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Dear Sir,

Please find enclosed our manuscript entitled "*A model for hydrophobic protrusions on peripheral membrane proteins*" by Edvin Fuglebakk and myself. We hope that this manuscript can be considered for publication as a general research article in *PLOS Computational Biology*.

In this contribution, we tackle the difficult problem of distinguishing membrane binding sites on soluble proteins, from other soluble protein-surfaces. These peripheral membrane proteins play key roles in many processes at cellular interfaces, such as recognition, signalling and trafficking, but few distinguishing features have been identified to recognize and understand membrane binding sites. We provide exactly this, through a formal, but simple and interpretable model, that we expect to be of interest to molecular biologists and computational scientists investigating processes at cellular interfaces.

In contrast to membrane-embedded proteins, the interfaces between peripheral proteins and membranes are poorly characterized. The general mechanism for peripheral membrane binding relies on the two almost universal traits of biological membranes; their hydrophobic core and anionic surface. Electrostatics between the negatively charged membranes and basic amino acids is recognized as playing an important role in membrane binding, but has also been shown to play a minor role for some protein families. Hydrophobic insertion is the other important contribution. Consequently, peripheral protein binding interfaces are described as consisting of a combination of hydrophobic amino acids and patches of basic amino acids but the role of small hydrophobic patches has been (i) particularly elusive and (ii) difficult to distinguish from the surfaces of non-membrane-binding soluble proteins. In the submitted manuscript, we propose a novel formulation of a structural pattern for the recognition of biological membranes by soluble proteins. The formulation explains how small hydrophobic motifs can facilitate membrane recognition, and effectively discriminate membrane binders from other soluble proteins. This is to our knowledge the first report of a structural motif that discriminates peripheral protein surfaces from non-membrane-binding surfaces.

Our approach isolates mechanisms and concepts to clearly demonstrate the role of structure in hydrophobe-membrane interactions. This enables us to formulate a simple and interpretable model, which is well suited to inform both experimentalists and computational scientists. The concepts developed in this manuscript can be directly applied as a framework to understand membrane-binding, engineer proteins and design experiments. For development of predictive tools and automatic annotation efforts we have demonstrated how these concepts can be formalised and leveraged for predictive power.

Sincerely,
Nathalie Reuter