The unclosed loop—ESF minibrains meeting report

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The ESF–EMBO conference ‘Functional Neurobiology in Minibrains’ was held in the sunny Spanish seaside resort of Sant Feliu de Guíxols in October 2010. The meeting brought together approximately 100 scientists to discuss the interactions between neurobiology and robotics.

Studies of *Drosophila* behaviour pre-date Morgan’s choice of the tiny fly to investigate evolution; a choice that would eventually lead him and his group to make some of the most important scientific discoveries of the twentieth century. In 1907, William Morton Burrows published a description of the olfactory responses of the ‘pomace fly’. Five years later, Morgan’s PhD student Alfred Sturtevant was simultaneously helping to prove that genes are on chromosomes, looking at the sexual behaviour of flies and pondering the role of chemical communication in this key phenotype.

Although *Drosophila* helped to develop our basic knowledge of genetics and also made vital contributions to studies of evolution, it was many decades before it began to fulfil its promise as a model organism for studying behaviour. Crucial to this progress was the rise of the single-gene-mutant approach, pioneered by Seymour Benzer following the widespread adoption of molecular-genetic techniques. It is only in the past few years—with the development of precise techniques for imaging and manipulating neurons—that it has been possible to imagine using *Drosophila* as a starting point for robotic implementations of behaviour.

This dramatic and novel aspect of *Drosophila* neurobiology was the focus of the ESF–EMBO conference ‘Functional Neurobiology in Minibrains’, which was organized by three of the new leaders of *Drosophila* neurogenetics: Richard Benton (CIG, Lausanne, Switzerland), Bertram Gerber (Universität Leipzig, Leipzig, Germany) and Matthieu Louis (CRG, Barcelona, Spain). The 100-strong meeting

had a subtitle that can be taken as a research programme for the coming decades: “From flies to robots, and back again”.

The conference was intended to provide a pioneering opportunity for researchers in fly neurobiology and robotics to exchange and compare their findings and approaches. More specifically, it was set up to explore how robotic models of fly behaviour might express accurate and potentially useful functions, and how differences between robotic and fly behaviours—or any alternative ways of solving computational or structural challenges developed in the robots—might generate hypotheses that fly researchers could test. Other insects including larger flies, ants, bees and locusts were also allowed through the door.

Although the talks and posters covered the traditionally popular subjects in *Drosophila* behaviour, such as olfactory processing, learning and sexual behaviour, the themes that most readily lent themselves to a comparison between organic and robotic implementations of a given behaviour were vision and movement.

This is a long tradition, which was nicely summarized by Nicolas Franceschini (IMS, Marseille, France), who has been working in this field for many years, both as an electrophysiologist and as a developer of robots that can navigate their environment. The fundamental feature shared by robots and insects is that moving autonomously in an unknown space requires the ability of the individual to estimate their position and velocity. The simplest way to acquire this information passively—rather than actively, for example through GPS or echolocation—is to compute ‘optic flow’, the changing patterns of external objects induced onto the retina as the autonomous agent moves through the environment. In both insects and robots, we were shown striking support from Frank Ruffier (CNRS, France) and Steven Fry (ETH, Switzerland) for a hypothesis that was first advanced by J. S. Kennedy (1951). Kennedy argued that simply by keeping the optic flow constant, insects and machines could successfully navigate complex environments. Video presentations at the conference showed that robotic aircraft can successfully fly around circuits in a tree-filled natural environment, passively sensing their position; a striking demonstration of Kennedy’s idea.

The different approaches adopted by the biologists and the computing/robotic

communities were highlighted in a fascinating difference of epistemological opinion between electrophysiologists and those aiming to make computer models of the system. Paul Verschure (ICREA, Barcelona, Spain) presented a computer model of the activity of the locust lobula giant movement detector (LGMD), which is thought to detect looming objects by performing complex, nonlinear calculations. Verschure's computer model was able to achieve a similar nonlinear output as an emergent property of the many neuronal interactions within the visual system of the locust. Furthermore, when this system and its associated architecture were implemented in a robot, the machine was able to avoid colliding with objects through the emergent properties of the network.

Verschure argued that this showed that nonlinear processing does not occur in the LGMD. However, as pointed out by interventions from the floor, although this demonstration was extremely elegant and showed that collision-avoidance behaviour does not require powerful, highly localized processing, it does not prove that the locust LGMD does not function in this way. In fact, there is biophysical data to support the suggestion that it does so.

This highlights two issues that will be fundamental for the field in the coming years. First, the powerful reductionist approach that is at the heart of the success of *Drosophila* as a model system tends to focus on individual genes and cells or groups of cells, and to overlook the potential of large-scale structures to produce emergent properties in which the whole is greater than the sum of its parts. If, or when, we have the 'connectome' or 'synaptosome' of *Drosophila*, will we be able to predict how it behaves? Is everything contained in the synapses (or the genes)? Clearly not.

Second, however elegant the model (virtual or robotic), data from the real world will determine which functions we ascribe to biological components. Furthermore, elegance is not always seen in biological systems, which are by definition historical, not designed. They have evolved through the tinkering of natural selection and, as a result, they can embody 'bad design' that might frustrate the engineer, but which represents a window into the evolutionary past and thereby an opportunity for investigation and discovery for the biologist. Where an engineer might seek to improve, a biologist will want to explore and compare. Finally, engineers often concentrate on optimizing

one particular feature; biological systems make optimality trade-offs in several, interconnected features, all of which might subtly affect the ultimate biological criterion: fitness.

During a discussion, Bassem Hassan (Katholieke Universiteit, Leuven, Belgium) mischievously undermined the whole logic of the conference by asking whether engineers and biologists really need to understand each other's approach at the level of neural processing on the one hand and electronics at the other. To be inspired by organisms, he argued, robotics merely needs accurate descriptions of behaviour and ecology; the exact processes by which biomimicry occurs are irrelevant.

Although this might be true at a functional level—aeroplanes are clearly inspired by birds, yet they fly in a very different way, partly because of the different materials involved—when it comes to 'closing the loop' and using the insights of robotics to provide predictions for biological functions, it is essential that the two worlds can talk to each other. By considering neuronal structures in terms of explicit algebraic or control functions established from robotic implementations, scientists will find inspiration and hypotheses that can be tested.

Dario Floreano (EPFL, Lausanne, Switzerland) emphasized the usefulness of implementing artificial systems, rather than just creating computer models. Sensory problems—in particular related to noise—might be overlooked by using *in silico* approaches, in which actors can be omnipotent, as the jargon puts it. This point was repeated by several speakers during the evening panel discussions; models are generally limited by the parameters of the programme and might simply give the expected results.

It could be argued that if we are to 'close the loop' from robots back to the fly, or any other organism, then a parallel between the two systems is necessary for solutions and problems found in simulations—electronic or embodied—to be tested in 'squidgy', organic processing systems. However, there are problems with requiring such a literal parallel between the two approaches. First, although raw computing power is not an issue for robotics, connectivity is; reflecting the degree of connectivity found in even a maggot brain is far beyond our current technological capabilities.

This was strikingly demonstrated by Albert Cardona (HHMI, Janelia Farm, USA), who described his contribution to

the Janelia Farm project of reconstructing the total neuroanatomy of a single larva, using 80,000 electron-microscopy images of the larval ventral nerve cord (VNC), taken from 458 sections. By using complex software to track the morphology and synapses of each neuron, Cardona presented data for a single segment of the VNC. One ICH5-1 chordotonal cell (a stretch receptor) had 53 presynaptic sites and 18 postsynaptic sites with 74 interneurons.

Alarming, this degree of connectivity is substantially increased by the fact that most, if not all, of these synapses are polyadic; a single, broad presynaptic site is faced with several qualitatively distinct postsynaptic sites, each potentially sensitive to a different neurotransmitter. Furthermore, this is in just a single cell in one of several abdominal segments devoted simply to movement and responses to touch and noxious stimuli. We can assume that the higher brain centres show a far greater degree of complexity.

In response to questions, Cardona emphasized that there could be not only inter- and intra-segmental and inter-individual variability—his wiring diagram is based on only one larva—but also intra-individual variability over time. The larva is a growing organism (that is its *raison d'être*), and these electron-microscopy images are a snapshot of one larva at one moment. It seems probable that many of the observed synapses and some of the fine detail of dendritic and axonal arbors might be sculpted by both development and experience, as well as the interaction between these two influences.

Including such a high level of varied connectivity in a machine would be incredibly difficult, and is probably beyond our technological abilities so far, but not outside the theoretical limits of computing power, were it to be modelled *in silico*.

Gerry Rubin (HHMI, Janelia Farm, USA) presented the current state of his project to provide the *Drosophila* community with a map of the whole adult *Drosophila* nervous system, in the form of 7,000 lines of genes with relatively limited and sparse expression that has been annotated using a complex and precise anatomical nomenclature, agreed by an international consortium of insect neuroanatomists. As these lines are created using the Gal4 system, they are not only components of a map, but also tools for investigating function through manipulating cells expressing each of these genes. This powerful resource will be available soon, free of charge.

Despite the new prospects for neuroscience that these lines will inevitably open, Rubin was remarkably measured about what they will be able to tell us, emphasizing that they are, above all, tools for exploring behaviours and testing hypotheses. These lines and the philosophy behind them—of identifying and manipulating cells involved in a given behaviour—will shape the whole of *Drosophila* neurobiology for years to come.

Richard Benton raised the problems of focusing on components—cells—and tending to ignore the subtle genetic and behavioural differences that have been revealed in the past by ‘unbiased’, forward genetic screens, such as ethyl methyl sulphate mutagenesis. In the 1970s, the random creation of point mutations in several genes led to the discovery of subtle genetic changes that had substantial effects on behaviour. Examples of these are *fruitless*, which has multiple splicing and is involved in the determination of sexual behaviour, and *period*, which is a key component of the fly’s biological clock and has both fast- and slow-running point-mutation variants, as well as a classic null allele. Benton’s argument implied that these kinds of effect might not have been discovered by using the powerful and attractive protocols that are emerging from Janelia Farm. Although these new approaches might close the door to discovering certain things, perhaps forever, they will open the door to the discovery of other amazing things. This is the way that science develops—we ask the questions we can answer, and technology determines much of what is possible, or what is seen as appropriate and exciting.

In a final, thought-provoking session, the delegates responded to the question posed by the ESF: where are the major gaps that prevent progress, and what would we need to resolve them? The answers were varied, but three of them focused around problems that had been revealed during the discussion. First, we need to develop high-volume, extremely rapid data analysis models to be able to approach the power of biological systems; second, the way in which biological systems capture sensory information is extremely rich and, with the partial exception of the visual system, we are far from being able to match this artificially; and finally, we know very few sensorimotor circuits in full detail, primarily because they are so complex, but also because of technological limitations.

Resolving the final issue might simply be a matter of waiting for the neurobiology community to describe the requisite

neuroanatomy. It is clear though, that a coordinated research effort, or an agreement to focus on certain model sensorimotor circuits, would be more productive. That would require intellectual leadership, and probably financial support. However, the concomitant technological developments—appropriate sensors and processing power—might not happen without planned intervention. For example, although more sophisticated sensors will be developed, they will not necessarily represent biological sensors in terms of their dynamic range. Indeed, it seems almost certain that they will not; in the absence of focused funding, they will be developed in order to respond to specific technological challenges, and therefore be designed to do one, or maybe two, things. Biological systems are generally far richer and less efficient, because of their many trade-offs and their history. Evolution does not design from scratch, it tinkers with what it has to hand.

This problem highlighted one of the striking features of the meeting. Although many speakers emphasized the importance of ‘closing the loop’—of using technological insights to inform biological investigations—no one seems to have done it. Indeed, apart from visual processing, little real progress seems to have been made on the first part of the loop—accurately modelling behaviour. Even in the realm of visual processing, identifying precise control mechanisms that might be located in particular structures might seem possible in general terms, but given that much of the final detail of the relevant circuitry and its temporal and developmental modulation remains to be discovered, this might be easier said than done.

One final suggestion—to both researchers and grant-awarding bodies—was made by Michael Dickinson (Caltech, California, USA). He pointed out the enormous advantage of having a dedicated engineer ‘embedded’ in a research project. This could be something that researchers add to their grant and should be something that research funders should encourage. By directly taking action to facilitate links between academics and engineers, such interactions (and their potential technological spin-offs) are more likely to occur.

If even part of the promise of this conference is fulfilled, it will suggest that a 60-year-long argument within behavioural science about how best to study and conceptualize behaviour is close to being resolved. The early ethologists, such as Konrad Lorenz and Niko Tinbergen, viewed behaviour as

being controlled by ‘instincts’ that were linked to accompanying ‘drives’. When this framework was criticized as experimentally unproven and theoretically doubtful it was abandoned, and ethology itself fragmented into neurogenetics and behavioural ecology. These fields each had a new explanatory framework that appeared to replace instinct (genetic determinism and adaptationist game theory, respectively). Only recently, with the extension of genetic manipulation to non-model systems, have the two approaches begun to converge.

Curiously, the victor might not be neurogenetics or behavioural ecology, but a third approach instead: neuroethology. Pioneered in the 1950s by Werner Reichardt and other researchers studying vision in insects, neuroethology developed computational models integrating behavioural and neuro-anatomical data, inspired by cybernetics and born of the computer age. Interestingly, it seems that in the 1950s and 1960s, cybernetics—the study of information control systems—had little effect on the other two branches of the study of behaviour, even though it influenced other parts of biology; molecular biology adopted simple cybernetic concepts, and Reichardt was recruited to Max Delbrück’s lab because of his espousal of cybernetics. The failure of cybernetics to make a greater impact on behavioural studies is a topic for science historians, but one obvious hypothesis is that—with the exception of the visual system—knowledge of behaviour and the underlying circuitry was not sufficient, and the relevant technology was too simple. *Plus ça change?*

Although the term cybernetics has somewhat gone out of fashion, it was clear from this meeting that this fundamental approach is alive and well, and might be due for a revival if the projected fusion of biology and robotics can be achieved. However, for the moment, the loop remains defiantly unclosed. As soon as there is one example of the power of this approach, it seems certain that scientists and technology companies will rush to adopt it.

REFERENCE

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Published online 15 April 2011

EMBO reports (2011) **12**, 389–391.
doi:10.1038/embo.2011.69