PRINCIPLE: TO EXIST, LIFE MUST SENSE AND RESPOND TO THE EXTERNAL ENVIRONMENT

DKN
- How do microbes sense and respond to their environment?
- What type of things do they sense?
- How does signal transduction work?

Skype with Prof. Ned Wingreen, Caltech Class of 1984, Physics

MMN
- How do multicellular organisms integrate sensory information across tissues, organs and organ systems?
- What is the basis of activity in the animal nervous system?

Clicker quiz round

Marvel's Fantastic Four comic #72

How do microbes sense their environment?

Overview cartoon:

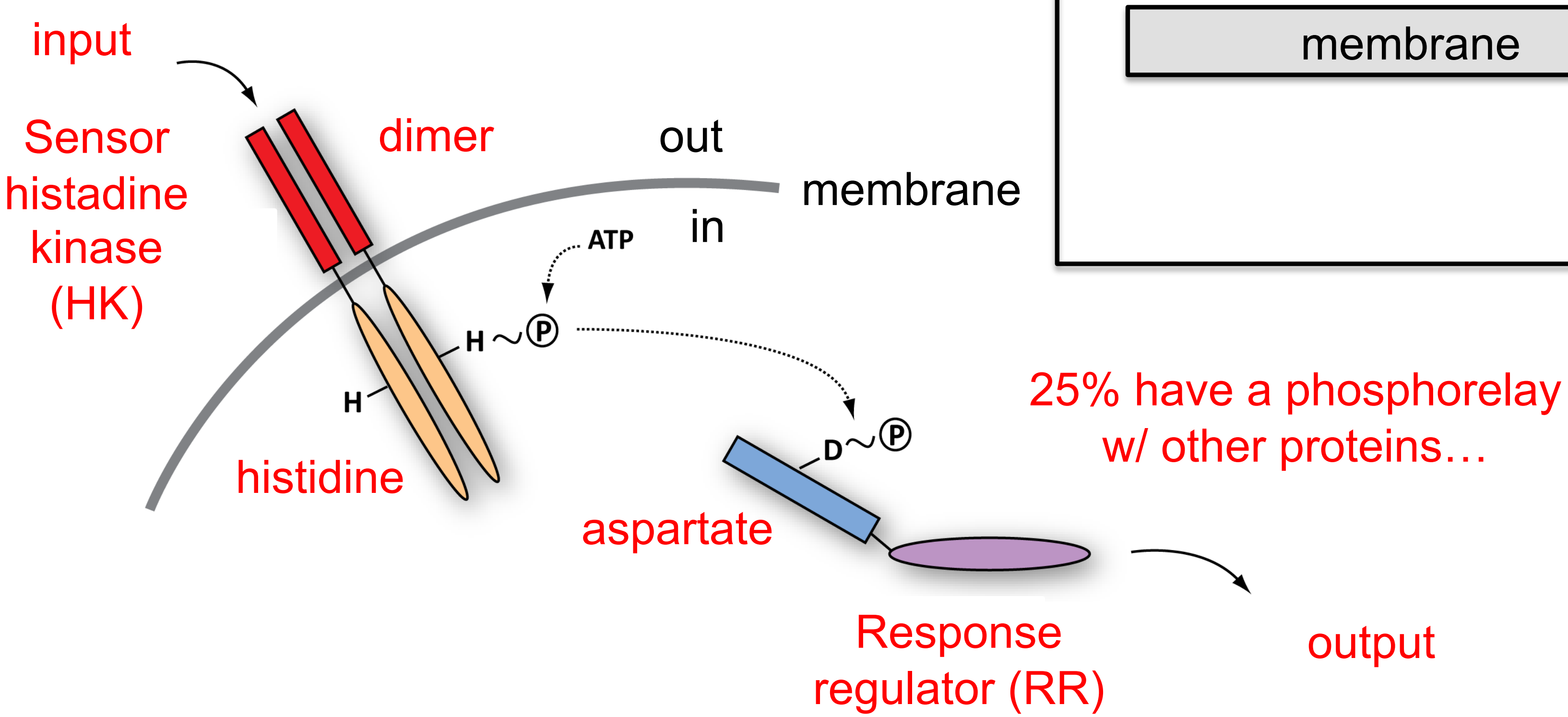
sense (input) → integrate → respond (output)

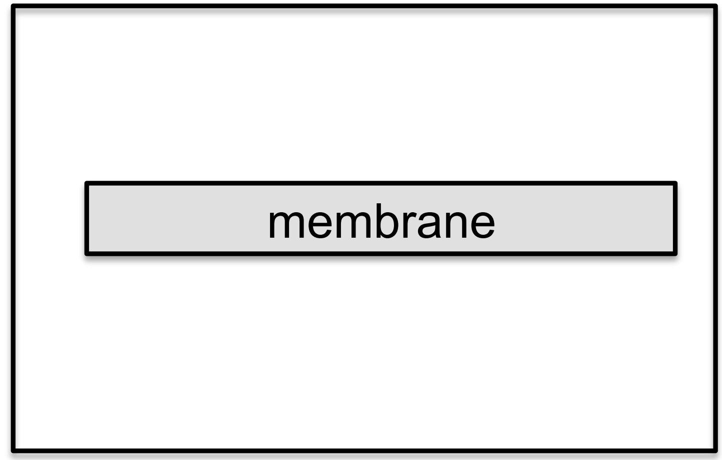
If you were a microbe, what information form the outside would you care about?

- Nutrients (attractants, *e.g.* light, organics, inorganics -- can be both substrates & products)
- Toxins (repellents)
- Stress (*e.g.* cell envelope stress)
- Time (circadian rhythms)
- Other cells (relatives)
- Other cells (competitors)

How do microbes sense, integrate and respond to external cues?

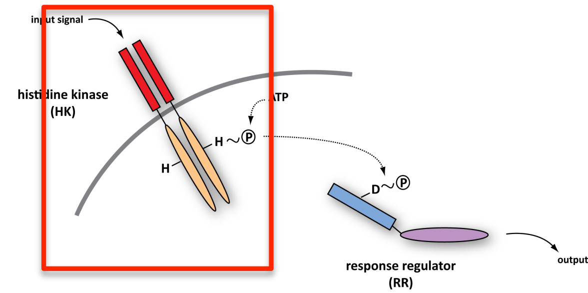
Answer: 2-component systems



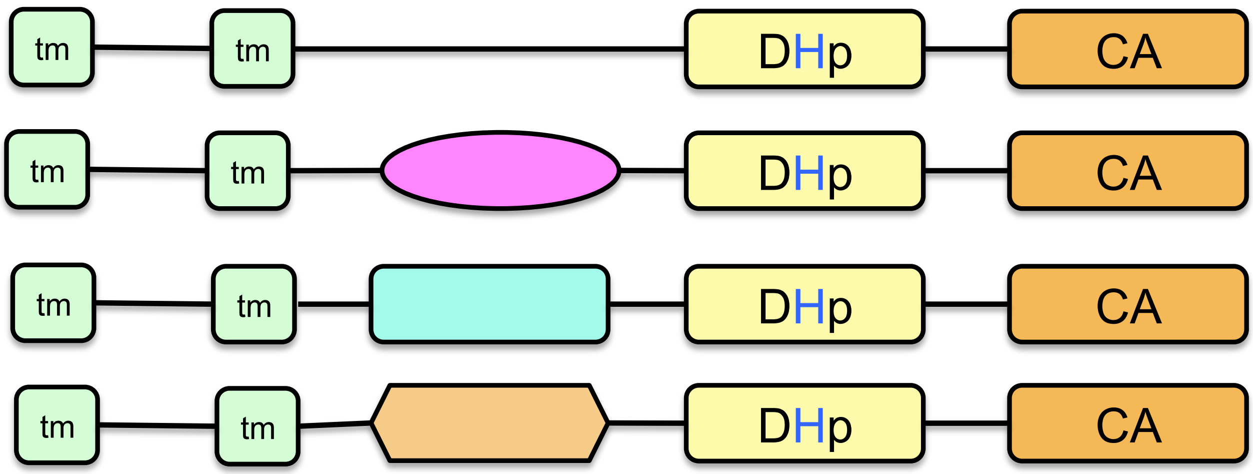


There are many different types of inputs, integration & outputs. Highly modular!

Domain architecture of sensor histidine kinases (HK)
(INPUT domain):



Dimerization/phosphotranser, catalytic

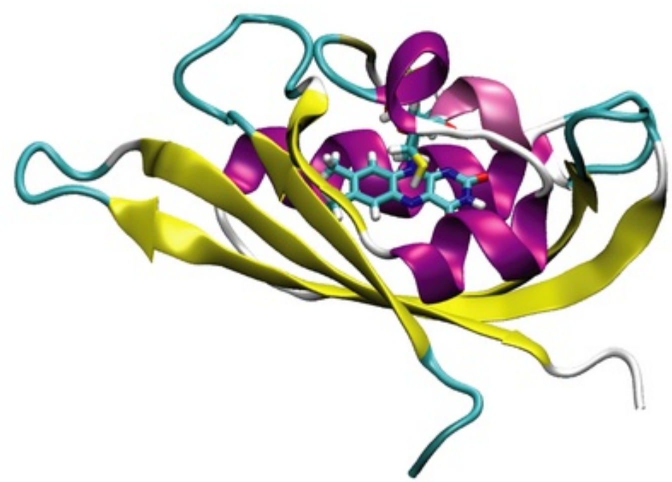


CA = ATP binding,
catalyzes auto-
phosphotransfer to
DhP domain,
Which then transfers
It to RR

Extracellular signal Transduce signal

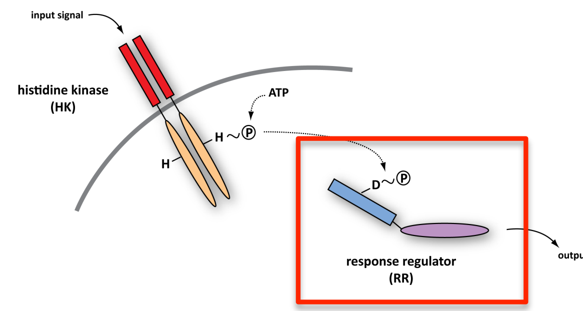
Examples of how a domain senses light:

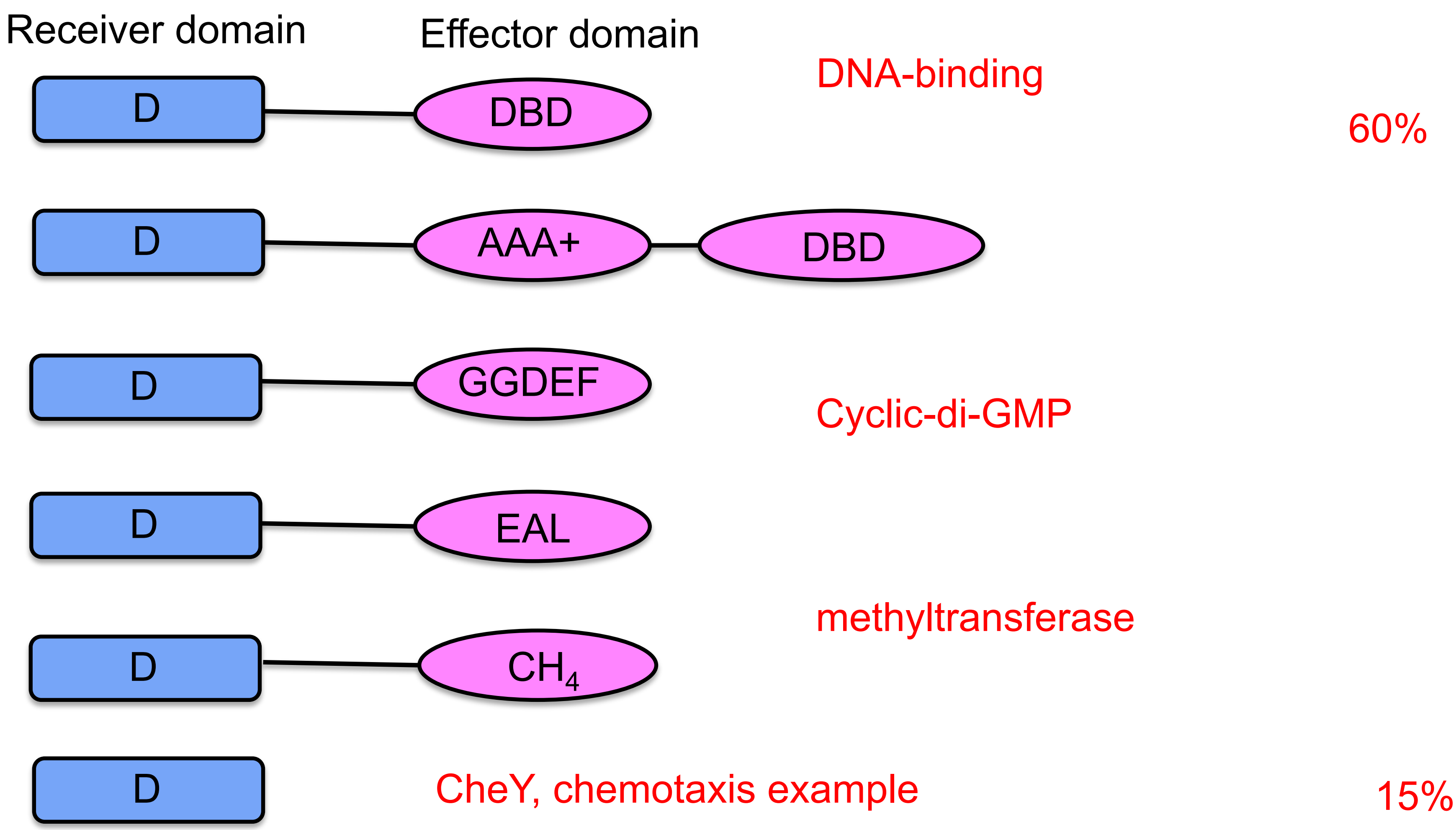
LOV (light-oxygen-voltage) domain,
belong to PAS superfamily (Per-Arnt-Sim)
Non covalently bound flavin cofactor,
makes a covalent bond when absorbs
blue light, results in conformational
rearrangement of the protein:



LOV domain of *C. reinhardtii*

Domain architecture of response regulators (RR) (OUTPUT domain):





Synthetic Biology
based on standard parts

Caltech iGEM 2011 Team – Designed bacteria to degrade endocrine-disruptors (compounds that disrupt development & reproduction of wild organisms)

A Sampling of Two-Component Signal Transduction Systems

Organism	Histidine Kinases	Response Regulators	Total
Caulobacter crescentus	62	44	106
Sinorhizobium meliloti	36	50	86
Bacillus subtilis	21	31	52
Escherichia coli	29	32	61
Geobacter sulfurreducens	86	75	161
Nostoc punctiforme	120	131	251
Streptomyces coelicolor	84	80	181
Pseudomonas aeruginosa	60	73	133
Streptococcus pneumoniae	7	12	19
Staphylococcus aureus	9	13	22
Saccharomyces cerevisiae	1	2	3
Dictyostelium discoideum	13	2	23
Arabidopsis thaliana	8	23	31

Figure from M. Laub, MIT

1.) A lot in bacteria but absent in metazoans: antibiotic target! 2.) What challenge might this abundance of 2-component systems pose?

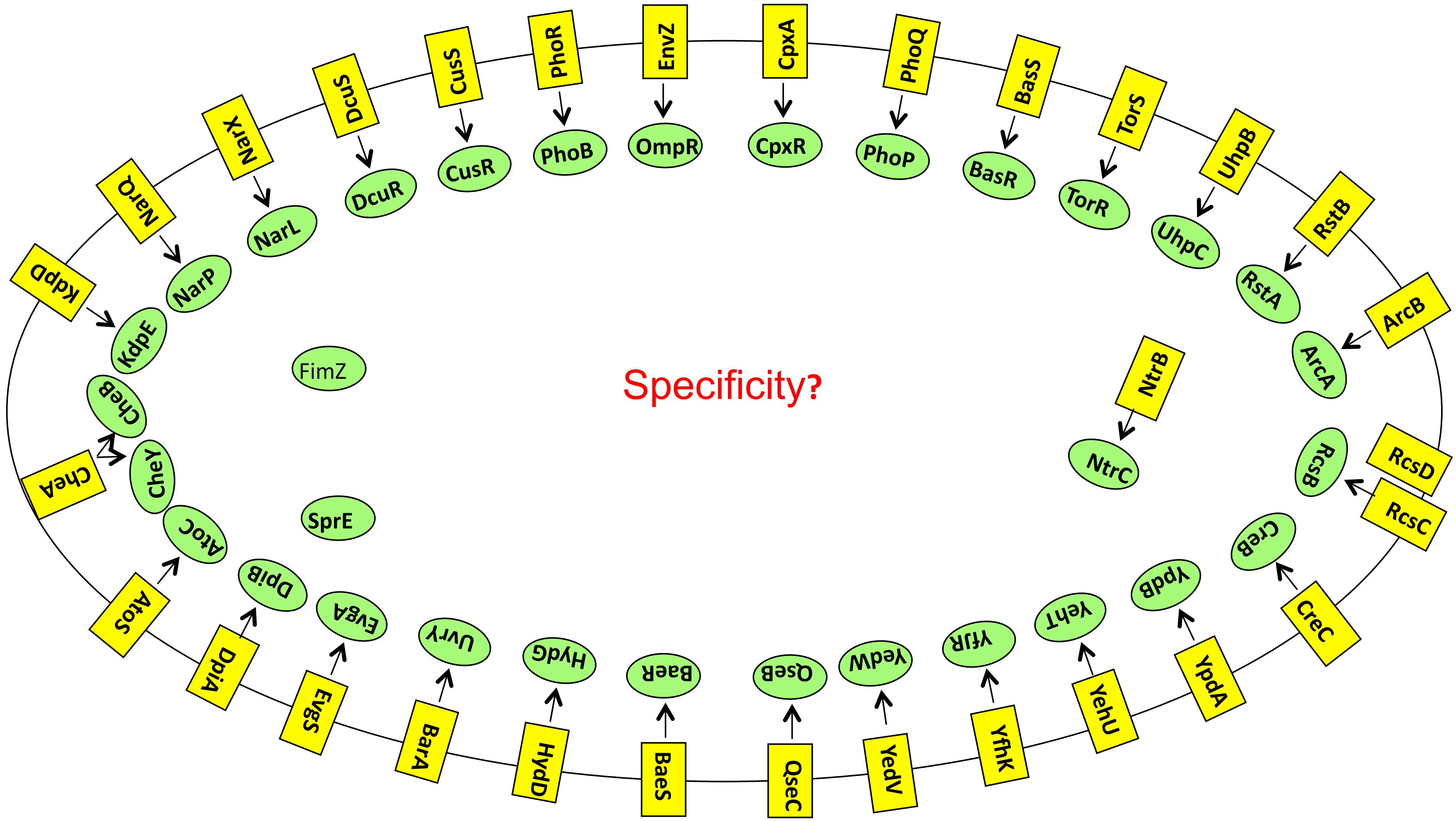


diagram by Mark Goulian

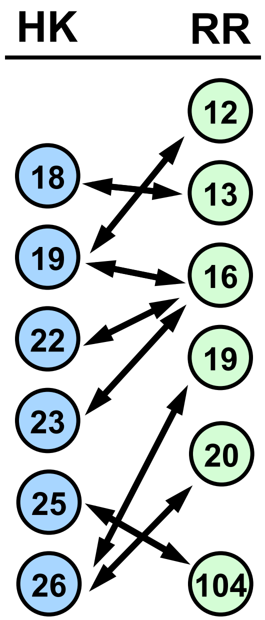
Solving the problem of specificity….

Control over production of the sensor (regulation)

Control over spatial localization of the sensor/response regulator

Fine-tuned molecular specificity***, achieved by co-evolution

Specificity determining residues identified by coevolution analysis



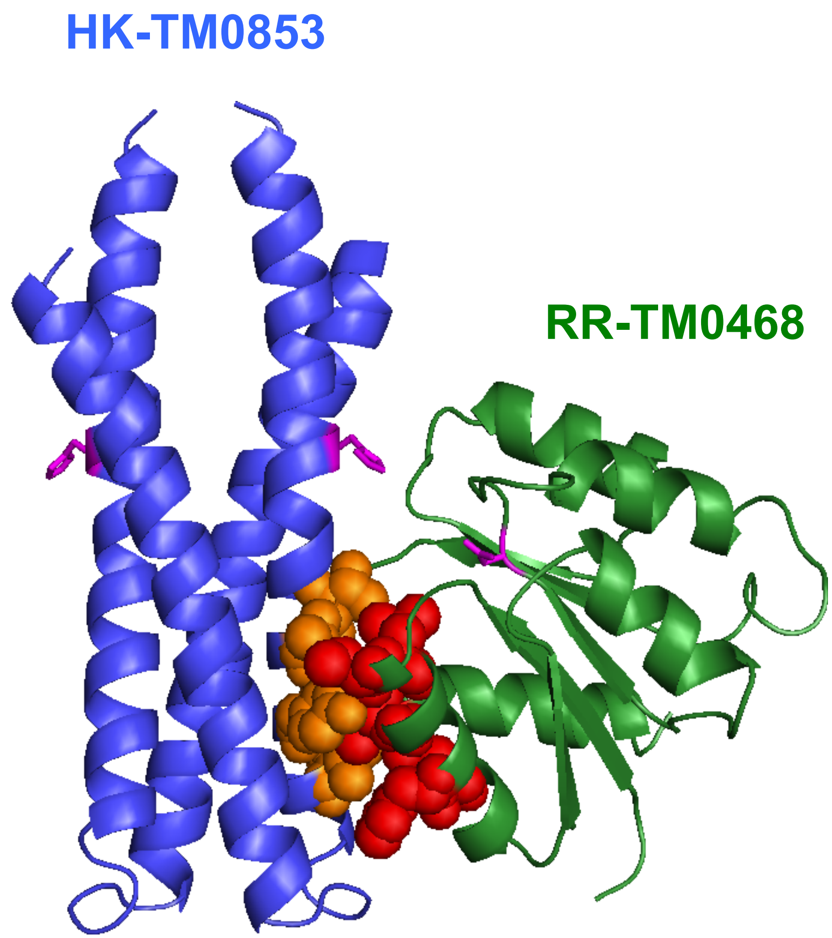
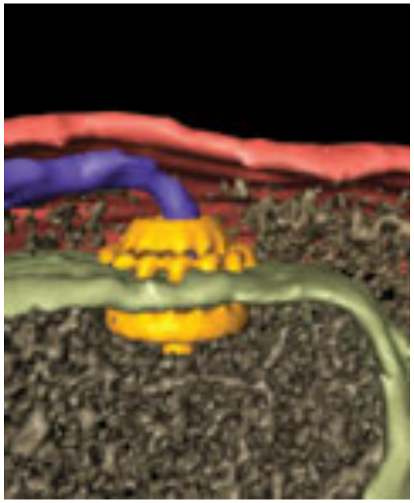


Figure from M. Laub, MIT

structure: PDB 3DGE

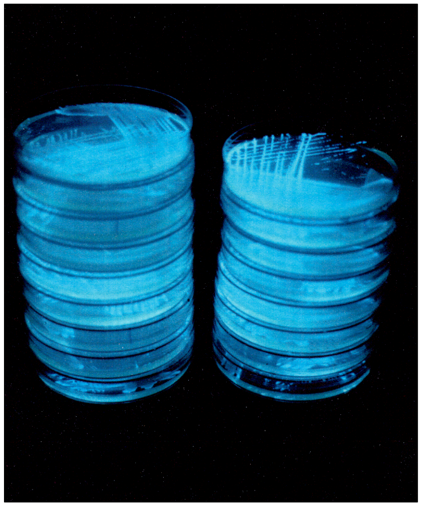
Two examples of signal transduction:

A.) Chemotaxis



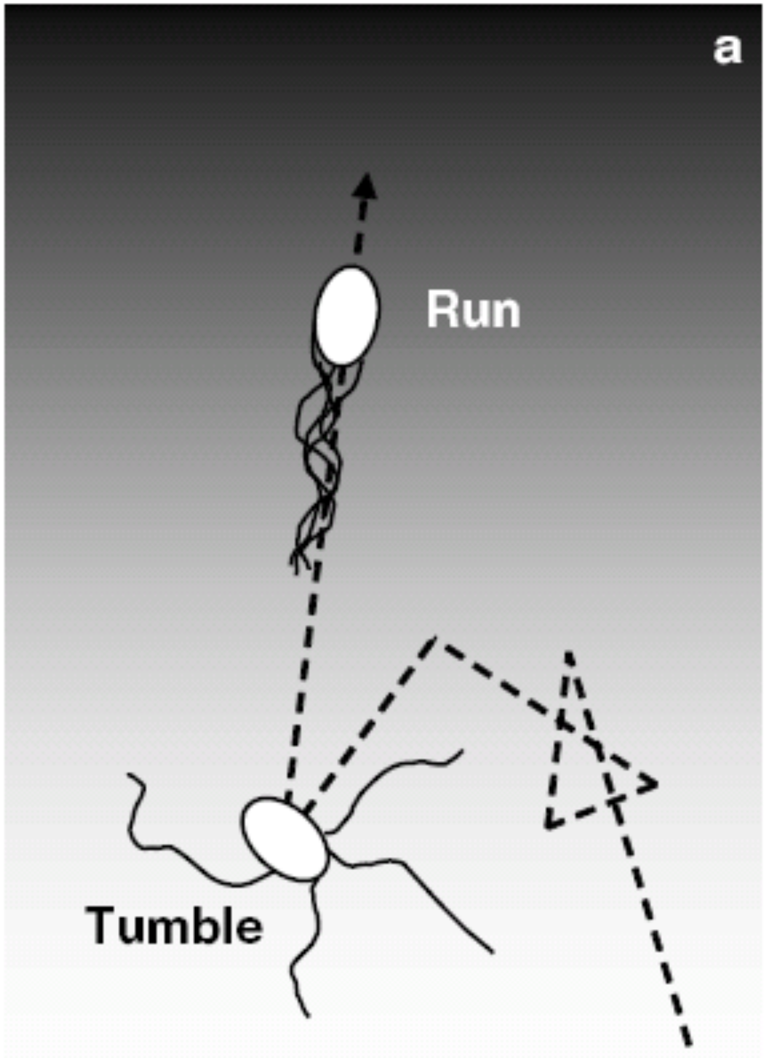
input	output
attractant	tumbling frequency

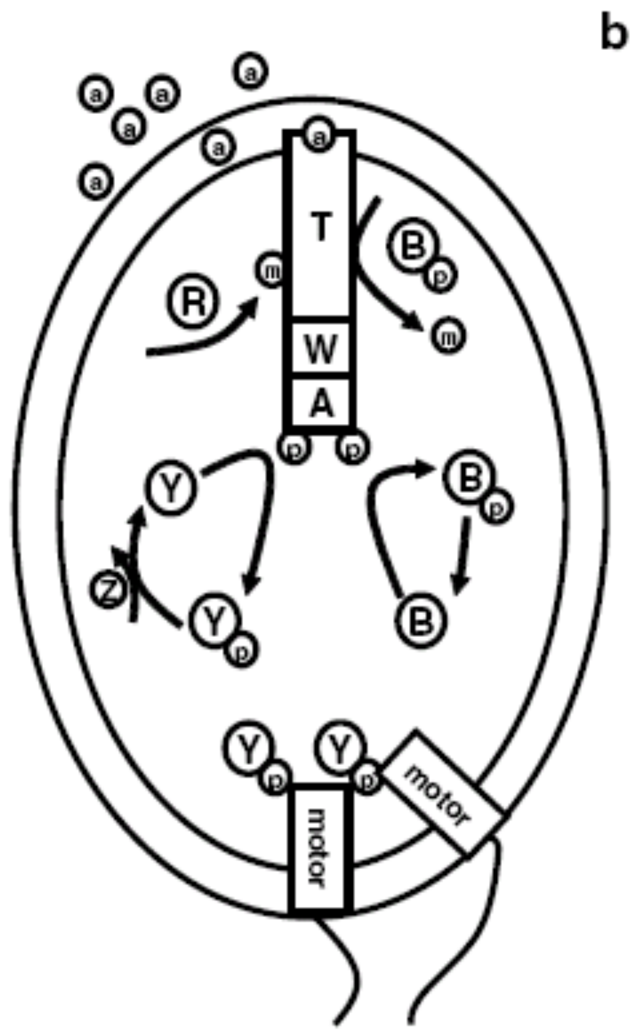
B.) Quorum Sensing (bacteria can count!)



input	output
counts cell #	makes light (other things)

Chemotaxis: Biased random walk



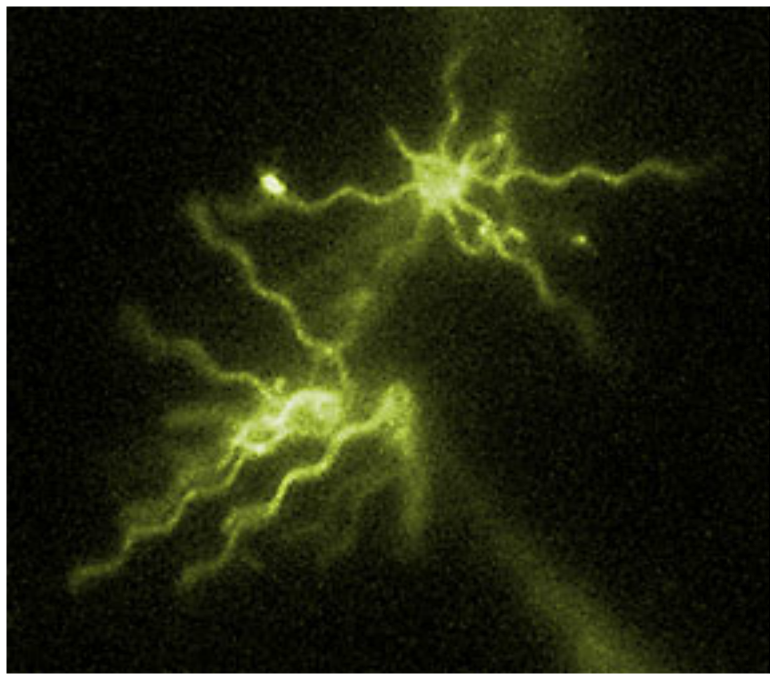


CW rotation: tumble; CCW rotation: run

http://emonet.biology.yale.edu/agentcell/

Movie of chemotaxis – run and tumble

Howard Berg (Caltech class of 1956, Chemistry)
Professor of Physics, Harvard



How do cells adapt to new conditions yet preserve their ability to respond?

Concept of robust exact adaptation – lecture reading assignment!

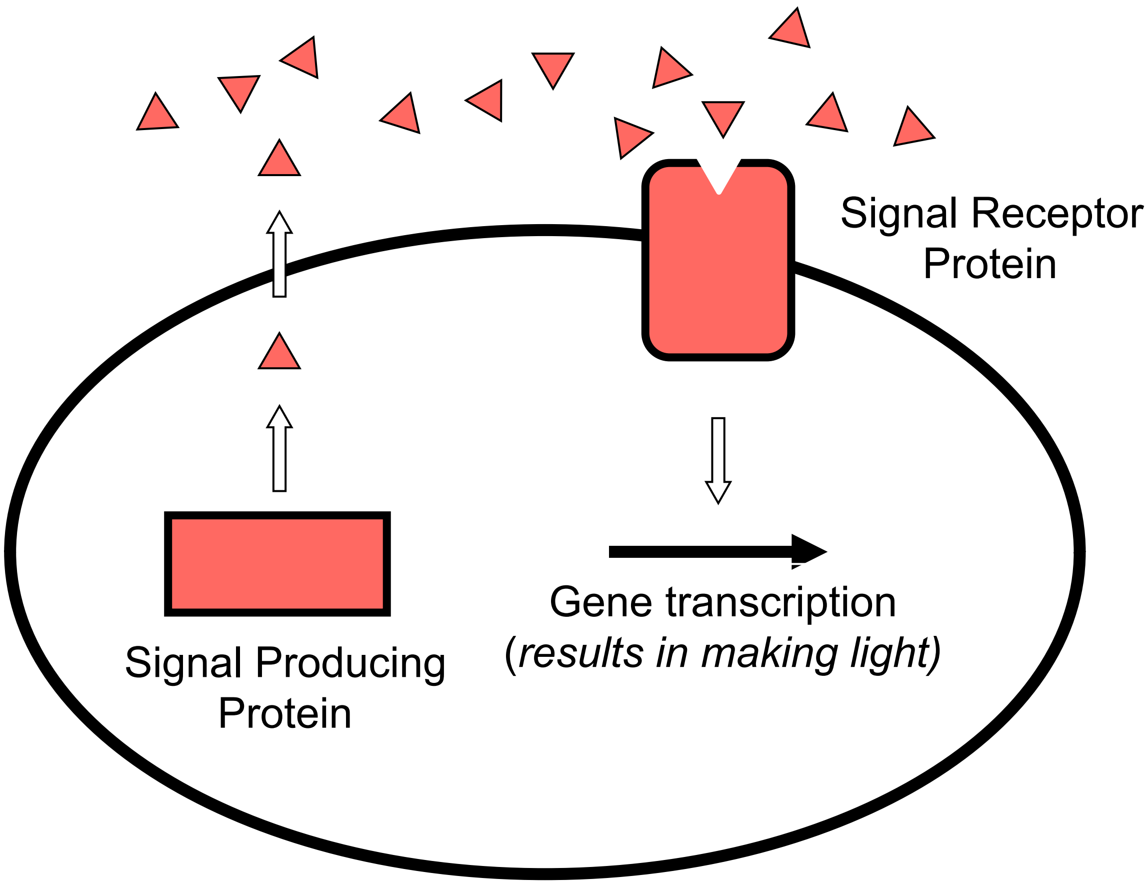
Sketch out Figure 7.5, 7.10 from reading! Moral of the story: ability to return to the steady state activity does not depend on ligand levels (robustness)
But the ligand levels *fine tune* the exact steady state level (data in Fig. 7.11)

Extra credit question (worth one iClicker question): under what conditions does robustness break down? Solve mathematically, using specific components of the chemotaxis network. Due in class next Tuesday at beginning of lecture.

Quorom sensing: sensing oneself (mechanism for “social behavior”)

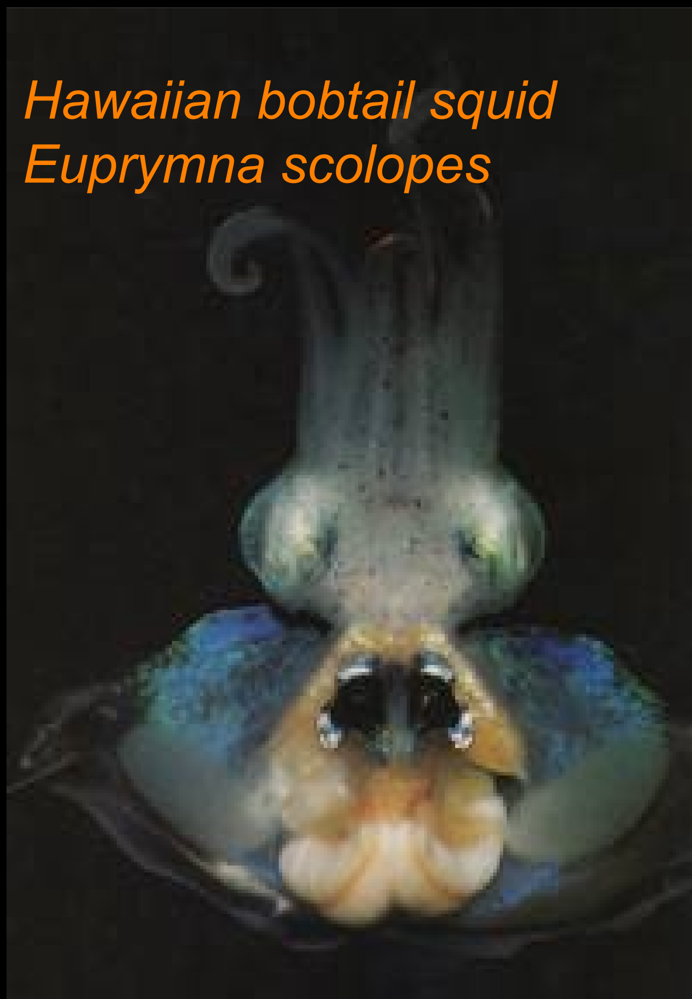
K. Nealson and W. Hastings discovered in **1970** (Nealson Thursday!)

Auto-induction, critical threshold



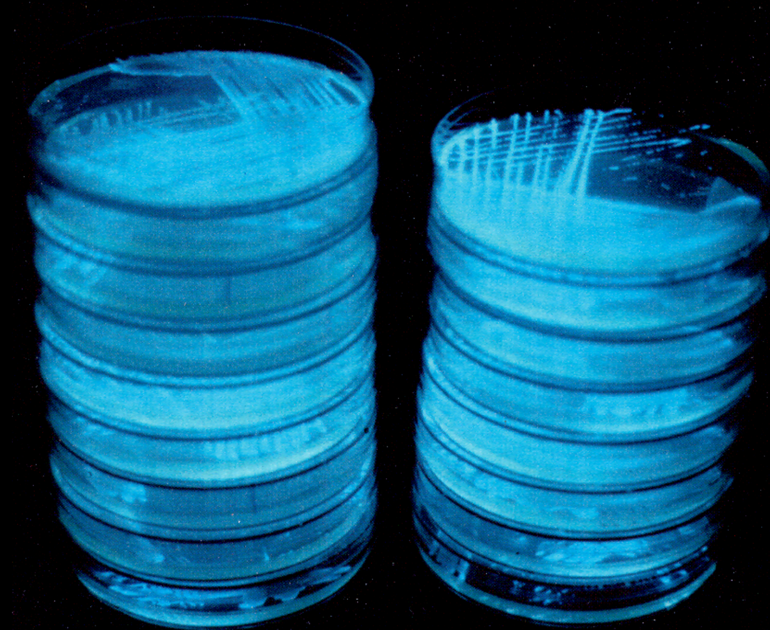
This is another two component system

Dramatic examples of quorum sensing…



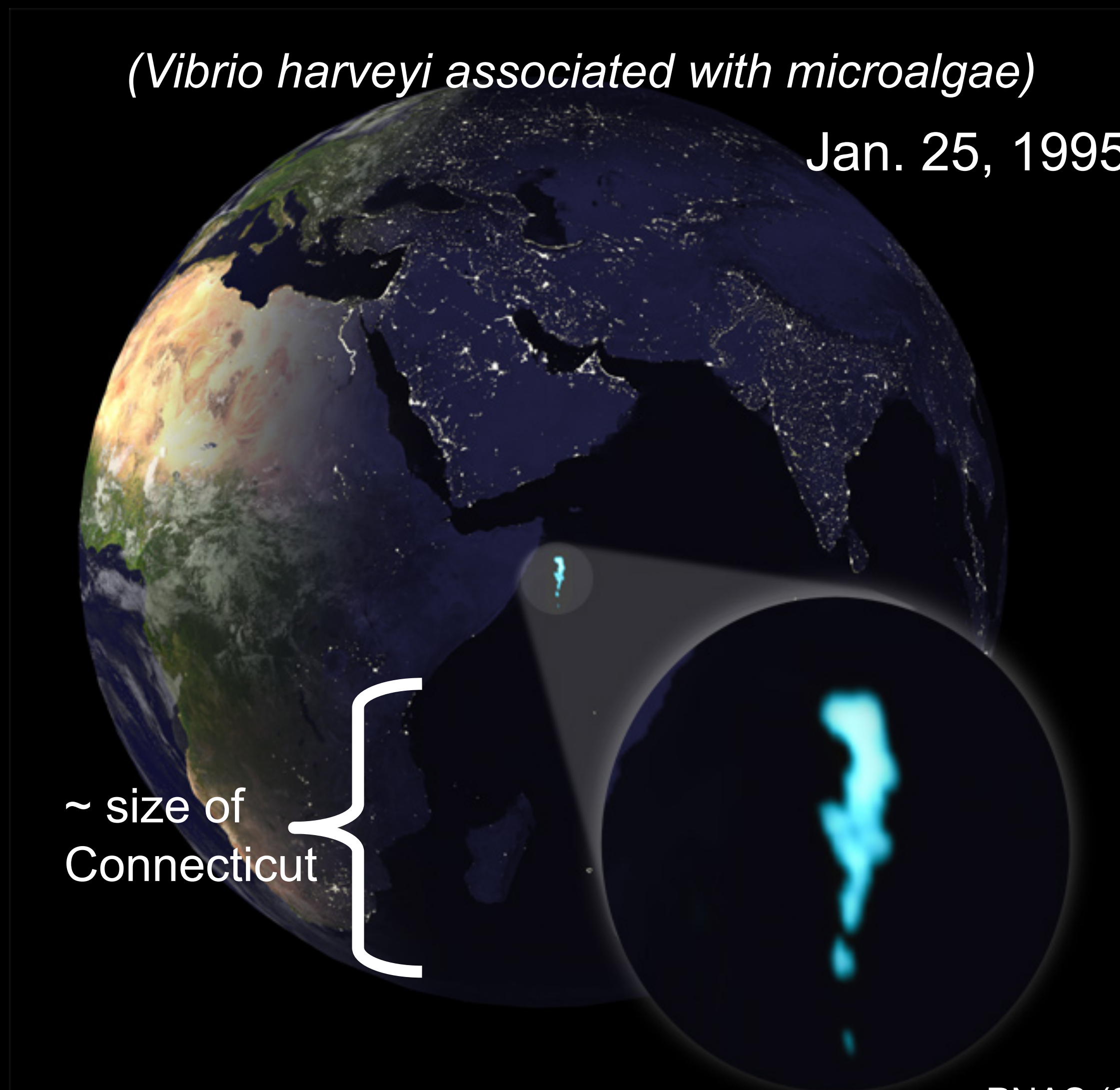
Ruby and Mcfall-Ngai

Vibrio fisherii, bioluminescence



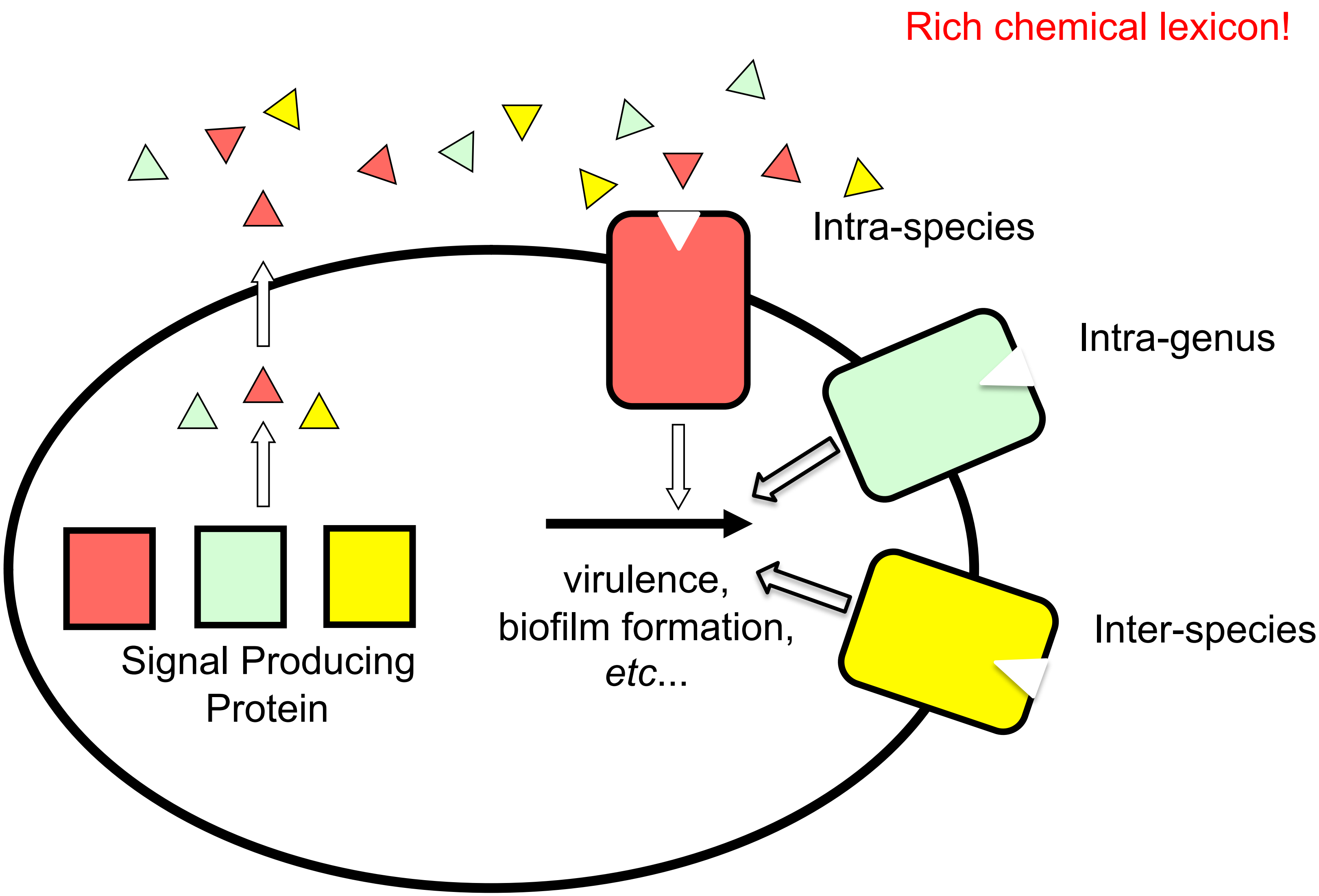
Egland and Leadbetter

…responsible for the "milky seas" described by ancient mariners



PNAS (2005) 102:14181-14184

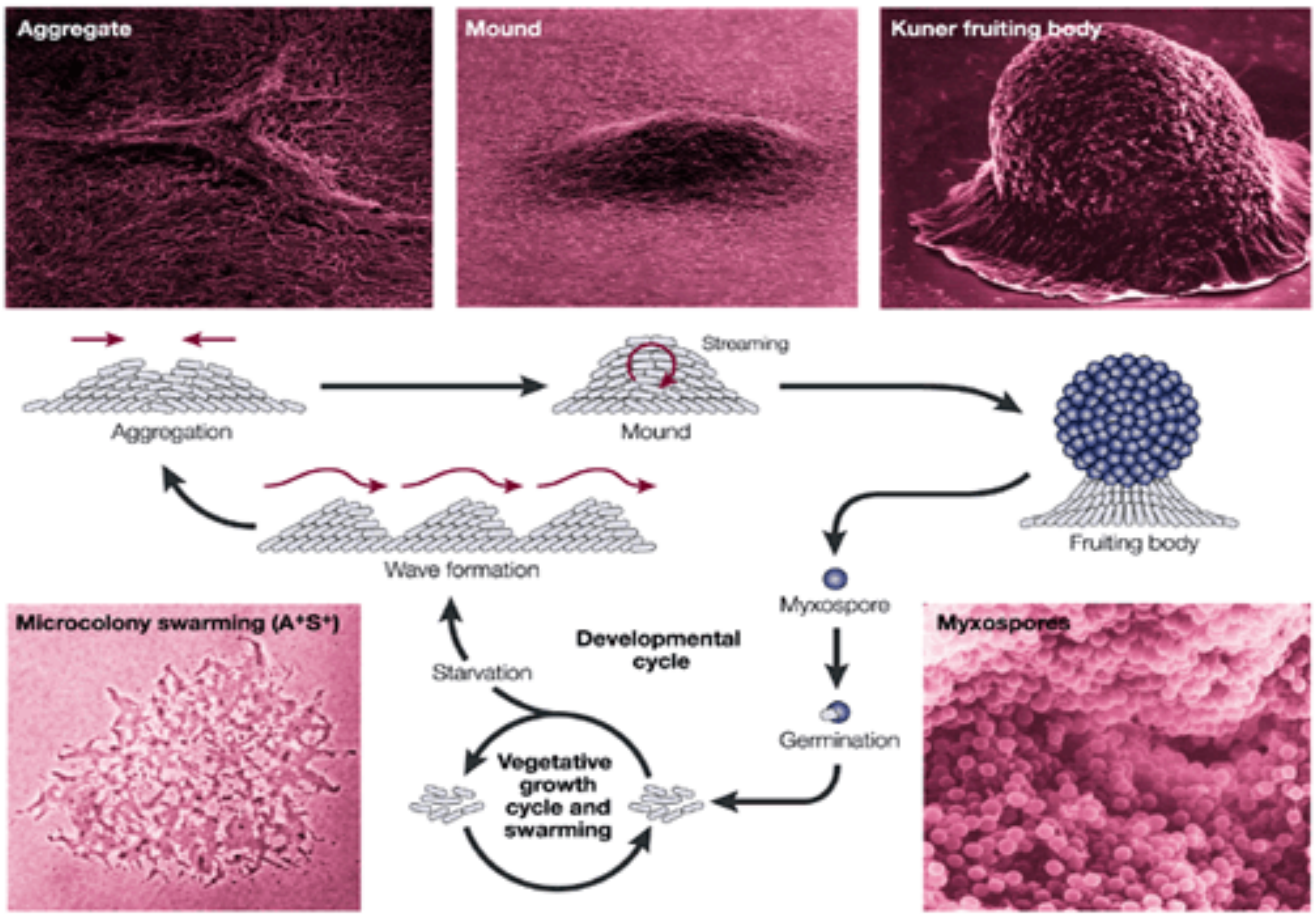
Quorom sensing: sensing oneself AND OTHERS!



http://www.ted.com/talks/bonnie_bassler_on_how_bacteria_communicate.html

Movie of traveling waves in *Myxobacteria*

Dale Kaiser (Ph.D. Caltech, 1955)
Professor of Developmental Biology, Stanford



Nature Reviews | Microbiology

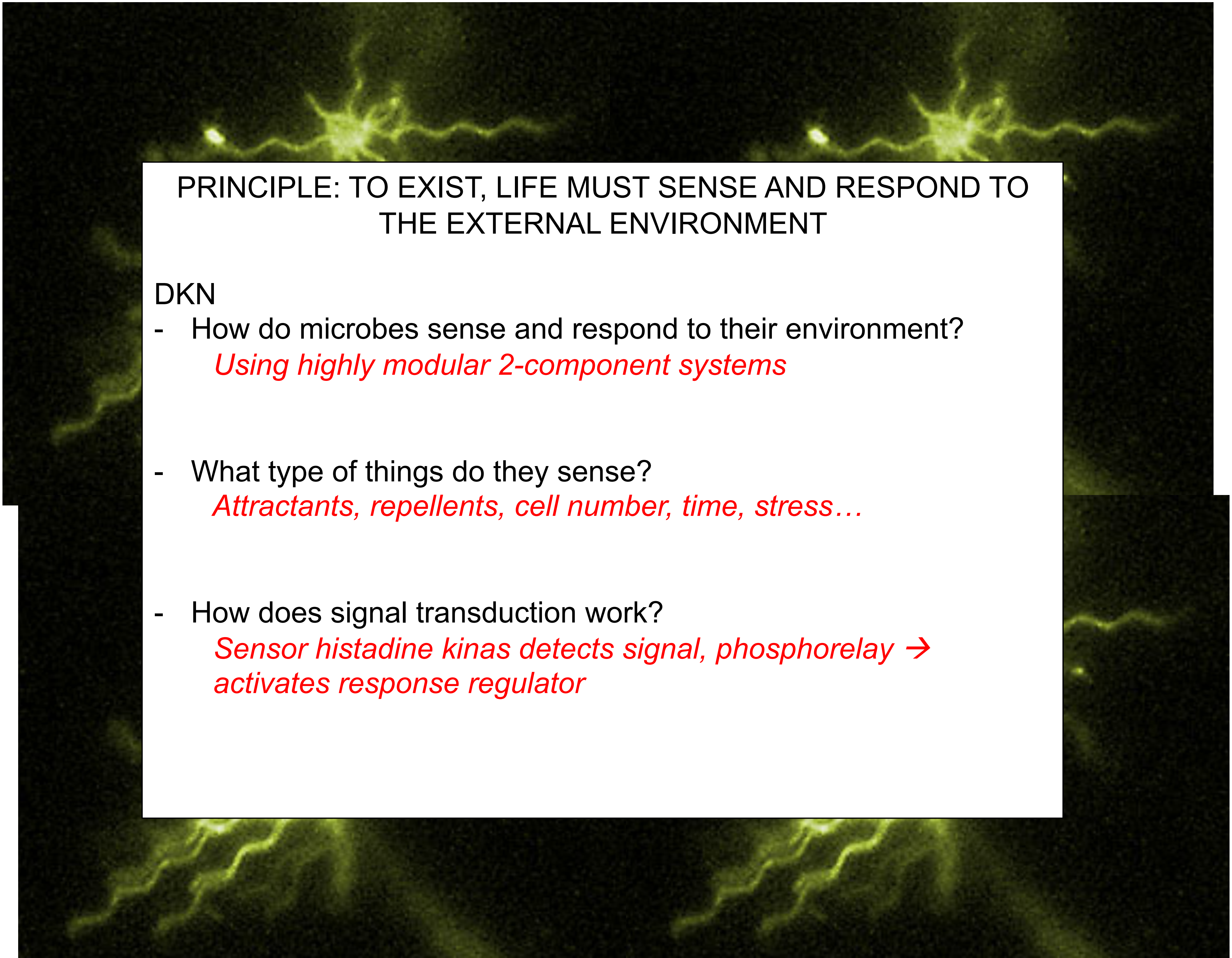
Accessible application of blocking QS: prevent refrigerator rot!

How could you do this?

Erwinia carotovora

Application of blocking QS: prevent rotten lettuce in your refrigerator!
How could you do this?

Erwinia carotovora



PRINCIPLE: TO EXIST, LIFE MUST SENSE AND RESPOND TO THE EXTERNAL ENVIRONMENT

DKN

- How do microbes sense and respond to their environment?
  Using highly modular 2-component systems

- What type of things do they sense?
  Attractants, repellents, cell number, time, stress…

- How does signal transduction work?
  Sensor histadine kinas detects signal, phosphorelay → activates response regulator

PRINCIPLE: TO EXIST, LIFE MUST SENSE AND RESPOND TO THE EXTERNAL ENVIRONMENT

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Skype with Prof. Ned Wingreen, Caltech Class of 1984, Physics

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Clicker quiz round

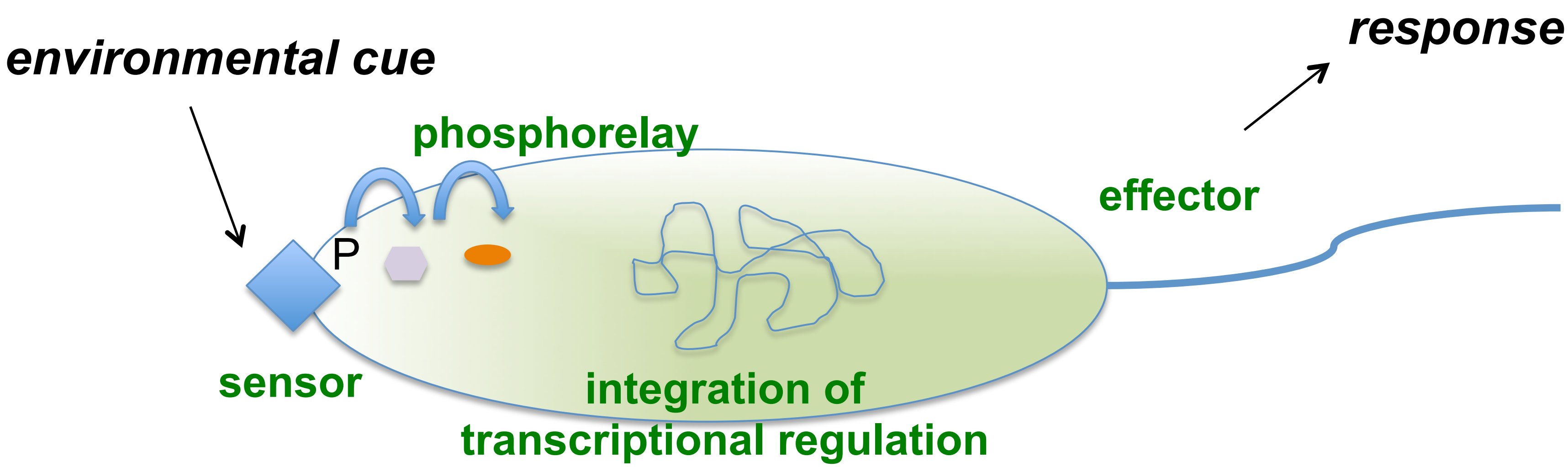
<u>Sensing/integrating/responding to the environment</u>

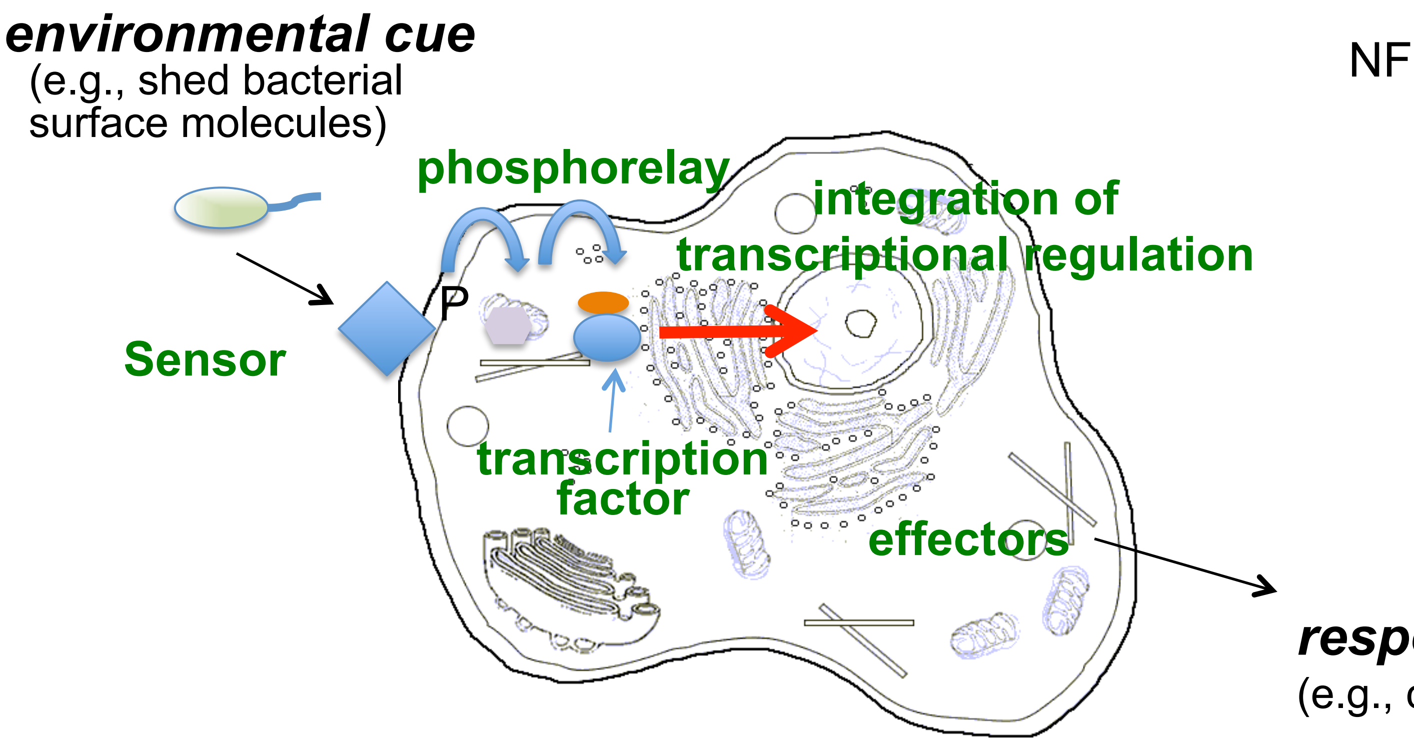
Unicellular – receptor on the cell/ integration across the cell/ effector mediates response

Multicellular – 2 interacting tasks:
1) responding to the abiotic environment
2) coordinating cells

Nature of the:
- Sensors
- Integrators
- Effectors

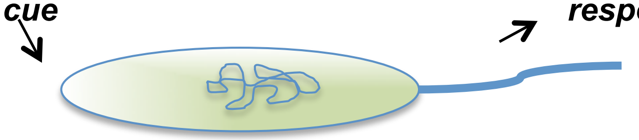
A. Animals - nervous and endocrine systems in animals – typical short vs. sustained
B. Plant hormones





NF-kappaB pathway

David Baltimore

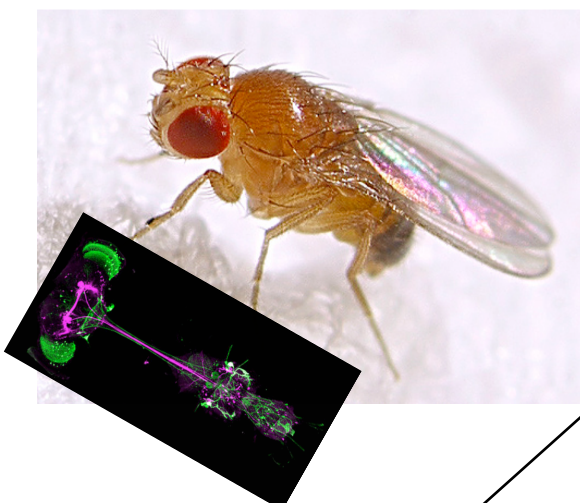


Coordination of a multicellular organism

cells – tissues – organs – organ systems

FASTER RESPONSE

nerve cell - e.g., myelin – e.g. brain - **nervous system**



SLOWER, SUSTAINED RESPONSE

plant growth

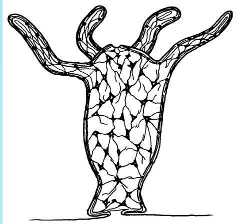
progression of insect development

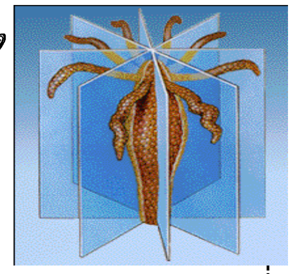
secretory cell - e.g., islet cells – pancreas – endocrine system (make insulin)

Trends in Nervous System Evolution and Correlations with Body Plan

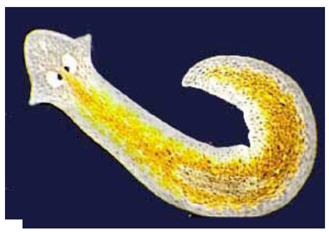
No well coordinated NS, no symmetry

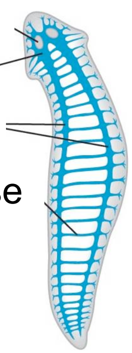
nerve net

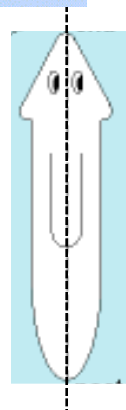




Bidirectional nervous conduction
Radial symmetry



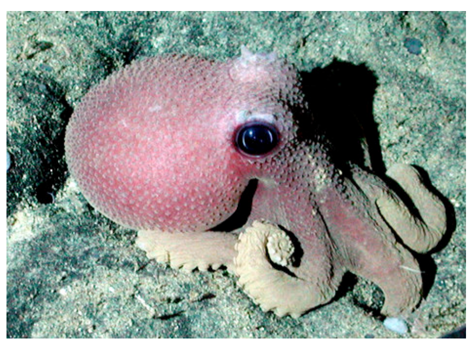




Unidirectional nervous conduction
Bilateral symmetry

~100 billion neurons in brain
Spinal cord 1 billion

Increasing cephalization



~300 million neurons in brain

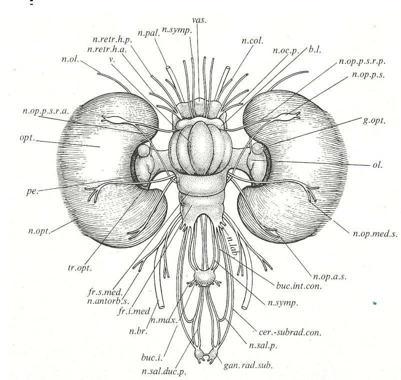
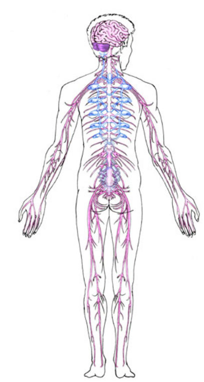
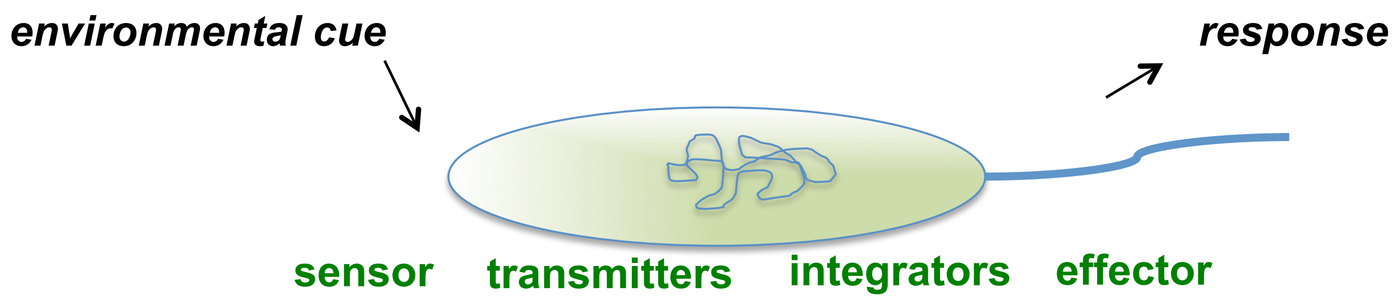
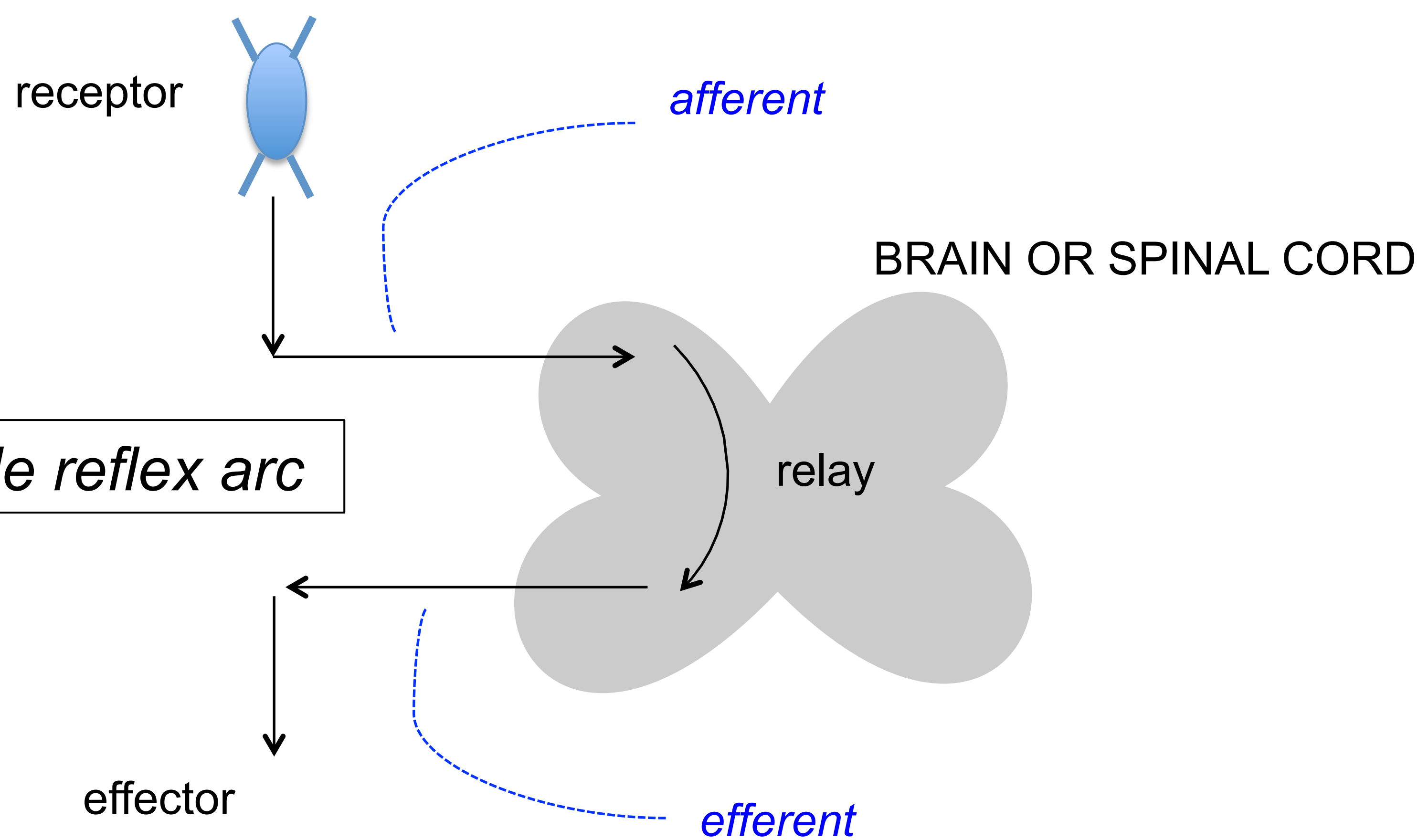


FIG. 1.6. Diagrammatic drawing of central nervous system of *Octopus* as seen from above (modified from Young 1964b).





ANIMAL NERVOUS SYSTEMS



FROM : Simple reflex arc

Example of a reflex arc

Z-fish movie

Complexity of wiring for complex human behavior:

Human brain ~100 billion neurons –

10,000 neuronal classes

each nerve cell or neuron communicates with 1000 others.

HAR1

To: More complex behaviors

Neural circuitry and the genetics of aggression

David Anderson
Div Biology, Caltech

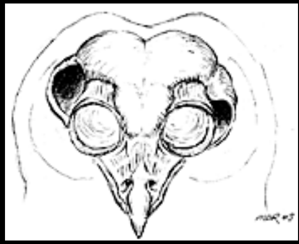
Movie

M Konishi
Caltech

E Knudsen
Stanford U

Multiple exposure (infrared) of owl hunting in the dark

Locates prey by using time over which sound reaches the two ears, which are assymmetric



Interaural time difference

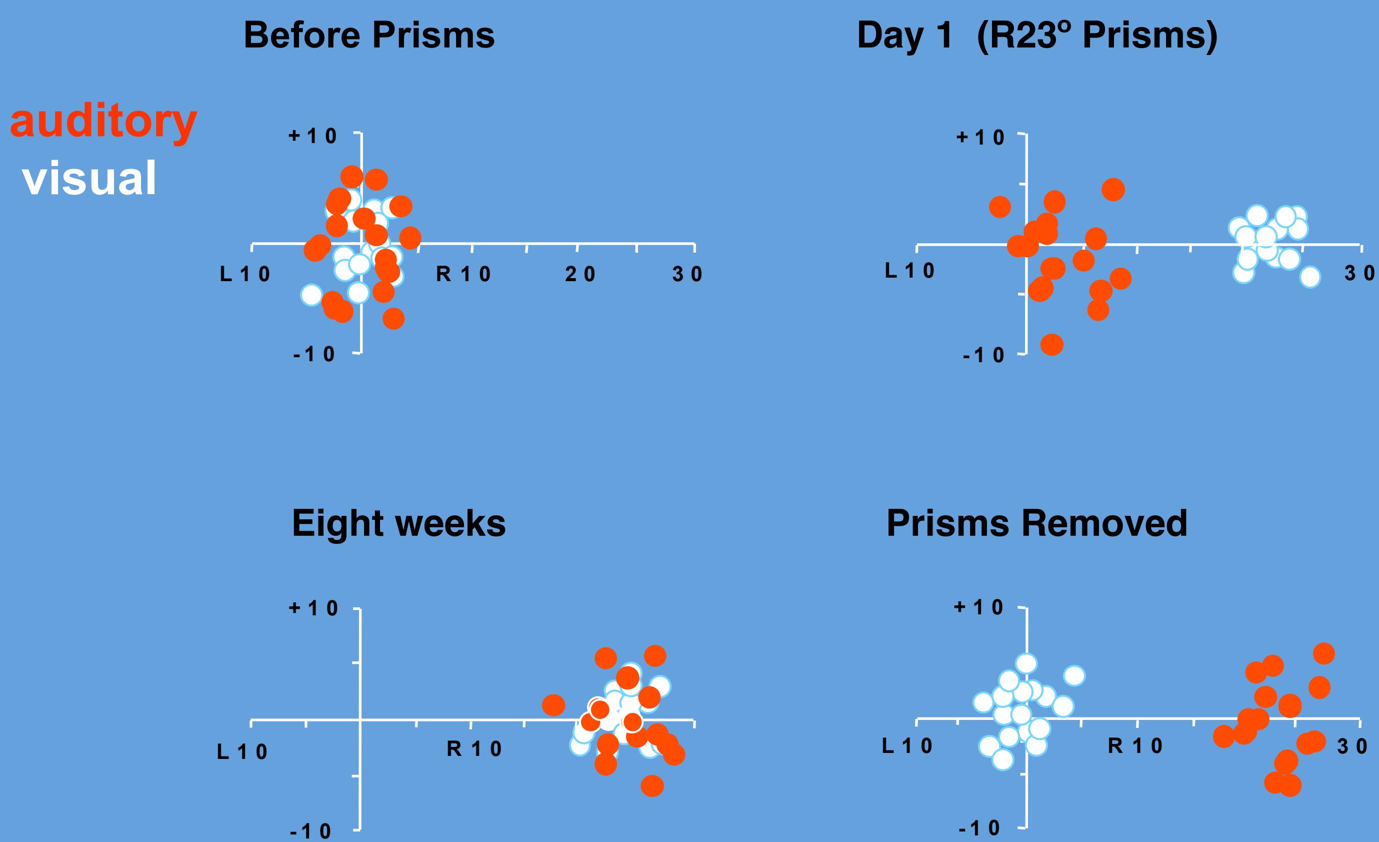
Sound-source localization

Complex neural computation that translate auditory location cues into representations in space.

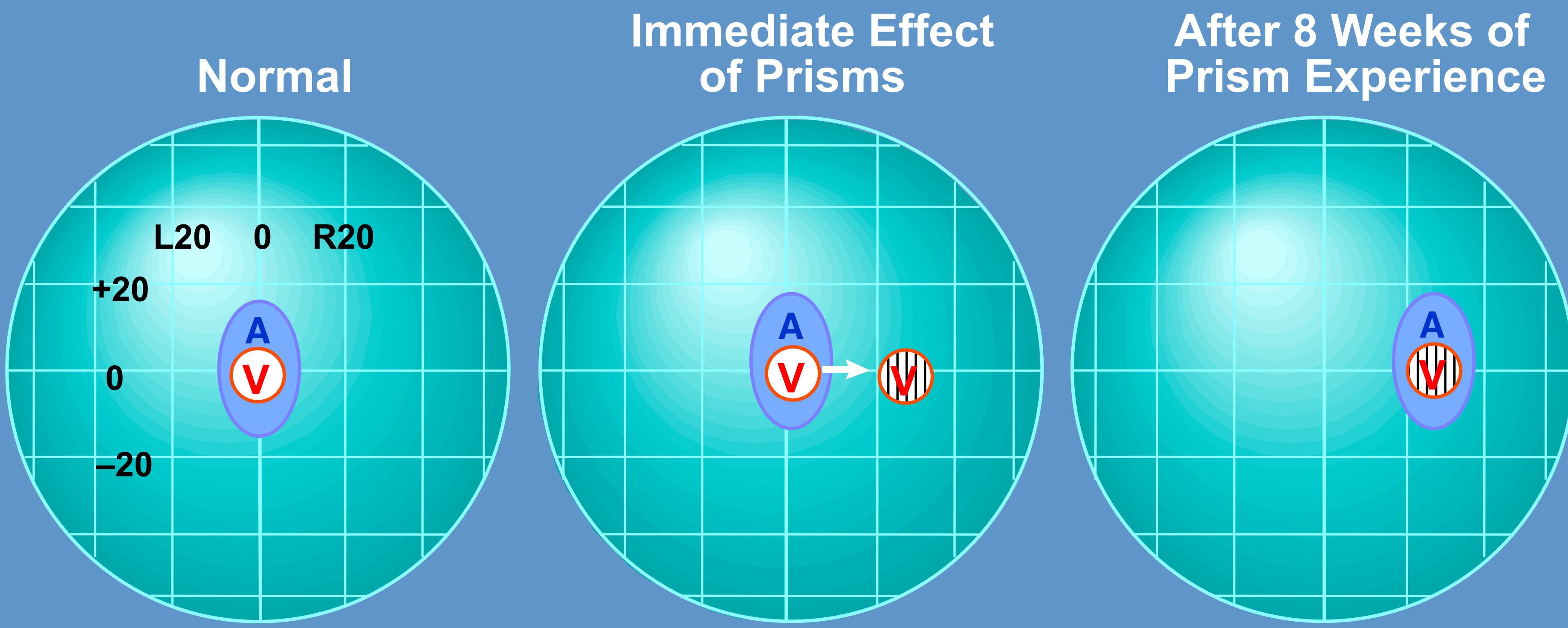
The system is integrated with the owls visual system; learned.

Owl chicks – with prisms.

Orienting responses to auditory or visual targets



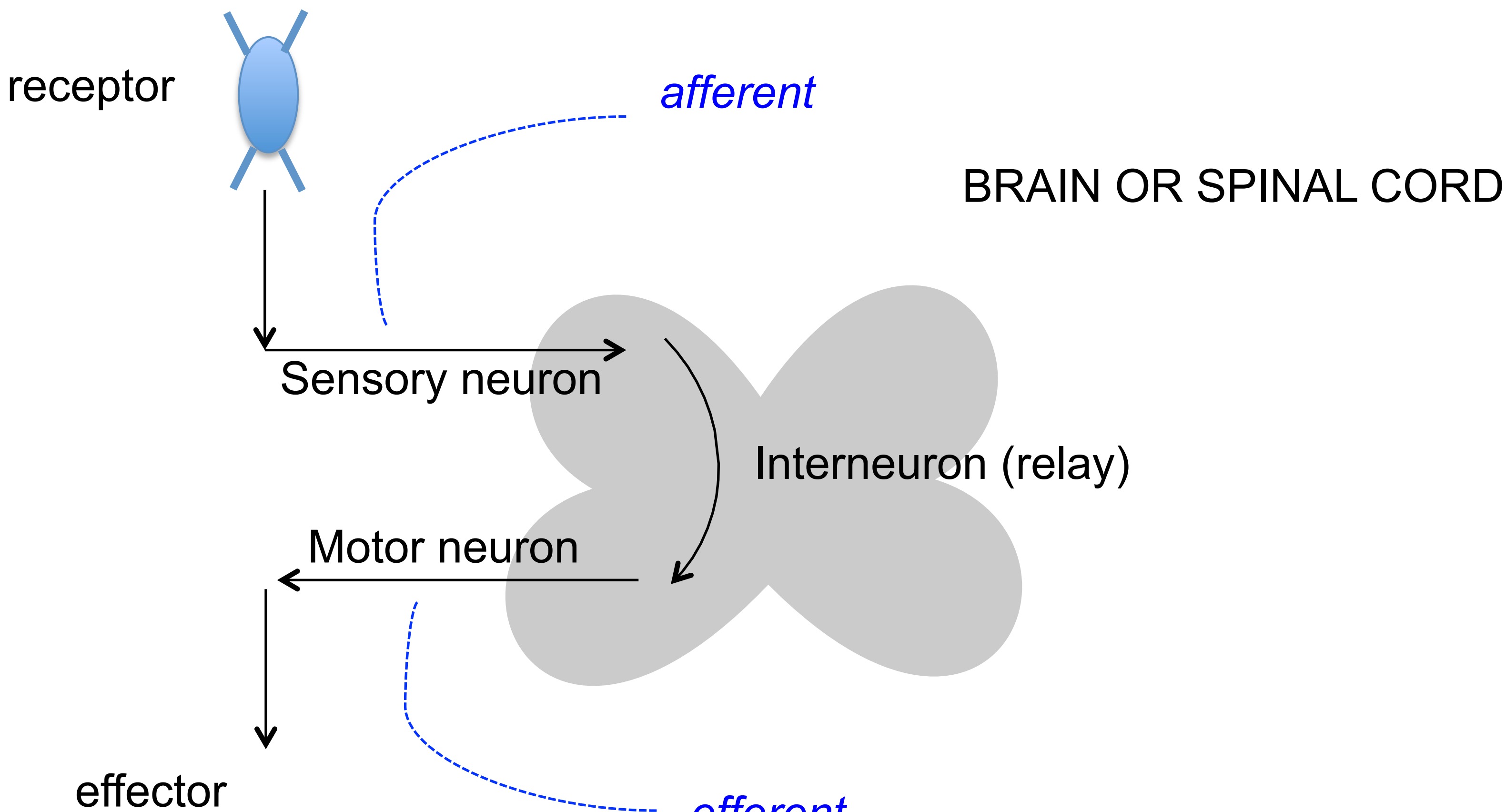
Prism experience shifts auditory receptive fields



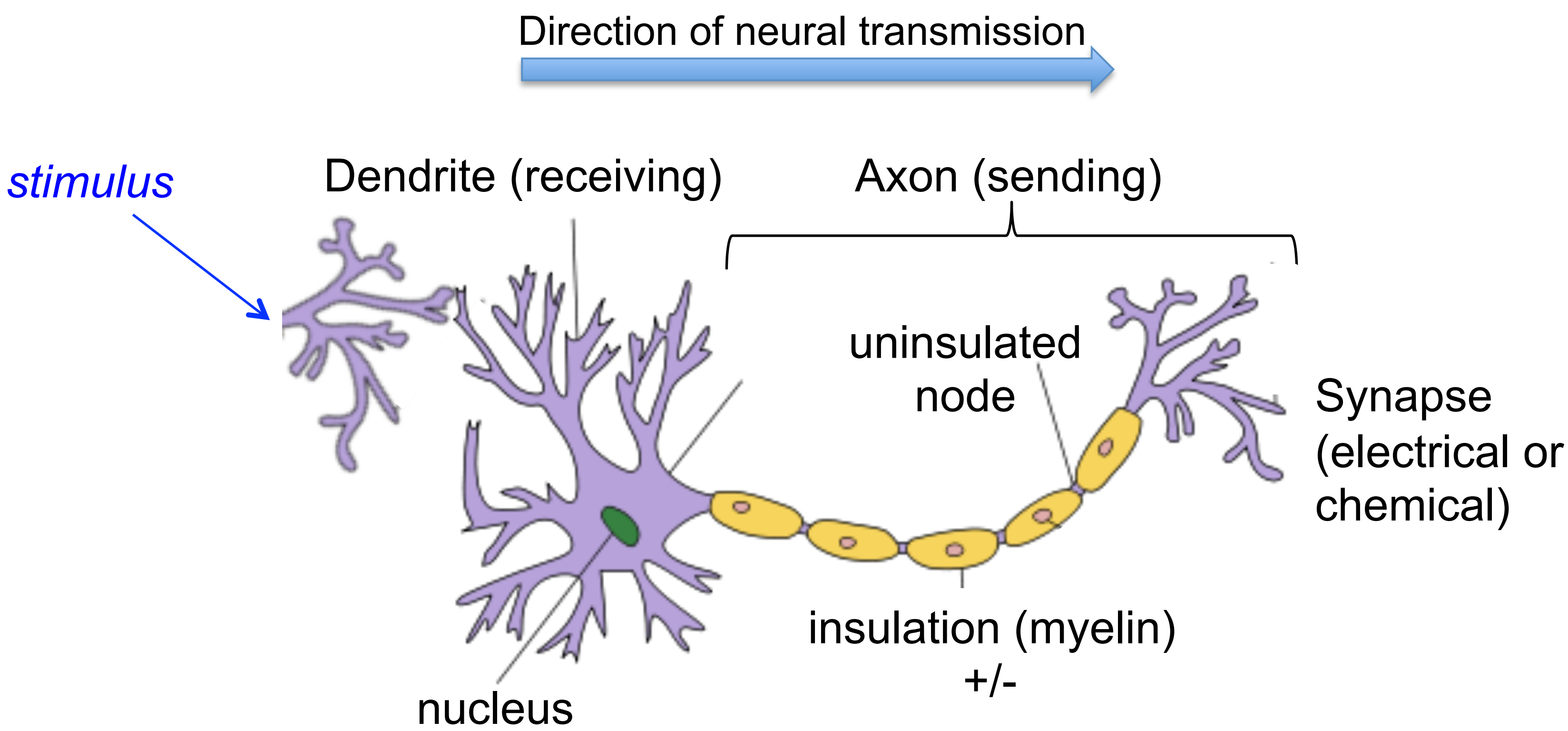
What are these cells and how do they function?

Nerve cell = neuron

3 principal kinds:



Structure of a neuron



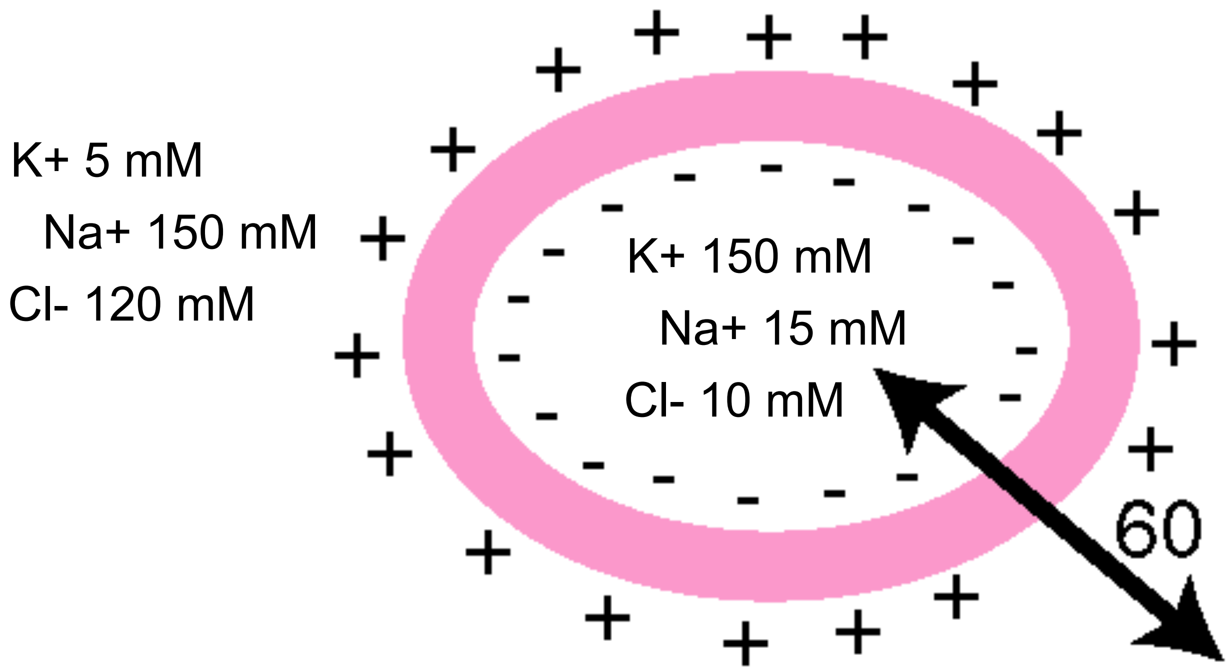
Speed:

nervous conduction – myelinated (vertebrate nerves, with an exception) – up to 100 m/sec

unmyelinated (invertebrate) – typical up to 1 m/sec

giant axon (1 mm diameter max) aver 0.5 mm - 25 m/sec

Physiology of a neuron – selection on a pre-existing character of all cells – membrane potential - difference in charge across the membrane



Amount of membrane voltage at equilibrium = equilibrium potential (E_{ion}) is given by Nernst equation, applies to single ion type.

$$E_{ion} = 62 \text{ mV} \left[\frac{\log [\text{ion}] \text{ outside}}{\log [\text{ion}] \text{ inside}}\right]$$

Thus, for K+ $\quad Ek = 62 \text{ mV} \dfrac{\log 5 \text{ mM}}{\log 150} \quad = -92 \text{ mV}$ (at body temp)

Na+ + 62 mV

Membrane potential always described as inside relative to outside

Typical membrane potentials:

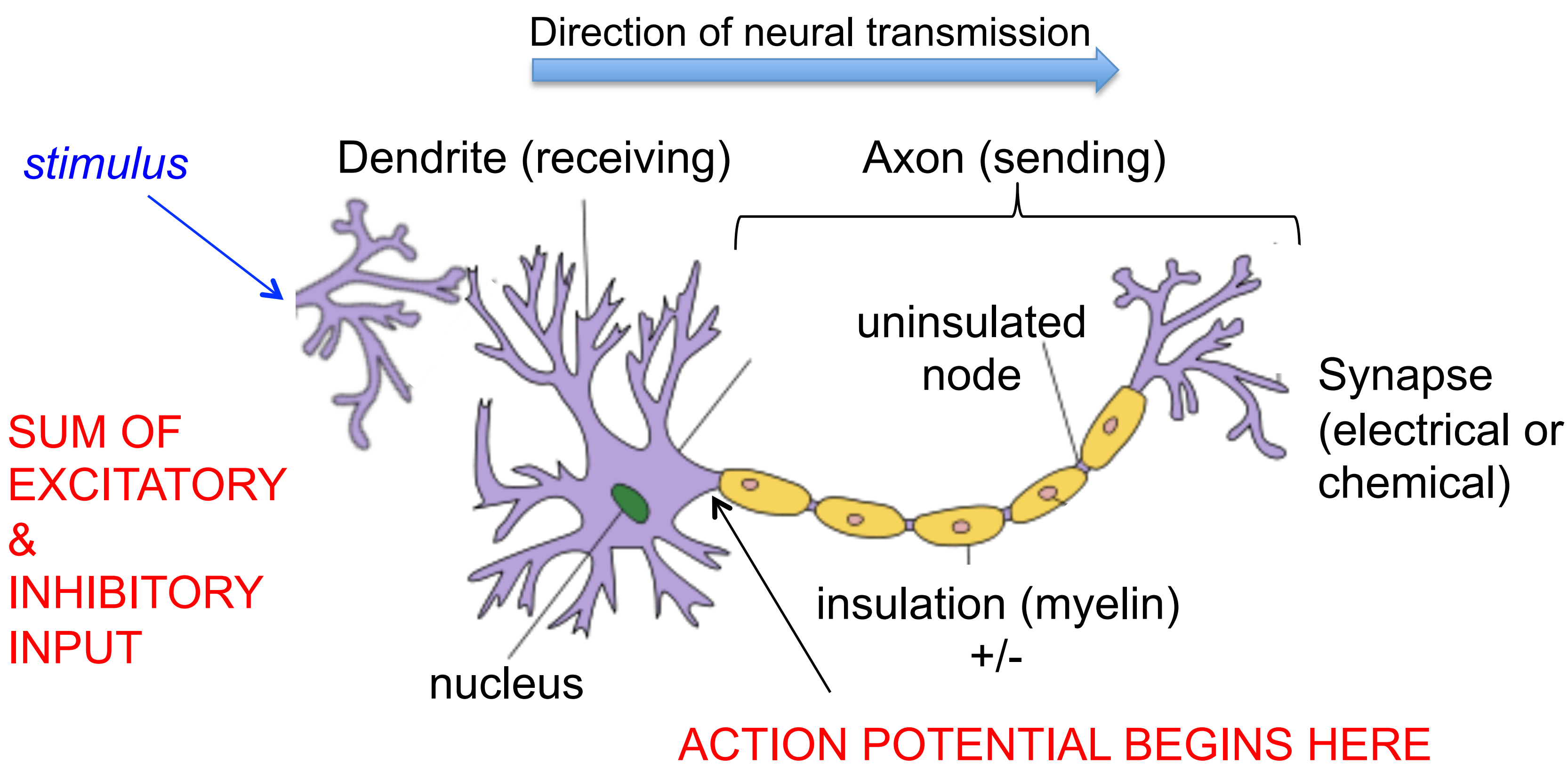
bacterial cell = -140 to -105 mV

mammalian neuron = - 60-70 mV

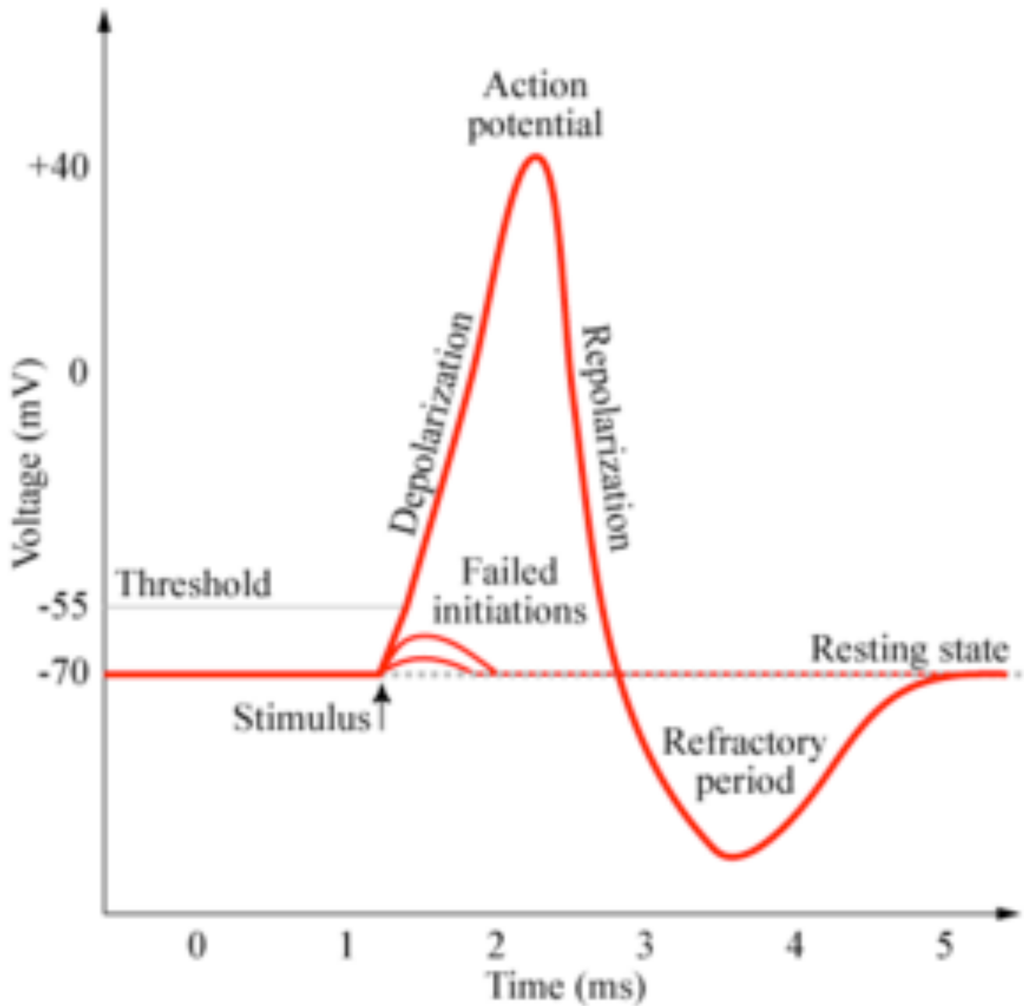
MEMBRANE POTENTIAL ACTUALLY SET BY K+, as more K+ channels open at rest

MAINTAINED BY PUMPS IN THE MEMBRANE

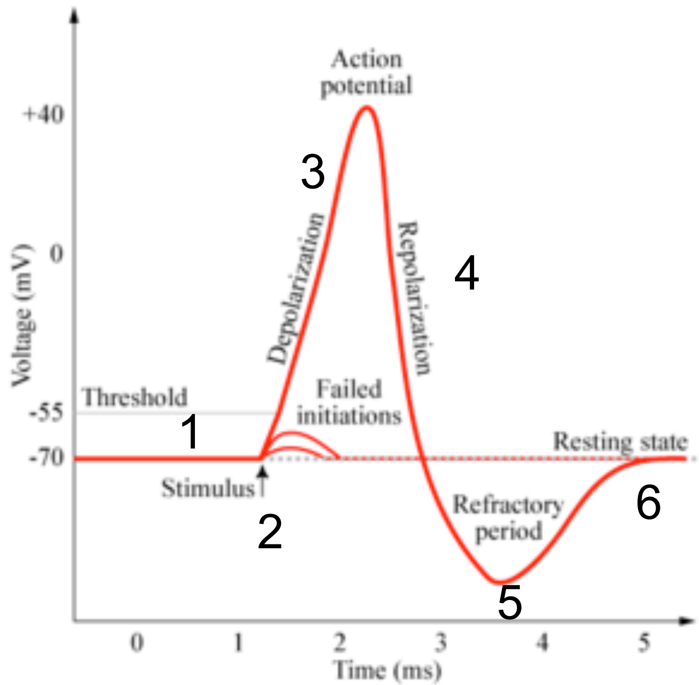
Action potential a depolarization of the membrane - nerve fires

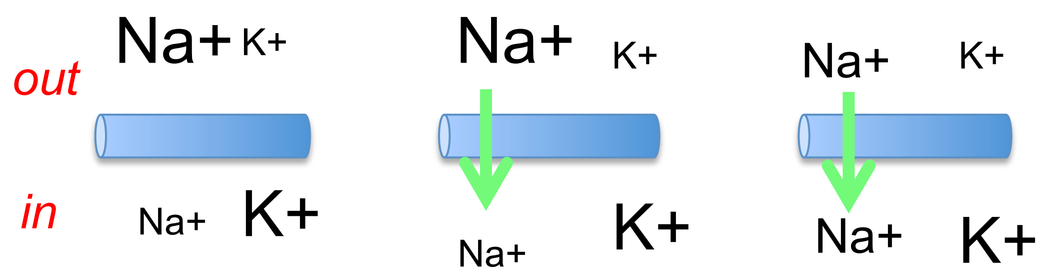


Action potential - a depolarization of the membrane

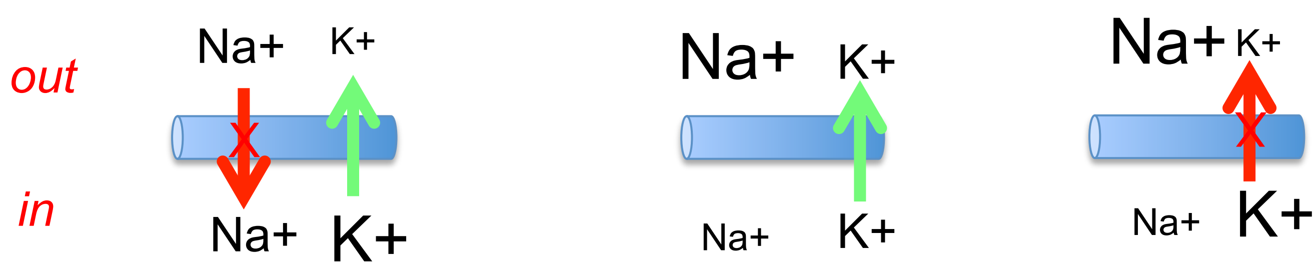


Action potential - a depolarization of the membrane



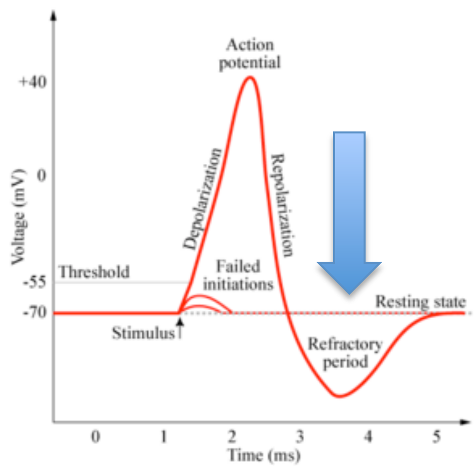


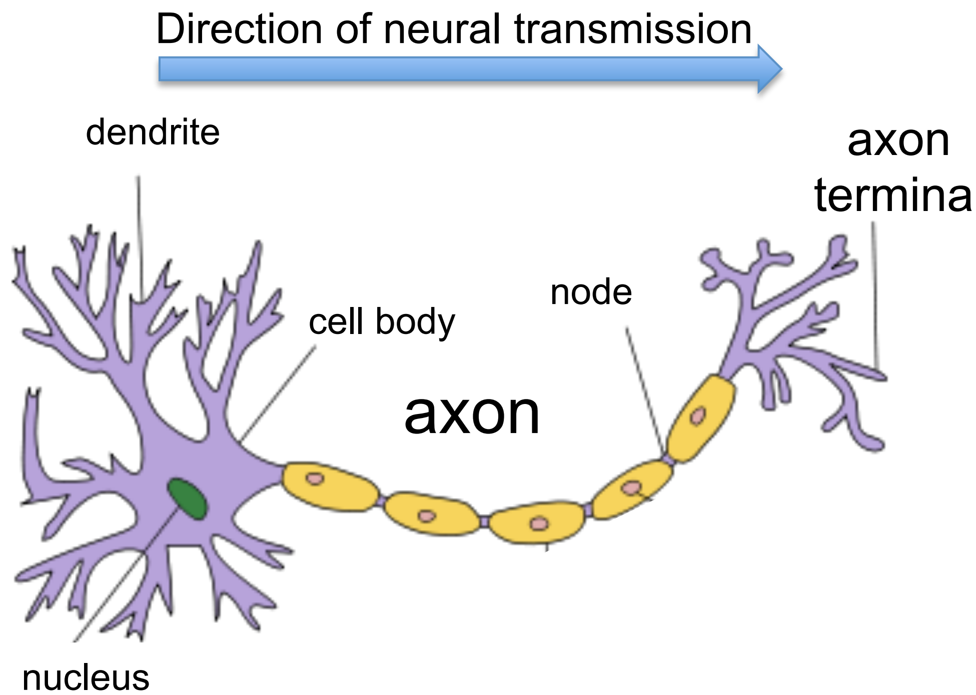
Na+ channels open



Na+ channels close/K+ channels open

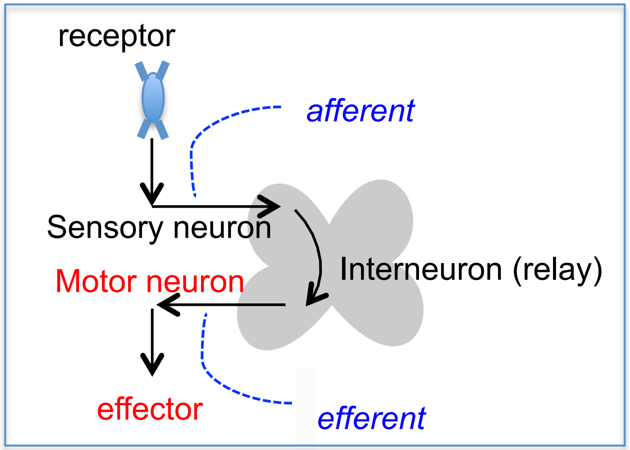
Potassium channels close

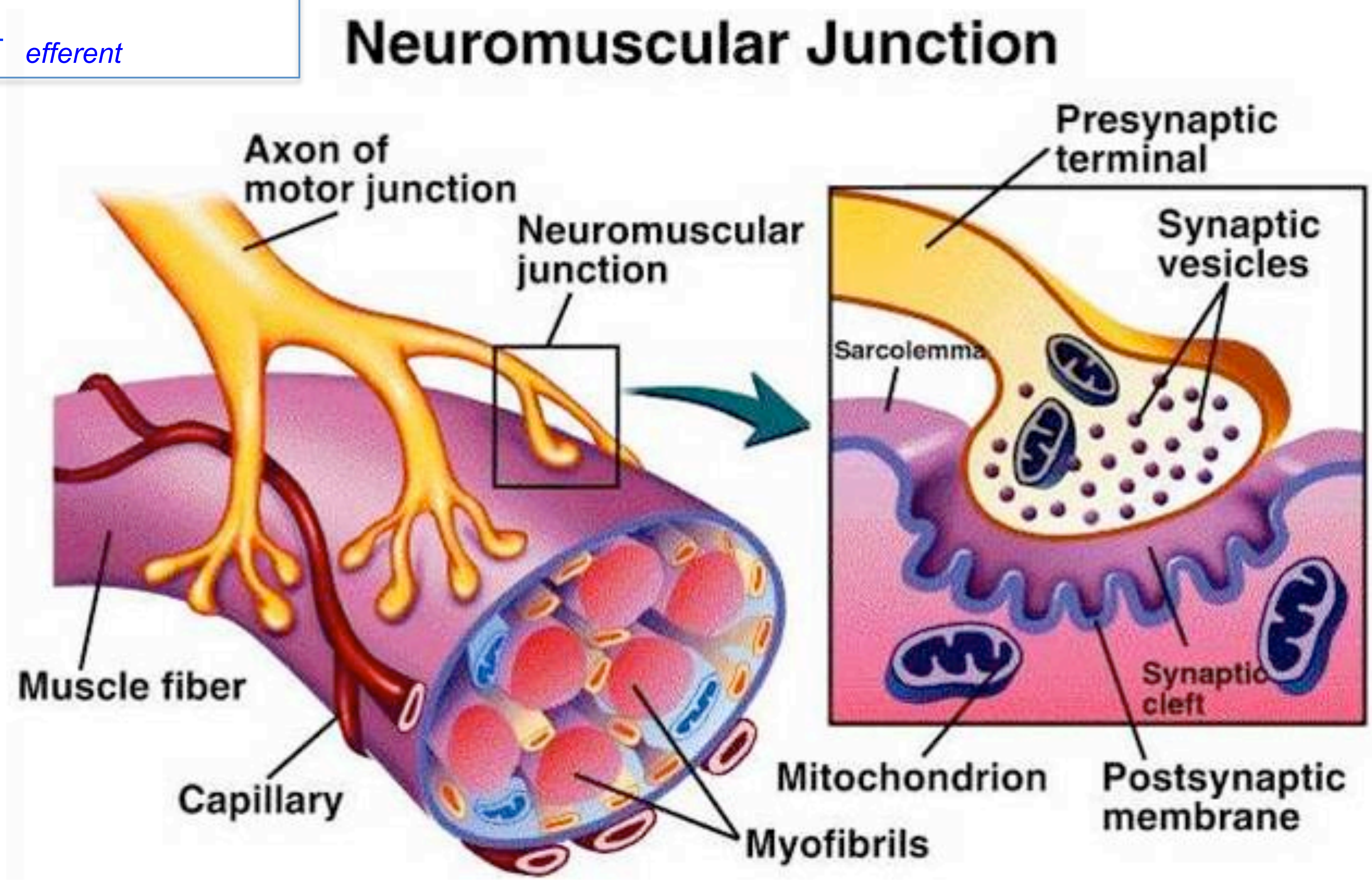




Axon terminal of motor neuron interfaces with effectors:

e.g.,
muscles
chromatophores


receptor
afferent
Sensory neuron
Motor neuron
Interneuron (relay)
effector
efferent


Neuromuscular Junction
Axon of
motor junction
Neuromuscular
junction
Presynaptic
terminal
Synaptic
vesicles
Sarcolemma
Muscle fiber
Capillary
Myofibrils
Mitochondrion
Synaptic
cleft
Postsynaptic
membrane