

IBI* SERIES WINNER

Aipotu: Simulation from Nucleotides to Populations and Back Again

Aipotu, the IBI Prize-winning module, creates a world where students manipulate the DNA of virtual organisms and examine resulting effects.

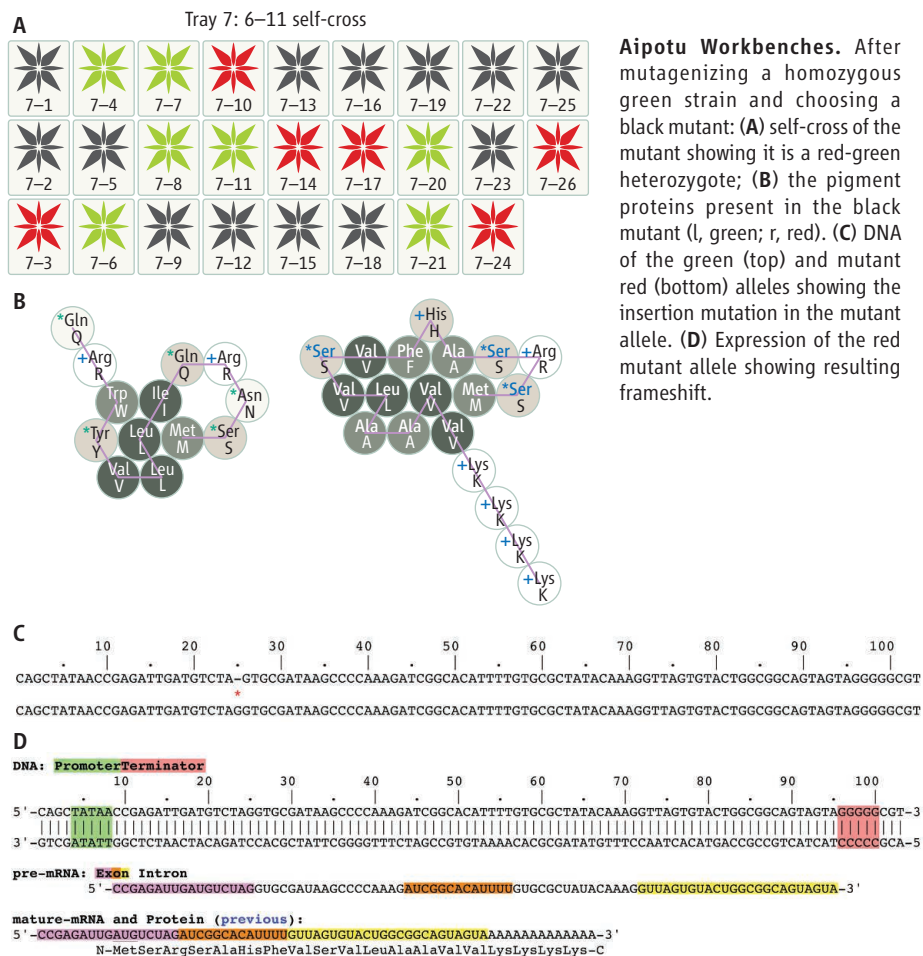
Brian T. White

Imagine an undergraduate research project where students are given samples of an uncharacterized plant species. The flowers in these samples appear in several different colors, and the students' task is to not only discover how these colors are produced but also construct a plant with a novel flower color. They begin by crossing plants to determine what color alleles are present and how these alleles interact. Students then investigate the biochemical mechanism behind color formation and the DNA sequences responsible for each color allele and use this information to engineer a transgenic plant strain with a novel flower color. Finally, they undertake a long-term study of the evolution of flower color in this species. This "flower-engineering" project would give students the opportunity to develop and test hypotheses in an authentic research environment.

Unfortunately, the time, equipment, and expertise required for this type of experience are not typically available in undergraduate teaching laboratories. For this reason, I built Aipotu to provide a virtual microworld where students could carry out a reasonable approximation of this flower-engineering project. In Aipotu, organisms can be manipulated at the DNA level with resulting effects on RNA, protein, phenotype, and populations. The Aipotu software and associated lab activities retain many of the pedagogically relevant features of the flower-engineering project in a form that can be completed by high school or beginning undergraduate students. These activities have been developed over the past 5 years through collaboration with Ethan Bolker (Mathematics and Computer Science, University of Massachusetts, Boston), several dozen teaching assistants, and more than 2000 students who have taken my courses since Aipotu was first tested in 2007. The Aipotu software is part of the Bio-QUEST Collection (1) and runs on Windows, OS X, and Linux. You can download Aipotu software, documentation, and lab manuals free from <http://aipotu.umb.edu>.

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Aipotu Workbenches. After mutagenizing a homozygous green strain and choosing a black mutant: (A) self-cross of the mutant showing it is a red-green heterozygote; (B) the pigment proteins present in the black mutant (l, green; r, red). (C) DNA of the green (top) and mutant red (bottom) alleles showing the insertion mutation in the mutant allele. (D) Expression of the red mutant allele showing resulting frameshift.

Each aipotian organism contains two DNA sequences, one from each parent. Students can use the software to analyze the DNA sequences to determine the phenotype of the organism in a manner that includes many of the pedagogically relevant features of real-world organisms (2). Each DNA sequence is scanned for specific promoter and transcription terminator sequences. Any resulting pre-mRNA is then scanned for specific splicing control sequences, spliced, and processed, and any resulting open reading frame is then translated. The structure of the protein is then determined by an energy-minimization algorithm that uses ionic bonds, hydrogen bonds, and the hydrophobic effect to fold the protein on a two-dimensional hexagonal lattice. The software determines the function of the protein on the

basis of its shape and amino acid composition. Proteins with a specific shape can be colored, and the particular color depends on the particular amino acids in a critical region of the protein (this is analogous to the mechanism of color formation in rhodopsins and green fluorescent protein). Finally, the overall color of the flowers produced is determined via a set of color combination rules encoded in the software.

To compress the real world into a practical simulation, I have taken some significant biochemical liberties. Real protein folding is a three-dimensional and highly complex process and flower color typically results from enzymatic production of small pigmented molecules rather than from pigmented proteins. However, the purpose of Aipotu is not to illustrate how flowers are

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colored in nature but to allow students to explore a biological phenomenon in detail. Aiptotian proteins fold in a manner that is explicable, if not predictable, in terms taught in introductory-level biology courses, and the mechanism of color formation is not unreasonable from a student's point of view. Previous studies of this protein-folding simulation show that it leads to significant increases in students' understanding of protein structure and does not leave a significant number of students with the misconception that proteins are two-dimensional (3). Most important, this model of protein folding, in which structures and phenotypes can be determined in less than a second, allows the students to carry out their studies in a reasonable amount of time.

Aipotu invites students to work at four Workbenches—Genetics, Biochemistry, Molecular Biology, and Evolution—and a virtual Greenhouse allows organisms to be passed from one Workbench to another. At the start of the exercises, the Greenhouse contains four organisms with different-colored flowers: white, red, and two green strains. In time, students discover that one is homozygous green and the other a yellow-blue heterozygote. These choices can be customized by the instructor, as can the order of the exercises.

In the Genetics lab session, students use the tools in the Genetics Workbench to cross organisms of their choice in order to characterize the color alleles present. Students are then introduced to two ongoing themes that will frame their work in the following labs. In the first of these, students are challenged to engineer a pure-breeding purple organism. In the second framing task, each group of students creates an organism with a novel color by introducing a random mutation and saving it to the Greenhouse. They will use their developing understanding of the molecular mechanism of color formation to explain the properties of this mutant as they carry out the remaining labs.

The Biochemistry Workbench provides tools for students to determine the relations among protein sequence, protein shape, and protein color. By examining the structures of proteins present in the Greenhouse strains, students use the existing colored proteins to develop hypotheses about the factors that influence color and test their hypothesis by observing the colors that result from protein sequences they have designed. Students post hypotheses, experiments, and results to a lab blog (see Supplementary Materials). At regular intervals throughout the lab session, the instructor holds a classwide

“minisymposium” to review the class's work so far, to determine which hypotheses have been supported or refuted, to identify remaining open questions, and to design the next round of experiments. At the end of this 3-hour session, students use what they have discovered to explain the color of their mutant and to design a purple protein.

Students use the Molecular Biology Workbench to explore the DNA sequences of the various color alleles, to complete their explanation of the color of their mutant strain, and to construct a gene encoding the purple protein they engineered in the Biochemistry lab. They then construct an organism with two copies of this DNA sequence, save it to the Greenhouse, and use the crossing tools in the Genetics Workbench to show that it is true-breeding. A series of screenshots (see the figure) illustrates the steps in this process.

To conclude the module, students select organisms from the Greenhouse to form a starting population of 100 individuals in the Evolution Workbench. This population is then subjected to random mutations at the DNA level followed by natural selection with user-adjustable fitness for each color. Tools from other Workbenches can be used both to create organisms for study and to analyze the organisms that result. Students use multiple evolution runs to address particular misconceptions about evolution, including “selection causes beneficial mutations,” “mutations are always deleterious,” and “mutations cannot create new features.” Experiments that target these include observing the evolution of particular colors in the presence and absence of selection, as well as the evolution of colored flowers from colorless ancestors.

Students are sometimes frustrated by the open-ended nature of these labs. They expect that the software will “tell them the answer” rather than act as a tool that they must thoughtfully wield in order to discover the answer. Also, they do not often see how all the pieces of this project fit together until the Evolution Workshop, where they take a newly evolved organism and explore the specific changes in DNA and the resulting changes in RNA and protein that give rise to its new phenotype. It is important to emphasize that this is constructive frustration that leads to a deeper understanding of how biologists investigate and understand living things.

Aipotu provides a virtual microworld where students can explore a biological

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the introductory courses for Biology majors and studies the development and evaluation of materials for teaching biology. He has developed many different simulations and activities for teaching introductory biology (<http://intro.bio.umb.edu/BW/>). He earned a B.S. in Biology from Massachusetts Institute of Technology and a Ph.D. in Biological Sciences from Stanford University. He is an active member of the BioQUEST Curriculum Consortium (which has been a constant source of inspiration and encouragement throughout this project), as well as the Center for Scientific Teaching (cst.yale.edu).

phenomenon using tools from some of the key domains in modern biology. Because the aiptotian organisms' simulated biology includes some of the detail and complexity found in living organisms, students can directly explore the connections between these domains in depth, using a wide range of approaches. Furthermore, a far wider range of activities is possible, limited chiefly by the imagination of the instructor. For example, the Workbenches can be used independently to explore these domains on their own or in any order. Going further, students could design genes that encode proteins with specific shapes, explore the effects of different types of mutations, and compare evolution in different worlds. Finally, future software development could include other organisms, genes, phenotypes, and multigenic interactions—a world of aiptotian creatures. I look forward to working with fellow “aiptotian explorers” to develop both the software and activities to their full potential.

References and Notes

1. BioQUEST Curriculum Consortium, <http://bioquest.org>.
2. B. T. White, E. D. Bolker, Interactive computer simulations of genetics, biochemistry, and molecular biology. *Biochem. Mol. Biol. Educ.* **36**, 77 (2008).
3. B. White, A. Kahrman, L. Luberic, F. Idleh, Evaluation of software for introducing protein structure: Visualization and simulation. *Biochem. Mol. Biol. Educ.* **38**, 284 (2010).

Supplementary Materials

www.sciencemag.org/cgi/content/full/337/6093/424/DC1

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