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Perspective

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Biofilms: from the cradle of life to life support

Katherine J. Baxter[1] ✉, Eszter Sas[2], Kevin B. Clark[3,4], Michaela Walsh[5,6], Nikhil Pradeep[7], Alavia Batool[8], Charles Naney[9], Miguel Angel Vargas Cruz[10], Niamh Kennerdale[11], Kajari Das[12], Zhihan Shi[13], Anish Kelam[14], Vandana Verma[15,16], Marta Filipa Simões[17,18], Dirk Neefs[19], Vinothkannan Ravichandran[20], Madhan R. Tirumalai[21], Borja Barbero Barcenilla[22], Guerrino Macori[6,23], Emmanuel Gonzalez[24,25,26], Benjamin Sikes[27], Fathi Karouia[28,29,30,31] & Nicholas J. B. Brereton[6] ✉

Biofilms are intricately associated with life on Earth, enabling functions essential to human and plant systems, but their susceptibility to spaceflight stressors and functional disruption in space remains incompletely understood. During spaceflight, biofilms have largely been considered as potential infrastructure, life support or infection risks. This review focuses on the prevailing beneficial roles of biofilms in human and plant health, and examines evidence of biofilm adaptability in space environments.

Biofilms and the emergence of life

The earliest stages of life are thought to have involved the gradual transition from abiotic synthesis of simple organic molecules into nascent biotic chemistry at surface attached compartments, where physical scaffolding and local chemical exchange may have supported the emergence of primitive microbial life[1].

Mineral-rich environments, such as hydrothermal vents and hot springs, provide catalytic surfaces and sources of fluctuating energy, such as thermal fluxes, electrochemical gradients and photochemical processes, that could have supported nonadiabatic synthesis pathways to produce organic compounds without proto-enzymes. These environments may have promoted the aggregation or polymerisation of simple organic molecules through adsorptive forces and repeated hydration-evaporation cycles[2], which then condensed into structured assemblies or non-membrane bound "naked" matrices enriched in the basic building blocks of life, including amino acids, fatty acids, peptides and monosaccharides[3–5].

The accumulation of simple and macro amphiphilic molecules may have enhanced chemical partitioning and retention, supporting exchange with the environment while maintaining cooperative structure. These surface bound assemblies likely formed interconnected clusters, where spatial proximity facilitated molecular exchange, cohesion and rudimentary functional integration. Internal heterogeneity within these surface-bound and polymer-rich matrices may have supported simple metabolic cycling, directional transport and division of function, while also providing the spatial and chemical context for increasingly complex coordination, selective exchange and surface-level organisation. These emerging features define true biofilms[6–8], the predominant microbial lifestyle across Earth's major habitats[7].

Ancestral biofilm-embedded protocell networks would have supported cooperative and competitive interactions, aiding persistence in extreme environments. In extant biofilms, this persistence involves fundamental functions related to transformation, structure, communication and movement, derived from elemental processes (Fig. 1)[9,10] which underpin survival and proliferation, but also enable the emergence of higher-order behaviour.

Biofilms enable complex life

Early biofilms can be observed in fossilised stromatolites, structures where sediment has become trapped by microbially produced extracellular polymeric substances (EPS)[11]. Their similarity to modern-day stromatolites suggests conservation of function in microbial community protection and survival[11,12]. Extant stromatolite-producing organisms include Cyanobacteria, gram-negative photoautotrophic bacteria that can survive environmental extremes of UV, temperature, salinity, and desiccation[13,14], conditions analogous to those of early Earth[15,16]. Their EPS includes UV-screening pigments that enhance matrix stability[17], polysaccharides that buffer pH[18], proteins involved in metal homeostasis, carbon cycling, oxidative stress resistance[19–21], enzymes able to modulate matrix density and organisation[22], and a capacity for water and nutrient storage[20]. Similarly, fossilised fungal-like structures such as *Grypania spiralis* and ancient mycelial networks suggest that surface-attached microbial communities with biofilm-like traits emerged early in Earth's history[23–25].

Biofilms are not merely microbial aggregates, but typically heterogeneous dynamic communities with intricate cell-to-cell communication systems and characterised by regulation of collective behaviour through quorum sensing (QS). Microbial QS systems include, but are not limited to, the LuxI/LuxR system in *Vibrio fischeri*, the Agr system in *Staphylococcus*

A full list of affiliations appears at the end of the paper. ✉e-mail: Katherine.Baxter@glasgow.ac.uk; nicholas.brereton@ucd.ie

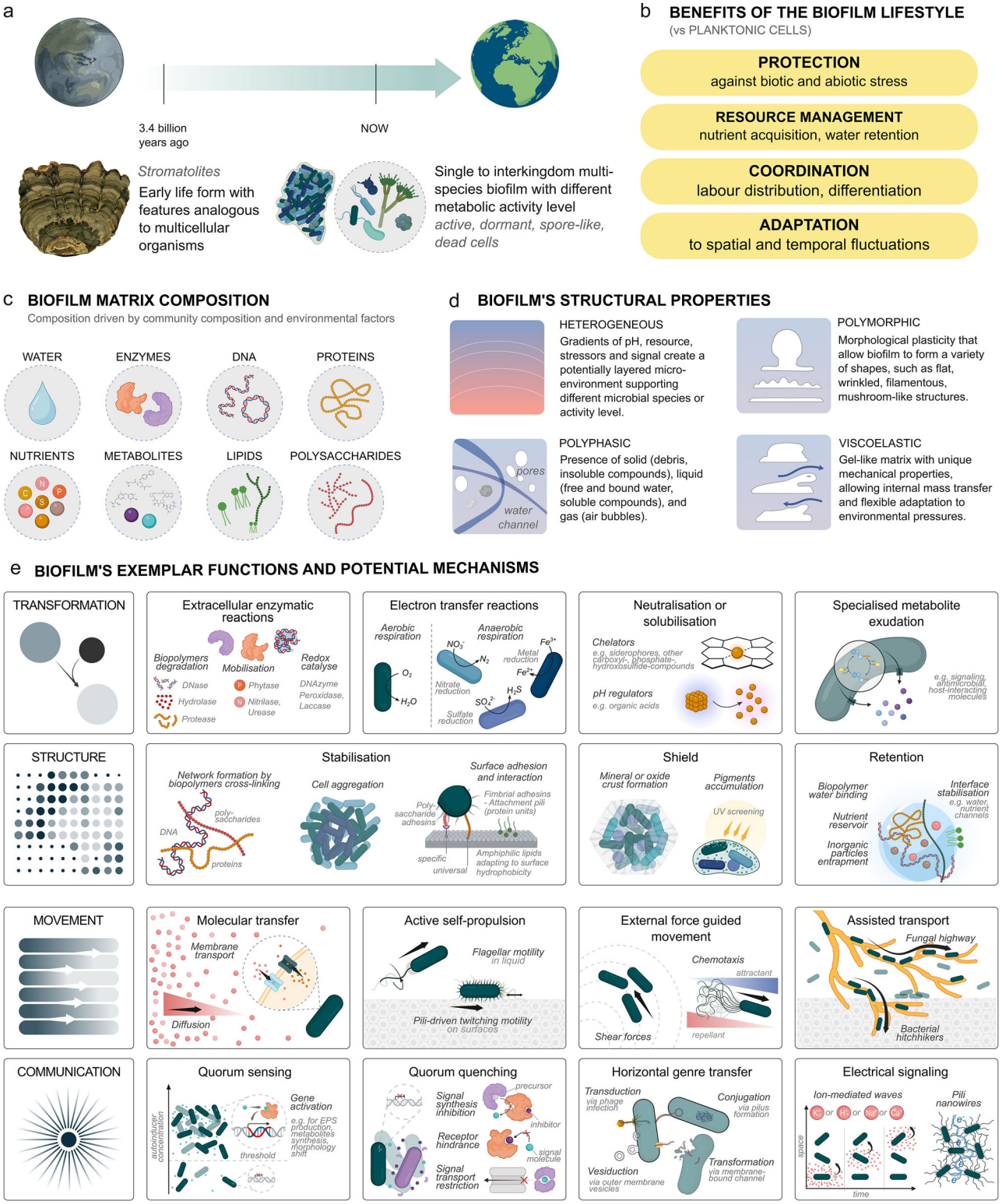

Fig. 1 | Biofilms in early life, composition, morphology, benefits and exemplar functions. a Evolutionary timeline showing early stromatolite biofilms to modern interkingdom biofilms. b Biofilms provide fundamental benefits over planktonic life through protection against environmental stressors, efficient resource management and improved coordination and adaptability in response to spatial and temporal fluctuations. **c** Modern extracellular polymeric substances (EPS) matrices comprise water (up to 97% by mass), polysaccharides, proteins, extracellular DNA, lipids, secondary metabolites, nutrients, and exoenzymes, each contributing to hydration, cohesion, signalling, metabolism, structural integrity, and chemical defence. EPS composition is shaped by both microbial community structure and environmental conditions. d Biofilm structure varies by environmental gradients, containing solid, liquid, and gas phases, with flexible morphology and mechanical properties. e) Representative biofilm functions grouped by transformation, structure, movement, and communication, with example mechanisms.

aureus, and farnesol-mediated signalling in *Candida albicans*. These modulate gene expression for processes such as bioluminescence, virulence, morphogenesis, and biofilm maturation[26–28]. Coordinated communication underpins a functional division of labour within biofilms. In *Bacillus subtilis*, subpopulations differentiate into EPS producers, motile cells, or spore-forming cells, governed by complex regulatory networks involving the TasA amyloid protein and the master regulator SinR[29]. Such differentiation mirrors the division of labour seen in multicellular life forms and provides adaptive advantages under environmental stress.

Recent studies have identified intercellular structures that support material and signal exchange within microbial communities. For instance, bacterial nanotubes and membrane-derived vesicles enable the transfer of nutrients, proteins, and even DNA between neighbouring cells in a biofilm, revealing a rudimentary form of intercellular communication similar to gap junctions in eukaryotes[30]. The evolution of these cooperative as well as competitive traits within biofilms likely set the stage for the transition from unicellularity to multicellularity[31]. Biofilm-associated resource sharing, collective defence, and spatial organisation provide a scaffold upon which multicellular complexity can evolve. These findings support the hypothesis that biofilms served as evolutionary incubators for early multicellular traits in both prokaryotic and early eukaryotic lineages[32]. As metazoan life evolved, the role of biofilms shifted from initial incubators to facilitators of multicellular life. Today, biofilms are intrinsically linked with the health and well-being of all organisms on Earth.

Biofilms enable human health on Earth

Biofilms are fundamental in maintaining human health, especially in the skin, gut, genitourinary tract, and oral cavity, where microbiomes modulate immunity, nutrient absorption and pathogen defence (Fig. 2). Biofilms train the host-immune system to distinguish between beneficial and harmful microbes, critical for the prevention of chronic inflammation and autoimmune disorders[33]. Human microbial biofilms act not only as physical barriers to block pathogen access via their extracellular matrix, but also by competing for resources[34], synthesising antimicrobial agents, and preventing pathogen establishment[35]. In the gut, for example, biofilms perform important digestive function by breaking down complex carbohydrates and producing important metabolites[36,37], and provide physical protection to the gut lining[38,39].

Multispecies biofilm community diversity and dynamics are crucial to human health outcomes[9,40–43]. However, the role of interkingdom intra-community biofilm dynamics in health support is poorly understood. Host-associated biofilms span domains of life, including Eukarya (e.g., Fungi), Archaea, Bacteria and Viruses[44–46], but there is notable lack of detail in the literature regarding how the combined synergistic, antagonistic and mutualistic interplay of this complex, multi-kingdom biofilm community may promote health at the system level.

For health maintenance, a delicate balance must exist between biofilms and the host. For acute and chronic infections, underlying health conditions such as immunodeficiencies, diabetes and cystic fibrosis can lead to commensal biofilm organisms becoming opportunistic pathogens, often manifesting as polymicrobial biofilm infections of the lungs, foot ulcers, bone and deep tissues, and indwelling medical devices[47–51]. These infections are refractory to treatment due to species diversity, variability of the infectious microenvironment[52] and the upregulation of virulence and resistance pathways via quorum sensing and metabolic interaction[52–54]. Furthermore, antimicrobial resistance is promoted through limiting drug penetration, the presence of dormant "persister" cells, and enhancement of horizontal gene transfer[55]. These result in either chronic, recurring disease or systemic life-threatening infection[56,57].

Biofilm-associated disease extends beyond direct infection. For example, amyloid curli fibers of *E.coli* and *Salmonella enterica* gut biofilms confer structural integrity, but their structural similarity to human amyloids can trigger immune responses linked to chronic conditions such as inflammatory bowel disease and even neurodegenerative diseases[58]. These findings highlight that biofilms are not incidental to pathogenesis but become central to the persistence, resistance, and systemic risk posed by microbial disease when their normal role in host resistance is disrupted.

Biofilms enable plant production on Earth

Soil defines terrestrial plant productivity, with the rhizosphere representing a dynamic interface where interkingdom biofilm communities govern nutrient cycling and plant health. The most well-known contributors are plant growth promoting bacteria (PGPB)[59,60], whose biofilms aid germination and plant growth through enhanced nutrient uptake, water retention, and suppression of root pathogens. Biofilms enhance soil fertility through multiple mechanisms (Fig. 2), such as fixing atmospheric N_2, and enhancing the bioavailability of existing nutrients, including phosphorus, iron, potassium and zinc[61,62]. Furthermore, biofilms modify key soil properties, increasing aggregate stability, erosion resistance, and hydrophobicity[63,64], while reducing reliance on chemical inputs and improving both crop yields and soil health. These key soil alterations are evident in pioneer biofilm consortia that form biological soil crusts (biocrusts)[65], reducing erosion and establishing conditions that facilitate primary succession in degraded landscapes[66,67]. While studied less, biocrusts for farming in potentially challenging substrates, may reduce reliance on chemical inputs and improve both crop yields and soil health.

Intra-community dynamics within biofilms are potential targets to enhance agriculture. Arbuscular mycorrhizal fungi (AMF) associate with most plant species, providing nitrogen and phosphate in exchange for plant sugars. Associated mycorrhizal helper bacteria (MHB) further alter fungal behaviour to enhance nutrient access[68]. Biofilms also help plant hosts resist stress through multifactorial dynamics. For example, microbial recruitment and formation of beneficial root-associated biofilms are mediated by root exudates[9,62,69–72]. Biofilms can help hosts resist diseases by modulating the plant immune system, notably via the induced systemic resistance pathway (ISR)[73]. Biofilm EPS can also act as a reservoir of both microbial and host-derived factors, including quorum-sensing disruptors and antimicrobial compounds, that further outcompete and inhibit the activity of pathogenic microorganisms[73]. Other metabolic resources captured and concentrated by the EPS can promote plant growth and stress tolerance, including antioxidants, phytohormones, osmoprotectants, and signalling molecules[74,75].

Biofilms, however, can also pose important challenges. *Listeria monocytogenes*[76] and *Salmonella* sp[77]. biofilms on processing surfaces, for example[78], are difficult to eradicate and are significant sources of foodborne outbreaks. Taking these potential benefits and risks into account, manipulation of these complex interkingdom relationships could drive profound changes in sustainable agricultural practices.

Spaceflight perturbs biofilm structure and function

The extent to which the biofilms that enable plant and human health are disrupted in space remains unclear, but studies under simulated and spaceflight conditions reveal critical changes[79–81]. Findings include altered quorum sensing activity, modulation of EPS production, changes in adhesion and antibiotic resistance, and restructuring of biofilm architecture (Table 1). *Niallia tiangongensis*, for example, is a novel spore-forming species recently isolated from the Tiangong Space Station, with potentially altered biofilm genetics[82]. Interestingly, *Staphylococcus aureus* exhibited both suppression and activation of the Agr quorum sensing system under different spaceflight conditions[26,27], while *Pseudomonas aeruginosa* formed distinct canopy-like biofilms with elevated EPS and altered virulence factor expression[83–85]. In fungi, *Aspergillus niger* exhibited thicker biofilms and increased sporulation under simulated microgravity[86], while *C. albicans* cultured on the ISS formed larger aggregates with transcriptional signatures of biofilm growth[87], and *Penicillium rubens* developed biofilms on diverse spacecraft materials on the ISS, varying in surface coverage, biomass, and thickness[88].

Spaceflight exposes biota to Galactic Cosmic Radiation (GCR) from the interstellar medium, consisting of high energy protons, alpha particles and heavy ions, and Solar Energetic Particles (SEP), mostly comprising protons ejected from the Sun[89]. There are limited studies on biofilm

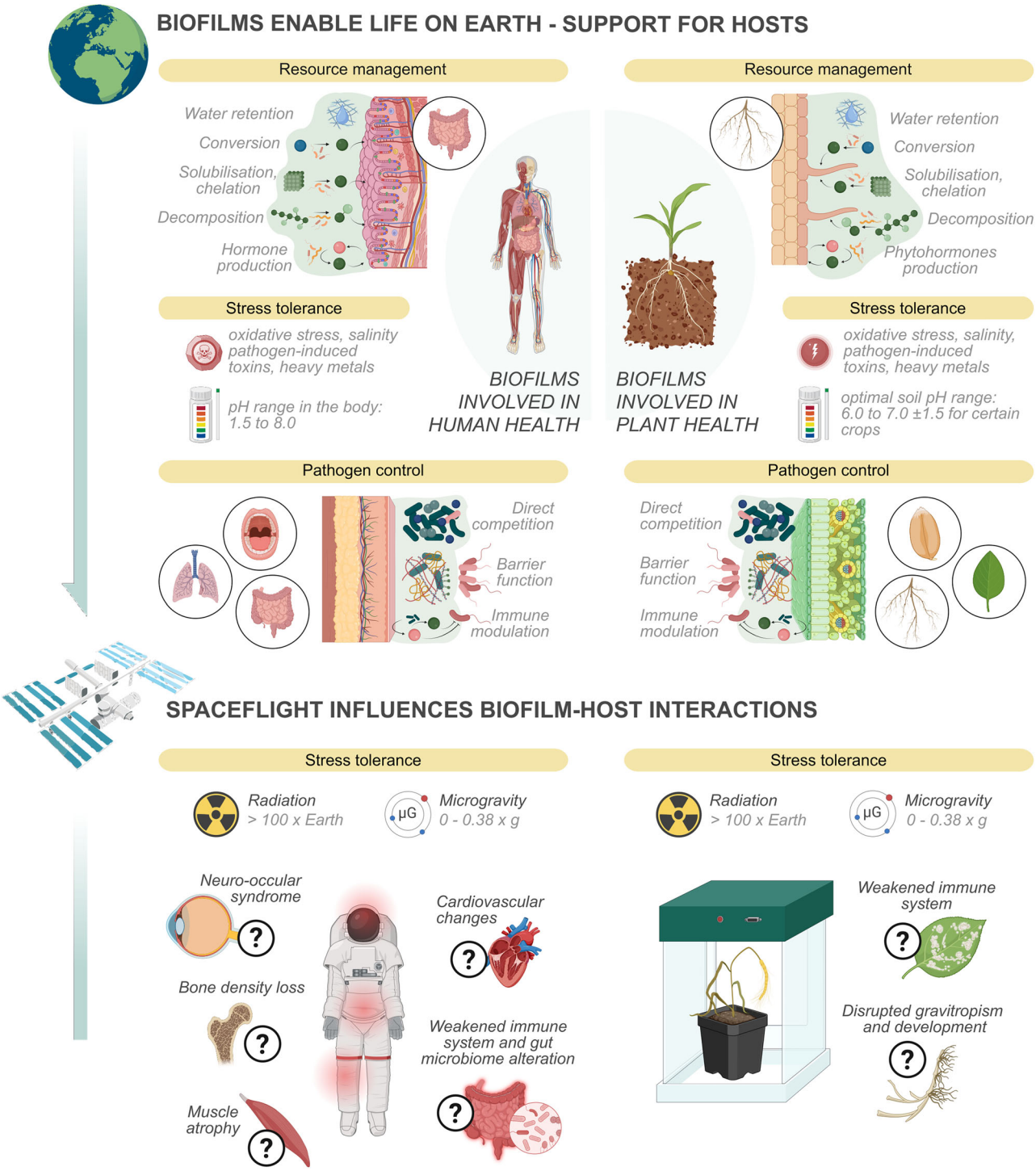

Fig. 2 | Biofilm adaptations to spaceflight stress in living systems. The human gut and plant rhizosphere both support microbial biofilms embedded in hydrated polymer matrices, mucin in the gut and mucilage in the rhizosphere, that provide functionally analogous environments which mediate eukaryote-microbial interactions. These matrices enable common resource management functions, including conversion, solubilisation, chelation, decomposition, and water retention, and support pathogen control through barrier function, direct competition, and immune modulation. Spaceflight stressors (including microgravity and increased radiation) may disrupt biofilm host interactions, altering human immunity and the gut microbiome, and weakening plant immunity and disrupting gravitropism and development. However, the sensitivity of these essential biofilm-host functions to space stressors is still largely unknown.

response to sources of high-radiation. In *Cryptococcus neoformans*, melanin, a biofilm matrix component, was associated with higher post-flight viability, suggesting adaptation to spaceflight stressors, including ionising radiation[90]. On Earth, Bratkic et al.[91] isolated *Bacillus flexus* from mixed-species biofilms developed on nuclear reactor pool walls (2 m from the core) that could tolerate 15kGy from combined gamma and neutron radiation, demonstrating ionising radiation (IR) resistance comparable to extremophiles, such as *D. radiodurans*[92]. Similar tolerance was observed in biofilms formed in a spent nuclear fuel pool[93], accumulating radionuclides, and on spent nuclear fuel rod cladding, surviving doses 2.1 Gy/h for 64 days[94]. Additional studies reported increased abundance of UV- and desiccation-adapted microbes in the Chernobyl exclusion zone[95], and increased biofilm

Table 1 | In vitro biofilm studies under spaceflight-related stressors

Space stressor	Microorganism	Impacted gene expression and significance
LSMMG (24 h)	*Escherichia coli*	↑ Biofilm thickness; ↑ Resistance to salt, ethanol, penicillin and chloramphenicol[187]
LSMMG (192 h)	*Escherichia coli*	↑ Biofilm formation, curli and lipid biosynthesis, starvation related metabolism and stress genes[188]
LSMMG	*Escherichia coli*	Adhesion and surface interaction gene mutations (fimH, surA, betA) - after 1000 generations; No variation in antibiotics resistance[189]
LSMMG	*Escherichia coli*	↑ Biofilm formation[190]
LSMMG (24 h)	*Pseudomonas aeruginosa*	↑ Cell aggregation and biofilm clustering; ↓ Pyocyanin production, related to virulence and QS for extracellular DNA and H_2O_2 secretion[191]
LSMMG (6 d)	*Pseudomonas aeruginosa*	↓ Biofilm formation; ↓ Pyocyanin production; Importance of surface attachment genes (flgK, pelA)[192]
LSMMG (24 h)	*Staphylococcus aureus*	↓ AIP production; ↓ Cytotoxicity; ↑ Fibronectin binding[26]
LSMMG	*Bacillus cereus*	↑ EPS; ↑ Cell aggregation; ↑ MIC damage on aluminium alloy surfaces[193]
LSMMG	*Candida albicans*	↑ Biofilm formation; ↑ Filamentous form; Wrinkled morphology[194]
Simulated μG	*Micrococcus luteus*	↑ EPS amount related to attachment; ↑ Growth rate and biomass; ↓ EPS colloidal components related to thickness and stability[195]
Simulated μG (20 d)	*Synechocystis* sp. *PCC6803*	↑ EPS synthesis and secretion, via glgP (glycogen catabolism), exoD (extracellular synthesis) and epsB (transportation) expression[196]
Simulated μG (12 d)	*Stenotrophomonas maltophilia*	↑ Growth rate and biofilm formation; ↑ Motility and adhesion[197]
Simulated μG	*Enterococcus faecium*	Trends based on 42 vancomycin-resistant strains: ↑ and ↓ Antibiotics susceptibility; ↑ Biofilm production; ↑ Desiccation tolerance[198]
Simulated μG (24 h)	*Bacillus cereus*	↑ Growth rate and biofilm production; ↑ Cell aggregation; ↑ Membrane FA unsaturation; ↑ Antibiotic resistance[199]
Simulated μG (3-5 d)	*Aspergillus niger*	↑ Surface colonisation; ↑ Biofilm thickness; ↑ Vegetative mycelium growth (racA-mediated, actin-based polarity); ↑ Spore production[86]
Spaceflight (STS-95,1-8 d)	*Pseudomonas aeruginosa (PAO-1)*	↑ Biofilm formation with strong adhesion under microgravity; No major morphological differences detected[200]
Spaceflight (STS-132,135)	*Pseudomonas aeruginosa (PA14)*	↑ Biofilm biomass and thickness; Space-specific column-and-canopy architecture using flagella-driven motility[83]
Spaceflight (ISS, 1-3 d)	*Pseudomonas aeruginosa (PA14)*	↓ Biofilm biomass and thickness; ↑ Pyochelin gene expression; Minimal transcriptional changes overall[201]
Spaceflight	*Staphylococcus aureus*	↑ QS (RNAIII, Agr); Altered virulence factors[27]
Spaceflight	*Niallia tiangongensis*	↑ Gelatinase activity; ↑ Biofilm formation; ↑ Oxidative stress response; ↑ Radiation damage repair[82]
Spaceflight (STS-115)	*Candida albicans*	↑ Cell aggregation; ↑ Random budding; ↑ Oxidative stress resistance genes; No variation in virulence[87]
Spaceflight (STS-115)	*Salmonella typhimurium*	↑ Cell aggregation and extracellular matrix production; ↑ Virulence[202]
Spaceflight (ISS, 10–20 d)	*Penicillium rubens*	Biofilm formation varied by surface material and time; No variation in biofilm coverage or morphology (thickness, shape)[88]
Simulated μG + Radiation (~1mGy)	*Mixed biofilm*	↑ Penicillin resistance with radiation only but not with microgravity or combined stressors; Altered community structure[203]
Radiation (15kGy)	*Bacillus flexus*	Evidence of microbial succession; *B. flexus* tolerated high IR[91]
Radiation (2.1 Gy/h, 64 d)	*Mixed biofilm*	Viable biofilms formed on spent fuel cladding; chronic IR exposure; MIC implications[94]
Radiation	*Mixed biofilm*	Evidence of biofilm growth; Radionuclides retained in EPS matrix[93]
Radiation (Chernobyl)	*Mixed biofilm*	↑ ITS mutations rate induced by radiation; Stable biofilm diversity including UV/desiccation-adapted taxa[95]

AIP autoinducing peptide, *d* days, *EPS* extracellular polymeric substances, *FA* fatty acid, *h* hours, *IR* ionising radiation, *ISS* International space Station, *ITS* internal transcribed spacer, *LSMMG* low-shear modelled microgravity, *MIC* minimal inhibitory concentration, *QS* quorum sensing, *STS* space transportation system, *μG* Microgravity, *UV* ultra-violet.

growth in root canal dentine after repeated IR exposure, with doses of 55 Gy and 70 Gy[96]. While these terrestrial radiation sources differ from GCR and SEP exposure experienced in long-duration spaceflight, they provide initial insights into biofilm radiation resistance capabilities and underlying mechanisms.

Most taxa explored in vitro in space to date have been opportunistic pathogens or generalist lab strains[97]. This in vitro research provided mechanistic insight into microbial adaptations to space environments, helping to interpret the observed microbial shifts within host-associated biofilms under spaceflight stressors such as microgravity, radiation, and confinement. However, relevance of findings to healthy human or plant biofilm functions is often limited. Essential short-chain fatty acid producers, bile acid-modifying, PGPBs, or mycorrhizal partners remain, as yet, underexplored.

Does spaceflight influence gut–biofilm interactions?

Microbiome studies in human and murine hosts have revealed changes under spaceflight, including the analog Mars500 mission[98,99], Rodent Research-1[100], Rodent research-5[101], a 1-year ISS mission[102], Inspiration4[103], and the NASA Twin study[104]. In the Rodent Research-6 (RR-6) mission, multiomics combining colon and liver transcriptomics and metagenomic profiling of faecal samples capture coordinated host-microbiome

responses[105]. Modifications were observed in butyrate-associated taxa, including *Dysosmobacter welbionis*, implicated in host lipid metabolism and mitochondrial function[106], as well as bile acid modifying species, such as *Extibacter muris*, *Eisenbergiella massiliensis*, and *Blautia pseudococcoides*. *E. muris*, in particular, was significantly enriched and possesses full bai operon clusters (*BaiBCDEFGI, BaiJKL, and BaiA*) able to alter the host bile acid pool[107]. These changes coincided with depletion of *Clostridium scindens* and *Ligilactobacillus murinus*, species associated with biofilm-mediated epithelial support, bile detoxification, and suppression of pathogen colonisation[108–111].

These microbial changes aligned with repression of hepatic bile acid synthesis (*Cyp7a1*) and altered intestinal transport, including *Slc10a2, Ugt1a1, Slc51a/b, Abcg5/8*, and *Abcc2*, suggesting bile retention and FGF15-FGFR4 feedback inhibition[105]. Enrichment of extracellular matrix, tight junction, and O-glycan biosynthesis pathways, alongside bacterial invasion, indicates progressive disruption of the host-biofilm boundary likely to impact immune containment and nutrient cycling.

Colon transcriptomics of RR-6 further showed broad suppression of mucosal immune networks, notably IgA production, chemokines (*Ccl3, Ccl5, Ccl22*), receptors (*Ccr4, Ccr7, Ccr9*), and co-stimulatory ligands (*Cd2, Cd80, Icoslg*)[105]. While *Muc2* was upregulated, *Muc3* and *Mptx1* were suppressed, suggesting altered mucus layering and spatial disturbance of biofilms. This widespread downregulation likely impairs IgA-mediated tolerance, which would compromise the host capacity to recognise commensal microbes within the gut biofilm, preventing "Friend or Foe" discrimination[112,113]. Comparable host-microbiome effects occurred during Inspiration4, where oral enrichment of *Fusobacterium* and *Actinomyces* coincided with immune transcriptomic shifts[114]. Occurrence of reduced antigen presentation, systemic immune suppression, and cortisol elevation may drive impaired barrier immunity and increased infection risk for astronauts during long-duration missions.

The causal links between spaceflight-induced changes in mucin inhabiting microbiome community and the crew health outcomes are largely speculative. How microbial metabolites, immune mediators or compromise of microbiome-mediated host metabolic functions might contribute to known spaceflight pathologies, including Spaceflight Associated Neuro-ocular Syndrome (SANS), cardiovascular dysfunction, bone loss and muscle atrophy, remains to be established (Fig. 2).

Does spaceflight alter rhizosphere–biofilm exchange?

To support plant adaptation in microgravity or high-radiation environments, beneficial symbiosis with bacterial or fungal biofilms may enhance stress resistance and enable growth in nutrient-poor substrates, as observed on Earth. Differential gene expression analysis studying *Arabidopsis thaliana* exposed to spaceflight stressors[115], using GeneLab data OSD-7, OSD-120, OSD-37, OSD-38, and OSD-46, showed common upregulation of genes associated with genomic and transcriptional stability (*PARP1*, *BRCA1*, *RS31A* and *TSO2*), suggesting that spaceflight imposes persistent genomic and transcriptional stress, potentially constraining growth and the formation or maintenance of beneficial biofilms.

Microgravity alters the biophysics of surrounding pore spaces around roots in substrate-grown plants and affects root wettability in hydroponic or aeroponic systems[116]. Biofilms coating the root and fungal hyphae extending into the rhizosphere will alter solute contact angles in ways that may dictate local hypoxia, nutrient delivery, and overall plant health. On the leaf surface, particularly around stomata, biofilms may mediate gas exchange and oxygen buildup in microgravity. *A. thaliana* and *Brassica nigra* can germinate and grow in sealed, minimal habitats suitable for robotic lunar landers, supporting future studies into plant adaptation to partial gravity and radiation environments[117]. Such closed systems lack the structure and microbial diversity of soil ecosystems, making stable rhizosphere and phyllosphere biofilms particularly important for nutrient cycling, stress mitigation, and microbial signalling. Future work building on this potential role of biofilms in enhancing or ameliorating biophysical limitations is essential.

Few studies have explored plant-microbe interactions directly during spaceflight in detail, *Rhizobium leguminosarum* bv. *trifolii* had enhanced binding to succinate and acetylsalicylic acid under simulated microgravity, suggesting increased adhesive capacity and altered EPS-mediated interactions[118]. In *Medicago truncatula*, the growth suppression associated with microgravity and inoculation with *Sinorhizobium meliloti* alone was mitigated by arbuscular mycorrhizal colonisation with *Rhizophagus irregularis*, suggesting that dense hyphal networks in the mucilage-rich matrix of the rhizosphere may support nutrient uptake and protect against space stressors[119].

The role of biofilm-associated microbiota in spaceflight-induced changes to plant immunity and development, much like with mammal host-gut microbiome interactions, is poorly understood. While microgravity alters immune signalling, nodulation, and mycorrhizal interactions[119–121], it is unclear how ISR and pathogen recognition are affected, and the detection of opportunistic plant pathogens such as *Fusarium oxysporum* on the ISS[122] raises concerns about plant immunity. Similarly, developmental changes under disrupted gravitropism may reshape plant-microbe signalling and exudation, yet changes to plant-microbe architecture, hormone signalling, and microbial function remain to be elucidated (Fig. 2).

Space as a new frontier of biofilm discoveries

Complex environments such as the human gut, plant rhizosphere, human-built habitats, and extraterrestrial surfaces provide an incredibly wide range of environmental factors influencing biofilm formation. However, effective capture and interpretation of these combined factors to identify their influence on biofilm formation is a challenge using traditional biofilm analyses. The field is moving towards greater understanding of biofilm dynamics, with recent advances in multiomics, microscopy and synthetic biology (Fig. 3) providing a pathway for biofilm discoveries.

EPS synthesis, secondary metabolite production, cellular morphological switches and ROS protection are coordinated by quorum sensing[123–125]. However, multifaceted biofilm formation (Fig. 1) is also directed by gradients of nutrients, oxygen, metabolic activity, the hydrodynamic environment and shear forces[126–129], adhesive properties conferred by initial attachment mechanisms of individual species[130–132], and the subsequent synthesis of extracellular matrix components[133,134]. Together, these inputs orchestrate a biofilm output to a given environmental scenario, a multifactorial-driven event which we cannot yet predict in precise, accurate detail. Emerging technologies such as advanced biofilm microscopy[135–137], biofilm-based biosensors[138] and improved biofilm models[139] now offer the opportunity to determine how these processes, fundamental to biofilm-host dialogue, interact with space stressors (Fig. 3). As missions extend beyond low Earth orbit, with exposure to partial gravity and increased radiation, these technological innovations should be applied to explore major knowledge gaps in the behaviour of fungal, archaeal and interkingdom biofilm communities under spaceflight constraints[140].

Development of biofilm-specific medical diagnostics and therapeutics includes the leveraging of interspecies and host signalling systems to encourage immune clearance or augmentation of antimicrobial treatment[141,142], the disturbance of quorum sensing or biofilm signalling pathways by inhibitors[143,144] and quorum quenching peptides[145], and the use of nanoparticles to mitigate pathogenic biofilm formation and virulence[146,147]. Other pharmaceutical and device applications include extracellular vesicles for vaccine development[148] and as biofilm-targeting systems[149]. In addition, pathogenic biofilms can be physically removed using magnetic nanoparticles[150,151]. Such precision biofilm-based approaches are emerging to meet the long-duration spaceflight challenges of aerospace medicine and food security.

Precision and regenerative medicines utilising biofilms may protect against spaceflight-associated microbiome shifts, with strain-based biosensors detecting changes in biofilm-host dialog during early disease development and activating appropriate drug or nutrient delivery responses[152–156]. Probiotic microorganisms, such as some *Lactobacillus* sp., *Bifidobacterium* sp. and *Escherichia coli* Nissle 1917[152–154], could promote

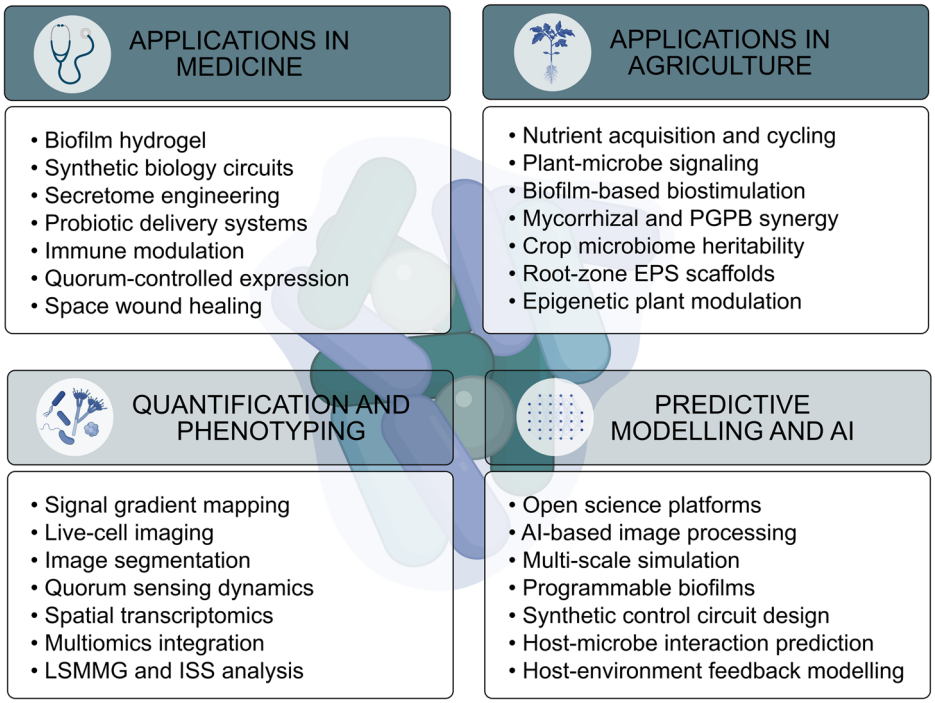

Fig. 3 | Innovative methodologies and future applications for studying biofilm. Addressing biofilm knowledge gaps relevant to spaceflight and terrestrial contexts requires targeted research. There is a need to determine how signalling inputs from environmental cues of shear stress, microgravity and oxidative stress are integrated with the spatio-temporal dynamics of quorum-sensing (QS) molecules and nutrient, oxygen and metabolite gradients to modulate specific microbial behaviour. Similarly, understanding the mechanistic links between signalling and metabolic systems, microbial community population dynamics, and the biofilm life-cycle in spaceflight, clinical or agricultural contexts is also essential. The emerging technologies listed can capture signalling system dynamics, metabolomic processes and biofilm architecture in space-analogue and Low Earth orbit environments. This will generate the data required for the predictive modelling and AI methods to drive forward innovation in biofilm technology platforms for both medicine and agriculture.

biofilm formation and act as drug delivery systems[157], along with nanoparticles to augment or reseed biofilms[155,156], and applications including microbially-doped implant surfaces[158] and probiotics for osteoporosis[159]. Biofilm dressings for wounds, bone and deep tissue trauma may also scaffold tissue regrowth and deliver immunotherapy and growth factors to halt disease progression and improve recovery time[158,159].

Considering plant health, engineering of plant-associated biofilm communities to support immunity and nutrient exchange should enhance crop growth, resilience, and yield with reduced chemical inputs or pesticides required in closed-system off-Earth environments[29,75,160,161]. Development of plant-associated biofilm interventions, which could harness natural plant microbiome-modulating exudates[162], for nutrition-enriched fresh foods[163,164] and plant-derived medical provisions[165,166] must be prioritised to support human health in long-duration spaceflight.

Programmable living materials are being developed, either through EPS matrix-derived delivery technologies[167] or encapsulation of microorganisms in hydrogel-based synthetic matrix for specific body sites[168,169] and biofilm-directed wound healing[170]. Programmable biofilm communities would enable on-demand pharmaceutical production, alleviating drug stockpiling and degradation concerns[171] through strategic off-Earth resource utilisation. The divided labour and cross-feeding characteristics of biofilm communities may be exploited for 3D-printed biofilms, layered with microbes engineered to catalyse specific steps in drug biosynthesis[172]. A biobank of strains with defined enzymatic functions could one day enable a 'plug and play' 3D printing system to produce mission-specific pharmaceuticals.

Space provides an unprecedented opportunity to explore biofilm as a functional structure in its own right, as a component of healthy humans and plants, and as a biological technology. Clear scientific priorities must be met to coordinate research that reduces these knowledge gaps (Fig. 4).

Data-driven Open Science to accelerate biofilm discovery

The NASA Open Science Data Repository (OSDR) curates accessible spaceflown and ground-based analogue data for use by the global research community[173]. OSDR is an exemplary Open Science model (Fig. 4) that promotes inclusive, cutting-edge research and maximises the scientific productivity of low sample size experiments and costly space missions. Several key papers furthering our understanding of spaceflight on organism health have been enabled by NASA OSDR[105,174–177], demonstrating how the integration of multiomics, physiological and imaging data can uncover new insights into biofilm biology. OSDR data analysis pipelines can be used as a foundation to help drive artificial intelligence (AI) and machine learning (ML) based biofilm research, as is already occurring in other fields[115,178].

Computational architectures and models integrating data could predict biofilm formation, growth dynamics and interactions with host organisms under spaceflight conditions, or for specific terrestrial scenarios, generating risk profiles and informing tailored interventions. AI/ML approaches have been used to explore biofilms, including for deep learning segmentation of dense bacterial communities (e.g. MiSiC, U-Net and StarDist frameworks)[179,180], ML and network analysis of *S. aureus* transcriptomic data to identify biofilm-associated modules[181], and interpretable classifiers predicting bacterial attachment to material surfaces[182].

Transparency of AI/ML modelling continues to be a significant issue for trustworthy analysis and collaborative interpretation across life scientists, clinicians, engineers and mission operations teams. Depending on the structure and dimensionality of the data, analysis can involve models with intrinsically interpretable structure, such as linear or generalised models[182], or moderately flexible approaches that retain interpretability, such as additive models or penalised regression[183]. In reasing model complexity may be preferred when more interpretable models fail to capture key non-linearities in the data. Deep learning or ensemble models[184], including more computationally tractable graph neural networks[185], allow enhanced complexity with satisfactory explainability. For highly flexible, or black box models, model-agnostic explanation tools have the potential to help interpretability[186] by estimating the contribution of specific taxa, analytes, environmental conditions, or material interfaces to biofilm behaviour. By introducing model complexity incrementally, predictive accuracy may be improved with greater confidence and lead to effective decision-making and more meaningful collaboration. However, next-generation foundational models with high performance and interpretability require more biofilm data than is currently available, highlighting the need for greater cooperation across the international space-based biofilm research community.

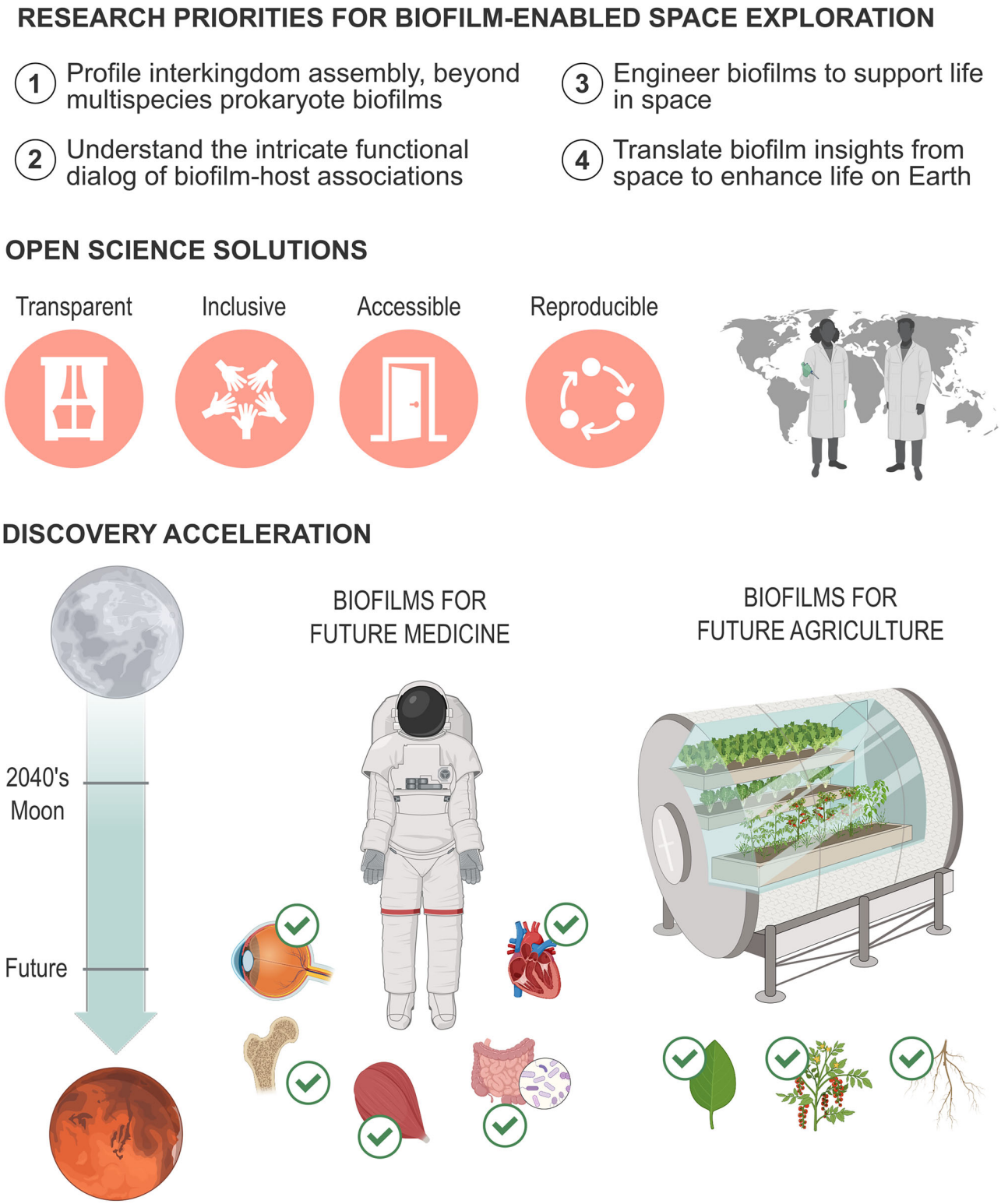

Fig. 4 | Biofilm research priorities and open science accelerated discovery. Four proposed research priorities could realise biofilm-based innovations. These should aim to move beyond multispecies prokaryote biofilms to characterise interkingdom assembly, to better understand the functions of biofilm host-associations, to engineer biofilms for life in space and to translate discoveries from space to applications on Earth. Transparent, inclusive, accessible and reproducible Open Science can accelerate these discoveries to provide solutions for both future medicine and agriculture in space. A rigorous, systematic programme of Open Science biofilm spaceflight and ground-based experiments designed to answer these research priorities will generate comprehensive insight into biofilm structure, formation and biofilm-host dynamics. Coupled with emerging methodologies, these experiments could provide the discoveries required to build biofilm-based platforms for health support on missions, but also on Earth.

Concluding statement

Biofilms have supported life since primordial Earth. Embedded in multicellular life, biofilms should be understood not only as risk agents to be eliminated but also as complex and adaptive biological tools to be harnessed. Space-based biofilm inquiry, built on Open Science principles, offers an opportunity to develop innovative biofilm-based technologies. These novel technologies will both enable deep-space exploration ambitions and generate sustainable, meaningful impacts on Earth.

Data availability

No datasets were generated or analysed during the study.

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Additional information
Correspondence and requests for materials should be addressed to Katherine J. Baxter or Nicholas J. B. Brereton.

[1]School of Molecular Biosciences, University of Glasgow, Glasgow, UK. [2]Department of Biology, Maynooth University, Maynooth, Ireland. [3]Cures Within Reach, Chicago, IL, USA. [4]Frontier Development Lab, NASA Ames Research Center & SETI Institute, Mountain View, CA, USA. [5]Centre for Physics in Health and Medicine, University College Dublin, Dublin, Ireland. [6]School of Biology and Environmental Science, University College Dublin, Dublin, Ireland. [7]Blue Marble Space Institute of Science, Seattle, WA, USA. [8]School of Interdisciplinary Engineering & Sciences, National University of Sciences & Technology, Islamabad, Pakistan. [9]Department of Biology, North Carolina Agricultural and Technical State University, Greensboro, NC, USA. [10]Grupo Alianza Empresarial, Mexico City, Mexico. [11]Kinray Hub, Cotacachi, Ecuador. [12]Department of Biotechnology, College of Basic Science and Humanities, OUAT (Odisha University of Agriculture and Technology), Bhubaneswar, Odisha, India. [13]Johns Hopkins University, Baltimore, MD, USA. [14]Georgia State University, Atlanta, GA, USA. [15]Space Biosciences, NASA Ames Research Center, Moffett Field, CA, USA. [16]Amentum, Chantilly, VA, USA. [17]State Key Laboratory of Lunar and Planetary Sciences, Macau University of Science and Technology, Macau SAR, China. [18]China National Space Administration, Macau Center for Space Exploration and Science, Macau SAR, China. [19]Department of Biomedical Surgical and Dental Sciences, Università degli Studi di Milano "La Statale", Milan, Italy. [20]Amity Centre of Excellence in Astrobiology & Center for Drug Discovery and Development (CD3), Amity Institute of Biotechnology, Amity University Maharashtra, Mumbai, Maharashtra, India. [21]Department of Biology and Biochemistry, University of Houston, Houston, TX, USA. [22]Biochemistry and Biophysics, Texas A&M University, College Station, TX, USA. [23]Centre for Food Safety, University College Dublin, Dublin, Ireland. [24]McGill Centre for Microbiome Research, McGill University, Montreal, QC, Canada. [25]Canadian Center for Computational Genomics, McGill University and Genome Quebec Innovation Center, Montreal, QC, Canada. [26]Department of Human Genetics, McGill University, Montreal, QC, Canada. [27]Department of Ecology and Evolutionary Biology, Kansas Biological Survey and Center for Ecological Research, University of Kansas, Lawrence, KS, USA. [28]Space Blue Marble Institute of Science, Exobiology Branch NASA Ames Research Center, Moffett Field, CA, USA. [29]Research Within Reach, San Francisco, CA, USA. [30]Center for Space Medicine, Baylor College of Medicine, Houston, TX, USA. [31]BioServe Space Technologies, Smead Aerospace Engineering Science Department, University of Colorado, Boulder, CO, USA. ✉e-mail: Katherine.Baxter@glasgow.ac.uk; nicholas.brereton@ucd.ie