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Switching Stomatal Aperture Dynamics Through Computationally Algebraic Node Control

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ABSTRACT

This article provides an in-depth overview of the guard cell signaling network and its role in regulating stomatal aperture in plants via computational algebra. Stomatal pores in plant leaves allow for gas exchange but also result in water loss through transpiration, making the regulation of stomatal aperture critical for plant water balance, photosynthesis, and stress response. The guard cell signaling network is a complex regulatory network that controls the opening and closing of stomatal pores in plants. It consists of a variety of signaling pathways, including those involving calcium, nitric oxide, and second messengers such as Cyclic guanosine monophosphate (cGMP) and cyclic ADP-ribose (cADPR). The article discusses the interactions between these pathways and the mechanisms by which guard cells respond to environmental cues such as light, CO2 levels, and humidity. Overall, this article provides valuable insights into the regulatory structure of the guard cell signaling network and its potential applications in optimizing plant traits.

1. INTRODUCTION

Control of stomatal aperture is essential for plant water balance, photosynthesis, and stress response (Yoshida et. al., 2015). While stomatal movements are regulated by complex signaling networks, existing interventions lack mechanistic precision (Rodrigues and Shan, 2022). Boolean modeling offers a framework for identifying potential regulatory nodes that finely tune aperture dynamics (Saandatpour et. al., 2011) and (Albert, 2003). The node control technique systematically uncovered control targets able to modify attractors when modulated (Su and Pang, 2023). By fixing values of nodes within minimum control sets, dynamics constrain to alternative attractors (Ruths and Ruths, 2014), representing implementable interventions. (Saadatpour et al., 2010) constructed an asynchronous Boolean model of guard cell signaling. Leveraging this established network, we aimed to:

- Apply node control analysis to identify potential regulators of stomatal aperture.
- Recover known and discover novel control targets within the boolean model.
- Propose experimentally testable hypotheses about key nodes mediating aperture control.

More broadly, we sought to demonstrate how integrating Boolean modelling with systems control methods may inform

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development of mechanism-based interventions for biological systems.

2. MATERIALS AND METHODS

The guard cell is a specialized cell found in the leaves of plants that plays a critical role in regulating gas exchange and water loss. The behavior of guard cells is controlled by a complex network of molecular interactions, and understanding the dynamics of this network is important for developing strategies to improve plant water use efficiency (Kim, 2010). To study the behavior of the guard cell network, researchers have developed a Boolean model that represents the interactions between key molecules involved in the control of stomatal opening and closing (Roelfsema and Hedrich, 2005). A Boolean network is a type of dynamical system that operates in discrete time and variable states (Kauffman, 1969). It consists of a collection of binary variables, each taking values of either 0 or 1. The network is defined by a function $F = (f_1, \dots, f_n): \{0,1\}^n \to \{0,1\}^n$ where each component function $f_i: \{0,1\}^n \to \{0,1\}$ is a Boolean function that determines how the future value of the *i*-th variable depends on the present values of the other variables. This model consists of a set of Boolean equations that describe the behavior of each node in the network. Leveraging on the reconstructed network of (Saadatpour et. al., 2010) as shown in Figure 1, the boolean model equation are;

$$y_1 = ADPRc, y_2 = CIS, y_3 = Ca2, y_4 = Ca2ATP, y_5 = GC, y_6 = InsP3, y_7 = KAP, y_8 = KEV, y_9 = NO, y_{10} = NOS, y_{11} = PLC, y_{12} = cADPR, y_{13} = cGMP \quad (1)$$

Following the above assumptions, the boolean model equation from (Saadatpour et. al., 2010) becomes;

$$f_1 = y_9$$
$$f_2 = y_{12} \wedge y_{13} \vee y_6$$
$$f_3 = y_2 \wedge \neg y_4$$
$$f_4 = y_3$$
$$f_5 = y_9$$
$$f_6 = y_{11}$$
$$f_7 = \neg y_3$$
$$f_8 = y_3$$
$$f_9 = y_{10}$$
$$f_{10} = y_3$$
$$f_{11} = y_3$$
$$f_{12} = y_1$$
$$f_{13} = y_5$$

(2)

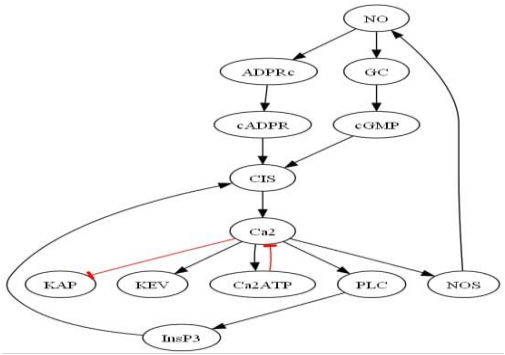

Figure 1: Guard Cell Signalling Pathway see (Saadatpour et. al., 2010)

The Boolean model used in studying the guard cell network represents logical operations using certain symbols. The ampersand symbol (∧) corresponds to the logical AND operation, which requires the combination of multiple inputs for activation. The pipe symbol (∨) corresponds to the logical OR operation, which allows for activation by either of two independent inputs. The tilde symbol (¬) corresponds to the logical NOT operation, which represents negative regulation that inactivates the target (Roelfsema, 2005). Figure 1 displays the wiring diagram of the reconstructed network of (Saadatpour et. al., 2010).

By endowing the set $\{0,1\}$ with the structure of a finite field using standard addition and multiplication, denoted as $F_2 = \{0,1\}$, the functions $f_i : \mathbb{F}_2^n \to \mathbb{F}_2$ can be expressed as polynomials over F_2. Consequently, the dynamical system $F = (f_1, \dots, f_n) : \mathbb{F}_2^n \to \mathbb{F}_2^n$ can be represented as a polynomial dynamical system, which is described in (Murrugarra et. al., 2016). This polynomial representation of Boolean networks is a valuable tool for analyzing their dynamics. To transform Boolean functions into polynomials, we follow a set of rules that govern how Boolean operations are computed modulo 2 in $F_2[y_1, \dots, y_n]$. Specifically, the logical AND operation between variables x and y, denoted by $x \wedge y$, is equivalent to their product, xy. The logical OR operation, denoted by $x \vee y$, is equivalent to their sum plus their product, $x + y + xy$. The squaring of a variable x is equivalent to itself, $x^2 = x$. The multiplication of a variable x by a scalar λ is equivalent to 0 for any scalar $\lambda \in \Re$, $\lambda x = 0$. Finally, the logical NOT operation, denoted by $\neg x$, is equivalent to 1 plus the variable $x, \neg x = 1 + x$. Applying these rules to the network yields a set of polynomials that describe the dynamics of the system.

$$
\begin{aligned}
f_1 &= y_9 \\
f_2 &= y_6 y_{12} y_{13} + y_6 + y_{12} y_{13} \\
f_3 &= y_2(1 + y_4) = y_2 + y_2 y_4 \\
f_4 &= y_3 \\
f_5 &= y_9 \\
f_6 &= y_{11} \\
f_7 &= 1 + y_3 \\
f_8 &= y_3 \\
f_9 &= y_{10} \\
f_{10} &= y_3 \\
f_{11} &= y_3 \\
f_{12} &= y_1 \\
f_{13} &= y_5
\end{aligned}
$$

(3)

Identifying attractors is a crucial step in understanding and controlling complex systems, and computational algebra provides useful tools for doing so. See (Veliz-Cuba et. al. 2010) and (Veliz-Cuba et. al. 2014). To identify the steady states of the network, we need to solve a system of equations where $f_i = y_i$ for each node i in the network. This means we are looking for the roots of a set of equations $g_1 = 0$, where $g_i = f_i - y_i$. By solving this system of equations, we can determine the possible steady states of the network and gain insights into the underlying mechanisms that govern its behavior.

$$
\begin{aligned}
g_1 &= y_9 - y_1 \\
g_2 &= y_6 y_{12} y_{13} + y_6 + y_{12} y_{13} - y_2 \\
g_3 &= y_2 + y_2 y_4 - y_3 \\
g_4 &= y_3 - y_4 \\
g_5 &= y_9 - y_5 \\
g_6 &= y_{11} - y_6 \\
g_7 &= 1 + y_3 - y_7 \\
g_8 &= y_3 - y_8 \\
g_9 &= y_{10} - y_9 \\
g_{10} &= y_3 - y_{10} \\
g_{11} &= y_3 - y_{11} \\
g_{12} &= y_1 - y_{12} \\
g_{13} &= y_5 - y_{13}
\end{aligned}
$$

(4)

As the system is non-linear, traditional methods such as Gaussian elimination cannot be used to solve it. However, computational algebra provides an alternative approach by encoding the solutions as an algebraic object known as an ideal of polynomials. In our case, the ideal is represented as $I = \{g_1, g_2, g_3, g_4, g_5, g_6, g_7, g_8, g_9, g_{10}, g_{11}, g_{12}, g_{13}\}$. We can then seek a simpler representation of this ideal by finding its Gröbner basis (Cox, 1998) using mathematical software tools like (Sagemath, 2021). By finding the

Gröbner basis of the ideal, we obtain a simpler system that has the same solutions as the original system. This approach provides a powerful tool for solving non-linear systems and understanding their behavior. After solving the above equation (4), we arrive at;

$g_1 = 0 \quad g_2 = 0 \quad g_3 = 0$
$g_4 = 0 \quad g_5 = 0 \quad g_6 = 0$
$g_7 = 1 \quad g_8 = 0 \quad g_9 = 0$
$g_{10} = 0 \; g_{11} = 0 \; g_{12} = 0$
$g_{13} = 0$

(5)

Hence 0000001000000 is a steady state of the network.

a. Node Control

One approach to identifying control targets in this network is the node control method. This method involves analyzing the structure of the network and identifying the minimum set of nodes that must be controlled to achieve a desired outcome.

Let us consider a node x_i in the wiring diagram W. We can encode the control of this node, which can be either a knock-out or a constant expression, using the function.

$F_j(y, u_i^-, u_i^+) \coloneqq (u_i^- + u_i^+ + 1)f_j(y) + u_i^+ \; \forall \; i, j = 1, \dots, n$ (6)

where $f_j(y)$ represents the Boolean function at node j see (Murrugarra, 2016). By setting u_i^- and u_i^+ to all possible values in F_2^2, we obtain the following control settings:

- If $u_i^- = 0$ and $u_i^+ = 0$ then $F_j(y, 0, 0) = f_j(y)$, indicating that the control is not active.
- If $u_i^- = 1$ and $u_i^+ = 0$ then $F_j(y, 1, 0) = 0$, representing the knock-out of node y_j.
- If $u_i^- = 0$ and $u_i^+ = 1$ then $F_j(y, 0, 1) = 1$, representing the constant expression of node y_j.
- If $u_i^- = 1$ and $u_i^+ = 1$ then $F_j(y, 1, 1) = f_j(y_1, \dots, y_m) + 1$, which changes the Boolean function of node j to its negative value, but this might not be a relevant case of control.

Therefore, by manipulating u_i^- and u_i^+, we can control the behavior of node y_i and study the dynamics of the network under different conditions (Chaves et. al., 2005). In the context of the guard cell network, these outcomes might include increasing water use efficiency or improving drought tolerance. To apply node control analysis to the guard cell model, we first convert the Boolean equations into a set of linear equations (3) in the form

$F_j(y, u_i^-, u_i^+) - y_j = 0$ (7)

We are going to use computational algebra to identify the minimum set of nodes that must be controlled to achieve $y_3 = 1$, which is a potential node control that will block the undesired state. Hence

$(u_1^+ + u_1^- + 1)y_9 + u_1^+ - y_1 = 0$
$(u_2^+ + u_2^- + 1)(y_6 y_{12} y_{13} + y_6 + y_{12} y_{13}) + u_2^+ - y_2 = 0$
$(u_3^+ + u_3^- + 1)(y_2 + y_2 y_4) + u_3^+ - y_3 = 0$
$(u_4^+ + u_4^- + 1)y_3 + u_4^+ - y_4 = 0$
$(u_5^+ + u_5^- + 1)y_9 + u_5^+ - y_5 = 0$
$(u_6^+ + u_6^- + 1)y_{11} + u_6^+ - y_6 = 0$
$(u_7^+ + u_7^- + 1)(1 + y_3) + u_7^+ - y_7 = 0$
$(u_8^+ + u_8^- + 1)y_3 + u_8^+ - y_8 = 0$
$(u_9^+ + u_9^- + 1)y_{10} + u_9^+ - y_9 = 0$
$(u_{10}^+ + u_{10}^- + 1)y_3 + u_{10}^+ - y_{10} = 0$
$(u_{11}^+ + u_{11}^- + 1)y_3 + u_{11}^+ - y_{11} = 0$
$(u_{12}^+ + u_{12}^- + 1)y_1 + u_{12}^+ - y_{12} = 0$
$(u_{13}^+ + u_{13}^- + 1)y_5 + u_{13}^+ - y_{13} = 0$

(8)

In Equation 8, we can find all the parameter values that lead to a steady state where Ca^{2+} is ON. Our objective is to identify the parameter values for which this system of equations has no solution. However, given that each node can have one of three possible states (no control, deletion, or constant expression), there are a total of 3^{13} networks that need to be analyzed. Hence, performing an exhaustive search is computationally challenging (Katebi et. al., 2020).

Fortunately, computational algebra (groebner basis of the ideals) offers an alternative approach that enables us to identify the parameter combinations that prevent the disease states from being fixed points of the system. The parameter combinations are enclosed in brackets and consist of entries that are equal to zero which includes;

$\{u_4^- = 1, u_{13}^+ = 1, u_1^+ = 1\}, \{u_5^+ = 1, u_{12}^+ = 1, u_4^- = 1\}$
$\{u_5^- = 1, u_4^- = 1, u_1^+ = 1\}, \{u_{12}^+ = 1, u_4^- = 1, u_{13}^+ = 1\}$
$\{u_{10}^+ = 1, u_4^- = 1\}, \{u_9^+ = 1, u_4^- = 1\}$
$\{u_4^- = 1, u_{11}^+ = 1\}, \{u_4^- = 1, u_2^+ = 1\}$
$\{u_4^- = 1, u_6^+ = 1\}$ (9)

However, identifying the minimum set of control targets is not the only criterion for evaluating control targets. Researchers must also consider whether the predicted control targets are biologically plausible based on existing knowledge of the network. This involves considering factors such as the functional role of each node in the network, the degree to which each node is affected by external factors such as light and temperature, and the known interactions between nodes.

In this model, all attractors are steady states, which means that the basin sizes include the steady states themselves. However, it's important to note that node $y_3 = Ca2$, which corresponds to Ca^{2+}, is a conceptual node and doesn't affect network control. Therefore, it is not a relevant solution for our purposes. Overall, the node control method provides a powerful tool for identifying control targets in complex biological networks such as the guard cell network. However, researchers must carefully evaluate predicted control targets based on biological knowledge to ensure that they are relevant and actionable.

Table 1: Control Nodes for the Gaurd Cell Signalling Network

Solution	Control Targets	Attractor	Bazin Size (%)
u_4^- u_6^+	$Ca2ATP = OFF$ $InsP3 = ON$	1110111111101	100
u_4^- u_2^+	$Ca2ATP = OFF$ $CIS = ON$	1110111111101	100
u_4^- u_{11}^+	$Ca2ATP = OFF$ $PLC = ON$	1110111111101	100
u_9^+ u_4^-	$NO = ON$ $Ca2ATP = OFF$	1110111111101	100
u_{10}^+ u_4^-	$NOS = ON$ $Ca2ATP = OFF$	1110111111101	100
u_{12}^+ u_4^- u_{13}^+	$cADPR = ON$ $Ca2ATP = OFF$ $cGMP = ON$	1110111111101	100
u_5^+ u_4^- u_1^+	$GC = ON$ $Ca2ATP = OFF$ $ADPRc = ON$	1110111111101	100
u_5^+ u_{12}^+ u_4^-	$GC = ON$ $cADPR = ON$ $Ca2ATP = OFF$	1110111111101	100
u_4^- u_{13}^+ u_1^+	$Ca2ATP = OFF$ $cGMP = ON$ $ADPRc = ON$	1110111111101	100

3. RESULT

Stomatal pores in plant leaves allow for gas exchange, but also result in water loss through transpiration. Therefore, the regulation of stomatal aperture is critical for plant water balance, photosynthesis, and stress response. The opening and closing of stomatal pores are regulated by guard cells, which are specialized cells that surround the stomatal pore (Hetherington and Woodward, 2003). Guard cells sense environmental cues, such as light, CO_2 levels, and humidity, and respond by changing their shape and volume, resulting in either stomatal opening or closure. The guard cell signaling network is a complex regulatory network that controls the opening and closing of stomatal pores in plants. It consists of a variety of signaling pathways, including those involving calcium, nitric oxide, and second messengers such as cGMP and cADPR (Li et. al., 2019). The interactions between these pathways are complex and not well understood. In this article, we provided an overview of the guard cell signaling network and its role in regulating stomatal aperture in plants, using approaches, such as Boolean modeling and node control analysis, to identify potential control targets within the network.

Calcium is a critical signaling molecule in the guard cell signaling network. It plays a key role in regulating stomatal aperture by controlling the opening and closing of ion channels in the guard cell plasma membrane. In response to environmental cues, guard cells increase their cytosolic calcium concentration, which leads to the activation of downstream signaling pathways that ultimately result in either stomatal opening or closure. Calcium is stored in two organelles in the guard cells - the endoplasmic reticulum (ER) and the vacuole. Calcium release from the ER is mediated by inositol triphosphate (InsP3) and cyclic ADP-ribose (cADPR), which are produced in response to phospholipase C (PLC) and ADP-ribosylcyclase (ARC) activity, respectively. Calcium release from the vacuole is mediated by the vacuolar calcium channel (VCC). Calcium extrusion is mediated by the plasma membrane Ca2+-ATPase and the Ca2+/H+ exchanger (CAX1) (MacRobbie, 2006).

Based on the results obtained from Boolean modeling and node control analysis, several potential control targets within the guard cell signaling network have been identified.

- Nitric Oxide Signaling: Nitric oxide (NO) is a key signaling molecule that plays a critical role in regulating stomatal aperture. Fixing NOS (nitric oxide synthase) or NO while constraining Ca2+ ATPase (a calcium pump) can enable attractor switching, suggesting that these nodes play a role in regulating calcium dynamics that ultimately control stomatal aperture.
- Phosphoinositide Signaling: Manipulating components upstream of calcium, such as PLC, CIS (constitutive photomorphogenic 1 interacting protein), and InsP3, can allow attractor modification when combined with fixing Ca2+ ATPase. This aligns with current knowledge of how phosphor inositide signaling and cGMP/cADPR mediate changes in cytosolic calcium levels during stomatal movements.
- Second Messengers: Targeting second messengers like cGMP, cADPR, and InsP3 in conjunction with suppressing Ca2+ ATPase activity may be a potential control strategy. These calcium mediators

are well-positioned to finely tune aperture by integrating various hormonal and environmental signals.

- Calcium Homeostasis: The frequent appearance of Ca2+ ATPase in the minimum control sets highlights the centrality of calcium homeostasis in governing stomatal behavior. Strict control of calcium pumping and extrusion appears critical for modulating apertures.

These potential control targets provide valuable insights into the activity of key components in the guard cell signaling network and may help to inform further research into the regulation of stomatal aperture in plants.

4. CONCLUSION

The guard cell signaling network is a complex regulatory network that controls stomatal aperture in plants. Calcium, nitric oxide, and second messenger pathways are critical components of this network, and recent studies have used systems biology approaches, such as Boolean modeling and node control analysis, to identify potential control targets within the network. Prior study (Dinwoodie, 2016) also identified control targets using basin cylinders within asynchronous models. Though differing assumptions yield insights, experimentation validates predictions, refining conceptual insights into purposeful network interventions. Iteratively refining computational analyses via experimentation transforms conceptual insights into manipulated outcomes. This methodology illustrates a blueprint for intervening in biological networks to realize solutions - a rigorous yet humble process guiding ethical action.

Appendix

Table 2: Boolean Transition Function (Rules)

Node	Boolean Rule
ADPRc*	NO
CIS*	cADPR AND cGMP OR InsP3
Ca^{2+*}	CIS AND NOT Ca^{2+}ATP
Ca^{2+}ATP	Ca^{2+}
GC*	NO
InsP3	PLC
KAP*	NOT Ca^{2+}
KEV*	Ca^{2+}
NO	NOS
NOS*	Ca^{2+}
PLC*	Ca^{2+}
cADPR*	ADPRc
cGMP*	GC

Table 3: Nodes and their corresponding gene names

Abbreviation	Full Name
ADPRc	ADP-ribosyl cyclase
CIS	Ca2+ influx to the cytosol
Ca^{2+}	Calcium ions
Ca^{2+} ATP	Calcium ATPase
GC	Guanylyl cyclase
KAP	K+ efflux antiporter
NO	Nitric oxide
PLC	Phospholipase C
InsP3	Inositol trisphosphate
KEV	K^{+} efflux vacuolar channel
NOS	Nitric oxide synthase
cADPR	Cyclic ADP-ribose
cGMP	Cyclic guanosine monophosphate

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