

# A concept of antifragility for dynamical systems

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2024-11-12

## Abstract

This paper defines antifragility for dynamical systems in terms of the convexity of a newly introduced “logarithmic rate”. It shows how to compute this rate for positive linear systems, and it interprets antifragility in terms of pulsed alternations of extreme strategies in comparison to average uniform strategies.

## 1 Introduction

Nassim Nicholas Taleb introduced in 2012 the concept of “antifragility” to refer to systems that *benefit* from uncertainty [1]. In contrast to *robustness* (resilience to uncertainty) being desirable, Taleb emphasized the advantages of devoting resources to “placing bets” on unlikely events, provided that their payoff is large enough, or more precisely that the expected return from a bet on extremes is higher than the expected return from an intermediate bet, as will be the case with convex payoff functions (Jensen’s inequality, in mathematical terms). Much work has followed Taleb’s original paper, including formalizations in [2] and recently a paper placing these ideas in the context of mathematical oncology [3].

In this paper, we propose a definition of antifragility for dynamical systems. The definition relies upon our introduction of a quantity, which we call the “logarithmic rate” of an output, and which we write as  $\rho(u)$ . The rate is a function of a parameter  $u$  (and possibly initial states). Although antifragility is a very general idea that plays a role in areas ranging from hedging strategies in finance to engineering [4], to be concrete we will phrase our discussion in terms of infectious diseases or tumors. In that context, we may think of  $u$  as quantifying a dose of an antiviral or antibiotic to fight an infection, or a dose of chemotherapy, immunotherapy, or targeted therapy in oncology, and we may think of  $\rho(u)$  as representing the rate of growth of an infection or tumor, as discussed below. Antifragility will mean that the function  $\rho(u)$  is convex, if the objective is the maximization of a reward (as seen by a tumor or a microorganism carrying an infection) or that the function  $\rho(u)$  is concave, if the objective is the minimization of a cost (as seen by the infected individual). We will show how to compute  $\rho(u)$  for the special, but important, case of systems defined by positive linear dynamics, and we will focus on comparing “pulsed” versus “uniform” treatment protocols.

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## 1.1 Motivation

To start the discussion, let us suppose that we have a cell population (consisting, for example, of cells infected by a pathogen, or a type of tumor cells), and we wish to administer a certain drug with the purpose of minimizing the population size. Let us say that the size of the population at time  $t$  is represented by the scalar variable  $x(t)$ , which evolves according to the linear differential equation

$$\dot{x} = \rho(u)x, \quad x(0) = x_0.$$

Here a dot indicates time derivative of  $x = x(t)$  and  $x_0$  is an initial state, which we assume positive. The function  $\rho(u)$  quantifies the net growth rate when our drug is given at a concentration quantified by  $u$  (for example,  $u = 10$  in units of mg per hour). Note that  $x(t) = e^{\rho(u)t}x_0$ . Our goal is that  $x(t)$  should be small at some predetermined future time  $t = N$ . When the drug is given at a high concentration, typically  $\rho(u)$  will be negative, so that the cell population tends to become extinct,  $x(t) = e^{\rho(u)N}x_0 \rightarrow 0$  as  $N \rightarrow \infty$ . For lower concentrations, on the other hand, we might expect the rate of growth to be higher;  $\rho(u)$  could even be positive, in which case the population grows out of control,  $x(t) = e^{\rho(u)N}x_0 \rightarrow \infty$  as  $N \rightarrow \infty$ . Clearly, we wish for  $\rho(u)$  to be small. Assuming that a formula for the function  $\rho$  is known, such a minimization can be done by solving a simple calculus problem. We could then administer the obtained optimal dose  $u$ . Fig 1 shows the graphs of two possible functions  $\rho$ . If our purpose is that  $\rho(u)$  should be as small as possible, we can pick the rightmost points (both labeled  $u$ ) in the graphs, that is to say, the largest dose.

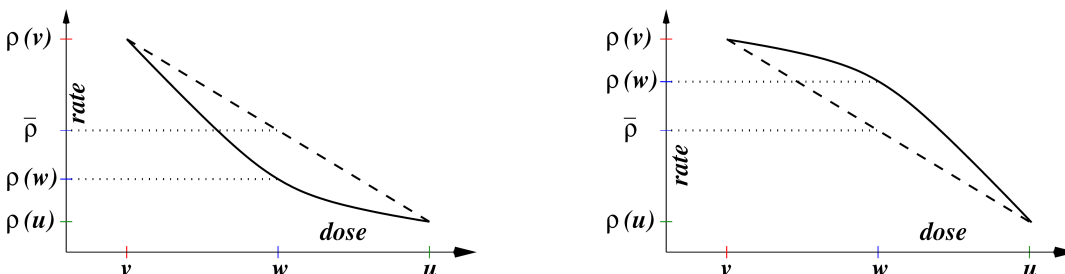


Figure 1: Left: A convex function  $\rho$ , with dosages  $u$ ,  $v$ , and  $w = \frac{u+v}{2}$ . Here  $\rho(w)$  is smaller than  $\bar{\rho}$ . Right: Concave  $\rho$ ; now  $\rho(w)$  is larger than  $\bar{\rho}$ .

However, suppose now that, because of toxicity, or to minimize the emergence of drug-induced resistance [5], we wish to consider more complicated therapies than simply administering a constant drug concentration. Is it better to use alternations of high and low doses or to use an average dose? This question has been discussed in the context of chemotherapy, where high or low variance treatment schedules may be superior depending on the convexity of  $\rho(u)$  [3, 4]. Specifically, let us compare the following two scenarios for treatment.

In the first scenario, during a treatment period of total length  $N$  we use the following *pulsed protocol*: we alternate between two drug dosages: a higher dose  $u$  followed by a lower dose  $v$  (for example,  $v = 0$  would represent a “drug holiday” between treatments), each applied for time  $1/2$ . That is, dose  $u$  is applied on the time intervals

$$[0, 0.5], [1, 1.5], \dots, [N-1, N-0.5]$$

and dose  $v$  is applied on the intervals

$$[0.5, 1], [1.5, 2], \dots [N - 0.5, N]$$

(see Fig 2).

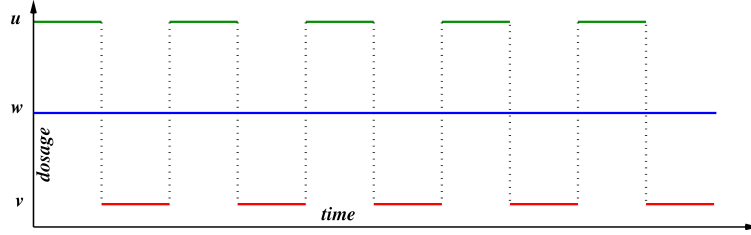


Figure 2: A pulsed protocol: iteration of high dose  $u$  (green) followed by low dose  $v$  (red). Shown also is a uniform protocol with average dose  $w = \frac{u+v}{2}$  (blue).

As a result, in each period of length 1, the population size is first multiplied by  $e^{\rho(u)/2}$  and then by  $e^{\rho(v)/2}$ , so by the end, at time,  $t = N$ , the size of the population will be:

$$x_{\text{pulsed}}(N) = \left( e^{\rho(v)/2} e^{\rho(u)/2} \right)^N = \left( e^{\rho(u)/2 + \rho(v)/2} \right)^N = e^{\bar{\rho}N} x_0,$$

where  $\bar{\rho}$  is the average of the rates of  $u$  and  $v$ ,  $\bar{\rho} = \frac{1}{2}(\rho(u) + \rho(v))$ . See Fig 3. Observe that

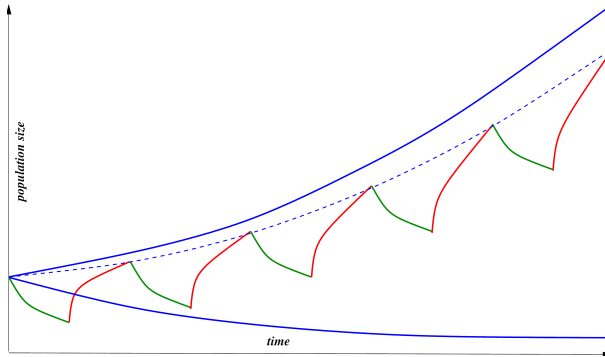


Figure 3: Population growth under pulsed protocol. Iteration of dose  $u$  (green, with negative growth rate) followed by  $v$  (red, positive growth rate). The resulting equivalent growth rate  $\bar{\rho}$  is the average of the two rates; blue dashed line shows the equivalent growth under this rate,  $e^{\bar{\rho}N} x_0$ . A uniform protocol (solid blue lines) will provide a lower growth rate (perhaps negative) or a higher one, depending on the convexity of the rate function  $\rho$ .

the total amount of drug delivered during the even intervals is  $Nv/2$  (there are  $N$  intervals of length  $1/2$ , and in each of them the total amount of drug is  $v/2$ ). Similarly, the total amount drug during the odd intervals is  $Nu/2$ , So the total amount of drug applied is

$$\frac{Nu}{2} + \frac{Nv}{2} = N \frac{u+v}{2} =: Nw.$$

The second scenario is the following *uniform protocol*: we simply apply the constant dosage  $w$  during the whole period  $[0, N]$  (see Fig 2). Now the size of the population at time  $N$  is

$$x_{\text{uniform}}(N) = e^{\rho(w)N} x_0.$$

The total amount of drug applied is  $wN$ , which is the same as in the first scenario. However, if the rate function  $\rho$  is not linear, the outcome will generally be very different than in the first scenario. A uniform protocol will result in a better (or at least not worse) outcome –i.e. a lower  $x(N)$ – than a pulsed protocol, if  $\rho(w) \leq \bar{\rho}$ :

$$\rho\left(\frac{u+v}{2}\right) \leq \frac{1}{2}\left(\rho(u) + \rho(v)\right), \quad (1)$$

which happens if the rate function  $\rho$  is convex (see Fig 1, left). Conversely, if the reverse inequality holds, which happens if the rate function is concave, then a pulsed protocol is superior in decreasing the population size (see Fig 1, right).

So far, the discussion has been limited to a very special situation, that of a one-dimensional system, that is to say, there is only one state variable describing the dynamics of the system. In a more complex biological system, the effect of drugs can be complicated by phenomena such as the emergence of therapy resistance, in which different subpopulations, with different growth and death rates, react differently to the drug. The main purpose of this paper is to provide a more complex setting in which one can make a similar convexity-based comparison. In this, we were motivated by the work in [3, 4] and closely related work in [6].

Still in the one-dimensional case, note that value of the initial condition is not critical to the comparison of the sizes of the variable  $x(t)$  for different strategies, at least for large enough time. This is because the ratio  $e^{\rho_1 t} x_1 / e^{\rho_2 t} x_2$  equals  $k e^{(\rho_1 - \rho_2)t}$ , for the constant  $k = x_1 / x_2$ , and this ratio will be large if  $\rho_1 > \rho_2$ , and will tend to zero if the opposite inequality holds. Thus we define a notion which is independent of the initial state. (In section 4, we briefly discuss what is “large enough” time.) Since  $x(t) = e^{\rho(u)t} x_0$ , we can write  $\ln x(t) = \rho(u)t + \ln x_0$ , which means that we may estimate the rate as  $\rho(u) = \ln x(t) / t + \ln x_0 / t$ . For large enough times  $t$ , the effect of the initial condition is fades:

$$\rho(u) = \lim_{t \rightarrow +\infty} \frac{\ln x(t)}{t}.$$

We will provide an entropy-like quantity similar to  $\rho$  for arbitrary nonlinear dynamics, and show how to compute this quantity for a class of linear systems  $\dot{x}(t) = A(u)x(t)$ , where now  $x(t)$  is vector valued and  $A(u)$  is a matrix instead of the scalar  $\rho(u)$ . When attempting to generalize to matrices the scalar case discussed earlier, a key difficulty is that the formula  $e^{A(v)/2} e^{A(u)/2} = e^{A(u)/2 + A(v)/2}$  is false (though true in the special case that the matrices commute,  $A(u)A(v) = A(v)A(u)$ ). However, for the special class of “positive” systems, which arguably includes all examples of biological interest, we are able to derive an analogue of (1) stated in terms of  $\rho$ , thus allowing a comparison between uniform and pulsed protocols using convexity of  $\rho$  for linear positive systems of dimension greater than one. In the convex case, a pulsed protocol consisting of sequential alternations of two drug concentrations results in a larger growth rate than a uniform treatment using an average concentration. Thus from the

point of view of the tumor or infection, the pulsed protocol results in a higher “win” compared to the uniform one. From the patient’s point of view, who wants to minimize instead of maximize  $\rho$ , a constant strategy is best. When the concavity is reversed, the opposite choices hold.

## 1.2 Mathematical preliminaries

Consider a parameterized system of differential equations as follows:

$$\dot{x} = f(x, u), \quad x(0) = x_0, \quad y = h(x). \quad (2)$$

Dot indicates time derivative, and arguments  $t$  are not displayed. Here  $x = (x_1, \dots, x_n)$  is a state vector whose coordinates specify population sizes, expression levels or differential expression levels of molecular components such as mRNAs, or other quantities of interest. We assume that states  $x(t)$  are required to belong to a prespecified subset  $\mathbb{X}$  of Euclidean space  $\mathbb{R}^n$ . this set  $\mathbb{X}$  might include constraints such as positivity of coordinates or maximal allowable values for these coordinates. Here,  $x_0 \in \mathbb{X}$  is an initial condition. The solution  $x(t) = x(t, u, x_0)$  of (2) is assumed to be unique and defined for all  $t \geq 0$ , taking values  $x(t) \in \mathbb{X}$  for all  $t$ , and  $h : \mathbb{X} \rightarrow \mathbb{Y}$  is an output or readout map. See [7] for control-theory formalism and conditions guaranteeing existence and uniqueness. The symbol  $u$  denotes a parameter that takes values in a convex subset  $\mathbb{U}$  of some Euclidean space. We will denote by

$$y(t, u, x_0)$$

the output trajectory with input and initial state  $x_0$ . That is,  $y(t, u, x_0) = h(x(t, u, x_0))$ , for all  $t \geq 0$ .

There are many applications of this setup. One cell biology interpretation is as follows. Each coordinate  $x_i(t)$  of the state vector quantifies the number (or volume) of cells of a certain type “ $i$ ” at time  $t$ ,  $u$  represents a constant-in-time drug dosage being applied during an interval of time, and  $y(t) = h(x(t))$  is some observable quantity, such as for example the total number of cells at time  $t$ ,  $y(t) = \sum_{i=1}^n x_i(t)$ .

**Definition 1** The *logarithmic rate* of the system is defined as follows:

$$\rho(u, x_0) := \limsup_{t \rightarrow +\infty} \frac{1}{t} \ln |y(t, u, x_0)|$$

(when  $y(t, u, x_0) = 0$ , we interpret the log as  $-\infty$ ). □

Note that when the limit exists, and if  $y$  is positive, as will be the case with the class of positive linear systems studied below, this is simply

$$\rho(u, x_0) := \lim_{t \rightarrow +\infty} \frac{1}{t} \ln y(t, u, x_0).$$

In a typical application, we can think of  $\rho$  is the slope of a semi-log plot of cell number (or volume) vs. time.

The main motivation for this definition is as follows. Suppose that we have a scalar ( $n = 1$ ) linear system  $\dot{x} = \lambda x$  with measurement  $y = cx$ ,  $x_0 > 0$ , and  $c > 0$ . Then  $y(t) = ce^{\lambda t}x_0$ , and therefore (since  $cx_0 \neq 0$  and thus its logarithm is well defined):

$$\rho(u, x_0) = \lim_{t \rightarrow +\infty} \frac{1}{t} \ln y(t, u, x_0) = \lambda + \lim_{t \rightarrow +\infty} \frac{\ln(cx_0)}{t} = \lambda$$

is independent of the initial state  $x_0$ . This is the rate of growth (or decay, if  $\lambda < 0$ ) of the output  $y(t)$ . When  $\rho(u, x_0)$  is independent of  $x_0$ , as here, we write simply  $\rho(u)$ . Our main purpose here is to generalize this one-dimensional motivating example to linear systems of higher dimension than one.

**Remark 1** A formula similar to that for  $\rho$  is used when defining Lyapunov exponents in chaos theory. A difference is that for Lyapunov exponents one looks at differences between responses for two different initial states, which would become an “incremental” variant of  $\rho$ , related to ideas of logarithmic norms and contractive systems [8].  $\square$

### 1.3 Antifragility: reward maximization or cost minimization

Intuitively, we want to define a system as “antifragile” if mixed strategies are better than constant ones. For simplicity of exposition, we assume from now on that  $\rho$  does not depend on the initial state. Mathematically:

**Definition 2** The parameterized system (2) is *antifragile for reward maximization* if for any  $u_1, u_2 \in \mathbb{U}$  and any nonnegative  $\alpha_1, \alpha_2$  with  $\alpha_1 + \alpha_2 = 1$ ,

$$\rho(\alpha_1 u_1 + \alpha_2 u_2) \leq \alpha_1 \rho(u_1) + \alpha_2 \rho(u_2),$$

that is to say, the rate function  $\rho$  is convex. The parameterized system (2) is *antifragile for cost minimization* if the rate function  $\rho$  is concave (that is, the opposite inequality holds).  $\square$

**Remark 2** We motivated antifragility through sequential therapies. A more standard probabilistic interpretation of antifragility is as follows. Suppose that  $\rho$  is a convex function, as the one shown in the left panel of Fig 1. Now we think of  $\rho(u)$  as the “payoff” of using an input  $u$ , thought of as a move in a game, an investment strategy, or a bet on the outcome. Then, we get a better expected payoff  $\bar{\rho}$  when placing half of the time our bets on  $u$  and half of the time on  $v$ , compared to placing all our bets at the average  $w = (u + v)/2$ , since  $\rho(w) \leq \bar{\rho}$ . If instead the rate is concave, the expected payoff is better when using the average  $w$ .  $\square$

We next discuss an important special case.

## 2 Positive linear systems

From now on, the set of states will be  $\mathbb{X} = \mathbb{R}_+^n$ , the set of  $n$ -tuples  $(x_1, \dots, x_n)$  with positive coordinates. In particular, the initial condition  $x_0$  will have positive entries. Outputs will take

values in  $\mathbb{Y} = \mathbb{R}_+$ , the set of positive real numbers. These are of course reasonable assumptions when we are dealing with biological populations, volumes, levels of protein expression, and so forth. The main example of systems (2) to be discussed here is as follows. We consider *positive linear systems*, meaning systems of the form

$$\dot{x} = A(u)x, \quad x(0) = x_0, \quad y = cx \quad (3)$$

where  $A(u) \in \mathbb{R}^{n \times n}$  is a parameterized *Metzler matrix*, meaning [9] a matrix whose off-diagonal elements are nonnegative (diagonal elements are allowed to be positive, zero, or negative; also called an “essentially nonnegative” matrix in [10]). and  $c$  is a row vector  $(c_1, \dots, c_n)$  with positive entries. It is known that for such systems, if the initial condition has positive entries then the solution  $x(t)$  will also have positive entries for every  $t > 0$ . We will assume the following irreducibility condition: for some  $r \in \mathbb{R}$ , and some positive integer  $k$ , the matrix  $(rI + A)^k$  has all entries positive. A sufficient condition for irreducibility to hold is if the off-diagonal elements of  $A$  are all strictly positive: indeed, just add a sufficiently large  $r$  to make all diagonal elements positive; then the condition holds with  $k = 1$ . (Metzler irreducible matrices are closely related to a more general class called primitive matrices, for which the properties stated below are also true, but we do not need the more general concept.)

Using the Jordan canonical form, it is known that the general solution of a system  $\dot{x} = Ax$  is a sum of terms of the form

$$\beta_{ij} e^{\lambda_i t} \left( \frac{t^{j-1}}{(j-1)!} v_{i,1} + \frac{t^{j-2}}{(j-2)!} v_{i,2} + \dots + \frac{t}{1!} v_{i,j-1} + v_{i,j} \right) = \beta_{ij} e^{\lambda_i t} \tilde{v}_{ij}(t) \quad (4)$$

where the  $\lambda_i$ 's are eigenvalues of  $A$  and the  $v_{i,j}$ 's are eigenvectors or generalized eigenvectors of  $A$ . Each  $\tilde{v}_{ij}(t)$  is a vector of polynomials in  $t$ . The constants  $\beta_{ij}$  (which may be complex) are obtained from the initial condition  $x_0$ , which we assume to be positive, by expanding  $x_0$  in terms of eigenvectors and generalized eigenvectors of  $A$ . The coefficients of this expansion are obtained from a linear transformation of the coordinates of  $x$  in the canonical basis, so there are row vectors  $q_{ij}$  such that  $\beta_{ij} = q_{ij} x_0$ .

We now specialize this general solution to irreducible Metzler matrices  $A$ . For such matrices, it is known [9] that there is an eigenvalue  $\lambda_F$  of  $A$ , called the Frobenius eigenvalue, which is real and which dominates all other eigenvalues, meaning that all other eigenvalues have real part less than  $\lambda_F$ . Moreover, there is a (real) eigenvector  $v_F$  associated to  $\lambda_F$  which has all its entries positive, and all other eigenvectors associated to  $\lambda_F$  are multiples of  $v_F$  ( $\lambda_F$  has algebraic multiplicity one). Therefore, among the expressions in (4) there is one of the form  $\beta e^{\lambda_F t} v_F$  with  $\beta$  real, and all others have the form  $[q_{ij} x_0] e^{\lambda_i t} \tilde{v}_{ij}(t)$  with  $\Re \lambda_i < \lambda_F$ . Each such term can be written as  $e^{\lambda_F t} [q_{ij} x_0] e^{\mu_i t} \tilde{v}_{ij}(t)$  with  $\Re \mu_i < 0$ . Collecting all these other terms, we can write them together as  $e^{\lambda_F t} W(t) x_0$ , where  $W(t)$  is an  $n \times n$  matrix whose entries are linear combinations of terms of the form  $t^k e^{\mu_i t}$  with  $\Re \mu_i < 0$ , and hence  $W(t) \rightarrow 0$  as  $t \rightarrow +\infty$ . Thus the general solution has the form  $x(t) = e^{\lambda_F t} (\beta v_F + W(t) x_0)$ . Moreover,  $\beta v_F$  is the projection of the initial condition onto the eigenspace corresponding to  $\lambda_F$ ,  $P x_0 = \beta v_F$ . The matrix  $P$  is the *Perron projection*, which has the formula  $P = v_F w_F$ , where  $w_F$  is a row vector, a positive left eigenvector of  $A$  with eigenvalue  $\lambda_F$ , i.e.  $w_F A = \lambda_F w_F$ , and it is picked so that  $w_F v_F = 1$ . In summary,

$$x(t) = e^{\lambda_F t} (P + W(t)) x_0. \quad (5)$$

Recall that our system is positive, so  $x(t)$  has positive entries as long as the initial condition was also positive. Suppose now that  $y(t) = y(t, u, x_0) = c x(t, u, x_0)$ , where  $c = (c_1, \dots, c_n)$  with all  $c_i > 0$ . It follows that

$$y(t) = e^{\lambda_F t} (\kappa + \mu(t)) \quad (6)$$

where  $\kappa = c P x_0$  is positive since  $P$ ,  $c$ , and  $x_0$  all have positive entries, and  $\mu(t) = c W(t) x_0 \rightarrow 0$  as  $t \rightarrow \infty$ . Moreover,  $y(t)$  is positive for every  $t > 0$ , so that the natural log  $\ln y(t)$  is well defined. Thus

$$\lim_{t \rightarrow \infty} \frac{1}{t} \ln y(t) = \lambda_F + \lim_{t \rightarrow \infty} \frac{1}{t} \ln(\kappa + \mu(t)) = \lambda_F.$$

Let us write now  $\lambda_F(u)$  instead of  $\lambda_F$  in order to emphasize that  $A = A(u)$ . We have proved:

**Theorem 1** *For irreducible positive systems,  $\rho(u) = \lambda_F(u)$ .* ■

This allows us to calculate  $\rho(u)$  explicitly, as well as to compute the effect of sequential strategies, as done below.

### 3 Sequential inputs

Suppose now that we consider two inputs,  $u_1$  and  $u_2$ , and these are consecutively applied: first input  $u_1$  is applied for time duration  $\alpha t$ , and then input  $u_2$  is applied, for time duration  $\beta t$ , where  $\alpha$  and  $\beta = 1 - \alpha$  are positive numbers. So the total time is  $t$ .

Let us write  $x(t, u_1, u_2, x_0)$  for the resulting state at time  $t$ , and  $y(t, u_1, u_2, x_0) = h(x(t, u_1, u_2, x_0))$ . Equivalently, we first solve the differential equation with initial state  $x_0$  and input  $u_1$ , for time  $\alpha t$ , and then use the resulting state  $x(\alpha t)$  as a new initial state and then solve the differential equation for time  $\beta t$ , but now with input  $u_2$ . This means that

$$x(t, u_1, u_2, x_0) = x(\beta t, u_2, x(\alpha t, u_1, x_0)).$$

We define, if the limit exists,

$$\rho(u_1, u_2, \alpha) := \lim_{t \rightarrow +\infty} \frac{1}{t} \ln y(t, u_1, u_2, x_0).$$

We can think of this quantity as a logarithmic rate for a sequential application of inputs. (A longer periodic alternation of  $u_1$  and  $u_2$  would be defined in a similar way.) From now on, we specialize to irreducible positive linear systems.

Using (5), we know that

$$x(t) = e^{\lambda_F(u_2)\beta t} (P(u_2) + W_2(t)) x_1(\alpha t)$$

where  $\lambda_F(u_2)$  and  $P(u_2)$  are the Perron eigenvalue and projection matrix, respectively, corresponding to input  $u_2$ ,  $W_2(t) \rightarrow 0$  as  $t \rightarrow +\infty$ , and  $x_1(\alpha t) = x(\alpha t, u_1, x_0)$ . Once again using (5),

$$x_1(\alpha t) = e^{\lambda_F(u_1)\alpha t} (P(u_1) + W_1(t)) x_0$$



where  $\lambda_F(u_1)$  and  $P(u_1)$  are the Perron eigenvalue and projection matrix, respectively, corresponding to input  $u_1$ , and  $W_1(t) \rightarrow 0$  as  $t \rightarrow +\infty$ . It follows that

$$\begin{aligned} x(t) &= e^{[\alpha\lambda_F(u_1)+\beta\lambda_F(u_2)]t} (P(u_2) + W_2(t)) (P(u_1) + W_1(t)) x_0 \\ &= e^{[\alpha\lambda_F(u_1)+\beta\lambda_F(u_2)]t} (P(u_2)P(u_1) + W(t)) x_0 \end{aligned}$$

where

$$W(t) = P(u_2)W_1(t) + W_2(t)P(u_1) + W_1(t)W_2(t) \rightarrow 0 \text{ as } t \rightarrow +\infty.$$

Therefore

$$y(t) = e^{(\alpha\lambda_F(u_1)+\beta\lambda_F(u_2))t} (\kappa + \mu(t))$$

where  $\kappa = cP(u_2)P(u_1)x_0$  is positive (since both matrices  $P(u_1)$  and  $P(u_2)$  and the vectors  $c$  and  $x_0$  have all entries positive) and  $\mu(t) = cW(t)x_0 \rightarrow 0$  as  $t \rightarrow +\infty$ . Thus

$$\lim_{t \rightarrow \infty} \frac{1}{t} \ln y(t) = \alpha\lambda_F(u_1) + \beta\lambda_F(u_2) + \lim_{t \rightarrow \infty} \frac{1}{t} \ln(\kappa + \mu(t)) = \alpha\lambda_F(u_1) + \beta\lambda_F(u_2).$$

We have therefore proved:

**Theorem 2** *For irreducible positive systems,  $\rho(u_1, u_2, \alpha) = \alpha\lambda_F(u_1) + (1 - \alpha)\lambda_F(u_2)$ . ■*

The significance of this result is that, if we wish to compare the “gain” from an average input  $u$  to that of using sequential inputs  $(u_1, u_2)$ , the second will give a better (or equal) result, at least for large total time  $t$ , if and only if

$$\alpha\lambda_F(u_1) + (1 - \alpha)\lambda_F(u_2) \geq \lambda_F(u),$$

in other words, if and only if the rate function  $\lambda_F$  is convex.

## 4 Flux-growth interpretation

Observe that any  $n \times n$  matrix  $A$  with positive off-diagonals elements can be written in the following form:

$$\begin{pmatrix} -\sum_{j \neq 1} a_{j1} + b_1 & a_{12} & \cdots & a_{1n} \\ a_{21} & -\sum_{j \neq 2} a_{j2} + b_2 & \cdots & a_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & \cdots & -\sum_{j \neq n} a_{jn} + b_n \end{pmatrix}$$

with  $a_{ij} > 0$  for every  $i \neq j$ , and some  $b_i$ 's: to see this, simply define  $b_i := a_{ii} + \sum_{j \neq i} a_{ij}$ .

This trivial observation allows the following interpretation: the matrix  $A$  can be seen as describing fluxes  $a_{ij}$  from cells of type  $j$  into cells of type  $i$ : the negative diagonal elements combine the sum of all fluxes “out of” the cell  $i$  with the net growth rate  $b_i$  (negative or positive) of cells of type  $i$ .

**Remark 3** Suppose now that all off-diagonal elements are positive and *large*, corresponding to high fluxes between compartments. In that case, the term  $\mu(t)$  in (5) will tend to zero very fast, and thus comparisons based on  $y(t)$  instead of rates will still be valid for “small” times. Let us sketch the argument. Introduce the matrix  $A_0$  obtained from  $A$  by setting all  $b_i$  to zero. The sum of each column of  $A_0$  is zero, implying that the matrix  $A_0$  has an eigenvalue  $\lambda = 0$  corresponding to the right eigenvector  $\mathbf{1} = [1, 1, \dots, 1]^T$ , and all the other eigenvalues  $\lambda_2, \dots, \lambda_n$  of  $A_0$  have negative real parts (irreducible Metzler matrix). These real parts will be large in magnitude, since we can think of  $A_0$  as a rescaling by a large scalar of a matrix with  $n - 1$  eigenvalues with negative real part and one eigenvalue at zero. Note that  $A = A_0 + B$ , where  $B$  is a diagonal matrix which has the  $b_i$ ’s on its diagonal. Thus  $A$  is a bounded perturbation of  $A_0$  ( $B$  is fixed, but the other entries of  $A$  can be thought of as tending to infinity). By continuity of eigenvalues on matrix entries (see for example Corollary A.4.3 in [7]), the eigenvalues of  $A$  will be near those of  $A_0$ . Therefore, the gap between  $\lambda_F$  and the real part of the next larger eigenvalue remains large even after the perturbation. This means that the term  $\mu(t)$  converges to zero very fast, as claimed. In the next section, we make this argument explicit for the two-dimensional case.  $\square$

## 4.1 An example: two-dimensional systems

In the special case  $n = 2$  of two cell types, this would be written as:

$$A = \begin{pmatrix} -k_{\text{on}} + b_1 & k_{\text{off}} \\ k_{\text{on}} & -k_{\text{off}} + b_2 \end{pmatrix} \quad (7)$$

where  $k_{\text{on}}$  and  $k_{\text{off}}$  are positive numbers and  $b_1$  and  $b_2$  are arbitrary numbers. Thus  $k_{\text{on}}$  is the rate at which cells of type 1 transition to cells of type 2,  $k_{\text{off}}$  is the rate at which cells of type 2 transition to cells of type 1, and  $b_1, b_2$  are the respective growth rates of cells of types 1 and 2.

In general, all four numbers might depend on  $u$ . An even more specific example would have the  $u$  dependence in just the  $k_{\text{on}}$  term, so we replace  $k_{\text{on}}$  by  $k_{\text{on}} = k_{\text{on}}^* u$  in (7) and assume that the remaining entries do not depend on  $u$ . For notational simplicity in future calculations, let us rewrite such a matrix as follows:

$$A(u) = \begin{pmatrix} b - au & ak \\ au & d - ak \end{pmatrix} \quad (8)$$

where we are letting  $a = k_{\text{on}}^*$ ,  $b = b_1$ ,  $d = b_2$ , and  $k = k_{\text{off}}/k_{\text{on}}^*$ . This represents a system in which cells of type 1 transition to cells of type 2 at a rate  $k_{\text{on}}^* u$  that is proportional to the drug concentration  $u$ . Conversely, cells of type 2 transition back to type 1 at a rate that is independent of the drug concentration. (For simplicity, we use the term “drug concentration” but this term typically represents the actual effect of the drug, which could be a pharmacokinetically derived Michaelis-Menten or Hill function of the dose being applied to the system.)

## 4.2 Connection to drug-induced proliferation rate

The paper [6] introduced the idea of using the *drug-induced proliferation rate* (“DIP”) as a metric to quantify and compare drug effects, in the  $n = 2$  case. We show next that the DIP rate

is the same as the logarithmic rate of the system, under the same approximation as used in [6] to derive it.

The paper defines the DIP as “the steady-state rate of proliferation of a cell population in the presence of a given concentration of drug.” Specifically, the  $A$  matrix is of the form shown in equation (8), and  $c = (1, 1)$ . The paper provides the approximate formula

$$y(t) \approx e^{\rho_{\text{DIP}}(u)t} x_0, \quad (9)$$

where

$$\rho_{\text{DIP}}(u) = \frac{bk + du}{k + u}.$$

The formula is derived by assuming a fast exchange between cell types, giving an equilibrium approximation  $k_{\text{on}}^* u x_1(t) = k_{\text{off}} x_2(t)$ , and substituting into the two differential equations (see Supplementary Note equations S14-S20 in [6]). This amounts to asking that both  $k_{\text{on}}^*$  and  $k_{\text{off}}$  ( $a$  and  $ak$ ) are large while keeping the ratio  $k = k_{\text{on}}^*/k_{\text{on}}$  constant. In other words, the assumption is that  $a \rightarrow +\infty$  while maintaining  $c, d, k$  constant. We write  $\rho(a, c, k, u)$  to emphasize the dependence of  $\rho$  on the parameters.

**Theorem 3**  $\lim_{a \rightarrow +\infty} \rho(a, c, k, u) = \rho_{\text{DIP}}(u)$ .

*Proof.* A little calculus exercise (see below) shows that for any positive numbers  $p, q$ :

$$\lim_{x \rightarrow \infty} \left( -x + \sqrt{x^2 - px + q} \right) = -p/2. \quad (10)$$

Now note that

$$\text{trace}(A) = T = b + d - a(k + u)$$

and

$$\det(A) = D = bd - a(bk + du).$$

Let us define:

$$p := -\frac{4(bk + du)}{k + u}$$

$$q := \frac{4(kb^2 + ud^2)}{k + u}$$

$$x := a(k + u) - (b + d).$$

A substitution and simplification shows that

$$T^2 - 4D = x^2 - px + q.$$

Therefore, the largest eigenvalue of  $A$  is:

$$\lambda(a, b, k, u) = (1/2) \left( T - \sqrt{T^2 - 4D} \right) = (1/2) \left( -x + \sqrt{x^2 - px + q} \right).$$

Since  $x \rightarrow \infty$  is equivalent to  $a \rightarrow \infty$ , and applying (10) to our  $p$ , we conclude that:

$$\lim_{x \rightarrow \infty} \lambda(a, b, k, u) = \frac{bk + du}{k + u}$$

as claimed.

For completeness, let us show how to establish (10). let  $L := \lim_{x \rightarrow \infty} \left( -x + \sqrt{x^2 - px + q} \right)$ . We will show that  $L = -p/2$ . The given expression is of the indeterminate form “ $-\infty + \infty$ ” so we need to apply L’Hôpital’s rule. We first multiply and divide by the conjugate:

$$\begin{aligned} L &= \lim_{x \rightarrow \infty} \frac{\left( -x + \sqrt{x^2 - px + q} \right) \left( -x - \sqrt{x^2 - px + q} \right)}{-x - \sqrt{x^2 - px + q}} \\ &= \lim_{x \rightarrow \infty} \frac{px - q}{-x - \sqrt{x^2 - px + q}}. \end{aligned}$$

Now the expression is in the form  $\frac{\infty}{\infty}$ , so we apply L’Hôpital’s rule by differentiating the numerator and the denominator. The derivative of the numerator  $px - q$  is  $p$ . The derivative of the denominator  $-x - \sqrt{x^2 - px + q}$  is computed as:

$$\begin{aligned} \frac{d}{dx} \left( -x - \sqrt{x^2 - px + q} \right) &= -1 - \frac{1}{2\sqrt{x^2 - px + q}} \cdot (2x - p) \\ &= -1 - \frac{x - \frac{p}{2}}{\sqrt{x^2 - px + q}}. \end{aligned}$$

Thus, applying L’Hôpital’s Rule gives:

$$L = \lim_{x \rightarrow \infty} \frac{p}{-1 - \frac{x - \frac{p}{2}}{\sqrt{x^2 - px + q}}}.$$

As  $x \rightarrow \infty$ , the term  $\frac{x - \frac{p}{2}}{\sqrt{x^2 - px + q}}$  approaches 1, so the denominator converges to -2. Thus, the limit becomes:

$$L = \frac{p}{-2} = -\frac{p}{2}$$

as claimed. ■

## Acknowledgments

The author thanks Dr. Jeffrey West for very productive and informative discussions, as well as making his papers and preprints available. This research was supported in part by grants ONR N00014-21-1-2431 and AFOSR FA9550-21-1-0289.

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