Commentary

Passing the El Greco test

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(Received 3 August 2007; accepted 6 August 2007; published online 4 September 2007)

In recent years, the increasing use of modelling to capture biological complexity has revealed two complementary approaches. One is to build ever more comprehensive models in the hope that they will lead to useful predictions. The other approach is to get to the essence of the underlying processes by simplifying and clarifying complex problems through various levels of abstraction. Unfortunately, these two approaches are sometimes confounded, as is highlighted by a recent commentary by Alvarez-Buylla *et al.* [*HFSP Journal*, 1(2), 99–103 (2007)]. Their commentary raises several concerns about a paper we published on the development of inflorescences, the branching structures that bear flowers. Alvarez-Buylla *et al.* claim that the model we propose is too simplistic and propose an alternative "toy model", which they believe is more realistic and can account for the data just as effectively. However, they do not run simulations based on their model. We show here that, depending on how this toy model is interpreted, it either does not deliver what Alvarez-Buylla *et al.* claim, or is a special case of the model we proposed, or is so vague that its consequences are unclear. Our analysis demonstrates the importance of modelling in simplifying, clarifying and following through the consequences of particular hypotheses. Without this it is all too easy to construct elaborate models on shaky foundations. [DOI: 10.2976/1.2776103]

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In his book *Advice to a Young Scientist,* Peter Medawar gives a test in logic based on the paintings of El Greco (Medawar, 1979). A striking feature of many of El Greco's pictures is the way figures and faces often appear to be excessively elongated (Fig. 1). In trying to account for this idiosyncratic style, an ophthalmologist proposed in 1913 that El Greco may have had a form of astigmatism, which distorted his vision and led to elongated images forming on his retina (Trevor-Roper, 1970). Although such an explanation may initially seem reasonable, it does not stand up to logical scrutiny. This is because even if El Greco did see the world through a distorting lens, the same distortion would apply to what he saw on his canvas. These two distortions would cancel each other out, and the proportions in pictures would remain realistic. Thus "if some of El Greco's figures seem unnaturally tall and thin, they appear so because this was El Greco's intention" (Medawar, 1979).

The story illustrates the importance of following through the logic and consequences of a hypothesis. In the case of the ophthalmologist's theory, a moment's reflection is enough to reveal the logical flaw. But sometimes it is more difficult to think through the consequences of an idea, particularly when it involves dynamic interactions between many components. In such situations it often helps to use formal models to clarify what is going on. This is the approach we adopted in our recent paper, in which we showed how a simple mechanism could account for a range of observations on the development, genetics and evolution of inflorescences (Prusinkiewicz *et al.*, 2007).

Our analysis failed to impress Alvarez-Buylla *et al.* (2007) who, in writing a commentary on our paper for this journal, concluded that our model lacks "explanatory power", is "too simplistic", and is "one of several *ad-hoc* models yielding inflorescence structures similar to those observed in nature". They propose

HFSP Journal © HFSP Publishing $25.00
Vol. 1, No. 3, September 2007, 152–155 http://hfspj.aip.org

Figure 1. Detail from *Mary Magdalen in Penitence* by El Greco, early 1580's. Reproduced with permission from the Worcester Art Museum, Massachusetts. Notice the elongated neck and face.

an alternative "toy model", which they believe provides a more realistic explanation. Alvarez-Buylla *et al.* did not carry out simulations based on their toy model to show that it delivers what they claim. They presumably felt that the output from their model was sufficiently obvious on intuitive grounds to make such simulations unnecessary. However, by not following through with their ideas, they overlook the issues that arise from the iterative nature of branching.

The inflorescences observed in nature fall into three broad categories [Fig. 2(A)]. Panicles comprise a branching structure of axes that terminate in flowers. Racemes comprise axes bearing flowers in lateral positions; this pattern

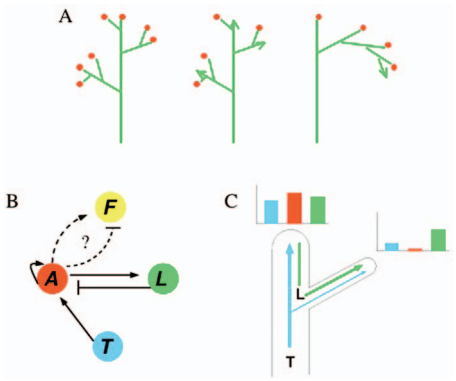

Figure 2. Inflorescence types and description of "toy model" proposed by Alvarez-Buylla *et al.* (2007). (A) Types of inflorescences: from left to right, panicle, raceme, and cyme. (B) Network underlying the proposed toy model. (C) Illustration of the operation of the toy model, which is claimed to render the inflorescence architectural types observed in real plants. Figure taken from Alvarez-Buylla *et al.* (2007).

may be reiterated in lateral axes to give open racemes with multiple indeterminate branches. Finally, cymes consist of axes that terminate in flowers and lateral axes that repeat this pattern. These three basic arrangements reflect an iterative pattern of developmental decisions in which meristems (growing tips) may either switch to floral identity or continue to produce further meristems and hence branches. Prior to publication of our paper, separate developmental models had been proposed to account for the different inflorescence categories. We showed, however, that a single model could capture all three inflorescence types. A key feature of our model is that newly initiated meristems pass through a transient phase, in which they may be more or less prone to form flowers than mature meristems. Although, once formulated, this concept is straightforward, it is difficult to follow its consequences through iterations of meristem switches in a growing branching structure without the help of modelling. This may account for why our proposal, called the transient model, had not been previously suggested.

The toy model proposed by Alvarez-Buylla *et al.* as an alternative to ours is illustrated in Fig. 2(B) and 2(C) (taken from their commentary). According to this model, two proteins, *A* and *L*, are synthesised within meristems. *A* promotes its own synthesis and that of *L*, whereas *L* inhibits synthesis of *A* and can diffuse to nearby meristems. To account for the different behavior of main and lateral meristems, Alvarez-Buylla *et al.* suggest that the apical meristem receives more of a mobile signal *T* that is made in the leaves and transported to the meristems. As *T* promotes synthesis of *A*, there will be high levels of *A* in the main apical meristem, whereas the nearby lateral meristems will have low levels of *A*, i.e. $[A_{main}] > [A_{lat}]$. Alvarez-Buylla *et al.* postulate that if *A* represses flowering [inhibits *F* in Fig. 2(B)], the apical meristem will remain indeterminate, while lateral meristems, which have less *A*, will form flowers, and thus racemes will arise. By contrast, if *A* promotes flowering (activates *F*), the apex will flower while lateral meristems will keep branching, giving rise to cymes. Alvarez-Buylla *et al.* claim that various kinds of racemes, cymes or panicles could be produced by varying parameter values such as branching, decay and diffusion rates. However, they do not explore this statement further, so the detailed properties of their model and its relationship to ours are left entirely open. To clarify matters, we carried out some simulations based on their toy model.

A key issue is how to deal with the transition to the flowering state, as this will influence the fate of inflorescence branches. Alvarez-Buylla *et al.* do not consider this transition explicitly, but by relating the mobile signal *T* to flowering-time gene *FT*, they imply that the level of *T* increases upon the switch from the vegetative to flowering phase. What are the possible consequences of this event? According to the toy model, this increase in *T* promotes the expression of *A* [Fig. 2(B)]. If *A* inhibits flowering, the switch of apices to the flowering state will now be even more inhib-

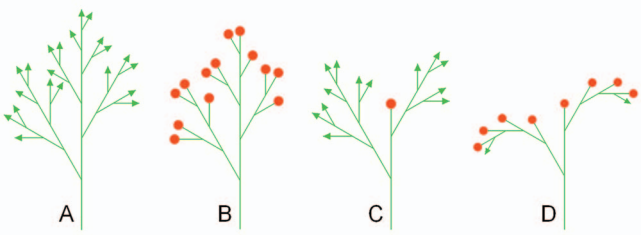

Figure 3. Representative structures generated by the toy model (A-C) and its transient interpretation (D).

ited that in the vegetative state of the plant, and thus the plant will never flower. It is possible to circumvent this problem with an even more complex model, in which *T* (or some other signal) promotes floral identity in parallel with activating *A*. This would bring in the further issue of how the effects of *T* and *A* are integrated to influence floral identity. However, rather than delve into a more complex version of the toy model, we go on to consider the other scenario proposed by Alvarez-Buylla *et al.*, in which *A* promotes flowering.

Denoting by *th* the threshold value of the expression of *A* above which the switch to flower identity occurs, we can distinguish three possibilities: (1) $th > [A_{main}] > [A_{lat}]$; (2) $[A_{main}] > [A_{lat}] > th$; and (3) $[A_{main}] > th > [A_{lat}]$. In the first case, the expression of *A* is too weak to induce the switch to flowering in any apices, and the entire branching structure remains vegetative [Fig. 3(A)]. In the second case, the arrival of signal *T*, followed by the expression of *A*, turns all the apices into flowers. This structure is a determinate (closed) panicle [Fig. 3(B)]. The toy model can thus readily account for one of the main inflorescence types. In analyzing the third case, we need to consider two further scenarios (a distinction Alvarez-Buylla *et al.* failed to recognize in their description of the toy model). The first possibility is that low concentrations of *A* and *T* will persist in a lateral apex as it grows on to form a branch. The resulting "inflorescence" will then consist of a terminal flower and indeterminately growing branching structures that do not support any flowers [Fig. 3(C)]. This does not correspond to an inflorescence type observed in nature. Another possibility is that a lateral apex, after producing a next-order lateral, reverts to the "main" state, characterized by high concentrations of *A* and *T*. In other words, the lateral state is transient. In this case, each lateral apex present upon the arrival of signal *T* will produce an indeterminate cyme [Fig. 3(D)]. The toy model proposed by Alvarez-Buylla *et al.* can thus generate an open cyme, but the use of the transient state would make the toy model a special case of our model rather than an alternative to it.

The above analysis is based on the description of the toy model by Alvarez-Buylla *et al.* who consider two apical states within the inflorescence: the first characterized by high concentrations of *T*, *A* and *L*, the second by low concentrations of *T* and *A*, and an intermediate concentrations of *L* [Fig. 3(C)]. We may loosen this constraint, and allow the concentrations *T*, *A* and *L* to change continuously. This creates an enormous space of possibilities and detailed questions, such as how these values propagate from the main to the lateral apex, how they change over time and with position within the inflorescence, and what inflorescence architectures will arise in each specific case. In their commentary, Alvarez-Buylla *et al.* ignore these questions, leaving the discussion of their toy model precisely where the questions that are essential to our work begin. Our analysis reveals that, depending on how the toy model is interpreted, it either does not deliver all three inflorescence types as claimed, or is a special case of the model we proposed, or is so vague that its consequences are unclear.

Alvarez-Buylla *et al.*'s failure to appreciate the logic and aims of our modelling approach is reflected in the many other criticisms raised in their commentary. For example, after outlining the general transient model in our paper, we produced a more detailed implementation of the model that incorporated molecular genetic data from *Arabidopsis*. This more detailed model involved two key genes that influence inflorescence development, *LFY* and *TFL1*. In accordance with previous studies, we assumed that *LFY* promotes floral identity while *TFL1* inhibits it. To incorporate transience into the model, we also proposed that *TFL1* expression is repressed and *LFY* expression enhanced in newly initiated (i.e, immature) meristems. This gives a transient expression pattern for these genes in lateral meristems that go on to form branches, in accordance with experimental observations. The resulting model allowed the observed mutant phenotypes to be accounted for. It also made sense of the observed transience in gene expression patterns, for which no explanation had previously been given. Alvarez-Buylla *et al.* believe that our argument is circular because we assume transient expression patterns in our model and therefore cannot use data on observed transient expression as supportive evidence. But they miss the point that transient expression patterns for genes controlling inflorescence architecture were incidental phenomena with no obvious functional significance according to previous accounts, whereas we deduced them from our general model.

Alvarez-Buylla *et al.* misunderstand our aims when they criticize us for ignoring the role of additional genes, such as *AP1* or *FT*, in our model. We have developed versions of our model that incorporate *AP1* and *FT*, but decided not to describe these more elaborate versions in our paper because they would distract from the fundamental issue we were addressing. We do not deny the importance of further interactions, but we find it important to get a clear grasp of the key principles before incorporating too many genes. The toy model of Alvarez-Buylla *et al.* illustrates how making a model more elaborate may actually obscure the underlying logic.

Alvarez-Buylla *et al.* also criticize us for assuming that developmental fate depends on meristem age, believing that

this implies we are denying a role for cell-cell communication. However, at no point in our paper do we claim that age is determined autonomously within the meristem. Rather, we state that we use age as a simplifying general term to denote a property that changes with time, accepting that this property may depend on interactions within the plant as well as with the environment. We did not go into the details of these interactions, not because we were denying their existence, but because this would have been a distraction from the main focus of the paper. A similar confusion arises over our use of the notion of *vegetativeness* or *veg*, which Alvarez-Buylla *et al.* interpret as referring to a hypothetical substance. We never claim that *veg* is a substance. Instead, we define it as a continuous variable that represents the extent to which a meristem is vegetative or floral. It is an abstraction, like age, that may depend on numerous contributing factors, and proves useful in analyzing the dynamics of inflorescence development.

The commentary by Alvarez-Buylla *et al.* illustrates a problem that arises in modelling complex biological systems. One approach is to build even more elaborate models and hope that they will provide some insights. This seems to be the approach advocated by Alvarez-Buylla *et al.* who are keen to incorporate as many genes and complexities as possible. But the risk of building up such complex edifices is that, unless there is a clear grasp of the basis of the models, they may end up being castles in the air. It would be as if someone who fails to see the El Greco fallacy happily proceeded to accumulate large amounts of data on the distorting effect of different lens shapes to further their case. Piling up features may obscure underlying principles instead of clarifying them.

The alternative approach is to simplify the problem through various levels of abstraction, and focus on the underlying principles. Darwin's theory of natural selection and Mendel's theory of the gene are good examples of such an approach; they provide a deeper understanding because they focus on a simple underlying truth. The process of simplification requires judgment and insight to decide on the appropriate form of abstraction, and what to consider of primary or secondary significance. These are not arbitrary choices; they form an essential part of the scientific process.

In our paper, we use the approach of abstraction and simplification to arrive at a mechanism that allows observed inflorescence architectures to be explained in a unifying manner. Modelling serves to clarify the logic and follow through the consequences of particular ideas. With the foundations established and further supported by experimental evidence, more genes and interactions could and should be added to provide more detailed understanding of the development of inflorescences. However, clearly stating and analyzing the foundations is essential. Without this, we risk failing the many El Greco tests that nature puts before us.

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