Applying NLP to Nature's Language (DNA!)

An examination of perplexity in the genetic grammar of microorganisms

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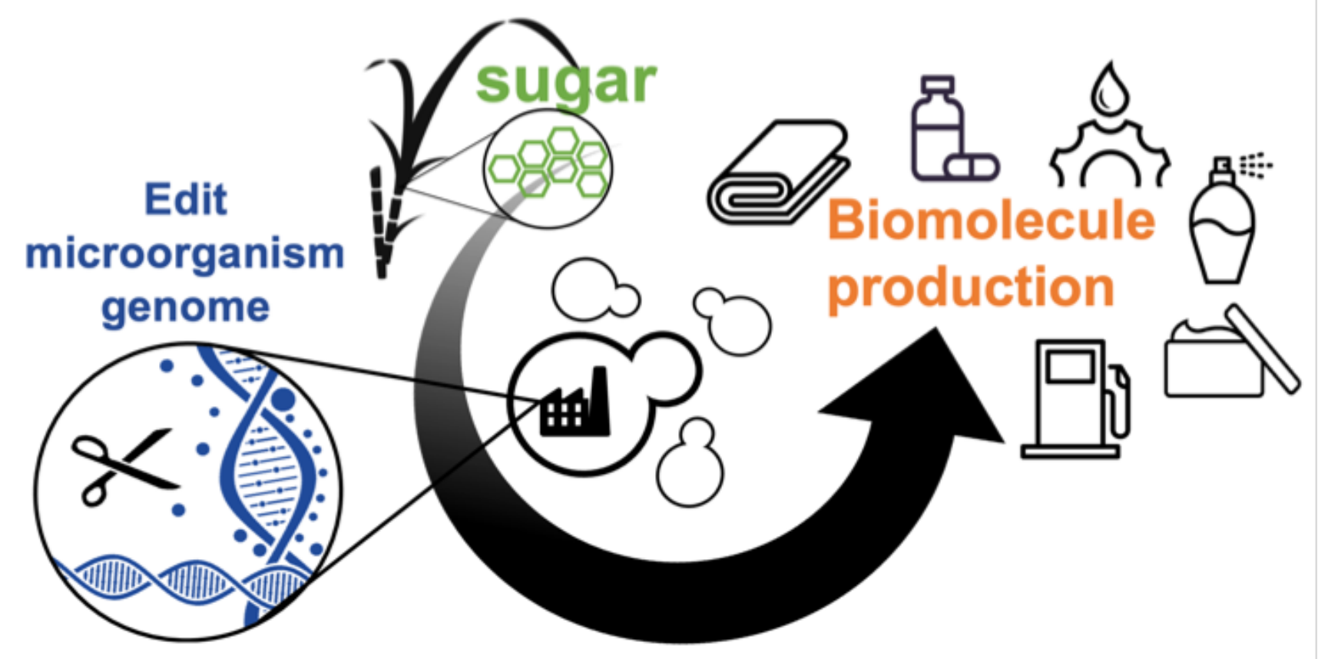
Motivation: sustainable molecule production



Globally, human societies are consuming finite resources at unsustainable rates. Transitioning away from our dependencies on non-renewable resources and towards a cyclical, sustainable use of natural products is critical for preserving Earth's most threatened ecosystems. An alternative way to source many natural products is to engineer microorganisms into **biological molecule factories**[1].

How?

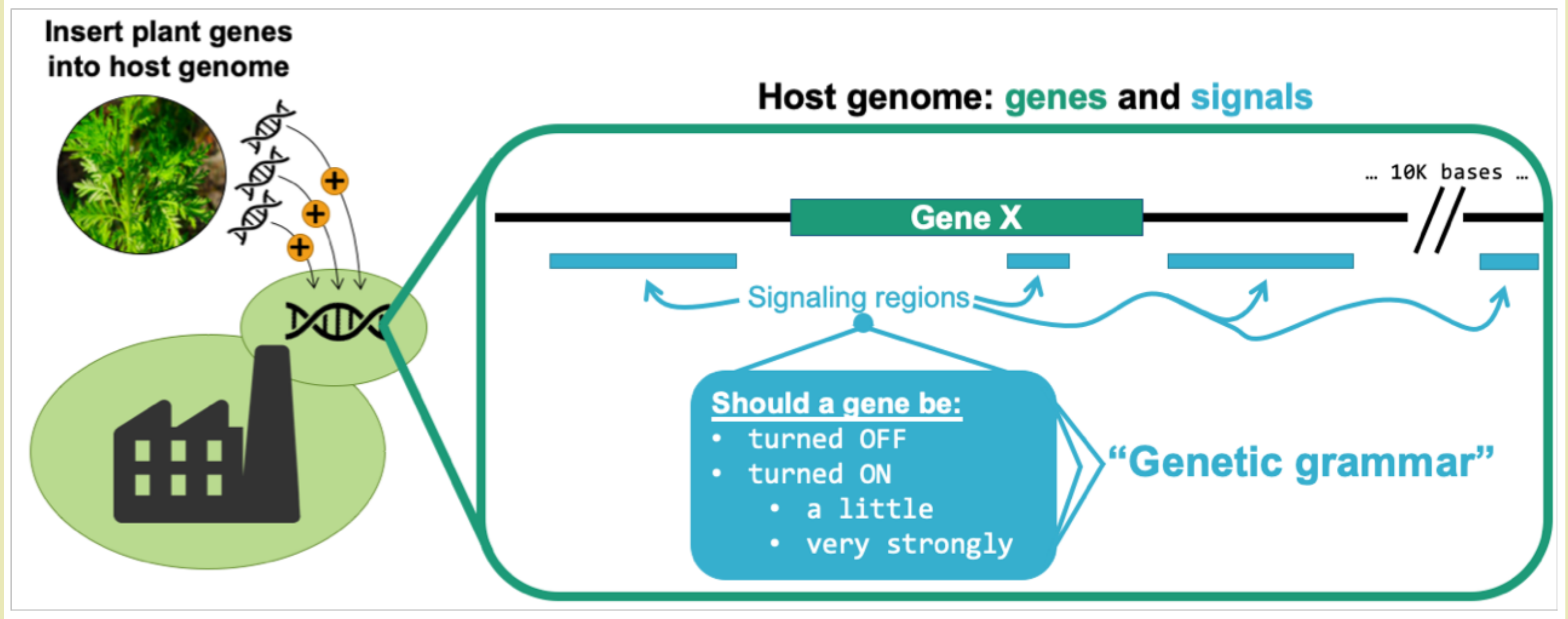
- Introduce foreign plant genes into microorganism
- Organism consumes renewable sugarcane
- Reroute carbon to new target molecule (naturally produced in plant)

The Challenge

- Every organism has a distinct "genetic grammar"
- It is difficult to express foreign genes with host microorganism's grammar
- Low gene expression leads to inefficient molecule production

Gene regulation: a cell's genetic grammar

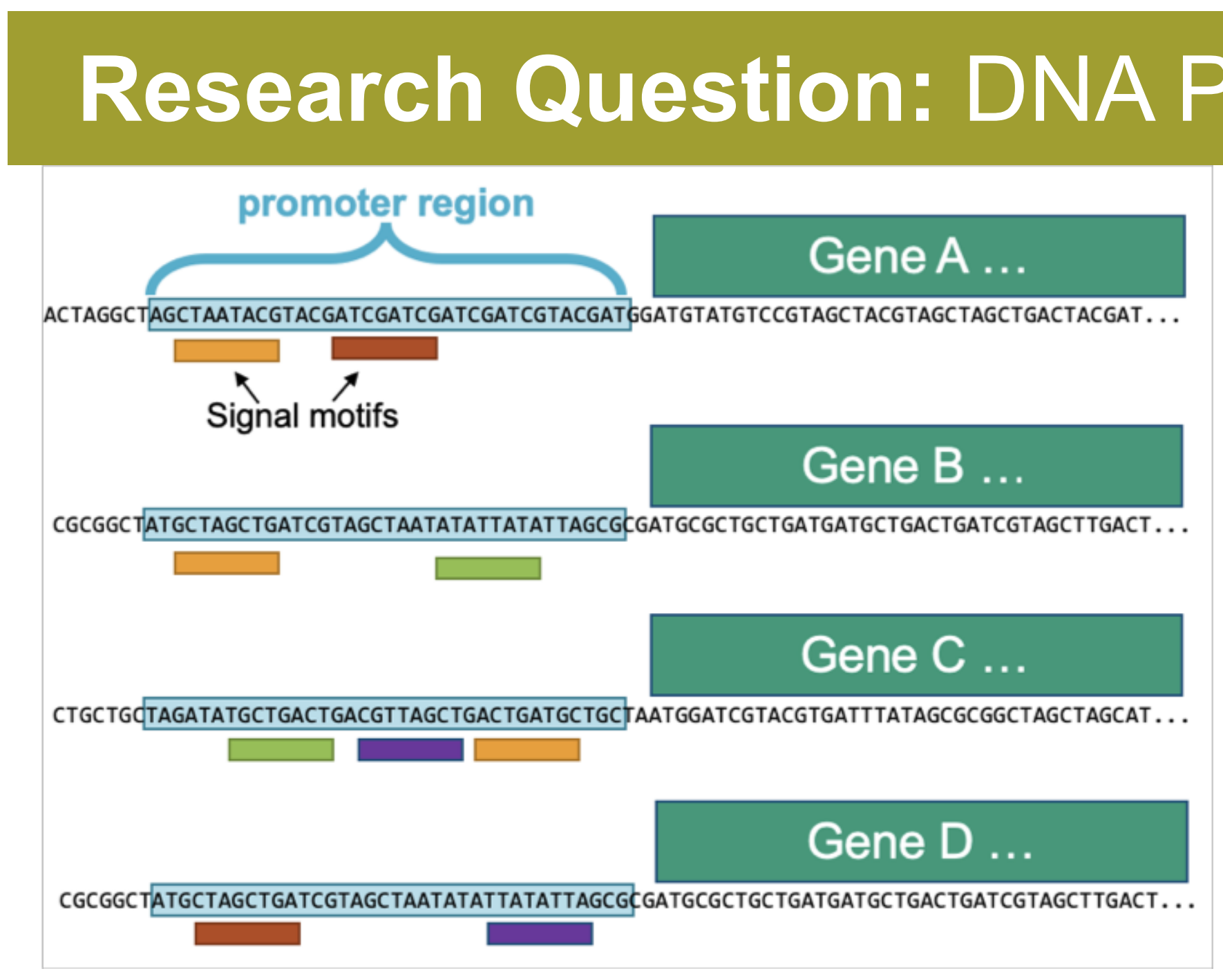
- In addition to genes that code for proteins, genomes contain **signaling regions**
- Signaling regions help **control** which genes are turned ON or OFF ("expressed")
- These regions contain a sort of "grammar": patterns in the DNA sequence that guide a cell to turn specific genes on in specific situations ("gene regulation")


Insert plant genes into host genome
Host genome: genes and signals
… 10K bases …
Gene X
Signaling regions
"Genetic grammar"

Should a gene be:

- turned OFF
- turned ON
  - a little
  - very strongly

Research Question: DNA Perplexity?



```
ACTAGGCTAGCTAATACGTACGATCGATCGATCGATCGTACGATGGATGTATGTCCGTAGCTACGTAGCTAGCTGACTACGAT...
CGCGGCTATGCTAGCTGATCGTAGCTAATATATTATATTAGCGCGATGCGCTGCTGATGATGCTGACTGATCGTAGCTTGACT...
CTGCTGCTAGATATGCTGACTGACGTTAGCTGACTGATGCTGCTAATGGATCGTACGTGATTTATAGCGCGGCTAGCTAGCAT...
CGCGGCTATGCTAGCTGATCGTAGCTAATATATTATATTAGCGCGATGCGCTGCTGATGATGCTGACTGATCGTAGCTTGACT...
```

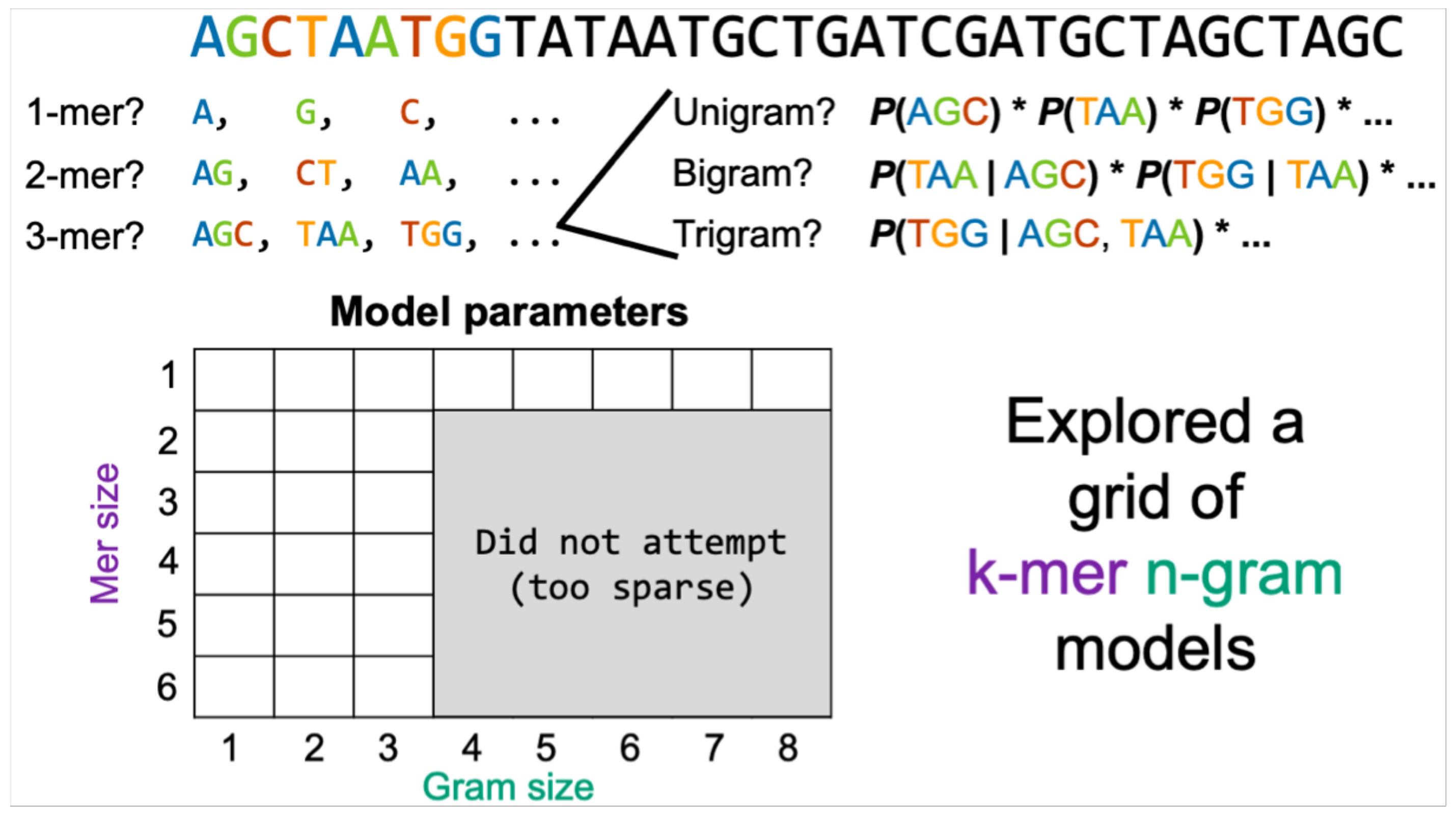
- We know generally where signaling regions are, but the exact signals and what they mean are still not well understood
- The promoter region (the area right before a gene starts) contains shorter **signal motifs**
- Motifs can be combined and rearranged in many configurations
- Modeling the **regulatory grammar** is very complex

Can **NLP language modeling** capture regulatory patterns in DNA sequences?

Do we observe **lower perplexity** in signaling regions?

Convert DNA into "words"

- Regulatory DNA sequences don't have a natural word boundary
- Test various model parameters for how to break a DNA sequence into words



AGCTAATGGTATAATGCTGATCGATGCTAGCTAGC

1-mer? A, G, C, ...
2-mer? AG, CT, AA, ...
3-mer? AGC, TAA, TGG, ...

Unigram? $P(AGC) * P(TAA) * P(TGG) * ...$
Bigram? $P(TAA \mid AGC) * P(TGG \mid TAA) * ...$
Trigram? $P(TGG \mid AGC, TAA) * ...$

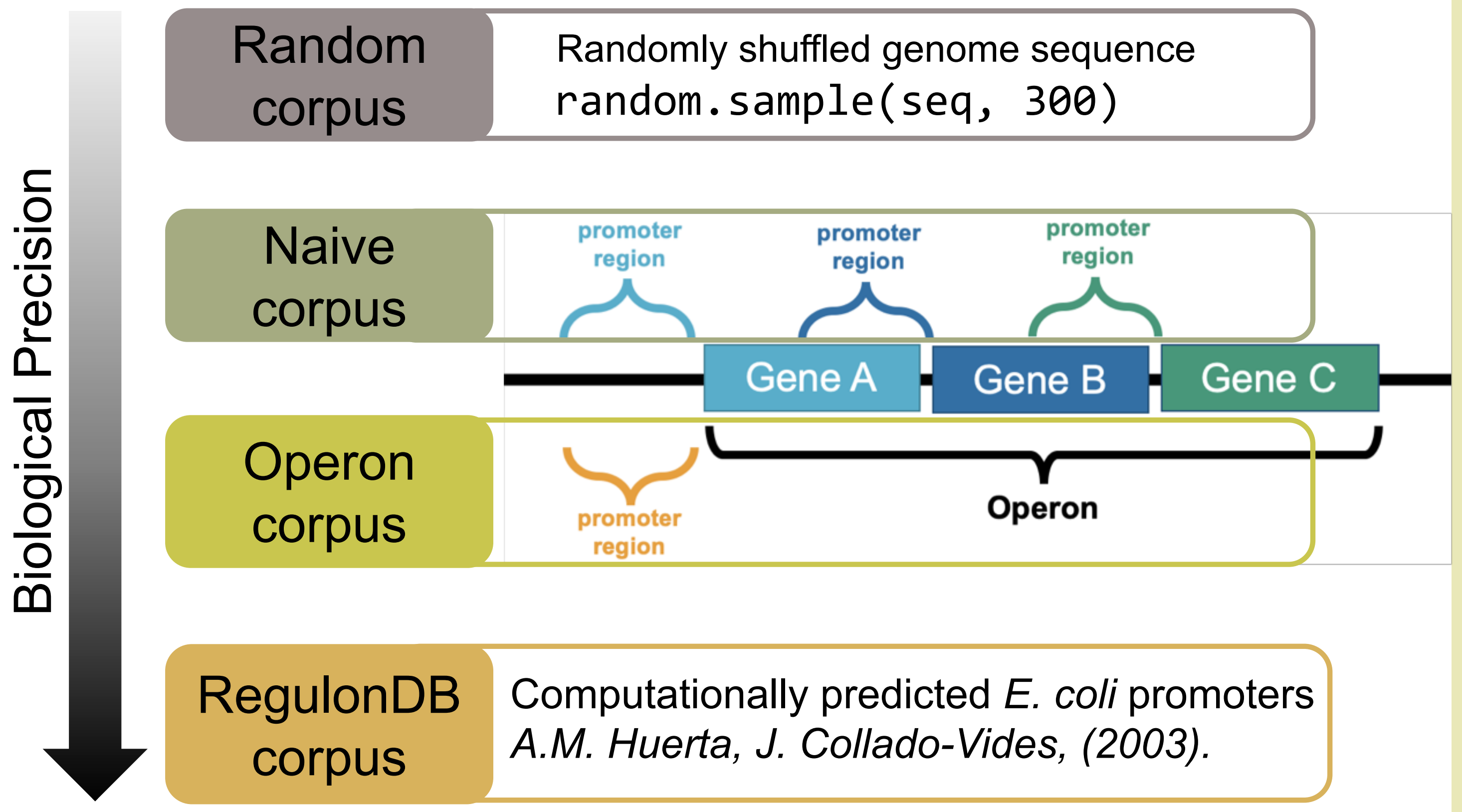
Model parameters

Mer size: 1, 2, 3, 4, 5, 6
Gram size: 1, 2, 3, 4, 5, 6, 7, 8

Did not attempt (too sparse)

Explored a grid of k-mer n-gram models

Generate a "corpus" of promoters



Random corpus: Randomly shuffled genome sequence `random.sample(seq, 300)`

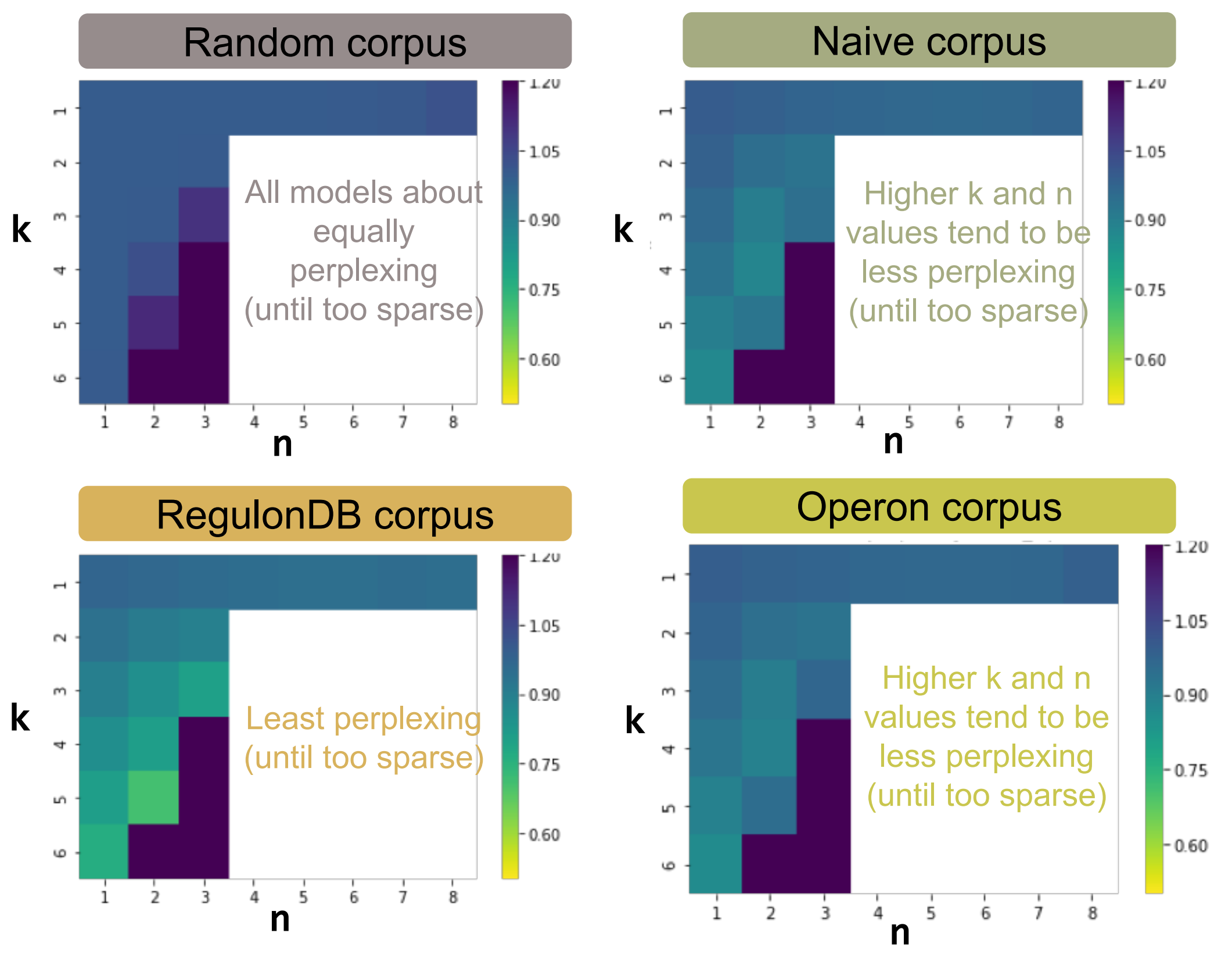
Naive corpus

Operon corpus

RegulonDB corpus: Computationally predicted *E. coli* promoters *A.M. Huerta, J. Collado-Vides, (2003).*

Results: Perplexity decreases with sequence prior context and biological precision

Normalized Perplexity across k-mer n-gram grid



Random corpus: All models about equally perplexing (until too sparse)

Naive corpus: Higher k and n values tend to be less perplexing (until too sparse)

RegulonDB corpus: Least perplexing (until too sparse)

Operon corpus: Higher k and n values tend to be less perplexing (until too sparse)

Perplexity:

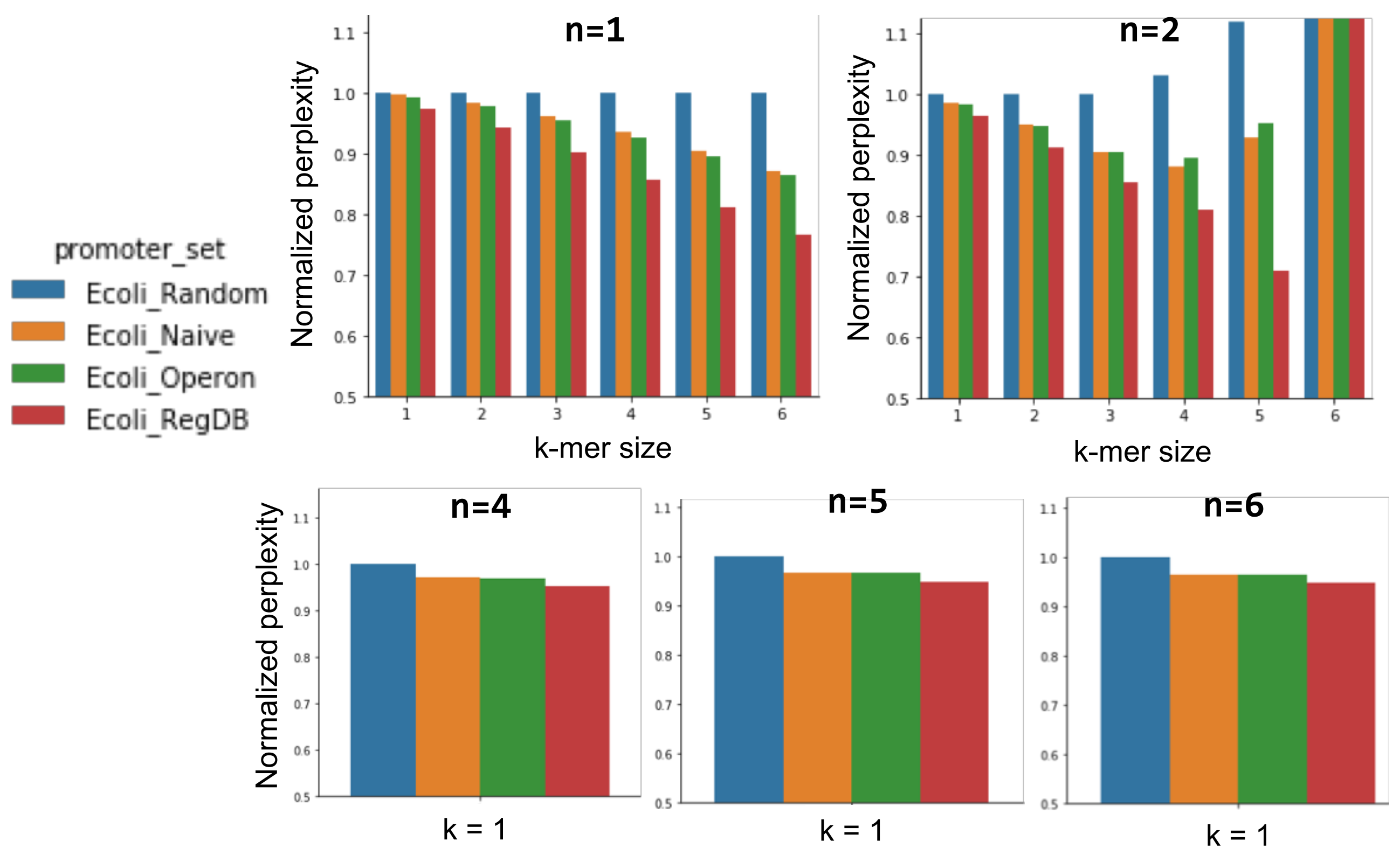
$$2^{-l} \text{ where } l = \frac{1}{M}\sum_{i=1}^{m}\log p(s_i)$$

Normalized Perplexity:

$$\frac{\texttt{test\_pplex}}{\texttt{worst\_possible\_pplex}}$$

- close to 1: as perplexed as can be
- 1.2: infinite perplexity

Normalized Perplexity between corpora

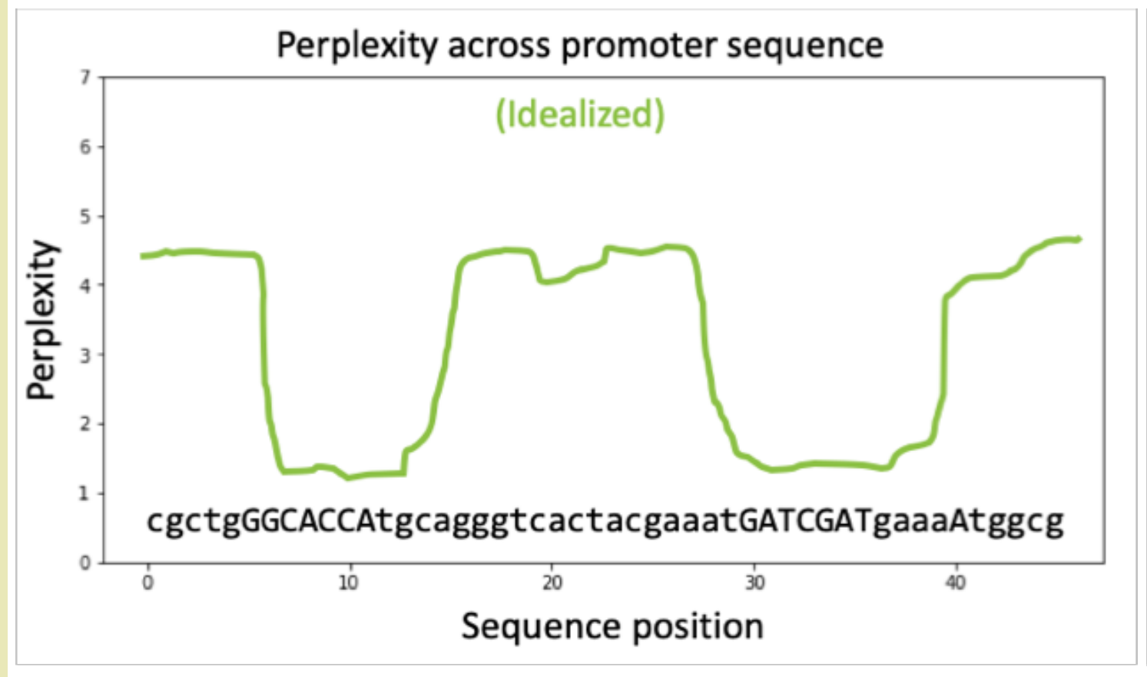


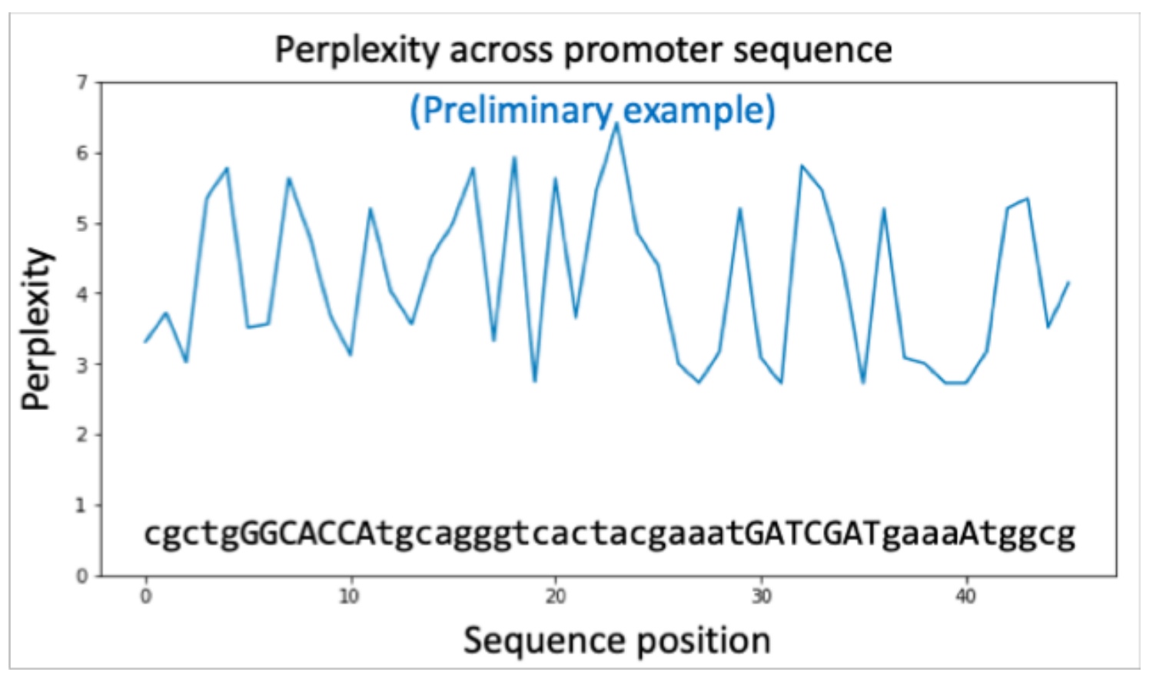
Discussion: promoters are less perplexing

- The data show that **random** sequences are all about **equally perplexing**, regardless of the choice of k-mer or n-grams.
- Corpora of actual promoter sequences show **lower perplexity than random** and that models which use **more biological context** (higher values of k and n) decrease perplexity until the counts become too sparse
- Corpora of actual promoter sequences generally show that **perplexity decreases with increased biological precision** of the promoter set
- This all suggests that language modeling can indeed **capture some underlying pattern** in promoter regions!
- However, the discrepancy between model performance on the operon corpus and the RegulonDB corpus suggests that this approach **needs more refinement** before applying to other microorganisms without a "ground truth database" available.

Future work: perplexity across a sequence

- If the language model has captured the grammar well, there hypothetically should be low perplexity regions in the sequence which represent the "true promoter signal"
- Can we **map low perplexity regions** to important regulatory signals?





References

- [1] A. Meadows et al. (2016) "Rewriting yeast central carbon metabolism for industrial isoprenoid production." *Nature*.
- [2] A.M. Huerta, J. Collado-Vides. (2003) "Computational Prediction of Promoters in the Escherichia coli genome." *J Mol Biol.*
- [3] J. T. Cuperus et al. (2017) "Deep learning of the regulatory grammar of yeast 5′ untranslated regions from 500,000 random sequences." *Genome Research.*

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