

Review

Harmful algal blooms: A climate change co-stressor in marine and freshwater ecosystems

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ABSTRACT

Marine and freshwater ecosystems are warming, acidifying, and deoxygenating as a consequence of climate change. In parallel, the impacts of harmful algal blooms (HABs) on these ecosystems are intensifying. Many eutrophic habitats that host recurring HABs already experience thermal extremes, low dissolved oxygen, and low pH, making these locations potential sentinel sites for conditions that will become more common in larger-scale systems as climate change accelerates. While studies of the effects of HABs or individual climate change stressors on aquatic organisms have been relatively common, studies assessing their combined impacts have been rare. Those doing so have reported strong species- and strain-specific interactions between HAB species and climate change co-stressors yielding outcomes for aquatic organisms that could not have been predicted based on investigations of these factors individually. This review provides an ecological and physiological framework for considering HABs as a climate change co-stressor and considers the consequences of their combined occurrence for coastal ecosystems. This review also highlights critical gaps in our understanding of HABs as a climate change co-stressor that must be addressed in order to develop management plans that adequately protect fisheries, aquaculture, aquatic ecosystems, and human health. Ultimately, incorporating HAB species into experiments and monitoring programs where the effects of multiple climate change stressors are considered will provide a more ecologically relevant perspective of the structure and function of marine ecosystems in future, climate-altered systems.

1. Introduction

Climate change is transforming aquatic ecosystems and, in turn, negatively impacting their overall health (Harley et al., 2006; Doney et al., 2012; Hoegh-Guldberg et al., 2014). Among the many symptoms of climate change, rising temperatures, acidification, and deoxygenation are perhaps the most prominent. Warming alters basal metabolic functioning (Pörtner and Farrell, 2008; Donelson et al., 2011), species distributions (Hochachka and Lutz, 2001; Harley et al., 2006), and the timing (i.e. phenology) of pivotal biological events (Edwards and Richardson, 2004; Asch, 2015). Acidification causes physiological stress among sensitive marine species (Michaelidis et al., 2005; Pörtner, 2008; Pörtner and Farrell, 2008) and inhibits the growth of calcifying organisms (Talmage and Gobler, 2009; Doney et al., 2012; Waldbusser and Salisbury, 2014). Ocean deoxygenation and hypoxia can alter the distribution, aerobic scope, and survival of aquatic organisms (Diaz and Rosenberg, 2008; Breitburg et al., 2018). As anthropogenic forcing persists, it is expected that these stressors will intensify, further altering

the structure and functioning of marine and freshwater ecosystems (Harley et al., 2006; Woodward et al., 2010; Doney et al., 2012).

Beyond direct harm to aquatic organisms, climate change will modify the distribution and intensity of multiple co-stressors within marine and freshwater ecosystems. For example, rising temperatures are predicted to impact the occurrence and intensity of marine diseases (Burge et al., 2014), ocean deoxygenation (Diaz and Rosenberg, 2008; Breitburg et al., 2018), habitat loss (Waycott et al., 2009; Hoegh-Guldberg and Bruno, 2010; Friedland et al., 2013), and various environmental contaminants (e.g. persistent organic pollutants and pesticides; Noyes et al., 2009). Additionally, eutrophic estuaries can host seasonal hypoxia and acidification (Cai et al., 2011; Wallace et al., 2014; Baumann et al., 2015), a phenomenon that will intensify at an accelerated rate in the future (Sunda and Cai, 2012). Habitats constricted by warming may be further limited by over-development of coastal zones (Harley et al., 2006). Climate change stressors, therefore, co-occur with other stressors having complex interactive effects on aquatic species.

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Within coastal zones, harmful algal blooms (HABs) have expanded geographically and become increasingly common (Hallegraeff, 2010; Glibert et al., 2014; Gobler et al., 2017). While these trends are partly related to enhanced monitoring and coastal eutrophication (Anderson et al., 2002; Heisler et al., 2008; Anderson, 2012), there is a growing recognition of the role of climate change in the intensification of several HABs globally (Anderson, 2012; Glibert et al., 2014; Wells et al., 2015; Gobler et al., 2017). Many HAB species are capable of producing potent biotoxins that concentrate in the tissues of bivalve shellfish and, when consumed by humans, can result in severe, even fatal, shellfish poisoning syndromes (Shumway, 1990; Hégaret et al., 2009). Some toxins can also become aerosolized, causing respiratory harm to individuals near or down-wind of blooms (Backer et al., 2003; Pierce et al., 2003; Cheng et al., 2007). HAB-derived toxins are also a threat to marine organisms including marine mammals, fish, sea birds, invertebrates, and sea grasses (see review by Landsberg, 2002). Caged (i.e. aquacultured) fish and shellfish are particularly vulnerable to HABs (Shumway, 1990; Kim, 1997) exhibiting large-scale die-offs during blooms that can have dire impacts on coastal economies (Anderson et al., 2000; Shumway et al., 2003; Proenca and Hallegraeff, 2017). For example, a bloom of *Cochlodinium* (aka *Margalefidinium*) *polykrikoides* in South Korea resulted in the loss of an estimated \$100 M in aquaculture products (Kim, 1997, 1998) and more recently, a large-scale HAB in Chile resulted in the loss of caged fish amounting to nearly \$800 M (Proenca and Hallegraeff, 2017). In the US, conservative estimates of the costs of HABs amount to ~\$100 M annually (Hoagland and Scatista, 2006).

Individually, climate change stressors can have significant impacts on aquatic organisms and coastal processes (Diaz and Rosenberg, 2008; Talmage and Gobler, 2009; Doney et al., 2012). The combined occurrences of two or more stressors can often have even more complex and intense negative outcomes (Melzner et al., 2011; Byrne and Przeslawski, 2013; Gobler et al., 2014). The presence of a co-stressor may partly mitigate the adverse effects (i.e. antagonistic) of either stressor, cause a predictable linear increase in effects (i.e. additive), or, in some cases, result in consequences more severe than those predicted from the summed effects of each stressor (i.e. synergistic). Interactive effects are often manifested in a species-, strain-, and stressor-specific manner and are the outcome of complex biotic and abiotic processes (Crain et al., 2008; Melzner et al., 2011, 2011; Byrne and Przeslawski, 2013; Griffith and Gobler, 2016). While multi-factorial studies incorporating multiple stressors are logistically challenging to implement, progress has been made. There is a growing body of literature addressing the combined impacts of exposure to climate change-associated stressors (e.g. temperature, acidification, hypoxia, etc.). Lacking in this literature, however, has been a consideration of HABs as a co-stressor. This review, therefore, is focused on the co-occurrence of HABs with other climate change stressors and the implications of their combined impacts on aquatic ecosystems (Fig. 1).

2. Co-occurrences and interactive effects of climate change stressors

The projected impacts of individual climate change stressors are well-studied (see reviews by Harley et al., 2006; Doney et al., 2012; Breitburg et al., 2018) and their co-occurrences are relatively well-documented. For example, many habitats subjected to hypoxia can also be stricken by prolonged warming (Rabalais et al., 2002; Vargas-Yáñez, 2005; Pörtner, 2008; Cossellu and Nordberg, 2010) and habitats with low levels of oxygen also host high levels of CO₂ and subsequent declines in pH (Cai et al., 2011; Waldbusser et al., 2011; Wallace et al., 2014). The combined occurrence of these stressors pose complex challenges for aquatic organisms as individual stressors can have common physiological targets. For example, warming that reduces oxygen availability within aquatic ecosystems also stimulates basal metabolism and oxygen demand, further constraining the aerobic scope

of organisms in hypoxic zones (Abele et al., 2002; Pörtner, 2008, 2010). The transport of oxygen via pH-sensitive blood pigments may become reduced as tissues and body fluids are challenged with exogenous H⁺ in acidified environments (Pörtner, 2005), a scenario that could intensify oxygen-limitation associated with hypoxia. Given finite energy resources, the combined presence of two or more stressors may limit the ability of an organism to compensate for one or more stressors as energetic resources are depleted (Crain et al., 2008; Sokolova, 2013). While later-life stage organisms may be more tolerant to acute and even longer-term environmental perturbations, the onset of these conditions (e.g. thermal stress, hypoxia, and acidification) in many coastal zones coincides with the reproductive conditioning and/or the spawning and hatching of early-life stage organisms (Kennedy and Krantz, 1982; Sherman et al., 1984) that are often more sensitive to individual and interacting stressors (Gobler and Talmage, 2013; Gobler et al., 2014).

Interactive effects between climate change stressors is an area of growing interest and meta-analyses have revealed interactions between warming, acidification, and hypoxia (Crain et al., 2008; Vaquer-Sunyer and Duarte, 2008; Kroeker et al., 2013). For example, Vaquer-Sunyer and Duarte (2011) discovered that exposure to thermal stress combined with hypoxia accelerated time-to-death by 74% among benthic macrofauna and lead to a significant increase in lethal oxygen thresholds. Meta-analyses of multiple marine taxa have revealed a heightened sensitivity to acidification for individuals concurrently exposed to elevated temperatures (Kroeker et al., 2013) and while responses to co-stressors are taxa-specific, combined exposure can elicit strong synergistic effects on key biological processes including calcification, photosynthesis, reproductive output, and survival (Harvey et al., 2013). Laboratory-based investigations also suggest significant interactive (positive and negative) effects between climate change stressors. Hypoxia and acidification interact to additively and synergistically reduce the growth and survival of early-life stage finfish and molluscs, often producing outcomes more severe than would be predicted based upon separate exposures to singular stressors (Kim et al., 2013a, 2013b; Gobler et al., 2014; DePasquale et al., 2015). Interactive outcomes, however, are not always negative. For example, Jansson et al. (2015) observed greater growth among juvenile *Macoma balthica* exposed to low oxygen at ambient pH and greater survival among individuals exposed to low DO and low pH concurrently. Despite the global expansion of HABs (Anderson, 2012; Gobler et al., 2017), few climate change studies have included HAB species as a co-stressor (see Table 1). Given the complex interactions between other climate change stressors, exposure to HABs may further complicate dynamic interactions among stressors (see Fig. 1).

3. The early manifestation of climate change stressors in coastal zones

Coastal zones are host to a diverse array of aquatic life and are among the most productive ecosystems on the planet (Valiela, 2009). Their proximity to terrestrial nutrient sources, topographical features, and hydrodynamically-retentive properties render coastal habitats host to large, natural variations in environmental conditions (e.g. salinity, temperature, mixing, nutrients, etc.). Coastal zones are predicted to be the most impacted by climate change (Halpern et al., 2008) and many coastal regions are warming more rapidly than the open-ocean (Belkin, 2009; Baumann and Doherty, 2013). Coastal areas are also prone to eutrophication, a root cause of several stressors. Excessive nutrient loading and prolonged residence times can promote many types of HABs (Anderson et al., 2002; Glibert and Burkholder, 2006; Heisler et al., 2008; O'Neil et al., 2012). Large amounts of organic matter associated with algal blooms can stimulate microbial respiration that depletes dissolved oxygen and produces CO₂, promoting hypoxia (Fig. 1; Diaz and Rosenberg, 2008; Gilbert et al., 2010; Breitburg et al., 2018) and acidification (Fig. 1; Cai et al., 2011; Waldbusser et al., 2011; Wallace et al., 2014; Baumann et al., 2015). Light attenuation and

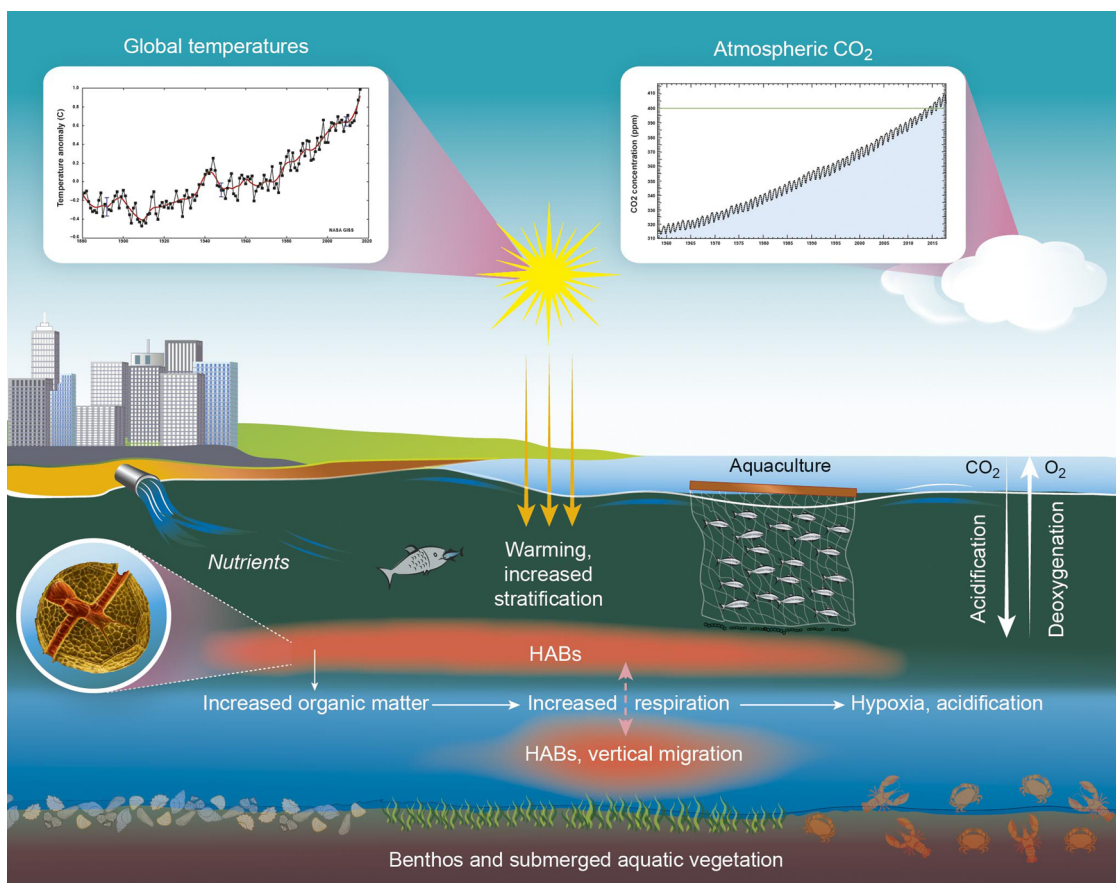


Fig. 1. The co-occurrence of climate change stressors and HABs in coastal ecosystems. Figure depicts how successive increases in temperature, carbon dioxide, and nutrient loading since the 20th century independently and interactively promote HABs.

heterotrophic carbon acquisition by many HABs (Sunda et al., 2006; Burkholder et al., 2008; Gobler and Sunda, 2012) may further exacerbate these phenomena. Through such processes, climate change stressors and HABs have already emerged in some coastal zones, making them an early-predictor of changes likely to occur in larger systems where HABs and climate change have yet to intensify or emerge.

Many factors increase the likelihood for low dissolved oxygen, acidification, and HABs to co-occur in coastal zones (Fig. 1). Following spring diatom blooms within temperate latitudes, surface waters rapidly warm and stratify, isolating bottom waters from surface influxes of dissolved oxygen and lower CO_2 water, conditions that promote concurrent hypoxia and acidification (Gobler and Baumann, 2016). Since many HABs thrive in stratified water columns (Smayda and Reynolds, 2003; Heisler et al., 2008), this is also a period when bloom-favorable conditions are established. The late spring and early-summer are also times when the stressor-sensitive, early-life stages of multiple aquatic genera (Green et al., 2009; Talmage and Gobler, 2009, 2010; Waldbusser et al., 2010) are present in coastal systems (Kennedy and Krantz, 1982; Sherman et al., 1984; Helluy and Beltz, 1991). Hence, identifying the interactive effects of combined stressors on these early-life stage organisms is essential to elucidate potential effects on coastal fisheries and other populations.

Beyond seasonal exposure to HABs and climate change stressors, there are likely to be vertically-segregated, diurnal patterns of exposures within coastal habitats. In many locales, hypoxia and acidification display diurnal patterns with dissolved oxygen and pH being lowest at night and in deeper environments (Fig. 1; Baumann et al., 2015; Gobler and Baumann, 2016; Baumann and Smith, 2018). Given many harmful dinoflagellates vertically migrate to depth at night, benthic animals may be more likely to suffer from co-exposure to HABs,

hypoxia, and acidification at night (Fig. 1). Conversely, vertically migrating HABs congregate in heated surface waters by day, making the co-occurrences of HABs and thermal stress more likely for pelagic and aquacultured organisms (Fig. 1). Consistent with this concept, Griffith et al., in press, 2019) reported that bay scallops (*A. irradians*) cultured in surface waters experienced near-complete mortality during *C. polykrikoides* blooms while scallops maintained in deeper locations displayed near-complete survival.

Beyond coastal areas, upwelling zones may also display the future co-symptoms of climate change stressors and HABs. Upwelled waters are known to be rich in CO_2 , low in dissolved oxygen, and high in nutrients, conditions that may directly or indirectly promote the growth of several types of HABs (Ryan et al., 2009; Kudela et al., 2010; McCabe et al., 2016; Pitcher et al., 2017) leading to marine animal mortalities (McCabe et al., 2016; Ryan et al., 2017), fisheries closures (Pazos et al., 2006), and economic loss (Anderson et al., 2000). Recently, the co-occurrence of seasonal upwelling and regional warming stimulated a bloom of *Pseudo-nitzschia australis* along the west coast of the US resulting in the largest harmful algal bloom ever recorded (Trainer et al., 2019; McCabe et al., 2016; Ryan et al., 2017). Following this particular event, widespread marine mammal deaths including whales, dolphins, porpoises, sea lions, and seals were attributed to domoic acid exposure (McCabe et al., 2016; Ryan et al., 2017). Given the corrosive properties of upwelled water, its low oxygen content, and association with many HABs, coastal upwelling systems are a prime example of locales where complex interactions between climate change stressors and HABs occur and are likely to intensify in the near-future.

Table 1
Summary of known interactions between marine and freshwater HABs and climate change stressors.

Climate change stressor	Harmful algal species	Strain information	Toxic mechanism	Target organism	Interaction	Reference
Thermal stress	<i>Microcystis aeruginosa</i>	UV-006	Microcystin	<i>Mus musculus</i> (mouse)	Diminished toxicity at warmer temperatures	van der Westhuizen and Eloff (1985)
Thermal stress	<i>Microcystis aeruginosa</i>	M228	Microcystin	<i>Mus musculus</i> (mouse)	Higher LD ₅₀ at warmer temperature	Watanabe and Oishi (1985)
Thermal stress	<i>Cochlodinium polykrikoides</i>	CP1	Reactive oxygen species (ROS)	<i>Argopecten irradians</i> (bay scallop)	Increased toxicity (i.e. inhibited swimming by larval scallops) at cold temperature	Griffith and Gobler (2016)
Thermal stress	<i>Cochlodinium polykrikoides</i>	CP1	Reactive oxygen species (ROS)	<i>Mercenaria mercenaria</i> (hard clam, northern quahog)	Increased lethality at cold temperature	Griffith and Gobler (2016)
Thermal stress	<i>Cochlodinium polykrikoides</i>	CP1, field samples	Reactive oxygen species (ROS)	<i>Menidia beryllina</i> (inland silverside)	Increased lethality at cold temperature	Griffith and Gobler, 2016
Thermal stress	<i>Cochlodinium polykrikoides</i>	CP1, CP8B-1 G	Reactive oxygen species (ROS)	<i>Cyprinodon variegatus</i> (sheepshead minnow)	Increased lethality at cold temperature	Griffith and Gobler, 2016
Thermal stress	<i>Microcystis aeruginosa</i>	purified toxins – MCLR	Microcystin	<i>Danio rerio</i> (zebrafish)	increased toxicity at warmer temperatures	Kim et al. (2014)
Thermal stress	<i>Microcystis aeruginosa</i>	purified toxins – MCLR	Microcystin	<i>Moina macrocopa</i> (freshwater daphnids)	increased toxicity at warmer temperatures	Zhang et al. (2011)
Acidification	<i>Heterosigma akashiwo</i>	CCMP 2393	<i>na</i>	<i>na</i>	Increased swimming speed and net-downward movement of algal cells in high pCO ₂ environments	Kim et al. (2013a, 2013b)
Acidification	<i>Aureococcus anophagefferens</i>	CCMP 1984	unidentified toxins	<i>A. irradians</i>	Increased lethality in low pH treatments	Talmage and Gobler (2012)
Acidification	<i>Aureococcus anophagefferens</i>	CCMP 1984	unidentified toxins	<i>Crassostrea virginica</i> (eastern oyster)	Increased lethality in low pH treatments	Talmage and Gobler (2012)
Acidification	<i>Cochlodinium polykrikoides</i>	CP1	Reactive oxygen species (ROS)	<i>M. mercenaria</i>	Increased mortality by larvae in acidification treatments	Griffith and Gobler (2017)
Acidification	<i>Cochlodinium polykrikoides</i>	CP1	Reactive oxygen species (ROS)	<i>A. irradians</i>	Increased mortality by larvae in acidification treatments	Griffith and Gobler (2017)
Hypoxia	<i>Microcystis aeruginosa</i>	FACHB-905	Microcystin	<i>Hyopsis cumingi</i> (sail mussel)	Reduced scope for growth among mussels within hypoxic treatments	Hu et al. (2016)
Hypoxia	<i>Microcystis aeruginosa</i>	FACHB-905	Microcystin	<i>Hyopsis cumingi</i> (sail mussel)	Diminished immune response among mussels within hypoxic treatments	Hu et al. (2015)
Hypoxia	<i>Microcystis aeruginosa</i>	FACHB-905	Microcystin	<i>Hyopsis cumingi</i> (sail mussel)	Increased cellular damage among mussels within hypoxic treatments	Wu et al. (2017)

4. Co-effects of climate change stressors and HABs on aquatic life

4.1. Interactions between HABs and warming

Warmer temperatures can benefit some HABs via accelerated growth and an expanded realized niche (Paerl and Huisman, 2008; Fu et al., 2012; Glibert et al., 2014; Wells et al., 2015; Gobler et al., 2017). Recent warming has been attributed to more rapid growth and a longer bloom season for multiple toxin-producing HABs (Gobler et al., 2017). The relationships between temperature, growth rate, and toxin production, however, are highly strain- and species-specific. Temperature increases (up to 25 °C) generally promote the growth of *Dinophysis* spp. and an increase in the production of diarrhetic shellfish toxins (DSTs; Kamiyama et al., 2010). For other toxin-producing species, inverse relationships between toxin production and growth rate have been described. Specifically, while the growth of *Alexandrium* spp. increases with temperature to a strain-specific optimum, toxin content is generally greater among slower-growing cells maintained at lower temperatures (Ogata et al., 1987; Anderson et al., 1990; Hamasaki, 2001; Etheridge and Roesler, 2005). Similarly, the toxin content (per cell) of yessitoxin-producing dinoflagellates within the genera *Protoceratium* is greater within slowly dividing cells (Guerrini et al., 2007; Röder et al., 2012). For other organisms the relationship between temperature, growth, and toxin production are poorly understood and/or highly variable. Patterns between temperature and toxin production by *Pseudo-nitzschia* spp. are unclear with reports of variable production between temperature treatments (Lundholm et al., 1997) as well as higher cellular quotas among slower growing cells (Zhu et al., 2017). While several studies have investigated the impacts of warming on the growth and toxin products/content of HABs, most studies have not advanced to characterizing the activity of toxins and/or how organismal vulnerability is affected by temperature-induced changes. The limited number of studies doing so have described strong interactive effects (Table 1).

The impacts of temperature on the growth of toxic cyanobacteria are well-established, with growth rates increasing with warming temperatures (Rapala et al., 1997; Paerl and Huisman, 2008; Davis et al., 2009; Paerl and Paul, 2012; Brutemark et al., 2015; Lürling et al., 2017; Walls et al., 2018; Burford et al., 2019) to a thermal optimum that is generally higher than it is for most eukaryotic phytoplankton (Paerl and Huisman, 2008; Paerl and Paul, 2012; Brutemark et al., 2015; Lürling et al., 2017; Walls et al., 2018). The impact of warming on toxin production by cyanobacteria, however, is less clear with multiple studies demonstrating that warming can stimulate toxin production by cyanobacteria including *Microcystis aeruginosa* (Davis et al., 2009; Lürling et al., 2017), *Planktothrix agardhii* (Walls et al., 2018), and *Dolichospermum* spp. (formerly *Anabaena* spp.; Brutemark et al., 2015). More recently, however, toxin content among *M. aeruginosa* cells was found to be greater within slower-growing cells maintained at cooler temperatures (e.g. 18 °C; Peng et al., 2018). Few studies have assessed the toxicity of cyanobacteria at differing temperatures using biological assays. Those doing so report varying activities of toxins along a thermal gradient. For example, earlier studies suggest that warming temperatures may reduce the lethal effects of microcystins produced by *M. aeruginosa*. Toxic strains of *M. aeruginosa* (strain UV-006) cultivated across a range of temperatures (16–36 °C) were found to grow more quickly at warmer temperature (e.g. 32 °C) but were less toxic (as determined via mouse bio assay) compared to cultures at 20 °C (van der Westhuizen and Eloff, 1985). Similarly, Watanabe and Oishi, (1985) reported the LD₅₀ of mice injected with *M. aeruginosa* (strain M228) extracts from cultures maintained at higher temperature (e.g. > 30 °C) increased relative to mice injected with extracts from cooler-temperature cultures. More recent investigations have reported enhanced toxic effects of microcystins at warmer temperatures. For zebrafish (*Danio rerio*) exposed to microcystin (MC-LR) across a range of temperatures (12, 22, and 32 °C), mortality was greatest at the highest temperature

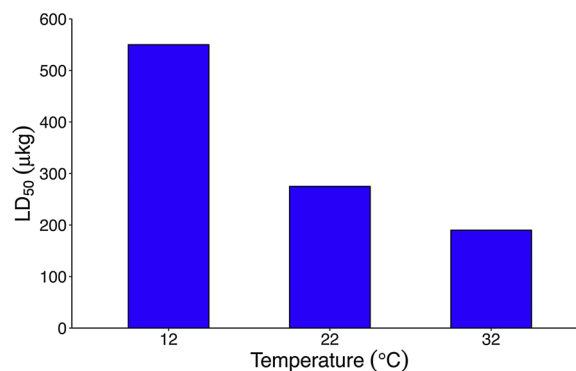


Fig. 2. LD₅₀ (determined via mouse bio assay) of toxins extracted from *M. aeruginosa* cultures at various temperatures (Zhang et al., 2011).

(Fig. 2; Zhang et al., 2011). Kim et al. (2014) conducted a series of exposures of *Moina macrocopa* (freshwater daphnids) to microcystins (MC-LR) at 20 and 25 °C and found reproductive output among microcystin-exposed individuals at warm temperatures was significantly lowered compared to those exposed at the colder temperature. Hence, warming may promote growth of cyanobacteria and intensification of blooms, but the relationship between temperature and total bloom toxicity may be non-linear and strain-specific.

Recently, Griffith and Gobler, (2016) characterized the impacts of temperature on the growth and toxicity of the ichthyotoxic dinoflagellate, *C. polykrikoides*. While growth rates increased as cultivation temperatures increased to a maximum at 24–27 °C, lethal effects determined via biological assays with fish and shellfish revealed an inverse relationship between temperature and lethality. Specifically, cultures maintained at 16 and 20 °C were more toxic on a per cell basis than more-rapidly growing cultures maintained at > 24 °C (Fig. 3). While the mechanisms of *C. polykrikoides* toxicity are not fully clear, the majority of evidence indicates adverse effects are linked to the production of reactive oxygen species (ROS; Kim, 1998; Tang and Gobler, 2009a, 2009b). Subsequent trials revealed antioxidant enzymes were more efficient at neutralizing ROS at warm temperatures and/or that the ROS compounds were more stable at cooler temperatures (Griffith and Gobler, 2016). Thus, rising ocean temperatures may intensify *C. polykrikoides* blooms in temperate zones (Griffith et al., 2019), but could render *C. polykrikoides* less toxic on a per cell basis (Griffith and Gobler, 2016). As such, mass-mortality events associated with *C. polykrikoides* blooms in tropical regions (Bauman et al., 2010; Richlen et al., 2010) may have been, in part, the result of interactions with low dissolved oxygen given potential reductions in lethality at warmer temperatures,

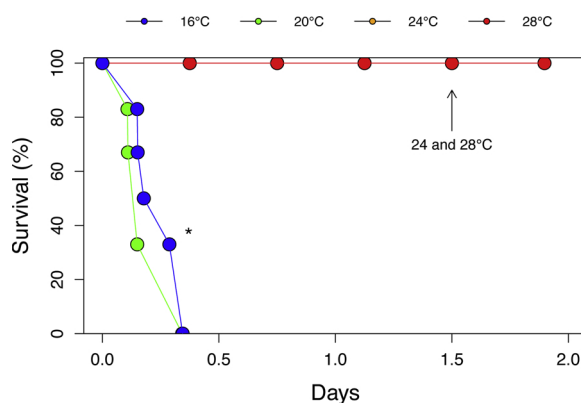


Fig. 3. Survival and time to death of sheepshead minnows (*Cyprinodon variegatus*) exposed to *C. polykrikoides* at varying temperature (24 and 28 °C data series overlap; * indicates significant differences in time-to-death between 16, 20 °C and 24, 28 °C treatments; Griffith and Gobler, 2016).

the elevated respiration rates of high-biomass blooms, and the low solubility of oxygen in warm waters.

While the impacts of temperature on the growth of HABs are well-characterized, the relationships between toxin production, toxic effects, and changing temperatures have been poorly studied. The rates at which organisms accumulate and/or depurate HAB-toxins at differing temperatures have also been poorly studied, but are likely to alter the harmful effects of HABs within aquatic food webs. Future work should consider quantifying the kinetics of HAB-toxins and their bioactivities across ranges of temperatures in conjunction with other stressors. Given that relationships between toxin production, growth rate, and adverse outcomes for aquatic life may be non-linear, identifying species-specific interactions with climate change stressors will better predict the impacts of HABs in the future as climate change continues.

4.2. Interactions between HABs and acidification

The effects of ocean acidification on the growth of many HAB species has been well-studied with complex intra- and inter-species-specific responses reported (Raven et al., 2019). Toxin production by several harmful algae increases under high $p\text{CO}_2$ conditions including saxitoxins produced by *Alexandrium* spp. (Tatters et al., 2013; Hattenrath-Lehmann et al., 2015a, 2015b), karoloxins produced by *Karolodinium venefecum* (Fu et al., 2010), and domoic acid produced by *P. multiseriis* (Sun et al., 2011; Tatters et al., 2012). Species-specific responses, however, complicate general trends. For example, growth and toxin production by *A. catenella* (Tatters et al., 2013; Hattenrath-Lehmann et al., 2015a, 2015b) and *A. ostenfeldii* (Kremp et al., 2012) are expected to increase under high $p\text{CO}_2$ whereas mixed responses with regard to growth and toxin production have been reported for *A. tamarensis* (Van de Waal et al., 2014; Pang et al., 2017). Strain-specific differences have been reported for *P. multiseriis*, with some groups reporting an increase in growth and toxin production (Sun et al., 2011; Tatters et al., 2012) at low pH/high $p\text{CO}_2$ (Sun et al., 2011; Tatters et al., 2012) and others reporting enhanced toxin production at high pH (Lundholm et al., 2004; Trimborn et al., 2008). Culture methods varied between these studies, however, with groups reporting enhanced toxicity at high pH (Lundholm et al., 2004; Trimborn et al., 2008) adjusting culture pH via the direct addition of acids and bases (Lundholm et al., 2004; Trimborn et al., 2008) and those observing higher toxin content achieving low pH conditions via direct injection of CO_2 into cultures (Sun et al., 2011; Tatters et al., 2012), suggesting enhanced toxin production associated with excess carbon, an outcome consistent with Van de Waal's stoichiometric hypothesis for toxin production (Van de Waal et al., 2009, 2014). For harmful cyanobacteria, responses to acidification are phenotype-specific with some toxic strains losing competitive advantages over non-toxic ones at low pH (Van de Waal et al., 2011; Yu et al., 2015) and others becoming more competitive (Sandrini et al., 2014). While growth and toxin production by HAB species within acidified environments is well-studied, the toxicokinetics and impacts of HAB toxins under these conditions are not known with few studies investigating harmful outcomes (i.e. biological responses among exposed marine life) in low pH environments. Here, we summarize currently known interactions between HAB species and acidification.

Studies have demonstrated that several key attributes of *Heterosigma akashiwo* are altered under high $p\text{CO}_2$ that, in turn, may have important consequences for marine life. For example, separate studies using two strains of *H. akashiwo* (CCMP 2393 and CCMP 2809) isolated from two estuaries (Delaware Bay (USA) and Puget Sound (WA; USA), respectively, demonstrated cultures experienced increased growth rates when provided high $p\text{CO}_2$ (~750 ppm CO_2 ; Fu et al., 2008; Kim et al., 2013). Beyond growth, cells grown at low pH (high $p\text{CO}_2$) exhibited increased swimming speed with the movement of cells being largely downward, potentially making cells increasingly light-limited as they migrate deeper into the water column (Kim et al., 2013a). Such migration may alter predator/prey dynamics (i.e. zooplankton grazing) as well as the

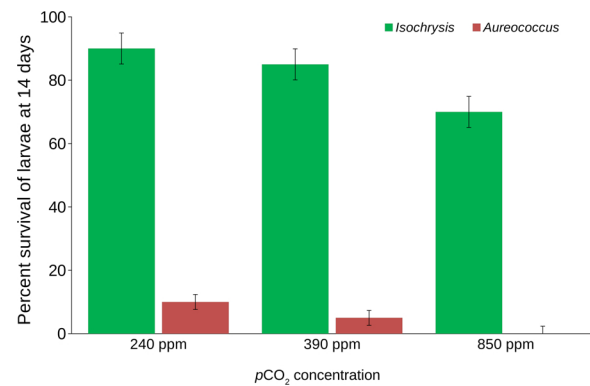


Fig. 4. Survival of bay scallop larvae (*Argopecten irradians*) exposed to high $p\text{CO}_2$ with and without the addition of *Aureococcus anophagefferens*.

harmful effects of these blooms as cells may migrate away from wild pelagic or caged/aquacultured organisms towards the benthos. Hence, while higher $p\text{CO}_2$ may promote the growth of *H. akashiwo* blooms, altered swimming behavior may change their harmful effects.

The brown tide pelagophyte, *Aureococcus anophagefferens*, is well-known for its lethal effects on bivalves along coastal areas of the northeast US (Casper et al., 1987; Gobler et al., 2005; Bricej and MacQuarrie, 2007) and China (Zhang et al., 2012; Dong et al., 2014). Further, many eutrophied, net-heterotrophic estuaries including those that experience brown tides already exhibit extreme levels of acidification (Cai et al., 2011; Waldbusser et al., 2011; Wallace et al., 2014; Baumann et al., 2015) and are already a threat to larval bivalves (Talmage and Gobler, 2010). Talmage and Gobler (2012) investigated the interactive effects of the brown tide alga and CO_2 (e.g. 240, 390, and 850 ppm $p\text{CO}_2$; delivered via bubbling) on larval oysters (*Crassostrea virginica*) and bay scallops (*Argopecten irradians*). The authors found that the combined effects of acidification and *A. anophagefferens* were more intense than the individual stressors, depressing larval growth, development, lipid content, and survival (Fig. 4; Talmage and Gobler, 2012). This phenomenon is particularly problematic for larval bivalves as the onset of coastal acidification (Baumann et al., 2015) and the emergence of brown tides (Gobler and Sunda, 2012) overlap with the period when larval marine bivalves are spawned in temperate estuaries (Kennedy and Krantz, 1982; Sherman et al., 1984; Helly and Beltz, 1991). Given this outcome, the net effects of HABs in coastal ecosystems that are already experiencing acidification may be underestimated.

Recently, Griffith and Gobler (2017) characterized the transgenerational responses of marine bivalves exposed to acidification (~600 and 2400 ppm CO_2 ; achieved via aeration with CO_2) from the onset of reproductive development (i.e. reproductive conditioning) through the end of larval life-stages. Larvae from transgenerational treatments were exposed to multiple additional stressors, including harmful algae. When exposed to the ROS-producing dinoflagellate, *C. polykrikoides* (Tang and Gobler, 2009a, 2009b), larvae of hard clams (*Mercenaria mercenaria*) and bay scallops (*A. irradians*) originating from adults undergoing reproductive conditioning within acidified environments or exposed to low pH during initial larval development (e.g. 48 h) exhibited significantly lower survival than larvae originating from parents undergoing gametogenesis under normal $p\text{CO}_2$ conditions (Griffith and Gobler, 2017). Given that high $p\text{CO}_2$ environments can increase respiration rates in larval shellfish (Waldbusser et al., 2015) and likely stimulate intra-cellular production of ROS, additional, extracellular ROS exuded by *C. polykrikoides* may overwhelm antioxidant defenses of larvae, leading to increased mortality.

Marine organisms are often more susceptible to ocean acidification when food is limited (Thomsen et al., 2013; Pansch et al., 2014; Ramajo et al., 2016; Gobler et al., 2018). Recently, Mellado et al. (2018)

demonstrated the combined presence acidification (e.g. 1000 μatm $p\text{CO}_2$ modified via air- CO_2 mixed gasses) and *A. catenella* limited absorption rates of algal cells by *M. chilensis* (Chilean mussels), more so than by exposure to each stressor separately. In addition, significant interactive effects between HAB exposure and acidification were found to limit scope for growth, presumably as a consequence of decreased feeding efficiency (Mellado et al., 2018). Given that many HAB species are poor sources of nutrition (Shumway, 1990; Wikfors and Smolowitz, 1995; Bricelj and Lonsdale, 1997; Tango et al., 2005; Rountos et al., 2019), the presence of HABs may intensify the impacts of ocean acidification by reducing the quality of available food.

4.3. Interactions between HABs and hypoxia

Despite the awareness of ocean deoxygenation as an emergent climate change stressor (Levin and Breitburg, 2015; Breitburg et al., 2018), the interactive effects between HABs and hypoxia are relatively unknown. It is possible that HABs and hypoxia rarely occur simultaneously as HABs would be expected keep ecosystems well-oxygenated via photosynthesis. Alternatively, many HABs can be heterotrophic, relying on organic matter and/or prey for growth (Burkholder et al., 2008; Flynn et al., 2018; Glibert et al., 2018) and thus contributing to the net depletion of dissolved oxygen via respiration. This may be more extreme for dense HABs that promote severe light attenuation and minimize photosynthesis (Sunda et al., 2006). The dominance of respiratory processes at night may draw down oxygen levels further (Tyler et al., 2009) and given the downward vertical migration of some HAB-forming dinoflagellates (Fraga et al., 1989; Smayda and Reynolds, 2003; Doblin et al., 2006), exposure of benthic communities to HABs and hypoxia may commonly occur in some ecosystems (Fig. 1). The termination of HABs may also threaten the health of the benthos whereby dying HABs sink and contribute organic carbon to bottom waters, accelerating rates of microbial respiration, deoxygenation, and the release of intra-cellular HAB toxins.

There are seasonal and latitudinal gradients that influence the co-occurrence of HABs and hypoxia, which are likely to strengthen as climate change accelerates. Since the saturation of dissolved oxygen in water is inversely proportional to temperature, temperate HABs occurring in summer and tropical HABs are more likely to co-occur with hypoxia than HABs in cooler environments. As climate change accelerates, an earlier onset and later termination of hypoxic conditions along with latitudinal expansions (Breitburg et al., 2018), may also make the co-occurrence of HABs and hypoxia more common. The Baltic Sea is a high-latitude ecosystem prone to both hypoxia and cyanobacterial HABs during summer (Funkey et al., 2014) and these occurrences may be related as hypoxic conditions provide a flux of phosphorus that can promote the growth of diazotrophic and toxic HABs such as *Aphanizomenon* and *Anabaena* spp. (O'Neil et al., 2012). However, the co-effects of hypoxia and toxic cyanobacteria from this region have not been studied.

A series of studies with microcystin-producing *M. aeruginosa* cultures and the sail mussel, (*Hyriopsis cumingii*; Hu et al., 2015, 2016; Wu et al., 2017), represent some of the only efforts to examine the co-effects of HABs and hypoxia on aquatic life. Strong interactive effects between hypoxia (e.g. 1, 3, and 6 mg L^{-1} O_2) and *M. aeruginosa* occurred whereby combined exposure to stressors elicited more severe negative responses for *H. cumingii* than the individual stressors. Scope for growth (i.e. energy available for growth) among mussels within the combined treatments (e.g. 1 $\text{mg O}_2 \text{ L}^{-1}$ and 100% *M. aeruginosa*) was the lowest of all treatments (Hu et al., 2016) and, after seven days of exposure to < 1 mg L^{-1} dissolved oxygen, clearance rates were lowest within combined treatments and remained low throughout the recovery period. Combined exposure to hypoxia and *M. aeruginosa* also inhibited the activities of superoxide dismutase (SOD) and lysozymes (Yu et al., 2015). Mussels exposed to hypoxia and *M. aeruginosa* exhibited damage to gill, digestive, and stomach tissues with the more severe damage in

the combined treatments compared to mussels exposed to only one stressor (Wu et al., 2017). Collectively, these studies demonstrate potential for *Microcystis* spp. and hypoxia to interact, yielding more severe outcomes than either stressor individually.

5. Future directions

Climate change will continue to intensify within coastal zones throughout this century, having transformative impacts on aquatic ecosystems (Doney et al., 2012; IPCC, 2014). At the same time, the co-occurrences of climate change stressors, eutrophication, and HABs (Hallegraeff, 2010; Fu et al., 2012; Glibert et al., 2014; Gobler et al., 2017) pose significant threats to the structure and function of aquatic food webs. While the impacts of climate changes on HAB characteristics (i.e. growth, toxin production, phenology) have been well-studied, the effects of combined exposure to climate change stressors (e.g. low pH, hypoxia, and warming) and HABs on aquatic life have not. The toxicokinetics (i.e. stability, distribution, and reactivity) of HAB toxins in climate change-altered environments have been poorly studied, preventing a clear understanding of their fate and impacts under different climate change scenarios. Limited assessments to date suggest the relationships between HAB growth, toxin production, cellular toxin quotas, and harmful impacts are often non-linear (Ogata et al., 1987; Anderson et al., 1990; Etheridge and Roesler, 2005; Griffith and Gobler, 2016). Further, altered aerobic scope in response to climate change perturbations (Sokolova and Portner, 2001; Pörtner and Knust, 2007; Donelson et al., 2011; Waldbusser et al., 2015) may influence the metabolism or depuration of HAB toxins in aquatic organisms, a process that may alter their potency and effects. For example, given that the depuration of saxitoxin within bivalve shellfish can be slowed by warming and acidification, this toxin may be retained for longer periods of time, increasing the risk for human exposure and trophic transfer (Braga et al., 2018).

For species producing a suite of toxins, climate change stressors may alter the synthesis of specific congeners, changing their composition, content, (Rapala et al., 1997; Fu et al., 2008; Tatters et al., 2013; Hattenrath-Lehmann et al., 2015a, 2015b) and ultimately, toxicity (Gupta et al., 2003; Miles et al., 2004; Baden et al., 2005; Munday et al., 2013). Given that changes in toxin congeners may not be detected by structure-based toxin assays, (Rivasseau et al., 1999; Naar et al., 2002; Litaker et al., 2008), biological assays using ecologically appropriate organisms will be more representative of harmful impacts elicited by HABs and other co-stressors. Climate change processes may also alter the solubility, stability, distribution, and fate of HAB toxins, scenarios that will ultimately dictate the severity of their harmful impacts. Unfortunately, these dynamics are difficult to model or predict given the scarcity of information on this topic, emphasizing the need for multi-factorial investigations. In addition to changes in the kinetics and activities of HAB-toxins, climate change may alter the vulnerabilities of marine life exposed to multiple stressors. Trends, as detailed above, are likely to be species-/strain- and toxin-specific.

An important, but understudied question regarding the co-impacts of climate change and HABs is how climate-altered migration patterns may alter the temporal and/or spatial overlap of HABs and organisms sensitive to their effects. Ocean warming is changing the ranges in which HABs occur (e.g. Gobler et al., 2017) as well as the distribution of aquatic life (Walther et al., 2002; Harley et al., 2006; Nye et al., 2009). These changes may expose naïve populations to HABs, an outcome that may be particularly severe and lead to rapid natural selection in aquatic populations (Bricelj et al., 2005). For example, copepods (*Acartia hudsonica*) originating from regions historically void of *Alexandrium catenella* are more sensitive to exposure than populations originating from areas with frequent blooms, suggesting that as blooms expand, geographically-naïve copepod populations could be vulnerable (Colin and Dam, 2002). Further, brown tides caused by *Aureocymbra lagunensis* have recently emerged within the Indian River Lagoon (FL, USA; Gobler and

Talmage, 2013) and have been found to negatively impact the physiology and feeding behavior of resident bivalves (Galimany et al., 2017), confounding bivalve restoration efforts. In addition to changing marine animal distributions, recent ocean warming has caused bloom-favorable conditions for several HABs to become established earlier and persist longer, a phenomenon that may increase the risk and/or duration of exposure to marine life from certain HABs (Gobler et al., 2017; Griffith et al., 2019).

Although eutrophication can concurrently promote HABs, acidification, and deoxygenation within coastal systems (Heisler et al., 2008; Wallace et al., 2014), combined impacts of these stressors are poorly understood. Few studies have investigated the combined impacts of two of these stressors, and those studies have reported strong interactive effects (Talmage and Gobler, 2012; Hu et al., 2015, 2016; Wu et al., 2017). No study has examined all three of these stressors concurrently. Beyond examining the immediate effects of these co-stressors, it is important to understand how sequential exposure to these stressors may affect organisms. For example, dense blooms of primarily autotrophic HABs may prohibit acidification and hypoxia during the day, but may lead to intense exposure at night or HAB exposure followed by low pH/DO conditions. Identifying the combined impacts of these stressors may be especially important for high-production aquaculture facilities/locations contributing large quantities of organic matter to the water column (Shumway, 1990; Burkholder and Shumway, 2011) that can promote deteriorating water quality (e.g. acidification, hypoxia, and HABs). Given that caged organisms are unable to avoid HABs, aquaculture operations may be particularly vulnerable to the co-exposure to these stressors. As climate change advances and HABs become more frequent and intense (Fu et al., 2012; Paerl and Paul, 2012; Glibert et al., 2014; Gobler et al., 2017), understanding the combined impacts of hypoxia, acidification, and HABs on aquaculture production could help minimize future losses. More specifically, strains or species of aquacultured organisms that are resistant to HABs and their co-stressors may be needed to replace those that are highly vulnerable.

6. Conclusion

As anthropogenic perturbations (e.g. climate change and eutrophication) continue along coastal zones, HABs are becoming an aquatic stressor of increasing concern. Incorporating harmful algae into experiments and monitoring where multiple climate change stressors are considered will provide a more ecologically relevant perspective regarding the structure and function of marine ecosystems in future, climate-altered environments. While few studies have examined the combined impacts of HABs and other climate change stressors on aquatic organisms, strong species- and strain-specific interactions that modify the outcomes for exposed organisms have been described. Furthermore, responses of HAB growth, toxin production, and their effects in altered environments have been highly dynamic and non-linear. A deeper and more nuanced understanding of how HABs and climate change stressors interact to affect aquatic life in marine and freshwater ecosystems is needed to formulate management plans that protect human health, fisheries, and aquaculture.

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