Developmental Neurobiology

Textbook Readings:

Chapter 1 Studying Nervous Systems
7 Intracellular Signal Transduction
21 Early Brain Development
22 Construction of Neural Circuits

(23) Modification of Developing Brain Circuits by Neural Activity,
(24) Plasticity in the Adult Nervous System

References:
1) "Principles of Neural Development",
   Dale Purves and Jeff Lichtman, Sinauer Press.
2) "Developmental Biology, 5th Edition",
   Scott Gilbert, Sinauer Press.

Why Study Developmental Neurobiology?

• Terrific scientific challenge.
• To understand human neuronal diseases and the repair and regeneration of the nervous system.
• To understand neuronal plasticity / learning and memory.
• To understand the evolution of nervous systems.
Emphases of lectures

• Neurodevelopment survey: Highlights of a few key stories.
• Cellular and molecular mechanisms.
• Synergy of observational and experimental science.
• Model organisms.
• Impact of Genomics.

*Drosophila Optic Lobe*

(Courtesy of N. Strausfeld, U. Arizona)
Neuronal Circuits Contain Diverse Neurons Which Must Be Wired Precisely.

(Scott, Raabe, Luo, 2002)

Embryonically Regulated Genes are the Most Abundant Genes in the Drosophila Genome (Most of these are Neuronal Genes)

(Arbeitman, et al., 2002)
Major Questions

1. Origins.
   Where do neurons come from?

2. Identity.
   How does a neuron know what to be?

   How does a neuron make the right connections?

4. Plasticity.
   How does the nervous system adapt to mistakes and experience?

Specific Topics

Lecture 17 (Mon Oct 31)
Embryology of the Nervous System
• Germ bands and cell types.
• Body axes.
• Folding, involutions and movements.
• Origin, migration and differentiation of neurons.

Lecture 18 (Wed Nov 2)
Embryonic Neural Induction
• Spemann organizer.
• Molecular mechanisms of induction (TGF-β).
• Intra- and intermolecular signaling.

Lecture 19 (Mon Nov 7, Wed Nov 9)
Cell Death (Apoptosis)
• Cell death and trophic factors (NGF) in developing NS.
• Molecular mechanism of apoptosis.

Lecture 20 (Mon Nov 14)
Patternning Neuronal Connections
• Growth Cones.
• Axonal guidance cues.
Development proceeds by progressive *developmental restrictions*.

(pluripotent, *stem cell*)

(differentiated)

Developmental Restrictions may be:

1) *Genetic* (programmed by genes)
   or
2) *Epigenetic* (determined by environment).

(pluripotent, *stem cell*)

(differentiated)
How to Construct a Nervous System

Proliferation → Selective Assortment → Morphogenesis (& Segmentation) → Specification of Identity → Axonal Outgrowth & Synapse Formation → Modification by Cell Death & Experience (Plasticity)

Vertebrate Embryology (Frog)

1. The unfertilized oocyte contains positional information (cytoplasmic determinants) contributed maternally. Some maternal RNAs are not equally distributed.

2. Fertilization triggers an influx of calcium, that sweeps across the egg. This causes rapid release of cortical granules, forming the fertilization envelope, blocking polyspermy.
3. The point of entry of the sperm creates a second positional axis, dorsal (opposite side of entry point) and ventral (entry point).

Cortical Rotation mixes cytoplasmic determinants and creates the dorsal-ventral axis.

Cortical Rotation Leads to Unequal Combinations of Cytosolic Maternal Determinants Which Partition into Dividing Embryonic Cells
Time-Lapse Videos

Gray Crescent Formation in *Xenopus* (Courtesy of Jeffrey Hardin, University of Wisconsin)

Early Cell Divisions of an Amphibian Embryo to Create the Blastula.

![Diagram of cell divisions](image)
Fate Mapping the Blastula:
3 Major Spatial Axes Formed by Gradients of Signaling Molecules.

1. Animal/Vegetal (Maternal Determinants)
2. Dorsal/Ventral (Sperm Entry, Cortical Rotation)

1. Animal/Vegetal (Maternal Determinants)
2. Dorsal/Ventral (Sperm Entry, Cortical Rotation)
3. Anterior/Posterior (Spemann Organizer)
Fate Map of the Blastula: 3 Principle Germ Bands Created.

Ectoderm (Skin, Neurons)

Mesoderm (Notocord, Muscle, Bone, Blood)

Endoderm (Lining of Gut, Placenta in Mammals)

Gastrulation of the Amphibian Blastula.
Gastrulation of Xenopus Blastula: 3-D Microscopic Reconstruction.

(Ewald, et al., 2004)

Time-Lapse Videos

Gastrulation and Neurulation in *Xenopus*

(Courtesy of Jeffrey Hardin, University of Wisconsin)

Early Cell Divisions in Zebrafish embryo

(Courtesy of Paul Myers, University of Minnesota)
Endoderm and Mesoderm Involute with Gastrulation. Mesoderm Apposes Overlying Neuroectoderm, and Induces the Neural Plate.

Neural plate (Apposition of Different Germbands)

Neurulation.

Formation of Neural Crest Cells (makes PNS, endocrine cells, pigment cells, connective tissue).
Neurulation: Cross-sectional views.

- **Neural Crest**
- **Notocord** (induces floor plate)
- **Neural Floor Plate** (rich source of neuronal morphogens & axonal cues)

Cephalization and Segmentation of the Neural Tube

- **Closure of Neural Tube**
- **Anterior (Rostral)**
- **Posterior (Caudal)**
- **Enlargement of Cephalic Vesicles**
- **Segmentation of the Spinal Cord**
- **Ventricular Zone of Proliferation**
Cortical Development.

1. Neurons are born in the ventricular layer and migrate radially along glia to their final layer.

2. Earliest born neurons are found closest to the ventricular surface.

Radial and tangential movement of neuronal precursors in the developing chick diencephalon.

(C. Cepko, Harvard U.)
The amount of yolk determines early cleavages and the shape of the blastula.

1. Isolecithal eggs (protochordates, mammals):

2. Mesolecithal eggs (amphibians):

3. Telolecithal eggs (reptiles, birds, fish):

4. Mammalian eggs have no yolk. Early divisions resemble isolecithal eggs. Later stages resemble the blastodisc of telolecithal eggs.

a) Blastula flattens into the inner cell mass.

b) Endodermal cells form the trophoblast and placental structures.
Key Points of Lecture 17

1. Three germ bands, ectoderm (skin and neurons), mesoderm (muscle, blood and internal organs) and endoderm (lining of the gut).

2. Development proceeds from pluripotency (stem cells) to the differentiated state (adult neuron).

3. Neuronal induction requires specific contact between groups of cells; embryonic morphogenesis allows this occur.

4. Positional information is created early by asymmetric distribution of molecules. These form axes (Animal/Veg, D/V, Ant/Post) that guide the movement of embryonic cells.

5. Key morphological landmarks of embryogenesis:
   a) Fertilization/Cortical Rotation.
   b) Blastula (hollow ball of cells).
   c) Gastrulation (inside-out involution of surface cells to the interior, through the blastopore).
   d) Neurulation (neural tube formation).
   e) Segmentation/Cephalization.
   f) Birth of neurons from the ventricular zone. Radial, then tangential migration to final destination.

Embryogenesis (Key Steps):

1. Oocyte with maternal cytoplasmic determinants.

2. Fertilization triggers calcium influx, and creates dorsal-ventral axis by cortical rotation.

3. Cell divisions, synchronous at first, then asynchronous.

4. Blastula created. (Hollow ball of cells)

5. Germ bands (ectoderm, mesoderm, endoderm) created by molecular signals along the Animal/Vegatinal axis.

6. Gastrulation. (Involution of superficial cells through the blastopore).

7. Anterior-posterior axis created by Spemann organizer.

8. Neurulation. (Lateral neural folds bend over the midline and fuse into the neural tube.)

9. Neural crest cells derived from leading edge of neural folds, migrate into somites to form the PNS.

10. Segmentation, anterior enlargement (cephalization), cortical development and spinal specification.