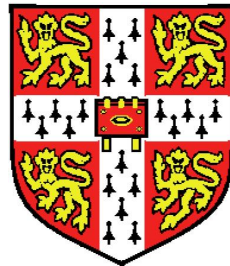


Motif based computational identification of protein subcellular localisation



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To my deeply missed father,
Sami Han Doḡruel.

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text.

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[Mutlu Doğruel](#), January 2008, Cambridge, UK.

Abstract

Discovering overrepresented patterns in amino acid sequences is an important step in protein functional annotation which includes the identification of subcellular localisation. I adapted and extended NestedMICA, an *ab initio* protein motif finder originally developed for finding transcription binding site motifs, to find short protein signals, and compared its performance with another popular protein motif finder, MEME.

In order to assess NestedMICA as a protein motif finder, I have tested it on synthetic datasets produced by spiking instances of known motifs from protein databases into a randomly selected set of protein sequences. Apart from the artificially implanted motifs, NestedMICA also successfully recovered subcellular localisation signals from biologically-authentic test sets. NestedMICA found most of the short test protein motifs spiked into a test set of sequences at different frequencies. In all the assessment experiments, its overall motif discovery performance was better than that of MEME.

As a practical application of NestedMICA, I developed a novel Support Vector Machines based protein subcellular classification tool,

Lokum, for eukaryotic protein subcellular localisation prediction, covering all major localisation classes for animal, fungal and plant sequences. It uses targeting and retention signal motifs reported by NestedMICA, and other protein features including transmembrane topologies and amino acid composition. Additionally, in Lokum I use bipartite nuclear localisation signals obtained by adding protein support to Eponine, a tool originally developed for transcription start site modeling. Lokum does not use sequence similarity, or any other *a priori* knowledge such as known nuclear localisation signals by searching databases.

I compared proteins targeted into the nuclei and nucleoli in terms of the features used in Lokum, and also their predicted disorder regions. I demonstrate that it is possible to computationally distinguish these two sub-nuclear protein categories.

Finally, as an alternative to the transmembrane topology predictor TMHMM that is used in Lokum, I designed and tested a new prototype program that is based on hidden Markov models (HMM). The HMM has been trained by a novel, nested sampling based transition probability optimisation procedure.

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