



HAL
open science

Comparison Between Effective and Individual Fitness in a Heterogeneous Population

Marie Doumic, Anaïs Rat, Magali Tournus

► **To cite this version:**

Marie Doumic, Anaïs Rat, Magali Tournus. Comparison Between Effective and Individual Fitness in a Heterogeneous Population. 2024. hal-04852370

HAL Id: hal-04852370

<https://cnrs.hal.science/hal-04852370v1>

Preprint submitted on 9 Jan 2025

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Comparison Between Effective and Individual Fitness in a Heterogeneous Population

Marie Doumic¹, Anaïs Rat^{2,3}, Magali Tournus²

Subject Areas:

biomathematics

Keywords:

population dynamics, effective fitness, growth-fragmentation equation, heterogeneity, bacterial growth, mother-daughter inheritance

Author for correspondence:

Anais Rat

e-mail: anais.rat@centrale-marseille.fr

¹ CMAP, Inria, IP Paris, Ecole polytechnique, CNRS, 91128 Palaiseau cedex.

² Aix Marseille Univ, CNRS, I2M, Centrale Marseille, Marseille, France

³ Univ Brest, CNRS UMR 6205, Laboratoire de Mathématiques de Bretagne Atlantique, 14 F-29200 Brest, France

Is there an advantage of displaying heterogeneity in a population where the individuals grow and divide by fission? This is a wide-ranging question, for which a universal answer cannot be easily provided. This article thus aims at providing a quantitative answer in the specific context of growth rate heterogeneity by comparing the fitness of homogeneous versus heterogeneous populations. We focus on a size-structured population, where an individual's growth rate is chosen at its birth through heredity and/or random mutations. We use the long-term behaviour to define the Malthus parameter of such a population, and compare it to the ones of averaged homogeneous populations. We obtain analytical formulae in two paradigmatic cases: first, constant rates for growth and division, second, linear growth rates and uniform fragmentation. Surprisingly, these two cases happen to display similar analytical formulae linking effective and individual fitness. They allow us to investigate quantitatively the crossed influence of heredity and heterogeneity, and revisit previous results stating that heterogeneity is beneficial in the case of strong heredity.

Introduction

Heterogeneity in living populations has been evidenced and questioned in many different studies, for instance – among many others – variability in metabolism, genes and growth rate in bacteria [15, 13, 8], variability in protein production, morphology and growth rate in yeasts [26, 18], heterogeneity in telomere lengths in eukaryotic cells [16, 14], etc.

An important question for ecology is how to relate these variable traits to the concept of *fitness*, either at a population or at an individual level: which trait is beneficial or detrimental to growth? Does variability increase or decrease this *fitness*?

At the population level, the fitness may be defined as the Malthusian fitness, that is the exponential growth rate of the number of individuals, called the *Malthus parameter* of the population. At an individual level however, it is uneasy to find which traits may be directly related to fitness [23], except in an important and paradigmatic case: when individuals grow exponentially in size, the individual growth rate is equal to the Malthus parameter of a clonal population sharing the same trait [33]. Such an individual exponential growth, or elongation, is the case for some bacteria – e.g. *E. coli* in normal growth condition.

This is one of the reasons why the study of heterogeneity in *individual* growth rate is of central importance [20, 11]. Other motivations are the study of heredity through mother-daughter correlation [5, 34], and it has also been used as an individual fitness to study mutation effects [33].

These considerations led us to the following question: What is the effective growth rate or fitness of a population where individuals display different growth rates? In other words, does there exist an *equivalent* homogeneous population, i.e. with the same fitness but where all individuals grow at the same speed? If so, how does this “effective” rate relates to the growth rates of the heterogeneous population? This wide-ranging question has evolutionary interpretations, to understand for instance whether or not heterogeneity ensures not only more robust survival [17] or adaptation to a varying environment [22], but also inherently faster growth, or growth at a lower energetic cost, or yet if heritable heterogeneity is more or less advantageous than non-heritable traits [4, 24].

No universal answer can be provided, since it depends on the various traits of the population and how the individual growth is related to the population one [13, 19]. In this article, we propose a methodological approach that we believe could be adapted to other cases, and we apply it to size-structured populations where reproduction occurs by division into smaller individuals – as is typically the case for microbial populations. This context allows us to derive exact formulae for the effective fitness of the population as an explicit weighted average of the individual ones, in two cases: first, constant growth and division rates, with general and possibly asymmetric size distribution between daughters; and second, linear growth rate and uniform

size distribution between newborns, with general division rates. Surprisingly, we obtain almost identical analytical formulae for the weighted averages in these two cases. We also derive new explicit analytical formulae for the steady size distribution [10]. We complete the study with a numerical investigation of the emblematic case of exponential individual growth and division into two cells of equal size, for which no analytical formula can be derived.

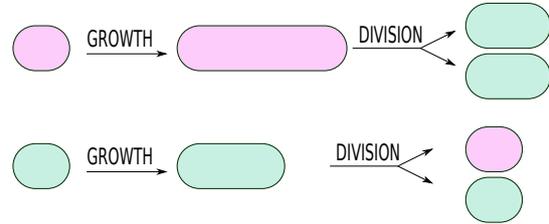


Fig. 1: Schematic representation of a heterogeneous mixing population: pink cells grow faster than green ones, and dividing cells can give rise to both types according to a certain heredity law. For simplicity, equal mitosis (when a cell divides into two cells of equal size) is represented.

Methods

(a) Definition of the effective fitness

Let us first explain our approach in a general setting. We consider a population where each individual grows and reproduces by division, independently from each other, and possibly in variable ways. Individuals are described by two traits: a “master” trait x – think of the size, the physiological age, or any quantity that evolves through the individual’s life and may influence their rate of division – and an “individual” trait v , conserved through life, that characterizes the growth of x – it could represent protein production rate, growth or ageing rate, phenotypic trait, gene expression, etc. This last trait thus accounts for the heterogeneity in growth rates. For simplicity, let us consider this trait as a discrete variable, taking a finite number of values M , values that we denote $v_1 < \dots < v_M$.

An individual with trait v_i gives birth to an individual with trait v_j with a certain probability κ_{ij} . We call the heredity kernel the matrix $\kappa = (\kappa_{ij})_{1 \leq i, j \leq M}$, which is a stochastic irreducible matrix in $\mathcal{M}_M(\mathbb{R})$, i.e. it satisfies

$$\forall 1 \leq i, j \leq M, \quad \kappa_{ij} \geq 0, \quad \sum_{j=1}^M \kappa_{ij} = 1, \quad (0.1)$$

$$\forall (i, j), \exists m \in \mathbb{N}^* : \kappa_{ij}^{(m)} := (\kappa^m)_{ij} > 0. \quad (0.2)$$

Assumption (0.1) ensures that for any i , $(\kappa_{ij})_{1 \leq j \leq M}$ is a probability law, while the irreducibility assumption (0.2) ensures that any ancestor of trait i has a non-zero probability to give birth to a descendant of any trait j in a finite number of divisions. If it fails, asymptotic behaviours may also be characterised but several Malthusian behaviours

can emerge for unconnected subpopulations, and some subpopulations may also extinct.

Under balance assumptions on the laws of growth and birth, it can be proven that the population reaches what we can call *homeostasis*, defined here as a stable distribution of traits (see Fig. 3 for an illustration). With this formalism, the question of the influence of heterogeneity and heredity can thus be formulated as follows: How can we compare this heterogeneous (in trait v_i) population with an homogeneous one? We notice that for each trait v_i we can define a homogeneous population by assuming that it shares all the characteristics of the heterogeneous population, except that the trait v_i is common to all individuals and unchanged at birth – in other words, the population is given by v_i for its trait, $M = 1$ and $\kappa = \kappa_{11} = 1$. This results in the following definition.

Definition 0.1 (Effective fitness/trait of a heterogeneous population). Consider a population composed of M subpopulations with traits $\mathbf{v} = (v_1, v_2, \dots, v_M)$ transmitted at birth according to a kernel κ satisfying (0.1)-(0.2). We assume that growth and birth laws ensure the existence and uniqueness of a Malthusian growth at exponential rate $\lambda_{(\mathbf{v}, \kappa)} > 0$ and the convergence of the traits distribution towards a steady homeostatic profile, and similarly, in the case of a unique trait v , the existence and uniqueness of a Malthusian growth at a rate λ_v . An effective fitness or effective trait of the heterogeneous population of traits \mathbf{v} is a trait v such that $\lambda_v = \lambda_{(\mathbf{v}, \kappa)}$ is the Malthus parameter of a homogeneous population of trait v , i.e. a population with the same characteristics as the heterogeneous one, but with homogeneous trait v .

The term “effective trait” makes clear the homogeneity between the individual trait and their equivalent “effective fitness”. We also use “effective fitness” in what follows because the effective trait is, in many cases of interest, an increasing function of the Malthus parameter – in our study, it is even proportional to it. It is also a term used for evolutionary systems, see e.g. [35], and in monotonous cases the trait distribution can thus be related to the “fitness landscape” [9, 27].

If the function $w \mapsto \lambda_w$ is strictly increasing and covers a sufficiently wide range of values, the definition 0.1 ensures the existence and uniqueness of the effective fitness v . To better understand whether heterogeneity is beneficial or detrimental to the population growth, we propose to compare v with the distribution of traits v_i . As discussed in many articles [28, 35], the definition of neutrality is difficult since it requires estimating the costs of heterogeneity compared to its benefits – in other words, we need not only to know how frequent individuals with a given trait are in the population (this can be answered in our framework), but also to model the individual’s “expense” related to that trait – and this last point cannot be answered in a universal way, it depends strongly on the case studied.

Our method thus consists in comparing the effective trait, which is itself a certain weighted average of the traits,

see below (0.17), with three frequently used means, namely geometric, arithmetic and harmonic means, and discuss the influence of heredity and of the traits distribution on their respective evolution. The same method can also apply to compare the effective fitness with a model of heterogeneity cost which would imply any other weighted average.

In the following, we apply our approach to the case of a population where the individuals are characterised by their size and display heterogeneous growth.

(b) Heterogeneous growth rates

From now on, we consider the population structuring trait as being a *size* variable – i.e., a trait which grows with time and is partitioned between offspring at division – and where the heterogeneous trait is the individual growth rate. Size is called a “master trait” for ecological and biodiversity studies [1, 21], since for many species – phytoplankton, marine fauna, bacteria, micro-organisms in general – it has a positive correlation with many other functional traits. Size-structured equations appear in many applications, from bacterial growth [32, 20] to polymerisation models [12]. In the case of bacteria, individual growth rates have been measured and their distribution reveals an important indicator for mutation [33] or heredity [5].

We describe the behaviour of such a population by a system of equations satisfied by the concentrations $n_i(t, x)$ of particles of size x and type i at time t . We assume that the individuals all share a common growth rate $\tau(x)$ modulated by a trait $v_i > 0$ which depends on their type, so that type i individuals grow at a rate $v_i \tau(x)$. The division rate per unit of size is denoted $\beta(x)$. When embedded in a time-dependent equation, the division rate “per unit of size” has to be multiplied by the growth rate, namely $v_i \tau(x)$, to obtain the division rate “per unit of time” [36, 6], namely $v_i \tau(x) \beta(x)$ for type i . This is a pivotal point in our modelling choices: the variable x – called size, but which could represent any quantity partitioned by division – is assumed to structure the division. To guarantee homeostasis at equilibrium, we assume

$$\beta \text{ is integrable at } x = 0, \quad \lim_{x \rightarrow \infty} x\beta(x) = +\infty. \quad (0.3)$$

Finally, the division of a cell or particle of size y gives rise to two particles of respective size x and $y - x$ with a probability law $b(y, dx) = b(y, y - dx)$. This law is often called in the literature the *fragmentation kernel*. The fragmentation kernel b must satisfy $\text{Supp}(b(y, \cdot)) \subset [0, y]$ (the daughters are smaller than the mother) and

$$\int_0^y b(y, dx) = 1, \quad \int_0^y xb(y, dx) = \frac{y}{2}. \quad (0.4)$$

The first equality ensures that $b(y, dx)$ is a probability law, while the second ensures that the division preserves the overall size – the sum of the daughter sizes equals the mother size. We refer to Fig. 1 for an illustration of the model. All these assumptions lead to the following system

of equations:

$$\begin{cases} \frac{\partial}{\partial t} n_i(t, x) + v_i \frac{\partial}{\partial x} (\tau(x) n_i(t, x)) = -v_i \tau(x) \beta(x) n_i(t, x) \\ + 2 \int_x^\infty \tau(y) \beta(y) b(y, x) \sum_{j=1}^M \kappa_{ji} v_j n_j(t, y) dy, \\ \tau(0) n_i(t, 0) = 0, \quad n_i(0, x) = n_i^{in}(x). \end{cases} \quad (0.5)$$

This system is a particular case of the heterogeneous growth-fragmentation system studied in [31]. In this article, under assumptions on the parameters that we recall in Appendix A, it is proven that there exists a unique Malthus parameter $\lambda = \lambda_{(v, \kappa)} > 0$, a unique nonnegative steady profile $N = (N_i)_{1 \leq i \leq M}$ and a unique nonnegative adjoint state $\phi = (\phi_i)_{1 \leq i \leq M}$ (the adjoint is obtained by duality when formulating the equation in the sense of distributions) such that for all $i \in \{1, \dots, M\}$

$$n_i(t, x) e^{-\lambda t} \xrightarrow{t \rightarrow \infty} \rho N_i(x), \quad (0.6)$$

where the multiplicative factor ρ is expressed as

$$\rho = \sum_{j=1}^M \int_0^\infty n_j(0, x) \phi_j(x) dx. \quad (0.7)$$

The triplet (λ, N, ϕ) is characterised as being the unique solution to the following system, derived from (0.5) (and its adjoint equation) by replacing $n_i(t, x)$ by $e^{\lambda t} N_i(x)$:

$$\begin{cases} v_i (\tau N_i)'(x) + \lambda N_i(x) = -v_i \tau(x) \beta(x) N_i(x) \\ + 2 \int_x^\infty \tau(y) \beta(y) b(y, x) \sum_{j=1}^M \kappa_{ji} v_j N_j(y) dy, \\ \tau(0) N_i(0) = 0, \quad N_i \geq 0, \quad \sum_{j=1}^M \int_0^\infty N_j(s) ds = 1, \end{cases} \quad (0.8)$$

$$\begin{cases} -v_i \tau(x) \phi_i'(x) + \lambda \phi_i(x) = -v_i \tau(x) \beta(x) \phi_i(x) \\ + 2 v_i \tau(x) \beta(x) \int_0^x b(x, y) \sum_{j=1}^M \kappa_{ij} \phi_j(y) dy, \\ \phi_i \geq 0, \quad \sum_{j=1}^M \int_0^\infty N_j(s) \phi_j(s) ds = 1. \end{cases} \quad (0.9)$$

To define the effective fitness/trait v introduced in Definition 0.1, we consider (0.8) for $M = 1$ and a given $v > 0$, namely find (λ_v, N_v, ϕ_v) solutions to

$$\begin{cases} v (\tau N_v)'(x) + \lambda_v N_v(x) = -v \tau(x) \beta(x) N_v(x) \\ + 2v \int_x^\infty \tau(y) \beta(y) b(y, x) N_v(y) dy, \\ \tau(0) N_v(0) = 0, \quad N_v \geq 0, \quad \int_0^\infty N_v(s) ds = 1, \end{cases} \quad (0.10)$$

$$\begin{cases} -v \tau(x) \phi_v'(x) + \lambda \phi_v(x) = -v \tau(x) \beta(x) \phi_v(x) \\ + 2v \tau(x) \beta(x) \int_0^x b(x, y) \phi_v(y) dy, \\ \phi_v \geq 0, \quad \int_0^\infty N_v(s) \phi_v(s) ds = 1. \end{cases} \quad (0.11)$$

The effective trait v is such that $\lambda_v = \lambda$; it is uniquely defined thanks to the linearity property of $w \mapsto \lambda_w$, and we have the bounds $v \in [v_1, v_M]$, see Theorem 3.2. in [31]

and Proposition B.1 in Appendix. The method described in Section (a) consists in comparing v to the distribution of $(v_i)_{1 \leq i \leq M}$. However, all the quantities $N_i, N_v, \lambda, \lambda_v$ being defined in an implicit way as solutions to equations (0.8) or (0.10), theoretical comparisons in the general case are difficult, so that only numerical investigation has been carried out till now, see [28].

We considered two paradigmatic cases for the growth rate.

Case A: the growth rate $\tau(x)$ is constant, so that without loss of generality we take $\tau(x) \equiv 1$ and the growth rate for type i is $v_i > 0$. We obtain analytical formulae for constant fragmentation rates $\beta(x) \equiv \beta > 0$ and general fragmentation kernel $b(y, x)$:

$$\tau(x) \equiv 1, \quad \beta(x) \equiv \beta, \quad b \text{ general}. \quad (0.12)$$

Case B: the growth rate depends linearly on the size, so that without loss of generality we take $\tau(x) \equiv x$ and the growth rate for type i is $x \mapsto v_i x$ with $v_i > 0$. We derive analytical formulae for general fragmentation rates $\beta(x)$ in the case of a uniform fragmentation kernel $b(y, x) = \frac{1}{y} \mathbb{1}_{x \leq y}$. In such a case, the fragmenting particle has a uniform probability to break at any place of the interval $(0, y)$:

$$\tau(x) = x, \quad \beta(x) \text{ general}, \quad b(y, x) = \frac{1}{y} \mathbb{1}_{x \leq y}. \quad (0.13)$$

Results

Let us detail the results obtained for size-structured heterogeneous populations reproducing by division. We first derive explicit formulae in Cases A and B defined above, and use them to compare the effective fitness with averaged fitness. We also perform numerical simulations for non-explicit cases, in order to conjecture whether or not the results of the explicit cases can be generalised.

We recall the expression of the arithmetic, geometric and harmonic means of $\mathbf{v} = (v_1, \dots, v_M)$, respectively:

$$\begin{cases} m_A(\mathbf{v}) = \frac{v_1 + \dots + v_M}{M}, \\ m_G(\mathbf{v}) = \sqrt[M]{v_1 \times \dots \times v_M}, \\ m_H(\mathbf{v}) = \frac{M}{\frac{1}{v_1} + \dots + \frac{1}{v_M}}, \end{cases} \quad (0.14)$$

and their comparison: $m_H \leq m_G \leq m_A$.

(c) Case A: Constant growth

Assuming a constant rate of size growth is a reasonable approximation for many applications, e.g. *E. coli* in fast growth conditions [2]. It is also one of the most mathematically-studied cases [29]. Constant division rate is a much more specific assumption, however important as it corresponds to a "neutral" case, where size does not influence the division process. Assuming (0.12), we can

rewrite (0.8) and (0.9)

$$\begin{cases} v_i N_i'(x) + \lambda N_i(x) = -v_i \beta N_i(x) \\ \quad + 2\beta \int_x^\infty b(y, x) \sum_{j=1}^M \kappa_{ji} v_j N_j(y) dy, \\ N_i(0) = 0, \quad N_i \geq 0, \quad \sum_{j=1}^M \int_0^\infty N_j(s) ds = 1, \end{cases} \quad (0.15)$$

$$\begin{cases} -v_i \phi_i'(x) + \lambda \phi_i(x) = -v_i \beta \phi_i(x) \\ \quad + 2v_i \beta \int_0^x b(x, y) \sum_{j=1}^M \kappa_{ij} \phi_j(y) dy, \\ \phi_i \geq 0, \quad \sum_{j=1}^M \int_0^\infty N_j(s) \phi_j(s) ds = 1. \end{cases} \quad (0.16)$$

In the homogeneous case $M=1$, a direct computation (where we recall that $\int_0^\infty b(x, dy) = 1$) shows that the adjoint vector $\phi_v \equiv 1$ is constant, and we also have $\lambda_v = v\beta$ [30]. Moreover, we have explicit solutions for $N_v(x)$ for the two emblematic cases of the fragmentation kernel:

- If $b(x, y) = \delta_{y=2x}$ (division into two equally-sized daughters), it has been proven in [30, Lemma 2.1] that the triplet solution to (0.10)-(0.11) is given by the following analytical expression:

$$\lambda_v = \beta v, \quad \phi_v \equiv 1, \quad N_v(x) = C \sum_{n=0}^{+\infty} (-1)^n \alpha_n e^{-2^{n+1} \beta x},$$

with C a normalization constant and

$$\alpha_0 := 1, \quad \alpha_n := \frac{2^n}{(2^n - 1) \dots (2^1 - 1)}, \quad n \geq 1.$$

- If $b(x, y) = \frac{1}{y} \mathbb{1}_{x \leq y}$ (uniform division), we compute that the triplet solution to (0.10)-(0.11) is given by

$$\lambda_v = \beta v, \quad \phi_v \equiv 1, \quad N_v(x) = 4\beta^2 x e^{-2\beta x}.$$

The formula $\lambda_v = \beta v$ implies that the effective trait of the heterogeneous case is explicitly given by $v := \frac{\lambda}{\beta}$. Integrating (0.15) and summing for all i , we also obtain

$$v = \sum_{i=1}^M v_i \int_0^\infty N_i(x) dx = \frac{\lambda}{\beta}. \quad (0.17)$$

This formula expresses the effective trait as being the average of the traits v_i weighted by $\int_0^\infty N_i dx$, i.e. by the relative amount of the population i in the total population. It implies that $v \in [v_1, v_M]$ and illustrates well the fact that the effective trait is a certain weighted average of the traits v_1, \dots, v_M ; in our case study, it is weighted by the proportion of cells sharing each trait in the population.

The proof of Proposition B.1 shows that to have information on the Malthus parameter, we may study either the direct problem (0.10) or the adjoint one (0.11). Explicit solutions in the homogeneous case however suggest that this second option – looking for solutions to (0.9) rather than (0.8) – may be easier and thus constitute a better chance to get information on λ . For this reason, we looked for constant solutions $\phi_i(x) \equiv \phi_i$ which reduces (0.16) to a matrix system; this revealed equivalent to integrating (0.15)

and look for (λ, \bar{N}, ϕ) , with $\bar{N} := (\int_0^\infty N_j dx)_{1 \leq j \leq M}$ and $\phi = (\phi_i)$ constant, positive solution of

$$\begin{cases} \lambda \bar{N}_i = -\beta v_i \bar{N}_i + 2\beta \sum_{j=1}^M \kappa_{ji} v_j \bar{N}_j, \quad 1 \leq i \leq M, \\ \lambda \phi_i = -\beta v_i \phi_i + 2\beta v_i \sum_{j=1}^M \kappa_{ij} \phi_j, \quad 1 \leq i \leq M. \end{cases}$$

Denoting the diagonal matrix $\mathbf{Diag}(v) := (v_j \delta_{i,j})_{1 \leq i, j \leq M}$, we write the system under the form of a matrix equation

$$\begin{cases} \lambda \bar{N} = \beta (-\mathbf{Id} + 2\kappa^T) \mathbf{Diag}(v) \bar{N} \\ \lambda \phi = \beta \mathbf{Diag}(v) (-\mathbf{Id} + 2\kappa) \phi. \end{cases} \quad (0.18)$$

Perron-Frobenius theorem applied to

$$\beta (-\mathbf{Id} + 2\kappa^T) \mathbf{Diag}(v) + 2\beta v_M$$

provides us with a unique eigen triplet $(\tilde{\lambda} > 0, \bar{N} > 0, \phi > 0)$, where $\tilde{\lambda}$ is the dominant eigenvalue of the matrix. Then $(\lambda_1 = \tilde{\lambda} - 2\beta v_M, \bar{N}, \phi)$ is also solution to (0.18), and $\lambda_1 > 0$ since it satisfies (0.17). We thus have found a positive solution (λ_1, ϕ) to (0.16). By Theorem A.1, we have uniqueness of a positive eigensolution, so that we can conclude that $\lambda_1 = \lambda$ is the dominant eigenvalue, i.e. the Malthus parameter of the system, and $\phi = (\phi_i)_{1 \leq i \leq M}$ constant is its adjoint eigenvector. This provides us with an efficient way of computing λ numerically, by using for instance the `linalg.eig` function of Python's Numpy package, and it enables us to build a tractable characterization of λ as the unique positive root of a polynomial in some particular cases (see Theorem D.1, Appendix).

Let us now detail some particular cases where the formula is still more explicit.

Bimodal case In the case of two populations ($M=2$), we define κ by

$$\kappa := \begin{pmatrix} 1 - k_1 & k_1 \\ k_2 & 1 - k_2 \end{pmatrix}.$$

with $k_1, k_2 \in (0, 1)$. We obtain the following formula for the effective fitness (see Proposition C.1 in Appendix for detailed calculations):

$$v = \frac{\lambda}{\beta} = \left(\frac{1}{2} - k_1 \right) v_1 + \left(\frac{1}{2} - k_2 \right) v_2 + \sqrt{\left(\left(\frac{1}{2} - k_1 \right) v_1 - \left(\frac{1}{2} - k_2 \right) v_2 \right)^2 + 4k_1 k_2 v_1 v_2} \quad (0.19)$$

From this expression we deduce cases where λ superimposes with the geometric and arithmetic means of the traits:

- If κ is uniform, i.e. $k_1 = k_2 = \frac{1}{2}$, the effective fitness is the geometric mean of the traits:

$$v = m_G(v_1, v_2) = \sqrt{v_1 v_2}.$$

- If $k_1 = k_2 = \frac{1}{4}$, the effective fitness is the arithmetic mean of the traits:

$$v = m_A(v_1, v_2) = \frac{v_1 + v_2}{2}.$$

We illustrate this result on Fig. 2, and we will see for the general case how to interpret the case $k_1 = k_2 = \frac{1}{4}$.

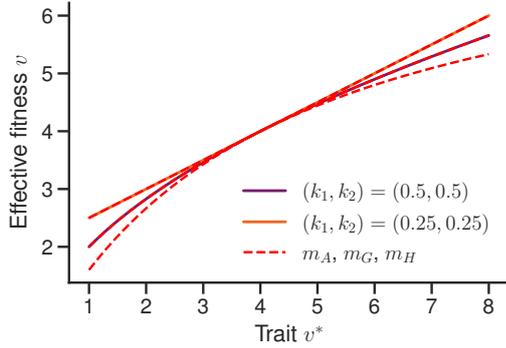


Fig. 2: (Case A, $M = 2$). Variation of the effective fitness of a population with two traits: one trait fixed, equal to $v_0 = 4$, and the other one, v^* , varying in $[1, 8]$, for different κ (full lines). Red dashed lines correspond to the arithmetic, geometric and harmonic means of v_0 and v^* , with $m_H \leq m_G \leq m_A$. When κ is uniform, i.e. $k_1 = k_2 = 0.5$ (purple), the effective fitness coincides with $m_G(v_0, v^*)$; when $k_1 = k_2 = 0.25$ (orange), v coincides with $m_A(v_0, v^*)$.

Formula (0.19) appears as a complicated average of v_1 and v_2 , which is not so easy to interpret in the general case.

Testing other types of kernel (by distinguishing whether or not k_1 and k_2 are greater than $\frac{1}{2}$) indicates that none of the classical means (arithmetic, geometric and harmonic) is, for every kernel κ and every set of traits, a bound of the effective fitness, see Fig. 5. The bounds $v \in (v_1, v_2)$ are optimal: assuming $v_1 < v_2$, we know that the species 2 having the highest growth rate tends to dominate in the case with perfect heredity (i.e. if the species 2 always give rise to individuals of the same species 2): we observe in (0.19) that if $k_2 \rightarrow 0$ (perfect heredity) then $v \rightarrow v_2$ for any value of k_1 . This is not sufficient to have reciprocally $v \rightarrow v_1$ if $k_1 \rightarrow 0$: indeed, if $k_1 \rightarrow 0$ we have $v \rightarrow \max(v_1, (1 - 2k_2)v_2)$, so that $v \rightarrow v_1$ if and only if $v_1 \geq (1 - 2k_2)v_2$. Fig. 4 illustrates this behaviour.

Finally, the case with no heredity can be modeled by coefficients $\kappa_{ij} = \kappa_j$, which in our case gives $1 - k_1 = k_2$ and the formula

$$v = \left(\frac{1}{2} - k_1\right)(v_1 - v_2) + \sqrt{\left(\frac{1}{2} - k_1\right)^2(v_1 - v_2)^2 + 4k_1k_2v_1v_2}.$$

For $k_1 = k_2 = \frac{1}{2}$ (uniform kernel) we recover the geometric mean, for $k_1 \rightarrow 0$ (and $k_2 \rightarrow 1$) we have $v \rightarrow v_1$, for $k_1 \rightarrow 1$ (and $k_2 \rightarrow 0$) we have $v \rightarrow v_2$.

In order to better illustrate how the weights ($\int N_1, \int N_2$) are influenced by κ , thus giving rise to a Malthus parameter closer to v_1 or v_2 , we plotted in Fig. 6 a 3D visualisation of N_1 and N_2 as functions of x and of a parameter of the kernel κ . As expected, we see that in all cases, the faster population dominates when its heredity is stronger.

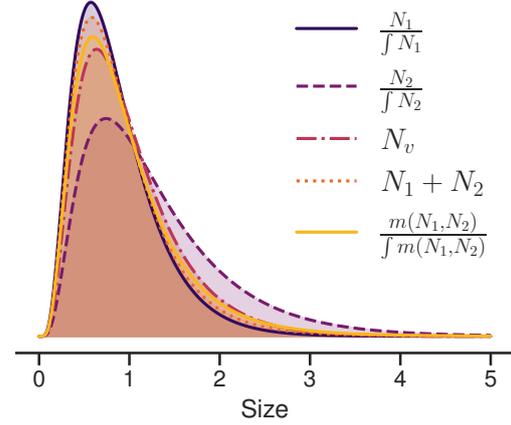


Fig. 3: (Case A, $M = 2$). Comparison of the homeostatic size distributions $\mathbf{N} = (N_1, N_2)$ in a heterogeneous population with traits $\mathbf{v} = (0.5, 2.5)$ and heredity kernel defined by $(k_1, k_2) = (0.3, 0.5)$, with the size distribution N_v in a homogeneous population. Note that in this case the profile N_v is independent of v . All the distributions have been normalized to be compared with each other. m_A stands for the arithmetic mean and m for the mean weighted by $\int N_1$ and $\int N_2$, that is such that $v = m(\mathbf{v})$ (see (0.17)).

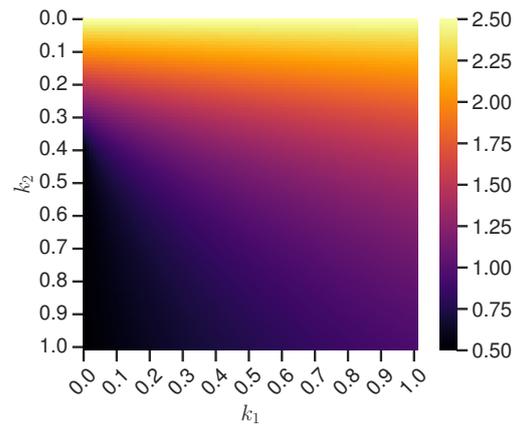


Fig. 4: (Case A, $M = 2$). Effective fitness v of a heterogeneous population with traits $\mathbf{v} = (0.5, 2.5)$ with respect to the heredity kernel κ , described by its coefficients $k_1 = \kappa_{12}$ and $k_2 = \kappa_{21}$. In particular, the map is not symmetric and we retrieve that $v \rightarrow v_2$ when $k_2 \rightarrow 0$ while v does not necessarily go to v_1 when $k_1 \rightarrow 0$.

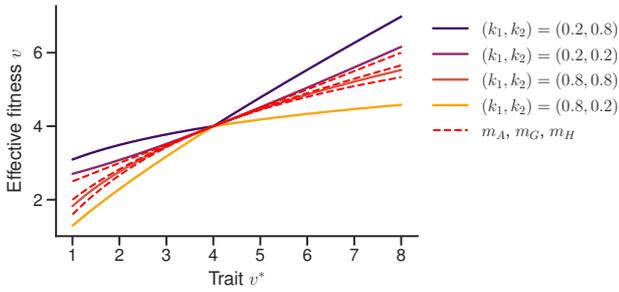


Fig. 5: (Case A, $M = 2$). Variation of the effective fitness of a population with one trait fixed, equal to $v_0 = 4$, and another trait, v^* , varying in $[1, 8]$, for different kernels κ (full lines). Red dashed lines correspond to the arithmetic, geometric and harmonic means of v_0 and v^* , with $m_H \leq m_G \leq m_A$. The first two cases display symmetric roles for the two traits, first with high self-reproducing heredity (less mixture), second when heredity consists in favoring the other species (more mixture). The third and fourth cases favor one of the trait – v^* for the third figure, 4 for the fourth. We see that for some kernels κ , the effective fitness can be smaller or larger than any classical mean of the traits. When heredity is strong (first case), the effective fitness is larger than the standard means.

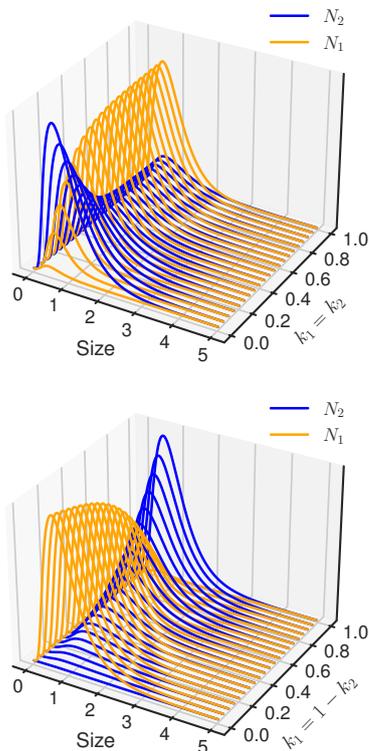


Fig. 6: (Case A, $M = 2$). Homeostatic size distributions $N = (N_1, N_2)$ in a heterogeneous population with traits $v = (0.5, 2.5)$ and heredity kernel defined by $k_1 = k_2$ (top) or $k_1 = 1 - k_2$ (bottom), with respect to k_1 .

General multimodal case For the general multimodal case, we may solve numerically (0.18) to obtain the dominant eigenvalue λ , but there is no fully explicit formula as for $M = 2$.

In the specific case where there is no heredity (the distribution of the daughter traits is independent to the mother trait), we express λ as the unique positive root of a polynomial (see Theorem D.1 and its proof in Appendix for more details). In the case of a uniform kernel $\kappa_{ij} = \frac{1}{M}$ we no longer have that the effective fitness equals the geometric mean; we can prove that depending on the trait distribution it may be larger or smaller, see Fig 2 for a numerical illustration.

In the case $\kappa_{ii} = \frac{1}{2} + \frac{1}{2M}$ and $\kappa_{ij} = \frac{1}{2M}$ however, we can prove that the effective fitness, as for $M = 2$, is equal to the arithmetic mean: to do so, we notice that

$$v = \frac{1}{M} \sum_{i=1}^M v_i, \quad \phi_j = \frac{v_j}{\frac{1}{M} \sum_{i=1}^M v_i}$$

is a solution to (0.16), and conclude by uniqueness. We also notice that

$$\int N_j = \frac{1}{v} \sum_{i=1}^M v_i \int N_i = \frac{1}{M}.$$

This case may be interpreted as one daughter keeping the trait of its mother, whereas the other daughter picks its own uniformly among all traits: then division creates all species in a uniform manner, irrespective to the species division rate, while keeping the amount of the dividing species unchanged. This may be considered as “more uniform than the uniform kernel”, in the sense that for the uniform kernel the species with higher growth rate divide more often, and when dividing gives rise to all species uniformly, thus it disappears more from the population than the species with lower growth. At equilibrium, this leads to a respective amount which is lower for the fast-dividing species than for the slowly-dividing species, as may be seen explicitly for the case $M = 2$ by the formula

$$\int N_1 = \sqrt{\frac{v_2}{v_1}} \int N_2.$$

(d) Case B: linear growth rate

Many bacteria, among other species, display a linear growth rate $\tau(x) = x$. In the homogeneous case, a simple integration of (0.10) multiplied by x shows that $\lambda_v = v$: the individuals grow exponentially at the same rate as the Malthusian parameter characterising the growth of the population. Moreover, the adjoint function is $\phi_v(x) \equiv x$. This remarkable fact remains true for any fragmentation kernel and rate, as soon as balance assumptions between coefficients ensure homeostasis. Unfortunately, these properties are not satisfied in general for heterogeneous populations. We thus restrict ourselves to the uniform division kernel $b(y, x) =$

$\frac{1}{y}\mathbb{1}_{x \leq y}$. The systems (0.8)–(0.9) become

$$\begin{cases} v_i(xN_i(x))' + \lambda N_i(x) = -v_i x \beta(x) N_i(x) \\ \quad + 2 \sum_{j=1}^M \kappa_{ji} v_j \int_x^\infty \beta(y) N_j(y) dy, \\ N_i \geq 0, \quad \sum_{j=1}^M \int_0^\infty N_j(x) dx = 1, \end{cases} \quad (0.20)$$

$$\begin{cases} -v_i x \phi_i'(x) + \lambda \phi_i(x) = -v_i x \beta(x) \phi_i(x) \\ \quad + 2v_i \beta(x) \sum_{j=1}^M \kappa_{ij} \int_0^x \phi_j(y) dy, \\ \phi_i \geq 0, \quad \sum_{j=1}^M \int_0^\infty N_j(s) \phi_j(s) dx = 1. \end{cases} \quad (0.21)$$

In [7], an explicit solution for the homogeneous case with $\beta(x) = \beta x^{n-1}$ with $n \geq 1$ is given by

$$N_v(x) = C e^{-\frac{\beta}{n} x^n}.$$

We notice that this formula remains true for any division rate $\beta(x)$, for which we obtain, for a certain normalization constant C ,

$$N_v(x) = C e^{-\int_0^x \beta(s) ds}.$$

We thus look for solutions $N_i(x)$ of the form

$$N_i(x) := C \left(\int N_i \right) e^{-\int_0^x \beta(s) ds}, \quad (0.22)$$

with $C = \left(\int e^{-\int_0^x \beta(s) ds} dx \right)^{-1}$. Denoting the effective fitness $v = \lambda$, by plugging (0.22) into (0.20) and dividing by $C e^{-\int_0^x \beta(s) ds}$, we obtain the system

$$v \int N_i = -v_i \int N_i + 2 \sum_{j=1}^M \kappa_{ji} v_j \int N_j. \quad (0.23)$$

This is exactly the matrix equation (0.18) in the case $\beta = 1$, so that all the same conclusions as for Case A hold. We can thus write the effective fitness v as a weighted average of the traits v_i : summing all the equations (0.23), we obtain once again (0.17). Note that whereas the shape of the solution is preserved for the eigenfunctions N_i , the adjoint eigenfunctions ϕ_i are no longer defined by linear functionals.

(e) Is heterogeneity detrimental or beneficial?

In all of the previous analyses, we have shown that the question of whether heterogeneity is detrimental or beneficial cannot be answered rigorously without deciding which is the correct average to model the costs associated with each trait. However, let us explore here how the number of traits and their variance can affect the effective fitness of the population.

Influence of the number of traits We fix the interval \mathcal{V} of the traits and we test the influence of the number M of traits

on the value of the effective fitness. In the framework of Cases A or B, for various M , we compute an approximation of the effective fitness v^M for a given kernel κ_M when the set of traits is uniformly distributed over \mathcal{V} . The two first plots of Fig. 7 show that, for a kernel "more uniform than uniform", the effective fitness does not depend of the number M of traits. The last plots shows that even when the kernels $(\kappa_M)_{M \geq 2}$ are independent and identically distributed random matrices, the effective fitness seems v^M converges to some value v^∞ as M grows.

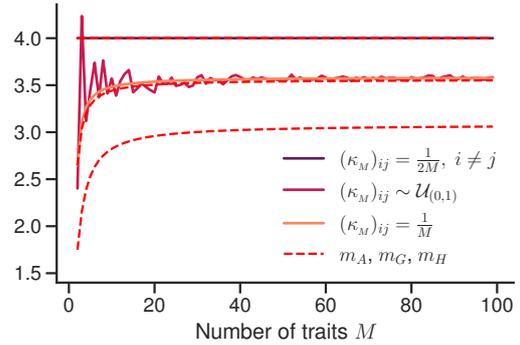


Fig. 7: (Case A, $M > 2$). Variation of the effective fitness of a population defined by traits \mathcal{V}_M regularly spaced in \mathcal{V} and the kernel κ_M , with respect to M . Obtained with $\mathcal{V} = [1, 7]$.

Varying the variance σ of the set of traits \mathcal{V} for fixed number of traits M and fixed mean trait \bar{v} . We test the influence of the variance between traits by fixing the number M of traits and considering the sets of traits $v^\sigma = (v_1^\sigma, \dots, v_M^\sigma)$, for several values of σ , distributed over the interval \mathcal{V}_σ such that:

$$v_M^\sigma - v_1^\sigma = \sigma, \quad m(v^\sigma) = \bar{v}, \quad \forall \sigma > 0, \quad (0.24)$$

for m one of the means defined by (0.14). When $m = m_A$ is the arithmetic mean, the v_i^σ are distributed uniformly in \mathcal{V}_σ , while for $m = m_G$ and m_H this is the $\log(v_i^\sigma)$ and $\frac{1}{v_i}$ which are equally spaced, respectively.

It was observed by Olivier [28] that for a linear growth rate, in the absence of heredity and for \bar{v} defined as the mean trait at birth

$$\bar{v} = \sum_{i=1}^M v_i \kappa_i,$$

reducing the variance σ among individual traits enhances the overall growth of the population (i.e. increases the Malthus parameter, or equivalently the effective fitness). The same type of result is stated by Lin and Amir [20]: they besides consider the case of heredity with positive correlations (reported e.g. in *E. coli*) reporting that the variability in growth rate is detrimental to population growth providing that the mother and daughter cells' growth rates are not too strongly positively correlated. This may be directly observed on the formula (0.19): if $k_1, k_2 \rightarrow 0$, v tends to v_2 , the largest possible value for v . Similarly, in

the general case, we can see on (0.23) that if $\kappa_{Mi} \rightarrow \delta_{i=M}$, we have $v \rightarrow v_M$ and $\frac{N_i}{N_M} \rightarrow 0$ for $i < M$ (see Fig. 6). The population with higher growth rate reproduces itself more, and thus dominates the other subpopulations.

To specifically assess the influence of the mother-daughter correlations in growth rate in how variability affects population growth, we consider kernels $\kappa = \kappa(\alpha)$ of the form

$$\kappa_{ij}(\alpha) = \begin{cases} \alpha, & \text{if } i = j, \\ \frac{1-\alpha}{M-1}, & \text{if } i \neq j, \end{cases} \quad \forall (i, j) \in \{1, \dots, M\}, \quad (0.25)$$

for different values of $\alpha \in [0, 1)$. We extend the results of Olivier [28] and Lin and Amir [20] (linear growth rate and equal mitosis) to the Case A (constant coefficients, Fig. 8). In Supplementary Information, we simulated the case of equal mitosis with linear growth rate and constant or linear β .

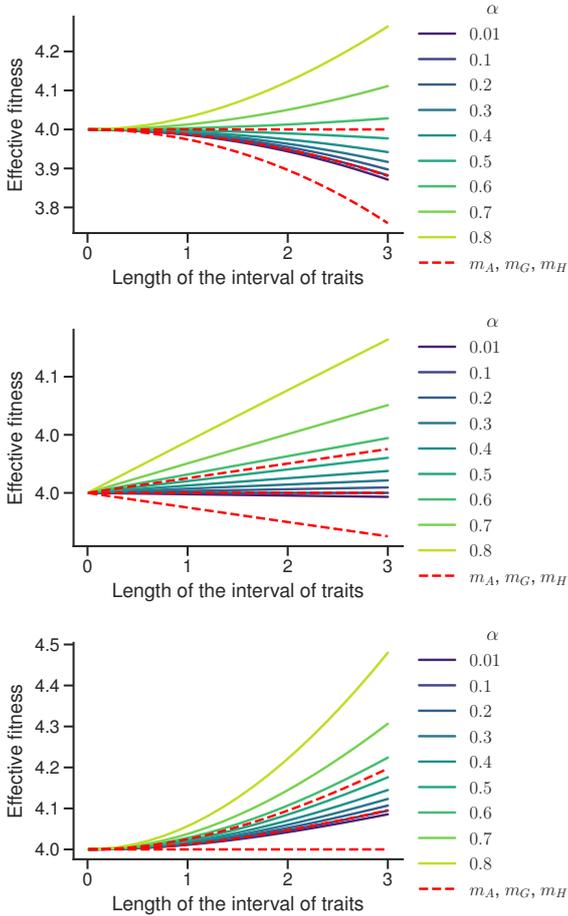


Fig. 8: (Case A, $M = 10$). Variation of the effective fitness of a population of $M = 10$ traits distributed as described in (0.24) with $m = m_A$ for the figure on top, $m = m_G$ for the figure in the middle and $m = m_H$ for the figure on the bottom. The parameters are $\bar{v} = 4$, and kernel $\kappa(\alpha)$ satisfying (0.25), with respect to σ and for different values of α .

The numerical results, plotted on Fig. 8 and Fig. 9 (and Fig. 10) are the following:

- When the variance σ of the set of traits is fixed, the effective fitness v_α increases with α , i.e with the mother-daughter correlations in growth rate α .
- Cell-to-cell variability in growth rate, when leaving the arithmetic mean unchanged, either decreases or increases population growth depending on whether or not α is lower or greater than a threshold α_0 . Numerical simulations on Fig. 9 illustrate that for $M > 2$, the threshold value is $\alpha_0 := \frac{1}{2} + \frac{1}{2M}$ and $v_{\alpha_0} = v_A$ the arithmetic mean.

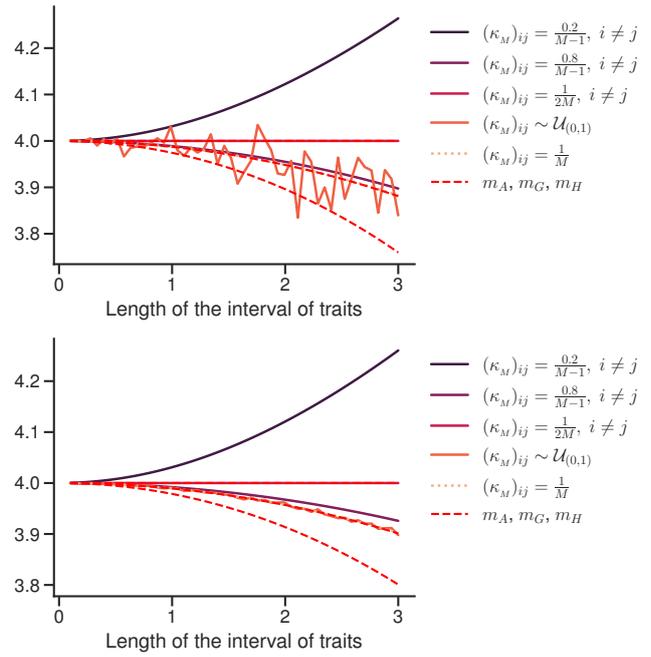


Fig. 9: Variation of the effective fitness of a population whose traits are distributed as described in (0.24) with $m = m_A$, with the kernel κ_M , with respect to σ for $M = 10$ and $M = 100$. The last four pairs of figures correspond to kernels $\kappa = \kappa(\alpha)$ satisfying (0.25) (with α equal, from top to bottom, to 0.8, 0.2, $\frac{1}{2} + \frac{1}{2M}$ and $\frac{1}{M}$). Variability is beneficial for α large enough, i.e mother/daughter cells' growth rates are strongly positively correlated. $M = 10$ for the figure on top and $M = 100$ for the figure on the bottom.

Conclusion

In this article, we have examined the impact of heterogeneous growth on the fitness of a population. To this end, we have put forth and discussed a general framework that could be adapted to other situations. This framework involves comparing a heterogeneous population, taken in a constant environment without competition, with a fitness-identical homogeneous population. In two relatively general case studies, namely constant growth and division and general division kernel (case A), and linear growth

with uniform division kernel and general division rate (case **B**), explicit formulae of the effective fitness as a weighted average of the traits were obtained. The weights are represented by the relative number of individuals exhibiting a given trait. It is noteworthy that in both cases, these weights are expressed as quantities dependent on the *total* population, rather than on the *dividing* population or on the population at birth. We have then explored numerically these two cases. To reach a conclusion regarding the impact of heterogeneity, and whether it is beneficial or detrimental, further exploration of the associated costs is necessary. This entails investigating when and how the cost of each trait is supported by individuals. For example, is it supported by cells uniformly all along their life, i.e. proportional to $\int N_i$, or is it proportional to the individuals' sizes, i.e. proportional to $\int x N_i$, or yet is it supported only by dividing cells, then involving quantities like $\int \tau(x)\beta(x)N_i(x) dx$, or is it something else, such as another moment or any other weight? Only by exploring this question can we give a definitive answer to the problem at hand.

References

- [1] Dag L Aksnes and Francisco J Cao. Inherent and apparent traits in microbial nutrient uptake. *Marine ecology progress series*, 440:41–51, 2011.
- [2] Ariel Amir. Is cell size a spandrel? *Elife*, 6:e22186, 2017.
- [3] Étienne Bernard, Marie Doumic, and Pierre Gabriel. Cyclic asymptotic behaviour of a population reproducing by fission into two equal parts. *Kinetic & Related Models*, 12(3), 2019.
- [4] Oana Carja and Joshua B Plotkin. The evolutionary advantage of heritable phenotypic heterogeneity. *Scientific reports*, 7(1):5090, 2017.
- [5] Bertrand Delyon, Benoite de Saporta, Nathalie Krell, and Lydia Robert. Investigation of asymmetry in e. coli growth rate. *Case Studies In Business, Industry And Government Statistics*, 7(1):1–13, 2018.
- [6] Marie Doumic and Marc Hoffmann. Individual and Population Approaches for Calibrating Division Rates in Population Dynamics: Application to the Bacterial Cell Cycle. In *Modeling and Simulation for Collective Dynamics*, volume Volume 40 of *Lecture Notes Series, Institute for Mathematical Sciences, National University of Singapore*. WORLD SCIENTIFIC, 2023.
- [7] Marie Doumic Jauffret and Pierre Gabriel. Eigenelements of a general aggregation-fragmentation model. *Mathematical Models and Methods in Applied Sciences*, 20(05), 2010.
- [8] Michael B Elowitz, Arnold J Levine, Eric D Siggia, and Peter S Swain. Stochastic gene expression in a single cell. *Science*, 297(5584):1183–1186, 2002.
- [9] Ines Fragata, Alexandre Blanckaert, Marco Antonio Dias Louro, David A Liberles, and Claudia Bank. Evolution in the light of fitness landscape theory. *Trends in ecology and evolution*, 34(1):69–82, 2019.
- [10] Arthur Genthon. Analytical cell size distribution: lineage-population bias and parameter inference. *Journal of the Royal Society Interface*, 19(196):20220405, 2022.
- [11] Arthur Genthon and David Lacoste. Fluctuation relations and fitness landscapes of growing cell populations. *Scientific Reports*, 10(1):11889, 2020.
- [12] Stéphane Honoré, Florence Hubert, Magali Tournus, and Diana White. A growth-fragmentation approach for modeling microtubule dynamic instability. *Bulletin of Mathematical Biology*, 81:722–758, 2019.
- [13] Lionel Jouvét, Alexandro Rodriguez-Rojas, and Ulrich K Steiner. Demographic variability and heterogeneity among individuals within and among clonal bacteria strains. *Oikos*, 127(5):728–737, 2018.
- [14] R Kachouri-Lafond, B Dujon, E Gilson, E Westhof, C Fairhead, and MT Teixeira. Large telomerase rna, telomere length heterogeneity and escape from senescence in candida glabrata. *FEBS letters*, 583(22):3605–3610, 2009.
- [15] Daniel J Kiviet, Philippe Nghe, Noreen Walker, Sarah Boulineau, Vanda Sunderlikova, and Sander J Tans. Stochasticity of metabolism and growth at the single-cell level. *Nature*, 514(7522):376–379, 2014.
- [16] Peter M Lansdorp, Nico P Verwoerd, Frans M Van De Rijke, Visia Dragowska, Marie-Terese Little, Roeland W Dirks, Anton K Raap, and Hans J Tanke. Heterogeneity in telomere length of human chromosomes. *Human molecular genetics*, 5(5):685–691, 1996.
- [17] Sasha F Levy. Cellular heterogeneity: benefits besides bet-hedging. *Current Biology*, 26(9):R355–R357, 2016.
- [18] Sasha F Levy, Naomi Ziv, and Mark L Siegal. Bet hedging in yeast by heterogeneous, age-correlated expression of a stress protectant. *PLoS biology*, 10(5):e1001325, 2012.
- [19] Mary E Lidstrom and Michael C Konopka. The role of physiological heterogeneity in microbial population behavior. *Nature chemical biology*, 6(10):705–712, 2010.
- [20] Jie Lin and Ariel Amir. The effects of stochasticity at the single-cell level and cell size control on the population growth. *Cell systems*, 5(4):358–367, 2017.
- [21] Elena Litchman, Paula de Tezanos Pinto, Christopher A. Klausmeier, Mridul K. Thomas, and Kohei Yoshiyama. *Linking traits to species diversity and community structure in phytoplankton*, pages 15–28. Springer Netherlands, Dordrecht, 2010.
- [22] LA Magdanova and NV Golyasnaya. Heterogeneity as an adaptive trait of microbial populations. *Microbiology*, 82:1–10, 2013.
- [23] Guillaume Martin and Lionel Roques. The nonstationary dynamics of fitness distributions: asexual model with epistasis and standing variation. *Genetics*, 204(4):1541–1558, 2016.
- [24] Henry H Mattingly and Thierry Emonet. Collective behavior and nongenetic inheritance allow bacterial populations to adapt to changing environments. *Proceedings of the National Academy of Sciences*, 119(26):e2117377119, 2022.
- [25] P. Michel. Existence of a solution to the cell division eigenproblem. *Math. Models Methods Appl. Sci.*, 16(7, suppl.):1125–1153, 2006.

- [26] John RS Newman, Sina Ghaemmaghami, Jan Ihmels, David K Breslow, Matthew Noble, Joseph L DeRisi, and Jonathan S Weissman. Single-cell proteomic analysis of *s. cerevisiae* reveals the architecture of biological noise. *Nature*, 441(7095):840–846, 2006.
- [27] Takashi Nozoe, Edo Kussell, and Yuichi Wakamoto. Inferring fitness landscapes and selection on phenotypic states from single-cell genealogical data. *PLoS genetics*, 13(3):e1006653, 2017.
- [28] Adelaïde Olivier. How does variability in cells aging and growth rates influence the malthus parameter? *Kinetic and Related Models*, 10(2):481–512, 2017.
- [29] Benoit Perthame. *Transport Equations in Biology*. Frontiers in Mathematics. Birkhäuser Verlag, 2007.
- [30] Benoit Perthame and Lenya Ryzhik. Exponential decay for the fragmentation or cell-division equation. *Journal of Differential Equations*, 210(1), 2005.
- [31] Anais Rat and Magali Tournus. Growth-fragmentation model for a population presenting heterogeneity in growth rate: Malthus parameter and long-time behavior. *Kinetic and Related Models*, 17(4):533–576, 2024.
- [32] Lydia Robert, Marc Hoffmann, Nathalie Krell, Stéphane Aymerich, Jérôme Robert, and Marie Doumic. Division in *escherichia coli* is triggered by a size-sensing rather than a timing mechanism. *BMC biology*, 12:1–10, 2014.
- [33] Lydia Robert, Jean Ollion, Jerome Robert, Xiaohu Song, Ivan Matic, and Marina Elez. Mutation dynamics and fitness effects followed in single cells. *Science*, 359(6381):1283–1286, 2018.
- [34] Chao Shi, Lin Chao, Audrey Menegaz Proenca, Andrew Qiu, Jasper Chao, and Camilla U Rang. Allocation of gene products to daughter cells is determined by the age of the mother in single *escherichia coli* cells. *Proceedings of the Royal Society B*, 287(1926):20200569, 2020.
- [35] Siliang Song and Jianzhi Zhang. Effective fitness under fluctuating selection with genetic drift. *G3 Genes | Genomes | Genetics*, page jkad230, 10 2023.
- [36] Sattar Taheri-Araghi, Serena Bradde, John T. Sauls, Norbert S. Hill, Petra Anne Levin, Johan Paulsson, Massimo Vergassola, and Suckjoon Jun. Cell-Size Control and Homeostasis in Bacteria. *Current Biology*, 25(3), 2015.

Data Accessibility. The code and data to reproduce the figures in the paper are available at: <https://github.com/anais-rat/growth-fragmentation>.

Competing Interests. The authors declare that they have no competing financial interests.

Funding. M.D. and A.R. have been partially supported by the ERC Starting Grant SKIPPER AD (number 306321)

Disclaimer. We have not used AI-assisted technologies in creating this article.

Appendices

A Assumptions for a Malthusian behaviour

Theorem A.1. Assume that case **A** (0.12) or case **B** (0.13) holds for τ, β and b , and that b satisfies (0.4), β satisfies (0.3) and κ satisfies (0.1)–(0.2). Then there exists a unique Malthus parameter $\lambda = \lambda_{(v, \kappa)} > 0$, a unique nonnegative steady profile $(N_i)_{1 \leq i \leq M} \in W_1^1(\mathbb{R}_+)^M$ and a unique nonnegative adjoint state $(\phi_i) \in (L_{loc}^\infty(0, +\infty))^M$ solution to (0.8)–(0.9). If in addition to that, for all $i \in \{1, \dots, M\}$, we have $0 \leq n_i^{in}(x) \leq CN_i(x)$ for some $C > 0$, then the long time behaviour of the unique solution $n = (n_1, \dots, n_M) \in \mathcal{C}(\mathbb{R}_+, L^1(\Phi_1(x)dx)) \times \dots \times \mathcal{C}(\mathbb{R}_+, L^1(\Phi_M(x)dx))$ to (0.5) is given by

$$n_i(t, x)e^{-\lambda t} \xrightarrow[t \rightarrow \infty]{} \rho N_i(x), \quad L^1(\mathbb{R}_+, \phi_i(x)dx), \quad \text{for all } i \in \{1, \dots, M\},$$

where the multiplicative factor ρ is

$$\rho = \sum_{j=1}^M \int_0^\infty n_j^{in}(x)\phi_j(x) dx.$$

In the case $M = 1$, a proof of Theorem A.1 is written in [29], chapter 4.2, for cases which include the assumptions of case **A**, i.e. a constant growth rate $\tau(x) = 1$, a constant division rate $\beta(x) = 1$ and a general division kernel b satisfying (0.4). A generalisation to $M \geq 2$ can be easily made from this result.

In [31], a proof of Theorem A.1 is written for cases which almost include the assumptions of Case **A** and **B**, except that it assumed a division in equal sizes $b(x, y) = \delta_{x=y}$. The mitosis case was studied preferentially due to the fact that interestingly, if $\tau(x) = x$, having $M \geq 2$ allowed to avoid the oscillatory behaviour observed in the case $M = 1$ [3]. However, the proof from [31] can be generalized to include Cases **A** and **B**.

B Existence and uniqueness of the effective fitness

Proposition B.1 (Existence and uniqueness of the effective fitness). Let $M \geq 2$ an integer, $0 < v_1 < \dots < v_M$ given traits. Assume τ, β and b are such that the existence and uniqueness of the triplet (λ, N_i, ϕ_i) with $\lambda = \lambda_{v, \kappa} > 0$, $(N_i)_{1 \leq i \leq M} \in W^{1,1}(\mathbb{R}_+)^M$ and $(\phi_i)_{1 \leq i \leq M} \in (L_{loc}^\infty(0, +\infty))^M$ solution to (0.8)–(0.9) is guaranteed. Then there exists a unique effective trait $v \in [v_1, v_M]$ as defined by Definition 0.1. In Cases **A** and **B**, it satisfies

$$v = \sum_{i=1}^M v_i \int_0^\infty N_i(x) dx. \quad (\text{A } 1)$$

Proof. Consider the eigenproblem (0.10) (0.11) for $M = 1$, and with parameters τ, β, b . For a given $v > 0$, existence and uniqueness of the triplet (λ_v, N_v, ϕ_v) follows as a particular case of the eigenproblem studied in several articles [30, 25, 29, 7]. We notice that for homogeneity reasons we have $\lambda_v = v\lambda_1$, hence the existence and uniqueness of v such that $\lambda_v = \lambda_{v, \kappa}$: we simply define $v := \frac{\lambda_{v, \kappa}}{\lambda_1}$. Though the proof of the inclusion $v \in [v_1, v_M]$ is already briefly sketched in [31, Theorem 2.3], we detail it here for sake of completeness. More precisely, we prove that

$$v \geq v_1,$$

i.e. that

$$\lambda_{v, \kappa} \geq \lambda_{v_1},$$

where $(\lambda_{v_1}, N_{v_1}, \phi_{v_1})$ is the solution to (0.10) (0.11) with $v = v_1$. We multiply (0.8) by $\phi_{v_1}(x)$, integrate the result with respect to x and sum for $i = 1 \dots M$ to get

$$\begin{aligned} \lambda_{v, \kappa} \sum_{i=1}^M \int_0^\infty N_i(x)\phi_{v_1}(x) dx &= -v_i \sum_{i=1}^M \int_0^\infty (\tau N_i)'(x)\phi_{v_1}(x) dx - v_i \sum_{i=1}^M \int_0^\infty \tau(x)\beta(x)N_i(x)\phi_{v_1}(x) dx \\ &\quad + 2 \sum_{i=1}^M \int_0^\infty \phi_{v_1}(x) \int_x^\infty \tau(y)\beta(y)b(y, x) \sum_{j=1}^M \kappa_{ji}v_j N_j(y) dy dx \end{aligned}$$

Then we integrate by part the first term of the right hand side, use Fubini for the third term and we obtain

$$\lambda_{v, \kappa} \sum_{i=1}^M \int_0^\infty N_i(x)\phi_{v_1}(x) dx = \lambda_{v_1} \sum_{i=1}^M \frac{v_i}{v_1} \int_0^\infty N_i(x)\phi_{v_1}(x) dx$$

which implies the result since $v_i \geq v_1$ for all i . The proof for $v \leq v_M$ is similar.

In particular, in Case **A**, $\lambda_w = \beta w$ and in Case **B**, $\lambda_w = w$. The effective fitness is then defined in Case **A** by

$$v = \frac{\lambda_{\mathbf{v}, \kappa}}{\beta}$$

and in Case **B** by

$$v = \lambda_{\mathbf{v}, \kappa}.$$

Finally, in case **A**, we sum and integrate (0.15) with respect to i and x , which implies

$$\lambda_{\mathbf{v}, \kappa} = \beta \sum_{i=1}^M v_i \int_0^{\infty} N_i(x) dx,$$

In case **B**, we plug $N_i(x) = N_i(0)e^{-\int_0^x \beta(s) ds}$ into (0.20), then we sum on all i and integrate to obtain (A 1). \square

C Proof of the formula for the weighted average for $M = 2$

Proposition C.1 (General kernel – $M = 2$). Assume $M = 2$ and that case **A** (0.12) holds for τ, β and b , and that b satisfies (0.4). Let $k_1, k_2 \in (0, 1)$ and κ a kernel defined by

$$\kappa := \begin{pmatrix} 1 - k_1 & k_1 \\ k_2 & 1 - k_2 \end{pmatrix}.$$

Then κ satisfies (0.2)(0.1), and the adjoint vector (ϕ_1, ϕ_2) solution to (0.9) is constant with respect to x and the associated Malthus parameter $\lambda > 0$ is

$$\lambda = \beta \left(\frac{1}{2} - k_1 \right) v_1 + \left(\frac{1}{2} - k_2 \right) v_2 + \sqrt{\left(\left(\frac{1}{2} - k_1 \right) v_1 - \left(\frac{1}{2} - k_2 \right) v_2 \right)^2 + 4k_1 k_2 v_1 v_2} =: \beta v; \quad (\text{A } 1)$$

where v is the effective fitness associated with (0.5).

Proof. We look for a constant solution $\phi := (\phi_1, \phi_2) \in \mathbb{R}^2$, with $\phi_1, \phi_2 > 0$, to the adjoint problem (0.9), i.e.

$$\begin{cases} (\lambda + \beta v_1) \phi_1 = 2\beta (v_1(1 - k_1)\phi_1 + v_1 k_1 \phi_2), \\ (\lambda + \beta v_2) \phi_2 = 2\beta (v_2 k_2 \phi_1 + v_2(1 - k_2)\phi_2). \end{cases} \quad (\text{A } 2)$$

With the notation $\alpha := \frac{\phi_2}{\phi_1}$, this resumes to find $(\lambda, \alpha) \in (0, \infty)^2$ satisfying

$$\begin{cases} 2\beta v_1 \left(\left(\frac{1}{2} - k_1 \right) + k_1 \alpha \right) = \lambda, \\ 2\beta v_2 \left(k_2 + \left(\frac{1}{2} - k_2 \right) \alpha \right) = \lambda \alpha. \end{cases} \quad (\text{A } 3)$$

We deduce the following equation of degree 2 on α

$$k_1 v_1 \alpha^2 + \left(\left(\frac{1}{2} - k_1 \right) v_1 - \left(\frac{1}{2} - k_2 \right) v_2 \right) \alpha - k_2 v_2 = 0$$

with real solutions (since $k_1, k_2 > 0$)

$$\alpha_{\pm} = \frac{\left(\frac{1}{2} - k_2 \right) v_2 - \left(\frac{1}{2} - k_1 \right) v_1 \pm \sqrt{\left(\left(\frac{1}{2} - k_1 \right) v_1 - \left(\frac{1}{2} - k_2 \right) v_2 \right)^2 + 4k_1 k_2 v_1 v_2}}{2k_1 v_1}.$$

Since $\alpha_- < 0$ and $\alpha_+ > 0$, this implies $\alpha = \alpha_+$, and thus we obtain (0.19). It remains to prove that this defines a positive λ . If $s := \left(\frac{1}{2} - k_1 \right) v_1 + \left(\frac{1}{2} - k_2 \right) v_2 \geq 0$, then $\lambda > 0$. If $s < 0$, $\lambda > 0$ if and only if

$$\begin{aligned} & \left(\left(\frac{1}{2} - k_1 \right) v_1 + \left(\frac{1}{2} - k_2 \right) v_2 \right)^2 < \left(\left(\frac{1}{2} - k_1 \right) v_1 - \left(\frac{1}{2} - k_2 \right) v_2 \right)^2 + 4k_1 k_2 v_1 v_2 \\ \iff & \left(\frac{1}{2} - k_1 \right) \left(\frac{1}{2} - k_2 \right) v_1 v_2 < k_1 k_2 v_1 v_2 \\ \iff & k_1 + k_2 > \frac{1}{2} \end{aligned}$$

which is verified for $s < 0$ (indeed $k_1 + k_2 \leq \frac{1}{2}$ implies that k_1 and k_2 are lower than $\frac{1}{2}$ and thus that $s \geq 0$). We have proven that λ defined by (0.19) is always positive, so by uniqueness of a solution (λ, ϕ) to (0.9), it is the Malthus parameter associated with (0.8)-(0.9). \square

D The effective fitness as the (unique) positive root of a polynomial in the multimodal case with no heredity

For a given M and a set of traits $\{v_1, \dots, v_M\}$, we introduce the following notations

$$S_0 := 1, \quad S_k := \sum_{\substack{I \subset \{1, \dots, M\} \\ \#I=k}} \prod_{\ell \in I} v_\ell, \quad k \in \{1, \dots, M\}. \quad (\text{A } 1)$$

Note that we call *heredity* the fact that the trait of the dividing individual influences the trait of its offspring, either positively, favoring its own trait, or negatively, favoring other traits. Hence the non-hereditary case consists in an heredity kernel which does not depend on the parental trait, namely satisfying the following assumption:

$$\kappa_{ij} = \kappa_j, \quad \forall (i, j) \in \{1, \dots, M\}^2. \quad (\text{A } 2)$$

For such kernels, we obtain the following explicit expression for the effective fitness.

Theorem D.1 (Effective fitness as the unique positive root of an explicit polynomial). *Assume $M > 0$ and that case A (0.12) holds for τ, β and b , and that b satisfies (0.4). Let $\kappa = (\kappa_{ij})$ satisfy (0.1)-(0.2), let us moreover assume that the kernel κ satisfies (A 2), i.e. that there is no heredity at division. Let (λ, ϕ_i, N_i) be the unique solution to (0.8)-(0.9). Then we have $\lambda = \beta v$ where the effective fitness v is the unique positive root of the following polynomial, whose coefficients only depend on $(v_i)_{1 \leq i \leq M}$ and κ*

$$P(u) = \sum_{n=0}^M \left(S_{M-n} - 2 \sum_{j=1}^M \kappa_j \sum_{\substack{I \subset \{1, \dots, M\} \setminus \{j\} \\ \#I=M-n}} \prod_{k \in I} v_k \right) u^n \quad (\text{A } 3)$$

with the conventions given by

$$\prod_{x \in \emptyset} x = 1, \quad \sum_{x \in \emptyset} x = 0. \quad (\text{A } 4)$$

In addition, the adjoint vector $\phi = (\phi_1, \dots, \phi_M)$ solution to (0.9) is constant with respect to x and is defined up to renormalization by

$$\phi_i : x \mapsto \frac{v_i}{v_i + v}, \quad i \in \{1, \dots, M\}. \quad (\text{A } 5)$$

Proof. Looking for a non-zero solution to (0.16) that is constant with respect to x is equivalent to looking for $(\lambda, \phi) \in (0, +\infty) \times (0, +\infty)^M$ solution to

$$\lambda \phi_i = -\beta v_i \phi_i + 2\beta v_i \sum_{j=1}^M \kappa_j \phi_j, \quad i \in \{1, \dots, M\}. \quad (\text{A } 6)$$

Using $v = \frac{\lambda}{\beta}$, (A 6) is equivalent to

$$\begin{aligned} \frac{v + v_i}{2v_i} \phi_i &= \sum_{j=1}^M \kappa_j \phi_j, \quad \forall i \in \{1, \dots, M\}, \\ \Leftrightarrow \begin{cases} \frac{v + v_1}{2v_1} \phi_1 = \sum_{j=1}^M \kappa_j \phi_j, \\ \phi_i = \frac{v_i(v + v_1)}{v_1(v + v_i)} \phi_1, \quad \forall i \in \{2, \dots, M\}, \end{cases} \\ \Leftrightarrow \begin{cases} \phi_1 = 2 \sum_{j=1}^M \kappa_j \frac{v_j}{(v + v_j)} \phi_1, \\ \phi_i = \frac{v_i(v + v_1)}{v_1(v + v_i)} \phi_1, \quad \forall i \in \{2, \dots, M\}, \end{cases} \end{aligned}$$

We multiply the first line by $\prod_{1 \leq k \leq M} (v + v_k)$ and obtain

$$\begin{cases} P(v) \phi_1 = 0, \\ \phi_i = \frac{v_i(v + v_1)}{v_1(v + v_i)} \phi_1, \quad \forall i \in \{2, \dots, M\}, \end{cases} \quad (\text{A } 7)$$

where P is the polynomial defined by:

$$\begin{aligned}
P(u) &= 2 \sum_{j=1}^M \left(\kappa_j v_j \prod_{\substack{k=1 \\ k \neq j}}^M (u + v_k) \right) - \prod_{k=1}^M (u + v_k), \\
&= 2 \sum_{j=1}^M \kappa_j \prod_{k=1}^M (u + v_k) - 2u \sum_{j=1}^M \kappa_j \prod_{\substack{k=1 \\ k \neq j}}^M (u + v_k) - \prod_{k=1}^M (u + v_k), \\
&= \prod_{k=1}^M (u + v_k) - 2u \sum_{j=1}^M \kappa_j \prod_{\substack{k=1 \\ k \neq j}}^M (u + v_k), \\
&= \sum_{n=0}^M \left(S_{M-n} - 2 \sum_{j=1}^M \kappa_j \sum_{\substack{I \subset \{1, \dots, M\} \setminus \{j\} \\ \#I = M-n}} \prod_{k \in I} v_k \right) u^n.
\end{aligned}$$

From the first equality of (A 7), either $\phi_1 = 0$ or $P(v) = 0$. If $\phi_1 = 0$, the second line of (A 7) implies that for all $j \in \{1, \dots, M\}$ we also have $\phi_j = 0$, i.e. $\phi \equiv 0$. By contradiction, $P(v) = 0$. Then, if $(\beta v, \Phi)$ is a constant solution to (0.16), then $P(v) = 0$ and $\Phi_i = \frac{v_i(v+v_1)}{v_1(v+v_i)} \Phi_1$. Conversely, for any $v > 0$ such that $P(v) = 0$, then there exists $\lambda = \beta v$ and $\phi = (\phi_1, \dots, \phi_M) \in (0, +\infty)^M$ such that (A 6) is satisfied. By uniqueness of the adjoint problem (0.16), this proves that P has at most one positive root. Recalling the conventions (A 4), the term in front of u^M is

$$S_0 - 2 \sum_{j=1}^M \kappa_j \prod_{k \in \emptyset} v_k = 1 - 2 \sum_{j=1}^M \kappa_j = -1,$$

and the constant term is

$$S_M - 2 \sum_{j=1}^M \kappa_j \sum_{I \in \emptyset} \prod_{k \in I} v_k = S_M.$$

Therefore, we have

$$P(+\infty) = -\infty, \quad P(0) > 0,$$

so that P has at least one positive root v .

□

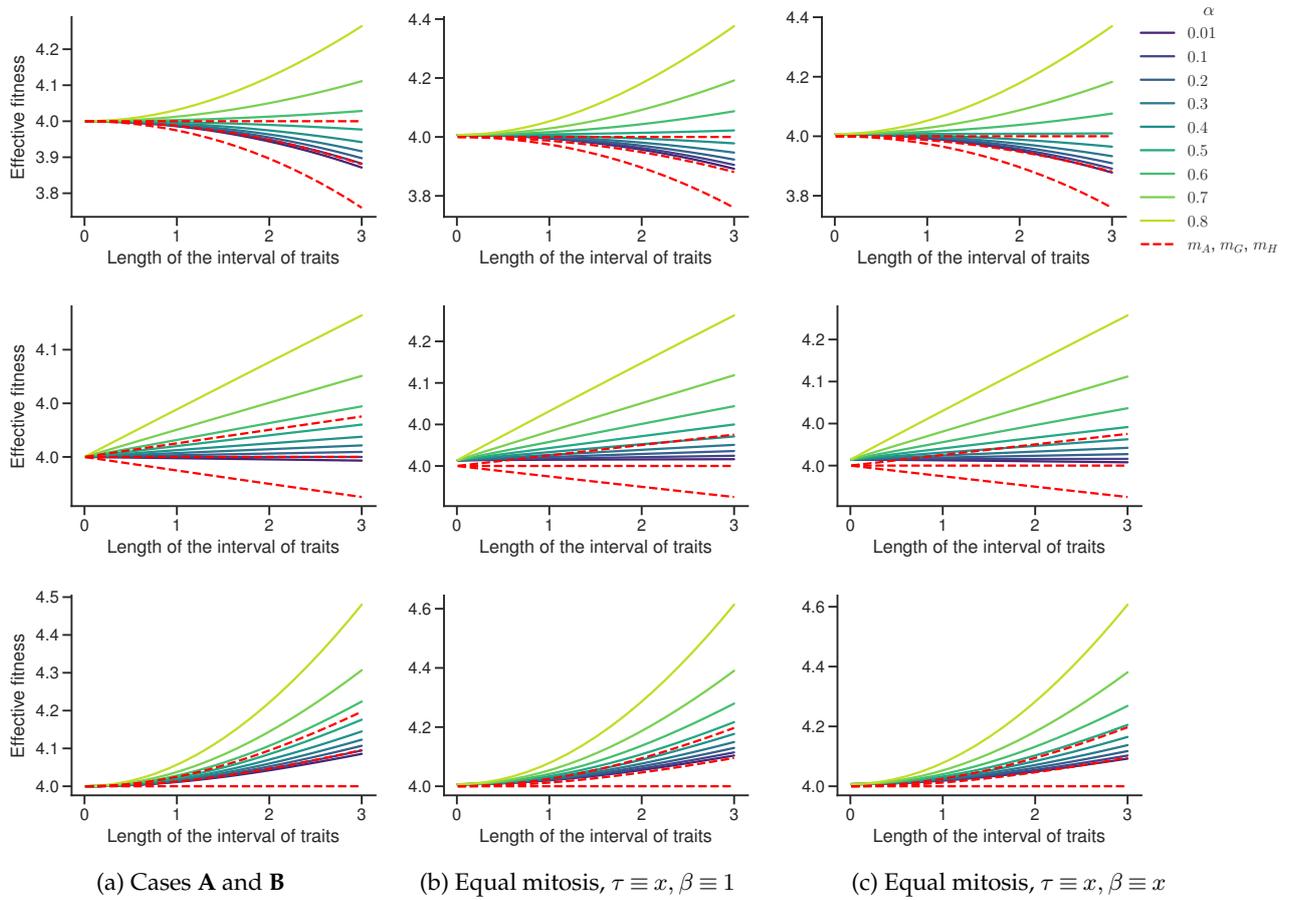


Fig. 10: Variation of the effective fitness of a population of $M = 10$ traits distributed as described in (0.24) with $m = m_A$ for the figures on top, $m = m_G$ for the figures in the middle and $m = m_H$ for the figures on the bottom. The parameters are $\bar{v} = 4$, and kernel $\kappa(\alpha)$ satisfying (0.25), with respect to σ and for different values of α .