Adaptive metabolic strategies explain diauxic shifts and promote species coexistence

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Abstract

Competitive systems are most commonly described mathematically using MacArthur's consumer-resource model [1], leading to the "competitive exclusion principle" which limits the number of coexisting competing species to the number of available resources. Nevertheless, several empirical evidences – in particular bacterial community cultures – show that this principle is violated in real ecosystems. Another experimental evidence that cannot be explained in this framework is the existence of diauxic (or polyauxic) shifts in microbial growth curves: bacteria consume resources sequentially, using first the one that ensures the highest growth rate and then, after a lag phase, they start growing slower using the second one. By introducing adaptive metabolic strategies whose dynamics tends to maximize species' relative fitness, we are able to explain both these empirical evidences, thus setting the paradigm for adaptive consumer-resource models.

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One of the most fascinating aspects of nature is biodiversity: from microbial to continental scales we observe complex communities of hundreds or thousands of species competing yet coexisting. The scientific community has always tried to explain such complexity, but this task requires the solution of many challenging problems. One of the most famous ones involves the so-called "competitive exclusion principle" [2] (known in the literature with many other names, like "Gause's law" or "niche-dimensionality hypothesis"), which limits the number of coexisting competing species. In particular, this principle states that if m consumers compete for p resources (with no predation between them), then they will coexist only if $m \leq p$. Even if this fact can be reproduced by mathematical models [3–5], there are many known cases in nature where the competitive exclusion principle is clearly violated [6, 7]; in particular, such violations have been recently observed in controlled bacterial community experiments [8–13]. It is clear, therefore, that we are missing something essential in order to explain the high biodiversity found in nature.

Competitive ecosystems are generally described mathematically using MacArthur's consumer-resource model [1, 4], which prescribes that for a system of m species and p resources the population $n_\sigma(t)$ of species σ evolves following (we omit for simplicity the time dependence on both n_σ and c_i from now on)

$$\dot{n}_\sigma = n_\sigma \left(\sum_{i=1}^{p} v_i \alpha_{\sigma i} r_i(c_i) - \delta_\sigma \right) , \tag{1}$$

where c_i represents the abundance of resource of type i (whose dynamics will be soon introduced), δ_σ is the death rate of species σ, $r_i(c_i)$ is the uptake rate of resource i (which we assume to have the form of a Monod function $r_i(c_i) = c_i/(K_i + c_i)$), and $\alpha_{\sigma i}$ are the "metabolic strategies", i.e. the rates at which species σ absorbs resource i; the parameters v_i are often called "resource values" and give a measure of how much efficiently a resource is converted into biomass: the larger v_i the larger the population growth that is achieved for unit resource, and thus the "more favorable" resource i is. Eq. (1) and many other mathematical models [5, 14, 15] – inspired by MacArthur's consumer-resource model – obey the aforementioned exclusion principle. This is easily seen to hold for Eq. (1): indeed a non-trivial stationary state is obtained if the term in the parentheses is zero, and this happens if the m dimensional vector whose components are δ_σ's, $\delta_\cdot$, can be expressed as a suitable linear combination of the p m-dimensional vectors $\alpha_{\cdot i}$. If $m > p$ this doesn't happen unless

the vector $\delta_{\cdot}$ does not lie in the subspace spanned by the p vectors $\alpha_{\cdot i}$, which occurs with zero probability if the vectors are drawn randomly.

In this setting the metabolic strategies $\alpha_{\sigma i}$ are treated as fixed parameters instead of being considered as dynamical (see however [16] for recent work, where microbes can instantaneously switch from using one nutrient to another); there is however incontrovertible evidence that microbes' metabolic strategies *do* change over time according to their surrounding environmental conditions. As early as the '40s Jacques Monod [17, 18] observed for the first time that *Escherichia coli* and *Bacillus subtilis* exhibit a particular growth curve, which he called "diauxie", when exposed to an environment containing only two different sugars. In particular, instead of metabolizing the two sugars simultaneously it turned out that bacteria consume them sequentially, using first their "favorite" resource (i.e. the one that ensures the highest growth rate) and then, after a lag phase, they start growing slower using their "least favorite" one. Since then diauxic growth has always been the subject of thorough experimental study [19–22] with experiments that generally involve the growth of one microbe on two resources, and has been observed to happen widely across different microbial species [23–25] [26, Supporting Information]. The many models that have been proposed in order to explain this phenomenon are all focused on gene regulation and expression (they generally involve *carbon catabolite repression* [27–30]), and sometimes are tailored in order to explain the growth of particular species of bacteria on particular resources, involving also enzyme dynamics [31–38]. Furthermore, as highlighted in [38], it is generally said that the existence of diauxic shifts is "adaptive", and the central idea of related modeling frameworks is that regulatory processes behind diauxic shifts may be considered as the outcome of some strategy of optimization [39]. Overall, it is clear that bacteria are capable to change the gene expression of metabolic pathways through which they absorb energy from the environment, but a connection between this phenomenon and consumer-resource ecological modeling is still missing.

Besides experiments of single species dynamics with multiple resources, in the last years there has been an increasing number of works studying laboratory controlled microbial communities coming from different type of natural environments [8–13, 26, 40]. These studies have confirmed that complex microbial communities with many species can be sustained in laboratory conditions even with few carbon sources, in apparent violation of the competitive exclusion principle.

The two problems that we have mentioned above, the existence of diauxic shifts and the violation of the competitive exclusion principle, have always been considered as separate and independent. In this work we will show that they are actually related, since they can be solved together by allowing the metabolic strategies, $\alpha_{\sigma i}$, of a MacArthur's consumer-resource model to be dynamical variables evolving according to an appropriately defined differential equation that tends to increase the relative fitness of each species, measured as its growth rate. In this letter we show that by introducing an adaptive dynamics regulating the evolution of the metabolic strategies $\alpha_{\sigma i}$ so that to increase the growth rate of each species, we can explain both the existence of diauxic shifts and the coexistence of any number of species independently of the number of different resource types.

We first consider the equation for the resources' dynamics, coupled with Eq. (1):

$$\dot{c}_i = s_i - \sum_{\sigma=1}^{m} n_\sigma \alpha_{\sigma i} r_i(c_i) \ , \tag{2}$$

where s_i is a constant nutrient supply rate (we are assuming that the resources are being supplied constantly from the outside world), and the second term in this equation represents the action of the consumers on the resources, which depends on the metabolic strategies $\alpha_{\sigma i}$. In the above equation we have not considered a term accounting for the resource degradation; we assume that it is sufficiently small and its effect is felt on timescales larger than the one considered here.

We now introduce our adaptive mechanism: we require that each metabolic strategy $\vec{\alpha}_\sigma$ evolves in order to maximize its own species' relative fitness, that is typically [41, 42] measured by the growth rate $g_\sigma = \sum_{i=1}^{p} v_i \alpha_{\sigma i} r_i(c_i)$. In the Supp. Mat. [43] we show that this corresponds to maximizing the instantaneous abundances of each species – the standard game-theory treatment of microbes' fitness [44].

Changing the metabolic strategies has an energetic cost for microbes, as it requires the allocation of new enzymes. By taking into account also this aspect, it is possible to show (see Supp. Mat. [43]) that the metabolic strategies evolve in time following a simple "gradient ascent" equation:

$$\dot{\alpha}_{\sigma i} = \frac{1}{\tau_\alpha} \frac{\partial g_\sigma}{\partial \alpha_{\sigma i}} = \frac{1}{\tau_\alpha} v_i r_i(c_i) \ , \tag{3}$$

where τ_α is the characteristic timescale over which metabolic strategies evolve. For microbes this timescale is comparable with the one of the resource dynamics, and therefore we can set

$\tau_\alpha = 1$: in fact, changes in the gene expression of metabolic pathways are not instantaneous, but they occur based on the available resources (as in the case of diauxic shifts). Time scales will be discussed more accurately later. The values of the metabolic strategies, however, cannot be completely unbounded because microbes have limited amounts of energy they can use for metabolism: we must therefore introduce a trade-off in the utilization of resources. We translate this constraint by requiring that each species has a maximum amount of energy to be allocated for metabolism, i.e. $\sum_{i=1}^{p} w_i \alpha_{\sigma i}(t) \leq E_\sigma$; the parameters w_i are called "resource costs", and take into account the fact that the energetic cost for the metabolization of different resources can be different. In our setting E_σ/δ_σ represents the "efficiency" of species σ, and *a priori* we assume it to be a species-independent property, i.e. $E_\sigma/\delta_\sigma = \mathcal{Q}\ \forall\sigma$. In other words, in a neutral environment (i.e. before specifying $\vec{s}$) all species have the same potential to grow (but this could be no longer true once the resources are supplied to the system). With this requirement Eq. (3) must be modified in order to assure that the constraint is satisfied: we can do this by removing from the gradient $\partial g_\sigma/\partial \alpha_{\sigma i}$ all the components perpendicular to the surface $\sum_{i=1}^{p} w_i \alpha_{\sigma i}(t) = E_\sigma$ as soon as $\vec{\alpha}_\sigma(t)$ "touches" it (see Supp. Mat. [43]). Moreover, we also want to prevent the metabolic strategies from becoming negative (while continuing to satisfy the constraint $\sum_{i=1}^{p} w_i \alpha_{\sigma i} \leq E$). Eventually, the final equation for the metabolic strategies' dynamics is (see Supp. Mat. [43])

$$\dot{\alpha}_{\sigma i} = 2\alpha_{\sigma i}\left[v_i r_i - \Theta\left(\sum_{i=1}^{p} \alpha_{\sigma i} - E_\sigma\right) w_i \frac{\sum_{j=1}^{p} v_j r_j w_j \alpha_{\sigma j}}{\sum_{k=1}^{p} w_k^2 \alpha_{\sigma k}}\right] , \tag{4}$$

where Θ is Heaviside's step function with $\Theta(0) = 0$.

Let us now consider the typical case studied in diauxic shift experiments, i.e. one species ($m = 1$) with two type of resources ($p = 2$) supplied only initially ($s_1 = s_2 = 0$ and $c_1(0), c_2(0) \neq 0$). Figure 1 shows the result of a simulation of the model in the case $c_1(0) > c_2(0)$ and $v_1 < v_2$: in this example, therefore, resource 2 is the "favorite" one and is scarce, while resource 1 is the "less preferred" one and is highly abundant. As we can see, the population growth curve exhibits a diauxic shift, and resource 2 is consumed first even if it is less abundant than the other one.

We finally show that incorporating adaptive strategies in the competition-resource model is also a key factor allowing the coexistence of multiple species in the presence of one or few resources.

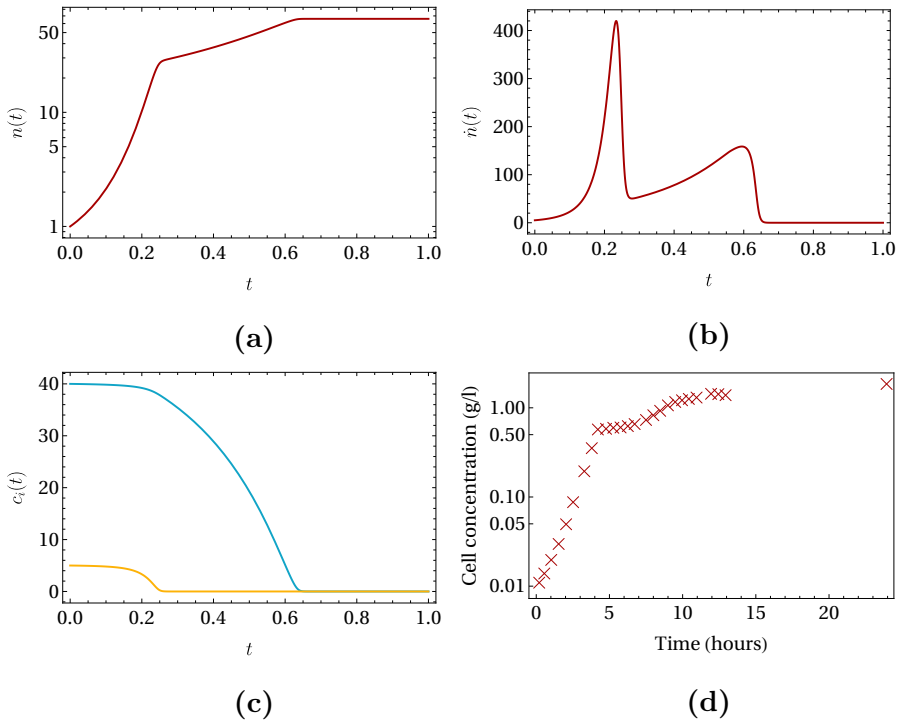

FIG. 1: Diauxic growth in our model. In this case we have used $n(0) = 1$, $\vec{c}(0) = (40, 5)$, $\vec{v} = (1, 5)$, $\vec{w} = (1, 1)$, $\vec{\alpha}(0) = (1, 1)$, $E = 10$, $K_1 = K_2 = 1$ and $\delta = 0$ for the sake of simplicity (using $\delta \neq 0$ doesn't change qualitatively our results, if δ is sufficiently small). **(a)**: Growth of the population over time. **(b)**: Time derivative of the population over time; from here it is clear how the population grows at two different rates, which correspond to the consumption of the two different resources. **(c)**: Resource consumption. **(d)**: Data of experimental measurements of the growth of *Klebsiella oxytoca* on glucose and lactose, taken from [19, figure 11], to be compared with the plot in panel (a).

Recently, Posfai et al. [45] have studied MacArthur's consumer-resource model with static metabolic strategies and the "hard" constraint $\sum_{i=1}^{p} w_i \alpha_{\sigma i} = E$, and have found that an arbitrary number of species can coexist if $\vec{s}E/S$ (with $S = \sum_{i=1}^{p} s_i$) lies in the convex hull of the metabolic strategies. In general, any broader constraint $\sum_{i=1}^{p} w_i \alpha_{\sigma i} \leq E$ will lead to the extinction of at least $m - p$ species, i.e. the system will obey the competitive exclusion principle; in this sense the system allows coexistence only when fine-tuned. If we allow $\alpha_{\sigma i}$ to evolve following Eq. (4) the system gains additional degrees of freedom, which makes it possible for the system to *self-organize* and find steady states where *all* species coexist [43]. In figure 2 we show the outcome of a numerical simulation of this model. As we can

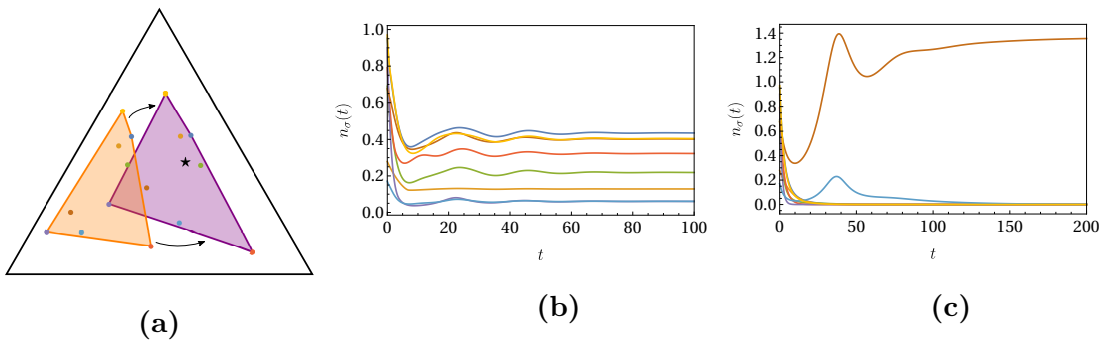

FIG. 2: Comparison of the evolution of our model with the soft constraint $\sum_{i=1}^{p} w_i \alpha_{\sigma i} \leq E_\sigma$ in the case of fixed and adaptive metabolic strategies. In this simulation we have considered a system with $m = 8$, $p = 3$, $v_i = w_i = K_i = 1\ \forall i$, $\delta_\sigma \in \mathcal{U}[0,1]$ (with $\mathcal{U}$ the uniform distribution), $E_\sigma = 2\delta_\sigma$ ($\mathcal{Q} = 2$), $n_\sigma(0) \in \mathcal{U}[0,1]$, $c_i \in \mathcal{U}[0,1]$; $\vec{s}$ and $\vec{\alpha}_\sigma(0)$ have been drawn randomly and such that $\sum_{i=1}^{p} \alpha_{\sigma i}(0) \in \mathcal{U}[0, E_\sigma]$ and $\sum_{i=1}^{p} s_i = 1$. In order to be represented on the same simplex, the metabolic strategies have been rescaled as $\hat{\alpha}_{\sigma i}(t) := w_i \alpha_{\sigma i}(t) / \sum_{j=1}^{p} w_j \alpha_{\sigma j}(t)$ so that $\sum_{i=1}^{p} \hat{\alpha}_{\sigma i}(t) = 1$ for all t. The Heaviside's step function has been approximated with the smooth function $\Theta(x) = 1/(1 + x \exp(-x \cdot 10^9))$, so that $\Theta(0) = 1$. **(a)**: Comparison between the initial (orange) and final (purple) convex hull of the metabolic strategies (colored dots) when they are allowed to evolve. As we can see, in the final state the species have changed their metabolic strategies so that their convex hull contains the nutrient supply rate vector (black star). **(b) and (c)**: Comparison of the time evolution of the species' populations between the case of adaptive (b) and static (c) metabolic strategies, with the same initial conditions (the colors of the curves match the corresponding strategies in (a)).

see, coexistence happens even if the nutrient supply rate vector initially lies outside of the strategies' convex hull, and at stationarity it is "incorporated" by them. It also turns out (see Supp. Mat. [43]) that the values of $\sum_{i=1}^{p} w_i \alpha_{\sigma i}(t)$ saturate very quickly to the maximum allowed, E_σ. It is therefore clear that our model is capable of self-organization, because the metabolic strategies change in order to put the system in the right conditions for coexistence even when they are initially not satisfied.

The system behaves interestingly if one of the components of $\vec{s}$ is small or null: in figure 3, for example, we show both the cases in which the nutrient supply rate vector lies close to one of the sides of the simplex or exactly on it, and we find that at stationarity the

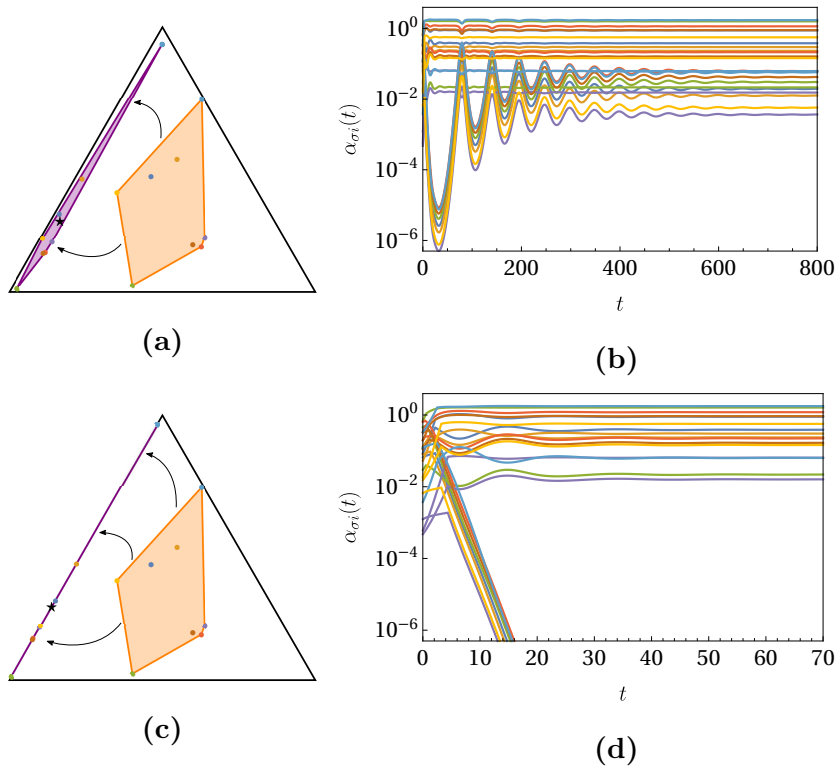

FIG. 3: Time evolution of our model with the soft constraint $\sum_{i=1}^{p} w_i \alpha_{\sigma i} \leq E_\sigma$. In this simulation we have considered the same parameters used in figure 2, but we have used different initial conditions; in particular, in (a)-(b) we have chosen $\vec{s} = (0.27, 0.70, 0.03)$. In this way one of its components is small compared to the others, while in (c)-(d) we have set $\vec{s} = (0.28, 0.72, 0.00)$. **(a) and (c):** Comparison between the initial (orange) and final (purple) convex hull of the metabolic strategies. **(b) and (d)**: Time evolution of the metabolic strategies. In this case we can notice that some components of some strategies either tend to small values (b) or to zero (d), which is graphically represented in (a) and (c) by the fact that the final convex hull is "squeezed" on the same size of the simplex where $\vec{s}$ is. This means that many species prefer not to waste much energy (or not to waste it at all) in order to use a scarce or absent resource.

metabolic strategies are all "squeezed" near to or exactly on that same side. This means that species do not waste energy producing enzymes needed to metabolize scarce or totally absent resources, and will focus their efforts on the more easily available ones.

Finally, we show that it is possible to derive a more general equation for the strategies, instead of Eq. (3), from a general property of the populations' dynamics. In fact, Eqs. (1)

and (2) are invariant under the following rescaling:

$$\alpha_{\sigma i} \to \lambda \alpha_{\sigma i} \qquad \delta_\sigma \to \lambda \delta_\sigma \qquad s_i \to \lambda s_i \qquad t \to \frac{t}{\lambda} \qquad \forall \lambda \in \mathbb{R}^+ \ , \tag{5}$$

i.e. the system is time-scale invariant. We can thus fix the time-scale using the following constraint:

$$\sum_{\sigma=1}^{m} E_\sigma(t)^2 = mE^2 \qquad \text{with} \qquad E_\sigma(t) = \sum_{i=1}^{p} w_i \alpha_{\sigma i}(t) \ , \tag{6}$$

and $E > \max(w_i/v_i)\sqrt{\sum_{\sigma=1}^{m} \delta_\sigma^2/m}$. This constraint is more general than the one used to derive Eq. (3) because it does not limit the value of each E_σ to be bounded, but limits an overall average energy budget for all species, independently of their identity. Accordingly, the equation for the metabolic strategies' dynamics is (see Supp. Mat. [43]):

$$\dot{\alpha}_{\sigma i} = 2\alpha_{\sigma i} \left(v_i r_i \delta_\sigma - w_i E_\sigma(t) \frac{\sum_{\tau=1}^{m} \sum_{j=1}^{p} v_j r_j \alpha_{\tau j} \delta_\tau w_j E_\tau(t)}{\sum_{\tau=1}^{m} \sum_{j=1}^{p} \alpha_{\tau j} w_j^2 E_\tau(t)^2} \right) \ . \tag{7}$$

Notice also that at variance of Eq. (4) the time scale of the time evolution of the $\alpha_{\sigma,i}$ is set by δ_σ, the death rate of species σ. In figure 4 we show the outcome obtained by simulating the species' abundance dynamics using adaptive strategies following Eq. (7). As we can see, the system is again capable to self-organize allowing the conditions for coexistence of all species. In particular, we notice that even when the initial values of the ratios $E_\sigma(0)/\delta_\sigma$ are very different for different σ, the adaptive dynamics nevertheless guides the system towards a final condition where E_σ/δ_σ does not depend on σ, i.e. we observe an emergent neutrality in the species' efficiencies [46].

In conclusion, introducing adaptive metabolic strategies in a MacArthur's consumer-resource model evolving so that each species' growth rate is maximized allows us to explain phenomena observed experimentally from the single-species to the community level, thus proving to be a determining factor in biological systems and setting the paradigm for adaptive consumer-resource models. However it is certainly not the only one: an increasing amount of attention is currently being focused on the study of inter-specific interactions via metabolic byproduct exploitation or cross-feeding relationships [14, 26, 40, 47], so a possible interesting development of the work presented here could be the inclusion of such interactions in the model, treating them as dynamical variables as well.

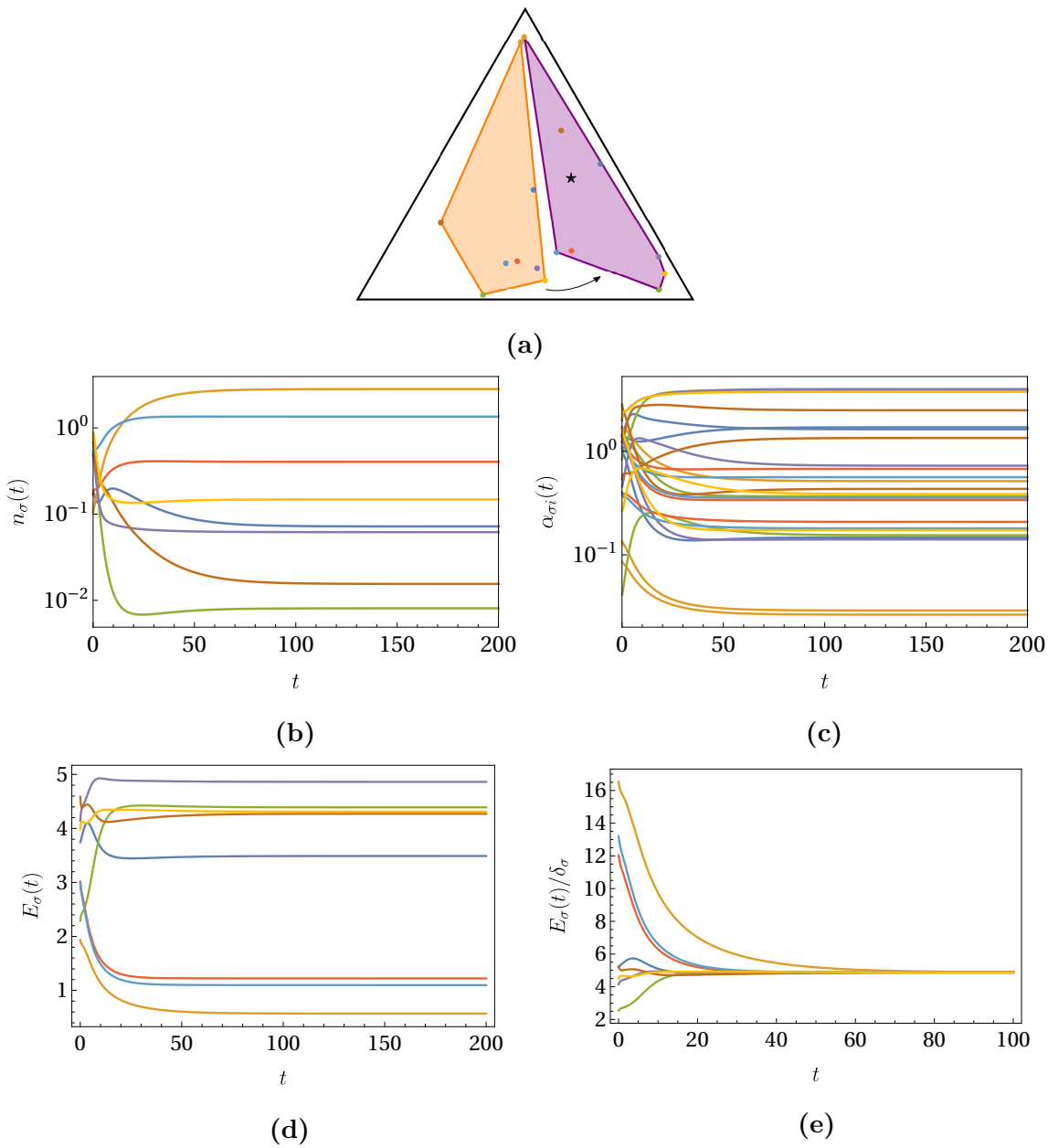

FIG. 4: Simulation of the model with Eq. (7) for the time evolution of the metabolic strategies. We have used $m = 8$, $p = 3$, $v_i = w_i = 1\ \forall i$, $\delta_\sigma \in \mathcal{U}[0,1]$, $E = 3.44$, $n_\sigma \in \mathcal{U}[0,1]$, $c_i \in \mathcal{U}[0,1]$; $\vec{s}$ and $\vec{\alpha}_\sigma(0)$ have been drawn randomly and such that $\sum_{i=1}^{p} \alpha_{\sigma i}(0) \in \mathcal{U}[1,5]$ so that $\alpha_{\sigma i}(0)$ satisfy Eq. (6), and $\sum_{i=1}^{p} s_i = 1$. In order to be represented on the same simplex, the metabolic strategies have been rescaled as in figure 2. **(a):** Comparison between the initial (orange) and final (purple) convex hull of the metabolic strategies. **(b):** Time evolution of the species' populations. **(c):** Time evolution of the metabolic strategies. **(d):** Time evolution of the values of $E_\sigma(t)$. **(e):** Time evolution of the values of the ratios $E_\sigma(t)/\delta_\sigma$. As we can see, the system self-organizes again in order to find the conditions for coexistence.

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