Neurogenetics of Brain Wiring and Maintenance

A Look Through the Fly's Eye

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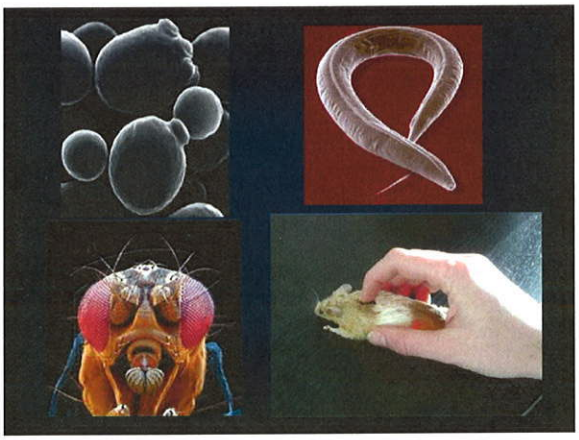
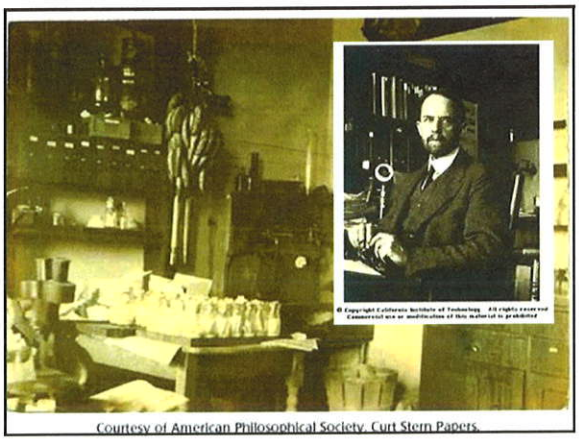


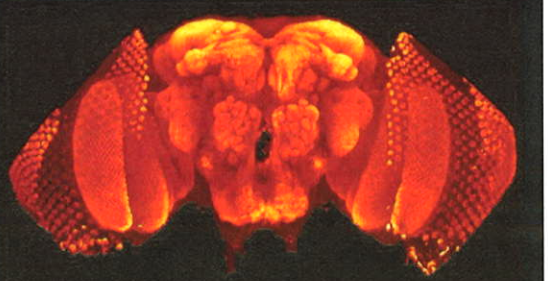


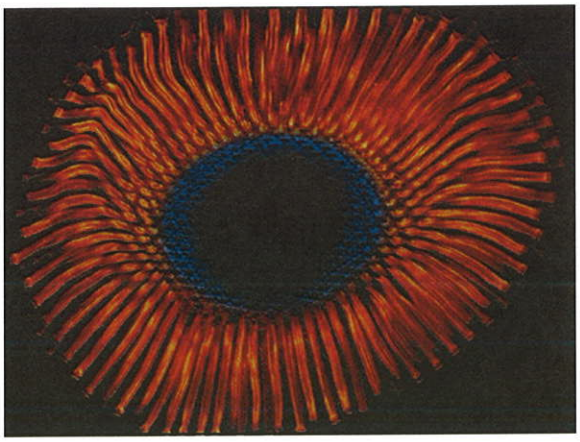
Courtesy of American Philosophical Society, Curt Stern Papers.

Drosophila is first and foremost a genetic model organism

- ~ 14.000 genes
- 1-4 mammalian homologs per fly gene
- ~ 25% at least partially characterized
- Genetic Engineering by 'Flypushing'

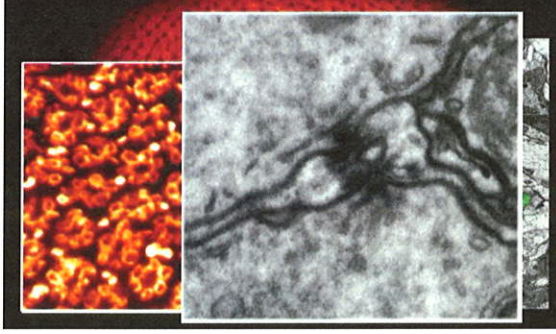
yes, it's a brain...



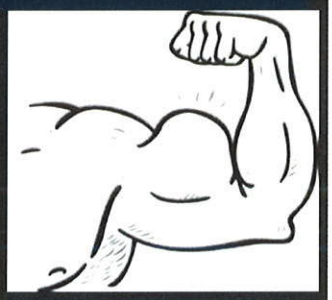


Photoreceptor Projections in the Brain

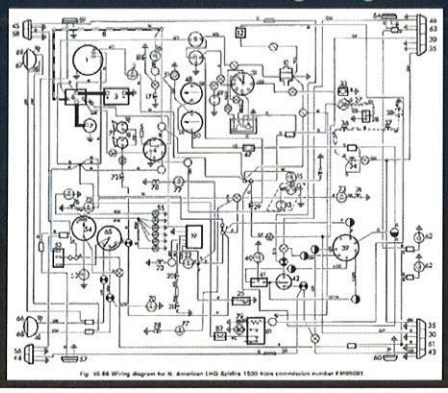
The Problem



Whence the Information… or: Why Neurons are (Maybe) Special

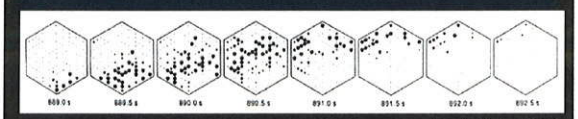


The Idea of the Wiring Diagram



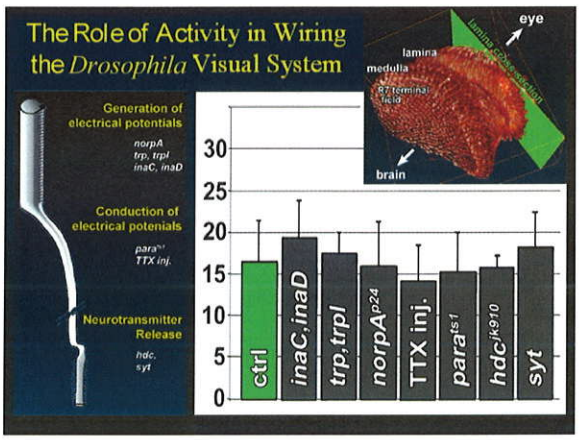
Nature vs Nurture…
Neuronal Activity to the Rescue!

- The Argument: There is not enough genetic information to encode the wiring diagram
- The Solution: Learning is life-long development (Cells the fire together, wire together)

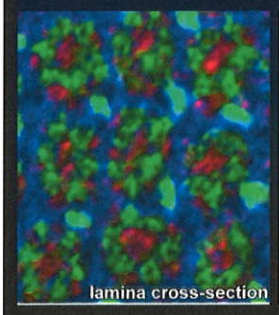


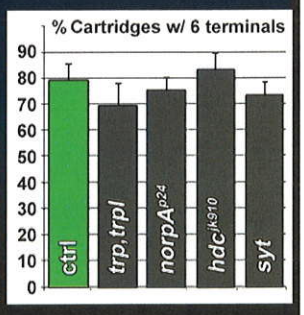
Carla Shatz, 1996

The Role of Activity in Wiring the *Drosophila* Visual System

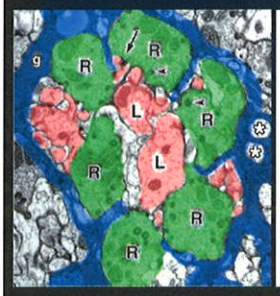


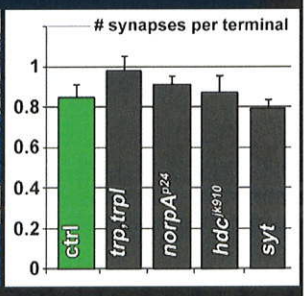
Cartridge formation is activity-independent



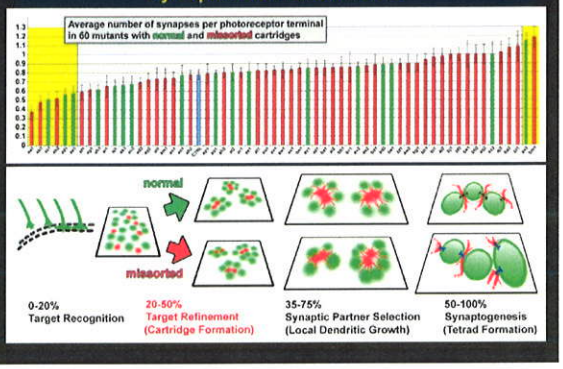


Formation of a precise number of synapses is activity-independent





Cartridge formation is easily disrupted, synapse formation is not



The *Drosophila* visual map is 'hard-wired'

Activity-independent

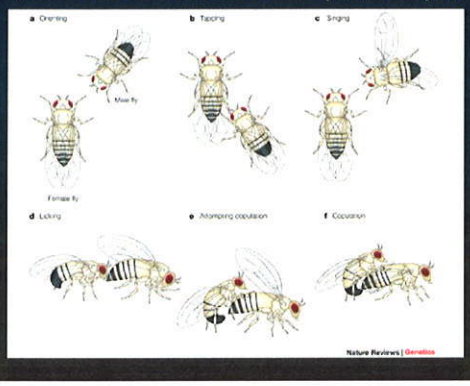
... quantitatively normal synapse formation without electrical activity and neurotransmitter release

Product of Genetically Separable Programs

... synapse formation and synaptic partner sorting are 'blind' towards each other

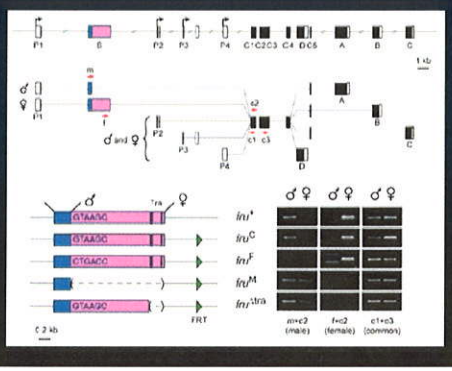
The Apparent Complexity of Synaptic Specificity is the Product of a Concatenation of Simple Genetic Programs

A Hard-Wired Behavior: Courtship in Drosophila



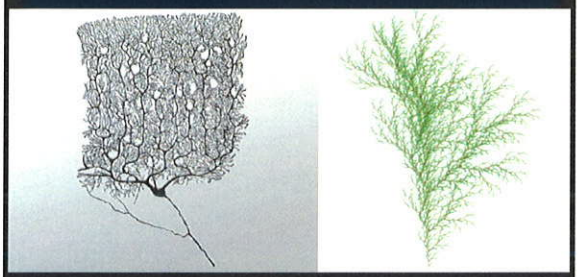
Courtship in Wild Type Flies

Transgenesis: Manipulation of a single gene



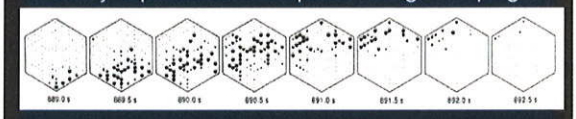
Brain Transgenics: 'Knock-in' of the male splice variant of a single transcription factor in a female

Complicated Structures Can be Encoded by Simple Rules



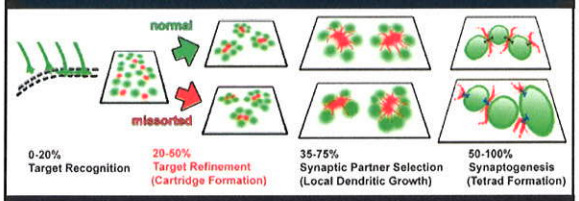
Complicated Structures Can be Encoded by Simple Rules

- Activity-dependence can be part of the 'genetic program'

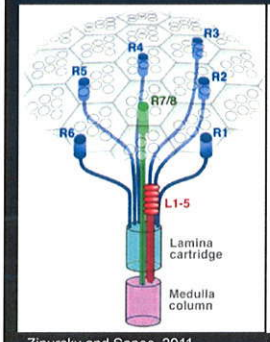


- *'Activity-dependent' vs. 'Genetically encoded' wiring is a not a useful categorization*
- Genetically encoded ≠ Wiring Diagram
- Genetically encoded = Developmental Rules

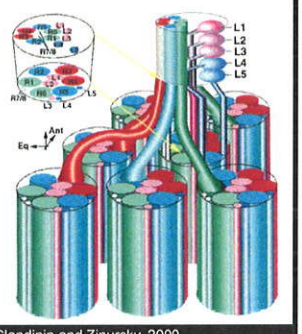
A Step-by-Step Model to Establish Synaptic Specificity in the *Drosophila* Visual System



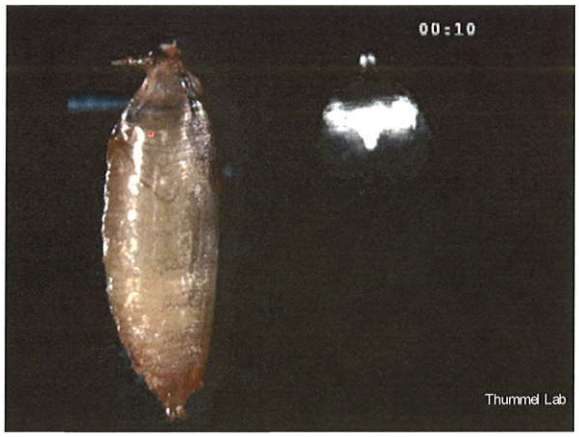
An Instance of the Brain Wiring Problem: Neural Superposition



Zipursky and Sanes, 2011



Clandinin and Zipursky, 2000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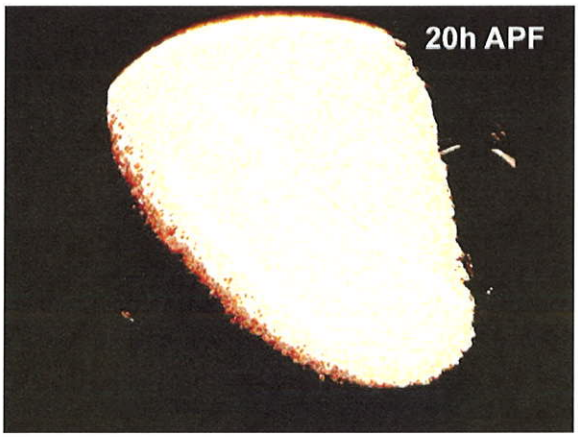
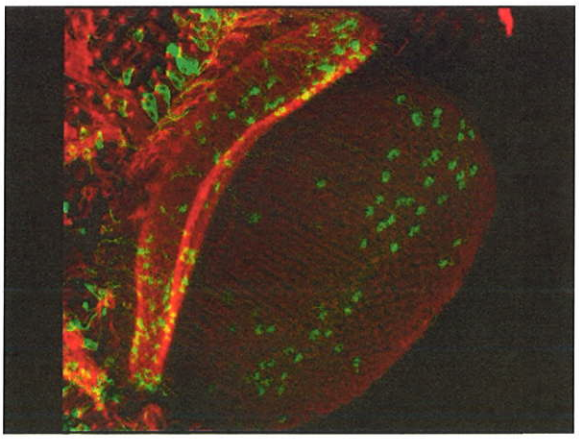
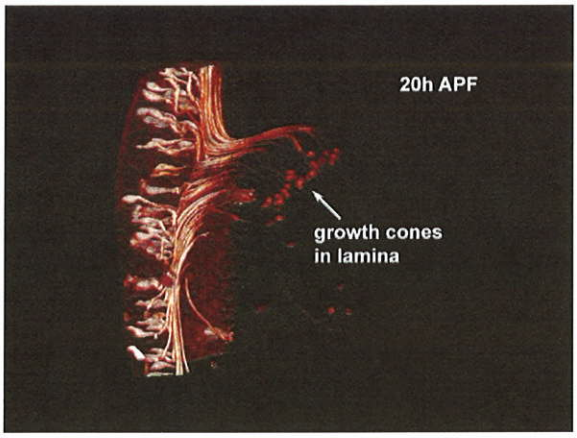
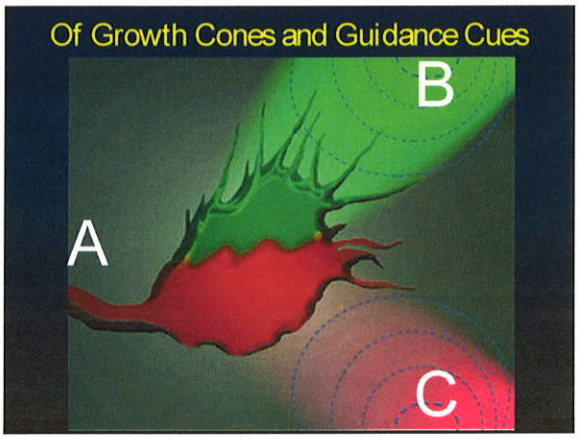
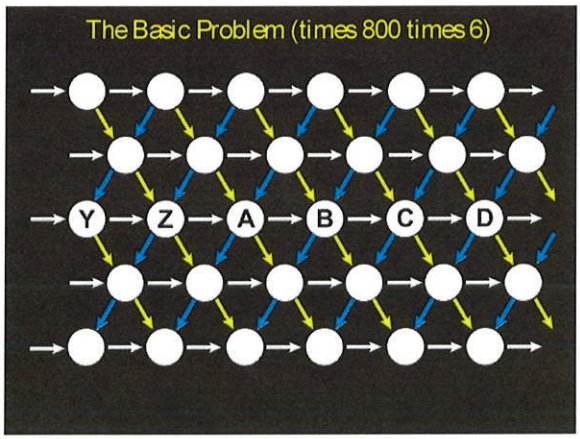
Thummel Lab

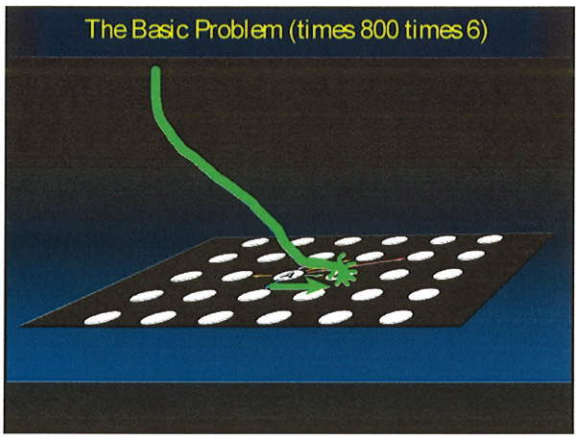

20h APF



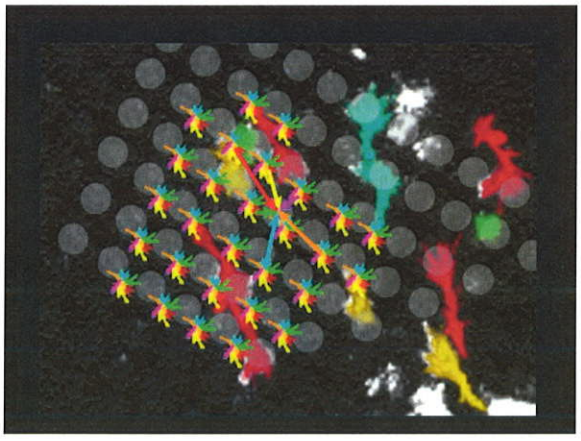

20h APF
growth cones
in lamina


Of Growth Cones and Guidance Cues
B
A
C


The Basic Problem (times 800 times 6)
Y
Z
A
B
C
D


The Basic Problem (times 800 times 6)


Growth Cone Heels Do Not Shift Relative To Each Other



A self-organizing pattern formation process in three steps:

1. Start Rule: Growth cone 'tips' elongate in orientation determined by the bundle/heels
2. The elongation program does not require a 'target cue', but may rely on growth cone interactions
3. Stop Rule: Growth Cone 'tip' density at a new position, off-grid from heels (quorum sensing?), followed by 'dive-in' to form actual cartridges

Just how genetically encoded are our brains?

By studying the fly brain we can understand to what extend complicated circuitry can be encoded genetically,

but we do not learn anything about how much complicated (human) circuitry is determined by the environment