Structural bioinformatics in the frame of integrative structural biology

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Réunion groupe de travail Paris, 16-17 November 2017

Structural Bioinformatics Unit

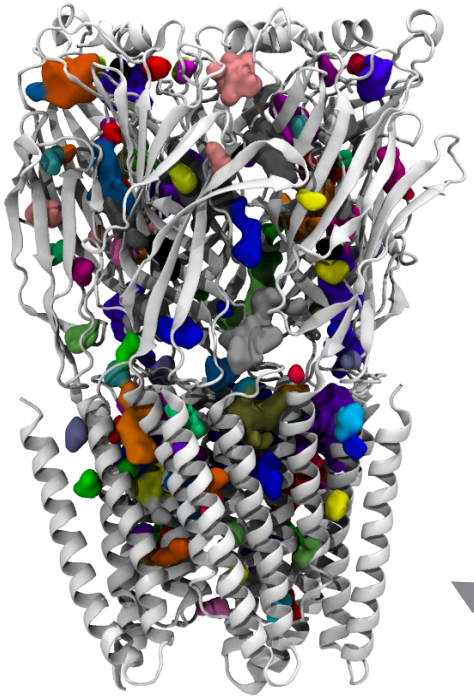
(head: Michael Nilges)

"Molecular modelling in structural biology"

Integrative Structure Determination

Data

Structure



MD/TAMD

Conformational sampling

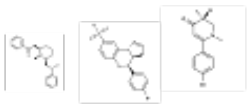
Thérèse Malliavin

Functional Dynamics

Arnaud Blondel

Dynamics & Drug Design

MD/Docking



rationalization of chemical space

PPI modulators

Olivier Sperandio

Chemoinformatics and proteo-chemometrics

NEW

data interpretation ↔model validation ↔ experiments design….

Software/Database

- **ARIA / YARIA** = automated NMR structure determination

  aria.pasteur.fr
  yasara.org/yaria

- **IMP/PMI** = Integrative Modeling Platform/ Python Modeling Interface

  integrativemodeling.org
  github.com/salilab/pmi

- **SOM** = Self-Organising maps for automatic clustering of macromolecular conformations

  github.com/bougui505/SOM

- **ibp-ng** = a software for exploring protein conformational space based on a branch-and-prune exploration

  github.com/geekysuavo/ibp-ng

- **iPPI-DB** = database of protein-protein interaction modulators

  ippidb.cdithem.fr

Structures under experimental restraints

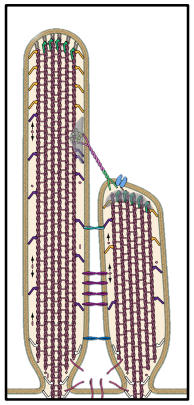
- **Ideal:** Determine ensemble of 3D structures explaining experimental data
- **Practice**:
  - Experimental data as geometrical restraints
  - Find ensemble of conformations best satisfying the restraints
  - Minimise an hybrid energy function

$$E_{hybrid} = E_{geom} + E_{nb} + E_{data}$$

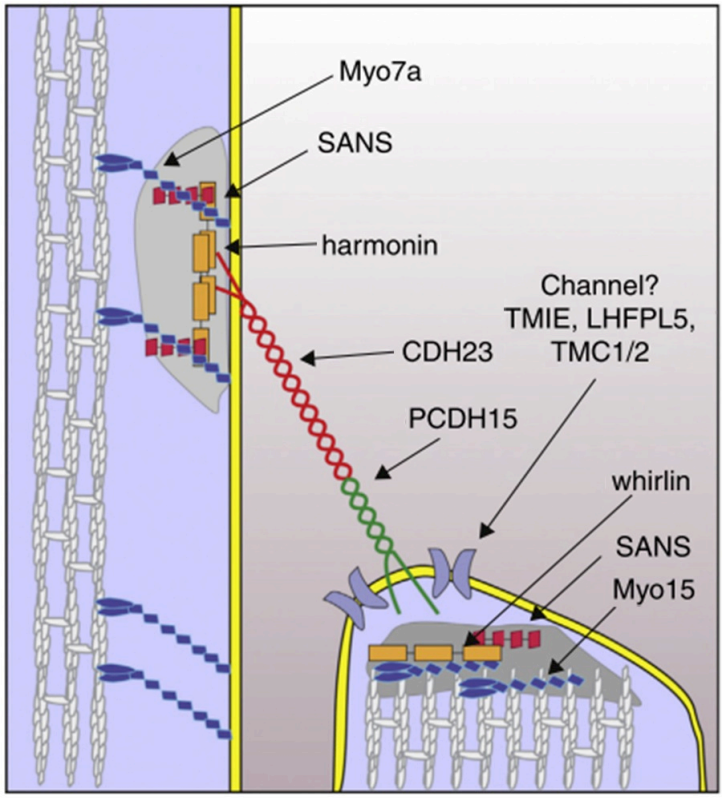
Examples:

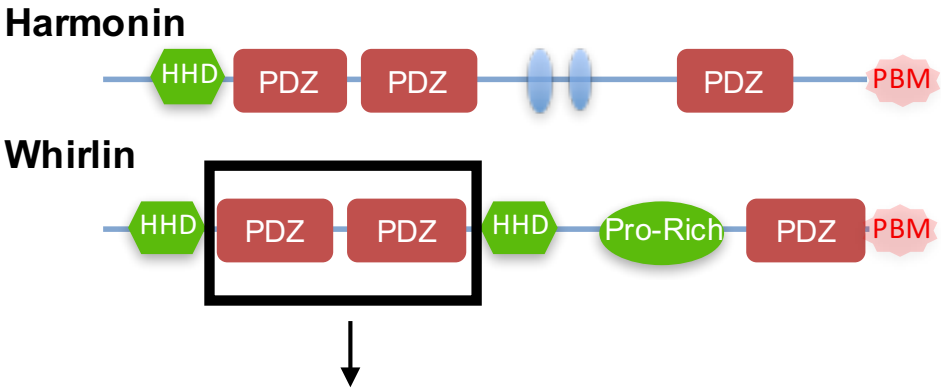
  - Structure of whirlin PDZ12 bi-domain from NMR and SAXS
  - Modelling of symmetric helical filaments from NMR and cryo-EM

Structure of whirlin PDZ12 bi-domain from NMR and SAXS

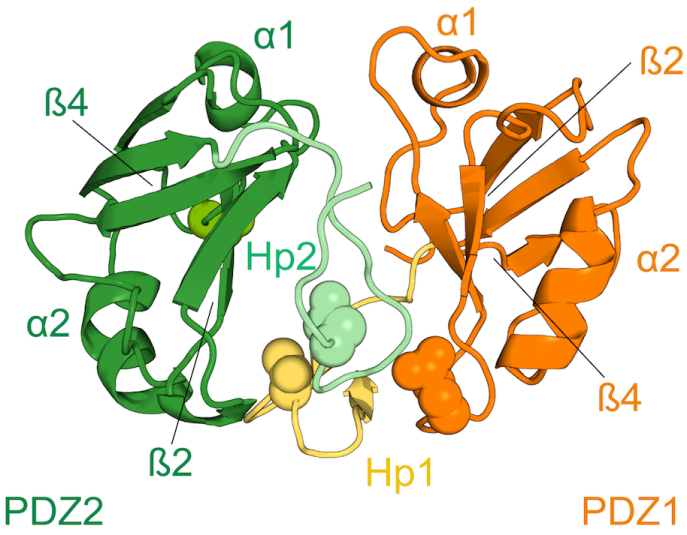


Hair cell bundle protein complexes





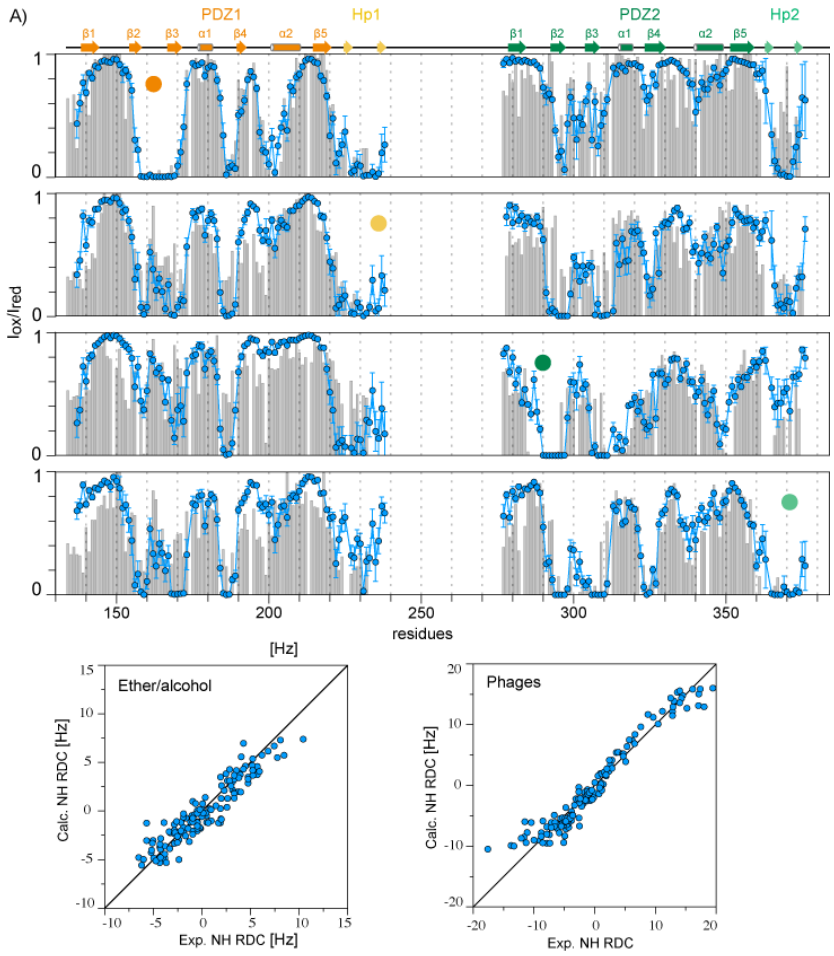
NMR (PRE+RDC) => Docking with Haddock



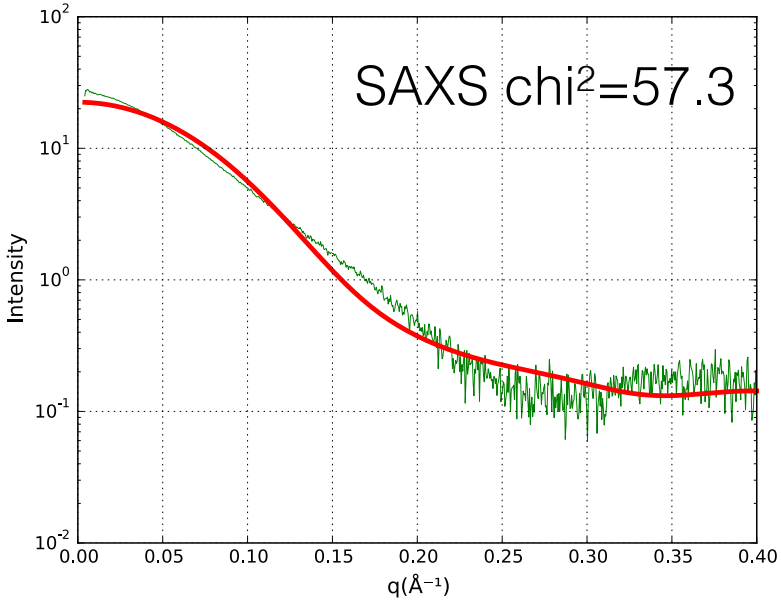
Collab. Nicolas Wolff, Institut Pasteur

Structure of whirlin PDZ12 bi-domain from NMR and SAXS

Docking of whirlin PDZ1 and PDZ2 with NMR Restraints



but…

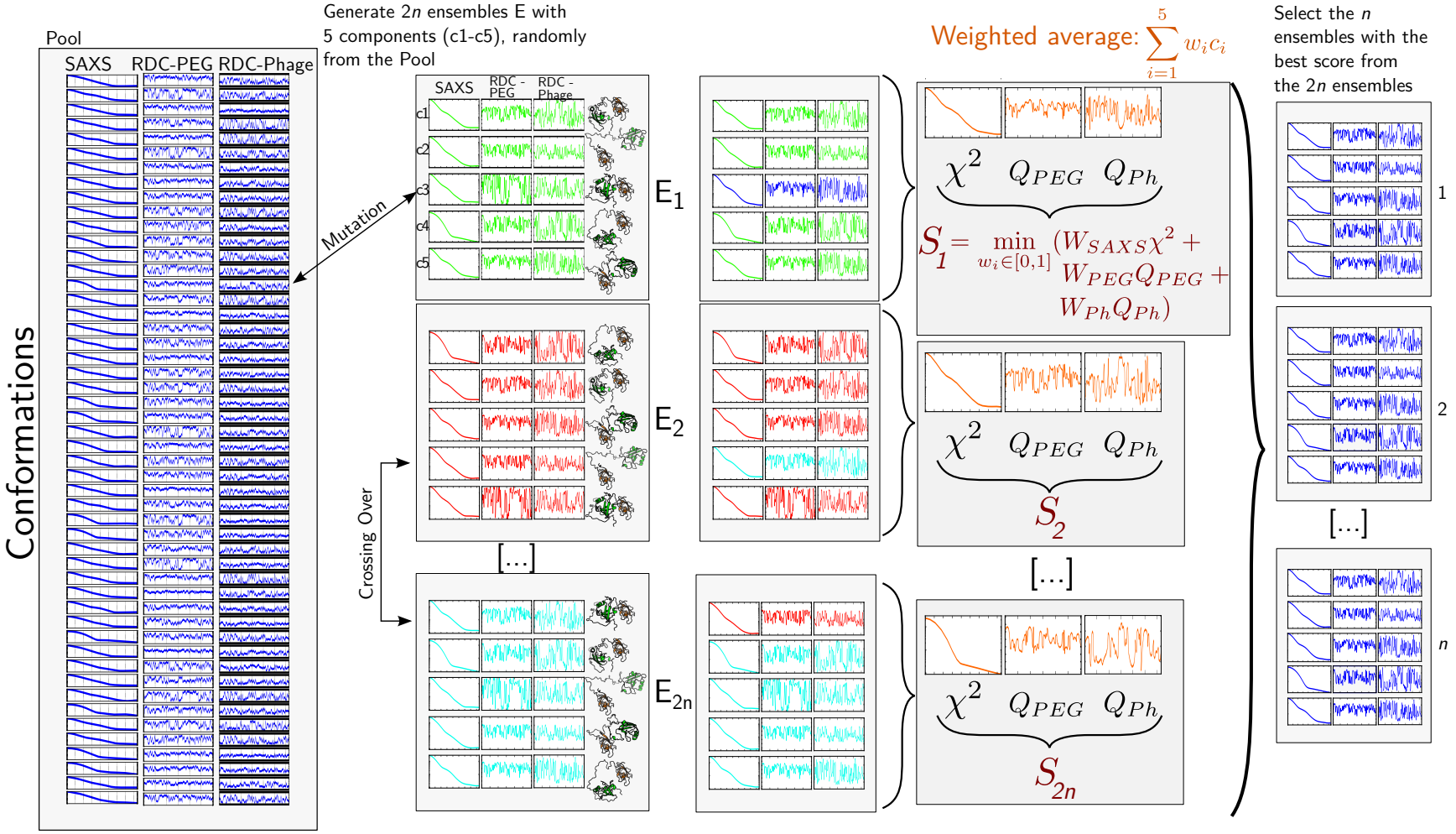


Q factor PRE = 0.35
Q factor RDC = 0.30

Structure of whirlin PDZ12 bi-domain from NMR and SAXS

Find ensemble satisfying both NMR and SAXS data

=> Genetic algorithm (160.000 conformations from MD)



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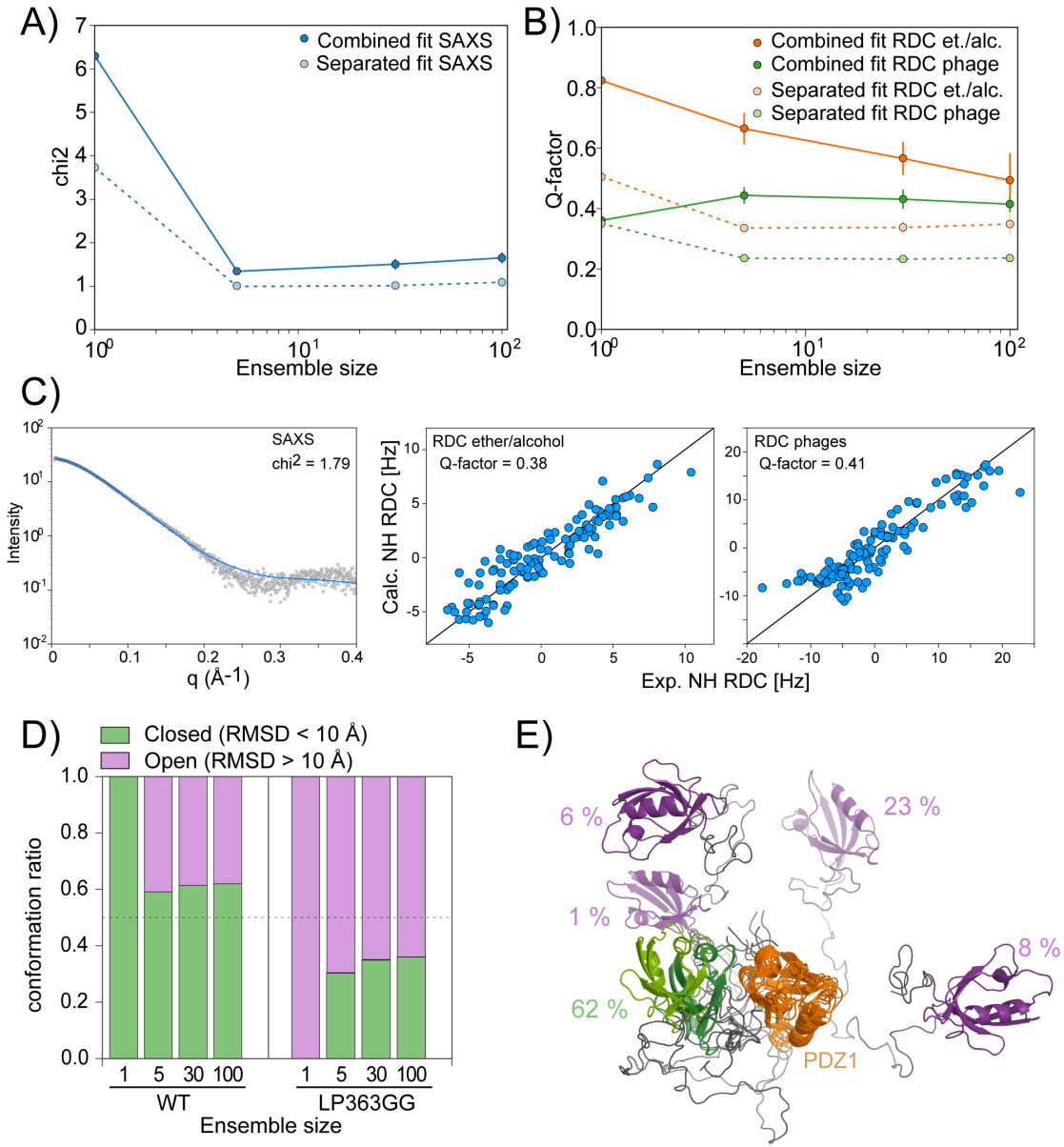
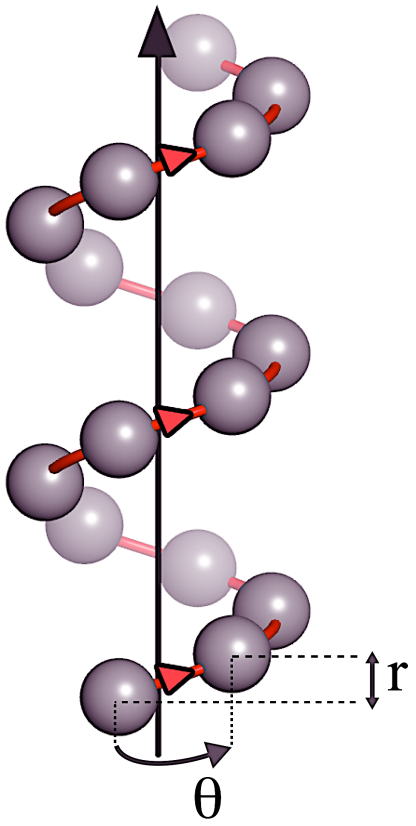


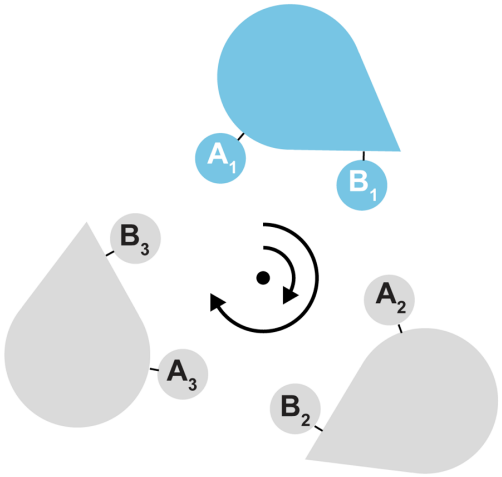
40% of “closed” structures

Modelling of symmetric helical filaments from NMR and cryo-EM

Helical assembly of subunits



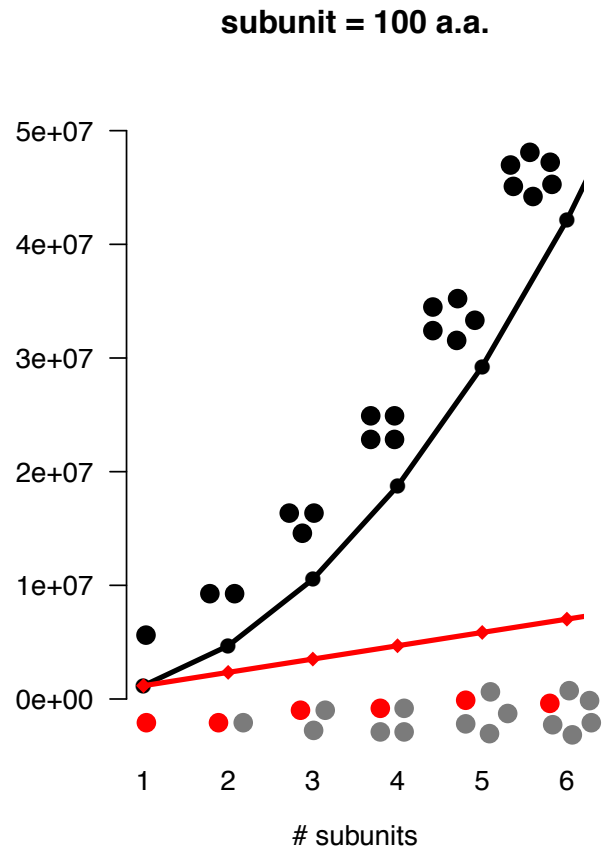
Only one subunit modelled explicitly



Symmetry operators to reconstruct "virtual" images

$$\begin{bmatrix} x' \\ y' \\ z' \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos(\alpha) & -\sin(\alpha) \\ 0 & \sin(\alpha) & \cos(\alpha) \end{bmatrix} \begin{bmatrix} x \\ y \\ z \end{bmatrix} + \begin{bmatrix} t_x \\ t_y \\ t_z \end{bmatrix}$$

Reduced # of potential non-bonded interactions to compute

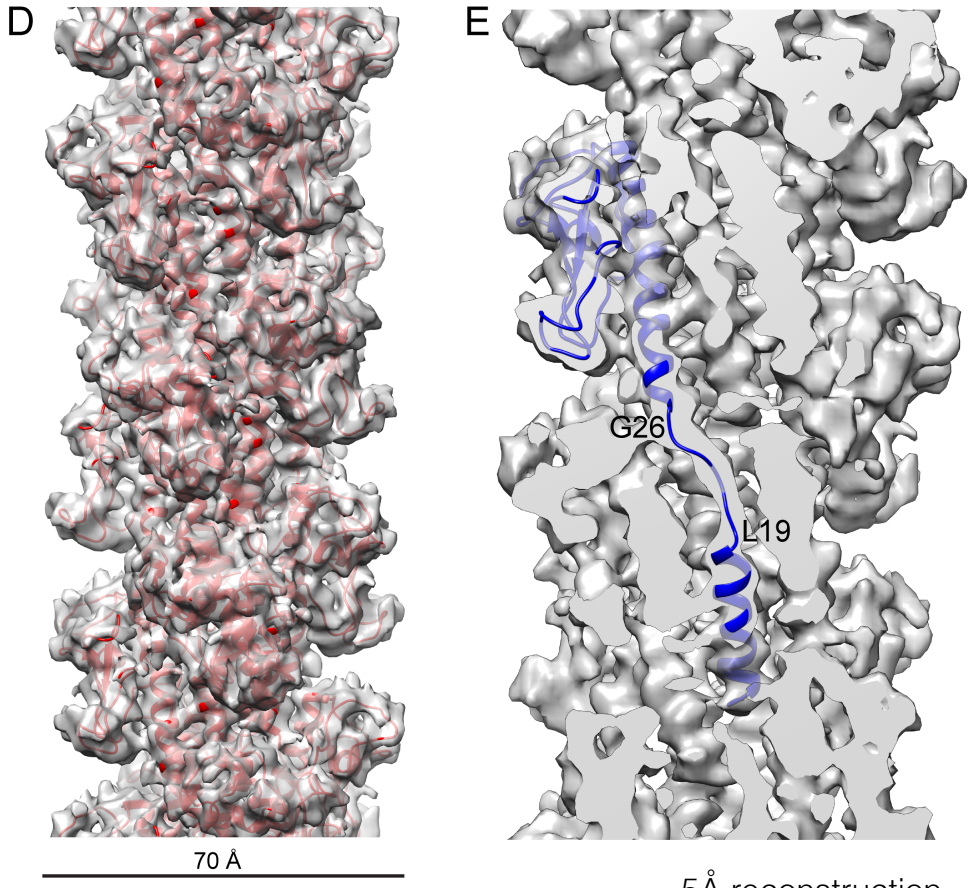


implemented in CNS, valid for all symmetries, CPU efficient

Bardiaux *et al.* **Angewandte Chemie**, 2012

Modelling of symmetric helical filaments from NMR and cryo-EM

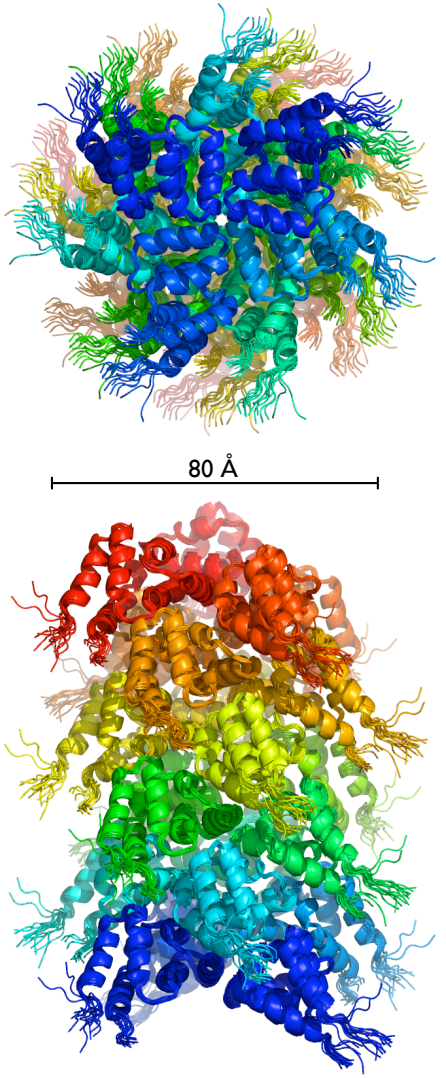
Atomic structure of type II secretion pilus
from **NMR** and **cryo-EM** (PDB 5WDA)



5Å reconstruction

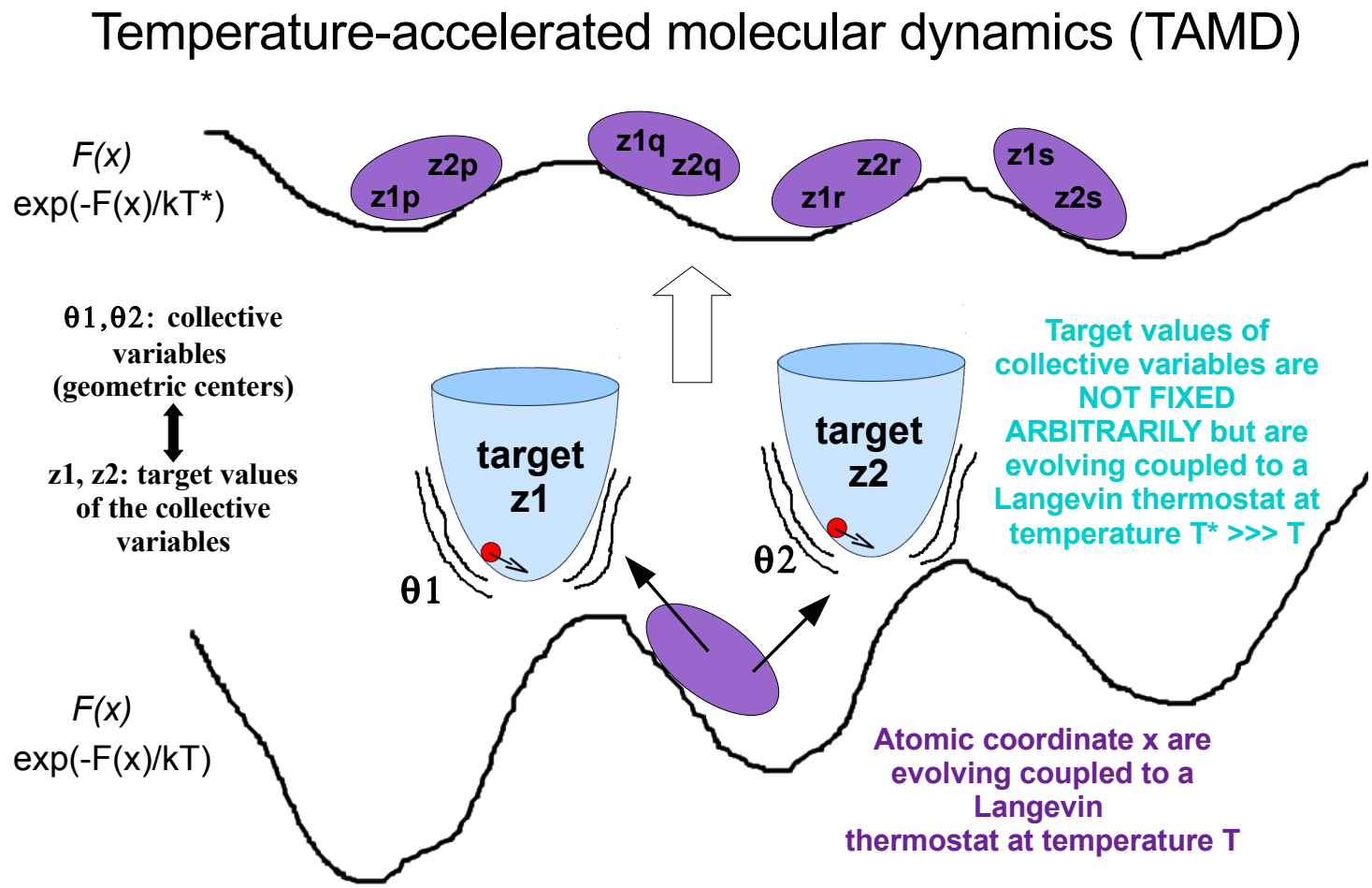
Lopez-Castilla*, Thomassin*, Bardiaux* *et al.* & Francetic,
Nat. Microbiology, 2017

Atomic structure of MAVS^{CARD} filament
from **solid-state NMR** (PDB 2MS7)



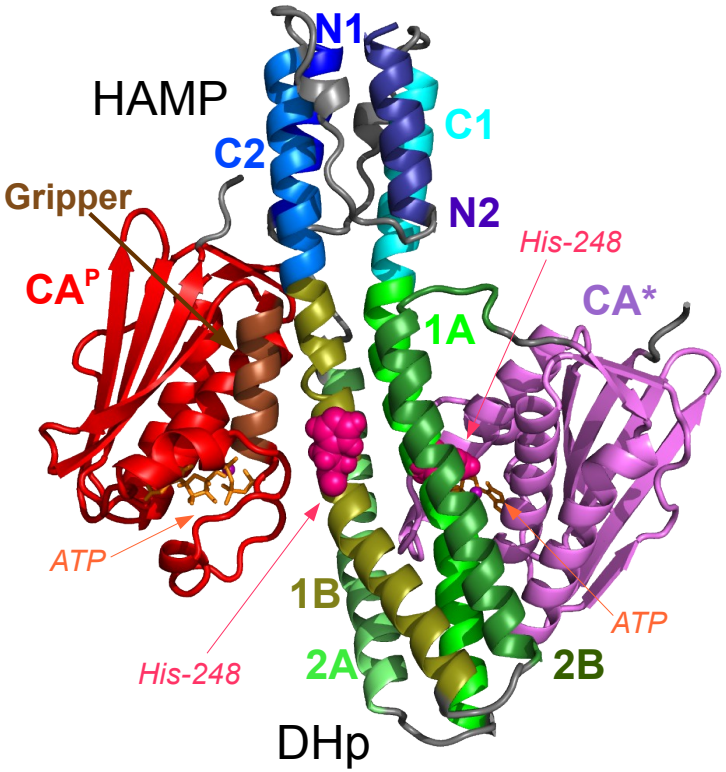
He*, Bardiaux* *et al.* & Ritter
PNAS, 2016

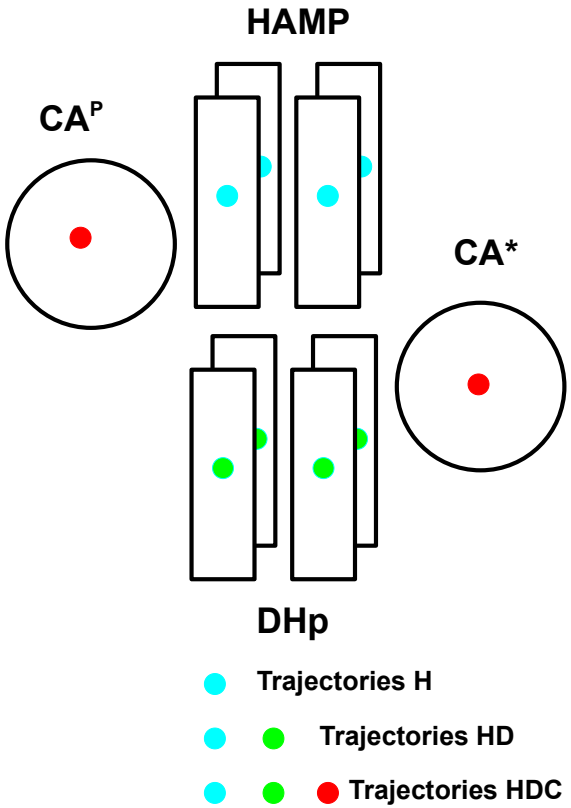
Enhanced sampling approach: TAMD



Maragliano, Vanden-Eijden, Chem Phys Lett 2006; Abrams, Tuckerman, JCP 2008

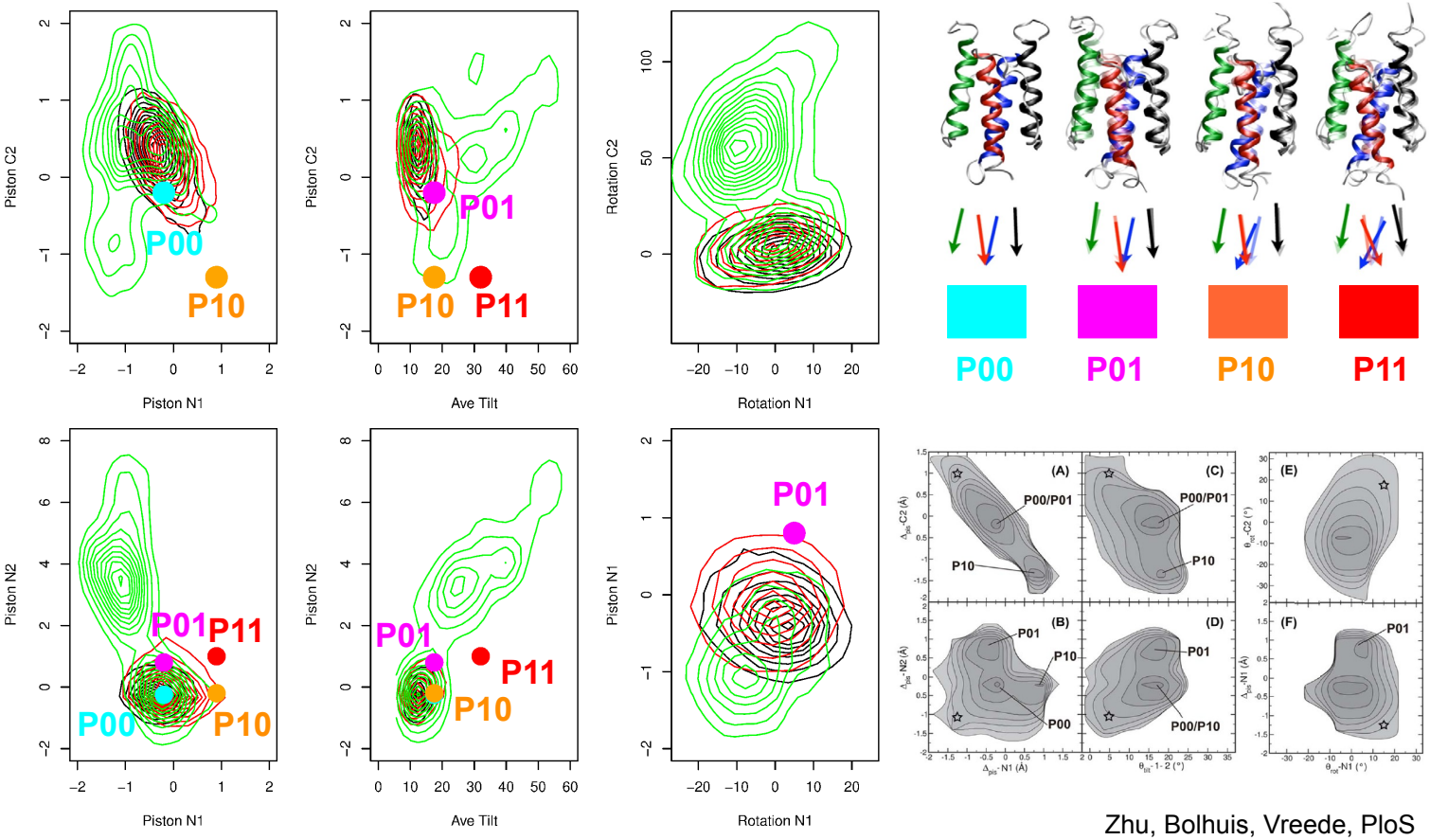
CpxA crystallographic structure





Martinez et al, Biopolymers 2016; Mechaly et al, PloS Pathogens, 2014

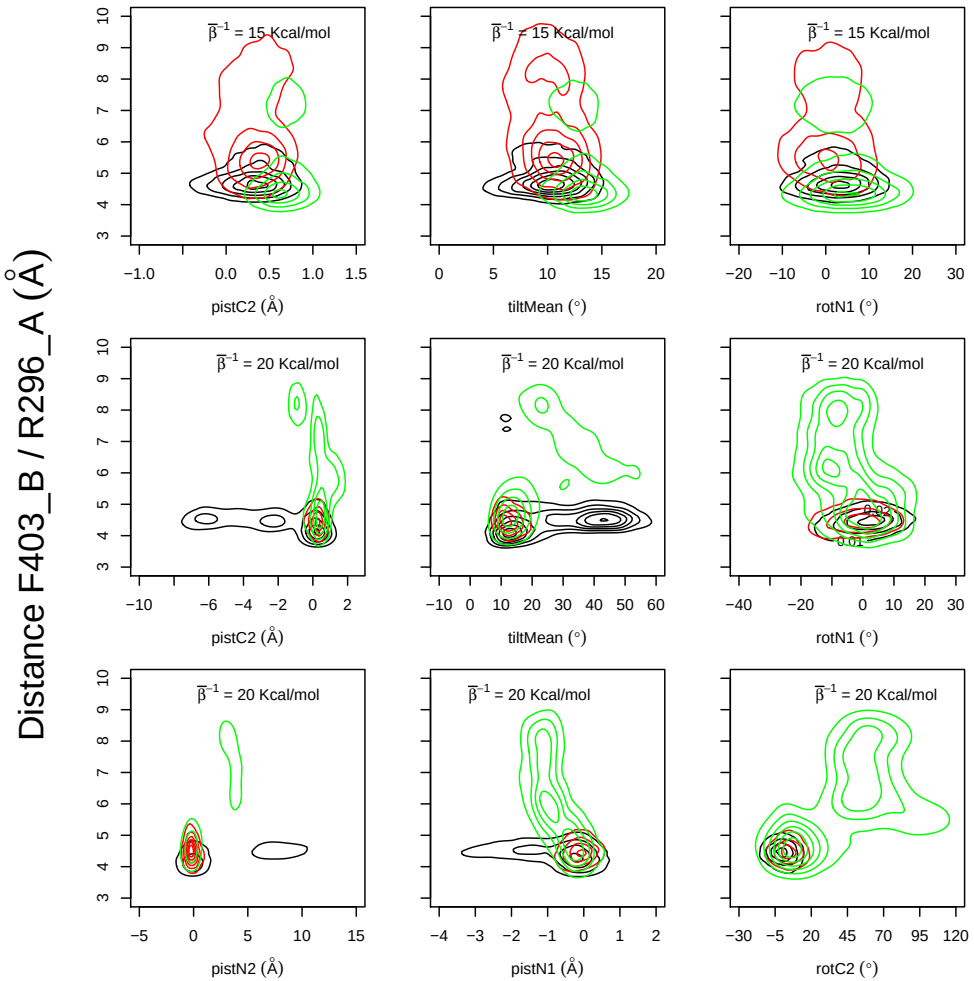
Effect of TAMD on HAMP motions

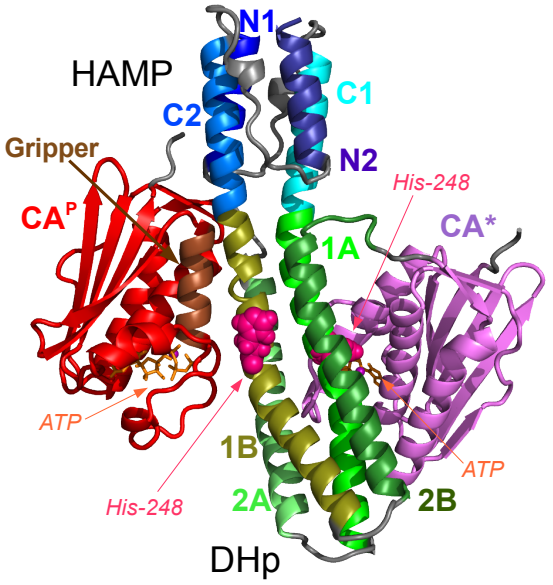


H(black), HD(red), HDC(green) 20 kcal/mol

Zhu, Bolhuis, Vreede, PloS Computational Biology 2013

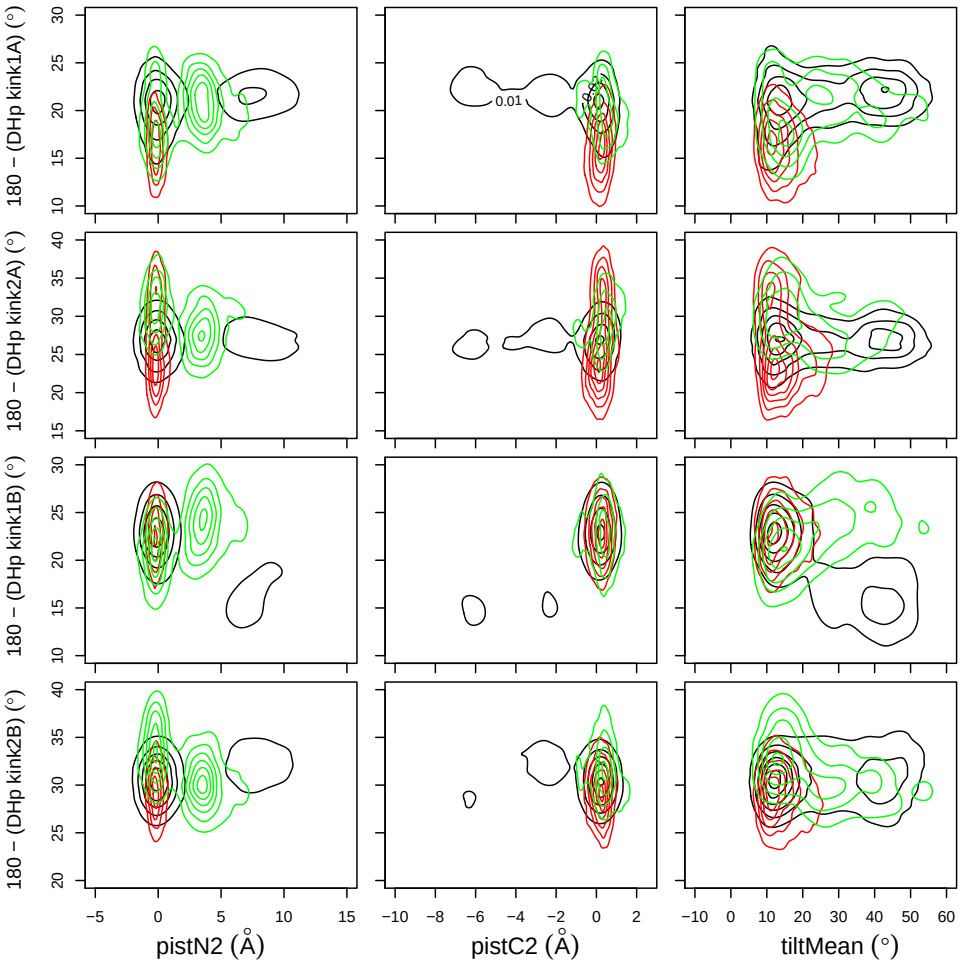
Connection of HAMP motions to CpxA function

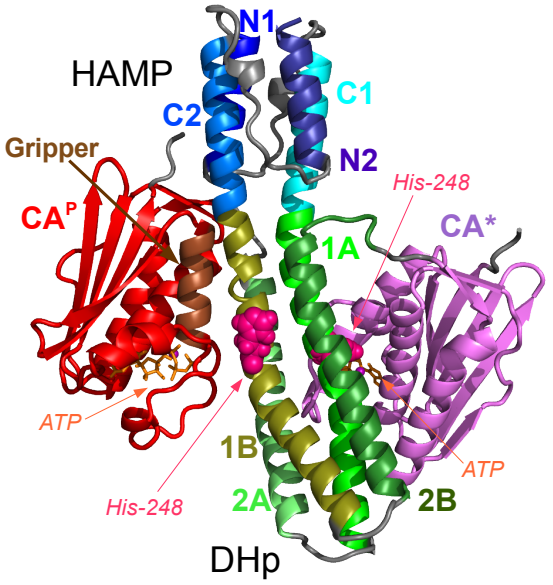




Duclert-Savatier et al, submitted to PloS Comput Biol

Connection of HAMP motions to CpxA function

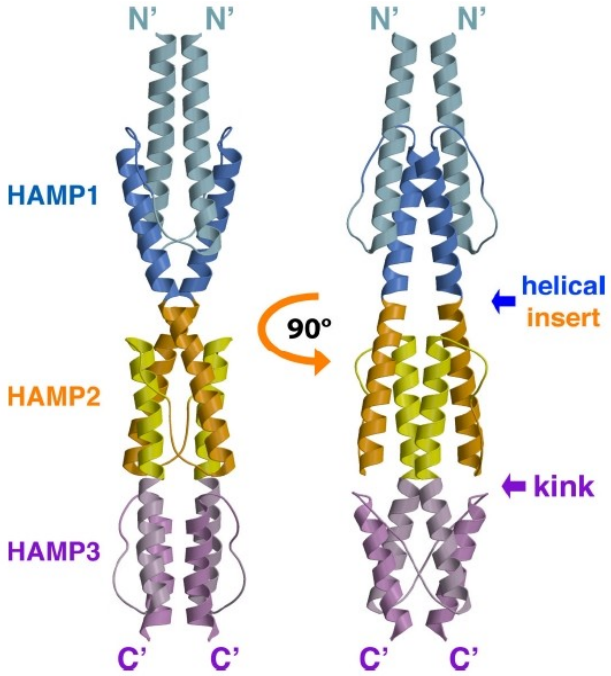




Duclert-Savatier et al, submitted to PloS Comput Biol

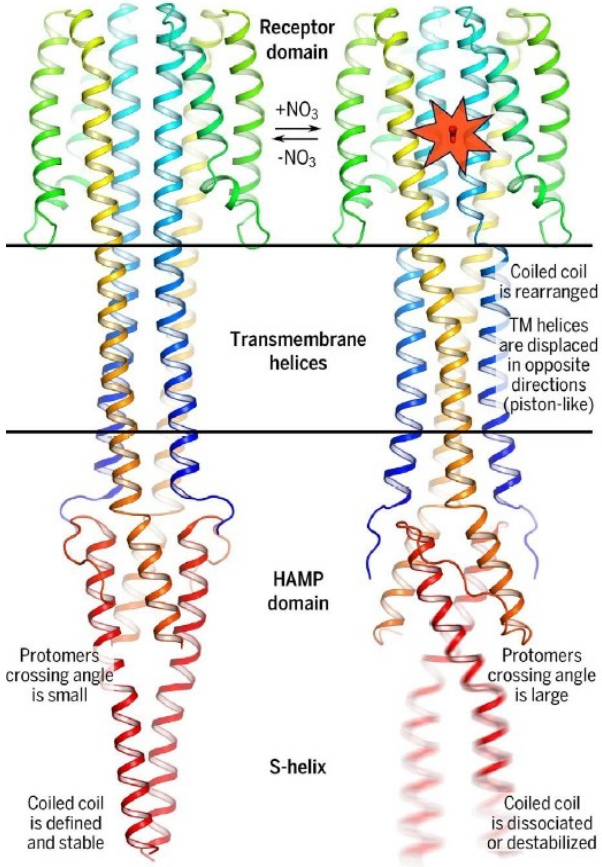
Comparison with X-ray structures of other histidine kinases

Crystal structure of the N-terminus of the soluble aerotaxis receptor Aer2 from *P. aeruginosa*



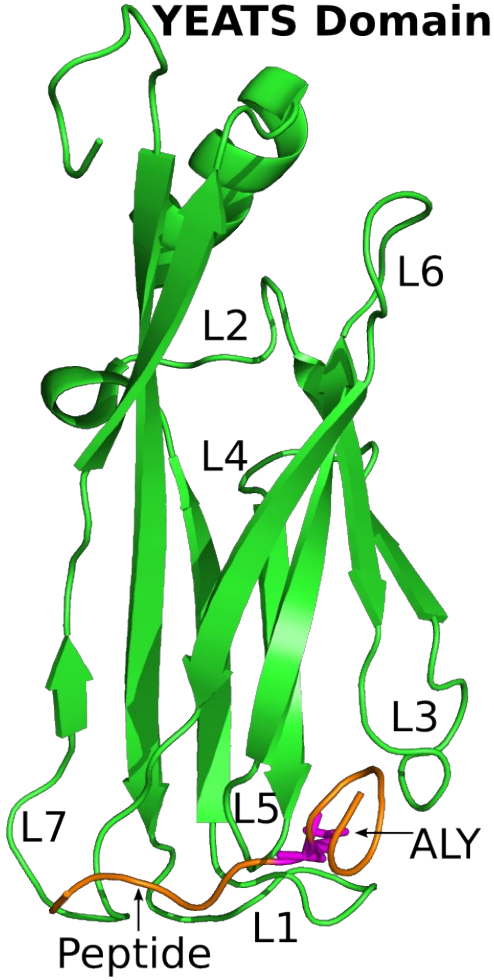
Airola, Watts, Bilwes, Crane. Structure 2010

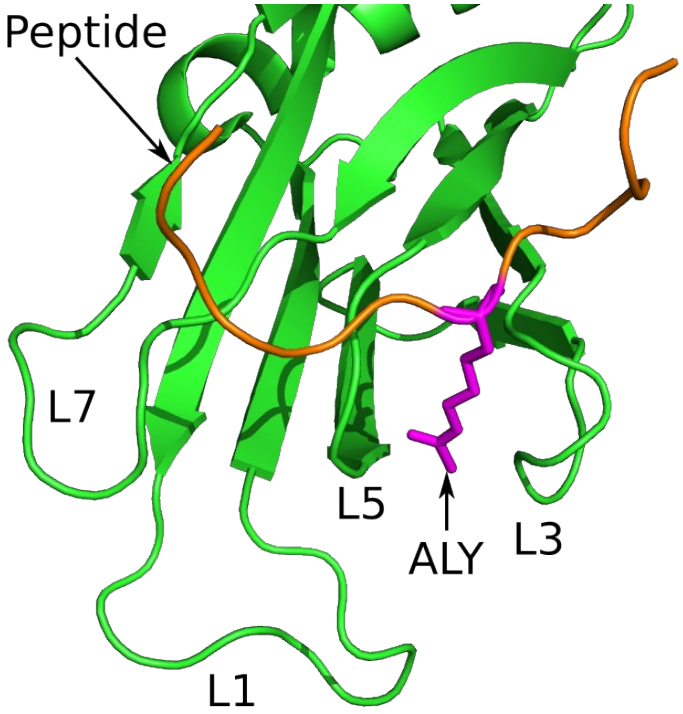
Escherichia coli nitrate/nitrite sensor kinase NarQ

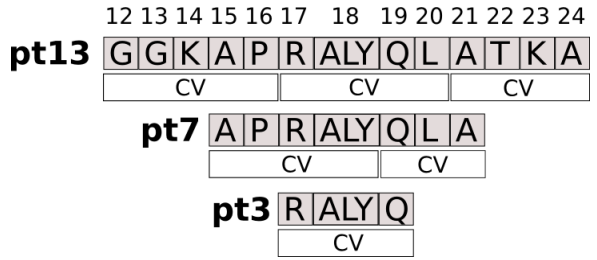


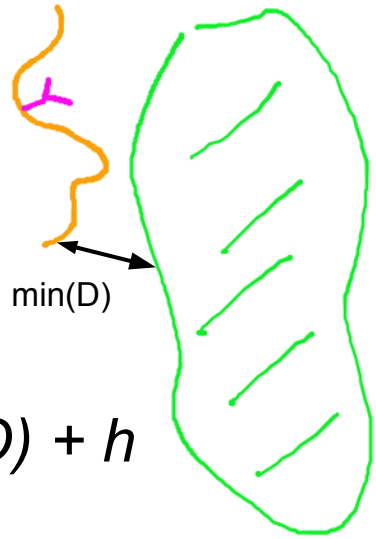
Gushchin, Melnikov, Polovinkin, Ishchenko, Yuzhakova, Buslaev, Bourenkov, Grudinin, Round, Balandin, Borshchevskiy, Willbold, Leonard, Büldt, Popov, Gordeliy, Science 2017

Interaction of YEATS and Nt peptide from H3





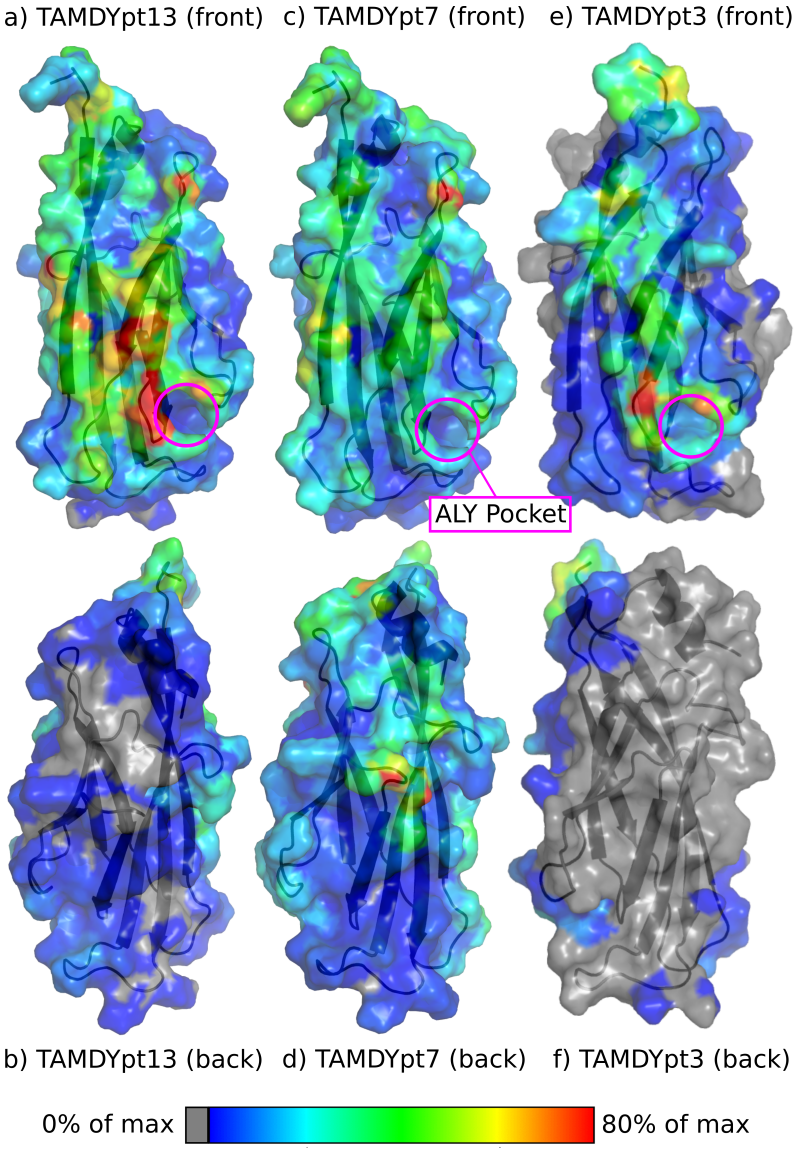




$$T^* = k/min(D) + h$$

Gilles Lamothe, in revision at *BMC Struct Biol*

Interaction of YEATS and Nt peptide from H3



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