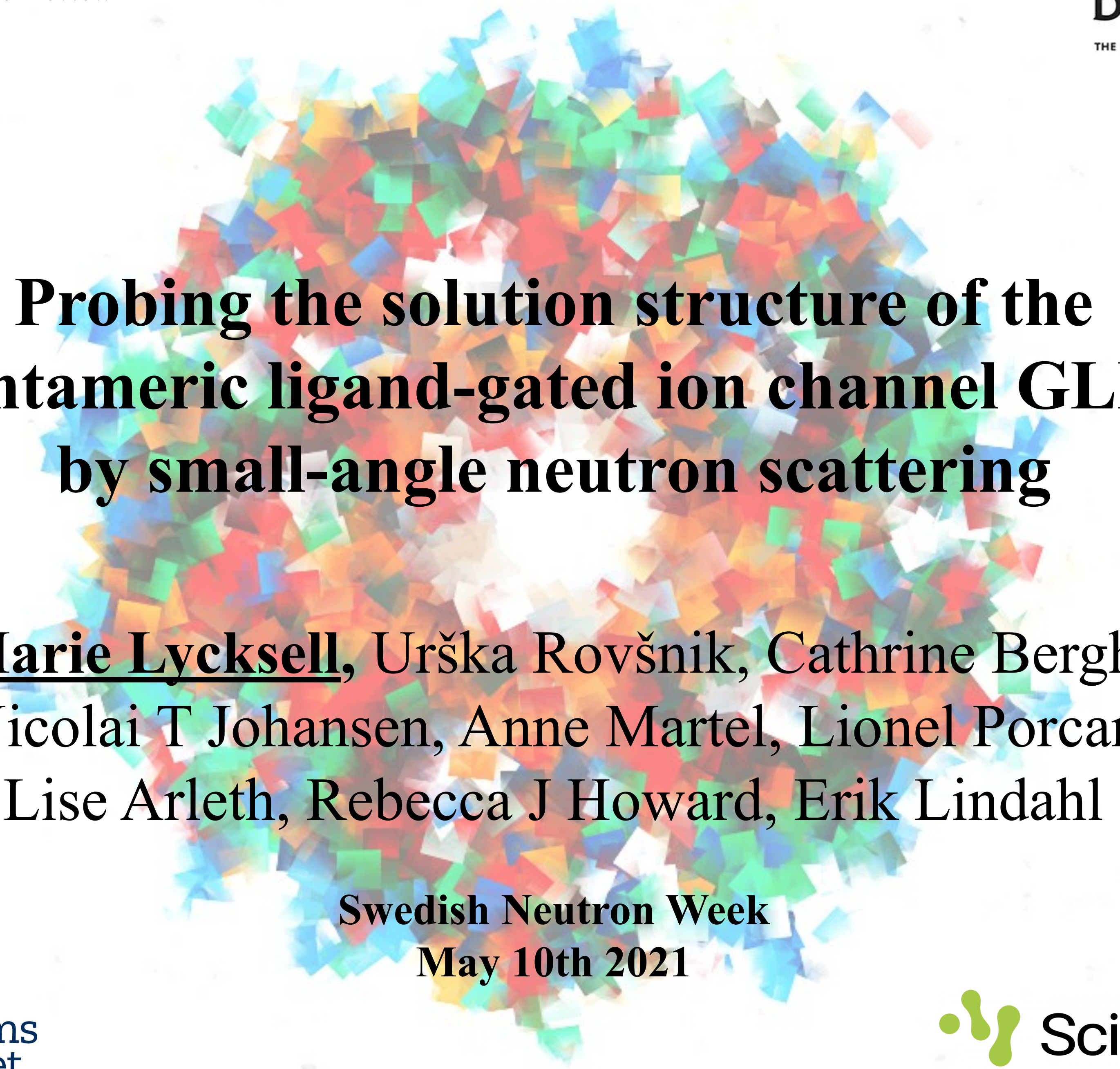
Manuscript under review

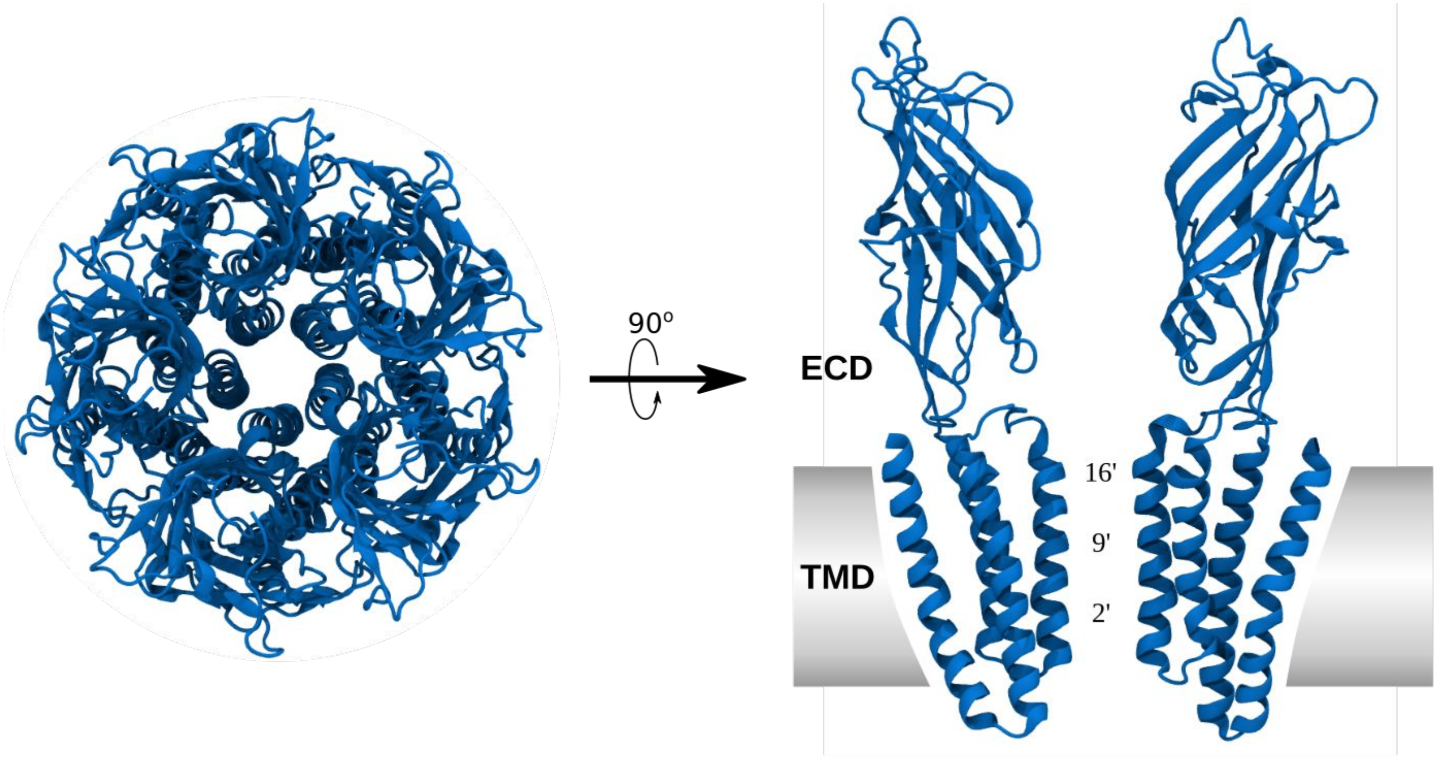


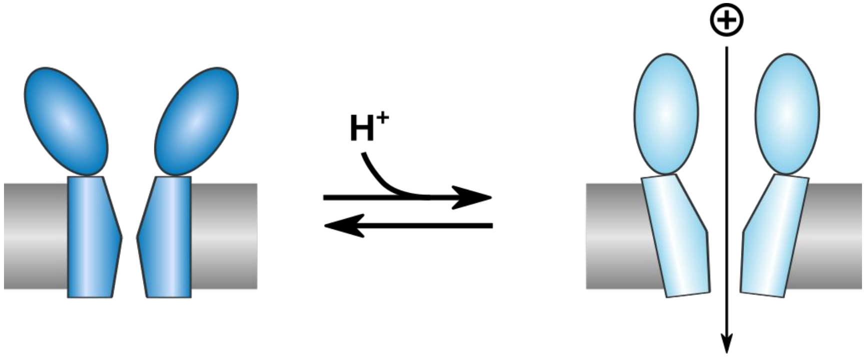
Probing the solution structure of the pentameric ligand-gated ion channel GLIC by small-angle neutron scattering

Marie Lycksell, Urška Rovšnik, Cathrine Bergh,
Nicolai T Johansen, Anne Martel, Lionel Porcar,
Lise Arleth, Rebecca J Howard, Erik Lindahl

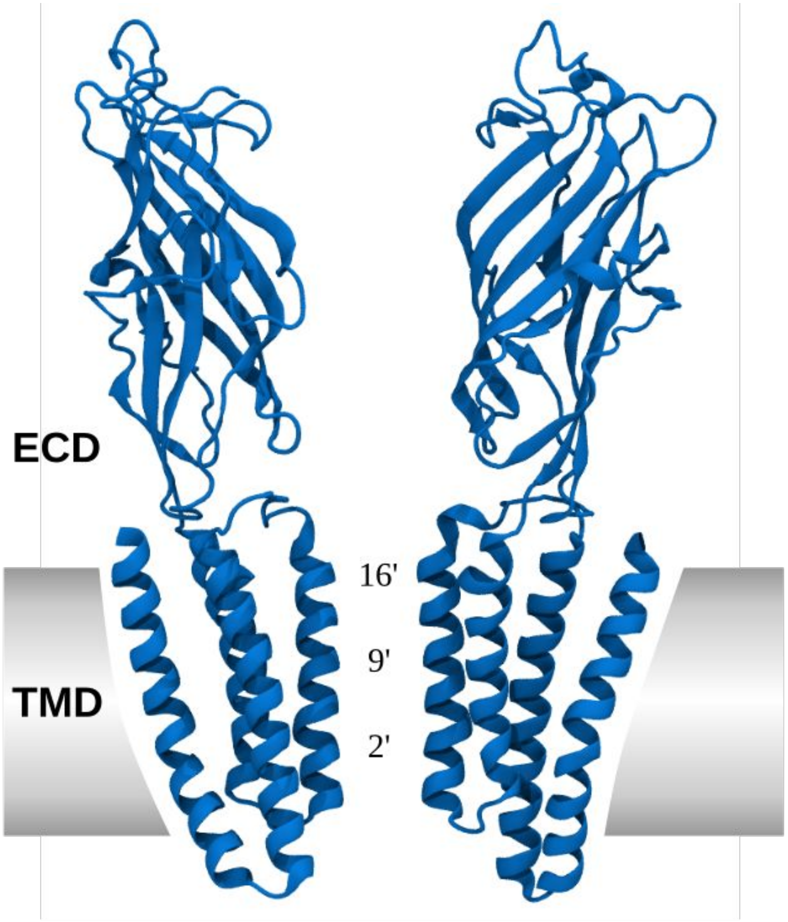
Swedish Neutron Week
May 10th 2021

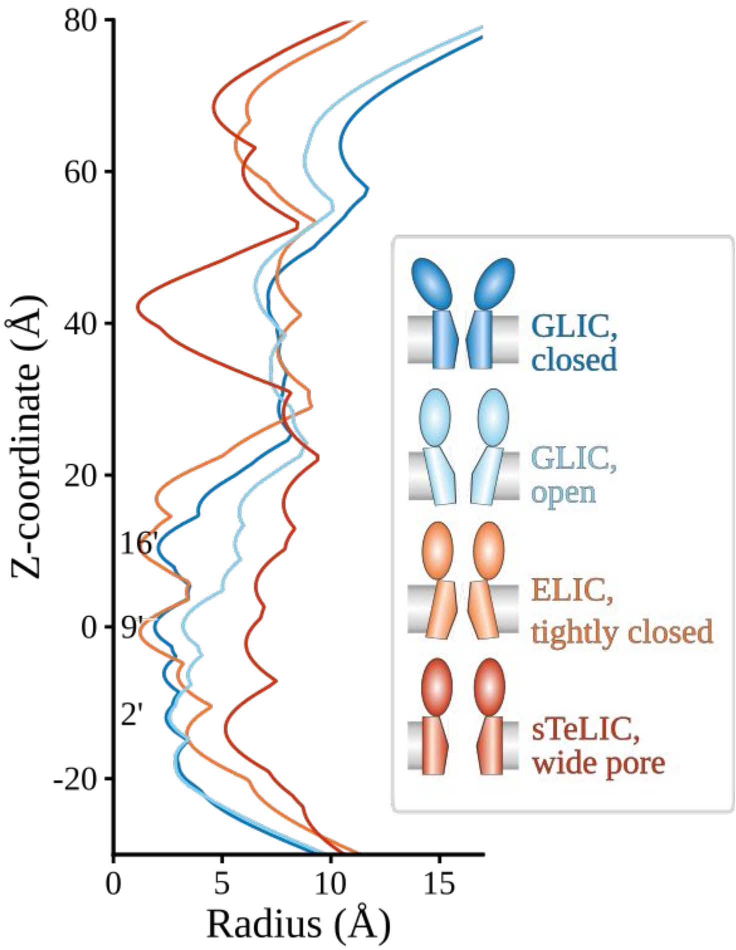
GLIC - a model system for pentameric ligand-gated ion channels



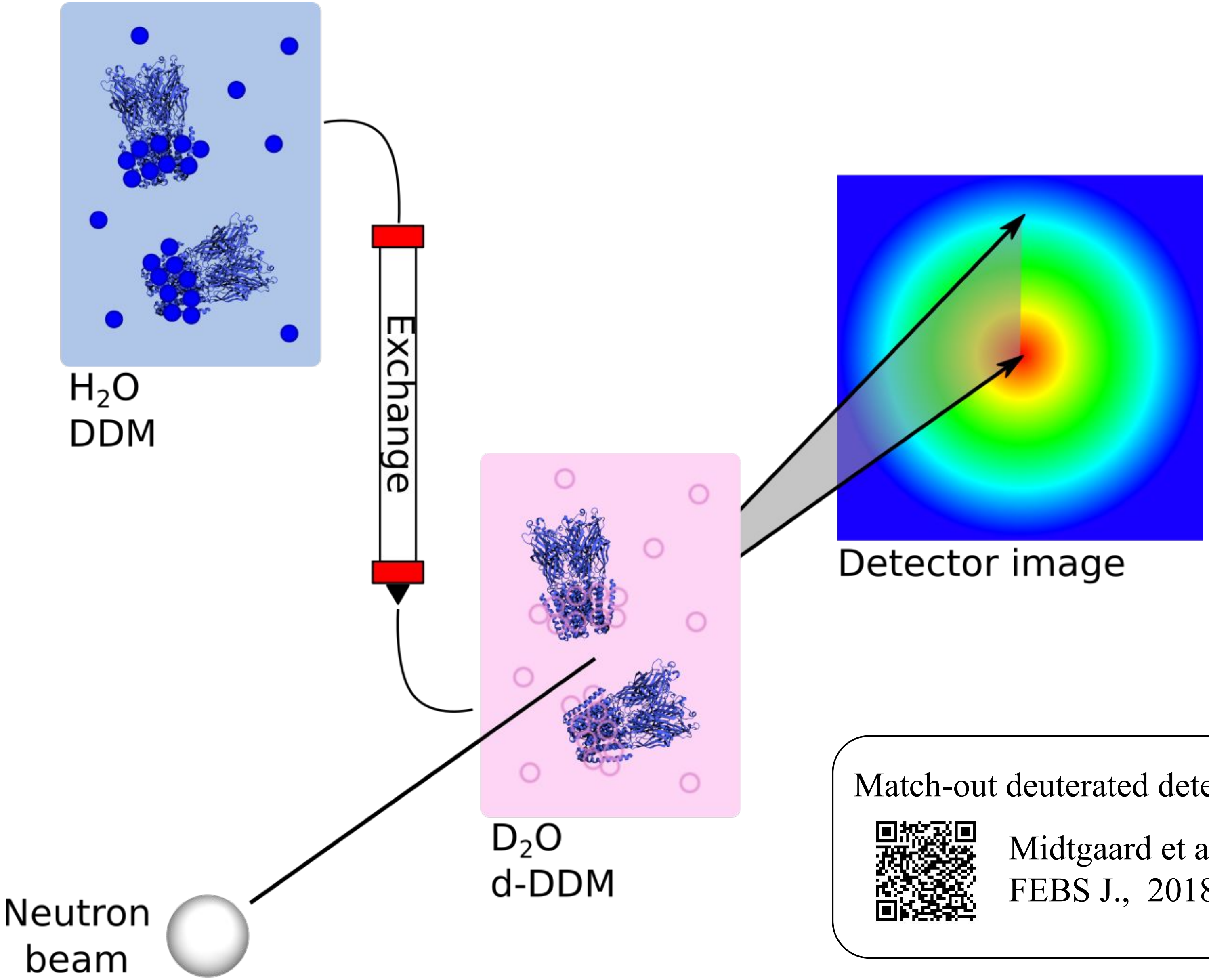


Multiple conformations are known from crystal structures





Invisible detergent & the SEC-SANS approach



H_2O
DDM

Exchange

D_2O
d-DDM

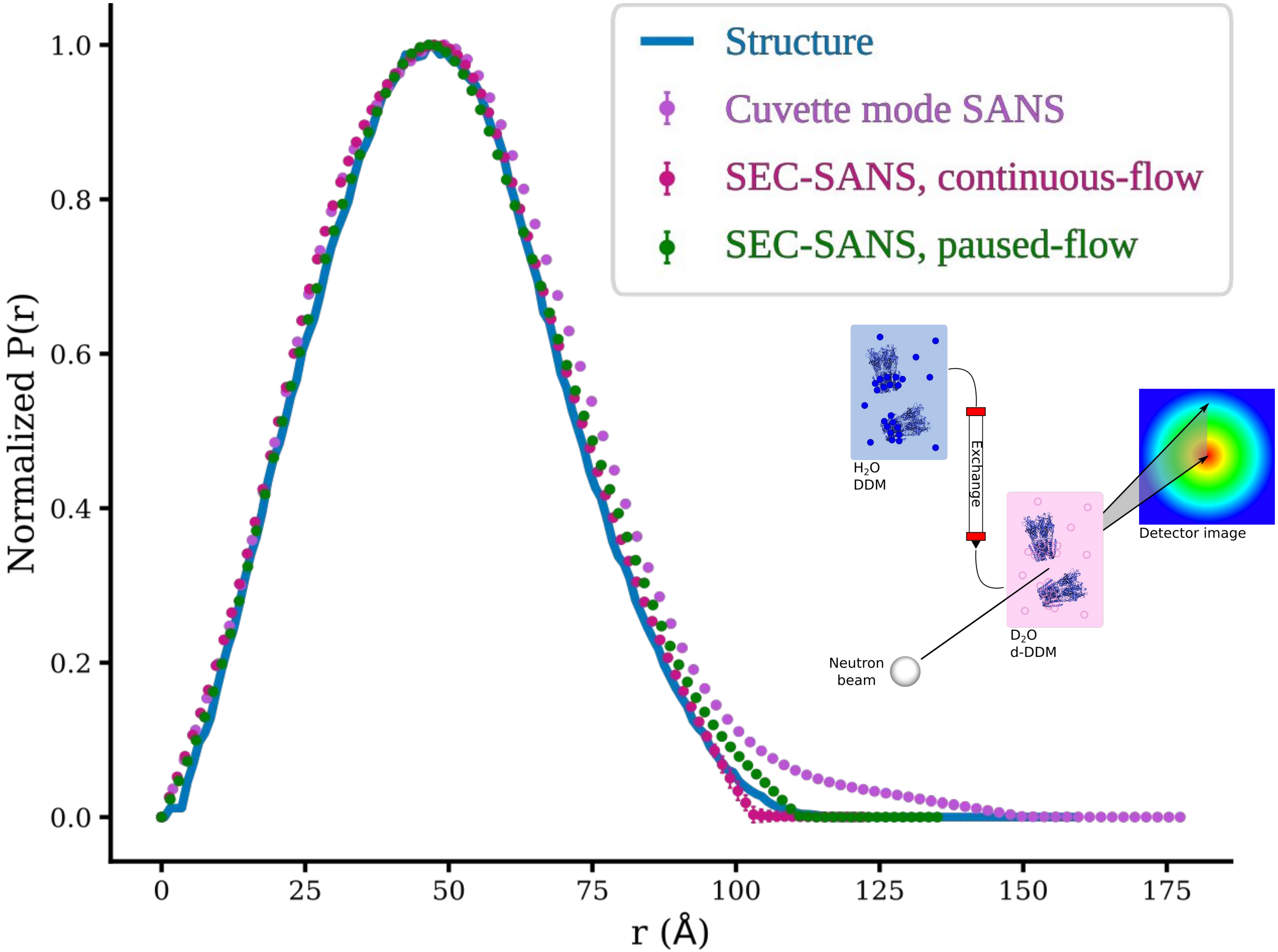
Detector image

Neutron
beam

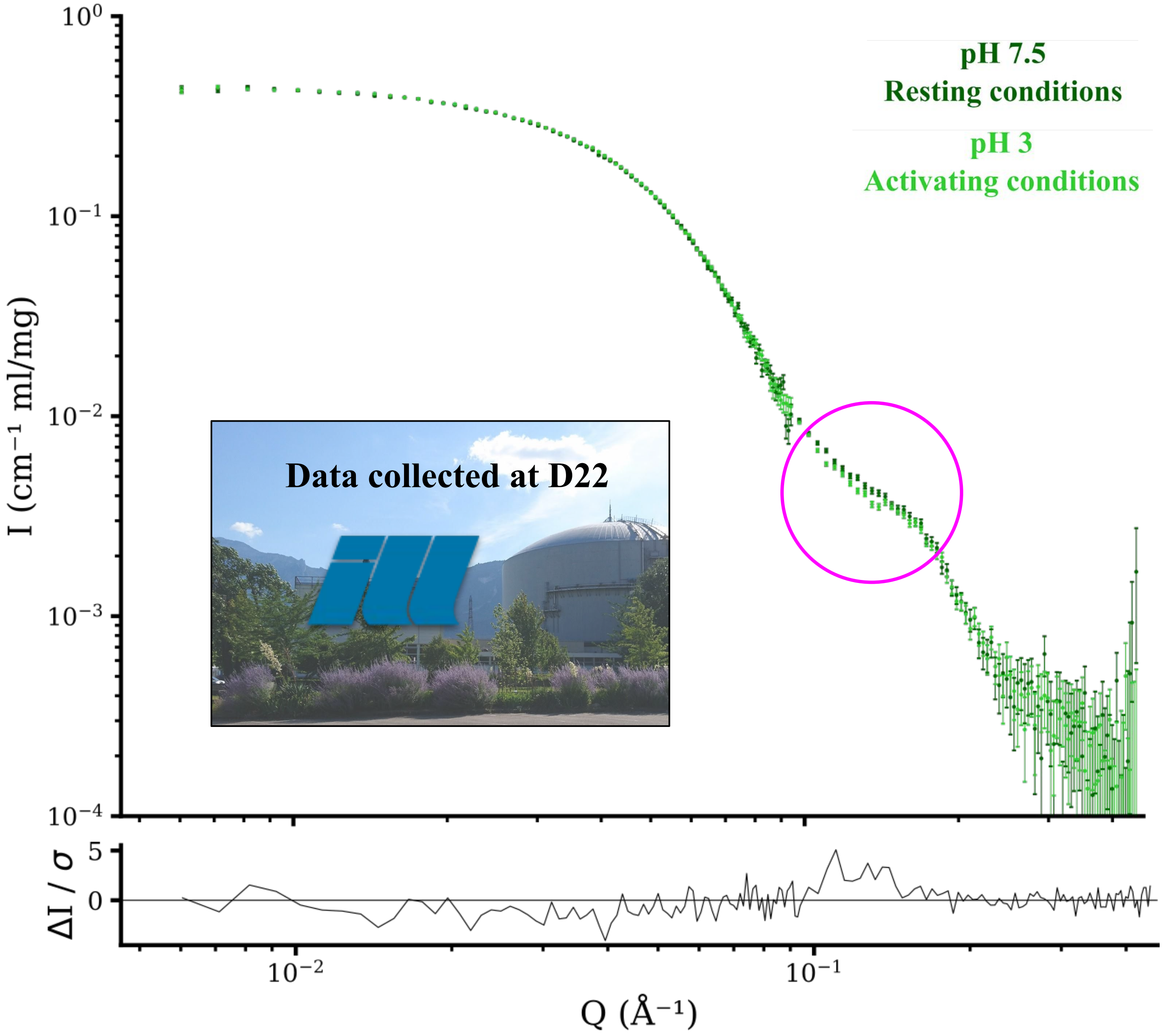
Match-out deuterated detergent:

Midtgaard et al.,
FEBS J., 2018

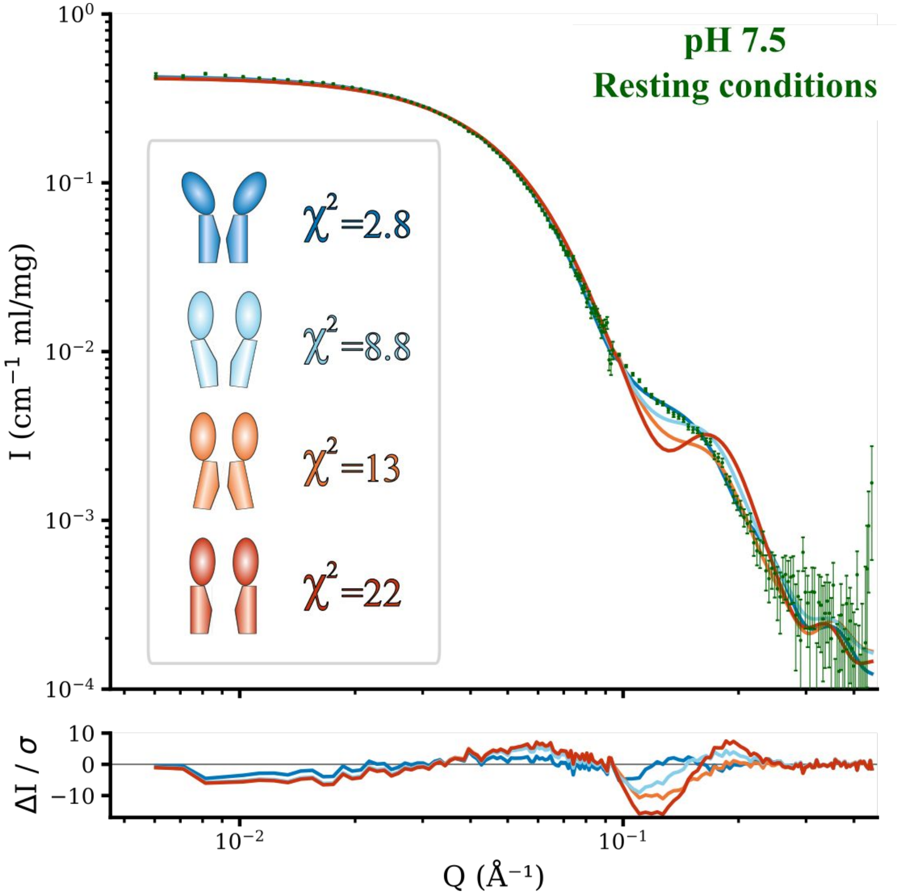
Paused-flow SEC-SANS maintains monodisperse protein

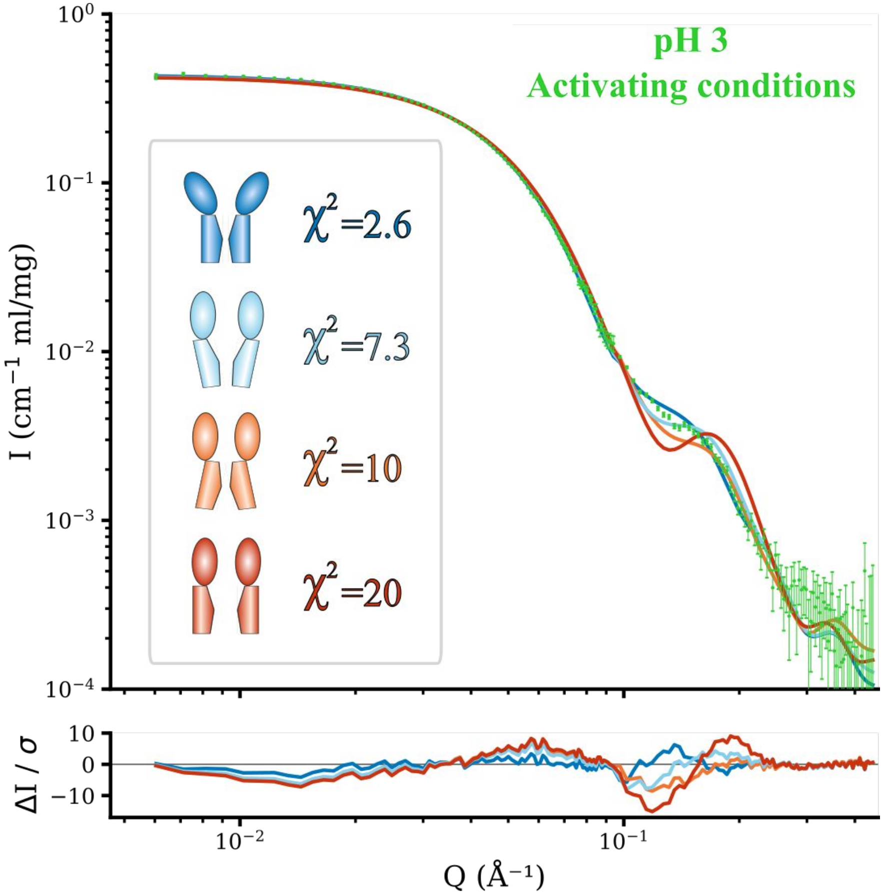


SANS data collected under resting and activating conditions



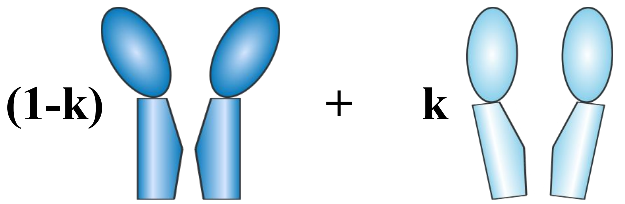
Solution scattering corresponds to the closed X-ray structure



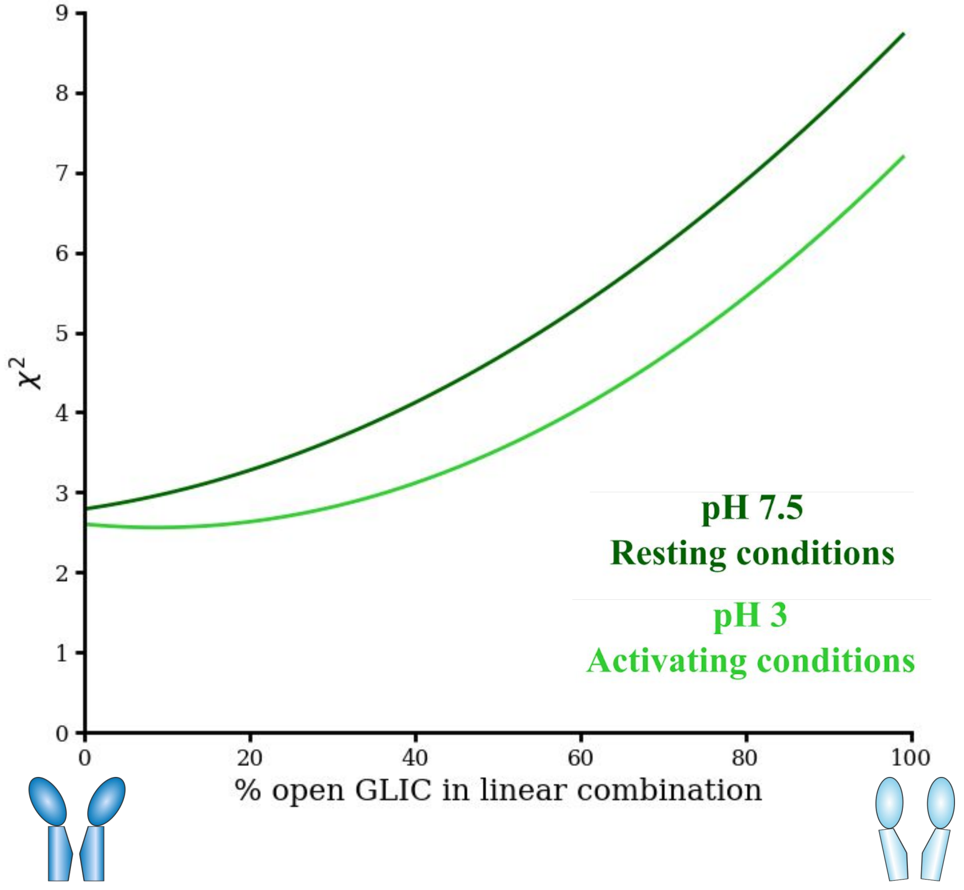


Linear combination reveals the amount of open population tolerated by the fit

Linear combination:

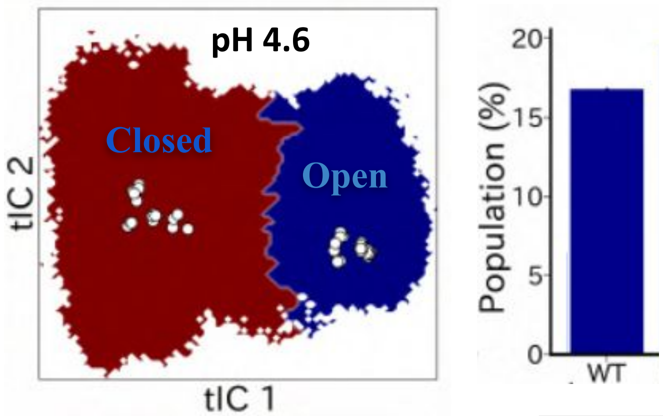


At **pH 3**, the linear combination gives as good fit as **Closed** up to **18% Open** included



In extensive MD simulations

17% Open at **pH 4.6**

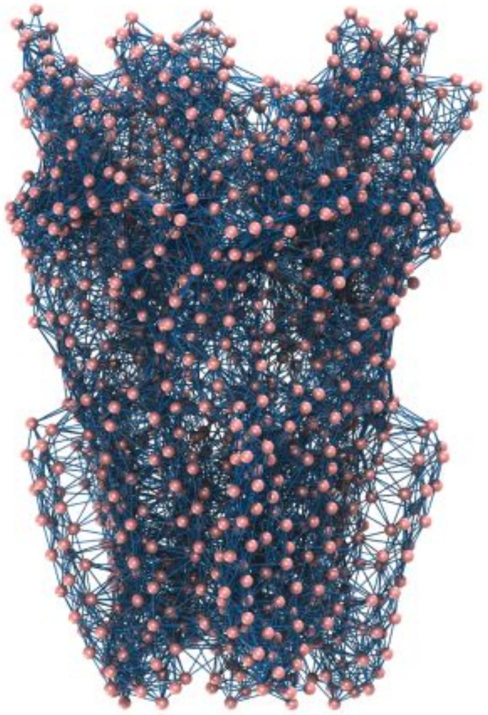


bioRxiv

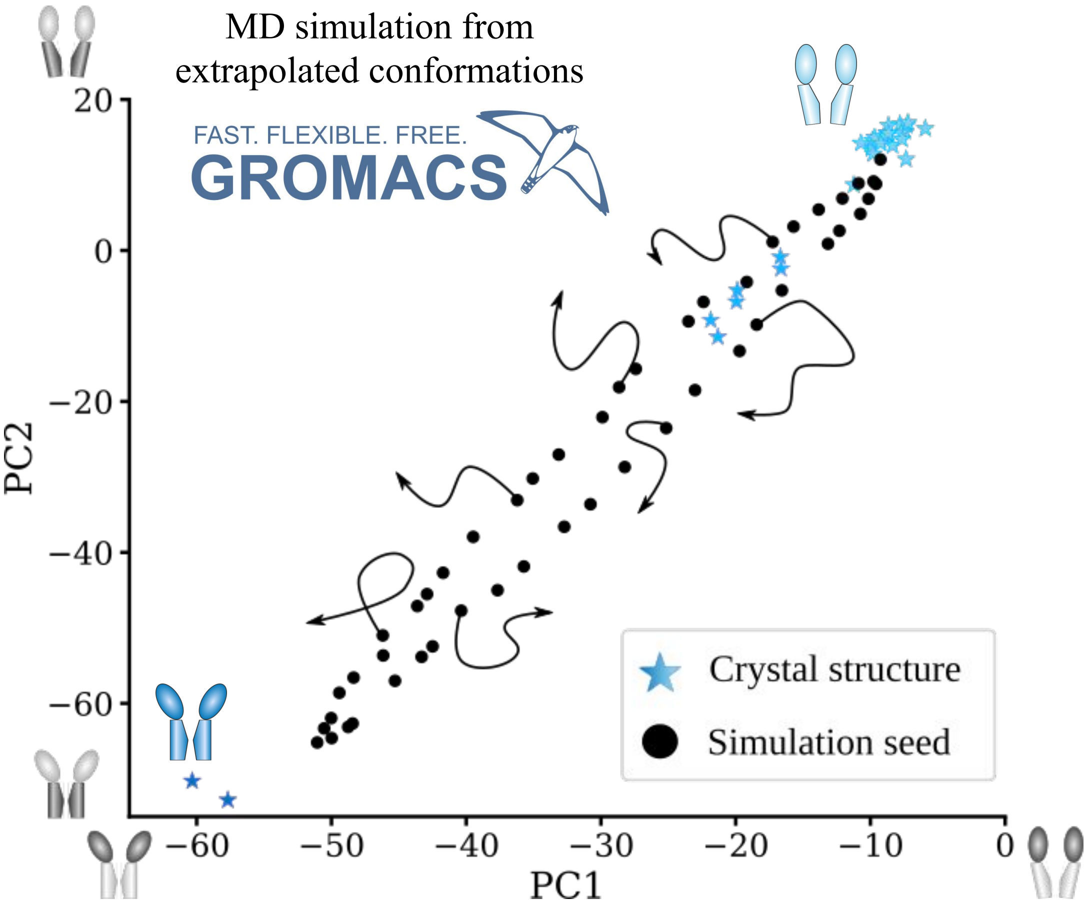
THE PREPRINT SERVER FOR BIOLOGY

Cathrine Bergh

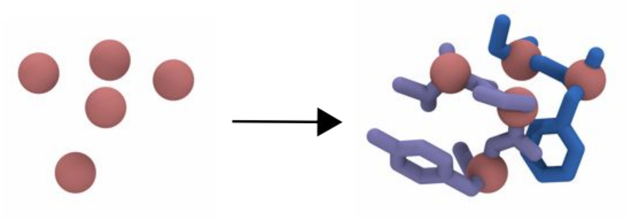
Coarse grained extrapolation & all-atom Molecular Dynamics simulations



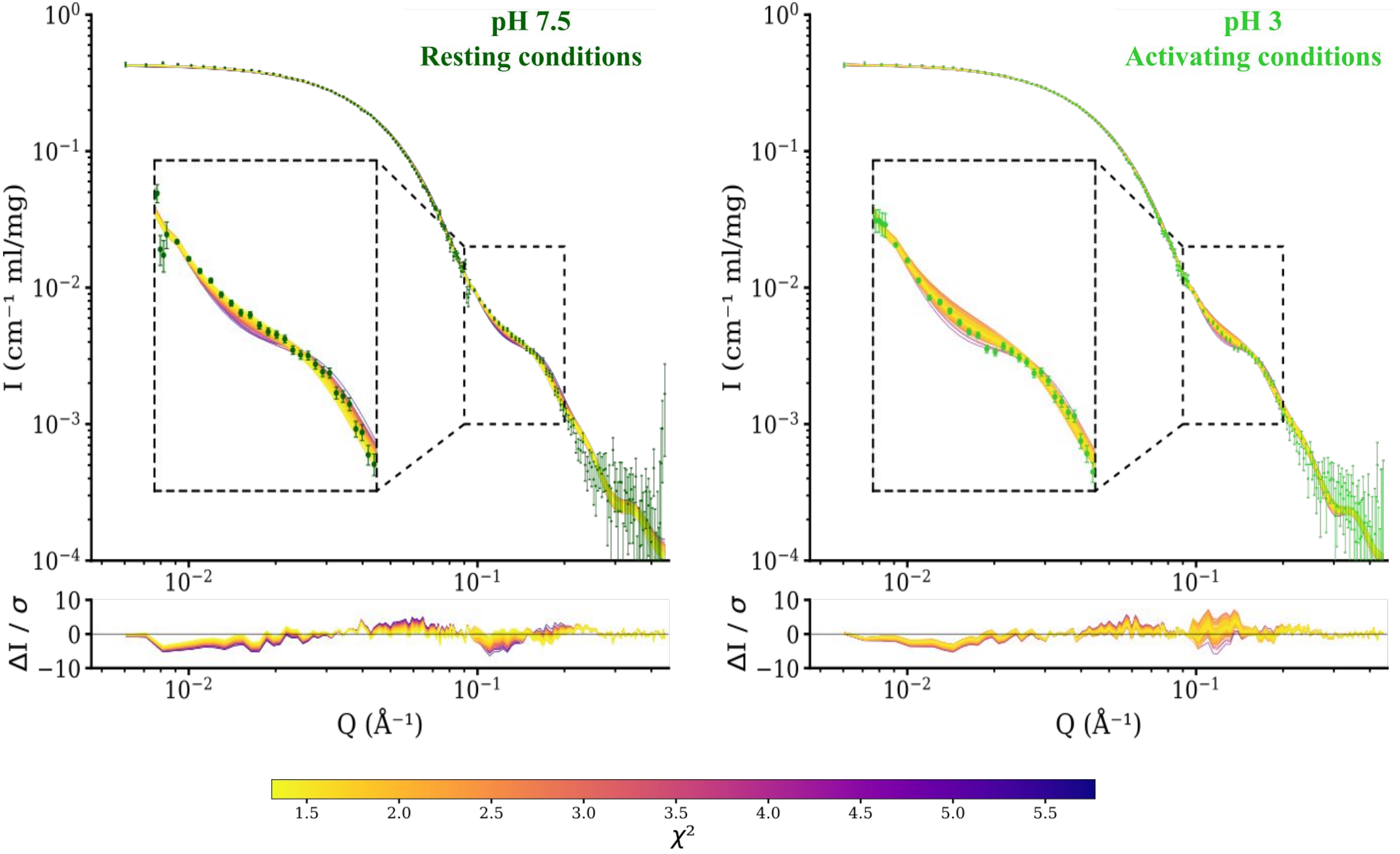
Coarse grained extrapolation using eBDIMS
https://ebdims.biophysics.se/



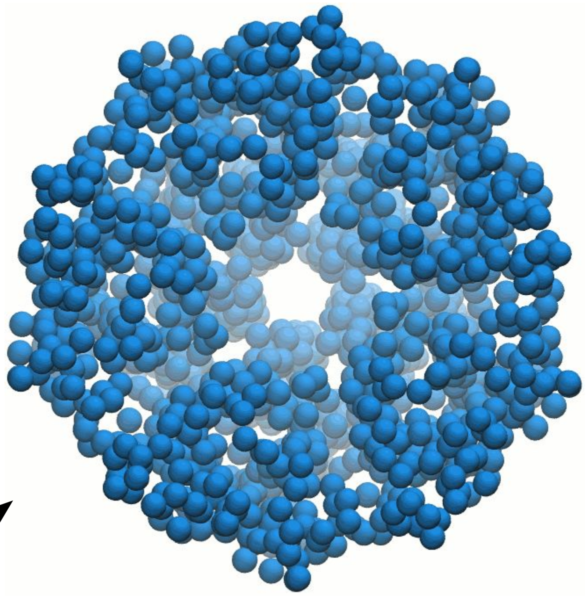
MD simulation from extrapolated conformations

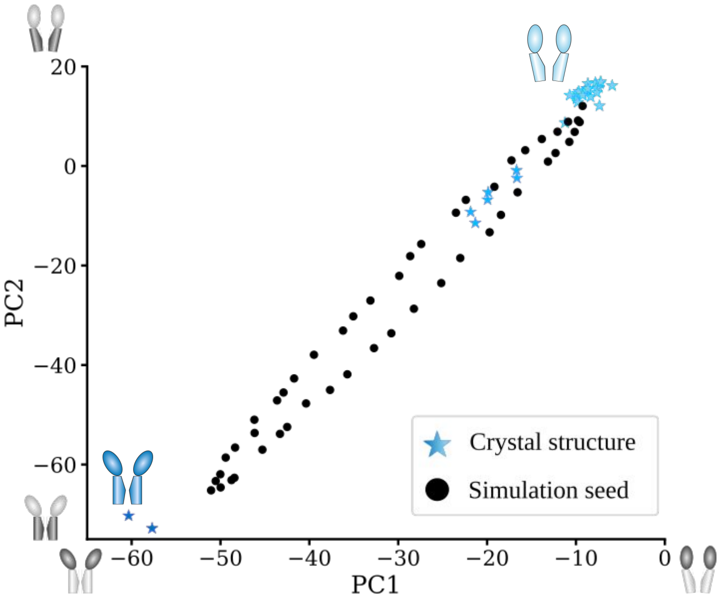


Improved fit using models from MD simulations



Conformational landscape as described by principal components



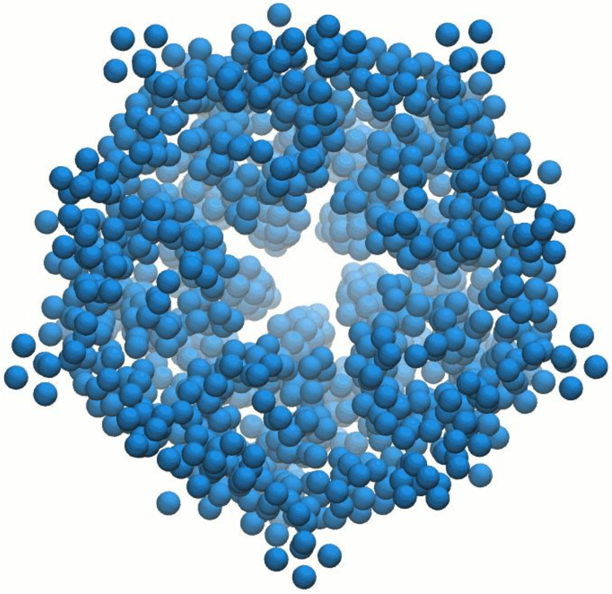


Principal component 2:

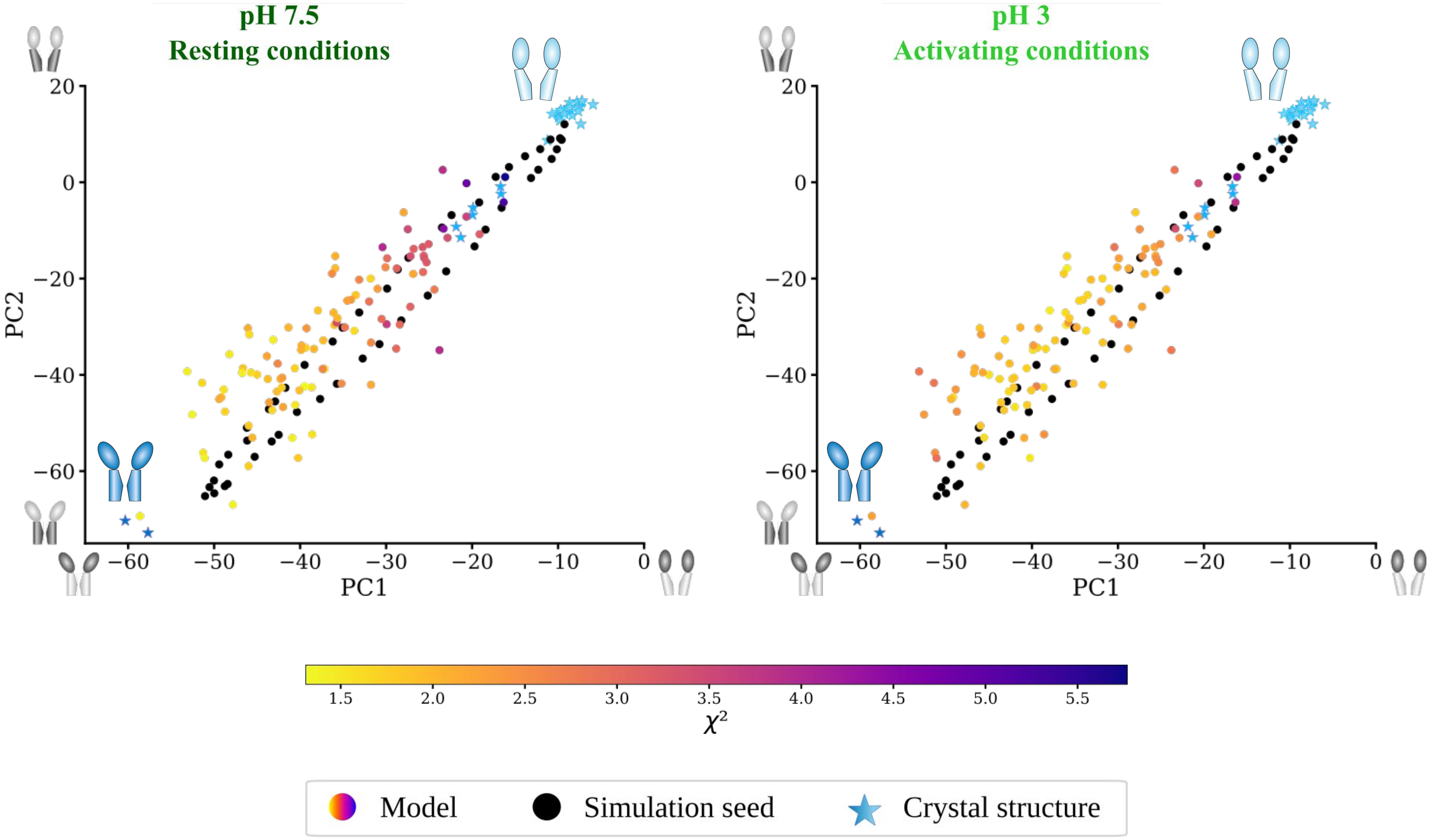
Contraction of pore lining helices

Principal component 1:

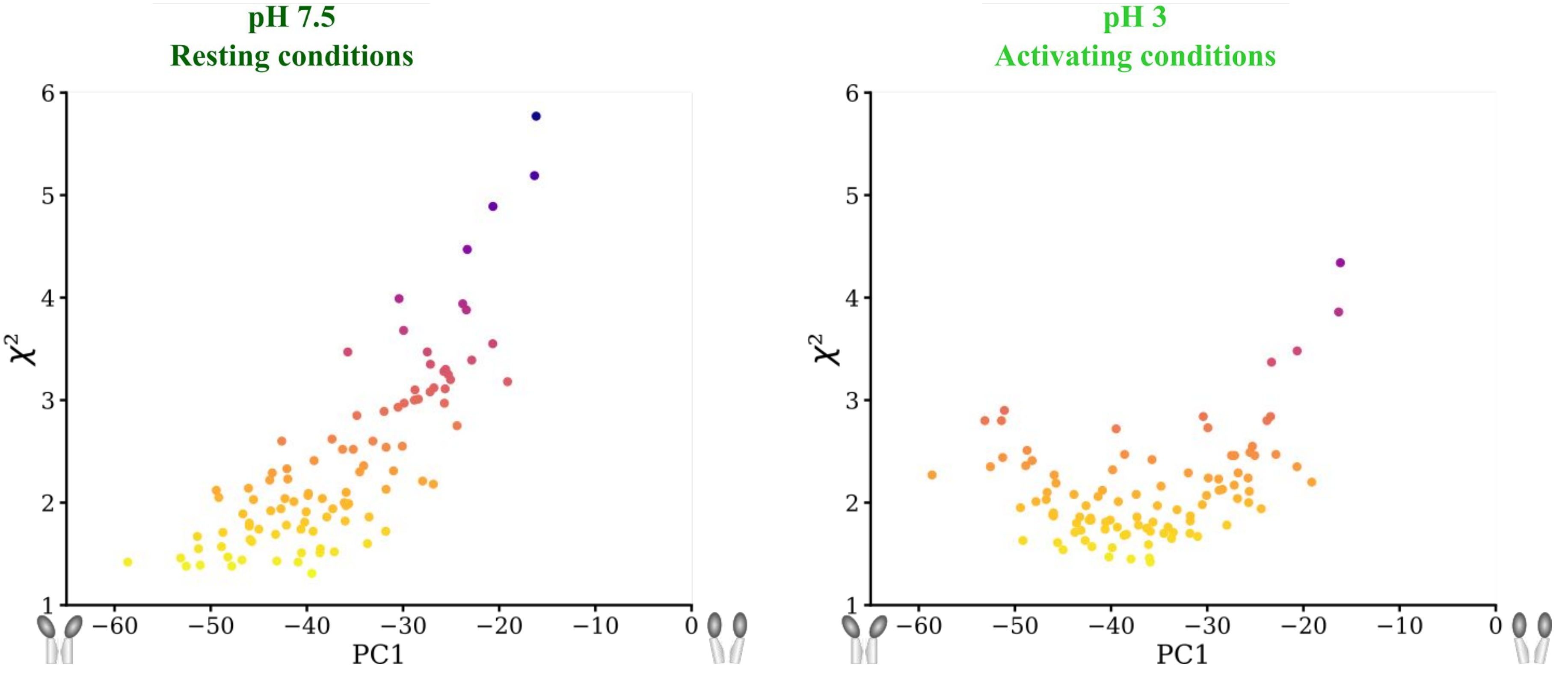
Expansion of ECD domain



Best fitting population shifts between the experimental conditions

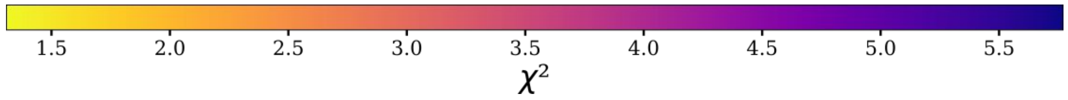


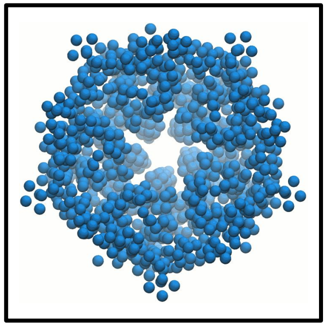
Expanded and intermediate ECD conformations give best fits



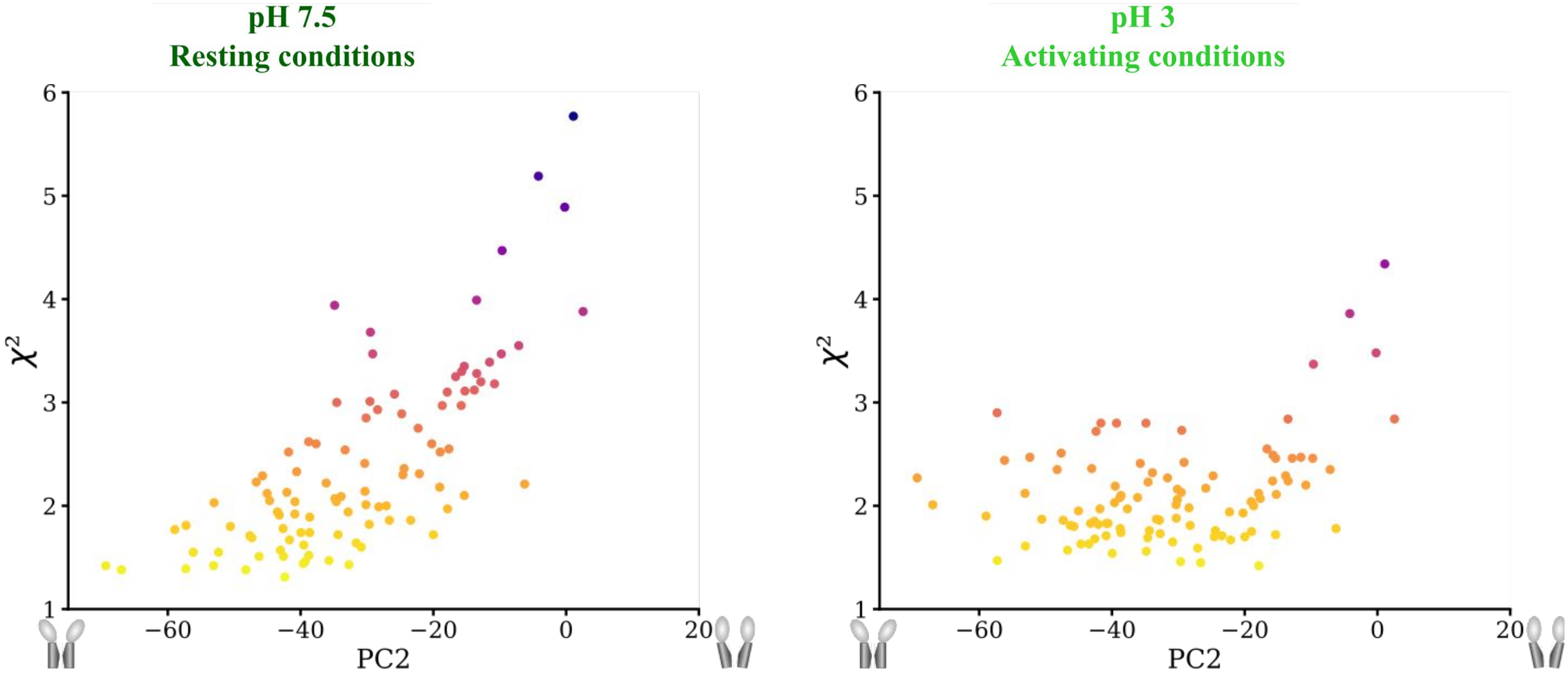
pH 7.5
Resting conditions

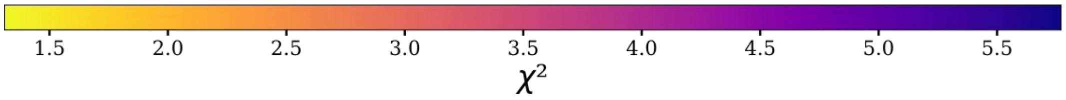
pH 3
Activating conditions

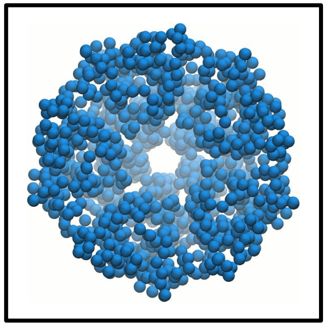




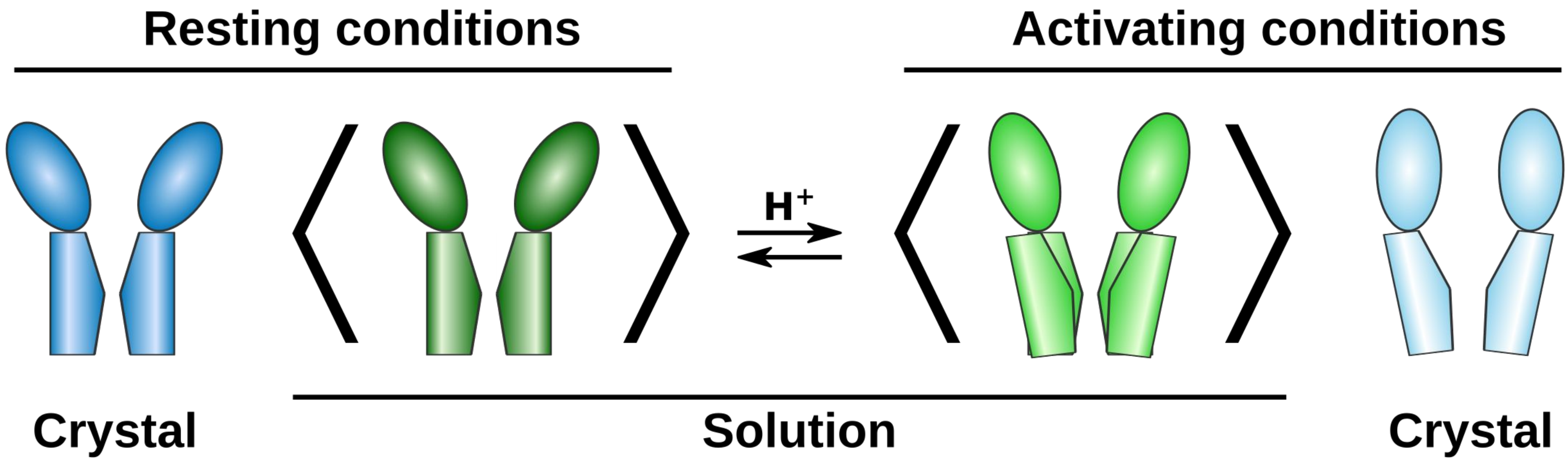
Multiple pore conformations are tolerated at activating conditions







The **average** solution structure of GLIC



Mainly resting state

Expanded ECD

Contracted pore

Likely mix of states

Intermediate ECD

Variable pore

MOLECULAR BIOPHYSICS STOCKHOLM

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