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Designing Molecular RNA Switches with Restricted Boltzmann Machines

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Riboswitches are structured allosteric RNA molecules that change conformation in response to a metabolite binding event, eventually triggering a regulatory response. Computational modelling of the structure of these molecules is complicated by a complex network of tertiary contacts, stabilized by the presence of their cognate metabolite. In this work, we focus on the aptamer domain of SAM-I riboswitches and show that Restricted Boltzmann machines (RBM), an unsupervised machine learning architecture, can capture intricate sequence dependencies induced by secondary and tertiary structure, as well as a switching mechanism between open and closed conformations. The RBM model is then used for the design of artificial allosteric SAM-I aptamers. To experimentally validate the functionality of the designed sequences, we resort to chemical probing (SHAPE-MaP), and develop a tailored analysis pipeline adequate for high-throughput tests of diverse homologous sequences. We probed a total of 476 RBM designed sequences in two experiments, showing between 20% and 40% divergence from any natural sequence, obtaining ≈ 30% success rate of correctly structured aptamers that undergo a structural switch in response to SAM.

Auteur principal: FERNANDEZ-DE-COSSIO-DIAZ, Jorge (ENS Paris)

Orateur: FERNANDEZ-DE-COSSIO-DIAZ, Jorge (ENS Paris)

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