Extrapolative benchmarking of model-based discrete sampling methods for RNA design

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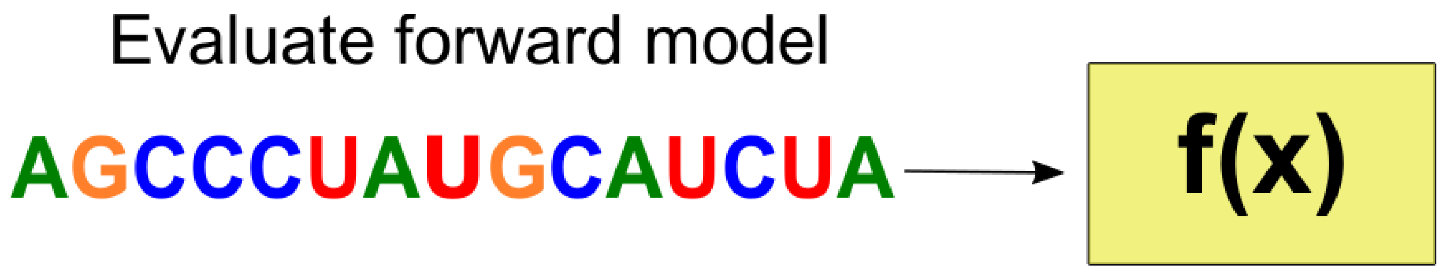
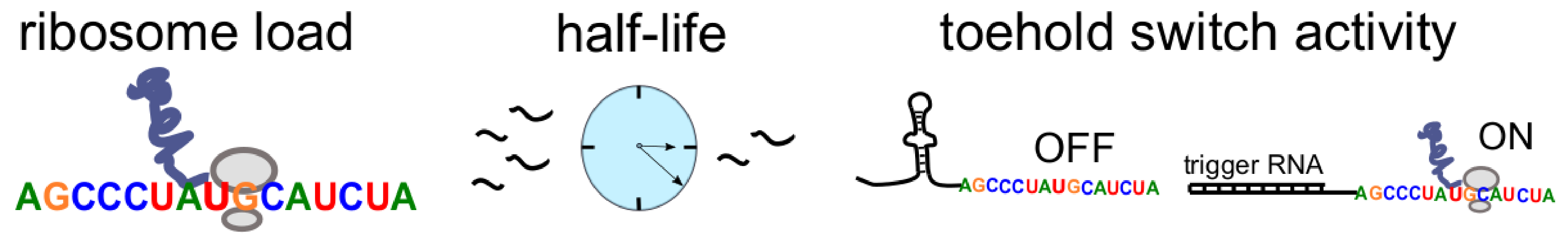
Code + References

Objectives

- Survey recent approaches to model-based optimization and sampling on discrete data
- Apply sampling algorithms to RNA design
- Evaluate best practices for generalization and extrapolation of designed sequences

Background





(Sample et. al 2019) (Agarwal and Kelley 2022) (Valeri et. al 2020)

A motivating use case -- mRNA vaccines

Require high/controllable protein expression, long half-life

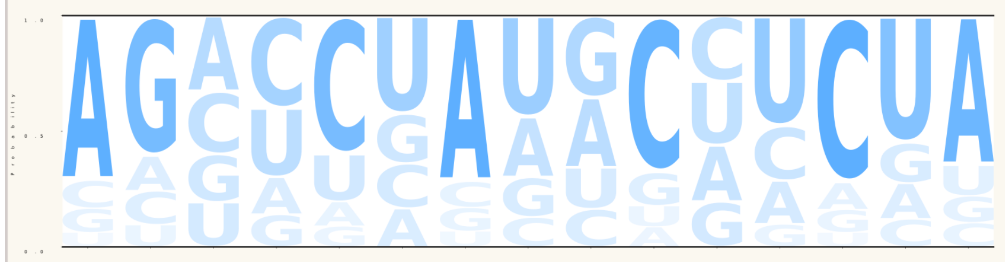
Given sequence → property models, how to efficiently explore a combinatorial space?

Possible guiding principle – incorporate gradients of discrete samples

Methods

(Bogard et al 2019, Linder and Seelig 2021)

Probabilistic Reparameterization



$$x \sim p(x|\theta) = \text{Categorical}(\text{Softmax}(\theta))$$

How to update the parameters?

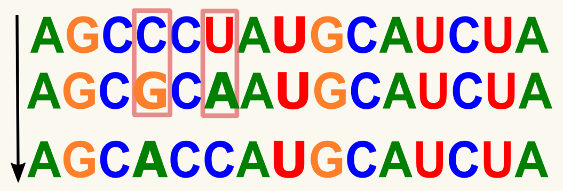
(REINFORCE estimator)

$$\nabla_\theta \mathbb{E}_{x\sim p(x|\theta)}[f(x)] = \mathbb{E}_{x\sim p(x|\theta)}[f(x)\nabla_\theta \log p(x|\theta)]$$

(Straight-through estimator)

$$\nabla_\theta f(x) \approx \nabla_x f(x)$$

Markov Chain Monte Carlo



Discrete Langevin Proposal (Zhang et. al 2022)

$$x \sim \text{Categorical}(\text{Softmax}(\frac{1}{2}D(x,x') - \frac{\|x_i' - x_i\|_2^2}{2\alpha}))$$

Taylor approx. likelihood ratio

$$f(x') - f(x) \approx \nabla_x f(x)^\intercal (x_i' - x_i) = D(x,x')$$

Gibbs-with-Gradients (Grathwohl et. al 2021)

$$x' - x \sim \text{Categorical}(\text{Softmax}(vec(D(x,x'))))$$

```
Algorithm 1 Extrapolative Benchmark
Require: $Z = \{(x_1,y_1),(x_2,y_x))\dots(x_n,y_n)\}$        ▷ Training data $(seq, property)$
Require: $q$                                                   ▷ Exclusion quantile
Require: $S$                                                   ▷ Seed sequences to redesign
  $Z^- = Z \setminus \{(x,y) \in Z | Q(y) > q\}$              ▷ Excludes highest quantile by property
  $f_O \leftarrow max_\theta f_\theta(y|x), \quad (x,y) \in Z$          ▷ Train oracle model on the full train set
  $f_D \leftarrow max_\theta f_\theta(y|x), \quad (x,y) \in Z^-$        ▷ Train designer model on the reduced train set
  $D \leftarrow \{\}$
  for $s \in S$ do
      $s' \leftarrow \text{DiscreteDesign}(f_D, s)$               ▷ MCMC or PR seeded by $s$
      $y' \leftarrow f_O(s')$                                    ▷ Impute property with oracle
      $D.add((s',y'))$
  end for
  $summary \leftarrow |\{(x,y) \in D | Q(y) > q\}|$           ▷ # designs exceeding train set maximum
```

Future Directions

- Hybrid straight-through/REINFORCE estimators
- Evaluate sample diversity
- Adaptive preconditioning for MCMC
- Gradient smoothness regularization (Miyato 2016)

Conditional sampling *Property model* ***Sequence Prior***

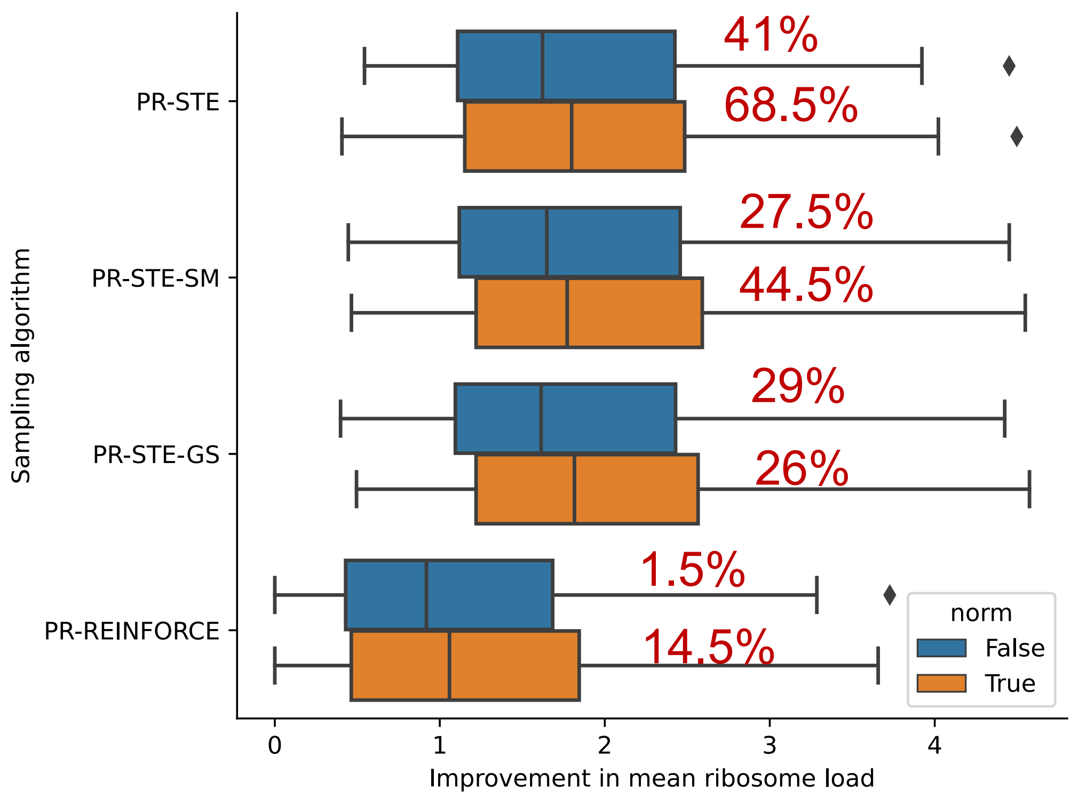
$$\nabla_x \log P(x \mid y) = \nabla_x \log P(y \mid x) + \nabla_x \log P(x)$$

As generative models of RNA become more available, incorporate a prior to mitigate pathological sampling

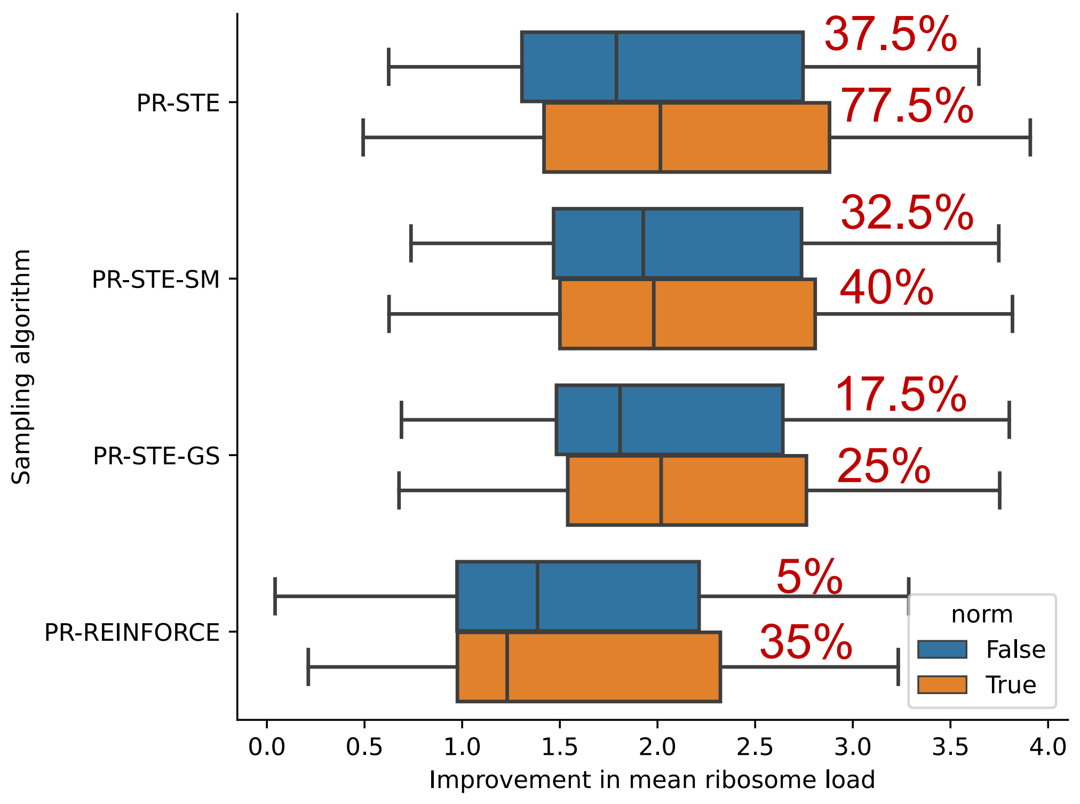
Preliminary Results

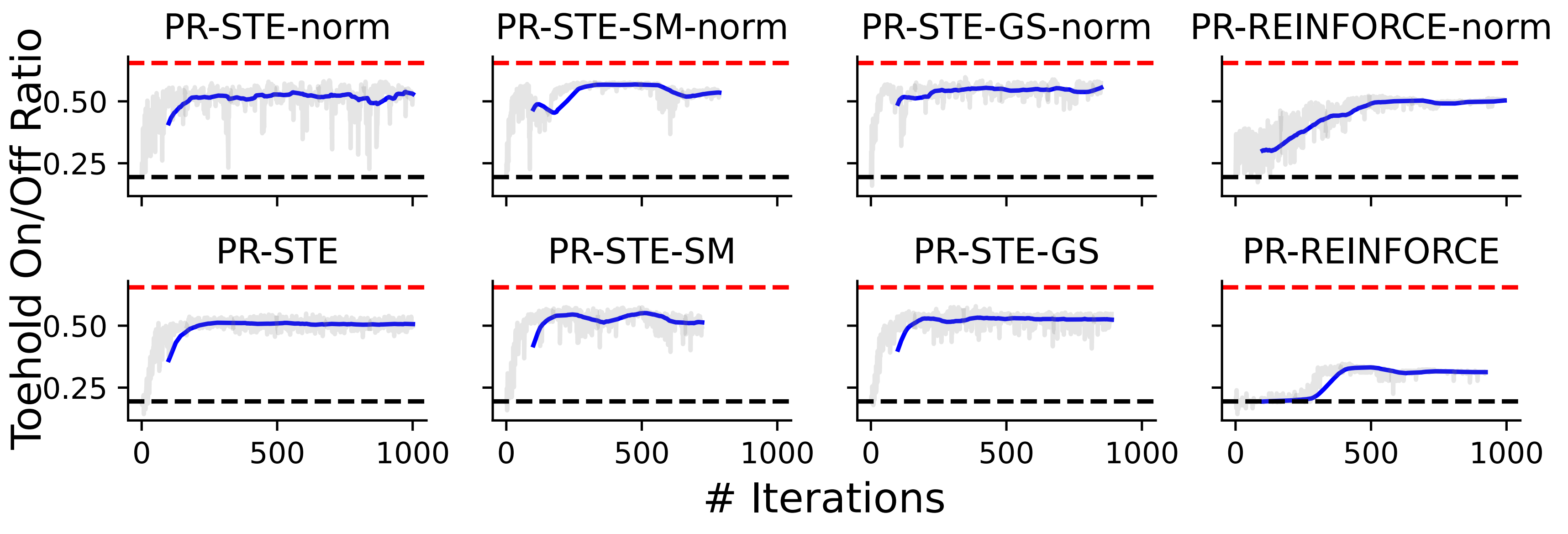
% = percentage exceeding train set max property value according to oracle

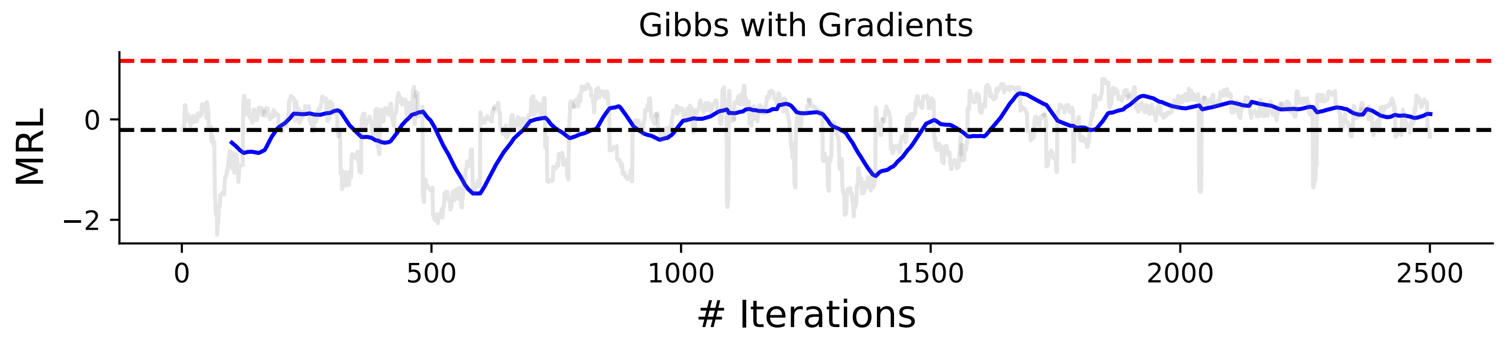
Iterations=10^3, samples/step = 32, trials=200



Iterations=10^4, samples/step = 4, trials=40


Sampling algorithm
PR-STE
PR-STE-SM
PR-STE-GS
PR-REINFORCE
norm
False
True
Improvement in mean ribosome load


PR-STE-norm
PR-STE-SM-norm
PR-STE-GS-norm
PR-REINFORCE-norm
PR-STE
PR-STE-SM
PR-STE-GS
PR-REINFORCE
Toehold On/Off Ratio
# Iterations


Gibbs with Gradients
MRL
# Iterations