Adaptive metabolic strategies in consumer-resource models

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(Dated: May 7, 2019)

Abstract

Microbial communities are most commonly described mathematically using MacArthur's consumer-resource model. One characteristic of such model is that the so-called "metabolic strategies", the rates at which species uptake and metabolize resources, are constant parameters. However, microbes can adapt their metabolic strategies to the availability of different resources in the environment: when exposed to different sugars they often consume them sequentially resulting in population growth curves with distinct phases of growth rates, a phenomenon known as "diauxic shift". In this work, we introduce adaptive metabolic strategies to consumer-resource models. We show that if the dynamics of metabolic strategies maximizes each species' relative fitness, consumer-resource models can reproduce diauxic shifts in agreement with experimental observations. Furthermore we gain new insights on the coexistence of multiple species on a finite pool of resources. Introducing adaptive metabolic strategies allows consumer-resource models to violate the "Competitive Exclusion Principle", a controversial theoretical argument according to which the number of coexisting species is limited by the number of available resources.

Introduction. 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 long tried to explain such an amazing complexity, but this task requires the solution of many challenging problems. In particular, the survival of a species depends on the availability of resources in the environment, but this environment is not static as it includes all other organisms in the community, and the competition among them determines how the concentrations of nutrients evolve. The flourishing field of microbial ecology [1–4] calls for theoretical developments capable of describing the dynamics of such complex ecosystems. There is a growing effort from the statistical physics community to develop such a framework [5–10] using MacArthur's consumer-resource model [11, 12]. In this context, an ecosystem composed of m microbial species competing for p resources evolves in time according to the following equations:

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

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

where $n_\sigma(t)$ describes the population density of species σ. We omit for simplicity the time-dependence of both $n_\sigma(t)$ and $c_i(t)$. Here, c_i is the concentration of resource i and δ_σ is the death rate of species σ. The quantity $r_i(c_i)$ is a function of the concentration c_i accounting for the fact that the dependence of a species' growth rate on a given resource saturates as c_i is increased [13]. Without loss of generality, we assume that $r_i(c_i)$ has the form of a Monod function [13], i.e. $r_i(c_i) = c_i/(K_i + c_i)$ with $K_i > 0$, and so $r_i(c_i) < 1 \; \forall \, c_i > 0$. The quantity $\alpha_{\sigma i}$ is a "metabolic strategy", i.e. the maximum rate at which species σ uptakes resource i. The parameter v_i is often called "resource value" and is related to the resource-to-biomass conversion efficiency: the larger v_i, the larger the population growth rate that is achieved for unit resource, and thus the more "favorable" resource i is. The quantity s_i is a constant nutrient supply rate, and the sum in Eq. (2) represents the action of all consumers on resource i. Such an action depends of course on the metabolic strategies $\alpha_{\sigma i}$. Finally, μ_i is the degradation rate of resource i.

An implicit assumption adopted systematically in the literature is that the metabolic strategies $\alpha_{\sigma i}$ are fixed parameters instead of dynamic variables [14]. Such an assumption is in contrast with the experimental evidence that microbes' metabolic strategies *can* and *do* change over time according to the availability of resources in the

environment. In fact, as early as in the '40s, Jacques Monod [13, 15] observed that *Escherichia coli* and *Bacillus subtilis* exhibit a bi-phasic growth curve, which he called "diauxie", when grown in a culture medium containing two different sugars. Instead of metabolizing the two sugars simultaneously, it turned out that bacteria consumed them sequentially using first the favorable one (i.e., the one that conferred the highest growth rate) and once it had been depleted, following a lag phase, they resumed growth using the other sugar. Since then, diauxic growth has been the subject of thorough empirical study [16–19] with experiments that generally involved the growth of one microbe on two resources, and has been documented to occur widely across different microbial species [20–22]. Many models have been proposed to describe this phenomenon, but all are focused on specific gene regulation and expression mechanisms (generally involving specific representations of the gene network responsible for *carbon catabolite repression* in a given species [23, 24]), and are generally tailored to describe the growth of a particular microbial strain on a specific set of resources [25–27]. Furthermore, as highlighted by Chu and Barnes [27], it is generally thought 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 optimization strategy [28]. Overall, it is clear that microbes are capable of changing the gene expression level of different metabolic pathways in response to environmental cues, but a connection between this phenomenon and consumer-resource ecological modeling , which transcends the specificities of any particular microbial strain and set of resources, is still missing.

An important feature of MacArthur's consumer-resource model is the fact that it reproduces the so-called "Competitive Exclusion Principle" (CEP) [29][30], a controversial theoretical argument [31] that poses an upper bound to the number of species that can coexist in a community given by the number of available resources in the system. Many different mechanisms have been proposed to explain the violation of the CEP, ranging from non-equilibrium phenomena (e.g., when an equilibrium cannot be reached because of spatio-temporal effects) [32], to the existence of additional limiting factors like the presence of predators [33], cross-feeding relationships [4], toxin production [34, 35], and complex or higher-order interactions [36–38]; see [39, 40] for comprehensive reviews. However, none of the current mathematical models used to describe consumer-resource population dynamics can explain the violation of the CEP without an *a priori* fine-tuning of the parameters [6]. From a theoretical point of view, however, we still completely lack an unifying framework capable of reproducing both the existence of diauxic shifts and the coexistence of a large number of species competing for a limited number of resources. In this letter, we show that these two phenomena can both be reproduced by allowing the metabolic strategies $\alpha_{\sigma i}$ of a consumer-resource model to be dynamic variables that vary temporally to increase the relative fitness of each species in the community.

Adaptive metabolic strategies. We now introduce our adaptive framework: we require that each metabolic strategy $\vec{\alpha}_\sigma$ evolves in time to maximize its own species' relative fitness, measured [41, 42] by its growth rate $g_\sigma = \sum_{i=1}^{p} v_i \alpha_{\sigma i} r_i(c_i) - \delta_\sigma$. This can be achieved by requiring that metabolic strategies follow a simple gradient ascent equation:

$$\dot{\alpha}_{\sigma i} = \frac{1}{\tau_\sigma} \cdot \frac{\partial g_\sigma}{\partial \alpha_{\sigma i}} \ , \tag{3}$$

where in general τ_σ is the characteristic timescale over which the metabolic strategy of species σ evolves. Since δ_σ is the only characteristic timescale for each species, a natural choice for τ_σ is to be proportional to the inverse of its corresponding death rate, i.e. $\tau_\sigma = (d\delta_\sigma)^{-1}$, where d regulates the speed of adaptation.

However, Eq. (3) is missing an important biological constraint, which is related to intrinsic limitations to any species' resource uptake and metabolic rates. Microbes, for example, have limited amounts of energy that they can use to produce the metabolites necessary for resource uptake [43], so we must introduce such a constraint in Eq. (3). The choice of imposing a soft constraint in the form of an inequality is not arbitrary, as it is rooted in the experimental evidence that microbes cannot devote an unbounded amount of energy to metabolize nutrients. Some experiments [43] have shown, in fact, that introducing a constraint for metabolic fluxes in the form of an upper bound [44] allows one to improve the agreement between Flux Balance Analysis modeling and experimental data of the growth of *E. coli* on several different substrates. Thus, we require that each species has a maximum amount of energy available for metabolism, i.e. $\sum_{i=1}^{p} w_i \alpha_{\sigma i}(t) := E_\sigma(t) \leq E_\sigma^*$ where E_σ^* is the maximum total resource uptake rate of species σ; the parameters w_i are called "resource costs" and take into account the fact that each resource could require more or less energy in order to be metabolized. Again, since E_σ^* is an uptake rate, it is reasonable to require that it is proportional to the death rate δ_σ, since it is the only characteristic timescale of each species (and this is also in accordance to the metabolic theory of ecology [45]). We therefore set $E_\sigma^* = \mathcal{Q}\delta_\sigma$, with $\mathcal{Q}$ a positive real number (one can take $\mathcal{Q} = 1$ without loss of generality, see the Supplemental Material [46]). A possible justification of this choice is the following. E_σ^* is a rate so its dimensions are the inverse of a time, and it refers to species σ, which is characterized by the time scale given by $1/\delta_\sigma$. Using the metabolic theory of ecology [45] we can assume that this time scale is unique for this species, so we must have indeed $E_\sigma^* = \mathcal{Q}\delta_\sigma$

The constraint on species' uptake rate capacities intro-

duces a trade-off between the use of different resources. In the Supplemental Material [46] we also present a geometrical interpretation of the maximization problem given by Eq. (3), i.e. $\dot{\vec{\alpha}}_\sigma = \vec{\nabla}_{\vec{\alpha}_\sigma} g_\sigma$ where $\vec{\nabla}_{\vec{\alpha}_\sigma}$ is the gradient with respect to the components of $\vec{\alpha}_\sigma$. In particular, if we want $\vec{\alpha}_\sigma$ to evolve so that $\varphi(\vec{\alpha}_\sigma(t)) := \sum_{i=1}^p w_i \alpha_{\sigma i}(t) - \mathcal{Q}\delta_\sigma \leq 0$, it is sufficient to remove from $\vec{\nabla}_{\vec{\alpha}_\sigma} g_\sigma$ the component parallel to $\vec{\nabla}_{\vec{\alpha}_\sigma} \varphi(\vec{\alpha}_\sigma(t))$ as soon as $\varphi(\vec{\alpha}_\sigma(t)) = 0$. Moreover, we also prevent the metabolic strategies from becoming negative. Eventually, the final equation for the metabolic strategies' dynamics is given by Eq. (4) (see Supplemental Material [46] for the full derivation), where Θ is the Heaviside's step function, i.e. $\Theta(x) = 1$ when $x \geq 0$ and $\Theta(x) = 0$ otherwise.

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

For the moment being, we assume that all the degradation rates μ_i are null and for the sake of simplicity $d = 1$, but we will later discuss a more general case.

Diauxic shifts. If Eq. (4) is used alongside Eqs. (1) and (2), the model is capable of reproducing the growth dynamics of microbial populations in the presence of multiple resources, and in particular the dynamics of diauxic shifts. To show this, we measured growth curves of the baker's yeast, *Saccharomyces cerevisiae*, grown in the presence of galactose as the primary carbon source. In these growth conditions, *S. cerevisiae* partially respires and partially ferments the sugar. As a byproduct of fermentation, yeast cells release ethanol in the growth medium, which can then be respired by the cells once the concentration of galactose in the medium is reduced. To model the growth of *S. cerevisiae* in these conditions, we modified the equations to account for the fact that the second resource, ethanol, is produced while the first one, galactose, is consumed (see the Supplemental Material [46] for further details on the experiment and on the model equations). In Figure 1A, we show that our adaptive consumer-resource model can reproduce the experimental data. Figure 1B shows that, instead, the best-fit of the "classic" MacArthur's consumer-resource model with fixed metabolic strategies to the same data is quite unsatisfactory. The purpose of this analysis is to show that, introducing adaptive metabolic strategies in the MacArthur's consumer-resource model, one can reproduce the experimental data. Neglecting the dynamic nature of metabolic strategies leads to inconsistencies between the classical MacArthur's consumer-resource model and experimental data. We also note that the best-fitting parameters for the model with adaptive strategies are within a physiologically reasonable range (see Table S.1 [46]). The Akaike Information Criterion, used to compare the relative quality of the two fits discounting the number of parameters, selects the model with adaptive strategies as the best-fitting one (see the Supplemental Material [46] for more information).

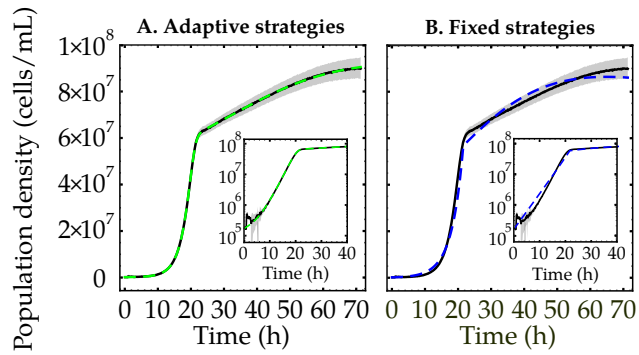

FIG. 1: Comparison between the fits of MacArthur's consumer-resource model (dashed lines) and experimental measures of the growth of *S. cerevisiae* on galactose as the primary carbon source and ethanol as a byproduct of fermentation, in the case of adaptive (A) and fixed (B) metabolic strategies. Shown are the mean (black lines) and 68% confidence intervals (gray bands) across $n = 8$ replicate populations. See [46] for further details on the experiment, the model equations and the best-fit parameters. **Inset:** Same plots, shown in logarithmic scale on the y-axis.

Species coexistence. We now show that incorporating adaptive strategies in our consumer-resource model is also a key factor that allows the coexistence of multiple species, in violation of the CEP. Recently, Posfai et al. [6] have studied MacArthur's consumer-resource model with static metabolic strategies and the "hard" constraint $\sum_{i=1}^p w_i \alpha_{\sigma i} = E_\sigma$. They found that an arbitrary number of species can coexist only if $E_\sigma/\delta_\sigma = \text{const}$ and if the rescaled nutrient supply rate vector $\hat{s}_i := v_i s_i / \sum_{j=1}^p v_j s_j$ belongs to the convex hull of the rescaled metabolic strategies $\hat{\alpha}_{\sigma i} := w_i \alpha_{\sigma i} / \sum_{j=1}^p w_j \alpha_{\sigma j}$ (see Supplemental Material [46]); notice that since $\sum_{i=1}^p \hat{s}_i = \sum_{i=1}^p \hat{\alpha}_{\sigma i} = 1$ we have that $\vec{\hat{s}}$ and $\vec{\hat{\alpha}}_\sigma$ lie on a $(p-1)$-dimensional simplex. In general, any looser constraint (including $\sum_{i=1}^p w_i \alpha_{\sigma i} \leq E_\sigma$) will lead to the extinction of at least $m - p$ species, i.e. the system will obey the CEP; in this sense the system allows coexistence only when fine-tuned. However, if we allow $\alpha_{\sigma i}$ to evolve following Eq. (4), the system gains additional degrees of freedom which make it possible to find steady states where an *arbitrary* number

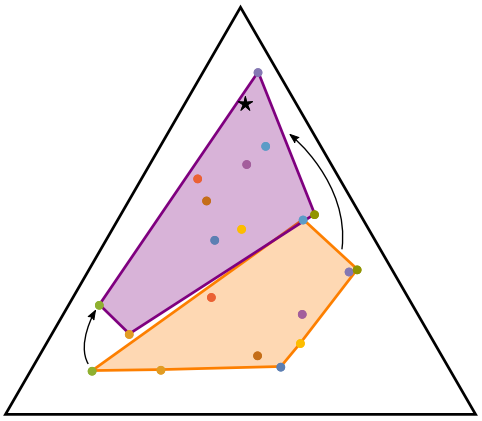

FIG. 2: Comparison between the initial (orange) and final (purple) convex hull of the rescaled metabolic strategies (colored dots) when they are allowed to evolve, using Eq. (4) for the temporal evolution of $\alpha_{\sigma i}$. These results have been obtained for a system with $m = 10$ species and $p = 3$ resources, so the rescaled metabolic strategies and nutrient supply rate vector (black star) all lie on a 2-dimensional simplex (i.e. the triangle in the figure), where each vertex corresponds to one of the resources; for details on the parameters used, and for the plots of the temporal evolution of the population densities and metabolic strategies, see Figure S.3 in the Supplemental Material [46]. In the final state, the $\vec{\hat{\alpha}}_\sigma$s have incorporated $\vec{\hat{s}}$ in their convex hull.

of species can coexist, even when initial conditions are such that $\vec{\hat{s}}$ does not lie in the convex hull of the rescaled metabolic strategies $\vec{\hat{\alpha}}_\sigma$, i.e. the system violates the CEP without having fine-tuned parameters (see Supplemental Material [46]). In Figure 2, we show the initial and final states of a temporal evolution of the model (for more information see Figure S.3 in the Supplemental Material [46]); as we can see, in the final state $\vec{\hat{s}}$ lies inside the convex hull of the rescaled strategies: thus, the community modeled by Eqs. (1-4) is capable of *self-organization*. Indeed, during the temporal evolution of the system, the metabolic strategies change and lead the community towards the right conditions for coexistence even if these conditions are not satisfied initially (see Supplemental Material [46]).

An independent prediction of our model is that if one of the available resources, e.g. resource j, is too "expensive", then adaptation will bring all the j-th components of the metabolic strategies to zero, i.e. species will stop using that resource. The "expensiveness" of resource i can be measured by w_i/v_i, i.e. its cost-to-value ratio, and an analytical analysis of the model with fixed metabolic strategies leads to the conclusion that a non-trivial stationary state is possible only if $w_i/v_i < \mathcal{Q}\ \forall i$ (see Supplemental Material [46]). However, when we allow the strategies to evolve following Eq. (4), the system reaches a non-trivial stationary state even if there is one or more resource j for which $w_j/v_j > \mathcal{Q}$. In this case, in fact, resource j becomes too expensive, and it is possible to show that the system "decouples" from this resource, i.e. the j-th component of *all* the metabolic strategies becomes null (see Figure S.4 [46]). Something analogous happens also when we let $\mu_i > 0$: in this case, at stationarity, the convex hull of the rescaled metabolic strategies will include the vector with components $\tilde{s}_i := v_i(s_i - \mu_i c_i^*)/\sum_{j=1}^{p} v_j(s_j - \mu_j c_j^*)$ with c_i^* the stationary value of $c_i(t)$ (see Supplemental Material [46]), and if one of the μ_i is sufficiently large this vector will lie on one of the sides of the $(p-1)$-dimensional simplex where our system can be represented. This result means that if the degradation rate μ_j of resource j becomes too large, then again all the j-th components of the metabolic strategies will become null (see Figures S.5 and S.6 [46]). Therefore, we have that species in our model will not waste energy metabolizing resources that are unfavorable (either because they are too expensive or volatile) and will focus their efforts on the more convenient ones.

Variable environmental conditions. Having adaptive metabolic strategies also allows the system to better respond to variable environmental conditions, i.e. when $\vec{s}$ is a function of time $\vec{s}(t)$. Let us consider a scenario where the nutrient supply rates change periodically; this can be implemented by shifting $\vec{s}$ between two different values at regular time intervals: one inside the convex hull of the initial (rescaled) metabolic strategies and one outside of it. We found that when $\vec{\alpha}_\sigma$ are allowed to evolve, then the species' populations oscillate between two values and manage to coexist, while when the metabolic strategies are fixed in time species go extinct and the CEP is recovered – see Figure 3. When we let $\vec{s}(t)$ lie outside of the convex hull for a short period of time, coexistence is again possible, but species population abundances fluctuate strongly (for more details see Figure S.7 in Supplemental Material [46]) and would be vulnerable to demographic noise. Also in the case of environments that vary with time, we find that when we introduce non-null resource degradation rates that are sufficiently large with respect to w_i/v_i, all the i-th components of the metabolic strategies vanish (Figure S.8 [46]). Therefore, adaptive metabolic strategies allow species in the community to efficiently deal with variable environmental conditions, a characteristic feature of natural ecosystems.

Adaptation velocity. A physically relevant parameter characterizing the capacity of a species to adapt to a new environment is d, which regulates the adaptation velocity of the metabolic strategies. Increasing the value of d leads to metabolic strategies that evolve more rapidly, and as a consequence species' growth rates will be optimized for longer periods of time. Therefore, when d has larger values, stationary populations will be higher (see Figure S.9 [46]) and less variable when $\vec{s}(t)$ changes with time (see Figure S.10 [46]). On the other hand, if d tends to zero we recover the case of fixed metabolic

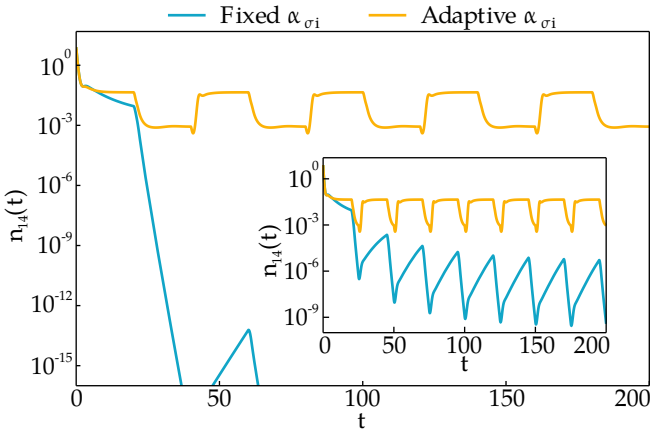

FIG. 3: Comparison between the temporal dynamics of the population density of species $\sigma = 14$ in the consumer-resource models with fixed and adaptive metabolic strategies, when the resource supply rate vector $\vec{s}$ varies with time. Here, we simulated a system with $m = 20$ species, $p = 3$ resources, and with the nutrient supply rate vector switching at regular intervals between two values. Specifically, we made $\vec{s}(t)$ alternate periodically between $\vec{s}_{\rm in}$ for a duration $\tau_{\rm in} = 20$ and $\vec{s}_{\rm out}$ for a duration $\tau_{\rm out} = 20$, with $\vec{s}_{\rm in}$ chosen within the convex hull of the initial rescaled metabolic strategies and $\vec{s}_{\rm out}$ chosen outside it (see Figure S.7 [46] for more information on the parameters used). **Inset:** Evolution of the population of the same species, with the same parameters and initial conditions, but with $\tau_{\rm in} = 20$ and $\tau_{\rm out} = 5$.

strategies and thus the CEP will determine the fate of the community. In other words, the distribution of stationary species' populations can change sensibly with the adaptation velocity d, and if d is small enough the CEP is recovered also in our model.

Conclusions. If we introduce adaptive metabolic strategies in MacArthur's consumer-resource model , with the strategies evolving to maximize each species' growth rate, we can explain experimentally observed phenomena ranging from the single-species to the community level within the same theoretical framework. In particular, we have shown that classic consumer-resource models (i.e. without adaptive metabolic strategies) are not capable to fully reproduce experimental data, while consumer-resource models with adaptive metabolic strategies can. Furthermore, by allowing metabolic strategies to vary with time we can naturally violate the CEP without any strong assumption on the model parameters, but at the same time we can explain why competitive exclusion still happens in some cases. We have therefore shown that having adaptive metabolic strategies is indeed a determining factor in microbial communities. Recently, an increasing amount of attention is being drawn on the study of cross-feeding relationships between microbial species [4, 9, 47]. A future development of our work is to generalize the approach used here to include also cross-feeding relationships in the model.

We are grateful to S. Maslov and J. Grilli for useful discussions. A. M. and L. P.-M. acknowledge Cariparo Foundation, S. S. acknowledges the University of Padua for SID2017 and STARS2018 grants. A. G. was supported by research fellowships from the Swiss National Science Foundation, Projects P2ELP2_168498 and P400PB_180823.

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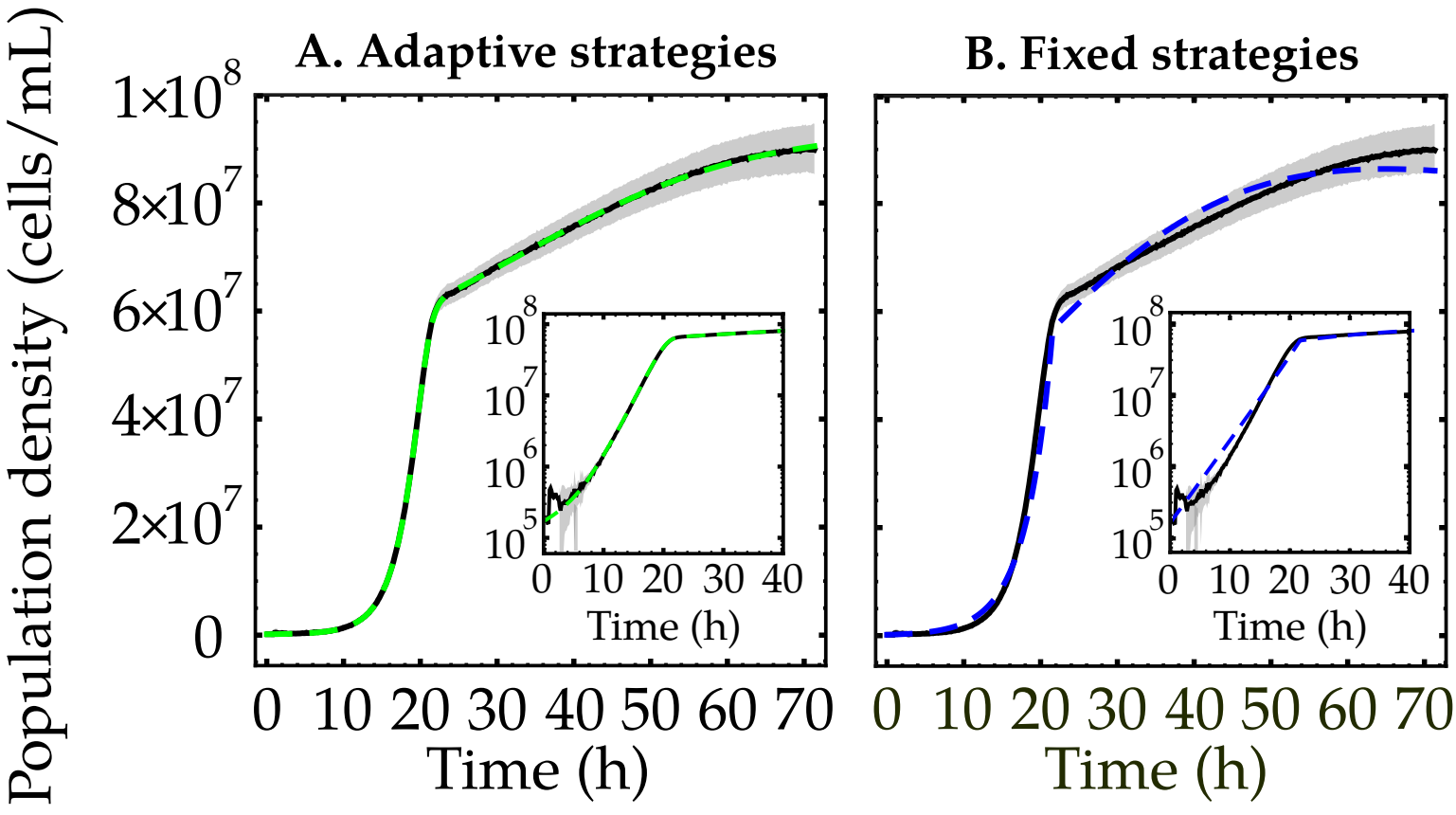
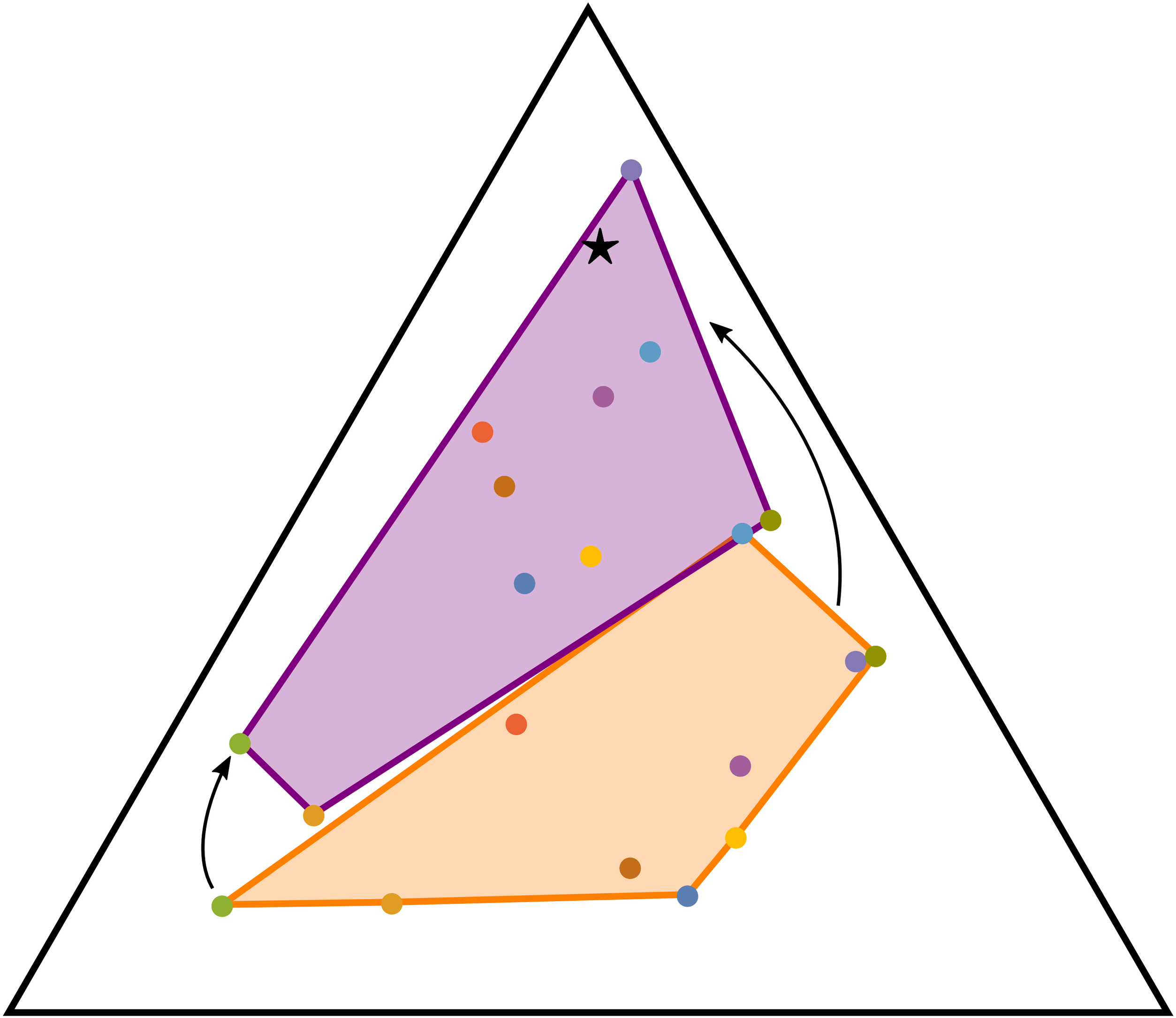
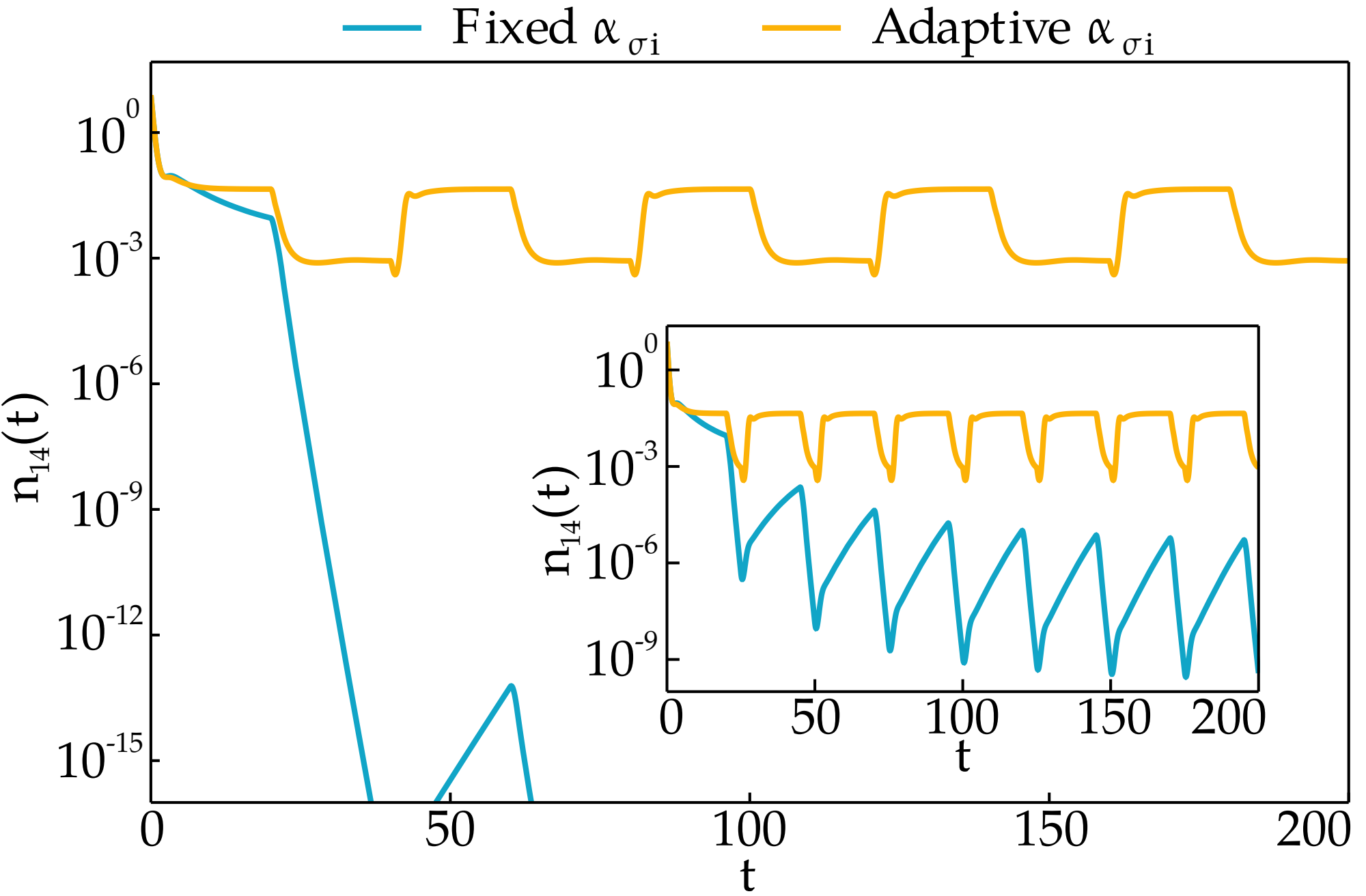

A. Adaptive strategies
B. Fixed strategies
Population density (cells/mL)
1×10^8
8×10^7
6×10^7
4×10^7
2×10^7
0
0 10 20 30 40 50 60 70
Time (h)
10^8
10^7
10^6
10^5
0 10 20 30 40
Time (h)




Fixed $\alpha_{\sigma i}$
Adaptive $\alpha_{\sigma i}$
10^{0}
10^{-3}
10^{-6}
10^{-9}
10^{-12}
10^{-15}
$n_{14}(t)$
0
50
100
150
200
t
10^{0}
10^{-3}
10^{-6}
10^{-9}
$n_{14}(t)$
0
50
100
150
200
t