

Reconciling the variability in the biological response of marine invertebrates to climate change

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ABSTRACT

As climate change increases the rate of environmental change and the frequency and intensity of disturbance events, selective forces intensify. However, given the complicated interplay between plasticity and selection for ecological – and thus evolutionary – outcomes, understanding the proximate signals, molecular mechanisms and the role of environmental history becomes increasingly critical for eco-evolutionary forecasting. To enhance the accuracy of our forecasting, we must characterize environmental signals at a level of resolution that is relevant to the organism, such as the microhabitat it inhabits and its intracellular conditions, while also quantifying the biological responses to these signals in the appropriate cells and tissues. In this Commentary, we provide historical context to some of the long-standing challenges in global change biology that constrain our capacity for eco-evolutionary forecasting using reef-building corals as a focal model. We then describe examples of mismatches between the scales of external signals relative to the sensors and signal transduction cascades that initiate and maintain cellular responses. Studying cellular responses at this scale is crucial because these responses are the basis of acclimation to changing environmental conditions and the potential for environmental ‘memory’ of prior or historical conditions through molecular mechanisms. To challenge the field, we outline some unresolved questions and suggest approaches to align experimental work with an organism’s perception of the environment; these aspects are discussed with respect to human interventions.

KEY WORDS: Coral, Plasticity, Eco-evolutionary forecasting

Introduction

As climate change progresses throughout the 21st century, oceans are experiencing increases in temperature and escalating heatwaves (Oliver et al., 2021), rising frequencies and magnitudes of tropical cyclones (Knutson et al., 2010), as well as a reduction in pH and a shift in carbonate chemistry owing to ocean acidification (Findlay and Turley, 2021). These stressors are affecting ocean life in often negative, accumulating and interdependent ways, resulting in substantial losses for systems such as reduced production of natural and aquaculture oysters (Barton et al., 2012; Thomas et al., 2018b), mass coral bleaching (Hughes et al., 2017a,b) and kelp forest die-offs (Arafeh-Dalmau et al., 2020; McPherson et al., 2021). Climate change is compromising ecosystem functioning and services (e.g. food resources, coastal protection, tourism and cultural services) in coastal marine habitats, with direct consequences for human health, goods and services, and food

security (Costello et al., 2020; Lotze et al., 2019). Collectively, climate change impacts are reducing marine ecosystem biodiversity, composition and function (Doney et al., 2012; Poloczanska et al., 2013; Worm and Lotze, 2021).

The accurate prediction of species’ success under climate change scenarios, known as eco-evolutionary forecasting (see Glossary), is crucial for conservation (e.g. Baltazar-Soares et al., 2023; Webb et al., 2023). However, a primary scientific challenge in eco-evolutionary forecasting is understanding how environmental signals trigger an organism’s responses across biological scales (e.g. molecules–cells–tissues–organisms) and phenotypic outcomes (i.e. genome-to-phenome connections; Burnett et al., 2020; Franklin and Hoppeler, 2021; Rexroad et al., 2019). Such an understanding requires high-resolution characterization of how organisms sense environmental changes and how this enables the plasticity that determines the organisms’ survival (Lavergne et al., 2010). The conditions that enhance plasticity generally include predictable environmental signals (e.g. seasonal changes in temperature, pH and light) of a sublethal, yet biologically detectable magnitude (Reed et al., 2010), as well as higher frequency fluctuations (e.g. diel fluctuations, Barshis et al., 2013; Safaie et al., 2018). However, much of the early research in marine invertebrates has focused on exposure to single stressors and non-fluctuating signals at a coarse-grain resolution, such as population-scale responses (reviewed in Boyd et al., 2018; Dupont and Pörtner, 2013). These essential studies have identified taxa that are particularly vulnerable under global change conditions (Kroeker et al., 2010); subsequent efforts have started to embrace environmental complexity and organismal plasticity (Foo and Byrne, 2016; Marshall and Morgan, 2011; Million et al., 2022; Putnam, 2021; Torda et al., 2017), as well as the interaction of plasticity and evolution (Burton et al., 2022; Catullo et al., 2019; Ghalambor et al., 2015; Kronholm and Collins, 2016; Nadeau et al., 2017; Phillips, 2006). This combined knowledge can improve forecasting outcomes (Duarte, 2014; Logan et al., 2021; Reusch, 2014), but the substantial variation in biological responses remains unexplained. To accurately predict how organisms will acclimate to ongoing environmental change, we must understand the extent to which organisms detect these environmental conditions and transduce them into a response (Podrabsky et al., 2015). In this Commentary, we describe such challenges and opportunities using reef-building corals as an example.

Reef-building corals are foundational ecosystem engineers and archetypal taxa for highlighting the effects of environmental perturbations on marine organisms owing to their existence very near their thermal thresholds and, thus, their significant environmental sensitivity. Although early research focused on characterizing and cataloging the diverse and complex communities of organisms that make up coral reefs (Mayer, 1915), and sought to describe the factors that shaped their distribution and abundance (Connell, 1978), subsequent identification of the fragile nutritional

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Glossary

Anthropocene

The current geological age, viewed as the period during which human activity has been the dominant influence on climate and the environment.

Branching corals

Corals with a branching or tree-like morphology, characterized by multiple branches extending from a central base and thinner tissue than massive corals.

Coefficient of variation (CV)

Statistical measure used to quantify the relative variability of a dataset in relation to its mean.

Coral holobiont

Coral animal (host) and its associated microorganisms consisting of bacteria, archaea, fungi, viruses and microeukaryotes including dinoflagellates of the family Symbiodiniaceae and endolithic organisms (Rohwer et al., 2002).

DNA methylation

DNA methylation is a fundamental epigenetic modification that involves the addition of a methyl group ($-CH_3$) to a DNA base.

Dysbiosis

A disruption, breakdown or imbalance of symbiosis.

Eco-evolutionary forecasting

Accurate prediction of species' success and distribution under climate change scenarios, utilizing principles from both ecology and evolutionary biology.

Environmental 'memory'

The ability of certain molecular marks or modifications, such as DNA methylation or histone modifications, to persist across generations or during an individual's lifetime, respectively, resulting in stable changes in gene expression patterns that contribute to adaptive or acclimatory responses to environmental stress.

'Environmentally mediated priming'

Processes such as respiration, photosynthesis, calcification and irradiance absorption by pigmented tissue drive changes physicochemical internal environment. These changes are more pronounced within thick coral tissues and have the potential to precondition these corals and provide stress hardening, thus decreasing sensitivity to environmental change (Putnam et al., 2017).

Gastroderm (gastrodermal cells)

Inner cell layer of cnidarians (as opposed to the epidermis) lining the gastrovascular cavity. In symbiotic cnidarians, this cell layer includes symbiocytes, which are cells that contain endosymbiotic algae (Symbiodiniaceae).

Gastrovascular cavity

Central body cavity of corals and other cnidarians, where food material is digested and several other key biological functions take place (Hughes et al., 2022).

Gene body DNA methylation

Refers to the pattern of DNA methylation occurring primarily within the coding regions (gene bodies) of genes. Traditionally, DNA methylation has been associated with gene silencing when it occurs in the promoter regions of genes, where it can interfere with the binding of transcription factors and other proteins necessary for gene expression. However, gene body methylation is generally associated with actively transcribed genes.

Massive corals

Corals with a mounding or boulder morphology, with a compact and rounded appearance and thick tissue.

Photosynthate translocation

In the context of symbiotic corals, this refers to the movement and distribution of organic compounds, primarily sugars, produced through photosynthesis by endosymbiotic dinoflagellates in the family Symbiodiniaceae to the coral host tissues, specifically in the gastroderm.

Preconditioning

Exposure to a mild or moderate stressor can confer protection or enhance resilience against subsequent, more severe stressors, thereby promoting the acclimation and survival of an organism to changing environmental conditions.

Spurious transcription

Occurrence of transcriptional activity that is erroneous or non-functional in nature.

Symbiosome

Specialized compartment in a host cell that houses an endosymbiont.

Tissue thickness

How far (depth, often measured in mm) coral tissue protrudes into the underlying skeleton; this is typically dependent on skeletal architecture.

Transcriptional noise

Stochastic fluctuations in gene expression that can occur even in the absence of external stimuli. These fluctuations can lead to the occasional production of RNA transcripts from regions of the genome that are typically inactive or non-functional.

symbiosis between the coral and its endosymbiotic Symbiodiniaceae resulted in an explosion of research into coral stress responses. Scientists increasingly focused on understanding the environmental limits of corals (Mayer, 1917, 1918; Yonge, 1930) and the mechanisms behind their responses to environmental perturbations (Gates et al., 1992; Jokiel and Coles, 1977; Lesser, 1996). A substantial body of research has been devoted to our working knowledge of the coral–Symbiodiniaceae nutritional symbiosis of carbon and nitrogen cycling (Edmunds and Davies, 1986; Falkowski et al., 1984; Matthews et al., 2018; Muscatine et al., 1984; Stat et al., 2008), characterizing the complex interplay of multiple symbioses (corals, dinoflagellates, bacteria, viruses and endoliths; Hernandez-Agreda et al., 2017; Rohwer et al., 2002; Thurber et al., 2017) that make up the coral 'meta-organism', or

holobiont (see Glossary) (Rohwer et al., 2002), and describing the mechanisms of calcification (Allemand et al., 2011; Barnes, 1970; Drake et al., 2021b; Goreau and Goreau, 1959). Collectively, this physiological work, along with long-term ecological time-series studies of coral cover worldwide (e.g. Bahr et al., 2017; McClanahan, 2014; Mellin et al., 2020; Moorea Coral Reef LTER and Edmunds, 2022), clearly demonstrates that climate change has created a coral reef crisis (Hughes et al., 2017b; Veron et al., 2009), resulting in considerable research efforts to understand the vulnerabilities of reef-building coral to changing environmental conditions.

While documenting the immense coral loss (Bruno and Selig, 2007; De'ath et al., 2012; Gardner et al., 2003), researchers are simultaneously highlighting the variability in the signals that occur

in the immediate vicinity of coral in comparison to external seawater (Guadayol et al., 2014; Klepac and Barshis, 2022; Kühl et al., 1995) and the consequent variability in the biological responses of corals (Krämer et al., 2022; Matsuda et al., 2020). For example, environmental parameters, or signals, such as temperature and pH fluctuate by different amounts on different scales (sea surface, seawater, colony, polyp, tissue and cells). Thus, a precise measurement at any one of those scales will not necessarily reflect its value at a different scale within a reef (Fig. 1; Cai et al., 2016; Guadayol et al., 2014; Kühl et al., 1995; Wangpraseurt et al., 2012). This creates a potential mismatch between what scientists are measuring in the seawater and what the coral is sensing (e.g. van Woesik et al., 2022). Therefore, it is essential to characterize the variability in signals at the tissue and cellular levels to build clear hypotheses regarding the biological responses (Dow, 2014) such as gene expression and epigenetic regulation (Hoppeler, 2015) in response to historic or immediate physicochemical environments.

At this critical juncture for improving our eco-evolutionary forecasting in the Anthropocene (see Glossary), we propose a re-examination of variability in organismal responses owing to the incongruity between the external seawater environment, the signals organisms are sensing and transducing intracellularly, and the scales at which we are investigating these biological responses. In this Commentary, we provide historical context to some of the longstanding challenges in global change biology approaches that constrain our capacity for eco-evolutionary forecasting using corals as a focal model. We then describe examples of mismatches between the scales of external signals relative to how the signals are modulated by the biology of corals, how these signals are sensed and transduced at the cellular level, and how the cellular responses are initiated and may be maintained through mechanisms of environmental ‘memory’ (see Glossary) of organisms, which may enable acclimation to stressful conditions. Lastly, we outline suggested approaches to align experimental work with the scale

of environmental signals that organisms are perceiving. This Commentary showcases Journal of Experimental Biology’s contributions to these topics throughout the past 100 years (e.g. Cheek et al., 1993; Dow, 2014; Franklin and Hoppeler, 2021; Hoppeler, 2015; Phillips, 2006; Podrabsky et al., 2015; Somero, 1998), particularly in exploring organismal responses to global change through meticulous experimental methods that challenge established paradigms in the field.

Perceived inconsistencies in biological responses

A cross-cutting theme in biology is the inconsistency, or variability, in organismal responses to environmental stressors, which remains one of the biggest challenges in our capacity for predicting the responses of organisms to climate change. Specifically, as coral bleaching has increased substantially since initial reports in the 1980s and early 1990s (Glynn, 1984, 1991), documentation of high variability within and across reefs is common. Coral bleaching is the breakdown of the symbiosis, often due to thermal stress, between the coral host and its primary nutritional endosymbionts: dinoflagellates of the family Symbiodiniaceae (Glynn, 1991; LaJeunesse et al., 2018). When this occurs, the loss of highly pigmented Symbiodiniaceae leaves behind transparent coral tissue through which the underlying white skeleton is visible. Corals can recover from this dysbiosis (see Glossary), but without recovery, coral bleaching can lead to the death of the coral host and even reef-scale mortality (Glynn, 1984). Studies have detailed the variation in bleaching severity across reefs (Bainbridge, 2017; Hughes et al., 2018; Yadav et al., 2023), between taxa within a reef (Loya et al., 2001; Matsuda et al., 2020), within a colony (Brown et al., 2000; Drake et al., 2021a) and even within a polyp (Levy et al., 2021; Traylor-Knowles et al., 2017b). This variability in bleaching occurrence, intensity, breadth and recovery has puzzled scientists, who have sought to understand why corals of the same species and genotype can have such differing responses to environmental stressors (Fig. 2; Lang et al., 2015), and how to include such variance in forecasting. Here, we focus on three explanations for this phenomenon: (1) variability in the stress tolerance of coral holobiont members, (2) the role of environmental history and (3) the discrepancy between traditional measurements of abiotic signals of bulk seawater and the signals at the level of tissue and cells.

Dynamic contributions of holobiont partners underlie variability in coral stress response

Symbiotic interactions between coral holobiont players allow for synergistic outcomes at the organismal level owing to the integration of processes such as calcification, photosynthesis and respiration. These include (1) light-enhanced calcification (Pearse and Muscatine, 1971); (2) differential performance of the holobiont owing to variation in symbiont photosynthesis and photosynthate translocation (see Glossary) to the host (Allen-Waller and Barott, 2023; Stat et al., 2008); and (3) benefits associated with partnering with nitrogen- and sulfur-cycling microbial taxa to enhance nutrient recycling (Moynihan et al., 2022; Rådecker et al., 2015; van Oppen and Blackall, 2019) and microbial taxa with abilities such as antioxidant scavenging (Santoro et al., 2021; Ziegler et al., 2017). Collectively, such work has enabled our current working understanding of the structure and function of the cnidarian symbiosis (LaJeunesse et al., 2018; Bove et al., 2022; Rosset et al., 2021; Cui et al., 2023) and of dysbiosis (Allen-Waller and Barott, 2023; Rådecker et al., 2021), all of which are increasingly apparent as climate change increases. Advances in technology have

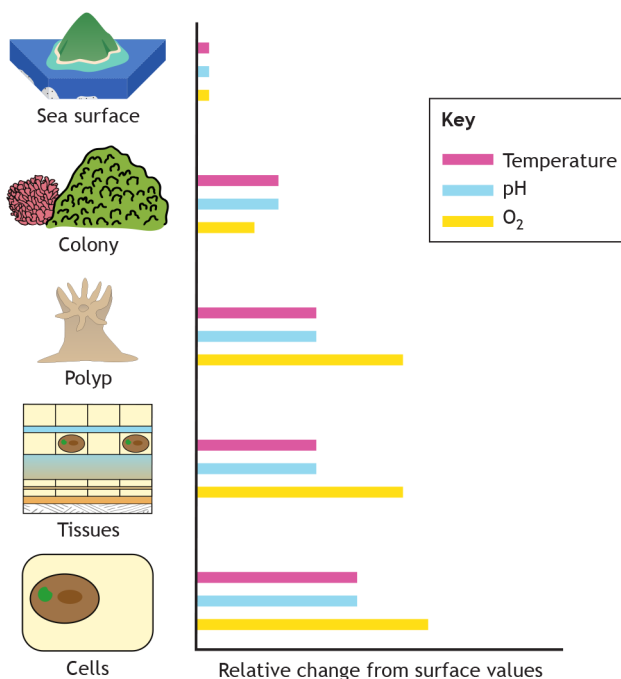


Fig. 1. Environmental signal mismatch across reef scales. Graphic credit is attributed in part to the Integration and Application Network (<https://ian.umces.edu/media-library/>; <https://creativecommons.org/licenses/by-sa/4.0/>).

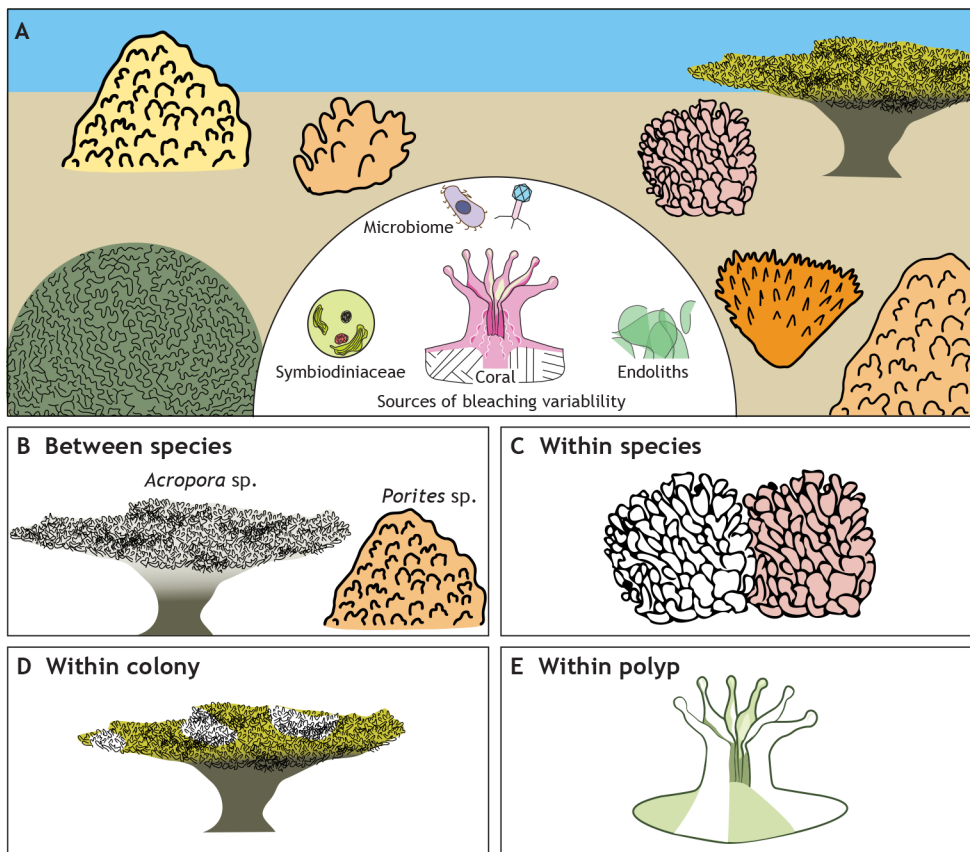


Fig. 2. Variability in coral bleaching phenotypes. Bleaching, or symbiont loss, is demonstrated by stark, white-colored tissues. (A) Illustration of variability of coral phenotypes across a reef, with possible sources of variation in bleaching (white dome). (B) Bleaching phenotypes can differ between species, such as between branching (e.g. *Acropora* sp.) and massive (e.g. *Porites* sp.) taxa. (C) Bleaching can also vary between two colonies of the same species. (D) Within a colony, bleaching can vary across different areas. (E) Even within a polyp, symbiont loss can be heterogeneous.

contributed to a greater understanding of the variance in the biological responses of corals, which can be explained in part by elucidating genetic (Baums et al., 2013; Bhattacharya et al., 2016; Dixon et al., 2015; Drury et al., 2022; Million et al., 2022) and epigenetic (Dixon et al., 2018; Eirin-Lopez and Putnam, 2019; Liew et al., 2018; Trigg et al., 2022) contributions to coral resilience. These studies of the roles of the various partners in the stress response have elevated our knowledge and the capacity for human interventions to address the mass mortality of coral reefs (National Academies of Sciences, Engineering and Medicine, 2019; van Oppen et al., 2015), but they have not yet fully reconciled our genome–phenome understanding across taxa.

Stress response is dependent on environmental history

A growing body of literature has shown that the historical environmental signals experienced by a coral affect its future performance. This was first documented in a pioneering study of *Goniastrea aspera* (*Coelastrea aspera*) in Phuket, Thailand, where a history of solar radiation-induced bleaching on their west-facing sides resulted in subsequent thermal bleaching only occurring on their east-facing sides, despite hosting the same species of photosynthetic symbionts throughout the colony (Brown et al., 2000). Further investigations into the effects of prior thermal signals on coral performance demonstrated clear evidence for the phenomenon of coral ‘environmental memory’, defined as the improved tolerance of corals to temperature and pH stress following preconditioning (see Glossary) to these stressors (reviewed in Hackerott et al., 2021).

The environmental history of all corals within one habitat is not homogeneous. Micro-scale variation in physical environmental parameters across a reef (Hoogenboom et al., 2017), in addition to

selecting for genetic differences (Thomas et al., 2018a; Voolstra et al., 2020) and inducing non-genetic differences (Durante et al., 2019) between and within species, leads to differences in thermal tolerance (Fig. 2D). Furthermore, environmental fluctuations in parameters such as pH (Brown et al., 2022; Dufault et al., 2012; Wall et al., 2018) and temperature (Ainsworth et al., 2016; Barshis et al., 2013; Carilli et al., 2012; Safaie et al., 2018) within the reef microhabitat can improve subsequent coral tolerance to these stressors. However, the protection conferred by acclimation to environmental fluctuation is not absolute (Ainsworth et al., 2016; Schoepf et al., 2015) – it depends on the regime of fluctuations (Schoepf et al., 2022) and, in some cases, exposure to environmental fluctuations can reduce tolerance (Brown et al., 2023; Klepac and Barshis, 2020).

Discrepancy between abiotic signals of bulk seawater, tissue and cells

Describing the contributions of the partners to the holobiont response and considering environmental history has advanced our ability to explain some of the variation in phenotypes between individuals on a reef and population scale (Fig. 2), but uncertainties remain. To effectively analyze the biological responses of corals to environmental change, it is important to accurately quantify the signals that corals detect (e.g. temperature, pH, oxygen, light) at the resolution at which corals perceive those signals (e.g. cell membrane receptors and intracellular sensors), not just the average of that signal in their external environment (e.g. sea surface temperature; Brown, 1997; Fanter et al., 2022) or the resolution of commonly used seawater probes. We argue that the high variability in biological responses (Fig. 2) may come from the discrepancy of abiotic signals between seawater and tissues (Fig. 3).

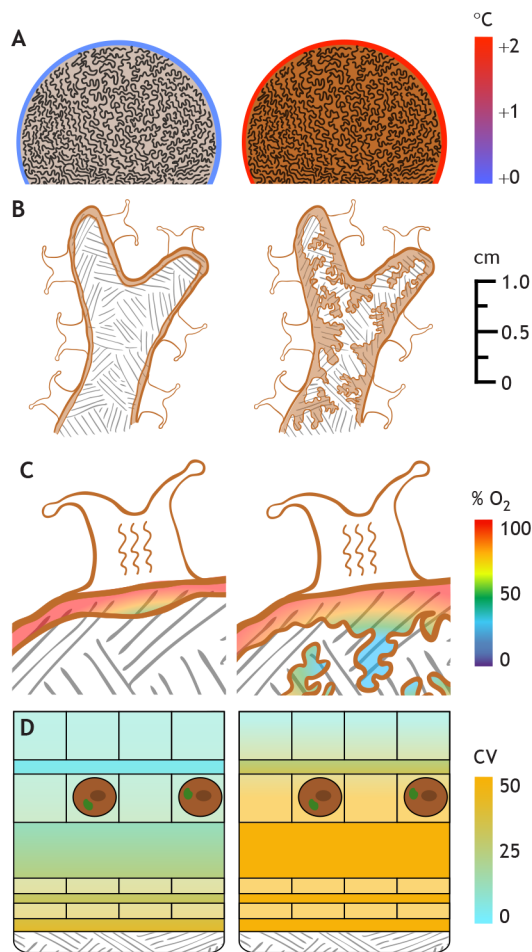


Fig. 3. Discrepancy of abiotic and biotic signals between seawater and tissues. Comparisons of (A) surface temperatures between a sparsely (left) and densely pigmented coral (right), and (B) tissue depth and anastomosis in a thin- (left) and thick-tissued coral (right). (C) Close-up of a single polyp of a thin- (left) and thick-tissued (right) coral showcasing how environmental parameters, such as oxygen saturation (% O₂), exhibit variability in these tissue architectures. (D) Diagram of coral cell layers of a thin- (left) and thick-tissued (right) coral illustrating the coefficient of variation (CV; see Glossary) in gene expression response of cell types across tissues. Cell-type-specific gene expression response to the immediate physicochemical environment can become 'averaged out' in bulk RNA sequencing, where multiple cell types and tissues are homogenized together.

There has been a clear progression in the development of literature quantifying differences in environmental signals when comparing the surrounding seawater with the depths of coral tissues. For example, the effects of solar heating interacting with the pigmentation of corals (Fig. 3A) can increase the tissue temperatures by up to 1.5°C warmer than the surrounding seawater (Fabricius, 2006; Jimenez et al., 2012; Shashar et al., 1993). Colony morphology also plays a role in modulating temperature, with massive corals (see Glossary) experiencing higher temperatures than branching corals (see Glossary) under the same external seawater conditions (Jimenez et al., 2008). Therefore, accumulation of thermal stress occurs at different rates between massive and branching corals and is a contributing factor in bleaching susceptibility (Loya et al., 2001; Sahin et al., 2023). The internal environment of coral is driven by factors such as irradiance, morphology, tissue location and tissue thickness (see Glossary; Fig. 3B). Foundational work by Kühl et al. (1995) applied

microprobes to measure oxygen, pH and light inside coral tissues, and identified that oxygen concentration within the tissue measured 600 $\mu\text{mol l}^{-1}$ compared with a concentration of 200 $\mu\text{mol l}^{-1}$ in the surrounding seawater in light conditions, dropping to nearly 0 $\mu\text{mol l}^{-1}$ in the absence of light when photosynthesis cannot occur (Fig. 3C). Within the polyp, the gastrovascular cavity (see Glossary) possesses a distinct chemical microenvironment, with very low oxygen ($\sim 7 \mu\text{mol l}^{-1}$) and pH levels that also vary with the levels of light and, therefore, photosynthetic activity of the coral holobiont (Agostini et al., 2012; Hughes et al., 2022). These studies exemplify the discrepancies in abiotic parameters between external seawater and intracellular compartments in corals and thus provide a clear rationale for the variability in responses seen across species, colonies, polyps and cells.

Within the internal environment of corals, tissue thickness drives variation in physicochemical conditions and creates unique internal environments between thick- and thin-tissued corals (Kühl et al., 1995; Wangpraseurt et al., 2012). Internal environments are strongly influenced by the density and variability in the distribution of symbionts across tissue depths (Fig. 3C; Huffmyer et al., 2020; Putnam et al., 2017; Yost et al., 2013). Thick-tissued corals experience a greater heterogeneity of environmental conditions within their tissue at any given time than thin-tissued corals (e.g. through the tissue depth, a thick-tissued coral can exhibit an 80% change in oxygen and 0.4 pH unit change in pH compared with 60% change in oxygen and 0.2 pH unit change in pH for a thin-tissued coral; Kühl et al., 1995), furthering the assertion that they may display more pronounced spatial, tissue-specific gene expression patterns compared with thin-tissued corals (Fig. 3D). Thick-tissued corals also exhibit a higher diversity of microbial taxa within their tissues (Bergman et al., 2022). At ecological scales, thick-tissued corals exhibit greater thermal tolerance (Loya et al., 2001; Thornhill et al., 2011) and ocean acidification resistance (Fabricius et al., 2011; Putnam et al., 2016), which could, in part, be explained by potential differences in energy reserves, metabolic rates or light attenuation throughout their thicker tissues (Gates and Edmunds, 1999; Loya et al., 2001; Dimond et al., 2012). The diversity of environmental parameters experienced in thick-tissued corals under ambient conditions could also underlie this greater tolerance by eliciting preconditioning through their experienced environmental variability and stress response, termed 'environmentally mediated priming' (see Glossary) (Putnam et al., 2017). Potentially driving this are (epi)genomic differences between thick- and thin-tissued corals, with thick-tissued corals showing higher global DNA methylation (see Glossary) (Trigg et al., 2022) and genome expansion of hypoxia stress response genes (Alderdice et al., 2022). Although these studies do not provide a causal link between genome expansion or higher DNA methylation of thick-tissued corals and their higher stress tolerance, these differences between thick- and thin-tissued corals provide promising avenues of further exploration into the mechanisms of coral environmental tolerance.

As described above, the data revealed from fine-scale measurements of coral surfaces and tissues paints a very different picture (Fig. 1) from that of the surrounding seawater and remote sensing data (Coles and Brown, 2003; Donovan et al., 2022). High-resolution studies that couple quantification of abiotic signals and biological responses at the cellular level have the potential to resolve inconsistencies in the literature between hypothesized and observed responses of corals to environmental change. One such example is the use of live confocal microscopy to quantify the pH of the coral-derived symbiosome (see Glossary) (Barott et al., 2015a).

That study found that corals use a molecular sensor and proton pump (V-type H^+ -ATPase) to acidify the symbiosome beyond that of the normal coral intracellular pH (~ 7) and the external seawater pH (~ 8). This carbon-concentrating mechanism, which the corals use to stimulate algal photosynthesis, would not have been discernible solely through external pH measurements. Furthermore, because the internal pH of corals does not match the surrounding seawater, coral responses to stressors such as ocean acidification will not necessarily align with predicted expectations based on bulk measurements of seawater pH (Gibbin et al., 2014). As we develop a better understanding of how environmental signals at the seawater level compare with how these signals are occurring within or are perceived by the coral, we can develop more well-informed hypotheses relating changes in the external environment to emergent phenotypes, thereby enhancing our genome-to-phenome understanding and environmental forecasting capacity.

Reconciling biological response variability in future studies

To better understand the potential for mismatches between the external and internal environments, we turn our focus to core stress response pathways. Cells use these pathways to sense their environment and initiate signaling cascades to enact changes in gene expression leading to a certain phenotype. Here, we focus on two example pathways, common across Metazoa, that have been demonstrated in corals as playing a role in stress response: the heat shock response pathway and the NF-E2-related factor 2 (Nrf2) pathway (Box 1) and their core signaling molecules.

Core intracellular signaling molecules

The intracellular signaling molecules of reactive oxygen species (ROS) and calcium (Ca^{2+}) are present in both the heat shock

response and Nrf2 pathways, are influenced by environmental signals such as temperature and underlie the complex signaling cascades that alter the phenotype of an organism (Castelli et al., 2020). ROS are essential intracellular messengers in normal metabolic processes of organisms such as cell proliferation and altering metabolism under varying conditions (Schieber and Chandel, 2014; Somero, 1998). Similar to ROS, Ca^{2+} is a ubiquitous signaling molecule (Cheek et al., 1993; Clapham, 2007) necessary for processes such as exocytosis (Burgoyne and Morgan, 1998; Weston et al., 2015) and biomineralization of the coral skeleton (Tambutté et al., 2011). Calcium can enter the cell through transient receptor potential (TRP) channels, some of which are thermosensitive in vertebrates (Feng, 2014; Tan and McNaughton, 2016). In the anemone *Nematostella vectensis*, a loss-of-function mutation of TRPM2 revealed its important role in thermal tolerance of cnidarians (Ehrlich et al., 2022). Early transcriptomic evidence suggests that TRP channels may play a role in how corals sense their environments (Bhattacharya et al., 2016). A study of stress-tolerant *Durudinium*-hosting corals revealed higher expression of TRP channel genes in these species compared with stress-susceptible *Cladocypium*-hosting corals (Yuyama et al., 2022). This could indicate variability in the temperature sensing ability of these corals, which may lead to different transduction of the same external signal into gene expression and, ultimately, different thermal performance. Determining whether corals utilize thermosensors (e.g. TRP channels) during and leading up to thermal stress may be impeded by the ubiquity of intracellular calcium in corals during the processes of calcification and exocytosis, especially during bleaching (Weston et al., 2015). The possible involvement of thermosensitive TRP channels in coral thermoregulation, however, presents a potential mechanism for environmental temperature

Box 1. Heat shock response pathway and the Nrf2 pathway

Heat shock response pathway

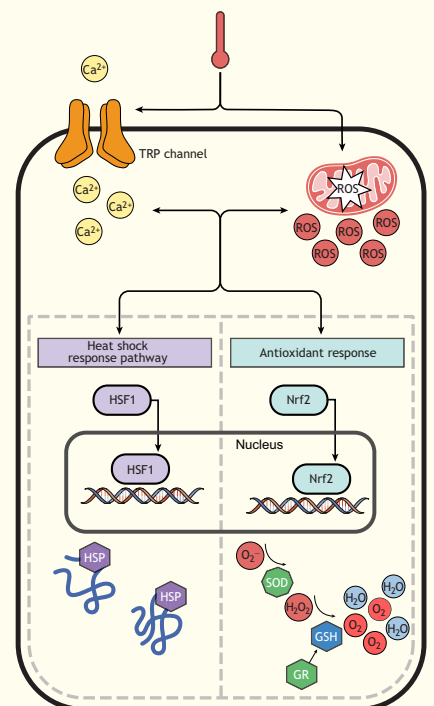
Heat shock proteins (HSPs) are molecular chaperone proteins that manage stress-induced denatured proteins to reduce the risk that these denatured proteins pose to the cell (Feder and Hofmann, 1999). HSPs have been extensively studied in corals and have been found to be part of the suite of genes that are upregulated by corals under thermal stress (reviewed in Drury, 2020) and other stressors (Dixon et al., 2020). Transcription factors called heat shock factors, such as HSF1, control the transcriptional activation of HSPs (Dayalan Naidu and Dinkova-Kostova, 2017; Zhang et al., 2011). Functional genomics work supports this connection, through the use of CRISPR-Cas9 to generate a targeted loss-of-function mutation of HSF1 in *Acropora millepora* larvae (Cleves et al., 2020b). With this approach, mutant larvae showed markedly decreased thermal tolerance, supporting the important role played by HSPs, modulated by HSF1, in the ability of corals to withstand thermal stress (Cleves et al., 2020b).

Nrf2 antioxidant response pathway

The Nrf2 antioxidant response pathway is driven by the transcription factor nuclear factor-erythroid 2 p45-related factor 2 (Nrf2), which upregulates antioxidant genes in the response to oxidative stress (Dayalan Naidu et al., 2015). Antioxidants play a crucial role in the coral thermal stress response by combatting increased concentrations of reactive oxygen species (ROS), which can lead to oxidative stress and cellular damage (Lesser, 2006). In corals, the Nrf2 pathway is putatively involved in the regulation of crucial antioxidant response genes, including catalase (CAT), glutathione reductase (GR) and superoxide dismutase (SOD; Chen et al., 2015; Lesser, 1997; Majerová and Drury, 2022).

Reciprocal regulation of Nrf2 and HSF1 under cellular stress

ROS and calcium (Ca^{2+}) activate both Nrf2 and HSF1 pathways. HSF1 translocates to the nucleus under heat stress and initiates transcription and translation of HSPs, which bind to denatured proteins to prevent their aggregation or target these proteins for degradation. Nrf2 translocates to the nucleus under oxidative stress and activates transcription of antioxidant genes including catalase, GR and SOD, which break down ROS into oxygen (O_2) and water (H_2O). GR reduces the oxidized form of glutathione into reduced glutathione (GSH), an important antioxidant pathway in corals. Nrf2 also activates the transcription of transient receptor potential (TRP) channels, which are important cellular sensors for temperature and ROS (Sakaguchi and Mori, 2020).



sensing by corals, and may trigger signal transduction cascades. This putative role is consistent with previous studies showing an increase in intracellular calcium concentrations during heat stress in reef-building corals (Fang et al., 1997; Huang et al., 1998). Further research is required to investigate whether transmembrane environmental sensors modulate the intracellular signaling molecules that contribute to the environmental sensitivity of corals, and whether differential thermosensor expression within or between colonies or species could explain the observed variability in thermal tolerance.

Differential modulation of sensing and signal transduction through core pathways leads to variability in phenotype

Historically, coral studies have been conducted at bulk levels, where the homogenization of tissues and cell types for the assays can also homogenize measured responses. Diverging tissue micro-environments within a colony (Fig. 3) can exhibit varying levels of stress response proteins, which could lead to inconsistent results during bulk measurements of coral tissue homogenates. Spatial analysis of tumor necrosis factor receptors, another crucial gene family involved in the coral heat stress response, revealed that the expression of these genes is tissue-specific, with high expression in epidermal cells and low expression in symbiocytes and other gastrodermal cells (see Glossary) (Traylor-Knowles et al., 2017b). Moreover, single-cell RNA sequencing of the coral *Stylophora pistillata* emphasized the diversity of expression patterns, with over 40 distinct cell types in reef-building corals (Levy et al., 2021), further confirmed by *in situ* hybridization. Because each cell type has a specific baseline gene expression profile under normal environmental conditions, it is also expected that these cell types will respond to environmental stress in diverging ways (Fig. 3D). For example, superoxide dismutase has been shown to have tissue-specific and spatially varying levels of expression in different coral tissues (Brown et al., 2002). High-resolution studies can solidify our understanding of the complex temporal and tissue-specific expression involved in the signal transduction cascades underlying the various modules of co-expressed genes that are clearly associated with coral stress responses to different stressors.

Connection of signal transduction cascades into longer-term environmental memory – the role of epigenetic mechanisms

Signal transduction cascades activate specific sets of genes that are needed for an organism to respond to environmental stress. Through the process of frontloading (increasing constitutive levels of gene expression following a conditioning exposure, thus reducing the transcription requirement for inducible stress responses), marine invertebrates can reinforce signal transduction cascades to longer-term environmental memory (Barshis et al., 2013; Collins et al., 2021; Gurr et al., 2022). For example, corals preconditioned to sublethal heat or light stress can exhibit an enhanced antioxidant response to heat stress and remain unbleached for longer compared with non-preconditioned corals (Brown et al., 2002; Majerová and Drury, 2022). Evidence suggests that conditioning corals to increased temperature triggers a gene regulatory cascade in which the increased expression of protein BI-1 leads to the upregulation of glutathione reductase (Majerová and Drury, 2022), possibly through the activation of the Nrf2 pathway (Lee et al., 2007). Glutathione reductase maintains an active pool of the antioxidant glutathione, which acts to scavenge ROS (Couto et al., 2016; Mapson and Goddard, 1951). This recently documented coral acclimation response provides an example of the value of considering high-

resolution signal transduction and supports a role for environmental memory through individual epigenetic mechanisms (Eirin-Lopez and Putnam, 2019), or as a complex interplay of epigenetic and regulatory processes contributing to inherited gene expression regulation (*sensu* Adrian-Kalchhauser et al., 2020).

The current paradigm of epigenetic regulation in marine invertebrates posits that gene body DNA methylation (GBM; see Glossary) is correlated with increased transcription of genes and reduced transcriptional variability. For example, in the anemone *Exaiptasia pallida* and the coral *S. pistillata*, genes with high levels of GBM show decreased spurious transcription (see Glossary) and transcriptional noise (see Glossary) (Li et al., 2018; Liew et al., 2018). Data generally support these patterns in corals, but the relationships between gene expression and GBM are not always strongly correlated, especially when averaging across all genes in an organism (Dixon and Matz, 2022; Dixon et al., 2018). Although DNA methylation is likely to be one player in a larger epigenetic and regulatory cascade (Adrian-Kalchhauser et al., 2020; Eirin-Lopez and Putnam, 2019; Fanter et al., 2022), we posit that the lack of statistical support for these patterns in all cases may arise from an issue of scale. In the majority of invertebrate DNA methylation studies, gene expression and DNA methylation data were gathered from bulk assays and, therefore, the presented data were the average of all tissue types in the coral polyp. However, DNA methylation is highly tissue specific (Liew et al., 2018) and can vary by species and tissue thickness (Trigg et al., 2022). Therefore, it is crucial to perform assays on single cells or groups of cells within one tissue type, as all cells and tissues may not upregulate or downregulate the same genes during a stress response.

Addressing ongoing questions and recommended future directions

Although considerable progress has been made in understanding how invertebrates respond to environmental change, there are still significant unresolved issues that, if tackled with emerging technologies, could help to explain the variability in responses observed both within and across taxa. Recent developments in our ability to reconcile microscale differences in abiotic signals, gene expression, (epi)genomics and signal transduction hold promise in addressing some of these questions. In Table 1 we outline some ongoing questions and suggest approaches to better align experimental work with the scale of the environmental signals that organisms perceive and integrate.

To improve the accuracy of future studies, we recommend the following. (1) Performing high-resolution and bulk assays simultaneously where possible. By integrating both results, it may be possible to extract more accurate signals from pre-existing datasets and future studies that use bulk methods, as these methods are more accessible in the field and require less time, money and analysis. (2) Sampling time points should be data-driven based on time courses that have documented the temporal pattern of gene expression to different levels and types of stress (e.g. detailed, high-temporal-resolution studies of gene expression changes in the first hours following heat stress including Cleves et al., 2020c; Majerová et al., 2021; Traylor-Knowles et al., 2017a). (3) Experiments should be designed with genetic variability in mind and, when possible, genetically identical fragments should be used to minimize the effect of genotype on results (Durante et al., 2019; Andrade Rodriguez et al., 2021; Dilworth et al., 2021). (4) Biochemical functional studies should be conducted alongside gene expression analyses to gain a better understanding of gene functions and protein activity (Majerová and Drury, 2022). (5) Multi-omics analyses

Table 1. Key ongoing questions and suggested ways forward

Key questions	Targeted signal quantification	How to target the biological response	Suggested approaches and example applications
What signals are being transduced by corals under stress and what stress response proteins are being activated?	Quantify signaling molecules such as ROS, reactive nitrogen species (RNS) and Ca ²⁺ following various stressors	Use functional assays to trigger or block desired cascades	Confocal microscopy (Nielsen et al., 2018); NanoSIMS (Mass et al., 2017)
How do tissue architecture and microscale variability influence the transmission of signal transduction pathways? Could differences in signal transmissibility lead to differences in resilience?	Track the tissue-specific distribution of signaling molecules such as ROS and Ca ²⁺ in corals of different species, tissue thicknesses and bleaching susceptibility	Use tissue- or cell-specific gene expression to connect local signal transduction to expression	Laser capture microdissection (Liew et al., 2018); <i>in situ</i> hybridization (Traylor-Knowles, 2018); Immunohistochemistry (Barott et al., 2015b; Loussert-Fonta et al., 2020); single cell RNASeq (Levy et al., 2021)
Do environmental sensors, such as transient receptor potential (TRP) channels, play a role in the rapid initiation of signal transduction pathways initiating the coral stress response and do these enhance resilience?	Determine the localization of TRP channels and other ion transporters that are sensitive to environmental signals	Assess environmental sensitivity when sensors are knocked-down or overexpressed	siRNA/CRISPR gene knockdown (Cleves et al., 2020b; Majerová and Drury, 2022)

targeting specific hypotheses should be performed when possible because metabolite and protein level/activity do not always correlate strongly with gene expression (Cziesielski et al., 2018; Williams et al., 2021). (6) Broadening the range of studies of coral epigenetics to investigate mechanisms beyond DNA methylation, such as histone modifications and noncoding RNA (Eirin-Lopez and Putnam, 2019), spatial transcriptomics (Tian et al., 2022), as well as methods that can capture chromatin accessibility (Weizman and Levy, 2019) or capture multiple modes of (epi)genetic information concurrently, such as sequencing of chromatin accessibility (ATAC-seq), DNA methylation and RNA on the same sample (Zhu et al., 2020). (7) Finally, effort should be made to uncover the function of unknown genes and improve genomic resources for a diversity of coral species, as reviewed by Cleves et al. (2020a). This will help bridge gaps in our current understanding of coral signal transduction cascades.

Technological advancements, such as optical coherence tomography (Jaffe et al., 2022; Wangpraseurt et al., 2019), live confocal microscopy to measure tissue thickness (Huffmyer et al., 2020), tissue clearing coupled with light sheet fluorescence microscopy (Liu et al., 2020), chemical and hyperspectral imaging (Ricci et al., 2023), bioprinting of coral microhabitats (Wangpraseurt et al., 2022), mathematical modeling (Bouderlique et al., 2022; Murthy et al., 2023) and nanobiotechnology (Roger et al., 2023a,b), have already begun to further elucidate the internal environment of coral tissue with respect to oxygen levels, pH and light and the consequent biological responses to these environmental factors. These advances provide important avenues for continued research into how fine-scale differences in environmental parameters impact the biological responses of corals to various stressors.

Conclusion

In this Commentary, we have provided an overview of the variability in the responses to environmental change documented in marine invertebrates, with reef-building corals as a model. We have highlighted mismatches between environmental signals and the resolution at which corals experience these signals, which provides further explanation for the variance in expected and observed outcomes in studies of the coral stress response. We challenge the field to explore biological responses at high resolution

to better capture environmental change and its biological effects at a level of resolution that is relevant to the organism and to adjust their hypotheses accordingly. With this framework, we hope to improve our understanding of adaptation and plasticity in light of genome-to-phenome outcomes modulated by environmental change, as well as our capacity for eco-evolutionary forecasting.

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ECR Spotlight
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