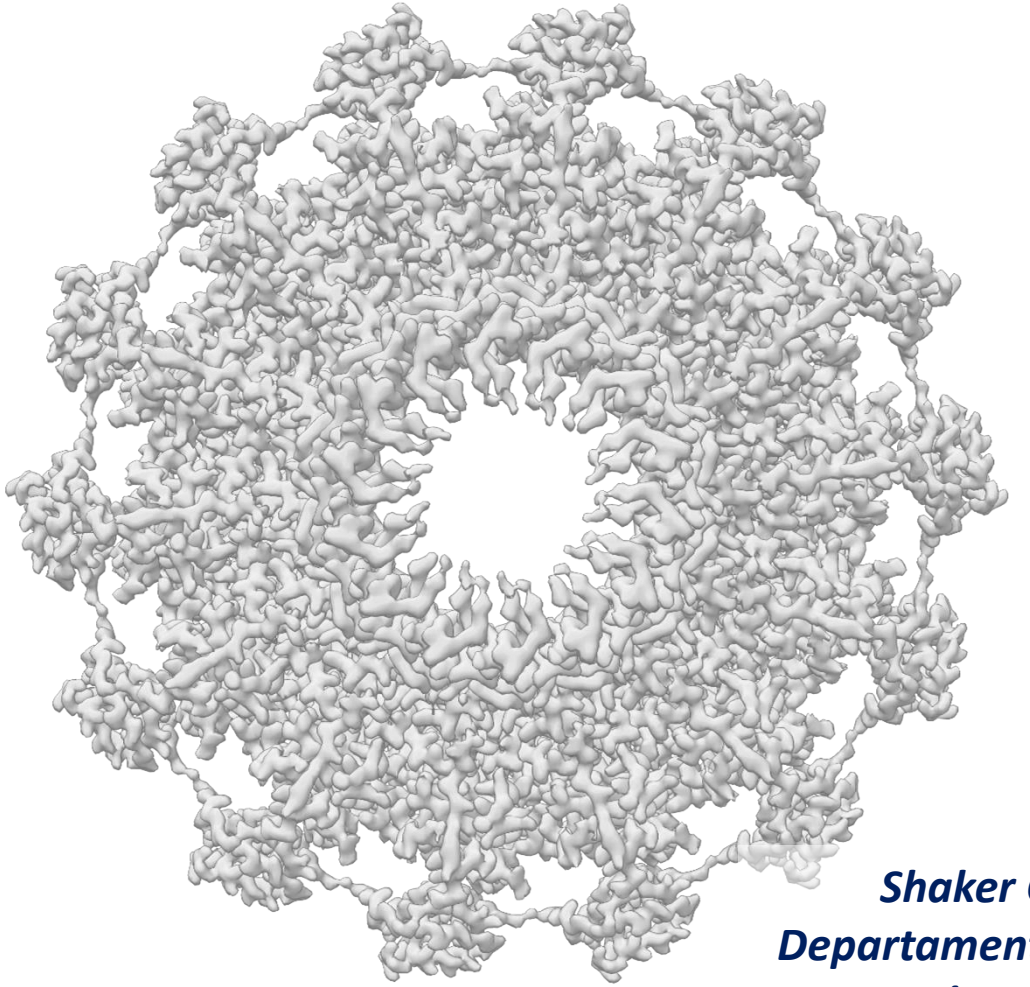
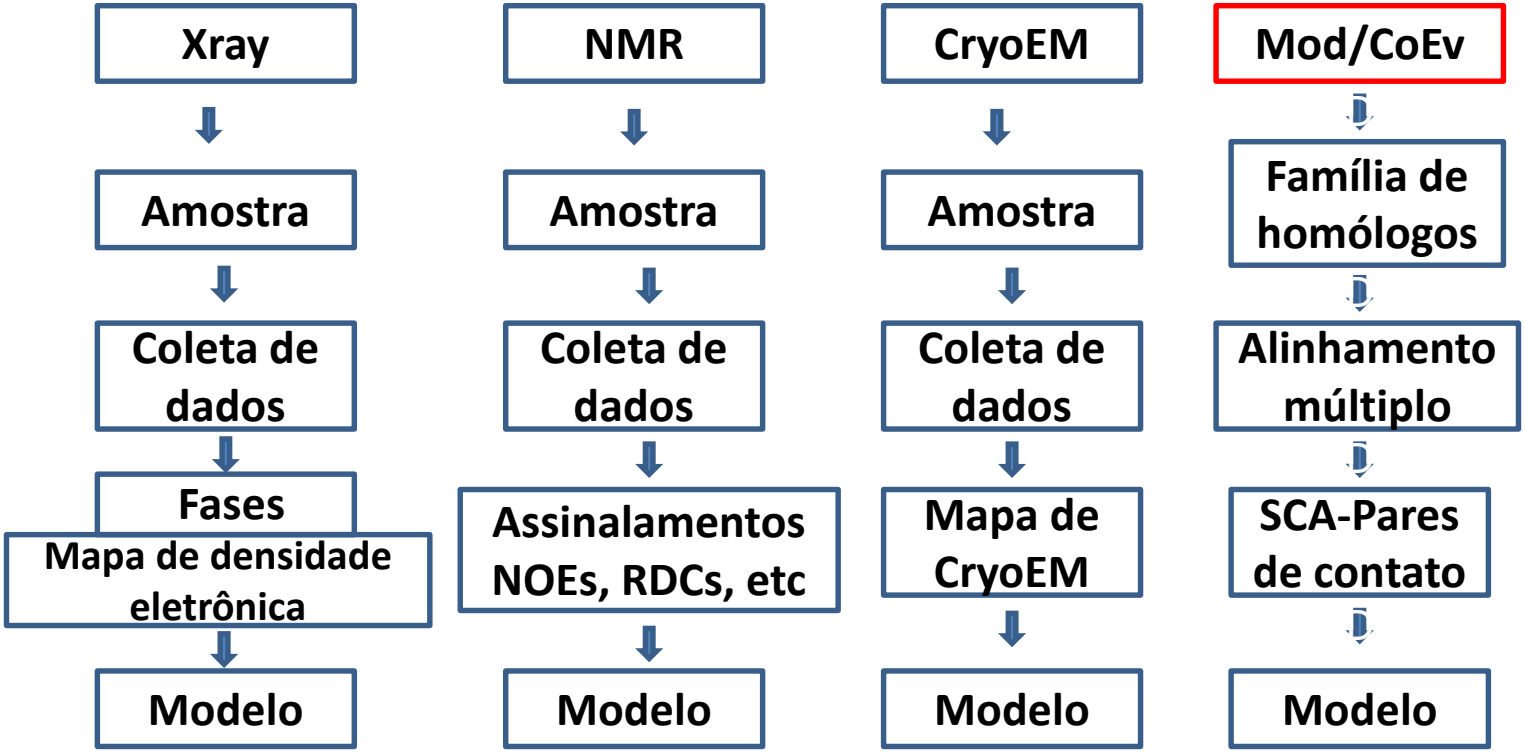
Biologia Estrutural: Métodos experimentais para elucidar a estrutura de proteinas



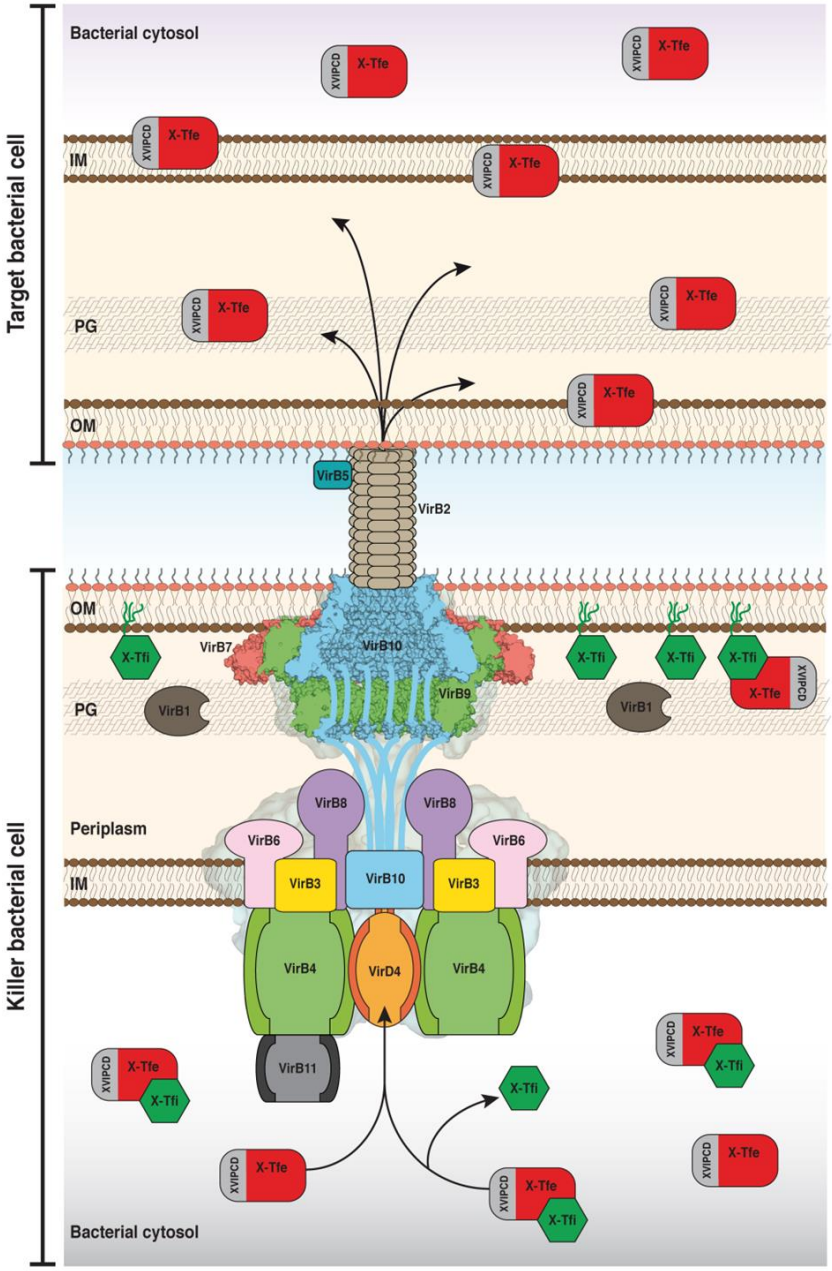
Shaker Chuck Farah
Departamento de Bioquímica
Instituto de Química
Universidade de São Paulo

Quatro métodos principais para obter modelos moleculares de proteínas e outras macromoléculas

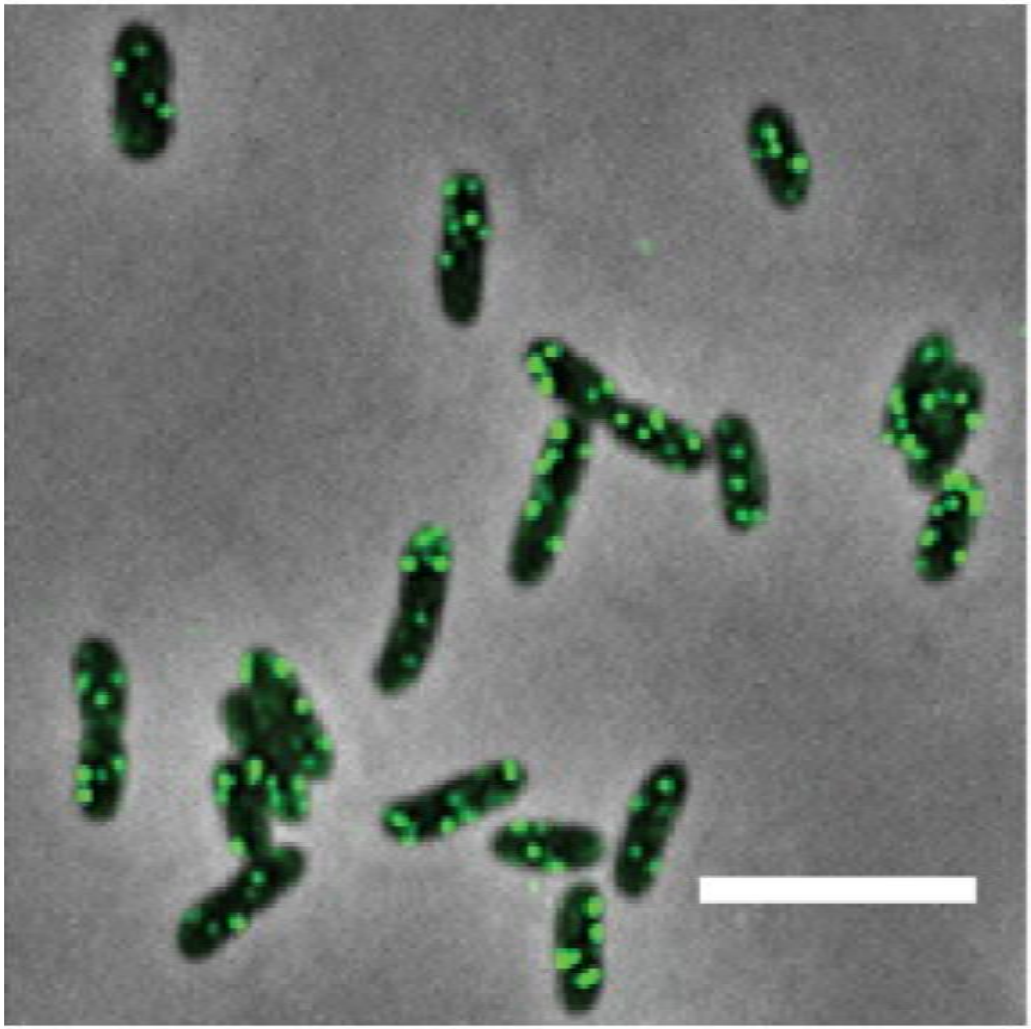
1) Cristalografia/Difração de Raios X (Xray)
2) Ressonância Magnética Nuclear (NMR)
3) Crio-microscopia eletrônica (CryoEM)
4) Modelagem molecular / aprendizagem de máquina guiada com informação de co-evolução de pares de resíduos (Mod/CoEv)



Sistema de Secreção do Tipo IV de *Xanthomonas citri* - Uma potente arma em guerras bacterianas

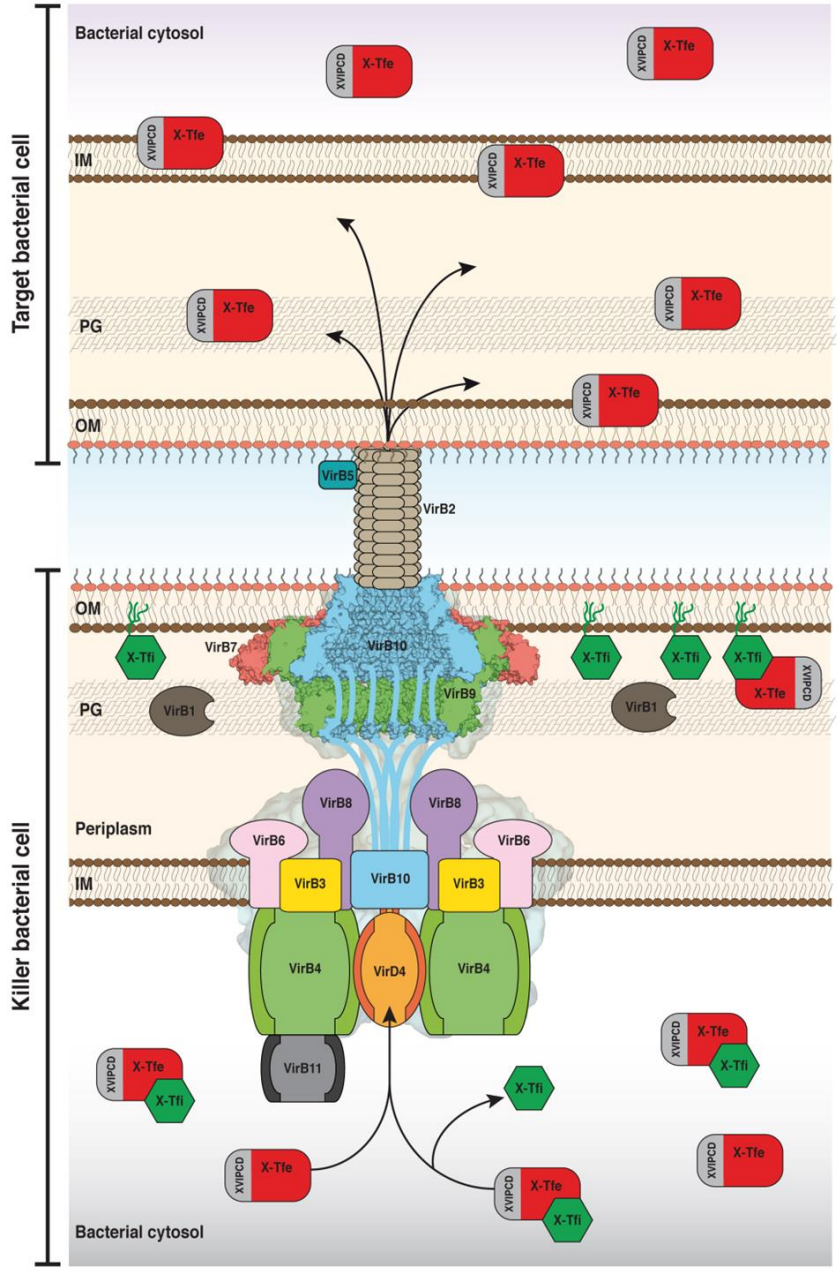


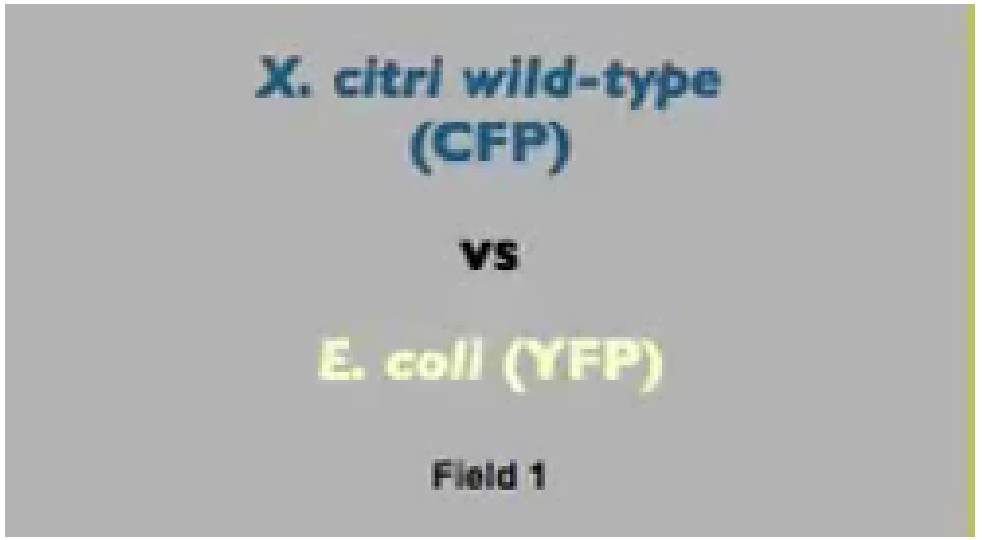
Sgro et al (2019) Frontiers in Microbiology



Cenens et al, 2020) PLoS Pathogens
Sgro et al (2018) Nature <icrobiology

Sistema de Secreção do Tipo IV de *Xanthomonas citri* - Uma potente arma em guerras bacterianas





Souza et al (2015) *Nature Communications*

Quatro métodos principais para obter modelos moleculares de proteínas e outras macromoléculas

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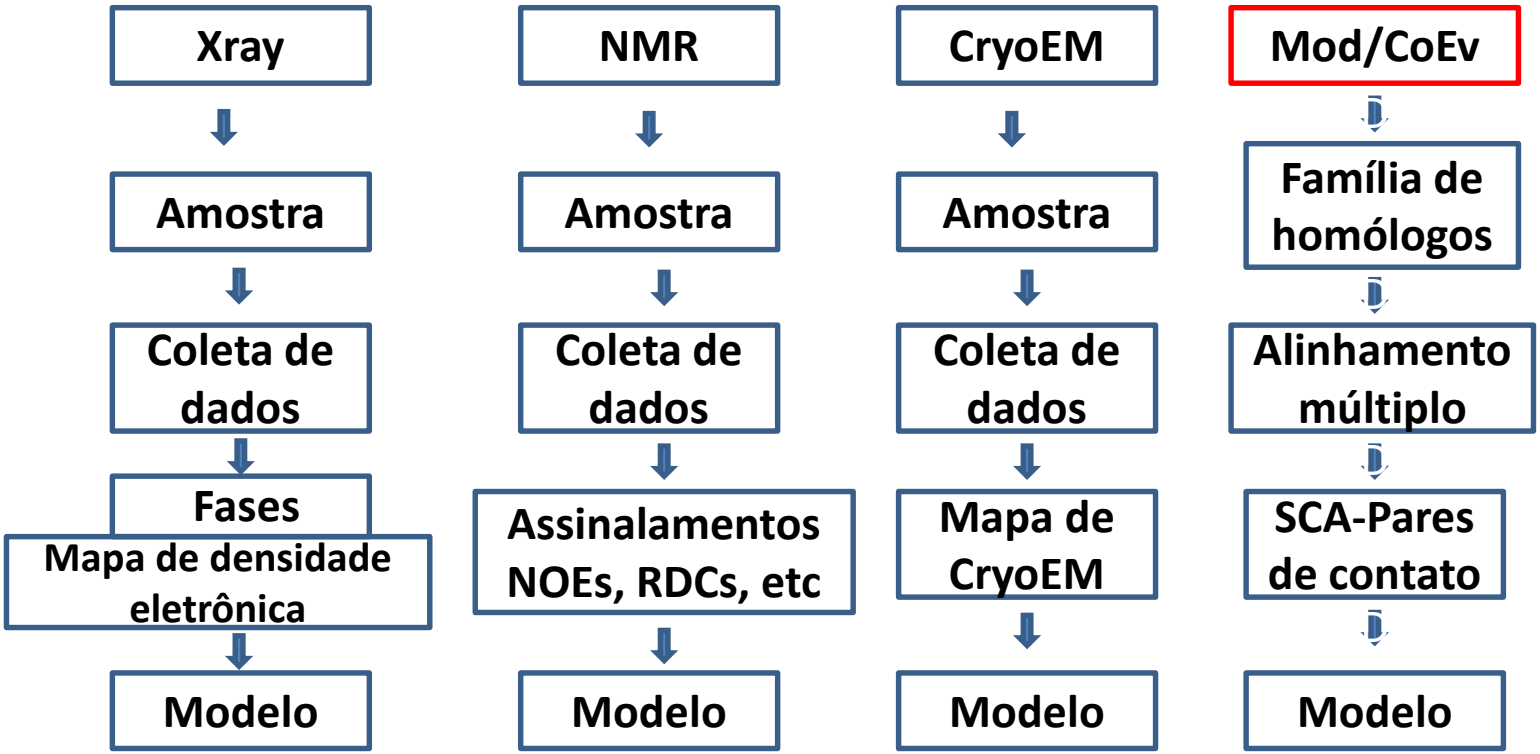


1) Cristalografia/Difração de Raios X (Xray)

Xray

↓

Amostra

↓

Coleta de dados

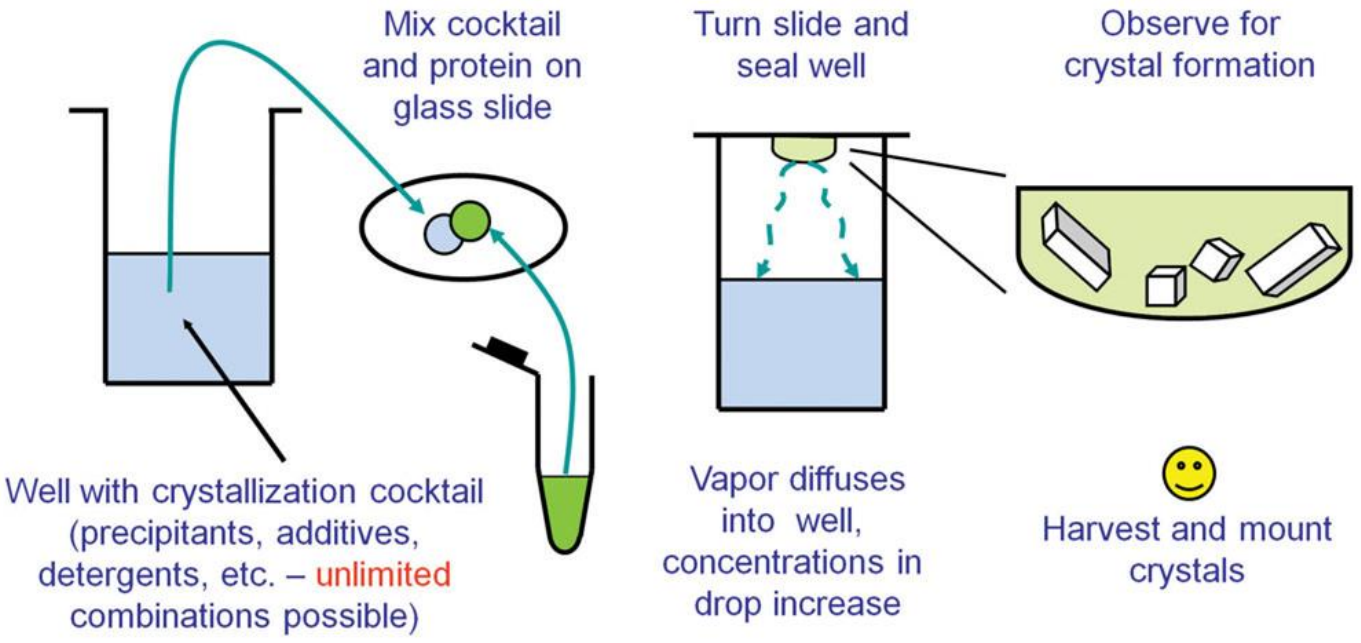
↓

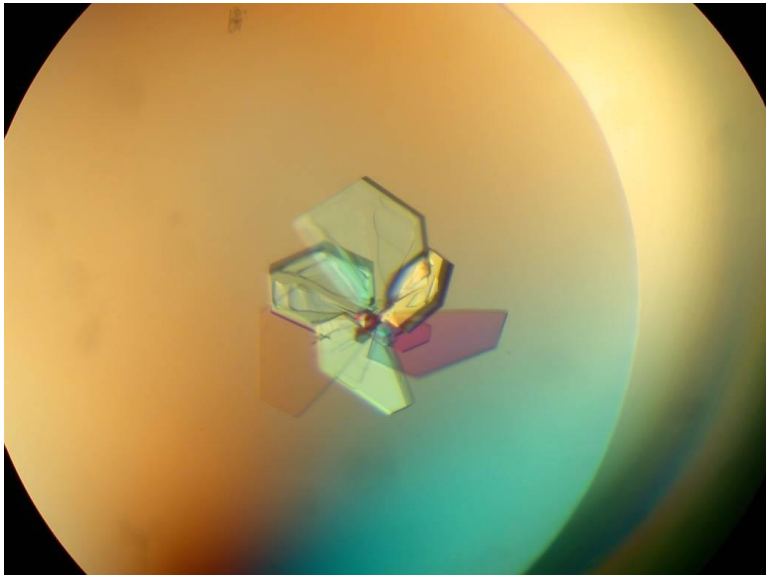
Fases

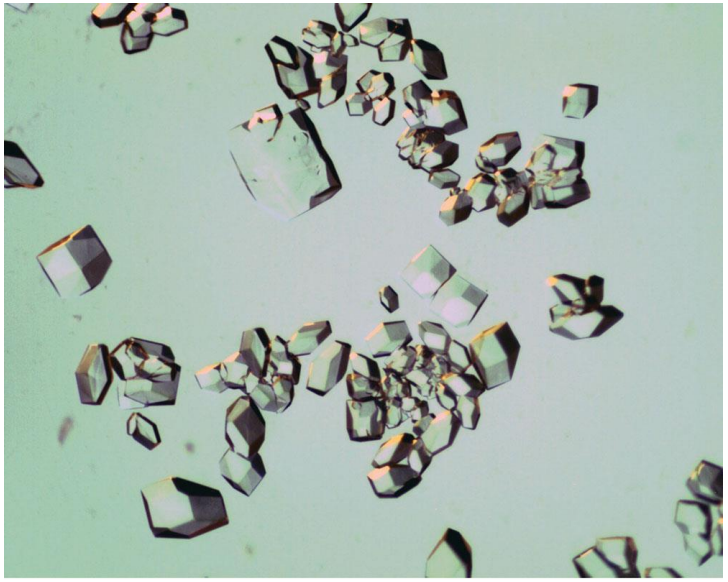
Mapa de densidade eletrônica

↓

Modelo

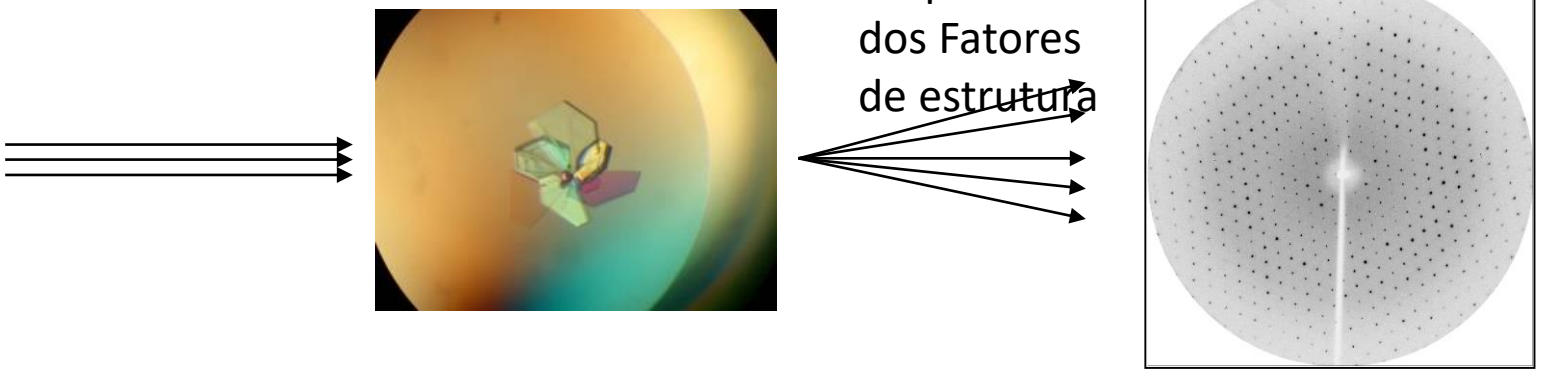






1) Cristalografia/Difração de Raios X (Xray)

- Xray
- Amostra
- Coleta de dados
- Fases
- Mapa de densidade eletrônica
- Modelo



1) Cristalografia/Difração de Raios X (Xray)

Xray

↓

Amostra

↓

Coleta de dados

↓

Fases

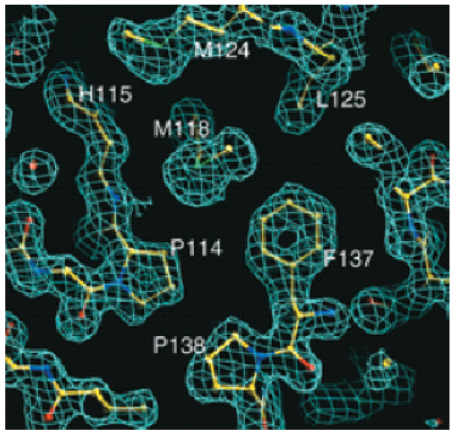
Mapa de densidade eletrônica

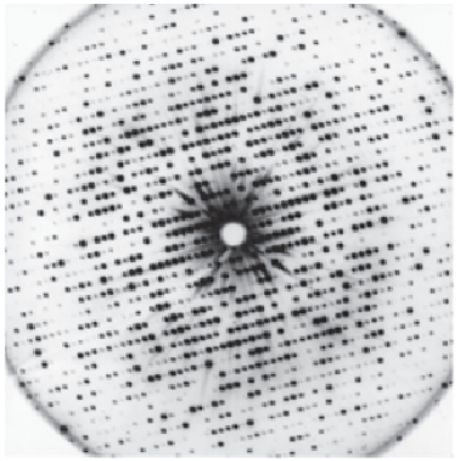
↓

Modelo

O padrão de difração é o FT do mapa de densidade eletrônica do cristal

$$F_{hkl} = \int_x \int_y \int_z \rho(x, y, z) e^{2\pi i(hx+ky+lz)} \, dx \, dy \, dz$$





amplitudes

$$\rho(x, y, z) = \frac{1}{V} \sum_h \sum_k \sum_l \left| F_{hkl} \right| e^{-2\pi i (hx + ky + lz - \Phi_{hkl})}$$

fases

O mapa de densidade eletrônica do cristal é o FT reversa do padrão de difração

1) Cristalografia/Difração de Raios X (Xray)

Xray

↓

Amostra

↓

Coleta de dados

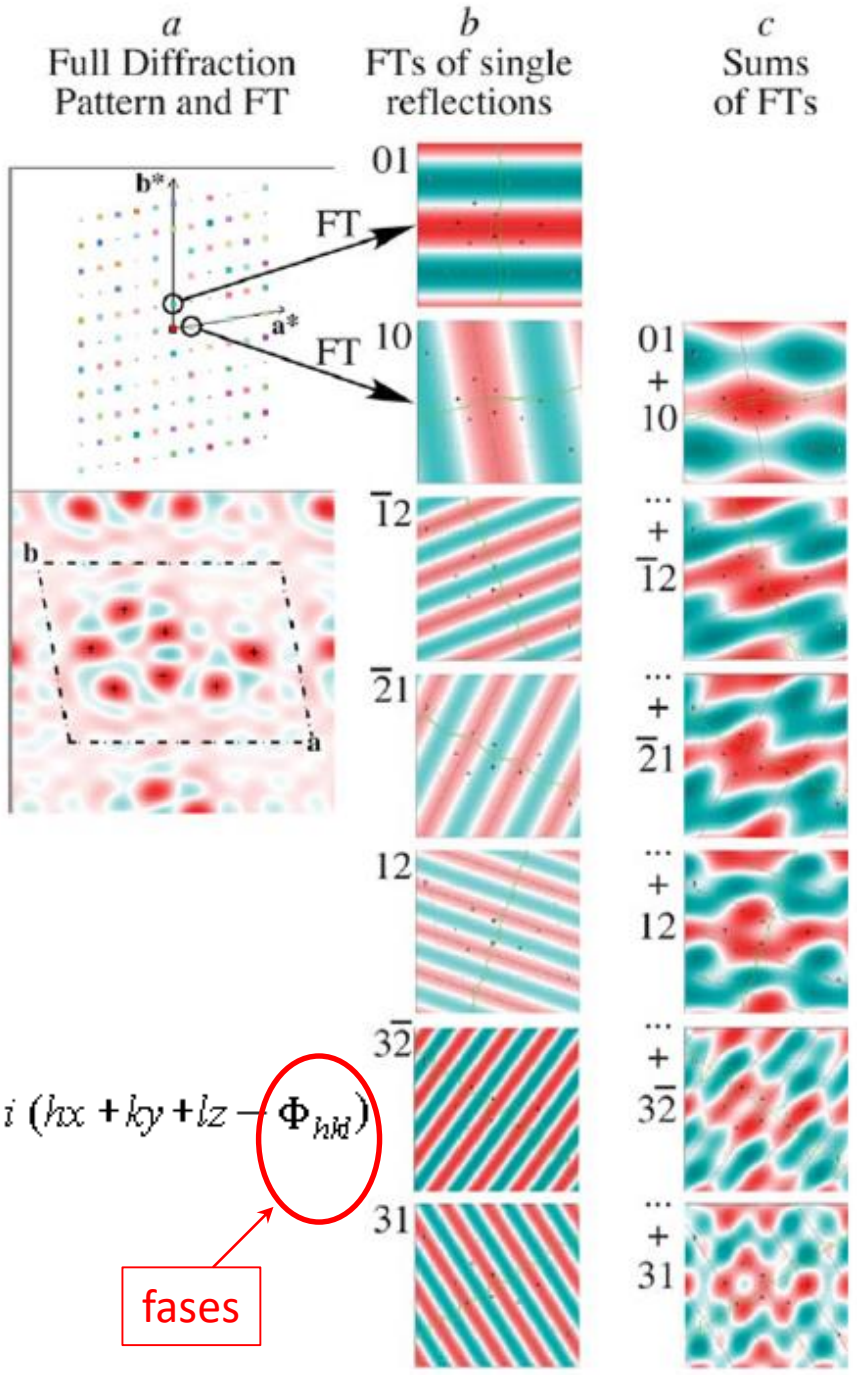
↓

Fases

Mapa de densidade eletrônica

↓

Modelo



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fases

1) Cristalografia/Difração de Raios X (Xray)

Xray

⬇

Amostra

⬇

Coleta de dados

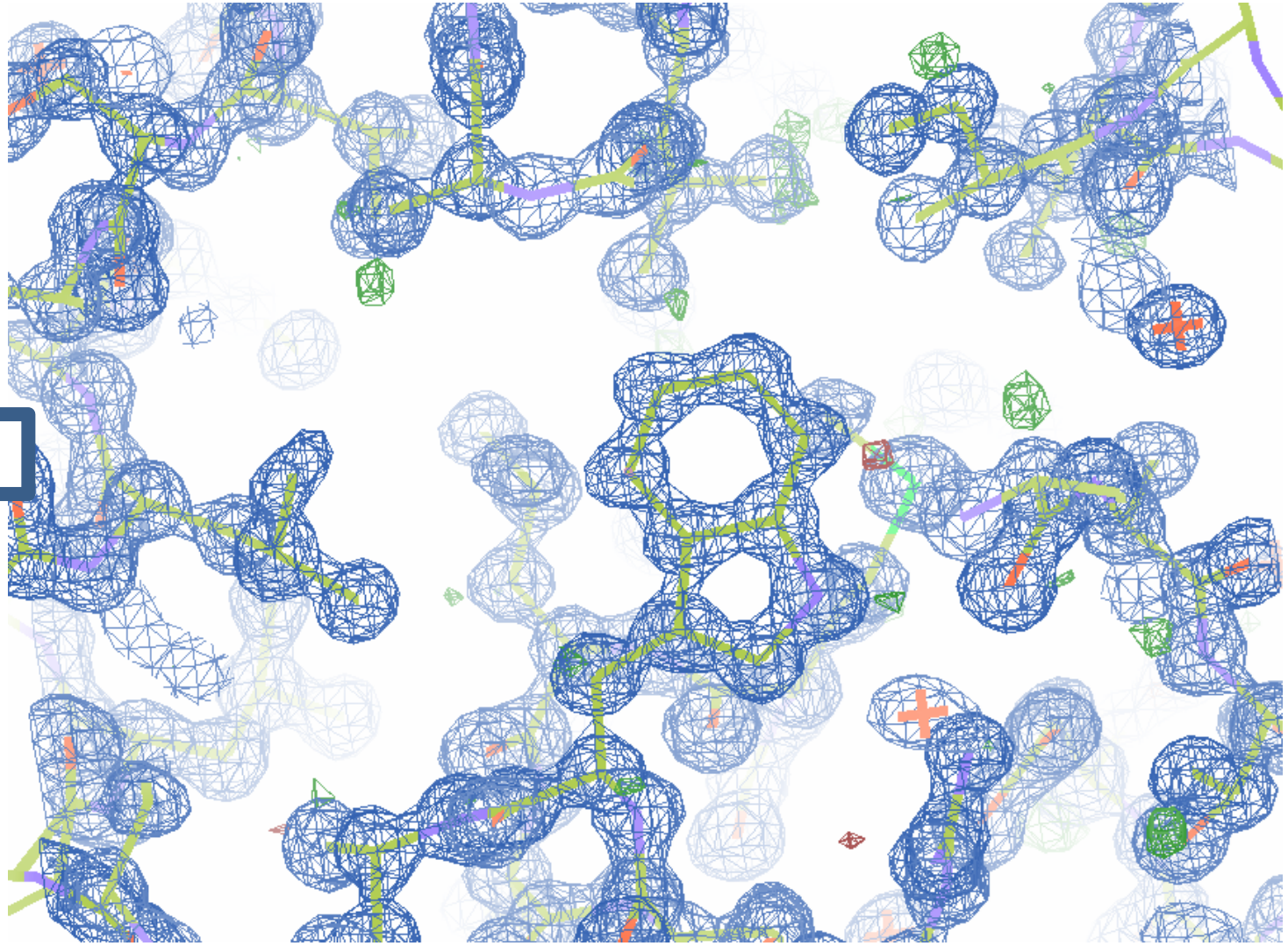
⬇

Fases

Mapa de densidade eletrônica

⬇

Modelo



1) Cristalografia/Difração de Raios X (Xray)

- Xray
- Amostra
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- Fases
- Mapa de densidade eletrônica
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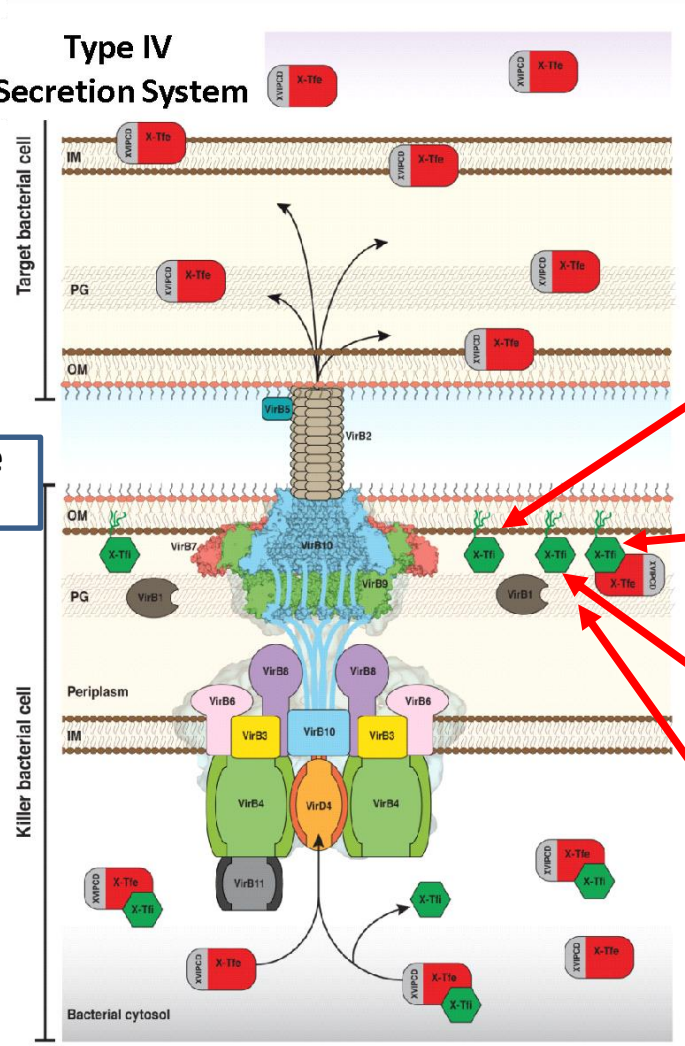

Souza et al et al, 2015
Bayer-Santos et al, 2019
and unpublished

1) Cristalografia/Difração de Raios X (Xray)

Xray

↓

Amostra

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Coleta de dados

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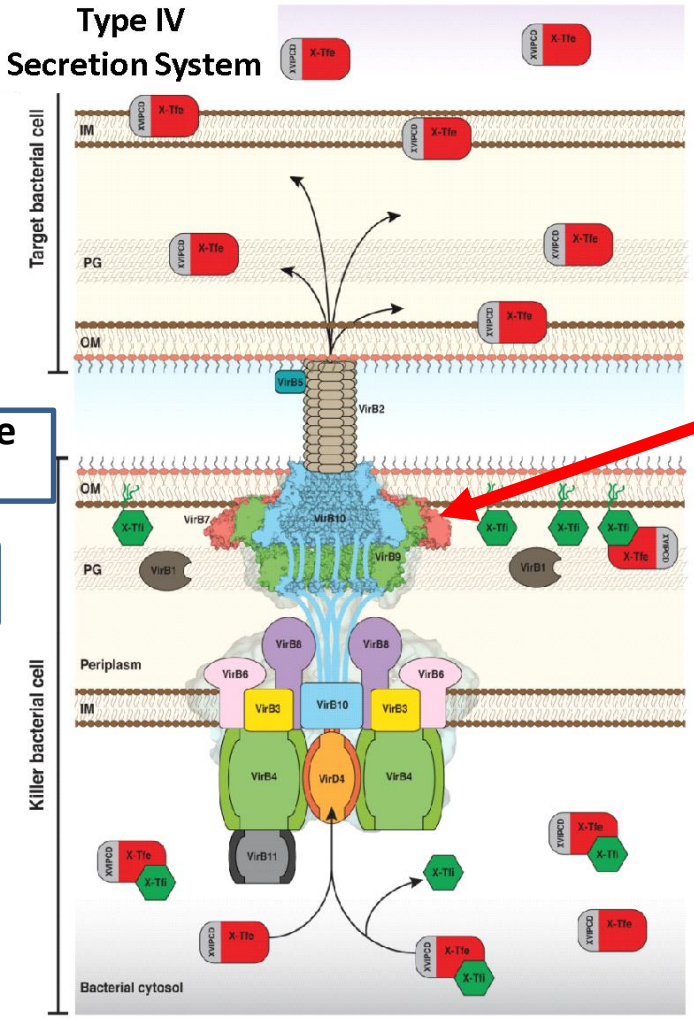
Fases

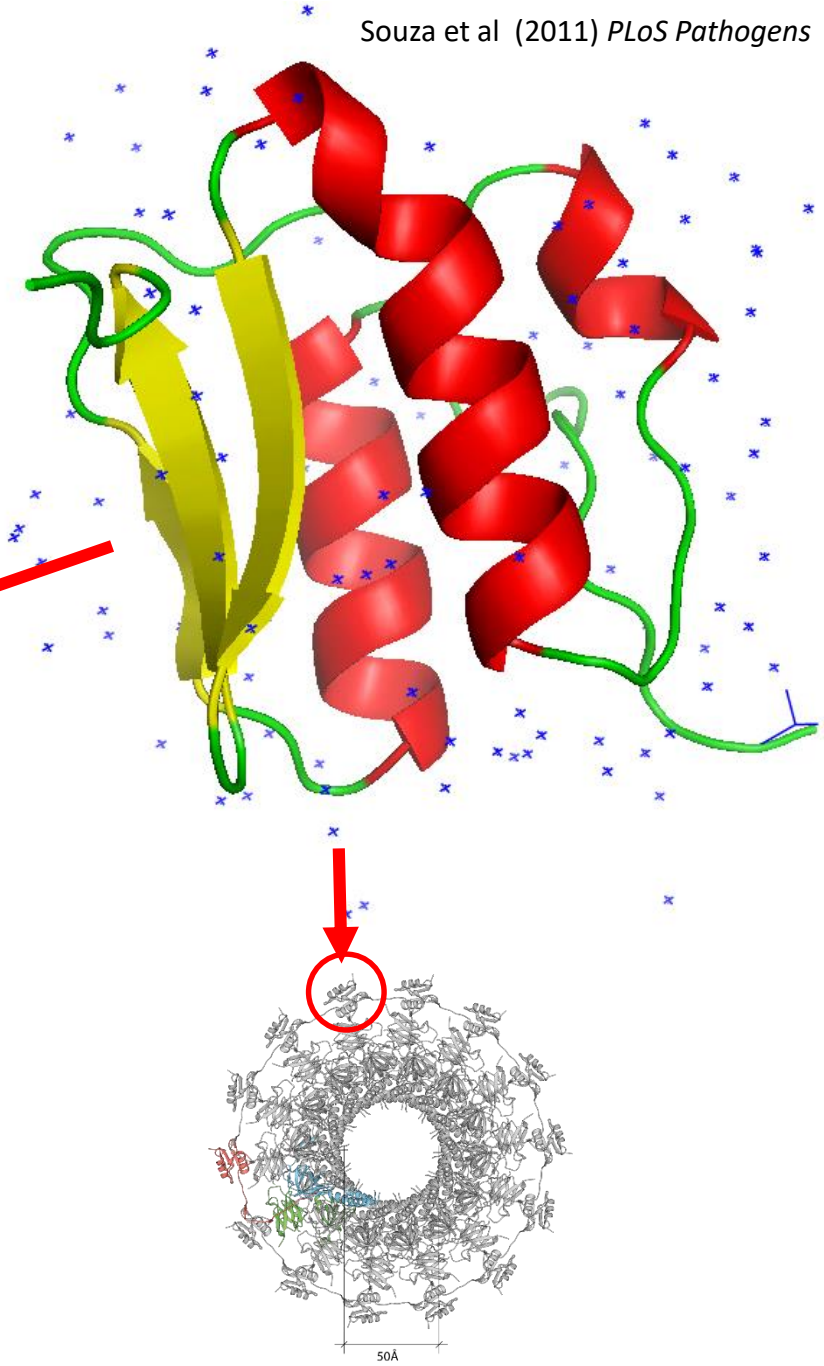
Mapa de densidade eletrônica

↓

Modelo



Souza et al (2011) *PLoS Pathogens*



1)X-ray Crystallography

Advantages:

- Highest resolution
- No theoretical size limit (5000 g/mol to 10^7 g/mol)

Disadvantages:

- Not applicable to highly flexible proteins
- Difficult to study kinetics and dynamics
- Limiting step is obtaining well-diffracting crystals
- Serial Crystallography may overcome many of these limitations

2) Ressonância Magnética Nuclear (NMR)

NMR

↓

Amostra

↓

Coleta de dados

↓

Assinalamentos
NOEs, RDCs, etc

↓

Modelo

2) Ressonância Magnética Nuclear (NMR)

NMR

⬇

Amostra

⬇

Coleta de dados

⬇

Assinalamentos NOEs, RDCs, etc

⬇

Modelo

Central Analítica do IQ-USP

800MHz + cryoprobe,
500 MHz,
300 MHz Instruments

2) Ressonância Magnética Nuclear (NMR)

NMR

⬇

Amostra

⬇

Coleta de dados

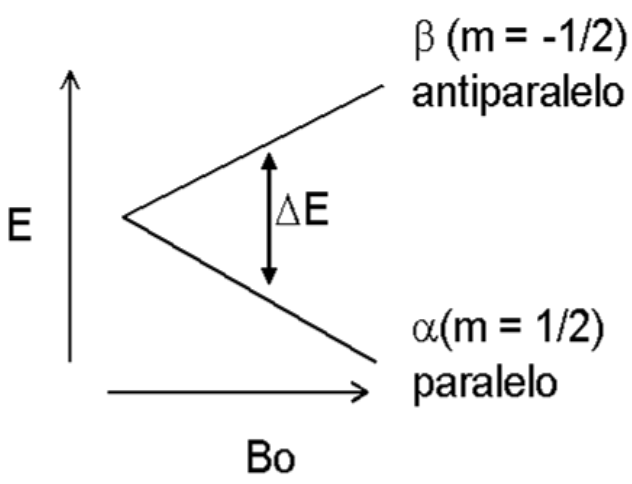
⬇

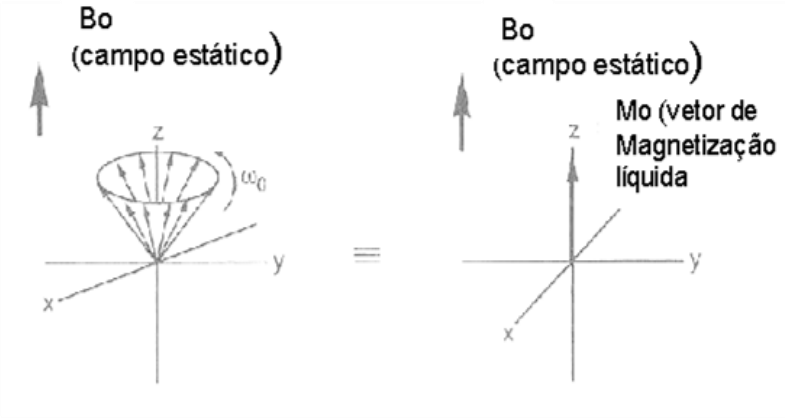
Assinalamentos NOEs, RDCs, etc

⬇

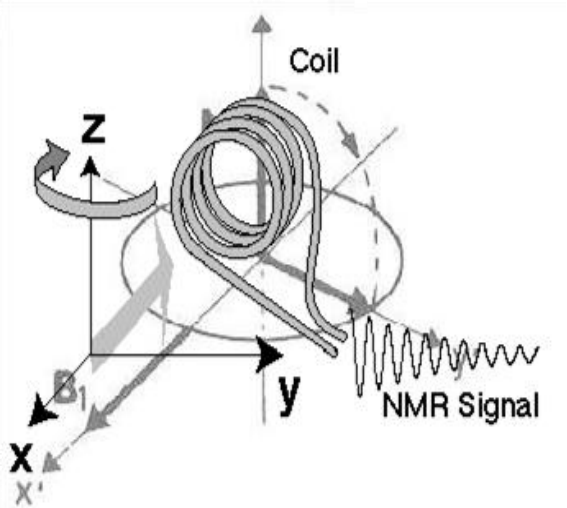
Modelo

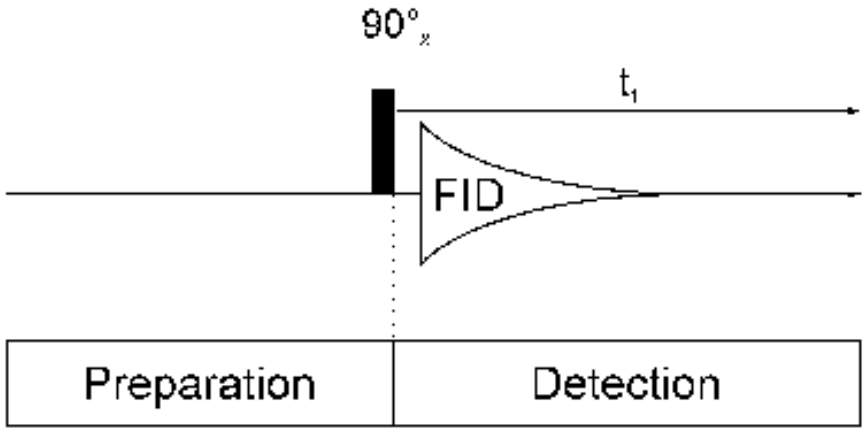
O experimento básico de RMN





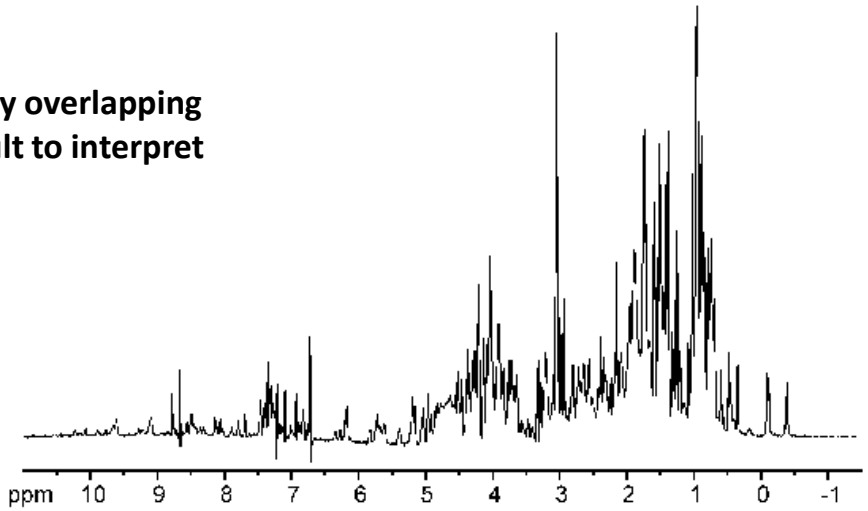
O momento magnético resultante pode ser manipulado por pulsos de radiofrequência, gerando estados de spin que podem ser detectados na bobina da sonda.



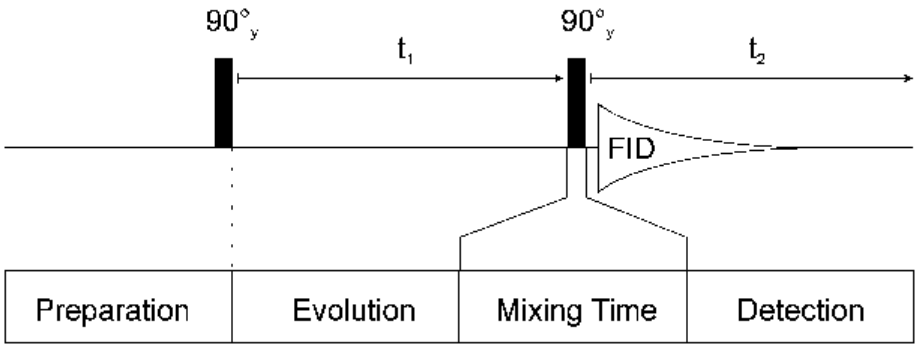


Each 1D NMR experiment consists of two sections: **preparation and detection**.
During preparation the spin-system is set to a defined state.
During detection the resulting signal is recorded.
- In the simplest case the preparation is a 90° pulse which rotates the equilibrium magnetization M_z onto the y axis (M_y).
After this pulse **each spin precesses with its own Larmor frequency** around the z axis and induces a signal in the receiver coil.
- The signal decays due to T2 relaxation and is therefore called **free induction decay (FID).**
Usually, the experiment is repeated several times and the data are summed up to increase the signal to noise ratio.
After summation the data are Fourier transformed to yield the final 1D spectrum.

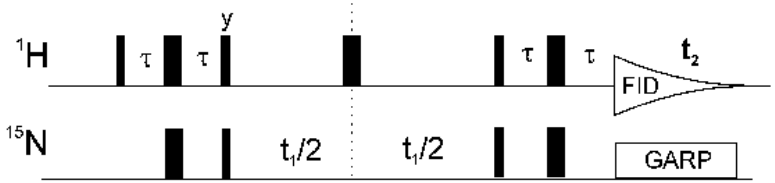
1-D spectrum: many overlapping peaks – very difficult to interpret for large molecules



Homonuclear expts.

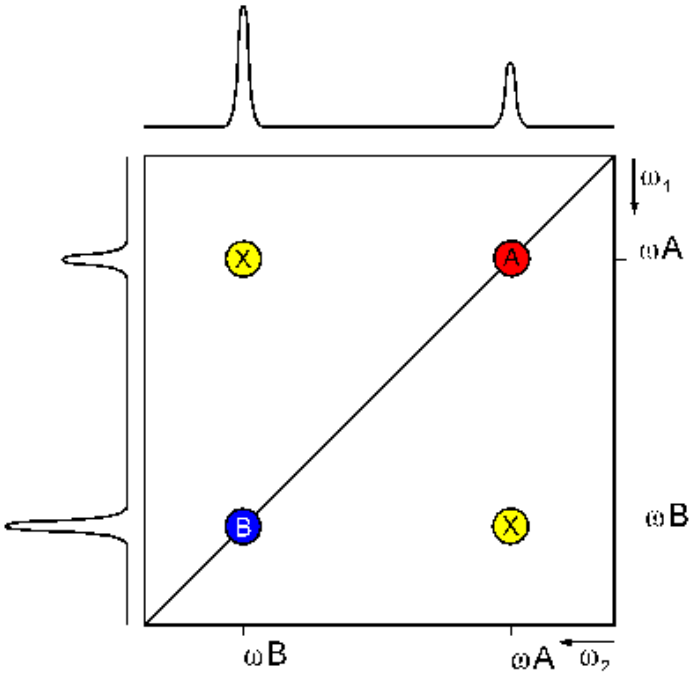


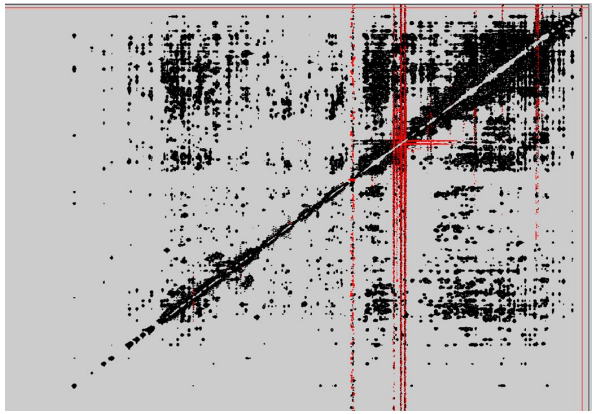
Heteronuclear expts.

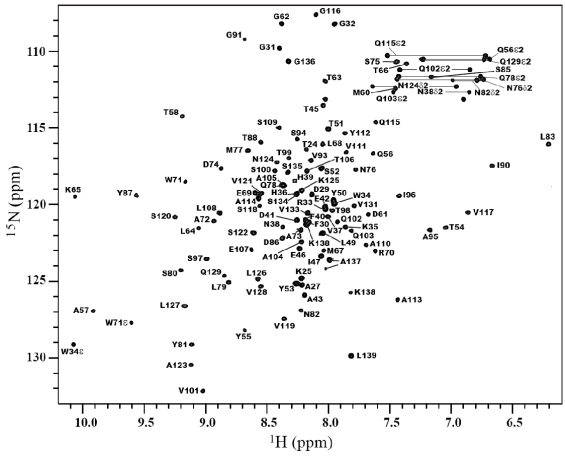


• The construction of a 2D experiment is simple: In addition to preparation and detection which are already known from 1D experiments the 2D experiment has an indirect evolution time t_1 and a mixing sequence. This scheme can be viewed as:
i) Do something with the nuclei (preparation),
ii) let them precess freely (evolution),
iii) do something else (mixing),
iv) and detect the result (detection, **FT of the FID**).

- After preparation the spins can precess freely for a given time t_1. During this time the magnetization is labelled with the chemical shift of the first nucleus.
- During the mixing time magnetization is then transferred from the first nucleus to a second one.
- Mixing sequences utilize two mechanisms for magnetization transfer: scalar coupling or dipolar interaction (NOE).
- Data are acquired at the end of the experiment (detection, often called direct evolution time); during this time the magnetization is labelled with the chemical shift of the second nucleus.







Two dimensional FT yields the 2D spectrum with two frequency axes

The diagonal results from contributions of the magnetization that has not been changed by the mixing sequence (equal frequency in both dimensions) i.e. from contributions which remained on the same nucleus during both evolution times.

The cross signals (“cross peaks”) originate from nuclei that exchanged magnetization during the mixing time (frequencies of the first and second nucleus in each dimension, respectively). They indicate an interaction of these two nuclei. Therefore, the cross signals contain the really important information of 2D NMR spectra.

2) Ressonância Magnética Nuclear (NMR)

NMR

↓

Amostra

↓

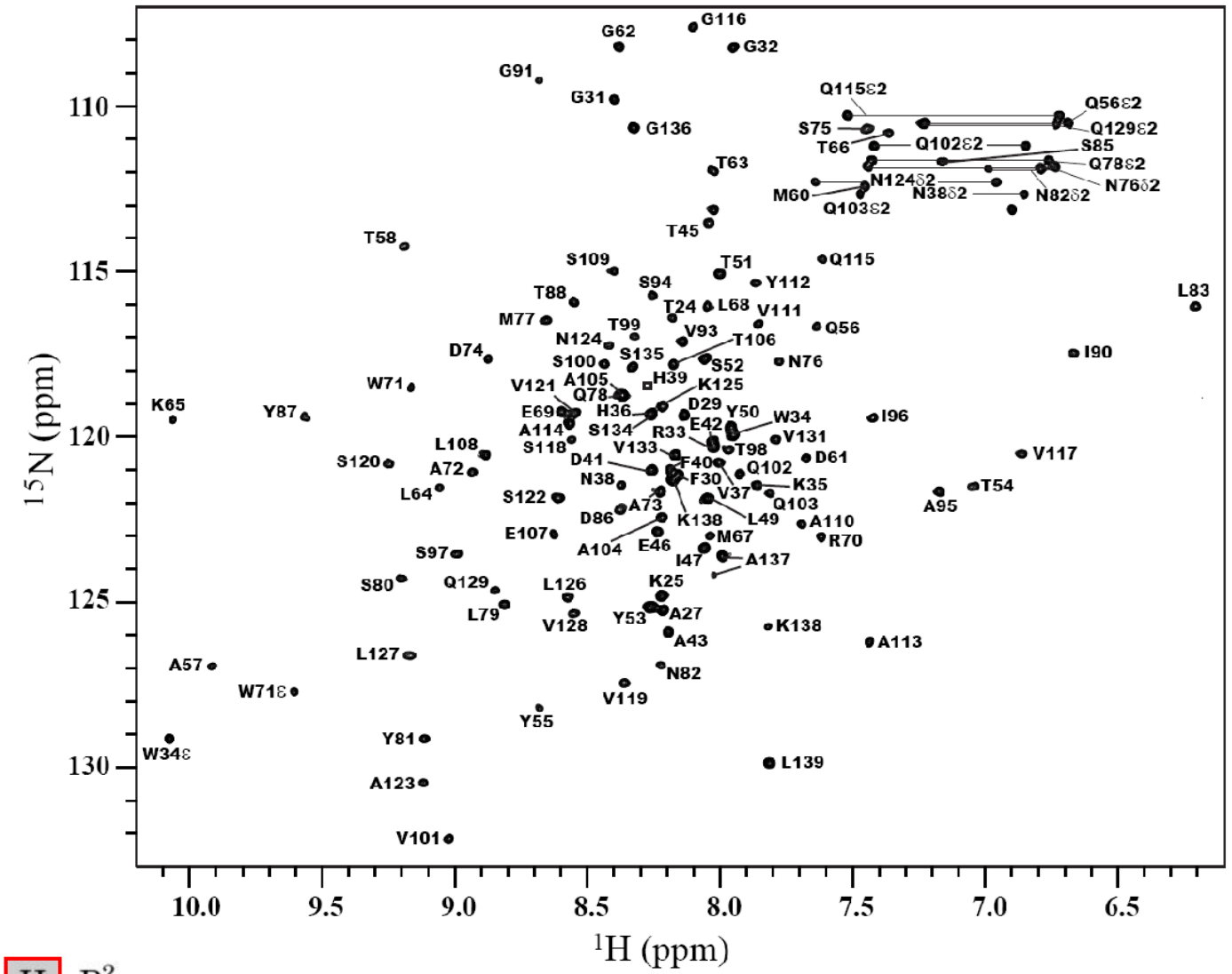
Coleta de dados

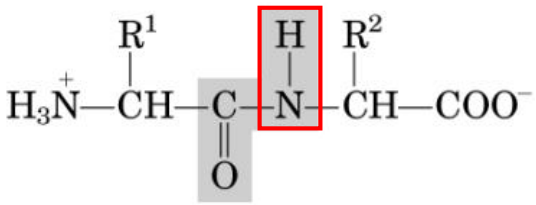
↓

Assinalamentos NOEs, RDCs, etc

↓

Modelo





Assinalamento por meio de experimentos para identificar sinais de átomos conectados por um ou mais ligações no mesmo resíduo ou em resíduos adjacentes.

2) Ressonância Magnética Nuclear (NMR)

NMR

⬇

Amostra

⬇

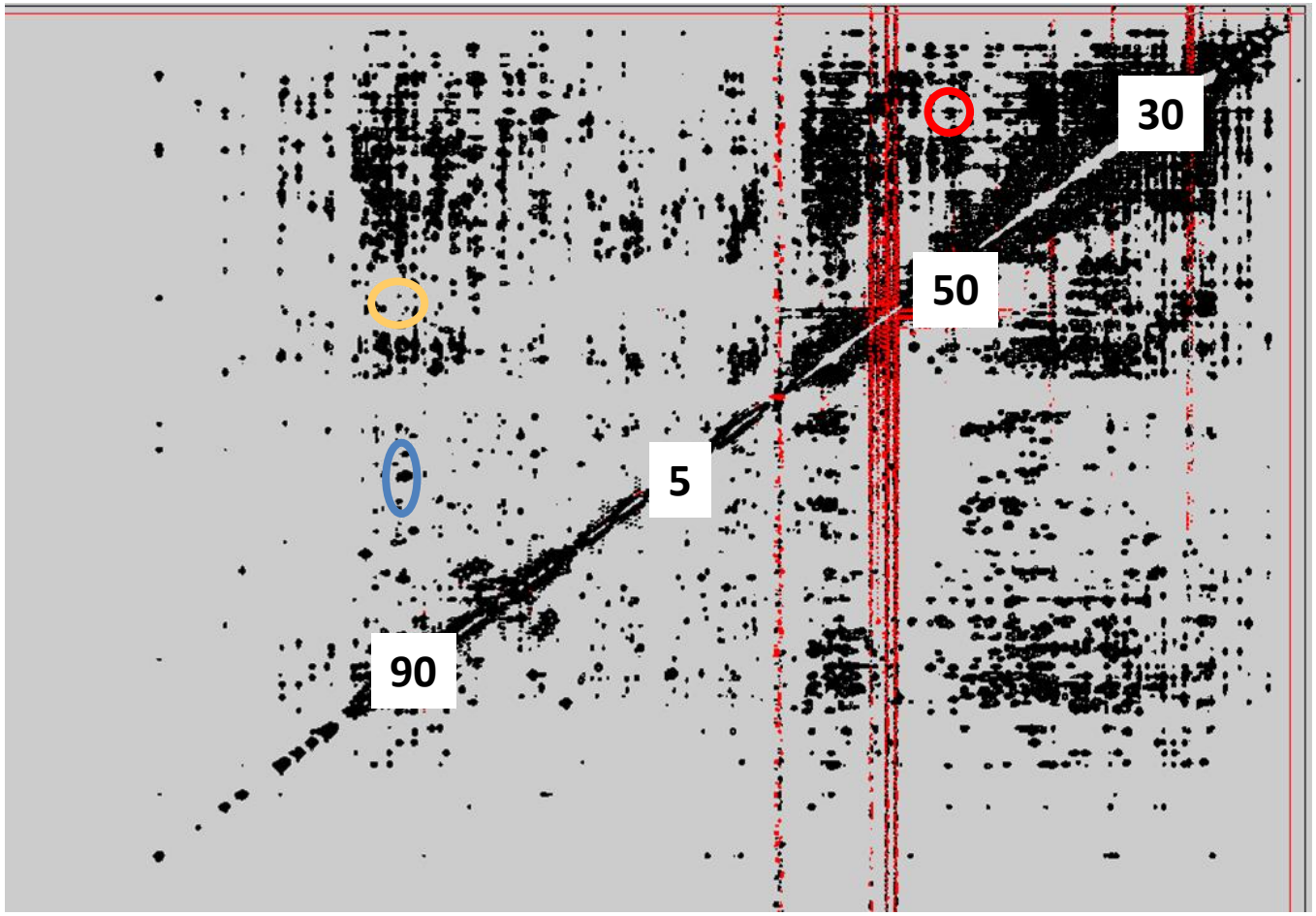
Coleta de dados

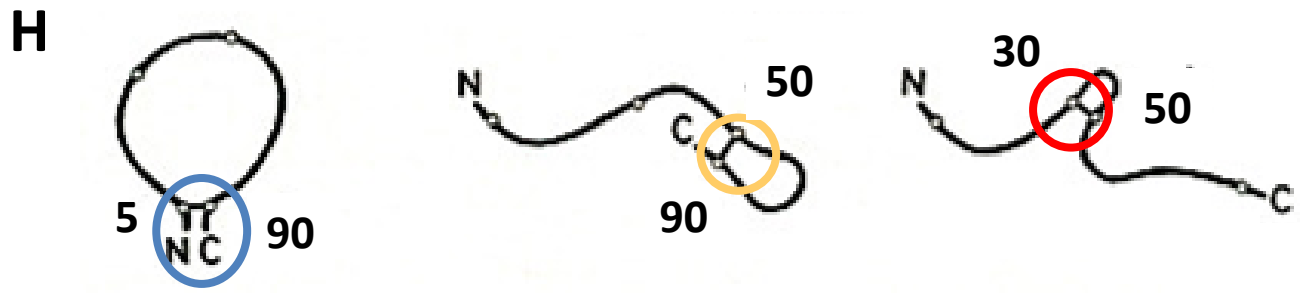
⬇

Assinalamentos NOEs, RDCs, etc

⬇

Modelo





Experimentos para detectar sinais de hidrogênio que estão próximos no espaço (5 Å)

2) Ressonância Magnética Nuclear (NMR)

NMR

↓

Amostra

↓

Coleta de dados

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Assinalamentos NOEs, RDCs, etc

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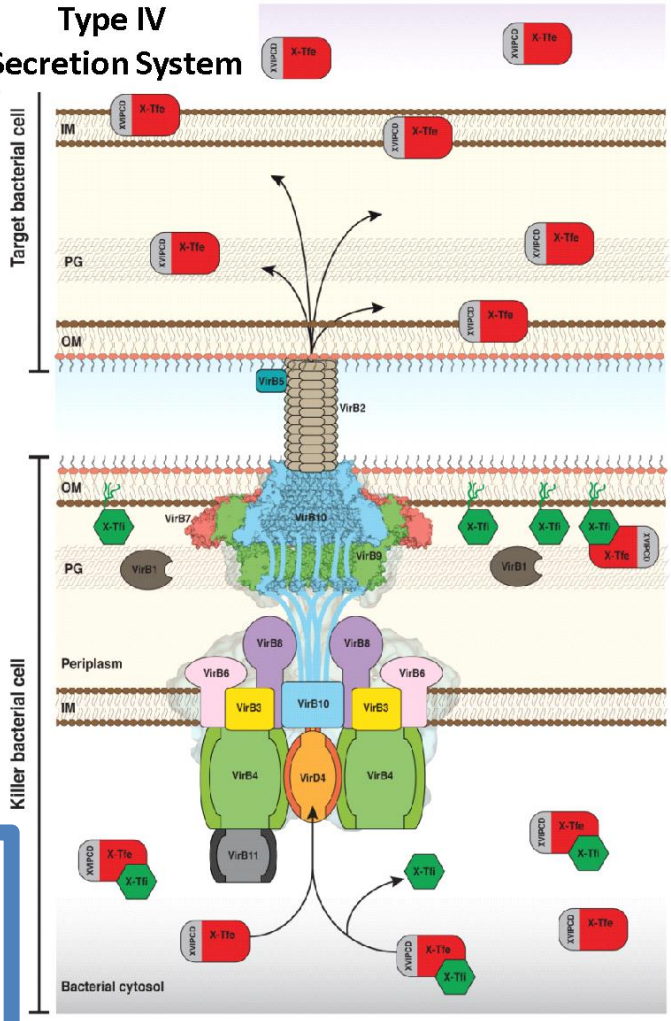
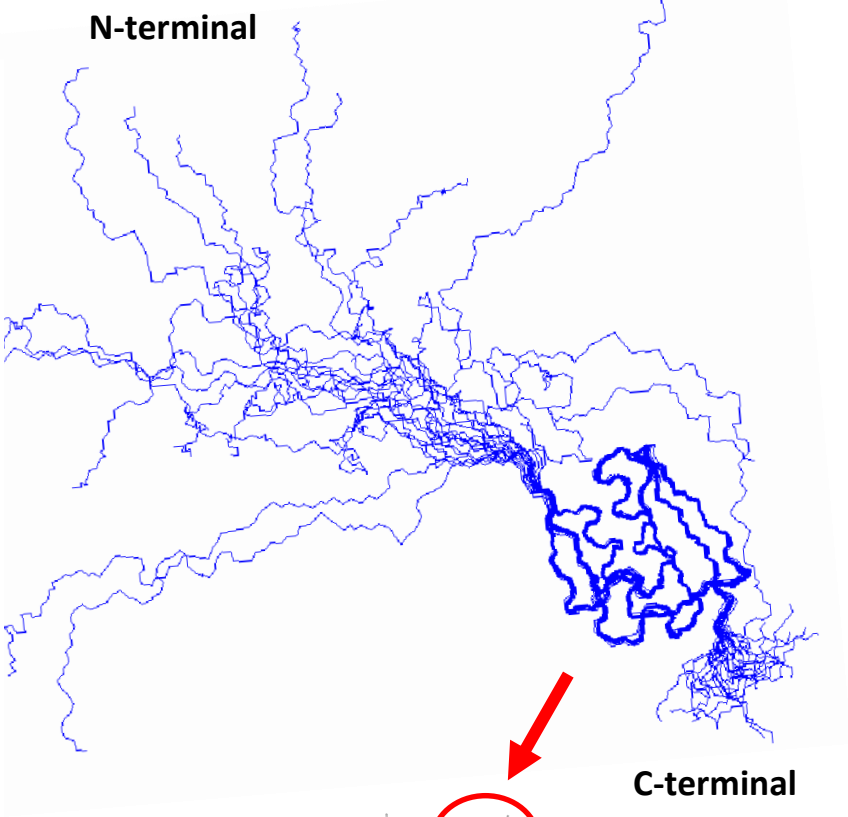
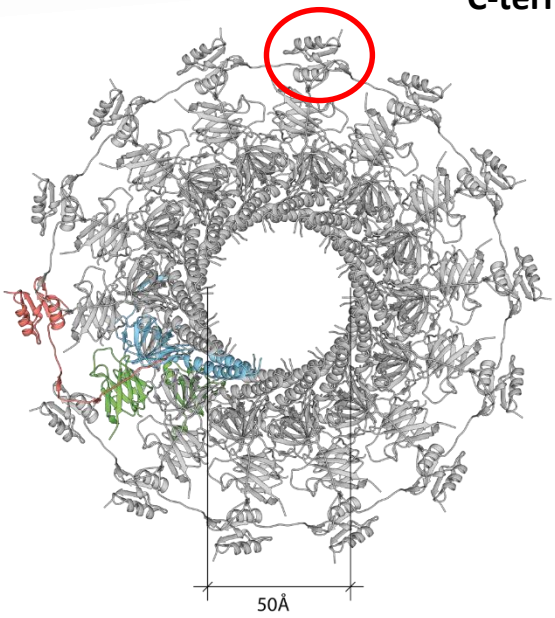
Modelo

↓

Dinâmica conformational, Interações,







Souza et al (2011) *PLoS Pathogens*

2) Ressonância Magnética Nuclear (NMR)

NMR

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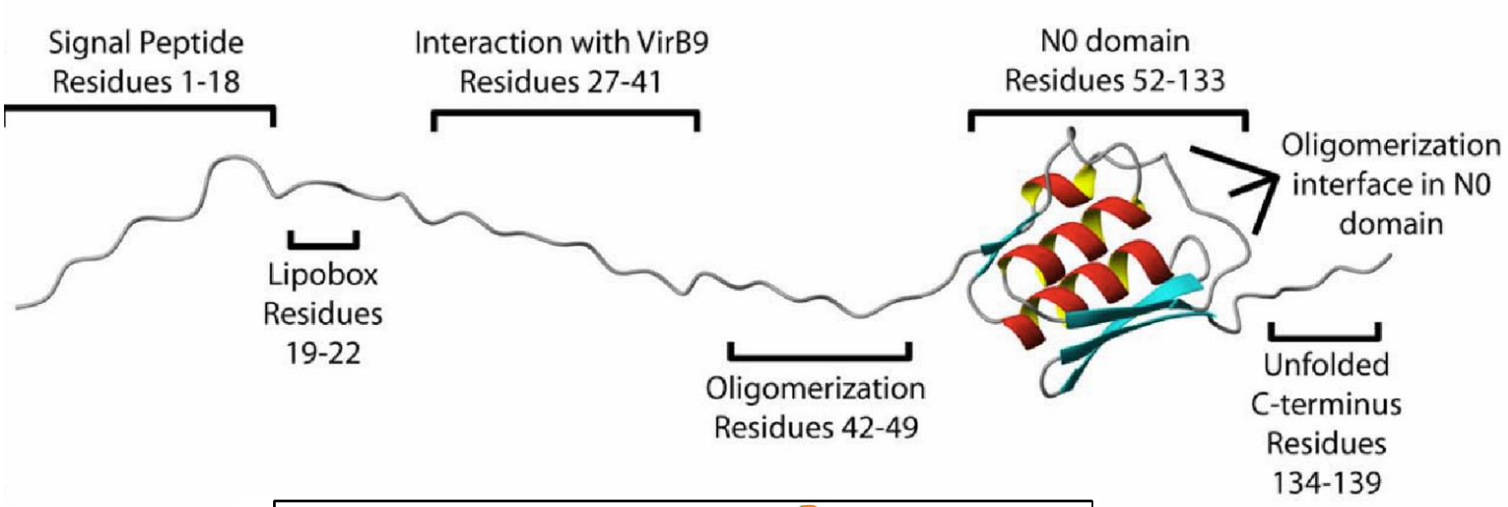

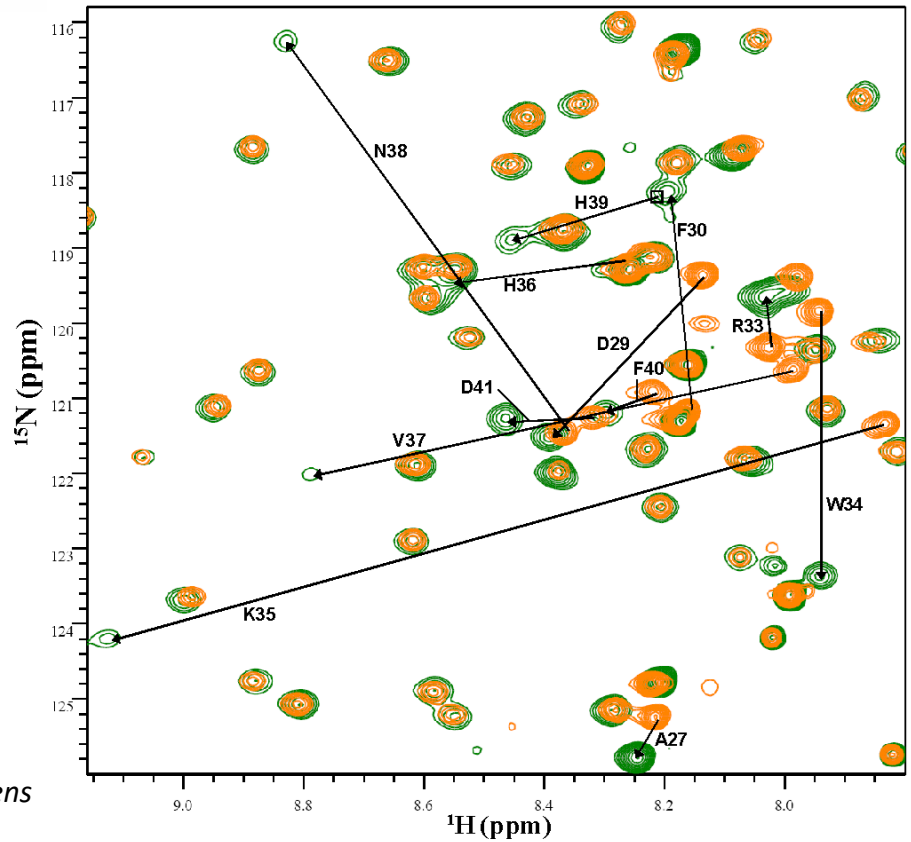

Souza et al (2011) *PLoS Pathogens*

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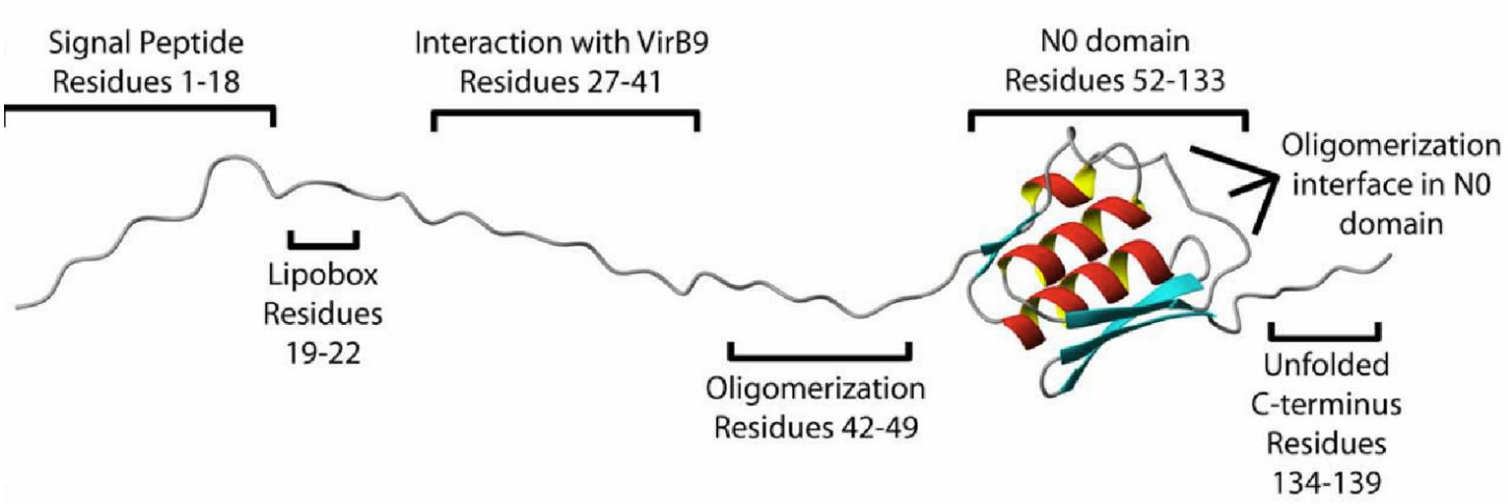
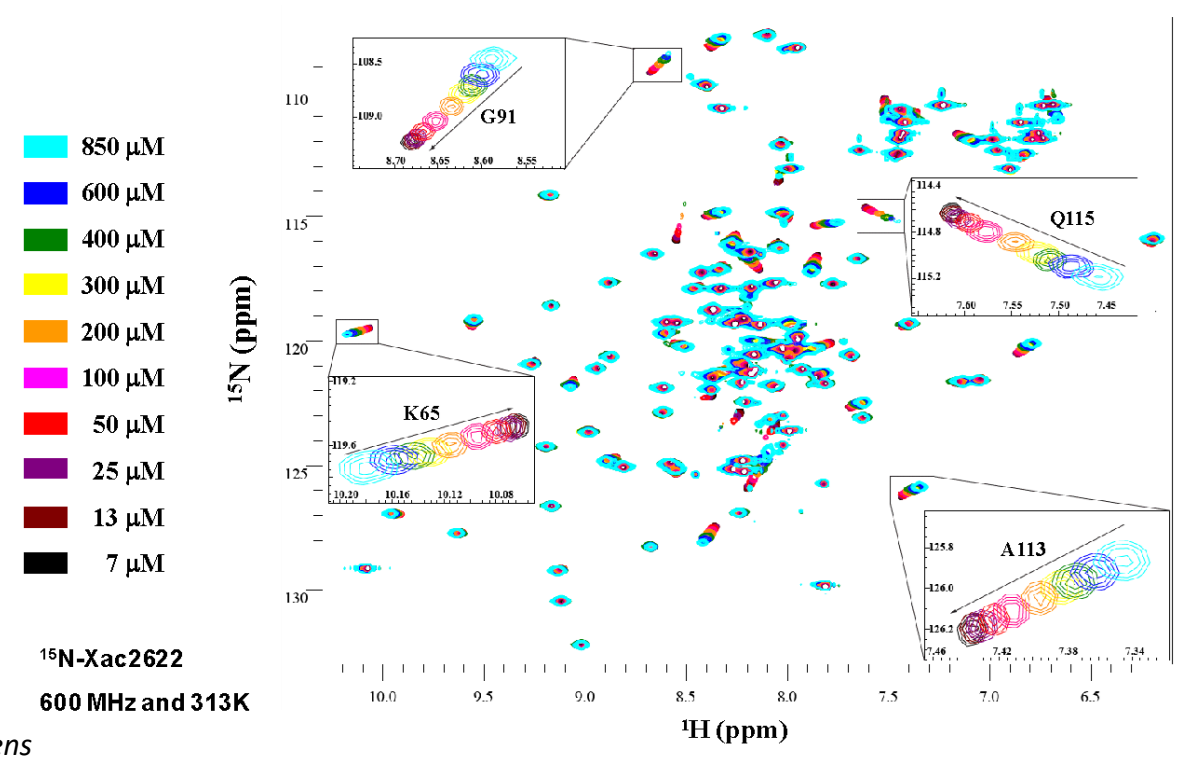
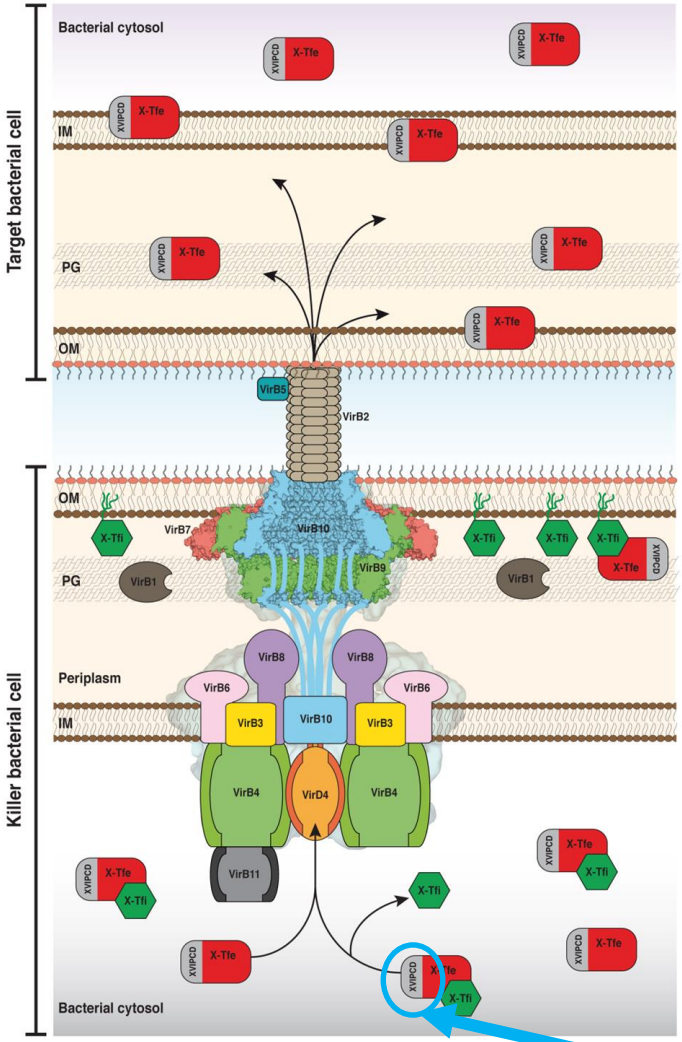
Dinâmica conformational, Interações,

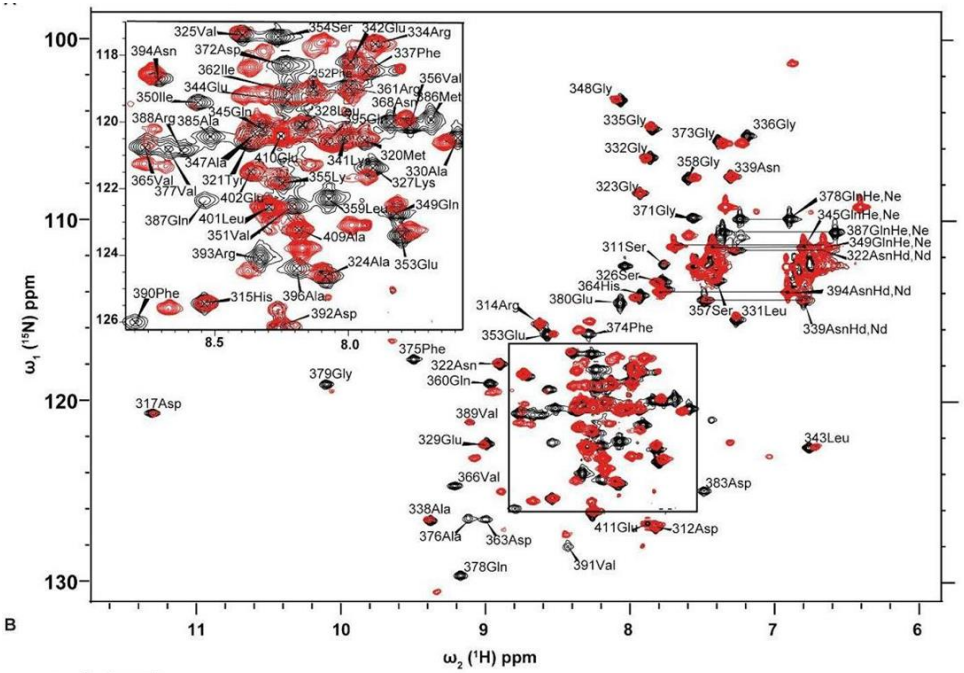


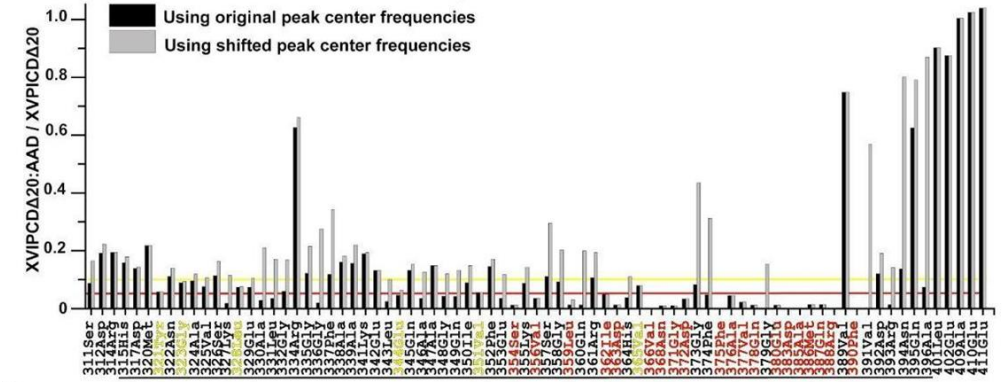


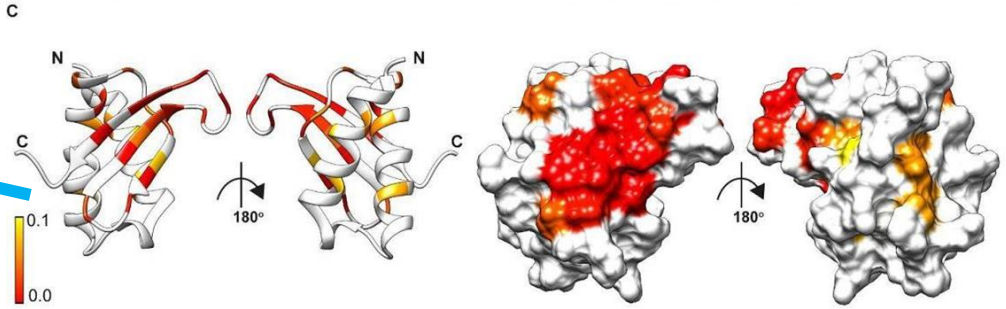
Souza et al (2011) *PLoS Pathogens*

2) Ressonância Magnética Nuclear (NMR)









Gabriel Oka *et al.* (2022) PNAS

2) NMR

Advantages:

- Applicable to small proteins and peptides (up to 30 – 50 kDa)
- Can be used to study conformational dynamics with frequencies of 10^{-9} s to 1 s
- Can be used to study kinetics of molecular interactions and protein folding

- *Disadvantages:*

- Upper size limit: < 30 - 50 kDa

3) Crio-microscopia eletrônica (CryoEM)

CryoEM

⬇

Amostra

⬇

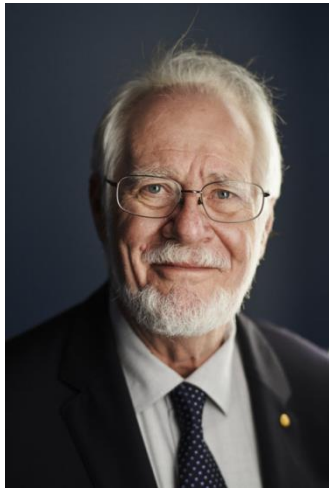
Coleta de dados

⬇

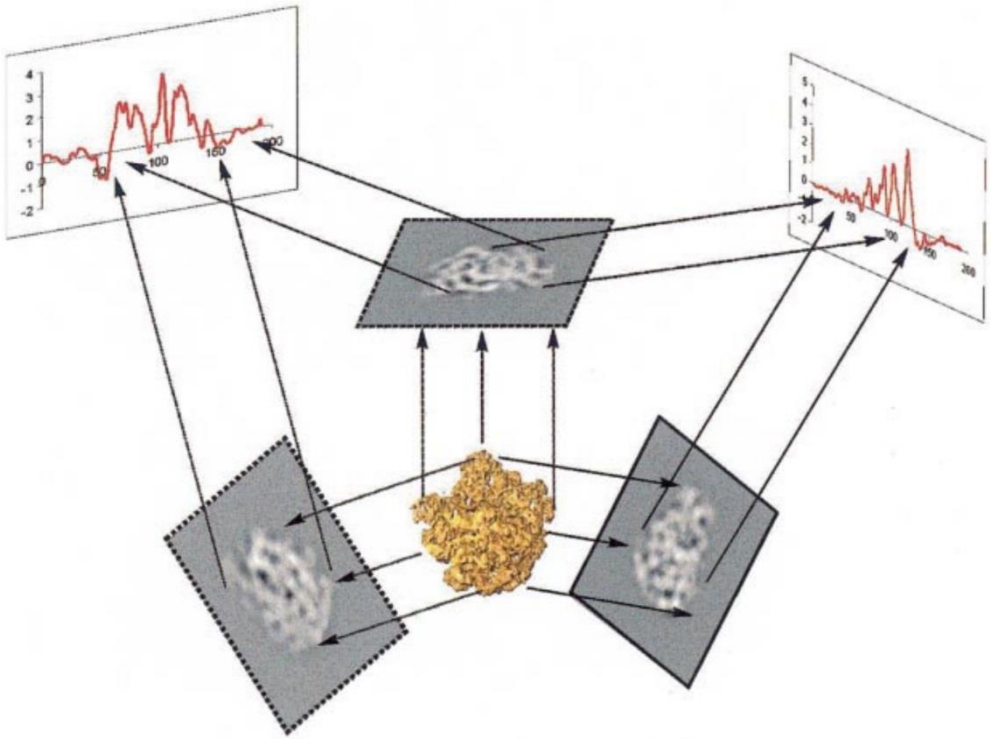
Mapa de CryoEM

⬇

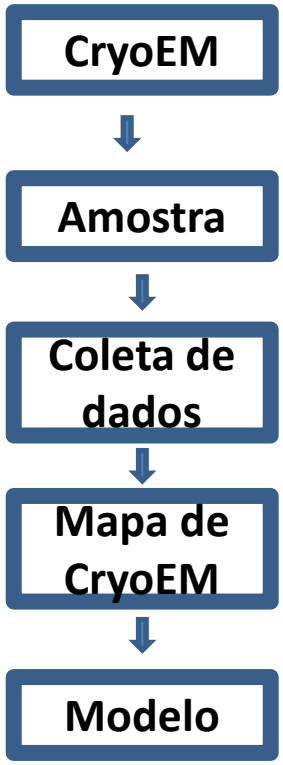
Modelo



The Nobel Prize in Chemistry 2017 was awarded jointly to Jacques Dubochet, Joachim Frank and Richard Henderson "for developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution."



3) Crio-microscopia eletrônica (CryoEM)



https://www.youtube.com/watch?v=BJKkC0W-6Qk&feature=youtu.be

INFRAESTRUTURA PARA CRYO-EM SP

Laboratório Nacional de Nanotecnologia (LNNano)
Rodrigo Portugal and Marin van Heel

IQ-USP
Central Analítica

JEOL JEM 2100
LaB6 filament
200 kV
×1,500,000 mag
Cryogenic sample holder

FEI Talos Arctica G2
Falcon 3
Ceta

FEI Titan Krios G3i
Cs Corrected
Energy filter, Phase Plate
Falcon 3, Bioquantum K3
Ceta

Complete sample preparation lab

Cryobot for preparation of frozen samples
Glow-discharge apparatus

3) Crio-microscopia eletrônica (CryoEM)

CryoEM

⬇

Amostra

⬇

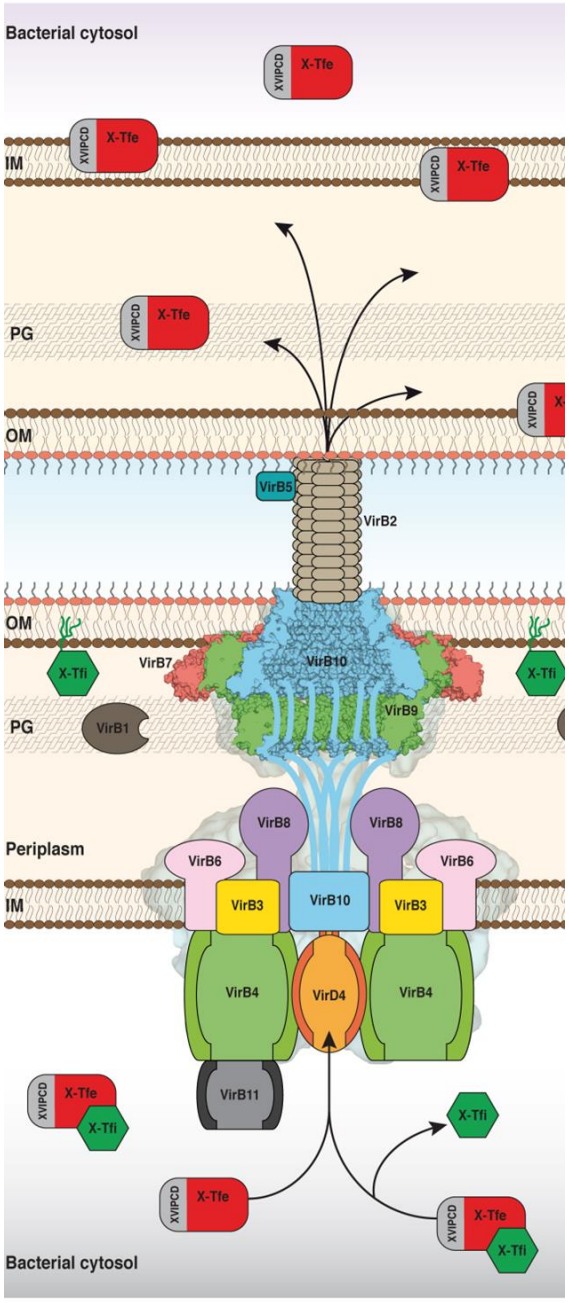
Coleta de dados

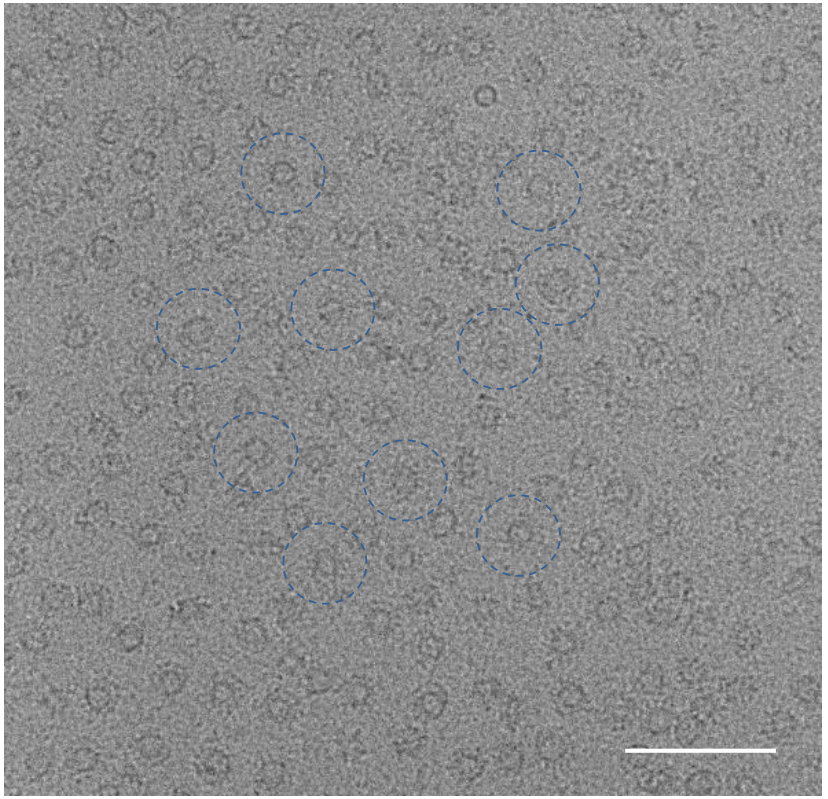
⬇

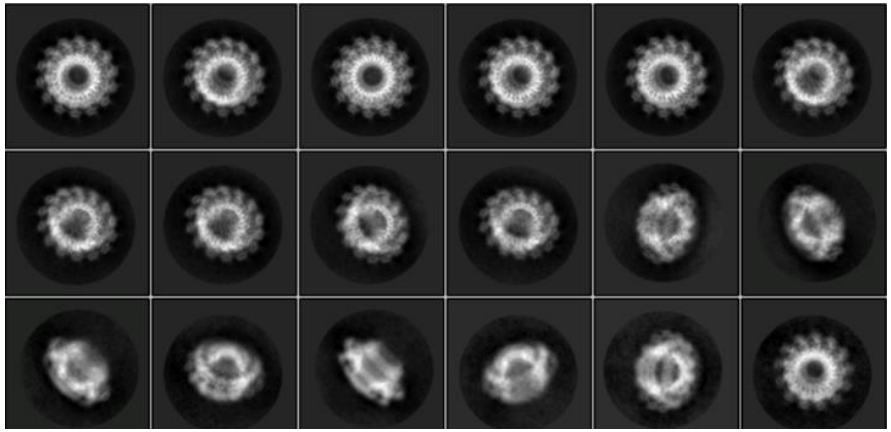
Mapa de CryoEM

⬇

Modelo







Sgro *et al.* (2018) *Nature Microbiology*

3) Crio-microscopia eletrônica (CryoEM)

CryoEM

⬇

Amostra

⬇

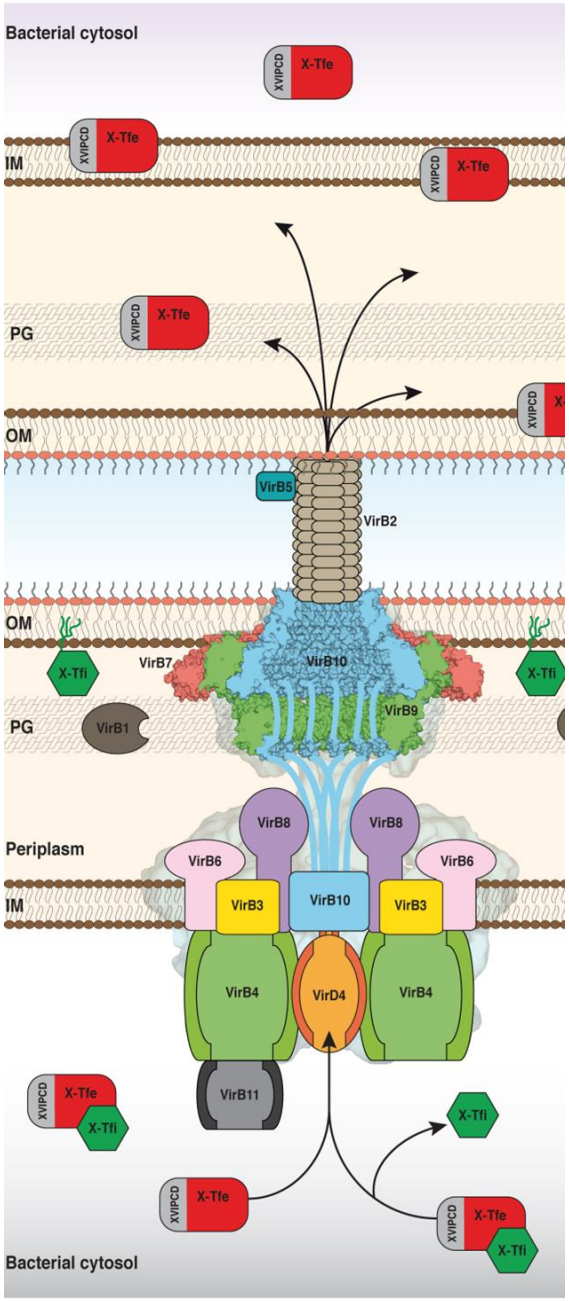
Coleta de dados

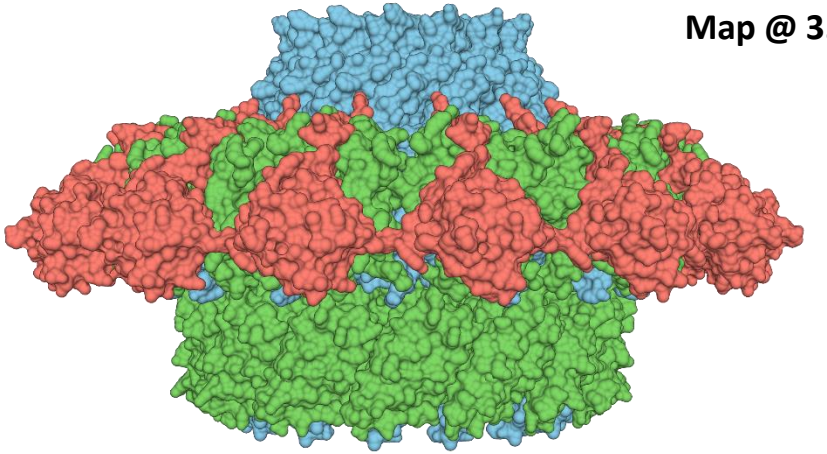
⬇

Mapa de CryoEM

⬇

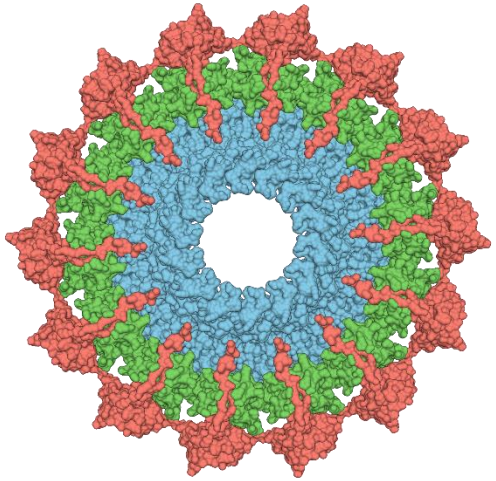
Modelo



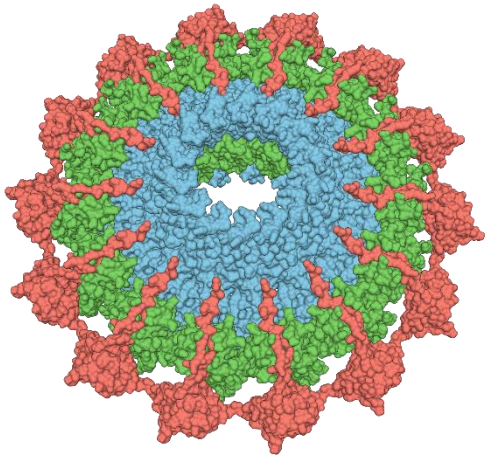


Map @ 3.3 Å

Side view



Top view



Tilt view

Sgro *et al.* (2018) *Nature Microbiology*

3) Crio-microscopia eletrônica (CryoEM)

CryoEM

⬇

Amostra

⬇

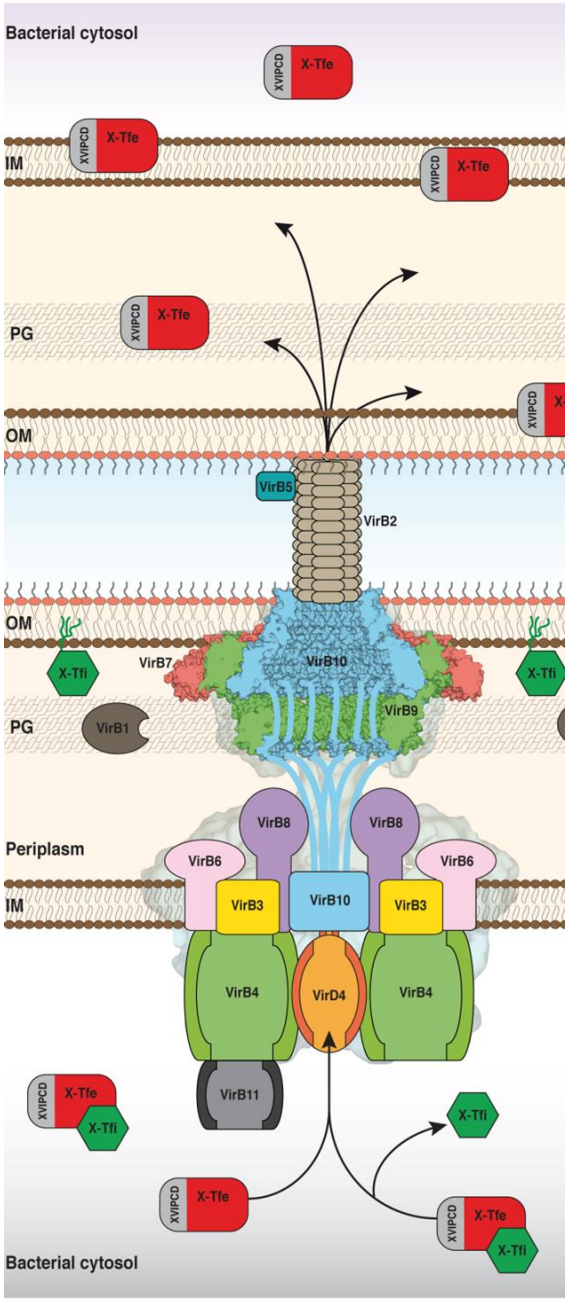
Coleta de dados

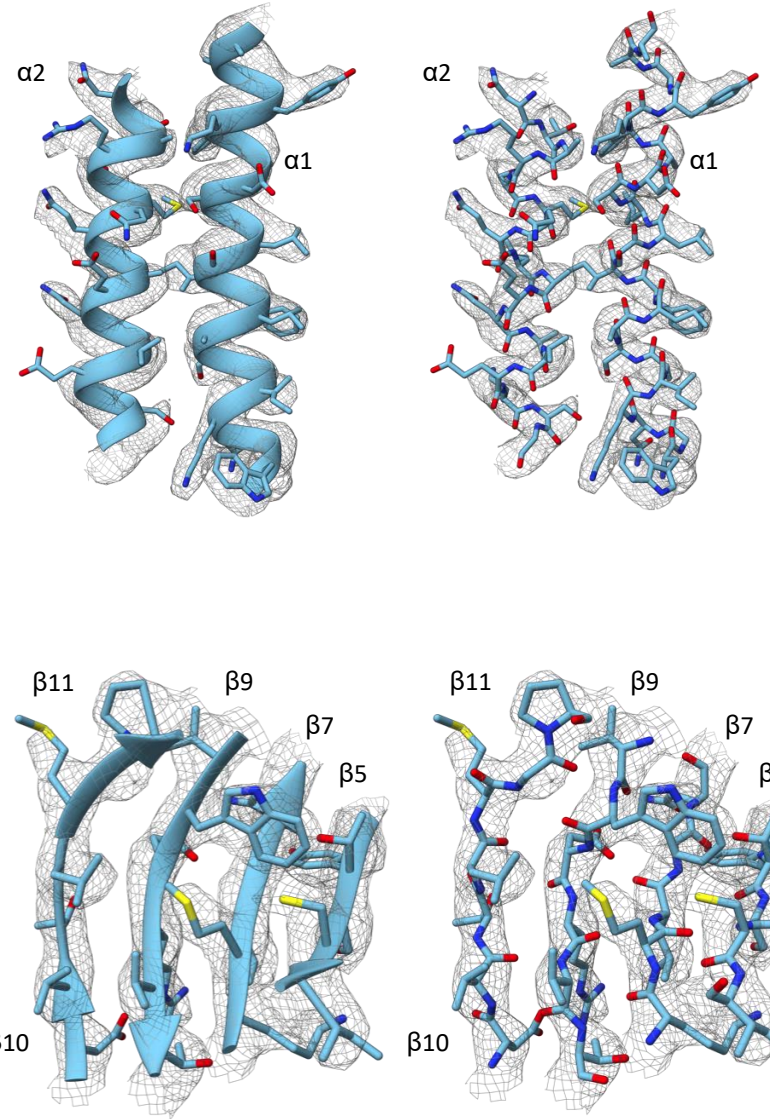
⬇

Mapa de CryoEM

⬇

Modelo



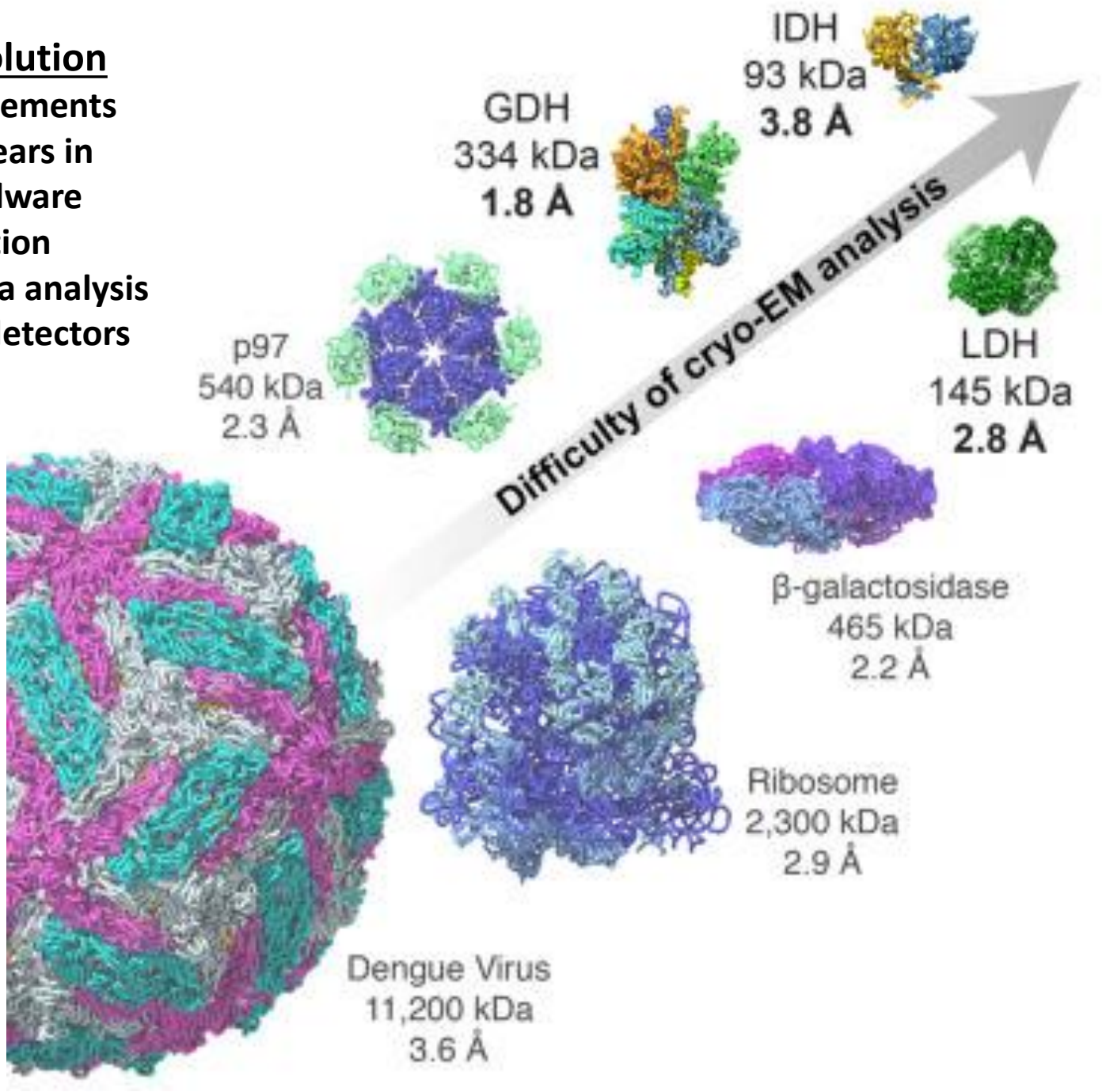


Sgro *et al.* (2018) *Nature Microbiology*

Resolution Revolution

important improvements over the last 10 years in

- **Microscope hardware**
- **Sample preparation**
- **Software for data analysis**
- **Direct electron detectors**



Breaking the next Cryo-EM resolution barrier – Atomic resolution determination of proteins!

bioRχiv
THE PREPRINT SERVER FOR BIOLOGY

Ka Man Yip, Niels Fischer, Elham Paknia, Ashwin Chari, Holger Stark
doi: https://doi.org/10.1101/2020.05.21.106740

Here we report a 1.25 Å resolution structure of apoferritin obtained by cryo-EM with a newly developed electron microscope providing unprecedented structural details.

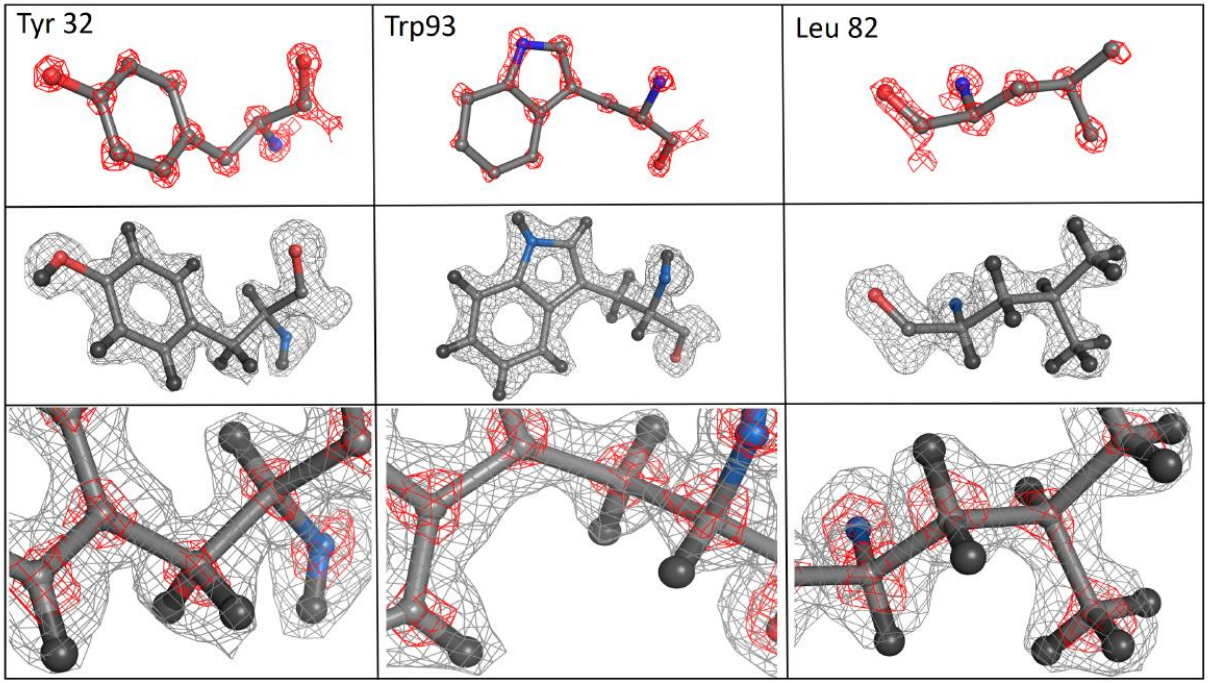


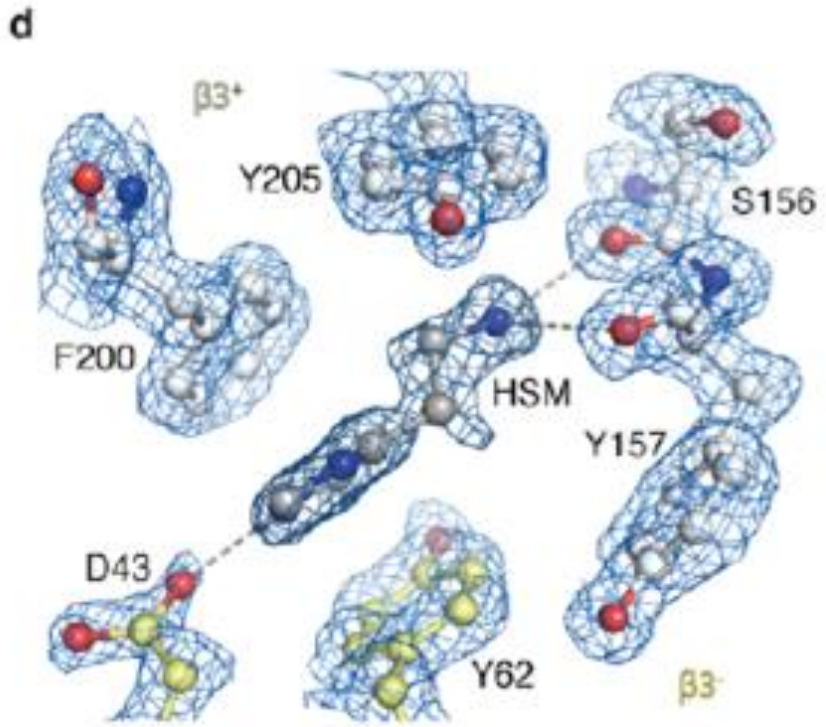
Fig. 3 True atomic resolution: Visualization of individual atoms and hydrogens at 1.25 Å resolution

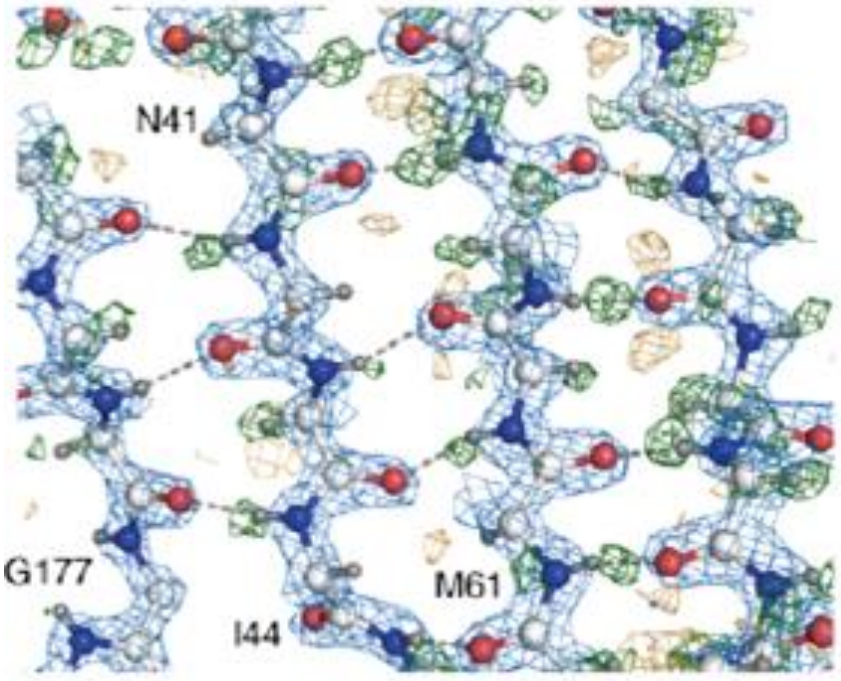
Single-particle cryo-EM at atomic resolution

bioRχiv
THE PREPRINT SERVER FOR BIOLOGY

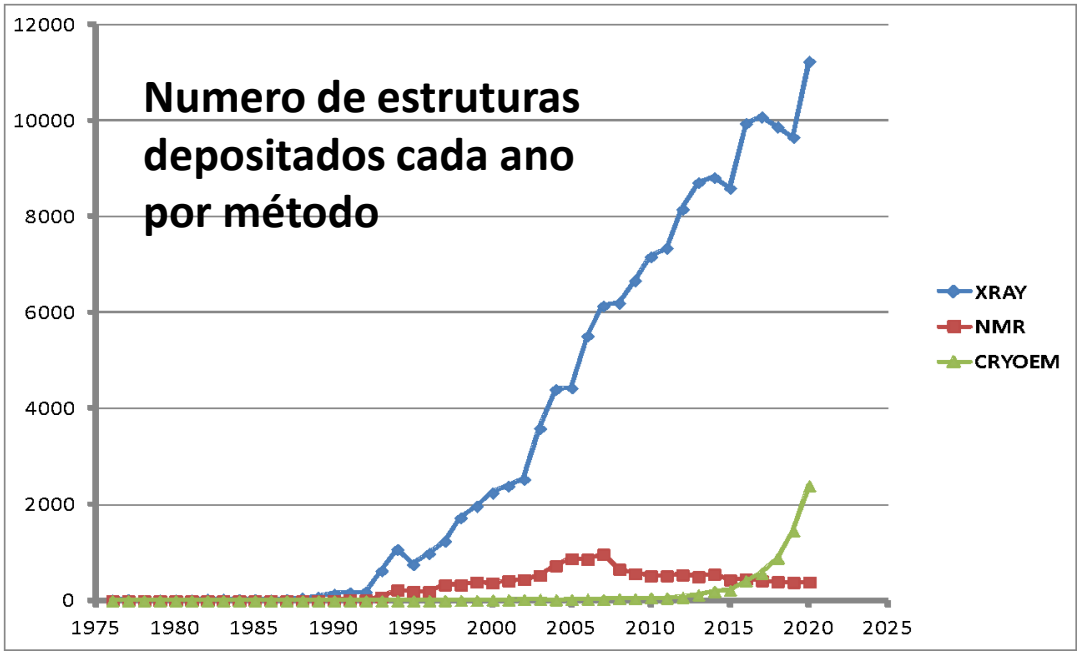
Takanori Nakane, Abhay Kotecha, Andrija Sente, ... and Sjors H.W. Scheres
doi: https://doi.org/10.1101/2020.05.22.110189

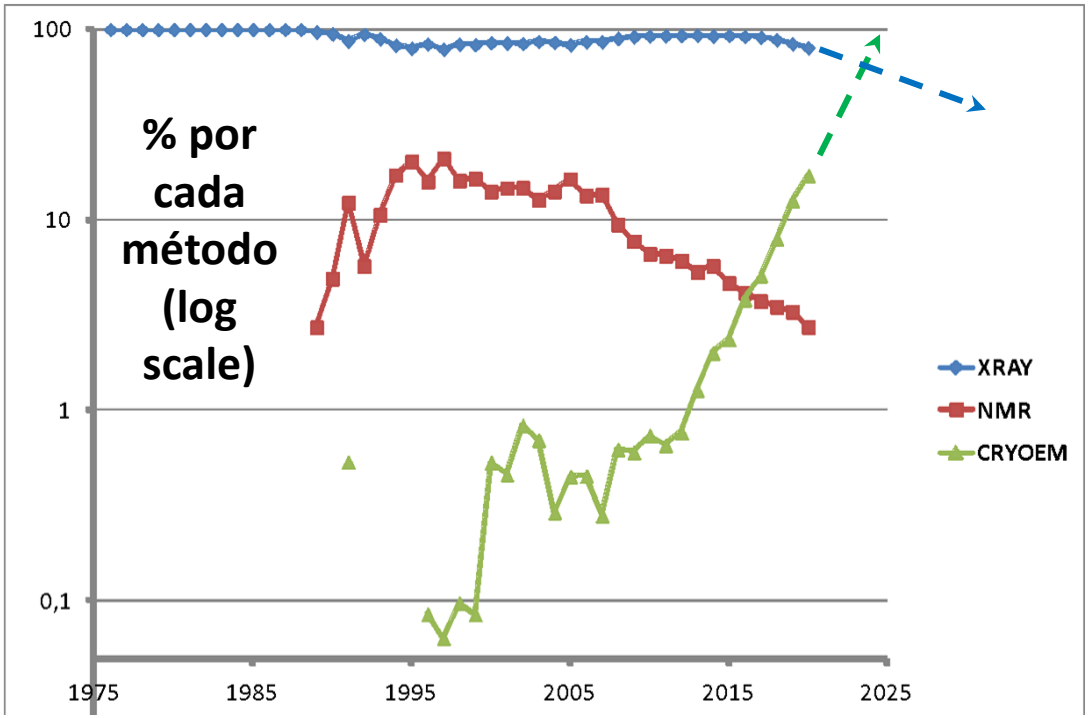
Here, we show that using a new electron source, energy filter and camera, we obtained a 1.7 Å resolution cryo-EM reconstruction for a prototypical human membrane protein, the β3 GABAA receptor homopentamer. Applied to mouse apo-ferritin, our strategy led to a 1.2 Å resolution





O número de novas estruturas determinadas por Cryo-EM está crescendo exponencialmente e pode igualar a de cristalografia nos próximos 5 anos





1) X-ray Crystallography

Advantages:

- Highest resolution
- No theoretical size limit (5000 g/mol to 10^7 g/mol)

Disadvantages:

- Not applicable to highly flexible proteins
- Difficult to study kinetics and dynamics
- Limiting step is obtaining well-diffracting crystals

2) NMR

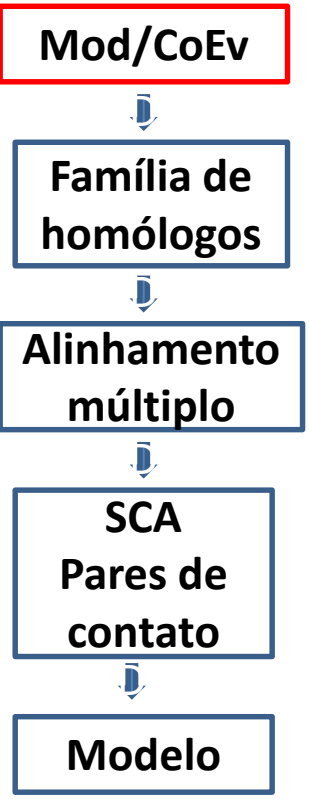
Advantages:

- Applicable to small proteins and peptides (up to 30 – 50 kDa)
- Can be used to study conformational dynamics with frequencies of 10^{-9} s to 1 s
- Can be used to study kinetics of molecular interactions and protein folding
- *Disadvantages:*
- Upper size limit: < 30 - 50 kDa

3) Cryo-EM

- *Advantages:*
- No crystallization
- Good for large macromolecular complexes
- Can study multiple conformational states
- *Disadvantages:*
- Lower size limit: > 100 - 300 kDa
- Lowest resolution (but improving every year)
- Very large data sets (Tb) and intensive data processing required

4) Modelagem guiada com informação de co-evolução de pares de resíduos (Mod/CoEv)



~ 10^5 estruturas determinadas experimentalmente nos últimos 50 anos

> 10^9 sequencias de proteínas conhecidas (principalmente de projetos de metagenômica nos últimos anos)

14th Critical Assessment of protein Structure Prediction (CASP14)
(https://predictioncenter.org/casp14/)

Alpha Fold 2 (Deep Mind, Google, London, UK)
RoseTTaFold (David Baker Lab, University of Washington, Seattle, USA)

4) Modelagem guiada com informação de coevolução de pares de resíduos (Mod/CoEv)

Mod/CoEv

↓

Família de homólogos

↓

Alinhamento múltiplo

↓

Pares de contato

↓

Modelo

Protein structure determination using metagenome sequence data

Sergey Ovchinnikov,[1,2,3] Hahnbeom Park,[1,2] Neha Varghese,[4] Po-Ssu Huang,[1,2] Georgios A. Pavlopoulos,[4] David E. Kim,[1,5] Hetunandan Kamisetty,[6] Nikos C. Kyrpides,[4,7] David Baker[1,2,5]*

Despite decades of work by structural biologists, there are still ~5200 protein families with unknown structure outside the range of comparative modeling. We show that Rosetta structure prediction guided by residue-residue contacts inferred from evolutionary information can accurately model proteins that belong to large families and that metagenome sequence data more than triple the number of protein families with sufficient sequences for accurate modeling. We then integrate metagenome data, contact-based structure matching, and Rosetta structure calculations to generate models for 614 protein families with currently unknown structures; 206 are membrane proteins and 137 have folds not represented in the Protein Data Bank. This approach provides the representative models for large protein families originally envisioned as the goal of the Protein Structure Initiative at a fraction of the cost.

Ovchinnikov *et al.*, *Science* **355**, 294-298 (2017) 20 January 2017

Análise de Acoplamento Estatística (*Statistical Coupling Analysis – SCA*)

The EVolutionary Couplings Server (https://evcouplings.org/)

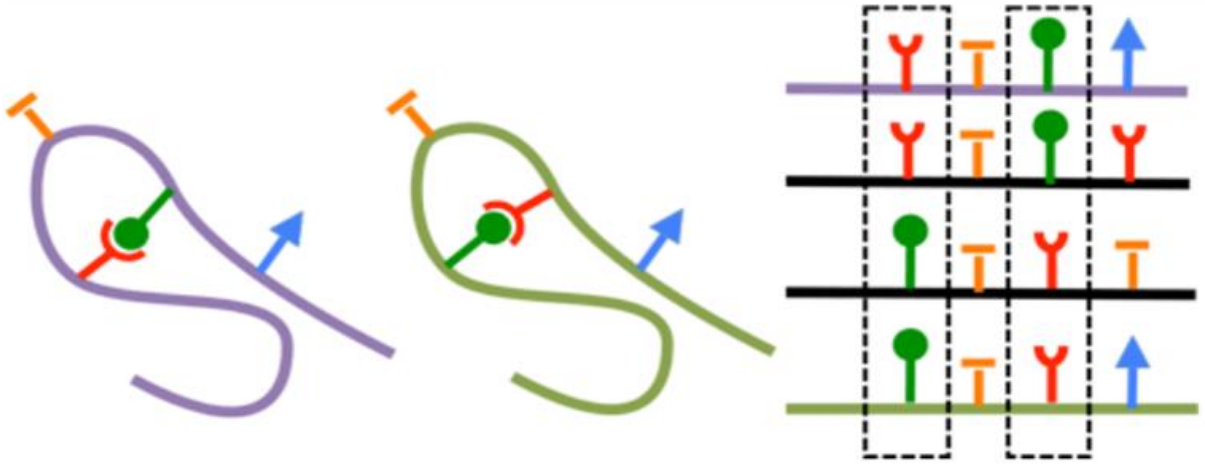
Bis2Analyzer (http://www.lcqb.upmc.fr/BIS2Analyzer/index.php)

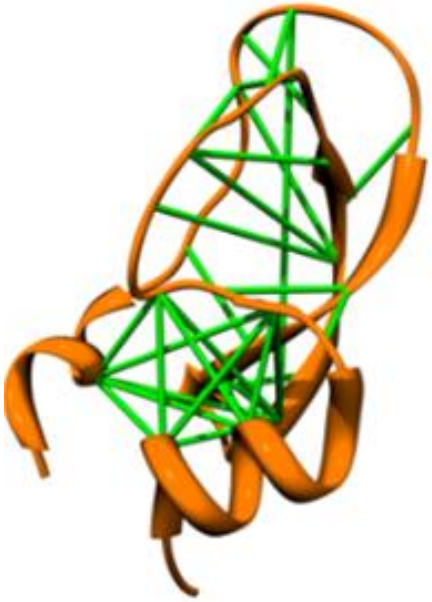
Gremlin e RosettaFold (https://www.bakerlab.org/; https://robetta.bakerlab.org/login.php)

RaptorX (http://raptorx.uchicago.edu/)

AlphaFold (https://alphafold.ebi.ac.uk/)

What is Coevolution, Covariance and Correlated Mutations?



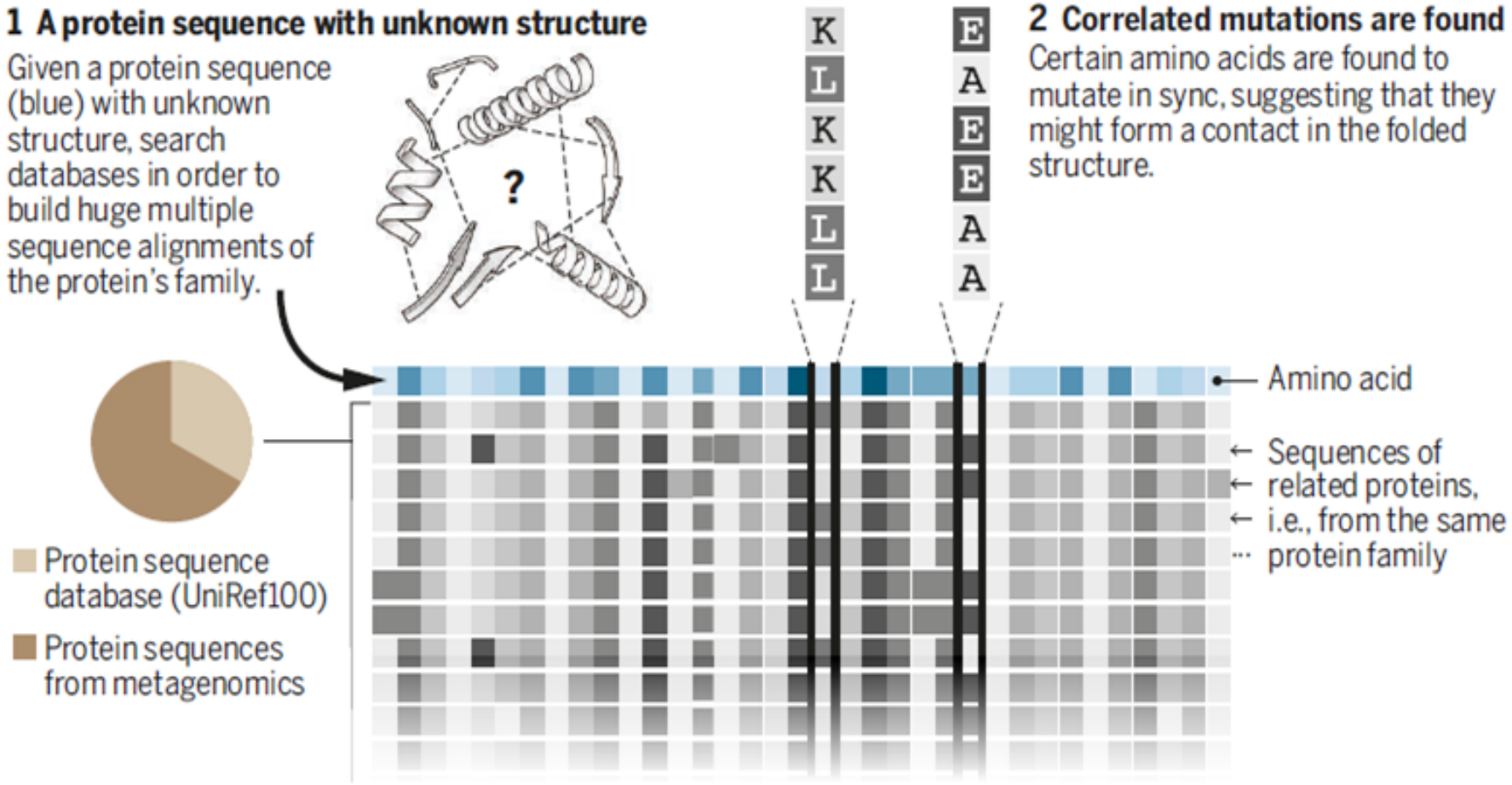


- For protein coding genes, when a residue mutates a compensatory mutation follows. These mutations are captured in our DNA and in the DNA of all living organisms. By analyzing a MSA (multiple sequence alignment) of homolgous protein sequences, we can measure coupling of any given residue pairs.
- Example on the left shows two shapes complementing eachother (red and green). If one of them changes, the other has to change. By comparying positions in a MSA, we can determine which pairs of positions might be in contact.

Filling in the protein fold picture

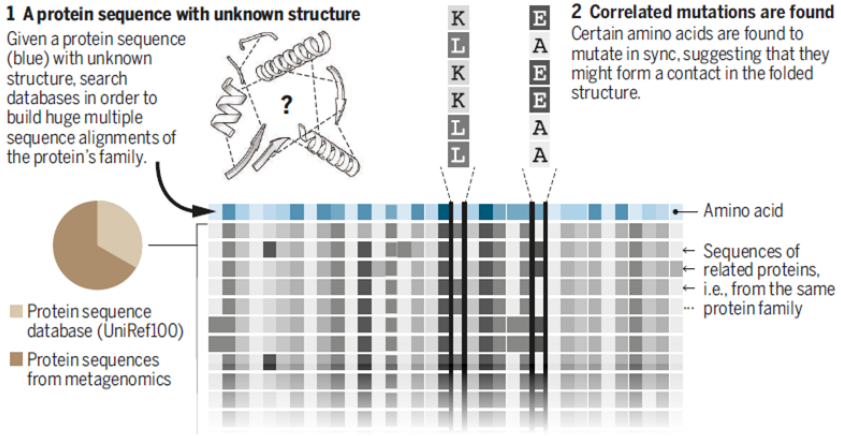
Fewer than a third of the 14,849 known protein families have at least one member with an experimentally determined structure. This leaves more than 5000 protein families with no structural information. Protein modeling using residue-residue contacts inferred from evolutionary data has been successful in modeling unknown structures, but it requires large numbers of aligned sequences. Ovchinnikov *et al.* augmented such sequence alignments with metagenome sequence data (see the Perspective by Söding). They determined the number of sequences required to allow modeling, developed criteria for model quality, and, where possible, improved modeling by matching predicted contacts to known structures. Their method predicted quality structural models for 614 protein families, of which about 140 represent newly discovered protein folds.

Science, this issue p. 294; see also p. 248



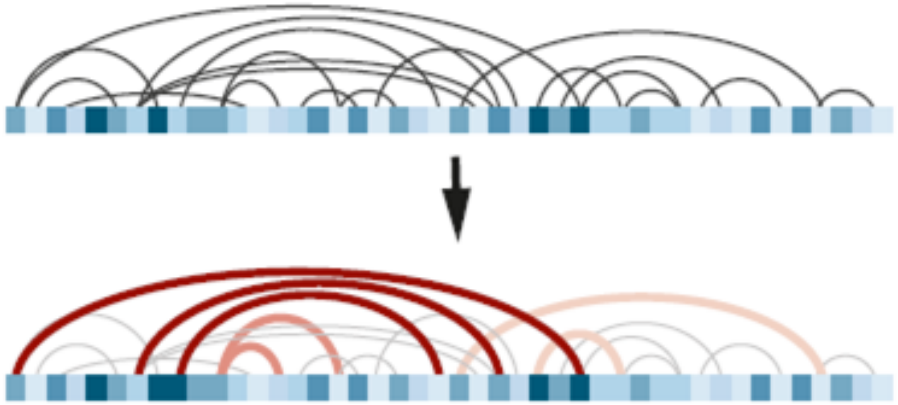
Structures from sequences

Protein structures are reliably predicted from nothing more than large multiple sequence alignments (*13*).



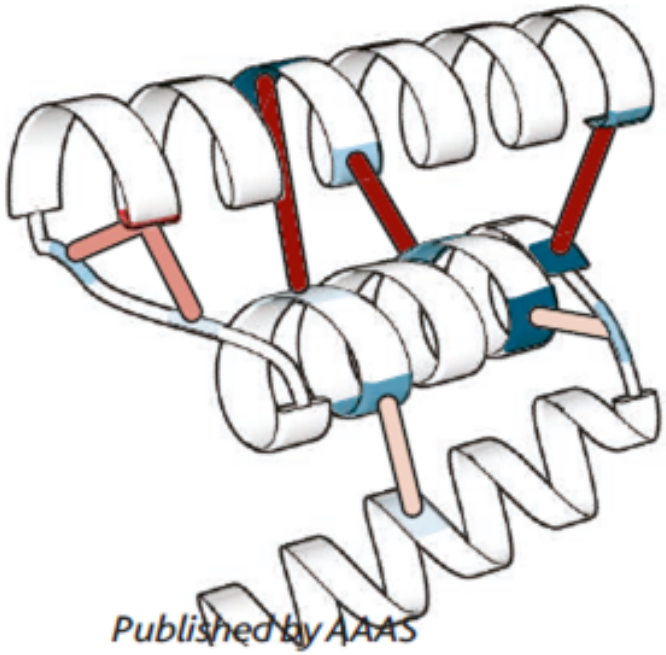
3 Find the 3D contacts

Using a statistical method, predict which of the correlations could be due to direct contacts of the amino acids and which ones arise only indirectly from chains of interactions.



4 Predict the structure

A 3D structure is predicted de novo, now knowing which residues should be in contact with one another.



SCIENCE sciencemag.org

Published by AAAS

Highly accurate protein structure prediction with AlphaFold

Nature (2021)

John Jumper ✉, Richard Evans, [...]Demis Hassabis ✉

Abstract

… Predicting the 3-D structure that a protein will adopt based solely on its amino acid sequence, the structure prediction component of the 'protein folding problem'[8], has been an important open research problem for more than 50 years[9]. Despite recent progress[10–14], existing methods fall far short of atomic accuracy, especially when no homologous structure is available.

Here we provide the first computational method that can regularly predict protein structures with atomic accuracy even where no similar structure is known.

We validated an entirely redesigned version of our neural network-based model, AlphaFold, in the challenging 14th Critical Assessment of protein Structure Prediction (CASP14)[15], demonstrating accuracy competitive with experiment in a majority of cases and greatly outperforming other methods.

Underpinning the latest version of AlphaFold is a novel machine learning approach that incorporates physical and biological knowledge about protein structure, leveraging multi-sequence alignments, into the design of the deep learning algorithm.

NEWS | 22 July 2021

Callaway, (2021) Nature

DeepMind's AI predicts structures for a vast trove of proteins

AlphaFold neural network produced a 'totally transformative' database of more than 350,000 structures from *Homo sapiens* and 20 model organisms.

The human genome holds the instructions for more than 20,000 proteins. But only about one-third of those have had their 3D structures determined experimentally. And in many cases, those structures are only partially known.

Now, a transformative artificial intelligence (AI) tool called AlphaFold, which has been developed by Google's sister company DeepMind in London, has predicted the structure of nearly the entire human proteome (the full complement of proteins expressed by an organism). In addition, the tool has predicted almost complete proteomes for various other organisms, ranging from mice and maize (corn) to the malaria parasite.

The more than 350,000 protein structures, which are available through a public database, vary in their accuracy. But researchers say the resource — which is set to grow to 130 million structures by the end of the year — has the potential to revolutionize the life sciences.

NEWS | 15 July 2021

Callaway, (2021) Nature

DeepMind's AI for protein structure is coming to the masses

Machine-learning systems from the company and from a rival academic group are now open source and freely accessible.

On 15 July, the London-based company DeepMind released an open-source version of its deep-learning neural network AlphaFold 2 and described its approach in a paper in *Nature*[1].

The network dominated a protein-structure prediction competition last year.

Meanwhile, an academic team has developed its own protein-prediction tool inspired by AlphaFold 2, which is already gaining popularity with scientists. That system, called RoseTTaFold, performs nearly as well as AlphaFold 2, and is described in a *Science* paper also published on 15 July[2]

RESEARCH ARTICLE

Science 15 Jul 2021

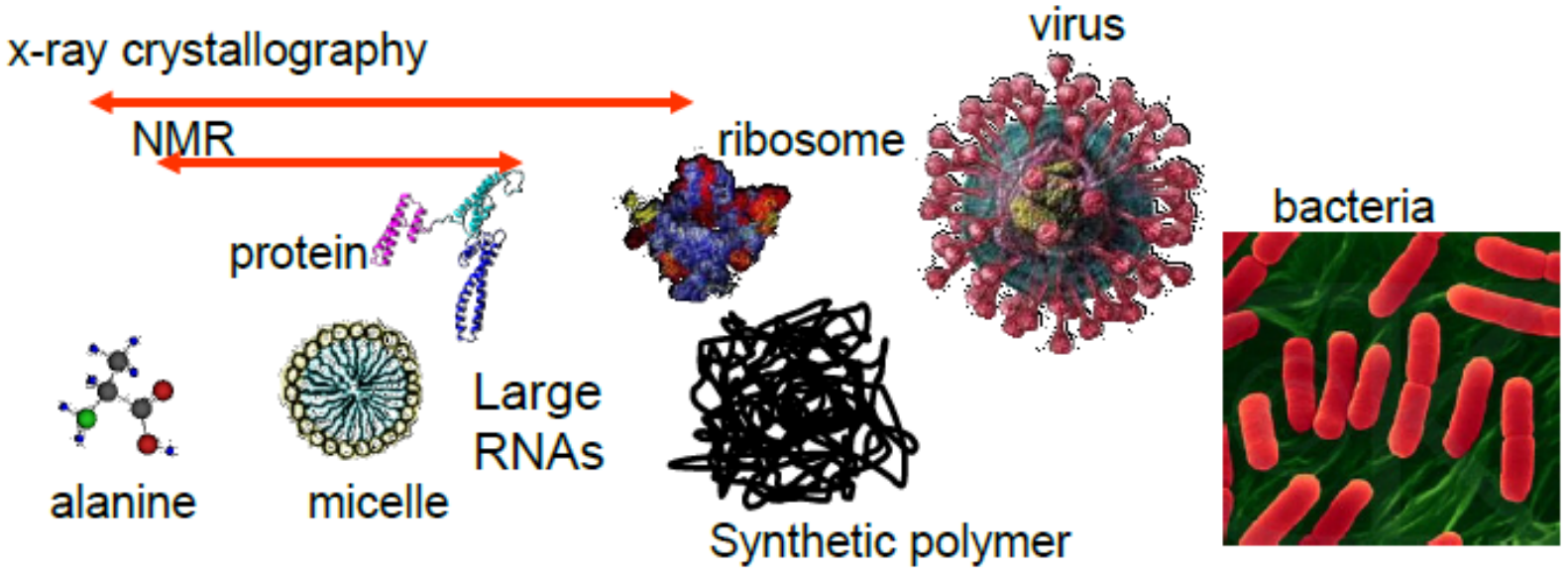
Accurate prediction of protein structures and interactions using a three-track neural network

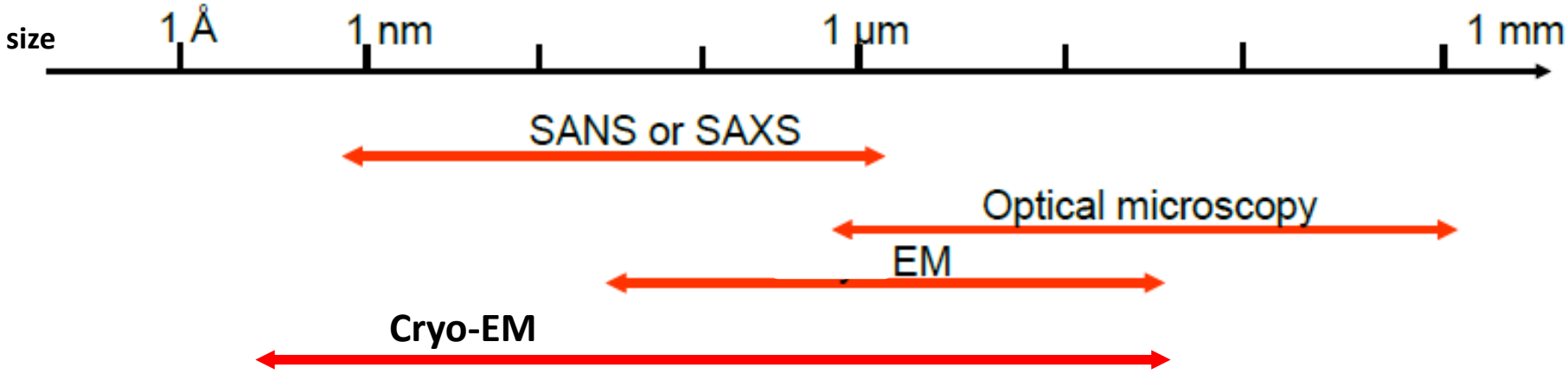
Minkyung Baek[1,2], Frank DiMaio[1,2], Ivan Anishchenko[1,2], Justas Dauparas[1,2], Sergey Ovchinnikov[3,4], Gyu Rie Lee[1,2], Jue Wang[1,2], Qian Cong[5,6], Lisa N. Kinch[7], R. Dustin Schaeffer[6], Claudia Millán[8], Hahnbeom Park[1,2], Carson Adams[1,2], Caleb R. Glassman[9,10], Andy DeGiovanni[12], Jose H. Pereira[12], Andria V. Rodrigues[12], Alberdina A. van Dijk[13], Ana C. Ebrecht[13], Diederik J. Opperman[14], Theo Sagmeister[15], Christoph Buhlheller[15,16], Tea Pavkov-Keller[15,17], Manoj K. Rathinaswamy[18], Udit Dalwadi[19], Calvin K. Yip[19], John E. Burke[18], K. Christopher Garcia[9,10,11,20], Nick V. Grishin[6,21,7], Paul D. Adams[12,22], Randy J. Read[8], David Baker[1,2,23,*]

Abstract

DeepMind presented remarkably accurate predictions at the recent CASP14 protein structure prediction assessment conference. We explored network architectures incorporating related ideas and obtained the best performance with a three-track network in which information at the 1D sequence level, the 2D distance map level, and the 3D coordinate level is successively transformed and integrated. The three-track network produces structure predictions with accuracies approaching those of DeepMind in CASP14, enables the rapid solution of challenging X-ray crystallography and cryo-EM structure modeling problems, and provides insights into the functions of proteins of currently unknown structure. The network also enables rapid generation of accurate protein-protein complex models from sequence information alone, short circuiting traditional approaches which require modeling of individual subunits followed by docking. We make the method available to the scientific community to speed biological research.

Scales of various methods

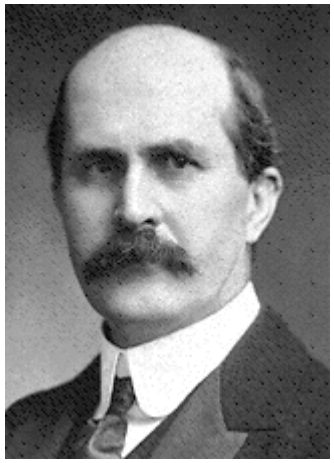
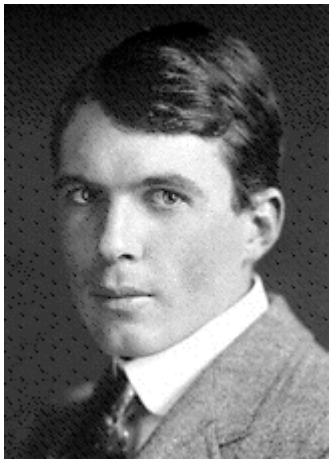




Biologia Estrutural se destaca entre ganhadores do prêmio Nobel

... somente alguns exemplos

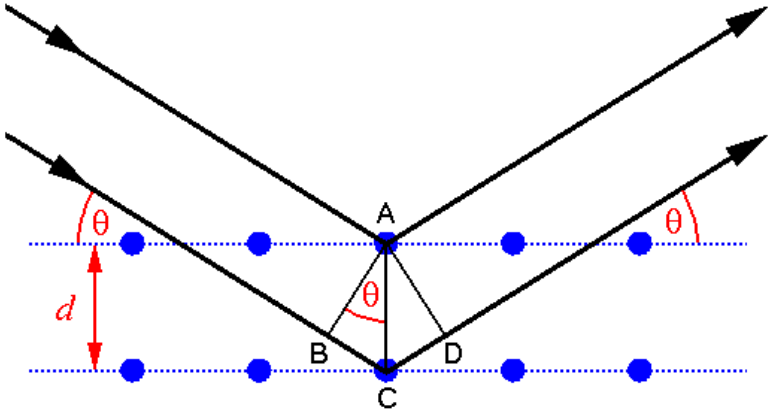


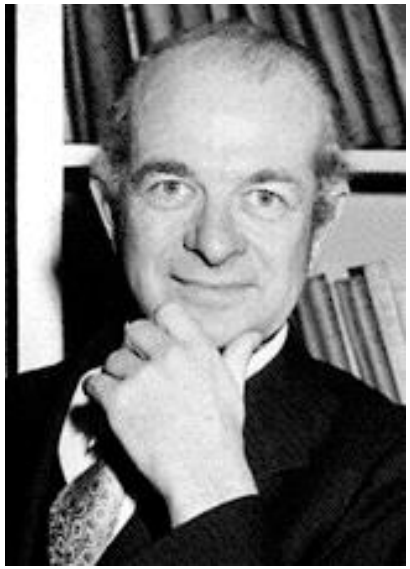



X-rays

Wilhelm Conrad Röntgen (Nobel Prize in physics, 1901), **Max von Laue** (Nobel Prize in physics, 1914), and father and son **Sir William Henry Bragg** and **William Lawrence Bragg** (Nobel Prize in physics,1915): The prizes were awarded to these 4 persons for their contribution to the discovery of X-rays, understanding their nature as electromagnetic waves and their use in revealing the atomic structure of matter.

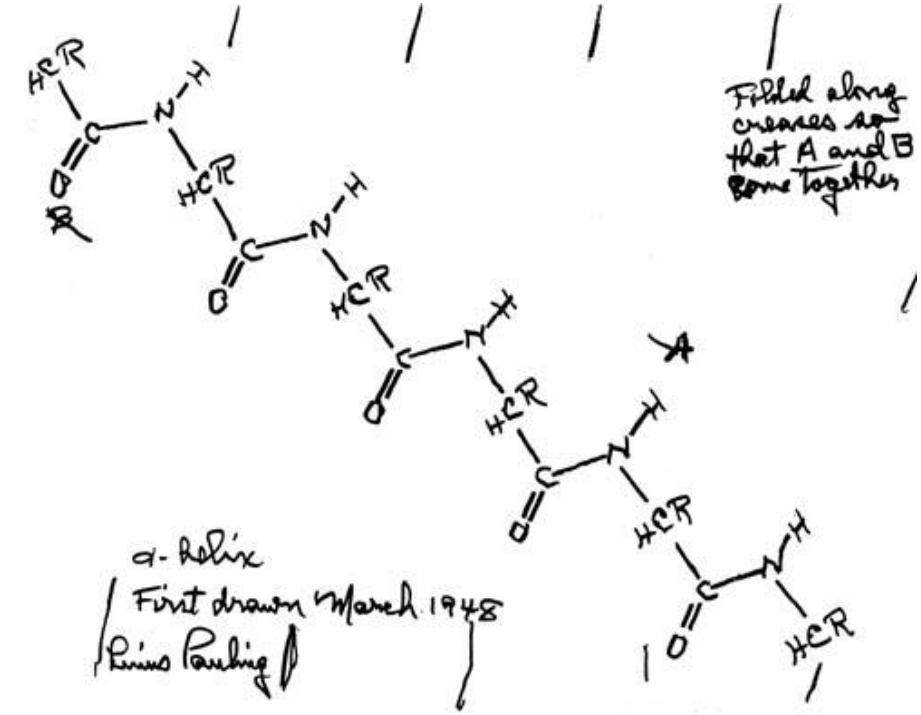
$$n\lambda = 2d\sin\theta$$

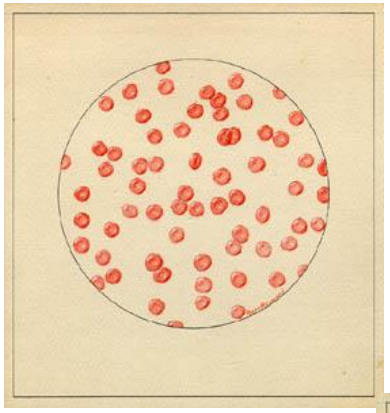


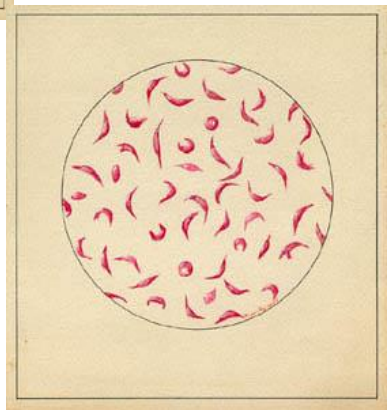


Linus Pauling,
Nobel Prize in chemistry 1954,
California Institute of Technology (Caltech)
Pasadena, CA, USA. b 1901, d. 1994

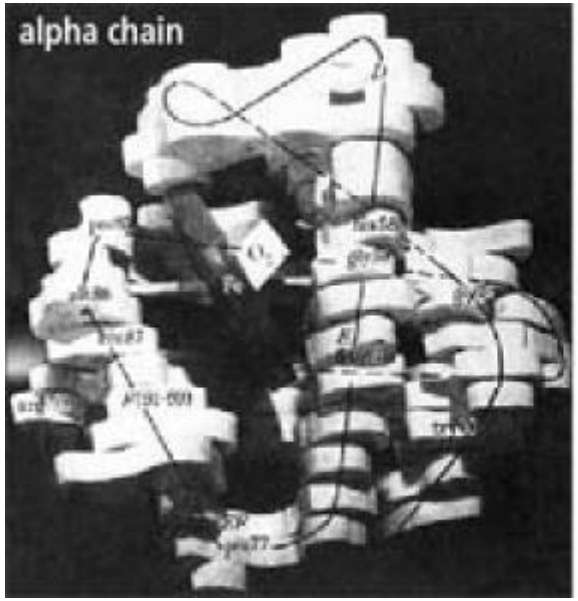
"for his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances".



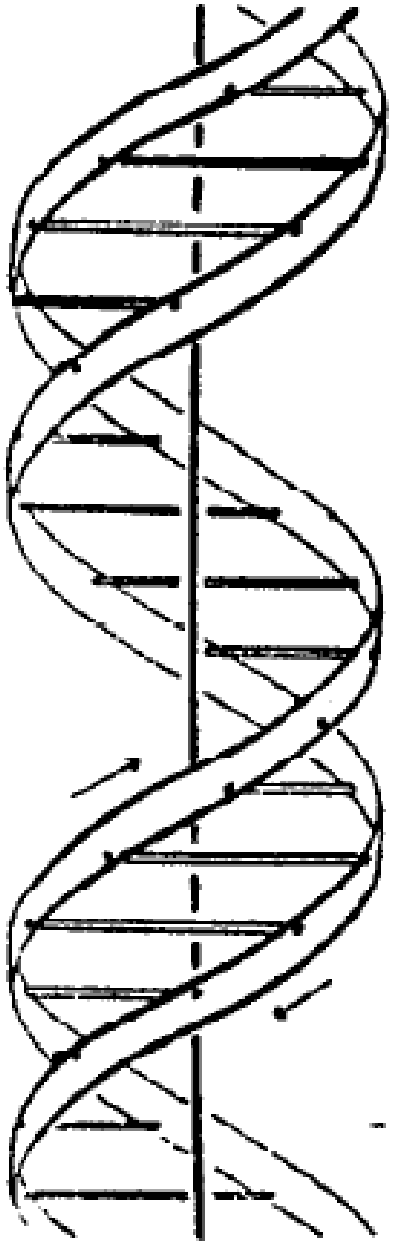




Max Ferdinand Perutz
(b. 1914, d. 2002) and
John Cowdery Kendrew
(b. 1917, d. 1997).
Nobel Prize in Chemistry 1962. MRC Laboratory of Molecular Biology, Cambridge, United Kingdom.



The Nobel Prize in Chemistry 1962 *"for their studies of the structures of globular proteins"*

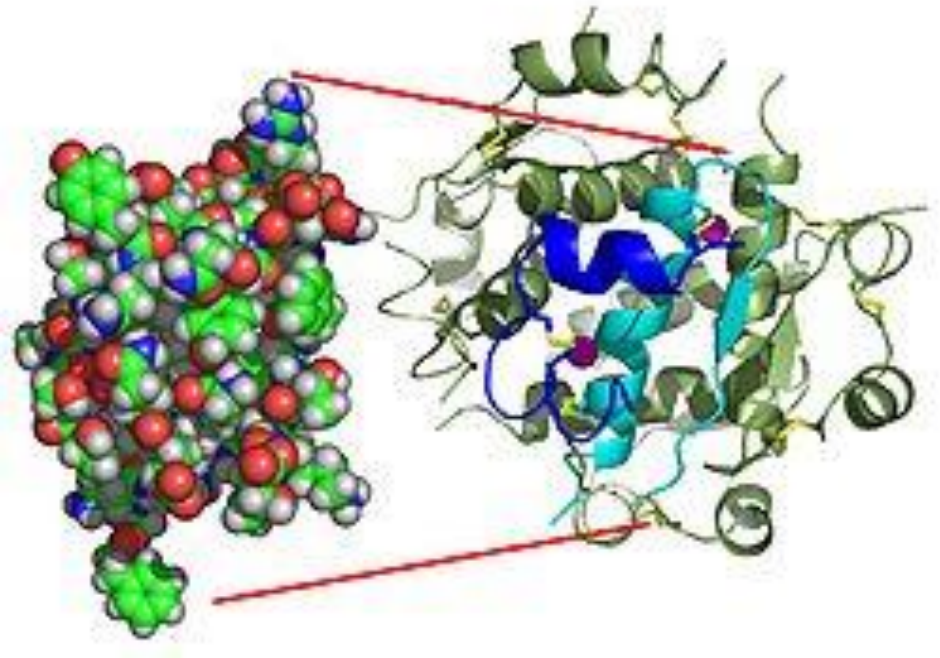


The Nobel Prize in Physiology or Medicine 1962 was awarded jointly to
Francis Harry Compton Crick,
James Dewey Watson and
Maurice Hugh Frederick Wilkins *"for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material"*.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

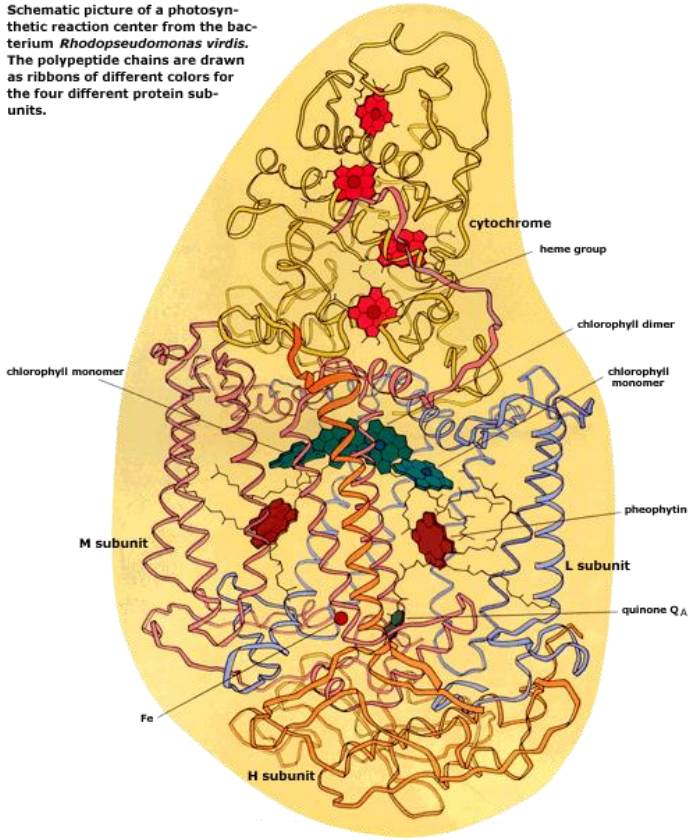
Dorothy Crowfoot Hodgkin
(b. 1910, d. 1994)
Nobel Prize in Chemistry 1964. University of Oxford, Royal Society, Oxford, United Kingdom.

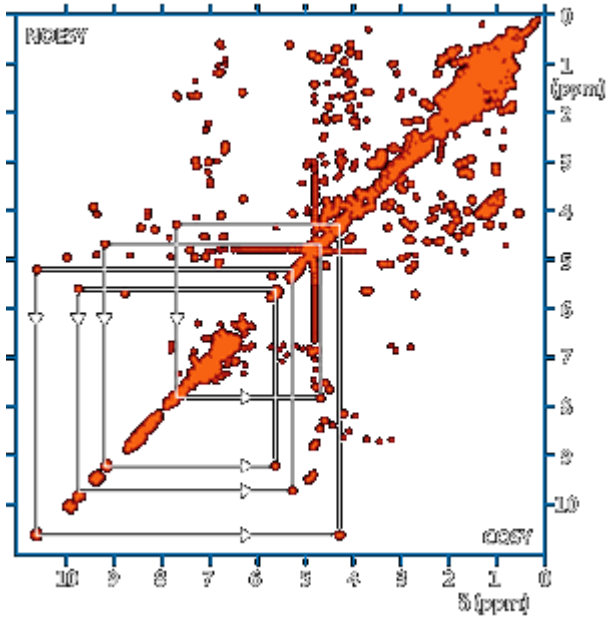
The Nobel Prize in Chemistry 1964 was awarded *"for her determinations by X-ray techniques of the structures of important biochemical substances"*.

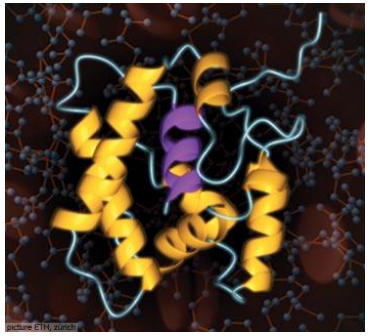


The Nobel Prize in Chemistry 1988
"for the determination of the three-dimensional structure of a photosynthetic reaction centre"

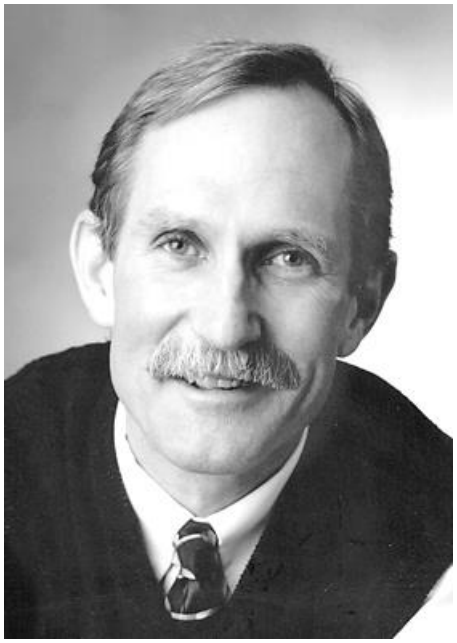
Johann Deisenhofer (b. 1943), University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA; Howard Hughes Medical Institute;
Robert Huber (b. 1937) & **Hartmut Michel** (b. 1948); Max-Planck-Institut für Biochemie, Martinsried, Federal Republic of Germany



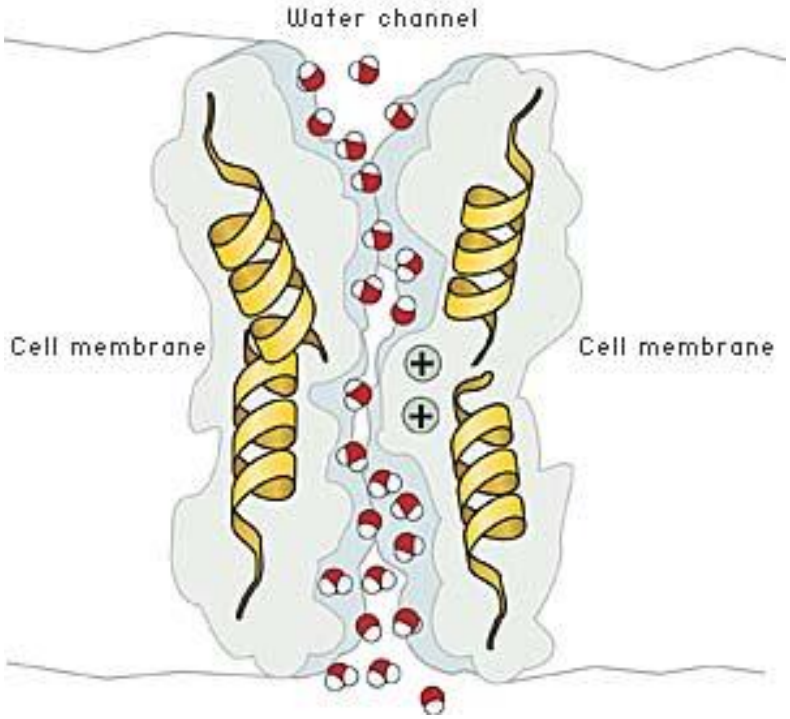




John B. Fenn, Koichi Tanaka and **Kurt Wüthrich** were awarded the 2002 Nobel Prize in Chemistry for the development of methods for identification and structure analyses of biological macromolecules, mass spectrometric analyses of biological macromolecules and nuclear magnetic resonance spectroscopy for determining the three-dimensional structure of biological macromolecules in solution.

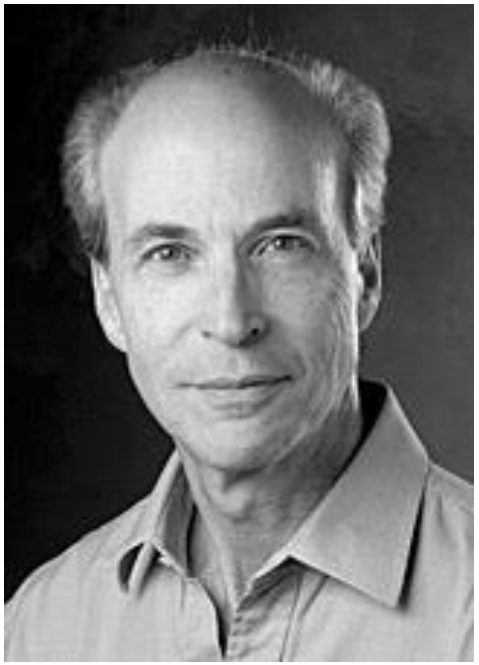


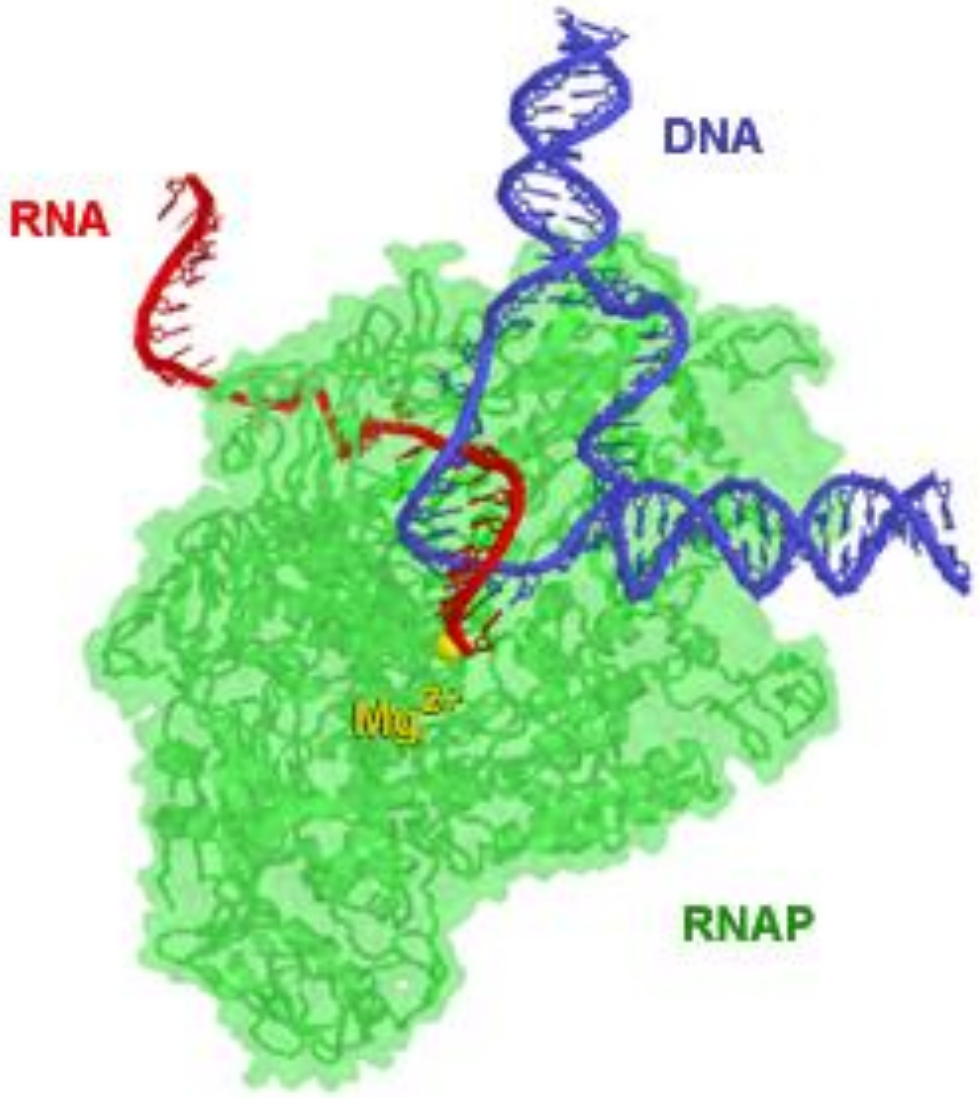
Structure and function of ionic and water channels, 2003

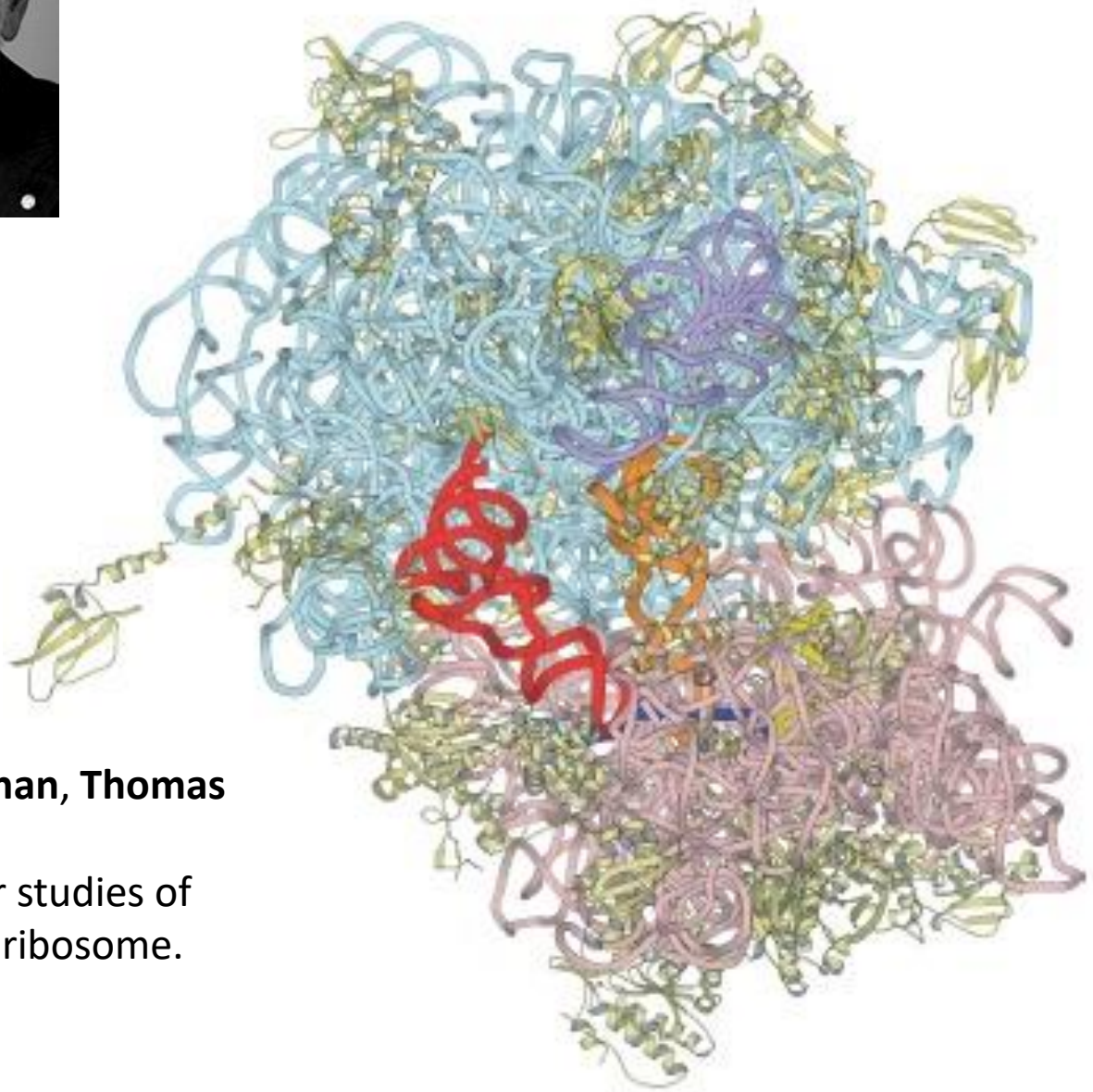


Peter Agre & **Roderick MacKinnon**, Nobel prize in Chemistry 2003 or discoveries concerning channels in cell membranes

Roger Kornberg, Nobel prize in Chemistry, 2006 for his studies of the molecular basis of eukaryotic transcription

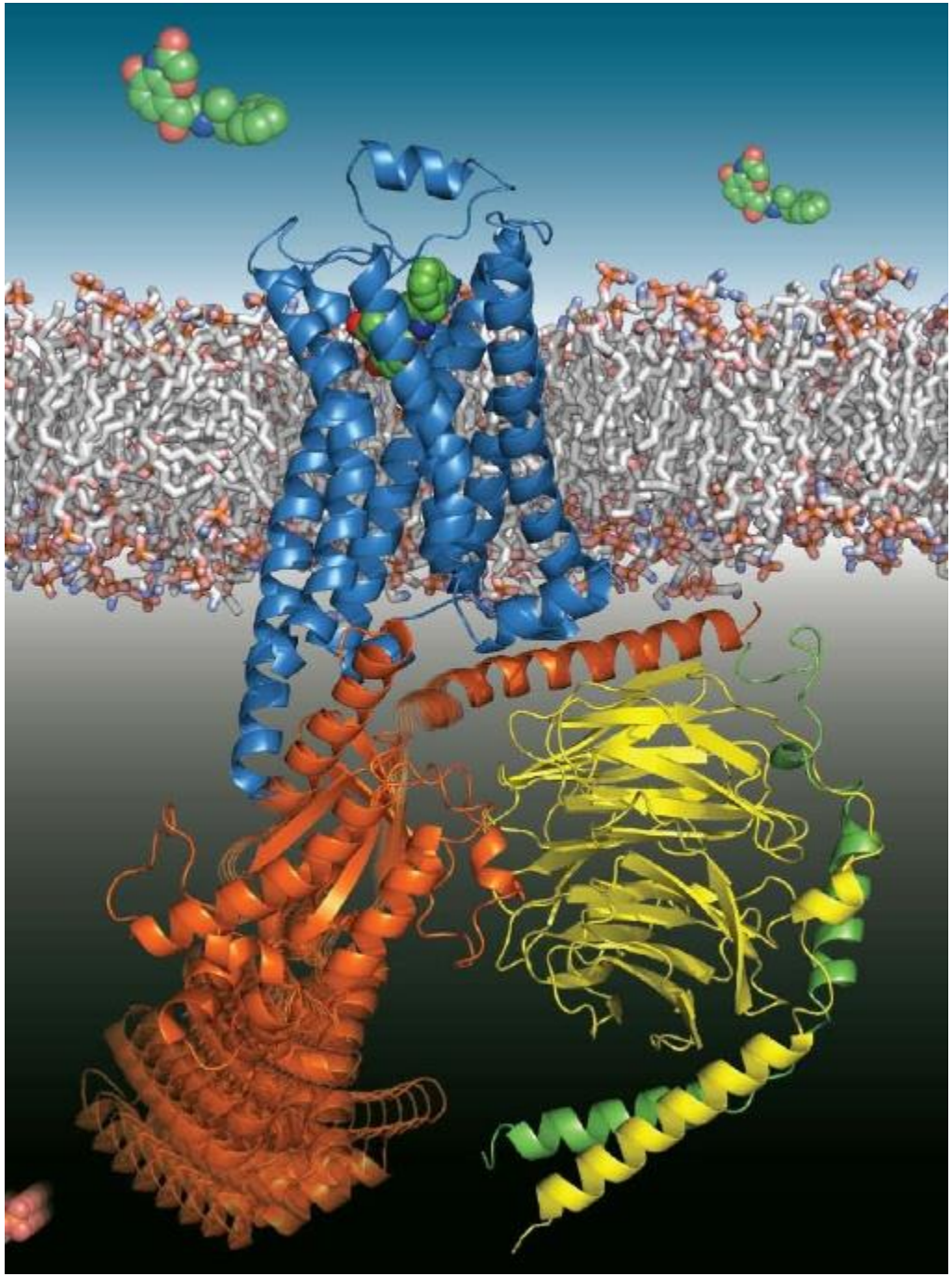


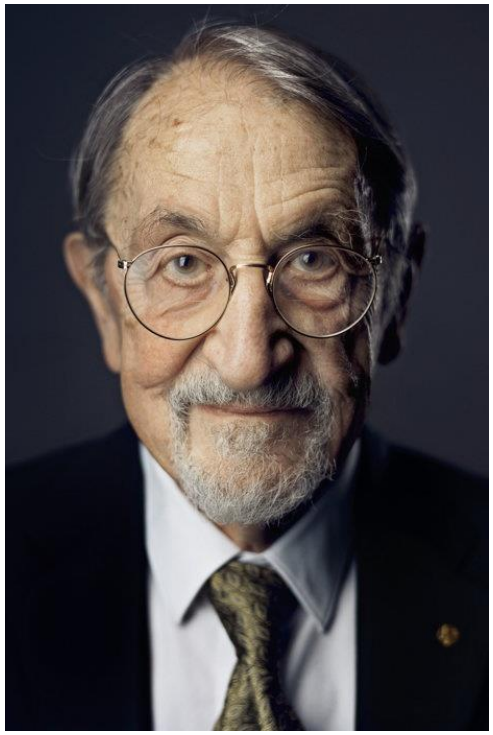


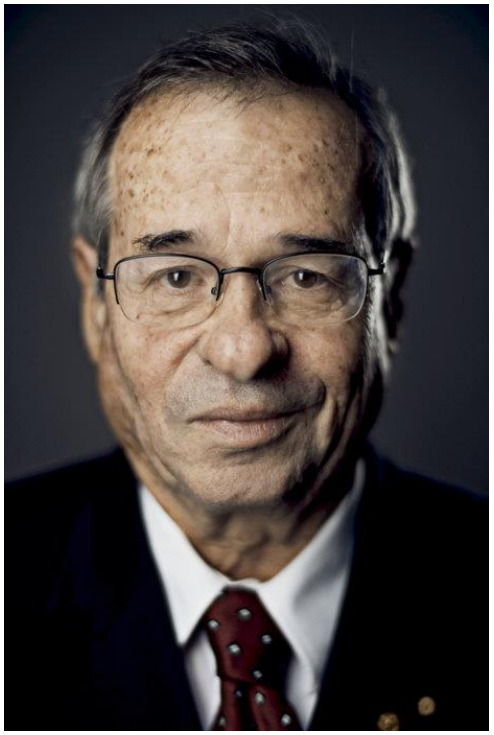


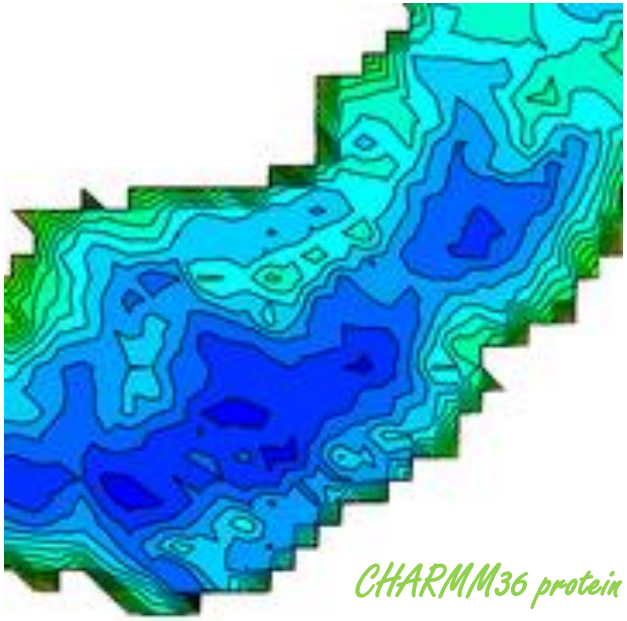
Venkatraman (Venki) Ramakrishnan, **Thomas A. Steitz,** and **Ada Yonath**
2009 Nobel prize in chemistry, for studies of the structure and function of the ribosome.

The Nobel Prize in Chemistry 2012 was awarded jointly to Robert J. Lefkowitz and Brian K. Kobilka *"for studies of G-protein-coupled receptors"*



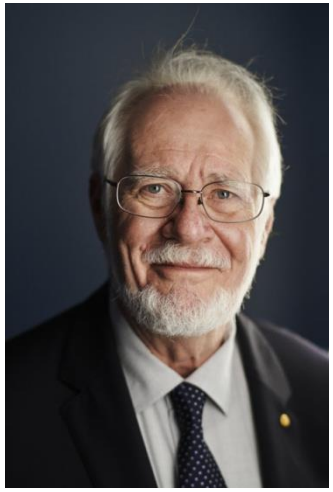




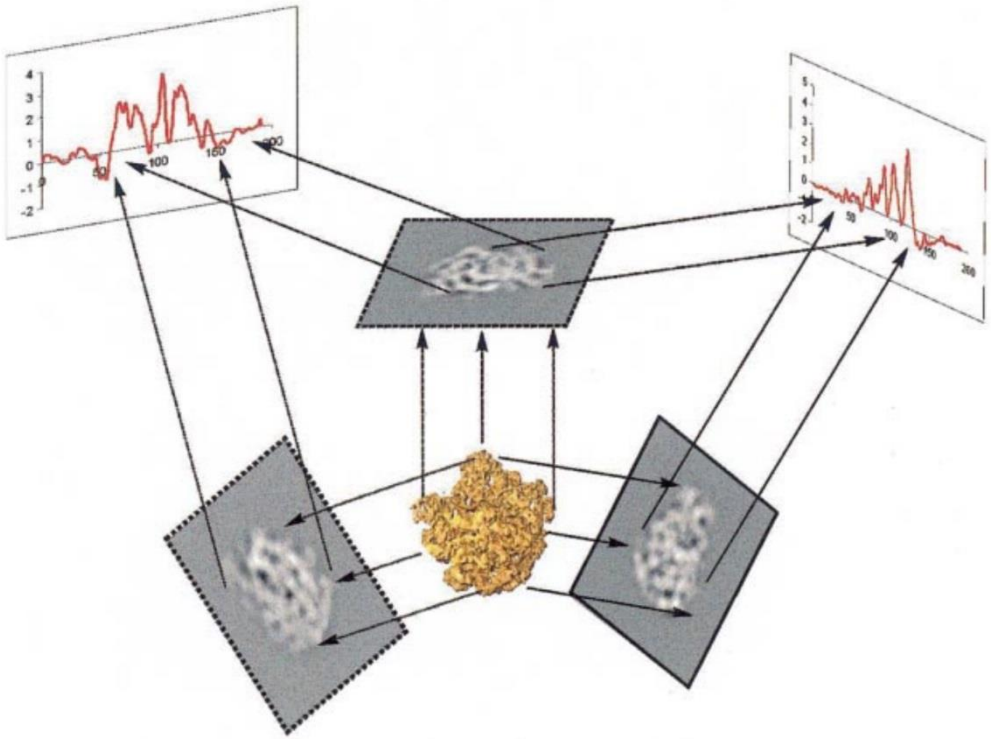


CHARMM36 protein force field

The 2013 Nobel Prize was awarded to Martin Karplus, Michael Levitt and Arieh Warshel “for the development of multiscale models for complex chemical systems”



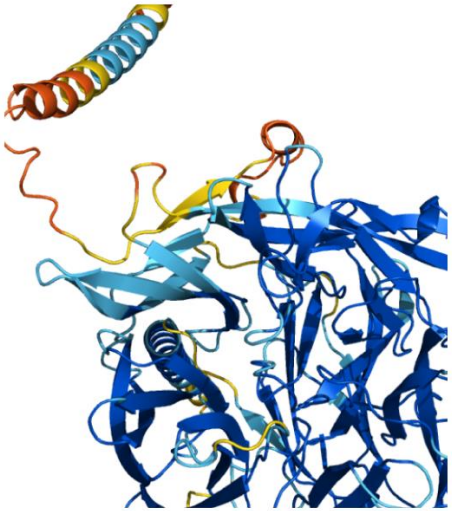
The Nobel Prize in Chemistry 2017 was awarded jointly to Jacques Dubochet, Joachim Frank and Richard Henderson "for developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution."



MINHA PREDIÇÃO PARA PRÊMIO NOBEL NOS PRÓXIMOS ANOS

AlphaFold is an AI system developed by DeepMind that predicts a protein's 3D structure from its amino acid sequence. It regularly achieves accuracy competitive with experiment.

DeepMind and EMBL's European Bioinformatics Institute (EMBL-EBI) have partnered to create AlphaFold DB to make these predictions freely available to the scientific community. The first release covered the human proteome and the proteomes of several other key organisms, while the second release added the majority of manually curated UniProt entries (Swiss-Prot). In 2022 we plan to expand the database to cover a large proportion of all catalogued proteins (the over 100 million in UniRef90).



Q8I3H7: May protect the malaria parasite against attack by the immune system. Mean pLDDT 85.57.

DEMIS HASSABIS

JOHN JUMPER

INSTITUTE FOR Protein Design
UNIVERSITY of WASHINGTON

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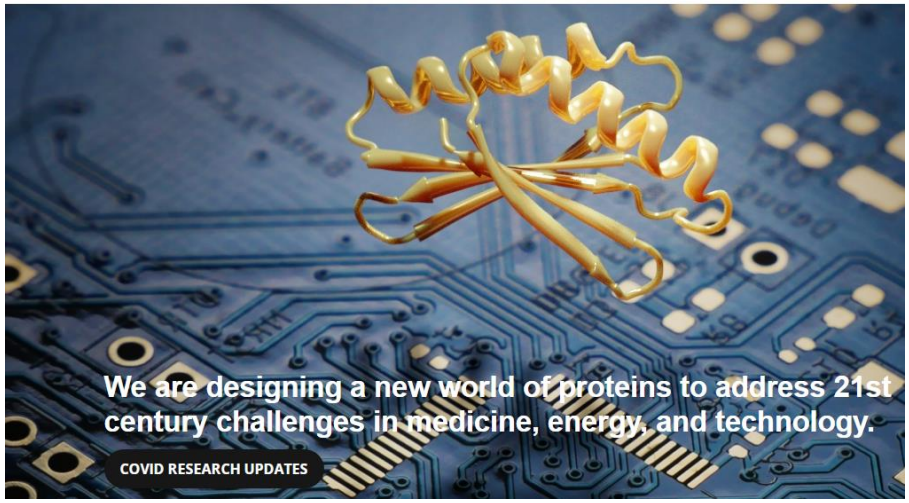

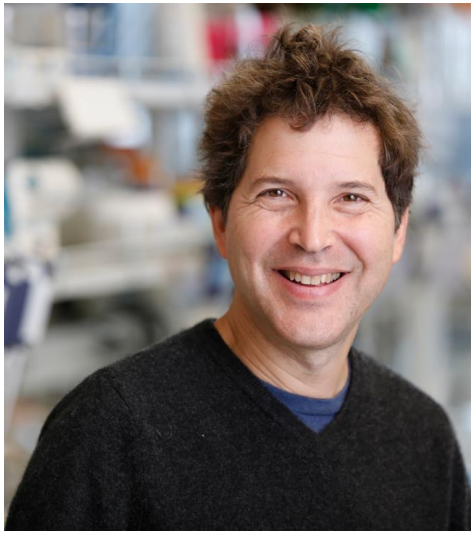

DAVID BAKER