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Editorial: The methane moment - Cross-boundary significance of methanogens: Preface

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Editorial on the Research Topic

[The methane moment - Cross-boundary significance of methanogens](#)

Introduction

Methanogens are anaerobic methane-producing archaea that derive energy from methanogenesis, a biological process responsible for most global methane emissions. Because methane is a potent greenhouse gas and a high-energy fuel, methanogens could help solve the dual challenge humanity is facing—climate change and energy shortage (Buan, 2018). On the one hand, mitigating methane emissions is a high priority in tackling global warming and climate change. On the other hand, promoting methane production in well-controlled environments such as waste digesters convert waste into high purity methane as a sustainable biofuel.

There are also good reasons to believe that the significance of methanogens would extend beyond climate and energy. For example, methanogens were one of the earliest life forms on Earth, they have evolved enormous diversity for ~3.5 billion years (Wolfe and Fournier, 2018), they possess many essential genes uniquely shared between archaea and eukaryotes (Lyu and Whitman, 2017), and they are now collectively distributed in a wide range of ecosystems—on the land, in the oceans, across extreme environments (Liu and Whitman, 2008), closely associated with humans, animals, and plants (Borrel et al., 2020), and even adapted to oxic niches (Lyu and Lu, 2018). A good understanding and translation of their functions across the biosphere will unravel the untapped

cross-boundary significance of methanogens relevant to the environment, energy, agriculture, biotechnology, and health and disease of humans, animals, and plants.

Therefore, we have formed a guest editorial team with diverse expertise in microbiology, environmental science, biotechnology, and medicine to bring forward this new Frontiers Research Topic “*The Methane Moment—Cross-boundary Significance of Methanogens*” (Lyu et al., 2022). To showcase methanogen-relevant research across multiple disciplines, this topic is cross listed with 3 Frontiers journals and 6 sections. To facilitate the discussion of this topic, our editorial team presents here a preface article envisaging, within our expertise, the significance of methanogens in diverse settings.

Evolution of methanogens and methanogenesis

While the origin of methanogens and their ancestral pathway of methanogenesis is debatable, modern methanogens operate five unique pathways: CO₂-reducing, aceticlastic, methylotrophic (Lyu et al., 2018b), methoxytrophic (Mayumi et al., 2016) and alkylotrophic (Zhou et al., 2022). All the pathways use a methyl-coenzyme M reductase complex (MCR) to catalyze the final step of methanogenesis. MCR homologs are also shown to be involved in anaerobic methanotrophy and alkane metabolism (Laso-Perez et al., 2016; Borrel et al., 2019). Previously, it was reported that methanogens were classified into two distantly related groups within the phylum Euryarchaeota (Baptiste et al., 2005; Borrel et al., 2016). In recent years, genomic and sequencing analysis has proposed many novel methanogens outside Euryarchaeota, expanding the diversity of methanogens and methanogen-like archaea (Baker et al., 2020). For example, Korarchaeota, Thaumarchaeota, Verstraetearchaeota, and Nezharchaeota, also contain MCRs, suggesting that they have the potential of methanogenesis (Wang et al., 2019). Bathyarchaeota, Hadesarchaea, and Helarchaeota contain alkyl-coenzyme M reductase complex (ACR), enzymes that are similar to MCR but activate alkanes instead (Seitz et al., 2019).

The findings of MCR and ACR in non-Euryarchaeota challenged the hypothesis that methanogenesis originated from Euryarchaeota, suggesting a more complex evolutionary history of methanogens (Garcia et al., 2022). Some studies suggested that the hydrogen-dependent CO₂-reducing (hydrogenotrophic) methanogenesis may be the ancestral form of biological methane production and methanogens evolved from hydrogenotrophic to methylotrophic methanogenesis (Berghuis et al., 2019). Others suggested that hydrogen-dependent methylotrophic methanogenesis was the ancestral form and hydrogenotrophic methanogenesis developed later by phylogenetic analysis of methanogens based on concatenated ribosomal proteins and on functional proteins (Wang et al., 2021). Further studies on

the origin, evolution, and ecophysiology of methanogens will be instrumental in understanding their adaptation across the biosphere and their cross-boundary significance thereof.

Significance in the global carbon cycle

As part of the Earth’s ‘biogeochemical engine,’ methanogens transform annually 2% of the ~70 Gt global net primary production carbon into ~1 Gt of methane, of which ~60% is oxidized by methane oxidizers. The remaining ~0.4 Gt escapes into the atmosphere, accounting for ~70% of the global methane emission (Thauer et al., 2010). Notably, this well-established model does not consider that biological methane emission can also occur in non-methanogens which may encompass all living organisms including plants, fungi, algae, bacteria, archaea, and human cells (Günthel et al., 2019; Bižić et al., 2020; Ernst et al., 2022). Non-methanogens do not produce methane via methanogenesis where substrates are stoichiometrically converted into methane for energy conservation. Instead, their methane appears to be a metabolic byproduct likely derived from methyl radicals induced by reactive oxygen species under oxic conditions. Consequently, the observed methane yield in non-methanogens is extremely unstable and varies in the range of sub-attomole to micromole per gram of dry cellular weight (Ernst et al., 2022), dwarfed by typical methanogens yielding at the mole level (Thauer et al., 2008). Moreover, methanogens predominate all the major methane-emitting habitats such as ruminants and rice fields (see below). Therefore, while it is of significance to develop a quantitative global model for the elusive methane emissions from non-methanogens, methanogens remain the most potent biological methane producer and the top contributor to the global methane emission.

Abiotic sources such as mining and combustion of fossil fuel and biomass burning contribute to ~30% of the global methane emission (Conrad, 2009; Rosentreter et al., 2021). Since the industrial revolution, the atmospheric methane has almost tripled from ~700 to an alarming ~1900 ppb, contributing substantially to global warming and climate change (Earth Org, 2022). The increase in abiotic emission is almost exclusively human-induced, while a large share of that increase in biological emission is also anthropogenic (Conrad, 2009). About 40% of the biological methane come from methanogens in the ruminants and rice fields for producing meat, milk, and rice, and another ~16% from methanogens in landfills and sewage treatment facilities (Lyu et al., 2018b). As the world population continues to grow, food consumption and waste disposal will inevitably increase, fueling more methane emissions. This creates a nexus of heated conflicts between global warming, food and agriculture security, and waste management. To add insult to injury, biological emission from at least certain natural sources such as tropical wetlands may have entered a positive feedback loop (Voosen, 2022). In these wetlands,

elevated methane emission makes climate warmer and wetter which in turn fuels more methane emission. This is of immense concern, as wetlands are a top habitat for methanogens and the single largest natural source of methane emission, responsible for emitting ~ 0.15 Gt of methane annually (Lyu et al., 2018b; Rosentreter et al., 2021).

Significance in environmental microbiome

Methanogens proliferate in natural and engineered habitats limited in typical electron acceptors (O_2 , nitrate, or sulfate), such as deep subsurface environments (Underwood et al., 2022), intestinal tracts of animals and insects (Borrel et al., 2020), and anaerobic digestors for residential and industrial waste treatment (Vítězová et al., 2020; De Bernardini et al., 2022). Here, methanogens act as a terminal electron sink driving anaerobic oxidation of organic matter to completion. Specifically, methanogens syntrophically couple their reductive metabolism with bacterial partners' oxidative metabolism via indirect or direct electron transfers facilitated by H_2 /formate (Schink, 1997), conductive mineral grains like iron-oxides or activated carbon (Rotaru et al., 2018), or electron-carrying cell surface molecules such as multiheme c-type cytochromes (Rotaru et al., 2021).

A general assumption is that the thermodynamically more efficient respiratory bacteria such as nitrate and sulfate reducers would competitively displace methanogens in habitats where typical electron acceptors are abundant. However, that is not always the case. For example, in oxic and sulfate-rich seagrass meadows, methylotrophic methanogens occupied an unconventional niche via demethylation of compounds like betaine, an osmolyte of seagrasses (Schorn et al., 2022). This unconventional niche may even harbor novel methanogens or methanogen-like archaea, evidenced by the presence of *Ca.* Helarchaeota metagenomes encoding the *mcrA* (Schorn et al., 2022). Other unconventional niches include steel structures suffering corrosion (Lahme et al., 2021), and electrode materials for bio-electricity generation (Aryal et al., 2022). These examples highlight the robustness of methanogens in adapting to a wide range of habitats. Regardless of the habitats, a key to the proliferation of methanogens is to obtain electrons from their surrounding microbiome. Further studies on this electron exchange process will contribute to a functional assessment of the overall electron flow in environmental microbiomes. This has implications for methane mitigation, biofuel production, and ecosystem stability.

Significance in human health and beyond

Methanogens in human health and disease have a complicated story. While detection of gut-derived methane

in human breath was first studied in the 1970's (Bond et al., 1971), it was initially believed that methanogens and methane production had no physiological consequence. However, it is now known that methanogens colonize the gastrointestinal tract commonly but when they do so more prominently, they can be associated with human disease. The strongest relationship is with constipation (Triantafyllou et al., 2014). The presence of methane is not only associated with constipation, it is proportional to the amount of methane and studies of intestinal physiology point to methane as the cause and perhaps even as a potential gasotransmitter (Pimentel et al., 2006; Wang, 2014). Studies go on to identify the main human gut methanogen as *Methanobrevibacter* spp. (Kim et al., 2012), and other notable gut methanogens also belong to *Methanosphaera* spp. and *Methanomassiliicoccales* (Hoegenauer et al., 2022).

While typically associated with constipation, gut methanogens and methane is linked to other conditions including obesity. In an elegant study using germ free animals, methanogens promoted obesity when animals were co-colonized with *Bacteroides thetaiotamicron* demonstrating that methanogens are dependent on syntrophic bacteria (Samuel et al., 2007). Work in obesity suggests that methanogens are associated with higher body-mass-index in obesity and their presence may also predict a less ideal outcome for weight loss after bariatric surgery (Basseri et al., 2012; Mathur et al., 2016). Beyond the gut, oral methanogens are strongly associated with polymicrobial oral infections such as periodontitis (Lepp et al., 2004; Horz and Conrads, 2011), while the gut methanogen *Methanobrevibacter smithii* could produce 2-hydroxypyridine that might drive Parkinson's disease pathogenesis (Wilmes et al., 2022). It is clear from these examples that it is important to understand the roles of methanogens at least in the context of nutrition, constipation, polymicrobial infection, and gut-brain axis. Furthermore, basic principles established for human-associated methanogens would have implications in the poorly studied animal- and plant-associated methanogens. Together, studies of these host-associated methanogens will help to elucidate their roles in the health and disease of humans, animals, and plants.

Significance in biotechnology

Besides their commercial applications in waste treatment and biogas production, methanogens emerge also as cell factories for sustainable biomanufacturing, owing to their intriguing ecophysiological characteristics. Notable examples include their high gas or hydrostatic pressure tolerance, ranging from 300 kPa to 400 MPa (Ver Eecke et al., 2013; Taubner et al., 2018; Pappenreiter et al., 2019); their wide range of growth temperature, from approx. -4 to $122^\circ C$ (Taubner et al., 2015); and their abilities to reduce CO_2 with diverse gaseous and volatile compounds such as H_2 , CO, formate, ethanol, and secondary alcohols (Kurth et al., 2020). Moreover, certain

methanogens are also fast growing (Abdel Azim et al., 2017; Palabikyan et al.) and genetically tractable (Mondorf et al., 2012; Nayak and Metcalf, 2017; Susanti et al., 2019; Lyu et al., 2020; Fink et al., 2021; Bao et al., 2022; Li et al., 2022).

With these features, methanogens are poised to help drive the next biotechnological boom through a gas fermentation bioprocess. Of special interests to this process are CO₂-reducing microbes, which can be regarded as a carbon-negative cell factory that enables carbon fixation, bioenergy transition, and production of high-value bioproducts (Müller, 2019; Pfeifer et al., 2021; Liew et al., 2022). As a proof of concept, methanogens capable of CO₂-reduction have already been engineered to produce geraniol (Lyu et al., 2016), isoprene (Aldridge et al., 2021), acetate (Schone et al., 2022), enzymes (Lyu et al., 2018a; Akinyemi et al., 2021), and bioplastics (Thevasundaram et al., 2022) under laboratory conditions. Additionally, several high performance and high pressure gas fermenting methanogen cell factories have been identified under bioreactor conditions (Mauerhofer et al., 2018, 2021). Because the biomass of methanogens is already rich in valuable compounds such as ether lipids (Baumann et al., 2018, 2022), carboxylic acids, and complex coenzymes (Lyu and Whitman, 2019), coupling synthetic biology with bioprocess development holds high potential for advancing methanogens into an economically feasible platform for green biomanufacturing.

Discussion

Although invisible to the naked eye, many have acknowledged the significant influence of methanogens and their surrounding microbiome on humanity's fate. This is evidenced by the Global Methane Pledge endorsed by 120 nations aiming for a 30% cut in methane emissions by 2030 (The White House, 2021). However, beyond methanogenesis and methane reduction, more research is needed to understand the functional roles of methanogens in both free-living and host-associated microbiomes. Bioengineering of and bioprocess development for methanogens are also of high importance, which echoes the unprecedented investments in low-carbon biomanufacturing (The White House, 2022). Ultimately, the convergence of these research areas would lead to a more sustainable future by not only mitigating global warming and climate change but tapping the potential of methanogens in environmental, agricultural, industrial, and medical biotechnology.

Author contributions

ZL coordinated this collaboration and drafted the sections—Introduction, Significance in the global carbon cycle, Discussion, and edited the manuscript. A-ER drafted the section—

Significance in environmental microbiome. MP drafted the section—Significance in human health and beyond. C-JZ drafted the section—Evolution of methanogens and methanogenesis. SK-MRR drafted the section—Significance in biotechnology. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Author SK-MRR is co-founder of Arkeon GmbH. Author MP is a consultant for Bausch Health, Ferring Pharmaceuticals Inc., Salvo Health, and Vivante Health Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

- Abdel Azim, A., Pruckner, C., Kolar, P., Taubner, R.-S., Fino, D., Saracco, G., et al. (2017). The physiology of trace elements in biological methane production. *Bioresour. Technol.* 241, 775–786. doi: 10.1016/j.biortech.2017.05.211
- Akinyemi, T. S., Shao, N., Lyu, Z., Drake, I. J., Liu, Y., and Whitman, W. B. (2021). Tuning gene expression by phosphate in the methanogenic archaeon *Methanococcus maripaludis*. *ACS Synth. Biol.* 10, 3028–3039. doi: 10.1021/acssynbio.1c00322
- Aldridge, J., Carr, S., Weber, K. A., and Buan, N. R. (2021). Anaerobic production of isoprene by engineered *Methanosarcina species* archaea. *Appl. Environ. Microbiol.* 87, e02417–20. doi: 10.1128/AEM.02417-20
- Aryal, N., Zhang, Y., Bajracharya, S., Pant, D., and Chen, X. (2022). Microbial electrochemical approaches of carbon dioxide utilization for biogas upgrading. *Chemosphere* 291, 132843. doi: 10.1016/j.chemosphere.2021.132843
- Baker, B. J., De Anda, V., Seitz, K. W., Dombrowski, N., Santoro, A. E., and Lloyd, K. G. (2020). Diversity, ecology and evolution of archaea. *Nat. Microbiol.* 5, 887–900. doi: 10.1038/s41564-020-0715-z
- Bao, J., De Dios Mateos, E., and Scheller, S. (2022). Efficient CRISPR/Cas12a-based genome-editing toolbox for metabolic engineering in *Methanococcus maripaludis*. *ACS Synth. Biol.* 11, 2496–2503. doi: 10.1021/acssynbio.2c00137
- Bapteste, É., Brochier, C., and Boucher, Y. (2005). Higher-level classification of the archaea: evolution of methanogenesis and methanogens. *Archaea* 1, 859728. doi: 10.1155/2005/859728
- Basseri, R. J., Basseri, B., Pimentel, M., Chong, K., Youdim, A., Low, K., et al. (2012). Intestinal methane production in obese individuals is associated with a higher body mass index. *Gastroenterol. Hepatol* 8, 22–8.
- Baumann, L. M. F., Taubner, R.-S., Bauersachs, T., Steiner, M., Schleper, C., Peckmann, J., et al. (2018). Intact polar lipid and core lipid inventory of the hydrothermal vent methanogens *Methanocaldococcus villosus* and *Methanothermococcus okinawensis*. *Org. Geochem.* 126, 33–42. doi: 10.1016/j.orggeochem.2018.10.006
- Baumann, L. M. F., Taubner, R.-S., Oláh, K., Rohrweber, A.-C., Schuster, B., Birgel, D., et al. (2022). Quantitative analysis of core lipid production in *Methanothermobacter marburgensis* at different scales. *Bioengineering* 9, 169. doi: 10.3390/bioengineering9040169
- Berghuis, B. A., Yu, F. B., Schulz, F., Blainey, P. C., Woyke, T., and Quake, S. R. (2019). Hydrogenotrophic methanogenesis in archaeal phylum Verstraetearchaeota reveals the shared ancestry of all methanogens. *Proc Natl Acad Sci USA* 116, 5037–5044. doi: 10.1073/pnas.1815631116
- Bizic, M., Klintzsch, T., Ionescu, D., Hindiyeh, M. Y., Günthel, M., Muro-Pastor, A. M., et al. (2020). Aquatic and terrestrial cyanobacteria produce methane. *Sci. Adv.* 6, eaax5343. doi: 10.1126/sciadv.aax5343
- Bond, J. H., Engel, R. R., and Levitt, M. D. (1971). Factors influencing pulmonary methane excretion in man. *J. Exp. Med.* 133, 572–588. doi: 10.1084/jem.133.3.572
- Borrel, G., Adam, P. S., and Gribaldo, S. (2016). Methanogenesis and the wood-ljungdahl pathway: an ancient, versatile, and fragile association. *Genome Biol Evol* 8, 1706–1711. doi: 10.1093/gbe/evw114
- Borrel, G., Adam, P. S., McKay, L. J., Chen, L.-X., Sierra-García, I. N., Sieber, C. M. K., et al. (2019). Wide diversity of methane and short-chain alkane metabolisms in uncultured archaea. *Nat. Microbiol.* 4, 603–13. doi: 10.1038/s41564-019-0363-3
- Borrel, G., Brugère, J.-F., Gribaldo, S., Schmitz, R. A., and Moissl-Eichinger, C. (2020). The host-associated archaeome. *Nat. Rev. Microbiol.* 18, 622–36. doi: 10.1038/s41579-020-0407-y
- Buan, N. R. (2018). Methanogens: pushing the boundaries of biology. *Emerg. Top. Life Sci.* 2, 629–646. doi: 10.1042/ETLS20180031
- Conrad, R. (2009). The global methane cycle: recent advances in understanding the microbial processes involved. *Environ. Microbiol. Rep.* 1, 285–292. doi: 10.1111/j.1758-2229.2009.00038.x
- De Bernardini, N., Basile, A., Zampieri, G., Kovalovszki, A., De Diego Diaz, B., Offer, E., et al. (2022). Integrating metagenomic binning with flux balance analysis to unravel syntrophies in anaerobic CO₂ methanation. *Microbiome* 10, 117. doi: 10.1186/s40168-022-01311-1
- Earth Org (2022). *Global Methane Levels*. available online at: <https://earth.org/data/global-methane-data> (accessed August 25, 2022).
- Ernst, L., Steinfeld, B., Barayeu, U., Klintzsch, T., Kurth, M., Grimm, D., et al. (2022). Methane formation driven by reactive oxygen species across all living organisms. *Nature* 603, 482–487. doi: 10.1038/s41586-022-04511-9
- Fink, C., Beblawy, S., Enkerlin, A. M., Mühling, L., Angenent, L. T., and Molitor, B. (2021). A shuttle-vector system allows heterologous gene expression in the thermophilic methanogen *Methanothermobacter thermautotrophicus* ΔH. *MBio* 12, e02766–21. doi: 10.1128/mBio.02766-21
- García, P. S., Gribaldo, S., and Borrel, G. (2022). Diversity and evolution of methane-related pathways in archaea. *Annu. Rev. Microbiol.* 76, 727–755. doi: 10.1146/annurev-micro-041020-024935
- Günthel, M., Donis, D., Kirillin, G., Ionescu, D., Bizic, M., McGinnis, D. F., et al. (2019). Contribution of oxic methane production to surface methane emission in lakes and its global importance. *Nat. Commun.* 10, 5497. doi: 10.1038/s41467-019-13320-0
- Hoegenauer, C., Hammer, H. F., Mahner, A., and Moissl-Eichinger, C. (2022). Methanogenic archaea in the human gastrointestinal tract. *Nat. Rev. Gastroenterol. Hepatol.* 0123456789, 491–525. doi: 10.1038/s41575-022-00673-z
- Horz, H.-P., and Conrads, G. (2011). Methanogenic archaea and oral infections—ways to unravel the black box. *J. Oral Microbiol.* 3, 5940. doi: 10.3402/jom.v3i0.5940
- Kim, G., Deepinder, F., Morales, W., Hwang, L., Weitsman, S., Chang, C., et al. (2012). *Methanobrevibacter smithii* is the predominant methanogen in patients with constipation-predominant IBS and methane on breath. *Dig. Dis. Sci.* 57, 3213–3218. doi: 10.1007/s10620-012-2197-1
- Kurth, J. M., Op den Camp, H. J. M., and Welte, C. U. (2020). Several ways one goal—methanogenesis from unconventional substrates. *Appl. Microbiol. Biotechnol.* 104, 6839–6854. doi: 10.1007/s00253-020-10724-7
- Lahme, S., Mand, J., Longwell, J., Smith, R., and Enning, D. (2021). Severe corrosion of carbon steel in oil field produced water can be linked to methanogenic archaea containing a special type of [NiFe] hydrogenase. *Appl. Environ. Microbiol.* 87, 1–17. doi: 10.1128/AEM.01819-20
- Laso-Perez, R., Wegener, G., Knittel, K., Widdel, F., Harding, K. J., Krukenberg, V., et al. (2016). Thermophilic archaea activate butane via alkyl-coenzyme M formation. *Nature* 539, 396–401. doi: 10.1038/nature20152
- Lepp, P. W., Brinig, M. M., Ouverney, C. C., Palm, K., Armitage, G. C., and Relman, D. A. (2004). Methanogenic archaea and human periodontal disease. *Proc. Natl. Acad. Sci. USA* 101, 6176–6181. doi: 10.1073/pnas.0308766101
- Li, J., Zhang, L., Xu, Q., Zhang, W., Li, Z., Chen, L., et al. (2022). CRISPR-Cas9 toolkit for genome editing in an autotrophic CO₂-fixing methanogenic archaeon. *Microbiol. Spectr.* 10, e01165–22. doi: 10.1128/spectrum.01165-22
- Liew, F. E., Nogle, R., Abdalla, T., Rasor, B. J., Canter, C., Jensen, R. O., et al. (2022). Carbon-negative production of acetone and isopropanol by gas fermentation at industrial pilot scale. *Nat. Biotechnol.* 40, 335–344. doi: 10.1038/s41587-021-01195-w
- Liu, Y., and Whitman, W. B. (2008). Metabolic, phylogenetic, and ecological diversity of the methanogenic archaea. *Ann. N. Y. Acad. Sci.* 1125, 171–189. doi: 10.1196/annals.1419.019
- Lyu, Z., Chou, C. W., Shi, H., Wang, L., Ghebream, R., Phillips, D., et al. (2018a). Assembly of methyl coenzyme M reductase in the methanogenic archaeon *Methanococcus maripaludis*. *J. Bacteriol.* 200, e00746-17. doi: 10.1128/JB.00746-17
- Lyu, Z., Jain, R., Smith, P., Fetchko, T., Yan, Y., and Whitman, W. B. (2016). Engineering the autotroph *Methanococcus maripaludis* for geraniol production. *ACS Synth Biol* 5, 577–581. doi: 10.1021/acssynbio.5b00267
- Lyu, Z., and Lu, Y. (2018). Metabolic shift at the class level sheds light on adaptation of methanogens to oxidative environments. *ISME J.* 12, 411–423. doi: 10.1038/ismej.2017.173
- Lyu, Z., Rotaru, A.-E., Pimentel, M., Zhang, C., and Rittmann, S. K. -M. R. (2022). *Frontiers Research Topic*. Available at: <https://www.frontiersin.org/research-topics/44807/the-methane-moment---cross-boundary-significance-of-methanogens> (accessed August 04, 2022).
- Lyu, Z., Shao, N., Akinyemi, T., and Whitman, W. B. (2018b). Methanogenesis. *Curr. Biol.* 28, R727–R732. doi: 10.1016/j.cub.2018.05.021
- Lyu, Z., Shao, N., Chou, C., Shi, H., Patel, R., Duin, E. C., et al. (2020). Posttranslational methylation of arginine in methyl coenzyme m reductase has a profound impact on both methanogenesis and growth of *Methanococcus maripaludis*. *J. Bacteriol.* 202, 1–18. doi: 10.1128/JB.00654-19
- Lyu, Z., and Whitman, W. B. (2017). Evolution of the archaeal and mammalian information processing systems: towards an archaeal model for human disease. *Cell. Mol. Life Sci. C.* 74, 183–212. doi: 10.1007/s00018-016-2286-y

- Lyu, Z., and Whitman, W. B. (2019). Transplanting the pathway engineering toolbox to methanogens. *Curr. Opin. Biotechnol.* 59, 46–54. doi: 10.1016/j.copbio.2019.02.009
- Mathur, R., Mundi, M. S., Chua, K. S., Lorentz, P. A., Barlow, G. M., Lin, E., et al. (2016). Intestinal methane production is associated with decreased weight loss following bariatric surgery. *Obes. Res. Clin. Pract.* 10, 728–733. doi: 10.1016/j.orcp.2016.06.006
- Mauerhofer, L.-M., Reischl, B., Schmider, T., Schupp, B., Nagy, K., Pappenreiter, P., et al. (2018). Physiology and methane productivity of *Methanobacterium thermaggregans*. *Appl. Microbiol. Biotechnol.* 102, 7643–7656. doi: 10.1007/s00253-018-9183-2
- Mauerhofer, L.-M., Zwiirtmayr, S., Pappenreiter, P., Bernacchi, S., Seifert, A. H., Reischl, B., et al. (2021). Hyperthermophilic methanogenic archaea act as high-pressure CH₄ cell factories. *Commun. Biol.* 4, 289. doi: 10.1038/s42003-021-01828-5
- Mayumi, D., Mochimaru, H., Tamaki, H., Yamamoto, K., Yoshioka, H., Suzuki, Y., et al. (2016). Methane production from coal by a single methanogen. *Science* 354, 222–225. doi: 10.1126/science.aaf8821
- Mondorf, S., Deppenmeier, U., and Welte, C. (2012). A novel inducible protein production system and neomycin resistance as selection marker for *Methanosarcina mazei*. *Archaea* 2012, 1–8. doi: 10.1155/2012/910205
- Müller, V. (2019). New horizons in acetogenic conversion of one-carbon substrates and biological hydrogen storage. *Trends Biotechnol.* 37, 1344–1354. doi: 10.1016/j.tibtech.2019.05.008
- Nayak, D. D., and Metcalf, W. W. (2017). Cas9-mediated genome editing in the methanogenic archaeon *Methanosarcina acetivorans*. *Proc. Natl. Acad. Sci.* 114, 2976–81. doi: 10.1073/pnas.1618596114
- Pappenreiter, P. A., Zwiirtmayr, S., Mauerhofer, L., Rittmann, S. K. R., and Paulik, C. (2019). Development of a simultaneous bioreactor system for characterization of gas production kinetics of methanogenic archaea at high pressure. *Eng. Life Sci.* 19, 537–544. doi: 10.1002/elsc.201900035
- Pfeifer, K., Ergal, I., Koller, M., Basen, M., Schuster, B., and Rittmann, S. K.-M. R. (2021). Archaea biotechnology. *Biotechnol. Adv.* 47, 107668. doi: 10.1016/j.biotechadv.2020.107668
- Pimentel, M., Lin, H. C., Enayati, P., Van Den Burg, B., Lee, H. R., Chen, J. H., et al. (2006). Methane, a gas produced by enteric bacteria, slows intestinal transit and augments small intestinal contractile activity. *Am. J. Physiol. Gastrointest. Liver Physiol.* 290, 1089–1095. doi: 10.1152/ajpgi.00574.2004
- Rosentreter, J. A., Borges, A. V., Deemer, B. R., Holgerson, M. A., Liu, S., Song, C., et al. (2021). Half of global methane emissions come from highly variable aquatic ecosystem sources. *Nat. Geosci.* 14, 225–230. doi: 10.1038/s41561-021-00715-2
- Rotaru, A.-E., Calabrese, F., Stryhanyuk, H., Musat, F., Shrestha, P. M., Weber, H. S., et al. (2018). Conductive particles enable syntrophic acetate oxidation between *Geobacter* and *Methanosarcina* from coastal sediments. *MBio* 9, e00226–18. doi: 10.1128/mBio.00226-18
- Rotaru, A. E., Yee, M. O., and Musat, F. (2021). Microbes trading electricity in consortia of environmental and biotechnological significance. *Curr. Opin. Biotechnol.* 67, 119–129. doi: 10.1016/j.copbio.2021.01.014
- Samuel, B. S., Hansen, E. E., Manchester, J. K., Coutinho, P. M., Henriessat, B., Fulton, R., et al. (2007). Genomic and metabolic adaptations of *Methanobrevibacter smithii* to the human gut. *Proc. Natl. Acad. Sci. USA.* 104:10643–8. doi: 10.1073/pnas.0704189104
- Schink, B. (1997). Energetics of syntrophic cooperation in methanogenic degradation. *Microbiol. Mol. Biol. Rev.* 61, 262–280. doi: 10.1128/mmbr.61.2.262-280.1997
- Schone, C., Poehlein, A., Jehmlich, N., Adlung, N., Daniel, R., von Bergen, M., et al. (2022). Deconstructing *Methanosarcina acetivorans* into an acetogenic archaeon. *Proc. Natl. Acad. Sci. USA.* 119, 1–7. doi: 10.1073/pnas.2113853119
- Schorn, S., Ahmerkamp, S., Bullock, E., Weber, M., Lott, C., Liebeke, M., et al. (2022). Diverse methylotrophic methanogenic archaea cause high methane emissions from seagrass meadows. *Proc. Natl. Acad. Sci. USA.* 119, 1–12. doi: 10.1073/pnas.2106628119
- Seitz, K. W., Dombrowski, N., Eme, L., Spang, A., Lombard, J., Sieber, J. R., et al. (2019). Asgard archaea capable of anaerobic hydrocarbon cycling. *Nat Commun.* 10, 1822. doi: 10.1038/s41467-019-09364-x
- Susanti, D., Frazier, M. C., and Mukhopadhyay, B. (2019). A genetic system for *Methanocaldococcus jannaschii*: an evolutionary deeply rooted hyperthermophilic methanarchaeon. *Front. Microbiol.* 10, 1256. doi: 10.3389/fmicb.2019.01256
- Taubner, R.-S., Pappenreiter, P., Zwicker, J., Smrzka, D., Pruckner, C., Kolar, P., et al. (2018). Biological methane production under putative enceladus-like conditions. *Nat. Commun.* 9, 748. doi: 10.1038/s41467-018-02876-y
- Taubner, R.-S., Schleper, C., Firneis, M., and Rittmann, S. (2015). Assessing the ecophysiology of methanogens in the context of recent astrobiological and planetological studies. *Life* 5, 1652–1686. doi: 10.3390/life5041652
- Thauer, R. K., Kaster, A.-K., Goenrich, M., Schick, M., Hiromoto, T., and Shima, S. (2010). Hydrogenases from methanogenic archaea, nickel, a novel cofactor, and H₂ storage. *Annu. Rev. Biochem.* 79, 507–536. doi: 10.1146/annurev.biochem.030508.152103
- Thauer, R. K., Kaster, A. K., Seedorf, H., Buckel, W., and Hedderich, R. (2008). Methanogenic archaea: ecologically relevant differences in energy conservation. *Nat. Rev. Microbiol.* 6, 579–591. doi: 10.1038/nrmicro1931
- The White House (2021). *Joint US-EU Press Release on the Global Methane Pledge*. Available online at: <https://www.whitehouse.gov/briefing-room/statements-releases/2021/09/18/joint-us-eu-press-release-on-the-global-methane-pledge/> (accessed August 25, 2022).
- The White House (2022). *FACT SHEET: The United States Announces New Investments and Resources to Advance President Biden's National Biotechnology and Biomanufacturing Initiative*. Available online at: <https://www.whitehouse.gov/briefing-room/statements-releases/2022/09/14/fact-sheet-the-united-states-announces-new-investments-and-resources-to-advance-president-bidens-national-biotechnology-and-biomanufacturing-initiative/> (accessed September 19, 2022).
- Thevasundaram, K., Gallagher, J. J., Cherng, F., and Chang, M. C. Y. (2022). Engineering nonphotosynthetic carbon fixation for production of bioplastics by methanogenic archaea. *Proc. Natl. Acad. Sci. USA.* 119, e2118638119. doi: 10.1073/pnas.2118638119
- Triantafyllou, K., Chang, C., and Pimentel, M. (2014). Methanogens, methane and gastrointestinal motility. *J. Neurogastroenterol. Motil.* 20, 31–40. doi: 10.5056/jnm.2014.20.1.31
- Underwood, G. J. C., Dumbrell, A. J., McGenity, T. J., McKew, B. A., and Whitby, C. (2022). The microbiome of coastal sediments. *Marine Microbiome*, 3, 479–534. doi: 10.1007/978-3-030-90383-1_12
- Ver Eecke, H. C., Akerman, N. H., Huber, J. A., Butterfield, D. A., and Holden, J. F. (2013). Growth kinetics and energetics of a deep-sea hyperthermophilic methanogen under varying environmental conditions. *Environ. Microbiol. Rep.* 5, 665–71. doi: 10.1111/1758-2229.12065
- Vítězová, M., Kohoutová, A., Vítěz, T., Hanišáková, N., and Kushkevych, I. (2020). Methanogenic microorganisms in industrial wastewater anaerobic treatment. *Processes* 8, 1–27. doi: 10.3390/pr8121546
- Voosen, P. (2022). Ominous feedback loop may be accelerating methane emissions. *Science* 377, 250–251. doi: 10.1126/science.add9091
- Wang, R. (2014). Gasotransmitters: growing pains and joys. *Trends Biochem. Sci.* 39, 227–232. doi: 10.1016/j.tibs.2014.03.003
- Wang, Y., Wegener, G., Hou, J., Wang, F., and Xiao, X. (2019). Expanding anaerobic alkane metabolism in the domain of archaea. *Nat Microbiol* 4, 595–602. doi: 10.1038/s41564-019-0364-2
- Wang, Y., Wegener, G., Williams, T. A., Xie, R., Hou, J., Tian, C., et al. (2021). A methylotrophic origin of methanogenesis and early divergence of anaerobic multicarbon alkane metabolism. *Sci. Adv.* 7, eabj1453. doi: 10.1126/sciadv.abj1453
- Whitman, W. B., Coleman, D. C., and Wiebe, W. J. (1998). Prokaryotes: the unseen majority. *Proc. Natl. Acad. Sci. USA.* 95, 6578–83. doi: 10.1073/pnas.95.12.6578
- Wilmes, P., Trezzi, J.-P., Aho, V., Jäger, C., Schade, S., Kassel, P.-E.-K., et al. (2022). An archaeal compound as a driver of Parkinson's disease pathogenesis. *Research Square Preprint*. doi: 10.21203/rs.3.rs-1827631/v1
- Wolfe, J. M., and Fournier, G. P. (2018). Horizontal gene transfer constrains the timing of methanogen evolution. *Nat. Ecol. Evol.* 2, 897–903. doi: 10.1038/s41559-018-0513-7
- Zhou, Z., Zhang, C., jing, Liu, P. fei, Fu, L., Laso-Pérez, R., Yang, L., et al. (2022). Non-syntrophic methanogenic hydrocarbon degradation by an archaeal species. *Nature* 601, 257–262. doi: 10.1038/s41586-021-04235-2