

# **Biomolecule Design Rules from an Internet-scale Videogame with Experiments**

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## **Abstract**

This talk will present an unconventional approach to empirical scientific problems. Self-assembling RNA molecules present compelling substrates for the rational interrogation and control of living systems, but imperfect computational models hinder the design of new RNAs that function properly when synthesized. The Eterna project seeks to engage an internet-scale community to solve currently intractable RNA design problems. Uniquely, Eterna participants not only manipulate simulated molecules but also control remote experimental pipelines for high-throughput RNA synthesis, structure mapping, and functional characterization. In its initial phase, the Eterna community leveraged dozens of cycles of continuous wet laboratory feedback to learn strategies for solving in vitro RNA secondary structure design problems on which automated methods fail. The top strategies, including several previously unrecognized negative design rules, were distilled by machine learning into an algorithm, EteRNABot. More recently, Eterna participants have discovered principles enabling improved design of functional RNA molecules, making use of array-based library syntheses and repurposed Illumina sequencers for in vitro tests. Recent achievements include the design of ligand-sensing riboswitches that operate at their thermodynamic limit, instantiation of all binary logic gates responding to oligonucleotide inputs, and calculators of analog arithmetic expressions involving input molecule concentrations.

## **About Dr. Das**

Dr. Das strives to make the computer modeling of life as agile and engaging as the design of software. His lab at Stanford focuses on medically relevant RNA molecules, developing computational and high-throughput chemical tools for the rapid modeling and design of these molecules. Dr. Das trained in particle physics and cosmology at Harvard and Cambridge before switching to molecular biophysics during his Ph.D. at Stanford and postdoctoral work at the University of Washington. He is currently an associate professor in the departments of biochemistry and physics at Stanford.