Assessing a Kinetic System's Vulnerability to Bifurcation-Induced Regime Shifts through Elementary Flux Mode Analysis [??]

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Abstract: A regime shift occurs when small external variations in system parameters shift the system's state from a *nominal* to an *alternative* qualitative behavior. This paper uses robust stability margins to evaluate a kinetic system's vulnerability to bifurcation-induced regime shifts. The results are derived for an important class of nonnegative polynomial systems defined with respect to a directed graph characterizing mass/energy flows within the system. Such systems are sometimes called *kinetic systems* and they are often found in mathematical ecology and biochemical reaction networks. This paper characterizes a kinetic system's robust stability in terms of the system's *elementary flux modes* (EFM). EFM's are often used to characterize fundamental pathways controlling an ecological or biochemical system's function. We establish sufficient conditions characterizing the largest variation in EFM activity for which system's equilibrium is guaranteed to be asymptotically stable with respect to a specified region of attraction. The main contribution is that these stability conditions can be posed as a separable bilinear program whose local solution can be obtained using quadratic programming software. These stability margins are used to evaluate the vulnerability to regime shifts for biochemical and ecological system exhibiting limit cycle behavior

Keywords: Regime shift, Robust Stability, Polynomial Systems, Kinetic Realizations

1. INTRODUCTION

A *regime shift* occurs in a dynamical system if small perturbations or disturbances abruptly shift the system state from the neighborhood of a *nominal* to an *alternative* equilibrium. The term has its origins in the ecological systems community (see **?** and **?**), where it was used to describe abrupt changes in ecosystem function as a result of external stressors such as climate change and human activities. As stated, therefore, we're referring to systems that are multi-stable, but the concept is easily generalized to shifts between any type of qualitative behavior.

The shifts we're concerned with represent "large" variations in system behavior that are triggered by what one would think of as "small" disturbances. Such disturbances can be categorized as either being "fast" or "slow" with respect to the system's natural time constants. Fast disturbances appear as impulsive inputs that cause a jump in the system state. We refer to these as *shock-induced* regime shifts. Slow disturbances appear as long-term changes in the system's parameters that generate a bifurcation in which the nominal qualitative behavior disppears. We therefore refer to these as *bifurcation-induced* regime shift.

An important question concerns the *vulnerability* of a system to bifurcation-induced regime shifts. Since the global behavior of a system is often determined by the stability types of all of its equilibria, one can then use a change in the stability type (i.e. node, focus, center) of any equilibrium as a necessary condition for a regime shift. Assessing a system's vulnerability to such shifts, therefore, may be estimated by determining the largest parameter set containing a known nominal parameter for which we know the stability type will not change. Stated in this way, the problem of regime shift vulnerability is recast as a robust stability problem and that is the approach that is taken in this paper.

This paper studies regime shifts in dynamical system that can be realized using nonnegative polynomials defined on a directed graph modeling the balanced flows of energy or mass within the system. Such systems are sometimes called *kinetic systems* since they are used in modeling chemical reaction networks with mass action kinetics. While this type of system has its origins in biochemical reaction networks, the models are actually very general in that a *kinetic realization* can be constructed for just about any networked dynamical system generated by flows of energy/mass. The main modeling requirement is that the flows within the system be finitely generated over some suitable algebra of functions with some rather mild structural conditions on these functions. These conditions are satisfied by many networked dynamical systems such as traffic flows, power distribution systems, ecological food webs, and cellular signaling networks. This paper focuses on applications in ecology and cellular biology, though the methods should be applicable to engineering networks also.

The robust stability problem is to determine the largest parameter set in which some specified stability concept is guaranteed. There has, already, been a great deal of work in this area for linear systems. Applying these ideas to nonlinear systems, however, can be relatively difficult. For example, early work

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in **?** determined the "distance-to-bifurcation" for simple power systems using continuation methods. The problem with this is that one is usually limited to a rather small number of parameters (2-3) and that the answers we obtain are local estimates of the distance-to-bifurcation. More recent work in **?** and **?** has attempted to pose the problem using the *positivstellensatz* theorem (see **?**), which searches for a barrier certificate (see **?**) whose existence certifies that the stability concept holds within a specified test set of the parameter space. When the system is polynomial one can pose this problem as a semidefinite program (SDP) (see **?**) and then take advantage of SDP solvers to find a global bound on the distance to bifurcation. The problem with this approach, is that the time and memory complexity of these solvers does not scale well with respect to the number of parameters and the degree of the polynomial constraints (see **?**). This again limits the size of the problems we can consider. Recent work in **?** has used diagonal stability concepts that require a specified matrix to be an M-matrix. Unfortunately the formation of the required matrix and the subsequent checking to see if it is an M-matrix requires symbolic methods that may again not scale well for a large systems.

The issues identified with the preceding approaches limit the utility of these tools in the "real-life" applications of interest to biologists. In general, a biologist is confronted by large-scale systems with a high degree of parametric uncertainty. For example in **?**, a cyclic adenosine monophosphate (cAMP) system was used to study biological oscillations, the "simple" system consists of 7 states and 14 parameters. Another system in **?** was used to explain the onset of limit cycling in aquatic food webs consists of 6 states and least 7 parameters. These are "idealized" systems in the sense that they greatly simplify the actual complexity found in these systems, and yet we've found these "idealized" problems are still too large to be efficiently handled using the methods discussed above.

One way to handle the inherent complexity of these problems is to find a more compact way of parameterizing the system's equilibria. In kinetic systems, this is often done in **?** through the use of *elementary flux modes* (EFM). Due to graph structure upon which a kinetic realization is built, one can study its equilibria through a set of *equilibrium fluxes*. These fluxes describe the physical transport of materials within the system and they must lie in a convex polyhedral cone that is finite generated by a set of elementary flux modes (i.e. the extreme rays generating the convex polytope). From a physical standpoint, these elementary flux modes represent fundamental process pathways in the system (see **?**) . When the activity in these pathways becomes too great, the system may become congested and it is the "congestion" that triggers the bifurcation-induced regime shift. This work, therefore, shifts attention from establishing robust stability with respect to system parameters and focuses on characterizing variation in EFM activity levels for which asymptotic stability of a given equilibrium can be guaranteed. The key finding in this paper, is that characterizing robust stability in this way gives rise to a separable bilinear programming problem for which solutions can be obtained using interior-point quadratic programming algorithms. The solutions, of course, are only local but each local solution can be computed rather easily for large problems of the size mentioned above and this suggests that we can use this approach to solve our problem for problems that are not seen as "toy" problems by biologists.

The remainder of this paper is organized as follows. Section **??** discusses kinetic realizations. Section **??** discusses elementary flux modes. The main results in section **??** describes the EFM parameterization used to solve the robust stability problem and section **??** uses the solution to this problem to examine regime shifts in a biological system known to exhibit limit cycling.

2. SYSTEM MODEL

This section describes the class of systems being studied in this paper. Subsection **??** establishes some notational conventions. Subsection **??** introduces kinetic realizations of nonnegative polynomial systems and presents an example.

2.1 Notation:

The set of real numbers (integers) is denoted as $\mathbb{R}$ ($\mathbb{Z}$). The nonnegative real cone is denoted as $\mathbb{R}_{\geq 0}$. If $A \in \mathbb{R}^{n\times m}$ is a real matrix then a_{ij} denotes the element in A's ith row and jth column. Given a vector $x \in \mathbb{R}^n$, we define vectors $\exp(x)$ in $\mathbb{R}^n$ in a component-wise manner so that $[\exp(x)]_i = e^{x_i}$ for $i = 1, 2, \ldots, n$. Component wise division and multiplication of two vectors $x, y \in \mathbb{R}^n$ will be denoted as x/y and xy, respectively.

A polynomial, $p(x; k)$, defined over the variables $x = \{x_1, \ldots, x_n\}$ and parameters $k = \{k_1, \ldots, k_m\}$ is a formal series

$$p(x;k) = \sum_{j=1}^{m} \pm k_j \prod_{\ell=1}^{n} x_\ell^{y_{j\ell}} \tag{1}$$

where $y_{j\ell}$ are nonnegative integers for $j = 1, 2, \ldots, m$ and $\ell = 1, 2 \ldots, n$. The set of all such polynomials whose parameters take values in the real field is denoted as $\mathbb{R}(k)[x]$. A polynomial in which $m = 1$ is called a monomial. The n-dimensional row vector $\overline{y}_j = [y_{j1}, y_{j2}, \ldots, y_{jn}]$ for $j = 1, 2, \ldots, n$ is called a *multi-index* and we will use $x^{[\overline{y}_j]}$ to denote the monomial generated by multi-index $\overline{y}_j$. Let $Y \in \mathbb{Z}_{\geq 0}^{m\times n}$ be an integer matrix whose rows are the m distinct monomial terms in $p(x; k)$, then the m-vector of monomials in $p(x; k)$ will be written in multi-index notation as $x^{[Y]}$.

A labeled directed graph, $G = (V, E, L)$ is a triple consisting of a finite set, V of n vertices, a finite set L of m labels, and a set $E \subset V \times V \times L$ consisting of m labeled edges. For an edge, $e = (v, w, k)$, we refer to $v \in V$ as the edge's initial vertex, $w \in V$ as the edge's terminal vertex, and $k \in L$ is the edge's label.

2.2 Kinetic System

Consider a polynomial system whose n-dimensional state trajectory $x(\cdot) : \mathbb{R}_{\geq 0} \to \mathbb{R}^n$ satsifies $\dot{x} = f(x; k)$ with initial condition $x(0) = x_0$. This system is *polynomial* if $f(x; k) \in \mathbb{R}(k)[x]$. The polynomial vector $f(x; k)$ for a given $k \in \mathbb{R}^m$ is *essentially nonnegative* if and only if $f_i(x; k) \geq 0$ for all $i = 1, 2, \ldots, n$ and all $x \geq 0$ for which $x_i = 0$. A necessary and sufficient condition for the nonnegative real cone $\mathbb{R}^n_{\geq 0}$ to be positively f-invariant is that $f(x; k)$ is essential nonnegative. Such systems are also said to be nonnegative.

Consider an n-dimensional nonnegative polynomial system $\dot{x} = f(x; k)$. This system has a *kinetic realization* if there exists a labeled directed graph, $G = (V, E, L)$ where V is a finite set of p multi-indices of length n, L is a set of m parameters, and $E \subset V \times V \times L$ is a set of labeled of q edges such that

$$\dot{x} = f(x;k) = Y^T B I_k x^{[Y]} \tag{2}$$

where Y is a $p \times n$ matrix whose rows are multi-indices in the vertex set V, B is a $p \times q$ incidence matrix from graph G, I_k is a $q \times p$ matrix whose rows have only one nonzero element corresponding to one parameter (label) in L, and $x^{[Y]}$ is the vector of monomials generated by the multi-indices in Y.

Remark: Realizations in (**??**) appear in chemical reaction networks with x being a set of chemical *species*, the monomials in $x^{[Y]}$ representing a set of chemical complexes, and k representing reaction rates. The graph G is sometimes called a *complex-graph* since its vertices are complexes and the edges describe the chemical reactions transforming one complex into another complex.

A sufficient condition for a nonnegative polynomial system $\dot{x} = f(x;k)$ to have a kinetic realization is that for all $i = 1, 2, \ldots, n$ there exist polynomials $g_i(x;k)$ and $h_i(x;k)$ in $\mathbb{R}(k)[x]$ with nonnegative coefficients such that

$$f_i(x;k) = g_i(x;k) - x_i h_i(x;k) \tag{3}$$

This condition is presented in **?** with a constructive proof that describes an algorithm used to automate the construction of the kinetic realization from the polynomials in $f(x;k)$.

The construction algorithm may be described as follows. Consider the nonnegative polynomial system $\dot{x} = f(x;k)$ with n states and m parameters. Let Z by an $m \times n$ integer matrix whose rows are the multi-indices of all monomial terms in $f(x;k)$. Construct an $n \times m$ matrix N such that the original differential equation can be written as

$$\dot{x} = f(x;k) = N \mathrm{diag}(k) x^{[Z]} \tag{4}$$

Note that N is an integer matrix whose ijth element, n_{ij}, satisfies

$$n_{ij} = \begin{cases} 1 \;\; k_j x^{[\overline{z}_j]} \text{ is positive in } f_i(x;k) \\ -1 \;\; k_j x^{[\overline{z}_j]} \text{ is negative } f_i(x;k) \\ 0 \;\; \text{otherwise} \end{cases} \tag{5}$$

Initialize the vertex set, V, and edge set E to the empty set. Definite the label set $L = \{k_1, k_2, \ldots, k_m\}$. For each nonzero element n_{ij} in the matrix N, create a new multi-index

$$\overline{y} = \overline{z}_j + \mathrm{sign}(n_{ij}) \overline{u}_i \tag{6}$$

where $\overline{u}_i$ is an n-dimensional row vector whose only nonzero element is 1 at the ith component. Create the edge $e = (\overline{z}_j, \overline{y}, k_j)$ if $\mathrm{sign}(n_{ij}) < 0$ or create the edge $e = (\overline{y}, \overline{z}_j, k_j)$ if $\mathrm{sign}(n_{ij}) > 0$. Add the multi-indices $\overline{z}_j$ and $\overline{y}$ to V if they are not already there. Add the created edge to the edge set E. This algorithm terminates after a finite number of steps and the realizations matrices, Y, B, and I_k are directly constructed from the graph G.

Remark: The construction does not create a minimal realization. But one can combine the construction with optimization procedures as done in **?** to obtain canonical realizations that have useful properties such as minimal deficiency.

As an example, consider the cAMP molecular network from **??**

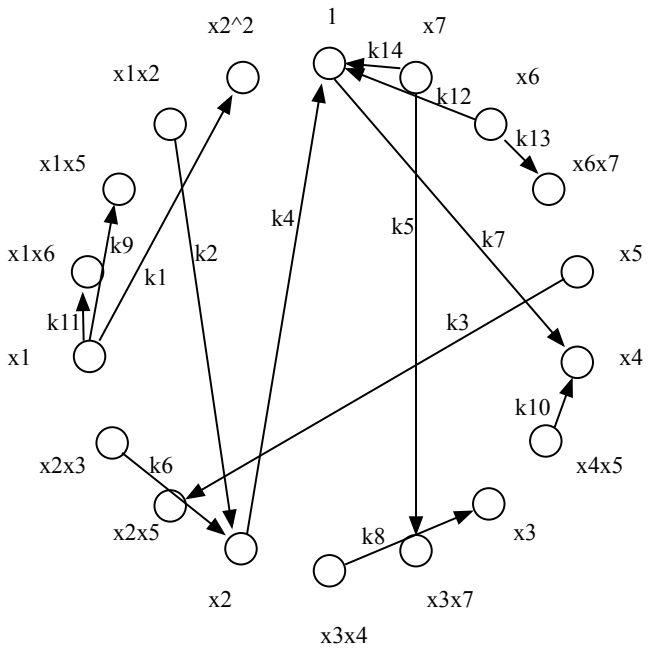

Fig. 1. cAMP Complex Graph

$$\begin{aligned} \dot{x}_1 &= k_1 x_7 - k_2 x_1 x_2 \\ \dot{x}_2 &= k_3 x_5 - k_4 x_2 \\ \dot{x}_3 &= k_5 x_7 - k_6 x_2 x_3 \\ \dot{x}_4 &= k_7 - k_8 x_3 x_4 \\ \dot{x}_5 &= k_9 x_1 - k_{10} x_4 x_5 \\ \dot{x}_6 &= k_{11} x_1 - k_{12} x_6 \\ \dot{x}_7 &= k_{13} x_6 - k_{14} x_7 \end{aligned} \tag{7}$$

In this system, extracellular adenosine monophosphate (ext. cAMP, x_6) binds to the surface receptor (CAR1, x_7) which activates adenylyl cyclase (ACA, x_1) and the MAP kinase ERK2 (x_3). The internal concentration of cAMP (int. cAMP x_5) is activated by ACA and inhibited by ERK2 though the cAMP phosphodiesterase (REGA, x_4). Increased levels of internal cAMP activates the protein kinase A (PKA, x_2) which in turn inhibits ERK2. Numerical solutions describing these interactions show that each of these components is necessary for the network to generate oscillatory behavior whose frequency is robust to large variations in the reaction rates. The kinetic realization computed using the above algorithm generated a complex-graph with 18 complexes and 14 edges. The monomials defining these complexes are

$$x^{[Y]} = \begin{bmatrix} 1 & x_7 & x_6 & x_6 x_7 & x_5 & x_4 & x_4 x_5 & \cdots \\ \cdots & x_3 & x_3 x_7 & x_3 x_4 & x_2 & x_2 x_5 & x_2 x_3 & \cdots \\ \cdots & x_1 & x_1 x_6 & x_1 x_5 & x_1 x_2 & x_1^2 & & \end{bmatrix} \tag{8}$$

A picture of the complex graph is shown in Figure **??**.

3. ELEMENTARY FLUX MODES

Consider the kinetic system in (**??**) with a nominal parameter vector k_0. A *state equilibrium* for that nominal parameter, $x^*(k_0)$, is any real vector in $\mathbb{R}^n_{\geq 0}$ such that $0 = f(x^*(k_0); k_0)$. Let us assume that a given equilibrium $x^*(k_0)$ is asymptotically stable with a compact set D_a being known to lie within that equilibrium's region of attraction. The traditional robust stability problem determines the largest $\beta > 0$ such that $x^*(k)$ is asymptotically stable with a region-of-attraction that contains D_a for all k such that $|k - k_0| < \beta$.

It is difficult to find the stability margin, β, for nonlinear systems such as those in (**??**) with so many parameters. The difficulty arises because it may be impossible to find closed form expressions for the state equilibria, $x^*(k)$, as a function of parameter k. This means that one must numerically solve for $x^*(k)$ as an algorithm recursively searches through the parameter space for that point at which asymptotic stability can no longer be guaranteed. This is what is done in continuation algorithms (see **?**) and the complexity of the search usually limits us to problems with no more than 2 or 3 parameters.

An alternative to continuation methods must be to study the robust stability of systems with many parameters. One approach used in **?** projects the system states into a higher dimensional space of *fluxes* for which the projected equilibria have a convex parameterization. This convex parameterization is finitely generated by a unique set of *elementary flux modes* (EFM) for the system as described in **?**. In **?**, EFMs and their extensions provide a framework for describing fundamental process pathways through the system's complex graph. The activity level in each pathway becomes a transformed system state and because the "flux" equilibria have a convex parameterization with respect to the EFM activity levels; the subsequent analysis of the equilibria' robust stability is greatly simplified.

A more formal description of elementary flux modes is given below. Consider the kinetic system in (**??**) and define the system's *flux vector* as $v(x;k) = I_k x^{[Y]}$. A flux vector $v^* \in \mathbb{R}^q_{\geq 0}$ is a *flux equilibrium* if $Y^T B v^* = 0$ and v^* is nonnegative. Note that this means any equilibrium flux must lie in the intersection of the right null space of $Y^T B$ and the nonnegative cone $\mathbb{R}^q_{\geq 0}$. This set is denoted as as

$$K_v = \ker(Y^T B) \cap \mathbb{R}^q_{\geq 0} \tag{9}$$

K_v is a convex polyhedral cone (see **?**) and is finitely generated by the positive linear combination of a set of r *flux modes*, $\{e_1, e_2, \ldots, e_r\}$. This means that any flux equilibrium can be written as $v^* = \sum_{j=1}^r e_j \lambda_j$ where e_j is a nonnegative real q-vector and λ_j is a nonnegative real number. We let E denote the $\mathbb{R}^{q\times r}$ matrix whose columns are the flux modes e_j and then express the equilibrium flux as $v^* = E\lambda$ where $\lambda \in \mathbb{R}^r_{\geq 0}$ is a non-negative real vector parameterizing the equilibrium flux v^*. The vector λ is sometimes called K_v's *convex parameters* and each λ vector may be viewed as the system's "flux" state vector whose components characterize the activity level in each fundamental pathways associated with the system's flux modes.

Consider the matrix E of flux modes for a given kinetic system. If no flux mode in E can be expressed as the positive linear combination of other elements in E, one says the set of flux modes is *elementary* and we refer to E as the elementary flux mode or EFM matrix. The EFM matrix, E, is uniquely determined up to a reordering of the matrix columns. This can be proven by contradiction. Assume that K_v has two sets of EFMs, $\{e_i\}_{i=1}^r$ and $\{d_i\}_{i=1}^s$. Clearly e_k for any $k = 1, 2, \ldots, r$ can be positively generated by $\{d_i\}_{i=1}^s$ and similarly any d_ℓ for $\ell = 1, 2, \ldots, s$ can be positively generated by $\{e_i\}_{i=1}^r$. This means that

$$e_k = \sum_{i=1}^s \mu_i d_i = \sum_{i=1}^s \mu_i \left(\sum_{j=1}^r \lambda_{ij} e_j \right)$$

This shows that the e_k could not be elementary and hence contradicts the assumption that the EFM matrix is not unique.

flux mode	reactions	species
e_1	$\{(x_1 \overset{k_1}{\to} x_1^2), \quad (x_1x_2 \overset{k_2}{\to} x_2)\}$	x_1 (ACA)
e_2	$\{(x_6 \overset{k_{13}}{\to} x_6x_7), \quad (x_7 \overset{k_{14}}{\to} 1)\}$	x_7 (CAR1)
e_3	$\{(x_5 \overset{k_3}{\to} x_2x_5), \quad (x_2 \overset{k_4}{\to} 1)\}$	x_2 (PKA)
e_4	$\{(x_1 \overset{k_{11}}{\to} x_1x_6), \quad (x_6 \overset{k_{12}}{\to} 1)\}$	x_6 (ext. cAMP)
e_5	$\{(x_7 \overset{k_5}{\to} x_3x_7), \quad (x_2x_3 \overset{k_6}{\to} x_2)\}$	x_3 (ERK2)
e_6	$\{(x_1 \overset{k_9}{\to} x_1x_5), \quad (x_4x_5 \overset{k_{10}}{\to} x_4)\}$	x_5 (int. cAMP)
e_7	$\{(1 \overset{k_7}{\to} x_4), \quad (x_3x_4 \overset{k_8}{\to} x_3)\}$	x_4 (REGA)

Table 1. Elementary Flux Modes in cAMP System

Remark: A useful observation about elementary flux modes is that each one corresponds to the "fate" of a particular species (i.e. x_i) in the system. This can be readily inferred from the way in which the kinetic realization was constructed. The construction algorithm only adds an edge when it changes the degree of one term in the complex. Since $Y^T B e_i = 0$ for any $i = 1, 2, \ldots, r$, one can readily conclude that every elementary flux mode corresponds to the balance of a particular species entering or exiting the complex. This gives a very concrete physical meaning to each EFM in terms of defining *fundamental pathways* governing the system. This is same reasoning that led **?** to use EFMs to characterize fundamental cellular metabolic pathways. Each EFM, therefore, can be treated as a fundamental process from which the entire networked system's dynamics can be generated. This means we can treat the activity level in each EFM as a degree-of-freedom that we can control.

There are a number of software tools to compute the EFM matrix of a kinetic system. A well known general purpose tool `CellNetAnalyzer` described in **?** uses the open source code, EFMTOOL, of **?** to compute EFM matrices. This tool was used to compute the elementary flux modes of the cAMP network introduced in section **??**. This tool identified 7 elementary flux modes for the cAMP system. The EFM are shown in Table **??**. The first column represents the flux mode, the second column shows which edges are in the flux mode, and the third column identifies the species whose growth is controlled by the flux mode.

4. EFM ROBUST STABILITY

This section presents the paper's main result; a characterization of a kinetic system's robust stability in terms of the EFM's convex parameter vector λ. Consider the n-dimensional kinetic system in (**??**) whose directed graph consists of p vertices and q edges. Let k_0 denote a *nominal* system parameter and assume that the nominal state equilibrium, $x^*(k_0)$, is asymptotically stable and that a known compact set $D_a \subset \mathbb{R}^n_{\geq 0}$ is contained within the equilibrium's region of attraction. Consider a candidate Lyapunov function $V(\cdot) : \mathbb{R}^n_{\geq 0} \to \mathbb{R}^n$ that takes values

$$V(x) = \sum_{i=1}^n \left(x_i^* - x_i + x_i \log\left(\frac{x_i}{x_i^*}\right)\right) \tag{10}$$

The following lemma states that $V(x)$ is a positive definite function that goes to zero at the equilibrium x^*.

Lemma 1. For the system in (**??**) with state-equilibrium x^*, the function V defined in (**??**) satisfies $V(x) > 0$ for all $x \neq x^*$ and $V(x^*) = 0$.

Proof: Note that $z - 1 \geq \log(z)$ for all $z \geq 0$. We can use this relation to see that $x_i^* - x_i \geq x_i \log(x_i^*/x_i)$, which implies

that the function $V_i(x_i) \equiv x_i^* - x_i + x_i \log(x_i/x_i^*) \geq 0$ for all nonnegative x_i. Since V_i is convex, it has a unique minimum of 0 that occurs when $x_i = x_i^*$ and so $V_i > 0$ for all $x_i \neq x_i^*$. This is sufficient to establish the result since it must hold for all $i = 1, 2, \ldots, n$. □

Remark: The function in (**??**) is similar to entropy functions used to establish the global stability of Lotka-Volterra equations (see **?**) and their extensions (see **?**). The particular function in (**??**) was used in **?** to establish global stability of kinetic systems whose matrix BI_k has zero row/column sums. The kinetic systems in this paper only guarantee that the column sums of BI_k are zero.

The following lemma presents a useful parameterization of V's directional derivative in terms of the EFM parameter vector λ. An important feature of this representation is that it is linear in the convex parameters.

Lemma 2. Consider the n-dimensional kinetic system (**??**) with parameter vector k and state equilibrium x^*. Let the system's complex graph have p vertices and q edges. Let $\lambda \in \mathbb{R}^r_{>0}$ be a nonnegative vector of the system's EFM activity levels. Then there exist matrices $P_j \in \mathbb{Z}^{q \times q}$ for $j = 1, 2, \ldots, r$ such that the directional derivative of V may be written as

$$\dot{V} = \frac{\partial V}{\partial x}\dot{x} = z^T \left[\sum_{j=1}^{r} \lambda_j P_j\right] e^z \tag{11}$$

where $z = Y \log(x/x^*)$.

Proof: This is proven by direct computation. Note that $\frac{dV(x_i)}{dx_i} = \log\left(\frac{x_i}{x_i^*}\right)$. Therefore the directional derivative may be written as

$$\dot{V}(x) = \sum_{i=1}^{n} \frac{dV_i(x_i)}{dx_i}\dot{x}_i = \left[\log\left(\frac{x}{x^*}\right)\right]^T Y^T B I_k x^{[Y]} \tag{12}$$

The flux vector $v(x;k) = I_k x^{[Y]}$ may be rewritten as

$$I_k x^{[Y]} = I_k \mathrm{diag}\left([x^*]^{[Y]}\right)\left[\frac{x}{x^*}\right]^{[Y]} = I_{v^*}\left[\frac{x}{x^*}\right]^{[Y]} \tag{13}$$

where $I_{v^*} = I_k \mathrm{diag}\left([x^*]^{[Y]}\right)$ is a $q \times p$ matrix in which each row has only one non-zero element that is equal to one component of the equilibrium flux $v^* = I_k[x^*]^{[Y]}$. This means the directional derivative in (**??**) may be written as

$$\dot{V}(x) = \left[\log\left(\frac{x}{x^*}\right)\right]^T Y^T B I_{v^*}\left[\frac{x}{x^*}\right]^{[Y]} \tag{14}$$

Since each row of I_{v^*} has only one nonzero element that is equal to one of the equilibrium fluxes. Recall that any equilibrium flux vector can be written as $v^* = E\lambda$ where E is a unique EFM matrix and λ is a vector of EFM parameters. One may use this reparameterization of the equilibrium fluxes rewrite BI_{v^*} in terms of the EFM flux parameters λ. In particular this means that there exist r matrices $P_1, P_2, \ldots, P_r$ such that

$$BI_{v^*} = \sum_{j=1}^{r} P_j \lambda_j \tag{15}$$

Finally, let us introduce the state transformation $z = Y \log(x/x^*)$. Under this transformation, we can use the methods employed in **?** to show that

$$\left[\frac{x}{x^*}\right]^{[Y]} = \exp\left(Y \log\left(\frac{x}{x^*}\right)\right) = e^z. \tag{16}$$

Using these new state variables in (**??**) yields equation (**??**) and therefore completes the proof. □

With lemma **??** it is now possible to state one of the paper's main results. This result is an upper bound on the directional derivative of V. This bound is useful because it is a separable bilinear function of the EFM parameters and the transformed system states, z, defined in lemma **??**. This bilinear bound will then be used to pose sufficient conditions for the a given equilibrium to be asymptotically stable with respect to a specified region of attraction.

Lemma 3. Under the assumptions of lemma **??**, there exists a matrix Q such that the directional derivative of V is bounded above as

$$\dot{V}(z, \lambda) \leq [e^z]^T Q\lambda \tag{17}$$

for $z \geq 0$ and $\lambda \geq 0$.

Proof: From lemma **??** define the matrix $P(\lambda) = \sum_{j=1}^{r} P_j \lambda_j$. One can expand the expression for $\dot{V}$ to obtain

$$\dot{V}(x) = \sum_{i=1}^{q} z_i \sum_{j=1} p_{ij}(\lambda) e^{z_j} \tag{18}$$

Since $P(\lambda)$ has zero column sums and since $p_{ii}(\lambda) = -\sum_{j \neq i} p_{ji}(\lambda)$, we can rewrite (**??**) as

$$\dot{V}(z, \lambda) = \sum_{i=1}^{q} \sum_{j \neq i} (z_i - z_j) p_{ij}(\lambda) e^{z_j} \tag{19}$$

Since the exponential function is convex, one can show that

$$(\beta - \alpha)e^{\alpha} \leq e^{\beta} - e^{\alpha} \tag{20}$$

for any $\alpha, \beta \geq 0$. Using this inequality in the same way as was done in **?**, we can then bound $\dot{V}$ as

$$\dot{V}(z, \lambda) \leq \sum_{i=1}^{q} \sum_{j \neq i}^{q} p_{ij}(\lambda)(e^{z_j} - e^{z_i}) \tag{21}$$

$$= [e^z]\, \tilde{P}(\lambda)\mathbf{1} \tag{22}$$

where $\mathbf{1}$ is a vector of ones. $\tilde{P}(\lambda)$ is a $q \times q$ matrix whose off-diagonal elements satisfy $\tilde{p}_{ij}(\lambda) = p_{ij}(\lambda)$. The diagonal elements are the negative of the row sums; so that $\tilde{p}_{ii}(\lambda) = \sum_{j \neq i} p_{ij}(\lambda)$. Note that this is different from the original P matrix which had zero column sums. $\tilde{P}(\lambda)\mathbf{1}$ is linear in λ, we can rewrite it as $Q\lambda$ which when substituted in (**??**) completes the proof. □

The bound in (**??**) is bilinear and separable with respect to transformed system state, z, and the EFM parameter vector, λ. Because the bound is bilinear, it can usually be made arbitrarily large by simply making the appropriate component of z or λ large. So it will not usually be the case that $\dot{V}$ is negative definite over the entire state space or the entire parameter space. Instead, all that can be guaranteed is that for a compact set of states and parameters that $\dot{V}$ is negative definite.

In particular, let λ_0 denote the EFM parameterization of a nominal flux equilibrium with associated state equilibrium x^*.

Consider a known positive q-vector, α, a positive real number β, and define the following compact sets

$$\begin{aligned} D_\alpha &= \left\{ x \in \mathbb{R}^n_{\geq 0} \,:\, 0 \leq z(x) = Y \log(x/x^*) \leq \alpha \right\} \\ \Omega_\beta &= \left\{ \lambda \in \mathbb{R}^q_{\geq 0} \,:\, |\lambda - \lambda_0| \right\} \end{aligned} \tag{23}$$

If we can verify that $\dot{V}$ is negative definite for all $x \in D_\alpha$ and $\lambda \in \Omega_\beta$, then we know that the equilibrium is asymptotically stable for all EFM parameters in Ω_β with a region of attraction that contains D_α. The largest β for which this occurs becomes an estimate on the equilibrium's robust stability margin. So the problem of characterizing the robust stability of the kinetic system with respect to a known domain D_α is reduced to solving a separable bilinear programming problem of the form

$$\begin{aligned} &\text{maximize: } \beta \\ &\text{subject to: } \overline{W} = \max_{z \in D_a, \lambda \in \Omega_\beta} [e^z]^T Q \lambda \leq 0 \end{aligned} \tag{24}$$

The problem in (**??**) is a bilinear program and such problems are NP-hard. Global solvers exist for such problems often use semidefinite programming relaxations (see **?**). Matlab interfaces such as **?** or **?** make it relatively easy for users to access these solvers, but in general one can only get answers for relatively small problems.

To deal with larger problems one can use local solvers. For the applications considered in this paper, we've had success in using interior-point quadratic programming algorithms based on trust-region methods (see **?**). This algorithm is used in the Matlab function `quadprog`. To use this algorithm, one transforms the bilinear constraint in (**??**) into a quadratic constraint. This is done by recognizing that

$$[e^z]^T Q \lambda = \frac{1}{2} \xi^T \tilde{Q} \xi \tag{25}$$

where $\tilde{Q} = \begin{bmatrix} 0 & Q \\ Q^T & 0 \end{bmatrix}$ and $\xi = \begin{bmatrix} e^z \\ \lambda \end{bmatrix}$. Making use of (**??**), the optimization problem in (**??**) can be restated as

$$\begin{aligned} &\text{maximize: } \beta \\ &\text{subject to: } \overline{W} = \max_{\xi \in D_a \times \Omega_\beta} \xi^T \tilde{Q} \xi \end{aligned} \tag{26}$$

which can be easily addressed using Matlab's `quadprog` function. The algorithm has quadratic convergence, but it is only guaranteed to converge to a local extremum.

5. REGIME SHIFT ANALYSIS