Biological Networks
Metabolic Networks

Krebs cycle:
- Aconitate
- Isocitrate
- Oxaloacetate
- Citrate
- Acetate
- Pyruvate
- Oxaloacetate
- Malate
- Fumarate
- Succinate
- α-Ketoglutarate
Enzymatic Reactions

Set of enzymatic reactions that convert substrate molecules into product molecules. The enzyme is a protein or protein complex.

Mechanism of enzyme activity

Substrate

Enzyme

Enzyme-substrate complex

Products

Enzyme
**Example: Glycolysis**

First half of the glycolytic pathway or network

Nodes: metabolites (substrate and product molecules)

Directed Edges: enzymatic reactions from substrate to product
Example: Citric Acid Cycle

- Malate dehydrogenase
- Acetyl CoA
- Citrate synthase
- Citrate
- Aconitase
- cis-Aconitate
- Malate
- NADH + H^+
- NAD^+
- Oxaloacetate
- Fumarase
- Fumarate
- Succinate dehydrogenase
- Succinate
- Succinyl-CoA
- GTP (will generate one ATP)
- FADH^-2
- FAD
- FADH^-2 synthetase
- α-Ketoglutarate
dehydrogenase
- NAD^+
- NADH + H^+ + CO_2
- Isocitrate dehydrogenase
- Isocitrate
- 6 NADH + 2 FADH^-2 + 2 ATP (per glucose)
Networks of Protein-Protein Interactions
Proteins Often Physically Interact

The 3-D structure of proteins determine which other proteins they will interact with, and what those interactions will produce. These are typically achieved through the formation of hydrogen bonds.
Examples of Protein-Protein Interactions

Signal transduction: The activity of the cell is regulated when an extracellular protein signaling molecule binds to a protein-based receptor in the cell’s plasma membrane.

Transport across membranes: A protein may bind to and transport another protein across the cell’s plasma membrane or membrane of an organelle.

Cell metabolism: Enzymes that are in the form of dimers (two coupled proteins) or trimers (three coupled proteins) or N-mers are sometimes more active than single protein molecule.

Muscle contractions: Myosin filaments act as molecular motors and by binding to actin enables filament sliding.
Myocin Moving Along Actin
Protein Interaction Networks

Proteins or protein complexes can interact with several other proteins, forming an undirected network.

- **Nodes**: proteins or protein complexes
- **Edges**: interactions
Example: A Protein-Protein Interaction Network for Yeast

Yeast is a much-studied single-cell organism. Bakers yeast (Saccharomyces cerevisiae) is good for bread and science!

Jeong et al., 2001
Networks of Protein-Protein Activation
Signal Transduction Networks

Networks can be used to describe how some proteins interact with enzyme proteins and activate (or inactive) them.

- **Nodes**: proteins or protein complexes
- **Directed edges**: activation or inactivation interactions (positive or negative weights)
Example: Tyrosine Kinase Signaling

Pullamsetti and Shermully, 2010
Example: G-Protein Signaling

Zhang and Xie, 2012
Genetic Regulatory Networks
How are Proteins Made?

Small biomolecules are made through metabolism, using enzymes to break down nutrients and build up molecules like sugars and fats.

Proteins are much larger biomolecules, and are made in a very different way.
Three Key Biopolymers

- Deoxyribonucleic Acid (DNA)
- Ribonucleic Acid (RNA)
- Proteins
A single DNA strand (called a **biopolymer**) consists of a combination of *4 nucleotides*: adenine (A), cytosine (C), guanine (G), and thymine (T).

Three consecutive nucleotides forms a **codon**, such as AAC. There are 64 different codons.

Each codon codes for one of 20 amino acids, or is a start or end codon.
RNA Polymerase Transcribes a DNA Fragment to Messenger RNA (mRNA)
RNA Polymerase Transcribes a DNA Fragment to Messenger RNA (mRNA)

Transcription starts at a **Start Codon** and stops at a **Stop Codon**
RNA Polymerase Transcribes a DNA Fragment to Messenger RNA (mRNA)
Translation Outside Nucleus Converts mRNA Into a Protein

Ribonucleic Acid (RNA)

Proteins
Ribosomes Translate mRNA Into a Protein
Ribosomes Translate mRNA Into a Protein
What Are Genes?

A gene is a sequence of codons between a start codon and an end codon.
What Causes Genes to be Expressed?

A gene is expressed if it is first transcribed into mRNA and then translated into protein. This happens when a specific transcription factor binds to the promoter region for a gene. This is a segment of DNA near the gene.

Transcription factors may be activators (promote binding of RNA polymerase) or repressors (prevent the binding of RNA polymerase).
Genetic Regulatory Networks

Genes that code for transcription factors regulate the expression of other genes. These genetic interactions form networks.

**Nodes**: proteins or the genes that code for them

**Directed Edges**: transcription of node B by node A
Genetic Regulatory Network from E. coli
The Brain Is a Large Network of Interconnected Neurons

Soma: cell body
Dendrites: input lines
Axon: output line
Axon terminals: splitting of axon to connect with multiple downstream neurons
Synapse: the junction structure connecting presynaptic and postsynaptic neurons
A Single Neuron

A stained neuron with an extensive dendritic tree
Synapses Convert Electrical Impulses to a Chemical Signal

The chemical transmitter is called a neurotransmitter. There are many types, such as acetylcholine, glutamate, GABA, and dopamine.
Neural Networks Have Two Types of Edges

**Nodes:** neurons

**Directed Edge:** axon of neuron A synapsing onto neuron B

- **Excitatory neurotransmitter:** e.g., glutamate, acetylcholine
- **Inhibitory neurotransmitter:** e.g., GABA, dopamine

Neurotransmitters can stimulate the postsynaptic neuron or inhibit it, depending on the neurotransmitter and the receptor. So there are **two types of edges** in the network, so the edges can have positive or negative weights.
A Simple Neural Network

From the Eve Marder lab, Brandeis University

Contained within the **stomatogastric ganglion**, which has about 30 neurons that comprise two central pattern generators, the **pyloric network** and the **gastric mill network**
Part of the Brain Circuitry of a Worm

White et al., 1986

Constructed by hand using electron micrographs. Note: this is really hard and really slow. Current technology does not allow full construction of most neural networks.
Structural vs Functional Networks

Growth-hormone-secreting somatotrophs and prolactin-secreting lactotrophs form networks surrounding blood vessels in the pituitary gland.
These Electrically-Active Cells are Coupled via Gap Junctions

The gap junction proteins provide a pathway for the flow of electrical current between cells, proportional to the difference in their membrane potentials ($V$).
This Coupling Can Synchronize the Bursting Electrical Activity in the Cells

In the top panel the electrical activity of the two cells is synchronized. They can be considered functionally coupled. In the bottom the bursts are anti-phasic. The structural coupling strength is the same in both.

Fazli & Bertram, 2022
A Structural Network Displays How the Cells in the Population are Connected Through Gap Junctions

Edges indicate gap-junctional coupling. The node size and color reflects its degree in the structural network.

Fazli & Bertram, 2022
A Functional Network Displays How the Activity of the Cells in the Population is Coordinated

Edges indicate synchronization of bursting activity. The node size reflects its degree in the structural network, while its color reflects its degree in the functional network.

Fazli & Bertram, 2022
A Functional Network Displays Coordinated Spiking Activity in Cortical Neural Networks

Neurons from the mouse cortex were grown in vitro on a microelectrode array, forming new synaptic connections.

Node: neuron, Edge: coordinated spiking activity

Bettencourt et al., 2007
The End