Cell Communication
• For cells to function in a biological system, they need to communicate with other cells and respond to their external environment.

• Cell-to-cell communication is found in both unicellular and multicellular organisms.

• These communication schemes are the products of evolution.
Chemical signals allow cells to communicate without physical contact.

The distance between the signal generating cell(s) and the responding cell can be small or large.

In signaling pathways, there is often a gradient response, and a threshold concentration is required to trigger the communication.
quorum sensing -- use of chemical messengers (pheromones) by microbes to communicate with other nearby cells to regulate overall population growth
• Yeast reproduce sexually but do not have distinct genders (isogamous)

**homeobox** – has genes producing enzymes for production of pheromones and pheromone **receptors** in yeast.

Sexual reproduction thereby depends on pheromones produced from **variant alleles** of the same gene.
Diagram of pheromones produced in yeast allowing sexual reproduction
Nutrient deficient bacteria secrete a chemical into their environment that attracts others. Within the fruiting body, the cells produce thickened walls, forming spores that withstand the poor environment.
Communication between cells requires:

**ligand**: the signaling molecule

**receptor protein**: the molecule to which the receptor binds
- may be on the plasma membrane or within the cell
The receptor protein must have a specific shape for the molecule it binds to.
Integrins -- receptors that mediate attachment between a cell and the tissues surrounding it, which may be other cells or the extracellular matrix (ECM)

They play a role in cell signaling and cellular shape, mobility, and regulate the cell cycle.
Integrins have two main functions:

1. **Attachment** of the cell to the ECM (extracellular matrix)
2. **Signal transduction** from the ECM to the cell

Integrins couple the ECM outside a cell to the cytoskeleton microfilaments inside the cell.
Integrins play an important role in cell signaling. Connection with ECM molecules can cause a signal to be relayed into the cell through protein kinases that are indirectly and temporarily connected with the intracellular end of the integrin molecule, likely following shape changes directly stimulated by ECM binding.
Integrin role in cell migration

Cell migration

Spermidine & Spermine

N\(^1\)-Acetyl Polyamines

Unblock of Kir 4.2 Potassium Channel

Increased Cell Migration

Spermidine/Spermine/ Acetyl Transferase

α9β1 Integrin

α9β1

Kir 4.2 Potassium Channel

K^+

Extracellular Matrix
There are five basic mechanisms for cellular communication:

1. autocrine signaling
2. direct contact (juxtacrine signaling)
3. paracrine signaling
4. endocrine signaling
5. synaptic signaling
Some Cell Communication Mechanisms

- **Autocrine**: Communication between cells of the same kind.
- **Juxtacrine**: Communication between cells in close proximity.
- **Paracrine**: Communication between cells that are not in direct contact, typically through diffusible signaling molecules.
- **Endocrine**: Communication through the bloodstream, involving hormones released into the bloodstream to affect cells throughout the body.

Image source: http://www.informaworld.com/ampp/image?path=/781715625/909884138/tiea_a_372856_o_f0006g.png
Cell Communication

1. **autocrine signaling** -- intracellular signals that trigger receptors within their own membrane.

Such signals often trigger **differentiation** or other developmental processes. 
*(embryonic induction)*
Cell Communication

2. **Direct contact** (juxtacrine signaling) – molecules on the surface of one cell are recognized by receptors on the adjacent cell

**connexons** – 6 proteins which form gap junctions between cells
• Gap junctions and plasmodesmata provide for metabolic cooperation between adjacent cells, and may help maintain homeostasis in connected cells for ion balance. Some signal molecules may move through gap junctions.

Hormone signals in plants move through plasmodesmata within tissues for more rapid responses.
3. **Paracrine signaling** – signal released from a cell has an effect on neighboring cells

--- Is a **short lived** signal which is either reacting with receptors on nearby cells or is quickly destroyed by extracellular enzymes. **Growth factors** in development are typical paracrine signal molecules.
4. **Endocrine signaling** – hormones released from a cell affect other cells throughout the body
5. **Synaptic signaling** – nerve cells release the signal (**neurotransmitter**) which binds to receptors on nearby cells.
The Three Stages of Cell Signaling:

- 1. reception
- 2. transduction
- 3. response
• **Reception** -- the target cell detection of a signal molecule coming from outside the cell.

A chemical signal is “detected” when it binds to a **receptor protein** located at the cell’s surface or inside the cell.
• **Transduction** – occurs when the binding of the signal molecule changes the receptor protein in some way

• The transduction stage converts the signal to a form that can bring about a specific cellular response.
• **Response** — occurs when the transduced signal finally triggers a specific cellular response.
The response may be almost any imaginable **cellular activity** — such as catalysis by an enzyme (for example, glycogen phosphorylase), rearrangement of the cytoskeleton, or activation of specific genes in the nucleus.
• The cell–signaling process helps ensure that crucial activities like these occur in the right cells, at the right time, and in proper coordination with the other cells of the organism.
When a ligand binds to a receptor protein, the cell has a response.

**signal transduction**: the events within the cell that occur in response to a signal

Different cell types can respond differently to the same signal.
A cell’s response to a signal often involves activating or inactivating proteins. Phosphorylation is a common way to change the activity of a protein.

**protein kinase** – an enzyme that adds a phosphate to a protein

**phosphatase** – an enzyme that removes a phosphate from a protein
Receptor Types

Receptors can be defined by their location.

intracellular receptor – located within the cell

cell surface receptor or membrane receptor – located on the plasma membrane to bind a ligand outside the cell
3 subclasses of membrane receptors:

1. **channel linked receptors** – ion channel that opens in response to a ligand

2. **enzymatic receptors** – receptor is an enzyme that is activated by the ligand

3. **G protein-coupled receptor** – a G-protein (bound to GTP) assists in transmitting the signal
Intracellular Receptors

steroid hormones
- have a nonpolar, lipid-soluble structure
- can cross the plasma membrane to a steroid receptor
- usually affect regulation of gene expression

An inhibitor blocks the receptor from binding to DNA until the hormone is present.
A steroid receptor has 3 functional domains:

1. **hormone-binding** domain
2. DNA binding domain
3. domain that interacts with coactivators to affect **transcription** (how a gene is expressed)
1. Hormones cross plasma membrane and bind to cytoplasmic receptors.

2. Hormone binding alters receptor conformation so it no longer binds inhibitor.

3. Hormone–receptor complex translocates to nucleus.

4. Hormone–receptor complex binds to DNA. This usually turns on transcription, but can also turn it off.

5. Cellular response is a change in gene expression.
Receptor Kinases

**receptor tyrosine kinases**

- membrane receptor
- when bound by a ligand, the receptor is activated by dimerization (association of the two receptors) and autophosphorylation
- activated receptor adds a phosphate to tyrosine on a response protein
- an example is the insulin receptor
1. Ligand binds to the receptor.

2. Two receptors associate (dimerize) and phosphorylate each other (autophosphorylation).

3. Response proteins bind to phosphorylated tyrosine on receptor. Receptor can phosphorylate other response proteins.
1. Insulin binds to the extracellular domain of the α-subunit of the insulin receptor.

2. The β-subunit of one insulin receptor phosphorylates the other, allowing the insulin response proteins to be activated.


4. Glycogen synthase converts glucose into glycogen.
Receptor Kinases

**kinase cascade** – a series of protein kinases that phosphorylate each other in succession -amplifies the signal because a few signal molecules can elicit a large cell response

**mitogen-activated protein (MAP) kinases** are activated by kinase cascades
• **Signal transduction** -- the process by which a signal is converted to a cellular response.
  
  1. Signaling cascades **amplify** incoming signals.
  2. Many signal transduction pathways include **protein modifications** that provide means to amplify the incoming signal.
  3. Many signal transduction pathways include **phosphorylation cascades** in which a series of protein kinases add a phosphate group to the next in the sequence, **activating** it.
  4. **Second messengers** help to propagate signals quickly.
G-Protein Coupled Receptors

G-protein – protein bound to GTP

G-protein-coupled receptor (GPCRs) – receptors bound to G proteins
- G-protein is a switch turned on by the receptor
- G-protein then activates an effector protein (usually an enzyme)
G-Protein Coupled Receptors

Once activated, the effector protein produces a **second messenger**.  
- second messenger generates the cellular response to the original signal.  
For example – one common effector protein is **adenylyl cyclase** which produces cAMP as a second messenger.  
Other second messengers include: inositol phosphates, calcium ions (Ca$^{2+}$)
G proteins with cholera

• https://www.sumanasinc.com/webcontent/animations/content/diphtheria.swf
Cell-to-Cell Interactions

Cells can identify each other by cell surface markers.

- **glycolipids** are commonly used as tissue-specific markers
- major histocompatibility complex (MHC) **proteins** are used by cells to distinguish “self” from “non-self”
Cells within a tissue are connected to each other by **cell junctions**

1. **tight junctions** – create sheets of cells
2. **anchoring junctions** – connect the cytoskeletons of adjacent cells
3. **communicating junctions** – permit small molecules to pass between cells

Types of Communicating Junctions

a. **gap junctions** – in animal cells allowing ion exchange – high levels of Ca++ close
Gap Junctions

Image source
http://academic.brooklyn.cuny.edu/biology/bio4fv/page/gap%20junctions1000a.JPG
b. **plasmodesmata** – in plant cells allowing communication
Anchoring Junction
Practical applications of Cell Communication

-- Some situations
1.) Type II Diabetes often results because of problems with cell receptors.
Effect of insulin on glucose uptake and metabolism.

Insulin binds to its receptor (1), which in turn starts many protein activation cascades (2). These include: translocation of Glut-4 transporter to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and fatty acid synthesis (6).

http://upload.wikimedia.org/wikipedia/commons/thumb/c/ce/Insulin_glucose_metabolism_ZP.svg/400px-Insulin_glucose_metabolism_ZP.svg.png
2.) Cardiac cell function depends of hormones, calcium, and second messenger molecules.
3.) Grave’s disease is an auto-immune disease caused by anti-thyroid antibodies that have the effect of stimulating the thyroid into overproduction of thyroid hormone. The pituitary gland produces thyroid-stimulating hormone (TSH), which regulates the production of thyroid hormones. TSH normally binds to a receptor on thyroid cells and activates adenylate cyclase, which in turn stimulates the synthesis of thyroid hormones
Auto-antibodies are produced which **mimic** the action of TSH and binds to the **receptor** for TSH.
4.) **Defective receptors associated with the production of ras cyclin cause some cancers.**

_Hatched proteins have been found to be defective (mutant) in some cancer cells._
The cell cycle and ras cyclin checkpoint – if ras is continuously produced, the cell will divide without stop = cancer
• Acetylcholine is a common neurotransmitter found in the nervous system. When acetylcholine is released from an axon, it moves across the synapse to bind to a receptor on the adjacent neuron, causing the nerve impulse to continue. The nerve impulse would continue for ever if acetylcholine was not destroyed. The action of acetylcholine is stopped by an enzyme called "acetylcholinesterase" (AChE).
5.) **Nerve agents** bind to part of the AChE molecule. This makes the AChE inactive and **blocks the action of AChE**. Therefore,

- there is no way to stop the action of acetylcholine
- acetylcholine builds up at the synapse.
- acetylcholine **continues to act** and the organism will literally twitch to death
Normal neuron with acetylcholine breakdown.

Acetylcholine not broken down due to nerve agents, so neuron keeps getting stimulated.

Images from http://faculty.washington.edu/chudler/weap.html
• Many neurological disorders are associated with membrane transduction errors.

• 6.) Parkinson’s Disease (PD) is a degenerative, progressive disorder that affects nerve cells in deep parts of the brain called the basal ganglia and the substantia nigra. Nerve cells in the substantia nigra produce the neurotransmitter dopamine and are responsible for relaying messages that plan and control body movement.
Some Neurons “talk” to each other in the following manner:

- Incoming messages from the dendrites are passed to the end of the axon, where sacs containing neurotransmitters (dopamine) open into the synapse.
- The dopamine molecules cross the synapse and fit into special receptors on the receiving cell.
- That cell is stimulated to pass the message on.
- After the message is passed on, the receptors release the dopamine molecules back into the synapse, where the excess dopamine is "taken up" or recycled within the releasing neuron.
- Chemicals called MAO-B and COMT break down any remaining dopamine so that the synapse area is “clean” and ready for the next message.
How might Parkinson’s be treated?

- Conserve dopamine blocking the breakdown action of MAO-B and COMT.
- Introduce agents that mimic dopamine and bind to the receptors in the neuron's synapse.
- Replace missing dopamine in the brain. The drug levodopa is transformed into dopamine by the remaining cells in the substantia nigra.
Certain drugs target specific signal transduction pathways.

- Many anesthetics work by blocking the sodium channels preventing a nerve impulse from occurring. Many anesthetics such as lidocaine are tertiary amines.
• **Histamines** are chemical released by mast cells which cause the inflammatory symptoms of allergies.

• This histamines bond to the cells causing the symptoms of allergy. **Antihistamines** act by attaching to these receptor sites, thereby preventing histamine from binding to them. This action prevents the histamine from causing allergic symptoms.
7.) “The Pill” fools the body into thinking it is pregnant by providing synthetic levels of estrogen and progesterone-like compounds. These high levels of estrogen and progesterone inhibit the production of LH.
Day 1
- hypothalamus secretes releasing hormone

- endometrium is shed

Lower levels of estrogen in pill prevent pituitary gland from releasing LH

Birth control pill

With no LH present, egg does not mature and ovulation does not occur
• **Blood pressure medications** such as beta blockers block beta receptors decreasing the ability of the cardiac tissue to contract.