Scientific Citizenship

Games that Enlist Collective Intelligence to Solve Complex Scientific Problems

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There is great value in employing the collective problem-solving power of large groups of people. Technological advances have allowed computer games to be utilized by a diverse population to solve problems. Science games are becoming more popular and cover various areas such as sequence alignments, DNA base-pairing, and protein and RNA folding. While these tools have been developed for the general population, they can also be used effectively in the classroom to teach students about various topics. Many games also employ a social component that entices students to continue playing and thereby to continue learning. The basic functions of game play and the potential of game play as a tool in the classroom are discussed in this article.

INTRODUCTION

Citizen science can appear in many forms. Online gaming is one form that can serve as a tool to connect students in the science classroom with individuals outside of science to crowdsource solutions to scientific problems. Adding a gaming aspect to solving science problems can be a useful tool for engaging people from diverse backgrounds to use their collective intelligence to solve sometimes difficult scientific challenges (2). Currently, there are several online games related to various biological and biochemical processes. Each of these games has different levels of sophistication and usefulness both as citizen science and as a classroom tool. We describe four different online science games (Phylo, Nanocrafter, Foldit, and EteRNA) that engage players in citizen science and also have potential for classroom application.

While these games may not have been originally established for pedagogical purposes, they have many facets that can be utilized in the classroom. In the four online science games we discuss below, a simple set of rules is established, and the user must employ critical thinking and logic skills to solve a problem relevant to science. Since critical thinking and logic skills are essential to the mastery of science curricula (and students enjoy playing games), these games provide an ideal opportunity for science faculty to engage students in entertaining activities that can enhance their essentials skills and knowledge of valuable and sound science. Since most of these games do not require players to have a scientific background, the scientific basis of the game can be taught in the classroom, either before or after introduction of the specific game.

An additional aspect of some games, namely EteRNA and Foldit, is the incorporation of psychological motivating factors that increase game play. These games have both a rewards schedule to monitor progress in the game and a social chat capability that allows players to establish relationships within the game (11). While these two attributes may seem inconsequential at first, they become very important in keeping players motivated toward progressing to more challenging game levels, which is important if one intends to use these games to strengthen students' knowledge and problem-solving skills.

Phylo

Phylo (http://phylo.cs.mcgill.ca/) is a web-based citizen-science project that allows users to perform a multiple sequence alignment (MSA) without requiring significant background in biology or a high degree of technical knowledge of MSA algorithms used by computers. This means that while the program can be used by anyone, it has potential as a tool for undergraduate education.

The program uses four different colored blocks on the screen to represent the sequences, so players can take advantage of the human brain's ability to categorize and interpret visual input quickly (7). A game starts with a pair of sequences to align, and, depending on the choice of the player, may include up to ten separate sequences that will

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be aligned together. The sequences are arranged with each organism's sequence filling up a separate row, with the rows one on top of the other. There are additional empty blocks on the screen, allowing the sequences to be expanded with gaps. The sequences are adjusted by using the mouse to click and drag portions of the sequence (one or more colored blocks) in an attempt to reach a better match score. As the blocks are moved, the scores are adjusted, showing how the different penalties for misaligned sequences or gaps in the sequences will affect the score. This allows players to then make adjustments and see the effects immediately in an intuitive way (6). When all the blocks at a given point in every sequence are of the same color, they are highlighted to indicate that they are matched. The method used to align the sequences matches the techniques used in MSA progressive alignment algorithms (i.e., first aligning different pairs of sequences, then trying to align the overall set of sequences) (1), meaning that players are exposed to the underlying process without needing to understand it in detail. Since Phylo has a simple gameplay mechanism, the usefulness to undergraduate education may be limited to classes that introduce MSA. One significant problem from an educational perspective is the lack of significant instructions and/or tutorials that would help all students get familiar with the concepts and tools. This is particularly significant if the goal was to help the students develop a deeper understanding of sequence alignment and its application for evolutionary biology. It is easy to imagine that a lower-level student would get frustrated trying to build alignments without having sufficient understanding of the purpose, and a more advanced student would be deprived of a greater understanding of how the alignments are produced. While this game currently has limitations as a stand-alone teaching tool for MSA education, the basic understanding students obtain by initially playing Phylo could then be leveraged as a foundation for a deeper understanding of the details and applications of sequence alignment taught in the classroom. The system does have a mechanism for an instructor to set up a class where students can register for the "assignment" and have their results tracked. However, there does not appear to be significant opportunity for the professor to customize how the system works (e.g., by specifying which sequences will be analyzed). It is possible that new educational capabilities could be added, making the tool much more useful in a classroom setting. The software currently would be appropriate for introduction in a lower-level biology course to give a quick overview of the process of performing alignments, or as a review in an upper-level course prior to a more sophisticated discussion of sequence alignment.

One of the major strengths of Phylo is the simplicity of the interface, making it easy for anyone to play without significant explanation. Phylo is clearly designed as a tool for players with limited knowledge of biology, and it appears to be quite successful based on the number of players it has attracted (7, 10), as well as by the fact that the human-derived modifications to the alignments have shown significant improvement over alignments produced by MSA algorithms in 70% of the sequences that have been analyzed (7). Also, in 2013, the researchers created a site called Open-Phylo that allows researchers to input their sequences into the system so that the crowdsourced activity can improve the quality of their alignments (9). These two facts make it clear that Phylo has a significant chance to benefit the research community, even if the people using the system do not have expert knowledge of molecular or evolutionary biology.

Nanocrafter

Nanocrafter (nanocrafter.org) is an online game designed by the Center for Game Science at the University of Washington to simulate the use of DNA in nanotechnology. The modern ability to produce synthetic DNA has potential for use in applications such as building nanomolecules or in the relatively new fields of DNA computing and molecular programming (13). By manipulating the sequences of DNA molecules, it is possible to build DNA molecules that can perform logical functions. This game is built on the concept of using strand displacement, which occurs when a DNA strand displaces a hybridized DNA strand from an existing molecule. Strand displacement occurs when the new strand is a better match than, or more complementary to, one of the existing strands.

The game emphasizes that DNA strands can only bind together if they are complementary to each other. The DNA in Nanocrafter can essentially be categorized as one of three types: a piece—analogous to a nucleotide; a strand—analogous to a chain of nucleotides; or a molecule—analogous to a double-stranded DNA molecule. The game uses colors to represent the bases. Each piece of DNA in Nanocrafter is colored, and same-colored pieces are complementary to each other. Pieces that are complementary can bind to each other, or hybridize, via hydrogen bonds. In addition to colors, pieces can have one of two shapes. Pieces must be complementary shapes in order to hybridize, and pieces that have the same shape will not form hydrogen bonds. Pieces must be the same color, but opposite shapes, to hybridize and form double-stranded molecules, illustrating the role of antiparallel strands in the hybridization process. Once the player understands the rules behind hybridization, they are introduced to longer DNA strands by forming covalent bonds between pieces to connect them together. Longer strands can also hybridize, assuming they meet the complementary and antiparallel requirements.

Once the basics are in place, the player is introduced to strand displacement. Strands of DNA that are better matched will hybridize to each other, displacing shorter strands or strands that are not as complementary that may already be hybridized. The player must understand that strands which are longer, or better matches, will always win and displace shorter or poorer matches. As the player masters strand displacement, the game adds further levels of complexity, introducing the importance of strand

concentration and eventually working up to the concept of toeholds, or short pieces of DNA that are analogous to primers. Even if they are complementary to each other, toeholds will not stay hybridized unless they are covalently connected to a longer strand. This allows complicated reactions based on logic and simulates situations which are critical for DNA computing. The goal of each level or challenge varies but is based on keeping uniquely marked strands hybridized and other marked strands unhybridized. The ultimate challenge of the game involves building molecules from scratch that can form complex molecular structures, such as wheels, spheres, triangles, or other "tools" which could be used as molecular motors.

Nanocrafter has some value for use in various science courses, but its use could also apply to general logic or math classes. For example, it could be used in upper level genetics, molecular biology, or biotechnology courses where the techniques of DNA hybridization are taught. However, it could also be used in logic courses or perhaps even specialized computer courses since much of the game is focused on the logical outcomes of the challenges. This game has increasing difficulty levels that encourage players to continue playing. However, it lacks the social structure which could be used for class interaction and is better designed for the individual player.

Foldit

Foldit (http://fold.it/portal/) is an online game that models protein folding. Foldit has been used in various capacities for several years (3). While most people are using online games as an opportunity to crowdsource creativity in order to solve science problems (4, 8), there are also direct classroom applications. Foldit is a great tool for teaching about the forces involved in three-dimensional protein folding. In addition, Foldit provides a way for students to "see" the interactions and forces within various areas of the molecule in three-dimensional space, allowing them to visualize the concepts of protein folding taught in the classroom.

While crowdsourcing difficult protein folding problems and designing peptides in advanced classes are valuable to the scientific community, there are other ways to use Foldit to reach more people. For example, Foldit has a set of tutorials built in to the game. The tutorials, as well as the game puzzles, can be used in the classroom of any biochemistry course (5). These tutorials are divided into eight different groups, representing common learning objectives in a biochemistry class. The first four levels of tutorials represent side-chain interactions, backbone interactions, hydrogen bonding, and hydrophobic/hydrophilic interactions. After completing a level where users learn to use the tools of Foldit, there are three more tutorials that involve advanced biochemistry, such as sequence alignments, designing sequences (mutagenesis), and ligand interactions. These different tools can be used to help students visualize the concepts discussed in class.

Following the completion of the tutorials, there are contests and puzzles that can be done. The contests are developed by the Center for Game Science at the University of Washington and have specific goals with expiration dates. The challenges are limited to several that have been developed by the Center for Game Science, but also include a freestyle design option. It can be useful to create a group for one's class and assign a challenge. You can monitor the progress of everyone in your group and assign grades based on standings or total points on the challenge. One example of use in the classroom allows advanced biochemistry students to "build" a Zn^{2+} binding peptide virtually in the Foldit game (12). This modeling provides a cheap and robust method to predict and manipulate peptides and proteins outside of the lab.

Foldit has some clear advantages in the classroom over the previous two games. Foldit has both individual game scores and rankings for overall proteins solved. This allows the player to constantly advance in the game. In addition, it has a social aspect, with both a puzzle chat and a regional chat. This allows the player to interact with other players on the same puzzle, or in the game in general. These are valuable tools to use in the classroom to foster community and group cooperation.

EteRNA

EteRNA (eterna.cmu.edu) was developed through a collaboration between Carnegie Mellon University and Stanford University to crowdsource RNA design and structure prediction. EteRNA consists of puzzles, lab activities, player projects, strategy design, and community support.

EteRNA offers a tutorial to get players started, introducing the basics of RNA hybridization, similar to Nanocrafter. However, EteRNA is far more specific, denoting exact bases and base-pairing rules. EteRNA has a companion site, NOVA labs (www.pbs.org/wgbh/nova/labs/), which offers more animated tutorials and trials that could be used to engage a wider audience, including middle and high school students.

Once the tutorials are completed, the puzzle mode is an effective means of introducing students to the principles of how RNA sequences fold in nature. The player's goal is to build the primary sequence of the RNA so that it folds into a given target structure. Each puzzle provides the player some facts about the molecule, and most puzzles have one or two rules that have to be followed, such as limits on the number of certain base pairs in the sequence. At the bottom of the screen, the player is provided with the base pairing rules, including a display of the bond energies.

The game play of EteRNA is very simple, and the game has puzzles that range in difficulty. The advantages of the game are the progressive levels and the social aspects of the game. As a player makes appropriate base-pair choices, the game will provide formative feedback ("great pairing"), providing motivation to continue. Once the player has predicted

a correct sequence that would naturally fold into the target structure, the player is rewarded with points based on the puzzle's difficulty, adding to the player's cumulative score, which can be compared to other players in the community. A player who solves enough puzzles and reaches 10,000 points is admitted to the RNA lab, allowing them to solve specifically designed sequences that fold into the target structures. The EteRNA community of players then votes on other players' solutions. The sequences with the highest votes are actually synthesized in the University's research lab, and observations about how the resulting molecules behave are relayed to the players, allowing students and other players to see applications of their work and classroom instruction in the real world. Finally, once a player reaches 20,000 points, they will unlock the ability to design their own puzzles, which are offered to the EteRNA community for solving. The developers are currently working to create an aspect where a player can "follow" other players, exchange information in chat windows, and even interact at a conference for EteRNA players. These social aspects to the game help players develop confidence, problem-solving skills, and mastery of fundamental aspects of RNA folding while learning the value of collaboration.

CONCLUSION

Online games are a growing industry attracting worldwide players daily. The scientific community has engaged many of these individuals, allowing them to use their gaming, critical thinking, and logic skills to solve science problems. The four games covered in this article have already been used to solve difficult research problems with multiple sequence alignments, protein folding, and RNA folding using crowdsourced intellect. However, these games could also be used to help develop critical thinking and logic skills of young scientists in and out of the classroom. In addition to the basic skills necessary to be a successful scientist, these games also teach the basics of several biological processes and offer an opportunity to connect with more students in the classroom. Several of the games offer basic tutorials that initiate the player to the game, while indirectly helping the player to understand the basic principles of the science behind the game. These games will not completely replace the technical lessons for scientists but could be used to motivate more individuals to be interested in science and science-related problems. Finally, these games could be used as an outreach tool to attract young students (K–12) to science. While they may not fully understand the science

behind the game, they could be effective players, and the games could foster a curiosity for science while simultaneously building valuable critical thinking skills.

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