Sponsored Research Proposal, 2007-2008
Paul R. McCreary

Creating Undergraduate Research Activities Based on Visual and Nanoscale Molecular Dynamics Software.

Statement of Proposed Activity.

My goal is to develop research-level activities for undergraduates in the interdisciplinary areas of biophysics and biochemistry, combined with computer graphics. Through these activities undergraduates will be introduced to protein complexes and processes that are essential to cellular functions. The primary focus will be to investigate the dynamics of ATP binding in cellular proteins. I will use visual software developed by a research group that has offered to consult with me over the summer of 2008. They have indicated a deep interest in collaborating on undergraduate curriculum development using their software and will be providing access to very high level computational equipment at their site in Urbana, Illinois.

Purpose and Scope of Activity.

The purpose is to produce activities that introduce undergraduates to cellular elements, processes, and general concepts that are essential to the life and health of a cell. The means will be visual and computational software that has been developed to investigate the dynamical structure of proteins. The process will be for undergraduates to create animations that depict recent discoveries and understanding of molecular level activities in the cell. For an individual student, once a few animations are constructed, that student will be equipped to model virtually any molecular reaction described in scientific journals today.

I am proposing to construct example animations and outline a procedure that students could follow to construct animations of their own, learning how to use the software and learning the science embedded in their animations. The visualization and computational software for molecular dynamics on which the activities are based is free, available over the web, and continuously supported. The series of activities that introduce the software use to undergraduates will also prepare the undergraduates for research opportunities.

While working on interdisciplinary science lesson plans last summer (see attached report) I became convinced that research-level activities could be constructed for Evergreen students, in particular, those students on the Tacoma campus. These potential activities would have substantial value for Evergreen students who are planning to become science or mathematics teachers in middle schools or high schools. The recent, ongoing initiative on the Tacoma campus to develop high-quality science course offerings for such students would be supported by the results of this project.

Interdisciplinary Nature of Activity.

The proposed activity would integrate biochemistry, biophysics, and computer graphics for undergraduates. I have extensive background in computer graphics, have been engaged in biochemical work for the past five years, and have been offered assistance during this coming summer by a team of biophysics researchers to develop the proposed curriculum products for this project. This is an ideal state for me: it calls on my past and most recent technical experiences and will open up new understandings in biophysics for my professional development.

Statement of Professional Agenda.

My current research program is to use scientific visualization to connect our Evergreen undergraduates, particularly those planning careers in secondary science and mathematics teaching, with research-level activities in life science. Prior to the hurricane Katrina, I was developing computer graphics tools to investigate biochemical phenomena. I was awarded an NIH grant to embark on this program, which was interrupted by Katrina's arrival. With last year's Evergreen Sponsored Research award, I was able to connect my previous work with undergraduate future teachers through high school science lesson plans (see attached report). Late last summer, an offer to collaborate with the Theoretical Computational Biophysics Group in Urbana, Illinois, allowed me to extend some of those lesson ideas into research-level activities for myself and for undergraduate future teachers. Recognizing the potential value in these activities, I am proposing to extend my efforts from last summer by focusing on research-level activities for future science teachers. This would be a huge step in the development of my current research program and directly benefit the current science initiative of the Tacoma campus.

Benefits Expected Within the College.

All Evergreen students will benefit by having undergraduate research activities to enable their scientific investigations. These activities will be appropriate for individual or small group projects. They will most specifically be designed for students planning to become science teachers in middle or high schools. The activities will be particularly valuable in the context of the Tacoma campus initiative to enrich science offerings for all students and particularly for future teachers. Evergreen students and faculty will benefit by having "starter kits" outlined to assist student and instructor in initiating interdisciplinary research projects in the area of molecular dynamics. These offering will allow almost any sufficiently prepared student to quickly become immersed in investigations of dynamic protein structures. Some of the activities will be designed to serve as general templates on which to construct investigations of the students' own design.

Benefits Expected Beyond the College.

My colleagues in the Theoretical Computational Biophysics Group are optimistic that my proposed project could result in visualization tools useful to research scientists who wish to investigate quantum molecular dynamic properties of protein interactions. Thus, this project could result in tools of substantial use to biophysics research scientists throughout the scientific community. The curricular developments from the project would also be made available on a website for all educational institutions.

Detailed Project Plan. My plan includes three steps.

1. Develop a procedure for creating an animation that undergraduates will be able to follow to carry out their own investigations. To accomplish this, I will create an example animation based on recent published results by members of the Theoretical Computational Biophysics Group (TCBG), with whom I will be collaborating. This result consists of two pathways for ATP hydrolysis described by Dittrich & Schulten in a paper published last year (PcrA Helicase, a Prototype ATP-Driven Molecular Motor. Structure. *14*, 1345-1353, 2006). They carried out extensive simulations to investigate these potential pathways for the hydrolysis reaction and have already created some of the materials needed for such an animation. This initial work will also

result in a general procedure for developing high quality molecular dynamics animations. Besides describing an important ATP hydrolysis, which powers a molecular motor, the discussion in their paper also provides a very clear example of the role of spatial placement and orientation of amino acids in enzymatic proteins. Thus, this first animation will be of general interest to biology and biochemistry instructors and students. This first step in the project will take approximately one week.

2. Explore the possibilities of using this type of animation procedure to guide research in new investigations. I will construct a second animation based on muscle contraction. This allosteric (shape changing) reaction is less familiar to the TCBG members. Thus, we will be embarking on an investigation that is new to all of us. It is here that we may discover new areas for which an animated visual approach could guide the investigations of research scientists. Since our collaboration for this step will be on new grounds for all of us, the estimated time for completion is two weeks.

3. Mine the rich data collections of the TCBG to develop raw material "kits" that can serve as the core of future projects for our undergraduates. I will catalog protein interactions that could serve as bases for future animation investigations. I will gather results from the work of the TCBG members, particularly those involving allosteric reactions. These shape changing reactions will provide raw materials for future descriptive animations. This will require interviewing members of the research group, recording their interpretations of visual and computational data, and archiving the raw data and materials to produce animations that communicate these results. This will result in a wealth of material for future undergraduate research projects. This step will take approximately one week to accomplish. The reactions that I already am aware of include stabilization of LAC repressor attachment, 3-phase ATP synthesis cycle, stalk-base rotation on ATP synthase, and control of aquaporin channels,

Dates and Length of Request and Feasibility of Completion.

The proposed work will take place during July and August of 2008. Much of this time will be spent in the offices of the Theoretical Computational Biophysics Group at the Beckman Institute for Advanced Science and Technology in Urbana, Illinois, who have offered to consult with me about development of curricular activities based on their own molecular dynamics software. My own experience in scientific computer graphics and the deep background of experience in biophysics of the research group make it very likely that the project will be successfully completed.

I am requesting support for four (4) weeks of the summer of 2008. Since it is essential that a good portion of the work take place in Illinois, I am also requesting travel expenses, which would amount to approximately $1000.

Letters of support: Letters of support from Artee Young and Bracey Dangerfield are submitted separately. Letter of support from Klaus Schulten is included in mailing.
Current Curriculum Vita: Attached.

Respectfully,

Paul R. McCreary

The Evergreen State College - Tacoma Campus

October 26, 2007

I am writing in support of the Supported Research Proposal of Paul McCreary. Paul and I collaborated in the *Statistics* course on the Tacoma campus in the winter quarter of 2007 and in *Molecules and Math* in the spring quarter of 2007.

Paul made effective use of animations in the classroom during *Molecules and Math*. Student access to the dynamics of oxygen binding to hemoglobin and to the geometry of muscle structure and contraction was enhanced through the several animations he located and used to demonstrate some of the core principles of the course. Moreover, he demonstrated a very able command of these dimensions of human biology. His expressions were clear and the logical structure of the discussion was laid out well and easy to follow.

Paul has a strong focus on finding a way to integrate animations in the classroom as a learning tool. He has a done a lot of homework into the biochemical knowledge needed to understand, construct, and utilize visual organization. His commitment to this modality lends itself to finding workable ways of improving student concept formation.

As a biochemistry instructor for some ten years, I recognize the importance and the need to develop this method of instruction and support his effort to create new learning possibilities through this medium.

Sincerely,

Bracey Dangerfield
Visiting Faculty, Tacoma campus

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Website: http://www.evergreen.edu/tacoma/

UNIVERSITY OF ILLINOIS
AT URBANA-CHAMPAIGN

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October 10, 2007

To: The Evergreen State College Supported Research Committee

Dear Committee:

Dr. McCreary has had an ongoing connection with our research group over the past several years. We hosted him during his initial period of displacement from New Orleans. During this time he worked with various members of our group as he investigated the structure of ATP-synthase. He made a significant contribution to our software project by developing a plug-in that allows mouse controlled navigation within our visual models of cellular complexes. Last summer we were pleased to have the opportunity to collaborate with Dr. McCreary as he developed resources to offer high school students and his own Evergreen College students. These resources could easily be developed into undergraduate research projects based on the software that we have developed for biophysics research.

We will be pleased to host Dr. McCreary in the summer of 2008, and support his efforts to extend his previous work to investigate the structure of ATP binding sites. This is an active area of research and holds great promise for undergraduate research projects. He will be welcome to make use of our equipment and software. Further, our group members will be available to consult with Dr. McCreary as he pursues his topic with the use of our resources here at the Beckman Institute for Advanced Science and Technology at the University of Illinois at Urbana-Champaign.

With best wishes,

Klaus Schulten
Swanlund Professor of Physics

Report on Summer, 2007
The Evergreen State College Supported Research:

Helping High School Students and Future Teachers Investigate Biochemical Ideas.

Submitted by
Paul R. McCreary
September 3, 2007

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Report on Summer Research: Helping High School Students and Future Teachers to Investigate Biochemical Ideas.

Introduction.

When I first proposed this project of constructing interdisciplinary science lessons for high school students and future high school teachers, I intended for the content to focus on pollutants and the effects on proteins. However, this focus changed when I met with high school students last spring and as I tried out some preliminary ideas with the group. They made it very clear that they could not develop an interest in the interactions with proteins without first gaining an understanding of what proteins are, what they can do, and what their role is in the human body. Thus, the focus of my project became an investigation and introduction of proteins with an emphasis on muscles as an example of complex system made up primarily of proteins. The students also indicated a great interest in sickle cell anemia, so I constructed lessons centered on the hemoglobin protein complex. The focus on sickle cell anemia also offered a wonderful opportunity to consider heredity, evolution, and the mechanisms of transcription and translation from DNA into the resulting proteins.

During the early part of the summer I completed five lesson plans. Later I conducted four classes with a group of high school students who had agreed to help test the lessons. This activity helped me a great deal in refining the plans and organizing the material. Finally a serendipitous invitation to work with a research group in Urbana, Illinois, allowed me to investigate and develop resources for research-level experiences for our undergraduates who are planning to become high school sciences teachers. These research activities center on visualization of dynamical structures of a protein important in energy metabolism of *Escherichia coli* bacteria. The animation products of this work are QuickTime movies that are embedded in the electronic version of this report Appendix D.

The content of the lessons were highly interdisciplinary. Consequently, I sought and received assistance from a number of Evergreen colleagues. In particular I would like to acknowledge Bracey Dangerfield who proofed the lessons on physiology. Clarissa Dirks was very helpful in consulting with general biological issues. Finally, I am greatly indebted to the members of the Theoretical Computational Biophysics Group of research scientists at the Beckman Institute in Urbana, Illinois. In particular, the director, Klaus Schulten was most hospitable in offering me use of his group's software and equipment. He also encouraged his group members to assist me in my investigations. Groups member Barry Isralewitz was particularly helpful and willing to listen to my innumerable questions about biophysical issues and the nuances of their visualization software.

My own teaching experiences have influenced me to construct lessons that take advantage of intensive collaborative learning activities in the classroom. I plan to introduce the lesson plans from this project to Evergreen-Tacoma students during the 2007-8 academic year.

Methods and Materials.

During the early part of the summer, June17-29, I collected and adapted materials to use for classroom lessons. I found illustrations in biology and biochemistry textbooks and animations on the web. The topics of these illustrations and animations were vertebrate skeletal muscles, proteins associated with sickle cell anemia, DNA transcription into RNA, and RNA translation into polypeptides. In addition I compiled a collection of mathematical puzzles and problems that are appropriate for high school students. This was in preparation for sessions to be held with high school students participating in the summer program for the Girls and Boys Math Science and Engineering Club, which is associated with The Evergreen State College-Tacoma campus.

During the month of July, I constructed a series of lesson plans and classroom materials to teach biological and biochemical ideas to high school students. A number of these lesson plans were tried out on a group of high school students participating in the summer program for the Girls and Boys Math Science and Engineering Club.

Students engaged in collaborative science activities during Summer, 2007

Each lesson plan includes some or all of the following: a summary of intended outcomes, a worksheet for students to work on in small groups, suggested activities for the students to engage in, and additional resources for the instructor and/or students to explore. (Appendix B) There are notes about the students' reactions and about what seemed most effective for the lessons presented during the summer. (Appendix C)

During the two weeks of August 10-24, I collaborated with members of the Theoretical and Computational Biophysics Group at the Beckman Institute for Advanced Science and Technology at the University of Illinois at Urbana-Champaign. With their help I investigated the structure and function of a particular protein complex found in *Escherichia coli.* The protein complex is variously referred to as Catabolite gene Activator Protein (CAP) or Cyclic-AMP Receptor Protein (CRP). In particular, I investigated the use of two software applications, Visual Molecular Dynamics (VMD)

and NAnoscale Molecular Dynamics (NAMD) to create interactive visualizations and simulations involving the protein complex. At the end of my stay with the Biophysics Group I made a presentation to their science subgroup on the possibilities of translating some of my results to high school students and high school instructors as either classroom activities or individual/small-group investigations. (Animation products in Appendix D)

In Appendix A there is a list of webpages, each of which has a number of animations for life sciences. From these sources I gathered a number of animations used in the lessons. Following each address is a brief description of the content and comments about my intended use for the animation.

For the class session on skeletal muscles, I scanned illustrations from two texts: The fourth edition of *Biology* by Neil Campbell and the fourth edition of *The World of the Cell* by Bracken, Kleinsmith, and Hardin. Over the summer, I discovered that a large number of science texts are available on line through the ~ governmental agency. This valuable source of life science texts includes all of the original illustrations from the texts and are free to use for lectures and class activities.

The Harvard University-sponsored animation, *The Inner Life of the Cell,* is singular in the exceptional quality of animation, accompanying music score, and attention to scientific detail. It is the result of collaboration between scientists and Harvard University and the animations artists at XVIVO, a scientific animation company near Hartford, CT. The animation artists produced a spectacular video and the scientists assured that the depicted story holds to the most recent scientific understanding of cellular proteomic mechanisms. The result is a stunning account of the current understandings of cellular functions, some of which it is difficult to believe they are not from a science fiction account!

Some of the visualization technology is sufficiently difficult to operate that it would not be recommended for high school students to work with independently. Some advanced students may be able to work up to the more sophisticated software, such as VMD and NAMD, after they have been introduced to basic ideas and become more motivated to extend their own technical skills. It can be used by more experienced students and instructors to produce illustrations and movies. However, it seems to me that such software has too high a learning curve to introduce to beginners. On the other hand, Quick-Time movies on the web are easy to use and can be very instructive. Further, there are enough of these ready-made animations that student may be able to find interesting examples searching on their own or in small groups. Such web searches could be useful, interesting activities for individuals and small groups.

The following are descriptions of the VMD/NAMD software.

VMD is designed for the visualization and analysis of biological systems such as proteins, nucleic acids, lipid bilayer assemblies, etc. It may be used to view more general molecules, as VMD can read standard Protein Data Bank (PDB) files and display the contained structure. VMD provides a wide variety of methods for rendering and coloring a molecule: simple points and lines, CPK spheres and cylinders, licorice bonds, backbone

tubes and ribbons, cartoon drawings, and others. VMD can be used to animate and analyze the trajectory of a molecular dynamics (MD) simulation. In particular, VMD can act as a graphical front end for an external MD program by displaying and animating a molecule undergoing simulation on a remote computer. (from VMD website)

NAMD is a parallel molecular dynamics code designed for high-performance simulation of large biomolecular systems. Based on Charm++ parallel objects, NAMD scales to hundreds of processors on high-end parallel platforms and tens of processors on commodity clusters using gigabit ethernet. NAMD uses the popular molecular graphics program VMD for simulation setup and trajectory analysis, but is also file-compatible with AMBER, CHARMM, and X-PLOR. NAMD is distributed free of charge with source code. You can build NAMD yourself or download binaries for a wide variety of platforms. Our tutorials show you how to use NAMD and VMD for biomolecular modeling. (from NAMD website)

The great advantages are that these software packages are available at no cost and supported for most operating systems, including Windows, Mac-OSX, Linux, Sgi-IRIX, and Sun-SOLARIS. The graphics are very good and many of the simulations can be carried out on desktop machines even though the more advanced simulations require super computing facilities. One significant advantage of the software is that if one gains access to more high-powered computation equipment, the software is the same, so one is not required to learn a new system. Further, there are numerous accessories or plug-ins that can be added. Advanced users can modify these accessories or even write new ones for specific investigations. For instance, I wanted to be able to navigate around a molecule in a more intuitive manner, so I was allowed to install a system that controls the scene motions by mouse maneuvers as in some 3D video games. The software technicians in charge of developing the VMD software were very helpful throughout.

Results and Discussion.

Each lesson plan lists what students will learn, in what activities students will engage, presents comments about potential difficulties or adaptations that may be required, and lists additional resources available for further work. Lessons 1a and 1b are intended to give students experience at collaborative classroom activities. I have found that it is often advisable to provide an introduction to the process of group work and collaboration prior to beginning work on the content that is considered crucial for the course. Becoming accustomed to the collaborative process can be distracting from the content. If the content is such that the subsequent material does *not* depend on it, that releases some of the pressure during the initial few sessions, as students become acquainted with each other and with group-work processes. Investing a few of the early class sessions to allow student to adjust the process will provide benefits later in the course. If, as an instructor, one does not feel there is enough time to spend on non-core content, an instructor should at least be aware that students may need to revisit the early material because of the distracting nature of the early class sessions for student inexperienced with collaborative group work. Embedded in each worksheet are the web addresses of web animations that student are to view and discuss in groups. It is most convenient to have

electronic copies of the worksheets on computers in a lab for student groups to use during class sessions.

Description of Lessons.

Lessons 1a and 1b.

Goals/intentions. The primary goal for the first two lessons, 1a and 1b, is for students to gain experience in working collaboratively on mathematical and science questions. These lessons also provide instructors opportunities to observe and facilitate group work for their students. There are a number of problems on the worksheets for these lessons that, if the appropriate approach is taken, are quite straightforward. On the other hand, if a student does not identify a useful approach, the problems can be quite confounding. This situation sets up opportunities for students, who are not normally the fastest, to make more headway than their peers. This puts them in the position, unusual for them, of providing assistance to their classmates. These can be uplifting and motivating experiences for the individuals and can be cultivated and facilitated by the observant instructor. The instructor should also be aware and be sensitive to the potential frustration that some students may feel when engaging in activities that are not familiar to them. Students who have experienced success in so-called traditional classroom settings may balk at trying new activities. Thus, the instructor should make clear the reasons for introducing collaborative activities and the potential gain for students. Otherwise some students may feel betrayed by a "change of rules" for their academic performance and evaluation. There will be some problems on each worksheet so challenging that the best students feel themselves stretched beyond their usual limits. There should be too many problems to finish in a single session. This conveys the message that no one is ever done with the class work. It should also be clear that it is *not* required for the remaining unfinished problems to be completed outside of class. The worksheet problems are designed to provide an enriched context in which students can stretch themselves with challenges sufficiently great that there is good reason to collaborate.

Lesson 1a.

Introduction/summary: This first lesson contains a series of interesting puzzles and problems. The intent is to give problems interesting enough to engage the students and challenging enough to encourage collaboration. The collaboration should be encouraged among individuals in small groups and between the groups as well. The more interactive the students are the better. In fact, one can safely take the stance that it does not matter if any content is mastered in this first lesson, as long as the students gain experience in collaborating and sharing ideas. The problems on the worksheet range for moderately easy to very difficult. Students can be encouraged to skip around. If the instructor keeps track of which students engage on which problems, then students can more easily be directed towards each other when questions arise or when it comes time to compare answers. As is often the case with collaborative worksheets, the list of problems is extensive enough so that no student or group will completely finish all problems before the session ends.

Lesson 1b.

This lesson is, in some sense, a continuation of the preceding lesson. It could be conducted during the immediately subsequent class session or it could be held until a later session. Its primary purpose is to provide further opportunities for students to interact in collaboration and in discussions. Unlike many of the mathematical problems puzzles of the preceding lesson, those for this lesson are more open ended, have several possible correct solutions, depending on logic and cleverness rather than mathematical or computational techniques.

Lesson 2.

The topic of lesson 2 is transcription of DNA to RNA and the translation of RNA to polypeptides. To introduce the ideas, students are asked to determine how many possible strings of various lengths could be constructed using various sizes of symbol collections ("alphabets"). The ultimate realization is that codons of length two from a four-letter "alphabet" yield 16 distinct strings while codons of length three from the same alphabet yield 64 distinct strings. This answers the question of why protein producing mechanisms in all cells use codons of length three to code for the 20 different amino acids used by most cells. It turns out that these lead-up activities took most of one session with the summer high school students. Thus the follow-up activities were pursued in the following session. These activities were geared to show examples of transcription from DNA to RNA, and translation from RNA into polypeptide strings. One web site offered an interactive "game" with students entering each nucleotide in a transcription and then choosing the correct amino acid residues in translating the resulting RNA string into a polypeptide string.

Lesson 3.

The topic of lesson three is the mechanics of the skeletal muscle system. This is a way to look closer at the mechanisms of a particular set of proteins that, in some sense, are very familiar to everyone. We look at the way that the system is comprised of parallel units of increasingly smaller fibers with the smallest unit being the sarcomere containing (interlaced) actin and myosin fibers. We view animations that depict the mechanism of the myosin heads moving along the actin fibers. The myosin fibers are intertwined with each other. Double strands of fibrous actin have strands of Tropomyosin coiled around it. These two types of fibrous units are interspersed in a honey comb arrangment so that they can easily interact with each other. The Tropomyosin fiber is regulated by the Troponin complexes which alternately cover and uncover the sites at which the myosin heads can bind to the actin fibers, the necessary step which allows the myosin fiber to move in relation to the actin fibers and which ultimately leads to the muscle contraction. We see the role that ATP plays in priming the Myosin head to take its power stroke and move along the actin fiber.

Lesson 4.

The principal topic of this lesson is the mechanics of the mutation that leads to sickle cell anemia. This provides an application of transcription and translation. It also introduces aspects of protein-protein interaction. Small changes can lead to dramatically large-scale transformations. A single nucleotide mutation in the second of the three nucleotides in the codon for glutamic acid (Glu) leads to a codon for valene (Val). Further, the single change of an amino acid from glutamic acid, which is hydrophilic, to valene, which is hydrophobic, is not enough to disrupt the function of the protein. However the exposed hydrophobic amino acid presents a "sticky" spot that causes hemoglobin complexes to adhere and form well defined and relatively stable fibers. These fibers cause the cell to extend and bend into the representative shape. The process causes the red blood cells to "wear out" faster than they can be replaced, thus causing anemia, the lack of sufficient red blood cells. The extended red blood cells also block the small blood vessels, causing oxygen derivation in affected cells and intense pain.

Sickle cell trait is having one of the two chromosomes with this mutation. The evolutionary significance of this mutation is that this sickle cell *trait* affords an individual an enhanced resistance to malaria microbes. The mechanism of this disease resistance is not currently known. However, when both chromosomes have the sickle cell mutation, then sickle cell anemia results and the likelihood of survival past childhood is slim. Thus, no mutation leaves the individual vulnerable to malaria, mutation inherited from just one parent leaves the individual with some symptoms of sickle cell anemia, but with a substantially greater chance of surviving a childhood case of malaria. Mutations inherited from both parents result in the sickle cell disease and the likelihood of death in childhood.

This lesson provides a context to discuss the secondary, tertiary, and quaternary structure of globular proteins. There is an opportunity to compare the fibration of the hemoglobin complexes with the transformation of the globular actin protein into fibrous actin.

Appendix A: Descriptions of Web Animations and Additional Web Sources.

Animations.

http://www.biocourse.com/mhhe/bcc/resources/concept.xsp?id=000012181&type=MOVIE (bioCourse RNA translation: protein synthesis movie) short: very good
Format: QuickTime.
Load time: 1-2 minutes.
Run time: 2 minutes
Begins audio and video as soon as loaded.
Content: "Translation is the process by which the information contained in messenger RNA…"
mRNA, ribosome subunits (reasonably correct shapes), tRNA, start codon, P/A sites, translocation, release factor.

http://vcell.ndsu.nodak.edu/animations/translation/movie.htm (North Dakota State protein synthesis) longer: excellent!
Format: Embedded Windows Media.
Load time: immediate.
Run time: 4 minutes
Begins audio and video as soon as loaded.
Content: Introduces all "players" in the process. Shapes for components are correct.
Initiation, elongation, termination, eucariotic RNA: poly-A tail, codons, methylated cap, large ribosome subunit, fast elongation.

http://telstar.ote.cmu.edu/Hughes/HughesArchive/tutorial/polypeptide/tutorial.swf
(carnagie-mellon protein synthesis) advanced-very good
Format: interactive slide show. Comes up in new window
Load time: immediate.
Run time: 8-15 minutes depending on how much text is read.
Must click on "play" button to start.
Content: Very detailed. Many slides have extensive text, some are silent to allow reading of text, others have animations and narration, note that a few slides have an "echo" glitch in the narration.
Folding of tRNA into tertiary structure, ribosome structure, simplified animations plus pictures of pdb file structures.

http://learn.genetics.utah.edu/units/basics/transcribe/ (You do it transcription and translation) pretty good
Format: interactive "game".
Load time: immediate.
Run time: about 7 minutes once "rules" are mastered.
"click here to begin" button to start.
Content: Directions are in text below graphics. Incorrect matches produce hints in text. Correct matches produce a squeaky sound. Once construction of RNA strand is complete, student must identify start codon. Then, amino acid icons from table on screen

are dragged to codons until stop codon is reached. Process can be repeated any number of times. Note that each time a correct amino acid match is made, a chemically correct graphic is displayed on the polypeptide string.

Summary:

Transcription: DNA is "read" by RNA polymerase (-ase ending means "maker" or producer), which produces the RNA "copies" of the DNA code. Where ever there is a T on the DNA strand, that T is transcribed as a U on the RNA strand. So, if the DNA strand is GTTACGTAA, the RNA strand that is produced is GUUACGUAA. This process is called *transcription.*

Translation: The RNA strand is passed out of the nucleus and is processed by a very large object called a ribosome. There is a hole in the ribosome through which the RNA passes and depressions that hold the amino acid carriers. The amino acids are fused together to make a chain, which when folded makes a functional protein.

http://www.xvivo.net/press/harvard_university.htm
The Inner Life of the Cell.
Format: QuickTime (Adobe Flash?).
Load time: immediate.
Run time: 3 minutes 07 seconds.
XVIVO webpage comes up with "Click here to play" spot.
Content: Fantastic animations and music score. No narration.
:20 fibers for "walking".
:51 actin fibration.
1:12 tubule disassociation.
1:20 walking the pipet.
1:46 ribosome – protein translation.
2:04 ribosome – depositing protein products into sac.
2:21 reticulum compartment breaking off – then erupting.
2:36 membrane-attached proteins "reaching out".
2:56 white blood cell seeping between blood vessel wall cells.

http://www.dnai.org/text/mediashowcase/index2.html?id=609 (Very Good!)
Format: web animation (Media Showcase?)
Load time: almost immediate.
Run time: 1.5 minutes.
Begins audio and video immediately. No controls. Automatic repeats.
Content: hemoglobin: single nucleotide change->single amino acid change-> glombing hemoglobin into rods-> sickle shape-> red blood cells die off early and result in anemia.

Muscles.

http://www.sci.sdsu.edu/movies/actin_myosin_gif.html the players

Format: GIF animation or Quicktime; stand alone also available.
Load time: immediate.
Run time: automatic repeat of 2 second cycle.
Video only.
Content: power stroke of Myosin head against actin. Roles of calcium, ATP, Troponin, magnesium, and Tropomyosin

http://www.sciencemag.org/feature/data/1049155s1.mov globular protein
Format: QuickTime.
Load time: immediate. Video only.
Run time: 15 seconds.
Automatic beginning with QuickTime controls for stop/start/repeat.
Content: Two power strokes of myosin head against actin filament. ATP embedding, Phosphorus and ADP discharge.

http://www.blackwellpublishing.com/matthews/myosin.html calcium's role
Format: Two webpages. Some of text off screen. Must scroll some.
Load time: immediate. Video only.
Run time: Short animation segments on each page.
Click "Next" button to proceed.
Content: Nerve signal releases calcium from sarcoplasmic reticulum. Presence of calcium uncovers binding sites for myosin heads and the thick fiber crawl along the thin fiber. Click on arrow to evacuate calcium and binding sites are covered so myosin heads cannot bind and the two fibers do not move relative to each other.

Second Lecture Hemoglobin.

http://www.dnai.org/text/mediashowcase/index2.html?id=572 (hemoglobin polymerizing. Short(45 sec?). Indicates the replacement of single amino acid, which leads to polymerization.)
Format: Media Showcase.
Load time: immediate. Video only.
Run time: One minute.
Automatic begin and repeat.
Content: hemoglobin molecules bouncing against each other, but not binding. Bright, glowing oxygen? Attached. => oxygen released, valene amino acid highlighted in green, fibration occurs.

http://www3.interscience.wiley.com:8100/legacy/college/boyer/0471661791/structure/HbMb/hbmb.htm (begins with space filling of myocin. Animation choice leads to run through of alpha chains. Second animation colors by polar/nonpolar and then shows cross sections: nonpolar are mostly internal. Hemoglobin: first animation rotates tetramer in space filling, second animation "dissolves" space filling to helices, alpha/beta choices show helix structures of the two units, next animation shows heme unit build in sticks and then puff up to space filling, next animation slides heme into stick of alph/beta unit and

surrounds with binding amino acids, next two animations show interacting histidines interacting with iron and O2, binding oxygen, alpha helices)
Format: Jmol. Can rotate visual with mouse.
Load time: Few seconds. Video only.
Run time: One minute for each.
"View Animation" button for each.
Content: Short animations. display structure of myoglobin and hemoglobin molecules:
Myoglobin: 1) alpha helices of myoglobin; 2) hydrophobic/philic composition with cross section viewing
Hemoglobin: 1) tetramer with heme ligands; 2) alpha helices of four subunits; alpha and beta units; 3) Heme structure; 4) Heme binding site; 5) Proximal histidine; 6) Distal histidine and oxygen; 6) Allosteric change between oxy- and deoxy-hemoglobin; 7) BPG binding affecting oxygen binding;
Two follow up questions: 1) identify proximal and distal His in 3D image of all His. 2) Nature of side chains holding BPG in place. Answers available.

http://highered.mcgraw-hill.com/sites/0072495855/student_view0/chapter21/animation__hemoglobin_breakdown.html animation of recycling of red blood cells) From Chapter 21 of Human Anatomy.
Format: McGraw-Hill animation.
Load time: Few seconds. Video and audio.
Run time: 1.5 minute.
Control buttons at bottom of video screen.
Content: recycling hemoglobin: Macrophage, bilirubin.

http://accad.osu.edu/~vberezin/ibp/hemoglobin2.htm (animation of blood circulation and release of oxygen from hemoglobin – only so-so)
Format: web animation.
Load time: immediate. Video only. Very coarse quality
Run time: 30 seconds.
"Play" button.
Content: Animation of blood circulation and release of oxygen from hemoglobin.

http://accad.osu.edu/~vberezin/ibp/hemoglobe3.mov (hemoglobin movie. release of oxygen - short)
Format: web animation.
Load time: immediate. Video and audio.
Run time: 10 seconds.
Automatic start. Pause and replay controls at bottom of video screen.
Content: Short animation of release of oxygen from and attachment of carbon dioxide to hemoglobin.

http://accad.osu.edu/~vberezin/ibp/vita_cell320.mov (blood cell carrying hemoglobin, which releases oxygen – not so clear)
Format: web animation.

Load time: immediate. Video only.
Run time: 15 seconds.
Automatic start. Pause and replay controls at bottom of video screen.
Content: Short animation of release of oxygen from attachment of carbon dioxide to hemoglobin (same as above only in context of capillaries and body cells).

http://misterguch.brinkster.net/eqnbalance.html (balancing equations)
Text only

Additional sources
http://science.nhmccd.edu/biol/ap2int.htm#blood
source page for numerous animations including
Hemostasis: complicated cascading processes resulting in blood clots to plug tears in blood vessels.
Blood tutorials: interactive tutorials.
Many more of mixed content and quality.

http://bio.lundberg.gu.se/edu/view.html (hemoglobin change of structure movies)

http://www.medtropolis.com/VBody.asp interactive animations

http://gingi.uchicago.edu/hbs3.html Sickle cell anemia. Choices of slow, medium, and fast versions, depending on your machine's speed of connection to the web.

Appendix B: Worksheets.

Worksheet 1a. Part I. Some interesting problems.

1. How much do you get when you add all the integers from 1 through 9?
2. Arrange the integers 1 through 9 in a tic-tac-toe box so that all rows add up to the same number. What will that number be?
3. Arrange the integers 1 through 9 in a tic-tac-toe box so that all columns add up to the same number. What will that number be?
4. Do you know of an easy way to add all the numbers between 1 and 100?
5. Choose four consecutive odd counting numbers. Take the product of the middle two numbers and subtract the product of the first number and the last number. Try a few samples and formulate a rule.
6. What would happen if you used four consecutive even counting numbers in the above problem? Would your rule change? If so, find a new rule, and explain why this new rule works and why it is different from the original rule. If the rule does not change, does your explanation change?
7. What would happen if you used four consecutive counting numbers in the above problem? Would your rule change? If so, find a new rule, and explain why this new rule works and why it is different from the original rule. If the rule does not change, does your explanation change?
8. Find three whole numbers, a, b and c, which will make this fraction a whole number:

$$\frac{bc + ac + ab}{a + b + c}$$

   Can you find a method which will give many such solutions? Explain why your method works.
9. A professional bass fisherman caught 385 bass during a 14-day tournament. Each day he caught three more fish than he did the day before. How many fish did the fisherman catch on each individual day?
10. pascal's patterns

1

1 1

1 2 1

1 3 3 1

1 4 6 4 1

1 5 10 10 5 1

1 6 15 20 15 6 1

1 7 21 35 35 21 7 1

1 8 28 56 70 56 28 8 1

What is the sum of each row? Find a way to describe the pattern of sums by comparing each row's sum to the corresponding row number.

11. Draw nine dots on a sheet of paper so that they lie in a 3x3 square. Try to connect all nine dots with as few straight lines as possible.
12. Two elevators leave the nth floor at 2:00 P.M. The faster elevator takes one minute to travel between floors and the slower elevator takes two minutes to travel between floors. The first elevator to reach a floor must stop for three minutes to take on passengers. If both elevators arrive at a floor at the exact same time, they become confused and do not stop for passengers.

    If the final stop for an elevator is the lobby (1st floor), then describe n if the faster elevator arrives at the lobby first. Describe n if the slower elevator arrives at the lobby first.
13. Hypatia was an Egyptian female mathematician born in A.D. 370. One problem she posed was the following:

    Find a number that is the sum of two squares and whose square is also the sum of two squares.

    Can you solve Hypatia's problem? Are there more solutions? Is there a pattern between any pair of solutions? Justify your answers.
14. Hansel has goldfish that quadruple, or become four times as many, every month. Gretel has goldfish that increase by 20 every month. Right now, Hansel has 4 goldfish and Gretel has 128 goldfish. In how many months will they have the same number of goldfish? Show how you arrived at your answer.
15. The numbers 3 and 6 are consecutive triangular numbers. Their sum is 9, which is a square number. Find some other pairs of triangular numbers whose sum is a square number. Draw a picture to illustrate any pattern you observe.
16. Does a natural number n exist such that 1+2+3+4+...+n is a three-digit number with identical digits?
17. “Guess my rule” game.
18. Monty Hall game.
19. Cut a 40 pound block into four pieces so that those four pieces can be used to balance any (integer) weight from one through 40. Note that you may put any of the pieces on *either* side of the balancing scale.
20. Odds of flipping more heads with two coins compared to flipping one coin.
21. Cut a 23 link chain into pieces so that the different pieces can be arranged together so that a pile can be made of any number of links 1 through 23. Do this making as few cuts as possible.

Part II. Careful of your assumptions!

1. One night my uncle was reading an exciting book when his wife turned out the light. Even though the room was pitch dark, he went right on reading. How could he do that?
2. Osgood Farkle of Podunk County has married twenty different women from the same town. All are still living and he never divorced any of them. Yet he broke no law. Can you explain?
3. "This parrot will repeat any word it hears," said the pet shop owner. A lady bought the bird but brought it back a week later complaining that the bird had not yet spoken a single word. Yet the salesperson had told the truth. Explain.
4. A man and his son were in a car accident. The father was killed, the son critically injured. The son arrives at the hospital and is wheeled immediately into surgery. The surgeon declares, "I cannot operate on this boy; he is my son." How is this possible?
5. A doctor, a lawyer, and an engineer were in a house. A policeman walking by heard, "Oh no, John, don't!" and then a shot. The policeman went into the and saw a dead woman and a gun lying on the floor. He turned to the lawyer and said, "You are under arrest." How did the policeman know?
6. You earn $20 per day. How much will you earn in a month? What assumptions are you making in this situation?

Part III. Recycling.

The approximate garbage produced by each person in the United States is as follows.

a) over 3 lb. each day
b) 96 lb. each month
c) 1,168 lbs. each year

Use the information show above to answer the following questions.

1. In one year, if you recycle 278 pounds of garbage, how much of your garbage would be left that was not recycled?
2. How many people are in your family? How much garbage will be produced by your family each month? Each year?
3. Approximately, how many pounds of garbage have you produced in your life?
4. There are 2000 pound in one ton. Approximately how many tons of garbage have you produced in your life?
5. Estimate the amount of garbage produced by all the students in this room during their lifetimes.

Worksheet 1b.

Part I.

1. Cut a 40 pound block into four pieces so that those four pieces can be used to balance any (integer) weight from one through 40. Note that you may put any of the pieces on *either* side of the balancing scale.
2. Arrange the integers 1 through 9 in a tic-tac-toe box so that all rows, all columns and all diagonals add up to the same number.
3. Monty Hall game.
4. Odds of flipping more heads with two coins compared to flipping one coin.
5. Cut a 23 link chain into pieces so that the different pieces can be arranged together so that a pile can be made of any number of links 1 through 23. Do this making as few cuts as possible.

Part II. Careful of your assumptions!

7. One night my uncle was reading an exciting book when his wife turned ou the light. Even though the room was pitch dark, he went right on reading. How could he do that?
8. Osgood Farkle of Podunk County has married twenty different women from the same town. All are still living and he never divorced any of them. Yet he broke no law. Can you explain?
9. "This parrot will repeat any word it hears," said the pet shop owner. A lady bought the bird but brought it back a week later complaining that the bird had not yet spoken a single word. Yet the salesperson had told the truth. Explain.
10. A man and his son were in a car accident. The father was killed, the son critically injured. The son arrives at the hospital and is wheeled immediately into surgery. The surgeon declares, "I cannot operate on this boy; he is my son." How is this possible?
11. A doctor, a lawyer, and an engineer were in a house. A policeman walking by heard, "Oh no, John, don't!" and then a shot. The policeman went into the and saw a dead woman and a gun lying on the floor. He turned to the lawyer and said, "You are under arrest." How did the policeman know?
12. You earn $20 per day. How much will you earn in a month? What assumptions are you making in this situation?

Part III. Recycling.

The approximate garbage produced by each person in the United States is as follows.

d) over 3 lb. each day
e) 96 lb. each month
f) 1,168 lbs. each year

Use the information show above to answer the following questions.

1. In one year, if you recycle 278 pounds of garbage, how much of your garbage would be left that was not recycled?

2. How many people are in your family? How much garbage will be produced by your family each month? Each year?
3. Approximately, how many pounds of garbage have you produced in your life?
4. There are 2000 pound in one ton. Approximately how many tons of garbage have you produced in your life?
5. Estimate the amount of garbage produced by all the students in this room during their lifetimes.

Worksheet 2: DNA transcription into RNA and translation into polypeptides.
Summer Girls and Boys Science, Math, and Engineering Programs.
Math/Science Session II, July 20, 2007.

Theme: How do genes tell protein factories in the cell how to make hemoglobin?

Counting chains of symbols.

1. Two symbols. Use the two symbols 0 and 1.

    a. How many different 2-symbol sets can be made from two symbols? (Repeated symbols are allowed.)

    # of 2-sets_____

    b. What about 3-symbol sets?
    Some of them: 111, 110, 000…

    # of 3-sets_____

    c. What about 4-symbol sets?
    Some of them: 1111, 1110, 1000…

    # of 4-sets_____

2. Three symbols. Use any three letters as your symbols.

    Will the number of sets change depending on which letters you use?

    a. How many different 2-symbol sets can be made from the three symbols? (Repeated symbols are allowed.)

    # of 2-sets_____

    b. What about 3-symbol sets?

# of 3-sets_____

c. What about 4-symbol sets?

# of 4-sets_____

3. Four symbols. Use the letters G,C, A, and U. For problems 1 and 2, did you use a pattern to keep track of the different sets that you found? You will definitely need a pattern to keep track of the different sets we get using four symbols!

   a. How many different 2-symbol sets can be made from the four symbols? (Repeated symbols are allowed.)

   Using the four letters GCAU, we can start the list as

   GG, GC, GA, GU
   CG, CC, CA, CU
   …etc.

   The total number of different 2-sets is_____.

   b. What about 3-symbol sets made from the four symbols?

# of 3-sets_____

c. What about 4-symbol sets made from the four symbols?

# of 4-sets_____

4. Do you know how many different protein building blocks (amino acids) are there? How many amino acids are used by the human body? Do you know how to look for the answer on the web?

5. If RNA, with 4 possible letters, "wants" to represent all possible building blocks for proteins, what must be the length of segments of RNA that do the representing? (These segments are called codons.)

http://www.biocourse.com/mhhe/bcc/resources/concept.xsp?id=000012181&type=MOVIE (bioCourse RNA translation: protein synthesis movie) short: very good

http://vcell.ndsu.nodak.edu/animations/translation/movie.htm (North Dakota State protein synthesis) longer: excellent!

http://telstar.ote.cmu.edu/Hughes/HughesArchive/tutorial/polypeptide/tutorial.swf (carnagie-mellon protein synthesis) advanced-very good

6. DNA strands are *transcribed* into RNA strands, with everything copied, except that T's are changed into U's. So the four letters for DNA are GCAT, while for RNA it is GCAU.

7. What is the machinery that cells use to *translate* RNA tapes of codons into strings of protein "pearls" (polypeptides)?
    a. Ribosomes. (big pieces that have cavities to hold the amino acid carriers)

    b. Transfer RNA (amino acid carriers)

http://learn.genetics.utah.edu/units/basics/transcribe/ (You do it transcription and translation) pretty good

http://www.xvivo.net/press/harvard_university.htm

8. What are the number of different 3-letter sets that can be made from four letters (repeated letters are allowed)? Using the same three letters, we can start the list by writing all of the two-letter sets and adding on a G at the end, then repeating the same list of two-letter sets only this second time adding a C to all of the sets, and so on…

    Or we could make a grid like one of the following, which show two different ways to organize the different three-letter sets.

CODON TABLE

First Position & Second Position	Third Position: A	C	G	U
AA	Lys	Asn	Lys	Asn
AC	Thr	Thr	Thr	Thr
AG	Arg	Ser	Arg	Ser
AU	Ile	Ile	MET	Ile
CA	Gln	His	Gln	His
CC	Pro	Pro	Pro	Pro
CG	Arg	Arg	Arg	Arg
CU	Leu	Leu	Leu	Leu
GA	Glu	Asp	Glu	Asp
GC	Ala	Ala	Ala	Ala
GG	Gly	Gly	Gly	Gly
GU	Val	Val	Val	Val
UA	Z	Tyr	Z	Tyr
UC	Ser	Ser	Ser	Ser
UG	Z	Cys	Trp	Cys
UU	Leu	Phe	Leu	Phe

Z = STOP CODON

Table 1 : Codon table. This table illustrates the 64 possible codon triplets.

		2nd base			
		U	**C**	**A**	**G**
1st base	**U**	UUU Phenylalanine	UCU Serine	UAU Tyrosine	UGU Cysteine
		UUC Phenylalanine	UCC Serine	UAC Tyrosine	UGC Cysteine
		UUA Leucine	UCA Serine	UAA Ochre *Stop*	UGA Opal *Stop*
		UUG Leucine	UCG Serine	UAG Amber *Stop*	UGG Tryptophan
	C	CUU Leucine	CCU Proline	CAU Histidine	CGU Arginine
		CUC Leucine	CCC Proline	CAC Histidine	CGC Arginine
		CUA Leucine	CCA Proline	CAA Glutamine	CGA Arginine
		CUG Leucine	CCG Proline	CAG Glutamine	CGG Arginine
	A	AUU Isoleucine	ACU Threonine	AAU Asparagine	AGU Serine
		AUC Isoleucine	ACC Threonine	AAC Asparagine	AGC Serine
		AUA Isoleucine	ACA Threonine	AAA Lysine	AGA Arginine
		[1]AUG Methionine	ACG Threonine	AAG Lysine	AGG Arginine
	G	GUU Valine	GCU Alanine	GAU Aspartic acid	GGU Glycine
		GUC Valine	GCC Alanine	GAC Aspartic acid	GGC Glycine
		GUA Valine	GCA Alanine	GAA Glutamic acid	GGA Glycine
		GUG Valine	GCG Alanine	GAG Glutamic acid	GGG Glycine

http://learn.genetics.utah.edu/units/basics/transcribe/ (You do it transcription and translation) pretty good

Summary:

Transcription: DNA is “read” by RNA polymerase (-ase ending means “maker” or producer), which produces the RNA “copies” of the DNA code. Where ever there is a T on the DNA strand, that T is transcribed as a U on the RNA strand. So, if the DNA strand is GTTACGTAA, the RNA strand that is produced is GUUACGUAA. This process is called *transcription.*

Translation: The RNA strand is passed out of the nucleus and is processed by a very large object called a ribosome. There is a hole in the ribosome through which the RNA passes and depressions that hold the amino acid carriers. The amino acids are fused together to make a chain, which when folded makes a functional protein.

Worksheet 3: Muscle contraction.

Structure and Function of Vertebrate Skeletal Muscle
Molecules and Math: Form and Function in Human Biology

1. What is a muscle made of?
2. How does a muscle do its work (contract)?
3. How is the muscle turned on and off again?
4. Where does the muscle's energy come from?
5. How does a muscle work with different intensities?

Note: On the following pages, if the illustrations are too small to see well, you can copy them, paste them at the end of the page, and enlarge their size any amount.

1. A muscle is

   a. Characterized by a hierarchy of smaller and smaller parallel units.

   b. Bundle of long fibers running the length of the muscle.

   c. Each fiber is a single cell with many nuclei (formed by the fusion of many embryonic cells) and is itself a bundle of smaller myofibrils.

Myofibrils are composed of two kinds of myofilaments.

Thin filaments: two strands of actin and strands of regulatory proteins.

Thick filaments: staggered arrays of myosin molecules.

Skeletal muscles also called *striated* muscle; regular arrangement of myofilaments creates a repeating patter of light and dark bands.

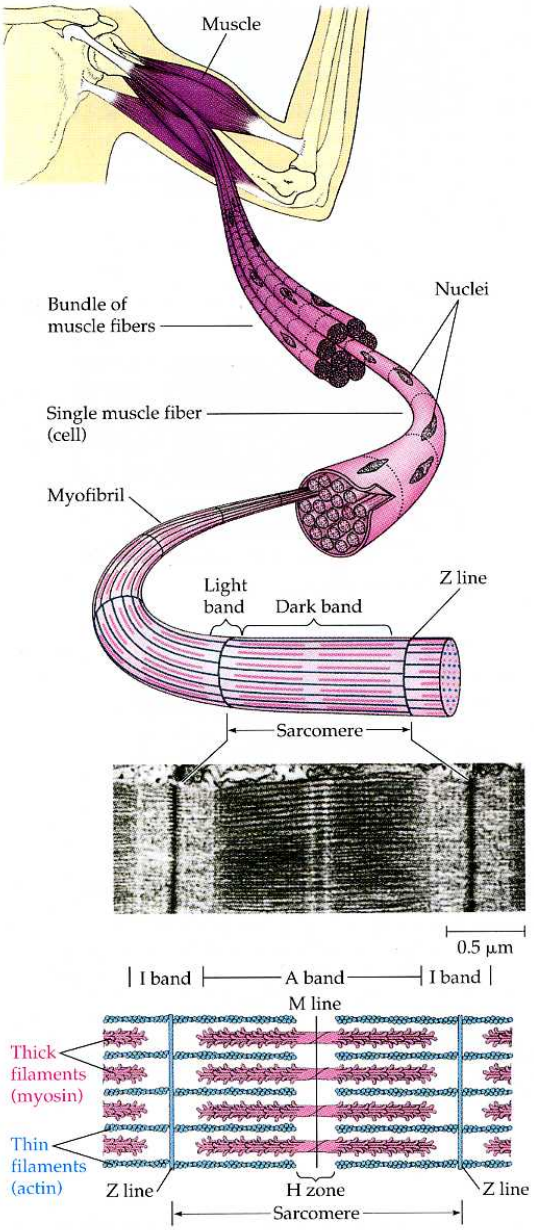


FIGURE 45.25

The structure of skeletal muscle. A muscle consists of bundles of multinucleated muscle fibers (cells), each of which is a bundle of myofibrils. Each myofibril is made of thick and thin filaments aligned in contractile units called sarcomeres. The arrangement of thick and thin filaments appears as alternating light and dark bands when striated muscle is viewed with a microscope, as in the TEM here. As the bottom diagram indicates, only thin filaments occur in the I bands, and the dark zone in the center of each I band, called the Z line, is attached to the thin filaments. The sarcomere is the entire apparatus between two Z lines. The A band includes regions where thick and thin filaments overlap, and a central H zone containing only thick filaments. Connections among the thick filaments form the thin M line within the H zone.

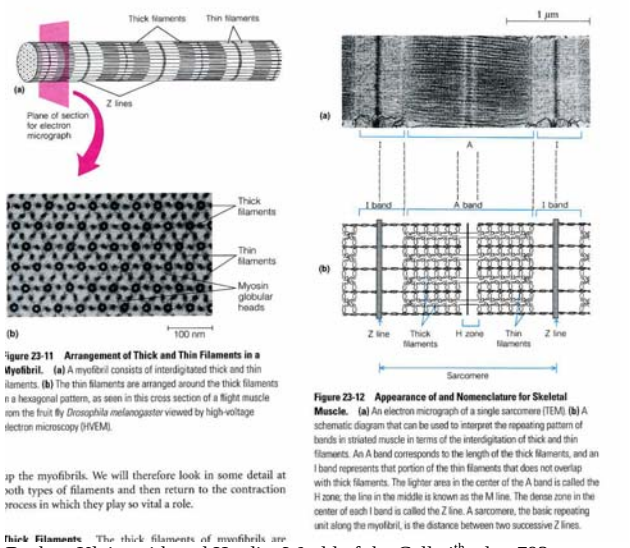
Campbell, Biology, 4th ed., p 1049

Thin filaments are arranged with six around every thick filament, making a honeycomb pattern

Each repeating unit is a *sarcomere*. Borders are the Z lines (discs); thin filaments attached. Thick filaments centered in the sarcomere.

I bands: area near edge where there are only thin filaments. A bands: broad region corresponding to length of thick filaments. H zone in center of A band that contains only thick filaments.

.



igure 23-11 Arrangement of Thick and Thin Filaments in a Myofibril. **(a)** A myofibril consists of interdigitated thick and thin laments. **(b)** The thin filaments are arranged around the thick filaments n a hexagonal pattern, as seen in this cross section of a flight muscle rom the fruit fly *Drosophila melanogaster* viewed by high-voltage lectron microscopy (HVEM).

ıp the myofibrils. We will therefore look in some detail at oth types of filaments and then return to the contraction rocess in which they play so vital a role.

hick Filaments. The thick filaments of myofibrils are

Figure 23-12 Appearance of and Nomenclature for Skeletal Muscle. **(a)** An electron micrograph of a single sarcomere (TEM). **(b)** A schematic diagram that can be used to interpret the repeating pattern of bands in striated muscle in terms of the interdigitation of thick and thin filaments. An A band corresponds to the length of the thick filaments, and an I band represents that portion of the thin filaments that does not overlap with thick filaments. The lighter area in the center of the A band is called the H zone; the line in the middle is known as the M line. The dense zone in the center of each I band is called the Z line. A sarcomere, the basic repeating unit along the myofibril, is the distance between two successive Z lines.

Becker, Kleinsmith and Hardin, World of the Cell, 4th ed., p793

Every thick filament is hundreds of myosin molecules organized in a repeating pattern with heads facing out towards the surrounding thin filaments.

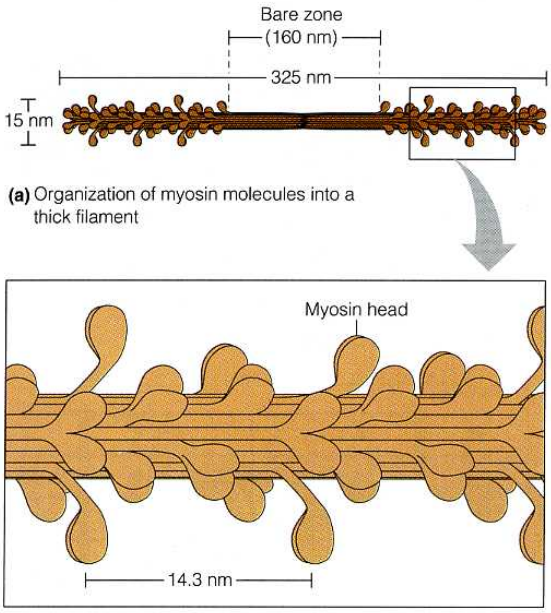
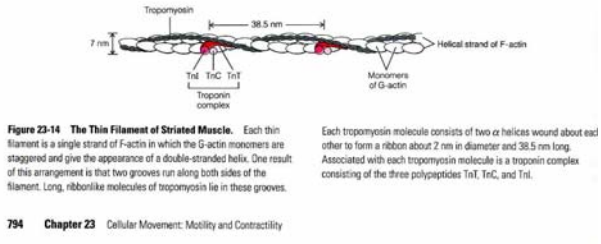
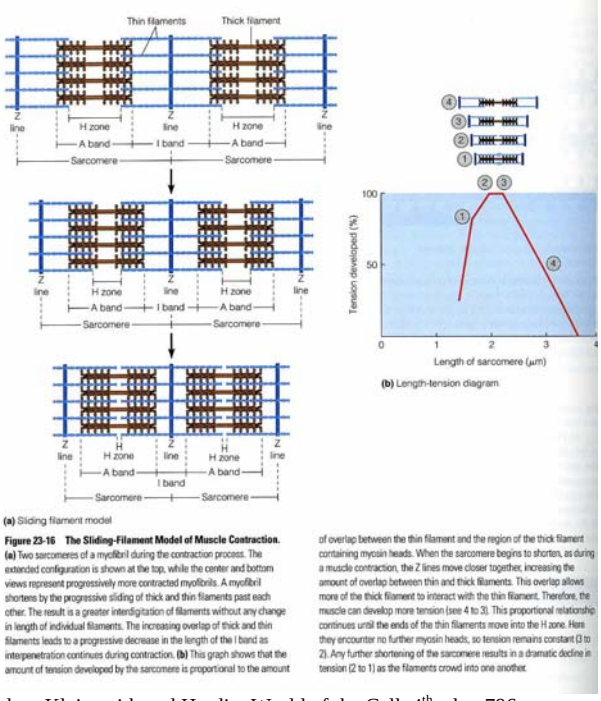
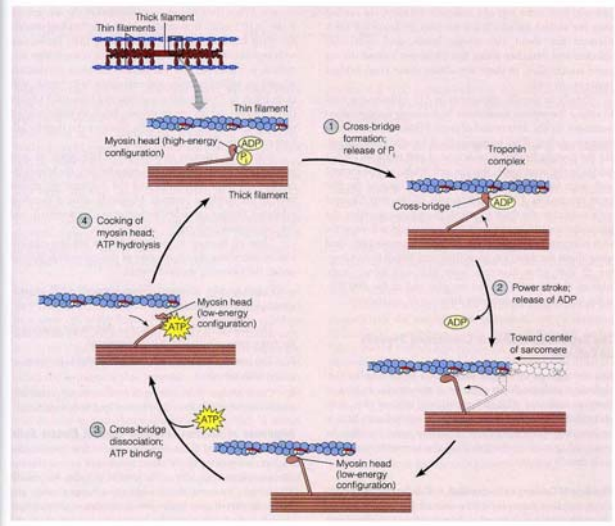
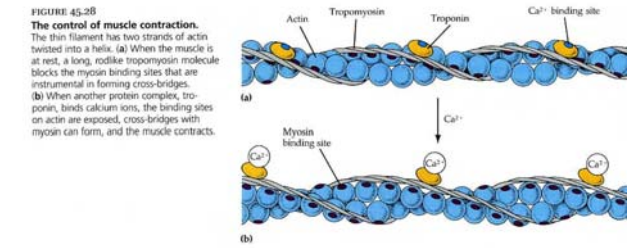
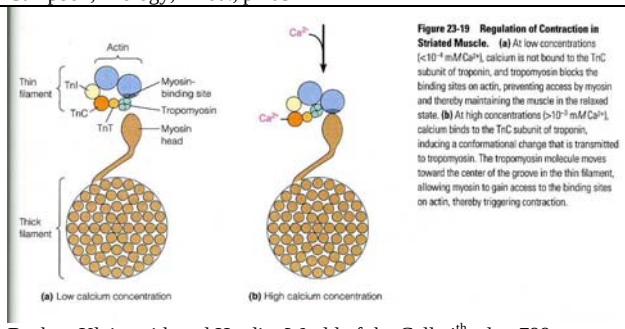
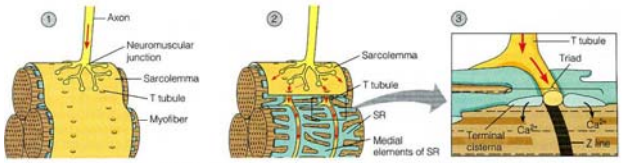


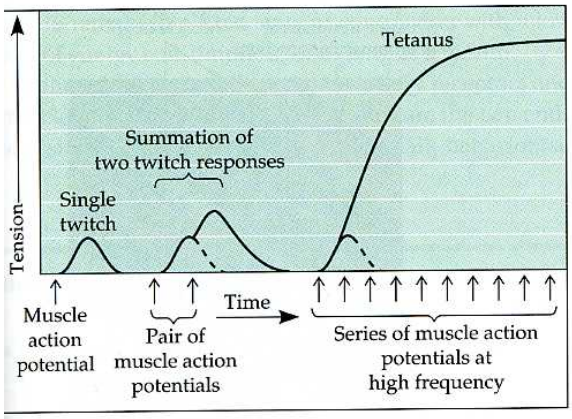
Figure 23-13 The Thick Filament of Skeletal Muscle. **(a)** The thick filament of the myofibril consists of hundreds of myosin molecules organized in a repeating, staggered array. A typical thick filament is about 1.6 μm long and about 15 nm in diameter. Individual myosin molecules are integrated into the filament longitudinally, with their ATPase-containing heads oriented away from the center of the filament. The central region of the filament is therefore a bare zone containing no heads. **(b)** This enlargement of a portion of the thick filament shows that pairs of myosin heads are spaced 14.3 nm apart.

Becker, Kleinsmith and Hardin, World of the Cell, 4th ed., p794

http://www.sciencemag.org/feature/data/1049155s1.mov

Every thin filament is a double strand of actin protein polymers, long fibers of other proteins wrapped around it to keep it together, and small proteins that cover or uncover the binding sites.	 **Figure 23-14 The Thin Filament of Striated Muscle.** Each thin filament is a single strand of F-actin in which the G-actin monomers are staggered and give the appearance of a double-stranded helix. One result of this arrangement is that two grooves run along both sides of the filament. Long, ribbonlike molecules of tropomyosin lie in these grooves. Each tropomyosin molecule consists of two α helices wound about each other to form a ribbon about 2 nm in diameter and 38.5 nm long. Associated with each tropomyosin molecule is a troponin complex consisting of the three polypeptides TnT, TnC, and TnI. 794 **Chapter 23** Cellular Movement: Motility and Contractility Becker, Kleinsmith and Hardin, World of the Cell, 4th ed., p794 http://www.sci.sdsu.edu/movies/actin_myosin_gif.html
2. Muscle contraction. (thick) myosin strands "climb" the thin strands in both directions causing the Z "lines"(discs) to come closer.	 **Figure 23-16 The Sliding-Filament Model of Muscle Contraction.** **(a)** Two sarcomeres of a myofibril during the contraction process. The extended configuration is shown at the top, while the center and bottom views represent progressively more contracted myofibrils. A myofibril shortens by the progressive sliding of thick and thin filaments past each other. The result is a greater interdigitation of filaments without any change in length of individual filaments. The increasing overlap of thick and thin filaments leads to a progressive decrease in the length of the I band as interpenetration continues during contraction. **(b)** This graph shows that the amount of tension developed by the sarcomere is proportional to the amount of overlap between the thin filament and the region of the thick filament containing myosin heads. When the sarcomere begins to shorten, as during a muscle contraction, the Z lines move closer together, increasing the amount of overlap between thin and thick filaments. This overlap allows more of the thick filament to interact with the thin filament. Therefore, the muscle can develop more tension (see 4 to 3). This proportional relationship continues until the ends of the thin filaments move into the H zone. Here they encounter no further myosin heads, so tension remains constant (3 to 2). Any further shortening of the sarcomere results in a dramatic decline in tension (2 to 1) as the filaments crowd into one another. Becker, Kleinsmith and Hardin, World of the Cell, 4th ed., p796
Cyclic process of muscle contraction. Myosin: double head and tail. Tail is where individual myosin molecules cohere to form the thick filaments. Head is center of bioenergetic reactions that power muscle contractions. Changes shape to a high-energy configuration and binds to (a specific site on) actin, forming a *cross-bridge*. Stored energy is released when myosin head goes through its power stroke. When a new ATP molecule attaches to the myosin head, then the head un-attaches from the actin.	 **Figure 23-18 The Cyclic Process of Muscle Contraction.** A small segment of adjacent thick and thin filaments (see the orienting inset at upper left) is used to illustrate the series of events in which the cross-bridge formed by a myosin head draws the thin filament toward the center of the sarcomere, thereby causing the myofibril to contract. Step 1 shows the cross-bridge configuration of relaxed muscle, whereas the end of step 2 shows the configuration of a muscle in rigor. A detailed description of all the steps is given in the text. Filament-Based Movement in Muscle 797 Becker, Kleinsmith and Hardin, World of the Cell, 4th ed., p797

~350 myosin heads in each thick fiber forms and reforms 5 cross-bridges each second.	
Control of muscle contraction	 FIGURE 45.28 **The control of muscle contraction.** The thin filament has two strands of actin twisted into a helix. (a) When the muscle is at rest, a long, rodlike tropomyosin molecule blocks the myosin binding sites that are instrumental in forming cross-bridges. (b) When another protein complex, troponin, binds calcium ions, the binding sites on actin are exposed, cross-bridges with myosin can form, and the muscle contracts. Campbell, Biology, 4th ed., p 1052
3. Regulating muscles. In at rest muscles, binding sites on actin molecules are blocked by regulatory protein *tropomyosin.* Another set of regulatory proteins, the*troponin complex*, controls the position of tropomyosin on the thin filament. For a muscle to contract, the myosin binding sites on the actin must be uncovered. This happens when calcium ions bind troponin. Ca^{2+} binding cause the whole tropomyosin-troponin complex to change shape and expose the myosin binding sites on actin.	 **Figure 23-19 Regulation of Contraction in Striated Muscle.** (a) At low concentrations [$<10^{-6}$ m*M* Ca^{2+}], calcium is not bound to the TnC subunit of troponin, and tropomyosin blocks the binding sites on actin, preventing access by myosin and thereby maintaining the muscle in the relaxed state. (b) At high concentrations [$>10^{-5}$ m*M* Ca^{2+}], calcium binds to the TnC subunit of troponin, inducing a conformational change that is transmitted to tropomyosin. The tropomyosin molecule moves toward the center of the groove in the thin filament, allowing myosin to gain access to the binding sites on actin, thereby triggering contraction. Becker, Kleinsmith and Hardin, World of the Cell, 4th ed., p799
Calcium concentration in the cytoplasm of the muscle cell is regulate by the *sarcoplasmic reticulum*. The stimulus leading to the contraction of a skeletal muscle cell is an action potential in the motor neuron that makes synaptic connection with the muscle cell. The action potential changes the permeability of the sarcoplasmic reticulum causing it to release calcium ions. Muscle contraction stops when the sarcoplasmic reticulum	 **igure 23-21 Stimulation of a Muscle Cell by a Nerve Impulse.** ① An action potential moves down the axon of the neuron until it aches the end. The ends of the axon branch out over the surface of the uscle cell at the neuromuscular junction to form synapses (contact oints) between the neuron and the muscle cell. ② Depolarization of the erminals of the axon causes the release of neurotransmitter molecules, which bind to the acetylcholine receptors on the sarcolemma. Binding of neurotransmitter to the acetylcholine receptors starts an action potential in the muscle cell. As the action potential spreads over the surface of the muscle cell, it travels down into the T tubules. ③ T tubules carry the action potential into the interior of the muscle cell, where it stimulates calcium release from the terminal cisternae of the SR. Campbell, Biology, 4th ed., p 1054 http://www.blackwellpublishing.com/matthews/myosin.html

pumps the calcium back out to the cytoplasm, and the tropomyosin-troponin complex again blocks the myosin binding sites.	
4. Muscle energy. Most of the energy needed for repetitive muscle contractions is stored in *phosphagens, creatine phosphate* in vertebrates. This supplies the phosphate group to ADP to make ATP. 5. Graded contractions. Single muscle cell fiber either contracts all the way or not at all, all or nothing, on or off. Twitches control the endurance of the tension. Motor unit: single motor neuron and all the muscle fibers it controls. How many motor units and whether they are large or small units and recruitment of motor neurons determine strength of contraction.	 FIGURE 45.30 **Temporal summation of muscle cell contractions.** This graph compares the tension developed in a muscle in response to a single action potential, a pair of action potentials, and a series of action potentials. The dashed lines show the response that would have resulted if only the first action potential had occurred. Campbell, Biology, 4th ed., p 1053
Muscle fatigue: caused by depletion of ATP, dissipation of the ion gradient required for normal electric signaling, and accumulation of lactate. Mechanism to avoid fatigue (as in posture muscles) different motor units take turns maintaining the prolonged contraction. Fast muscle fibers: some insect flight muscles can provide their own neuron signals faster than the neurological system could deliver them.	

Slow muscle fibers: less sarcoplasmic reticulum than fast fiber, so calcium remains in cytoplasm longer. Twitch lasts about 5 times longer. Specialize to make use of steady energy supply: have may mitochondria, rich blood supply, and oxygen storing protein call myoglobin (causes coloration in "dark meat")	

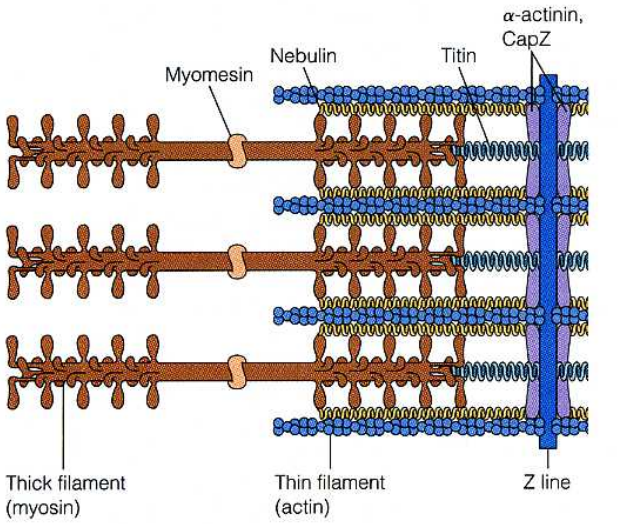


Figure 23-15 Structural Proteins of the Sarcomere. The thick and thin filaments require structural support to maintain their precise organization in the sarcomere. The support is provided by two proteins, α-actinin and myomesin, which bundle actin and myosin filaments, respectively. Titin attaches thick filaments to the Z line, thereby maintaining their position within the thin filament array. Nebulin stabilizes the attachment of thin filaments to the Z line.

Becker, Kleinsmith and Hardin, Wld of the Cell, 4th ed.,p795

Structure and Function of Vertebrate Skeletal Muscle
Molecules and Math: Form and Function in Human Biology

Exercises.

1. What role does calcium play in muscle contraction?
2. Where is calcium stored in the muscle cell?
3. How is calcium moved in and out of storage?
4. What causes rigor mortis?
5. Where are the muscles that cause the fingers to flex?
6. Where are the muscles that cause the fingers to extend?

Why do the thick and thin filaments not slip away from each other when the myosin heads become un-attached?

Worksheet 4: Hemoglobin and Sickle Cell Anemia.
Summer Girls and Boys Science, Math, and Engineering Programs.
Math/Science Session III, July 27, 2007.

Part 1.
http://www.xvivo.net/press/harvard_university.htm

1. What does a protein have to do with sickle cell anemia?
2. What is anemia? (Low number of red blood cells.)
3. What is sickle cell anemia? (Red blood cells "die off" early. They wear out too soon.)
4. What so red blood cells do? (Carry oxygen to cells.)
5. Why is oxygen so important? (Keeps H+ gradient.)
6. How does the body use proteins that we eat?
7. What is the difference between "essential" and other (standard?) proteins?
8. What are proteins made of? (20 amino acids)
9. What are the amino acids made of? (carbon, oxygen, hydrogen, nitrogen, sulpher)
10. Why is carbon the atom of choice? (It can attach so many different ways and do it stably.)
11. Why nitrogen? (Nitrogen likes to react.)
12. What is life? (Complications from simple beginnings.)

For class.

- One example of a protein essential for the human body: hemoglobin.
- Code for making proteins.
- DNA (inside nucleus) ⇨RNA (sent out from nucleus) ⇨ protein.
- Evolution/disruption/neutral mutation
  helpful mutation
  damaging mutation

Part 2.

Genes and how they "talk" to the cell.

9. Where is DNA stored in the cell?

10. Recall how many different protein building blocks (amino acids) are there. How many are there? _____

11. How many different "letters" or "symbols" does DNA have available to represent the different amino acids? _____

12. If DNA used two-letter words to represent the amino acids, how many different amino acids could it represent? _____

13. If DNA used three-letter words, how many different amino acids could it represent? ____

14. Should DNA use 2 or 3-letter words to represent the different amino acids? Why?

15. What is the difference between the codons for Glu (Glutamic acid) and Val (Valine)?

16. DNA strands are *transcribed* into RNA strands, with everything copied, except that T's are changed into U's. So the four letters for DNA are GCAT, while for RNA it is GCAU.

17. What is the machinery that cells use to *translate* RNA tapes of codons into strings of protein "pearls" (polypeptides)?
    a. Ribosomes. (big pieces that have cavities to hold the amino acid carriers)

    b. Transfer RNA (amino acid carriers)

http://learn.genetics.utah.edu/units/basics/transcribe/ (You do it transcription and translation) pretty good

http://www.dnai.org/text/mediashowcase/index2.html?id=609 (hemoglobin: single nucleotide change->single amino acid change-> glombing hemoglobin into rods-> sickle shape-> red blood cells die off early and result in anemia. Very Good!)

18. What are the number of different 3-letter sets that can be made from four letters (repeated letters are allowed)? Using the same three letters, we can start the list by writing all of the two-letter sets and adding on a G at the end, then repeating the same list of two-letter sets only this second time adding a C to all of the sets, and so on…

    Or we could make a grid like one of the following, which show two different ways to organize the different three-letter sets.

CODON TABLE

Third Position

First Position & Second Position	A	C	G	U
AA	Lys	Asn	Lys	Asn
AC	Thr	Thr	Thr	Thr
AG	Arg	Ser	Arg	Ser
AU	Ile	Ile	MET	Ile
CA	Gln	His	Gln	His
CC	Pro	Pro	Pro	Pro
CG	Arg	Arg	Arg	Arg
CU	Leu	Leu	Leu	Leu
GA	Glu	Asp	Glu	Asp
GC	Ala	Ala	Ala	Ala
GG	Gly	Gly	Gly	Gly
GU	Val	Val	Val	Val
UA	Z	Tyr	Z	Tyr
UC	Ser	Ser	Ser	Ser
UG	Z	Cys	Trp	Cys
UU	Leu	Phe	Leu	Phe

Z = STOP CODON

Table 1 : Codon table. This table illustrates the 64 possible codon triplets.

		2nd base			
		U	**C**	**A**	**G**
1st base	**U**	UUU Phenylalanine	UCU Serine	UAU Tyrosine	UGU Cysteine
		UUC Phenylalanine	UCC Serine	UAC Tyrosine	UGC Cysteine
		UUA Leucine	UCA Serine	UAA Ochre *Stop*	UGA Opal *Stop*
		UUG Leucine	UCG Serine	UAG Amber *Stop*	UGG Tryptophan
	C	CUU Leucine	CCU Proline	CAU Histidine	CGU Arginine
		CUC Leucine	CCC Proline	CAC Histidine	CGC Arginine
		CUA Leucine	CCA Proline	CAA Glutamine	CGA Arginine
		CUG Leucine	CCG Proline	CAG Glutamine	CGG Arginine
	A	AUU Isoleucine	ACU Threonine	AAU Asparagine	AGU Serine
		AUC Isoleucine	ACC Threonine	AAC Asparagine	AGC Serine
		AUA Isoleucine	ACA Threonine	AAA Lysine	AGA Arginine
		[1]AUG Methionine	ACG Threonine	AAG Lysine	AGG Arginine
	G	GUU Valine	GCU Alanine	GAU Aspartic acid	GGU Glycine
		GUC Valine	GCC Alanine	GAC Aspartic acid	GGC Glycine
		GUA Valine	GCA Alanine	GAA Glutamic acid	GGA Glycine
		GUG Valine	GCG Alanine	GAG Glutamic acid	GGG Glycine

http://learn.genetics.utah.edu/units/basics/transcribe/ (You do it transcription and translation) pretty good

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http://www.biocourse.com/mhhe/bcc/resources/concept.xsp?id=000012181&type=MOVIE (bioCourse RNA translation: protein synthesis movie) short: very good

http://vcell.ndsu.nodak.edu/animations/translation/movie.htm (North Dakota State protein synthesis) longer: excellent!

http://telstar.ote.cmu.edu/Hughes/HughesArchive/tutorial/polypeptide/tutorial.swf (carnagie-mellon protein synthesis) advanced-very good

http://learn.genetics.utah.edu/units/basics/transcribe/ (You do it transcription and translation) pretty good

Appendix C: Miscellaneous Comments.

In the previous class session, we asked students to investigate (between classes) the following questions. What is sickle cell anemia? What is hemoglobin? We suggested that they look on the web, ask friends and ask family members.

We first establish an understanding of what sickle cell anemia is. In particular, we identify hemoglobin as the central figure. We further establish that hemoglobin is a protein and that a single mutation of hemoglobin results in malaria resistance and sickle cell (anemia or trait).

We investigated how many distinct chains of symbols can be generated from alphabets of 2,3, and 4 symbols. The goal is for students to realize that for 4 symbols (the case for DNA and RNA), chains ("words") of 3 symbols are long enough to provide unique representation of all twenty amino acids that the human body (and virtually all known life forms) use to construct all proteins in our bodies. Thus, the universal DAN/RNA code (for all life) uses units of 3 nucleotides (called codons) to record the blueprints for constructing the needed proteins. This is a basis for the genetic code. 20 "words" are enough to specify which amino acid to use. Three letter "words" with an alphabet of 4 symbols yields 4^2 = 64 different words. This gives room for the few additional signals, such as the sop codon, which do not code for any amino acid, but rather signal to the protein factory to cut off production and send the finished polypeptide on its way to finish folding and become a functioning protein.

We expect substantial discussion about the connection between the number of possible distinct words and the codon "message" to the protein factories. We may also encourage some discussion about how many "symbols" are available in DNA and RNA sequences.

Future directions.

- Inheritance of traits from parents.
- Odds of offspring of sickle cell trait parents being sickle cell trait (1/2), non-mutated (1/4), or sickle cell anemia (1/4).
- Anemia is low level of red blood cells. Sickle cell causes this by "wearing out" the red blood cells early.
- Hemoglobin is a tetramer with ligands (heme) that themselves attach oxygen molecules, one for each heme unit.
- Hydrophilic/hydrophobic amino acids and their relatioinships.
- Hemoglobin shape change when binding O2.
- Mutation of Glutamic Acid to Valine. Glu ⇨ Val.

- Hydrogen bonds (a need for alpha helices and beta sheets). That is, the need for the nitrogen and hydroxyl groups to form hydrogen bonds is what causes alpha helices and beta sheets to form and remain stable.

Following week 2, July 20, 2007.

For the first 10-15 minutes we sat where the students gather before class and eat their early morning snack. (They often arrive not having eaten anything for breakfast.) Three individuals had substantial reports to make regarding what the answers to the two questions posed last class session. What is sickle cell anemia? What is hemoglobin? One of them (Terrell) had written a paragraph of what he found at a web site. There was enough interest that several students got the dchance to essentially repeat what others had said. I also took the opportunity to mention that a single amino acid mutation in hemoglobin was responsible for the sickle cell trait and anemia disease.

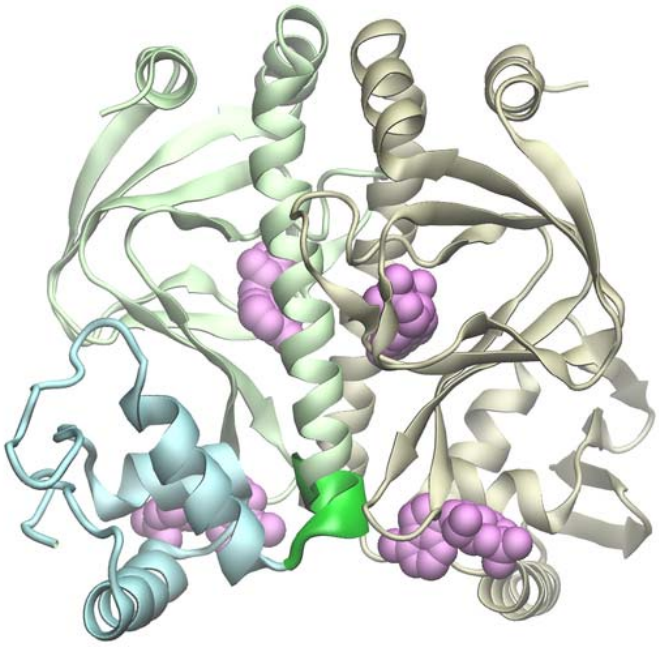
Liishai and Chelsea spoke together at length about how nucleotides pair-up for defense and communication. Liishai termed it the "buddy system". Oshai spent over a half hour inspecting an interactive animated genetics lesson. He repeated parts of the narration until he could say them all himself!

I found positive things to say to a number of the students, to encourage them to continue struggling and putting forth effort. Na Pua and Oshai were awesome in their efforts and their final understanding of how to count the combinations of letters. Liishai was incredibly persistent in listening and trying to use what she gathered from what was said by me or one of her classmates.

Napua and Oshai gave a joint presentation on how they figured how many different 3- and 4-symbol sets of four possible letters there are.

Tre-Onna spent time with the younger students trying to help them understand how to work some of the problems.

Appendix D: Animations of Dynamical Structure of Proteins.



Still image of CAP dimer with pairs of cyclic-AMP in each monomer.

Note: The following QuickTime movies are embedded in the electronic version of this report.

cap-protein-yspin.mpg

QuickTime animation of the CAP complex spinning

dnaWhelices.mpg

QuickTime animation of the CAP dimer complexed with DNA strand.

cap-eq-first-56ps.mpg

QuickTime animation of molecular dynamic simulation of CAP monomer equilibrating.