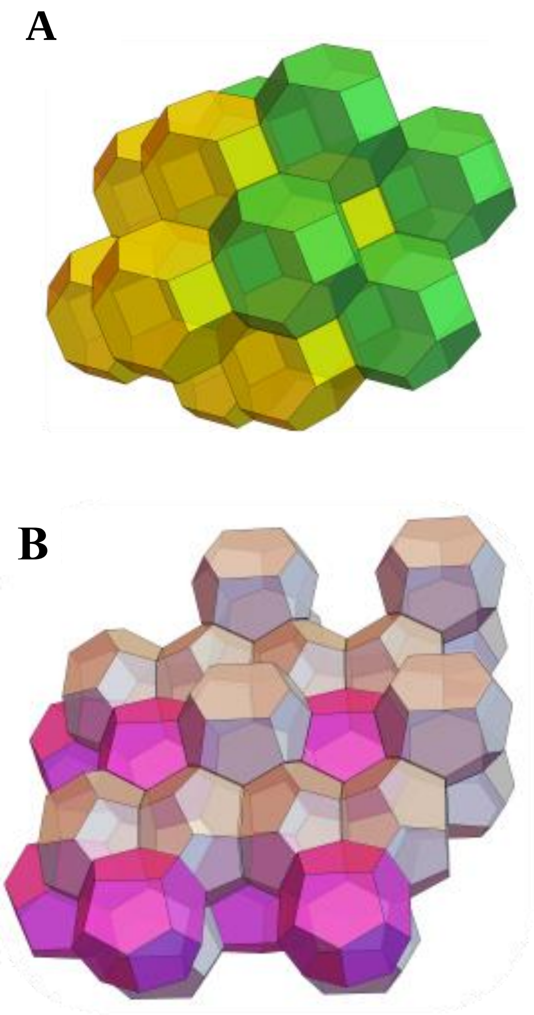

Figure 2: (**A**) Kelvin's foam with rhombic dodecahedron and (**B**) Weaire and Phelan foam with the pyritohedron (magenta) and the hexagonal trapezohedron (gray).

Jamming and Rheology

It is important to know the structure of foam to understand its behavior. The phenomena involved in its structure determine how the foam reacts to a force. The structural components can slide and change conformation or break [17]. Roughly, foam is described as a viscoelastic fluid. Since its structure is influenced by the liquid fraction, so is its behavior.

With dry foam, the bubbles are pushing one against another. The channels are thin, and the Plateau borders are well-defined. The interacting surfaces make the foam harder to deform since the stiff channels transmit a great portion of the force [5]. The force transmitted through the foam is said to be the "elastic" component of the foam behavior. When the force is large enough, the channels will simply break, reorganizing the network. The force at which this phenomenon happens is called yield strain.

With a wet foam, the bubbles inside the foam are rounder, and the Plateau borders lose their definition [4,5]. The channels are larger, and the bubbles slide more freely as well. Less force is transmitted by the channels as most of it is "lost" in the movement of the bubbles [5]. The force lost inside the foam is called the "viscous" component of the foam behavior.

To obtain a suitable evaluation of those properties, the oscillatory shear test has often been used in the literature [4,5]. It has the advantage of being non-destructive, and it can also give information about the thixotropic nature of foam and the yield stress. Oscillatory shear tests can be performed in a parallel plane or in a Couette geometry, where the surfaces are often textured to limit the wall effect.

The transition between dry and wet foam can be observed by the degradation of the "elastic" behavior. Once the critical fraction is reached, the bubbles do not interact anymore, leading to the absence of yielding, at least in theory. In reality, the foam becomes unordered, and the yielding phenomenon gradually disappears, as stated in Katgert et al. [5].

The critical fraction and the surrounding phenomena have been studied and reported in a large number of articles using different strategies: geometry, physics simulation, statistics, and so on. Notable publications are from Lui's group [18], which describe and explain the phenomena in general (not focusing solely on foam). Another report, more specific, by Katgert et al. [5], is more concise and focuses on foam jamming.

Several articles have reported on the two-dimensional packing aspect. A recent example is an article published by Dune reporting on the change induced in a two-dimensional foam by variation of the liquid fraction [19]. The study, using computer software, focused on the Plateau border geometry and demonstrated how the constraints on the bubble surface are released with a rise in the liquid fraction.

Surface and Drainage

The forces maintaining foam structures are mostly related to their surface. Many phenomena occur at the gas-liquid interface, and some are still the subject of intense research. From those phenomena, the surface tension and the Marangoni and the Gibbs effects are of high importance for foam formation and stability. They influence how the foam ages with time, how it is drained, how gas is exchanged between bubbles, and when the membrane will yield.

The surface tension is one of the most important forces in the foam. The surface tension is created by the molecules at the interface, which have fewer interactions than those in bulk. The energy that would be involved in those interactions is, therefore, transferred to their surroundings. This makes the molecules at the interface pull stronger on each other. In foam, the surface tension manifests itself in the form of capillary pressure. As the liquid pulls on the surface, a differential pressure is created. This gradient pulls the water from the membrane toward the Plateau border [7].

Surfactants are molecules that affect surface tension. Since they are more stable at the interfaces, they will preferentially remain there [20]. The surfactant molecules are mobile and can be involved in the creation of gradients [20]. The Gibbs and the Marangoni effects, which are important for foam formation and its stabilization, originate from those gradients [7,20].

The Marangoni effect results from the creation of a surface tension gradient at the surface of a liquid. The force, created by the gradient, can then pull the fluid. Wine "tears" and the soap propelled toy boat are two examples of the Marangoni effect. In the case of foam, the same gradient retains the fluid inside the channels against gravity [21,22]. In this situation, the surfactant creating this interesting phenomenon comes from the liquid phase. The surface tension gradient is produced by fluid displacement inside the channels. The Marangoni effect is also responsible for a counter-flow, happening between the Plateau border and the membrane.

The Gibbs effect is an important phenomenon while applying mechanical stress on a membrane. As the Marangoni effect, it is also created by a gradient in surface tension. When a film is stretched, the molecules at the surface are displaced, creating a gradient. The force of the gradient is opposed to the stretching. The Gibbs elasticity (ϵ) is a parameter, which represents the force formed in opposition to the stretching of the channels. It is experimentally determined and formulated by Equation 1, where γ is the surface tension, and A is the area of the surface. In contrast to the Marangoni effect, there is no exchange of surfactants between the surface and the liquid phase.

$$\epsilon = \frac{d\gamma}{d(Ln(A))} \qquad (1)$$

In foam, the Gibbs and Marangoni effects depend on the presence of a surfactant to exist; consequently, pure water alone cannot sustain foam [7,23]. Therefore, in foam, the behavior of the surface of the membranes and that of the Plateau border is highly linked to the surfactant distribution. This is the subject of many studies, the most recent being a computational fluid dynamics (CFD) simulation proposed by Anazadehsayed and Naser [24] and some models proposed by Vitasarie et al. [21,22].

As the foam ages, the liquid is drained from the foam toward the bulk liquid. The major driving forces are gravity and, again, the capillary pressure existing in the Plateau border, but factors influencing the gas exchange inside the membrane also influence aging. Gravity pulls the liquid at the surface, while the capillary pressure pulls it into the Plateau borders. The gas in the bubble is then redistributed against the capillary pressure gradient. This exchange is affected by the surfactant, which does not only affect the surface tension involved in the capillary pressure but also affect the permeability of the membrane. This would, with membrane thickness and composition, influence the speed of the gas exchange between the bubbles and the conditions for equilibrium [25].

The draining of the Plateau border forces more water out of the membrane and slowly reduces the distance between the air-liquid interfaces composing the membranes. When the membrane becomes thinner (~100 nm [7]), the forces exerted by the membrane towards each other become important.

If they enter in equilibrium with the capillary pressure, they will prevent further draining and create a metastable system. If the surfaces come closer, as the liquid is depleted, the pressure exerted by the interfaces will ultimately join them together. This will rupture the membrane and cause the coalescence of the bubbles and, therefore, coarsening of the foam. The first chapter of Garrett's book *The Science of Defoaming* [7] covers those phenomena in great detail.

A few models have been created to calculate the draining of the foam toward the bulk. One way of doing so has been proposed by Verbist et al. [26]. By using the Plateau border geometry, it is possible to model the draining of the foam. This equation would effectively work on the dry foam when the Plateau borders are well-defined. With this method, the cross-section (*A*) of an idealized vertical channel is used. Equation 2 can be used to obtain the velocity (v_y) of the liquid in a channel of the cross-section A that varies in function of its height (y) in a static foam [26,27]. In this equation, k_1 (Equation 3) regroups gravity (v_g) and viscosity (μ), while k_2 (Equation 4) regroups surface tension (γ) and viscosity.

$$v_y = -k_1 A - \frac{k_2}{\sqrt{A}}\frac{\delta A}{\delta y} + v_g \qquad (2)$$

$$k_1 = \frac{\rho g}{3 C_{PB} \mu} \qquad (3)$$

$$k_2 = \frac{\left(\sqrt{\sqrt{3}-\frac{\pi}{2}}\right)\gamma}{6 C_{PB} \mu} \qquad (4)$$

Starting with the equation of continuity for incompressible flow and using the Plateau border geometry, it is also possible to estimate the liquid fraction (ϕ_{liq}) in the foam using Equation 5 [28,29]. With this equation, ξ is a dimensionless number, which represents the relative position in foam height (x_0).

$$\frac{\partial \phi_{liq}}{\partial t} = \frac{\partial}{\partial \xi}\left(\phi_{liq}^2 - \frac{\sqrt{\phi_{liq}}}{2}\frac{\partial \phi_{liq}}{\partial \xi}\right) \qquad (5)$$

$$\xi = \frac{x}{x_0} \qquad (6)$$

The model above is based on a unidimensional analysis. It's a simple model that doesn't include the surface theories, like those described previously. It helps a lot to develop an understanding of how the liquid flows in the foam network. Better models have been developed since, but are much more complex and are necessitating an adequate introduction. Those models are described with few others in the review of Wang and Narsimhan [30]. Their review also includes foam drainage in the presence of solid particles, the kinetics of foam columns, and few models of growth and collapse.

Apparent Viscosity

High shear conditions break the channels, which makes the foam more viscous and less plastic. When this is abstracted to apparent global viscosity, it can be said that the foam reacts as shear-thinning fluid. Foam ages and its liquid fraction change through time, and this has the consequence of changing its rheology. This implies that foam is considered as a thixotropic fluid.

A good model for the shear-thinning viscosity of the foam is the Herschel–Bulkley law [31] (Equation 7). In this equation, τ is the shear stress, $\dot{\gamma}$ is the strain, and τ_0 represents the yield stress. The two parameters are *k*, the viscosity coefficient, and *n* is the power-law index.

$$\tau(\dot{\gamma}) = \tau_0 + k(\dot{\gamma}^n) \qquad (7)$$

Other authors have proposed other laws, often based on this equation. In his work on particles stabilized foam, Ozarmut and Steeb proposed that the Herschel–Bulkley–Papanastasiou equation is better at low shear values [32]. The Herschel–Bulkley equation may be extended to a thixotropic equation by adding a structural decay parameter (λ) [31].

$$\tau(\lambda, \dot{\gamma}) = \lambda(\tau_0 + k\dot{\gamma}^n) \qquad (8)$$

The yield stress (τ_0) is also difficult to determinate. This is not a problem only for foam as numerous tests have been created, and the yield value obtained for each test varied [31,33]. A literature review about the different methods used to evaluate the yield stress, using non-thixotropic flow, was written by Coussot [34].

The structure of foam does not uniformly wrap around surfaces. The term "wettability" is used to represent how much contact the surface has with the foam liquid phase. A surface with a low number of contacts, therefore, low "wettability", will slip and transfer less energy to the foam. This effect, called wall slip, is to be accounted for a good characterization of foam behavior [35]. Most of the studies on foam's apparent viscosity have used a serrated or rough surface to avoid this wall effect.

Foaming in Bioreactors

Consequences

Foam formation in bioreactors is a common phenomenon and is very often regarded as a nuisance [2,3]. Its formation can cause many problems, some of them serious, while other ones are often disregarded. The first obvious problem caused by foam generation is its volume, which can occupy a large fraction of the bioreactor working volume. An example of this is the volume problem during beer fermentations, which was studied by Kordialik-Borgacka and Ambroziak [36], where the foam occupied nearly 25% to 33% of the vessel. Foam volume can be a significant problem, but it would be ill-advised to consider this as the sole consequence of foaming. Foaming also has an impact on the behavior of the bioreactor, and it can impact not only the broth but also the microorganism involved.

The presence of foam can significantly affect bioreactor operations, leading either to a decrease in overall efficiency or to inhibition of a particular operation. The bioreactor design, choice of the impeller(s), and positioning of the baffles all aim at maximizing mixing and aeration and at minimizing the creation of dead zones. Such work is usually performed using the physical properties of water, such as viscosity and rheology. As seen in the previous section, foam behaves differently from water. This translates, in the end, into a drop-in bioreactor efficiency caused by lower mixing quality and higher energy consumption [3]. Foam presence can also hinder the probes by disturbing measurement, leading to false readings and analysis of the data. If the foam reaches the air filters, serious clogging may occur, leading to pressure build-up and contamination of the culture [3]. Also, the presence of foam in a bioreactor creates a barrier to the air in the headspace, while the oxygen present inside the bubbles becomes rapidly consumed [3], thus, potentially leading to suboptimal aeration conditions which, in turn, might affect cellular metabolism more or less seriously depending on the microorganism or cellular system being used.

Foam has also an impact on the composition of the culture broth. The amphiphilic molecules found in the medium will have a better chance to find an energetic equilibrium at the interface between water and air [20]. By its nature, the foam provides a large number of interfaces, offering a preferential environment for amphiphilic molecules. Key molecules involved in the desired bioconversion can be trapped into the foam, making it inaccessible to the microorganism or absent in the final fraction recovered [36]. This phenomenon may deliberately be used to withdraw the target product from the overall broth [21]. The process, called fractionation, is used in many fields. This approach may either be used during the fermentation or post-fermentation [37]. Using the former strategy has the added benefit of withdrawing the foam from the bioreactor while possibly enhancing surfactant production whenever desired [37]. The foam may still have to be treated to minimize the volume of the receiving tank [18]. This type of fractionation seems to be of high interest in the microalgal field. It was seen as useful for withdrawing contaminants [38], for creating a favorable environment [39], and for recovering the microorganism following cultivation [40].

Foaming also influences the growth of microorganisms. Microorganisms may be trapped around a rising bubble. Entrapped microorganisms are dragged to the surface of the fluid, and this phenomenon can be used to isolate them in a fractionation. At this point, the bubble can burst or be added to the foam structure with the microorganisms attached. A lot of strain force is involved in a bursting bubble at a free surface. Chisti provided a good depiction of this phenomenon in his review of animal cell damages in sparged bioreactors [41]. While unicellular organisms are usually less affected, this event is destructive for animal cells [41,42]. When the bubble is added to the existing foam, there is no immediate damage to the microorganism, but the strain produced by the collapse of the bubbles and the draining of the lamellae can damage the microorganism [43,44]. Overall, for the cultivation of animal cells, the damage caused by the air/liquid interface can compromise the fermentation. Often serum and a shear protectant, like Pluronic F-68, are added to the cellular suspension to reduce the damages caused by force at the air/liquid interface [41]. They hinder the attachment of the cell on the rising bubble and strengthen the cell membrane [42,45,46]. Interestingly, the hydrophobic nature of shear protectants may also protect the cells by increasing the stability of the foam and lowering its draining [44].

Controlling Foam production

Many events may occur during any fermentation process, and foam can be produced via several mechanisms (Figure 3). The presence of microorganisms itself may contribute to foaming but, nevertheless, foaming remains difficult to predict. It was said earlier that pure water could not maintain a foam. In any fermentation process, the foaming agent(s) may come from the broth [2] and the microorganism. As the energy for foam formation may come from various sources, it is possible to control some of those sources to mitigate its production.

Presence in the broth or production by the microorganism of certain types of molecules will raise the foaminess of the system [36]. Molecules of an amphiphilic or hydrophobic nature will tend to be at the interfaces between the liquid and the gas and, thus, they will stabilize the bubble interfaces. The cellular membrane, which is formed of amphiphilic molecules, is a source of foaming agents. Hence, the high death rate of the microbial population should naturally promote foam formation. Also, to a lesser extent, the production of polymeric molecules, such as proteins, polysaccharides, or fat, can contribute even further to foam stability.

Knowledge of the microorganism phenotype can help to predict its propensity to generate foam. Any microorganism, which is known to produce foaming agents, such as surfactants, under appropriate conditions, is susceptible to promote foam formation, at least, at some time during the fermentation process. If the route for the production of the foaming agent is known, then, finding a way to mitigate its production could help to solve the foaming problem. An example of this approach was described by Koridalik-Bogacka and Ambroziak, involving a hydrophobic polypeptide during beer fermentation [36]. They noted that less production of the hydrophobic polypeptide, thus less foaming, occurred when recycling yeast biomass from a prior fermentation.

It is also possible to evaluate the propensity of a broth to produce foam. In 1938, Bikerman proposed a unit called "foaminess" to characterize this property [47,48]. In his book, he described how to evaluate this property [47]. Even if the unit does not seem to be commonly used anymore, the techniques proposed by Bikerman are still being cited [2,9,49]. In practice, whenever possible, a simple solution for foaming mitigation could be to select a culture medium less prone to foaming. In addition, it is important to keep in mind that foaming agents can be produced at any step of a given fermentation process. An example of this could be the sterilization step, during which Maillard reactions occur to produce foam-enhancing molecules [3,50]. Therefore, a well-designed sterilization process (for instance, slow depressurization) can reduce the foaming propensity of the medium in comparison to other sterilization processes.

With the presence of foaming agents, the foam needs some energy to build its structure. Many operations inside the bioreactor can be a source of energy for foam formation. The obvious one comes from the oxygenation process, where bubbles are sparged inside the liquid phase of the bioreactor. A high gas flow rate combined with a sparger with larger holes will tend to produce even more foam [3,51]. As a potential solution, one could think of using an alternative carrier for delivering oxygen. One way for supplying oxygen to the culture could be, for instance, using a membrane for the oxygen exchange. An even simpler solution could be to use anaerobic conditions or bubble-less reactors, whenever possible, for producing the same metabolite of interest. Another source of energy favoring foam formation is the intensive agitation conditions often associated with fermentation processes [52]. A bioreactor shares similarity with two chemical reactor models often used: the mixer and the bubble column. One approach to minimize this problem could involve optimization of the mixing conditions, leading to lower energy input. Finally, high temperature is known to reduce foam generation, and this could offer a solution in several fermentation cases [53].

Foam fractionation [54], anaerobic fermentation [55], and bubble-less reactors [56,57] solutions, to avoid foaming problems, have been applied to fermentation using *Bacillus subtilis*. *B. subtilis* is an organism producing surfactin, a foam promoting agent. Willenbacher et al. reported a summary of the results of those trials in his article about the anaerobic fermentation of *B. subtilis* [55].

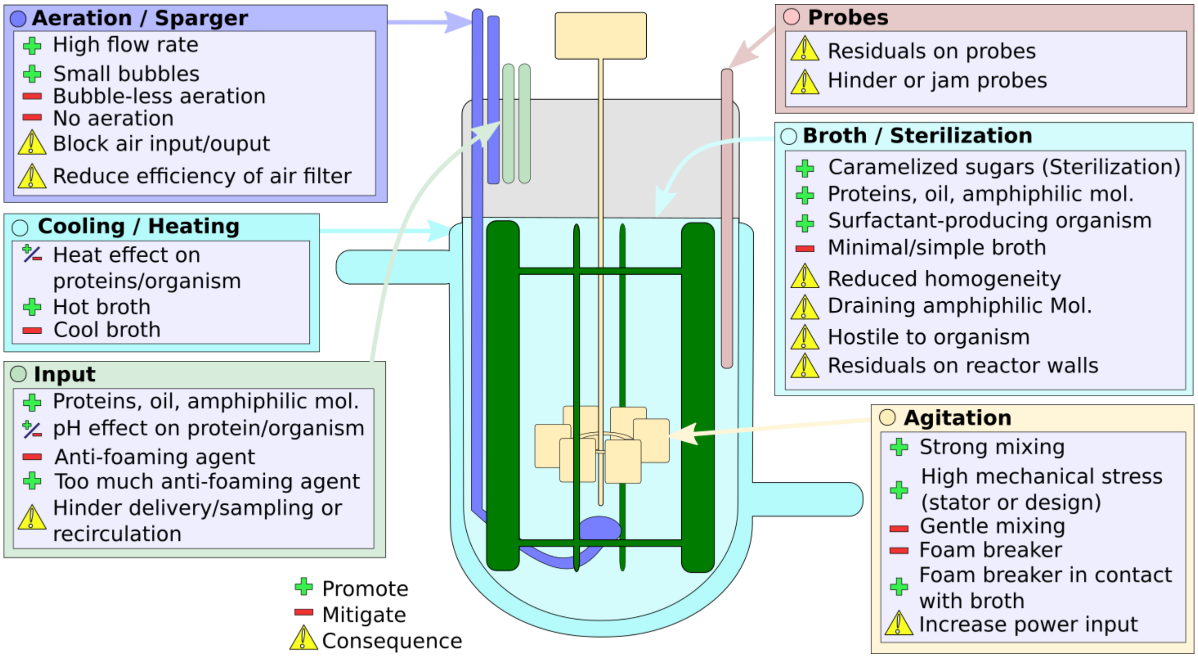

Figure 3: Foaming Control / Troubleshooting.

It is important to keep in mind that foam production is a desirable attribute in several fermentation processes. In those processes, foam can be used to augment the number of gas-liquid interfaces, improving the production of microorganisms or helping to control the content of the broth. This is particularly useful for the production of autotrophic organisms, like algae, which necessitate a large amount of light and CO2 [58]. In the foam-bed photobioreactor, used for this kind of fermentation, the foam is continuously regenerated to deliver fresh CO2 bubbles and avoid the accumulation of O2 [58]. This implies that the older foam has to be broken. It is usually done using mechanical foam breakers since the content in surfactants is usually high, which is desirable for foam-bed photobioreactors [58]. Numerous studies keep being published on various approaches aiming at increasing the quality of the foam and the reactor efficiency for this purpose. Among the various approaches used so far, one may mention the following ones: the production mechanism, the biosurfactant(s) itself/themselves, bioreactor design, or the producing microorganism itself. Several examples of such studies may be found in recent publications by Janoska et al., dealing with microalgae production, where the authors' goal was to improve the efficiency of a foam-bed photobioreactor [39,58] together with a selection of the best surfactant [59]. In addition, Vasquez et al. evaluated the potential of several different algae [60] for growth in such bioreactors.

Controls Using Anti-Foaming Agents

Mechanism

It is not always possible to avoid the formation of foam during a fermentation process. Important or excessive foaming can arise rapidly, at any given time during the fermentation, catching the operator by surprise irrespective of the production scale. That is why bioreactors are often equipped with one or more foam sensors coupled to an antifoam distribution system. Anti-foaming agents are chemicals that are added, either as needed or in a more or less planned way, to the broth to interact with the foaming agents in the gas-liquid interfaces. Such antifoams are usually organic or inorganic oils, particles, or a mixture of both. They can be used to prevent or mitigate excessive foam formation during the fermentation or to disturb or destroy the already formed foaming structures [61]. They all have characteristics making them interact with the gas-liquid interfaces. They show a few modes of action by which they can prevent the formation of foam or provoke its collapse.

Antifoam particles are known to slip inside the membrane and to force the two surfaces to fuse. This dewets the membrane and ultimately ruptures it [62]. To successfully bend the surfaces, the particles must be hydrophobic. Spherical particles with a contact angle over 90° will burst the membrane. For other shapes, the orientation of the particles will influence their actions. Their surfaces have to be at the right contact angle for dewetting the membrane. If placed along the surface, polyhedral shapes can stabilize the membrane instead of breaking it. The mechanism by which the particles act has been well-studied. Both simulation and visual observations appear to confirm this mechanism.

A liquid antifoam, usually composed of oil, has many foam-breaking modes of action, and these are still the subjects of intense discussion. Often, in the literature, they are split into two categories, either as slow/fast [35,63] or as antifoam/defoamer [2,61]. This observation is linked to the existence of many mechanisms by which anti-foaming agents operate. One of those mechanisms, which seems broadly acknowledged, occurs inside the liquid phase in a fully built foam. In such a case, as the oil forms, it disturbs the surface, stops the flow, and thereby makes the membrane collapse. The other potential scenarios, where the oil is interacting with the surface, still seem unclear. In one of the scenarios, theorized by Denkov [35], the oil would partially occupy the surface and force the dewetting of the membrane by increasing the disjoining forces. Both organic or inorganic compounds control foaming via the same mechanisms. Many of the organic compounds used to produce antifoams are already established food additives; however, they might be consumed by the targeted microorganism.

There are numerous articles and reviews about antifoam agents. One article from Garrett [64] addressed in detail the mechanisms presented above. Denkov offered a review of methods to characterize antifoam properties [35]. The review by Junker [2] contained an extensive list of chemical antifoams together with their composition. Finally, the review from Karakashev and Grozdanova [65] covered the development of antifoams and methods to evaluate their efficiency.

Influence of Anti-Foaming Agents on the Fermentation

Although chemical antifoams usually provide the most effective mechanism to control foaming in bioreactors, their presence in the broth has consequences. While mechanical methods do not add any additional elements to the broth, chemical antifoams are adjuvants. Consequently, because of their composition or their general nature, they can generate diverse problems that can be critical for numerous fermentation processes.

Because the composition of antifoams is not always well known, it is usually wise to perform screening to identify the optimal antifoam for a particular fermentation. Antifoams can directly interact with some molecules present in the medium or with the microorganism itself. Such interactions are usually negative. Zhang et al. described a mechanism where the antifoam reduces the resilience of the cells and limits its exchange with the broth [53,66]. Sometimes, the interaction with the antifoam can be positive, as observed by Routledge et al. for *Pichia pastoris* [63]. Tests proposed by Denkov [35] might be used for investigating a proper antifoam, like the one performed by Etoc et al. [67] for fermentations using *Yarrowia lipolytica*.

Even if the antifoams composition is uncertain, most are usually designed to interact with surfactants. This usually means that they will, themselves, be composed of surfactants. As a consequence, their use should be limited since their optimal efficiency holds only if they are used in the right concentration range [3,53]. A high concentration can even promote foaming, and their presence at the gas-liquid interface may lead to numerous consequences. By altering the surface tension, anti-foaming influences the bubble distribution, making the bubble larger [2,61,68] while reducing their velocity. Those two phenomena reduce the exchange between the gas and the liquid, lowering the oxygen transfer rate, often identified as k_lA. In some publications, it was observed that the addition of anti-foam coupled with sparging damage animal cells [66,69]. The presence of a chemical antifoam at the interface of rising bubbles makes them more prone to drag the microorganism to the surface [66], where they can be damaged by bubble bursting or trapped in the foam. The addition of shear protectant, like Pluronic F-68, seems to mitigate this mechanism [66].

Finally, chemical antifoams will often create difficulties in downstream processing [2,70] or contaminate the final product. For example, they can clog filtration membranes or at least reduce their filtration rate [70], or be co-extracted with the product of interest. Finally, if the antifoam is used in a regulated industry, it is important to make sure the chemical has been approved by a pertinent regulatory body.

Foam Control Using Mechanical Means

Foam Breakers

Foam breakers are devices that use a wide array of physical means to accelerate the collapse of the foam. Their use does not add new molecules to the broth, contrary to using a chemical antifoam, but they add stress and often require additional power when activated. A large number of mechanical foam breakers exist, and new ones are patented each year. The shape, the composition, and the motion influence the way a foam breaker will interact with the foam. Usually, those characteristics are found by empirical means [7] with little consideration for the physical phenomena involved. Foam breakers can be designed to be used in-line, in a drain, or outside of the reactor. Such designs are often seen in processes that exploit fractionation or in foam-bed bioreactors. The design of a foam breaker may take advantage of different physical phenomena. The main ones are the centrifugal force, shearing, pressure gradient, and ultrasonic waves. Other mechanisms are exploited, but examples are scarce, at least in biotechnology, to name few: electric field, thermal treatment, and capillary effects.

Mechanism of Foam Collapsing by Shearing

The channel in the foam structures is an obvious target for the use of physical force. This and the simplicity of the devices make shear-based foam breakers a popular approach. Nonetheless, the foam-breaking mechanisms behind those simple devices are surprisingly complex. The shearing force can come from the direct mechanical input of the foam breaker, the turbulence in bulk, or from distorting pressure gradients. Ng and Gutierrez [71] decomposed the mechanical collapse of foam into two steps: the bubble is stretched by pressure gradients and become unstable, then, the blade cuts into the disturbed membranes, breaking them. The bubble membrane can also collapse during the first step without being cut by the blade. Takesono et al. [72] stated that the shearing mostly comes from the low-pressure zone in the fluid created by the foam breaker movements.

Breaking down the bubbles, i.e., creating more, smaller bubbles, instead of fusing them, i.e., creating less, but larger bubbles, to control foaming is counterintuitive. The foam treated by such an approach will, indeed, have a finer structure, with a smaller bubble diameter, thicker channels, and a lower gas fraction. In a bioreactor, a denser foam may be advantageous. Indeed, lowering foam volume could be sufficient to avoid difficulties arising from a small spontaneous formation. Also a dense foam, like the one produced by a foam breaker, ages more quickly. Foams with high liquid fractions have larger channels and offer less resistance against draining. This makes the surface drain quicker to the bulk downstream [73] and facilitates the delivery of chemical-based antifoam. On the other hand, a thicker foam will be more of a problem for shear-based foam breakers. In the literature, a foam that was treated using a foam breaker is sometimes distinguished as "secondary foam" because of its different rheological behavior. The high liquid fraction of a "secondary foam" makes the membrane more unresponsive to yielding since a secondary foam has partially lost its plastic behavior. A good foam breaker design should be able to push out the secondary foam for better performance [74]. An alternative could be to operate the foam breaker in a cyclic mode, as proposed by Vetoshkin [75,76].

Draining by Centrifugal Force

The major contributor to the natural collapse of foam is gravity. As mentioned previously, this force creates a hydrostatic pressure that pushes the water down in the lamella. The centrifugal force can have an equivalent impact on foam. Although foam breakers using the centrifugal force are often set apart from other devices, many rotating devices that are fixed on the impeller will produce some centrifugal effect.

Using the Plateau border geometry, Equation 9 can be used to determine a critical pressure on which the liquid phase is drained [7,77]. The equation of pressure across a Plateau border (Equation 9) can be integrated to give the total pressure drop across the network (Equation 10).

$$\frac{dP}{dr} = \rho_l \omega^2 r \qquad (9)$$

$$\Delta P_r = 0.5\rho_l \omega^2 H_0 (2r_0 - H_0^e) \qquad (10)$$

At equilibrium, the sum of the pressure exerted in the network of the foam, the capillary force, and the atmospheric pressure will cancel out. Using those equations, Vetoshkin verified whether or not the pressure in a section of a commercial foam breaker was sufficient to separate the liquid from the air [77].

For a large part, foam breakers are rotating devices and, therefore, will also produce centrifugal force. Even devices that focus on different means to break foam could take advantage of this. The centrifugal force can be useful to push out foam with high liquid fractions, which would contribute to a more efficient design [78]. Also, in numerous applications, this force is used to drive foam in the geometry.

Draining Using Vibration

The idea is to use mechanical vibrations or sound to accelerate foam drainage and, ultimately, rupture bubbles film [79]. This technique has the added advantage of being less intrusive than the other mechanical options [79] since no additional hardware comes in contact with the liquid. Vibration can be generated using a whistle, a horn, or by making a surface vibrate. The ions are transported by the gas over the fluid (ultrasounds) or by the container itself. The material in which the vibrations are transported is important and can influence both the cost and efficiency of the foam breaker. Mechanical vibrations on the surface of the container can be efficient, but the modification needed can be costly. Using a horn or a whistle is less expensive, but their influence on foam is limited to a thin layer in front of the device.

Morey et al. [80] concluded that mechanical vibrations were ineffective on static foam formed from a Newtonian liquid. Sadly, the sound wave mechanism for breaking the foam seems to be subjected to debate. An interpretation for this could be that surface waves push the fluid into the film, therefore accelerating foam drainage [79,81]. The acoustic pressure deforms the lamella by creating thin and thick zones. Then, the Gibbs effect pushes the fluid back to the thin section of the lamella. If the amplitude of the phenomenon is large enough, the film will break [81]. The effective frequency of a foam-breaking horn will vary depending on the foam. The reported frequency ranges between 0.02 kHz and 20 kHz [79,81–83].

Rotating Devices

Rotating devices are widespread, and they can be directly fixed to the shaft in a bioreactor [84], making their implementation easy. In their articles, Takesono et al. [72] compared different kinds of mechanical foam breakers together: a six-blade turbine, a six-blade vaned disk, a two-blade paddle, a conical rotor, a device called fluid-impact dispersion apparatus, and a rotating disk foam breaker. The authors concluded that the fluid-impact dispersion apparatus and the conical rotor quickly failed to control foaming at a low foaming set-up. The six-blade turbine and the rotating disk performed better and successfully controlled foaming in all of the scenarios tested. A follow-up article [85] focused on the blade turbine, where it was observed that pumping flow, which is influenced by the rotation velocity and size, seemed the most important factor for foam breaker efficiency [85]. The foam breaker was also tested using a *Saccharomyces cerevisiae* fermentation, and the results confirmed that the mechanical foam breaker proved superior to the chemical antifoam tested in parallel [85].

Deshpande and Barigou studied the effect of the paddles variations [84,86]. The idea behind this was to increase shearing using a narrow passage, sharp corners, and even needles. They concluded that the geometry proposed (shown in Figure 4) needed less velocity and less power to control the foam than the more widespread disk-based foam breakers. Interestingly, they also observed a rise in the performance of the foam breaker when the clearance between the liquid surfaces was larger [86]. It was probably due to the lower liquid fraction at the top of the foam. Also, it is worth noting that their article also featured a table that contains references on various foam breakers.

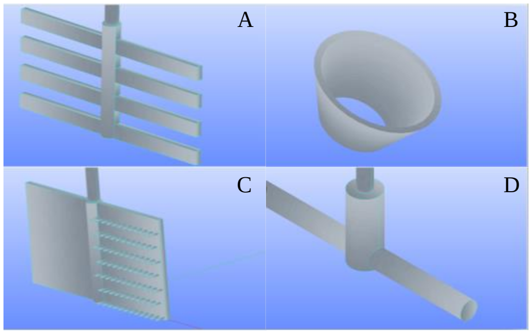

Figure 4: (**A**) Paddle and (**C**) needle foam breakers from Deshpande et al. [84,86]. (**B**) Cone foam breaker from Cooke et al. [87]. (**D**) A simple bar foam breaker.

Inspired by the degasser technologies used in other industries, Cooke et al. [87] proposed to use an inverted cone to control foaming. This approach was also employed in some older patents, like the foam breaker described by Marko in 1985 [88]. As the cone spins, the foam is pumped in and travels in a thin layer on the surface. At the top edge of the cone, the foam gets projected as a film, ligaments, or drops. The cone shape also induces sufficient centrifugal force on the foam to drain the water out the channel [7,87]. The efficiency of a cone foam breaker in a bioreactor was tested by Stocks et al. to control foaming in a *Bacillus* fermentation [89].

The perforated disk design is another interesting approach [90,91]. Liu et al. [91] compared the efficiency of unperforated disks and perforated disks in a fractionation fermentation. They proposed that perforations could create a pressure gradient that would stretch the bubbles beyond the Gibbs elasticity capacity, making the bubble collapse. This claim seems backed by their experimental results.

Adding a stator to a rotary foam breaker can improve the efficiency of the foam breaker, while moderately increasing implementation difficulties. Gutwald and Mersmann [78] presented two foam breakers using both a rotor and a stator. Using the flow created with the rotor, the bubbles are forced on a perforated plate. Then, they enter in a separated section where the rotor, either a six-blade foam breaker or a radial accelerator, is in operation. The foam is ultimately projected on the side of the setup, where a drain is placed. The impeller velocity is important, but it was also observed that both the size and the angle of the plate hold the plate together with the distance between the impeller and the wall as important factors to obtain a dense secondary foam. This suggests that the addition of a stator can have a high impact on the efficiency of the foam breakers.

Even if the majority of mechanical foam breakers used in bioreactors are rotating devices, other designs can also be used with success. Good examples would be devices using vibrations, airstream, pulverization, or the Coanda effect. The use of vibrations in the form of ultrasounds or mechanical ones has been addressed in the previous section. Airstreams may also be used to control foam formation. Vetoshkin studied the mechanism of foam breakers using airstream [75,92]. These authors observed that foam breaker capacity was hindered by the accumulation of secondary foam. To maximize the foam breaker efficacy, they proposed to optimize the location of the probe that operates the air stream and the time the stream is on after foam has been detected. Foam breakers using the Coanda effect push the foam through a high-velocity nozzle. The Coanda effect creates a depressurized zone, and the foam is broken by the high-pressure gradient. Although less commonly seen in the biotech world, those apparatuses seem to be used in the petroleum industry [93,94]. Wang et al. [94] proposed a two-stage version of the original concept.

More approaches exist, but they are only documented in a few patents and some sporadic references in the literature (Table 1). Some of them proposed to directly drain the lamella employing various mechanisms. A remarkable one is the use of the capillary effect in a foam breaking tower. Kang et al. in 2016 [95] reported on using a sponge wall to exploit this effect with success. Junker [2] and Wang et al. [94] reported on the potential of thermal treatment for the control of foaming. An electric field may also be used to break the foam. Pinkel, in 1944, patented a high-voltage foam breaker, which used a brush discharge to break the foam bubbles. Many of the approaches consume a lot of energy and look rather harsh to microorganisms. This might explain why biotechnology has not shown interest in them. In addition, the same approaches do not seem to have attracted significant interest elsewhere too.

Advances in Computer-Assisted Research

Problems involving foaming have been tackled since the 19th century, and most of the underlying mechanisms have been understood only recently. The development of better imaging tools and the use of computer-assisted research are two contributing factors to this evolution. They are essential to our understanding of foam structure and of various mechanisms, such as draining, the displacement of surfactant, and foam coarsening. The use of computer software to compute forces and predict foam structure in the dry foam is one example of computer-assisted research contributions to the field [11]. By using the Brakke's Surface Evolver software, Weaire and Phelan were able to compute an idealized mono-disperse foam configuration [6]. Surface Evolver computes the surface, offering minimal energy using the gradient descent method. In a more recent publication, Surface Evolver was used to observe

Table 1: Relevant literature on foam control.

Solution	References
Rotary device	[78,86,87,89,91]
Sonication/Vibrations	[79,80,82,83]
Other mechanical approaches/device	[72,93–95]
Chemical antifoams and defoamers	[2,7,61,62,70]
“Foaminess” of the broth	[2,9,49]
Control of aeration parameters	[52]
Surfactant production	[36]
Foam collection and fractionation	[40]
Advantageous uses of foam	[58,59]

the evolution of the channel network when the foam was pushed against a circular structure [96]. The PLAT software, developed by Bolton, is another software that was developed to model foam behavior. PLAT is designed to model wetter foams and focuses on the Plateau border. It was used by Dunne et al. to evaluate changes in a two-dimensional foam from low to high liquid fraction [19].

Presently, efficient mathematical models to be used in the modeling of foam for biotechnological applications are sparse. However, recent advances in CFD offer new hopes. From the draining of non-Newtonian fluid in the Plateau border [24] to froth behavior on a surface [97], a CFD approach may be used to understand foam behavior. The use of statistics can simplify many aspects of foaming; an example of this is the modeling of the expansion of polyurethane foam. Such a model was proposed by Karimi et al. to predict the development of polyurethane foam injection [98], including modeling of polymerization [99]. Using their model, the authors have solved a population balance equation to find the distribution of bubble sizes, the density, and the apparent viscosity of the foam under study. By omitting certain characteristics of foam, a CFD software was also used to help in the design of some foam breakers and to understand their mechanisms of action [94,100]. An interesting method, which has not been integrated yet in conventional numerical methods, is the Lattice Boltzmann Method (LBM), which gives a good representation of the interactions between the surfaces of the bubbles [101,102]. The LBM targets the microscopic and mesoscopic phenomena by using a simplified kinetic equation derived from the Boltzmann equation. This differs from the commonly used approach involving the Navier–Stoke equation. An example of an application of the LBM could be its application on the modeling of bubbles' behavior in metallic foam [103].

Conclusion

Foaming is a very interesting phenomenon and has been the subject of research for more than two centuries. Even if the phenomenon still holds some little mystery, foaming is, now, slowly yielding its secrets. This review covered only a small fraction of the large documentation about the physics, the chemistry, and even the mathematics of the foaming phenomenon. The goal of this review was to create a bridge between the various bodies of information available regarding foaming and the newcomer. Hopefully, the review would raise awareness, particularly in the biotechnical community, of the advances made over the years on the foaming phenomenon. As indicated previously, foaming is common in the fermentation world and brings lots of serious problems. Various approaches and methods to mitigate foaming and even take advantage of foam have been described in the second half of the review. Our new understanding of the chemical interactions taking place in foam helps to understand how chemical antifoams perform. Presently, the literature on mechanical foam breakers appears to be quite limited from the physical/mechanical side, and future research will probably fill the gaps using CFD. Such investigations should yield an improved understanding of the foaming phenomenon and new approaches for mitigating foaming when seen as undesirable.

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Conflicts of interest

The authors declare that they have no conflict of interest.

List of Symbols

Symbol	Meaning
A	Area (m^2)
ρ	Density (kg/m^3)
P	Pressure (Pa)
r	Radius Variable (m)
R	Radius Constant (m)
ϵ	Gibbs Elasticity (N/m^2)
γ	Surface Tension (N/m)
v	Velocity (m/s)
g	Gravity Constant (m^2/s)
μ	Dynamic Viscosity (Pa*s)
Φ_{liq}	Liquid Fraction (v/v %)
ξ	Relative Height (%)
k	Viscosity Coefficient
n	Power Law Index
λ	Structural Decay
τ	Shear Stress (N/m^2)
τ_0	Yield Stress (N/m^2)
$\dot{\gamma}$	Strain

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