Efficiently Testing Thermodynamic Compliance of Chemical Reaction Networks

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20 July 2015
Chemical Reaction Networks

A ⇌ B

A + C → D

B + E
Thermodynamic Analysis

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

A+B → C
B → A
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Second Law of Thermodynamics
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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.

- 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”.

Chemical Reaction Network

\[
\begin{bmatrix}
-1 & -1 & 1 \\
0 & 1 & -1 \\
1 & 0 & 0
\end{bmatrix}
\] Stoichiometric Matrix

\[
\begin{bmatrix}
0 \\
-1 \\
1
\end{bmatrix}
\] Stoichiometric Nullspace

\[
\begin{bmatrix}
0 \\
-
\end{bmatrix}
\] Signed Vector
What is a cycle?

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.

\[ v = (1, -1, 0, 1, 1, -1) \]

\[ v^+ = \{1, 4, 5\} \]

\[ v^- = \{2, 6\} \]

Cycle

A cycle is a signed vector with minimal signed support.

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Cycle Axioms

1. If $\alpha$ is a cycle, then $-\alpha$ is a cycle.

2. If $\alpha$ and $\beta$ are cycles, and the signed support of $\alpha$ is contained in the signed support of $\beta$, then $\alpha = \beta$ or $\alpha = -\beta$.

3. Suppose $\alpha$ and $\beta$ are cycles such that $\alpha \neq -\beta$, and $i$ is an index with $\alpha_i = +$ and $\beta_i = -$. Then there exists a cycle $\gamma$ 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 $B = \{v_1, \ldots, v_k\}$ be a basis for $\xi$ such that

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

is in Reduced Row Echelon form.

Ex.

$$
\begin{pmatrix}
  1 & 0 & 0 & -3 & -2 \\
  0 & 1 & 0 & -2 & 4 \\
  0 & 0 & 1 & 1 & -1
\end{pmatrix}
$$
Theorem
The signed vector of every basis vector is a cycle.

Definitions
Vectors $v$ and $w$ have a disagreement if there exists an index $\ell$ such that $v_\ell$ and $w_\ell$ have opposite signs, i.e. one is negative and one is positive.

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

$v = (1, 0, -3), w = (0, 1, 4) \rightarrow 4v + 3w = (4, 3, 0)$

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

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

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

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

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 \(C\).
Computing Cycles

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

$$(+, +, 0) \perp (+, -, -) \quad (+, +, 0) \not\perp (+, 0, -)$$
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.

$$(+, +, 0) \perp (+, -, -) \quad (+, +, 0) \nparallel (+, 0, -)$$

Orthogonality to $\text{sgn}($Flux Vector$)$
There exists a cycle *not orthogonal* to the signed vector of the flux vector if there is $\alpha \in \mathbb{N}$ such that each entry of $\alpha$ is nonnegative.

$$(1, 1, 1) \nparallel (1, 0, 1)$$
Determining Orthogonality

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

Then \( w = c_1 v_1 + c_2 v_2 + c_3 v_3 \).
Determining Orthogonality

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

Then \( w = c_1 v_1 + c_2 v_2 + c_3 v_3. \)

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.

\[
x_i \geq 0
\]

\[
a_{1,1}x_1 + \ldots + a_{1,k}x_k \leq b_1
\]

\[
a_{2,1}x_1 + \ldots + a_{2,k}x_k \leq b_2
\]

\[
\vdots
\]

\[
a_{n-k,1}x_1 + \ldots + a_{n-k,k}x_k \leq b_{n-k}
\]
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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Take any line with positive x and y intercepts.

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

\[
\begin{align*}
a_{1,1}x_1 + \ldots + a_{1,k}x_k & \leq b_1 \\
a_{2,1}x_1 + \ldots + a_{2,k}x_k & \leq b_2 \\
& \vdots \\
a_{n-k+1,1}x_1 + \ldots + a_{n-k+1,k}x_k & \leq b_{n-k+1}
\end{align*}
\]
Linear Programming

Objective function: maximize $Z = -x_0$

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

$-x_0 + a_{1,1}x_1 + \ldots + a_{1,k}x_k \leq b_1$

$-x_0 + a_{2,1}x_1 + \ldots + a_{2,k}x_k \leq b_2$

$\vdots$

$-x_0 + a_{n-k+1,1}x_1 + \ldots + a_{n-k+1,k}x_k \leq b_{n-k+1}$

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

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

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