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Can prebiotic systems survive in the wild? An interference chemistry approach

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It is challenging to evaluate the relevance of any given chemical system or geological environment to the origin of life. At the same time, life is the product of prebiotic chemistry that took place in some environment. We may attempt to quantify the probability landscape of organic systems and their host environments on prebiotic worlds as a preliminary step to solving the origin of life. Mapping out the environments and chemical systems of prebiotic habitable worlds requires an integration of at least two fields: prebiotic chemistry, which can discover relevant systems of reactions; and geosciences, which can identify likely planetary environments in which prebiotic systems can develop. However, parallel exploration of prebiotic environmental conditions and chemical systems is inefficient given the immense parameter space available. Here, we propose to emphasize the combined experimental study of prebiotic systems and their proposed host environments, which we term *interference chemistry*. Environmental variables may interfere either constructively, neutrally, or destructively with specific pathways of organic chemical synthesis, as tracked by e.g., yields or rates of reactions. In turn, prebiotic chemical systems may modify the wider environment, e.g., bulk solution chemistry. Interference chemistry therefore offers an efficient way to construct, describe, and discover prebiotic environmental scenarios, which should in turn assist us assess plausibility for origin of life scenarios.

KEYWORDS

origins of life, prebiotic chemical evolution, early earth, geochemistry, environments

Introduction: Interference chemistry and the prebiotic earth

Life relies upon reactions between organic molecules that do not proceed in the absence of enzymes (Benkovic and Hammes-Schiffer, 2003). In doing so, biology exploits energy sources in the environment that abiotic chemical pathways fail to eliminate. However, enzyme assembly without biochemical intervention has not yet been observed in naturally occurring settings. Therefore, whilst almost everything about the origin of life remains uncertain, we can be sure that organic chemical pathways on the prebiotic Earth,

TABLE 1 A geochemical roadmap of prebiotic Earth.

Interferences	Alkaline lake	Acid lake	Glacial brine	Alkaline vent	Acid vent	Shallow fresh-water	Seawater
pH (log units)	> 10 ^A	< 5 ^D	~ 5 ^F	~ 9 ^H	~ 3 ^H	~ 6 ^O	< 7 ^T
PO ₄ (mM)	1000 ^A	< 1 ^E	< 10 ⁻³ ^F	< 10 ⁻³ ^I	< 10 ⁻³ ^I	0.05 ^O	< 0.1 ^V
SO ₄	1000 ^A	1 ^D	50 ^F	0 ^H	0 ^H		10 ⁻³ ^W
HS-	0.1 ^B	10 ⁻⁴ ^D		0.05 ^H	1 ^H	10 ⁻³ ^P	10 ⁻⁶ ^W
HSO ₃ -						< 1 ^P	
SO ₃ ²⁻						< 1 ^P	
Li	10 ^B	1 ^D	1 ^F	0.05 ^H	0.5 ^M	10 ^Q	0.05 ^H
B	1000 ^A	1 ^D	1 ^F	0.05 ^J	0.5 ^M	5 x 10 ⁻³ ^R	0.5 ^X
Cl	1000 ^A	10 ^D	1000 ^F	500 ^H	1000 ^H	0.1 ^Q	500 ^H
Ca	10 ^A	0.1 ^D	100 ^F	50 ^H	50 ^H	0.5 ^O	50 ^Y
Mg	10 ^A	0.01 ^D	100 ^F	1 ^H	0 ^H	0.1 ^O	10 ^Y
K	1000 ^A	1 ^D	10 ^F	10 ^H	10 ^H	0.01 ^O	10 ^H
Na	10 ^A	10 ^D	1000 ^F	50 ^H	500 ^H	0.1 ^O	500 ^H
Br	100 ^A	0.01 ^D	1 ^F	1 ^K	0.5 ^K	0.01 ^S	1 ^H
DIC	1000 ^A	5 ^D	100 ^F	0 ^L	10 ^J	1 ^T	< 1 ^T
Fe(II)	5 x 10 ⁻⁴ ^A	0.1 ^D	0.5 ^F	< 10 ⁻³ ^H	50 ^H	0.1 ^O	0.1 ^Y
Si	1 ^C	10 ^D	0.5 ^F	0.1 ^M	10 ^M	0.1 ^O	1 ^Y
Wet/dry cycles				Mineral surfaces?	Mineral surfaces?		Aerosols? Evaporites?
UV irradiation				Shallow variants only	Shallow variants only		Near-surface only
Serpentinization	Hydrothermal end-members?		Hydrothermal interface?			Low temperature serpentinization?	Deep sea?
Exogenous material				Shallow variants only	Shallow variants only		Tidal variants?
Temperature (°C)	1-100	1-100	0-10 ^G	10-100 ^N	10-100 ^N	10-50 ^U	10-50 ^Z
Strength of constraint	Based on dedicated experimental/theoretical studies of prebiotic conditions				Uncertain		

Notes: Maximum estimated concentrations in mM for each environment are rounded to nearest gradation (1 < 5 → 10). Colour shading indicates where available constraints on a given environment are either especially uncertain (orange), or conversely based on dedicated experimental/theoretical studies of prebiotic conditions (green). DIC – Dissolved Inorganic Carbon, Fe(II) – dissolved ferrous iron. Additional references for acid and alkaline vent fluids in end-member compositions of Hodgkinson et al (2015) are as follows: (Kelley et al., 2001; Charlou et al., 2002; Douville et al., 2002). This compilation is not intended to be exhaustive. References cited from A-Z: (Toner and Catling, 2020), B (Visscher et al., 2020), C (Zheng et al., 2016), D (McCleskey et al., 2005), E (Mulkidjanian et al., 2012), F (Lyons et al., 2019), G (Harrison, 2009), H (Hodgkinson et al., 2015), I (Edmonds and German, 2004), J (Lang et al., 2018), K (Berndt and Seyfried, 1990), L (Bradley et al., 2009), M (Seyfried et al., 2011), N (Barley et al., 2005), O (Hao et al., 2017), P (Ranjian et al., 2018), Q (Dellinger et al., 2014), R (Negrel et al., 2002), S (Neal et al., 2007), T (Morse and Mackenzie, 1998), U (Rollinson, 2007), V (Rasmussen et al., 2021), W (Crowe et al., 2014), X (Uppström, 1974), Y (Jones et al., 2015) Z (Zahnle et al., 2007).

occurring at least to begin with in the absence of enzymes, differed hugely from those observed today.

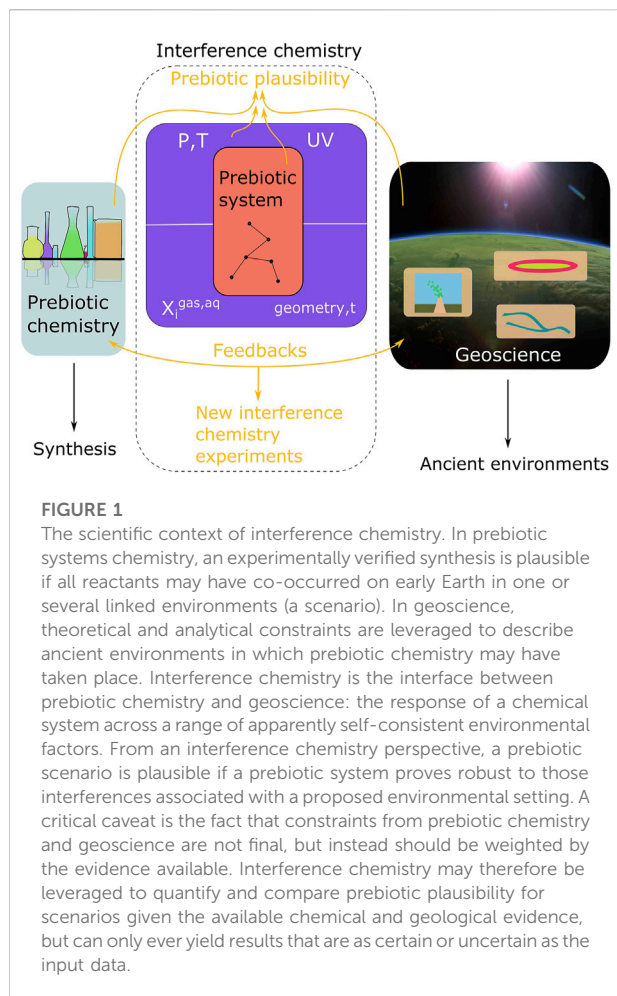
The diversity and prevalence of organic molecules on prebiotic Earth will have depended crucially on their stability and interactions with habitable—but uninhabited—geochemical environments. It is therefore necessary at some level to link geoscience constraints on planetary environments with experimentally demonstrable chemical systems when defining a prebiotic scenario (Schwartz, 2013). This situation applies both to scenarios simply describing environmental chemistry and those that attempt to explain the emergence of biochemistry.

Prebiotic scenarios must describe reaction pathways (collectively a chemical system) hosted in one or more geochemical environments. Prebiotically plausible syntheses have now been published for membranes, information-storing polymers, and compounds that appear universally in extant metabolism, and systems chemistry research linking some of these pathways has been pursued (Deamer and Oro, 1980; Leboutteiller and KuassiviFerlet, 2005; Griffith and Vaida, 2012; Ritson and Sutherland, 2012; Barge et al., 2014; Damer and Deamer, 2015; Patel et al., 2015; Islam and Powner, 2017; Milshteyn et al., 2018; Barge et al., 2019; Bonfio et al., 2019; Morasch et al., 2019; Pasek, 2019; Wu and Sutherland, 2019; Bonfio et al., 2020; Liu et al., 2020; Yadav et al., 2020). New

discoveries about early Earth geochemistry offer constraints on the possible environmental settings for these systems (see Section 3, Table 1). Despite this progress, substantial challenges remain with linking these promising chemical and geological constraints into prebiotically plausible scenarios.

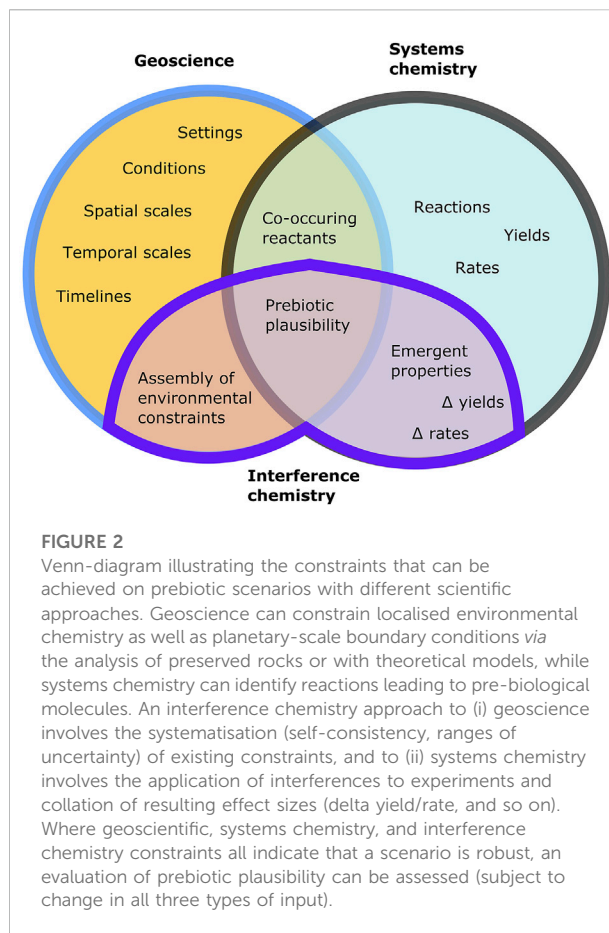
Experiments are necessarily run under controlled conditions that are generally absent in naturally occurring environmental scenarios. The mismatched complexity between experiments investigating prebiotic chemistry and naturally occurring environments may be seen as broadly problematic (Shapiro, 1984). On the other hand, this discrepancy might be viewed as an opportunity for great progress. In order to make that progress, we require some broad agreement on the nature of the problem, the tools at our disposal, and the way in which discrete approaches to the study of prebiotic chemistry should interact.

Firstly, it is important to state that prebiotic systems experimentation is often carefully designed in order to 1) obtain a result in the timeframe of a project, 2) understand the reaction(s) at hand, and 3) to satisfy the burden of proof that is typically expected for a novel chemical synthesis. Including the complete inorganic and organic complexity inherent to a naturally occurring environment in a novel synthesis experiment is not conducive to these aims—especially to understanding the novel chemistry being explored in any



given experiment. However, as an understanding of plausible prebiotic chemistry accumulates, increasingly multi-faceted approaches may usefully be pursued to evaluate their efficacy. In particular, it is now increasingly common to study a series of linked reactions—prebiotic systems chemistry (Islam and Powner, 2017)—and, separately, the efficacy of those prebiotic systems in the context of environmental perturbation (Miller, 1987; Robertson et al., 1996; Miyakawa et al., 2002; Todd et al., 2019). What is currently lacking is a widely shared and systematic approach to recording, reporting, and ultimately leveraging insights from interference chemistry. Here, we present a formalisation of the latter approach: interference chemistry.

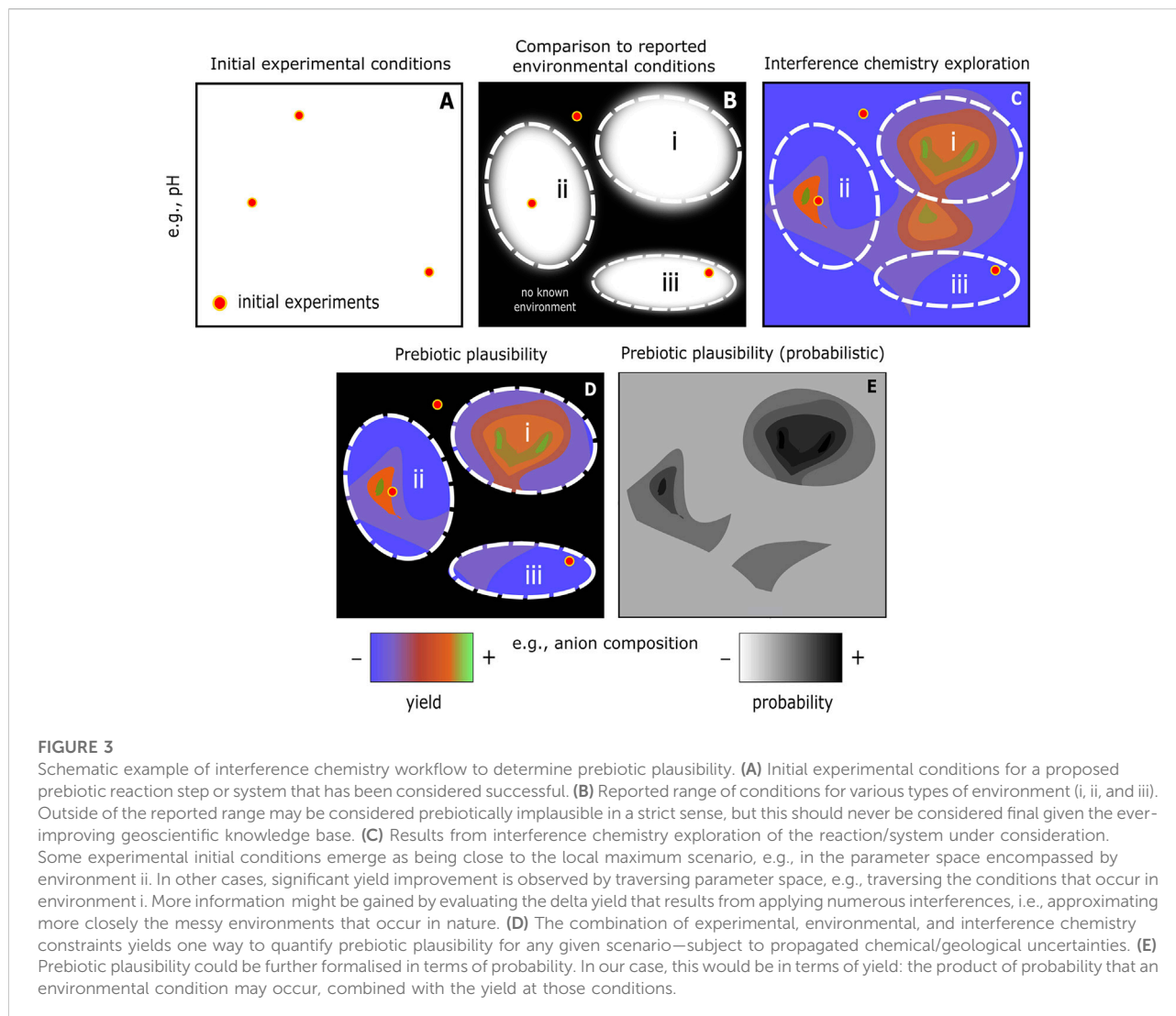
We define interference chemistry as the study of interactions between a prebiotic system and a host environment (Figure 1). The environmental scenario encompasses the pressure and temperature conditions at which reactions take place as well as environmental context, e.g., atmospheric, aqueous and substrate composition, environmental geometry, fluid dynamics, timescales, etc. Prebiotic systems encompass abiotic organic chemical reactions, which may or may not have synthesized molecules of purported relevance to the origin of



life. Natural environments in which prebiotic systems could have developed are messy, containing many spectator ions, mineral phases, and spatially and temporally variable physical processes, e.g., wet/dry cycles. Each of these environmental variables may interfere with prebiotic systems.

Interference chemistry involves tracking some measurable outcome of inorganic (environmental or chemical) and abiotic organic (potentially prebiotically relevant) processes. This outcome may be as complex and broad as the overall chemical make-up of an environment of interest (this may be local, e.g., a pond, or global, e.g., a planetary atmosphere) or as simple as the yield of a reaction deemed to be of particular interest. Where the goal is simply to describe in detail plausibly prebiotic environments then individual interferences need not be categorized as constructive or destructive. The outcome in this general case is of interest regardless of the details, as we are learning about which environments may have prevailed on early Earth.

Alternatively, we may test the performance of the system given some environment, e.g., yield of a specific product. In this case we require some way to categorize the outcomes and implications of interference chemistry. Take the example of a



reaction pathway known to produce a molecule of known prebiotic interest, e.g., synthesis of RNA in water, and temperature—a universal environmental parameter. In this case, interference may be constructive, e.g., the warming of an environment to melt ice and allow aqueous reactions to occur; destructive, e.g., the continued heating of the environment and eventual thermal degradation of organic products; or neutral, having no effect on the pathway at hand, e.g., insensitivity of a particular reaction to temperature across some range of measurement.

Combining the logic of systems and interference chemistry approaches, we propose a new over-arching definition of prebiotic plausibility: a prebiotically plausible scenario is one in which the proposed prebiotic system is 1) demonstrable in the laboratory setting, 2) utilises only reactants and processes that likely co-occurred in geological environments. Where the scenario is to be extended from merely a description of

plausible environmental chemistry to a plausible synthesis for a specific molecule or set of molecules (or complex chemical interaction, or life itself) then additional constraints must be met: 3) remaining efficacious given interference by the local environment, or suite of connected environments, and 4) producing sufficiently high yields at each step to continue—without arbitrary intervention—through to completion.

Interference chemistry encapsulates the testing of point (3): the direct incorporation of multiple environmental factors into successful prebiotic systems, and then—by a process of iteration—identifying prebiotically plausible parameter space (Sasselov et al., 2020). As such, interference chemistry draws on distinct types of information to geoscience or systems chemistry alone (Figure 2). Moreover, by leveraging insights unique to geoscience, systems chemistry, and interference chemistry, quantitative constraints may be obtained for

scenarios that address each component of prebiotic plausibility, as defined above (Figure 3). Crucially, this definition of prebiotic plausibility applies to the conjunction of chemistry and environment, and only provides information within certain logical bounds. For example, if some proposed chemistry fails in environment A (contradicting points 1 and 3), it might still work in environment B, and if some species X needed for the chemistry is unlikely to be present in environment A (contradicting 2), it says nothing about whether species X is likely to be found in environment B.

An interference chemistry study is distinct from a chemical or geoscience study in that it does not set out to demonstrate a novel synthetic system or to place novel constraints on an environment, but to systematically examine the response of the chemical system to relevant environmental conditions (Figure 3), i.e., a multi-factor experimental approach. In Figure 3 we have illustrated for the sake of simplicity a (schematic) two-dimensional parameter space showing interactions between pH and anion composition. In reality, prebiotic chemical systems are high-dimensional systems. Visualizations of real systems will therefore be correspondingly more complex. Tackling and overcoming this complexity is the main opportunity and difficulty of implementing interference chemistry.

Implementing interference chemistry requires overcoming three main challenges: 1) that mapping destructive interferences necessarily means running experiments that produce low yields of a desired product—this is a challenge to a culture where we may be encouraged to report only on successful experiments; 2) the volume of environmental parameter space to be explored is too large to be exhausted in the lab; and 3) the reality that what is considered environmentally plausible is uncertain, and subject to continual advances being made in geoscience.

Screening for multi-factor interactions is commonplace in the study of certain biological and chemical industrial processes (Novack, 2000), and has been commented on before in the context of synthetic biology (Moschner et al., 2022) and even in prebiotic chemistry (Cleaves, 2013). The outstanding question, then, is not merely whether interference chemistry might be a useful pursuit, but whether its widespread implementation is both feasible and justifiable.

Interference chemistry in practice

We examine the experimental feasibility of interference chemistry by considering both published studies that might be categorized as investigating the interference chemistry prebiotic systems, and by briefly reviewing what is currently known about early Earth environmental conditions. We propose distinct burdens of proof for progress in the study of prebiotic systems, environments, and interference chemistry, respectively, arguing that agreement on what these different

approaches should individually seek to achieve has the potential to unlock information flow between disparate fields that collectively seek to understand the environmental chemistry of prebiotic Earth.

Previous interference chemistry approaches

There are numerous published studies that might be considered as falling under the umbrella of interference chemistry. These studies share the common trait of having taken a particular prebiotically relevant species/reaction/system and systematically exploring its response to environmental variables of interest. We consider several specific examples, from prebiotic compartmentalisation, to UV transmission, to bystander-ion-driven catalysis.

Prebiotic membrane-bound compartments have previously been subjected to a diverse range of environmental analogue conditions—both in the lab, and in the field. An outcome of these studies is that certain simple prebiotically plausible amphiphiles will spontaneously assemble into compartments in freshwater and modern hot spring systems but will not do so in seawater (Milshteyn et al., 2018). Meanwhile, other classes of amphiphiles are quite robust to the interferences present in seawater (Jordan et al., 2019a). Much is also known about the response of these structures to pH, ionic strength, and temperature (Yanagawa et al., 1988; Terasawa et al., 2012; Joshi et al., 2017; Milshteyn et al., 2018; Jordan et al., 2019a; Jordan et al., 2019b; Lopez and Fiore, 2019; Bonfio et al., 2020), from which a picture is emerging of which compartments may plausibly have been present in end-member prebiotic environments.

Ultra-violet light is a crucial component of several recently proposed reaction schemes, acting to drive otherwise challenging steps in a high yielding and stereoselective manner (Ritson and Sutherland, 2012; Patel et al., 2015; Rimmer et al., 2018; Rimmer et al., 2021). However, many by-stander species may attenuate the transmission of UV light in geochemically realistic complex aqueous solutions. Ranjan et al. (2021) found that Fe-containing species in e.g., ferrocyanide lakes are efficient at attenuating UV transmission, diminishing the potential for UV-driven constructive organic synthesis, but similarly slowing UV-driven degradation of other molecules that may go on to accumulate and constructively interact along different paths, e.g., meteoritic nucleobases (Pearce et al., 2017). The existing body of work on compartment stability and UV light transmission in the presence of varying environmental interferences provides a model for future work on more complex systems.

The projects outlined above are strong examples of how interference chemistry may be experimentally tractable in some cases. However, there are other examples where novel combinations of prebiotic systems and geological conditions

yielded surprising constructive interferences, without necessarily having focussed on parameter space exploration. An important example are the cases of phosphate and borate in prebiotic chemistry. These topics have received a great deal of attention previously (Fernández-García et al., 2017; Liu et al., 2019), and we make no attempt to summarise the breadth of previous discussion on the issue here. Instead, we point to the fact that these anions have proved diversely useful in prebiotic chemical synthesis when used at high concentrations. Phosphate in these experiments has utility either as a general acid-base catalyst or as a chemical buffer, greatly enhancing reaction selectivity and yield (Powner and Sutherland, 2010; Patel et al., 2015; Islam and Powner, 2017; Morasch et al., 2019). Similarly, borate acts to make the formidably messy formose reaction far more selective for the synthesis of compounds of apparent prebiotic interest, e.g., by stabilizing, ribose sugar (Benner et al., 2012; Kim et al., 2016).

The above constructive interferences by phosphate and borate in prebiotic chemical synthesis occur only when these anions are present at high concentrations. Both phosphate and borate are scarce in most modern aqueous environments, which may at first glance appear to damage the plausibility of prebiotic scenarios relying on the use of either (Table 1). However, geochemical scenarios are now being independently developed in which phosphate and/or borate may indeed have been present at the high concentrations required by published syntheses (>10 mM), reshaping our view of what may count as prebiotically plausible (Rasmussen et al., 2021; Ingalls et al., 2022).

If the once prevailing view of limited phosphate and/or borate availability on early Earth had been used as a stringent guide for experimental progress, the valuable constructive roles in prebiotic organic synthesis of anions which are currently scarce in surface environments—but might not always have been—may never have been fully recognized. Examples of such unexpected interactions inform us that it is crucial for prebiotic environmental constraints to be explored in the intentionally broad manner that we hope interference chemistry can help to promote. That is to say, prebiotic plausibility only applies to a combination of both chemistry and environment, and is a matter of probabilities and degrees of confidence. Wandering outside what we think of as plausible, even as defined here, can be immensely scientifically rewarding. However, this type of research is limited not only by experimental practicality, but also by our knowledge of which specific interferences are associated with prebiotic environments—an uncertainty that makes it difficult to bridge lab and environment (Figure 1).

Environmental parameter space of prebiotic earth

Much is uncertain about the nature of prebiotic Earth. The timeline, surface conditions, and basic geology of the planet in

this state are all difficult to ascertain, owing to a lack of a rock record for the first half billion years of Earth history (4.45–4.0 Ga—early Earth, from here-on-in). *Via* a combination of extrapolation and theoretical study, there is consensus that early Earth atmosphere was anoxic, with somewhat clement surface temperatures, and that there were surface oceans rich in dissolved iron (Valley et al., 2002; Zahnle et al., 2007; Shaw, 2008; Harrison, 2009; Sessions et al., 2009; Planavsky et al., 2011; Partin et al., 2013; Scott et al., 2013; Lyons et al., 2014; Planavsky et al., 2014; Ge et al., 2018). Much more uncertain is the extent of emergent land (of any rock type), the composition and mere existence of continents, whether or not the atmosphere was highly reducing, and if those generically habitable surface conditions leaned towards global icehouse or hothouse conditions (Valley et al., 2002; Barley et al., 2005; Rollinson, 2007; Zahnle et al., 2007; Harrison, 2009; Sleep, 2010; Bell et al., 2011; Marchi et al., 2014; Roberts and Spencer, 2014; Thomassot et al., 2015; Hastie et al., 2016; Johnson et al., 2017; Smit and Mezger, 2017; O'Neill et al., 2018).

In Table 1, we summarize the geochemical characteristics of commonly invoked prebiotic environmental scenarios for early Earth. Our compendium provides an overview of environmental parameters that can be used as a starting point for interference chemistry research, e.g., by the exposure of a proposed prebiotic systems to a set of environmental interferences.

We rely on modern analogues that have been studied in detail as the basis of our compendium, supplemented where possible with what is known about each specific environmental interference on early Earth. Some species found in key environments for prebiotic chemistry are highly sensitive to surface conditions yet have not received detailed modelling or experimental studies relevant to early Earth conditions. In Table 1, such especially uncertain estimates are shaded in orange. Conversely, estimates derived from studies designed to investigate prebiotic and/or early Earth (Archean) conditions are shaded in green.

As a key example of these uncertainties, we highlight alkaline lakes. Restricted subaerial and confined submarine crustal environments are increasingly proposed in scenarios for the origin of life (Westall et al., 2018; Deamer et al., 2019; Toner and Catling, 2019; Toner and Catling, 2020). However, there are many open questions about the interference chemistry of such basins on early Earth. Sulphate concentrations in alkaline lakes are very high in the modern, approaching molal concentrations (Table 1). However, such systems are unlikely to have generated the same sulphate concentrations under an anoxic atmosphere and in the absence of sulphide-oxidising bacteria (Visscher et al., 2020). Similarly, dissolved iron concentrations are directly linked to oxidising power in the environment. With soluble ferrous iron (Fe^{2+}) being dominant in early Earth surface environments, it is likely that prebiotic analogues of modern surficial aqueous environments may have been fed by iron-rich inflow—although, iron carbonate mineral precipitation may

have acted to limit final concentrations (Toner and Catling, 2020).

Finally, atmospheric $p\text{CO}_2$ of early Earth is poorly constrained, rendering Dissolved Inorganic Carbon (DIC) estimates uncertain for all environments (Krissansen-Totton et al., 2018; Kadoya et al., 2020). This uncertainty is problematic, as $p\text{CO}_2$ and DIC are a major control on the pH and overall chemistry of restricted subaerial solutions in equilibrium with the atmosphere, e.g., phosphate content of soda lakes (Toner and Catling, 2020). Available DIC is also required for abiotic production of organic carbon in many proposed prebiotic environments (Lang et al., 2018).

On the other hand, dedicated studies on ancient weathering processes and ocean chemistry more tightly constrain several key interferences in early river and ocean water (see Table 1). However, for most environments in Table 1, we do not highlight interferences as especially likely or unlikely to be reflective of plausibly prebiotic environments: for now, we simply do not know either way.

Our survey is far from all-encompassing. Mapping out environmental chemistry on Earth prior to the rise of life is a huge undertaking—independent of the specific question of where life first began, and currently lacking deep integration with organic prebiotic chemistry. The critical next step is to understand more deeply the feedbacks between inorganic planetary chemistry and prebiotic organic chemistry, i.e., the defining features of prebiotic Earth. It is this broad base of knowledge that we argue interference chemistry can contribute to.

The interference chemistry framework has at its core the two-way flow of information between prebiotic chemistry and the study of early Earth conditions: whereby the reactions that drove the origin of life—as well as those that did not, but still widely occurred—will have acted to shape both local environments and ultimately global planetary conditions. At the same time, prevailing environmental conditions will have determined the plausibility and feasibility of proposed origin of life scenarios. Interference chemistry may therefore be leveraged in pursuit of dual constraints on 1) wider environmental conditions at the dawn of life and 2) the specific environments in which life may have emerged.

Difficulties in assessing prebiotic plausibility

From the perspective of planetary science, it is often much easier to say what interferences were not present than to establish those which were, and to establish limited global constraints on environmental conditions, rather than to specify the detailed local environmental conditions needed to constrain origin of life scenarios. Especially when studying the ancient past, geoscience

may be more suited to obtaining constraints on processes that operate over long timescales and large length-scales. In contrast, prebiotic chemistry—especially those systems that are tractable in the lab—may largely operate under ephemeral conditions in local environments (Table 2). Published environmental constraints may therefore fail to readily describe local environments that may have hosted prebiotic chemistry. Moreover, geoscience constraints are constantly updated as new data is made available. Formulating an assessment of prebiotic plausibility with environmental constraints may therefore be flawed, creating an unhelpful barrier to synthetic chemistry exploration.

Our proposal for the recognition of interference chemistry as a discrete approach (Figure 1) is intended to smooth out the difficulties that may arise when judging systems chemistry results with a geochemical filter. Geoscience should continue to strive to understand the initial environmental conditions of early Earth. Meanwhile, projects explicitly pursuing interference chemistry can examine the interplay between state-of-the-art prebiotic systems and knowledge of the early Earth. In doing so, insights should be gained about which processes are viable based on current knowledge, offering up new routes for biomolecule synthesis and novel perspectives on early environmental chemistry. Here, we suggested a path for systematic exploration of interference chemistry parameter space. This exploration can be systematic without being comprehensive (which represents an impossible ideal).

It is worth explicitly stating that the implementation of interference chemistry might be considered as a valuable opportunity to diminish the extent of geochemical gatekeeping in prebiotic chemistry. The lessons of the past inform us that even widely held views about what is plausible from a geochemical perspective should not be used to inhibit progress in the field of systems chemistry, as those conceptual boundary conditions may 1-day change. However, given that we must ultimately strive to find a scenario for the origin of life that is both experimentally verified and consistent with our understanding of environmental chemistry on the early Earth, interference chemistry offers a conceptual space where attempting to fulfil this high burden of proof seems reasonable.

Interferences provide a sensible metric to quantify whether or not a chemical system is valuable on its own merits, e.g., can it provide the products we desire, exist in an environment known to exist in nature, and function in a timeframe that is testable in the lab? However, quantifying the relevance of a given system to the origin of life is a much more challenging prospect. We might contemplate metrics such as degrees of self-organisation, self-catalysis, longevity, discovery of new function, and so on, but the challenge here is formidable. Until prebiotic synthesis can in any sense bridge the gap between chemical and biological, it seems more tractable at present to tackle the smaller—but

TABLE 2 Timescales of prebiotic chemistry and environmental processes.

Timescale	Prebiotic systems	Environmental processes				
		Hot springs	Glacial brine	Vents	Shallow fresh-water	Seawater
second	proto-enzymes					
minute	catalysed reactions	rain		mineral dissolution / precipitation	evaporation	waves
hours						tides
days	uncatalysed reactions		diurnal cycles			
weeks		evaporation		volcanism		
years			melt cycles			
centuries				bolide impact		basin evaporation
Kyr						
Myr						
Gyr			tectonics (e.g., continental drift, subduction)			

still vast—problem of mapping out prebiotic environments and their organic chemical systems.

Data collection *versus* integration

We have argued that interference chemistry provides a way to explore, make sense of, and leverage geochemical complexity in a prebiotic context, in terms of evaluating the plausibility of specific regions of chemical-environmental parameter space with respect to a specific system of reactions. However, there are numerous theoretical issues branching from an interference chemistry approach that will demand future attention. One such issue is data collection *versus* integration.

Interference chemistry as we have pitched it could help to collect increasingly prebiotically relevant data. However, we are still then faced with evaluating the relative plausibility of one prebiotic scenario *versus* another, some of which may be mutually exclusive, i.e., integrating disparate data. More complex forms of environmental and chemical interference then emerge for us to consider in our quest to map out the nature of prebiotic Earth, related to the dynamics, timescales, and sizes of environments.

For example, if we propose that one environment (e.g., glacier ice) hosting a particular prebiotic chemistry existed on early Earth, could it have co-existed with another environment (e.g., high pCO₂ atmosphere) invoked in another step of the same proposed sequence of events? Are these environmental conditions mutually exclusive? Similarly, would the prebiotic chemistry of one environment have in fact inhibited that proposed to have occurred in another, after considering local/regional/global feedbacks? Can we be sure that the regions of

parameter space involved in a given scenario—explored and tested for plausibility (using interference chemistry or otherwise)—remain plausible when placed into a complete planetary context?

Integrating interference chemistry constraints on the nature of prebiotic Earth will require reaching ever further beyond the initial focus of *in-situ* prebiotic chemistry, e.g., considering the compositions of planetary crusts that determine local environmental diversity, and to astrophysical constraints that determine the chemistry of those crusts. There is no way to directly account for these types of interferences and boundary conditions in the context of an individual experiment. Therefore, whilst the relatively simple multi-factorial experimental design that we suggested here for interference chemistry may give us some measure of plausibility for a specific system (within available experimental or theoretical constraints at the time) it will fall short of helping us integrate resulting data from many disparate experiments.

Given the absence of empirical evidence for the nature of environments and chemistry on the prebiotic Earth, we envisage that data integration accounting for interference effects will at some level rely on linked simulations. Progress in this regard has been made in several relevant areas, including the formulation of self-consistent global biogeochemical models, which are being employed to reconstruct the evolution of Earth's surface environment over time (Lenton et al., 2018; Mills et al., 2018), and rule-based models of complex chemical systems in the modelling of physical chemistry (Goldford et al., 2019; Wolos et al., 2020; Arya et al., 2022). We view these tools as being likely essential for bridging spatial and timescales that are not tractable in the lab and for linking fields (e.g., feeding simulations of prebiotic systems into models of planetary geochemistry). Experimental and observational approaches then have the pivotal role of informing the mechanics at play in such simulations.

As with experiments, which we have focused on in this article (systems and interference chemistry), results from simulations will only be as strong as the validity of their core assumptions. Predictions made by simulations may be less unhelpful if they are left untested and, in some cases, it may not be tractable to perform an equivalent experiment in the lab. However, data generated by exoplanetary science may provide us with the empirical data needed to test planetary-scale simulation results. Exoplanetary science provides the possibility to observe worlds of a similar stellar parent body, orbital configuration, and chemical composition to Earth, of various ages. Mapping out the distribution of life in our galaxy will permit us to test origin of life scenarios using real planetary laboratories, and to build statistical descriptions of prebiotic chemistry at the planetary scale. Ultimately, we will be able to answer crucial questions: what do prebiotic Earth-like worlds look like, and how many Earth-like worlds give rise to life? These data may then enable cross-environmental data integration in prebiotic chemistry, i.e., the ability to test predictions made by planetary-scale simulations of prebiotic chemistry, and then within that context to re-evaluate which scenarios for prebiotic environments (and eventually, the origin of life) can be constructed in a truly self-consistent manner.

Conclusion

As far back as we have been able to reach in Earth's past, whether through rocks or through genetics, life's origins have remained beyond the horizon. In stark contrast, the alternative route of working from the ground up *via* prebiotic chemistry, aiming to build life in the laboratory, has made outstanding progress. Carefully regulated laboratory experiments have now been able to create the building blocks of life: RNA, protein and lipid precursors. These experiments place prebiotic chemistry in a firmly testable physical and chemical context, i.e., they point to specific astrophysical and geological settings where this chemistry could occur. Whilst in the lab these reactions are carried out under ideal conditions, in nature the chemistry will inevitably be messier. Nonetheless, prebiotic chemistry must have emerged from geochemistry; linking the two is therefore fundamental for establishing how rocky worlds can give rise to life.

We propose a term to describe research that explicitly investigates the robustness of prebiotic chemistry to environmental conditions: interference chemistry. By identifying the geochemical characteristics of prebiotic environments, and testing prebiotic organic systems under these natural conditions, we will refine our view of the prebiotic planetary 'wild'. In this article, we summarised previous experimental approaches fall under our definition of interference chemistry and presented an initial library of environmental conditions that could be implemented in future experiments.

Interference chemistry has the potential to help evaluate the prebiotic plausibility of a given scenario. However, this possibility must come with the overarching caveat that any and all input constraints are subject to change, as our knowledge of fundamental physical chemistry and the nature of early Earth continuously improves. Nonetheless, separating the burden of proof for environmental plausibility into a separate strand of research—interference chemistry—might have the positive outcome of diminishing the role of geochemical 'gatekeeping' in prebiotic chemical research. The revised approach in interference chemistry, where these two fields are inherently linked, may more often lead to geoscientific constraints that inspire, rather than unproductively inhibit, exploration and innovation in the field of prebiotic chemistry.

Author contributions

All authors contributed equally to the conceptual aspects of the manuscript. CW wrote the manuscript and prepared the figures. All authors reviewed and edited the final manuscript.

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Conflict of interest

The 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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