Models of biological development

The sequencing of the Human Genome, Mouse, Drosophila, Arabidopsis and others opens the way to detailed studies relating genes to function.

There have been a number of individual successes in the computational modelling of development patterns in some detail, and the use of L-systems to model visual and other aspects of development has been very successful. Coen [98] has shown the connection between Antirrhinum flower symmetry and gene expression. Sharpe et al have shown [400] how the three dimensional expression pattern of genes visualized using fluorescence can be recorded directly using optical computed tomography of fixed tissue. Clonal analysis can be coupled to mathematical models to infer the pattern of cell division and its relation to shape [381]. The development of markers such as Green Fluorescent Proteins (GFP) now allows a systematic approach to tracking growth through expression and by following division after microinjection.

The computational aspects of this work are being developed in close collaboration with Professor Coen in the John Innes Centre (adjacent campus) and Professor Prusinkiewicz (Calgary).

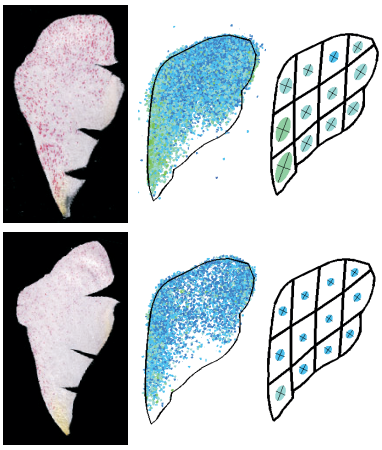

Figure 7.7: Snapdragon dorsal petal lobe showing pink clones that form growth markers. Right, analysis of many such clones and the associated mesh model.

Development of shape in plants and animals

Clonal analysis involves genetically marking dividing cells followed by identification of their clonal descendants. Growth parameters can be inferred by analysis of the resulting clone patterns. Although less direct than tracking, the advantage of this approach is that information from large numbers of clones can be extracted when the structure is at an easily accessible stage (often the mature organ). The approach has been used to estimate some growth parameters. For example, clones induced at various times in developing leaves or Drosophila wings have given estimates of the distribution and rates of cell division (Subtelny and Sussex, 1985; Poethig and Szymkowiak, 1995; Dolan and Poethig, 1998; Garcia-Bellido and Merriam, 1971; Gonzalez-Gaitan et al., 1994; Resino et al., 2002). One problem with conventional clonal analysis is that the orientation of growth cannot be inferred simply from final clone shape because the regional map of the organ will often be deformed by growth itself. Relating a mature clone to its growth orientation at the time of initiation can only be done when this deformation is known.

The Coen and Bangham groups have recently addressed this problem in the context of petal development by integrating clonal analysis with a dynamic

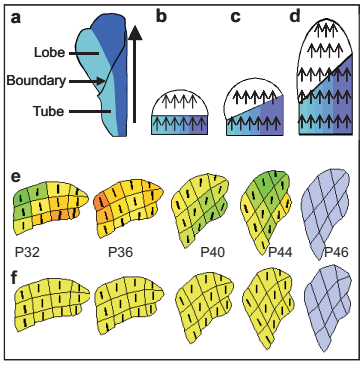

Figure 7.8: Top, the predicted growth field. Middle, predicted shapes during development using the full model and, bottom, using the model with just four parameters.

growth map [381]. The principle of the method is that the organ is first subdivided into a set of sub-regions interconnected by springs with resting lengths initially set according to the shape of the mature organ. The growth parameters just before the organ reaches maturity are then calculated for each sub-region, based on comparisons of clone shapes induced late in development. The resting lengths of the springs are then adjusted (shortened) according to these parameters and the model relaxed to allow each sub-region to shrink. As the springs relax, an estimate of the shape of the organ shortly before growth arrest is obtained.

By repeating this procedure with examples of organs, grown in parallel, in which clones are initiated at earlier and earlier intervals, the corresponding organ shapes can be computed for the earlier stages. The approach therefore gives a description of average parameters, velocity fields and the associated shape changes during development.

Semi-automated image processing algorithms were developed to analyse the many thousands of flowers needed for the experiment. Then the spring model was used to build a predictive model (82 parameters distributed over the mesh 7.7), from which it has been shown that the asymmetrical growth of the dorsal lobe petal of snapdragon can be accounted for by a much simpler model. Just four coefficients are sufficient to predict the final shape. Interestingly, we found it essential to include a *field* in the model (against which the growth can be aligned), Figure 7.8. Such fields have long been discussed, but this is the first time quantitative experimental evidence has been presented. The work is now being extended to Arabidopis leaves and drosophila wings.

Proposal for a Spatio-temporal atlas for Arabidopsis A spatio-temporal framework to access gene expression data is important both for experimental and theoretical biologists who build formal models. The Edinburgh Mouse Atlas has been developed to provide such a framework for mouse development but it is neither continuous over time nor does it include the concept of an underlying growth model. Plants are particularly appropriate for developing the required concepts because mathematical models of development have already been constructed and, recently optical projection tomography has been shown suitable to capture gene expression data. It is proposed that an Arabidopsis atlas be created that incorporates descriptive-models of plant growth as the spatio-temporal framework itself.

Thus descriptive-models producing “shells” or approximations to the morphology of the plant at the different stages of growth. It is obvious that the features (spatial x,y,z coordinates, shape, colour, etc.) of identifiable regions, such as leaves, vary considerably within a plant during growth and between plants .

A significant part of this observed variation is explained by the changing shape and can be normalised out by 3D warping (spatially fitting) the 3D volume or region into a reference 3D shape or shell . (The idea is well developed with 2D images where data bounded by a shape is warped to a reference, often the average shape, to allow further 'shape-free' analysis of the data.) Better reference shells will account for more of the variation and, by reducing the variability of the volumetric structures dragged into position by the warp inside the shell, therefore allow better cross-indexing of data through these internal mapped regions (such as expression patterns). If this shell is created from a parameterised descriptive model then we can claim that the model captures a quantitative description of the development of shape, which is a step towards being able to predict the development of shape. Moreover, if the model can be improved and the experimental data organised into the ever latest model the overall strategy provides spatio-temporal framework for linking the acquisition of complex biological data with the development of computational models to account for them. The gap between experimental data and explanatory model is reduced and the understanding of the data in terms of biological processes becomes easier.

In short this is a (bold) strategy for building reactive, developing mathematical model of the plant itself.

Research Team: Professor J. Andrew Bangham, Dr. Andy Hannah, Dr. Lilian Blot, and Jerome Avondo. Collaborators: Professor Enrico Coen (John Innes Centre), Professor Przemyslaw Prusinkiewicz and Anne-Gaelle Rolland at the University of Calgary, Dr. Nick Brown (Cambridge). Funding: BBSRC

Computational Aspects of growth

Computers play an increasingly dominant role in the process by which the natural Scientist records, explores and models natural phenomena. This has potentially enormous consequences particularly for the Life Sciences, as they move from their traditional largely descriptive role to one involving accurate modelling and prediction:

1. There is a growing mass of biological data, now computer accessible either statically or as movies.
2. Theories are emerging that give causative explanations of this data and predictions.
3. Many of these theories can be expressed directly as computer simulation programs - active models with both discrete and continuous abstractions or approximations.

We believe that the state of the art in Computing Science for specifying, modelling and realising complex systems has advanced sufficiently to realise *fully detailed, accurate and predictive models* of some of the most studied life forms used as models in biology, such as Arabidopsis, or the Nematode worm (C. elegans, Figure 7.9). This would build on partial computer models that are already under development many laboratories, to create a complete, consistent, integrated representation of *all that is known about a particular plant or animal*. This representation should be accessible to humans via extensible view selection mechanisms that include the interaction modes possible between an experimenter and the real life form, and also between the life forms themselves.

This vision is the basis for the Grand Challenge proposal sponsored by the UK Computing Research Committee, with support from EPSRC and NeSC. The coping stone of a successful challenge would be a generic approach to modelling of complex systems which becomes a standard medium for representing knowledge about model lifeforms in the life sciences, and which also has major applications in the design of man made complex distributed reactive adaptive systems.

For the life sciences, the prize is a single unified coherent approach to integrating the growing mass of knowledge about particular life forms. For systems sciences, the prize is a new approach to specifying complex reactive systems that construct and maintain themselves from small and perhaps sketchy initial specifications. Perhaps we can uncover some fundamental system design principles which nature uses to realise an effective SYSTEM = NATURE + NURTURE paradigm, creating a new generation of system design methodologies for complex adaptive self-maintaining systems

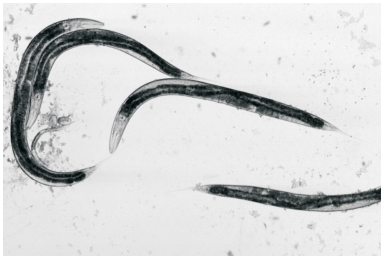

Figure 7.9: Adult nematode worm *C-elegans*, *http://elegans.swmed.edu/*.

Classical computational models of biological systems include the action potential, reaction-diffusion patterning [422, 121] and L-Systems [344, 346, 345]. We are just beginning work on this exciting new venture. Our initial objective is to build a demonstrator showing the development of Arabidopsis up to the torpedo stage. This will allow us to explore some of the key modelling issues, and if we are successful to convince many others to join us in tackling this Grand Challenge. We are in touch with a growing number of workers worldwide who are interested in this work, and our location at a key European centre for plant science, together with the Computer Sciences track record in Graphics and Computational Models, gives us an excellent starting platform. Further Details: $http://www.nesc.ac.uk/esi/events/Grand_Challenges/$ - see GC1

Research Team: Professor Ronan Sleep and Ioannis Elpidis.