The Future of UK Plant Systems Biology

Community Forum

GARNet

Genomic Arabidopsis Resource Network

John Innes Centre

March 20th 2006

http://garnet.arabidopsis.org.uk

Background

Systems biology has a grand vision – understanding all the components of a biological system and their interactions, across all relevant levels of organisation.

A laudable aim but how do we achieve this goal?
To date the EPSRC and BBSRC have funded three Centres for Integrative Systems Biology (CISB) in Newcastle, Imperial College and Manchester and will fund another three from the second round of the initiative this year. These centres are intended to concentrate all the expertise and facilities required for systems biology in a single location, even a single building.
http://www.bbsrc.ac.uk/science/initiatives/cisb_phase2.html

But is this a successful way to approach to system biology in a widely distributed community such as plant research, which has over 350 laboratories spread across the UK? In addition to this approach would it possible for groups of plant laboratories in the UK to coordinate their work, in order to tackle large-scale projects? Or can we set up a distributed centre for plant systems biology?
These are the types of questions posed to GARNet by BBSRC's panel on Integrative Systems Biology (ISB) which has asked GARNet to produce a report on how systems biology can best be approached in UK Arabidopsis research. This report must incorporate the communities view and be with the BBSRC by June 2006.

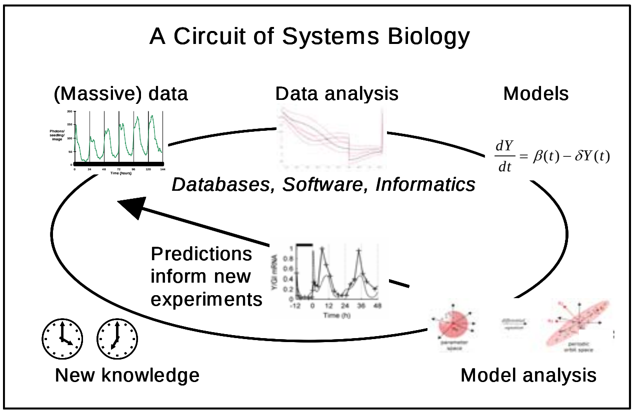
No specific objectives were set by the ISB panel for this report though the following were provided as potential areas for discussion:-

1. What might be the realistic research objectives of a UK Arabidopsis systems biology programme over the next 5/10 years?
2. What capabilities does the community currently have, what additional capabilities (skills, equipment, tools etc) need to be developed, and how should this be done?
3. What benefits might be expected from this?
4. What potential is there for international engagement?

So what is Systems Biology?

The ISB panel has avoided an exclusive definition of Systems Biology, preferring to list the characteristics of a systems approach and noting that the balance among these will vary among projects:

- An integrative approach to the subject
- Large experimental data sets (we would add, of high quality).
- Predictive capability based on modelling
- A mix of inputs not only from across biology but also from the chemical, physical, engineering, mathematical and/or computational sciences.



The result is an iterative interaction between experiments and modelling.

The story so far

A) Edinburgh Workshop

To kick start discussions in this area the BBSRC and GARNet held a workshop entitled 'Succeeding in Plant Systems Biology' in Edinburgh in July 2005. The workshop aimed to investigate systems biology approaches to plant science and consider the advantages and problems in applying such approaches to research. A full report of this meeting is available on line http://www.bbsrc.ac.uk/about/gov/panels/isb/docs/PSB_workshop_report_sept05.html

Delegates attending the workshop were asked to consider the current challenges and barriers to applying systems biology to research by addressing four main questions. A summary of these discussions are provided in Appendix A.

B) Interim Report

During the autumn of 2005 the GARNet committee deliberated over the issues raised by the Edinburgh workshop and carried out consultations with international researchers to generate an interim report on UK plant systems biology (submitted to the ISB panel in January). A full copy of the report is provided in Appendix B

The GARNet committee discussions for this report were wide ranging, covering a variety of topics including;

Can systems biology be carried out in a multicellular organism?

Is a collegiate effort possible in the context of the diverse research objectives and priorities of individual scientists and their institutions?

Should a community driven project focus on a single biological research goal or just provide the necessary new theory, data analysis and modeling tools?

What type of training is required to promote closer collaboration of biologists with theoreticians and modellers?

How will data quality, capture, storage and distribution be assured in a multi site project?

How do we attract the appropriate theoreticians to work in plant science?

Potential solutions to some of these questions are provided in the report whilst others required further community input.

C) Town Hall Meetings

To canvass community opinion on the interim report and the questions it raises GARNet has and will be holding town hall meetings during 2006.
The first of these meetings was in conjunction with the New Phytologist conference 'Networks in Plant Biology' 26th-27th January in London.
http://www.newphytologist.org/networks/

Those attending the meeting were asked to read the interim report and consider the following

1. What concrete steps would most facilitate systems biology approaches in the UK Arabidopsis community? Examples include: a national 4-year PhD programme with central facilities; ‘study group’ events that allow plant scientists to present their research questions to theoreticians for preliminary analysis; a set of demonstrator projects that show what can be accomplished by the systems approach in plants; a networked research activity focussing on a longer-term goal; tools and resources for the acquisition of large-scale data sets.

2. Agreeing a single research goal might have significant advantages. What would be a suitable goal for a coordinated, national project? Examples might include: systems biology of the leaf, of the guard cell, of the auxin signalling pathway. For comparison, the systems biology centre in Cambridge proposes to have 100 researchers focussing on the *Notch* and *wnt* signalling pathways in Drosophila.

3. One aim of a large-scale systems biology project could be to collect a particular data set or to provide a particular resource in support of a national project, in addition to gathering researchers with the relevant expertise. Which data sets or resources would convince you to work in a new area, or which could you contribute to providing? Examples might include: a protein-protein interaction map, completion of the metabolic map, imaging of protein localisation throughout development, integrating biological databases, informatics that automates the link between data and models.

There was a lively debate over the report and those attending the meeting agreed that:-

1. Training was an essential part of a community led effort in systems biology. However, it is not part of BBSRC remit to allocate initiative funds for studentships (a policy that the audience were critical of).

2. A single goal which all the community could sign up to was not agreed upon. Instead there were suggestions that all proposals in this area should be enabling and used as a foundation for other projects to build on in the future from responsive mode funding.

3. Delegates requested a generic level of systems biology support in a similar manner to the support and advice GARNet previously provided for genomic technologies. Examples provided by the floor to achieve this included; an annual retreat for life and theoretical scientists, a summer school for students and a centre to which labs could send personnel for training.

The next town hall meeting open to the whole community will take place during the SEB Canterbury Meeting on the 5th April 2006.

Norwich is a site for cutting-edge plant science research, and since two Garnet committee members are located here (Jonathan Jones and Nick Harberd), we have decided to implement a “town meeting” at JIC to enable questions and answers with, and feedback from, JIC, UEA and IFR scientists.

Appendix A
<u>Edinburgh Workshop - Discussion Summary</u>

Q1 What advantages might systems biology offer to plant sciences?

Formal representation as a 'system' allows:

- Better comparison between organisms
- Integration of disciplines
- Scalability from pathways and subsystems to landscapes
- Common structures for data collection, analysis and design
- Mathematical abstraction with predictive power
- Development of new tools

Q2 What areas of the plant sciences might be particularly amenable to such approaches?

All areas were seen as amenable to a systems approach from single cells to ecology, and even the landscape examples included; environmental responses, the leaf as a system, plant pathogen interactions

Q3 What are the current technical and other barriers in applying systems biology approaches to plant research?

- Lack of multidisciplinary training (MSc, PhD)
- Poor communication with other disciplines, need to develop common languages.
- Lack of "best practice" for data handling
- Spatial heterogeneity (many cell types contribute to each data point)
- Lack of examples of good predictive models that have been demonstrated to work.
- Project Timescales are too short to develop interdisciplinary research.

Q4 What scientific expertise can the UK in particular offer in this context?

- Broad excellence in plant science, computational biology and informatics
- (not always well connected)
- Numerous resources
    - Germplasm collections in a range of species
    - Large data sets e.g. Transcriptomic data sets (NASC)
    - Genomic databases
    - Metabolomics at Rothamsted and Aberystwyth
    - Large *in silico* crop breeding databases,
- Wide range of species studied

Interim report of the GARNet Advisory Committee on Arabidopsis Systems Biology in the UK

1. Key recommendations

Biological research using *Arabidopsis thaliana* can profitably adopt systems approaches and is doing so in some areas. Arabidopsis researchers must build the capacity for systems analysis, if the UK's strength in Arabidopsis biology is to be reflected in systems models that, ultimately, will lead to a whole-plant model. Challenges include the acquisition of data from single cells or cell types (see 3B) and increasing theoretical research on Arabidopsis biology (see 3C). The committee's interim recommendations are to establish:

- A distributed, 4-year PhD training school in Arabidopsis systems biology, with central facilities (see 4A)
- Networking activities for Arabidopsis researchers with physical, computer and mathematical sciences (see 4B)
- Demonstration systems research projects on tractable subsystems (see 4C)
- Additional of tools and resources, contributing to the acquisition of large-scale data sets (see 4D, 4E)
- A networked research activity focussing on a longer-term goal, comprising 20-25 research groups (see 5)

The GARNet committee's consultation will continue in 2006, particularly on the longer-term goals in Arabidopsis systems biology (5A), on mechanisms to address these goals (5B) and on involvement with international institutions (5D).

2. Goals

Systems biology in plants, as in other organisms, aims to understand all the components of a biological process, together with their interactions and emergent behaviour, at all relevant levels of biological organisation. This approach emphasizes an integrated understanding of biological systems. Modelling is central as a philosophy and as a tool to support data integration, simulation, analysis, prediction, knowledge delivery and the design of new experiments. One aim is to test the mutual compatibility of ideas derived from reductionist studies of individual components or small subsystems. Ultimately, systems biology will result in the development of a whole-plant model, a 'virtual Arabidopsis' or 'computable plant'. This will aim to account quantitatively for all stages of the Arabidopsis life cycle from seed to seed, together with variations in growth and cellular function due to environmental responses. One proposal sets a target date of 2017 for this goal (www.cmp.uea.ac.uk/ivis).

The whole-plant model will probably integrate multiple, subsystem models that are appropriate to address different biological questions. The model will describe macroscopic functions from the level of intracellular processes at the scale of macromolecular complexes and metabolite pools. It will be based upon specific, observed biochemical and biophysical mechanisms and validated by experimental data at multiple levels. For some topics, the Arabidopsis model will be extended to larger scales, incorporating interactions in plant populations, or to smaller scales, extending to the atomic description of particular protein surfaces, for example. Crop modelling on the field scale, where a plant population develops under well-characterised conditions, may allow plant systems models to extend above the level of the individual more easily. Crossing scales from the macromolecular to the individual organism will, however, be a central activity of plant systems biology for the next decade or more.

3. Benefits and challenges

3A. Benefits

The UK Arabidopsis community is generally enthusiastic about the prospects for systems research and is realising the opportunities for systems insight across many areas of Arabidopsis biology. The benefits of generating predictive models are obvious to the community. A virtual Arabidopsis will be a significant and highly visible achievement in biology, with spinoff benefits across multiple fields of scientific research, in addition to direct applications in areas ranging from pharmacobotany to global climate change. Basing this activity on a plant, rather than another organism, has major advantages that arise from fundamental plant biology as well as from the current status and organisation of the Arabidopsis research community. Spatio-temporal models of growth and development will be significantly easier to develop at the cellular level for plants compared to animal species, because cell migration and changes in cell shape are very limited in plants. Whole-cell models of microbial species, which are currently in development, should greatly facilitate the modelling of intracellular processes in plant cells. The technical and logistical issues facing plant systems biology are also well recognised by the community. In sections 3B and 3C, we highlight specific issues and propose solutions in sections 4 and 5, below.

3B. Technical challenges

Experimental screening methods that are readily applicable to single cell systems will often require further technical development to return data on single cell types within a complex multicellular organism, such as Arabidopsis. A workshop at the 2005 GARNet meeting specifically considered this issue (see report by Prof. Jones, at garnet.arabidopsis.info/garnet_meeting.htm). Data from defined cell types will be important for many but not all projects. Data on whole seedlings remains relevant for subsystems that are similar in all cells or conversely for processes that are active in only one cell type, and more generally in generating preliminary models that average across heterogeneous cell types.

Cell purification and cell cultures. Certain plant cells can be physically separated at high purity and in high numbers, including pollen and stomatal guard cells, permitting a wide range of experimental methods. Cell culture systems can produce data amenable to modelling, for example time-course data following application of a low-molecular-weight compound. They have been used in transcriptional and proteomic profiling of cell division and senscence pathways, for example, and could be used to provide baseline data, such as a protein-protein interaction network, that contribute to network inference. However, plant cell suspension cultures are not analogous to animal cell cultures, because they do not obviously represent a cell type that is present in the plant: they typically fail to express secondary metabolic pathways, may be unable to differentiate, and are genetically and physiologically heterogeneous. Many biological questions cannot be addressed in plant cell cultures, so a major focus remains on the intact plant. Purified cell types may be an option for some of these studies.

Extraction from defined cell types. Techniques exist to allow RNA and, potentially, protein and metabolite profiling of single cell types, if not single cells. These include laser-capture microdissection, fluorescently tagging and purifying single cell-type protoplasts, the use of micropipettes to sample the cytoplasmic contents of single cells, or the extraction of mRNA from polyribosomes that carry a cell-type-specific protein tag. These have been used in plants for the analysis of high-resolution transcriptional changes, exploiting linear amplification systems for RNA populations. While such amplification techniques are not applicable for protein and metabolite analysis, advances in dye technology and sensitive mass-spectrometry are allowing higher resolution identification of proteins and metabolites. There is clearly the potential to integrate transcriptome, proteome and metabolome data from defined plant cell types, particularly if there is continued technical development in this area.

3C. Logistical challenges

Research in plant systems biology is currently carried out in relatively few biology laboratories in the UK, in diverse geographical locations. Systems for collaborative interaction and discussion will be required to share experiences and solutions among groups, in addition to systems for sharing diverse data. This will be essential to develop systems-level research in the UK Arabidopsis community.

Related to this is the requirement for mathematical and computational expertise in an accessible form for plant biologists. Not every institution will be able to provide the necessary theoretical/modelling expertise or indeed enthusiasm for problems in plant biology. At the project level, individual biologists must identify collaborators, who may be in other institutions. This is not necessarily a barrier to progress, as many already have collaborators at distant locations, but ready access is clearly advantageous. At the community level, a significant increase in the number of theoreticians working on questions in plant science will be required to achieve any large-scale goals in Arabidopsis systems biology. The BBSRC workshop in July 2005 identified this as a major issue for the field (see http://149.155.200.17/about/gov/panels/isb_docs/PSB_workshop_report_sept05.html).

4. Near-term objectives

Projects that can and should be tackled now will contribute directly to the overarching goal of a whole-plant model: here we outline the near-term objectives that have particular importance. Training and networking activity (4A and 4B) must be as widely spread as possible and should result in the adoption of some systems methods in many Arabidopsis research projects. Methodological research (4D) clearly requires the participation of multiple disciplines; most research coordination required in this area will not be specific to plant research. The benefits from systems research projects will be significantly enhanced if they are coordinated: in section 5, we address longer-term goals, including a large-scale network for Arabidopsis systems biology. The requirement for theoretical expertise in plant systems biology must be addressed by multiple mechanisms to attract sufficient numbers of researchers into interdisciplinary Arabidopsis projects, both in the short and longer term.

4A. Interdisciplinary teaching, training and re-training.

The GARNet Advisory committee recommends:

i. A national, 4-year PhD training programme in Plant Systems Biology, along the lines of an EPSRC/BBSRC Doctoral Training Centre, to provide trained researchers. Students would be based across a distributed network of Arabidopsis biology laboratories, linking major centres of Arabidopsis research and several locations with less activity. Central investment in computing support and theoretical training, together with networking activities, would address the need for communication among Arabidopsis systems biology groups (see 3C) and provide added value.

ii. Increased investment in discipline-hopping and sabbatical visiting awards (including international awards) should continue, to address the need for training and retraining at the postdoctoral and senior levels. These awards should be on flexible terms to allow for the wide range of disciplines required in systems biology.

4B. Networking with the physical, computer and mathematical sciences

GARNet is pursuing two actions in this key area, to promote the traditional, distributed interaction among individual biology laboratories and their collaborators.

i. Researchers in plant bioinformatics and crop modelling provide a pool of research expertise that is relevant to plant systems biology. There is relatively little networking in this community, so the national potential for input to systems biology is hard to judge. Prof. Howard Thomas and Dr. Helen Ougham (IGER) have agreed to organise a workshop to bring together researchers in this area before Easter 2006, to enhance awareness of current research and discuss future involvement in systems biology.

ii. 'Study Groups' provide a week-long opportunity for mathematicians to tackle specific problems in an area of science, to give an informed view of the opportunities and approaches for further research. GARNet is working with Marcus Tindall (Oxford) to develop a proposal for a mathematics study group in Arabidopsis biology, along the lines of the Mathematics in Medicine Study Groups.

In the longer term, any coordinated funding for Arabidopsis systems biology should invest in central bioinformatics, programming and/or modelling support as a core activity (see 5B).

4C. Systems biology approaches to tractable subsystems in Arabidopsis

Systems-oriented projects that can be tackled immediately will achieve several, related objectives in the context of plant systems biology, in addition to the immediate objectives of each project:

- to complete case studies that plant biologists can turn to as exemplars of the systems approach, demonstrating concrete benefits to plant science from systems biology
- to promote interdisciplinary collaborations (see 4B above)
- to accelerate model building and validation in Arabidopsis biology, which is currently minimal but will contribute directly to the whole-plant model
- to increase the scope of Arabidopsis research objectives progressively from a focus on a particular gene or pathway to a sub-system and ultimately full-system approach
- to increase the volume and diversity of data that can be routinely analysed, interpreted and modelled in Arabidopsis research groups

It is therefore doubly important that early efforts in this area are appropriately reviewed and that the evaluation committees include members with suitable expertise. Completing a small number of highly interdisciplinary research projects may be more beneficial for the take-up of systems research than a broader spread of more conventional activity, particularly given the increased funding and longer timescales required for systems research even on a sub-system. Awards greater than £1M should be anticipated.

There is scope for such projects across many areas of plant science and at this early stage it is undesirable to be selective based on subject area. It is desirable that the projects make best use of the current engagement of theoreticians and informaticians. This could be achieved by extending current modelling/bioinformatics projects into related biological areas, widening the group of Arabidopsis biologists that collaborate with each modelling/bioinformatics group. Coordination by GARNet might facilitate such a process.

4D. Technological development of Systems-level tools, both experimental and theoretical

The tools required will be common to other model species and to conventional plant research. Particular goals might include methods to:

- obtain cell specific, or cell type-specific, biochemical data that are suitable for systems modelling (high quality, high time resolution, genome-scale)

- monitor multiple plant and plant cell functions *in vivo*
- allow dynamic manipulation of multiple biological components *in vivo*
- maintain the differentiation status of Arabidopsis cell cultures
- model Arabidopsis growth patterns at the cellular level (already underway)
- visualise experimental data in the context of plant architecture
- capture data from the experimental literature
- facilitate public access to quality-controlled experimental data of multiple types
- integrate multiple data types, both in individual research projects and in public databases
- infer network models from ‘omics data
- convert static to dynamic models
- optimise experimental testing of models, exploiting the available tools and resources

Arabidopsis biologists must engage strongly with infrastructural and methodological development in other research communities, to make most rapid progress and to avoid duplication of resource development and provision. Structures that allow international and European coordination in Arabidopsis research should be harnessed for this purpose. Greater integration with resources developed in biomedical research will likely be beneficial, not limited to sequencing facilities.

4E. Baseline data sets underpinning Plant Systems biology

This activity aims to provide the global data sets, the biological resources to produce the data and the network models from analysis of the data. Genome-wide analysis of DNA- and RNA-binding protein binding sites, proteome-wide protein interaction analysis, and development of plant-specific ontologies are already underway. Other data sets might include:

- Proteome-wide interaction analysis of key ligands
- Completion of a core metabolic map
- Description of all Arabidopsis cell types and their numbers in different organs
- Image timeseries of Arabidopsis development

The provision of such data could be coordinated internationally; the UK will be in a strong position to contribute to some elements. These data sets, together with data analysis tools and results (e.g. network maps) in public access knowledge bases, are the starting resources for systems biology research. Their importance for systems biology is analogous to the importance of populations of sequence-mapped insertion lines for Arabidopsis functional genomics. The Arabidopsis community, with BBSRC, has a good track record of balancing resource provision with hypothesis-led research. The GARNet committee recommends that the Integrative and Systems Biology Panel and the Tools and Resources Panel jointly establish ways to fund the new resource provision for Systems Biology.

5. Goals and organisation of Arabidopsis systems biology in the UK

5A. Longer-term goals

Setting a number of ambitious goals of lesser scope than the whole-plant model will be important if the international plant research community is to achieve a whole-plant model within a reasonable timeframe. The goal-oriented philosophy developed in such projects is some distance from current research practice in most parts of the community, but will produce concrete benefits to justify the necessary changes. For example, there will be growing benefits from the coordination and standardisation of experiment, data and model formats, maximizing the inter-lab comparability and thus the value of data and models from different groups. The visibility of larger-scale projects should facilitate interactions with other research communities (e.g. increase engagement by theoreticians), funding agencies, policy-makers and the public.

The UK Arabidopsis community could realistically undertake one or possibly two large-scale projects, each of which would be much larger than the subsystem projects (see 4C), involving many groups together with their interdisciplinary collaborators. There is widespread acceptance that a set of guidelines should be provided to select projects in plant systems biology that are consistent with an agreed goal. The nature, scope and particular benefits of such goals are the subject for ongoing consultation by GARNet. As described above, the characteristics of Arabidopsis development provides a major advantage over other multicellular models for spatial modelling, so a goal that exploits this advantage might be attractive. In other areas, Arabidopsis systems biology may be at least as tractable as other multicellular model species, for example in understanding environmental response networks. Further areas may be less tractable but have strong relevance to global geochemical processes and to end users, for example photosynthetic metabolism and yield measures.

The possibilities under discussion include different combinations of these factors, ranging from organ-scale goals, e.g. "The Leaf" (see box), through projects focussing on a single, experimentally tractable cell type, e.g. "The Guard Cell", to projects focussing on a single signalling pathway or subsystem, e.g. "The Photoperiod Response System". The balance between inclusiveness and research focus will be crucial. A strongly-focussed activity has great potential for synergy among groups but must also offer attractive research questions together with powerful resources and baseline data, in order for sufficient Arabidopsis researchers to align their current activity with the broader goal.

> A sample project: Systems Biology of the Leaf
>
> One way to encourage the community to work more coherently on a broad problem is to focus everyone's attention on a physical entity, such as the leaf.
>
> Many features of leaves commend themselves to the systems approach. The cell number of the Arabidopsis leaf has been defined (Pyke & Leech [1991] J Exp Bot 42:1407), and the proportion of mesophyll, epidermal and vascular tissue measured. The growth of leaves from primordia on the apical meristem is already a subject of mathematical modelling. Leaves also perform a wide range of important metabolic and signalling processes, studied by many Arabidopsis research groups in the UK. Leaves first import then export sugars over their life times. Leaves receive and export hormone signals. When challenged by pathogens and pests, attacked leaves export and systemic leaves receive signals such as oxylipins. Stomatal guard cells regulate the flow of CO2 into and water out of the leaf, under the control of various environmental signals. Differing light intensities will also affect aspects of leaf performance, and differentially at different times of day.
>
> Other levels of biological organization could be chosen; but the choice of an organ such as the leaf would force researchers to consider how the intracellular pathways they study play out in the context of whole tissues and organs, and whether different cell types are behaving in the same way. This choice would force integration in studies of physiology and development, and of intra- and inter- cellular signalling. A long-term UK project in this area would be a major contribution to any international effort to develop a whole-plant model.

5B. Networked research activity to tackle a longer-term goal

How would research teams be organised, in order to address one of the longer-term goals outlined in section 5A? Possible structures for a networked Arabidopsis systems biology were considered by the GARNet advisory committee. The logistical issues in coordinating research across groups even within the UK will be significant. However, experience of and mechanisms for national coordination will be a major advantage when international coordination is required on the whole-plant model. A single overarching network linking the current Arabidopsis biology community, with inputs from chemical, physical, engineering, mathematical and computational sciences, would be too diffuse (would lack focus) and would be too cumbersome to manage effectively. A more likely structure would comprise a network of collaborations with a shared core component. The majority of activity would be in (say) 4-5 interdisciplinary collaborations, each collaboration consisting of (say) 4-5 partners, with a mix of 'traditional' Arabidopsis biology labs and theoreticians, focussed on a particular biological problem. The problems selected should be sufficiently close to allow integration of the results and models to achieve a larger goal (see 5A) and would probably include one or more of the subsystems project areas (see 4C). The core component would provide project management and infrastructure that are shared by all the sub-groups, with infrastructure to support modelling and bioinformatics rather than experimental facilities. Interactions with the core and across collaborations, together with regular meetings of the entire network, would facilitate the exchange of modelling tools and experiences. The minimum level of funding required to make this an internationally competitive activity with minimal activity in the core is ~£5M over 5 years: this assumes that some of the subsystems funding has been allocated in the same research area. Increased core activity or generation of a large data set would increase this figure. The 5-year duration is also a minimum.

5C. Contribution of academic groups, NASC and the CISBs

A networked research activity would comprise a wide variety of groups in universities and BBSRC-funded institutes, with some participation of other institutes, such as those funded by the Scottish Executive. It should make best use of the bioinformatics resources and materials at the European Arabidopsis Stock Centre (NASC), and those to be provided by the BBSRC Centres for Integrative and Systems Biology (CISBs). Outreach of the various CISB research programmes to plant science will be encouraged by greater activity in Arabidopsis systems biology, particularly if a CISB is funded in phase 2 to focus on research in an area of plant science. A plant-focussed CISB would complement and not preclude the successful operation of a networked activity in Arabidopsis systems biology.

5D. International context

The extent to which interdisciplinary Arabidopsis research is termed systems biology varies with the working definition of systems biology in force locally. There is generally greatest enthusiasm where the research areas that are of most interest locally are also tractable for systems approaches. The GARNet committee will consult additional international sources in the months ahead. Locations in continental Europe that are strongly engaged in plant systems biology will be natural partners for a large-scale activity in the UK. These include the Max Plank Institute of Molecular Plant Physiology in Golm, Germany, and the department of Plant Systems Biology in Ghent, Belgium. At least one integrated proposal (coordinated from Ghent) has recently been submitted to the EU under Framework Programme 6 to support large-scale, coordinated acquisition of systems data in Arabidopsis, with data analysis and limited modelling.

Activity in the US is significant, particularly through NSF funding. There is as yet no national coordination specific to plant systems biology, nor is there a consensus on the need for such coordination. The NSF 2010 programme on Arabidopsis functional genomics recently produced its mid-course report, recommending a focus on the provision of biological data and informatics resources (compare section 4E, above) and on understanding "exemplary networks" to facilitate the transition to systems biology. Several NSF FIBR grants of US$2-3M have been awarded to interdisciplinary collaborations focussing on particular questions in plant systems biology (compare section 4C above), including projects on meristem architecture (led by Mjolsness, UC-Irvine and Meyerowitz, Caltech), on nitrogen and carbon signalling (Coruzzi, NYU) and on flowering time (Schmitt, Brown). A recent NSF workshop considered the establishment of an interdisciplinary 'Synthesis Centre' or 'Cyber-Infrastructure Centre' in plant science, to provide core support and technical development in informatics and modelling (compare 5B, above).

6. Potential risks and alternatives

Implications of the adoption of systems approaches in plant research include:

- Selection of model species for systems research. At this early stage of plant systems biology, focussing on more than one model species risks losing the interaction between research areas that will be crucial in order to combine sub-systems models within a reasonable timeframe. Achieving this synergy even within one model species requires collaboration across research areas that may never have previously occurred. The only model species that can realistically be supported is therefore Arabidopsis. Arabidopsis systems biology projects should clearly make their data, tools and resources available for systems-oriented research in other species (plant and non-plant).
- Conflict of research priorities between translational and fundamental research in Arabidopsis labs. The 'models to crops' agenda will have significant effects on the UK Arabidopsis community at the same time as the systems biology effort develops. Smaller academic labs may be unable to sustain activity at both interfaces. For larger groups and the community more generally, there is a risk of diluting research effort in both areas.

7. Conclusion

Multiple initiatives will be necessary to develop Arabidopsis systems biology in the UK on the scale required to tackle the challenge of a whole-plant systems model. A distributed research activity, including a fraction of the 200+ Arabidopsis research groups in the UK together with their interdisciplinary collaborators, could establish a leading position in plant systems biology if it were suitably coordinated.

Acknowledgements: The committee is grateful to BBSRC for funding the Plant Systems Biology workshop held in Edinburgh, in July 2005, to many participants at the workshop, and to individuals who have contributed their time to this interim report, including: Steve Russell, Elliot Meyerowitz, Chris Somerville, Pierre Hilson, Mark Stitt, Stefan Hohmann, Igor Goryanin.

GARNet Advisory Committee (for interim report): Ian Furner (Chair), Philip Gilmartin, Julie Gray, Claire Grierson, Nick Harberd, Jonathan Jones, Marc Knight, Ottoline Leyser, Keith Lindsey, Andrew Millar (Co-ordinator), Simon Turner, Sophie Laurie (BBSRC contact). We are extremely grateful to the GARNet administrator, Dr. Ruth Bastow.

GARNet

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