

# Cyanobacterial blooms

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**Abstract** | Cyanobacteria can form dense and sometimes toxic blooms in freshwater and marine environments, which threaten ecosystem functioning and degrade water quality for recreation, drinking water, fisheries and human health. Here, we review evidence indicating that cyanobacterial blooms are increasing in frequency, magnitude and duration globally. We highlight species traits and environmental conditions that enable cyanobacteria to thrive and explain why eutrophication and climate change catalyse the global expansion of cyanobacterial blooms. Finally, we discuss management strategies, including nutrient load reductions, changes in hydrodynamics and chemical and biological controls, that can help to prevent or mitigate the proliferation of cyanobacterial blooms.

## Eutrophication

The excessive enrichment of ecosystems with dissolved nutrients (for example, nitrate and phosphate), usually through human activity.

Cyanobacteria are oxygen-producing bacteria that use sunlight as an energy source to convert carbon dioxide (CO<sub>2</sub>) into biomass. They originated around 3 billion years ago<sup>1,2</sup>, and their photosynthetic activity triggered one of the most dramatic events during the evolution of our planet — the oxidation of the Earth's atmosphere<sup>3</sup>. Cyanobacteria are also known as blue-green algae, but strictly speaking, they are not algae, which is a name reserved for eukaryotic phototrophs. Moreover, many cyanobacteria are not blue-green. The distinct cyan (blue-green) hue of their accessory pigment phycocyanin (FIG. 1a) is usually masked by the ubiquitous green pigment chlorophyll *a* and by other accessory pigments, such as red phycoerythrin and yellow-orange carotenoids. Hence, cyanobacteria exhibit a staggering array of colours, including various shades of green, red, brown, yellow and pink<sup>4,5</sup>.

Cyanobacteria can form dense blooms (FIG. 1). Here, we define a cyanobacterial bloom as a marked visible discoloration of the water that is caused (predominantly) by cyanobacteria. Common bloom-forming genera include *Aphanizomenon*, *Cylindrospermopsis*, *Dolichospermum*, *Microcystis*, *Nodularia*, *Planktothrix* and *Trichodesmium* (FIG. 2). Cyanobacterial blooms can cause major problems for water quality<sup>6–8</sup>. They increase turbidity and smother submerged aquatic vegetation<sup>9</sup>. Oxygen depletion by the microbial degradation of senescent blooms may induce hypoxia and anoxia, causing the death of fish and benthic invertebrates<sup>10</sup>. Cyanobacteria produce taste and odour compounds, which interfere with the recreational function of lakes and the use of reservoirs for drinking water<sup>11,12</sup>. Moreover, cyanobacterial blooms can produce a variety of cyanotoxins that cause liver, digestive and neurological diseases when ingested by birds, mammals and humans<sup>13–15</sup>.

In recent years, numerous studies have indicated that eutrophication, rising CO<sub>2</sub> levels and global warming are likely to increase the frequency, intensity and duration of cyanobacterial blooms in many aquatic ecosystems across the globe<sup>16–31</sup>. This trend is of great concern, as it may have negative effects on the biodiversity and functioning of aquatic food webs and threatens the use of affected waters for drinking water, bathing, fishing and other recreational uses. This Review presents a concise assessment of available evidence for the global expansion of blooms, the traits and mechanisms underlying bloom formation, the toxins produced by cyanobacteria, their interactions with other species, the presumed environmental drivers of bloom development and possible measures to prevent and control cyanobacterial blooms.

## Global rise of cyanobacterial blooms

Although cyanobacterial blooms have been known since ancient times (BOX 1), several studies indicate that they are currently increasing globally. For example, analysis of cyanobacterial pigments in sediment cores from over 100 lakes in North America and Europe shows that cyanobacteria have increased substantially in almost 60% of the lakes since the industrial revolution, that cyanobacterial abundance has increased disproportionately relative to other phytoplankton and that this increase has accelerated since 1945 (REF.<sup>26</sup>). This trend is likely to continue in the next decades. A recent study used climate change projections from five global circulation models as input for a coupled water quantity and quality model of the USA<sup>28</sup>. The model predicts that, in the USA, the mean number of days with harmful cyanobacterial blooms will increase from about 7 days per year per waterbody under current conditions to 18–39 days in 2090. The expansion of cyanobacterial blooms and their economic and societal

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**Fig. 1 | Cyanobacterial blooms.** **a** | A bloom of senescent cyanobacteria, in which degradation of the green chlorophyll pigment reveals the distinct cyan colour of the accessory pigment phycocyanin (St. Lucie River, Florida, USA). **b** | Satellite photograph of a cyanobacterial bloom in the western part of Lake Erie (USA and Canada). **c** | Satellite photograph of the annually recurring cyanobacterial blooms in the Baltic Sea<sup>43</sup>. **d** | Lesser flamingo foraging in a toxic cyanobacterial bloom in Lake Bogoria (Kenya), which killed ~30,000 flamingos in 1999 (REF.<sup>186</sup>). **e** | A dense *Microcystis* bloom covering Lake Taihu (China). **f** | The Burgundy-blood phenomenon<sup>70</sup>, a dense surface bloom of the red cyanobacterium *Planktothrix rubescens* (Lake Hallwil, Switzerland). **g** | A *Trichodesmium* bloom in the Gulf of Mexico; James Cook and Charles Darwin noted during their ocean voyages that sailors often call these brown surface blooms 'sea sawdust'. Image in part **a** courtesy of E. Killer, TCPalm, USA. Images in parts **b** and **c** courtesy of the European Space Agency, © ESA 2011, CC-BY-SA-3.0 IGO. Image in part **d** courtesy of L. Krienitz, Leibniz Institute of Freshwater Ecology and Inland Fisheries, Germany. Image in part **f** courtesy of S. Flury, EAWAG, Switzerland.

blooms have proliferated in Lake Taihu (FIG. 1e), currently extending across almost its entire surface area of ~2,400 km<sup>2</sup>. Analysis of 11 years of satellite data from the lake shows that high temperatures and nutrient concentrations in spring promote cyanobacterial growth, while low wind speeds and low atmospheric pressure favour the formation of surface blooms<sup>30</sup>. The cyanobacterial blooms in Lake Taihu have led to serious environmental and societal problems, with long-term negative impacts on water quality, fisheries and aesthetics, limiting tourism and other economic activities<sup>32-34</sup>. One example is the highly publicized drinking water crisis in the city of Wuxi in May 2007, when approximately 2 million inhabitants were without drinking water for more than a week owing to a massive toxic bloom of *Microcystis* spp.<sup>32,33</sup> (FIG. 1e).

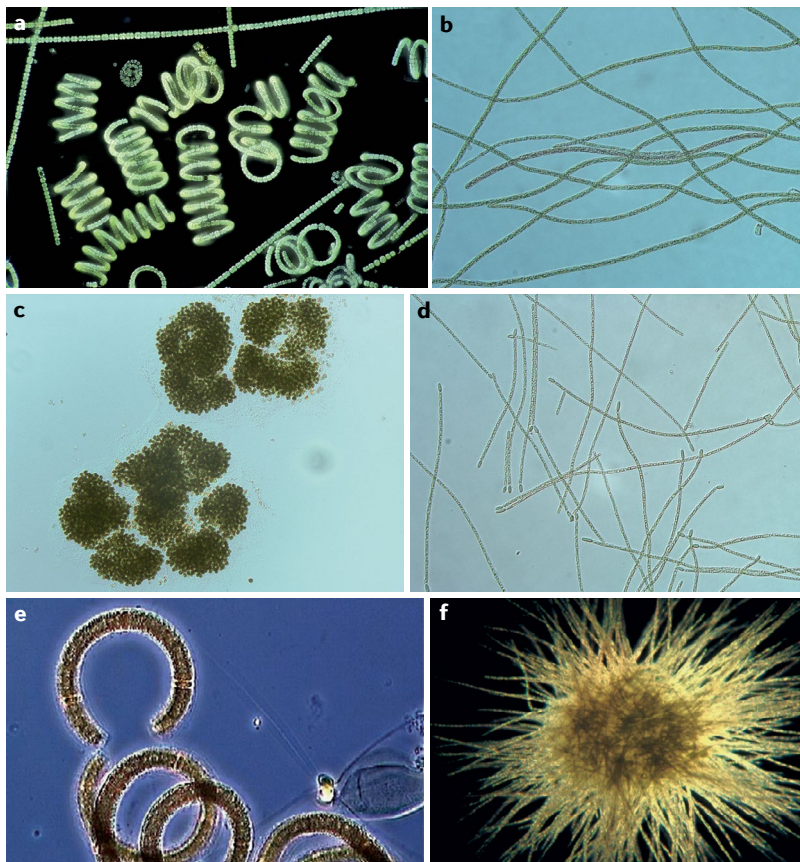
The North American Great Lakes are a vital freshwater resource, containing ~18% of the world's available surface fresh water. Lake Erie is the shallowest and warmest of the Great Lakes and receives nutrients from urban, industrial and agricultural sources. In the 1960s and early 1970s, dense phytoplankton blooms, including the nitrogen-fixing cyanobacteria *Dolichospermum* spp. (FIG. 2a; then named *Anabaena* spp.) and *Aphanizomenon flos-aquae*, were common<sup>35</sup>. The intensity and frequency of these blooms decreased during the 1970s and 1980s with the implementation of phosphorus loading reductions<sup>36</sup>. However, by the mid-1990s, cyanobacterial blooms returned to Lake Erie<sup>37</sup> (FIG. 1b), now dominated by the non-nitrogen-fixing cyanobacteria *Microcystis* spp. and *Planktothrix* spp. (FIG. 2b,c), which produce potent cyanotoxins (microcystins)<sup>38</sup>. In 2011, a wet spring caused high nutrient run-off from agriculture and, in combination with a prolonged period of warm summer weather, led to a record-setting cyanobacterial bloom that extended across 5,000 km<sup>2</sup> (REF.<sup>24</sup>). Consequently, human exposure to cyanotoxins has been of growing concern. In August 2014, a 'do not drink' advisory was issued for Toledo, Ohio, USA, because microcystin concentrations

impacts can best be illustrated by some prominent and representative examples.

Lake Taihu (meaning 'Great Lake' in Chinese) is a large shallow lake in the Yangtze River Delta in China. Rapid economic and population growth in the Taihu Basin has led to a substantial increase in nutrient pollution from agricultural run-off, industries and wastewater treatment facilities that discharge into the numerous tributaries of the lake<sup>32</sup>. Since the 1980s, cyanobacterial

**Phytoplankton**  
Microscopically small photosynthetic algae, such as green algae and diatoms, and cyanobacteria drifting in the water.





**Fig. 2 | Six common bloom-forming cyanobacteria.** **a** | *Dolichospermum* spp. (formerly *Anabaena* spp.) are nitrogen-fixing cyanobacteria. These spiralling filaments were already described by Antonie van Leeuwenhoek<sup>182,183</sup> in 1674 (BOX 1). The glassy cells in some of the filaments are heterocysts that can fix nitrogen. **b** | *Planktothrix agardhii* is a filamentous cyanobacterium that occurs in shallow eutrophic lakes. One filament in the middle of the picture is of *Planktothrix rubescens*, which is a red-coloured filamentous cyanobacterium that is responsible for the Burgundy-blood phenomenon<sup>70</sup>. **c** | *Microcystis aeruginosa* is a colonial cyanobacterium that caused recent drinking water crises in Lake Taihu<sup>32–34</sup> (China) and Lake Erie<sup>39</sup> (USA). **d** | *Cylandrospermopsis raciborskii* is a filamentous nitrogen-fixing cyanobacterium that originated in tropical and subtropical areas but is currently invading temperate waters<sup>95,96</sup>. The elongate cells at the tips of the filaments are heterocysts. **e** | *Nodularia spumigena* is a nitrogen-fixing cyanobacterium that often dominates in brackish waters such as the Baltic Sea<sup>40–43</sup> and was held responsible for mass mortalities of livestock in the classic 1878 study of George Francis<sup>184,185</sup>. **f** | *Trichodesmium* sp. is a marine nitrogen-fixing cyanobacterium whose filaments aggregate in puffs (this photo) and tufts. It can form massive blooms in tropical and subtropical oceans<sup>44</sup>. Image in part **a** courtesy of W. van Egmond, Netherlands. Images in parts **b–d** courtesy of A. Ballot, Norwegian Institute for Water Research (NIVA), Norway. Image in part **e** courtesy of M. Stomp, University of Amsterdam, Netherlands.

**Benthic cyanobacteria**  
Cyanobacteria that live on sediments, rocks and other benthic organisms.

**Macroalgae**  
Macroscopic multicellular algae, such as seaweeds.

**Turf algae**  
Heterogeneous assemblages of benthic algae and cyanobacteria, visible by the naked eye but smaller than 1 cm in height.

exceeded the WHO guideline value for safe drinking water, which resulted in over 400,000 people being without tap water for nearly 48 hours<sup>39</sup>.

Cyanobacterial blooms are also expanding in estuarine and marine ecosystems. During summer, the Baltic Sea is covered by massive blooms of nitrogen-fixing cyanobacteria (FIG. 1c), mainly *Nodularia spumigena* (FIG. 2e) and *Aphanizomenon* spp. Fossil pigments in the layered sediments indicate that blooms have occurred in the Baltic Sea for thousands of years<sup>40</sup>. However, they have been much more common since the 1960s than in the late 19th and early 20th centuries<sup>41</sup>, presumably owing to a combination of human-induced eutrophication and

climate change<sup>21,42</sup>. Today, cyanobacterial blooms in the Baltic Sea can span ~200,000 km<sup>2</sup> (REF.<sup>43</sup>).

*Trichodesmium* (FIG. 2f) is a genus of marine nitrogen-fixing cyanobacteria that forms large surface blooms in the tropical and subtropical open ocean<sup>44</sup> (FIG. 1g). An extensive *Trichodesmium erythraeum* bloom was reported for the first time in the Mediterranean Sea in 2010 (REF.<sup>45</sup>), much further northwards than ever documented before, following a warm summer period with the highest sea surface temperature and lowest wind speeds recorded since 1955.

In some tropical waters, the degradation of coral reefs is accompanied by a marked increase in benthic cyanobacteria<sup>46,47</sup>. For example, a recently published 40-year study from the island of Curaçao in the Caribbean Sea showed that coral reefs were initially overgrown by macroalgae and turf algae, but these organisms are currently being displaced by the rapid expansion of benthic cyanobacterial mats<sup>48</sup>.

### Traits involved in bloom development

Cyanobacteria are a diverse group of organisms, and different species can vary in their traits. Several of these traits provide cyanobacteria with a distinct competitive advantage over eukaryotic phytoplankton, which tends to favour their dominance and enables the development of dense cyanobacterial blooms.

**Nitrogen fixation.** Some key bloom-forming cyanobacteria (for example, members of the genera *Dolichospermum*, *Aphanizomenon*, *Nodularia* and *Cylandrospermopsis*, FIG. 2) can fix nitrogen (N<sub>2</sub>), which gives them access to the vast atmospheric nitrogen pool that is not directly available to eukaryotic species. Nitrogen fixation is carried out by the nitrogenase enzyme complex, which is irreversibly inactivated by oxygen<sup>49</sup>. To separate nitrogen fixation from photosynthetic oxygen production, some cyanobacterial genera form specialized cells called heterocysts<sup>50</sup> (FIG. 2a,d). Heterocysts produce no oxygen during photosynthesis and maintain high respiration rates to consume oxygen<sup>50,51</sup>. Furthermore, they have thick cell walls to suppress the diffusion of oxygen into the cell while still allowing a sufficient influx of N<sub>2</sub> for nitrogen fixation<sup>52</sup>. In the subtropical and tropical oceans, bloom-forming *Trichodesmium* spp. (FIG. 2f) are among the major nitrogen-fixing organisms. They produce no heterocysts but grow in large colonies in which nitrogen fixation and oxygenic photosynthesis are spatially separated<sup>44</sup>.

Nitrogen-fixing (diazotrophic) cyanobacteria have a competitive advantage over non-diazotrophic cyanobacteria and eukaryotic phytoplankton in nitrogen-limited waters, where they can develop dense blooms if other nutrients, especially iron and phosphorus, are plentiful. Nitrogen fixation is an energetically costly process, and many diazotrophic cyanobacteria suppress N<sub>2</sub> fixation when alternative forms of nitrogen, such as ammonium and nitrate, are available. Similar to other enzymatic processes, nitrogenase activity is temperature-dependent. Furthermore, nitrogen-fixing cells can respire inflowing oxygen more rapidly at high temperatures, thereby

## Box 1 | Blooms in the past

Toxic cyanobacterial blooms have probably been around for millions of years. Prehistoric mass mortalities involving deer, horses, elephants, aurochs and cave lions in Pleistocene and Eocene lakes have been attributed to toxic cyanobacteria<sup>176,177</sup>. A severe drought ~4,000 years ago led to dense cyanobacterial blooms in wetlands on the island of Mauritius, coinciding with mass mortalities of thousands of dodos and giant turtles<sup>178</sup>.

Written accounts suggest an early awareness of cyanobacterial blooms. Algal scums feature in Shakespeare's *Merchant of Venice*, written in the 16th century<sup>179</sup>. In 1672, the English traveller Christopher Kirkby wrote to the Royal Society in London about the deaths of dogs, cattle and poultry associated with annual summer accumulations of green scum in Tuchomske Lake, Poland<sup>180</sup>. His detailed account provides one of the first descriptions of animal poisonings related to cyanobacterial blooms<sup>181</sup>. Two years later, Antonie van Leeuwenhoek wrote to the same Royal Society about samples that he had taken from "green clouds" floating in a productive lake near Delft, Netherlands<sup>182</sup>. Under the microscope, he observed several "green tendrils, spiralling serpent-wise in an orderly manner" consisting of "small green globules joined together". As recently pointed out by the Dutch microscopist Wim van Egmond, these words paint a highly accurate description of the spiral filaments of *Dolichospermum* spp.<sup>183</sup> (FIG. 2a). The small green globules described by van Leeuwenhoek most likely represent the first bacterial cells ever observed, 2 years before his widely acclaimed discovery of bacteria in 1676<sup>183</sup>.

The first detailed scientific inquiry of the toxic actions of a cyanobacterial bloom dates back to a *Nature* publication in 1878 (REFS<sup>184,185</sup>). George Francis, a local chemist, had been commissioned to investigate the cause of mass mortalities of farm livestock along the River Murray and shores of Lake Alexandrina, South Australia. He observed that a dense bloom of the cyanobacterium *Nodularia spumigena* (FIG. 2e) floated to the surface during calm weather, forming scums at the lee shores of the lake. Livestock along the shores ingested this scum while drinking from the lake and died a few hours later. Francis reproduced the characteristic signs and timing of illness, mortalities and gross organ pathology by dosing healthy sheep with fresh scum material<sup>184</sup>. He correctly inferred that *N. spumigena* contained a toxin responsible for the sheep deaths, which is now known as the cyanotoxin nodularin. Following Francis' findings, a system was rapidly introduced for the reporting of cyanobacterial blooms. This involved riverboat captains, the police and local farmers and represents one of the earliest examples of risk management of hazardous cyanobacterial blooms<sup>185</sup>.

### Carboxysomes

Microcompartments in cyanobacterial cells that hold the enzyme Rubisco, a key enzyme involved in the first step of CO<sub>2</sub> fixation.

### Stokes' law

A mathematical equation describing the terminal velocity of small particles in a fluid medium such as water.

### Secondary metabolites

Organic compounds that are produced by organisms but not directly involved in the growth or reproduction of these organisms.

### Zooplankton

Small animals that drift in water.

### Copepods

A group of small crustaceans of the subclass Copepoda, often with a cylindrical body, two large antennae and a head that is fused with the thorax.

reducing the respiratory costs of nitrogen fixation<sup>51,53</sup>. Therefore, high temperatures strongly increase the nitrogen fixation rates of several diazotrophic cyanobacteria<sup>53,54</sup>, which may further increase their proliferation in nitrogen-limited waters.

**CO<sub>2</sub>-concentrating mechanisms.** Like plants and algae, cyanobacteria fix CO<sub>2</sub> for photosynthesis and growth. Dense cyanobacterial blooms can deplete dissolved CO<sub>2</sub> concentrations to <1 μmol per litre and thereby raise the pH to 9 or even 10, thus shifting the equilibrium of inorganic carbon towards bicarbonate and carbonate<sup>25,55</sup>. To sustain CO<sub>2</sub> fixation, cyanobacteria have evolved CO<sub>2</sub>-concentrating mechanisms (CCMs) that enable cells to increase the CO<sub>2</sub> concentration in cellular microcompartments called carboxysomes to levels at which the carbon-fixing enzyme Rubisco can operate efficiently<sup>56,57</sup> (FIG. 3). Five different inorganic carbon uptake systems have been identified in cyanobacteria to date: two for CO<sub>2</sub> uptake and three for bicarbonate uptake. These uptake systems have different substrate affinities and flux rates<sup>56,57</sup>, and cyanobacterial strains can combine these carbon uptake systems in different ways to tune their carbon fixation rates to environmental changes in inorganic carbon availability<sup>58,59</sup> (FIG. 3).

**Gas vesicles providing buoyancy.** Gas vesicles are hollow protein structures filled with gas (FIG. 3), which provide buoyancy to the cells of several bloom-forming cyanobacterial species so that they may float upwards<sup>60,61</sup>. In stagnant waters with little wind mixing, accumulation of large numbers of cyanobacteria at the water surface can lead to the development of intense blooms (FIG. 1). Cells in these surface blooms are exposed to high amounts of light and ultraviolet radiation<sup>55,62</sup> and may suffer from local depletion of inorganic carbon and nutrients. Surface blooms provide buoyant cyanobacteria with a major competitive advantage, however, because they intercept the influx of light and atmospheric CO<sub>2</sub> and shade non-buoyant phytoplankton deeper in the water column<sup>63,64</sup>. In this manner, dense surface blooms of buoyant cyanobacteria can effectively suppress other, often less harmful, phytoplankton species<sup>17,64</sup>.

According to Stokes' law, the flotation velocity of buoyant cyanobacteria increases with size<sup>65</sup>. Large colonies of buoyant cyanobacteria can migrate several metres through the water column within a few hours, whereas small single cells may migrate only a few centimetres<sup>66</sup>. Surface blooms of buoyant cyanobacteria therefore often consist of species forming large colonies or aggregates (for example, *Microcystis* spp., *Aphanizomenon* spp. and *Trichodesmium* spp.; FIG. 2c,f). These colonies can migrate up and down in the water column by dynamically adjusting their carbohydrate ballast, thereby counteracting the buoyancy provided by gas vesicles<sup>66–68</sup>. Diel vertical migration enables cyanobacteria to exploit light at the surface as well as nutrients in deeper waters<sup>69</sup>. Other cyanobacteria, such as the red *Planktothrix rubescens* (FIG. 2b), can adjust their buoyancy to form thin layers at specific depths in stratified lakes, which may float up during lake turnover in autumn to form spectacular red blooms at the water surface known as the Burgundy-blood phenomenon<sup>70</sup> (FIG. 1f).

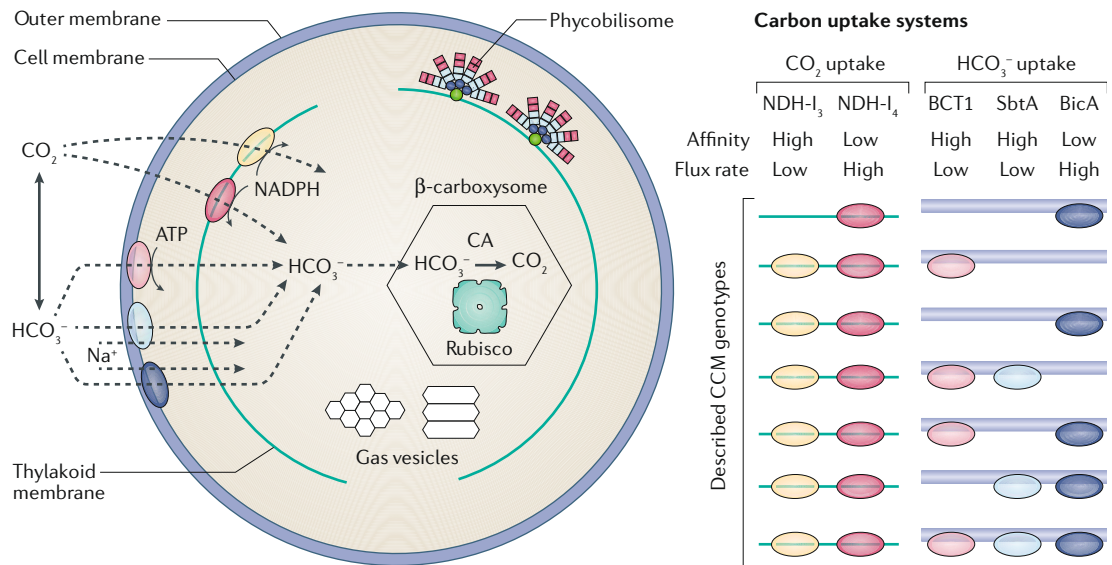
### Cyanotoxins

Bloom-forming cyanobacteria produce a diverse array of secondary metabolites, and several of these are toxic to plants, invertebrates and vertebrates, including humans, at naturally occurring concentrations<sup>6,13–15,71</sup>.

Why cyanobacteria produce these secondary metabolites is not yet resolved. Cyanotoxins might function as deterrents against grazing, and there is clear evidence of co-evolutionary adaptation between toxin-producing cyanobacteria and zooplankton<sup>72–74</sup>. It is intriguing, however, that one of the most abundant families of cyanotoxins, the microcystins, likely evolved before the origin of their metazoan predators, such as copepods and cladocerans<sup>75</sup>. Hence, in addition to their toxicity, microcystins may have completely different physiological or ecological functions in cyanobacteria. For example, binding of microcystins might protect the carbon-fixing enzyme Rubisco and other cyanobacterial proteins from oxidative stress<sup>76</sup>.

Toxin production by cyanobacterial blooms is highly variable in space and time<sup>77–79</sup> and cannot be easily predicted from species composition and cyanobacterial abundance. Although laboratory studies have shown that many environmental factors affect cellular cyanotoxin





**Fig. 3 | The CO<sub>2</sub>-concentrating mechanism of cyanobacteria.** The CO<sub>2</sub>-concentrating mechanism (CCM) of cyanobacteria consists of up to five inorganic carbon uptake systems: two for carbon dioxide (CO<sub>2</sub>) (NDH-I<sub>3</sub> and NDH-I<sub>4</sub>) and three for bicarbonate (HCO<sub>3</sub><sup>-</sup>) (BCT1, SbtA and BicA). These uptake systems accumulate intracellular inorganic carbon in the form of bicarbonate, which is transported to a microcompartment called the carboxysome. In the carboxysome, carbonic anhydrase (CA) converts bicarbonate to CO<sub>2</sub>, raising the local CO<sub>2</sub> concentration to levels at which the CO<sub>2</sub>-fixing enzyme Rubisco can operate efficiently<sup>56,57</sup>. The five carbon uptake systems differ in their kinetic properties. Different strains combine these uptake systems in different ways, causing variation among strains in their response to the availability of CO<sub>2</sub> and bicarbonate<sup>58,59</sup>. The right-hand side of the figure shows the genetic variation in carbon uptake systems that has been described thus far in  $\beta$ -cyanobacteria<sup>56–59</sup>. Na<sup>+</sup>, sodium.

contents in subtle ways<sup>80–82</sup>, variation within strains seldom exceeds a factor of 2–4 (REF.<sup>83</sup>). Cyanotoxin contents vary widely among different strains of the same species, however. Cyanobacterial blooms often consist of mixtures of toxic and non-toxic strains<sup>77,78,84</sup>, and changes in strain composition can therefore cause major alterations in the toxin content and toxin composition of cyanobacterial blooms<sup>77,78</sup>.

**Microcystins and nodularins.** Microcystins are cyclic heptapeptides with several unusual amino acids, including the characteristic tail-shaped amino acid 3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4(E),6(E)-dienoic acid (ADDA) (TABLE 1). Microcystins are potent inhibitors of protein phosphatases<sup>85,86</sup>, with a wide range of toxic effects. They can cause severe liver damage<sup>13,87,88</sup> but also affect other mammalian tissues, and they can have tumour-promoting, pulmonary, neurological and reproductive effects<sup>14,89</sup>. Microcystins have been implicated in the deaths of diverse birds, fish and mammals, including sheep, dogs, cattle and even sea otters<sup>14,71,90</sup>. Some human fatalities are also known<sup>13,88</sup>. The widespread ability to produce microcystins by many extant genera, including *Microcystis*, *Planktothrix*, *Oscillatoria* and *Dolichospermum*, is consistent with the early evolutionary origins of microcystin biosynthesis<sup>75</sup>. At least 246 microcystin variants that differ in amino acid composition and toxicity have been recorded<sup>71</sup>.

Nodularins are cyclic pentapeptides with structural similarities to microcystins (TABLE 1). Nodularins are produced by the brackish water species *Nodularia spumigena*, and ten structural variants are currently known<sup>71</sup>.

A large fraction of the microcystins and nodularins in cyanobacterial cells is bound to proteins<sup>76,91,92</sup>. Protein-bound microcystins are not detected by commonly used analytical approaches, and many studies may therefore have underestimated the actual microcystin contents of cyanobacterial blooms<sup>91</sup>. To what extent these findings affect the risk assessment of cyanobacteria is still unclear.

**Cylindrospermopsin.** Cylindrospermopsin is a guanidine alkaloid produced by *Cylindrospermopsis raciborskii* and several other cyanobacteria<sup>93</sup> (TABLE 1). It affects multiple organs and tissues in mammals and inhibits protein synthesis in animals and plants<sup>14,93</sup>. *C. raciborskii* was recognized as a harmful species after causing a waterborne, hepatitis-like illness among 10 adults and more than 100 children on Palm Island, Australia, in 1979 (REF.<sup>94</sup>). It was originally believed to be a tropical and subtropical species, but *C. raciborskii* has expanded its range to temperate latitudes in recent decades<sup>95,96</sup>.

**Anatoxins and saxitoxins.** Other alkaloid cyanotoxins include anatoxin-a, which shows rapid neurotoxicity in mammals and birds<sup>14</sup> (TABLE 1). Anatoxin-a(s) differs structurally from anatoxin-a and is a potent neurotoxin that also causes excessive salivation (TABLE 1). Saxitoxins are heterocyclic guanidines, with at least 57 structural variants<sup>97</sup> (TABLE 1). They are some of the most potent natural toxins known and are produced by several species of marine dinoflagellates and freshwater cyanobacteria<sup>93,97</sup>. Saxitoxins block the voltage-gated sodium channels of neurons, which prevents the transmission

#### Cladocerans

A group of small crustaceans of the order Cladocera with a carapace covering the thorax and abdomen, for example, water fleas.

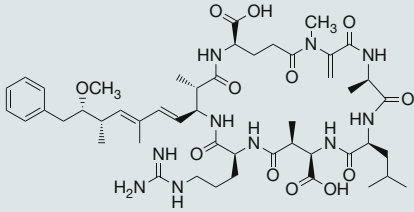
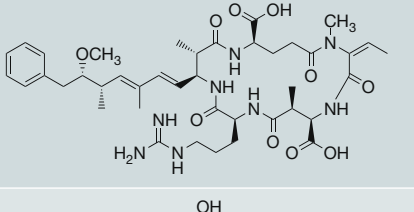
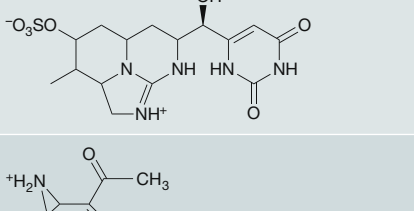
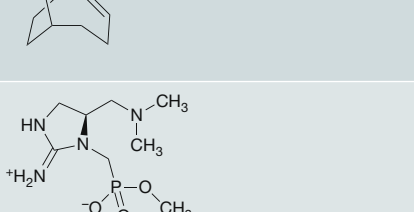
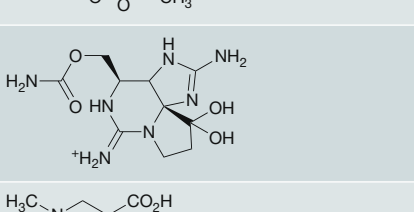
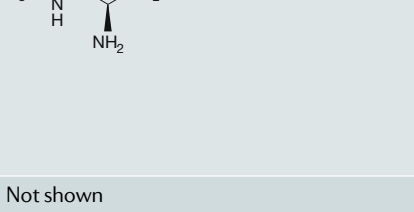
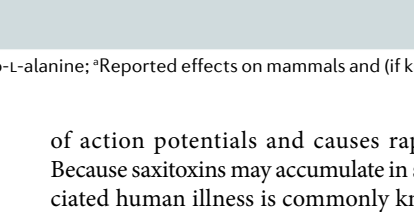
#### $\beta$ -Cyanobacteria

A common group of cyanobacteria with a specific type of carboxysome and Rubisco that differ from the carboxysome and Rubisco in other cyanobacteria.

#### Dinoflagellates

A highly diverse group of unicellular photosynthetic and non-photosynthetic organisms that move through water using one longitudinal and one transverse flagellum.

Table 1 | Examples of cyanotoxins

Toxin	Chemical structure	Main producing genera <sup>71</sup>	Modes of action	Toxic effects <sup>a</sup>
Microcystins		<i>Microcystis</i> , <i>Anabaena</i> , <i>Dolichospermum</i> , <i>Leptolyngbya</i> , <i>Nostoc</i> , <i>Phormidium</i> , <i>Planktothrix</i> and <i>Synechococcus</i>	Inhibition of eukaryotic protein phosphatases	Liver and kidney damage, gastroenteritis, tumour promotion, reduced DNA repair and reproductive toxicity
Nodularins		<i>Nodularia</i>	Inhibition of eukaryotic protein phosphatases	Same effects as microcystins plus weak carcinogenicity
Cylindrospermopsins		<i>Cylindrospermopsis</i> , <i>Anabaena</i> , <i>Aphanizomenon</i> , <i>Chrysochlorum</i> and <i>Raphidiopsis</i>	Inhibition of protein synthesis, DNA damage and cell death	Damage to multiple organs, gastroenteritis and genotoxicity
Anatoxin-a		<i>Anabaena</i> , <i>Aphanizomenon</i> , <i>Cuspidothrix</i> , <i>Dolichospermum</i> , <i>Oscillatoria</i> and <i>Phormidium</i>	Agonist of nicotinic acetylcholine receptors at neuromuscular junctions	Loss of coordination, muscle tremors and respiratory failure
Anatoxin-a(s)		<i>Dolichospermum</i>	Inhibitor of acetyl-cholinesterase	Salivation, incontinence, muscle tremors and respiratory failure
Saxitoxins		<i>Aphanizomenon</i> , <i>Cuspidothrix</i> , <i>Cylindrospermopsis</i> and <i>Dolichospermum</i>	Block voltage-gated sodium channels of neurons	Paraesthesia, numbness, paralysis and respiratory failure
BMAA		<i>Microcystis</i> and <i>Nostoc</i> ; possibly widespread among cyanobacteria <sup>187</sup> but no consensus yet <sup>188</sup>	Excessive stimulation of glutamate receptors in neurons and association with proteins	Loss of coordination, muscle atrophy and possible contributions to neurodegenerative diseases (for example, amyotrophic lateral sclerosis and Alzheimer disease)
Lipopolysaccharides	Not shown	All cyanobacteria	Inflammation and promotion of cytokine production	Skin irritation, fever and gastrointestinal upset

BMAA,  $\beta$ -N-methylamino-L-alanine; <sup>a</sup>Reported effects on mammals and (if known) humans.

of action potentials and causes rapid paralysis<sup>14,97</sup>. Because saxitoxins may accumulate in shellfish, the associated human illness is commonly known as paralytic shellfish poisoning<sup>97</sup>.

**BMAA.** Cyanobacterial non-encoded amino acids, including  $\beta$ -N-methylamino-L-alanine (BMAA; TABLE 1), are of interest owing to their neurotoxicity<sup>71,98</sup> and postulated association with human neurodegenerative diseases, such as amyotrophic lateral sclerosis

and Alzheimer disease<sup>99,100</sup>. Whether the association is causative is under investigation.

**Lipopolysaccharides.** Lipopolysaccharides (LPS) are structural components of the outer membrane of Gram-negative bacteria, including cyanobacteria<sup>14,101</sup> (TABLE 1). Contact with cyanobacterial LPS (for example, during swimming) may cause human skin irritation, blisters and gastrointestinal upsets. Other skin irritant and inflammatory cyanotoxins include lyngbyatoxins,

aplysiatoxins and jamaicamides<sup>14,102</sup>, which are produced by marine cyanobacteria.

### Community dynamics

Cyanobacterial blooms often cause a cascade of changes in benthic and planktonic microbial communities. Heterotrophic bacteria benefit from associations with cyanobacteria that produce oxygen, organic carbon and fixed nitrogen<sup>103,104</sup>. Some of the associated bacteria are attached to cyanobacterial cells<sup>105,106</sup>, whereas others grow on extracellular mucus or develop free-living populations<sup>104</sup>. Together, they inhabit the 'cyanosphere' (REF.<sup>107</sup>), the region in immediate vicinity of cyanobacterial colonies and filaments that is enriched in molecules exuded by the cyanobacteria. Metagenomic studies have revealed that changes in cyanobacterial species composition are accompanied by marked shifts in the cyanosphere community<sup>108</sup>. Furthermore, major changes in taxonomic composition and gene expression of the cyanosphere community may occur during different phases of bloom development<sup>109</sup>. In particular, heterotrophic bacteria involved in the biodegradation of complex organic molecules tend to become dominant during lysis of cyanobacterial blooms<sup>109,110</sup>. In Lake Taihu, for example, Alphaproteobacteria of the family Sphingomonadaceae, which can degrade microcystins, dominated the cyanosphere during decomposition of the *Microcystis* bloom<sup>111</sup>.

Cyanobacterial blooms also host several microbial pathogens of cyanobacteria<sup>112,113</sup>. In particular, cyanophages<sup>114,115</sup> and parasitic fungi<sup>112,116</sup> can cause high cyanobacterial mortality. Cyanobacteria are not defenceless, however. For example, *Microcystis aeruginosa* has an exceptionally large number of antiviral defence genes in its genome<sup>117</sup> and highly diversified CRISPR–Cas systems<sup>118</sup>. *Planktothrix* spp. produce oligopeptides that reduce the virulence of parasitic fungi and thus increase survival<sup>119</sup>. Many cyanobacterial pathogens have a narrow host range and can be highly strain-specific<sup>112,113</sup>. As a consequence, infections by cyanophages and parasitic fungi can lead to dynamic shifts between sensitive and resistant cyanobacterial genotypes<sup>115,116,120</sup>, thus contributing to the maintenance of a high genetic diversity in cyanobacterial blooms.

Many studies have shown that zooplankton have a limited ability to graze on colonial and filamentous cyanobacteria, which fosters the proliferation of cyanobacterial blooms and limits the transfer of primary production to higher trophic levels in the food web<sup>31,121</sup>. Large colonies and filaments of cyanobacteria can be difficult to ingest and interfere with the filter-feeding activity of cladocerans, including the water flea *Daphnia*<sup>121,122</sup>. Furthermore, cyanobacteria tend to be of low food quality compared with eukaryotic phytoplankton species because they contain only low amounts of polyunsaturated fatty acids<sup>123</sup> and sterols<sup>124</sup>. Finally, some cyanobacterial secondary metabolites can be toxic to zooplankton<sup>125,126</sup>. Several zooplankton species have evolved adaptations to circumvent these obstacles, however. Some zooplankters feed effectively on cyanobacterial filaments in a spaghetti-slurping manner<sup>127</sup>; others are well adapted to the low nutritional quality of cyanobacteria<sup>127,128</sup> or have developed tolerance against

cyanotoxins<sup>72–74</sup>. Field experiments have demonstrated that *Daphnia* strains isolated from lakes with a history of blooms can suppress toxic cyanobacterial populations<sup>129</sup>. Thus, there is increasing evidence for a co-evolutionary arms race between bloom-forming cyanobacteria and their grazers, which may or may not enable cyanobacteria to escape control from grazing<sup>72,73</sup>.

### Environmental drivers

**Eutrophication.** Human activity, in particular intensified agriculture, has dramatically increased the inputs of nitrogen and phosphorus into aquatic ecosystems. The resulting eutrophication of rivers, lakes and estuaries promotes algal and cyanobacterial blooms, a global environmental problem that has been recognized since the 1960s<sup>130,131</sup>. Since then, measures to reduce nutrient inputs have been implemented to improve water quality and control harmful blooms<sup>131–133</sup>. These efforts have generally been far more effective in reducing phosphorus than nitrogen inputs<sup>134</sup>, and the global use of nitrogen fertilizer has gradually outpaced the use of phosphorus fertilizer in recent decades<sup>135</sup>. Consequently, the nitrogen to phosphorus ratio is currently rising in many lakes, rivers and coastal waters<sup>132,134,135</sup>. Increased nitrogen loading and higher nitrogen to phosphorus ratios may change the species composition of cyanobacterial blooms. In particular, they can increase the amount of non-nitrogen-fixing cyanobacteria, such as *Microcystis* spp. and *Planktothrix* spp., at the expense of nitrogen-fixing cyanobacteria<sup>136,137</sup>. Moreover, increased nitrogen loading may favour production of the nitrogen-rich cyanotoxin microcystin<sup>82</sup>, as witnessed in Lake Erie<sup>138</sup>.

**Rising CO<sub>2</sub> concentrations.** The concentration of dissolved CO<sub>2</sub> in water is seldom in equilibrium with the partial pressure of CO<sub>2</sub> in the atmosphere. In particular, the photosynthetic activity of dense blooms can deplete dissolved CO<sub>2</sub> (REFS<sup>25,55</sup>). In response, cyanobacteria have evolved sophisticated CCMs, including several CO<sub>2</sub> and bicarbonate uptake systems<sup>56–58</sup> (FIG. 3).

Cyanobacteria are therefore often thought to be superior competitors at low dissolved CO<sub>2</sub> concentrations and high pH, whereas eukaryotic phytoplankton, such as green algae, may benefit more from high dissolved CO<sub>2</sub> concentrations<sup>139,140</sup>. However, recent studies have shattered this long-standing paradigm<sup>58,59,141</sup>. Cyanobacteria combine different inorganic carbon uptake systems in various ways (FIG. 3), which causes considerable variation in CO<sub>2</sub> responses within and among taxa<sup>58,142</sup>. For instance, selection experiments and a lake study have shown that *Microcystis* strains with high-affinity bicarbonate uptake systems tend to be favoured at low concentrations of dissolved CO<sub>2</sub> (REFS<sup>58,59</sup>). Conversely, *Microcystis* strains with high-flux bicarbonate uptake systems are well adapted to high concentrations of dissolved inorganic carbon and become strong competitors at high CO<sub>2</sub> concentrations compared with other *Microcystis* strains<sup>59</sup> and eukaryotic phytoplankton<sup>141</sup>. In summary, this recent work indicates that the genetic diversity and physiological flexibility of cyanobacterial CCMs enable rapid adaptation of bloom-forming cyanobacteria to rising CO<sub>2</sub> concentrations.

Rising concentrations of atmospheric  $\text{CO}_2$  will result in steeper  $\text{CO}_2$  gradients across the air–water interface of  $\text{CO}_2$ -depleted waters, which will enhance the  $\text{CO}_2$  influx into the surface layer that can be intercepted by surface-dwelling blooms<sup>27,55</sup>. Mathematical models and laboratory experiments therefore predict that rising atmospheric  $\text{CO}_2$  concentrations are likely to intensify cyanobacterial blooms in eutrophic and hypertrophic waters<sup>25,141</sup>.

**Global warming.** High temperatures stimulate cyanobacterial blooms in several ways<sup>16–23</sup> (FIG. 4). Many (but not all) bloom-forming cyanobacteria reach their maximal growth rates at relatively high temperatures, often above 25°C (REFS<sup>8,143</sup>) (FIG. 4a). Furthermore, the growth rates of cyanobacteria seem to increase faster with temperature than those of eukaryotic phytoplankton<sup>27</sup>. Warming of the water surface also leads to a more stable

stratification of the water column, with less vertical mixing<sup>17–20</sup>. Stratified waters provide ideal conditions for buoyant cyanobacteria to float upwards, where they have better access to light and shade non-buoyant phytoplankton<sup>63,64</sup>. With global warming, lakes at temperate and high latitudes will have shorter ice covers during winter, an earlier onset of stratification in spring, warmer summers and prolonged stratification into the autumn. These factors all contribute to a longer duration and range expansion of cyanobacterial blooms<sup>16–24,27–31</sup> (FIG. 4b).

Nutrient availability and lake morphology can modify this temperature response<sup>21–24,29,144–146</sup>. In shallow eutrophic lakes, nutrients and temperature often have synergistic effects on cyanobacterial growth<sup>22,145</sup>. This implies that, in a future warmer climate, nutrient loads may need to be reduced even more to suppress cyanobacterial blooms<sup>22</sup>. In deep mesotrophic and oligotrophic lakes, however, a stronger thermal

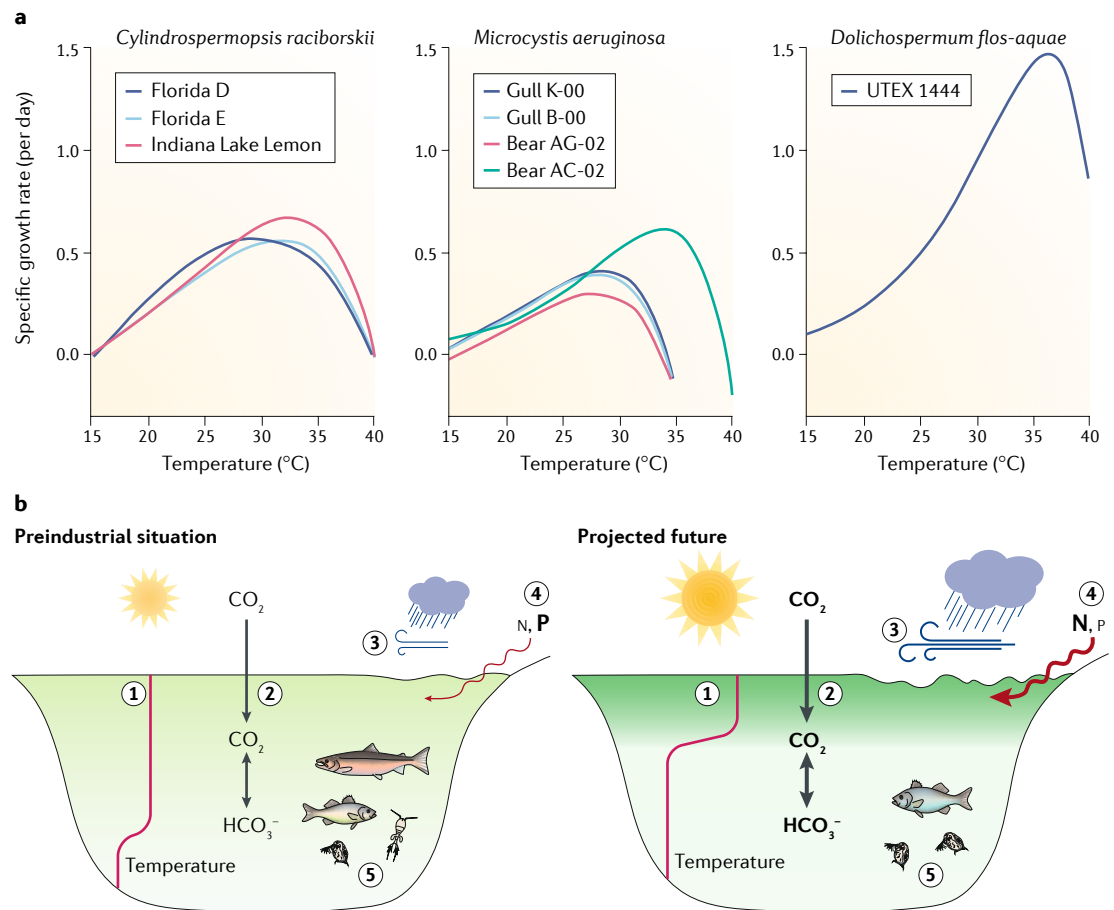


Fig. 4 | **Climate change will affect cyanobacterial blooms in multiple ways.** **a** | High temperatures stimulate the growth of many bloom-forming cyanobacteria, although the exact temperature dependence varies among species and even among different strains within the same species. **b** | Climate change is predicted to affect several environmental factors that influence bloom formation. (1) High temperatures favour a more stable temperature stratification compared with the preindustrial situation, which suppresses vertical mixing and thereby enables buoyant cyanobacteria to float upwards and form dense surface blooms more easily. (2) Rising atmospheric carbon dioxide ( $\text{CO}_2$ ) concentrations will increase the  $\text{CO}_2$  influx in  $\text{CO}_2$ -depleted surface waters covered by dense cyanobacterial blooms, which will intensify bloom development. (3,4) Climate change will increase weather variability, which may result in more intense storms and rainfall events, bringing in more nutrients, and protracted droughts with long water residence times. (5) Climate change may cause major changes in food web structure, which may or may not benefit cyanobacterial blooms.  $\text{HCO}_3^-$ , bicarbonate; N, nitrogen; P, phosphorus. Part **a** adapted from REF.<sup>143</sup>, Macmillan Publishers Limited.



### Thermocline

A thin layer in lakes and seas in which temperature decreases rapidly with depth, separating the warmer surface mixed layer from the colder deep water below.

### Diatoms

A highly diverse group of microscopically small photosynthetic algae of the class Bacillariophyceae that are enclosed by a cell wall of silica.

stratification tends to diminish the influx of nutrients from below into the surface layer, thereby suppressing rather than enhancing the development of cyanobacterial blooms<sup>146</sup>.

Effects of nutrients and temperature on cyanobacterial growth also vary among species. For example, statistical analysis of cyanobacterial abundances in more than 1,000 lakes revealed that some taxa were more responsive to increasing nutrients, whereas others were more responsive to increasing temperature<sup>145</sup>. Some species may even benefit from re-oligotrophication in combination with warming, as illustrated by the increasing dominance of *Planktothrix rubescens* in Lake Zürich<sup>137</sup>. The total phosphorus concentration in this lake decreased fivefold since the 1970s, which was accompanied by a decline in eukaryotic phytoplankton in the surface mixed layer. Concomitantly, warming has led to stronger thermal stratification of the lake, which favours pronounced blooms of *P. rubescens* near the thermocline during the summer period<sup>137</sup>.

Another anticipated symptom of climate change is that storm events, including tropical cyclones and summer thunderstorms, will become more extreme with higher amounts of rainfall, while droughts also intensify and may last longer<sup>147</sup>. In the short term, severe storms and rain can temporarily disrupt cyanobacterial blooms owing to destratification and flushing<sup>148</sup>. However, intense rainfall enhances nutrient run-off, which can lead to profound nutrient enrichment of downstream waters. If such rain events are followed by periods of protracted drought during the summer period and the residence time of nutrient-rich waters increases, conditions that favour cyanobacterial blooms will greatly increase<sup>18,24,149</sup> (FIG. 4b).

### Bloom prevention and control

Several strategies have been developed to prevent or suppress cyanobacterial blooms, including reduction of nutrient loads, hydrodynamic changes and chemical and biological control (FIG. 5). Each of these strategies has been successful in at least some lakes, but success is not guaranteed.

**Nutrient management.** Reduction of external nutrient inputs addresses the root of the problem. Nutrients enter lakes and coastal waters through a wide range of diffuse and point sources. Reducing nutrient inputs therefore requires measures that target the whole watershed, and, at times, national or international efforts. Examples include the ban on phosphates in detergents in the 1970s and 1980s and strict regulations on the use of nitrogen and phosphorus fertilizers. However, it may take years and sometimes decades before measures to reduce external nutrient inputs become successful<sup>132,133</sup> owing to an often long legacy of excessive nutrient inputs, which supports internal nutrient recycling (particularly of phosphorus) from lake sediments<sup>150</sup>. Recovery may be further delayed if the earlier eutrophication period has shifted the lake ecosystem to an alternative stable state that is resistant to change<sup>9,151</sup>. In several lakes, addition of phosphorus-binding clays<sup>152,153</sup>, sediment removal by dredging<sup>152</sup> or capping of lake sediments<sup>154</sup> has been

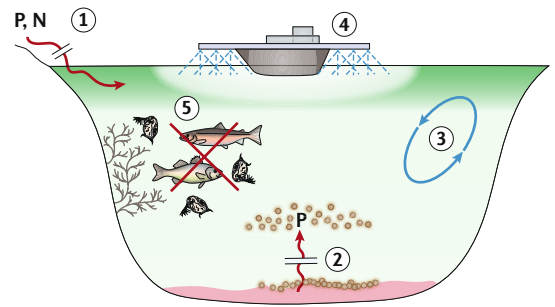


Fig. 5 | **Strategies for the prevention and control of cyanobacterial blooms.** (1) Nutrient management tackles the root of the problem through the reduction of external nutrient inputs. (2) Addition of phosphate-binding clays and capping of sediments remove nutrients from the water column and store them in the sediment. (3) Artificial mixing of lakes suppresses buoyant cyanobacteria. (4) Chemical control can be used in emergencies. (5) Manipulation of aquatic food webs by removal of planktivorous fish increases zooplankton populations that graze on cyanobacteria. N, nitrogen; P, phosphorus.

applied to suppress internal phosphorus loading and to accelerate lake recovery. Phosphorus-binding clays are less effective, however, in the presence of humic substances or competing oxyanions<sup>153</sup>. Furthermore, sediments of shallow lakes may be easily resuspended by wind and benthivorous fish, reintroducing nutrients into the water column. Therefore, each of these geoengineering approaches must be accompanied by the reduction of external nutrient inputs for successful long-term mitigation of blooms<sup>155</sup>.

**Hydrodynamics.** Artificial mixing of lakes can be a relatively costly but very effective method to prevent blooms of buoyant cyanobacteria<sup>156,157</sup>. If the rate of vertical mixing exceeds their flotation velocity, cyanobacteria no longer benefit from the buoyancy provided by their gas vesicles and tend to be displaced by diatoms and green algae<sup>64,157</sup>. Because the development of cyanobacterial blooms takes time, shortening the residence time by increasing water flow may also offer a promising mitigation approach for stagnant rivers and reservoirs<sup>158,159</sup>.

**Chemical control.** Chemical treatments can rapidly eradicate cyanobacterial blooms but seldom offer long-term solutions. Copper sulfate, diuron and several other algicides are not recommended because of their environmental persistence and toxic effects on other aquatic organisms<sup>160</sup>. Moreover, chemical treatments lead to cell lysis and release of cyanotoxins, thereby exacerbating water quality problems<sup>94,161</sup>. Low concentrations of hydrogen peroxide are a highly effective method to selectively eliminate cyanobacterial blooms<sup>162,163</sup> because cyanobacteria are more sensitive to hydrogen peroxide than eukaryotic phytoplankton<sup>164</sup>. A key advantage of this method is that the added hydrogen peroxide degrades to water and oxygen within a few days<sup>162</sup> and therefore leaves no long-term chemical traces in the environment. After the peroxide is gone, however, cyanobacteria may invade and gradually develop new blooms.

#### Dreissenid mussels

Freshwater bivalve mussels of the genus *Dreissena* (for example, zebra and quagga mussels) indigenous to the Ponto-Caspian area and invasive species in Western Europe and North America.

#### Planktivorous fish

Fish feeding on plankton.

#### Benthivorous fish

Fish feeding on prey from the sediment.

#### Piscivorous fish

Fish feeding on fish.

#### Macrophytes

Emergent, submerged or floating aquatic plants.

**Biological control.** Although cyanobacteria have several natural enemies, biological control of cyanobacterial blooms is not straightforward. Suppression of bloom development by viruses, pathogenic bacteria or fungi is an attractive idea. However, many of these microbial antagonists are host-specific<sup>112,113</sup> and cannot prevent the invasion of resistant strains. Therefore, viral or fungal infections may cause sudden collapses of cyanobacterial biomass but only rarely achieve a long-lasting decline of cyanobacterial blooms<sup>113–115</sup>.

Molluscs, including the zebra mussel *Dreissena polymorpha*, filter large volumes of water and thereby remove phytoplankton and other suspended particles. Their effect on cyanobacterial blooms is still under debate. It has been shown that dreissenid mussels from European lakes can mitigate cyanobacterial blooms quite effectively<sup>165,166</sup> because they filter cyanobacteria across a broad size range regardless of their toxicity<sup>167</sup>. However, dreissenid mussels from the North American Great Lakes seem to filter only single cells and small colonies, which may favour large and buoyant colonial cyanobacteria<sup>168,169</sup>. Invasion by zebra mussels in the 1980s and 1990s largely coincided with the proliferation of *Microcystis* blooms in Lakes Erie and Huron<sup>168,170</sup>. It is conceivable that European and North American zebra mussels differ in their genetic traits and adaptation history, and differences in nutrient status of the lakes might also play a role<sup>171</sup>. These contrasting results warrant further investigation.

Alteration of the entire food web by removal of planktivorous fish and benthivorous fish and/or introduction of piscivorous fish has been applied in several shallow lakes<sup>172,173</sup> (FIG. 5). This form of biomanipulation aims to suppress fish-induced sediment resuspension and to increase the abundance of large zooplankton that keep the phytoplankton biomass under control. The resulting increase in water transparency allows the establishment

of submerged macrophytes that capture available nutrients, further suppress sediment resuspension and shift the lake into a clear-water state<sup>9</sup>. Initial results are often promising. In waters with high internal nutrient loads or continued external nutrient inputs, however, phytoplankton blooms tend to return after several years<sup>173,174</sup>. Hence, this drastic measure appears to be effective in the long term only if external nutrient loads are also reduced or if fish are removed repeatedly<sup>173–175</sup>.

#### Conclusions

Cyanobacteria have inhabited aquatic ecosystems throughout much of Earth's history. There is mounting evidence, however, that harmful cyanobacterial blooms have increased on a global scale during recent decades, and they are likely to expand further in coming decades owing to continued eutrophication, rising atmospheric CO<sub>2</sub> concentrations and global warming<sup>16–31</sup>. Several strategies have been developed to prevent or control cyanobacterial blooms. Some of these attempts have been successful, whereas others were less successful or had only temporary effects. The current problems caused by cyanobacterial blooms and their anticipated further expansion demand extensive efforts to monitor bloom formation, call for further research into the mechanisms that determine the species composition and toxin production of cyanobacterial blooms and highlight the need for appropriate mitigation strategies. At local and regional scales, prevention of cyanobacterial blooms will require more effective control of nutrient inputs into aquatic ecosystems. At the global scale, curbing the emissions of CO<sub>2</sub> and other greenhouse gases is the most logical step to avoid a climate in which cyanobacterial blooms will thrive.

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#### Author contributions

J.H. researched data for the article. J.H., G.A.C., H.W.P., J.M.H.V. and P.M.V. wrote the article. All authors contributed substantially to discussion of the content and reviewed and edited the manuscript before submission.

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