

# Models for navigating biological complexity in breeding improved crop plants

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**Progress in breeding higher-yielding crop plants would be greatly accelerated if the phenotypic consequences of making changes to the genetic makeup of an organism could be reliably predicted. Developing a predictive capacity that scales from genotype to phenotype is impeded by biological complexities associated with genetic controls, environmental effects and interactions among plant growth and development processes. Plant modelling can help navigate a path through this complexity. Here we profile modelling approaches for complex traits at gene network, organ and whole plant levels. Each provides a means to link phenotypic consequence to changes in genomic regions via stable associations with model coefficients. A unifying feature of the models is the relatively coarse level of granularity they use to capture system dynamics. Much of the fine detail is not directly required. Robust coarse-grained models might be the tool needed to integrate phenotypic and molecular approaches to plant breeding.**

## Biological complexity confounds crop improvement

*'Everything should be made as simple as possible, but not simpler' [1]*

Plant breeding is driven by the need to continually increase sustainable yield and quality of crop plants and meet projected increases in global food demand [2]. This involves manipulating complex traits, such as those associated with plant growth and development or tolerances to abiotic and biotic stresses, usually in production environments that are highly variable and unpredictable. Over the past century, empirical plant breeding has been used successfully to improve several crops [3]. Although it remains the cornerstone approach, cost-per-unit yield gain has risen substantially. Plant breeding requires the prediction of phenotype based on genotype to underpin any advances

in yield. Traditionally, this has been achieved by measuring phenotypic performance in large segregating populations and by applying rigorous statistical procedures based on quantitative genetic theory [4]. Genes have been virtual entities in this approach.

With recent progress in molecular technologies for genome sequencing and functional genomics, genes have become tangible rather than virtual entities. It is widely anticipated that a gene-by-gene engineering approach will enable enhanced efficiency in plant breeding [5]. Indeed, there have been successes in developing plants that better resist pests or tolerate herbicides. Those cases involved single-gene transformations where plant phenotypic response scaled directly from the level of molecular action. However, little of this promise has been realized for key complex traits where relationships among components and their genetic controls involve quantitative multi-gene interactions [6]. Integrating gene effects across scales of biological organization in such situations is not straightforward [7]. Complexities associated with gene interactions [8,9], mediated via transcriptional and post-transcriptional regulation [10], or distributed control of fluxes in plant metabolic pathways [11] are major impediments to scaling from gene network to phenotype. Hence, phenotypic prediction based on a gene-by-gene approach remains elusive.

Here we review the role of plant modelling as a linking technology between phenotypic and molecular approaches to plant breeding. We profile modelling approaches where the physiological perspective afforded by modelling has helped in understanding and predicting gene-to-phenotype relationships for complex traits. We discuss how such plant modelling could be used to enhance progress in plant breeding and consider the nature of the models likely to be most relevant in this pursuit.

## Plant modelling, phenotypic prediction and the navigation problem

Plant modelling offers potential for phenotype prediction [12,13]. The models are simplified mathematical

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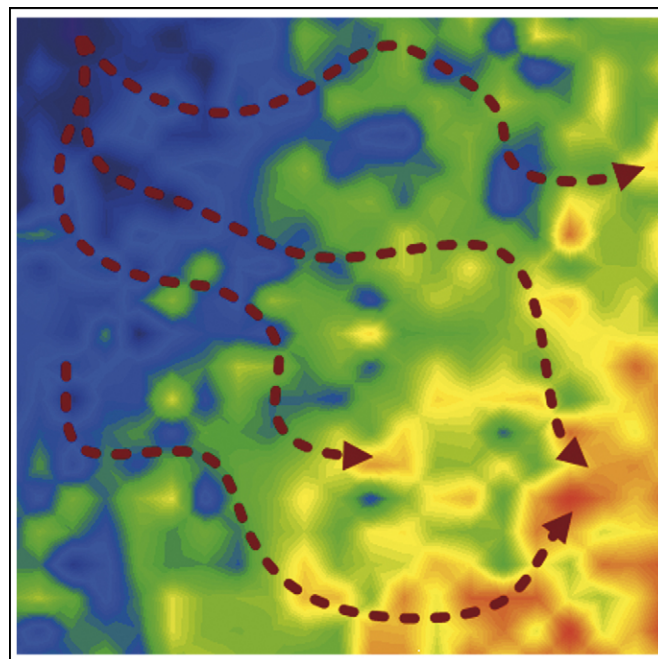
Available online 7 November 2006.

representations of the interacting biological and environmental components of the dynamic plant system. Plants are complex, adaptive, robust systems that have evolved via selection pressures acting on the organism. The functioning of such systems is best understood by exploring how they handle information and use it to drive morphogenesis and cope with environmental perturbations [14,15]. Intrinsic information systems and their controls are encoded in the genetic ‘programmes’ of organisms [16,17]. Hence, evolution of organisms can be viewed as the evolution of control systems [18].

There is a rich experience in understanding and modelling the complex adaptive response systems of plants that is beginning to be applied to crop improvement [19,20]. Such models capture the interacting dynamics of major plant growth and development processes and their control systems as they predict trajectories of organism status throughout the crop life cycle. They bring a quantitative physiological perspective to the integration of environmental (E), genetic (G) and management (M) influences. The E, G and M influences are incorporated via the nature and coefficients of the response and control equations in the model [21].

The phenotypic prediction challenge faced in dealing with complex traits in breeding improved crop plants is akin to the navigation problem faced by early mariners who lacked the means to determine longitude accurately [22]. When setting out on a journey with a map and existing knowledge, they seldom reached their desired destination via a consistent path, and sometimes did not arrive at all. This great scientific problem of the 18th century was solved by the development of tools for accurate measurement of time (and hence prediction of longitude) at sea. With reliable and robust nautical timepieces, mariners could better predict their location and voyage reliably. Today we are at a similar early stage in the exploration of biological systems. We build the genetic maps and knowledge, make phenotypic predictions, and set out on voyages. But most of these voyages do not end up at the destination we seek and are difficult to repeat. More often than we would like, the complexity of the system impairs our attempts at prediction. Our current statistical quantitative genetics tools [23], although effective in conventional breeding, have a limited ability to predict the phenotypic destination from the genetic map. We need the equivalent of the mariners’ timepiece to help us better navigate across the scales of biological organization from gene to phenotype.

Parallels exist between exploring unknown geographic and biological spaces. For the general scientific challenge of finding solutions within complex problem space, Stuart Kauffman [24] introduced the concept of exploring the ‘adjacent possible’ (i.e. the process of moving from a known part of the problem state-space to a part that is unexplored). The concept of exploring the ‘adjacent possible’ relates directly to the scientific problem of genetic improvement of complex traits in plant breeding (Figure 1). In this case we seek more informed navigation of the complex adaptation landscape of possibilities associated with crop improvement. We can consider breeding programs as exploring the adjacent possible of the genetic and phenotypic space that is associated with extant and potential



**Figure 1.** Breeding trajectories on the crop adaptation landscape (blue = low yield, red = high yield) generated in the sorghum modelling study outlined in Box 3.

genetic variation for complex traits of crops. The scientific challenge for crop improvement lies in developing improved predictive tools to better explore the complex gene-to-phenotype problem space of the adjacent possible.

Novel modelling approaches to predict gene-to-phenotype associations might help us to deal with this complexity and operate across scales of biological organization for breeding improved crop plants. Various modelling approaches are emerging as attempts at creating the navigational tools we require. They span a range of levels of biological organization from gene network (Box 1), to cell and organ level (Box 2), to plant and crop system level (Box 3). Hence, they vary in the degree of direct association of the models with gene action, and in their capacity to predict whole organism phenotypic responses. They all implicitly incorporate important non-linear interactions among system components and their control and thus enhance predictive ability in the gene-to-phenotype system. Although no approach is yet a mature method with proven properties for the biological navigation required, each approach enables an increased understanding of gene-to-phenotype systems for complex traits.

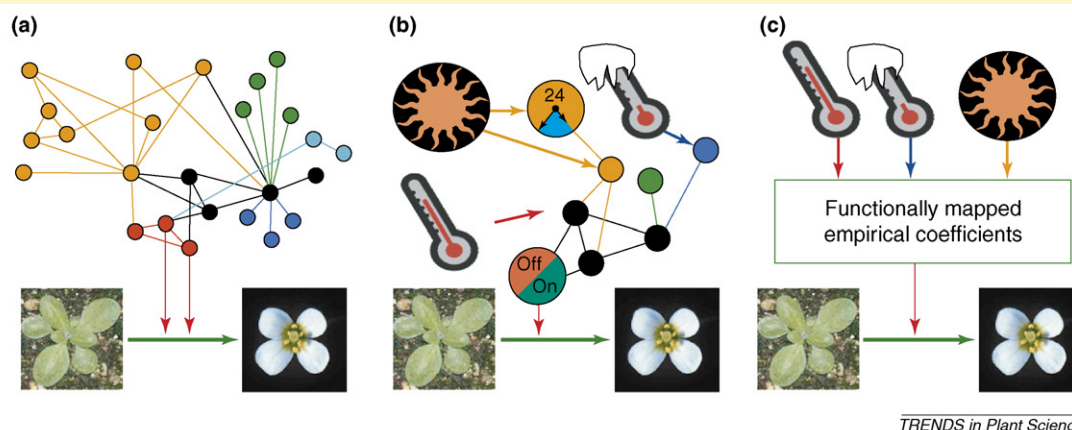
### How can modelling enhance progress in breeding improved crop plants?

Biological models capable of predicting gene-to-phenotype associations for complex traits provide a way of overcoming the uncertainties associated with gene and environment context dependencies that currently impede the progress of molecular breeding [25–27]. Such dependencies arise because the genetic background and environments, within which many genes (or genomic regions) are studied, influence the statistical estimates of their effects. Typically, important epistatic (G–G) and genotype-by-environment (G–E) interactions are not adequately accounted for in either the mapping of quantitative trait loci (QTLs), the

### Box 1. Gene network modelling of transition to flowering in *Arabidopsis*

Extensive research has elucidated many qualitative topological details of the gene network controlling flowering time in *Arabidopsis thaliana* [43] (Figure 1a). However, empirical thermal and photo-thermal models of flowering time originated as early as 1735 [44] and modern versions can account for >90% of flowering time variation in optimized agricultural settings [30] (Figure 1c). The mathematical simplicity of the empirical models is in sharp contrast to the apparent complexity of the gene network, which, at present, comprises >100 genes. Key features of intricate gene networks can be reproduced by models with the same complex topology but with highly abstracted 'ON/OFF' nodal behaviour [45]. In the case of photo-thermal control of transition to flowering, a second feasible axis of simplification seems to be toward systems with far fewer nodes (<12), each retaining complex environmentally driven dynamics, linked in a topology that subsets the full network, and parameterized with expression and phenotype data [31] (Figure 1b). The reason for this success appears to be congruence between the signal processing features of the gene network as captured within the simplified model [32] and the empirical, predictive phenology equations that have evolved through researcher trial and error over the past 270 years.

On mapping the coefficients in empirical phenology equations [30], or linking them quantitatively to sets of alleles occurring at known controlling loci [35], stable associations across environments and genotypes were found. By implication, simplified network models might also serve as tools to forge genome-to-phenome links. Single-gene sequence similarities between model and non-model plants might not be easily exploited by breeders given the functional diversity that conserved genes can exhibit. However, at a slightly higher level, essentially identical, multi-gene signal processing circuits have been found in numerous contexts (e.g. switches [46]). Higher still, network functional dynamics in model organisms suggest the existence of mathematical signal processing schema for non-model plants. For example, many computer simulation efforts have targeted the recalcitrant topic of wheat vernalization [47,48]. No *Arabidopsis*/wheat vernalization orthologues are known. Nevertheless, much wheat behaviour is readily comprehensible in terms of a generalized, *Arabidopsis*-like virtual mechanism [43] wherein a cold-responsive 'gene' down-regulates floral repression in a manner that is subsequently stabilized. Actionable breeding information could result from mapping the coefficients in models derived from such analogies (e.g. Ref. [39]).



**Figure 1.** Modelling transition to flowering in *Arabidopsis*. (a) Genetic network control of the transition to flowering in *Arabidopsis*. (b) Simplified gene network showing environmental drivers. (c) Empirical photothermal model for direct phenotypic prediction.

genomic regions associated with traits, or in the definition of gene targets for genetic engineering. Hence, statistical QTL models and transgenic approaches have limited utility in breeding for complex traits where context dependencies from G–G and G–E interactions are important and not taken into consideration. Ecophysiological models (Box 2) [28–30] and gene network models (Box 1) [31,32] have the potential to accommodate these context dependencies by enabling improved gene-to-phenotype predictions. Many of the G–G and G–E interactions are implicit in the model structure and dynamics. Their coefficients therefore provide robust connection points for QTLs and/or genes.

The potential value of physiological knowledge and integrative crop modelling to yield advance via molecular breeding strategies for complex traits has been demonstrated *in silico* (Box 3) [15,33]. Simulations have shown that an increased rate of yield gain per cycle of selection is expected from the improved prediction of the value of QTL and trait combinations in the population of environments targeted by the breeding programme. Improved phenotypic predictions via crop modelling resulted from an ability to deal with the complex interactions among plant growth

and development processes, environmental effects and genetic controls. This predictive capacity of the dynamic model could be used for favourably weighting more important QTL during their selection in a marker-assisted breeding programme. The approach provides a means to focus on the value of genomic regions, even for complex traits and their combinations. It thus has the potential to change crop improvement dramatically by integrating phenotypic and molecular approaches in breeding improved crop plants.

Despite the potential that modelling has demonstrated, there is not yet an accepted approach to predict gene-to-phenotype associations. We do not have the mature time-piece. The three cases reviewed (Boxes 1–3) suggest that a range of models is likely to prevail, depending on the situation and the trait. However, from these case studies, some unifying themes arise about the nature of the models required and implications for the future.

### Future integrated plant improvement technologies

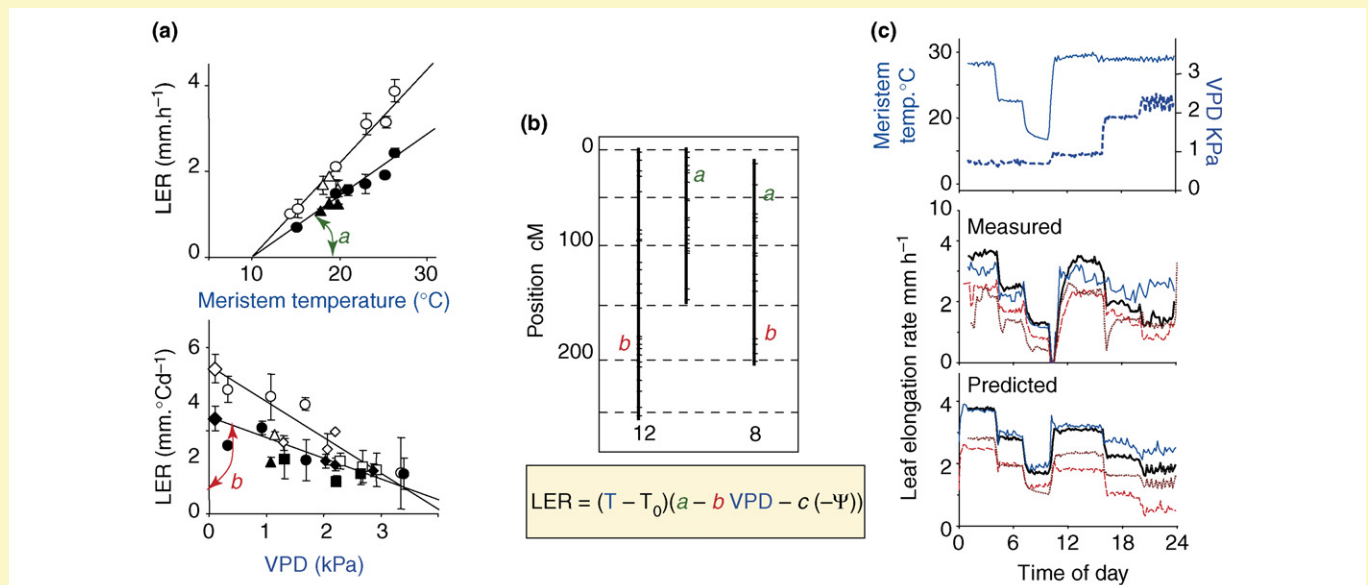
A key, unifying feature of the models considered in this review is the level of granularity that adequately captures the crucial elements of system dynamics. A coarse level of



## Box 2. Modelling the leaf elongation rate of maize

Leaf growth is extremely sensitive to low soil water status or high evaporative demand [28,29]. The resulting reduction in transpiration is an adaptive process enabling soil water to be saved and damaging leaf water potentials avoided. Maize plants of different origins have contrasting responses – some maintain growth under stress whereas others reduce it even under mild stress. Many physiological processes underlie these differences, including changes in the cell cycle, cell wall mechanical properties, hormonal balances and plant hydraulic properties. These processes interact in such a way that any of them could be claimed to account for the emergent behaviour. Quantitative genetics provides a means of approaching this difficulty. When contrasting lines are crossed, the offspring show a large variability in response, depending on the set of alleles each has. The aim is then to associate alleles (QTLs) with particular responses. However, genotype rankings for elongation rate and for final leaf area vary greatly depending on environmental conditions (high G-E interaction), and QTLs are unstable (high QTL-E interaction). Therefore, using classical phenotyping procedures, it is impossible to identify alleles for maintained growth under stress.

Modelling enables the identification of hidden invariant behaviours under an apparent erratic variability [21]. Although final leaf area varies with conditions, the responses of leaf elongation rate to three key environmental variables – meristem temperature, evaporative demand, and soil water potential – remain stable (Figure 1a). Common response curves apply for several experiments conducted at different times in the field, in the greenhouse and under controlled conditions. They can be assembled in a model that predicts leaf elongation rate under any combination of these three climatic variables (Figure 1b). Because each maize genotype is characterized by a unique set of response curves, the QTL for coefficients of the response curves can be identified (Figure 1b). Model coefficients can therefore be estimated for ‘virtual genotypes’ consisting of arbitrary combinations of alleles. Real plants with such combinations (not included in any prior analysis) behaved in a similar way to their virtual counterparts [28,29] (Figure 1c). This opens the way to predicting the leaf growth of completely novel genotypes in any climatic scenario.



**Figure 1.** Modelling genetic and environmental control of leaf elongation rates in maize. (a) Response of maize leaf elongation rate (LER) to the environmental drivers meristem temperature (T) and leaf to air vapour pressure deficit (VPD). (b) Model for LER and related QTL for coefficients on maize linkage groups, where T<sub>0</sub> is the base temperature for maize development, Ψ is pre-dawn leaf water potential, and a, b, c are fitted coefficients. (c) Comparison of LER for ‘virtual’ and corresponding real genotype. Adapted, with permission, from Ref. [28].

granularity is shown to be adequate in all cases ‘...as simple as possible, but no simpler’ [1]. Much of the fine detail is not required in generating a robust prediction of system behaviour.

But when is a model too simple? The case studies indicate that the structure and coefficients underpinning the explanatory capability of the model must link effectively to the genomic regions associated with variability in the complex trait. Other studies [19,34,35] reinforce this need. Gene-to-phenotype prediction based on associations of model architecture with genomic regions must diminish the uncertainties arising from gene and environment context dependencies that often limit the effectiveness of current linear statistical and transgenic approaches. That is, the dynamic model must improve on the existing empirical methods that operate directly from genomic region to phenotypic response. This requires close attention to biological rigour in the structure and representation of

process dynamics in the model while retaining predictive capacity. An appropriate level of rigour and granularity is achieved when one can obtain both stable gene-to-phenotype linkages (i.e. QTL associations with model coefficients that are independent of environment and genetic contexts) and credible predictive extrapolation of effects onto target combinations of genotypes and environments (i.e. the ‘adjacent possible’). The efficacy of early attempts at gene-to-phenotype prediction using crop models [36,37] was restricted by the validity with which the model architecture and associated input coefficients captured and integrated the physiological basis of genetic variation [19].

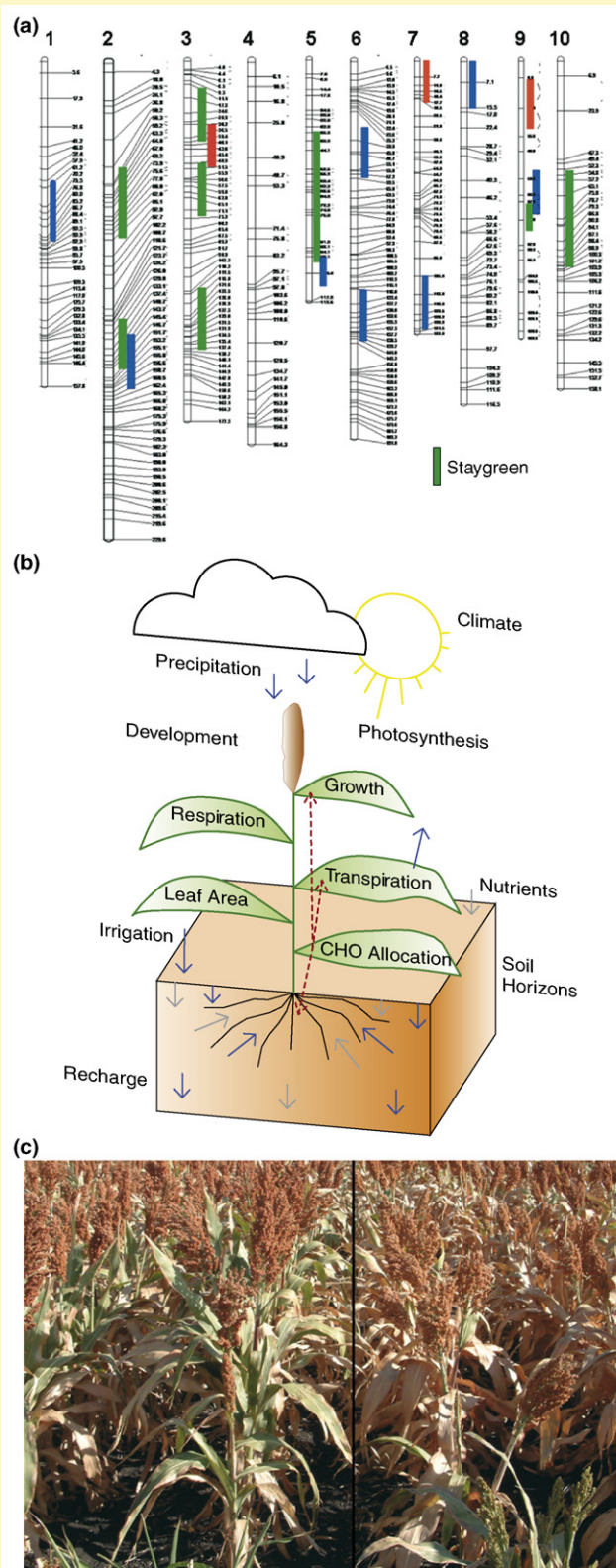
This synthesis implies an emerging central role for a new generation of models in future plant improvement technologies. Such models should:

- Facilitate unravelling of the genetic variation associated with key features of system structure and function.

### Box 3. Multi-trait modelling in grain sorghum

In crops such as sorghum, the molecular knowledge of associations between genomic regions or QTL and trait phenotypes is accumulating rapidly (Figure 1a). However, statistical associations between QTL and complex target traits such as yield are frequently so poor that it would take many years of breeding to combine the large number of QTL into a single high-yielding genotype. Associations between some QTL and component traits are stronger and could be exploited if their consequence on yield could be predicted. For example, although there is genetic control of the trait 'stay-green' [49], its realized effect on yield is complicated by the dynamics of carbon, nitrogen and water 'capture' by the crop, and their internal use over the season [50].

Crop models are typically used to investigate interactions that include unpredictable inputs (future daily weather), predictable inputs (soil parameters) and interventions (e.g. planting date, application of fertilizer). When designed using a framework of physiological determinants for crop growth and development, as in the Agricultural Production Systems sIMulator (APSIM) platform [51] (Figure 1b), they can also be used to study interactions among traits [13]. In the case of stay-green in sorghum, the model becomes the tool to predict the effects on yield of genotypic differences and genotype–environment interactions. Phenotypic expression of stay-green (Figure 1c) becomes an emergent consequence of the interplay of underlying traits such as leaf size, leaf nitrogen, dry matter partitioning, nitrogen uptake and transpiration or transpiration efficiency [33]. Within this context, any genotype could be described by a specific vector of coefficients. Multi-trait simulation studies have been conducted by linking this vector to hypothetical allelic combinations at responsible loci or QTL and using the APSIM crop model to provide predicted phenotypes to the breeding system simulation platform QU-GENE [52,53]. Within the limitations of their underpinning assumptions, these *in silico* studies [33] demonstrated the likely value of crop physiological understanding and modelling in accelerating genetic gain in breeding for yield. That is, the ability to navigate the complex adaptation landscape (Figure 1, see main text) was enhanced.



**Figure 1.** Multi-trait gene-to-phenotype modelling in sorghum. (a) Map of QTLs regulating a range of adaptive traits in sorghum. Updated map courtesy of David Jordan, Queensland Department of Primary Industries, based on an earlier version from Ref. [49], used with kind permission of Springer Science and Business Media. (b) Crop process model. Yield =  $\int \{f(\text{process interaction, } G, M, E)\} dt$  (i.e. yield is the integral over time (dt) of a function (f) of these interacting processes and the influences of G, M and E, where G = genotype, M = management and E = environment). Schematic courtesy of E.A. Bernard, Landscape Architecture, Kansas State University, USA. (c) Contrasting staygreen phenotypes in sorghum. Photograph courtesy of David Jordan, Queensland Department of Primary Industries.

- Provide an analytical framework for understanding the role of genetic variation in system dynamics.
- Provide a dynamic predictive framework that facilitates scaling to whole organism phenotypic consequence from changes in genomic regions.

Challenges remain in finding improved means to connect model coefficients to tangible genomic regions (or genes), as organized on genetic and physical sequence maps. Approaches to linking dynamic system modelling capabilities with advanced statistical methods for molecular breeding provide a plausible way forward. For example, Fred van Eeuwijk *et al.* [38] have presented a statistical multiple QTL model linked to an analysis of plant response curves so that the genotypic responses captured by the coefficient values of the curves were associated with genomic regions. Other studies [39,40] are also progressing this capability by allowing for non-linear responses and simple feedback effects in the analysis system. It seems feasible that a dynamic ecophysiological crop model, of the desired nature outlined, or a gene network model, could be linked in a similar manner.

Nesting different modelling approaches might be required to simultaneously capture stable gene-to-phenotype associations for key processes and prediction of phenotypic consequences at the organism level. For example, the more mechanistic component models and/or gene network models can be embedded within whole crop models [32]. This would allow credible extrapolation of novel combinations of genomic regions to phenotypic consequences in the range of target environments. We are at the starting point but there is some agreement on using this general modelling approach as a way to proceed [19,20,34,41,42]. The ultimate yardstick is whether new methods, such as gene-to-phenotype modelling, enhance the effectiveness of plant breeding. Adding complexity by seeking finer resolution is not always necessary [33]. Furthermore, a fine resolution is not always the best starting point.

### Concluding remarks

Models that capture the dynamics of system function in a way that crosses scales of biological organization to link effectively with genetic variability are indicated as the crucial navigation tools needed for breeding improved crop plants. Like the development of the early mariners' timepiece, building and refining these tools and their applications will not be trivial. Nonetheless, we anticipate that the availability of models capable of navigating biological complexity will revolutionize how we deal with complex traits and underpin a new era of crop improvement.

### Acknowledgements

This work was supported in part by a GRDC grant to G.H. in Australia and an NSF grant 0425908 to S.W. in the USA.

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In celebration of the House of Elzevir's 425th anniversary and the 125th anniversary of the modern Elsevier company, Elsevier donated books to ten university libraries in the developing world. Entitled 'A Book in Your Name', each of the 6700 Elsevier employees worldwide was invited to select one of the chosen libraries to receive a book donated by Elsevier. The core gift collection contains the company's most important and widely used STM publications, including *Gray's Anatomy*, *Dorland's Illustrated Medical Dictionary*, *Essential Medical Physiology*, *Cecil Essentials of Medicine*, *Mosby's Medical, Nursing and Allied Health Dictionary*, *The Vaccine Book*, *Fundamentals of Neuroscience*, and *Myles Textbook for Midwives*.

The ten beneficiary libraries are located in Africa, South America and Asia. They include the Library of the Sciences of the University of Sierra Leone; the library of the Muhimbili University College of Health Sciences of the University of Dar es Salaam, Tanzania; the library of the College of Medicine of the University of Malawi; and the University of Zambia; Universite du Mali; Universidade Eduardo Mondlane, Mozambique; Makerere University, Uganda; Universidad San Francisco de Quito, Ecuador; Universidad Francisco Marroquin, Guatemala; and the National Centre for Scientific and Technological Information (NACESTI), Vietnam.

Through 'A Book in Your Name', these libraries received books with a total retail value of approximately one million US dollars.

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