

Intrinsically disordered region of talin's FERM domain functions as an initial PIP₂ recognition site

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Abstract

Focal adhesions mediate the interaction of the cytoskeleton with the extracellular matrix (ECM). Talin is a central regulator and adaptorprotein of the multiprotein focal adhesion complexes and is responsible for integrin activation and force-sensing. We evaluated direct interactions of talin with the membrane lipid phosphatidylinositol 4,5-bisphosphate (PIP₂) by means of molecular dynamics simulations. A newly published autoinhibitory structure of talin, where common PIP₂ interaction sites are covered up, sparked our curiosity for a hitherto less examined loop as a potential site of first contact. We show that this unstructured loop in the F1 subdomain of the talin1 FERM domain is able to interact with PIP₂ and can facilitate further interactions by serving as a flexible membrane anchor.

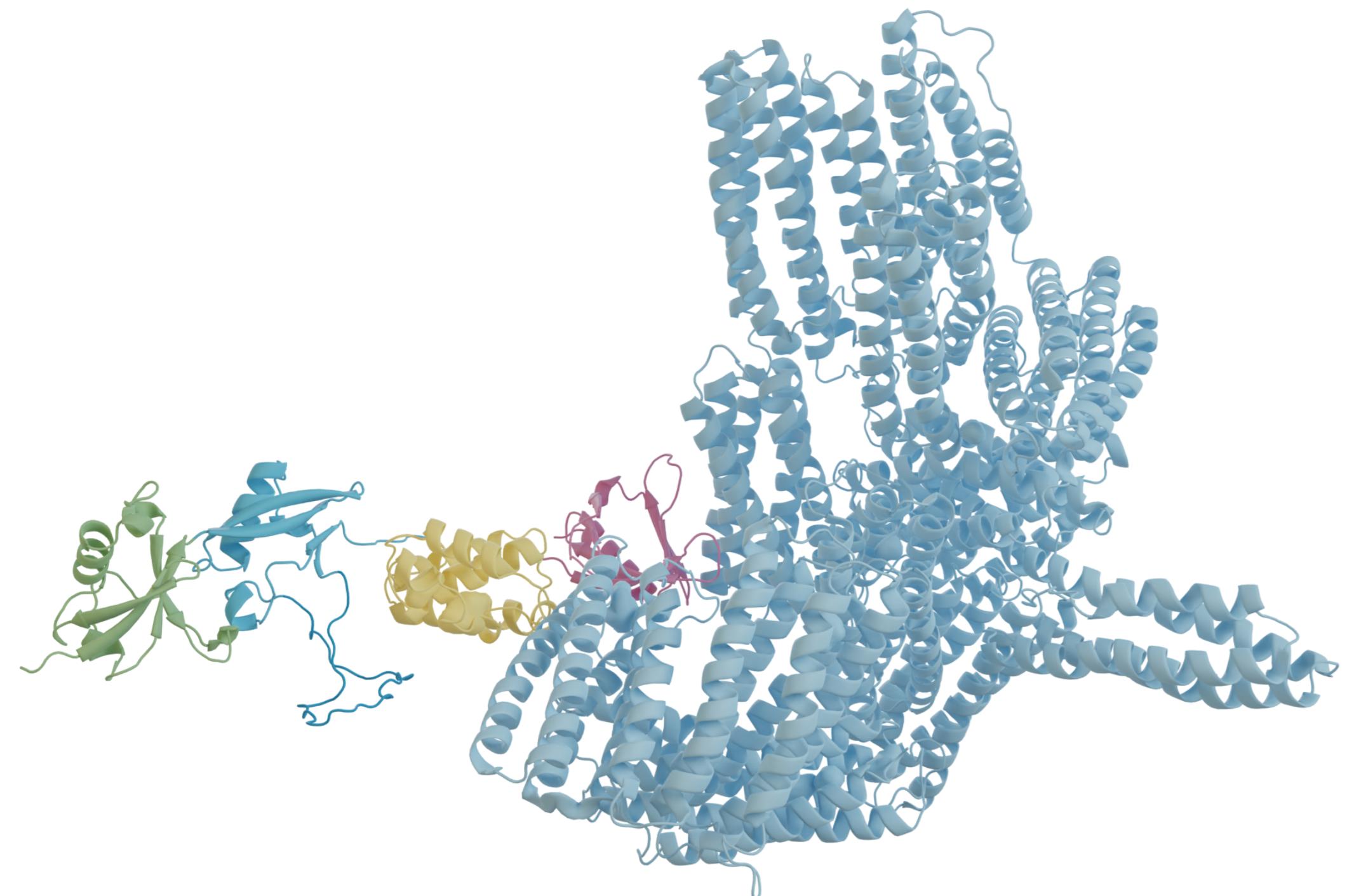


Figure 1. The autoinhibited (Cryo-EM) structure of Talin1 found by Dedden et al. (2019) aligned with the structure of the FERM domain by Goult et al. (2010) and the modelled flexible loop in F1 (darker cyan)

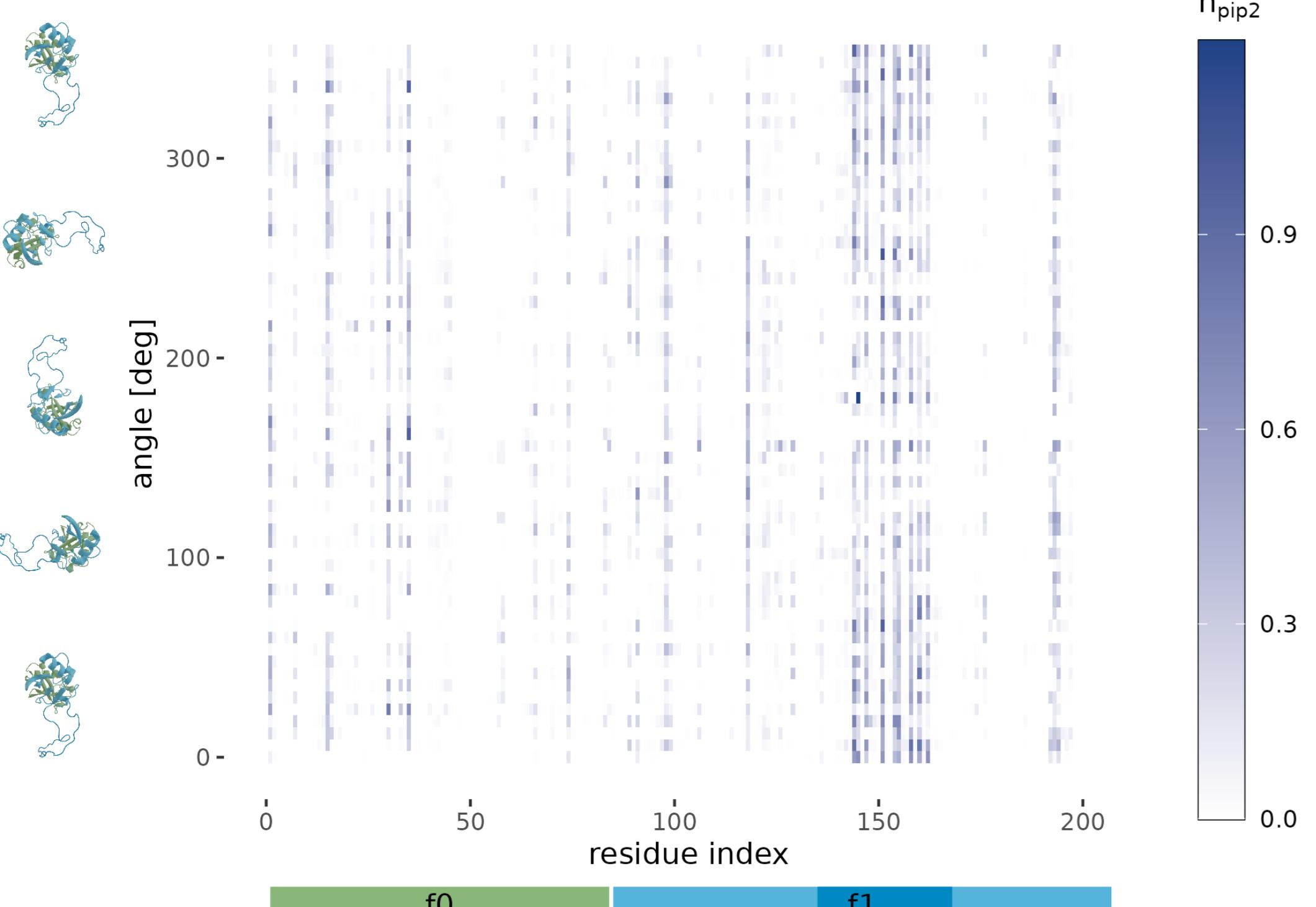


Figure 2. A rotational sampling of the FOF1 domain reaveals the strong propensity of the F1 loop to interact with the membrane. Even in the most unfavorable position, the loop still has a large probability to find the membrane and interact with PIP₂ due to the large search space it can cover.

Unstructured loop of Talin's FERM domain can serve as a flexible membrane anchor

This allows for interaction with PIP₂ even in Talin's autoinhibited form and paves the way to establish known binding surfaces.

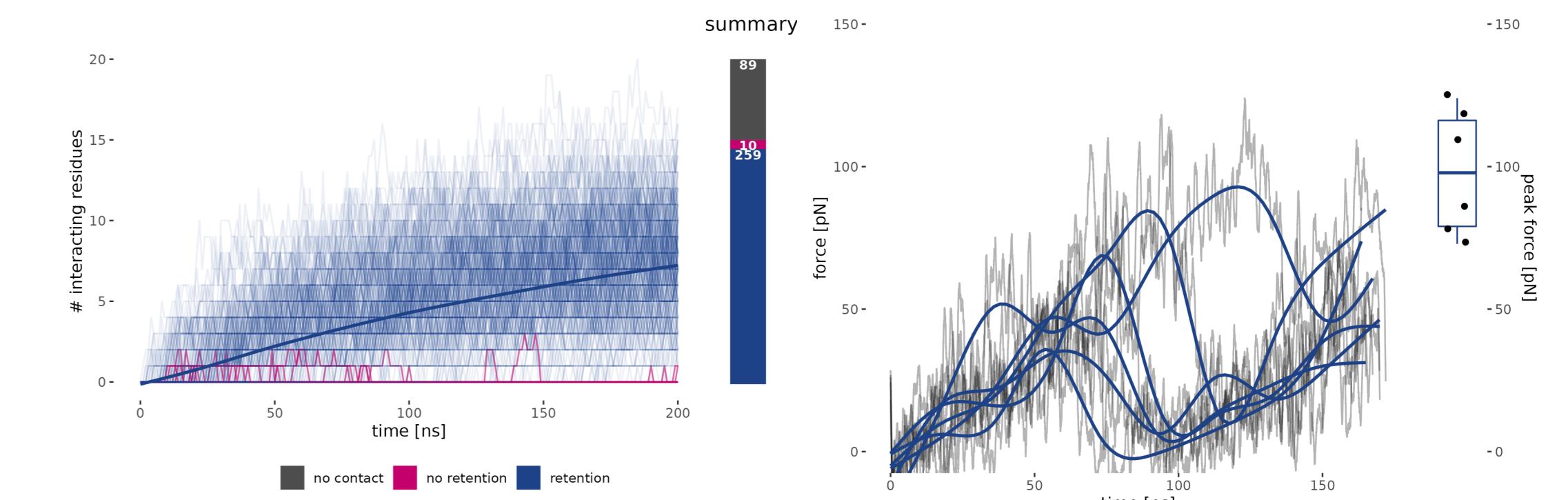
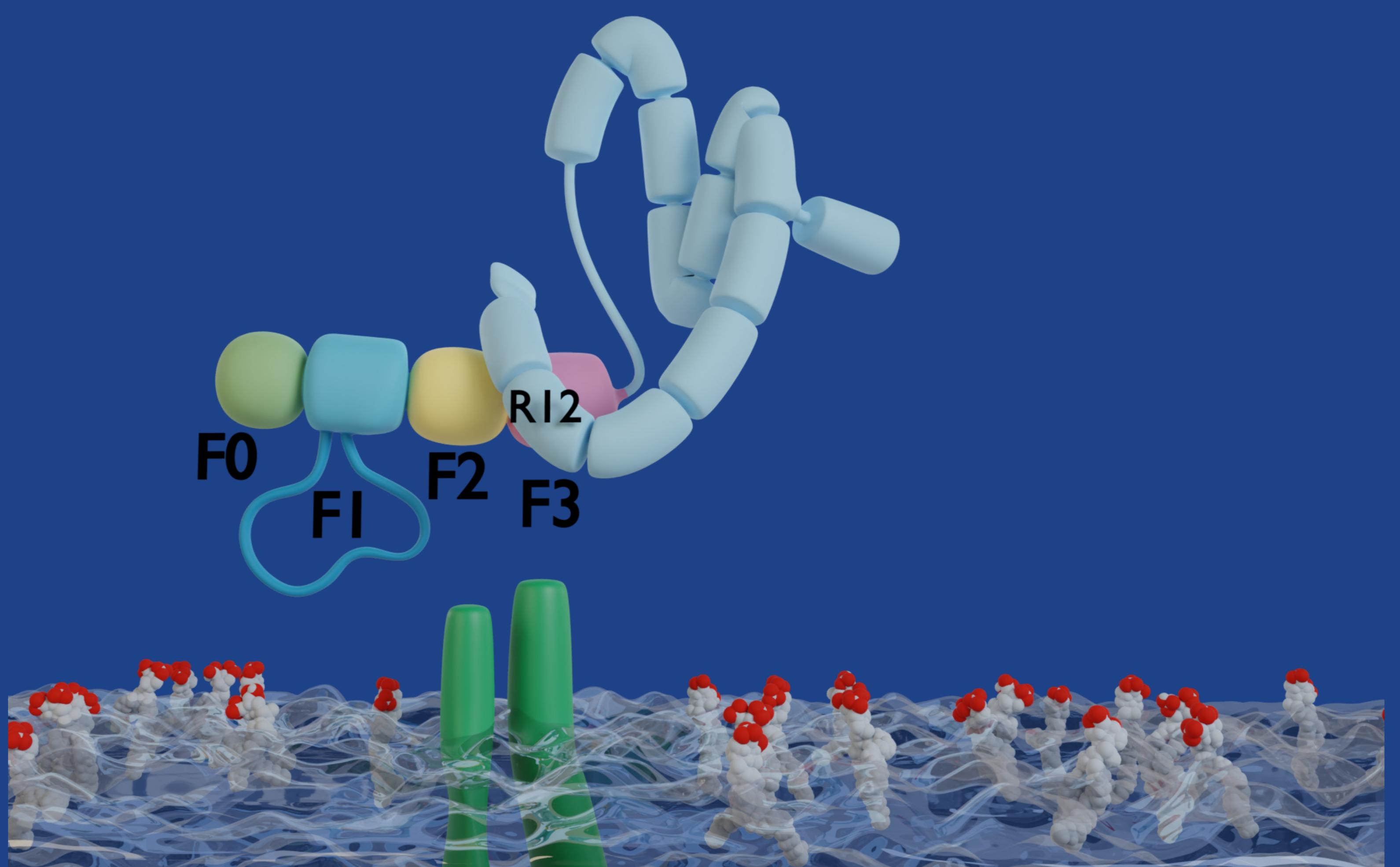


Figure 3. Left: Once a certain number of residues are interacting it becomes highly unlikely for F0F1 to dissociate from the membrane. Right: Pulling F0F1 from the membrane does need some force, but the most important aspect for remaining bound is its flexibility.

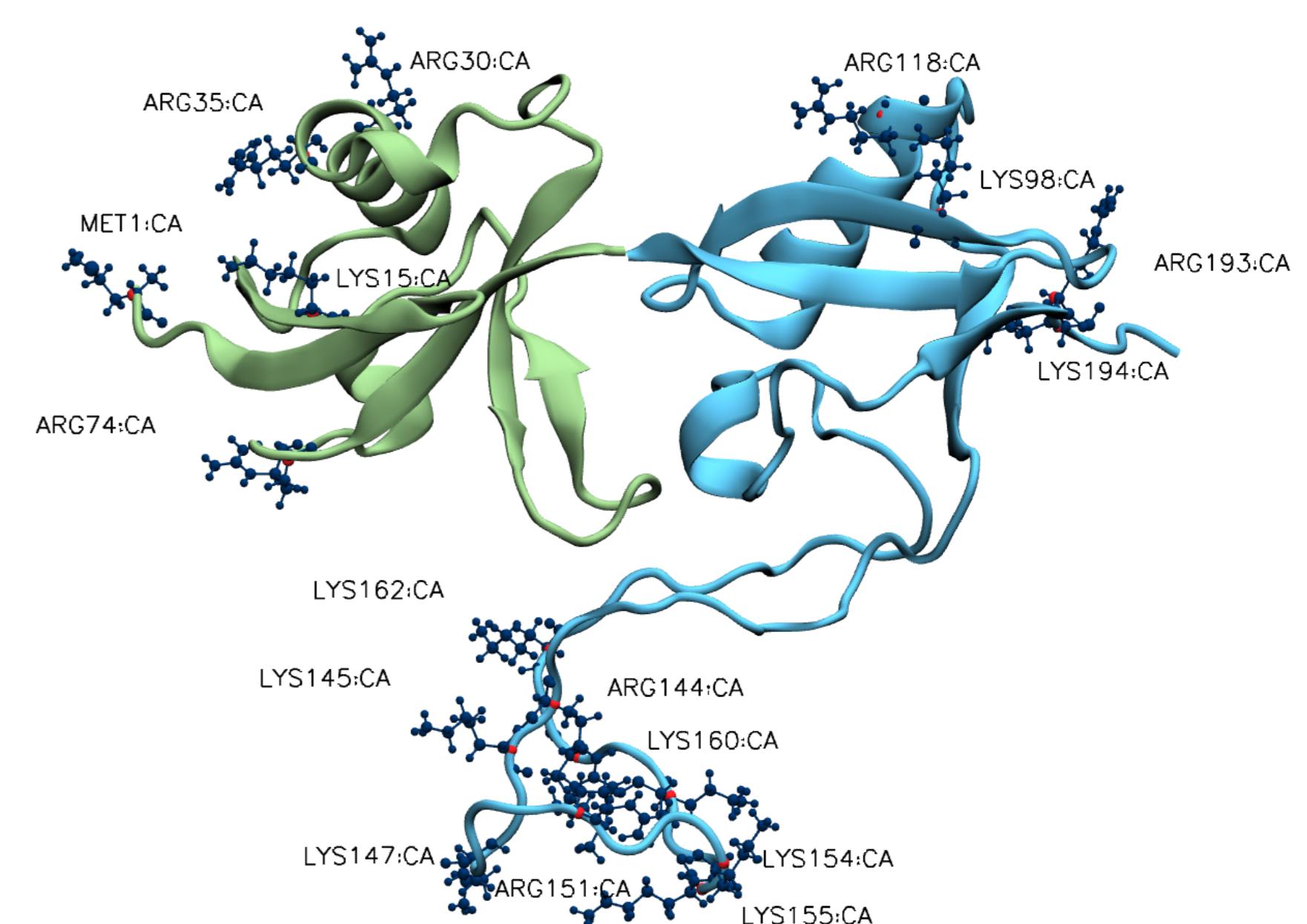


Figure 4. The residues of F0F1 interacting with PIP₂ are highlighted in blue, with their CA-atoms labelled

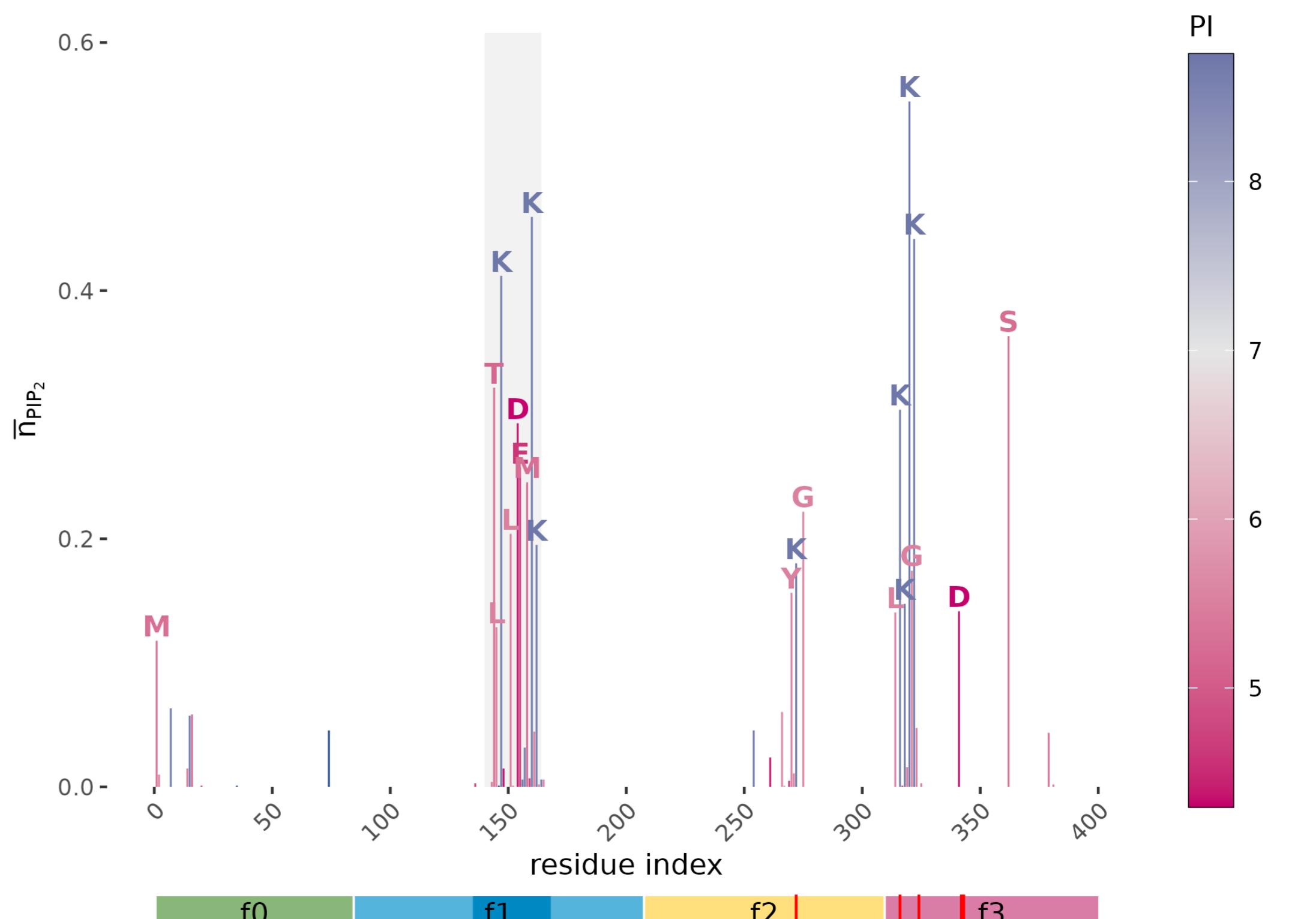


Figure 5. Once contact has been established via the loop, simulations with the full length FERM domain show that known PIP₂ interaction sites are recovered

Acknowledgments

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References

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