It's not a cell membrane party without peripheral protein hats!
Signal Transduction Pathways

• If it helps, think of signal transduction pathways like what happens when you get a text message:
  – **Reception** = Your phone vibrates or dings.
  – **Transduction** = You unlock the phone and read the message.
  – **Response** = You write back, smile, cry, or laugh.
The Signal Transduction Pathway
Three Steps

- **Step 1: Reception**
  - The cell needs to receive a chemical signal (a **ligand**).
    - A ligand is any small molecule that binds to a larger one.
    - The larger molecule is usually a receptor protein.
The Signal Transduction Pathway

Three Steps

• **Step 2: Transduction**
  – The membrane receptor protein then activates one or more other molecules to carry the signal deeper into the cell.
  – These other molecules are called **relay molecules** and may be involved in a phosphorylation cascade.
The Signal Transduction Pathway
Three Steps

• **Step 3: Response**
  
  – The cell does something.
  
  – This could be the activation of a gene, change in the cytoskeleton, activity of an enzyme, or just about anything else.
Kinase Action

ATP
KINASE

PROTEIN MINDING ITS OWN BUSINESS

P
ADP
KINASE
Phosphorylation Cascade

Signal molecule → Receptor → Activated relay molecule → Inactive protein kinase 1 → Active protein kinase 2 → Inactive protein kinase 3 → Active protein kinase 3 → Active protein → Cellular response

ATP → ADP → P_i

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Time to Practice

- *Signal Transduction Pathways POGIL*
Model 1 – Basic Signal Transduction Pathway

Ligand

Cell membrane

Cytoplasm

Receptor protein

Activated relay protein 1

Activated relay protein 2

Activated relay protein 2

Response

Response

Response
Model 2 – Phosphorylation Cascade

1. Cell membrane 
2. Active relay protein
3. Active protein kinase 1
4. ATP, ADP
5. Active protein kinase 2
6. Active protein kinase 3
7. Nucleus

Nonamplification step
Amplification step

Inactive protein kinase 2
Inactive protein kinase 1
Inactive protein kinase 3
Active transcription factor
ATP, ADP
Model 3 – Secondary Messengers

1. Cell membrane
2. Active relay protein
3. Transport protein
4. Secondary messenger
5. Response
Examples of Signal Transduction Pathways

• A signal transduction pathway can be “achieved” through one of these four total methods:
  – Intracellular Receptors
  – Extracellular (Cell Surface Transmembrane) Receptors
    1. G Protein-Coupled Receptors
    2. Tyrosine-Kinase Receptors
    3. Ion Channel Receptors
Intracellular Receptors

• This is when a signal molecule, still called a ligand, enters a cell to elicit a response.

• Inside the cell, it binds to a receptor protein in the cytoplasm and then can affect transcription or other cell activities.
  – In this case, we could call the ligand/receptor complex a transcription factor.

• Onto the extracellular receptors!
1. G Protein-Coupled Receptor

- G proteins are guanine nucleotide-binding proteins.
- So, a **G protein-coupled receptor (GPCR)** is a membrane receptor that is linked in some way to a G protein.
  - There’s the G protein and there’s the receptor (they’re different).
- G protein-linked receptors have seven α helices spanning the membrane.
- These receptors are responsible for relaying a signal from a ligand to the interior of the cell (NOT relaying the ligand itself).
Energy Molecules

• Before we launch into how a G protein-coupled receptor works, we need to look into a molecule that powers the G protein.

• What am I talking about?

• No, not ATP...GTP!
  – ATP = Adenosine triphosphate
  – GTP = Guanosine triphosphate

• **Key:** Each is a nucleotide with THREE phosphate groups.

• **Key:** When “used up,” the molecule is reduced to TWO phosphate groups, known as adenosine/guanosine diphosphate.
ATP vs. GTP

• They’re similar, but different in the same way that adenine and guanine are different.
  – Adenosine = adenine (a nitrogenous base) + ribose
  – Guanosine = guanine (a nitrogenous base) + ribose

• ATP is the more familiar energy “currency” of the cell, but GTP plays a role too.
  – The key is not so much the “adenosine” or “guanosine” part as is the “triphosphate” part.
  – The bonds between the phosphate groups contain the energy.
Back to G Protein-Coupled Receptors

- **Inactive:**
  - The receptor is spanning the membrane.
  - The G protein is bound to GDP and stuck to the inner membrane.
  - An enzyme also exists on the inner surface of the cell membrane.
Back to G Protein-Coupled Receptors

• **Activation:**
  – The orange ligand activates the GPCR, changing its tertiary structure, which bonds to the G protein.
  – GTP replaces GDP, and the G protein moves to the enzyme.
  – The enzyme prompts the next cellular responses.
Back to G Protein-Coupled Receptors

- **Deactivation:**
  - The enzyme hydrolyzes GTP and removes a phosphate.
  - The G protein is released. The process can start again.
And I care...because?

- So why are G protein-coupled receptors important?
  - Your vision and smell senses use G protein-coupled receptors.
  - Diseases like botulism, pertussis (whooping cough), and cholera produce toxins that interfere with GPCRs.
  - Around 60% of medicine works by affecting GPCRs, and a whole lot of drugs (including heroin) work the same way.
  - PTC paper: tasted (or not)?
    - Your ability to taste PTC is based on whether you have a gene coding for a G protein-coupled receptor for that substance.
    - No GPCR, no PTC taste.
2. Tyrosine-Kinase Receptors

- Tyrosine-kinase is an enzyme stuck in the cell membrane.
- Its job is to dephosphorylate ATP and move that phosphate group to the attached tyrosine.
- It has a binding site in the ECM for signal molecules and single α helix in the membrane.
Tyrosine-Kinase Receptors

• Inactive
  – The tyrosine-kinase receptor proteins are two separate monomers, and relay proteins are not active.

• Take a guess where this is going...
Tyrosine-Kinase Receptors

- **Activated**
  - A ligand activates the monomers and they make a dimer.
  - Once joined, the kinase dephosphorylates ATP and adds that phosphate group to its tyrosine (amino acid), which activates relay proteins.
Tyrosine-Kinase vs. G Protein

- G proteins tend to elicit only one type of response per G protein.
- A single tyrosine-kinase receptor can cause multiple responses.
  - Errant receptor tyrosine-kinases have been linked to cancer.
3. Ion Channel Receptors

- These are protein channels that open only when activated by a ligand.
- Nerve cells use these frequently.
Receptors: Big Ideas

- **Versatility**: Different cell types can respond to the same ligand in different ways:

  - **Cell A**: Pathway leads to a single response
  - **Cell B**: Pathway branches, leading to two responses
  - **Cell C**: Cross-talk occurs between two pathways
  - **Cell D**: Receptor is different from the ones in cells A–C
Receptors: Big Ideas

- **Scaffolding**: Some proteins serve as intermediates and hold relay proteins together.
Receptors: Big Ideas

- **Amplification**: A single signal molecule can lead to a massive response.

  - *This is the point of a phosphorylation cascade.*

<table>
<thead>
<tr>
<th>(a) Signaling pathway</th>
<th>(b) Number of molecules activated</th>
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</thead>
<tbody>
<tr>
<td>RECEPTION</td>
<td>1 molecule</td>
</tr>
<tr>
<td>Binding of epinephrine to G-protein-linked receptor</td>
<td></td>
</tr>
<tr>
<td>TRANSDUCTION</td>
<td>10² molecules</td>
</tr>
<tr>
<td>Inactive G protein</td>
<td></td>
</tr>
<tr>
<td>Active G protein</td>
<td>10² molecules</td>
</tr>
<tr>
<td>Inactive adenylyl cyclase</td>
<td>10⁴ molecules</td>
</tr>
<tr>
<td>Active adenylyl cyclase</td>
<td></td>
</tr>
<tr>
<td>ATP</td>
<td>10⁴ molecules</td>
</tr>
<tr>
<td>Cyclic AMP</td>
<td>10⁵ molecules</td>
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<tr>
<td>Inactive protein kinase A</td>
<td>10⁶ molecules</td>
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<tr>
<td>Active protein kinase A</td>
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<tr>
<td>Inactive phosphorylase kinase</td>
<td>10⁸ molecules</td>
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<tr>
<td>RESPONSE</td>
<td>10⁹ molecules</td>
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<tr>
<td>Glycogen</td>
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<tr>
<td>Glucose-1-phosphate</td>
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</table>

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Second Messengers

- Signal transduction pathways often activate **second messengers**.
  - These are molecules *within* cells that act as signals just like the original *extracellular* signal.

- The three major classes of second messengers:
  - Cyclic nucleotides
  - DAG and IP$_3$
  - Calcium ions (Ca$^{2+}$)
Second Messenger: Cyclic Nucleotides

• The enzyme **adenylyl cyclase** is activated by a G protein.
  – Adenylyl cyclase uses ATP to make **cAMP**, or **cyclic AMP**.
  – AMP = adenosine monophosphate

• Similarly, **guanylyl cyclase** uses GTP to make **cGMP** (cyclic GMP).

• These second messengers then serve to turn on other responses within cells.
Second Messenger: IP₃ and DAG

- DAG is **diacylglycerol** which stays in the cell membrane and activates other enzymes, which often use...
- ...IP₃, which is **inositol triphosphate**.
  - This helps release Ca²⁺ ions (which are themselves considered a second messenger) from the ER.
- **Calcium ions**, by the way, are used widely throughout the body.
  - Including making your muscles contract.
Aside: *Clown Anemonefish*

- You’ve seen *Finding Nemo*, right?
- What that movie didn’t tell you is that clownfish (clown anemonefish, officially) have an interesting structure in their social groups.
- There is only one female and one reproductive male.
  - All others are smaller males whose sperm is inhibited by the female. All clown anemone fish are born male.
- When the female dies, the reproductive male **becomes female** with a rush of *estradiol hormone*.
  - The next biggest (not necessarily oldest) male becomes the reproductive male.

http://2.bp.blogspot.com/-0aMLlUGGLI/TV9-haWanCI/AAAAAAAAAzk/goTrWowOCZE/s1600/2c64d3bfebwnfish.jpg.jpg
Aside: *Clown Anemonefish*

- What does this mean?
- It means that, assuming there were no other individuals in Nemo’s group, after Nemo’s mom’s death, Nemo’s dad will soon become Nemo’s mom.
- Nemo, meanwhile, will become reproductive and mate with his fathermother, until he/she dies and Nemo becomes female, perhaps mating with his own offspring.

– *Dory should have just stayed away…*
The Catch: Homeostasis

• All this signaling is great, but there’s one major catch: organisms still need to maintain homeostasis.
• They can achieve this through feedback loops.
• **Positive feedback** amplifies the original signal.
• **Negative feedback** inhibits the original signal.
  – As you might guess, negative feedback is far more useful to homeostasis.
Negative Feedback
Examples

• Predator-Prey Relationships
  – Increase in prey leads to an increase in predators...which decreases prey.

• Body Temperature
  – A rise in body temperature is sensed by neurons which signal the brain, which sends signals to dilate the blood vessels (vasodilation), decreasing temperature.
    • And making you red in the face.
Negative Feedback
Another Example

• If the pH in the duodenum (part of the intestine) drops too low...
• ...the cells in the intestine release secretin, a chemical signal, into the blood.
• Secretin travels to the pancreas, which releases bicarbonate...
• ...which raises the pH.
Positive Feedback
Examples

• **Stampedes**
  - A few animals start to stampede, causing more to run, leading to a mass movement.

• **Uterine contractions**
  - Oxytocin causes uterine contractions, which moves the fetus further down the birth canal, which stimulates more oxytocin release.

• **Students packing up at the end of class?**

*Awkward stock photo from old PowerPoint...at what exactly are they all looking?*
Positive Feedback
Another Example

- If a break occurs in a blood vessel...
- ...platelets adhere to it and release chemicals...
- ...which attract more platelets until the process ends.
Positive Feedback
One last one...

• The ocean is a major **carbon sink**.

• Carbon dioxide dissolves best in cold water.

• As CO$_2$ levels cause temperatures to rise, more CO$_2$ precipitates from the ocean.

• More CO$_2$ coming out of the ocean raises temperatures...

• ...which releases more CO$_2$. 
Coupling Feedback Loops

• Remember that negative feedback loops are best for homeostasis.
• To prevent any level or rate from getting too high, you need a feedback loop.
• To prevent any level or rate from getting too low, you need another feedback loop.
• **Key:** A coupled (or double) feedback loop is needed to keep homeostasis.
  – Let’s look at some examples. **Know the key components.**
Calcium Homeostasis

- Blood $\text{Ca}^{2+}$ high
  - Calcitonin released
  - Blood $\text{Ca}^{2+}$ lowered

- Blood $\text{Ca}^{2+}$ low
  - Parathyroid Hormone (PTH) released
  - Blood $\text{Ca}^{2+}$ raised
**Insulin**

Body cells take up more glucose

**Liver takes up glucose and stores it as glycogen**

**Blood glucose level declines to a set point; stimulus for insulin release diminishes**

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**Beta cells of pancreas stimulated to release insulin into the blood**

**STIMULUS:** Rising blood glucose level (e.g., after eating a carbohydrate-rich meal)

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**Low**

**Blood glucose level rises to set point; stimulus for glucagon release diminishes**

**Alpha cells of pancreas stimulated to release glucagon into the blood**

**Glucagon**

**Liver breaks down glycogen and releases glucose to the blood**

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**STIMULUS:**

- Removal of excess glucose from blood
- Low blood glucose level (e.g., after skipping a meal)

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**Homeostasis:** Blood glucose level
Glucose Homeostasis

- Blood glucose high
  - Insulin released
  - Glucose Homeostasis
  - Blood glucose lowered

- Blood glucose low
  - Glucagon released
  - Glucose Homeostasis
  - Blood glucose raised
Closure: Feedback Mechanisms POGIL

• It’s time to put our knowledge of feedback mechanisms to the test using a POGIL.

• *Feedback Mechanisms POGIL*

• Also:
  
  – TED: Anje-Margriet Neutel – *Feedback Loops: How Nature Gets its Rhythms*