Normal form for dynamic absolute concentration robustness

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Abstract

In a reaction network, the concentration of a species with the property of dynamic absolute concentration robustness (dynamic ACR) converges to the same value independent of the overall initial values. This property endows a biochemical network with output robustness and therefore is essential for its functioning in a highly variable environment. It is important to identify structure of the dynamical system as well as constraints required for dynamic ACR. We propose a normal form of dynamic ACR and obtain results regarding convergence to the ACR value based on this form. Furthermore, we study an archetypal model of dynamic ACR in the context of a chemostat, where the network is coupled with inflows and outflows of the species. We prove that dynamic ACR persists at the same value as the uncoupled system in a wide variety of situations.

Keywords: biochemical reaction network, absolute concentration robustness, normal form, dynamical systems, robust network output, chemostat.

AMS subject codes: 34C20, 37N25, 37N35, 92C42

1 Introduction

Dynamic absolute concentration robustness (dynamic ACR), introduced in [1], is a property of dynamical systems wherein one variable converges to a unique value independent of the initial values. This variable is the dynamic ACR variable and the unique value is its ACR value. Dynamic ACR is significant for applications to biochemistry. Biochemical systems need to perform robustly in a wide variety of conditions. Dynamic ACR provides a mechanism for such robustness.

Mathematically, dynamic ACR is the property that the hyperplane \( \{x_i = a_i^\ast\} \) is an attractor for all trajectories (with some minor restrictions on allowed initial values). Dynamic ACR properties in the context of complex balanced systems has been discussed in [1]. A classification of small networks with dynamic ACR appears in [2].

Static absolute concentration robustness (static ACR) is the property that all positive steady states are in the hyperplane \( \{x_i = a_i^\ast\} \). In the seminal work of Shinar and Feinberg [3], where static ACR was introduced, there appear several examples of biochemically realistic networks with static ACR. Most, perhaps all of these networks, may have the property of dynamic ACR as well, although this remains an open question. It is difficult to characterize dynamic ACR because it requires understanding the limiting behavior for arbitrary initial values. We take a significant step in the direction of establishing dynamic ACR in this paper. We propose a normal form for the differential equation satisfied by the dynamic ACR variable, see (2.1). In Theorem 2.5 one of the two main theorems in this paper, we establish sufficient conditions for convergence to the ACR value, based on properties of the terms appearing in the normal form equation.

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An archetypal model of dynamic ACR is the reaction network \( \{ A + B \rightarrow 2B, B \rightarrow A \} \). We show that even when this reaction network is implemented as a chemostat (an apparatus that allows for inflows and outflows of chemical species), dynamic ACR can persist. A summary of these results is in Theorem 3.1, the other main theorem, and even more detail of the dynamics is in Table 1.

Dynamic ACR has been experimentally observed in bacterial two-component signaling systems such as the EnvZ-OmpR system and the IDHKP-IDH system \([4, 5, 6, 7, 8, 9]\). Dynamical properties of ACR systems have been studied in the control theory literature \([10, 11, 12]\), where a related concept, called robust perfect adaptation, appears. For a biochemical perspective on perfect adaptation, see \([13]\). Structural requirements for robust perfect adaptation in biomolecular networks are studied in \([14]\). A normal form for output robustness based on internal model representation is proposed in \([15]\). A contemporary review of internal models can be found in \([16]\).

This article is organized as follows. Section 2 introduces a normal form for dynamic ACR, examples, and convergence results. Section 3 studies an archetypal ACR system in the context of chemostat. Section 4 discusses the larger context, significance and future work on the properties of networks with dynamic ACR.

2 Normal form for dynamic ACR

Dynamic absolute concentration robustness (dynamic ACR) in a general dynamical system was defined in \([1]\). We repeat the definition here. Throughout the paper, we assume that \( \mathcal{D} \) is a dynamical system defined by \( \dot{x} = F(x, t) \) with \( x \in \mathbb{R}_0^n \) for which \( \mathbb{R}_0^n \geq 0 \) is forward invariant.

**Definition 2.1.** The kinetic subspace of \( \mathcal{D} \) is defined to be the linear span of the image of \( F \), denoted by \( \text{span}(\text{Im}(F)) \). Two points \( x, y \in \mathbb{R}_0^n \) are compatible if \( y - x \in \text{span}(\text{Im}(F)) \). The sets \( S, S' \subseteq \mathbb{R}_0^n \) are compatible if there are \( x \in S \) and \( x' \in S' \) such that \( x \) and \( x' \) are compatible. A compatibility class \( S \) is a nonempty subset of \( \mathbb{R}_0^n \) such that \( x, y \in S \) if and only if \( y - x \in \text{span}(\text{Im}(F)) \).

**Definition 2.2.** \( \mathcal{D} \) is a dynamic ACR system if there is an \( i \in \{1, \ldots, n\} \) with \( F_i \neq 0 \) and a positive \( a_i^* \in \mathbb{R}_0 \) such that for any \( x(0) \in \mathbb{R}_0^n \) that is compatible with \( \{ x \in \mathbb{R}_0^n \mid x_i = a_i^* \} \), a unique solution to \( \dot{x} = F(x, t) \) exists for all time and \( x_i(t) \xrightarrow{t \to \infty} a_i^* \). Any such \( x_i \) and \( a_i^* \) is a dynamic ACR variable and its dynamic ACR value, respectively.

A slightly more general definition that allows for finite-time blowup is provided in \([1]\).

We discuss a normal form for dynamic ACR. Suppose that \( x \in \mathbb{R}^n \) and for some \( 1 \leq i \leq n \), \( x_i \) satisfies

\[
\frac{dx_i}{dt} = \underbrace{f(x(t), t)}_{\text{fuel}} \cdot \underbrace{(x_i^* - x_i(t))}_{\text{engine}} + \underbrace{g(x(t), t)}_{\text{load}}
\]

then under some reasonable conditions on “fuel” \( f(x(t), t) \) and “load” \( g(x(t), t) \), the variable \( x_i \) will have dynamic ACR with the value \( x_i^* \). An example of sufficient conditions is \( g \equiv 0, f > 0 \), and \( \int_0^\infty f(x(t), t) \, dt = \infty \). We state the precise result in Section 2.3.

2.1 Mass action systems

An example of a reaction is \( A + B \rightarrow 2C \), which is a schematic representation of the process where a molecule of species \( A \) and a molecule of species \( B \) react with one another and result in two molecules
of a species $C$. The abstract linear combination of species $A + B$ that appears on the left of the reaction arrow is called the reactant complex while $2C$ is called the product complex of the reaction $A + B \rightarrow 2C$. We assume that for any reaction the product complex is different from the reactant complex. A reaction network is a nonempty, finite set of species and a nonempty, finite set of reactions such that every species appears in at least one complex. We will use mass action kinetics for the rate of reactions. In mass action kinetics, each reaction occurs at a rate proportional to the product of the concentrations of species appearing in the reactant complex. We conventionally use lower case letters $a, b, c$ to denote the species concentrations of the corresponding species $A, B, C$, respectively. Under mass action kinetics, the reaction $A + B \rightarrow 2C$ occurs at rate $k_{ab}$ where $k$ is the reaction rate constant, conventionally placed near the reaction arrow, as follows: $A + B \xrightarrow{k} 2C$.

Consider the reaction network $\{A + B \xrightarrow{k_1} 2B, \quad 2C \xrightarrow{k_2} 2A\}$. Application of mass action kinetics results in the following dynamical system, called mass action system, that describes the evolution of the species concentrations.

$$\begin{align*}
\dot{a} &= -k_1 ab + 2k_2 c^2 \\
\dot{b} &= -k_1 ab \\
\dot{c} &= 2k_1 ab - 2k_2 c^2
\end{align*}$$

For further details on reaction networks and mass action systems, see for instance [17, 18]. We use standard notation and terminology of dynamical systems, such as steady states, stability, basin of attraction etc., see for instance [19, 20].

### 2.2 Examples of dynamic ACR normal form in mass action systems

**Example 1.** The simplest example of a mass action system with normal form ACR is the reaction network $0 \xleftrightarrow{k} X$ and its associated ODE

$$\frac{dx}{dt} = k'(k/k' - x).$$

It is straightforward to show that $x$ has dynamic ACR with value $k/k'$.

**Example 2.** Biologically interesting cases require a reactant complex with more than one species (so that a ‘reaction’ can occur) and some positive mass conservation law involving all species. The following network is the simplest that satisfies these requirements of species interaction and mass conservation, and therefore will serve as an archetypal model of normal form dynamic ACR in this work.

$$A + B \xrightarrow{k_1} 2B, \quad B \xrightarrow{k_2} A.$$  \hspace{1cm} (2.2)

The positive mass conservation law $a + b = \text{const}$ is apparent from the mass action ODE system:

$$\begin{align*}
\dot{a} &= k_1 b(k_2/k_1 - a), \\
\dot{b} &= -k_1 b(k_2/k_1 - a).
\end{align*}$$  \hspace{1cm} (2.3)

The ODE for $a$ has normal form and it is known (see for instance [1]) that $a(t) \xrightarrow{t\to\infty} k_2/k_1$ for any initial value $(a(0), b(0)) = (a_0, b_0)$ that satisfies $a_0 + b_0 \geq k_2/k_1$.

**Example 3.** In bacterial two-component signaling systems, the circuit mechanism for robust signal transduction from the cell environment to its interior involves a bifunctional component, $a$
mechanism that is found in thousands of biological systems [5]. One such system is the E. coli IDHKP-IDH glyoxylate bypass regulation system whose core ACR module is

\[
X + E \xrightarrow{k_1} C_1 \xrightarrow{k_3} Y + E \\
Y + C_1 \xrightarrow{k_4} C_2 \xrightarrow{k_6} X + C_1.
\] (2.4)

It is known that (2.4) has static ACR in \(Y \) [3]. Moreover, we plan to show in future work that it has dynamic ACR in \(Y \) as well. The mass action ODE equation for the concentration of \(Y \) can be written in normal form, using the fact that the static ACR value of \(y \) is \(k_3/k_4(1 + k_5/k_6) \), as follows.

\[
\dot{y} = k_3c_1 - k_4c_1y + k_5c_2 \\
= k_3c_1 - k_4c_1y + k_5c_1 + \frac{k_5}{k_6}(k_6c_2 - k_3c_1) \\
= k_4c_1\left(\frac{k_3}{k_4}\left(1 + \frac{k_5}{k_6}\right) - y\right) + \frac{k_5}{k_6}(k_6c_2 - k_3c_1).
\]

The load is not identically zero in this case. We will prove in future work that \(y \) has dynamic ACR with ACR value \(k^* = \frac{k_3}{k_4}\left(1 + \frac{k_5}{k_6}\right) \). As shown in Theorem 2.5, a sufficient condition for dynamic ACR is that for any positive initial value \((k_6c_2(t) - k_3c_1(t)) \) that either ensure or prevent dynamic ACR.

Converting to normal form may require a priori dynamical insights, ingenious choices of coordinate transforms, substitutions, approximations and quasi steady state (QSS)-type arguments. This subject will be discussed in depth in future work. In the present work, our goal is to discuss conditions on the “fuel” \(f(x(t), t) \) and “load” \(g(x(t), t) \) that either ensure or prevent dynamic ACR.

2.3 Convergence results for normal form dynamic ACR

**Theorem 2.3** (Zero load). Consider the dynamical system \(\dot{x} = F(x, t) \) with continuously differentiable \(F : \mathbb{R}_{\geq 0}^n \times \mathbb{R}_{\geq 0} \to \mathbb{R}^n \) and for which \(\mathbb{R}_{\geq 0}^n \) is forward invariant. Suppose there is an \(x_i^* \in \mathbb{R}_{> 0} \) such that \(F_i(x(t), t)|_{x \in \mathbb{R}_{> 0}^n} = 0 \) if and only if \(x_i = x_i^* \). The following hold for every solution \((x(t))_{t \geq 0} \) of \(\dot{x} = F(x, t) \).

1. \(x_i^* - x_i(t) \) has the same sign as \(x_i^* - x_i(0) \) for all \(t \geq 0 \).

2. Suppose \(x_i(0) \neq x_i^* \). Then \(\frac{F_i(x(t), t)}{x_i^* - x_i(t)} \) has the same sign as \(\frac{F_i(x(0), 0)}{x_i^* - x_i(0)} \) for all \(t \geq 0 \).

3. Suppose \(x_i(0) \neq x_i^* \).

   (a) If \(\frac{F_i(x(0), 0)}{x_i^* - x_i(0)} > 0 \) then \(|x_i(t) - x_i^*| \) is strictly decreasing on \([0, \infty) \) and

   \[
   |x_i(\infty) - x_i^*| = |x_i(0) - x_i^*| \exp\left(-\int_0^{\infty} \frac{F_i(x(s), s)}{x_i^* - x_i(s)} ds\right).
   \]

   (b) If \(\frac{F_i(x(0), 0)}{x_i^* - x_i(0)} < 0 \) then \(|x_i(t) - x_i^*| \) is strictly increasing on \([0, \infty) \).
4. Suppose \( x_i(0) \neq x_i^* \). Then \( x_i(t) \xrightarrow{t \to \infty} x_i^* \) if and only if

\[
\int_0^\infty \frac{F_i(x(t), t)}{x_i^* - x_i(t)} \, dt = \infty.
\]

Proof. If \( x_i(0) = x_i^* \) then \( \dot{x}_i|_{t=0} = F_i(x(0), 0) = 0 \) and so \( x_i(t) = x_i^* \) for all \( t \geq 0 \). If there is a \( t > 0 \) such that \( x_i(t) - x_i^* \) and \( x_i(0) - x_i^* \) have different signs then by continuity of \( x_i(t) \), there must be a \( t' \in (0, t) \) such that \( x_i(t') = x_i^* \). But then \( x_i(t) = x_i^* \) for all \( t \in \mathbb{R} \), which is a contradiction.

If \( x_i(0) \neq x_i^* \) then by the previous part \( \frac{F_i(x(t), t)}{x_i^* - x_i(t)} \) is defined for all time \( t \geq 0 \). Since \( F_i(x, t) \neq 0 \) for \( x \neq x_i^* \), the second result follows. Since \( x_i(t) \neq x_i^* \) for all \( t \geq 0 \), we can divide by \( x_i^* - x_i \) and integrate to get

\[
\frac{dx_i}{x_i^* - x_i} = \frac{F_i(x(t), t)}{x_i^* - x_i(t)} \, dt \implies \frac{x_i^* - x_i(t)}{x_i^* - x_i(0)} = \exp \left( -\int_0^t \frac{F_i(x(s), s)}{x_i^* - x_i(s)} \, ds \right).
\]

By the previous result, the integrand has the same sign as \( \frac{F_i(x(0), 0)}{x_i^* - x_i(0)} \) for all positive time, and so result 3 follows. Finally, result 4 follows from taking \( \lim_{t \to \infty} \) on both sides. \( \square \)

**Example 4.** Consider the mass action system \((2.3)\), \( \dot{a} = k_1 b (k-a) \), \( \dot{b} = -k_1 b (k-a) \). The variable \( a \) has normal form for dynamic ACR with zero load and fuel \( k_1 b > 0 \) for every \((a, b) \in \mathbb{R}^2_{>0} \).

It is clear that \( a(0) = k \) if and only if \( \dot{a}|_{t \geq 0} = 0 \). So assume that \( a(0) \neq k \). The mass action system with initial value \((a(0), b(0)) = (a_0, b_0) \in \mathbb{R}^2_{>0} \) has the explicit solution (see Section 3.2) given by

\[
b(t) = \begin{cases} 
\frac{a_0 + b_0 - k}{1 + \left( \frac{a_0 - k}{b_0} \right) e^{-(a_0 + b_0 - k)t}} & \text{if } a_0 + b_0 \neq k, \\
\frac{k - a}{1 + (k - a_0)t} & \text{if } a_0 + b_0 = k.
\end{cases}
\]

and \( a(t) = a_0 + b_0 - b(t) \). For \((a_0, b_0) \in \mathbb{R}^2_{>0} \), it is known that \( a(t) \xrightarrow{t \to \infty} k \) if and only if \( a_0 + b_0 \geq k \). We now argue that \( \int_0^\infty b(t) \, dt = \infty \) if and only if \( a_0 + b_0 \geq k \) and \( a_0 \neq k \). Indeed, for any \( a_0 < k \),

\[
\int_0^\infty \frac{k - a_0}{1 + (k - a_0)t} \, dt = \infty.
\]

Moreover

\[
\lim_{t \to \infty} \frac{a_0 + b_0 - k}{1 + \left( \frac{a_0 - k}{b_0} \right) e^{-(a_0 + b_0 - k)t}} = \begin{cases} 
0 & \text{if } a_0 + b_0 < k, \\
0 & \text{if } a_0 + b_0 > k,
\end{cases}
\]

implies that

\[
\int_0^\infty \frac{a_0 + b_0 - k}{1 + \left( \frac{a_0 - k}{b_0} \right) e^{-(a_0 + b_0 - k)t}} \, dt = \begin{cases} 
\infty & \text{if } a_0 + b_0 > k, \\
< \infty & \text{if } a_0 + b_0 < k,
\end{cases}
\]

because in the first case \((a_0 + b_0 > k)\) the integrand does not go to zero, the integral is clearly divergent and in the latter case \((a_0 + b_0 < k)\) the integrand is \( \approx \exp\{(a_0 + b_0 - k)t\} \), so the integral is convergent.

This shows that \( a \xrightarrow{t \to \infty} k \) if and only if either \( a(0) = k \) or \( \int_0^\infty k_1 b(t) \, dt = \infty \). \( \triangle \)
Corollary 2.4. Suppose the hypotheses of Theorem 2.3 hold and \( x_i(0) \neq x_i^* \). If
\[
\liminf_{t \to \infty} \frac{tF_i(x(t), t)}{x_i^* - x_i(t)} \in (0, \infty],
\]

then \( x_i(t) \xrightarrow{t \to \infty} x_i^* \).

Proof. By (2.7), there is a \( \delta > 0 \) and a \( t_0 \geq 0 \) such that \( \frac{tF_i(x(t), t)}{x_i^* - x_i(t)} > \delta \) for all \( t \geq t_0 \). Then
\[
\int_0^\infty \frac{F_i(x(t), t)}{x_i^* - x_i} \, dt > \int_0^\infty \frac{F_i(x(t), t)}{x_i^* - x_i} \, dt = \int_{t_0}^\infty \frac{1}{t} \frac{tF_i(x(t), t)}{x_i^* - x_i} \, dt > \delta \int_{t_0}^\infty \frac{1}{t} \, dt = \infty,
\]
and so by Theorem 2.3, \( x_i \to x_i^* \). \( \square \)

Example 5. The condition (2.7) is sufficient but not necessary for \( x_i \to x_i^* \). Consider the mass action system of the following reaction network:
\[
2X_1 \xrightarrow{k_1} X_1, \quad 2X_2 \xrightarrow{k_2} X_2, \\
X_1 + X_2 \xrightarrow{k_5} X_2, \quad X_0 + X_1 \xrightarrow{k_4} X_1, \tag{2.8}
\]
where the rate constants are the same for the reactions \( 2X_2 \to X_2 \) and \( X_1 + X_2 \to X_2 \) (\( X_2 \) degrades both \( X_1 \) and \( X_2 \) at the same rate). The mass action ODEs are
\[
\begin{align*}
\dot{x}_2 &= -k_2 x_2^2, \\
\dot{x}_1 &= -k_1 x_1^2 - k_2 x_1 x_2, \\
\dot{x}_0 &= k_5 x_1 \left( \frac{k_4}{k_5} - x_0 \right). \tag{2.9}
\end{align*}
\]

It is simple to check that given an arbitrary positive initial value \( (x_0(0), x_1(0), x_2(0)) = (b_0, b_1, b_2) \in \mathbb{R}_0^3 \), the unique solution satisfies
\[
\begin{align*}
x_2(t) &= \frac{b_2}{1 + k_2 b_2 t}, \\
x_1(t) &= \frac{b_1 b_2 k_2}{(1 + b_2 k_2)(b_2 k_2 + b_1 k_1 \log(1 + b_2 k_2))} \approx \frac{1}{k_1 t \log(1 + b_2 k_2)}
\end{align*}
\]
and so \( \int_{t_0}^\infty x_1(t) \, dt = \infty \) for any \( t_0 > 0 \) which implies that \( x_0 \to k_4/k_5 \) by Theorem 2.3. However, \( \liminf_{t_\to \infty} (tx_1(t)) = 0 \), so Corollary 2.4 does not apply. \( \triangle \)

When the load \( g \) is nonzero, the fuel \( f \) must overpower the load \( g \) for convergence of \( x_i \) to \( x_i^* \).

Theorem 2.5. Consider the dynamical system \( \dot{x} = F(x, t) \) with \( F : \mathbb{R}_{\geq 0}^n \times \mathbb{R}_{\geq 0} \to \mathbb{R}^n \) and for which \( \mathbb{R}_{\geq 0}^n \) is forward invariant. Suppose that for some \( i \in \{1, \ldots, n\} \) we have
\[
F_i(x, t) = f(x, t) \cdot (x_i^* - x_i) + g(x, t),
\]
with \( f(x, t) > 0 \) in \( \mathbb{R}_{\geq 0}^n \times \mathbb{R}_{\geq 0} \), and \( g \neq 0 \). Let \( (x(t))_{t \geq 0} \) be a solution of \( \dot{x} = F(x, t) \) such that
\[
\int_0^\infty f(x(t), t) \, dt = \infty,
\]
and such that the limit \( \alpha := \lim_{t \to \infty} \frac{g(x(t), t)}{f(x(t), t)} \) exists, with \( \alpha > -x_i^* \). Then we have \( x_i(t) \xrightarrow{t \to \infty} x_i^* + \alpha \).
Proof. Note that the equation \( \frac{dx_i}{dt} = F_i(x, t) \) can be rewritten as

\[
\frac{dx_i}{dt} = f(x, t) \left( x_i^* + \frac{g(x, t)}{f(x, t)} - x_i \right).
\]  

(2.10)

Then, if we denote \( \tilde{x}_i^* = x_i^* + \alpha \) and \( \tilde{g} = g/f - \alpha \), we can reduce our problem to showing that if \( x_i(t) \) satisfies the equation

\[
\frac{dx_i}{dt} = f(x, t) \left( \tilde{x}_i^* - x_i + \tilde{g}(x, t) \right),
\]  

(2.11)

and \( \lim_{t \to \infty} \tilde{g}(x(t), t) = 0 \), then \( x_i(t) \xrightarrow{t \to \infty} \tilde{x}_i^* \).

For any fixed \( \varepsilon \in (0, \tilde{x}_i^*) \) we will now show that there exists some \( T_0 > 0 \) such that \( x_i(t) \in (\tilde{x}_i^* - \varepsilon, \tilde{x}_i^* + \varepsilon) \) for all \( t > T_0 \). For this, let us first choose some \( T_1 > 0 \) such that \( \tilde{g}(x(t), t) \in (-\frac{\varepsilon}{2}, \frac{\varepsilon}{2}) \) for all \( t > T_1 \). Note that this implies that the interval \( (\tilde{x}_i^* - \varepsilon, \tilde{x}_i^* + \varepsilon) \) is an invariant set of (2.10) for \( t > T_1 \). Therefore, if \( x_i(T_1) \in (\tilde{x}_i^* - \varepsilon, \tilde{x}_i^* + \varepsilon) \), we can choose \( T_0 = T_1 \). Assume now that \( x_i(T_1) \notin (\tilde{x}_i^* - \varepsilon, \tilde{x}_i^* + \varepsilon) \), and for example \( x_i(T_1) > \tilde{x}_i^* + \varepsilon \) (the case where \( x_i(T_1) \leq \tilde{x}_i^* - \varepsilon \) is analogous).

Let us assume that the inequality \( x_i(t) \geq \tilde{x}_i^* + \varepsilon \) holds for all \( t > T_1 \); we will show that this leads to a contradiction. Indeed, for any such \( t \) we have

\[
\tilde{x}_i^* - x_i + \tilde{g}(x, t) < -\frac{\varepsilon}{2},
\]

which implies that

\[
\frac{dx_i}{dt} \leq -\frac{\varepsilon}{2} f(x, t),
\]  

(2.12)

for all \( t > T_1 \); but this, together with the hypothesis that \( \int_0^\infty f(x(t), t) dt = \infty \), would imply that \( \lim_{t \to \infty} x_i(t) = -\infty \), which contradicts our assumption that for all \( t > T_0 \) we have \( x_i(t) \geq \tilde{x}_i^* + \varepsilon \).

Therefore we obtain the desired conclusion that \( x_i(t) \) will enter the interval \( (\tilde{x}_i^* - \varepsilon, \tilde{x}_i^* + \varepsilon) \) in some finite time \( T_0 \), and will remain inside it for all \( t > T_0 \). \( \square \)

3 Archetypal ACR model in a chemostat

In this section, we discuss the effect of the load resulting from inflows and outflows on the archetypal dynamic ACR network (2.2). Inflows and outflows are common in biological systems since such systems are open and constantly interacting with the environment. Moreover, chemostat is a standard laboratory setup that models inflows and outflows. We depict the inflows and outflows as reactions, and we fix the notation as shown below:

\[
\begin{align*}
0 & \xrightarrow{g_a} A, & 0 & \xrightarrow{g_b} B, \\
\ell_a & \quad \ell_b \\
A + B & \xrightarrow{k_1} 2B, & B & \xrightarrow{k_2} A.
\end{align*}
\]  

(3.1)
The gain rate constants $g_a, g_b$ are allowed to be zero if there is no corresponding inflow, similarly for the loss rate constants $\ell_a, \ell_b$. The mass-action ODE system is:

$$\begin{align*}
\dot{a} &= k_1 b (k^* - a) + g_a - \ell_a a \\
\dot{b} &= -k_1 b (k^* - a) + g_b - \ell_b b,
\end{align*}$$

(3.2)

where $k_1, k^* := k_2/k_1 > 0$ and $g_a, g_b, \ell_a, \ell_b \geq 0$.

It is known that the variable $a$ has static and dynamic ACR with ACR value $k^*$ when all flow rate constants $g_a, g_b, \ell_a, \ell_b$ are zero. Comparing the equation for $a$ in (3.2) with the normal form ACR equation (2.1), $k_1 b$ is the fuel, $k^* - a$ is the engine and $g_a - \ell_a a$ is the load. Our goal in the rest of the paper is to prove the following theorem.

**Theorem 3.1.** Consider (3.2) with arbitrary flow constants $g_a, g_b, \ell_a, \ell_b \geq 0$ and arbitrary initial value $(a(0), b(0)) = (a_0, b_0) \in \mathbb{R}_{\geq 0}^2$. Then the following are equivalent:

1. $a(t) \xrightarrow{t \to \infty} k^*$.
2. $\int_0^\infty b(t) dt = \infty$ and $\lim_{t \to \infty} \frac{g_a - \ell_a a(t)}{b(t)} = 0$.
3. $b_0 + g_b > 0$ and one of the following hold:
   (a) $g_a = g_b = \ell_a = \ell_b = 0$ and $a_0 + b_0 \geq k^*$, or
   (b) $\ell_b = 0$ and $g_a + g_b \geq \ell_a k^*$, or
   (c) $\ell_b > 0$, $g_b > 0$ and $\ell_a = g_a = 0$, or
   (d) $\ell_b > 0$, $\ell_a > 0$, $g_a > 0$ and $g_a + g_b = \ell_a k^*$.

The rest of the paper is a proof of this theorem and a study of related dynamical properties of the system. We note that 2. $\implies$ 1. by Theorem 2.5.

### 3.1 Isolated system

The isolated system $(g_a, g_b, \ell_a, \ell_b = 0)$ was originally presented as an example of a network with static ACR [3], and was shown to also have the property of dynamic ACR in [1]. In fact, for all choices of mass action rate constants $k_1$ and $k_2$, $A$ is a dynamic ACR species (see [2] for definition) with ACR value $k^* = k_2/k_1$. Every initial condition $(a(0), b(0)) \in \{(a, b) : a \geq 0, b > 0, a + b \geq k^*\}$ results in a trajectory such that $a(t) \xrightarrow{t \to \infty} k^*$. See Figure 1 for some representative solutions.

### 3.2 An away impulse speeds up convergence!

We highlight the importance of the fuel $f$. Consider two initial conditions with the same $b(0)$. Clearly, for the higher initial $a(0)$, the trajectory has further to travel to converge to the ACR value. For the two cases, the initial fuel $b(0)$ is the same, however speed increases as $b(t)$ increases, and moreover the speed increases faster for the initial value that is further away and has more ground to cover. We consider the non-trivial question of convergence time for initial values that are different distances from the ACR value.

It seems plausible that adding to the initial concentration of species $A$ will result in longer convergence time to the ACR value. However, the actual result is that convergence to ACR value is even faster as the initial point moves further away. In fact, the time to converge to a neighborhood
Figure 1: (Left): A few representative phase plane trajectories of (3.2) with $k_1 = 1, k_2 = 1$. The green vertical line is the set of positive steady states $a = k_2/k_1$, all of which are stable. Any trajectory with initial condition in the cyan triangle converges to the $b = 0$ boundary, while any trajectory with initial condition outside the triangle converges to the green line. (Right): Concentrations $a(t)$ and $b(t)$ as functions of time $t$ for the initial condition $(a(0), b(0)) = (2.2, 0.1)$.

Figure 2: Effects of different initial values of $a$. Initial $b(0) = 1$ for all trajectories.

of the ACR value goes to zero as the initial distance from the ACR value goes to infinity. We show this by explicitly calculating the time to convergence.

Using the conservation law $a(t) + b(t) = a(0) + b(0) = T$ to eliminate $b(t)$ from the mass action ODE system $\dot{a} = -k_1a + k_2b$, $\dot{b} = k_1ab - k_2b$, we write $\dot{a} = -k_1(a - k)(T - a)$ where $k := k_2/k_1$. This ODE has can be solved exactly using an elementary calculation

$$a(t) = \begin{cases} 
  k + \frac{(T - k)m e^{-(T-k)t}}{1 + \frac{m e^{-(T-k)t}}{k - a_0}} & \text{if } T \neq k, \\
  k - \frac{a_0}{1 + (k - a_0)t} & \text{if } T = k.
\end{cases}$$

where $m := \frac{a_0 - k}{T - a_0}$. Assume that $T > k$, so that there is a positive steady state and let $\tilde{T} = T - k$, $\delta = T - a_0 = \tilde{T} + k - a_0$ and let $t_\varepsilon > 0$ be such that $a(t_\varepsilon) = k + \varepsilon$ for some $\varepsilon > 0$. Then
\[ a(t) = k + \frac{\tilde{T}me^{-\tilde{T}t}}{1 + me^{-\tilde{T}t}}, \text{ with } m = (\tilde{T} - \delta)/\delta \text{ and } \varepsilon = \frac{\tilde{T}me^{-\tilde{T}t}}{1 + me^{-\tilde{T}t}}, \] which can be solved for \( t_\varepsilon \) to give
\[
t_\varepsilon = \frac{1}{\tilde{T}} \left[ \ln \left( \frac{\tilde{T}}{\varepsilon} - 1 \right) + \ln \left( \frac{\tilde{T}}{\delta} - 1 \right) \right].
\] (3.3)

Note that \( \lim_{\tilde{T} \to \infty} t_\varepsilon = 0 \), so that the time to convergence can be made arbitrarily small by adding more initial \( A \)! In fact, letting \( \delta = \varepsilon \), the convergence time is
\[
t_\varepsilon = \frac{2}{\tilde{T}} \ln \left( \frac{\tilde{T}}{\varepsilon} - 1 \right) \approx \frac{2 \ln \tilde{T}}{\tilde{T}}.
\]

### 3.3 Open system: inflows only

We consider the case \( g_a + g_b > 0 \) and \( \ell_a = \ell_b = 0 \) in (3.2). Figure 3, which depicts the vector field

![Figure 3: Vector field for (3.2) with \( g_a = 0 \), \( g_b = 10 \), \( k_1 = 1 \), \( k_2 = 3 \) (left), and for \( g_a = 5 \), \( g_b = 5 \), \( k_1 = 1 \), \( k_2 = 3 \) (right). The green vertical line is \( a = k_2/k_1 = 3 \). On the left, the green line is also the \( a \)-nullcline. On the right, the magenta curve \( R_0 \) defined by \( h(b) = \left( g_a/b + k_2 \right)/k_1 \) is the \( a \)-nullcline. This curve partitions the region to the right of \( a = k_2/k_1 \) into \( R_+ \), \( R_0 \), and \( R_- \). For two cases: (i) \( g_a = 0 \) and (ii) \( g_a > 0 \) along with the regions \( R_+ \), \( R_0 \), and \( R_- \), may be a useful guide to the reader while following the proof of Theorem 3.2.]

**Theorem 3.2.** Consider (3.2) with \( g_a + g_b > 0 \). For any initial value \((a(0), b(0)) \in \mathbb{R}_\geq 0^2\), (3.2) has a unique solution for all time \( t \geq 0 \), and the following holds:

\[
a(t) \xrightarrow{t \to \infty} \infty, \quad b(t) \equiv 0 \quad \text{if} \quad b(0) + g_b = 0,
\]
\[
a(t) \xrightarrow{t \to \infty} k^*, \quad b(t) \xrightarrow{t \to \infty} \infty \quad \text{if} \quad b(0) + g_b > 0.
\]

**Proof.** Clearly, \( a(t) + b(t) = a(0) + b(0) + (g_a + g_b)t \xrightarrow{t \to \infty} \infty \). If \( b(0) + g_b = 0 \), the \( a \)-axis is invariant, and \( a(t) \to \infty \). Otherwise, \( \mathbb{R}_\geq 0^2 \) is absorbing for all initial values.

First consider the case \( g_a = 0 \) and \( g_b > 0 \). Then, \( \dot{a} < 0 \) on \( \{a > k^*\} \), \( \dot{a} > 0 \) on \( \{a < k^*\} \) and \( \dot{a} = 0 \) on \( \{a = k^*\} \). Thus each region is invariant. Since \( \dot{b} \) is linearly bounded, i.e. \( \left| \dot{b}(t) \right| \leq b(t)k_1a(t) - k_2 \leq b(t)k_1a(0) - k_2 \leq g_b \), \( b(t) \) is defined for all positive time, and so is \( a(t) \).
To show that \( a(t) \xrightarrow{t \to \infty} k^* \), we only need to show that \( \dot{a} \) is bounded away from zero outside a strip of arbitrarily small width \( \varepsilon > 0 \) around \( a = k^* \). In order to argue this, we first show that the region \( \{(a, b) \in \mathbb{R}^2 \mid b > M\} \) is absorbing for any \( M > 0 \). Indeed, in \( \{a \geq k^*\} \), this follows from \( \dot{b} = g_b > 0 \). Now, \( \dot{a} + \dot{b} = g_a > 0 \) implies that \( a(t) + b(t) > g_b t \) for any \( (a(0), b(0)) \in \mathbb{R}^2 \). It follows that \( b(t) > g_b t - a(t) > g_b t - k^* \) in the region \( \{0 \leq a < k^*\} \), and so for all \( t > (k^* + M)/g_b \), \( b(t) > M \in \{0 \leq a < k^*\} \). Finally, for \( b > M > 0 \), \( |\dot{a}(t)| = |b(k_1 a - k_2)| > M |k_1 a - k_2| > M k_1 \varepsilon \) for any \( (a, b) \) such that \( |a - k^*| > \varepsilon \). Thus we have shown that \( a(t) \xrightarrow{t \to \infty} k^* \) and \( \dot{a} \to 0 \).

Now suppose that \( g_a > 0 \). We argue that all trajectories are absorbed in \( R_+ := \{(a, b) : a > h(b)\} \) where \( h(b) = (g_a/b + k_2)/k_1 \) (see Figure 3). The curve \( R_0 := \{a = h(b)\} \) is the \( a \)-nullcline. Indeed, \( \dot{a} \geq g_a > 0 \) on \( \{a \leq k^*\} \) implies that every trajectory leaves \( \{a \leq k^*\} \) in finite time. Consider an initial value \((a_0, b_0)\) in \( R_- := \{(a, b) : k^* < a < h(b)\} \). Consider the bounded region formed by intersection of \( R_0 = \{(a, b) : a = h(b)\} \), \( a = a_0 \), and \( b = b_0 \). Since the vector field in this bounded region is non-vanishing and \( \dot{a}, \dot{b} > 0 \), it follows that the trajectory originating at \((a_0, b_0)\) must leave the bounded region in finite time by crossing \( R_0 \). Now, arguing similarly to the case of \( g_a = 0 \), we show that \( \dot{a} \) is bounded away from zero outside a strip of arbitrary positive width \( \varepsilon \) around \( R_0 \). Thus, any trajectory with initial condition in \( R_+ \) approaches \( R_0 \) from the right and furthermore \( b(t) \xrightarrow{t \to \infty} \infty \). Finally, \( \lim_{t \to \infty} a(t) = \lim_{t \to \infty} b(t) = \lim_{b \to \infty} h(b) = k^* \).

3.4 Open system: outflows only

Consider (3.2) with at least one of \( A \) and \( B \) in outflow and no inflow, \( g_a = g_b = 0, \ell_a + \ell_b > 0 \). We argue for each case that there is no dynamic ACR.

(i) For the case \( \ell_a > 0, \ell_b > 0 \), it is clear from \( \dot{a} + \dot{b} = -\ell_a a - \ell_b b \) that \( a + b \) is monotonically decreasing everywhere in \( \mathbb{R}^2 \setminus \{0\} \) and so all trajectories converge to the origin.

(ii) For the case \( \ell_a > 0, \ell_b = 0 \), the only steady state is the origin, \( a(t) + b(t) \) decreases monotonically in \( \{a > 0\} \), while \( \{a = 0, b > 0\} \) is a repeller, which means that all trajectories converge to the origin.

(iii) Finally, for the case \( \ell_a = 0, \ell_b > 0 \), \( a(t) + b(t) \) decreases monotonically in \( \{b > 0\} \), while
{b = 0} is made up only of steady states. So, all trajectories converge to \( \{b = 0\} \), the limit point depends on the initial value.

### 3.5 Both species in outflow and some inflows present

Consider (3.2) with \( \ell_a > 0, \ell_b > 0, g_a + g_b > 0 \). The steady states are solutions of

\[
\ell_b b + \ell_a a = g_b + g_a, \quad b = \frac{g_b}{k_2 + \ell_b - \ell_a a}
\]

The first equation represents a line segment in the positive orthant with a negative slope and intercept \( b = (g_a + g_b)/\ell_b \). The right side of the second equation is a monotone increasing function of \( a \) with domain \([0, (k_2 + \ell_b)/k_1)\) and range \([g_b/(k_2 + \ell_b), \infty)\). For all allowed values of flow rate constants, \((g_a + g_b)/\ell_b > g_b/(k_2 + \ell_b)\), and so there is a precisely one nonnegative steady state \((a^*, b^*)\) which is positive. Moreover, the positive steady state \((a^*, b^*)\) is locally stable since the determinant and trace of the Jacobian at \((a^*, b^*)\) are \(k_1b^*\ell_b + g_b/b^* > 0\) and \(-g_b/b^* - k_1b^* - \ell_a < 0\), respectively. Note that the coordinates of the unique positive steady state depend on all the flow rate constants. In fact, \(a^* = k_2/k_1\) if and only if \(k_2/k_1 = g_a/\ell_a\). Indeed, let \(\delta = k_2/k_1 - g_a/\ell_a\), then the result follows from:

\[
\dot{a} = (k_1 b + \ell_a) \left( \frac{k_2}{k_1} - a \right) - \ell_a \delta.
\]

We now argue that the basin of attraction of the positive steady state \((a^*, b^*)\) is \(\mathbb{R}_{\geq 0}^2\). For a two-dimensional system such as this, it suffices to show: (i) persistence (which rules out going to infinity or boundary), (ii) absence of periodic orbits, and (iii) existence of a unique asymptotically stable steady state (which rules out homoclinic orbits, for instance). We have already shown (iii). For (ii), we use the Bendixson-Dulac theorem \[19\] which states that given a planar autonomous system \(\dot{a} = f(a, b), \dot{b} = g(a, b)\), if there is a \(C^1\) function \(\varphi(a, b)\) (called Dulac function) such that

\[
\frac{\partial (\varphi f)}{\partial a} + \frac{\partial (\varphi g)}{\partial b}
\]

has the same sign almost everywhere in a simply connected region of \(\mathbb{R}^2\), then there are no non-constant periodic solutions in that region. Define \(\varphi(a, b) = (ab)^{-1}\). Then

\[
\frac{\partial (\varphi f)}{\partial a} + \frac{\partial (\varphi g)}{\partial b} = \frac{k_2}{a^2} - \frac{g_a}{a^2 b} - \frac{g_b}{ab^2},
\]

which is clearly negative everywhere in \(\mathbb{R}_{\geq 0}^2\) (and therefore, negative almost everywhere in \(\mathbb{R}_{\geq 0}^2\)) for all possible choices of inflow and outflow rates. Therefore, by the Bendixson-Dulac theorem, bounded oscillations (non-constant periodic solutions) are impossible. We note that we have not ruled out the possibility of damped oscillations or unbounded oscillations. In fact, for the case when only \(B\) is in outflow and only \(A\) has an inflow, we do see damped oscillations, by which we mean a positive steady state that is a stable spiral, in the usual sense of continuous dynamical systems, see Figure 6.

Finally, to show persistence, given an arbitrary initial value \((a_0, b_0) \in \mathbb{R}_{\geq 0}^2\), we construct a trapping region (a compact region that is forward-invariant) of the shape shown in Figure 5. More precisely, the claim is that there are \(\delta, M, N > 0\) such that the polygon \(P_{M,N}\) formed by intersection of (i) \(a = \delta\), (ii) \(b = \delta\), (iii) \(b = M\), (iv) \(a = N\), and (v) line of slope \(-1\) containing the intersection point of \(b = M\) and the \(b\)-nullcline has the following properties: (a) \((a(0), b(0)) \in P_{M,N}\), (b)
Figure 5

\[(a^*, b^*) \in \mathcal{P}_{M,N}, \text{ and } (c) \mathcal{P}_{M,N} \text{ is a trapping region. Indeed, it is clear that the vector field points towards the interior on the horizontal and vertical edges of } \mathcal{P}_{M,N}. \text{ For the line of slope } -1, \text{ we calculate}

\[
\frac{db}{da} = \frac{\dot{b}}{\dot{a}} = \frac{k_1ab - k_2b - \ell_b b + g_b}{-k_1ab + k_2b - \ell_a a + g_a} = \frac{k_1 - k_2/a - \ell_b/a + g_b/ab}{-k_1 + k_2/a - \ell_a/a + g_a/ab}
\]

\[
\approx \frac{k_1 - k_2/a - \ell_b/a}{-k_1 + k_2/a} = -1 + \frac{\ell_b/a}{k_1 - k_2/a} > -1,
\]

where, in the approximation step, we used that \(b\) is large which can be ensured by choosing \(M\) sufficiently large, and in the last step, we used that the \(b\)-nullcline is to the right of the \(a\)-nullcline, so that in particular \(a > k_2/k_1\). This shows that \(\mathcal{P}_{M,N}\) is the desired trapping region and hence completes the proof that \((a^*, b^*)\) is a global attractor.

3.6 Only \(B\) in outflow and some inflows

Consider (3.2) with \(\ell_a = 0, \ell_b > 0, g_a + g_b > 0\). The mass-action ODE system is:

\[
\dot{a} = -k_1ab + k_2b + g_a
\]

\[
\dot{b} = k_1ab - k_2b + g_b - \ell_b b = -\dot{a} + g_a + g_b - \ell_b b
\]

We find the steady state value of \(b\) from \(\dot{a} + \dot{b} = 0 = g_a + g_b - \ell_b b^*\) and so \(b^* = (g_a + g_b)/\ell_b\). This value may be plugged into the equation for \(\dot{a}\) to find the steady state value of \(a\),

\[
a^* = \frac{1}{k_1} \left( \frac{\ell_b g_a}{g_a + g_b} + k_2 \right)
\]

By similar reasoning as the previous subsection, \((a^*, b^*)\) is locally stable. However, \(a^*\) is a function of the flow parameters unless \(g_a = 0\), in which case \(a^*\) is the same as the flow-free system. For \(g_a = 0\), we show that \((a^*, b^*) = (k_2/k_1, g_b/\ell_b)\) has basin of attraction \(\mathbb{R}^2_{\geq 0}\). Clearly, the positive
orthant $\mathbb{R}^2_{\geq 0}$ is invariant, $\{b = 0\}$ is repelling and for positive $b$, $\{a = 0\}$ is repelling. The trajectories in the positive orthant are the same as those for the following system:

\[
\begin{align*}
\dot{a} &= -k_1 a + k_2 \\
\dot{b} &= k_1 a - k_2 + \frac{g_b}{b} - \ell_b
\end{align*}
\]

(3.5)

The equation for $a$ is autonomous and therefore $a$ clearly converges to $k_2/k_1$ and it’s immediate that $b$ converges to $g_b/\ell_b$. The global attractor can be a spiral as shown in Figure 6.

\[
g_a = 0.1, \ell_b = 1
\]

\[
\begin{array}{c}
\text{Concentrations of A and B} \\
\text{Time t}
\end{array}
\]

\[
\begin{array}{c}
\text{Concentration of B} \\
\text{Concentration of A}
\end{array}
\]

Figure 6: $B$ is in outflow while $A$ is in inflow. For small values of inflow $g_a$, we see damped oscillations.

### 3.7 Only $A$ in outflow and some inflows

Consider (3.2) with $\ell_a > 0$, $\ell_b = 0$, $g_a + g_b > 0$. The mass-action ODE system is:

\[
\begin{align*}
\dot{a} &= -k_1 ab + k_2 b + g_a - \ell_a a \\
\dot{b} &= k_1 ab - k_2 b + g_b
\end{align*}
\]

(3.6)

(i) $(g_b = 0)$ The $b$-nullcline (the set of points where $\dot{b} = 0$) is $\{b = 0\} \cup \{a = k_2/k_1\}$. The $a$-nullcline, restricted to the $\mathbb{R}^2_{\geq 0}$, can be written as:

\[
b(a) = \frac{\ell_a a - g_a}{k_2 - k_1 a}.
\]

It is easy to see that $b(a)$ has domain either $[g_a/\ell_a, k_2/k_1)$ or $(k_2/k_1, g_a/\ell_a]$ depending on which is greater, range $[0, \infty)$, and is monotone.

(a) $(g_a/\ell_a = k_2/k_1)$ The ODE system reduces to

\[
\begin{align*}
\dot{a} &= (k_1 b + \ell_a) \left(\frac{k_2}{k_1} - a\right), \\
\dot{b} &= -k_1 b \left(\frac{k_2}{k_1} - a\right)
\end{align*}
\]

(3.7)

Clearly, $a(t) \xrightarrow{t \to \infty} k_2/k_1$ and $b(t)$ converges to some finite value that depends on the initial condition. See the middle panel in Figure 7.
Figure 7: A is in outflow and inflow while B is in neither. There are three qualitative cases depending on the sign of $g_a/\ell_a - k_2/k_1$.

(b) $(g_a/\ell_a < k_2/k_1)$ The nullclines clearly partition $\mathbb{R}^2_{>0}$, the partition comprises of the nullclines and three open regions, see first panel of Figure 7. Let $\delta = k_2/k_1 - g_a/\ell_a$.

$$\dot{a} = k_1 b \left( \frac{k_2}{k_1} - a \right) + \ell_a \left( \frac{g_a}{\ell_a} - a \right) = \left( k_1 b + \ell_a \right) \left( \frac{k_2}{k_1} - a \right) - \delta \ell_a$$  (3.8)

For $a \geq k_2/k_1$, we have $\dot{a} \leq -\delta \ell_a$ and so for all initial values, $a < k_2/k_1$ after some finite time $t^*$. Since $\dot{b} < 0$ for all $t > t^*$, $a(t)$ does not converge to $k_2/k_1$. Simple analysis shows that there is a unique globally attracting steady state on the boundary, i.e. for all initial values, $(a(t), b(t)) \xrightarrow{t \to \infty} (g_a/\ell_a, 0)$.

(c) $(g_a/\ell_a > k_2/k_1)$ The nullclines clearly partition $\mathbb{R}^2_{>0}$, the partition comprises of the nullclines and three open regions, see last panel of Figure 7. Let $\delta = g_a/\ell_a - k_2/k_1$.

$$\dot{a} = k_1 b \left( \frac{k_2}{k_1} - a \right) + \ell_a \left( \frac{g_a}{\ell_a} - a \right) = \left( k_1 b + \ell_a \right) \left( \frac{k_2}{k_1} - a \right) + \delta \ell_a$$  (3.9)

For $a \leq k_2/k_1$, we have $\dot{a} \geq \delta \ell_a$ and so for all initial values, $a > k_2/k_1$ after some finite time $t^*$, after which $\dot{b} > 0$. Similar reasoning as used in the proof of Theorem 3.2 shows that $b(t) \xrightarrow{t \to \infty} \infty$ and all trajectories asymptote to the $a$-nullcline which itself asymptotes to the vertical line $a = k_2/k_1$ and therefore $a(t) \xrightarrow{t \to \infty} k_2/k_1$. 

15
Figure 8: $A$ is in outflow while both $A$ and $B$ are in inflow. The sign of $(g_a + g_b)/\ell_a - k_2/k_1$ determines whether nullclines intersect and the long-term behavior of $a(t)$.

(ii) $(g_b > 0, (g_a + g_b)/\ell_a < k_2/k_1)$ See first panel of Figure 8. There is a unique steady state

$$a^* = \frac{g_a + g_b}{\ell_a}, \quad b^* = \frac{g_b \ell_a}{k_2 \ell_a - k_1 (g_a + g_b)},$$

which is positive. The coordinates of the steady state clearly depend on the flow parameters and a simple calculation shows that $(a^*, b^*)$ is locally stable. In fact, the steady state is globally attracting, but we don’t need this result.

(iii) $(g_b > 0, (g_a + g_b)/\ell_a \geq k_2/k_1)$ The $a$-nullcline intersects the $a$-axis at $g_a/\ell_a$, the $b$-nullcline intersects the $b$-axis at $g_b/k_2$ and both nullclines are graphs of monotone functions. The $a$-nullcline and $b$-nullcline are non-intersecting and both asymptote to $a = k_2/k_1$. See second and third panels of Figure 8. Analysis similar to the one used in the proof of Theorem 3.2 shows that for all initial values, $b(t) \xrightarrow{t \to \infty} \infty$ and $a(t) \xrightarrow{t \to \infty} k_2/k_1$.

**Rate of growth:** The rate at which $b(t)$ goes to infinity depends on whether $(g_a + g_b)/\ell_a - k_2/k_1$ is 0 or positive. In the latter case, $b(t) = O(t)$ while in the former case $b(t) = O(\sqrt{t})$. To see this, we use a quasi-steady state (QSS) argument. Since $a(t)$ converges to a finite value, we have that $\dot{a}(t) \approx 0$ for large times, i.e. for large times, the following algebraic-differential
Figure 9: Response curve for the reaction network \( \{ A + B \overset{k_1}{\rightarrow} 2B, B \overset{k_2}{\rightarrow} A \overset{\ell_a}{\rightarrow} 0, 0 \overset{g_a}{\rightarrow} A, 0 \overset{g_b}{\rightarrow} B \} \). For all choices of rate constants, \( a(t) \) converges to a finite value \( a(\infty) \) that depends only on the rate constants and not on the initial values. We fix the reaction rate constants \( k_1, k_2 \) and the outflow rate \( \ell_a \). Initially, \( a(\infty) \) increases linearly with the net inflow \( g_a + g_b \). For \( g_a + g_b \geq \ell_a k_2 / k_1 \), \( a(\infty) = k_2 / k_1 \).

The response of \( a(\infty) \) as a function of the net inflow rate \( g_a + g_b \) is shown in Figure 9. Combining these results, we see that \( a(\infty) \) is a simple reaction network implementation of the \( \text{“min”} \) function, the precise result is stated below.
Theorem 3.3. Consider the mass action system determined by

\[ A + B \xrightarrow{k_1} 2B, \]

\[ B \xrightarrow{k_2} A \]

For all possible choices of positive rate constants and all initial values \((a(0), b(0))\) with \(g_b + b(0) > 0\),

\[
a(t) \xrightarrow{t \to \infty} \min \left( \frac{g_a + g_b}{\ell_a}, \frac{k_2}{k_1} \right).
\]

It is useful to interpret the net inflow rate \(g_a + g_b\) as the signal received by the system while \(a(\infty)\) as the response to the signal. The above theorem says that the response is directly proportional to the signal up to a point, with the proportionality factor equal to the reciprocal of the outflow rate \(1/\ell_a\). Once the signal strength \(g_a + g_b\) reaches the value \(\ell_a k_2/k_1\), the response immediately saturates to the constant value of \(k^*/k_1\).

Proof of Theorem 3.3. The results obtained in the previous sections are summarized in Table 1 and it also completes proof of Theorem 3.1 as can be verified from the tabulated results.

| 0 \(\xrightarrow{+} A\) | 0 \(\xrightarrow{+} B\) | 0 \(\xrightarrow{\to} 0\) | 0 \(\xrightarrow{\to} 0\) | 0 \(\xrightarrow{\to} 0\) | 0 \(\xrightarrow{\to} 0\) | 0 \(\xrightarrow{\to} 0\) |
|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| A \(\xrightarrow{\to} 0\) | B \(\xrightarrow{\to} 0\) | Dynamic ACR condition on ICs | Dynamic ACR condition on flow | \(a(\infty)\) | \(b(\infty)\) |
| Dynamic ACR | Dynamic ACR | \(a(0) + b(0) \geq k^\star\) | \(k^\star\) | \(a(0) + b(0) - k^\star\) | \(b(\infty)\) |
| \(\checkmark\) | \(\checkmark\) | \(b(0) > 0\) | Not ACR | \(a(0) \geq -\frac{g_a}{\ell_a}\) | \(k^\star\) | \(k^\star\) | \(a(0) + b(0) - k^\star\) | \(b(\infty)\) |
| \(\checkmark\) | \(\checkmark\) | \(b(0) > 0\) | Not ACR | \(a(0) \geq -\frac{g_a}{\ell_a}\) | \(k^\star\) | \(k^\star\) | \(a(0) + b(0) - k^\star\) | \(b(\infty)\) |
| \(\checkmark\) | \(\checkmark\) | \(b(0) > 0\) | Not ACR | \(a(0) \geq -\frac{g_a}{\ell_a}\) | \(k^\star\) | \(k^\star\) | \(a(0) + b(0) - k^\star\) | \(b(\infty)\) |
| \(\checkmark\) | \(\checkmark\) | \(b(0) > 0\) | Not ACR | \(a(0) \geq -\frac{g_a}{\ell_a}\) | \(k^\star\) | \(k^\star\) | \(a(0) + b(0) - k^\star\) | \(b(\infty)\) |
| \(\checkmark\) | \(\checkmark\) | \(b(0) > 0\) | Not ACR | \(a(0) \geq -\frac{g_a}{\ell_a}\) | \(k^\star\) | \(k^\star\) | \(a(0) + b(0) - k^\star\) | \(b(\infty)\) |
| \(\checkmark\) | \(\checkmark\) | \(b(0) > 0\) | Not ACR | \(a(0) \geq -\frac{g_a}{\ell_a}\) | \(k^\star\) | \(k^\star\) | \(a(0) + b(0) - k^\star\) | \(b(\infty)\) |
| \(\checkmark\) | \(\checkmark\) | \(b(0) > 0\) | Not ACR | \(a(0) \geq -\frac{g_a}{\ell_a}\) | \(k^\star\) | \(k^\star\) | \(a(0) + b(0) - k^\star\) | \(b(\infty)\) |
| \(\checkmark\) | \(\checkmark\) | \(b(0) > 0\) | Not ACR | \(a(0) \geq -\frac{g_a}{\ell_a}\) | \(k^\star\) | \(k^\star\) | \(a(0) + b(0) - k^\star\) | \(b(\infty)\) |

Table 1: Robustness properties of \(A + B \xrightarrow{k_1} 2B, B \xrightarrow{k_2} A\) taken with inflow and outflow reactions. “fin” means the concentration converges to finite, positive value that may depend on the initial values. “def” means the concentration converges to finite, positive value independent of the initial values. “ACR” means converges to the ACR value of the isolated (without-flow) system. The ACR value in the isolated network is \(k^\star = k_2/k_1\). Convergence to the ACR value \(k^\star\) in chemostat is characterized by signs of two parameters, \(\ell_a\) and \(\sigma \equiv g_a + g_b - \ell_a k^\star\).
3.8 Rates of convergence compared

For (3.2) with \( g_a > 0 \) and \( g_b = \ell_a = \ell_b = 0 \), we have shown that \( a \to k^* \). We now inquire about the speed of convergence. For \( g_a = 0 \), we have exponential convergence of \( a \) to \( k^* \). As Figure 10 (right) shows, the convergence rate for large time is a power of \( t \) and appears independent of the inflow rate \( g_a \). Recall from proof of Theorem 3.2 that all trajectories approach the \( a \)-nullcline from the right. Moreover, after sufficiently large time has passed \( \dot{a} \approx 0 \) and \( \dot{b} \approx g_a \). This means that \( b(t) \approx g_a t \) and

\[
\dot{a} = k_1 b(k^* - a) + g_a \approx 0 \implies a - k^* \approx \frac{g_a}{k_1 b} \approx \frac{g_a}{k_1 g_a t} = \frac{1}{k_1 t},
\]

thus the convergence rate is \( 1/t \), independent of \( g_a \), see Figure 10.

Figure 10: Effect of different inflow rates of \( A \). \((a(0), b(0)) = (10, 1)\).

4 Discussion and future work

In this paper, we proposed a normal form for dynamic absolute concentration robustness. We think that most systems with dynamic ACR can be brought into normal form after some coordinate transformations or quasi-steady state approximations. The normal form representation produces an explicit formula for the “fuel” and “load” functions. The normal form theory suggests checking some conditions on the fuel and load, which will establish the presence or absence of dynamic ACR.

An important experimental as well as theoretical setup is when a system which has dynamic ACR has inflows added in some species. This corresponds to a positive constant load when the inflow is in the ACR species. Even when the inflow is in a non-ACR species, the fuel function of the ACR species changes accordingly. We showed here that the archetypal model of normal form dynamic ACR preserves dynamic ACR with the same value when inflows are added to the system. We refer to this property as dynamic homeostasis with respect to inflows. Note that dynamic homeostasis is a different concept from dynamic ACR. A species has dynamic ACR if its concentration converges to the same value independent of the overall initial value of the system. A species has dynamic homeostasis when its concentration converges to the same value independent of certain rate parameters. In the case of the archetypal model, the value that the ACR variable converges to is independent of the inflow rate constants, and therefore the ACR variable has dynamic homeostasis with respect to inflows as well as having dynamic ACR. We conjecture that this
behavior is generic for dynamic ACR systems in the sense that most choices of inflows will preserve dynamic ACR in the same species at the same value as without inflows. This statement, however, has several important caveats and interesting exceptions and therefore requires careful mathematical analysis and discussion, which is our plan for future work.

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