HyPaLib: a database of RNAs and RNA structural
elements defined by hybrid patterns

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ABSTRACT

The database, called HyPaLib (for Hybrid Pattern Library), contains annotated structural elements characteristic for certain classes of structural and/or functional RNAs. These elements are described in a language specifically designed for this purpose. The language allows convenient specification of hybrid patterns, i.e. motifs consisting of sequence features and structural elements together with sequence similarity and thermodynamic constraints. We are currently developing software tools that allow a user to search sequence databases for any pattern in HyPaLib, thus providing functionality which is similar to PROSITE, but dedicated to the more complex patterns in RNA sequences. HyPaLib is available at http://bibiserv.techfak.uni-bielefeld.de/HyPa/.

INTRODUCTION

Determining or finding a protein gene in genomes of eubacteria or archaea is thought to be easy; due to the presence of introns and other complexities it is more difficult to do so in eukaryotes. On the contrary, finding an RNA gene (not a mRNA gene) in genomic DNA is a challenging and difficult task in most cases. To support this task, it would be very helpful to have a general tool that allows the user to define his/her own RNA-related patterns or to use an existing library of RNA-related patterns and to search for such patterns in biological sequences. In this paper, we describe our ‘Hybrid Pattern Library’ (HyPaLib, for short), which contains annotated structural elements characteristic for certain classes of structural and/or functional RNAs. These elements are described in a language HyPaL (for Hybrid Pattern Language) specifically designed for this purpose. The language allows convenient specification of hybrid patterns, i.e. motifs consisting of sequence features and structural elements together with sequence similarity and thermodynamic constraints. We are currently developing software tools that allow a user to search sequence databases for any hybrid pattern in HyPaLib, thus providing functionality which is similar to PROSITE (1), but dedicated to the more complex patterns in RNA sequences. HyPaLib is available at http://bibiserv.techfak.uni-bielefeld.de/HyPa/.

FEATURES OF THE LANGUAGE HyPaL

HyPaL is a declarative language; that is, the user specifies what to search without specifying how to search it. Essential properties of the language are:

- HyPaL is modular: patterns can be reused as part of descriptions of more complex patterns.
- HyPaL contains approximative elements: specification of a pattern with a (numerical) tolerance interval allows for searches of related (homologous, paralogous) sequences with insertions, deletions and mutations.
- HyPaL allows for: (i) user-defined scoring functions, and (ii) user-defined constraints (based on a set of standard functions).

For example, the free energy of a specified structure is an allowed search criterium (c.f. Fig. 1). The availability of such scoring functions and constraints is the major difference between HyPaL (and its associated search tool) and other languages/search tools known from the literature.

HyPaL provides many different linguistic elements. For a complete definition of the language, see http://bibiserv.techfak.uni-bielefeld.de/HyPa/. In the following, we list only the most important elements, and give corresponding examples.

- Simple sequences: e.g. a nucleic acid ATUGCYT or a protein sequence LWYMN.
- Wildcards: the symbol . matches any character.
- Character classes: the expression [ACG] matches one of the characters A, C or G.
- Concatenation: AC[GT]C.G AAGGT means that AC[GT]C.G is followed by AAGGT.
- Repetitive elements: p{3,5} matches p three to five times.
- Spacers: p1 <3,5> p2 specifies a gap of length 3–5 between p1 and p2.
- Spacers with overlaps: p1 <–3,14> p2 specifies that p1 and p2 may overlap up to three positions or there is a gap of length at most 14.
- Profiles or consensus matrices: [[10,5,4,3,6],[6,11,5,4,2]]>15 specifies scores for the characters A, [UT], G, C and gap, at the first and second position, and a total score of 15 to be exceeded. Thus this profile matches the sequences AA, AT, TT and –T.

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References to sequence parts by variables: @v:= (AT.....GC) binds the variable v to the sequence matching the pattern AT.....GC.

Reverse complement of sequences: @^(@v) matches the sequence that is the reverse complement of the sequence bound to the variable v.

Thermodynamic constraints depending on variables: @energy(@v) < –15 means that the thermodynamic free energy of the structure bound to the variable v has to be lower than –15 kJ/mol.

Logical operators may be used to combine constraints.

**FORMAT OF HyPaLib**

HyPaLib is available as a plain text file formatted according to the general rules of the EMBL and related databases. We also provide a version in HTML format with hyperlinks to sequence and citation databases. Each entry in HyPaLib describes an annotated RNA or DNA pattern (for an example see Fig. 1) on different lines called items. An item consists of two uppercase letters specifying the kind of item, followed by the information stored for that item (see Table 1 for a description of the items).

**CURRENT STATUS OF HyPaLib**

HyPaLib contains sequential and structural elements characteristic for different classes of RNA. In the following, we enumerate the classes and give a few examples of corresponding HyPaLib entries.

- Simple patterns of DNA or RNA sequences with specific biological function like Pribnow box, –35 region, promoter region or definition of codons and stop codons. Most examples are adopted from Mehldau et al. (2). Because of their
low specificity these patterns should mainly be used as building blocks for construction of more complex patterns [for reviews on further important components of the ‘kit’ of RNA structural elements see Batey et al. (3), Conn and Draper (4) and Moore (5)].

- Simple patterns of RNA secondary structure like hairpin, pseudoknot, clover leaf, attenuator, TMV 3’ end. Examples are taken from Searls et al. (6); these patterns are not very specific.
- Patterns for RNA protein binding motifs like the secondary structure of the four Rev-binding elements (RBE) (7) or the putative Tat-binding elements (TBEs) in viruses linked to human immunodeficiency infections (8). Patterns are taken from Bourdeau et al. (9).
- Patterns describing chemically and catalytically active motifs like hammerhead ribozyme, UV-sensitive loop E, leadzyme and DNAzyme. Patterns are adopted from Bourdeau et al. (9).
- Profiles of small nuclear RNAs like 5’ end of U2, 5’ end of U3 or the central part of 7S RNA. These patterns are derived from alignments and structures in the uRNA Database (10) and the Signal Recognition Particle Database (11), respectively. After inclusion of additional sequences and refinement using ClustalX (12) and ConStruct (13) these patterns give no false positive results with searches in the EMBL database except for non-annotated entries.
- Patterns describing motifs with thermodynamic constraints like hairpin C (14), a structural feature from mRNA of prion proteins, or the selenocysteine insertion sequence element (Fig. 1). Both patterns contain thermodynamic constraints to exclude a large number of false negative matches.

Specification of most patterns is a time consuming task, because consensus sequences or structures from text books and older references are unspecific in most cases due to the enormous growth of recent EMBL or GenBank releases. To cover a more complete set of relevant RNA patterns and to make the library more useful, we would like to encourage the reader to suggest other hybrid patterns (in any format). Please contact the corresponding author.

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