EE430
Introduction to Systems Biology

Week 1 Course Notes

Instructor: Bilge Karaçağalı, PhD
Meeting times: Tuesday 11:45; Thursday 10:45, 11:45
Instructor: Bilge Karaçalı, PhD
Office: EEE Building Room 219
Phone: 6534
E-mail: bilgekaracali@iyte.edu.tr
Summary:
This course will begin with a broad description of the molecular organization of living cells. The signal transduction networks and the regulation of gene transcription will be studied with regards to molecular circuits modeled by kinetic equations. Mathematical aspects of the development of robustness and functionality will be overviewed.
Grading:
Midterm 20% Final 30%
Homework 20% Project 30%
Course Outline:
Week 1: Introduction to cell biology
Week 2: Molecules of life: Genes and proteins
Week 3: Transcription networks
Week 4: Regulation of gene transcription
Week 5: Network motifs in transcription regulation
Week 6: Network motifs in signaling networks
Week 7: Origins of biological robustness
Week 8: Optimal gene circuits
Week 9: Kinetic modeling of biochemical reactions
Week 10: Kinetic modeling of large scale biomolecular networks
Week 11: Integration of regulatory and metabolic networks
Week 12: Graph theoretic analysis of biological networks
Week 13: Biological networks and drug development
Week 14: Overview
URL:
http://web.iyte.edu.tr/~bilgekaracali/EE430/
Topics

• Introduction to cell biology
  – Prokaryotes, eukaryotes, and viruses
  – Eukaryotic cell
  – Cell cycle
  – Cell signaling
The Tree of Life

“A process which led from the amoeba to man appeared to the philosophers to be obviously a progress though whether the amoeba would agree with this opinion is not known.”

Bertrand Russell

• Species past and present can be linked to each other by their molecular organization
  – Phylogenetic trees
• The linkage can be derived from the similarities of the genetic code
• Branching implies diversification from a common past ancestor
  – The time of bifurcation can be estimated from the alterations on the genetic code
  ➔ The genetic code determines the organism
• Higher and lower organisms on the tree does not imply more and less evolved species!!!
  • Bacteria had the exact same amount of evolution time as mammals

Source: http://www.nbii.gov/
Prokaryotes

• Prokaryotes are the simplest cells in terms of cellular organization (single cell organisms)
  – consist of a cellular membrane with a cell wall enclosing a “molecular soup”
  – lack subcellular organization in the form of organelles
  – come in small sizes to allow rapid diffusion of important molecules across the cell

• Even as such they carry out typical cellular functions such as division and motion
  – Organizational simplicity does not mean molecular simplicity, but only relative simplicity compared to eukaryotic cells

Source: http://www.ebi.ac.uk/2can/biology/organisms3.html
Eukaryotes

- Eukaryotes represent a higher level of cellular organization compared to prokaryotes
  - Can be single or multiple cell organisms
    - Amoeba vs. vertebrates
  - Are typically much larger than prokaryotes
    - Metabolic rates are therefore much slower (smaller surface to volume ratio)
  - Contain well-defined subcellular structures in the form of organelles
    - Nucleus, endoplasmic reticulum, Golgi apparatus, cytoskeleton, ...
    - Nucleus is the defining organelle separating eukaryotes from the prokaryotes

Source:
http://nobelprize.org/nobel_prizes/medicine/laureates/1999/illpres/
Viruses

- Viruses have no cellular organization; they are not cells in the technical sense of the word
  - Consist of genetic code enclosed in a protein membrane
  - Cannot carry out any cell functions on their own
  - Infect cells and take the molecular mechanism of the host cell hostage
    - Exclusively parasite organisms
    - The protein membrane contains proteins that lock onto the host cell
    - The virus injects its proteins/RNA and induce the host cell to manufacture new copies of the virus
    - Eventually the host cell ruptures and the newly manufactured copies of the virus go on to infect other cells
  - For all practical purposes, they are disease-causing organisms responsible of many deaths every year across the world
    - polio, smallpox, chickenpox, human immunodeficiency virus, ...

Source:
Eukaryotic Cell

- Cellular functions are carried out by organelles
  - Each organelle is responsible for a well-defined set of operations
  - The cellular operations are carried out in synchronization with the rest of the cell
  - This synchronization is the main subject matter of the field of systems biology
Eukaryotic Cell: The Plasma Membrane

- All cells (eukaryotic and prokaryotic) are enclosed by a membrane
- The membrane separates the inside of the cell from the outside
  - Provides a protected environment for carrying out cellular operations
  - Controls the transport of molecules to and from the intracellular space
  - Contains embedded molecular triggers for a variety of environmental variables → sensors

Source:
Eukaryotic Cell: The Endoplasmic Reticulum

- Consists of an interconnected network of tubules and sacks
  - Enclosed is a large internal space called the *lumen* or the *cisternal space*
- Carries out production and transport duties for many biochemical compounds
  - Rough ER: Protein synthesis in ribosomes and folding by glycosylation (adding of sugars) in the lumen
    - In coordination with the mitochondria (steroid hormone) and the Golgi apparatus
  - Smooth (Transitional) ER: Production of lipids, calcium storage, and detoxification

Eukaryotic Cell: The Golgi Apparatus

• A structure composed of stacked membranes
  – Disappears during cell division

• Main activity is protein processing, especially glycosylation
  – Post-translational modifications
    • Finalizes proteins coming from the endoplasmic reticulum

• The finalized proteins are then transferred to
  – the plasma membrane (either for anchorage or for secretion)
  – the lysosomes

Source:
http://tainano.com/chin/Molecular%20Biology%20Glossary.htm
Eukaryotic Cell: The Mitochondria

- A distinct subcellular structure with its own membrane and DNA
  - Replicates on its own like a bacterial cell
  - Believed to originate from captured bacteria in a symbiotic relationship
- Carries out metabolic activities as the powerhouse of the cell
  - Uses the energy stored in sugars and fat to synthesize ATP
- Mitochondrial DNA can be used to trace maternal ancestry

Source: http://www.mitochondrial-disorder-information.com/what_is_mitochondria.html
Eukaryotic Cell: Ribosomes

- A cellular structure lacking its own membrane
  - Carries out protein synthesis
  - Itself synthesized inside the nucleus by the nucleoli
    - RNA-protein complex
  - Usually bound to the endoplasmic reticulum; rarely free-floating inside the cytoplasm
  - Made up of two subunits
    - One small, one large
    - The two subunits come together for protein synthesis

Source:
http://publications.nigms.nih.gov/insidethecell/chapter2.html
Eukaryotic Cell: Lysosomes

- A membrane-enclosed sack of potent enzymes
  - Responsible for the degradation of various substances
    - damaged or excess compounds
    - infecting organisms
    - any and all groups of biologically significant macromolecules
  - Components of the degraded substances are recycled within the cell
  - Rupture of the lysosomal membrane causes dissolution of the cell
    - Elimination of the larval tissues in development
    - Degeneration of the corpus luteum at the end of mammalian ovarian cycle in which fertilization does not occur
  - Formed by the Golgi apparatus

Source: http://publications.nigms.nih.gov/insidethecell/chapter1.html
Eukaryotic Cell: The Nucleus

• The control structure of the eukaryotic cell
• Formed by
  – a porous nuclear envelope enclosing
  – the chromosomes and
  – one or more nucleoli
• Carries the genetic instructions for development and growth (the genotype)
  – Genetic instructions are packaged in the DNA molecule
    • Double helix (Watson & Crick)
  – All cellular activity is governed by the transcription of the critical regions on the DNA code
    • Critical regions are the genes
    • Presence of genes and their combinations determine the phenotype of the organism
• Houses the molecular machinery for gene expression and starts the information flow towards protein synthesis

Source: http://universe-review.ca/R10-01-cellnucleus.htm
Cell Cycle

• Cells are the smallest units of life
  – Reproduction
  – Metabolism
  – Response to environment
  – ...

• All activity in cells is characterized by molecular interactions
  – Membrane-enclosed molecular machinery
    • No membrane, no cell
  – Sufficiently capable molecular machinery enclosed in a synthetic membrane → artificial cell → artificial life (?)

• No “living” without reproduction

→ Cell cycle
Cell Cycle: The Diagram

Source: http://nobelprize.org/nobel_prizes/medicine/laureates/2001/cellcycle_eng.jpg
Cell Cycle: The Phases

• G1 phase
  – The interval (time gap) between the last mitosis and the start of DNA replication
  – The period is marked by cell growth
    • The demand for nutrients and structural molecules is high
  – The cell readies itself for the future phases of the cell cycle
    • When the cell is large enough
    • The environment is suitable
    • If the cell is marked for proliferation
  – If the cell will not divide further, it enters a dormancy phase called G0 (quiescence)
    • If the cell will never divide again, it enters the G0 senescence phase
Cell Cycle: The Phases

• **S phase:**
  - The time period during which the cell DNA is replicated
    - Doubling of the chromatin content (for diploid organisms, 2n → 4n)
    - Histone proteins and mRNA also synthesized
  - Requires
    - Intact (i.e. undamaged) DNA
    - Sufficient raw materials
    - Functioning molecular machinery
  - Replication errors are to be detected and repaired
Cell Cycle: The Phases

• G2 phase:
  – Following DNA synthesis, the cell readies itself for division
    • The replicated chromosomes are arranged in the proper position for biomechanical separation
    • The cell continues to grow
      – Protein synthesis
      – ...
    – Extensive DNA verification is carried out
      • The cell does not enter mitosis unless all checks are satisfied
Cell Cycle: The Phases

• Mitosis:
  – The process of actual cell division occurs
    • The cell separates into two daughter cells with one copy of DNA each
      – At the end of the S phase, diploid cells have 4n chromosomes
      – After division, each daughter cell ends up with 2n chromosomes
  – The process is carried out in several steps
    • Interphase, prophase, prometaphase, metaphase, anaphase, telophase, ending with cytokinesis
      – The chromosomes condense
      – The nuclear envelop disappears
      – Each chromosome copy is pulled apart towards the opposite poles of the cell
      – An actin protein circumscribing the cell shrinks and divides it into two while nuclear membranes form around the chromosomes gathered at each pole
Regulation of the Cell Cycle

• The cell cycle is an immensely complicated process with many steps that are carried out in synchrony
  – Individual steps must be performed at the right moment
  – This represents the readiness of a step’s inputs and the correct completion of the prerequisites
• In order to ensure the proper operation of all steps, a tight control is exercised
  – Towards the end of G1, the readiness for DNA synthesis is verified at a checkpoint
  – At the end of S, DNA replication errors are detected and corrected
  – Towards the end of G2, the readiness for mitosis is evaluated at another checkpoint
  – If an unrecoverable error occurs anywhere, the cell is aborted
  – Cyclins and cyclin-dependent kinases have been identified as key molecular regulators of the cell cycle
    • 2001 Nobel Prize in Physiology or Medicine jointly to Leland Hartwell, Tim Hunt and Paul Nurse for their discovery
• Regulation means the progression is monitored and the proper actions are carried out by the molecular machinery
  → Massively parallel molecular information gathering and processing system
Biological Information Flow: Cellular Communications

- Cell-to-cell signaling
  - Coordination between cells in a multicellular organism is crucial to its survival
    - Growth and differentiation
      - Embryonic development
    - Metabolic activity
      - Tissues and organs
    - Response to environment
      - Healing of wounds
  - Coordination is achieved through a variety of cellular communication media
    - Cell binding
    - Gap junctions
    - Molecular signaling
  - The basis of all cellular communication is the transfer of signaling molecules between cells
- Presence or absence, activity or inactivity of signaling molecules is information to cells
Cell-to-cell Communications: Cell Binding

- Cell binding is characteristic to multicellular organisms
  - No binding, no macro structures
    - No trees, no animals, no grass, just lumps of undifferentiated cells
- Binding occurs between proteins embedded in cellular membranes
  - Compatible membrane-bound proteins from neighboring cells
  - Binding thus controlled by the expression of membrane proteins
- Cellular recognition is achieved by temporary or permanent binding
  - Epithelial cells stop dividing when the wound is healed
  - Leukocytes separate foreign bodies from the organism’s own cells by the presence or absence of recognition proteins on the membrane
    - Cancer proliferates partly because leukocytes fail to recognize tumor cells as foreign or abnormal
Cell-to-cell Communications: Gap Junctions

- In some cases, neighboring cells form physical channels connecting one’s cytoplasm to the other’s
  - Junctions occur between connexons facing each other
  - The channels can be dynamically controlled
- This allows rapid sharing of small molecules and ions between cells
  - Rapid transmission of cellular signals
  - Effectively couples the cells together causing them to generate identical responses to stimuli
    - Electrical coupling (heart muscle cells)
    - Metabolic coupling (hormonal stimulation of a cell cluster)

Source: http://academic.brooklyn.cuny.edu/biology/bio4fv/page/gap-junctions.html
Cell-to-cell Communications: Extracellular Signaling

• Remote communications among cells is achieved via extracellular signaling molecules
  – Released by signaling cells
  – Detected via membrane receptors by target cells

• Three types of extracellular signaling:
  – Endocrine signaling: The signaling molecules (hormones) are carried to target cells far away from the signaling cells (by blood)
  – Paracrine signaling: Signaling molecules affect target cells in close proximity (neurotransmitters in neuronal synapse)
  – Autocrine signaling: The cell responds to its own signaling molecule (growth factors released by tumor cells)

• Signal transduction: The process of converting extracellular signals into cellular responses
  → Cellular signaling pathways
Cellular Signaling Pathways

- All activity in cells is carried out by biochemical reactions
  - Biochemical reactions have inputs and outputs
  - These reactions are catalyzed or inhibited by specific enzymes
  - The enzymes can be activated or deactivated by adding or removing key groups
    - Phosphate
    - Sugar
- Groups of biochemical reactions are linked by their inputs, outputs, and catalytic enzymes
  - The output of one can act as an enzyme to another
  - One reaction may add a phosphate group to an enzyme altering its activity
  - A triggered reaction may produce a transcription factor that travels to the nucleus and causes the transcription of a specific gene, later translated into a protein that performs a specific function
  - ...
- Sequences of such biochemical reactions linked together through their inputs, outputs, or catalytic enzymes are termed cellular pathways
- These pathways essentially indicate the flow of information across the cell, regulating all cellular activity
  - Responding environmental stimulus
  - Regulating cell metabolism, growth, division, differentiation
  - ...
Example: The MAPK Signaling Pathway

- MAPK: Mitogen-activated protein kinase
- Kinase: enzyme that adds a phosphate group to its substrate
- Stimulus $\rightarrow$ MAPKKK $\rightarrow$ MAPKK $\rightarrow$ MAPK $\rightarrow$ Biological response
  - Stimuli includes growth factors, inflammatory cytokines, mitogens, GPCRs, stress
  - The biological response is often cell division
- Activation of this pathway has been linked to cancer
  - Unregulated cell growth
  - The pathway includes several oncogenes

Source: http://www.sigmaaldrich.com/Area_of_Interest/Life_Science/PathFinder/Pathway_Maps/MAPK_Signaling.html
MAPK SIGNALING PATHWAY

Summary

• Cells carry out all activity by a series of coupled biochemical reactions forming signaling pathways
• Understanding cellular mechanisms is tantamount to identifying the individual molecular components along the associated signaling pathways
• Diseases are characterized by intrusions effected upon “normal” cell function
  – Infectious diseases (host-pathogen interactions)
  – Genetic diseases
  – Cancer
  – …
• Accurately modeling the relevant cellular signaling pathways offers predicting outcomes of interventions with specific targets on the pathways