Biol Theory (2014) 9:414–422
DOI 10.1007/s13752-014-0191-x

THEMATIC ISSUE ARTICLE: ECOSYSTEMS OR ORGANISMS?

Ecological Models for Gene Therapy. II. Niche Construction, Nongenetic Inheritance, and Ecosystem Perturbations

Arnaud Pocheville · Maël Montévil · Régis Ferrière

Received: 16 December 2013 / Accepted: 10 July 2014 / Published online: 25 November 2014

Abstract In this article, we apply the perspective of intraorganismal ecology by investigating a family of ecological models suitable to describe a gene therapy for a particular metabolic disorder, the adenosine deaminase deficiency. The gene therapy is modeled as the prospective ecological invasion of an organ (here, bone marrow) by genetically modified stem cells, which then operate niche construction in the cellular environment by releasing an enzyme they synthesize. We show that depending on the order chosen for the model (a choice that cannot be made on a priori assumptions), different kinds of dynamics are expected, possibly leading to different therapeutic strategies. This drives us to discuss several features of the extension of ecology to intraorganismal ecology.

Keywords Adenosine deaminase deficiency · Ecosystem engineering · Gene therapy · Intraorganismal ecology · Nongenetic inheritance · Severe combined immunodeficiency

This paper forms a two-part article with DOI 10.1007/s13752-014-0190-y.

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

R. Ferrière
Equipe Eco-Evolution Mathematique, Institut de Biologie de l'Ecole Normale Superieure, CNRS INSERM UMR 8197, Ecole Normale Supérieure, 46 rue d'Ulm, 75005 Paris, France
e-mail: ferriere@biologie.ens.fr

R. Ferrière
Department of Ecology and Evolutionary Biology, University of Arizona, Tucson, AZ 85721, USA

Introduction

In this second article (see companion paper), we will study the impacts of niche construction by genetically modified cells on cell population dynamics. This will enable us to propose some recommendations and new empirical questions to the practitioner. We will show that the conclusions will depend on sensitive hypotheses on timescale separation (or entanglement) of the considered cellular processes. We will then discuss how ecological concepts can be implemented in cell biology in general, and how extending ecology to cell biology can in turn enrich ecological questions.

Our biological model is the deficiency in adenosine deaminase (ADA), a rare monogenic disease (occurrence between 1:300,000 and 1:1,000 000) (Cavazzana-Calvo et al. 2004, 2005). From a biochemical point of view, ADA deficiency causes a dysfunction of the metabolism of purines characterized by the accumulation of metabolites in intra- and intercellular compartments, which results in particular in a premature apoptosis of lymphocytes (Cavazzana-Calvo et al. 2005). The lymphocyte anomaly is still not completely elucidated (Gaspar et al. 2009). ADA deficiency leads to severe anomalies in the immune system (that is, SCID: severe combined immunodeficiency), as well as to other systemic problems, and without treatment the disease is fatal within the first year. Three kinds of treatments are possible: hematopoietic stem cell transplantation (HSCT), enzyme injection, and gene therapy. Hematopoietic stem cell transplantation represents a

good option if and only if a related and compatible donor is available (88 % survival after one year, versus 29 and 67 % in the case of non-compatible or non-related donors respectively). Enzyme injection takes place every one or two weeks, using polyethylene-glycol bovine adenosie deaminase (PEG-ADA), and enables a high level of plasmatic ADA to be maintained, but the restoration of the immune function is suboptimal in the long term. Last, gene therapy enables the immune and metabolic function to be restored, with a complete restoration in the best cases, even without preliminary myeloablation (Aiuti and Giovannetti 2003; Aiuti et al. 2007).[1]

When a patient who is initially receiving enzyme therapy receives an injection of modified cells within a gene therapy, there is a trade-off between continuing the enzyme treatment that enables maintenance of a high level of plasmatic ADA, and discontinuing the enzyme treatment with the aim of providing a selective advantage to modified cells, possibly due to their own enzyme production, to favor engraftment (Aiuti et al. 2002b).[2] The modeling aim of the present work is to investigate the conditions for engraftment from an intraorganismal point of view and the impact enzyme injections can have on cell population dynamics.

First-Order Model

We now modify the general first-order system (Eqs. 4, 5, first article) to model in particular the intraorganismal ecological dynamics of an ADA-SCID gene therapy. We consider that non-modified cells (i.e., the autochthons, hereafter noted A) and the genetically modified cells (noted G) are identical, except with respect to the construction of the environment (by enzyme synthesis) and the response to the enzyme (noted E). All cells are in competition for the limiting factor φ.

G cells are supposed to have a normal dynamics (Cassani et al. 2009), as described by Eq. 4 (first article). To facilitate model interpretation, we separate the cost of enzyme production (noted c) from the intrinsic mortality (m),

$$\frac{dG}{Gdt} = \frac{a\varphi}{A+G} - m - c$$

A cells follow the same dynamics as G cells, but they do not pay the cost of enzyme production. In contrast, when the enzyme is missing in the environment, A cells undergo an additional mortality d due to the accumulation of intracellular metabolites. The presence of the enzyme lowers the additional mortality, times a scale factor denoted b. We consider that A cell detoxification by the enzyme depends on the enzyme plasmatic concentration, and not on the *per capita* quantity, which is assumed to be negligibly modified by the interaction with A cells.[3] Notice that now the model is not scale-independent anymore: multiplying the quantity G, A, E by a given factor will lower the additional mortality of A due to the increase in enzyme concentration. The dynamics for A becomes:

$$\frac{dA}{Adt} = \frac{a\varphi}{A+G} - m - \frac{d}{1+bE} \quad (1)$$

The enzyme undergoes an intrinsic decay (with a characteristic time τ_E), and is synthesized by G cells, times an "engineering" factor (in reference to ecosystem engineering, Jones et al. 1994), denoted e. The enzyme can also be injected in a given quantity i. The injection frequency (once or twice a week) is of the same order of magnitude as the cell generation time (ca. five days). If injections were more sporadic, i should be replaced by a Dirac comb $i(t)$.

$$\frac{dE}{dt} = \frac{-1}{\tau_E}E + i + eG$$

This system admits several equilibria (the stability conditions are discussed below):

1. In the absence of both A and G cells, $E^* = i\tau_E$
   This biological equilibrium describes the state of the system in case of a myeloablation, before the injection of modified cells.
2. $G^* = 0$, $E^* = i\tau_E$ and:
   $$A^* = \frac{a\varphi}{m + \frac{d}{1+bi\tau_E}}$$
   This is the hypothetical equilibrium before gene therapy or after G cells have been eliminated if the graft fails.
3. $A^* = 0$, and:
   $$G^* = \frac{a\varphi}{m+c}$$
   $$E^* = \tau_E\left(i + e\frac{a\varphi}{m+c}\right)$$
   This is the therapeutic target equilibrium, where A cells have been replaced by functionally supplemented G cells.
4. $A^* \neq 0$, $G^* \neq 0$, then:

[1] On the subject of gene therapy to treat ADA-SCID, see Aiuti (2002), Aiuti and Giovannetti (2003), Aiuti et al. (2007), Cappell and Aiuti (2010), and the reviews Cavazzana-Calvo et al. (2004), Gaspar et al. (2009), Sauer and Aiuti (2009).

[2] A similar selective advantage of modified cells has been observed for a gene therapy of another pathology of hematopoïesis, the Wiksott–Aldrich syndrome (WAS) (Marangoni et al. 2009).

[3] This hypothesis amounts to positing that the limiting factor is the enzyme *concentration* in a large compartment, on which enzyme use by A cells has little effect. Using a per capita effect would amount to positing that the limiting factor is the enzyme *quantity* (say, in a local compartment).

$$E^* = \frac{1}{b}\left(\frac{d}{c} - 1\right)$$

$E^* > 0$ when $d > c$. If $d < c$, there is no coexistence: non-modified autochthons always win. From a biological point of view, $d < c$ would mean that even in the absence of enzyme, the additional mortality of defective non-modified cells is inferior to the cost of producing the enzyme. If there is coexistence, the equilibrium is stable. Knowing E^* gives G^*:

$$G^* = \frac{1}{e}\left(\frac{E^*}{\tau_E} - i\right)$$

Substituting the value of E^* in G^*, we find that $G^* > 0$ when:

$$\frac{1}{b\tau_E}\left(\frac{d}{c} - 1\right) > i$$

If i is too large, the inequality is not satisfied and $G^* < 0$. From a biological point of view, this means that above a certain injection threshold, engraftment is impossible. We find here the behavior empirically observed by Aiuti et al. (2002b).

Knowing G^*:

$$A^* = \frac{a\varphi}{m + c} - G^*$$

$A^* > 0$ when $a\varphi/(m + c) > G^*$: the coexistence between A and G is not scale-independent, that is, it depends on the carrying capacity of the system (this comes for the scale-dependence introduced by the enzyme concentration).

We can notice that at this equilibrium, the enzyme concentration E^* does not depend on the injection constant i: enzyme injection has merely the effect of decreasing G^*, because of competition with non-modified A cells (also observed by Aiuti et al. (2002b)). From a therapeutical point of view, enzyme injection is thus counterproductive *at the equilibrium*.

When there is coexistence, the system follows a regime of exponential relaxation, or a pseudoperiodical regime with damped oscillations (Fig. 1), or is unstable (see section "Linearized First-Order Model, with Two Species and Niche Construction (Enzyme Synthesis)" in Appendix). These oscillations result from the coupling of A and G population via the enzyme compartment, that itself has some inertia, with a characteristic time τ_E.

Second-Order Model

In this section, we modify the first-order model into a second-order model following the reasoning exposed for the general model (see companion paper), to be able to investigate the therapeutic impacts of a potential timescale non-separability between the per capita growth rate dynamics (dr/dt) and the population dynamics $(dN/Ndt = r)$. The second-order system is given by:

$$\frac{dr_A}{dt} = \frac{a\varphi}{A + G} - m - \frac{d}{1 + bE}$$
$$\frac{dr_G}{dt} = \frac{a\varphi}{A + G} - m - c$$

The equation for enzyme dynamics is as before:

$$\frac{dE}{dt} = \frac{-1}{\tau_E}E + i + eG$$

This system admits the same equilibria as the first-order system, but its behavior in the neighborhood of the equilibria is different.

If the enzyme dynamics is fast compared to the population dynamics, we may approximate E by $\tau_E(i + eG)$. (In ecological terms, this amounts to supposing that G cells do not have any posthumous phenotypes, sensu Lehmann (2008).) The system has the same equilibria. Linearizing near the equilibrium, it turns out that the system can either oscillate around the equilibrium, or diverge with amplified oscillations (see section "Linearized Second-Order System with Two Species, Enzyme Construction, and Timescale Separation on the Enzyme Dynamics" in Appendix). Injection quantity i can destabilize the system when $d(m + c) < 4c^2$. However, if we consider that coexistence occurs when $d > c$, and that, a priori, $m \gg c$ (that is, synthesizing the enzyme is only a minor fraction of the metabolic work of a G cell), such a destabilization is not expected to occur except for extreme parameters values.

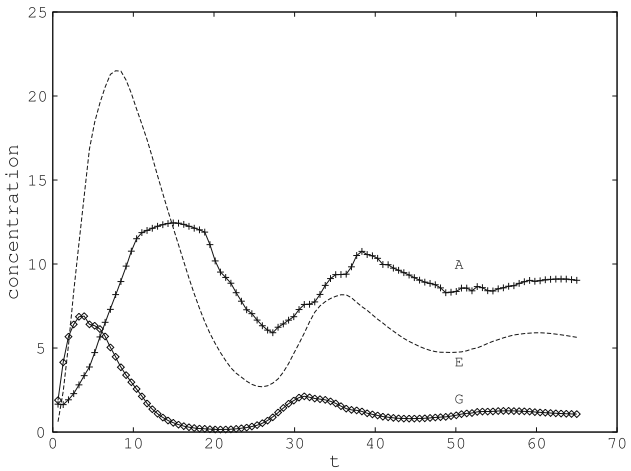

Fig. 1 First-order niche construction model (i.e., with enzyme synthesis). Abscissae: time. Ordinates: concentrations. (Arbitrary units.) *Dashed line*: enzyme E. *Squares*: G cells. *Stars*: A cells. $d = 6$; $b = 2$; $c = 0.5$; $e = 1$; $\tau_E = 5$; $i = 0$; $a\varphi = 10$; $m = 0.5$; $A(0) = 5$; $G(0) = 0.5$; $E(0) = 0$

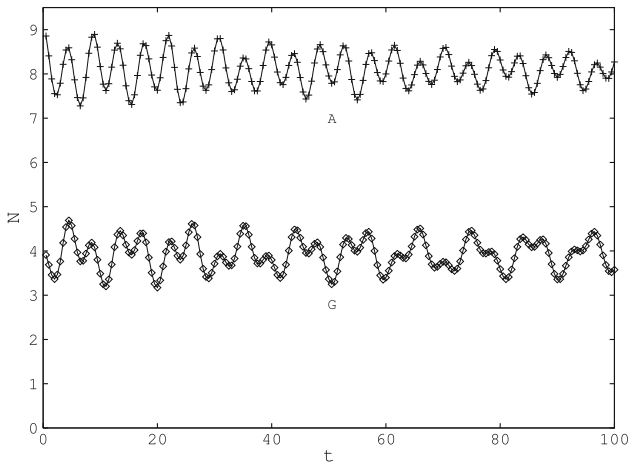

Fig. 2 Second-order niche construction model with a timescale separation of the enzyme dynamics. Abscissae: time. Ordinates: concentrations. (Arbitrary units.) *Squares*: G cells. *Stars*: A cells. $A(0) = 9$, $dA/dt = 0.1$, $G(0) = 4$, $dG/dt = 0$, $a\varphi = 30$; $c = 0.5$; $m = 2$; $b = 10$, $d = 20$, $i = 0$, $e = 1$, $\tau_E = 1$

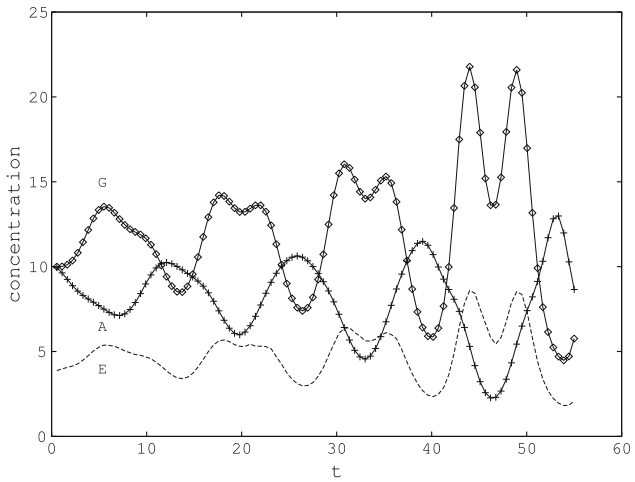

Fig. 3 Second-order niche construction model without friction. Oscillations are amplified. Abscissae: time. Ordinates: concentrations. (Arbitrary units.) *Dashed line*: enzyme E. *Squares*: G cells. *Stars*: A cells. $d = 5$; $b = 2$; $c = 0.5$; $e = 2$; $i = 0$; $a\varphi = 30$; $m = 1$; $\tau_E = 0.2$; $f = 0$

We can investigate the structural stability of the second-order model by adding a friction term. (Recall that this term represents also the sharing of intracellular resources between daughter cells when the limiting factor has non-heritable effects; see our discussion on friction in the companion paper.)

$$\frac{dr_A}{dt} = \frac{a\varphi}{A+G} - m - \frac{d}{1+bE} - fr_A$$

$$\frac{dr_G}{dt} = \frac{a\varphi}{A+G} - m - c - fr_G$$

The equation for enzyme dynamics is as before:

$$\frac{dE}{dt} = \frac{-1}{\tau_E}E + i + eG$$

We treat this case by numerical experimentation (Figs. 3, 4, 5). It turns out that friction counteracts the inertia introduced by the enzyme decay rate (τ_E). Starting from a case with amplified oscillations (without friction, Fig. 3), we first add a relatively low friction term (compared to the parameter $1/\tau_E$ having the same dimension), and damped oscillations obtain (Fig. 4). Last, when increasing the enzyme characteristic time enzyme τ_E, G population crashes, which can be interpreted as an effect of the competitive advantage of A cells taking advantage of the longest presence of the plasmatic enzyme (Fig. 5). It turns out that f and $1/\tau_E$, conjointly, increase the stability of the coexistence. This might be interpreted as an effect of f, which opposes to extreme fluctuations that can drive a population to extinction and slows down the dynamics at the same time, and as an effect of $1/\tau_E$, which makes A cells more dependent on G cells. In timescale separation terms, it can be said that coexistence is favored when the enzyme has a fast dynamics ($1/\tau_E$ important) as regards the population dynamics (slowed down by f).

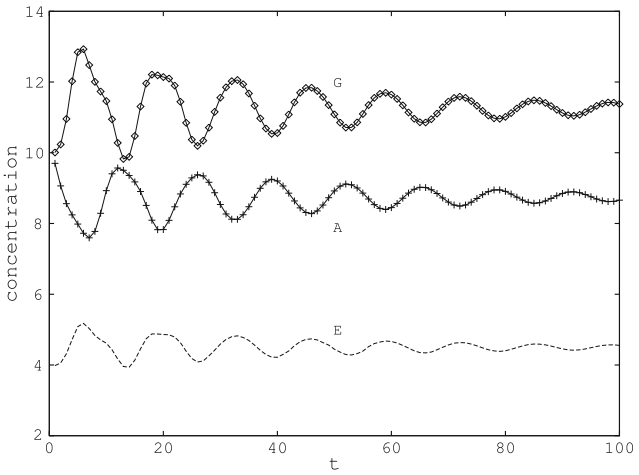

Fig. 4 Second-order niche construction model with friction. Here friction is weak but oscillations are damped. Abscissae: time. Ordinates: concentrations. (Arbitrary units.) *Dashed line*: enzyme E. *Squares*: G cells. *Stars*: A cells. $d = 5$; $b = 2$; $c = 0.5$; $e = 2$; $i = 0$; $a\varphi = 30$; $m = 1$; $\tau_E = 0.2$; $f = 0.1$ (same parameters as in Fig. 3, friction excepted)

Gene Therapy Model: Discussion

This work seeks to investigate the possible perturbations of cell population dynamics with a therapeutic aim. From the therapeutic point of view, such a modeling work can be considered as a means to optimize the research of relevant empirical variables.

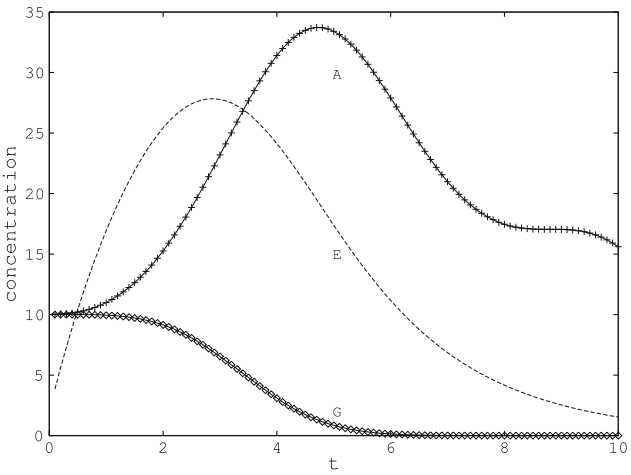

Fig. 5 Second-order niche construction model with friction. Here friction is weak, but the enzyme lifetime has been increased. The G cells are eliminated because of enzyme inertia. Abscissae: time. Ordinates: concentrations. (Arbitrary units.) *Dashed line*: enzyme E. *Squares*: G cells. *Stars*: A cells. $d = 5$; $b = 2$; $c = 0.5$; $e = 2$; $i = 0$; $a\varphi = 30$; $m = 1$; $\tau_E = 2$; $f = 0.1$ (same parameters as in Fig. 4 but for τ_E which has been multiplied by ten)

Therapeutic Perspectives

When considering the first-order model, it appears that enzyme injection is counterproductive for ADA-SCID gene therapy, in the sense that within a stable coexistence equilibrium, injections do not increase the quantity E^* of enzyme and decrease the amount G^* of modified cells. This result is structurally stable. Generally speaking, let us write $\theta(E)$, the increase in mortality of non-modified cells due to the lack of enzyme (in our model, $\theta(E) = d/(1 + bE)$); we also write f, the response function to resources, and h, the function describing the enzyme dynamics. Our system is:

$$\frac{dG}{Gdt} = f(a\varphi, A + G, m) - c$$
$$\frac{dA}{Adt} = f(a\varphi, A + G, m) - \theta(E)$$
$$\frac{dE}{dt} = h(E, \tau_E, i, e, G)$$

Coexistence at the equilibrium entails that $\theta(E^*) = c$. When the equation $\theta(E) = c$ cannot be satisfied whatever the value of E, the coexistence is impossible at the equilibrium, and A always wins when $\theta(E) < c$, G always wins when $\theta(E) > c$.

The equilibrium is stable when $d\theta(E)/dE < 0$. This condition means that for the equilibrium to be stable, the increase in mortality due to lack of enzyme decreases when the enzyme quantity increases (this condition is fulfilled in our model).

Under coexistence, $\theta(E^*)$ determines E^*, which does not depend on i. E^* determines G^* *via* the function $h(E, \tau_E, i, e, G)$. If h is increasing as a function of i and increasing as a function of G^* (which seems reasonable), keeping fixed E^* and all the parameters in h except i and G^*, then:

$$\frac{dE^*}{dt} = 0 = \frac{\partial h}{\partial i} di + \frac{\partial h}{\partial G^*} dG^*$$

that is:

$$\frac{dG^*}{di} = \frac{-\frac{\partial h}{\partial i}}{\frac{\partial h}{\partial G^*}}$$

As $\partial h/\partial i > 0$ and $\partial h/\partial G^* > 0$ according to our biological hypotheses, it turns out that $dG^*/di < 0$. Thus $G^*(i)$ is decreasing, and can eventually become negative. From a biological point of view, this means that above a given injection threshold, engraftment of modified G cells is impossible, and that injections lower the amount of enzyme effectively produced by G cells. These two behaviors were empirically observed by Aiuti et al. (2002b).

We would like to draw attention to the fact that this reasoning holds at the equilibrium only (and, also, if there is coexistence, which seems to be the case at the scale of several years). From a therapeutic point of view, it can be unavoidable to resort to sporadic enzyme injections when the patient is in bad condition (Aiuti et al. 2002b), to temporarily increase the enzymatic level above its equilibrium value. Notice however, that the injections should then take place in a period as short as possible (in approximately one month, the plasmatic enzyme seems to go back to its pre-injection equilibrium value despite the injections (Aiuti et al. 2002b), Fig. 1). In addition to the observed decrease in G cells, it is possible that the synthesis of the enzyme by G cells is decreased in presence of the enzyme.

Generalization to Other Gene Therapies

In this study, we focused on a permanent gene therapy. However, the perspective of gene therapies also concerns transitory gene therapies. For instance, in case of a bone fracture, it is possible to modify cells in such a way that they produce osteogenic growth factors and thus improve bone welding. This kind of therapy enables a more spatially targeted treatment than the injection of an exogenous protein (Baltzer and Lieberman 2004). In this case, the aim is not the invasion of a tissue by G cells, but in contrast their elimination by A cells: the focal transient behavior is the tissue relaxation time. Using a model in the same vein as above, and assuming that the modified G cells do not benefit more from the growth factors they produce than the non-modified A cells, we could write:

$$\frac{dA}{Adt} = f(a\varphi, A + G, m)$$
$$\frac{dG}{Gdt} = f(a\varphi, A + G, m) - c$$

It turns out that the relaxation time is of the magnitude of $1/c$, where c is the cost of growth factor synthesis by the cell.

A similar model could be used for cancer gene therapies using mesenchymal stem cells. These cells have a positive tropism for tumors and their metastases, and can be transformed to deliver oncolytic viruses of therapeutic proteins specifically on tumoral sites, and their persistence in the patient's organism is not necessarily wanted (see the review by Dwyer et al. 2010).

Demographic Inertia and Population Fluctuations

To our knowledge, the available data do not enable a conclusion with respect to the importance of demographic inertia in the case of intraorganismal cell population dynamics. Demographic inertia, in particular inertia due to maternal effects, has been discussed in ecology (e.g., Ginzburg and Taneyhill 1994, but see Berryman 1995). We know of no such a discussion in intraorganismal ecology.

In the case of demographic inertia, the populations have their own pulsation and can oscillate around the equilibrium, in particular when they experience perturbations. Oscillatory behaviors, and fluctuations in general, are numerous in intraorganismal ecology (e.g., Wagner et al. 1996; Perazzo 2000). Notably, some hematological disorders (some leukemias and neutropenias in particular) result in oscillatory behaviors of cell population dynamics with periods ranging from ten to one hundred days depending on the disease; in this case, the temporal pattern is even part of the clinical description (Birgens and Karle 1993; Haurie et al. 1999; Hirase et al. 2001; Hirayama et al. 2003; Xiao et al. 2003; Colijn and Mackey 2005).

As for ADA-SCID gene therapy, the lymphocyte number fluctuates (from a factor of one to six, see Aiuti et al. 2002a) but the data are insufficient to assess the potential intrinsic period of the population dynamics. Given the state of current knowledge, we thus cannot ascribe oscillatory behaviors to an intrinsic demographic inertia, in contrast with an external forcing. However, the search for oscillatory mechanisms could answer this question, in a potentially easier way than for macroorganisms, thanks to the shorter characteristic time of demographic renewal. Notice however that in intraorganismal ecology, we could expect that the organism exerts a friction on potential oscillations of cell populations to be able to maintain a certain homeostasis. This friction would result from cell relationships with their environment and would thus be difficult to isolate in vitro.

The demographic inertia, if proven, could be of importance for cell population management (that is, in our case, for managing non-modified A and modified G cells populations), first because short time actions can have effects on a longer timescale, second because oscillatory behaviors could lead to destabilization or resonance effects. We have shown that in our case (second-order model with injection and enzyme synthesis), the system is not destabilized by enzyme injections, except for extreme values of the parameters. (Notice however that this conclusion holds for relatively frequent injections, as more sporadic injections should be modeled by a Dirac comb, and could still lead to resonance effects with cell population dynamics.[4])

Generally speaking, even in the absence of external perturbations like enzyme injections, it turns out that demographic inertia can be a source of supplementary instability leading to engraftment failing.

The ecological cell niche can be a source of demographic inertia (in our model, because of the enzyme's characteristic time τ_E), and niche construction can result both in an amplification or, on the contrary, in a damping of oscillations. To have a better grasp on the structural origin of this effect, we can derive once more the equation of the enzyme dynamics. The second-order equation is given by:

$$\frac{d^2E}{dt^2} = -\frac{1}{\tau_E}\frac{dE}{dt} + e\frac{dG}{dt}$$

Writing r_E the speed dE/dt to help identifying structural homologies, we can write the equation of the acceleration d^2E/dt^2 as:

$$\frac{d^2E}{dt^2} = -\frac{1}{\tau_E}r_E + eGr_G$$

It appears that r_E/τ_E behaves as a friction term with respect to the acceleration d^2E/dt^2. The term Gr_G represents a nonlinearity that explains the complexity of the behaviors described in this article. Generally speaking, in the linearized system the enzyme dynamics introduces first-order terms that are typical of friction and antifriction, while without friction nor niche construction the characteristic polynomial is of the form $P(X^2)$.

As regards the effect of the enzyme on the dynamics, we have chosen a simple model where G cells are not affected by the enzyme concentration (assuming that the intracellular synthesized enzyme concentration is non-limiting), and where the additional mortality (or the additional metabolic cost in the second-order model) in A cells is additive to their dynamics. A more general model could consider a non-complete restauration of the cell function by gene therapy and/or that the enzyme effect is not additive with respect to the first-order dynamics (that is, the function f would have E as a variable). In this case, G cells dynamics would depend on E, but also, G cells could have a

[4] The importance of taking the dynamical aspects into account to optimize the therapeutics has already been shown as regards cancer (Netti et al. 1995; Sangalli et al. 2001).

privileged access to the enzyme they themselves synthesize. A simple way to deal with this kind of competitive advantage would be to model the enzyme as being synthesized in an intracellular compartment (E_c, accessible only to G cells), with a transit to an intercellular compartment (here, the blood plasma with a concentration E, that would also depend on injections), where it would be both accessible to A and G cells.[5]

Conclusion

Non-Equilibrium Ecology

In this article, we investigated the impact of a cell niche-construction activity (the synthesis of a missing enzyme) that would not be timescale-separable from the cell population dynamics. This drove us to focus on the importance of transitory dynamics (oscillations, relaxation times) that are due to niche and demographic inertia.

Two different perspectives emerge, given that we consider that ecological interactions should be described as first- or second-order systems. First-order systems describe demographic dynamics that are directly affected by demographic factors (resources, sources of mortality), while second-order systems describe demographic dynamics that are indirectly affected, through the interplay at the individual level between metabolism and resource acquisition. At the second order, demographic factors are analogous to forces in the Newtonian mechanics that impact the acceleration of a movement and not its speed. In mathematical terms, a supplementary dynamical dimension is added to the definition of the niche.

Ginzburg and Colyvan (2004, pp. 102–103), in a programmatic conclusion, urged ecologists to identify the ecological "forces," force here having to be understood as a cause inducing a modification of the energetic state of the individuals or of the corresponding growth rate. Among such forces, Ginzbug & Colyvan see energetics, maternal effects, and predator-prey relationships. The niche as a substrate for demographic inertia, and niche construction as an ecological force, could be added to this program.

From Enrichment by Ecology to Enrichment of Ecology

In this article, we have chosen to describe the lymphocyte population with the minimal model of an unstructured population. However, the populations of interest (lymphocyte strains) are, from an ecological point of view, metapopulations that are structured in source–sink populations because of cell differentiation, which might also be correlated to cell age (e.g., hematopoietic stem cell → lymphoid progenitor → lymphoblast → prolymphocyte → lymphocyte → T lymphocyte, to mention just one strain). The fact that differentiated cells can de-differentiate could be modeled in a structurally homologous way as migration occurring from a sink population in ecology.

Most probably, such a highly structured cell fate, constrained by the cellular environment posed by the organism, should have major dynamical effects. Then "the organism would be an ecosystem, but it would be more than an ecosystem,"[6] and intraorganismal ecology would have to be not just an application, but also a true extension of classical ecology.

Acknowledgments This work is based on a project started at the CEMRACS 2004, whose participants were Antonio Cappucio, Etienne Couturier, Michel de Lara, Regis Ferrière, Olivier Sester, Pierre Sonigo, Christian, and Carlo. The authors also wish to thank the organizers and participants of the StabEco workshop, held at the Laboratory Ecology and Evolution, University of Paris 6, on December 17, 2010. Philippe Huneman and Minus van Baalen provided invaluable comments on earlier versions of the manuscript.

This work consists of a partial update of a previous work in French (Pocheville 2010, Chap. 3), realized while both A.P. and M.M. were benefiting from funding from the Frontiers in Life Sciences PhD Program and from the Liliane Bettencourt Doctoral Program. The paper was written while A.P. was benefiting from a Postdoctoral Fellowship from the Center for Philosophy of Science, University of Pittsburgh. M.M. is currently benefiting from a Postdoctoral Fellowship from the Region Ile-de-France, DIM-ISC.

Appendix

Linearized First-Order Model, with Two Species and Niche Construction (Enzyme Synthesis)

After linearization, we seek for the eigenvalues of the system (of dimension 3). These eigenvalues are roots of the characteristic polynomial:

$$X^3 + X^2\left(M + \frac{1}{\tau_E}\right) + X\frac{M}{\tau_E} + Be\frac{c^2 b}{d}$$

where $M = m + c$ and:

$$B = \frac{M^2}{a\varphi}\left(\frac{a\varphi}{M} - G^*\right)$$

It turns out that in the case where there is coexistence, two scenarios are possible:

[5] An explicit spatial description would require using partial differential equations that are less tractable, and knowing the exact geometry of the space we would be dealing with.

[6] Giuseppe Longo, oral remark, IHPST, Paris, 28 November 2013.

1. The polynomial has three negative roots: in this case the system converges exponentially toward equilibrium,
2. or the polynomial has a negative root and two conjugated complex solutions. In this case the system is stable or unstable according to the sign of the real part of the roots. In the case where the system is stable, the regime is pseudoperiodical with damped oscillations.

The literal resolution of the polynomial can be easily realized, but the literal expression of the solutions is too complicated to be informative.

Linearized Second-Order System with Two Species, Enzyme Construction, and Timescale Separation on the Enzyme Dynamics

The following characteristic polynomial obtains:

$$X^2 + MX + B\frac{c^2}{d}$$

where $M = m + c$ and:

$$B = \frac{M^2}{a\varphi}\left(\frac{a\varphi}{M} - G^*\right)$$

and:

$$G^* = \frac{1}{be\tau_E}\left(\frac{d}{c} - 1 - bi\tau_E\right)$$

The polynomial discriminant Δ is:

$$\Delta = M^2 - 4B\frac{c^2}{d}$$

Thus

$$\Delta = M^2\left(1 - 4\frac{c^2}{da\varphi}\left(\frac{a\varphi}{M} - G^*\right)\right)$$

If $\Delta > 0$, then:

$$X = \frac{-M \pm \sqrt{\Delta}}{2}$$

If there is coexistence then we have $a\varphi/M - G^* > 0$, then these two roots are negative and the system has oscillations near the equilibrium.

If $\Delta < 0$, then:

$$X = \frac{-M \pm j\sqrt{\Delta}}{2}; \text{ where } j^2 = -1.$$

In this case the eigenvectors have a dynamics in a $\exp(Zt)$ form, where $Z^2 = X$. However, the real part of the roots is negative, thus for each root one of the Z has a positive real part and the equilibrium is unstable. The system diverges with amplified oscillations.

When the quantity i of the injections increases, G^* decreases thus Δ decreases. Increasing i makes the instability closer. If $1 < 4c^2/(dM)$, then increasing i destabilizes the system. We then do not know which of the two populations A and G will survive; which in particular depends on the initial conditions.

References

Aiuti A (2002) Advances in gene therapy for ADA-deficient SCID. Current Opin Mol Ther 4:515–522

Aiuti A, Slavin S, Aker M et al (2002a) Correction of ADA-SCID by stem cell gene therapy combined with nonmyeloablative conditioning. Science 296:2410–2413. 10.1126/science.1070104, http://www.sciencemag.org/content/296/5577/2410.abstract, http://www.sciencemag.org/content/296/5577/2410.full.pdf

Aiuti A, Vai S, Mortellaro A et al (2002b) Immune reconstitution in ADA-SCID after PBL gene therapy and discontinuation of enzyme replacement. Nat Med 8:423–425

Aiuti A, Cassani B, Andolfi G et al (2007) Multilineage hematopoietic reconstitution without clonal selection in ADA-SCID patients treated with stem cell gene therapy. J Clin Invest 117:2233–2240

Aiuti F, Giovannetti A (2003) Structured interruptions of therapy: looking for the best protocol. Aids 17:2257–2258

Baltzer A, Lieberman J (2004) Regional gene therapy to enhance bone repair. Gene Ther 11:344–350

Berryman AA (1995) Population cycles: a critique of the maternal and allometric hypotheses. J Anim Ecol 64:290–293

Birgens HS, Karle H (1993) Reversible adult-onset cyclic haematopoiesis with a cycle length of 100 days. Br J Haematol 83:181–186

Cappell B, Aiuti A (2010) Gene therapy for adenosine deaminase deficiency. Immunol Allergy Clin North Am 30:249

Cassani B, Montini E, Maruggi G et al (2009) Integration of retroviral vectors induces minor changes in the transcriptional activity of T cells from ADA-SCID patients treated with gene therapy. Blood 114:3546–3556

Cavazzana-Calvo M, Thrasher A, Mavilio F (2004) The future of gene therapy. Nature 427:779–781

Cavazzana-Calvo M, Lagresle C, Hacein-Bey-Abina S, Fischer A (2005) Gene therapy for severe combined immunodeficiency. Annu Rev Med 56:585–602

Colijn C, Mackey MC (2005) A mathematical model of hematopoiesis—I. Periodic chronic myelogenous leukemia. J Theor Biol 237:117–132

Dwyer RM, Khan S, Barry FP et al (2010) Advances in mesenchymal stem cell-mediated gene therapy for cancer. Stem Cell Res Ther 1:25

Gaspar HB, Aiuti A, Porta F et al (2009) How I treat ADA deficiency. Blood 114:3524–3532

Ginzburg LR, Taneyhill DE (1994) Population cycles of forest lepidoptera: a maternal effect hypothesis. J Anim Ecol 63:79–92

Ginzburg LR, Colyvan M (2004) Ecological orbits: how planets move and populations grow. Oxford University Press, New York

Haurie C, Dale DC, Mackey MC (1999) Occurrence of periodic oscillations in the differential blood counts of congenital, idiopathic, and cyclical neutropenic patients before and during treatment with G-CSF. Exp Hematol 27:401–409

Hirase N, Abe Y, Muta K et al (2001) Autoimmune neutropenia with cyclic oscillation of neutrophil count after steroid administration. Int J Hematol 73:346–350

Hirayama Y, Sakamaki S, Tsuji Y et al (2003) Cyclic platelet and leukocyte count oscillation in chronic myelocytic leukemia regulated by the negative feedback of transforming growth factor β. Int J Hematol 77:71–74

Jones CG, Lawton JH, Shachak M (1994) Organisms as ecosystem engineers. Oikos 69:373–386

Lehmann L (2008) The adaptive dynamics of niche constructing traits in spatially subdivided populations: evolving posthumous extended phenotypes. Evolution 62:549–566

Marangoni F, Bosticardo M, Charrier S et al (2009) Evidence for long-term efficacy and safety of gene therapy for Wiskott–Aldrich syndrome in preclinical models. Mol Ther 17: 1073–1082

Netti PA, Baxter LT, Boucher Y et al (1995) Time-dependent behavior of interstitial fluid pressure in solid tumors: implications for drug delivery. Cancer Res 55:5451–5458

Perazzo C, Fernandez E, Chialvo D, Willshaw P (2000) Large scale-invariant fluctuations in normal blood cell counts: A sign of criticality? Fractals 8:279–283. 10.1142/S0218348X00000329, http://www.worldscinet.com/fractals/08/0803/S0218348X00000329

Pocheville A (2010) La Niche Ecologique: Concepts, Modèles, Applications. PhD Thesis, Ecole Normale Supérieure Paris. http://hal.upmc.fr/tel-00715471/

Pocheville A, Montévil M (2014) Ecological models for gene therapy. I. Models for intraorganismal ecology. Biol Theory. doi:10.1007/s13752-014-0190-y

Sangalli M, Maroni A, Zema L et al (2001) In vitro and in vivo evaluation of an oral system for time and/or site-specific drug delivery. J Control Release 73:103–110

Sauer AV, Aiuti A (2009) New insights into the pathogenesis of adenosine deaminase-severe combined immunodeficiency and progress in gene therapy. Curr Opin Allergy Clin Immunol 9:496–502

Wagner C, Nafz B, Persson P (1996) Chaos in blood pressure control. Cardiovasc Res 31:380–387

Xiao Z, Hao Y, Qin T, Han Z (2003) Periodic oscillation of blood leukocytes, platelets, and hemoglobin in a patient with chronic eosinophilic leukemia. Leuk Res 27:89–91