1P266 Development of Ligand Based Virtual Screening considering protein-ligand interaction

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Virtual screening plays an important role in the early drug discovery stage. There are two broad categories of screening techniques: ligand-based and structure-based. Both techniques have their own advantages and weaknesses and there is still much room of improvement for both techniques. Here, we developed a new virtual screening method that combines the both techniques. The method is basically based on the ligand based techniques; A candidate ligand is compared with one or more active ligand structures by the 3D geometric hashing method. Besides, it also takes into account of ligand-protein interactions. The performance of the method was evaluated against the DUD set. We will report the detailed description of the method and the results.

1P267 H-DROP:サポートベクターマシンを用いたヘリカルリンカーの予測

H-DROP: an SVM based helical domain linker predictor trained with optimal selected features

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Domain linker prediction is the focus of interest as it can help identify novel domains suitable for high throughput analysis. Yet, most domain linker predictors focus on non-helical linkers, and there are no performant predictor for helical linker. Here, we present H-DROP, an SVM-based helical linker predictor trained with a dataset consisting of helical boundary regions between two structural domains. Optimal features were selected by combining a random forest and a stepwise feature selection protocols. The prediction sensitivity and precision of H-DROP were 35.2% and 38.8%. These values are over 10.7% and 23.0% higher than the respective values of other predictors and random prediction. H-DROP is the only efficient helical linker predictor that is currently reported.

1P268 スプライシングアイソフォームの機能的有意性の評価

Evaluation of functional significance of splicing isoforms

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Although many genes in higher eukaryotes undergo alternative splicing, functions of the majority of Splicing isoforms are not analyzed experimentally. We developed a pipeline to evaluate functional significance of splicing isoforms using three criteria: expression in the protein level, positional conservation among different species and regulation of expression in the mRNA level. About 80% of known functional splicing isoforms were judged as functionally significant, showing the validity of the pipeline. We, then, evaluated splicing isoforms losing their parts of hydrophobic core, which accounted for a large fraction of splicing isoforms in human. As a result, about 20% of them were judged as functionally significant.

1P269 タンパク質における分子トンネルの高速簡易探索法の開発ートリプトファン合成酵素への適用

A Simple Method to Detect Molecular Tunnels in Proteins - Application to Tryptophan Synthase

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The active sites of tryptophan synthase α - and β - subunits are connected with a long molecular tunnel and the ligand is transferred through it, avoiding accidental reactions with other molecules. This tunnel was first discovered by visual inspection of the protein structure. Enormous number of known protein structures, however, prevents us from finding tunnels by visual inspection, and an automatic method to detect a tunnel is required. We, therefore, developed a new and fast method to search the whole proteins in PDB for molecular tunnels. The method is applied to different entries of tryptophan synthases in PDB. We found that the structures of the tunnel were diverse and the differences may relate to the regulation of the ligand transport between the subunits.

1P270 mRNA切断ポリアデニル化特異因子複合体構成サブユニットの四次構造推定

Predicting a Quaternary Structure of mRNA Cleavage-Polyadenylation Specificity Factor Complex

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A messenger RNA (mRNA) undergoes a polyadenylation process after being transcribed from DNA. The process is regulated by quite a number of proteins associated with the mRNAs, but the three-dimensional (3D) structure of the proteins and the mechanisms of the regulation remain to be elucidated. Here, we predicted a 3D structure of cleavage and polyadenylation specificity factor (CPSF), a hetero-tetramer molecule and one of the components for regulating polyadenylation of mRNA. The 3D structures of the subunits were built by comparative modeling method. We then docked the four subunits utilizing information obtained from docking software and amino acid sequence conservation. Based on the obtained reasonable quaternary structure, we predicted the mRNA interfaces of CPSF.

1P271 ヒトリン酸化部位のデータベース解析で明らかになるシグナル伝達経路間のクロストーク

Crosstalk between signaling pathways revealed by database analysis of human phosphorylation sites

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Cellular fate depends on the spatio-temporal separation and integration of signaling processes which in turn can be provided by phosphorylation events. We address this topic at both the systems and molecular levels by linking distinct phosphorylation events with their functional outcomes and signaling pathways. We find that multiple phosphosites are clustered in sequence and space, and have a coherent effect on protein stability if they share regulatory functions and regulate similar pathways. In addition we observe a strong association of tyrosine phosphorylation with activating signaling events, and activating phosphosites more extensively participate in switching the signals from different pathways than inhibitory ones.