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Review

Understanding the combined effects of multiple stressors: A new perspective on a longstanding challenge

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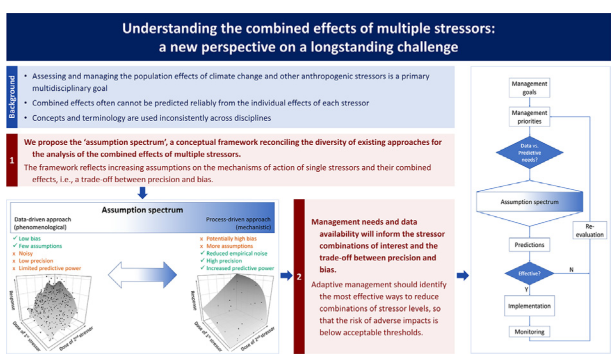
HIGHLIGHTS

- Assessing the combined effects of stressors is a primary multidisciplinary goal.
- We review the science of multiple stressors and inconsistencies across disciplines.
- We present a conceptual framework encompassing existing analytical approaches.
- We reinforce the centrality of management in guiding analysis and interpretation.
- Our approach reconciles cross-disciplinary differences and supports management.

GRAPHICAL ABSTRACT



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ABSTRACT

Wildlife populations and their habitats are exposed to an expanding diversity and intensity of stressors caused by human activities, within the broader context of natural processes and increasing pressure from climate change. Estimating how these multiple stressors affect individuals, populations, and ecosystems is thus of growing importance. However, their combined effects often cannot be predicted reliably from the individual effects of each stressor, and we lack the mechanistic understanding and analytical tools to predict their joint outcomes. We review the science of multiple stressors and present a conceptual framework that captures and reconciles the variety of existing approaches for assessing combined effects. Specifically, we show that all approaches lie along a spectrum, reflecting increasing assumptions about the mechanisms that regulate the action of single stressors and their combined effects. An emphasis

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on mechanisms improves analytical precision and predictive power but could introduce bias if the underlying assumptions are incorrect. A purely empirical approach has less risk of bias but requires adequate data on the effects of the full range of anticipated combinations of stressor types and magnitudes. We illustrate how this spectrum can be formalised into specific analytical methods, using an example of North Atlantic right whales feeding on limited prey resources while simultaneously being affected by entanglement in fishing gear. In practice, case-specific management needs and data availability will guide the exploration of the stressor combinations of interest and the selection of a suitable trade-off between precision and bias. We argue that the primary goal for adaptive management should be to identify the most practical and effective ways to remove or reduce specific combinations of stressors, bringing the risk of adverse impacts on populations and ecosystems below acceptable thresholds.

Contents

1. Introduction: the science of multiple stressors and the problems of inconsistent concepts and terminology

Most terrestrial and aquatic populations in the Anthropocene are exposed to a myriad of physical, chemical, or biotic factors that can move them out of their normal operating range (hereafter, 'stressors'; see Glossary in Appendix A) (Geldmann et al., 2014; Halpern et al., 2015; National Academies, 2017; Ormerod et al., 2010). Expanding human activities are increasing the variety and intensity of stressors, whose effects are also exacerbated by accelerating climate change (Brown et al., 2013; Gissi et al., 2021; He and Silliman, 2019; Li et al., 2018). Assessing, predicting, and managing the combined effects of multiple natural and anthropogenic stressors is therefore a primary management and conservation goal, as reflected in many regulatory frameworks. Because stressors are heterogeneous and can affect individuals, populations, communities, and their habitats, estimating their combined effects is salient in many disciplines, from pharmacology and epidemiology (Groten et al., 2001; Taylor et al., 2016), to toxicology (Altenburger et al., 2013; Hernandez et al., 2019), environmental science, conservation biology, and ecology (Breitburg et al., 1998; Côté et al., 2016; Folt et al., 1999; Orr et al., 2020; Rudd and Fleishman, 2014; Simmons et al., 2021; Vinebrooke et al., 2004).

Across disciplines, a common challenge is that combined effects cannot be predicted reliably from the individual effect of each stressor, because the way each stressor operates in isolation may change or be modified in the presence of other stressors (Folt et al., 1999; Orr et al., 2020; Piggott et al., 2015). The terms 'additivity' and 'interaction' (either 'synergistic' or 'antagonistic', depending on whether the additional stressors mitigate or aggravate effects) are frequently used to describe how stressors operate in combination, albeit with contrasting and often controversial interpretations. In a recent review, Orr et al. (2020) discussed the lack of communication across disciplines, highlighting that the same term may have dissimilar meanings and different terms may be used for the same meaning by different communities. Even within disciplines, terminology has been used inconsistently (e.g., Hertzberg and MacDonell, 2002; Orr et al., 2020; Webster, 2018). This has distracted research on the topic from its applied goals and complicated development of a unified, cross-disciplinary approach to multiple stressors (Orr et al., 2020).

Many existing methods draw on concepts from pharmacology and toxicology and use data-driven analyses to assess whether two stressors interact. The classic approach involves factorial studies, where the effect of a dose of each stressor is evaluated in isolation, and compared to the effect of a mixture of both stressors (Schäfer and Piggott, 2018). Here, we define 'dose' as the magnitude or amount of a stressor that is directly experienced, ingested, inhaled, or absorbed by an animal. The implicit null model, known as response addition in toxicology, assumes the combined effect is equal to the sum of the separate effects. This equivalence is tested via linear models (e.g., analysis of variance, or ANOVA) and, whenever it is not met, studies conclude that there has been an interaction.

There are alternative null models for predicting the combined effect of two stressors assuming they do not interact (Schäfer and Piggott, 2018). For example, a dose addition null model can be used when two stressors share the same molecular mechanism. In this case, stressor doses are corrected based on their relative potency (e.g., their toxicity) and summed into a joint dose to determine the combined effect (Bliss, 1939; Loewe and Muischnek, 1926) via a dose-response function (Fig. 1).

Non-linear dose-response functions complicate the analysis of factorial experiments. Consider an experiment that tests the effect of adding a fixed dose of stressor B to a population of subjects exposed to stressor A. Each subject is characterised by a given sensitivity to stressor A, defined as the minimum stressor intensity leading to an effect (Schäfer and Piggott, 2018). If there is a uniform distribution of sensitivity (Fig. 2A1), the dose-response function for the population is linear (Fig. 2A2), and the additional effect of stressor B is constant across all doses of stressor A (Fig. 2A3). However, the distribution of subjects' sensitivity could be unimodal (Fig. 2B1) (Schäfer and Piggott, 2018), leading to a sigmoidal dose-response function (Fig. 2B2). In this case, the additional effect of the second stressor is not constant even when the two stressors are additive (Fig. 2B3). In other words, the same function can lead to opposite conclusions on the occurrence and direction of an interaction depending on the selected range of stressor doses.

As a result, classic factorial experiments seldom conclude that combined effects are additive (Schäfer and Piggott, 2018). This fallacious interpretation of interactions is still common, even though it has been repeatedly rejected in many fields (e.g., Hertzberg and MacDonell, 2002; Howard and Webster, 2009; National Academies, 2017; Schäfer and Piggott, 2018; Tekin et al., 2020; Webster, 2018). Similarly, sudden changes in response with small changes in stressor doses, often referred to as tipping points (Hillebrand et al., 2020) and attributed to complex stressor interactions, may simply emerge from the transition from low to steep slope in non-linear dose-response functions (Kreyling et al.,

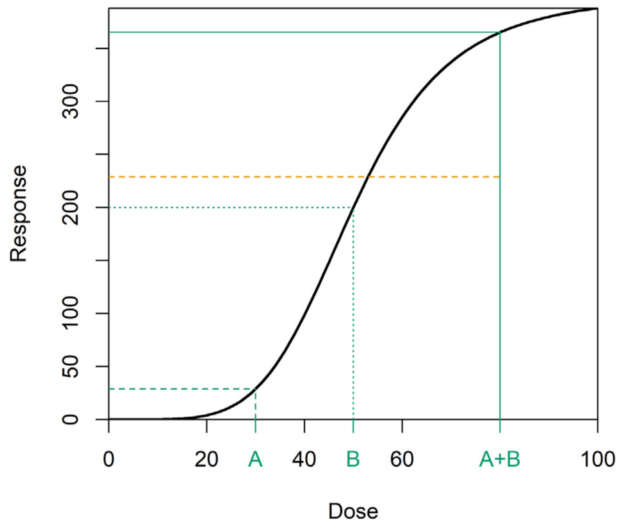

Fig. 1. Combined effect of two stressors A and B, which share the same molecular mechanism and dose-response function (solid black line), obtained by adding the dose of stressor A to that of stressor B (dose addition). The dashed and dotted green lines represent the effect of A and B alone, respectively. The combined effect of A + B (solid green line) is much higher than the prediction if their effects are assumed to be additive (orange line). More details are given in Appendix B.

2018). Factorial studies testing only one combination of stressor doses are also less useful from a management perspective, because they only support predictions of the effects of other doses if a linear relationship is assumed (Orr et al., 2020).

Besides discussion of available null models to test (Schäfer and Piggott, 2018), alternative definitions of 'interaction' have also been put forward. For example, Gennings et al. (2005) defined interactions as occurring when the presence of one stressor changes the shape of the dose-response function of the other stressor. They used a link function to linearise the dose-response in a generalised linear modelling framework and referred to the 'shape' as the slope in the linear predictor. Here, we extend their definition and postulate that an interaction occurs whenever the second stressor modifies the coefficient(s) linking the first stressor and the response. In other words, two stressors are additive when the dose-response function describing their combined effect can be separated into two functions without shared terms (Appendix D). While conceptually valid, this definition is challenging to use in real-world ecological scenarios. Estimating the dose-response function for a stressor in the presence and absence of a second stressor is seldom feasible (Hertzberg and MacDonell, 2002; National Academies, 2017). Moreover, a change in the shape of such a function does not, on its own, illuminate any of the mechanisms that underpin the way stressors combine.

Data-driven analyses that focus on detecting and categorizing interactions are thus of limited use for understanding combined effects because their outcome depends on how the absence of interaction is defined, which varies across research fields (Hertzberg and MacDonell, 2002). Additional confounding factors include the context-dependent nature of many effects, the sequence of exposure, the temporal scale and interval between exposures, and the organisational level (biochemical, physiological, individual, population, ecosystem) at which effects are measured (Boyd and Brown, 2015; Clements et al., 2012; Gunderson et al., 2016; Jackson et al., 2021; Orr et al., 2020). As a result, attempts to find common patterns in the prevalence and direction of stressor interactions in various systems have generated conflicting results (Ban et al., 2014; Côté et al., 2016; Crain et al., 2008; Darling and Côté, 2008; Dieleman et al., 2012; Harvey et al., 2013; Holmstrup et al., 2010; Jackson et al., 2016; Lange et al., 2018; Piggott et al., 2015; Przeslawski et al., 2015; Tekin et al., 2020; Yue et al., 2017). The only broad conclusion is that situations where the effects of multiple stressors are simply additive are likely rare (National Academies, 2017; Orr et al., 2020).

In summary, the debate over interactions has limited applied relevance (Côté et al., 2016; Hertzberg and MacDonell, 2002; Schäfer and Piggott, 2018). In contrast, there has been growing cross-disciplinary recognition that a detailed understanding of the mechanisms in which stressor effects combine, from chemical to ecological, provides greater predictive power (Ankley et al., 2010; Hernandez et al., 2019; Hertzberg and MacDonell, 2002; Hooper et al., 2013; Schäfer and Piggott, 2018; Simmons et al., 2021). In pharmacology, pharmacokinetic models are increasingly used to capture the movements of compounds in the body (Cohen Hubal et al., 2019). In toxicology, combined effects are formulated in terms of adverse outcome pathways (AOPs), which describe the linkages across levels of biological organisation, mostly focusing on sub-organismal levels (Ankley et al., 2010). In ecology, the cascade of effects that connect individuals to populations and ecosystems has been formulated into explicit transfer functions (National Academies, 2017; Pirotta et al., 2018; Wilson et al., 2020). These mechanistic approaches help address the more relevant questions: do combined effects result in an adverse impact for the unit of interest (e.g., an individual or population), and how can that risk be reduced?

The aim of this paper is therefore twofold. First, we present a conceptual framework that encompasses the diversity of approaches proposed to analyse the combined effects of multiple stressors, demonstrating that they lie on a spectrum of mechanistic assumptions that are built into the analysis. Second, we reaffirm the centrality of management needs in guiding the interpretation of combined effects. We argue for a pragmatic approach where case-specific priorities, predictive power and data availability drive the choice of analytical methods.

2. Reconciling the diverse approaches for studying the combined effects of multiple stressors: the assumption spectrum

Initially, we consider a management scenario where only two stressors are operating, and assume that a common response variable can be identified. As we show below, there is a spectrum of approaches for assessing their combined effects. This 'assumption spectrum' reflects increasing mechanistic assumptions about how the system works (Fig. 3), formalised into a functional model. The increasingly theoretical description of the underlying biological processes results in a progressive move away from a phenomenological, or data-driven, analysis of the relationship between stressors and effects. The distinction between mechanistic and phenomenological models has been discussed before, and all ecological models lie somewhere between these two extremes (e.g., White and Marshall (2019) and references therein). Here, we argue that organising the analysis of combined effects in this light provides a useful framework for selecting effective modelling techniques in different scenarios of data availability and management needs.

At one extreme of the assumption spectrum, where sufficient data are available from a range of stressor doses, combined effects can simply be described empirically. Under this data-driven approach, minimal assumptions are made about how the two stressors act, alone or in combination. For example, a minimum assumption could be that the effect of varying stressor levels is locally smooth. Such an approach is largely unbiased, because any pattern is directly inferred from the data, but it may be highly imprecise, because extensive data are required to reduce variance around the described relationships. A fully empirical approach does not require a test for the occurrence of interactions, because combined effects are described (and can be predicted) across the observed range of stressor doses. However, it has limited predictive power beyond this range. Surfaces describing how varying responses as a function of stressor doses have been fitted to the effects of mixtures of chemical compounds in toxicology (Ren, 2003; Webster, 2018), and of combined environmental and anthropogenic stressors in epidemiology (e.g., Burkart et al., 2013). In ecology, they have been used to model the effects of precipitation and temperature on vegetation index (Larsen et al., 2011), the physiological consequences of combined environmental stressors (e.g., Porter et al., 1999) and the

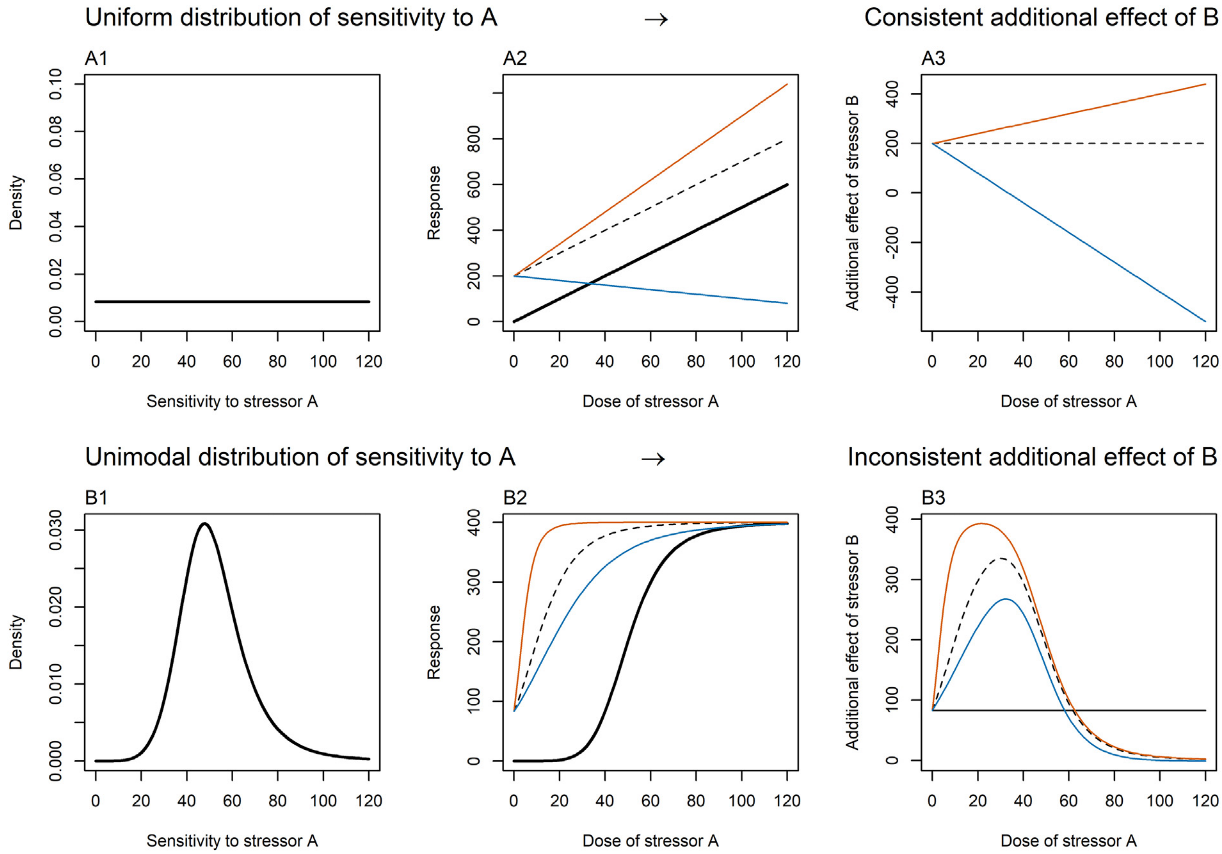

Fig. 2. Illustration of the problems with classic factorial experiments. A1) Uniform distribution of sensitivity to stressor A, i.e., the minimum stressor intensity leading to an effect. This results in a linear dose-response function (solid black line; A2); A2 also reports the combined effect of stressor A with a fixed dose of stressor B, when A and B are additive (dashed line) or interacting (blue and orange lines). A3) The additional effect of the fixed dose of stressor B is constant across the doses of stressor A when the two stressors are additive (dashed black line) and increases or decreases when the two are interacting (blue and orange lines). B1) Unimodal distribution of sensitivity to stressor A: a minority of individuals are sensitive to high or low doses of the stressor, while the majority are sensitive to intermediate values. This results in a sigmoidal dose-response function for stressor A (solid black line; B2); B2 also reports the combined effect of stressor A with a fixed dose of stressor B, when A and B are additive (dashed line) or interacting (blue and orange lines). B3) Because the dose-response function is not linear, the additional effect of the fixed dose of stressor B is not constant even when A and B are additive (dashed black line). Therefore, adding a second stressor may cause a combined effect that is either larger or smaller than the sum of the effects of the stressors acting in isolation. The solid black line indicates the effect of the fixed dose of stressor B on its own. More details are given in Appendix C.

behavioural responses to disturbance sources as a function of contextual factors (e.g., Dunlop et al., 2017). At higher organisational levels, multivariate auto-regressive models have been fitted to time-series data (often from freshwater plankton communities) to assess the effects of multiple abiotic and biotic stressors on species density (Hampton et al., 2013). When the data are subject to large measurement errors, hierarchical modelling techniques (e.g., state-space models; Auger-Méthé et al., 2021) can be used to explicitly model uncertainty in the observation process. Another data-driven example is the robust definition of interaction based on Gennings et al. (2005), which requires extensive data to characterise dose-response functions.

Moving along the spectrum, the problem can be progressively constrained by making increasingly stringent mechanistic assumptions. In doing so, precision should be increased, because the assumed functional forms reduce the influence of empirical noise on the estimation, and predictive power beyond the observed range of doses is enhanced. However, these advantages come at the risk of introducing biases if the assumptions are incorrect. Information about the mechanisms through which stressors operate is available at all levels of stressor effects, from molecular to ecological. For example, a sigmoidal dose-response function (the 'Hill equation') is traditionally used to represent the effect of chemical stressors binding to a receptor (Goutelle et al., 2008) (Fig. 4A). Physiological dose-response functions can be used to represent the variation of biological rates in response to environmental stressors. For example, the dependence of biological rates on temperature can be described using thermal performance curves (Angilletta, 2009), e.g., the Sharpe-Schoolfield model (Schoolfield et al., 1981), which are typically unimodal (Fig. 4B). At the level of the individual, exposure to a stressor can elicit changes in behaviour. Behavioural dose-response functions have been estimated using a probit transformation of the probability of responding (Miller et al., 2014) (Fig. 4C). A further generalization of this approach could involve time-to-event hazard models, where the 'hazard' of responding is modelled as a function of exposure to stressor doses, either in discrete (Tutz and Schmid, 2016) or continuous time (Kleinbaum and Klein, 2014). A focus on mechanisms can also help investigate the functional forms for ecological dose-response functions. For example, prey limitation can act as a stressor affecting energy acquisition by a predator (where available prey density represents the dose). Holling (1965) and Real (1977) considered the mechanisms for foraging and developed a general equation encompassing different functional responses (Fig. 4D).

Mechanistic assumptions can similarly guide investigation of the combined effects of stressors. For chemical toxicants, deviations from the dose-addition model emerge if the presence of one chemical changes the bioavailability, uptake, metabolisation, or excretion of the other (Cedergreen, 2014). For example, Delfosse et al. (2015) showed how a pharmaceutical oestrogen and a persistent organochlorine pesticide can each enhance the binding affinity of the other to a shared receptor. The choice of alternative null models in factorial studies (e.g., independent

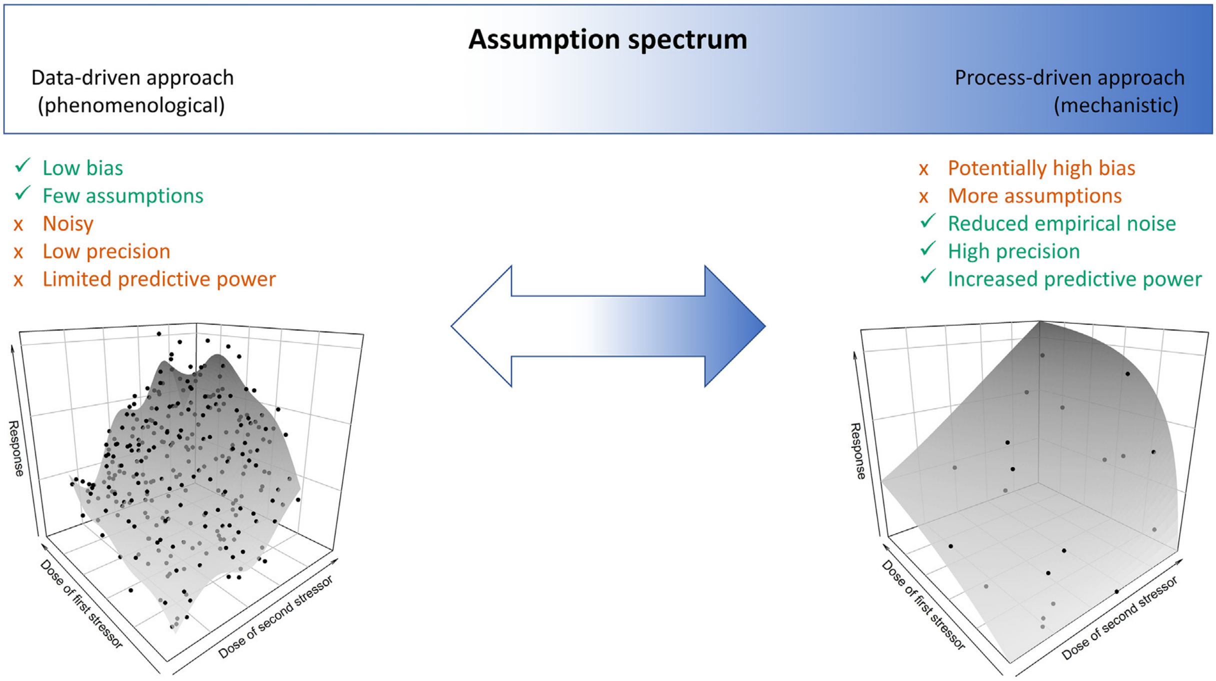

Fig. 3. The assumption spectrum, encompassing approaches to conceptualise and analyse the combined effects of multiple stressors. Data-driven approaches require a lot of empirical information and have limited predictive power but make few assumptions and thus show low bias. Process-driven approaches have higher precision and predictive power but make stronger assumptions about mechanisms; incorrect assumptions may introduce bias.

action or dominance models) can also be guided by appropriate mechanistic assumptions (Schäfer and Piggott, 2018). In the behavioural response scenario described above, a second stressor could increase the average threshold at which individuals respond, while, for ecological functional responses, a second stressor could decrease prey encounter rate or increase handling time. Analysis of data from factorial experiments using linear models (see Introduction) is an example of a stringent mechanistic assumption that is likely to introduce bias.

At the mechanistic end of the spectrum, a fully mechanistic approach uses extensive a priori assumptions about the underlying functional processes (Fig. 3). While most mechanistic models are not fitted directly to data, there has been progress in fitting complex, process-driven models, e.g., using approximate Bayesian computation or emulation (Hooten et al., 2020). Mechanistic approaches have high predictive power (and therefore wide management applicability), but also high structural uncertainty and concomitant risk of bias from selecting an inappropriate model (Barton et al., 2007; Regan et al., 2002). Chemical, biological and ecological knowledge can be used to describe the pathways linking stressor exposure to potential adverse outcomes at different organisational levels (Simmons et al., 2021). This idea has been formalised in the concept of biological upscaling in conservation physiology (Cooke et al., 2014) and AOPs in ecotoxicology (Ankley et al., 2010). For example, Hooper et al. (2013) used AOPs to predict that toxicants may alter the ability of organisms to respond to climate change and, in turn, climate stressors may affect chemical toxicity. Highly mechanistic models have also been used for mixtures of drugs and toxicants. For example, physiologically based pharmacokinetic and toxicokinetic models describe the absorption, distribution, metabolism, and excretion of chemicals, mapping chemical movement among organs and tissues, and modelling their combined effects mechanistically (Cohen Hubal et al., 2019).

When stressors operate along the bioenergetic response pathway (i.e., they interfere with the baseline flow of energy acquisition and allocation), a Dynamic Energy Budget (DEB) model can be used to capture energy fluxes mechanistically and specify the level at which stressors operate (Costa, 2012; Kooijman, 2009; Nisbet et al., 2012). Bioenergetic modelling could also integrate the energetic consequences of stressors traditionally considered to act along different response pathways. For example, Bennett et al. (2021) showed that persistent organic pollutants can interfere with energy balance regulation in marine mammals, Regnault and Lagardere (1983) found that noise exposure increases metabolism in shrimp, and Anestis et al. (2010) reported that changes in seawater temperature alter the metabolism of mussels and promote the outbreak of parasites that further impair energy balance. In ecology, mechanistic models of combined effects on individuals and populations (e.g., using bioenergetic principles) can be formulated as individual-based models (IBMs, also known as agent-based models), where individual agents characterised by internal state variables are simulated to interact with dynamic landscapes over time (Grimm and Railsback, 2013). Galic et al. (2018) provided an example involving a freshwater amphipod, Semeniuk et al. (2014) used an IBM to assess the effects of anthropogenic stressors on the habitat use and energetics of a terrestrial mammal, while McRae et al. (2008) used this approach to predict the population consequences of heterogeneous stressors on two bird species under different land-use and climate change scenarios.

In a recent paper, Simmons et al. (2021) argue that classifying stressors by their target and ecological scale can reconcile the disparate nature of their sources and provide a focus on their operating mechanisms of impact. They reviewed a series of mechanistic models that can be used to simulate combined effects, particularly at higher organisational levels. For example, interconnections between multiple stressors and the unit of interest can be visualised using threat webs (Geary et al., 2019), which can then be parameterised using network-based methods such as structural equation modelling (e.g., Villeneuve et al., 2018) and Bayesian belief networks (e.g., Molina-Navarro et al., 2020).

National Academies (2017) proposed a general mechanistic framework to study the Population Consequences of Multiple Stressors (PCoMS) that captures and connects multiple scales, targets and organisational levels (up to population). The health of an individual is defined as its "ability to adapt and self-manage" (Huber et al., 2011), and is assumed to result from the integration of multiple currency variables (Cohen et al., 2017; Simmons et al., 2021), such as energy stores, stress hormones, immune function, oxidative damage and organ status (National Academies, 2017; Pirotta et al., 2018). The PCoMS framework aims to estimate how stressors

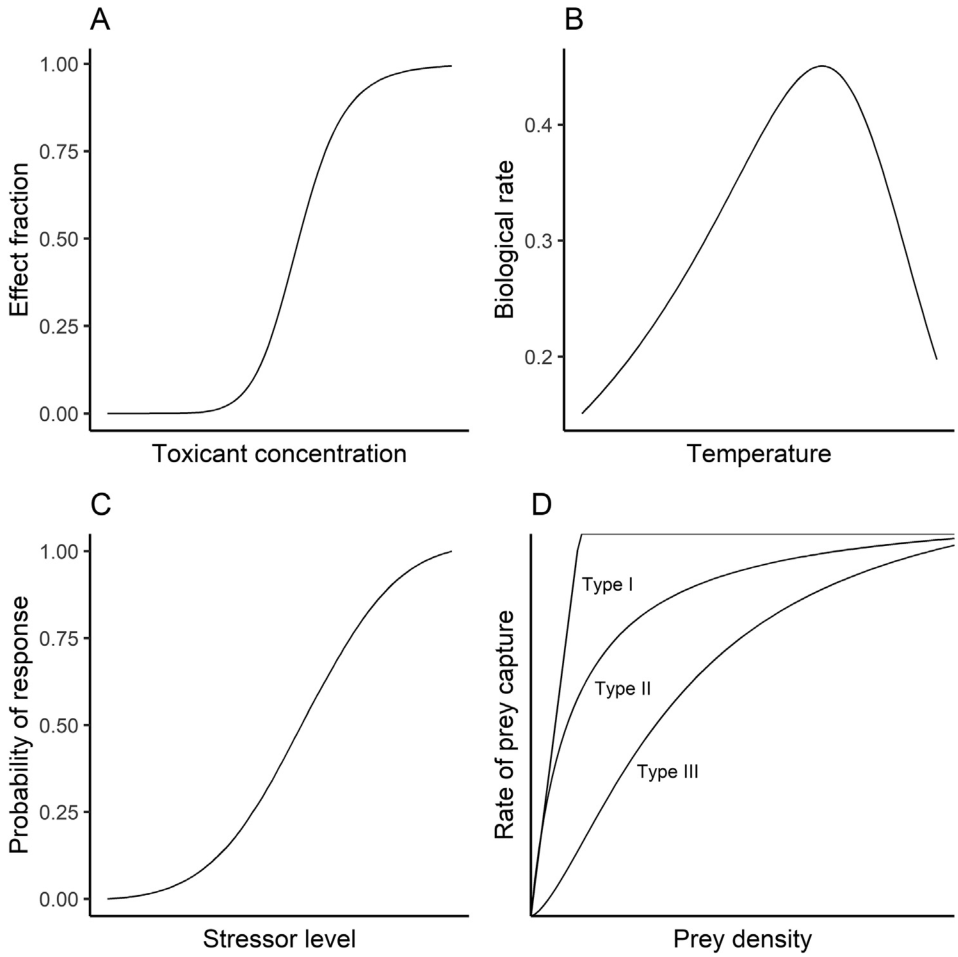

Fig. 4. Examples of dose-response functions informed by knowledge of the mechanisms. A) Sigmoidal dose-response function of a toxicant (the Hill equation), representing the effect of ligands binding to a receptor. B) Thermal performance curve described using the Sharpe-Schoolfield model. C) Probability of individual animals changing their behaviour in response to increasing levels of a source of disturbance. D) Examples of type I, II and III functional responses, i.e., prey consumption rate as a function of prey density.

affect these health variables using empirical data, where available, and appropriate mechanistic models. For example, a bioenergetic model can be used to describe the energetic response pathway, through which an individual's energy budget may be disrupted by stressors that affect its ability to feed. Sub-lethal, toxic effects on an organ or system can also cause irreparable damage or initiate disease processes, leading to higher risk of mortality (Hall et al., 2018). Moreover, reproduction might be directly impaired by an individual's stress levels, contaminant burden or compromised immune status (Aulsebrook et al., 2020; Hall et al., 2018; Rolland et al., 2017; Viney et al., 2005), while stress levels and survival probability can vary if stressors alter predation risk (Madin et al., 2015). Different response pathways in the PCoMS framework can also affect each other. For example, there are metabolic costs of mounting an immune response (Lochmiller and Deerenberg, 2000), and the chronic elevation of stress hormones is known to downregulate immune responses (Råberg et al., 1998; Sheldon and Verhulst, 1996). Upscaling these mechanistic models to the level of communities and ecosystems involves a series of conceptual and methodological complications, discussed in Appendix E.

Many analytical approaches described in this section involve a combination of empirical estimation and mechanistic assumptions, and the strength of comparable assumptions may vary among systems. This makes it difficult to place different approaches at specific positions along the assumption spectrum. However, this framework is useful to explicitly explore the strengths and limitations of each model component and, particularly, the trade-off between precision and bias (Fig. F.1; Appendix F).

3. The assumption spectrum in practice: an ecological example

We illustrate the assumption spectrum and explore its conceptual and methodological implications through an ecological example. We consider a system where a consumer acquires energy from a limiting resource, whose availability may be affected by natural fluctuations and climate change. We envisage that human activities also affect the consumer. It is likely that data across combinations of stressor doses for such a system will be limited, and we thus use it to demonstrate the progression from data-driven to process-driven analytical approaches.

For example, the recovery of the critically endangered North Atlantic right whale (*Eubalaena glacialis*) is impaired by prey limitation and accidental entanglement in fishing gear, among other stressors (Fortune et al., 2013; Moore et al., 2021; Rolland et al., 2016; van der Hoop et al., 2017). Both can be thought of as continuous stressors, i.e., a range of prey densities is available in the species' habitat, and entanglement in fishing gear can vary in severity and duration (which, for simplicity, we assume can be summarised into some measure of entanglement level). Severe entanglement can kill animals by physical injury (Cassoff et al., 2011; Sharp et al., 2019); non-lethal entanglement can worsen the effects of prey limitation by interfering with prey capture and increasing drag forces while swimming (Pettis et al., 2017; van der Hoop et al., 2017). The combined effect of the two stressors that we analyse here is at the energetic level, where the prey acquired by an individual over some temporal window of interest (e.g., a day) is the shared response variable.

First, we consider a hypothetical scenario where consumption rate can be observed under many combinations of prey density and entanglement level (Fig. F.2; Appendix F). In this situation, a data-driven, non-parametric surface could be used to describe their combined effect (Wood, 2006) (Fig. 5A). We could include additional constraints to the surface, make it smoother, set consumption rate to zero when prey density is zero, and constrain the function to be monotonic (Pya and Wood, 2014). However, if only a subset of prey density values are observable in practice, the results of this estimation would not support predictions of consumption rate in a novel, unobserved ecological scenario (e.g., unprecedented conditions caused by climate change; Fig. 5B).

We can impose further assumptions to improve predictive power. A factorial experiment would be inappropriate in this case (Fig. 5C). A better solution is obtained by assuming a type II functional response to represent feeding activity at varying prey densities, assuming that entanglement level affects the parameters of the function (Fig. 5D). This more process-driven approach supports predictions beyond the range of observed stressors and identifies clear mechanisms for how the stressors operate in isolation and in combination. However, mistakes can still arise: for example, a type III functional response might better represent the feeding process (Fig. 5E). Alternative scientific hypotheses can be encoded as different parametric functions, using model selection methods to identify the best fitting one.

When empirical information is scarce, a fully mechanistic approach may be used, informed by existing knowledge of this or other comparable systems. We might develop, for example, a simple movement simulation model to describe how individuals in an area explore their environment and encounter food patches (Fig. F.3; Appendix F). We could simulate varying levels of entanglement affecting both feeding rate and the maximum amount of prey intake per unit time. This simple IBM could be used to reconstruct the average daily consumption rate for an individual under various combinations of prey density and entanglement level (Fig. 5F). It may be extended beyond one day, introducing rules for leaving the area and longer-term motivations, or modelling energy levels explicitly (e.g., using a DEB model). Ultimately, it may be formulated as a population model under the PCoMS framework.

4. Management implications: identifying thresholds for adverse impacts and selecting combinations of stressors to manage

From a management and conservation perspective, establishing whether stressors interact or not is secondary compared to finding practical

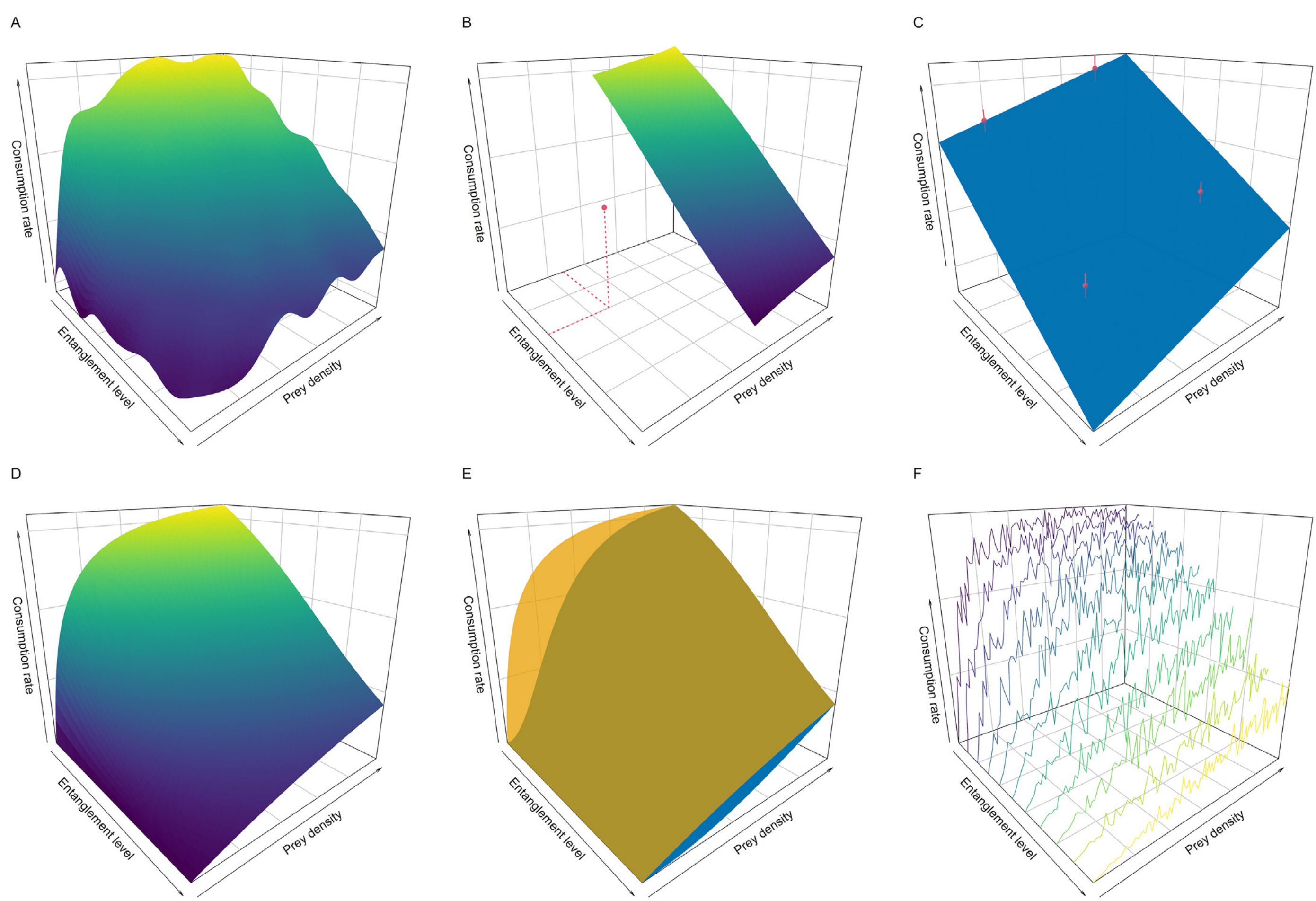

Fig. 5. The assumption spectrum, illustrated using an ecological example involving North Atlantic right whales. A) Non-parametric surface fitted to the data, using a tensor product with fixed degrees of freedom in a Generalised Additive Model (GAM). B) GAM surface where the range of the data does not cover the combination of stressor levels of interest (red dot). C) Results of a factorial experiment, only measuring consumption rate for four combinations of the two stressors (the red dots and segments are the sampling means and standard deviations of consumption rate); a traditional two-way analysis of variance implicitly assumes that each stressor has a linear effect on the response variable, as represented by the blue plane. D) Type II functional response, with entanglement level affecting the search rate and prey handling time parameters, fitted to the data in a Bayesian setting (using Markov chain Monte Carlo algorithms). E) Comparison of type II (orange) and type III (blue) functional responses. F) Results of a simple mechanistic model simulating the movements of 10 individuals over a day for different combinations of 100 prey density scenarios and 11 entanglement levels; mean consumption rates across individuals for increasing prey density, given each simulated level of entanglement. More details are given in the text and Appendix F.

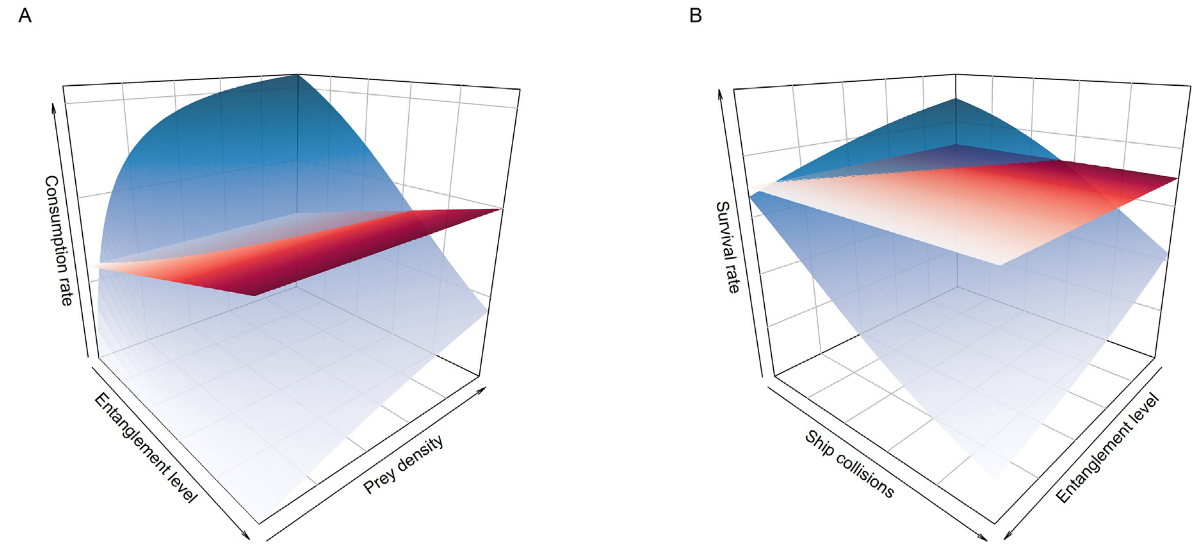

Fig. 6. Example of management objective defining acceptable combinations of stressor levels. In shaded blue, the dose-response surface; in A, this represents variation in consumption rate for varying levels of prey density and entanglement level, and in B this represents variation in survival rate for varying levels of entanglement and ship collisions. The shaded red surface represents the rates required to meet the management objective; in A, the surface is tilted because entanglement imposes additional energetic costs that are not captured in the dose-response surface (but need to be accounted for when calculating the minimum consumption rate).

solutions to reduce the current risk to populations. Management goals could guide the selection of which stressors within the available mixture can effectively be manipulated to ensure that the risk of adverse impacts on populations remains below acceptable thresholds (Groffman et al., 2006; Huggett, 2005; Kelly et al., 2015), i.e., the stressors that are relevant in practice (Diefenderfer et al., 2021; National Academies, 2017).

Some stressors, such as climate change, persistent pollutants, or the regime shifts resulting from centuries of human activities (e.g., overfishing or deforestation) (e.g., Jepson and Law, 2016; Pauly et al., 2005; Solomon et al., 2009) cannot be mitigated rapidly. In the short term, the focus must therefore be on tackling stressors that can be reduced, such as anthropogenic noise, non-persistent pollutants, extraction of biotic and abiotic resources (e.g., mining, local fishing effort, farming, unintended harvesting), and disturbance from human presence (Brown et al., 2013; Falkenberg et al., 2013). Empirical evidence or mechanistic predictions of interactions can help quantify the cascading benefits of reducing each stressor. In particular, a surface could be drawn across the dose-response surface identifying acceptable combinations of stressor doses, i.e., those resulting in a combined effect within the target management objective.

In the ecological example described in Section 3, this surface would be at the level of consumption rate that results in individual energy budgets supporting a viable population (Fig. 6A). The surface might have to be tilted to account for other stressor effects: for example, higher consumption rate is required at higher entanglement levels to compensate for the increased cost of movement, which is not accounted for in the functional response (Fig. 6A). While our example focused on the energetic effects of prey availability and entanglement, two of the controllable stressors (entanglement and collision with vessels) kill enough individuals to hinder the species' recovery (Moore et al., 2021). Risk factors for these stressors and their effects on whales have been well studied, enabling a data-driven analysis of their combined effects on survival rate (e.g., Fig. 6B). Therefore, two management objectives could be envisioned for this case study: one defining a minimum consumption rate to ensure a favourable energy budget (and thus reproductive rate), and another setting a minimum acceptable survival rate. Survival and reproductive rates supporting a viable, recovering population could then be derived using population modelling tools.

This alternative way of addressing multiple stressors is a form of adaptive management (Holling, 1978; Walters, 1986) (Fig. 7). In passive adaptive management, current scientific evidence is used to choose the policy action most likely to bring the unit of interest closest to the management goals. In active adaptive management, the selection process also involves considering what could be learned from its implementation (Williams, 2011). The effects of the implemented action are monitored to reduce uncertainty and inform the next management round. This iterative process incorporates the best available evidence when making a decision under uncertainty, but explicitly requires a re-evaluation once the policy measure has been put in place and enforced. Adaptive management promotes data collection and progressively leads to an improving evidence base. In the context of multiple stressors, managers could use political judgments and cost-benefit analyses (including the value of information that can be gained, Bolam et al., 2019) to identify the set of stressors whose reduction is predicted to achieve the management goal while balancing costs and societal values. It may also be possible to implement alternative manipulations in different areas to compare their efficacy (Breitburg et al., 1998; Wilson et al., 2006). The changes that result from these management actions would both refine the supporting analyses and inform the selection of effective stressor combinations in other areas. To this purpose, adaptive monitoring can be used to assess the effectiveness of adopted management strategies (Côté et al., 2016; Lindenmayer and Likens, 2009).

5. Where along the spectrum should we model? Data limitations, relevance for management and the role of mechanisms

While the assumption spectrum is conceptually appealing, it does not provide practical guidance on whether or when a more data- or process-driven approach should be preferred. We argue that choosing a position along the spectrum in specific cases should be based on the objectives of the potential management applications. Specifically, the guiding principle should be a pragmatic assessment of the predictive power of the resulting analysis in light of data availability and management priorities.

As discussed above, only the effects of a limited number of combinations of doses for a selected set of stressors may be of management interest. Ideally, experimental or observational studies can then be designed to determine stressor responses over this range, and a data-driven analytical approach will be most effective, since it results in minimum bias while supporting relevant predictions.

The pragmatic solution of targeting analytical approaches to combinations of stressors and stressor levels of interest has been previously highlighted in toxicology, when assessing the effects of complex but defined mixtures of compounds (Hernandez et al., 2019). Here, the effects of the

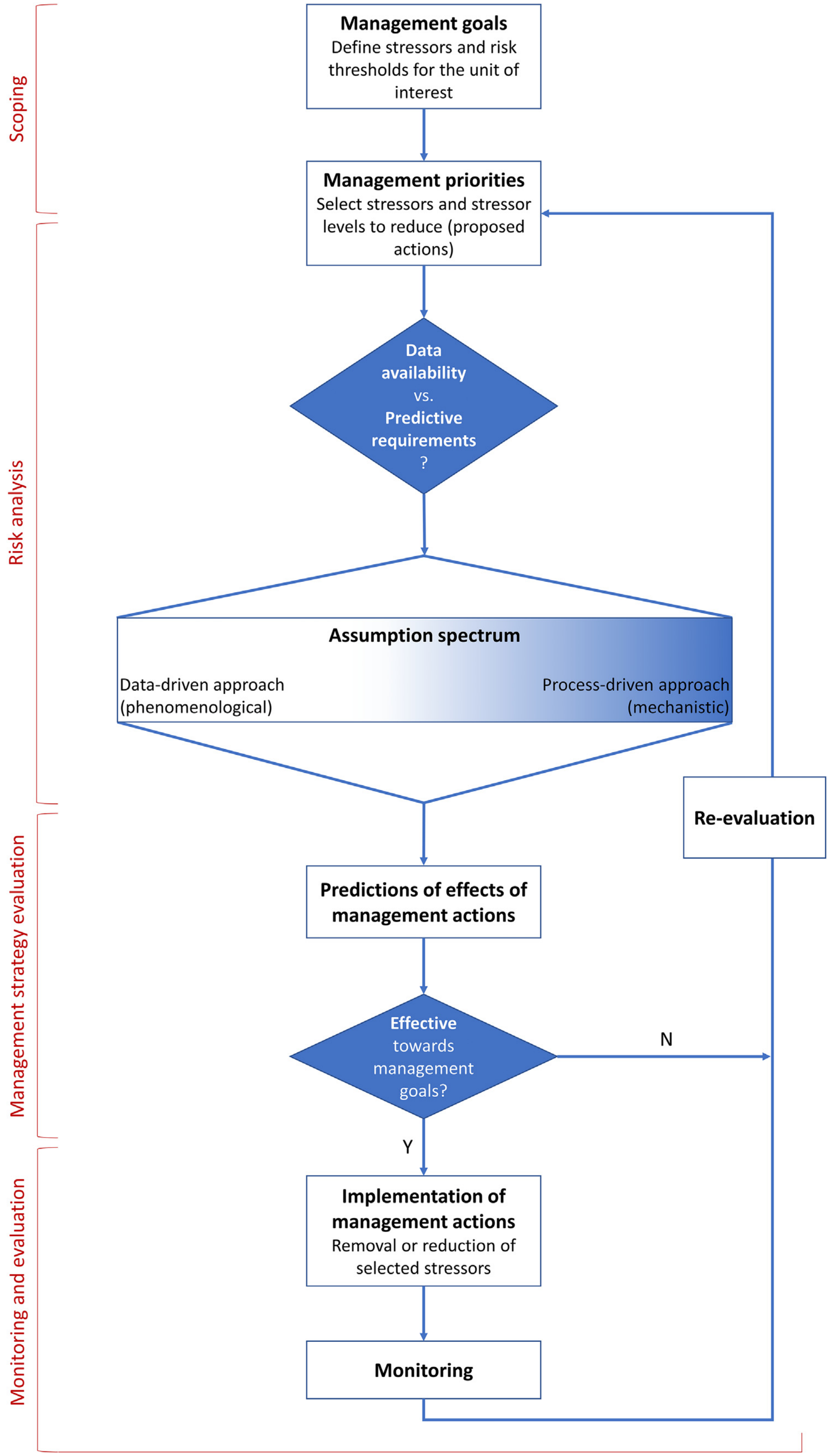

Fig. 7. The iterative framework to assess and manage the combined effect of multiple stressors on a unit of interest (e.g., a population). The definition of management goals (i.e., the thresholds of adverse impacts) guides the identification of the priority set of stressors and stressor combinations that can be manipulated. In turn, these priorities help select the correct analytical approach along the assumption spectrum, in light of data availability. Analyses generate predictions of the combined effects of stressor reductions, which inform applied management. The effects of implemented actions are monitored, and the management strategy is re-evaluated as a result. Text in red along the left-hand margin shows the equivalent terminology from the integrated ecosystem assessment framework proposed by Levin et al. (2009).

complete, environmentally realistic mixture can be tested directly (Feron et al., 1998; Webster, 2018). More generally, the number of possible combinations of doses is often limited, with many combinations not occurring and thus not requiring investigation (Carlin et al., 2013). Similarly, in ecology, Boyd et al. (2018) advocated the identification of the most relevant combinations and levels of key stressors in marine systems (which they called 'drivers', see Appendix G), and presented practical solutions to the challenges of designing and carrying out multi-stressor experiments for quantifying their combined effects. Despite these considerations, there are several challenges to using purely data-driven approaches (Box 1).

To tackle these complexities, a mechanistic understanding of the response pathways is helpful. In extreme cases, this would make it possible to completely bypass data collection. For example, when modelling the effects of climate change on a population of consumers, the future availability and abundance of food resources may be unknown. However, a mechanistic ecosystem model could still support reliable predictions based on the connections between features of the abiotic environment and reverberations across trophic levels (Griffith et al., 2012; Simmons et al., 2021). Mechanistic approaches should address structural uncertainty by comparing the predictions of multiple, plausible functional forms, acknowledging knowledge gaps explicitly, and re-evaluating assumptions whenever additional data become available (Milner-Gulland and Shea, 2017).

6. Conclusion: we need a coherent framework for the study of the combined effects of multiple stressors across disciplines

Given rapid changes in the environment under the pressure of climate change and encroachment of human activities on all ecosystems, various authors (Paine et al., 1998; Rudd, 2014; Steffen et al., 2011) have argued that understanding and managing combined effects of multiple stressors is the most pressing challenge facing researchers, conservationists, managers and policy makers in the 21st century. How best to quantify these effects has been debated across diverse disciplines. However, these debates are frequently reduced to sensational claims of synergisms or detailed discussions of how to detect the occurrence of functional (as opposed to statistical) interactions (Hertzberg and MacDonell, 2002), resulting in limited ability to provide quantitative analyses for regulatory applications. It is particularly important that stakeholders across disciplines that have historically dealt with different sets of stressors operating along separate response pathways find a shared language and methodology to facilitate cross-fertilisation (Orr et al., 2020).

We show that existing, heterogeneous approaches for analysing multiple stressor effects can be placed along an assumption spectrum, providing a conceptual background that guides the selection of a suitable methodology in different scenarios. We suggest that, in most cases, some reliance on a mechanistic description of the functional processes that underpin a system will be necessary, as recognised in toxicology, environmental science and ecology (Ankley et al., 2010; Griffen et al., 2016; Hernandez et al., 2019; Hertzberg and MacDonell, 2002; Hooper et al., 2013; Schäfer and Piggott, 2018). This mechanistic emphasis reflects a shared goal of capturing complexity, ensuring realism, and, ultimately, enhancing predictive power (Orr et al., 2020).

We also believe that management objectives should be central to this discussion. Finding solutions to the risk incurred by target populations requires identifying thresholds for adverse impact (Groffman et al., 2006; Huggett, 2005; Kelly et al., 2015), estimating the probability that combined effects of stressors may be nearing or exceeding those thresholds, and deciding which stressors can be managed, in a practical combination that reduces the risk (National Academies, 2017) (Fig. 6). Focus on management objectives also helps select the most effective approach along the assumption spectrum on a case-by-case basis.

In conclusion, we have shown how cross-disciplinary methodological differences can be reconciled by taking account of the goals and predictive needs of the management scenario to which they are applied. The unified view we propose can help conceptualise and structure the analysis of the combined effects of multiple stressors and guide the development of successful strategies that will ensure the future persistence of species and ecosystems.

Box 1
Challenges to the use of data-driven approaches for the study of combined effects of multiple stressors.

1) Relevant data may not be available and designing suitable studies to inform the combinations of interest may be challenging or unrealistic in practice. This is the case for many populations of large animals that cannot be manipulated in the laboratory, or that are already endangered (e.g., North Atlantic right whales, Section 3).
2) The sequence of stressor addition or removal may be critical to determine combined effects (Gunderson et al., 2016; Jackson et al., 2021). For example, contaminants can compromise an individual's immune status and cause a greater susceptibility to infectious diseases (Lafferty and Holt, 2003), but contaminant exposure must precede exposure to the pathogen for it to increase the risk of acute infection.
3) The time intervals between stressor exposures might alter their combined effects (Jackson et al., 2021; Orr et al., 2020).
4) Stressors can operate at distinct organisational levels, affecting different proximate response variables (Segner et al., 2014; Simmons et al., 2021). Even though there might be some common level at which a combined effect can be measured, this shared response currency could be too far down the cascade of effects (i.e., at higher organisational levels) to allow collection of relevant data and efficient management. For example, if we only observe the combined effects of disease and contaminants on individual survival, and if the unit of interest is a population of a long-lived species, then experimental manipulation is likely unfeasible and any effect would only be observed when it is too late to intervene and reverse impacts (National Academies, 2017).
5) Combined effects may have opposite signs, or emerge at different time scales, for distinct organisational levels (Orr et al., 2020; Segner et al., 2014). For example, Lafferty and Holt (2003) discussed how exposure to a stressor might enhance an individual's risk of contracting a disease; however, if the same stressor also reduces the density of the host population, it might ultimately restrict the ability of a specialist pathogen (i.e., infecting only that host) to spread.
6) Exposure to some stressors may be transient, making dose-response relationships difficult to assess, but the resulting health effects may be chronic or permanent, potentially leaving individuals more vulnerable to other stressors. In these cases, the dose of the first stressor may be unmeasurable, but the resulting consequences on an individual's health are specific to that stressor and its modulation of the effects of a second stressor can be measured (Ryan et al., 2007). For example, exposure to chemical or biological toxins might compromise the status of some organs, which in turn could affect an individual's ability to mount a physiological response or change its behaviour in response to a disturbance source; e.g., compromised neurological or pulmonary function might impair anti-predatory responses, leading to an increased risk of being injured or killed by a predator or human activity (Smith et al., 2017; Tablado and Jenni, 2017; Thomas et al., 2010). Different degrees of organ compromise may be measurable, but the corresponding toxin doses that caused them might not.
7) Real-world scenarios generally involve more than two stressors, all of which may modify each other's effects in complex ways (Orr et al., 2020; Simmons et al., 2021). For example, climate change is modifying the exposure rate and intensity of many stressors simultaneously (e.g., Hooper et al., 2013), leading to new, often unpredictable combinations of stressor levels that populations experience (Doak et al., 2008). Rillig et al. (2021) and Simmons et al. (2021) have proposed ways to classify stressors based on different criteria, which can guide the assessment of combined effects.

CRediT authorship contribution statement

Enrico Pirotta: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing – Original Draft, Visualization. **Len Thomas:** Conceptualization, Methodology, Writing – Original Draft, Visualization, Supervision, Funding acquisition. **Daniel P. Costa:** Conceptualization, Writing - Review & Editing. **Ailsa J. Hall:** Conceptualization, Writing - Review & Editing, Visualization. **Catriona Harris:** Conceptualization, Writing - Review & Editing, Project administration, Supervision, Funding acquisition. **John Harwood:** Conceptualization, Methodology, Writing - Review & Editing. **Scott D. Kraus:** Conceptualization, Writing - Review & Editing. **Patrick J.O. Miller:** Conceptualization, Writing - Review & Editing, Visualization. **Michael J. Moore:**

Conceptualization, Writing - Review & Editing. **Theoni Photopoulou:** Conceptualization, Writing - Review & Editing, Visualization. **Rosalind M. Rolland:** Conceptualization, Writing - Review & Editing. **Lori Schwacke:** Conceptualization, Writing - Review & Editing. **Samantha E. Simmons:** Conceptualization, Writing - Review & Editing, Visualization. **Brandon L. Southall:** Conceptualization, Writing - Review & Editing. **Peter L. Tyack:** Conceptualization, Methodology, Investigation, Writing – Original Draft, Visualization, Supervision, Project administration, Funding acquisition.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.153322.

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