January 8th: Introduction to the course

ANNOUNCEMENTS

The class consists of three major sections:

1. Biological energetics (metabolism):
    a. Types of energy relevant to cells
    b. Cellular mechanisms for energy uptake from environment
    c. Energy conversion
2. Building a cell:
    a. Use of energy to create internal organization
    b. Determining shape and structure
    c. Building complex behaviour
3. Cell physiology:
    a. Synthesis of parts 1 and 2
    b. Mechanisms behind complex cellular behaviour (ex: cell division, cell death)

Evaluations:

- 6 quizzes – 10%
    - Have to be completed during class hours (open 1 hour)
    - Prof and TAs will be available in class to help during the quiz
- 2 midterms – 25% each
    - Correspond to part 1 and 2 respectively
    - Crib sheets are allowed:
        - Letter, double-sided
        - **Handwritten**
- Final – 40%
    - 25% part 3
    - 15% part 1 and 2
    - You are allowed the crib-sheets for your midterms + an additional crib sheet for part 3

Textbook:

Lodish et al., *Molecular Cell Biology*, 8th Edition

LECTURE

WHY STUDY CELLS?

- Basic unit of life
- Basic unit of medicine
- Basic unit of evolution

ENERGY "CONSUMPTION"

- Do animals consume energy? => No.
    - According to the first law of thermodynamics, energy is neither created nor destroyed and remains constant within a closed system.
    - Energy is either kinetic or potential:

        - Kinetic energy is dynamic energy created by the movement of particles. Relevant kinetic energies are:
            - Thermal energy (heat): kinetic energy of matter particles
            - Radiant energy: kinetic energy of photons/electromagnetic waves
            - Mechanical energy (work): energy due to motion or position. Usually will result in something being pushed, pulled or twisted.
            - Electrical energy: the energy of moving electrons
        - Potential energy is static, stored energy:
            - Chemical potential energy: energy stored in chemical bonds
            - Concentration gradient: stored energy resulting from a difference in concentrations of a particle on either side of a semi-permeable membrane (ex: the Na-K concentration gradients in neurons)
            - Electric potential: stored energy due to a difference in electric charge (the sodium-potassium gradient in neurons is also an example of this)
- Living systems transform energy:
    - Plants transform radiant energy into chemical potential energy (ex: through carbon fixation)
    - Animals convert chemical potential energy into mechanical energy and heat (among other things)
    - Living systems store energy in the form of chemical potential energy:
        - Long-term during growth: forming complex molecular structures to form a body
        - Short-term during ATP synthesis
- Around 20% of genomes are devoted to metabolism

ENERGY CONVERSIONS AND THE SECOND LAW OF THERMODYNAMICS:

- Second law of thermodynamics: All systems tend towards disorder (increase in entropy)
- Living organisms seemingly *organise* matter—what is going on?
    - Not all energy is created equal—living organisms convert high quality, organized energy to low quality, disorganized energy.
        - To prove different energy qualities: Joule's pulley experiment
            - https://www.youtube.com/watch?v=5yOhSIAIPRE
            - A mass is suspended by a string. Dropping the mass results in the rotation of a stick with paddles which agitate water, whose temperature is then recorded.
            - In a closed system, the energy gained by the water is the same as the potential energy lost by the mass.
            - However, heating the water will not lift the mass back up.
                - Different quality of energy:
                    - Mechanical energy is ordered, and the result of all particles in an object moving in the same direction (hence, it is efficient in transferring energy)
                    - Heat is the disordered movement of particles. Since the particles do not move in the same direction, heat cannot be converted into mechanical energy in Joule's experiment. Heat is a low quality form of energy
    - Animals consume high quality energy (chemical potential energy) and release part of it as low-quality energy (heat) => the law of entropy is conserved.
    - The quality of energy depends on how much of the energy is free => next lecture.

January 10th, 2018

ANNOUNCEMENTS

There is a subreddit for the course as well as a Facebook page: /r/BIOL201/

LECTURE

FREE ENERGY AND REACTIONS

- The quality of energy depends on how much of the energy is free, or not used up as heat and disorder
    - Enthalpy/total energy: H
    - Free energy: G
        - $\Delta G = \Delta H - T\Delta S$
            - T is temperature (Kelvins)
            - S is entropy, the measure of disorder in a system
- The change of free energy determines whether a reaction will react spontaneously or not.
    - ΔG = final G – initial G
    - $\Delta G < 0$:
        - There is a net release of free energy
            - EXERGONIC reaction achieved with three scenarios:
                - Reaction is exothermic ($\Delta H<0$) and entropy (S) increases (very favourable)
                - Reaction is endothermic ($\Delta H>0$), but the increase of entropy is larger than the net energy gain of the system
                - Reaction is exothermic enough as to counteract the decrease of entropy
        - Reaction is thermodynamically favourable and will occur spontaneously under the right conditions
    - $\Delta G > 0$:
        - There is a net gain of free energy
            - ENDERGONIC reaction achieved with three scenarios:
                - Reaction is endothermic ($\Delta H>0$) and entropy (S) decreases (very unfavourable)
                - Reaction is endothermic ($\Delta H>0$), and the increase of entropy is insufficient to counterbalance the net energy gain of the system
                - Reaction is not exothermic enough to counteract the decrease of entropy
        - Reaction is not thermodynamically favourable and will not occur spontaneously under normal conditions.
    - $\Delta G = 0$:
        - The system is in equilibrium.
- The standard free energy change in a system is denoted $\Delta G^{0'}$
    - $\Delta G^{0'}$: free energy change at normal conditions:
        - Normal conditions:
            - T = 298 K
            - P = 1 atm
            - pH = 7
            - Concentrations = 1 M
    - $\Delta G^{0'}$ are additive: $\Delta G^{0' A\rightarrow C} = \Delta G^{0' A\rightarrow B} + \Delta G^{0' B\rightarrow C}$

- Releasing free energy in chemical reactions usually require an activation energy to reach a transition state
  - Transition state: state of highest energy in a reaction, **rate-determining factor**.
    - If the reaction is exergonic, the reaction usually proceeds: old bonds are broken to form new, lower energy bonds.
    - If the reaction is endergonic, old bonds are not broken and the reaction usually does not proceed.
  - How do you make it to a transition state? Why do bonds form and fall apart despite transition states?
    - The kinetic energy of molecules in a system is *dynamic* due to the constant collision between molecules
  - Catalysts such as enzymes lower the activation energy required to achieve transition states and therefore increase reaction rates.
    - Achieve this through energy coupling.

ENERGY COUPLING

- Energy coupling is the process of forcing a thermodynamically unfavourable reaction to occur by using the energy released by a thermodynamically favourable reaction.
- Metabolism can be seen as the coupling of anabolic reactions with catabolic reactions
  - Anabolic reactions: thermodynamically unfavourable reactions (endergonic) which build molecules (ex: protein synthesis)
  - Catabolic reactions: thermodynamically favourable reactions (exergonic) which break down molecule (ex: hydrolysis of ATP to ADP)
- Energy coupling is **protein-mediated** and a **mechanical process**

ATP IN METABOLISM

- Cells capture free energy in the form of ATP
  - ATP is produced in photosynthesis (capturing the radiant energy of photons)
  - ATP is produced during glycolysis and cellular respiration (capturing chemical potential energy from breaking bonds and the proton gradient at the electron transport chain)
- Hydrolysis of ATP is an exergonic process which drives many cellular reactions.
  - ATP has a lot of energy in the phospho-anhydride bonds between its phosphates. This is due to the sheer amount of energy required to hold the negatively charged phosphates together.
    - Hydrolysis of the bond between the β and γ phosphate releases 7.3 kcal/mol (a lot of energy)
- ATP can be coupled to reactions in many ways.
- Two examples:
  - We want to make A + B => C + D
    - ATP is hydrolysed and the enzyme transfers the γ phosphate onto one of the reactants:
      - A + ATP => A~Pi + ADP
    - The phosphate (Pi) added to reactant A changes its shape and increases its energy. The reaction with reactant B is now exergonic and thermodynamically favourable:
      - A~Pi + B => C + D +Pi
  - We want to make E + F => G + H
    - ATP binds to the enzyme catalyst, forcing it to change its shape and acquire energy through the subsequent bond strain.
      - Depending on the enzyme, this change occurs either when binding ATP, when ATP hydrolyses, when the phosphate is expulsed, or when the ADP is expulsed.

        - The bond strain in the catalyst can:
            - Force reactants in close proximity to enable a reaction to occur
            - Strain specific bonds in the reactants in order to make them easier to break (and hence lowering the energy that needs to be added to the system to fully break the bonds)
                - Ex: binding of ATP by glycogen phosphorylase torques the enzyme's bound glycogen, breaking it into glucose molecules.
        - Release of ATP resets the protein.

REDOX REACTIONS CREATE THE ATP REQUIRED IN ENERGY COUPLING

- Reminder:
    - Reduction: gain of electrons (since electrons are negative, this consists of a reduction of positive charge)
    - Oxidation: loss of electrons (named because the first observed reactions of this type were reactions where oxygen, which is very electronegative, would strip whatever it was reacting with (ex: metals) of its electrons)
- The molecules in charge in capturing the electrons necessary to produce ATP are:
    - NAD+ and FAD in cellular respiration (reduced to NADH and $FADH_2$)
    - NADP and FAD in photosynthesis (reduced to NADH and $FADH_2$)
- NAD+/NADH is the most important form of electron transport
    - Useful in certain therapies:
        - Ex: Isoniazid in an anti-tuberculosis treatment which binds to bacterial NADH and prevents it from being used as a source of energy in cell-wall synthesis
        - Overproduction of NAD+ inhibits axonal regrowth after injury (Wallerian degeneration)
- FAD/ $FADH_2$ captures electrons when they do not have enough energy to be captured by NAD.
- $\Delta G^{0'}$:
    - For NAD+ capture of electrons: 52.6 kcal/mole
    - For FAD capture of electrons: 43.4 kcal/mole
- Electron-capture is mediated by enzymes:
    - GADPH is the enzyme responsible for holding NAD+ in the proper position for electron capture

EQUILIBRIUM REVIEW

- Equilibrium is:
    - The state at which free energy has been minimized
    - The state at which forward and reverse reactions rates are equal
    - Dynamic
- Reactions rates: (For a reaction aA + bB <=> xX + yY)
    - Forward reaction rate: formation of products depending on how likely it is that reactants will come together and react
        - Determined by k_f, the forward reaction rate:
        - $Rate_{forward} = k_f[A]^a[B]^b$
        - [A] = concentration of reactant A
        - a = number of moles of A
    - Backwards reaction rate: formation of reactants from the products, also called "microscopic reversibility"
        - Determined by k_r, the reverse reaction rate:
        - $Rate_{reverse} = k_r[X]^x[Y]^y$
    - At equilibrium, $k_f[A]^a[B]^b = k_r[X]^x[Y]^y$, and therefore the equilibrium constant is:
        - $K_{eq} = ([X]^x[Y]^y) \div ([A]^a[B]^b) = k_f/kr$

- $\Delta G^{0'}$ can be calculated from initial conditions and the equilibrium constant:

$$\Delta G^{0'} = -RTln(K_{eq})$$
$$\Delta G^{0'} = -RTln\left(\frac{[Products]}{[Reactants]}\right)$$
$$\Delta G^{0'} = -1362log(K_{eq}) \ \left(\frac{cal}{mol}\right)$$
$$\Delta G = \Delta G^{0'} + 1362log\left(\frac{[Products]}{[Reactants]}\right) \ \left(\frac{cal}{mol}\right)$$

Note : concentrations are the initial concentrations, not the final concentrations.

January 12th, 2018

LECTURE

- ATP is often referred to as the "energy currency" of the cell. However, that's not a very descriptive name. The purpose of this lecture is to understand how much the cell can do with the hydrolysis of one ATP molecule.
- Hydrolysis of ATP under normal conditions: $\Delta G^{0'}$=-7.3 kcal/mol

BROWNIAN MOTION AND SIMULTANEOUS MOTION OF MOLECULES IN CELLS (RANDOM KINETIC ENERGY)

- Molecules are always moving and diffusing
- Their movement is due to the transfer of kinetic energy acquired when one molecule runs into another.
- Molecules move and diffuse according to their size and have a diffusion coefficient *D*.
    - Smaller molecules diffuse faster due to less drag and acquiring more speed with kinetic energy
- Molecules take what we call a "random walk"
    - Exactly what it sounds like: at any instance, a molecule has a 50-50 chance to move left or right, a 50-50 chance to mode up or down, and 50-50 chance to move forward or backwards.
    - The result is like a coin toss: the most probable result is that the molecule will have the same amount of left-right, up-down and front-back displacements and end up back where it started (no net movement)

UNDERSTANDING THE MAGNITUDE OF ENERGY RELEASED BY ATP IN THE CELL: SETTING THE BASELINE

- In order to draw comparisons between ATP and other forms of energy, let's compare it to the baseline, which is the amount of random kinetic energy naturally in physiological conditions.
    - We can calculate the energy contained with this formula:

$$E> = 3/2\ k_BT$$

        - k_B = Boltzmann's constant
        - Usually end up using k_BT (which is equal to 0.6 kcal/mol of kinetic energy) as a unit.
        - Therefore, in physiological conditions, we can say that ATP hydrolysis is equivalent to around 20 k_BT.
            - This is ***not*** directly equivalent to $\Delta G^{0'}$, because physiological conditions are not normal conditions (ex: you probably don't have one mole of ATP hanging around)

COMPARING ATP HYDROLYSIS TO OTHER FORMS OF ENERGY

- Mechanical energy
    - Cellular forces
        - The cell applying a force on its surrounding
        - Measured by placing cells on a plastic sheet and measuring how much cells are able to deform the sheet
        - Forces like these are measured in pN to nN (10^{-12} to 10^{-9} Newtons)
            - 1 pN is about the amount of energy the photons from a laser pointer exert when you shine it on something.
        - k_BT → pN*nm = 4.1 pN*nm
        - ATP hydrolysis in pN*nm → around 80 pN*nm.
            - Therefore, ATP hydrolysis is powerful enough to affect mechanical change on cells.
- Electromagnetic energy

- These are electrostatic potentials and the kinetic energies of photons.
  - Kinetic energy of photons (relevant to chloroplasts or bioluminescent organisms)
    - Light photons have an energy of around 2 eV.
    - k_BT → eV = 25 meV
    - Therefore, a photon is around 80 k_BT
      - This is four times as much energy as the energy released during ATP hydrolysis (remember: 20 k_BT)
  - Electrostatic potentials: attraction or repulsion between electric charges, or the amount of energy required to move two charges from infinity to a certain distance from one another
    - Here we will look at moving opposite charges on a protein from 0.3 nm to a bond length (0.15 nm) apart to see if ATP would have enough energy to deform a protein in this way
      - E = 2.3 k_BT
      - Random kinetic energy (1 k_BT) is technically insufficient to provide this energy.
      - ATP hydrolysis has around 10 times more energy than this.
  - Hydrogen bonds (interaction between + and – charges)
    - Energy = 2-12 k_BT
    - Random kinetic energy (1 k_BT) is technically insufficient to provide this energy.
    - ATP hydrolysis has around 2-10 times more energy than this.
- We know that hydrogen bonds and electrostatic bonds are very transient. How then can kinetic energy, which is at least half the energy of these interactions, break them apart (AKA why are hydrogen bonds, for example, not permanent in physiological conditions?)
  - Remember that kinetic energy fluctuates; there is always a likelihood that a molecule will acquire more than 1 k_BT of energy
    - Around 1 in 20 collisions will break a H-bond, and…
      - Probability of breaking a bond is calculated with the following formula:

$$P = e^{-\frac{E}{k_B T}}$$ (where E is the energy in k_BT)

    - Molecules on average undergo 10^{11} collisions per second!

- Chemical energy
  - Covalent bonds have an energy of around 100 k_BT
  - Run that through the probability formula, and you get P = 3.7E-44…
    - Translation: random kinetic energy in cells on average break a covalent bond every 10^{27} years. We need ATP.

CONCLUSION

- ATP hydrolysis has enough energy to drive most processes in the cell without generating too much waste of energy.