Bicontinuous cubic phases in biological and artificial self-assembled systems

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ABSTRACT Nature has created innumerable life forms with miraculous hierarchical structures and morphologies that are optimized for different life events through evolution over billions of years. Bicontinuous cubic structures, which are often described by triply periodic minimal surfaces (TPMSs) and their constant mean curvature (CMC)/parallel surface companions, are of special interest to various research fields because of their complex form with unique physical functionalities. This has prompted the scientific community to fully understand the formation, structure, and properties of these materials. In this review, we summarize and discuss the formation mechanism and relationships of the relevant biological structures and the artificial self-assembly systems. These structures can be formed through biological processes with amazing regulation across a great length scales; nevertheless, artificial construction normally produces the structure corresponding to the molecular size and shape. Notably, the block copolymeric system is considered to be an applicable and attractive model system for the study of biological systems due to their versatile design and rich phase behavior. Some of the phenomena found in these two systems are compared and discussed, and this information may provide new ideas for a comprehensive understanding of the relationship between molecular shape and resulting interface curvature and the self-assembly process in living organisms. We argue that the copolymeric system may serve as a model to understand these biological systems and could encourage additional studies of artificial self-assembly and the creation of new functional materials.

Keywords: triply periodic minimal surface, self-assembly, cubic membrane, lyotropic liquid crystal, block copolymer

INTRODUCTION

Triply periodic minimal surfaces (TPMSs) are smooth and nonintersecting curved surfaces that have three-dimensional (3D) periodicity and vanishing mean curvature $H$ everywhere [1,2]. This balanced continuous surface separates the space into two intertwining labyrinths known as bicontinuous structures. A skeletal graph can be used for their structural visualization by modeling the centers of the labyrinths using simple rods connecting corresponding nodes. The most common and important TPMSs are the Schwarz primitive (P), Schwarz diamond (D) and Schoen gyroid (G) surface structures. The P surface is also known as “plumber’s nightmare”, which has two interpenetrating cubic networks with six-fold connectivity with space group $I\bar{m}-3m$ (No. 229). The D surface separates two diamond networks with four-fold connectivity with space group $Pn-3m$ (No. 224). The most popular G surface has three-fold connectivity with neither a straight line nor a mirror plane in the structure. Although various screw axes from different directions exist, the gyroid structure is achiral due to the double networks with opposite handedness, and its space group is $Ia-3d$ (No. 230). On the other hand, a family of constant mean curvature (CMC) surface with $H \neq 0$ and parallel surfaces shifted off the TPMS along the surface normal with fixed distance can be generated from their corresponding TPMS families.

The TPMSs and their corresponding CMC/parallel surface companions are attractive not only because of their complexity and geometrical beauty but also due to their unique physical properties. These surfaces have been used to model various crystalline structures both in nature and in artificial systems. Examples include the echinoderm skeletons [3,4], cell endomembrane systems [5,6], butterfly wing scales and exoskeletons of beetles and weevils [7–11], the retinal cone photoreceptor cells of tree shrews [12], lyotropic liquid crystals (LLCs) [13–18], and block copolymer self-assemblies [19–25]. These surfaces can also be used to model zeolites [26,27] and periodic...
zero potential surfaces in atomistic crystals [28]. Such structures and their analogues have been found to possess unique functions, such as structural colors [7–11], unique mechanical and electronic properties [29,30], membrane protein crystallization and drug delivery [31–33]. Additionally, it is noteworthy that their formation mechanism might have much in common with cell membrane-related processes [34,35].

Among the biological structures, the cubic cell membranes with TPMSs and related CMC surfaces are of great interest. These structures have been frequently discovered in numerous biomembranes under various conditions, such as the plasma membrane, endoplasmic reticulum, nuclear envelope, chloroplasts, inner mitochondrial membrane [12]. However, the formation mechanism and the corresponding biological functions of such delicate structures are still unknown, largely due to the difficulties in revealing their formation process in the complex biological environment and their structural characterizations due to the soft nature of these systems. In addition, in some of these structures, the unit cell parameters can be up to several hundred nanometers in order to show the corresponding optical functionalities [7,11,12,36]. These phenomena pose challenges to the research field in its attempts to fully understand the detailed structure, structural relationship, and the formation process of these cubic membranes.

On the other hand, the liquid crystal (LC) systems and the microphase separation of the block copolymers have been used as a versatile tool for fabricating periodic structures due to the high flexibility of molecular design (Fig. 1). However, the artificial fabrication only achieves basic structural categories that natural systems have evolved, and the typical unit cell parameter is normally limited to a range of several nanometers for LC systems and 5–100 nm for block copolymer systems [25,37]. Regarding the artificial fabrication of these structures, it has been generally accepted that the structures formed in amphiphilic systems can be understood by cross correlation between the interface curvatures and the geometrical characteristics of the chemicals employed. Recently, new developments in the microphase separation of copolymeric systems have brought new insight into the formation of hyperbolic surface structures [38–40]. The addition of solvent enables the solubilization of the block copolymer and the swelling of the whole system, which forms structures with different Gaussian curvatures. This self-assembly process presents a challenge to the correlation between molecular shape and the interfacial curvature, which may shed light on the formation mechanism of these structures with hyperbolic surfaces, in addition to our understanding in biology-derived relevant structures [41].

This review article introduces three aspects of understanding the formation and structures of biological and artificial self-assembly systems. First, we introduce several representative cubic membrane structures in vivo. We then review the self-assembly of block copolymers into cubic phases, from pure block copolymer melts to complex systems involving inorganics. Finally, we compare the biological and copolymeric systems with respect to their formation mechanism and structural relationship. By highlighting the similarities and differences in biological and artificial self-assembly systems, we demonstrate that amphiphilic self-assembly may be inspired by biological systems. More importantly, artificial self-assembly may provide a good model system for understanding the formation mechanism of these delicate structures in nature.

### BIOLOGICAL Bicontinuous Cubic Structures
In biological systems, highly organized and delicate
structures are amazingly optimized to serve biological function(s) (if there is), which may be far beyond the capabilities of artificial fabrication. In order to adapt to external environmental changes, organisms have evolved to form a series of complex structures with corresponding functions at microscopic, mesoscopic, and macroscopic scales. Biological membranes that are essential for living cells are considered to be one of the most attractive assemblies in nature. They define the interface between the outside and inside of cells and organelles, enabling different biochemical reactions to occur in different intracellular compartments. These membranes are often formed by steroid lipids with embedded membrane proteins, which, through noncovalent forces, form a series of complexes with corresponding functions at microscopic, mesoscopic, and macroscopic scales.

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a unit cell parameter ~50 nm in size, which was interpreted as intersection bilayer stacking. However, this structure was later revealed to be a tetragonal deformation of the P surface (tP) [70]. The bicontinuous P surface structure is believed to show some advantages in gas exchange due to its interconnected framework with an open channel system.

It is noteworthy that not only a large number of single-bilayer and double-bilayer cubic membrane structures have been found, but multilayer cubic membranes also exist. The inner segment of the retinal cone photoreceptors of the common tree shrew (Tupaia glis) and northern tree shrew (Tupaia belangeri) contain several layers of mega-sized mitochondria. The inner membrane of these mitochondria forms a gyroid cubic membrane structure with an 8 to 12 bilayer membrane. (Fig. 3a1–3) [54,75] This is the most complex cubic membrane structure ever discovered. These multilayer gyroid cubic membrane structures are capable of forming multiple focal points and blocking ultraviolet (UV) light independent of angle [12].

Furthermore, unbalanced CMC surface/parallel surface structures also exist in biological systems, specifically the biophotonic crystals discovered in certain insects. Some butterflies (e.g., Callophys rubi) generate a metallic green color in their wing scales by making a gyroid CMC scaffold (Fig. 3b1–3) [7–9,36]. It has been discovered that the scaffold is formed by the deposition of chitin inside a

Figure 2 (a) Isolated mitochondria from 7-day starved amoeba Chaos carolinense revealed by TEM. (b) SEM micrograph showing the intact outer surfaces of the isolated mitochondria. Reproduced with permission from Ref. [71]. Copyright 2014, Springer-Verlag Wien. (c) SARS-CoV-induced cubic membranes in Vero cell. Reproduced under the terms of the CC BY 4.0 License [74]. Copyright 2004, The Authors. (d) 3D model of gyroid surfaces.

Figure 3 (a1) TEM images of mitochondria with multilayer cubic membranes in a tree shrew cone photoreceptor cell. (a2) 3D model of 12-layered G surfaces and (a3) the corresponding 2D projection map. The TEM image exactly matches the 2D simulated projection. Reproduced with permission from Ref. [75], Copyright 1987, Springer-Verlagl and Ref. [54], Copyright 2009, Elsevier. (b1) Photograph of T. opisena. (b2) Optical micrograph of the green ventral wing area. (b3) SEM image of SG crystallites. Reproduced under the terms of the CC BY 4.0 License [76]. Copyright 2017, The Authors. (c1) Photograph of the weevil L. augustus. (c2) Optical micrograph of individual scales attached to the exoskeleton of L. augustus. (c3) Cross-sectioned SEM image of a region of a scale of L. augustus. Reproduced with permission from Ref. [11]. Copyright 2008, American Physical Society.
convoluted membrane described by gyroid TPMS in the subcellular organelle of the endoplasmic reticulum (ER) [76]. As only one labyrinth of the gyroid TPMS was filled with chitin, the scaffold structure is single gyroid (SG). Similarly, a single diamond (SD) scaffold with a diamond CMC surface was identified in the exoskeletons of various beetles and weevils (Fig. 3c1–3) [10,11]. Of note, both SG and SD structures are extraordinary 3D photonic crystal structures with complete bandgap properties. However, these photonic properties are absent in their corresponding double framework structures due to the increased symmetry [77].

ARTIFICIAL SELF-ASSEMBLY OF AMPHIPHILIC MOLECULES

On the other hand, TPMSs and their companions have been widely discovered in self-assembly systems containing amphiphilic molecules. For amphiphilic molecules with incompatible hydrophobic and hydrophilic components linked by covalent bonds, various types of LLC phases with periodic arrangements can be obtained depending on the geometric parameter \( g = v/a_0l \) [78], where \( v \) is the chain volume, \( a_0 \) is the effective hydrophobic/hydrophilic interfacial area, and \( l \) is dynamical chain length. According to this scheme, spherical, cylindrical, TPMS, lamellae, and their corresponding inverse phases can be formed. Particularly, TPMSs can be formed when \( g = 2/3 \) or \( g > 1 \) for inverse phases. Work pioneered by Luzzati et al. [79] investigated bicontinuous LLC phases in the soap/water system, and the following studies dealing with lipidic LLC phases and other systems have extensively stimulated this research field [1,80]. Self-assembled structures can be regulated by changing the lipid type and adding different amphiphilic mixtures. Angelova et al. [81–86] studied the self-assembly of monoolein to form bicontinuous cubic phases in a mixture of different lipids or amphiphilic polymers. The effects of the additives on the packing of nonlamellar lipid monoolein have been recognized, and result in a change in its phase transition temperature. The change in the solubility of the additive with temperature has been shown to be due to the adjustable pore diameter \( v \) the expansion or contraction of water channels [86–88]. It has also been proposed that the formation of cubic nanostructures is related to the accumulation and fusion of curved bilayers into an ordered membrane structure [89,90].

Compared to the LLC phases formed by lipid or surfactant molecules, the block copolymeric systems show great diversity due to the versatile design of blocks with various chemicals and physical properties. During the self-assembly of block copolymers, various mesostructures with complex morphologies can be formed by microphase separation [19,20,25,91–96]. This process is jointly driven by mixed enthalpy and mixed entropy [19,97,98]. The thermodynamic equilibrium of the linear AB diblock copolymer self-assembled morphology depends on the volume fraction of each block (\( f_A \) or \( f_B \), \( f_A + f_B = 1 \)), the Flory-Huggins parameter (\( \chi \)), and the total degree of polymerization (\( N \)) [19]. \( \chi \) is usually a small positive value and varies inversely with temperature when there is no strong interaction (e.g., hydrogen bonding) [91]. The segregation product of the \( \chi N \) value determines the degree of microphase separation of the two blocks at a given temperature. As the temperature increases, \( \chi N \) decreases to the weak segregation limit (\( \chi N \ll 10 \)) and the copolymer becomes disordered (i.e., homogeneous). When the \( \chi N \) is large enough, the copolymer is in a strong segregation limit (\( \chi N \gg 10 \)) to enable microphase separation [97,99–101]. The morphological changes in copolymer self-assembly are a function of \( \chi N \) and \( f_A \), and can be predicted using the self-consistent mean-field theory [24,102,103]. The double gyroid is found to be stable in a narrow window between the cylindrical hexagonally phase and the lamellar phase. The experimental phase diagram [104] of the polyisoprene-\( b \)-polystyrene (PI-PS) diblock copolymer bulk is similar to the theoretical calculation (Fig. 4) [24]. The experimental phase diagram is not completely symmetrical because the molecular shape of isoprene and styrene are different, and the interactions are also different.

The ABC triblock terpolymers extend the parameter space \( (\chi_{AB}, \chi_{AC}, \chi_{BC}, N, f_A, f_B, f_C) \), resulting in the morphological complexity of self-assembly [19,105–109]. It is noteworthy that the bicontinuous cubic phases can be more precisely manipulated, and several unique phases have been obtained. Notably, a core-shell gyroid structure was discovered in the microphase separation of polyisoprene-\( b \)-polystyrene-\( b \)-polydimethylsiloxane (PI-PS-PDMS) triblock terpolymer [110]. The two independent polydimethylsiloxane (PDMS) networks are encased in the polystyrene (PS) shell and separated by the continuous polysoprene (PI) segment. These boundaries divided the space into five independent continuous domains, which is sometimes called “pentacontinuous” in polymer science. Considering the topology that only two identical gyroidal frameworks exist, it is reasonable to name this a “core-shell bicontinuous” structure. More interestingly, a new cubic phase has been discovered in the self-assembly of ABC triblock terpolymers such as...
polyisoprene-b-polystyrene-b-poly(2-vinylpyridine) (PI-PS-P2VP) and polyisoprene-b-polystyrene-b-polyethylene oxide (PI-PS-PEO) [37,111–114], which is recognized as an alternating gyroid (Q$^{214}$) [115–117]. In this phase, the B block forms the TPMS interface (matrix), while the A and C blocks separately form the two labyrinths with opposite handedness. As the A and C blocks are chemically distinguishable, the alternating gyroid is a useful technique for creating the thermodynamically unstable SG structure. This process can be performed either by infiltrating inorganic precursors into the polymer template, or by directly introducing the inorganic particles into the polymer self-assembly [20,118,119].

In the above publications, the unit cell size of the polymer-based cubic phase structure is strongly dependent on the molecular weight of the polymer, and the typical unit cell parameter of the block polymer self-assembled is 5–100 nm [37]. To the best of our knowledge, the largest structure in the equilibrium microphase separation of block copolymer has a unit cell parameter of 258 nm. The formation of such a large structure requires a two-week annealing treatment using a PS-PI block copolymer with a molecular weight of up to 750 kg mol$^{-1}$ [120].

The microphase separation can be also tuned by adding solvent. A selective solvent (usually water) for one of the blocks of copolymer would drive copolymer aggregation into micelles via hydrophobic interactions. The morphology of the micelles is determined by the solvent selectivity [121,122] and the composition of the copolymer [123,124]. As the volume fraction of the hydrophilic block decreases, spherical, cylindrical, and/or vesicular micelles are favored. A crew-cut micelle can be observed when the hydrophobic block has a very large volume fraction [123–126], especially cubosomes with an internal bicontinuous cubic structure [123–131]. Lin et al. [128] employed a simple polystyrene-b-poly(ethylene oxide) (PS-PEO) diblock copolymer to obtain cubosomes with P and D surface mesophases, after which the selective solvent water was added to the dioxane/dimethylformamide solvent mixture to induce self-assembly. By using block copolymers comprised of different block types and structures, cubosomes with different structures and functions can be obtained [129–137].

Swelling the block copolymer using solvent is an effective way of increasing the unit cell size and can introduce a new parameter for the controlled organization of block copolymers. Han et al. [38,39,138] reported a delicate method for the fabrication of bicontinuous scaffolds using an amphiphilic AB or ABC block copolymer, e.g., poly(ethylene oxide)-b-polystyrene (PEO-PS) or poly(ethylene oxide)-b-polystyrene-b-poly(tert-butyl acrylate) (PEO-PS-PtBA), and an inorganic precursor in a tetrahydrofuran (THF)/water mixed solvent. The block copolymer used in this method (Fig. 5) is highly soluble in the common solvent THF; however, microphase separation can be induced by the addition of a small amount of the selective solvent water. The hydrophobic block (PS or PtBA-PS) is dissolved in the THF-rich phase, whereas water is mainly present in the hydrophilic region (PEO), forming two water-rich cores with interwoven frameworks. With a large THF/water ratio, a structure containing two equivalent labyrinths with multilayer
core-shell bicontinuous double diamond (DD) framework is formed following the inverse phase (water-in-oil) configuration. Simultaneously, the silica precursor condenses in the hydrophilic regions to form the rigid silica scaffold. As the block copolymer exists only at the interface of THF-rich and water-rich phases, the entire structure can be swelled by solvents, and the size of the structure can thus be scaled up significantly. The unit cell parameter can be as large as ~340 nm (original cubic unit cell) using a polymer with a relatively small molecular weight of ~35.7 kg mol$^{-1}$. Therefore, the unit cell parameters of the silica scaffold can go beyond the normal synthesis and are comparable with biological photonic structures [38]. Due to the large amount of THF that occupies space and separates the two interlocking double networks, the double networks shift and adhere each other to form a low-symmetry shifted DD (SDD) structure with the evaporation of the solvent, and this shifted structure introduces the photonic bandgap feature due to decreased crystal symmetry [38,138–140].

To understand the structural relationship and structural control in the self-assembly process, 108 triblock terpolymers PEO-PS-PtBA with different polymerization degrees have been synthesized to direct the formation of the inorganic scaffolds. Eight different structures have been obtained, including the normal-phase (oil-in-water) spherical type, normal-phase 2D hexagonal, lamellar, inverse-phase (water-in-oil) SDD, shifted double-primitive (SDP) and SG, and inverse-phase 2D hexagonal and inverse-phase spherical-type structures. The formation of these structures is dependent on the effect of the geometrical packing parameter determined by the volume fraction of the hydrophobic segment and the segregation product ($\chi_N$). Additionally, the different volume fraction ratios of the hydrophobic/hydrophilic block (PS/PEO, PtBA/PEO) and those of the hydrophobic/hydrophobic block (PS/PtBA) divide the resulting structures in several regions. It has been found that the formations of the bicontinuous structures are dependent on low volume fraction ratios of PS/PEO and PS/PtBA with similar packing parameters.

SIMILARITIES AND DIFFERENCES BETWEEN BIOLOGICAL MEMBRANES AND ARTIFICIAL SYSTEMS

Structure and formation mechanism
From a structural point of view, bicontinuous structures in biology and the artificial polymer system show high similarity. It is of great interest to determine whether this structural resemblance is due to a shared formation mechanism. LLC is only one of many important methods that nature employs to produce complex biological forms. The formation of bicontinuous structures in LLC can be understood by the chain stretching and film bending associated with hydrophilic/hydrophobic interfaces, which lead to either a pair of CMC surface companions to the TPMS or a pair of parallel surfaces off the TPMS equidistant from the surface normal. The two surfaces correspond to the uniform curvature and the uniform length of the amphiphilic molecules [141–143]. However, the frustration present in most of the LLC phases is due to the nonuniformity of the curvature and chain length. Charvolin and Sadoc [144] discussed the
curvature frustration in the formation of bicontinuous structures. Helfrich and Hyde [145,146] proposed independently that the frustration in LLC corresponds to the fluctuations of the Gaussian curvature in TPMS. The stability of the bicontinuous structures has been further studied with regards to the balance between universal geometrical properties and the concentration constraints. After calculating the distribution of the Gaussian curvature, only G, D, and P surfaces were found to be stable phases among several TPMSs, and the G surface was the most stable [147,148]. Later, Schröder-Turk et al. [149] studied bicontinuous structures and molecular self-assembly by comparing the local curvature and the global packing homogeneity, which is defined as the standard deviation of the channel diameter of the labyrinths. The results confirmed that the G surface is the most stable structure among the hyperbolic surface categories, followed by D and P surface structures. A recent publication indicated that bicontinuous phases are determined by the competition and compromise between the CMC and parallel surface models [150].

The formation of cubic membranes in nature is frequently associated with the overexpression of ER membrane-bound proteins. Lipids and proteins are not randomly distributed in biological membranes, and instead consist of a highly dynamic lipid raft and a stable submicron lipid domain [151–153]. These domains are composed of unique proteins and lipids [154–156]. Protein-protein and lipid-protein interactions, and/or lipid alterations, appear to play important roles in cubic membrane formation. In plants, it has been reported that the membrane domain of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is key for the proliferation of the ER and the formation of organized smooth endoplasmic reticulum (OSER) [157]. Additionally, it has been reported that the concentration of docosapentaenoic acid (DPA, C22:5n-6) in the cubic membrane of mitochondria in starved amoeba Chaos cells is about 1.6-fold higher than in fed cells. Under starvation conditions, the content of plasmalogen lipid is about 1.2-fold that of fed cells [158,159]. The cubic membrane can be induced by over-expression of cytochrome b(5) tagged with a green fluorescent protein in COS-7 and CV-1 cells [160]. In this system, the formation of cubic membranes is considered to be the consequence of weak protein-protein interactions, since point mutations preventing these protein-protein interactions also prevent the formation of cubic membranes [160].

Because the biological membranes are a mixture of a large number of molecules in different forms, the g value could not accurately predict their phase structures. In contrast, block polymers have the advantage of a clear molecular structure, and the molecule can be extensively designed. The phase morphology and geometric properties of block copolymers can be controlled by adjusting the block copolymer type, polymerization degree, additives, and environmental parameters to control the moduli and the spontaneous curvatures. As discussed above, the microphase separation is driven by incompatibilities between different blocks according to their chemical compositions. During the melting of block copolymers, microphase separation approaches thermodynamic balance after several rounds of heating and annealing, and the obtained structure represents the minimum thermodynamic free energy of the bulk system [19,103,161]. The self-assembly process needs to be completed over a long period of time, while relying on kinetic limitations can result in an unusual metastable state (e.g., the perforated lamellar phase) [162]. In addition, the introduction of a solvent can effectively increase the diffusion rate of the system. The self-assembly process of block copolymers in solution is more like the LLC system. Compared to the phases in bulk, the introduction of solvent increases the complexity of self-assembly (Fig. 6) [40,163].

### Structural length scale and unit cell size

Various structures with different length scales as well as different Gaussian curvatures can be generated from the same molecules in biological systems. The cubic membrane structure and unit cell parameters in different tissues can vary, from a P surface structure with unit cell parameter a of 50 nm (tubular myelin of rabbit lung lavage) [70] to a multilayer G surface structure with a of 400 nm (mitochondria in retinal cones of tree shrew) [12], and even an SD structure with a of 450 nm (exoskeleton of beetles) [11]. Nevertheless, this is very difficult to replicate in artificial fabrications, and the length scales of the cubic structures formed by the self-assembly of amphiphilic molecules are significantly smaller than those of cubic membranes in biology. The unit cell parameters in the polymer micelle system are difficult to adjust without changing the template molecules. In addition, the multilayer gyroid structure present in biological cubic membranes is also a huge challenge for polymer self-assembly systems to mimic.

Therefore, scaling artificial fabrication is a huge challenge encountered by scientists. It has been reported that inverse bicontinuous cubic phases can be formed when charged phospholipids are introduced, with the unit cell...
parameter increased from 10 to 50 nm \[164–166\]. Therefore, the formation of inverse micelles could be a promising method for creating materials containing a lattice size comparable to biological cubic membranes, especially those associated with structural colors.

The involvement of lipid and protein molecules with many different geometric parameters may be one of the reasons why biological cubic membranes have such large lattice and pore (channel) size parameters. As shown in the previous section, the typical unit cell size of the bicontinuous cubic phases is strongly dependent on the structural scale of the template molecules. For the LLCs formed by small molecules, the chain length plays a key role in channel size. For polymer-based cubic phases, the polymer chains are more extended in the structural size, the obtained structures are in the range of 5–100 nm, and block copolymers with extremely high molecular weight are required for a large unit cell parameter \[37\]. On the other hand, it has been recognized that the swelling of the cubic phase of lipid molecules can be achieved by the addition of different types of lipid molecules \[86,87\]. The effects of the polydispersity of block polymers on self-assembly behavior have also been recognized. Hustad et al. \[167\] obtained self-assembled mesophases with domain spacing over 100 nm using polydispersity olefin block copolymers with a total molecular weight below 100 kg mol\(^{-1}\). Nevertheless, the spacing of self-assembled block polymers with similar molecular weights is typically in the range of 30–50 nm. Kim et al. \[168\] reviewed the results of these experiments and calculations. The polydispersity of the block polymer can significantly increase the size of the domains during microphase separation. It can expand the accessible window of the gyroid cubic phase and the perforated lamellae.

Furthermore, the method of solvent swelling in the block copolymer region provides an effective means of adjusting the unit cell parameters of inverse bicontinuous cubic phases. Using this method, the block copolymer molecules stay only at the hydrophilic/hydrophobic interface and the space can be filled with a large amount of solvent. Typically, in the synthetic system of the reference \[31\], the unit cell parameter \(a\) of the original cubic cell can be varied from 240 to 340 nm by adjusting the ratio of THF/water. As the unit cell parameters become larger, the SDD silica structure shows a partial band gap in the visible wavelength range, resulting in a structural color range ultraviolet to blue \[38\].

**Structural transition and structural determination**

In the study of biological bicontinuous phases, the defects and intergrowth of crystal structures are very important because they often provide information about the structural relationship in addition to the formation mechanism. The transformation of these structures has been extensively explored by several theoretical studies \[149,169–172\]. For membrane transformation, researchers generally believe that protein-driven changes in

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Figure 6 (a) Synthetic phase diagram of polyisoprene-\(b\)-poly(ethylene oxide) (PI-PEO) and inorganic components (in weight fractions). White areas are marked as different structures. A schematic of the phase of pure PI-PEO is shown at the bottom. Reproduced with permission from Ref. \[163\]. Copyright 2009, American Chemical Society. (b) Synthetic phase diagram of the structure of macroporous silica based on the PEO-PS-PtBA polymer system (in volume fractions). Different points represent different structures: from normal-phase (oil in water) cage-type (n-C, black), normal-phase 2D hexagonal (n-H, purple), and lamellar (L, pink) to unique inverse-phase (water in oil) hyperbolic-surface (i-HS) structures, including the shifted double-diamond (i-SDD, red), single-gyroid (i-SG, dark green), and shifted double-primitive (i-SDP, blue), inverse-phase 2D hexagonal (i-H, orange) and inverse-phase micellar (i-M, reeda). Reproduced with permission from Ref. \[40\]. Copyright 2018, American Chemical Society.
cell membrane curvature, the formation of stalks between the contacting monolayers, and vesicle fusion are the main reasons for biomembrane transformation [173–176]. In this process, the stems are formed by transient contact between the membranes, which are then fused and expanded to form a tubular joint. These tubular connections constitute the basic connecting elements of bicontinuous cubic phases. Due to the sensitivity of biological membranes to external stimuli, these mechanisms cannot be easily observed or studied dynamically by experimentation. In addition, Norlén [177] proposed an intersection-free membrane-folding/unfolding model based on the formation of the mammalian skin barrier that merits attention. There is a continuous, dynamic film folding/unfolding process between cubic and lamellar structures in this model, and this process exists in many biological systems [178–180]. It does not involve budding or fusion or reducing energy consumption. At the same time, the continuity of the membrane can be maintained, which is essential for the barrier function of biological membranes. In addition, it is capable of forming parallel multilayer cubic membranes with large lattice parameters (50–500 nm).

These biological systems can be highly dynamic, coinciding with the nature of soft matters. It is extremely difficult to fully solve and characterize the structure by recognizing the 3D electrostatic potential map of the detailed structure in these biological systems. One of the key challenges in understanding their structure and structural transformation is experimental observation. Diffraction techniques such as X-ray diffraction (XRD) and small angle X-ray scattering (SAXS) have been widely used for the structural characterizations of LLC systems [181–184]. XRD and SAXS techniques provide overall information, but detailed morphological changes and intermediate structures cannot be easily revealed. TEM is a powerful technique that possesses certain advantages in its structural characterization abilities. TEM not only produces the electron diffraction patterns in reciprocal space, but also shows direct imaging in real space. Structural information can be obtained via 3D reconstruction of the target from a series of 2D projected images collected at incremental degrees of rotation around the specimen center. Furthermore, the structures can be identified based on pattern recognition through direct comparison with the experimental TEM images or the sliced samples with the 2D projection map generated by mathematical modeling with TPMS and related CMC/parallel surfaces [6,55,56].

The structural transformation of lipid and surfactant systems has been also extensively investigated by these technologies. Researchers have generated many phase diagrams for given lipids or mixture of lipids, describing the existence of various phase structures as a function of parameters such as composition, temperature, and pressure [183,185–187]. Meanwhile, LLC has a particular property that the phase structures can be fixed into inorganic frameworks. The mesostructures can be formed by cooperative self-assembly or true liquid crystalline template of the lipids or surfactants with the hydrolysis and condensation of inorganic precursors [188]. Various inorganic mesostructured materials can be produced according to the packing parameter $g$. The inorganic scaffolds can also be formed using amphiphilic block copolymers as templates [189–193]. Due to the stable inorganic framework, the electron crystallographic method can be applied to the structural investigation, and both the phases and amplitudes of crystal structure factors can be obtained from a Fourier transform of the high resolution TEM (HRTEM) images. Thus, a 3D electrostatic potential map can be directly reconstructed to elucidate characteristic structural features [194–196].

In the cooperative self-assembly of PEO-PS-PtBA and silica precursors, the epitaxial intergrowth of different hyperbolic surface structures has been discovered [39,41]. The “side-by-side” epitaxial relationship between SDD and SDP structures was identified. The $[001]_{\text{cub}}$ direction of SDP is parallel to the $[111]_{\text{cub}}$ direction of SDD (the subscript “cub” indicates the direction of the original cubic unit cell without shift), and the ratio of the unit cell parameters of double primitive (DP) to those of DD was 1.30 [39]. This is consistent with the theoretical value of 1.279 in Bonnet transformation, which keeps the Gaussian curvature unchanged (Fig. 7a, b). Furthermore, the intermediate interface was directly observed and found to be related to the rhombohedral deformation of D and P surfaces (rPD family) [149,171,172,183].

For the intergrowth of SDD and the thermodynamically unstable SG structure, a similar epitaxial relationship was confirmed, wherein the $[001]$ of SG is parallel to the $[110]_{\text{cub}}$ of DD. Interestingly, the unit cell parameter of SG is only $\sqrt{2}/2$ of the DD, revealing the significance of the structural scale during the transition. Therefore, the nodes of both structures cannot be perfectly connected and the nodes in DD need to be branched to connect to that of the SG. Obviously, the structural transition is not a curvature-driven process, as there is a large lap in their Gaussian curvature. In order to explain the structural transformation, a modified alternating gyroid model was proposed, in which the TPMS is...
formed by the hydrophobic part of the polymer while the two interwoven labyrinths are occupied by either the water-rich core or the THF-rich phase (Fig. 7c, d) [41].

It is noteworthy that the 2D projected TEM images of biological cubic membranes and macroporous silica formed by the block copolymer template show extremely high similarity, suggesting a 3D structural similarity. Interestingly, a similar structural transformation is also observed (Fig. 8). Biological membranes, as a complex, dynamic system, have a larger number of deformed phases, which are difficult to be accurately analyzed and characterized. Additionally, biological cubic membrane structures are often deformed and transformed from other structures, especially lamellar structures, so a large number of structural extension relationships exist [197,198]. After slicing the samples into ultra-thin sections, their structural features, including the structural transition and defects, can be seen using TEM. TEM is generally applied for cell ultrastructural studies and is also highly suitable for artificial materials synthesized with amphiphilic molecules. We managed to slice the intergrowth samples of DD and SG, which clearly show the structural transition of the epitaxial intergrowth of both structures via surface deformation and the connection of nodes with different Gaussian curvatures. These results demonstrate the possibility of exploring the structural information and formation mechanism of cell membrane systems via TEM of the corresponding synthetic structures of the block copolymer system.

Importantly, kinetic control of the evaporation process yields some important and thermodynamically unstable intermediate phase structures. It may also provide a usable model and a powerful tool for investigating the complex structural transformation process of intracellular membrane systems. Because it directly reveals real space information, the analysis of electron crystallography possesses an advantage in studies of the defects and intergrowth of the mesophase structures.

**SUMMARY AND OUTLOOK**

Despite great achievements in this field in the past few decades, several challenges remain. As we have shown in this review, nature has many intelligent ways of producing complex biological bicontinuous structures. Some cubic membranes are spontaneously formed in cells, while others appear in response to external or internal stimuli. Researchers have found that there are many
important physical and chemical properties of cubic cell membranes, including their interactions with biological macromolecules as well as optical and antioxidant properties, etc. However, their formation mechanisms and potential bionic applications are still poorly understood. Although the formation mechanism of cubic membranes in living organisms remains unclear, there must be a specific purpose for their formation aside from the simple geometric relationship of molecular packing. To address this question, experimental investigations conducted by mimicking the external and internal environments of the cells seem to be a good approximation. The difficulty lies in the complexity of the system, which is affected by numerous factors. Additionally, to understand their structure, an accurate description of their surface arrangement and the dynamic formation mechanism is essential. The advantages of contemporary cryo-TEM and environmental TEM may provide a deeper understanding of these cell membrane systems. Still, existing methods make it difficult to characterize and resolve fine details and dynamic structures in vivo.

In contrast, the formation of corresponding bicontinuous cubic phases in artificial polymer systems seems to be more straightforward. There are advantages to the well-defined, controllable, and designable molecular structure of artificial systems. The phase behavior of block copolymer systems with a stimulus responsive block can mimic biological membranes, and the formation of bicontinuous cubic phases may provide an ideal way to understand the much more complex cell membrane system. Specifically, electron microscopic techniques can be applied to the structural study of inorganic replicas of the LLC and copolymeric systems. Their stable inorganic framework makes a detailed structural study doable, particularly for the study of the structural transition, epitaxial growth, and crystal defects. Furthermore, the structure-determined functions in cell membrane systems can be deduced and studied using synthetic structures.

Learning from natural systems and bridging different research topics is key for the study of relevant structures. With this in mind, we attempted to compare the structural transformation and formation mechanisms of cell membrane systems and artificial systems by introducing the bicontinuous cubic phase in cell membranes and block copolymer systems. Therefore, the LLC and block polymer self-assembled system may serve as a suitable model system, wherein tunable synthesis and effective characterization methods can be fairly employed. Bridging the gap between the cell membrane system and the self-assembly process may provide new ideas for our understanding of the formation of cubic membranes, and this understanding may further guide approaches to synthesizing new functional materials. For instance, it remains a challenge to create a thermodynamically unbalanced single network CMC/parallel surface structure, which has been shown to possess excellent photonic properties. Additionally, in-depth study of the structure and properties of lipid bilayer membranes and soft materials is very valuable for the design and manufacture of biomimetic structural materials as stimuli responsive nanomaterials, drug delivery carriers, and hydrogels for regenerative medicine. By incorporating inorganic sources into the self-assembly system, novel functional materials may also be created with stable nano-network structures, enhanced functionalities, and expanded applications.

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