Cell Communication (Plan)

- Origin of cell communication using chemical (biochemical) signaling
- Types of cell signaling as a function of distance travelled by chemical signal
- Important features of cell signaling.
- The three stages of cell signaling in general and map of details:
  - **Reception:**
    - a. external ligands or hormones (1st messengers): chemistry
    - b. protein receptors (membrane-bound & soluble)
  - **Signal transduction:** intracellular 2nd messengers; proteins and enzymes; kinases & phosphatases; phosphorylation cascades
  - **Response:** variety
- **Protein receptors:**
  - Steroid hormones
  - Chemical to electric signal during neurotransmission
  - Epinephrine- anxiety
  - Growth factors- G1 check point
- Different cells respond differently to the same chemical signal
Cell signaling: allows cells to receive and respond to surrounding biochemical signals

The same basic cellular function is involved in:

- Fruit ripening
- Sensing pain & wound healing
- Diabetes
- Anxiety
- Learning & memory
- Psychoactive substances- caffeine, nicotine, marijuana, etc...
Cell Communication

Individual cells
• Cells sense and respond
• Interact with each other

Multi-cellular organisms
• Cell to cell direct contact
• Chemical Signaling
  Short distance
  Long distance

http://nhscience.lonestar.edu/biol/ap1int.htm#endocrine
Communication by **Direct Contact** between cells

**Cell junctions**

(a) Cell junctions

**Surface cell-cell recognition**

(b) Cell-cell recognition
Types of Chemical Signaling

Cells produce **chemical signals** targeting others to respond

Local signaling:
- Paracrine-
  - Synaptic-
- Autocrine-

Long-distance signaling
- **Endocrine**- circulated through the blood
**Paracrine signaling**

Local chemical regulators

- e.g. histamine release by mast cells leads to edema (congestion)

Controlled release of histamine

[http://www.youtube.com/watch?v=ywdk3BTjK2s&NR=1](http://www.youtube.com/watch?v=ywdk3BTjK2s&NR=1)
**Synaptic signaling** (Neurotransmission)

Nerve cells turn electric signals (membrane potential) into a chemical signal secreted into synapse, which is turned back into an electric impulse in the second cell.

[http://outreach.mcb.harvard.edu/animations/synaptic.swf](http://outreach.mcb.harvard.edu/animations/synaptic.swf)
Long-distance Signaling

**Endocrine signaling**-hormones

- In animals- released into the circulatory system.

- In plants- may travel in vessels, by diffusion in air.

Insulin secretion by Beta cells of the pancreas

http://www.youtube.com/watch?v=OYvav8aDGCc
http://vcell.ndsu.edu/animations/regulatedsecretion/movie-flash.htm
Important features of cell signaling

• Specific response to chemical signal
• Amplified requiring minute amounts of chemical signal
• Built-in control- transient
Overview: The three stages of cell signaling:

- **Reception**: membrane receptor of intracellular receptors
- **Transduction**: multi-step signal-transduction pathway
- **Response**: a specific cellular activity
The intracellular pathway dictates the speed of the cellular response

Epinephrin (Adrenalin)

Sex hormones/growth factors
Overall Process of Cell Signaling

1. Reception
   - Chemical signal/ Ligand (1st messenger)
   - Receptor

2. Signal Transduction
   - Enzyme
   - Chemical signal (2nd messenger)
   - Protein Kinase 1
   - Protein Kinase 2
   - Protein A
   - Protein B

3. Response
   - Protein X
   - Protein X$_{PO4}$
   - Protein Y
   - Protein Y$_{PO4}$
Phosphorylation by a kinase typically converts a protein from an inactive form to an active form.

De-phosphorylation by a phosphatase converts it back to an inactive form.
## Signal Transduction Intra-cellular Molecular Mechanisms

<table>
<thead>
<tr>
<th>Conformational changes to existing proteins</th>
<th>Production of new proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activated by</strong></td>
<td><strong>Activation of</strong></td>
</tr>
<tr>
<td>- Phosphorylation <em>(Kinase)</em></td>
<td>transcription factors</td>
</tr>
<tr>
<td>- Allosteric changes</td>
<td>- Expression of new genes</td>
</tr>
<tr>
<td><strong>Deactivated by</strong></td>
<td></td>
</tr>
<tr>
<td>- Dephosphorylation <em>(phosphatase)</em></td>
<td></td>
</tr>
<tr>
<td>- Allosteric changes</td>
<td></td>
</tr>
</tbody>
</table>
Chemistry of Ligands and Hormones (1\textsuperscript{st} messengers)

- **Gas**
  - Ethylene gas \((\text{C}_2\text{H}_4)\)
  - NO (nitric oxide)
- **Polypeptide**
- **Amino acid based**
- **Fatty acid based**
- **Lipophilic hormones**

Additional Website
Second Messengers

• Small, nonprotein, water-soluble molecules or ions.
• Rapidly diffuse throughout the cell.

Two of the most important are cyclic AMP and Ca$^{2+}$.

Others DAG & IP3 (membrane-derived)
The Ca\textsuperscript{2+} concentration in the cytosol is typically much lower than that outside the cell

- Various active pumps transport Ca\textsuperscript{2+}

- Increase in cytosolic Ca\textsuperscript{2+} activates cellular functions.

In animals, secretion & muscle contraction
cAMP as a Second Messengers

- **adenylyl cyclase** converts ATP to cAMP.
- cAMP is short-lived as **phosphodiesterase** converts it to AMP.
Cellular **Receptors** of Chemical Signals

**Soluble intracellular protein receptors**
- hydrophobic ligands: steroid and thyroid hormone

**Three major types of membrane-bound receptors**
1. **Gated ion-channel receptors** - acetylcholine (neurotransmission)
2. **G-protein-linked receptors** - epinephrine
3. **Tyrosine-kinase receptors** - PDGF & insulin
Intra-cellular Signal receptors

- Cytosol or nucleus
- Ligands include:
  - Steroid and thyroid hormones
  - Nitric oxide (NO)

Steroid hormone receptors & signaling

http://highered.mcgraw-hill.com/sites/0072437316/student_view0/chapter47/animations.html#

• Testosterone enters cells

• A cytoplasmic receptor protein, inactive transcription factor.

• The hormone-receptor complex, active transcription factor, enters the nucleus

• Turn on genes that control male sex characteristics
Membrane-bound Receptors

1. Ligand-gated ion channels

- Very important in the nervous system
Neurotransmission

Action potential across the membrane and the nerve impulse

http://outreach.mcb.harvard.edu/animations/actionpotential.swf
2. G-protein linked receptor systems

- Widespread and diverse.
- Evolved very early.
- Several human diseases are the results of activities, including bacterial infections.
- 60% of medicinal drugs target G-protein pathways
2. **G-Protein-linked receptor** (Epinephrine Cell Signaling)

A. Plasma membrane
- Epinephrine
- Receptor (conformation)
- G protein (GDP-GTP)
- Adenylyl cyclase

B. In cytosol
- ATP- cAMP
- kinase A
- Phosphorylation of proteins
- Phosphorylation glycogen phosphorylase
- glycogen to glucose

Epinephrine cell signaling
The G-protein system cycles between on and off
Ligand binding causing the G protein to substitute GTP for GDP

GTP-binding to G protein is short lived
G protein acts as a GTPase hydrolyzing the GTP back to GDP turning itself off
**Signal Specificity**

(a) Signaling pathway

- **RECEPTION**
  - Binding of epinephrine to G-protein-linked receptor

- **TRANSDUCTION**
  - Inactive G protein → Active G protein
  - Inactive adenylyl cyclase → Active adenylyl cyclase
  - ATP → Cyclic AMP
  - Inactive protein kinase A → Active protein kinase A
  - Inactive phosphorylase kinase → Active phosphorylase kinase
  - Inactive glycogen phosphorylase → Active glycogen phosphorylase

- **RESPONSE**
  - Glycogen → Glucose-1-phosphate

**Signal Amplification**

(a) Signaling pathway

- **RECEPTION**
  - Binding of epinephrine to G-protein-linked receptor

- **TRANSDUCTION**
  - Inactive G protein → Active G protein
  - Inactive adenylyl cyclase → Active adenylyl cyclase
  - ATP → Cyclic AMP
  - Inactive protein kinase A → Active protein kinase A
  - Inactive phosphorylase kinase → Active phosphorylase kinase
  - Inactive glycogen phosphorylase → Active glycogen phosphorylase

- **RESPONSE**
  - Glycogen → Glucose-1-phosphate

(b) Number of molecules activated

- 1 molecule
- $10^2$ molecules
- $10^4$ molecules
- $10^5$ molecules
- $10^6$ molecules
- $10^8$ molecules

3. Tyrosine-Kinase Receptors (Platelet-derived growth factor (PDGF))

- Dimeric receptors
- Auto-phosphorylate
- Relay proteins

Cell Signaling and cell growth
http://www.learner.org/courses/biology/units/cancer/images.html
Activated relay proteins trigger many different transduction pathways and responses, simultaneously

http://www.learner.org/courses/biology/units/cancer/images.html

http://arbl.cvmbs.colostate.edu/hbooks/pathphys/endocrine/moaction/surface.html
**Phosphorylation cascade in signal transduction**
- Important for signal amplification.
Cell responses to signaling

1) Change metabolism
   (epinephrine activating an existing enzyme glycogen phosphorylase)
   breakdown of glycogen to glucose

2) Rearrangement of cytoskeleton

3) Transport across membrane (neurotransmitters)

4) Activation of gene expression leading to synthesis of a new protein promoting cell division (passage through the G1 check point)
The response of a particular cell to a signal depends on its particular collection of receptor proteins, relay proteins, and proteins needed to carry out the response.