Web servers and stand-alone codes for modeling effect of mutations on thermodynamic properties of macromolecules.

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Abstract

Mutations play fundamental roles in evolution by introducing diversity into genomes that either can be selectively advantageous or disadvantageous to the organism by affecting protein stability and/or interfering with interactions between partners. Their effect on molecular level is manifested as alterations of wild type properties of the corresponding macromolecules such as proteins, DNAs and RNAs. While experimental investigations are preferred, they are too expensive and time consuming to be applied on a large number of cases. Thus, we propose a series of novel approaches to the study of non-synonymous mutations, called SAAMBE-3D, SAAMBE-SEQ, SAAFEC-SEQ and SAMPDI-3D, which predict not only protein stability but also protein-protein and protein-DNA interactions. SAAMBE-3D: a structure-based approach to predict protein-protein binding affinity upon mutation, resulting in accurate predictions and is extremely fast. SAAMBE-SEQ: a completely sequence-based method to predict protein-protein binding affinity upon mutations. The accuracy is either better or comparable to most advanced structure-based methods. SAAFEC-SEQ: a sequence-based method to predict the change of the folding free energy caused by mutations. It's shown to consistently outperform all existing sequence-based methods. SAMPDI-3D: a structure-based method to predict the change of the binding free energy caused by mutations in protein or DNA. The method can not only predict the effect of protein mutations, but also mismatch and substitution mutations. It was trained on newer and more reliable datasets. It's better than all existing methods and maintains extremely fast speed. In summary, we present a series of new approaches for studying the impact of missense mutations in proteins or DNA. They were successfully applied and evaluated in different predictive tasks and were shown to outperform earlier methods. All of them provide friendly web servers and stand-alone codes at http://compbio.clemson.edu/.

Gaussian-based method for quick estimation of entropy change upon protein-protein binding.

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Abstract

Protein-protein binding spans over diverse kinds of biomolecular processes, e.g., enzyme substrate binding, signaling and so on. Proteins participating in such processes undergo small or large conformational changes upon complex formation with its cognate partners. Therefore, it is expected that the entropy change upon complex formation is an important component of binding free energy. Here, we employ a Gaussian-based model of atomic densities; it models an atom as a spherical object whose density decreases according to a Gaussian distribution while moving away from its center. In this method, we infer entropy change from energy minimized protein-protein complex structure via computing changes in mean density around atoms forming sidechain-torsions with reference to energy minimized structure of single amino acid. Entropy derived from this method in combination to energy terms: Molecular Mechanics (MM), polar solvation using Poisson Boltzmann (PB), and non-polar solvation from Surface Area change are used to assess the improvement in correlation of predicted/computed values against experimental binding energy values over a protein-protein dataset is estimated.

Opioid addiction and opioid receptors dimerization: Plausible linkage of mu opioid receptor missense mutations and elevated opioid addiction risk.

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Abstract

Opioid addiction is a complex phenomenon having genetic, social and other components. Because of such a complexity, it is difficult to interpret the impact of genetic mutations on the outcome of opioid addiction. Mu opioid receptor **(**OPRM1) and delta opioid receptor **(**OPRD1) are proteins that associate with opioid addiction. OPRM1 and OPRD1 proteins could bind together as a heterodimer and be activated by natural peptides for specific signaling pathways. We computationally investigated two such genetic mutations, A6V and N40D, found in OPRM1 protein and have been found to be associated with substance dependence. The mutations are located in the extracellular domain of the corresponding protein (OPRM1), which is important to dimerization of OPRM1 with OPRD1 protein. In this study, we focus on analyzing the impact of these two variants on the stability of OPRM1-OPRD1 heterodimer which may affect G-protein signaling pathway and β-arrestin signaling pathway (*Figure 1*). We calculated the folding free energy change and binding free energy change due to those mutations. Current analysis indicates that missense mutations N40D may affect protein stability.

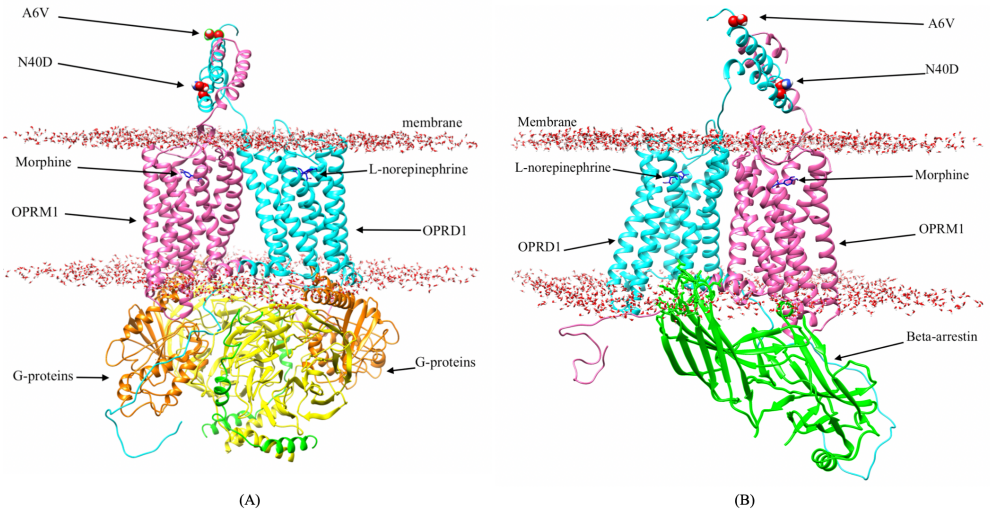

Figure 1. Molecular signaling pathways (A). G-protein signaling pathway. (B). β-arrestin signaling pathway.

Using Gaussian-based Dielectric Model to Predict Positions of Non-specifically Bound Ions.

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Abstract

Interactions between ions and biological macromolecules play significant role in many biological processes. Ions support to maintain protein stability, catalysis, electron/proton transfer reaction and many other biological processes. The ions can be free in the water phase, or ions can be bound specifically or non-specifically to the macromolecule. Of particular interest to us are non-specifically bound ions, since identifying their positions is a challenge both from experimental and computational point of view. Here we report an upgrade of the computational method BION, called BION-2, to predict the non-specifically bound ions. The BION-2 applies the Gaussian-based dielectric model which is implemented in DelPhi program. This allows the predictions to be made accounting for both electrostatic interactions between ions and protein and at the same time the desolvation penalty. To validate the BION-2, we benchmark it against experimentally identified surface bound ion positions. Finally, we show that BION-2 outperforms the old BION and the other available computational tools such as VMD and FoldX.

Revealing creatine pathway across creatine transporter protein.

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Abstract

Creatine is an essential component for the temporal and spatial maintenance of the energy supply to skeletal and cardiac muscles. Creatine transporter protein (CRT) encoded by X-linked gene SLC6A8 helps transporting creatine from outside of skeletal and cardiac cells to inside the cells. Deficiency of creatine is found to be associated with creatine deficiency syndrome (CDS) in inborn characterized by clinical features like mental retardation, hypotonia, seizures, behavioral problem, speech delay etc. Here we focus on revealing the pathway of creatine through the CRT via steered molecular dynamics (MD) simulations. We show that creatine follows well-defined pathway despite of the choice of initial CRT structure and creatine position. The role of Na^+ is also investigated and it was found that they affect creatine transport. Furthermore, we use the residues involved in creatine pathway to explain the molecular mechanism of known pathogenic mutations.

Modeling pH-dependence of melanosome formation

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Abstract

pH plays a crucial role for melanosome maturation and function. Melanosomal pH changes during maturation from very acidic in the early stages to neutral in late stages. Neutral pH is critical for providing optimal conditions for the rate-limiting, pH-sensitive melanin synthesizing enzyme tyrosinase (TYR). This dramatic change in pH is thought to result from the activity of several proteins that control melanosomal pH. Here, we investigated the pH-dependence of the stability of these proteins and compare it with the pH dependence of the stability of TYR. We confirmed that the pH-optimum of TYR is neutral, and we also found that proteins that are negative regulators of melanosomal pH also function optimally at neutral pH. In contrast, positive pH regulators tended to have an acidic pH-optimum. Building on previous work that demonstrated that pH-optima of stability and activity are correlated, our findings are consistent with the expected activity of positive and negative regulators. Thus, positive pH regulators are most active at low pH, while negative regulators are most active at high pH. Furthermore, we investigated the effects of disease-causing mutations on the pH-dependence of these proteins and show that a significant fraction of these mutations perturb their pH dependence; this is particularly prominent for the OCA2 protein. In conclusion, melanosomal pH appears to affect the activity of multiple proteins beyond TYR.