Electron transfer networks

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Abstract

In this paper we study electron transfer networks. These are generalisations of electron transport chains, and consist of a set of substrates which can exist in reduced and oxidised forms. The reduced forms can transfer electrons to the oxidised forms, and there are some electron inflow and outflow processes. We show that under mild assumptions, such systems can have only very simple behaviour, with a single globally stable equilibrium. To prove this we show that the Jacobian of the system has negative logarithmic norm in an appropriate norm. From this result, uniqueness and global stability of any equilibrium follows. The results extend, with only minor modifications, to binary interconversion networks, where the only allowed reactions are interconversions between substrates, and inflow/outflow processes.

Key words: reaction networks, global stability, electron transfer, logarithmic norms

AMS subject classification: 80A30, 34D23, 65F35

1 Introduction

Electron transfer networks are generalisations of electron transport chains, for example in mitochondria as described in [1] and studied mathematically in [2, 3]. In both cases there are a set of substrates, each of which is assumed to exist in either a reduced or an oxidised state. In a chain, the assumption is that a given reduced substrate can only transfer its electron to the next substrate in the chain, while in a network, each reduced substrate is able, in principle, to transfer electrons to any oxidised substrate. Since

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we may choose to rule out some electron transfers, a given network has a particular topology, of which a chain is one example. We will prove a strong result about networks with arbitrary topology and under very general dynamical assumptions: that there must be a single globally stable equilibrium. Although initially phrased in terms of electron transfers, we will show that with minor modifications the results apply to arbitrary interconversion networks.

This paper is in the spirit of [3, 4] in that only weak dynamical assumptions need to be made for the results to hold – essentially that reaction rates depend monotonically on substrate concentrations. However the techniques used here are somewhat different, involving "logarithmic norms" (also known as Lozinskii measures) rather than monotonicity. Thanks to these tools, the tridiagonal structure which proved important for the results in [3] is no longer necessary.

Our attention was drawn to the fact that powerful global stability results can be obtained using logarithmic norms by the exciting work of Li, Muldowney and co-workers ([5, 6] for example). In this work, a criterion which rules out the existence of nonwandering points other than equilibria is constructed. The basic technique involves showing that if some logarithmic norm on the second additive compound of the Jacobian of a system is always negative, then this severely restricts the asymptotic behaviour of trajectories. Here we use simpler and older results on logarithmic norms, needing only to find an appropriate norm for the Jacobian rather than its second additive compound (although, incidentally, the second strategy is also successful).

2 The system

In this section the chemical system to be studied is described. We assume that there are n substrates, each of which can exist in an oxidised state A_i and a reduced state B_i. These states are related by the transfer of an electron:

$$A_i + e^- \rightleftharpoons B_i$$

x_i will refer to the concentration of B_i. The total quantity of $A_i + B_i$ is assumed constant at $x_{i,tot}$ so that $[A_i] = x_{i,tot} - x_i$. It is useful to define the vector $x \equiv [x_1, x_2, \ldots, x_n]^T$. For each i:

$$0 \leq x_i \leq x_{i,tot}$$

We call the closed rectangle in $\mathbb{R}^n$ satisfying these inequalities R, so that $x \in R$. The fact that the phase space for this system is bounded and convex will prove important to later results. Since the totals are conserved, it is useful to refer to the "ith substrate", meaning this substrate in either reduced or oxidised form.

2.1 Electron transfers between substrates

An electron transfer between the ith and jth substrates takes the form

$$B_i + A_j \rightleftharpoons A_i + B_j$$

Given any $1 \leq i < j \leq n$, we define f_{ij} to be the net rate at which the above reaction proceeds to the right, and allow f_{ij} to take both positive and negative values. Because the totals are conserved, we can write $f_{ij}(x_i, x_j)$. If a transfer cannot occur between ith and jth substrates, then f_{ij} is identically zero. We also allow the possibility that some transfers are irreversible – if this is so then we will have one of the conditions $f_{ij} \geq 0$ or $f_{ij} \leq 0$. Clearly if substrate i is entirely reduced then it can accept no more electrons, and if it is entirely oxidised, then it can donate no electrons, so we get the natural conditions

$$f_{ij}(0, \cdot) \leq 0, \quad f_{ij}(x_{i,tot}, \cdot) \geq 0, \quad f_{ij}(\cdot, x_{j,tot}) \leq 0 \quad \text{and} \quad f_{ij}(\cdot, 0) \geq 0$$

In order to be able to refer to a reaction, it is helpful to order the reactions. To do this, we order lexicographically ordered pairs of the form (i, j), where $1 \leq i < j \leq n$. There are $m = \frac{n(n-1)}{2}$ such pairs. The kth member of this sequence is the pair (i_k, j_k), and the kth reaction is the reaction which transfers electrons between substrates i_k and j_k. It is useful to use this terminology, even when no electron transfer takes place, in which case $f_{i_k,j_k} = 0$. When $j < i$, we formally define $f_{ij} \equiv -f_{ji}$. This introduces no new reactions into the system, but is useful for notational purposes later.

Define the m-vector of reaction rates $f \equiv [f_{i_1,j_1}, \ldots, f_{i_m,j_m}]^T$, and define an $n \times m$ matrix $\tilde{S}$ as follows: $\tilde{S}_{ik} = 0$ if the ith substrate does not participate in the kth reaction, i.e. either $i \notin \{i_k, j_k\}$ or $i \in \{i_k, j_k\}$ but $f_{i_k,j_k} = 0$; $\tilde{S}_{ik} = -1$ if $i = i_k$ (i.e. it is the smaller index) and the kth reaction has nonzero rate; $\tilde{S}_{ik} = 1$ if $i = j_k$ (i.e. it is the larger index) and the kth reaction has nonzero rate. The matrix $\tilde{S}$ is a generalised stoichiometric matrix.

Defining $f_{ij}^k \equiv \frac{\partial f_{ij}}{\partial x_k}$, we have three possibilities

- if $k \notin \{i, j\}$, then f_{ij}^k is identically 0,
- if $k \in \{i, j\}$ but there is no electron transfer between the ith and jth substrates then f_{ij}^k is identically 0.
- if $k \in \{i, j\}$ and there is an electron transfer between the ith and jth substrates, then $f_{ij}^i > 0$ and $f_{ij}^j < 0$.

Note that the final statement contains an **assumption** – it says that an increase in reduction levels increases rates of electron transfer, and vice versa. It could be rephrased as "reaction rates depend strictly monotonically on substrate concentrations", and is our only assumption on the functions f_{ij}. The assumption is compatible with either reversible or irreversible electron transfers, but even for irreversible transfers, the redox states of both substrates influence the rate of transfer. Note also that the statement is mathematically meaningful even on the boundaries of phase space – i.e. when $x_i = 0$ or $x_i = x_{i,tot}$ for some i.

2.2 Inflow and outflow of electrons

In order to complete the definition of the system we need to include one more set of processes: These are processes which reduce or oxidise individual substrates, but are external to the network, which we will term inflow and outflow processes. We can lump all inflow and outflow processes for the ith substrate into a single process. We will refer to $g_i(x_i)$ as the rate of reduction minus the rate of oxidation of the ith substrate by external processes. If substrate i is entirely reduced it can accept no more electrons, and if it is entirely oxidised, it can donate no electrons, so we get:

$$g_i(0) \geq 0, \quad g_i(x_{i,tot}) \leq 0$$

Defining $g_i^j \equiv \frac{\partial g_i}{\partial x_j}$ we see that again there are three possibilities

- if $i \neq j$, then g_i^j is identically zero
- if there are no inflow/outflow processes involving substrate i, then g_i^i is identically zero.
- Otherwise $g_i^i < 0$

Again the third possibility is a monotonicity **assumption** – it says that an increase in reduction of substrate i causes a decrease in the rate at which substrate i accepts electrons from outside the network, or donates electrons to substrates outside the network. If, for some i, g_i is not identically zero – i.e. the ith substrate is subject to an inflow or outflow process – then we will say that substrate i is "terminal". We will term the set of indices of terminal substrates $\alpha^{(1)}$. Letting $g = [g_1, \ldots, g_n]^T$, the dynamics of the system now becomes

$$\dot{x} = \tilde{S} f(x) + g(x)$$

Defining an augmented matrix

$$S = [\tilde{S} | I_n]$$

where I_n is the $n \times n$ unit matrix, and a function

$$v(x) \equiv \begin{bmatrix} f(x) \\ g(x) \end{bmatrix}$$

the system can be written more concisely as

$$\dot{x} = S v(x) \tag{1}$$

Our assumptions so far mean that the closed rectangle R is forward invariant under (1). This follows quite naturally from the conditions we have placed on the functions f_{ij} and g_i, and the proof is an easy extension of the analogous proof in [3].

3 The Jacobian matrix

We define the $m \times n$ matrix $\tilde{V}$ by

$$\tilde{V}_{kj} \equiv \frac{\partial f_{i_k, j_k}}{\partial x_j},$$

the diagonal matrix G by $G_{ij} \equiv g_i^j$, and the matrix V by

$$V = \begin{bmatrix} \tilde{V} \\ \hline G \end{bmatrix}$$

so that the Jacobian matrix of the system can be written either as $J = \tilde{S}\tilde{V} + G$ or more concisely as

$$J = SV$$

A direct calculation gives that:

$$J = \begin{bmatrix} g_1^1 - \sum_{j\neq 1} f_{1j}^1 & f_{21}^2 & f_{31}^3 & \cdots & f_{n1}^n \\ f_{12}^1 & g_2^2 - \sum_{j\neq 2} f_{2j}^2 & f_{32}^3 & \cdots & f_{n2}^n \\ f_{13}^1 & f_{23}^2 & g_3^3 - \sum_{j\neq 3} f_{3j}^3 & \cdots & f_{n3}^n \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ f_{1n}^1 & f_{2n}^2 & f_{3n}^3 & \cdots & g_n^n - \sum_{j\neq n} f_{nj}^n \end{bmatrix}$$

Note that all diagonal entries are clearly nonpositive, and we will later make an assumption which ensures that they are all negative. Further, all off-diagonal entries are nonnegative, though many of them may be zero. These off-diagonal zeros are symmetrically placed, and their positions reflect the topology of the network. It is immediate that J is diagonally dominant i.e.

$$|J_{jj}| - \sum_{i\neq j} |J_{ij}| \geq 0$$

If substrate j is terminal – i.e. $g_j^j \neq 0$ – then the Jacobian is strictly diagonally dominant in the jth column. When we want to make explicit that the Jacobian depends on x, we will write $J(x)$.

3.1 The Jacobian structure as a graph

Given any set of matrices with the same sign structure, it is generally useful to represent this structure as a directed graph. In this case we construct an *undirected* graph $\mathcal{G}$ on $n+1$ nodes as follows: Nodes 1 to n correspond to the n substrates, while one node, which we will call node 0, corresponds to the "outside" (this follows the original terminology of Feinberg [7] who refers to the "zero complex"). For $1 \leq i, j \leq n$, an edge between nodes i and j means that f_{ij} is not identically zero, i.e. $J_{ij}, J_{ji} \neq 0$. On the other hand, an edge between nodes i and 0 means that node i is terminal, i.e. $g_i^i \neq 0$.

The reason that $\mathcal{G}$ is an undirected graph is that even though electron transfers may be irreversible, the rate of transfer always depends on both redox states, reflected mathematically in the fact that $J_{ij} \neq 0 \Leftrightarrow J_{ji} \neq 0$. We now introduce a minimal assumption on the network to ensure nondegenerate behaviour: $\mathcal{G}$ **is connected.** This holds true if and only if there is a path in $\mathcal{G}$ from any node to node

0, but should not be interpreted as meaning that any substrate can eventually transfer electrons to some substrate outside the network. The correct interpretation is that the redox state of any substrate is eventually affected by that of some substrate outside the network. It follows that all diagonal entries in J are negative since any substrate is either involved in some electron transfer or is terminal.

So we characterise the Jacobian of an electron transfer network by the following four conditions:

1. J has nonpositive diagonal elements, and nonnegative offdiagonal elements
2. J is columnwise diagonally dominant
3. J has symmetrically placed off-diagonal zeros (i.e. $J_{ij} \neq 0 \Leftrightarrow J_{ji} \neq 0$)
4. The associated undirected graph $\mathcal{G}$ is connected.

The first three conditions are automatic from physical assumptions. Condition 4 is a genericity assumption which, together with the first three conditions implies that J has negative diagonal entries, and J is strictly dominant in columns from some nonempty set $\alpha^{(1)} \subset \{1, \ldots, n\}$.

We have the following preliminary result:

Lemma 1. *Given a matrix J which satisfies the conditions (1)-(4) above, every principal submatrix of J is strictly diagonally dominant in at least one column.*

Proof. The statement for J itself follows because $\alpha^{(1)}$ is nonempty. Any principal submatrix of J can be constructed by sequentially removing rows and columns from J. Consider $J_{\{j\}}$, the principal submatrix of J of order $n-1$ with jth row and column removed. If substrate j was not terminal, or was not the only terminal substrate, then $J_{\{j\}}$ remains strictly dominant in some other column corresponding to a terminal substrate. On the other hand, if j was the only terminal substrate, then there must be some substrate i involved in an electron transfer with substrate j so that $J_{ji} \neq 0$. $J_{\{j\}}$ is now clearly strictly dominant in the column corresponding to substrate i. Thus the set of columns in which $J_{\{j\}}$ is strictly dominant is

$$\alpha^{(1)}_{\{j\}} \equiv \alpha^{(1)} \backslash \{j\} \ \cup \ \{i | i \neq j, J_{ji} \neq 0\}$$

which is not empty (if $\alpha^{(1)} = \{j\}$, then $\{i | i \neq j, J_{ji} \neq 0\}$ cannot be empty). This proves that all principal submatrices of J of order $n-1$ are diagonally dominant and strictly dominant in at least one column.

Now each of these submatrices itself fulfils the four assumptions on J. Formally, the new graph $\mathcal{G}_{\{j\}}$ corresponding to $J_{\{j\}}$ is constructed from $\mathcal{G}$ by identifying vertices 0 and j. It is clearly still connected, and nodes from $\alpha^{(1)}_{\{j\}}$ are terminal.

We can continue the argument inductively to get that every principal submatrix of order $n-2$ is diagonally dominant in at least one column. And so on for all principal submatrices.

□

The above argument shows that J is certainly Hurwitz (and thus any fixed points of the system must be locally stable). Further, $-J$ is a nonsingular M matrix [8]. We now develop the machinery to prove directly global stability of a unique equilibrium.

4 Global stability

In this section, we will show that with the assumptions we have made so far, the system has a unique, globally stable, equilibrium. The existence of an equilibrium follows immediately from the fact that the phase space R is a compact, convex, invariant set. The Brouwer fixed point theorem then assures us that the flow will have a fixed point in R. Uniqueness and global stability of this equilibrium then follow from two facts:

1. There is a logarithmic norm μ such that $\mu(J) < 0$.
2. This implies global stability of the equilibrium.

4.1 Logarithmic norms

Logarithmic norms – or Lozinskii measures – were introduced independently by Dahlquist and Lozinskii in 1958, and have found a wealth of applications since. A survey can be found in [9] or the more recent [10].

If $\|\cdot\|$ denotes a vector norm on $\mathbb{R}^n$, and also the induced matrix norm on $n \times n$ matrices, then the logarithmic norm of an $n \times n$ matrix A is defined by

$$\mu(A) = \lim_{h \to 0^+} \frac{\|I + hA\| - 1}{h} \tag{2}$$

The following observations will prove useful later:

1. The limit in (2) always exists [9].

2. Convergence in (2) to the limit is monotonic and decreasing. Given any norm $\|\cdot\|$ and any matrix A, the function $\|I+hA\|$ is convex (as a function of h). This follows immediately from the triangle inequality since for $\lambda \in (0,1)$ and any h_1, h_2:

$$\begin{aligned}\|I+\lambda h_1 A+(1-\lambda)h_2 A\| &= \|\lambda(I+h_1 A)+(1-\lambda)(I+h_2 A)\| \\ &\leq \lambda\|(I+h_1 A)\|+(1-\lambda)\|(I+h_2 A)\|\end{aligned}$$

It follows trivially that $c(h) \equiv \|I+hA\|-1$ is convex. We now see that $\frac{c(h)}{h}$ is an increasing function of h. We show this for $h \geq 0$, the case relevant to logarithmic norms (the argument for $h \leq 0$ is similar). Consider any two values $h_2 > h_1 > 0$. Define $\lambda = \frac{h_2-h_1}{h_2}$, so that $0<\lambda<1$ and $h_1 = (1-\lambda)h_2$. Convexity of c implies that

$$\lambda c(0)+(1-\lambda)c(h_2) \geq c((1-\lambda)h_2) = c(h_1)$$

Noting that $c(0)=0$ and dividing through by $(1-\lambda)h_2$ gives

$$\frac{c(h_2)}{h_2} \geq \frac{c(h_1)}{h_1}$$

confirming that $\frac{c(h)}{h}$ is an increasing function. Thus, as $h \to 0^+$, $\frac{c(h)}{h}$ decreases to its limit.

3. Any logarithmic norm μ is convex and hence continuous. Convexity of μ follows from subadditivity (i.e. $\mu(A+B) \leq \mu(A)+\mu(B)$ for any matrices A and B), and the fact that $\mu(\lambda A) = \lambda\mu(A)$ for $\lambda > 0$ [9].

4.2 Constructing an appropriate logarithmic norm

Having defined $\alpha^{(1)}$ as the set of indices of terminal substrates, it is useful to define $\alpha^{(2)}$ as the union of $\alpha^{(1)}$ and the set of indices of substrates involved in electron transfers with substrates from $\alpha^{(1)}$. We can proceed inductively and defined $\alpha^{(k)}$ as the union of $\alpha^{(k-1)}$ and the set of indices of substrates involved in electron transfers with substrates from $\alpha^{(k-1)}$. More formally in terms of the Jacobian

$$\begin{aligned}\alpha^{(1)} &= \{j|\ |J_{jj}(x)| - \sum_{i\neq j}|J_{ij}(x)| > 0\} \\ \alpha^{(k)} &= \alpha^{(k-1)} \cup \{i|\ \exists j \in \alpha^{(k-1)} \text{ s.t. } J_{ji} \neq 0\} \quad k = 2,\ldots,n\end{aligned}$$

Note that by our assumption, $|\alpha^{(k)}| \geq k$ for $1 \leq k \leq n$. Since there are only n substrates, $\alpha^{(n)} = \{1, \ldots, n\}$.

Given any electron transfer network with Jacobian $J(x)$, we now construct a logarithmic norm μ such that $\mu(J(x)) < 0$. If we define the logarithmic norm μ_1 as that derived from the $\| \cdot \|_1$ norm, then a matrix has negative logarithmic norm μ_1 if and only if diagonal entries are negative, and the matrix is strictly diagonally dominant in every column [9]. From earlier observations about diagonal dominance of the Jacobian, it is clear that $\mu_1(J) \leq 0$ (everywhere). This suggests that by an appropriate recoordinatisation we might find some logarithmic norm μ for which the inequality becomes strict. Since the phase space is compact this can easily be done:

Theorem 2. *Consider a parameterised family of matrices $J(x)$ defined over a compact metric space X, satisfying*

1. *$J(x)$ have nonpositive diagonal elements, and nonnegative offdiagonal elements*
2. *$J(x)$ are columnwise diagonally dominant*
3. *The sets $\alpha^{(k)}$ defined as above are the same for every $J(x)$ and fulfil $|\alpha^{(k)}| \geq k$ $(k = 1, \ldots, n)$.*

Then there is a logarithmic norm μ such that $\mu(J(x)) < 0$ for all x.

Proof. We have seen that the Jacobians of an electron transfer network fulfil the hypotheses of the theorem. We will construct in stages a coordinate transformation such that in the new coordinates every Jacobian will be strictly diagonally dominant in every column. The end point will be a diagonal matrix D, such that $DJ(x)D^{-1}$ is strictly diagonally dominant in every column.

$J(x)$ is diagonally dominant so we have:

$$|J_{jj}(x)| - \sum_{i \neq j} |J_{ij}(x)| \geq 0$$

with the inequality being strict if $j \in \alpha^{(1)}$. Define

$$q_j^{(1)}(x) = \frac{1}{2}\left(1 + \frac{|J_{jj}(x)|}{\sum_{i \neq j} |J_{ij}(x)|}\right) \quad \text{if} \quad \sum_{i \neq j} |J_{ij}(x)| \neq 0$$

and $q_j^{(1)}(x) = 2$ otherwise. So $q_j^{(1)}(x) > 1$ for $j \in \alpha^{(1)}$ and $q_j^{(1)}(x) = 1$ otherwise. The $q_j^{(1)}(x)$ are designed so that for any number $1 \leq q \leq q_j^{(1)}(x)$ we have that

$$|J_{jj}(x)| - q \sum_{i \neq j} |J_{ij}(x)| \quad > \quad 0 \quad j \in \alpha^{(1)} \tag{3}$$

$$|J_{jj}(x)| - q \sum_{i \neq j} |J_{ij}(x)| \quad = \quad 0 \quad j \notin \alpha^{(1)} \tag{4}$$

i.e. if we have strict dominance in column j, one can multiply all off-diagonal entries in column j by q without losing strict dominance.

Let $q_j^{(1)} = \min_x q_j^{(1)}(x)$. Because $q_j^{(1)}(x) > 1$ for all $j \in \alpha^{(1)}$, and a real valued continuous function on a compact metric space achieves its maximum and minimum values, we know that $q_j^{(1)} > 1$ for all $j \in \alpha^{(1)}$. Clearly $q_j^{(1)} = 1$ if $j \notin \alpha^{(1)}$. Define the constant diagonal matrix $D^{(1)}$ by $D_{jj}^{(1)} = 1/q_j^{(1)}$, and the matrices $J^{(1)}(x) = D^{(1)} J(x) (D^{(1)})^{-1}$. The matrices $J^{(1)}(x)$ are all strictly diagonally dominant in columns from the set $\alpha^{(2)}$. To see this we check that

$$|J_{jj}^{(1)}(x)| - \sum_{i \neq j} |J_{ij}^{(1)}(x)| \quad = \quad |J_{jj}(x)| - q_j^{(1)} \sum_{i \neq j} \frac{|J_{ij}(x)|}{q_i^{(1)}} \tag{5}$$

$$\geq \quad |J_{jj}(x)| - q_j^{(1)} \sum_{i \neq j} |J_{ij}(x)| \tag{6}$$

$$\geq \quad 0 \tag{7}$$

If $j \in \alpha^{(2)} \backslash \alpha^{(1)}$ (i.e. substrate j is involved in electron transfers with substrates from $\alpha^{(1)}$), then the first inequality (6) is strict, because for some $i \in \alpha^{(1)}$, $|J_{ij}(x)|$ is nonzero and is divided by $q_i^{(1)}$ which is strictly greater than 1. On the other hand, if $j \in \alpha^{(1)}$, then the second inequality (7) is strict from (3). So for $j \in \alpha^{(2)}$, the inequality is strict.

We have constructed a constant diagonal matrix $D^{(1)}$ such that $J^{(1)}(x) = D^{(1)} J(x) (D^{(1)})^{-1}$ is diagonally dominant, and strictly diagonally dominant in columns from $\alpha^{(2)}$. We can now continue this process, and find a constant diagonal matrix $D^{(2)}$ such that $J^{(2)}(x) = D^{(2)} J^{(1)}(x) (D^{(2)})^{-1}$ is diagonally dominant, and strictly diagonally dominant in columns from $\alpha^{(3)}$. And so on. After at most $n-1$ steps this construction gives us a matrix $J^{(n-1)}(x)$ which is strictly dominant in all columns since $\alpha^{(n)} = \{1, \ldots, n\}$. Defining

$$D \equiv D^{(n-1)} D^{(n-2)} \cdots D^{(1)}$$

we have $J^{(n-1)}(x) = D J(x) D^{-1}$.

Now clearly $\mu_1(J^{(n-1)}(x)) < 0$. Defining the new logarithmic norm μ_D by $\mu_D(A) = \mu_1(DAD^{-1})$. We see that by the construction above $\mu_D(J(x)) < 0$ for the Jacobian J of the system. □

It is worth noting that we have nowhere needed to make the assumption that the Jacobian is irreducible.

4.3 A negative logarithmic norm implies global stability

We now come to the second claim and show that the fact that the Jacobian has a negative logarithmic norm ensures uniqueness and hence global stability of an equilibrium for the system.

Theorem 3. *Consider an autonomous differential equation $\dot{x} = f(x)$ defined on some convex, forward invariant subset $X \subset \mathbb{R}^n$. Assume that the system has an equilibrium, and that the Jacobian $J(x) = D_x f$ satisfies $\mu(J(x)) < 0$ for some logarithmic norm μ. Then the equilibrium is unique and globally stable.*

Proof. Assume that $0 \in X$ and the equilibrium is at $x = 0$ (if the equilibrium is at $x = c$, we can define a new variable $z = x - c$ and carry out the working below). We will prove global stability of the equilibrium, and uniqueness will follow trivially.

Because $f(0) = 0$, we can write

$$f(x(t)) = A(t)x(t) \quad \text{where} \quad A(t) \equiv \int_0^1 J(\theta x(t))\mathrm{d}\theta$$

The integral is defined because we have assumed X to be convex. This rewriting gives us the ODE in a new form:

$$\dot{x} = A(t)x$$

We want to show that for every initial condition $x(0) \in X$, $\lim_{t\to\infty} \|x(t)\| = 0$ in the norm associated with μ. This follows from an easy and well known result provided we can first show that $\mu(A(t)) < 0$. We will now show that

$$\mu(A(t)) \equiv \mu\left(\int_0^1 J(\theta x(t))\mathrm{d}\theta\right) \leq \int_0^1 \mu(J(\theta x(t)))\mathrm{d}\theta < 0$$

The final inequality is obvious since $\mu(J(x)) < 0$. So, by the definition of the logarithmic norm, we need only to show that

$$\lim_{h\to 0^+} \frac{\|I + h\int_0^1 J(\theta x(t))\mathrm{d}\theta\| - 1}{h} \leq \int_0^1 \lim_{h\to 0^+} \frac{\|I + hJ(\theta x(t))\| - 1}{h}\mathrm{d}\theta$$

Choose a positive sequence $h_i \to 0^+$ and define

$$p_i = \frac{\|I + h_i \int_0^1 J(\theta x(t))\mathrm{d}\theta\| - 1}{h_i} \quad \text{and} \quad q_i = \int_0^1 \frac{\|I + h_i J(\theta x(t))\| - 1}{h_i}\mathrm{d}\theta$$

For each i, $p_i \leq q_i$ because

$$\frac{\|I + h_i \int_0^1 J(\theta x(t))\mathrm{d}\theta\| - 1}{h_i} = \frac{\|\int_0^1 (I + h_i J(\theta x(t)))\mathrm{d}\theta\| - 1}{h_i} \leq \frac{\int_0^1 \|I + h_i J(\theta x(t))\|\mathrm{d}\theta - 1}{h_i}$$

We want to show that the limit of each sequence exists and the inequality holds in the limit, i.e. that:

$$p \equiv \lim_{i\to\infty} p_i = \mu\left(\int_0^1 J(\theta x(t))\mathrm{d}\theta\right) \quad \text{and} \quad q \equiv \lim_{i\to\infty} q_i = \int_0^1 \mu(J(\theta x(t)))\mathrm{d}\theta$$

and that $p \leq q$. Since p is a logarithmic norm, it follows immediately from the properties of logarithmic norms in Section 4.1 that $p_i \downarrow p$. It is a little harder to show that $q_i \downarrow q$. For fixed t, define

$$r_i(\theta) = \frac{\|I + h_i J(\theta x(t))\| - 1}{h_i}$$

Again from Section 4.1, $r_i \downarrow \mu(J(\theta x(t)))$. Since r_i is decreasing, q_i is clearly a decreasing sequence. To see that it is convergent, we show that $r_i(\theta)$ is bounded uniformly above and below and then use the dominated convergence theorem ([11] for example). Because the sequence is decreasing, $r_i(\theta) \leq \max_{\theta\in[0,1]} r_0(\theta) \equiv r_{max}$. And since $r_i(\theta) \downarrow \mu(J(\theta x(t)))$, we get $r_i(\theta) \geq \min_{\theta\in[0,1]} \mu(J(\theta x(t))) \equiv r_{min}$ (this minimum exists because μ is convex and hence continuous). So we have

$$|r_i(\theta)| \leq \max\{|r_{max}|, |r_{min}|\}$$

$\max\{|r_{max}|, |r_{min}|\}$ is a constant and clearly integrable. Now, by the dominated convergence theorem,

$$\lim_{i\to\infty} q_i = \lim_{i\to\infty} \int_0^1 r_i(\theta)\mathrm{d}\theta = \int_0^1 \lim_{i\to\infty} r_i(\theta)\mathrm{d}\theta = \int_0^1 \mu(J(\theta x(t)))\mathrm{d}\theta$$

So $q_i \downarrow q$.

We have shown that $p_i \downarrow p$, $q_i \downarrow q$ and $p_i \leq q_i$ for each i. It follows trivially that $p \leq q$, for suppose that $p > q$, then for i sufficiently large $q_i < p < p_i$, a contradiction. This completes the proof that $\mu(A(t)) < 0$.

Now by Lemma 2 in [9], $\|x(t)\| \leq e(t)$ where $e(t)$ is any solution to the scalar differential equation

$$\dot{e} = \mu(A(t))e \quad \text{with} \quad e(0) \geq \|x(0)\|$$

This has solution

$$e(t) = e(0) \exp\left(\int_0^t \mu(A(s)) \mathrm{d}s \right)$$

So $e(t) = e(0)\exp(-S(t))$, where $S(t)$ is an increasing function of time. Thus $\|x(t)\|$ decreases along trajectories (except when $x(t) = 0$), and serves as a Liapunov function for the system.

This shows that every trajectory must converge to the equilibrium at 0. It follows that 0 is the unique equilibrium since the orbit of any other equilibrium must also converge to 0, a contradiction.

□

A technical note: In the above theorem we needed to insist that the system has an equilibrium. It is possible to construct systems with negative logarithmic norm on unbounded phase spaces which have no equilibria. For example the one dimensional system

$$\dot{x} = 2 - x/(1 + x)$$

defined on $\mathbb{R}_+$ clearly has negative logarithmic norm in any norm, while it is also clear that all orbits are unbounded. On the other hand if the phase space X is compact then existence of an equilibrium is guaranteed by the assumptions of the theorem.

5 Extension to general binary interconversion networks

The results above extend with minor technical modifications to general interconversion networks. We define a general interconversion network as follows. There are n substrates B_i with concentrations x_i. The only reactions allowed are of the form

$$B_i \rightleftharpoons B_j$$

Given any $1 \leq i < j \leq n$, we define f_{ij} to be the total rate of the above reaction in the forward direction, and allow f_{ij} to take both positive and negative values. f_{ij} is in general a function of x_i and x_j so we can write $f_{ij}(x_i, x_j)$. We allow the possibility that some conversions are irreversible – if this is so then we will have one of the conditions $f_{ij} \geq 0$ or $f_{ij} \leq 0$. As before

$$f_{ij}(0, \cdot) \leq 0 \quad \text{and} \quad f_{ij}(\cdot, 0) \geq 0$$

Further, we allow inflow and outflow processes. We will refer to $g_i(x_i)$ as the rate of production minus the rate of loss of the ith substrate. So:

$$g_i(0) \geq 0$$

Again we define $f_{ji} = -f_{ij}$, $f_{ij}^k \equiv \frac{\partial f_{ij}}{\partial x_k}$ and $g_i^j \equiv \frac{\partial g_i}{\partial x_j}$. The Jacobian takes exactly the same form as for an electron transfer network. If $g_i^i < 0$, then we term i a **terminal** substrate, and refer to the set of indices of terminal substrates as $\alpha^{(1)}$.

Now we come to two important differences between interconversion networks and electron transfer networks.

1. The phase space of a general interconversion network is not necessarily bounded. There is no reason why concentrations cannot become arbitrarily large.

2. If some reactions are genuinely irreversible, then even though some f_{ij} might not be identically zero, f_{ij}^i or f_{ij}^j might still be identically zero. This means that in the Jacobian we can no longer assume that $J_{ij} \neq 0 \Leftrightarrow J_{ji} \neq 0$.

The first difference means that we can no longer state that the system must have an equilibrium *a priori*. So we introduce *as an assumption* that the system has an equilibrium. This is a reasonable assumption because chemical concentrations cannot become arbitrarily large, implying that in reality the phase space is bounded.

The second difference means that the structure of the Jacobian is somewhat different. So now we define a **directed** graph $\mathcal{G}$ on $n+1$ nodes which encodes the sign structure of the Jacobian – i.e. there is an edge from node i to node j if and only if $J_{ji} > 0$. In practice, $J_{ji} > 0$ means that either

- substrate i can be converted to substrate j, or
- substrate j can be converted to substrate i at a rate which is inhibited by an increase in the concentration of substrate i.

A directed edge from node i to node 0 means that i is terminal, and equivalently that J is strictly dominant in the ith column. In practice this implies that either

- substrate i is subject to an outflow process, or

- substrate i is subject to an inflow process whose rate is inhibited by increases in its concentration.

We now introduce a minimal assumption on an interconversion network to ensure nondegenerate behaviour: **There is a directed path in $\mathcal{G}$ from any node to node 0.** This assumption has the physical interpretation that the concentration of any substrate is eventually affected by the concentration of a terminal substrate. We again have the definitions

$$\begin{aligned}\alpha^{(1)} &= \{j|\ |J_{jj}(x)| - \sum_{i\neq j} |J_{ij}(x)| > 0\} \\ \alpha^{(k)} &= \alpha^{(k-1)} \cup \{i|\ \exists j \in \alpha^{(k-1)} \text{ s.t. } J_{ji} \neq 0\} \quad k = 2, \ldots, n\end{aligned}$$

and, as before, $|\alpha^{(j)}| \geq j$ for $1 \leq j \leq n$, (and hence $\alpha^{(n)} = \{1, \ldots, n\}$).

The Jacobian of an interconversion network satisfies the following conditions

1. J has nonpositive diagonal elements, and nonnegative offdiagonal elements
2. J is columnwise diagonally dominant
3. In the associated directed graph $\mathcal{G}$, there is a directed path from any node i to node 0.

Since we have lost the condition that $J_{ij} \neq 0 \Leftrightarrow J_{ji} \neq 0$, we have had to strengthen the final assumption about directed paths. This new assumption still implies that J has negative diagonal entries, and that J is strictly dominant in columns from some nonempty set $\alpha^{(1)} \subset \{1, \ldots, n\}$.

We now have immediately:

Theorem 4. *Assume that we have an interconversion network with Jacobian satisfying the three conditions above, and that the phase space contains a convex, forward invariant set $\mathcal{B}$ containing an equilibrium. Then this equilibrium is unique and globally stable.*

Proof. The proof is identical to the case of an electron transfer network. The hypotheses of Theorem 2 are fulfilled, so there is a logarithmic norm μ such that $\mu(J) < 0$ everywhere in $\mathcal{B}$. This in turn means, by Theorem 3, that all trajectories converge to the equilibrium in $\mathcal{B}$, and hence that the equilibrium is unique.

□

6 Conclusions

We have shown that under mild assumptions electron transfer networks and binary interconversion networks can only have a unique, globally stable steady state. There are a number of natural continuations to this work.

1. In general, electron transfer networks may involve substrates able to exist in more than two redox states (e.g. the haem a_3 centre in cytochrome c oxidase [12]). How do the results generalise in this situation?

2. Do the results on interconversion networks still hold if we replace individual substrates with complexes, as in [4]?

3. Since the systems studied here have such simple behaviour, what claims can one make about their behaviour when interconnected, using for example the tools of monotone dynamics [13, 14]?

4. How is the behaviour described here affected when the electron transfer/ interconversion processes interact with an external potential as in mitochondria [2, 3], where they are coupled to proton pumping processes (e.g. [12])? This question is of some biological importance and is a subject we are tackling in work in preparation.

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