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Some remarks on a model for immune signal detection and feedback

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Abstract—

This note analyzes incoherent feedforward loops in signal processing and control. It studies the response properties of IFFL's to exponentially growing inputs, both for a standard version of the IFFL and for a variation in which the output variable has a positive self-feedback term. It also considers a negative feedback configuration, using such a device as a controller. It uncovers a somewhat surprising phenomenon in which stabilization is only possible in disconnected regions of parameter space, as the controlled system's growth rate is varied. This phenomenological setup might explain some interesting and apparently contradictory features of immune regulation of cancer and infections.

I. INTRODUCTION

This note derives several theoretical results regarding the use of incoherent feedforward loops (IFFL's) in signal processing and control. We will study the system:

$$\begin{aligned} \dot{x} &= -ax+bu && \text{(1a)}\\ \dot{y} &= c\frac{u}{x}-\delta y && \text{(1b)}\\ \dot{u} &= (\lambda-\kappa y)u && \text{(1c)} \end{aligned}$$

as well as a modified system in which there is also an autocatalytic term in (1b):

$$\dot{y} = c\frac{u}{x} - \delta y + \frac{Vy^n}{K^n+y^n} \qquad \text{(1b')}$$

which represents a positive feedback of the y variable on itself. The constants

$$a,b,c,\delta,\kappa,V,K$$

are positive (but λ is allowed to be negative), dot indicates d/dt, n is typically an integer>1 that represents molecular cooperativity, and the scalar functions of time $x=x(t)$, $y=y(t)$, and $u=u(t)$ take positive values. (It is easy to verify that, for any positive initial conditions, solutions remain positive for all times.) Of course, setting $V=0$ allows seeing (1b') as a special case of (1b), but it is more interesting to treat the non-autocatalytic case by itself.

We will separately study the first two equations (1ab) (or (1ab') when there is an autocatalytic term), viewing $u=u(t)$ as an external input to the IFFL described by (1ab) (or (1ab')), and viewing $y=y(t)$ as an output or response of the system. Later, we "close the loop" by letting u be described by (1c), thinking of it as a variable that is controlled by y through a negative feedback with gain κ, and which, conversely, feeds back into the IFFL through the x variable. In that context, we study the full system (1abc) (or (1ab'c)). The motivation for this work is explained in detail in the preprint [3], but we summarize some of the main points in the last section of this extended abstract. For reasons of space, we do not include many of the proofs here nor generalizations to more abstract equations; these can be found in [4] as well as a journal paper in preparation.

Remark 1.1: In the system (1abc), and in particular in the system (1ab), one may assume without loss of generality that $a=b=c=1$. This is because we may eliminate these parameters by rescaling variables. Indeed, substituting

$$x=\frac{b}{a}x^*,\; y=\frac{c}{b}y^*,\; t=\frac{1}{a}t^*,$$

$$\delta^*=\frac{\delta}{a},\; \lambda^*=\frac{\lambda}{a},\; \kappa^*=\frac{c\kappa}{ab},$$

into system (1abc), one obtains:

$$\begin{aligned} \frac{dx^*}{dt^*} &= -x^*+u && \text{(2a)}\\ \frac{dy^*}{dt^*} &= \frac{u}{x^*}-\delta^*y^* && \text{(2b)}\\ \frac{du}{dt^*} &= (\lambda-\kappa y^*)u\,. && \text{(2c)} \end{aligned}$$

□

II. IFFL'S RESPONSES TO VARIOUS CLASSES OF INPUTS

Let us consider the system (1ab), a differentiable function $u=u(t)$ viewed as an external input or forcing function, and any (positive) solution $(x(t),y(t))$ corresponding to this input. We are interested first in understanding how the growth rate of the input affects the asymptotic values of the output variable y.

We denote the derivative of $\ln u(t)$ with respect to t as follows:

$$v(t) := \frac{\dot{u}(t)}{u(t)}$$

and its limsup and liminf as $t\to\infty$

$$\underline{\mu}=\liminf_{t\to\infty} v(t)\,,\quad \overline{\mu}=\limsup_{t\to\infty} v(t)\,.$$

We assume that v is bounded, and thus both of these numbers are finite. We also introduce the following function:

$$p(t) := \frac{u(t)}{x(t)}\,.$$

One may show that p satisfies the following ODE with input v:

$$\dot{p} = p(a+v-bp)\,. \qquad (3)$$

Lemma 2.1: Let u be a differentiable input to system (1ab) with $a=b=c=1$. With the above notations,

$$\max\{0,1+\underline{\mu}\} \le \liminf_{t\to\infty} p(t)$$

$$\leq \limsup_{t\to\infty} p(t) \leq \max\{0,1+\overline{\mu}\}$$

Proof: Since $a=b=c=1$,

$$\dot{p} = p(1+v-p)\,.$$

To prove the upper bound, we consider two cases,

$$1+\overline{\mu}<0 \,\text{and}1+\overline{\mu}\geq 0.$$

In the first case, let

$$\varepsilon := -(1+\overline{\mu})>0;$$

the definition of $\overline{\mu}$ gives that, for some $T\geq 0$,

$$1+v(t)<-\varepsilon/2 \text{ for all } t\geq T.$$

It follows that

$$\dot{p} \leq p(-\varepsilon/2-p) \text{ for all } t\geq T.$$

Thus, $\dot{p}<0$ whenever $p>0$, from which it follows that

$$\limsup_{t\to\infty} p(t) = \lim_{t\to\infty} p(t) = 0.$$

Suppose now that $1+\overline{\mu}\geq 0$. Pick any $\varepsilon>0$ and a $T=T(\varepsilon)\geq 0$ such that

$$v(t)\leq \overline{\mu}+\varepsilon \text{ for all } t\geq T.$$

For such t,

$$\dot{p} = p(1+v-p)\leq p(1+\overline{\mu}+\varepsilon-p).$$

This implies that $\dot{p}<0$ whenever $p(t)>1+\overline{\mu}+\varepsilon$, which implies that

$$\limsup_{t\to\infty} p(t)\leq 1+\overline{\mu}+\varepsilon.$$

Letting $\varepsilon\to 0$, we conclude that

$$\limsup_{t\to\infty} p(t)\leq 1+\overline{\mu}.$$

We next prove the lower bound. Pick any $\varepsilon>0$ and a $T=T(\varepsilon)\geq 0$ such that

$$v(t)\geq \underline{\mu}-\varepsilon \text{ for all } t\geq T.$$

Thus

$$\dot{p} = p(1+v-p)\geq p(1+\underline{\mu}-\varepsilon-p) \text{ for all } t\geq T.$$

This implies that $\dot{p}>0$ whenever $p(t)<1+\underline{\mu}-\varepsilon$ (recall that $p(t)>0$ for all t, since by assumption $u(t)>0$ and $x(t)>0$ for all t). Therefore $\liminf_{t\to\infty} p(t)\geq 1+\underline{\mu}-\varepsilon$, and letting $\varepsilon\to 0$ we have

$$\liminf_{t\to\infty} p(t)\geq 1+\underline{\mu}.$$

Since $p(t)\geq 0$ for all t, we also have

$$\liminf_{t\to\infty} p(t)\geq \max\{0,1+\underline{\mu}\}.$$

This completes the proof. ■

In particular, if $v(t)\to\mu$ as $t\to\infty$ then $\underline{\mu}=\overline{\mu}=\mu$, so we have as follows.

Corollary 2.2: If $v(t)\to\mu$ as $t\to\infty$ then

$$\lim_{t\to\infty} p(t) = \max\{0,1+\mu\}.$$

□

For the original system (1ab), we have as follows.

Proposition 2.3: Consider a solution of (1ab), with a differentiable $u(t)>0$ as input and $x(t)>0$, $y(t)>0$. Assuming that $v=\dot{u}/u$ is bounded, we have:

$$\begin{aligned}\frac{c}{b\delta}\max\left\{0,a+\underline{\mu}\right\} \;&\leq\; \liminf_{t\to\infty} y(t) \;\leq\; \limsup_{t\to\infty} y(t)\\ &\leq\; \frac{c}{b\delta}\max\{0,a+\overline{\mu}\}\end{aligned}$$

Proof: We first assume that a=b=c=1. Let $\underline{p} := \liminf_{t\to\infty} p(t)$ and $\overline{p} := \limsup_{t\to\infty} p(t)$. Equation (1b) can be written as $\dot{y}=p-\delta y$. This is a linear system forced by the input $p=p(t)$. Pick any $\varepsilon>0$. Then there is some $T=T(\varepsilon)$ such that $\underline{p}-\varepsilon<p(t)<\overline{p}+\varepsilon$ for all $t\geq T$. For such t, $\dot{y}(t)>0$ whenever $y(t)<(1/\delta)(\underline{p}-\varepsilon)$ and $\dot{y}(t)<0$ whenever $y(t)>(1/\delta)(\overline{p}+\varepsilon)$. It follows that $(1/\delta)(\underline{p}-\varepsilon)\leq y(t)\leq (1/\delta)(\overline{p}+\varepsilon)$ for all $t\geq T$. Letting $\varepsilon\to 0$ we conclude that

$$\underline{p}/\delta \;\leq\; \liminf_{t\to\infty} y(t) \;\leq\; \limsup_{t\to\infty} y(t) \;\leq\; \overline{p}/\delta \tag{4}$$

and the desired inequalities follow when a=b=c=1. To deal with general parameters, we recall that are obtained with $x=\frac{b}{a}x^*$, $y=\frac{c}{b}y^*$, $t=\frac{1}{a}t^*$, and $\delta^*=\frac{\delta}{a}$. Note that $t^*\to\infty$ if and only if $t\to\infty$. Thus (4) holds for $p^*=u/x^*=(b/a)p$, y^*, and $\delta^\star$ in place of p, y, and δ. Similarly, the inequalities in Lemma 2.1 hold for $p^*=u/x^*$ and

$$\underline{\mu}^* = \liminf_{t\to\infty} v^*(t^*)\,,\quad \overline{\mu} = \limsup_{t\to\infty} v^*(t^*)\,,$$

where $v^*=\frac{du/dt^*}{u}=(1/a)v$, so $\underline{\mu}^*=(1/a)\underline{\mu}$ and $\overline{\mu}^*=(1/a)\overline{\mu}$. Therefore,

$$\begin{aligned}\liminf_{t\to\infty} y(t) \;&=\; \liminf_{t^*\to\infty}\frac{c}{b}y^*(t^*) \;\geq\; \frac{c}{b}\frac{\underline{p}^*}{\delta^\star} \;=\; \frac{c}{b}\frac{\underline{p}^*}{\delta/a}\\ &=\; \frac{ac}{b\delta}\underline{p}^* \;=\; \frac{ac}{b\delta}\max\left\{0,1+\underline{\mu}^*\right\}\\ &=\; \frac{c}{b\delta}\max\left\{a+\underline{\mu}\right\}.\end{aligned}$$

A similar remark applies to $\limsup$, and the result follows. ■

The proof using $p(t)$ is convenient, because the Theorem stated later uses the same constructions for a closed-loop feedback control problem.

Corollary 2.4: If $v(t)\to\mu$ as $t\to\infty$ then

$$\lim_{t\to\infty} y(t) = \frac{c}{b\delta}\max\{0,a+\mu\}.$$

□

Three particular cases are:

- When $u(t)$ has sub-exponential growth, meaning that $d\ln u/dt\leq 0$, then $\limsup_{t\to\infty} y(t)\leq \dfrac{ac}{b\delta}$.

- In particular, if $u(t)=\alpha+\beta t$ is linear, then $\mu=0$ and thus $\lim_{t\to\infty} y(t)=\frac{ac}{b\delta}$.
- If $u(t)=\beta e^{\mu t}$ is exponential, then $\lim_{t\to\infty} y(t)=\frac{c}{b\delta}\max\{0,a+\mu\}$.

In conclusion, when u is constant, or even with linear growth, the value of the output $y(t)$ converges to a constant, which does not depend on the actual constant value, or even the growth rate, of the input. For constant inputs, this is called the "perfect adaptation" property (i.e., rejection of constant disturbances). If, instead, u grows exponentially, then $y(t)$ converges to a steady state value that is a linear function of the logarithmic growth rate. (Note that $x=be^{\mu t}/(a+\mu)$ is a particular solution of $\dot{x}=-ax+bu$ when $u=e^{\mu t}$, so $u/x=(a+\mu)/b$ for this solution, which explains the formula; however this solution is not positive when $a+\mu<0$.) In [2], we study a general theoretical framework regarding the response of IFFL's, as well as other scale-invariant systems, to exponential inputs, and specifically the fact that –under mild conditions– the output converges to a steady state value that is a function of the logarithmic growth rate.

Remark 2.5: A possible alternative IFFL model is that in which y follows this equation:

$$\dot{y} \;=\; cu-\delta xy\,. \tag{5}$$

instead of (1b). This model represents a different way of implementing the negative effect of x on y, through degradation instead of inhibition of production. A reduction to $a=b=c=1$ is again possible. Now the substitutions

$$x=\frac{b}{a}x^*\,,\; y=\frac{c}{a}y^*\,,\; t=\frac{1}{a}t^*\,,$$

$$\delta^*=\frac{b\delta}{a^2}\,,\; \lambda^*=\frac{\lambda}{a}\,,\; \kappa^*=\frac{c\kappa}{a^2}\,,$$

into (1a-5-1c) transform the system into:

$$\frac{dx^*}{dt^*} \;=\; -x^*+u \tag{6a}$$

$$\frac{dy^*}{dt^*} \;=\; u-\delta^* x^* y^* \tag{6b}$$

$$\frac{du}{dt^*} \;=\; (\lambda^*-\kappa^* y^*)u \tag{6c}$$

Consider a model that uses (5) instead of equation (1b) and suppose that, for some $\gamma>0$, $u(t)\geq\gamma>0$ for all $t\geq 0$ (for example, $u(t)=\beta e^{\mu t}$ or $u(t)=\alpha+\beta t$). Then the inequalities in Proposition 2.3 again hold, as does Corollary 2.4. This is because we one may rewrite $\dot{y}=cu-c\delta y$ as $\dot{y}=x(cu/x-\delta y)$, and, provided that, for some $\xi>0$, $x(t)>\xi>0$ for all t, solutions have the same asymptotic behavior as for (1b). On the other hand, from the fact that $p(t)=u(t)/x(t)$ is bounded, we know that, for some $\gamma'>0$, for all t, $x(t)\geq\gamma' u(t)>\gamma'\gamma>0$. □

III. IFFL'S AS FEEDBACK CONTROLLERS

As we remarked, in the case of exponential inputs $u(t)=\beta e^{\mu t}$, $\lim_{t\to\infty} y(t)=\bar{y}=\frac{c}{b\delta}\max\{0,a+\mu\}$. This holds both for (1ab) and for the combination (1a)-(5). Now suppose that, in turn, $u(t)$ satisfies equation (1c), which means that $v(t)=\lambda-\kappa y(t)$, and therefore $\mu=\lim_{t\to\infty} v(t)=\lambda-\kappa\bar{y}$. This gives an implicit equation for the rate μ:

$$\mu=\lambda-\frac{c\kappa}{b\delta}\max\{0,a+\mu\}\,. \tag{7}$$

We now solve this equation.

Denote

$$F(\lambda) \;=\; \frac{\lambda b\delta-c\kappa a}{b\delta+c\kappa}\,.$$

Suppose first that $\lambda\leq a$. Then, since $a+F(\lambda)=(a+\lambda)\theta$ (where $\theta=b\delta/(b\delta+c\kappa)$), $\mu=F(\lambda)$ satisfies $a+\mu\geq 0$ and also, rewriting $\mu=F(\lambda)$, μ is the unique solution of (7) with $a+\mu\geq 0$. There are no solutions with $a+\mu<0$, because such a solution would have to satisfy $\mu=\lambda$, but $a+\lambda\geq 0$. Suppose instead that $\lambda>a$. Then $\mu=\lambda$ is the unique solution of (7) with $a+\mu<0$. There are no solutions with $a+\mu\geq 0$, because such a solution would have to satisfy $\mu=F(\lambda)$ and therefore have $a+\mu=a+F(\lambda)=(a+\lambda)\theta<0$, a contradiction. In summary, when $\lambda\geq -a$, the unique solution of (7) is $\mu=F(\lambda)$, and when $\lambda<-a$ it is $\mu=\lambda$.

Note that when

$$ca\kappa \;>\; b\delta\lambda \tag{8}$$

(which happens automatically when $\lambda<0$) the formula $\mu=F(\lambda)$ gives that $\mu<0$, that is, $u(t)\to 0$ as $t\to+\infty$. Conversely, if $ca\kappa<b\delta\lambda$, then $\mu>0$ and so $u(t)\to\infty$ as $t\to+\infty$. Qualitatively, this makes sense: a large feedback gain κ, or a small growth rate λ in the absence of feedback, leads to the asymptotic vanishing of the u variable.

In addition, from the formula $\bar{y}=\frac{c}{b\delta}\max\{0,a+\mu\}$ we conclude the following piecewise linear formula for the dependence of the limit of the output on the parameter λ that gives the growth rate of u when there is no feedback:

$$\bar{y} \;=\; \begin{cases} 0 & \text{if } \lambda<-a \\ \dfrac{c(a+\lambda)}{b\delta+c\kappa} & \text{if } \lambda\geq -a\,. \end{cases} \tag{9}$$

These considerations provide helpful intuition about the closed-loop system, but they do not prove that (8) is necessary and sufficient for stability, nor do they show the validity of (9) for the closed-loop system. The reason that the argument is incomplete is that there is no *a priori* reason for $u(t)$ to have the exponential form $u(t)=\beta e^{\mu t}$.

The precise theorem is as follows:

Theorem 1: Suppose that $(x(t),y(t),u(t))$ is a (positive) solution of (1abc), and define

$$v(t) \;:=\; \dot{u}(t)/u(t)=\lambda-\kappa y(t)\,,$$

$$p(t) \;:=\; u(t)/x(t)\,,$$

$\bar{y}$ by formula (9), which we repeat here:

$$\bar{y} = \begin{cases} 0 & \text{if } a+\lambda < 0 \\ \dfrac{c(a+\lambda)}{b\delta + c\kappa} & \text{if } a+\lambda \geq 0 \end{cases}$$

$\bar{p} := (\delta/c)\bar{y}$. and

$$\bar{v} = \begin{cases} \lambda & \text{if } a+\lambda < 0 \\ \lambda - \kappa\dfrac{c(a+\lambda)}{b\delta + c\kappa} & \text{if } a+\lambda \geq 0 . \end{cases}$$

Then:

$$\begin{aligned} \lim_{t\to\infty} y(t) &= \bar{y} \\ \lim_{t\to\infty} p(t) &= \bar{p} \\ \lim_{t\to\infty} v(t) &= \bar{v} . \\ \lim_{t\to\infty} u(t) &= \begin{cases} 0 & \text{if } ac\kappa > b\delta\lambda \\ \infty & \text{if } ac\kappa < b\delta\lambda . \end{cases} \end{aligned}$$

For a detailed proof of this theorem, see [4]. It is based on the existence of a nonlinear transformation that brings the third order system into a cascade form, in which a second order system described by p and y drives a linear system. The second order system, which is a variant of a predator-prey system, is analyzed using phase-plane techniques (Poincaré-Bendixson Theorem combined with the Dulac-Bendixson criterion), by first finding a compact forward-invariant region that attracts all trajectories.

IV. ADDING POSITIVE FEEDBACK

We now study a model in which there is an additional autocatalytic positive feedback on y variable. We first consider the open loop system (1ab'), and then discuss the full feedback system (1ab'c), which we repeat here for convenience:

$$\begin{aligned} \dot{x} &= -ax + bu && \text{(10a)} \\ \dot{y} &= c\frac{u}{x} - \delta y + \frac{Vy^n}{K^n + y^n} && \text{(10b)} \\ \dot{u} &= (\lambda - \kappa y)u && \text{(10c)} \end{aligned}$$

A. Open-loop system with autocatalysis

We first consider only the open-loop system (10ab), in which $u = u(t)$ is seen as an input function (stimulus) and y as an output (response).

For appropriate parameters, and assuming that the Hill exponent (cooperativity index) n is greater than one, the system

$$\dot{y} = q - \delta y + \frac{Vy^n}{K^n + y^n} \qquad (11)$$

admits more than one steady state. (In contrast, if there is no autocatalytic feedback, $V = 0$, then there is a unique steady state, $\bar{y} = q/\delta$.) Let us fix all parameters except q, which we temporarily view as a bifurcation parameter. Adjusting the value of q, one may obtain a low steady state, multiple steady states, or a higher steady state. As an illustration, pick

$$a = b = c = 1,\ \delta = 3,\ n = 2,\ V = 10, \text{ and } K = 2.$$

Fig, 1 shows the right-hand side of (11) plotted for $q = 0.8$ and $q = 1.1$. For the latter value of q, there is larger steady state. (Intermediate values typically give a system with two stable states and one unstable state.)

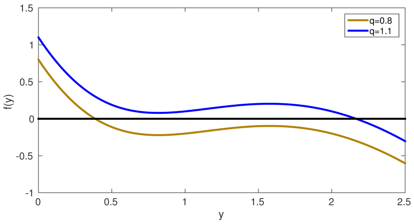

Fig. 1. Plots of $f(y) = q - \delta y + \frac{Vy^n}{K^n+y^n}$, with $a = b = c = 1$, $\delta = 3$, $n = 2$, $V = 10$, and $K = 2$, comparing $q = 0.8$ (brown) and $q = 1.1$ (blue). The steady state changes from a low to a high value.

Let us now write

$$q(t) = c\frac{u(t)}{x(t)}$$

in the system (10ab). Suppose that we consider an input u which has a step increase at time $t = 0$, from $u(t) = u_-$ for $t < 0$ to $u(t) = u_+$ for $t \geq 0$. Suppose also that

$$x(0) = x_0 = (b/a)u_-,$$

that is, that the system at time $t = 0$ has an internal steady state preadapted to u_-. Since $x(t)$ is a continuous function of time, we have that, for small times $t > 0$, $x(t) \approx x_0$ and $u(t) = u_0$, and thus $q(t) \approx \alpha u_+/u_-$, where $\alpha = ac/b$. This means that the value of $q(t)$ for $0 \leq t \ll 1$ is proportional to the "fold change" in the input. On the other hand, as $t \to \infty$, $x(t) \to b/a$, so $q(t) \to ac/b = \alpha$. In the system with no autocatalytic effect ($V = 0$), the differential equation $\dot{y} = q - \delta y$ has a unique globally asymptotically stable equilibrium, and therefore

$$y(t) \to q/\delta = \alpha/\delta.$$

That is to say, there is *complete adaptation*: after a step increase in the input u, y responds in a way that transiently depends on the fold change, but it eventually returns to its adapted value.

On the other hand, if there is an autocatalytic feedback term ($V \neq 0$), the initial input $q(t)$ to the y-subsystem may trigger an irreversible transition to a different state y than the adapted value. Since the initial value of $q(t)$ depends on the fold change of the input, this implies that for different ranges of fold-change magnitudes, y might switch to different states, and remain there. As an example, using the same parameters

$$a = b = c = 1,\ \delta = 3,\ n = 2,\ V = 10, \text{ and } K = 2$$

as earlier, Fig, 2 shows how a step change in the input can result in an irreversible locking to a higher activation state, for the system with feedback, compared with the system without feedback, which does not switch but has only a transient change in activity.

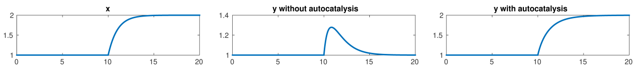

Fig. 2. Response to an input stepping from u=1 to u=2 (fold change of input is 2). Comparing system with no positive feedback to system with positive feedback. State $x(t)$ is the same in both systems, so only one panel is shown. Parameters are $a = b = c = 1$, $\delta = 3$, $n = 2$, $V = 10$, and $K = 2$ in system with feedback, substituting $V = 0$ in system without feedback.

B. Closed-loop system with autocatalysis

We now turn to the full feedback system (10abc). Just as in the case in which there was no autocatalytic terms, we may again reduce to a two-dimensional system written in terms of $p = u/x$ and y. The system is now:

$$\dot{p} = p(a+\lambda-\kappa y - bp) \qquad (12a)$$

$$\dot{y} = cp - \delta y + \frac{Vy^n}{K^n+y^n}. \qquad (12b)$$

For appropriate parameter regimes, there is a unique positive steady state $(\bar{p}, \bar{y})$. Specifically, for $n > 1$ the derivative of $\frac{Vy^n}{K^n+y^n}$ attains its maximum at $y = \left(\frac{n-1}{n+1}\right)^{1/n} K = K/\sqrt{3}$ when $n = 2$, and the derivative is $\frac{3V\sqrt{3}}{8K}$ there. Thus, the function

$$g(y) = a+\lambda-\kappa y-(b/c)\left(\delta y - \frac{Vy^n}{K^n+y^n}\right),$$

whose roots determine the nonzero equilibrium values of y, has derivative $\leq -\kappa - b\delta/c + \frac{3V\sqrt{3}}{8K}$. Thus, when

$$\frac{3V\sqrt{3}}{8K} < \kappa + b\delta/c$$

the function g is strictly decreasing and therefore (in the nontrivial case $a+\lambda > 0$), since $g(0) > 0$ and $g(y) \to -\infty$ as $y \to \infty$, there is a unique zero $\bar{y}$. See for example the phase plane drawn in Fig. 3. and globally asymptotically stable

A remarkable feature emerges for this system. When does $u(t) \to 0$ as $t \to \infty$, corresponding to elimination of a pathogen or tumor, in the motivating context of immunology? When does $u(t) \to \infty$ as $t \to \infty$, corresponding to proliferation? Note that, if

$$(p(t), y(t)) \to (\bar{p}, \bar{y}) \text{ as } t \to \infty,$$

then, since $\dot{u} = (\lambda - \kappa y)u$, $u(t)$ behaves like $\alpha e^{\mu t}$ for large t. On the other hand, at steady state $a+\lambda-\kappa\bar{y}-b\bar{p} = 0$, which means that

$$\mu - \lambda - \kappa\bar{y} = b\bar{p} - a.$$

Therefore:

$$\bar{p} < \frac{a}{b} \quad \Rightarrow \quad u(t) \to 0 \text{ as } t \to \infty$$

$$\bar{p} > \frac{a}{b} \quad \Rightarrow \quad u(t) \to \infty \text{ as } t \to \infty.$$

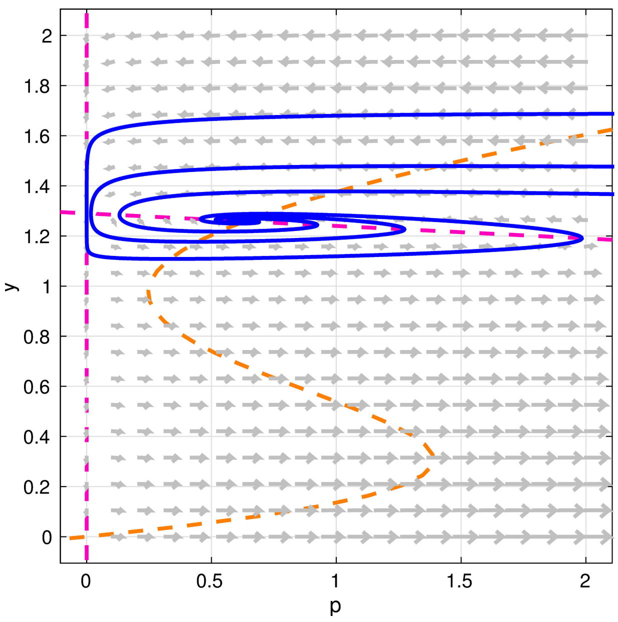

Fig. 3. Phase-plane for system (12), with $a = 0.8$, $b = 1$, $c = 0.1$, $\delta = 1$, $n = 2$, $V = 1.95$, $K = 1$, $\kappa = 20$, $\lambda = 25$. The y-nullcline is $cp - \delta y + \frac{Vy^n}{K^n+y^n} = 0$ (dot-dashed orange). The p-nullcline has two components: $p = 0$ (the y-axis) and the line $y = (a+\lambda-bp)/\kappa$ (dashed red). Three representative trajectories are shown (solid blue). Notice the vertical-looking motion of one trajectory near the y-axis: along such solutions, $p(t) = u(t)/x(t)$ stays ≈ 0 for a time interval, after which this ratio converges to $\bar{p}$. Gray arrows indicate directions of movement in phase plane. The equilibrium point $(\bar{p}, \bar{y})$ is such that $p < 0.8$ and thus, since $\dot{u} = (\lambda - \kappa y)u$, $u(t)$ behaves like $\alpha e^{\mu t}$ for large t, where $\mu = \lambda - \kappa\bar{y} = bp - a = p - 0.8$, we have $\mu < 0$ (elimination).

Note that $(\bar{p}, \bar{y})$ is a positive equilibrium if and only if $b\bar{p} = a+\lambda-\kappa\bar{y}$ and $c\bar{p} = -f(\bar{y})$ where $f(y) = -\delta y + \frac{Vy^n}{K^n+y^n}$. To find equilibria, we can first solve $a+\lambda-\kappa\bar{y} = -(b/c)f(\bar{y})$ for $\bar{y}$, and then obtain

$$\bar{p} = (1/b)(a+\lambda-\kappa\bar{y}).$$

Note that $\mu = \lambda - \kappa\bar{y} < 0$ is equivalent to $\bar{p} > a/b$, or $-(1/c)f(\bar{y}) > a/b$, and $\mu = \lambda - \kappa\bar{y} < 0$ is equivalent to $\bar{p} < a/b$, or $-(1/c)f(\bar{y}) < a/b$. Therefore, leaving all other parameters constant, μ switches sign whenever $f(\bar{y}) = -ac/b$. The formula $\lambda = \kappa\bar{y} - (b/c)f(\bar{y}) - a$ gives those values of λ where there is change from $\mu < 0$ (which means $u(t) \to 0$ as $t \to \infty$) to $\mu > 0$ ($u(t) \to \infty$ as $t \to \infty$), or viceversa. *As λ increases, we may expect several such switches*, as may be seen graphically as one draws parallel nullclines corresponding to different values of λ. For the example in Fig. 3, several of these are shown in Fig. 4. Simulations confirm these predictions, see Fig. 5.

DISCUSSION

The immune system is now recognized as playing an important role in tumor control. Our very simple phenomenological model recapitulates some of the basic features of immunoediting. Our model employs both feedforward and feedback regulation (which play roles vaguely analogous to

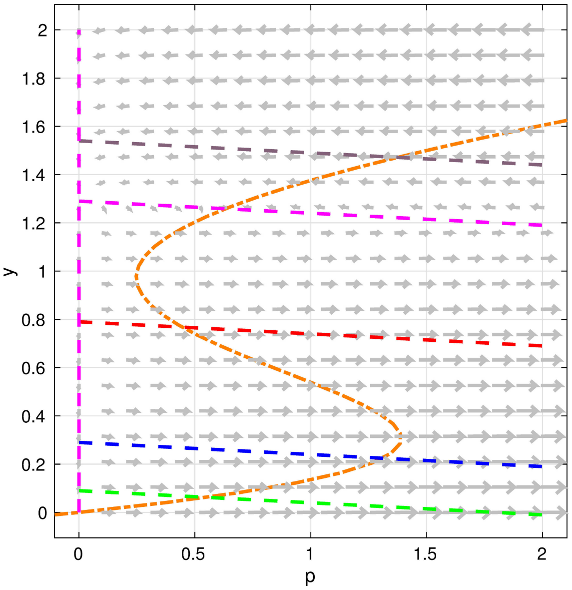

Fig. 4. Phase plane for system (12), with same parameters as in Fig. 3, but now with with several values of λ. The y-nullcline is $cp-\delta y+\frac{Vy^n}{K^n+y^n}=0$ (dot-dashed orange). The p-nullcline has two components: one is $p=0$ (the y-axis, dashed magenta) and the second component is the line $y=(a+\lambda-bp)/\kappa$ which depends on the value of λ, and is shown for $\lambda=1$ (green), $\lambda=5$ (blue), $\lambda=15$ (red), $\lambda=25$ (magenta), and $\lambda=30$ (black). Gray arrows indicate directions of movement in phase plane for $\lambda=25$. Observe that the equilibrium point $(\bar{p},\bar{y})$ is such that $p<0.8$ for $\lambda=1$, $p>0.8$ for $\lambda=5$, $p<0.8$ for $\lambda=15$ and $\lambda=25$, and $p>0.8$ for $\lambda=30$. Since $\dot{u}=(\lambda-\kappa y)u$, $u(t)$ behaves like $\alpha e^{\mu t}$ for large t, where $\mu=\lambda-\kappa\bar{y}=bp-a=p-0.8$, these growth rates λ corresponds respectively to $\mu<0$ (elimination), $\mu<0$ (proliferation), again $\mu<0$ (elimination, two nullclines values shown), and yet again $\mu>0$ (proliferation).

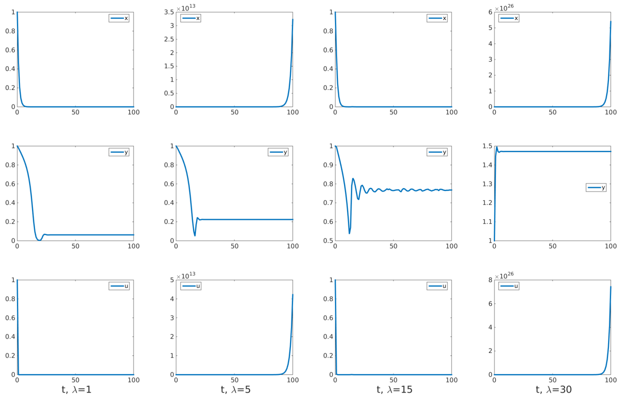

Fig. 5. Simulations of system (10), with same parameters as in Fig. 3, but now with with several values of λ. Initial states $x(0)=y(0)=u(0)=1$. Left to right: $\lambda=1,5,15,30$. As the growth rate λ increases, we obtain elimination (for $\lambda=1$), proliferation ($\lambda=5$), elimination ($\lambda=15$; plot for $\lambda=25$ not shown but similar), and again proliferation ($\lambda=30$)

innate and adaptive responses), and leads to perhaps unexpected conclusions regarding transitions between tolerance and elimination. In that context, one might view the x variable as representing the level of activity of a regulatory inhibitory component (such as a population of $\mathrm{T_{reg}}$ cells at a particular infection site or in a certain tumor microenvironment), y as the level of activity of an immune response component (such as cytotoxic T cells), and u as a population of pathogens or the volume of a tumor, which might grow exponentially (if $\lambda>0$) in the absence of immune action, but which is killed at a rate proportional to the immune response. The feedback into x and y represents the activation of both the response and of the regulatory mechanism in response to the infection or tumor.

In an immunological context, autocatalytic feedback might be implemented by a cytokine-mediated recruiting of additional immune components, or by autocrine stimulation. This results in an excitable system, which allows y to "lock" into a high state of activity given a sufficiently rapid rate of change in its input. Changing the growth rate λ of the pathogen or tumor, while fixing all other parameters, results in elimination of u for small growth rates λ, and in proliferation as λ increases. This is, of course, obvious. However, and very surprisingly, it may happen in this model that further increase of the growth rate λ, that is, when presented with a more aggressive pathogen or tumor, leads to the eventual elimination of the pathogen or tumor. This might be intuitively interpreted as a higher growth rate triggering locking of the immune response at a higher value. An even larger increase in λ leads again to proliferation. In other words, the pattern "elimination, proliferation, elimination, proliferation" can be obtained simply by gradually increasing λ. This is consistent with experimental results, going back to the 1980 and eariler. We do not further discuss these potential applications here, but we mention that this approach helps extend and unify several threads in the theoretical immunology literature that deal with the role of dynamics in self/nonself discrimination, as well as tumor dormancy and the tolerance of slow-growing tumors and chronic infections, and is related to the "sneaking-through" phenomenon in tumor immunology [1] (which has been mathematically modeled using alternative aproaches). See [3] (and journal paper to be published) for details and many references to a very active literature, as well as Weber-like logarithmic sensing and "fold change detection" of inputs.

V. REFERENCES

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