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Adaptation of the membrane in Archaea

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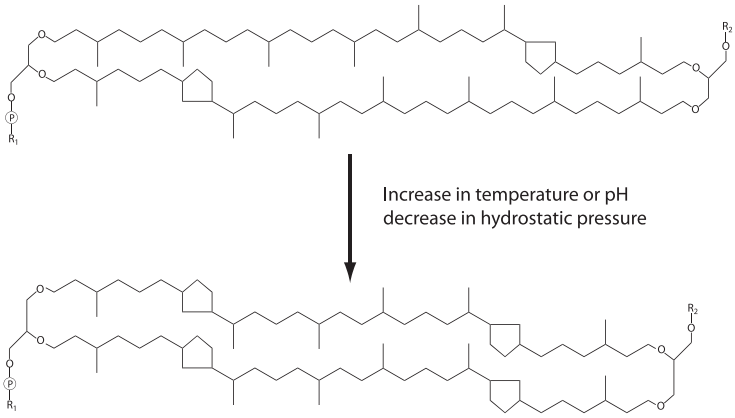
HIGHLIGHTS

- We present evidence that Archaea regulate membrane composition as a function of environmental stressors.
- Lipid composition variations are consistent with homeoviscous adaptation to maintain membrane functionality under stress.
- Specific modifications include the incorporation of cycles, unsaturation or modifying the ratio of di- to tetraether lipids.
- We highlight the limits of homeoviscous adaptation to interpret several specific membrane lipid compositions.
- These limits are attributed to imprecise lipid comopsition or poor understanding of the archael membrane structure.

GRAPHICAL ABSTRACT



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ABSTRACT

Microbes often face contrasted and fluctuating environmental conditions, to which they need to adapt or die. Because membranes play a central role in regulating fluxes inward and outward from the cells, maintaining the appropriate structure of the membrane is crucial to maintain cellular integrity and functions. This is achieved in bacteria and eucarya by a modification of the membrane lipid compositions, a strategy termed homeoviscous adaptation. We review here evidence for homeoviscous adaptation in Archaea, and discuss the limits of this strategy and our knowledge in this very peculiar domain of life.

1. Introduction

As the first and ultimate barrier between the intracellular space and the wild-world, biological membranes play a fundamental role in the adaptation of microbes to their environments. Membranes are not just physical barriers to regulate inward and outward trafficking, they play a central role in energy storage and processing via the ion gradients, provide a matrix for environmental sensing, multicomponent metabolic and signaling pathways as well as motility. Maintaining optimal membrane function is therefore crucial for the cell. Thus, temperature-, hydrostatic pressure-, or pH-induced perturbations in membrane organization pose a serious challenge. Bacteria and eucarya regulate membrane fluidity by regulating the level of unsaturations and the length of the lipid acyl chains or incorporate lipids with different polar head groups, an

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adaptation referred to as homeoviscous adaptation. We review here evidence for membrane adaptation in Archaea as a function of environmental constraints, and discuss about the possibility and limits of homeoviscous adaptation in these organisms.

2. The structure of archaeal lipids

Archaeal membranes are composed of phospho-, glyco- and phospho-glyco-lipids which differ substantially from their bacterial counterparts. The structures of these lipids have been detailed in recent reviews [1–4]. In contrast to their bacterial homologues which, to rare exceptions, are based on straight chain hydrocarbons linked by ester bonds on the *sn* − 1 and *sn* − 2 positions of glycerol, archaeal polar lipids are composed of isoprenoid hydrocarbon chains bound by ether bonds to the *sn* − 2 and *sn* − 3 positions of glycerol (Fig. 1). Polar groups consist of phosphodiester-linked polar head groups or sugar moieties on the *sn* − 1 position of the glycerol backbone (*sn*-glycerol-1-phosphate or G-1-P structure). Therefore, the archaeal G-1-P is an enantiomer, a mirror image stereoisomer of the *sn*-glycerol-3-phosphate or G-3-P backbone of bacterial phospholipids. It is noteworthy that this enantiomeric difference, although central to the divergence between Archaea and the Bacteria/eucarya in terms of evolution, e.g. the lipid divide [3], is insignificant in terms of chemical behavior, since enatiomers have essentially equivalent physical behavior.

In addition to the G-1-P backbone structure, archaeal lipids have other unique characteristics. The core hydrocarbon chains of archaeal glycerol polar lipids are composed exclusively of isoprenoid hydrocarbons most often made up of a phytanyl chain (20 carbons, or C20, Fig. 1A and B) or a head-to-head condensation dimer of two phytanyl chains, e.g. a biphytanyl chain (40 carbons, C40, Fig. 1C, D and E). C20-based archaeal lipids are glycerol-dialkyl-glycerol-diether (GDGD) and are usually referred to as archaeol and archaeol derivatives, while C40-based lipids are glycerol-dialkyl-glycerol-tetraether (GDGT) are usually referred to as caldarchaeol [5]. Archaeol and caldarchaeol and derivatives represent the vast majority of archaeal lipids (Table 1). However, archaeal lipids containing 1 or 2 C25 isoprenoid chains have been described in several species [6]. Halobacteriales such as *Haloterrigena*, *Halococcus*, *Natronobacterium* or *Natronomonas* produce C20–C25 diether lipids [7], while the hyperthermophile *Aeropyrum pernix* [8,9] or methanogens such as *Methanobacter thermoautotrophicus* [10] produce C25–C25 diether lipids.

Additional modifications on the core isoprenoid chains include the presence of unsaturations at position C3 of the phytanyl chain of archaeol, the presence of hydroxy groups at the same position (hydroxyarchaeol),

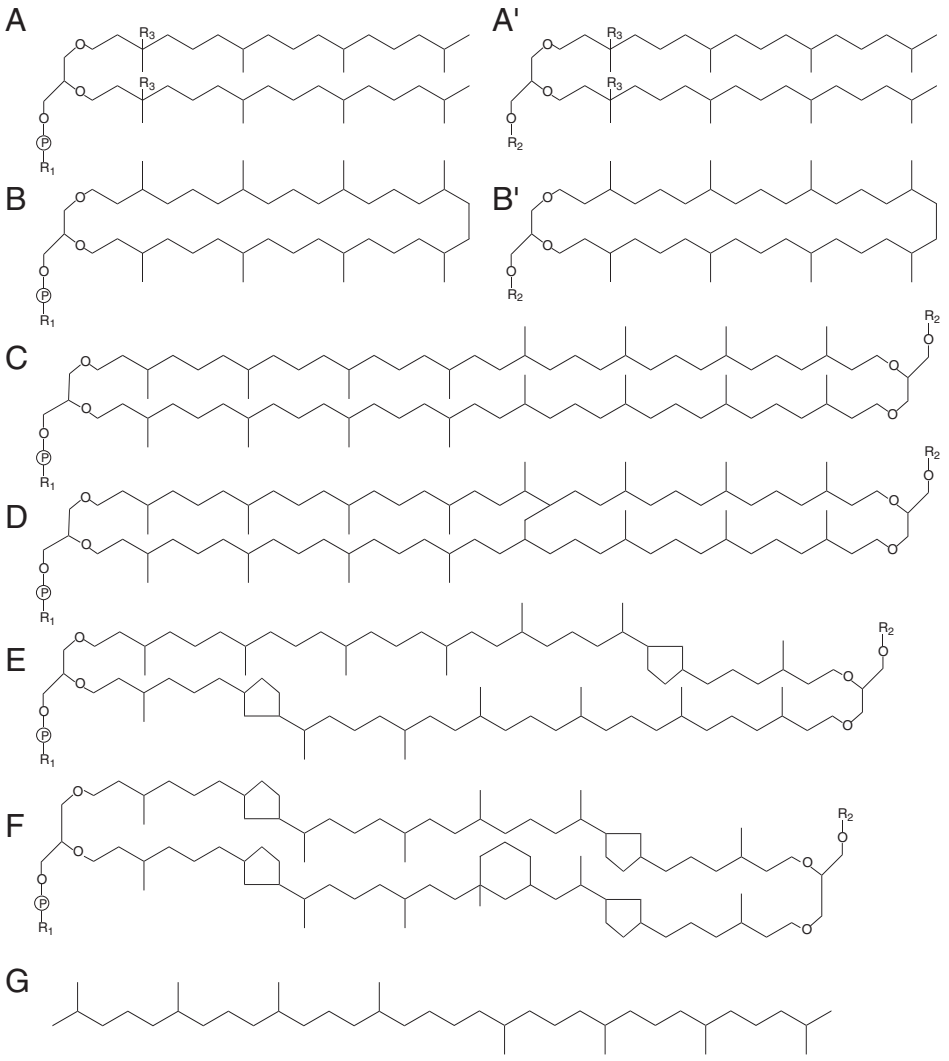

Fig. 1. Structures of archaeal lipids (A) diphytanylglycerol (archaeol: archaeal diether lipid); (B) cyclic archaeol; (C) caldarchaeol (archaeal tetraether lipid); (D) H-shaped caldarchaeol; (E) cyclopentane-containing caldarchaeol; (F) crenarchaeol; (G) lycopane-type isoprenoid hydrocarbons. R1, R2, R3: polar head groups. The headgroups of phospholipids can be a range of polar compounds — for example, glycerol, serine, inosine, ethanolamine, myo-inositol or aminopentanetetrols (see Table 1). Glycolipids also exhibit a range of sugar residues — for example, glucose, mannose, galactose, gulose, N-acetylglucosamine or combinations thereof.

the presence of 1 to 4 cyclopentane rings along the biphytanyl chains of caldarchaeol (Fig. 1E) or the presence of cyclopentane and cyclohexane rings as in crenarchaeol (Fig. 1F). The number of cyclopentane rings in the caldarchaeol derivatives will depend on the species. Tetraethers of *Thermoplasma* or *Sulfolobus* may contain up to 4 cyclopentane rings [11,12] while those in *Archaeoglobus* contain only up to two cycles [13,14]. Unsaturated analogs of archaeol have been reported in several species, especially among the halophilic Archaea [15–20]. Although long thought to be the result of technical and analytical difficulties, the presence of these unsaturated lipids is now well established in at least two different species, a methanogen, *Methanopyrus kandleri* [21] and a member of the Thermococcales, *Thermococcus* sp. S557 [22]. Macrocyclic archaeol (Fig. 1B), a derivative of Archaeol in which the two phytanyl chains are bridged by a covalent bond was first described in *Methanocaldococcus jannaschii*, a thermophilic methanogen, in which it represents ca. half the membrane lipids [23,24]. Similarly, an H-shaped cross-linked derivative of caldarchaeol (Fig. 1D) was shown to represent 30% of the core lipids in another methanogen, *Methanothermus fervidus* [25]. Numerous derivatives of the above structures with cycles or bridges between the two isoprenoid chains have been identified in different Archaea. These include but are not limited to archaeol with cyclopentane rings or archaeol and macrocyclic archaeol with bridges at position C2 of the isoprenoid chains.

Two major polar headgroup types are found in archaeal lipids, with either a phosphatidyl or a sugar moiety, which are similar to that of bacteria and eucaryotes. Bipolar archaeal lipids are asymmetrical, harboring a phosphatidyl moiety at one end of the lipid and a sugar moiety at the other end [26]. Phosphodiester-linked polar head groups are very similar to that observed in bacteria, with phosphatidylserine, phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylglycerol, phosphatidylglycerophosphate, phosphatidylglycerosulfate, etc. [1]. There is a large diversity in sugar moieties, with molecules harboring one, two, or three units of different sugars such as gulose, glucose and galactose (Table 1). The diversity of polar lipids in a single archaeon can be important, with species displaying more than 25 different lipid molecules, each of which may also present various unsaturation level or cyclopentane ring number [5,27]. Bipolar lipids, which harbor hydrophilic moieties on both ends and long hydrophobic central domain can form monolayer membranes, which contrast with the typical lipid bi-layer observed in most organisms, including bacteria and eucarya. Bipolar lipids are oriented in the membranes with the phosphatidyl moiety inside the cell and the bulkier sugar moiety pointed towards the outside [26]. The distributions of these ether lipids vary with the archaea classes (Table 1). In halophiles, e.g. salt-adapted archaea, the polar lipids are mainly comprised of diether lipids with phytanyl (C20), or sesterterpenyl (C25) isoprenoid chains. In methanogens, acidophiles (low pH-adapted) and hyperthermophiles (high-temperature-adapted), the polar lipids typically consist of a mixture of diphytanylglycerol diether and dibiphytanyl tetraether lipids, with or without cyclopentane rings.

In addition to polar lipids, archaea were shown to produce several irregular isoprenoid hydrocarbons of the lycopene/squalene structure, with a chain length of 15 to 50 carbons (Fig. 1G) [28–30]. Archaea derive their lipids from the mevalonate pathway by the successive condensation of isoprenoid units to form di-phosphorylated C20 chains which are further incorporated on the glycerol backbone, to generate a poly unsaturated archaeol derivative [3,4]. The biphytanyl chains are formed by head-to-head condensation of the phytanyl chains from 2 archaeol molecules. Oppositely, lycopene-type isoprenoid chains are derived from a tail-to-tail condensation of two poly-isoprenoid chains. Thus, archaeal lipid synthesis does not yield lycopene-type hydrocarbons. It has been proposed that their synthesis may be similar to that of squalene synthesis in plants, for which pathway a homologous gene is present in most Archaea. The presence of straight chain fatty acid-based lipids in Archaea reported in several studies remains highly questionable because they can often be tracked down to the growth medium used for the cultures [31,32].

3. Homeoviscous adaptation: how bacterial and eucaryal membrane adapt to environmental stressors

Because membranes act as physical barriers to regulate inward and outward trafficking, play a central role in energy storage and processing via the ion gradients, and provide a matrix for environmental sensing, multicomponent metabolic and signaling pathways as well as motility, maintaining optimal membrane biological function is crucial for any organism. Thus, temperature-, pH-, salinity- or hydrostatic pressure-induced perturbations in membrane organization pose a serious challenge for the cell. Based on the observation that the membrane lipids of *Escherichia coli* cells grown under the contrasting temperatures of 43 °C and 15 °C were different [33,34], but the respective membranes displayed similar physical properties at their respective growth temperature (Table 2), Sinensky posed the basis of homeoviscous adaptation [35]. This theory states that membrane lipids composition variations in response to temperature (or other stresses) in a given organism favor the maintenance of the appropriate membrane fluidity for it to function optimally. Since its inception and despite it being limited to a very static model of the membrane, the homeoviscous adaptation theory has been commonly used to explain the patterns of membrane lipid variations in organisms. With the later realization that membrane fluidity was one of the many critical aspects of the biological roles of membranes, a dynamic rather than static homeoviscous adaptation concept has been proposed by McElhaney which takes in consideration the patchy nature of the membranes (inhomogeneous lipid repartition, presence of proteins) and the mobility of the lipids within the membrane [36,37]. Similarly, the observation that tended to show similar permeabilities to water and proton regardless of the growth optima of the bacterium lead to the definition of homeostasis of proton permeability, or homeoproton adaptation [38,39]. It should be noted that for the purpose of this review the term homeoviscous adaptation is taken in a very broad acception, encompassing the modifications of lipid compositions to maintain the membrane in a biologically functional state in response to fluctuations in environmental variables. Thus, it involves the regulation of the membrane fluidity, permeability, proton and ion gradient across the membrane or the regulation of lipid protein interactions.

The impact of temperature or pressure on membrane lipids is most evident in the alteration of the properties of the lipid chains inside the bilayer [40]. Under physiological conditions, membranes are relatively fluid, disordered liquid-crystalline phases. When temperature drops, or hydrostatic pressure increases, the membrane lipids may undergo the fluid to gel phase transition. When the temperature increases above the physiological conditions, or the pressure decreases from these, the rate of motion of lipids in the membrane will be increased, which may impact membrane stability and intrinsic permeability. Interestingly, in bacterial and eucaryal membranes, is has been shown that the physiological conditions correspond to a temperature range of 10–20 °C in which domains of fluid and gel phases may coexist in regions of phase separation. As can be expected from the central role of the membrane for the cell, perturbation in lipid phase state has profound consequences on membrane structure and function [41,42]. Transition to the gel phase may induce the clustering of membrane proteins, which appear de facto excluded from the zones in the gel phase, reduces the diffusion and the activity of proteins in the membrane, slows the flux of transported solutes, but in contrast increases the permeability to cations and water. Ultimately, membrane function defines the limits for growth of an organism.

The gel/fluid transition is specific for each lipid. It will depend on several parameters such as: the type of lipid, bacterial/eucaryal acyl- vs. archaeal isoprenoyl-based lipids, the length of the chains, the number of unsaturations along the chains, and the type and nature of the polar head groups [43]. To adapt the behavior of their membrane bacteria and eucarya can adapt the chain length of their fatty acids. An increase in chain length by two carbons will increase the phase transition

Table 1
Temperature and pH optima, percentage or diether (C20), tetraether (C40) and H-shape tetra ether (H-C80) lipids, type of core lipids, polar head groups for the major groups of Crenarcheota and Euryarchaeota. Phosphatidyl headgroups: PI, phosphatidylinositol; PG, phosphatidylglycerol; PE, phosphatidylethanolamine; PGS,phosphatidylglycerylsulphate; PGP-Me, phosphatidylglycerylphosphate methyl ester. The number of cyclopentane ring is given per lipid molecule.

Genus	Species	pH	T	C20	C40	H-C80	Lipid type	polar head	reference
Caldisphaera	*lagunensis*	4	75	Traces	100		Cyclic and acyclic tetraethers		[102]
Aeropyrum	*pernix*	7	90	100	0		C25–C25	PI; glucose	[8,9]
Desulfurococcus	*mobilis*	5.8	88	0	100			PI; galactose, glucose	[103]
Ignicoccus	*islandicus*	5.8	90	50	50				[104]
Ignicoccus	sp.	5.5	90	80	20			Mannose, glucose	[105]
Sulfophobococcus	*zilligii*	7.6	87	0	100			PI; mono and di glycosides	[106]
Thermosphaera	*aggregans*	6.5	85	5	95		Majority of tetraether with up to 4 cyclopentane rings		[107]
Hyperthermus	*butylicus*	7	100	15	95		Majority of tetraether with up to 2 cyclopentane rings		[108,109]
Pyrolobus	*fumarii*	5.5	106	5	95				[110]
Metallosphaera	*sedula*	2.8	75	0	100		20% caldarchaeol, 80% calditoglycerocaldarchaeol		[111,112]
Sulfolobus	*solfataricus*	4	87	0	100		Tetraethers with up to 6 cyclopentane rings	PG;	[73,88]
Sulfolobus	*acidocaldarius*	2.5	70	0	100		Tetraethers with up to 8 cyclopentane rings	PI;glucose, galactosyl-glucose	[113,114]
Sulfurisphaera	*ohwakuensis*	2	84	0	100		20% caldarchaeol, 80% calditoglycerocaldarchaeol		[115]
Pyrobaculum	*aerophilum*	7	100	5	95		Majority of tetraether with up to 4 cyclopentane rings		[116]
Pyrobaculum	*islandicum*	6	95	0	100		Majority of tetraether with up to 4 cyclopentane rings	PI; β-D-glucose	[117]
Pyrobaculum	*organotrophum*	6	95	0	100		Majority of tetraether with up to 4 cyclopentane rings	PI; β-D-glucose	[117]
Thermoproteus	*tenax*	5	90	0	100			PI; glucose	[118]
Caldivirga	*maquiligensis*	4	85	Traces	100		Cyclic and acyclic tetraethers		[119]
Thermocladium	*medestius*	4	75	traces	100		Cyclic and acyclic tetraethers		[120]
Methanothermus	*fervidus*	6.5	85	9	91	31	31% of an H-shaped caldarchaeol derivative		[25]
Methanobrevibacter	*arboriphilicus*	7.5	37	52	48				[121]
Methanobacter	*thermoautotrophicus*	7.4	65	17	83				[10]
Methanobacterium	sp. *AZ*	7	37	37.5	62.5				[122]
Methanobacterium	sp. *MOH*	7	37	43.5	56.5				[122]
Methanobacterium	*ruminatium*	7	39	44.7	55.3				[122]
Methanococcus	*jannaschii*	6	85	100	0		15% Archaeol; 85 macrocyclic Archaeol	PE; glucopyranose	[23,24,123]
Methanococcus	*voltae*	7	35	100	0				[124]
Methanocaldococcus	*jannaschii*	6	65	82	18				[123]
Methanocaldococcus	*jannaschii*	6	85	95	5				[24]
Methanococcus	*vannielli*	7.2	25	100	0				[10]
Methanospirillum	*hungatei*	7.4	37	41	59				[125,126]
Methanospirillum	*hungatei*	7.4	37	40.5	59.5				[122]
Methanosarcina	*barkeri*	7	37	100	0		Archaeol		[127]
Methanolobus	*tindarius*	6.5	25	100	0		Archaeol		[10]
Methanohalophilus	*mahii*	7.5	37	100	0		Archaeol		[10]
Methanosaeta	*soehngenii*	7.5	37	100	0		Archaeol		[10]
Methanosaeta	*concilii*	7.5	35	100	0		Archaeol		[128,129]
Archaeoglobus	*fulgidus*	7	83 °C	50	50		Diether and tetraether with 0–2 cyclopentane rings	PI, PE; galactose, mannose with minor amounts of glucose	[13,14]
Halorubrum	*lacuprofundi*	7.4	25	100	0		C20–C20, C20–C25	PG, PGS, PGP-Me; monoglycosyl, sulphate ester of adiglycosyl	[130]
Halalkalicoccus	*tibetensis*	9.5–10.0	40	100	0		C20–C20, C20–C25	PG, PGP-Me; no glycolipids	[131]
Halarchaeum	*acidiphilum*	4.4–4.5	37	100	0		C20–C20, C20–C25	PG, PGP-Me; 4 unidentified glycolipids	[132]
Natrialba	*hulunbeirensis*	9	37	100	0		C20–C20, C20–C25	PG, PGP-Me; no glycolipids	[133]
Natrialba	*chahannaoensis*	9	37	100	0		C20–C20, C20–C25	PG, PGP-Me; no glycolipids	[133]
Natronomonas	*pharaonis*	8.5	37–40	100	0		C20–C20, C20–C25	PG, PGP-Me; no glycolipids	[134]
Natronorubrum	*tibetense*	9	45	100	0		C20–C25	PG, PGP-Me; no glycolipids	[135]
Natronorubrum	*bangense*	9.5	45	100	0		C20–C25	PG, PGP-Me; no glycolipids	[135]
Methanopyrus	*kandleri*	6.5	97	100	0			Mannose, glucose, galactose, N-acatylglucosamine	[87]
Palaeococcus	*ferrophilus*	6	83 °C	20	80		Archaeol and caldarchaeol derivatives		[136]
Pyrococcus	*woesei*	6	101.5	0	100		Archaeol and caldarchaeol derivatives	PI	[86]
Pyrococcus	*abyssi*	6.8	96	15	85		73.5 acyclic and 9.5% bipentacyclic C40 biphytanyl chains		[137]
Pyrococcus	*furiosus*	6	98	80–90	10–20		Archaeol and caldarchaeol derivatives	PI, PG; glucose	[84]
Pyrococcus	*horikoshii*	7	85	5.9	60.1	34	Archaeol and caldarchaeol derivatives		[84]
Pyrococcus	*Sp 4557*	7	98	100	0		Archaeol and caldarchaeol derivatives		[84]
Thermococcus	*aegeus*	6	85	27.2	72.8		[86]		
Thermococcus	*aggregans*	7	85	42.1	57.9		[84]		
Thermococcus	*barophilus*	7	85	100	0		Archaeol	PI; glycerol	[138]

(continued on next page)

Table 1 (*continued*)

Genus	Species	pH	T	C20	C40	H-C80	Lipid type	polar head	reference
Thermococcus	*celer*	5.8	88	100	0		Archaeol and caldarchaeol derivatives	PI	[139]
Thermococcus	*fumicolans*	8	85	70	30		Tetraethers with up to 2 cyclopentane rings		[140]
Thermococcus	*gorgonarius*	7	85	16.8	83.2		[84]		
Thermococcus	*guaymasensis*	7.2	85	12.7	75.3	12	[84]		
Thermococcus	*hydrothermalis*	6	85	25	75		Archaeol and caldarchaeol derivatives		[140]
Thermococcus	*kodakarensis*	6.8	85	17.7	82.3		Archaeol and caldarchaeol derivatives		[79]
Thermococcus	*litoralis*	7.2	85	26.8	73.2		Archaeol and caldarchaeol derivatives		[84]
Thermococcus	*pacificus*	7	85	25.4	74.6		Archaeol and caldarchaeol derivatives		[84]
Thermococcus	*peptonophilus*	6	85	14.3	85.7		Archaeol and caldarchaeol derivatives		[84]
Thermococcus	*profundus*	7.5	85	16	84		Archaeol and caldarchaeol derivatives		[84]
Thermococcus	*stetteri*	6.5	85	9.6	90.4		Archaeol and caldarchaeol derivatives		[84]
Thermococcus	*waiotapuensis*	7	85	15.2	35.9	48.9	Archaeol and caldarchaeol derivatives		[84]
Thermococcus	*zilligii*	7.4	85	33.2	66.8		Archaeol and caldarchaeol derivatives		[84]
Thermoplasma	*acidophilum*	1	59	0	100		Tetraether with 0, 2 or 4 cyclopentane rings		[141,142]
Picrophilus	*oshimae*	0.7	60	0	100		Tetraether with up to 5 cyclopentane rings, the majority has 0 or 3 rings	glucose	[143]
Thermoplasma	*acidophilum*	2	59	0	100		Caldarchaeol with 1 to 3 cyclopentane rings as major tetraethers	PG; glucose, gulose	[77,144]
Thermogymnomonas	*acidicola*	3	60	0	100		Cyclic and acyclic tetraethers		[145]
Aciduliprofundum	*boonei*	4.5	70	0	100	++	Cyclic and acyclic tetraethers; cyclid and acyclid H-shaped tetraethers	PG	[146]

temperature of the lipid by 10 to 20 °C, and decrease membrane permeability to proton and water [40]. Another of the major lipid composition variation observed in bacteria is the accumulation of unsaturated fatty acids as a response to a decrease in temperature reviewed in Russell [44]. The incorporation of a single unsaturation can shift the fluid/gel phase transition by 10 to 20 °C [40]. Many organisms accumulate polyunsaturated fatty acid, the rationale for which is still unclear, knowing that the incorporation of more than 2 unsaturations does not lower the fluid/gel phase transition of the lipid, and may eventually increase it [44]. This trend was clearly confirmed in the moderately piezophilic bacterium *Photobacterium profundum* strain SS9, in which mutants unable to synthesize monosaturated lipids but able to synthesize the polyunsaturated fatty acids eicosapentaenoic acid (EPA, 20:5) and docosahexanoic acid (DHA, 22:6) were low-temperature and high-pressure sensitive in contrast to the parent strain [45]. Under high hydrostatic pressure conditions or low temperature conditions, bacteria tend to accumulate phosphatidylcholine (PC) or phosphatidylglycerol (PG) containing lipids in place of lipids with phosphatidylethanolamine (PE) polar head groups, which would result in a drastic shift of the fluid/gel transition temperature of the lipid for the same acyl chains [46,47]. The nature of the polar headgroup also has a strong impact on the fluid/gel transition. For example, a change in the proportion of PE relative to PC lipids will increase the order in the membrane for lipids of similar acyl chain composition [40,48]. This is due in part to the reduced hydration and stearic bulk of the ethanolamine compared to choline, and the capacity of PE, and incapacity of PC, groups to form hydrogen bonds. It is important for cells to maintain a balance between attractive and repulsive charges at the surface of the membrane for it to perform optimally. Thus, by modifying the lipid composition of its membrane, the cell can adapt and maintain its fluidity in a range suitable with its various functions. Homeoviscous adaptation to fluctuations in pressure, temperature, or pH involves one or a combination of the following adjustments mentioned above: adapting the mean number of cis unsaturation in lipid chains; decreasing/increasing the proportion of branched fatty acid; decreasing/increasing the length of hydrocarbon chains; and modifying the proportion of various polar headgroups.

Homeoviscous adaptation can be understood in its evolutionary inception, e.g. as an adaptation in the long term. There is ample evidence from the lipid composition of cells from animals of a large range of body temperature that the lipid composition follows this general trend. In the long term, the substitution of one type of lipid by another one of more appropriate behavior is the preferred option. However, in the procaryotes, homeoviscous adaptation must also be understood as a mean to rapidly adapt the composition, and thus the fluidity sensu largo, of the membrane to brutal environmental fluctuations, or aggressions, which include heat and cold, salinity, osmotic, or pH stresses. In this view, the cellular response to adapt the membrane composition needs to be very quick. Modifying existing membrane lipids is by far quicker than synthesizing new ones, whether these are synthesized by existing protein or proteins needing to be expressed and traduced. This may explain the prevalence of certain adaptive mechanisms when different lipid alterations may lead to similar changes in physical behavior. For example, the incorporation of unsaturations in the acyl chain of a lipid in the membrane will decrease the fluid/gel transition to an extent similar to the shortening of one of the acyl chains, or the substitution of a phosphatidylcholine to phosphatidylethanolamine polar head. However, the last two reactions are performed during the synthesis of the lipids while the incorporation of unsaturations in the acyl chains is performed

Table 2
The viscosity and phase transition of *E. coli* lipid extracts and intact membranes from cells grown at different temperatures. Adapted from Sinensky [35].

	Temperature of growth (T_G)	Temperature of analysis	Rotational correlation time | (ns)	Coefficient of viscosity η (P)	Phase transition temperature (T_T)	$T_G - T_T$
Lipid extracts	15	15	2.8	1.8	-1 ± 1	16 ± 1
	30	30	2.7	1.9	16 ± 2	14 ± 1
	37	37	2.6	1.8		
	43	43	2.7	2.0	27 ± 1	16 ± 1
	43	15	13.8	15		
Membranes	23	23	3.5	2.5		
	23	37	1.6	1.0		
	37	37	3.3	2.5		

inside the cytoplasmic membrane by a membrane protein [49–52] which make it more efficient to adapt on a short term the fluidity of the membrane. Thus regulating the level of unsaturation constitutes a fast and efficient way to adapt membrane properties to changing environmental conditions. If the conditions endure, then the cell has enough time to opt for the synthesis of lipids of different structure. It should be noted that the cell response to stress, short or long term, may vary as a function of the stress experienced. Indeed, while pH, temperature or salinity may vary on the very short term, this cannot be expected in nature for hydrostatic pressure which is a quite stable through time and space.

4. Specific properties of ether-lipid based membranes

Most known Archaea have been isolated from the most extreme environments. It has been suggested that many of their cellular features have adapted to maintain the integrity and form of the cells to resist the extremes in pH, temperature, salinity or pressure experienced in these environments. Indeed, the ether linkages are more chemically stable than esther linkages to oxidation or pH [53,54]. In Archaea, diether lipids organize as bilayer of lipid molecules similar in structure to the bacterial or eukarial membrane. The bipolar nature of the tetraether lipids gave rise to questions about how these molecules were organized in the membrane. It was rapidly demonstrated that tetraether lipids form monolayers in which the molecule is fully stretched and spans the entire membrane thickness. Archaeal lipid membranes have, in general, much lower phase transition temperature than fatty acyl ester lipids [54]. While membranes made of fatty acyl ester lipids are in the gel phase or in the liquid crystalline phase depending mostly on their fatty acid composition, archaeol- and caldarchaeol-based polar lipid membranes of archaea are assumed to be in the liquid crystalline phase at a wide temperature range of 0–100 °C [55,56]. Small phase transitions have been observed in liposomes of *S. acidocaldarius* between 42 °C and 69 °C [57,58]. These phase transitions are associated to very small volume changes, which suggest that the polar headgroup region of the lipid may still be rigid and tightly packed through hydrogen-bond network at elevated temperatures. Archaeal diether lipid based bilayer membranes and tetraether monolayers exhibit a very high thermal stability [59,60]. The monolayer organization of the tetraether lipids provides extreme rigidity to these membranes. Lateral mobility studies of bipolar tetraether lipids from *S. acidocaldarius* [8,61] or *T. acidophilum* [62] demonstrate that lateral diffusion rate under physiological temperature is in the order of 2.10^{-8} cm/s, comparable to those of diacylglycerophospholipids in the liquid crystalline phase at 37 °C for *E. coli*. In contrast to bacterial lipids which exhibit similar lateral diffusion rates for temperatures close to the phase transition temperature, in *T. acidophilum* these values are observed approximately 65 °C above the nominal lipid phase transition temperature [62]. In a similar way, membranes in acidophiles and halophiles demonstrate optimal fluidity and permeability under optimal pH and salinity. The isoprenoid structure of the phytanyl biphytanyl chains of the lipids further increases the rigidity and packing of the lipids in the membrane. As a consequence, the permeability to ions of the archaeal membrane is extremely low under mesophilic conditions. Proton permeability increases with the temperature, and has a comparable value for most species at their respective growth temperatures [63]. This data demonstrate that in agreement with a physiological adaptation of the archaeal membrane to temperature, the properties of the membrane are optimized in Archaea [63]. Similar conclusions were later obtained for pH and salinity [64]. The incorporation of cyclopentane rings along the isoprenoid chains of the lipid will further increase the packing efficiency of the membrane lipids [65,66], which in turn increases membrane stability as a function of increasing temperature or salinity, and decreasing pressure or pH, and consequently lowers the permeability [67]. Interestingly, the proton permeability coefficient in ether based membrane is sufficiently low to explain the maintenance of an intracellular pH gradient of several pH units between the cellular space and the environment in acidophiles [68]. Similarly, the cross linking of the two archaeol isoprenoid chain to yield macrocyclic archaeol diether phospholipids improves the membrane impermeability to water and the membrane stability, probably due to a more closely packed structure [55]. Interestingly, the macrocyclic archaeol and caldarchaeol lipids reduced the water, ammonia, urea, and glycerol permeability of liposomes several folds compared with diphytanylphosphatidylcholine liposomes [53]. Proton permeability of macrocyclic diether and tetraether membranes was equivalent, which clearly indicates that the limited mobility of the midplane hydrocarbon region of the membranes formed by macrocyclic archaeol is similar to that formed by caldarchaeol lipids. These results are in agreement with the observed accumulation of macrocyclic archaeol in the hyperthermophilic methanogen, *M. jannaschii* [28].

It is yet unclear if the ether linkage is or not involved in the regulation of permeability. Experiments with acyl chains linked by ester or ether bounds to glycerols show a reduced permeability of the liposomes composed of ether lipid in comparison with ester lipids [53,69,70]. However, in the context of polyisoprenoid lipids, the ether or ester linkage does not impact significantly the permeability of the structures [68,71]. In contrast to the ester lipid, the ether bond in the ether lipid is located inside the hydrophobic interior of the bi- or monolayer. This will affect the local electronic structure and bring the polar headgroups in closer proximity, reinforcing the electronic interactions and facilitating the packing of the polar headgroup. This may in part explain the impact of ether linkage on the acyl chains [69]. Permeability in the membrane is due to the diffusion by collision of charged molecules that are present in defects or gaps in the structure. The low permeability of archaeal membrane is due for a large part to the tight packing of the phytanyl chains inside the membrane, which limits the penetration of water molecules [68]. However, it is now well established that polar headgroups play an essential role in the regulation of the stability and permeability of the archaeal membranes. For example, the lipids extracted from the acidophile *Pycrophilus oshimae* were incapable to self organize into liposomes for pH above 4, while they form extremely stable and impermeable liposomes at lower pH [72]. These observations contrast with that of the formation of liposomes for lipids of the same core structure isolated from thermophilic Archaea. Repulsive charges of the polar headgroups at high pH may prevent the spatial organization of the lipids from the acidophile. Similarly, in most halophiles, the archaeol based archaetidylglycerol methylphosphate (PGP-Me) is the major membrane lipid. This lipid can form membranes that are stable in multimolar concentrated NaCl solutions, while membranes formed with other archaeol lipids are leaky and unstable [64]. The large polar headgroup of PGP-Me, and possibly its double charge contribute to the low permeability of the membrane under high salt, as well as prevent membrane aggregation. Archaeal lipids demonstrate several adaptations that contribute together to a very low water, proton and ion permeability. This very low permeability of the archaeal membrane is one of the key adaptations of archaea to their environment.

5. Evidence for homeoviscous adaptation in Archaea

There is a body of evidence suggesting that archaeal membrane lipid compositions vary with environmental constraints, and that these variations may be interpreted within the framework of homeoviscous adaptation. The impact of temperature variations on the archaeal membrane composition was first studied in *Sulfolobus solfataricus* (formerly *Caldariella acidophila*) a hyperthermophilic acidophile. The lipids of *S. solfataricus* are limited to bipolar tetraethers of different head groups containing up to 4 cyclopentane rings [73]. The mean number of cyclopentane rings increases from 1.94 to 2.52 from 75 °C to 89 °C (Table 3). Incorporating cyclopentane rings is expected to increase the gel/fluid phase transition temperature of the lipid [65]. Each such cyclization reduces the available modes of movement of the lipids. The increase in cyclopentane rings also affects lipid packing in the

Table 3
Effect of growth temperature, hydrostatic pressure, pH, growth phase and salinity on the composition of archaeal membrane lipids. T_g: growth temperature in °C, P_g: hydrostatic pressure in MPa, pH_g: growth pH, Na_g: growth medium salinity in %. The mean increase of cyclopentane ring is reported per biphytanyl chain.

Species	T_{opt} (°C)	Stress	Range	Mechanism	Reference
Methanococcoides burtonii	23	T_g	4–23	2-Fold increase of the mean number of unsaturation 2-Fold increase of the proportion of unsaturated lipids	[147]
Archaeoglobus fulgidus	83	T_g	70–90	Increase in tetraether over diether lipids from 30 to 90% Increase in the mean number of cyclopentane rings	[13]
Thermococcus kodakarensis	85	T_g	60–93	Increase in tetraether over diether lipids from 34 to 66%	[79]
Methanocaldococcus jannaschii	85	T_g	47–75	Decrease of the tetraether/diether lipid ratio Increased proportion of macrocyclic archaeol	[28]
Sulfolobus solfataricus	87	T_g	75–89	1 unit increase of the mean number of cyclopentane rings	[75]
Thermoplasma acidophilum	59	T_g	40–60	0.5 unit increase of the mean number of cyclopentane rings	[77]
Thermoplasma acidophilum	55	T_g	39–59	0.5 unit increase in the mean number of cyclopentane rings	[76]
Pyrococcus horikoshii	98	T_g	82–103	0.2 unit increase of the mean number of cyclopentane rings	[148,149]
Picrophilus torridus	55	T_g	45–62	0.5 increase of the mean number of cyclopentane rings	[78]
Thermoplasma valcanium	60	T_g	45–62	1.2 units increase of the mean number of cyclopentane rings	[78]
Picrophilus oshimae	55	T_g	45 à 62	0.5 unit increase of the mean number of cyclopentane rings	[78]
Ferroplasma acidophilum	35	T_g	35 à 45	0.2 unit increase in the mean number of cyclopentane rings	[78]
Acidilobus	81	T_g	65–81 °C	0.5 unit increase of the mean number of cyclopentane rings	[150]
Methanocaldococcus jannaschii	85	P_g	0.1–50 MPa	Decrease of the proportion of tetraether and diether from 46 to 36% Increase in the proportion of macrocyclic diether from 36 to 64%	[151]
Thermoplasma acidophilum	59	pH_g	1.2–3.0	1.1 unit increase in the mean number of cyclopentane rings	[81]
Acidilobus sulfurireducens	81	pH_g	3.0–5.0	0.5 unit increase of the mean number of cyclopentane rings	[150]
Thermococcus kodakarensis	85	Growth phase	Log vs. stationary	Increase of the tetraether over diether ratio (mean increase between 20 and 45%)	[79]
Archaeal halophiles		Na_g	1%–10%	Strict correlation between the mean number of unsaturation of the lipids and the optimal salinity	[82]

membrane, further affecting membrane rigidity and membrane compressibility [74]. Similar to what is observed for polyunsaturated phospholipids in bacteria (see above), the impact of the increase in cyclopentane rings on the lipid packing, compressibility and membrane rigidity is not linear. Thus, it has been proposed that an increase in the number of cyclopentane rings is a homeoviscous strategy in archaea to help maintain membrane stability, help cope with the increase in molecule agitation and membrane expansion as the temperature increases [75]. Similar temperature-dependent increase in cyclopentane ring numbers have been reported for several archaeal species (Table 3). In *Thermoplasma acidophilum*, *Picrophilus oshimae* and *P. torridus*, which grow optimally at 55 °C, the mean number of cyclopentane rings increases by ca. 0.5 unit from 39 °C to 60 °C [76–78]. This increase reaches 1.2 units for *Thermoplasma volcanium*,

Table 4
Temperature and pH optima for archaea harboring only tetraether or diether lipds in their membranes.

Genus	Species	pH	T	Ar	CalAr
Species with only bipolar tetraether lipids in their membranes					
Pyrococcus	*woesei*	6	101.5	0	100
Pyrobaculum	*islandicum*	6	95	0	100
Pyrobaculum	*organotrophum*	6	95	0	100
Thermoproteus	*tenax*	5	90	0	100
Desulfurococcus	*mobilis*	5.8	88	0	100
Sulfophobococcus	*zilligii*	7.6	87	0	100
Sulfolobus	*solfataricus*	4	87	0	100
Caldivirga	*maquiligensis*	4	85	0	100
Sulfurisphaera	*ohwakuensis*	2	84	0	100
Metallosphaera	*sedula*	2.8	75	0	100
Caldisphaera	*lagunensis*	4	75	0	100
Thermocladium	*medestius*	4	75	0	100
Aciduliprofundum	*boonei*	4.5	70	0	100
Picrophilus	*oshimae*	0.7	60	0	100
Thermogymnomonas	*acidicola*	3	60	0	100
Thermoplasma	*acidophilum*	1	59	0	100
Thermoplasma	*acidophilum*	2	59	0	100
Species with only diether lipids in their membranes					
Methanococcus	*vannielli*	7.2	25	100	0
Methanolobus	*tindarius*	6.5	25	100	0
Halorubrum	*lacuprofundi*	7.4	25	100	0
Methanococcus	*voltae*	7	35	100	0
Methanosaeta	*concilii*	7.5	35	100	0
Methanosarcina	*barkeri*	7	37	100	0
Methanohalophilus	*mahii*	7.5	37	100	0
Methanosaeta	*soehngenii*	7.5	37	100	0
Methanococcus	*jannaschii*	6	85	100	0
Thermococcus	*barophilus*	7	85	100	0
Thermococcus	*celer*	5.8	88	100	0
Aeropyrum	*pernix*	7	90	100	0
Methanopyrus	*kandleri*	6.5	97	100	0
Pyrococcus	sp. *4557*	7	98	100	0

which optimal growth temperature is 60 °C, but is only of 0.2 units for *Ferroplasma acidophilum* which optimum is the lowest at 35 °C. This data suggests that the mean increase in number of cyclopentane rings per degree increases with the optimal growth temperature of the studied strain. Although tempting, this trend has not yet been confirmed for other archaeal families. Alternatively, since *F. acidophilum* has a very narrow range of temperatures suitable for cultivation (35–45 °C), it could be interpreted as the consequence of its inability to adapt its membrane lipid composition with the increasing temperature.

In archaea harboring mixed diphytanyl diether and dibiphytanyl tetraether lipids, the tetraether-to-diether lipid ratio has been shown to vary with growth temperature [13,28,79]. In *Archaeoglobus fulgidus* the tetraether to diether core lipid ratio increases from 0.3 for cells grown at 70 °C to 0.9 for cells grown at 89 °C. It is expected that the increase in the tetraether lipid will stabilize the membranes by forming monolayer-type membranes or domains in the membrane. The presence of tetraether lipids will also help regulate the flux of solutes and proton across the membrane (see above). This putative homeoviscous adaptation strategy is not limited to *Archaeoglobus*, since in the *Thermococcales* species *Thermococcus kodakarensis*, the tetraether lipid composition of cells in the exponential phase is also shifted up with increasing temperature from 36% at 60 °C to 66% at 93 °C [79]. It is thus very probable that the homeoviscous adaptation in archaea harboring mixed C20–C40 membrane lipids will involve the regulation of the ratio of these lipids to accommodate with the variations in temperature. Variations of the tetraether/diether ratio are observed in the hyperthermophilic methanogen *M. jannaschii*. In this later strain, tetraether proportion was shown to decrease with temperature rather than increase. However, the lipid composition of that strain is abruptly shifted towards another type of membrane lipid, the macrocyclic derivative of archaeol (Fig. 1B). This increase in macrocyclic archaeol proportions constitutes the third homeoviscous adaptive mechanism existing in Archaea. It has been shown that the covalent bound between the two free ends of the isoprenoid chains of the archaeol in macrocyclic archaeol reduces the motion of the molecule drastically, to values close to that observed for tetraether lipids [55]. In addition, macrocyclic archaeol has been demonstrated to be an efficient barrier against proton and solute leakage under high temperature. Thus, increasing the proportion of macrocyclic archaeol is expected to have similar impacts on membrane stability and permeability as an increase in the tetraether/diether ratio.

A single example study of cold adaptation in archaea performed on the methanogen *Methanococcoides burtonii* has shown that homeoviscous adaptation may proceed along a fourth route. *M. burtonii* is the first archaeal eurypsychrophile described with a relative broad growth temperature range (−2.5 to 29 °C) and an optimal growth temperature of 25 °C. It has been isolated from cold (2 °C), anaerobic, methane saturated waters from the Antarctic Ace Lake lake [15]. Membrane of *M. burtonii* contains 4 different diether lipids with a phosphatidylinositol (PI) or a phosphatidylglycerol (PG) polar head. The archaeol core lipid may contain a hydroxyl group (Ar-OH) at position C-3 of the isoprenoid chain on the *sn*−3 position of the glycerol backbone. In addition, these lipids are polyunsaturated with up to 5 unsaturations, although the unsaturation pattern is not fully known. Under a decrease in temperature from 23 °C to 4 °C, the mean number of unsaturation per lipid molecule is increasing almost two-fold, regardless of the lipid core (ArPI, ArPG, Ar-OHPI, Ar-OHPG). Thus the strategy adopted by *M. burtonii* is similar to that adopted by many psychrophilic bacteria [44]. It is noteworthy that the presence of the hydroxyl group is also likely to modify the properties of the lipid in the membrane and contribute to increased fluidity. Indeed, the presence of the hydroxyl group in close proximity to the head group might increase the surface area and shorten the chain length [80]. Chain-length regulation is a common homeoviscous adaptive strategy in bacteria, in which a reduction in length is associated with increase membrane fluidity.

Membrane lipid composition in archaea not only varies with temperature conditions for growth. Shifting conditions of pressure induce essentially the same cellular response in *M. jannaschii*. The proportion of tetra ether decreases from 46 to 36% when the cells are grown under 50 MPa. Macrocyclic archaeol is the most abundant lipid in this organism under shifting pressure and temperature conditions. Concomitantly, there is an increase of macrocyclic diether from 36 to 64%. Membrane lipid composition has also been shown to vary substantially in *T. acidophilum* as a response to pH increase. In this strain, at the growth temperature 55 °C, each caldarchaeol molecule contains 5.1 cyclopentane rings at pH 3.0, 4.8 rings at pH 2.4, 4.1 rings at pH 1.8 and 4.0 at pH 1.2 [81]. This increase of cyclopentane rings in the tetraether lipids mirrors that observed for an increase in temperature (0.5 unit for 20 °C increase).

Due to the very few studies that have addressed this issue it is very unlikely that the range of homeoviscous adaptive strategies in archaea is limited to the few described above. In addition, one should note that these strategies are not mutually exclusive. As mentioned above, the hyperthermophilic methanogenic archaeon, *M. jannaschii*, controls both the proportions of its various di- and tetraether lipids, but also the degree of cyclization of its archaeol derivatives in response to temperature and hydrostatic pressure variations. It should be also noted that *M. jannaschii* accumulates more non-polar lipids such as lycopene-type hydrocarbons at high temperature, e.g. 14% of total lipids at 75 °C, vs. 9% at 44 °C [28]. In *A. fulgidus*, the drastic variation of the tetraether/diether ratio observed with a shift from 70 °C to 90 °C is accompanied by the increase of the mean number of cyclopentane rings in the tetraether lipids from 1 to 2 cycles. Lastly, although not yet formally demonstrated experimentally, there is a strong possibility that archaea can regulate membrane composition in response to fluctuation of salinity. Indeed, in mesophilic and halophilic archaea there is a strict correlation between the mean number of lipid unsaturation and the optimal salinity of the species tested [82].

6. The limits of homeoviscous adaptation in the Archaea

The above data strongly supports the existence of homeoviscous adaptation in the ether lipid-based membrane of Archaea in response to environmental conditions. Mechanistically, the archaeal homeoviscous adaptation resembles in part that of bacteria and eucarya, e.g. the regulation of the unsaturation level of membrane lipids in the psychrophile *Methanobacterium burtonii*. Other mechanisms are specific to Archaea because their specificity takes root in the nature of the archaeal lipids, e.g. the existence of bipolar ether-linked transmembrane lipids. All lipid composition fluctuations presented above can be explained within the framework of homeoviscous adaptation taken sensu largo to include the regulation of membrane permeability. Yet, when one considers the lipid compositions of the different archaeal species (Table 1), several membrane lipid compositions may prove more difficult to interpret within this framework. We will use here four examples to illustrate this point.

Tetraether synthesizing archaea have been shown to regulate the number of the cyclopentane rings in their tetraether as a function of temperature or pH. The range of the increase is dependent of the strain tested, but there is so for too few studies available to determine a possible trend. Archaea that have cyclopentane ring containing tetraethers may grow over a large range of temperature, e.g. from 59 °C for the thermoacidophile *T. acidophilum* to 100 °C for *Hyperthermus butylicus* (Table 1) and a large range of pH, from 0.7 for *Picrophilus acidophilum* to 7 for *H. butylicus*. Despite the observation of a temperature or pH induced increase in the number of cyclopentane rings, it is difficult to determine a correlation between the number of ring and the temperature or pH, considered separately or in conjunction. For example, *H. butylicus*, which optimal growth temperature is 100 °C, was shown to accumulate up to 2 cyclopentane rings, while others such as *S. solfataricus* will accumulate lipids with up to 6 rings when growing

optimally at 87 °C. It is noteworthy that the difference between the lipid composition of these two species is actually more important than that observed in a given species to compensate a similar difference of temperature ($\Delta T = 20$ °C, Table 3). Overall, the composition in tetraether lipids seems to reflect the speciation of the organism, e.g. its position in the taxonomic tree, rather than its optimal growth characteristics. This later view is supported by several reports on the presence of tetraether with or without cyclopentane rings in mesophilic and cold environments and cold-adapted archaea, and especially from marine environments [83]. The number or cyclopentane rings reported is in the same order, e.g. up to 4 cyclopentane rings, as those observed for many hyperthermophiles or thermoacidophiles. This composition would predict a very stable, but fairly rigid, and impermeable membrane. Thus it is not clear, how membrane viscosity is regulated in these low temperature-adapted organisms.

Similar conclusions can be drawn from the comparison of the growth optima of archaea that are able to synthesize a single type of ether lipid, either di- or tetra ether (Table 4). Most of the species synthesizing only tetraether lipids are thermophiles. Hyperthermophiles with optimal growth close to neutral pH have an optimal growth temperature between 87 and 101.5 °C, while thermoacidophiles have an optimal growth temperature which is closely related to their optimal pH for growth ranging from ca. 60 °C for strain growing at pH 1 to ca 85 °C for strain growing at pH 4. As discussed above, bipolar tetraether lipid based membranes exhibit both a low permeability and viscosity at high temperature and low pH, which itself can explain the lipid composition exhibited by these archaea. With the combined impact of temperature and pH, the lower temperature optima exhibited by the thermoacidophiles are in good agreement with the homeoviscous concepts. However, considering the diversity of Archaea only able to synthesize monopolar diether lipids, one can see two populations exhibiting divergent temperature optima: the first set is mesophile, composed essentially of methanogens and halophiles (represented in Table 4 by *Halorubrum lacusprofundi*) with optima ranging from 25 to 37 °C, and the second is hyperthermophilic with optima ranging from 85 to 98 °C. Halophiles synthesize a mixture of C20–C20 and C20–C25 ether lipids with a particular polar headgroup (discussed below). *M. jannaschii*, which synthesize a macrocyclic derivative of archaeol (discussed above). All other species synthesize archaeol. Archaeol, the C20–C25, or the C25–C25 diether lipids define membrane with higher permeability and fluidity at low temperature than tetraether lipids, which justifies their synthesis in mesophiles. It is more difficult to explain archaeol-based membranes in hyperthermophiles within the framework of the homeoviscous adaptation. It is clear here that the lipid composition in these organisms is linked to their taxonomic position as is observed with cyclic tetraether lipids, and that other yet undetermined factors are explaining the compatibility of the lipid composition with the optimal growth parameters.

If there is a correlation between the phylogenetic position and the membrane lipid composition, related organisms may exhibit a large diversity of lipid composition when grown in the same conditions, e.g. in the same medium, at the same pH and at the same temperature [84]. Archaea from the *Thermococcales* were all isolated from hydrothermal systems, and exhibit very close physico-chemical growth requirements. Most *Thermococcus* species have growth temperature optima close to 85 °C, while *Pyrococcus* usually growth at temperature close to 100 °C. It has long been known that *Thermococcales* could synthesize both di- and tetraether lipids [31,85–87]. As discussed above, homeoviscous adaptation in this group involves the regulation of the ratio of these two lipid types [79]. However, species of this group exhibit a large range of lipid compositions (Table 5). Among the 17 strains tested, most strains synthesized archaeol and caldarchaeol, but 4 also synthesized an H-shaped caldarchaeol derivative [84]. The proportion of di-ether ranged from 42.1% in *T. aggregans* to 5.9% in *P. horikoshii*, while the proportion of H-shaped caldarchaeol reached 48.9% in *T. waiotapuensis*. Once again, it is striking that the variations observed in this group of phylogenetically related organisms grown in the same conditions are larger than those evidenced upon thermal, pH or high pressure treatment. In this study polar headgroups were not analyzed so it is not possible to know whether their proportions were different. However, the known structure of these polar headgroups is very similar for all these species, so the basis for the observed differences remains unclear and difficult to interpret with this set of data within the scope of the homeoviscous adaptation. Along the same line of reasoning, it should be noted that some archaea also produce tetraether lipids called GDNT in which the glycerol backbone present on one side of the molecule is condensed to a C6 sugar to form a nonitol moiety [88]. Although there is no evidence that GDNT might be produced in *Thermococcales*, it makes little doubt that the nonitol moiety, and the regulation of the proportion of such lipids, will also be involved in homeoviscous adaptation in species able to synthesize them.

Lastly, another interesting archaeal lipid is the novel tetraether containing four cyclopentane rings and one cyclohexane ring, named crenarchaeol, which has been found exclusively in crenarchaea, and especially in marine planktonic cells [89,90]. These environments have very low temperature, ca 1–2 °C in average. Thus it is quite difficult to understand why such low-temperature adapted organisms would form membrane with lipids containing 5 cycles. Molecular dynamics simulations suggested a possible explanation to this paradox, by showing that the cyclohexane ring decreases membrane density, which could be a cold adaptation strategy. The molecular basis for the different behavior between cyclopentane and cyclohexane rings remains to be elucidated and the role in cold adaptation remains to be confirmed experimentally. The later discovery of the predominance of crenarchaeol in hot spring craenarchaea would argue against such a mechanism, and rather favor the synthesis of crenarchaeol as a crenarchaea specific lipid [91,92] as mentioned for other Archaea.

In the results presented above, we have shown that Archaea may regulate their membrane lipid composition as a function of temperature, hydrostatic pressure or pH fluctuations. Similar to what was observed for bacteria, it was also shown that the lipid composition of Archaea may vary with the carbon source, but somewhat marginally [30]. Similarly, it is not so surprising to find that membrane lipid composition may vary with the growth phase of the cell, whether they are in the exponential phase, e.g. with cells replicating at their quickest, or whether they are in stationary phase, e.g. with cells in replicative and metabolic rest. What is more surprising is the impact of the growth phase on the lipid composition reported for the hyperthermophilic archaeon *T. kodakarensis* [79]. In this archaeon, only fully saturated archaeol and caldarchaeol are synthesized. The proportion of the tetraether caldarchaeol increases with temperature from 34% at 60 °C to 66.1% at 93 °C in cells in exponential growth, which in

Table 5
Membrane lipid composition of *Thermococcales* species grown at 85 °C [84].

Genus	Species	C20	C40	H-C80
Thermococcus	*barophilus*	100	0	
Thermococcus	*aggregans*	42.1	57.9	
Thermococcus	*zilligii*	33.2	66.8	
Pyrococcus	*furiosus*	31.2	68.8	
Thermococcus	*fumicolans*	27.3	72.7	
Thermococcus	*aegeus*	27.2	72.8	
Thermococcus	*litoralis*	26.8	73.2	
Pyrococcus	*woesei*	26.5	73.5	
Thermococcus	*pacificus*	25.4	74.6	
Thermococcus	*gorgonarius*	16.8	83.2	
Thermococcus	*profundus*	16	84	
Thermococcus	*peptonophilus*	14.3	85.7	
Palaeococcus	*ferrophilus*	12.2	87.8	
Thermococcus	*stetteri*	9.6	90.4	
Thermococcus	*guaymasensis*	12.7	75.3	12
Thermococcus	*celer*	38.8	45.7	15.5
Pyrococcus	*horikoshii*	5.9	60.1	34
Thermococcus	*waiotapuensis*	15.2	35.9	48.9

agreement with the regulation of the viscosity and permeability of the membrane with increasing temperature. The proportion of caldarchaeol is however much higher in stationary phase cells especially at high temperature, e.g. 50.9% vs. 34% and 84.9% vs. 66.1% at 60 °C and 93 °C, respectively. In cells growing under optimal conditions (85 °C), the cells increase their caldarchaeol proportion from 58.8% to 82.3%. While a caldarchaeol proportion in the order of 80% is quite typical of other thermophilic Archaea (Table 1), and especially other Thermococcales which optimal growth temperatures are close or higher than 85 °C, proportions in the order of 60% are typical of mesophilic methanogen such as *Methanobacterium ruminatium* or *Methanospirillum hungatei* which have been shown to harbor also only saturated archaeol and caldarchaeol lipids. Thus, during growth at 85 °C, the fluidity of the *T. kodakarensis* cell membrane will be substantially more fluid and permeable to water, proton, and ions in general. These observations may be interpreted in two different ways, whether one takes the lipid composition in the stationary or exponential phase as a reference. First, it may be an increase in membrane fluidity in the exponential required by the cell to ensure growth of the cell, e.g. synthesize novel membrane and divide. Second, it may be a decrease in membrane fluidity required by the cell in stationary phase to reduce membrane permeability along with the reduction of the metabolic activity of the cells. Both hypotheses make sense in terms of cellular physiology. However, these results point out to a possible difficulty in interpreting the lipid data available to date in terms of adaptation if membrane fluidity and permeability varies during the cell cycle on a larger scale than during environmental condition fluctuations.

7. The archaeal membrane and cell wall

It has long been believed that Archaea were only inhabiting extreme environments. Their ability to endure extremely harsh and hostile conditions has intrigued researchers to decipher the molecular basis of this adaptation. It was clear at the early stages that archaeal membrane differed from that of bacteria not only in their membrane lipids as discussed above, but also in the fact that Archaea, to the exception of the genus *Ignicoccus*, have only a single cytoplasmic membrane, which is itself literally enclosed in an outer protein matrix, the S-layer [93]. *Ignicoccus* is an exception among Archaea in several other aspects, noticeably because it is living in symbiotic association with another archaeon, *Nanobacterium equitans* [94,95]. In other Archaea the S-layer is basically a two-dimensional crystal structure, which defines a periplasmic-like environment around the archaeal cell (Fig. 2). For further details, a very detailed review on cell structure of archaea in comparison to bacterial cell structure has been recently published [96]. Another peculiarity of archaeal membrane protein is that most are glycosylated via N- of O-glycosylation. The assembly of this extracellular structure begins to be quite well understood. This structure shapes the cell and strengthens it. It also isolates the cell from the environment and defines a pseudo-periplasmic space, which may function as a buffering space for the cytoplasmic membrane [97]. Thus the chemical composition of the pseudo-periplasmic space will likely differ substantially from the outside, and the membrane lipids may not experience the full draft of the hostile conditions and their fluctuations. In addition, it is probable that the presence and the anchorage of the S-layer in the cytoplasmic membrane will influence the behavior of membrane lipids. The anchorage of the S-layer is expected to involve a significant fraction of the lipids of the membrane, which will depend between archaeal species. Since lipids interacting with membrane proteins have a slower motion than those that are not in contact with proteins, this may impact membrane properties significantly [42]. Furthermore, depending on the length of the transmembrane domain, the presence of the protein may induce substantial spatial perturbation in the membrane, increase or decrease the thickness of the membrane and packing of the lipids, which in turn will influence the proton and solute permeability at the protein–lipid contact [42]. Detailed studies of the pressure and temperature behavior of archaeal envelopes would therefore be crucial to address these questions.

As discussed above, very few archaea produce only either diether or tetraether polar lipids. In fact, the large majority of archaea have both di- and tetra-ether polar lipids in various proportions, which may vary

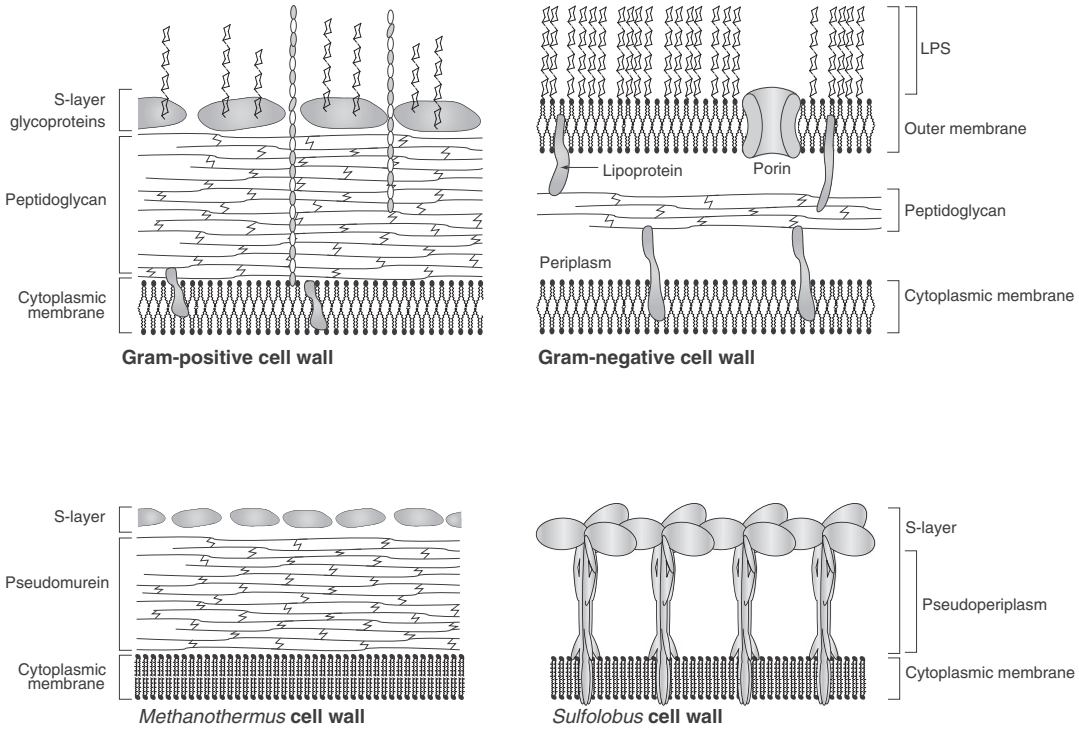

Fig. 2. Schematic view of cell wall profiles from *Methanothermus* and *Sulfolobus* in comparison with bacterial Gram-positive and Gram-negative cell walls. Redrawn from Albers et al. [96].

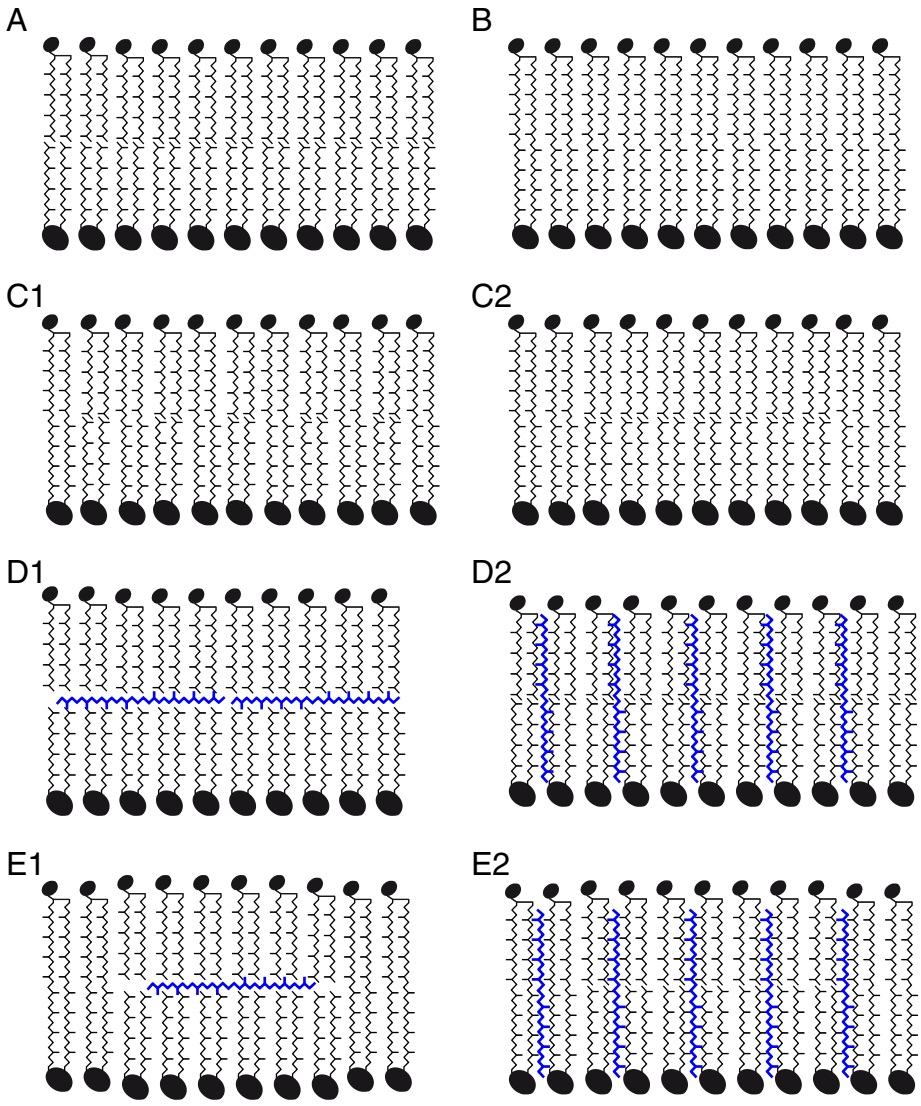

Fig. 3. Schematic views of archaeal membrane composed of di-ether (A1, C1, C2), tetraether (A2) or combinations of di- and tetraether lipids (B1, B2, C3, C4). The position of lycopene-type hycrocarbon molecules (in blue) is shown in the midplane of the bilayer (C1, C3) as seen in bacterial halophiles, or parallel to the isoprenoid chains (C2, C4) as seen for sterols in bacteria and eucarya.

with environmental conditions fluctuations or growth phase. There is to date a lot of uncertainties with regards to the spatial organization of these lipids and how the archaeal membrane is spatially organized. Membrane lipids can be organized as a fully mitigated population (Fig. 3C1) or in separate domains (Fig. 3C2). This spatial organization in the membrane may have a great impact on the properties of the membrane, as is observed in bacteria which maintain membranes with domains in different, gel and fluid, phases. There is little doubt that these domains have both a regulatory function on the protein activity and an impact on membrane fluidity and permeability. It is therefore clearly crucial to determine how lipids are organized in an archaeal membrane in which transmembrane tetraether lipids can form monolayers and diether lipids can form monolayers. It will be also interesting to determine whether the behavior of a fully mitigated membrane (Fig. 3C1) differs substantially from that of the spatially organized one (Fig. 3C2), and if this differs from the behavior of membranes composed of a single lipid type (Fig. 3A and B). In bacteria, lipids in contact with membrane protein transmembrane domains have a mean composition identical to that of the membrane harboring the protein. It would be interesting to determine whether this is also observed for monolayer forming tetraether lipid and characterize the impact of the di- and tetraether lipids on membrane protein activities.

The existence of hyperthermophilic isolates only able to synthesize di-ether lipids is also of concern, because the stability and permeability of di-ether based membranes are supposed to be more suited for mesophiles. As a first approximation, proton leakage across the cytoplasmic membrane can be considered to result from the transfer of oppositely charged particles situated across the two sides of the membrane bilayer [98]. Permeability is essentially due to the presence of water molecules at low level inside the hydrophobic core of the lipid bilayer, in defects of the structure. Thus, permeability increases with temperature, and the increase in molecule motion. Transbilayer proton leakage can be reduced if the transfer of particles across the two sides of the bilayer can be reduced. One option is to reduce the amount of water entering the bilayer. In bacteria and eucarya, sterols, by crowding the hydrophobic interior of the bilayer, play this role and strongly reduce the permeability of the membrane. Another option is to pack the center of the bilayer with hydrocarbon molecules to create a physical barrier to the transfer of charges across the bilayer. The presence of terminally branched fatty acid chains in several bacterial species is expected to create a bilayer with an increased hydrocarbon density at its center. Similarly, the presence of lipophilic hydrocarbon molecules that would reside in the cleavage plane of the bilayer would inhibit charge transfer [98]. Among such putative molecules, polyisoprenoid hydrocarbons, such as squalene or

lycopene, would be very suitable, since their many lateral branches would stabilize them within the cleavage of the bilayer, without disturbing the cooperativity of the fatty acid chains of each monolayer. Polyisoprenes are present in significant amounts in the membranes of alkaliphile bacteria, where they may account for up to 40% of the lipids [99]. Using neutron diffraction on bilayers of dioleoyl phosphatidyl choline (DOPC) doped with dioleoyl phosphatidyl glycerol (DOPG) into which 10% perdeuterated squalane had been incorporated, Haußß and colleagues could clearly show that the squalane lies predominantly in the bilayer center, parallel to the plane of the membrane [100]. The presence of squalene in the midplane has two consequences: a decrease in proton and water permeability and an increased in membrane rigidity. Squalene/lycopene-type poly-isoprenoid hydrocarbons are synthesized by several species of Archaea, especially species that produce di-ether lipids [28–30,85]. These isoprenoid hydrocarbons have between 15 and 50 carbons in length, with the majority ca. 30–40 carbons. These hydrocarbons are not synthesized by the same pathway as the core lipids. Lycopenes have been shown to represent a significant proportion of lipids in hyperthermophilic archaea that synthesize little or no tetra ether lipids, such as the methanogenic archaeon *Methanococcus jannaschii* and several species of the *Thermococcales* [85]. Their synthesis in diverse archaea strongly suggests a possible role in membrane structure, similar to that observed for sterols in eucaryotes and poly-isoprenoids in bacterial alkaliphiles. Their length is compatible with an insertion in parallel to the core lipid isoprenoid chains in monolayers formed by tetraether lipids (Fig. 3D2 and E2). In accordance to what is observed in alkaliphiles they can also insert in the midplane of bilayer membranes or in the midplane of bilayer domains in membranes composed of mixed di- and tetraether lipids (Fig. 3D1 and E1). Lanyi and colleagues have demonstrated that the addition of squalene to liposomes decreased the viscosity of the structures [101]. If a lycopene derivative is present in the midplane of archaeol bilayers in hyperthermophilic archaea such as *Pyrococcus* sp. 4557, it could help explain the apparent discrepancy between the membrane lipid composition based on di-ether lipids and the extreme tolerance to temperature they exhibit, e.g. maximal growth temperature close or over 100 °C. In acidophiles, lycopenes in the midplane of the bilayer could participate in the maintenance of the extreme pH gradient observed between the intracellular space and the environment, which is often superior to 4 pH units.

8. Conclusions

There is conclusive evidence that archaea use mechanisms resembling the homeoviscous adaptation observed in bacteria and eucarya. When these latter essentially regulate the length and the saturation level of their lipid chains to regulate membrane fluidity, archaea because of their specific lipids have to adopt different strategies, e.g. the incorporation of cyclopentane rings into the isoprenoid chains or the modification of the proportions of diether vs. tetraether lipids. Despite these differences, the impact on membrane behavior is essentially the same, to regulate the packing of lipids as a function of fluctuations in temperature, or other environmental parameters. Homeoviscous adaptation offers a convenient and simple conceptualization to explain the variations of the composition of membrane lipids. Several aspects remain difficult to explain within this framework though. The most puzzling are linked to the composition in tetraether lipids of Archaea. These lipids form extremely rigid, packed and impermeable structures, which fit in the membranes of hyperthermophilic archaea from which they were first isolated. Yet these tetraether lipids are common in many mesophilic, and psychrophilic archaea, and are also abundant in samples of low-temperature environments, although it is difficult to understand why these low-temperature adapted microbes would incorporate these lipids in their membranes. Conversely, numerous hyperthermophilic archaea often capable of growth over 100 °C do not have tetraether lipids in their membranes. Rather than suggesting that homeoviscous adaptation does not exist in Archaea, it suggests that we may have overlooked important parameters taking part in the adaptation of the Archaeal membrane in response to stress. Among these, four seem to be able to influence the behavior of the membrane: (1) The S-layer: archaeal cells are encased in a 2D protein matrix, anchored in the membrane which defines a pseudoperiplasm space around the cell, but which influence on membrane dynamics has not yet been evaluated; (2) The spatial organization of lipids in the membrane, especially in those composed of a mix of di- and tetraethers may influence local membrane dynamics; (3) The presence of nonpolar membrane lipids, such as lycopene-type poly-soprenoid hydrocarbons, in the structure of the membrane may modify substantially the behavior of the membrane, in a similar way that the presence of sterols in bacteria and eucarya modify the fluidity and biological function of membranes. (4) The nature of polar headgroups. The few examples presented above show that similar core lipids may demonstrate drastically divergent properties when linked to different polar headgroups. There is a need to obtain precise descriptions of these polar headgroups and the relative proportions and structures of the lipids. Keeping in mind that lipid compositions in Archaea are strongly influenced by growth conditions, future research to address these questions will require the close cooperation between the biophysicists who can described the behavior of the biological systems at the molecular level, the biochemist who can provide detailed analyses of the composition of the membrane lipids and the microbiologists who can provide control on the cell cycle of the model organisms and prepare biological significant material.

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