

Hormesis and Hydra Effects Revealed by Intraspecific Overcompensation Models and Dose-Response Curves

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Overcompensation, defined as recovery beyond a baseline state, arises from both hormetic and hydra effects, illustrating adaptive responses to stress. The overcompensation framework of a re-evaluated fishery resource management model was examined through nonlinear growth patterns based on logistic or Ricker models, emphasizing population size over carrying capacity. This complete overcompensation model's threshold conditions reveal an interplay between hydra and hormetic effects. Also, when dividing a population into distinct subgroups, such as susceptible and infected classes in disease transmission, the population size can be modelled as a function of the basic reproduction number (R_0). A threshold condition of R_0 allows examination of how disease infectivity triggers hydra or hormetic effects and, also, development of a partial overcompensation model that elucidates the internal mechanisms of overcompensation. Analysis of data from 24 groups of U-shaped or inverted U-shaped dose-response curves validated the dose-response curves. The simplified modelling approach developed revealed the mechanisms underlying hydra and hormetic effects, highlighting the importance of strong growth or regenerative capabilities, over-compensatory responses (strong nonlinearity), mild external stimuli

(weak stressors), and the baseline population size. Our new analytical techniques for overcompensation modelling can be adapted to many fields, including tumour treatment and toxicology.

1. Introduction

Overcompensation is a biological phenomenon in which the value of some variable of an organism, e.g. its population size, exceeds its original state following a detrimental external stimulus. This can be observed in various contexts¹⁻⁷. An hormetic effect occurs when there is a biphasic dose-response relationship in which exposure to low doses of a stressor or toxin results in beneficial effects, whereas higher doses can be harmful or inhibitory⁸⁻¹³. The hydra effect refers to when prolonged exposure to mild stressors mitigates or reverses detrimental effects, challenging traditional linear dose-response models¹⁴⁻²⁰. The hydra effect is named after the Lernean Hydra, a mythological serpentine creature of Greek and Roman legends that regenerated one or more new heads whenever one of its nine heads had been severed, which in turn led to the naming of the freshwater hydrozoan animal *Hydra*, renowned for its regenerative abilities in response to injury. Thus, in population dynamics, there is a hydra effect if the mean density of a population increases after mortality rates increase^{13,18,19}.

Connections between overcompensation, hormesis, and the hydra effect stem from shared biological responses to external stimuli. Under suitable conditions, organisms may utilize overcompensation or hormesis to navigate challenges, thereby enhancing their survival or fitness. The hydra effect exemplifies how organisms can display characteristics of both overcompensation and hormesis in response to varying stress levels. The dose-response curve is essential for understanding these concepts, as it illustrates how different levels of stress or exposure to external stimuli influence biological responses^{5,10-13}. However, limitations exist within existing models such as the widely recognized Brain-Cousens and Cedergreen-Ritz-Streibig models, including the restricted applicability of hormetic dose-response curves, challenges in parameter estimation, and a lack of mechanistic explanations²¹⁻²³.

A notable example of overcompensation occurs in plants in response to herbivory,

particularly in studies of *Arabidopsis thaliana* and *Plantago major*²⁻⁴. When grazed or damaged, these plants can produce more biomass, flowers, or seeds than if undisturbed. Mechanisms behind this overcompensation include activating dormant buds, increased photosynthesis, and re-allocation of resources from roots to new growth, which influence growth rates and survival. Consequently, overcompensation serves as an adaptive strategy that enhances survival and reproductive success by enabling plants to recover more robustly from damage. In fisheries resource management, harvesting provides an excess of resources for the remaining fish population, leading to overcompensation that accelerates their growth beyond baseline levels^{13,14,24}. In cancer treatment, competition for resources differs significantly between susceptible and resistant cells; as susceptible cells decline under treatment pressure, while resistant cells can overly compensate and dominate, leading to treatment failure²⁵. Similarly, in infectious diseases, infected individuals reduce their resource use, thereby allowing re-allocation of resources to uninfected individuals, which fosters an overcompensation effect and increases overall population numbers despite the disease^{18,19}.

To reveal the intrinsic mechanisms of overcompensation, we revisit the following maximum sustainable yield (MSY) model²⁴:

$$\frac{dN}{dt} = rN \left(1 - \frac{N}{K}\right) - qEN,$$

where N is the population size of the fish stock, r is the intrinsic growth rate, K is the carrying capacity (reflecting environmental limitations and interactions such as competition, predation, and resource availability), q is the catchability coefficient and E represents the fishing effort (conveniently fixed at 1). It is well known that the optimal fishing level q_{MSY} , stable fish stock N_{MSY} and maximum sustainable yield Y_{MSY} are as follows²⁴:

$$q_{MSY} = \frac{r}{2}, \quad N_{MSY} = \frac{K}{2} \quad \text{and} \quad Y_{MSY} = \frac{rK}{4}.$$

When focusing on the total quantity of fishery resources under MSY, we have

$$M_{MSY} = N_{MSY} + Y_{MSY} = (1 + q_{MSY})N_{MSY} = \frac{K}{2} \left(1 + \frac{r}{2}\right).$$

This equation indicates that when a population's intrinsic growth rate r is relatively low, M_{MSY} is less than the carrying capacity K . However, when r is high (greater

than 2), M_{MSY} exceeds K . This suggests that a total population size with strong reproductive or regenerative capabilities experiences an overcompensation effect in fishery growth due to harvested resources, resulting in a hydra effect.

This understanding clarifies how the harvesting of fish can compensate for resources that would have been utilized, ultimately benefiting the remaining individuals in the fishery and achieving MSY, and it underpins our development of the complete or partial overcompensation models described later and enhances our comprehension of the mechanisms behind overcompensation, hormesis and hydra effects, revealing their intrinsic interrelationships. Additionally, this approach yields more interpretable dose-response curves, serving as a model reference for analyzing a wide range of U-shaped or inverted U-shaped dose-response data from numerous experiments and studies^{5,8-13}.

We conducted a systematic and in-depth analysis of stable total population levels using a simplified model framework that incorporates overcompensation recruitment (shown in the electronic supplementary material). Our objective is to uncover the mechanisms behind the hydra and hormetic effects linked to overcompensation, emphasizing the relationships between model parameters and the intensity of external interventions to establish a fundamental understanding of the quantitative relationships and identify the biological mechanisms underlying overcompensation.

2. Methods

2.1. Overcompensatory recruitment

This study identifies growth functions enabling population overcompensation under external stressors during growth phases. As shown in Fig.1(A), linear growth functions maintain monotonic population dynamics despite disturbances. Conversely, logistic and Ricker functions exhibit distinct behaviour: strong intraspecific competition induces growth rate deceleration beyond specific population thresholds (e.g. curve maxima in Fig.1(A)). In such systems, perturbation-induced population reduction may initiate overcompensatory responses, when residual individuals enter accelerated growth phases across broad population ranges. Populations following these non-linear growth patterns demonstrate overcompensatory recruitment^{3,6,18,19}, providing the foundation

for overcompensation modelling.

2.2. The complete overcompensation model

It is assumed that the population growth of fishery resources, pests, tumour cells, or other living systems adheres to either the logistic growth model or the Ricker growth model. The corresponding strategies for harvesting, pest control and tumour cell treatment can be represented as a proportional function dependent on population density, leading to the following universal model^{13,24}:

$$\frac{dN}{dt} = F(N) - qN, \quad (2.1)$$

where the logistic growth rate function $F(N) = rN \left(1 - \frac{N}{K}\right)$ and Ricker growth rate function $F(N) = rNe^{-bN} - \mu N$ with carrying capacity $K = -\frac{1}{b} \ln \left(\frac{\mu}{r}\right)$ and $r > \mu$, see the electronic supplementary material (ESM) for detailed parameter definitions. Let $M = (1 + q)N$, then

$$\frac{dM}{dt} = F(M) - qM \quad (2.2)$$

with for the logistic growth rate function $F(M) = rM \left(1 - \frac{M}{(1+q)K}\right)$ and for the Ricker growth rate function $F(M) = rMe^{-\frac{b}{1+q}M} - \mu M$. The equilibrium is denoted by $M^*(r, q)$.

A key feature of model (2.2) is that a detrimental external stimulus with an intensity q reduces the intraspecific competition of individuals in the population from $\frac{1}{K}$ to $\frac{1}{(1+q)K}$. This change consequently influences the dynamics of the carrying capacity by affecting population growth rates and resource utilization. Note that the removed population will fully compensate for the resources and space available to the remaining individuals and, consequently, we refer to model (2.2) as a growth model with complete overcompensation effects, i.e. the complete overcompensation model. For convenience, we denote COM-logistic and COM-Ricker as the complete overcompensation models with logistic and Ricker growth rate functions, respectively.

2.3. The partial overcompensation model

To deepen our understanding of how a population reduced by external interventions

leads to overcompensation in the remaining individuals^{3,6,13}, we explore more complex scenarios. For instance, consider a situation where a virus spreads through a population, dividing the total population N into two categories: S (susceptible) and I (infected). In this context, infected individuals I influence both the birth rate and density dependence of the population, prompting us to examine the following SI model with a Ricker growth pattern^{18,19}:

$$\begin{cases} \frac{dS}{dt} = r(S + \omega_0 I)e^{-b(S+\omega_1 I)} - \beta SI - \mu S, \\ \frac{dI}{dt} = \beta SI - (\mu + q)I, \end{cases} \quad (2.3)$$

here the disease transmission is modelled by mass action incidence, with a transmission rate $\beta > 0$, a per capita disease death rate q and a per capita death rate μ . ω_0 and ω_1 are parameters which represent the relative reproductive capacity and resource competitiveness of infected individuals with $\omega_0, \omega_1 \in [0,1]$. Note that model (2.3) always exists with a disease-free equilibrium $(S_D, 0)$ with $S_D = -\frac{1}{b} \ln\left(\frac{\mu}{r}\right)$ if $r > \mu$ and, further, if $R_0 = \frac{\beta S_D}{q + \mu} > 1$ then model (2.3) always exists with an endemic equilibrium (S^*, I^*) . Denote $N = S + I$, with the stable total population size $N^*(r, R_0) = S^* + I^*$, see ESM for more details. To reveal the effects of overcompensation directly, we denote

$$p = \frac{S + \omega_1 I}{S + I} \quad \text{and} \quad \delta \triangleq \frac{1-p}{p} = \frac{(1-\omega_1)I}{S + \omega_1 I} \geq 0,$$

here, p represents the proportional reduction in overall competition for resources due to the presence of infected individuals, while δ represents the spatial and resource compensation rate induced by the infection. It quantifies how much the infection changes the resource competition dynamics, considering both the relative competitiveness of infected individuals and their proportion in the population. Thus, model (2.3) can be re-written as follows:

$$\begin{cases} \frac{dS}{dt} = r(S + \omega_0 I)e^{-\frac{b}{1+\delta}(S+I)} - \beta SI - \mu I, \\ \frac{dI}{dt} = \beta SI - (\mu + q)I. \end{cases} \quad (2.4)$$

Since the ability of infected individuals to compete for resources and utilize space is weaker than that of susceptible individuals, the former does not completely abandon resources, as in the complete overcompensation model (2.1). Thus, we call model (4) a

partial overcompensation model (denoted by POM-DI) of (2.3) as δ varies dynamically, i.e.

$$\frac{d\delta}{dt} = -\frac{1-\omega_1}{(S+\omega_1 I)^2} \left[r(S+\omega_0 I) I e^{-\frac{b}{1+\delta}(S+I)} - S(\beta SI - (\mu+q)I) - I(\beta SI + \mu I) \right],$$

which indicates that the compensation effect of infected individuals on the susceptible population exhibits a complex dynamic pattern with strong nonlinearity.

In the ESM, by analyzing four specific cases with $\omega_0 = 0, 1$, and $\omega_1 = 0, 1$, we identify the parameter threshold spaces for hydra and hormetic effects. We then analyze the partial overcompensation model for $\omega_0 = 0$ and $\omega_1 \in [0, 1)$, determining the threshold parameter ω_1 that triggers these effects. This provides a threshold that indicates the extent to which the competitive ability of infected classes must decline compared to susceptible classes to induce overcompensation effects. The case when $\omega_1 = \omega_0 = \omega$ has been studied previously^{18,19}, where it was concluded that a hydra effect occurs if the derivative of $N^*(r, R_0)$ with respect to R_0 is positive. We clarify in the ESM that this conclusion is not entirely accurate.

Considering the special case with $\omega_0 = \omega_1 = 0$, we have

$$\begin{cases} \frac{dS}{dt} = rS e^{-bS} - \beta SI - \mu S, \\ \frac{dI}{dt} = \beta SI - (\mu + q)I \end{cases} \quad (2.5)$$

with

$$p = \frac{S}{S+I} \quad \text{and} \quad \delta = \frac{1-p}{p} = \frac{I}{S}$$

and then the complete overcompensation model, denoted by COM-DI, is as follows:

$$\begin{cases} \frac{dS}{dt} = rS e^{-\frac{b}{1+\delta}(S+I)} - \beta SI - \mu S, \\ \frac{dI}{dt} = \beta SI - (\mu + q)I, \end{cases}$$

and thus

$$\frac{d\delta}{dt} = -\frac{1}{S^2} \left[rS I e^{-\frac{b}{1+\delta}S} - S(\beta SI - (\mu + q)I) - I(\beta SI + \mu I) \right]$$

with

$$\delta^* = \frac{I^*}{S^*} = \frac{r \left[e^{-\frac{bK}{R_0}} - e^{-bK} \right]}{q + r e^{-bK}},$$

indicating that the overcompensation effect is an increasing function of the basic

reproduction number R_0 . However, due to the high-dose inhibitory effects of the hormesis, the R_0 cannot be too high and must be maintained within a certain threshold range.

2.4. Mathematical definition of hormetic or hydra effect

Let q (or R_0) be a dose related parameter. We assume that the proposed overcompensation model has a stable equilibrium $M^*(r, q)$ (or $N^*(r, R_0)$), representing the homeostatic state at the carrying capacity when $q = 0$ (or disease-free equilibrium when $R_0 = 1$), i.e. $M^*(r, 0) = K$ (or $N^*(r, 1) = S_D$). Hormesis, defined by a biphasic dose-response relationship and represented by inverted U-shaped or U-shaped curves, is described by the following paradoxical effect (taking $M^*(r, q)$ as an example)^{13,15-17}:

$$\frac{dM^*(r, q)}{dq} > 0 (< 0) \text{ for small } q \Leftrightarrow \text{low-level stimulation (low-level inhibition)}$$

and

$$\frac{dM^*(r, q)}{dq} < 0 (> 0) \text{ for large } q \Leftrightarrow \text{high-level stimulation (high-level inhibition)}$$

with $M^*(r, q) < K (> K)$ when q is large enough.

In particular, if $\frac{dM^*(r, q)}{dq} > 0$ and $M^*(r, q) > K$ for a certain range of q , then the hydra effect occurs. Note that in some publications^{16,17}, the hydra effect is defined solely through $\frac{dM^*(r, q)}{dq} > 0$.

2.5. Universal dose response curves

When external suppression intensity is treated as a dose-dependent function, the stable total population for both complete and partial overcompensation models naturally generates dose-response curves, such as U-shaped or inverted U-shaped curves^{5,12,13,21,26}. These functions are concise and feature parameters with clear biological significance and interpretability, offering greater simplicity and practical utility compared with the models proposed by Brain and Cousens²¹⁻²³. This provides a valuable reference for analyzing dose-response data across various fields, as detailed in Table 1 and related references. To this end, we can treat the dose-related parameter q or R_0 (reflecting pesticide or drug dosage, effectiveness or infectivity) as a function of dosage D_s , making q or R_0 dose-dependent as follows¹³:

$$q \text{ (or } R_0) = \kappa(1 - e^{-\rho D_s}),$$

where κ is a scaling parameter indicating the strength of external perturbation. $e^{-\rho D_s}$ represents the survival rate under the control conditions, and $1 - e^{-\rho D_s}$ reflects the effectiveness of external stress or intervention.

Logistic dose-response curve:

$$M^*(r, q) = K(1 + q) \left(1 - \frac{q}{r}\right) \quad (2.6)$$

with $M^*(r, 0) = K$, where K denotes the untreated control (baseline value). The term $1 + q$ represents the resource compensation effect arising from population reduction due to external suppressive strategies, such as harvesting, which enhances the environment's carrying capacity for the remaining population. The condition $r > q$ signifies strong regenerative capacity and relatively weak external suppression, resulting in a small value of $1 - \frac{q}{r}$. This condition is essential both for ensuring that M^* exceeds the baseline value and for the emergence of hydra and hormetic effects. The unknown parameters in (2.6) which need to be estimated are $\Theta = \{K, \rho, r, \kappa\}$.

Ricker dose response curve:

$$M^*(r, q) = -\frac{1+q}{b} \ln \left(\frac{q+\mu}{r} \right) \quad (2.7)$$

with $M^*(r, 0) = K = -\frac{1}{b} \ln \left(\frac{\mu}{r} \right)$. Similarly, $1 + q$ and $r > q + \mu$ have exactly the same biological significance as above. The unknown parameters in (2.7) which need to be estimated are $\Theta = \{\rho, b, \mu, r, \kappa\}$.

The basic reproduction number R_0 is a more accurate indicator of the impact of disease infectivity on steady-state population levels. Specifically, when $R_0 \leq 1$, the population stabilizes at a disease-free equilibrium S_D (baseline value), whereas when $R_0 > 1$, a stable internal equilibrium is achieved. Consequently, utilizing R_0 as a determinant for disease effects on population size results in the following disease infectivity induced dose-response curve:

$$N^*(r, R_0) = \frac{K \left(r e^{-\frac{bK}{R_0} + q} \right)}{R_0 (r e^{-bK} + q)} \quad (2.8)$$

with $N^*(r, 1) = K = -\frac{1}{b} \ln \left(\frac{\mu}{r} \right) = S_D$, the term $e^{-\frac{bK}{R_0}}$ encapsulates the resource

compensation effect resulting from the reduction in population size due to external suppression strategies, such as increased infectivity, which subsequently enhances the carrying capacity for the susceptible population. The condition $r > \mu$ indicates a strong regenerative capacity within the population, accompanied by relatively weak external suppression. This suggests that R_0 must be relatively small to facilitate the emergence of hydra and hormetic effects, as indicated by $\lim_{R_0 \rightarrow +\infty} N^*(r, R_0) = 0$. The unknown parameters in (8) which need to be estimated are $\Theta = \{\rho, b, q, S_D, r, \kappa\}$.

2.6. Source of data and parameter estimation

We selected 24 data sets from various publications to verify the universality of the three types of dose-response curves²⁶⁻³⁵, including both U-shaped and inverted U-shaped patterns, as detailed in Table 1. These data sets describe the changes in response values of different agonists at different doses in various systems, spanning a variety of fields: encompassing disease treatments such as tumours (DS1, 13, 20), trigeminal neurinoma (DS2), cardiovascular disease (DS3), and cancer (DS4, 5). Additionally, they include chemical drug reactions (DS6, 9–11, 14, 15, 19, 21), pest control studies (DS7, 8, 16), species abundance analyses (DS17, 18, 22–24) and plant management (DS12). Collectively, these datasets provide a rich array of examples derived from diverse biological models and experimental contexts, enhancing our understanding of dose-response relationships across multiple domains.

For simplicity, disease induced, Ricker and logistic dose-response curves are denoted as DI-DRC, Ricker-DRC and logistic-DRC, respectively. Using the *fmincon* (i.e. least squares method) function in MATLAB and given a dataset from Table 1, the goal of fitting is to find Θ that minimizes the following loss function³⁶

$$\mathcal{L} = \sum_{D_S \in \mathcal{H}} [\hat{x}(D_S) - R(D_S)]^2, \epsilon$$

where $\mathcal{H}$ represents the dosage set, $R(D_S)$ and $\hat{x}(D_S)$ denote the measured response and the fitted response, respectively, by the above three curves at dosage D_S . To assess the fitting performances of the above three dose-response curves, we applied three classical evaluation metrics^{37,38}, root mean square error (RMSE), mean absolute

error (MAE), and relative error (RE), which were calculated according to the following formulae:

$$\begin{aligned} \text{RMSE} &= \sqrt{\frac{1}{|\mathcal{H}|} \sum_{D_S \in \mathcal{H}} [\hat{x}(D_S) - R(D_S)]^2}, \quad \text{MAE} = \frac{1}{|\mathcal{H}|} \sum_{D_S \in \mathcal{H}} |\hat{x}(D_S) - R(D_S)| \quad \text{and} \\ \text{RE} &= \frac{\sqrt{\sum_{D_S \in \mathcal{H}} [\hat{x}(D_S) - R(D_S)]^2}}{\sqrt{\sum_{D_S \in \mathcal{H}} [R(D_S)]^2}}. \end{aligned}$$

3. Results

3.1. Threshold conditions and mechanism of overcompensation in COM-logistic:

Model (2.1) or (SM1.1) in the ESM achieves a stable equilibrium $N^* = K \left(1 - \frac{q}{r}\right)$ when $r > q$. The total population $M^*(r, q) = K(1 + q) \left(1 - \frac{q}{r}\right)$ is an equilibrium of COM-logistic with $M^*(r, 0) = K$. Based on the threshold condition for overcompensation (i.e. $r > 1 + q$), it can be shown that $\frac{K(1+q)}{r} < K$. This, along with the inequalities (SM1.5)

$$N_c = \frac{(r-q)K}{2r} < \frac{K}{2} < M_c = \left(1 - \frac{q}{r}\right) \frac{K(1+q)}{2} \leq M_c^m, \quad r > r_0 = 1 + q \quad (3.1)$$

related to the functions $H_1(N) = rN \left(1 - \frac{N}{K}\right) - qN$, $F(N) = rN \left(1 - \frac{N}{K}\right)$ and $G_1(N) = rN \left(1 - \frac{N}{K(1+q)}\right) - qN$, Fig.1(B) and (C) clarify the mechanism of overcompensation in the population with the logistic growth rate function. Initially, with a small population size, growth rates are similar under mild external perturbations (small q), as illustrated by the pink and green curves in Fig.1(B). However, as the population size exceeds $\frac{K(1+q)}{r}$, density-dependent effects intensify, leading to faster growth in populations exhibiting overcompensation (see Fig.1(B)). After reaching the peak of the overcompensation effect, growth will decline more slowly than in populations without such effects (compared with pink and green curves in Fig.1(B)). Thus, both the hydra effect and the potential hormetic effect occur (here $M^*(r, q) > K$) for a larger intrinsic growth rate r and a smaller detrimental external stimulus q , as shown in Fig.1(C).

Moreover, the larger the intrinsic growth rate ($r > 1 + q$ or $r > 1 + 2q$), the

stronger the overcompensation effect, even causing the maximum response to exceed the M_{MSY} , as indicated by the green curve in Fig.1 (C). This means that a population with over-compensatory growth and a given intrinsic growth rate r can respond to a stressor or perturbation, resulting in a response that exceeds its original state, as long as the strength of the stressor is maintained within the interval $(0, r - 1)$. The inflection point M_c at which the population growth rate is maximized, as detailed in equation SM1.5, occurs when $M_c > \frac{K}{2}$ in the logistic model without stressors, as shown in Fig.1(D). M_c is a monotonically increasing function of q for small values of q , meaning that overcompensation reaches its maximum effect as q increases before declining. Once q exceeds the hormetic zone $(0, r - 1)$, the overcompensation effect disappears (Fig. 1(C) and D)).

Therefore, the underlying mechanism of overcompensation in COM-logistic should enable populations to grow more rapidly and sustain growth over extended periods across a broad range of population sizes. This facilitates hydra and hormetic effects and generates an inverted U-shaped curve (see Fig. 1(C)) when the intrinsic growth rate is sufficiently high and when the detrimental external stimulus is sufficiently low.

3.2. Threshold conditions and mechanism of overcompensation in COM-Ricker:

Model (1) or SM2.1 in the ESM exists with a stable equilibrium $N^* = -\frac{1}{b} \ln\left(\frac{q+\mu}{r}\right)$ under the condition $r > q + \mu$ (or $0 \leq q < r - \mu$). The total population $M^*(r, q) = -\frac{1+q}{b} \ln\left(\frac{q+\mu}{r}\right)$ is an equilibrium of COM-Ricker with $M^*(r, 0) \triangleq K = -\frac{1}{b} \ln\left(\frac{\mu}{r}\right) = N_0^*$. By comparing the inequalities

$$N_c = \frac{1}{b} \left[1 - W\left(\frac{\mu+q}{r} e\right) \right] < \frac{1}{b} \left[1 - W\left(\frac{\mu e}{r}\right) \right] < M_c = \frac{(1+q) \left[1 - W\left(0, \frac{\mu+q}{r} e\right) \right]}{b}, \quad r > r_c$$

related to $H_1(N) = rNe^{-bN} - \mu N - qN$, $F(N) = rNe^{-bN} - \mu N$ and $G_1(N) = rNe^{-\frac{bN}{1+q}} - \mu N - qN$, where W denotes the Lambert W function in SM2.4 of the ESM and Fig.2(A) with those in (3.1) and Fig.1(B), we can elucidate the mechanisms of overcompensation across different growth functions. The COM-Ricker induces a stronger overcompensation effect than the COM-logistic, with its instantaneous growth

rate being more sensitive to population density changes. Moreover, by comparing the hydra and hormetic effects observed in Fig. 1(C) and Fig. 2(B), we find that the COM-Ricker, with its stronger overcompensation effect, results in a complex pattern in Fig. 2(B). This indicates that the threshold conditions for the hydra and hormetic effects, as well as the mechanisms of overcompensation in the COM-Ricker, become more intricate.

The condition $r > q + \mu$ ensures that $M^*(r, q)$ may exceed the baseline value and facilitates hydra and hormetic effects. It follows from Theorem SM.4 that $\mathbf{r}_1 \triangleq \max\{q + \mu, (1 - \mu)e^2\} \leq r < \min\{r_c(q_c), r_0\} = r_c(q_c) = (q_c + \mu)e^{\frac{1+q_c}{q_c+\mu}}$, and further we have $\frac{dM^*}{dq} < 0$ for $q \in [0, q_c^{-1})$, $\frac{dM^*}{dq} > 0$ for $q \in (q_c^{-1}, q_c^0)$ and $\frac{dM^*}{dq} < 0$ for $q \in (q_c^0, r - \mu)$, where q_c^i ($i = 0, 1$) are defined as

$$q_c^i = -\frac{[W(i, \frac{(\mu-1)e}{r}) - 1]\mu + 1}{W(i, \frac{(\mu-1)e}{r})}. \quad (3.2)$$

Moreover, $M^* < K = N_0^*$ for all $q \in (0, r - \mu)$, as shown in Fig.3(A-B). This demonstrates that while external pressure generates U-shaped and inverted-U-shaped curves as q increases from 0 to $r - \mu$, no hormetic or hydra effects occur due to an inadequate intrinsic growth rate or regenerative capacity (i.e., $r < r_c(q_c)$ and $\mu < 1/2$), indicating that $\frac{dM^*}{dq} > 0$ does not necessarily lead to the occurrence of the hydra effect^{16,17}.

Under specific conditions, a low mortality rate and weak external intervention induce a U-shaped hormetic curve (green curve in Fig. 2(B) and Fig.3(C-D)) with $\mu = 0.03$. When $\mu < 1/2$ and $r_c(q_c) \leq r < r_0 = \mu e^{\frac{1}{\mu}}$, the function $M^*(r, q)$ maintains the same monotonicity as for $r < r_c(q_c)$. However, a higher intrinsic growth rate enhances the population's overcompensation response to external pressure, resulting in hydra effects for all q satisfying $r > r_c(q)$, as indicated in Fig.3(C-D). Both hormetic effects with low-level inhibitions and high-level stimulations (where $M^* < N_0^*$) and low-level stimulations with high-level inhibitions (where $M^* > N_0^*$) occur concurrently, leading to successive U-shaped and inverted U-shaped curves as external

stress intensity increases.

If the intrinsic growth rate increases such that $\max\{r_1, r_0\} \leq r$, the U-shaped curve vanishes. In this scenario, $\frac{dM^*}{dq} > 0$ for $q \in [0, q_c^0)$ and $\frac{dM^*}{dq} < 0$ for $q \in (q_c^0, r - \mu)$, as shown in Fig.3(E-F). With $r > r_0$, both hydra and hormetic effects occur for all q satisfying $r > r_c(q)$. Additionally, the maximum response and the occurrence range of these effects increase with a higher intrinsic growth rate. If $\mu \geq 1/2$, then $r_1 \leq r_0 < r$, making the threshold conditions and occurrences of hormetic and hydra effects consistent with those for $\mu < 1/2$, as shown in Fig.3(G-H).

By setting $V(N) = F(N) - G_1(N) = 0$, two critical values, x_{c1} and x_{c2} , are identified in the ESM. As population density increases within the interval $[x_{c1}, x_{c2}]$, strong overcompensation effects emerge, indicating that the instantaneous growth rate under the COM-Ricker substantially exceeds the natural growth rate. During this phase, even minor external interventions can trigger pronounced hormetic and hydra effects, as shown in Fig. 2(B-D). Once density exceeds x_{c2} , populations rapidly decline due to intense density dependence. In Fig. 2(C-D), a critical level of external suppression leads to the inflection point M_c reaching its maximum value, M_c^m , which can surpass the baseline N_0^* at high mortality rates μ , as depicted in Fig. 2(D). This further supports the idea that populations following a Ricker growth model may experience strong overcompensation effects under certain conditions, resulting in more complex hydra and hormetic effects.

3.3. Threshold conditions and mechanism of overcompensation in COM-DI and POM-DI:

As highlighted in the introduction, using the spread of infectious diseases as an example, it is natural to categorize populations into susceptible and infected groups. This division facilitates the analysis of their impacts on resource utilization, birth rates, and the resulting overcompensation effects. To explore these dynamics, we first examine the simplest case and establish the exact threshold conditions, i.e. $\omega_0 = \omega_1 = 0$ in model (4) (i.e. COM-DI), which has a stable disease-free equilibrium $(S_D, 0)$ with $S_D = -\frac{1}{b} \ln\left(\frac{\mu}{r}\right)$ provided that $r > \mu$, and a stable endemic equilibrium $(S^*, I^*) =$

394 $\left(\frac{q+\mu}{\beta}, \frac{re^{-\frac{b(q+\mu)}{\beta}} - \mu}{\beta} \right)$ provided that $R_0 = \frac{\beta S_D}{q+\mu} > 1$ or $r > \mu e^{\frac{b(q+\mu)}{\beta}}$. Based on the
 395 relationships among β , μ , S_D , and R_0 , we select the disease infectivity R_0 as the
 396 dosage-related parameter and treat the total population as a function of R_0 , i.e.

$$397 \quad N^*(r, R_0) = \frac{re^{-\frac{bS_D}{R_0}} + q}{\beta} = \frac{S_D \left(re^{-\frac{bS_D}{R_0}} + q \right)}{R_0 (re^{-bS_D} + q)}, \quad R_0 \geq 1 \quad (3.3)$$

398 with $N^*(r, 1) = S_D$ as the baseline value.

399 According to Theorem SM.5 in the ESM, if $r < qe^2$ then $\frac{dN^*}{dR_0} < 0$, indicating
 400 that $N^* < S_D$ always holds true (the pink curve in Fig.4(A)). If $r \geq qe^2$, then there
 401 exists one threshold value $R_0^M = \frac{bS_D}{1 - W\left(0, -\frac{qe}{r}\right)}$ for R_0 such that an inverted-U shape
 402 curve appears for all $bS_D > 2$ and $q \in (0, q_{c1})$ with $q_{c1} = r(bS_D - 1)e^{-bS_D}$ (the
 403 green curve in Fig.4(A)); there exist two threshold values $R_0^m = \frac{bS_D}{1 - W\left(-1, -\frac{qe}{r}\right)}$ and R_0^M
 404 for R_0 such that the U-shaped curve and inverted U-shaped curve appear consequently
 405 for all $bS_D > 2$ and $q \in \left(q_{c1}, \frac{r}{e^2}\right)$ (the red and blue curves in Fig.3(A)). Also, there
 406 exists one threshold value R_0^M for R_0 such that an inverted-U shape curve appears
 407 for all $1 \leq bS_D < 2$ and $q \in (0, q_{c2})$ with q_{c2} satisfying $R_0^M(q_{c2}) = 1$; $\frac{dN^*}{dR_0} < 0$
 408 for all $1 \leq bS_D < 2$ and $q \in \left(q_{c2}, \frac{r}{e^2}\right)$ (or $bS_D < 1$). This indicates that a higher
 409 mortality rate from illness or weaker intraspecific competition cannot lead to an
 410 increase in the total population size due to infectious diseases, and consequently
 411 hormetic or hydra effects will not occur.

412 Furthermore, if $bS_D > 2$ and $q > \frac{r}{e^2} \frac{4 - bS_D e^{-bS_D + 2}}{bS_D}$, or $0 < bS_D < 2$ and $q \in$
 413 $\left(q_c^0, \frac{r}{e^2} \frac{4 - bS_D e^{-bS_D + 2}}{bS_D}\right]$, then both threshold values R_0^0 and R_0^{-1} , defined in SM3.8 of
 414 the ESM, either do not exist or exist but they are both less than one, resulting in $N^* <$
 415 S_D . This indicates that, while monotonic increase or decrease is possible, excessive
 416 mortality from illness does not lead to hydra or hormetic effects in the total population.
 417 If $R_0^0 > 1$ and $R_0^{-1} < 1$ (i.e. $q \in (0, q_c^0)$), then $N^* > S_D$ for all $R_0 \in (1, R_{c1})$,
 418 resulting in an inverted U-shaped curve and indicating that hydra and hormetic effects

occur, where R_{c1} is a unique root of equation $f(R_0) = 0$. If both R_0^0 and R_0^{-1} exceed one, the U-shaped and inverted U-shaped curves emerge successively as R_0 increases, as shown in Fig.4(A). Furthermore, if $f(R_0^0) > 0$ hydra and hormetic effects will occur. However, the precise threshold conditions are complex, as detailed in Fig. SM.1 of the ESM.

If $\omega_0 = \omega_1 = 1$, the infected and susceptible classes are identical in resource utilization and reproductive capacity, resulting in no resource compensation from the infected class to the susceptible class. Consequently, there are no hormetic or hydra effects, as shown in^{18,19} and the ESM. If $\omega_0 = 1, \omega_1 = 0$, the infected and susceptible classes share reproductive capacity, but the infected class does not compete for resources. While this model lacks strong biological significance, threshold theory analysis reveals an appropriate parameter space where total population size exhibits U-shaped hormetic or hydra effects in response to increasing R_0 . Conversely, if $\omega_0 = 0, \omega_1 = 1$, both classes share the same intraspecific competitive ability and infected individuals cannot reproduce. In this scenario, the total population size decreases monotonically with the basic reproduction number, indicating no hormetic or hydra effects across all parameter spaces.

The scenarios where the infected class does not compete for resources ($\omega_1 = 0$) and where it shares the same competitive ability as the susceptible class ($\omega_1 = 1$) represent two extremes. These cases reveal the underlying mechanisms for the occurrence or absence of overcompensation effects and indicate a threshold ω_c for the infected class's resource competition (i.e. POM-DI), and the effects of ω_1 on the occurrence of hormetic and hydra effects have been shown in Fig.4(B). Specifically, when $\omega_1 \in [\omega_c, 1]$, the compensation effect of the infected class on the susceptible class is too weak to produce hormetic or hydra effects across all parameter spaces, as shown in Fig.4(B), indicating that ω_c is small enough. Conversely, when $\omega_1 \in [0, \omega_c)$, the compensation effect is sufficiently strong, establishing a threshold parameter space linked to key factors such as intrinsic growth rate r , disease transmission ability R_0 , and population size S_D , where hormetic and hydra effects may occur, as shown in Section 3.5 of the ESM, i.e. the POM-DI can exhibit hormetic effects

and hydra effects within a certain parameter space.

To further explore the impact of multiple parameters on the threshold space defined by COM-DI ($\omega_0 = \omega_1 = 0$), we conducted a multi-parameter bifurcation analysis based on Theorems SM.5 and SM.6, selecting r , R_0 and bS_D . This analysis provides the parameter space for determining the signs of $\frac{dN^*}{dR_0}$ and $N^* - S_D$, offering deeper insight into the overcompensation mechanism and the conditions for hydra and hormetic effects, as shown in Fig. 4(C-D). In Fig. 4(C), we have:

Region II: $bS_D > 2$, $q \in (q_{c1}, \frac{r}{e^2})$ and $R_0 \in [1, R_0^m]$ indicating $\frac{dN^*}{dR_0} < 0$ and $N^* < S_D$;

Region III₁: $bS_D > 2$; $q \in (q_{c1}, \frac{r}{e^2})$ and $R_0 \in [R_0^m, R_0^M]$ indicating $\frac{dN^*}{dR_0} > 0$ and $N^* < S_D$;

Region III₂: $bS_D > 2$, $q \in (q_{c1}, \frac{r}{e^2})$ and $R_0 \in [R_0^m, R_0^M]$ indicating $\frac{dN^*}{dR_0} > 0$ and $N^* > S_D$;

Region IV₁: $bS_D > 2$, $q \in (q_{c1}, \frac{r}{e^2})$ and $R_0 > R_0^M$ indicating $\frac{dN^*}{dR_0} < 0$ and $N^* < S_D$;

Region IV₂: $bS_D > 2$, $q \in (q_{c1}, \frac{r}{e^2})$ and $R_0 > R_0^M$ indicating $\frac{dN^*}{dR_0} < 0$ and $N^* > S_D$,

which indicates that for fixed r (such as $r = 5$), when the parameter R_0 increases from 0 to 5 (i.e. from region II to III₁, and then to IV₁), the equilibrium $N^*(r, R_0)$ first decreases, then increases, and then decreases again, and the equilibrium state is always less than S_D , indicating that no hormetic or hydra effects have occurred. However, for larger r (such as 10), when the parameter R_0 increases from 0 to 5 (i.e. from region II to III₂, and then to IV₂), the monotonicity of the equilibrium $N^*(r, R_0)$ remains unchanged. However, when R_0 is located in regions III₂ and IV₂ we have $N^*(r, R_0) > S_D$, indicating the occurrence of hormetic and hydra effects, such as those shown in Fig.4(C). The other scenarios in Fig.4(C) and (D) can be discussed similarly, revealing that relatively large intrinsic growth rates and small transmission rates, as well as compensatory effects of infected individuals, can induce hormetic and hydra effects.

3.4. Data fitting for universal dose-response curves

The procedure involved fitting the universal logistic-DRC, Ricker-DRC, and DI-DRC to both U-shaped and inverted U-shaped datasets, as outlined in Table 1. To begin with, four datasets were selected from each group (U-shaped and inverted U-shaped) to determine which of the three models provided the best fit. This initial evaluation was based on model accuracy and goodness-of-fit criteria. Once the optimal model was identified for each dataset type, we conducted further validation by applying the selected model to an additional eight datasets from each group.

For the U-shaped datasets (DS1–DS12), the DI-DRC was found to provide the best fit. The estimated parameter values and corresponding fitting results are presented in Table SM.1 of the ESM and Fig.5, respectively. For the inverted U-shaped datasets (DS13–DS24), the Ricker-DRC was the most appropriate, with the parameter estimates and fitting results provided in Table SM.2 of the ESM and Fig.6.

As demonstrated in Figs. 5 and 6, the DI-DRC consistently provided a superior fit for the U-shaped datasets, while the Ricker-DRC more accurately captured the characteristics of the inverted U-shaped datasets. Additionally, the fitting performances of all three dose-response models, evaluated through RMSE, MAE, and RE, are further validated in Fig.SM.3 of the ESM. These results indicate that the selection of the dose-response model is highly dependent on the shape of the data, and the models chosen effectively capture the underlying response patterns across the different dataset types.

4. Discussion

The biphasic response of hormesis is characterized by a low-stimulation-high-inhibition curve, where mild stress enhances growth, development, or resistance, while excessive stress suppresses performance. This phenomenon is observed across various contexts and is crucial for optimizing pest control¹³, understanding plant growth stimulation²¹ and improving environmental toxicology assessments²³ and disease treatments^{5,12,39}. The hydra effect, associated with species that exhibit strong intrinsic growth rates and reproductive capabilities, typically occurs when external pressures,

such as predation or resource depletion, are temporarily alleviated. This effect has been explored in predator-prey systems^{14,15}, stable communities^{16,17} and disease dynamics^{18,19,42}. These studies independently addressed the threshold parameters for the hormetic or hydra effects respectively, which can be complex or analytically unresolved, limiting insight into their underlying mechanisms.

The hormetic and hydra effects can be unified through the concept of overcompensation, where both involve an initial suppression followed by an exaggerated recovery or growth phase. In hormesis, mild stress leads to beneficial outcomes, while in the hydra effect, population growth accelerates after a disturbance. By integrating these effects, we view them as adaptive responses to external pressures, driven by strong intrinsic growth or reproductive capabilities and influenced by density-dependent factors. Unifying these effects within a single framework is valuable, as it illustrates how external stressors, when managed within specific thresholds, promote dynamic behaviour such as overcompensation, resilience and rapid recovery. Therefore, by developing these simplified overcompensation models, this study unified the mechanisms of the hormetic and hydra effects, providing essential insights into ecological stability, species survival, and adaptive capacity in fluctuating environments.

Through comparative analysis of two completely overcompensatory population growth models developed in this study, the COM-logistic and COM-Ricker, we demonstrated that the Ricker function's heightened sensitivity to density dependence creates intricate interactions between external suppression and species growth, leading to more pronounced overcompensation effects, as shown in Figs.1 and 2. This analysis identifies a complex threshold parameter space among intrinsic growth rate r , external inhibition factor q and other factors, when under varying conditions, the COM-Ricker model exhibits both low-stimulation-high-inhibition and high-stimulation-low-inhibition hormetic effects, along with hydra effects. Crucially, both models share a common principle: strong intrinsic reproductive or growth capabilities, such as rapid growth and early maturation, combined with moderate external inhibition and compensatory growth, are key to inducing hormetic and hydra effects.

Furthermore, in this paper we developed partial and complete overcompensation

models, POM-DI and COM-DI, which highlight the resource competition between susceptible and infected subpopulations. In these models, infected individuals compensate for others while exhibiting hydra or hormetic effects. The main results reveal that the impact of infected individuals on birth rates has a minimal effect on the occurrence of overcompensation. However, resource utilization intensity is highly sensitive to overcompensation effects. When considering the special case where $\omega_0 = \omega_1 = \omega$ in the POM-DI, as studied in previous investigations^{18,19}, it was found that the occurrence of overcompensation induces the hydra effect. However, the underlying mechanism behind the occurrence of overcompensation remains unclear, specifically whether it is the compensation related to regenerative ability or resource utilization and competition that induces the hydra effect, making it difficult to provide a definitive distinction.

In this study, we adopt two distinct parameters, ω_0 and ω_1 , and through the consideration of five different scenarios, we demonstrate that the extent to which disease inhibits reproductive output in infected individuals does not directly influence overcompensation, offering a more accurate mechanism than those proposed in the literature^{18,19}. Notably, overcompensation-induced hydra and hormetic effects occur only when the resource competition ability of infected individuals is significantly weaker than that of susceptible individuals (i.e., when ω_1 is small enough).

These results highlight the necessity for strict thresholds regarding population size, growth rate, and disease infectiousness, offering a valuable methodological framework for understanding overcompensation mechanisms and the underlying principles of hydra and hormetic effects. These concepts are relevant to cancer treatment research. Resistant cells affect the survival of sensitive cells through inhibitory signals and alterations to the microenvironment²⁴. Treatment pressures often decrease sensitive cells while promoting resistant ones. Chemotherapy and targeted therapies create selective pressures that allow resistant cells to thrive, leading to treatment failure. Resistant cells interact with sensitive ones via cytokines and exosomes, further altering the microenvironment. The death of sensitive cells can also influence resistant cell behaviour, resulting in the rapid growth of resistant cancer cells.

Expanding upon our novel overcompensation model framework, we have demonstrated its capacity to derive various dose-response relationships relevant to cancer treatment and other domains. These models not only adeptly capture the U-shaped or inverted U-shaped dose-response patterns commonly observed but also offer robust analytical methodologies for exploring intricate mixed-dose-response data sets. The primary findings confirm that a substantial body of experimental data across various fields supports the universality of the Ricker-DRC and DI-DRC models. These models, therefore, provide reliable tools for predicting response values at unknown doses. In practical applications, such as clinical decision-making, pest management, and disease treatment, these curves can guide optimal dosing strategies to maximize therapeutic efficacy while minimizing adverse reactions^{5,11,13,39}. Furthermore, we emphasize that the Ricker-DRC and DI-DRC, compared to the well-known Brain-Cousens dose-response curve and its extensions²¹⁻²³, offer simpler forms with interpretable parameters that have clear biological significance. They also exhibit universal applicability, providing excellent fits to the data listed in Table 1 and other dose-response data. Therefore, adopting similar approaches to those presented in this study and developing new concepts for overcompensation models may reveal more complex overcompensation mechanisms and provide insights into hydra and hormetic effects. This could lead to the development of more efficient, interpretable, and widely applicable dose-response curves with superior fitting performance.

The COM-logistic, COM-Ricker and COM-DI (POM-DI) proposed in this study provide a comprehensive theoretical analysis, revealing the mechanisms of overcompensation and the precise threshold conditions for the hydra and hormetic effects. However, the major limitation of this study is the use of phenomenological population models, such as the logistic and Ricker growth rate functions, along with the corresponding COM-logistic and COM-Ricker, which capture general population dynamics but fail to account for the underlying biological mechanisms driving resource competition in complex ecosystems. Even in the POM-DI model, which considered only the interaction between susceptible and infected populations, the compensation

effect $\frac{1}{1+\delta}$ in model (4) varies dynamically based on the numbers of susceptible and infected individuals, with δ satisfying the differential equation given in section 2.3. This reveals a complex, nonlinear dynamic pattern in the compensation effect of infected individuals on the susceptible population. Additionally, infectious agents do not consistently reduce competitive ability or resource consumption: in some cases, they may even increase them⁴⁰⁻⁴³.

As a result, these models overlook key factors like resource dynamics, exploitation/consumption patterns, and utilization efficiency, all of which are essential for understanding phenomena like overcompensation in the hydra effect. In the future, we aim to incorporate more mechanistic models that explicitly account for realistic resource consumption and competition within ecosystems. These models have the potential to offer deeper insights into how resource availability interacts with population regulation, thereby enhancing our understanding of the underlying mechanisms driving hormetic and hydra effects. A significant challenge will be determining the threshold conditions for the hormetic and hydra effects, but we remain committed to further exploring these models to integrate biological mechanisms with the phenomenological outcomes observed in this study.

References

1. Ricker WE. 1954. Stock and recruitment. *J. Fish. Res. Bd. Canada* 11(5), 559-623.
2. Bergelson JM, Crawley MJ. 1988. Mycorrhizal infection and plant species diversity. *Nature* 334, 202-202.
3. Paige KN. 1992. Overcompensation in response to mammalian herbivory: from mutualistic to antagonistic interactions. *Ecology* 73, 2076-2085. (doi: 10.2307/1941456)
4. Agrawal AA. 1998. Induced responses to herbivory and increased plant performance. *Science* 279, 1201-1202. (doi: 10.1126/science.279.5354.1201)
5. Calabrese EJ., Baldwin LA. 2003. Toxicology rethinks its central belief. *Nature* 421, 691-692. (doi: 10.1038/421691a)
6. De Roos AM. et al. 2007. Food-dependent growth leads to overcompensation in stage-specific biomass when mortality increases: the influence of maturation versus reproduction regulation. *The American Naturalist* 170, E59-E76. (doi: 10.1086/520119)
7. Zipkin EF. et al. 2009. When can efforts to control nuisance and invasive species backfire? *Ecol. Appl.* 19(6), 1585-1595. (doi: 10.1890/08-1467.1)
8. Jocelyn, K. 2003. Hormesis. Sipping from a poisoned chalice. *Science* 302, 376-379. (doi:

-
- 10.1126/science.302.5644.376)
9. Calabrese EJ, Baldwin LA. 2002. Defining hormesis. *Hum. Exp. Toxicol.* 21, 91-97. (doi: 10.1191/0960327102ht217oa)
 10. Calabrese EJ, Mattson MP. 2011. Hormesis provides a generalized quantitative estimate of biological plasticity. *J. Cell Commun. Signal.* 5, 25-38. (doi: 10.1007/s12079-011-0119-1)
 11. Calabrese EJ, Blain RB. 2011. The hormesis database: the occurrence of hormetic dose responses in the toxicological literature. *Regul. Toxicol. Pharm.* 61, 73-81. (doi: 10.1016/j.yrtph.2011.06.003)
 12. Pearce OMT. et al. 2014. Inverse hormesis of cancer growth mediated by narrow ranges of tumor-directed antibodies. *Proc. Natl. Acad. Sci. USA* 111, 5998-6003. (doi: 10.1073/pnas.1209067111)
 13. Tang S. et al. 2019. A general model of hormesis in biological systems and its application to pest management. *J. R. Soc. Interface* 16, 20190468. (doi: 10.1098/rsif.2019.0468)
 14. Abrams PA, Matsuda H. 2005. The effect of adaptive change in the prey on the dynamics of an exploited predator population. *Can. J. Fish. Aquat. Sci.* 62, 758-766. (doi: 10.1139/F05-051)
 15. Sieber M, Hilker FM. 2012. The hydra effect in predator-prey models. *J. Math. Biol.* 64, 341-360. (doi: 10.1007/s00285-011-0416-6)
 16. Cortez MH, Abrams PA. 2016. Hydra effects in stable communities and their implications for system dynamics. *Ecology* 97, 1135-1145. (doi: 10.1890/15-0648.1)
 17. Abrams PA. 2009. When does greater mortality increase population size? The long history and diverse mechanisms underlying the hydra effect. *Ecology Letters* 12(5), 462-474. (doi:10.1111/j.1461-0248.2009.01282.x)
 18. Jaramillo JM, Ma J, van den Driessche P, Yakubu AA. 2022. Disease-induced hydra effect with overcompensatory recruitment. *Bull. Math. Biol.* 84, 17. (doi: 10.1007/s11538-021-00975-4)
 19. Strube LF, Elgart S, Childs LM. 2024. Infection-induced increases to population size during cycles in a discrete-time epidemic model. *J. Math. Biol.* 88, 60. (doi:10.1007/s00285-024-02074-z)
 20. Bai D, Wu J, Zheng B, Yu J. 2024. Hydra effect and global dynamics of predation with strong Allee effect in prey and intraspecific competition in predator. *J. Differ. Equations* 384, 120-164. (doi: 10.1016/j.jde.2023.11.017)
 21. Brain P, Cousens R. 1989. An equation to describe dose responses where there is stimulation of growth at low doses. *Weed Research* 29, 93-96. (doi: 10.1111/j.1365-3180.1989.tb00845.x)
 22. Nweke CO, Ogbonna CJ. 2017. Statistical models for biphasic dose-response relationships (hormesis) in toxicological studies. *Ecotoxicol. Environ. Contam.* 12, 39-55. (doi: 10.5132/eec.2017.01.06)
 23. Cedergreen N, Ritz C, Streibig JC. 2005. Improved empirical model describing hormesis. *Environ. Toxicol. Chem.* 24, 3166-3172. (doi: 10.1897/05-014r.1)
 24. Clark CW. 1990. *Mathematical Bioeconomics: The Optimal Management of Renewable Resources* (Second ed). John Wiley and Sons, Inc, New York.
 25. McGranahan N, Swanton C. 2017. Clonal heterogeneity and tumor evolution: past, present, and the future. *Cell* 168, 613-628. (doi: 10.1016/j.cell.2017.01.018)
 26. Calabrese EJ. 2005. Paradigm lost, paradigm found: the re-emergence of hormesis as a fundamental dose response model in the toxicological sciences. *Environ. Poll.* 138(3), 378-411. (doi:10.1016/j.envpol.2004.10.001)
 27. Xue N. et al. 2017. Chlorogenic acid inhibits glioblastoma growth through repolarizing macrophage from M2 to M1 phenotype. *Scientific reports* 7(1), 1-11. (doi:10.1038/srep39011)
 28. Xu X. et al. 2015. Concentration-dependent diversification effects of free cholesterol loading on macrophage viability and polarization. *Cell. Phy. Bioche.* 37(2), 419-431. (doi:10.1159/000430365)

29. Wang C. et al. 2020. DT-13 induced apoptosis and promoted differentiation of acute myeloid leukemia cells by activating AMPK-KLF2 pathway. *Pharmacol. Res.* 158, 104864. (doi:10.1016/j.phrs.2020.104864)
30. He L, Marneros AG. 2014. Doxycycline inhibits polarization of macrophages to the proangiogenic M2-type and subsequent neovascularization. *J. Biol. Chem.* 289(12), 8019-8028. (doi:10.1074/jbc.M113.535765)
31. Calabrese EJ. 2008. Hormesis: why it is important to toxicology and toxicologists. *Environ. Toxicol. Chem.* 27(7), 1451-1474. (doi:10.1897/07-541)
32. Beckon WN. et al. 2008. A general approach to modeling biphasic relationships. *Environ. Sci. Tech.* 42(4), 1308-1314. (doi:10.1021/es071148m)
33. Dang ZC, Lowik CW. 2004. The balance between concurrent activation of ERs and PPARs determines daidzein-induced osteogenesis and adipogenesis. *J. Bone Min. Res.* 19(5), 853-861. (doi:10.1359/JBMR.040120)
34. Elisia I. et al. 2016. DMSO represses inflammatory cytokine production from human blood cells and reduces autoimmune arthritis. *PloS One* 11(3), e0152538. (doi:10.1371/journal.pone.0152538)
35. Niethammer A. 1927. The stimulation effect of toxins on fungus and the Arndt-Schulz axion. *Biochemische Zeitschrift* 184, 370-382.
36. Morf M, Kailath T. 1975. Square-root algorithms for least-squares estimation. *IEEE Trans. Autom.* 20, 487-497. (doi:10.1109/TAC.1975.1100994)
37. Chai T, Draxler RR. 2014. Root mean square error (RMSE) or mean absolute error (MAE). *Geosci. Model Dev. Discuss.* 7, 1525-1534. (doi:10.5194/gmdd-7-1525-2014)
38. Liu J. et al. 2019. Remaining useful life prediction of PEMFC based on long short-term memory recurrent neural networks. *Int. J. Hydrogen Energy* 44, 5470-5480. (doi:10.1016/j.ijhydene.2018.10.042)
39. Tang et al. 2023. Hormetic and synergistic effects of cancer treatments revealed by modelling combinations of radio-or chemotherapy with immunotherapy. *BMC Cancer* 23,1040. (doi:10.1186/s12885-023-11542-6)
40. Dick JTA. et al. 2010. Parasitism may enhance rather than reduce the predatory impact of an invader. *Biol. Lett.* 6, 636-638. (doi: 10.1098/rsbl.2010.0171)
41. Ponton F. et al. 2011. Hosts use altered macronutrient intake to circumvent parasite-induced reduction in fecundity. *Inter. J. Parasit.* 41 (2011), 43-50.(doi: 10.1016/j.ijpara.2010.06.007)
42. Penczykowski RM et al. 2021. Virulent disease epidemics can increase host density by depressing foraging of hosts. *The American Naturalist* 199,75-90. (doi: 10.1086/717175)
43. Pfenning-Butterworth AC, Rachel EV, Jessica LH. 2023. Natural variation in host feeding behaviors impacts host disease and pathogen transmission potential. *Ecol. Evol.* 13, e9865. (doi: 10.1002/ece3.9865)

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Data Accessibility The data used are all from published sources which have been cited in Table 1. MATLAB codes for data fitting and figure production and for the logistic, Ricker and SIR Ricker models have been uploaded to <https://doi.org/10.6084/m9.figshare.28655825>.

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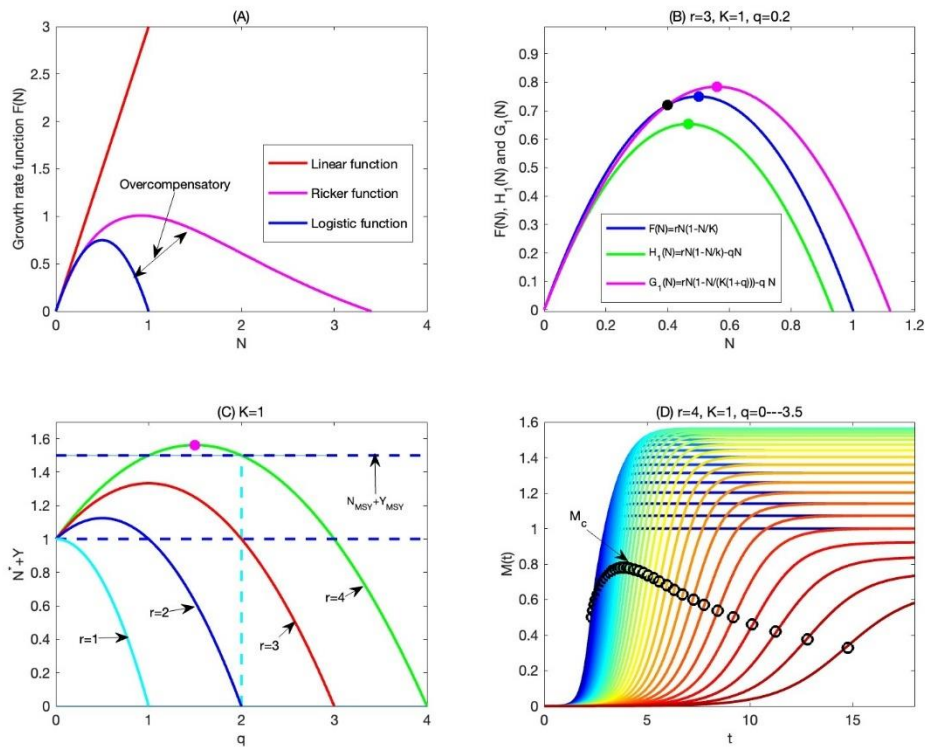


Fig. 1 | Complete logistic overcompensation model (COM-logistic): hydra and hormetic effects. (A) Three growth rate functions $F(N)$: Linear function rN , overcompensatory recruitment Ricker function $rNe^{-bN} - \mu N$ and logistic function $rN(1 - \frac{N}{K})$. (B) Comparison of three growth rate functions with maximal values marked to reveal the underlying mechanism of overcompensation, where the black dot denotes the intersection of curves $F(N)$ and $G_1(N)$; (C) Hydra and hormetic effects for the model with Logistic growth rate function and hormetic zone $q \in (0, r - 1)$, where the pink dot represents the maximal response of the hormetic effect which can be greater than the total population size $N_{MSY} + Y_{MSY}$ at the maximum sustained yield, and the different colours related to different growth rates r as marked in each curve; (D) Simulations of the COM-logistic with carrying capacity $K = 1$, indicating a long-term high-speed growth pattern. The black open circles represent the inflection points (i.e. M_c) of each growth curve corresponding to different q values, ranging from 0 to 3.5, with colours varying from blue to red, at which the population exhibits the fastest growth.

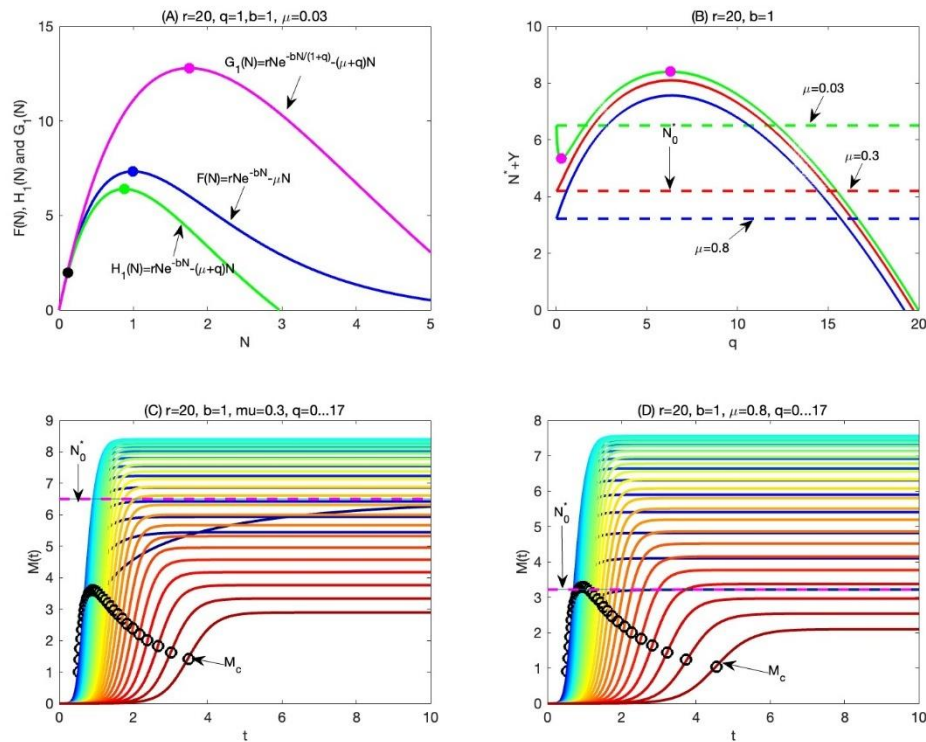


Fig. 2 | Complete Ricker overcompensation model (COM-Ricker): hydra and hormetic effects. (A) Comparison of three growth functions to reveal the underlying mechanism of overcompensation, where the black dot denotes the intersection of curves $F(N)$ and $G_1(N)$; (B) Hydra and hormetic effects for the model with the Ricker growth function for different values of μ : U-shaped and inverted U-shaped hormetic curves under various parameter sets, where the two pink dots on the green curve indicate the minimal and maximal responses of the hormetic effects, relative to the baseline equilibrium level N_0^* (dashed line), respectively; (C-D) Simulations of the COM-Ricker with variations in q and μ , where N_0^* is the base line equilibrium level. The black open circles represent the inflection points (i.e. M_c) of each growth curve corresponding to different q values, ranging from 0 to 17, with colours varying from blue to red, at which the population exhibits the fastest growth.

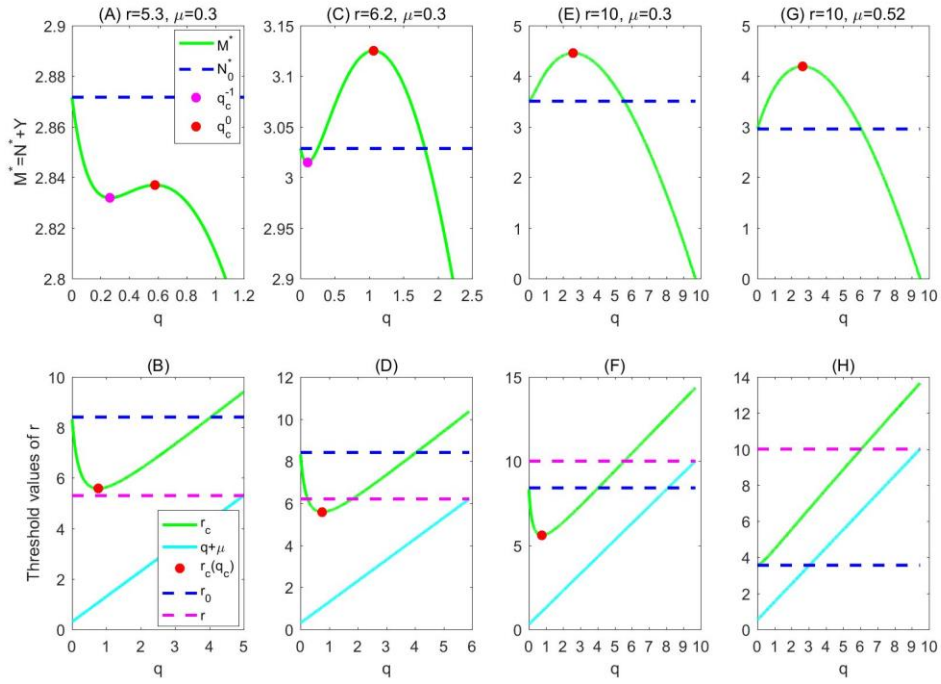


Fig. 3 | Threshold values of the intrinsic growth rate r with respect to the key parameters μ and q , revealing the occurrence of hormetic and hydra effects for the COM-Ricker. Here q_c^i for $i = 0, -1$ are given in (10). (A-B) $r_1 \leq r < \min\{r_c(q_c), r_0\} = r_c(q_c)$ with $\mu < 1/2$; (C-D) $r_c(q_c) = \max\{r_1, r_c(q_c)\} \leq r < r_0$ with $\mu < 1/2$; (E-F) $\max\{r_1, r_0\} \leq r$ with $\mu < 1/2$; (G-H) $r_1 \leq r_0 < r$ with $\mu \geq 1/2$. For clarity, the coordinates of (A) and (C) are locally enlarged graphics. The parameter b is fixed as 1 for all subplots and $q \in (0, r - \mu)$. Note that all critical values and inequalities are given in Theorem SI.4 of ESM.

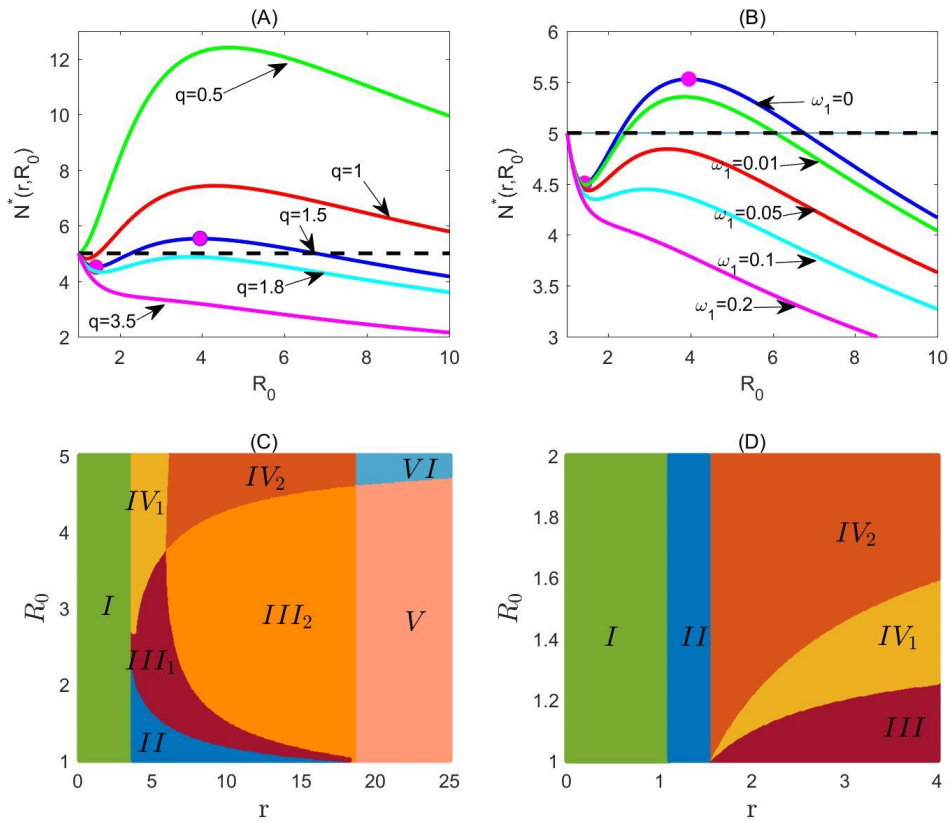


Fig. 4 | Infectious disease partial overcompensation model: hydra and hormetic effects. (A) The effects of disease infectivity R_0 and disease related death rate q on the population size $N^*(r, R_0)$, where $\omega_0 = 0, \omega_1 = 0$ and the other parameters are fixed as $r = 20, b = 1, S_D = 5$ with $R_0 \in [1, 10]$, and the pink dots represent R_0^m and R_0^M , respectively; (B) The impact of the ability of infected individuals to compete for resources relative to susceptible individuals on the total population $N^*(r, R_0)$, where $\omega_0 = 0$ and the other parameters are fixed as $r = 20, b = 1, q = 1.5, S_D = 5$ with $R_0 \in [1, 10]$; (C-D) The effects of disease infectivity R_0 and intrinsic growth rate r on the occurrence of hormetic and hydra effects, where $b = 1, S_D = 5, q = 0.5$ satisfying $bS_D > 2$ in (C) and $b = 1, S_D = 1.2, q = 0.15$ satisfying $1 \leq bS_D < 2$ in (D). Region I with $r < qe^2$ and the others with $r \geq qe^2$ in (C-D). In (C): $\frac{dN^*(R_0)}{dR_0} < 0$ in II, IV₁, IV₂ and VI, $\frac{dN^*(R_0)}{dR_0} > 0$ in III₁, III₂ and V; $N^* < S_D$ in II, III₁ and IV₁, $N^* > S_D$ in III₂ and IV₂. In (D): $\frac{dN^*(R_0)}{dR_0} < 0$ in II, IV₁ and IV₂, $\frac{dN^*(R_0)}{dR_0} > 0$ in III; $N^* < S_D$ in II and IV₁, $N^* > S_D$ in III and IV₁.

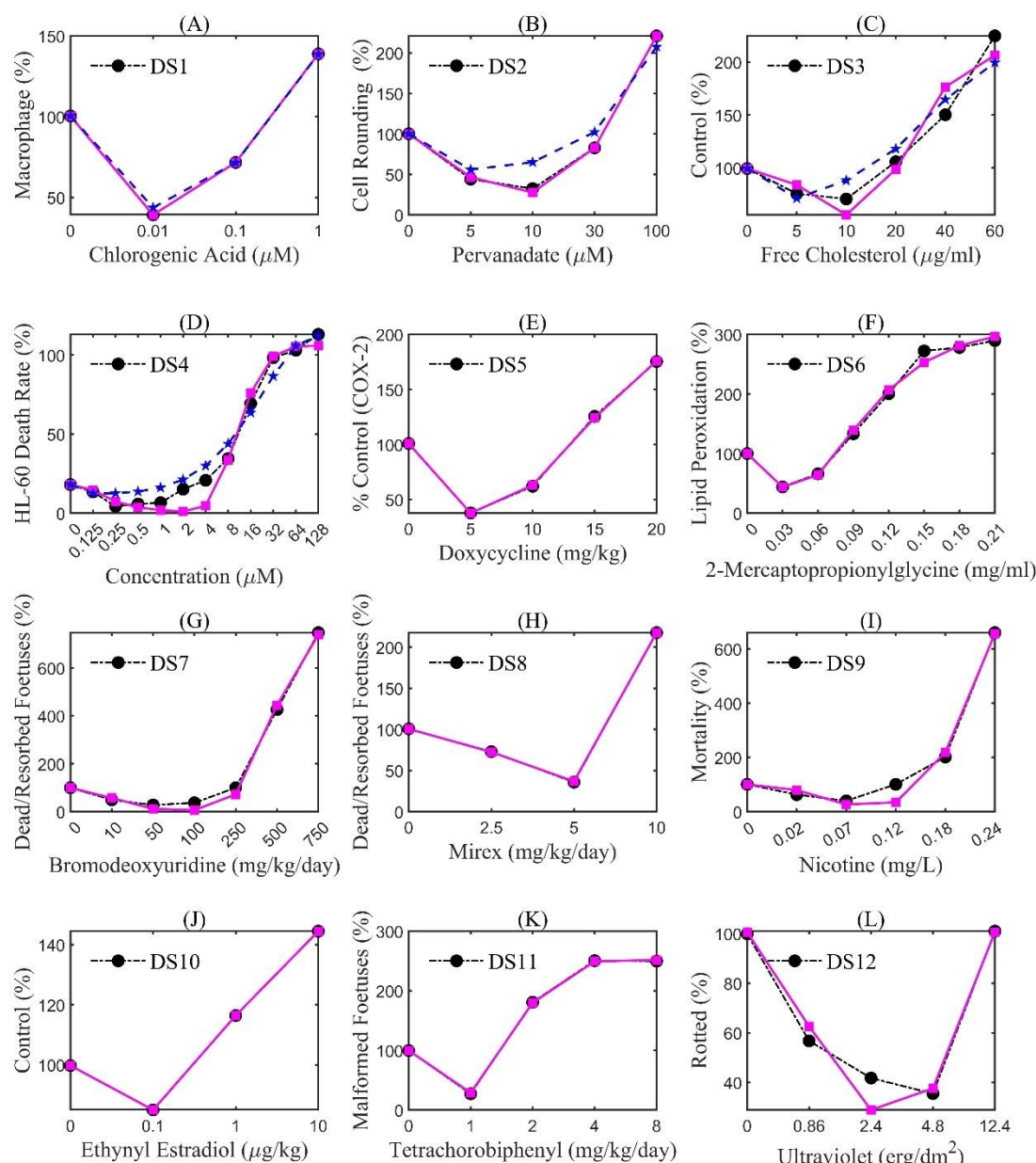


Fig. 5 | U-shaped data fitting with Ricker-DRC and DI-DRC. (A--L): The fitting results correspond to datasets DS1--DS12, respectively. In each subplot, the black dots represent the experimental data, the magenta squares represent the fitted DI-DRC, and the blue stars denote the fitted Ricker-DRC. Note that DS1--DS4 (A--D) were used in comparisons to determine which model fits better. Among them, in subgraphs (E), (H), (J) and (K), due to the excellent fitting effect, almost all of the black real data points are obscured and cannot be seen. It should be noted that the logistic-DRC struggles to effectively fit U-shaped dose-response curves and is not a suitable candidate for such fittings.

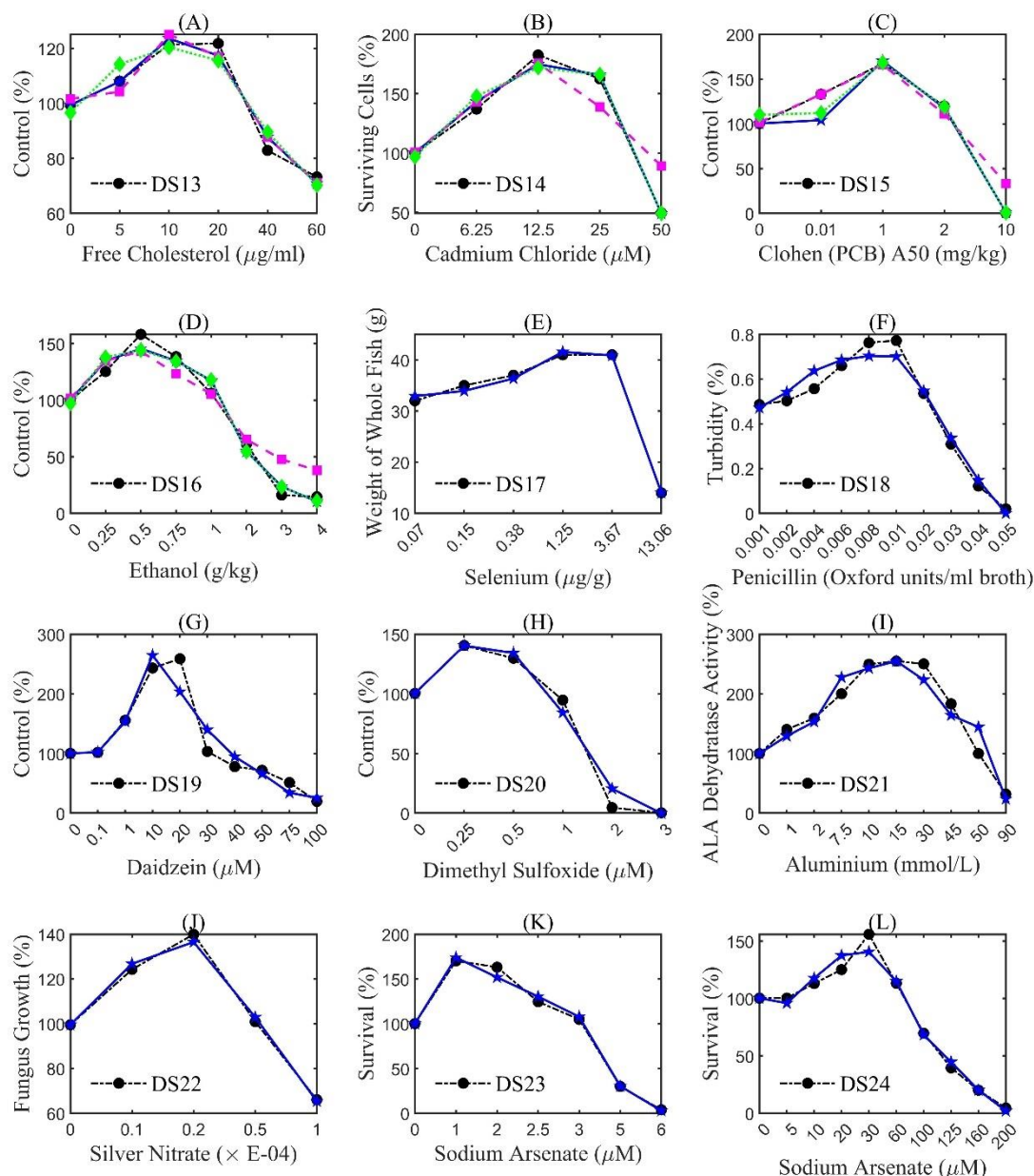


Fig. 6 | Inverted U-shaped data fitting with DI-DRC, Ricker-DRC and logistic-DRC. (A--L): The fitting results correspond to datasets DS13--DS24, respectively. In each subplot, the black dots represent the experimental data, the blue stars denote the fitted Ricker-DRC, the magenta squares represent the fitted DI-DRC, and the green diamonds correspond to the fitted logistic-DRC. Note that DS13--DS16 (A--D) were used in comparisons to determine which model fits better.

Table 1: Summary of U-shaped (DS1-DS12) and inverted U-shaped (DS13-DS24) hormetic data sets.

Data	Agonist (units) / Response (units)	System description	Reference
DS1	Chlorogenic Acid (μM) Macrophage (%)	Effect of chlorogenic acid on macrophage polarization marker expression induced by interleukin-4	27
DS2	Pervanadate (μM) Cell Rounding (%)	Effect of pervanadate on the cell rounding in trigeminal neurinoma cells	26
DS3	Free Cholesterol ($\mu g/ml$) Control (%)	Effect of cholesterol on macrophage polarization	28
DS4	Concentration (μM) HL-60 Death Rate (%)	Effect of Chinese drugs on cancer cells	29
DS5	Doxycycline (mg/kg) Control (%)	Effect of doxycycline on COX-2 activity in human macrophages	30
DS6	2-Mercaptopropionylglycine (mg/ml) Lipid Peroxidation (%)	Effect of 2-Mercaptopropionylglycine on lipid peroxidation of liver cells from Swiss mice	26
DS7	Bromodeoxyuridine (mg/kg/day) Dead/Resorbed Fetuses/L (%)	Effect of bromodeoxyuridine on the number of dead or resorbed per litter in CD-1 mice	26
DS8	Mirex (mg/kg/day) Dead/Resorbed Fetuses/L (%)	Effect of mirex on the number of dead or resorbed per litter in CD-1 mice	26
DS9	Nicotine (mg/L) Mortality (%)	Effect of nicotine on the percent mortality of daphnia	26
DS10	Ethinyl Estradiol ($\mu g/kg$) Control (%)	Select genes with cDNA microarray analysis	26
DS11	Tetrachlorobiphenyl (mg/kg/day) Malformed Fetuses/Litter (%)	Effect of PCB on the incidence of malformed fetuses of the CD-1 mouse	26
DS12	Ultraviolet (erg/dm^2) Rotted (%)	Effect of ultraviolet radiation on the incidence of rot on sweet potatoes	26
DS13	Free Cholesterol (g/ml) Control (%)	Effect of cholesterol on macrophage polarization	28
DS14	Cadmium Chloride (μM) Surviving Cells (%)	Effect of cadmium chloride on the survival of Chinese hamster ovary cell line CHO-Cd r	26
DS15	Clohen (PCB) A50 (mg/kg) Control (%)	Effect on number of live kits per mated female	26
DS16	Ethanol (g/kg) Control (%)	Effect of acute ethanol on overall social activity of adolescent rats tested on postnatal day 30	31
DS17	Selenium Concentration ($\mu g/g$) Weight of Whole Fish (g)	Average weights of rainbow trout juveniles after 20 weeks exposure to diets spiked with sodium selenate	32
DS18	Penicillin (Oxford units/ml broth) Turbidity (%)	Effect of penicillin on the growth of Staphylococcus	32
DS19	Daidzein (μM) Control (%)	Effect of daidzein on cell alkaline phosphatase activity in osteoprogenitor KS483 cells	33

DS20	Dimethyl Sulfoxide (μM)	Effect of dimethyl Sulfoxide on the IL-6 secreted in a whole human blood assay	34
	Control (%)		
DS21	Aluminum (mmol/L)	Effect of aluminum on ALA dehydratase activity in human erythrocytes	26
	ALA Dehydratase Activity (%)		
DS22	Silver Nitrate Concentration (%)	Effect of silver nitrate on the growth of fungus	35
	Fungus Growth (%)		
DS23	Sodium Arsenate (μM)	Effect of sodium arsenate on the survival of a Syrian hamster embryonic cell line LSH/ss LAK	26
	Survival (%)		
DS24	Sodium Arsenate (μM)	Effect of sodium arsenate on the survival of a Syrian hamster embryonic cell line LSH/ss LAK	26
	Survival (%)		

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