COMPETITION BETWEEN TRANSIENTS IN THE RATE OF APPROACH TO A FIXED POINT

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Abstract.
The goal of this paper is to provide and apply tools to analyze a specific aspect of transient dynamics not covered by previous theory. The question we address is whether one component of a perturbed solution to a system of differential equations can overtake the corresponding component of a reference solution as both converge to a stable node at the origin, given that the perturbed solution was initially farther away and that both solutions are nonnegative for all time. We call this phenomenon *tolerance*, for its relation to a biological effect. We show using geometric arguments that tolerance will exist in generic linear systems with a complete set of eigenvectors and in excitable nonlinear systems. We also define a notion of inhibition that may constrain the regions in phase space where the possibility of tolerance arises in general systems. However, these general existence theorems do not yield an assessment of tolerance for specific initial conditions. To address that issue, we develop some analytical tools to determine if particular perturbed and reference solution initial conditions will exhibit tolerance.

Key words. endotoxin tolerance, transient behavior, dynamical systems

AMS subject classifications. 37C10, 70G60, 34C11

1. Introduction.

Dynamical systems theory has traditionally focused on asymptotic behavior or on invariant manifolds and other structures derived from asymptotic and local calculations [23, 41]. However, in the last two decades there has been an increased awareness of the necessity of analyzing transient behavior and associated effects. The work of researchers in the fields of fluid mechanics [1, 4, 5, 6, 16, 18, 22, 24, 32, 35, 38], meteorology [15, 17, 19, 26], and mathematical ecology [9, 8, 10, 28, 29, 30, 39] has brought significant insight to this once underappreciated topic. In ecology, for example, the concept of *reactivity* (transient growth) is important in understanding any short term (transient) effects of changes made to an environment rather than only focusing on long term (asymptotic) consequences [8, 25].

In this work, we study a different aspect of transience in dynamical systems. In particular, we consider a comparison of the transient dynamics of pairs of trajectories with similar asymptotic behaviors. The motivation for this work arises from a biological phenomenon in which a reduction is observed in the effect induced by the application of a substance, due to an earlier exposure to that substance. For example, administration of a toxin to rodents, at a given reference dose, induces a reproducible acute inflammatory response featuring a rise in a variety of immune system elements followed by a return to near-baseline conditions [2, 11, 34, 40]. If a small pre-conditioning dose of the toxin is given to an animal prior to the reference dose then the activation of immune agents by the reference dose is attenuated. This phenomenon is called tolerance.

A previous study [13] analyzed tolerance in the context of a four dimensional ordinary differential equation (ODE) model of the acute inflammatory response. Within

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the four dimensional ODE model, the origin represents a healthy equilibrium state, and the abrupt administration of a toxin is represented by a jump of a trajectory to another point in phase space. Thus, starting from a given initial condition, tolerance occurs precisely when the sequence of a pre-conditioning dose, a period of ensuing flow, and a subsequent reference dose leads to a trajectory position that features a higher initial level of activated immune agents yet from which a lower level of activated immune agents ensues. From the observation of tolerance in the acute inflammatory response model, we reasoned that similar tolerance effects should be a general feature of trajectories generated from different initial conditions by a dynamical system with negative feedback. Our goal in this work is to provide a framework for the study of tolerance in ODE systems.

Here, we address two questions regarding tolerance. The first is whether or not a system will exhibit tolerance at all and the second is whether or not a specific perturbation from a specific initial condition will yield tolerance in a given system. For tolerance to occur, the perturbed trajectory must overtake the reference trajectory, with respect to the distance of one component from the origin. In regard to the first question, we find that tolerance is a generic property of linear and nonlinear systems that feature some fairly general properties. We show using geometric arguments that in systems possessing these properties, for a given reference trajectory, there is some region of phase space for which initial conditions of the perturbed solution will yield tolerance. This outcome arises from features of the flow that allow the perturbed trajectory to take a more rapid route to the origin than that taken by the reference trajectory, which may result if the perturbed trajectory moves through phase space faster or if it takes a shorter path to the origin.

In linear systems with distinct real negative eigenvalues, tolerance can be analyzed by an examination of the geometry of the eigenvectors. In nonlinear systems, tolerance occurs in systems that are excitable, i.e. where trajectories initially move away from the origin but eventually return because of negative feedback or inhibition. While the presence or absence of inhibition can be used to constrain where tolerance may arise in general systems, in general it does not allow us to determine precisely where tolerance does or does not occur. To address this question, we demonstrate how analytical estimates can be made on a case by case basis.

2. Definition of Tolerance.

Consider the autonomous ODE system

$$\dot{x} = f(x) \tag{2.1}$$

where $x \in \mathbb{R}^n$ and $f : \mathbb{R}^n \to \mathbb{R}^n$ is locally Lipschitz. Let $x_i \in \mathbb{R}$ and $f_i : \mathbb{R}^n \to \mathbb{R}$ be the components of x and f respectively.

(A1) Assume that there exists an asymptotically stable fixed point of (2.1) at the origin $(0, 0, \cdots, 0) \stackrel{\text{def}}{=} 0$, the eigenvalues of which are real and negative (to eliminate spirals and center directions).

Let $\Gamma_0 = \mathbb{R}^{n+} \cap \{x(0) | x(t) \to 0 \text{ as } t \to \infty\}$ be the basin of attraction of the origin in the positive n-hyperoctant $\mathbb{R}^{n+} \stackrel{\text{def}}{=} [0, \infty)^n$.

Let $\Gamma_0^+ = \{x(0) \in \Gamma_0 | x(t) \in \mathbb{R}^{n+} \text{ for all } t \geq 0\}$, namely the collection of trajectories that converge to the origin without leaving the positive n-hyperoctant. Let $\phi(t) = (\phi_1(t), \phi_2(t), \cdots, \phi_n(t))$ and $\psi(t) = (\psi_1(t), \psi_2(t), \cdots, \psi_n(t))$ be two solutions to the initial value problem of (2.1).

(A2) Assume that $\phi(t), \psi(t) \in \Gamma_0^+$.

(A3) Assume that $\psi_1(0) \geq \phi_1(0)$.

Under $(A3)$, $\psi(0) \in [\phi_1(0), \infty) \times [0, \infty)^{n-1}$; that is, the initial value for the P solution could lie at any point on or to the right of the hyperplane $\{x_1 = \phi_1(0)\}$ in the positive n-hyperoctant. Correspondingly, for any $x_1 > 0$, we define $\Gamma_0^{x_1} = \Gamma_0^+ \cap [x_1, \infty) \times [0, \infty)^{n-1}$ to be the subset of Γ_0^+ in $[x_1, \infty) \times [0, \infty)^{n-1} \subset \mathbb{R}^{n+}$.

Definition 2.1. *Define* $\phi(t)$ *as the* reference (R) trajectory *or* solution.

Definition 2.2. *Define* $\psi(t)$ *as the* pre-conditioned *or* perturbed (P) trajectory *or* solution.

We are interested in determining whether or not there exists a time when the first component of a P trajectory overtakes that of an R trajectory, given that it was initially behind, as they approach the origin. Our ensuing discussion would apply equally if we considered any other component instead of the first.

Definition 2.3. *The system (2.1) is said to* exhibit tolerance for $\langle \phi(0), \psi(0) \rangle$ *if there exists* $\tau > 0$ *such that* $\psi_1(\tau) < \phi_1(\tau)$, *where* $\langle \cdot\, , \,\cdot \rangle$ *indicates a pair of points.*

Definition 2.4. *If* $\psi_1(t) \geq \phi_1(t)$ *for all* $t \in [0, \infty)$, *then* (2.1) does not exhibit tolerance for $\langle \phi(0), \psi(0) \rangle$.

Remark 1. *We will also use the terminology that* $\psi(0)$ or ψ produces (or does not produce) tolerance in (2.1) *with respect to* $\phi(0)$ *or* ϕ *to mean that Definition 2.3 (Definition 2.4) holds. Figure 2.1 illustrates definitions 2.3 and 2.4 with hypothetical time courses of the first components of solutions* $\phi(t)$ *and* $\psi(t)$ *in a two dimensional example.*

Remark 2. *Our analysis is restricted to the origin as the fixed point, which is the biologically relevant choice for tolerance in the immune system. However, a theory of tolerance could be developed using similar methods for any other choice of fixed point in the positive hyperoctant. We return to this point in the Discussion.*

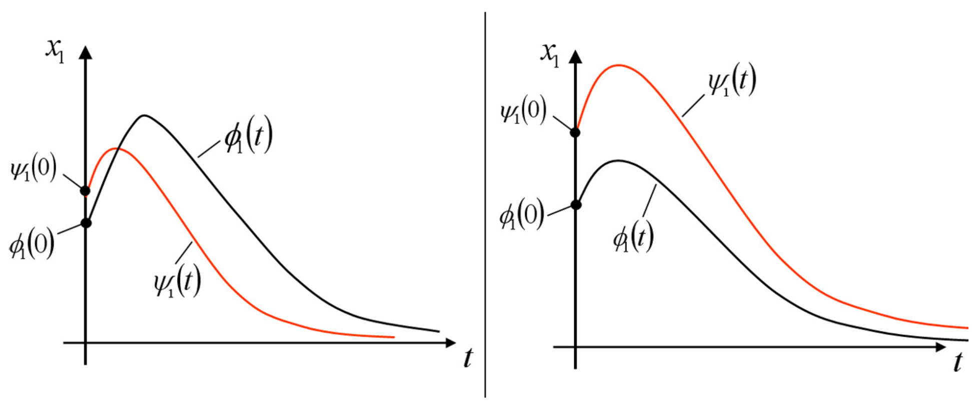

Fig. 2.1. *Illustration of Definitions 2.3 and 2.4. Left (Right) panel: Time course of the first component* x_1 *of a pre-conditioned (P) solution,* $\psi(t)$, *with* $\psi_1(0) = x_p$, *which produces ((does not produce) tolerance with respect to the reference (R) solution,* $\phi(t)$, *with* $\phi_1(0) = x_r$.

Definition 2.3 refers only to the presence of tolerance at one time point $\tau > 0$ such that $\psi_1(\tau) < \phi_1(\tau)$. However, continuity arguments can extend this window from a single time point to an open interval, (t_1, t_2), around τ, with $\psi_1(t_1) = \phi_1(t_1)$. This observation is stated formally in Proposition 2.5 below.

Proposition 2.5. *Assume (A1), (A2), and (A3). If (2.1) exhibits tolerance for* $\langle \phi(0), \psi(0) \rangle$ *at* $\tau > 0$, *then there exists an open neighborhood* (t_1, t_2) *around* τ *such that* $\psi_1(\hat{t}) < \phi_1(\hat{t})$ *for every* $\hat{t} \in (t_1, t_2)$ *and* $\psi_1(t_1) = \phi_1(t_1)$. *Furthermore,*

$f_1(\psi(t_1)) \le f_1(\phi(t_1))$.

The window of tolerance can also be extended with respect to $\phi(0)$ and $\psi(0)$.

Proposition 2.6. *Assume (A1), (A2), and (A3). If (2.1) exhibits tolerance for* $\langle \phi(0), \psi(0) \rangle$, *then there exists an open ball,* B_r, *of radius* r *around* $\phi(0)$ *such that if* $x \in B_r(\phi(0)) \cap \Gamma_0^+$ *and* $\psi(0) \in \Gamma_0^{x_1}$, *then there exists a corresponding time* $t_k > 0$ *such that tolerance is exhibited for* $\langle x, \psi(0) \rangle$.

Proposition 2.7. *Assume (A1), (A2), and (A3). If (2.1) exhibits tolerance for given* $\langle \phi(0), \psi(0) \rangle$, *then there exists an open ball,* $B_{\tilde{r}}$, *of radius* $\tilde{r}$ *around* $\psi(0)$ *such that if* $\tilde{x} \in B_{\tilde{r}}(\psi(0)) \cap \Gamma_0^{\phi_1(0)}$, *then there exists a corresponding time* $\tilde{t}_k > 0$ *such that tolerance is exhibited for* $\langle \phi(0), \tilde{x} \rangle$.

Propositions 2.6 and 2.7 are easily proved by noting that solutions of (2.1) are continuous and depend continuously on initial conditions. Each time t_k or $\tilde{t}_k$ can also be extended to an interval of times for which tolerance occurs, by Proposition 2.5.

Remark 3. *The above definitions of tolerance are related to the biological setting that motivated this study through the interpretation of the P trajectory. Consider a non-negative pre-conditioning solution* $\rho(t)$ *of (2.1) with initial value* $\rho(0)$, *with* $0 < \rho_1(0) \le \phi_1(0)$ *and* $0 \le \rho_i(0)$ *for* $i = 2, \cdots, n$. *The quantity* $\rho(0)$ *corresponds to the state of the inflammatory response immediately after administration of a pre-conditioning dose of toxin. We think of the perturbed trajectory* $\psi(t)$ *as the solution of (2.1) with initial value*

$$\psi(0) = \rho(s) + z \text{ for some } 0 \le s < \infty, \tag{2.2}$$

where $z \in \mathbb{R}^{n+}$ *corresponds to a second dose of toxin given at time* s *after pre-conditioning. If* $\phi(0) = z$, *which is typical for inflammation experiments, then for* $\phi(0)$ *and* $\rho(0)$, *every time* s *between doses defines a unique initial value for* ψ *as defined in equation (2.2), which satisfies (A3). Thus, for a continuum of* s *values ranging from* 0 *to* ∞, *a curve of possible* $\psi(0)$ *values is formed, and it is of biological interest to know which of these* $\psi(0)$ *lead to tolerance.*

3. Tolerance in linear systems.

Consider the linear system

$$\dot{x} = Ax, \tag{3.1}$$

where $A \in \mathbb{R}^{n \times n}$, $x \in \mathbb{R}^{n+}$, and assumption (A1) applies. To begin our consideration of tolerance, suppose that A has n distinct eigenvalues $\lambda_n < \lambda_{n-1} < \ldots < \lambda_2 < \lambda_1 < 0$ and denote an associated set of linear independent eigenvectors by $V = \{v_1, v_2, \ldots, v_n\}$. Given a pair of initial conditions $\phi(0), \psi(0)$ that satisfy assumptions (A2) and (A3), each can be expressed as a linear combination of the elements of V. A key factor in whether or not tolerance occurs in the long term for this pair is the relative magnitudes of the coefficients of their v_1 terms, corresponding to the direction of slowest decay. That is, let v_{jk} denote the k^{th} component of the j^{th} eigenvector. Suppose we can rescale so that $v_{ji} > 0$ for all j and write

$$\phi_i(t) - \psi_i(t) = (c_1 - d_1)v_{1i}e^{\lambda_1 t} + (c_2 - d_2)v_{2i}e^{\lambda_2 t} + \ldots + (c_n - d_n)v_{ni}e^{\lambda_n t}. \tag{3.2}$$

If $c_1 - d_1 > 0$, then for t large enough, say $t = T_n$, $\phi_i(T_n) - \psi_i(T_n) > 0$, implying tolerance in the ith component, because λ_1 is the slowest eigenvalue and $v_{1i} > 0$. That is, $c_1 > d_1$, together with additional assumptions to ensure that the initial conditions involved satisfy assumptions $(A2)$ and $(A3)$, is sufficient for eventual tolerance when all the v_{ji} are nonzero. More generally, tolerance in linear systems is determined by the relative magnitudes of all components in the eigenvector expansions of the initial conditions involved, including generalized eigenvectors when the set of eigenvectors is complete, due to the connection between eigenvectors and rates of decay toward the origin.

Now, we consider what else can be established about tolerance in linear systems, beyond this fundamental observation. We will show that under fairly general conditions, if we fix an appropriate R trajectory of system (3.1), then there exists a region, the location of which can be characterized, such that a P trajectory produces tolerance if and only if its initial condition lies in this region. Again, we emphasize that we will consider tolerance with respect to the first component of solutions, but that all arguments can be converted directly to apply to tolerance in any other component.

3.1. General tolerance result for linear systems. Recall that Γ_0 is the basin of attraction of 0 in the positive n-hyperoctant $\mathbb{R}^{n+}$ and that Γ_0^+ is the subset of initial conditions in Γ_0 generating trajectories that stay in $\mathbb{R}^{n+}$ for all $t \geq 0$. Analogously, define $\Gamma_1 = \{x \in \mathbb{R}^n : x_1 > 0\}$ and $\Gamma_1^+ = \{x(0) \in \Gamma_1 : x(t) \in \Gamma_1 \text{ for all } t \geq 0\}$. Also, for any set $\Gamma \subset \mathbb{R}^n$, we define the translate of the set $T_y(\Gamma) = \{x + y | x \in \Gamma\}$.

DEFINITION 3.1. *Given a matrix $A \in \mathbb{R}^{n\times n}$ with n distinct eigenvalues, the ith* eigenplane *is the $(n-1)$-dimensional hyperplane spanned by the $n-1$ eigenvectors that are not associated with the ith eigenvalue. That is, $E_i = sp\{v_1, \cdots, v_{i-1}, v_{i+1}, \cdots, v_n\}$ where (λ_i, v_i) are the eigenpairs of A.*

DEFINITION 3.2. *The ith* coordinate hyperplane *is the $(n-1)$-dimensional hyperplane defined by the equation $x_i = 0$.*

THEOREM 3.3. *If*

(i) A has n real eigenvalues, $\lambda_n \leq \lambda_{n-1} \leq \ldots \leq \lambda_1 < 0$, with n linearly independent eigenvectors $v_1, \ldots, v_n$,

(ii) no eigenplanes coincide with the 1st coordinate hyperplane, and

(iii) Γ_0^+ is non-empty,

then (3.1) will exhibit tolerance. More precisely, given an R trajectory $x(t) \in \mathbb{R}^n$ with initial condition $(x_1, \ldots, x_n)$ in the interior of Γ_0^+, a P trajectory will exhibit tolerance with respect to $x(t)$ if and only if its initial condition lies in $\Gamma_0^+ \cap T_{\phi(0)}(\Gamma_1 \setminus \Gamma_1^+)$, and moreover, this set is always non-empty.

Proof. For tolerance, we are interested in an R trajectory $\phi(t)$, $t \geq 0$, $\phi(0) \in \Gamma_0^+$ and a P trajectory $\psi(t)$, $t \geq 0$,$\psi(0) \in \Gamma_0^+$ such that $\phi_1(0) < \psi_1(0)$. Note that $\dot{\phi} = A\phi$ and $\dot{\psi} = A\psi$ since both ϕ, ψ are trajectories, and hence $\dot{\xi} = A\xi$, for $\xi = \psi - \phi$. Since $\phi_1(0) < \psi_1(0)$, it follows that $\xi(0) \in \Gamma_1$, and for tolerance, we require that there exists $t^* > 0$ with $\xi(t^*) \notin \Gamma_1$. Thus, tolerance occurs if and only if $\xi(0) \in \Gamma_1 \setminus \Gamma_1^+$. Considering ξ is equivalent, by linearity, to studying ψ in a coordinate system with $\phi(0)$ at its origin. Under this translation (denoted by $T_{\phi(0)}(\cdot)$), we see that given any $\phi(0) \in \Gamma_0^+$, tolerance occurs if and only if $\psi(0) \in \Gamma_0^+ \cap T_{\phi(0)}(\Gamma_1 \setminus \Gamma_1^+)$.

It remains to show that $\Gamma_0^+ \cap T_{\phi(0)}(\Gamma_1 \setminus \Gamma_1^+)$ is always non-empty. Observe that each eigensurface E_i of A includes the origin and is invariant under $\dot{x} = Ax$. The n eigensurfaces partition $\mathbb{R}^n$ into 2^n invariant regions, each with n boundaries. We will consider the partition $\mathcal{P}$ of Γ_1 formed from the n eigensurfaces together with $\{x_1 = 0\}$, consisting of at least 2^{n-1} regions, each of which includes the origin on its boundary, since each bounding hyperplane does.

Note that the x_1-nullsurface, defined as the hyperplane $\mathcal{N}_1$ that satisfies $\dot{x}_1 = 0$, cannot coincide with the hyperplane $\{x_1 = 0\}$ by our assumptions, since that would imply $\dot{x}_1 = cx_1$ for a constant c, such that E_1 would be $\{x_1 = 0\}$. Hence, $\mathcal{N}_1$ partitions

$\{x_1 = 0\}$ into two components, one with $\dot{x}_1 > 0$ and one with $\dot{x}_1 < 0$. There must exist a region $\mathcal{R}$ within the partition $\mathcal{P}$ of Γ_1 such that one of its boundaries is a part of $\{x_1 = 0\}$ on which $\dot{x}_1 < 0$. By construction, the region $\mathcal{R}$ is contained in $\Gamma_1 \setminus \Gamma_1^+$.

Now, let $\phi(0)$ be in the interior of Γ_0^+. Translate $\phi(0)$ to the origin of a new coordinate system, as previously. Any neighborhood of $\phi(0)$ intersects the translates of all regions in $\mathcal{P}$, including $T_{\phi(0)}(\mathcal{R})$. Hence, $\Gamma_0^+ \cap T_{\phi(0)}(\mathcal{R})$ is a nonempty subset of $\Gamma_0^+ \cap T_{\phi(0)}(\Gamma_1 \setminus \Gamma_1^+)$. □

Remark 4. *Note that the non-empty subset of $\Gamma_0^+ \cap T_{\phi(0)}(\Gamma_1 \setminus \Gamma_1^+)$ specified in the above proof favors points $\psi(0)$ with $\psi_1(0) - \phi_1(0)$ small, since this subset is defined using the translate of a region with $\{x_1 = 0\}$ as its boundary. After translation, this region will have $\{x_1 = \phi_1(0)\}$ as its boundary.*

The sets defined here are determined by the eigenstructure of the matrix A. As noted in the above proof, the eigenplanes E_i of A are each invariant under $\dot{x} = Ax$, and these n eigenplanes partition $\mathbb{R}^n$ into 2^n regions, each with n boundaries. We can denote these regions by $\mathcal{R}_1, \ldots, \mathcal{R}_{2^n}$, where the subscripts are assigned arbitrarily. Any such region $\mathcal{R}_i$ such that $bd(\mathcal{R}_i \cap \Gamma_1)$ is entirely contained within $\bigcup E_i$ yields a corresponding region of no tolerance after translation. That is, $T_{\phi(0)}(\mathcal{R}_i) \subset T_{\phi(0)}(\Gamma_1^+)$, so $\psi(0) \in T_{\phi(0)}(\mathcal{R}_i)$ implies no tolerance. Let $\mathcal{R}' = \bigcup_{i=1}^{r} \mathcal{R}_i$ denote the union of all such regions, if any exist, with $\mathcal{R}' = \phi$ otherwise. The proof of Theorem 3.3 shows how the tolerance properties of $T_{\phi(0)}(\Gamma_1) \setminus T_{\phi(0)}(\mathcal{R}')$ are determined by the vector field on the 2^{n-1} faces[1] of $\{x \in \mathbb{R}^n : x_1 = 0\}$.

We now illustrate the above ideas in two dimensions, where the sets $\mathbb{R}^{2+}$ and Γ_1 are the first quadrant and the right half plane, respectively (see Figure 3.1(a)), and where the E_i are simply the eigenvectors themselves. In Figure 3.1(b), a specific eigenstructure is considered and relevant sets are identified. Figure 3.1(c) translates these sets so that the point $\phi(0)$ is the origin of the new axes. Finally, Figure 3.1(d) marks the regions where tolerance will and will not occur, according to Theorem 3.3. A second eigenstructure is considered in Figure 3.2(a) with relevant regions identified. While applying Theorem 3.3 directly, we also look at regions $\mathcal{R}_i$ as discussed above to illustrate how regions of no tolerance can be identified. Figure 3.2(b) shows the regions where tolerance will and will not occur for this case. A third eigenstructure is considered in Figures 3.3(a-b), and tolerance regions identified using the same techniques.

In two dimensions, it is not necessary to use the $\mathcal{R}_i$ and $\mathcal{R}'$ to determine tolerance properties. However, we include them in these examples because these supply the easiest regions on which to decide tolerance, since it is always the case that there can be no tolerance on $T_{\phi(0)}(\mathcal{R}')$, and because they bear a relation to the normality of the matrix A. Normality of A has significant implications for the transient dynamics of individual trajectories of system (3.1) [37]. If A is normal, then its eigennplanes are orthogonal, which ensures that $\mathcal{R}'$ is non-empty and represents a significant part of Γ_1. If A is far from normal, then the E_i may be nearly parallel, which also has implications for the extent of $\mathcal{R}'$.

Finally, these examples illustrate the general point that in $\mathbb{R}^2$, given the constraints imposed by assumptions $(A1), (A2)$, there is a relation between the location of $\mathcal{R}'$ and the boundedness of the tolerance region. Specifically, when $\mathcal{R}' \subset \mathbb{R}^{2+}$, the tolerance region is unbounded, while the failure of this condition yields a bounded tol-

[1]By *faces* we mean regions separated by sign changes such as $\{x : x_1 = 0, x_2 > 0, x_3 > 0, \cdots, x_n > 0\}, \{x : x_1 = 0, x_2 < 0, x_3 > 0, \cdots, x_n > 0\}$, etc.

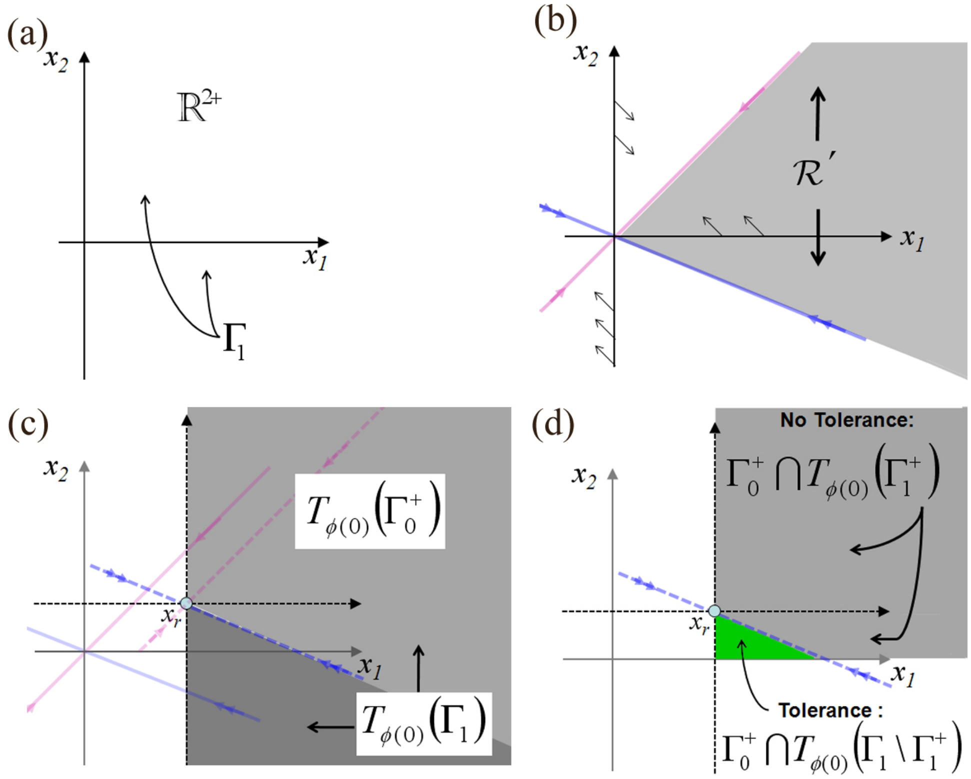

FIG. 3.1. *In $\mathbb{R}^2$, the $2^{n-1} = 2$ "faces" of the set $\{x = 0\}$ are the positive and negative branches of the y-axis. $\mathbb{R}^{2+}$ is the first quadrant, and the set Γ_1 is the right half plane. (b) A specific eigen structure is considered in which $\Gamma_0 \equiv \Gamma_0^+ \equiv \mathbb{R}^{2+}$, by positive invariance. The eigenvectors partition $\mathbb{R}^2$ into four regions $\mathcal{R}_1, \dots, \mathcal{R}_4$, while the eigenvectors and axes partition Γ_1 into S_1, S_2, S_3, and S_4, from which we define the sets $\Gamma_1^+ := S_2 \cup S_3 \cup S_4$ (i.e. starting in Γ_1, implies staying in Γ_1 for all $t \geq 0$) and $\Gamma_1 \setminus \Gamma_1^+ := S_1$. (c) An arbitrary $x_r \in \mathbb{R}^{2+}$ is chosen and the axes and eigenvectors are translated (dashed lines) such that x_r is now the origin. Correspondingly, translated sets are drawn and labeled. (d) Tolerance properties are classified using Theorem 3.3, based on possible choices $x_p \in \Gamma_0^+ \cap \overline{(\Gamma_1)^{x_1}}$. For $x_p \in \Gamma_0^+ \cap \overline{(\Gamma_1^+)^{x_1}}$ tolerance does not occur, while for $x_p \in \Gamma_0^+ \cap \overline{(\Gamma_1 \setminus \Gamma_1^+)^{x_1}}$ tolerance does occur.*

erance region, as can be seen by considering all possible eigenvector configurations in $\mathbb{R}^2$. When A is normal, this condition will always fail and hence a bounded tolerance region will result. Although nonnormality of A does not guarantee an unbounded tolerance region, we still expect some general relationship to hold between the extent of the tolerance region and the normality of A, which remains to be explored in greater than 2 dimensions.

3.2. Tolerance in linear planar systems. While Theorem 3.3 is quite general, it does not complete the theory of tolerance for linear systems. There are several issues that remain to be addressed, including relating the nature of the tolerance region to the (non)normality of A, what happens with eigenvalues for which algebraic multiplicity exceeds geometric multiplicity, and how to estimate the time at which tolerance occurs. We address the latter two issues in the planar case. We also discuss how certain parts of this approach can be extended to n dimensions. As noted at the start of Section 3, tolerance in linear systems is determined by the magnitudes

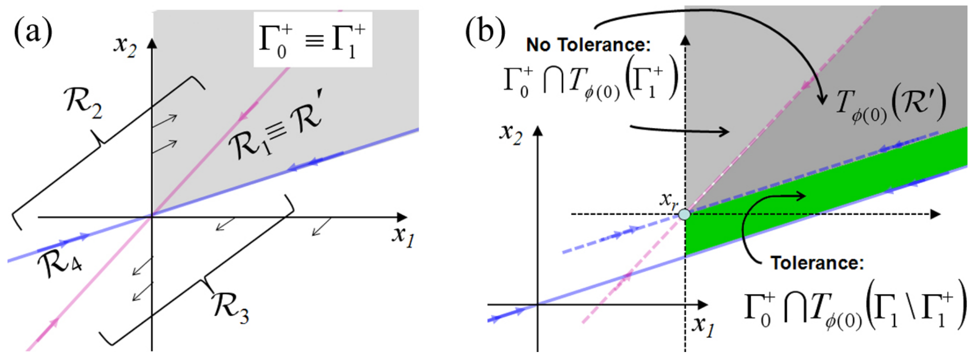

FIG. 3.2. *(a) A second eigen structure, different from that shown in Figure 3.1, is considered and the regions $\mathcal{R}_1 \cdots \mathcal{R}_4$ are identified. In this case, $\mathcal{R}' \equiv \mathcal{R}_1$. The shaded region is Γ_0^+, which is identical, in this case, to Γ_1^+. (b) An arbitrary $x_r \in \Gamma_0^+$ is chosen and the axes and eigenvectors are translated (dashed lines) such that x_r becomes the origin. Correspondingly, translated sets are drawn and labeled. As before, tolerance properties are classified using Theorem 3.3. For $x_p \in \Gamma_0^+ \cap \overline{(\Gamma_1^+)^{x_1}}$ tolerance does not occur, while for $x_p \in \Gamma_0^+ \cap \overline{(\Gamma_1 \setminus \Gamma_1^+)^{x_1}}$ tolerance does occur. Note that $\mathcal{R}_1$ is immediately ruled out as a tolerance region because $bd(\mathcal{R}_1 \cap \Gamma_0^+)$ is entirely contained within $\bigcup E_i$.*

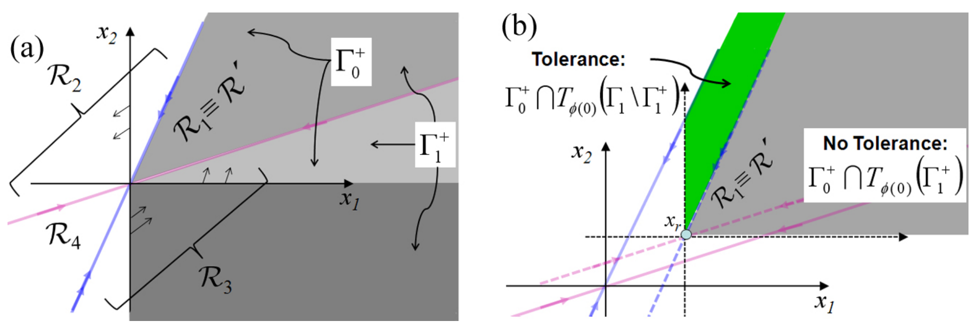

FIG. 3.3. *(a) A third distinct eigen structure is considered and regions $\mathcal{R}_1, \ldots, \mathcal{R}_4$ are identified, with $\mathcal{R}' \equiv \mathcal{R}_1$ as in Figure 3.2. The sets Γ_0^+ and Γ_1^+ are also identified. (b) An arbitrary $x_r \in \Gamma_0^+$ is chosen and the axes and eigenvectors are translated (dashed lines) such that x_r becomes the origin. Correspondingly, translated sets are drawn and labeled. As before, tolerance properties are classified using Theorem 3.3. For $x_p \in \Gamma_0^+ \cap \overline{(\Gamma_1^+)^{x_1}}$ tolerance does not occur, while for $x_p \in \Gamma_0^+ \cap \overline{(\Gamma_1 \setminus \Gamma_1^+)^{x_1}}$ tolerance does occur. Again, $\mathcal{R}_1$ is immediately ruled out as a tolerance region.*

of the components of the initial conditions in the direction of slowest eigenvector (or generalized eigenvector). The analysis done here will correspondingly be intimately tied to these magnitudes. A geometric representation off this analysis is given in the Supplementary Materials, along with analysis of necessary and sufficient conditions for tolerance in the 3D case if $c_1 < d_1$ (see equation (3.2).

We consider the linear system (3.1) in two dimensions with eigenvalues λ_1 and λ_2, and we adopt the notation $\phi(0) = (x_r, y_r)$, $x_r \geq 0$, $y_r \geq 0$ and $\psi(0) = (x_p, y_p), x_p \geq 0$, $y_p \geq 0$.

3.2.1. Case 1: $\lambda_1 \neq \lambda_2$**.** This case is covered by Theorem 3.3 but we will now take a more explicit approach that yields more concrete tolerance conditions and a precise time at which tolerance occurs. Without loss of generality, assume that $\lambda_2 < \lambda_1 < 0$. Let v, w be eigenvectors corresponding to λ_1, λ_2, respectively. Since λ_1 and λ_2 are distinct, v and w are linearly independent. Thus, any initial condition can be uniquely written as a linear combination of v and w. In particular, $(x_r, y_r) = c_1 v + c_2 w = (c_1 v_1 + c_2 w_1, c_1 v_2 + c_2 w_2)$, with $c_1, c_2 \in \mathbb{R}$. Correspondingly, the solution $\phi(t)$ to the initial value problem (IVP) $\dot{x} = Ax$, $\phi(0) = (x_r, y_r)$ is

$$\phi(t) = c_1 v e^{\lambda_1 t} + c_2 w e^{\lambda_2 t} = (c_1 v_1 e^{\lambda_1 t} + c_2 w_1 e^{\lambda_2 t}, c_1 v_2 e^{\lambda_1 t} + c_2 w_2 e^{\lambda_2 t}). \quad (3.3)$$

Similarly, consider the initial condition (x_p, y_p), which can be uniquely written as $(x_p, y_p) = d_1 v + d_2 w = (d_1 v_1 + d_2 w_1, d_1 v_2 + d_2 w_2)$, with $d_1, d_2 \in \mathbb{R}$. The solution $\psi(t)$ to the IVP $\dot{x} = Ax$, $\psi(0) = (x_p, y_p)$ is

$$\psi(t) = d_1 v e^{\lambda_1 t} + d_2 w e^{\lambda_2 t} = (d_1 v_1 e^{\lambda_1 t} + d_2 w_1 e^{\lambda_2 t}, d_1 v_2 e^{\lambda_1 t} + d_2 w_2 e^{\lambda_2 t}). \quad (3.4)$$

Since we know $x_p \geq x_r$ by (A3), we have that

$$d_1 v_1 + d_2 w_1 \geq c_1 v_1 + c_2 w_1. \quad (3.5)$$

The first component of each eigenvector can be scaled to be positive whenever it is nonzero. Since $\lambda_1 \neq \lambda_2$, v_1 and w_1 cannot both be zero for this case. If either v_1 or w_1 is zero, then this implies A is a lower triangular matrix and the first component is decoupled from the others, reducing the problem to the one dimensional case. However by uniqueness of solutions, tolerance cannot occur in one dimension (i.e. a trajectory cannot pass another trajectory in one dimension). Hence, tolerance is not possible when either (a) $v_1 = 0$ and $w_1 = 1$ or (b) $v_1 = 1$ and $w_1 = 0$. Note that these cases fall outside of the tolerance guarantee given by Theorem 3.3, since E_i coincides with the 1st coordinate hyperplane for $i = 1$ or 2 in these cases.

Alternatively, suppose $v_1 > 0$ and $w_1 > 0$. Proposition 3.4 below states necessary and sufficient conditions on the coefficients of the solutions ϕ and ψ in order for tolerance to be exhibited and also specifies the precise time value beyond which it occurs.

PROPOSITION 3.4. *Let $(x_r, y_r), (x_p, y_p)$ be given such that (A1), (A2), (A3) hold and assume that $\lambda_2 < \lambda_1 < 0$ and that $v_1 > 0$, $w_1 > 0$ for eigenvectors v and w corresponding to λ_1 and λ_2, respectively. There exists $T_1 > 0$ such that (3.1) will exhibit tolerance for all $t > T_1$ if and only if $(x_r, y_r), (x_p, y_p)$ are such that $c_1 > d_1$ and $c_2 < d_2$. Furthermore,*

$$T_1 = \frac{\ln[(d_2 - c_2) w_1 / (c_1 - d_1) v_1]}{\lambda_1 - \lambda_2}. \quad (3.6)$$

Proof. (Necessary Conditions) Assume that $c_1 \leq d_1$. Consider the difference between $\phi_1(t)$ and $\psi_1(t)$. Using (3.3), (3.4), and (3.5), we have

$$\begin{aligned} \phi_1(t) - \psi_1(t) &= (c_1 - d_1) v_1 e^{\lambda_1 t} + (c_2 - d_2) w_1 e^{\lambda_2 t} \\ &\leq (c_1 - d_1) v_1 (e^{\lambda_1 t} - e^{\lambda_2 t}). \end{aligned}$$

Since $\lambda_2 < \lambda_1 < 0$, v_1, $w_1 > 0$, and $c_1 \leq d_1$, it follows that $\phi_1(t) - \psi_1(t) \leq 0$, which means that $\psi_1(t) \geq \phi_1(t)$ for all $t \geq 0$. Hence, tolerance cannot be exhibited for $c_1 \leq d_1$. Similarly, it can be shown that (3.1) cannot exhibit tolerance for $c_2 \geq d_2$. Thus, $c_1 > d_1$ and $c_2 < d_2$ are both necessary conditions for tolerance.

(Sufficient Conditions) Assume that $c_1 > d_1$ and $c_2 < d_2$ both hold. Using (3.3) and (3.4), we have

$$\begin{aligned} \phi_1(t) - \psi_1(t) &= (c_1 - d_1) v_1 e^{\lambda_1 t} + (c_2 - d_2) w_1 e^{\lambda_2 t}. \\ &= \left(e^{(\lambda_1 - \lambda_2) t} v_1 + \frac{c_2 - d_2}{c_1 - d_1} w_1 \right) e^{\lambda_2 t} (c_1 - d_1). \end{aligned}$$

By assumption, $(c_1 - d_1) > 0$, $(c_2 - d_2) < 0$, and $w_1 > 0$; thus,

$$e^{\lambda_2 t}(c_1 - d_1) > 0 \text{ and } \frac{(c_2 - d_2)}{(c_1 - d_1)} w_1 < 0.$$

Therefore,

$$\begin{aligned} \phi_1(t) - \psi_1(t) &= \left(e^{(\lambda_1 - \lambda_2)t} v_1 + \frac{(c_2 - d_2)}{(c_1 - d_1)} w_1 \right) e^{\lambda_2 t}(c_1 - d_1) > 0 \\ &\Leftrightarrow \left(e^{(\lambda_1 - \lambda_2)t} v_1 + \frac{(c_2 - d_2)}{(c_1 - d_1)} w_1 \right) > 0 \\ &\Leftrightarrow e^{(\lambda_1 - \lambda_2)t} v_1 > \frac{(d_2 - c_2)}{(c_1 - d_1)} w_1 \\ &\Leftrightarrow t > \frac{\ln[(d_2 - c_2)w_1/(c_1 - d_1)v_1]}{\lambda_1 - \lambda_2} \equiv T_1. \end{aligned}$$

This inequality is satisfied by large enough t and T_1 gives a lower bound for t such that $\phi_1(t) - \psi_1(t) > 0$. Note that $T_1 > 0$ when $(d_2 - c_2)w_1/(c_1 - d_1)v_1 > 1$, which is equivalent to the initial conditions assumption $(A3)$ when $c_1 > d_1$ and $c_2 < d_2$. □

3.2.2. Case 2: $\lambda_1 = \lambda_2 = \lambda < 0$. In this case, λ has either a one- or two-dimensional eigenspace. If λ has a two-dimensional eigenspace, then solutions are linear combinations of the function $e^{\lambda t}$. Hence, we would arrive at the following:

$$\phi_1(t) - \psi_1(t) = x_r e^{\lambda t} - x_p e^{\lambda t} = (x_r - x_p)e^{\lambda t} \le 0.$$

Therefore, if A has identical eigenvalues with a complete set of linear independent eigenvectors, then the situation reduces to the one dimensional case and tolerance does not occur.

When λ has a one dimensional eigenspace, the analysis is not as straightforward. In this case, let v be an eigenvector of λ. One solution to (3.1) is $x^{(1)}(t) = ve^{\lambda t}$. A second solution to (3.1) is $x^{(2)}(t) = vte^{\lambda t} + \bar{v}e^{\lambda t}$, where $\bar{v}$ is a generalized eigenvector satisfying $(A - \lambda I)\bar{v} = v$. The initial condition (x_r, y_r) can be uniquely written as a linear combination of v and $\bar{v}$,

$$(x_r, y_r) = c_1 v + c_2 \bar{v} = (c_1 v_1 + c_2 \bar{v}_1, c_1 v_2 + c_2 \bar{v}_2), \text{with } c_1, c_2 \in \mathbb{R}.$$

The solution $\phi(t)$ to the IVP $\dot{x} = Ax$, $\phi(0) = (x_r, y_r)$ is

$$\begin{aligned} \phi(t) &= c_1 v e^{\lambda t} + c_2(vte^{\lambda t} + \bar{v}e^{\lambda t}) \\ &= (c_1 v_1 e^{\lambda t} + c_2(v_1 te^{\lambda t} + \bar{v}_1 e^{\lambda t}), c_1 v_2 e^{\lambda t} + c_2(v_2 te^{\lambda t} + \bar{v}_2 e^{\lambda t})). \end{aligned} \quad (3.7)$$

Similiary, the initial condition, (x_p, y_p), can be uniquely written as a linear combination of v and $\bar{v}$,

$$(x_p, y_p) = d_1 v + d_2 \bar{v} = (d_1 v_1 + d_2 \bar{v}_1, d_1 v_2 + d_2 \bar{v}_2), \text{with } d_1, d_2 \in \mathbb{R},$$

and the solution $\psi(t)$ to the IVP $\dot{x} = Ax$, $\psi(0) = (x_p, y_p)$ is

$$\begin{aligned} \psi(t) &= d_1 v e^{\lambda t} + d_2(vte^{\lambda t} + \bar{v}e^{\lambda t}) \\ &= (d_1 v_1 e^{\lambda t} + d_2(v_1 te^{\lambda t} + \bar{v}_1 e^{\lambda t}), d_1 v_2 e^{\lambda t} + d_2(v_2 te^{\lambda t} + \bar{v}_2 e^{\lambda t})). \end{aligned} \quad (3.8)$$

The following proposition states the results for this case. We will assume that v_1 can be scaled to be positive when it is nonzero.

PROPOSITION 3.5. *Let $(x_r, y_r), (x_p, y_p)$ be given such that (A1), (A2), (A3) hold and assume that $\lambda_1 = \lambda_2 = \lambda < 0$. Suppose that λ has a one-dimensional eigenspace. Let v be an eigenvector of λ and let $\bar{v}$ be a corresponding generalized eigenvector.*

(i) *If $v_1 > 0$, then we can choose $\bar{v}_1 = 0$ and (3.1) will exhibit tolerance for $\langle (x_r, y_r), (x_p, y_p) \rangle$ for all $t > T_2 \equiv (d_1 - c_1)/(c_2 - d_2)$ if $c_2 > d_2$; otherwise, no tolerance occurs.*

(ii) *If $v_1 = 0$, then (3.1) will not exhibit tolerance for $\langle (x_r, y_r), (x_p, y_p) \rangle$.*

Proof. Consider the difference between $\phi_1(t)$ and $\psi_1(t)$. Equations (3.7) and (3.8) yield

$$\phi_1(t) - \psi_1(t) = ((c_1 - d_1)v_1 + (c_2 - d_2)\bar{v}_1)e^{\lambda t} + (c_2 - d_2)te^{\lambda t}v_1$$

Assumption $(A3)$ on the initial conditions of ϕ and ψ implies

$$0 \geq (c_1 - d_1)v_1 + (c_2 - d_2)\bar{v}_1. \tag{3.9}$$

(i) *Assume that $v_1 > 0$.* Without loss of generality, we can assume that $\bar{v}_1 = 0$. That is, since v is an eigenvector of A, $(A - \lambda I)v = 0$. Thus, $\bar{v}$, which satisfies $(A - \lambda I)\bar{v} = v$, also satisfies $(A - \lambda I)(\bar{v} - av) = v$ for any scalar a, implying that $(\bar{v} - av)$ is also a generalized eigenvector of λ, linearly independent of v. Further, there exists an a such that $(\bar{v} - av) = [0\ b]^T$, which, for simplicity of notation, can be redefined as $\bar{v}$.

Therefore, in this case, (3.9) implies that $c_1 \leq d_1$. Moreover, $\phi_1(t) - \psi_1(t) = (c_1 - d_1 + (c_2 - d_2)t)v_1 e^{\lambda t}$, so $\phi_1(t) > \psi_1(t)$ requires $c_2 > d_2$ and holds for $t > (d_1 - c_1)/(c_2 - d_2) \equiv T_2$.

(ii) *Assume that $v_1 = 0$ and, thus, $\bar{v}_1 \neq 0$.* Then, we have

$$\phi_1(t) - \psi_1(t) = c_2\bar{v}_1 e^{\lambda t} - d_2\bar{v}_1 e^{\lambda t} \tag{3.10}$$

$$= (c_2 - d_2)\bar{v}_1 e^{\lambda t}. \tag{3.11}$$

By (3.9) with $v_1 = 0$, $(c_2 - d_2)\bar{v}_1 \leq 0$. Thus, (3.11) implies that $\phi_1(t) \leq \psi_1(t)$ for all t. ∎

REMARK 5. *If $\bar{v}_1 \neq 0$ is chosen, then the constants c_1, c_2, d_1, d_2 change correspondingly. For the new constants, the formula for T_2 generalizes to $T_2 = \frac{d_1 - c_1}{c_2 - d_2} - \frac{\bar{v}_1}{v_1}$ and inequality (3.9) replaces the condition $c_1 \leq d_1$.*

Propositions 3.4 and 3.5 give analytical conditions for the existence of tolerance in terms of coefficients of general solutions to (3.1). The existence of tolerance is determined by projecting (x_r, y_r) and (x_p, y_p) onto the eigenvectors. In the case of distinct eigenvalues, there is a fast eigenvector corresponding to the larger magnitude eigenvalue and a slow eigenvector corresponding to the smaller magnitude eigenvalue. Tolerance will exist if the component of the projection of x_r along the slow eigenvector is larger than the corresponding projection of x_p and if the component of the projection of x_r along the fast eigenvector is smaller than that of x_p. Thus for any point (x_r, y_r) there is a region of tolerance that will be defined by the two eigenvectors of the flow. The conditions are different in the case of repeated eigenvalues. Examples of trajectories and tolerance regions for various initial conditions and eigenvector configurations are shown in Figure 3.4, with each figure linking to an animation of the given example. [INSERT LINKS FOR LinearEx_a_Reg3.gif, LinearEx_b_Reg1.gif, LinearEx_c_Reg2.gif, and LinearEx_d_Reg1.gif)] Compare Figures 3.4(a-c) with Figures 3.1(d), 3.3(b), 3.2(b), respectively. The complete enumeration of all possible

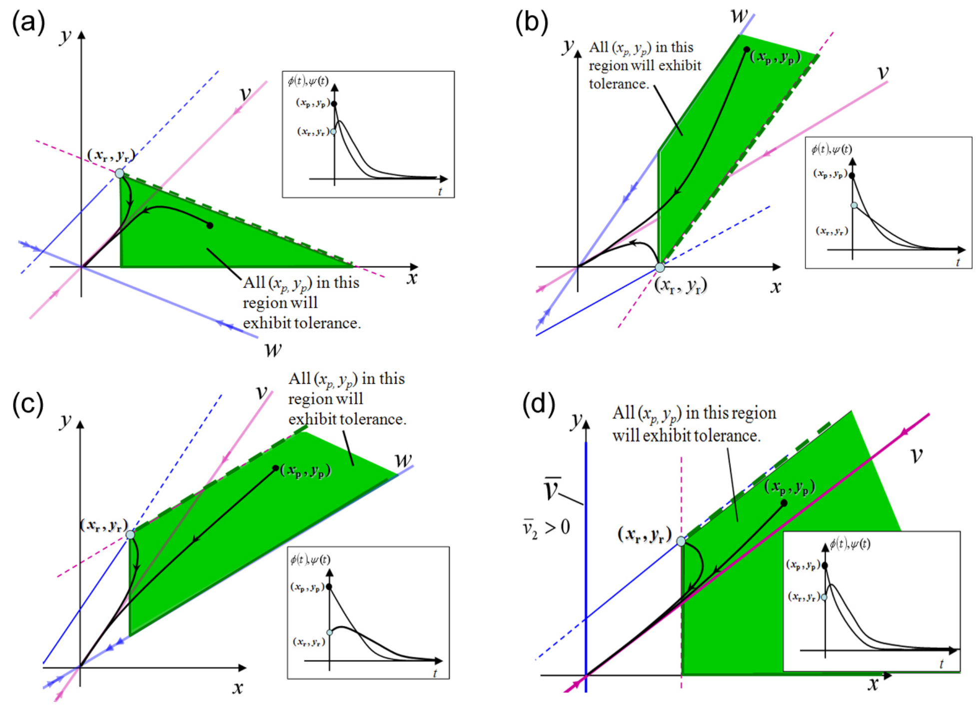

FIG. 3.4. *Four example eigenvector configurations, initial conditions and trajectories. In each case, tolerance will occur for* $\langle(x_r, y_r), (x_p, y_p)\rangle$ *if and only if* (x_p, y_p) *lies in the green region for* (x_r, y_r). *Each figure links to an animation of the given example.*

initial conditions and relevant eigenvector configurations is given in the Supplementary Materials.

Some special cases allow trivial generalization to n-dimensional systems. For example, if one component of a linear system decouples from the other components (i.e. the one dimensional tolerance case), then there cannot be tolerance in that component. Similarly, if a 2×2 block including the component of interest decouples, then 2-d analysis can be used, and so on. Alternatively, if A has n identical eigenvalues, $\lambda_n = \lambda_{n-1} = \ldots = \lambda_1 = \lambda < 0$, with a complete set of n linearly independent eigenvectors, then $\phi_i(t) - \psi_i(t) = (\phi_i(0) - \psi_i(0))e^{\lambda t} \leq 0$ for all $t \geq 0$, such that tolerance cannot occur. More generally, as noted at the start of Section 3, if A has n distinct eigenvalues and eigenvectors and equation (3.2) holds, then $c_1 > d_1$ is sufficient for eventual tolerance when all the v_{ji} are nonzero, together with additional restrictions on $\phi(0), \psi(0)$ to ensure that assumptions $(A2)$ and $(A3)$ hold. On the other hand, if $c_1 \leq d_1$ in this case, then tolerance may or may not be possible. For a 3D system with distinct eigenvalues, if $c_1 = d_1$, then the 2D analysis applies, while necessary and sufficient conditions for tolerance if $c_1 < d_1$ are given in part 2 of the Supplementary Materials.

3.3. Algorithms for locating regions of tolerance. We conclude our linear analysis by commenting on practical algorithms for identifying tolerance regions or for determining whether or not tolerance will occur for a particular choice of initial conditions $\phi(0), \psi(0)$. Theorem 3.3 implies that to fully characterize tolerance for (3.1), we should first find the eigenvectors of A. For a fixed $\phi(0) \in \Gamma_0^+$, recall that

$\Gamma_0^{\phi_1(0)}$ denotes the region from which $\psi(0)$ can be chosen such that $(A1), (A2), (A3)$ hold. If we can find $\Gamma_0^{\phi_1(0)}$, then we can translate it by taking $x_1 - \phi_1(0)$ for each $x = (x_1, \ldots, x_n) \in \Gamma_0^{\phi_1(0)}$. Tolerance for $\psi(0)$ is determined by the region $\mathcal{R}_i$ in which its translate, say $\psi(0)'$, lies, with no tolerance for $\psi(0)' \in \mathcal{R}'$ and with tolerance determined by the vector field on the boundaries of $\mathcal{R}_i$ that belong to the coordinate hyperplane $\{x_1 = 0\}$ for $\psi(0)' \notin \mathcal{R}'$. It remains for future work to determine computationally efficient algorithms for making this assessment.

A non-optimal but more explicit algorithm can be derived by attempting to locate a maximum of $(\phi_1(t) - \psi_1(t))$ at which this difference is positive. (A related approach can be used to obtain necessary and sufficient conditions for tolerance for linear systems in $\mathbb{R}^3$, as shown in the supplementary materials.) Since there are two possible inequality relationships ($\leq$ and $>$) between c_j and d_j for every $j = 1 \ldots n$ in equation (3.2), there are 2^n possible *sets* of coefficient relationships, each having n inequalities. Thus, one could set up 2^n linear programming problems each with n constraints made up of sets of possible coefficient inequalities. For instance, given a 4×4 matrix A and an initial condition $\phi(0) = (x_r, y_r)$ (and hence coefficients c_1, c_2, c_3, and c_4), one linear programming problem to solve would be:

$$\text{maximize } (\phi_1(t) - \psi_1(t))$$
$$\text{subject to: } c_1 <= d_1,\ c_2 <= d_2,\ c_3 > d_3, \text{ and } c_4 > d_4.$$

Under these constraints, if values for d_1, d_2, d_3, and d_4 can be found such that $(\phi_1(t) - \psi_1(t))$ has a maximum at which it is positive, then a region of tolerance has been found with respect to $\phi(0) = (x_r, y_r)$. Then, systematically, the other sets of inequalities can be checked. In fact, we can avoid checking the one inequality set that has $c_j \leq d_j$ for all $j = 1 \ldots n$, since this implies no tolerance, from equation (3.2).

4. General systems. A natural question to ask is, how effective is linear analysis for assessing tolerance in general systems? Just as linearization about a critical point tells us nothing about global properties of a flow in many nonlinear systems, linear analysis of tolerance based on linearization about the origin is not always a useful approach to tolerance. For example, tolerance in the first component can occur for the system

$$\begin{aligned} \dot{x} &= -x - xy, \\ \dot{y} &= x - 2y, \end{aligned}$$

yet the first component of the system obtained by linearizing about the origin decouples, and linear theory predicts no tolerance.

Is there another way to exploit linearization? As in the linear case, the eigenvalues and eigenvectors obtained from the linearization of a nonlinear system about an asymptotically stable node determine how trajectories approach the node asymptotically. The difficulty in the nonlinear case is that, even if an initial condition is expressed as a linear combination of these eigenvectors, the relative magnitudes of the components associated with different eigenvectors is not preserved under the flow. Theoretically, the dynamics of a nonlinear system with an asymptotically stable node can be characterized in terms of a fiber structure through which trajectories are slaved to counterparts on invariant manifolds, in this case associated with negative eigenvalues of different magnitudes and their corresponding eigenspaces [20, 21]. However, although it is known that this fiber structure exists, there is no means to calculate how an arbitrary point is situated with respect to the fiber system, and other ideas are needed to make the analysis of tolerance for nonlinear systems practical.

An alternative to linearization about a node would be to linearize about an initial condition of an R trajectory. If linearization yields distinct negative real eigenvalues and the conditions for Theorem 3.3 hold, then a corresponding tolerance region sufficiently close to the R trajectory will exist. On the other hand, linearization may yield complex eigenvalues and hence be inconclusive, or nonlinearity may cause or prevent tolerance away from a neighborhood of the R trajectory in ways that linearization cannot predict.

Hence, an analysis of tolerance in fully nonlinear systems is required. In this section, we demonstrate that tolerance can occur generically provided that trajectories satisfy a geometric property called *excitability*. The existence of excitability in turn depends on a property of the dynamics called *inhibition* where the increase of some components enhances the rate of approach towards the origin in the first component. However, given the presence of inhibition in general, an analytical estimate is required to address whether or not a given pair of reference and perturbed trajectory initial conditions will lead to tolerance.

4.1. Geometric analysis of tolerance: excitability. Consider the general system (2.1), $\dot{x} = f(x)$, for $x \in \mathbb{R}^n$. We start with a simple proposition.

PROPOSITION 4.1. *Assume (A1), (A2), and (A3). Given* $\langle \phi(0), \psi(0) \rangle$, *assume* $\phi_1(t)$ *and* $\psi_1(t) \to 0$ *monotonically as* $t \to \infty$. *If there exists* $\hat{t} > 0$ *such that* $\phi(-\hat{t}) = \psi(0)$, *then (2.1) does not exhibit tolerance for* $\langle \phi(0), \psi(0) \rangle$.

This proposition follows immediately from the group property of flows[2] and is another explanation for why tolerance is ruled out in one dimensional systems. However, this property also allows the possibility of tolerance in higher dimensions if the reference trajectory does not approach the origin monotonically. In particular, the first components of solutions generated by two initial conditions on the same trajectory may exchange order, depending on the geometry of the trajectory. We now focus on a situation where the reference trajectory ϕ is what we call a *k-excitable* trajectory as represented, for example, in the left panel of Figure 4.1. We make this concept precise with the following definition.

DEFINITION 4.2. *Assume that (A1), (A2), and (A3) hold for system (2.1). Fix a positive integer* k. *The trajectory* $\phi(t)$ *is* k-excitable *if there exist times* t_{ei}, *where* $t_{e_0} = 0 < t_{e_1} < t_{e_2} < \ldots < t_{e_{2k-1}}$, *such that*
(a) $\phi_1(t_{e_i}) > \phi_1(0)$ *for all* $i > 0$,
(b)
$$\begin{cases} f_1(\phi(t)) > 0, \ t \in [t_{e_0}, t_{e_1}) \ \text{and} \ (t_{e_{2i}}, t_{e_{2i+1}}), \ i \in \{1, 2, \ldots, k-1\}, \\ f_1(\phi(t)) < 0, \ t \in (t_{e_{2i+1}}, t_{e_{2(i+1)}}), \ i \in \{0, 1, \ldots, k-2\}, \quad \text{or} \ \ t > t_{e_{2k-1}}. \end{cases}$$
The trajectory $\phi(t)$ *is* excitable *if it is* 1*-excitable.*

Excitable trajectories are those that transiently grow (in one component) prior to approaching 0 and can be related to the amplification of a perturbation known as *reactivity* [28], a common feature in various models [7, 9, 10, 27, 28, 30]. In the context of acute inflammation, an excitable trajectory represents the initial activation of the immune system by a stimulus followed by a relaxation to a stable baseline state [13].

PROPOSITION 4.3. *Assume (A1), (A2), and (A3) hold for system (2.1). If* $\phi(t)$ *is a* k*-excitable trajectory, then system (2.1) exhibits tolerance for all* $\langle \phi(0), \psi(0) \rangle$ *such that* $\psi(0) = \phi(\hat{t})$, *for some* $0 < \hat{t} \le t_{e1}$.

[2] If $\phi^t(x)$ denotes the flow/trajectory generated by evolving a differential equation from initial point x for time t, the group property of flows is defined as $\phi^{t+s}(x) = \phi^t(\phi^s(x))$.

The proof again follows from the group action of flows and the observation that $\phi_1(t_{e_{2k-1}}) > \phi_1(t_{e_{2k-1}} + \hat{t}) = \psi_1(t_{e_{2k-1}})$. For points on the outgoing branch of an excitable trajectory, those further away from the origin are "ahead" of those that are closer. By propositions 2.6 and 2.7, we note that the two initial conditions need not be exactly on the same trajectory. Hence, there is a "tube" around the outgoing branch of an k-excitable trajectory in which tolerance can exist. The regions for which tolerance exist can be computed more explicitly in a planar system.

4.1.1. Planar excitable systems. Now we look at the implication of an excitable trajectory in two dimensions, again using the notation

$$\begin{aligned} \dot{x} &= f(x,y), \\ \dot{y} &= g(x,y). \end{aligned} \tag{4.1}$$

REMARK 6. *We add the following condition on $\dot{y} = g(x,y)$ to Definition 4.2: (c) $g(\phi_1(t), \phi_2(t)) > 0$ for $t \in [0, t_{e_{2k-1}}]$. Although not necessary for our approach, this assumption clarifies the presentation to follow.*

Below, we define a set T such that tolerance with respect to (x_r, y_r) occurs whenever $(x_p, y_p) \in T$, when $\phi(t)$ is a k-excitable trajectory.

DEFINITION 4.4. *For a k-excitable trajectory ϕ, define $t_r > 0$ to be the first positive time where $\phi_1(t_r) = x_r$, which exists since ϕ is k-excitable and continuous, under (A1) and (A2). Note also that $\phi_1(t) > \phi_1(t_r) = x_r$ for all $t \in (0, t_r)$ by definition of an k-excitable trajectory.*

DEFINITION 4.5. *Assume that ϕ is an k-excitable trajectory. In terms of t_r, define $G = \{(x,y)|(x,y) = \phi(t) \text{ for } t \in (0, t_r]\}$. Further, define the line segment $L = \{(x,y) : x = x_r, y \in (y_r, \phi_2(t_r)]\}$ and define the region S (see Figure 4.1) as the union of L and the interior of the region bounded by G and L. Finally, let $T = G \cup S$.*

DEFINITION 4.6. *Define $M = \max_{t \geq 0}\{\phi_1(t)\}$, which exists by (A1), (A2), and the continuity of ϕ. Let $t_m > 0$ ($t_M > 0$) be the minimal (maximal) positive time such that $\phi_1(t) = M$.*

PROPOSITION 4.7. *Let $\phi(0) = (x_r, y_r)$ and (x_p, y_p) be given. Suppose that (A1), (A2), and (A3) hold and that ϕ is an k-excitable trajectory. Under these conditions, T is a non-empty set. Moreover, if $(x_p, y_p) \in T$, then (4.1) will exhibit tolerance for $\langle (x_r, y_r), (x_p, y_p) \rangle$.*

Proof. By the assumptions, a region $T = G \cup S$ as defined above is non-empty. We divide the proof into two parts since T is defined as the union of two sets.

Part 1: Suppose $\psi(0) = (x_p, y_p) \in G$. This implies that $\psi(0) = (x_p, y_p) = \phi(\tau)$, for some $\tau > 0$. Recall that $\phi_1(t) < M$ for all nonnegative $t > t_M$. It follows that $\psi_1(t_M) = \phi_1(t_M + \tau) < M = \phi_1(t_M)$. Thus, (4.1) exhibits tolerance for $\langle (x_r, y_r), (x_p, y_p) \rangle \in G$ at time t_M.

Part 2: Suppose $(x_p, y_p) \in S$. We first consider the case where $x_p > x_r$ and define $t_p = \min_{t>0}\{t : \psi_1(t) = x_r\}$, such that $\psi(t) \in S$ for all $t \in [0, t_p]$. If $t_p \geq t_r$ then since $t_r > t_M \geq t_m$, $t_m \in (0, t_p)$. Hence, $\psi_1(t_m) < M = \phi_1(t_m)$ and tolerance is exhibited at t_m. Now, if $0 < t_p < t_r$, then it is possible that $\psi_1(t_m) > M$ (see bottom panel of Figure 4.1). However, from the definition of t_r, $\phi_1(t_p) > \phi_1(t_r) = x_r = \psi_1(t_p)$ and tolerance is exhibited at t_p. Now, consider the special case that $x_p = x_r$. If $f(x_p, y_p) > 0$ then t_p can be defined and the analysis proceeds as above. If $f(x_p, y_p) < 0$, then there exists $\epsilon > 0$ such that $\psi_1(\epsilon) < x_r$ and $\phi_1(\epsilon) > x_r$. Thus, $\phi_1(\epsilon) > \psi_1(\epsilon)$ and tolerance occurs at ϵ. □

Figure 4.1 illustrates Proposition 4.7 in both phase space (left panel) and with time courses (right panel). Notice that if we consider the special case when $(x_r, y_r) = (x_r, 0)$ for a k-excitable trajectory, then uniqueness of solutions is sufficient to guarantee tolerance.

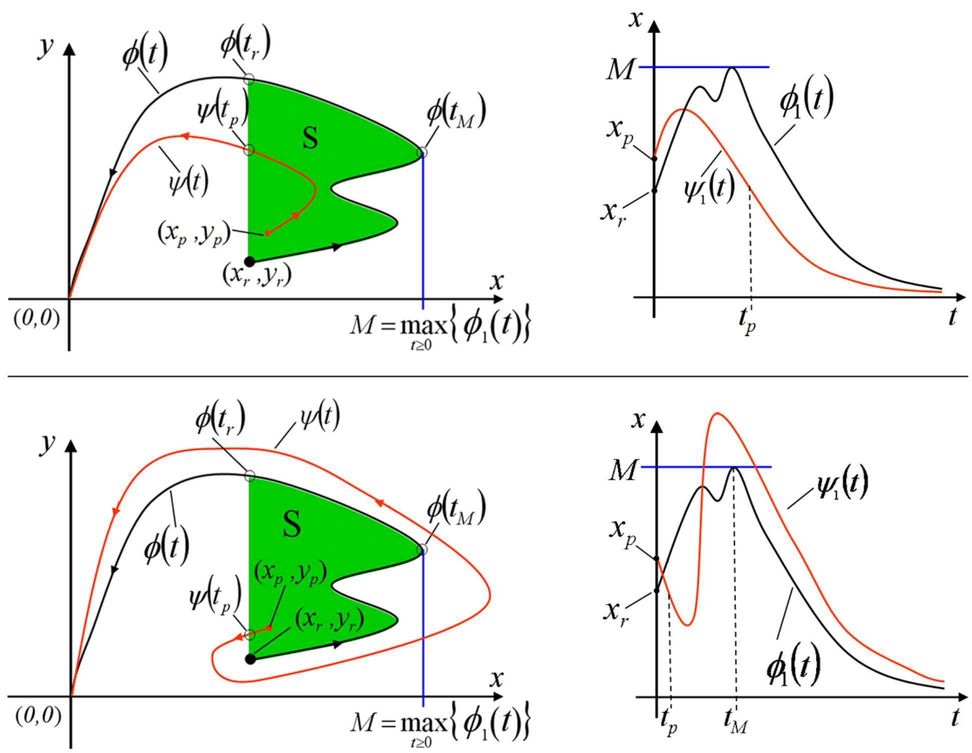

FIG. 4.1. *Illustration of Proposition 4.7 in the case that ϕ is k-excitable. P trajectories with initial conditions in region S exhibit tolerance. Left Panel: A 2-excitable R trajectory, $\phi(t)$, initial condition, (x_r, y_r) (black) and two example P trajectories, $\psi(t)$, with corresponding initial conditions $(x_p, y_p) \in S$ (red). The maximum value in the x-direction for $\phi(t)$ is marked with a vertical blue line and denoted by M. Additionally, note that $G = \{\phi(t)|t \in (0, t_r]\}$ (not labeled) is the section of the graph of $\phi(t)$ that forms a portion of the boundary of region S and that $L = \{(x, y) : x = x_r, y \in (y_r, \phi_2(t_r)]\}$ (not labeled) is the vertical line segment which forms the remaining boundary of the S. Right Panel: Time courses of both $\phi_1(t)$ (black) and $\psi_1(t)$ (red). Time t_p is where ψ_1 first takes on the value x_r and t_M is the time when $\phi_1(t)$ last attains its maximal value.*

If more constraints are imposed on the vector field f then the region that guarantees tolerance can be immediately expanded to include the strip above T in $\Gamma_0^{x_r}$. To be precise, we introduce the following definition.

DEFINITION 4.8. *Define $\hat{T}$ by the set*

$$\hat{T} = ((x_r, M) \times (\phi_2(t_M), \infty) \setminus T) \cap \Gamma_0^{x_r}. \tag{4.2}$$

PROPOSITION 4.9. *Assume (A1), (A2), (A3), and that ϕ is an k-excitable trajectory with $\phi(0) = (x_r, y_r)$. If $f(x, y) \leq 0$ for all $(x, y) \in \hat{T}$, then for $(x_p, y_p) \in \hat{T}$, (4.1) will exhibit tolerance.*

Proof. If $(x_p, y_p) \in \hat{T}$ and $f \leq 0$, then $\psi_1(t) \leq x_p < \phi_1(t_M)$ for $t \geq 0$. Thus, $\phi_1(t_M) > \psi_1(t_M)$. Hence, (4.1) exhibits tolerance for $(x_p, y_p) \in \hat{T}$ at time t_M. □

4.2. Inhibition. In the previous section we found specific conditions under which tolerance would occur for individual points or regions defined by the shape of the reference trajectory R. Now, we introduce the concept of inhibition, which is based on the vector field, rather than on a particular trajectory. Inhibition allows us to characterize whether or not certain special regions in phase space at least admit the possibility of tolerance and will also be used in the next subsection in an analytical approach to tolerance for individual trajectories.

The term *inhibition*, which is often associated with negative feedback, is widely used in the context of mathematical models of biological systems to refer to the suppression of one quantity by another. However, the use of this term, while intuitive and heuristically understood, is not always mathematically precise. Hence, we give a precise definition of what we mean by inhibition. Subsequently, we prove two results relating to inhibition and tolerance.

DEFINITION 4.10. *Given $\Omega \subseteq \mathbb{R}^{n+}$, we say x_i, $i \neq 1$,* inhibits *x_1 in Ω, and Ω is a* region of inhibition *with respect to x_i for (2.1), if $f(x_1, \ldots, x_i = u, x_{i+1}, \ldots) \leq f(x_1, \ldots, x_i = v, x_{i+1}, \ldots)$ if $u > v$ (i.e. $f_1(x)$ is a monotone decreasing function of x_i everywhere in Ω).*

REMARK 7. *Note that the sign of $f_1(x)$ is not specified in Definition 4.10. Thus, when x_i inhibits x, it may either slow the growth of x_1 or speed up its decay.*

REMARK 8. *A region of inhibition must be present for a k-excitable trajectory to exist.*

REMARK 9. *More than one component x_j can inhibit x_1 and the regions of inhibition need not be contiguous.*

A key first observation that follows from the definition of inhibition is that there is always the possibility of tolerance when x_i inhibits x_1, as long as the perturbed trajectory samples larger x_i values than the reference trajectory. In the context of the inflammatory response, a preconditioning dose can cause an above normal amplification of anti-inflammatory mediators which can inhibit the response to inflammatory stimuli significantly enough to cause tolerance. We formalize this observation by stating two further definitions and two results that follow from these definitions, which establish the necessity of a region of inhibition and of certain relative positions of the perturbed and reference trajectories for tolerance to occur.

DEFINITION 4.11. *The trajectory ψ is* bounded below *by the trajectory ϕ in the x_i direction if $\phi_i(s_1) < \psi_i(s_2)$ whenever $\phi_1(s_1) = \psi_1(s_2)$ for any $s_1, s_2 > 0$, not necessarily equal. For brevity, we say ψ is* bounded below *by ϕ in x_i.*

PROPOSITION 4.12. *Assume that (A1), (A2), and (A3) hold and that ψ is bounded below by ϕ in x_i for each $i > 1$. If (2.1) exhibits tolerance for a given pair $\langle \phi(0), \psi(0) \rangle$, then there exist a region of inhibition with respect to x_i, call it Ω_i, for some i and a time $s \in \mathbb{R}^+$ such that $\psi(s) \in \Omega_i$ or $\phi(s) \in \Omega_i$.*

DEFINITION 4.13. *The trajectory of ψ is* bounded above *by the trajectory of ϕ in the x_i direction if $\phi_i(s_1) > \psi_i(s_2)$ whenever $\phi_1(s_1) = \psi_1(s_2)$ for any $s_1, s_2 > 0$, not necessarily equal. For brevity, we say ψ is* bounded above *by ϕ in x_i.*

PROPOSITION 4.14. *Assume that (A1), (A2), and (A3) hold. For given $\langle \phi(0), \psi(0) \rangle$, if the graph of ψ is bounded above by the graph of ϕ in x_i for each $i > 1$, and there exists Ω that is a region of inhibition with respect to x_i for all $i > 1$ with $\phi(t)$, $\psi(t) \subset \Omega$ for all $t \geq 0$, then (2.1) cannot exhibit tolerance for $\langle \phi(0), \psi(0) \rangle$.*

Proposition 4.12 states that the existence of a region of inhibition is necessary for tolerance to occur when the P trajectory, ψ, is bounded *below* in all components $i > 1$ by the R trajectory, ϕ, while Proposition 4.14 states that for tolerance to be a possibility for a P trajectory ψ that is bounded above in all components $i > 1$ by the R trajectory ϕ, it is necessary that at least one of ϕ, ψ lies outside of a region of inhibition with respect to at least one component at some time. Note that we do not need to worry about ϕ but not ψ being excitable here, because ϕ, ψ are contained in a region of inhibition with respect to x_i for all $i > 1$. These results can be quite useful in low-dimensional systems. In higher dimensions, as more components interact, the assumptions involved become more restrictive and hence less likely to be satisfied.

4.3. Time interval estimates. To obtain more precise conditions for the existence of tolerance, direct estimates regarding specific trajectories of (2.1) are necessary. Here, we show how to derive estimates in the two dimensional plane for upper and lower bounds on the amount of time it takes for the relevant trajectories to reach a specified x-value x_f that is crossed by both trajectories, $\phi(t)$ and $\psi(t)$. We again adopt the two dimensional notation of section 3.2. If an (x_p, y_p) can be found such that $\psi(t)$ takes a shorter time interval to reach x_f than $\phi(t)$, then tolerance exists for that (x_p, y_p). To do this, we will use the x-isoclines, which we now define.

DEFINITION 4.15. *The* x-isoclines *of (2.1) are the family of curves (or level sets), parametrized by a parameter $C \in \mathbb{R}$, each defined by $f(x, y) = C$.*

A nullcline, for instance, is an isocline for which $C = 0$. The vector field points in the positive (negative) x-direction when C is positive (negative).

REMARK 10. *We may define y-isoclines analogously to x-isoclines. Since we do not consider these, we will drop the x- and just use isocline to refer to the x-isoclines here.*

Now, consider the ODE (2.1) and assume that (A1), (A2), and (A3) hold. Suppose that there is a positive integer n for which the graph of ϕ can be decomposed into a union of n graph segments such that the y component of the graph is single valued with respect to x on each. This assumption holds, for example, when ϕ is m-excitable for some m. Let x_i, $i \in \{1, \ldots, n+1\}$ be the $n+1$ terminal points of the n segments, defined by $x_1 = x_r$, $x_i = \phi_1(t^i_\phi)$, for $i = 2, \ldots, n$, where $t^i_\phi = \inf_{t > t^{i-1}_\phi}\{t : f(\phi_1(t), \phi_2(t)) = 0\}$ with $t^1_\phi = 0$, and $x_{n+1} = x_f$. Let $t^{n+1}_\phi = \inf_{t>t^n_\phi}\{t : \phi_1(t) = x_f\}$. The total time to traverse the trajectory from x_r to x_f is then given by $t_\phi = \sum_{i=1}^n \Delta t^i_\phi$, where $\Delta t^i_\phi = t^{i+1}_\phi - t^i_\phi$.

On each graph segment we can express the graph of ϕ as a function $y = v_i(x)$, where v_i is defined on the interval $x_i \le x \le x_{i+1}$, $i \in \{1, \ldots, n\}$. We can compute Δt_i for each segment directly by integrating the first equation of (2.1) along the graph segment defined by $y = v_i(x)$, i.e. $\dot{x} = f(x, v_i(x))$, to obtain

$$t_\phi = \sum_{i=1}^{n} \int_{x_i}^{x_{i+1}} \frac{du}{f(u, v_i(u))}. \tag{4.3}$$

A similar construction can give t_ψ, with initial x-coordinate x_p. Tolerance then implies $t_\psi < t_\phi$. In general, it is not possible to obtain v_i in closed form, but depending on the structure of f, estimates can be made to obtain various bounds for t_ϕ and t_ψ.

For example, with respect to (2.1), consider the family of x-isoclines $f(x, y) = C$, where $C \in \mathbb{R}$. Let $c^i_\phi = \sup_{t \in [t^i_\phi, t^{i+1}_\phi)}\{|f(\phi_1(t), \phi_2(t))|\}$, i.e. the largest magnitude isocline through which the trajectory ϕ passes on the segment $[x^i_\phi, x^{i+1}_\phi]$. Then from (4.3) we obtain $t_\phi \ge \sum_{i=1}^n |x^{i+1}_\phi - x^i_\phi|/c^i_\phi$. Likewise, let $c^i_\psi = \inf_{t \in [t^i_\psi, t^{i+1}_\psi)}\{|f(\psi_1(t), \psi_2(t))|\}$, i.e. the smallest magnitude isocline through which the trajectory $\psi(t)$ passes on the segment $[x_\psi^i, x_\psi^{i+1}]$, yielding $t_\psi \le \sum_{i=1}^n |x_\psi^{i+1} - x_\psi^i|/c_\psi^i$. Thus, if

$$\sum_{i=1}^{n} \frac{|x_\psi^{i+1} - x_\psi^i|}{c_\psi^i} < \sum_{i=1}^{n} \frac{|x_\phi^{i+1} - x_\phi^i|}{c_\phi^i}, \tag{4.4}$$

then $t_\psi < t_\phi$, which implies tolerance.

We can use condition (4.4) to show, for example, that if $\psi(t)$ is bounded below by an m-excitable trajectory $\phi(t)$, and $\phi(t)$ and $\psi(t)$ both lie in a region of inhibition, then the region on which tolerance is guaranteed to occur can be expanded from that defined in Proposition 4.9. As an example, suppose that $\phi(t)$ is an excitable trajectory. We can then divide ϕ into two segments. In the first segment $\phi_1(t)$ and $\phi_2(t)$ are increasing, and in the second $\phi_1(t)$ is decreasing. By continuity and (A1), $\phi_2(t)$ must first increase and then decrease on the second segment. The end point of the first segment is $x_M = \max_{t>0} \phi_1(t)$. Define x_f as the x-value where $\phi_2(t)$ is maximal and let $\phi_2(t) = y_f$ at this point. Since $\phi(t)$ belongs to a region of inhibition, the largest magnitude isocline through which the first segment of $\phi(t)$ passes is given by $c_\phi^1 = f(x_r, y_r) = C_r$. On the second segment, the largest magnitude isocline passes through $\phi(t)$ when $\phi_2(t)$ is maximal. Thus $c_\phi^2 = |f(x_f, y_f)| = C_f > 0$.

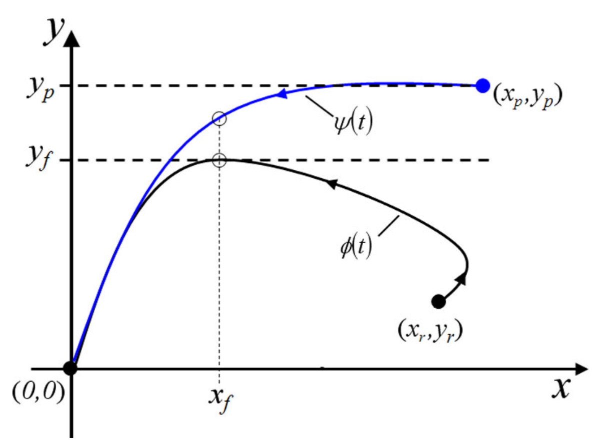

FIG. 4.2. *Illustration for time interval estimates.*

Now, using Figure 4.2 as a reference, consider a trajectory $\psi(t)$ such that $f < 0$ along the trajectory, so there is only one segment and it is bounded below by the line $y = y_f$. Thus, $c_\psi^1 = C_\psi > C_f$, and tolerance is observed if

$$\frac{|x_f - x_p|}{C_\psi} < \frac{|x_M - x_r|}{C_r} + \frac{|x_f - x_M|}{C_f}. \tag{4.5}$$

If we consider an excitable trajectory, then $x_p > x_f$, $x_M > x_r$, and $x_M > x_f$. Taking these inequalities in (4.5) gives the tolerance condition

$$x_p < x_M + \frac{C_\psi - C_f}{C_f}(x_M - x_f) + \frac{C_\psi}{C_r}(x_M - x_r) \stackrel{\text{def}}{=} \hat{x}_M. \tag{4.6}$$

Since $C_\psi > C_f$, (4.6) implies that $\hat{x}_M > x_M$, which expands the region obtained from Proposition 4.9. We note that C_ψ is a function of y_p, so (4.6) defines a region R such that if $(x_p, y_p) \in R$, then tolerance occurs in (2.1).

4.4. Examples. In the examples below, we illustrate the ideas introduced in the previous subsection. We consider examples within the class of negative feedback mechanisms appearing naturally in biological models, such as our earlier model of the acute inflammatory response [13], selected based on the types of isoclines they generate. The examples selected provide a progressive increase in isocline complexity, while specific coefficients in each were chosen for ease of presentation. In each figure, regions are labeled with the following conventions: T (green) or $\hat{T}$ (light green) as in Definitions 4.5 and 4.8 (on pages 15 and 16), where tolerance is guaranteed; PT (light blue) for possible tolerance region; NT (gray) for a no tolerance region.

Example 1. *Consider the system given by*

$$\begin{aligned} \dot{x} &= f(x,y) &= x^2/(1+y) - x \\ \dot{y} &= g(x,y) &= x^2 - y/2. \end{aligned} \tag{4.7}$$

The $1/(1+y)$ term is typical of the damping effect of anti-inflammatory mediators in inflammation models. Note that $(0,0)$ is a stable node for (4.7). The isoclines for this system are the family of curves given by the equation

$$y = \frac{x^2 - x - C}{x + C} \tag{4.8}$$

for $C \in \mathbb{R}$. Figure 4.3 shows a subset of the isoclines for $C \in [-4.0, 50]$ shown in increments of 0.5 for those above the $C = 0$ isocline and in increments of 1.0 for those below.

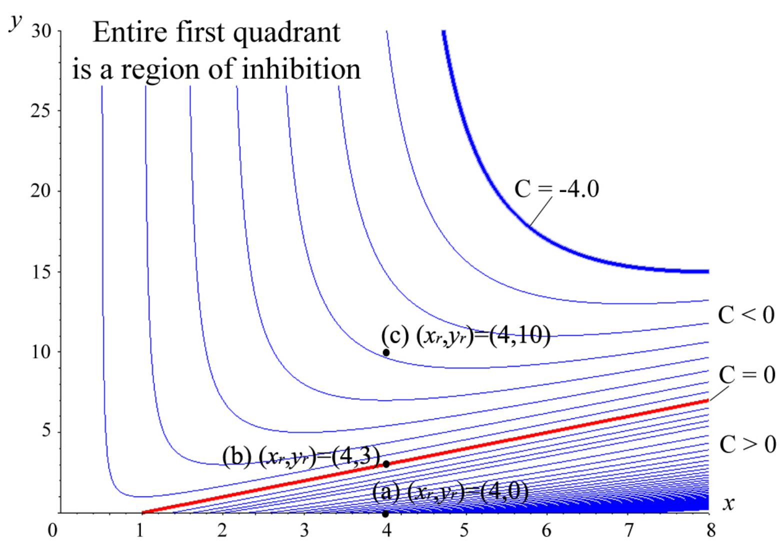

Fig. 4.3. *Isoclines for Example 1 defined by Equations 4.8 for $C \in [-4.0, 50]$.*

For each $C < 0$, the corresponding isocline has a local minimum at $x = -2C$ and a vertical asymptote at $x = -C$. Direct differentiation of f in (4.7) yields $f_y < 0$, or equivalently, from (4.8), $dy/dC < 0$, for all (x, y) in the first quadrant. Thus, the entire first quadrant is a region of inhibition. We will consider several different initial conditions (x_r, y_r) for $\phi(t)$ in this example: (a) $(x_r, y_r) = (4.0, 0.0)$, $C = 12$; (b) $(x_r, y_r) = (4.0, 3.0)$, $C = 0$; (c) $(x_r, y_r) = (4.0, 10.0)$, $C = \frac{-28}{11}$. If x and y are

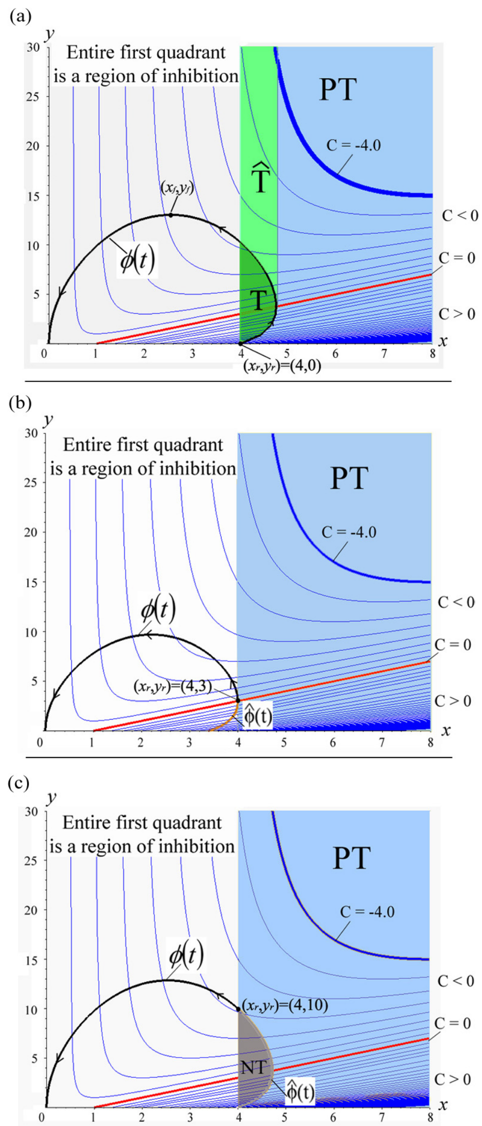

FIG. 4.4. *Isoclines and various initial values (x_r, y_r) for Example 1. (a) For $(x_r, y_r) = (4, 0)$, tolerance is guaranteed for (x_p, y_p) in regions T and $\hat{T}$. Tolerance is possible but not guaranteed for (x_p, y_p) in region PT. (b) For $(x_r, y_r) = (4, 3)$, tolerance is possible but not guaranteed for (x_p, y_p) in region PT. (c) For $(x_r, y_r) = (4, 10)$, tolerance is not possible for (x_p, y_p) in region NT and possible but not guaranteed for (x_p, y_p) in region PT.*

mediators in the inflammatory response, these initial conditions would correspond to possible mediator levels at the start of a tolerance experiment.

Figure 4.4(a) gives the regions where tolerance can occur for initial condition (a). By Proposition 4.7, any $(x_p, y_p) \in T$ will produce tolerance. Furthermore, define G as the part of the boundary of T for which $x \in [x_r, \infty)$, as in Definition 4.5. By Proposition 2.7, for each $(x_p, y_p) \in G$, there exists an open ball, $B_{\tilde{r}}$, of radius $\tilde{r}$ around (x_p, y_p) such that $(\tilde{x}_k, \tilde{y}_k) \in B_{\tilde{r}} \cap \Gamma^{x_r}_{(0,0)}$ produces tolerance with respect to $(4.0, 0)$.

Region $\hat{T}$ is inhibitory ($f < 0$). Thus, by Proposition 4.9, any $(x_p, y_p) \in \hat{T}$ will produce tolerance. Tolerance is also possible, although not guaranteed, for $(x_p, y_p) \in PT$. In this case, for $\psi_1(t) > M \stackrel{\text{def}}{=} \max_{t\geq 0}\{\phi_1(t)\}$, $\psi(t)$ is bounded below by $\phi(t)$ and there is inhibition. For $\psi_1(t) < M$, which is possible for small y_p, $\psi(t)$ will eventually be bounded below by $\phi(t)$ and hence tolerance is again possible. The following link supplies four separate animations that illustrate the presence or absence of tolerance in Example 1(a) using various choices of $\psi(0)$ from the different regions shown in Figure 4.4(a). Each animation displays both phase space trajectories of ϕ and ψ and time courses of $\phi_1(t)$ and $\psi_1(t)$ in a side-by-side comparison. [INSERT LINKS FOR EX1a_T_Animation.gif, EX1a_That_Animation.gif, EX1a_PT_tol_Animation.gif, and EX1a_PT_notol_Animation.gif.]

Now consider initial condition (b). Note that if y_r is increased with x_r fixed, the regions T and $\hat{T}$ shrink. Finally, when y_r reaches 3.0, corresponding to initial condition (b), these regions disappear; see Figure 4.4(b). For this example, if $x_p = x_r = 4.0$, then for all $(x_p, y_p) \in PT$, the corresponding graph of ψ is or will eventually be bounded below by the graph of ϕ. Since the graph of ψ lies in $\mathbb{R}^{2+}$ and $\mathbb{R}^{2+}$ is a region of inhibition, Proposition 4.12 implies that it is possible that tolerance can be exhibited by any $(x_p, y_p) \in PT$, although, as in the previous case, tolerance is not guaranteed.

For initial condition (c), there is the possibility of tolerance for all (x_r, y_r) and (x_p, y_p) since the entire first quadrant is a region of inhibition, except when $x_r \leq x_p < \max_{t\geq 0}\hat{\phi}_1(t)$ and ψ is bounded above by ϕ, as illustrated in the light blue region PT in Figure 4.4(c). However, by Proposition 4.14 and Proposition 4.1, there cannot be tolerance for $(x_p, y_p) \in NT$. The following link provides three animations for Example 1(c) with $\psi(0)$ chosen from the different regions shown in Figure 4.4(c). As before, each animation shows phase space and time courses in a side-by-side comparison. [LINK TO EX1C_NT_notol_Animation.gif, EX1C_PT_tol_Animation.gif, and EX1C_PT_notol_Animation.gif]

We now use time interval estimates to expand the region that guarantees tolerance. Consider initial value (a). We choose (x_f, y_f) such that $y_f = \max_{t\geq 0}\phi_2(t)$ (as labeled on Figure 4.4(a)). We note that the extremal points of $\phi(t)$, (x_M, y_M) and (x_f, y_f), are on the x-nullcline and y-nullcline respectively so that $y_M = x_M - 1$ and $y_f = 2x_f^2$ from (4.7). Given that initial value (a) results in an excitable trajectory, we can apply (4.6) with $C_r = 12$ and $C_\psi = C_f = |x_f^2/(1+2x_f^2) - x_f|$. This then establishes a bound on $\hat{x}_M$, such that tolerance occurs for $x_r < x_p < \hat{x}_M$, in terms of the initial value and extremal points of the reference trajectory $\phi(t)$. For example, rough bounds on x_f and x_M can be obtained from a visual inspection of $\phi(t)$. From Fig 4.4, we can propose $2 < x_f < 3$, leading to $1.55 < C_f < 2.53$, and $4.5 < x_M < 5$, with $\hat{x}_M = x_M + (C_f/C_r)(x_M - x_r)$ from (4.6) with $C_\psi = C_f$. More stringent bounds can be obtained by performing numerical integration using interval arithmetic. Moreover, as y_p increases, C_ψ increases while C_f remains fixed, such that tolerance can be guaranteed for larger x_p, given larger y_p.

In fact, example 1 is simple enough that we can obtain more precise estimates on t_ϕ and t_ψ, as defined in Section 4.3. Let t_ϕ (similarly, t_ψ) be the time of passage from $\phi_1 = x_r$ ($\psi_1 = x_p$) to $\phi_1 = x_f$ ($\psi_1 = x_f$). $\phi(t)$ can be represented by two segments. Denote the graph of ϕ for $t \in [0, t_\phi]$ by $(u, v_i(u))$, $i = 1, 2$ on the two segments. t_ϕ is given by (4.3), with $(x_\phi)_1 = x_r$, $(x_\phi)_2 = x_M$ and $(x_\phi)_3 = x_f$, where $x_M = \max_{t>0}\phi_1(t)$. Recall that in this example, the entire first quadrant is a region of inhibition. Our approach is to estimate the time intervals by setting $v_i(u)$ to a constant in (4.3) and then integrating to obtain $t_\phi > \Delta(y_r, x_r, x_M) + \Delta(y_f, x_M, x_f)$, where

$$\Delta(w, a, b) = \int_a^b \frac{du}{u^2/(1+w) - u} = \log\frac{|1+w-b|}{|1+w-a|} + \log\frac{a}{b}. \tag{4.9}$$

Next, we compute t_ψ for the trajectory $\psi(t)$ with initial condition (x_p, y_p), ending at (x_f, y_f). Now, consider those (x_p, y_p) such that $x_p > x_r$ and $y_p > y_f$. Since the y-nullcline is the curve $y = 2x^2$, by uniqueness of solutions to (4.7), the latter condition ensures that $\psi_2(t) > y_f$ for all t such that $\psi_1(t) > x_f$. By the continuity of $\Delta(w, x_f, x_p)$ in w, $t_\psi = \Delta(y_\psi, x_p, x_f)$ for some $y_\psi > y_f$. Thus, for the tolerance condition $t_\psi < t_\phi$ to hold, it is sufficient that

$$\Delta(y_r, x_r, x_M) + \Delta(y_f, x_M, x_f) > \Delta(y_\psi, x_p, x_f). \tag{4.10}$$

If $x_p = x_M$, then the observation that $\Delta(y_f, x_M, x_f) > \Delta(y_\psi, x_M, x_f)$ implies that (4.10) holds, and hence tolerance occurs, as expected from Proposition 4.9. For $x_p > x_M$, writing $\Delta(y_\psi, x_p, x_f) = \Delta(y_\psi, x_p, x_M) + \Delta(y_\psi, x_M, x_f)$ shows immediately that the upper bound for tolerance can be extended from x_M to some $x_p > x_M$.

Assuming that both sides of (4.10) are positive, as in Figure 4.4, condition (4.10) can be expressed as

$$\frac{x_r(1 - x_f + y_f)(x_M - 1 - y_r)}{(1 - x_M + y_f)(x_r - 1 - y_r)} > \frac{(1 + y_\psi - x_f)x_p}{1 + y_\psi - x_p}. \tag{4.11}$$

Condition (4.11) still depends on y_ψ, which can be estimated under the assumption that $y_\psi > \psi_2(t_\psi)$ (which holds, for example, if $g < 0$ along $\psi(t)$ from $t = 0$ to $t = t_\psi$). Formally integrating the second equation of (4.7) gives $\psi_2(t_\psi) = y_p e^{-t_\psi/2} + \int_0^{t_\psi} e^{-(t_\psi - t')/2} x^2 dt'$. On the trajectory $\psi(t)$, $x_f \le x \le x_p$, hence $\psi_2(t_\psi) > y_p e^{-t_\psi/2} + \int_0^{t_\psi} e^{-(t_\psi - t')/2} x_f^2 dt' = y_f + (y_p - y_f)e^{-t_\psi/2}$, where we have used $y_f = 2x_f^2$. Now $t_\psi = \Delta(y_\psi, x_p, x_f) < \Delta(y_f, x_p, x_f)$. Therefore, $y_\psi > \psi_2(t_\psi) > y_b$, where

$$y_b = y_f + (y_p - y_f)\exp[-\Delta(y_f, x_p, x_f)/2], \tag{4.12}$$

and y_b is an affine function of y_p. Note that the right hand side of (4.11) is a monotonic decreasing function of y_ψ. Hence, (4.11) is guaranteed to hold if

$$\frac{x_r(1 - x_f + y_f)(x_M - 1 - y_r)}{(1 - x_M + y_f)(x_r - 1 - y_r)} > \frac{(1 + y_b - x_f)x_p}{1 + y_b - x_p}, \tag{4.13}$$

which is a condition on tolerance for the initial value (x_p, y_p) of $\psi(t)$ in terms of the initial value and extremal points of the reference trajectory $\phi(t)$.

To conclude, note that condition (4.13) is also applicable for initial condition (b) or (c). In those cases, set $x_M = x_r$. Alternatively, if we choose an initial condition (x_r, y_r) on $\phi(t)$ that is closer to the origin than (x_M, y_M), then the analogous condition for tolerance after the time t such that $\phi(t) = (x_f, y_f)$, with $x_f < x_r$, simplifies to the direct comparison $\Delta(y_f, x_r, x_f) > \Delta(y_\psi, x_p, x_f)$. This inequality can be rewritten similarly to (4.13), with the same right hand side and a simplified left hand side.

Remark 11. *If y_p is increased for fixed x_p, then y_ψ increases, such that the right hand side of (4.11) decreases. Thus, the larger y_p is, the more likely it is that (4.11) is satisfied.*

EXAMPLE 2. *Let $\dot{y} = rx - y$, $r > 0$ and consider the following general equations as possibilities for $\dot{x} = f(x, y)$:*

$$\dot{x} = f(x,y) = \frac{ax^n}{1+by^m} - cx \tag{4.14}$$

$$\dot{x} = f(x,y) = g(x) - by^m \tag{4.15}$$

$$\dot{x} = f(x,y) = g(x) - bxy^m, \tag{4.16}$$

where $a, b, c > 0$, $n, m \in \mathbb{Z}^+$ and $g(0) = 0$. Equations of the form (4.14) arise in models describing the inflammatory response [33, 13, 12], in which anti-inflammatory agents (y) can mitigate the production or activation of various quantities, including phagocytes that in turn produce anti-inflammatories. Equations (4.15,4.16) are activator-inhibitor systems if $g'(0) > 0$ and may arise in other biological settings [14]. Each of the above equations models has $f_y < 0$ in the first quadrant, implying that the entire first quadrant is a region of inhibition. Assuming parameters are chosen so that $(0, 0)$ is an asymptotically stable fixed point, results will be completely analogous to those in Example 1. More diverse possibilities arise when $f_y \geq 0$ on at least a subset of the first quadrant. For example, suppose that $f(x, y)$ is the product of two inhibitory terms, such as

$$f(x,y) = (ax + by)(\frac{cx}{1+dy} + h),$$

with $b < 0$ and $a, c, d > 0$. Indeed,

$$sgn(f_y) = sgn(cx(b - adx) + bh(1 + dy)^2).$$

If $h > 0$, then $f_y < 0$ for all $(x, y) \in \mathbb{R}^{2+}$, as in the previous example. If, however, $h < 0$, then f_y changes signs in $\mathbb{R}^{2+}$.

EXAMPLE 3. *Consider the nonlinear system:*

$$\left.\begin{array}{rcccl} \dot{x} & = & f(x,y) & = & x\left(\frac{1+y^2}{1-y+y^2} - \frac{19}{10}\right) \\ \dot{y} & = & g(x,y) & = & x - y \end{array}\right\} \tag{4.17}$$

The isoclines for this system are the family of curves given by the equations

$$y^{(1)} = \frac{\frac{1}{2}\left(19x + 10C + \sqrt{37x^2 - 340xC - 300C^2}\right)}{9x + 10C}, \tag{4.18}$$

$$y^{(2)} = \frac{\frac{1}{2}\left(19x + 10C - \sqrt{37x^2 - 340xC - 300C^2}\right)}{9x + 10C}, \tag{4.19}$$

where $C \in R$. In Figure 4.5, the isoclines are drawn in increments of 0.1 for values of $C \in [-1.2, 0]$ and in increments of 0.01 for $C \in [0, 1]$. For $C \in [0, 1]$, the two curves defined by equations (4.18) and (4.19) together form a continuous curve. The black line, $y = 1$, in the figure emphasizes the two parts, with equation (4.18) forming the curves above and equation (4.19) forming those beneath.

A saddle exists near $(0.7176, 0.7176)$. The stable manifold of this saddle point forms a boundary for the basin of attraction of $(0, 0)$, $\Gamma_{(0,0)}$. The blue shaded region in Figure 4.5 shows the subset of $\Gamma_{(0,0)}$ in the first quadrant. A third fixed point (stable spiral, not labeled) in the first quadrant is located near $(1.3935, 1.3935)$, outside of $\Gamma_{(0,0)}$. This third fixed point could be interpreted as an ‘unhealthy’ outcome of an

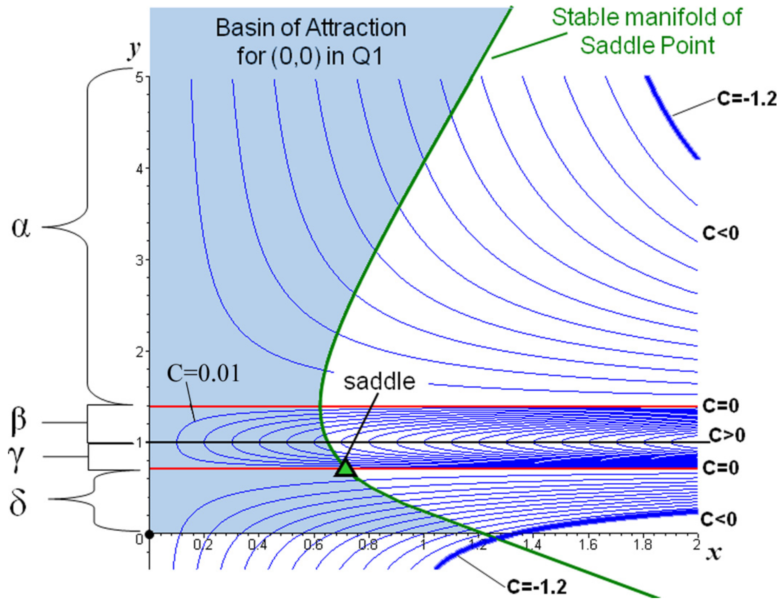

FIG. 4.5. *Isoclines for Example 3, drawn for various values of* $C \in (-1.2, 1)$.

immune response, with the stable manifold forming a boundary between it and the 'healthy' stable fixed point corresponding to $(0,0)$. The x-nullclines ($C = 0$) are marked (red) to help delineate where the speeds associated with the isoclines (i.e. $\dot{x}$) are positive or negative.

We define four disjoint subregions (see Figure 4.5) of the basin of attraction of $(0,0)$ in the first quadrant, as follows. 1) α: above (and including) the top component of the $C = 0$ isocline, 2) β: below the top component of the $C = 0$ isocline and above (and including) the line $y = 1$, 3) γ: below the line $y = 1$ and above (and including) the bottom component of the $C = 0$ isocline, and 4) δ: below the bottom component of the $C = 0$ isocline. These subregions are relevant because C varies nonmonotonically in y. If looked at separately, subregions α and β are both regions of inhibition and subregions γ and δ are not regions of inhibition. However, additional complications may arise if ϕ and ψ are not in the same subregion on some time interval.

Figure 4.6 shows one specific solution, $\phi(t)$ with $\phi(0) = (0.5, 0.5)$, that will be considered for this example. As usual, we consider points (x_p, y_p) that lie on or to the right of the line $\{x = x_r\}$. For $(x_p, y_p) \in PT_1 \setminus \hat{\phi}$, ψ will be bounded above by ϕ. From Proposition 4.14, since there are no regions of inhibition that contain both $\psi(t)$ and $\phi(t)$ for all $t \geq 0$, (x_p, y_p) might produce tolerance. It is clear that tolerance occurs if $x_p = 0.5$ and $0 \leq y_p < y_r$. In particular, tolerance occurs if $(x_p, y_p) = (0.5, 0)$. Tolerance does not occur if (x_p, y_p) lies on $\hat{\phi}$, by Proposition 4.1, so tolerance does not occur if $(x_p, y_p) = (1, 0)$. Thus, there exists a unique $\hat{x}_p \in (0.5, 1)$ and a continuous curve connecting $(0.5, 0.5)$ to $(\hat{x}_p, 0)$ such that tolerance occurs for all (x, p) in PT_1 below this curve and does not occur in PT_1 above this curve. Time interval estimates are necessary to prove that tolerance occurs or does not occur for specific choices of (x_p, y_p) in PT_1.

For $(x_p, y_p) \in NT$, $\phi \subset \delta$ and ψ will be bounded below by ϕ. Note that γ is not a region of inhibition and that β, although a region of inhibition by itself, has $f > 0$,

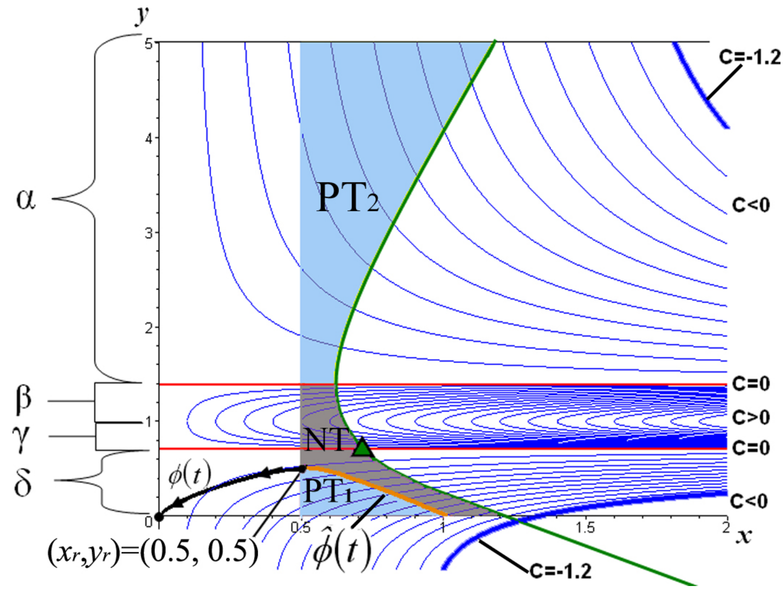

FIG. 4.6. *Tolerance in example 3. The orange curve, denoted as $\hat{\phi}$, is the curve of points obtained by integrating $\phi(t)$ backwards in time from $t = 0$ to $t \approx -1.75$, at which time it intersects the x-axis at $\hat{x} \approx 1.0$. PT_1 is the lower light blue region together with the boundaries made by the line segment $\{(x, y)|x = 0.5, 0 \leq y \leq 0.5\}$, the orange curve $\hat{\phi}$, and the x-axis. NT is the gray region, defined as $NT \stackrel{\text{def}}{=} \Gamma^{x_r}_{(0,0)} \setminus (\alpha \cup PT_1)$. PT_2 is the upper light blue region defined as $PT_2 \stackrel{\text{def}}{=} \Gamma^{x_r}_{(0,0)} \cap \alpha$.*

such that no tolerance can occur before ψ enters δ. But δ is not a region of inhibition, and hence from Proposition 4.12, any $(x_p, y_p) \in NT$ does not produce tolerance.

For $(x_p, y_p) \in PT_2$, since $C < 0$ in PT_2, it is possible that tolerance will occur before ψ leaves α. Alternatively, suppose that this does not happen. After ψ leaves α, it enters β, γ, and finally δ as it converges toward $(0, 0)$. In theory, tolerance could occur after ψ enters δ. However, ψ is bounded below by ϕ and δ is not a region of inhibition. Hence, as in Case 2, Proposition 4.12 implies that tolerance will not occur. In summary, if $\phi(0) \in \delta$ and $(x_p, y_p) \in PT_2$, then either tolerance occurs before ψ leaves α or it does not occur at all.

Using the same nonlinear system given by (4.17), consider an alternative choice for (x_r, y_r), namely one in α. Such a choice demonstrates some additional complexities that can arise in this type of example. Now, ϕ passes through regions where $f < 0$, then $f > 0$, and finally $f < 0$ again as it converges to $(0, 0)$. In terms of inflammation, this corresponds to an initial decrease in the inflammatory variable, (x), followed by a transient increase in the response before the final, decreasing approach to the baseline level. For different ψ trajectories, either bounded above or below by ϕ (see Figure 4.7), there are different time intervals when tolerance cannot occur or might possibly occur, which can be inferred from the isoclines.

In the particular example shown, for the ψ that is bounded below by ϕ, tolerance cannot be ruled out in any region. On the other hand, for the ψ that is bounded above by ϕ, tolerance is only possible after ψ enters δ. The following link provides access to two animations for Example 3 using $\phi(0) = (0.5, 2)$ in Region PT_2 and two choices of $\psi(0)$ also in Region PT_2, similar to those shown in Figure 4.7: [INSERT LINK FOR EX3_PT2_tol_Animation.gif and EX3_PT2_notol_Animation.gif]

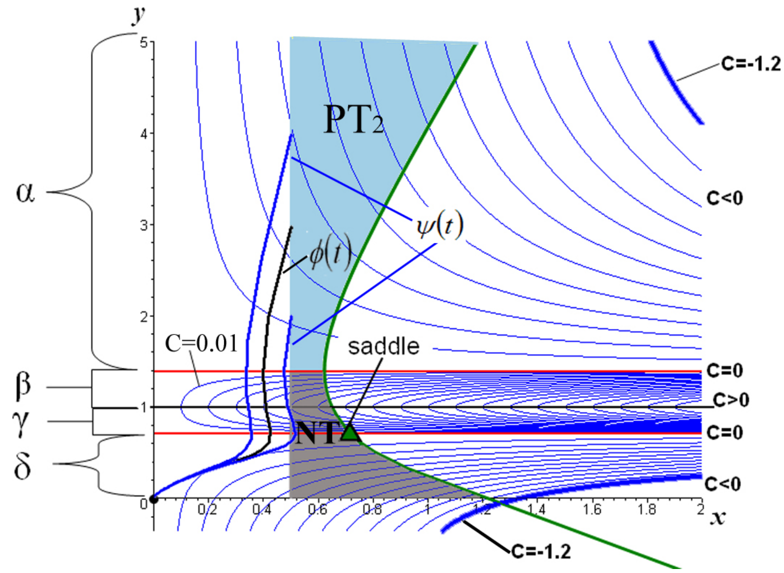

FIG. 4.7. *Nonmonotonic convergence to* $(0,0)$ *in Example 3.*

5. Discussion. Our consideration of tolerance serves as an example of how dynamical systems questions can arise from biological phenomena and adds to the ongoing efforts to characterize transient dynamics. The concept of tolerance, which we studied numerically from a dynamical systems perspective in our previous work [13], has not received previous analytical treatment. However, related research that addresses transient effects has been done in the fields of fluid mechanics, mathematical ecology and meteorology, where many of the ideas and techniques developed by Trefethen, Schmid, Farrell and collaborators have been used [38, 37, 35, 19]. Specifically, this body of work addresses many questions about how solutions approach equilibria in the case where the matrices or operators describing the time evolution of a system are nonnormal.

We initiated our analysis of tolerance under assumptions representative of typical experimental preconditioning protocols used in the study of the acute inflammatory response [13, 3, 31, 36, 42]. However, in this paper, we present a generalized analysis, allowing relatively general choices of initial conditions for the reference and perturbed trajectories, since the ideas of inhibition and tolerance, as we have defined them, are themselves quite general. The goal of this analysis is to use information about the initial conditions of the R and P trajectories and the vector field to determine *a priori* if the associated trajectories will or will not exhibit tolerance. In tolerance experiments, by applying the challenge dose to the preconditioning trajectory at different times, an experimentalist could generate a continuous curve of possible initial conditions for what we call the P trajectory, as described in Remark 3, and our analysis aims to consider all such initial conditions, to fully characterize the possibility of tolerance within a given experimental set-up.

We find that tolerance is actually quite natural for linear and nonlinear systems satisfying certain general conditions. The intuitive idea of tolerance is that a system's vector field sets up different directions in phase space that are associated with different rates of contraction to an asymptotically stable node. An initial condition that is dominated by components in strongly contracting directions may yield a trajectory that approaches the node faster than another trajectory that is initially closer but has larger components in weakly contracting directions. These geometric ideas can be exploited most directly in linear systems, where the relative magnitudes of these components can be obtained by expressing an initial condition as a linear combination of eigenvectors and generalized eigenvectors. In the linear case, we have also gone beyond these ideas to prove that, given that there are trajectories that remain in the positive hyperoctant as they approach a stable node at the origin, a region of tolerance will exist, relative to a given admissible reference trajectory, as long as the matrix specifying the flow has a complete set of eigenvectors and satisfies a genericity condition. We find it somewhat unexpected that tolerance is so ubiquitous here. Indeed, given that tolerance sufficiently close to a reference trajectory is determined by linearization about that trajectory, and that this linearization will yield a complete set of distinct, negative real eigenvalues for a significant class of systems, tolerance is quite widespread, at least for small perturbations. In the nonlinear case, we have discussed how tolerance arises in systems that are excitable, namely those for which trajectories may exhibit a strong initial flow away from the equilibrium followed by a decay back to the stable fixed point. The existence of excitability in turn is contingent on the presence of inhibition, through which growth in one component prevents growth, or enhances decay, in another component; inhibition also influences tolerance in systems that are not excitable.

Although we obtain general results on the existence of tolerance for linear systems and the possibility of tolerance when inhibition is present, the knowledge that there exists a region of initial conditions that yield or may yield tolerance does not necessarily translate to knowledge about the extent of this region or about tolerance for a specific pair of reference and perturbed trajectory starting points. We have noted that when the matrix associated with a linear system is normal, a significant region of possible perturbed trajectory initial conditions will not yield tolerance, and in fact normal matrices yield bounded tolerance regions in $\mathbb{R}^2$. Hopefully, future work can exploit the large body of work on transient dynamics and (non)normality (cf. [37]) to illuminate how the properties of a nonnormal matrix constrain the tolerance regions of the associated linear system. To specifically assess tolerance for a given initial condition pair, analytical methods are necessary. Our analytical approach is based on direct estimation of times of passage resulting from the isocline structure of the vector field, which must be made on a case by case basis, as we illustrate.

Our work only considers tolerance for orbits approaching the origin. For a fixed point not at the origin, the concept of tolerance could be generalized to include initial conditions such that $\psi_1(0)$ is less than $\phi_1(0)$, but $\psi_1(0)$ is farther away from the fixed point in the x_1-direction than is $\phi_1(0)$. If the fixed point was at (1,1) for instance, with $\phi_1(0) = (1.5, 1)$ and $\psi_1(0) = (0, 0.5)$, then $\psi_1(0)$ would be farther away from the fixed point in the x_1-direction, but $\psi_1(0) < \phi_1(0)$ would hold, which is not permitted in the set-up we consider. This situation could be addressed by comparing the distance of each trajectory from the fixed point, with respect to the component deemed relevant for tolerance. Additionally, it may be of interest to generalize the concept and analysis of tolerance to allow for complex eigenvalues for fixed points in the interior of the positive hyperoctant, as these are likely to be important in certain biological settings. Finally, a more complete connection between linear and nonlinear systems is currently lacking. Specifically, this paper does not explicitly provide a link between approaches to tolerance analysis for general systems, such as those presented in Section 4, and the tolerance regions predicted to exist from linearization about a reference trajectory, when such predictions can be made.

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