Supporting Information

Exploring Allosteric Pathways of a V-Type Enzyme with Dynamical Perturbation Networks

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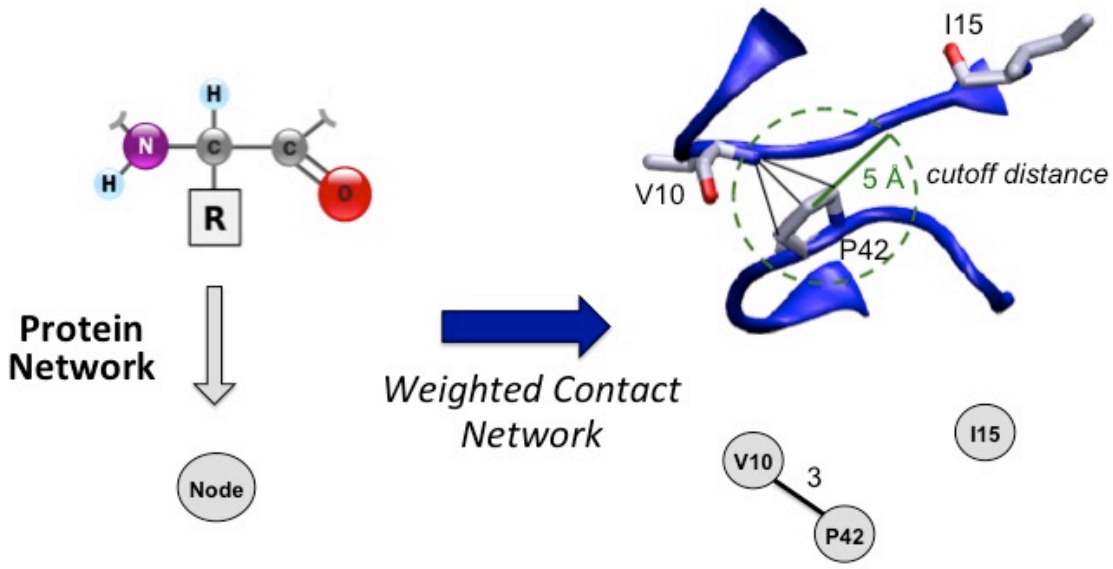

Figure S1. Each amino acid residue represents a node in the protein network. The presence of atomic contacts within the cutoff distance (5 Å) ensures the link between two nodes (i.e. the edge) in the protein network. The edges are weighted according to the number of atomic contacts for each residue pair. The picture shows a general example (not directly related to IGPS) for the construction of connections between three residues and assignment of weights to existing edges.

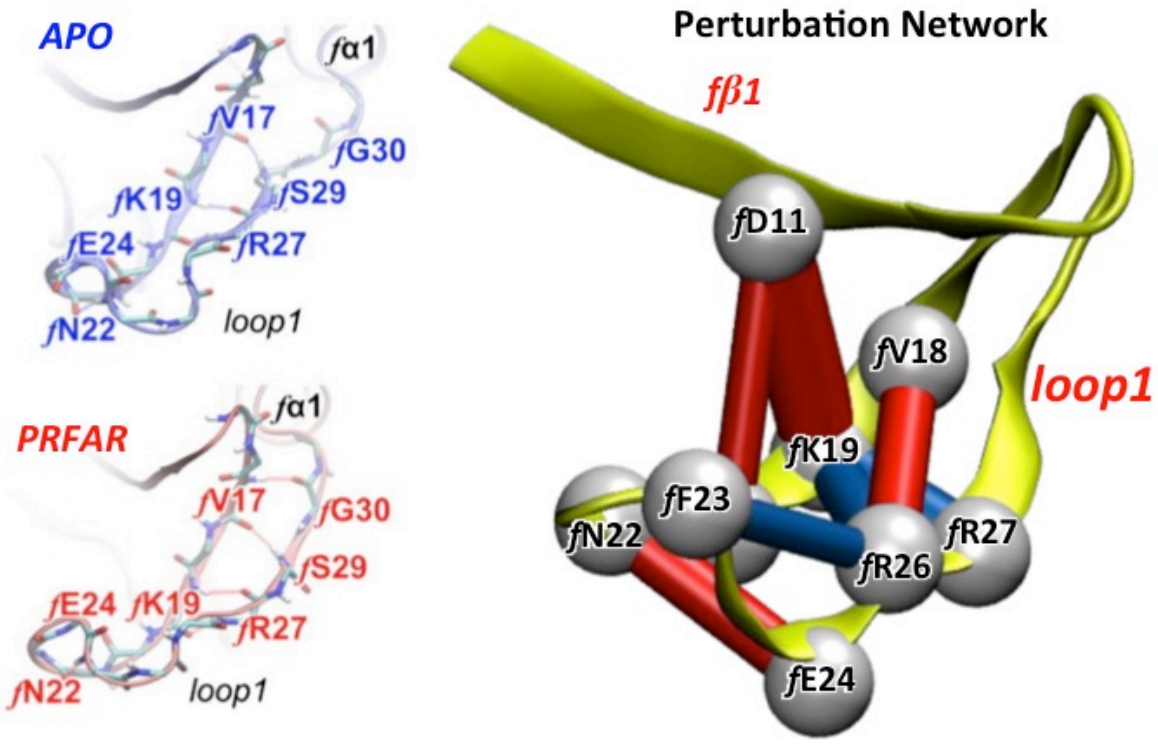

Figure S2. Comparison between hydrogen bonds modifications observed for *loop1* in the MD simulations of apo and PRFAR-bound complexes (left panels) and perturbations of heavy atoms contacts detected by means of the perturbation network analysis (right panel). A weight threshold $w_t = 6$ is used for the 3D representation of the network.

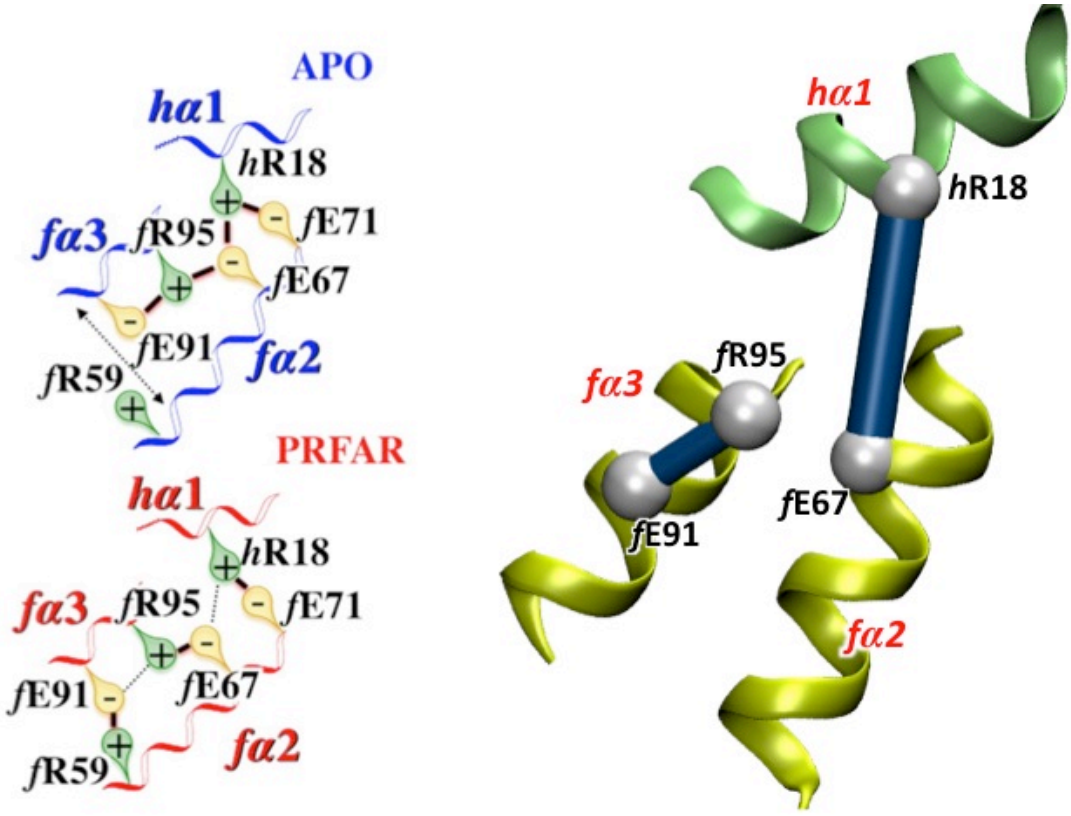

Figure S3. Comparison between ionic interactions modifications observed for $h\alpha1$, $f\alpha2$ and $f\alpha3$ in the MD simulations of apo and PRFAR-bound complexes (left panels) and perturbations of heavy atoms contacts detected by means of the perturbation network analysis (right panel). A weight threshold $w_t = 6$ is used for the 3D representation of the network.

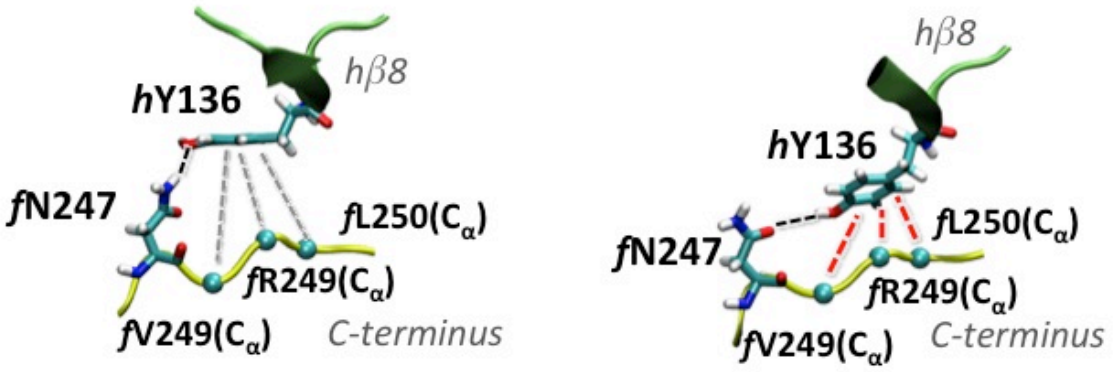

Figure S4. Schematic representation of contacts between the invariant *h*Y136 residue in *hβ*8 and residues *f*V248, *f*R249 and *f*L250 in the C-terminal domain of HisF, showing the change of H-bonding between *h*Y136 and *f*N247 that brings *h*Y136 closer to the flexible C-terminus.

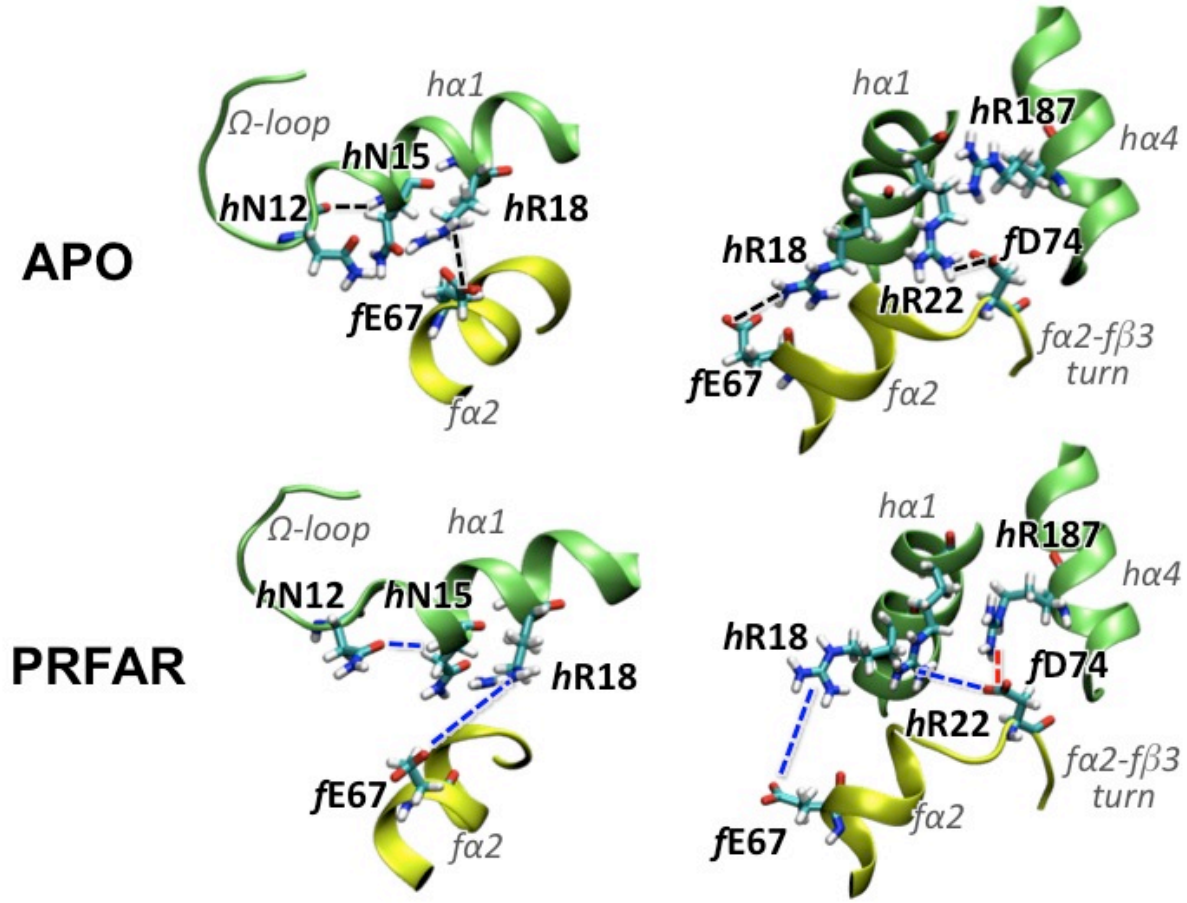

Figure S5. Representative configurations extracted from the MD simulations of the apo (top panels) and PRFAR bound (bottom panels) IGPS complexes, showing the *h*R18-*f*E67 salt–bridge disruption and the resulting partial unfolding of *hα*1 helix (propagating towards the active site via the *Ω-loop*) and rearrangement of interactions between polar/charged residues in *hα*1 and *hα*4 helices and the *fα*2–*fβ*3 turn.

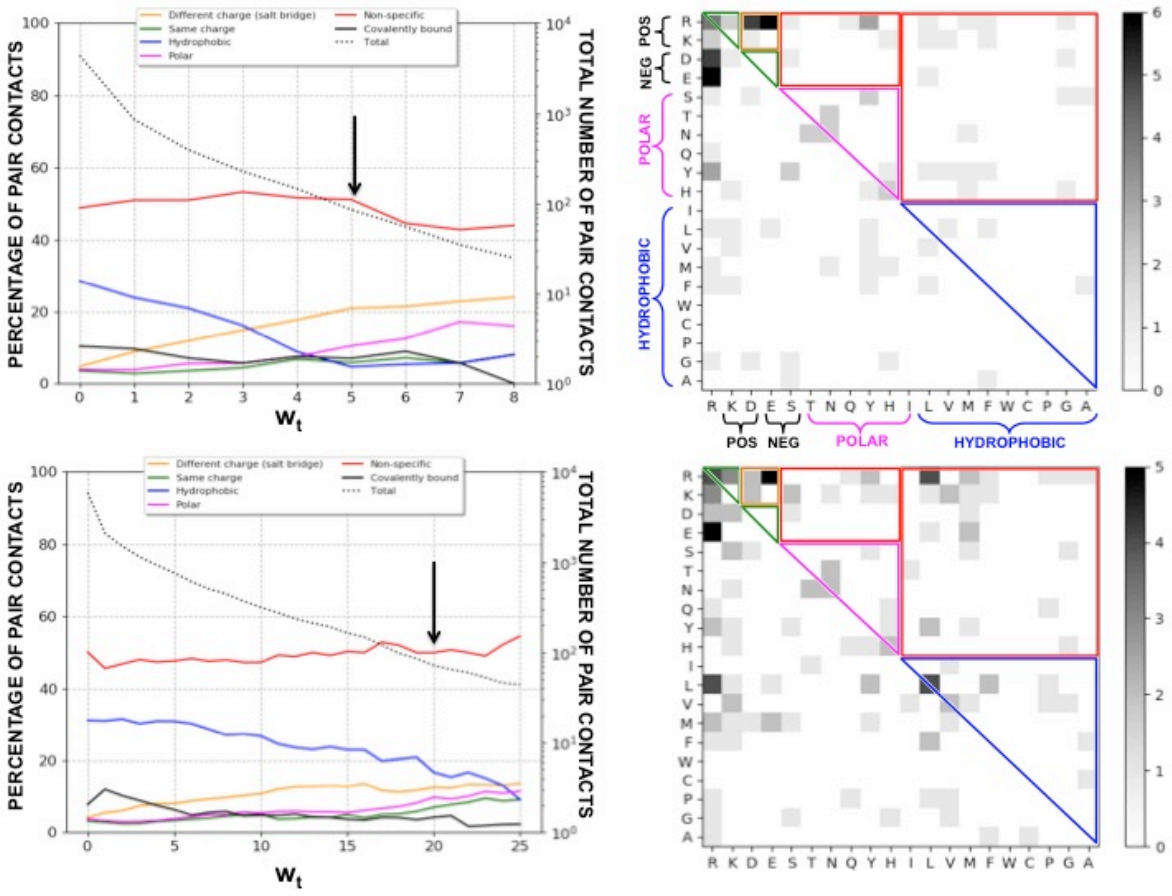

Figure S6. Analysis of the types of pair contacts detected by the perturbation networks using contacts between heavy atoms (top panels) and between all atoms including hydrogens (bottom panels). Left panels plots show the total number of pair contacts (dotted lines) and the percentage of pair contacts in the perturbation networks according to the type of interactions, which are defined as following: different charge (yellow lines) = R or K with D or E; same charge (green lines) = R with K or D with E; hydrophobic (blue lines) = I, L, V, M, F, W, C, P, G, A with themselves; polar (magenta lines) = S, T, N, O, Y, H with themselves. Note that since all histidine residues are not protonated (according to standard protonation at pH=7 for this enzyme), H is considered as a polar residue. Right panels maps show the contributions of specific amino acids to the pair contacts for a given perturbation weight threshold (w_t = 5 for heavy atoms and w_t = 20 for all atoms), with boxes highlighting the type of interactions involved.

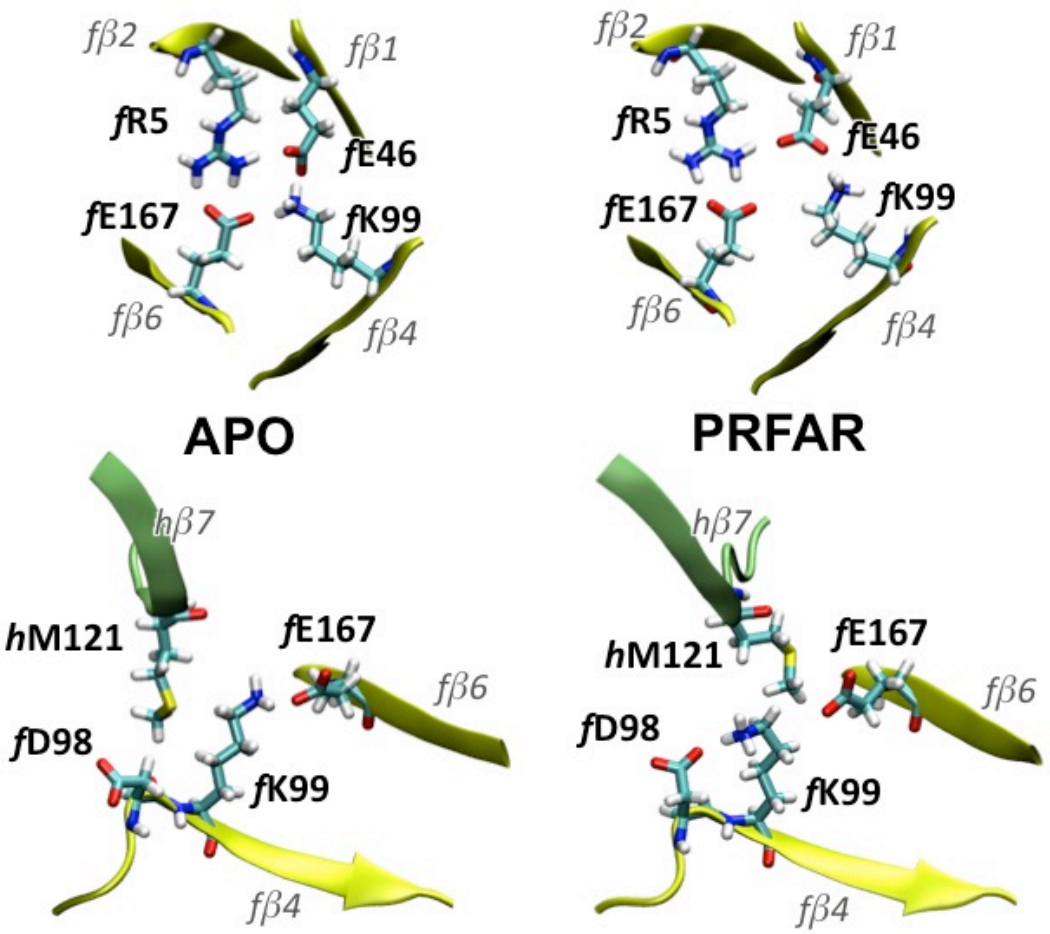

Figure S7. Representative configurations extracted from the MD simulations of the apo (left panels) and PRFAR bound (right panels) IGPS complexes, showing the effects of PRFAR binding to the interactions between the *h*M121 residue (features several contacts perturbations in the network analysis) and the invariant *f*R5, *f*K99 and *f*E167 residues that belong to the ammonia tunnel gate of the HisF barrel (top panels) and with the highly conserved *f*D98 (bottom panels) of the structurally important *f*D98–*h*K181 salt–bridge anchor.