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Leveraging Video Game Playing to Improve Computational Biology Research

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Abstract

Many problems in computational biology, such as predicting the native structure of proteins, are so computationally difficult to solve that even the most powerful supercomputers today cannot produce an exact solution within a reasonable amount of time. As a result, heuristic algorithms are used to approximate solutions to these problems. However, such algorithms often produce inaccurate solutions that do not hold up when tested in the laboratory. Recently, scientists created an approach that crowdsources solutions to these complex problems by providing video games called "games with a purpose" (GWAP) to the general public. Using GWAPs as a means of problem solving has been shown to be more efficient and accurate in solving computational biology problems, such as protein folding prediction, inverse RNA folding, and multiple sequence alignment. By finding ways to entice more people to play GWAPs, we can more effectively solve more problems, truly unlocking the potential of GWAPs.

Major hurdles in computational biology research include the lack of efficient algorithms to solve complex problems as well as the inability of existing approximation algorithms to accurately model biological structures and systems. One recent approach to circumventing these issues has been to leverage citizen science, in which solutions to scientific problems are crowdsourced utilizing video games. These video games, which utilize peoples' mental capabilities to perform certain tasks, are called "games with a purpose" (GWAPs). GWAPs harness the power of human creativity, which is highly idiosyncratic and diverse, in problem-solving.

One of the first GWAPs created was the ESP game, a game wherein players assign textual labels to images (von Ahn & Dabbish, 2004). This game essentially consigned image recognition—a task challenging for computers—to humans. In addition, Amazon later developed the Mechanical Turk, a crowdsourcing concept similar to GWAPs wherein "requesters" set up jobs for "turkers" (human workers) to complete in exchange for monetary compensation. For instance, a requester could create a job in which a turker would have to label images for compensation. GWAPs have now been created specifically for computational biology research, including discovering the three-dimensional folded structure of proteins, predicting the sequence of nucleotides needed to create a RNA molecule of a given structure, and determining the optimal alignment of multiple sequences of amino acids or nucleotides.

To demonstrate the utility of GWAPs, this paper will review the success of some recent GWAPs designed for problems in computational biology. The paper will then propose methods to increase the efficacy of GWAPs by increasing the number of users as well as audience retention rates.

One recent, successful GWAP is Foldit, a video game designed to discover the native state of proteins (Cooper et al., 2010). This game was created to address limitations with leading protein structure prediction algorithms, such as the Rosetta method. The Rosetta method uses a Monte Carlo search algorithm to minimize an energy function approximating the free energy of a protein conformation. However, finding the best protein configuration by searching through the colossal free energy landscape is computationally inefficient (Cooper et al., 2010; Das & Baker, 2008). Furthermore, once the Rosetta simulation comes across a low energy configuration, it is unlikely to perform major protein restructuring that could cause a temporary energy increase before an ultimately lower energy conformation (Cooper et al., 2010).

However, with Foldit, which harnesses human three-dimensional spatial reasoning, players ended up making decisions that Rosetta did not make, as they were able to "see" the potential in remodeling the protein that the simulation missed. For instance, for a few of the proteins with experimentally determined structures, Foldit players made decisions that

rearranged the protein backbone, producing low energy structures very close (based on root mean squared deviation) to the native conformation. These conformations are far closer than the structures produced by Rosetta (Cooper et al., 2010). Furthermore, when Foldit players were challenged to come up with an accurate model of the Mason-Pfizer monkey virus (M-PMV) retroviral protease, a previously unsolved protein structure, they successfully solved it (Khatib et al., 2011). These results show how humans playing GWAPs can not only outperform standard algorithmic conformational sampling techniques, they can also figure out novel protein structures *in silico*.

On top of the ability to obtain multiple solutions to get the best result, GWAPs also allow for iterative assessment and feedback, further improving results. One GWAP specializing in this feedback loop is EteRNA, a GWAP used to design RNA that folds into specific secondary structures (Lee et al., 2014). The algorithm for finding the exact solution to the Inverse RNA folding problem has been suggested to be an NP-complete or an NP-hard problem (Dotu et al., 2014; Schnall-Levin, Chindelevitch, & Berger, 2008). NP-complete and NP-hard means that an efficient way to compute the solution to this problem is not known to exist. Although heuristic algorithms, such as RNAinverse and INFO-RNA, exist to provide approximate solutions (Dotu et al., 2014), many RNA designs produced by these algorithms do not fold into the intended structure when assessed *in vitro* (Lee et al., 2014). In EteRNA, players design RNA to match a given structure by putting together nucleotides using an interface that shows the player information about their current design, including a predicted minimum free energy structure. Players then vote on each other's designs, and the top-voted designs are synthesized in the lab and assessed for their similarity to the intended structure. These experimental results are then returned to players, who use them to guide their subsequent RNA designs. This cycle of designing and receiving feedback has been successful; EteRNA players eventually outperformed algorithms like RNAinverse in predicting the structure of complex RNA molecules (Lee et al., 2014). In addition, EteRNA players can submit design rules if they find a tendency that leads to successful designs. The player-submitted designs are incorporated into an RNA design algorithm called EteRNABot. The RNA designs produced by EteRNABot also outperform state-of-the-art inverse RNA folding algorithms (Lee et al., 2014). The success of EteRNA players and EteRNABot in designing RNA shows the power of GWAPs in helping solve difficult problems in science.

Another success story is Phylo, another GWAP used to solve a difficult problem in computational biology (Kawrykow et al., 2012). Phylo was created to crowdsource a solution to the multiple sequence alignment (MSA) problem, an NP-hard problem (Kawrykow et al., 2012; Wang & Jiang, 1994). MSA involves finding the optimal alignment of a set of biological sequences in order to unveil sequence similarity and to provide a lens into the evolutionary history of particular sequences. Although

heuristic algorithms designed to sidestep the computational complexity of MSA have been developed, these algorithms often produce inaccurate alignments (Kawrykow et al., 2012). In Phylo, players move colored blocks (representing DNA nucleotides) and attempt to maximize conservation within columns and minimize the number of gaps. Phylo was tested on the alignment of promoters of selected genes across 44 species. The best MSA produced by Phylo players performed better than the MSA produced by Multiz—a prominent alignment program—for 70% of the alignment blocks (Kawrykow et al., 2012). This again highlights the benefits of crowdsourcing solutions to challenging problems in science.

One obstacle that can limit the success of GWAPs is not having enough players. GWAPs, by design, rely on a large number of players to be successful. After all, if more players are trying to solve a problem, the chances of finding a solution to the problem will increase. This is because not only are more human minds at work on the problem, but GWAPs utilizing elements of collaboration will disseminate more ideas and designs (Cooper et al., 2010). Although GWAPs incentivize people to play using features such as a user-friendly interface, abstractions away from the science, competition between players, or in-game rewards (e.g. points) for discoveries (Cooper et al., 2010; Kawrykow et al., 2012), these strategies are likely insufficient, since there are thousands of high quality video games around that are more entertaining. In order to attract more people and to retain players, a monetary incentive could be introduced. For instance, someone who solves the structure of a protein could receive cash or a gift card. A lot of research involving people, such as surveys, offer a monetary incentive. GWAPs should too, to stay competitive. In this way, these GWAPs would retain both the elements of a video game while also incorporating the monetary incentive of the mechanical turk concept.

Additionally, increasing advertising of GWAPs and raising publicity about these games could attract more players. Finally, increasing accessibility, such as making these games available on mobile devices, would also greatly expand the audience. However, mobile phones may not be able to handle these computationally intensive functions, so they may need to be carried out remotely. These proposals are just some ways that will increase the number of GWAP players, which will improve GWAPs' contributions to science.

Ultimately, although stochastic simulations, deterministic simulations, or algorithms consisting of a hybrid of the two are the typical workhorses within computational biology, human intuition is just as powerful a tool. The ways humans explore these problems involves much more creativity and variation than any computer algorithm. Even so, human minds alone cannot do these tasks; they need the computer to guide them via predictions, such as the predicted energy of a protein conformation. As such, GWAPs combine the best of both worlds by having computers and humans work together to accomplish a task. By implementing measures

that can entice more people to play GWAPs, GWAPs will potentially have a huge impact on computational biology research.

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