Lecture 1

Developmental Overview:
Strength of Comparative Analysis Between Organisms

1. Course Basics


Optional Text: The Coiled Spring by Ethan Bier

Additional References:
1) Molecular Biology of the Cell by Alberts, Bray, Lewis, Raff, Roberts & Watson
2) Principles of Neural Science by Kandel, Schwartz, and Jessell

Course will also include material just in lectures since the field is very fast moving and changes year to year. Lecture notes and diagrams are posted on course website.

Familiarity with molecular biology and genetics is strongly recommended

Exams: Two midterms and a final (based only on material presented in class)

General philosophy regarding course: Two problems concerning facts:
1) Too many of them, overwhelm memory and distract from principles
   Goal: provide minimum number of facts needed to establish concepts.
2) Facts on their own have no meaning. Need to understand an experiment and how it is interpreted. Interpretations of the same facts can change.

2. Developmental Issues in Neurobiology

Mechanisms of early pattern formation
Development as a series of simple events
Fate maps vs. cell determination

Establishment of dorsal-ventral polarity in the egg:
Maternal determinants = morphogens/environmental factors
Zygotic genes implement patterning

Gastrulation/Initiation of morphogenesis
Subdivision of D/V axis into three germ layers
   Inner layer: endoderm- gut
   Middle layer: mesoderm- muscle, heart, skeleton, connective tissue
   Outer layer: skin, nervous system

Neural Induction: Subdivision of ectoderm into neural vs non-neural domains
Neural Competence: Establishment of early neuronal potential
Lateral Inhibition: Mutual inhibition among cells in equivalence groups
Birth of neuronal precursor cells = neuroblasts in CNS and SOPs in PNS
Neuronal precursor proliferation: determined or stochastic lineages
Neuronal Differentiation
Establishment of crude wiring diagram
   Axon navigation (or pathfinding)
   Synaptic formation (target selectivity)
Experience driven refinement of initial map
Learning and memory
3. The Model Systems

**VERTEBRATES**

A. Humans

**Advantages**
- Many diseases - self reporting mutants (>5,000 genetically based diseases) - some good family pedigrees
- Genome sequence complete
- Plasticity - injury and recovery
- Detailed behavior/ontogeny - critical periods e.g. spacial relationships; language

**Disadvantages**
- Fetal material hard to get but possible
- No experimental access

B. Monkeys

**Advantages**
- Developmental connections and physiology - postnatal
- Very similar to humans

**Disadvantages**
- Fetal experiments difficult
- No genetics

C. Cats, Ferrets, and Dogs

**Advantages**
- Visual system - born immature
- Still very human like brains
- Dog genome and well established breeds
- identify genetic basis of dog behaviors (e.g., “eye” in sheep dogs)

**Disadvantages**
- No genetics for cats or ferrets

D. Rats and Mice

**Advantages**
- Still mammals - homologous brain areas/cell types and developmental sequence
- Gene knockouts by homologous recombination routine in mice
- Significant mutant collection - weaver, staggerer, walzer, realer
- Construction of mosaic embryos possible (part mutant, part normal)
- Availability of material at all stages
- Source of primary cells for culture

**Disadvantages**
- Unbiased genetic screens difficult
- Hard to study early mutants (resorbed by mother)
- Hard to manipulate embryos (inside mother)
- Development relatively slow (months)

E. Chicks and quail

**Advantages**
- Genome sequence known for chicken
- Accessibility - outside of mother
- Well suited for embryological manipulation - tissue grafts between chick and quail
- Evolution of brain organization: Conserved circuits?

**Disadvantages**
- Little genetics
F. Amphibia

Advantages
- Still a vertebrate (*Xenopus laevis* and *Xenopus tropicalis*)
- Accessibility of embryo - pond no shell
- Excellent experimental embryology (particularly the larger *X. laevis*): grafting, induction studies (e.g., animal caps), RNA injection into identified blastomeres, interruption of gene function with morpholinos (block translation of specific RNAs)

Disadvantages:
- Genetics just getting started (*X. tropicalis*: http://faculty.virginia.edu/xtropicalis/)
- Difficult to make transgenic animals

G. Zebrafish

Advantages
- Good genetics: genome sequence, many existing mutants, morpholinos
- Easy examination of morphological defects (clear embryos)
- Embryological manipulations still possible (not as easy as xenopus)
- Rapid development
- Transgenics possible

Disadvantages
- Cannot easily target genes for disruption

INVERTEBRATES

H. Flies: *Drosophila*

Advantages
- Excellent genetics: genome sequence, unbiased genetic screens (morphological, behavioral, identify interacting genes), targeted gene disruption/ tagging, RNA-interference (RNAi), easy transgenesis, gene mis-expression studies.
- Mosaic analysis - where gene acts - e.g., signals versus receptors; nerve vs. muscle; eye vs. brain
- Fast generation time (2 weeks)

Disadvantages
- Miniature nervous system: embryological manipulations difficult
- Not a vertebrate

I. Nematodes: *Caenorhabditis elegans* (*c. elegans*)

Advantages
- Excellent genetics: genome sequence, hermaphrodites - self fertilization, targeted gene disruption possible, RNAi
- Few cells - 959 cells -302 neurons
- Morphology and development fully characterized - serial EM reconstruction
  -> all cells and connections known and named
- Full cell lineage known - time lapse microscopy of whole of development
- Laser ablation

Disadvantages
- Structurally poor external morphology
- Even less similar to vertebrates than flies (61% fly genes have human counterparts vs. 43% of *c. elegans* genes)