The structure of infinitesimal homeostasis in input-output networks

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Abstract

Homeostasis occurs when an observable of a system (such as *inner body temperature*) remains approximately constant over a range of an external parameter (such as *ambient temperature*). More precisely, homeostasis refers to a phenomenon whereby the output x_o of a system is approximately constant on variation of an input $\mathcal{I}$. Homeostatic phenomena are ubiquitous in biochemical networks of differential equations and these networks can be abstracted as digraphs $\mathcal{G}$ with a fixed input node ι and a different fixed output node o. We assume that only the input node depends explicitly on $\mathcal{I}$ and that the output is the output node value $x_o(\mathcal{I})$. We then study *infinitesimal homeostasis*: points $\mathcal{I}_0$ where $\frac{dx_o}{d\mathcal{I}}(\mathcal{I}_0) = 0$ by showing that there is a square *homeostasis matrix H* associated to $\mathcal{G}$ and that infinitesimal homeostasis points occur where $\det(H) = 0$. Applying combinatorial matrix theory and graph theory to H allows us to classify types of homeostasis. We prove that the homeostasis types correspond to a set of irreducible blocks in H each associated with a subnetwork and these subnetworks divide into two classes: *structural* and *appendage*. For example, a *feedforward loop* motif is a structural type whereas a *negative feedback loop* motif is an appendage type. We give two algorithms for determining a menu of homeostasis types that are possible in $\mathcal{G}$: one algorithm enumerates the structural types and one enumerates the appendage types. These subnetworks can be read directly from $\mathcal{G}$ without performing calculations on model equations.

1   Introduction

A system exhibits homeostasis if on variation of an input $\mathcal{I}$ some observable $x_o(\mathcal{I})$ remains approximately constant. Many researchers have emphasized that homeostasis is an important phenomenon in biology. For example, the extensive work of Nijhout, Reed, Best and collaborators [1–7] considers networks whose nodes represent the concentrations of certain biochemical substrates. In their work the input-output function $x_o(\mathcal{I})$ is derived from an asymptotically stable equilibrium X_0 of a biochemical system of differential equations (see Definition 1.1).

In related work under the name of *perfect adaptation* Ma et al. [8] identify, among all three-node enzyme networks with Michelis-Menten chemical kinetics, two networks that are able to *adapt*, that is, to reset themselves after responding to an external stimulus.

Further examples include regulation of cell number and size [9], the control of sleep [10], and the expression level regulation in housekeeping genes [11]. The literature is huge, and these articles are a small sample.

This paper approaches the classification of homeostasis types that can occur in a given input-output network $\mathcal{G}$ by using the notion of *infinitesimal homeostasis* [12] (see Definition 1.2) and generalizes the methods used in [13] for three-node networks. This approach is related to *robust perfect adaptation* [14, 15], where $\frac{dx_o}{d\mathcal{I}}(\mathcal{I})$ is assumed to be identically zero. *Adaptation* has been used widely, for example, in ecology, chemistry, and control engineering (cf. [8, 14–20]).

Our classification is graph theoretic. The types of homeostasis that admissible systems of differential equations of $\mathcal{G}$ can exhibit are characterized by the topology of certain subnetworks. Given an input-output network $\mathcal{G}$ we make three key observations. (i) There is a homeostasis matrix $H(\mathcal{I})$ such that $\frac{dx_o}{d\mathcal{I}}(\mathcal{I}) = 0$ if and only if $\det(H) = 0$ (Lemma 1.4). (ii) $\det(H)$ factors ((11)) and each factor corresponds to a subnetwork of $\mathcal{G}$ (Definition 1.13). (iii) There is an algorithm for determining both the subnetworks and the homeostasis conditions (§1.61.7).

We begin by introducing input-output networks and their associated input-output functions in §1.1. A straightforward application of Cramer's rule (Lemma 1.4) gives a useful method for computing infinitesimal homeostasis points. This result motivates the introduction of the *homeostasis matrix* H in (5), whose entries are linearized coupling strengths and linearized self-coupling strengths associated with the input-output network. This matrix H is the central object in our theory. The homeostasis matrix has appeared in the literature under different names and notations (cf. [8, 12, 14–16, 20]).

We introduce the notion of *core network* in §1.3, where every node is both downstream from the input node and upstream from the output node. It allows one to go from the original network to a 'minimal network' that retains all essential features of homeostasis. We define *core equivalence* of core networks in such a way that the determinant of a homeostasis matrix is determined by its core equivalence class.

Combinatorial matrix theory [21] lets us put H into block upper triangular form and each diagonal block B_η is irreducible (no further triangularization is possible) and corresponds to an infinitesimal homeostasis type (see §§1.4-1.5). The degree of the type is the size of the square block k. In fact, each block B_η has either k or $k-1$ self-couplings (Theorem 4.7). In the first case we call the type *appendage class* and in the second *structural class*. In §§1.61.6.1-1.61.6.2, we characterize combinatorially both homeostasis types. As noted, our main result is that we have an algorithm stated in §1.61.7 that determines the blocks and their types, and the form of this algorithm depends on the class.

The principle tools used to uncover the combinatorial properties of the subnetworks $\mathcal{K}_\eta$ are *determinant formulas* (Theorem 3.2) and graph theory ideas adapted to input-output networks. The formulas connect the summands of $\det(H)$ with the collection of paths of the network $\mathcal{G}$. These formulas are reminiscent of the connection between a directed graph and its adjacency matrix [22]. The combinatorial properties include *simple* paths from input to output nodes (that divide nodes into simple and appendage) and path components of appendage nodes. These terms will be defined.

We end with a classification of low degree homeostasis types, the analysis of an artificial 12-node network, and a short discussion of chair singularities. There are two homeostasis types of degree 1 and two of degree 2. Golubitsky and Wang [13] showed that three of these four types (and no others) can occur in three-node core networks.

1.1 Input-output networks and infinitesimal homeostasis

We now define the basic objects: *input-output networks*, *network admissible systems of differential equations*, and *input-output functions*.

An *input-output network* $\mathcal{G}$ has a distinguished *input node* ι, a distinguished *output node* o (distinct from ι), and n *regulatory nodes* $\rho = (\rho_1, \ldots, \rho_n)$. The network $\mathcal{G}$ also has a specified set of arrows connecting nodes ℓ to nodes j. The associated network systems of differential equations have the form

$$
\begin{aligned}
\dot{x}_\iota &= f_\iota(x_\iota, x_\rho, x_o, \mathcal{I}) \\
\dot{x}_\rho &= f_\rho(x_\iota, x_\rho, x_o) \\
\dot{x}_o &= f_o(x_\iota, x_\rho, x_o)
\end{aligned}
\tag{1}
$$

where $\mathcal{I} \in \mathbf{R}$ is an *external input parameter* and $X = (x_\iota, x_\rho, x_o) \in \mathbf{R} \times \mathbf{R}^n \times \mathbf{R}$ is the vector of state variables associated to the network nodes.

We write the network system (1) as

$$
\dot{X} = F(X, \mathcal{I})
\tag{2}
$$

where $F = (f_\iota, f_\rho, f_o)$. Let f_{j,x_ℓ} denote the partial derivative of the jth node function f_j with respect to the ℓth node variable x_ℓ. We make the following assumptions about the vector field F throughout:

(a) F is smooth and has an asymptotically stable equilibrium at $(X_0, \mathcal{I}_0)$.

(b) The partial derivative f_{j,x_ℓ} can be nonzero only if the network $\mathcal{G}$ has an arrow $\ell \to j$.

(c) Only the input node coordinate function f_ι depends on the external input parameter $\mathcal{I}$ and the partial derivative of f_ι with respect to $\mathcal{I}$ at the equilibrium point $(X_0, \mathcal{I}_0)$ satisfies

$$
f_{\iota,\mathcal{I}}(X_0, \mathcal{I}_0) \neq 0
\tag{3}
$$

It follows from (a) and the implicit function theorem applied to

$$
F(X, \mathcal{I}) = 0
\tag{4}
$$

that there exists a unique family of stable equilibria $X(\mathcal{I}) = (x_\iota(\mathcal{I}), x_\rho(\mathcal{I}), x_o(\mathcal{I}))$ such that $X(\mathcal{I}_0) = X_0$.

Definition 1.1. The mapping $\mathcal{I} \mapsto x_o(\mathcal{I})$ is called the *input-output function*.

Local homeostasis is defined near $\mathcal{I}_0$ when the input-output function x_o is approximately constant near $\mathcal{I}_0$. An important observation is that locally homeostasis occurs when the derivative of x_o with respect to $\mathcal{I}$ is zero at $\mathcal{I}_0$. More precisely:

Definition 1.2. *Infinitesimal homeostasis* occurs at $\mathcal{I}_0$ if $x_o'(\mathcal{I}_0) = 0$ where $'$ indicates differentiation with respect to $\mathcal{I}$.

It follows from Taylor's theorem that infinitesimal homeostasis implies local homeostasis, though the converse need not be valid in model equations (see [5]). A notion similar to infinitesimal homeostasis, called *perfect homeostasis* or *perfect adaptation*, requires the stronger condition that the derivative of the input-output function be identically zero on an interval. This notion has been used by many authors (cf: [8, 14–16]).

Terms that involve coupling in network systems are:

Definition 1.3. Let $F = (f_\iota, f_\rho, f_o)$ be an admissible system for the network $\mathcal{G}$.

(a) The partial derivative $f_{j,x_\ell}(X_0, \mathcal{I}_0)$ is the linearized *coupling* associated with the arrow $\ell \to j$ at the equilibrium $(X_0, \mathcal{I}_0)$.

(b) The partial derivative $f_{j,x_j}(X_0, \mathcal{I}_0)$ is the linearized *self-coupling* of node j at the equilibrium $(X_0, \mathcal{I}_0)$.

1.2 Infinitesimal homeostasis using Cramer's rule

As noted previously [5, 12, 13], a straightforward application of Cramer's rule gives a formula for determining infinitesimal homeostasis points. See Lemma 1.4.

We use the following notation. Let J be the $(n+2) \times (n+2)$ Jacobian matrix of (2) and let H be the $(n+1) \times (n+1)$ *homeostasis matrix* given by dropping the first row and the last column of J:

$$J = \left[\begin{array}{ccc} f_{\iota,x_\iota} & f_{\iota,x_\rho} & f_{\iota,x_o} \\ f_{\rho,x_\iota} & f_{\rho,x_\rho} & f_{\rho,x_o} \\ f_{o,x_\iota} & f_{o,x_\rho} & f_{o,x_o} \end{array} \right] \quad H = \left[\begin{array}{cc} f_{\rho,x_\iota} & f_{\rho,x_\rho} \\ f_{o,x_\iota} & f_{o,x_\rho} \end{array} \right] \tag{5}$$

Here all partial derivatives f_{ℓ,x_j} are evaluated at the equilibrium X_0.

Lemma 1.4. *Let $(X_0, \mathcal{I}_0)$ be an asymptotically stable equilibrium of* (2)*. The input-output function $x_o(\mathcal{I})$ satisfies*

$$x'_o = \pm \frac{f_{\iota,\mathcal{I}}}{\det(J)} \det(H) \tag{6}$$

Hence, $\mathcal{I}_0$ is a point of infinitesimal homeostasis if and only if

$$\det(H) = 0 \tag{7}$$

at $(X_0, \mathcal{I}_0)$.

Proof. Implicit differentiation of (4) with respect to $\mathcal{I}$ yields the matrix system

$$J \left[\begin{array}{c} x'_i \\ x'_\rho \\ x'_o \end{array} \right] = - \left[\begin{array}{c} f_{\iota,\mathcal{I}} \\ 0 \\ 0 \end{array} \right] \tag{8}$$

Since X_0 is assumed to be a stable equilibrium, it follows that $\det(J) \neq 0$. On applying Cramer's rule to (8) we can solve for x'_o obtaining

$$x'_o(\mathcal{I}_0) = \frac{1}{\det(J)} \det \left[\begin{array}{ccc} f_{\iota,x_\iota} & f_{\iota,x_\rho} & -f_{\iota,\mathcal{I}} \\ f_{\rho,x_\iota} & f_{\rho,x_\rho} & 0 \\ f_{o,x_\iota} & f_{o,x_\rho} & 0 \end{array} \right] \tag{9}$$

which leads to (6). By assumption, $f_{\iota,\mathcal{I}} \neq 0$. Hence, the fact that infinitesimal homeostasis for (2) is equivalent to (7) follows directly from (6). $\qquad \square$

1.3 Core networks

Homeostasis in a given network $\mathcal{G}$ can be determined by analyzing a simpler network that is obtained by eliminating certain nodes and arrows from $\mathcal{G}$. We call the network formed by the remaining nodes and arrows the *core subnetwork*.

Definition 1.5. A node τ in a network $\mathcal{G}$ is *downstream* from a node ρ in $\mathcal{G}$ if there exists a path in $\mathcal{G}$ from ρ to τ. Node ρ is *upstream* from node τ if τ is downstream from ρ.

These relationships are important when trying to classify infinitesimal homeostasis. For example, if the output node o is not downstream from the input node ι, then the input-output function $x_o(\mathcal{I})$ is identically constant in $\mathcal{I}$. Although technically this is a form of infinitesimal homeostasis, it is an uninteresting form.

Definition 1.6. The input-output network $\mathcal{G}$ is a *core network* if every node in $\mathcal{G}$ is both upstream from the output node o and downstream from the input node ι.

Every input-output network $\mathcal{G}$ has a maximal core subnetwork; namely, $\mathcal{G}_c$ is the *core subnetwork* whose nodes are the nodes in $\mathcal{G}$ that are both upstream from the output and downstream from the input and whose arrows are the arrows in $\mathcal{G}$ whose head and tail nodes are both nodes in $\mathcal{G}_c$.

The next result concerning core networks follows from Theorem 2.4.

Theorem 1.7. *Let $\mathcal{G}$ be an input-output network and let $\mathcal{G}_c$ be the associated core subnetwork. The input-output function associated with $\mathcal{G}_c$ has a point of infinitesimal homeostasis at $\mathcal{I}_0$ if and only if the input-output function associated with $\mathcal{G}$ has a point of infinitesimal homeostasis at $\mathcal{I}_0$.*

It follows from Theorem 1.7 that classifying infinitesimal homeostasis for networks $\mathcal{G}$ is equivalent to classifying infinitesimal homeostasis for the core subnetwork $\mathcal{G}_c$.

Definition 1.8. (a) Two $(n+2)$-node core networks are *core equivalent* if the determinants of their homeostasis matrices are identical polynomials of degree $n+1$.

(b) A *backward arrow* is an arrow whose head is the input node ι or whose tail is the output node o.

Corollary 1.9. *If two core networks differ from each other by the presence or absence of backward arrows, then the core networks are core equivalent.*

Proof. The linearized couplings associated to backward arrows are of form f_{ι,x_k} and f_{k,x_o}, which do not appear in the homeostasis matrix (7). $\qquad\square$

Therefore, backward arrows can be ignored when computing infinitesimal homeostasis with the homeostasis matrix H. However, backward arrows cannot be totally ignored, since they are involved in the determination of both the equilibria of (2) and their stability.

Corollary 1.9 can be generalized to a theorem giving necessary and sufficient graph theoretic conditions for core equivalence. See Theorem 3.3.

1.4 Infinitesimal homeostasis blocks

The previous results imply that the computation of infinitesimal homeostasis reduces to solving $\det(H) = 0$, where H is the homeostasis matrix associated with a core network. From now on we assume that the input-output network $\mathcal{G}$ is a core network.

It is important to observe that the nonzero entries of H are the linearized coupling strengths f_{j,x_ℓ} for the network connected nodes $\ell \to j$ and the linearized self-coupling strengths f_{j,x_j}. It follows that $h = \det(H)$ is a homogeneous polynomial of degree $n+1$ in the $(n+1)^2$ entries of H. The assumption that the network is core implies that this polynomial is nonzero. We use combinatorial matrix theory to show that in general h can factor and that there is a different type of infinitesimal homeostasis associated with each factor.

Frobenius-König theory (see [23] for an historical account) applied to the homeostasis matrix H implies that there are two constant $(n+1) \times (n+1)$ permutation matrices P and Q such that

$$
PHQ = \begin{bmatrix} B_1 & * & \cdots & * \\ 0 & B_2 & \cdots & * \\ \vdots & & & \vdots \\ 0 & 0 & \cdots & B_m \end{bmatrix} \tag{10}
$$

where the square matrices $B_1, \ldots, B_m$ are unique up to permutation. More precisely, each block B_η cannot be brought into the form (10) by permutation of its rows and columns. Hence

$$\det(H) = \det(B_1) \cdots \det(B_m) \quad \text{or} \quad h = h_1 \cdots h_m \tag{11}$$

is a unique factorization since $h_\eta = \det(B_\eta)$ cannot further factor for each η; that is, each $\det(B_\eta)$ is an irreducible homogeneous polynomial. Specifically:

Theorem 1.10. *The polynomial $h_\eta = \det(B_\eta)$ is* irreducible *(in the sense that it cannot be factored as a polynomial) if and only if the block submatrix B_η is* irreducible *(in the sense that B_η cannot be brought to the form (10) by permutation of rows and columns of B_η).*

Proof. The decomposition (10) corresponds to the irreducible components in the factorization (11) follows from [21, Theorem 4.2.6 (pp. 114–115) and Theorem 9.2.4 (p. 296)]. $\square$

A consequence of (11) and (7) is that for each $\eta = 1, \ldots, m$ there is a *defining condition* for infinitesimal homeostasis given by the polynomial equation $\det(B_\eta) = 0$. Recall that the input-output function is implicitly defined in terms of the external input $\mathcal{I}$ and $\det(B_\eta)$ is a homogeneous polynomial in the linearized coupling strengths f_{j,x_ℓ} evaluated at $X(\mathcal{I})$. Hence, there are m different defining conditions for infinitesimal homeostasis, $h_\eta(\mathcal{I}) = 0$, where each one gives a nonlinear equation that can be solved for some $\mathcal{I} = \mathcal{I}_0$. In practice, for a given model, it is unlikely that these equations can be solved in closed form; however, it is possible that each defining condition can be solved numerically. So, the decomposition of the homeostasis matrix H into blocks B_η simplifies the solution of $\det(H) = 0$.

Definition 1.11. Given the homeostasis matrix H of an input-output network $\mathcal{G}$, we call the unique irreducible diagonal blocks B_η in the decomposition (10) *irreducible components*. We say that homeostasis in $\mathcal{G}$ is *of type B_η* if $\det(B_\eta) = 0$ and $\det(B_\xi) \neq 0$ for all $\xi \neq \eta$.

1.5 Infinitesimal homeostasis classes

The next results assert that the irreducible components B_η of H determine two distinct *homeostasis classes* (appendage and structural) and that one can associate a subnetwork $\mathcal{K}_\eta$ of $\mathcal{G}$ with each B_η (see §4).

Let B_η be an irreducible component in the decomposition (10), where B_η is a $k \times k$ diagonal block, that is, B_η has degree k. Since the entries of B_η are entries of H, these entries have the form f_{ρ,x_τ}; that is, the entries are either 0 (if $\tau \to \rho$ is not an arrow in $\mathcal{G}$), *self-coupling* (if $\tau = \rho$), or *coupling* (if $\tau \to \rho$ is an arrow in $\mathcal{G}$).

Since P and Q in (10) are constant permutation matrices, all entries in each row (resp. column) of B_η must lie in a single row (resp. column) of H. Hence, B_η has the form

$$B_\eta = \begin{bmatrix} f_{\rho_1,x_{\tau_1}} & \cdots & f_{\rho_1,x_{\tau_k}} \\ \vdots & \ddots & \vdots \\ f_{\rho_k,x_{\tau_1}} & \cdots & f_{\rho_k,x_{\tau_k}} \end{bmatrix} \tag{12}$$

It follows that the number of self-coupling entries of B_η are the same no matter which permutation matrices P and Q are used in (10) to determine B_η. In Theorem 4.4 we show that a $k \times k$ submatrix B_η has either k or $k - 1$ self-coupling entries.

Definition 1.12. The homeostasis class of an irreducible component B_η of degree k is *appendage* if B_η has k self-couplings and *structural* if B_η has $k - 1$ self-couplings.

Definition 1.13. The subnetwork $\mathcal{K}_\eta$ of $\mathcal{G}$ associated with the homeostasis block B_η is defined as follows. The *nodes* in $\mathcal{K}_\eta$ are the union of nodes p and q where f_{p,x_q} is a nonzero entry in B_η and the *arrows* of $\mathcal{K}_\eta$ are the union of arrows $q \to p$ where $p \neq q$.

Theorem 4.7 implies that when B_η is appendage, the subnetwork $\mathcal{K}_\eta$ has k nodes and B_η can be put in a *standard Jacobian form* without any distinguished nodes ((36)). Also, when B_η is structural, the subnetwork $\mathcal{K}_\eta$ has $k+1$ nodes and B_η can be put in a *standard homeostasis form* with designated input node and output node ((37)). Moreover, in this case, the subnetwork $\mathcal{K}_\eta$ has no backward arrows. That is, $\mathcal{K}_\eta$ has no arrows whose head is the input node or whose tail is the output node. See Remark 4.8 for details.

1.6 Combinatorial characterization of homeostasis

Core input-output networks $\mathcal{G}$ have combinatorial properties that we now define and exploit. The key ideas are the concepts of ιo-simple paths and super-simple nodes.

Definition 1.14. Let $\mathcal{G}$ be a core input-output network.

(a) A directed path connecting nodes ρ and τ is called a *simple path* if it visits each node on the path at most once.

(b) An *ιo-simple path* is a simple path connecting the input node ι to the output node o.

(c) A node in $\mathcal{G}$ is *simple* if the node lies on an ιo-simple path and *appendage* if the node is not simple.

(d) A *super-simple* node is a simple node that lies on every ιo-simple path.

Nodes ι and o are super-simple since by definition these nodes are on every ιo-simple path. Lemma 6.1 shows that super-simple nodes are well ordered (by downstream ordering) and hence adjacent super-simple pairs of nodes can be identified.

1.6.1 Properties of appendage homeostasis

Characterization of appendage homeostasis networks requires the following definitions.

Definition 1.15. Let $\mathcal{G}$ be a core input-output network.

(a) The *appendage subnetwork* $\mathcal{A}_\mathcal{G}$ of $\mathcal{G}$ is the subnetwork consisting of all appendage nodes and all arrows in $\mathcal{G}$ connecting appendage nodes.

(b) The *complementary subnetwork* of an ιo-simple path S is the subnetwork $\mathcal{C}_S$ consisting of all nodes not on S and all arrows in $\mathcal{G}$ connecting those nodes.

(c) Nodes ρ_i, ρ_j in $\mathcal{A}_\mathcal{G}$ are *path equivalent* if there exists paths in $\mathcal{A}_\mathcal{G}$ from ρ_i to ρ_j and from ρ_j to ρ_i. An *appendage path component* is a path equivalence class in $\mathcal{A}_\mathcal{G}$.

(d) A *cycle* is a path whose first and last nodes are identical.

(e) Let $\mathcal{K} \subset \mathcal{A}_\mathcal{G}$ be a subnetwork. We say that $\mathcal{K}$ satisfies the *no cycle condition* if for every ιo-simple path S, nodes in $\mathcal{K}$ do not form a cycle with nodes in $\mathcal{C}_S \setminus \mathcal{K}$.

In §5 we prove that every subnetwork $\mathcal{K}_\eta$ of $\mathcal{G}$ associated with an irreducible appendage homeostasis block B_η consists of appendage nodes (Theorem 5.2), is an appendage path component of $\mathcal{A}_\mathcal{G}$, and satisfies the no cycle condition (Theorem 5.4). The converse is proved in Theorem 7.1.

Remark 1.16. Nodes in the appendage subnetwork $\mathcal{A}_\mathcal{G}$ can be written uniquely as the disjoint union

$$\mathcal{A}_\mathcal{G} = (\mathcal{A}_1 \dot{\cup} \cdots \dot{\cup} \mathcal{A}_s) \dot{\cup} (\mathcal{B}_1 \dot{\cup} \cdots \dot{\cup} \mathcal{B}_t) \tag{13}$$

where each $\mathcal{A}_i$ is an appendage path component that satisfies the no cycle condition and each $\mathcal{B}_i$ is an appendage path component that violates the no cycle condition. Moreover, each $\mathcal{A}_i$ (resp. $\mathcal{B}_i$) can be viewed as a subnetwork of $\mathcal{A}_\mathcal{G}$ by including the arrows in $\mathcal{A}_\mathcal{G}$ that connect nodes in $\mathcal{A}_i$ (resp. $\mathcal{B}_i$). We call $\mathcal{A}_i$ a *no cycle appendage path component* and $\mathcal{B}_i$ a *cycle appendage path component*.

1.6.2 Properties of structural homeostasis

Corollary 6.10 shows that if B_η corresponds to an irreducible structural block, then $\mathcal{K}_\eta$ has two adjacent super-simple nodes (Theorem 6.9) and these super-simple nodes are the input node ℓ and the output node j in $\mathcal{K}_\eta$. In addition, it follows from the standard homeostasis form (Theorem 4.7) that the network $\mathcal{K}_\eta$ contains no backward arrows. That is, no arrows of $\mathcal{K}_\eta$ go into the input node ℓ nor out of the output node j.

We use the properties of structural homeostasis to construct all structural homeostasis subnetworks $\mathcal{K}_\eta$ up to core equivalence. First, we introduce the following terminology.

Definition 1.17. The *structural subnetwork* $\mathcal{S}_\mathcal{G}$ of $\mathcal{G}$ is the subnetwork whose nodes are either simple or in a cycle appendage path component $\mathcal{B}_i$ (see Remark 1.16) and whose arrows are arrows in $\mathcal{G}$ that connect nodes in $\mathcal{S}_\mathcal{G}$.

Lemma 5.5 implies that all structural homeostasis subnetworks are contained in $\mathcal{S}_\mathcal{G}$, which is an input-output network. That is, $\mathcal{G}$ and $\mathcal{S}_\mathcal{G}$ have the same simple, super-simple, input, and output nodes. Lemma 6.2 shows that every non-super-simple simple node lies between two adjacent super-simple nodes. Using this fact, we can define a subnetwork $\mathcal{L}$ of $\mathcal{S}_\mathcal{G}$ for every pair of adjacent super-simple nodes.

Definition 1.18. Let ρ_1, ρ_2 be adjacent super-simple nodes.

(a) A simple node ρ is *between* ρ_1 and ρ_2 if there exists an ιo-simple path that includes ρ_1 to ρ to ρ_2 in that order.

(b) The *super-simple subnetwork*, denoted $\mathcal{L}(\rho_1, \rho_2)$, is the subnetwork whose nodes are simple nodes between ρ_1 and ρ_2 and whose arrows are arrows of $\mathcal{G}$ connecting nodes in $\mathcal{L}(\rho_1, \rho_2)$.

It follows that all $\mathcal{L}(\rho_1, \rho_2)$ are contained in $\mathcal{S}_\mathcal{G}$. By Lemma 6.3 (d), each appendage node in $\mathcal{S}_\mathcal{G}$ connects to exactly one $\mathcal{L}$. This lets us expand a super-simple subnetwork $\mathcal{L} \subset \mathcal{S}_\mathcal{G}$ to a super-simple structural subnetwork $\mathcal{L}' \subset \mathcal{S}_\mathcal{G}$ as follows.

Definition 1.19. Let ρ_1 and ρ_2 be adjacent super-simple nodes in $\mathcal{G}$. The *super-simple structural subnetwork* $\mathcal{L}'(\rho_1, \rho_2)$ is the input-output subnetwork consisting of nodes in $\mathcal{L}(\rho_1, \rho_2) \cup \mathcal{B}$ where $\mathcal{B}$ consists of all appendage nodes that form cycles with nodes in $\mathcal{L}(\rho_1, \rho_2)$; that is, all cycle appendage path components that connect to $\mathcal{L}(\rho_1, \rho_2)$. Arrows of $\mathcal{L}'(\rho_1, \rho_2)$ are arrows of $\mathcal{G}$ that connect nodes in $\mathcal{L}'(\rho_1, \rho_2)$. Note that ρ_1 is the input node and ρ_2 is the output node of $\mathcal{L}'(\rho_1, \rho_2)$.

In §6 we prove that every subnetwork $\mathcal{K}_\eta$ of $\mathcal{G}$ associated with an irreducible structural homeostasis block B_η is a super-simple structural subnetwork (Theorem 6.11). The converse is proved in Theorem 7.2.

1.7 Algorithm for enumerating homeostasis subnetworks

Below is an algorithm for enumerating subnetworks corresponding to the m homeostasis blocks.

Step 1: Determining the appendage homeostasis subnetworks from $\mathcal{A}_{\mathcal{G}}$. Let

$$\mathcal{A}_1 ,\ldots, \mathcal{A}_s \tag{14}$$

be the no cycle appendage path components of $\mathcal{A}_{\mathcal{G}}$ (see Remark 1.16). Theorem 7.1 implies that these appendage path components are the subnetworks $\mathcal{K}_\eta$ that correspond to appendage homeostasis blocks. In addition, there are s independent defining conditions for appendage homeostasis given by the determinants of the Jacobian matrices $\det(J_{\mathcal{A}_i}) = 0$ for $i = 1, \ldots, s$.

Step 2: Determining the structural homeostasis subnetworks from $\mathcal{S}_{\mathcal{G}}$. Let $\iota = \rho_1 > \rho_2 > \ldots > \rho_{q+1} = o$ be the super-simple nodes in $\mathcal{S}_{\mathcal{G}}$ in downstream order. Theorems 6.11 and 7.2 imply that up to core equivalence the q super-simple structural subnetworks

$$\mathcal{L}'(\iota, \rho_2),\ \mathcal{L}'(\rho_2, \rho_3) ,\ldots,\ \mathcal{L}'(\rho_{q-1}, \rho_q),\ \mathcal{L}'(\rho_q, o) \tag{15}$$

are the subnetworks $\mathcal{K}_\eta$ that correspond to structural homeostasis blocks. In addition, there are q defining conditions for structural homeostasis blocks given by the determinants of the homeostasis matrices of the input-output networks: $\det\big(H(\mathcal{L}'(\rho_i, \rho_{i+1}))\big) = 0$ for $i = 1, \ldots, q$.

Therefore, the $m = s + q$ subnetworks listed in (14) and (15) enumerate the appendage and structural homeostasis subnetworks in $\mathcal{G}$.
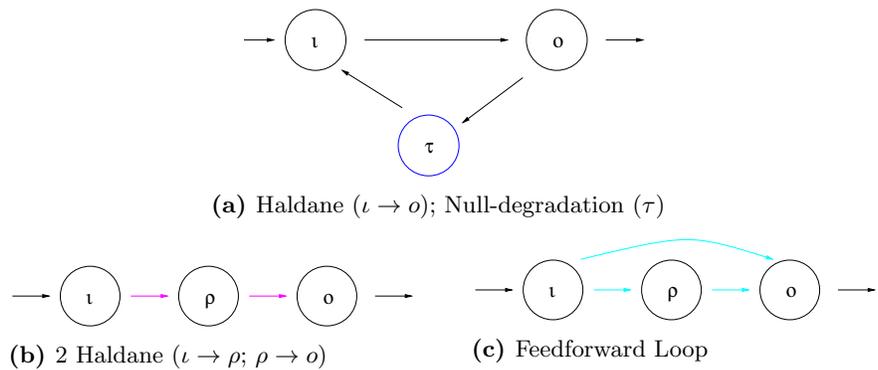
1.8 Low degree homeostasis types

Here we specialize our discussion to the low degree cases $k = 1$ and $k = 2$ where we determine all such homeostasis types (see Figure 1). The first three types appear in three node networks and are given in the classification in [13]. The fourth type has degree $k = 2$, but can only appear in networks with at least four nodes (see Figure 2(A)). We note that the lowest degree of a structural homeostasis block with an appendage node (that is, $\mathcal{L}' \supsetneq \mathcal{L}$) is $k = 3$ (see Figure 2(B)).

(a) Haldane ($\iota \to o$); Null-degradation (τ)

(b) 2 Haldane ($\iota \to \rho$; $\rho \to o$)   **(c)** Feedforward Loop

Fig 1. Homeostasis types in three-node networks. Classification of three-node core networks up to core equivalence (see [13]).

1.8.1 Degree 1 no cycle appendage homeostasis (*null-degradation*)

This corresponds to the vanishing of a degree 1 irreducible factor of the form (f_{τ,x_τ}). The single node τ is a no cycle appendage path component. Apply Step 1 in Algorithm §1.61.7 to Figure 1(A).

1.8.2 Degree 1 structural homeostasis (*Haldane*)

This corresponds to the vanishing of a degree 1 irreducible factor of the form (f_{j,x_ℓ}) whose associated subnetwork is $\mathcal{L}'(\ell, j)$ of the form $\ell \to j$. Apply Step 2 in Algorithm §1.61.7 to Figure 1(B).

1.8.3 Degree 2 structural homeostasis (*feed-forward loop*)

This corresponds to a three-node input-output subnetwork $\mathcal{L}'(\ell, j)$ with input node ℓ, output node j, and regulatory node ρ, where ℓ and j are adjacent super-simple and ρ is a simple node between the two super-simple nodes. It follows that both paths $\ell \to \rho \to j$ and $\ell \to j$ are in $\mathcal{L}' = \mathcal{L}$. Hence, $\mathcal{L}'$ is a feedforward loop motif. Homeostasis occurs when

$$\det \left(H(\mathcal{L}'(\ell, j)) \right) = f_{\rho,x_\ell} f_{j,x_\rho} - f_{j,x_\ell} f_{\rho,x_\rho} = 0$$
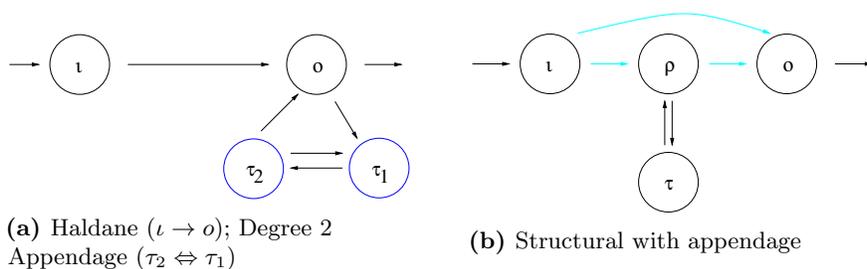
Apply Step 2 in Algorithm §1.61.7 to Figure 1(C).

1.8.4 Degree 2 no cycle appendage homeostasis

This is associated with a two-node appendage path component $\mathcal{A} = \{\tau_1, \tau_2\}$ with arrows $\tau_1 \to \tau_2$ and $\tau_2 \to \tau_1$. Homeostasis occurs when

$$\det \left(J(\mathcal{A}) \right) = f_{\tau_1,x_{\tau_1}} f_{\tau_2,x_{\tau_2}} - f_{\tau_1,x_{\tau_2}} f_{\tau_2,x_{\tau_1}} = 0$$

Apply Step 1 in Algorithm §1.61.7 to Figure 2(A).

(a) Haldane ($\iota \to o$); Degree 2 Appendage ($\tau_2 \Leftrightarrow \tau_1$)

(b) Structural with appendage

Fig 2. Homeostasis types in four-node networks. (A) is the smallest network with degree 2 no cycle appendage homeostasis. (B) is the smallest network that has appendage nodes in structural homeostasis.

1.9 12-Node artificial network example

We use an artificial example to illustrate the algorithm for enumerating homeostasis blocks. The network shown in Figure 3 has input node (ι), output node (o), six regulatory nodes ($\rho_1, \ldots, \rho_6$), and four appendage nodes ($\tau_1, \tau_2, \tau_3, \tau_4$). The input-output network $\mathcal{G}$ in Figure 3 has four ιo-simple paths (see Table 1) and six homeostasis subnetworks that can be found in two steps using the algorithm in §1.7.

    The input-output network $\mathcal{G}$ in Figure 3 has six homeostasis subnetworks, which can be found in two steps:

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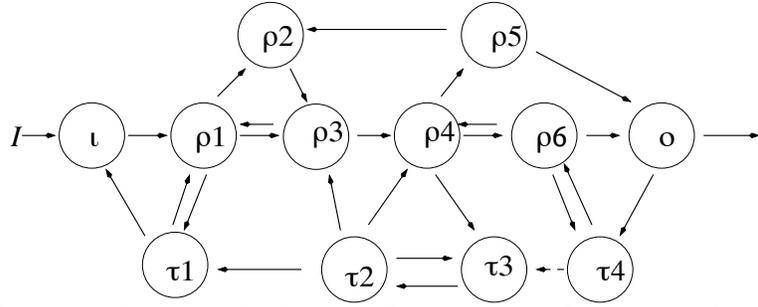
Fig 3. The 12-node example. Input node ι, output node o, six regulatory nodes $\rho_1, \ldots, \rho_6$, and four appendage nodes $\tau_1, \ldots, \tau_4$. The network has four ιo-simple paths (see Table 1) and five super-simple nodes $\iota, \rho_1, \rho_3, \rho_4, o$. The six homeostasis blocks are listed in Table 2.

Table 1. Four ιo-simple paths for network in Figure 3

Simple path (S)	Complementary subnetwork $(\mathcal{C}_S)$
$\iota \to \rho_1 \to \rho_2 \to \rho_3 \to \rho_4 \to \rho_5 \to o$	$\{\tau_1, \tau_2, \tau_3, \tau_4, \rho_6\}$
$\iota \to \rho_1 \to \rho_2 \to \rho_3 \to \rho_4 \to \rho_6 \to o$	$\{\tau_1, \tau_2, \tau_3, \tau_4, \rho_5\}$
$\iota \to \rho_1 \to \rho_3 \to \rho_4 \to \rho_5 \to o$	$\{\tau_1, \rho_2, \tau_2, \tau_3, \tau_4, \rho_6\}$
$\iota \to \rho_1 \to \rho_3 \to \rho_4 \to \rho_6 \to o$	$\{\tau_1, \tau_2, \tau_3, \tau_4, \rho_5, \rho_2\}$

Step 1: $\mathcal{G}$ has three appendage path components ($\mathcal{A}_1 = \{\tau_1\}$, $\mathcal{A}_2 = \{\tau_2, \tau_3\}$, $\mathcal{B}_1 = \{\tau_4\}$) in $\mathcal{A}_{\mathcal{G}}$. Among these, $\mathcal{A}_1$ and $\mathcal{A}_2$ satisfy the no cycle condition, whereas $\mathcal{B}_1$ does not since τ_4 forms a cycle with simple node ρ_6. Hence, there are two appendage homeostasis subnetworks given by $\mathcal{A}_1$ and $\mathcal{A}_2$.

Step 2: $\mathcal{G}$ has five super-simple nodes (in downstream order, they are $\iota, \rho_1, \rho_3, \rho_4, o$). The five super-simple nodes lead to four structural homeostasis subnetworks given (up to core equivalence) by $\mathcal{L}'(\iota, \rho_1)$, $\mathcal{L}'(\rho_1, \rho_3)$, $\mathcal{L}'(\rho_3, \rho_4)$, $\mathcal{L}'(\rho_4, o)$.

Table 2 lists the six homeostasis subnetworks in $\mathcal{G}$, which give the six irreducible factors of $\det(H)$ where H is the 11×11 homeostasis matrix of $\mathcal{G}$. The factorization of the degree 11 homogeneous polynomial $\det(H)$ is given by

$$\det(H) = \pm f_{\tau_1, x_{\tau_1}} \det(B_2) f_{\rho_1, x_\iota} \det(B_4) f_{\rho_4, x_{\rho_3}} \det(B_6)$$

where

$$B_2 = \begin{bmatrix} f_{\tau_2, x_{\tau_2}} & f_{\tau_2, x_{\tau_3}} \\ f_{\tau_3, x_{\tau_2}} & f_{\tau_3, x_{\tau_3}} \end{bmatrix} \qquad B_4 = \begin{bmatrix} f_{\rho_2, x_{\rho_1}} & f_{\rho_2, x_{\rho_2}} \\ f_{\rho_3, x_{\rho_1}} & f_{\rho_3, x_{\rho_2}} \end{bmatrix}$$

$$B_6 = \begin{bmatrix} f_{\rho_5, x_{\rho_4}} & f_{\rho_5, x_{\rho_5}} & 0 & 0 \\ f_{\rho_6, x_{\rho_4}} & 0 & f_{\rho_6, x_{\rho_6}} & f_{\rho_6, x_{\tau_4}} \\ 0 & 0 & f_{\tau_4, x_{\rho_6}} & f_{\tau_4, x_{\tau_4}} \\ 0 & f_{o, x_{\rho_5}} & f_{o, x_{\rho_6}} & 0 \end{bmatrix}$$

1.10   Remark on chairs

Nijhout, Best and Reed [24] observed that homeostasis often appears in models in the form of a *chair*. That is, as $\mathcal{I}$ varies, the input-output function $x_0(\mathcal{I})$ has the piecewise linear description: increases linearly, is approximately constant, and then increases

Table 2. Homeostasis subnetworks in Figure 3.

Class	Homeostasis subnetworks	Name
appendage	$\mathcal{A}_1 = \{\tau_1\}$	null-degradation
appendage	$\mathcal{A}_2 = \{\tau_1 \Leftrightarrow \tau_2\}$	no cycle appendage
structural	$\mathcal{L}'(\iota, \rho_1) = \{\iota \to \rho_1\}$	Haldane
structural	$\mathcal{L}'(\rho_1, \rho_3) = \{\rho_1, \rho_2\,\rho_3\}$	feedforward loop
structural	$\mathcal{L}'(\rho_3, \rho_4) = \{\rho_3 \to \rho_4\}$	Haldane
structural	$\mathcal{L}'(\rho_4, o) = \{\rho_4, \rho_5, \rho_6, \tau_4, o\}$	degree 4 structural

linearly again. Golubitsky and Stewart [12] observed that it follows from elementary catastrophe theory that smooth *chair singularities* have the normal form $\mathcal{I}^3$, defining conditions

$$x_o'(\mathcal{I}_0) = x_o''(\mathcal{I}_0) = 0$$

and nondegeneracy condition $x_0'''(\mathcal{I}_0) \neq 0$. Moreover, [13] noted that if $x_0'(\mathcal{I}) = g(\mathcal{I})h(\mathcal{I})$, where $g(\mathcal{I}_0) \neq 0$, then the defining conditions for a chair singularity are equivalent to

$$h(\mathcal{I}_0) = h'(\mathcal{I}_0) = 0 \qquad \text{and} \qquad h''(\mathcal{I}_0) \neq 0 \tag{16}$$

It follows from Lemma 1.4 and (11) that a chair singularity for infinitesimal homeostasis is of type B_η if $h_\eta(\mathcal{I})$ satisfies (16) at $\mathcal{I} = \mathcal{I}_0$.

1.11 Commentary

In this paper we propose a strategy for understanding the different ways that infinitesimal homeostasis can occur in admissible network dynamical systems. We consider input-output networks with a designated input node ι, a designated output node o, and admissible network differential equations, where the 1-dimensional input parameter $\mathcal{I}$ only affects the network through the input node. This setup allows us to consider the level of output x_o as a function of the input parameter $\mathcal{I}$, called the input-output function. Apart from these conditions, this class of networks includes arbitrarily large and complex networks with no prior assumption as to how the nodes are interconnected. The dynamics considered can also be arbitrary, as long as it is compatible with the network, that is, the results do not depend on the functional form of the associated model equations. This flexibility comes from the fact that our approach is based on the notion of infinitesimal homeostasis – points where the derivative of the input-output function is zero [12]. This makes the theory widely applicable – and not restricted only to biochemical network model equations. In fact, the theory is applicable to any class of model equations where the singularity theory point of view of homeostasis advanced in [12] is applicable.

1.12 Structure of the paper.

In §2 we show that infinitesimal homeostasis in the original system (1) occurs in a network if and only if infinitesimal homeostasis occurs in the core network for the associated frozen system. See Theorem 2.4. We discuss when backward arrows can be ignored when computing the determinant of the homeostasis matrix and the limitations of this procedure (see Corollary 1.9). In §3 we relate the form of the summands of the determinant of the homeostasis matrix H with the form of ιo-simple paths of the input-output network. See Theorem 3.2. In Theorem 3.3 we also discuss 'core equivalence'. In §4 we prove the theorems about the appendage and structural classes of homeostasis. See Definition 4.3, Theorem 4.4, and the normal form Theorem 4.7. In §5

we prove the necessary conditions that appendage homeostasis must satisfy. See
Theorem 5.4. §6 and §§6.5 introduce an ordering of super-simple nodes that leads to a
combinatorial definition of structural blocks. See Definitions 1.18 and 1.19. The
connection of these blocks with the subnetworks $\mathcal{K}_\eta$ obtained from the homeostasis
matrix is given in Corollary 6.7 and Theorem 6.11. §7 summarizes our algorithm for
finding infinitesimal homeostasis directly from the input-output network $\mathcal{G}$. It also gives
a topological classification of the different types of infinitesimal homeostasis that the
network $\mathcal{G}$ can support.

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2 Core networks

Let $\mathcal{G}$ be an input-output network with input node ι, output node o, and regulatory
nodes ρ_j. We use the notions of upstream and downstream nodes to construct a core
subnetwork $\mathcal{G}_c$ of $\mathcal{G}$.

The stable equilibrium $(X_0, \mathcal{I}_0)$ of the system of differential equations (1) satisfy a
system of nonlinear equations (4), that can be explicitly written as

$$
\begin{array}{rcl}
f_\iota(x_\iota, x_\rho, x_o, \mathcal{I}) & = & 0 \\
f_\rho(x_\iota, x_\rho, x_o) & = & 0 \\
f_\iota(x_\iota, x_\rho, x_o) & = & 0
\end{array}
\tag{17}
$$

We start by partitioning the regulatory nodes ρ into three types:

- those nodes σ that are both upstream from o and downstream from ι,

- those nodes d that are not downstream from ι,

- those nodes u that are downstream from ι and not upstream from o.

Based on this partition, the system (17) has the form

$$
\begin{array}{rcl}
f_\iota(x_\iota, x_\sigma, x_u, x_d, x_o, \mathcal{I}) & = & 0 \\
f_\sigma(x_\iota, x_\sigma, x_u, x_d, x_o) & = & 0 \\
f_u(x_\iota, x_\sigma, x_u, x_d, x_o) & = & 0 \\
f_d(x_\iota, x_\sigma, x_u, x_d, x_o) & = & 0 \\
f_o(x_\iota, x_\sigma, x_u, x_d, x_o) & = & 0
\end{array}
\tag{18}
$$

In Lemma 2.1 we make this form more explicit.

Lemma 2.1. *The definitions of σ, u, and d nodes imply the admissible system* (18)
has the form

$$
\begin{array}{rcl}
\dot{x}_\iota & = & f_\iota(x_\iota, x_\sigma, x_d, x_o, \mathcal{I}) \\
\dot{x}_\sigma & = & f_\sigma(x_\iota, x_\sigma, x_d, x_o) \\
\dot{x}_u & = & f_u(x_\iota, x_\sigma, x_u, x_d, x_o) \\
\dot{x}_d & = & f_d(x_d) \\
\dot{x}_o & = & f_o(x_\iota, x_\sigma, x_d, x_o)
\end{array}
\tag{19}
$$

*Specifically, arrows of type $\sigma \to d$, $\iota \to d$, $u \to d$, $o \to d$, $u \to \sigma$, $u \to o$, $u \to \iota$ do not
exist.*

Proof. We list the restrictions on (18) given first by the definition of d and then by the
definition of u.

$\sigma \nrightarrow d$ If a node in σ connects to a node in d, then there would be a path from ι to a
node in d and that node in d would be downstream from ι, a contradiction.
Therefore, f_d is independent of x_σ.

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$\iota \nrightarrow d$ Similarly, the node ι cannot connect to a node in d, because that node would then be downtream from ι, a contradiction. Therefore, f_d is independent of x_ι.

$o \nrightarrow d$ If there is an arrow $o \to d$, then there is a path $\iota \to \sigma \to o \to d$. Hence there is a path $\iota \to d$ and that is not allowed. Therefore, f_d is independent of x_o.

$u \nrightarrow d$ Note that nodes in u must be downstream from ι. Hence, there cannot be a connection from u to d or else there would be a connection from ι to d. Therefore, f_d is independent of x_u.

$u \nrightarrow \sigma$ if a node in u connects to a node in σ, then there would be a path from u to o and u would be upstream from o, a contradiction. Therefore, f_σ is independent of x_u.

$u \nrightarrow o$ Suppose a node in u connects to o. Then that node is upstream from o, a contradiction. Therefore, f_o is independent of x_u.

$u \nrightarrow \iota$ Finally, if u connects to ι, then u connects to o, a contradiction. Therefore, f_ι is independent of x_u.

The remaining types of connections can exist in $\mathcal{G}_c$. Arrows that can exist in $\mathcal{G}_c$ are shown in Figure 4. $\square$
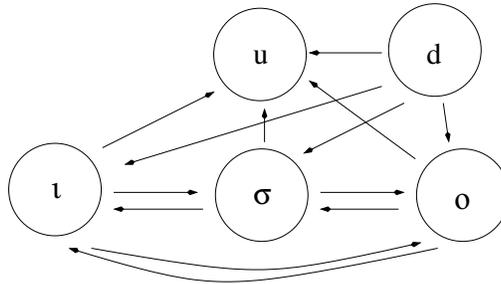
Fig 4. Core networks. Arrows indicating paths connecting nodes in partitioned input-output network.

Lemma 2.2. *Suppose $X_0 = (x_\iota^*, x_\sigma^*, x_u^*, x_d^*, x_o^*)$ is a stable equilibrium of* (19). *Then the core admissible system (obtained by freezing x_d at x_d^*)*

$$
\begin{aligned}
\dot{x}_\iota &= f_\iota(x_\iota, x_\sigma, x_d^*, x_o, \mathcal{I}) \\
\dot{x}_\sigma &= f_\sigma(x_\iota, x_\sigma, x_d^*, x_o) \\
\dot{x}_o &= f_o(x_\iota, x_\sigma, x_d^*, x_o)
\end{aligned}
\tag{20}
$$

has a stable equilibrium at $Y_0 = (x_\iota^*, x_\sigma^*, x_o^*)$.

Proof. It is straightforward that Y_0 is an equilibrium of (20). Reorder coordinates (ι, σ, u, d, o) to (ι, σ, o, d, u). Then Lemma 2.1 implies that the Jacobian J of (19) has the form

$$
J = \begin{bmatrix}
f_{\iota,x_\iota} & f_{\iota,x_\sigma} & 0 & f_{\iota,x_d} & f_{\iota,x_o} \\
f_{\sigma,x_\iota} & f_{\sigma,x_\sigma} & 0 & f_{\sigma,x_d} & f_{\sigma,x_o} \\
f_{u,x_\iota} & f_{u,x_\sigma} & f_{u,x_u} & f_{u,x_d} & f_{u,x_o} \\
0 & 0 & 0 & f_{d,x_d} & 0 \\
f_{o,x_\iota} & f_{o,x_\sigma} & 0 & f_{o,x_d} & f_{o,x_o}
\end{bmatrix}
\tag{21}
$$

and on swapping the u and o coordinates we see that J is similar to

$$J_1 = \begin{bmatrix} f_{\iota,x_\iota} & f_{\iota,x_\sigma} & f_{\iota,x_o} & f_{\iota,x_d} & 0 \\ f_{\sigma,x_\iota} & f_{\sigma,x_\sigma} & f_{\sigma,x_o} & f_{\sigma,x_d} & 0 \\ f_{o,x_\iota} & f_{o,x_\sigma} & f_{o,x_o} & f_{o,x_d} & 0 \\ 0 & 0 & 0 & f_{d,x_d} & 0 \\ f_{u,x_\iota} & f_{u,x_\sigma} & f_{u,x_o} & f_{u,x_d} & f_{u,x_u} \end{bmatrix} \tag{22}$$

It follows that the eigenvalues of J at X_0 are the eigenvalues of f_{d,x_d}, f_{u,x_u}, and the eigenvalues of the Jacobian of (20) at Y_0. Since the eigenvalues of J_1 have negative real part, the equilibrium Y_0 is stable. $\square$

Lemma 2.3. *Suppose that $\mathcal{G}$ is an input-output network with core network $\mathcal{G}_c$. Suppose that the core admissible system*

$$\begin{aligned} \dot{x}_\iota &= f_\iota(x_\iota, x_\sigma, x_o, \mathcal{I}) \\ \dot{x}_\sigma &= f_\sigma(x_\iota, x_\sigma, x_o) \\ \dot{x}_o &= f_o(x_\iota, x_\sigma, x_o) \end{aligned} \tag{23}$$

has a stable equilibrium at $Y_0 = (x_\iota^*, x_\sigma^*, x_o^*)$ and a point of infinitesimal homeostasis at $\mathcal{I}_0$. Then the admissible system for the original network $\mathcal{G}$ (obtained by lifting x_u and x_d)

$$\begin{aligned} \dot{x}_\iota &= f_\iota(x_\iota, x_\sigma, x_o, \mathcal{I}) \\ \dot{x}_\sigma &= f_\sigma(x_\iota, x_\sigma, x_o) \\ \dot{x}_d &= -x_d \\ \dot{x}_u &= -x_u \\ \dot{x}_o &= f_o(x_\iota, x_\sigma, x_o) \end{aligned} \tag{24}$$

has a stable equilibrium at $X_0 = (x_\iota^*, x_\sigma^*, 0, 0, x_o^*)$ and infinitesimal homeostasis at $\mathcal{I}_0$.

Theorem 2.4. *Let $x_o(\mathcal{I})$ be the input-output function of the admissible system (19) and let $x_o^c(\mathcal{I})$ be the input-output function of the associated core admissible system (20). Then the input-output function $x_o^c(\mathcal{I})$ associated with the core subnetwork has a point of infinitesimal homeostasis at $\mathcal{I}_0$ if and only if the input-output function $x_o(\mathcal{I})$ associated with the original network has a point of infinitesimal homeostasis at $\mathcal{I}_0$. More precisely,*

$$x_o'(\mathcal{I}) = k(\mathcal{I}) \, x_o^{c\,\prime}(\mathcal{I}) \tag{25}$$

where $k(\mathcal{I}_0) \neq 0$.

Proof. It follows from Lemma 1.4 that $x_o'(\mathcal{I}_0) = 0$ if and only if

$$\det \begin{bmatrix} f_{\sigma,x_\iota} & f_{\sigma,x_\sigma} & 0 & f_{\sigma,x_d} \\ f_{u,x_\iota} & f_{u,x_\sigma} & f_{u,x_u} & f_{u,x_d} \\ 0 & 0 & 0 & f_{d,x_d} \\ f_{o,x_\iota} & f_{o,x_\sigma} & 0 & f_{o,x_d} \end{bmatrix} = 0$$

if and only if

$$\det(f_{u,x_u}) \det \begin{bmatrix} f_{\sigma,x_\iota} & f_{\sigma,x_\sigma} & f_{\sigma,x_d} \\ 0 & 0 & f_{d,x_d} \\ f_{o,x_\iota} & f_{o,x_\sigma} & f_{o,x_d} \end{bmatrix} = 0$$

if and only if

$$\det(f_{u,x_u}) \det(f_{d,x_d}) \det \begin{bmatrix} f_{\sigma,x_\iota} & f_{\sigma,x_\sigma} \\ f_{o,x_\iota} & f_{o,x_\sigma} \end{bmatrix} = 0$$

Both matrices f_{u,x_u} and f_{d,x_d} are triangular with negative diagonal entries and thus have nonzero determinants. It then follows from Lemma 1.4 that $x_o{}'(\mathcal{I}_0) = 0$ if and only if

$$\det \begin{bmatrix} f_{\sigma,x_\iota} & f_{\sigma,x_\sigma} \\ f_{o,x_\iota} & f_{o,x_\sigma} \end{bmatrix} = 0 \tag{26}$$

is satisfied. $\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\square$

It follows from Theorem 2.4 and Lemma 2.3 that classifying infinitesimal homeostasis for networks $\mathcal{G}$ is identical to classifying infinitesimal homeostasis for the core subnetwork $\mathcal{G}_c$. Specifically, an admissible system with infinitesimal homeostasis for the core subnetwork yields, by Lemma 2.3, an admissible system with infinitesimal homeostasis for the original network which in turn yields the original system for the core subnetwork with infinitesimal homeostasis by Theorem 2.4.

Remark 2.5. Corollary 1.9 implies that backward arrows can be eliminated when computing zeros of $\det(H)$. These arrows cannot be eliminated when computing equilibria of the network equations or their stability. See (29) in Example 2.6.

Example 2.6. Consider the network in Figure 5. Assume WLOG that an admissible vector field for this network
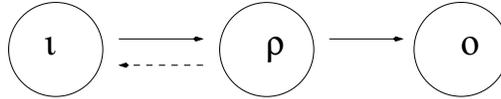
$$\begin{array}{rcl} \dot{x}_\iota & = & f_\iota(x_\iota, x_\rho, \mathcal{I}) \\ \dot{x}_\rho & = & f_\rho(x_\iota, x_\rho) \\ \dot{x}_o & = & f_o(x_\rho, x_o) \end{array} \tag{27}$$

has an equilibrium at the origin $(X_0, \mathcal{I}_0) = (0, 0)$; that is

$$f_\iota(0,0,0) = f_\rho(0,0) = f_o(0,0) = 0.$$

Begin by noting that the Jacobian of (27) is

$$J = \begin{bmatrix} f_{\iota,x_\iota} & f_{\iota,x_\rho} & 0 \\ f_{\rho,x_\iota} & f_{\rho,x_\rho} & 0 \\ 0 & f_{o,x_\rho} & f_{o,x_o} \end{bmatrix} \tag{28}$$

Fig 5. Network with a (dashed) backward arrow.

The origin is a linearly stable equilibrium if and only if

$$f_{o,x_0} < 0 \qquad f_{\iota,x_\iota} + f_{\rho,x_\rho} < 0 \qquad f_{\iota,x_\iota} f_{\rho,x_\rho} - f_{\iota,x_\rho} f_{\rho,x_\iota} > 0 \tag{29}$$

Whether the third inequality in (29) holds depends on the value of the backward coupling $f_{\iota,x_\rho} = 0$. However, whether infinitesimal homeostasis $(x_o'(0) = 0)$ occurs is independent of the backward coupling since

$$\det \begin{bmatrix} f_{\rho,x_\iota} & f_{\rho,x_\rho} \\ f_{o,x_\iota} & f_{o,x_\rho} \end{bmatrix} = \det \begin{bmatrix} f_{\rho,x_\iota} & f_{\rho,x_\rho} \\ 0 & f_{o,x_\rho} \end{bmatrix} = f_{\rho,x_\iota} f_{o,x_\rho} = 0$$

3   Determinant lemmas

Let H be the $(n+1) \times (n+1)$ homeostasis matrix (5) of the input-output network $\mathcal{G}$
with input node ι, n regulatory nodes ρ_j, and output node o, and admissible system (1).

Lemma 3.1. *Every nonzero summand of* $\det(H)$ *corresponds to a unique ιo-simple*
path and has all coupling strengths within this ιo-simple path as its factors.

Proof. Each nonzero summand in $\det(H)$ has $n+1$ factors and each factor is the
strength of a coupling arrow or of the linearized internal dynamics of a node. We can
write H as

$$
H = \begin{array}{c} \begin{array}{cccccc} \iota & \rho_1 & & \rho_{n-1} & \rho_n \\ \downarrow & \downarrow & & \downarrow & \downarrow \\ \rule{1em}{0.4pt} & \rule{1em}{0.4pt} & & \rule{1em}{0.4pt} & \rule{1em}{0.4pt} \end{array} \\ \begin{bmatrix} f_{1,\iota} & f_{1,1} & \cdots & f_{1,n-1} & f_{1,n} \\ f_{2,\iota} & f_{2,1} & \cdots & f_{2,n-1} & f_{2,n} \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ f_{n,\iota} & f_{n,1} & \cdots & f_{n,n-1} & f_{n,n} \\ f_{o,\iota} & f_{o,1} & \cdots & f_{o,n-1} & f_{o,n} \end{bmatrix} \begin{array}{l} | \leftarrow \rho_1 \\ | \leftarrow \rho_2 \\ \\ | \leftarrow \rho_n \\ | \leftarrow o \end{array} \end{array} \tag{30}
$$

The columns of H correspond to $n+1$ nodes in the order $\iota, \rho_1, \ldots, \rho_n$ and the rows of
H correspond to $n+1$ nodes in the order $\rho_1, \ldots, \rho_n, o$. The entry $f_{j,\iota} = f_{\rho_j, x_\iota}$ in
column ι is the linearized coupling strength of an arrow $\iota \to \rho_j$. The entry $f_{o,k} = f_{o,x_{\rho_k}}$
in row o is the linearized coupling strength of an arrow $\rho_k \to o$. The entry $f_{j,k} = f_{\rho_j, x_{\rho_k}}$
is the linearized coupling strength of an arrow $\rho_k \to \rho_j$. If $j = k$, the entry
$f_{k,k} = f_{\rho_k, x_{\rho_k}}$ is the linearized internal dynamics of node k. Note that each summand in
the expansion of $\det(H)$ has one factor associated with each column of H and one
factor associated with each row of H.

Fix a summand. By assumption there is a unique factor associated with the first
column. If this factor is $f_{o,\iota}$, we are done and the simple path is $\iota \to o$. So assume the
factor in the first column is $f_{k,\iota}$, where $1 \leq k \leq n$. This factor is associated with the
arrow $\iota \to \rho_k$.

Next there is a unique factor in the column called ρ_k and that factor corresponds to
an arrow $\rho_k \to \rho_j$ for some node ρ_j. If node ρ_j is o, the summand includes $(f_{k,\iota} f_{o,k})$
and the associated simple path is $\iota \to \rho_k \to o$. Hence we are done. If not, we assume
$1 \leq j \leq n$. Since there is only one summand factor in each row of H, it follows that
$k \neq j$. This summand is then associated with the path $\iota \to \rho_k \to \rho_j$ and contains the
factors $(f_{k,\iota} f_{j,k})$.

Proceed inductively. By the pigeon hole principle we eventually reach a node that
connects to o. The simple path that is associated to the given summand is unique
because we start with the unique factor in the summand that has an arrow whose tail is
ι and the choice of ρ_i is unique at each step. Moreover, every coupling within this
simple path is a factor of the given summand. □

The determinant formula (31) for $\det(H)$ in Theorem 3.2 is obtained by indexing
the sum by the ιo-simple paths of $\mathcal{G}$ as described in Lemma 3.1.

Theorem 3.2. *Suppose $\mathcal{G}$ has k ιo-simple paths $S_1, \ldots, S_k$ with corresponding*
complementary subnetworks $C_1, \ldots, C_k$. Then

(a) *The* determinant formula *holds:*

$$
\det(H) = \sum_{i=1}^{k} F_{S_i} \, G_{C_i} \tag{31}
$$

where F_{S_i} is the product of the coupling strengths within the ιo-simple path S_i and
G_{C_i} is a function of coupling strengths (including self-coupling strengths) from C_i.

(b) Specifically,

$$G_{C_i} = \pm \det(J_{C_i}) \tag{32}$$

where J_{C_i} is the Jacobian matrix of the admissible system corresponding to the complementary subnetwork C_i. Generically, a coupling strength in $\mathcal{G}$ cannot be a factor of G_{C_i}.

Proof.   (a) Let S_i be the $r+2$ node ιo-simple path $\iota \to j_1 \to \cdots \to j_r \to o$ and let

$$F_{S_i} = f_{i_1,x_\iota} f_{i_2,x_{i_1}} \cdots f_{i_r,x_{i_{r-1}}} f_{o,x_{i_r}}$$

be the product of all coupling strengths in S_i. By Lemma 3.1, $\det(H)$ has the form (31). We claim that G_{C_i} is a function depending only on the coupling strengths (including self-coupling strengths) from the complementary subnetwork C_i. Since each summand in the expansion of $\det(H)$ has only one factor in each column of H and one factor in each row of H, the couplings in G_{C_i} must have different tails and heads from the ones that appear in the simple path. Hence, G_{C_i} is a function of couplings (including self-couplings) between nodes that are not in the simple path S_i, as claimed.

(b) Next we show that up to sign G_{C_i} is the determinant of the Jacobian matrix of the admissible system for the subnetwork C_i (see (32)). To this end, relabel the nodes so that the ιo-simple path S_i is

$$\iota \to 1 \to \cdots \to r \to o$$

and the nodes in the complementary subnetwork C_i are labeled $r+1,\ldots,n$. Then

$$F_{S_i} = (-1)^\chi f_{1,x_\iota} f_{2,x_1} \cdots f_{r,x_{r-1}} f_{o,x_r}$$

where χ permutes the nodes of the ιo-simple path S_i to $1,\ldots,r$. The summands of $\det(H)$ associated with S_i are $F_{S_i} G_{C_i}$, where

$$G_{C_i} = \sum_\sigma (-1)^\sigma f_{r+1,x_{\sigma(r+1)}} \cdots f_{n,x_{\sigma(n)}} \tag{33}$$

and σ is a permutation of the indices $r+1,\ldots,n$. Observe that the right hand side of (33) is just $\det(J_{C_i})$ up to sign.

Lastly, we show that no coupling strength in $\mathcal{G}$ can be a factor of $\det(J_{C_i})$. The coupling strengths correspond to the arrows and the self-coupling strengths correspond to the nodes. The self-coupling strengths are the diagonal entries of J_{C_i}, which are generically nonzero. If we set all coupling strengths to 0 (that is, assume they are neutral), then the off-diagonal entries of $\det(J_{C_i})$ are 0 and $\det(J_{C_i}) \neq 0$. Now suppose that one coupling strength is a factor of $\det(J_{C_i})$, then $\det(J_{C_i}) = 0$ if that coupling is neutral and we have a contradiction. It follows that no coupling strength can be a factor of $\det(J_{C_i})$.

$\square$

Theorem 3.3. *Two core networks are core equivalent if and only if they have the same set of ιo-simple paths and the Jacobian matrices of the complementary subnetworks to any simple path have the same determinant up to sign.*

Proof. $\Rightarrow$ Let $\mathcal{G}_1$ and $\mathcal{G}_2$ be core networks and assume they are core equivalent. Therefore, $\det(B_1) = \det(B_2)$ and by Theorem 3.2

$$\det(B_1) \equiv \sum_{i=1}^k F_{S_i} G_{C_i} = \sum_{j=1}^\ell F_{T_j} G_{D_j} \equiv \det(B_2)$$

If a simple path of $\mathcal{G}_1$ were not a simple path of $\mathcal{G}_2$, the equality would fail; that is, the polynomials would be unequal. Therefore, we may assume $\ell = k$ and (by renumbering if needed) that $T_i = S_i$ for all i. It follows that

$$\sum_{i=1}^{k} F_{S_i} \left(G_{C_i} - G_{D_i} \right) = 0$$

Since the F_{S_i} are linearly independent it follows that $G_{C_i} = G_{D_i}$ for all i; that is, $\det(J_{C_i}) = \pm \det(J_{D_i})$ where J_{C_i} and J_{D_i} are the Jacobian matrices associated with $\mathcal{G}_1$ and $\mathcal{G}_2$. Hence the Jacobian matrices of the two complementary subnetworks have the same determinant up to sign.

$\Leftarrow$ The converse follows directly from Theorem 3.2. $\qquad\square$

Corollary 3.4. *Two core networks are core equivalent if they have the same set of ιo-simple paths and the same complementary subnetworks to these simple paths.*

Proof. Follows directly from Theorem 3.3. $\qquad\square$

4 Infinitesimal homeostasis classes

In this section we prove that there are two classes of infinitesimal homeostasis: *appendage* and *structural*. See Definition 4.3 and Theorem 4.4. The section ends with a description of a 'normal form' for appendage and structural homeostasis blocks. These 'normal forms' are given in Theorem 4.7.

§5 discusses graph theoretic attributes of appendage homeostasis and §§6.5 discusses graph theoretic attributes of structural homeostasis. This material leads to the conclusions in §7 where it is shown that each structural block is generated by two adjacent super-simple nodes and each appendage block is generated by a path component of the subnetwork of appendage nodes.

Recall from (10) that we can associate with each homeostasis matrix H a set of m irreducible square blocks $B_1, \ldots, B_m$ where

$$PHQ = \begin{bmatrix} B_1 & * & \cdots & * \\ 0 & B_2 & \cdots & * \\ \vdots & & & \vdots \\ 0 & 0 & \cdots & B_m \end{bmatrix} \tag{34}$$

and P and Q are $(n+1) \times (n+1)$ permutation matrices.

Lemma 4.1. *Let H be an $(n+1) \times (n+1)$ homeostasis matrix and let P and Q be $(n+1) \times (n+1)$ permutation matrices. Then the rows (and columns) of PHQ are the same as the rows (and columns) of H up to reordering. Moreover, the set of entries of H are identical with the set of entries of PHQ.*

Proof. The set of rows of PH are identical to the set of rows of H. A row of HQ contains the same entries as the corresponding row of H—but with entries permuted. The second statement follows from the first. $\qquad\square$

Recall that the entries of the homeostasis matrix H, defined in (5) for an admissible system of a given input-output network $\mathcal{G}$, appear in three types: 0, coupling, and self-coupling. The following lemma is important in our discussion of homeostasis types.

Lemma 4.2. *The number of self-coupling entries in each diagonal block B_η is an invariant of the homeostasis matrix H.*

Proof. Suppose H is transformed in two different ways to upper triangular form (34). Then one obtains two sets of diagonal blocks $B_1, \ldots, B_m$ and $\tilde{B}_1, \ldots \tilde{B}_{\tilde{m}}$. Since one set of blocks is transformed into the other by a permutation, it follows that the number of blocks in each set is the same. Moreover, the blocks are related by

$$\tilde{B}_{M(\nu)} = P_\nu B_\nu Q_\nu$$

where M is a permutation of the index sets and for each ν, P_ν and Q_ν are permutation matrices. It follows from Lemma 4.1 that the size and the number of self-coupling entries of the square matrices $\tilde{B}_{M(\nu)}$ and B_ν are identical. □

We can now define the two homeostasis classes.

Definition 4.3. Let B_η be an irreducible $k \times k$ square block associated with the $(n+1) \times (n+1)$ homeostasis matrix H in (34). The homeostasis class associated with B_η is *appendage* if B_η has k self-coupling entries and *structural* if B_η has $k-1$ self-coupling entries.

Theorem 4.4 shows that each square block is either appendage or structural.

Theorem 4.4. *Let H be an $(n+1) \times (n+1)$ homeostasis matrix and let B_η be a $k \times k$ square diagonal block of the matrix PHQ given in (34), where P and Q are permutation matrices and $k \geq 1$. Then B_η has either $k-1$ self-couplings or k self-couplings.*

Proof. Note that either

$$PHQ = \begin{bmatrix} B_\eta & D \\ 0 & E \end{bmatrix} \quad \text{or} \quad PHQ = \begin{bmatrix} A & B & C \\ 0 & B_\eta & D \\ 0 & 0 & E \end{bmatrix} \tag{35}$$

where A is an nonempty square matrix. In the first case in (35) B_η has single self-coupling entries in each of either $k-1$ or k columns.

We assume the second case in (35). From Lemma 4.1 it follows that PHQ has exactly one row and exactly one column without a self-coupling entry. Hence, if B_η has more than k self-couplings, then B_η and hence H have a row with at least two self-couplings, which is not allowed.

We show by contradiction that B_η has at least $k-1$ self-couplings. Suppose B_η has $\ell \leq k-2$ self-coupling entries. Note that there are ℓ self-couplings in B_η by assumption, and there are no self-couplings in the 0 block. Let b be the number of self-couplings in B. Then $b + \ell$ is the number of self-couplings in $[B\ B_\eta\ 0]^t$. Now, either every column or every column but one in $[B\ B_\eta\ 0]^t$ has a self-coupling. Therefore,

$$k - 1 \leq b + \ell \leq k \quad \text{or} \quad k - \ell - 1 \leq b \leq k - \ell$$

We consider the two cases:

- Assume $b = k - \ell - 1$. Then there exists one column in $[B\ B_\eta\ 0]^t$ that has no self-couplings. Therefore, every column in A has a self-coupling. Since B has a self-coupling, it follows that one row in $[A\ B\ C]$ has two self-couplings – a contradiction.

- Assume $b = k - \ell$. Since $[B\ B_\eta\ 0]^t$ has self-couplings in every column, it follows that A has a self-coupling in every column save at most one. It then follows that A has a self-coupling in every row save at most one. Since $k - \ell \geq 2$, at east one row in $[A\ B\ C]$ has two self-couplings – also a contradiction.

Therefore, $\ell = k - 1$ or $\ell = k$. □

We build on Theorem 4.4 by putting B_η into a standard form of type (39). Its proof uses the next two lemmas about shapes and summands. A *shape* $\mathcal{E}$ is a subspace of $m \times n$ matrices $E = (e_{ij})$, where $e_{ij} = 0$ for some fixed subset of indices i, j. A square shape $\mathcal{D}$ is *nonsingular* if $\det(D) \neq 0$ for some $D \in \mathcal{D}$. A *summand* of a nonsingular shape $\mathcal{D}$ is a nonzero product in $\det(D)$ for some $D \in \mathcal{D}$.

Lemma 4.5. *The nonzero summands of* $\det(PHQ)$ *and* $\det(H)$ *are identical.*

Proof. Since $\det(P) = \det(Q) = \pm 1$, it follows that $\det(PHQ) = \pm \det(H)$. Hence, the nonzero summands must be identical. $\square$

Lemma 4.6. *Suppose* $\mathcal{B}$ *and* $\mathcal{C}$ *are nonsingular shapes. Let* $\mathcal{E}$ *be the shape whose size is chosen so that* $\mathcal{D}$ *is the shape consisting of matrices*

$$D = \left[\begin{array}{cc} B & E \\ 0 & C \end{array} \right]$$

where $B \in \mathcal{B}$, $C \in \mathcal{C}$, $E \in \mathcal{E}$. *Then each summand of* $\mathcal{D}$ *is the product of a summand of* $\mathcal{B}$ *with a summand of* $\mathcal{C}$.

Proof. Suppose d is a summand of $\mathcal{D}$. The product d cannot have any entries in the 0 block of $\mathcal{D}$. Hence, $\mathsf{d} = \mathsf{bc}$. Moreover, there is a matrix $B \in \mathcal{B}$ such that $\det(B) = \mathsf{b}$ and a matrix $C \in \mathcal{C}$ such that $\det(C) = \mathsf{c}$. In fact, we can assume that the nonzero entries of B are precisely the entries in the nonzero product b. Similarly for c. Since $\det(D) \neq 0$ and $\det(D) = \det(B) \det(C)$, it follows that $\det(B) = \mathsf{b} \neq 0$ and $\det(C) = \mathsf{c} \neq 0$. Therefore, b and c are summands of $\mathcal{B}$ and $\mathcal{C}$, respectively. Conversely, assume that b and c are summands and conclude that d is also a summand. $\square$

It follows from Lemma 4.1 that the number of each type of entry in PHQ is the same as the number in H. Moreover, generically, the coupling and self-coupling entries are nonzero. It follows from (5) that the n superdiagonal entries of H are self-coupling entries and these are the only self-coupling entries in H. In addition, H has one self-coupling entry in each row except the last row, and one self-coupling in each column except the first column. By Lemma 4.1 there are exactly n self-coupling entries in PHQ with one in each row but one, and one in each column but one. We use these observations in the proof of Theorem 4.7.

Theorem 4.7. *Let* H *be an* $(n+1) \times (n+1)$ *homeostasis matrix. Suppose* $\det(H)$ *has a degree* $k \geq 1$ *irreducible factor* $\det(B_\eta)$, *where* B_η *be a* $k \times k$ *block diagonal submatrix of the matrix* PHQ *given in (34) and* P *and* Q *are permutation matrices. If* B_η *has* $k - 1$ *self-coupling entries, then we can assume that* B_η *has the form*

$$\left[\begin{array}{ccc} f_{\rho_1, x_{\rho_1}} & \cdots & f_{\rho_1, x_{\rho_k}} \\ \vdots & \ddots & \vdots \\ f_{\rho_k, x_{\rho_1}} & \cdots & f_{\rho_k, x_{\rho_k}} \end{array} \right] \tag{36}$$

and if B_η *has* k *self-coupling entries, then we can assume that* B_η *has the form*

$$\left[\begin{array}{cccc} f_{\rho_1, x_{\rho_1}} & \cdots & f_{\rho_1, x_{\rho_{k-1}}} & f_{\rho_1, x_\ell} \\ \vdots & \ddots & \vdots & \vdots \\ f_{\rho_{k-1}, x_{\rho_1}} & \cdots & f_{\rho_{k-1}, x_{\rho_{k-1}}} & f_{\rho_{k-1}, x_\ell} \\ f_{j, x_{\rho_1}} & \cdots & f_{j, x_{\rho_{k-1}}} & f_{j, x_\ell} \end{array} \right] \tag{37}$$

Proof. Theorem 4.4 implies that B_η has either $k-1$ or k self-couplings. Since B_η is a $k \times k$ submatrix of PHQ (a matrix that has the same set of rows and the same set of columns as H), B_η must consists of k^2 entries of the form

$$B_\eta = \begin{bmatrix} f_{\rho_1, x_{\tau_1}} & \cdots & f_{\rho_1, x_{\tau_k}} \\ \vdots & \ddots & \vdots \\ f_{\rho_k, x_{\tau_1}} & \cdots & f_{\rho_k, x_{\tau_k}} \end{bmatrix} \tag{38}$$

Since self-couplings must be in different rows and different columns we can use permutation matrices of the form

$$\begin{bmatrix} I_p & 0 & 0 \\ 0 & S & 0 \\ 0 & 0 & I_q \end{bmatrix}$$

where S is a $k \times k$ permutation matrix to put B_η in the form:

$$\begin{bmatrix} * & sc & \cdots & * \\ * & * & \ddots & \vdots \\ \vdots & \vdots & \vdots & sc \\ * & \cdots & \cdots & * \end{bmatrix} \quad \text{or} \quad \begin{bmatrix} sc & * & * \\ * & \ddots & * \\ * & * & sc \end{bmatrix} \tag{39}$$

where sc denotes a self-coupling entry and $*$ denotes either a 0 entry or a coupling entry. Note that we could just as well have put the self-coupling entries along the diagonal in (39) (left).

If B_η has $k-1$ self-couplings, as in (39) (left), then $\rho_k \neq \tau_k$ and $\rho_j = \tau_j$ for $1 \le j \le k-1$. If B_η has k self-couplings, as in (39) (right), then we may assume $\rho_j = \tau_j$ for all j. It follows that the matrices in (39) have the form (37) or (36). $\square$

Remark 4.8. We use Theorem 4.7 to associate a subnetwork $\mathcal{K}_\eta$ with each homeostasis $k \times k$ block B_η. This construction implements the one in Definition 1.13 for appendage and structural homeostasis blocks. The network $\mathcal{K}_\eta$ will be an input-output subnetwork with $k+1$ nodes when B_η is structural and the network $\mathcal{K}_\eta$ will be a standard subnetwork with k nodes when B_η is appendage.

If B_η is appendage, then the k nodes in $\mathcal{K}_\eta$ will correspond to the k self-couplings in B_η and the arrows in K_η will be $\tau_i \to \tau_j$ if $h_{\tau_j, x_{\tau_j}}$ is a coupling entry in (36).

If B_η is structural, then the $k-1$ regulatory nodes of $\mathcal{K}_\eta$ will correspond to the self-couplings in B_η and the input node ℓ and the output node j of $\mathcal{K}_\eta$ will be given by the coupling entry in (37). The arrows in $\mathcal{K}_\eta$ are given by the coupling entries of B_η.

Note that the constructions of $\mathcal{K}$ from H do not require that H is a homeostasis block; the constructions only require that H has the form given in either (37) or (36).

5   Appendage homeostasis blocks

An appendage block B_η has k self-couplings and the form of a $k \times k$ matrix (36), that is rewritten here as:

$$B_\eta = \begin{bmatrix} f_{\tau_1, x_{\tau_1}} & \cdots & f_{\tau_1, x_{\tau_k}} \\ \vdots & \ddots & \vdots \\ f_{\tau_k, x_{\tau_1}} & \cdots & f_{\tau_k, x_{\tau_k}} \end{bmatrix} \tag{40}$$

As discussed in Remark 4.8 this homeostasis block is associated with a subnetwork $\mathcal{K}_\eta$ consisting of distinct nodes $\tau_1, \ldots, \tau_k$ and arrows specified by B_η that connect these nodes. In this section we show that $\mathcal{K}_\eta$ satisfies three additional conditions:

(a) Each node $\tau_j \in \mathcal{K}_\eta$ is an appendage node (Theorem 5.2).

(b) For every ιo-simple path S, nodes in $\mathcal{K}_\eta$ do not form a cycle with nodes in $\mathcal{C}_S \setminus \mathcal{K}_\eta$ (Theorem 5.4(a)).

(c) $\mathcal{K}_\eta$ is a path component of the subnetwork of appendage nodes of $\mathcal{G}$ (Theorem 5.4(b)).

Lemma 5.1. *Suppose a nonzero summand β of $\det(B_\eta)$ in (40) has $f_{\tau_j, x_{\tau_i}}$ as a factor, where $\tau_j \neq \tau_i$. Then the arrow $\tau_i \to \tau_j$ is contained in a cycle in $\mathcal{K}_\eta$.*

Proof. To simplify notation we drop the subscript η below on $\tilde{H}$, $\mathcal{K}$, and $\tilde{\mathcal{K}}$. Let $\tilde{H}$ be the $(k-1) \times (k-1)$ submatrix obtained by eliminating the jth row and the ith column of B_η in (40). Since $\tau_i \neq \tau_j$, $\tilde{H}$ has $k-2$ self-coupling entries. Specifically, the two self-couplings $f_{\tau_i, x_{\tau_i}}$ and $f_{\tau_j, x_{\tau_j}}$ have been removed when creating $\tilde{H}$ from B_η.

It follows from Remark 4.8 that since $\tilde{H}$ has the form (37), we can associate an input-output network $\tilde{\mathcal{K}}$ with $\tilde{H}$, where the input node is τ_j since it does not receive any input and the output node is τ_i since it does not output to any node in $\tilde{\mathcal{K}}$. By Lemma 3.1, every nonzero summand in $\det(\tilde{H})$ corresponds to a simple path from $\tau_j \to \tau_i$. Hence, the nonzero summand β is given by $f_{\tau_j, x_{\tau_i}}$ times a nonzero summand corresponding to a simple path from $\tau_j \to \tau_i$. Therefore, the arrow $\tau_i \to \tau_j$ coupled with the path $\tau_j \to \tau_i$ forms a cycle in $\mathcal{K}$. $\square$

Theorem 5.2. *Let $\mathcal{K}_\eta$ be a subnetwork of $\mathcal{G}$ associated with an appendage homeostasis block B_η that consists of a subset of nodes $\tau_1, \cdots, \tau_k$ of $\mathcal{G}$. Then B_η equals the Jacobian $J_{\mathcal{K}_\eta}$ of the network $\mathcal{K}_\eta$ and each node τ_j is an appendage node.*

Proof. Admissible systems associated with the network $\mathcal{K}_\eta$ have the form

$$\begin{aligned}
\dot{x}_{\tau_1} &= f_{\tau_1}(x_{\tau_1}, \ldots, x_{\tau_k}) \\
&\vdots \\
\dot{x}_{\tau_k} &= f_{\tau_k}(x_{\tau_1}, \ldots, x_{\tau_k})
\end{aligned}$$

where the variables that appear on the RHS of each equation correspond to the couplings in (40). It follows that the matrix B_η in (40) equals the Jacobian $J_{\mathcal{K}_\eta}$, as claimed.

We show that $\tau_j \in \mathcal{K}_\eta$ is an appendage node for each j. More specifically, we show that τ_j is in the complementary subnetwork C_S of each ιo-simple path S. We now fix τ_j and S.

We make two claims. First, every nonzero summand α of $\det(H)$ either contains the self-coupling $f_{\tau_j, x_{\tau_j}}$ as a factor or a coupling $f_{\tau_j, x_{\tau_i}}$ for some $i \neq j$ as a factor. Second, this dichotomy is sufficient to prove the theorem.

First claim. It follows from Lemma 4.6 that each summand of $\det(PHQ)$ has a summand of $\det(B_\eta)$ as a factor. Therefore, each summand α of $\det(H)$ has a summand β of $\det(B_\eta)$ as a factor. The claim follows from two facts. The first is that B_η is the Jacobian $J_{\mathcal{K}_\eta}$ and hence either the self-coupling is in β or the off diagonal entry is in β; and the second is that once these entries are in β, they are also in α.

Second claim. Recall that Theorem 3.2 (the determinant theorem) implies that the summand α has the form $F_S g_{C_S}$ where S is an ιo-simple path, C_S is the complementary subnetwork to S, F_S is the product of the coupling strengths within S, J_{C_S} is the Jacobian matrix of the admissible system corresponding to C_S, and g_{C_S} is a summand in $\det(J_{C_S})$.

If the summand α has $f_{\tau_j, x_{\tau_j}}$ as a factor, it follows that $f_{\tau_j, x_{\tau_j}}$ is a factor of g_{C_S} since it is a self-coupling and cannot be a factor of F_S. Hence, node τ_j is a node in C_S.

If the summand α has $f_{\tau_j,x_{\tau_i}}$ as a factor, then $f_{\tau_j,x_{\tau_i}}$ is either not a factor of F_S or is a factor of F_S. In the first case, $f_{\tau_j,x_{\tau_i}}$ is a factor of g_{C_S}. It follows that τ_j is a node in C_S. In the second case, the arrow $\tau_i \to \tau_j$ is on the simple path S. Recall that $f_{\tau_j,x_{\tau_i}}$ is also a factor of the summand β. It follows from Lemma 5.1 applied to β that $\tau_i \to \tau_j$ is contained in a cycle in K_η. This is a contradiction since we show that $\tau_i \to \tau_j$ cannot be contained in both the simple path S and a cycle in $\mathcal{K}_\eta$.

Since $\tau_i \to \tau_j$ is contained in a cycle in $\mathcal{K}_\eta$, there exists an arrow $\tau_k \to \tau_i$ where τ_k is a node in $\mathcal{K}_\eta$ (τ_k can be τ_j). Since every nonzero summand of $\det(H)$ has a summand of $\det(B_\eta)$ as a factor, there exists a summand $F_S g_{C_S}$ having both $f_{\tau_j,x_{\tau_i}}$ and $f_{\tau_i,x_{\tau_k}}$ as factors. Note that $f_{\tau_j,x_{\tau_i}}$ is a factor of F_S and g_{C_S} is a summand in $\det(J_{C_S})$. Since $\tau_k \to \tau_i$ cannot be contained in S it must be a factor of g_{C_S}. However, C_S is the complementary subnetwork to S that does not contain any arrow connecting to τ_i in the simple path S. $\qquad\square$

Lemma 5.3. *Let $\mathcal{K}$ be a proper subnetwork of a subnetwork C of $\mathcal{G}$. If nodes in $\mathcal{K}$ do not form a cycle with nodes in $C \setminus \mathcal{K}$, then upon relabelling nodes J_C is block lower triangular.*

Proof. The no cycle condition implies that we can partition nodes in C into three classes:

(i) nodes in $C \setminus \mathcal{K}$ that are strictly upstream from $\mathcal{K}$,

(ii) nodes in $\mathcal{K}$,

(iii) nodes in $C \setminus \mathcal{K}$ that are not upstream from $\mathcal{K}$.

By definition nodes in sets (i) and (iii) are disjoint from nodes in (ii). Also, nodes in sets (i) and (iii) are disjoint because nodes in $\mathcal{K}$ do not form a cycle with nodes in $C \setminus \mathcal{K}$. Finally, it is straightforward to see that $\mathcal{C} = \text{(i)} \cup \text{(ii)} \cup \text{(iii)}$. Using this partition of $\mathcal{C}$, we claim that the Jacobian matrix of C has the desired block lower triangular form:

$$J_C = \left[\begin{array}{ccc|c|ccc} * & \cdots & * & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ * & \cdots & * & 0 & 0 & \cdots & 0 \\ \hline * & \cdots & * & J_\mathcal{K} & 0 & \cdots & 0 \\ \hline * & \cdots & * & * & * & \cdots & * \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ * & \cdots & * & * & * & \cdots & * \end{array}\right] \tag{41}$$

Specifically, observe that there are no connections from (i) to (iii) because then a node in (iii) would be strictly upstream from $\mathcal{K}$. By definition there are no connections from (ii) to (iii). Finally, the cycle condition implies that there are no connections from (i) to (ii). $\qquad\square$

Theorem 5.4. *Let $\mathcal{K}_\eta$ be a subnetwork of $\mathcal{G}$ associated with an appendage homeostasis block B_η. Then:*

(a) *For every ιo-simple path S, nodes in $\mathcal{K}_\eta$ do not form a cycle with nodes in $C_S \setminus \mathcal{K}_\eta$.*

(b) *$\mathcal{K}_\eta$ is a path component of $\mathcal{A}_\mathcal{G}$.*

Proof. By Theorem 5.2, $\mathcal{K}_\eta \subset \mathcal{A}_\mathcal{G}$ is an appendage subnetwork that is contained in each complementary subnetwork C_S, $B_\eta = J_{\mathcal{K}_\eta}$ and $\det(J_{\mathcal{K}_\eta})$ is a factor of $\det(H)$. To simplify notation in the rest of the proof, we drop the subscript η and use $\mathcal{K}$ to denote the appendage subnetwork.

Proof of (a) We proceed by contradiction and assume there is a cycle. Let S be an ιo-simple path. Let $\mathcal{B} \subset C_S \setminus \mathcal{K}$ be the nonempty subset of nodes that are on some cycle connecting nodes in $\mathcal{K}$ with nodes in $C_S \setminus \mathcal{K}$. It follows that nodes in $\mathcal{K}$ do not form any cycle with nodes in $(C_S \setminus \mathcal{K}) \setminus \mathcal{B} = C_S \setminus (\mathcal{K} \cup \mathcal{B})$. Since $\mathcal{K} \cup \mathcal{B} \subset C_S$ and nodes in $\mathcal{K} \cup \mathcal{B}$ do not form a cycle with nodes in $C_S \setminus (\mathcal{K} \cup \mathcal{B})$, by Lemma 5.3 we see that the Jacobian matrix of C_S has the form

$$J_{C_S} = \begin{bmatrix} U & 0 & 0 \\ * & J_{\mathcal{K} \cup \mathcal{B}} & 0 \\ * & * & D \end{bmatrix} \tag{42}$$

where

$$J_{\mathcal{K} \cup \mathcal{B}} = \begin{bmatrix} J_{\mathcal{K}} & f_{\mathcal{K}, x_{\mathcal{B}}} \\ f_{\mathcal{B}, x_{\mathcal{K}}} & J_{\mathcal{B}} \end{bmatrix}$$

Note that $f_{\mathcal{K}, x_{\mathcal{B}}} \neq 0$ and $f_{\mathcal{B}, x_{\mathcal{K}}} \neq 0$, since there is a cycle containing nodes in $\mathcal{K}$ and $\mathcal{B}$. We claim that the polynomial $\det(J_{\mathcal{K}})$ does not factor the polynomial $\det(J_{\mathcal{K} \cup \mathcal{B}})$. It is sufficient to verify this statement for one admissible vector field.

Relabel the nodes so that there is a cycle of nodes $1 \to 2 \to \cdots \to p \to 1$ where the first q nodeas are in $\mathcal{K}$. We can choose the cycle so that the remaining nodes are in $\mathcal{B}$. An admissible system for this cycle has the form

$$(f_1, f_2, \ldots, f_p)(x) = (f_1(x_1, x_p), f_2(x_2, x_1), \cdots, f_p(x_p, x_{p-1}))$$

and all other coordinate functions $f_r(x) = x_r$. Hence the associated Jacobian matrix is

$$J_{\mathcal{K} \cup \mathcal{B}} = \left[\begin{array}{cccc|cccc|ccc} f_{1,x_1} & 0 & \cdots & 0 & 0 & \cdots & f_{1,x_p} & \cdots & \cdots & 0 \\ f_{2,x_1} & f_{2,x_2} & \cdots & 0 & 0 & \cdots & \cdots & \cdots & \cdots & 0 \\ \vdots & \ddots & \ddots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ * & \cdots & f_{q,x_{q-1}} & f_{q,x_q} & 0 & \cdots & \cdots & \cdots & \cdots & 0 \\ \hline 0 & \cdots & 0 & f_{q+1,x_q} & f_{q+1,x_{q+1}} & \cdots & \cdots & \cdots & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \ddots & \vdots & \vdots & \vdots & \vdots \\ 0 & \cdots & 0 & 0 & 0 & f_{p,x_{p-1}} & f_{p,x_p} & \cdots & \cdots & \cdots \\ \hline 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & 0 \\ 0 & \cdots & 0 & 0 & 0 & \cdots & \cdots & 0 & \cdots & 1 \end{array} \right]$$
$$\tag{43}$$

where the upper left block is $J_{\mathcal{K}}$. It follows from direct calculation that the determinant of the $J_{\mathcal{K} \cup \mathcal{B}}$ is

$$\det(J_{\mathcal{K} \cup \mathcal{B}}) = f_{1,x_1} f_{2,x_2} \cdots f_{p,x_p} + (-1)^{(p-1)} f_{1,x_2} f_{2,x_3} \cdots f_{p,x_1} \tag{44}$$

Hence

$$\det(J_{\mathcal{K}}) = f_{1,x_1} f_{2,x_2} \cdots f_{q,x_q}$$

is not a factor of $\det(J_{\mathcal{K} \cup \mathcal{B}})$, given in (44). We claim that $\det(J_{\mathcal{K}})$ is also not a factor of $\det(J_{C_S})$ because by (42), $\det(J_{C_S}) = \det(U) \det(J_{\mathcal{K} \cup \mathcal{B}}) \det(D)$. Suppose $\det(J_{\mathcal{K}})$ is a factor of $\det(J_{C_S})$, then it must be a factor of $\det(J_{\mathcal{K} \cup \mathcal{B}})$, which is a contradiction. Thus $\det(J_{\mathcal{K}})$ is not a factor of $\det(J_{C_S})$, which contradicts the fact that $\mathcal{K}_\eta$ is an appendage homeostasis block. Hence, nodes in $\mathcal{K}$ cannot form a cycle with nodes in $C_S \setminus \mathcal{K}$.

Proof of (b)   We begin by showing that $\mathcal{K}$ is path connected; that is, there is a path from τ_i to τ_j for every pair of nodes $\tau_i, \tau_j \in \mathcal{K}$. Suppose not, then the path components of $\mathcal{K}$ give $\mathcal{K}$ a feedforward structure. It follows that we can partition the set of nodes in $\mathcal{K}$ into two disjoint classes: A and B where nodes in B are strictly downstream from nodes in A. Thus, there exist permutation matrices P_η and Q_η such that

$$
P_\eta B_\eta Q_\eta = \left[\begin{array}{cc} J_A & 0 \\ * & J_B \end{array} \right]
$$

which contradicts the fact that B_η is irreducible. Therefore, $\mathcal{K}$ is path connected.

Next, we show that $\mathcal{K}$ is a path component of $\mathcal{A}_\mathcal{G}$. Suppose that the path component $\mathcal{W} \subset C_S$ of $\mathcal{A}_\mathcal{G}$ that contains $\mathcal{K}$ is larger than $\mathcal{K}$. Then there would be a cycle in $\mathcal{W} \subset C_S$ that starts and ends in $\mathcal{K}$, and contains nodes not in $\mathcal{K}$. This contradicts (a) and $\mathcal{W} = \mathcal{K}$. □

Recall from Definition 1.17 that $\mathcal{S}_\mathcal{G}$ is a subnetwork of $\mathcal{G}$ that can be obtained by removing all appendage path components that satisfy the no cycle condition.

Lemma 5.5. *Let $\mathcal{G}$ be an input-output network with homeostasis matrix H. Then the structural subnetwork $\mathcal{S}_\mathcal{G}$ is an input-output network with homeostasis matrix H' and $\det(H')$ is a factor of $\det(H)$.*

Proof. By Theorem 5.2, if B_η is an appendage homeostasis block, then the associated subnetwork $\mathcal{K}_\eta$ consists of appendage nodes, and $B_\eta = J_{\mathcal{K}_\eta}$. Relabel the blocks so that $B_1, \cdots, B_p$ are appendage homeostasis blocks. We can write

$$
PHQ = \left[\begin{array}{ccccc} J_{\mathcal{K}_1} & * & \cdots & & * \\ 0 & \ddots & & * & \vdots \\ \vdots & & 0 & J_{\mathcal{K}_p} & * \\ 0 & \cdots & & 0 & H' \end{array} \right]
$$

Hence $\det(H')$ is a factor of $\det(H)$.

Recall H is an $(n+1) \times (n+1)$ matrix with n self-couplings. Since the main diagonal entries of $J_{\mathcal{K}_i}$ are all self-couplings, H' is a $(n+1-\gamma) \times (n+1-\gamma)$ matrix where γ is the total number of self-couplings in $\mathcal{K}_1, \cdots, \mathcal{K}_p$. It follows that H' has $n - \gamma$ self-couplings. By Theorem 4.7 we can assume H' has the homeostasis matrix form and is associated with an input-output subnetwork $\mathcal{S}_\mathcal{G}$ of $\mathcal{G}$.

It follows from the upper triangular form of PHQ that $\mathcal{S}_\mathcal{G}$ does not contain any node in appendage blocks or any coupling whose head or tail is a node in an appendage block. Moreover, a node that is not associated with any appendage block must be contained in $\mathcal{S}_\mathcal{G}$. Otherwise, the self-coupling of this node will appear in some $J_{\mathcal{K}_i}$, which is a contradiction.

Hence, $\mathcal{S}_\mathcal{G}$ is an input-output network that consists of all nodes not associated with any appendage block and all arrows that connect nodes in $\mathcal{S}_\mathcal{G}$. □

Remark 5.6. Suppose $\mathcal{K}_\eta$ is an input-output subnetwork of $\mathcal{G}$ associated with an irreducible matrix B_η in (37). Then, it follows from Lemma 5.5 that B_η is a structural block of $\mathcal{G}$ if and only if B_η is a structural block of $\mathcal{S}_\mathcal{G}$.

6   Structural homeostasis blocks

In this section we give a combinatorial description of $\mathcal{S}_\mathcal{G}$ in terms of input-output subnetworks defined by super-simple nodes. We do this in four stages.

§6.1 shows that the super-simple nodes in $\mathcal{G}$ can be ordered by $\iota > \rho_1 > \cdots > \rho_q > o$ where $a > b$ if b is downstream from a. See Lemma 6.1.

§6.2 defines the sets $\mathcal{L}$ of simple nodes that lie between adjacent super-simple nodes. See Definition 1.18 and Lemma 6.2.

§6.3 shows how to assign each appendage node in $\mathcal{S}_\mathcal{G}$ to a unique $\mathcal{L}$, thus forming combinatorially the subnetwork $\mathcal{L}'$. See Definition 1.19.

§6.4 shows that the homeostasis matrix of $\mathcal{S}_\mathcal{G}$ can be put in block upper trimngular form with blocks given by the homeostasis matrices of the $\mathcal{L}'$. See Corollary 6.7.

6.1 Ordering of super-simple nodes

Lemma 6.1. *Super-simple nodes in $\mathcal{G}$ are ordered by ιo-simple paths.*

Proof. Let ρ_1 and ρ_2 be distinct super-simple nodes and let S and T be two ιo-simple paths. Suppose ρ_2 is downstream from ρ_1 along S and ρ_1 is downstream from ρ_2 along T. It follows that there is a simple path from ι to ρ_2 along T that does not contain ρ_1 and a simple path from ρ_2 to o along S that does not contain ρ_1. Hence, there is an ιo-simple path that does not contain ρ_1 contradicting the fact that ρ_1 is super-simple. $\square$

6.2 Simple nodes between adjacent super-simple nodes

A super-simple subnetwork $\mathcal{L}(\rho_1, \rho_2)$ is a subnetwork consisting of all simple nodes between adjacent super-simple nodes ρ_1 and ρ_2 (see Definition 1.18). The following Lemma shows that each non-super-simple simple node belongs to a unique $\mathcal{L}$.

Lemma 6.2. *Every non-super-simple simple node lies uniquely between two adjacent super-simple nodes.*

Proof. Let ρ be a simple node that is not super-simple. By definition ρ is on an ιo-simple path S and ρ lies between two adjacent super-simple nodes ρ_1 and ρ_2 on S. Suppose ρ is also on an ιo-simple path T. Then, by Lemma 6.1 ρ_1 and ρ_2 must be ordered in the same way along T and ρ_1 and ρ_2 must be adjacent super-simple nodes along T. If ρ is downstream from ρ_2 along T, then there would be an ιo-simple path that does not contain ρ_2, which is a contradiction. A similar comment holds if ρ is upstream from ρ_1 along T. Therefore, ρ is also between ρ_1 and ρ_2 on T. $\square$

Definition 1.18 implies that if ρ_3 is downstream from ρ_2 then

$$\mathcal{L}(\rho_1, \rho_2) \cap \mathcal{L}(\rho_3, \rho_4) = \left\{ \begin{array}{ll} \emptyset & \text{if } \rho_3 \neq \rho_2 \\ \{\rho_2\} & \text{otherwise} \end{array} \right. \tag{45}$$

Lemma 6.3 identifies several properties of the subnetworks $\mathcal{L}$.

Lemma 6.3. *Let the pairs of super-simple nodes ρ_1, ρ_2 and ρ_3, ρ_4 be adjacent.*

(a) *No arrow connects an upstream node ρ in the subnetwork $\mathcal{L}(\rho_1, \rho_2)$ to a downstream node τ in the subnetwork $\mathcal{L}(\rho_3, \rho_4)$ unless $\rho = \rho_2$, $\tau = \rho_3$ and ρ_2 and ρ_3 are adjacent super-simple nodes.*

(b) *No arrow connects an upstream node ρ in the subnetwork $\mathcal{L}(\rho_1, \rho_2)$ to a downstream node τ in the subnetwork $\mathcal{L}(\rho_2, \rho_4)$ unless $\rho = \rho_2$ or $\tau = \rho_2$.*

(c) *Suppose that a path of appendage nodes connects $\mathcal{L}(\rho_1, \rho_2)$ to $\mathcal{L}(\rho_3, \rho_4)$. Then ρ_4 is upstream from ρ_1.*

(d) *Suppose that the appendage path component $\mathcal{B}$ fails the no cycle condition and there is a cycle that connects nodes in $\mathcal{B}$ with nodes in $C_S \setminus \mathcal{B}$, where C_S is a complementary subnetwork. Then the nodes in $C_S \setminus \mathcal{B}$ that are in the cycle are non-super-simple simple nodes that are contained in a unique super-simple subnetwork.*

Proof. (a) Suppose an arrow connects a node $\rho \neq \rho_2$ in $\mathcal{L}(\rho_1, \rho_2)$ to a node τ in $\mathcal{L}(\rho_3, \rho_4)$ where ρ_3 is downstream from ρ_2. Then there would be an ιo-simple path that connects ρ_1 to ρ to τ to ρ_4 in that order. That ιo-simple path would miss ρ_2, contradicting the fact that ρ_2 is super-simple. A similar statement holds if $\tau \neq \rho_3$ or ρ_2 and ρ_3 are not adjacent. This proves (a).

(b) Suppose an arrow connects a node $\rho \neq \rho_2$ in $\mathcal{L}(\rho_1, \rho_2)$ to a node $\tau \neq \rho_2$ in $\mathcal{L}(\rho_2, \rho_4)$. Then there would be an ιo-simple path that connects ρ_1 to ρ to τ to ρ_4 in that order. That ιo-simple path would miss ρ_2, contradicting the fact that ρ_2 is super-simple.

(c) Suppose ρ_4 is strictly downstream from ρ_1. Then there is an ιo-simple path from ι to ρ_1 to some nodes in $\mathcal{A}_\mathcal{G}$ to ρ_4 to o. Therefore, at least one node in $\mathcal{A}_\mathcal{G}$ is not an appendage node. A contradiction.

(d) If the cycle contains a super-simple node, then the cycle cannot be in C_S. Since the cycle must contain simple nodes that simple node cannot be super-simple.

Suppose the cycle contains a simple node τ_1 in $\mathcal{L}(\rho_1, \rho_2)$ and another simple node τ_2 in $\mathcal{L}(\rho_3, \rho_4)$ where ρ_3 is downstream from ρ_1, then there would be a path connecting τ_1 to τ_2 that does not contain any super-simple node. This would lead to an ιo-simple path from ρ_1 to τ_1 to τ_2 to ρ_4 that misses ρ_2 and ρ_3. Hence, the simple nodes contained in the cycle must come from a single super-simple subnetwork. $\qquad\square$

Remark 6.4. Lemma 6.3 (a,b) implies that two different super-simple subnetworks $\mathcal{L}(\rho_1, \rho_2)$ and $\mathcal{L}(\rho_3, \rho_4)$ where ρ_2 is upstream from ρ_3 can only be connected by either having a common super-simple node ($\rho_2 = \rho_3$) or by having an arrow $\rho_2 \to \rho_3$ where ρ_2 and ρ_3 are adjacent super-simple nodes.

6.3 Assignment of appendage nodes to $\mathcal{L}$

By Lemma 6.3 (d) any appendage path component that fails the cycle condition forms cycles with non-super-simple simple nodes in a unique super-simple subnetwork. We can therefore expand a super-simple subnetwork $\mathcal{L}$ to a super-simple structural subnetwork $\mathcal{L}'$ by recruiting all appendage nodes that form cycles with nodes in $\mathcal{L}$ (see Definition 1.19).

It follows that if ρ_3 is downstream from ρ_2, then

$$\mathcal{L}'(\rho_1, \rho_2) \cap \mathcal{L}'(\rho_3, \rho_4) = \left\{ \begin{array}{ll} \emptyset & \text{if } \rho_3 \neq \rho_2 \\ \{\rho_2\} & \text{otherwise} \end{array} \right. \tag{46}$$

In particular, each appendage node in $\mathcal{G}$ is attached to at most one $\mathcal{L}$.

Remark 6.5. Suppose ρ_3 is downstream from ρ_2. By Lemma 6.3 (c) and Remark 6.4, no arrow connects a node ρ in $\mathcal{L}'(\rho_1, \rho_2) \setminus \{\rho_2\}$ to a node τ in $\mathcal{L}'(\rho_3, \rho_4)$ unless $\rho_2 = \rho_3$ and $\tau = \rho_2$.

6.4 Relating $\mathcal{S}_\mathcal{G}$ with $\mathcal{L}'$

Theorem 6.6. *Let $\mathcal{K}$ be an input-output core subnetwork of $\mathcal{S}_\mathcal{G}$ with $q+1$ super-simple nodes $\rho_1, \ldots, \rho_{q+1}$ in downstream order in $\mathcal{G}$. Then the homeostasis matrix $H_\mathcal{K}$ of $\mathcal{K}$ can be written in an upper block triangular form*

$$H_\mathcal{K} = \begin{bmatrix} H_{\mathcal{L}'_1} & * & \cdots & * \\ 0 & H_{\mathcal{L}'_2} & \cdots & * \\ \vdots & & \ddots & \vdots \\ 0 & 0 & 0 & H_{\mathcal{L}'_q} \end{bmatrix} \tag{47}$$

where for $\ell = 1, \ldots, q$, $H_{\mathcal{L}'_\ell}$ is the homeostasis matrix of the super-simple structural subnetwork $\mathcal{L}'_\ell = \mathcal{L}'(\rho_\ell, \rho_{(\ell+1)})$.

Proof. Since $\mathcal{K}$ is an input-output core subnetwork of $\mathcal{S}_\mathcal{G}$, it follows that $\mathcal{K}$ consists of all simple nodes between adjacent super-simple nodes of $\mathcal{K}$ and appendage nodes that form cycles with non-super-simple simple nodes in $\mathcal{K}$. Hence, $\mathcal{K}$ consists of nodes and arrows in $\mathcal{L}'(\rho_1, \rho_2) \cup \cdots \cup \mathcal{L}'(\rho_q, \rho_{q+1})$ plus backward arrows between different super-simple structural subnetworks. Hence, for $\ell = 1, \ldots, q$, nodes in $\mathcal{K}$ can be partitioned into disjoint classes: $(\ell) = \mathcal{L}'_\ell \setminus \{\rho_{\ell+1}\}$. We claim that the homeostasis matrix $H_\mathcal{K}$ of $\mathcal{K}$ is given by (47).

It follows from Remark 6.5 that an arrow from a node in one class (ℓ) to a node in another class (j) where $j > \ell$ can exist only when the two classes are adjacent (that is, $j = \ell + 1$) and the head of this arrow is the input node $\rho_{\ell+1}$ of the downstream class $(\ell + 1)$. Since entries below $H_{\mathcal{K}_\ell}$ denote the arrows from nodes in class (ℓ) to nodes in classes $(\ell + 1)$ through (q) except the input node $\rho_{\ell+1}$ in class $(\ell + 1)$. It follows that all entries below $H_{\mathcal{K}_\ell}$ are zero and hence $H_\mathcal{K}$ has the upper block triangular form shown in (47). □

Corollary 6.7. *Suppose that $\tau_1, \ldots, \tau_{p+1}$ are the super-simple nodes of $\mathcal{G}$ in downstream order. Then the homeostasis matrix H' of $\mathcal{S}_\mathcal{G}$ can be written in upper block triangular form*

$$H' = \begin{bmatrix} B'_1 & * & \cdots & * \\ 0 & B'_2 & \cdots & * \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & B'_p \end{bmatrix} \tag{48}$$

where B'_ℓ is the homeostasis matrix of the super-simple structural subnetwork $\mathcal{L}'(\tau_\ell, \tau_{\ell+1})$ for $1 \le \ell \le p$. In addition, p is less than or equal to the number m of structural blocks $\mathcal{K}_\eta$.

Proof. It follows from Definition 1.17 that $\mathcal{S}_\mathcal{G}$ has the same super-simple nodes as $\mathcal{G}$ and $\mathcal{S}_\mathcal{G}$ is a core subnetwork. By Theorem 6.6, the homeostasis matrix H' of $\mathcal{S}_\mathcal{G}$ is given by (48). The number of irreducible blocks is the number of $\mathcal{K}_\eta$ and that is m. Since m is the maximum number of blocks in H', it follows that $m \ge p$ by (48). □

If we can show that the number of super-simple nodes in K_η is two, then we will show that $\mathcal{K}_\eta$ is core equivalent to one of the $\mathcal{L}'$.

6.5 Relation between structural homeostasis and $\mathcal{L}'$

This section shows that each structural subnetwork $\mathcal{K}_\eta$ is core equivalent to the $\mathcal{L}'$ having the same input node. Specifically, we show that the input and output nodes in $\mathcal{K}_\eta$ are adjacent super-simple and that no other nodes in $\mathcal{K}_\eta$ are super-simple.

Theorem 6.8. *Let $\mathcal{K}_\eta$ be an input-output subnetwork of $\mathcal{G}$ associated with an irreducible structural homeostasis matrix B_η in (37). Then the input and output nodes of $\mathcal{K}_\eta$ are super-simple nodes.*

Proof. We prove this theorem by proving that both the input and output nodes ℓ and j of $\mathcal{K}_\eta$ are on the *ιo*-simple path associated with α for all summands α of $\det(H)$. Theorem 3.2 (the determinant theorem) implies that α has the form $F_S g_{C_S}$ where S is an *ιo*-simple path, C_S is the complementary subnetwork to S, F_S is the product of the coupling strengths within S, J_{C_S} is the Jacobian matrix of the admissible system corresponding to C_S, and g_{C_S} is a summand in $\det(J_{C_S})$.

It follows from Lemma 4.6 that the summands of form (35) are the summands of A times the summands of B_η times the summands of E. Hence, every nonzero summand of $\det(H)$ contains a nonzero summand of $\det(B_\eta)$ as a factor. Since ℓ and j are the input output nodes for the homeostasis matrix B_η, it follows that every nonzero summand of $\det(B_\eta)$, and hence $\det(H)$, has both f_{m,x_ℓ} (where m is one of $\rho_1,\ldots,\rho_{k-1},j$) and f_{j,x_n} (where n is one of $\rho_1,\ldots,\rho_{k-1},\ell$) as factors.

From the form of PHQ (and hence H) we see that f_{ℓ,x_ℓ} and f_{j,x_j} are not factors of nonzero summands of $\det(H)$. Suppose the summand α has f_{m,x_ℓ} as a factor, then f_{m,x_ℓ} is either a factor of F_S or not a factor of F_S. In the first case, it follows that the arrow $\ell \to m$ is on the simple path S. Hence, the node ℓ is contained in S. In the second case, suppose f_{m,x_ℓ} is not a factor of F_S, then it must be a factor of g_{C_S}. That implies that ℓ is a node in C_S. It follows that there exists another nonzero summand α' of $\det(H)$ which contains f_{ℓ,x_ℓ} as a factor, which is is a contradiction. Therefore, we conclude every *ιo*-simple path contains node ℓ. By the same type of argument we can also conclude that every *ιo*-simple path contains node j. $\square$

Theorem 6.9. *If a structural block B_η of $\mathcal{G}$ is irreducible, then $\mathcal{K}_\eta$ is an input-output subnetwork that has exactly two super-simple nodes.*

Proof. By Remark 5.6, $\mathcal{K}_\eta$ is an input-output subnetwork of $\mathcal{S}_\mathcal{G}$ and $\mathcal{K}_\eta$ is a core subnetwork because it is irreducible. Suppose in addition to the input and output nodes there are other $q > 1$ super-simple nodes in $\mathcal{K}_\eta$, then by Theorem 6.6, the homeostasis matrix B_η of $\mathcal{K}_\eta$ can be written in an upper block triangular form with $q + 1 > 2$ diagonal blocks and hence $\mathcal{K}_\eta$ is reducible, a contradiction. $\square$

Corollary 6.10. *The input and output nodes of a structural homeostasis block are adjacent super-simple nodes.*

Proof. Super-simple nodes can be well-ordered. The proof then follows from Theorem 6.9. $\square$

Theorem 6.11. *In $\mathcal{G}$, there is a 1:1 correspondence between structural homeostasis blocks $\mathcal{K}_\eta$ and super-simple structural subnetworks $\mathcal{L}'$ and that correspondence is given by having the same input node. Moreover, the corresponding $\mathcal{K}_\eta$ and $\mathcal{L}'$ are core equivalent.*

Proof. By Corollary 6.10, the input and output nodes of each $\mathcal{K}_\eta$ are adjacent super-simple nodes and hence each $\mathcal{K}_\eta$ leads to a unique $\mathcal{L}'$ that has the same input node. Therefore, the number of $\mathcal{K}_\eta$ (equal to m) is less than or equal to the number p of $\mathcal{L}'$. Corollary 6.7 states that $p \le m$; hence, $p = m$. That is, there is a 1:1 correspondence between $\mathcal{K}_\eta$ and $\mathcal{L}'$.

Let ℓ and j be the input and output nodes of the structural block $\mathcal{K}_\eta$. Then the corresponding super-simple structural subnetwork is $\mathcal{L}'(\ell, j)$. By Definition 1.13, $\mathcal{K}_\eta$ consists of simple nodes between the two adjacent super-simple nodes ℓ and j and appendage nodes that form cycles with non-super-simple simple nodes in $\mathcal{K}_\eta$. Arrows in $\mathcal{K}_\eta$ are non-backward arrows that connect nodes in $\mathcal{K}_\eta$. It follows from Definition 1.19

that $\mathcal{L}'(\ell, j)$ is the union of $\mathcal{K}_\eta$ and arrows whose head is ℓ or whose tail is j. By Proposition 1.9, $\mathcal{K}_\eta$ is core equivalent to $\mathcal{L}'(\ell, j)$. $\qquad \square$

7 Classification and construction

In the Introduction we showed how Cramer's rule coupled with basic combinatorial matrix theory can be applied to the homeostasis matrix H to determine the different types of infinitesimal homeostasis that an input-output network $\mathcal{G}$ can support. Specifically the zeros of $\det(H)$, a homogeneous polynomial in the linearized couplings and self-couplings, can be factored into $\det(B_1) \cdots \det(B_m)$. In this paper we show that there are two types of factors that depend on the number of self-couplings: one we call appendage and the other we call structural. Each factor corresponds to a type of homeostasis in subnetworks $\mathcal{K}_\eta$ for $\eta = 1, \ldots, m$ that can be read directly from $\mathcal{G}$.

Appendage blocks   Theorem 5.4 shows that an appendage block B_η leads to a subnetwork $\mathcal{K}_\eta$ that is a path component of the appendage network $\mathcal{A}_\mathcal{G} \subset \mathcal{G}$. Moreover, the nodes in $\mathcal{K}_\eta$ do not form a cycle with other nodes in the complementary subnetwork $\mathcal{C}_S$ for every ιo-simple path S. The factors of $\det(H)$ that stem from appendage nodes are $\det(J_\mathcal{A})$, the determinant of the Jacobian of the appendage path components $\mathcal{A}$. The converse is also valid as shown in Theorem 7.1.

Theorem 7.1. *Suppose $\mathcal{K}_\eta$ is an appendage path component. If $\mathcal{K}_\eta$ satisfies the no cycle condition, then $\det(J_{\mathcal{K}_\eta})$ is an irreducible factor of $\det(H)$.*

Proof. Let C_S be the complementary subnetwork of an ιo-simple path S. By Definition 1.14(c), $\mathcal{K}_\eta \subset C_S$. Since nodes in $\mathcal{K}_\eta$ do not form a cycle with other nodes in C_S, by Lemma 5.3, J_{C_S} has the following block lower triangular form:

$$J_{C_S} = \begin{bmatrix} * & \cdots & * & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ * & \cdots & * & 0 & 0 & \cdots & 0 \\ \hline * & \cdots & * & J_{\mathcal{K}_\eta} & 0 & \cdots & 0 \\ \hline * & \cdots & * & * & * & \cdots & * \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ * & \cdots & * & * & * & \cdots & * \end{bmatrix} \qquad (49)$$

Hence $\det(J_{\mathcal{K}_\eta})$ is a factor of $\det(J_{C_S})$, and so a factor of $\det(H)$. Since $\mathcal{K}_\eta$ is a path component and hence is path connected, it follows that $J_{\mathcal{K}_\eta}$ is irreducible. $\qquad \square$

It follows that we can construct appendage blocks as follows. First we determine the path components of the appendage subnetwork of $\mathcal{G}$ and second we determine which of these components $\mathcal{K}_\eta$ satisfy the cycle condition in Theorem 5.4.

Structural blocks   Next, we form the subnetwork $\mathcal{S}_\mathcal{G}$ that is obtained from $\mathcal{G}$ by deleting the appendage path components identified above. The last result that is needed is:

Theorem 7.2. *Let ℓ and j be adjacent super-simple nodes in $\mathcal{S}_\mathcal{G}$, then $\det(\mathcal{L}'(\ell, j))$ is an irreducible factor of $\det(H)$.*

Proof. It follows from Corollary 6.7 that $\det(\mathcal{L}'(\ell, j))$ is a factor of $\det(H')$ and hence a factor of $\det(H)$ by Lemma 5.5. Theorem 6.11 states that $\mathcal{L}'(\ell, j)$ is core equivalent to a unique $\mathcal{K}_\eta$ that is irreducible. Hence, $\det(\mathcal{L}'(\ell, j))$ is an irreducible factor of $\det(H)$. $\quad \square$

Next, we compute the super-simple nodes in $\mathcal{S}_\mathcal{G}$ in downstream order, namely,

$$\iota = \rho_1 > \rho_2 > \cdots > \rho_q > \rho_{q+1} = o$$

It follows that the subnetworks $\mathcal{L}'(\rho_i, \rho_{i+1})$ are core equivalent to the structural networks $\mathcal{K}_\eta$. Let B_i be the homeostasis matrix associated with the input-output networks $\mathcal{L}'(\rho_i, \rho_{i+1})$ and $\det(B_i)$ is a factor of $\det(H)$.

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