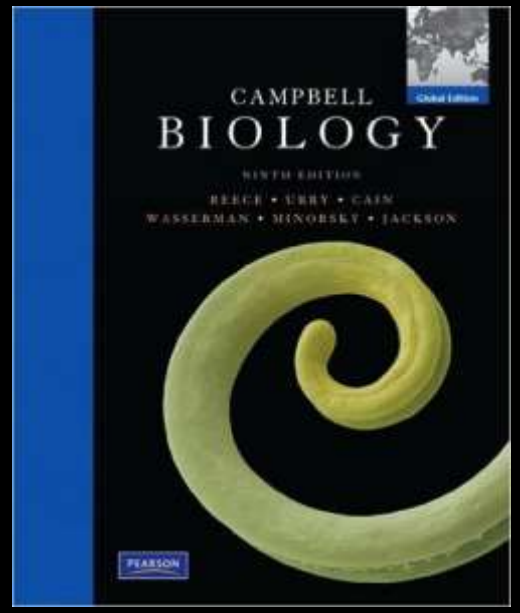
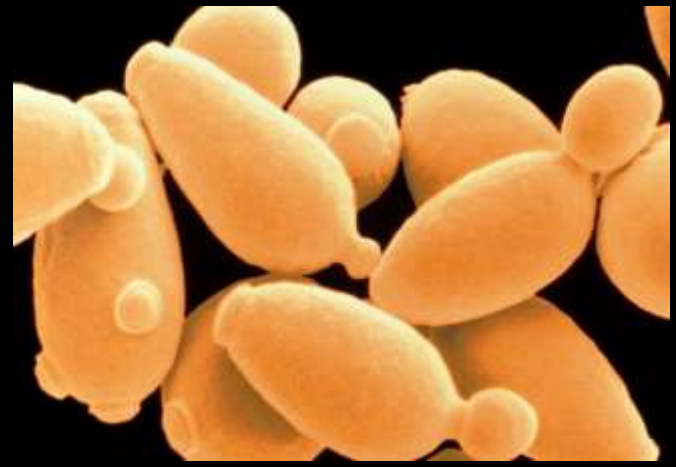
Class 7: Cells communicate with each other

- Example of cell communication: Quorum sensing
- What happens inside the cell?
- Signal transduction – an overview
- Illustrative examples
  - Reception
  - Transduction
  - Response



Unmanned / autonomous units built by IIT Bombay students (except one!)



Intelligent Ground Vehicles

These units may need to communicate with each other

Communication and signal processing

Shorter distance
Longer distance
Amplifiers

Satellites communicate with Earth

Chandrayaan 2 (photo courtesy: ISRO)

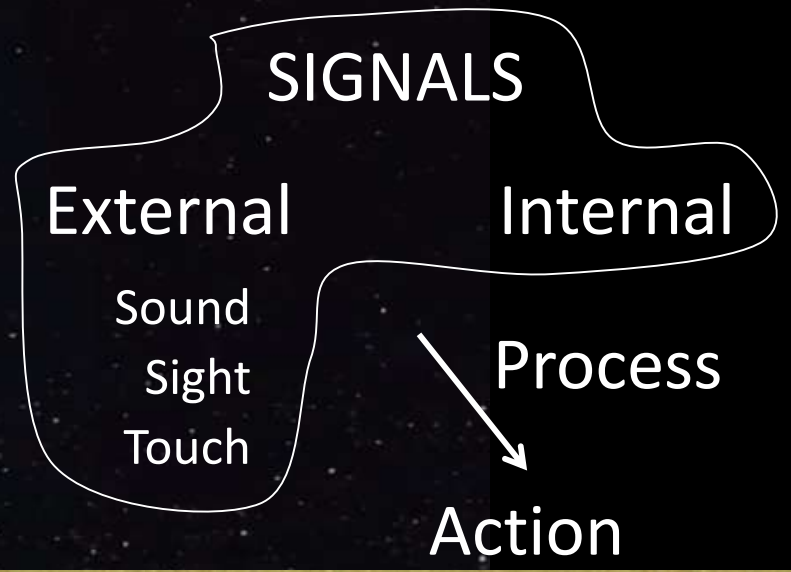


Figure 9.1
Biology. A global approach

Signaling in biological systems

Dictyostelium discoideum (Dicty, for short)

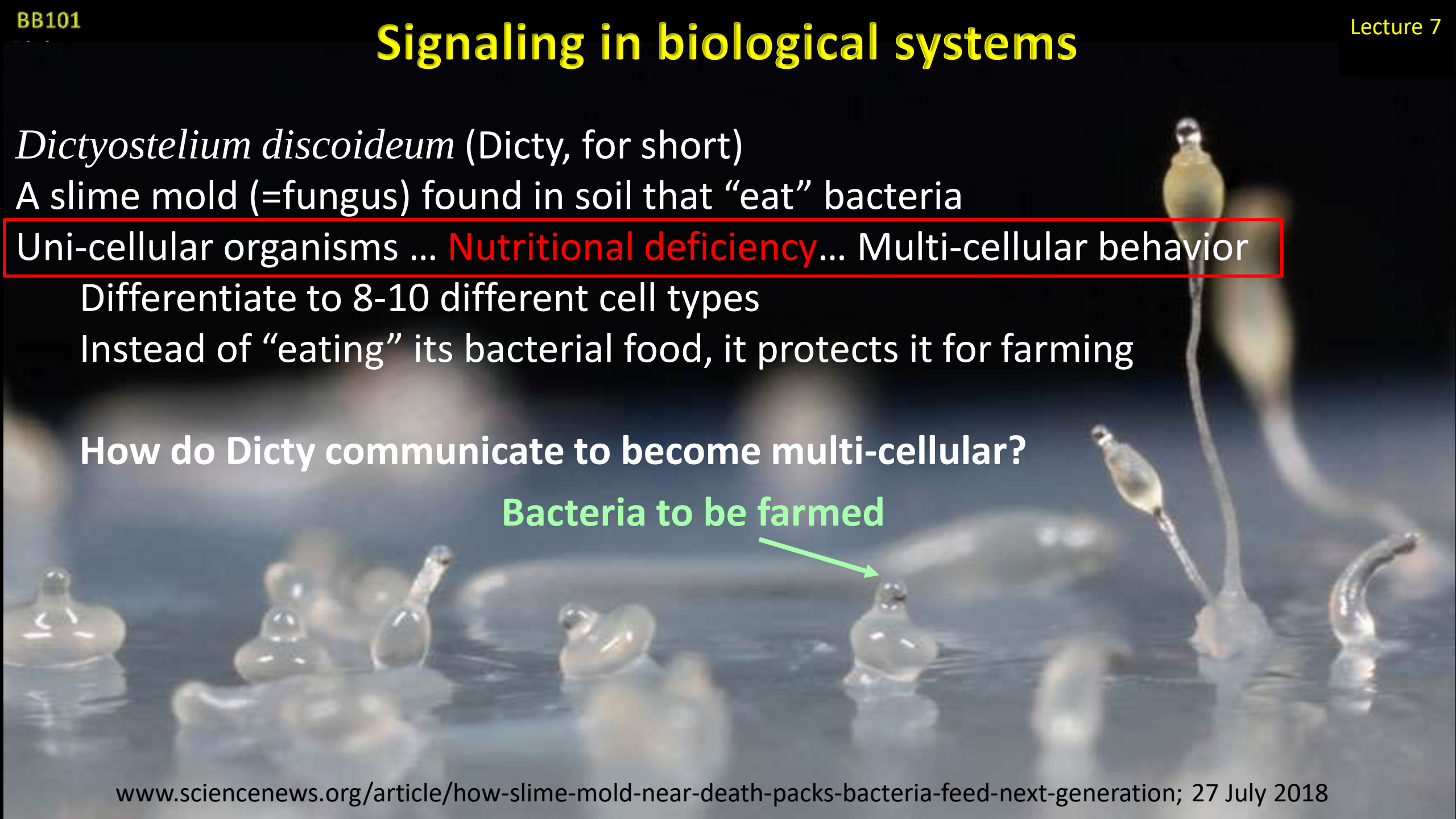
A slime mold (=fungus) found in soil that "eat" bacteria

Uni-cellular organisms … Nutritional deficiency… Multi-cellular behavior

- Differentiate to 8-10 different cell types
- Instead of "eating" its bacterial food, it protects it for farming

How do Dicty communicate to become multi-cellular?

Bacteria to be farmed



www.sciencenews.org/article/how-slime-mold-near-death-packs-bacteria-feed-next-generation; 27 July 2018

Some seawater bacteria emit light

- Plating seawater samples revealed the presence of bioluminescent bacteria

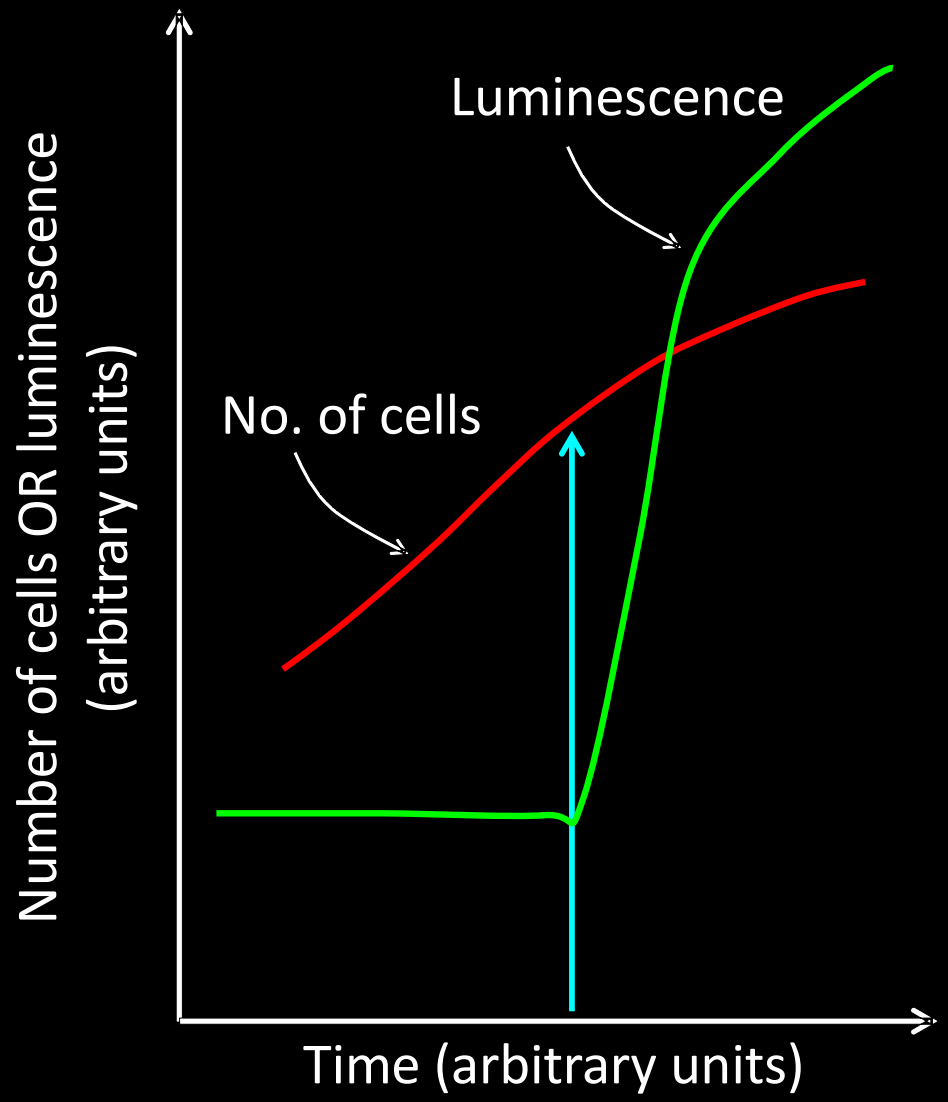
  Luminescence: emission of light by a substance that is not heated
- Abundance in sea water: <100 cells per mL
- Maximum light emission: 10^3 to 10^4 photons/sec/cell

- What does this have to do with cell communication?

https://jb.asm.org/content/181/9/2667.long

Luminescence vs. growth: lag, sudden increase

1970s



When the number of cells hits a certain threshold, then luminescence suddenly increases

https://jb.asm.org/content/181/9/2667.long

Quorum (ko-rum)

The minimum number of members of a society/group that must be present in a meeting to make the proceedings of that meeting valid

Bacteria are capable of quorum sensing!
Regulate gene expression depending upon cell-population density

1990s

How do the bacteria “know” the population density of their surroundings?

Luminescence and bioluminescence

Quorum-sensing is most extensively studied in the bacteria *Vibrio fischeri*

Luminescence: emission of light by a substance that is not heated

Lux: unit of luminescence

Genes involved in bioluminescence are named as lux genes in *V. fischeri*

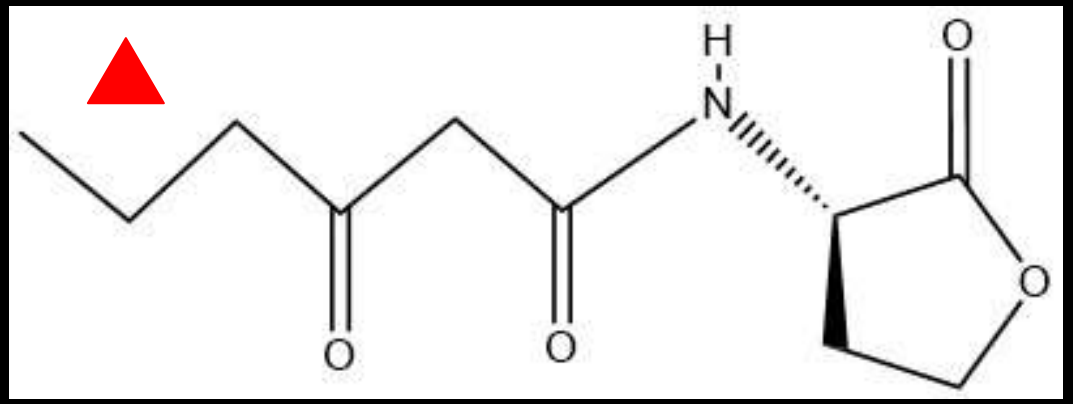
Gene names: italics + all letters in lower case

Encoded proteins: normal font + first letter in upper case

Quorum sensing in *Vibrio fischeri*

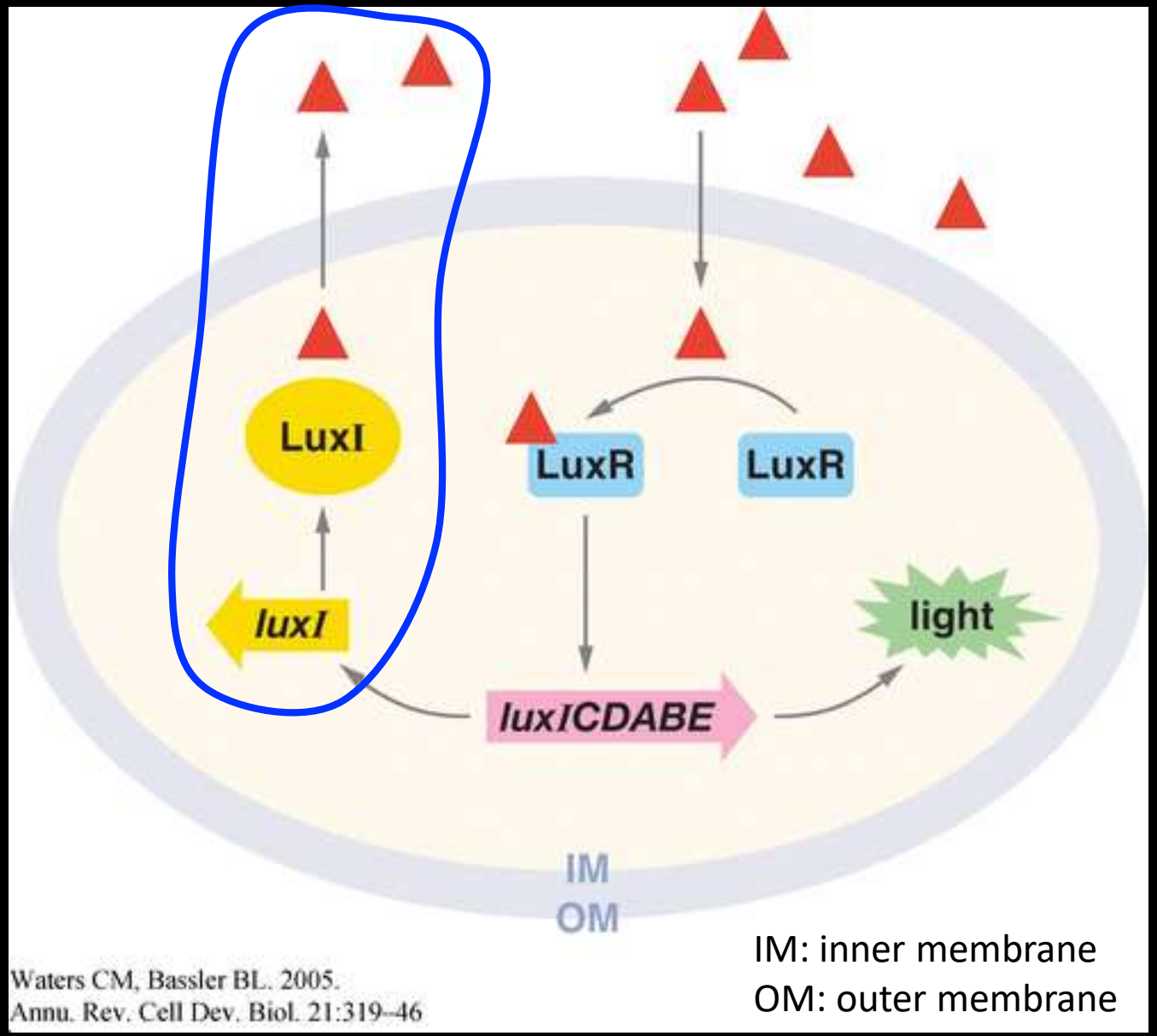
luxI: basal level of expression

LuxI: is an enzyme responsible for the synthesis of "auto-inducer"



3-Oxo hexanoyl homoserine lactone

Auto-inducer (AI) diffuses out of the cell



Waters CM, Bassler BL. 2005.
Annu. Rev. Cell Dev. Biol. 21:319–46

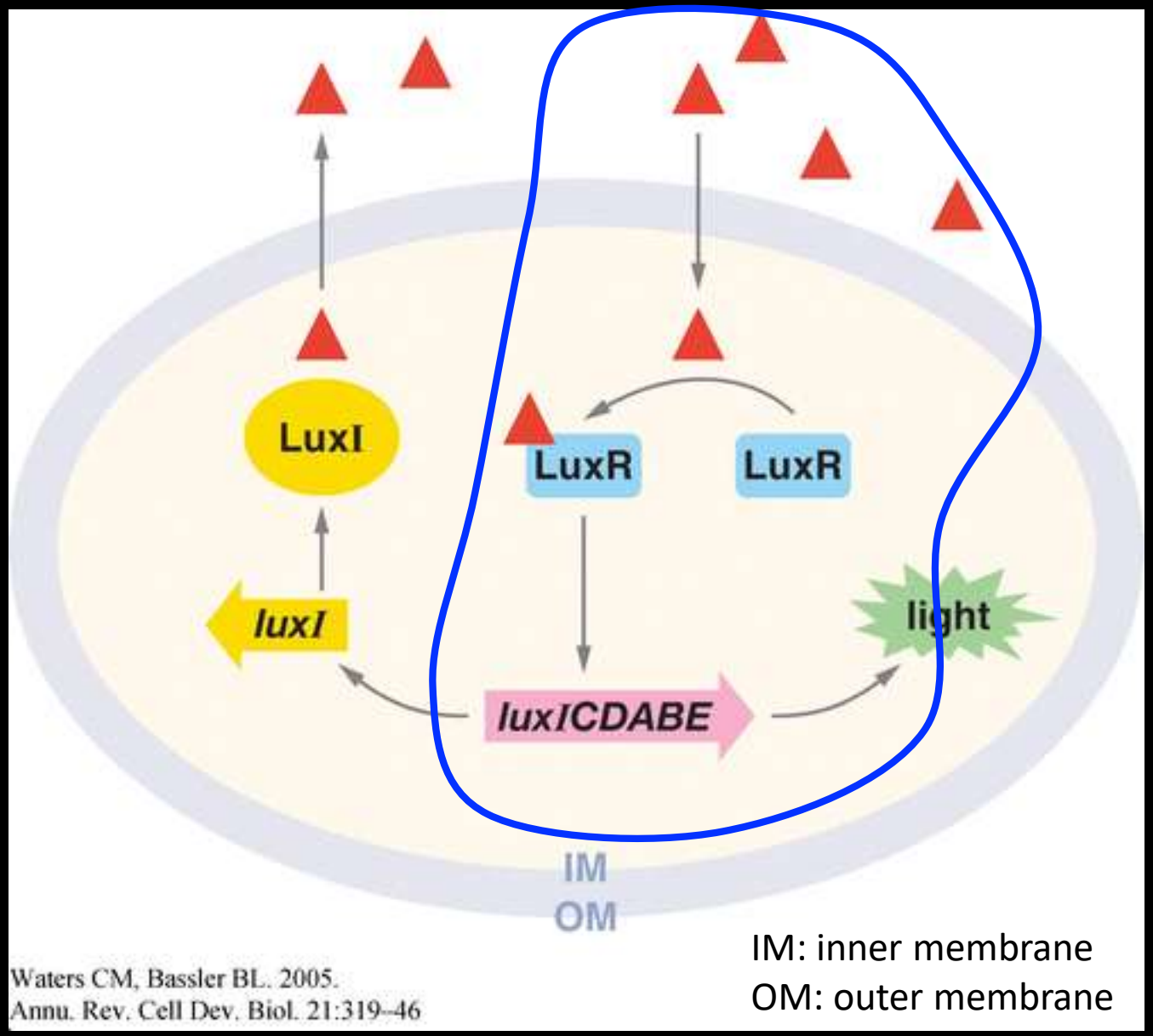
IM: inner membrane
OM: outer membrane

Quorum sensing in *Vibrio fischeri*

If quorum is met i.e., the number of bacteria reaches a certain critical level, then $[AI]_{extracellular}$ reaches a critical level

AI diffuses back into the cell and binds to LuxR, its cytosolic receptor

The LuxR-AI complex activates the transcription of the *lux* operon (*luxI* and *luxC* + *luxD* + *luxA* + *luxB* + *luxE*) resulting in **LIGHT!**



Waters CM, Bassler BL. 2005.
Annu. Rev. Cell Dev. Biol. 21:319–46

IM: inner membrane
OM: outer membrane

luxA, *luxB*: α, β subunits of luciferase
luxC, *luxD*, *luxE*: synthesis + recycling of luciferase substrate

Luminescence in *Vibrio fisheri*: purpose?

Luminescence is an energy-consuming process

- For the generation of light
- For the biosynthesis of the relevant proteins / associated molecules

Inference:

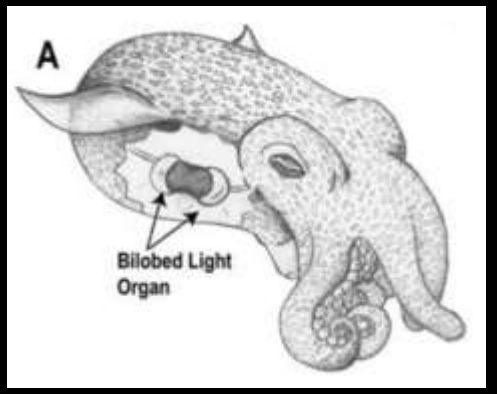
- Luminescence ought to be beneficial
- Why retain this phenotype if there is no advantage (growth / survival)?

Absence of luminescence in seawater suggests that the luminescent phenotype is produced under some other condition(s)

What are these other conditions?

J. Molec. Microbiol. Biotechnol. (1999) 1:5

Squid – bacteria (*Vibrio fischeri*) symbiosis



- Hawaiian bobtailed squid
- Luminescence in the light organ by symbiont *V. fischeri*
- Matches light intensity of the light organ to that of background light (moonlight / starlight), helps the squid to “cloak” and catch its prey
- Bioluminescence also controls circadian rhythms of the squid

What do the bacteria get out of this symbiosis? Nutrients from the light organ.

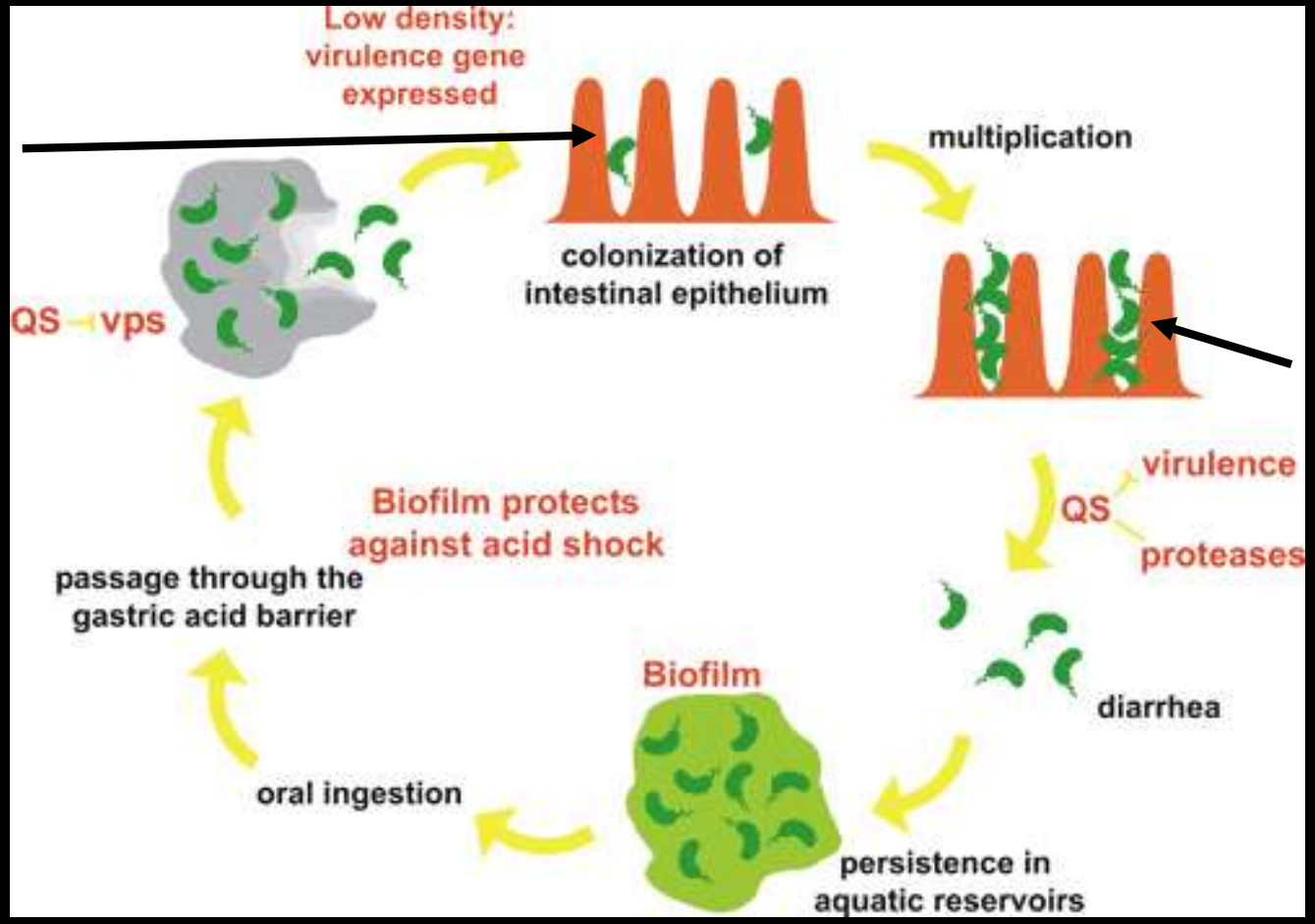
http://nishsymbiosislab.com/wp-content/uploads/2017/07/2-2004-JonesNish.pdf https://multimediaquest.com/watch/L71RyeRA2YL

Any other quorum-dependent phenotypes?

Vibrio cholerae: causes diarrhea

Quorum Sensing (QS) at different parts of the pathogenic cycle

Low density of bacteria:
Virulence genes expressed



High density of bacteria:
Protease genes expressed, leading to diarrhea so that the bacteria can escape from the human host

As cells communicate for the "common good", we can study cooperation/cheating/etc.

Once the cells get signals from outside, how do they react/respond?

- Quorum sensing
- Signal transduction – an overview
- Illustrative examples
  - Reception
  - Transduction
  - Response

IMPORTANT NOTE: The rest of the class will be about processes that occur in eukaryotes

Signal transduction

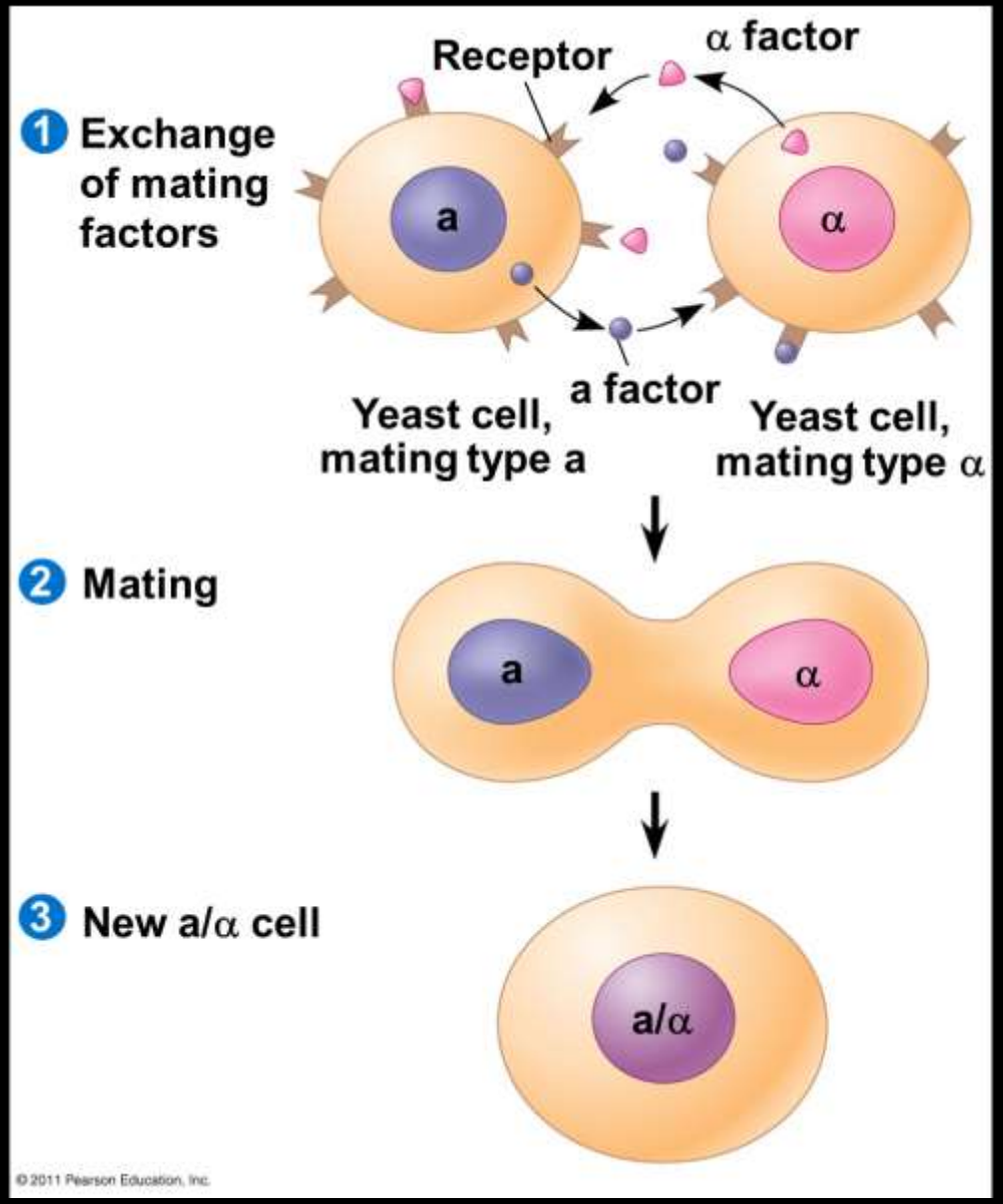
transduce (*verb*): to convert energy or message into another form
(www.merriam-webster.com)

A chemical outside a cell…
triggers a response inside the cell

Quorum sensing…
illustrates the concept of cell-cell communication and intra-cellular signal transduction

Communication among microbes…
insight into cell communication in multicellular organisms

Eukaryotic cells also communicate



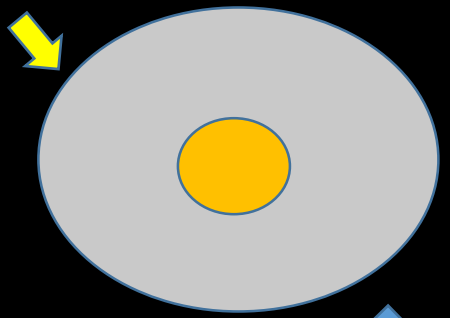
Two different types of yeast cells can signal to each other when they decide to mate

Signal transduction: three stages

- The cell is compartmentalized
- External signals need to reach the nucleus

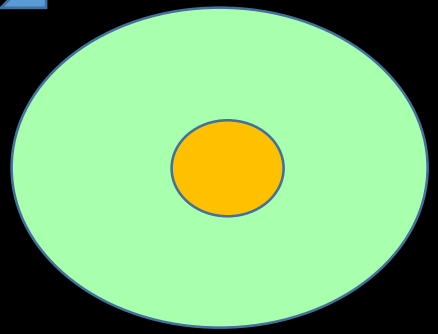
Reception

A knock on the door



Transduction

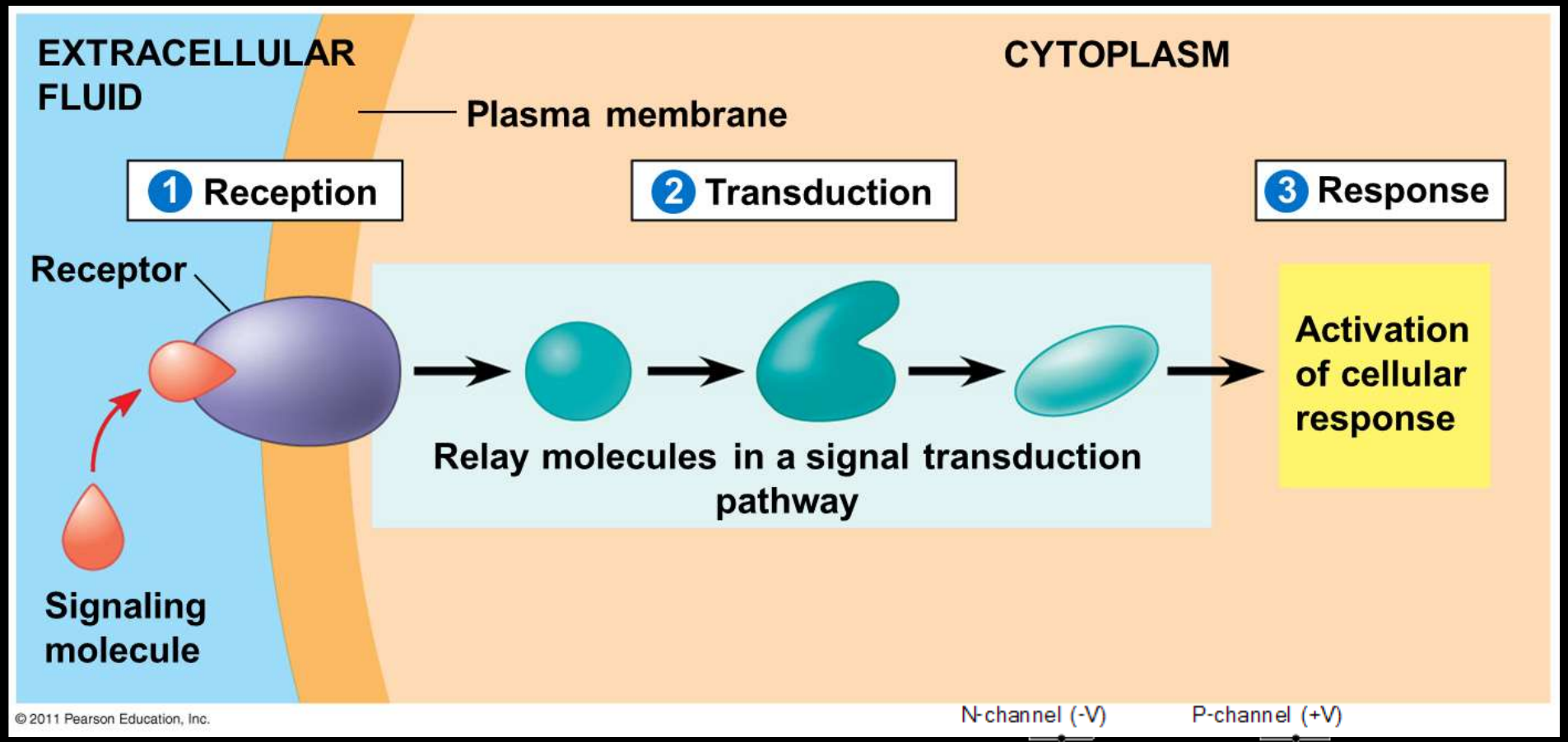
message received at the door



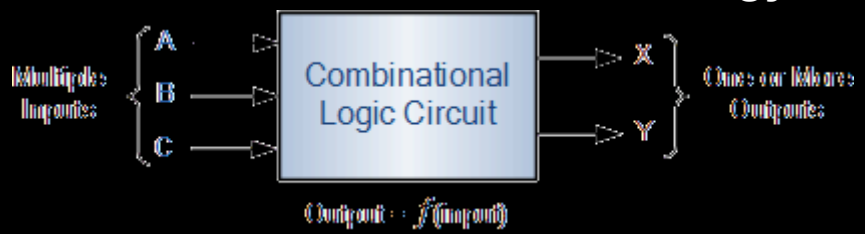
Response

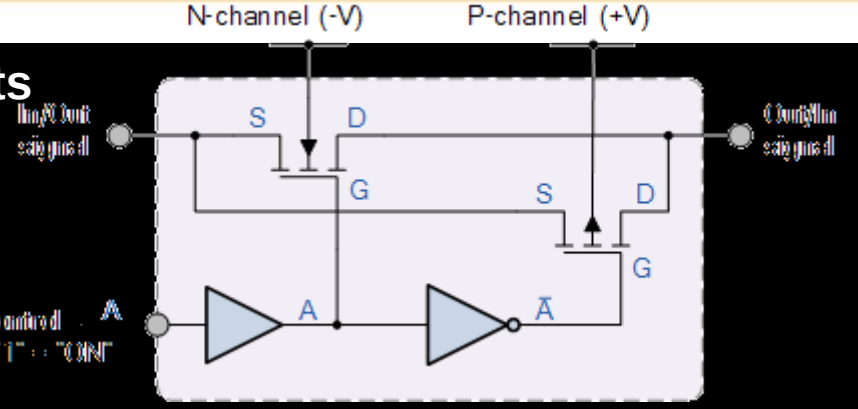
message conveyed to the inside…
and an action is triggered

In Single Cells: Three Stages of Cell Signaling



Analogy: circuits





Signal transduction: 1. Reception

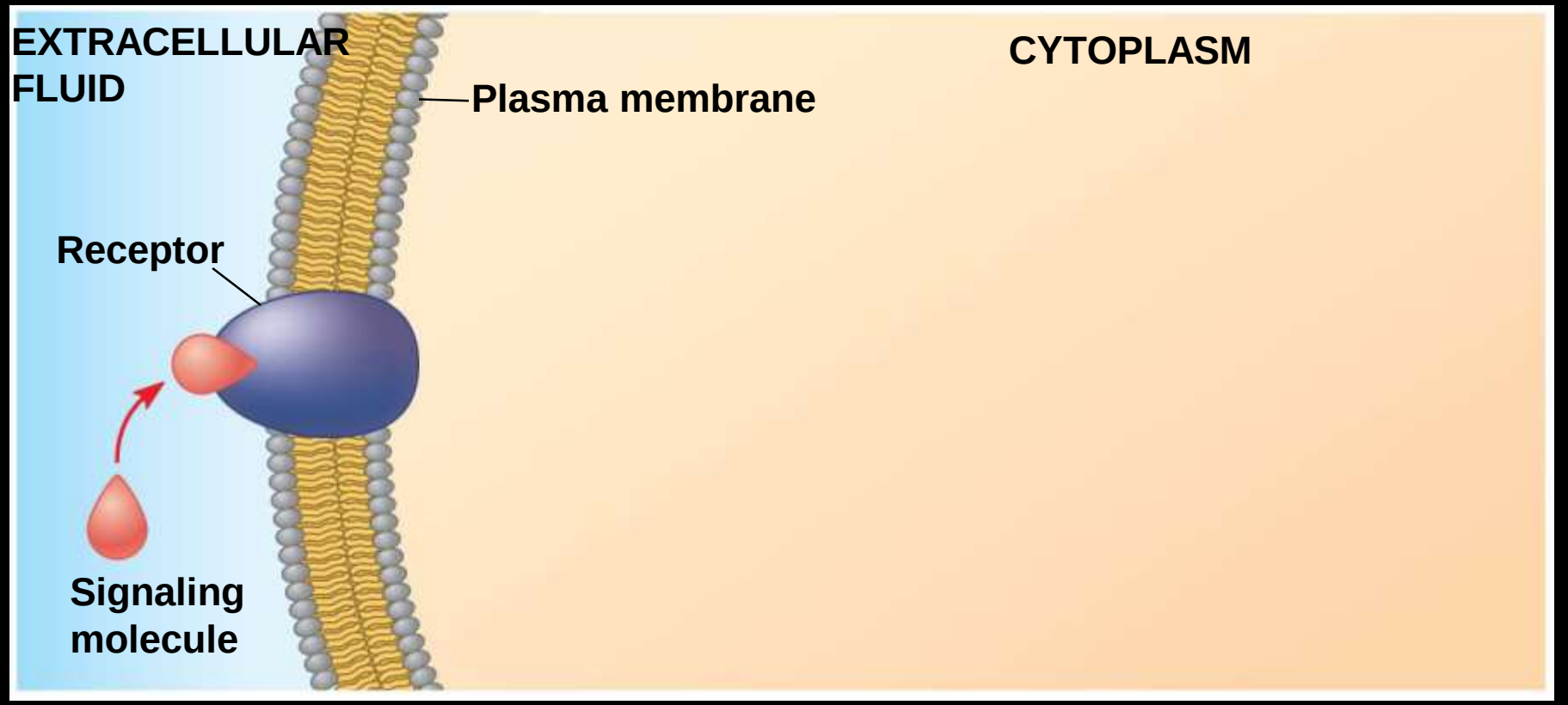


Figure 11.6

A signaling molecule binds to a cell surface receptor
Receptor is on the target cell

Signal transduction: 2. Transduction

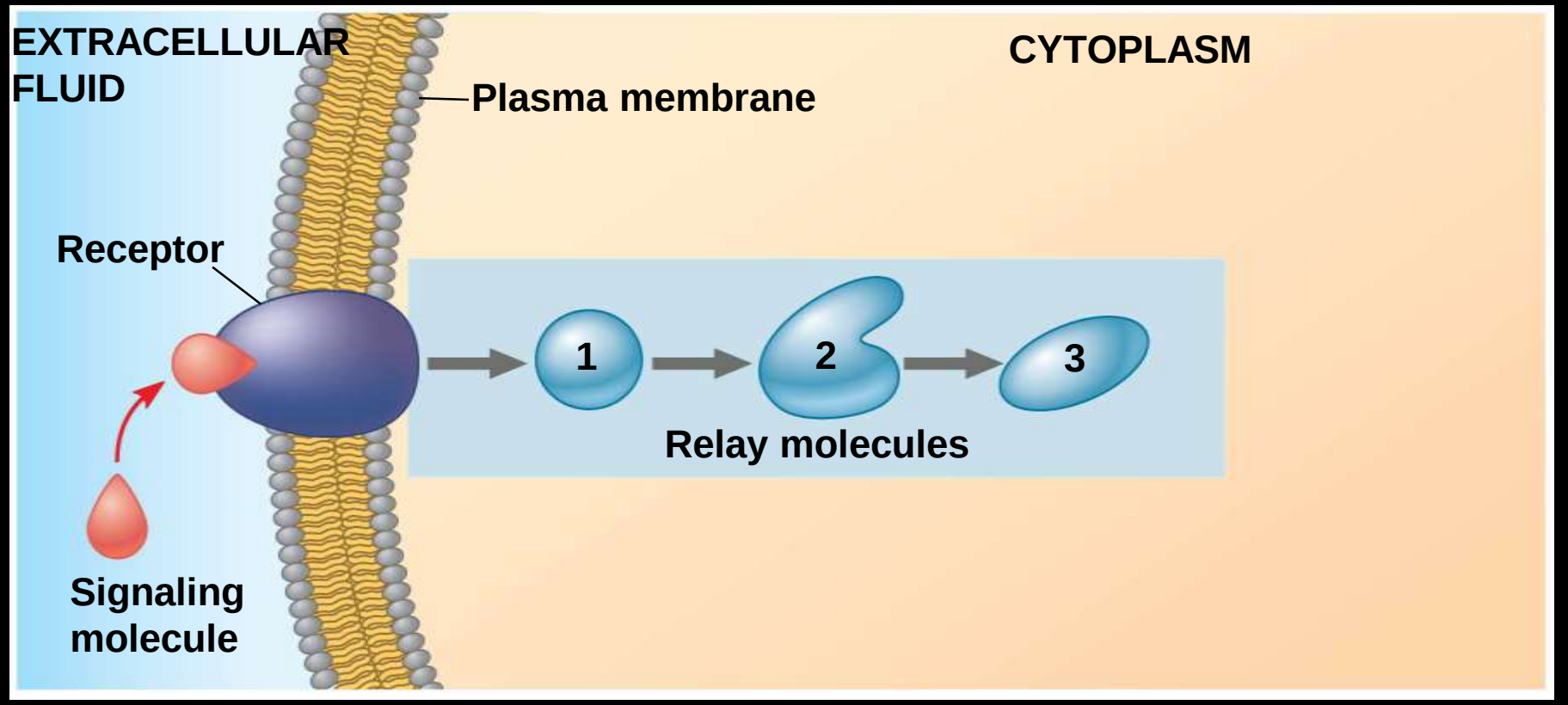


Figure 11.6

Binding leads to a change in the shape of the receptor (Note: shape change is not shown in the schematic)

Shape change leads to a cellular response

Can be in one step; often, in multiple steps and involves relay molecules

Signal transduction: 3. Response

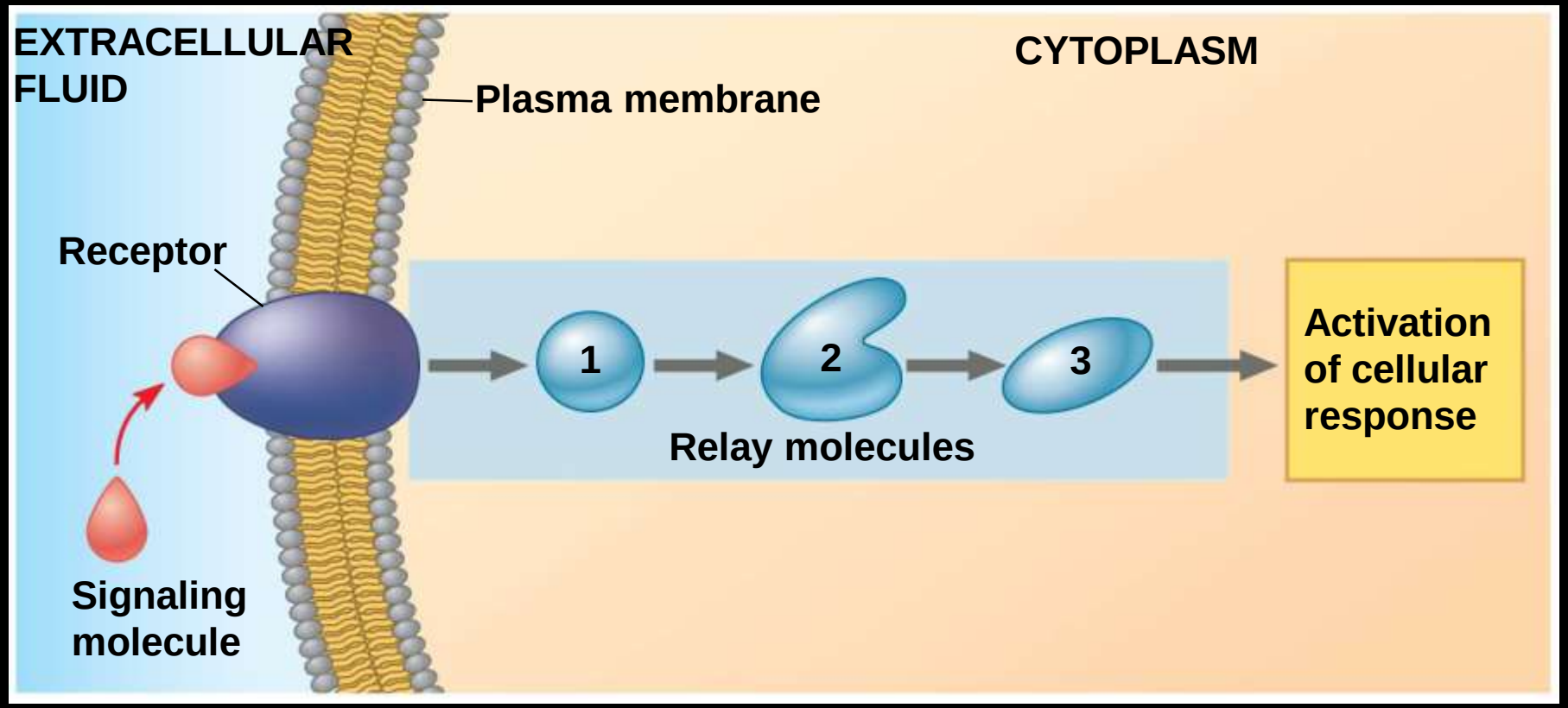


Figure 11.6

Response can be of different types:

1. Catalysis of a reaction by an enzyme
2. Rearrangement of the cytoskeleton
3. Activation of specific genes (gene expression)
4. Many others….

Examples of signal transduction

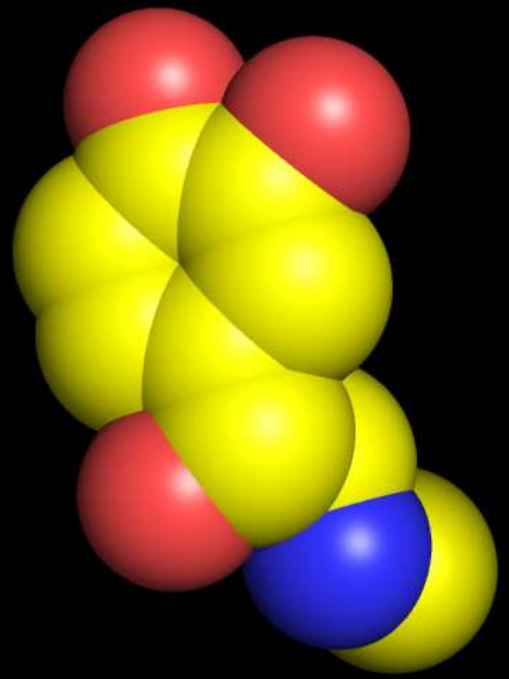
- Quorum sensing
- Signal transduction – an overview
- Illustrative examples
  - Reception
  - Transduction
  - Response

How does adrenaline mobilize energy?

Earl W. Sutherland
Nobel prize (1971)

www.nasonline.org

Figure 9.1. Biology. A global approach

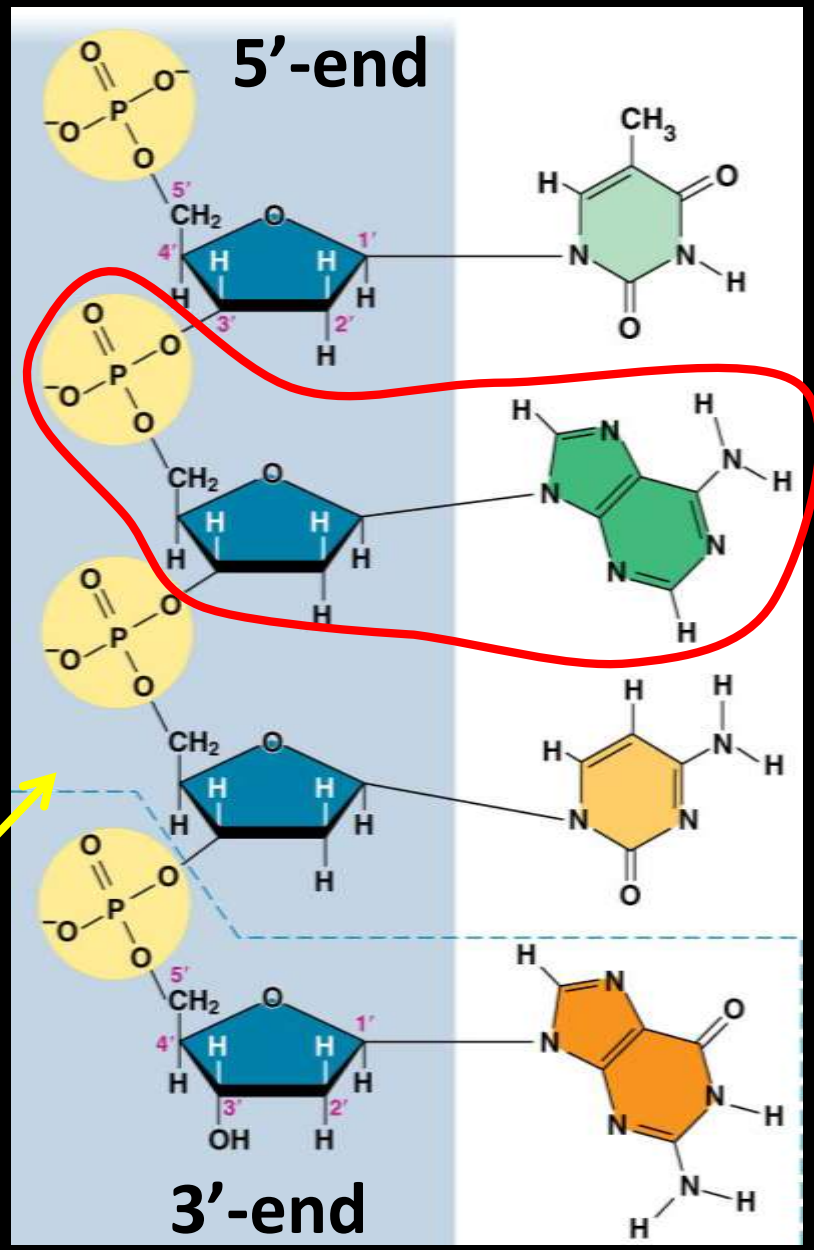


Adrenaline

4LDO.pdb

Nucleotides in DNA

Figure 16.5



Thymine (T)

Adenine (A)

Cytosine (C)

Guanine (G)

Nitrogenous bases

Sugar phosphate backbone

A nucleotide

Dual role of nucleotides

Nucleotides have other roles also

ATP is an energy currency

GTP, CTP, TTP, UTP (from uracil) are also energy currencies, but far less widely used than ATP

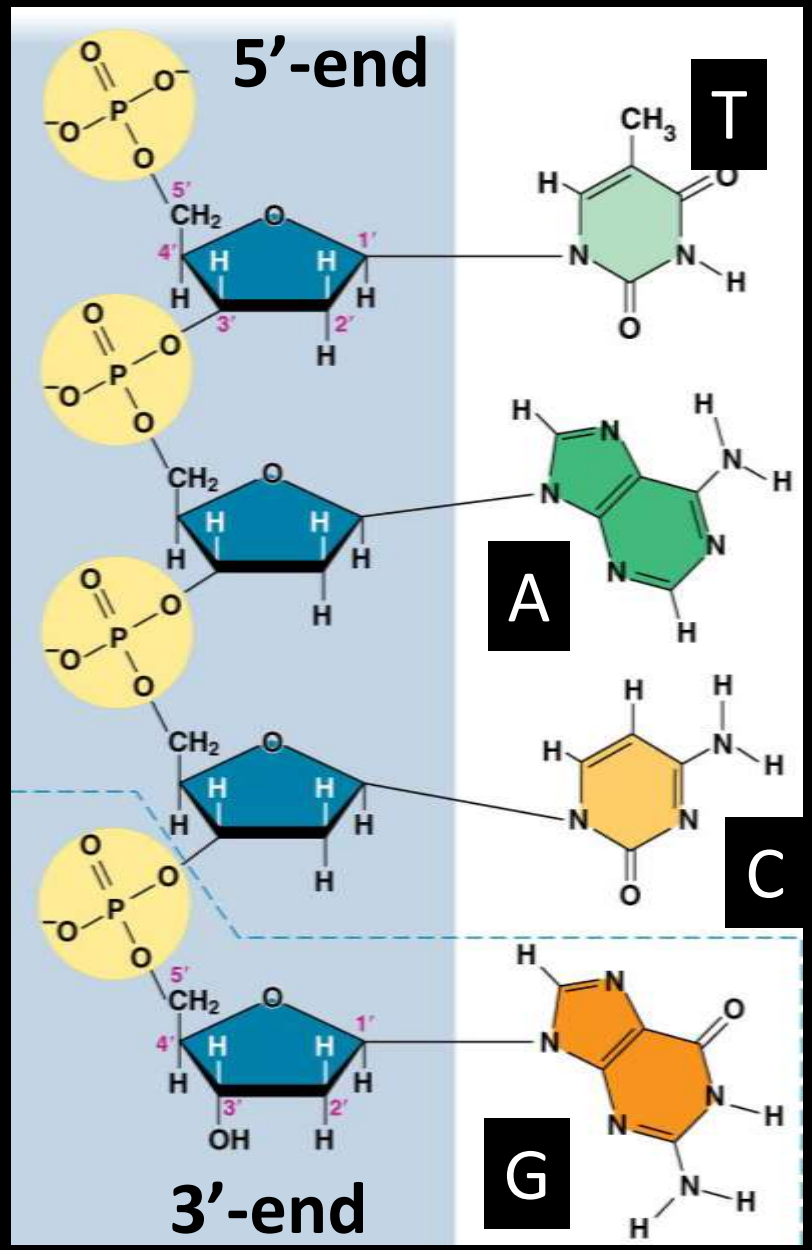


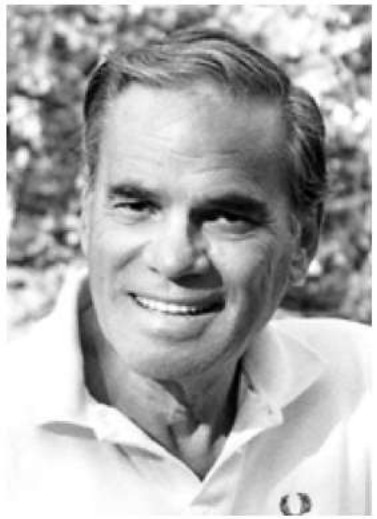
Figure 16.5

GTP plays an important role in signal transduction

G proteins

The Nobel Prize in Physiology or Medicine 1994

Alfred G. Gilman
Prize share: 1/2



Martin Rodbell
Prize share: 1/2

The Nobel Prize in Physiology or Medicine 1994 was awarded jointly to Alfred G. Gilman and Martin Rodbell *"for their discovery of G-proteins and the role of these proteins in signal transduction in cells"*

G protein-coupled receptors (GPCRs)

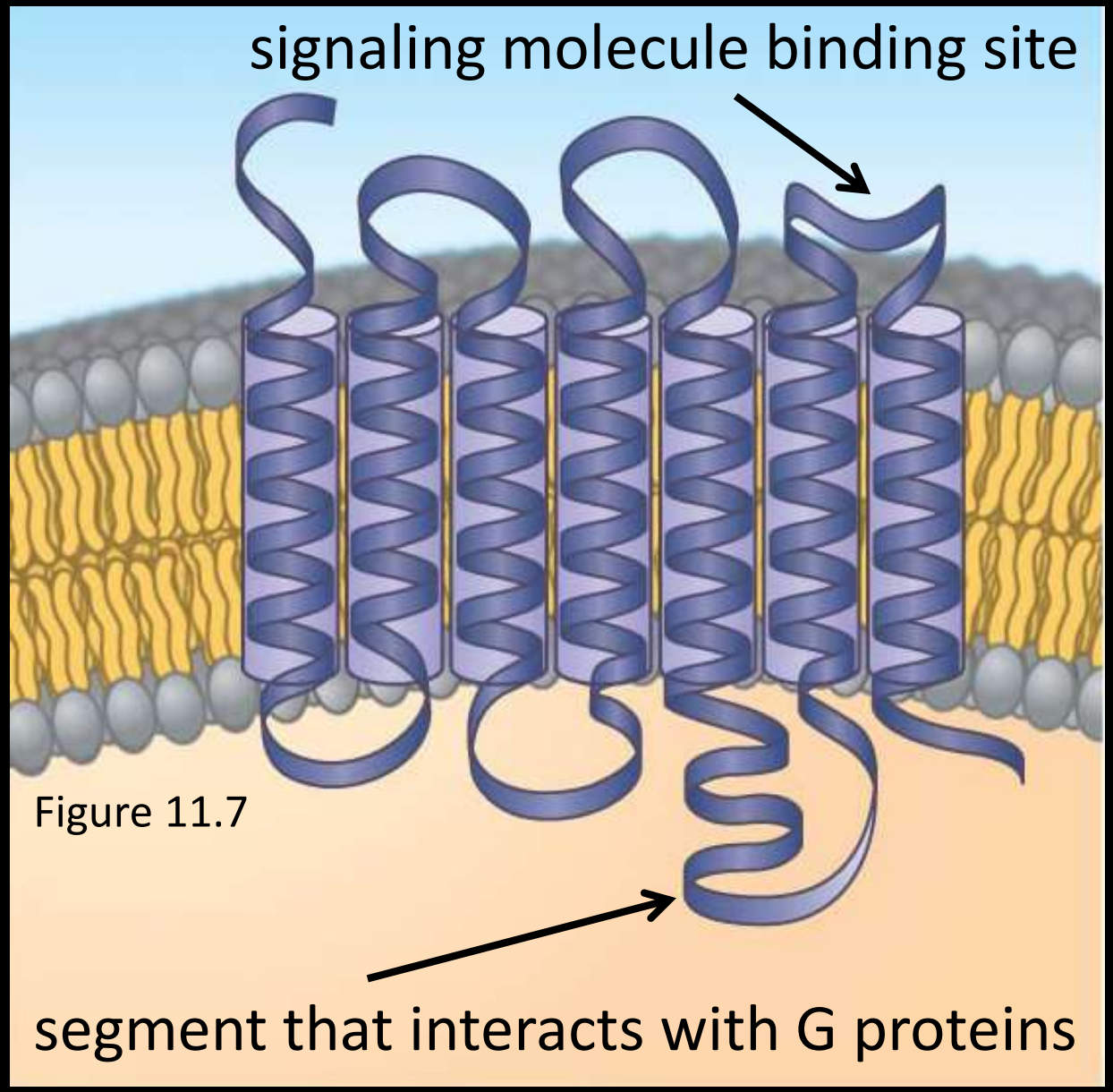
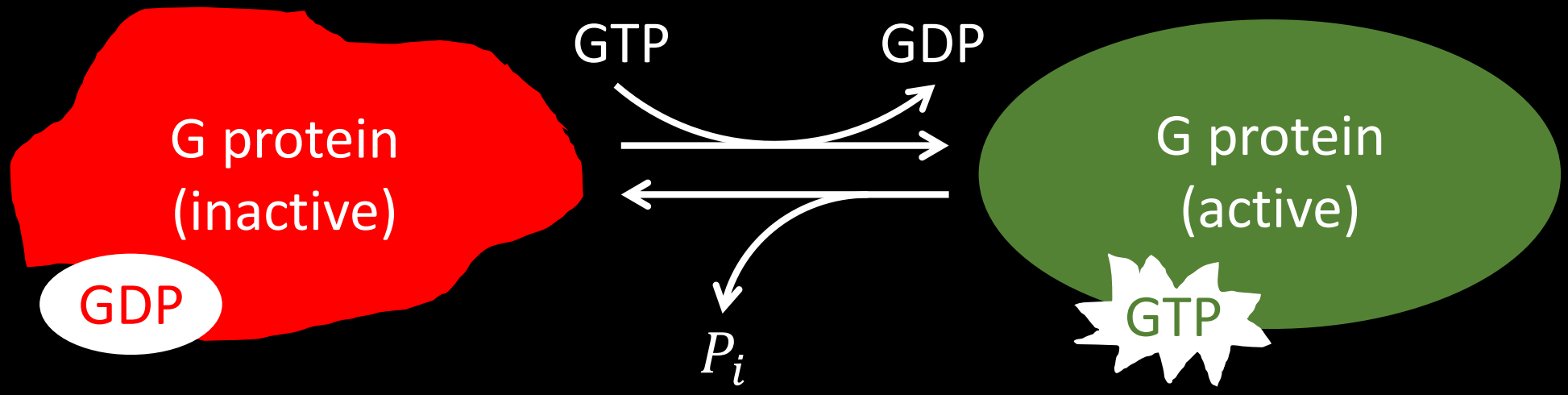


Figure 11.7

- Extremely widespread
- Involved in a variety of processes e.g., embryonic development, vision, taste, smell, …
- Involved in several human diseases e.g., cholera, pertussis, botulism
- ~60% of all medicines used today target GPCRs
- Share a common architecture seven transmembrane receptors

G proteins (GTP/GDP binding proteins)

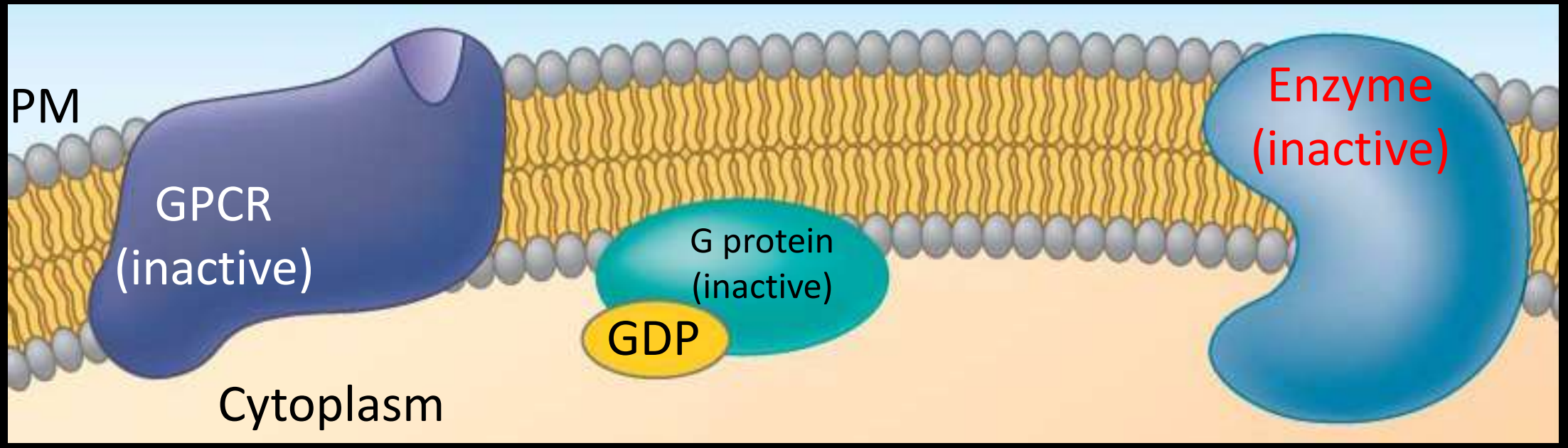
- G proteins are a large family of proteins found ubiquitously
- They act as molecular switches
- Exchange GTP/GDP as part of signaling events



Energy is spent in conversion from active to inactive state

Change in shape or conformation

How GPCRs receive and transduce signal



GPCR is in an inactive conformation (since the ligand binding site is empty)
G protein is also inactive (since it is bound to GDP)
Enzyme is also inactive (since it is NOT bound by G protein)

Figure 11.7

PM: plasma membrane

GPCRs are vectoral proteins:
Ligand binding site of GPCR is on the outside
G protein binding site of GPCR is on the inside

How GPCRs receive and transduce signal

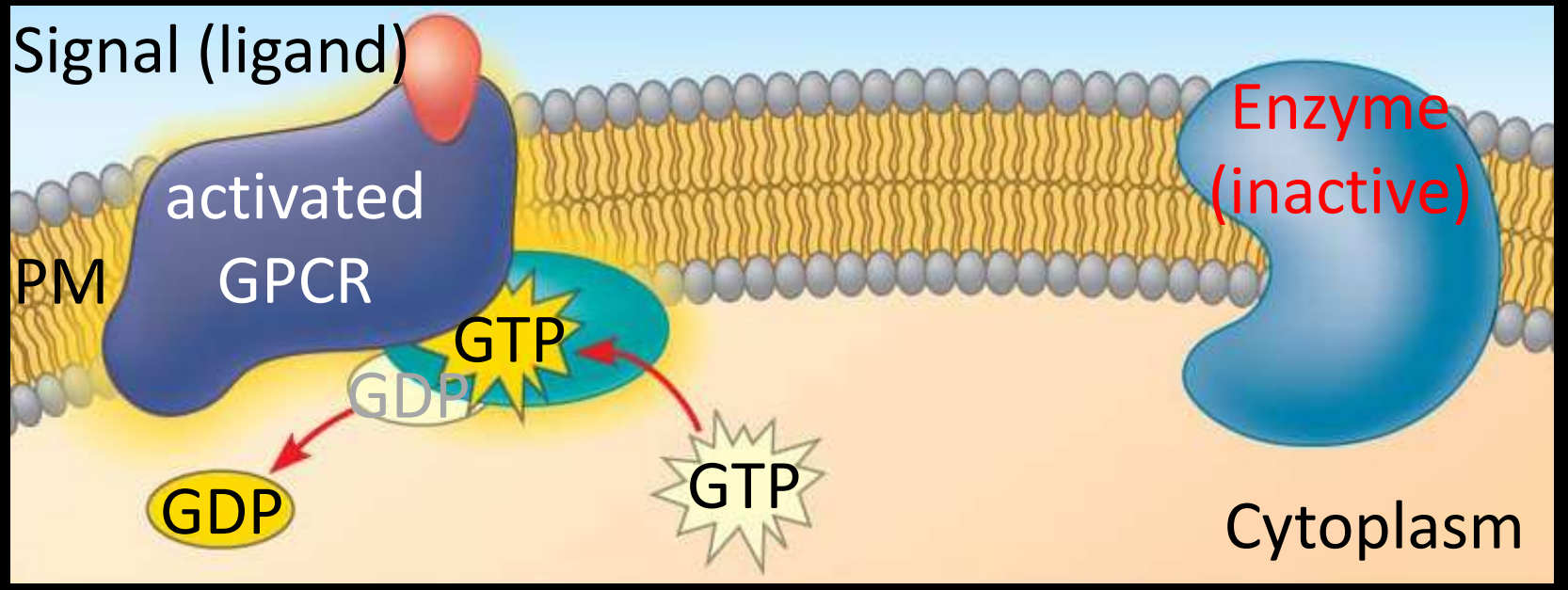


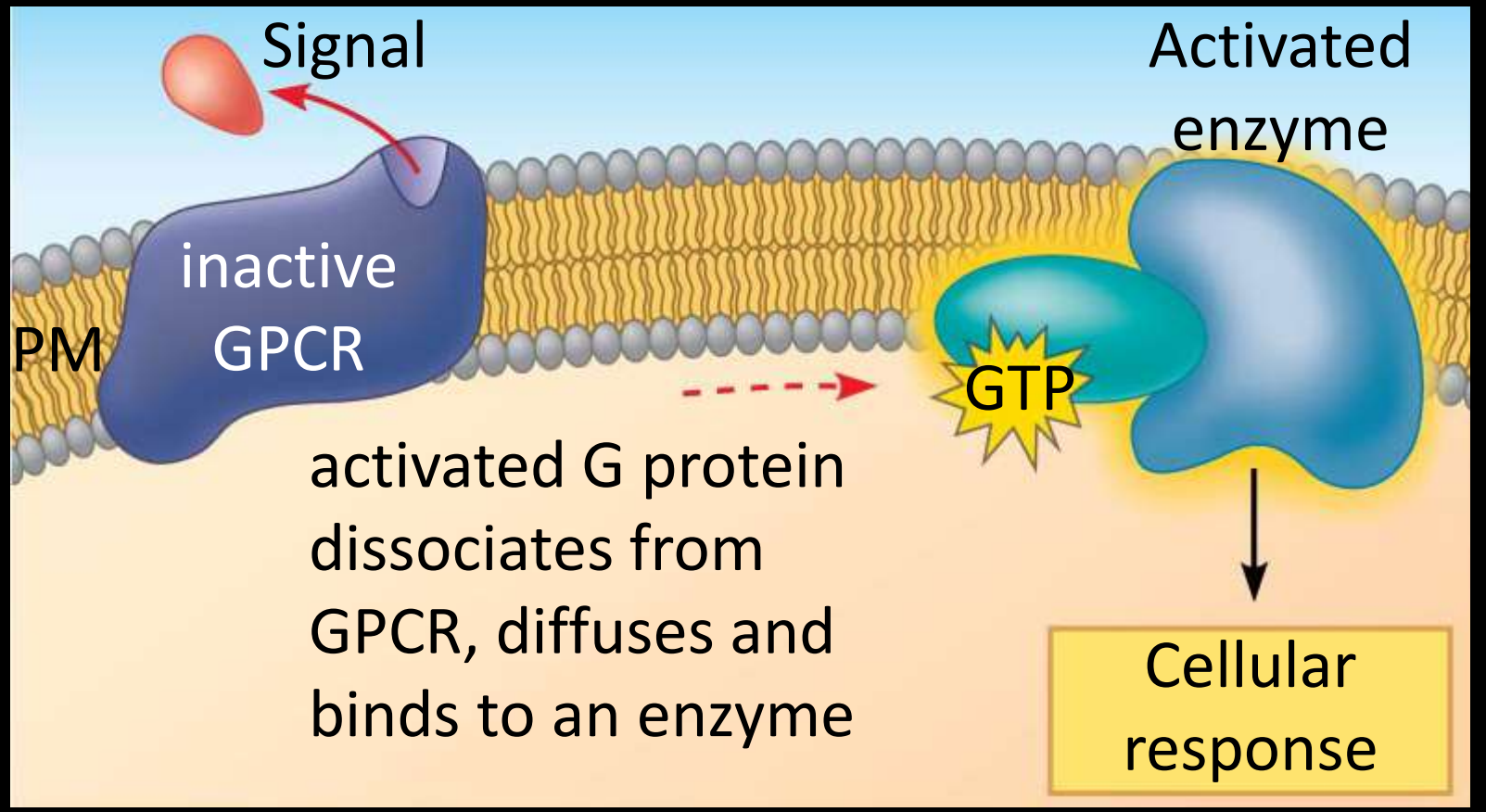
Figure 11.7

1. Signaling molecule (ligand) binds to GPCR on the outside
2. Binding induces change of shape (conformation)
3. Conformation change leads to binding of G-protein on the inside
4. Binding leads to exchange of GDP with GTP
5. GTP binding activates the G protein

How GPCRs receive and transduce signal

Reversible binding of the signal (ligand)
$[ligand]$ determines $binding \rightleftarrows dissociation$

Figure 11.7



Activated enzyme triggers a cellular response

How GPCRs receive and transduce signal

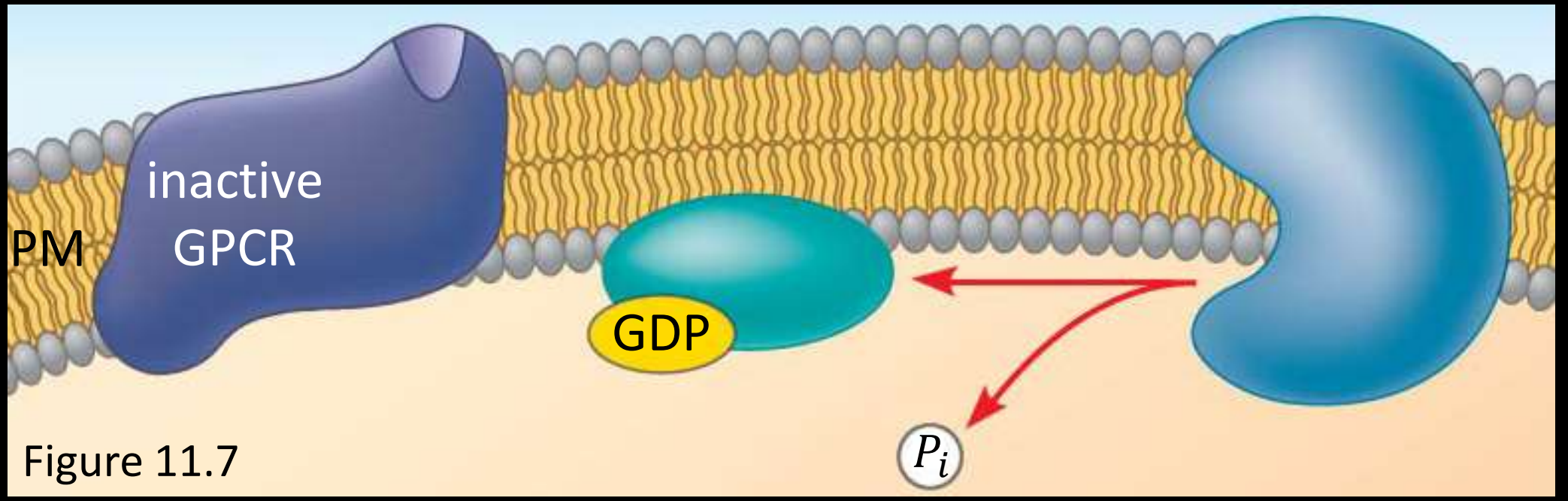


Figure 11.7

- Changes in the enzyme and G protein are transient
- G protein has GTPase activity – hydrolyzes GTP to GDP and P_i
- G protein is now GDP-bound – dissociates from the enzyme

This is a built-in controlling mechanism

Examples of transduction

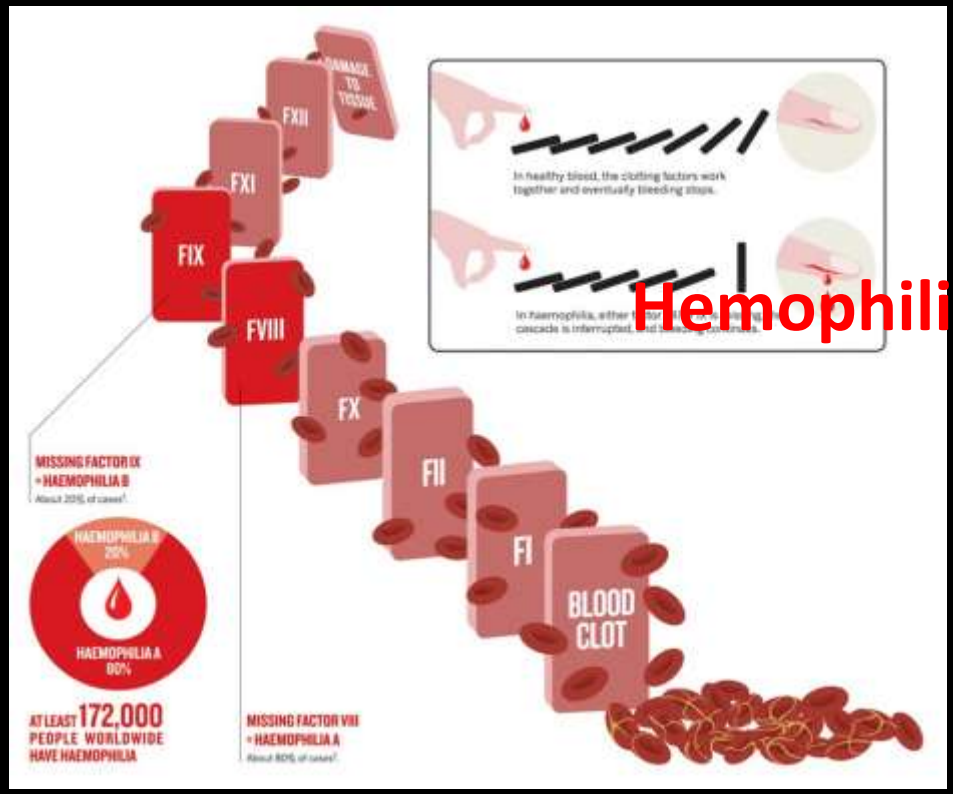
- Quorum sensing
- Signal transduction – an overview
- Illustrative examples
  - Reception
  - Transduction
  - Response

Cascade

cascade (*noun*): A large number of things that happen quickly in a series

Water cascade

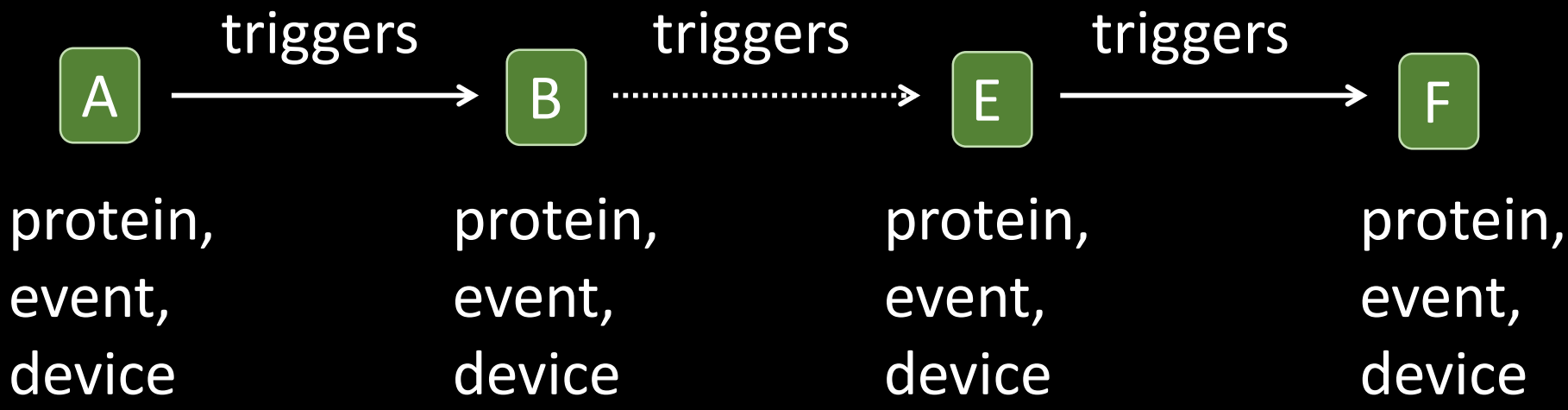
Blood clotting cascade



Hemophilia

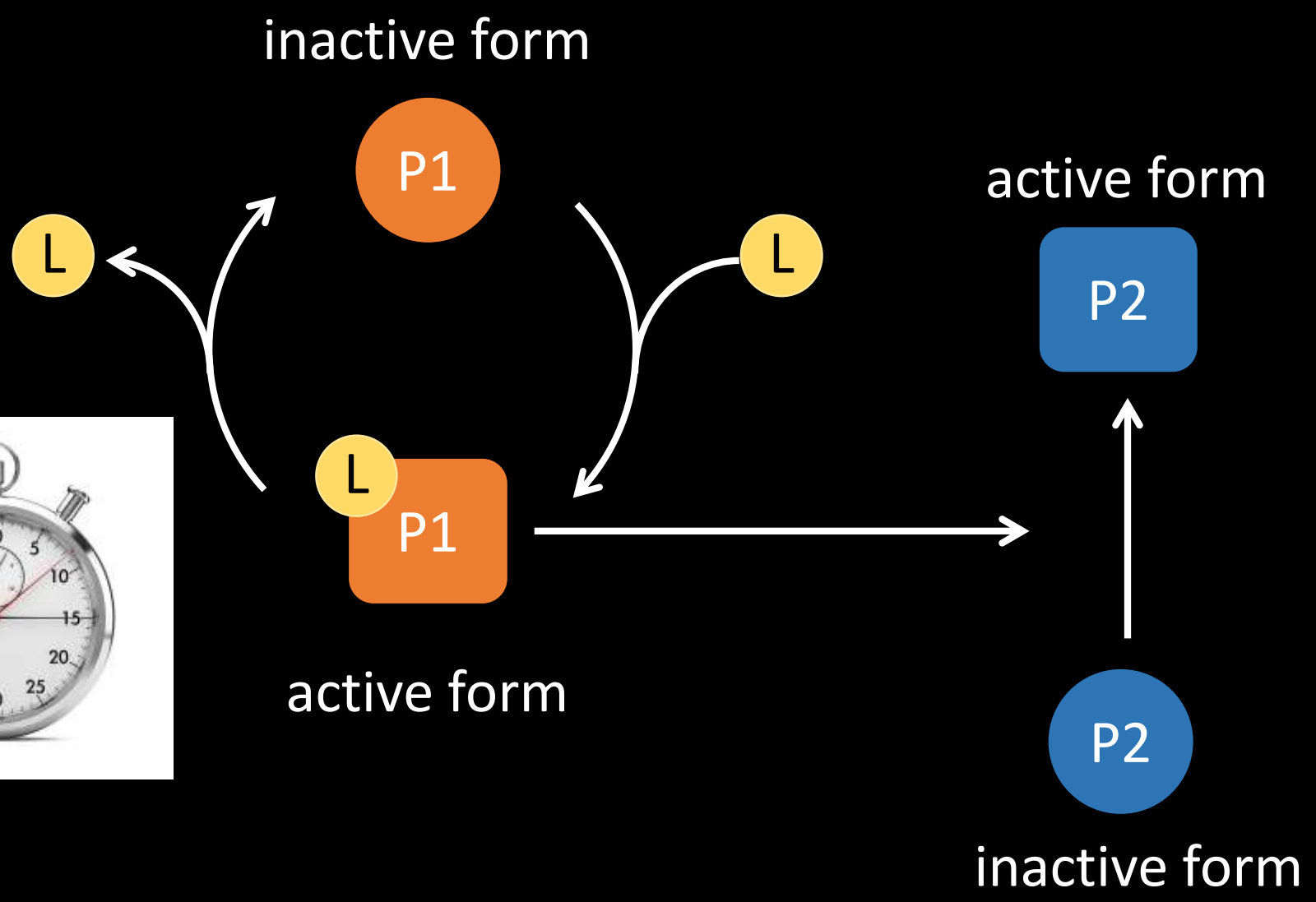
www.scientificamerican.com/article/a-primer-on-haemophilia-graphic/
http://blog.gardenloversclub.com/structures/20-solar-water-fountain-ideas-for-your-

Cascade

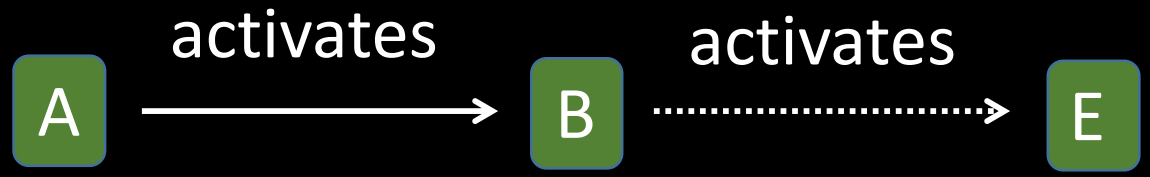


What is the advantage?

1) Cascade with timer devices



2) Cascades can be tuned



protein is activated by ligand (signal)

Remains active only for a short duration

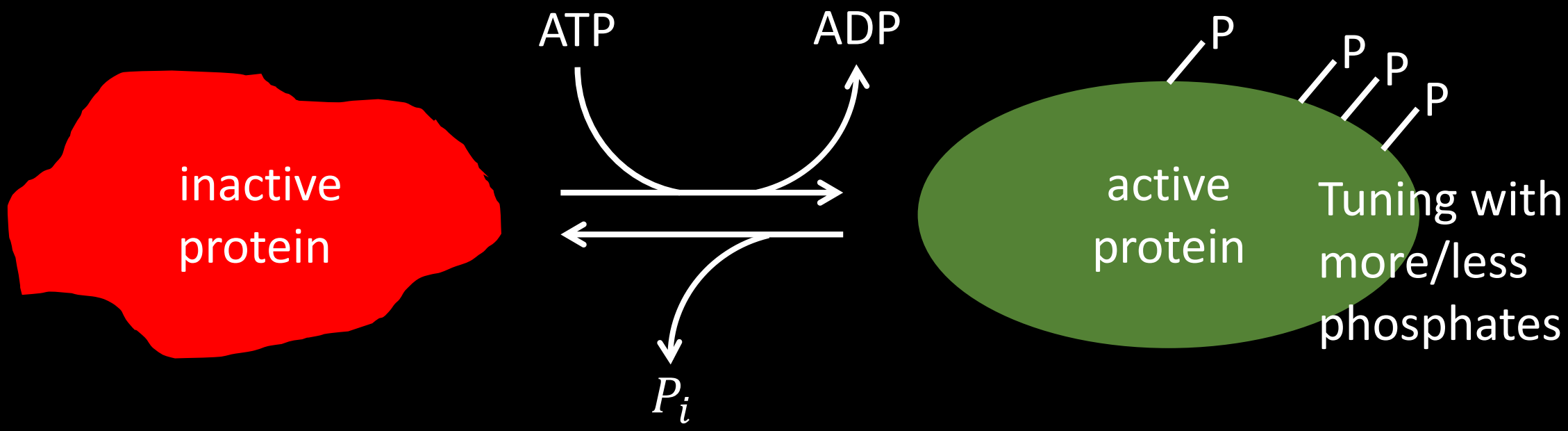
e.g., by phosphorylation

is deactivated by a phosphatase

The number of phosphate groups can lead to different levels of response

Kinase and phosphatase: phosphorylation activates the protein

Kinase (an enzyme which phosphorylates a protein)



Phosphatase (an enzyme which dephosphorylates the protein)

Phosphorylation – dephosphorylation bring about shape (conformation) changes

3) Phosphorylation cascades amplify the signal

Dominos

- Signal transduction usually involves multiple steps
- Multiple steps greatly amplify a signal
- Binding of ligand to a receptor triggers the first step
- Domino effect: sequential activation of proteins
- Each step involves signal transduction – usually, a change in the shape of a protein

http://dataquarks.com/am-i-alright-jack-the-domino-effect-of-brexit

Phosphorylation cascade

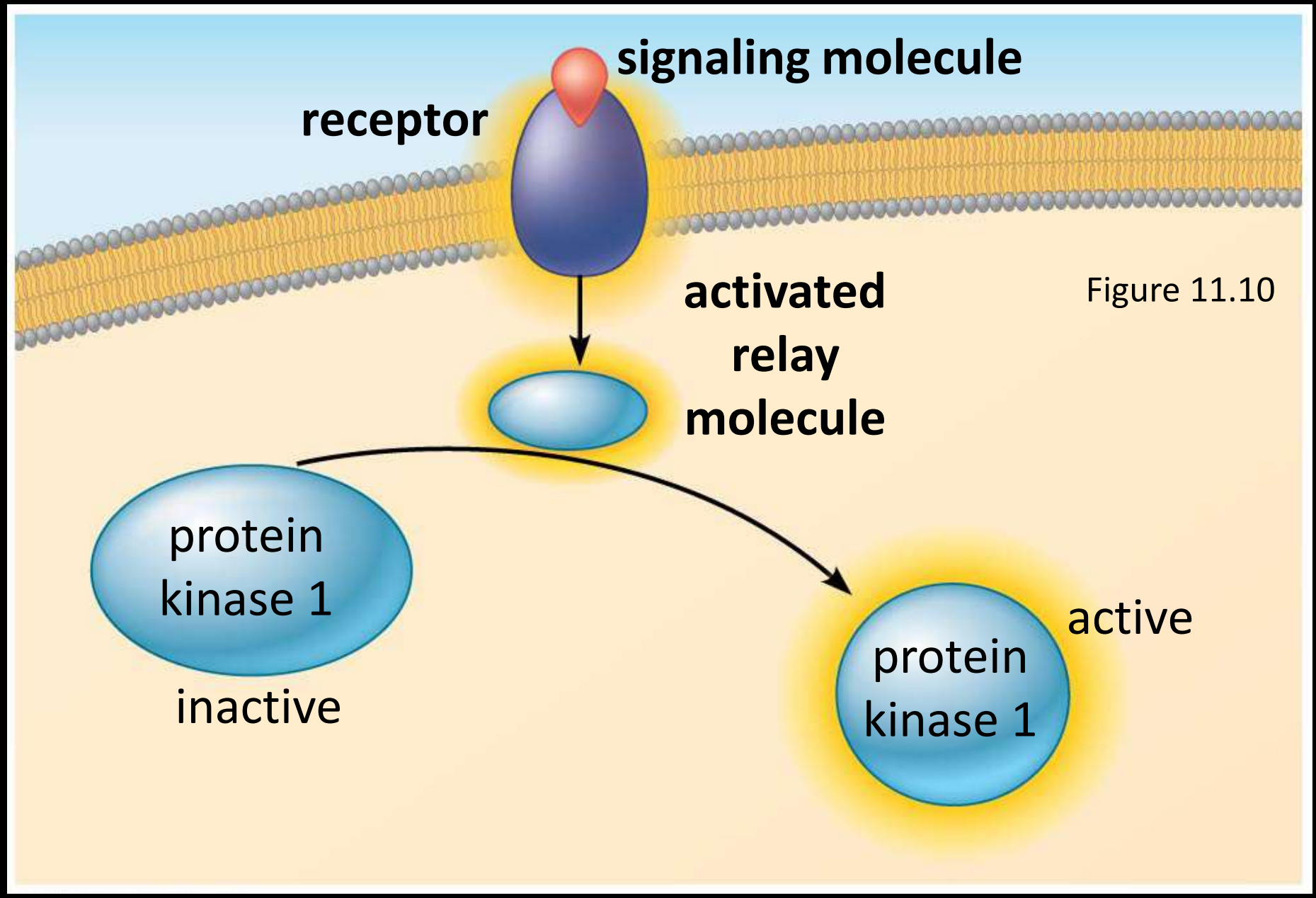
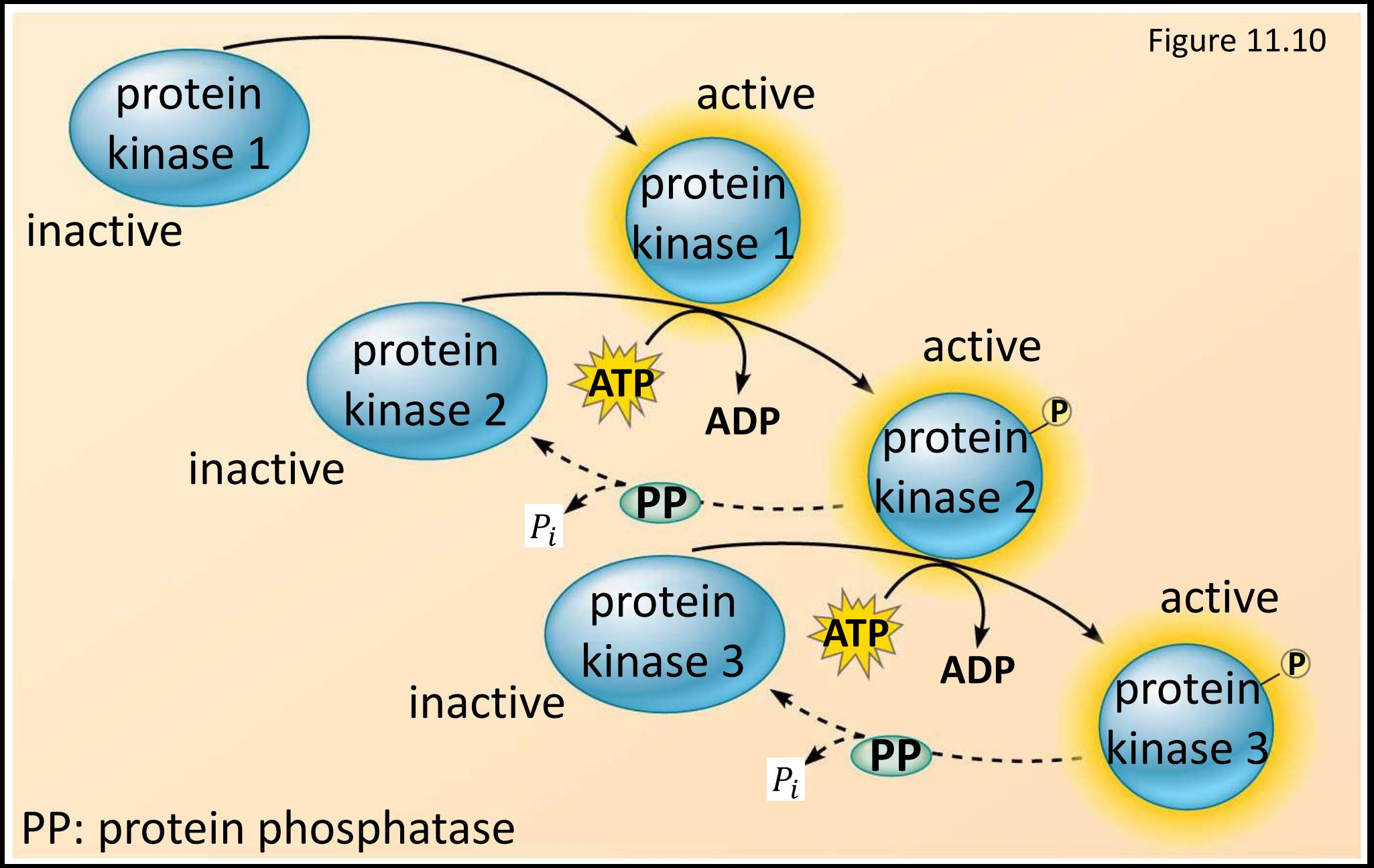


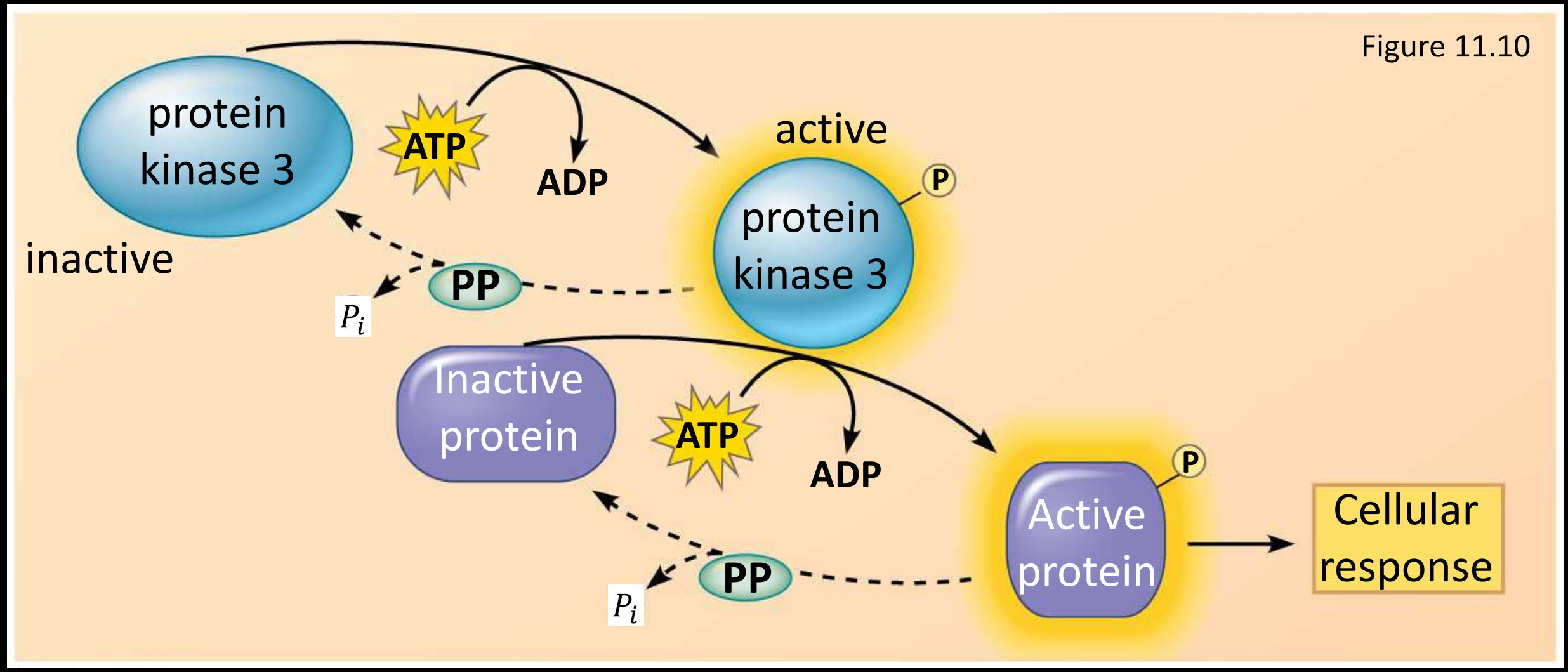
Figure 11.10

Phosphorylation cascade

Figure 11.10



Phosphorylation cascade

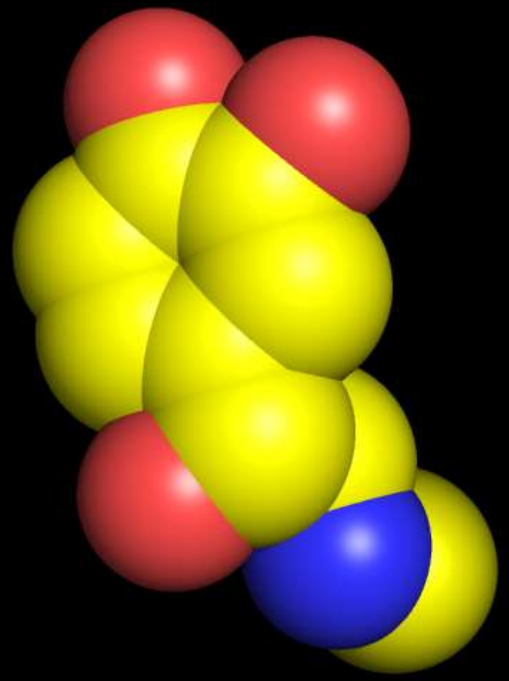


So, how does adrenaline mobilize energy?

Earl W. Sutherland
Nobel prize (1971)

www.nasonline.org

Figure 9.1. Biology. A global approach



Adrenaline

4LDO.pdb

Signal amplification by cascades

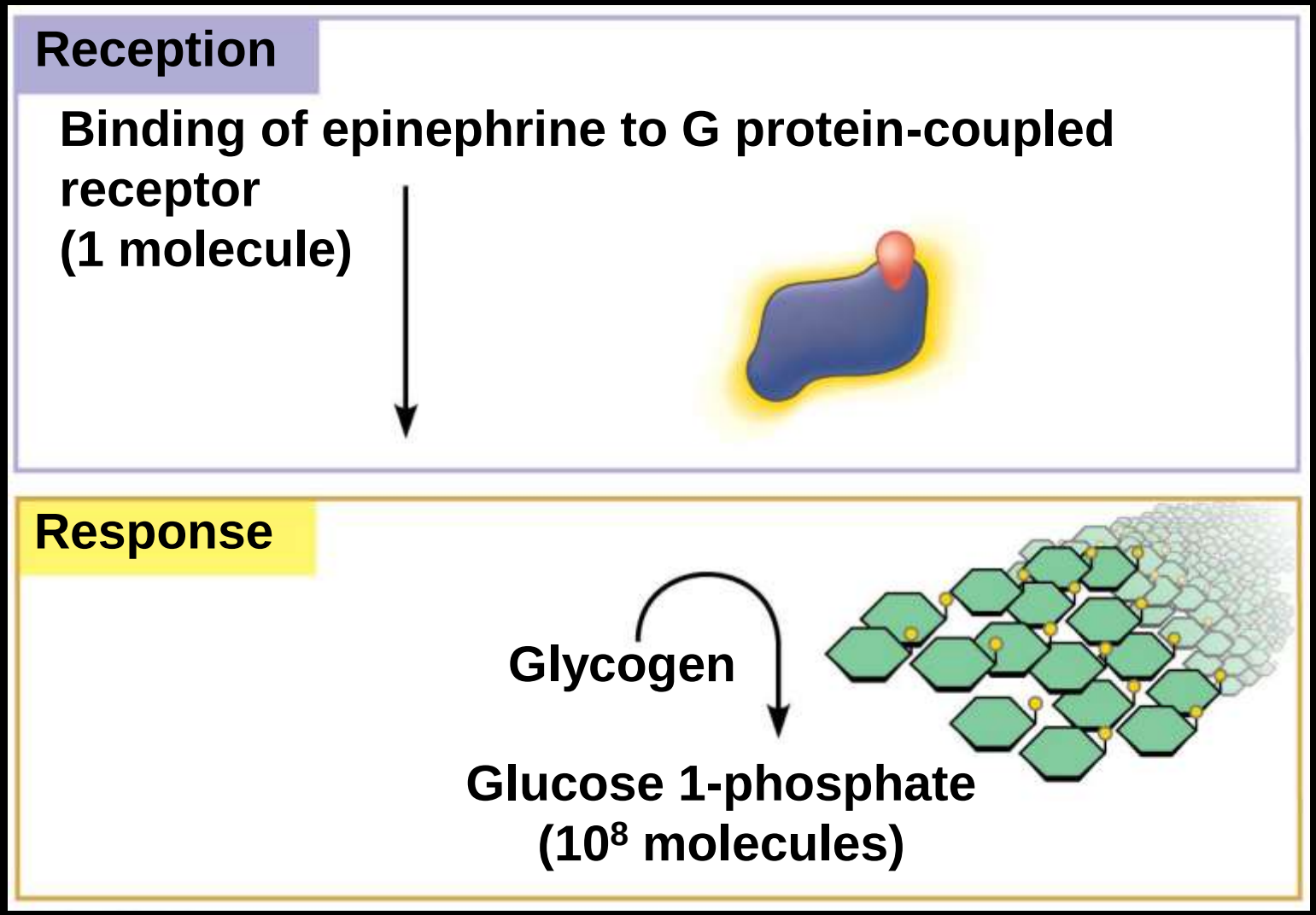


Figure 9.16 in Biology. A global approach

Glucose is stored as glycogen

Epinephrine is produced

Signal transduction cascades will activate the enzyme to break down glycogen to glucose

Energy for fight or flight response

Signal amplification by cascades

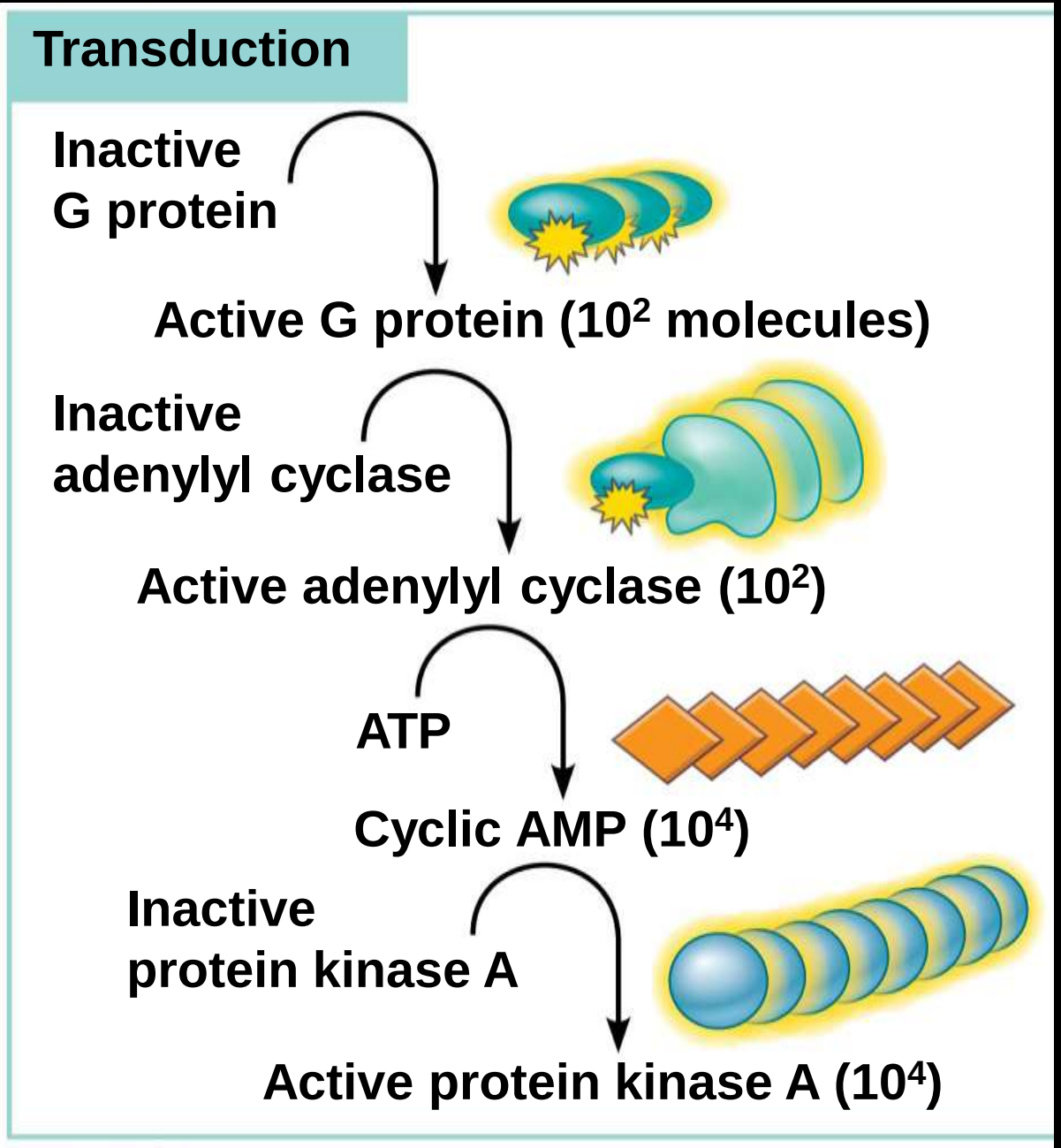
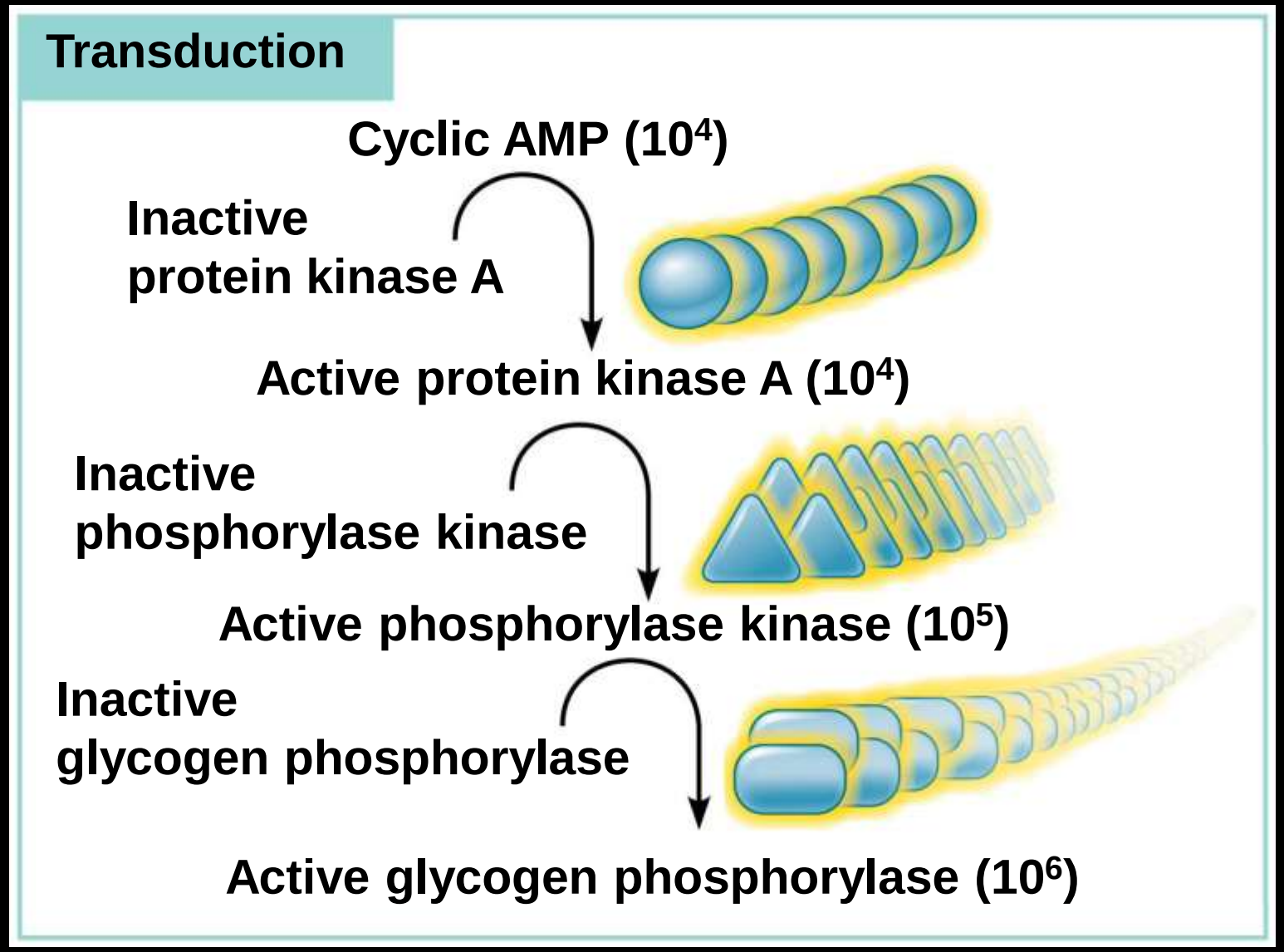


Figure 9.16 in Biology. A global approach

Signal amplification by cascades



Note: many steps, each can be tuned

Figure 9.16 in Biology. A global approach

Commonly used drugs that target GPCRs

GPCR Class	Drug(s)	Indication
Adrenoreceptor		
Alpha-1	alfuzosin, terazosin	Benign prostate hyperplasia, high blood pressure
Alpha-2	clonidine, bisoprolol, betaxolol	High blood pressure
Beta-1	metoprolol, atenolol	High blood pressure
Beta-2	albuterol, nadolol, penbutolol	Asthma
Acetylcholine Receptor		
M1, M2, M3, M4 and M5	tolterodine	Overactive bladder
M1, M2, M3, M4 and M5	atropine	Poisoning
M1	scopolamine	Motion sickness; diarrhea
Calcitonin	calcimar	Osteoporosis
Dopamine		
D2	metoclopramide	Heartburn
D2	haloperidol, olanzapine	Schizophrenia
D2	ropinirole, pramipexole	Parkinson's disease; Restless legs syndrome
Histamine		
H1	loratadine, cetirizine	Allergies
H1	demenhydrinate	Motion sickness
H2	cimetidine, ranitidine	Ulcers/heartburn
5-HT (serotonin)		
5-HT1B	trazodone	Anxiety; depression
5-HT1D	sumatriptan	Migraine headaches
GLP-1	exenatide	Type-2 diabetes
Opioid		
Mu	fentanyl, codein, meperidine	Pain
Mu/kappa	oxycodone	Pain
CysLT1	montelukast	Asthma
Prostaglandin E2 receptors	misoprostol	Gastric ulcers

https://www.drugdiscoverytrends.com/gpcrs-desirable-therapeutic-targets-in-oncology/

Examples of the response

- Quorum sensing
- Signal transduction – an overview
- Illustrative examples
  - Reception
  - Transduction
  - Response

Signal reception by mobile phones

Message is received by the mobile of specific student, ignored by others

Cells have a variety of receptors; signaling molecules are also varied

Signaling molecules and receptors bind only their respective partners

Specificity achieved by different receptors

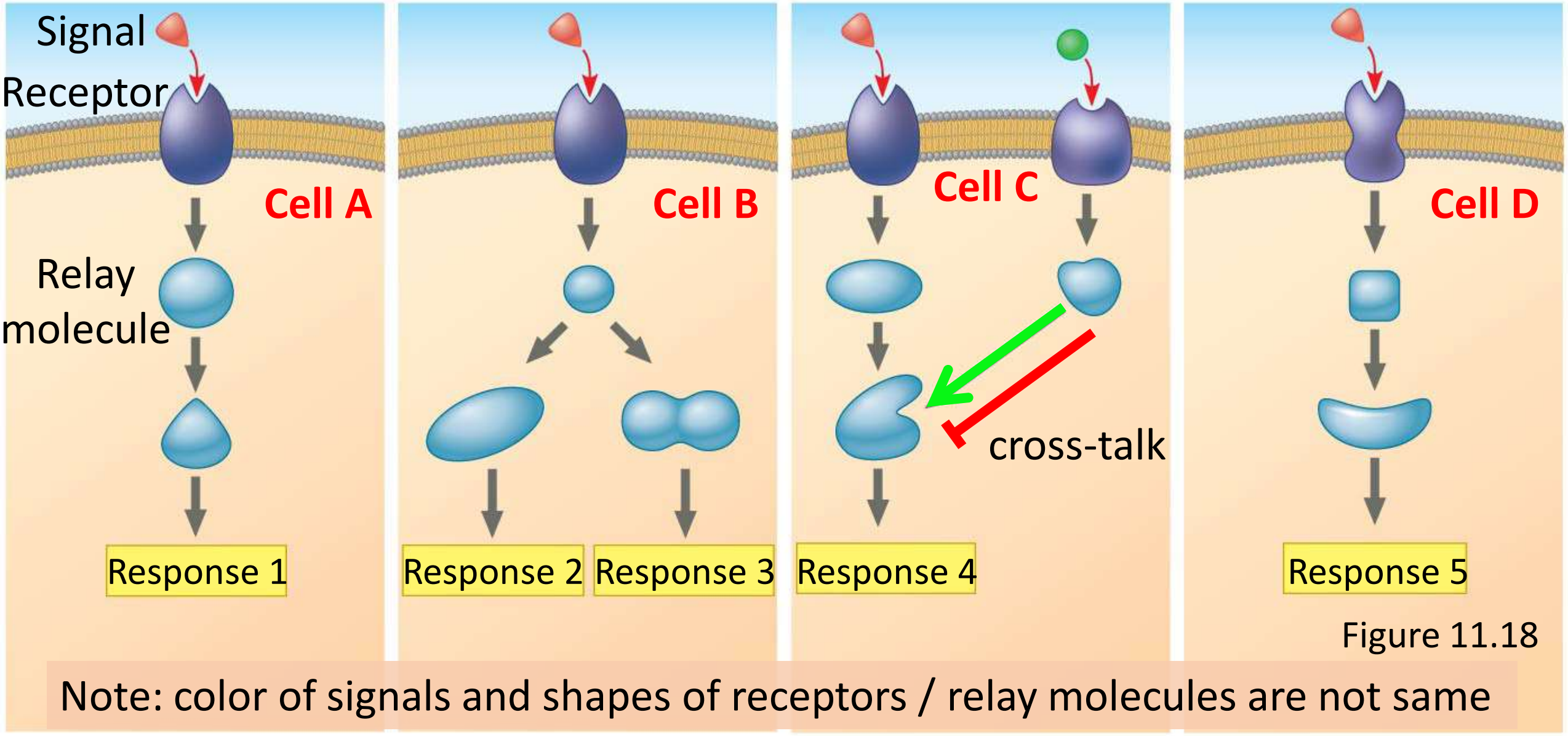
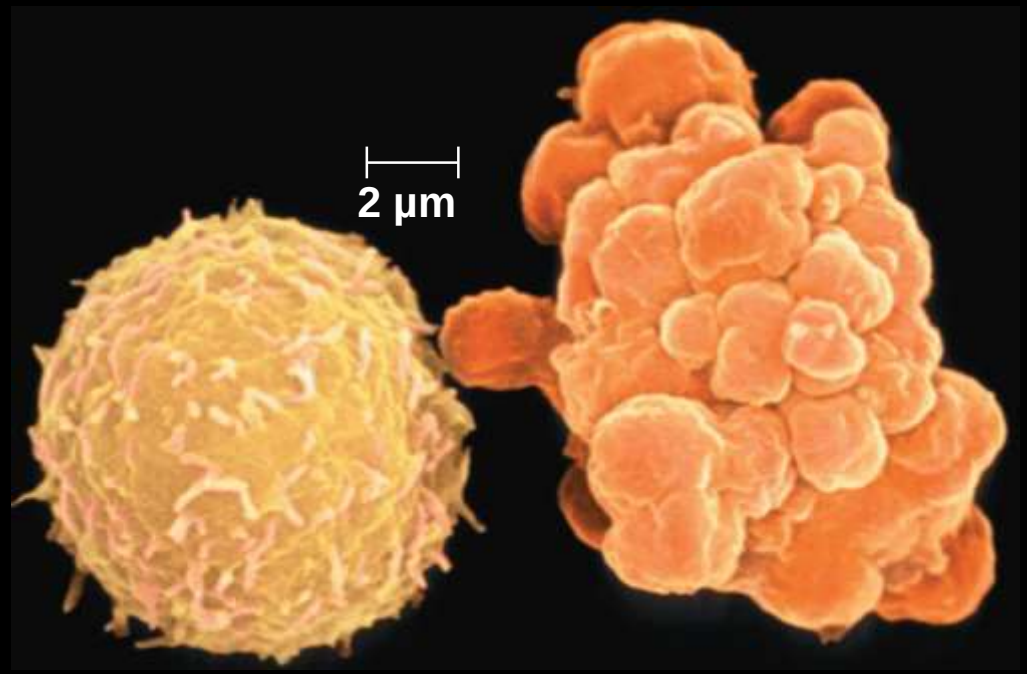


Figure 11.18

Note: color of signals and shapes of receptors / relay molecules are not same

Apoptosis: integration of many signaling pathways

Human white blood cell



Normal

Undergoing apoptosis
(apoptosis=programmed cell death)

Figure 11.20

Apoptosis: paw development in mouse

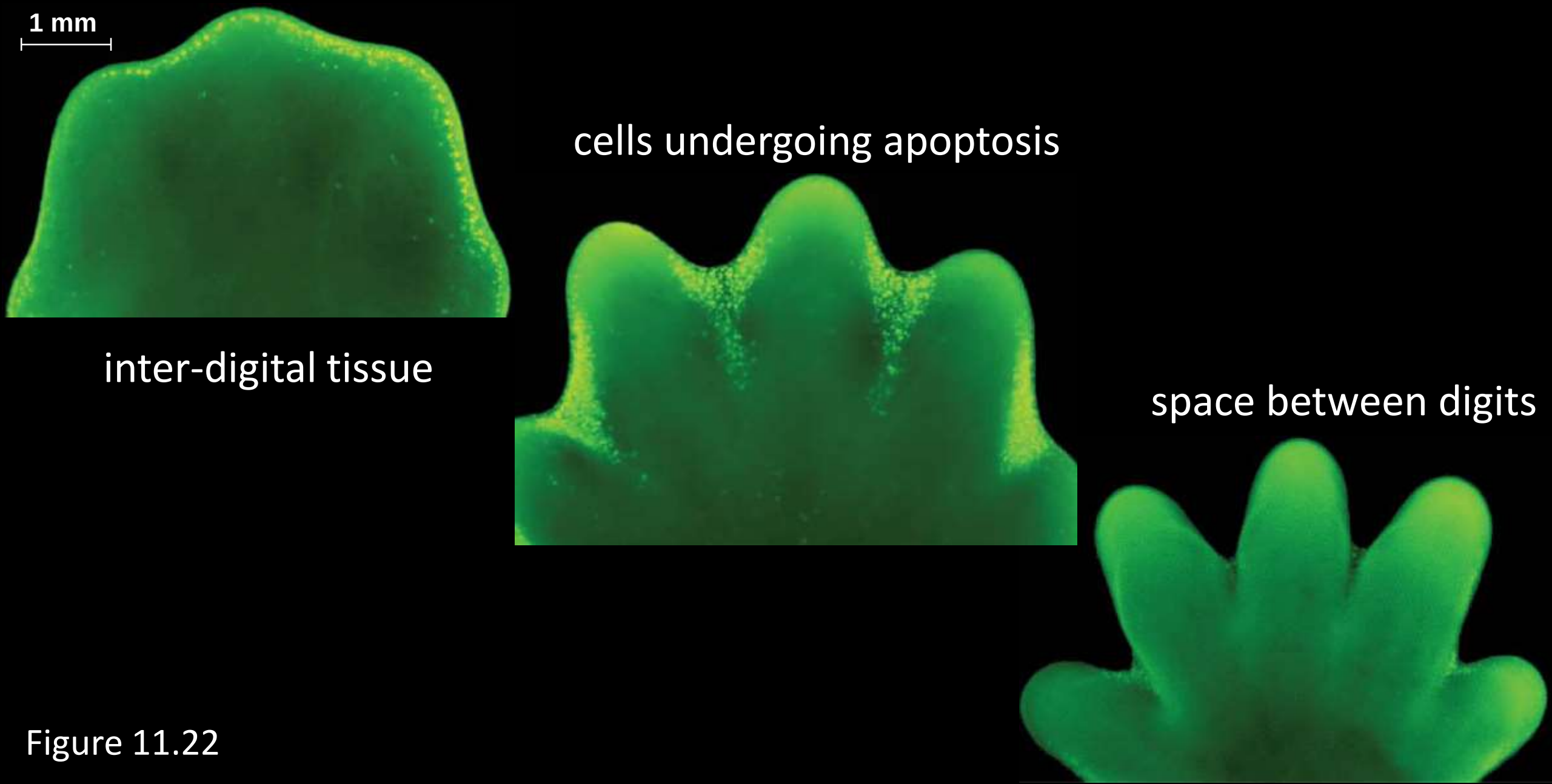


Figure 11.22

Snapshot: bacterial quorum sensing
https://reader.elsevier.com/reader/sd/pii/S0092867418310195?token=7F89B86A17759821325E749D757075E308AFFEB283DE3AF4C412ECF553E3391CEAF01A814A63838203470B8C60D977E1

The Vibrio fischeri LuxR protein is capable of bidirectional stimulation of transcription and both positive and negative regulation of the luxR gene
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC207047/pdf/jbacter00092-0162.pdf

Let there be light (a blog on the discovery that bioluminescence controls circadian rhythms in the squid
https://schaechter.asmblog.org/schaechter/2013/07/let-there-be-light.html

Small talk: cell-to-cell communication in bacteria
https://www.sciencedirect.com/science/article/pii/S0092867402007493

Quorum sensing in bacteria
https://www.annualreviews.org/doi/pdf/10.1146/annurev.micro.55.1.165

Quorum sensing: cell-tocell communication in bacteria
https://www.annualreviews.org/doi/pdf/10.1146/annurev.cellbio.21.012704.131001