MethanoGram and alignment-free phylogeny

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Outline

MethanoGram is able to relate frequency of n-grams derived from molecular markers to culture conditions.

n-gram frequency is reflecting phylogenetic relationships between bacterial strains which are direcly associated with culture conditions.

Alignment-free, n-gram based methods for sequence comparison:

- are usually faster,
- do not require scoring schemes,
- **do not require gene selection**.

More than just a gut feeling: constraint-based genome-scale metabolic models for predicting functions of human intestinal microbes, Willem M de Vos Laboratory, Microbiome 2017
Input: Genome-scale metabolic models (GEMs).
Results:

- the prediction of minimal, synthetic, or defined media;
- the prediction of possible functions and phenotypes;
- the prediction of interspecies interactions.

Aim

Replace GEMs with improved n-gram analysis.
Challanges:

- more diverse species;
- lower quality of data;
- longer branches.

Outline

Although alignment-free methods can be used to recover topology of a phylogeny, they cannot represent lengths of the branches, which require number of substititutions per site. Despite that, some n-gram based methods can also calculate branch lenghts (Yi & Jin, 2013).

First usage of n-gram analysis: differences of overlapping and countinous 2- or 3-grams between sets of sequences (Blaisdell, 1986).

We consider only two sequences, Q and S, that contain only symbols from the alphabet u.

$$d_{ngram}(Q,S) = \sum_{i=1}^{u^n} (q_i - s_i)^2 \tag{1}$$

- d_{ngram}: n-grams distance between sequences;
- q_i: frequency of the i-th of u^n possible substrings of length n in Q;
- s_i: frequency of the i-th of u^n possible substrings of length n in S;

The simple n-gram distance is not powerful when applied to very similar sequences (Höhl & Ragan, 2007).

The frequency of words varies between sequences independently of their relationships.
Practical corrections to remove random background:

- zero-order Markov method substracts background (Pride, Meinersmann, Wassenaar, & Blaser, 2003);
- composition vector method (Qi, Wang, & Hao, 2004);
- feature frequency profile (Sims & Kim, 2011).

The composition vector method substracts random background by normalizing counts of the n-grams (Qi et al., 2004).

$$d_{cv}(Q,S) = \frac{1 - C(Q,S)}{2} \tag{2}$$

$$C(Q,S) = \frac{\sum q_{ni} s_{ni}}{\sqrt{\sum q_{ni}^2 \sum s_{ni}^2}} \tag{3}$$

- d_{cv}: composition vector distance;
- q_i: normalized frequency of the i-th of u^n possible substrings of length n in Q;
- s_i: normalized frequency of the i-th of u^n possible substrings of length n in S.

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Closely related sequences contain more exact matches than divergent sequences (Kurtz et al., 2004).
Differences between semi-grammar methods and n-gram methods:

- no longer requires specifying n;
- preserves sequence of the substrings;
- potentially much longer computation time.

Suffix tree allows quicker deconstruction of the sequence.
See:

$$S = \mathrm{TCCT\$}$$

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A grammar is a set of rules for decomposing a string into its elements.

$$\mathrm{TCCT} \rightarrow \mathrm{T_1C_2T_1}$$

Differences between semi-grammar methods and grammar methods:

- even slower than grammar methods;
- calculates mutation distances.

Common methods of compression: Lempel-Ziv factorization, average common substring.

Grammar methods are the msot powerful aligment-free methods (Otu & Sayood, 2003), but are **more sensitive** to imperfections in data.

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