

Introduction to the EteRNA Project

The EteRNA project (<http://eterna.cmu.edu/web/>) was created at Stanford University and Carnegie-Mellon for the development of useful synthetic RNAs. EteRNA is a combination of a puzzle game and a lab experiment. We know the canonical base pairing rules for RNA: A = U and C = G. However, what we don't know are the principles that would allow us to predict how a particular RNA sequence might fold in nature. Discovering these principles and putting them to use is the goal of the EteRNA project. The project includes some basic RNA tutorials, some training puzzles, and the EteRNA lab, in which you can propose an RNA sequence that folds into some specific shape. All players participating in the lab create their own sequences and then examine those proposed by others. A selection of the player produced sequences is then real-world synthesized and tested to see if it actually assumes the target shape.

Your ultimate task would be to create your own puzzle. However, in order to qualify for puzzle design, you must demonstrate some skill in folding RNA. Before beginning, create your own account at EteRNA so that any points you earn will be associated with your account. Your first task will be to complete a short series of tutorial puzzles: <http://eterna.cmu.edu/web/tutorials/>. Just completing the tutorials gives you nearly 2000 points in the game. However, you need 20,000 points to qualify for puzzle design, so you should then complete enough challenge puzzles to earn the necessary points. <http://eterna.cmu.edu/web/challenges/>

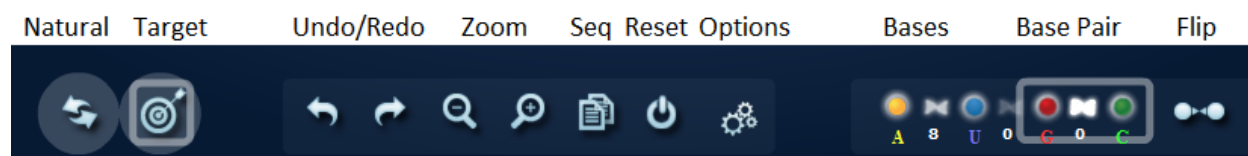
There are more than 500 challenge puzzles. Most challenge puzzles are based on real-world RNAs – tRNAs, riboswitches, microRNAs, ribozymes and others – from specific organisms. They are organized



more or less in order of difficulty, and will award you between 25 and 1000 points, depending on the difficulty of the puzzle. The link to each puzzle includes two numbers: the number on the left indicates the number of players who have completed the puzzle, and the number on the right indicates the points awarded for completing it.

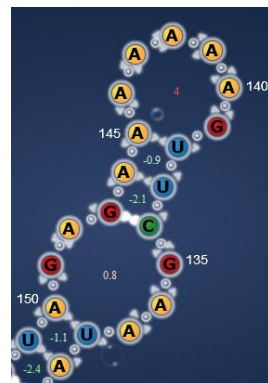
Most challenge puzzles will tell you a little about the molecule you are trying to duplicate, and some will include minimum or maximum limits on the number of specific base pairs to be used in solving the puzzle. RNAs can have unusual bases and some unusual base pairs, like the UG pair.

Each challenge puzzle begins with a “blank” shape, in which all of the bases are adenine. You can modify the blank shape using the puzzle control panel shown below. The Natural/Target buttons toggle



between the target shape and a prediction of how your sequence might fold naturally. You can use the Natural view to spot unstable base pairings in your design. The Bases buttons allow you either to add individual bases to your design or to add them in pairs by clicking on the white bonding symbol between two adjacent bases. The Flip button lets you reverse the order of paired bases, e.g. CG to GC. If you


mouse over this region, you will also see keyboard letters or numbers that will select each base or base combination. Use Undo/Redo controls to return to a previous sequence if you suddenly make a change that has disastrous consequences. The Zoom controls enlarge or reduce the field of view. The Sequence button puts the current sequence for your design to your computer's clipboard. The Reset button returns the puzzle to its all-A form AND erases your previous moves from memory. The Options button opens a menu that lets you customize your display. It is useful to display the base letters, base numbers and energy levels for specific regions of your puzzle. See the example on the right.



As you work on a puzzle, your progress is recorded at the upper left of your screen, which shows which parts of the puzzle are stable (white), which parts are still unstabilized (red) and how many base pairs you have used to

meet the required puzzle limits. When you have successfully completed a puzzle, all of the boxes will be highlighted and you will get the EteRNA equivalent of bells and whistles!

When you have completed enough challenge puzzles to earn 20,000 points, you will be allowed to submit your own design problem. <http://www.eternagame.org/web/playerpuzzles/>. Your instructor will explain the tRNA challenge to you.

The EteRNA Project is now in its seventh year, and has about 20000 active players (players who have at least 3000 points), including over 8000 players who have qualified for designing RNAs that are actually synthesized. The lab challenge changes from time to time and we will see what the current lab problems are. Qualifying for the lab now requires completion of a fairly rigorous set of training puzzles, and we probably won't have time for that in the space of just a few weeks. 

However, I would encourage you to continue to play on your own. In recent years several players have accumulated over 1 million points for puzzle solving and lab participation. About 50 players are on line at any one time. Players include professional scientists, science students, and people of all ages who just like science games. Several experienced players have written tutorials for solving challenge puzzles or for designing specific kinds of lab puzzles. Links to these tutorials have been posted on Blackboard, and you will find them very helpful.

Project Schedule:

Week 1: Introduction to EteRNA. Complete tutorials and begin challenge puzzles.

Week 2: Complete challenge puzzles to qualify for puzzle design. Group tRNA project.

Note: Most students find it necessary to spend some outside of the lab period to collect enough points to qualify for puzzle design.

Project Wiki:

As you proceed through the puzzles and your tRNA design, reflect on what you are learning and post your observations and insights each week to the lab wiki on Blackboard.

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