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Stoichiometric Network Analysis: a Critical Review of its Algorithmic Strength

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Abstract

We survey the mathematical foundations of Clarke Stochiometric Network Analysis (SNA, for short). We show that SNA is heavily based on a special change of coordinates that we call *Clarke's velocity function*.

Given a chemical reaction network Ω, the associated system of *Clarke's coordinates* (also called *convex coordinates*) allows one to compute a polyhedral definition for the set of steady states of Ω. The latter fact yields a reduction to linear programming of some algorithmic tasks that are related to the linear stability analysis of chemical reaction networks.

We discuss the algorithmic potential of Clarke's theory, which is strongly limited by its dependence on a hard intractable problem, the problem of computing spanning sets of polyhedral cones. We discuss how the hardness of the latter problem reduces the algorithmic potential of SNA.

We also show that SNA can be happily applied in some scenarios. To this end we study a problem that is related to the linear stability analysis of network models of biological homochirality. We show that SNA provides us with algorithmic tools that can be used to solve the aforementioned problem.

This work is intended to be a critical review of *Clarke's Stoichiometric Network Analysis* (SNA, for short, see [6] and the references therein).

SNA provides us with tools that can be applied in the stability analysis of *chemical reaction networks*. Those networks are rough descriptions of chemical reaction mechanisms,

which can be either real or abstract. Thus, the analysis of chemical reaction networks is an important task related to the prediction and control of chemical processes.

A chemical network is just a pair of sets:

- The first set is a set of chemical species: the species involved in the chemical process.
- The second set is a set of chemical reactions: the reactions that take place along the chemical process.

If one assumes the *law of mass-action*, then he should assume that the dynamics of the network (process) is driven by a system of nonlinear ordinary differential equations that can be effectively computed from the above two sets. Those ODE-systems (*mass-action kinetics systems*) are the systems that we have to analyze, using the tools of linear stability analysis and SNA.

Let Ω be a chemical network. The mass-action dynamics of Ω is naturally expressed in a system of concentration coordinates. It can be argued that SNA reduces to a very special change of coordinates. The latter change of coordinates, computed by *Clarke's velocity function* (see below), maps the set of steady states of Ω onto a polyhedral cone called the *current cone.* Clarke's change of coordinates is, to some extent, a linearization of the dynamics of Ω : let $\mathcal{J}_\Omega$ be the symbolic Jacobian of Ω, if we express $\mathcal{J}_\Omega$ in the system of *convex coordinates*, then all the entries of this symbolic matrix become linear polynomials.

We discuss in some depth the algorithmic potential of Clarke's theory. We also discuss the weakness of SNA, which is mainly related to the algorithmic hardness of generating all the *extreme currents* (extreme rays of the current cone). The intractability of this enumeration problem strongly reduces the algorithmic potential of SNA. However, we show that SNA can be happily applied in some scenarios. To this end, we study a problem that is related to the linear stability analysis of network models of biological homochirality. We show that SNA provides us with algorithmic tools that can be used to solve the aforementioned problem.

Notation 1 *Let us fix some notation*

1. *Given $v \in \mathbb{R}^n$ and given $i \leq n$, we use the symbol $v[i]$ to denote the i-th entry of v.*
2. *Given a $k \times r$ matrix A, and given $i \leq k, j \leq r$, we use the symbol $A[i,j]$ to denote the entry of A that is located at row i column j.*

3. *We use the symbol* $\mathbb{R}^n_+$ *to denote the set*

$$\{(a_1, ..., a_n) \in \mathbb{R}^n : a_1, ..., a_n \geq 0\},$$

and we use the symbol $\mathbb{R}^n_>$ *to denote the set*

$$\{(a_1, ..., a_n) \in \mathbb{R}^n : a_1, ..., a_n > 0\}.$$

1 Chemical reaction networks

Chemical reactions are the chemical processes *par excellence*.

Definition 2 *A chemical reaction over the chemical species* $X_1, ..., X_n$ *is an expression like*

$$c_1 X_1 + \cdots + c_n X_n \to d_1 X_1 + \cdots + d_n X_n,$$

where $c_1, ..., c_n$ *and* $d_1, ..., d_n$ *are small integers (some of which could be equal to zero). The above expression indicates that the mixture of* c_1 *units of* $X_1, ...,$ *and* c_n *units of* X_n *gives place to* d_1 *units of* $X_1, ...,$ *and* d_n *units of* X_n.

If for all $i \leq n$ *the equality* $c_i = 0$ *holds, the reaction represents an in-flow. On the other hand, if for all* $i \leq n$ *the equality* $d_i = 0$ *holds, the reaction represents an out-flow.*

Definition 3 *A chemical network over the species* $\{X_1, ..., X_n\}$ *is a set of chemical reactions, say the set* $\{R_1, ..., R_r\}$, *over this set of species. Thus, a chemical network is a pair* $(\{X_1, ..., X_n\}, \{R_1, ..., R_r\})$.

Notation 4 *Given a chemical network*

$$\Omega = ((X_1, ..., X_n), (R_1, ..., R_r)),$$

we use the expression

$$c_{1i} X_1 + \cdots + c_{ni} X_n \to d_{1i} X_1 + \cdots + d_{ni} X_n$$

to denote the reaction R_i.

We use variables $[X_1], ..., [X_n]$ *to denote the concentrations of the* n *chemical species.*

Let us consider an example of a chemical reaction network. We use the symbol Ω_0 to denote the network $(\{I, A\}, \{R_1, R_2, R_3\})$, where:

- Reaction R_1 is equal to $3I \to 3A$,

- Reaction R_2 is equal to $2I + A \to 3I$ and
- Reaction R_3 equal to $I + A \to 2A$.

Thus, we assume that Ω_0 describes a chemical process involving only two species that react in three different ways. What can be said about this abstract chemical mechanism? We have to consider a qualitative approach to the latter question given the nonlinearity of its dynamics.

1.1 Stability analysis of chemical reaction networks

Let $\Omega = ((X_1, ..., X_n), (R_1, ..., R_r))$ be a chemical network. We want to analyze the dynamical behavior of network Ω. To do the latter we have to associate to each reaction a *reaction rate constant* that measures the likelihood of the corresponding reaction. Let $(k_1, ..., k_r)$ be a vector of rate constants, we have: if the values of $k_1, ..., k_r$ correspond to the rate constants of the reactions $R_1, ..., R_r$, then, and according to the law of mass-action, the dynamics of the network is governed by the polynomial system of differential equations given below

$$\frac{d[X_i]}{dt} = \sum_{j=1}^{r} k_j (d_{ij} - c_{ij}) \left([X_1]^{c_{ij}} \cdot \cdots \cdot [X_n]^{c_{ij}} \right), \ i = 1, ..., n.$$

We have, for instance, that the dynamics of Ω_0 is driven by the nonlinear system

$$\begin{aligned} \frac{d[I]}{dt} &= -3k_1 [I]^2 + k_2 [I]^2 [A] - k_3 [I] [A], \\ \frac{d[A]}{dt} &= 3k_1 [I]^2 - k_2 [I]^2 [A] + k_3 [I] [A], \end{aligned}$$

which cannot be solved by analytical means.

The impossibility of solving those nonlinear systems lead us to consider a steady-state analysis of the dynamics.

Definition 5 *We say that* $(\mathbf{a}, \mathbf{b}) \in \mathbb{R}^n \times \mathbb{R}^r$ *is a steady state of* Ω*, if and only if, the equalities*

$$\sum_{j=1}^{r} b[j] (d_{ij} - c_{ij}) \left(a[1]^{c_{ij}} \cdot \cdots \cdot a[n]^{c_{ij}} \right) = 0; \ i = 1, ..., n$$

hold. Here, we use the symbol $\mathbf{a}$ *to denote the subtuple constituted by the* n *concentrations, and the symbol* $\mathbf{b}$ *to denote the subtuple constituted by the* r *reaction rate constants.*

We have, for instance, that a state of Ω_0 is a quintuple $([I],[A],k_1,k_2,k_3)$, where $\mathbf{a}$ corresponds to the pair $([I],[A])$, and $\mathbf{b}$ corresponds to the triple (k_1,k_2,k_3). Moreover, the set of steady states of Ω_0 is the set

$$\mathcal{SS}(\Omega_0)=\left\{([I],[A],k_1,k_2,k_3)\in\mathbb{R}_+^5 : -3k_1[I]^3+k_2[I]^2[A]-k_3[I][A]=0\right\},$$

which has a quite complex structure: given $r,s,t\in\mathbb{R}_+$, the two dimensional section determined by the conditions $k_1=r,k_2=s,k_3=t$ is the complex curve given by equation

$$[A]=\frac{-3r[I]^3}{\left(s[I]^2-t[I]\right)}.$$

Definition 6 *We say that $(\mathbf{a},\mathbf{b})\in\mathbb{R}^n\times\mathbb{R}^r$ is a positive steady state, if and only if, for all $i\leq n$ and for all $j\leq r$ the inequalities*

$$\mathbf{a}_0[i],\mathbf{b}_0[j]>0$$

hold. We use the symbol $\mathcal{SS}_+(\Omega)$ to denote the set of positive steady states.

Definition 7 *The symbolic Jacobian of Ω is the symbolic matrix $\mathcal{J}_\Omega$ that is defined by*

$$\mathcal{J}_\Omega[i,j]=\frac{\partial\left(\sum_{j=1}^{r}k_j(d_{ij}-c_{ij})([X_1]^{c_{ij}}\cdot\cdots\cdot[X_n]^{c_{ij}})\right)}{\partial[X_j]}.$$

The symbolic Jacobian of Ω can be seen as a function $\mathcal{J}_\Omega:\mathcal{SS}(\Omega)\to\mathcal{M}_{nn}(\mathbb{R})$ that assigns to each steady state a $n\times n$ numerical matrix that we denote with the symbol $\mathcal{J}_\Omega(\mathbf{a},\mathbf{b})$. We assume this point of view in this work.

We have, for instance, that $\mathcal{J}_{\Omega_0}$ is the matrix-valued function defined by

$$\mathcal{J}_{\Omega_0}(([I],[A],k_1,k_2,k_3))=\begin{bmatrix}-9k_1[I]^2+2k_2[I][A]-k_3[A] & k_2[I]^2-k_3[I]\\ 9k_1[I]^2-2k_2[I][A]+k_3[A] & -k_2[I]^2+k_3[I]\end{bmatrix},$$

and which encodes many key features of the dynamics of Ω_0: the Theorem of Grobman-Hartman tells us that the stability (instability) properties of a hyperbolic state $(\mathbf{a},\mathbf{b})$ can be deduced from the spectrum (the *eigenstructure*) of $\mathcal{J}_\Omega(\mathbf{a},\mathbf{b})$ [12].

Definition 8 *Let $(\mathbf{a},\mathbf{b})$ be a steady state, and let $\lambda_1,...,\lambda_n$ be the eigenvalues of $\mathcal{J}_\Omega(\mathbf{a},\mathbf{b})$. We say that $(\mathbf{a},\mathbf{b})$ is stable, if and only if, for all $i\leq n$ the inequality $Re(\lambda_i)<0$ holds. On the other hand, we say that $(\mathbf{a},\mathbf{b})$ is unstable, if and only if, there exists i such that $Re(\lambda_i)\geq 0$.*

Given a state $(\mathbf{a}, \mathbf{b})$, it is easy to check wether this state is unstable. To this end, one just has to compute the spectrum of $\mathcal{J}_\Omega(\mathbf{a}, \mathbf{b})$. Let us pick, for instance, the steady state $(1,1,1,5,2) \in \mathcal{SS}(\Omega_0)$. We have that $\mathcal{J}_{\Omega_0}(1,1,1,5,2)$ is equal to

$$\begin{bmatrix} -1 & 3 \\ 1 & -3 \end{bmatrix},$$

while its spectrum is equal to $\{0, -4\}$. We get that $(1,1,1,5,2)$ is unstable.

We are not interested in the easy problem of checking if a given steady state is unstable, we are interested in a closely related but very much harder problem: suppose we are given a chemical network Ω, we would like to check if there exist steady states of Ω that are unstable.

We would like to solve this latter problem as efficiently as possible. This means that we are looking for a polynomial time algorithmic solution.

To begin with, we notice that the set of steady states of Ω is a *semialgebraic set* defined by a finite list of polynomial equalities (the steady state conditions). Moreover, we have that the set of unstable states is a subset of the aforementioned algebraic variety that is defined by an algebraic condition: the non-negativity of the Jacobian eigenvalues. The latter implies that our two problems can be solved with the algorithmic tools provided by computational algebraic geometry [8]. However, we have to remark that those algorithmic tools are very inefficient in the general case (the worst case behavior of most of those algorithmic tools is double exponential).

2 The mathematical basis of SNA: Scopes and limitations

Let Ω be a chemical network, using SNA in the stability analysis of Ω corresponds to apply a special change of coordinates. What do we gain with this change of coordinates? Let $\mathcal{J}_\Omega$ be the (symbolic) Jacobian of Ω, the entries of $\mathcal{J}_\Omega$ are (nonlinear) polynomials over the variables $[X_1], ..., [X_n], k_1, ..., k_r$. One of the main gains with SNA is that all the entries of $\mathcal{J}_\Omega$ become linear polynomials over the new system of coordinates (*Clarke's convex coordinates*). The latter implies that any linear constraint over the entries of $\mathcal{J}_\Omega$ can be suitably translated into a linear constraint over the set of convex coordinates (see below).

2.1 The system of convex coordinates

Let

$$\Omega = (\{X_1, ..., X_n\}, \{R_1, ..., R_r\}),$$

and suppose that for all $i \leq r$ the reaction R_i is equal to

$$c_{1i}X_1 + \cdots + c_{ni}X_n \rightarrow d_{1i}X_1 + \cdots + d_{ni}X_n.$$

The combinatorial structure of Ω can be completely described by a $n \times r$ matrix that is called the *stoichiometric matrix* of Ω, and which is denoted with the symbol S_Ω. Matrix S_Ω is defined by

$$S_\Omega[i,j] = d_{ij} - c_{ij}.$$

This stoichiometric matrix has a companion, the *kinetic matrix*, which is also known as *the matrix of orders of reaction* (Kirchhoff matrix). We use the symbol K_Ω to denote the latter matrix. Matrix K_Ω is the $r \times n$ matrix defined by

$$K_\Omega[i,j] = c_{ji}$$

Definition 9 *We can associate to network Ω a function $\mathcal{R}_\Omega : \mathbb{R}_+^n \times \mathbb{R}_+^r \rightarrow \mathbb{R}_+^r$ that we call Clarke's velocity function and which is defined by:*

$$\text{Given } j = 1, ..., r \text{ we have that } \mathcal{R}_\Omega(\mathbf{a}, \mathbf{b})[j] = \mathbf{b}[j]\left(\prod_{i \leq n}(\mathbf{a}[i])^{c_{ij}}\right).$$

Remark 10 *Notice that $\mathcal{R}_{\Omega_0}$ is equal to $\left(k_1[I]^3, k_2[I]^2[A], k_3[I][A]\right)$, and notice that $\mathcal{R}_\Omega$ is a vector field that collects together the r monomial terms encoding the mass-action contribution of each one of the r reactions in Ω.*

Clarke noticed (see [6]) that the nonlinear system governing the dynamics of Ω can be written in matrix form as

$$\frac{dX}{dt} = S_\Omega \cdot \mathcal{R}_\Omega(X, K).$$

S_Ω is a numerical matrix that does not depend on parameter values (it is the same numerical matrix for all the states of Ω). Thus, let $(\mathbf{a}_0, \mathbf{b}_0), (\mathbf{a}_1, \mathbf{b}_1) \in \mathcal{SS}(\Omega)$, and suppose that $\mathcal{R}_\Omega(\mathbf{a}_0, \mathbf{b}_0) = \mathcal{R}_\Omega(\mathbf{a}_1, \mathbf{b}_1)$. We have that

$$\left.\frac{dX}{dt}\right|_{(\mathbf{a}_0, \mathbf{b}_0)} = \left.\frac{dX}{dt}\right|_{(\mathbf{a}_0, \mathbf{b}_0)}.$$

Variational mathematics is based on the idea that the vector $\left.\frac{dX}{dt}\right|_{(\mathbf{a},\mathbf{b})}$ completely determines the dynamics of X within a small vicinity of $(\mathbf{a}, \mathbf{b})$. Then, it can be said that

Clarke's function is a *projection* that identifies steady states that are different but which support the same type of local dynamics. Thus, if one is interested in studying the dynamics that occur in the vicinities of the steady states of Ω, it makes sense if he focus his attention on the quotient $\mathcal{R}_{\Omega}\left(\mathcal{SS}\left(\Omega\right)\right)$.

The set $\mathcal{SS}\left(\Omega\right)$ is a semialgebraic set that could have a quite complex nonlinear structure [3]. On the other hand, we have that $\mathcal{R}_{\Omega}\left(\mathcal{SS}\left(\Omega\right)\right)$ is the intersection of a linear space and the positive orthant of $\mathbb{R}^{n+r}$: let $\left(\mathbf{a},\mathbf{b}\right)\in\mathbb{R}_{+}^{n}\times\mathbb{R}_{+}^{r}$, the $n+r$-dimensional vector $\left(\mathbf{a},\mathbf{b}\right)$ belongs to $\mathcal{SS}\left(\Omega\right)$, if and only if, the equality $S_{\Omega}\cdot\mathcal{R}_{\Omega}\left(\mathbf{a},\mathbf{b}\right)=0$ holds.

Notation 11 *We use the symbol $\mathcal{C}_{\Omega}$ to denote the set $\mathcal{R}_{\Omega}\left(\mathcal{SS}\left(\Omega\right)\right)$.*

Theorem 12 *Let $\left\langle S_{\Omega}\right\rangle$ be the linear space spanned by the rows of S_{Ω}, and let $\left\langle S_{\Omega}\right\rangle^{\perp}$ be the orthogonal complement of $\left\langle S_{\Omega}\right\rangle$. We have that $\mathcal{C}_{\Omega}$ is equal to the polyhedral cone*

$$\left\{v\in\mathbb{R}_{+}^{r}:v\in\left[S_{\Omega}\right]^{\perp}\right\}.$$

Thus, we have that the nonlinear set $\mathcal{SS}\left(\Omega\right)$ is mapped by $\mathcal{R}_{\Omega}$ onto the polyhedral cone $\mathcal{C}_{\Omega}$. Moreover, this correspondence is effective.

Theorem 13 *There exists a polynomial time algorithm $\mathcal{M}$ that computes, on input $v\in\mathcal{C}_{\Omega}$, a steady state $\left(\mathbf{a}_{v},\mathbf{b}_{v}\right)$ satisfying the equality*

$$\mathcal{R}_{\Omega}\left(\mathbf{a}_{v},\mathbf{b}_{v}\right)=v.$$

Proof. Let $v\in\mathcal{C}_{\Omega}$ and let us suppose that for all $i\leq r$ the inequality $v\left[i\right]>0$ holds. We use the latter to compute $\left(\mathbf{a}_{v},\mathbf{b}_{v}\right)$, the computation of $\left(\mathbf{a}_{v},\mathbf{b}_{v}\right)$ is done in the following way:

1. We compute the solution set of the following system of linear equations:

$$\begin{aligned}\log\left(v\left[1\right]\right) &= \log\left(k_{1}\right)+c_{11}\log\left(i_{1}\right)+\cdots+c_{n1}\log\left(x_{n}\right)\\ &\vdots\\ \log\left(v\left[r\right]\right) &= \log\left(k_{r}\right)+c_{1r}\log\left(i_{1}\right)+\cdots+c_{nr}\log\left(x_{n}\right).\end{aligned}$$

2. We pick a solution, say $\left(a_{1},...,a_{n},b_{1},...,b_{r}\right)$, and then we set

$$\left(\mathbf{a}_{v},\mathbf{b}_{v}\right)=\left(2^{a_{1}},...,2^{a_{n}},2^{b_{1}},...,2^{b_{r}}\right).$$

Notice that the above system of linear equations can be written in matrix form as

$$M_{\Omega}\cdot\left(\log\left(k_1\right),...,\log\left(k_r\right),\log\left(x_1\right),...,\log\left(x_n\right)\right)^{\top}=\left(\log\left(v\left[1\right]\right),...,\log\left(v\left[r\right]\right)\right),$$

where M_{Ω} is the $r\times(r+n)$ matrix

$$\left[\begin{array}{ccccccc}1&0&\cdots&0&c_{11}&\cdots&c_{n1}\\0&1&\cdots&0&c_{12}&\cdots&c_{n2}\\\vdots&\vdots&\ddots&\vdots&\vdots&\ddots&\vdots\\0&0&\cdots&1&c_{1r}&\cdots&c_{nr}\end{array}\right].$$

Then, it is clear that our system of linear equations has a nonempty set of solutions whose dimension is equal to the column rank of K_{Ω}. The latter implies that the above procedure can be effectively executed.

Let $S=\{i\leq r:v\left[i\right]=0\}$ and suppose that this set is nonempty. We set $k_i=0$ for all $i\in S$, and we solve the system

$$v\left[j\right]=k_j\cdot\left[X_1\right]^{c_{1j}}\cdot\cdots\cdot\left[X_n\right]^{c_{nj}},\ j\notin S.$$

To do the latter we proceed exactly as above, the theorem is proved. ■

Conclusion 14 *We can sample the set* $\mathcal{SS}\left(\Omega\right)$, *provided that we can sample the set* $\mathcal{C}_{\Omega}$.

The set $\mathcal{C}_{\Omega}$ has a pleasant *polyhedral structure*, and it means that any element of $\mathcal{C}_{\Omega}$ is a nonnegative linear combination of *extreme rays* [9]. Thus, given a minimal spanning set of extreme rays for $\mathcal{C}_{\Omega}$, say the set $\mathbf{v}=\{v_1,...,v_s\}$, we can define a bijection $Coord_{\mathbf{v}}:\mathbb{R}_{+}^{s}\to\mathcal{C}_{\Omega}$ as follows

$$Coord_{\mathbf{v}}\left(j_1,...,j_s\right)=j_1v_1+\cdots+j_sv_s.$$

The bijection $Coord_{\mathbf{v}}$ determines a system of *convex coordinates* for $\mathcal{C}_{\Omega}$: given $w\in\mathcal{C}_{\Omega}$, its tuple of convex coordinates is the s-tuple $Coord_{\mathbf{v}}^{-1}\left(w\right)$.

We can use the latter to sample the set $\mathcal{C}_{\Omega}$ as well as the set $\mathcal{SS}\left(\Omega\right)$. To this end we proceed as follows:

1. *Compute a minimal spanning set for the cone* $\mathcal{C}_{\Omega}$, say the set $\mathbf{v}=\{v_1,...,v_s\}$.
2. *Compute a sample* $\mathbf{j}_1,...,\mathbf{j}_K\in\mathbb{R}_{+}^{s}$.
3. *Compute* $Coord_{\mathbf{v}}\left(\mathbf{j}_1\right),...,Coord_{\mathbf{v}}\left(\mathbf{j}_K\right)$.
4. *Compute samples of the sets* $\mathcal{R}_{\Omega}^{-1}\left(Coord_{\mathbf{v}}\left(\mathbf{j}_1\right)\right),...,\mathcal{R}_{\Omega}^{-1}\left(Coord_{\mathbf{v}}\left(\mathbf{j}_K\right)\right)$.

2.2 An illustrative and trivial example

Let us use network Ω_0 to illustrate the previous concepts.

The reduced stoichiometric matrix S_{Ω_0} is equal to

$$\left[\begin{array}{ccc} -3 & 1 & -1 \end{array}\right],$$

and a minimal spanning set for the polyhedral cone $\mathcal{C}_{\Omega_0}$ is given by the vectors $(1,3,0)$ and $(0,1,1)$. This means that the complex 5-dimensional set $\mathcal{SS}(\Omega_0)$ is mapped by $\mathcal{R}_{\Omega_0}$ onto the infinite triangle spanned by those two vectors. If we choose nonnegative values for j_1, j_2, we can be sure that

$$j_1 \cdot (1,3,0) + j_2 \cdot (0,1,1)$$

is an element of $\mathcal{C}_{\Omega_0}$ that represents an equivalence class of steady states. We can use the latter to sample the set $\mathcal{SS}(\Omega_0)$, we proceed in the following way:

1. *Pick a tuple* $(j_1, j_2) \in \mathbb{R}^2_+$ *(for instance* $j_1 = 1$ *and* $j_2 = 2$*).*
2. *Compute the corresponding convex combination of extreme rays (in our case we compute* $1 \cdot (1,3,0) + 2\,(0,1,1)$*).*
3. *Compute the solution set of the linear system*

$$\begin{aligned} 0 &= \log(k_1) + 3\log(i) \\ \log(5) &= \log(k_2) + 2\log(i) + \log(a) \\ 1 &= \log(k_3) + \log(i) + \log(a). \end{aligned}$$

4. *Pick an element, say* $\left(\widehat{i}, \widehat{a}, \widehat{k_1}, \widehat{k_2}, \widehat{k_3}\right)$*, of the set computed in the previous step (for instance the vector* $(0,0,0,\log(5),1)$*).*
5. *Compute the vector* $\left(2^{\widehat{i}}, 2^{\widehat{a}}, 2^{\widehat{k_1}}, 2^{\widehat{k_2}}, 2^{\widehat{k_3}}\right)$ *(in our case we compute the vector* $(1,1,1,5,2)$*).*

Given a chemical network Ω, we can proceed as above and use Clarke's projection to define a system of convex coordinates for the set $\mathcal{SS}(\Omega)$. Moreover, we can use this system of coordinates to sample the set $\mathcal{SS}(\Omega)$.

2.3 Clarke's factorization

Let Ω be a chemical reaction network, the applicability of Clarke's formalism in the stability analysis of Ω relies on the following two facts:

1. The pleasant polyhedral structure of the set $\mathcal{R}_{\Omega}\left(\mathcal{SS}\left(\Omega\right)\right)$.

2. *Clarke's factorization* (see Theorem 15, and see [6]).

Theorem 15 *Let $\Omega = \left(\{X_1, ..., X_n\}, \{R_1, ..., R_r\}\right)$ be a chemical reaction network, let $(\mathbf{a}, \mathbf{b}) \in \mathcal{SS}_{+}\left(\Omega\right)$, and let $\mathcal{J}_{\Omega}\left(\mathbf{a}, \mathbf{b}\right)$ be the Jacobian matrix at the state $(\mathbf{a}, \mathbf{b})$, we have that*

$$\mathcal{J}_{\Omega}\left(\mathbf{a}, \mathbf{b}\right) = H_{\Omega}\left(\mathbf{a}, \mathbf{b}\right) \cdot \begin{pmatrix} \frac{1}{\mathbf{a}[1]} & 0 & \cdots & 0 \\ 0 & \frac{1}{\mathbf{a}[2]} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \frac{1}{\mathbf{a}[n]} \end{pmatrix},$$

where $H_{\Omega}\left(\mathbf{a}, \mathbf{b}\right)$ is equal to

$$S_{\Omega} \cdot \begin{pmatrix} \mathcal{R}_{\Omega}\left(\mathbf{a}, \mathbf{b}\right)[1] & 0 & \cdots & 0 \\ 0 & \mathcal{R}_{\Omega}\left(\mathbf{a}, \mathbf{b}\right)[2] & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \mathcal{R}_{\Omega}\left(\mathbf{a}, \mathbf{b}\right)[r] \end{pmatrix} \cdot K_{\Omega}.$$

Recall that $\mathcal{J}_{\Omega}$ is a matrix-valued function. We use the symbol $\mathcal{J}_{\Omega} \restriction_{\mathcal{SS}_{+}(\Omega)}$ to denote the restriction of the latter function to the set $\mathcal{SS}_{+}\left(\Omega\right)$. We can use Clarke's factorization to express the function $\mathcal{J}_{\Omega} \restriction_{\mathcal{SS}_{+}(\Omega)}$ in the system of convex coordinates.

To begin with we have to fix a set of extreme currents (and the corresponding system of convex coordinates). Thus, suppose we fix the set $\{v_1, ..., v_s\}$. We use the symbol E_{Ω} to denote the $r \times s$ matrix whose rows are the vectors $v_1, ..., v_s$; and we use the symbol $\Delta\left(E_{\Omega}\right)$ to denote the diagonal (symbolic) matrix defined by

$$\Delta\left(E_{\Omega}\right)[i, i] = \sum_{i=1}^{s} v_i[k] \cdot j_k,$$

here, we use the symbols $j_1, ..., j_s$ to represent the convex coordinates determined by $v_1, ..., v_s$.

Definition 16 *We use the symbol H_{Ω} to denote the symbolic matrix defined by*

$$H_{\Omega} = S_{\Omega} \cdot \Delta\left(E_{\Omega}\right) \cdot K_{\Omega}.$$

Clarke proved that if one switches to the system of convex coordinates, then the function $\mathcal{J}_\Omega \restriction_{\mathcal{SS}_+(\Omega)}$ becomes equal to $H_\Omega \cdot \Delta$, where Δ is the symbolic matrix

$$\begin{pmatrix} \frac{1}{[X_1]} & 0 & \cdots & 0 \\ 0 & \frac{1}{[X_2]} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \frac{1}{[X_n]} \end{pmatrix}.$$

Then, he noticed that the scaling matrix Δ has few influence on the stability properties of $\mathcal{J}_\Omega$, and he concluded that one can focus the stability analysis on the matrix H_Ω [6]. The main gain, if we do the latter, is a strong degree reduction: notice that the entries of the latter matrix are linear polynomials over the set of convex coordinates.

Let us illustrate the above facts using network Ω_0 once again. Recall that S_{Ω_0} is equal to

$$\begin{bmatrix} -3 & 1 & -1 \\ 3 & -1 & 1 \end{bmatrix}$$

while the matrix K_{Ω_0} is equal to

$$\begin{bmatrix} 3 & 0 \\ 2 & 1 \\ 1 & 1 \end{bmatrix}.$$

We know that a minimal spanning set for Ω_0 is the set

$$\{(1,3,0),(0,1,1)\},$$

and it means that the matrix E_{Ω_0} is equal to

$$\begin{bmatrix} 1 & 0 \\ 3 & 1 \\ 0 & 1 \end{bmatrix}.$$

The Jacobian matrix is equal to

$$\begin{bmatrix} -9k_1[I]^2 + 2k_2[I][A] - k_3[A] & k_2[I]^2 - k_3[I] \\ 9k_1[I]^2 - 2k_2[I][A] + k_3[A] & -k_2[I]^2 + k_3[I] \end{bmatrix},$$

The matrix $\Delta(E_{\Omega_0})$ is equal to

$$\begin{bmatrix} j_1 & 0 & 0 \\ 0 & 3j_1 + j_2 & 0 \\ 0 & 0 & j_2 \end{bmatrix},$$

and according to Clarke's factorization, the matrix-valued function $\mathcal{J}_{\Omega_0} \restriction_{\mathcal{SS}_+(\Omega_0)}$ is equal to

$$\begin{bmatrix} -3 & 1 & -1 \\ 3 & -1 & 1 \end{bmatrix} \cdot \begin{bmatrix} j_1 & 0 & 0 \\ 0 & 3j_1 + j_2 & 0 \\ 0 & 0 & j_2 \end{bmatrix} \cdot \begin{bmatrix} 3 & 0 \\ 2 & 1 \\ 1 & 1 \end{bmatrix} \cdot \begin{bmatrix} \frac{1}{[I]} & 0 \\ 0 & \frac{1}{[A]} \end{bmatrix}.$$

Clarke's factorization allows us to focus on the matrix

$$H_\Omega = \begin{bmatrix} -3 & 1 & -1 \\ 3 & -1 & 1 \end{bmatrix} \cdot \begin{bmatrix} j_1 & 0 & 0 \\ 0 & 3j_1 + j_2 & 0 \\ 0 & 0 & j_2 \end{bmatrix} \cdot \begin{bmatrix} 3 & 0 \\ 2 & 1 \\ 1 & 1 \end{bmatrix},$$

which is equal to

$$\begin{bmatrix} 6j_1 + 3j_2 & 3j_1 \\ -6j_1 - 3j_2 & -3j_1 \end{bmatrix}$$

Observe that the entries of the latter matrix are linear polynomials over the variables j_1, j_2, while the entries of $\mathcal{J}_{\mathbf{\Omega_0}}$ are 3-degree polynomials over the variables $[I], [A], k_1, k_2$ and k_3. Thus, we get an important degree reduction if we switch to the system of convex coordinates.

Clarke's stoichiometric network analysis is the proposal of studying the stability properties of chemical networks using the convex coordinates of the current cone instead of the concentration coordinates associated to the symbolic Jacobian. Clarke's factorization is the bridge connecting those two coordinate systems: one can analyze the *linear* matrix H_Ω instead of analyzing the *nonlinear* matrix $\mathcal{J}_{\mathbf{\Omega}}$.

2.4 The fundamental trade–off

There are two main gains with stoichiometric network analysis:

1. Extreme currents of $\mathcal{C}_\Omega$ are in correspondence with the minimal subnetworks (*reaction pathways*) of Ω [7]. The latter implies that critical parameters in the velocity space are in correspondence with critical reaction pathways. Thus, when one performs the stability analysis in the velocity space, he is simultaneously doing a structural analysis of the network.

2. The entries of the Jacobian matrix get transformed into linear polynomials over the set of convex coordinates.

We have to pay attention to the prize that we are paying for that. Constructing a set of convex coordinates for $\mathcal{C}_\Omega$ allows us to control and sample the latter set, and, as we showed before, it allows us to sample the set $\mathcal{SS}(\Omega)$. However, the computation of the extreme currents, that are necessary for the construction of the system of convex coordinates, is a hard intractable problem [4]. Thus, we are reducing dimensionality at the cost of solving a hard intractable problem. This is the fundamental trade-off behind SNA. Can we avoid this latter computation?

We want to search the set constituted by all the unstable states of Ω. The instability condition is a highly nonlinear condition that involves the determinant of the Jacobian matrix as well as other high order subdeterminants of this matrix [17]. Then, we cannot use linear programming to analyze this condition over the cone $\mathcal{C}_\Omega$: the determinant of H_Ω is a polynomial of degree n over the set of convex coordinates. However, there is a special scenario where SNA reaches its algorithmic potential, namely: the stability condition is given by a finite set of inequalities that are linear with respect to the entries of $\mathcal{J}_\Omega$. Notice that the latter type of inequalities can be expressed as linear inequalities over the set of convex parameters. Thus, in this latter case, one can use the tools of linear programming and convex geometry to carry out the intended analysis.

In the remainder of this paper we will study a problem that is related to the stability analysis of biochemical networks, and which fits well with the above second scenario.

3 Using SNA: Chiral networks and biological homochirality

The homochirality of biomolecules is one of the most intringuing phenomena related to the chemistry of life (see [14], [5] and the references therein). We show, in the remainder of this paper, that one can effectively use SNA in the mathematical analysis of network models of biological homochirality.

Definition 17 *Suppose that*

$$\Omega = (\{L, D, X_3, ..., X_n\}, \{R_1, ..., R_r\})$$

is a chemical network and suppose that L and D represent a pair of enantiomeric species. We say that Ω is a chiral network, if and only if, species L and D cannot be distinguished within the network, that is:

If the reaction R_i is equal to

$$aL + bD + c_3X_3 + \cdots + c_nX_n \to a^*L + b^*D + d_3X_3 + \cdots + d_nX_n,$$

then there exists $j \leq r$ such that R_j is equal to

$$bL + aD + c_3X_3 + \cdots + c_nX_n \to b^*L + a^*D + d_3X_3 + \cdots + d_nX_n.$$

We say, in the latter case, that reactions R_i and R_j are dual reactions.

Remark 18 *If the equalities $a = b$ and $a^* = b^*$ hold, we say that R_i is self-dual since it is equal to its dual reaction.*

Let

$$\Omega = (\{L, D, X_3, ..., X_n\}, \{R_1, ..., R_r\})$$

be a chiral network. The set $\{R_1, ..., R_r\}$ can be decomposed as a disjoint union of pairs, where each pair is either a pair of dual reactions or a *self-dual pair* (a pair constituted by a self-dual reaction that is listed twice). From now on we assume that $r = 2m$, and we assume that

$$\{R_1, ..., R_r\} = \{RL_1, RD_1, ..., RL_m, RD_m\},$$

where for all $i \leq m$ the pair (RL_i, RD_i) is a dual (self-dual) pair.

Definition 19 *We say that a steady state $(\mathbf{a}, \mathbf{b})$ is racemic, if and only if, the following two conditions are satisfied:*

1. *The equality $\mathbf{a}[1] = \mathbf{a}[2]$ holds.*
2. *For all $i \leq m$ the equality $\mathbf{b}[2i-1] = \mathbf{b}[2i]$ holds.*

It is important to remark, at this point, that the symmetry constraint fulfilled by chiral networks is related to the supposed indiscernibility of enantiomers: *when present in a symmetric environment, enantiomers have identical chemical and physical properties except for their ability to rotate plane-polarized light by equal amounts but in opposite directions (although the polarized light can be considered an asymmetric medium)* [14].

Definition 20 *We say that a chiral network exhibits chiral amplification, if and only if, there exist racemic steady states, which, after being perturbed, give place to states that exhibit a large gap between the concentrations of the two enantiomeric species.*

Remark 21 *Chiral amplification dynamics are also called spontaneous mirror symmetry breaking in the related literature (see [13], [11], [15] and the references therein).*

We are interested in network models of *enantioselective synthesis*, which is the term that is used to designate all the chemical mechanisms that, acting on symmetric (achiral) environments, can produce homochiral compounds from racemic ones. Notice that any model of enantioselective synthesis must exhibit chiral amplification.

Let us consider an example of a chiral network. *Frank network* is the network

$$\Omega_F = (\{L, D, A\}; \{R_1, R_2, R_3\})$$

where:

1. R_1 is equal to $L + A \to 2L$,
2. R_2 is equal to $D + A \to 2D$ and
3. R_3 is equal to $L + D \to 2A$.

Notice that Ω_F is a chiral network: R_1 and R_2 are dual reactions, and R_3 is a self dual reaction ($a = b = 1$ and $a^* = b^* = 0$). An equivalent presentation of Ω_F is given by the pair

$$(\{L, D, A\}; \{RL_1, RD_1, RL_2, RD_2\}),$$

where $R_1 = RL_1$, $R_2 = RD_1$ and $R_3 = RL_2 = RD_2$.

From now on we identify Frank network with this second pair that includes four reactions.

Remark 22 *Network Ω_F was the first and most elementary model of enantioselective synthesis proposed in the literature [10].*

Recall that we are looking for a mathematical characterization of the chiral networks admitting chiral amplification. The intended characterization must yield an efficient algorithm for the recognition of those networks.

3.1 Frank inequality and Frank region

Let Ω be a chiral network, and let $(\mathbf{a}, \mathbf{b})$ be a racemic steady state, we say that it produces chiral amplification *(chiral symmetry breaking* or *mirror symmetry breaking)*, if and only if, small perturbations of $(\mathbf{a}, \mathbf{b})$ trigger dynamics that produce a non-negligible gap between the concentrations of the two enantiomers. There exists an algebraic condition that characterizes the racemic states of Ω that can produce chiral amplification (see [3] and [1]).

Theorem 23 *Let Ω be a chiral network, let $(\mathbf{a}, \mathbf{b})$ be a racemic state of Ω, and let $\mathcal{J}_\Omega(\mathbf{a}, \mathbf{b})$ be the Jacobian matrix at state $(\mathbf{a}, \mathbf{b})$. State $(\mathbf{a}, \mathbf{b})$ can produce chiral amplification, if and only if, the inequality*

$$\mathcal{J}_\Omega(\mathbf{a}, \mathbf{b})[1, 1] - \mathcal{J}_\Omega(\mathbf{a}, \mathbf{b})[1, 2] \geq 0$$

holds

Remark 24 *We use the term Frank inequality to denote the above inequality. Notice that Frank inequality is a linear inequality over the entries of $\mathcal{J}_\Omega$. However, if we work in the*

system of concentration coordinates, this linearity is just apparent: most of the entries of $\mathcal{J}_\Omega$ *are nonlinear polynomials over the concentration variables* $[L], [D], [X_3], ..., [X_n]$.

Notation 25 *We use the symbol* $\mathcal{SS}^{ra}(\Omega)$ *to denote the subset of* $\mathcal{SS}(\Omega)$ *constituted by all the racemic states.*

Definition 26 *Let* Ω *be a chiral network, the Frank region of* Ω *is the set*

$$\mathcal{F}(\Omega) = \{(\mathbf{a}, \mathbf{b}) \in \mathcal{SS}(\Omega) : \mathcal{J}_\Omega(\mathbf{a}, \mathbf{b})[1,1] - \mathcal{J}_\Omega(\mathbf{a}, \mathbf{b})[1,2] \geq 0\}.$$

Remark 27 *If* $\mathcal{F}(\Omega) \cap \mathcal{SS}^{ra}(\Omega) = \emptyset$, *then the steady states of* Ω *cannot produce chiral amplification [16].*

Definition 28 *We say that* Ω *is a feasible model of enantioselective synthesis, if and only if, the set* $\mathcal{F}(\Omega) \cap \mathcal{SS}^{ra}(\Omega)$ *is nonempty.*

3.2 The problem

We study the following algorithmic problem.

Problem 29 ***Check-and-Sample***

- *Input:* Ω, *where* Ω *is a chiral network.*
- *Problem: check if* Ω *is a feasible model of enantioselective synthesis.*

Let Ω be a network. We observe that $\mathcal{F}(\Omega) \cap \mathcal{SS}^{ra}(\Omega)$ is defined by a finite list of polynomial constraints: the steady state equations, Frank inequality, the non-negativity conditions and the racemic condition. The sets defined by finite lists of polynomial constraints are called *semialgebraic sets* (see [3]). The good thing about semialgebraic sets is that there exist algorithms which, given a finite list of polynomial constraints, check if the set defined by those constraints is nonempty and, in that case, compute a sample [8]. However, all those algorithms are inefficient (their running time is double exponential) and hard to implement.

Can one exploit the special structure exhibited by the semialgebraic definition of $\mathcal{F}(\Omega)$ in order to construct an efficient algorithmic solution to the above problem? The answer to the latter question is positive, and we will exhibit a polynomial time algorithm solving the above problem. We use *stoichiometric network analysis* and the related *velocity coordinates* to develop such an algorithm. It is important to remark that there is some previous work related to the application of SNA in the study of biological homochirality [2].

3.3 A check–and–sample algorithm

Let

$$\Omega = ((I_1, I_2, X_3, ..., X_n), (RL_1, RD_1, ..., RL_m, RD_m))$$

be a chiral network. We want to check if there exist racemic states of Ω that are positive and which satisfy Frank's inequality. We have to take into account the following fact: suppose we compute a tuple of convex coordinates, say the tuple $(j_1, ..., j_s)$, such that $\mathcal{R}_\Omega^{-1}(j_1 v_1 + \cdots + j_s v_s) \cap \mathcal{F}(\Omega)$ is nonempty. It could happens that $\mathcal{R}_\Omega^{-1}(j_1 v_1 + \cdots + j_s v_s)$ does not contain racemic states.

We have to focus on the subset of $\mathcal{C}_\Omega$ that is the image of $\mathcal{SS}^{ra}(\Omega)$ under the function $\mathcal{R}_\Omega$.

Definition 30 *The set of racemic velocities is the set*

$$\mathcal{C}_\Omega^{ra} = \left\{ v \in \mathcal{C}_\Omega : \mathcal{R}_\Omega^{-1}(v) \cap \mathcal{SS}^{ra}(\Omega) \neq \emptyset \right\}.$$

On the other hand, we define the racemic cone of Ω *as the set*

$$\mathcal{C}_\Omega^{*} = \mathcal{C}_\Omega \cap \langle \mathbf{r}_1, ..., \mathbf{r}_m \rangle^{\perp},$$

where $\mathbf{r}_i$ *is the vector defined by*

$$\mathbf{r}_i[l] = \begin{cases} 0 & if \quad l \neq 2i, 2i-1 \\ -1 & if \quad l = 2i \\ 1 & if \quad l = 2i-1 \end{cases}.$$

We have

Theorem 31 $\mathcal{C}_\Omega^{*} = \mathcal{C}_\Omega^{ra}$.

Proof. Let us prove the containment $\mathcal{C}_\Omega^{*} \subseteq \mathcal{C}_\Omega^{ra}$.

Let $v \in \mathcal{C}_\Omega^{*}$, we have that v is a $2m$-dimensional vector satisfying the conditions

$$v[2i-1] = v[2i] \geq 0,\ i = 1, ..., m.$$

We show that $\mathcal{R}_\Omega^{-1}(v) \cap \mathcal{SS}^{ra}(\Omega)$ is nonempty. To do the latter we have to compute a tuple

$$([L], [D], [X_3], ..., [X_n], r_1, s_1, ..., r_m, s_m)$$

of nonnegative reals satisfying the equalities

$$\begin{aligned} [L] &= [D],\ i = 1, ..., k; \text{ and} \\ r_j &= s_j,\ j = 1, ..., m, \end{aligned}$$

and such that for all $i \leq m$ the equalities

$$\begin{aligned} v\left[2i-1\right] &= r_i \cdot \left[L\right]^{c_{1,2i-1}} \cdot \left[D\right]^{c_{2,2i-1}} \cdot \left[X_3\right]^{c_{3,2i-1}} \cdot ... \cdot \left[X_n\right]^{c_{n,2i-1}} \\ v\left[2i\right] &= s_i \cdot \left[L\right]^{c_{1,2i}} \cdot \left[D\right]^{c_{2,2i}} \cdot \left[X_3\right]^{c_{3,2i}} \cdot ... \cdot \left[X_n\right]^{c_{n,2i}} \end{aligned}$$

also hold.

Set $h_i = v\left[2i-1\right] = v\left[2i\right]$.

Recall that RL_i and RD_i are dual reactions. We have that the equalities

$$\begin{aligned} c_{1,2i-1} &= c_{2,2i},\ i = 1, ..., m; \\ c_{2,2i-1} &= c_{1,2i},\ i = 1, ..., m \text{ and} \\ c_{l,2i-1} &= c_{l,2i},\ l = 3, ..., n \end{aligned}$$

hold. Then, it suffices if we compute a tuple

$$\left(\left[L\right], \left[X_3\right], ..., \left[X_n\right], r_1, ..., r_m\right)$$

satisfying the equalities

$$h_i = r_i \cdot \left[L\right]^{c_{1,2i-1}+c_{2,2i-1}} \cdot \left[X_3\right]^{c_{3,2i-1}} \cdot ... \cdot \left[X_n\right]^{c_{n,2i-1}},$$

and hence we set

$$\left[D\right] = \left[L\right] \text{ and } s_i = r_i \text{ for all } i \leq m.$$

It is easy to compute the latter tuple. The theorem is proved. ■

Remark 32 *Notice that $\mathcal{C}_{\Omega}^{ra}$ is the interception of two polyhedral cones.*

The above remark implies that $\mathcal{C}_{\Omega}^{ra}$ is a polyhedral cone. Then, we have that $\mathcal{C}_{\Omega}^{ra}$ is spanned by a finite set of extreme rays.

Definition 33 *Let $\{v_1, ..., v_{rs}\}$ be a minimal spanning set of extreme rays for $\mathcal{C}_{\Omega}^{ra}$, we say that $\{v_1, ..., v_{rs}\}$ is a minimal spanning set of racemic currents for Ω.*

The set $\{v_1, ..., v_{rs}\}$ can be used to construct a system of convex coordinates for $\mathcal{C}_{\Omega}^{ra}$: any point of $\mathcal{C}_{\Omega}^{ra}$ can be uniquely expressed as a positive combination of $v_1, ..., v_{rs}$.

Notation 34 *We use the symbols $j_1, ..., j_{rs}$ to denote the convex coordinates of $\mathcal{C}_{\Omega}^{ra}$ determined by this set of extreme rays.*

Next theorem is an easy corollary of Theorem 31.

Theorem 35 *Let* $\mathbf{j} \in \mathbb{R}_{+}^{rs}$, *we have that*

$$\mathcal{R}_{\Omega}^{-1}\left(\mathbf{j}\left[1\right] \cdot v_1 + \cdots + \mathbf{j}\left[rs\right] \cdot v_{rs}\right) \cap \mathcal{SS}^{ra}\left(\Omega\right) \neq \emptyset.$$

Moreover, if $(\mathbf{a}, \mathbf{b}) \in \mathcal{SS}^{ra}\left(\Omega\right)$ *there exists* $\mathbf{j} \in \mathbb{R}_{+}^{rs}$ *such that*

$$\mathbf{j}\left[1\right] \cdot v_1 + \cdots + \mathbf{j}\left[rs\right] \cdot v_{rs} = \mathcal{R}_{\Omega}\left(\mathbf{a}, \mathbf{b}\right).$$

The above theorem tells us that we can work with the cone $\mathcal{C}_{\Omega}^{ra}$ exactly as we worked with $\mathcal{C}_{\Omega}$. It is important to remark that:

1. One can compute a set of racemic currents for any chiral network Ω.
2. Given the computed set of racemic currents, say the set $\{v_1, ..., v_{rs}\}$, and given $(\mathbf{a}, \mathbf{b}) \in \mathcal{SS}^{ra}\left(\Omega\right)$, one can effectively compute the convex coordinates of $(\mathbf{a}, \mathbf{b})$.
3. Given $\mathbf{j} \in \mathbb{R}^{rs}$, one can effectively sample the set

$$\mathcal{R}_{\Omega}^{-1}\left(\mathbf{j}\left[1\right] \cdot v_1 + \cdots + \mathbf{j}\left[rs\right] \cdot v_{rs}\right) \cap \mathcal{SS}^{ra}\left(\Omega\right).$$

Remark 36 *Notice that the containment* $\mathcal{C}_{\Omega}^{ra} \subseteq \mathcal{C}_{\Omega}$ *always holds.*

Let us consider the case of network Ω_F. *The set* $\mathcal{C}_{\Omega_F}$ *is equal to the set* $\{(k, k, k, k) : k > 0\}$, *while the set* $\mathcal{C}_{\Omega_F}^{ra}$ *is equal to*

$$\mathcal{C}_{\Omega_F} \cap \left\langle (1, -1, 0, 0), (0, 0, 1, -1) \right\rangle^{\perp}.$$

We get, in this special case, that $\mathcal{C}_{\Omega_F}$ *is equal to* $\mathcal{C}_{\Omega_F}^{ra}$.

On the other hand, there are networks for which the containment is strict. Let $n \geq 2$, *we use the symbol* Ω_n *to denote the network*

$$\left(\{L, D\}, \{RL_1, RD_1, ..., RL_n, RD_n\}\right),$$

where given $i \leq n$ *the reaction* RL_i *is equal to* $iL \to iD$ *(and* RD_i *is equal to the dual reaction* $iD \to iL$*). We have that*

$$\begin{aligned} \mathcal{C}_{\Omega_n} &= \left\langle (-1, 1, 2, -2, ..., -n, n) \right\rangle^{\perp} \text{ and} \\ \mathcal{C}_{\Omega_n}^{ra} &= \mathcal{C}_n \cap \left\langle w_1, ..., w_n \right\rangle^{\perp}, \end{aligned}$$

where w_i *is equal to* $-e_{2i-1} + e_{2i}$, *(here we use the symbol* e_j *to denote the* j*-th canonical vector of* $\mathbb{R}^{2n}$*). It is easy to check that* $\mathcal{C}_{\Omega_n}^{ra} \subset \mathcal{C}_{\Omega_n}$.

Definition 37 *We use the symbol* E_{Ω}^{ra} *to denote the matrix*

$$\left[v_1, \cdots, v_{rs}\right],$$

whose columns are the racemic currents $v_1, ..., v_{rs} \in \mathbb{R}^{2m}$.

Any element of $\mathcal{C}_{\Omega}^{ra}$ is a convex combination of racemic currents, and it means that given $v \in \mathcal{C}_{\Omega}^{ra}$, there exists $\mathbf{j}_v \in \mathbb{R}_{+}^{rs}$ such that the equality

$$v = E_{\Omega}^{ra} \cdot \mathbf{j}_v$$

holds.

Definition 38 *We use the symbol* $\Delta^{ra}(\mathbf{a}, \mathbf{b})$ *to denote the* $2m \times 2m$ *diagonal matrix defined by*

$$\Delta^{ra}(\mathbf{a}, \mathbf{b})[i, i] = \sum_{r=1}^{rs} v_r[i] \cdot \mathbf{j}_v[r],$$

where $v = \mathcal{R}_{\Omega}(\mathbf{a}, \mathbf{b})$.

Recall that the symbolic Jacobian of Ω is a function $\mathcal{J}_{\Omega} : \mathcal{SS}(\Omega) \to \mathcal{M}_{nn}(\mathbb{R})$ that assigns to each steady state $(\mathbf{a}, \mathbf{b})$ a numerical $n \times n$ matrix, the matrix $\mathcal{J}_{\Omega}(\mathbf{a}, \mathbf{b})$. If we restrict $\mathcal{J}_{\Omega}$ to $\mathcal{SS}^{ra}(\Omega)$, we can try to express this latter function in the system of convex coordinates determined by $v_1, ..., v_{rs}$. To begin with we have

Theorem 39 *Let* $(\mathbf{a}, \mathbf{b}) \in \mathcal{SS}^{ra}(\Omega)$, *and suppose that for all* $i \leq n$ *the inequality* $\mathbf{a}[i] > 0$ *holds, we have that*

$$\mathcal{J}_{(\mathbf{a},\mathbf{b})} = S_{\Omega} \cdot \Delta^{ra}(\mathbf{a}, \mathbf{b}) \cdot K_{\Omega} \cdot \begin{pmatrix} \frac{1}{\mathbf{a}[1]} & 0 & \cdots & 0 \\ 0 & \frac{1}{\mathbf{a}[2]} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \frac{1}{\mathbf{a}[n]} \end{pmatrix}.$$

Proof. Let v be equal to $\mathcal{R}_{\Omega}(\mathbf{a}, \mathbf{b})$. We know that v can be written as

$$E_{\Omega}^{ra} \cdot \mathbf{j}_v,$$

where $\mathbf{j}_v$ is the vector of convex coordinates of $(\mathbf{a}, \mathbf{b})$.

Let e_{ij} be equal to $E_{\Omega}^{ra}[i, j]$, we have that for all $i \leq 2m$ the equality

$$v[i] = \sum_{k=1}^{rs} \mathbf{j}_v[k] \cdot e_{ik}$$

holds. We get that

$$S_{\Omega}\cdot\Delta^{ra}\left(\mathbf{a},\mathbf{b}\right)\cdot K_{\Omega}=S_{\Omega}\cdot diag\left(v\right)\cdot K_{\Omega},$$

where $diag\left(v\right)$ is equal to

$$\begin{pmatrix}\mathcal{R}_{\Omega}\left(\mathbf{a},\mathbf{b}\right)[1] & 0 & \cdots & 0\\ 0 & \mathcal{R}_{\Omega}\left(\mathbf{a},\mathbf{b}\right)[2] & \cdots & 0\\ \vdots & \vdots & \ddots & \vdots\\ 0 & 0 & \cdots & \mathcal{R}_{\Omega}\left(\mathbf{a},\mathbf{b}\right)[2m]\end{pmatrix}.$$

Then, we invoke Clarke's factorization (Theorem 15) to conclude that

$$\mathcal{J}_{(\mathbf{a},\mathbf{b})}=S_{\Omega}\cdot\Delta^{ra}\left(\mathbf{a},\mathbf{b}\right)\cdot K_{\Omega}\cdot\begin{pmatrix}\frac{1}{\mathbf{a}[1]} & 0 & \cdots & 0\\ 0 & \frac{1}{\mathbf{a}[2]} & \cdots & 0\\ \vdots & \vdots & \ddots & \vdots\\ 0 & 0 & \cdots & \frac{1}{\mathbf{a}[n]}\end{pmatrix}.$$

■

Definition 40 *We use the symbol $\Delta\left(E_{\Omega}^{ra}\right)$ to denote the diagonal (symbolic) matrix defined by*

$$\Delta\left(E_{\Omega}^{ra}\right)[i,i]=\sum_{r=1}^{rs}v_{r}[i]\cdot j_{r}.$$

Definition 41 *We use the symbol H_{Ω}^{ra} to denote the symbolic matrix defined by*

$$S_{\Omega}\cdot\Delta\left(E_{\Omega}^{ra}\right)\cdot K_{\Omega}.$$

Moreover, given $\mathbf{j}\in\mathbb{R}^{rs}$, we use the symbol $H_{\Omega}^{ra}\left(\mathbf{j}\right)$ to denote the evaluation of H_{Ω}^{ra} at $\mathbf{j}$.

Theorem 42 *Let Ω be a chiral network, we have:*

1. *Let $\mathcal{SS}_{+}^{ra}\left(\Omega\right)$ be the subset of $\mathcal{SS}^{ra}\left(\Omega\right)$ constituted by all the positive states of the latter set. The restriction of $\mathcal{J}_{\Omega}$ to $\mathcal{SS}_{+}^{ra}\left(\Omega\right)$ can be expressed as*

$$H_{\Omega}^{ra}\cdot\begin{pmatrix}\frac{1}{[L]} & 0 & 0 & \cdots & 0\\ 0 & \frac{1}{[L]} & 0 & \cdots & 0\\ 0 & 0 & \frac{1}{[X_3]} & \cdots & \vdots\\ \vdots & \vdots & \vdots & \ddots & \vdots\\ 0 & 0 & 0 & \cdots & \frac{1}{[X_n]}\end{pmatrix}.$$

2. *Let $\left(\mathbf{a},\mathbf{b}\right)\in\mathcal{SS}_{+}^{ra}\left(\Omega\right)$, and let $\mathbf{j}_{(\mathbf{a},\mathbf{b})}$ be its tuple of convex coordinates. We have that $\left(\mathbf{a},\mathbf{b}\right)$ satisfies Frank inequality, if and only if, the inequality*

$$H_{\Omega}^{ra}\left(\mathbf{j}_{(\mathbf{a},\mathbf{b})}\right)[1,1]-H_{\Omega}^{ra}\left(\mathbf{j}_{(\mathbf{a},\mathbf{b})}\right)[1,2]\geq 0$$

holds.

Proof. We prove the second item, the first one is a corollary of Theorem 39.

To prove the second item we only have to notice that

$$\begin{aligned}\mathcal{J}_{(\mathbf{a},\mathbf{b})}[1,1] &= \left\langle H_1 \mid \left(\frac{1}{[L]},0,...,0\right)\right\rangle \text{ and}\\ \mathcal{J}_{(\mathbf{a},\mathbf{b})}[1,2] &= \left\langle H_1 \mid \left(0,\frac{1}{[L]},0,...,0\right)\right\rangle,\end{aligned}$$

where H_1 is equal to the first row of $H_\Omega^{ra}\left(\mathbf{j}_{(\mathbf{a},\mathbf{b})}\right)$. The theorem is proved. ■

We get that the linear inequality

$$H_\Omega^{ra}[1,1] - H_\Omega^{ra}[1,2] \geq 0,$$

is the translation of Frank's inequality to convex coordinates. Recall that we are interested in sampling the set $\mathcal{F}(\Omega) \cap \mathcal{SS}^{ra}(\Omega)$. Thus, we have to sample the set

$$\mathcal{F}^{con}(\Omega) = \left\{\mathbf{j} \in \mathbb{R}_+^{rs} : H_\Omega^{ra}(\mathbf{j})[1,1] - H_\Omega^{ra}(\mathbf{j})[1,2] \geq 0\right\}.$$

To do the latter, we use the polyhedral definition of the set $\mathcal{F}^{con}(\Omega)$. The sampling algorithm goes as follows:

Algorithm 43 ***(CSF: Clarke Sampling of Frank States)***

Algorithm ***CSF*** *works, on input*

$$\Omega = (\{L, D, X_3, ..., X_n\}, \{RL_1, RD_1, ..., RL_m, RD_m\}, l),$$

as follows:

1. *Compute a minimal spanning set for the set* $\mathcal{C}_\Omega^{ra}$.
2. *Compute the matrices* S_Ω, K_Ω, $\Delta(E_\Omega^{ra})$ *and* H_Ω^{ra}.
3. *Use the polyhedral definition of* $\mathcal{F}^{con}(\Omega)$ *to compute a* l*-sample of this set.*
4. *Let* $\mathbf{j}$ *be an element of the computed sample, sample the set*

$$\mathcal{R}_\Omega^{-1}(\mathbf{j}[1] \cdot v_1 + \cdots + \mathbf{j}[rs] \cdot v_{rs}) \cap \mathcal{SS}^{ra}(\Omega).$$

We have to observe that this algorithm is inefficient since it forces up to compute a spanning set for the polyhedral cone $\mathcal{C}_\Omega^{ra}$. We ask: can we overcome the computation of the racemic currents?

3.4 Linear programming

In the previous section we sketched a method for sampling the set $\mathcal{F}(\Omega) \cap \mathcal{SS}^{ra}(\Omega)$. However, we cannot consider this algorithm as the final solution of our problem since it is an exponential time algorithm. We have already detected the problem: the computation of the racemic currents. Therefore we asked: can we overcome the explicit computation of those extreme currents?

Notice that our challenge is similar in nature to the challenge that one has to face when he is solving a linear programming problem. Linear programming teach us that given a convex polyhedra Φ, one can compute many useful things related to Φ without computing its extreme rays. We can, for instance, compute the maximum of any linear functional defined over Φ.

Let $\mathcal{F}_\Omega : \mathcal{SS}^{ra}(\Omega) \to \mathbb{R}$ be the *Frank Function* defined by

$$\mathcal{F}_\Omega(\mathbf{a}, \mathbf{b}) = \mathcal{J}_{(\mathbf{a},\mathbf{b})}[1,1] - \mathcal{J}_{(\mathbf{a},\mathbf{b})}[1,2].$$

Observe that our problem reduces to determine if function $\mathcal{F}_\Omega$ takes nonnegative values. To do the latter, we can compute the maximum of $\mathcal{F}_\Omega$ over the set $\mathcal{SS}^{ra}(\Omega)$. The latter problem seems similar to a linear programming problem. However, we have to take into account that:

1. $\mathcal{SS}^{ra}(\Omega)$ is not polyhedral.
2. Function $\mathcal{F}_\Omega$ is not linear.

If we switch to the system of convex coordinates, the set $\mathcal{SS}^{ra}(\Omega)$ becomes suitably represented by the polyhedral cone $\mathbb{R}^{rs}_+$, and the function $\mathcal{F}_\Omega$ (now defined as $H^{ra}_\Omega[1,1] - H^{ra}_\Omega[1,1]$) becomes linear. Unfortunately, we cannot switch to this latter system of coordinates (given that we want to avoid the computation of the racemic currents). What can be done?

There is an intermediate system of coordinates that, so far, we have not used, it is the system of *velocity coordinates* of the space $\mathbb{R}^{rs}$. In this latter system of coordinates the set $\mathcal{SS}^{ra}(\Omega)$ is suitably represented by the polyhedral cone $\mathcal{C}^{ra}_\Omega$. Then, it remains to compute a suitable linear expression for $\mathcal{F}_\Omega$ with respect to this latter system of coordinates.

Set

$$\begin{aligned} \mathcal{R}^\Omega_1 &= \{j \leq 2m : d_{1j} - c_{1j}, c_{1j} \neq 0\} \text{ and} \\ \mathcal{R}^\Omega_2 &= \{j \leq 2m : d_{1j} - c_{1j}, c_{2j} \neq 0\}. \end{aligned}$$

Let $(\mathbf{a},\mathbf{b}) \in \mathcal{SS}_{+}^{ra}(\Omega)$, we have that

$$\begin{aligned}\mathcal{J}_{(\mathbf{a},\mathbf{b})}[1,1] &= \frac{1}{\mathbf{a}[1]}\sum_{j\in\mathcal{R}_1^{\Omega}} c_{1j}\cdot(d_{1j}-c_{1j})\cdot\mathbf{b}[j]\cdot\mathbf{a}[1]^{c_{1j}}\cdot\cdots\cdot\mathbf{a}[n]^{c_{nj}} \text{ and}\\ \mathcal{J}_{(\mathbf{a},\mathbf{b})}[1,2] &= \frac{1}{\mathbf{a}[2]}\sum_{j\in\mathcal{R}_2^{\Omega}} c_{2j}\cdot(d_{1j}-c_{1j})\cdot\mathbf{b}[j]\cdot\mathbf{a}[1]^{c_{1j}}\cdot\cdots\cdot\mathbf{a}[n]^{c_{nj}}.\end{aligned}$$

If we set $h=\mathbf{a}[1]=\mathbf{a}[2]$, we get that

$$\begin{aligned}\mathcal{F}_{\Omega}(\mathbf{a},\mathbf{b}) &= \frac{1}{h}\sum_{j\in\mathcal{R}_1^{\Omega}} c_{1j}\cdot(d_{1j}-c_{1j})\cdot\mathbf{b}[j]\cdot\mathbf{a}[1]^{c_{1j}}\cdot\cdots\cdot\mathbf{a}[n]^{c_{nj}}\\ &\quad -\frac{1}{h}\sum_{j\in\mathcal{R}_2^{\Omega}} c_{2j}\cdot(d_{1l}-c_{1l})\cdot\mathbf{b}[j]\cdot\mathbf{a}[1]^{c_{1j}}\cdot\cdots\cdot\mathbf{a}[n]^{c_{nj}}.\end{aligned}$$

Then, we have that $\mathcal{F}_{\Omega}$ is suitably represented by the expression

$$f_{\Omega}([I],y_1,...,y_{2m}) = \frac{1}{[I]}\left(\sum_{j\in\mathcal{R}_1^{\Omega}} c_{1j}\cdot(d_{1j}-c_{1j})\cdot y_j - \sum_{l\in\mathcal{R}_2^{\Omega}} c_{2l}\cdot(d_{1l}-c_{1l})\cdot y_l\right),$$

that involves the velocity variables $y_1,...,y_{2m}$ as well as the concentration variable $[I]$.

Set

$$F_{\mathbf{\Omega}}(y_1,...,y_{2m}) = \sum_{j\in\mathcal{R}_1^{\Omega}} c_{1j}\cdot(d_{1j}-c_{1j})\cdot y_j - \sum_{l\in\mathcal{R}_2^{\Omega}} c_{2l}\cdot(d_{1l}-c_{1l})\cdot y_l.$$

We get that:

Lemma 44 *Frank Function $\mathcal{F}_{\Omega}$ takes nonnegative values over $\mathcal{SS}^{ra}(\Omega)$, if and only if, the function $F_{\mathbf{\Omega}}(y_1,...,y_{2m})$ takes nonnegative values over $\mathcal{C}_{\Omega}^{ra}$.*

Remark 45 *Notice that $F_{\mathbf{\Omega}}(y_1,...,y_{2m})$ is a linear function.*

Set

$$\mathcal{K}_{\Omega} = \left\{ v\in\mathcal{C}_{\Omega}^{ra} : \sum_{i\leq s} v[i] \leq 1 \right\}.$$

We get that

Lemma 46 *Function $F_{\mathbf{\Omega}}(y_1,...,y_{2m})$ takes nonnegative values over $\mathcal{C}_{\Omega}^{ra}$, if and only if, the quantity*

$$m_{\Omega} = \max\{F_{\Omega}(y_1,...,y_r) : (y_1,...,y_r)\in\mathcal{K}_{\Omega}\}$$

is nonnegative.

Altogether we get a reduction of our problem to linear programming:

Let Ω be a chiral network, we have that $F(\Omega) \cap SS_{+}^{ra}(\Omega)$ is nonempty, if and only if, the quantity m_{Ω} is positive.

Remark 47 *The quantity m_{Ω} can be defined as the output of the linear program*

$$\begin{array}{l} \textit{Maximize: } F_{\Omega}(y_1, ..., y_r), \\ \textit{Subject to the restriction: } (y_1, ..., y_r) \in \mathcal{K}_{\Omega}. \end{array}$$

Theorem 48 *There exists a polynomial time algorithm which, on input the chiral network Ω, decides if the set $\mathcal{F}(\Omega) \cap \mathcal{SS}^{ra}(\Omega)$ is nonempty. Moreover, if $\mathcal{F}(\Omega) \cap \mathcal{SS}^{ra}(\Omega) \neq \emptyset$ the algorithm computes an element of this set.*

Proof. Let

$$\Omega = (\{L, D, X_3, ..., X_n\}, \{RL_1, RD_1, ..., RL_m, RD_m\})$$

be a chiral network. The algorithm works, on input Ω, as follows:

1. Compute m_{Ω}.
2. If $m_{\Omega} < 0$ halt and reject the input, otherwise go to step 3.
3. Use a (polynomial time) linear programming algorithm to compute a vector $v \in \mathcal{K}_{\Omega}^{\circ}$ such that $F_{\Omega}(v) \geq 0$. Sample the set $\mathcal{R}_{\Omega}^{-1}(v) \cap \mathcal{SS}^{ra}(\Omega)$.

We get, from the previous facts, that the above algorithm is correct, and it is clear that it runs in polynomial time. ■

The above algorithm can be adapted to deal with other important tasks related to the analysis of Ω. This algorithm can be used to detect the reaction pathways of Ω that favour chiral amplification. Let $v_1, ..., v_{rs}$ be a minimal spanning set of racemic currents, and let $0, a_1, ..., a_{rs}$ be the nodes of $\mathcal{K}_{\Omega}$. We can suppose that $a_i \in v_i$. We have that the maximum m_{Ω} is attained at one of those nodes, say the node a_i. We can suppose that our linear programming algorithm computes the latter node. We can also use a variant of the simplex method to compute a sample of the set

$$\mathcal{H}_{\Omega} = \{a_j : F_{\Omega}(a_j) \geq 0\}.$$

Notice that the latter set is constituted by all the racemic currents of Ω that can produce chiral amplification. Recall that any element of $\mathcal{C}_{\Omega}^{ra}$ is a nonnegative linear combination of racemic currents. Thus, given $v \in \mathcal{C}_{\Omega}^{ra}$ there exist nonnegative reals $\alpha_1, ..., \alpha_{rs}$ such that

$$\mathbf{v} = \alpha_1 \cdot a_1 + \cdots + \alpha_{rs} \cdot a_{rs}.$$

We have that

$$F_\Omega(v) = \alpha_1 F_\Omega(a_1) + \cdots + \alpha_{rs} F_\Omega(a_{rs}),$$

and we get that the inequality $F_\Omega(v) > 0$ cannot hold if the the intersection

$$\{i \leq rs : \alpha_i > 0\} \cap \{i \leq rs : F_\Omega(a_i) \geq 0\}$$

is empty.

The latter fact allows us to claim that $\mathcal{H}_\Omega$ is the *homochirality core* of Ω. SNA tells us that the nodes of $\mathcal{K}_\Omega$ are in a natural correspondence with the subnetworks (reaction pathways) of Ω (see [2]). Thus, it seems that it is straightforward to adapt our algorithm in order to get a software tool which, on input Ω, computes all the subnetworks of Ω that favour the emergence of homochirality (the homochirality core of Ω).

4 Concluding remarks

The algorithmic strength of SNA is strongly restricted by the hardness of computing the extreme currents. SNA promises to reduce the stability analysis of chemical reaction networks to linear programming, but this promise is not fulfilled, and the promised reduction can only be achieved in some very specific scenarios. We could find a scenario where the linearization of the Jacobian matrix can be fully exploited, given us the opportunity of designing a polynomial time algorithm based on SNA. However, it should be clear that this scenario is specific and very restricted.

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