Simple network motifs can capture key characteristics of the floral transition in *Arabidopsis*

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The floral transition is a key decision during plant development. While different species have evolved diverse pathways to respond to different environmental cues to flower in the correct season, key properties such as irreversibility and robustness to fluctuating signals appear to be conserved. We have used mathematical modeling to demonstrate how minimal regulatory networks of core components are sufficient to capture these behaviors. Simplified models inevitably miss finer details of the biological system, yet they provide a tractable route to understanding the overall system behavior. We combined models with experimental data to qualitatively reproduce characteristics of the floral transition and to quantitatively scale the network to fit with available leaf numbers. Our study highlights the value of pursuing an iterative approach combining modeling with experimental work to capture key features of complex systems.

Global approaches to understand the regulatory transcriptional network involved in controlling the floral transition have revealed that hundreds of transcripts are specifically affected in their expression in the apex upon floral induction.¹⁻⁴ Modeling such large genetic regulatory networks is a challenging task as the determination of all relevant parameters is rarely experimentally feasible. The limited knowledge of component concentrations and kinetic interactions can result in a mathematically highly underdetermined problem. This means that the available data are not sufficient to uniquely determine the underlying parameters in the model, something that with typical biological data and models is rarely achieved.⁵ Methods have been developed, such as Boolean networks or systems identification, which simplify the description, thereby reducing the numbers of parameters. Boolean networks aim to capture the underlying biology in that the gene network structure is maintained but the complexity of the interactions is reduced, whereas systems identification (“black box”) focuses on capturing the overall behavior, typically employing small systems of linear equations that do not map well onto the underlying biological mechanisms.⁶⁻⁷ Another approach is to reduce the gene network while preserving its core structure. Following this strategy,⁸ we sought to simplify the large regulatory network that controls flowering down to a core set of regulatory activities.⁹ As shown in Jaeger et al. (2013), a fairly simple network of core flowering time hubs¹⁰ is able to capture important characteristics of the floral transition.⁸ We approximated the effect of the various regulatory pathways that govern the floral transition by assuming they converge on the key regulator of flowering in higher plants, FT¹¹⁻¹³ FT expression increases under inductive conditions, and together with the FD transcription factor,¹⁶⁻¹⁷ FT activates key floral meristem identity genes such as *AP1*. For a number of species, homologs of the *Arabidopsis* master regulator *FT* are a core element of the photoperiod pathway.¹⁸⁻¹⁹ We use *AP1* hub levels as a proxy for the flowering state. Rosette leaves, cauline leaves, or flowers are produced based on the levels of *API* in the model. Increasing *FT* signals promote flowering time, noisy input signals are filtered out, and once initiated, the transition is irreversible. Although the degree to which this behavior manifests itself is very
much parameter dependent, at a qualitative level the model is consistent with the experimental observations. Furthermore, the model could be scaled to available leaf number data for a number of mutant genotypes. The modeling suggested how \textit{TFL1} signals contribute to the molecular basis for a non-flowering phenotype that has not been understood until now. For an extended network we found that, for some parameter values, initial levels of \textit{LFY} and \textit{TFL1} seem to control the final determinacy of the cell. Cells with higher initial \textit{TFL1} levels are able to repress \textit{LFY}, and thus also \textit{API}, to remain in a vegetative state, or high initial \textit{LFY} levels can cause a floral fate as specified by \textit{API} levels.

Here we demonstrate how 2 important properties of the floral transition, namely noise-filtering and irreversibility, can be implemented by 3-node networks in feed-forward loops. The coherent feed-forward loop is a network motif that is commonly found in signaling networks. \cite{20}

As a major floral pathway integrator, we have placed the active \textit{FT/FD} complex \cite{16,17} at the start of the transcriptional feed-forward loop, upregulating another integrator, the \textit{LFY} hub (which includes the functional effect of \textit{SOC1}), which both activate the floral initiator hub \textit{AP1} \cite{21,22} (Fig. 1A). If the joint regulation is with AND logic, this simple network has persistence detection and thus is able to be used as a noise filter \cite{20}. The equations are shown in Figure 1 and explained in the supplemental information along with the parameters and an IPython notebook. \cite{27} As the correct timing of the floral transition is crucial, it is
important that the system is not incorrectly activated by noise. Another similar network, called regulated feedback, that uses an OR gating can exhibit irreversibility. With the same 3-node set up, an extra activating connection between the two targets, FT/FD and TFL1, of the first transcription factor, FT/FD, will result in the targets being stably on once activated, (Fig. 1B). API mutually activates LFY in a positive feedback loop, thus creating the important memory element that is responsible for irreversibility of a plant committed to flowering. So while these simple network motifs capture separate characteristics of the floral transition, they are a crude approximation to the larger system.

In summary, we have sought to show how simple regulatory networks can capture important properties of the floral transition. Genes with similar effects can be grouped into distinct hubs (denoted by underlining) or functional modules.

Such a reduced network that represents the core structure underlying the floral transition can be mapped to the simple feed-forward loops discussed above. Such a simple 3-node system, as presented here, can give intuitive understanding to a complex biological system. We point out that even for these simple networks, the available data was not sufficient to provide good estimates of the parameters. However, predictions can be made without precise knowledge of all the parameters. Adding further hubs to this network, for example including the floral repressor TFL1, is relatively straightforward. To begin modeling a new pathway, looking for the basic properties of simple networks that exhibit the desired behavior may be a good first step. As with all simplifications, this approach inevitably cannot account for the full spectrum of interacting pathways and variables seen in nature, but it may be a useful entry point for an iterative modeling-experimental cycle.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Supplemental Materials

Supplemental materials may be found here: http://www.landesbioscience.com/journals/psb/article/26149/

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