Mapping networks of light-dark transition in LOV photoreceptors

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1 SUPPLEMENTARY INFORMATION

Network construction

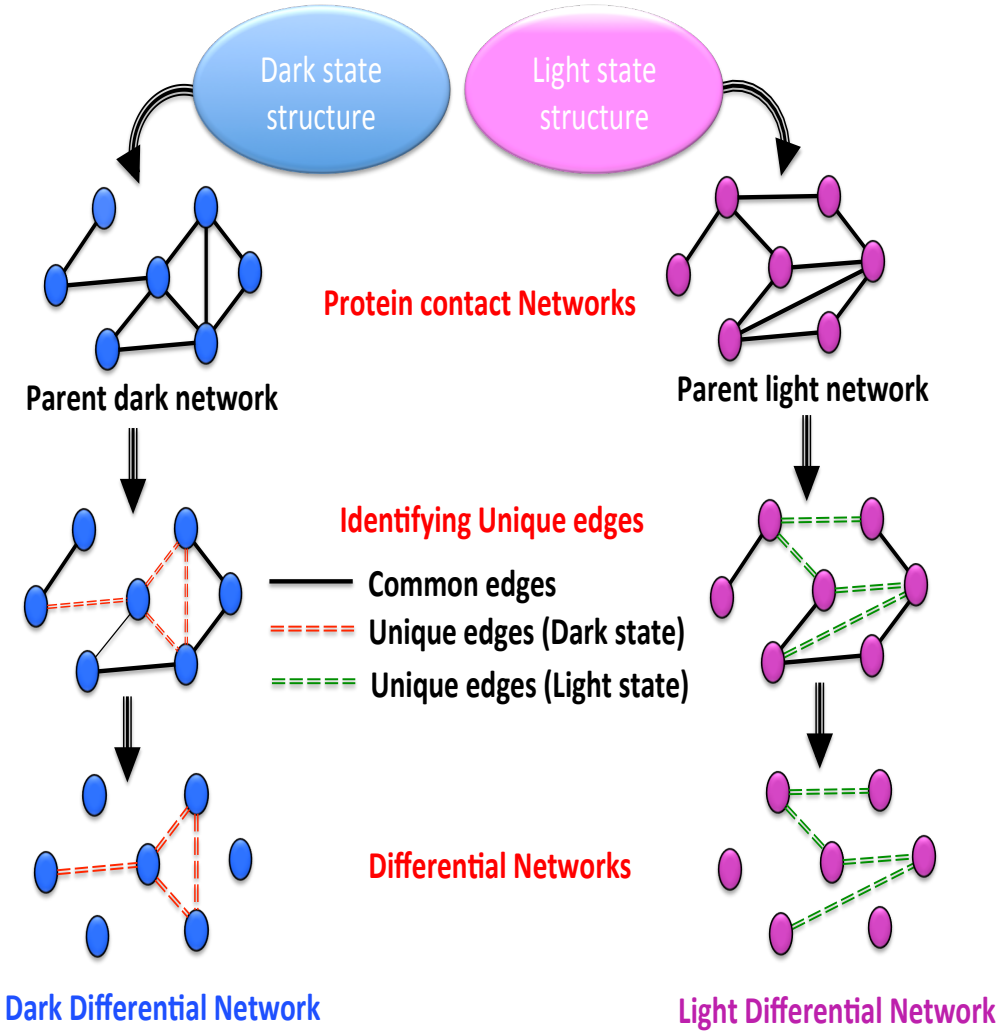
We model the crystal structures, both light and dark state, of LOV domains as network of interacting residues [1, 2, 3]. In protein structure graphs (PSG) [1], the interaction strength between i^{th} and j^{th} residue is determined as

$$I_{ij} = \frac{n_{ij}}{\sqrt{N_i N_j}} \ , \tag{1}$$

where, n_{ij} is the total number of side chain atom interactions between i^{th} and j^{th} residue lying within 4.5Å (except Glycine, for which C-alpha atom is considered).

In the present study, the normalization factors N_i and N_j are the total number of heavy atoms present in the i^{th} and j^{th} residue respectively [3]. The cutoff of 4.5Å is approximately the average value of the peptide bond length. Departure from 4.5Å would lead to consideration of too many interactions due to the obliged contacts coming from sequence proximity and would add a lot of noise in the model leading to the dilution in the analysis of the system [1, 3, 4]. So, we have to filter interactions in our study. On the other hand, considering too many interactions like weakly connected electrostatic interactions will result in a rather dense network and hence we would not be able to differentiate the two states and measure changes via network theory for two states. Because, two almost completely connected networks will have similar network metric distributions.

The protein structure graphs identify a critical interaction strength, I_C, at which size of the largest connected component, $L(I)$, or simply L, has underwent a sharp transition [1], i.e. to say, the interaction strength at which the largest fall in the size of the largest connected component (LCC) has taken place. $L(I)$ is the ratio of the number of nodes in the LCC at interaction strength, I, to the total number of nodes in the *original network* (which might have more than one component). Consider the case of Phy3-LOV (light state) in Fig. S 2. The maximum fall in the size of the largest connected component occurs at the interaction strength $I = 0.1$. The value of $L(I)$ at $I = 0.1$, i.e., $L(0.1) = 88$ nodes. The value of $L(0.1)$ is same as the value of the initial LCC, $L(0)$. The value of $L(I)$ at $I = 0.2$, i.e., $L(0.2) = 22$ nodes. Thus, in the present case, there is a *sharp* fall in value of $L(I)$ from $I = 0.1$ to $I = 0.2$. Infact, this sudden fall leads to a situation where in a single step, the new LCC at $L(0.2)$ is even less than half of $L(0)$. The next drop in the value of $L(I)$ is from



Supplementary Figure S 1: **A schematic diagram showing the construction of differential networks from the parent crystal states.**

Supplementary Table S 1: I_C **value for all six LOV domains in light and dark state.**

LOV domain	Space Group	I_C	
		Light state	Dark State
YtvA LOV	P 2_1 2_1 2	0.3	0.3
VVD	P 1 2_1 1	0.3	0.2
Oat LOV	P 2_1 2_1 2_1	0.25	0.3
Aureo1 LOV	P 4_3	0.2	0.2
Cr LOV LOV	P 6_5 2 2	0.2	0.2
Phy3 LOV	P 1	0.2	0.2

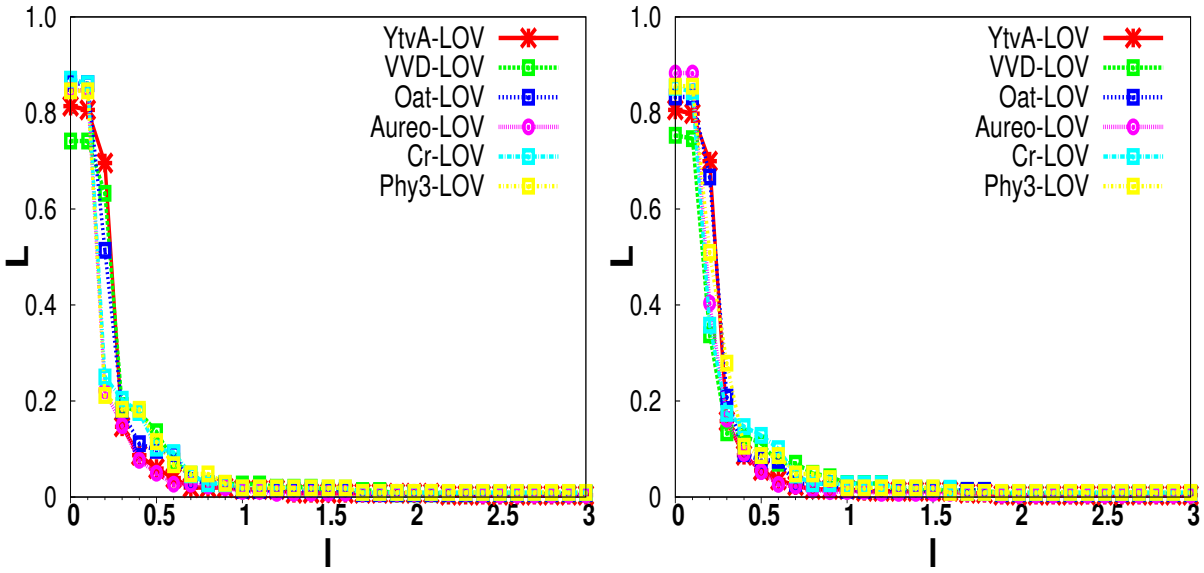
$L(0.2) = 22$ nodes to $L(0.3) = 19$ nodes. This is obviously insignificant when compared to the drop from $L(0.1)$ to $L(0.2)$. Therefore, $I_C = 0.2$ for Phy-3 LOV (Light state). Thus, the sharp decrease in size of L at $L(I_C)$, will not be exceeded for subsequent drops in $L(I)$ for $I > I_C$.

I_C has also been used to study the unfolding of lysozyme structure [5]. The normalization mentioned above [1] was designed for entire proteins. We have used a slightly modified form of Ref. [1], from earlier literature [3], since the focus herein is on LOV domain.

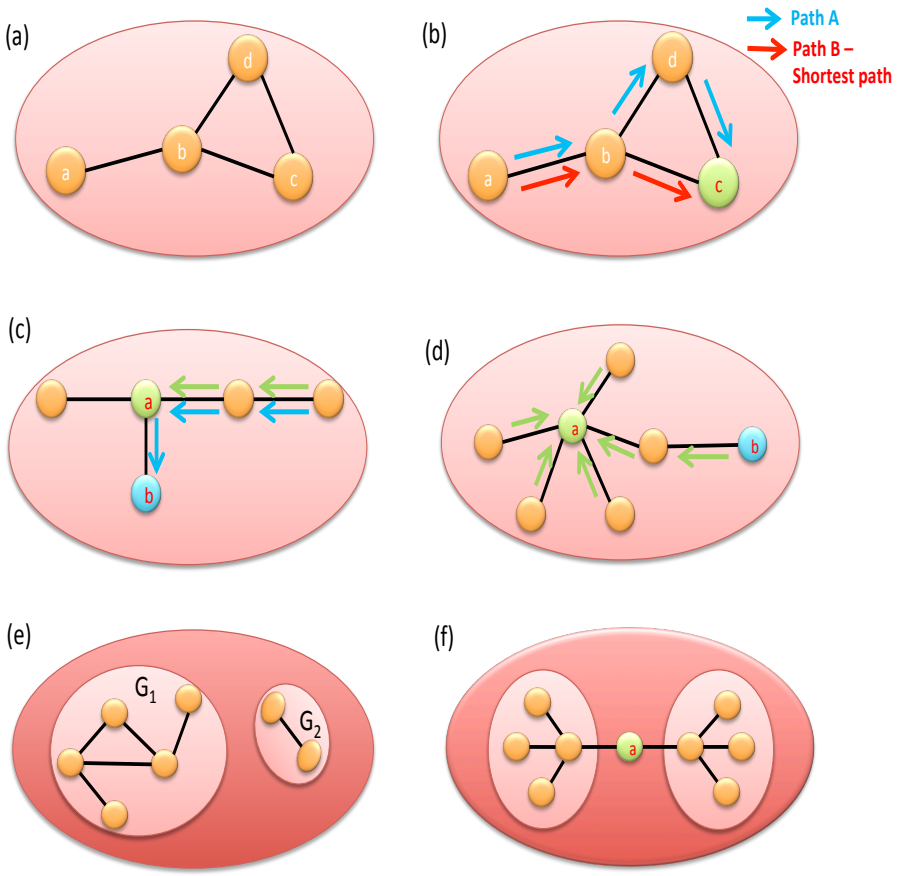
As shown in Fig. S2, we observe a sharp transition in the L versus I curve just as in Ref. [1], for all six LOV domains considered here. In fact, the transition occurs over a narrow range of I for both light and dark states. Thus, an edge is formed between i^{th} and j^{th} residue only when $I_{ij} > I_C$. Value of I_C for all six LOV domains is shown in Table 2. For cases with almost identical decrease in largest connected component size, I_C is the interaction strength at which the transition has already taken place. YtvA and Aureo LOV are considered as dimers whereas VVD, Oat, Cr-LOV and Phy3 LOV are taken to be monomers for network construction.

Edge deletion

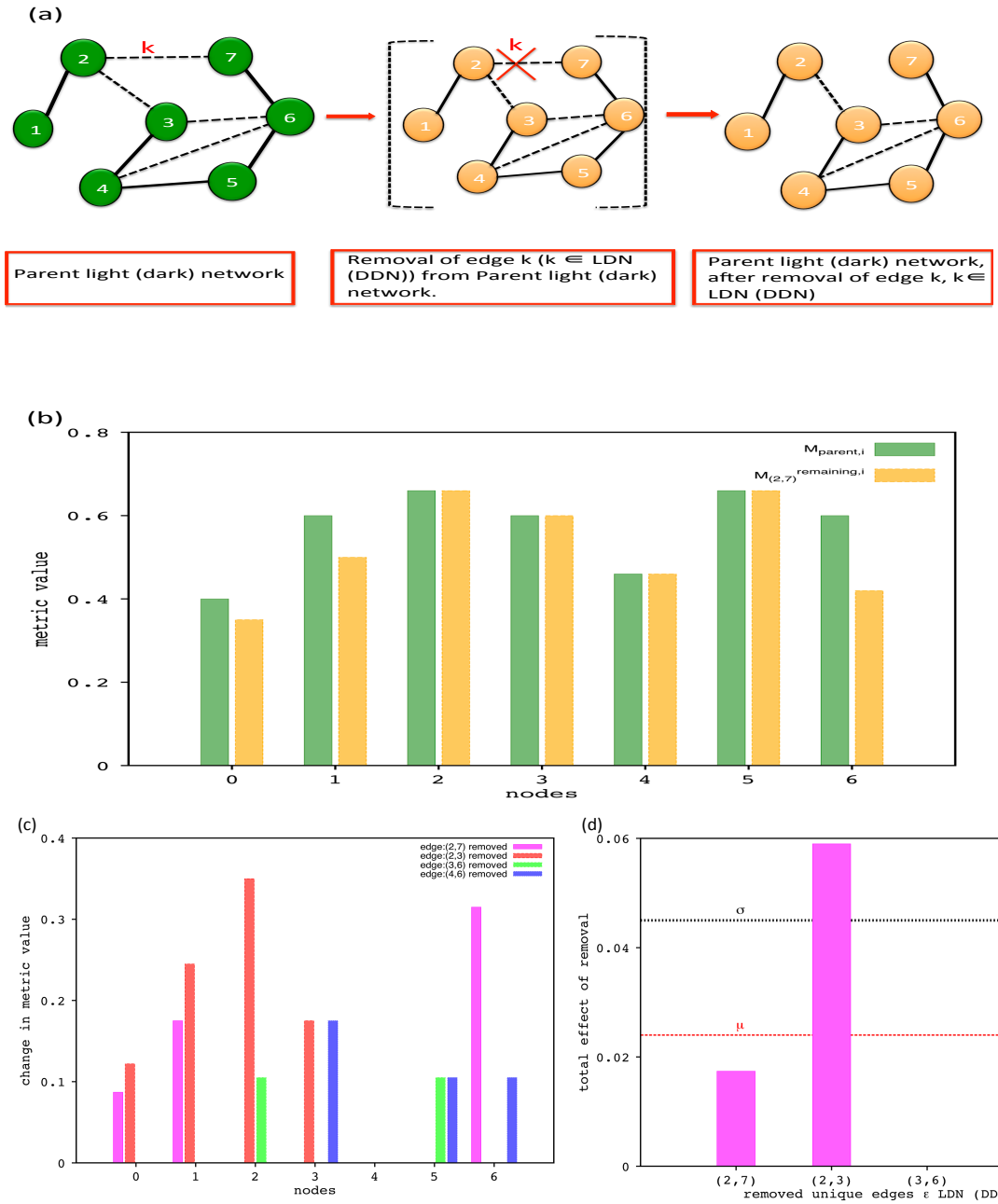
Testing the effect of deletion of nodes or edges in a network is a very common exercise in network theory. Node deletion in a network is obviously quite different from edge removal as the former also leads to removal of edges incident on a node, apart from the node itself. This is important especially when the node under consideration is a hub. Additionally, the implication of node deletion is an arbitrary removal of residue(s) from the protein structure, which apart from being unphysical, is fraught with biological consequences. Thus, node deletion in any biological network obviously needs to be conducted with utmost caution and not as a mere academic process. Therefore, we deal with only edge deletions, which are physically far more viable, i.e. the protein structure would physically exist even without individual edges in either light or dark state.



Supplementary Figure S 2: A sharp transition like Ref [1] is observed when the normalized size of largest connected component, L, is plotted against the interaction strength, I, for both light (left) and dark (right) states.



Supplementary Figure S 3: **Brief overview of Network Theory** (a) A toy *network*, $\mathcal{G}(\mathcal{V}, \mathcal{E})$ where $\mathcal{V} = \{a, b, c, d\}$ and $\mathcal{E} = \{(a, b), (b, c), (b, d), (c, d)\}$ denote the set of nodes and edges respectively. (b) *Path* is defined as the number of edges travelled to reach one node from another. The figure shows two different paths, A and B, between node 'a' and node 'c'. Path A corresponds to the *shortest path*, i.e. the minimum of edges needed to reach node 'c' starting from node 'a' (c) *Eccentricity* of a node is its distance from farthest node in the network or its largest component. Here, the eccentricity of node 'a' is 2 whereas eccentricity for node 'b' is 3. (d) *Closeness* of a node measures its "nearness" to other nodes in the network. Here, node 'a' has the highest closeness as almost every node in the network is just one edge away from it. 'b' is obviously not closer to most nodes in the network, compared to 'a' (e) Disconnected network with two connected components, G_1 and G_2. Here, G_1 is the *largest connected component* because it has the highest number of connected nodes. (f) *Betweenness* of a node reflects the importance of the node for communication within the network. Here, if node 'a' is removed, the network would become disconnected; resulting in loss of communication between nodes in the network. Node 'a' has the highest betweenness in the network, as most of the shortest paths in the network pass through it.



Supplementary Figure S 4: **Edge removal strategy.** (a) A toy example showing network edge removal. Edge k belongs to the differential network. The dotted edges form the corresponding differential network (DN). (b) Node metric value, for each residue within the network, before removal (green) and after removal (orange) of edge $(2,7)$ shown in Fig S4(a). (c) Change in metric value, ΔM_k^i, for each node i within the network using Eqn. 6 of main text. Here $k \in \{(2,7),(2,3),(3,6),(4,6)\}$, which is the set of edges forming the DN. (d) Total effect, ΔM_k for each edge $k \in$ Differential network calculated using Eqn. 7 of main text. The red line represents the mean of $\Delta M_k, \forall k$ which is denoted by $\langle \Delta M_k \rangle$. The black line represents the standard deviation from $\langle \Delta M_k \rangle$. Those edges for which the total effect of their removal lies above the black line are considered as *key-interaction and the incident residues are termed as key-residues.* Here, edge $(2,3)$ is a key-interaction.

Supplementary Table S 2: **Measure of Standard Deviation (σ)and percent change for eccentricity and edge betweenness distribution for all six LOV domains during dark to light transition.**

Eccentricity distribution			
Domain	$\sigma_{\mathbf{light}}$	$\sigma_{\mathbf{dark}}$	$\%_{\mathbf{change}} = (\sigma_{\mathbf{dark}} - \sigma_{\mathbf{light}})/\sigma_{\mathbf{dark}}$
Phy3 LOV	2.69	7.84	191.44%
Aureo1 LOV	4.92	8.32	69.10%
Cr LOV LOV	3.51	4.77	35.89%
VVD	3.48	4.37	25.57%
Oat LOV	3.48	3.75	7.76%
YtvA LOV	4.26	4.56	7.04%
Edge betweenness distribution			
Domain	$\sigma_{\mathbf{light}}$	$\sigma_{\mathbf{dark}}$	$\%_{\mathbf{change}} = (\sigma_{\mathbf{dark}} - \sigma_{\mathbf{light}})/\sigma_{\mathbf{dark}}$
Phy3 LOV	0.0037	0.036	872.97%
Aureo1 LOV	0.0041	0.016	290.24%
Cr LOV LOV	0.0035	0.011	214.28%
VVD	0.0035	0.0087	148.57%
Oat LOV	0.0038	0.0046	21.05%
YtvA LOV	0.0018	0.0021	16.66%

Light-dark transition and Monomer-Dimer Equilibrium

To further understand the dependence of this approach upon crystal artefacts, we performed the Differential Network analysis for light-activated dimer structure of VVD-LOV (PDB id: 3rh8) and compared it with the variant dark state dimer structure (PDB id: 3d72), due to the unavailability of wild type dimer crystal structure of VVD-LOV. For this case, some of the residues that are identified as key-residues are important for dimerization e.g. Ile52 And Met55 [7]. Also, Met48 and Asp46 are known to form hydrogen bond with Val67 (located at A'_α) within the dimer interface [6]. All these three residues are well identified as key-residues. Thus, the present approach of this study clearly reflects the nature of crystal structures under consideration. If the crystal grown in dark is illuminated at room temperature, we do see very good reversion to the light state e.g. Microspectrophotometry on Aureo1 LOV, of course within the constraints of lattice. Oat LOV structure has been solved at both cryogenic and room temperature. However, room temperature Oat is preferred here to include maximum light induced changes. Once again, we would like to emphasize that our DN approach needs both states to be either monomers or dimers and of course sequentially identical, else the effect of individual residue interaction on LDN or DDN cannot be assessed properly.

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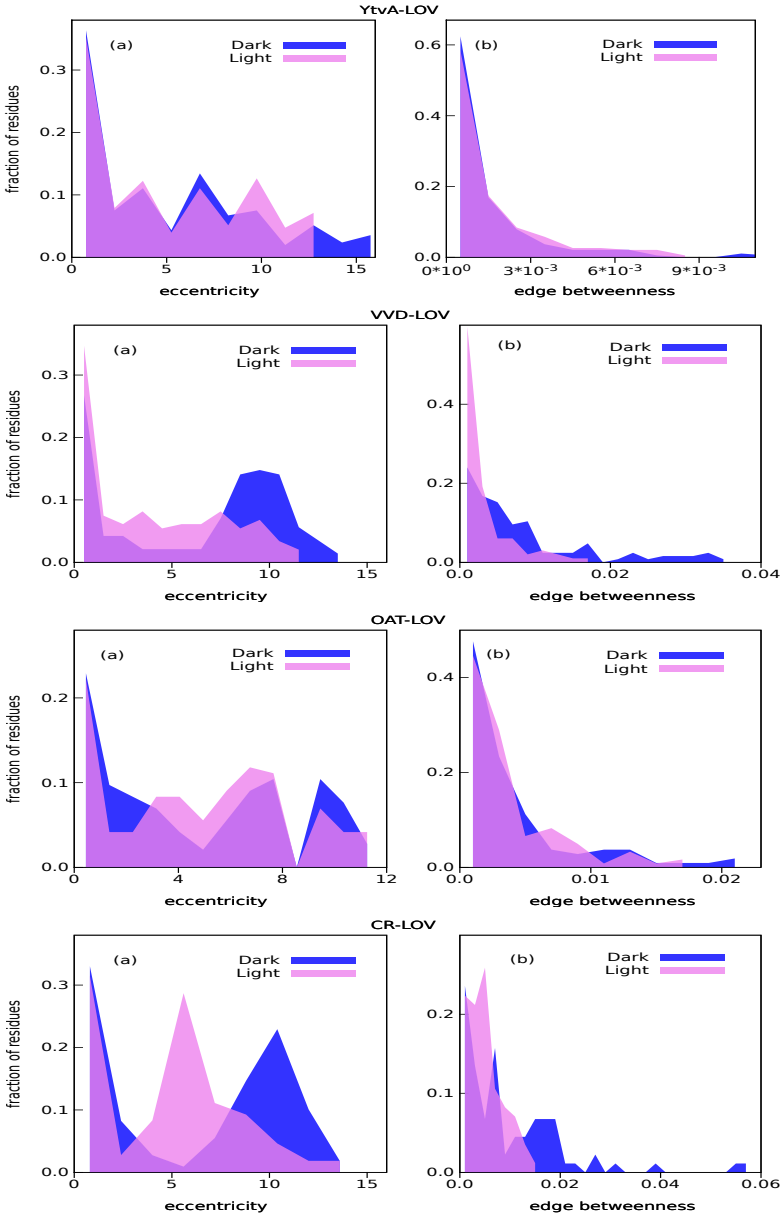
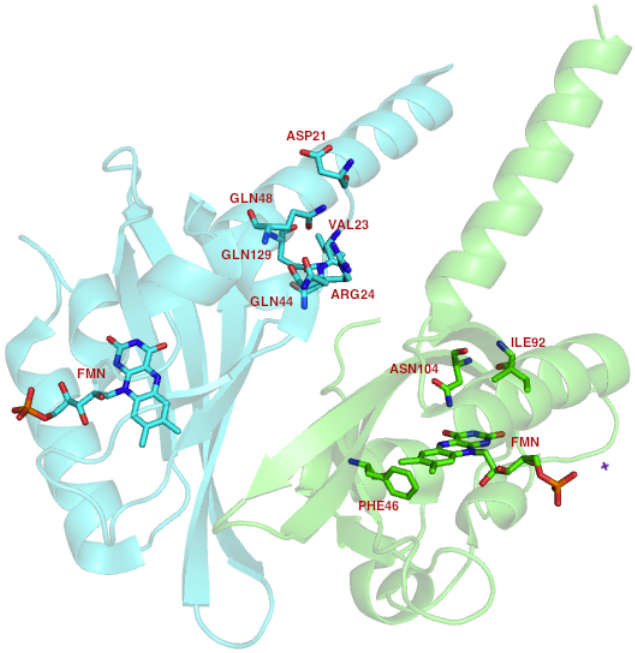


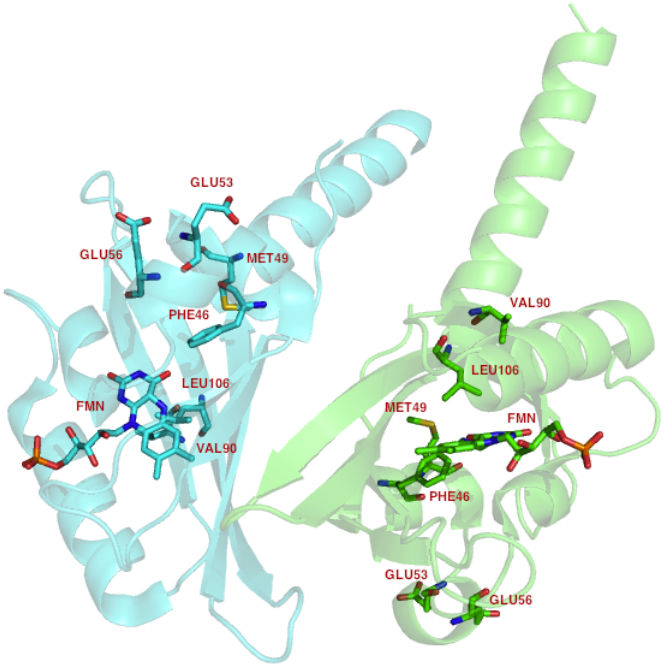
Supplementary Figure S 5: Distribution of (a) Eccentricity and (b) Edge betweenness for YtvA-LOV, VVD, Oat-LOV and Cr-LOV respectively. Phy3 and Aureo1 LOV in Fig. 1 of main text show similar behaviour.

Supplementary Table S 3: **Interacting residues obtained by using network metrics.** Functional importance of residues in **bold** are already known in literature. Edges mentioned in *italics* demonstrate significant impact on more than one network metric, when they are removed from the network. " ′ " sign denotes residues from second chain of crystallographic dimer.

YtvA LOV			
State	Nature of network metric	Key interactions	$\mathcal{Z}_k$
Light	Closeness	***(Val90, Leu106)***	2.96
		(Val90′, Leu106′)	2.10
		(Phe46′, *Met49′)*	1.24
	Betweenness	***(Val90, Leu106)***	2.07
		(Phe46′, *Met49′)*	1.94
		(Glu53′, ***Glu56′)***	1.66
		(Val90′, Leu106′)	1.45
		(Glu53, ***Glu56****)*	1.38
	Edge Betweenness	***(Val90, Leu106)***	2.21
		(Phe46′, *Met49′)*	1.98
		(Val90′, Leu106′)	1.52
		(Glu53′, ***Glu56′)***	1.50
		(Glu53, ***Glu56****)*	1.26
	Edge Proximity	***(Val90, Leu106)***	2.42
		(Phe46′, *Met49′)*	1.99
		(Val90′, Leu106′)	1.57
		(**Phe46**, Met49)	1.51
Dark	Closeness	***(Ile92, Asn104)***	3.05
		(Asp21′, *Gln48′)*	2.01
	Betweenness	***(Asp21′***, *Gln48′)*	3.37
		(Arg24′, ***Gln44′)***	1.69
		(Val23′, Gln129′)	1.23
	Edge Betweenness	***(Asp21′***, *Gln48′)*	3.33
		(Arg24′, ***Gln44′)***	1.56
		(Val23′, Gln129′)	1.19
	Edge Proximity	***(Ile92, Asn104)***	2.35
		(Asp21′, *Gln48′)*	1.94
		(**Phe46**, Ile57)	1.26



(a)

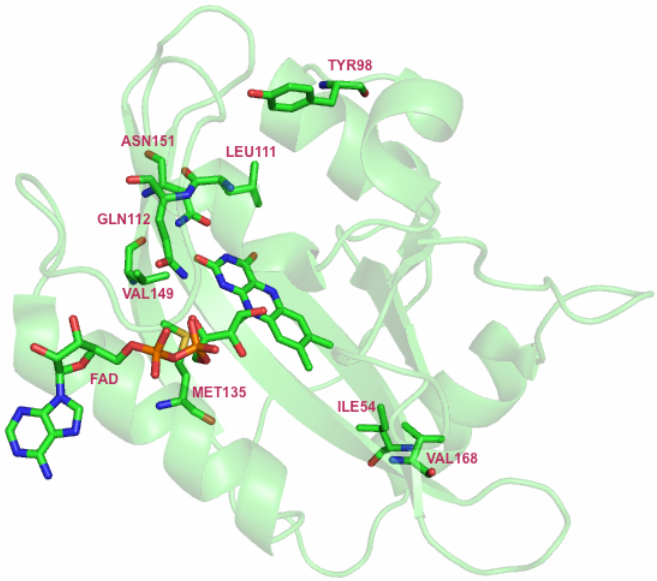


(b)

Supplementary Figure S 6: Distribution of functionally important residues inYtvA LOV (dimer) before and after photon absorption. (a) Dark crystal structure (pdb - 2pr5). (b) Light crystal structure (pdb - 2pr6)

Supplementary Table S 4: **Interacting residues obtained by using network metrics.** Functional importance of residues in **bold** are already known in literature. Edges mentioned in *italics* demonstrate significant impact on more than one network metric, when they are removed from the network.

VVD			
State	Network metric	key interactions	$\mathcal{Z}_k$
Light	Closeness	*(**Tyr40**, Val86)*	2.93
		*(**Tyr40**, Leu104)*	1.61
	Betweenness	*(**Tyr40**, Val86)*	2.81
		*(**Tyr40**, Leu104)*	2.28
	Edge Betwenness	*(**Tyr40**, Val86)*	2.88
		*(**Tyr40**, Leu104)*	2.23
	Edge Proximity	*(**Tyr40**, Val86)*	2.06
		(Leu64, Ile166)	1.83
Dark	Closeness	*(Tyr98, **Leu111**)*	3.39
		*(**Ile54**, Val168)*	3.36
		*(**Gln112**, **Asn151**)*	3.35
		(**Met135**, Val147)	1.42
	Betweenness	*(**Ile54**, Val168)*	4.14
		*(Tyr98, **Leu111**)*	2.95
		*(**Gln112**, **Asn151**)*	2.08
		*(**Met135**, Val149)*	1.29
		*(Val149, **Asn161**)*	1.17
	Edge Betweenness	*(**Ile54**, Val168)*	3.83
		*(Tyr98, **Leu111**)*	2.77
		*(**Gln112**, **Asn151**)*	2.35
		*(Val149, **Asn161**)*	1.59
		*(**Met135**, Val149)*	1.44
	Edge Proximity	*(**Gln112**, **Asn151**)*	4.15
		*(Tyr98, **Leu111**)*	3.23
		*(**Ile54**, Val168)*	2.98



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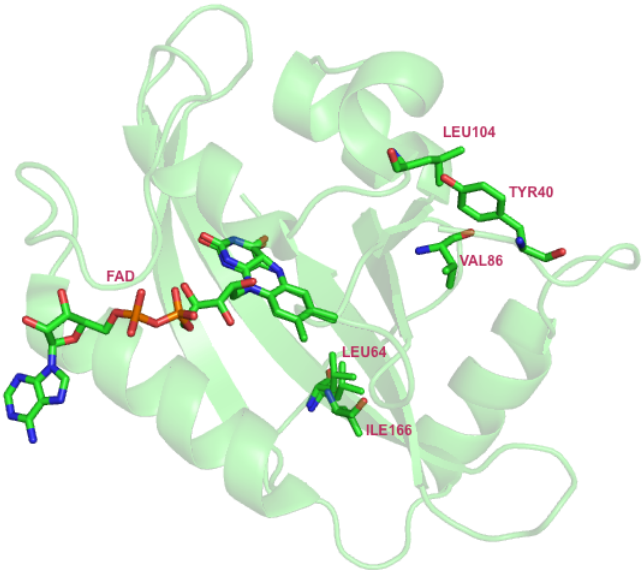
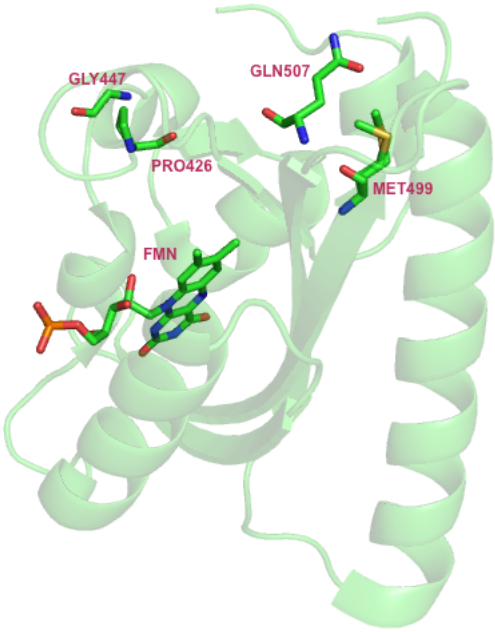


(b)

Supplementary Figure S 7: Distribution of functionally important residues inVVD LOV before and after photon absorption. (a) Dark crystal structure (pdb - 2pd7). (b) Light crystal structure (pdb - 2pdr)

Supplementary Table S 5: **Interacting residues obtained by using network metrics.** Functional importance of residues in **bold** are already known in literature. Edges mentioned in *italics* demonstrate significant impact on more than one network metric, when they are removed from the network.

Oat LOV			
State	Nature of network metric	Key interactions	$\mathcal{Z}_k$
Light	Closeness	*(Ile466, Val478)*	2.82
		(Ile470, Phe509)	1.56
		*(Met499, **Ile510**)*	1.48
		(**Leu493**, Val529)	1.15
	Betweenness	*(Met499, **Ile510**)*	3.04
		(Ile466, Val478)	2.62
	Edge Betweennes	*(Ile466, Val478)*	3.30
		*(Met499, **Ile510**)*	2.51
	Edge Proximity	***(Ile470, Phe509)***	1.59
		(Ile466, Val478)	1.57
		(**Val476**, **Leu496**)	1.48
		(Ala405, **Glu409**)	1.30
		*(Met499, **Ile510**)*	1.23
		(**Asn414**, **Gln513**)	1.15
Dark	Closeness	*(Met499, Gln507)*	2.60
	Betweenness	*(Met499, Gln507)*	1.88
		(Pro426, Gly447)	1.19
	Edge Betweenness	*(Met499, Gln507)*	2.16
	Edge Proximity	*(Met499, Gln507)*	2.87



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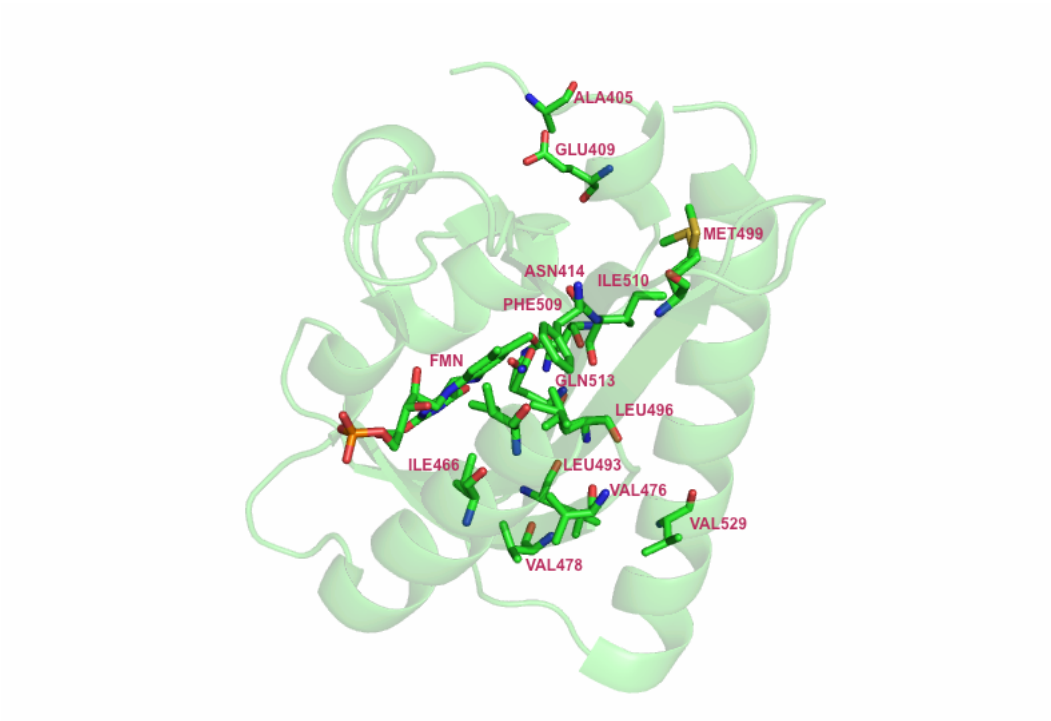
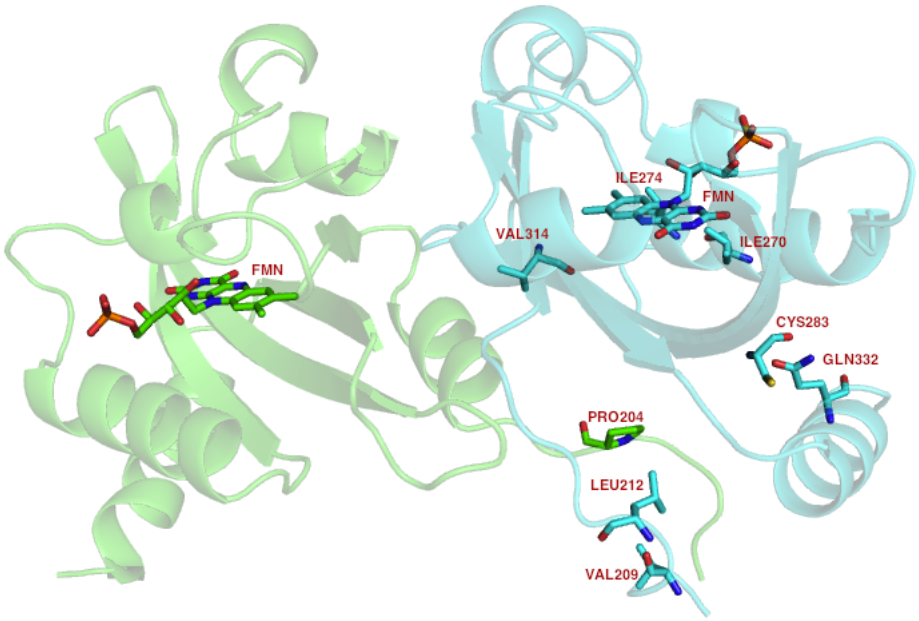


(b)

Supplementary Figure S 8: Distribution of functionally important residues in Oat LOV before and after illumination. (a) Dark crystal structure (pdb - 2v1a). (b) Light crystal structure (pdb - 2v1b)

Supplementary Table S 6: **Interacting residues obtained by using network metrics.** Functional importance of residues in **bold** are already known in literature. Edges mentioned in *italics* demonstrate significant impact on more than one network metric, when they are removed from the network. " ′ " sign denotes residues from second chain of crystallographic dimer.

Aureo1 LOV			
State	Network metric	key interactions	$\mathcal{Z}_k$
Light	Closeness	*(Lys269, Val282)*	3.72
		*(**Gln258** ′, **Asn286** ′)*	3.09
		*(**Gln258**, **Asn286**)*	1.63
		*(Thr262 ′, **Leu284** ′)*	1.57
		(Ala266 ′, **Leu284** ′)	1.22
	Betweenness	*(**Gln258** ′, **Asn286** ′)*	4.35
		*(**Gln258**, **Asn286**)*	2.44
		(Lys269, Val282)	1.97
		(Tyr244 ′, **Leu257** ′)	1.13
	Edge Betweenness	*(**Gln258** ′, **Asn286** ′)*	4.49
		*(**Gln258**, **Asn286**)*	2.38
		(Lys269, Val282)	2.04
	Edge Proximity	*(**Gln258** ′, **Asn286** ′)*	3.39
		(Lys269, Val282)	2.91
		*(**Gln258**, **Asn286**)*	2.13
		*(Thr262 ′, **Leu284** ′)*	1.61
		(**Leu284** ′, **Phe298** ′)	1.03
Dark	Closeness	*(Pro204, Leu212 ′)*	4.93
		*(**Ile270** ′, **Ile274** ′)*	2.27
		(Cys283 ′, Gln332 ′)	1.14
	Betweenness	*(Pro204, Leu212 ′)*	5.69
		*(**Ile270** ′, **Ile274** ′)*	1.20
	Edge Betweenness	*(Pro204, Leu212 ′)*	5.59
		*(**Ile270** ′, **Ile274** ′)*	1.19
		(Val209, **Val314** ′)	1.15
	Edge Proximity	*(Pro204, Leu212 ′)*	5.59
		*(**Ile270** ′, **Ile274** ′)*	1.17
		(Cys283 ′, Gln332 ′)	1.03



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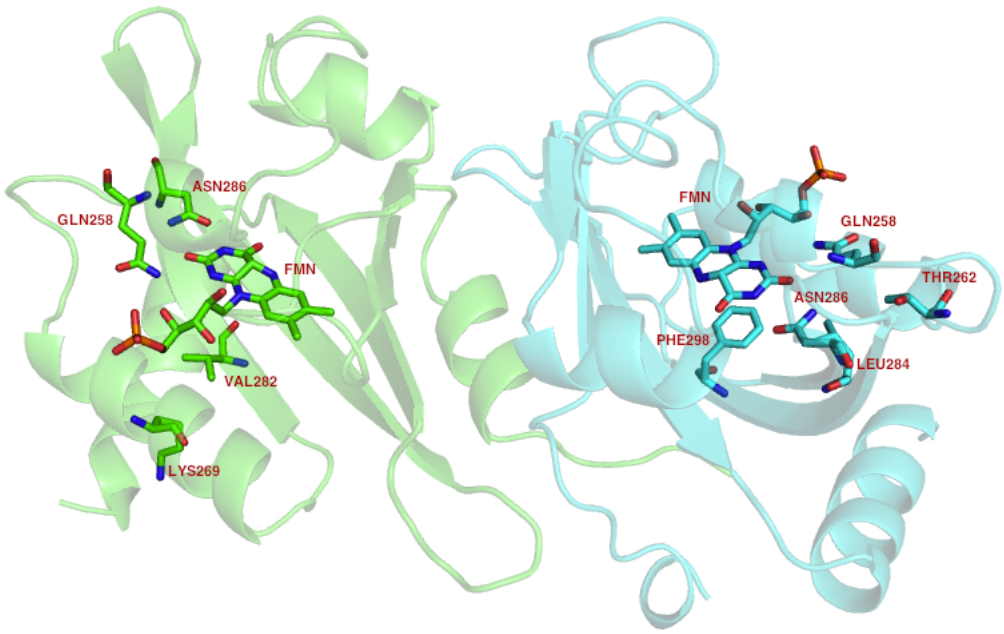


(b)

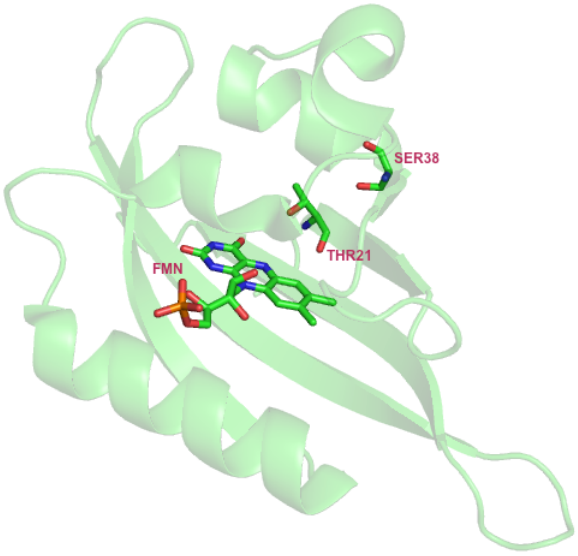
Supplementary Figure S 9: Distribution of functionally important residues in Aureo1 LOV (dimer) before and after illumination. (a) Dark crystal structure (pdb - 3ue6). (b) Light crystal structure (pdb - 3ulf)

Supplementary Table S 7: **Interacting residues obtained by using network metrics.** Functional importance of residues in **bold** are already known in literature. Edges mentioned in *italics* demonstrate significant impact on more than one network metric, when they are removed from the network.

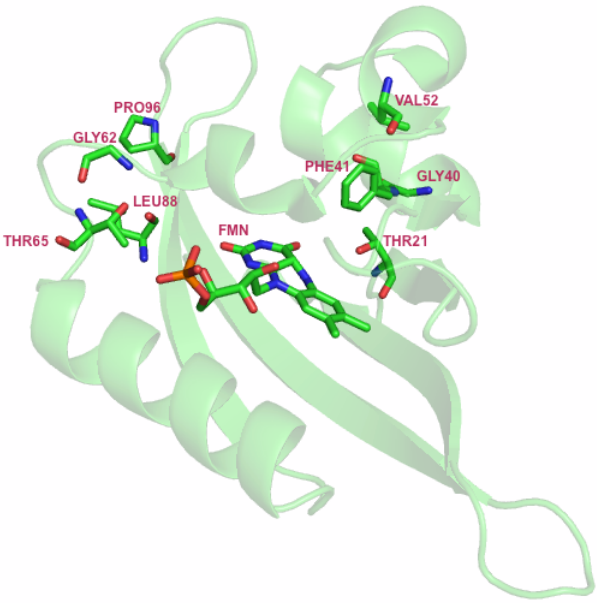
Cr LOV			
State	Network metric	key interactions	$\mathcal{Z}_k$
Light	Closeness	*(Thr21, Gly40)*	2.97
	Betweenness	*(Pro96, Leu88)*	2.18
		(Gly62, Thr65)	2.04
	Edge Betweenness	*(Pro96, Leu88)*	2.04
		(Gly62, Thr65)	1.94
	Edge Proximity	(Phe41, Val52)	1.61
		(Thr21, Gly40)	1.49
Dark	Closeness	*(Thr21, Ser38)*	3.86
	Betweenness	*(Thr21, Ser38)*	3.95
	Edge Betweenness	*(Thr21, Ser38)*	3.96
	Edge Proximity	*(Thr21, Ser38)*	3.90

Supplementary Table S 8: **Interacting residues obtained by using network metrics.** Functional importance of residues in **bold** are already known in literature. Edges mentioned in *italics* demonstrate significant impact on more than one network metric, when they are removed from the network.

Phy3 LOV			
State	Network metric	key interactions	$\mathcal{Z}_k$
Light	Closeness	*(Ala946, Phe950)*	1.38
		(Val996, **Asn1008**)	1.32
	Betweenness	*(Ala946, Phe950)*	1.22
		*(Val932, **Gln1029**)*	1.03
	Edge Betweenness	*(Val932, **Gln1029**)*	1.47
	Edge Proximity	(Val1022, **Phe1025**)	1.42
Dark	Closeness	*(**Ser930**, Ser947)*	1.66
		(Asp991, Val1014)	1.16
		(Gln1013, Ile1026)	1.10
	Betweenness	*(**Ser930**, Ser947)*	1.71
		(Gln1013, Ile1026)	1.44
		(Asp991, Val1014)	1.25
	Edge Betweenness	*(**Ser930**, Ser947)*	1.74
		(Gln1013, Ile1026)	1.42
		(Asp991, Val1014)	1.22
	Edge Proximity	*(**Ser930**, Ser947)*	1.43
		(Gln1013, Ile1026)	1.38
		(Asp991, Val1014)	1.17

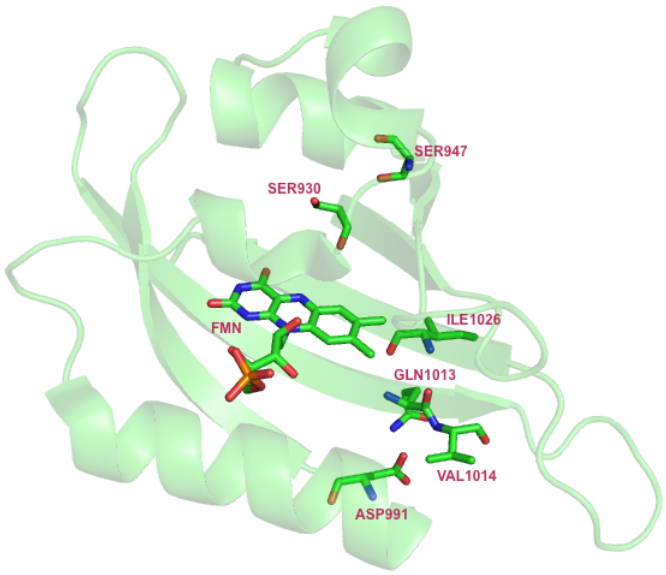


(a)

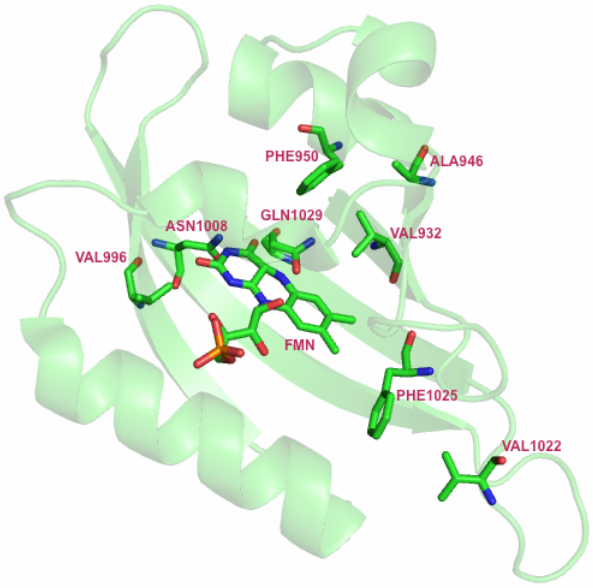


(b)

Supplementary Figure S 10: **Distribution of functionally important residues inCr LOV before and after photon absorption.** (a) Dark crystal structure (pdb - 1n9l). (b) Light crystal structure (pdb - 1n9o)

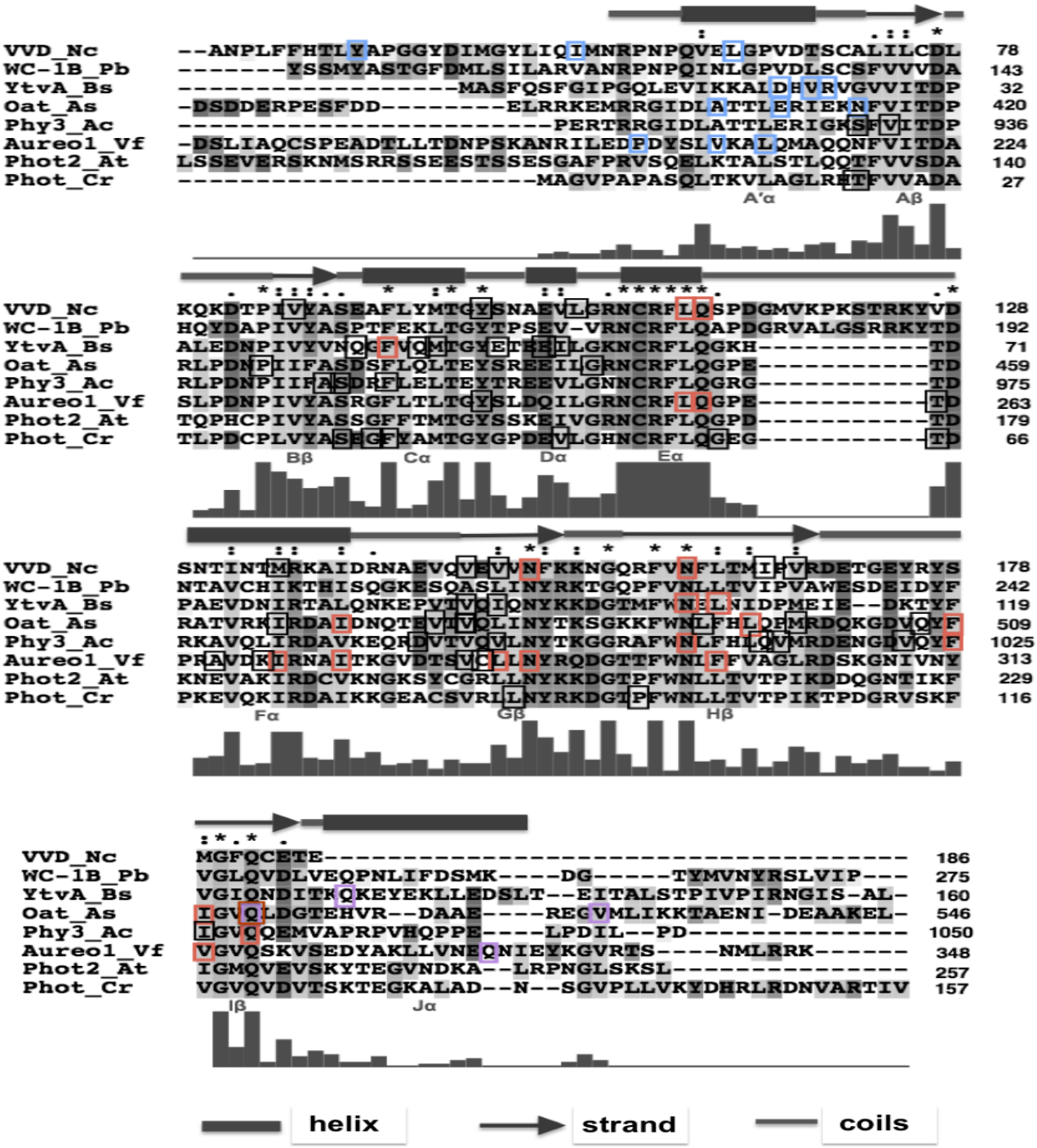


(a)



(b)

Supplementary Figure S 11: **Distribution of functionally important residues inPhy3 LOV before and after photon absorption.** (a) Dark crystal structure (pdb - 1g28). (b) Light crystal structure (pdb - 1jnu)



Supplementary Figure S 12: **Structure sequence alignment of LOV photosensors.** The key-residues are marked by rectangles. Color code: blue − surrounding A'_α signaling helix, purple − J_α signaling helix, red − residues residing in the FMN/FAD region and black − remaining key-residues.

LOV-domain	Key Interactions	
	LDN	DDN
YtvA LOV	(**Val90**$_{G_\beta}$, **L106**$^{\mathbf{FMN}}_{H_\beta}$) (**F46**$^{\mathbf{FMN}}_{C_\alpha}$, M49$_{C_\alpha}$) (E53$_{D_\alpha}$, **E56**$_{D_\alpha}$)	(**I92**$_{G_\beta}$, **N104**$^{\mathbf{FMN}}_{H_\beta}$) (**Asp21**$_{A'_\alpha}$, Q48$_{C_\alpha}$) (**V23**$_{A'_\alpha}$, **Q129**$_{J_\alpha}$) (R24$_{(A'_\alpha,A_\beta)}$, **Q44**$_{C_\alpha}$) (**F46**$^{\mathbf{FMN}}_{C_\alpha}$, I57$_{D_\alpha}$)
VVD	(**Y40**$_{\mathbf{before}A'_\alpha}$, V86$_{B_\beta}$) (**Y40**$_{\mathbf{before}A'_\alpha}$, L104$_{D_\alpha}$) (L64$_{(A'_\alpha,A_\beta)}$, I166$_{H_\beta}$)	(Y98$_{(C_\alpha,D_\alpha)}$, **L111**$^{\mathbf{FAD}}_{H_\beta}$) (**Q112**$^{\mathbf{FAD}}_{E_\alpha}$, **N151**$^{\mathbf{FAD}}_{G_\beta}$)) (**I54**$_{A'_\alpha}$, V168$_{H_\beta}$) (**M135**$_{F_\alpha}$, V147$_{G_\beta}$) (**M135**$_{F_\alpha}$, V149$_{G_\beta}$) (V149$_{G_\beta}$, **N161**$^{\mathbf{FAD}}_{H_\beta}$)
Oat LOV	(A405$_{A'_\alpha}$, **E409**$_{A'_\alpha}$) (**N414**$_{(A'_\alpha,A_\beta)}$, **Q513**$^{\mathbf{FMN}}_{I_\beta}$) (**I470**$^{\mathbf{FMN}}_{F_\alpha}$, **F509**$^{\mathbf{FMN}}_{I_\beta}$) (**V476**$_{G_\beta}$, **L496**$^{\mathbf{FMN}}_{H_\beta}$) (I466$_{F_\alpha}$, V478$_{G_\beta}$) (**L493**$_{H_\beta}$, V529$_{J_\alpha}$) (M499$_{H_\beta}$, **I510**$^{\mathbf{FMN}}_{I_\beta}$)	(P426$_{B_\beta}$, G447$_{(D_\alpha,E_\alpha)}$) (M499$_{H_\beta}$, Q507$_{I_\beta}$)
Aureo1 LOV	(K269$_{F_\alpha}$, V282$_{G_\beta}$) (**Q258**$^{\mathbf{FMN}}_{E_\alpha}$, **N286**$^{\mathbf{FMN}}_{G_\beta}$) (T262$_{E_\alpha,F_\alpha}$, **L284**$^{\mathbf{FMN}}_{G_\beta}$) (A266$_{F_\alpha}$, **L284**$^{\mathbf{FMN}}_{G_\beta}$) (Y244$_{C_\alpha,D_\alpha}$, **L257**$^{\mathbf{FMN}}_{E_\alpha}$) (**L284**$^{\mathbf{FMN}}_{G_\beta}$, **F298**$^{\mathbf{FMN}}_{H_\beta}$)	(**I270**$^{\mathbf{FMN}}_{F_\alpha}$, **I274**$^{\mathbf{FMN}}_{F_\alpha}$) (C283$_{G_\beta}$, Q332$_{J_\alpha}$ (P204$_{\mathrm{before}A'_\alpha}$, L212$_{A'_\alpha}$) (V209$_{A'_\alpha}$, **V314**$^{\mathbf{FMN}}_{I_\beta}$)
Cr LOV	(T21$_{A_\beta}$, G40$_{C_\alpha}$) (P96$_{H_\beta}$, L88$_{G_\beta}$) (G62$_{(E_\alpha,F_\alpha)}$, T65$_{F_\alpha}$) (V52$_{D_\alpha}$, F41$_{C_\alpha}$)	(T21$_{A_\beta}$, S38$_{C_\alpha}$)
Phy3 LOV	(A946$_{A_\beta}$, F950$_{C_\alpha}$) (**N1008**$^{\mathbf{FMN}}_{H_\beta}$, V996$_{G_\beta}$) (V932$_{A_\beta}$, **Q1029**$^{\mathbf{FMN}}_{I_\beta}$) (V1022$_{I_\beta}$, **F1025**$^{\mathbf{FMN}}_{I_\beta}$)	(S930$_{A_\beta}$, S947$_{C_\alpha}$) (Q1013$_{H_\beta}$, I1026$_{I_\beta}$) (Asp991$_{F_\alpha,G_\beta}$, V1014$_{H_\beta}$)

Supplementary Table S 9: **Interactions (residues) identified as functionally important by network approach.** Functional importance of the residues in **bold** are already known from experimental findings. The location of each residue is specified as subscript. Any residue that lies between sheets/helices are given within first brackets "()".