

The human genome's vocabulary as proposed by the DNA language model GROVER

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Abstract

Large Language Models (LLMs) on natural language have achieved a level of performance that allows the generation of coherent and syntactically correct text. DNA sequence of genomes follows rules similar to natural language, but a distinguishing factor is the absence of a concept analogous to words. We established byte-pair tokenization on the human genome and trained a foundation language model called GROVER ("Genome Rules Obtained Via Extracted Representations") to select the optimal vocabulary with a custom fine-tuning task of next-k-mer prediction. We thus defined a dictionary of words/tokens in the human genome that best carries the information content for DNA language models. Analyzing GROVER's learned representations, we observed that token embeddings primarily encode information related to their frequency, sequence content, and length. Some tokens are almost exclusively localized in repeats, while the vast majority widely distributes over the genome. The model also learns context and lexical ambiguity. Average embeddings of genomic regions relate to functional genomics annotation and thus indicate that GROVER has learned these structures purely from the contextual relationships of tokens. That we can extract functional annotations from the genome, purely based on sequence representation to the trained model, highlights the extent of information content encoded by the sequence. This is supported by fine-tuning tasks on genome biology with questions of promoter identity and protein-DNA binding. GROVER learns sequence context, a sense for grammatical structures and language rules in the genome. This knowledge can be extracted and used to compose a grammar book for the code of life.

Introduction

Genomes carry the instruction manuals for whole organisms. The first draft of the human genome has been available for >20 years ¹, and genome sequences of multiple species have become available since. We know the letters and the text, but we still understand very little about the "genetic code". DNA triplets encode for amino acids ² in 1-2% of the genome ¹, but there are additional layers to the "code of life". There is encryption on how those genes are regulated, how transcripts and RNAs are structured, how they function and keep stable, how, where, and when the genome replicates, and also how all this is achieved with keeping the genome stable and functional. Extracting comprehensively these different layers of code requires complex algorithms that only recently became available through progress in natural language processing (NLP). Natural language can be studied with large language models (LLMs) that are based on transformer architectures ³ and very suitable for tasks involving text data due to their unprecedented performance and transparency. Pretrained LLMs like GPT-3 ⁴ and successors can also function as foundation models that can be fine-tuned with different classification, regression, or generative tasks. These models have changed how we can view language and they can be very useful for a variety of purposes. For example, they can make up very believable text, when given a generative task.

Vocabulary Review The Human Genome

Harry Harris



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