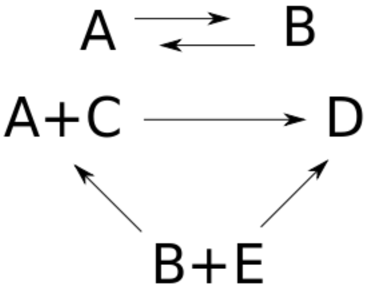
Efficiently Testing Thermodynamic Compliance of Chemical Reaction Networks

Meredith McCormack-Mager, Carlos Munoz, Zev Woodstock

20 July 2015

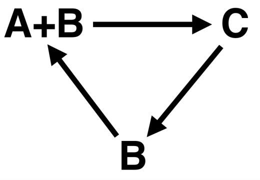
Chemical Reaction Networks



Thermodynamic Analysis

Second Law of Thermodynamics

In any closed system, the entropy of the system will either remain constant or increase.



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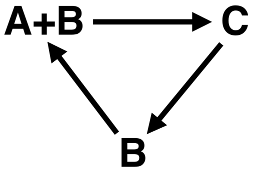


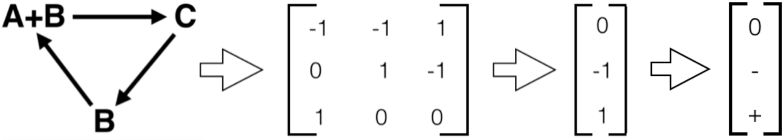
Question

Can we quickly determine when a chemical reaction network is thermodynamically feasible?

Previous Work

Algorithm (Beard et al., 2004)

Determines if a chemical reaction network is thermodynamically feasible for a given set of reaction rates.



Chemical Reaction Network   Stoichiometric Matrix   Stoichiometric Nullspace   Signed Vector

- Step 1: Form stoichiometric matrix from reaction network.
- Step 2: Compute nullspace of stoichiometric matrix.
- Step 3: Compute signed vectors of nullspace.
- Step 4: Check orthogonality between flux vector and "cycles".

What is a cycle?

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Signed Support of a Vector

The *positive/negative support* of a vector is the set of indices at which the vector has a positive/negative value.

$$v = (1, -1, 0, 1, 1, -1) \qquad v^+ = \{1, 4, 5\}, \quad v^- = \{2, 6\}$$

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Cycle

A *cycle* is a signed vector with minimal signed support.

$$w = (1, -1, 0, 0, 0, 0) \qquad w^+ = \{1\}, \quad w^- = \{2\}$$

Cycle Axioms

1. If α is a cycle, then $-\alpha$ is a cycle.
2. If α and β are cyles, and the signed support of α is contained in the signed support of β, then $\alpha = \beta$ or $\alpha = -\beta$.
3. Suppose α and β are cycles such that $\alpha \neq -\beta$, and i is and index with $\alpha_i = +$ and $\beta_i = -$. Then there exists a cycle γ with $\gamma^+ \subseteq (\alpha^+ \cup \beta^+)$ and $\gamma^- \subseteq (\alpha^- \cup \beta^-)$.

Row-Reduced Echelon Basis

Let $\xi \subseteq \mathbb{R}^n$ be a k-dimensional subspace. Then let $B = \{v_1, ..., v_k\}$ be a basis for ξ such that

$$\begin{pmatrix} v_1 \\ \vdots \\ v_k \end{pmatrix}$$

is in Reduced Row Echelon form.

Ex.

$$\begin{pmatrix} 1 & 0 & 0 & -3 & -2 \\ 0 & 1 & 0 & -2 & 4 \\ 0 & 0 & 1 & 1 & -1 \end{pmatrix}$$

Computing Cycles

Theorem

The signed vector of every basis vector is a cycle.

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Definitions

Vectors v and w have a *disagreement* if there exists an index ℓ such that v_ℓ and w_ℓ have opposite signs, i.e. one is negative and one is positive.

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We say that a *resolution vector* u is a linear combination of v and w such that $u_\ell = 0$.

$\mathrm{v} = (1, 0, \text{-}3), \; \mathrm{w} = (0, 1, 4) \qquad 4\mathrm{v} + 3\mathrm{w} = (4, 3, 0)$

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Theorem

The signed vector of any pairwise resolution of basis vectors is a cycle.

Computing Cycles

Ex.

$$N = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 & 1 & 1 & 0 \\ 0 & 1 & 0 & -1 & 0 & 1 \\ 0 & 0 & 1 & 0 & -1 & -1 \end{pmatrix}$$

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Then $(+, 0, 0, +, +, 0)$, $(0, +, 0, \text{-}, 0, +)$, and $(0, 0, +, 0, \text{-}, \text{-})$ are cycles.

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Then (+, 0, 0, +, +, 0), (0, +, 0, -, 0, +), and (0, 0, +, 0, -, -) are cycles.

And (+, +, 0, 0, +, +), (+, 0, +, +, 0, -), and (0, +, +, -, -, 0) are cycles.

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But $\text{sgn}(v_1 + v_2 + v_3) = (+, +, +, 0, 0, 0)$ is also a cycle.

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But $\text{sgn}(v_1 + v_2 + v_3) = (+, +, +, 0, 0, 0)$ is also a cycle.

Bad News

Depending on the number of disagreements between basis vectors, we could have $2^k - 1$ independent cycles in $\mathscr{C}$.

Exponential Condition

Sign Orthogonality

Two sign vectors are *orthogonal* if there is an index i at which they have the same (nonzero) sign and another index j at which they have opposite signs.

$$(+,+,0) \perp (+,-,-) \qquad\qquad (+,+,0) \not\perp (+,0,-)$$

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Orthogonality to sgn(Flux Vector)

There exists a cycle *not orthogonal* to the signed vector of the flux vector if there is $\alpha \in N$ such that each entry of α is nonnegative.

$$(1,1,1) \not\perp (1,0,1)$$

Determining Orthogonality

Ex.

$$\begin{pmatrix} 1 & 0 & 0 & -3 & -2 \\ 0 & 1 & 0 & -2 & 4 \\ 0 & 0 & 1 & 1 & -1 \end{pmatrix}$$

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Suppose there exists w such that all entries in w are nonnegative.

Then $w = c_1 v_1 + c_2 v_2 + c_3 v_3$.

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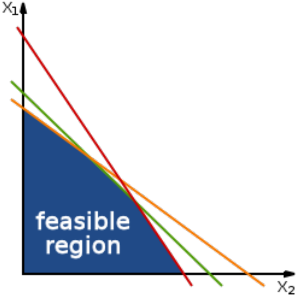
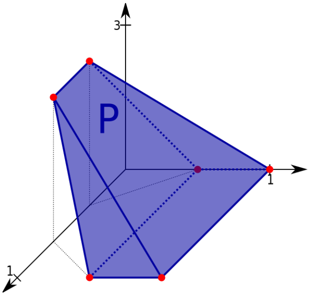
So $c_3 \geq 3c_1 + 2c_2$ and $4c_2 \geq 2c_1 + c_3$.

Constraint Analysis

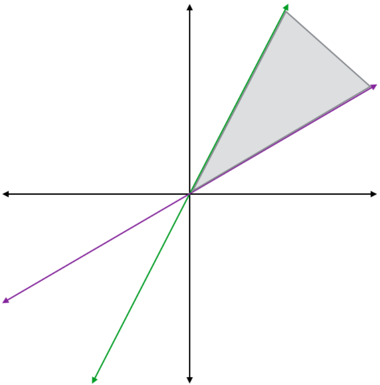
We can have up to n inequalities, where n is the number of reactions.

$$
\begin{aligned}
& x_i \geq 0 \\
& a_{1,1}x_1 + \ldots + a_{1,k}x_k \leq b_1 \\
& a_{2,1}x_1 + \ldots + a_{2,k}x_k \leq b_2 \\
& \quad \vdots \\
& a_{n-k,1}x_1 + \ldots + a_{n-k,k}x_k \leq b_{n-k}
\end{aligned}
$$





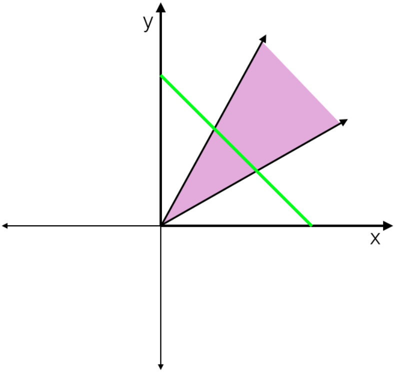
Special Properties



- All boundary hyperplanes intersect at the origin.
- Origin is always feasible.
- Every nontrivial feasible region is unbounded.

Bounding the System in 2D

Take any line with positive x and y intercepts.



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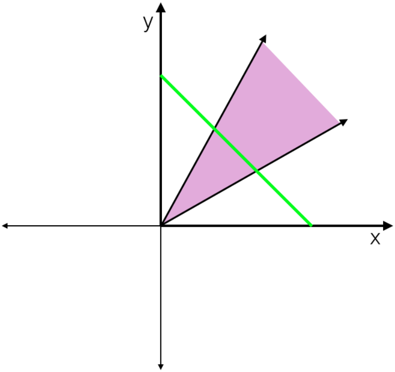

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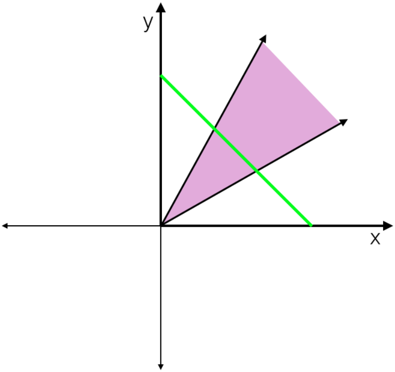
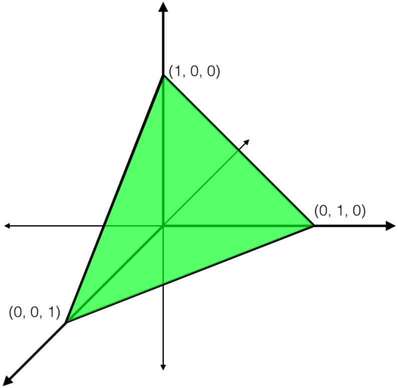


- The intersection of this line and the feasible region is bounded and does not contain the origin.
- The intersection is nonempty if and only if a feasible region exists.

Bounding the System in General

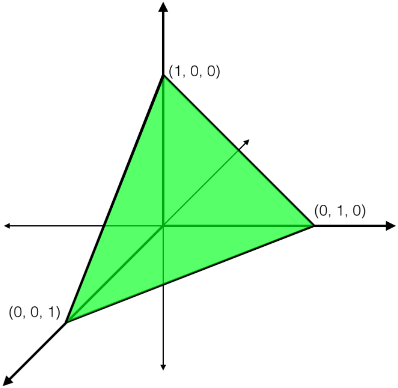
Suppose $x_1 + \ldots + x_k = 1$.



Bounding the System in General

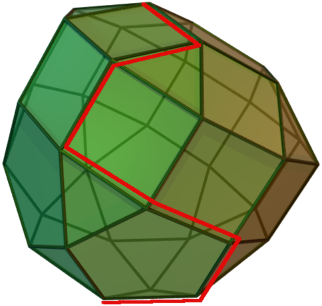
Suppose $x_1 + \ldots + x_k = 1$.

Then $x_1 = 1 - x_2 - \ldots - x_k$.



Linear Programming

Finds an optimal solution to a linear function based on a set of linear constraints.



Linear Programming

Objective function maximize Z = ?

Constraints: $Ax \leq b, x \geq 0$

$$
\begin{aligned}
a_{1,1}x_1 + \ldots + a_{1,k}x_k &\leq b_1 \\
a_{2,1}x_1 + \ldots + a_{2,k}x_k &\leq b_2 \\
\vdots \\
a_{n-k+1,1}x_1 + \ldots + a_{n-k+1,k}x_k &\leq b_{n-k+1}
\end{aligned}
$$

Linear Programming

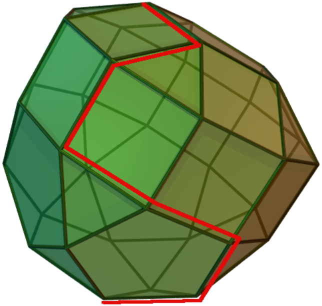
Objective function maximize $Z = -x_0$

Constraints: $A\hat{x} \leq b, x \geq 0$

$$\begin{aligned}
-x_0 + a_{1,1}x_1 + \ldots + a_{1,k}x_k &\leq b_1 \\
-x_0 + a_{2,1}x_1 + \ldots + a_{2,k}x_k &\leq b_2 \\
&\vdots \\
-x_0 + a_{n-k+1,1}x_1 + \ldots + a_{n-k+1,k}x_k &\leq b_{n-k+1}
\end{aligned}$$

Our original system of constraints has a feasible region if and only if $Z = -x_0$ maximizes to 0.

Polynomial Time?



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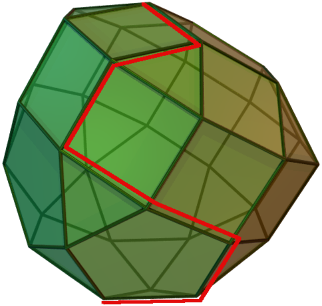

Anstreicher's interior point method (1999) runs in polynomial time in the worst case: $O(\frac{k^3}{log(k)} n)$.

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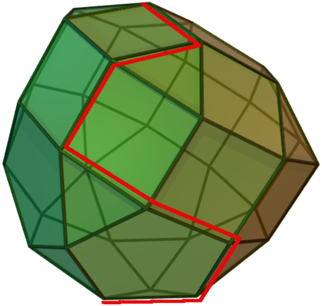

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Interior point algorithms are at most $O(\sqrt{k}log(k))$ on average.

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