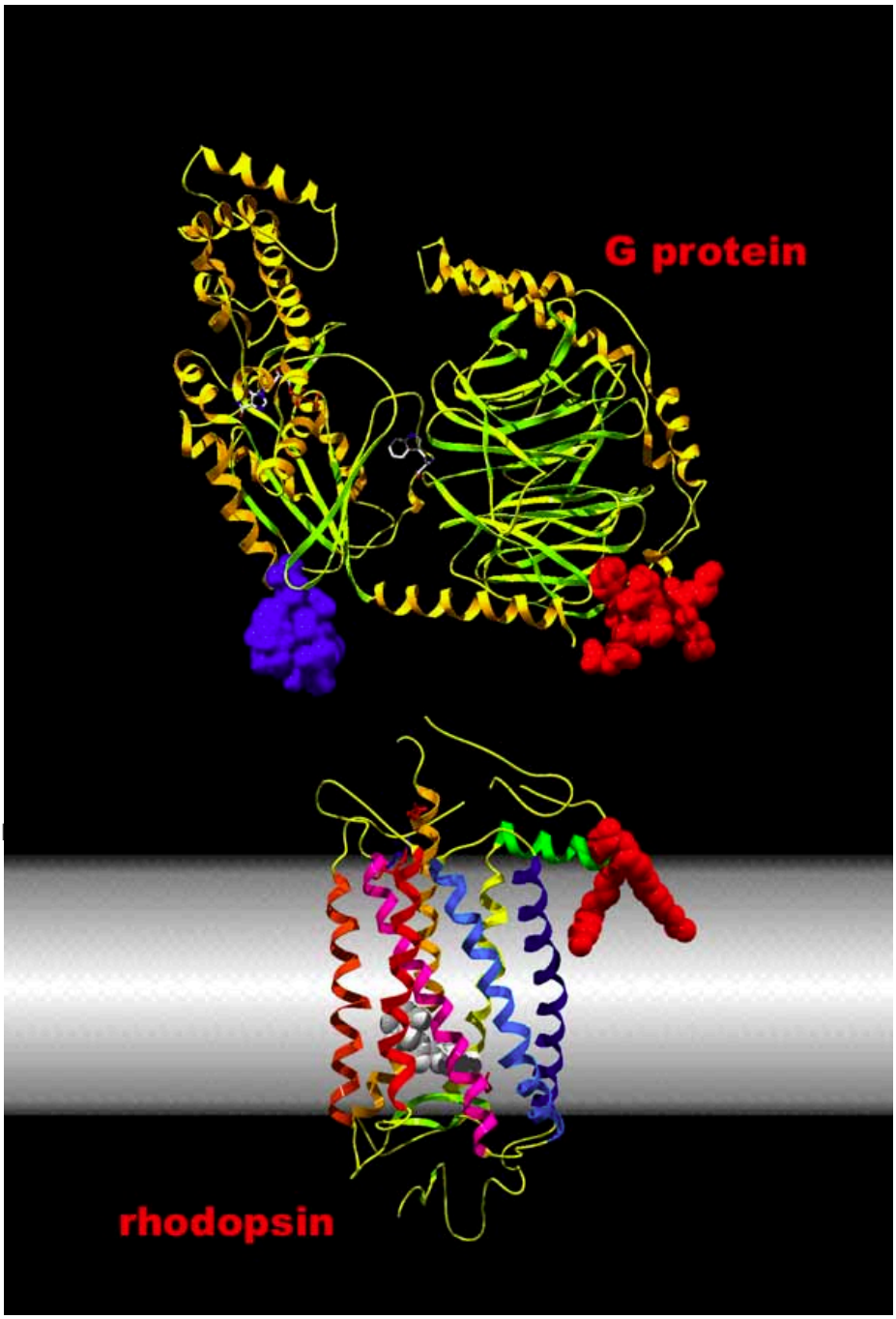
Dr. Reiner Vogel

Tel. (49) 761 203 5391
Fax.(49) 761 203 5390
reiner.vogel@biophysik.uni-freiburg.de

Biophysics Group
Institut für Molekulare Medizin und Zellforschung
Universität Freiburg
Hermann-Herder-Str. 9
79104 Freiburg

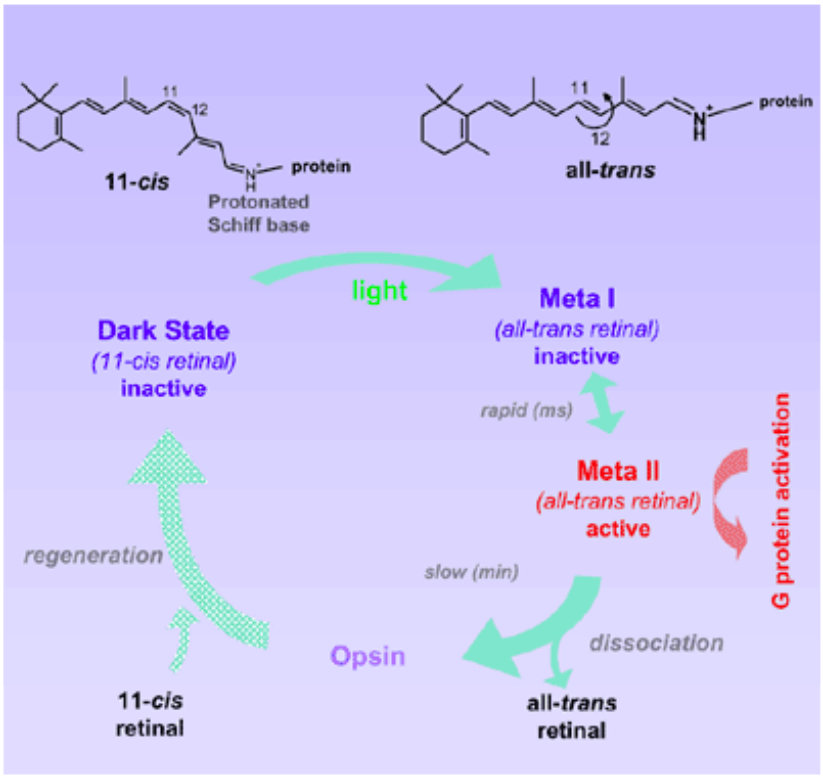
Rhodopsin as a Prototypical G Protein-Coupled Receptor

G protein-coupled receptors (GPCRs) constitute a large class of structurally related cell receptors. They detect hormones, neurotransmitters, metabolites, odorants, and, in the case of the visual pigments, light outside the cell and mediate an intracellular response by activating a G protein-coupled transduction cascade. They do not only constitute a physiologically very important class of proteins, but are also the major target of pharmaceutics.



Rhodopsin is the visual pigment for dim light vision and the probably best studied GPCR. Up to now, rhodopsin is the only receptor of this family, of which a crystal structure of the inactive state is available. Rhodopsin is a transmembrane protei consisting of 7 membrane-spanning helices, that are interconnected by extracellular and cytoplasmic loops. As a chromophore, it has covalently bound in its inactive dark state 11-*cis retinal*, which isomerizes after photon absorption to an all-*trans* geometry. This initial structural change within the chromophore binding pocket is propagated to the cytoplasmic surface of the receptor, enabling the docking and activation of

visual G protein and activation of downstream elements of the visual signal transduction cascade.



The decay of the signaling state, *Meta II,* occurs in vitro, in the absence of regulatory proteins, by hydrolysis of the retinal-protein linkage and dissociation of the receptor to retinal and the apoprotein *opsin*. Opsin is then supplied by the visual cycle with regenerated 11-*cis* retinal to restore the "dark pigment".

My research interest focuses on the properties of rhodopsin as a GPCR on a molecular level, particularly on the steps leading to its activation, on the characterization of its active state(s), and on the eventual decay of these signaling states.

As principal methods I use Fourier-transform infrared difference spectroscopy, both in transmission and ATR (attenuated total reflection) mode, which is capable of detecting changes arising from single residues within the protein, as well as UV-visible spectroscopy, both combined with biochemical methods. Further a fluorescence assay is used to monitor activation of the G protein transducin by active receptor conformations of rhodopsin or rhodopsin analogs.

Presently, two PhD students, Steffen Lüdeke and Daniel Winter, contribute to this work on rhodopsin. Furthermore, I have fruitful collaborations with other groups.

With *Mudi Sheves* and his organic chemistry group at the Weizmann Institute of Science in Rehovot, Israel, we are investigating chromophore-protein interactions. Our main goal is to understand how chromophore isomerizations change the conformation of the protein. This is supported by *Paul Tavan* and his Biomolecular Optics group at the LMU München, who are able e.g. to calculate vibrational frequencies of chromophore isomers by quantum chemical methods.

We are further studying structure and function of rhodopsin by using rhodopsin mutants, which is done in collaboration with *Thomas P. Sakmar* and his molecular biology group at the Rockefeller University in New York.

Finally, we are working together with *Gebhard Schertler* and his structural biology group at the MRC in Cambridge, UK, who are studying rhodopsin by electron and X-ray crystallography to obtain crystal structures of the dark state of rhodopsin as well as of its photoproduct states.

The computer screen shows a picture of the total eclipse of the sun of August 11,1999, which was observable not far from Freiburg

Recent Research Projects

- **Metarhodopsin III - The unbelievable truth**
  Thermal isomerization of the chromophore's C=N double bond leads to deactivation of the receptor

- **An unbleachable and photocycling visual pigment**
  Activation and relaxation behavior of 11-cis-locked rhodopsin

- **Membrane protein conformation and stability**
  Influence of salts on protein unfolding and conformational transitions of rhodopsin

- **Active and inactive conformations of opsin**
  Conformational equilibrium of the receptor protein in the absence of ligands

- **The protonation state of the Schiff base in the active receptor state**
  Anion binding mediates formation of an active Meta II state with protonated Schiff base

- **Influence of protein-ligand interaction on receptor activation**
  Removal of the 9-methyl group changes all-trans retinal from a full to an only partial agonist

See also:* *Rhodopsin Mutants

Publications

Rhodopsin and G Protein-Coupled Receptors

2004

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Vogel R, Siebert F, Mathias G, Tavan P, Fan GB, and Sheves M (2003) Deactivation of rhodopsin in the transition from the signaling state Meta II to Meta III involves a thermal isomerization of the retinal chromophore C=N double bond. *Biochemistry* 42: 9863-9874 *Medline* *URL*

Vogel R, Siebert F (2003) New insights from FTIR spectroscopy into molecular properties and activation mechanisms of the visual pigment rhodopsin. *Biospectroscopy* 72: 133-148 *Medline* *URL*

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Fan GB, Siebert F, Sheves M, Vogel R (2002) Rhodopsin with 11-*cis*-locked chromophore is capable of forming an active state photoproduct. *J Biol Chem* 277: 40229-40234 *Medline* *URL*

Vogel R, Fan GB, Lüdeke S, Siebert F, Sheves M (2002) A non-bleachable rhodopsin analogue with a slow photocycle. *J Biol Chem* 277: 40222-40228 *Medline* *URL*

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Siebert F, Vogel R, Fan GB, Sheves M (2001) Conformation and stability of rhodopsin photoproducts are influenced by salts: General implications of the Hofmeister effect on membrane proteins. *Biophys J* 80: 47A *abstract*

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Vogel R (1998) About the quenching of the chemiluminescence from liquid culture media by microorganisms and weak light emission patterns from bacterial cultures. PhD Thesis, University of Hohenheim, Germany *abstract* *pdf*

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Theoretical Polymer Physics

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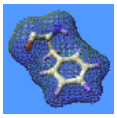
Links

SMA MeteoSchweiz

Building Telescopes

Glen Canyon Without the Lake

Die Maus

Molecular graphics on this site were generated with  Deep View and  Pov-Ray ray tracing.

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