Zebrafish: Implications for Neuroscience

Zebrafish are increasingly being used by neuroscientists and pharmacologists for in vivo studies. The characteristic of zebrafish which makes them particularly attractive, is the unique combination of scalability, genetic and chemical tractability and human relevance.

Scalability: A single pair of adults will breed once a week generating 1-200 offspring per breeding. With a typical stocking density of 10 fish per gallon, a modest aquarium can generate millions of larvae per year. High throughput approaches are possible as larvae are no more than 1-2 mm in size, develop ex-utero with the basic body plan laid out in 24 hours and behavioural analysis possible from 72 hours, at a time when they are still smaller than flies.

Relevance: Zebrafish are teleosts, higher order fish and are vertebrates. Their genome has been sequenced at the Sanger Centre and is currently being annotated. Genome size is similar to humans with a high degree of conservation between protein binding domains. Though deletions, duplications and divergence of particular genes will mean that in certain areas zebrafish are less relevant than in others, something which still needs to be established, the overall assessment rates zebrafish quite close behind rodents in terms of overall relevance and considerably ahead of the invertebrate models. Anatomical and functional comparisons are gradually being published with a number of complex behaviours having been reported, including sleep, parkinsonian states and addictive responses.

Genetic and compound tractability: Zebrafish were originally proposed as an experimental species by geneticists, with the major momentum being generated in the mid 90s as a result of two large mutagenesis screens undertaken by developmental biologists. This is a reflection of their genetic tractability and has also led to the creation of a suite of tools and associated infrastructure for genetic manipulation. In terms of chemistry tractability, fish are tolerant to standard compound solvents and readily absorb compounds administered to the fish water, making assessment of action of a compound added directly to the water feasible.

Neurological models known to be in development

Parkinson's disease, Huntington's disease, Alzheimer's disease, myelination, pre-pulse inhibition, sleep, startle responses, retinal degeneration, memory, muscle disease, epilepsy.

Whilst there are all of the standard caveats of modelling complex human phenomena in a much simpler system, which brings with it both advantages and disadvantages and questions of relevance and predictability, it is also worth stressing the strong ethical argument for supplementing drosophila research with zebrafish research, using both to reduce dependence on mammalian systems.

Tools available for zebrafish analysis

- Transgenics easy to create by injection of genes.
- Gene knockdown standardly achieved through injection of morpholinos (modified oligonucleotides) directed to 5' sequence.
- Knockout possible using Tilling (Targeting Induced Local Lesions In Genomes - a method of creating stable mutant lines).

Examples of conserved pharmacology in zebrafish

- Terfenadine. QT prolongation.
- Diazepam. Sedative.
- Carbamazepine. Anticonvulsant action.
- Prednisolone. Anti-inflammatory action.
- Atorvastatin. Decreased cholesterol synthesis.
- Pilocarpine. Pro-convulsant action.

Conclusion

To date zebrafish research has largely been driven by developmental biologists. However, a second wave of zebrafish researchers is emerging; the physiologists, neuroscientists, and medically focused researchers, who are integrating zebrafish into their armamentarium, establishing what they are good for and what they are not good for in a particular area. Over the next few years, this work will begin to come through in publications.

Dr Paul Goldsmith is Research Director of DanioLabs, a spin-out company from the Department of Anatomy, University of Cambridge, creating zebrafish models of neurological disease. He is also a neurology SpR at Cambridge with a research interest in modeling neurological disease in zebrafish.

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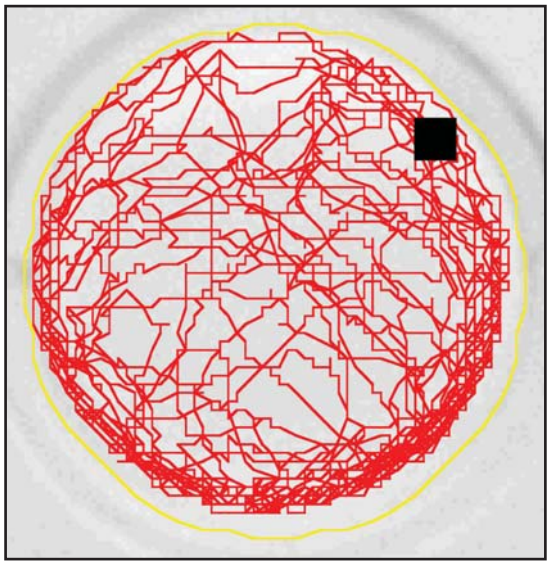
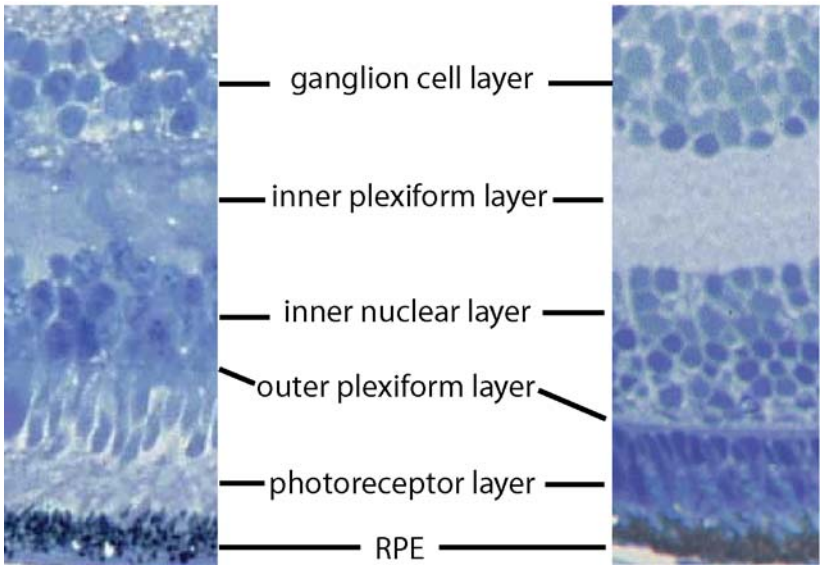


This figure illustrates a 2-mm larval zebrafish being automatically tracked. The black square marks the fish, the red lines the track it has taken. Speed and duration of movement as well as accuracy of swim can be analysed.

The retinal cell layout is highly stereotyped



These are plastic sections through an adult human (left) and embryonic zebrafish (right) retina. The type and relative positions of the various cell types are the same in both.