Invention Activities for University Cell Biology

A Guide for Instructors

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August 2010

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Chapter 1
General Information about Invention Activities

What are Invention Activities?

Invention activities are a class of discovery activities during which students "invent" solutions to problems based on their own prior knowledge. For this manual, two key features of these activities will be described. For a more exhaustive description of invention activities, one can refer to the citations at the end of this chapter.

The first key feature is that the activities appear to have little to do with the actual course material. In calculation heavy courses (such as math and physics), these activities often present situations in which students must analyze "real-world" data and attempt to invent relationships and formulae. In non-calculation heavy courses, such as biology, these activities present "real-world" situations that are partial analogies to actual systems within living cells, and the students invent the remainder of the analogy (although they are unaware of this). For the inventions developed here (which were designed to be used in a cell biology class), the students are inventing solutions to problems that living cells have already solved.

The second key feature is that the activities are tackled by the students before the relevant material is presented to them. This is important, as one of the primary goals of invention activities is to prime student thinking about core concepts and relationships. This priming can then be used as a foundation for introducing and building the structure of the actual course related concepts.

While invention-type activities have been explored and developed at several institutions, the biology-based invention activities presented in this manual were based on the work of Daniel Schwartz (Stanford School of Education). Schwartz developed invention activities for introducing mathematical relationships in statistics and chemistry. He subsequently studied how these activities prepared students for future learning and primed them to transfer knowledge.

Invention Activities in Cell Biology

Cell biology-based invention activities task the students with solving problems that are analogous to problems living cells have solved, such as transport across a membrane, repairing DNA, or regulating genes in response to external signals. These problems are presented as partial analogies, and the students invent the rest of the analogy. This is best explained by using one of our invention activities as an example.

The invention activity that relates to membrane transport uses a wall separating two sides of a rodent zoo exhibit to restrict rodent movement from one side to another. In this case, the wall (which is presented as part of the activity) is directly analogous to a cell membrane. However, the students are tasked with redesigning the wall so that some of the rodents can pass through the wall while others can't. This requires the students to invent portals of some kind, which are analogous to transport proteins within cell membranes. In this way, part of the analogy is structured for the students, and the rest they must invent.

It should be stressed that this activity structure is not made explicit to the students. How the activity and their solutions are analogous to living cells is not made clear to them until after they have finished the inventing phase of the activity. Giving the students any information about the analogy before they generate solutions will short circuit the creative process and limit their thinking.

In the event the use of any of our invention activities (either as shown or modified) leads to a publication, please cite reference #1 below (we also recommend citing at least #2).

Extra Reading about Invention Activities

If you are interested in reading some educational literature about invention activities, the following references are a good place to start.

1. Taylor, J. L., Smith, K. M., van Stolk , A. P., Spiegelman, G. B. (2010). Using Invention to Change How Students Tackle Problems. CBE – Life Sciences Education, 9 (4), 504-512.

2. Schwartz, D. L., and Martin, T. (2004). Inventing to Prepare for Future Learning: The Hidden Efficiency of Encouraging Original Student Production in Statistics Instruction. Cognition and Instruction 22, 129-184.

3. Belenky, D. M., and Nokes, T. J. (2009). Motivation and Transfer: The Role of Achievement Goals in Preparation for Future Learning. Proceedings of the 31st Annual Conference of the Cognitive Science Society, 1163-1168.

4. Roll, I., Aleven, V., and Koedinger, K. R. (2009). Helping Students Know 'Further' - Increasing the Flexibility of Students' Knowledge Using Symbolic Invention Tasks. Proceedings of the 31st Annual Conference of the Cognitive Science Society, 1169-1174.

Chapter 2
Using Invention Activities in Class

An important note!

In order for students to get the maximum benefit from the activities, it is important to prevent students seeing the activities ahead of time. The problem with the invention activities being viewed prematurely by students is that they can think of a "best" solution ahead of time and shut down the valuable discussion of their group during the activity time. Unfortunately, students are notorious for collecting course materials and passing them on to future students, and this will include the invention activities

In order to prevent this from happening, the following precautions should be taken:

- The activities are printed on legal size paper and all work must be included on this sheet. One of these sheets is handed out to each group, and is collected at the end of the class (this works for all class sizes).
- All diagrams related to the activities are not handed out. Instead, they are projected onto a screen at the front of the class. This in effect splits the activity in half (so even if someone leaves with the written part of the activity, it is less useful by itself). This works for all class sizes although it has the disadvantage that some of the activities have multiple diagrams that must be changed at certain time.
- Another option that works **for small classes only** is to place the diagrams (and even part of the text) into plastic cover sheets, number them, and hand them out one per group. These can then be collected at the end of activity to ensure no student leaves with an activity.

Scheduling the Invention Activities

Given that the activities do not appear to be related to the material, it is reasonable to assume that the activities could be given at any time. However, as mentioned in Chapter 1, invention activities are designed to be completed by the students before they see the related course material. In fact, the timing of the activities is critical for two reasons:

1. The activities are meant to encourage students to think about concepts before they are shown them in class, thereby priming them to learn the concepts and build upon them.

2. In our experience, students will often try to think of the biological system that the invention activity relates to, and then design their solution accordingly. While this may seem useful, it actually short circuits their creative thinking and renders the activity ineffective.

While whenever possible, the invention activities should be carried out in the class immediately prior to the class during which the related material we be presented. Anecdotally, we feel that the students should see the invention activity no more than three days in advance of the related material.

Invention Activities in Small Classes (30 students or fewer)

The invention activities outlined in this manual were originally developed for small classrooms, although we have successfully implemented them in large lecture halls (see below). The class should be arranged into groups of 3-4. We recommend that this arrangement be random and fixed for the entire term. If possible, having each group work around a single table is optimal.

At the beginning of the activity session, each group should receive:

- One activity worksheet (legal size paper) which includes the activity text.
- One plastic covered sheet with the diagrams (if applicable; see the previous section).
- One large flipchart paper.
- Extra scrap paper.

Note that the flipchart paper can be replaced with dry-erase whiteboards if available (or anything which the students can use to present their ideas to the class).

The activity follows a consistent 50 minute format:

1. Introduction (5 minutes): a brief introduction is given to the students during which the salient points of the activity are highlighted, and the diagrams are introduced. Important restrictions within the activities should be emphasized.
2. Group work (usually 20-25 minutes, depending on the activity): the groups should be encouraged to generate multiple solutions and discuss them. Once they have decided on one or two good solutions, they should write down details (including diagrams) on the provided worksheet AND flipchart paper.
3. Group presentations (10 minutes): each group takes about 1-2 minutes to quickly outline their idea to the rest of the class.
4. Wrap-up (10 minutes): the facilitator explains how the activity and the solutions developed by the groups relate to the upcoming material in the course.
5. All students hand in their worksheets, activity sheets, and any scrap paper.

Invention Activities in Large Classes

We have successfully used invention activities on a regular basis in large lecture halls of up to 300 students, and our research indicates that the activities are just as effective in this setting when compared to the small class setting. The activity format is similar to that outlined for small classes, with some important changes. In our experience it is very useful to have additional help with passing out and collection papers in large classes. We have used course assistants (upper level undergraduates) for this. A minimum of two people are needed for a class of 250 (3-4 people are optimum).

At the beginning of the activity session, each group should receive one activity worksheet (legal size paper) which includes the activity text. Flipchart paper and scrap paper are not needed, and the activity diagrams are projected onto the main screen. The 50 minute format of the activity is as follows:

1. Introduction (5 minutes): a brief introduction is given to the students during which the salient points of the activity are highlighted, and the diagrams are introduced. Important restrictions within the activities should be emphasized.
2. Group work (usually 20-25 minutes, depending on the activity): the groups should be encouraged to generate multiple solutions and discuss them. Once they have decided on one or two good solutions, they should write down details (including diagrams) on the provided worksheet.
3. All students hand in their worksheets.
4. Group presentations (10 minutes): a small number (3-6) groups volunteer to verbally present their ideas to the class. If a paper projector is available, this can be used to project the solutions on their worksheet to the rest of the class. If no groups are willing to volunteer, several of the worksheets can be selected to show a variety of possible solutions.
5. Wrap-up (10 minutes): the facilitator explains how the activity and the solutions developed by the groups relate to the upcoming material in the course.

Alternate step 4

We have tested a variation of step 4 above, which we have found to be very effective. All groups are instructed to explain their solution to one or two nearby groups. During this time, each group presents their solutions and the other groups provide feedback (the groups can compare the relative merits of the solutions and discuss whose solution is superior and why). Each group is permitted to adjust the solution on their worksheet based on any feedback they receive. If time permits, one or two groups can present their ideas to the entire class. This alternative step 4 may also be effective in a small class setting, although we have not tested this.

An important note about active learning in large classes

In our experience, instructors experienced in lecturing to large classes are often nervous when first introduced to the idea of active group learning in large lecture rooms. This is understandable; the lecture-style classroom and active learning classroom are completely different. Most instructors are quite comfortable talking for an hour to a quiet audience. Being in a large lecture hall full of students noisily talking to their group members can be very disconcerting. After discussing this with others instructors and others in science education, it is clear that instructors often fear losing control of the class and worry that students will simply disengage to socialize.

In our experience, this is not the case with invention activities (and many other types of active learning activities). The activities are designed to be interesting and easily engaging, and the vast majority of the students will be engaged with the activities. The volume of the room will be high, but we take that to be a good thing. Anecdotally, when we walk around the room, we observe far more students actively communicating with each other about the problem rather than socializing. From our observations of large lecture-style classes, we estimate that the number of students disengaged during lectures (whispering, surfing the internet, doing homework from other classes) is far greater than during the invention activities.

Some general tips for running the invention activities can be found at the end of this chapter.

Introducing Invention Activities to the Class

First day of class (or first day of instruction)

In our experience, it is vitally important that any instructor wishing to use active learning in their class must set the precedent at the very beginning of the term. This sets the structure of the class right away, and makes it clear to the students how the class will be run and how they will be expected to participate. Introducing active learning later in the course can lead to lack of student buy-in and a less than satisfactory experience.

In order to set the tone for invention activities, we use a simple group activity that takes about 20 minutes on the first day of class, shown below:

Assume you've gotten a job with a mad scientist who wants to create "a thing" that is self-replicating. It's not clear if this thing is a machine or a something else.

By "self-replicating" we mean that if it is left on its own, it will make copies of itself, and the copies will also be able to make copies of themselves.

To start this task you need to make a list of the characteristics this thing must have. Talk with your neighbours and make the list. We'll collect ideas and see what we get.

After 5-10 minutes of group discussion, ask for people to volunteer one characteristic from their list and keep track of the ideas on the screen. We generally keep taking ideas from the class until the list has ideas that relate to the following list of characteristics:

- The thing must be able to gather raw materials.
- The thing must be able to make (or gather) its parts.
- The thing must have some sort of container to keep its parts together.
- The thing must be able to gather and transform energy.
- The thing must have a set of instructions that tell it what to do. Note that this encompasses a lot of ideas such as timing, blueprints, lifespan, error checking, and so on.
- The thing must be able to pass on its instructions into its copies.
- The thing must have the machinery (parts) necessary to read and carry out the instructions.

This activity is easy to do in any size class, and is a good primer for the class in terms of the types of activities they will work on. We usually tell the class that they will be working on group activities in future classes.

During the first invention activity

Deciding on which invention activity to use first during the term depends on the order of the material presented in the course. However, we recommend using either the Zoo Exhibit activity (chapter 3) or the Rubber Ducky activity (chapter 7) as these activities are the easiest for students to complete (in our experience, students are usually unsure of what to do during the first activity).

During the first invention activity, it is important spend about five minutes explaining the purpose and expectations of the activities:

- The activities will not appear to be related to the class material. The activities will allow the students to generate analogies to biological concepts. In essence, the students will be solving the same problems that living cells have solved.
- There are multiple possible solutions to the activities, and students should be encouraged to consider, discuss, and develop more than one option.
- Inform them that it is not critical that they get through every stage of the activity, but rather to be thorough and get as far as they can.
- It is important to stress that these activities are meant to give them practice tackling unfamiliar problems and help them develop scientific thinking skills. Research has shown that these types of activities have a positive effect on how student think about problems and approach problem solving.

As with any type of active learning, it is very important to stress to the students that doing these types of activities is known to be beneficial for developing problem solving skills. We also usually mention that these activities are based on research carried out at Stanford University. Most students will accept active learning readily if they are assured that you are doing this because you believe that they will benefit from it.

General Tips

- During every activity, walk around the room and interact with the students.
- If possible, have a second facilitator (TA or course assistant) available to help answer questions, hand out and collect worksheets, etc.
- Give only enough information for the students to figure out what they need to accomplish. Answer any questions that help clarify the activity, but avoid giving out any information that will focus or restrict their thinking. Be Socratic…answer questions with questions whenever possible.
- Don't interrupt the class unless absolutely necessary. If you do need to give the entire class some clarification, be brief but make sure you have everyone's attention. The goal is to train them to understand that any information you give during the activity is essential and will help them solve the problem.
- Always be positive! Always treat every idea as good when you give feedback. We have had groups shut down without deriving a solution because well-meaning facilitators gave them too much negative feedback.
- Always encourage the groups to discuss multiple ideas and to develop multiple solutions.
- Try to always leave time for some group to present their ideas to the class. This is often the most fun part of the activity, and the student enjoy seeing other ways of solving the problems
- It is critical for the instructor to communicate that the process is valuable and interesting. Students are exceptionally good at picking up social clues (i.e. they can easily detect if an instructor is not interested in the material or an activity). We are certainly convinced that active learning is a better use of 50 minutes than doing something that could be replaced by a video, and students need to be convinced of that as well.

Following the Invention Activities

We find it important to refer back to the invention activities while presenting the relevant material in the subsequent lectures. Consistently making comparisons between the analogies developed during activities and the actual biological systems helps students make the connections and give them a framework upon which they can build their knowledge.

In addition, some of the invention activities have follow-up problem sets included with them (and suggested answers). These problems sets are designed to make students work through the concepts that are introduced during the activities. We generally distribute these problem sets via the course website immediately after the activity a few hours after the activity, and post the suggested answers a week later. We have never counted these problem sets for grade, although they could potentially be used that way in order to encourage student participation.

Chapter 3
Invention: Zoo Exhibits

Description

This activity uses the analogy of a wall between two rooms as an analogy for a cell membrane. The activity presents the students with several model zoo exhibits that house some combination of mice and squirrels. The students are tasked with designing a separating wall such that one type of rodent can pass from room to room while the other type of rodent cannot. The different possible mechanisms that the students can use to accomplish the task can be directly mapped onto the concepts of semi-permeable cell membranes and membrane transport.

Also included below is a follow-up problem set (and suggested answers) that is designed to have students work though some of the concepts of membranes and membrane transport that the invention activity relates to. We generally distribute the problem to the students via the course website and make the suggested answers available a week later.

Related Topics: Membranes, Diffusion, and Transport

Key Features

- The separating wall is analogous to a cell membrane.
- Part I is designed to make students think about the concept of selectivity and how different features can be used for selectivity. This is meant to be reinforced by Part II.
- Part III is designed to have students think about concepts that relate to diffusion, energy, and active transport.

Activity Handout:

Invention – Rodent Zoo Exhibits

You are in charge of creating new rodent exhibits for a zoo. The exhibits consist of two glass rooms (of equal size) which are separated by a single wall that runs floor to ceiling. Two types of rodents will be housed in these exhibits, as shown on the screen.

Consider the exhibits that are also shown on the screen. Each exhibit has two conditions that must be fulfilled at all times (not just during feeding time, for example). You need to design a separating wall to allow one type of rodent to pass from room to room while preventing another type of rodent from passing through. Also, for the purposes of this activity you can assume the following:

- The dimensions for each rodent are consistent (i.e. all the mice are the same size and mass).
- The movement of each rodent is essentially constant (i.e. they are always running around).
- The rodents move independently of each other (i.e. they don't follow each other).

Design the wall in for each exhibit (the walls can be different in each exhibit) to fulfill the requirements shown on the screen for each exhibit. Note that you are free to be creative in modifying each wall, but you are not permitted to redesign anything else about the exhibits. The rodents must not be harmed by your invention. NOTE: you should make your wall designs to be as simple as possible (simple meaning the cheapest to design, build, and operate).

Draw a diagram for each wall design you come up with, and add any necessary explanation.

Slides (not to be handed out to the students):

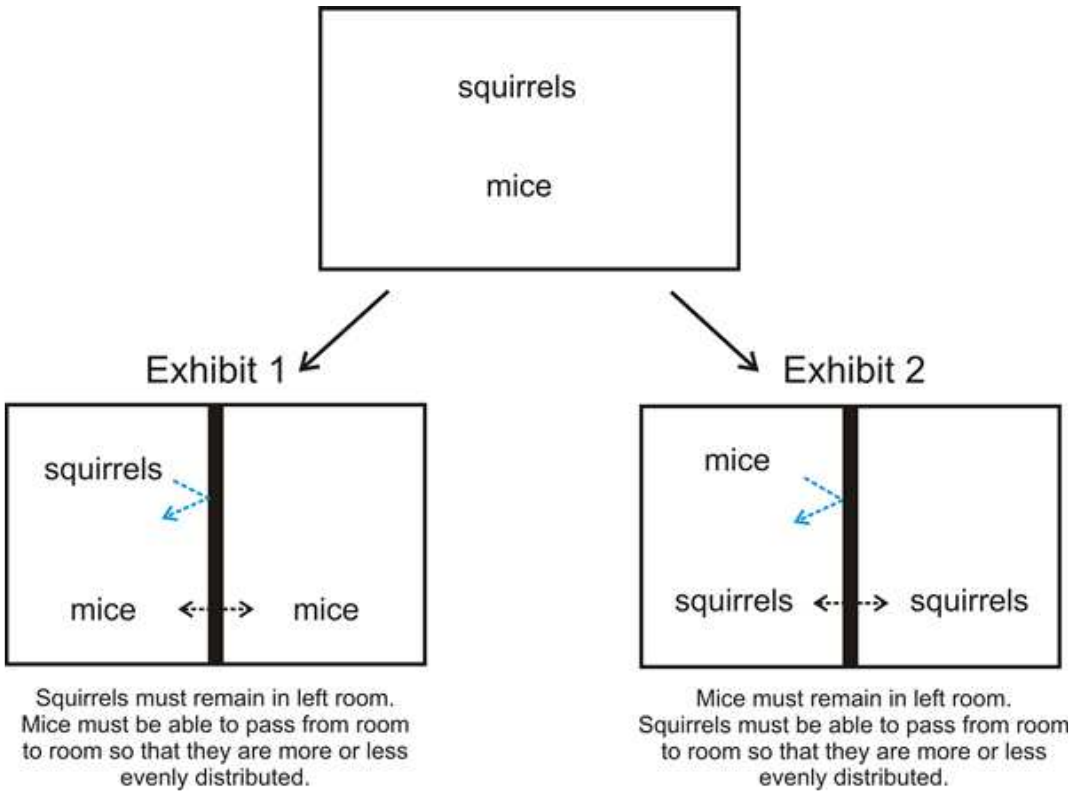
Photo by William C. Miller III, www.theazaleaworks.com
Used with permission

Squirrel
25 cm long, 8 cm wide
400 g

Photo by Michael Pereckas, www.mspland.com
Used with permission

Mouse
7 cm long, 2 cm wide
20 g

Part I



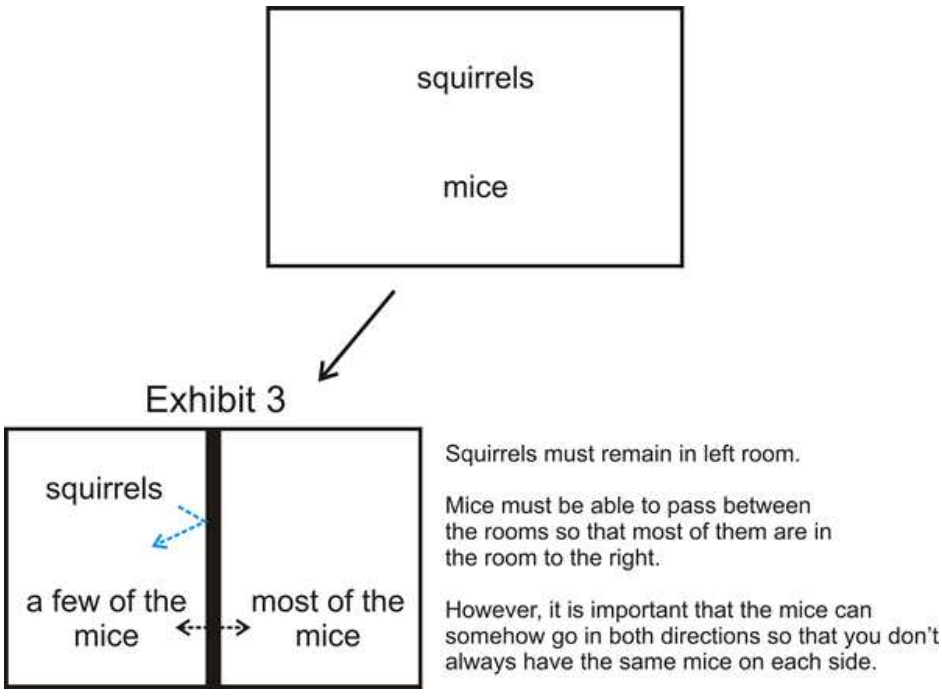
Squirrels must remain in left room. Mice must be able to pass from room to room so that they are more or less evenly distributed.

Mice must remain in left room. Squirrels must be able to pass from room to room so that they are more or less evenly distributed.

Part II

Imagine a rat gets into the exhibits, and it has the same body size and mass as the squirrels. Based on your inventions for Exhibits 1 and 2, could the rat cross through the wall in either case? Why or why not? Write a short explanation.

Part III: Challenge



Delivery

Introduce the zoo exhibit invention as follows:

- Hand out the worksheet portion of the activity and stress that they should read it carefully (1-2 minutes).
- Verbally explain the activity and show them the first two exhibits (generally the groups will work through exhibit 1 quickly and spend more time on exhibit 2). Encourage them to draw detailed diagrams of their solutions whenever possible.
- After another 10-15 minutes (try to gauge their progress), introduce Part II and verbally explain the question.
- Optional: Part III can be introduced about 5-7 minutes before the end in order to give them something challenging to try, although it is likely that many groups will not complete this part.
- Collect the activities from the students prior to presentation of some of the ideas.

Possible Solutions to Expect

Part I – Exhibit 1

As the first exhibit is designed to be and easy task, most groups will produce the solution of simply making a hole big enough for the mice but too small for the squirrels (there may be slight variations of this).

Part I – Exhibit 2

The second exhibit requires more thought to solve, and the groups will need more time to develop and draw out a solution. Common solutions include:

- A pressure sensitive pad that opens a door. Only the squirrels have enough mass to trigger the pad (note: it is worth asking the class at some point to consider if multiple mice could mimic a squirrel and cross the wall).
- A door with a spring. Only squirrels are strong enough to push through.
- A tail or paw sensor. This solution is entertaining for the students, and it is very useful as an analogy during the wrap-up discussion.
- A hole in the wall that is low enough for the squirrels to jump to, but too high for the mice. The wall can be coated with a surface that the mice cannot climb (like glass).

Part II

This part of the activity depends on their inventions in Part I, although they can answer the question in any case. This part is designed to be an explanation point during the wrap-up.

Part III: Challenge (optional)

This part of the activity is quite new, and so we have little experience with it. The purpose of this was to have the groups invent a system that required energy input in order to create an imbalance in the mice. We discovered that many groups use a passive method that creates an imbalance due to probabilities. For example, creating funnel shaped holes that are large on one side and small on the other could allow the mice to find them faster on one side versus the other, creating an imbalance.

Wrap-Up Discussion

The wrap-up discussion centers on cell membranes, transport, and diffusion. The following points are usually covered:

- The cell membrane is a solution to the problem of diffusion, that is, cells need some kind of barrier in order to prevent all of their stuff from floating away.
- Unfortunately, even though the cell membrane solves a problem, it also creates new problems. Specifically, the cell must get certain things across the barrier (like food and waste) while preventing other things from crossing.
- Therefore the membrane must be semi-permeable, and it must be selective. This is achieved by using proteins that act like gates (this should map well to the different invention ideas).
- In some cases, proteins can simply make a hole through the membrane (porins) which often allow molecules that are small enough (or have the correct properties) to cross.
    - This links well to the inventions from exhibit 1.
- In some cases the proteins need to be very selective to allow one molecule through the membrane while preventing other molecules from passing. To accomplish this, proteins recognize certain specific features of the molecule.
    - This links well to the invention in exhibit 2, where the mass or size or physical features of the squirrels can be used to differentiate them from the mice.
- Different molecules that share a common feature that is recognized by a transport protein may both be transported across the membrane. In the same vein, similar molecules that differ in a key feature may not both be recognized by a transport protein, and only one is transported.

  - This links well to the question involving a rat. No matter if the rat could or could not cross through the wall, the invention can be used as an analogy.
  - For example, if their invention used mass as the factor in exhibit 2, then the rat could cross (i.e. different molecules with a common feature that is recognized by a transporter).
  - On the other hand, if they used a tail sensor in exhibit 2, the rat won't cross as its tail is different from a squirrel's tail (i.e. similar molecules that differ in a key feature and so can be differentiated).
- Energy can be used to create an imbalance of molecules on one side of the membrane (active transport).
  - This concept is meant to link to the challenge question, as described on the previous page.

Follow-Up Problem – Transport

Part I

Consider the data from two membrane transport experiments shown on the next page. Assume that the uptake by the cells does not change the concentration outside the cells (the volume of the cells is extremely small compared to the medium they are in). You can assume that the transport proteins involved are different in each experiment, so they are named Protein 1 and Protein 2, and that each protein transports only the molecule indicated.

Compare the sets of data. Can you determine whether the transport is active transport or facilitated diffusion is being used in each case?

Suppose you wanted to devise a way to graph transport data to quickly indicate the type of transport being used visually (in other words, you could quickly glance at the graph and be able to say whether active transport or facilitated diffusion is being used). Can you devise a way to manipulate and graph the data to show this?

We recommend that you copy and paste the data on the next page into a spreadsheet program in order to plot the data.

Part I Data

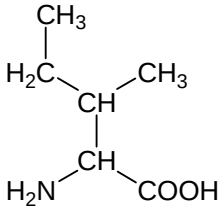
Protein 1 + Molecule X		**Protein 2 + Molecule Y**	
Molecule X Concentration Outside the Cell (□M)	14.0 (constant)	Molecule Y Concentration Outside the Cell (□M)	0.14 (constant)
Time (min)	Molecule X Concentration Inside the Cell (□M)	Time (min)	Molecule Y Concentration Inside the Cell (□M)
1	6.8	1	0.1
2	9.5	2	0.5
3	10.6	3	0.7
4	11.4	4	1.0
5	12.0	5	1.3
6	12.5	6	1.6
7	12.9	7	1.9
8	13.2	8	2.2
9	13.4	9	2.5
10	13.6	10	2.8
11	13.7	11	3.1
12	13.8	12	3.3
13	13.9	13	3.6
14	13.9	14	3.9
15	13.9	15	4.1
16	14.0	16	4.3
17	14.0	17	4.4
18	14.0	18	4.5
19	14.0	19	4.6
20	14.0	20	4.7

Note the experiments use different concentrations outside the cells.

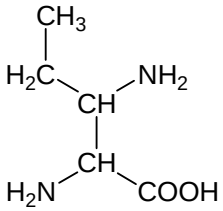
Part II

Consider the data on the next page taken from several transport experiments. Each experiment uses a different amino acid (shown below). Note that the second and third amino acids are not natural amino acids. One important thing to notice is that their structures are all very similar.

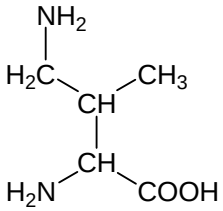
Compare the three data sets on the next page (plotting them may be useful). **If we assume that the transport of all three amino acids involves the same transport protein**, what can you conclude about the structures of the amino acids relative to their transport by the protein?



Isoleucine



β-amino-ethylalanine



γ-aminovaline

Part II Data

Protein 3			
All Concentrations Outside the Cell (□M)	5.5 (constant)		
Time	Isoluecine Concentration Inside the Cell (□M)	□-amino-ethylalanine Concentration Inside the Cell (□M)	□-aminovaline Concentration Inside the Cell (□M)
1	0.3	0.3	0.0
2	0.7	0.6	0.0
3	0.9	0.8	0.0
4	1.2	1.1	0.1
5	1.5	1.4	0.1
6	1.8	1.6	0.1
7	2.1	1.9	0.1
8	2.4	2.2	0.1
9	2.7	2.4	0.1
10	3.0	2.7	0.2
11	3.3	2.9	0.2
12	3.5	3.2	0.2
13	3.8	3.4	0.2
14	4.1	3.7	0.2
15	4.3	3.9	0.2
16	4.5	4.0	0.2
17	4.6	4.1	0.2
18	4.7	4.3	0.2
19	4.8	4.3	0.2
20	4.9	4.4	0.2

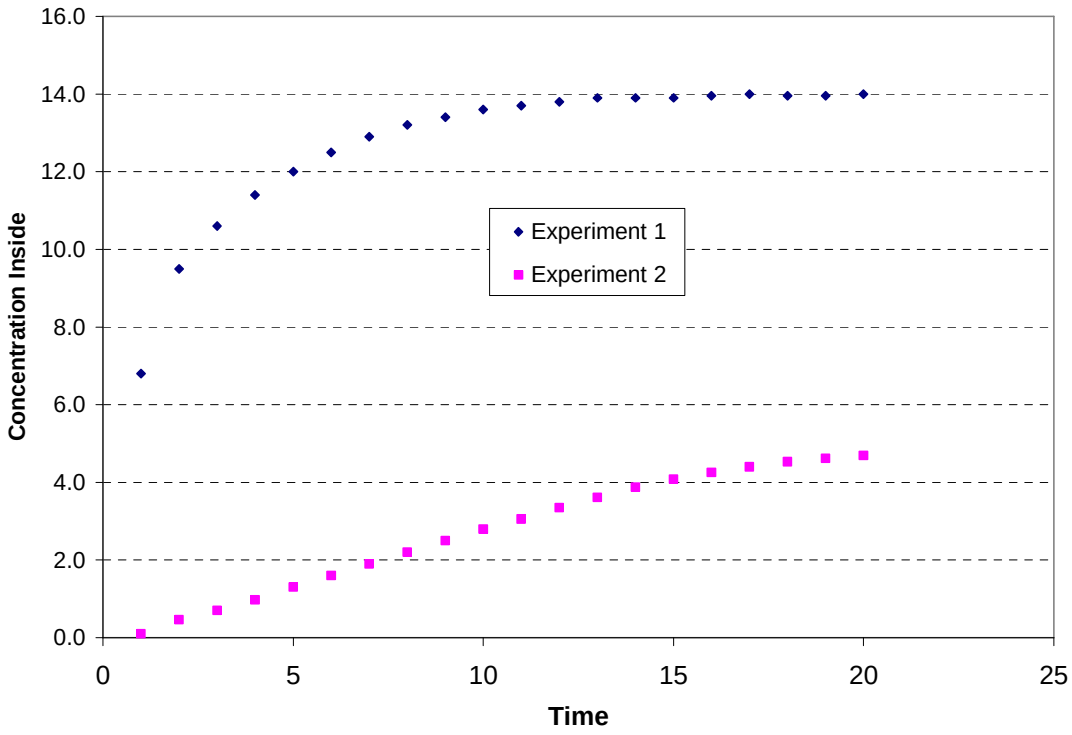
We recommend that you copy and paste the above data into a spreadsheet program in order to plot the data.

Follow-Up Problem – Transport
Suggested Answers

Part I

The most important thing to notice about the data is the difference between the starting concentrations outside the cell versus the final concentrations inside the cell for both experiments.

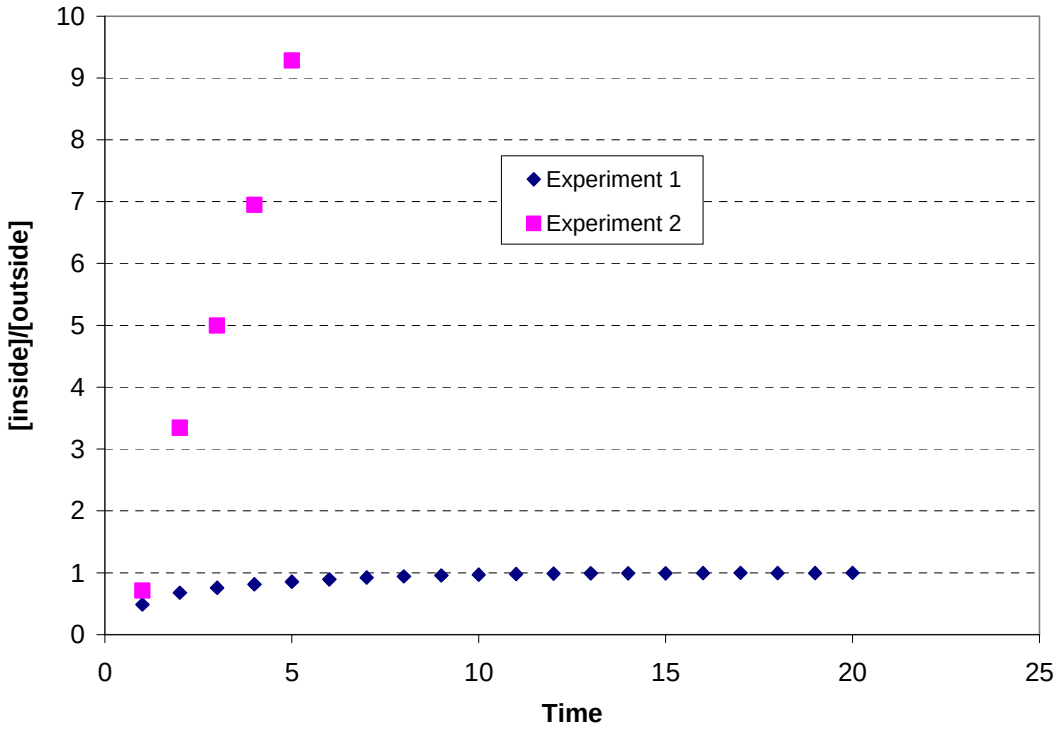
In experiment 1, the concentration inside the cell increases until it matches the outside concentration and then appears to level off. In experiment 2, the inside concentration appears to pass the outside concentration and keeps going. These match the situations seen during the invention activity (even distribution of the animals vs. having more on one side).



These observations are typical of the different types of transport that use proteins. Facilitated diffusion allows molecules to cross a cell membrane as long as the concentrations inside and outside are different. If the concentrations even out, net movement across the membrane stops. Active transport on the other hand will continue to transport molecules across a membrane regardless of concentration. From the data it appears that experiment 1 involves facilitated diffusion while experiment 2 involves active transport.

Notice that plotting and comparing the data graphically doesn't easily distinguish between the types of transport. Experiment 1 seems to be transporting things faster, even though it is actually facilitated diffusion. Knowing the outside concentrations help distinguish them, but at first glance it is not obvious.

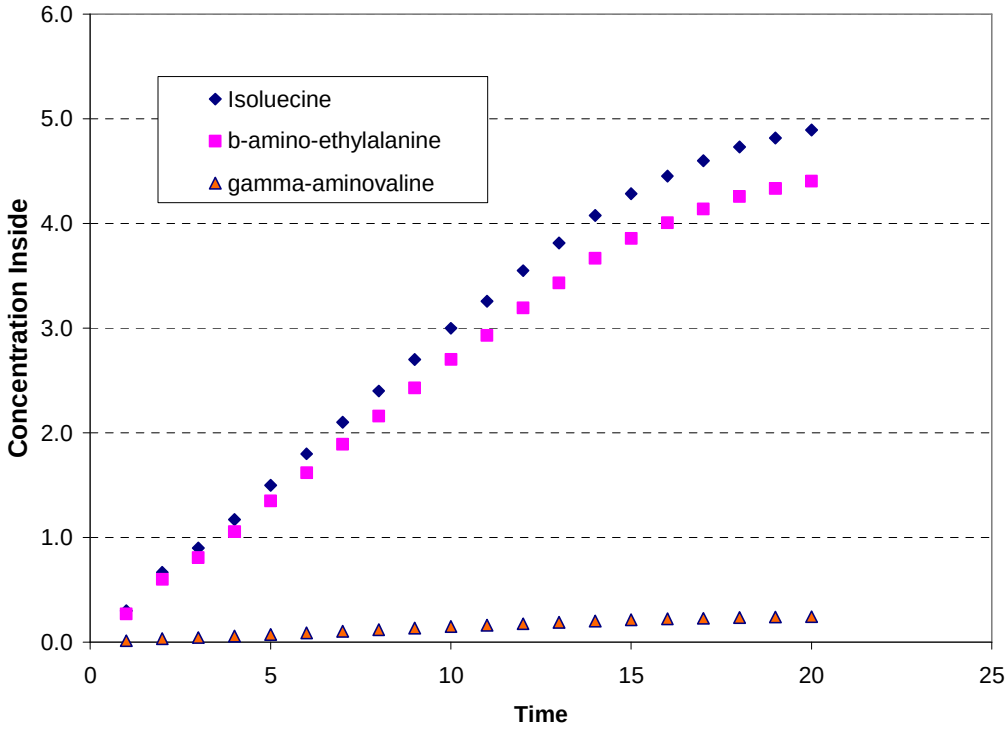
A better way to graphically distinguish them is to plot the ratios of the inside concentrations to the outside concentration in both cases (plot [inside]/[outside] vs. time). The graph would then look like the one below (it is zoomed in so you can't see all of the data for Experiment 2).



Notice that in Experiment 1 the plot levels off at a ratio of about 1. This is typical for things that depend on diffusion; the ratio of concentrations will approach 1. On the other hand, the Experiment 2 plot passes 1 and keeps going. This is typical of active transport; the ratio of concentrations does not approach 1.

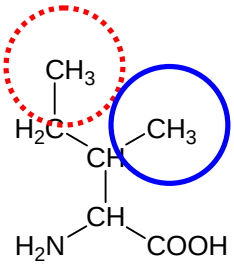
Part II

If we plot the data, we get a graph similar to the one shown below.

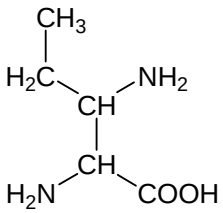


From the data it appears that both isoleucine and β-amino-ethylalanine are transported easily by the protein, with isoleucine being slightly better (perhaps the protein in question is transport protein for isoleucine). On the other hand, γ-aminovaline is not transported very well by the same protein. Since all three molecules have a similar overall structure, we can probably conclude that specific groups on each molecule are responsible for enzyme recognition and binding.

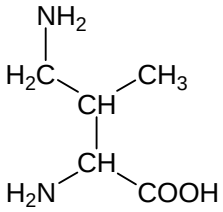
Looking at isoleucine and γ-aminovaline it appears that changing the last methyl group (CH_3) into an amino group (NH_2) has a large impact on the protein's ability to transport the molecule. On the other hand, changing the branched methyl group into an amino group (as in β-amino-ethylalanine) appears to have only a small impact on transport. From this we can conclude that the group circled in dashed red (see the next page) is the most critical for the transport protein recognizing the molecule, while the group circled in blue is not important.



Isoleucine



β-amino-ethylalanine



γ-aminovaline

Chapter 4
Invention: The Chain Machine

Description

This activity is designed to introduce the concept of template direction synthesis to students. A machine that links chain pieces together is used as an analogy for the enzymes responsible for DNA replication (DNA polymerase), transcription (RNA polymerase), and translation (ribosome). The students are tasked with designing a method for the machinery to correctly link the chain pieces together, and the activity is designed such that they will invent some form of a template mechanism. The concepts of directionality and code reading/translating are also introduced.

Also included below is a follow-up problem set (and suggested answers) that is designed to have students work though some of the concepts of template directed synthesis that the invention activity relates to. We generally distribute the problem to the students via the course website and make the suggested answers available a week later.

Related Topics: Template Directed Synthesis (transcription, translation, DNA replication).

Key Features

- The machine and all solutions must be purely mechanical in nature. This is a critical point that must be stressed, as the analogous systems within cells also work in a mechanical fashion (enzymes, substrates, and reactants colliding and reacting).
- Part I represents the mechanics of template directed synthesis. The students will generate inventions that are analogies to how cells read a template and make a corresponding molecule based on the template sequences.
- Part II specifically relates to triplets and the genetic code. It can also be used to discuss the concept of template directionality.

Activity Handout:

Invention – Chain Machine

Part I

You are a design engineer for a company that produces special chains of large plastic objects and magnets. These chains are used in ships as spacers between the inner and outer hulls and are extremely valuable. The current machine being used to make these chains efficiently connects one piece to the others (magnets and plastic) along the nylon rope. But this is all it can do, requiring someone to manually feed the components into the machine in the correct order (boring and slow).

You are given the job of redesigning the machine to scale up production. The machine needs to be able to mass produce the chains with the following conditions:

- The machine must be able to mass produce different chains for ships, although it only needs to produce one type of chain at a time.
- The machine must be able to select the types of pieces and link them in the correct order.
- The machine must link the magnets in the correct orientation.
- The machine must be purely mechanical in nature (no electronics or computers).

Your job is to redesign the machine so that it can mass produce any chain design. You are free to be as creative as you like as long as your design satisfies the conditions outlined above. You are not permitted to change the chain designs or change the types of pieces used.

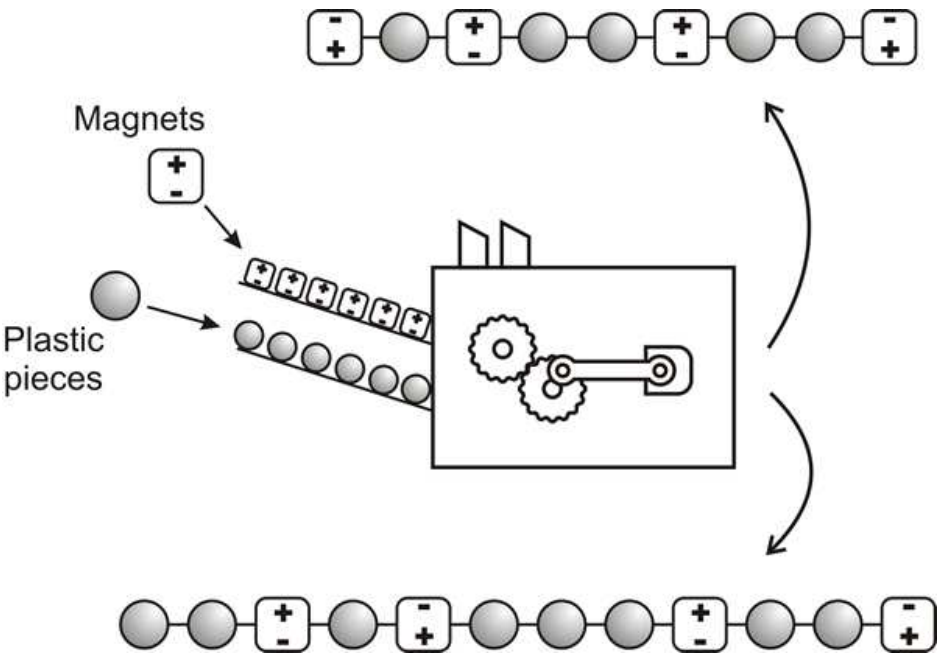
Part II **(only attempt this once Part 1 is complete)**

A customer that has purchased a large number of different chains send them back to have them fitted with special casings, which are designed to fit three adjacent chain pieces (an example will be shown on the screen). These casings must match the chains in both shape and magnet polarity. If we assume that the two halves of the casing shown on the screen make up ONE whole casing, how many different casings are possible? The casing always fits the chains in groups of three chain pieces.

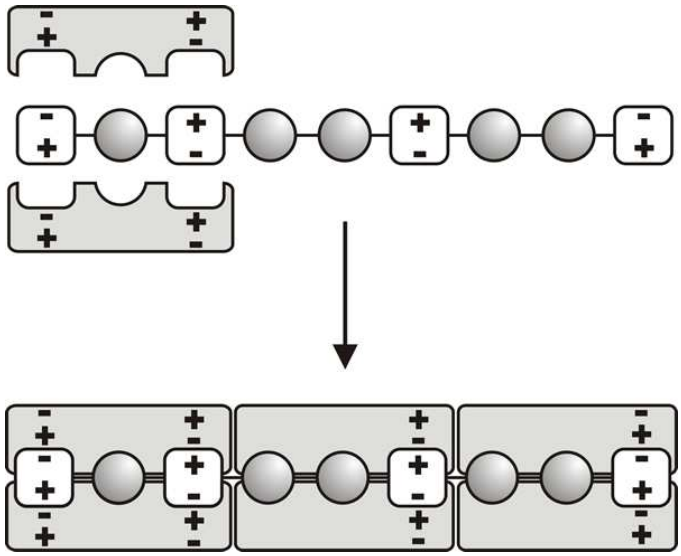
Can you think of a way a second machine could correctly choose and fit the casings to the chains?

Slides (not to be handed out to the students):

Part I



Part II



Delivery

Introduce the invention as follows:

- Hand out the worksheet portion of the activity and stress that they should read it carefully (1-2 minutes).
- Verbally explain the activity and show them the diagram of the machine and the two example chains.
    - Explain to them that these chains are examples, and that their invention should be able to make any sequence of magnets and plastic pieces.
    - Emphasize that the plastic pieces and the magnets are not delivered to the machine in any particular order or orientation, and therefore the machine must be able to automatically select the pieces and the orientation of the magnets.
    - The machine only needs to make one type of chain at a time, and it needs to know how to make the same chain over and over again until it is recalibrated for a chain with a different sequence.
    - Emphasize that the machine must be completely mechanical in nature (all moving parts and no electronic parts).
- Encourage them to draw detailed diagrams of their solutions whenever possible.
- After another 10-15 minutes (try to gauge their progress), introduce Part 2 and verbally explain the question and show them the diagram on the screen.
- Collect the activities from the students prior to presentation of some of the ideas.

Possible Solutions to Expect

Part I

Usually the students quickly realize that in order for the machine to continually make the same type of chain using the correct pieces in the correct order, the machine needs some kind of "blueprint". However, with no electronics allowed, this blueprint needs to be physical in nature. In other words, the design needs to use some kind of template in order to ensure the proper chain is made. The students may or may not use the term "template" in their invention, but all of the solutions we have observed (or imagined) can be classified as a template. Some of the common solutions are:

- A piano roll template.
- A punch card template.
- A large template that use holes with the correct shapes and in the correct sequence.
- A cog-wheel template with specific shapes in the wheel that can pick up the correct piece in the correct order (sometimes several wheels are used).

- There is one solution that is rare but worth mentioning. A prototype chain can be used as the template for the machine (the machine needs a way to "read" the chain). This solution is probably the best analogy to the concepts that relate to this activity.

In addition to the template solutions listed above, the students must also consider how the machine can orient the magnetic pieces correctly. In general this is not difficult and they easily incorporate a magnetic component into the templates that can pick up the magnetic pieces in the correct orientation use magnetic polarity.

Part II

With regards to the number of possible casings, there are actually four possible answers depending on the assumptions made.

- If the students assume that direction of the casings matter in terms of back to front and top to bottom, then there would be 27 possible casings (i.e. three possibilities in each of the three positions).
- If the students assume back to front direction matters, but not top to bottom (i.e. the same half-casing can be used on the top or bottom) then there would be 14 casing designs needed.
- If the students assume that top to bottom direction matters, but not front to back (i.e. a half-casing on the top could be turned around to face the other way along the chain) then there would be 18 casing designs needed.
- If the students assume that direction doesn't matter at all (i.e. the casings halves can be rotated around back to front and bottom to top) then only 10 casing designs are needed.

In terms of designing a second machine to match the proper casings to the chains, the students only need to think of general solutions and not necessarily have a detailed design (although for groups that have time, encourage them to do so). In general, there are two mechanisms that could be used:

- The machine can somehow read the triplets and choose the correct casings pieces.
- The machine tries every casing (either randomly or in some order) until it finds the casing that fits (due to shape and polarity, the wrong casing halves should fall off).

Wrap-up Discussion

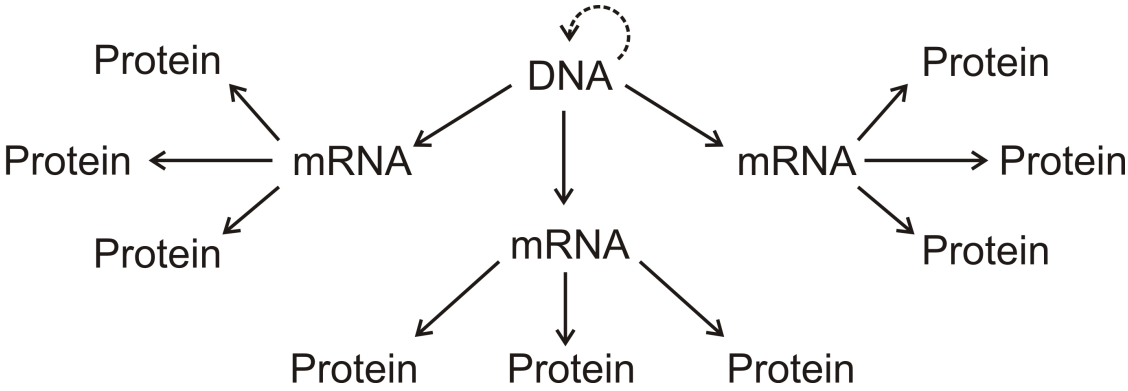
The wrap-up discussion centers on template directed synthesis. It is worth telling this to the class and then asking them to identify the three main types of TDS (transcription, translation, and DNA replication). The following points are usually covered:

- Cells don't "know" how to do or make anything. The cell needs a physical set of instructions that tell it how to make things, and this set of instructions is used each time.
- The physical characteristics of the instructions tell the cell how to make something. Such a set of instructions is called a template, and the physical structure of the template defines the physical structure of the product.
    - It is worth pointing out to them that even though the class came up with many different solutions, they all use a physical template of some kind to define the chain that is made. Each type of chain requires a different template.
- Synthesizing something based on a template is called "template directed synthesis, and there are three critical examples of this process within cells: transcription, translation, and DNA synthesis.
- In all cases the template must be present for new DNA, RNA, or protein to be made. It is also critical that the template is read in a certain direction (i.e. directionality is important).
    - It should be noted that for this activity direction does not appear to be important (i.e. in both Part I and Part II, reading the chain from the opposite direction would still give the same results). This is because the two ends of the chain are not unique in anyway. However, the concept of directionality does come into play in Part II as noted in the solutions section, and the point of directionality being important for DNA, RNA, and proteins should be impressed upon the students.
- Changes to the template often, but not always (they will learn why), lead to direct changes in the product.
    - For example, a change in the template would lead to a different chain in Part I, and that would require different casings in Part II.
- In cells, the most obvious consequence of a changed template is a changed protein structure, and this could possibly lead to a different three dimensional shape of the protein. Since the shape is critical for proper protein function, such changes can have drastic, and often dire, results for the cell.
- As a result, cells have many ways to prevent the template from changing (mutation repair is a good example of this).

Follow-Up Problem – Template Directed Synthesis

Part I

The information flow in cells can be summarized with the figure below.



DNA is used as the template for the synthesis of mRNA, which is in turn used as the template for protein synthesis. DNA is also used as the template for synthesis of new DNA.

Scientists can track the progress of mRNA synthesis and protein synthesis by adding radioactive uracil (for RNA) and leucine (for proteins) to cells and observing how much is incorporated in RNA and protein (i.e. observing the amount of mRNA strands and protein that have radioactivity).

Suppose we add a compound to the cell that stops all RNA synthesis, and we observe that the no new radioactive mRNA molecules are produced. However, we observe that new radioactive proteins are made for up to five minutes after RNA synthesis stops.

What can you conclude from this?

Part II

Recall from the invention that the machine you designed was able to read a template and make a new chain based on that template. If the DNA and mRNA are the templates, then the proteins that read the templates and make the new molecules are the machines. For DNA synthesis, the "machine" is DNA polymerase, and for RNA synthesis it is RNA polymerase.

A difference between DNA polymerase and RNA polymerase is the ability to "proof-read" the strands they are synthesizing. DNA polymerase has the ability to correct

errors that it makes, thereby making DNA synthesis accurate (there is about 1 error per billion base pairs replicated when the correction mechanisms is operating). RNA polymerase does not have this ability, and therefore if it adds the wrong piece to the chain it is making it cannot correct it (it makes about 1 out error per ten thousand bases transcribed).

Give a rationale for why the cell can tolerate the mistakes made by RNA polymerase. In the bacterial species where it has been investigated, it was possible to find a mutant of the cells that had lower rates of error during DNA replication. Give a rationale for not always having the lowest possible rate of error. What would limit the upper rate of error in DNA replication?

Part III

The invention activity part 2 (fitting the casings to the chain) is very similar to the mechanism that is used to select the right tRNA during translation. This mechanism might be related to why cells tend to try to reduce the number of tRNAs that carry any particular amino acid. Explain.

Part IV

On page 324 of the Freeman textbook you will find the codon table that represent the genetic code used by cells to make proteins based on the DNA/RNA templates.

Redraw the entire codon table as shown but without adding any of the amino acids names (i.e. make your table with just the codons). Beside each codon, place a symbol corresponding to the list below:

Hydrophobic amino acids: ●

Polar neutral amino acids: ▲

Charged amino acids: ✕

From your table, look at the distribution of symbols. What can you conclude about the genetic code and the codons?

Follow-Up Problem – Template Directed Synthesis
Suggested Answers

Part I

Since RNA synthesis is halted, no new RNA, including mRNA, can be made. However, this would have no effect on any mRNA molecules that were already made. Given that protein synthesis continues for a while after RNA synthesis is halted, we can conclude that the mRNA molecules already made are stable within the cell (are not immediately degraded). These mRNA molecules can serve as the template for protein synthesis for a short while before they are degraded.

Part II

Since the DNA serves as the template for RNA, it makes sense that cells would want to keep the DNA as error free as possible, as mutations could cause problems not only for the cell itself, but also all future daughter cells.

RNA, on the other hand, is not as critical. This is because the DNA is used as a template for many copies of the RNA. Even if one mRNA molecule contains an error, there will be many other correct versions of that mRNA made by the cell, and so normal proteins will still be produced.

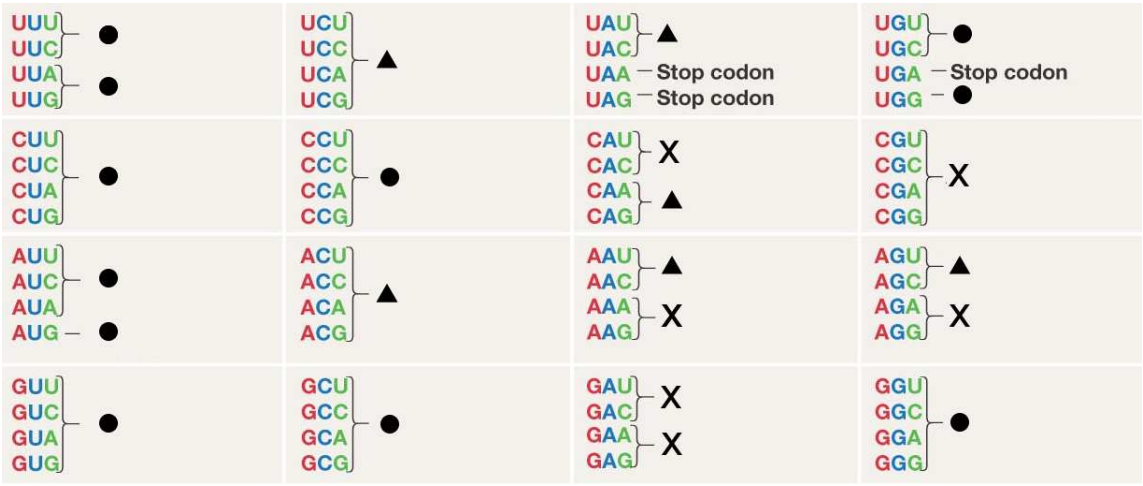
DNA replication is not perfect, however, and errors can occur with the DNA. This is advantageous to cells, since the ability for DNA to mutate provides cells with a mechanism by which they can change and adapt. Cells that used perfect DNA replication could never adapt to long-term changes in the environment.

On the other hand, cells do not want the error rate to be too high, otherwise mutations would cause proteins to be non-functional too often, and the cell would not survive.

Part III

Recall that simply trying all casings until one fit was one solution some of you suggested for part 2 of the invention activity. In this case, it stands to reason that having few types of casings would make this method more efficient. This is similar to the situation inside of cells. Having fewer tRNA molecules in use means that protein synthesis is more efficient (does not need to try as many tRNA molecules for each codon to find the correct “fit”).

Part IV



Your table should look something like the one shown above. The most important thing to notice is that the distribution of the amino acids is not random. Hydrophobic groups tend to use similar types of codons, and polar or charged amino acids do the same. It is even more obvious if you grouped all the hydrogen bond forming amino acids (polar neutral and the charged amino acids) together.

Chapter 5
Invention: Controlling the Chain Machine

Description

This activity revisits the chain-making machine introduced in the previous activity, this time to introduce the concept of gene regulation and something we call the "logic of gene regulation" (why it makes sense to make proteins under certain conditions and not others). In this activity, the students are tasked designing the control mechanism of the machine such that it makes the correct type of chain based upon the availability of pieces. The students are also asked to consider what could cause certain types of malfunctions within the machine that cause the wrong chain to be made or no chains to be made at all.

Also included below is a follow-up problem set (and suggested answers) that is designed to have students work though some of the concepts of gene regulation that the invention activity relates to. We generally distribute the problem to the students via the course website and make the suggested answers available a week later.

Related Topics: Gene Regulation, the Logic of Gene Regulation, the *Lac* Operon

Key Features

- The student will be generating inventions that are analogous to inducer/repressor systems, inducer exclusion, and the effect of mutations on gene regulation.
- Part I represents direct induction/repression of gene expression and the student inventions will relate directly to this. Some of the student inventions will also be direct analogies for inducer exclusion.
- Part II represent the effect of mutations on gene regulation. This part requires the students to reflect on their inventions in Part I, rather than invent something new. This part is designed to make students consider how a control system can fail and the consequences of these failures, which directly relate to the failure of gene regulation due to mutations.

Activity Handout:

Invention – Controlling the Chain Machine

Part I

Thanks to your recent redesign break-through, your company has had great success in mass producing the magnet chains that are used for ship construction. After analyzing the market, it has become clear that the company would be most profitable by concentrating on the production of its two best selling chains.

Chain Type A uses Type A magnets, and demand is so high that the company can sell these chains as quickly as they are made. Chain Type B uses Type B magnets, and does not sell as quickly as Chain Type A, but is still profitable.

The supply of both magnet types fluctuates (and is often limited), and the machine can only be configured to produce one type of chain at any given time. As such, it is important to closely control which type of chain is produced in order to increase efficiency and profits. Note that the plastic pieces used are easily obtained and their supply is not limited. Also, recall that the new machine uses a unique template for each type of chain that is produced, and the templates need to be switched when a different chain type is needed.

Your company assigns you with the task of further redesigning the manufacturing process, this time with the control system of the machine. In particular, the control system must do the following:

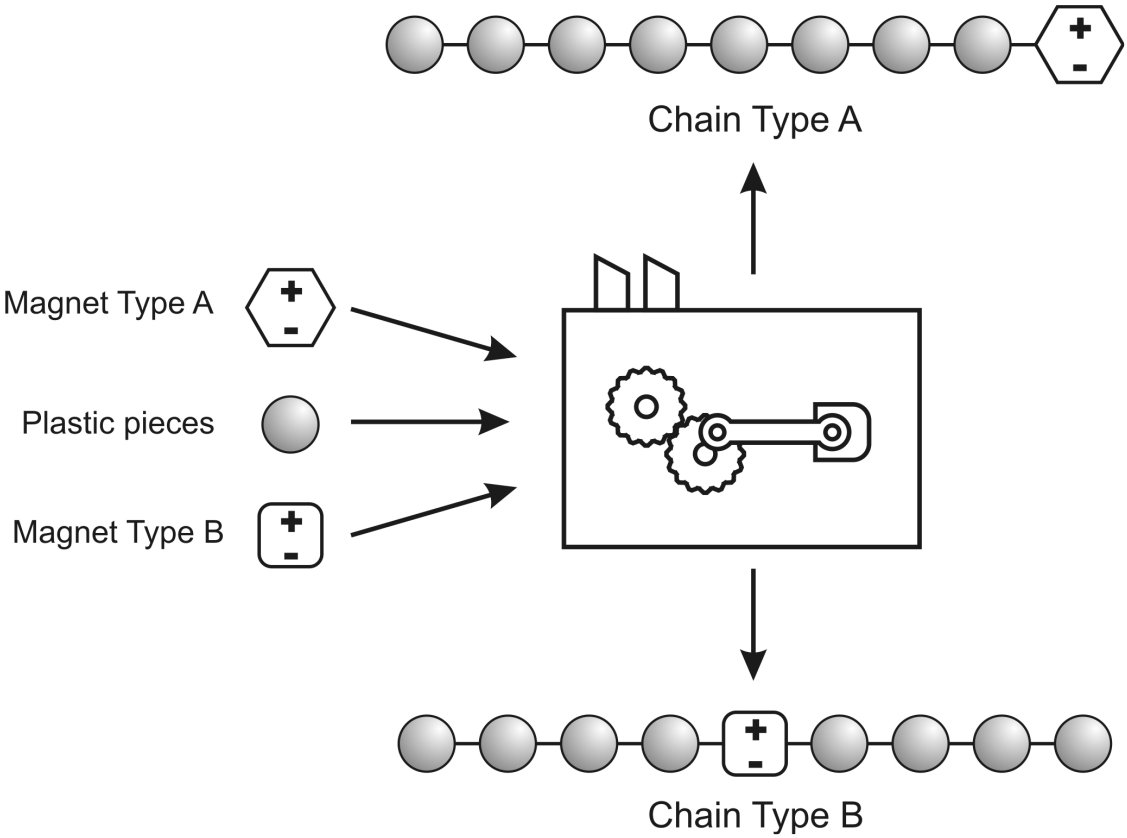
1. If only Type A magnets are available, the machine must produce Chain Type A.
2. If both types of magnets are available, the machine must produce Chain Type A.
3. If only Type B magnets are available, then machine must produce Chain Type B.

Your job is to redesign the control mechanism of the machine so that it follows the above three rules. In particular, the machine must be able to switch (as quickly as possible) the templates and produce the correct type of chain based upon the supply of the magnets. As with the previous activities, your solution must be mechanical in nature, and cannot use electronics or computers. As before, you can add anything that would be useful to the inner workings of the machine, or as an external component of the machine.

Parts II and III will be shown on the screen.

Slides (not to be handed out to the students):

Part I



Part II (slide)

Of course, the control mechanism might malfunction. Consider two possible problems that could occur:

- The machine would constantly make Type B chains, even when Type A magnets are available.
- The machine does not make any chains, even when pieces are available and the rest of the machine is in good working order.

Looking at the control mechanism you have designed so far, is it possible for either of these malfunctions to occur? Explain why or why not (and be realistic…saying the machine is made of indestructible materials in not sufficient).

Part III (slide)

It would be very useful if the control mechanism could tell when the availability of Type A magnets is getting low, instead of waiting until they are not there at all.

Looking at your control, is it possible for it to respond to this condition? Explain.

If it isn't possible based on your design, explain why, or redesign it if you have time.

Delivery

Introduce the activity as follows:

- Hand out the worksheet portion of the activity and stress that they should read it carefully (1-2 minutes).
- Inform the students that this activity is an extension of the previous invention (Chain Machine). It is important to tell them that this activity does not depend on their solution to the previous activity.
- Tell the students that the chain-making machine that they designed is a big success and they need to further automate it.
- Verbally explain the activity and show them the diagram of the machine and the Type A and Type B chains.
    - Emphasize that, as before, the machine must be completely mechanical in nature (all moving parts and no electronic parts).
    - Emphasize the three conditions that must be followed, and also emphasize that the machine must be able to respond as quickly as possible to the changing supply of the magnets
- As always, encourage the students to consider multiple mechanisms, and to draw, in detail, their final solution.
- Give the student about 15 minutes to work on Part I before introducing Part II, and then give them another 5-10 minutes (gauge their progress by walking around the room).
- Also, in Part II, encourage the students to think critically about the design of their mechanism and to be detailed in how their mechanism could fail (i.e. what could break) and lead to one or both of the types of malfunctions.
- Collect the activities from the students prior to presentation of some of the ideas.

Possible Solutions to Expect

Part I

This activity often generates a wide variety of solutions. These solutions involve a control mechanism that "senses" the presence of Type A and responds by blocking the delivery of the Type B magnets to the machine, or by blocking the use of Type B magnets within the machine. The solutions should also include some mechanism for switching the templates. Some common examples include:

- The presence of Type A magnets physically blocks the movement of Type B magnets.
- The presence of Type A magnets in their delivery system physically push against a switch that mechanically closes a gate within the Type B delivery system. There

are many variations of this solution (for example, the Type A system uses the weight of the Type A magnets in a hopper to push down and close a gate in the Type B system).

- Some solutions involve a sorting mechanism that assumes the two types of magnets are mixed together. The sorting mechanism separates the two types of magnets and as long as the machine detects and sorts out the Type A magnets, the Type B magnets are not used and returned to storage. The magnets can be sorted by shape. Some students will also assume the Type A magnets are heavier and can be sorted based on weight.
- In terms of selecting the correct template to use based on the magnets available, most groups simply add a mechanical connection to the above systems that switches the templates.
- In the case of the sorting mechanism, the sorted magnets are simply delivered to their own template (in different parts of the machine). The Type B template is deactivated in some fashion while the Type A template is being used.

Part II

How the students answer Part II depends on the solutions they develop in Part I. In general there should always be a way for either type of malfunction to occur (the switch breaks, there is a blockage of the delivery systems, etc.). The main point of Part I is simply to get students to think about the possibility of the control systems failing and the wrong thing happening.

Part III

As this part of the activity is fairly new, we have only had limited experience with it. In addition, we found that most groups did not have enough time to consider this part of the activity in any great detail. However, for those groups that did consider it, the solutions were generally extensions of their original ideas. Commonly groups that used springs, scales, or physical switches redesigned their solution to include a series of these devices that would sequentially detect a decrease in the Type A magnet pool.

- For example, students that used a physical switch inside the Type A magnet delivery chute redesigned it to use a multiple switches all along the chute that would turn off as the end of the Type A magnet queue passed them. This would give a relative idea of the amount of Type A magnets remaining.

Wrap-Up Discussion

The wrap-up discussion should revolve around the logic of gene regulation, using the *lac* operon as an example (this is not essential, as other operons or examples of gene regulation could also be used). In our experience, emphasizing the logic of gene regulation is important as student often try to memorize the details without understanding why it makes sense. For example, in the case of the *lac* operon, students often miss the point that it makes sense that when glucose (preferred food) is available, lactose is excluded from the cell and the *lac* operon is turned off. With this in mind, the following points are usually covered (using the *lac* operon as an example):

- Gene regulation is about controlling when certain genes are expressed and proteins are made. It is as waste of energy and resources for cells to make proteins that aren't necessary.
    - In the case of the *lac* operon, the Lac proteins breakdown lactose to use as energy, and so it would be a waste of time to make these proteins if lactose is not available.
    - There isn't an exact match of this concept to the activity, but it would be similar to the machine continually trying to make Type B chains when no Type B magnets are available (would make chains of plastic pieces only).
- The regulation of genes changes in response to signals, and these signals can either increase or decrease expression of the genes. In the case of the *lac* operon, gene expression changes in response to two signals: lactose and glucose.
    - The presence of lactose within the cell directly alters the expression of the *lac* operon (increasing concentration leads to increasing expression).
    - The presence of glucose on the outside of the cell indirectly leads to a decrease in *lac* operon expression. As long as the cell is actively transporting glucose across the cell membrane into the cytoplasm, lactose is prevented from entering the cell. This process is called inducer exclusion **[see Note to Instructors on the next page]**.
- Gene regulation can malfunction, leading to expression of unneeded proteins.
    - There are many examples of mutations causing changes to gene regulation. For the *lac* operon, the obvious examples are mutations that cause the LacI protein to never bind to the DNA (*lac* operon always expressed) or to lose the ability to bind with lactose (always binds to the operator and turns turn off *lac* operon even when lactose is present).
    - These concepts relate to the ways in which the machine control can malfunction in Part II.
- Cells can detect gradual changes in amount of signal present, not just whether or not a signal is present.
    - This concept is a bit more difficult to explain in the short amount of time left for wrap-up, and may be better introduced during the subsequent lectures (simply refer back to the activity).

- Regulatory proteins constantly bind and release signal molecules (the rate of this is unique to each protein) in order to gauge the amount of signal present. The greater the amount of signal present, the larger the fraction of regulatory proteins that will have the signal bound at any given time.
- This concept relates to Part III of the activity.

Note to Instructors: Inducer Exclusion

We feel it is important to include information about inducer exclusion because, at the present time, instruction regarding the *lac* operon is often incorrect and leaves out the concept of inducer exclusion. There seem to be two reasons for this:

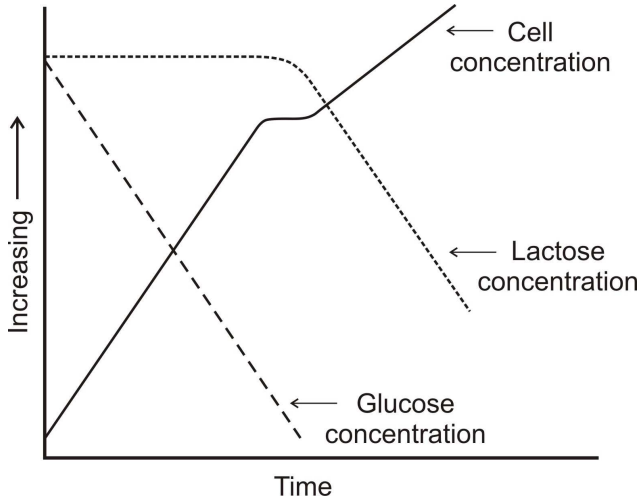
- Many textbooks continue to include incorrect information about how the *lac* operon is regulated by the concentration of glucose and how this leads to diauxic growth (despite this being contrary to the current scientific literature).
- Many instructors are not familiar with the concept of inducer exclusion.

The prevailing, but incorrect, explanation of how lac operon expression is affected by glucose is via the cAMP-CAP model. Textbooks incorrectly attribute the diauxic growth effect to the presence of glucose inhibiting the formation of cyclic-AMP (cAMP) and the formation of the cAMP-CAP protein complex. CAP (catabolite activator protein) is a protein that binds to the promoters of many operons, including the *lac* operon promoter, promoting transcription to occur. CAP binds upstream of the *lac* operon promoter (after first binding cAMP). Thus, students are taught that the presence of glucose decreases lac operon expression by reducing levels cAMP-CAP levels within the cell.

However, in reality, as long as **even a trace amount of cAMP-CAP is present**, it will be bound at the *lac* promoter (the cAMP-CAP complex exhibits exceptionally strong binding to the *lac* operon CAP binding site). As a result, under normal circumstances enough cAMP-CAP is always present to bind to the *lac* operon and the effect of glucose on cAMP synthesis does not affect regulation of the *lac* operon.

The effect of glucose on the expression of the lac operon, and diauxic growth, is due to inducer exclusion, which is a consequence of glucose transport across the cell membrane into the cytoplasm. One of the enzymes involved in glucose transport (Enzyme IIa) has the ability to bind to the LacY permease, causing a conformational change in LacY. When this happens, LacY cannot transport lactose into the cell. As long as glucose is available (and glucose transport continues) LacY does not transport lactose, even if lactose is readily available outside of the cell. Once the supply of glucose is exhausted, glucose transport stops and Enzyme IIa detaches from LacY, allowing transport of lactose to begin.

Diauxic growth is a direct consequence of inducer exclusion, as shown below.



In the presence of both glucose and lactose *E. coli* (for example) preferentially grow on the glucose and ignore the lactose. Essentially, the *E. coli* cells do not transport the lactose across into the cytoplasm due to glucose transport blocking lactose transport, as discussed on the first page. Once the glucose is used up, there is a small lag phase during which the lactose (after entering the cell) induces *lac* operon transcription and the LacZ and LacY enzyme levels begin to accumulate, and the cells begin to grow again using lactose as the energy/carbon source.

Extra Reading about Inducer Exclusion

If you are interested in reading some scientific literature about inducer exclusion, the following references are a good place to start.

Gorke, B., and Stulke, J. (2008). Carbon catabolite repression in bacteria: many ways to make the most out of nutrients. Nat Rev Micro 6, 613-624.

Crasnier-Mednansky, M. (2008). Is there any role for cAMP-CRP in carbon catabolite repression of the Escherichia coli lac operon? Nat. Rev. Micro 6, 954.

Gorke, B., and Stulke, J. (2008). Is there any role for cAMP-CRP in carbon catabolite repression of the Escherichia coli lac operon? Reply from Gorke and Stulke. Nat Rev Micro 6, 954.

Follow-Up Problem –Gene Regulation

Part I

Cells have thousands of genes that encode proteins, each of which has a different function within the cell. However, cells do not need every protein functioning all of the time; some proteins are only needed at certain times and in certain environments. As you can imagine, it would be a waste of energy and resources for a cells to make unneeded proteins. Because of this, cells have many ways of controlling when these proteins are produced. This is known as **regulating gene expression**.

How a gene is regulated is often related to the function of the protein it produces, and the presence of the signal. The signal can either induce (increase) or repress (decrease) the production of the protein.

For each of the proteins listed below, indicate what the appropriate signal molecule would be, and indicate whether the presence of the signal (or signals) is likely to induce of repress expression of the protein.

a) Degradation of the amino acid histidine as a carbon source.

b) Synthesis of the amino acid histidine.

c) Transport of phosphate across the cytoplasmic membrane.

d) Synthesis of an enzyme that is secreted to the outside of the cell to degrade DNA in the environment as a source of phosphate.

e) Enzyme to convert N_2 (nitrogen gas) to NH_4^+ when NH_4^+ is limiting in the medium.

f) Enzyme for the synthesis of polyhydroxybutarate. This chemical is used by the cell as a storage molecule under conditions when there is lots of glucose but limiting nitrogen or phosphate.

Part II

Consider the cases (a) and (b) on the first page for histidine. In both cases, there is a protein (different in each case) that controls whether or not RNA polymerase can transcribe the appropriate genes. Clearly, the protein in each case must interact with the signal in some way. It must also interact with the components of the cell that produce mRNA (think about what those are).

Propose a way that the signal in case (a) and in case (b) on the first page can interact with the control protein, and how that could possibly affect whether or not transcription occurs.

Follow-Up Problem – Gene Regulation
Suggested Answers

Part I

g) Higher concentrations of histidine in the cytoplasm should turn on transcription of the relevant genes.

h) Higher concentrations of histidine in the cytoplasm should turn off transcription of the relevant genes.

i) Higher concentrations of phosphate in the cytoplasm should turn off transcription of the relevant genes.

j) Higher concentrations of phosphate in the cytoplasm should turn off transcription of the relevant genes.

k) Higher concentrations of NH_4^+ in the cytoplasm should turn off transcription of the relevant genes.

l) Higher concentrations of glucose should turn on transcription of the relevant genes, while higher concentrations of nitrogen or phosphate should turn off transcription of the relevant genes.

Part II

Case (a): two possibilities

- There could be a regulatory protein that is bound to the DNA that blocks RNA polymerase from binding to the promoter of the relevant genes, thereby blocking transcription. When histidine is present, it binds to the regulatory protein and changes it shape so that the protein can no longer bind to the DNA.

- There could be a regulatory protein that histidine binds to, and together (histidine + protein) they bind to the DNA and help the RNA polymerase bind to the promoter of the relevant genes, thereby helping transcription start.

Case (b)

There could be a regulatory protein that histidine binds to, and together (histidine + protein) they bind to the DNA and block RNA polymerase from binding to the promoter of the relevant genes, thereby stopping transcription.

Chapter 6
Invention: Railway Safety and Repair

Description

This activity is meant to be an introduction to DNA mutation repair using the repair of damaged railway tracks as an analogy. Students are tasked with designing systems to locate certain types of damage along a railway track. While they do not need to design the actual mechanism by which the rails are replaced, they are also tasked with designing a quality control system that checks any replaced rails to ensure the correct type of rail is used.

Also included below is a follow-up problem set (and suggested answers) that is designed to have students work though some of the concepts of mutations and DNA repair that the invention activity relates to. We generally distribute the problem to the students via the course website and make the suggested answers available a week later.

Related Topics: DNA mutations, DNA error checking, DNA repair

Key Features

- This activity is designed to make students consider how cells can locate and repair mutations, and how cells use the DNA itself as the source of information to make the correct repairs.
- Part I represents how enzymes can locate and identify specific physical damage to one strand in the DNA double helix. The inventions developed by the students are analogies for these enzymes traveling up and down the DNA physically checking for damage.
- Part II represents the case of having a base-pair mismatch with the DNA. In this case, the students are meant to develop an information system whereby the repair system can determine which side is correct and which side needs to be replaced. This is a direct analogy to DNA marking, which provides a second piece of information that allows the cell to determine which base is the one that must be replaced (the base identity is used as the information to determine the correct base to use).

Activity Handout:

Invention – Railway Safety and Repair

Part I

You are a safety engineer for a high-speed railway company that has been contracted to lay a high-speed railroad track system across Canada. The rails used in such systems must be meticulously installed and maintained in order to prevent derailments. There are two types of rail damage that must be located and repaired immediately.

- Rail gaps can occur during construction if a shorter piece of rail is accidentally used (rare, but it does happen). At high speeds, the train wheels can be damaged from these gaps and the trains can derail. Even spaces as small as 1 cm in length are dangerous.
- Rail warping occurs when the rails bend outwards (or inwards) slightly. These warps can sometimes be hundreds of metres long, and allow the train to shift side to side. At the high speeds the train travels, even shifts of 1 cm can cause problems.

Invent a device that can travel along the tracks and identify any rails that need replacing by a repair team. Note that in order to save money, only the damaged rails must be replaced. This means that for gaps, the device must know which rail is shorter. For warps, the device must be able to tell when the warping begins and ends, and on which side it occurs.

Part II

To complicate things further, there are three types of rails used, each made of a different alloy (A, B, and C). The different alloys have different strength properties and are used in specific places along the track. They must match up so that a type A rail is always paired with a type A rail across from it, B across from B, and C across from C.

In order to identify the type, each rail must be marked in some way before being used along the track (you are free to decide how this marking works). This also means the device in *Part I* must be able to identify the type of rail needed for repairs so that the repair team brings the correct types of rails. Neither the device nor the repair team carries blueprints for the entire track.

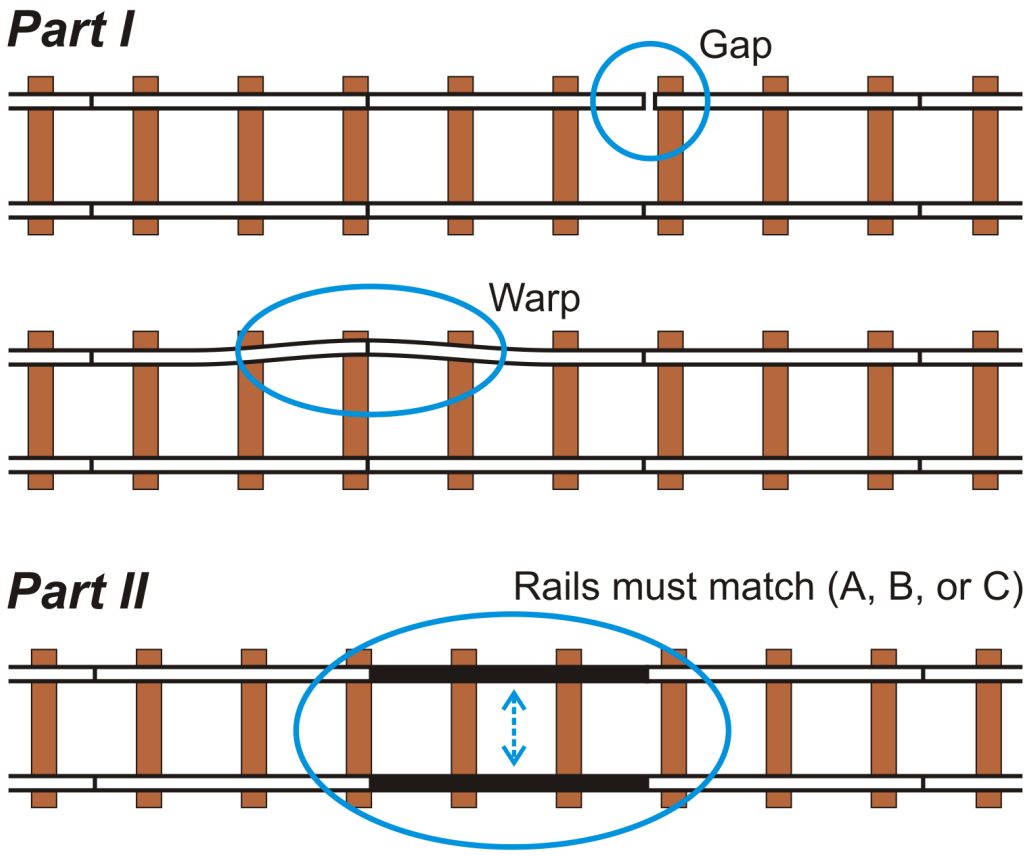
There also needs to be a back-up system to check the repairs and ensure that all new rails are of the right type (i.e. type A is only placed across from type A).

Invent a back-up system to check the work of repair team. Note that if it finds a mismatch, it must be able to identify which side is incorrect and which side is correct so that the repair team can make the proper correction (the repair team does not keep records on which rails they replace).

Also consider the following questions:

- What happens if your device finds a rail that it can't identify?
- What happens if the damaged rails are part of a bend in the track?
- Imagine an earthquake hits part of the track and rails on both sides are completely lost. How could this be handled?

Slide (not to be handed out to the students):



Delivery

It should be noted that this is one of the more difficult invention activities. In our experience many students have a difficult time catching and incorporating all the elements in this activity. As such, care should be taken to introduce all of the relevant elements, and the students should be encouraged to read the activity very carefully. It is worth mentioning to them that the activity is not as easy as it first appears (this is more true of Part II).

Introduce the activity as follows:

- Hand out the worksheet portion of the activity and stress that they should read it carefully (1-2 minutes). It is especially important that they read Part II very carefully.
- Verbally explain the activity and show them the diagram of the rails and the type of damage.
    - Emphasize that in Part I, their device must be able to find and mark only the damaged rails (shorter rails for the gaps and bent rails for the warps).
    - Tell the students to note that their system can use electronics in their solutions as long as they describe what the electronics are doing.
    - Emphasize that in Part II, they must decide upon the details of how the marking system described works. The students need to realize that there is no master blueprint, and so the type of each rail must be determined by its marking.
    - Also for Part II, emphasize that in the event of two mismatched rails, one of the rails is correct and one is not, and their system must be able to determine which rail is incorrect and mark it to be replaced again. It is worth mentioning again that there is no master blueprint that contains information about which rail is correct. **[Note: this is the part of the activity that the students most often don't address in their solution.]**
- As always, encourage the students to consider multiple mechanisms, and to draw out in detail their final solution to each part.
- Give the students up to 25 minutes for the entire activity (both parts are introduced together), although after about 10 minutes encourage them to try to leave time for Part II if they haven't yet started it.
- Encourage the students to consider and answer the extra questions if they complete Parts I and II early.
- Collect the activities from the students prior to presentation of some of the ideas.

Possible Solutions to Expect

Part I

In our experience, the students generate a fewer number of possible solutions during this activity (this may be due to it being more difficult than previous activities and many groups are slower to develop a solution). Common solutions include:

For gaps [note that the solutions often neglect to indicate how to find the shorter rail]

- Spring loaded pegs that push against the rails and then drop or push into a gap.
- Lasers that reflect off of the rails and bounces back to a sensor.
- Magnetic sensors that move along the tracks.
- For measuring the length of the rails, once a gap is detected, the device can move over the two adjacent rails and use sensors (laser or magnetic) to measure the lengths and mark the short rail.

For warps

- Two lasers in the center of the device pointing in opposite directions (towards the rails) that measure the distance on either side (this can also detect which side is farther away.
- Two wheels on a special axel that are spring loaded to push against the inside of each rail. When the distance changes the wheels move in and out with the warp and indicate to the device which side the movement occurred on.
- Two wheels that are designed to follow the tracks and pivot to follow the rails in a warp (this can also be done with lasers running parallel to the rails).

Part II

Part II is a recent addition to the activity, and as such we have little experience with it. The solutions we gathered from the students indicated that they spent most of the time figuring out the rail marking system and failed to invent a way to determine which rail was incorrect and needed replacing again. This can be remedied by emphasizing this objective during the introduction, as noted earlier.

The solution to this problem, which was missed by most of the students in our experience, is that the rails themselves must contain the information about not only the type of rail, but also some information about being correct. The easiest way to accomplish this is with a second marking system. For example, beside the mark identifying the rail type, rails can be marked in some way to indicate the date and time that the rail was first laid. Any new rails laid would have a later date and time, and in the event of a mismatch, the checking system can simple determine which rail is newer and have that rail replaced again.

In terms of the marking systems that students developed to indicate rail type, common solutions include:

- Rails of different colours or marked with different coloured paint spots.
- Rails marked with grooves, bumps, or holes in a particular pattern.
- Rails marked with bar codes.

Wrap-Up Discussion

The wrap-up discussion revolves around the details of DNA mutation repair, and in particular how repair enzymes locate damage and ensure the correct sequence is restored. The following points are usually covered:

- Some types of DNA mutations are caused by damage on one strand or the other.
  - For example, certain chemicals can cleave off the base portion of a nucleotide within a DNA strand, leaving a gap.
  - Another type of damage called, a thymine-dimer, is caused by UV radiation. In this case, the base portions of two neighbouring thymines within a DNA strand become covalently linked. This causes the DNA strand to kink and prevent DNA replication in this area.
  - These types of damage correspond to the gap and warping damage in the activity.
- These types of damage are detected by enzymes that run up and down the DNA looking for damage.
  - When these enzymes find the damage, the physical damage itself indicates which strand of DNA must be repaired.

For the next part, we usually draw out a small sequence of double stranded DNA with a single mismatched base pair, as shown below:

GTGTA
CATAT

We tell the students that rarely, during DNA replication, the DNA polymerase may pair up the wrong bases, causing a mismatch. This happens at a low but constant frequency. If these mismatches are not fixed, a mutation will occur in one of the daughter cells during the next round of replication (usually good to draw this out to show them).

Next, we ask them "if you wanted to repair the DNA, what would you do?" The students will say to replace one of the bases to make a proper pair, and we follow this up with "how do you know which one is correct?" At this point, the students will see the problem.

- DNA replication, on rare occasions causes a mismatch. Certain repair mechanisms travel along the DNA looking for this type of mutation.
    - The problem is that once found, how do the repair enzymes know which is the correct base, and which is incorrect. Each base provides the information about which base should be across from it, but does not have any information about which side is correct.
    - This corresponds to the situation presented in Part II of the activity.
- In order to properly repair these mismatches there must be a second piece of information that tells the enzymes which strand contains the correct bases.
    - This is accomplished by marking the DNA strands with chemical groups after certain amount of time (2-5 seconds, which is long time in the enzyme world) following replication.
    - During this 2-5 second window, the new DNA strand is unmarked [we usually use the above DNA strand with the mismatch to illustrate this]. If the repair enzymes find a mismatch, they know that the correct strand is the strand that has the extra chemical groups.
    - However, this process is a race between the repair enzymes and the marking enzymes. If the repair enzymes do not fix the mismatches before the new strand is marked, then the enzymes must guess which strand is correct (50% chance of mutation becoming permanent).
    - This part of the activity corresponds to the railway solution requiring a second marking system that designates which rail was the original.

Follow-Up Problem – DNA Mutation and Repair

Part I

E. coli, a typical bacterial species, has a specific enzyme that binds to G-T mismatched base pairs in DNA. The enzyme, which is called MutY, starts the repair process that will replace the T with a C. This repair system makes use of the DNA marking system where the older DNA strands are marked (by methylation of adenosines by an enzyme called Dam methylase) and the newly synthesized DNA strands are not marked right away.

In cells that are lacking MutY the frequency of mutation of GC base pairs to AT base pairs increases about 1000 times.

Draw out the rounds of DNA replication that are needed to change a GT base pair to a stable AT base pair.

Part II

Suppose you over hear a couple of researchers talking about mutation. One says to the other:

> "In this mutant strain I am studying, the frequency of GC to CG mutations is high, but the frequency of GC to AT base pairs is low."

Draw out a representation of what this person might mean using a short DNA sequence that you make up. What do you think might be different in this mutant strain versus a normal strain that could cause the observed mutations?

Part III

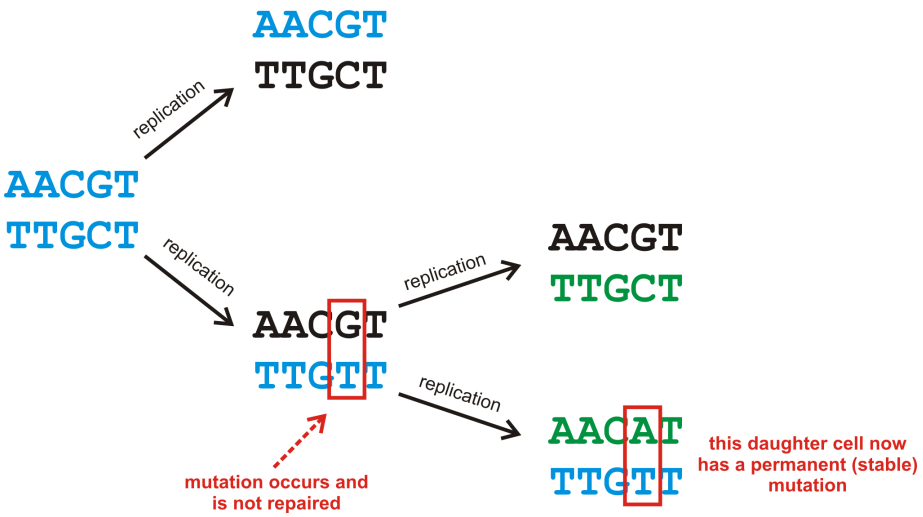
In *Part I* it says that loss of MutY increases the frequency of GC to AT base pair mutations 1000 fold. It also mentions that this system uses the Dam methylase to mark the DNA strands so that the repair system knows which strand is 'old', or correct.

In cells that have a normal MutY but lose the Dam methylase the frequency of GC mutating into AT only goes up by a factor of 2. Explain why that might be.

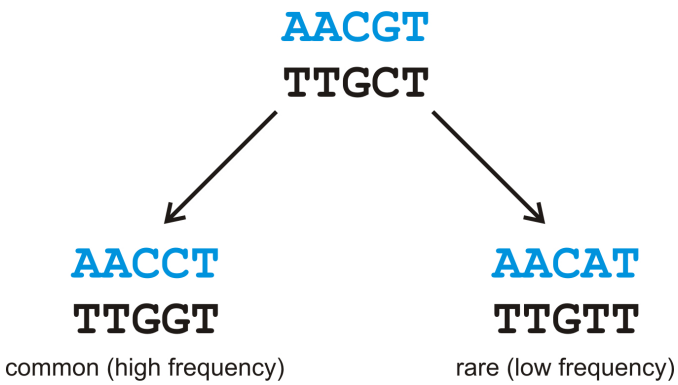
Follow-Up Problem – DNA Mutation and Repair
Suggested Answers

Part I

The rounds of replication are shown below. The DNA strands are colour-coded to help you see which strands are the templates for each round of replication.



Part II



An explanation for the high frequency of the GC to CG mutation is that this strain may lack a repair enzyme that is specific for looking for GG mismatched pairs (or CC pairs). This is similar to the strain in Part I that lacks the enzyme that specifically looks for GT mismatches.

Part III

Losing MutY means that repair of a GT will happen much less frequently. In contrast, cells lacking the Dam methylase still have MutY, which means GT mismatches are still possible. However, without the Dam methylase, the DNA is not marked properly, and so the MutY enzyme cannot tell which strand is the original and has to guess. On average, it will guess correctly 50% of the time and guess incorrectly (causing a stable mutation) 50% of the time. This causes the GC to AT mutation rate to only double.

Chapter 7
Invention: Rubber Ducky

Description

This activity is meant to be an introduction to the concepts of metabolism and energy transfer, particularly the concept of harnessing energy from diffusion and concentration gradients. This activity tasks students with inventing a way to collect rubber ducks in the center of a pool after as part of setting up for a carnival game. The activity also involves students developing a method to extract energy from the crowd watching the game.

It should be noted that while we use this activity to introduce metabolism, it could easily be adapted to introduce diffusion, concentration gradients, and active transport.

This activity does not include a follow-up problem set.

Related Topics: Diffusion and concentration gradients, entropy, energy transfer, metabolism, and active transport.

Key Features

- This activity is designed to have student think about how energy transfer occurs within cells and how energy can be extracted from unlikely sources (such as diffusion of atoms or molecules).
- Part I relates to the input of energy by cells to create a concentration gradient. The student inventions relate directly to active transport concepts, which in terms of metabolism can be used to explain the electron transport chain and the pumping of protons.
- Part II is designed to have them further think about how energy can be transferred from one place to another in order to do work and/or store energy.

Activity Handout:

Invention – Rubber Ducky

Part I

You run a carnival betting game which uses a circular pool, about 15 feet across, on which 200 small rubber ducks are floating. The ducks are gathered together in the center of a pool in a small ring enclosure that can be lowered to allow the ducks to float freely on the water. The ducks are all numbered, and people pay to place a bet on which duck will reach the edge of the pool first.

The game is a success and you make great money doing it. However, you find that collecting the ducks back in the center is both boring and time consuming, and you decide to design a way to have this done automatically.

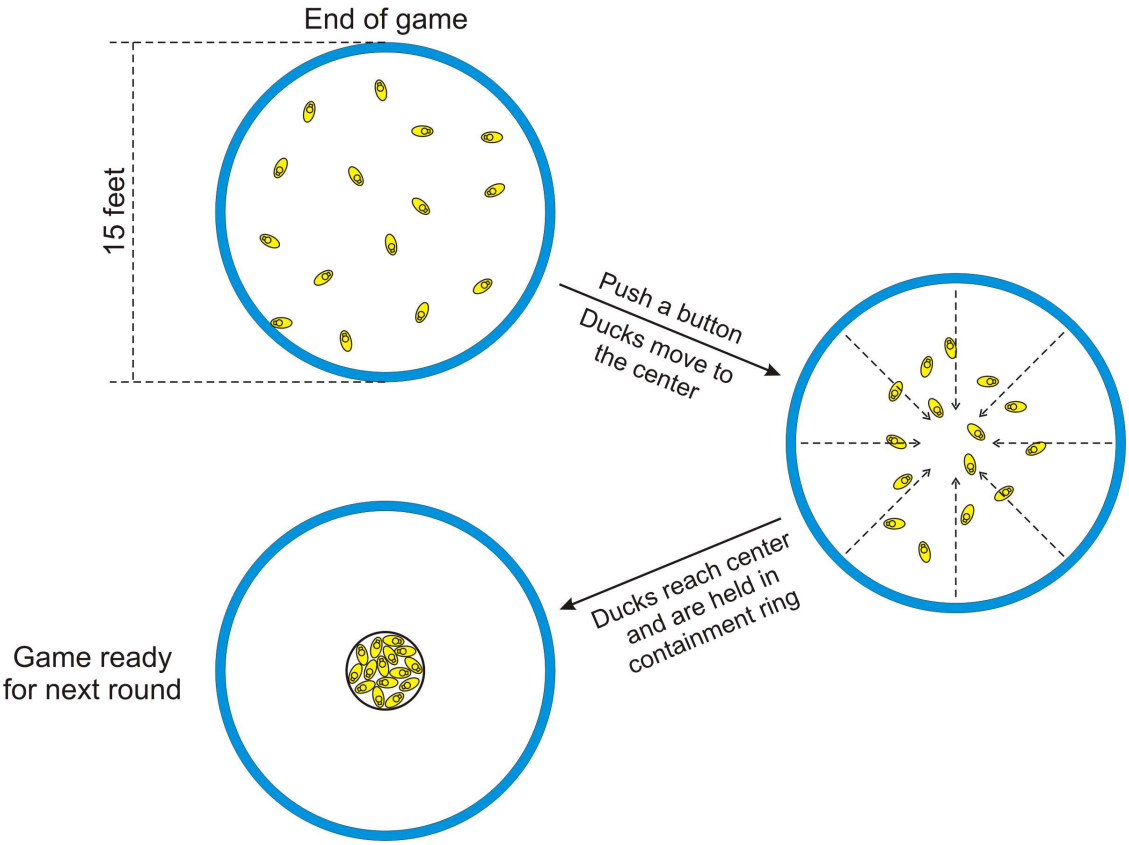
Invent two different mechanisms that would cause the ducks to gather (or be gathered) in the center of the pool once the game is complete with minimal effort on your part. You are free to redesign any part of the system except for the main pool (has to be a circular 15 foot pool with water) and the number of ducks. WARNING: whatever you invent MUST NOT prohibit the ducks from floating freely and randomly once the game starts!

Part II (make sure you finish Part I first)

Your inventions from Part I work well, but you want to minimize the costs of powering them. You decide that the people standing around the side of the pool watching the game are a free source of energy…you just need to figure out a way to harness that energy without them knowing (people generally don't like being taken advantage of).

Invent a way to have the people gathered around the pool to help power your inventions in *Part I* without them knowing.

Slide (not to be handed out to the students):



Delivery

This activity is by far one of the easiest (at least in Part I), and is also one of the more entertaining activities in terms of the solutions. We generally do this activity towards the end of the year due to the course scheduling of metabolism. However, because it is a very accessible activity, it could also be used as the introductory invention activity if the course material allows for it (possibly using the activity to introduce active transport rather than metabolism).

Introduce the activity as follows:

- Hand out the worksheet portion of the activity and stress that they should read it carefully (1-2 minutes).
- Verbally explain the activity and show them the diagram of the carnival game.
    - Emphasize that their invention in Part I must not interfere with the random movement of the rubber ducks during the game.
    - In Part II, emphasize that the invention must be able to extract energy from the crowd without their knowledge.
    - Make sure the students note that in Part I they must develop two different solutions (but as always, encourage them to consider as many as they can).
- This activity is usually quite easy for the student and they will only need about 20 minutes for the entire activity (both parts are introduced together).
- Collect the activities from the students prior to presentation of some of the ideas.
- An extra five minutes should be used for presentation (group to group presentations and/or presentations to the entire class). This activity generally produces some entertaining solutions, and the students really enjoy seeing the different ideas.

Possible Solutions to Expect

Part I

In our experience, the students generate a wide range of devices to collect the ducks. However, almost all of these solutions fall into three main categories, as shown below. It should be noted that many of these solution have the problem that they greatly disturb the water during their use and therefore it takes time for the water to settle down before running the game again. However, we do not usually make the students worry about this aspect.

Magnetism

- This is probably the most common solution, which involves an electromagnet in the center of the pool (usually beneath the water) and a small piece of iron inside each duck.
    - A common variation of this is to place small magnets inside of the ducks. We usually inform the students that one downside to this is that having magnets inside of each duck could potentially lead to the ducks attracting and repelling each other, thereby affecting the game. We also usually tell them there is a simple solution to this problem and ask them to think of it. We are often amazed how many students think that only magnets are attracted to other magnets. We have also been amazed at how many students will suggest "only positive" or "only negative" magnets inside of the ducks (this clearly indicates a misconception about magnets which we are sure would make many physics instructors cringe).

Vortex

- The second most common type of solution involves creating a vortex which gathers all of the ducks to the center.
    - Students will often suggest a drain in the center of the pool to create a vortex, with the water being pumped back into the pool.
    - Another common form is the use of a large turbine rotor (propeller) at the bottom of the pool to create a vortex.
    - Another variation of this uses water or air jets around the edge of the pool to create a vortex.

Contraction

- The third type of solution which is common is the use of some device that contracts from the outside of the pool to push the rubber ducks towards the center.
    - The most common form of this is a contracting ring that is made up of several flexible segments that can slide past each other, thereby creating an ever shrinking circle.
    - Other variations of this use nets or collapsing colander-like devices.

Other Solutions

- A large funnel that rises out of the water to funnel the rubber ducks to the center.
- The use of air or water jets that are above the surface of the pool and that point directly towards the center.
- Strings attached to every rubber duck that can be pulled towards the center *[note: we are always quick to point out that this does NOT allow the ducks to float freely during the game and is therefore not a suitable solution].*

Part II

This part of the activity is quite new, but it works quite well and the students generate some excellent ideas for extracting energy from the surround crowd. Some common ideas include:

- The crowd must pass through turnstiles (or revolving doors) in order to get to the game, and the turning of these turnstiles stores power (by powering a generator and charging a battery, for example).
- The floor surrounding the pool contains pressure pads that pump air as they are compressed by people walking over them, and this is used to power tiny generators.
- Similar to the above idea, some students had the brilliant idea of including a second "game" whereby free candy is suspended just out of reach of the crowd during the time the actual game is reset. The crowd jumps up and down to get the candy, and the pressure pads (or similar idea) harness the energy.

Wrap-Up Discussion

The wrap-up discussion revolves around the details of metabolism as a method for cells to transfer energy from one form into another. The discussion centers on the idea that cells want to convert the chemical energy contained in many food molecules (such as glucose) into the chemical energy of a very small number of energy carrier molecules (such as ATP). The main method for transferring this energy is to use a concentration gradient and diffusion during metabolism. We usually segue into this concept by using the following scenario which we present to the students:

We start by asking them some examples of common food molecules that bacteria can use as energy sources. They usually give plenty of examples such as glucose and lactose, and we make the point that cells can use a large number of food molecules as sources of energy. We then ask them what the universal energy carrier is in cells, to which they will answer ATP. Finally we ask them to consider why cells use ATP to power everything inside of cells, rather than using food molecules directly.

If enzymes used food molecules directly for energy, there would have to be many versions of the same enzyme in order to use all possible food molecules (since enzymes are so specific). This would be very complicated and messy in terms of the number of genes and the amount of regulation needed (in our class they have learned about gene regulation already). Instead, it makes sense that cells would use one universal energy molecule to power many different enzymes, and then simply convert the energy stored in the food molecules into the energy stored in ATP.

Once we have presented the scenario, we cover the following points:

- Food molecules, such as glucose, and energy carriers, such as ATP contain energy stored within their bonds. The problem cells face is transferring the energy from the many types of food molecules into ATP.
- Cells accomplish this by using a common system of energy reactions whose end product is ATP.
    - Enzymes unique to each food molecule allow the food molecules to be broken down and fed into this system at different points.
    - The system breaks down these food molecules and removes electrons from them.
    - Ultimately, these electrons are passed to the electron transport chain.
- The ETC has one major function: to transport protons across the cytoplasmic membrane (in bacteria).
    - This creates a gradient of protons with excess protons outside of the membrane.
    - Because this process creates a gradient, it requires energy which is provided by the electrons flowing from protein to protein within the membrane.
    - Eventually the electrons are passed to a terminal electron acceptor (such as oxygen).
- The protons outside of the cell are more concentrated than the protons inside of the cell, and they will spontaneously flow back into the cell if they can find an opening.
    - Remind the students that protons are charged and therefore can not pass through the membrane directly.
    - Because this flow is spontaneous, it must release energy (in our class, the students have already learned about diffusion).
    - This energy can be harvested by the cell by providing a gateway for the protons to move back into the cell and using their movement to power a process.
    - ATP Synthase is a large enzyme complex that allows the protons to move across the membrane, and the movement causes part of the enzyme to undergo structural transformations. These are used to bind ADP and P_i, and bring them close together to allow bond formation to occur.
    - The enzyme complex uses the energy from the gradient to produce ATP from ADP.
    - This is very much like the turnstile idea in Part II.
- We emphasize to the students that what is happening is that the energy is being transferred from food molecules to ATP by way of a gradient and diffusion.
    - The vast majority of ATP in the world is directly made via diffusion of protons.
    - This is the same concept as seen in their inventions in Part I. All of the different inventions have one thing in common: they all require an

investment of energy in order to create a concentration gradient of rubber ducks, and this gradient is what "powers" the game.

- In Part II the students are inventing a way to transfer the energy stored in the bodies within the crowd to the inventions that create the gradient of the ducks.

Chapter 8
Additional Invention Activities

In addition to the five invention activities described in the preceding chapters, we have also developed a number of other invention activities that have had limited testing and development. These activities are provided in this chapter, and may prove useful for some instructors. The description of each activity listed here includes the goals of the activity and comments on its use and effect, although this description is less extensive than in previous chapters due to their limited testing. It is hoped that the information provided in the preceding chapters is sufficient to give a clear idea about how invention activities are used, and thus many instructors will be able to successfully further develop and use the invention activities listed in this chapter (if they are interested in doing so).

Invention: Water Wheels

Description

This activity was designed to relate to gene regulation. In particular, this activity was meant to introduce the concept of multi-level regulation, whereby gene expression and protein production is controlled at the DNA and RNA level. We designed this activity with the tryptophan operon in mind, since the protein production from the *trp* operon is controlled at the DNA level (TrpR) and at the mRNA level (attenuation).

Most of the students will realize that in order to fulfill the power requirements and prevent flooding, the flow needs to be controlled at two points: at each individual farm, and at the entrance to the stream. Most of the solutions we observed used a system of gates and pumps to keep the water in the stream at an appropriate level based on the combined needs of the three farms.

Follow-up discussion involves relating the analogies in the activity to the levels of control within the *trp* operon.

Activity Handout:

Invention – Water Wheels

Mr. Jones decides to move to the interior of British Columbia to escape city life, and he settles in an area that does not have access to utilities. In order to have power and water, he digs a small stream from a nearby river to his house, as shown below. The water is used to drive a water wheel which powers a small generator. The water is also used for drinking, and for watering his crops (he grows his own food).

Mr. Jones enjoys his new life so much that his two friends, Mr. Calder and Mr. McTavish, also decide to move into the area, and each builds a house nearby. They also use the stream for power, drinking, and irrigation, as shown below.

Unfortunately, the three friends realise that the situation has some downfalls, especially for Mr. McTavish. When the power and water demands are high for all houses, there needs to be enough water in the stream to feed all three houses, otherwise Mr. McTavish (and possibly Mr. Calder) will be left dry.

On the other hand, when demands are low, too much water in the stream can cause flooding for any of the houses and crops. It is also important that the generators do not run when not needed (to prevent them from wearing out).

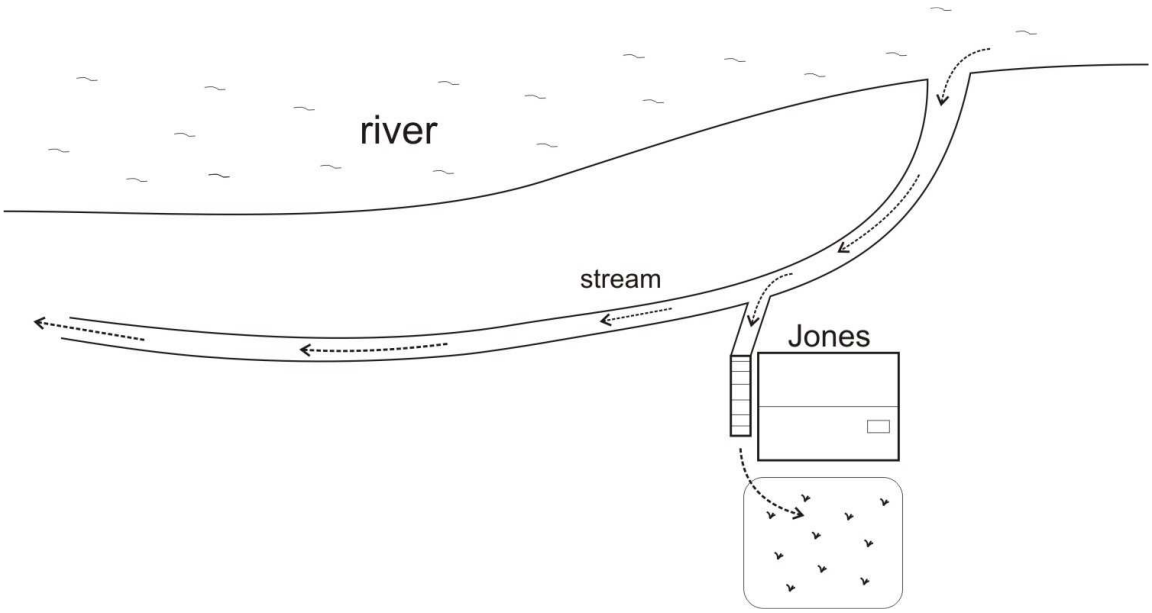
The three friends decide to design a control system to regulate the water as the demands of each house change. For example, the system must provide the correct amount of water flow to each house as shown in the table on the screen.

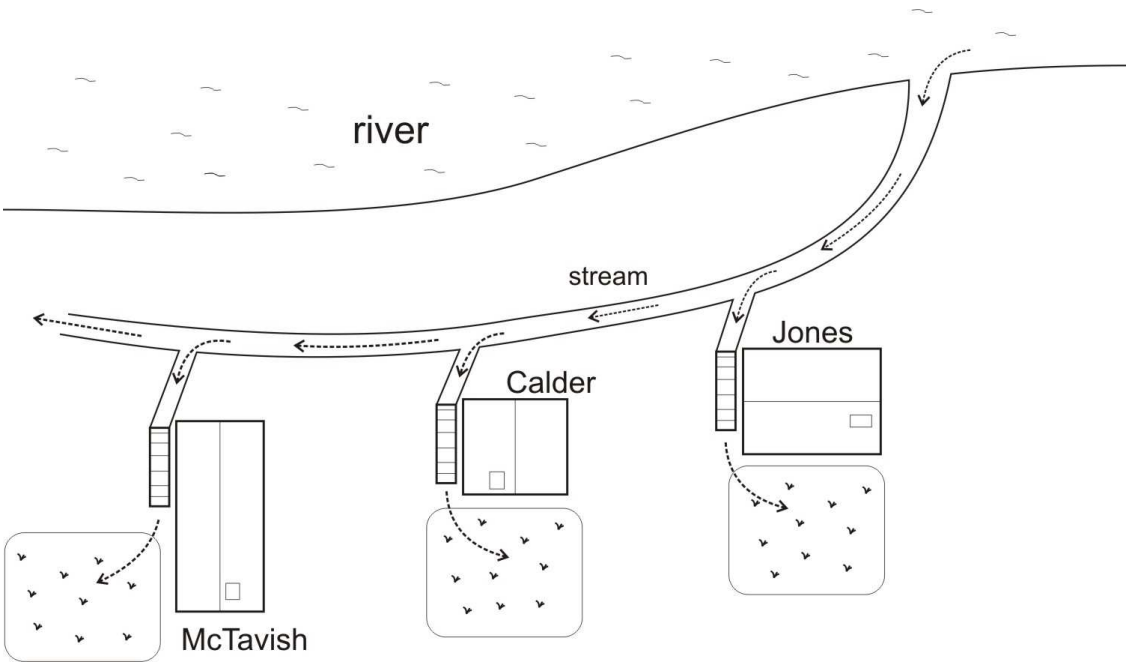
Keep in mind that in times of high or low rainfall the main river itself will have more or less water. However, you can assume that the main river always has some minimum amount of water in it and never runs dry.

Invent a system that will control the water flow to each of the houses and prevent flooding or water shortage. You can assume that there is electricity available from the generators in each house to power your invention. You can also assume that for each individual house, the demands for power and water increase and decrease together.

You are not permitted to change the overall plan of the water flow shown in the diagram (in other words, you must use the main stream with three independent parallel delivery streams for the houses).

Slides (not to be handed out to the students):





Slides continued (not to be handed out to the students):

	Water and Power Demands		
Time of day	McTavish	Calder	Jones
Morning	Low (potential for flooding)	Low (potential for flooding)	High
Noon	Low (potential for flooding)	High	Low (potential for flooding)
Evening	High (potential for water shortage)	High	High

Invention: The Chain Machine and Self-Folding Chains

Description

This activity was the original activity that used the chain-making machine concept
This activity was designed to introduce students to the topics of protein structure and protein folding. In particular, we wanted to introduce the following concepts about protein structure:

1. The function of a protein is determined by its three dimensional fold (shape).
2. All of the information necessary for a protein to fold into the correct shape is contained within its primary sequence (amino acid sequence). Many proteins can fold (and refold) correctly even when isolated from the rest of the cell.
3. For many proteins, the correct folding also requires two other important factors: timing and chaperone proteins.
    - By timing we mean that the protein must begin to fold while it is still being made by the ribosome. This allows parts of the protein to fold correctly before amino acids that could interfere with proper folding have been added to the growing chain. This is one reason many proteins cannot refold correctly after being denatured.
    - Chaperone proteins allow for correct folding by "hiding" parts of a protein's amino acid chain to allow other parts to fold correctly without interference.
    - Both timing and chaperone proteins depend on the amino acid sequence of the protein in question, so these factors do not violate concept 2 above.

The easy solution to the invention activity is to use as many different types of attractive plastics pieces as there are junctions in a given flotation device. For example, the three person device (three loops) has three junctions, and each junction could use two pieces of a particular type. In this case, the start junction would use two pieces of type A (or some similar designation), the mid junction would use two pieces of type B, and the stop junction would use two pieces of type C. This means three types of plastic pieces (four if the students count the normal pieces throughout the remainder of the chain. This correlates well to the idea that amino acid sequence defines the shape of a protein's fold.

However, the activity does ask for the minimum number of plastic types, and some students will realize that if the flotation devices can fold as they are being made, then only one type of attractive plastic is needed for the three person device. This is because the first junction uses the first pair of attractive plastic pieces in the chain, the mid junction use the second pair, and the stop junction uses the last pair. If these pieces pair up as they are being made, they are no longer available for pairing by the time the

next piece is added. In this case, all junctions can use the same type of attractive plastic. This correlates to the idea of timing being important for correct folding.

In the two man (figure-8) device, the junctions are made up from non-sequential pairs, and so timing cannot be used as detailed above. In this case, two types of attractive pieces must be used. Some students may think up a device that can mask the first piece of the chain to allow attractive pieces 2 and 3 to first pair up, and then release piece number 1 so that it can pair up with attractive piece 4 (end piece). This was not a common invention, but it does correspond well with the use of chaperone proteins to achieve proper folding.

Activity Handout:

Invention – The Chain-Making Machine and Self-Folding Chains

You are a brilliant chemist who is experimenting with the surface chemistry of plastics, and you discover a way to change plastics so that they attract each other (but not repel). In fact, you even discover how to make different types of plastics that only attract themselves (i.e. a piece of plastic type A can attract another piece of plastic type A).

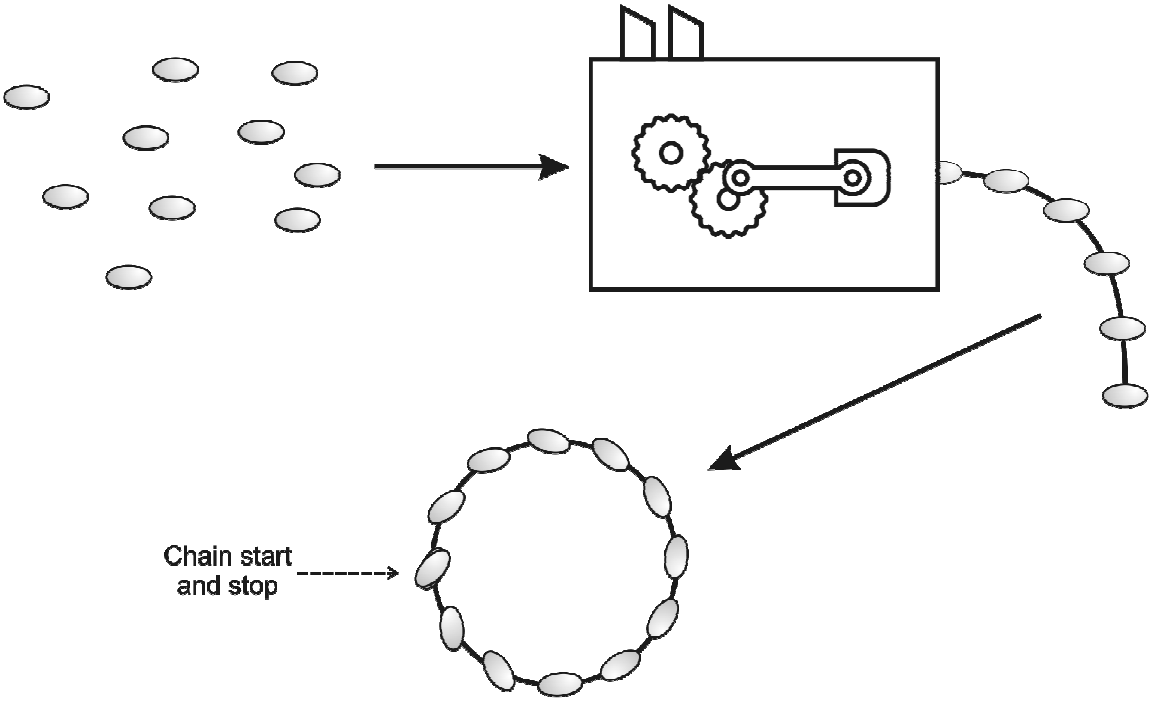
You decide to use these plastics to make various products, one of which is a flotation device that can be used on ships for people that fall overboard. By using the various attractive plastics that you have created, you are able to produce chains of plastic pieces that spontaneously fold into the desired shape.

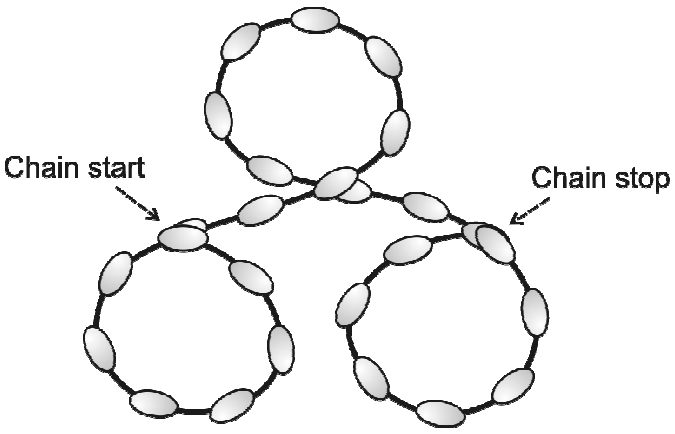
You build a machine that can link these pieces of plastic together into chains which can then fold into the desired shape, as shown on the screen. The simple circle flotation device is suitable for one person. Some ship companies, however, ask you to produce devices for two and three people, as shown on the screen.

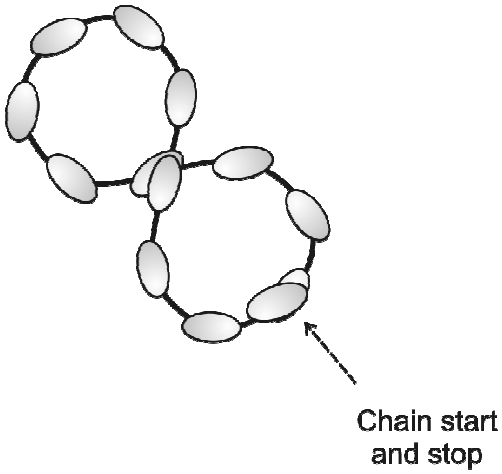
Invent a general manufacturing scheme that would allow you to make these devices using the least amount of different types of plastic pieces possible. Note that you are free to redesign any part of the above diagrams, except the shapes of the devices and the machine (it's only function is to link together the pieces of plastic that you feed into it).

Also, each attractive plastic piece only has enough "attractive force" to hold onto one other piece (i.e. only two pieces can stick together).

Slides (not to be handed out to the students):







Invention: Dragonflies

Description

This activity was designed to introduce the concept of specificity of binding. We used it to introduce the concept of primer binding during PCR, but it could also be used to introduce protein-DNA (or RNA) interactions where proteins recognize a specific nucleotide sequence. For PCR, the primers need to be long enough to be unique within the DNA template being used, and they need to be able to dissociate from sites that are partially complementary.

Most students developed solutions to this problem that used magnets or Velcro straps that had a specific orientation. Some students also resorted to electronic scanning or sensing devices which were not preferred solutions.

Activity Handout:

Invention – Dragonflies

You have designed a mechanical dragonfly that has a miniature battery and can fly around for hours in a specially designed box that you made for them. The box contains 2000 of these mechanical dragonflies, and when their batteries are drained they land on the floor. This presents a challenge, because at times you need to locate a certain dragonfly in the box.

In order to make locating a dragonfly easier, you decide to design a "home base" for each dragonfly along the walls of the box (sort of a small shelf big enough for a single dragonfly to land). However, you don't have enough money to design a complex signal tracking system. Instead, the dragonflies fly randomly throughout the box and will randomly land on the home bases. You want to make the home base such that if the dragonfly lands on its own home base, it is able to physically recognize it as its home, and it stays there because some mechanism holds it in place. If the dragonfly lands on the wrong home base, it will not stay there and will fly off.

You need to figure out how to design the home base and how the dragonfly interacts with it so the interaction between the proper home base and dragonfly is specific. The same system must ensure that if a dragonfly lands on the wrong base it will quickly fly away

Note: to do this you need to consider how 'strong' the wings of the dragonflies are in comparison to the strength of the force holding it on a home base. That is, if a dragonfly lands on it own base, the strength of the force holding it there is greater

than the strength of its wings (and therefore cannot lift off). On the other hand, if a dragonfly lands on the wrong home base, it wings need to be strong enough to overcome and attractive force from the base.

Slide (not to be handed out to the students):