Meetings

Systems biology and the biology of systems: how, if at all, are they related?

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It is said that Einstein never liked the term 'relativity', and indeed the word had already been used previously by Poincaré in connection with a rather different area of mathematical physics. Nevertheless, the expression quickly acquired a life of its own and soon 'relativity', 'relativistic' and so on became highly specific labels with tightly circumscribed connotations in the context of physics. The meanings of individual words matter, particularly when they can open up or narrow down whole areas of science.

We seem to be at such a point now with the term 'system' as used in biology. The founder of the present journal, Sir Arthur Tansley, introduced the concept of the ecosystem in 1935 (Willis, 1997). Agricultural systems have been recognized and studied since science was first applied to food production. Most biologists, particularly those working at the physiological or ecological level, think they have always aimed for system-level understanding. What is new about systems biology (SB) as currently conceived? It seeks to bring together understanding of structure (in terms of gene and biochemical networks), system dynamics (involving predictive modelling), system control methods and system design. But crop scientists, ecologists, developmental biologists and the like who use tools such as 'omics, large-scale data capture, informatics and modelling will say that they are also concerned with such systems properties.

Hence the title of the symposium, which sought to clarify whether SB really is a new and exclusive form of biology, and how it might benefit, and benefit from the experiences of, biologists who already approach their subject in a system-orientated fashion. This concern was expressed bluntly, echoing the title of John Sheehy's (IRRI, Manila, Philippines) presentation, in the final discussion session led by Malcolm Bennett (University of Nottingham, UK): are terms such as 'plant systems biology' and 'crop systems biology' useful or useless?

> *'As one moves up the scale of biological complexity, the environment becomes a bigger, and increasingly uncontrollable, factor.'*

What is a (biological) system and what are the benefits of analysing it?

Several speakers at the symposium set out what a biological system meant to them. Sheehy defined a system as 'a number of interacting elements existing within a boundary which is surrounded by an environment.' Interaction within a boundary is a common property of ideas about SB and the biology of systems. Interactivity takes the form of networks, circuits, feedback and feed-forward processes, iteration, recursion and proliferating complexity with increasing numbers of system components. Andrew Millar (University of Edinburgh, UK) visualized the SB discovery process as a cycle comprising data acquisition (typically in massive amounts, crossing time and length scales and dependent on powerful bioinformatics resources), analysis, modelling and validation and deployment of models for prediction and generation of new understanding. His own work on the circadian clock in Arabidopsis showed the SB approach in action. His group has developed a feedback loop-based model of gene interactions with the property of predicting connections and additional components that could then be sought experimentally (Locke *et al.*, 2006). In this way they hypothesized the existence of a previously unsuspected gene (*Y*) and, by analysis of mutants, confirmed that *Y* is identical to the *GIGANTEA* gene. This work is beginning to link up with that on other species such as mouse and Drosophila, indicating the potential of the systems approach to establish broad biological principles.

June Medford (Colorado State University, USA) provided a remarkable glimpse of what might become possible when we gain functional understanding of the cellular circuitry of the plant (Antunes *et al.*, 2006). Exploiting recent advances in knowledge of the biochemistry and genetics of chlorophyll synthesis and degradation (Kräutler & Hörtensteiner, 2006; Tanaka & Tanaka, 2006), her group has engineered plants that can report on specific abiotic stimuli in the environment by colour modulation. Noninvasive detection of pigmentation changes means that such plants become real-time sentinels. It is rare for participants at a plant science conference to witness images of detonations in a presentation, as happened here in discussions of the use of such sentinels to detect volatile explosives. The array of environmental sensor pathways that plants, as sedentary organisms, must deploy for acclimation, adaptation and survival makes them particularly suited for exploitation as sentinels, and SB can be expected to contribute knowledge for effective design of the underlying circuitry.

What types of data and tools are required for plant SB?

SB places great emphasis on massive data sets and the use of bioinformatics resources and computational power to shake meaning out of them. The implications of the data tsunami engulfing biology, the need for heavy-duty computing, data management and quantitative processing, and the issue of whether we are heading for a new kind of hypothesis-free science have been well aired and were discussed again at the present Symposium. Tools also need to be developed for quantifying attributes such as size and shape if models of growth and morphogenesis are to be brought into the same systems arena as the likes of 'omics. Andrew Bangham (University of East Anglia, Norwich, UK) described new approaches, illustrated by work on leaf growth and flower development. Time-lapse images of features tracked in two and three dimensions lead to models that can simulate closely the final forms of organs, how these were arrived at topologically and the morphogenetic fields that define them. These in turn are reflected in observed and hypothetical spatial patterns of gene expression (Lee *et al.*, 2006).

Just as observational approaches to system definition have undergone a major technology-driven quantitative and qualitative shift, so too is the world of plant modelling developing new and powerful tools for representing structures, functions and morphogenesis. Gerhard Buck-Sorlin (Wageningen University, the Netherlands) described recent developments in functional-structural plant modelling (FSPM; Godin & Sinoquet, 2005), which aims to define the complex interactions between plant architecture and the physical and biological processes that drive plant development at several spatial and temporal scales (Buck-Sorlin *et al.*, 2005). Buck-Sorlin argued that FSPM is effectively the upscaled equivalent of SB. He presented a new synthesis of the traditional programming paradigms used in plant modelling (procedural, object-oriented, and rule-based) and showed how modularity and embedding one paradigm into another can extend the range of processes that can be modelled. The elegance of the approach was in this case matched by the aesthetics of the virtual roses presented as examples.

Jan Kim (University of East Anglia, Norwich, UK) described transsys (Kim, 2005), a computer language framework for modelling regulatory gene networks. The transsys framework supports construction of computer models integrating regulatory gene networks with other levels, such as morphogenesis, and provides optimization tools that fit parameters on a global, system level. This language may be integrated with the Lindenmayer (L-system; Prusinkiewicz & Rolland-Lagan, 2006) approach to morphological modelling. Kim, with Bangham, has shown how L-transsys can be used to model floral structures and their genetic variants.

Is SB the privilege of scientists working at the cell-to-molecular level?

Xinyou Yin (Wageningen University, the Netherlands) articulated the question that has been on most people's minds since SB arrived on the scene: are the rules of SB such that only the molecular and subcellular aspects of biology can be addressed through application of its approach? It is of concern to many plant scientists that the plant SB community will be more concerned with sustaining its credibility in the eyes of people in the yeast or T-lymphocyte business than with translating their advances into new understanding of higher-order plant phenomena such as photosynthesis, crop yield and ecological fitness. The answer, of course, is dialogue, together with demonstrations of convincing cases connecting gene circuitry with real phenotypes. Yin argued that a way forward is to use trait mapping linked at a reductionist level to molecular genetics and genomics, and at the extensive, phenotype level to crop process models (Yin *et al.*, 2004). He showed examples of the dissection of complex characters into component traits based on ecophysiological insight and indicated that the integrated approach gives better resolution of genotype-by-environment interactions. This view of crop systems biology is highly consistent with, and enriches, the long-established plant breeding concept of the ideotype (Donald, 1968).

Can SB approaches aid studies at higher physical scales?

The systems discussed at this meeting share the characteristics of hierarchical structure and emergent properties. Scaling is a profound challenge in biology. For example, there are conceptually and mechanistically indisputable and statistically rigorous models of photosynthesis that provide highly effective simulations of the biochemistry and physiology of the process (e.g. Yin *et al.*, 2006; Dubois *et al.*, 2007); but moving up to the whole-plant, crop or community level, photosynthesis as modelled in this way bears only the most limited predictive relationship to productivity and fitness. In fact we might as well use the term 'vanishing' rather than 'emergent' for the properties of systems at such higher scales.

The issue of emergent (or vanishing) properties was addressed in the presentation by Sheehy. He surveyed the general field of empirical and mechanistic models and focused on how modelling starts with observations at the whole-system level and progresses as understanding of the component parts and subsystems increases, resulting in a caricature of the system represented in equations. Much is made of SB as the means of brokering agreements among biologists, computer scientists, engineers and mathematicians to direct their efforts towards resolving common problems. In fact such a convergence of disciplines seems to happen, apparently spontaneously, once a generation or so. It happened in the middle decades of the last century when physicists and chemists made common cause with the geneticists to crack the structure of the gene. In more recent times, crop science in the run-up to the Green Revolution had attracted physical scientists (like Sheehy), statisticians and modellers to put breeding and agronomy on a quantitative basis (motivated in part by idealistic 'feed the world' sentiment). Sheehy showed how lessons learned from that turn of the cycle could and should inform how contemporary SB develops. He also argued that SB should contribute to meeting an urgent global objective – increasing crop yield. The strategy for addressing this through the creation of C_4 rice (Mitchell & Sheehy, 2006) provoked much discussion.

As one moves up the scale of biological complexity, the environment becomes a bigger, and increasingly uncontrollable, factor. This is an understandable justification for confining the practice of SB to the subcellular and the time-limited. However, important biological insights can be overlooked because close control of experimental conditions causes critical environmental interactions to be excluded. Two dramatic examples were provided by Stefan Jansson (Umeå Plant Science Centre, Sweden). He described work on the regulation of light harvesting in Arabidopsis (Külheim *et al.*, 2002) in which a predicted fitness disadvantage of knocking out a component of the feedback de-excitation process of photosynthesis could not be verified under standard controlled cultivation conditions. If, however, the knock-out population was grown in a natural environment, its performance was significantly inferior to that of wild-type, measured in terms of a number of fitness parameters. In other words, the feedback de-excitation mechanism, which is pretty well described in molecular and biophysical detail and therefore clearly qualifies as a system in SB terms, did not reveal its true function and biological significance until it was analysed in an uncontrolled fluctuating and unpredictable environment. This is quite likely to be the rule for many of the critical adaptive and developmental systems of plants, and represents a challenge to some conventional SB thinking. Jansson also introduced a further example of the work of his group on 'real-world genomics'. Using DNA microarrays, they carried out transcript profiling in leaves of a single field-grown aspen tree (*Populus tremula*) over several years, focusing particularly on the period covering initiation through to completion of senescence. Gene expression certainly changed over each experimental period, but there was no consistent relationship to stage of senescence and nothing to suggest that a particular set of genes represented a senescence programme. This leads to the conclusion that transcriptional patterns during tree leaf senescence represent a timetable (Keskitalo *et al.*, 2005) rather than a programme. Inferring the existence and functions of genetic programmes, networks and circuits from 'omics data is at the heart of the SB philosophy. Perhaps particularly in the case of plants, it is important to bear in mind that the urge to keep uncontrollable environmental influences out of the picture has its dangers.

An implication of this conclusion concerns the current Minimum Information About a Microarray Experiment (MIAME) checklist, which researchers are required to use when submitting transcriptomics data to public databases. As currently implemented, MIAME cannot easily accommodate descriptions of field-based experiments. Discussion led to the conclusion that MIAME and other minimum-information checklist standards will need expansion to include the whole gamut of research on plant-based systems.

Can SB approaches aid ecological and agricultural studies (and vice versa)?

Molecular ecology considers the fitness of particular genes in particular environments. The flow of transgenes between crops and their wild relatives is a test-bed for the study of how the fitness game is played out in the natural world. Mike Wilkinson (Aberystwyth University, UK) discussed this subject from the systems perspective. Using the example of cultivated and wild *Brassica* species in the UK (Ford *et al.*, 2006), he showed that it is necessary to range across extremes of scale to gather the data necessary to model and predict. These studies extend from the level of the genes themselves, defined in molecular (DNA sequences) and cytogenetic (genomic regions) terms, all the way up to determination of landscape-level distributions of wild and cultivated populations by terrestrial ecological analysis and remote sensing. The objective is to construct a predictive model of gene flow and its ecological consequences that characterizes the selection pressures experienced by the wild recipients and their community associates on introduction of a novel gene.

Andy Taylor (Swedish University of Agricultural Sciences, Uppsala, Sweden) similarly defined a system that transcends scale and highlights the opportunities and challenges of driving the SB approach out from the cell and into the big wide, often hostile world. The ectomycorrhizal (ECM) symbiosis in boreal ecosystems is characterized by species richness and taxonomic diversity amongst the soil fungi that associate with the roots of a range of woody perennials (Toljander *et al.*, 2006). Taylor argued that there are many parallels between the approaches, concepts and ideas of SB and those used within ecosystems ecology. He showed that redundancy and modularity are principles underlying biological robustness in ecosystems as they do in narrow-sense SB. System degradation (both graceful and catastrophic) is also a feature of behaviour at both scales. Furthermore, system perturbation is a powerful tool for probing functions and interactions; in the case of the nutrient-poor boreal ecosystem, addition of nitrogen elicits a dramatic response from ECM fungal communities and such interventions are proving useful in developing and validating mechanistic models. It is undeniable that, at such extremities of scale and biological complexity, SB and agro-ecological systems biology stand either side of a yawning chasm. However, the present Symposium established that there is already a potential for a convergence of thinking and tools that can bridge the gap.

What are the grand challenges in plant biology that SB can help address?

The 21st century will be dominated by three global grand challenges: climate, energy and food. These are clearly linked both in origin and in the potential remedies for the problems they represent. Fundamental knowledge and practical applications of plant science are at the heart of humanity's response to the testing times it faces. The Symposium agreed that systems biologists and biologists of systems need to make common cause if taxpayers, charities and businesses are to continue to invest in the promises made by the research community. As William Blake put it: 'I must create a system, or be enslaved by another man's.' Whether the goal is the C_4 rice plant, the sustainable mycorrhiza-based forest ecosystem, the *in silico* Arabidopsis or the perfect rose, it seems clear that the future of plant science has to lie in engagement with biological systems in their entirety.

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