

Modelling Gene-Trait-Crop Relationships: Past Experiences and Future Prospects

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Abstract

Classical crop models have long been established to understand crop responses to environmental factors, by integrating quantitative functional relationships for various physiological processes. In view of the potential added value of robust crop modelling to classical quantitative genetics, model-input parameters or traits are increasingly considered to represent 'genetic coefficients'. A number of case studies, in which the effects of quantitative trait loci or genes have been incorporated into existing ecophysiological models to replace model-input traits, have shown promise of using models in analyzing genotype-phenotype relationships of more complex crop traits. Studies of functional genomics will increasingly enable the elucidation of the molecular genetic basis of these model-input traits. To fulfil the great expectations from this integrated modelling, crop models should be upgraded based on understandings at lower organizational levels. The recently proposed 'crop systems biology', which combines modern genomics, traditional physiology and biochemistry, and advanced modelling, is believed ultimately to realize the expected roles of *in silico* modelling in narrowing genotype-phenotype gaps. We will summarise recent research activities and express our opinions on perspectives for modelling genotype-by-environment interactions at crop level.

INTRODUCTION

A major challenge in field- and greenhouse- crop production today is breeding for genotypes and realizing their potential in given environments to produce sufficient quality products while maintaining the sustainability of production systems and resource use. This goal can be achieved via creating phenotypes of complex traits at the level of the crop – the community of mutually interacting plants, usually of the same species. A thorough insight into gene-trait-crop relationships is therefore crucial. Currently, there is an increasing recognition amongst geneticists and breeders (e.g. Tuberosa and Salvi, 2006; Dwivedi et al., 2007; Langridge and Fleury, 2011; Messina et al., 2011) and physiologists (e.g. Chenu et al., 2009; Zhu et al., 2011) of immediate need for computational tools to assist breeders more effectively in translating and integrating the outputs from high-throughput genomics research, and to help resolving genotype-by-environment interactions ($G \times E$) efficiently and selecting the best technology interventions and associated breeding systems for their target traits and target environments. Here, we present our views on elucidating the gene-trait-crop relationships by integrating modern plant biology, traditional crop science and advanced systems modelling.

CROP MODELLING TO ASSIST BREEDING

Process-based physiological models of crop growth quantify causality between relevant physiological processes and responses of these processes to environmental variables, and, therefore, allow predictions of crop yields not restricted to the environments in which the model parameters have been derived. Crop models require

environmental inputs (i.e. weather variables and management options) and physiological inputs. The latter inputs are used as model parameters for characterizing genotypic differences. These parameters are also referred to as '*genetic coefficients*' (White and Hoogenboom, 1996; Mavromatis et al., 2001) or '*model-input traits*' (Yin et al., 2000a), implying that model-input parameters might be (at least partly) under genetic control. As model parameters can reflect certain genetic characteristics, crop modelling has long been considered a useful computational tool to assist breeding (Loomis et al., 1979; Boote et al., 2001). Shorter et al. (1991) have long proposed collaborative efforts between breeders, physiologists and modellers, using models as a framework to integrate physiology with breeding.

Given the common experience that crop models based on physiologically sound mechanisms can quantify and integrate responses of crop yield to both genetic and environmental factors, crop physiologists, breeders and modellers have explored the potential of using crop models in various aspects of breeding. These activities include: (1) identifying main yield-determining traits, both under poor and conducive environments for crop growth (Yin et al., 2000b; Heuvelink et al., 2007; Semenov and Halford, 2009), (2) defining optimum selection environments in order to maximize selection progress (Aggarwal et al., 1997), (3) optimizing single trait values (Boote and Tollenaar, 1994; Setter et al., 1995; Yin et al., 1997), (4) designing ideotypes in which trade-offs between conflicting crop traits are properly evaluated (Penning de Vries, 1991; Dingkuhn et al., 1993; Kropff et al., 1995; Haverkort and Kooman, 1997), and (5) assisting multi-location testing (Dua et al., 1990) and explaining G×E (Mavromatis et al., 2001; Van Eeuwijk et al., 2005).

All these studies, based on model simulations, are to give suggestions that breeders may use. Stam (1998) and Koornneef and Stam (2001), from a geneticist's and breeder's point of view, expressed their concerns about this model-based approach that ignores the inheritance of the model-input traits. For example, for designing ideotypes by modelling, it is assumed, either tacitly or explicitly, that these traits can be combined at will in a single genotype. Such an assumption ignores the possible existence of constraints, feedback mechanisms and correlations among the traits. Constraints might be imposed simply by the fact that little genetic variation exists in the genetic material available for selection. Thus, models may not identify those traits for which gain via breeding may be easiest (Jackson et al., 1996). Correlations between the traits, due either to a tight linkage between genes or to a single gene that affects multiple traits (pleiotropy), may seriously hamper the realization of an ideotype (for example, an early-maturing potato cultivar with high resistance against late blight). Knowledge of the genetic basis of phenotypic variation, even described in terms of model-input traits, is crucial for a successful breeding programme (Stam, 1998). Therefore, understanding the inheritance of the model parameters within the framework is required (Stam, 1998). To assist the development of efficient breeding strategies, crop modelling requires quantitative understanding of the inheritance of the model-input parameters.

INTEGRATION OF CROP MODELLING WITH GENETICS

In genetics, complex crop traits can be unravelled into the effects of individual QTL – quantitative trait loci (Paterson et al., 1988), commonly using the materials of a segregating population derived from a bi-parental cross. This QTL approach can also be applied to model-input parameters to elucidate their inheritance (Yin et al., 1999a, b).

A common result of QTL analysis of complex crop traits is that QTL expression is usually conditional on the environment and this greatly impedes the application of QTL-mapping information for manipulating complex traits (Stratton, 1998). Crop models can potentially be of help in this respect to better address genotype-phenotype relationships, provided that model-input parameters can be easily measured (Yin et al., 2004) and vary little with environmental conditions (Reymond et al., 2003; Tardieu, 2003). Model-input parameters (or '*genetic coefficients*'), reflect effects of genetic origin in the way that one set of parameters represents one genotype (Tardieu, 2003). Hence, the models manifest

that the crop phenotype is achieved through nonlinear interactive and ontogenetic responses of component processes to multiple environmental factors. The models can help to identify traits having the greatest impact on yield and simulate G×E and even epistasis (e.g. Chapman et al., 2003). Such an approach has added value to classical genetics, since geneticists often ignore or overlook competition, density, nutrient supply, morphology, physiology and plasticity, lumping such matters vaguely under the ‘G×E’ term or introducing simple response functions in their statistical models (e.g. Van Eeuwijk et al., 2005). First attempts have been made through so-called ‘QTL-based ecophysiological modelling’.

Such studies attempted to link crop modelling with genetics, focusing on the G×E problem and genotype-phenotype relationships. A simple genetic model can be assumed for QTL analysis of the component traits, but more sophisticated genetic control (epistasis and G×E) on the complex trait per se can be manifested when QTL-based parameter values are fed-back to the ecophysiological model. The QTL-based models can be used to predict performance of any genotype in any environment.

This approach of QTL-based modelling was first illustrated to predict a very complex trait: the grain yield of barley (*Hordeum vulgare*) by Yin et al. (1999a,b, 2000a). The same approach for QTL-based modelling analyses was applied to crop traits such as leaf elongation rate in maize (Reymond et al., 2003) and flowering time in barley (Yin et al., 2005), rice (Nakagawa et al., 2005) and *Brassica oleracea* (Uptmoor et al., 2008), and fruit quality in peach (Quilot et al., 2004, 2005) and tomato (Bertin et al., 2010; Prudent et al., 2011), all relatively simple traits with well-defined influences of some dominant environmental factors (such as vapour pressure deficit, soil moisture content, temperature and photoperiod). In the domain of morphological traits, the phenotypic effects of QTL for culm length, grain number, and grain size in barley have been simulated using morphologically explicit models (Buck-Sorlin, 2002). A common feature of these studies is that predictability of QTL-based models is nearly comparable to that of the model using original parameter values, as the gain from removing random noise in original parameters by QTL-statistics is roughly cancelled out by the loss due to the fact that the identified QTL cannot explain 100% of the genetic variance of the parameter values (e.g. Yin et al., 2005). These studies on relatively simple developmental, morphology-related or growth traits demonstrate that the approach can unravel G×E, and highlight the potential to analyse more complex traits manifested through season-long growth dynamics.

While the proposed QTL-based modelling approach could potentially deal with G×E, it cannot solve all limiting factors, especially non-transferability of information obtained from one cross to another. The non-transferability can be largely due to the possibility that a QTL detected in one cross does simply not segregate in a second cross because the parents of the second cross carry identical alleles at that QTL. A gene ‘important’ for physiologists or modellers might be useless for geneticists or breeders because if the gene is physiologically crucial, its variation will have been strongly reduced over generations of breeding (Prioul et al., 1997); so QTL will hardly be detected at such a gene locus. In this context, the approach as practised for a bi-parental cross could be extended using linkage disequilibrium mapping, in which association between genotypes and phenotypes is scrutinized over a large germplasm collection (e.g. Remington et al., 2001). This development in association genetics may enhance opportunities for gene-based physiological modelling, especially with development of genome-wide surveys of variation using high-throughput genotyping tools (such as SNP - single-nucleotide polymorphism) across crop germplasm collections (McNally et al., 2009; Huang et al., 2010). This development in association genetics may enhance opportunities for gene-based crop modelling. So-called gene-based modelling has empirically practised by White and Hoogenboom (1996) and Messina et al. (2006), who predicted flowering and yield traits of crop cultivars via regressing input parameters against binary values of a few relevant candidate genes. The SNP-based association mapping can detect many genes and unravel their functions, thereby enabling model-input parameters to be potentially related to many genes.

In short, genetic mapping dissects a quantitative trait into various genetic factors – QTL (Paterson et al., 1988), but it can only predict the trait phenotype in independent new environmental conditions to a limited extent (Stratton, 1998). Ecophysiological modelling can reveal how G×E comes about (Tardieu, 2003), but it does not consider the genetic basis of model parameters that describe genotypic differences. Combining ecophysiological modelling and genetic mapping can dissect complex traits into component traits, integrate effects of QTL of the component traits over time and space at the whole-crop level, and predict yield performance of various genetic make-ups under different environmental conditions. There is *in silico* evidence that this combined approach can facilitate translating the QTL mapping into more efficient marker-assisted breeding strategies (Hammer et al., 2006). To this end, more accurate crop models would facilitate the improvement of efficiencies of combined model- and marker-assisted breeding.

CROP SYSTEMS BIOLOGY

Current crop models are mostly rough, in terms of their ability of treating gene-trait-crop relationships among relatively similar lines within a genetic population (McLaren, 1995). Systems simulation modelling has long been suggested as a powerful tool to understand crop yield formation and to assist crop improvement programmes. However, according to Lawlor (2002), the lack of truly ‘mechanistic’ crop simulation models (which make use of biochemical information) is a major constraint to advance the understanding of crop yield traits. The modelling studies at the crop level using some knowledge of fundamental plant biology (e.g. biochemistry) are currently sporadic, modelling results published so far to analyse yield traits are inconsistent, and some models are based on untested hypotheses. We, therefore, have proposed a more systematic modelling approach – ‘crop systems biology’ (Yin and Struik, 2007, 2008, 2010), to analyse complex traits at the crop level, not only with the aim of establishing close links with understanding at the gene or genome level, but also in terms of its comprehensive reliance on the whole-metabolism biochemistry and physiology. Therefore, the proposed crop systems biology is a crop-level approach to modelling complex crop traits relevant to global food production and energy supply, via establishing the links between ‘omics’-level information, underlying biochemical understanding, and physiological component processes.

Development of crop systems biology models certainly depends on what trait a researcher wants to target. Crop yield is a complex trait that most existing crop simulation models have attempted to predict. It may not be surprising that simulation of yield formation should be a first major focus trait in crop systems biology. In addition, if crop yield can be modelled accurately, underlying mechanisms for traits of resource use efficiencies (such as water use efficiency or nitrogen use efficiency) can be analysed accordingly. The question is how to achieve a crop systems biology model for the yield trait.

We propose a two-step strategy (Yin and Struik, 2007). First, a widely used framework of many existing crop simulation models including processes such as photosynthesis, respiration and assimilate partitioning can still be used, especially as a starting point. At the level of these processes, there are rich biological (physiological and biochemical) data and therefore the understandings are of the highest confidence. For this first step, crop systems biology models may not be necessarily more complex than existing crop simulation models in structure, nor is their computational requirement. However, model algorithms for individual processes are supposed to be more mechanistic. In many cases, a summary form of a detailed biochemical model – e.g., the photosynthesis model of Farquhar et al. (1980) coupled to CO₂ diffusion algorithms (Yin and Struik, 2009) – can be incorporated as a sub-model. In other cases, direct results or stoichiometries from biochemical studies (e.g., examination of the biochemical pathways for production of proteins, carbohydrates and lipids from glucose by Penning de Vries et al. (1974) can be utilized. A prototype of crop systems biology models needs to be made

available from this first step, in which physiological and biochemical information at the process level is assembled and then scaled up to the crop level in a way similar to temporal and spatial integrations as practised in conventional crop simulation models. In relation to crop improvement, a key element of the first step would be to identify the parts of mechanisms that are conservative in energy and water transfer, and in carbon and nitrogen metabolisms, and the parts of mechanisms that show genetic variation and are potentially amenable to selection and engineering. In case of grain yield, the prototype models should allow identification and quantitative assessment of specific parts of metabolic pathways and processes, which could be altered to achieve improvement of yield potential. The parts showing genetic variation can be identified by genetic analysis or the 'omics' approach in terms of the expressions of specific genes, proteins or enzyme activities.

After the first step is achieved, crop systems biology modelling could move to the second step as further progresses at the 'omics'-level understanding are being made, towards reaching down to lower organizational-levels. For this, it is necessary to map the organization levels and the communication systems between these levels for the different key processes (Struik et al., 2007). Modelling for reaching down to the lower levels is most likely to be done in a manner of one-process-at-a-time; and in this respect, a modular design of the model is important to ensure that changes of a sub-model will not affect other parts of the model. Welch et al. (2003) have already developed a neural network model of *Arabidopsis* flowering time control, based on studies on qualitative, genetic characterization of major flowering time genes in this model plant species. Similar modelling studies could be performed for phenology of crop species. Further, existing modelling of metabolisms, such as the Benson-Calvin cycle of photosynthesis and the photorespiratory cycle (cf. Giersch, 2000) and nitrogen assimilation in relation to the activity of key enzymes (e.g., nitrate reductase and glutamine synthetase), could also be added. With the rapid development of functional genomics in the wake of high-throughput technologies, combined studies of physiological components with gene expression profiles should illustrate the function of genes, biochemical pathways and cellular processes that are affected in a coordinated manner (Stitt and Fernie, 2003). Such studies should lay the groundwork for elucidating regulatory networks and causal linkages among gene products, biochemistry and whole-plant physiology. Integrated molecular systems biology models for particular metabolism or process are expected to increasingly become available. Such models can potentially be embedded into crop systems biology models. Clearly, different temporal, spatial and structural scales are required for different components, pathways, and processes of the model; and ultimately, crop systems biology will develop into a highly computer-intensive discipline. Such coupled models should enable in silico assessment of crop response to genetic fine-tuning under defined environmental scenarios, thereby being powerful tools in supporting breeding for complex crop traits.

FINAL REMARKS

Manipulation of a relatively small number of genes (notably, dwarfing and photoperiod-insensitivity genes in many crops) had resulted in the first 'Green Revolution'. For the next 'Green Revolution' to happen, we have to deal with many genes so that they work in concert. Alterations made at the genome level, though substantial, could have little effect on the crop-level phenotypes (Sinclair et al., 2004; Yin and Struik, 2008). Systems biology should not be the privilege of only those working on molecular, sub-cellular or cellular levels. To allow systems biology to have significant impact, the information from fundamental plant biology should reach up to the crop level, and 'crop systems biology' should be established to deal with complex 'gene-trait-crop' relationships. For that to happen, it is necessary to have the long-term, multi-disciplinary efforts towards the next 'Green Revolution' to solve some imminent food-, feed-, and energy-related, 'real-world' problems.

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