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Ideals, Big Varieties, and Dynamic Networks

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ABSTRACT. The advantage of using algebraic geometry over enumeration for describing sets related to attractors in large dynamic networks from biology is advocated. Examples illustrate the gains.

Biological applications of dynamical systems can be in discrete spaces like $\{0,1\}^5$, where "1" may code for "on" or "high" or "cancer cell terminated" and "0" may code for "off" or "low" or "cancer cell still going fine." Then the subset

$$***01 := \{00001, 00101, 01001, 01101, 10001, 10101, 11001, 11101\}$$

can be enumerated easily, and the rule for membership is clear: $x_4 = 0, x_5 = 1$.

Nowadays, some dynamic networks on $S := \{0,1\}^d$ (called Boolean networks) are fitted or "learned" or modeled with large d, d being the number of molecules or proteins or variables, using data and combined knowledge from experimentation and literature. The data involved for fitting may be Big Data, a term for large data sets often gathered mechanically ([21]), and the fitting procedures may include machine learning methods that can give complex models. One example is in [9], where a dynamical model of 15 nodes after variable selection was fitted with machine and statistical learning methods to data from motion sensors (see [13], [15], [22] for background on the data).

There are computational advantages in describing sets of interest as *varieties* – sets of roots of multivariate polynomials. Each coordinate gets an indeterminate, so for the set $***01$ above we could describe it as the roots to two polynomials

$$\langle s_4, s_5 - 1\rangle$$

in a ring of polynomials $\mathbb{C}[s_1, s_2, s_3, s_4, s_5]$. This set of two polynomials is the *ideal* for the variety $***01$. For large problems such as the $d = 58$ node example of Section 4, it is useful to use finite field coefficients to speed computations. So with field coefficients in characteristic 2, simply $\{0,1\}$ with mod 2 operations, we have the polynomial ring $F_2[s_1, s_2, s_3, s_4, s_5]$. The elements of $***01$ are the simultaneous roots of

$$\langle s_4, s_5 + 1\rangle.$$

The entire state space $\{0,1\}^d$ has size 2^d, yet it can be described as the roots of only d polynomials, the logarithm of its cardinality:

$$\langle s_1^2 + s_1, \ldots, s_d^2 + s_d\rangle.$$

So useful subsets of a big state space S can sometimes be studied more efficiently with the polynomials that vanish on the subset, rather than by enumeration.

Traditional logical models for dynamics were small and conceptual ([30]), but dynamical models on discrete state spaces have become larger as more data has helped fit and verify more complex interactions (see [18], [19], [26], [27], [28], [32]). Commutative

algebra – the algebra of multivariate polynomials – has become one tool for doing calculations (see [24]). The methods and foundations for using commutative algebra are in [5], whose title this article plays on, and [16]. Software implementations include CoCoA [1], Macaulay2 [12] and Singular [7]. The essential operations for our applications are elimination and primary decomposition.

The new example here is an exact calculation on the network of 58 nodes as described in [33], which first appeared in [32].

1. BOOLEAN NETWORKS.

The traditional Boolean network with values in $\{0,1\}$ at each node is exemplified by the *lac* operon network formulated in [14] and described in [24]. In logical notation the dynamics are

$$\begin{aligned} f_1(x_1,x_2,x_3) &= !u_1 \ \& \ (x_3 \mid u_2) \\ f_2(x_1,x_2,x_3) &= x_1 \\ f_3(x_1,x_2,x_3) &= !u_1 \ \& \ ((x_2 \& u_2) \mid (x_3 \& !x_2)) \end{aligned}$$

where $u_1, u_2 \in \{0,1\}$ are fixed parameters for control that can be set at 0 or 1, "!" means "not" and "|" means "or." Coding Boolean functions as polynomials is a standard procedure, with early foundations in [2], [34]. In practice it can usually be done easily without applying general theory.

A control problem for the *lac* operon is to find values of u_1, u_2 that lead to steady state (fixed point) $x_1x_2x_3 = 111$ (which means the operon is "on"). The problem has a geometric interpretation as follows. Expand the dynamics to $F : \{0,1\}^5 \to \{0,1\}^5$ with $F = (f_1, f_2, f_3, f_4, f_5)$ where $f_4 = u_1$ and $f_5 = u_2$ fix u_1 and u_2 respectively. Now we are looking for subsets of the form $***u_1u_2$ inside the basin of attraction of steady state $111u_1u_2$, where "$*$" is a wild card place holder and u_1, u_2 can be any values. Such a subset will have the property that setting u_1, u_2 at the specified values will drive the system to $(1,1,1,u_1,u_2)$ regardless of the initial values of x_1, x_2, x_3. The map F has four steady states, including one useful one 11101. The basin of attraction of this steady state is all eight points $***01$, so any initial values for $x_1x_2x_3$ with $u_1 = 0, u_2 = 1$ will lead to the "on" steady state. This is a small version of the general control problem for large networks in biology like our main example in Section 4.

Standard software for Boolean networks identifies basins of attraction by complete enumeration, and will solve this problem easily. However, in standard software the number of nodes or coordinate values is limited (typically to around 30 for basin analysis), their values must be 0-1, and the output as a list of elements does not explain what conditions imply membership. For large problems, a geometric approach can be better for computations and for comprehension.

2. BASINS OF ATTRACTION.

A Boolean network with d coordinates or nodes has a state space $\{0,1\}^d$, a d-fold product of logical or off/on or low/high symbols 0 and 1. Let $F = (f_1, \ldots, f_d)$ be an update function on $\{0,1\}^d$, where $f_j : \{0,1\}^d \to \{0,1\}$ is the rule for node j. This map is deterministic, called the synchronous update. For a state $\mathbf{x}$, define the limiting set

$$A_{\mathbf{x}} = \cap_{k=1}^{\infty} \cup_{n=k}^{\infty} \{F^n(\mathbf{x})\}$$

where F^n is the n-fold composition of F. The resulting sets, as $\mathbf{x}$ varies in the state space $\{0,1\}^d$, are the limiting sets or attractor sets of the system. These are fixed points or cycles.

Let B_A be the usual deterministic basin of attraction for an attractor A, the points that eventually hit A:

$$B_A := \cup_{k=1}^{\infty}\{\mathbf{x} : F^k(\mathbf{x}) \in A\} = \lim_{k\to\infty} F^{-k}(A).$$

The main control problem is to find simple conditions for membership of an initial state in the attractor basin B_A, as in the *lac* operon opening example where membership in $B_{\{11101\}}$ was determined by simple conditions $u_1 = 0, u_2 = 1$. These membership rules give the set $***01$ which we call a *cylinder set*, from the probability terminology for product spaces where a few of the coordinates are restricted and others are free.

But biological applications need a randomized version of the map F ([4], [25], [32]), since the timing of the coordinate maps may not be synchronized perfectly in the real world. One type of asynchronous updates, the one we use, proceeds by choosing a node or coordinate j with the uniform probability distribution, then changing current state $\mathbf{x}$ to $\mathbf{x}'$ like:

$$\mathbf{x} = (x_1, \ldots, x_{j-1}, x_j, x_{j+1}, \ldots, x_d) \to (x_1, \ldots, x_{j-1}, f_j(\mathbf{x}), x_{j+1}, \ldots, x_d) = \mathbf{x}'.$$

The resulting process $\mathbf{x}_0, X_1, X_2, X_3, \ldots$ is a Markov chain in state space $\{0,1\}^d$, starting at nonrandom initial configuration $\mathbf{x}_0$ and with random variables X_n for random states or configurations. The probability that X_n is in a set S will be written:

$$P_{\mathbf{x}_0}(X_n \in S).$$

The process has a probability transition matrix of size $2^d \times 2^d$. A 60 node example would be impossible to study with the transition matrix because of its size. Control methods that use a transition matrix ([17]) are not realistic for large Boolean networks.

Define the single coordinate updates on a state $\mathbf{x} = (x_1, \ldots, x_d)$ by

$$F_j(\mathbf{x}) = (x_1, \ldots, x_{j-1}, f_j(\mathbf{x}), x_{j+1}, \ldots, x_d),\ j = 1, 2, \ldots, d.$$

Now with $B_0 = B_A$, F_j^{-1} the inverse of F_j, and B^c the complement of a set B, define the exclusive asynchronous basin of the attractor A by

$$B_i = B_{i-1} \setminus \cup_{j=1}^{d} F_j^{-1}(B_{i-1}^c),\ i = 1, 2, 3, \ldots$$
$$B_{ex,A} := \lim_{i\to\infty} B_i.$$

Probabilistically, this can be described as

$$B_{ex,A} = \{\mathbf{x} : P_{\mathbf{x}}(X_n \in B_A,\ n = 0, 1, 2, 3, \ldots) = 1\}.$$

In words, the points in $B_{ex,A}$ are the states that can never leave the basin of attraction B_A over time under perturbations in the form of asynchronous updates.

The exclusive asynchronous basin $B_{ex,A}$ gives a robust basin for the purpose of targeting useful attractors, and the control problem is characterizing membership in $B_{ex,A}$ with settings on a few nodes.

3. Polynomial Dynamics for Basin Ideals.

An effective way to compute basins of attraction for large networks uses commutative algebra on dynamics written as polynomials, and basins are represented first with their ideals. Then the associated primes of the ideal of the basin lead to simple cylinder sets (sometimes an associated prime will give more than one cylinder), and these give simple conditions for basin membership and clear control strategies by setting values on nodes that appear in the cylinder sets. Although the notion of exclusive asynchronous basin involves

randomization, the polynomial calculations for basins are exact. This differs from methods based on computer simulation of randomized dynamics.

Now we describe an algorithm for finding B_A, using finite field coefficients for speed and memory efficiency. Let A be an attractor of interest, with basin of attraction B_A. We will use twice as many indeterminates as the number of coordinates d. Define the ring of polynomials $R := F_2[s_1, \ldots, s_d, t_1, \ldots, t_d] = F_2[\mathbf{s}, \mathbf{t}]$, and define ideals

$$\begin{aligned} I_{01} &= \langle s_1^2 + s_1, \ldots, s_d^2 + s_d, t_1^2 + t_1, \ldots, t_d^2 + t_d \rangle \\ F_{st} &= \langle f_1(\mathbf{s}) - t_1, f_2(\mathbf{s}) - t_2, \ldots, f_d(\mathbf{s}) - t_d \rangle \\ F_{ts} &= \langle f_1(\mathbf{t}) - s_1, f_2(\mathbf{t}) - s_2, \ldots, f_d(\mathbf{t}) - s_d \rangle \\ I_A &= \cap_{\mathbf{x} \in A} \langle t_1 - x_1, \ldots, t_d - x_d \rangle. \end{aligned}$$

Define the ideal I_1 by

$$I_1 = (F_{st} + I_A + I_{01}) \cap F_2[\mathbf{s}],$$

and define recursively a sequence of ideals $I_2, I_3, I_4, \ldots$ by

$$\begin{aligned} J &= (F_{ts} + I_i + I_{01}) \cap \ F_2[\mathbf{t}] \\ I_{i+1} &= (F_{st} + J + I_{01}) \cap \ F_2[\mathbf{s}], \ \ i = 1, 2, 3, \ldots \end{aligned}$$

Stop the iteration when $I_i \subset I_{i+1}$, an ideal containment condition that shows the reverse containment of varieties $\mathbf{V}(I_{i+1}) \subset \mathbf{V}(I_i)$ – when this happens the basin computation has reached its fixed "point" or fixed and final set. Note that this terminating condition can be established using the division algorithm on polynomials, the varieties themselves need not be examined. This comes from the "ideal membership" property of a Groebner basis – membership can be determined by reducing a polynomial using a Groebner basis ([5]). This is a place where algebraic geometry helps with big varieties.

Theorem 1. *At a positive integer $i^\star$ where $I_{i^\star} = I_{i^\star+1}$, the variety for $I_{i^\star}$ is the basin B_A.*

Proof. We sketch the ideas in a proof. The first elimination step

$$I_1 = (F_{st} + I_A + I_{01}) \cap F_2[\mathbf{s}]$$

gives the polynomials in $\mathbf{s}$ indeterminates on the set of points in $\{0,1\}^d$ that hit A in one step, $F^{-1}(A)$. Seidenberg's Lemma ([16]) shows that the ideal is radical. Adding in the state space set I_{01} guarantees no unwanted points are included after elimination (that is, there are no extra unwanted roots of the polynomials in $\mathbf{s}$ that actually do not map under F_{st} to points in I_A), by the Extension Theorem ([5]). The Extension Theorem requires a small extension to F_2 coefficients (not an algebraically closed field) but adding the I_{01} ideal makes it valid ([8]).

Then I_i is the ideal for points $\{\mathbf{x} \in \{0,1\}^d : F^{2i-1}(\mathbf{x}) \in A\}$, the $(2i-1)^{st}$ inverse image. When the inverse images become fixed, the set is fixed at the basin of attraction. □

A similar algorithm can compute the exclusive asynchronous basin $B_{ex,A}$. It is also based on elimination, and terminates when an ideal containment condition is satisfied.

4. EXAMPLE.

A 60-node Boolean model for leukemia was formulated in [32], and a version was studied in [25] and [33]. The model is given in Tables 1 and 2 on 58 nodes, two receptors that play no role in Apoptosis being removed. Apoptosis is an outcome where the cancer cell is terminated, and its onset is coded with a node Apoptosis hitting value 1. The goal is

to find out how to make that happen by setting values on other nodes that may be subject to intervention or control.

The model has 7 attractors, which are all cycles of length 4. Three of them have Apoptosis fixed at 1, so these are the ones to study first. Only one has a nonempty exclusive asynchronous basin of attraction, and it is the 4-cycle below, with the Apoptosis coordinate 48 underlined:

$$\{0011101110111111011001011101011110111011101100\underline{1}0010101010,$$
$$0111101110111111011001011101011110111011101100\underline{1}0010101010,$$
$$1111101110111111011001011101011110111011101100\underline{1}0010101010,$$
$$1011101110111111011001011101011110111011101100\underline{1}0010101010\}.$$

The exclusive asynchronous basin is given by the union of two cylinders, found with the associated primes of its ideal. The membership conditions are

S1P^{52}=0, Ceramide^{39}=1, sFas^{38}=0, Fas^{37}=1, FasT^{36}=1, FasL^{35}=1, TBET^{26}=1, IL2RB^{19}=1, IL2RBT^{18}=1, NFKB^{14}=1, PI3K^{13}=1, ERK^{12}=1, MEK^{11}=1, GAP^{10}=0, RAS^{9}=1, GRB2^{7}=1

S1P^{52}=0, Ceramide^{39}=1, sFas^{38}=0, Fas^{37}=1, FasT^{36}=1, FasL^{35}=1, NFKB^{14}=1, PI3K^{13}=1, PDGFR^{3}=1.

in addition to the fixed values 101010 on the last 6 signaling nodes 53-58 specified in Table 2.

In the wild card notation, they can be written:

1-12	13-25	26-34	35-52
* * * * * * 1 * 1 0 1 1	1 1 * * * 1 1 * * * * * *	1 * * * * * * * *	1 1 1 0 1 * * * * * * * * * $\underline{*}$ * * * 0
* * 1 * * * * * * * * *	1 1 * * * * * * * * * * *	* * * * * * * * *	1 1 1 0 1 * * * * * * * * $\underline{*}$ * * * * 0

So the two cylinder sets above specify the nodes and their initial settings to guarantee a robust evolution towards Apoptosis.

The size of the asynchronous exclusive basin is easy, from inclusion-exclusion: $2^{58-22}+2^{58-15}-2^{58-23}=8,830,452,760,576$. Yet finding and describing the basin did not require enumeration.

There are two out of seven attractors that cycle in the Apoptosis value, and both have empty exclusive asynchronous basins. (Any appearance of Apoptosis in the original model [32] would shut the cell down totally, so such cycles do not appear in that model.)

5. Generalized State Spaces.

It is not uncommon for network nodes to have values more general than $\{0,1\}$, and the algebraic methods generalize easily. The only changes to the Boolean methodology are to get the transition functions in polynomial form, and to write the state space of the system as the roots of an ideal.

The "ABC" dynamic model for flowering of the plant species *Arabidopsis thaliana* is explained in [29] and transition functions are given in Table 3.

Consider the following indicator polynomials:

$$l_i = (x_i^2 - 3x_i + 2)/2$$
$$m_i = -x_i^2 + 2x_i$$
$$h_i = (x_i^2 - x_i)/2,\ i = 1,2,3.$$

	nodes 1-29	logical rule
1	CTLA4	TCR
2	TCR	Stimuli & !CTLA4
3	PDGFR	S1P | PDGF
4	FYN	TCR | IL2RB
5	LCK	CD45 | ((TCR | IL2RB) & !ZAP70)
6	ZAP70	LCK & !FYN
7	GRB2	IL2RB | ZAP70
8	PLCG1	GRB2 | PDGFR
9	RAS	(GRB2 | PLCG1) & !GAP
10	GAP	(RAS | (PDGFR & GAP)) & !(IL15 | IL2)
11	MEK	RAS
12	ERK	MEK & PI3K
13	PI3K	PDGFR | RAS
14	NFKB	(TPL2 | PI3K) | (FLIP & TRADD & IAP)
15	NFAT	PI3K
16	RANTES	NFKB
17	IL2	(NFKB | STAT3 | NFAT) & !TBET
18	IL2RBT	ERK & TBET
19	IL2RB	IL2RBT & (IL2 | IL15)
20	IL2RAT	IL2 & (STAT3 | NFKB)
21	IL2RA	IL2 & IL2RAT & !IL2RA
22	JAK	(IL2RA | IL2RB | RANTES | IFNG) & !(SOCS | CD45)
23	SOCS	JAK & !(IL2 | IL15)
24	STAT3	JAK
25	P27	STAT3
26	TBET	JAK | TBET
27	CREB	ERK & IFNG
28	IFNGT	TBET | STAT3 | NFAT
29	IFNG	((IL2 | IL15 | Stimuli) & IFNGT) & !(SMAD | P2)

TABLE 1. Boolean model of T-LGL dynamics from [33].

	nodes 30-58	logical rule
30	P2	(IFNG | P2) & !Stimuli2
31	GZMB	(CREB & IFNG) | TBET
32	TPL2	TAX | (PI3K & TNF)
33	TNF	NFKB
34	TRADD	TNF & !(IAP | A20)
35	FasL	STAT3 | NFKB | NFAT | ERK
36	FasT	NFKB
37	Fas	FasT & FasL & !sFas
38	sFas	FasT & S1P
39	Ceramide	Fas & !S1P
40	DISC	FasT & ((Fas & IL2) | Ceramide | (Fas & !FLIP))
41	Caspase	(((TRADD | GZMB) & BID) & !IAP) | DISC
42	FLIP	(NFKB | (CREB & IFNG)) & !DISC
43	A20	NFKB
44	BID	(Caspase | GZMB) & !(BclxL | MCL1)
45	IAP	NFKB & !BID
46	BclxL	(NFKB | STAT3) & !(BID | GZMB | DISC)
47	MCL1	(IL2RB & STAT3 & NFKB & PI3K) & !DISC
48	Apoptosis	Caspase
49	GPCR	S1P
50	SMAD	GPCR
51	SPHK1	PDGFR
52	S1P	SPHK1 & !Ceramide
53	Stimuli	1
54	Stimuli2	0
55	PDGF	1
56	CD45	0
57	IL15	1
58	TAX	0

TABLE 2. Boolean model of T-LGL dynamics from [33].

One can check that for $\mathbf{x} \in \{0,1,2\}^3$, $l_i(\mathbf{x}) = I_{\{0\}}(x_i)$, where $I_A(x)$ is the usual indicator function notation for the set A with value 1 on the set and 0 off the set. That is, l_i serves

a b c	f_1 f_2 f_3
0 0 0	0 0 0
0 0 1	0 0 1
0 0 2	0 1 1
0 1 0	1 0 1
0 1 1	0 0 2
0 1 2	0 1 2
1 0 0	1 0 0
1 0 1	0 0 0
1 0 2	0 1 0
1 1 0	2 0 0
1 1 1	0 0 0
1 1 2	0 1 0
2 0 0	1 1 0
2 0 1	0 1 0
2 0 2	0 1 0
2 1 0	2 1 0
2 1 1	0 1 0
2 1 2	0 1 0

TABLE 3. Table of update functions $F = (f_1, f_2, f_3)$ from Table 2 of [29].

as an indicator function of the low value 0 for variable i. Similarly, m_i and h_i are indicator functions for medium and high values on the domain S. These functions are ternary analogs of "x_i" which works as an indicator function $I_{\{1\}}(x_i)$ in the 0-1 valued Boolean case.

We can represent f_1 from Table 3 in polynomial form as

$$f_1 = 2 \cdot (m_1 \cdot m_2 \cdot l_3 + h_1 \cdot m_2 \cdot l_3) + 1 \cdot (l_1 \cdot m_2 \cdot l_3 + m_1 \cdot l_2 \cdot l_3 + h_1 \cdot l_2 \cdot l_3)$$

and similarly for f_2, f_3. The use of polynomial indicator functions for defining subsets of domains is developed in [23] for similar applications in experimental design. The 3-level state space is the variety of the radical ideal

$$I_{012} = \langle s_1^3 - 3s_1^2 + 2s_1, s_2^3 - 3s_2^2 + 2s_2, \ldots, s_d^3 - 3s_d^2 + 2s_d \rangle$$

in the ring $\mathbb{C}[s_1, \ldots, s_d]$.

In the polynomial framework, one can quickly compute big biology examples with node values in $\{0, 1, 2\}$ like the 13-node flowering example of [3] (and further clarified in [10]). We have also done the four-level cancer example in [11].

In conclusion, sets related to attractors in discrete dynamics can be big and yet still have manageable ideals. Checking containment of sets can be done with the ideals. Probabilistic dynamics can be done with ideals. Sets can be represented efficiently and intuitively by means of associated prime ideals. And general node values beyond $\{0, 1\}$ are not a problem.

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