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Nodularia spumigena, toxická sinice tvořící vodní květ v Baltském moři
Nodularia spumigena, a toxic cyanobacterium forming blooms in the Baltic Sea

Bakalářská práce

Vedoucí práce/Školitel: doc. RNDr. Yvonne Němcová, Ph.D.

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Bachelor´s thesis

Supervisor: doc. RNDr. Yvonne Němcová, Ph.D.

Prague, 2025

Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce, ani její podstatná část, nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze dne 27.4.2025

Barbora Kociánová

Poděkování:

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Abstrakt

Baltské moře představuje jeden z největších brakických ekosystémů na světě, který je pouze omezeně spojen se Severním mořem přes dánské průlivy. Vyznačuje se silným sezónním kolísáním teploty a výrazným severojižním gradientem salinity. Baltské moře je silně eutrofizováno lidskou činností, což vede ke zvýšenému výskytu toxických sinic. Cílem bakalářské práce je představit hlavního producenta hepatotoxinu nodularinu, sinici *Nodularia spumigena*, její životní cyklus a vliv na ostatní organismy obývající Baltské moře. Práce se rovněž zaměří na časoprostorový cyklus vzniku a rozpadu květů v Baltském moři spolu se strategiemi přezimování *Nodularia spumigena*. V neposlední řadě by se práce měla dotknout modelování výskytu květů v souvislosti s probíhající změnou klimatu a klesající eutrofizací Baltského moře.

Klíčová slova: Baltské moře, eutrofizace, hepatotoxin, *Nodularia spumigena*, nodularin, potravní řetězec, sinice, vodní květ, životní cyklus

Abstract

The Baltic Sea represents one of the largest brackish ecosystems in the world, with only limited connection to the North Sea through the Danish straits. It is characterized by strong seasonal fluctuations in temperature and a pronounced north-south salinity gradient. The Baltic Sea is heavily eutrophicated by human activity, leading to an increased occurrence of toxic cyanobacterial blooms. The aim of the bachelor's thesis is to present the main producer of the hepatotoxin nodularin, the cyanobacterium *Nodularia spumigena*, its life cycle, and its impact on other organisms inhabiting the Baltic Sea. The thesis will also focus on the spatial-temporal cycle of the formation and degradation of blooms in the Baltic, along with the overwintering strategies of *Nodularia spumigena*. Finally, the thesis should touch upon the modelling of bloom occurrence in relation to ongoing climate change and the decreasing eutrophication of the Baltic Sea.

Key words: Baltic Sea, eutrophication, hepatotoxin, *Nodularia spumigena*, nodularin, food web, cyanobacteria, cyanobacterial bloom, life cycle

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1. Introduction

Cyanobacterial blooms in marine ecosystems have been a growing environmental concern, with *Nodularia spumigena* blooms in the Baltic Sea representing one of the most significant and well-documented occurrences. These blooms, fuelled by eutrophication, rising seawater temperatures and specific hydrographic conditions, have profound ecological and socio-economic implications. As a nitrogen-fixing cyanobacterium, *Nodularia spumigena* contributes to nutrient cycling in the Baltic Sea but also poses risks due to the production of nodularin, a hepatotoxin harmful to aquatic organisms, livestock and humans. The blooms' unpredictable nature, their link to climate-driven changes and their role in marine organisms' behaviour make them an important subject of study.

Understanding the formation, persistence and decline of *Nodularia spumigena* blooms is critical for managing their impact on the Baltic Sea ecosystem and mitigating their potentially harmful effects. Factors such as nutrient availability, water temperature, salinity, wind-driven transport, grazing and competition with other phytoplankton species influence bloom dynamics, yet many uncertainties remain regarding their year-to-year variability and long-term trends. Recent advances in remote sensing, predictive modelling and molecular approaches offer new opportunities to monitor and predict these events.

The aim of this thesis is to provide a comprehensive summary of *Nodularia spumigena* blooms in the Baltic Sea, exploring their environmental drivers, ecological consequences, and the latest developments in monitoring and modelling efforts. By gathering current knowledge, this review seeks to contribute to a deeper understanding of this phenomenon.

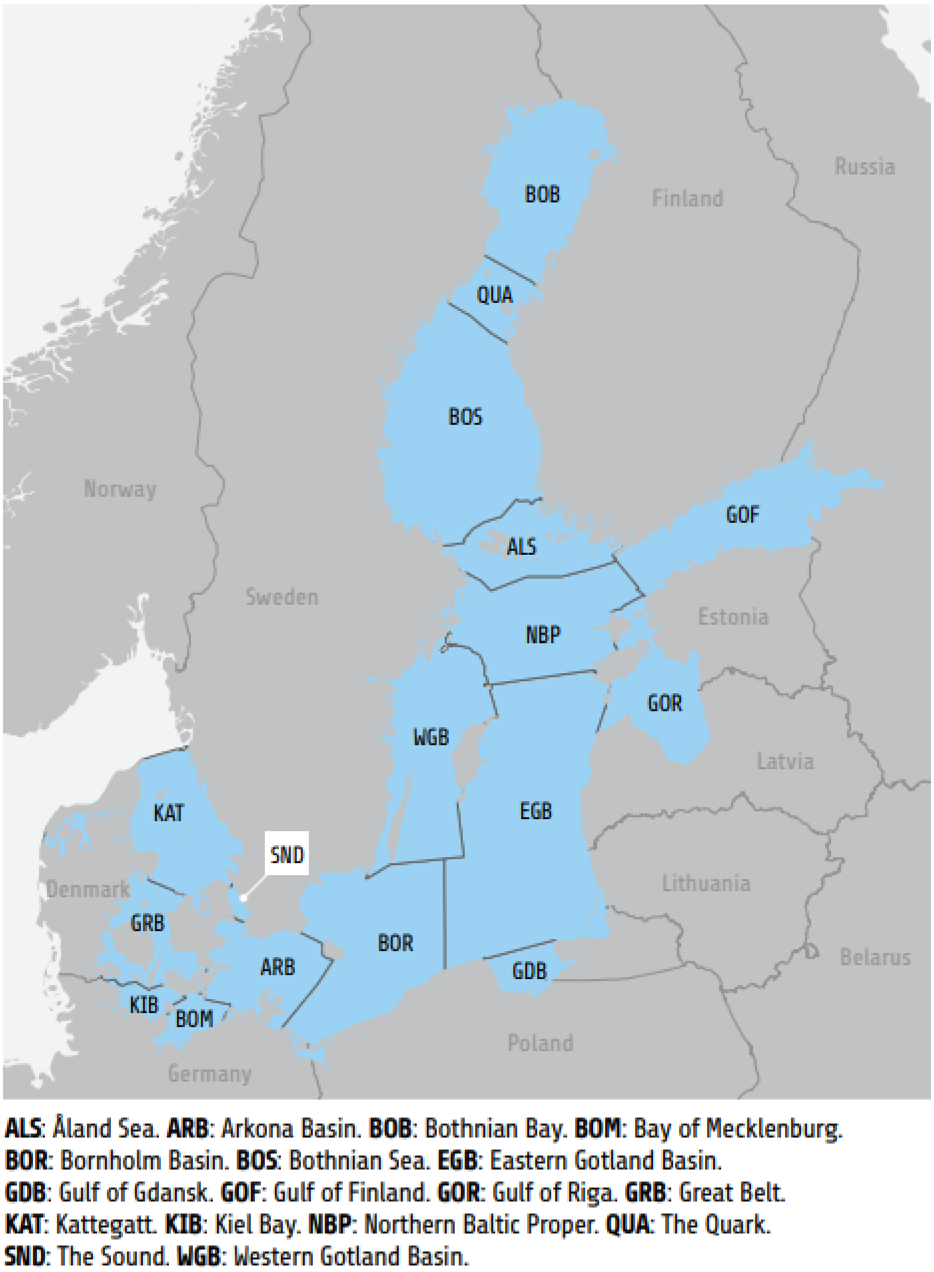
2. Baltic Sea

When the ocean water overflowed into what was then still a freshwater glacial lake approximately 9000 to 8500 years ago, an entirely new ecosystem was established. Today it bears the name Baltic Sea and although it is relatively shallow, with an average depth of only 60 m and a maximum depth of 460 m, it is one of the vastest brackish water ecosystems on Earth stretching over 415,000 km^2 wide (Rydin et al., 1999; Ducrotoy and Elliott, 2008; Cegłowska et al., 2018).

It is located in Northern Europe, with Sweden, Finland, Russia, Estonia, Latvia, Lithuania, Poland, Germany, Denmark, and Norway sharing its coastline. Most of the nutrients and freshwater find their way into the Baltic Sea through one of the seven major rivers: Daugava, Gota, Nemunas, Neva, Oder, Tornio and Vistula, which cover more than 50% of the Baltic Sea catchment area (HELCOM, 2018).

Ever since 2018, Baltic Sea is formally sectioned by HELCOM (Helsinki Commission) into 17 parts. These parts are (from north to south): Gulf of Riga, Gdansk Basin, Eastern Gotland Basin, Western Gotland Basin, Northern Baltic Proper, Bothnian Bay, Åland Sea, The Quark, Bay of

Mecklenburg, Bornholm Basin, The Bothnian Sea, Arkona Basin, Gulf of Finland, Kiel Bay, The Sound, Great Belt and Kattegatt (HELCOM, 2020).



ALS: Åland Sea. **ARB**: Arkona Basin. **BOB**: Bothnian Bay. **BOM**: Bay of Mecklenburg.
BOR: Bornholm Basin. **BOS**: Bothnian Sea. **EGB**: Eastern Gotland Basin.
GDB: Gulf of Gdansk. **GOF**: Gulf of Finland. **GOR**: Gulf of Riga. **GRB**: Great Belt.
KAT: Kattegatt. **KIB**: Kiel Bay. **NBP**: Northern Baltic Proper. **QUA**: The Quark.
SND: The Sound. **WGB**: Western Gotland Basin.

***Figure 1**. Formal Baltic Sea sectors by (HELCOM, 2020), alphabetically ordered, altered*

The deepest parts of the Baltic Sea are united under the term Baltic proper, describing the area between the Danish straits and Åland Sea, thus including Arkona basin, Bornholm basin, Gotland basin, Northen Baltic proper and Åland Sea (Lehmann et al., 2022). Baltic Sea is semi-enclosed, with limited access to the ocean, and is microtidal (the difference between low and high tide water levels is less than 2 m). This contributes to its poor flushing regime, with water retention time reaching 30 years (Stigebrandt, 2001; Ritchie et al., 2005; Ducrotoy and Elliott, 2008)

As for its other distinctive features, one of the most ecologically impactful is the sharp saline gradient throughout the entire Baltic Sea, which is oriented in a south-north direction due to the many inflowing rivers in the north and an opening into the North Sea in the south. This gradient can be very dynamic, as it depends both on the amount of incoming freshwater through the rivers, which is mainly driven by precipitation, and inflow of highly saline ocean water through the Danish straits, mainly through Øresund (Stigebrandt, 2001; Ojaveer et al., 2010).

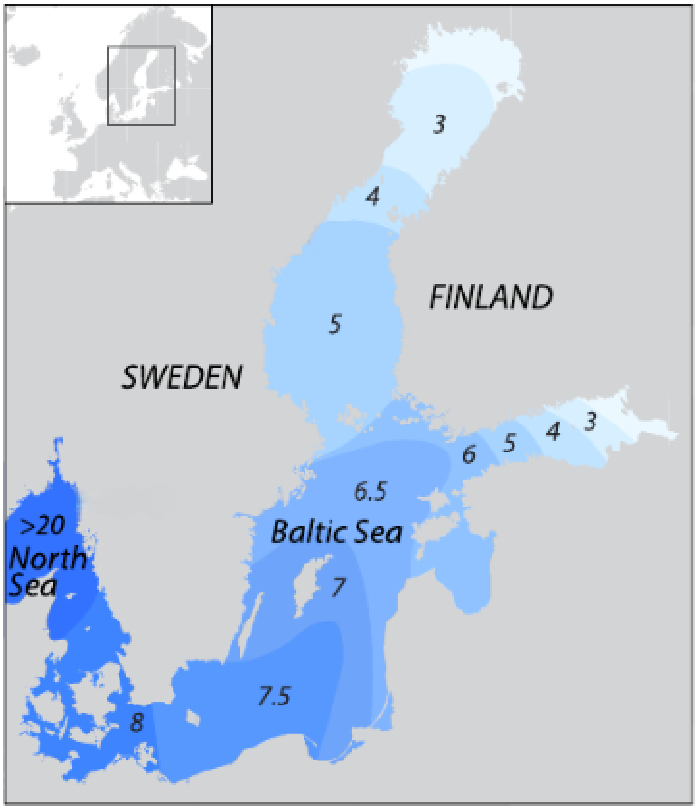


Figure 2. *Salinity gradient in the Baltic Sea in PSU (practical salinity unit), altered (Johansson et al., 2017)*

Enough water usually flows though the Danish straits to ventilate the water present at the surface, but this constant inflow lacks the strength necessary to flush out the deeper parts of the Baltic Sea. Influx of water powerful enough to execute this comes periodically and is not present year-round (Kõuts and Omstedt, 1993; Schinke and Matthäus, 1998). These periodical influxes, known as Major Baltic inflows (MBI), have sharply decreased in both frequency and magnitude since the 1970s, going from five to seven MBI per ten years to only one per ten years. A period from 1982 to 1993 was characterised by a complete absence of powerful inflows, as the amount of freshwater brought in by the rivers was exceptionally high, acting as a counterforce, preventing ocean water to flow into the Baltic Sea (Schinke and Matthäus, 1998; Döös et al., 2004; Carstensen et al., 2014; Mohrholz et al., 2015)

The MBI are needed for maintaining the brackish environment and ecosystem rejuvenation, as without them, the Baltic Sea experiences dramatic stagnation (Carstensen et al., 2014; Telesh et al., 2023). Its deeper areas (>60 m) are particularly impacted as the water in these regions has no way to replace otherwise. This results in a gradual decrease in water-dissolved oxygen, which was usually periodically raised by this event, and results in a deterioration of living conditions, decreasing salinity and hydrogen sulphide buildup (Schinke & Matthäus, 1998).

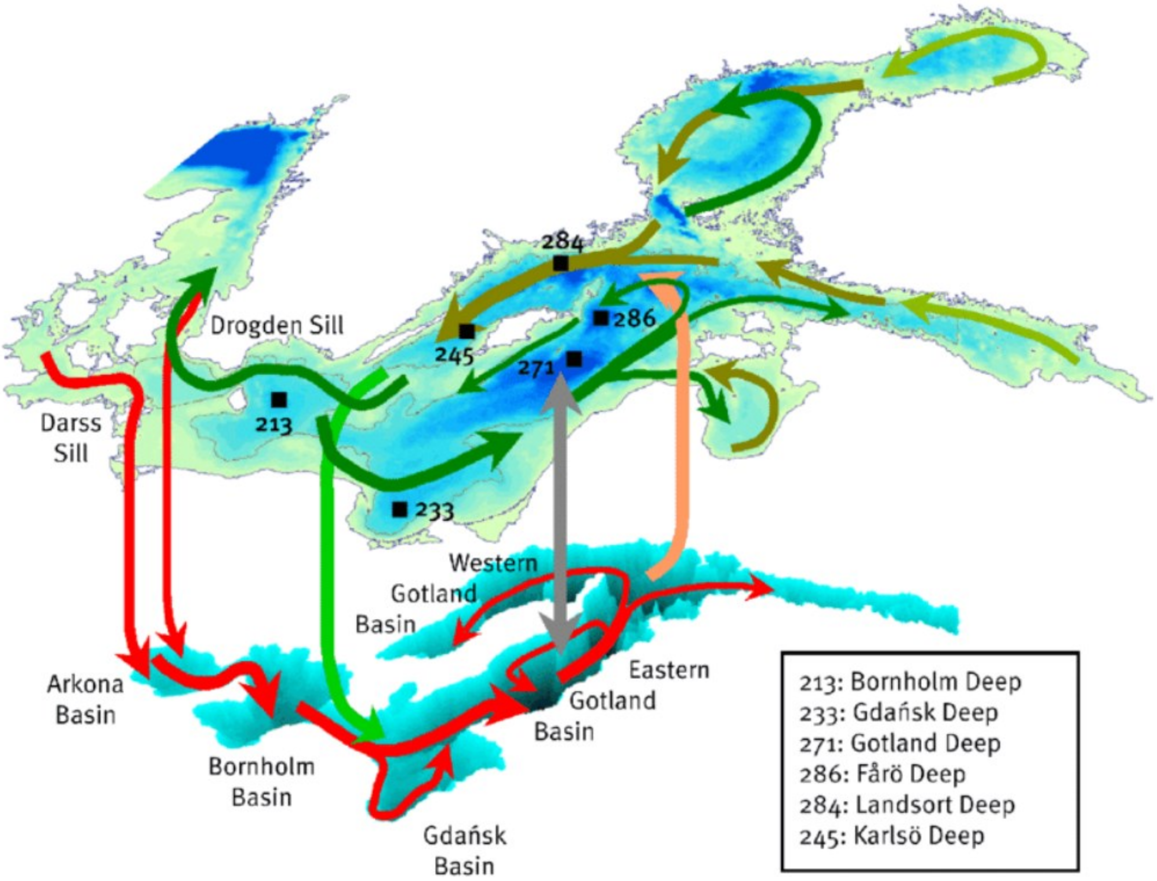


Figure 3. *Map of Baltic Sea topography, red arrows showing the progress of MBI ventilating the deeper areas (Feistel et al., 2016)*

Besides the shallow northern gulfs, vertical saline stratification can also be observed. At a depth of 70–100 m, there is a permanent halocline, forever dividing two bodies of water with salinity of 10‰ for the deeper water mass and 6‰ for the mass above (Granéli et al. 1990; Ojaveer et al., 2010). During high precipitation, water in the Baltic Sea becomes less saline, which means that a halocline forms at greater depth (especially in deeper areas such as the Gotland Basin) and thus breaking stratification. Resulting water mixing might bring nutrients trapped in the sediment back into the water column possibly increasing eutrophication (Carstensen et al., 2014; Telesh et al., 2023).

In summer, the halocline is accompanied by a seasonal thermocline. Because of this combination, the mixing of water in the water column is severely impaired and can result in hypoxic or anoxic regions especially in deeper parts of the Baltic seabed. The water temperature presents in wide amplitude, ranging from the sea completely freezing over with a thick ice cover in the north, sometimes lasting until May, to southern coastal waters reaching temperatures of over 25°C in warm summers (Stal et al., 2003; Lass and Matthäus, 2008; Ojaveer et al., 2010).

As the communication of the Baltic Sea with the world's ocean is restricted, it is even more vulnerable to anthropogenic factors such as overfishing, pollution and eutrophication, further amplified by its position, locked between technologically developed countries with more than 84 million people inhabiting its coast (Hannerz and Destouni, 2006; Munkes et al., 2021). In the early 2000s, the anthropogenic impact was so severe, that the Baltic Sea was proven to be the most degraded by pollution among similarly landlocked seas such as the Black Sea, the Wadden Sea or the Adriatic Sea (Lotze et al., 2006). Even though efforts have been made to improve this dire situation, eutrophication, pollution and overfishing remain the greatest threats to the Baltic Sea ecosystem (Boesch et al., 2006; Magnusson and Norén, 2012; Munkes et al., 2021).

3. Cyanobacterial water blooms in the Baltic Sea

Due to the decreasing severity and frequency of MBI (Major Baltic inflow) and rising temperature of the Baltic Sea water mass due to global climate change, the amount of dissolved oxygen in the Baltic Sea water is steadily decreasing. This coupled with increasing eutrophication of the Baltic Sea is leading to increasingly finer growing conditions for water blooms.

Eutrophication can be mitigated through effective management strategies; however, the key question remains whether these efforts will be sufficient. With rising seawater temperatures, nitrogen-fixing cyanobacteria are predicted to become more prevalent, potentially undermining nutrient inflow control measures by independently producing bioavailable nitrogen. Nevertheless, some researchers argue that cyanobacteria may not fully compensate for nitrogen deficits, as nitrogen fixation is inherently constrained. This limitation arises from several factors, including restricted light availability, which inhibits the energy-intensive process of nitrogen fixation, as well as the limited bioavailability of other essential elements such as phosphorus, iron, and molybdenum. Additionally, turbulent water movement can further hinder nitrogen fixation efficiency (Moisander et al., 2002; Paerl and Huisman, 2009; Molot et al., 2014; Munkes et al., 2021).

Cyanobacterial blooms can become gigantic, covering up to 200,000 km^2 (out of a total of 415,000 km^2) of the Baltic Sea's water surface each year. If cyanobacteria that form the bloom are equipped with gas vesicles, the bloom can form a continuous layer on the water surface, which promotes water stratification by weakening the mainly wind-driven mixing (Kahru and Elmgren, 2014; Telesh et al., 2023) Its sheer mass than decreases water clarity and this can become fatal to benthic macrophytes and organisms relying on them for survival. Communities inhabiting shoals and estuaries seem to be the most affected (Short and Wyllie-Echeverria, 1996; Munkes et al., 2021).

One of the many threats posed by cyanobacterial blooms is their ability to convert abundant N_2 in the atmosphere into its bioavailable forms, thus further increasing the amount of nutrients in an already eutrophic habitat. This gives cyanobacteria an advantage over other autotrophic organisms, especially in oligotrophic environments, and as a result their water blooms can reach enormous proportions extremely quickly (Zehr, 2011). Although these blooms are a seasonal event (usually lasting until autumn), as most cyanobacteria are thermophilic.

When the mass of the bloom collapses and sinks to the depths, more oxygen is needed to metabolise the released organic compounds, resulting in partial or complete depletion of oxygen and thus creating hypoxic or anoxic regions on the seafloor (Österblom et al., 2007; Turner et al., 2008). This has been proven to have detrimental effects on many organisms, including fish, although more sinister outcome of these areas can be the release of phosphorus from the so-called "phosphorus trap" established in the seabed (Conley et al., 2002; Funkey et al., 2014). As phosphorus is also often the limiting nutrient for cyanobacteria, if this newly released one is brought to existing cyanobacteria populations, it can further fuel their growth, consequently creating positive feedback loop (Degerholm et al., 2006; Unger et al., 2013).

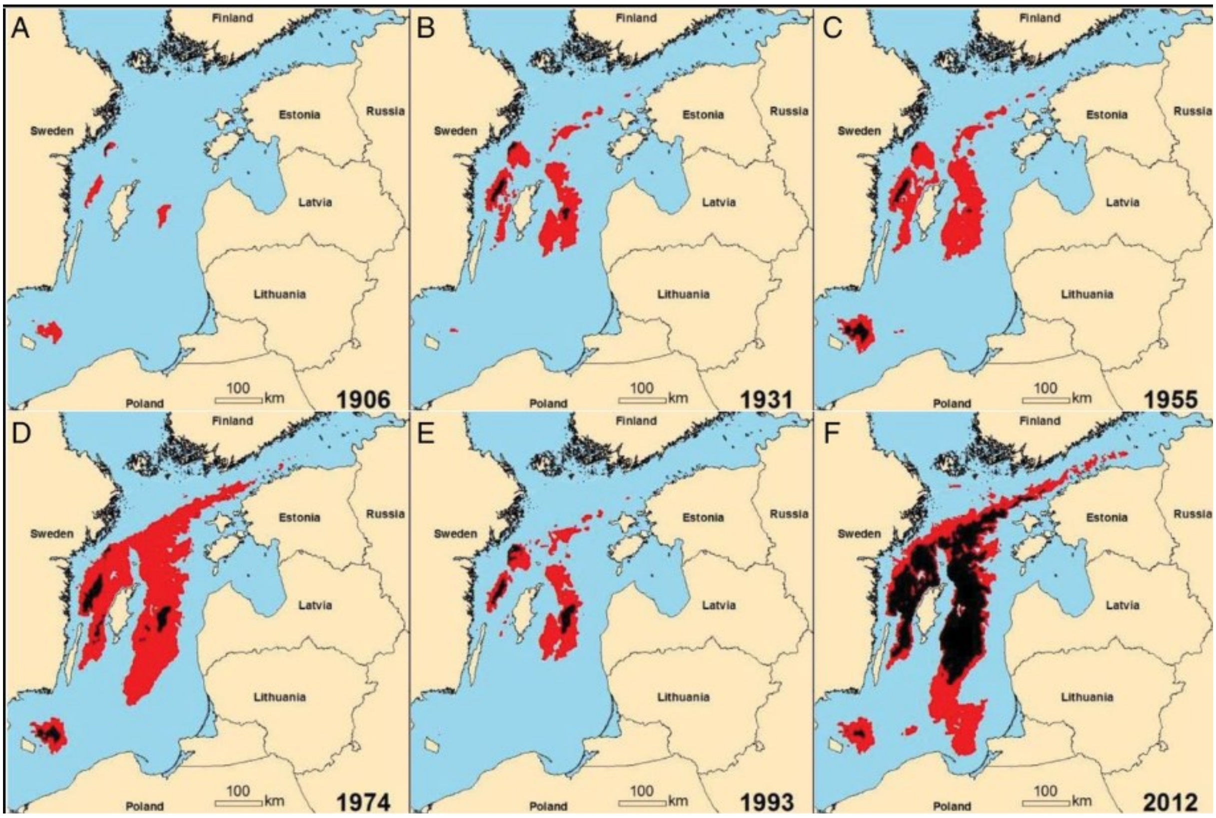


Figure 4. *Spatial distributions of bottom hypoxia and anoxia over time. Estimated bottom oxygen concentrations <2 mg/L are shown in red, and concentrations <0 mg/L are shown in black. The spatial distributions represent means across all months (January to December) (Carstensen et al., 2014)*

Cyanobacterial water blooms are not a recent phenomenon, as sediment research shows, but due to increasing eutrophication their abundancy is rising, as does their impact on the habitats. Before World War II practically no blooms were observed on the open sea, since the 1960s annual open-sea blooms have become common. Therefore, this subject is becoming more relevant for scientific research (Cegłowska et al., 2018).

The bloom itself is often formed by two distinct cyanobacterial groups: picocyanobacteria such as *Synechococcus* spp. which are not toxic, cannot fix N_2 and do not have aerotops. The second group consists of filamentous, N_2-fixing and often toxic cyanobacteria, which have increased buoyancy due to the presence of aerotopes (Stal et al., 2003).

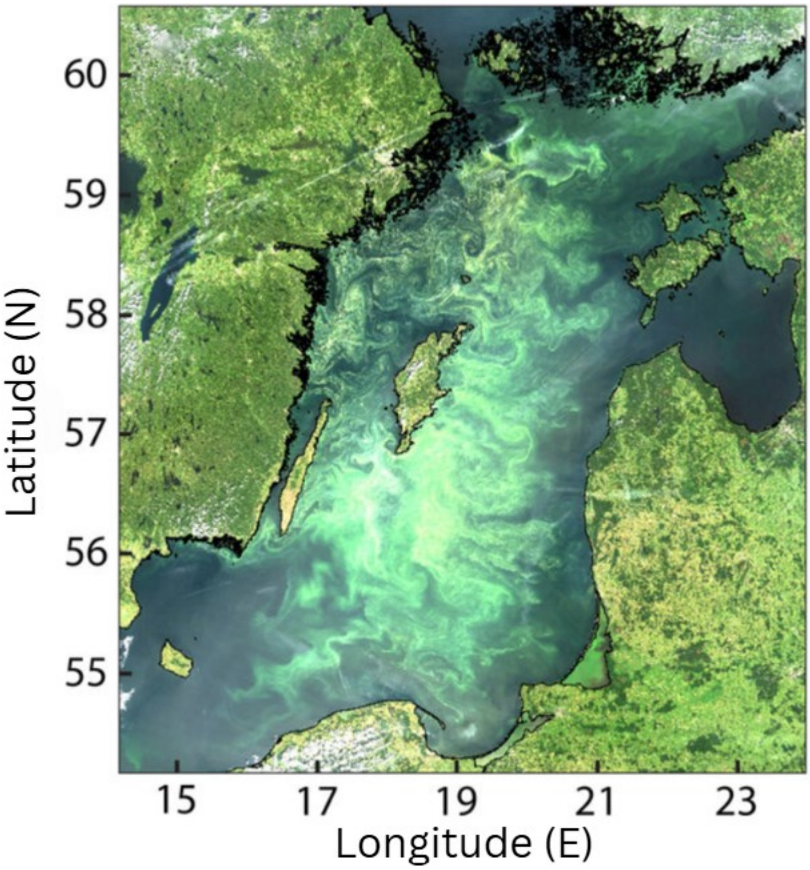


***Figure** 5. Cyanobacteria waterbloom (mainly Nodularia spumigena) around Gotland Island on 11 July 2005, altered (Kahru and Elmgren, 2014)*

The predominant filamentous, bloom-forming cyanobacteria of the latter group seem to be *Dolichospermum* spp., *Aphanizomenon flos-aquae* and *Nodularia spumigena*, the latter being the most toxic (Stal et al., 2003; Suikkanen et al., 2010).

All three taxa produce germinating akinetes that develop in late summer and remain near the seabed. However, their overwintering strategies appear to differ. *Dolichospermum* spp. has been confirmed as truly meroplanktonic, meaning it alternates between planktonic growth in the water column and a resting stage in the sediment (Hori et al., 2003; Suikkanen et al., 2010). In contrast, *Aphanizomenon flos-aquae* primarily follows a holoplanktonic life strategy, spending its entire lifecycle in the water column. However, when akinetes are formed, they can sink and germinate in the sediment (Wildman et al., 1975; Yamamoto, 2009; Suikkanen et al., 2010). *Nodularia spumigena* appears to employ both strategies to an extent sufficient to sustain the next generation. Notably, while blooms of *Nodularia spumigena* consistently begin in the northern Baltic Sea, the mechanisms by which germinating stages accumulate there remain unclear, given that akinete formation predominantly occurs in the southern Baltic Sea (Suikkanen et al., 2010).

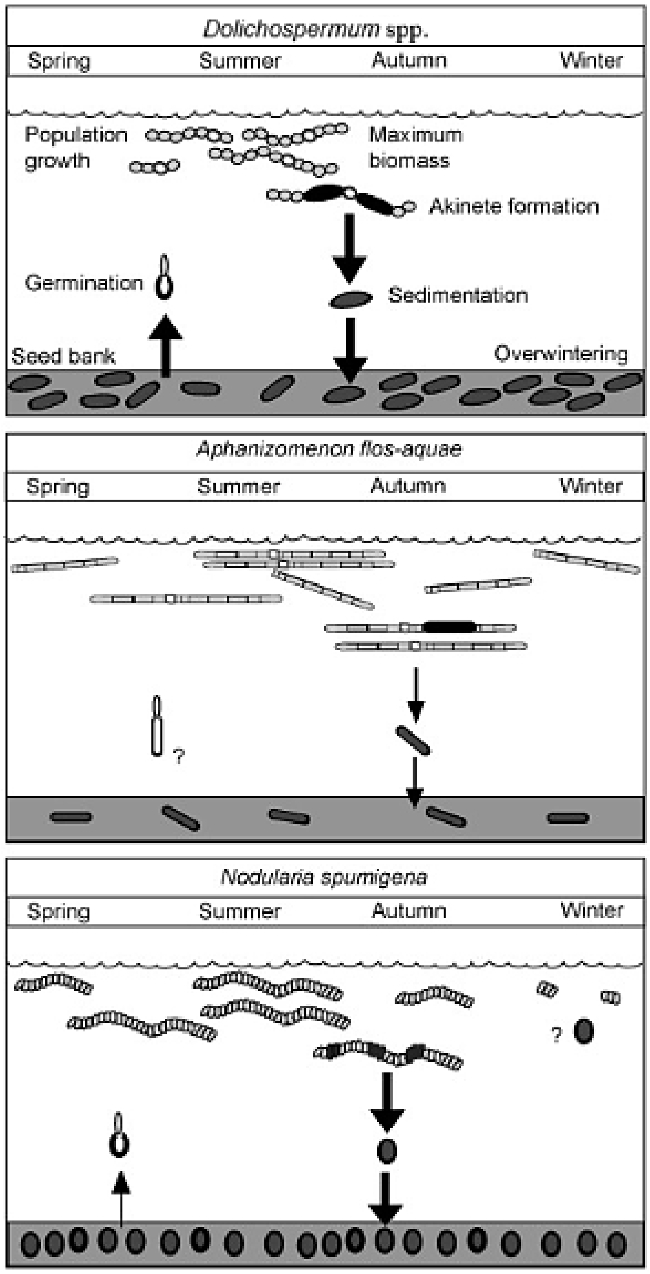


Figure 6. *Difference in overwintering strategies employed by Dolichospermum spp., Aphanizomenon flos-aquae and Nodularia spumigena (Suikkanen et al., 2010)*

Nodularia spumigena also requires specific conditions for its akinetes to geminate, such as very low concentration of phosphorus (<0.9 μM), low ammonia, relatively low salinity (>20‰) and more than 24 hours of constant red-light exposure followed by practically complete darkness (0.5 microeinstein m^{-2} s^{-1}). Without these factors the germination will not be initiated. Akinetes prefer temperatures over 22 °C to germinate, thus it can be expected for the initiation of germination to take place in the height of summer (Huber, 1985).

4. *Nodularia spumigena*

The genus *Nodularia* belongs to the class *Cyanophyceae*, order *Nostocales* and consists of both benthic and planktonic species, *Nodularia spumigena* is planktonic (da Silveira et al., 2017). It is filamentous, equipped with heterocysts for N_2-fixing and hormogonia for increased motility.

Cell size varies across individuals; however, the mean size of vegetative cells is 4.0 µm in length and 7.6 µm in width, of heterocysts 4.6 µm in length and 9.2 µm in width and akinetes 7.6 µm in length and 11.5 µm in width (da Silveira et al., 2017).

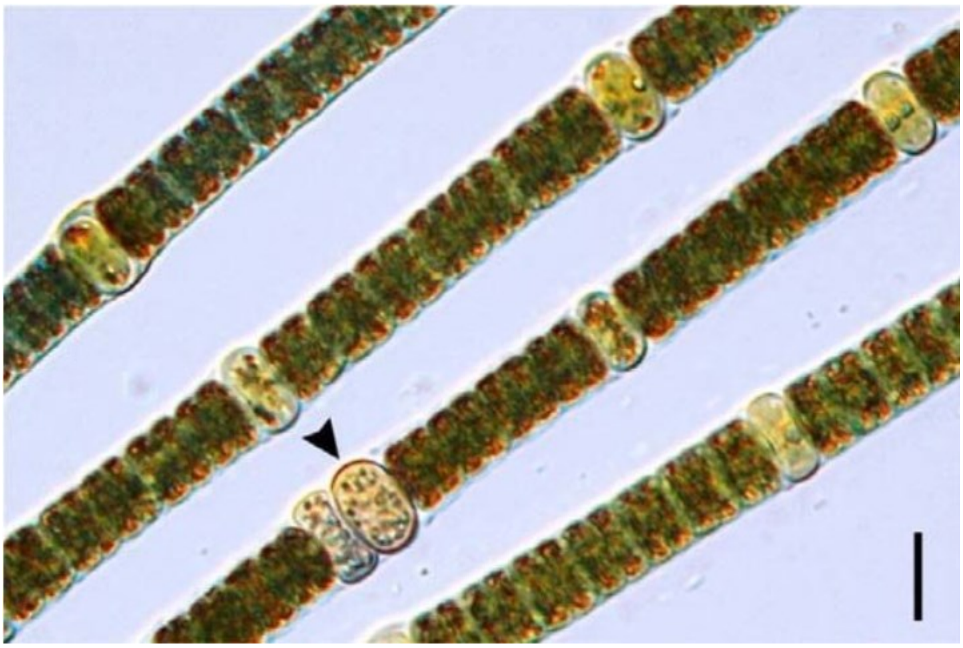


***Figure** 7. Nodularia spumigena, the arrow is pointing to an akinete, scale bar 10 µm, altered (McGregor et al., 2012)*

As in other *Nostocales* cyanobacteria, heterocyst differentiation in *Nodularia* is triggered by nitrogen deprivation. The process is regulated by NtcA, an autoregulatory transcription factor that acts as both an activator and repressor of heterocyst formation. NtcA binds to multiple genes involved in nitrogen assimilation and is essential for proper heterocyst development and function (Herrero et al., 2004).

A disruption in the carbon-to-nitrogen balance induces nitrogen stress, activating key signalling molecules such as 2-oxoglutarate (2-OG), Ca^{2+}, and cyclic-di-GMP. Among these, 2-OG plays a central role by binding to NtcA and initiating the differentiation cascade (Muro-Pastor and Hess, 2012). During the early stages of heterocyst development, HetR serves as a key regulator of differentiation. However, its role is limited to heterocyst formation, as it is not required for cellular growth in nitrate-rich environments (Black et al., 1993).

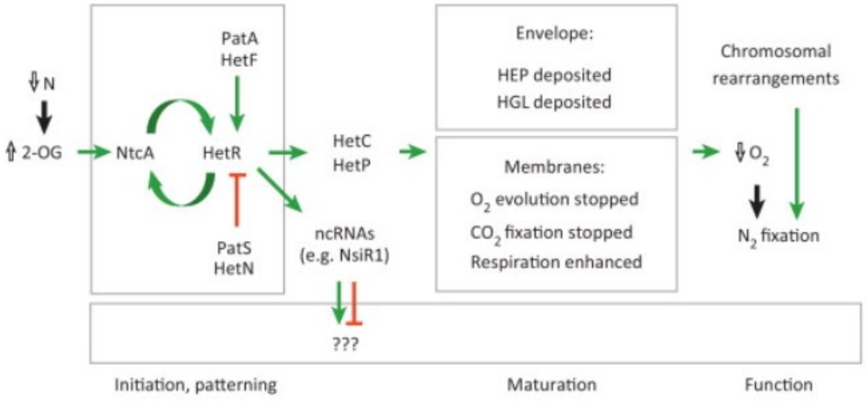


Figure 8*. Summary of heterocyst differentiation from vegetative cells in Anabaena and its regulation by NtcA and Het proteins (Muro-Pastor and Hess, 2012)*

Heterocysts are not the only specialized structures that differentiate from vegetative cells; hormogonia are another. Much like heterocyst development, this process is thought to be deeply conserved across the entire *Nostocales* order. The trigger of hormogonia development in *Nodularia spumigena* can be various factors, such as light quality or desiccation. Differentiation begins with synchronous, reductive cell division, producing shorter, rod-shaped cells with tapered filament termini. Notably, heterocysts are absent in hormogonia, resulting in short, motile filaments capable of gliding along surfaces. The upregulation of aerotopes enhances buoyancy, facilitating dispersal. Hormogonia exhibit a transiently senescent state, characterized by reduced biosynthetic activity and a complete cessation of cell growth and division. Additionally, their motility plays a crucial role in the formation of supracellular structures, such as colonial aggregates (Marsac, 1994; Risser, 2023). *Nodularia* forms loose colonies that are usually millimetres long, but they can cluster into groups measuring up to 10cm. These aggregates are remarkably fragile though, falling apart into separate colonies even with the slightest disruption (Stal et al., 2003).

Nodularia spumigena generally prefers brackish waters, growing the best at salinities around 7-8 PSU (practical salinity unit) (Laamanen et al., 2001; Möke et al., 2013). As most of the order *Nostocales* is freshwater-growing, *Nodularia* had to develop specific adaptations to survive in such conditions. To balance the osmotic potential *Nodularia spumigena* accumulates sucrose in its cells. In case of growing at particularly high salinities sucrose solution is accompanied by elevated levels of glutamate and potassium ions to further balance the osmotic pull of the seawater (Möke et al., 2013).

Nodularia is commonly found in estuaries and shallow brackish waters, predominantly occupying the uppermost water layer. This distribution is influenced by its production of mycosporine-like amino acids (MAAs), whose biosynthesis is upregulated in response to increased light intensity and elevated UVB radiation. MAAs function as efficient UVB absorbers, shielding *Nodularia* from photodamage, so the cells can fully utilize the solar energy (Sinha et al., 2003).

A study by Teikari et al. (2018) suggests that *Nodularia* may possess another unique metabolic advantage over other cyanobacterial species. It appears capable of utilizing methylphosphonic acid (MPn) as its sole phosphorus source when inorganic phosphate is unavailable. The degradation of MPn releases methane as a byproduct, positioning *Nodularia* alongside *Trichodesmium*, *Synechococcus*, and *Anabaena cylindrica* as a methane-producing cyanobacterium. This ability contributes to methane saturation in surrounding waters, potentially influencing biogeochemical cycles and climate dynamics. The independency from inorganic phosphorus might partially lift its role as a limiting factor for *Nodularia* survival, allowing it to thrive even in unfavourable conditions (Teikari et al., 2018).

It is a cosmopolitan species. Smaller populations were registered in the Mediterranean, Canada, USA and South Africa. However, these populations are not significant enough to form massive blooms annually. Besides the Baltic Sea, these bloom-forming populations seem to be present in Australia (including Tasmania) and New Zealand (Sivonen et al., 1989; Jones et al., 1994; McGregor et al., 2012)

Out of the entire genus *Nodularia*, *Nodularia spumigena* is the only species considered toxic (da Silveira et al., 2017). It is equipped with plethora of toxins, namely nodularins, anabaenopeptins, spumigins, aeruginosins and pseudoaeruginosins (Rinehart et al., 1988; Fewer et al., 2013; Liu et al., 2015; Spoof et al., 2015). The toxin profile largely depends on the genetic variety of the species as around 25 sub-strains were identified to this day, each with slightly different physiology and morphology. It is proved that only nodularins, spumigins and anabaenopeptins, are possessed by all strains. Whether other toxins are present depends on the particular strain (Mazur-Marzec et al., 2016).

5. Nodularin

As blooms of *Nodularia spumigena* form and collapse every year, one of the most abundant organic substances present in the Baltic Sea becomes its toxin, nodularin (Sivonen et al., 1989). It comes in many forms, to this day, 10 have been discovered, of which nodularin-R is the most plentiful in natural habitats (Yu et al., 2004).

Nodularin is a cyclic pentapeptide that shares similarities in structure with microcystin, and is composed of d-glutamic acid (d-Glu), *N*-methyldehydrobutyrine (MeDhb), 3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid (Adda), d-*erythro*-*β*-methylaspartic acid (d-MeAsp), and l-arginine (l-Arg) (Pearson et al., 2010).

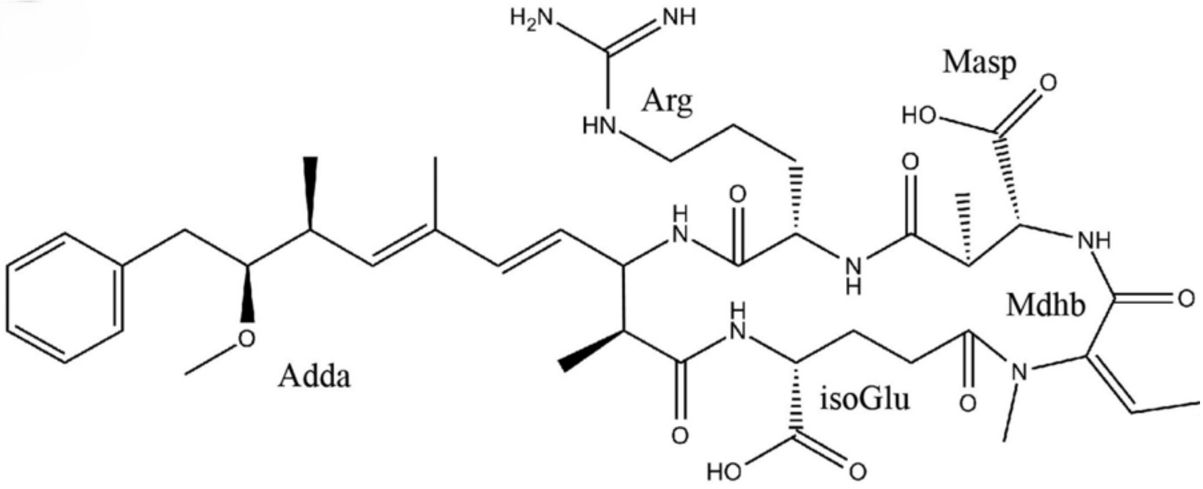


Figure 9*. Chemical structure of nodularin-R with major chemical structures highlighted: d-glutamic acid (isoGlu), 3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid (Adda), N-methyldehydrobutyrine (Mdhb), d-erythro-β-methylaspartic acid (Masp), and l-arginine (Arg), altered (Kelker et al., 2009)*

The biosynthesis of nodularin is controlled by a gene cluster called *nda*, which consists of nine genes (*ndaA-I*). *ndaA, B, F, G, H,* and *I* encode proteins involved in peptide synthesis, cyclization, and transport, while *ndaC, D, E,* and *F* are responsible for Adda synthesis (Moffitt and Neilan, 2004; Pearson et al., 2010).

Nodularin production is initiated and regulated by two enzyme complexes: non-ribosomal peptide synthetase (NRPS) and polyketide synthase (PKS), both encoded by *nda* genes. Specifically, *ndaA, B, C, D,* and *F* encode different modules that assemble into NRPS/PKS hybrid proteins. This biosynthetic pathway closely resembles that of microcystins, particularly in the assembly of the Adda chain (Moffitt & Neilan, 2004; Zhou et al., 2021).

For the NRPS and PKS enzymes to become active, they require post-translational modification by a phosphopantetheinyl transferase (PPT) enzyme. However, the genes encoding PPT are not part of the *nda* cluster. The initial product of the NRPS activity is a linear peptide, which undergoes further post-translational modifications to achieve cyclization, resulting in the final bioactive nodularin molecule (Chen et al., 2021; Moffitt & Neilan, 2004; Pearson et al., 2010).

Nodularin synthesis shares many similarities with the one of microcystin, as the gene cluster managing microcystin production *mcy* is believed to be homologous to *nda*. Unlike *mcy* however, *nda* is missing two NRPS modules thought to be a result of deletion during its insertion into the *Nodularia* genome (Moffitt and Neilan, 2004; Dittmann et al., 2013).

The end product, nodularin, is a potent hepatotoxin, inhibiting Ser/Thr protein phosphatases namely protein phosphatase-1 (PP1) and protein phosphatase-2A (PP2A) (Kelker et al., 2009). This interaction ends in accumulation of phosphorylated proteins and inhibition of all the functions of PP1 and PP2A, including cell cycle and cytoskeleton management, leading to cell death (Sheppeck et al., 1997). The necrosis leads to and intrahepatic bleeding, which in turn causes haemorrhagic shock and is usually the main cause of death. The bond with Ser/Thr protein phosphatases is not covalent, so nodularin can easily enter further into the hepatocytes, which might add to its carcinogenic properties in chronical poisoning, or sub-acute dosage (Bagu et al., 1997; Chen et al., 2013). However, to date, its full carcinogenetic potential has not been fully evaluated.

No fatal cases of acute nodularin poisoning in humans have been reported; however, fatalities in livestock and wild animals have occurred worldwide, mainly from poisoned water (Chen et al., 2013). In 1998 the World Health Organization (WHO) established 1 µg/l to be a maximum microcystin concentration in drinking water, but no such limit was set for nodularin despite its known tumor-promoting properties (World Health Organization, 2002; Žegura et al., 2004). This may be of concern as nodularin has been shown to accumulate in fish and seafood and enter the body though consumption (Falconer et al., 1992; van Buynder et al., 2001; Mazur-Marzec et al., 2007). For the full picture, a study on the prevalence of liver disease in populations known to consume nodularin-contaminated products or water would be valuable.

However, such assessments rely heavily on precise monitoring, as nodularin is typically detected in environmental water samples at extremely low concentrations, ranging from picograms to nanograms, necessitating the use of highly sensitive and efficient detection methods. Out of numerous methods, the most commonly used seem to be high performance liquid chromatography (HPLC), which may however be limited by the amount of nodularin in the sample (Sipiä et al., 2001; Spoof et al., 2001), immunosorbent assay (ELISA) (Sipiä et al., 2001) and liquid chromatography-mass spectrometry (LC-MS) (Neffling et al., 2009). Both biotic (organisms' tissue) and abiotic (sediments, water) samples can be analysed.

Due to its cyclic structure, nodularin is a highly stable and water-soluble compound which, like microcystins, causes problems with removing from drinking water at water treating facilities. It is resistant to heat, oxidation and chemical hydrolysis at neutral pH, light and microwaves. Only strong UV radiation causing partially degradation of the toxin (Chen et al., 2021; Merel et al., 2010; Twist, 1997). Therefore, the widely used purification processes such as flocculation, sand filtration and chlorination have so far mostly been ineffective in complete removal of toxins (Himberg et al., 1989). A promising, although expensive solution may be biological sand filtration, using a bacterial biofilm capable of cyclic peptide degradation (Ho et al., 2006). These filters mimic the natural process of nodularin removal, where bacterial and other microbial communities are responsible for toxin decomposition (Toruńska et al., 2008).

6. Negative effects of *Nodularia spumigena* on the Baltic Sea organisms

After the bloom dies, nodularin is released into the environment. The majority of *Nodularia spumigena* cells decompose in surface waters, while approximately 10% are transported to the seafloor (Kankaanpää et al., 2001). As a result, the highest accumulation of nodularin occurs near the water surface. During exceptionally favourable conditions for bloom development, nodularin concentrations can reach 20 mg/L (Toruńska et al., 2008).

Due to its stability, the natural degradation of nodularin is slow and limited. Various processes contribute to its breakdown, including dilution with uncontaminated water, adsorption to particles or sediments, and photolysis. However, microorganisms, particularly benthic bacteria, seem to play a key role in its degradation (Twist, 1997; Edwards et al., 2008). The rate of detoxification is influenced by bloom recurrence; areas without a bloom for several months exhibit slower detoxification compared to those recently affected by blooms (Heresztyn and Nicholson, 1997).

Studies indicate that the highest concentrations of nodularin are consistently detected in *Nodularia* filaments themselves, where levels can reach 4.01×10^6 ng/g dry weight. In August 2000, an even higher concentration of 6×10^6 ng/g dry weight was recorded in the Gulf of Finland (Laamanen et al., 2001; Mazur-Marzec et al., 2006).

Due to the significant uptake of nodularin by plankton, filter-feeding organisms are especially prone to bioaccumulation. In 2007, blue mussels collected from Gulf of Gdańsk were analysed for nodularin content, revealing concentrations of 139 ng/g dry weight in blue mussels with detectable concentrations even after the bloom collapse (Mazur-Marzec et al., 2007).

Nodularin remains dangerous even after the lysis of *Nodularia* cells, as it can still be ingested through drinking water or food consumption. This property facilitates its bioaccumulation in tissues and transfer through trophic levels. However, its uptake through gills is limited due to its polar nature (Malbrouck and Kestemont, 2006).

When fish are chronically exposed to nodularin and other contents of cyanobacterial cell, it can lead to disruption in homeostasis regulation (Svirčev et al., 2015). This results in osmotic imbalance and can lead to a massive oedema of secondary gill lamellae and separation of epithelium from the basement membrane. As the drinking response is stimulated, fluid build-up also occurs in the gut (Rodger et al., 1994). Some studies suggest that nodularin and microcystins could have an inhibitory effect on chloride ion pumps, thus causing the loss of osmotic regulation (Malbrouck and Kestemont, 2006).

Fish embryos are especially vulnerable to nodularin toxicity, even though the chorion seems to be partly resistant to nodularin transfer, mitigating its effects (Oberemm et al., 1999). Nodularin affects their development and leads to a plethora of defects such as higher mortality, abnormal heart rate, embryonic malformation, as well as defects in angiogenesis or cardinal vein remodelling. Nodularin can also cause a decreased rate of angiogenesis because it inhibits endothelial cell migration. Damage to DNA because of oxidative stress is also common (Wiegand et al., 1999; Chen et al., 2020).

Nodularin intoxication has proven to be a serious problem in shrimp farming, as 2.5 µg/L NOD can cause 50% mortality of the widely farmed pacific white shrimp (*Litopenaeus vannamei*) (Pacheco et al., 2016). The toxin severely damages hepatopancreas resulting in altered transcription pathways of immune genes tight to detoxification, prophenoloxidase and coagulation system, leading to decreased productivity and mass death (Duan et al., 2023).

In addition to nodularin toxicity, blooms of *Nodularia spumigena* pose significant ecological threats through multiple mechanisms. Due to the substantial biomass of these blooms, their metabolic demands for oxygen are high. During nighttime, when respiration predominates, the bloom can rapidly deplete dissolved oxygen in the surrounding water, creating hypoxic conditions that can lead to mass fish mortality through suffocation.

A similar anoxic effect occurs when the bloom undergoes rapid collapse, as microbial decomposition of the biomass requires substantial oxygen input. This process is often accompanied by elevated ammonia levels, worsening the stress on aquatic organisms (Rodger et al., 1994). Furthermore, fish entrapped within dense blooms may suffer from physical asphyxiation, as cyanobacterial filaments can obstruct gill function or clogging it completely, impeding respiratory efficiency (Toranzo et al., 1990).

Copepods exhibit a more diverse range of responses to algal blooms compared to fish. While some species experience reduced egg production, gonadal damage, and grazing avoidance (Kurmayer, 1999; Kozlowsky-Suzuki et al., 2009), others, such as *Acartia bifilosa* and *Eurytemora affinis*, appear unaffected by bloom presence. These species maintain normal reproductive rates and successfully graze on bloom-forming algae, potentially benefiting from the available resources (Koski et al., 2002). This variation in response suggests the presence of an effective detoxification mechanism that enables certain copepods to tolerate or even thrive in bloom conditions.

Metazoans are not the only organisms affected by nodularin. A study on the brown alga *Fucus vesiculosus* demonstrated that the entire thallus, including gametangia, absorbs nodularin. The uptake varies across different parts of the stele, ranging from 13.9 ± 1.1 µg/kg fresh weight in the blades to 45.1 ± 4.2 µg/kg fresh weight in the holdfast. Nodularin absorption also induces oxidative stress in the alga, as evidenced by an 11-fold increase in total antioxidant capacity after 48 hours of exposure, compared to the control (Pflugmacher et al., 2007).

A study investigating the allelopathic potential of nodularin on phytoplankton (cryptophyte *Rhodomonas salina*) found no evidence of inhibitory effects. Similarly, in a mixed culture experiment with six other plankton species, *Nodularia spumigena* did not exhibit allelopathic interactions. However, *Nodularia spumigena* successfully outcompeted five out of the six species, likely due to its ability to tolerate and thrive in highly alkaline conditions. These findings suggest that its competitive advantage is primarily driven by pH tolerance rather than the production of nodularin (Møgelhøj et al., 2006).

7. Enzymatic detoxification of nodularin

The main component of environmental biochemical degradation seems to be enzymes of *Mlr* gene cluster, which can be found in some bacteria (especially the *Sphingomonadaceae* family) (Yang et al., 2014; Yuan et al., 2021). MlrA starts the degradation by opening the ring structure of nodularin at the Adda-Arg bond, making it linear and easier to process further. Other enzymes, namely MlrB and MlrC then reduce it into smaller peptides. MlrD then removes these peptides and assists in next uptake of nodularin (Mutoti et al., 2022). This degradation pathway is shared by microcystins, providing similar results due to their structural similarity, although nodularin detoxification rate seems to be more influenced by environmental factors such as pH, temperature or initial toxin concentrations (Yuan et al., 2021).

To date, research suggests that bacteria may be the only organisms capable of fully metabolizing nodularin without any adverse effects. In contrast, while other organisms can detoxify nodularin, its presence induces physiological alterations. Moreover, nodularin uptake occurs rapidly, whereas its neutralization proceeds at a considerably slower rate, suggesting an inefficient detoxification process (Sipiä et al., 2002). Additionally, other bioactive compounds present in *Nodularia* spp., especially lipopolysaccharides, appear to further impede degradation by significantly reducing detoxicating enzymes' activity, potentially prolonging the toxin's bioavailability and exacerbating its harmful effects (Best et al., 2002).

A study on juvenile three-spined sticklebacks (*Gasterosteus aculeatus*) revealed intriguing findings. Fish fed by zooplankton that had previously consumed *Nodularia spumigena* exhibited an increased appetite, but experienced slower growth compared to the control group. This suggests a potential high metabolic cost associated with the detoxification of nodularin (Pääkkönen et al., 2008).

In vertebrates, nodularin enters cells via active transport through transmembrane multispecific organic anion-transporting polypeptides (OATPs), which are primarily expressed in the liver and, to a lesser extent, in the gastrointestinal tract and brain. Upon nodularin exposure, cells activate various detoxifying enzymes, leading to a significant increase in their activity (Faltermann et al., 2016; Chen et al., 2020).

All detoxifying enzymes are classified into three phases: Phase I, II, and III. Phase II enzymes, primarily transferases, play a crucial role in converting xenobiotics into more hydrophilic, readily excretable forms through conjugation reactions (Hayes et al., 2005; Jancova et al., 2010).

Additionally, they contribute to mitigating oxidative stress by regulating free radicals and minimizing cellular damage, including DNA damage, lipid peroxidation, and protein oxidation (Dasari, 2017).

Among these, glutathione-S-transferases (GSTs) are among the most ubiquitous and essential detoxification enzymes. GSTs catalyse the conjugation of nodularin with glutathione (GSH), a tripeptide involved in the detoxification of various xenobiotics (substances foreign to living systems). This reaction increases nodularin's water solubility, facilitating its excretion via bile or urine (Sherratt and Hayes, 2001; Persson et al., 2009). Moreover, GSTs are theoretically capable of conjugating nodularin via its reactive N-methyldehydroalanine (Mdha) residue, forming a detoxified complex (van der Oost et al., 2003). However, evidence suggests that this pathway is not predominantly utilized for nodularin detoxification, indicating that an alternative mechanism may be employed, particularly in higher organisms (Sipiä et al., 2002; Kankaanpää et al., 2007).

Another enzyme family involved in detoxification is cytochrome P450 (CYP), a group of heme-containing oxidases that play a role in sterol and vitamin metabolism, among other functions (Denisov et al., 2005). As phase I enzymes, cytochrome P450 oxidizes nodularin, converting it into a more hydrophilic compound, typically an alcohol, making it more accessible to conjugation reactions (Furge and Guengerich, 2006). However, the role of cytochrome P450 in nodularin detoxification is less well studied compared to glutathione-S-transferases (GSTs). It seems that CYP enzymes may be employed differently in different organs, unlike phase II enzymes (Biswas et al., 2024).

Additionally, other detoxification mechanisms, such as proteolysis, may also contribute to nodularin degradation; however, their overall impact is likely minimal.

Because of high levels of oxidative stress that nodularin causes, antioxidant enzymes, such as catalase (CAT) and superoxide dismutase (SOD), are also routinely engaged in response to nodularin exposure. However, these enzymes do not possess detoxifying properties, as they are only employed as a mean to control high levels of reactive oxygen in the cell (Harris, 1992).

8. Cycle of emergence and collapse of *Nodularia spumigena* blooms in the Baltic Sea

The formation of cyanobacterial blooms is mainly influenced by abiotic factors. Among the most critical are temperatures around 16°C, specific weather conditions characterized by wind speeds below 6 m/s, and high photosynthetically active radiation with total radiation exceeding 120 W/m^2. Additionally, a favourable nitrate-to-phosphorus ratio plays a crucial role, where the depletion of available nitrate coupled with readily accessible phosphorus creates optimal conditions for bloom development (Wasmund, 1997; Lips and Lips, 2008).

Over decades, deep-water anoxia near the seafloor and phosphorus availability have shown a strong correlation with cyanobacterial bloom abundance. On an interannual scale, the most significant factors influencing bloom intensity are the solar shortwave direct flux in July and surface water temperature during the same period. However, approximately half of the year-to-year variation remains unexplained (Kahru et al., 2020).

Proximity to the coastline may also influence bloom formation. Löptien & Dietze (2022) demonstrated that 90% of water parcels contributing to bloom formation remain more than 17 nautical miles offshore three weeks prior to bloom onset, after moving away from the coastline one month earlier. This pattern overlaps with upwelling zones in the Baltic Sea, typically found within 15 nautical miles of the coast, suggesting that upwelled water may inhibit bloom development. Several factors have been identified as inhibitors of bloom formation, including salinities exceeding 10 PSU, low irradiation, and strong winds (Wasmund, 1997; Rakko and Seppälä, 2014).

Recent research suggests that blooms are started by drifting vegetative fragments of *Nodularia* rather than akinetes, as previously thought. *Nodularia* rarely germinates from akinetes, and blooms instead recruit from drifting fragments located above the halocline rather than from akinetes resting in deeper waters (Wallström et al., 1992).

As bloom development begins, the initial dominant genus is *Aphanizomenon* spp., which grows slowly due to its high overwintering and spring biomass, reaching its peak in early summer. In contrast, *Nodularia spumigena* appears from very low spring concentrations, experiencing a lag phase, before rapidly outcompeting *Aphanizomenon* spp. by mid-summer. This succession is not only influenced by overwintering strategies but also by phosphorus availability. *Aphanizomenon* spp. thrives in high phosphorus concentrations during early spring, whereas *Nodularia spumigena* is a superior competitor in an environment with lower phosphorus concentration, such as those found in the seawater during summer (Wallström et al., 1992; Lehtimaki et al., 1997; Wasmund, 1997).

Nodularia spumigena blooms develop in nitrogen-deficient yet phosphorus-sufficiet environments, triggering nitrogen fixation. This process also supplies usable nitrogen to competing cyanobacteria and phytoplankton. Nitrogen fixation rates near *Nodularia spumigena* colonies are, on average, 18% higher than in bulk water, with NH_4^+ release rates approximately 60 times higher than in surrounding waters (LaRoche and Breitbarth, 2005; Ploug et al., 2011). The mechanisms that allow cyanobacteria to dominate despite competition remain unclear, but hypotheses include their ability to utilize organic phosphorus more efficiently, exploit low phosphorus concentrations, or experience lower grazing pressure compared to other phytoplankton (Eilola et al., 2009; Löptien and Dietze, 2020).

As the bloom expands, it is transported southward towards Øresund due to prevailing wind patterns and sea currents. Summer winds in the Baltic Sea are generally weaker than those in winter, but southward winds contribute to bloom movement. Additionally, the Baltic Sea's counterclockwise circulation pattern, which forms cyclonic gyres within both the main basin and sub-basins, promoting southward transport. Surface currents in the Baltic Sea are primarily wind-driven, leading to significant variability. Western winds generate stronger eastward currents, and long-term trends show increasing sea surface current intensity (Jędrasik et al., 2008; Barzandeh et al., 2024).

The collapse of the bloom occurs rapidly, often within days, triggered by a combination of physiological and environmental factors. Physiological cues for entering senescence or a vegetative resting include complete phosphorus depletion (Sigee et al., 2007). Physical factors such as decreasing temperatures, water column destratification, high turbidity, and increased wind velocities also contribute to bloom dispersal by mixing phytoplankton below the photic zone (Bormans, 2004). The rapid collapse of blooms results in substantial organic matter deposition on the seafloor, worsening anoxic conditions (Paerl, 1988).

Following akinete formation, *Nodularia* populations die off. However, evidence suggests that some individuals may enter a vegetative resting stage through fragmentation of the filament. These fragments likely function as drifters that initiate the next year's bloom cycle. The counterclockwise circulation of the Baltic Sea, combined with winter winds predominantly blowing from the west and southwest, facilitates the transport of these fragments back northward (Munkes et al., 2021; Pogumirskis et al., 2021).

As previously mentioned, in the brackish waters of the Baltic Sea, the majority of the bloom decomposes within the surface layers. However, upon reaching the Öresund Strait and progressing toward the Kattegat, *Nodularia spumigena* encounters the saline waters of the North Sea. In response to increasing salinity, the buoyancy of *Nodularia spumigena* cells decreases, with a pronounced effect observed at higher PSU levels. At the highest recorded salinity (32 PSU), the filaments exhibited a rapid sinking rate of up to 1.7 meters per day in undisturbed conditions. This suggests that a significant portion of *Nodularia spumigena* cells, along with the associated nodularin, ultimately settle on the seabed in these high-salinity waters, potentially leading to greater contamination of benthic food webs compared to brackish environments. Consequently, the ecological impact of the bloom extends beyond the boundaries of the Baltic Sea, influencing marine ecosystems even after its dispersal into more saline waters (Carlsson and Rita, 2019).

9. Modelling the occurrence of cyanobacterial blooms and future projections

The occurrence and extent of *Nodularia spumigena* blooms are primarily predicted using mechanistic models rather than statistical ones. These models, including the 3D Coupled Ecosystem Model of the Baltic Sea (CEMBS), Ecosystem Model (ECOSMO), Ecological Regional Ocean Model (ERGOM), Swedish Coastal and Ocean Biogeochemical Model (SCOBI), and Baltic Sea

Long-Term Large-Scale Eutrophication Model (BALTSEM), are constructed based on established physical, biological, and chemical processes present in the marine ecosystem.

All the listed models categorize phytoplankton into three functional groups. Cyanobacteria and diatoms are consistently included across all models, while the classification of the third group varies. ECOSMO, ERGOM, and SCOBI define it as flagellates, BALTSEM refers to it as summer species, and CEMBS classifies it as small phytoplankton.

By incorporating mathematical equations that describe key interactions - such as nutrient cycling, phytoplankton and zooplankton dynamics, light availability, and temperature fluctuations - these models aim to simulate the system's real-life behaviour with a high degree of accuracy. Specifically, a mechanistic model for *Nodularia spumigena* blooms would account for crucial factors such as nitrogen fixation, phosphorus availability, temperature-dependent growth rates, and water column stratification, all of which play a pivotal role in bloom formation and persistence (Eilola et al., 2011; Munkes et al., 2021).

Each equation within these models consists of both source and sink terms, which, in the case of cyanobacteria, primarily include nutrient uptake, grazing pressure, and viral-induced mortality. In addition to these fundamental parameters, some models incorporate additional constraints, such as threshold-based "switches." For instance, in SCOBI and ECOSMO, blooms are prevented from occurring when salinity exceeds 10 PSU and 11.5 PSU, respectively. Similarly, SCOBI employs an oxygen threshold above which the cyanobacterial growth gradually accelerates.

Achieving perfect precision in modelling bloom occurrence remains practically impossible due to the complexity of the system and the multitude of interacting variables. Variations in nutrient availability, grazing pressure, and cyanobacterial mortality rates introduce significant uncertainties that limit the accuracy of these models. Furthermore, data availability poses another major challenge; even large-scale observations are difficult to obtain, and acquiring comprehensive, high-resolution datasets for all relevant parameters - such as light irradiance, grazing dynamics, and viral concentrations - is nearly impossible. These limitations ultimately constrain the predictive capabilities of current models (Baker et al., 2018; Yates et al., 2018; Munkes et al., 2021).

Despite variations in model structure and assumptions, there is a strong consensus among most models that light availability, temperature, and phosphate concentration are the primary factors controlling the occurrence and intensity of *Nodularia spumigena* blooms. Model simulations consistently indicate that higher temperatures accelerate bloom development, reinforcing the well-documented relationship between warming trends and cyanobacterial proliferation. Additionally, these models concur that cyanobacteria possess a significant competitive advantage in nitrogen-depleted but phosphate-rich environments, outcompeting other phytoplankton species under such conditions (Munkes et al., 2021).

Due to the inherent uncertainties and complexities associated with mechanistic models, satellite observations have become the primary tool for analysing bloom dynamics. While satellite data also contain certain inaccuracies - particularly as bloom scum thickens, reducing measurement precision - their accessibility and broad spatial coverage make them the most widely utilized approach. However, satellite observations are predominantly used for assessing interannual and long-term bloom dynamics, rather than tracking short-term, intra-seasonal movements. These observations are particularly valuable for identifying year-to-year trends in maximum bloom coverage and estimating long-term average bloom extent, providing crucial insights into the changing distribution and magnitude of *Nodularia spumigena* blooms (Janssen et al., 2004; Reinart and Kutser, 2006; Eilola et al., 2011).

In recent years, new and promising approaches have emerged for predicting *Nodularia spumigena* blooms, including fuzzy logic and statistical models. Statistical models rely on historical data to identify correlations and patterns between bloom occurrences and key environmental variables such as temperature, nutrient concentrations, and wind speed. These models use regression analysis or machine learning techniques to generate predictions, offering a data-driven alternative to mechanistic modelling. By leveraging extensive observational datasets, statistical models can provide valuable insights into bloom dynamics, although their accuracy is inherently dependent on the quality and completeness of the available data (Ibelings et al., 2003; Laanemets et al., 2006; Håkanson, 2009).

Each model approach has different strengths and weaknesses, so it is crucial to choose correctly depending on the demanded outcome. Mechanistic models are more useful for understanding how *Nodularia spumigena* responds to environmental change and for making long-term climate projections. Statistical models are effective for near-term bloom forecasting based on observed patterns (Munkes et al., 2021; Löptien and Dietze, 2022; Garaba et al., 2023). Fuzzy logic models are hybrid – mainly statistical, but with mechanistic elements, making them more suitable for complex phenomena which are so abundant in ecology (Laanemets et al., 2006; Munkes et al., 2021).

Most of the current modelling seems to suggest that due to climate change the blooms are evolving. Over the last thirty years (from 1990 to 2019) the blooms are occurring on average nine days earlier and lasting fifteen days longer. This phenomenon is attributed to rising water temperatures and increased heat flux, both of which enhance water column stability, resulting in prolonged summer blooms and higher biomass accumulation (Beltran-Perez and Waniek, 2022).

The *Nodularia spumigena* strains themselves seem to be changing too. A study done with thirty-three-year-old resurrected strains confirmed a shift in an optimal photosynthesis temperature from 15.3°C to 21.1°C found in recent strains. This suggests that the species will thrive in warmer climate in the future (Medwed et al., 2024).

The combined influence of these factors is projected to result in more than a twofold increase in the average cyanobacterial biomass and nitrogen fixation rates. This anticipated rise is primarily driven by the prolongation of the bloom growth period, facilitated by enhanced water column stratification and rising temperatures. As climate change continues to alter environmental conditions, these trends suggest a significant intensification of cyanobacterial blooms in the Baltic Sea, with potential ecological and biogeochemical consequences (Hense et al., 2013).

However, all models exhibit significant divergence regarding the long-term future of the blooms, with some predicting continued interannual expansion, others suggesting a reduction in size, and some indicating the potential for complete decline over time (Hense et al., 2013; Meier et al., 2019). Different models also seem to predict vastly different amounts of nitrogen fixation in the future (Neumann, 2010; Hense et al., 2013; Saraiva et al., 2019).

10. Conclusion

Nodularia spumigena remains one of the most ecologically and toxicologically significant contributors to cyanobacterial blooms in the Baltic Sea. As this brackish, semi-enclosed basin continues to experience the compounded effects of anthropogenic eutrophication and climate change, *N. spumigena* thrives in increasingly favourable conditions - chiefly, elevated surface temperatures, prolonged thermal stratification, and persistently high phosphorus loads. These blooms pose profound challenges, not only by altering the food web structure and reducing biodiversity but also through the biosynthesis of the hepatotoxin nodularin, which accumulates through trophic levels and poses long-term ecological and health risks.

The physiological and ecological adaptations of *Nodularia spumigena*, such as nitrogen fixation, heterocyst and akinete formation, and potential hormogonia development, underscore its resilience in the nitrogen-depleted yet phosphate-rich waters. Equally, the persistence of nodularin in benthic sediments and the limited enzymatic detoxification pathways available to affected organisms raise concerns about the compound's long-term ecological footprint. As highlighted, the most effective detoxification mechanisms remain largely species-specific and insufficient at the ecosystem level.

In addition to its toxicological impact, *Nodularia spumigena* has recently been recognized as a biological source of methane. The degradation of methylphosphonate (MPn) *Nodularia spumigena* releases methane as a metabolic byproduct, placing it among a small group of cyanobacteria - *Trichodesmium*, *Synechococcus*, and *Anabaena cylindrica* - capable of contributing to methane supersaturation in aquatic systems. This ability not only adds a previously underappreciated dimension to the biogeochemical role of cyanobacterial blooms but may also influence local and regional climate dynamics by contributing to greenhouse gas fluxes in surface waters.

Mechanistic models - such as CEMBS, ECOSMO, ERGOM, SCOBI, and BALTSEM - have significantly advanced our understanding of bloom dynamics and nutrient cycling, yet they remain constrained by the inherent complexity of biological systems and the scarcity of high-resolution field data. Although statistical and machine learning approaches offer promising alternatives or complements to these models, their predictive capacity is still developing and reliant on robust historical datasets.

The future of *Nodularia spumigena* blooms in the Baltic Sea remains uncertain, shaped by both the environmental and anthropogenic factors. Efforts to mitigate eutrophication - such as reducing nutrient inflows - are essential but may have limited impact on diazotrophic cyanobacteria like *Nodularia spumigena*, which can compensate by fixing atmospheric nitrogen. As a result, nutrient reduction may shift bloom dynamics without fully eliminating them. Climate change further complicates projections - warmer temperatures, altered precipitation, and increased stratification could favour cyanobacterial dominance, while extreme weather, salinity changes, or disrupted mixing might suppress blooms. Given these uncertainties, strengthening ecological models and long-term monitoring is critical to better anticipate the conditions under which blooms persist, weaken, or disappear altogether.

The uncertainty surrounding future bloom trajectories - whether they will intensify, stabilize, or diminish - reflects both the biological plasticity of *Nodularia spumigena* and the unpredictable nature of future environmental change.

In conclusion, while considerable progress has been made in understanding the ecology, toxicity, and modelling of *Nodularia spumigena* blooms, many knowledge gaps remain. Its role in methane production highlights a broader contribution to global biogeochemical cycles that is only beginning to be understood. Addressing these gaps will require integrated, interdisciplinary research combining molecular biology, ecotoxicology, remote sensing, and advanced modelling frameworks. Only through such approaches can effective monitoring, mitigation, and management strategies be developed to safeguard the ecosystem of the Baltic Sea in the face of ongoing environmental change.

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