

International Journal of Mathematical Analysis and Modelling

**(Formerly Journal of the Nigerian Society
for Mathematical Biology)**

Volume 6, Issue 2 (Oct.-Nov.), 2023

ISSN (Print): 2682 - 5694

ISSN (Online): 2682 - 5708

Towards mechanism-based interventions for auxin signaling: application of algebraic edge control to a Boolean network model

C.O. Kayoh^{*†} and I.J. Ugbene^{†‡}

Abstract

This study developed a Boolean network model representing auxin signaling dynamics. Control techniques identified five (5) interactions that, when applied, may modulate auxin signaling dynamics. Interpreting mechanisms by which these predicted targets regulates auxin responses generated testable hypotheses regarding novel regulators. While the simplified model omits molecular details, validating predictions experimentally can inform iterative model refinements that deepen mechanistic understanding. Integrating computational modeling, control strategies and experiment-model cycles thus shows promise for developing target-based auxin interventions. This framework may inform applications beyond auxin signaling, illustrating a blueprint for progressing from abstract biological representations to meaningful mechanisms and practical tools for purposefully manipulating complex systems.

Keywords: Boolean network; Auxin signaling dynamics; control techniques; validating predictions; experiment-model cycles; target-based interventions.

1 Introduction

Auxin signaling coordinates nearly all aspects of plant growth and development by regulating gene expression, cell division and expansion [16]. Precisely controlling auxin responses therefore holds promise for optimizing plant productivity, stress tolerance and trait modification [24]. However, the molecular mechanisms underlying auxin perception, transmission and response remain incompletely understood [8]. Systems-level modeling approaches offer a means to gain novel mechanistic insights into auxin signaling [2].

Boolean modeling provides a simplified yet effective framework for capturing network dynamics [13]. The model output suggests potential regulatory modules as candidate intervention targets [3]. However, traditional boolean models lack rigor in identifying such controllable nodes [17]. The algebraic edge control approach developed by Murrugarra et al. computationally identifies control targets within boolean networks in a systematic manner [21]. Applying this method to available auxin signaling boolean models could reveal potential mechanisms for specifically modulating auxin responses [9].

Arellano et al. constructed a boolean model of auxin signaling components and their interactions in plants [3]. Triggered by auxin, the network incorporates perception, signal transmission and response elements, resembling auxin-mediated regulation of genes [12]. Leveraging this model, we aim at applying algebraic edge control analysis to predict potential regulators of auxin responses within the boolean network, generate experimentally testable hypotheses regarding candidate mediating edges, interpret predicted controls based on current knowledge to evaluate their biological plausibility and usefulness

*Corresponding Author. E-mail: kayohclinton@gmail.com

†Department of Mathematics, Federal University of Petroleum Resources, Effurun, Nigeria.

‡E-mail: ugbene.ifeanyi@fupre.edu.ng

and provide a foundation for iteratively refining model predictions through experiments, progressing towards mechanism-based auxin interventions.

The identified control targets are analyzed based on known functions of edges in auxin pathways [15]. Novel predictions generate experimentally verifiable hypotheses [5, 25]. Rigorously validating predictions through knockout and overexpression experiments then motivates refinement of model structures and parameters [4, 6]. This closed-loop process between modeling and experimentation may ultimately facilitate targeted manipulation of auxin responses [1, 20].

In all, applying algebraic edge control analysis to Arellano et al.'s auxin signaling Boolean model [3] aims to identify potential regulators of auxin responses within the network. Experimentally investigating predicted controls can reveal mechanisms underlying auxin signaling and motivate rational intervention design. This integrated framework generally enables mechanism-based innovation for biological systems [14].

2 Materials and Methods

A Boolean network model is a discrete dynamical system that captures the temporal evolution of a biological system [10, 19]. It consists of:

- A set of nodes representing molecular components (genes, proteins, etc.). Each node can be in one of two states: ON (1) or OFF (0) [10].
- A Boolean transition function for each node that determines its next state based on the current states of other nodes. This function is defined using Boolean operations (AND, OR, NOT) [19]. For a network with n nodes $\{y_1, y_2, \dots, y_n\}$, the Boolean transition function for node y_i is:

$$y_i(t+1) = f_i(y_1(t), y_2(t), \dots, y_n(t))$$

- A wiring diagram that specifies which nodes influence which others based on known or inferred interactions between components [10].
- A state transition table that lists the next state of each node for every possible combination of the network's states. From this table, temporal trajectories can be simulated *in silico* [19].

The transition functions are typically specified based on biological knowledge of the system, and calibrated to optimize how well model outputs match experimental observations. The Boolean abstraction, though simplistic, can reveal complex dynamical behaviors that provide insight into the system's emergent properties [10]. Arellano et al.'s Boolean auxin signaling model captures key dynamics of the pathway using a simplified, logical abstraction [3]. The model consists of 9 nodes (y_1 to y_9) representing major molecular components (see Appendix table 2), that includes:

$$\begin{aligned} y_1 &= ARF & y_2 &= AUXINS \\ y_3 &= IAA & y_4 &= JKD \\ y_5 &= MGP & y_6 &= PLT \\ y_7 &= SCR & y_8 &= SHR \\ y_9 &= WOX \end{aligned} \tag{1}$$

The Boolean transition function for node y_i is given by:

$$y_i(t+1) = f_i(y_1(t), y_2(t), \dots, y_9(t)) \tag{2}$$

Where f_i represents the boolean transition function (see Appendix table 2) determining y_i 's state from the states of other nodes at time t , in a more specific form we get;

$$\begin{aligned} f_1 &= \neg y_3 \\ f_2 &= y_2 \\ f_3 &= \neg y_2 \\ f_4 &= y_7 \wedge y_8 \\ f_5 &= y_7 \wedge y_8 \wedge \neg y_9 \\ f_6 &= y_1 \\ f_7 &= \neg y_5 \wedge y_7 \wedge y_8 \vee y_4 \wedge y_7 \wedge y_8 \\ f_8 &= y_8 \\ f_9 &= y_1 \wedge y_7 \wedge y_8 \wedge y_9 \vee y_1 \wedge \neg y_5 \wedge y_7 \wedge y_8 \end{aligned} \quad (3)$$

This model structure - comprised of nodes, interactions and update rules - allows simulating the temporal dynamics of auxin signaling under logical abstraction [11]. Though simple, the model recapitulates qualitative system-level properties while illuminating regulatory mechanisms [19]. The network diagram of the auxin signaling network [3], is displayed in Figure 1. The functions that describe the interactions between molecules in the network can be represented as polynomials over the finite field $\mathbb{F}_2$, which is defined as the set $\{0, 1\}$ with standard addition and multiplication operations. This allows the dynamical system $F = (f_1, \dots, f_n) : \mathbb{F}_2^n \rightarrow \mathbb{F}_2^n$ to be expressed as a polynomial dynamical system, as described in reference [13]. By using polynomial representations, researchers can analyze the dynamics of Boolean networks such as the auxin signaling network in a more efficient and effective manner.

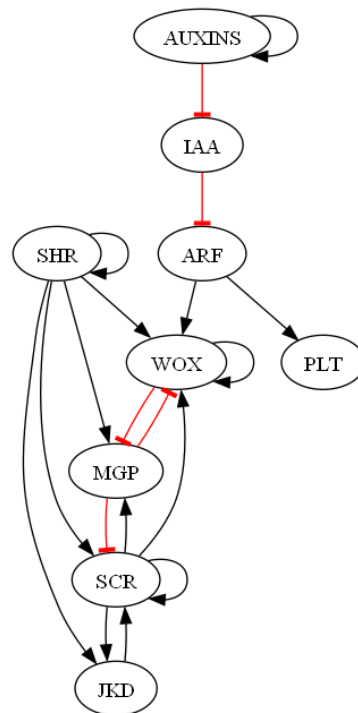


Figure 1: Auxin Signalling Network (Also see [3])

To convert Boolean functions into polynomials, we utilize a set of guidelines that dictate how Boolean operations are calculated with modulo 2 in $F_2[y_1, \dots, y_n]$. Specifically, the logical AND operation between variables x and y , which is denoted by $x \wedge y$, is equivalent to their product, xy . The logical OR operation, represented by $x \vee y$, is equivalent to their sum plus their product, $x + y + xy$.

The squaring of a variable x is equal to itself, $x^2 = x$. The multiplication of a variable x by a scalar λ is equal to 0 for any scalar $\lambda \in \mathbb{R} \setminus [-1, 1]$, $\lambda x = 0$. Finally, the logical NOT operation, denoted by $\neg x$, is equal to 1 plus the variable x , $\neg x = 1 + x$. By applying these rules to the auxin signaling network, we can obtain a set of polynomials that describe the behavior of the system.

$$\begin{aligned}
 f_1 &= 1 + y_3 \\
 f_2 &= y_2 \\
 f_3 &= 1 + y_2 \\
 f_4 &= y_7 y_8 \\
 f_5 &= y_7 y_8 (1 + y_9) = y_7 y_8 + y_7 y_8 y_9 \\
 f_6 &= y_1 \\
 f_7 &= y_4 y_5 y_7 y_8 + y_5 y_7 y_8 + y_7 y_8 \\
 f_8 &= y_8 \\
 f_9 &= y_1 y_5 y_7 y_8 y_9 + y_1 y_5 y_7 y_8 + y_1 y_7 y_8
 \end{aligned} \tag{4}$$

Determining attractors is a pivotal stride in comprehending and regulating intricate arrangements, and computational algebra presents beneficial instruments for accomplishing that [22, 23]. To unearth the unvarying conditions of the network, we must resolve a collection of equations in which $f_i = y_i$ for each unit i in the arrangement. This signifies that we are in quest of the origins of a set of equations $g_i = 0$, where $g_i = f_i - y_i$. By unraveling this assortment of equations, we can ascertain the plausible unvarying conditions of the network and acquire insights into the fundamental mechanisms that govern its conduct.

$$\begin{aligned}
 g_1 &= f_1 - y_1 \\
 g_2 &= f_2 - y_2 \\
 g_3 &= f_3 - y_3 \\
 g_4 &= f_4 - y_4 \\
 g_5 &= f_5 - y_5 \\
 g_6 &= f_6 - y_6 \\
 g_7 &= f_7 - y_7 \\
 g_8 &= f_8 - y_8 \\
 g_9 &= f_9 - y_9
 \end{aligned} \tag{5}$$

Since the system exhibits non-linear characteristics, conventional techniques like Gaussian elimination are inadequate for solving it. Nevertheless, computational algebra offers an alternative method by encoding the solutions as an algebraic entity called an ideal of polynomials. In our scenario, the ideal is denoted as $I = \{g_i\} \forall i = 1 \dots, 9$. Subsequently, we can simplify the representation of this ideal by identifying its Gröbner basis [7] utilizing mathematical software tools like Sagemath [18]. By determining the Gröbner basis of the ideal, we obtain a more streamlined system that encompasses the same solutions as the original system. This approach bestows a potent instrument for resolving non-linear systems and comprehending their behavior. Upon solving the aforementioned equation (5), we reach the following outcome:

$$\begin{aligned}
 g_1 &= 0 & g_2 &= 0 & g_3 &= 1 \\
 g_4 &= 0 & g_5 &= 0 & g_6 &= 0 \\
 g_7 &= 0 & g_8 &= 0 & g_9 &= 0
 \end{aligned} \tag{6}$$

Therefore, the value 001000000 represents a stable state of the network.

2.1 Edge Control

To control the edge $y_i \rightarrow y_j$ in the wiring diagram W , we utilize the function.

$$F_j(y, v_{i,j}) = f_j(y_1, \dots, (v_{i,j} + 1)y_i, \dots, y_n) \quad (7)$$

This function encodes the control settings for the edge $y_i \rightarrow y_j$, based on the possible values of $v_{i,j} \in \mathbb{F}_2$.

The control settings for the edge $y_i \rightarrow y_j$ can be described as follows:

- If $v_{i,j} = 0$, then $F_j(y, 0) = f_j(y_1, \dots, y_i, \dots, y_n)$. In this case, the control is not active.
- If $v_{i,j} = 1$, then $F_j(y, 1) = f_j(y_1, \dots, y_i = 0, \dots, y_n)$. Here, the control is active, and it represents the removal of the edge $y_i \rightarrow y_j$.

This can be expanded to encompass the control of multiple edges, resulting in $F : \mathbb{F}_2^n \times \mathbb{F}_2^e \rightarrow \mathbb{F}_2^n$, where e denotes the number of edges in the wiring diagram. Each coordinate, $v_{i,j}$, of v in $F(y, v)$ encodes the control for an edge $y_i \rightarrow y_j$ [13]. The above is the Murrugarra et al.'s algebraic edge control method and it provides a rigorous mathematical approach for identifying controllable nodes within Boolean network models [13]. We use the Boolean functions in equation (4) defining network dynamics into multivariate polynomials over GF(2), the Galois field with two elements $\{0, 1\}$. Here:

$$\begin{aligned} f_1 &= 1 + y_3(v_{3,1} + 1) \\ f_2 &= y_2(v_{2,2} + 1) \\ f_3 &= 1 + y_2(v_{2,3} + 1) \\ f_4 &= y_7 y_8 (v_{7,4} + 1)(v_{8,4} + 1) \\ f_5 &= y_7 y_8 (v_{7,5} + 1)(v_{8,5} + 1) + y_7 y_8 y_9 (v_{7,5} + 1)(v_{8,5} + 1)(v_{9,5} + 1) \\ f_6 &= y_1(v_{1,6} + 1) \\ f_7 &= y_4 y_5 y_7 y_8 (v_{7,7} + 1)(v_{5,7} + 1)(v_{4,7} + 1)(v_{8,7} + 1) + y_5 y_7 y_8 (v_{5,7} + 1) \\ &\quad (v_{8,7} + 1)(v_{7,7} + 1) + y_7 y_8 (v_{7,7} + 1)(v_{8,7} + 1) \\ f_8 &= y_8(v_{8,8} + 1) \\ f_9 &= y_1 y_5 y_7 y_8 y_9 (v_{1,9} + 1)(v_{5,9} + 1)(v_{7,9} + 1)(v_{8,9} + 1)(v_{9,9} + 1) + y_1 y_5 y_7 y_8 (v_{1,9} + 1)(v_{5,9} + 1)(v_{7,9} + 1) \\ &\quad (v_{8,9} + 1) + y_1 y_7 y_8 (v_{1,9} + 1)(v_{7,9} + 1)(v_{8,9} + 1) \end{aligned} \quad (8)$$

Suppose that $z_0 = (z_{01}, \dots, z_{0n}) \in F_2^n$ is a desirable cell state (for instance, it could represent the state of cell senescence) but is not a fixed point, i.e., $F(z_0) \neq z_0$. The problem is then to choose a control v such that $F(z_0, v) = z_0$. We now show how this can be achieved in our framework.

After encoding our Boolean Network (BN) with control as a polynomial system $F_j(y, v) \in F_2[y, v]$ in equation (8), we consider the system of polynomial equations in the v parameters:

$$F_j(z_0, v) - z_{0j} = 0, \quad j = 1, \dots, m. \quad (9)$$

Lets consider a scenario, where our goal is to control the edges in order to achieve a steady state where $z_0 = 111001010$ (desired steady state). If we evaluate the polynomial system in equation (8) at $z_0 = 111001010$, we obtain a system of equations that involves only the control parameters v . The specific equations depend on the structure of the Boolean Network and the chosen control actions, where $(v_{i,j} + 1) = \bar{v}_{i,j}$. Then;

$$\begin{aligned} f_1 &= \bar{v}_{3,1}, & f_2 &= v_{2,2} \\ f_3 &= \bar{v}_{2,3}, & f_4 &= 0 \\ f_5 &= 0, & f_6 &= v_{1,6} \\ f_7 &= 0, & f_8 &= v_{8,8} \\ f_9 &= 0 \end{aligned} \quad (10)$$

In the above, we set $F_i = z_{0i}$ for $i = 1, \dots, 9$. By solving for the control inputs that satisfy these conditions, we find that for this to be a stable state $v_{3,1} = v_{2,3} = v_{2,2} = v_{8,8} = v_{1,6} = 1$. In other words, if we delete the edges from nodes y_i to y_j and fix them, the network will reach the steady state 111001010 and remain there. This control scheme is unique for this particular steady state.

Let's suppose we have a Boolean network with n nodes, and there is a steady state $w_0 \in \{0, 1\}^n$ that we want to avoid. This steady state could represent an undesirable cell state, for example. Our goal is to find a set of control inputs that ensure the network never reaches this steady state. Alternatively, we may want to prevent the network from transitioning between two states z_0 and w_0 . To achieve this, we can use a polynomial equation that relates the control inputs to the network's dynamics.

The equation we use is given by:

$$(F_1(z_0, v) - w_{01} + 1) \cdots (F_n(z_0, v) - w_{0n} + 1) = 0 \quad (11)$$

This equation defines a polynomial in the control inputs $v_1, \dots, v_m$. If we can find a solution to this equation, then we can ensure that the network's dynamics will never reach the undesired state w_0 , or that it will not transition from z_0 to w_0 . In other words, if we can find a set of control inputs that satisfy the equation, then we have achieved our goal. Let's consider a scenario, where we are interested in identifying edges in the Boolean network that can block the transition from state $z_0 = 111001010$ to the undesired steady state $F(z_0) = 010001010$. Then again $v_{3,1} = v_{2,3} = v_{2,2} = v_{8,8} = v_{1,6} = 1$ can achieve this too.

Table 1: Disparity in the influence of removing edges on combinatorial operations.

Solution	Controllers	Description	% of Basin Size of z_0
$v_{3,1} = 1$	IAA $\rightarrow$ ARF	Control sets that force z_0	12.5
$v_{2,2} = 1$	AUXINS $\rightarrow$ AUXINS	to be a fixed point and block	
$v_{2,3} = 1$	AUXINS $\rightarrow$ IAA	its transition to 010001010	
$v_{1,6} = 1$	ARF $\rightarrow$ PLT		
$v_{8,8} = 1$	SHR $\rightarrow$ SHR		

3 Result

Auxin signaling is an important phytohormone pathway that regulates many aspects of plant growth and development. The dynamics and multistability of auxin-mediated gene networks allow plants to produce different phenotypes in response to environmental and genetic factors.

The results in the table [1](#) provide insights into how purposefully manipulating specific interactions within the Boolean model of auxin signaling can achieve desired control over network dynamics. Specifically, deleting the 5 edges listed as "Controllers" reduces the basin size of the initial state z_0 representing the desired state by 87.5% of its original size. This minimum control set suggests that:

- Deleting the IAA $\rightarrow$ ARF edge may disrupt negative feedback within the network, altering phenotypes
- removing the AUXINS self-interaction likely inhibits auxin accumulation, constraining responses
- the elimination of AUXINS $\rightarrow$ IAA edge relieves IAA inhibition of ARF, having the opposite intended effect
- the removal of ARF $\rightarrow$ PLT edge could prevent PLT activation downstream, perturbing outputs

- erasing the SHR self-interaction may disrupt SHR's co-regulation of targets with SCR

Together, this multi-faceted perturbation - systematically deleting specified interactions - appears to synergistically reroute network dynamics in a way that reduces 87.5% of state trajectories leading to the initial state z_0 , representing the desired attractor.

In summary, a rigorous analysis of how purposefully manipulating specific interactions achieves control over this Boolean auxin signaling model's dynamics affords insights into novel regulatory mechanisms - insights which, when validated experimentally, could inform engineering of plant phenotypes for agricultural applications. These results suggest that the auxin signaling network is highly sensitive to changes in its edge structure, and that targeted removal or addition of edges can be a powerful tool for controlling the network's behavior. By understanding the network's structure and dynamics, we can identify key edges that are critical for maintaining the network's behavior and use this knowledge to develop new strategies for controlling plant growth and development.

4 Conclusion

Our framework identified potential auxin response regulators via algebraic model analysis and control techniques. Validating these interventions experimentally can deepen our mechanistic insights, informing model refinements that yield improved predictions and hypotheses. Integrating modeling, control strategies and experiment-model cycles thus shows promise for purposefully manipulating molecular networks, paving the way for beneficial auxin-based applications. This auxin case study demonstrates a blueprint for developing mechanism-based interventions across biologically and medically relevant networks.

Appendix

Table 2: Boolean Rules For the Auxin Signalling Network

Node	Boolean Transition Rules
ARF	NOT IAA
AUXINS	AUXINS
IAA	NOT AUXINS
JKD	SCR AND SHR
MGP	SCR AND SHR AND NOT WOX
PLT	ARF
SCR	NOT MGP AND SCR AND SHR OR JKD AND SCR AND SHR
SHR	SHR
WOX	ARF AND SCR AND SHR AND WOX OR ARF AND NOT MGP AND SCR AND SHR

Table 3: Nodes and their corresponding gene names

Node	Gene Name
ARF	AUXIN RESPONSE FACTOR
AUX	AUXIN SIGNALING
IAA	INDOLE-3-ACETIC ACID
JKD	JAGGED
MGP	MORE GROWTH PLANT
PLT	PLETHORA
SCR	SCARECROW
SHR	SHORT ROOT
WOX	WUSCHEL-RELATED HOMEBOX

References

- [1] Abel, S., and Theologis, A. (1995). A polymorphic bipartite motif signals nuclear targeting of early auxin-inducible proteins related to PS-IAA4 from pea (*Pisum sativum*). *The Plant journal : for cell and molecular biology*, 8(1):87–96. <https://doi.org/10.1046/j.1365-3113.1995.08010087.x>
- [2] Albert, R., and Thakar, J. (2014). Boolean modeling: a logic-based dynamic approach for understanding signaling and regulatory networks and for making useful predictions. *Wiley interdisciplinary reviews. Systems biology and medicine*, 6(5):353–369. <https://doi.org/10.1002/wsbm.1273>
- [3] Arellano, G., Argil, J., Azpeitia, E., Benítez, M., Carrillo, M., Góngora, P., Rosenblueth, D. A., and Alvarez-Buylla, E. R. (2011). “Antelope”: a hybrid-logic model checker for branching-time Boolean GRN analysis. *BMC bioinformatics*, 12:490. <https://doi.org/10.1186/1471-2105-12-490>
- [4] Baslam, M., Mitsui, T., Sueyoshi, K., and Ohyama, T. (2020). Recent Advances in Carbon and Nitrogen Metabolism in C3 Plants. *International journal of molecular sciences*, 22(1):318. <https://doi.org/10.3390/ijms22010318>
- [5] Benková, E., Michniewicz, M., Sauer, M., Teichmann, T., Seifertová, D., Jürgens, G., and Friml, J. (2003). Local, efflux-dependent auxin gradients as a common module for plant organ formation. *Cell*, 115(5):591–602. [https://doi.org/10.1016/s0092-8674\(03\)00924-3](https://doi.org/10.1016/s0092-8674(03)00924-3)
- [6] Chen, L., Tong, J., Xiao, L., Ruan, Y., Liu, J., Zeng, M., Huang, H., Wang, J. W., and Xu, L. (2016). YUCCA-mediated auxin biogenesis is required for cell fate transition occurring during de novo root organogenesis in *Arabidopsis*. *Journal of experimental botany*, 67(14):4273–4284. <https://doi.org/10.1093/jxb/erw213>
- [7] Cox, D., Little, J., and O’Shea, D. (1998). *Using algebraic geometry*, Volume 185 of Graduate Texts in Mathematics. New York: Springer-Verlag.
- [8] Davies, P.J. (2010). *PLANT HORMONES: Biosynthesis, Signal Transduction, Action*.
- [9] Hayashi K. (2012). The interaction and integration of auxin signaling components. *Plant & cell physiology*, 53(6):965–975. <https://doi.org/10.1093/pcp/pcs035>
- [10] Kauffman S. A. (1969). Metabolic stability and epigenesis in randomly constructed genetic nets. *Journal of theoretical biology*, 22(3):437–467. [https://doi.org/10.1016/0022-5193\(69\)90015-0](https://doi.org/10.1016/0022-5193(69)90015-0)
- [11] Kauffman, S. A., Peterson, C., Samuelsson, B., and Troein, C. (2003). Random Boolean network models and the yeast transcriptional network. *Proceedings of the National Academy of Sciences*, 100(25):14796–14799.
- [12] Lee, S. B., and Suh, M. C. (2015). Advances in the understanding of cuticular waxes in *Arabidopsis thaliana* and crop species. *Plant cell reports*, 34(4):557–572. <https://doi.org/10.1007/s00299-015-1772-2>
- [13] Murrugarra, D., Veliz-Cuba, A., Aguilar, B., and Laubenbacher, R. (2016). Identification of control targets in Boolean molecular network models via computational algebra. *BMC systems biology*, 10(1):94. <https://doi.org/10.1186/s12918-016-0332-x>
- [14] Overvoorde, P., Fukaki, H., and Beeckman, T. (2010). Auxin control of root development. *Cold Spring Harbor perspectives in biology*, 2(6):a001537. <https://doi.org/10.1101/cshperspect.a001537>

- [15] Paponov, I. A., Paponov, M., Teale, W., Menges, M., Chakrabortee, S., Murray, J. A. H., and Palme, K. (2008). Comprehensive Transcriptome Analysis of Auxin Responses in Arabidopsis. *Molecular Plant*, 1(2): 321–337. doi:10.1093/mp/ssm021
- [16] Pattison, R. J., Csukasi, F., and Catalá, C. (2014). Mechanisms regulating auxin action during fruit development. *Physiologia plantarum*, 151(1):62–72. <https://doi.org/10.1111/ppl.12142>
- [17] Reinhardt, D., Pesce, E. R., Stieger, P., Mandel, T., Baltensperger, K., Bennett, M., Traas, J., Friml, J., and Kuhlemeier, C. (2003). Regulation of phyllotaxis by polar auxin transport. *Nature*, 426(6964): 255–260. <https://doi.org/10.1038/nature02081>
- [18] SageMath. (Version 9.2) [Computer software]. (2021). Available from <http://www.sagemath.org>.
- [19] Shmulevich, I., Dougherty, E. R., Kim, S., and Zhang, W. (2002). Probabilistic Boolean Networks: a rule-based uncertainty model for gene regulatory networks. *Bioinformatics* (Oxford, England), 18(2):261–274. <https://doi.org/10.1093/bioinformatics/18.2.261>
- [20] Teale, W. D., Paponov, I. A., and Palme, K. (2006). Auxin in action: signalling, transport and the control of plant growth and development. *Nature reviews. Molecular cell biology*, 7(11):847–859. <https://doi.org/10.1038/nrm2020>
- [21] Vanneste, S., and Friml, J. (2009). Auxin: a trigger for change in plant development. *Cell*, 136(6):1005–1016. <https://doi.org/10.1016/j.cell.2009.03.001>
- [22] Veliz-Cuba, A., Aguilar, B., Hinkelmann, F., and Laubenbacher, R. (2014). Steady state analysis of boolean molecular network models via model reduction and computational algebra. *BMC Bioinformatics*, 15: 221.
- [23] Veliz-Cuba, A., Jarrah, A. S., and Laubenbacher, R. (2010). Polynomial algebra of discrete models in systems biology. *Bioinformatics*, 26(13):1637–1644.
- [24] Woodward, A.W. and Bartel, B. (2005). Auxin: regulation, action, and interaction. *Annals of botany*, 95(5):707–735. <https://doi.org/10.1093/aob/mci083>
- [25] Zazimalová, E., Murphy, A. S., Yang, H., Hoyerová, K., and Hosek, P. (2010). Auxin transporters—why so many?. *Cold Spring Harbor perspectives in biology*, 2(3):a001552. <https://doi.org/10.1101/cshperspect.a001552>