Microbial community response to death-inducing stress in the thermodynamic limit

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Death-inducing stress such as antibiotics can reduce microbial community richness with negative consequences to its host or environment. I used the cavity method to derive self-consistency equations for community richness in a consumer-resource model modified to study the effect of death-inducing stress in the thermodynamic limit of many species and resources. I showed that community richness during stress increases with the correlation between a species' susceptibility to stress and its metabolic rate. Additionally, when the correlation is sufficiently large, richness can change non-monotonically with the stress magnitude.

Microbial communities in the human gut perform useful functions for their host [1]. However, when someone takes oral antibiotics or other drugs, these can target bacterial species in their gut [2], which can reduce community richness [3], leaving the host more susceptible to *Clostridium difficile* infection [4]. Similarly, stress such as pollutants can reduce the richness of soil microbiomes [5], which are important for plant health [6]. Predicting microbial community richness during stress could reduce unintended consequences of antibiotic treatment on the gut microbiome or of pollution in soil microbiomes.

Stress such as antibiotics can harm bacteria by reducing their consumption rate (bacteriostatic antibiotics) or by increasing their death rate (bactericidal antibiotics) [7]. In some cases, a species' susceptibility to antibiotics is positively correlated with its metabolic rate (resource consumption rate), since a species with a faster metabolic rate could "consume" an antibiotic faster and thus be more harmed by it [8].

Previous work suggests the interplay between resource consumption rates and susceptibility to stress are important for predicting community response to stress [9], but these studies primarily focused on communities with fewer than ten species and resources. However, microbial communities in nature are comprised of hundreds of bacterial species and chemical resources [10]. Previous work studying large communities has largely ignored correlations between metabolic rate and susceptibility to stress in a way that allows for the correlation to be tuned and explicitly investigated [11–14]. Here, I study the effect of varying the correlation between a species' metabolic rate and its susceptibility to a death-inducing stress (like bactericidal antibiotics) in large communities, which I believe is not in the literature.

The abundances of bacterial species and resources in microbial communities are well modeled by the steady state behavior of a system of non-linear ODE's called generalized consumer-resource models (GCRMs) [15–17]. GCRMs assume the abundance of species $i \in \{1, 2, ..., S\}$ N_i and the abundance of resource $\alpha \in \{1, 2, ..., M\}$ R_α are governed by,

$$\frac{dN_i}{dt} = N_i \left(\sum_{\alpha=1}^{M} c_{i\alpha} R_\alpha - m_i \right) \tag{1}$$

$$\frac{dR_\alpha}{dt} = h_\alpha(R_\alpha) - R_\alpha \sum_{i=1}^{S} N_i e_{i\alpha}, \tag{2}$$

where $c_{i\alpha}$ is the rate at which species i consumes resource α, m_i is the death rate of species i, $e_{i\alpha}$ is the extent to which species i reduces the abundance of resource α (the impact), and $h_\alpha(R_\alpha)$ is a resource-dependent function that often takes one of two forms:

$$h_\alpha(R_\alpha) = R_\alpha(K_\alpha - R_\alpha) \tag{3a}$$

$$h_\alpha(R_\alpha) = s_\alpha - R_\alpha \delta. \tag{3b}$$

Equation (3a) models a self-renewing resource with carrying capacity K_α, and (3b) models a resource supplied to the system at rate s_α and diluted at rate δ [13].

Generally, the maximum number of stably coexisting species S_{max} is equal to the number of resources M (the competitive exclusion principle) [18]. However, when the parameters ($c_{i\alpha}$, m_i, etc) are constrained, S_{max} might not be M. For example, with symmetric species-resource interactions ($e_{i\alpha} = c_{i\alpha}$), externally supplied resources (3b), and a metabolic constraint ($\sum_{\alpha=1}^{M} c_{i\alpha} = E$ for all species i), an infinite number of species can coexist with a finite number of resources ($S_{max} = \infty$) [17].

When the parameters are constrained to be drawn from certain probability distributions in the thermodynamic limit ($S, M \gg 1$ with S/M fixed), S_{max} depends on whether the resources are self-renewing or externally supplied [11, 13]. Namely, $S_{max} = M/2$ for externally supplied resources [11], while $S_{max} = M$ for self-renewing resources [11, 13]. However, with self-renewing resources and asymmetric species-resource interactions ($e_{i\alpha} \neq c_{i\alpha}$) a chaotic phase can emerge if the extent of asymmetry is sufficiently large [14], which could reduce S_{max} if a species drops below a realistic extinction threshold due to the chaotic dynamics. These results were derived by applying the cavity method to analyze GCRMs [11, 13, 14].

The cavity method was initially developed for solving an Ising model in which all spins are coupled via i.i.d. Gaussian interactions (Sherrington–Kirkpatrick model) [19–21]. The cavity procedure has been applied to mathematical models in many contexts, including ecology [11–14, 22, 23]. The steps were outlined in [11] as follows. Add one species and one resource to a community with many species and resources, then determine how that perturbation updates the growth rate equations with new effective parameters; then use a linear response approximation–that the species and resource abundances change linearly in response to the new effective parameters–which is valid in the thermodynamic limit. This allows one to derive self-consistency equations for the cavity species abundance distribution which is the same as that for any species in the community because the system is self-averaging (and similarly for the resource abundances). The self-averaging assumption, that the quenched distribution of the cavity species abundance equals the distribution of species abundances in a single realization of random parameters, is therefore crucial to this approach [23].

Here, I apply the cavity method procedure like in [11, 13, 14] to study the effect of stress that modifies the death rates m_i. I consider symmetric species-resource interactions ($e_{i\alpha} = c_{i\alpha}$) and self-renewing resources (3a). Like [11], I assume $c_{i\alpha}$, m_i and K_α are random variables drawn from the distributions defined by the representations:

$$K_\alpha = K + \sigma_K \delta K_\alpha, \tag{4a}$$

$$c_{i\alpha} = \frac{\mu_c}{M} + \frac{\sigma_c}{\sqrt{M}} d_{i\alpha} \tag{4b}$$

$$m_i = m + \sigma_m \delta m_i + s\xi_i, \tag{4c}$$

$$\xi_i = \xi + \rho \left(\sum_{\alpha=1}^{M} \frac{d_{i\alpha}}{\sqrt{M}} \right) + \sqrt{1-\rho^2} X_i \tag{4d}$$

where $\delta K_\alpha, d_{i\alpha}, \delta m_i, X_i$ are independent normal random variables with zero mean and unit variance, and $(K, \sigma_K, \mu_c, \sigma_c, m, \sigma_m, \xi, \rho)$ are fixed parameters, so the term in parentheses in (4d) is a random variable with zero mean and unit variance. Therefore, ξ_i is a random variable with mean ξ and unit variance. The term $s\xi_i$ in (4c) is the magnitude of stress s (e.g. antibiotic concentration) times the linear response of species i's death rate to the stress ξ_i and is new relative to [11, 13, 14]. In the absence of stress ($s = 0$), this is like previous work [11]. In the presence of stress ($s > 0$), the correlation ρ between species i's linear stress response ξ_i and its total consumption rate $\sum_\alpha c_{i\alpha}$ ("metabolic rate") is important. Mathematically, $\rho = \mathrm{corr}(\sum_\alpha c_{i\alpha}, \xi_i)$ since $\mathrm{Cov}(\sum_\alpha c_{i\alpha}, \xi_i) = \frac{\sigma_c \rho}{M} \mathrm{Cov}(\sum_\alpha d_{i\alpha}, \sum_{\alpha'} d_{i\alpha'}) = \sigma_c \rho$. When $\rho > 0$, the stress targets species with faster metabolism more, on average.

The stress increases the variance of the death rates from σ_m^2 to $\mathrm{Var}(m_i) = \sigma_m^2 + s^2$ regardless of ρ. The correlation between species i's death rate m_i and its metabolic rate is $\mathrm{corr}(m_i, \sum_\alpha c_{i\alpha}) = \frac{s\rho}{\sqrt{\sigma_m^2 + s^2}}$ since $\mathrm{Cov}(m_i, \sum_\alpha c_{i\alpha}) = \frac{\sigma_c s \rho}{M} \sum_{\alpha,\alpha'} \mathrm{Cov}(d_{i\alpha'}, d_{i\alpha}) = \sigma_c s\rho$.

Consider S species and M resources at steady state then consider the addition of a new species and new resource indexed by $i = 0$, $\alpha = 0$, respectively (cavity species and cavity resource). By inspecting the growth rate equations (1) and (2), the addition of the cavity species and resource effectively modifies the parameters $m_i \to m_i + \Delta m_i$ and $K_\alpha \to K_\alpha + \Delta K_\alpha$, with $\Delta m_i \equiv -\frac{\sigma_c}{\sqrt{M}} d_{i0} \bar{R}_0$ and $\Delta K_\alpha \equiv -\frac{\sigma_c}{\sqrt{M}} d_{0\alpha} \bar{N}_0$, where bar represents the variable's steady state value. Then the linear response approximation is,

$$\bar{R}_\alpha = \bar{R}_{\alpha\backslash 0} + \sum_{\beta=1}^{M} \Delta K_\beta \frac{\partial \bar{R}_\alpha}{\partial K_\beta} + \sum_{j=1}^{S} \Delta m_j \frac{\partial \bar{R}_\alpha}{\partial m_j} \tag{5}$$

where $\bar{R}_{\alpha\backslash 0}$ is the steady state abundance of species α before the cavity perturbation. And there is a similar equation for the species abundances.

Substituting (5) into (1) with $i = 0$, the equation for the steady state cavity species abundance $\bar{N}_0$ becomes,

$$\begin{aligned} 0 = \bar{N}_0 \Big[& \mu_c \langle R \rangle - m + \frac{\sigma_c}{\sqrt{M}} \sum_{\alpha=1}^{M} d_{0\alpha}\, \bar{R}_{\alpha\backslash 0} \\ & + \frac{\sigma_c}{\sqrt{M}} \sum_{\alpha,\beta=1}^{M} d_{0\alpha} \Big(\frac{\partial \bar{R}_{\alpha\backslash 0}}{\partial K_\beta} \Big) \Delta K_\beta \\ & + \frac{\sigma_c}{\sqrt{M}} \sum_{\alpha=1}^{M} \sum_{j=1}^{S} d_{0\alpha} \Big(\frac{\partial \bar{R}_{\alpha\backslash 0}}{\partial m_j} \Big) \Delta m_j \\ & + \frac{\sigma_c}{\sqrt{M}} d_{00}\, \bar{R}_0 - \sigma_m\, \delta m'_0 \Big], \end{aligned} \tag{6}$$

with $\langle R \rangle \equiv \frac{1}{M} \sum_{\alpha=1}^{M} \bar{R}_{\alpha\backslash 0}$ and $\delta m'_i \equiv \delta m_i + s\xi_i/\sigma_m$. I next take the expectation of both sides, then take the variance of both sides and throw away any terms with both zero mean and variance that is order $M^{-1/2}$ [14].

The expectation of the third term is zero since $d_{0\alpha}$ and $\bar{R}_{\alpha\backslash 0}$ are independent and $\langle d_{0\alpha} \rangle = 0$. The expectation of the fourth term is $-\bar{N}_0 \sigma_c^2 \chi$ with $\chi \equiv \frac{1}{M} \sum_{\alpha=1}^{M} \frac{\partial \bar{R}_{\alpha\backslash 0}}{\partial K_\alpha}$ since $\frac{\partial \bar{R}_{\alpha\backslash 0}}{\partial K_\alpha}$ and $d_{0\alpha}$ are independent, and I assume $\bar{N}_0$ can be pulled out of the expectation, then we use linearity of expectation and $\langle d_{0\alpha} d_{0\beta} \rangle = \delta_{i,0} \delta_{\alpha\beta}$. The expectation of the fifth term is zero since $\langle d_{0\alpha} d_{j0} \rangle = 0$ when $\alpha, j > 0$. The expectation of the sixth term is zero since we assume d_{00} and $\bar{R}_0$ are approximately independent since $M \gg 1$. The expectation of the final term $-\sigma_m \delta m'_0$ is $-s\xi$ by construction.

The variance of the fourth term and fifth term is order M^{-1} [14]. The variance of the sixth term is order $M^{-1/2}$, and I assume the variance of the first term is order M^{-1} [14]. Finally, I calculate,

$$\mathrm{Cov} \left(\frac{\sigma_c}{\sqrt{M}} \sum_{\alpha=1}^{M} d_{0\alpha} \bar{R}_{\alpha\backslash 0}, -\sigma_m \delta m'_0 \right) = -\sigma_c s \rho \langle R \rangle, \tag{7}$$

which was zero in previous work that used $\delta m_0' = \delta m_0$ [14]. So the variance of the expression in the brackets in (6) is approximately,

$$\sigma_g^2 = \sigma_c^2 q_R + \sigma_m^2 + s^2 - 2\sigma_c s \rho \langle R \rangle + O(M^{-1/2}), \quad (8)$$

with $q_R \equiv \frac{1}{M}\sum_{\alpha=1}^{M} \bar{R}_{\alpha\setminus 0}^2$, where (8) differs from previous work [14] because of the non-zero covariance (7). So defining the random variable $Z_N \sim N(0,1)$, the steady state abundance of the cavity species obeys,

$$0 = \bar{N}_0 \left[\mu_c \langle R \rangle - m - \bar{N}_0 \sigma_c^2 \chi - s\xi + \sigma_g Z_N\right] \quad (9)$$

which implies,

$$\bar{N}_0 = \max\left\{0, \frac{\mu_c \langle R \rangle - m - s\xi + \sigma_g Z_N}{\sigma_c^2 \chi}\right\}. \quad (10)$$

This is like the result in [14] except for the altered variance σ_g^2 which depends on the stress magnitude s and the ρ, and a correlation-independent term $s\xi$. I similarly calculate the steady state equation for the cavity resource abundance which is identical to previous results [14] so I quote the result here:

$$\bar{R}_0 = \max\left\{0, \frac{K - \mu_c \gamma^{-1} \langle N \rangle + \sigma_\kappa Z_R}{1 - \sigma_c^2 \gamma^{-1} \nu}\right\}, \quad (11)$$

where $\gamma \equiv M/S$, $\langle N \rangle \equiv \frac{1}{S}\sum_{i=1}^{S} \bar{N}_i$, $\sigma_\kappa^2 \equiv \sigma_K^2 + \gamma^{-1}\sigma_c^2 q_N$, $q_N \equiv \frac{1}{S}\sum_{i=1}^{S} \bar{N}_{i\setminus 0}^2$, $\nu \equiv \frac{1}{S}\sum_{i=1}^{S} \frac{\partial \bar{N}_{i\setminus 0}}{\partial m_i}$, and $Z_R \sim N(0,1)$. However, (10) shows $\bar{N}_0$ depends on $\chi, \langle R \rangle, q_R$, and (11) shows $\bar{R}_0$ depends on $\nu, \langle N \rangle, q_N$, so one solves for these unknowns by deriving self-consistency equations. Due to self-averaging [14],

$$\nu = \left\langle \frac{\partial \bar{N}_0}{\partial m} \right\rangle, \qquad \chi = \left\langle \frac{\partial \bar{R}_0}{\partial K} \right\rangle \quad (12)$$

$$\langle N \rangle = \langle \bar{N}_0 \rangle, \qquad \langle R \rangle = \langle \bar{R}_0 \rangle \quad (13)$$

$$q_N \approx \langle \bar{N}_0^2 \rangle = \langle N^2 \rangle, \qquad q_R \approx \langle \bar{R}_0^2 \rangle = \langle R^2 \rangle, \quad (14)$$

where the approximations in (14) use the fact that the perturbation is order $M^{-1/2}$ [14]. Taking the derivatives of (10), (11) with respect to m, K, respectively then taking the expectation value,

$$\nu = \frac{-\phi_N}{\sigma_c^2 \chi}, \qquad \chi = \frac{\phi_R}{1 - \sigma_c^2 \gamma^{-1} \nu}, \quad (15)$$

where, ϕ_N and ϕ_R are the expected number of species and resources with positive abundances at steady state. Using self-averaging [14], these are given by,

$$\phi_N = \langle \Theta(\bar{N}_0) \rangle = \Phi\left(\frac{\mu_c \langle R \rangle - m - s\xi}{\sigma_g}\right) \quad (16)$$

$$\phi_R = \langle \Theta(\bar{R}_0) \rangle = \Phi\left(\frac{K - \mu_c \gamma^{-1} \langle N \rangle}{\sigma_\kappa}\right), \quad (17)$$

where $\Theta(x)$ is the Heavyside step function and $\Phi(x)$ is the PDF of a standard normal random variable. The remaining four self-consistency equations are for the first and second moments of the species abundances and resource abundances. Equations (13), (14) and (10) imply for $j \in \{1,2\}$,

$$\langle N^j \rangle = \left\langle \mathrm{ReLU}\left(\frac{\mu_c \langle R \rangle - m - s\xi + \sigma_g Z_N}{\sigma_c^2 \chi}\right)^j \right\rangle, \quad (18)$$

and similarly using equations (13), (14), and (11),

$$\langle R^j \rangle = \left\langle \mathrm{ReLU}\left(\frac{K - \mu_c \gamma^{-1} \langle N \rangle + \sigma_\kappa Z_R}{1 - \sigma_c^2 \gamma^{-1} \nu}\right)^j \right\rangle. \quad (19)$$

These are the first and second moments of ReLU of Gaussian random variables, which can be written in terms of simple functions [14]. In summary, there are eight unknowns, $\phi_N, \phi_R, \chi, \nu, \langle N \rangle, \langle R \rangle, \langle N^2 \rangle, \langle R^2 \rangle$, and eight equations (15–19). Here, (16) and (18) are altered from previous work [14] because σ_g^2 has two additional stress and correlation-dependent terms (8).

To solve these equations, I numerically minimized an objective function that is the sum of the squared differences between the left-hand side and right-hand side of the eight self-consistency equations [14]. I found for fixed stress magnitude s, the richness $S\phi_N$ increased with the correlation between a species' stress susceptibility and its metabolic rate ρ (Fig. 1). Intuitively, when the correlation is decreased, stress is more likely to harm the slowest growers most susceptible to extinction. Furthermore, the richness is non-monotonic with stress s for sufficiently large ρ, since moderate stress reduces the advantage of species with faster metabolic rate without causing them to go extinct (Fig. 1). Intuitively, when stress s is sufficiently large, the richness decreases with s regardless of ρ (Fig. 1).

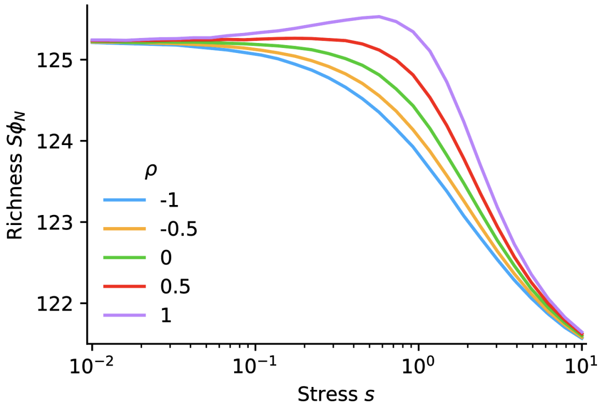

FIG. 1. Richness (the number of coexisting species) versus stress magnitude s for various ρ obtained by numerically solving the self-consistency equations (15–19) using scipy's differential_evolution with $S = 500, M = 10^3$, and $(K, \sigma_K, \mu_c, \sigma_c, m, \sigma_m, \xi) = (1, 1, 1, 1, 1, 1, .05)$.

Conclusion. I modified a GCRM in which species stress-induced death rates are correlated with their metabolic rates (4d). I followed the cavity method [11, 13, 14] to calculate self-consistency equations for relevant quantities like richness $S\phi_N$. I generalized previous work (SI equations 77 and 79 [13]) with the covariance in (7) and additional stress terms. Numerical solutions to the self-consistency equations showed that richness during stress increases with the correlation between a species' stress susceptibility and its metabolic rate, and for sufficiently large correlation, the richness is non-monotonic with stress (Fig. 1). Future work should compare the cavity-method results with simulations and investigate parameter regimes where the self-averaging assumption breaks down (replica symmetry breaking) [23]. In an extension of this project, I could consider externally supplied rather than self-renewing resources. Externally supplied resources have been studied with the cavity method before [13], but without explicitly interrogating effects captured in (4d).

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