Algebraic Experimental Design: Theory and Computation*

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Abstract. Over the past several decades, algebraic geometry has provided innovative approaches to biological experimental design that resolved theoretical questions and improved computational efficiency. However, guaranteeing uniqueness and perfect recovery of models are still open problems. In this work we study the problem of uniqueness of wiring diagrams. We use as a modeling framework polynomial dynamical systems and utilize the correspondence between simplicial complexes and square-free monomial ideals from Stanley-Reisner theory to develop theory and construct an algorithm for identifying input data sets $V \subset \mathbb{F}_p^n$ that are guaranteed to correspond to a unique minimal wiring diagram regardless of the experimental output. We apply the results on a tumor-suppression network mediated by epidermal derived growth factor receptor and demonstrate how careful experimental design decisions can lead to a unique minimal wiring diagram identification. One of the insights of the theoretical work is the connection between the uniqueness of a wiring diagram for a given $V \subset \mathbb{F}_p^n$ and the uniqueness of the reduced Gröbner basis of the polynomial ideal $I(V) \subset \mathbb{F}_p[x_1, \ldots, x_n]$. We discuss existing results and introduce a new necessary condition on the points in $V$ for uniqueness of the reduced Gröbner basis of $I(V)$. These results also point to the importance of the relative proximity of the experimental input points on the number of minimal wiring diagrams, which we then study computationally. We find that there is a concrete heuristic way to generate data that tends to result in fewer minimal wiring diagrams.

Key words. Design of experiments, biological network inference, polynomial dynamical systems, ideals of points, wiring diagrams, Gröbner bases, Stanley-Reisner ideals.

AMS subject classifications. 11T06, 92C42, 37N25, 13F55

1. Introduction. The abundance of numerous substantial data sets from laboratory experiments and myriad diverse methods for modeling and analysis render network inference a critical component of systems biology research; for a recent example, see [2]. A vital process linked to inference is experimental design, which optimizes data generation and collection for effective prediction of network structure. While traditional experimental design is rooted in statistical methods [14], algebraic geometry has offered innovative approaches to experimental design [17, 7]. In fact a fractional factorial design can be viewed as a set of $n$-tuples over a finite field and a special class of discrete models called polynomial dynamical systems can be used to capture all models which fit the design points for a network with $n$ nodes.

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*Submitted to the editors August 5, 2022.

**Funding**: Dimitrova, Fredrickson, and Rondoni were partially supported by NSF Award DMS-1419038; Stigler was partially supported by NSF Award DMS-1720335; Veliz-Cuba was partially supported by the Simons Foundation grant 516088.

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Associated to a polynomial dynamical system is a directed graph called the wiring diagram, which encodes the topology (connectivity) of the network. While the wiring diagram represents only a static picture of the network, knowledge of the connectivity is crucial for studying network robustness, regulation, and control strategies in order to develop, for example, therapeutic interventions [27, 32] and drug delivery strategies [34, 13], or to understand the mechanisms for the spread of an infectious disease [16, 36]. Moreover, it has been demonstrated that the role of network connectivity goes beyond static properties and can in fact dictate certain dynamical properties and be used for their control [10, 3, 30, 35, 33, 1, 24, 20, 21].

In this work, we will develop theory and algorithms for experimental design which reduce the size of the space of possible wiring diagrams. The central object of study is a minimal set for a node $x$, that is a set of variables representing the incoming edges to $x$ in the wiring diagram. Each minimal set, or minset for short, has the property that there exists a polynomial in those variables that fits the data (design points) and there is no such polynomial for any proper subset. Specifically, we aim to find properties on input-output data $(V, T)$ that guarantees that it has a unique minimal set. In this way, we contribute a number of distinct results. When only the design points, referred to as inputs, $V$ are known, we prove a necessary and sufficient condition on $V$ (Theorem 3.1); a necessary condition on $V$ (Theorem 3.12); and a sufficient condition on $V$ (Corollary 3.5). Each of these conditions on $V$ guarantees that for any corresponding output assignment $T$, the input-output data set $(V, T)$ has a unique minimal set. Furthermore, when both inputs $V$ and outputs $T$ are known, we provide a sufficient condition on polynomial functions which fit $(V, T)$ in Theorem 3.4.

In parallel, this work has uncovered interesting results for ideals of points. While it is known that for every monomial order $\prec$ there is a unique reduced Gröbner basis $G_\prec$ for $I(V)$, there are cases when the Gröbner basis is the same across all monomial orders: that is, there exists a generating set $G$ for $I(V)$ such that for all monomial orders $\prec$ the associated reduced Gröbner basis $G_\prec = G$. In this case we say that $I(V)$ has a unique reduced Gröbner basis for all monomial orders. We prove a necessary condition on fixed inputs $V$ (Corollary 3.13); a necessary condition on arbitrary outputs $T$ (Corollary 3.5); and a necessary and sufficient condition on polynomial functions which fit $(V, T)$ for any output $T$ (Corollary 3.10).

In an effort to provide guidance for designing experiments, we performed computational experiments that suggest the following rubric: having data with small Hamming distance between points results in fewer minsets than data with large Hamming distance between points. Moreover we provide computational evidence that design points generated using a small-distance scheme result in fewer minsets than randomly generated points.

The paper is organized as follows. We provide the relevant background in Section 2. Theoretical results are in Section 3, while computational results are in Section 4. We close with a discussion in Section 5.

2. Background. Much of the language in this section is taken from [15].

Discrete models have been used extensively and there is evidence that they provide a good framework for a variety of applications, e.g. [4, 1, 28, 12, 5]. Such models are collections of functions defined over a finite state set $X$ and can be described using polynomials when the state set size is constrained to a power of a prime. In the latter case, discrete models are often referred to as polynomial models and can be written as $n$-tuples of polynomial functions, one
for each node in the network, i.e. \( f = (f_1, \ldots, f_n) : X^n \to X^n \), where \( f_i : X^n \to X \) is a polynomial which determines the behavior of node (variable) \( x_i \). Examples of polynomial models are Boolean networks \((X = \mathbb{F}_2)\) and more generally \textit{polynomial dynamical systems} (PDSs) over finite fields \((X = \mathbb{F}_p)\).

Specifically a \textit{polynomial dynamical system} over \( F = \mathbb{F}_p \) is a polynomial map \( f : F^n \to F^n \) where \( f = (f_1, \ldots, f_n) \) and each coordinate function \( f_i : F^n \to F \) is a polynomial in \( F[x_1, \ldots, x_n] \). We say that \( f \) fits the input-output data \( D = \{(s_1, t_1), \ldots, (s_m, t_m)\} \subset F^n \times F^n \) if \( f(s_j) = t_j \) for each \( 1 \leq j \leq m \).

The \textit{monomials} or \textit{terms} of a polynomial model represent interactions among the nodes in a network, whereas the coefficient of a monomial can be interpreted as the strength or weight of the associated interaction. The \textit{support} of a polynomial \( f \in k[x_1, \ldots, x_n] \), denoted \( \text{supp}(f) \), is the collection of variables that appear in \( f \).

\textbf{Definition 2.1.} A \textit{wiring diagram} of a PDS \( f = (f_1, \ldots, f_n) \) is a directed graph \( W = (L, E) \) where \(|L| = n\), the vertices are labeled as the \( n \) variables, and there is a directed edge in \( E \) \( x_i \to x_j \) iff \( x_i \in \text{supp}(f_j) \).

Monomials in the polynomial ring \( \mathbb{F}_p[x_1, \ldots, x_n] \) are written as \( x_1^{\alpha_1}x_2^{\alpha_2} \cdots x_n^{\alpha_n} \), with exponent vector \( \alpha = (\alpha_1, \ldots, \alpha_n) \in \mathbb{Z}^n \). A \textit{monomial ideal} \( I \subseteq \mathbb{F}_p[x_1, \ldots, x_n] \) is an ideal generated by monomials, written as \( I = \langle x_1^{\alpha_1}, x_2^{\alpha_2}, \ldots \rangle \). A monomial \( x_1^{\alpha_1} \) is \textit{square free} if each \( \alpha_i \in \{0,1\} \). A monomial ideal is a \textit{Stanley-Reisner ideal} if it can be generated by square-free monomials.

A \textit{simplicial complex} over a finite set \( X \) is a collection \( \Delta \) of subsets of \( X \) that are closed under the operation of taking subsets. That is, if \( \beta \in \Delta \) and \( \alpha \subseteq \beta \), then \( \alpha \in \Delta \). The elements in \( \Delta \) are called \textit{simplices} or \textit{faces}. Given an ideal \( I \), we define the simplicial complex

\[
\Delta_I = \{ \alpha \ | \ x_\alpha \not\in I \},
\]

and given a simplicial complex \( \Delta \) on \( X = [n] = \{1, \ldots, n\} \), we define the square-free monomial ideal

\[
I_\Delta = \langle x_\alpha \ | \ \alpha \not\in \Delta \rangle,
\]

which is the Stanley-Reisner ideal of \( \Delta \).

Consider a set \( V = \{s_1, \ldots, s_m\} \subseteq \mathbb{F}_p^n \) of distinct input vectors, and a multiset \( T = \{t_1, \ldots, t_m\} \) of output values from \( \mathbb{F}_p \). We call

\[
D = \{(s_1, t_1), \ldots, (s_m, t_m)\} \subseteq \mathbb{F}^n \times \mathbb{F}
\]

the \textit{input-output data set}, where inputs may be stimuli applied to the network and outputs are its responses. A function \( f : \mathbb{F}_p^n \to \mathbb{F}_p \) is said to \textit{fit the data} if \( f(s) = t \) for all \((s, t) \in D\).

The \textit{model space} of \( D \) is the set of all functions that fit the data, i.e.

\[
\text{Mod}(D) = \{ f : \mathbb{F}_p^n \to \mathbb{F}_p \ | \ f(s) = t, \text{ for all } (s, t) \in D \}.
\]

For ease of presentation, we will focus on the wiring diagram of an individual node \( x_i \), that is, the edge set of the graph will be \( E_{x_i} = \{(t, x_i) \ | \ t \in \text{supp}(f_i)\} \). The union of the wiring diagrams of all nodes is, of course, the entire wiring diagram \( W \).
In [9], the authors developed an algorithm for constructing all wiring diagrams based on sets of input-output data. The method encoded certain coordinate changes in input data as square-free monomials, generated a monomial ideal from these monomials, and used Stanley-Reisner theory to decompose the ideal into primary components. These primary components were named \textit{minimal sets} or \textit{minsets} for short. A minset is a set $S$ of variables so that there is a function in terms of those variables that fits the given data and there is no such function on proper subsets of $S$ (a formal definition will be presented as Definition 2.3). A wiring diagram for a specific node $x$ can be constructed by drawing edges from the variables in the minset towards $x$. Details are provided in the following definitions and results from [9].

For every pair of distinct input vectors $s = (s_1, \ldots, s_n)$ and $s' = (s'_1, \ldots, s'_n)$ in $V$, we can encode the coordinates in which they differ by a square-free monomial

$$m(s, s') = \prod_{s_i \neq s'_i} x_i.$$ 

Let $\mathcal{M}(V)$ be the set of all such monomials from $V$, that is,

$$\mathcal{M}(V) = \{m(s, s') \mid s, s' \in V, \ s \neq s'\}.$$

If distinct input vectors $s, s' \in V$ have different output values, $t \neq t'$, then any function $f : \mathbb{F}_p^n \to \mathbb{F}_p$, satisfying $f(s) = t$ and $f(s') = t'$ must depend on at least one of the variables in $m(s, s')$. In this case, we say that the support of $m(s, s')$, i.e., the set of variables that appear in it, is a \textit{non-disposable set} of $D$.

For a fixed data set $D$, the non-disposable sets in the power set $2^{[n]}$, where $[n] = \{1, \ldots, n\}$, are clearly closed under unions. We call all other sets \textit{disposable}, i.e. $\alpha \subseteq [n]$ is a disposable set of $D$ if and only if there is some $f \in \text{Mod}(D)$ that depends only on the variables \textit{not} in $\alpha$. Equivalently, its support satisfies $\text{supp}(f) \subseteq \overline{\alpha} = [n] \setminus \alpha$. It is easy to see that disposable sets are closed under intersections. As such we can define the abstract \textit{simplicial complex of disposable sets} of $D$ to be

$$\Delta_D = \{\alpha \subseteq [n] \mid \alpha \text{ is a disposable set of } D\};$$

If we canonically identify square-free monomials with subsets of $[n]$, then the \textit{Alexander dual} of $\Delta_D$ is the Stanley-Reisner ideal

$$I_{\Delta_D} = \langle x^\alpha \mid \alpha \notin \Delta_D \rangle = \langle m(s, s') \mid t \neq t' \rangle,$$

which is called the \textit{ideal of non-disposable sets}. By the Alexander duality, the simplicial complex of disposable sets is

$$\Delta_D = \{\alpha \subseteq [n] \mid \alpha \notin I_{\Delta_D} \}.$$ 

Since $I_{\Delta_D}$ is squarefree, it has a unique primary decomposition, where the primary components are prime ideals generated by the variables in the complements of the facets (maximal faces) of $\Delta_D$ (i.e., complements of maximal disposable sets). For a facet $\alpha \subseteq [n]$, denote
of the corresponding primary component by \( p^\alpha \). For example, if \( n = 5 \) and \( \alpha = x_2x_5 \), then \( p^\alpha = \langle x_1, x_3, x_4 \rangle \). The primary decomposition is thus

\[
I_{\Delta_D} = \bigcap_{\alpha \in \Delta_D} p^\alpha = \bigcap_{\alpha \in \Delta_D, \alpha \text{ maximal}} p^\alpha.
\]

Over a field, being prime and being primary are equivalent properties for square-free monomial ideals. The ideal \( I_{\Delta_D} \) is prime if and only if it has only one primary component, which means that there is a unique maximal disposable set (i.e., a facet) \( \alpha \) in \( \Delta_D \), and so

\[
I_{\Delta_D} = p^\alpha = \langle x_i \mid i \notin \alpha \rangle.
\]

Theorem 2.2. The simplicial complex of disposable sets \( \Delta_D \) has a unique facet if and only if the ideal of non-disposable sets \( I_{\Delta_D^n} \) is prime.

By the Alexander duality, the primary components of \( I_{\Delta_D^n} \) are in bijection with the complements of the maximal disposable sets. Such a complement \( \overline{\alpha} \) is precisely a minimal subset of \( [n] \) on which a function in the model space \( \text{Mod}(D) \) can depend. This motivates the following definition.

Definition 2.3 ([9]). The complement \( \overline{\alpha} \) of a maximal disposable set \( \alpha \) in \( \Delta_D \) is called a minimal set, or minset for short.

Each minset is a set of variables on which a polynomial can depend based on the data, and one that is minimal with respect to inclusion. These variables also encode the wiring diagram of a minimal number of edges incident to the node under consideration. We call such wiring diagrams minimal as well.

We will use the following tumor-suppression network mediated by epidermal derived growth factor receptor (EGFR) [26] as a running example. We consider Boolean and non-Boolean data for the gene network of three parameters (EGFR, Rasgap, and miR221) and three variables (Rkip, Kras, and Raf1), and an outcome of this network is proliferation or suppression of a tumor. For illustration purposes, we focus on identifying the direct regulators of Raf1 from among the candidates Rasgap, Rkip, and Kras.

Example 2.4. Suppose we want to determine which nodes Raf1 depends on – Rasgap, Rkip, or Kras – based solely on experimental data. Suppose experiments are performed to generate the following input-output data (parentheses and commas are suppressed for readability):

\[
D = \{(s_1, t_1), (s_2, t_2), (s_3, t_3), (s_4, t_4)\} = \{(000, 1), (101, 1), (110, 0), (011, 1)\},
\]

where \( s_i = (\text{Rasgap}, \text{Rkip}, \text{Kras}) = (x_2, x_3, x_3) \) and \( t_i \) is the corresponding value of Raf1. That is, we want to determine the minimal sets of variables that appear in the unknown function \( f : \mathbb{F}_2^3 \to \mathbb{F}_2 \) which determines the behavior of Raf1 based on input from the other three nodes, and fits the experimental data, that is, \( f(000) = 1, f(101) = 1, f(110) = 0, \) and \( f(011) = 1 \).
Since $t_1 = t_2 = t_4 \neq t_3$, we compute $m(s_1, s_3) = x_1x_2$, $m(s_2, s_3) = x_2x_3$, and $m(s_3, s_4) = x_1x_3$. The ideal of non-disposable sets is thus $I_{\Delta_D} = \langle x_1x_2, x_2x_3, x_1x_3 \rangle$ and has primary decomposition $\langle x_1, x_2 \rangle \cap \langle x_1, x_3 \rangle \cap \langle x_2, x_3 \rangle$, corresponding to these minimal wiring diagrams:

\[
\begin{align*}
\text{Rasgap} & \quad \text{Rkip} & \quad \text{Kras} \\
\quad & & \\
\text{Raf1} & & \\
\text{Rasgap} & \quad \text{Rkip} & \quad \text{Kras} \\
\quad & & \\
\text{Raf1} & & \\
\text{Rasgap} & \quad \text{Rkip} & \quad \text{Kras} \\
\quad & & \\
\text{Raf1} & & \\
\end{align*}
\]

The limited information that these experimental data support is that any two of the three nodes can influence Raf1. If, in addition, we perform an experiment where the input nodes are all expressed and Raf1 happens to also be expressed as a result, this will add to $D$ the data point $(s_5, t_5) = (111, 1)$. As a result, the monomial $x_2$ will be added to $I_{\Delta_D}$ whose primary decomposition now becomes $\langle x_1, x_2 \rangle \cap \langle x_2, x_3 \rangle$, eliminating the middle wiring diagram from the figure above. Since $x_2$ is in both primary ideals, we are now confident that Rkip affects Raf1. While we still do not know if Rasgap and Kras participate in the regulation of Raf1, this may be sufficient if the role of Rkip is the focus of the experimental work.

On the other hand, if instead of adding $(s_5, t_5) = (111, 1)$, we added $(s'_5, t'_5) = (010, 0)$, the new monomials added to $I_{\Delta_D}$ will be not only $x_2$ but also $x_1x_2x_3$ and $x_3$. Now the primary decomposition becomes $\langle x_2, x_3 \rangle$, reducing the possible wiring diagrams to a unique one (rightmost above) and completely determining the regulation of Raf1.

This example shows that some input-output data sets result in multiple models, whereas well-chosen datasets can reduce the number of possible wiring diagrams and even lead to a unique model.

3. Main results.

3.1. Theoretical Results. The one-to-one correspondence between the minsets of $\Delta_D$ and the minimal wiring diagrams of $\text{Mod}(D)$ implies that finding input sets which uniquely identify the minimal wiring diagram underlying a system is equivalent to finding input sets $D$ whose corresponding simplicial complexes $\Delta_D$ have a unique minset. The theory of minsets developed in [9, 29] establishes methods for generating all minimal wiring diagrams for a given input-output data set $D$. In practice, however, one does not know the experimental output $T$ a priori. Therefore, it is desirable to develop theory and algorithms which allow us to design experiments whose output is guaranteed to reduce the size of the wiring-diagram space of the system without making assumptions for the unknown experimental outcome. In the next section, we provide necessary and sufficient conditions on the input data set which are computationally feasible to guarantee that the identified minset is unique regardless of the output.

3.1.1. Identifying input sets corresponding to a unique minset. Based on Theorem 2.2, our goal is to efficiently identify sets whose ideal of non-disposable sets in prime. Below we construct an algorithm for the identification of such input sets.

Let $V = \{s_1, \ldots, s_m\} \subseteq \mathbb{F}_p^n$ be an input set of distinct vectors. We define the multiset\
\[
M = \{m(s_i, s_j) \mid i, j \in [r], \, 1 \leq i < j \leq r\},
\]
where  \( m(s_i, s_j) = \prod_{s_{ih} \neq s_{jk}} x_i \) are square-free monomials which record the coordinates where each pair of points in \( V \) differ. The number of pairs in this set is \( |M| = (r-1) + (r-2) + \cdots + 1 = \frac{(r-1)r}{2} \) since, unlike in (2.1), monomials are repeated if they come from different input pairs. For example, if \( m(s_1, s_2) = m(s_2, s_6) = x_2x_5 \), then \( x_2x_5 \) will be listed twice and it will be recorded to which input pairs it corresponds. Let \( M_{MV} \) be the list of multivariate monomials in \( M \), again keeping track of which pairs of points in \( V \) yielded each monomial. For each \( m(s_a, s_b) \in M_{MV} \), let \( m(s_{i_1}, s_{j_1}), \ldots, m(s_{i_k}, s_{j_k}) \) be the single-variate monomials in \( M \) that divide \( m(s_a, s_b) \).

**Theorem 3.1.** Let \( V = \{s_1, \ldots, s_m\} \subseteq \mathbb{F}_p^m \) be an input set of distinct vectors, and \( M \) and \( M_{MV} \) be defined as above. Let \( t_k \) denote the unknown output of \( s_k \). There exists an output assignment \( T \) for which \( I_{\Delta^c} \) is not prime (and so there are multiple minsets) if and only if there is a monomial in \( M_{MV} \) for which the following system is consistent.

\[
\begin{align*}
t_a & \neq t_b \\
t_{i_1} &= t_{j_1} \\
& \vdots \\
t_{i_k} &= t_{j_k}
\end{align*}
\]

**Proof.** The system is set up so that if consistent, \( \mathcal{M}(V) \) from (2.1) will contain at least one multivariate monomial without a single-variate monomial that divides it. In that case, the primary decomposition of the ideal generated by the monomials in \( \mathcal{M}(V) \) will have more than one primary component.

Notice that the equations in (3.2) form a homogeneous linear system whose coefficient matrix is sparse and solving it is computationally easy. As soon as a consistent system is found for an element in \( M_{MV} \), we can stop and conclude that there exists a \( T \) for which \( I_{\Delta^c} \) is not prime. If no such system is found, then for any \( T \), the Gröbner basis of \( I_{\Delta^c} \) consists entirely of single-variate monomials and so \( I_{\Delta^c} \) is prime for all output assignments.

To illustrate the process above consider the following examples.

**Example 3.2.** Consider the following non-Boolean input data for the EGFR network in [26], where \( s_1 = (\text{Rasgap}, \text{Rkip}, \text{Kras}) = (x_1, x_2, x_3) \) and \( t_i \) is the corresponding value of Raf1: \( V = \{s_1, s_2, s_3, s_4\} = \{(010), (110), (210), (212)\} \subseteq \mathbb{F}_3^3 \). The set \( M \) contains the monomials \( m(s_1, s_2) = x_1, m(s_1, s_3) = x_1, m(s_1, s_4) = x_1x_3, m(s_2, s_3) = x_1, m(s_2, s_4) = x_1x_3, m(s_3, s_4) = x_3 \). The multivariate monomials are \( m(s_1, s_4) = x_1x_3 \) and \( m(s_2, s_4) = x_1x_3 \). The two corresponding systems below are both inconsistent and so \( V \) has a unique minset for any \( T \).

\[
\begin{align*}
t_1 & \neq t_4 \\
t_1 &= t_2 \\
t_1 &= t_3 \\
t_2 &= t_3 \\
t_3 &= t_4
\end{align*}
\]
The algorithm determines that regardless of the experimental output, this input set \( V \) is guaranteed to result in a unique minimal wiring diagram for Raf1. (Notice that while unique for any output, the wiring diagram will vary based on the output.)

Now consider the input data set \( U = \{s_1, s_2, s_3, s_4\} = \{(211), (002), (200), (201)\} \subseteq \mathbb{F}_3^3 \).

The monomials in \( M \) are \( m(s_1, s_2) = x_1x_2x_3, m(s_1, s_3) = x_2x_3, m(s_1, s_4) = x_2, m(s_2, s_3) = x_1x_2, m(s_2, s_4) = x_1, x_2, \text{ and } m(s_3, s_4) = x_3 \). Based on the multivariate monomial \( m(s_1, s_2) = x_1x_2x_3 \), we form the consistent system

\[
t_1 \neq t_2, \quad t_1 = t_4, \quad t_3 = t_4.
\]

The algorithm identifies that there exist output assignments for which \( I_{\Delta^e} \) is not prime. For example, \( T = \{0, 2, 0, 0\} \), i.e. \( t_1 = t_3 = t_4 = 0, t_2 = 2 \), corresponds to two minsets: \( \{x_2\} \) and \( \{x_3\} \); that is, we can have experimental output that will result in two possible minimal wiring diagrams for Raf1: in one Raf1 depends on Rkip only, and in the other Raf1 depends on Kras only.

Having built an algorithm for identifying if an input data set \( V \) corresponds to a unique minset, we next ask how a unique minset relates to the Gröbner basis of \( I(V) \) and to the normal form of polynomials that take \( V \) as input.

### 3.1.2. Polynomial normal forms and minsets.

The main result in this section is Theorem 3.4 which establishes that a unique normal form (regardless of monomial order) of a polynomial that fits a set of input-output pairs \( D \) implies a unique minset for \( D \).

**Lemma 3.3** ([7]). Let \( x^\alpha \), \( x^\beta \) be monomials with \( x^\alpha \nmid x^\beta \). There exists a weight vector \( \gamma \) and monomial order \( \prec_\gamma \) such that \( x^\beta \prec_\gamma x^\alpha \).

**Proof.** Let \( x^\alpha \nmid x^\beta \). As \( x^\alpha \nmid x^\beta \), \( \alpha_j > \beta_j \) for some coordinate \( j \). Take \( \gamma \) to be a vector in \( \mathbb{R}^n \) with a sufficiently large rational value in entry \( j \) and square roots of distinct prime numbers elsewhere such that \( \gamma \cdot \alpha > \gamma \cdot \beta \). Then the entries of \( \gamma \) are linearly independent over \( \mathbb{Q} \) and so \( \gamma \) defines a weight order. Define \( \prec_\gamma \) to be the monomial order weighted by \( \gamma \). It follows that \( x^\beta \prec_\gamma x^\alpha \).

**Theorem 3.4.** Let \( D \subseteq \mathbb{F}^n \times \mathbb{F} \) be a data set of input-output pairs and let \( f : \mathbb{F}^n \rightarrow \mathbb{F} \) be any polynomial that fits \( D \). If \( f \) has a unique normal form for all Gröbner bases of \( I(V) \), then \( D \) has a unique minset.

**Proof.** Let \( \overline{f} \) be the unique normal form of \( f \) with respect to \( I(V) \). For contradiction, suppose that there exists a polynomial \( h \) that fits \( D \) such that \( \text{supp}(\overline{f}) \) contains a variable \( x_i \) which is not in \( \text{supp}(h) \). Notice that \( \overline{f} - h \in I(V) \) and all monomials of \( \overline{f} \) that contain \( x_i \) are in
Since a monomial that contains $x_i$ does not divide a monomial that does not contain $x_i$, it follows by Lemma 3.3 that there is a monomial order $\prec$ under which some monomial $x^\alpha$ of $\overline{f} - h$ which contain $x_i$ is the leading monomial of $\overline{f} - h$ and thus it is in $in_\prec(I(V))$. This is a contradiction since $x^\alpha$ is a monomial of $\overline{f}$ which is a linear combination of monomials that are standard with respect to any monomial order as the normal form is unique.

One consequence of the previous theorem is that the support of a unique normal form is a minset. Another is the following key condition on inputs.

**Corollary 3.5.** Let $V$ be a set of inputs. If $I(V)$ has a unique Gröbner basis, then for all output assignments there is a unique minset.

Notice that the converse of Corollary 3.5 is false. For example, $V = \{00, 10, 01, 11, 02, 20, 22\} \subseteq \mathbb{Z}_2^3$ has an ideal $I(V)$ with two Gröbner bases, $\{x + y, y^2 - 1\}$ and $\{x^2 - 1, y + x\}$, but $V$ has only one minset for any output $T$.

Theorem 3.4 and its corollaries beg the following question in algebraic design of experiments: What input-output data corresponds to a model with a unique normal form? We answer that in Theorem 3.8 below.

**Definition 3.6.** Let $\lambda = \{u^1, \ldots, u^r\}$ be an $r$-subset of $\mathbb{N}^n_p$ and let $V = \{v^1, \ldots, v^s\}$ be an $s$-subset of $\mathbb{N}^n_p$. The evaluation matrix $\Xi(x^\lambda, V)$ is the $s \times r$ matrix whose element in position $(i, j)$ is $x^{u^i}(v^j)$, the evaluation of $x^{u^i}$ at $v^j$.

**Example 3.7.** Consider $V = \{(0,0,1), (0,1,0), (1,0,1)\} \subset \mathbb{F}_2^3$. One of its sets of standard monomials is $x^\lambda = \{1, z, x\}$ which corresponds to the set of exponent vectors $\lambda = \{(0,0,0), (0,0,1), (1,0,0)\}$ and produces the following evaluation matrix on $V$:

$$
\Xi(x^\lambda, V) = \begin{bmatrix}
1 & 1 & 0 \\
1 & 0 & 0 \\
1 & 1 & 1
\end{bmatrix}.
$$

**Theorem 3.8.** Let $\mathbb{F}$ be a field. Consider a set $V = \{s_1, \ldots, s_r\} \subseteq \mathbb{F}^n$ of distinct input vectors and an output vector $T = (t_1, \ldots, t_r) \in \mathbb{F}^r$. Let $f \in \mathbb{F}[x_1, \ldots, x_n]$ be such that $f(s_i) = t_i$ for all $i \in \{1, \ldots, r\}$. The normal form of $f$ is unique with respect to any Gröbner basis if and only if $T$ is a linear combination of the columns in $\Xi(x^\lambda, V)$ that correspond to monomials which are standard with respect to any Gröbner basis.

**Proof.** First suppose that $T$ is a linear combination of the columns of $\Xi(x^\lambda, V)$ which correspond to the standard monomials in the intersection of all sets of standard monomials. Therefore, the normal form of $f$ is unique with respect to any Gröbner basis and so will not change as we change the Gröbner basis.

Conversely, suppose that the normal form of $f$ is unique with respect to any Gröbner basis. Then the normal form of $f$ is a linear combination of monomials that are standard with respect to any Gröbner basis and so $T$ is (the same) linear combination of the columns in the evaluation matrix that correspond to the monomials that are standard for every Gröbner basis.

**Example 3.9.** Consider an input set $V = \{(0,0,1), (0,1,1), (1,0,1), (1,1,0)\} \subset \mathbb{F}_2^3$. $I(V)$ has exactly two distinct sets of standard monomials, namely $SM_1 = \{1, z, y, x\}$ and $SM_2 =$
\{1, y, x, xy\}, resulting from different monomial orderings, with \( SM_1 \cap SM_2 = \{1, x, y\} \). The evaluation matrices for each of these sets of standard monomials are

\[
\begin{array}{c|cccc}
SM_1 & 1 & z & y & x \\
(0, 0, 1) & 1 & 1 & 0 & 0 \\
(0, 1, 1) & 1 & 1 & 1 & 0 \\
(1, 0, 1) & 1 & 1 & 0 & 1 \\
(1, 1, 0) & 1 & 0 & 1 & 1 \\
\end{array}
\]

and

\[
\begin{array}{c|cccc}
SM_2 & 1 & y & x & xy \\
(0, 0, 1) & 1 & 0 & 0 & 0 \\
(0, 1, 1) & 1 & 1 & 0 & 0 \\
(1, 0, 1) & 1 & 0 & 1 & 0 \\
(1, 1, 0) & 1 & 1 & 1 & 1 \\
\end{array}
\]

Take, for example, the sum of the matrix columns that are the evaluations of the monomials in \( SM_1 \cap SM_2 = \{1, x, y\} \): \([1,0,0,1]^T\), i.e. one linear combination. We find a polynomial function \( f \in F_2[x,y,z] \) that maps each input point to the corresponding output value as follows:

\[
\begin{align*}
(0, 0, 1) & \mapsto 1 \\
(0, 1, 1) & \mapsto 0 \\
(1, 0, 1) & \mapsto 0 \\
(1, 1, 0) & \mapsto 1 \\
\end{align*}
\]

We find such \( f \) via, say, Lagrange interpolation, to be \( f = xy + xz + yz + z \). Now we compute the normal forms of \( f \) reduced by \( G_1 \) and \( G_2 \), where \( G_1 \) and \( G_2 \) are the Gröbner bases for the ideal \( I(V) \) corresponding to \( SM_1 \) and \( SM_2 \), arriving at

\[
\overline{f}^{G_1} = \overline{f}^{G_2} = x + y + 1.
\]

Since \( G_1 \) and \( G_2 \) are the only two reduced Gröbner bases for the ideal, this normal form is unique.

If, instead, we take the same input set \( V \) and corresponding standard monomials but choose a new output vector, one that is not a linear combination of the columns corresponding to monomials that are standard with respect to any monomial ordering, we expect to find more than one distinct normal form of \( f \). Consider, for example, the output vector \([0, 1, 1, 1]^T\).

That is, we are looking for a polynomial function \( f \in F_2[x,y,z] \) which maps

\[
\begin{align*}
(0, 0, 1) & \mapsto 0 \\
(0, 1, 1) & \mapsto 1 \\
(1, 0, 1) & \mapsto 1 \\
(1, 1, 0) & \mapsto 1 \\
\end{align*}
\]

This time, \( f \) has two distinct normal forms,

\[
\overline{f}^{G_1} = x + y + z + 1 \quad \text{and} \quad \overline{f}^{G_2} = xy + x + y.
\]

So as expected, \( \overline{f}^{G_1} \neq \overline{f}^{G_2} \).

**Corollary 3.10.** The normal form of \( f \in F[x_1, \ldots, x_n] \) that fits a data set with input \( V = \{s_1 \ldots s_r\} \subseteq F^n \) is unique for any output \( T \) if and only if \( I(V) \) has a unique reduced Gröbner basis.

Corollaries 3.5 and 3.10 point towards the importance of ideals \( I(V) \) that have a unique
reduced Gröbner basis. Such ideals were studied in [7, 23], where sufficient conditions for $I(V)$ to have a unique reduced Gröbner basis were introduced; in this paper, Corollary 3.13 is a necessary condition that depends on a special relation between the points in $V$ that we define next.

**Definition 3.11.** A pair of points $p, q \in \mathbb{F}_p^n$ form a diagonal if $p$ and $q$ differ in at least two coordinates. We will also say that a set $V$ contains a diagonal if there is a point $p \in V$ which forms a diagonal with all other points in $V$.

**Theorem 3.12.** If $V$ contains a diagonal, then there exists an output assignment that corresponds to multiple minsets.

**Proof:** Let $p \in V$ form a diagonal with all other points in $V$. Then there is a point $s \in V$ such that $m(p, s)$ is a multivariate monomial. Denote the corresponding outputs from $p$ and $s$ by $t_p$ and $t_s$.

Case 1: There are no points $s_i, s_j \in V$ such that $m(s_i, s_j)$ is a single-variate monomial that divides $m(p, s)$. Then according to Theorem 3.1 there is an output assignment for which there are multiple minsets.

Case 2: There are pairs of points $s_i, s_j \in V$ for which $m(s_i, s_j)$ is a single-variate monomial that divides $m(p, s)$. However, since $m(p, s_i)$ and $m(p, s_j)$ are multivariate, we know that $p \neq s_i$ and $p \neq s_j$. Therefore, one can choose an output assignment $T$ where $t_i = t_j$ for all pairs of input points $s_i, s_j \in V$ such that $m(s_i, s_j)$ is a single-variate monomial that divides $m(p, s)$, while also choosing $t_p \neq t_s$. According to Theorem 3.1, there are multiple minsets for this $T$.

**Corollary 3.13.** If $I(V)$ has a unique reduced Gröbner basis, then $V$ is diagonal-free.

**Proof.** The contrapositive of Theorem 3.12 is “If $V$ corresponds to a unique minset for any output assignment, then $V$ is diagonal-free.” which follows from Corollary 3.5.

**4. Experimental results.** Theorem 3.12 suggests the following heuristic idea that we will test computationally: the smaller the Hamming distance between points in $V$, the smaller the number of minsets. To quantify the Hamming distance between points in $V$, we use the following definition.

**Definition 4.1.** Given an input set $V$, we define $d(V)$ as the average value of the Hamming distance $H(p, q)$ between distinct points $p$ and $q$ of $V$. We call $d(V)$ the internal distance.

**Example 4.2.** Consider $f : \mathbb{F}_2^3 \to \mathbb{F}_2$ given by $f(x_1, x_2, x_3) = x_2 \vee x_1$ or equivalently, $f(x_1, x_2, x_3) = 1 + x_2 + x_2x_3$. To illustrate the definition we consider two different input sets, $V_1 = \{000, 001, 010, 100\}$ and $V_2 = \{000, 101, 110, 011\}$.

The distance between points in $V_1$ is given below.
Similarly, $d(V_2) = 2$. Now, we use $f$ to generate data sets for $V_1$ and $V_2$: $D_1 = \{(000, 1), (001, 1), (010, 0), (100, 1)\}$ and $D_2 = \{(000, 1), (101, 1), (110, 0), (011, 1)\}$. $D_1$ has the unique minset $\{x_2\}$ and $D_2$ has the minsets $\{x_1, x_2\}, \{x_1, x_3\}, \{x_2, x_3\}$.

In summary, $V_1$ has an internal distance of $d(V_1) = 1.5$ and resulted in $\#M(V_1) = 1$ minset. $V_2$ has an internal distance of $d(V_2) = 2$ and resulted in $\#M(V_2) = 3$ minsets.

The following table shows the statistics of all possible input sets with 4 points (there are $\binom{2^3}{4} = 70$ of them). Some of them have the same internal distance and/or number of minsets. This is reported in the following table and a scatter plot is shown in Figure 1.

| $d(V)$ | $\#M(V)$ | number of such $V$’s |
|--------|-----------|----------------------|
| 1.3    | 1         | 6                    |
| 1.5    | 1         | 8                    |
| 1.7    | 1         | 24                   |
| 1.8    | 1         | 10                   |
| 1.8    | 2         | 14                   |
| 2      | 1         | 1                    |
| 2      | 2         | 5                    |
| 2      | 3         | 2                    |

Table 1

Statistics of all 70 possible $V$’s with 4 elements, grouped by internal distance and number of minsets.

Figure 1. Scatter plot of $\#M(V)$ vs $d(V)$ and histogram of $\#M(V)$ for all input sets with 4 points. The area of each circle corresponds to the number of $V$’s that have the same values of $d(V)$ and $\#M(V)$. We can see that as the internal distance increases, the number of minsets can get larger.
The results from Figure 1 are consistent with the heuristic idea that the smaller the distance, the smaller the number of minsets. Now we would like to test two different strategies for generating data, one of which will tend to have small internal distance.

Consider a Boolean function \( f : \mathbb{F}_2^m \rightarrow \mathbb{F}_2 \). A trial will consist of selecting an input set with \( m \) elements, \( V \subseteq \mathbb{F}_2^m \). Then, we consider the data set \( D = \{(s, f(s)) : s \in V\} \) and compute the minsets \( M \). We are interested in the relationship between the internal distance of \( V \), \( d(V) \), and the number of minsets \( \#M(V) \). If we plot the points \((d(V), \#M(V))\) for several trials, we expect to see some type of relationship like in Figure 1. We used two different strategies or sampling schemes to generate the \( m / 2 \) points randomly. We refer to this as the random scheme. We refer to this as the small-distance scheme.

In both cases we get an input set \( V \) with \( m \) points, but the small-distance scheme favours a smaller internal distance.

The Boolean functions we selected for our analysis were fanout-free (that is, each variable appears only once in its Boolean representation). These functions cover the vast majority of functions used in modeling [19, 25, 18, 22, 31, 6, 8, 11, 18]. To keep the simulations tractable, we used Boolean functions \( f : \mathbb{F}_2^4 \rightarrow \mathbb{F}_2 \) such that \(|\text{supp}(f)| \leq 4\). Up to a relabeling of variables and states, there are 9 such functions (not counting the constant functions), given in Table 2.

| Function in polynomial form | Function in Boolean form |
|-----------------------------|--------------------------|
| \( x_1 \) | \( x_1 \) |
| \( x_1 x_2 \) | \( x_1 \land x_2 \) |
| \( x_1 x_2 x_3 \) | \( x_1 \land x_2 \land x_3 \) |
| \( x_1 x_2 x_3 x_4 \) | \( x_1 \land (x_2 \lor x_3) \) |
| \( x_1 x_2 x_4 + x_1 x_2 x_3 x_4 \) | \( x_1 \land x_2 \land x_3 \land x_4 \) |
| \( x_1 x_2 x_3 x_4 + x_1 x_2 x_3 + x_1 x_2 x_4 + x_1 x_2 + x_3 x_4 + x_3 + x_4 \) | \((x_1 \land x_2 \land x_3) \lor x_4 \) |
| \( x_1 x_2 + x_3 x_4 + x_1 x_2 x_3 x_4 \) | \((x_1 \land x_2) \lor x_3 \lor x_4 \) |
| \((x_1 x_2) \lor (x_3 \land x_4) \) | \((x_1 \land x_2) \lor (x_3 \land x_4) \) |

Table 2

Boolean functions used for the computational analysis in Figure 2. These represent all fanout-free functions with up to four variables.

The results of the simulations are shown in Figure 2. As expected, the internal distance \( d(V) \) is smaller when points are generated using the small-distance scheme (blue). Importantly, in the small-distance and random schemes, the smaller the internal distance, the smaller the number of minsets. The histograms compare the number of minsets for both schemes and clearly show that the small-distance scheme results in a smaller number of minsets. These computational results provide a straightforward way to generate data with a small number of minsets, the small-distance scheme.

5. Conclusions and future work. One of the difficulties in data-driven approaches is that there is typically a large number of models that fit the collected data and the known con-
Figure 2. Scatter plots of $\#M(V)$ vs $d(V)$ and histograms of $\#M(V)$ for the functions in Table 2. The scatter plots show that as the internal distance increases, the number of minsets can get larger (blue: small-distance scheme, yellow: random scheme). The histograms show that the small-distance scheme results in an overall smaller number of minsets. For each of the Boolean functions we run 10,000 trials with input sets with $m = 20$ elements (about 2% of the $2^{10}$ possible points).

strains of the system are not sufficient to reduce the pool of candidate models to a manageable size for testing and validation purposes. As each model contains a set of predictions about the network being studied, even small numbers of competing models result in a combinatorial growth in validation experiments to be performed. Thus it is desirable to design experiments in such a way that maximizes the chance that the outputs will increase our understanding of the system. We introduced a method which generates data sets that are guaranteed to result in a unique minimal wiring diagram regardless of what the experimental outputs are. A natural next step is to extend these results to signed minimal wiring diagrams and address the question of existence for this case. The somewhat surprising connection between uniqueness of interpolating polynomial normal forms and unique minsets (i.e. unique minimal wiring diagrams) elucidate the role of polynomial ideals with unique Gröbner bases. While partial results are available in our prior work and in this manuscript, a complete geometric or combinatorial characterization of sets $V \subset \mathbb{F}_p^n$ such that $I(V)$ has a unique reduced Gröbner basis is still an open question whose importance has been emphasized in this work.

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