

Begin session 14

Questions, chapter 13

11) Contrast tropic and trophic effects on growing axons.

More about diffusable growth factors:
Contrasting “trophic” and “tropic” effects of NGF

Tropic: Influencing the direction of growth

Trophic 1: Survival promotion

Trophic 2: Growth promoting. Greater growth vigor increases the ability of axons to compete with other axons.

Questions, chapter 13

12) How could the same molecule be critical for both axonal attraction and axonal repulsion?

Why is this an important issue? See slide 40: Netrin molecules secreted by floor plate cells in the spinal cord attract axons from dorsal horn neurons--axons of the developing spinothalamic tract. These axons cross the ventral midline of the cord and then keep growing until they reach the lateral column, where they turn rostrally towards the brain. How can the netrin molecules first attract these axons and then repel them? If they only attracted them, the axons would not keep growing after reaching the midline.

Guidance mechanisms are not fixed:

- Modulation by intrinsic metabolic factors (discoveries by Mu-ming Poo's group)

“Conversion of neuronal growth cone responses from repulsion to attraction by cyclic nucleotides”

by H.-j. Song, G.-L. Ming, Z. He, M. Lehmann, L. McKerracher, M. Tessier-Levine, M.-m. Poo. **Science**, 1998, 281, 1515-1518.

- How demonstrated?
 - Axons from dorsal root ganglion cells growing in culture
 - Pipette containing Semaphorin III placed on one side, causing axon to change direction
 - Addition of a cyclic GMP agonist to the culture medium caused the axon to change direction (*8-bromo-cGMP: a membrane permeable agonist of cGMP signalling pathways*)

Sema III* and cGMP (*M. Poo '98*)

Figure removed due to copyright restrictions.

Please see: Song, Hong-jun, Guo-li Ming, et al. "Conversion of Neuronal Growth Cone Responses from Repulsion to Attraction by Cyclic Nucleotides." *Science* 281, no. 5382 (1998): 1515-18.

Cyclic AMP causes an effect similar to that of cGMP.

A study of *Xenopus* spinal neuron axon growth in tissue culture:

Growth cone turning in a gradient of Sema III
 Effects of manipulating cGMP (A), cAMP (B), ...

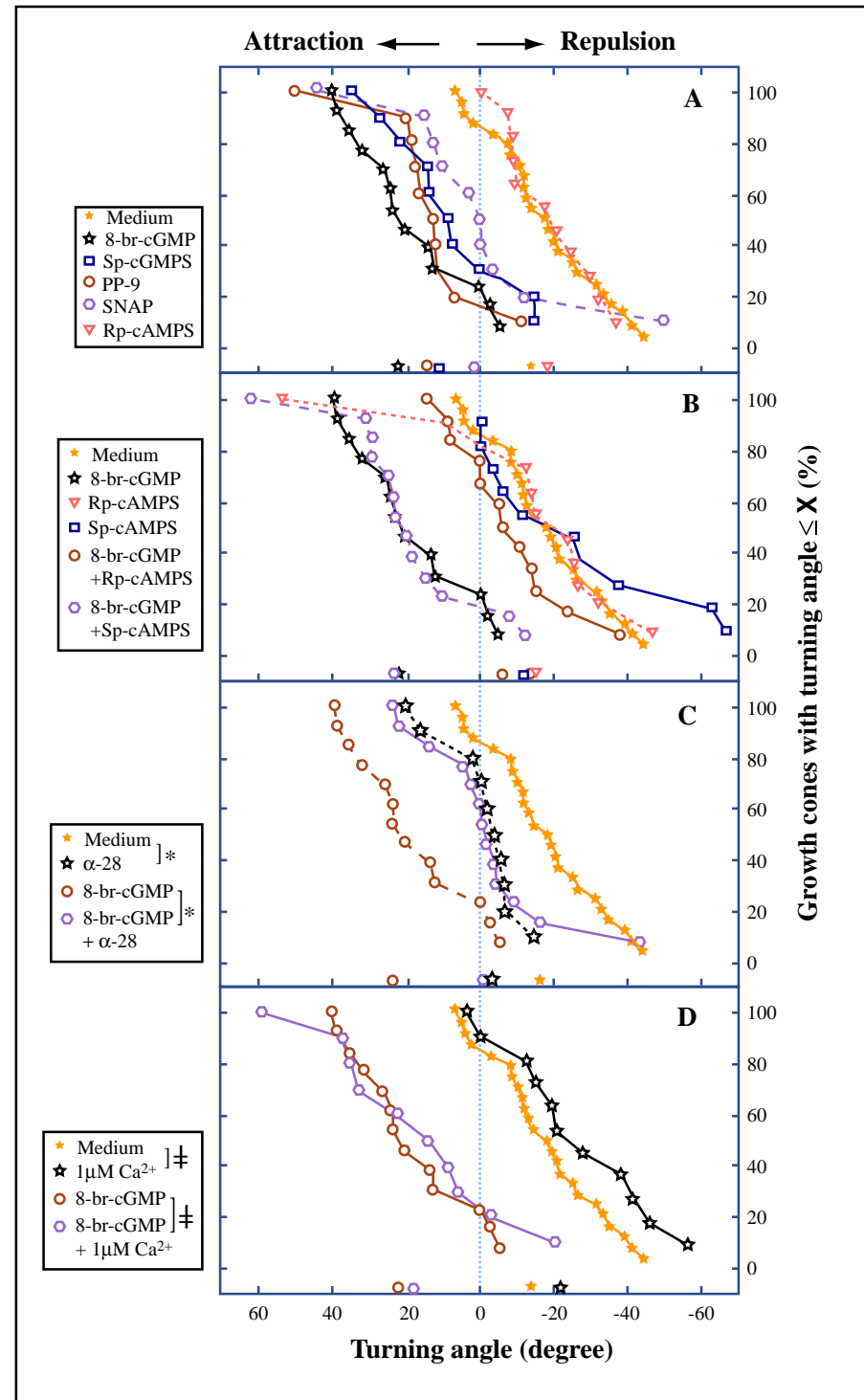


Image by MIT OpenCourseWare.

Application to spinal cord development:

An apparent role of Semaphorin III (collapsin) in the innervation of the spinal cord by dorsal root axons:

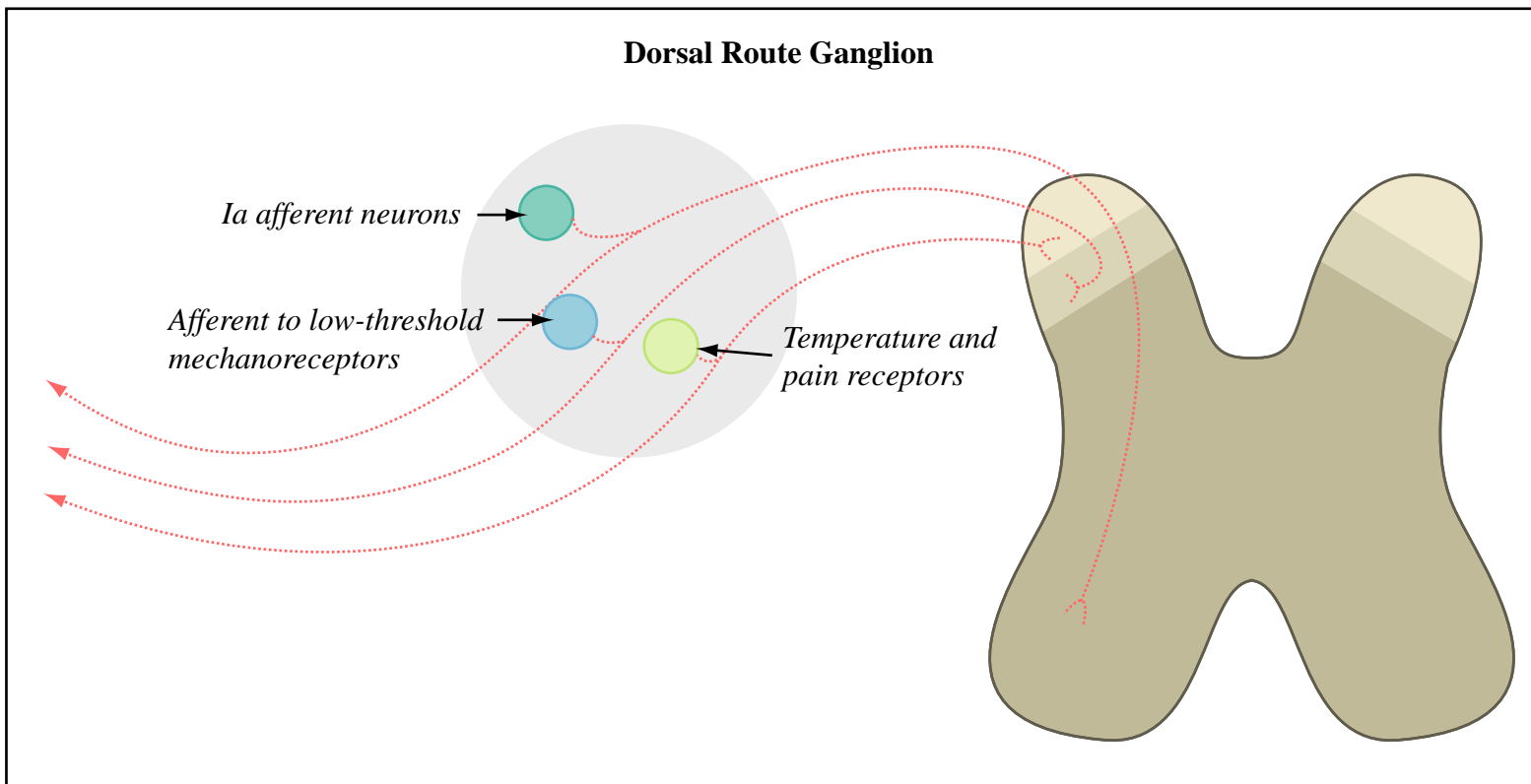


Image by MIT OpenCourseWare.

A molecular sieve? Semaphorin III produced in the ventral half of the embryonic spinal cord (dark tan) may repel axons of temperature- and pain-sensory neurons while allowing in those of Ia afferent neurons that respond to muscle stretch.

Similarly, we can describe a role of the netrin molecules in the formation of the spinothalamic tract decussations:

- Netrins diffuse from floor plate region
 - Discovery of the netrin molecules by Tom Jessell and co-workers at Columbia
- They have tropic effects on axons of dorsal horn cells which form the spinothalamic tract.
- *If they attract the axons growing from the dorsal horn, how can this result in a decussation?*
 - *We can postulate a shift in the axonal response to netrin, from attraction to repulsion.*

Questions, chapter 13

13) What is meant by exuberant axonal projections?

Projections of axons that are lost later in development

14) Describe how optic-tract axons, and no doubt other types of axons, shift from one mode of growth to another mode of growth during development.

Shift from elongation mode of growth (rapid, fasciculated) to arborization mode (much slower, non-fasciculated)

Developing axons do much more than simply find their path to a target

- We have been considering the elongation mode of axonal growth.
- In this mode, they grow much faster, and branch much less, than during the subsequent arborization mode of growth.
- This discovery, as well as many others, was made in investigations of the development of the optic tract in hamsters and other small animals.

From studies of the developing optic tract axons in Syrian hamsters:

Two modes of axon growth summarized

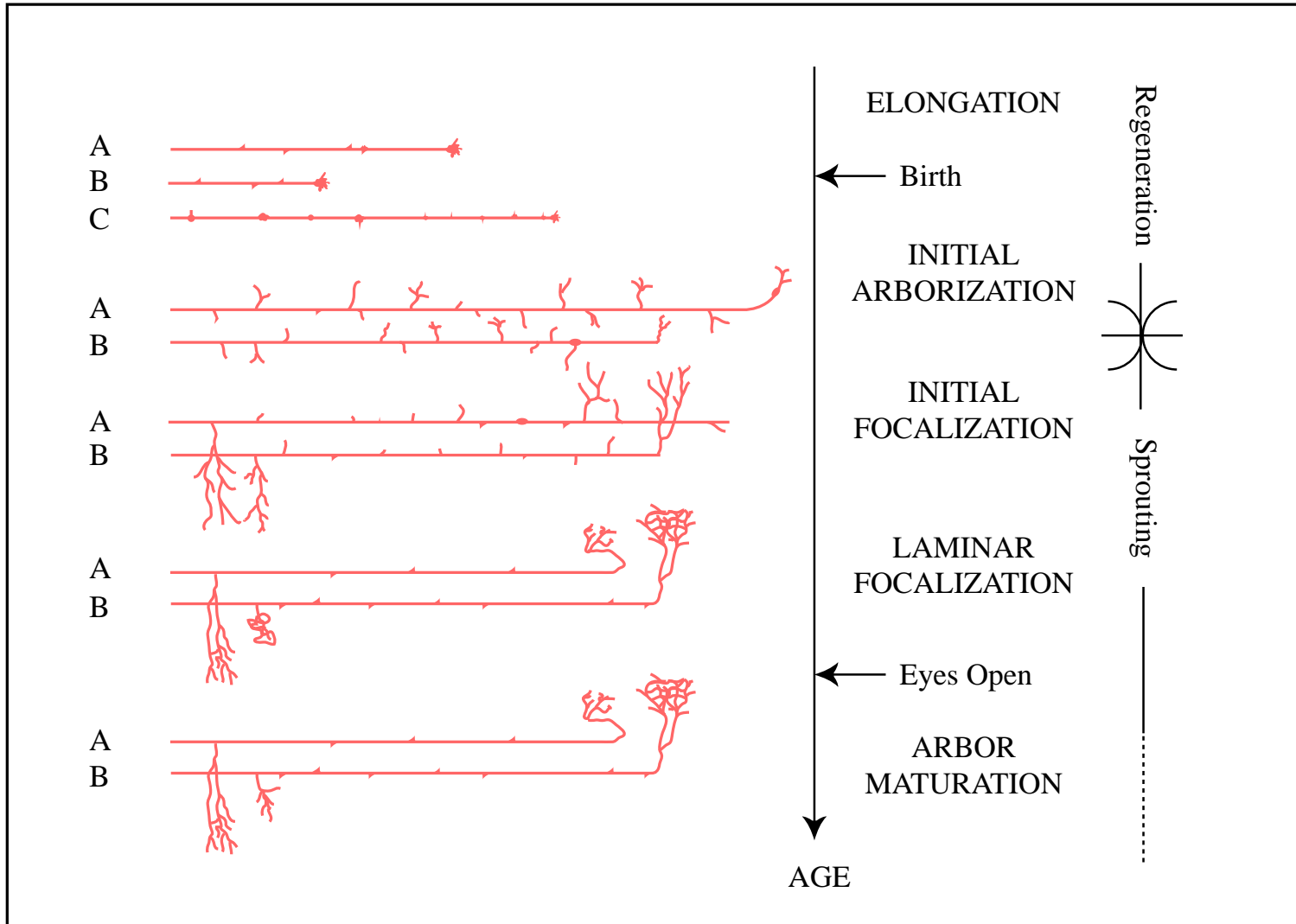


Image by MIT OpenCourseWare.

Differences between the two modes of axon growth

In the hamster optic tract:

- Elongating axons extend 10x faster than arborizing axons (60-100 $\mu\text{m/hr}$ vs. 6-10 $\mu\text{m/hr}$)
- Elongating axons form fascicles, whereas arborizing axons do not.

Questions on chapter 13

15) Describe the role of ephrins and ephrin receptors in the development of retinal projections to the midbrain tectum.

Topics in the study of optic-tract development & plasticity: these apply also to other axonal systems

- Embryonic formation; 2 modes of growth
 - *Optic tract*; geniculostriate pathway; other connections
- **Map formation; chemoaffinity**
- Map plasticity: lesions
- Collateral sprouting; competitive interactions in axonal growth
- Roles of cell death
- Regeneration in development and adulthood

Map formation; chemoaffinity

Ephrins and Eph receptors are responsible for the naso-temporal retinal axis representation in the tectum (superior colliculus). How does it work?

Discovery of specific mechanisms at the cell-molecular level came many years after Roger Sperry formulated his chemoaffinity theory, based on studies of regeneration in fish and amphibians (by himself and a few others)

Distribution of Eph receptors and ephrin ligands in the developing chick retinotectal system related to retinotopic projections

Figure of the distributions of Eph receptors and Ephrin ligands in chick retinotectal systems and retinotopic projections removed due to copyright restrictions.

Please see:

Figure 1 from O'Leary, Dennis DM, Paul A. Yates, et al. "Molecular Development of Sensory Maps: Representing Sights and Smells in the Brain." *Cell* 96, no. 2 (1999): 255-69.

After discoveries by Flanagan et al (at Harvard), and by Bonhoeffer et al (in Germany)

Figure removed due to copyright restrictions.

**The mechanism:
selective
repulsion.**

Response of
temporal and
nasal RGC
axons to a
gradient of tectal
membranes,
from purely
anterior to
purely posterior

**Axons from temporal retina
are repelled by membranes
of cells in the caudal
tectum.**

A sketch of the central nervous system and its origins

G. E. Schneider 2014

Part 5: Differentiation of the brain vesicles

MIT 9.14 Class 14

Some phenomena of axonal plasticity in the CNS

Topics in the study of optic-tract development & plasticity: these apply also to other axonal systems

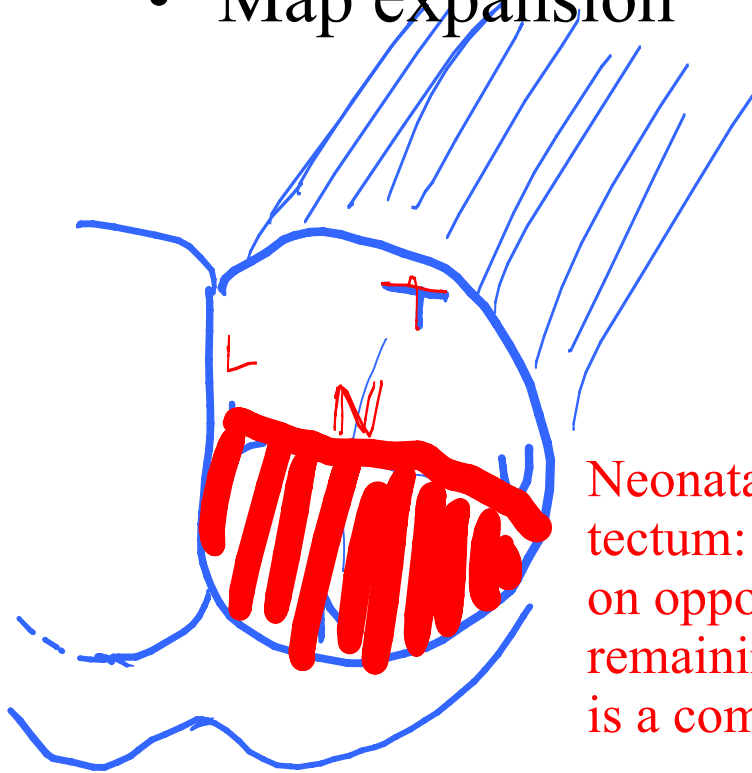
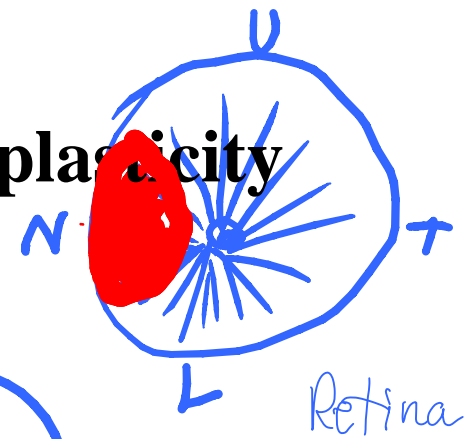
- Embryonic formation; 2 modes of growth
 - *Optic tract*; geniculostriate pathway; other connections
- Map formation; chemoaffinity
- **Map plasticity: lesions**
- Collateral sprouting; competitive interactions in axonal growth
- Roles of cell death
- Regeneration in development and adulthood

Questions on chapter 13

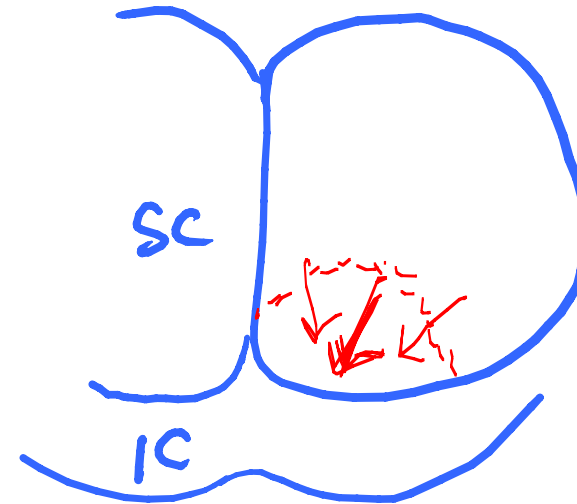
17) Describe a phenomenon of plasticity of the map of developing projections from the retina to the midbrain.

Such chemical specificity does not prevent plasticity of the developing maps

- Map compression
- Map expansion



Neonatal ablation of caudal tectum: Map of entire retina on opposite side forms in the remaining rostral tectum. It is a compressed map.



Large lesion of nasal retina in neonatal hamster eliminates axons destined to terminate in caudal tectum. Remaining axons expand their projections

- What factors other than chemospecific factors are active?
- Evidence for other factors has been obtained from studies of effects of damage during development.

Topics in the study of optic-tract development & plasticity: these apply also to other axonal systems

- Embryonic formation; 2 modes of growth
 - *Optic tract*; geniculo-striate pathway; other connections
- Map formation; chemoaffinity
- Map plasticity: lesions
- **Collateral sprouting; competitive interactions in axonal growth**
- Roles of cell death
- Regeneration in development and adulthood

Questions on chapter 13

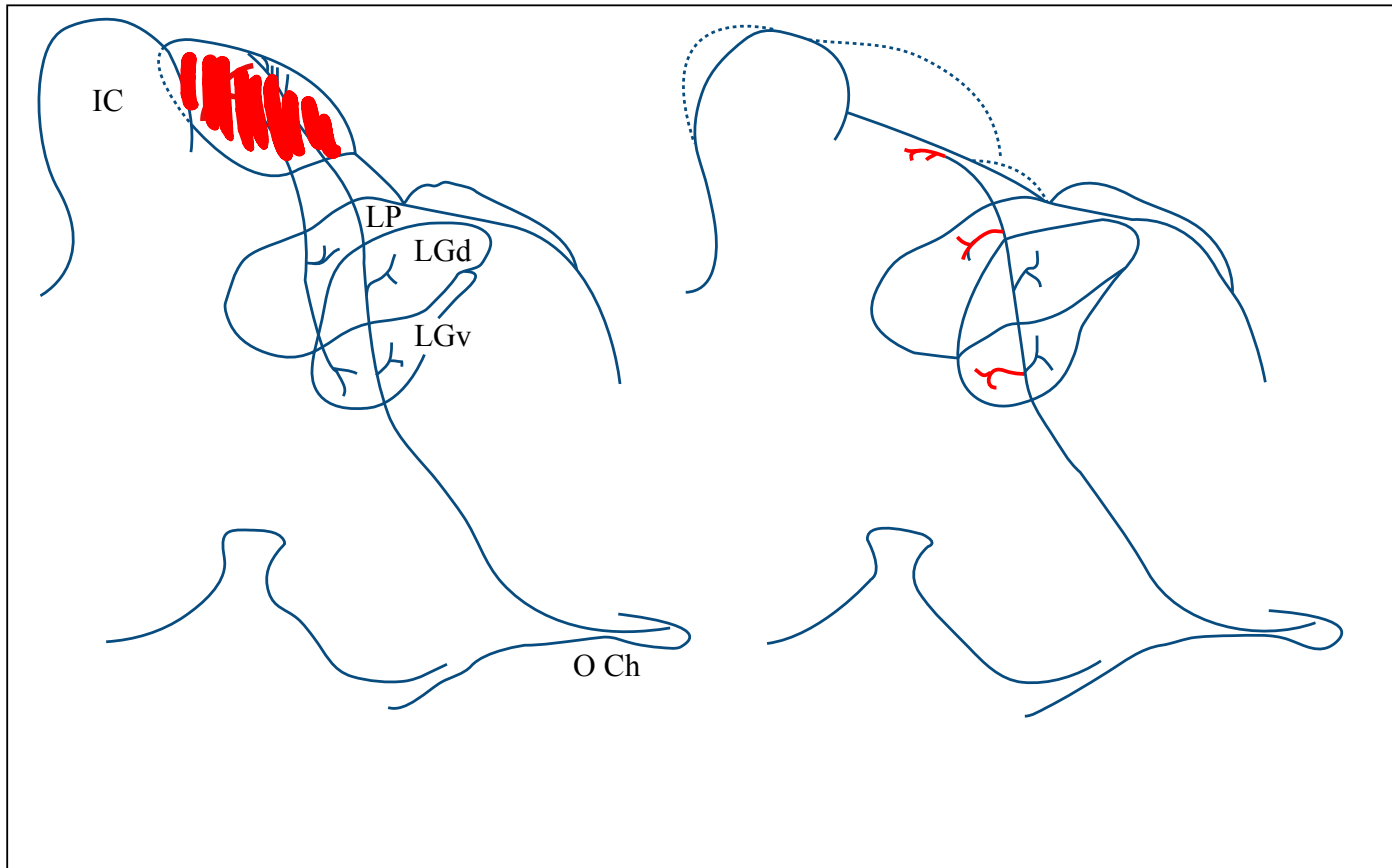
18) What is collateral sprouting in the development of CNS axons? Describe the phenomenon and two factors which affect when, where and in what axons it can occur. What can modulate the amount of collateral sprouting?

“Collateral sprouting“ in development

- Can cause developing axons to violate the normal rules of regional specificity:
 - e.g., in developing hamster or ferret, the optic tract can be induced to grow into the medial geniculate body of thalamus (normally part of auditory system) or the ventrobasal nucleus (normally in receipt of somatosensory system axons from spinal cord).

Effects of early ablation of SC:

Lesion in newborn hamsters; studies of adults using axonal tracing with Nauta silver stains for degenerating axons



*sprouting of axons
indicated by
double lines*

Image by MIT OpenCourseWare.

Note the sprouting in LP and LGv as well as in the remaining SC.

Effects of early ablation of SC and BIC

Newborn hamster, studies using axonal tracing with Nauta silver stains for degenerating axons

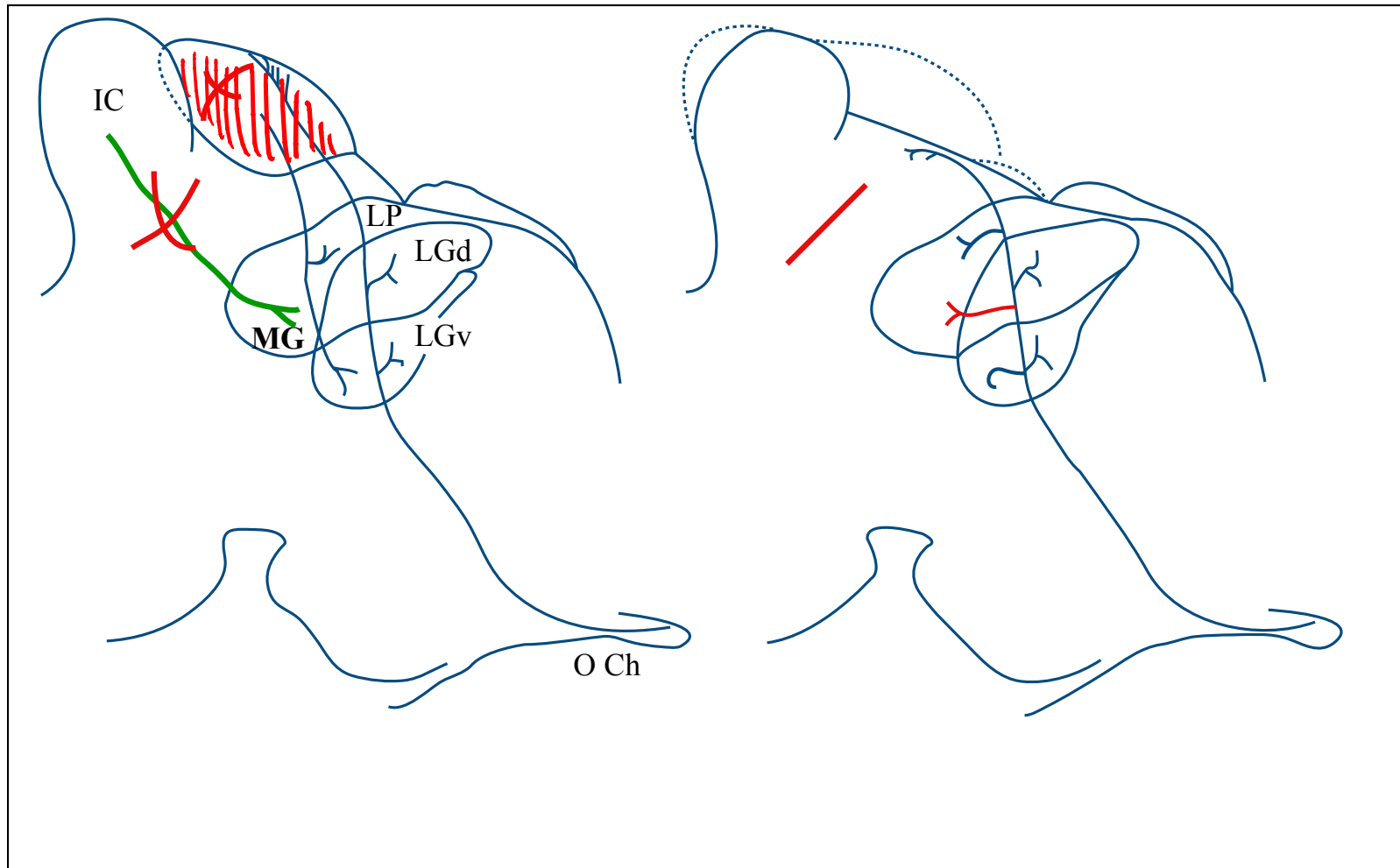


Image by MIT OpenCourseWare.

Next: Two major reasons for sprouting other than chemical specificity

Sprouting phenomena: axonal competition and spreading

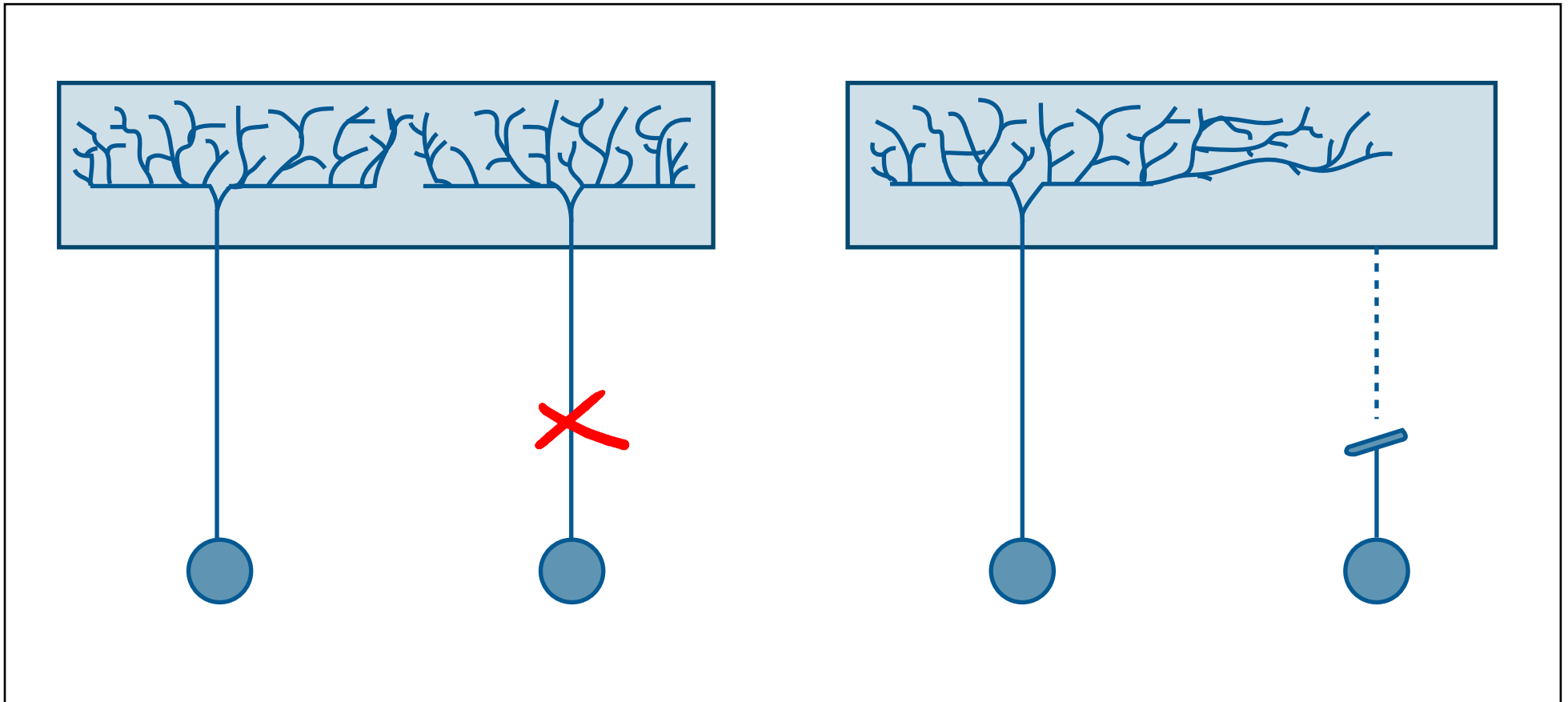


Image by MIT OpenCourseWare.

Competition among axons: What is it?

- Competition for terminal space
 - for growth factors
 - for occupancy of synaptic sites
- Axon-axon contact interactions
 - Retraction reactions; "collapsin" molecules causing a contact inhibition of extension

Questions on chapter 13

- 16) Describe two factors that can increase the competitive growth vigor of a developing axon.
- 18) What is collateral sprouting in the development of CNS axons? **Describe** the phenomenon and **two factors which affect when, where and in what axons it can occur. What can modulate the amount of collateral sprouting?**

Modulation of "competitive growth vigor"

The more growth vigor an axon has, the more it grows and the better it competes for terminal space.

- By chemical factors: more growth with more growth factor
 - E.g., NGF (see figure).
 - There are also molecular factors intrinsic to the cells which determine growth capacity, in either elongation or arborization.
- By activity:
 - More growth by more active axons, as in formation of ocular dominance columns in visual cortex
- By "pruning":
 - Sprouting in one region due to blockage of or damage to an axon in another region (see figure)

Figure removed due to copyright restrictions.

NGF: effects on growth vigor in DRG axons

Intrinsic, competitive vigor of axon growth

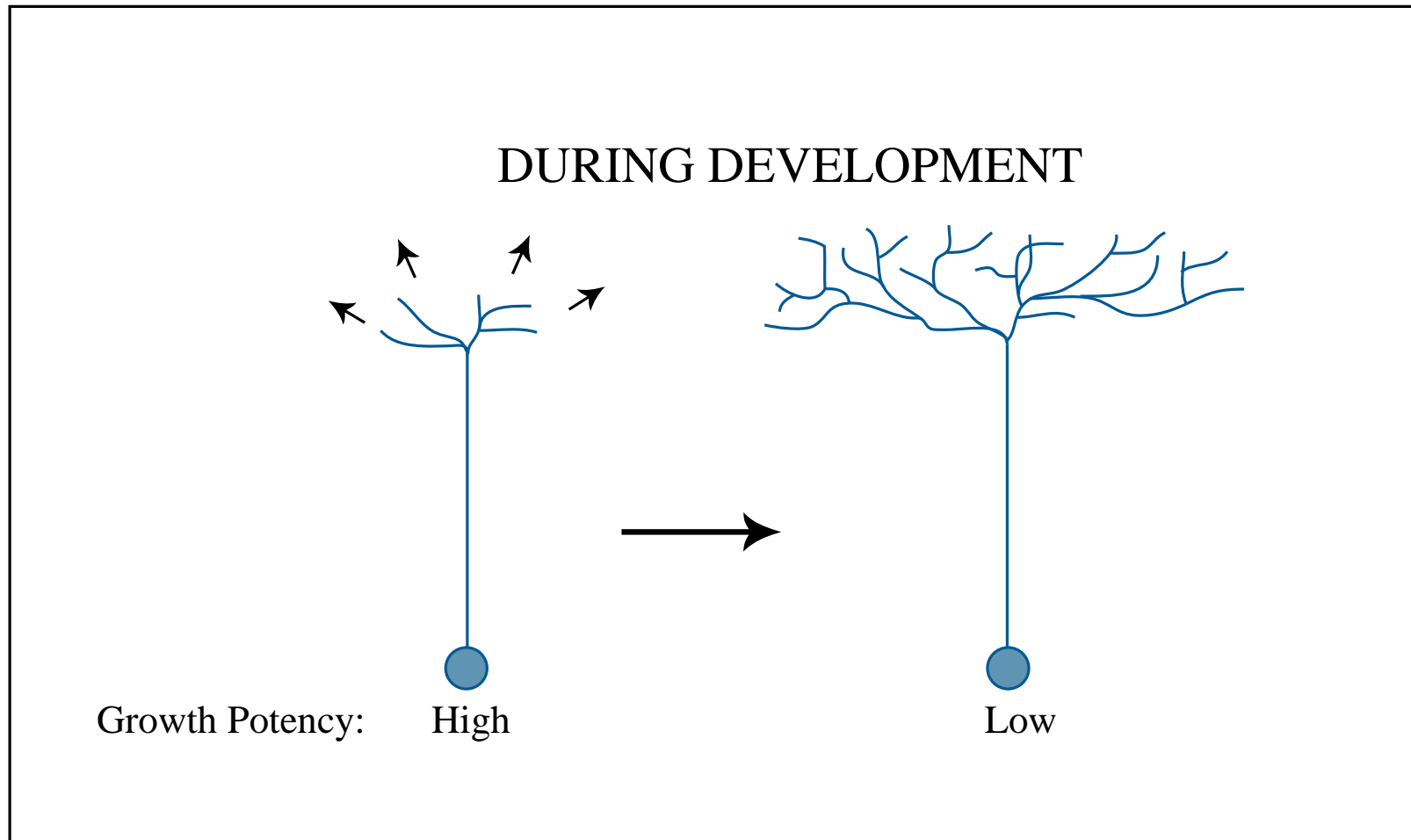


Image by MIT OpenCourseWare.

Intrinsic, competitive vigor of axon growth

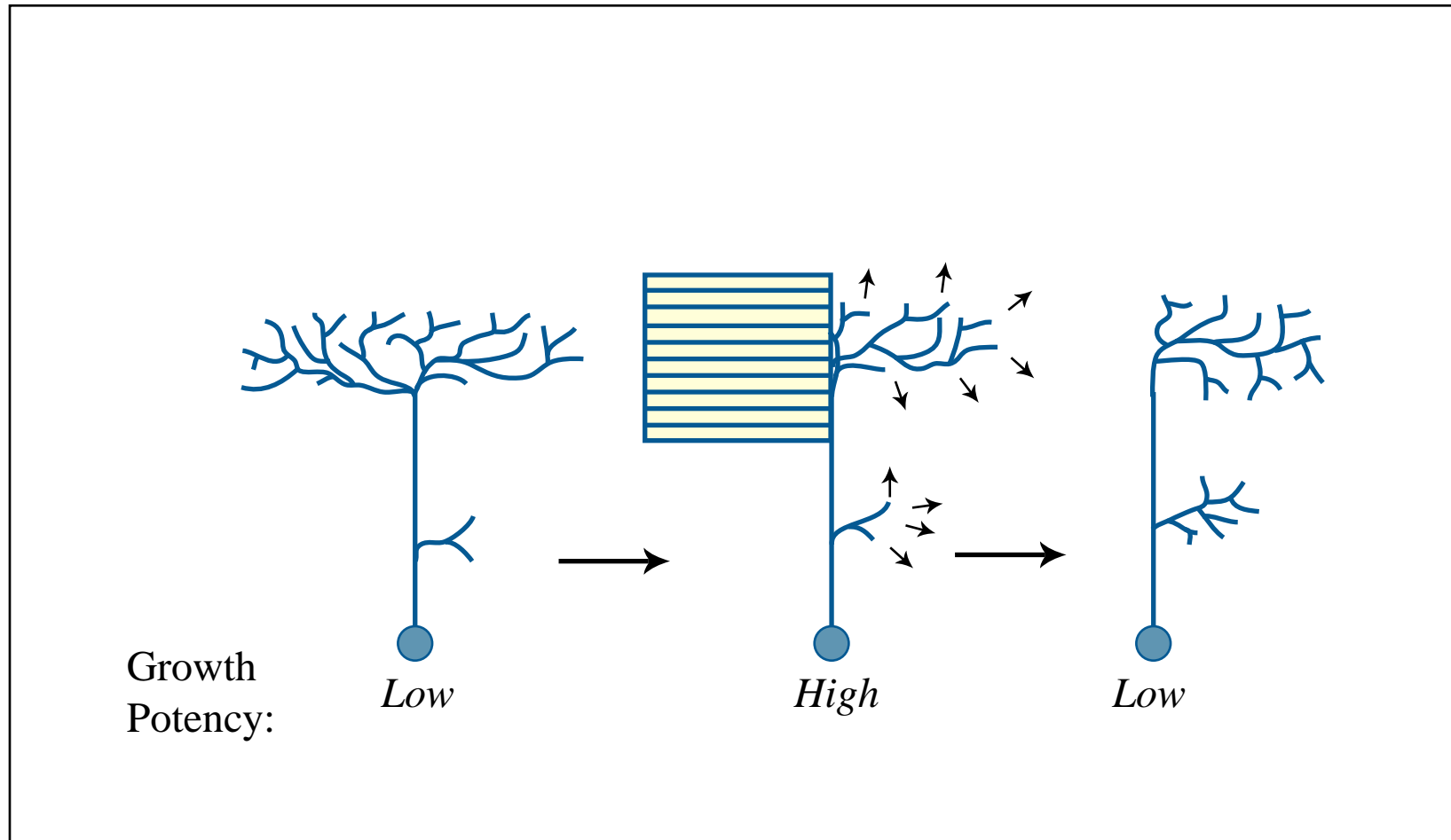


Image by MIT OpenCourseWare.

Pruning effect: Effects of pruning lesion on growth vigor. Such phenomena provide evidence for “Conservation of Terminal arbor size”, discovered in studies of developing optic and olfactory tracts.

Thus, we have two types of factors that could play roles in both **development** and **evolutionary** change

- 1) Extrinsic factors in axon-axon competition
- 2) Intrinsic factors in “conservation of terminal quantity”

Topics in the study of optic-tract development & plasticity: these apply also to other axonal systems

- Embryonic formation; 2 modes of growth
 - *Optic tract*; geniculostriate pathway; other connections
- Map formation; chemoaffinity
- Map plasticity: lesions
- Collateral sprouting; competitive interactions in axonal growth
- **Roles of cell death**
- Regeneration in development and adulthood

Questions on chapter 13

19) What is apoptosis?

Phenomena of neuronal death & survival; roles of neurotrophic factors and intrinsic factors

- Many neurons depend on axon target contact for survival. The target tissue gives them trophic factors.
- Without sufficient trophic factor (growth factor), they undergo **apoptosis (cell suicide, or “programmed cell death”)** unless protected by intrinsic factors.

Example:

CNS effects of limb-bud extirpation *vs.* grafting of a supernumerary limb in the embryo

- Greater than normal motor neuron death after limb-bud extirpation
- Less than normal motor neuron death after grafting of supernumerary limb in the embryo

Purves & Lichtman, ch. 6 pp 144f

Supernumerary Limb

(Purves & Lichtman)

Figure removed due to copyright restrictions.

Questions on chapter 13

20) Contrast two major possible purposes in naturally occurring neuronal death.

Two major possible purposes in naturally occurring neuronal death

- Population size matching
- Error correction

Purves & Lichtman, ch. 6 pp 144-149

Additional roles for neurotrophins

- Activity-induced plasticity
 - E.g., in visual cortex
- Learning
 - BDNF: associated with phosphorylation of specific subunits of the NMDA receptor.
- New neurons in adult brain (BDNF)

Topics in the study of optic-tract development & plasticity: these apply also to other axonal systems

- Embryonic formation; 2 modes of growth
 - *Optic tract*; geniculo-striate pathway; other connections
- Map formation; chemoaffinity
- Map plasticity: lesions
- Collateral sprouting; competitive interactions in axonal growth
- Roles of cell death
- **Regeneration** in development and adulthood

Questions on chapter 13

21) Describe what happens to regeneration of CNS axons in mammals early in development as the animal grows older. In brief, why does it happen?

MIT OpenCourseWare
<http://ocw.mit.edu>

9.14 Brain Structure and Its Origins

Spring 2014

For information about citing these materials or our Terms of Use, visit: <http://ocw.mit.edu/terms>.