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Designing Plants: Modeling Ideal Shapes

In an industrialized world, virtually everything we are using is first designed and then manufactured. Let us use the automobile manufacturing industry as an example: engineers design vehicles based on laws of physics; select proper materials for machine parts; and assemble parts following blueprints into cars, buses, and trucks. It is evident that we need not only parts but also technical drawings and instructions for the assembly of parts into a functional pump or clutch.

In biology, we have long been doing ''reverse engineering''. Using genetics, biochemistry, cell biology, and other approaches, we deconstruct an organism, an organ, a type of tissue, or even a cell to reveal the underlying designs and architecture to expand our knowledge base. Thanks to the accumulating advances over the past decades, we have learned a great deal about biological ''parts,'' including genes, proteins, and organelles. How are these ''parts'' assembled to yield a living organism? This is clearly an outstanding question in biology.

As plant biologists, we work hard to understand plants, and we dream to advance plants—to design plants for the well-being of humans. For example, we need crops with high yield, crops requiring minimal fertilizer and pesticide use, and crops adapted to harsh environments. Our ancestors selected natural variants for crop domestication and improvement, and the practice continues today. Such natural variations include spontaneous mutations, favorable offspring from hybridizations, and rare polyploidy events. With our expanding knowledge of the biological ''parts'' in plants, we are coming closer to designing crops in the way we design automobiles and airplanes.

One missing piece preventing us from assembling ''parts'' into a living plant is a full understanding of their regulatory systems: their structures, constraints, and possibilities. This is a challenging task insofar as there are simply too many ''parts'' in a plant, and disabling each of them, as mutants have taught us, do not always explain how the entire ''machine'' functions. In terms of the automobile analogy, it is almost impossible to understand the physical laws and designing principles by only disassembling a car.

Systems biology is well suited to deal with this particular challenge because it uses computational and mathematical modeling to explain complex biological systems. By testing a range of possible regulatory principles, modeling results indicate which regulatory circuits may explain a biological process. Because model predictions can in turn be subjected to reciprocal experimental testing and experimental data can be used to revise models, systems biology has the power to decipher the ''designing principles'' of biological ''parts'' (Roeder et al., 2011; Prusinkiewicz and Runions, 2012). For example, the power to dissect cybernetics in plants, i.e., control and communicate in plants, has been nicely illustrated by the modeling of plant organogenesis. The collective results of organogenesis determine plant architecture, which broadly affects crop traits (Wang et al., 2018).

Inflorescences, the branching reproductive shoot systems, are major determinants of crop yield. In crops, inflorescence complexity is often a selection target during domestication and improvement, especially in cereal crops. After flowering transition, the shoot apical meristems (SAMs) at the growing tips switch to reproductive growth to produce flowers. An iterative pattern of decisions at the SAM determines the inflorescence architecture (Kyozuka et al., 2014). The SAM may either transition and adopt the floral identity or produce branching meristems. Each branching meristem reiterates this developmental decision-making process using the same program or a revised one. In the model plant *Arabidopsis thaliana*, two genes, *LEAFY* (*LFY*) and *TERMINAL FLOWER1* (*TFL1*), regulate inflorescence architecture (Weigel et al., 1992; Bradley et al., 1997). *lfy* mutants have delayed floral transition and produce highly branched inflorescences, whereas *tfl1* mutants switch from an indeterminate inflorescence to a determinate structure with terminal flower formation.

Inflorescence structures are highly diversified in nature. In fact, many inflorescence types observed in nature have never been observed in *Arabidopsis*. Therefore, how much can studies in a model plant reveal about the wide range of inflorescence architectures found in nature? Computational modeling has provided a plausible answer (Prusinkiewicz et al., 2007). In the model, maturation rates are hypothesized for the apical meristem and branching meristems. The time to reach a threshold for flower formation is denoted as T. Using different relative values for flower transition speed in the apical meristem (T_A) and the branching meristems (T_B), the model output encompasses a range of inflorescence architectures, including panicle, raceme, and cyme (Figure 1A). The modeling results highlight possible directions for manipulating inflorescence architecture to obtain higher yield. In fact, subsequent studies have provided evidence for a progressive maturation of meristems in tomato and demonstrated that manipulation of genes controlling meristem maturation by gene editing can indeed be used for such applications (Park et al., 2012). Researchers have used gene editing to generate a spectrum of mutants with varying meristem maturation speed (T in the model) and found that favorable inflorescence architectures could be obtained in tomato (Soyk et al., 2017).

Leaf shape is another striking example of biological shape variation recently exploited by modelers. Leaves show tremendous

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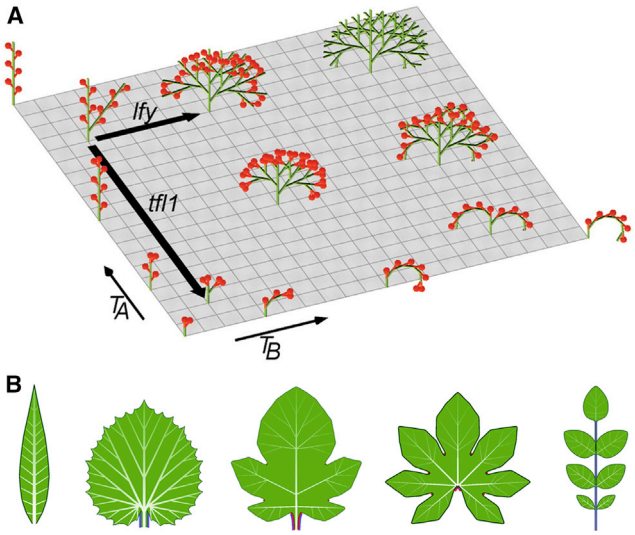

Figure 1. Examples of Simulated Biological Shapes.
(A) Different inflorescence architectures are generated by varying T_A and T_B, which are related to the effect of *TFL1* and *LFY* in *Arabidopsis* (Prusinkiewicz et al., 2007).
(B) Simulation of the development of simple and compound leaves (Runions et al., 2017).

morphological diversity, and these variations clearly affect the photosynthesis area as well as drought adaption. Leaf shapes range from simple to lobed to compound and are highly determined by margin morphology. Genetic analyses have shown that mutants in the auxin efflux carrier *PIN FORMED1* (*PIN1*) and transcription factor *CUP-SHAPED COTYLEDON2* (*CUC2*) both have smooth margins (Hay et al., 2006; Nikovics et al., 2006). It is puzzling how these two genes can generate iterative serrations, i.e., margin protrusions.

A computational model has tested the significance of the reciprocal repression between *CUC2* and the PIN1 module in the determination of leaf margin shape (Bilsborough et al., 2011). PIN1 transports auxin up the gradient to form auxin concentration maxima. High levels of auxin inhibit *CUC2*, restricting *CUC2* expression to auxin minima. The model also assumes that *CUC2* reorients PIN1 away. Based on these assumptions, the model recapitulates repeated serrations in the margin. Furthermore, by modulating the strength of feedback, a range of leaf marginal shapes can be derived. On top of that, veins, which serve as auxin sinks from leaf marginal auxin maxima, can model more complex serrations and compound leaves (Runions et al., 2017) (Figure 1B).

In addition to marginal serrations, leaf blade shapes are highly diversified among species, among ecotypes, and even within the same plant. A separate set of models introduces a set of spatiotemporal regulatory factors to describe the growth of each cell (Kuchen et al., 2012). These factors define cell growth anisotropy and growth rate, as well as cell division direction and division rate. These regulatory factors are interconnected to form feedbacks from early growth patterns, which dynamically adjust factor values. These models can generate a wide range of blade shapes seen in nature. However, it is important to note that the regulatory factors used in the model remain hypothetical and that their biological meanings remain to be determined.

The examples described above are only a small sampling of the available findings. There are many more examples of computational and mathematical modeling used to explain and predict morphogenesis patterns, such as phyllotaxis, apical dominance, and root patterning (Lavedrine et al., 2015). Modeling has also provided critical insight into traits not directly connected with morphogenesis, such as circadian clock feedback loops.

Although it is still insufficient, we now know a great deal about gene functions and have an expanding toolkit to manipulate genes. To precisely design and create new plant varieties, we need to understand the cybernetics of plants. How do genes reproducibly assemble to form regulatory circuits? How are biological shapes determined? How do organs respond to environmental cues? We have some answers and clues about each of these pathways. Simply overexpressing or knocking out one gene may lead to unexpected phenotypes and sometimes strong side effects. Similarly, in the automobile analogy, removing a part or adding a new part may not always boost the performance of a car. An understanding of design principles and access to technical drawings are necessary even for car tuning. Computational and mathematical modeling allows the prediction of the complex or even counterintuitive dynamics of the regulatory networks driving plant growth and crop traits. Such blueprints of regulatory networks will establish a foundation for the rational design of crops for the future. New advances in synthetic biology and gene editing speed up the move from principles to design.

Yuling Jiao[1,2,*]

[1]State Key Laboratory of Plant Genomics, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing 100101, China
[2]University of Chinese Academy of Sciences, Beijing 100049, China
***Correspondence: Yuling Jiao (yljiao@genetics.ac.cn)**
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