Genetic-metabolic networks can be modeled as toric varieties.

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Abstract. The mathematical modelling of genetic-metabolic networks is of utmost importance in the field of systems biology. Different formalisms and a huge variety of classical mathematical tools have been used to describe and analyse such networks. Michael A. Savageau defined a formalism to model genetic-metabolic networks called S-Systems. There is a limit in the number of nodes that can be analysed when these systems are solved using classical numerical methods such as non-linear dynamic analysis and linear optimization algorithms. We propose to use toric algebraic geometry to solve S-systems. In this work we prove that S-systems are toric varieties and that as a consequence Hilbert basis can be used to solve them. This is achieved by applying two theorems, proved here, the theorem about Embedding of S-Systems in toric varieties and the theorem about Toric Resolution on S-Systems. In addition, we define the realization of minimal phenotypic polytopes, phenotypic toric ideals and phenotypic toric varieties as a generalization of the phenotypic polytopes described by M. Savageau. The implications of the results here presented is that, in principle, they will facilitate solving large scale genetic-metabolic networks by means of toric algebraic geometry tools as well as facilitate elucidating their dynamics.

1. Introduction.

The paper is organized as follows. In the first part, we revise a few results of convex geometry, as the Gordan’s Lemma, as important preliminary concepts. We revise the standard background of combinatorial toric algebraic geometry, and make use of the definition of toric variety as an algebraic affine scheme, a definition that will permit the formalization we show for S-systems.

In the second part, we introduce the main concepts of power law modelling of biochemical systems (power law, dominant terms, phenotypic polytope), specifically in genetic-metabolic networks as studied by M. Savageau, see ref. We prove that S-systems are toric systems, both, assuming steady-state by demonstrating the Theorem (embedding of S-Systems in toric varieties), and beyond steady-state by demonstrating Theorem (toric resolution on S-Systems), and prove at the end of this paper. These results are important, because

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the practical realizations of them by means use of Hilbert basis, will enable the mathematical modelling for genetic-metabolic networks of hundreds of nodes. Furthermore, this approach will permit new computational applications for the study of the dynamics of large-scale networks.

2. Background of Combinatorial Toric Algebraic Geometry.

In this part, we revise the fundamental facts seen in combinatorial toric algebraic geometry, in order to present a proof with the last theorems. Given \( M \subset \mathbb{R}^n \), by \( \text{conv} M \) we mean the convex hull of \( M \), which is the set of all convex combinations of elements of \( M \). Moreover, if \( M \) is a finite set then \( \text{conv} M \) is called a convex polytope or polytope. A lattice \( N \) is a free abelian group of finite rank, and if its rank is \( n \in \mathbb{N} \), then \( N \) is isomorphic to \( \mathbb{Z}^n \).

Let \( M \) and \( N \) be two lattices both of rank \( n \), consider \( \langle \cdot,\cdot \rangle : M \times N \rightarrow \mathbb{Z} \), the usual homomorphism of lattice from the inner product in \( \mathbb{R}^n \) and identify to \( N \) with \( \text{Hom}_\mathbb{Z}(M,\mathbb{Z}) \), then we say that \( N \) is the dual lattice of the lattice \( M \), and reciprocally. In any case one denotes \( N = M^\vee \), see for more details of this formalism [7].

Given \( M \) and \( N \) as dual lattice, denote \( M_\mathbb{R} = M \otimes \mathbb{Z} \mathbb{R} \) and \( N_\mathbb{R} = N \otimes \mathbb{Z} \mathbb{R} \), and set \( \sigma = \text{Con}(S) \subseteq M_\mathbb{R} \), for some set \( S \subseteq M \); then \( \sigma \) is called a rational polyhedric cone or lattice polytope, [7].

**Lemma 2.1.** Let \( \sigma \subset \mathbb{R}^n \) be a lattice cone, then \( \sigma \cap \mathbb{Z}^n \) is a monoid, for the proof, see [8].

**Lemma 2.2.** Gordan’s Lemma. Let \( \sigma \subset \mathbb{R}^n \) be a lattice cone, then the monoid \( \sigma \cap \mathbb{Z}^n \) is finitely generated, for details of the proof, see [8].

By means of these lemmas, we enunciate the following results.

**Definition 2.3.** An affine toric variety is an irreducible affine variety \( X \) containing a torus \( T_N \cong (\mathbb{C}^*)^n \) as Zariski open subset, such that the action of \( T_N \) on itself, is extended to an algebraic action of \( T_N \) on \( X \); that is, there exists a morphism from \( T_N \times X \) to \( X \), [7].

Let \( \sigma \) be a lattice cone, the affine algebraic scheme:
\[
X_\sigma = \text{Spec} (R_\sigma).
\]

is called abstract toric affine variety or embedding of torus.

For example, set \( 0 \leq r \leq n \), and let \( \sigma \subset \mathbb{R}^n \) be a lattice cone generated as follows \( \sigma = \text{Con}(e_1,\ldots,e_r) \) where \( e_i \) are canonical vectors in \( \mathbb{R}^n \) for \( i = 1,\ldots,r \). Then computing its dual cone, one has \( \sigma^\vee = \text{Con}(e_1,\ldots,e_r,\pm e_1,\ldots,\pm e_n) \), and the affine toric variety is
\[
X_\sigma = \text{Spec} \ \mathbb{C}[t_1,\ldots,t_r,t_r^{\pm 1},\ldots,t_{r+n}^{\pm 1}] \cong \mathbb{C}^r \times (\mathbb{C}^*)^{n-r}.
\]

This example is seen in, [7].
2.1. Hilbert basis.

The theory of Hilbert basis is an important algebraic geometry tool, see refs. [7, 21]. The utilization of Hilbert basis associated to a monoid \( N \subset \mathbb{Z}^n \) to give explicitly a toric resolution in the last theorems, see [21], for computing of Hilbert basis.

Let \( N \simeq \mathbb{Z}^n \) be the lattice and set \( M = N^\vee \) its dual lattice. Let \( \sigma \) be a lattice cone defined in \( N \) and let \( \sigma^\vee \) be its dual cone in \( M \). Denote \( S_\sigma = \sigma^\vee \cap M \) and note that his monoid is finitely generated (see Gordan lemma).

**Lemma 2.4. (Basis Hilbert).** Set \( \sigma \subseteq N \), then \( \sigma \) is a \( n \)-dimensional cone if and only if it is a strongly convex cone; i.e., \( \sigma \cap (-\sigma^\vee) = \{0\} \). In this case the monoid \( S_\sigma \) has a finite minimal set of generators \( H \subseteq M \simeq \mathbb{Z}^d \) and these are minimal; for details of this proof, see [21]; also in [6, 7].

**Proposition 2.0.** Let \( I \) be an ideal of the affine toric variety \( X_\sigma \subseteq \mathbb{C}^n \). Then define
\[
(\text{I}(X_\sigma) = \left\langle t^{l_1} - t^{l_2} \mid l \in L \right\rangle = \left\langle t^\alpha - t^\beta \mid \alpha, \beta \in \mathbb{Z}^n_+ \right\rangle,
\]
where \( L \) is the kernel of the following morphism \( 0 \rightarrow L \rightarrow \mathbb{Z}^n \rightarrow M \) and \( M \) is a monoid such that \( M \simeq \mathbb{Z}^d \). The elements of \( l \in L \) satisfies \( \sum_{i=1}^n l_i m_i = 0 \), for details of this fact, see [7].

**Definition 2.5.** Let \( L \subseteq \mathbb{Z}^n \) be a sub-lattice.

(a). The ideal \( I_L = \left\langle t^\alpha - t^\beta \mid \alpha, \beta \in \mathbb{Z}^n_+ \right\rangle \), is called a lattice ideal.

(b). A prime lattice ideal is called a toric ideal.

**Proposition 2.1.** An ideal \( I \subseteq \mathbb{C}[t_1, ..., t_n] \) is toric if and only if it is prime and it is generated by binomials. For details of the proof, see ref. [7].

2.2. Toric Morphisms.

**Definition 2.6.** Let \( \Phi : \mathbb{C}^k \rightarrow \Phi(\mathbb{C}^k) \) be a monomial map, i.e., each component non zero of \( \Phi \) is a monomial with coordinates in \( \mathbb{C}^k \), and let \( X_\sigma \rightarrow \mathbb{C}^k \) and \( X_{\sigma'} \leftarrow \mathbb{C}^m \) be inclusions of toric affine varieties. If \( \Phi(X_\sigma) \subset X_{\sigma'} \), then \( \varphi := \Phi|_{X_\sigma} \) is called a toric affine morphism of \( X_\sigma \) to \( X_{\sigma'} \). If \( \varphi \) is bijective and its inverse map \( \varphi^{-1} : X_{\sigma'} \rightarrow X_\sigma \) is also a toric morphism, then \( \varphi \) is called an affine toric isomorphism and it is denoted by \( X_\sigma \simeq X_{\sigma'} \). [8].

**Proposition 2.2.** Every toric morphism \( \varphi : X_\sigma \rightarrow X_{\sigma'} \) determines a monomial homomorphism \( \varphi^* : R_{\sigma'} \rightarrow R_\sigma \) and reciprocally; for details of the proof, see [8].

**Definition 2.7.** For two lattice cones \( \sigma \subset \mathbb{R}^n = \text{lin}(\sigma) \) and \( \sigma' \subset \mathbb{R}^m = \text{lin}(\sigma') \), we say that \( \sigma \) and \( \sigma' \) are isomorphic and denote \( \sigma \simeq \sigma' \), if \( m = n \) and there exists an uni-modal transformation \( L : \mathbb{R}^n \rightarrow \mathbb{R}^n \) such that \( L(\sigma') = \sigma \). The monoids \( \sigma \cap \mathbb{Z}^n \) and \( \sigma' \cap \mathbb{Z}^n \) are isomorphic too.

**Definition 2.8.** Given \( R_\sigma \) and \( R_{\sigma'} \) two \( \mathbb{C} \)- algebras, there is a monomial isomorphic, \( R_\sigma \simeq R_{\sigma'} \), if there exists an invertible monomial homomorphism \( R_\sigma \leftrightarrow R_{\sigma'} \).

**Theorem 2.9.** Set \( \sigma \subset \mathbb{R}^n = \text{lin}(\sigma) \) and \( \sigma' \subset \mathbb{R}^m = \text{lin}(\sigma') \), then the following conditions are equivalent:
(a) \( \sigma \simeq \sigma' \)  \ (b) \( R_\sigma \simeq R_{\sigma'} \)  \ (c) \( X_\sigma \simeq X_{\sigma'} \)

Proof. The implications a) \( \Rightarrow \) b) \( \Rightarrow \) c) are proven by means of the following diagram, and we prove that it is commutative,

\[
\begin{array}{ccc}
\sigma & \rightarrow & R_\sigma \\
\uparrow & & \downarrow \\
L^{-1} & & \psi^{-1} \\
\sigma' & \rightarrow & R_{\sigma'} \\
\uparrow & & \downarrow \\
\phi^{-1} & & \\
\end{array}
\]

\( X_\sigma \rightarrow \text{Spec}(R_\sigma) \)

for details of this proof, see refs. [4] and [8]. □

Definition 2.10. Recall that a complex projective n-space \( \mathbb{C}P^n \) is the space of class of equivalence of pairs of points such that it consists of lines on \( \mathbb{C}P^n = \mathbb{C}^{n+1}/\sim \). The relationship between points \( \sim \) is of the following manner, given any vector \( v := (\eta_0, \ldots, \eta_n) \) it defines a line \( \mathbb{C}^*v \) and two of said vectors \( v \sim v' \in \mathbb{C}^{n+1}\backslash \{0\} \) define the same line if and only if, one is a scalar multiple of the other.

Theorem 2.11. (Hironaka-Atiyah) Let \( f \) be a real analytical function in a neighborhood of \( \omega = (\omega_1, \ldots, \omega_n) \in \mathbb{R}^n \) such that \( f(\omega) = 0 \). Then there exists an open set \( V \subset \mathbb{R} \), a real analytical variety \( U \) and a proper analytical map \( g : U \rightarrow V \) such that:

(a) \( g : U - \epsilon \rightarrow V - f^{-1}(0) \) is an isomorphism, where \( \epsilon = g^{-1}(f(0)) \).

(b) For each \( u \in U \), there exist local analytical coordinates \( (u_1, \ldots, u_n) \) such that \( f(g(u)) = \pm u_1^{s_1} u_2^{s_2} \cdots u_n^{s_n} \), where \( s_1, \ldots, s_n \) are non negative integers; see ref. [2].

The previous theorem is a version of the well-known theorem of resolution of singularities established by Hironaka in algebraic geometry; see ref. [11].

Theorem 2.12. Let \( X_\Sigma \) be a regular toric variety, and let \( X_{\Sigma_0} \) be a toric invariant sub-variety defined by the star \( \text{st}(\sigma, \Sigma) \simeq \Sigma_0 \) of \( \sigma \) into \( \Sigma \); \( 1 < k := \dim \sigma \leq n \).

(a) Under toric blow up \( \psi_{\sigma}^{-1} \), any point \( x \in X_{\Sigma_0} \) is substituted by a k-dimensional \((k-1)\) projective space.

(b) The blow down \( \psi_{\sigma} \) is a toric morphism which is bijective in the outside of \( \psi_{\sigma}^{-1} \).

See ref. for the proof of this fact, [8].

3. Biochemical Machines: Toric resolution in genetic-metabolic networks.

In this section we introduce biochemical systems particularly genetic-metabolic networks modelled using the power law formalism of enzyme kinetics, defined and widely studied by M. Savageau, [16], [17], [19]. And, subsequently, we prove that they are toric varieties.

Formalism of power law for biochemical systems.

The power law formalism is a particular representation of enzyme kinetics, formally a Taylor's expansion in several variables capable of describing biochemical reactions of metabolic and gene regulatory mechanisms, formulated as rational functions produced by the balance of mass equations.
\[
\dot{X}_i = \sum_{k=1}^{p_i} \alpha_{ik} \prod_{j=1}^{m} X_j^{g_{ijk}} - \sum_{k=1}^{q_i} \beta_{ik} \prod_{j=1}^{m} X_j^{h_{ijk}}, \quad i = 1, \ldots, n.
\]

This expression represents the basic principle of mass conservation, in the form of the power law formalism it is called \textit{general action mass}, (GAM). Each term is associated to elements of a network of reactions, where \(\dot{X}_i\) represents a derive in time \(t\) of \(X_i\) and it is called the rate law of degradation of any \(i\)-esim species \(X_i\) (gene, mRNA, proteins or metabolites) in the network. This variation in time governs the change of fluxes of biomass throughout all elements in any biochemical and genetic network. The first sum are the products that contribute to the production to the species \(X_i\) and the terms of the second sum are elements of consumption due to the degradation of \(X_i\), [16], [19].

**Definition 3.1.** (Dominant terms). A dominant term is defined as the largest term of a given sign for an equation of the GMA-system (equation defined above); and the dominant terms with positive and negative signs are the \textit{dominant positive term} and the \textit{dominant negative term}, respectively, see ref. [16].

**Definition 3.2.** (S-systems). Using the concept defined above, we can have a finite number of combinations of dominant terms, exactly

\[
\prod_{j=1}^{n} p_j q_j;
\]

partitions of the space of concentrations \((X_1, \ldots, X_n)\), where each partition is a dominant sub-system and it is associated with a particular system of equations, called \textit{S-systems}, M. Savageau, [17], [16], [12], [13], [14]; as shown below

\[
\dot{X}_i = \alpha_{ip} \prod_{j=1}^{m} X_j^{g_{ipj}} - \beta_{iq} \prod_{j=1}^{m} X_j^{h_{iqj}}, \quad i = 1, \ldots, t.
\]

\[
0 = \alpha_{ip+1} \prod_{j=1}^{m} X_j^{g_{ip+1}} - \beta_{iq+1} \prod_{j=1}^{m} X_j^{h_{iq+1}}, \quad t = 0, \ldots, m,
\]

for details, see M. Savageau [17].

**Definition 3.3.** (Phenotypic Polytope). A phenotype is defined as a set of concentrations or fluxes corresponding to a valid combination of dominant terms. They define boundary conditions obtained from the solution of S-systems under steady-state, in logarithmic-space. Each boundary condition defines an \(m\)-dimensional half-space and the intersection of these half-spaces yields an \(m\)-dimensional \textit{phenotypic polytope}.

The phenotypic polytope associated with the S-Systems can be considered to be a realization of a lattice polytope, taking the support of each S-systems related to the kinetic orders of the metabolic reactions.
Using the previous definitions, in the following we prove that S-Systems are toric varieties.

**Theorem 3.4. (Toric Embedding of S-systems)** Let $\dot{X}_i$ be an S-system, given by:

$$\dot{X}_i = \alpha_i \prod_{j=1}^{m} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{m} X_j^{h_{ij}}; \ X_i(0) = X_{i0}.$$  

Then the S-system $\dot{X}_i$, for all $i = 1, 2, ..., n$, is generated by toric ideals $I_H$ and as a consequence, each $\sigma_i \subseteq \mathbb{Z}^n$ phenotypic polytope is associated to an affine toric variety, namely,

$$X_{\sigma_i} = \text{Spec} (R_{\sigma_i}), \ \forall i = 1, 2, ..., n, j = 1, ..., m.$$  

With coordinate ring $R_{\sigma_i}$ associated to the monomial $\mathbb{C}$-algebra, $\mathbb{C}[X_j^{g_{ij}}, X_j^{h_{ij}}]$, and it is called a toric phenotypic variety or simply phenotypic variety.

**Proof.** We prove the result by construction, given the following polynomial $\dot{X}_i = \alpha_i \prod_{j=1}^{m} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{m} X_j^{h_{ij}}$, for some $i$ which is an S-system, where $\dot{X}_i \in \mathbb{C}[X_j^{g_{ij}}, X_j^{h_{ij}}]$. It is clear to see that the monomial $\mathbb{C}$-algebra is generated by the monomials $X_j^{g_{ij}}$ and $X_j^{h_{ij}}$; it is always possible to define the condition lattice vectors $a_i = (g_{i1}, ..., g_{im})$, $b_i = (h_{i1}, ..., h_{im}) \in \mathbb{Z}^m$, when $g_{ij}$ and $h_{ij}$ are rational numbers, one can always multiply by units of the ring $\mathbb{C}$ and $\mathbb{C}^2$ the polynomial equations $\dot{X}_i$, with $r, s, \in \mathbb{Z}$, such that, $rsa_i$, $rsb_i \in \mathbb{Z}^m$. We construct the sub-lattice cone $\sigma_i \subseteq \mathbb{Z}^m$ formed by the lattice vectors $a_i - b_i \in \sigma_i$; $a_i, b_i \in \mathbb{Z}^m$. Now we define the monoid $S_{\sigma_i} = \sigma_i^\vee \cap \mathbb{Z}^m$; this monoid is finitely generated (Lemma of Gordan), and has a finite minimal set of generators $H$ (Hilbert basis), the ideals associated to them, $I_H$ are primes and generate $\dot{X}_i$, and applying the definition 2.5 and proposition 2.0, we conclude that they are toric ideals. With these facts and using theorem 2.10 we construct the coordinate ring $R_{\sigma_i} = \{ \dot{X}_i \in \mathbb{C}[X_j^{g_{ij}}, X_j^{h_{ij}}] \mid \text{supp}(\dot{X}_i) \subset \sigma_i \}$, with lattice cone $\sigma_i \subset H$, thus there exists a monomial homomorphism $j_{\sigma_i}$ for all $i$ such that the following affine algebraic scheme $X_{\sigma_i} = \text{Spec} (R_{\sigma_i})$ is a toric variety with monomial $\mathbb{C}$-algebra associated $\mathbb{C}[S_{\sigma_i}] = \mathbb{C}[X_j^{g_{ij}}, X_j^{h_{ij}}]/I_H$; in this way we have proven that S-systems are toric or have an embedding in the algebraic torus, and $X_{\sigma_i}$ is the associated phenotypic variety; with this fact we conclude the proof, q.e.d.

S-systems are usually solved under steady-state conditions. In the following, we do a toric resolution in S-Systems without assuming steady-state. Theorem 3.5 will enable for the study of their dynamics.

**Theorem 3.5. (Toric resolution in S-systems)** Let $\dot{X}_i$ be an S-system,

$$\dot{X}_i = \alpha_i \prod_{j=1}^{m} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{m} X_j^{h_{ij}}; \ X_i(0) = X_{i0}.$$  

for all $i = 1, 2, ..., n, j = 1, ..., m$. Then there are maps of resolution $\psi_i : X_{\sigma_i} \rightarrow X_{\sigma_i}$ for each $i$ (toric morphisms) such that, they are a re-parametrization in the coordinate ring $\mathbb{C}[\omega_1, ..., \omega_m]$ thus:
\[ \dot{X}_i(\psi_i(\omega)) = h_{i1} \omega_1^{\alpha_1} \cdots \omega_m^{\alpha_m}, \text{ with } \omega_i(0) = \omega_{i0}. \]

where the \( h_{\alpha_1}, \ldots, \alpha_m \) are units of the ring, with \( \omega = (\omega_1, \ldots, \omega_m) \in \mathbb{R}^m \) and \( \alpha_1 > 0, \ldots, \alpha_m > 0 \), positive integers.

Proof. The proof is given by construction and follows by applying Theorems 2.9, and Theorem of Hironaka-Atiyah a finite number of times for each lattice cone \( \sigma_i \) up to reaching the toric resolution necessary for producing a polynomial \( \dot{X}_i(\psi_i(\omega)) \) for some coordinate-space \( \omega \in \mathbb{R}^m \); the lattice cones \( \sigma_i^{\vee} \) and \( (\sigma_i')^{\vee} \) are realized as follows, first: we take the lattice polytope for each S-system \( \dot{X}_i \), i.e., \( \text{supp}(\dot{X}_i) \), then, we compute the Hilbert basis \( H \) the necessary times to these associated lattice cones, obtaining the toric ideals \( I_H \) associated to these basis, and with the generators of the basis construct \( \sigma_i^{\vee} \), and applying the Theorem 2.9 on these lattice cones, we define the morphisms \( \varphi \) and \( \varphi^{-1} \). With these facts and in agreement with the Theorem of Hironaka-Atiyah, we re-parametrize the polynomial \( \dot{X}_i \) in the constructed coordinate ring as we can see, \( \mathbb{C}[\omega_1, \ldots, \omega_m] = \mathbb{C}[S_{\sigma_i}] = \mathbb{C}[X_j^{\alpha_j}, X_j^{\alpha_j}]/I_H, \) with \( S_{\sigma_i} \) monoid associated to \( \sigma_i^{\vee} \), and so we have the desired result, \( \text{q.e.d.} \)

4. Comments and future developments.

The mathematical results here presented will enable the study of S-Systems in steady state by means of computing toric ideals, since minimal generators contain the solution space of S-Systems. In this way the use of Hilbert basis is important for the solution of these systems, even more with Theorem 3.5 which gives a clear perspective for the study of dynamical solutions on genetic-metabolic networks at hand with Hilbert basis associated to the lattice polytope in S-Systems. These will enable us in a future work, to model large genetic- metabolic networks. Also, in the future we will study in more detail the concepts, of phenotypic toric variety and phenotypic toric ideals, since they are associated with sustained oscillating features in the periods of time, under environmental stress.

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6. Conclusions.

The main result in this work is the use of Theorem 2.9, and the Hironaka-Atiyah’s Theorem for the demonstrations given in Theorems, Theorem 3.4 (embedding of S-Systems in toric varieties), and Theorem 3.5 (toric resolution on S-Systems), that give the foundation to the toric formalization of genetic-metabolic networks in the approach studied by MA Savageau. These facts demonstrate that S-Systems are toric varieties. As a consequence of these results, the Theorem 3.4 give us a formalization for the study of S-Systems in steady-state. In more general terms, the Theorem 3.5 provides the formal support to the use of toric algebraic geometry tools to the study of the dynamics of genetic-metabolic networks. In both cases we have seen the use of Hilbert basis for the realizations.
of toric morphisms, and computationally it opens the possibility for this mathematical modelling of large-scale genetic-metabolic networks, since the algorithms to compute Hilbert basis in high-dimensional lattice polytope can be used.

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