From fibers to brain diseases

POLIMI

C. Lagisquet, J. Shillcock, C. Lesieur, L. Vuillon

May, 2022

LAMA
Laboratoire de Mathématiques
Université de Savoie

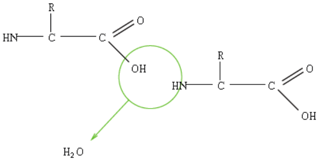
UMR 5127

Outline

1. Proteins
2. Tilings of the plane
3. Fibers
4. Coarse-grain simulations

Proteins

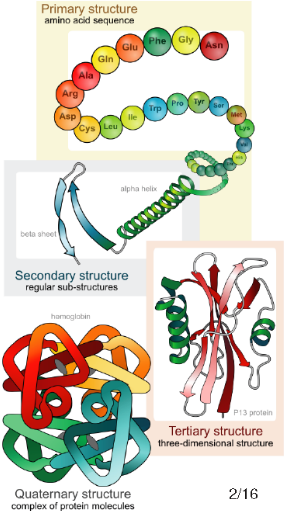
PROTEIN: sequence of amino acids that folds and realises a biological function



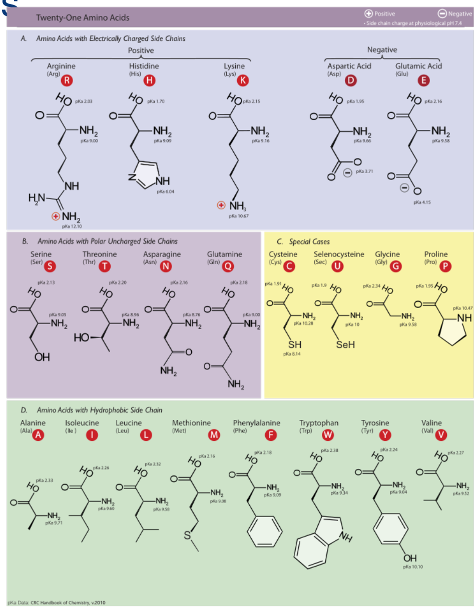
R: 20 standard amino acids = protein building blocks

Main chain (backbone), side chain

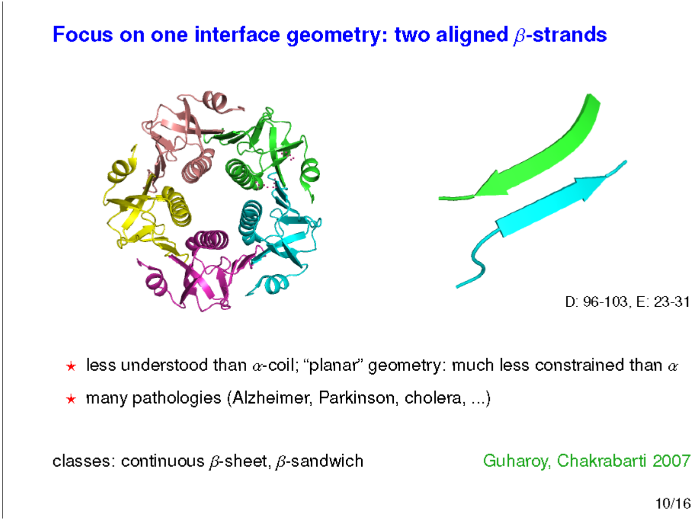
Information flow: 1D ⟶ 3D



Amino Acids



Dan Cojocari, Department of Medical Biophysics, University of Toronto, 2010



Focus on one interface geometry: two aligned β-strands

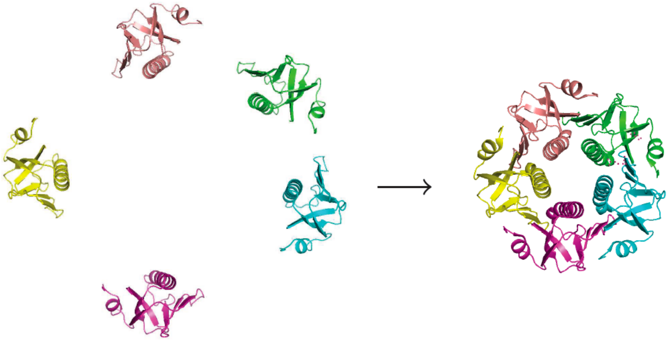
D: 96-103, E: 23-31

- less understood than α-coil; “planar” geometry: much less constrained than α
- many pathologies (Alzheimer, Parkinson, cholera, ...)

classes: continuous β-sheet, β-sandwich

Guharoy, Chakrabarti 2007

Cyclic



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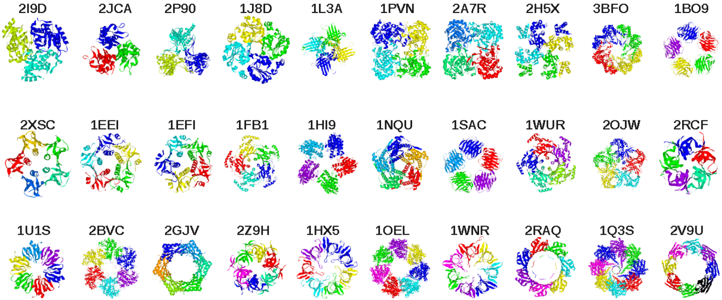
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1PVN
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3BFO
1BO9
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1EFI
1FB1
1HI9
1NQU
1SAC
1WUR
2OJW
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2RAQ
1Q3S
2V9U

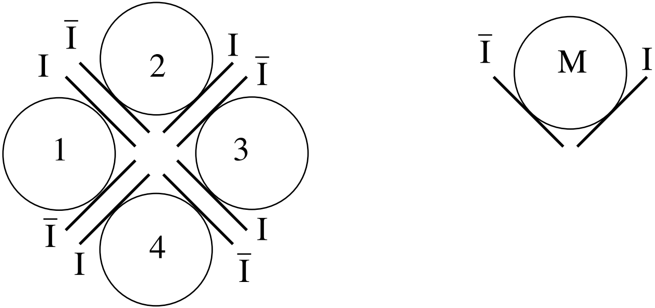


FIGURE – **Abstract view of C_4 symmetry.** A tetramer formed by a single interface between the part *I* and $\bar{I}$. Each chain is adjacent via the interface to exactly 2 other chains

Lethal

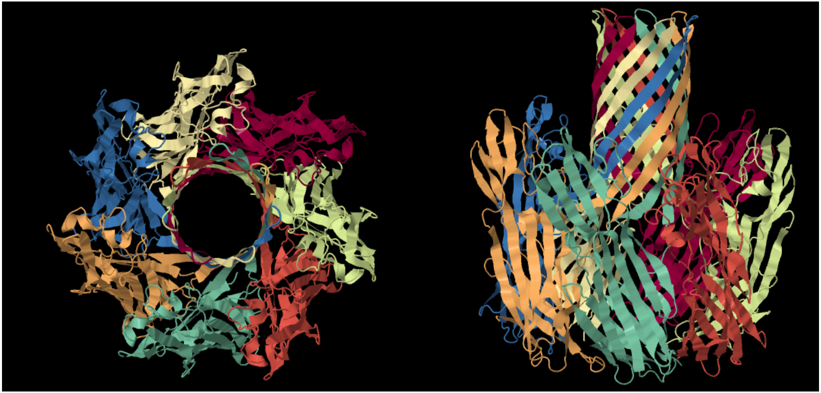
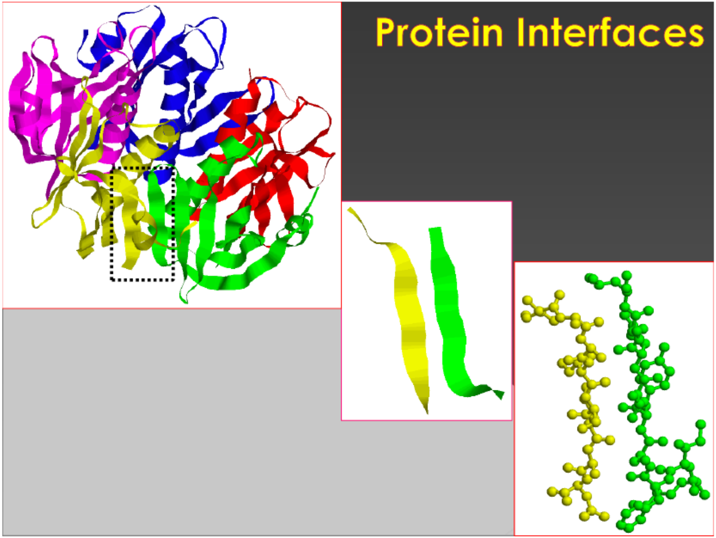
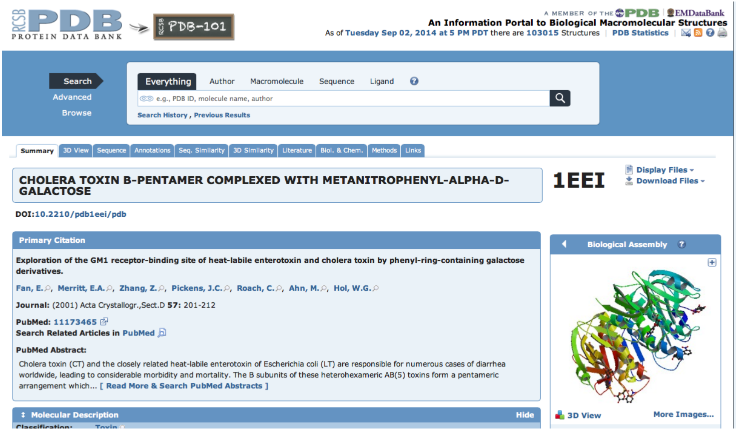


FIGURE – **Heptamer 4H56 in the PDB with each chain adjacent to 2 other chains.** Remark that in the beta barrel the adjacency between pairs of chains is the same as in the other part of the heptamer. This implies an oligomerization with exactly 1 interface.


Protein Interfaces

Protein Data Bank



An Information Portal to Biological Macromolecular Structures

As of Tuesday Sep 02, 2014 at 5 PM PDT there are 103015 Structures | PDB Statistics

CHOLERA TOXIN B-PENTAMER COMPLEXED WITH METANITROPHENYL-ALPHA-D-GALACTOSE

1EEI

DOI: 10.2210/pdb1eei/pdb

Primary Citation

Exploration of the GM1 receptor-binding site of heat-labile enterotoxin and cholera toxin by phenyl-ring-containing galactose derivatives.

Fan, E., Merritt, E.A., Zhang, Z., Pickens, J.C., Roach, C., Ahn, M., Hol, W.G.

Journal: (2001) Acta Crystallogr.,Sect.D **57:** 201-212

PubMed: 11173465

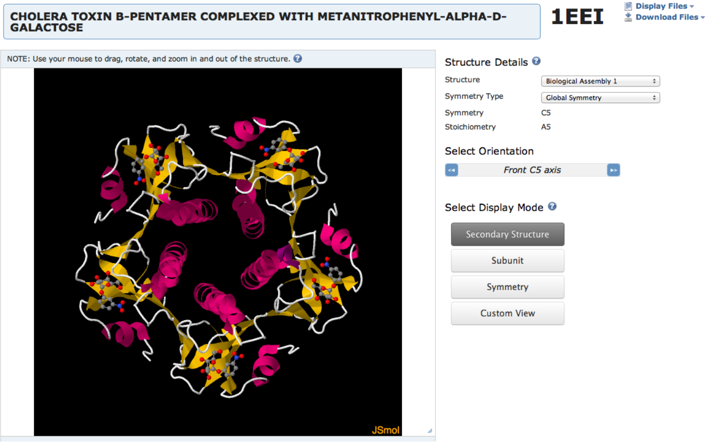
Search Related Articles in PubMed

PubMed Abstract:

Cholera toxin (CT) and the closely related heat-labile enterotoxin of Escherichia coli (LT) are responsible for numerous cases of diarrhea worldwide, leading to considerable morbidity and mortality. The B subunits of these heterohexameric AB(5) toxins form a pentameric arrangement which... [Read More & Search PubMed Abstracts]

Molecular Description

Classification: Toxin



CHOLERA TOXIN B-PENTAMER COMPLEXED WITH METANITROPHENYL-ALPHA-D-GALACTOSE

1EEI

NOTE: Use your mouse to drag, rotate, and zoom in and out of the structure.

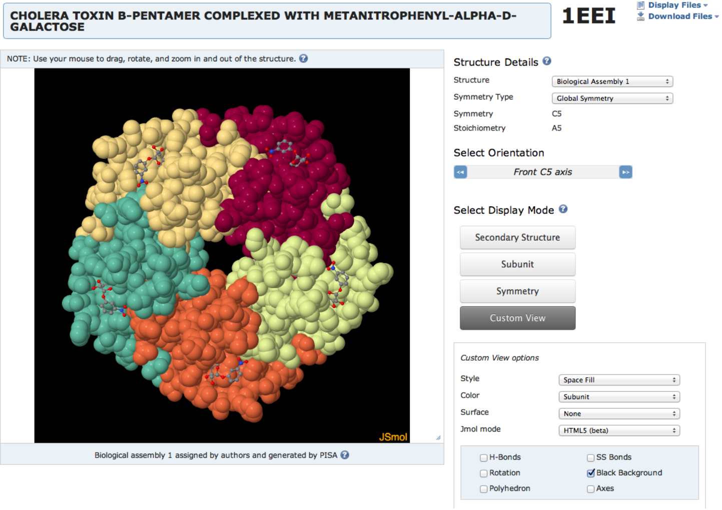
Structure Details

Structure	Biological Assembly 1
Symmetry Type	Global Symmetry
Symmetry	C5
Stoichiometry	A5

Select Orientation

Front C5 axis

Select Display Mode



CHOLERA TOXIN B-PENTAMER COMPLEXED WITH METANITROPHENYL-ALPHA-D-GALACTOSE

1EEI

NOTE: Use your mouse to drag, rotate, and zoom in and out of the structure.

Biological assembly 1 assigned by authors and generated by PISA

Structure Details

Structure	Biological Assembly 1
Symmetry Type	Global Symmetry
Symmetry	C5
Stoichiometry	A5

Select Orientation

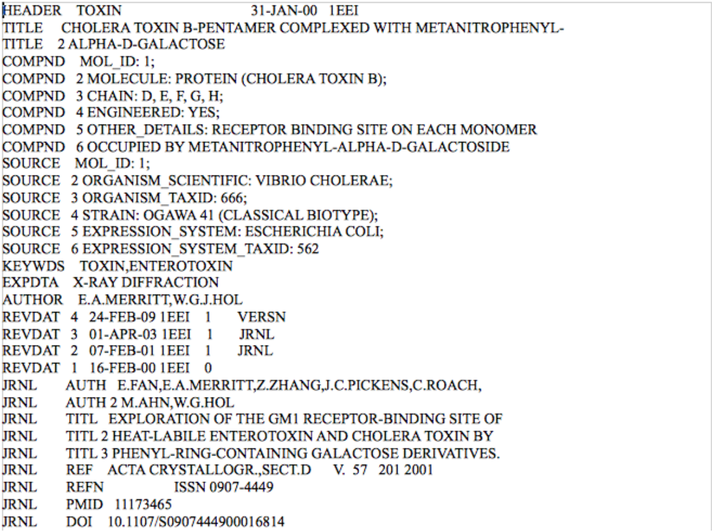
Front C5 axis

Select Display Mode

Custom View options

Style	Space Fill
Color	Subunit
Surface	None
Jmol mode	HTML5 (beta)

☐ H-Bonds ☐ SS Bonds
☐ Rotation ☑ Black Background
☐ Polyhedron ☐ Axes



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TITLE    2 ALPHA-D-GALACTOSE
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COMPND   2 MOLECULE: PROTEIN (CHOLERA TOXIN B);
COMPND   3 CHAIN: D, E, F, G, H;
COMPND   4 ENGINEERED: YES;
COMPND   5 OTHER_DETAILS: RECEPTOR BINDING SITE ON EACH MONOMER
COMPND   6 OCCUPIED BY METANITROPHENYL-ALPHA-D-GALACTOSIDE
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SOURCE   2 ORGANISM_SCIENTIFIC: VIBRIO CHOLERAE;
SOURCE   3 ORGANISM_TAXID: 666;
SOURCE   4 STRAIN: OGAWA 41 (CLASSICAL BIOTYPE);
SOURCE   5 EXPRESSION_SYSTEM: ESCHERICHIA COLI;
SOURCE   6 EXPRESSION_SYSTEM_TAXID: 562
KEYWDS    TOXIN,ENTEROTOXIN
EXPDTA    X-RAY DIFFRACTION
AUTHOR    E.A.MERRITT,W.G.J.HOL
REVDAT   4   24-FEB-09 1EEI    1       VERSN
REVDAT   3   01-APR-03 1EEI    1       JRNL
REVDAT   2   07-FEB-01 1EEI    1       JRNL
REVDAT   1   16-FEB-00 1EEI    0
JRNL        AUTH   E.FAN,E.A.MERRITT,Z.ZHANG,J.C.PICKENS,C.ROACH,
JRNL        AUTH 2 M.AHN,W.G.HOL
JRNL        TITL   EXPLORATION OF THE GM1 RECEPTOR-BINDING SITE OF
JRNL        TITL 2 HEAT-LABILE ENTEROTOXIN AND CHOLERA TOXIN BY
JRNL        TITL 3 PHENYL-RING-CONTAINING GALACTOSE DERIVATIVES.
JRNL        REF    ACTA CRYSTALLOGR.,SECT.D       V.  57   201 2001
JRNL        REFN                   ISSN 0907-4449
JRNL        PMID   11173465
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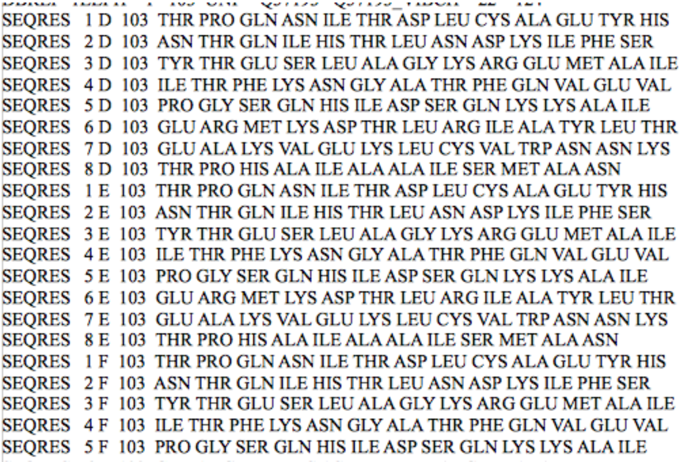

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SEQRES   4 D  103  ILE THR PHE LYS ASN GLY ALA THR PHE GLN VAL GLU VAL
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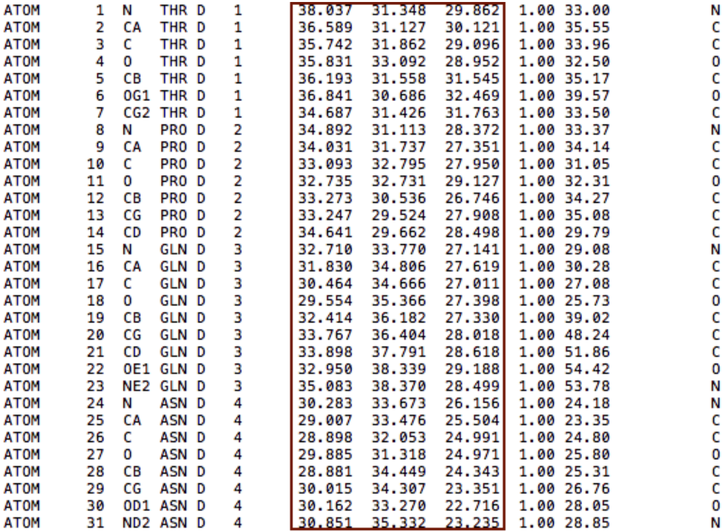

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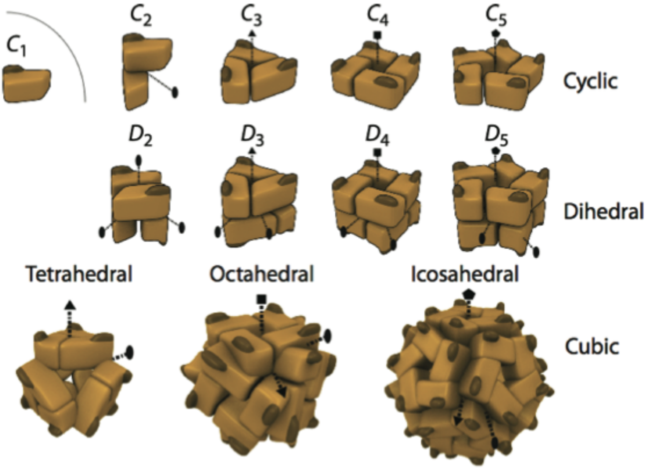
Symmetry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C_2
C_3
C_4
C_5
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D_2
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D_5
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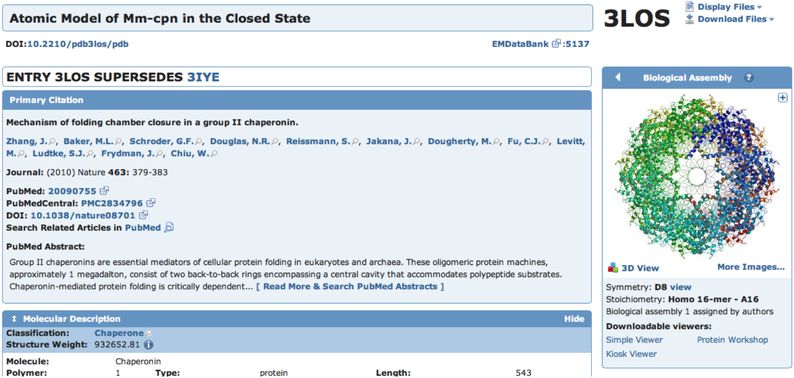
Tetrahedral
Octahedral
Icosahedral
Cubic

Dihedral



Atomic Model of Mm-cpn in the Closed State

3LOS

DOI: 10.2210/pdb3los/pdb

EMDataBank :5137

ENTRY 3LOS SUPERSEDES 3IYE

Primary Citation

Mechanism of folding chamber closure in a group II chaperonin.

Zhang, J., Baker, M.L., Schroder, G.F., Douglas, N.R., Reissmann, S., Jakana, J., Dougherty, M., Fu, C.J., Levitt, M., Ludtke, S.J., Frydman, J., Chiu, W.

Journal: (2010) Nature **463:** 379-383

PubMed: 20090755
PubMedCentral: PMC2834796
DOI: 10.1038/nature08701
Search Related Articles in PubMed

PubMed Abstract:

Group II chaperonins are essential mediators of cellular protein folding in eukaryotes and archaea. These oligomeric protein machines, approximately 1 megadalton, consist of two back-to-back rings encompassing a central cavity that accommodates polypeptide substrates. Chaperonin-mediated protein folding is critically dependent... [Read More & Search PubMed Abstracts]

Molecular Description Hide

Classification: Chaperone
Structure Weight: 932652.81

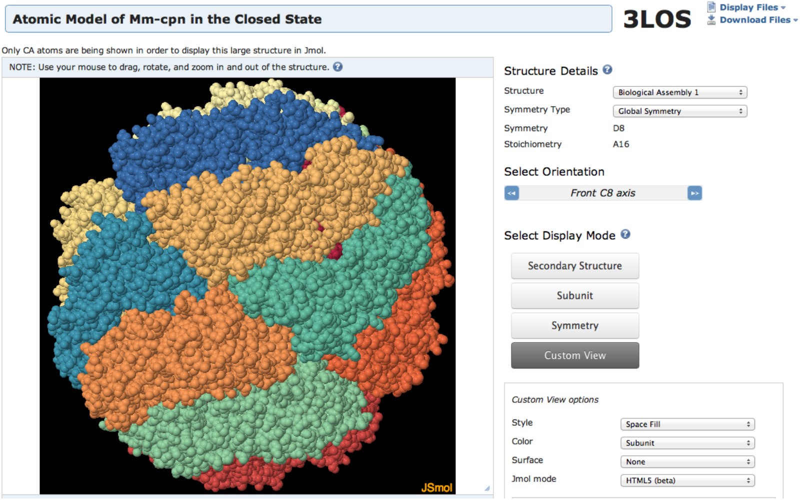
Molecule:	Chaperonin				
Polymer:	1	**Type:**	protein	**Length:**	543

Biological Assembly

Symmetry: **D8** view
Stoichiometry: **Homo 16-mer - A16**
Biological assembly 1 assigned by authors

Downloadable viewers:
Simple Viewer Protein Workshop
Kiosk Viewer

Dihedral



Atomic Model of Mm-cpn in the Closed State

3LOS

Only CA atoms are being shown in order to display this large structure in Jmol.

NOTE: Use your mouse to drag, rotate, and zoom in and out of the structure.

Structure Details

Structure: Biological Assembly 1
Symmetry Type: Global Symmetry
Symmetry: D8
Stoichiometry: A16

Select Orientation

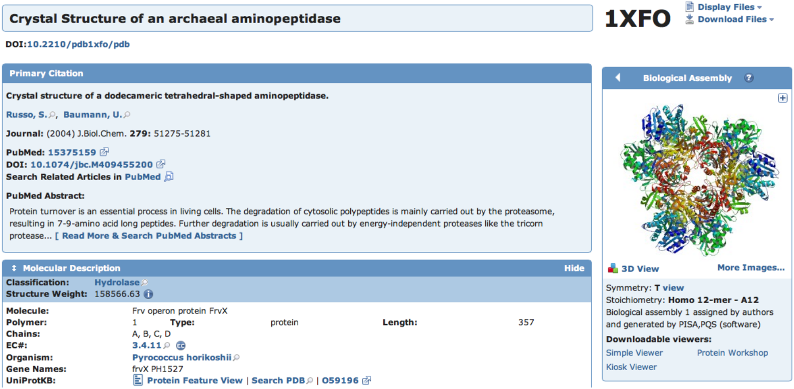
Front C8 axis

Select Display Mode

Custom View options

Style: Space Fill
Color: Subunit
Surface: None
Jmol mode: HTML5 (beta)

Tetrahedral



Crystal Structure of an archaeal aminopeptidase

1XFO

DOI: 10.2210/pdb1xfo/pdb

Primary Citation

Crystal structure of a dodecameric tetrahedral-shaped aminopeptidase.

Russo, S., Baumann, U.

Journal: (2004) J.Biol.Chem. **279:** 51275-51281

PubMed: 15375159
DOI: 10.1074/jbc.M409455200
Search Related Articles in PubMed

PubMed Abstract:

Protein turnover is an essential process in living cells. The degradation of cytosolic polypeptides is mainly carried out by the proteasome, resulting in 7-9-amino acid long peptides. Further degradation is usually carried out by energy-independent proteases like the tricorn protease... [Read More & Search PubMed Abstracts]

Molecular Description

Classification: Hydrolase
Structure Weight: 158566.63

Molecule: Frv operon protein FrvX
Polymer: 1 **Type:** protein **Length:** 357
Chains: A, B, C, D
EC#: 3.4.11
Organism: Pyrococcus horikoshii
Gene Names: frvX PH1527
UniProtKB: Protein Feature View | Search PDB | O59196

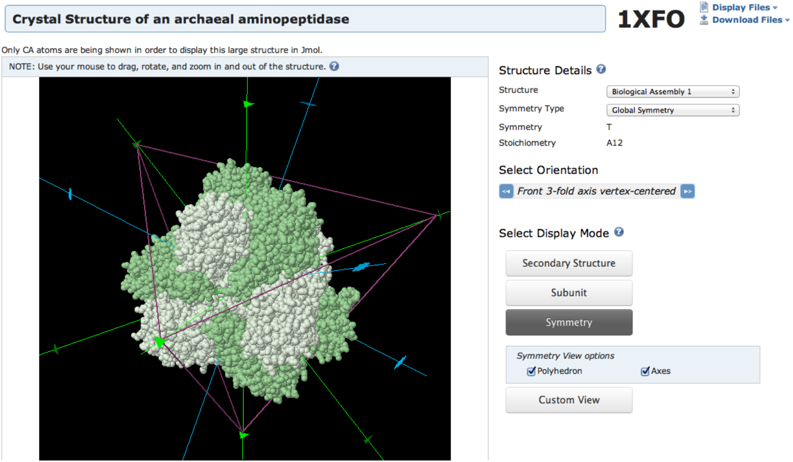
Biological Assembly

Symmetry: **T** view
Stoichiometry: **Homo 12-mer - A12**
Biological assembly 1 assigned by authors and generated by PISA,PQS (software)

Downloadable viewers:

Simple Viewer Protein Workshop
Kiosk Viewer

Tetrahedral



Crystal Structure of an archaeal aminopeptidase

1XFO

Only CA atoms are being shown in order to display this large structure in Jmol.

NOTE: Use your mouse to drag, rotate, and zoom in and out of the structure.

Structure Details

Structure: Biological Assembly 1

Symmetry Type: Global Symmetry

Symmetry: T

Stoichiometry: A12

Select Orientation

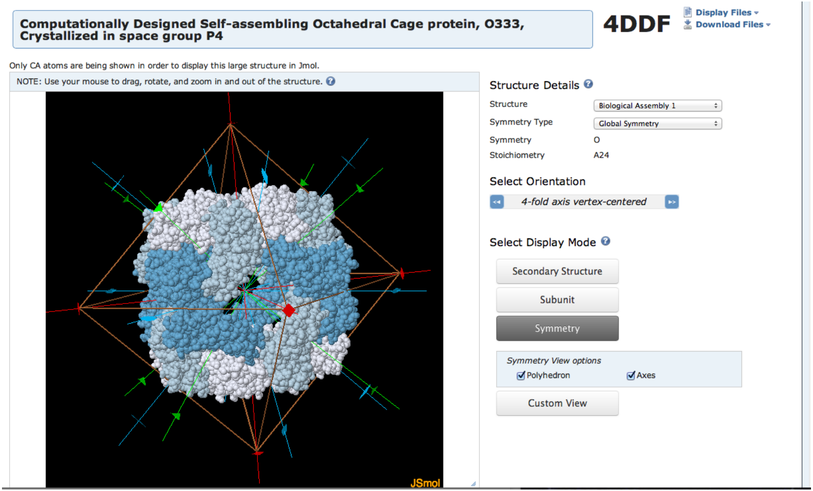
Front 3-fold axis vertex-centered

Select Display Mode

Symmetry View options

☑ Polyhedron ☑ Axes

Octahedral



Computationally Designed Self-assembling Octahedral Cage protein, O333, Crystallized in space group P4

4DDF

Only CA atoms are being shown in order to display this large structure in Jmol.

NOTE: Use your mouse to drag, rotate, and zoom in and out of the structure.

Structure Details

Structure	Biological Assembly 1
Symmetry Type	Global Symmetry
Symmetry	O
Stoichiometry	A24

Select Orientation

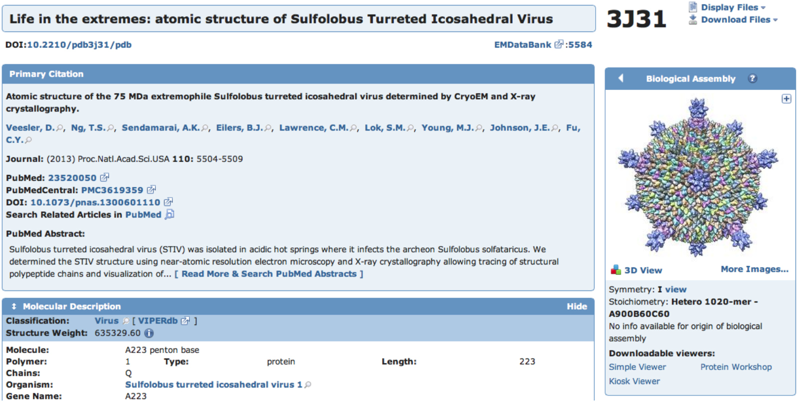
4-fold axis vertex-centered

Select Display Mode

Symmetry View options

☑ Polyhedron ☑ Axes

Icosahedral



Life in the extremes: atomic structure of Sulfolobus Turreted Icosahedral Virus

3J31

DOI:10.2210/pdb3j31/pdb

EMDataBank:5584

Primary Citation

Atomic structure of the 75 MDa extremophile Sulfolobus turreted icosahedral virus determined by CryoEM and X-ray crystallography.

Veesler, D., Ng, T.S., Sendamarai, A.K., Eilers, B.J., Lawrence, C.M., Lok, S.M., Young, M.J., Johnson, J.E., Fu, C.Y.

Journal: (2013) Proc.Natl.Acad.Sci.USA **110:** 5504-5509

PubMed: 23520050
PubMedCentral: PMC3619359
DOI: 10.1073/pnas.1300601110
Search Related Articles in PubMed

PubMed Abstract:

Sulfolobus turreted icosahedral virus (STIV) was isolated in acidic hot springs where it infects the archeon Sulfolobus solfataricus. We determined the STIV structure using near-atomic resolution electron microscopy and X-ray crystallography allowing tracing of structural polypeptide chains and visualization of... [Read More & Search PubMed Abstracts]

Molecular Description

Classification: Virus [VIPERdb]
Structure Weight: 635329.60

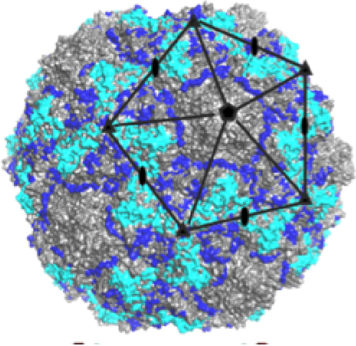
Molecule:	A223 penton base				
Polymer:	1	**Type:**	protein	**Length:**	223
Chains:	Q				
Organism:	Sulfolobus turreted icosahedral virus 1				
Gene Name:	A223				

Biological Assembly

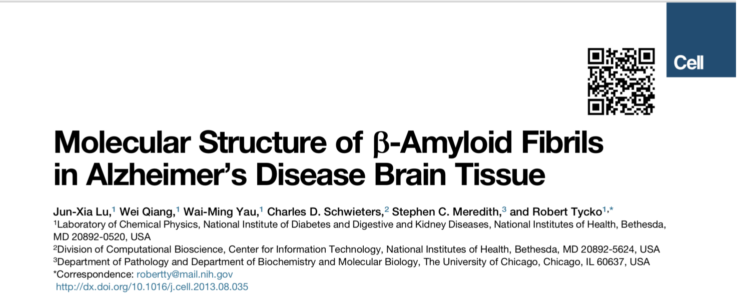
Symmetry: **I** view
Stoichiometry: **Hetero 1020-mer - A900B60C60**
No info available for origin of biological assembly

Downloadable viewers:
Simple Viewer
Protein Workshop
Kiosk Viewer

Icosahedral



Amyloid



Cell

Molecular Structure of β-Amyloid Fibrils in Alzheimer's Disease Brain Tissue

Jun-Xia Lu,[1] Wei Qiang,[1] Wai-Ming Yau,[1] Charles D. Schwieters,[2] Stephen C. Meredith,[3] and Robert Tycko[1],*
[1]Laboratory of Chemical Physics, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892-0520, USA
[2]Division of Computational Bioscience, Center for Information Technology, National Institutes of Health, Bethesda, MD 20892-5624, USA
[3]Department of Pathology and Department of Biochemistry and Molecular Biology, The University of Chicago, Chicago, IL 60637, USA
*Correspondence: robertty@mail.nih.gov

http://dx.doi.org/10.1016/j.cell.2013.08.035

Fibers in brain tissue

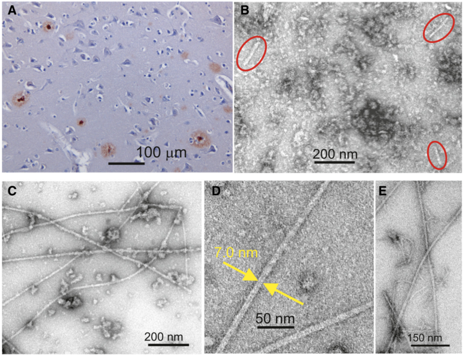


Figure 1. Evidence for a Single Predominant Aβ40 Fibril Structure in Brain Tissue of Patient I

(A) Light microscope image of cortical tissue from patient I, with immunohistochemical staining for β-amyloid using monoclonal antibody 6E10. Amyloid deposits are red or pink.

(B) Negatively stained TEM image of extract from occipital lobe tissue before addition of monomeric Aβ40. Fibril fragments are circled in red.

(C and D) TEM images of isotopically labeled Aβ40 fibrils, recorded 24 hr after addition of monomeric Aβ40 to sonicated extract from occipital lobe tissue. Aβ40 was uniformly ^{15}N,^{13}C-labeled at F19, V24, G25, A30, I31, L34, and M35.

(E) TEM image of fibrils prepared by seeding with sonicated extract from temporal/parietal lobe tissue.

(F and G) 2D ^{13}C-^{13}C and ^{15}N-^{13}C solid-state NMR spectra of Aβ40 fibrils, seeded with extract from occipital lobe tissue. Black lines and labels show site-specific cross-peak assignments.

(H and I) 2D ^{13}C-^{13}C and ^{15}N-^{13}C solid-state NMR spectra of Aβ40 fibrils, seeded with extract from temporal/parietal lobe tissue, with the same black lines as in (F) and (H).

See also Figures S1 and S2.

Amyloid fiber model

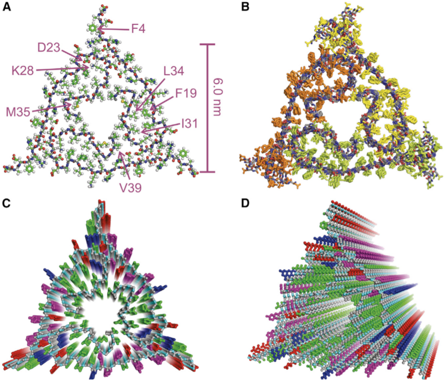


Figure 5. Molecular Structure of Aβ40 Fibrils from Patient I

(A) Structure with the lowest total experimental restraint energy in Xplor-NIH calculations. The 3-fold-symmetric repeat unit is shown, as viewed along the fibril growth axis. Backbone and sidechain carbon atoms are gray and green, respectively.

(B) Superposition of 20 structures that are consistent with experimental restraints (PDB code 2M4J). Sidechains of the three Aβ40 molecules in the repeat unit are yellow, green, or orange.

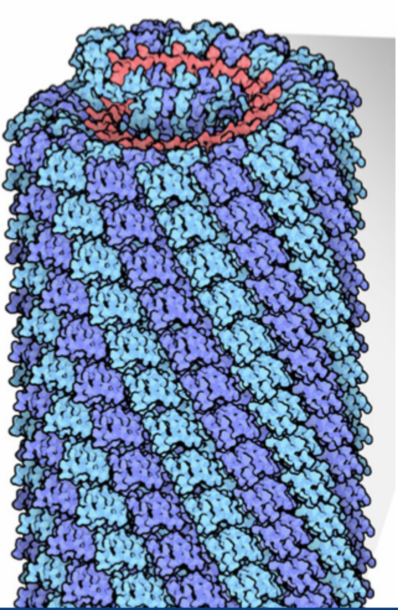
(C and D) Two views of the idealized fibril structure, created by repeating the trimeric unit 18 times with 0.48 nm displacements along the fibril axis.

(E and F) Structural models for Aβ40 fibril polymorphs with 3-fold and 2-fold symmetry about the fibril growth axis, developed previously from solid-state NMR and electron microscopy measurements on fibrils grown in vitro. Repeat units from these models are shown, calculated as regularized averages of structure bundles in PDB codes 2LMP and 2LMN, respectively.

See also Figures S4 and S6 and Tables S3 and S4.

The severity of cognitive impairment in

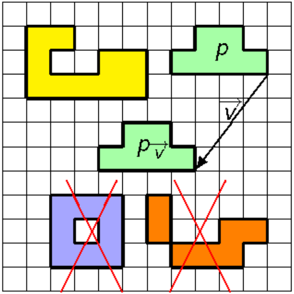
Fiber !



Tilings of the plane

Définition

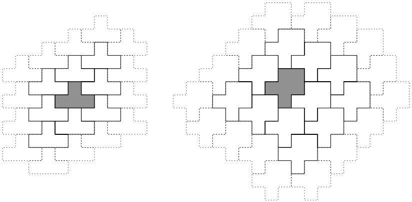
A *polyomino* is the interior of a closed non intersecting path in a square lattice.



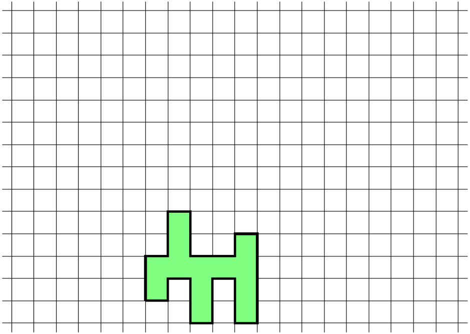
Tilings of the plane

Definitions

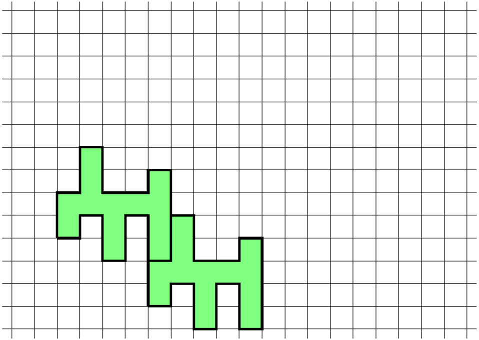
A *tiling by translation* of a polyomino P is a covering of $\mathbb{R}^2$ by translation of copies of P without overlapping or hole.



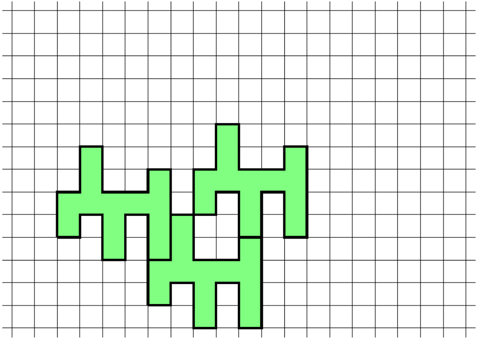
Tilings by translation



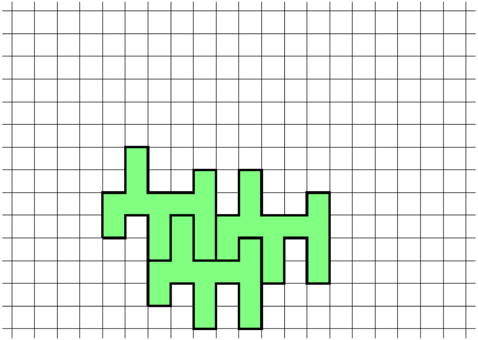
Tilings by translation



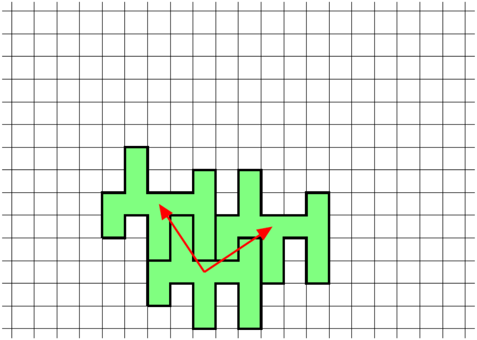
Tilings by translation



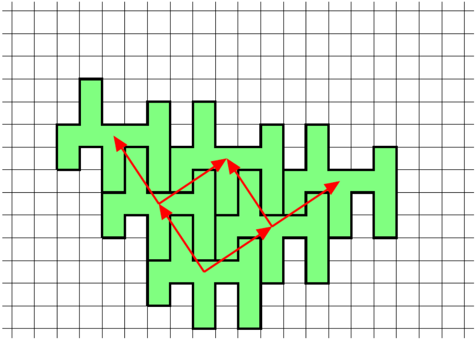
Tilings by translation



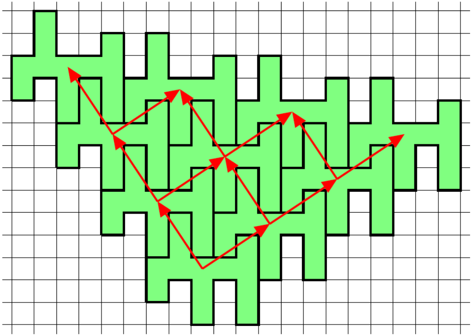
Tilings by translation



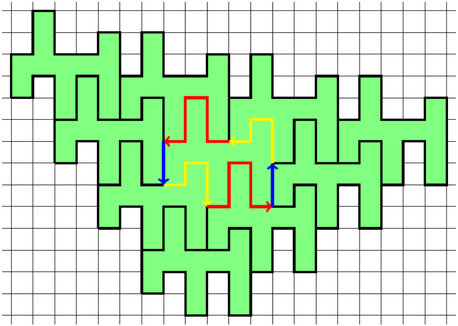
Tilings by translation



Tilings by translation



Tilings by translation

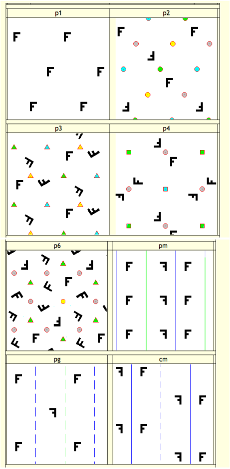


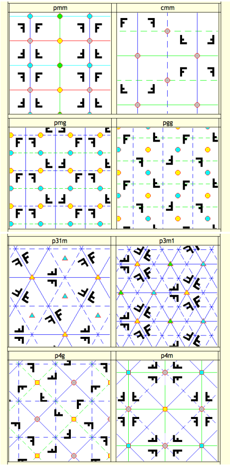
Tilings of the plane

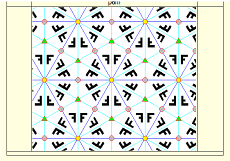
Isometries of the plane : translation, rotation, reflection and glide reflection.
17 crystalographic groups for the plane (Bravais 1847).

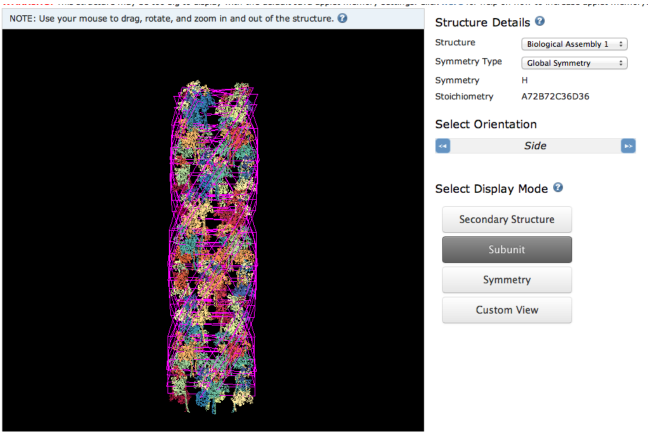
The 17 crystallographic groups are represented at the Alhambra of Grenada (by artists around 1350).

Cristallographic groups









NOTE: Use your mouse to drag, rotate, and zoom in and out of the structure.

Structure Details

Structure: Biological Assembly 1

Symmetry Type: Global Symmetry

Symmetry: H

Stoichiometry: A72B72C36D36

Select Orientation: Side

FIGURE – **Spider silk.**

From regular tilings of the plane to tilings of a fiber

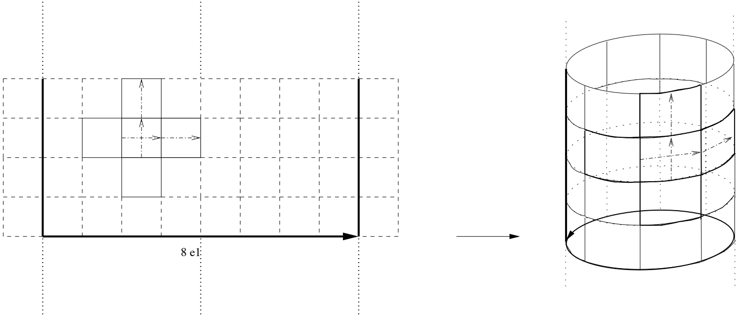


FIGURE – **From tiling to cylinder by using the translation of 8 times the vector $\vec{e}_1$.**

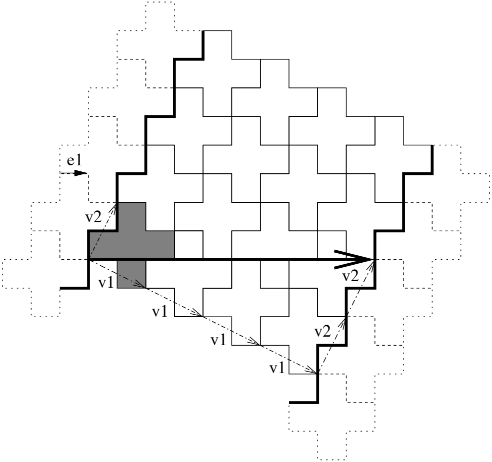


FIGURE – **Two boundaries in correspondence by the translation** $4\vec{v}_1 + 2\vec{v}_2$)

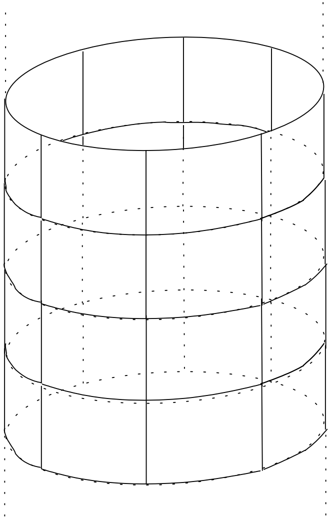


FIGURE – **Fiber with a pseudo square shape.** Each tile is surrounded by 4 tiles.

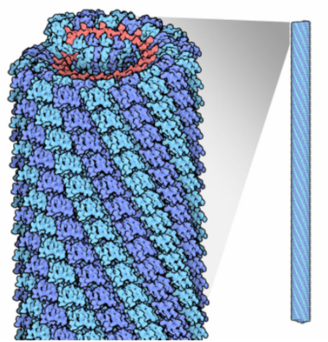


FIGURE – **Tobacco Mosaic Virus.**

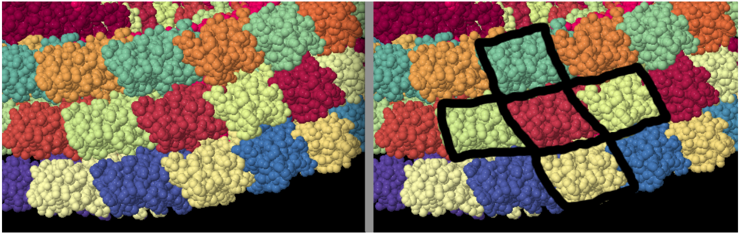


FIGURE – **Tobacco Mosaic Virus : an example of tiling of a fiber with 4 adjacent chains.**

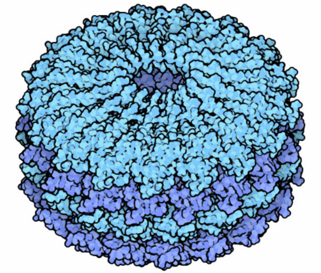


FIGURE – **Tobacco Mosaic Virus : a 17-mer.**

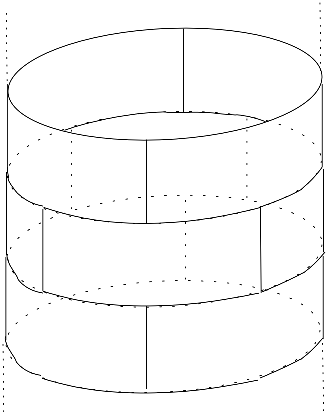


FIGURE – **Fiber with a pseudo hexagon shape.** Each tile is surrounded by 6 tiles. Remark that pseudo hexagon shapes appear in particular when there is a tilt on the fiber.

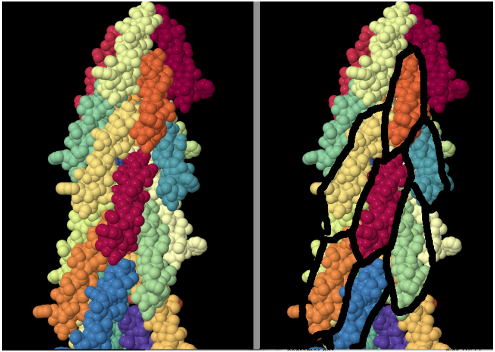


FIGURE – **3J1R : an example of tiling of a fiber with 6 adjacent chains.**

From fold plasticity to fibers : the P53 case

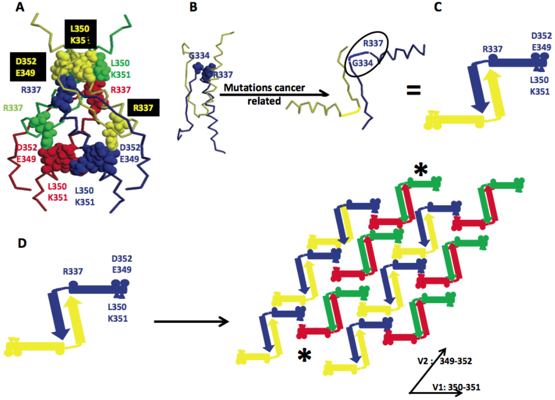


FIGURE – **A. The p53 tetrameric domain is made of 2 dimers.** Each monomer is made of a β-strand followed by a small helix ended by a long α-helix parallel to the β-strand (1SAK). The residue R337 is sensitive to mutation.

Parkinson disease

Model biomolecular condensates have heterogeneous structure quantitatively dependent on the interaction profile of their constituent macromolecules

Julian C. Shillcock[1*], Clément Lagisquet[2], Jérémy Alexandre[3,4], Laurent Vuillon[2*],

John H. Ipsen[5]

[1] Blue Brain Project and Laboratory of Molecular and Chemical Biology of Neurodegeneration, Ecole polytechnique fédérale de Lausanne, CH-1015 Lausanne, Switzerland

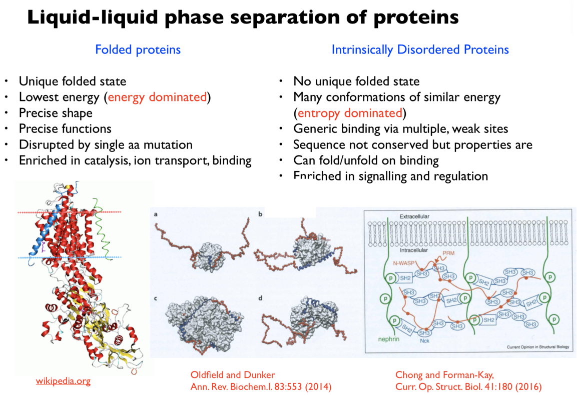
[2] LAMA, Univ. Savoie Mont Blanc, CNRS, LAMA, 73376 Le Bourget du Lac, France

[3] Brain Mind Institute, Ecole polytechnique fédérale de Lausanne, CH-1015 Lausanne, Switzerland

[4] Current address: Aktiia SA, Rue du Bassin 8a, 2000 Neuchâtel, Switzerland

[5] Dept. of Physics, Chemistry and Pharmacy, University of Southern Denmark, Campusvej 55, DK-5230 Odense M, Denmark

Intrinsically Disordered Proteins



Liquid-liquid phase separation of proteins

Folded proteins

- Unique folded state
- Lowest energy (energy dominated)
- Precise shape
- Precise functions
- Disrupted by single aa mutation
- Enriched in catalysis, ion transport, binding

Intrinsically Disordered Proteins

- No unique folded state
- Many conformations of similar energy (entropy dominated)
- Generic binding via multiple, weak sites
- Sequence not conserved but properties are
- Can fold/unfold on binding
- Enriched in signalling and regulation

wikipedia.org

Oldfield and Dunker
Ann. Rev. Biochem.l. 83:553 (2014)

Chong and Forman-Kay,
Curr. Op. Struct. Biol. 41:180 (2016)

Semi flexible polymers

Reduce an IDP to its simplest form: a semi-flexible polymer with sticky end-caps (*telechelic*)

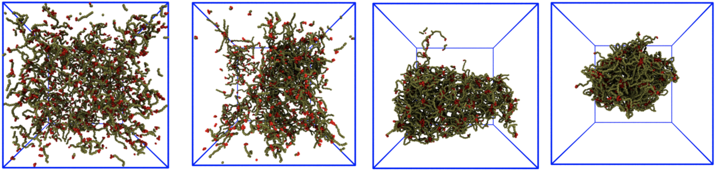
Still many parameters: molecular weight, backbone stiffness, end-cap affinity, concentration …

Choose two

A) Backbone length (molecular weight) = 16, 24, 32, … beads

B) Dimensionless end-cap affinity = [0, 1]; where 0 = no affinity and 1 = "very strong" affinity (defined in terms of the conservative interactions between end-caps and water)

N = 634 hydrophilic polymers with increasing affinity →



From fluide to solid aggregates

Fused in Sarcoma (FUS)

Low complexity NTD

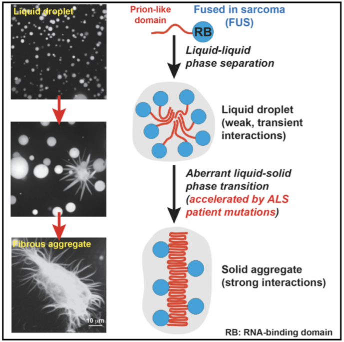
Full-length FUS phase separates

FUS LC phase separates

FUS \ LC does not separate

Soluble FUS undergoes LLPS into droplets

FUS droplets make pathological transitions to a rigid state in disease



A. Patel et al., Cell, 162:1066 (2015)

Network theory

Fluid network of polymers with *multiple* weak binding sites → 3D graph: vertices, edges → Apply graph theoretic analyses