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Computational Models for Rhodopsins: from Primary Structures to Optical Properties

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Any computational model is an approximation.

All computational models have to be validated against experimental data.

Computational models have to provide insight into a problem, not only numbers.

There are several thousands unique rhodopsins with amino acid sequence available.

There are only 24 (March 2018) unique X-ray rhodopsin structures in the RCSB database.

HOW TO PREDICT A PROTEIN STRUCTUR AND HOW TO VALIDATE IT?

DECREASE OF CONFORMATIONAL SPACE FOR STRUCTURE PREDICTION

Pure *ab initio*

Homology models

Cryo-electron microscopy

→

X-ray crystallography

How to validate predicted model:

Against its X-ray structure (compare the geometries)
Against experimental optical properties.

VALIDATION OF PREDICTED MODEL AGAINST PROTEIN X-RAY STRUCTURE

To unambiguously evaluate the quality of homology models we produced models only for rhodopsins whose struture has been determined experimentally.

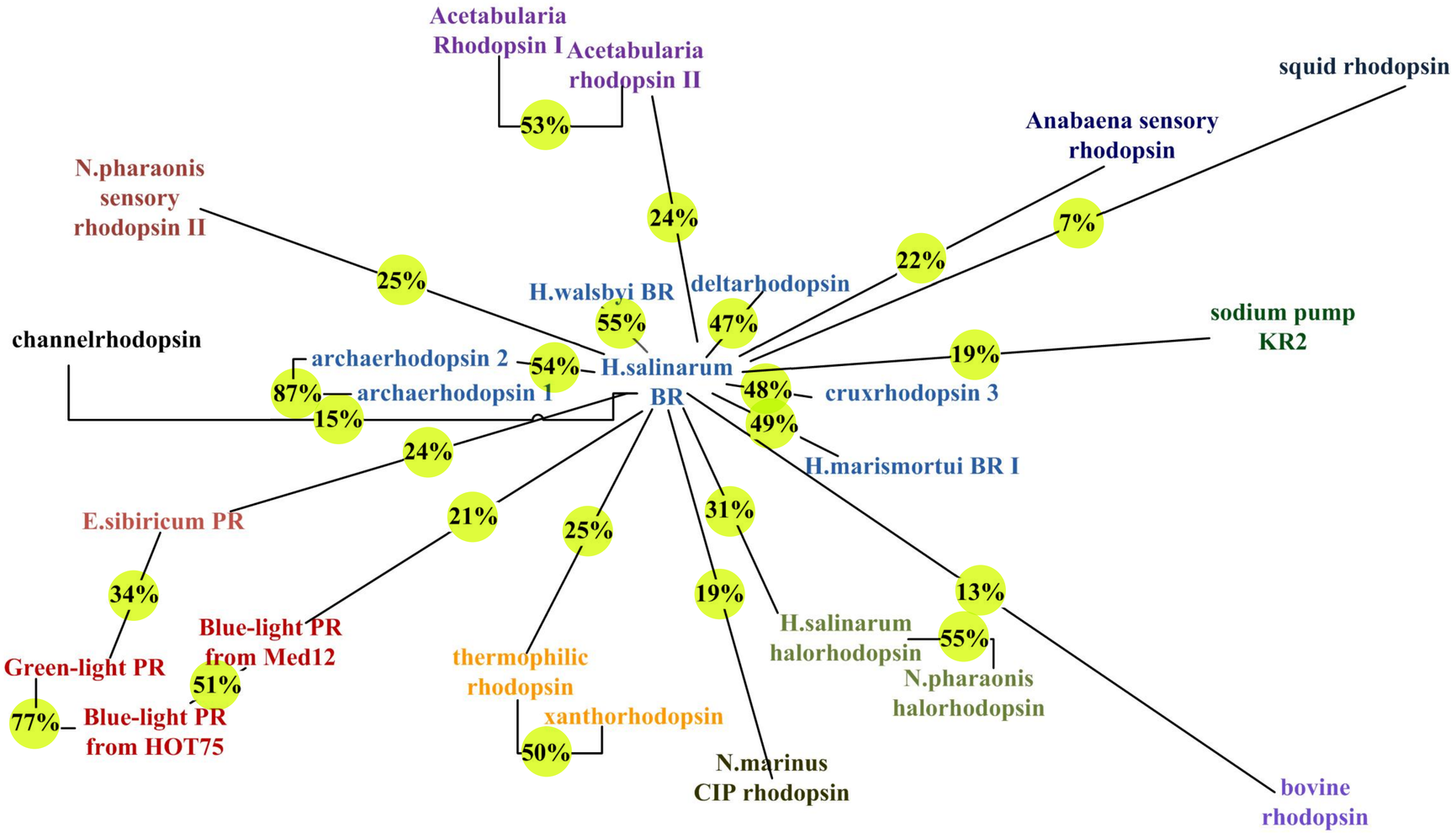
In this way, we could compare the resulting model with the corresponding experimental structure using common metrics (RMSD, GDT-HA).

In our study we formed pairs of experimental structures (A and B), and predicted structure of A using structure of B as a template and vice versa.

CLUSTERING OF RHODOPSINS WITH AVAILABLE X-RAY STRUCTURE

%

Percents denote sequence identity between proteins.

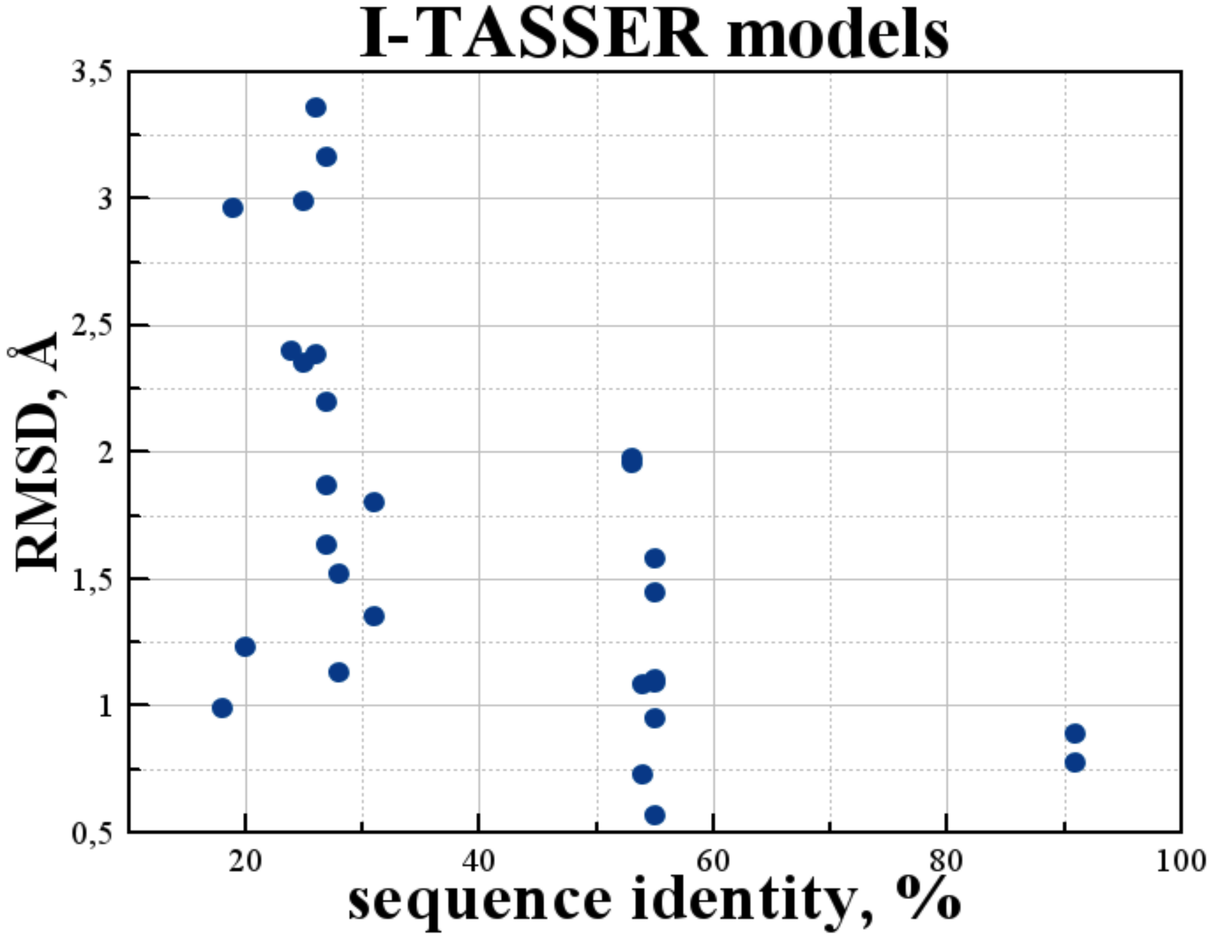


PREDICTION OF RHODOPSIN THREE-DIMENSIONAL STRUCTURES

Alignment:	***Structure building:***
MP-T	Medeller
AlignMe	I-TASSER
MUSTER	RosettaCM

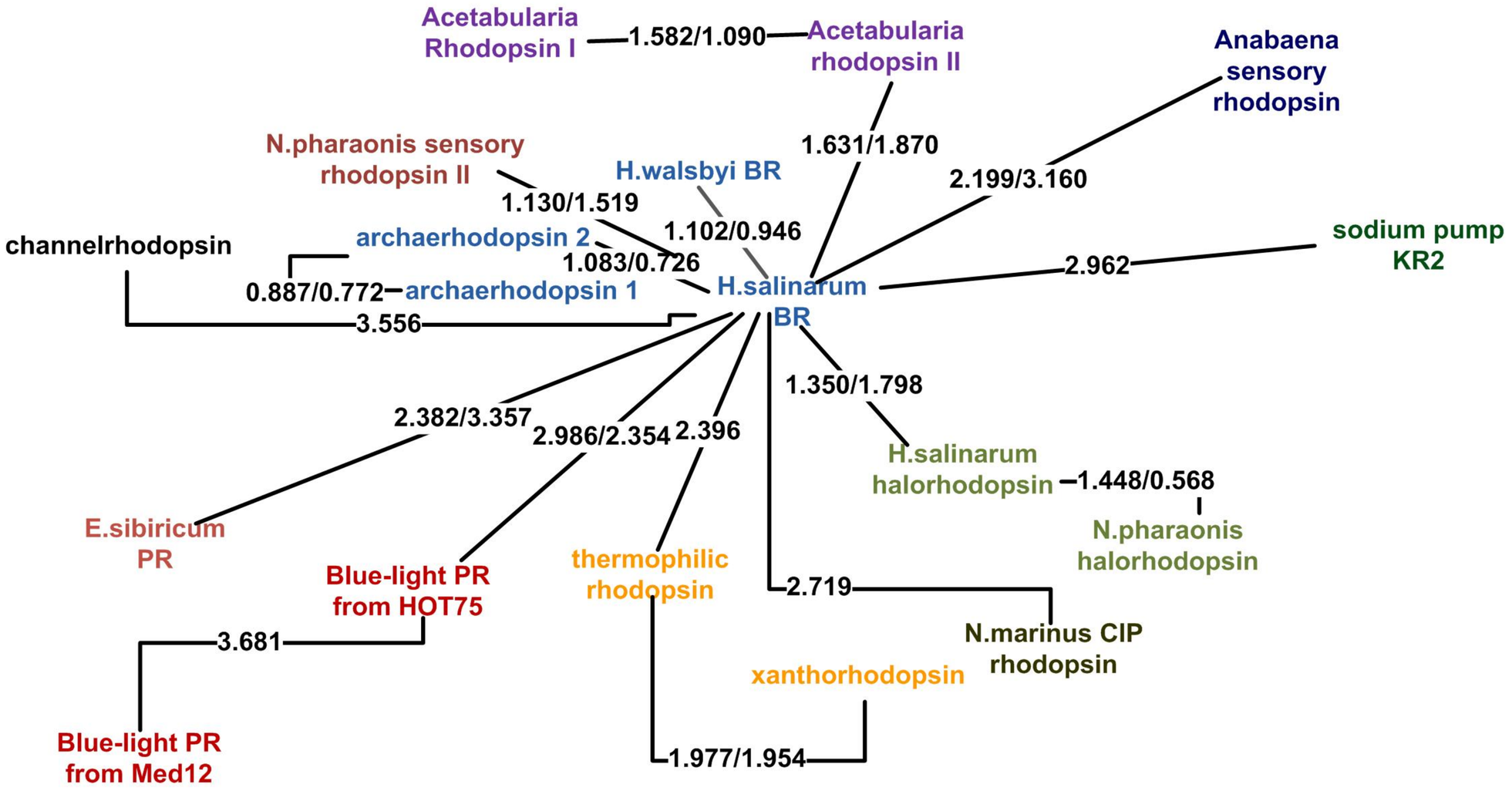
Cα-RMSD:

Root-Mean-Square Deviation of corresponding Cα atoms after structural superposition of model onto experimental structure.



36 models were produced for each methodology (alignment + structure building)

CLUSTERING BASED ON PREDICTED MODEL QUALITY



RESULTS

We obtained models with:

Average intracluster **Cα-RMSD** less than **1.5 Å**

Average overall **Cα-RMSD**: around **2 Å**

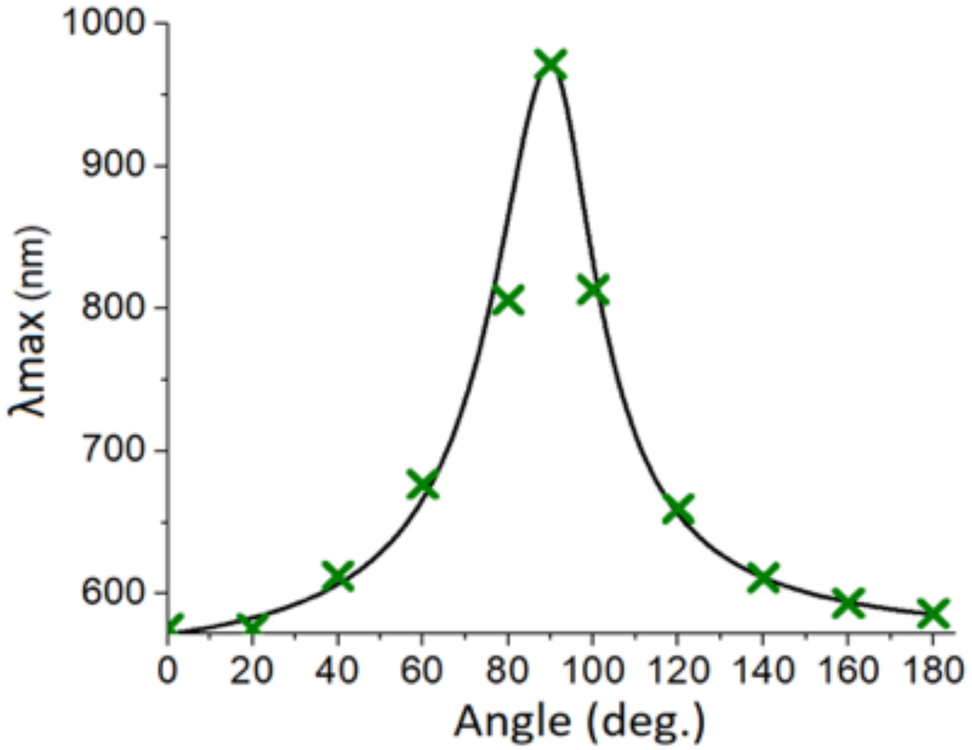
For the transmembrane part of rhodopsins average **RMSD** is less than **1 Å**

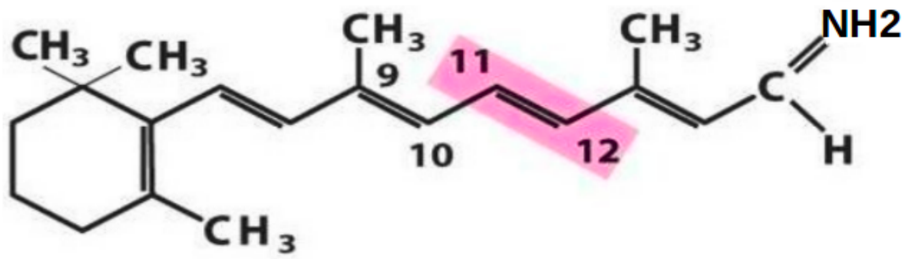
Conclusion:
with the right choice of template and methodology it is possible to predict rhodopsins with quality close to the X-ray one

Nikolaev, D.M., Shtyrov, A.A., Panov, M.S., Jamal, A., Chakchir, O.B., Kochemirovsky, V.A., Olivucci, M. and Ryazantsev, M.N., 2018. A Comparative Study of Modern Homology Modeling Algorithms for Rhodopsin Structure Prediction. ACS omega, 3(7), pp.7555-7566.

VALIDATION AGAINST SPECTRAL PROPERTIES

Influence of retinal distortion: rotation of C11=C12 bond

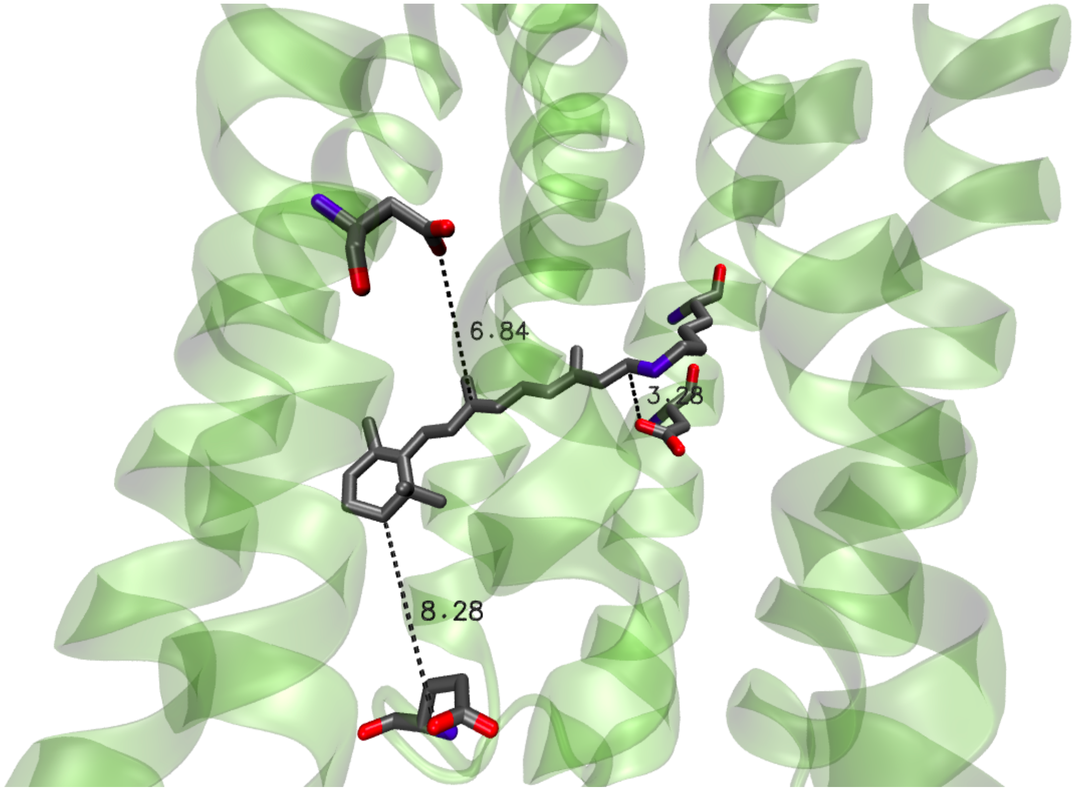


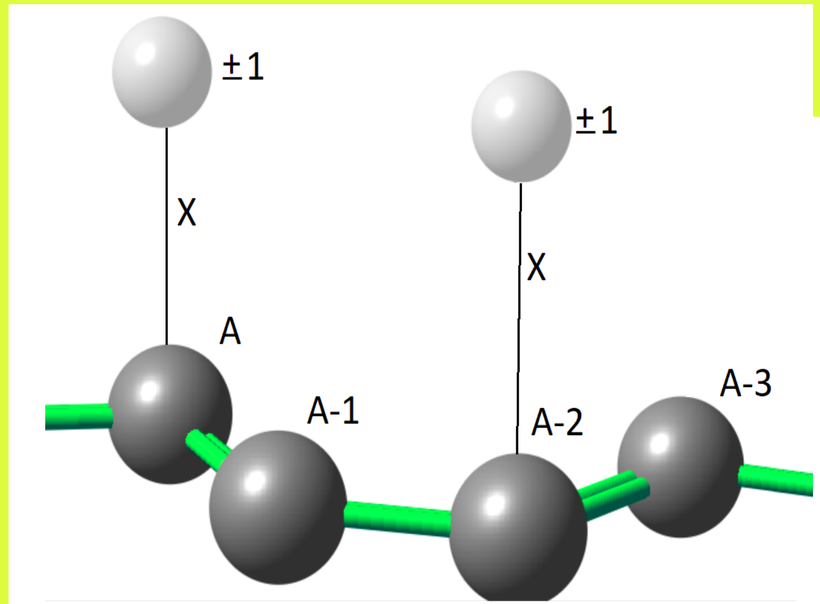


SORCI+Q/
6-31g*//B3lyp/6-31g*

VALIDATION AGAINST SPECTRAL PROPERTIES

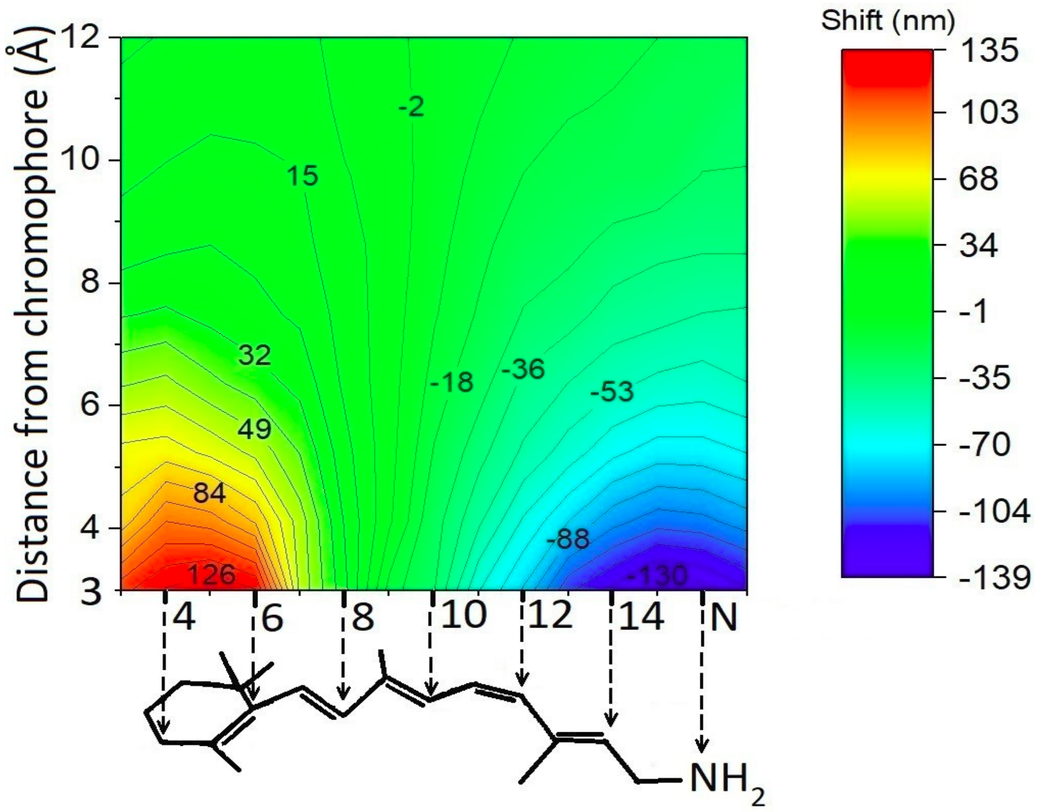
The effect of charged residues on λmax





VALIDATION AGAINST SPECTRAL PROPERTIES

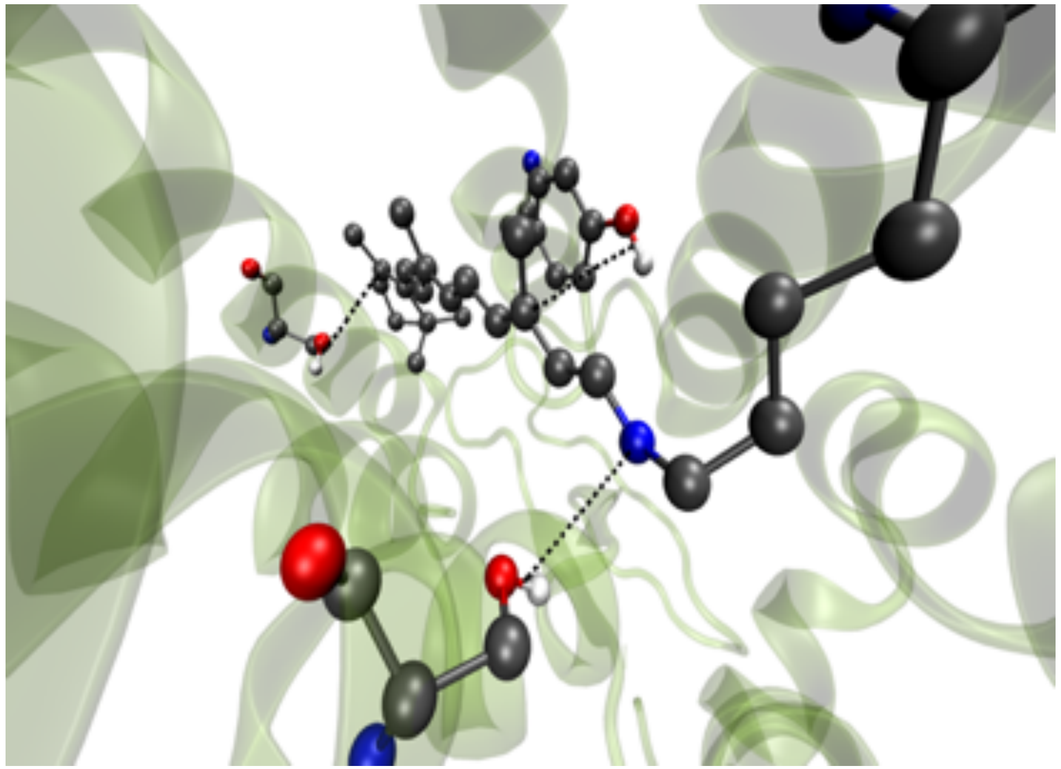
The effect of point negative charges on λmax

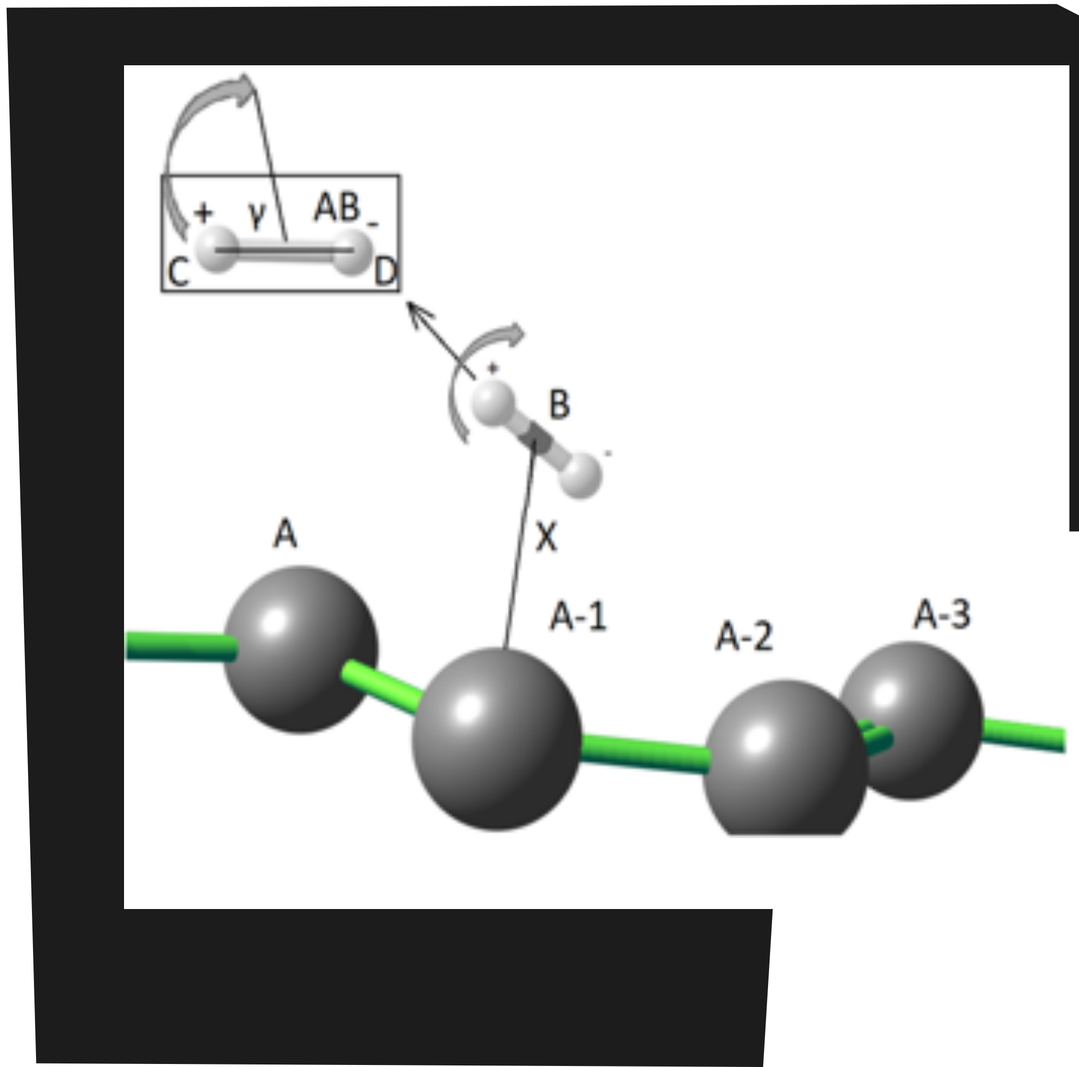


SORCI+Q/
6-31g*//B3lyp/6-31g*

VALIDATION AGAINST SPECTRAL PROPERTIES

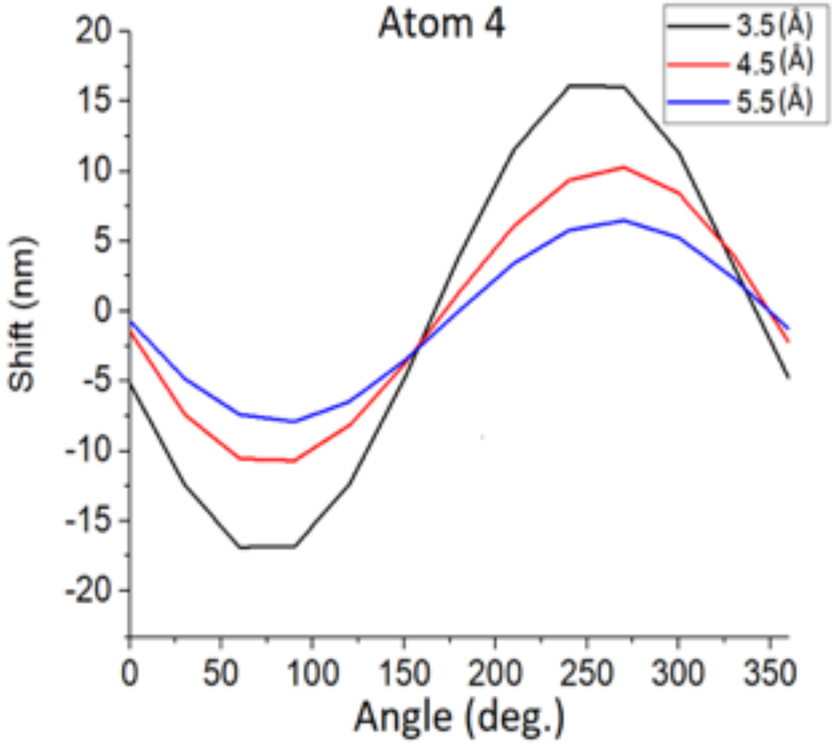
The effect of polar residues on λmax

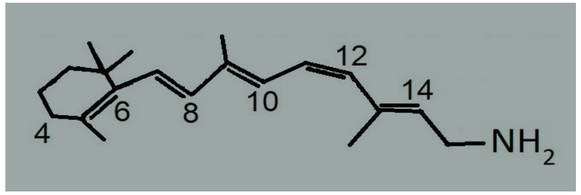


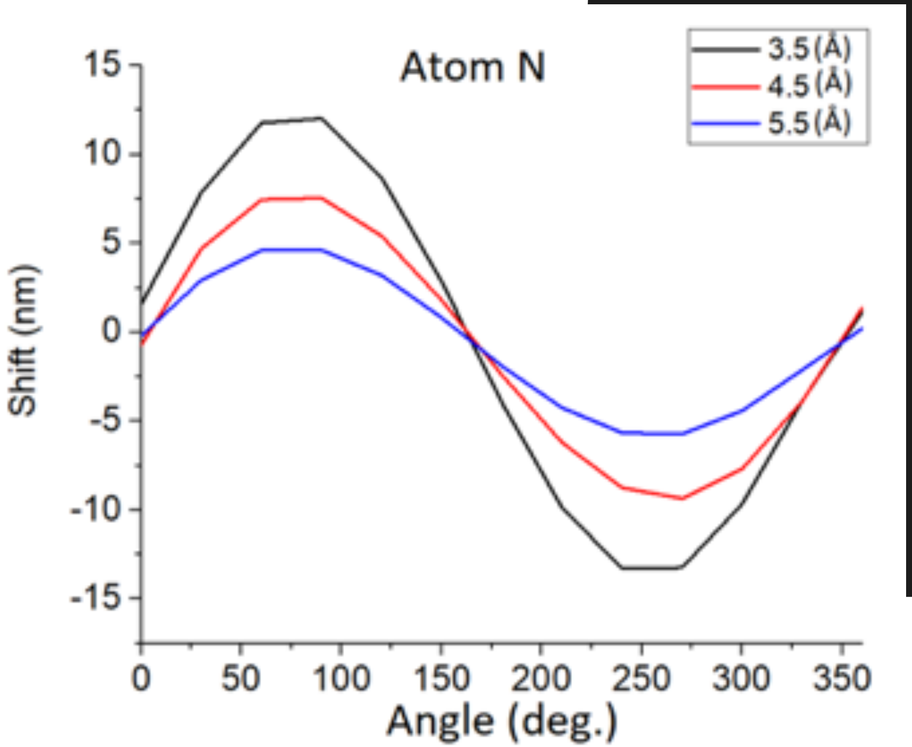


VALIDATION AGAINST SPECTRAL PROPERTIES

The effect of polar residues on λmax

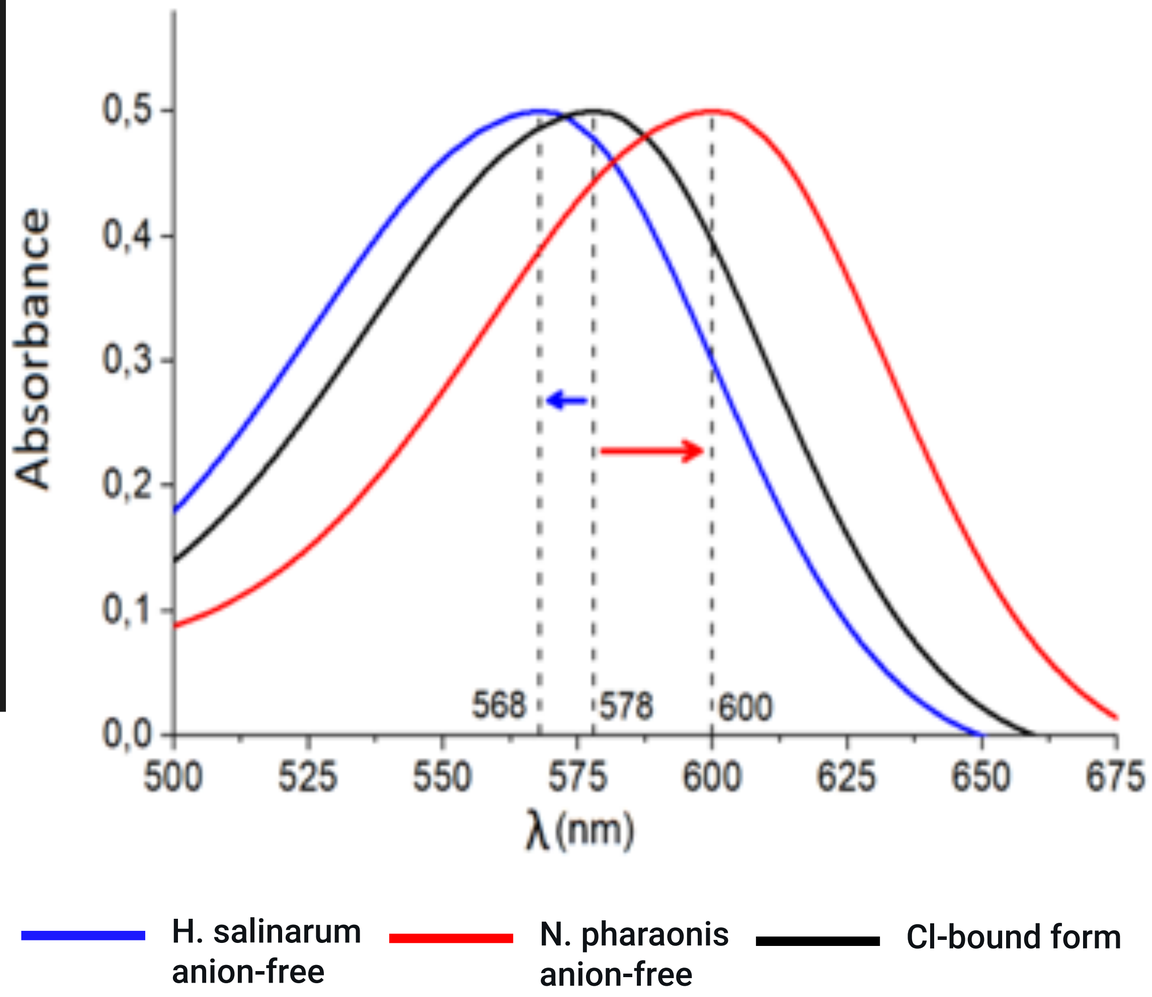






SORCI+Q/
6-31g*//B3lyp/6-31g*

CASE STUDY: CL-INDUCED SPECTRAL SHIFT IN HALORHODOPSINS



Cl-bound spectral shift: → anion free

	Calculated	Experiment
N. Pharaonis	+ 29	+ 22
H. Salinarum	- 10	- 9

Ryazantsev, M.N., Altun, A. and Morokuma, K., 2012.
Color tuning in rhodopsins: the origin of the spectral shift between the chloride-bound and anion-free forms of halorhodopsin. **JACS, 134(12).**

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