Phenotype Phase Plane Analysis Using Interior Point Methods

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Abstract

Phenotype phase plane analysis is a linear optimization procedure which can be used to study the value of the objective function (a desired phenotype) as two variables (external substrates) vary simultaneously. Existing methods for phenotype phase plane analysis are based on computing shadow prices as defined in classical linear programming duality theory. Since different bases may produce different "shadow prices", we present here an alternative way to determine the phenotype phase plane based on so-called interior point methods, which unambigously calculates the correct shadow prices. In addition, this work constitutes the first attempt at producing a mathematically rigorous algorithm to compute phenotype phase planes in a systematic way.

1 Introduction

The abundance of genomic data available today allows for construction of genome-scale metabolic networks for many organism. These data make up the "components" used to build computer models to simulate and predict cellular function. To obtain phenotypic information from the genotype and to illuminate the systemic properties of the network it is necessary to model the interaction of these components, for example by assuming that the cell optimizes some cellular function subject to environmental constraints, as in a linear programming model (other approaches include metabolic control analysis [5, 7, 9] and biochemical systems theory [11, 12, 13]). Phenotype phase plane analysis is a powerful method for interpreting a large number of optimal solutions to linear programming problems, and its applications include comparing growth of a strain on different substrates [4], analyzing the consequences of gene deletions [8], and designing of experiments [3, 6]. Phase plane analysis is an extension of flux-balance analysis [17, 18, 2], which uses linear optimization techniques to calculate optimal flux distribution for some objective (e.g., optimal growth rate) with the purpose of describing metabolic physiology quantitatively. (A related technique is the so-called metabolic flux analysis which includes experimental results in the calculation of the fluxes [15].) In flux-balance analysis, the solution set for the fluxes is determined by a set of metabolic constraints (mass balance equations) defined by the system's stoichiometry, the assumption that the system under consideration is in quasi-steady state, and capacity constraints on the magnitude of the fluxes. Formally, the feasible solution set is a polyhedron described by

$$\mathcal{C} = \{\mathbf{v} \,:\, \mathbf{S}\mathbf{v} = \mathbf{0},\ \mathbf{0} \le \mathbf{v} \le \mathbf{v}^{\max}\}, \tag{1.1}$$

where $\mathbf{S}$ is an $m \times n$ stoichiometric matrix whose rows correspond to metabolites and whose columns correspond to reactions. The capacity constraint vector, $\mathbf{v}^{\max}$, may have one or more coefficients set to $+\infty$. To interpret an optimal flux distribution in a biological context it is important that the environmental conditions are specified. The role of phenotype phase planes is to define the range of optimal phenotypic behavior when two such conditions vary.

Assuming a linear objective function has been specified, the first step in obtaining the phase plane is to project the feasible solution set $\mathcal{C}$ onto the 2-dimensional plane (3-dimensional projections have also been used, but will not be considered in this paper), where the projection is done with respect to two fluxes of specific interest (for example fluxes representing carbon and oxygen uptake of the cell [4]), whose respective values are represented on the axes of the positive quadrant. One then defines a function whose domain is the solution set projection described above, and whose values are determined as follows. Suppose v_j and v_k are the two fluxes which determine the projection. For each point (s, t) in the domain, let $v_j = s$ and $v_k = t$ in (1.1) (here we are assuming that v_j is represented on the horizontal axis, and v_k is represented on the vertical axis) and perform the linear optimization using the original objective function with the two fluxes restricted to these values. The optimal value obtained from this procedure is the value of the function at the point (s,t). This allows study of the optimal solutions under various environmental conditions represented by the two fluxes under investigation; for example, one could determine optimal growth of a cell depending on the levels of available carbon source and oxygen [4]. In this case, the phase plane may be viewed as a representation of all optimal phenotypes an organism can exhibit for aerobic and anaerobic growth on a single carbon substrate.

Since, in general, the optimal-value function (viewed as a function of the constraint vector of the linear optimization problem) is piece-wise linear, the projected polyhedron will be partitioned into distinct regions, called phases, in which the calculated flux maps and the (partial) derivatives of the optimal-value function are constant, i.e., the metabolic phenotypes exhibited by the organism are "similar" throughout such regions. Hence, to accurately determine the phases in this phase plane it is essential that one can compute the partial derivatives (a.k.a shadow prices) of the optimal value function. The demarcation lines separating the phases in the phase plane have, until now, been determined by traditional methods of computing shadow prices using classical linear programming duality theory [16]. According to the classical theory, the "shadow prices" are the values of the optimal dual variables determined from the corresponding dual linear program (the values are interpreted as "prices" in the economic literature). Since the classical method uses bases, determined by subsets of columns of the stoichiometric matrix, to calculate shadow prices, these values may differ depending on which basis is chosen when the dual problem has multiple optimal solutions. In this paper, we propose an alternative method for calculating shadow prices based on interior point methods which produces the correct shadow prices in all instances. We then provide a mathematically rigorous step-by-step program for calculating the phenotype phase plane, involving certain auxiliary linear optimization problems, which we believe could serve as a template for a computationally efficient algorithm to automate the process. The auxiliary linear optimization problems allow for a continuous systematic search of the positive quadrant, as opposed to previous somewhat ad-hoc methods that have been proposed which use a naïve search of the quadrant based on a grid determined by the constraint vector, $\mathbf{v}^{\max}$, for the two fluxes of interest.

In Section 2 we review the relevant results from linear optimization theory and the interior point method; in Section 3, we provide a mathematically rigorous definition of the phenotype phase plane; and in Section 4 we give a simple example illustrating our method and conclude by outlining the full procedure.

2 Interior Point Methods Review

In this section, we present background material about interior point methods which we will refer to throughout the paper. The reader may wish to skim this section on a first reading and return to the relevant parts when needed. Although all of the results below may be found in [10], we collect them here for the reader's convenience.

Any linear optimization problem may be put in so-called *standard form*:

$$\min_{\mathbf{x}} \{\mathbf{c}'\mathbf{x} \;:\; \mathbf{A}\mathbf{x} = \mathbf{b},\, \mathbf{x} \geq \mathbf{0}\}, \tag{2.1}$$

where $\mathbf{A}$ is an $m \times n$ matrix, $\mathbf{c}$, $\mathbf{x} \in \Re^n$, $\mathbf{b} \in \Re^m$, and the "prime" denotes matrix/vector transpose. We may also assume, without loss of generality, that $\mathbf{A}$ has full row rank.

The dual linear optimization problem to (2.1) is given by

$$\max_{\mathbf{y}} \{\mathbf{b}'\mathbf{y} \;:\; \mathbf{A}'\mathbf{y} + \mathbf{s} = \mathbf{c},\, \mathbf{s} \geq \mathbf{0}\}. \tag{2.2}$$

We say that (2.1) is *feasible* (and $\mathbf{x}$ is a feasible solution) if there exists a non-negative vector $\mathbf{x}$ satisfying the constraint $\mathbf{A}\mathbf{x} = \mathbf{b}$, otherwise (2.1) is *infeasible.* Analogous terminology will be used for the pair $(\mathbf{y}, \mathbf{s})$ in (2.2).

It can be shown that the optimal values (when they both exist and are finite) of (2.1) and (2.2) are equal, and we denote this common value by $Z_{\mathbf{A}}(\mathbf{b}, \mathbf{c})$. We let $Z_{\mathbf{A}}(\mathbf{b}, \mathbf{c}) = -\infty$ if (2.1) is unbounded and $Z_{\mathbf{A}}(\mathbf{b}, \mathbf{c}) = +\infty$ if (2.2) is unbounded. We call $Z_{\mathbf{A}}$ the *optimal-value function* for the matrix $\mathbf{A}$. In the sequel, we shall view $Z_{\mathbf{A}}$ as a function of $\mathbf{b}$ only, with $\mathbf{c}$ and $\mathbf{A}$ fixed. A useful fact is that $Z_{\mathbf{A}}$ is a continuous, convex, and piece-wise linear function of $\mathbf{b}$ (cf. Theorem IV.51 in [10]). When calculating the phenotype phase plane, one considers small perturbations of $\mathbf{b}$ and their associated effects on the optimal-value function (cf. Section 3). The partial derivative of the optimal-value function with respect to a coefficient of $\mathbf{b}$ is called a *shadow price*, and the interval around the coefficient in which the partial derivative stays constant is called the *range* of the coefficient. We say that a vector $\mathbf{b} \in \Re^m$ is a *break point* of the optimal-value function if any of its partial derivates does not exist at $\mathbf{b}$, and we refer to the left- and right- partial derivatives at a coefficient of $\mathbf{b}$ as the left- and- right shadow prices of that coefficient. If $\mathbf{b}$ is not a break point, then the (multi-dimensional) interval around $\mathbf{b}$, determined by the ranges of its coefficients, is a closed non-degenerate interval (cf. pg. 391 in [10]).

We now present two fundamental duality results for the linear optimization problems above (cf. [10] pg. 97).

Theorem 2.1 *If (2.1) and (2.2) are feasible then both problems have optimal solutions. If* $\mathbf{x}$ *and* $(\mathbf{y}, \mathbf{s})$ *are feasible solutions, then they are optimal if and only if* $\mathbf{x}'\mathbf{s} = 0$*. Otherwise neither of the two problems has optimal solutions.*

An optimal solution pair $(\mathbf{x}, \mathbf{s})$ is a *strictly complementary pair of solutions* if $\mathbf{x}+\mathbf{s} > \mathbf{0}$. (Here, and elsewhere in this paper, the strict inequality means that *every* component of the vector on the left hand side is strictly greater than the corresponding component of the vector on the right hand side.) Note that this latter condition implies that if for some $i \in \{1, 2, \ldots, n\}$, $x_i s_i = 0$, then either x_i is zero or s_i is zero, but not both.

Theorem 2.2 *If (2.1) and (2.2) are feasible then there exists a strictly complementary pair of optimal solutions.*

Let $\mathbf{x}^*$, $(\mathbf{y}^*, \mathbf{s}^*)$ be optimal solutions to (2.1) and (2.2), respectively, such that $(\mathbf{x}^*, \mathbf{s}^*)$ is a strictly complementary pair of solutions, and define the sets

$$B = \{i \,:\, x_i^* > 0\}, \quad N = \{i \,:\, s_i^* > 0\}. \tag{2.3}$$

Then by Theorems 2.1 and 2.2 we have that $B \cap N = \emptyset$ and $B \cup N = \{1, 2, \ldots, n\}$. It can be shown that any strictly complementary pair of solutions induce the same sets (B, N), and we call this pair the *optimal partition* of (2.1) and (2.2). The following result shows that the optimal partition can be used to find all optimal solutions.

Theorem 2.3 *Let $\mathcal{P}^*$ and $\mathcal{D}^*$ be the optimal sets of (2.1) and (2.2), respectively, and let (B, N) be the optimal partition. Then*

$$\begin{aligned}\mathcal{P}^* &= \{\mathbf{x} \,:\, \mathbf{Ax} = \mathbf{b},\, \mathbf{x}_B \geq \mathbf{0},\, \mathbf{x}_N = \mathbf{0}\},\\ \mathcal{D}^* &= \{(\mathbf{y}, \mathbf{s}) \,:\, \mathbf{A}'\mathbf{y} + \mathbf{s} = \mathbf{c},\, \mathbf{s}_B = \mathbf{0},\, \mathbf{s}_N \geq \mathbf{0}\},\end{aligned}$$

where for a vector z and an index set I, the vector z_I is the vector obtained by deleting all components from z whose indices are *not* in the set I. As mentioned in the Introduction, we will be interested in finding the shadow prices of the optimal-value function and the corresponding ranges of the coefficients. Let (B, N) be an optimal partition of (2.1) and (2.2). By considering the i^{th} coefficient of $\mathbf{b}$, b_i, as a variable, we may compute its range by minimizing and maximizing b_i over the set

$$\{b_i \,:\, \mathbf{Ax} = \mathbf{b},\, \mathbf{x}_B \geq \mathbf{0},\, \mathbf{x}_N = \mathbf{0}\}, \tag{2.4}$$

and by considering the i^{th} coefficient of y, y_i, as a variable, the left- and right- shadow prices of b_i can be computed by minimizing and maximizing y_i over the set

$$\{y_i \,:\, \mathbf{A}'\mathbf{y} + \mathbf{s} = \mathbf{c},\, \mathbf{s}_B = \mathbf{0},\, \mathbf{s}_N \geq \mathbf{0}\}. \tag{2.5}$$

Hence, from our discussion in the Introduction, if $\mathbf{b}$ is not a breakpoint, the range determined by (2.4) is a non-degenerate interval, and the solution set given by (2.5) is a singleton (i.e., the right- and- left derivatives at the point b_i coincide implying that the optimal-value function is differentiable there).

The classical approach to finding the ranges and shadow prices is to construct a basis for $\Re^m$ from m linearly independent columns of $\mathbf{A}$, $\mathbf{A}_{\tilde{B}}$, where $\tilde{B}$ is the index set of the columns in the basis. Letting $\tilde{N}$ be the index set of the remaining columns, a feasible solution to (2.1) is $\mathbf{x}_{\tilde{B}} = \mathbf{A}_{\tilde{B}}^{-1}\mathbf{b}$, $\mathbf{x}_{\tilde{N}} = \mathbf{0}$, if $\mathbf{x}_{\tilde{B}} \geq \mathbf{0}$. Let $\mathbf{y} = (\mathbf{A}'_{\tilde{B}})^{-1}\mathbf{c}_{\tilde{B}}$ and $\mathbf{s} = \mathbf{c} - \mathbf{A}'\mathbf{y}$. If $\mathbf{s}_{\tilde{N}} \geq \mathbf{0}$, we have by Theorem 2.1 that $(\mathbf{y}, \mathbf{s})$ is optimal since $\mathbf{s}_{\tilde{B}} = \mathbf{0}$ and $\mathbf{x}_{\tilde{N}} = \mathbf{0}$. Then the classical approach to finding the ranges and shadow prices amounts to using (2.4) and (2.5), as described above, but with (B, N) replaced with $(\tilde{B}, \tilde{N})$, there. Hence, in the classical approach, different "ranges" and "shadow prices" may be obtained depending on which basis is employed.

Phenotype phase plane analysis, until now, has essentially been using the classical approach. In the sequel, we will describe a method for calculating phenotype phase planes based on the interior point methods presented above. In particular, we shall use an optimal partition along with the sets in (2.4) and (2.5) to determine the phases. The central idea of this approach is that points inside a particular phase correspond to a unique optimal partition.

3 Phase Plane Definition

In this section, we set out to rigorously define the phases in the phenotype phase plane. Consider again the polyhedron, $\mathcal{C}$, in (1.1), and to avoid trivialities assume that $\mathcal{C} \neq \{\mathbf{0}\}$.

The phase plane is determined by two of the components of $\mathbf{v}$, v_j and v_k, say (for the remainder of this section we assume that j and k are fixed). The feasible set for v_j and v_k is

$$\mathcal{F} = \{(s,t) \in \Re^2 : \, s = v_j, \, t = v_k, \text{ for some } \mathbf{v} \in \mathcal{C}\}. \tag{3.1}$$

For each fixed $(s,t) \in \mathcal{F}$, let $v_j = s$ and $v_k = t$ in $\mathcal{C}$, and $\mathbf{b}_{s,t} = -(s\mathbf{S}_j + t\mathbf{S}_k)$, where $\mathbf{S}_j$ and $\mathbf{S}_k$ are the j^{th} and k^{th} column of $\mathbf{S}$, respectively. We will refer to the vector $\mathbf{b}_{s,t}$ as the constraint vector determined by the point (s,t). Our aim is to compute the phenotype phase plane by optimizing a linear function over the following set, determined by the remaining $n-2$ variables (see Section 4 for an example of how this is done),

$$\{\tilde{\mathbf{v}} \, : \, \tilde{\mathbf{S}}\tilde{\mathbf{v}} = \mathbf{b}_{s,t}, \, \mathbf{0} \leq \tilde{\mathbf{v}} \leq \tilde{\mathbf{v}}^{\max}\}, \tag{3.2}$$

where $\tilde{\mathbf{S}}$ is the $m \times (n-2)$ matrix obtained by deleting the j^{th} and k^{th} column of $\mathbf{S}$, and $\tilde{\mathbf{v}}^{\max}$ is the vector in $\Re^{n-2}$ obtained by deleting the j^{th} and k^{th} component of $\mathbf{v}^{\max}$.

For $\mathbf{b} \in \Re^m$ define the set

$$P(\mathbf{b}) = \{\tilde{\mathbf{v}} \, : \, \tilde{\mathbf{S}}\tilde{\mathbf{v}} = \mathbf{b}, \, \mathbf{0} \leq \tilde{\mathbf{v}} \leq \tilde{\mathbf{v}}^{\max}\}, \tag{3.3}$$

and for fixed $\mathbf{c} \in \Re^{n-2}$, define the optimal-value function Z (cf. Section 2) by

$$Z(\mathbf{b}) = \min_{\mathbf{v} \in P(\mathbf{b})} \mathbf{c}'\mathbf{v}.$$

For each $(s_0, t_0) \in \mathcal{F}$, let

$$\mathcal{P}_{s_0,t_0} = \left\{ (s,t) \in \mathcal{F} : \frac{\partial Z(\mathbf{b}_{s,t})}{\partial \mathbf{b}} = \frac{\partial Z(\mathbf{b}_{s_0,t_0})}{\partial \mathbf{b}} \right\}, \tag{3.4}$$

if all the partial derivatives of $Z(\cdot)$ exist at $\mathbf{b}_{s_0,t_0}$, otherwise let $\mathcal{P}_{s_0,t_0} = \emptyset$. (Here, $\partial Z/\partial \mathbf{b}$ is an m-dimensional vector whose i^{th} component is the partial derivatives of $Z(\cdot)$ with respect to b_i, and the equality in (3.4) is interpreted component-wise.) We call the set $\mathcal{P}_{s_0,t_0}$ a *phase*, i.e., a phase in the phenotype phase plane is defined as a set of points, in the feasible set $\mathcal{F}$, for which the partial derivatives (with respect to the coefficients of the constraint vectors determined by those points) of the optimal-value function stay constant. Since the optimal-value function, $Z(\cdot)$, is piece-wise linear (cf. Section 2), determining $\mathcal{P}_{s_0,t_0}$ for some $(s_0, t_0) \in \mathcal{F}$ amounts to finding the range of the coefficients of $\mathbf{b}_{s_0,t_0}$ and/or the range of the corresponding dual variables using the sets in (2.4) and (2.5). The points which have empty phases and lie on the same line separating the phases will be called a *demarcation line*. We then define the phenotype phase plane to be the set of phases along with the demarcation lines separating the phases.

4 Phase Planes Computation

In this section we present an outline of our proposed method for computing the phenotype phase plane. As a motivation, we first present a simple example. Consider the following linear optimization problem (here we use $\mathbf{x}$ as the variable to be optimized to agree with the notation in Section 2),

$$\begin{array}{l} \text{minimize } -x_3 - x_4 \\ \text{subject to} \\ \begin{array}{rcrcrcrcrcrcrcl} 3x_1 & - & x_2 & - & x_3 & & & - & x_5 & & & & & = & 0 \\ x_1 & - & x_2 & & & + & x_4 & & & + & x_6 & & & = & 0 \\ 4x_1 & - & x_2 & - & x_3 & - & x_4 & & & & & - & x_7 & = & 0 \end{array} \\ x_i \geq 0,\ i = 1, 2, \ldots, 7,\ x_1 \leq 3,\ x_2 \leq 5. \end{array} \tag{4.1}$$

The feasible set $\mathcal{F}$ (cf. (3.1)) for x_1 and x_2 is shown in Figure 1.

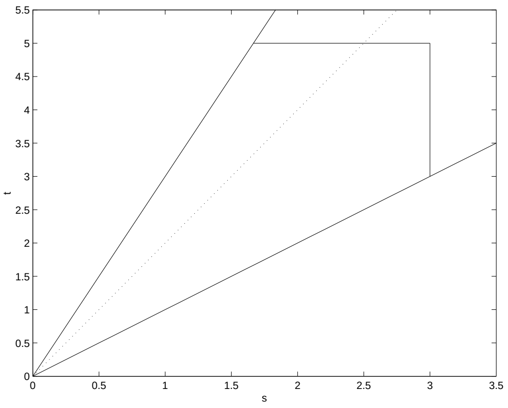

Figure 1: A phase plane for (4.1)

Letting $x_1 = s$ and $x_2 = t$, we obtain the reduced linear optimization problem (here, x_i is relabeled x_{i-2} for $i = 3, 4, \ldots, 7$),

$$
\begin{array}{ll}
 & \text{minimize } -x_1 - x_2 \\
 & \text{subject to} \\
 & \begin{array}{ccccccccccc}
x_1 & & & + & x_3 & & & & & = & 3s - t \\
 & & x_2 & & & + & x_4 & & & = & t - s \\
x_1 & + & x_2 & & & & & + & x_5 & = & 4s - t
\end{array} \\
(4.2) & \\
 & x_i \geq 0,\ i = 1, 2, \ldots, 5.
\end{array}
$$

The dual problem to (4.2) is given by

$$
\begin{array}{ll}
 & \text{maximize} \quad (3s - t)y_1 + (t - s)y_2 + (4s - t)y_3 \\
 & \text{subject to} \\
 & \begin{array}{ccccccccccccccccc}
y_1 & & & + & y_3 & + & s_1 & & & & & & & & & = & -1 \\
 & & y_2 & + & y_3 & & & + & s_2 & & & & & & & = & -1 \\
y_1 & & & & & & & & & + & s_3 & & & & & = & 0 \\
 & & y_2 & & & & & & & & & + & s_4 & & & = & 0 \\
 & & & & y_3 & & & & & & & & & + & s_5 & = & 0
\end{array} \\
(4.3) & \\
 & y_i \geq 0,\ i = 1, 2, 3,\ s_j \geq 0,\ j = 1, 2, \ldots, 5.
\end{array}
$$

Suppose we pick a feasible point on the line segment $t = 2.5s$, $s > 0$. We then have that the constraint vector $\mathbf{b}_{s,t} = \mathbf{b}_s = [0.5s, 1.5s, 1.5s]'$. A strictly complementary optimal solution to (4.2) and (4.3) is given by $\mathbf{x} = (0.25s, 1.25s, 0.25s, 0.25s, 0)$, $\mathbf{s} = (0, 0, 0, 0, 1)$, $\mathbf{y} = (0, 0, -1)$. So that $B = \{1, 2, 3, 4\}$ and $N = \{5\}$ is the optimal partition for (4.2) and (4.3), as defined in (2.3).

Let

$$\mathbf{A} = \begin{pmatrix} 1 & 0 & 1 & 0 & 0 \\ 0 & 1 & 0 & 1 & 0 \\ 1 & 1 & 0 & 0 & 1 \end{pmatrix}.$$

We then have that the set determining the range of the dual variables defined in (2.5) takes the form

$$\begin{aligned} &\{y_i \,:\, \mathbf{A}'\mathbf{y} + \mathbf{s} = \mathbf{c}, \mathbf{s}_B = \mathbf{0}, \mathbf{s}_N \geq \mathbf{0}\} \\ &= \{y_i \,:\, y_1 + y_3 = -1,\ y_2 + y_3 = -1,\ y_1 = 0,\ y_2 = 0,\ y_3 + s_5 = 0, \\ &\qquad s_1 = 0,\ s_2 = 0,\ s_3 = 0,\ s_4 = 0,\ s_5 \geq 0\} \\ &= \{y_i \,:\, y_1 = 0,\ y_2 = 0,\ y_3 = -1, s_1 = 0,\ s_2 = 0,\ s_3 = 0,\ s_4 = 0,\ s_5 = 1\}. \end{aligned} \tag{4.4}$$

We see that the problem of minimizing and maximizing y_i over this set has a unique solution for all $i = 1, 2, 3$. For the set defined in (2.4) we have,

$$\begin{aligned} &\{b_i \,:\, \mathbf{A}\mathbf{x} = \mathbf{b}, \mathbf{x}_B \geq \mathbf{0}, \mathbf{x}_N = \mathbf{0}\} \\ &= \{b_i \,:\, x_1 + x_3 = 0.5s,\ x_2 + x_4 = 1.5s,\ x_1 + x_2 = 1.5s,\ x_1 \geq 0\, x_2 \geq 0\, x_3 \geq 0\, x_4 \geq 0\}, \end{aligned}$$

where we have, for convenience, left off the subscript "s" of the vector $\mathbf{b}_s$.

Now, an optimal solution to the problem

$$\begin{array}{l} \text{minimize} \quad b_1 \\ \text{subject to} \\ \begin{array}{ccccccccc} x_1 & & & + & x_3 & & & = & b_1 \\ & & x_2 & & & + & x_4 & = & 1.5s \\ x_1 & + & x_2 & & & & & = & 1.5s \end{array} \\ x_1 \geq 0, x_2 \geq 0, x_3 \geq 0, x_4 \geq 0. \end{array} \tag{4.5}$$

is $\mathbf{x} = (0, 1.5s, 0, 0)$ and the optimal value of the objective function is $b_1 = 0$. If we replace the word "minimize" by "maximize" in (4.5), we see that the problem is unbounded (since $x_3 \geq 0$), so that the range of b_1 is $[0, \infty)$. By similar analyses, we obtain the ranges for b_2 and b_3, as $[s, \infty)$, and $[0, 2s]$, respectively. Then, using the expressions $b_1 = 3s - t$, $b_2 = t - s$, $b_3 = 4s - t$, together with the ranges for the coefficients of $\mathbf{b}$ as derived above, we deduce that $2s \leq t \leq 3s$, and hence the phase containing the line $t = 2.5s$ is given by

$$\{(s, t) \,:\, 2s < t < 3s,\ s \geq 0,\ t \leq 5\}.$$

Now, choose a feasible point on the line segment $t = 2s$, $s > 0$. Then, a strictly complementary solution to (4.2) and (4.3) is given by $\mathbf{x} = (s, s, 0, 0, 0)$, $\mathbf{y} = (-0.5, -0.5, -0.5)$, and $\mathbf{s} = (0, 0, 0.5, 0.5, 0.5)$. We have that $B = \{1, 2\}$, $N = \{3, 4, 5\}$, and

$$\begin{aligned} &\{b_i \,:\, \mathbf{A}\mathbf{x} = \mathbf{b}, \mathbf{x}_B \geq \mathbf{0}, \mathbf{x}_N = \mathbf{0}\} \\ &= \{b_i \,:\, x_1 = s,\ x_2 = s,\ x_1 + x_2 = 2s,\ x_1 \geq 0\, x_2 \geq 0\}, \end{aligned}$$

which has a unique solution for all $i = 1, 2, 3$. Hence, the interval around $\mathbf{b}$ determined by the ranges of the coefficients of $\mathbf{b}$ is a singleton. Also,

$$\begin{aligned} &\{y_i \,:\, \mathbf{A}'\mathbf{y} + \mathbf{s} = \mathbf{c}, \mathbf{s}_B = \mathbf{0}, \mathbf{s}_N \geq \mathbf{0}\} \\ &= \{y_i \,:\, y_1 + y_3 = -1,\ y_2 + y_3 = -1,\ y_1 + s_3 = 0,\ y_2 + s_4 = 0,\ y_3 + s_5 = 0, \\ &\qquad s_3 \geq 0,\ s_4 \geq 0,\ s_5 \geq 0\}. \end{aligned} \tag{4.6}$$

Solving the minimization- and- maximization problem for (4.6) as in (4.4), we have that $y_1 \in [-1, 0]$, $y_2 \in [-1, 0]$, and $y_3 \in [-1, 0]$ and hence the optimal value function has break points along the line $t = 2s$ (see the discussion in Section 2). Similarly, if a feasible point is chosen on the line segment $t = 1.5s$, $s > 0$, one can show that $s \leq t \leq 2s$, $0 \leq s \leq 3$, $t \leq 5$, so that the phase plane has two phases separated by the line $t = 2s$ as shown in Figure 1.

In the example above, we saw that the optimal partion along a line through the origin in the feasible set $\mathcal{F}$ was constant in all cases. That property is true in general, as the following argument will show. Let $(s_0, t_0) \in \mathcal{F}$, such that $s_0 > 0$, and consider points on the line segment $t = (t_0/s_0)s$, $0 \le s \le s_0$. Then, for all (s,t) on this line segment, the set in (3.2) is given by $\tilde{P}(s) = \{\tilde{\mathbf{v}} \; : \; \tilde{\mathbf{S}}\tilde{\mathbf{v}} = s\Delta\mathbf{b}, \; \mathbf{0} \le \tilde{\mathbf{v}} \le \tilde{\mathbf{v}}^{\max}\}$, where $\Delta\mathbf{b} = -(\mathbf{S}_j + (t_0/s_0)\mathbf{S}_k)$, i.e., on this line segment, the optimal-value function is a function of s only. Let

$$f(s) = \min_{\tilde{\mathbf{v}} \in \tilde{P}(s)} \mathbf{c}'\tilde{\mathbf{v}}, \tag{4.7}$$

and let $(\mathbf{y}^*, \mathbf{s}^*)$ be an optimal solution of the dual problem to the linear optimization problem given by the right hand side of (4.7) when $s = s_0$ (note the difference between $\mathbf{s}^*$ and s). We have, as in Section 2, that $f(\cdot)$ is a piece-wise linear function of s, and s_0 is contained in an interval in which the derivative of f with respect to s is constant. The left end point of this interval, s_1, say, is given by (cf. Theorem IV.73 in [10])

$$s_1 = \min_{s,\tilde{\mathbf{v}}} \{s \; : \; \tilde{\mathbf{v}} \in P(s), \; \tilde{\mathbf{v}}'\mathbf{s}^* = 0\},$$

and we have that $s_1 = 0$, since $s \ge 0$ and $\tilde{\mathbf{v}} = \mathbf{0}$ is feasible when $s = 0$. . Hence, for any point (s_0, t_0) in $\mathcal{F}$, the derivative of f with respect to s is constant on the line segment whose endpoints are the origin and (s_0, t_0), i.e., the optimal partition does not change on this line segment.

Based on the preceding discussion and the example given at the beginning of this section, we propose the following method for determining the phase plane and its constituent phases.

- Determine the feasible set $\mathcal{F}$, e.g., by using the *Fourier-Motzkin elimination method* (cf. [14] pg. 155).

- Pick a point (s,t), $s > 0$, on a ray originating at the origin and intersecting $\mathcal{F}$. Find a strictly complementary optimal solution to the reduced linear optimization problems induced by $\mathbf{b}_{s,t}$.

- Determine the ranges of the coefficients of $\mathbf{b}_{s,t}$ and the corresponding shadow prices from the linear optimization problems given in (2.4) and (2.5) as was done in the example above. If the range of a coefficient of $\mathbf{b}_{s,t}$ is a singleton, $\mathbf{b}_{s,t}$ is a break point of the optimal-value function and the corresponding interval determined by (2.5) is a non-degenerate closed interval whose extreme points are the left- and- right (partial) derivaties of the optimal-value function with respect to that coefficient. This implies that the ray on which the point (s, t) lies is a demarcation line between two phases. If, on the other hand, all ranges are closed non-degenerate intervals and the interval determined by (2.5) is a singleton, then the point (s, t) lies inside a phase, and the phase can be determined as in the example above by the ranges of the coefficients of $\mathbf{b}_{s,t}$.

The Fourier-Motzkin method is computationally inefficient ([1] pg. 73), hence for large systems some other means of determining the feasable set must be found. We conjecture that an auxiliary optimization problem analogous to (2.4) and (2.5) can be constructed to accomplish this. An alternative might be to start from a feasible point and then search the plane using (2.4) and (2.5). Any infeasible point should lead to inconsistencies in the optimization procedure: for instance, in the example above, if $t > 3s$ then the first line of the constraint conditions in (4.2) implies that either x_1 or x_3 is negative. Similarly, if $t < s$ then the second line in (4.2) implies that either x_2 or x_4 is negative.

There are several software programs available that use interior point methods. For example, the Matlab (MathWorks, Inc.) toolbox Mosek (http://www.mosek.com) can be used to find strictly complementary solutions in linear programs. Mosek can also be used for solving the auxiliary problems (as can the default Matlab method). From our experience with Matlab, we believe that genome-scale phase planes can be calculated using the method outlined above.

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