National Centre for the Replacement Refinement & Reduction of Animals in Research

NC3Rs/POEMS Network Maths Study Group - Applying mathematics to 3Rs problems

Improving the utility of Drosophila melanogaster for neurodegenerative disease research by modelling courtship behaviour patterns

Birgit Brüggemeier

University of Oxford

Background to the Problem

Courtship in Drosophila is used already to screen genes linked to memory-deficiency and neurodegeneration in humans. However the research community does not understand the mechanism which gives rise to courtship patterns. When a male fly encounters a female fly, he starts to follow her, licks her genitalia, sings a courtship song and eventually bends his abdomen to reach her genitalia [1]. Male courtship in Drosophila is overt, easily quantifiable, and occurs without any prior experience.

Despite being innate, courtship is complex in that the sequence of behaviours shown, does not necessarily appear in a precise order as suggested above. Rather there is a probabilistic component to behavioural switches which we believe originates from non-linear dynamics. Our problem is to model courtship patterns as a network of neurons and muscles. This will give the biological community an understanding of possible mechanisms disturbing courtship and will help in establishing fly courtship as an alternative to other animal models of human disease.

Details of the problem

In the 1950s, Bastock and Manning proposed an idea to account for the problem of behavioural switches in innate fly courtship [2]. Their theory involves excitatory thresholds and oscillating excitation in the male fly. In the course of courtship, male flies become increasingly sexually excited. Courtship behaviours are assumed to be hierarchical in the level of excitation they require to be displayed.

Neural Resonance is a physiologically sound mechanism to incorporate thresholds for each behaviour. Neural resonance entails a preference and increased responsiveness of neurons to a specific bandwidth of excitation frequencies. Resonance has been experimentally demonstrated in various types of neurons and has been mathematically modelled.

The idea of modelling courtship in the fly as resulting from neural resonators implies that courtship is generated by one common network, with neuronal subsets sensitive to different excitatory frequencies. The neural network determining courtship in the male fly consists of about 1700 cells. Through the use of genetic tools, it is possible to narrow down neuronal subsets which are responsible for specific courtship behaviours. These neuronal subsets can be tested both for their necessity in generating a given behaviour (through neuronal deactivation) and their sufficiency in generating a behaviour (by artificial neuronal excitation). Thus, a model of neural resonators, can be tested and refined with Drosophila melanogaster.

However neuronal activity is not sufficient to account for behaviour. Neuronal activity has to be transformed to muscle contractions, which then move limbs and produce behaviour. In a series of articles Brezina and colleagues pointed out that neural activity and muscle contraction are linked via a nonlinear transform that they call the neuro-muscular transform (NMT). Their model is one of relaxation oscillation on a sigmoid background. See figure 2 in the Appendix for an illustration. They show that their model of the NMT is able to reproduce experimental data of muscle contractions in the sea slug Aplysia [3].

Thus, to add a second dimension to the current model of courtship behaviour in the fruit fly, it is desirable to include muscle contraction. This could be achieved by constructing a network with nodes of different identity: neuronal resonators and muscle relaxation oscillators.

Modelling courtship behaviour in the fruit fly will not only allow the biological research community to gain mechanistic insights into the production of this complex innate behaviour, but will also serve as a powerful tool to systematically detect alterations in the patterning of the behaviour within various genetic paradigms. This is true in particular of the suggested model as it links physiology and behaviour.

Ideas and data for informing possible mathematical models

We can provide video and audio recordings. We can also provide processed scored and labelled courtship data. Participants in the study group will be taught about courtship with video and audio material. Video recordings are available from various transgenic fly strains. Potentially of special interest are Drosophila males expressing the thermo sensitive channel TrpA1 in parts of or even in their entire courtship network. When the ambient temperature is increased from 24 to 26 or more degrees celsius, neurons expressing TrpA1 become depolarized and fire. This elicits the display of courtship behaviours in males, even in the absence of a target female. We can also provide videos of males with suppressed activity of courtship neurons.

We will use ethograms of fly courtship behaviour from the literature to illustrate the network character of courtship behaviour (please refer to figure 1 in the supplement). To illustrate the complexity of the neuronal courtship network, we can show images of labelled neurons associated with courtship. They are spread throughout the body and are diverse in their properties.

For computational simulations, we can provide labelled data in the form of text-, or MATLAB-files. We can also present our model of fly courtship song and provide the MATLAB code for simulating the model. This model does not include resonators, although it distinguishes between neuronal activity, muscular tension and behaviour. This distinction is what we believe is most fruitful for subsequent experiments and therefore what we would like to see in a model of behavioural patterns in Drosophila courtship.

Questions you would like to see answered

1. Can courtship in the fruit fly be described as originating from a network of coupled resonators?
2. Can muscles be added to the network as nodes of different identity and with different properties?
3. Can contractions of the muscles that are involved in courtship be modelled as coupled relaxation oscillators?
4. Do simulated courtship patterns match the patterns observed in our lab and those reported in the literature?

The potential impact on animal use

Research on fruit flies can reduce and potentially replace preclinical research on non-human vertebrates and is commonly used in this way already. Courtship behaviour is not an obvious candidate for preclinical research though. However courtship behaviour of fruit flies has proven to be a useful measure of memory-deficiency and neurodegeneration [4-6].

The model we wish to develop during the workshop proposes a mechanism for complex pattern generation. With such a model we could simulate progressive neurodegeneration and study the effects on complex behavioral pattern generation. The model could be tested and improved by using the sophisticated genetic toolkit of D. melanogaster and by exposing flies to stress, toxins and drugs. Experiments including such manipulations are conducted already on flies and other animals. However traditional animal experiments on their own have been of little applicability to the clinical manifestation of Parkinson's Disease (PD) and other neurodegenrative diseases, and are associated with a considerable level of suffering. One reason for the lack of clinical translation of these experiments, beyond species differences, is that they only highlight one aspect of PD at a time. Connections between aspects of complex diseases are subject to theoretical models.

The network model resulting from this workshop, would play a role analogous to a model organism. As with model organisms we can manipulate mechanisms generating behavior. Manipulating neurons and muscles with a computational model offers a different translational approach to animal experiments – a theory-based one. A model of behavioral pattern generation could help reduce targeted induction of neuro- and muscle degeneration in animals used for drug development and behavioral studies.

We have taken PD as an example for the application of the current problem, but the theoretical model developed would be more widely applicable. If the model development was successful, we would be keen to explore its wider application with the research community.

Relevance to medicine and healthcare

Drosophila courtship is already used as a measure of memory deficiency. Memory deficiency is measured by the failure of males to learn suppressing their courtship when rejected by females. Male flies with a mutation in the gene analogous to Fragile X in humans do not learn to reduce their courtship [4].

Courtship has been used to study PD as well. Changes in the patterns of courtship were the first indicators of neurodegeneration in a Parkinson screen Shaltiel-Karyo and colleagues conducted with Drosophila [5]. Other papers have also demonstrated relevance of Drosophila courtship to human health [4,6].

Moreover courtship is more sensitive in measuring behavioural defects in PD than commonly used behavioural tests in Drosophila [5]. Behavioural defects resulting from α-synuclein aggregation in neurons – a candidate cause for PD – became apparent more quickly in courtship than in other behaviours, which are usually used for screens of motoric defects [5]. This suggests that courtship might function to study early signs of neurodegeneration.

The model we propose here, could act as translational tool for linking characteristic courtship patterns to function and connection of neurons and muscles. We could incorporate progression of neurodegeneration to the model, simulate resulting behavioral pattern, compare them with experimental results and thereby improve the model. Our model is not restricted to pattern generation of courtship in flies, but can be applied to behavioral pattern generation in general. This includes motor actions like walking and chewing, which are impaired in humans suffering from a neurodegenerative disease as Parkinson.

References

1. Billeter, J.-C. et al. (2006) Control of male sexual behavior in Drosophila by the sex determination pathway. Current biology 16, 766–776
2. Bastock, M. and Manning, A. (1955) The Courtship of Drosophila melanogaster. Behaviour 8, 85–111
3. Brezina, V. et al. (2000) The neuromuscular transform: the dynamic, nonlinear link between motor neuron firing patterns and muscle contraction in rhythmic behaviors. Journal of neurophysiology 83, 207–231
4. McBride, S.M.J. et al. (2005) Pharmacological rescue of synaptic plasticity, courtship behavior, and mushroom body defects in a Drosophila model of fragile X syndrome. Neuron 45, 753–764
5. Shaltiel-Karyo, R. et al. (2012) A novel, sensitive assay for behavioral defects in Parkinson's disease model Drosophila. Parkinson's disease 2012, 1–6
6. Feany, M.B. and Quinn, W.G. (1995) A neuropeptide gene defined by the Drosophila memory mutant amnesiac. Science (New York, N.Y.) 268, 869–873