Homeostasis in Three-Node Networks

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Abstract

Homeostasis occurs in a system where an output variable is approximately constant on an interval on variation of an input variable $I$. Homeostasis is known to play an important role in the regulation of biological systems. See [Nijhout et al. (2018)]. As a way of finding homeostasis, [Golubitsky and Stewart (2017)] introduce the notion of infinitesimal homeostasis – points where the derivative of the output variable with respect to $I$ is zero. [Reed et al. (2017)] give two examples of infinitesimal homeostasis in three-node chemical reaction systems: feedforward excitation and substrate inhibition. In this paper we show that there are 13 different three-node networks leading to many possible input-output system configurations. The different configurations are based on which node is the input node, which node is the output node, and whether individually the couplings are excitatory, inhibitory, or neutral. We show nonetheless that there are only two basic mechanisms that lead to infinitesimal homeostasis and they are illustrated by feedforward excitation and substrate inhibition. Feedforward excitation occurs only when the network has a feedforward loop as a subnetwork; that is, when there are two distinct simple paths connecting the input node to the output node. Moreover, one of the paths must be excitatory and one inhibitory to support infinitesimal homeostasis. Substrate inhibition occurs when there is a single simple path from the input node to the output node and then only when one of the couplings along this path is neutral. The paper ends with an analysis of substrate inhibition infinitesimal chair singularities.

1 Introduction and Results

Homeostasis refers to a phenomenon whereby the output $x_o$ of a system is approximately constant on variation of an input $I$. As emphasized by Nijhout and Reed this is an important phenomenon in many areas of biology. In particular, [Nijhout and Reed (2014)], [Nijhout et
al. (2018), Reed et al. (2017) have shown that homeostasis is especially important when studying the functioning of biochemical networks. Recently, Golubitsky and Stewart (2017) introduced the more computable notion of infinitesimal homeostasis. Specifically:

**Definition 1.1.** Homeostasis occurs near \( I_0 \) when the input-output function \( x_o(I) \) is approximately constant on a neighborhood of \( I_0 \). Infinitesimal homeostasis occurs at \( I_0 \) if \( x'_o(I_0) = 0 \)

where \(^'\) indicates differentiation with respect to \( I \).

It follows from Taylor’s theorem that infinitesimal homeostasis implies homeostasis, though the converse need not necessarily be valid. See Reed et al. (2017) and the discussion of product inhibition in Section 2.

In the remainder of this section, we define input-output functions for networks, coupling types, state the main results, and outline the paper.

### 1.1 The input-output function in three-node networks

This paper focuses on infinitesimal homeostasis in three-node networks. We assume that one node \( i \) is the input node, a second node \( o \) is the output node, and the third node \( \rho \) is the regulatory node. The network coordinates are \( X = (x_i, x_\rho, x_o) \). We assume that the network system has the form \( F = (f_i, f_\rho, f_o) \) where each coordinate function \( f_\ell \) depends on the internal state variable \( x_\ell \) and the state variables of the nodes coupled to node \( \ell \) in the network graph. We also assume that only the input node coordinate function \( f_i \) depends on the external input variable \( I \).

The definition of an input-output function begins with the assumption that

\[
\dot{X} = F(X, I)
\]

has a stable equilibrium \( X_0 \) at \( I_0 \). Stability together with the implicit function theorem implies that there exists an implicitly defined mapping \( X(I) \) such that

\[
F(X(I), I) = 0
\]

where \( X(I_0) = X_0 \). In coordinates, \( X(I) = (x_i(I), x_\rho(I), x_o(I)) \), where \( x_o(I) \) is the input-output function. In general, we can write the equilibrium equations of (1.1) as

\[
\begin{align*}
\dot{x}_i &\quad = 0 \\
\dot{x}_\rho &\quad = 0 \\
\dot{x}_o &\quad = 0
\end{align*}
\]
Linearized coupling types

Based on biochemical modeling we assume that in the absence of coupling each node degrades; that is, the linearized internal dynamics satisfies

\[ f_{\ell,x}(X_0) < 0 \]  

for \( \ell = \iota, \rho, o \). Throughout this paper we use the notation \( f_{\ell,y} \) to denote the partial derivative of the coordinate function \( f_\ell \) with respect to \( y \).

Suppose node \( m \) connects to node \( \ell \). Then the sign of the linearized coupling at the equilibrium \( X_0 \) is

\[ \varepsilon_{m\ell} = \text{sgn}(f_{\ell,x_m}(X_0)). \]

**Definition 1.2.** In a biochemical network coupling from node \( m \) to node \( \ell \) is *excitatory* at the equilibrium \( X_0 \) if \( \varepsilon_{m\ell} = +1 \), *inhibitory* if \( \varepsilon_{m\ell} = -1 \), and *neutral* if \( \varepsilon_{m\ell} = 0 \).

**Remark 1.3.** Neutral coupling between two nodes does not mean that the nodes are uncoupled—rather it means that the coupling exists and is at a transition state between excitation and inhibition.

### 1.2 Results on infinitesimal homeostasis

We ask the following mathematical question: Given a three-node network with designated input and output nodes, what conditions on the linearized couplings lead to the potential existence of infinitesimal homeostasis? The answer depends on the network architecture—specifically the number of simple paths from input node to output node. A path between nodes is *simple* if it visits each node on the path at most once.

In a three-node network there are only two possible simple paths from the input node to the output node: \( \iota \to o \) and \( \iota \to \rho \to o \). Hence, there are three possible configurations of simple paths in three-node networks and these configurations dictate the kind of infinitesimal homeostasis that can occur.

1) **The network has one simple path from the input node \( \iota \) to the output node \( o \) and that path is direct; namely, \( \iota \to o \).** It follows that either \( \iota \not\to \rho \) or \( \rho \not\to o \).

   In this case Theorem 3.4(a) shows that infinitesimal homeostasis occurs if and only if the linearized coupling along the direct path is neutral. That is,

   \[ f_{o,x}(X_0) = 0. \]  

2) **The network has one simple path from the input node \( \iota \) to the output node \( o \) and that path goes through the regulatory node \( \rho \); namely, \( \iota \to \rho \to o \).** It follows that \( \iota \not\to o \).

\[ \text{See http://www.people.vcu.edu/~gasmerom/MAT131/graphs.html} \]
In this case Theorem 3.4(b) shows that infinitesimal homeostasis occurs if and only if either the linearized coupling $\iota \rightarrow \rho$ is neutral or the linearized coupling $\rho \rightarrow o$ is neutral. That is, either

\[(a) \quad f_{\rho,x}(X_0) = 0 \quad \text{or} \quad (b) \quad f_{o,x}(X_0) = 0. \quad (1.6)\]

A biochemical example of (1.6a) is product inhibition and a biochemical example of (1.6b) is substrate inhibition. See Section 2.

3) The network has two simple paths from the input node $\iota$ to the output node $o$; namely, $\iota \rightarrow o$ and $\iota \rightarrow \rho \rightarrow o$.

Theorem 3.6 shows that infinitesimal homeostasis occurs only when one of the paths from $\iota$ to $o$ is excitatory and the other is inhibitory. That is,

\[(\varepsilon_{\iota o})(\varepsilon_{\iota \rho} \varepsilon_{\rho o}) = -1. \quad (1.7)\]

Figure 1 illustrates (1.7). A biochemical example of (1.7) is feedforward excitation. See Section 2. Specifically, the infinitesimal homeostasis point $X_0$ satisfies

\[f_{o,x}f_{\rho,x} - f_{o,x}f_{\rho,x} = 0. \quad (1.8)\]

**Definition 1.4.** We call homeostasis of types 1) and 2) substrate inhibition, since these types arise from neutral coupling and require homeostasis be built into the kinetics function. We call homeostasis of type 3) structural homeostasis, since this type typically arises from non-neutral couplings and requires a balance between the two simple paths in the network.

*Figure 1: Excitatory/inhibitory coupling in input-output feedforward loop motif.*

**Remark 1.5.** In each of the three possible network configurations infinitesimal homeostasis leads to a single equation that the one parameter $I$ must satisfy. Consequently, infinitesimal homeostasis is a generic phenomenon in input-output systems.

**Remark 1.6.** It follows from the classification of three-node networks (see the appendix Section 6) that there are eight three-node input-output networks that support two simple paths from the input node to the output node. These networks all include Figure 8b, the feedforward loop, as a subnetwork and they are pictured in Figure 6. Theorem 3.6 shows that structural homeostasis (homeostasis with non-neutral coupling) can only occur in these eight of the 78 choices of three-node input-output networks.

\[2\text{We thank Mike Reed for suggesting this term.}\]
1.3 Chairs in substrate inhibition homeostasis

A consequence of the theorems discussed above is that homeostasis typically occurs when $x_o'(I_0) = 0$ and $x_o''(I_0) \neq 0$; that is, when the input-output function $x_o(I)$ is shaped like a parabola on a neighborhood of the infinitesimal homeostasis point $I_0$.

[Nijhout and Reed (2014)] and [Nijhout et al. (2014)] introduce homeostasis and its applications through chairs and the notion of escape from homeostasis. The basic idea is that as the input $I$ varies the output $x_o(I)$ goes through three regions: increase, approximately constant, increase (see Figure 2 middle panel) or decrease, approximately constant, decrease. [Golubitsky and Stewart (2017)] discuss an infinitesimal version of chairs that brings singularity theory into the study of homeostasis. An infinitesimal chair occurs at a point $I_0$ if $x_o'(I_0) = x_o''(I_0) = 0$ and $x_o'''(I_0) \neq 0$; that is, up to a change of coordinates the input-output function is a homogeneous cubic on a neighborhood of $I_0$.

From a singularity theory point of view, a chair is a codimension one singularity. Near a chair singularity, the graph of $x_o$ changes on variation of a single additional parameter $a$, as illustrated in Figure 2. [Reed et al. (2017)] showed that nonlinear degeneracies in substrate inhibition and structural homeostasis lead to infinitesimal chairs. The precise statements describing chair existence in substrate inhibition are given in Section 4.

![Figure 2: Graphs of the input-output function are given as the universal unfolding parameter $a$ varies in this substrate inhibition chair singularity at $a_0$, see [Golubitsky and Stewart (2017)]. From left to right: $a < a_0$, $a = a_0$ and $a > a_0$.](image)

1.4 Organization of paper

Section 2 uses the theory stated in Section 1.2 to reproduce results in [Reed et al. (2017)] that show that infinitesimal homeostasis can occur in three-node networks with either non-neutral coupling (specifically in feedforward excitation) or with neutral coupling (specifically in substrate inhibition). For a detailed discussion of substrate inhibition see [Reed et al. (2010)]. We also discuss the relationship between homeostasis and infinitesimal homeostasis in product inhibition.

The results stated in Section 1.2 are proved in Section 3. Substrate inhibition chairs are discussed in Section 4 with proofs given in an appendix Section 7. The classification of
three-node networks is given in an appendix Section 6. The last main section, Section 5, is a short conclusions section.

2 Biochemical networks

We provide context for our results by relating them to those in [Reed et al. (2017)]. Since model systems form a proper subset of admissible systems, we emphasize the following: If infinitesimal homeostasis can only occur in a restricted form of an admissible system, then infinitesimal homeostasis can only occur in model systems with that same restricted form.

Common homeostatic mechanisms in cell metabolism include feedforward excitation Figure 3a, substrate inhibition Figure 4a, and product inhibition Figure 5a. In these motifs, taken from [Reed et al. (2017)], $X, Y, Z$ are the names of chemical substrates, and each straight arrow represents a flux coming into or going away from a substrate. In the absence of coupling, each substrate degrades. The righthand pictures in these figures are the corresponding mathematical input-output diagrams. The biochemical notation relates to the mathematical notation as follows: the $X$ substrate is the $ι$ node, the $Y$ substrate is the $ρ$ node, and the $Z$ substrate is the $ο$ node. The biochemical concentrations $(x, y, z)$ correspond to network variables $(x_ι, x_ρ, x_ο)$.

Figure 3: Feedforward excitation: (a) Motif from [Reed et al. (2017)]; (b) Input-output network with two simple paths from $ι$ to $ο$ corresponding to the motif in (a).

Figure 4: Substrate inhibition: (a) Motif from [Reed et al. (2017)]; (b) Input-output network with one simple path from $ι$ to $ο$ corresponding to the motif in (a).

Feedforward excitation

The input-output network corresponding to the feedforward excitation motif in Figure 3a is the network in Figure 3b which has two simple paths from the input node to the output node.
In our discussion of two simple path networks, we observe that infinitesimal homeostasis is possible in such networks if (1.7) is satisfied; that is, the two simple paths from X to Z have opposite signs. In this motif, one simple path consists of two excitatory couplings from X to Y and from Y to Z, and hence has a positive sign. The other simple path is an excitatory coupling from X to the synthesis or degradation of Z and hence is an inhibitory simple path from X to Z having a negative sign. By Theorem 3.6, infinitesimal homeostasis is possible in feedforward excitation admissible systems (2.1 right), and can be computed by solving (1.8).

\begin{align*}
\dot{x} &= I - g_1(x) - g_4(x) \\
\dot{y} &= g_1(x) - g_2(y) - g_5(y) \\
\dot{z} &= g_2(y) - h(x, z)
\end{align*}

(2.1)

Reed et al. (2017) showed that the model systems (2.1, left) for the feedforward excitation motif do indeed lead to infinitesimal homeostasis. Using (1.8) we reproduce their result by showing that infinitesimal homeostasis exists in the model systems when

\begin{equation}
\begin{split}
    h_x(x_0, z_0) &= \frac{g_1'(x_0)g_2'(y_0)}{g_2'(y_0) + g_5'(y_0)} 
\end{split}
\end{equation}

(2.2)

where \(X_0 = (x_0, y_0, z_0)\). Specifically, first compute

\begin{align*}
    f_{o,x} &= g_2'(y) \\
    f_{\rho,x} &= g_1'(x) \\
    f_{o,x_i} &= -h_x(x, z) \\
    f_{\rho,x} &= -g_2'(y) - g_5'(y)
\end{align*}

Equation (2.2) then follows directly from (1.8).

**Substrate inhibition**

Since the input-output network in Figure 4b corresponding to the substrate inhibition motif in Figure 4a contains only one simple path from \(\iota\) to \(o\), our results show that infinitesimal homeostasis is possible in an admissible system only through neutral coupling. Also, note that the coupling from X to Y is assumed to be excitatory \((g_1 > 0)\) in the model system (2.3 left) for the substrate inhibition motif; that is, \(f_{\rho,x} > 0\) in the admissible network system (2.3 right). It follows that neutral coupling is possible only in the \(\rho \rightarrow o\) coupling; that is,
\[ f_{o,x_\rho} = 0. \]

\[
\begin{align*}
\dot{x} &= \mathcal{I} - g_1(x) - g_4(x) & \dot{x}_i &= f_i(x_i, \mathcal{I}) \\
\dot{y} &= g_1(x) - g_5(y) - g_2(y) & \dot{x}_\rho &= f_\rho(x_i, x_\rho) \\
\dot{z} &= g_2(y) - g_3(z) & \dot{x}_o &= f_o(x_\rho, x_o)
\end{align*}
\] (2.3)

Hence, by Theorem 3.4 infinitesimal homeostasis can occur in this motif if and only if the coupling is neutral (that is, if \( f_{o,x_\rho} = g_2 = 0 \) at the equilibrium point). This observation agrees with the observation in Reed et al. (2017) that \( Z \) can exhibit infinitesimal homeostasis in the substrate inhibition motif if the infinitesimal homeostasis is built into the kinetics term \( g_2 \) between \( Y \) and \( Z \).

Reed et al. (2017) note that neutral coupling can arise from substrate inhibition of enzymes, enzymes that are inhibited by their own substrates. See the discussion in Reed et al. (2010). This inhibition leads to reaction velocity curves that rise to a maximum (the coupling is excitatory) and then descend (the coupling is inhibitory) as the substrate concentration increases. Infinitesimal homeostasis with neutral couplings arising from substrate inhibition often has important biological functions and has been estimated to occur in about 20% of enzymes Reed et al. (2010).

### Product inhibition

Since the input-output network in Figure 5b corresponding to the product inhibition motif in Figure 5a contains only one simple path from \( \iota \) to \( o \), our results show that infinitesimal homeostasis is possible in an admissible system (2.4, right) only through neutral coupling. Also, the coupling from \( Y \) to \( Z \) is assumed to be excitatory in the model system (2.4, left) based on the biochemical network in Figure 5a and used in Reed et al. (2017); that is, \( f_{o,x_\rho} > 0 \) in the admissible network system (2.4, right). It follows that neutral coupling is possible only in the \( \iota \to \rho \) coupling; that is, \( f_{\rho,x_\iota} = 0. \)

\[
\begin{align*}
\dot{x} &= \mathcal{I} - c_4 x - h(x, z) & \dot{x}_i &= f_i(x_i, x_o, \mathcal{I}) \\
\dot{y} &= h(x, z) - g_2(y) - g_5(y) & \dot{x}_\rho &= f_\rho(x_i, x_\rho, x_o) \\
\dot{z} &= g_2(y) - g_3(z) & \dot{x}_o &= f_o(x_\rho, x_o)
\end{align*}
\] (2.4)

So, infinitesimal homeostasis is possible only if \( f_{\rho,x_\iota} = h_x = 0 \). However, in the Reed et al. (2017) model, \( h \) is assumed to satisfy \( h_x > 0 \), which precludes infinitesimal homeostasis. It is shown in Reed et al. (2017) that homeostasis is possible in such systems if one chooses an \( h(x, z) \) for which \( h_x \) is close to zero. Moreover, such a choice is consistent with the biochemistry of product inhibition.

### 3 Infinitesimal homeostasis

We begin this section by showing that the output node must be downstream from the input node in any input-output network that admits infinitesimal homeostasis. We then use Cramer’s rule to determine explicitly the derivative \( x_o' \) of the input-output function in three-node input-output networks.
Definition 3.1. Node q is downstream from node p if there exists a path from p to q.

Lemma 3.2. In an n-node network, the existence of generic infinitesimal homeostasis implies that the output node o is downstream from the input node i.

Proof. Let U(o) be the set of nodes upstream from o and assume that i \notin U(o). Note that the phase space associated with U(o) is a flow invariant subspace of phase space. Let \hat{U} = G(U) be the restriction of the admissible vector field \hat{X} = F(X, I) to phase space of U(o). The fact that input node i is not upstream from o implies that G is independent of the input term I. Let U(I) equal the coordinates of X(I) on U(o). Then U(I) is a stable equilibrium of the vector field G and U(I) is independent of I. In addition, the input-output function is independent of I. So, only in a very degenerate way can infinitesimal homeostasis occur. For instance, simple homeostasis and chairs are not possible.

Next we compute x'_o. Begin by observing that the Jacobian of (1.3) is

\[ J = \begin{bmatrix} f_i,x_i & f_i,x_p & f_i,x_o \\ f_p,x_i & f_p,x_p & f_p,x_o \\ f_o,x_i & f_o,x_p & f_o,x_o \end{bmatrix} \]  

(3.1)

Note that J is invertible at (X_0, I_0) since the equilibrium X_0 at I_0 is assumed stable. Hence det(J) \neq 0.

Lemma 3.3. The input-output function x_o(I) satisfies

\[ x'_o = \frac{1}{\det(J)} \det \begin{bmatrix} f_i,x_i & f_i,x_p & -f_i,I \\ f_p,x_i & f_p,x_p & 0 \\ f_o,x_i & f_o,x_p & 0 \end{bmatrix} \]  

(3.2)

Assume

\[ f_i,I \neq 0. \]  

(3.3)

Then the input-output function x_o has a point of infinitesimal homeostasis if and only if

\[ \mathcal{H} \equiv \det \begin{bmatrix} f_p,x_i & f_p,x_p \\ f_o,x_i & f_o,x_p \end{bmatrix} = f_o,x_p f_p,x_i - f_o,x_i f_p,x_p = 0. \]  

(3.4)

Proof. Implicit differentiation of (1.3) with respect to I yields the matrix system

\[ J \begin{bmatrix} x'_i \\ x'_p \\ x'_o \end{bmatrix} = \begin{bmatrix} f_i,I \\ 0 \\ 0 \end{bmatrix} \]  

(3.5)

Apply Cramer’s rule to (3.5) to solve for the third coordinate x'_o yielding (3.2). By assumption, f_i,I \neq 0. Hence, I_0 is a point of infinitesimal homeostasis (that is, x'_o(I_0) = 0) if and only if \mathcal{H}(I_0) = 0, That is, (3.4) is valid.
3.1 Infinitesimal homeostasis with neutral coupling

**Theorem 3.4.** Given an input-output three-node network. Suppose there is only one simple path from the input node to the output node. Then infinitesimal homeostasis implies neutral coupling. Specifically,

(a) \( \iota \rightarrow o \): infinitesimal homeostasis occurs if and only if \( f_{o,x_i} = 0 \).

(b) \( \iota \rightarrow \rho \rightarrow o \): infinitesimal homeostasis occurs if and only if \( f_{o,x_\rho} = 0 \) or \( f_{\rho,x_\iota} = 0 \).

**Proof.** The proof proceeds in two parts.

(a) \( \iota \rightarrow o \) and \( \rho \not\rightarrow o \) or \( \iota \not\rightarrow \rho \). If there is one simple path from \( \iota \) to \( o \) and that path is the direct one \( \iota \rightarrow o \), then the other simple path \( \iota \rightarrow \rho \rightarrow o \) must not be present. Hence, at least one of the connections \( \rho \rightarrow o \) or \( \iota \rightarrow \rho \) must not be present. So, either \( f_{o,x_\rho} \equiv 0 \) or \( f_{\rho,x_\iota} \equiv 0 \). It follows from (3.4) that infinitesimal homeostasis occurs if and only if \( f_{\rho,x_\rho}f_{o,x_\iota} = 0 \). However, the genericity assumption (1.4) implies that \( f_{\rho,x_\rho} \neq 0 \). So infinitesimal homeostasis occurs if and only if \( f_{o,x_\iota} = 0 \), as desired.

(b) \( \iota \rightarrow \rho \rightarrow o \) and \( \iota \not\rightarrow o \). If there is one simple path from \( \iota \) to \( o \) and that path is the indirect one \( \iota \rightarrow \rho \rightarrow o \), then the direct path \( \iota \rightarrow o \) must not be present. Hence \( f_{o,x_\iota} \equiv 0 \). It follows from (3.4) that infinitesimal homeostasis occurs if and only if \( f_{\rho,x_\rho}f_{o,x_\iota} = 0 \).

To summarize: infinitesimal homeostasis plus (a) implies neutral coupling in \( \iota \rightarrow o \) and infinitesimal homeostasis plus (b) implies neutral coupling in either \( \iota \rightarrow \rho \) or \( \rho \rightarrow o \).

3.2 Infinitesimal homeostasis with non-neutral coupling

**Proposition 3.5.** Given a three-node input-output system with simple paths \( \iota \rightarrow o \) and \( \iota \rightarrow \rho \rightarrow o \). Homeostasis \( x'_o(I_0) = 0 \) is equivalent to (3.4) at \( I_0 \). Moreover, generically the couplings \( \iota \rightarrow o \), \( \iota \rightarrow \rho \), and \( \rho \rightarrow o \) are either excitatory or inhibitory.

**Proof.** The validity of (3.4) follows directly from Lemma 3.3. Moreover since the couplings \( \iota \rightarrow o \), \( \iota \rightarrow \rho \), and \( \rho \rightarrow o \) are in the network, they can be perturbed arbitrarily in admissible systems and are generically nonzero.

**Theorem 3.6.** Up to node relabeling there are eight input-output three-node networks that can support infinitesimal homeostasis with couplings that are either excitatory or inhibitory and these networks have a feedforward loop as a subnetwork. See Figure 6. Moreover, infinitesimal homeostasis implies that the couplings are restricted by

\[
(\varepsilon_{\iota \rho}\varepsilon_{\rho o})(\varepsilon_{\iota o}) = -1.
\]

(3.6)
Proof. As shown in Theorem 3.4 infinitesimal homeostasis in any network with a single simple path from the input node $i$ to the output node $o$ leads to neutral coupling. So we can assume that the network has two simple paths from the input node to the output node. In particular all arrows $i \to \rho, i \to o, \rho \to o$ are in the network. Hence the feedforward loop is a subnetwork. Generically, these couplings are excitatory or inhibitory.

It follows from Proposition 3.5 that

$$f_{o,x\rho}f_{\rho,x_i} = f_{o,x_i}f_{\rho,x\rho}.$$  

Since the four entries are generically nonzero (recall the degradation assumption \((1.4) f_{\rho,x\rho} < 0\)), the identity \((3.6)\) is valid. □ □

Figure 6: Two simple path input-output networks. Each network contains a feedforward loop (Figure 8b) as a subnetwork.

4 Chair homeostasis

Codimension one homeostasis occurs when on variation of a parameter, such as a rate constant, a double degeneracy is found. In the context of infinitesimal homeostasis the only such example is the chair point. [Nijhout and Reed (2014)] and [Nijhout et al. (2014)] argue that in fact the most important way that homeostasis appears in applications (in particular in biochemical networks) is through a chair. The proofs of results in this section require complicated calculations and are given in the appendix Section 7.

The singularity theory notion of an infinitesimal chair has normal form $\mathcal{I}^3$. Using elementary catastrophe theory, [Golubitsky and Stewart (2017)] observe that infinitesimal chairs satisfy the defining conditions

$$x_o'(\mathcal{I}_0) = x_o''(\mathcal{I}_0) = 0$$  \hspace{1cm} (4.1)

and the nondegeneracy condition

$$x_o'''(\mathcal{I}_0) \neq 0$$  \hspace{1cm} (4.2)
where \( \prime \) denotes differentiation with respect to \( I \).

Recall from (3.4) in Lemma 3.3 that infinitesimal homeostasis is given by solving \( \mathcal{H}(I) = 0 \) where
\[
\mathcal{H} \equiv f_{o,x_i} f_{o,x_i} - f_{o,x_i} f_{p,x_p}.
\]

In Proposition 4.1 we present the defining and nondegeneracy conditions for an infinitesimal chair in terms of derivatives of \( \mathcal{H} \).

**Proposition 4.1.** The input-output function \( x_o(I) \) associated to (1.3) satisfies the defining and nondegeneracy conditions of an infinitesimal chair at \( I_0 \) if and only if
\[
\mathcal{H} = \mathcal{H}' = 0 \quad \text{(4.3)}
\]
and
\[
\mathcal{H}'' \neq 0. \quad \text{(4.4)}
\]

In Theorems 4.2 and 4.3 we explicitly compute the defining and nondegeneracy conditions for an infinitesimal chair in terms of derivatives of \( f_i, f_p, f_o \) when the network has only one simple path from \( \iota \) to \( o \). We recall that chair points for structural homeostasis were found in [Reed et al. (2017)] by explicitly evaluating \( \mathcal{H} \) and \( \mathcal{H}' \). The corresponding general result for structural homeostasis is quite complicated and will not be pursued here.

**Theorem 4.2.** Given a three-node input-output network with only one simple path from input node to output node and that path is \( \iota \to o \). Suppose this path has a neutral coupling at an infinitesimal homeostasis point. Then the defining conditions for a chair (4.1) are equivalent to
\[
f_{o,x_i} = f_{o,x_i,x_i} = 0
\]
and the chair nondegeneracy condition (4.2) is valid if and only if
\[
f_{o,x_i,x_i} \neq 0.
\]

**Theorem 4.3.** Given a three-node input-output network with only one simple path from input node to output node and that path is \( \iota \to \rho \to o \). Suppose this path has a neutral coupling at an infinitesimal homeostasis point. Then the defining conditions for a chair (4.1) are equivalent to
\[
f_{o,x_p} = f_{o,x_p,x_p} = 0 \quad \text{or} \quad f_{\rho,x_i} = f_{\rho,x_i,x_i} = 0
\]
and the chair nondegeneracy condition (4.2) is valid if and only if either
\[
f_{o,x_p,x_p} \neq 0 \quad \text{or} \quad f_{\rho,x_i,x_i} \neq 0.
\]

**Remark 4.4.** It follows from Theorems 4.2 and 4.3 that having a chair in substrate inhibition implies that the kinetic term itself has a chair at that infinitesimal homeostasis point.
5 Conclusions and Future Developments

In this paper we showed how infinitesimal homeostasis can arise in three-node networks. We assume there is an input node \( \iota \) and an output node \( o \). If the network contains two simple paths from \( \iota \) to \( o \), then infinitesimal homeostasis is given by feedforward excitation and generically one of the paths is excitatory and the other inhibitory. If the network contains only one simple path from \( \iota \) to \( o \), then infinitesimal homeostasis is given by neutral coupling (as shown in substrate and product inhibition).

There are two natural questions:

(a) Can this classification be extended in some manner to networks with \( n > 3 \) nodes?

(b) Can new forms of homeostasis exist in larger networks?

There are 199 four-node networks and 9364 five-node networks. These facts indicate the complexity of question (a). However, we shall consider homeostatic behavior in four-node networks in future work. In a certain sense the answer to question (b) is yes. The framework for the exploration of infinitesimal homeostasis where the output is simultaneously approximately constant to variation of two parameters is given in Golubitsky and Stewart (2018). A variant of question (a) based on simultaneous infinitesimal homeostasis in four-node networks is itself an interesting question.

6 Appendix: Classification of three-node networks

Theorem 6.1. Up to node relabeling there are 13 three-node networks that are pictured in Figures 7-10.

It follows from Theorem 6.1 that there are \( 78 = 6 \times 13 \) possible choices of three-node input-output networks.

Proof. There are either 1, 2, or 3 transitive components in a three-node network.

If there are three transitive components, then there are four possible networks and they are given in networks 7a, 7b, 7c in Figure 7 and network 8b in Figure 8.

If there are two transitive components, then one of the components has two nodes each connected to the other. The third node connects to one node in the two-node component in either direction (networks 8c and 8d in Figure 8) or to both nodes in the two-node component in either direction (networks 9c and 9d in Figure 9).

The remaining networks have one transitive component. There are two possibilities: the network has a unidirectional cycle \( 1 \rightarrow 2 \rightarrow 3 \) or two cycles \( 1 \leftrightarrow 2 \) and \( 2 \leftrightarrow 3 \). There is one possibility in the last case and that is network 9a in Figure 9. The possible networks with a three-cycle are network 8a in Figure 8, network 9b in Figure 9, and networks 10a and 10b in Figure 10. These four are distinguished by how many additional arrows each has.

\(^3\)See the Online Encyclopedia of Integer Sequences at http://oeis.org/A003085
Figure 7: Inhomogeneous three-cell networks with two arrows.

Figure 8: Inhomogeneous three-cell networks with three arrows.

Figure 9: Inhomogeneous three-cell networks with four arrows.

Figure 10: Inhomogeneous three-cell networks with five and six arrows.

Remark 6.2. [Tyson and Novak (2010)] classify three-node networks with two types of coupling: excitatory and inhibitory. In this paper we will also allow neutral coupling, which complicates the classification, but we only consider networks that support infinitesimal homeostasis, which simplifies the classification.

7 Appendix: Proofs of Results in Section 4

Lemma 7.1. Suppose \( x'_0(\mathcal{I}) = \varphi(\mathcal{I})y'_0(\mathcal{I}) \) where \( \varphi(\mathcal{I}_0) \neq 0 \). Then for all \( m \geq 1 \)

\[
x'_0(\mathcal{I}_0) = \cdots = x'_o^{[m]}(\mathcal{I}_0) = 0 \quad \text{if and only if} \quad y'_0(\mathcal{I}_0) = \cdots = y'_o^{[m]}(\mathcal{I}_0) = 0.
\]

Proof. The proof is straightforward by induction. \( \square \) \( \square \)

Proof of Proposition 4.1. Recall from (3.2) that

\[
x'_o = \frac{1}{\det(J)} \det \begin{bmatrix} f_{i,x} & f_{i,x} & -f_{i,I} \\ f_{j,x} & f_{j,x} & 0 \\ f_{o,x} & f_{o,x} & 0 \end{bmatrix} = -\frac{f_{i,I}}{\det(J)} \mathcal{H}
\] (7.1)

where the Jacobian \( J \) is given by (3.1) and \( \det(J) \neq 0 \). It follows from Lemma 7.1 that the first few derivatives of \( x'_o \) vanish at \( \mathcal{I}_0 \) if and only if the same number of derivatives of \( \mathcal{H} \)
vanish at \( I_0 \). Therefore, \( I_0 \) satisfies the defining conditions of an infinitesimal chair if and only if \( x_o' = x_o'' = 0 \) if and only if (4.3) is satisfied; that is, \( \mathcal{H} = \mathcal{H}' = 0 \). Therefore, \( I_0 \) satisfies the nondegeneracy condition of an infinitesimal chair if and only if \( x_o''' \neq 0 \) if and only if (4.4) is satisfied; that is, \( \mathcal{H}'' \neq 0 \).

Proofs of Theorems 4.2 and 4.3 will use the following lemma. Recall that \( a \) is a backward arrow if either the head of \( a \) is \( \iota \) or the tail of \( a \) is \( o \).

**Lemma 7.2.** The infinitesimal homeostasis point in a three-node input-output network \( G \) is not affected by deletion of backward arrows from \( G \).

**Proof.** Let \( \tilde{G} \) be the reduced network obtained by removing all backward arrows from the original network \( G \). It follows that the Jacobian matrix \( \tilde{J} \) for the reduced network is lower triangular with eigenvalues \( f_{\ell,x_\ell} < 0 \) where \( \ell = \iota, \rho, o \). Hence the stable equilibrium in the original network system will remain stable in the new reduced network.

Next we show the two networks have the same infinitesimal homeostasis point \( I_0 \). It follows from Lemma 3.3 that the linearized couplings \( f_{\iota,x_\rho}, f_{\iota,x_o}, \) and \( f_{\rho,x_o} \) associated to backward arrows do not appear in \( \mathcal{H} \) given by (3.4). The formula (7.1) is therefore valid for both networks with the only difference being between \( \det(J) \) and \( \det(\tilde{J}) \), both of which are nonzero at \( I_0 \). It follows that

\[
x_o'(I) = \varphi(I)\tilde{x}_o'(I)
\]

where \( x_o, \tilde{x}_o \) are the input-output functions of the original network and the associated reduced network with no backward arrows, and \( \varphi(I) = \det(\tilde{J})/\det(J) \) with \( \varphi(I_0) \neq 0 \). Thus, Lemma 7.2 implies that the infinitesimal homeostasis point is identical in the two network systems; that is, removing backward arrows has no effect on computing the infinitesimal homeostasis point.

**Proof of Theorem 4.2.** By Proposition 4.1, an infinitesimal chair point occurs at \( I_0 \) if and only if \( \mathcal{H}(I_0) = \mathcal{H}'(I_0) = 0 \) and \( \mathcal{H}''(I_0) \neq 0 \). The proof therefore proceeds by showing that

\[
\mathcal{H} = \mathcal{H}' = 0; \mathcal{H}'' \neq 0 \text{ if and only if } f_o,x_\iota = f_o,x_\iota,x_\iota = 0; f_o,x_\iota,x_\rho \neq 0.
\]

(7.2)

By Lemma 7.2 we can assume there is no backward arrow in the admissible system:

\[
\begin{align*}
    f_{\iota}(x_\iota, I) &= 0 \\
    f_{\rho}(x_\iota, x_\rho) &= 0 \\
    f_o(x_\iota, x_\rho, x_o) &= 0
\end{align*}
\]

(7.3)

Thus

\[
\begin{bmatrix}
    f_{\iota,x_\iota} & 0 & 0 \\
    f_{\rho,x_\iota} & f_{\rho,x_\rho} & 0 \\
    f_{o,x_\iota} & f_{o,x_\rho} & f_{o,x_o}
\end{bmatrix}
\begin{bmatrix}
    x_\iota' \\
    x_\rho' \\
    x_o'
\end{bmatrix}
= \begin{bmatrix}
    -f_{\iota,I} \\
    0 \\
    0
\end{bmatrix}
\]

It follows that \( x_\iota' = -f_{\iota,I}/f_{\iota,x_\iota} \neq 0 \) and

\[
x_\rho' = -f_{\rho,x_\iota}x_\iota'/f_{\rho,x_\rho}
\]

(7.4)
Since there is only one simple path from \( \iota \) to \( o \) given by \( \iota \to o \), the other simple path \( \iota \to \rho \to o \) must not be present. It follows that
\[
f_{o,x}f_{\rho,x} \equiv 0. \tag{7.5}\]

Therefore the definition of \( H \) in (3.4) reduces to
\[
H \equiv -f_{o,x}f_{\rho,x}. \tag{7.6}\]

Since \( f_{\rho,x} \neq 0 \), by Lemma 7.1
\[
H = H' = 0; \quad H'' \neq 0 \text{ if and only if } f_{o,x} = f'_{o,x} = 0; \quad f''_{o,x} \neq 0.
\]

We therefore verify (7.2) by showing
\[
f'_{o,x} = 0 \text{ if and only if } f_{o,x,x} = 0 \tag{7.6}
\]
and
\[
f''_{o,x} \neq 0 \text{ if and only if } f_{o,x,x,x} \neq 0. \tag{7.7}
\]

Direct computation shows that
\[
f'_{o,x} \equiv f_{o,x,x,x}x'_i + f_{o,x,x,\rho}x'_\rho + f_{o,x,o}x'_o
\]
\[
\equiv f_{o,x,x,x}x'_i + f_{o,x,o}x'_o
\]
\[
= f_{o,x,x,x}x'_i \tag{7.8}
\]
where the second identity in (7.8) holds because
\[
f_{o,x,x,\rho}x'_\rho = -f_{o,x,x,\rho}f_{\rho,x}(x'_i/f_{\rho,x}) \equiv 0
\]
by (7.4) and (7.5). Since \( x'_i \neq 0 \), (7.6) holds. Differentiating \( f'_{o,x} \) in (7.8) with respect to \( I \) leads to
\[
f''_{o,x} \equiv (f_{o,x,x,x}x'_i + f_{o,x,o}x'_o')'
\]
\[
= f_{o,x,x,x}x''_i \tag{7.9}
\]
because \( x'_o(I_0) = x''_o(I_0) = 0 \) and \( f_{o,x,x,\rho}x'_\rho \equiv 0 \equiv f_{o,x,x,\rho}x'_\rho \) by (7.4) and (7.5). It follows that (7.7) is true.

**Proof of Theorem 4.3:** This theorem has two cases; we only prove the first as the arguments for the second case are identical.

By Proposition 4.1 an infinitesimal chair point occurs at \( I_0 \) if and only if \( H(I_0) = H'(I_0) = 0 \) and \( H''(I_0) \neq 0 \). The proof therefore proceeds by showing that
\[
H = H' = 0; \quad H'' \neq 0 \text{ if and only if } f_{o,\rho} = f_{o,\rho,\rho} = 0; \quad f_{o,\rho,\rho,\rho} \neq 0. \tag{7.10}
\]
Since the couplings \( \iota \rightarrow \rho \rightarrow o \) exist the coupling \( \iota \not\rightarrow o \) does not; that is, \( f_{o,\iota} \equiv 0 \). By Lemma 7.2 we can also assume there is no backward arrow in the admissible system:

\[
\begin{align*}
  f_{\iota}(x_{\iota}, \mathcal{I}) &= 0 \\
  f_{\rho}(x_{\iota}, x_{\rho}) &= 0 \\
  f_{o}(x_{\rho}, x_{o}) &= 0
\end{align*}
\]

(7.11)

Thus

\[
\begin{bmatrix}
  f_{\iota,\iota} & 0 & 0 \\
  f_{\rho,\iota} & f_{\rho,\rho} & 0 \\
  0 & f_{o,\rho} & f_{o,o}
\end{bmatrix}
\begin{bmatrix}
  x'_{\iota} \\
  x'_{\rho} \\
  x'_{o}
\end{bmatrix}
= \begin{bmatrix}
  -f_{\iota, \mathcal{I}} \\
  0 \\
  0
\end{bmatrix}
\]

It follows that \( x'_{\iota} = -f_{\iota, \mathcal{I}} / f_{\iota, \iota} \neq 0 \) and

\[
x'_{\rho} = -f_{\rho, \rho} / f_{\rho, \iota}.
\]

(7.12)

Since \( f_{o,\iota} \) is identically zero

\[ \mathcal{H} \equiv f_{o,\rho} f_{\rho,\iota} \].

(7.13)

Hence, \( \mathcal{H} = 0 \) if and only if \( f_{o,\rho} = 0 \) or \( f_{\rho,\iota} \neq 0 \). By Lemma 7.1

\[ \mathcal{H} = \mathcal{H}' = 0; \mathcal{H}'' \neq 0 \] if and only if \( f_{o,\rho} = f'_{o,\rho} = 0; f''_{o,\rho} \neq 0 \).

We therefore verify (7.10) by showing

\[ f'_{o,\rho} = 0 \] if and only if \( f_{o,\rho} x_{\rho} = 0 \)

(7.14)

and

\[ f''_{o,\rho} \neq 0 \] if and only if \( f_{o,\rho} x_{\rho} x_{\rho} \neq 0 \).

(7.15)

Direct computation shows

\[
\begin{align*}
  f'_{o,\rho} & \equiv f_{o,\rho} x_{\iota} + f_{o,\rho} x_{\rho} x_{\rho} + f_{o,\rho} x_{o} x_{\rho} \\
  & \equiv f_{o,\rho} x_{\rho} x_{\rho} + f_{o,\rho} x_{o} x_{\rho} \\
  & = f_{o,\rho} x_{\rho} x_{\rho}
\end{align*}
\]

(7.16)

where the second identity holds because \( f_{o,\iota} \equiv 0 \). By (7.12) \( x'_{\rho} \neq 0 \) and hence (7.14) holds.

Differentiating \( f'_{o,\rho} \) in (7.16) leads to

\[
\begin{align*}
  f''_{o,\rho} & \equiv (f_{o,\rho} x_{\rho})' + (f_{o,\rho} x_{o})' \\
  & = (f_{o,\rho} x_{\rho})' \\
  & = f_{o,\rho} x_{\rho} x_{\rho}
\end{align*}
\]

because \( x'_{o} = x''_{o} = 0 \) at \( \mathcal{I}_0 \) and \( f_{o,\iota} \equiv 0 \). It follows that (7.15) is true. Hence this case is verified. \( \square \)
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References


