Bioinformatics education dissemination with an evolutionary problem solving perspective

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Abstract

Bioinformatics is central to biology education in the 21st century. With the generation of terabytes of data per day, the application of computer-based tools to stored and distributed data is fundamentally changing research and its application to problems in medicine, agriculture, conservation and forensics. In light of this ‘information revolution,’ undergraduate biology curricula must be redesigned to prepare the next generation of informed citizens as well as those who will pursue careers in the life sciences. The BEDROCK initiative (Bioinformatics Education Dissemination: Reaching Out, Connecting and Knitting together) has fostered an international community of bioinformatics educators. The initiative’s goals are to: (i) Identify and support faculty who can take leadership roles in bioinformatics education; (ii) Highlight and distribute innovative approaches to incorporating evolutionary bioinformatics data and techniques throughout undergraduate education; (iii) Establish mechanisms for the broad dissemination of bioinformatics resource materials and teaching models; (iv) Emphasize phylogenetic thinking and problem solving; and (v) Develop and publish new software tools to help students develop and test evolutionary hypotheses. Since 2002, BEDROCK has offered more than 50 faculty workshops around the world, published many resources and supported an environment for developing and sharing bioinformatics education approaches. The BEDROCK initiative builds on the established pedagogical philosophy and academic community of the BioQUEST Curriculum Consortium to assemble the diverse intellectual and human resources required to sustain an international reform effort in undergraduate bioinformatics education.

Keywords: education; bioinformatics; evolution; faculty development; software tools

Bioinformatics education is crucial to biology students entering a world flooded with data generated by high-speed sequencers, microarray technology and robotics. While bioinformatics education initiatives have exploded, they usually fail to deeply influence the broad-spread teaching of undergraduate biology. Many bioinformatics programs have been housed in computer science, mathematics and engineering departments; traditionally, these have not had much depth in biology. Furthermore, the prerequisites are usually beyond the range of the mathematics and computer science coursework of most
biology undergraduates. The BioQUEST (Quality Undergraduate Educational Simulations and Tools in Biology) Curriculum Consortium <http://bioquest.org> was founded in 1986 to help fill this void while also emphasizing an explicit evolutionary perspective. In the 24 years since then, BioQUEST members have contributed significantly to numerous national reports urging reform of undergraduate education to reflect the revolutions occurring in biological research (e.g. National Academies 2003 [1], Steen 2005 [2], AAMC-HHMI Committee 2009 [3] and AAAS 2010 [4]).

In 2002, building on their long history of collaboration in bioinformatics [5–9], the authors received NSF funding to support a dissemination grant for curricular materials in bioinformatics education. The resulting BEDROCK Project (Bioinformatics Education Dissemination: Reaching Out, Connecting and Knitting together) was named in tribute to Birney’s assertion that ‘arguments of homology are the bedrock of bioinformatics’ [10]. From its inception, BEDROCK has emphasized that nucleotide sequences, gene-expression levels and other bioinformatics data result from evolutionary processes (e.g. natural selection, de novo mutation, gene duplication). An evolutionary perspective thus allows learners to pose and address a much broader range of bioinformatics questions.

A primary activity of the BEDROCK project has been a series of 4- to 9-day faculty development workshops (see ‘Faculty Development and Curriculum Development Workshops’). During these workshops, faculty learn to use multiple computational tools and databases to solve bioinformatics problems, develop new curricular materials and share their own syllabi and resources. Consistent with BioQUEST ‘3 Ps’ philosophy (problem posing, problem solving and peer persuasion) [11], BEDROCK curricula are designed to give students the experience of conducting authentic research (see ‘Bioinformatics Problem Spaces’). Another major role of the workshops is to establish long-term collaborations between educators at different institutions and different disciplines. Through this communication network (Figure 1) faculty can continue to share and develop teaching resources and to support each other in trying innovative approaches to bioinformatics education.

When BEDROCK first began, bioinformatics was such a recent field that it was just entering the graduate-level curriculum at many institutions. Relatively few faculties felt comfortable enough with bioinformatics and its applications to incorporate it into their undergraduate courses. As a result, the BEDROCK project’s activities in curriculum development and faculty support activities were organized to address some of the main barriers to the use of bioinformatics in biology education (Table 1). While undergraduate opportunities in bioinformatics have proliferated over the past 8 years, with over 30 institutions now offering specialized Bachelor degrees in bioinformatics [12], many of these concerns are still relevant today.

**BIOINFORMATICS PROBLEM SPACES**

Lab activities in undergraduate biology have traditionally asked students to follow a highly structured series of procedures to confirm an experimental result. This approach may reinforce student conceptions of science as a mere collection of facts to be memorized, a naïve understanding that has been critiqued as a ‘rhetoric of conclusions’ [13] and ‘ready-made science’ [14]. In contrast, BEDROCK is based in a learning approach that emphasizes the development of students’ ability to frame important and testable scientific questions. These questions serve as the motivation for mastering core biological principles, collecting and rigorously analyzing data and understanding the process by which scientific claims are developed and justified.

BEDROCK curricular materials are organized into specific ‘problem spaces’ (Figure 2). Each problem space defines a broad topic of investigation and provides an initial data set and recommended suite of analytical tools (Table 2). Individual student groups must then decide which particular component of this broader question they will investigate (problem posing), formulate specific hypotheses, determine how to extract and analyze the relevant data (problem solving), and convincingly present their conclusions to their peers (peer persuasion). Depending on particular students’ backgrounds and interests, individual groups may pursue a wide variety of research trajectories. In the process, problem spaces push students beyond the paradigm of simple problems with unambiguous solutions to embrace science as a creative process in which peer review defines the standard of significance and quality.

Problem spaces themselves are designed to be flexible and open ended. As more faculty adapt problem
Figure 1: The BioQUEST Curriculum Consortium is a group of faculty from heterogeneous disciplines such as biology, mathematics, computer science, education, history and philosophy of science and science and technology studies. These faculty maintain active collaborations with discipline-specific professional societies, educational reform alliances and other organizations committed to education in science, technology, engineering and mathematics (STEM) fields. While our primary outreach has been directly with professors, students and their respective colleges and universities, we work with a wide range of organizations across different communities. BioQUEST serves as a hub of this wheel, catalyzing communication, sharing resources, providing opportunities for collaboration and developing new curricular approaches among partners.

Table 1: Summary of perceived barriers to adopting bioinformatics, and of specific strategies adopted by BEDROCK to help overcome those concerns

<table>
<thead>
<tr>
<th>Faculty concerns</th>
<th>Strategies</th>
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<tr>
<td>‘My course is already full: I don’t have time to cover new content.’</td>
<td>Spotlight uses of bioinformatics resources to reinforce learning about core concepts.</td>
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<td>‘I haven’t used these tools before and don’t know where to find the right data.’</td>
<td>Facilitate workshops in which faculty learn to use multiple tools and data resources to solve specific biological problems.</td>
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<td>‘My textbook doesn’t cover bioinformatics: this material isn’t relevant to my course.’</td>
<td>Support faculty development and sharing of bioinformatics activities to build a collection of diverse examples across content areas.</td>
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<td>‘I’m not sure how bioinformatics can be used to address _____.’</td>
<td>Emphasize the comparative basis of bioinformatics analyses and their evolutionary interpretations.</td>
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<tr>
<td>‘I’m not comfortable teaching this until I know it better myself.’</td>
<td>Share open-ended curricula that empower students to explore scientific questions and position faculty as research advisors.</td>
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Figure 2: A BEDROCK problem space combines three components: (i) biological principles such as evolution, biochemistry and molecular genetics; (ii) analytic tools such as sequence alignment packages, phylogenetic reconstruction software and molecular visualization tools; and (iii) data sets such as nucleic acid sequences, microarray data and metabolic pathways. All three components are accessed through a single web portal.


<table>
<thead>
<tr>
<th>Problem space (authors)</th>
<th>Description</th>
<th>Data</th>
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<tr>
<td>Exploring HIV evolution: an opportunity for research (Sam Donovan and Anton E. Weisstein)</td>
<td>Identify patterns of evolution in a longitudinal study of HIV-positive patients with different patterns of disease progression</td>
<td>Retroviral nucleotide and amino acid sequences and patient CD4 counts from multiple visits over a period of several years [16]</td>
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<td>Proteins: historians of life on earth (Garry Duncan, Eric Martz and Sam Donovan) One cell, three genomes (John R. Jungck, Sam Donovan and John M. Greenler)</td>
<td>Reconstruct deep phylogenies using the sequence of a highly conserved protein Explore the evolutionary history of plants using paralogs in nuclear versus organelar genomes</td>
<td>Enolase sequences from diverse organisms spanning all three taxonomic domains Rubisco genes from chloroplasts, mitochondria and nuclei</td>
</tr>
<tr>
<td>Tree of life (Beverly Brown, Sam Fan, LeLeng To Isaacs and Min-Ken Liao) Molecular forensics (Sam Donovan)</td>
<td>Explore the phylogenetic relationships and molecular markers of microbes. Use nucleotide data to weigh the evidence for HIV transmission from a dentist to his patients</td>
<td>Ribosomal RNA sequences</td>
</tr>
<tr>
<td>Desiccation tolerance (Kristin Jenkins and Kirsten Fischer)</td>
<td>Explore the evolutionary relationships, relative gene expression levels and geographic distributions of desiccation-tolerant plants and their sensitive relatives</td>
<td>HIV sequences from the dentist, his patients and other HIV-positive individuals from the same geographic area. Amino acid sequences, microarray data and 3D structures for two desiccation-related proteins</td>
</tr>
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<td>Searching for amylase—visualizing microbial proteins (Keith D. Stanley and Ethel D. Stanley)</td>
<td>Track down candidates for the next generation of industrial microbes such as those involved in converting starch to high-dextrose corn syrup.</td>
<td>Amylase sequences from a broad variety of microbes</td>
</tr>
<tr>
<td>Whippo: resolving the whale-hippo phylogeny problem (Sam Donovan, Samantha Price, Ethel Stanley and Margaret Waterman)</td>
<td>Determine the phylogenetic relationships of the Cetacea with other mammalian orders to determine their closest living relatives</td>
<td>Short interspersed elements (SINES), skeletal and dental data and nucleotide and amino acid sequences for a variety of nuclear and mitochondrial genes [17]</td>
</tr>
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spaces for their own classroom needs, they produce additional data sets and curricular resources that further extend the problem space. For example, users have expanded the HIV problem space to include explorations of drug-resistant strains and of the structural effects of specific mutations. While user feedback rates are extremely low for most software tools, the communication network established through BEDROCK’s faculty development workshops encourages adopters to stay in contact with each other and with project staff.

FACULTY DEVELOPMENT AND CURRICULUM DEVELOPMENT WORKSHOPS

Approximately 400 faculty members have participated in 50 major BEDROCK workshops...
since the project began in 2002. These workshops consist of three main phases: (i) an initial introduction to and exploration of a specific bioinformatics problem, (ii) a series of formal presentations on important bioinformatics concepts, tools and data sets and (iii) a period of active collaboration to develop curricula to meet participants’ teaching and research interests. Table 3 summarizes the schedule for a representative 4-day workshop.

Phase I of a BEDROCK workshop introduces faculty to three to four specific problem spaces (Table 2). During hands-on work sessions, faculty learn to use new software such as Cn3D [18] and Biology Workbench [19], as well as major bioinformatics databases such as KEGG [20]. Phase I culminates in a poster session in which participants share their work and receive peer review evaluating their methods and critiquing their conclusions. This entire process gives faculty first-hand experience in BEDROCK’s approach to student learning, in which a complex data set and few leading questions are used to involve learners in significant, original problem solving.

Once faculty have collaborated with each other in addressing complex questions, and experienced the vulnerability of lacking familiar criteria for assessing the ‘correctness’ of a given solution, they are much more receptive to learning new scientific content. Phase II of a workshop engages faculty with several fundamental questions in evolutionary bioinformatics through structured lectures given by BEDROCK staff and/or invited speakers. Frequent topics for

<table>
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<th>Table 3: Typical schedule for a 4-day BEDROCK workshop</th>
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<td><strong>Day 1: evening only</strong></td>
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<tr>
<td>45 min Welcome and Introduction to Workshop</td>
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<tr>
<td>30 min Introduction to problem space #1 (e.g. West Nile Virus)</td>
</tr>
<tr>
<td>30 min Introduction to Software Tools for Problem Space #1</td>
</tr>
<tr>
<td>60 min Group work on Problem Space #1</td>
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| **Day 2** |
| 45 min Overview of BioQUEST and BEDROCK |
| 30 min Introduction to problem space #2 (e.g. Chimpanzee Genetics) |
| 60 min Group work on problem space #2 |
| 60 min Group work |
| 75 min Formal presentation (e.g. phylogenetic concepts and applications) |
| 30 min Introduction to problem space #3 (e.g. Whippo) |
| 60 min Group work on problem space #3 |
| 75 min Group work on selected project; poster preparation |

| **Day 3** |
| 60 min Poster presentation |
| 30 min Introduction to Problem Space #4 (e.g. *Tamarix*) |
| 60 min Group work on Problem Space #4 |
| 45 min Discussions of curricular project |
| 150 min Group work on curricular projects |
| 60 min Formal presentation (e.g. geometry and graph theory in bioinformatics) |

| **Day 4: morning only** |
| 60 min Group work on curricular projects |
| 90 min PowerPoint presentations of curricular projects |
| 45 min Workshop wrap-up; distribute resource CDs; collect participant feedback |
these lectures include different methods of phylogenetic reconstruction, combinatorics and computational complexity and gene trees versus species trees. The lectures and ensuing group discussions give educators who are new to bioinformatics an intellectual grounding in the subject, equipping them with a variety of theoretical as well as applied approaches to a given topic. (Note that Phase II frequently overlaps with the other two phases in the schedule—Table 3).

Finally, in Phase III, participants apply their new skills and conceptual knowledge to develop new curricular modules in their own specific subdiscipline. Workshop facilitators strongly encourage participants to collaborate in groups of two to four on these curricular projects: this serves the dual purpose of allowing faculty to draw on each other’s expertise and of producing both an intellectual and a social investment in the project. While a 4-day workshop seldom provides enough time for participants to complete a project, the real goal is for them to make enough progress to encourage follow-up work and continued collaboration after the workshop. Examples of participant products include a molecular and morphological study of the evolutionary relationships of New Zealand tree ferns [21], a phylogenetic and functional analysis of the horizontal transfer of antibiotic resistance alleles in *Salmonella* [22] and an investigation of the phenotypic effects of specific mutations in the tumor-suppressing gene p53 [23]. Additional projects from BEDROCK workshops have yielded at least four publications to date [24–27].

**CLASSROOM IMPLEMENTATION**

Once faculty have developed curricular materials relevant to their own course needs, the next step is to bring those materials into the classroom. Regardless of the specific learning venue (lecture hall, wet lab or computer lab), BEDROCK-based modules emphasize three main pedagogical objectives:

- putting students in control of their own learning through hands-on research in which they must pose an interesting and testable question, choose and rigorously conduct appropriate analyses and interpret and communicate the results;
- relating the project explicitly to other course material (e.g. cell signaling, metabolic pathways, evolutionary mechanisms); and
- developing students’ problem solving and critical thinking skills through giving them experience working on a realistically complex and open-ended problem.

Below, we briefly summarize three specific implementations of BEDROCK curricular materials and provide references for related resources.

Following a 2000 BioQUEST workshop, Stacey Kiser at Lane Community College (Eugene, OR, USA) co-authored a bioinformatics lab on prepriproinsulin, USA evolution that she currently uses in her sophomore-level cell biology course. Insulin is an excellent model protein for several reasons: its relatively short sequence facilitates analysis; its significance as the first protein to be sequenced fits well with discussions of the history of modern molecular genetics, and of course its medical importance in diabetes provides a ‘hook’ that captures student interest. At the start of the lab activity, the instructor introduces students to the software tool *Biology Workbench*, where they learn to search online databases for a human prepriproinsulin sequence. Next, students use BLASTP to find similar sequences, which they align and use to build a phylogenetic tree. Finally, students summarize their findings in a formal write-up. This activity conveys several key points: the presumed connection between sequence similarity and evolutionary homology, the different selective pressures in functional versus nonfunctional regions of the protein, and specific evolutionary relationships among animal taxa.

Following a 2005 BEDROCK workshop, Barbara Burkhardt at Zionsville Community High School (Zionsville, IN, USA) authored an activity on avian influenza that she uses in her AP Biology course. Although this flu strain (H5N1) has recently received less attention than the swine flu (H1N1), it remains a serious public health threat—and therefore a subject that again ‘hooks’ student interest. In the classroom activity, students first complete out-of-class readings on the biology and history of the avian flu. Individual student groups are then assigned specific roles to play and appropriate research questions for each role. For example, students playing health officials identify the particular flu strains found in their countries and track any antigenic changes, while students playing ornithologists correlate the virus’s
evolution with bird migration routes to search for evidence of interspecies transmission. The main resources for this research include reports from the World Health Organization, the National Institutes for Health and the Centers for Disease Control, as well as Biology Workbench for sequence analysis.

Finally, all student groups share their findings in a symposium and formulate official recommendations for pandemic preparedness and control.

Building on an exercise in Microbes Count! [15], Anton Weisstein at Truman State University (Kirksville, MO, USA) developed an activity on HIV evolution and transmission that he uses in his senior-level Bioinformatics course. The activity concerns a well-known 1990 case in which an HIV-positive Florida dentist was thought to have inadvertently transmitted the virus to several of his patients during invasive dental procedures. Students are divided into small groups, each of which contains at least one biology major and one computer science major. Students are then given a text file containing multiple viral sequences from the dentist, three of his patients and four other HIV-positive individuals from the same geographic area (54 sequences total). Groups spend 1 week looking over the data outside of class and discussing how to address the question of dental transmission, then re-convene to share their ideas during the class period. Students then have 3 weeks to analyze the data using whatever tools (e.g. Biology Workbench, NCBI) and analyses (e.g. split decomposition, bootstrapping, ANOVA and t-tests) they choose. Due to the advanced nature of the course, many students may write their own code to implement specific algorithms, or carefully review the literature for appropriate parameter values. Each group also meets at least once with the instructor to ensure that their analyses address essential points such as excluding the possibility of superinfection, determining the directionality of transmission, etc. Finally, students write up formal papers summarizing their work and present it to their peers.

While the above examples emphasize the computational side of bioinformatics, many outstanding resources are available for faculty wanting to involve their students in hands-on wet-lab activities as well. Many such resources were developed independently of the BEDROCK project, but embody the same philosophy of achieving student learning via open-ended research. For example, Brad Goodner at Hiram College (Hiram, OH, USA) has students in his sophomore-level cell biology course use

Figure 3: What can you determine about lifestyle from genome content or gene order? (A) The Excel-based software tool What’s in a Genome? [30] uses online sequence data and gene ontologies to highlight differences in genome content among a variety of microbes. In the pictured histogram, >7% of the characterized genes from Magnetospirillum play roles in signal transduction, reflecting this bacterium’s aero- and magnetotactic behavior. In contrast, only 3% of the characterized genes from Chlamydia and Bacillus are involved in signal transduction. (B) PGRAPH [31], developed by Noppadon Khiripet and colleagues at NECTEC (Thailand), estimates evolutionary distances between microbial species based on the number of chromosome inversions needed to match their gene order and polarity. Here, five inversions separate the pathogenic Bacillus anthracis Ames strain 0581 from the soil bacterium Bacillus clausii strain KSM K16.
amplification, cloning and directed mutagenesis to test gene function in *Agrobacterium tumefaciens* [28], while students in his subsequent genetics class performed a gene annotation on the same organism that was published in *Science* [29]. BEDROCK helps disseminate and promote this type of externally generated, high-quality resource through invited lectures at BioQUEST meetings and faculty institutes co-sponsored with professional organizations. In so doing, it continues to provide bioinformatics educators with a constant stream of new examples, data and tools, while also encouraging faculty who are new to bioinformatics to develop their own resources.

**SOFTWARE TOOLS FOR STUDENT EXPLORATION**

Introductory descriptions of bioinformatics often focus on methodological details such as specific databases, technologies and software. This approach can easily lead to the perception, by learners and educators alike, that bioinformatics research is conducted using a standard set of pre-packaged online materials. In contrast, the BEDROCK project takes the view that active learning must include the creative leap of piecing together components of existing tools into novel resources appropriate for the user’s individual needs. To that end, BEDROCK materials attempt to stimulate deep inquiry by emphasizing multiple approaches to and multiple visualizations of the same problem. Examples of this ‘triptych’ method include:

- elucidating interspecific relationships by simultaneously considering gene sequence, gene order and genome content (Figure 3);
- extracting the different information contained in unrooted versus rooted and distance-based versus character-based phylogenetic trees ([32], see also Figure 4); and
- exploring a gene’s evolutionary history by comparing sequence alignments and phylogenetic trees to the protein’s 3D structure (Figure 5).

BEDROCK workshops and course materials make use of many existing tools that support this triptych approach to bioinformatics problems. For example, ConSurf [35], Cn3D [18] and Protein Explorer [36] all permit users to superimpose evolutionary conservation scores onto rotatable 3D protein structures, facilitating identification of putatively functional regions. Other software tools [30, 31] have been developed by BEDROCK staff and participants to address specific questions such as differential genome content and evolutionary distance based on chromosome inversions (Figure 3).

In addition to these research-grade tools, the BEDROCK project has developed a number of new pedagogical software tools designed to help students (and faculty!) learn specific bioinformatics concepts (Figure 6). For example, *EvolSeq* generates multiple sequence alignments and corresponding distance matrices; students then use pencil and paper to devise their own methods for translating these data into the corresponding phylogenetic tree.
Figure 5: (A) Multiple sequence alignment of coagulation factor V using CLUSTAL W, as viewed in SEA VIEW [34]. Amino acids 325–456 in the A2 domain include a region of strong conservation. (B) Hypothetical model of the structure of human factor Va shown colored by domains (left) and a display of conservation scores generated by ConSurf [35] (right). The dark-colored region in the upper left-hand corner of the CONSURF image corresponds to the conserved region shown in part A.
This exercise helps students identify their intuitive concepts about basic phylogenetic principles (e.g., that high similarity suggests close relatedness) and serves as a useful introduction to other distance-based methods such as UPGMA and neighbor joining. Similarly, Pairwise Alignment allows users to work through the logic of dynamic programming algorithms for global and local sequence alignment, while Protein Analysis demonstrates many of the algorithms used to predict proteins’ secondary structure and the location of membrane-spanning regions. These Excel-based tools, many originally developed for use in BEDROCK workshops, have become a powerful educational resource in their own right [37].

CONCLUSION

In the 8 years since BEDROCK’s inception, the continuing torrent of new bioinformatics tools and data has gradually permeated deeper into many undergraduate curricula. More and more educators are recognizing the field’s potential for linking standard course material on cell function and gene expression to major research milestones such as the completion of the human genome and to current events such as tracking the evolution of the swine flu. BEDROCK’s use of problem spaces illustrates an active-learning approach to bioinformatics education, in which students explore genuine biological questions using an open ended yet circumscribed data set and suite of tools. Through faculty development workshops held around the country, BEDROCK has fostered a professional network of informed educators dedicated to incorporating collaborative bioinformatics projects into courses from the high school to the graduate level. This network doubles as a resource for developing, disseminating and field-testing new curricular materials and software tools. The eventual goal of these efforts is an approach to bioinformatics education that values both mastery of key wet-lab and computational techniques and framing and testing of meaningful questions about function and evolutionary history. Theodosius Dobzhansky, one of the main figures of the modern evolutionary synthesis, famously claimed in 1973 that ‘[n]othing in biology makes sense except in the light of evolution’ [38]; we argue that this statement is still just as true today.
Key Points
- Bioinformatics abounds with profound and relevant questions that engage student interest while reinforcing core biological concepts.
- Problem spaces are a pedagogical approach that combine one or more fundamental biological questions with analytical tools and rich data sets, allowing students to explore freely within a clear framework.
- The BEDROCK project has cultivated a network of biology and computer science educators eager to support each other in innovative ways of bringing bioinformatics concepts and techniques into their undergraduate courses.
- A wide variety of free online software tools and curricular resources are available to support inquiry based and evolutionary approaches to bioinformatics education.

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