# Ecological Models for Gene Therapy. I. Models for Intraorganismal Ecology

Arnaud Pocheville · Maël Montévil

**Abstract** In this article, we discuss the perspective of intraorganismal ecology by investigating a family of ecological models. We consider two types of models. First-order models describe the population dynamics as being directly affected by ecological factors (here understood as nutrients, space, etc). They might be thought of as analogous to Aristotelian physics. Second-order models describe the population dynamics as being indirectly affected, the ecological factors now affecting the derivative of the growth rate (that is, the population acceleration), possibly through an impact on nongenetically inherited factors. Second-order models might be thought of as analogous to Galilean physics. In a companion article, we apply these ideas to a situation of gene therapy.

**Keywords** Ecosystem engineering · Inertial dynamics · Intraorganismal ecology · Niche construction · Nongenetic inheritance

## Introduction

The organism can be seen as a biome, composed of organs that are ecosystems where ecological and evolutionary drama are played out (Kupiec and Sonigo 2003).

This perspective draws back to the speculations of Roux (1881) and Weismann (1904)[1] on selection occurring inside the organism. More recently, eco-evolutionary processes between cells within an organism have been considered, both to explain the existence of protection mechanisms against the proliferation of cancer cells within an organism (Cairns 1975; Nowak et al. 2003), to predict the spread of resistant phenotypes within cell populations during cancer treatments (Nowell 1976; Merlo et al. 2006), to describe intra-host dynamics of infectious diseases or cancers as predator-prey interactions between viruses and the immune system (Nowak

A. Pocheville (✉)
Department of Philosophy, University of Sydney, Sydney, NSW 2006, Australia
e-mail: arnaud.pocheville@pocket-mail.net

M. Montévil
Institut d'Histoire et de Philosophie des Sciences, CNRS, Université Paris 1, Paris, France
e-mail: mael.montevil@gmail.com

[1] See, e.g., Weismann et al. (1904), quoted by Gould (2002, p. 223): "I have called these processes which are ceaselessly going on within the germplasm, Germinal Selection, because they are analogous to those processes of selection which we already know in connection with the larger vital units, cells, cell-groups and persons. If the germplasm be a system of determinants, then the same laws of struggle for existence in regard to food and multiplication must hold sway among its parts which hold sway between all systems of vital units-among the biophors which form the protoplasm of the cell-body, among the cells of tissue, among the tissues of an organ, among the organs themselves, as well as among the individuals of a species and between species which compete with one another" (Weismann et al. 1904, vol. 2, p. 119).

and May 2000; Merlo et al. 2006),[2] or to apply the neutral theory of biodiversity (Hubbell 2001) to gut or skin flora communities (e.g., Turnbaugh et al. 2007; Roth and James 1988, 1989).

This article takes place in such an intraorganismal, eco-evolutionary perspective. The topic we are interested in is the study of a gene therapy. Gene therapy aims at correcting a physiological dysfunction whose origin is the inadequate expression of a defective gene. In practice, patient cells are genetically modified in vitro by inserting a given gene, and then reinjected to the patient, with the aim that these modified cells replace the resident cells, or at least that they durably persist within the patient's body: that is, that cells be successfully engrafted (Aiuti and Giovannetti 2003; Cavazzana-Calvo et al. 2005). From an ecological point of view, the prospective replacement of a cellular strain by another is similar to a competitive exclusion or a drift, while modification of the cellular environment, for instance by producing a missing enzyme, is similar to ecosystem engineering (Jones et al. 1994) or, in other terms, to niche construction (Odling-Smee et al. 2003, chap. 5).[3] Successful or unsuccessful engraftment qua species invasion will then depend on the details of the ecological interaction (Gonzalez et al. 2008). The aim of the present work is to determine the conditions of successful engraftment.

To this end, we will study a family of ecological models describing the dynamics of cell populations within an organism. In the first part, we will present the family of models of competition between cells in the general, non-pathological, case. This will enable us to more easily discuss those aspects of the models that are not limited to the particular case of gene therapy.

## General Model of Cell Population Dynamics

We consider that cells proliferate inasmuch as limiting constraints enable them to. More specifically, we will assume here that the population dynamics directly depends on a limiting factor $\varphi(t)$. $\varphi(t)$ may, in principle, be any kind of quantity that is extensive (i.e., proportional to the size of the system) and restricts the tendency of cells to proliferate: available space, fluxes of nutrients, oxygen, growth factors, etc. In the following models, we will not specify $\varphi(t)$'s dynamics; in particular, we will consider that $\varphi(t)$ is not modified by cell populations (e.g., there is no stock or consumption dynamics), and that it is determined by factors that are external to the considered organ. Thus, $\varphi(t)$ forces[4] the dynamics. This hypothesis could be relaxed by modeling $\varphi(t)$ as, for instance, a prey within a predator-prey system, but this generalization is not necessary at this step.

## First-Order Model

We consider that the limiting factor $\varphi(t)$ is instantaneously equitably shared among cells. This hypothesis is similar to the ratio-dependence hypothesis in predator-prey models (Arditi and Ginzburg 1989; Akçakaya et al. 1995). The model is assumed to be valid only when the number $N$ of cells is large enough, that is, the model is valid when the considered factors $\varphi(t)$ are limiting. The per capita growth rate $r$ increases instantaneously, linearly with the available quantity of limiting factor by cell: we thus consider a situation where doubling both the limiting factor and the population will not change the per capita growth rate by cell. Cells undergo a constant intrinsic mortality $m$.

$$r = \frac{dN}{Ndt} = \frac{a\varphi}{N} - m \qquad (1)$$

where $a$ is a scale constant.

Equation 1 admits one (stable) equilibrium:

$$N^* = \frac{a\varphi}{m}$$

The system relaxes towards the equilibrium with a characteristic time $\tau = 1/m$ (Fig. 1). This equilibrium

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[2] Among this corpus, we can mention the following works to give a sketch of the intraorganismal, ecological perspective. Phillips (1996) is a textbook example in this regard. Philips used a population dynamics model of virions and lymphocytes to explain that the diminution in the viral load of a patient infected by HIV did not necessarily come from an immune response of the organism, contrarily to what had been supposed until then. Alizon and Baalen (2008) used a nested approach to describe at the same time the intra-host dynamics during a coinfection, and the epidemiological dynamics within the host's population. They predicted the emergence of hyper-virulent parasitic strategies, a prediction that would have been impossible to obtain by making a classical trade-off hypothesis between transmission and virulence and without taking the intra-host dynamics into account (Alizon et al. 2009). Brown et al. (2008) imported the then-recent ecological concept of niche construction to produce epidemiological models of gut flora dynamics. Last, Cairns et al. (2009) applied the concept of predator-prey relationships to bacteriophage-bacteria dynamics in the field of phage-therapies.

[3] Modeling works on gene therapy do exist in the literature, but they rather adopt a molecular perspective such as, for instance, works on the optimization of transgenesis vectors (e.g. Tayi et al. 2010), the multi-scale treatment of angiogenesis (Billy et al. 2009; Mac Gabhann et al. 2010), or anti-HIV gene therapy (Murray et al. 2009). The models that are closer to an ecological perspective concern the treatment of cancer by oncolytic viruses: for instance, Novozhilov and colleagues apply a ratio-dependent predator-prey model (Arditi and Ginzburg 1989) to describe the destruction of a tumor by oncolytic viruses—a result that is impossible to predict, by the way, by more classical non-ratio-dependent models (Novozhilov et al. 2006). Bach et al. (2001) and Dingli et al. (2009), among others, are other examples of eco-evolutionary approaches to cancer therapies.

[4] Forcing here means that a variable imposes a certain dynamics on another variable without being itself affected by the interaction.

**Fig. 1** Relaxation toward the equilibrium in the first-order model. Abscissae: time. Ordinates: $N$. $a\varphi = 1.5$, $m = 0.5$, $N(0) = 3.2$ (arbitrary units)

requires $\varphi(t)$ to have a sufficiently slow dynamics to allow us to consider the limiting factor as locally constant. We can then consider that at the scale of $\varphi(t)$'s variations the system follows its equilibrium value in function of $\varphi(t)$:

$$N(t) \simeq \frac{a\varphi(t)}{m}$$

From then on, we consider only the case where $\varphi(t)$ is constant at the scale of $N(t)$ variations. To ease reading, we will write it $\varphi$.

## Second-Order Model

We now turn to a different type of modeling, following the work of Ginzburg and colleagues on demographic inertia (Ginzburg and Colyvan 2004). We consider that the per capita growth rate now shows a certain inertia (comparable to inertia in Newtonian physics) that is perceptible at the scale of population dynamics. To put it differently, we will not separate the timescales of the per capita growth rate dynamics and of the population dynamics.

From the biological point of view, such an inertia in the per capita growth rate can result from a dynamics in cell quality (e.g., available amount of intracellular resources or organization quantity, sensu Bailly and Longo 2009). Then, if environmental conditions worsen, intracellular resources lead to a delay in the demographic response; conversely if living conditions get better the cells first rebuild their intracellular resources before their demographic parameters (division and mortality) get affected. Individual quality can also be transmitted to offspring, a phenomenon known in ecology as maternal effects (e.g., Mousseau and Fox 1998).

In this model, it is the change of the per capita growth rate that depends on the per capita limiting factor $\varphi$, times a given constant $a$. In the absence or lack of the limiting factor, the per capita growth rate decreases at a rate $m$ ($m$ typically models the amount of the limiting factor required to sustain proliferation, for example the consumption of oxygen or nutrient). We can now write the equation of demographic acceleration:

$$\frac{dr}{dt} = \frac{a\varphi}{N} - m \qquad (2)$$

The model is formally similar to the first-order model, but notice that the dimensionality and the meaning of the variables has now changed. The equilibrium of Eq. 2 results when $r = 0$ and $N^* = a\varphi/m$. The equilibrium is stable.

### A Note on the Analogy with Physics

In this model, demographic factors ($\varphi$ and $m$) impact the acceleration $dr/dt$ and not the speed $r$ of demographic change. This conceptual change is worth discussing at some length, as it will enable some of the deep theoretical assumptions that lie behind modeling choices to be revealed. This will lead us to discuss ideal, default states in population dynamics, with the proviso that the aim of a theory is to describe the deviations from the default state (e.g., zero force case).

According to Eq. 2, in the idealized case where $\varphi = m = 0$, the population grows (or decreases) at a constant pace that depends on initial conditions, which is equivalent to the uniform straight movement of a body on which no force is exerted in Newtonian physics. By contrast, the first-order, non-inertial model (Eq. 1) is comparable to Aristotelian physics, where the absence of any factor modifying the dynamics results in zero speed (demographic stasis).

Our interpretation of demographic inertia departs from Ginzburg's here (Ginzburg and Colyvan 2004, Chap. 6), who consider that the default state of dynamics is the absence of limiting factors (i.e., $r = r_{max}$). With Ginzburg's interpretation, the default dynamics (equivalent to the straight uniform movement) depends on a biological property ($r_{max}$), and not from initial conditions (by contrast with the straight uniform movement, where the speed depends on the initial speed $v(0)$ and not on the properties of a physical body such as its mass). Ginzburg's interpretation of what the default dynamics should be is similar to Lotka's (1925) in his first-order equation $dN/Ndt = r(1 - N/K)$, where when $N$ is small in comparison with $K$, limiting factors ($K$) do not impact the dynamics and the speed $dN/Ndt$ is given by the maximum per capita growth rate.
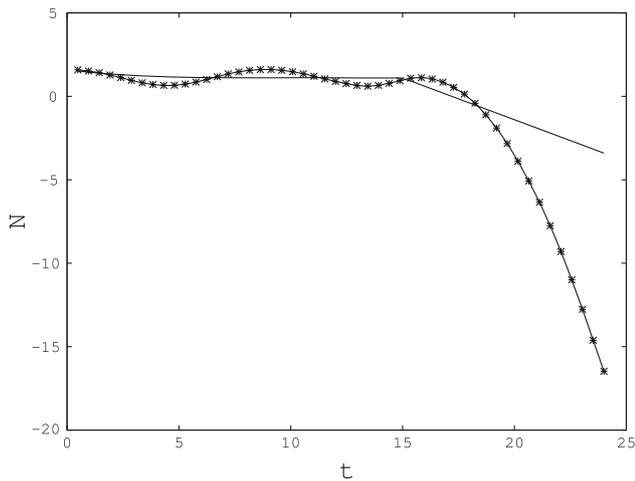
**Fig. 2** Comparison between the exponential death (*straight line*) and the accelerated death (*curved line*). Abscissae: time. Ordinates: $ln(N)$. *Plain line*: first-order model (Eq. 1). *Stars*: second-order model (Eq. 2). Limiting factor $a\varphi$ is set to zero at $t = 15$. Death is exponential (i.e., linear with $ln(N)$) in the first-order model, and accelerated (that is, faster than an exponential) in the second-order model. $a\varphi = 10$, $m = 0.5$, $N(0) = 5$ (arbitrary units)

By contrast, we consider here that the metabolism $m$ should count as a factor impacting the acceleration $dr/dt$, and we should accept ignoring metabolism to produce an idealization comparable to Newtonian idealization. In this case the idealized dynamics is given by the initial condition $r(0)$ and not the property $r_{max}$.

Contrary to Newtonian physics, however, where the default state is general, the idealized Eq. 2 where all factors are put to zero can make sense only in very special cases where cell quality is fully heritable during divisions (e.g., some environment-sensitive epigenetic marks), that is, it does not hold for intracellular resources that are shared among daughter cells. Below we will consider the impact of resource sharing among offspring, and see how it radically modifies the dynamics.

## Differences Between Inertial and Non-inertial Dynamics: Accelerated Death, Overshoot

In the inertial model (Eq. 2), death is accelerated when the limiting factor is the strongest (i.e., set to zero): the per capita growth rate decreases and can tend towards $-\infty$ (that is, death rate tends to be instantaneous). By contrast, in the non-inertial model (Eq. 1), in the absence of the limiting factor the per capita growth rate remains constant (and negative: $\varphi = 0$ implies $r = -m$) (Fig. 2). At the level of organisms population dynamics, accelerated death is empirically observed (Akçakaya et al. 1988; Ginzburg et al. 1988).
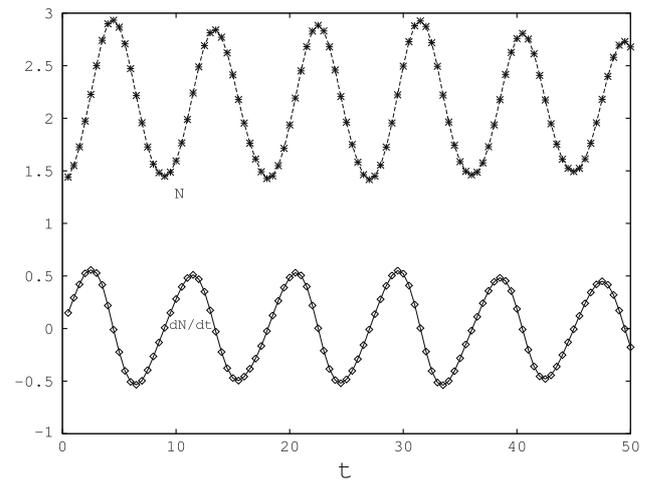


**Fig. 3** Demographic dynamics in the second-order model (Equation 2). Abscissae: time. *Stars*: $N$. *Squares*: $dN/dt$. The system undergoes non-damped oscillations. $a\varphi = 1$, $m = 0.5$, $N(0) = 1.5$, $dN/dt(0) = 0.1$ (arbitrary units)
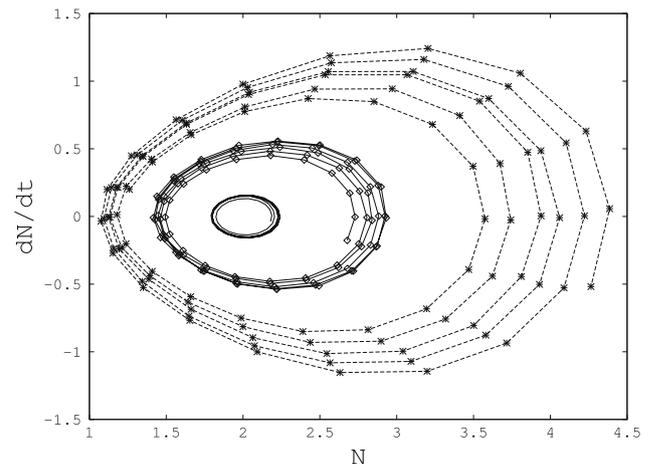


**Fig. 4** Trajectories within the second-order model (Eq. 2) in the state space $(N, dN/dt)$, and the basin of attraction of the stable equilibrium. Abscissae: $N$. Ordinates: $dN/dt$. Trajectories start on the *left* and end on the *right*. The *squares curve* and the *central curve* tend to the fixed point. The *stars curve* rolls away from the fixed point, which means that the basin of attraction is limited. Notice however that the model is designed for cases where $N$ is not small in comparison to $a\varphi$. $a\varphi = 1$ $m = 0.5$ $dN/dt(0) = 0$, $n(0) = 1; 1.4; 1.8$ (arbitrary units)

An inertial dynamics also allows to overshoot the demographic equilibrium value of the population (Figs. 3, 4). Overshoot leads to demographic oscillations around the equilibrium value with a pulsation $\sqrt{m}$, that is, a period $T = 2\pi/\sqrt{m}$ (see "Linearized Monospecific Second-Order System" in Appendix). In biological terms, metabolism accelerates the pulsation, which can be interpreted as an acceleration of biological time (Bailly et al. 2011).
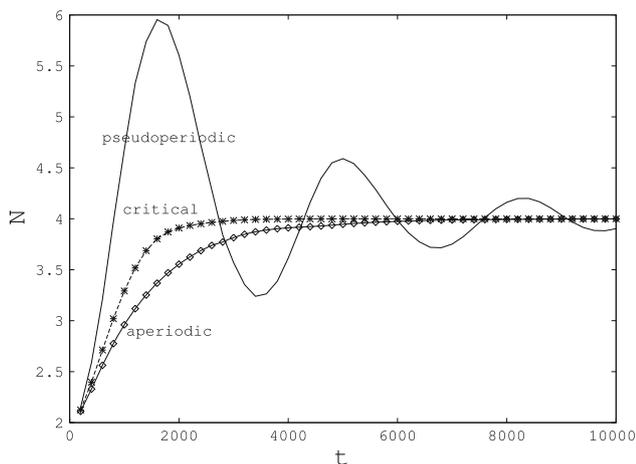
**Fig. 5** Second-order model with friction. Abscissae: time. Ordinates: *N*. *Plain line*: pseudoperiodical regime. *Stars curve*: critical regime. *Square curve*: aperiodical regime. In the pseudoperiodical regime, friction being small, it takes time for the system to dissipate its "kinetic energy." In the aperiodical regime, friction being strong, it takes time for the system to grow to the equilibrium. In the critical regime, the system converges more quickly. $a\varphi = 4$, $m = 1$, $f = 0.4$ (oscillations), 2 (critical regime), 3 (aperiodical regime)

### Friction, Antifriction

In the model described by Eq. 2, oscillations around the equilibrium value are neither damped nor amplified. Such a behavior is structurally unstable: small modifications of the model lead to the convergence toward stable equilibrium or to divergence (May 1973; Nowak and May 2000).

From a biological point of view, oscillations are damped when good quality cells ($r > 0$) tend to waste their intracellular resources more and/or when poor quality cells ($r < 0$) spare their resources. Also, when cells share their resources during a division between daughter cells, there is a negative impact of $r$ on itself, through cell quality, which leads to oscillation damping. By contrast, oscillations would be amplified if good quality ($r > 0$) entailed a virtuous circle improving cell organization and quality, and poor quality ($r < 0$) entailed a vicious cycle leading to even more decreased $r$. Note that the environment can also have friction, forcing, or resonance effects. We can capture this dynamical behavior whose causes are diverse with a simple phenomenological function that represents friction ($f > 0$) or antifriction ($f < 0$).

$$\frac{dr}{dt} = \frac{a\varphi}{N} - m - fr \tag{3}$$

Equation 3 cancels out when $r = r^*$:

$$r^* = \frac{1}{f}\left(\frac{a\varphi}{N} - m\right)$$
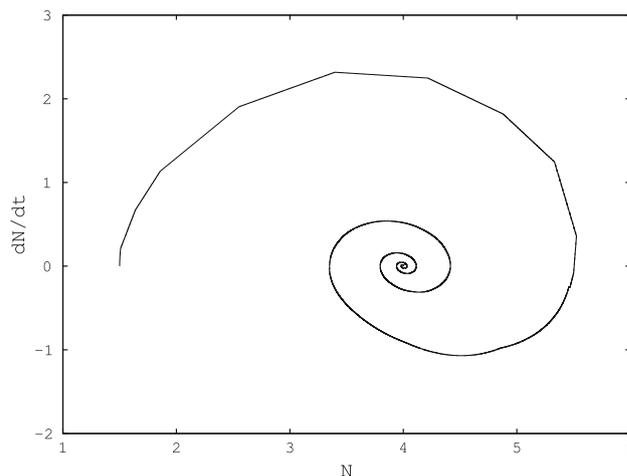


**Fig. 6** Phase portrait of the pseudoperiodical regime in the second-order model with friction (Eq. 3). Abscissae: *N*, ordinates: $dN/dt$. The trajectory starts on the left. The equilibrium is a global attractor. $a\varphi = 4$, $m = 1$, $f = 0.4$, $ln(N(0)) = 1.5$

$r^*$ corresponds to the limiting speed due to friction ($f > 0$, $r^*$ is a stable equilibrium) or antifriction ($f < 0$, $r^*$ is an unstable equilibrium).

In particular, in the case of a free fall ($N = \infty$ or $\varphi = 0$) with friction ($f > 0$), $r$ reaches a maximal value: $r^* = -m/f$. In this case, the per capita growth rate is given by two intrinsic cellular properties, metabolism and friction. This limiting speed is analogous to the limiting speed of a body in free fall in a medium with non-null viscosity, which is also given by medium and body properties.

Ginzburg and Colyvan (2004, p. 90) also modeled population dynamics with a second-order equation (that is, with $dr/dt$) with a phenomenological term of friction. However, the limiting speed (per capita) of a free fall in their model is proportional to $N/N^*$, which is not a property of the cells.[5]

Close to the equilibrium, the system with friction ($f > 0$) can follow three different regimes depending on the sign of $\Delta = f^2/4 - m$ (Figs. 5, 6; see calculations "Linearized Monospecific Second-Order System" in Appendix):

1. pseudoperiodical regime with damped oscillations ($\Delta < 0$): the pulsation is given by $\omega$:

$$\omega = \sqrt{m - \frac{f^2}{4}}$$

The period is given by $T = 2\pi/\omega$. The relaxation time is given by $\tau$:

$$\tau = \frac{2}{f}$$

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[5] The $N/N^*$ density dependence function can make sense, for instance, when the limiting factor is space.
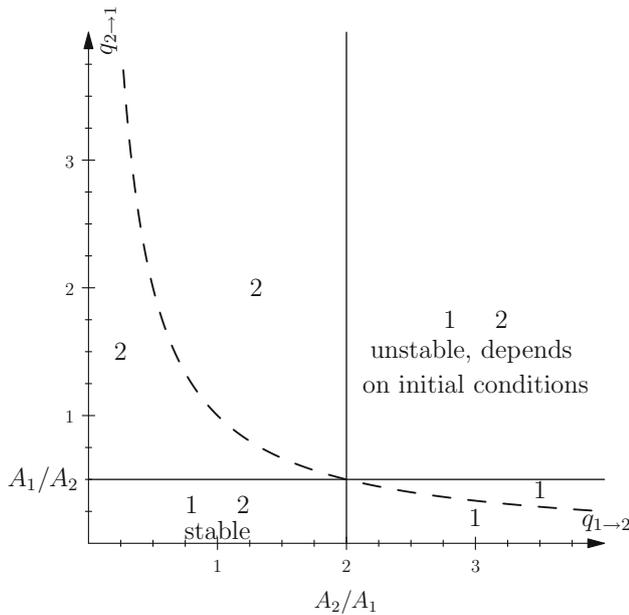
**Fig. 7** Results of competition in the parameter space. To ease reading, we write $A_1 = a_1\varphi/m_1$ and $A_2 = a_2\varphi/m_2$. Abscissae: $q_{12}$. Ordinates: $q_{21}$. *Dashed line*: $q_{12}q_{21} = 1$. The coexistence zone corresponds to the domain where there is less competition between species 1 and 2

2. critical regime ($\Delta = 0$): the system shows shows no oscillations and relaxes with a characteristic time $\tau = 2/f$.
3. aperiodical regime ($\Delta > 0$): the system returns to equilibrium with a relaxation time $\tau$:

$$\tau = \frac{2}{f - 2\sqrt{\frac{f^2}{4} - m}}$$

Note that relaxation is slower than in the damped oscillation regime, because now friction also opposes to the return to equilibrium.

We will see how, from a theoretical point of view, the existence of friction in cell population dynamics can have therapeutic implications.

## Model with Two Species

In this section we derive the models from above to describe the case of an interaction between two species (in our case, two cellular strains). These are the models we will use in the companion paper. Though we describe the dynamics from a general point of view in this section (that is, without making any symmetry assumption about the species in presence) we will be able to drastically reduce the number of parameters in the following part assuming that the cellular strains (genetically modified and non-modified) are identical in most respect.

### First-Order Model

We suppose that the two species interact in a competitive way via their dependency to the limiting factor $\varphi$. We describe the interaction by making a superposition hypothesis (i.e., of linear competition) comparable to the one used in the Lotka-Volterra interspecific competition model.

$$\frac{dN_1}{N_1 dt} = \frac{a_1\varphi}{N_1 + q_{2\rightarrow 1}N_2} - m_1 \tag{4}$$

$$\frac{dN_2}{N_2 dt} = \frac{a_2\varphi}{N_2 + q_{1\rightarrow 2}N_1} - m_2 \tag{5}$$

$q_{i-j}$ describes the per capita effect of $i$ on $j$. The model is valid only if $q \geq 0$, that is, in the case of competition. If $q < 0$, the interaction corresponds to facilitation and the hypothesis of superposition is not adequate anymore (we should then introduce for instance a reciprocal saturation term between $N_1$ and $N_2$).

The behavior of the system, and in particular the stability of the equilibria in the space of parameters is shown in Fig. 7. The system has three equilibria: two equilibria correspond to the loss of at least one species and reduce to the monospecific case, one corresponds to the coexistence between populations 1 and 2.

(a) $N_1^* = 0$ and $N_2^* = a_2\varphi/m_2$; or $N_2^* = 0$ and $N_1^* = a_1\varphi/m_1$.

(b) the equilibrium corresponding to coexistence is given by the couple $\{N_1^*, N_2^*\}$, when $q_{21}q_{12} \neq 1$:

$$N_1^* = \left(\frac{1}{1 - q_{21}q_{12}}\right)\left(\frac{a_1\varphi}{m_1} - q_{21}\frac{a_2\varphi}{m_2}\right)$$

$$N_2^* = \left(\frac{1}{1 - q_{21}q_{12}}\right)\left(\frac{a_2\varphi}{m_2} - q_{12}\frac{a_1\varphi}{m_1}\right)$$

The equilibrium is a coexistence if $N_1^* > 0$ and $N_2^* > 0$. There is never coexistence if $q_{21}q_{12} = 1$, except in the particular case where $a_1/m_1 = q_{21}a_2/m_2$. In this case, coexistence is neutral and the equilibrium is insensitive to the relative abundances of 1 and 2, as long as the equation $N_1 + q_{21}N_2 = a_1\varphi/m_1$ is true.

### Second-Order Model

We similarly extend the second-order monospecific model to the two-species case by making the same assumptions about the competitive interaction between 1 and 2:

$$\frac{dr_1}{dt} = \frac{a_1\varphi}{N_1 + q_{21}N_2} - m_1 \tag{6}$$
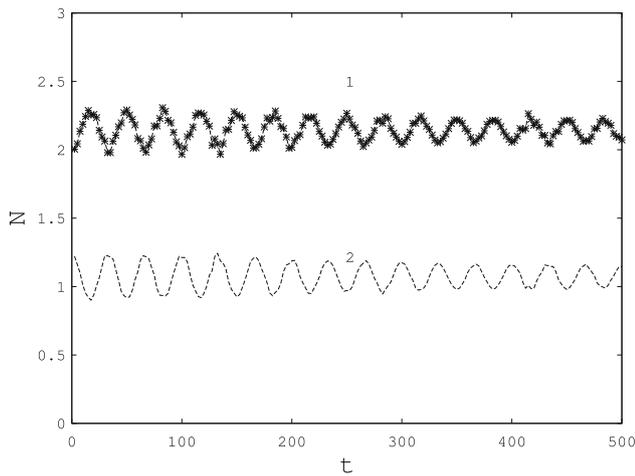
**Fig. 8** Superposed oscillations in the second-order model with two species. Abscissae: time. $a\varphi = 1.5$, $m = 0.5$, $q_{21} = 0.8$, $q_{12} = 0.9$, $n_1(0) = 1.6$ (*upper curve*), $dn_1/dt(0) = 0$, $n_2(0) = 1$ (*lower curve*), $dn_2/dt(0) = 0.3$; with $n = ln(N)$

$$\frac{dr_2}{dt} = \frac{a_2\varphi}{N_2 + q_{12}N_1} - m_2 \qquad (7)$$

The equilibrium of this system obtains for the same equilibrium values as the first-order system (steady $r$) and when the per capita growth rates are equal to zero ($r_1 = r_2 = 0$). The stability of the equilibrium is given by the sign of the highest eigenvalue (here noted $v$, the other eigenvalue being noted $\mu$; see "Linearized Two-Species Second-Order Model (Without Friction)" in Appendix). When $v > 0$ the fixed point $\{N_1^*, N_2^*\}$ is unstable and one of the two populations is eliminated. If $v < 0$, then $N_1$ and $N_2$ follow superimposed independent oscillations of pulsations $\sqrt{-\mu}$ and $\sqrt{-v}$ around the equilibrium value. The system does not show coupled oscillations (Fig. 8).

Second-Order Model with Friction

We now add friction to the two-species model:

$$\frac{dr_1}{dt} = \frac{a_1\varphi}{N_1 + q_{2\rightarrow1}N_2} - m_1 - f_1 r_1 \qquad (8)$$

$$\frac{dr_2}{dt} = \frac{a_2\varphi}{N_2 + q_{1\rightarrow2}N_1} - m_2 - f_2 r_2 \qquad (9)$$

From then on, we will only consider cases where $f_1 = f_2 = f$. In this case, it can be shown that the conditions for local stability are not affected by friction (see "Linearized Two-Species Second-Order System (with Friction)" in Appendix). In the stable case the dynamics corresponds to the linear superposition of two dynamics following Eq. 3, thus showing the same kind of behaviors. The main difference with the introduction of friction is that the system now tends towards its equilibrium, and near the

equilibrium it relaxes towards equilibrium with damped oscillations.

## Discussion

A model of population dynamics should exhibit three essential behaviors: decline in absence of resources, growth in non-limiting situations, ($r_{max}$),[6] and the potential existence of a carrying capacity ($N^*$) due to limiting factors (nutrients or space). These three behaviors can be biologically linked: for instance, an increase in mortality can affect both $r_{max}$ and $N^*$. In contrast, they can be biologically independent: for instance, if $N^*$ is due to limiting space, genetically modifying the cells can increase $r_{max}$ without affecting $N^*$.

It is impossible to represent the possible actions on these three independent behaviors with only two parameters (e.g., $a\varphi$ and $m$ in our model, $r$ and $K$ in Lotka-Volterra), and it is impossible to represent a $N^*$ independent from $r_{max}$ with first-order equations (Ginzburg 1992).[7]

Under these constraints, and to favor parsimony which is essential to our application on gene therapy (see companion paper), we have sacrificed the behavior of the population far from the $N^*$ (i.e., we did not introduce any $r_{max}$). An alternative choice would have been to use the logistic equation in Verhulst's (1838) form:

$$\frac{dN}{Ndt} = a - bN$$

or in the version of Lotka (1925):

$$\frac{dN}{Ndt} = r\left(1 - \frac{N}{K}\right)$$

We did not choose this model for the following reasons:

1. The difficulty of interpreting the parameters (Olson 1992). First, $a$, or $r$, both represent $r_{max}$ and have an impact on the density-dependence ($N^* = a/b$ in Verhulst's equation and thus depends on $r_{max} = a$; conversely, $N^* = K$ and is independent from $r$ in Lotka's equation but now the density parameter, that is, the amount to which the population is sensitive to itself, is $r/K$). Second, $K$ should not be interpreted as a carrying capacity but as an equilibrium value (Berryman 1992). In other terms, in the logistic equation the inflexion point is a center of symmetry between growth

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[6] We mean by $r$ here $dN/Ndt$, and not the $r$ parameter in Lotka's equation given above. $r_{max}$ thus means $(dN/Ndt)_{max}$.

[7] Such an independence between $N^*$ and $r_{max}$ can be approached, however (Watkinson 1992; Getz 1996, see also "Model of a Limiting Maximal per Capita Growth Rate $r_{max}$" in Appendix).

when the population is small, and growth near the equilibrium, which does not seem to have any obvious biological basis (Winsor 1932).

2. The unrealistic form of the density dependence (Getz 1996), when $N \ll N^*$ (McCarthy 1997; Courchamp et al. 1999; Etienne et al. 2002; Kent and Patrick Doncaster 2003), but also when $N \gg N^*$: in this case the per capita death rate is proportional to the ratio $N/N^*$, and not to a property of the biological system in the absence of resources (death by food shortage for instance). This behavior comes from the fact that Verhulst's equation is a truncated Taylor series. We find the same behavior in the inertial model of Ginzburg and Colyvan (2004, p. 90), which has the same form (but at the second order).

We have chosen here to model the dynamics for situations where $N$ is not far from $N^*$. The rationale for this hypothesis comes from our interest in modeling cell populations within an organism (see companion article), that can be supposed to undergo only small or slow variations because of constraints posed by the organism. We have privileged a density-dependence that is less abrupt (sensu Getz 1996) than that of the logistic equation when $N \gg N^*$; in particular, we have privileged a free-fall speed that is a property of the individuals, and not a function of the distance between $N$ and $N^*$. Such attention to the form of density dependence could turn out to be crucial in niche construction cases where the modification of the $N^*$ is the focal behavior (Odling-Smee et al. 2003; Pocheville 2010, Chap. 2). It would be most instructive to empirically study the form of the density-dependence that is better adapted to intraorganismal ecology: should chemical constraints (resources, signals, toxins) lead to a less abrupt density-dependence than physical constraints (mechanical constraints and limiting space)? Do these forms of density-dependence have the same timescales, or do the spatial constraints rather impact the first-order dynamics, and the chemical constraints the second-order?[8]

In this work, we limited ourselves to the ecological dimension of the cellular niche, that is, to the impact of density on competition. However, in intraorganismal ecology density-dependence has effects that are unknown in organism ecology. Physical constraints, in particular, are known to affect the differentiation of stem cells in given niches (Gerecht-Nir et al. 2004; Mohr et al. 2006; Stevens et al. 2007) as well as to affect the malignant phenotype and the response to treatments in the case of cancer (Ingber and Jamieson 1985; Huang and Ingber 2005; Paszek et al. 2005; Schwartz 2004, Chap. 15). This is a new behavior by

comparison with organism ecology, where the most similar behaviors would be migration and metamorphosis.[9]

Last, in classical population ecology, populations, once lost, do not reappear if there is no migration nor dormant propagule bank in the environment. Thus, $N = 0$ can be a biologically stable equilibrium, even when this equilibrium is described as mathematically unstable, as for instance in the paradigmatic Lotka-Volterra model - this is a limitation intrinsic to this formalism, that has been originally developed to deal with physical problems where small fluctuations always make sense (Jacobs and Metz 2003). With stem cell populations however, $N = 0$ is a biologically unstable equilibrium if there is any dedifferentiation (Niwa and Ji 2000; Fu et al. 2001; Brawley and Matunis 2004; Shen et al. 2000). A similar caveat would hold with transdifferentiation of differentiated cells.

The model being simple and basically describing a relaxation toward an equilibrium (at the first order, or at the second order with friction), some structural homogeneity is expected with existing models in the literature. We can notice in particular a certain formal homology (partial, except in cases where we introduce a $r_{max}$; see "Model of a Limiting Maximal per Capita Growth Rate ($r_{max}$)" in Appendix) of the order 1 model with Beverton & Holt's model in discrete time (Beverton and Holt 1957; Maynard Smith and Slatkin 1973; Getz and Kaitala 1989; Getz 1996). This homology explains in particular the analogy between the qualitative results of our two-species first-order model with the results of a Lotka-Volterra two-species system.

In this work, we focused on the structural stability of our modeling, by introducing a friction term. A strong friction makes the system tend towards a first-order behavior: inertia loses its dynamical importance. In the general models presented above, friction affects relaxation but not the equilibrium stability. This will not be the case anymore in the companion paper.

Our model shows how the same equational form can be interpreted at the first or the second order (keeping in mind that the dimension and the meaning of the parameters change according to the order). At the first order, the system describes the growth of an organ, or, in the model with two species, the potential invasion of an organ by a cellular strain. At the second order, our model is structurally identical to that of Ginzburg and Colyvan (2004, p. 44), modeling the quality of individuals. This structural homology between first and second order enables to study

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[8] On this question see in particular Ingber and Jamieson (1985).

[9] It is interesting to note a analogy between the dedifferentiation of stem cells (Niwa and Ji 2000; Fu et al. 2001; Brawley and Matunis 2004) and the transdifferentiation of differentiated cells (Shen et al. 2000) at the intraorganismal level, and the transdifferentiation leading to the reversion from a reproductive to a juvenile state in the Cnidaria *Turritopsis nutricula* (Piraino et al. 1996).

the importance of the time-scale separation hypotheses between the individual's quality ($dr/dt$) and the population dynamics ($dN/Ndt = r$). In effect, starting from Eq. 3, it is clear that the second-order dynamics can be transformed into the first-order dynamics of Eq. 1 if we assume that $|dr/dt| \ll |fr|$, that is, $|dr/dt| \ll |r/\tau_f|$.

The diversity of empirical results in population dynamics makes it difficult to a priori choose between the first- and second-order models. Qualitative results of the first-order model are in concordance with some empirical results as regards the growth of an organ or of the quality of a cell (see, e.g., resp. Kooijman 2000, p. 33, Fig. 2.5 and p. 2, Fig. 1.1). However the second-order model is in concordance with demographic oscillations (damped, amplified, or not) and accelerated death observed in organism ecology (see the review by Ginzburg and Colyvan (2004, pp. 92–93)), and in intraorganismal ecology (Corbin et al. 2002; see also companion article, Pocheville et al. 2014).

## Appendix

### Model of a Limiting Maximal Per Capita Growth Rate ($r_{max}$)

Let's start from Eq. 1:

$$\frac{dN}{Ndt} = \frac{a\varphi}{N} - m$$

Here the per capita growth rate tends toward infinity when $N(t)/\varphi$ tends toward zero. If we want to describe such cases we have to modify the per capita growth rate function such that it saturates at a maximal value $r_{max}$ in non-limiting conditions. This saturation is observed in vitro (e.g., Norris and Ribbons 1970, p. 263; Yufera and Navarro 1995). We can introduce a simple phenomenological function:

$$\frac{dN}{Ndt} = \frac{a\varphi}{N + b\varphi} - m \tag{10}$$
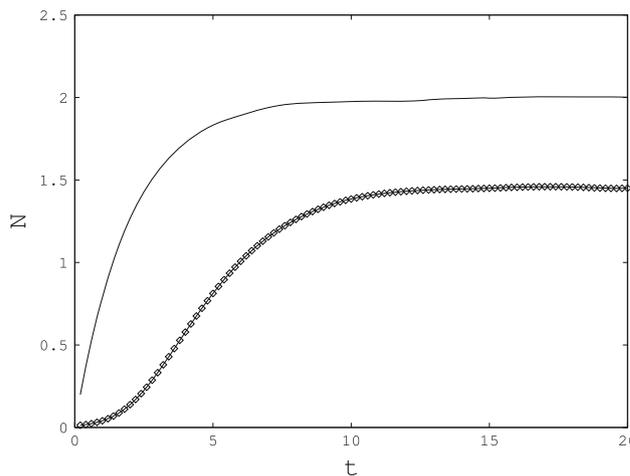


**Fig. 9** Comparison between the models without per capita growth rate saturation (*upper curve*, Eq. 1) and with saturation (*lower curve*, Eq. 10 , see "Model of a Limiting Maximal per Capita Growth Rate ($r_{max}$)" in Appendix). With per capita growth rate saturation, the model is qualitatively equivalent to Verhulst's and Lotka-Volterra's model. $a\varphi = 1$, $b\varphi = 0.5$, $m = 0.5$, $n(0) = 0.01$

where b is a scale constant (number of cells by limiting factor units) introduced to describe the behavior of the per capita growth rate at small cell densities.

The equation for the maximal per capita growth rate $r_{max}$ results from (10) when $N(t)/\varphi$ tends toward zero:

$$r_{max} = \frac{a}{b} - m$$

This equation describes $r_{max}$ as a limiting factor intrinsic to the living system, independent from the limiting factor $\varphi$.

The population tends towards an equilibrium value $N_{bis}^*$ that we suppose approximately equal to $N^*$ (this amounts to positing that the dynamics near the equilibrium is independent from the introduced modification on $r_{max}$):

$$N_{bis}^* = \left(\frac{a}{m} - b\right)\varphi \approx \left(\frac{a}{m}\right)\varphi = N^*$$

This leads to a condition on b: $b \ll a/m$. This condition implies $m \ll a/b$, that is: $r_{max} > 0$, a condition without which the model modification cannot make sense.

The behavior of model (1 *bis*) is very similar to the classical logistic model (Fig. 9).

### Linearized Monospecific First-Order System

See the two species system, with $q = 0$.

### Linearized Monospecific Second-Order System

We have:

$$\frac{d}{dt}\left(\frac{dN}{Ndt}\right) = \frac{dr}{dt} = \frac{a\varphi}{N} - m - fr$$

We can write the equation in function of $n = \ln(N)$:

$$\frac{d^2 n}{dt^2} = \frac{a\varphi}{e^n} - m - f\frac{dn}{dt}$$

The equilibrium obtains:

$$e^{n^*} = \frac{a\varphi}{m}$$

We consider the behavior near this equilibrium, that is $n = n^* + \delta n$. We have:

$$\frac{d^2 \delta n}{dt^2} = -m\delta n - f\frac{d\delta n}{dt}$$

Changing the variable:

$$\delta n = g(t)e^{\frac{-f}{2}t}$$

We obtain:

$$\frac{d^2 g}{dt^2} = g\left(\frac{f^2}{4} - m\right)$$

Noting $\Delta = (f^2/4 - m)$ the equation has the following solutions:

If $\Delta < 0$:

$$g = A\cos(t\sqrt{-\Delta}) + B\sin(t\sqrt{-\Delta})$$

$$\delta n = e^{\frac{-f}{2}t}(A\cos(t\sqrt{-\Delta}) + B\sin(t\sqrt{-\Delta}))$$

The pulsation is given by $\sqrt{-\Delta}$.

If $\Delta = 0$

$$g = At + B$$

$$\delta n = e^{\frac{-f}{2}t}(At + B)$$

If $\Delta > 0$

$$g = A\cosh(t\sqrt{\Delta}) + B\sinh(t\sqrt{\Delta})$$

$$\delta n = e^{\frac{-f}{2}t}(A\cosh(t\sqrt{\Delta}) + B\sinh(t\sqrt{\Delta})) = O\left(e^{\frac{-f}{2}t + t\sqrt{\Delta}}\right)$$

The pseudo-pulsation is given by $\sqrt{\Delta}$ and the relaxation time by the inverse of $-f/2$.

### Linearized Two-Species First-Order System

$$\frac{dN_1}{N_1 dt} = \frac{a_1\varphi}{N_1 + q_{2\to1}N_2} - m_1$$

$$\frac{dN_2}{N_2 dt} = \frac{a_2\varphi}{N_2 + q_{1\to2}N_1} - m_2$$

Near the equilibrium, we write: $n = \ln(N)$ and $n = n^* + \delta(n)$.

$$N_1 = e^{n_1} = e^{n_1^* + \delta n_1} = e^{n_1^*(1 + \delta n_1)}$$

$$N_2 = e^{n_2} = e^{n_2^* + \delta n_2} = e^{n_2^*(1 + \delta n_2)}$$

We get:

$$\frac{d\delta n_1}{dt} = \frac{a_1\varphi}{\exp(n_1^*(1 + \delta n_1)) + q_{21}\exp(n_2^*(1 + \delta n_2))} - m_1$$

Rearranging, we get:

$$\frac{d\delta n_1}{dt} = -\frac{\exp(n_1^*)\delta n_1 + q_{21}\exp(n_2^*)\delta n_2}{a_1\varphi}m_1^2$$

and:

$$\frac{d\delta n_2}{dt} = -\frac{q_{12}\exp(n_1^*)\delta n_1 + \exp(n_2^*)\delta n_2}{a_2\varphi}m_2^2$$

We seek for the eigenvalues of this system. They are the roots of the characteristic polynomial: $X^2 - TX + D$

We set:

$$B_1 = \frac{m_1^2}{a_1\varphi}\exp(n_1^*)$$

$$B_2 = \frac{m_2^2}{a_2\varphi}\exp(n_2^*)$$

With these parameters, we get:

$$T = -(B_1 + B_2)$$
$$D = B_1 B_2(1 - q_{21}q_{12})$$

The determinant $\Delta$ of the characteristic polynomial is given by:

$$\Delta = (B_1 + B_2)^2 - 4B_1 B_2(1 - q_{21}q_{12})$$

Thus:

$$\Delta = (B_1 - B_2)^2 + 4B_1 B_2 q_{21}q_{12}$$

Thus $\Delta > 0$.

Thus the eigenvalues are:

$$\mu = \frac{-(B_1 + B_2) - \sqrt{\Delta}}{2}$$

and:

$$v = \frac{-(B_1 + B_2) + \sqrt{\Delta}}{2}$$

$$= \frac{-(B_1 + B_2) + \sqrt{(B_1 + B_2)^2 - 4B_1 B_2(1 - q_{21}q_{12})}}{2}$$

It turns out that $v < 0$ when $(1 - q_{21}q_{12}) > 0$ and $v > 0$ when $(1 - q_{21}q_{12}) < 0$.

When $v > 0$ the fixed point is unstable. Biologically this means that competition is too important and one of the two populations gets excluded, whatever the initial conditions.

If $v < 0$ then the fixed point is stable and the relaxation time is given by $1/v$.
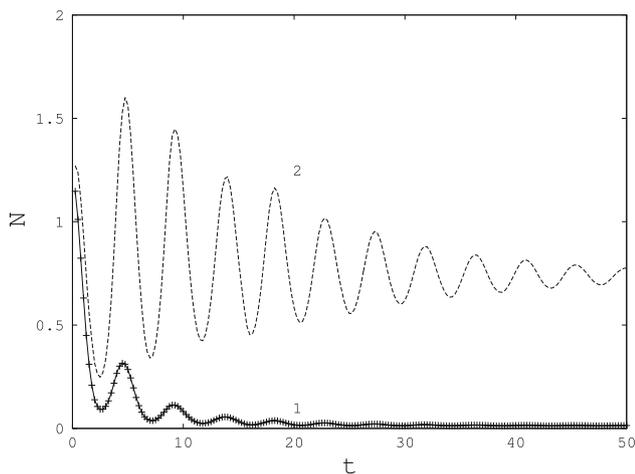
**Fig. 10** Two-species second-order model with friction, case of a linear divergence in the critical case. $v = 0$, $a\varphi = 1.5$, $m = 2$, $f = 0.1$, $q_{21} = q_{12} = 1$, $n_1(0) = 1.2$, $dn_1/dt(0) = 0$, $n_2(0) = 1.2$, $dn_2/dt(0) = 0.3$, with $n = ln(N)$ (See "Linearized Two-Species Second-Order System (with Friction)" in Appendix)

If $v = 0$, then $q_{21}q_{12} = 1$, which is excluded because $N_1^*$ and $N_2^*$ would be undefined.

In the case where $q_{21}q_{12} = 1$, we are facing three different situations according to the sign of $A_1\varphi/m_1 - a_2\varphi/(m_2q_{12})$: if this term is positive the species 1 wins, if it is negative the species 2 wins, if it is nul, then coexistence is neutral.

Linearized Two-Species Second-Order Model (Without Friction)

The calculus is identical to the first-order system, but the interpretation differs.

When $v > 0$ the fixed point is unstable and one of the two populations is eliminated.

If $v < 0$, then $\delta n_1$ and $\delta n_2$ follow superimposed independent oscillations of pulsations $\sqrt{-\mu}$ and $\sqrt{-v}$.

Linearized Two-Species Second-Order System (with Friction)

We consider the case where $f_1 = f_2 = f$. The behavior of the system is given by the $Z$ such as:

$$X = Z^2 + fZ$$

where $X = \mu$ or $v$.

$Z$ is thus given by:

$$Z = \frac{1}{2}\left(-f \pm \sqrt{f^2 + 4X}\right)$$

If $v > 0$, we have a $Z > 0$ and the system is thus unstable.

If $v < 0$, the system is stable. There are several possible regimes: if $X < -f^2/4$, the associated component to $X$ will be pseudoperiodical. If $X = -f^2/4$, then this component will be critical. If $X > -f^2/4$, the the component will be aperiodical. The behavior of $\delta n_1$ and $\delta n_2$ will be given by a superimposition of the behaviors associated to the two eigenvalues.

If $v = 0$, the system is unstable and diverges linearly, with in addition an oscillatory component (see "Linearized Two-Species Second-Order System (with Friction)" in Appendix).

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