Nanocrafter: Design and Evaluation of a DNA Nanotechnology Game

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ABSTRACT

In this paper we present the design and preliminary evaluation of a new *scientific discovery game*, Nanocrafter. The intent of Nanocrafter is to be a citizen science platform for the discovery of novel nanoscale devices built out of self-assembling strands of DNA. The game uses DNA strand displacement rules as its basic mechanics, allowing players to construct and simulate such devices. The aim is to have a simulation accurate enough that promising devices built in the game could be synthesized and tested in the wetlab. Semi-weekly challenges defined by open-ended text prompts and rated by the community encourage players to build towards a particular type of device. Nanocrafter was released online and has run a number of challenges. We discuss the design of the game in terms of visualizations, interactions, scoring, and introductory levels, and present an evaluation of preliminary results, analyzing several devices created by players using the state-of-the-art simulator Visual DSD.

Categories and Subject Descriptors

D.2.2 [**Software Engineering**]: Design Tools and Techniques; K.8.0 [**Personal Computing**]: General—*games*

1. INTRODUCTION

In this paper we present a new *scientific discovery game* called Nanocrafter (Figure 1). Taking DNA out of its natural function as a genetic library, Nanocrafter allows players to participate in the growing field of DNA nanotechnology by constructing and simulating devices—modeled at the nanoscale—out of short, self-assembling strands of DNA. As the space of possible designs is vast, we hope that involving the creativity of game players will assist scientists in not only refining and improving on known devices but also inventing entirely new classes of constructs that are of interest to the scientific community. Eventually, player designs from the game will be synthesized and tested in a real-world wet lab.

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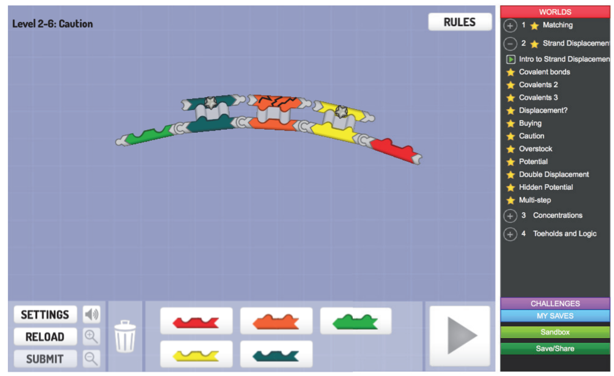


Figure 1: A screenshot of Nanocrafter, showing the introductory level *Caution*. The player must build an invention, using the domains from the menu on the bottom of the screen, that displaces the two starred domains while leaving the cracked domain hydrogen bonded (hybridized). The play button in the lower right starts and pauses the simulation. The sidebar on the right allows convenient navigation between different parts of the game.

The selection of DNA as a material for building devices is not due to its genetic encoding properties—Nanocrafter does not specify the exact sequence of base pairs, only that certain sequences are unique—but rather the fact that DNA base pairing mechanics can be effectively modeled and simulated. Because of this, DNA has proven a promising substrate for engineering self-assembling systems [20]. In the future, DNA-driven logic circuits might act as inexpensive broad-spectrum diagnostic tools, while therapeutic molecules attached to DNA "motors" could selectively deliver their treatment to cells afflicted with a target disease.

With Nanocrafter, we are further exploring the space of scientific discovery games. The key challenge presented in the design of Nanocrafter was to create a game that **allows amateur game players to make creative contributions to open-ended questions in a given scientific domain**. We discuss how we addressed new challenges in the *scoring*, *visualization*, *interactions*, and *introductory levels* [6] while creating a DNA nanotechnology-driven puzzle game, and present preliminary results of what players have designed so far.

Figure 2: Representations of DNA. (top-left) A quasi-realistic representation, (top-right) a detailed scientific representation showing all base pairings, (bottom-left) a domain representation that abstracts strand fragments into functional groups, and (bottom-right) Nanocrafter's representation, functioning both as a domain representation and as an intuitive, aesthetically pleasing puzzle piece. Some images made with NUPACK [15, 28] and Visual DSD [23].

2. RELATED WORK

Over the last several years, there has been significant interest in creating games in which players help to solve real-world scientific problems through gameplay. This approach has proven most fruitful in the domain of biochemistry and biology, with games for such applications as protein folding and design [5], RNA design [13], genetic sequence alignment [10], and mapping neurons [11]. Games have also been built around problems in computer science, including graph theory [1] and software verification [7].

These games can be seen as an intersection of citizen science projects that involve the public in scientific research, such as GalaxyZoo [4] (used for classifying galaxies) with "Games With a Purpose", including the ESP Game [2] and Peekaboom [3] (used for image labeling).

3. DNA STRAND DISPLACEMENT

The field of DNA nanotechnology uses DNA strands to manipulate the spatial and temporal distribution of matter. In DNA strand displacement, two DNA strands with partial or full complementarity hybridize to each other, forming hydrogen bonds between their nucleotides and displacing one or more pre-hybridized strands in the process. An in-game representation is shown in Figure 3. This simple mechanism has been used to engineer a variety of structural and dynamic DNA devices. DNA strand displacement networks have been used to produce repeating figures [19], self-assembling tiles [24], logic circuits [18], and walking robots [26], with potential applications such as tissue engineering or repair, diagnostics, and therapeutic delivery.

The greatest contribution game players can make to the field is a creative one. The upward limit of DNA species able to be used in a reaction has yet to be discovered. One of the largest DNA circuits published so far, the square-root circuit implemented with the seesaw DNA motif, uses 74 initial DNA species [17]. Ostensibly, anything players can imagine can be built. Large and complex devices are only waiting to be invented.

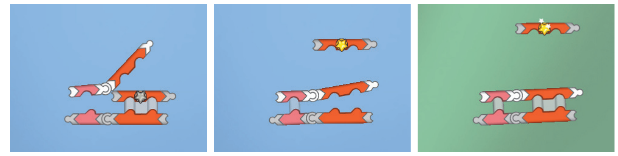


Figure 3: A displacement reaction. (left) When the player starts the simulation, the unhybridized, complementary pink domains react and form a bond. (middle) Strand displacement occurs, with the orange domain marked with a star dehybridizing as the longer strand displaces it. (right) The simulator reaches a metastable state, and triggers the win animation since the starred domain has been released.

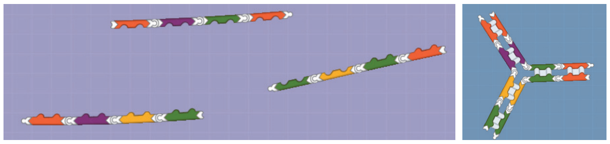
The Visual DSD project [23], which consists of a semantic language for describing DNA strand displacement reactions and simulation software that closely mimics the kinetics of real strand displacement reactions, has been used to evaluate experimental models and accurately predict real-world results [12, 16]. As the most widely used tool for simulation of strand displacement reactions, it is useful as a gold standard against which to measure new simulation efforts.

4. NANOCRAFTER

In Nanocrafter, players solve puzzles by constructing devices out of blocks, then initiating the game's core mechanic: a simulation of DNA strand displacement [29]. In the game, each individual block piece represents a short single strand of DNA, referred to as a *domain*. Domains can be *connected* together, head to tail, to create longer *strands*. Domains can also be hybridized to complimentary domains—referred to in the game as *bonded*. In the game, a group of domains that is connected or bonded together is referred to as a *plex* (short for complex), and the collection of all the plexes is referred to as an *invention*. Players assemble inventions by snapping domains together, then run the simulator to observe the results of their inventions in action. As is standard in the field, Nanocrafter includes two different lengths of domains, long and short, that differ in their bonding stability. Long domains can, by themselves, maintain their bond. Short domains will stay bonded only if they are part of a longer bonded strand, otherwise they will fall apart.

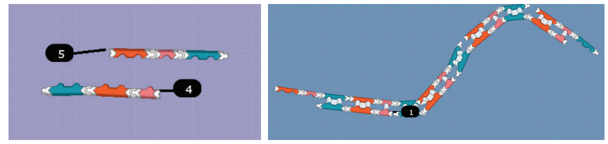
The game hosts challenge puzzles that generally last for two weeks and invite players to create inventions that address open-ended text prompts, such as "Create three totally independent reactions using as few distinct colors as you can" or "Build two double-stranded molecules that exchange a strand when play is pressed". Players can submit their inventions to an online gallery where other players can view and rate them.

To develop and refine the game, we undertook an iterative design strategy involving the development team, playtesters, and domain experts in synthetic biology [6], incorporating feedback to improve the game and address design challenges. Nanocrafter was released online in April 2014. The game is available to play for free on its website [14]. Since its release, the game has had 12,000 players, who have submitted 540 inventions to 55 challenges.



```
directive duration 1000.0 points 100
( 1 * <1^ 2^ 3^ 1^> | 1 * <1^* 3^* 4^ 3^>
| 1 * <3^* 4^* 2^* 1^*> )
```

Figure 4: A player-created self-assembling three-way self-assembling Y junction, showing (top) the start and end states from Nanocrafter and (bottom) the Visual DSD code we derived. Note that in Visual DSD the long domains were changed to short domains to satisfy Visual DSD's constraint that there are no reactive long domains in the initial state.




```
directive duration 10000.0 points 100
( 5* [1]<2^>::[3]<2^>
| 4* {3* 2^* 1* 2^*} )
```

Figure 5: A player-created self-assembling polymer, showing (top) the start and end states from Nanocrafter and (bottom) the Visual DSD code we derived. Note that in Visual DSD the higher-concentration strand had complements added to its long domains, to satisfy Visual DSD's constraint that there are no reactive long domains in the initial state, and a second toehold was added to each strand to compensate for the bound long domains. The option "Polymers" must be enabled, and simulation mode should be set to "JIT".

Scoring inventions in Nanocrafter presented a particular challenge due to the extremely open-ended nature of the game—there is no standard scoring function to use. We wanted to reward players for creatively addressing the challenge puzzle prompt, but also to be as flexible as possible so that we would not presuppose specific types of solutions. Therefore we chose not to implement any automated or objective scoring for challenge puzzles, but rather allow other players to rate inventions and for players to accumulate score through these ratings. Inventions can be rated as *practical* (meaning they satisfy the challenge prompt) and/or *original*, with those receiving votes in both categories also being rated *creative*. The player who created an invention will receive one point for each rating their invention receives in any category, shown on a leaderboard.

The basic element of **visualization** in the game is the domain. For each domain, there are four main properties to visualize: the sequence (which string of bases it represents), the directionality (which end is the "head" and which is the "tail"), the complementarity (whether the strand represents a base sequence or its antiparallel counterpart), and the length (long or short). These properties define which domains can bond with each other. Figure 2 shows multiple different visual representations of DNA, including Nanocrafter's. We chose a representation that abstracts many of the low-level details of the DNA, such as the exact sequence of bases. It also does not look like the familiar helical DNA representation, and this may help to dispel any preconceived notions of DNA in its natural context.

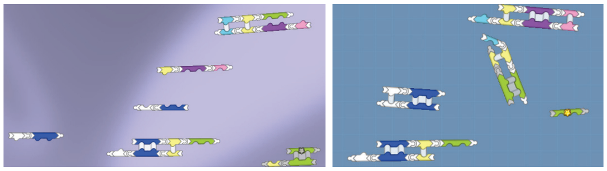
The sequence of a domain is denoted by its color. Domains are each a single color by default, but if more distinct sequences are required than colors in the palette, the game will use two colors for each domain. Directionality and complementarity are represented by the domain's shape: the chevrons on a domain point towards its head, and a domain with bonding points that point outward is complementary to a domain with bonding points that point inward. Bonding points are angled slightly to reinforce directionality. In addition to their length differences, long domains have two bonding points and short domains have one. Domains can be connected by their head or tail to two other domains, and bonded to one other domain. Domains that are the same color, same length, and complementary shapes can bond, and they will point in opposite directions once bonded. This representation can be seen in Figures 2 and 3. Connections and bonds are shown as areas external to the color-filled regions of domains, which makes it visually distinct whether two domains are connected or bonded in the context of a plex.

Additionally, if there is more than one copy of a plex, we collapse all of those copies into a single stacked instance of the plex with the concentration noted in a callout, as seen in Figure 5.

The primary modes of **interaction** for players in the game are *constructing* an invention and *simulating* it. In order to construct an invention, players can create domains from a menu on the bottom of the screen (seen in Figure 1), within which they can customize the available domains. Once domains have been created, players can create bonds or connections by dragging domains close to each other, and break existing connections or bonds by clicking on them. The layout is handled by a 2D rigid body system. This allows the player to build a variety of spatially complex systems. Players can adjust concentrations using buttons in the respective callouts. Players control the simulation through the use of a play/pause button on the menu. They can also rewind and reset the simulation.

Nanocrafter features a sequence of **introductory levels**, meant to teach players about strand displacement and other game mechanics and build their knowledge of DNA nanotechnology. Unlike challenge levels, the introductory levels have specific goals that must be met to complete the level and move on to the next one, and players do not share their solutions for rating. Some domains in the initial setup of the levels are grayed out and cannot be edited by the player.

In the introductory levels, particular *goal domains* are marked with stars. These domains must end up unbonded when the simulation completes (or oscillates), usually accomplished by displacing them. If the simulation completes and any goal domains are still bonded, the level is lost and the player can try again. Goal domains are inspired by "molecular bea-



```
directive sample 1000000.0 1000
def GOAL() = {1^*}[2]
def NAND1() = [5^ 1^]<2>:[3]{4^*}
def NAND2() = {6^*}[7 1^]<2>
def ACTIVATOR1() = <1^ 3 4^>
def ACTIVATOR2() = <6^ 7 8^>
def INPUT1() = {1^*}[3]{4^*}
def INPUT2() = {6^*}[7]{8^*}
( 1*GOAL() | 1*NAND1() | 1*NAND2()
| 1*ACTIVATOR1() | 1*ACTIVATOR2()
| 1*INPUT1() | 1*INPUT2() )
```

Figure 6: A player-created, partially-functional NAND gate, showing (top) the start and end state from Nanocrafter with one of the two possible inputs created, and (bottom) the Visual DSD code we derived. Note that in Visual DSD, one of the two logic gates and both receptors had complements added to their long domains, to satisfy Visual DSD's constraint that there are no reactive long domains in the initial state, and we corrected a directionality error. With both inputs present, the `GOAL` never reacts to produce a lone <2> domain. Deleting either or both inputs results in the `GOAL` reaction taking place.

cons": fluorophore-tagged DNA segments hybridized with segments that have been tagged with a quenching dye, resulting in easily-measured fluorescence when an experiment completes successfully, and limited or absent fluorescence when it fails [22]. To add challenge, some levels also contain *cracked domains*, which must remain bonded throughout the simulation of the invention. If a cracked domain ever becomes unbonded, the level is lost immediately. Cracked domains have no scientific analog, rather they were added to have an easily-understood failure state in the early introductory levels. In Figure 1, the top-right yellow domain is a goal domain, and the top orange domain is a cracked domain.

5. EVALUATION

Informal assessment of a subset of submissions suggests that the game is having some success in cultivating mastery of DNA nanotechnology concepts in its players. Figures 4, 5, and 6 demonstrate solutions submitted by Nanocrafter players that were the highest-rated for their respective challenges, along with our manually-derived Visual DSD code. In each case, the player's solution partially or wholly satisfied the conditions of the challenge. Because of differing constraints between the two simulations—Visual DSD does not allow unbound long domains in the initial state—the derived code does not exactly match the game's starting state.

Branched DNA is an important topic in DNA nanotechnology [20]. The player solution to the challenge "Create three strands that, when played, each bind to the other two strands" (Figure 4) demonstrates a working understanding of how multi-way junctions in DNA are formed.

Self-assembly of arbitrarily large DNA structures is being investigated by several labs [29]. We put forth the challenge "Create some number of molecules that combine into a single repeating figure when played" to see if players could create a self-assembling system. The player solution (Figure 5) creates a system very similar to the one detailed in [8], elegantly building a polymer using many copies of two distinct strands.

Reaction networks driven by DNA-based logic circuits are a key feature of DNA nanotechnology research [29]. The challenge "Make a system that releases the star only if one or both of the inputs on the left are deleted" tested to see if players could construct a working NAND gate. The player solution (Figure 6) comes extremely close to building a functional NAND gate, with a flaw in the directionality of one input and receptor preventing correct execution in some cases. Early demonstration of how a relatively complex logic gate is meant to function was encouraging. We were able to demonstrate that a very similar system in Visual DSD, with adjustments detailed in the figure, produced the expected NAND gate logic table over the range of inputs.

6. CONCLUSION

In this paper we have presented the design of a new scientific discovery game, Nanocrafter, along with an initial evaluation, in the form of some early devices that players have created in the game. These devices demonstrate early evidence of players constructing and preferentially rating inventions of interest.

In future work, we believe there are many opportunities to support and foster player creativity in Nanocrafter. Existing work has examined methods for leveraging and improving human creativity for design or problem solving in open-ended domains. For example, Yu and Nickerson [27] examined crowdsourced creativity through generation, recombination, and rating of chair designs and Dow *et al.* examined the effects of parallel prototyping on design [9]. Similar techniques could be applied in Nanocrafter. Tools such as those developed for game design by Smith *et al.* [21] and Yannakakis *et al.* [25] could potentially support mixed-initiative co-creativity for players faced with open-ended real-world challenges by making suggestions of variations or improvements. We are also interested in helping players recognize and rate the most creative inventions created by other players, by adding more focused rating categories and automated tools for comparing solutions.

7. ACKNOWLEDGMENTS

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