Chemical Networks of Reversible Binding Reactions

Gilles Gnacadja

Research and Development Information Systems, Amgen

gnacadja@amgen.com

http://math.GillesGnacadja.info

Abstract

Systems of reversible binding reactions occur in biopharmaceutical research, e.g. in the study of the receptor-mediated effects of pathogenic and therapeutic ligands. The class of complete networks encompasses a large collection of such systems. For a complete network, the nonnegative stoichoimetric compatibility classes are convex polytopes represented by chemically genuine conservation equations. Each contains an equilibrium state that is unique, detailed-balanced and globally attractive. These properties derive in part from the remarkable features of a polynomial system that describes the equilibrium state, e.g. its Jacobian matrix is a P-matrix everywhere. A simple formula gives the deficiency.

1. A Remarkable Positive Polynomial Map

Theorem. Let $n \in \mathbb{Z}_{>0}$, let I finite $\subset \mathbb{Z}^n_{\geqslant 0}$, and let $(a_\alpha)_{\alpha\in I}$ be a family over $\mathbb{R}_{\geqslant 0}$. The map $f = (f_1, \ldots, f_n) : \mathbb{R}^n_{\geqslant 0} \to \mathbb{R}^n_{\geqslant 0}$ given by $f_i(x) = x_i + \sum_{\alpha\in I} \alpha_i\, a_\alpha\, x^\alpha$ is a C^∞-diffeomorphism.

Proof of surjectivity. Let the map $F = (F_1, \ldots, F_n) : \mathbb{R}^n_{\geqslant 0} \times \mathbb{R}^n_{\geqslant 0} \to \mathbb{R}^n_{\geqslant 0}$ be defined by $F_i(b, x) = \dfrac{b_i}{1 + \sum_{\alpha\in I, \alpha_i \geqslant 1} \alpha_i\, a_\alpha\, x^{\alpha - e_{n,i}}}$. We have $f^{-1}(b) = \mathrm{FixPt}(F(b, -))$ and, by the Brouwer Fixed Point Theorem, $\mathrm{FixPt}(F(b, -)) \neq \varnothing$.

Proof of injectivity. Consider the matrix $M(x)$ such that the Jacobian matrix of f at x is $\mathsf{J}(f, x) = \mathsf{Id}_n + M(x)$. We have $M(x) \cdot \mathrm{diag}(x) = \sum_{\alpha\in I} a_\alpha\ x^\alpha\ \alpha^{\mathrm{T}}\alpha$. Each matrix $\alpha^{\mathrm{T}}\alpha$ is positive-semidefinite. Therefore the matrix $M(x) \cdot \mathrm{diag}(x)$ is positive-semidefinite, and consequently is a P_0-matrix. It follows that $M(x)$ is a P_0-matrix, and then that $\mathsf{J}(f, x)$ is a P-matrix. By the Global Univalence Theorem of Gale and Nikaidô, the map f is injective.

Computation. A possible approach to computing $f^{-1}(b)$ is to solve the fixed point problem for $F(b, -)$. Iteration starting at b yields an enclosing sequence that converges linearly if $\max_{\alpha\in I} \|\alpha\|_{\ell^1} \leqslant 2$. We are considering interval methods to cover all cases.

2. Normal Networks of Reversible Binding Reactions

Definition. Let I finite $\subset \mathbb{Z}^n_{\geqslant 0} \backslash \{0_n, e_{n,1}, \ldots, e_{n,n}\}$. A normal network of reversible binding reactions with composition I is given by the following items:

Elementary species : $X_1, \ldots, X_n$

Composite species : $Y_\alpha = (X_1)_{\alpha_1} \cdots (X_n)_{\alpha_n}\ ,\ \alpha \in I$

Reactions : $\alpha_1 X_1 + \cdots + \alpha_n X_n \rightleftharpoons Y_\alpha\ ,\ \alpha \in I$

- Kinetic : Mass action
- k^+_α, k^-_α : Association and dissociation rate constants
- $a_\alpha = k^+_\alpha / k^-_\alpha$: Equilibrium binding constants

Example. Normalization (see section 3) of a network of a receptor R with two allosteric ligands A and B, a case with $I = \{(1, 1, 0), (1, 0, 1), (1, 1, 1)\}$:

$$R + A \rightleftharpoons RA \qquad R + B \rightleftharpoons RB \qquad R + A + B \rightleftharpoons RAB\ .$$

By stoichiometric accounting or analyzing the mass-action dynamical system, one gets:

Proposition. For each $i \in [1..n]$, the total concentration of (free and bound) elementary species X_i, $b_i = [X_i] + \sum_{\alpha\in I} \alpha_i\, [Y_\alpha]$, is independent of time.

This leads to a convenient description of the stoichiometric compatibility classes.

Proposition. For $b = (b_1, \ldots, b_n) \in \mathbb{R}^n_{\geqslant 0}$, let $P(b) \subset \mathbb{R}^{[1..n]\sqcup I}$ be defined by the system

$$x_i + \textstyle\sum_{\alpha\in I} \alpha_i\, y_\alpha = b_i\,, \forall\, i \in [1..n]\ ; \quad x_i \geqslant 0\,, \forall\, i \in [1..n]\ ; \quad y_\alpha \geqslant 0\,, \forall\, \alpha \in I\ .$$

The set $P(b)$, a convex polytope, is a nonnegative stoichiometric compatibility class. The correspondence $b \mapsto P(b)$ establishes a bijection from $\mathbb{R}^n_{\geqslant 0}$ onto the set of all nonnegative stoichiometric compatibility classes.

Based in part on the properties of the polynomial map f of section 1, we have:

Theorem. Let $b = (b_1, \ldots, b_n) \in \mathbb{R}^n_{\geqslant 0}$. There exists in the stoichiometric compatibility class $P(b)$ a unique concentration vector $(x, y) = (x_i, i \in [1..n]; y_\alpha, \alpha \in I)$ that is an equilibrium state. It is detailed-balanced and is the nonnegative solution of the following system:

$$x_i + \textstyle\sum_{\alpha\in I} \alpha_i\, a_\alpha\, x^\alpha = b_i\,, \forall\, i \in [1..n]\ ; \quad y_\alpha = a_\alpha\, x^\alpha\,, \forall\, \alpha \in I\ .$$

It is believed that binding reactions with $\|\alpha\|_{\ell^1} = 3$ (termolecular reactions) are rare and it appears that reactions with $\|\alpha\|_{\ell^1} \geqslant 4$ are unheard of. Composite species usually result from multistep reactions. The class of complete networks accounts for these.

3. Complete Networks of Reversible Binding Reactions

Definition. Let I finite $\subset \mathbb{Z}^n_{\geqslant 0} \backslash \{0_n, e_{n,1}, \ldots, e_{n,n}\} = \mathbb{Z}^n_{\geqslant 0} \backslash \{\|\cdot\|_{\ell^1} \leqslant 1\}$ and let $(J_\alpha)_{\alpha\in I}$ be a family of finite, nonempty and pairwise disjoint subsets of $\mathbb{Z}^{[1..n]\sqcup I}_{\geqslant 0} \backslash \{\|\cdot\|_{\ell^1} \leqslant 1\}$. The following items and requirements specify a complete network of reversible binding reactions:

Elementary species : $X_1, \ldots, X_n$

Composite species : $Y_\alpha = (X_1)_{\alpha_1} \cdots (X_n)_{\alpha_n}\ ,\ \alpha \in I$

Reactions : $\sigma_1 X_1 + \cdots + \sigma_n X_n + \sum_{\beta\in I} \sigma_\beta Y_\beta \rightleftharpoons Y_\alpha\ ,\ \alpha \in I\ ,\ \sigma \in J_\alpha$

- Kinetic : Mass action
- $k^+_{\alpha,\sigma}$, $k^-_{\alpha,\sigma}$: Association and dissociation rate constants
- $a_{\alpha,\sigma} = k^+_{\alpha,\sigma} / k^-_{\alpha,\sigma}$: Equilibrium binding constants

Conservation of composition : $\alpha = (\sigma_1, \ldots, \sigma_n) + \sum_{\beta\in I} \sigma_\beta\, \beta\ ,\ \forall\, \alpha \in I,\ \forall\, \sigma \in J_\alpha$

Principle of detailed balance : There exists a family $(a_\alpha)_{\alpha\in I}$ over $\mathbb{R}_{>0}$ such that $a_\alpha = a_{\alpha,\sigma} \prod_{\beta\in I} (a_\beta)^{\sigma_\beta}\ ,\ \forall\, \alpha \in I,\ \forall\, \sigma \in J_\alpha$

Thanks to the conservation of composition and the principle of detailed balance, we can sensibly and purposefully associate a normal network with a complete network:

Definition. The normalization of the complete network is the normal network of reversible binding reactions in which the elementary species are $X_1, \ldots, X_n$, the composite species are Y_α, the reactions are $\alpha_1 X_1 + \cdots + \alpha_n X_n \rightleftharpoons Y_\alpha$, and their equilibrium binding constants are a_α, where $\alpha \in I$. The association and dissociation rate constants are unspecified.

Example. Network of a receptor R with two allosteric ligands A and B, a complete network. Its normalization is the example of section 2.

$$R + A \rightleftharpoons RA \qquad R + B \rightleftharpoons RB \qquad RA + B \rightleftharpoons RAB \qquad RB + A \rightleftharpoons RAB\ .$$

The height of a species is the maximum number of steps its formation can take. Elementary species have height zero and composite species have height one or larger. A normal network is a complete network in which all composite species have height one.

If Y_α has height one, then $J_\alpha = \{\sigma\}$ where $\sigma = (\alpha, 0_I)$, i.e. $(\sigma_1, \ldots, \sigma_n) = \alpha$ and $\sigma_\beta = 0$ for $\beta \in I$; and $a_\alpha = a_{\alpha,\sigma}$. If Y_α has height larger than one, then for every $\sigma \in J_\alpha$, $\sigma_\beta > 0$ for some $\beta \in I$.

The concentration conservation equations and the characterization of the nonnegative stoichoimetric compatibility classes for normal networks apply to complete networks. The class $P(b)$ is the disjoint union of its interior $P_{>0}(b)$, in which vectors have positive components, and its boundary $P_{\not>0}(b)$, in which each vector has at least one zero component.

Theorem. Let $b = (b_1, \ldots, b_n) \in \mathbb{R}^n_{>0}$. The boundary $P_{\not>0}(b)$ contains no equilibrium states.

Proof. Two inductive arguments on height show that if an equilibrium state satisfies $x_i = 0$ for some $i \in [1..n]$, then $b_i = 0$; and that if such state satisfies $y_\alpha = 0$ for some $\alpha \in I$, then $b_i = 0$ for some $i \in [1..n]$ with $\alpha_i \geqslant 1$.

This theorem says that all species are present at an equilibrium state provided every elementary species is present in some (free or bound) form.

We can now characterize the equilibrium states.

Theorem. Let $b = (b_1, \ldots, b_n) \in \mathbb{R}^n_{\geqslant 0}$. There exists in the stoichiometric compatibility class $P(b)$ a unique concentration vector $(x, y) = (x_i, i \in [1..n]; y_\alpha, \alpha \in I)$ that is an equilibrium state of the complete network. It is detailed-balanced and is the detailed-balanced state of the normalization network, and thus is the nonnegative solution of the following system:

$$x_i + \textstyle\sum_{\alpha\in I} \alpha_i\, a_\alpha\, x^\alpha = b_i\,, \forall\, i \in [1..n]\ ; \quad y_\alpha = a_\alpha\, x^\alpha\,, \forall\, \alpha \in I\ .$$

Not only does the boundary not contain equilibrium states, it is weakly repelling:

Theorem. Let $b = (b_1, \ldots, b_n) \in \mathbb{R}^n_{>0}$. A concentration trajectory in the class $P(b)$ that originates on the boundary $P_{\not>0}(b)$ immediately enters and stays in the interior $P_{>0}(b)$.

Proof. All species are reachable, in the sense of Vol'pert, from the set of species that are present at initial time. Hence, the Vol'pert Strict Positivity Theorem applies.

We use this to derive the following global attraction result.

Theorem. Let $b = (b_1, \ldots, b_n) \in \mathbb{R}^n_{\geqslant 0}$. Every concentration trajectory in the nonnegative stoichoimetric compatibility class $P(b)$ of the complete network converges to the unique detailed-balanced state within $P(b)$.

We close with the deficiency of complete networks. Note that the normal networks are precisely the complete networks of deficiency zero.

Theorem. Deficiency $=$ (Number of binding reactions) $-$ (Number of composite species).

4. Concluding Remarks

The existence, uniqueness and stability results discussed herein are usually associated with networks of deficiency zero and the interior of stoichoimetric compatibility classes. Here, networks of arbitrary deficiency are included and we have global attraction also from the boundary. The latter fact has applicative implications, as in experiments, some species, in particular some composite species, may not be present at initial time.

We are interested in extensions of this work to (weakly reversible) complex-balanced networks with a notion of composition that is chemically sensible but need not alone determine species, so as to account for isomeric species.

Selected References

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