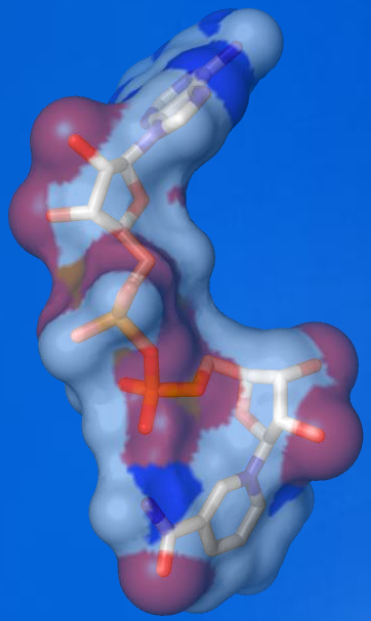
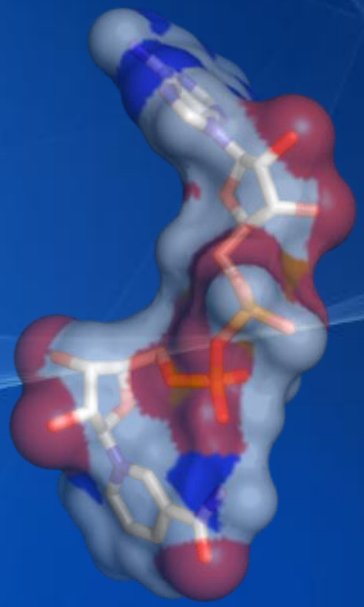
FFI0750 – Biologia Molecular Estrutural





Prof. Rafael V. C. Guido

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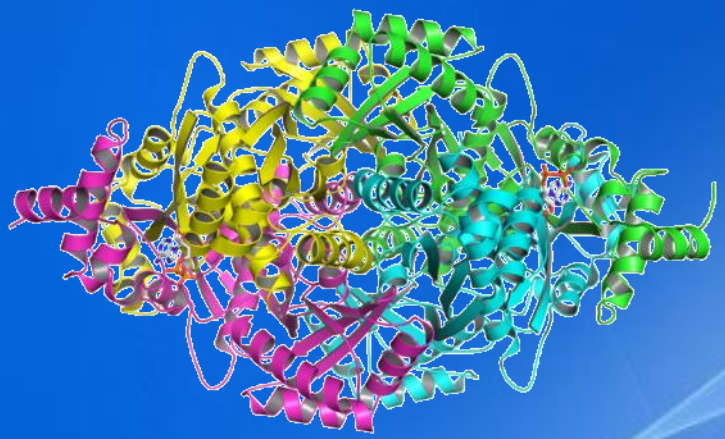
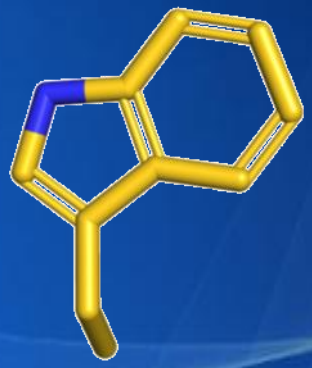
Aula 02

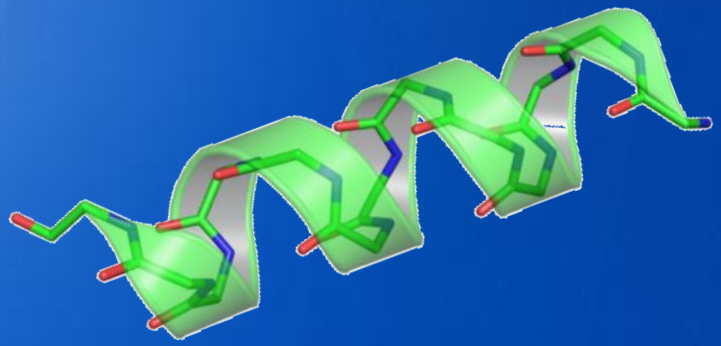
Bacharelado em Ciências Físicas e Biomoleculares

Instituto de Física de São Carlos - USP

Por que estudamos proteínas?

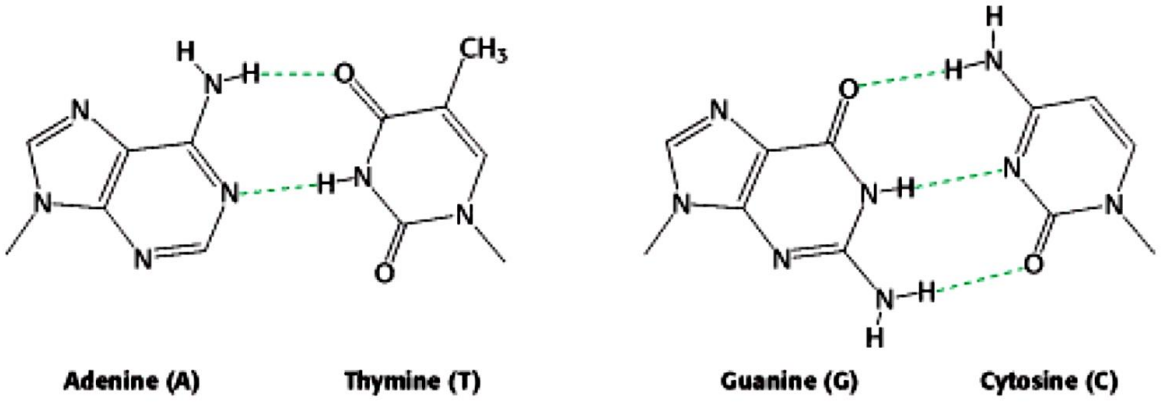






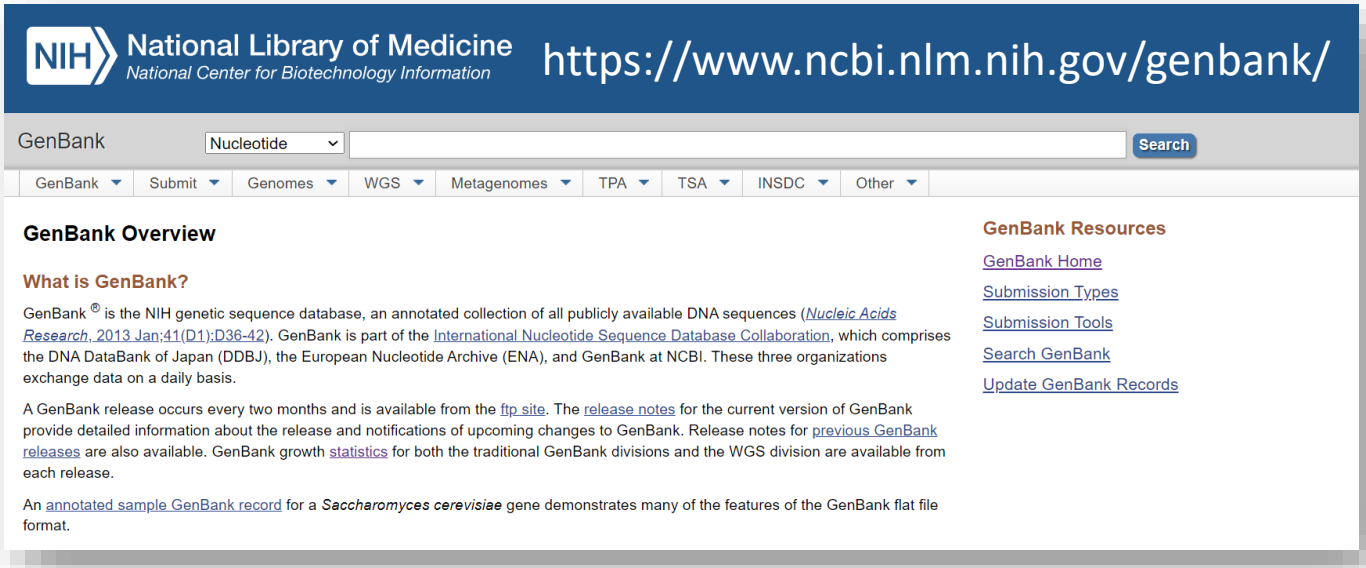
Genoma

GACTTCACTTCTAATGATGATTATGGGAGAACTGGAGCCTTCAGAGGGT
AAAAATTAAGCACAGTGGAAGAATTTCATTCTGTTCTCAGTTTTCCTGGA
TTATGCCTGGCACCATTAAAGAAAATATCTTTGGTGTTTCCTATGATGAAT
ATAGATACAGAAGCGTCATCAAAGCATGCCAACTAGAAGAG...

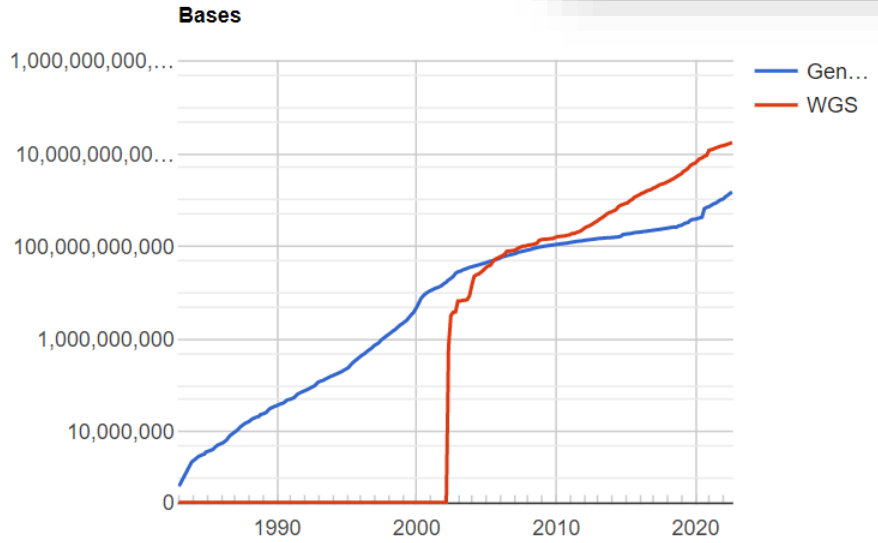


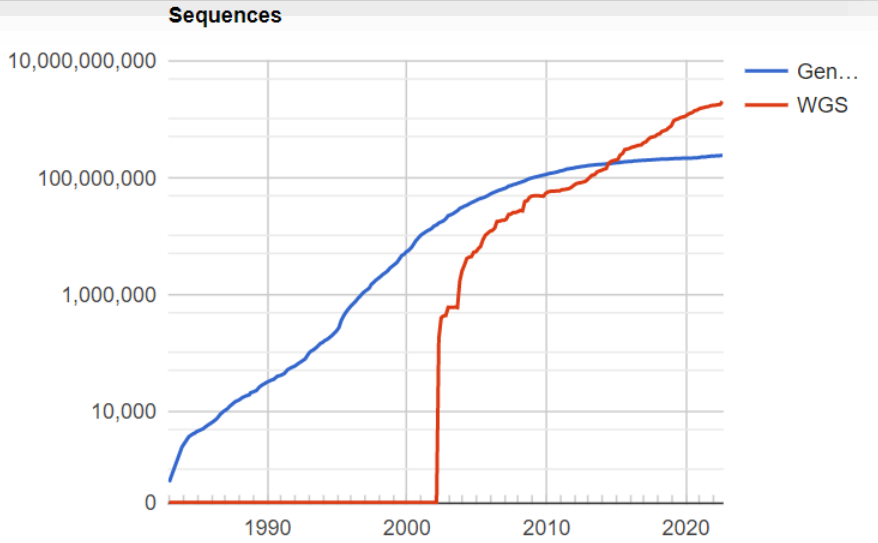
- Mais de 3 bilhões de nucleotídeos
- O genoma humano se fosse escrito em páginas de papel A4 necessitaria de mais de 500.000 páginas

GenBank



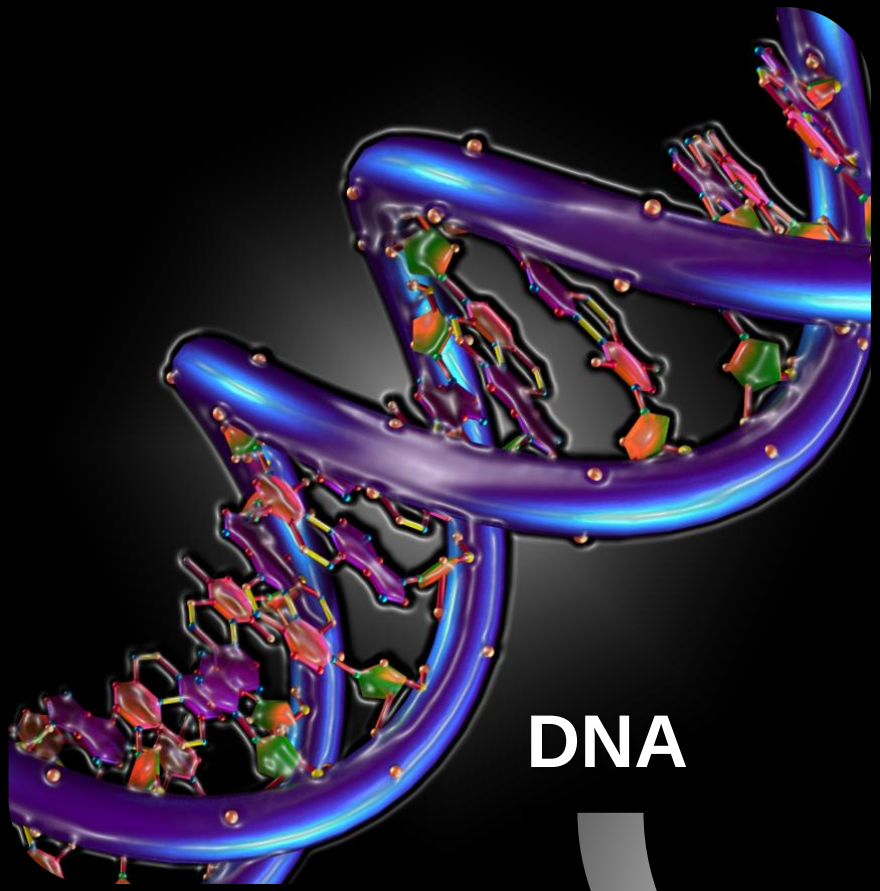
GenBank and WGS Statistics





https://www.ncbi.nlm.nih.gov/genbank/statistics/

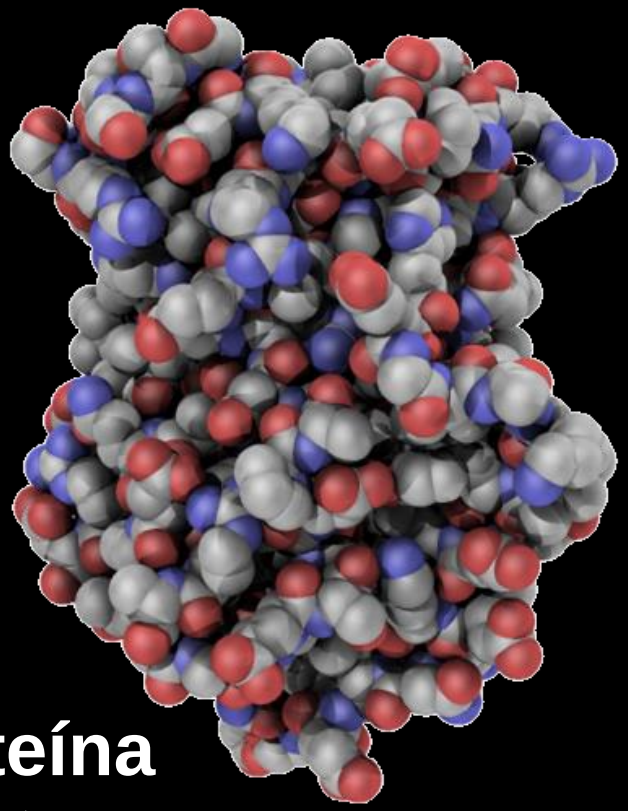
DNA → RNA → Proteínas



DNA

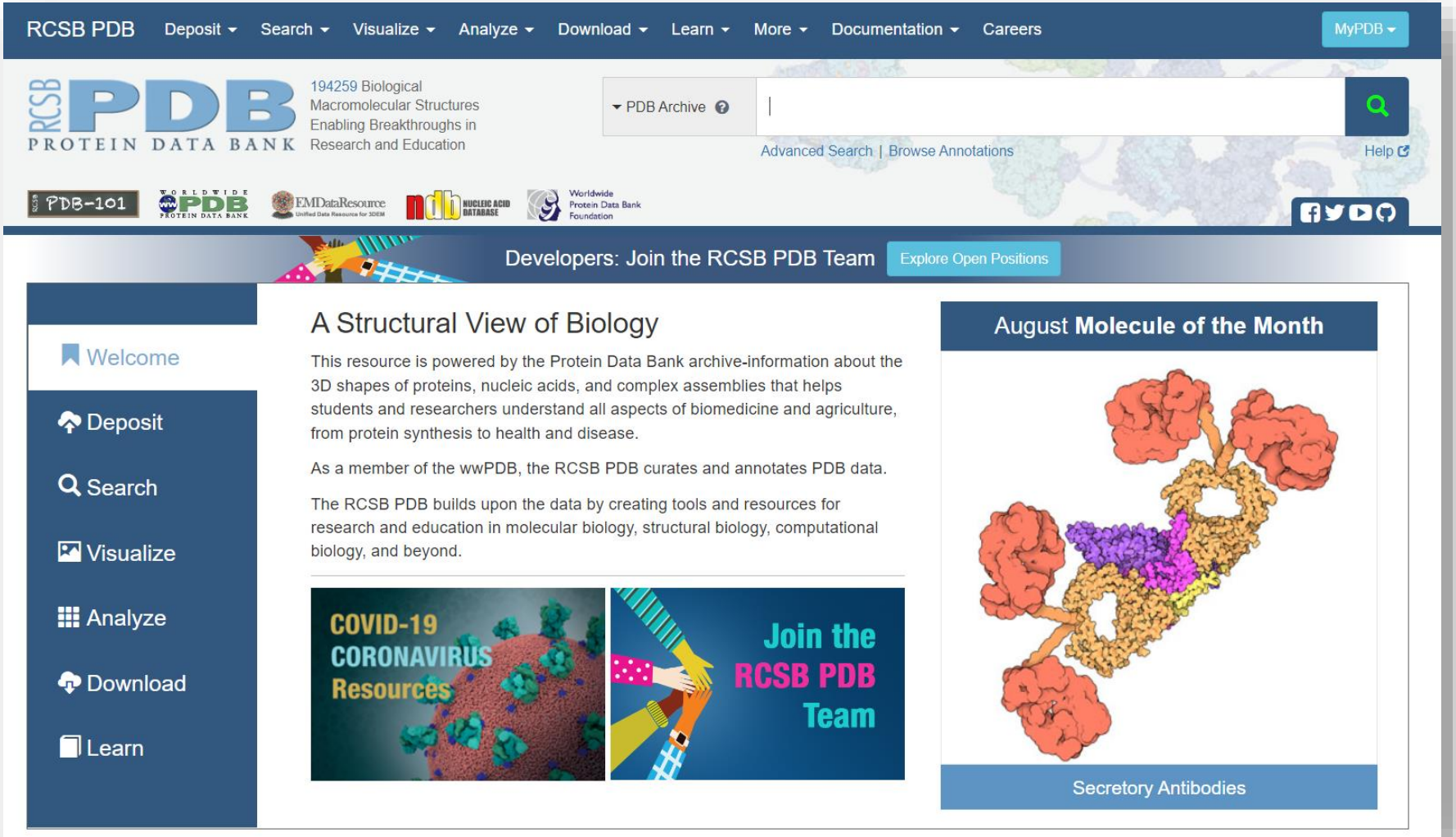
RNA

Proteína



Protein data bank (PDB)

https://www.rcsb.org/



Protein data bank (PDB)

https://www.rcsb.org/

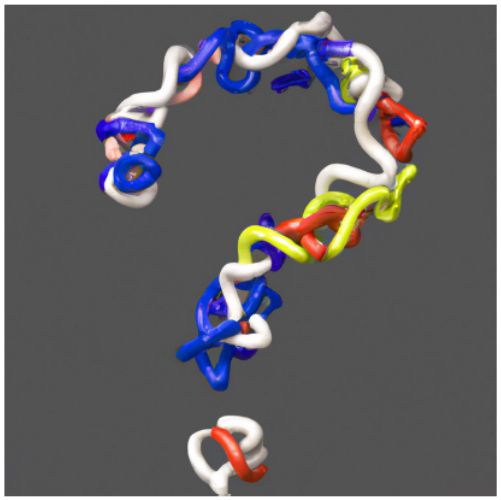
Protein data bank (PDB)

editorial https://journals.iucr.org/m/issues/2023/04/00/me6233/index.html

Acta Cryst D STRUCTURAL BIOLOGY
ISSN 2059-7983

AlphaFold and the future of structural biology[1]

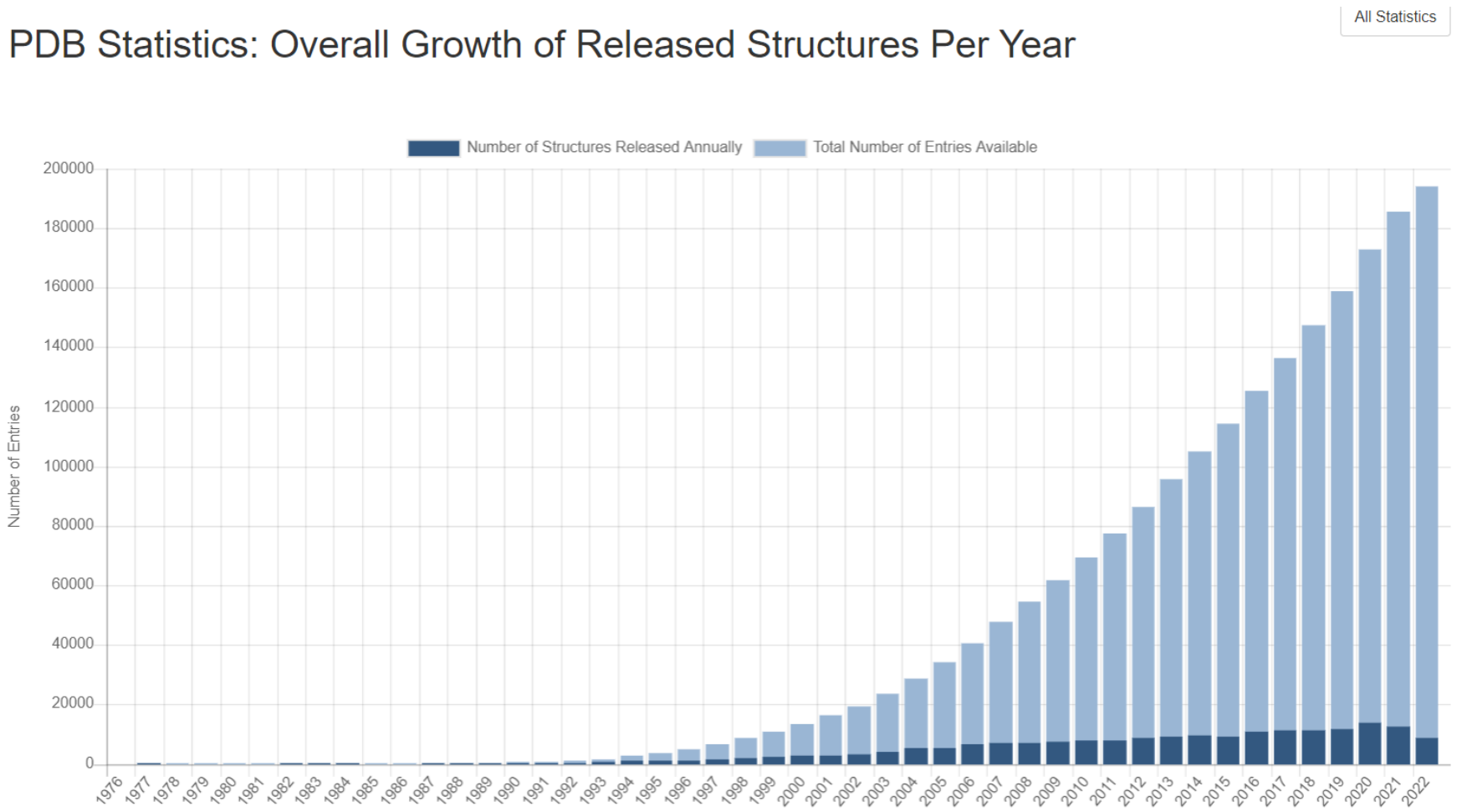
Randy J. Read,[a]* Edward N. Baker,[b]* Charles S. Bond,[c]* Elspeth F. Garman[d]* and Mark J. van Raaij[e]*



Structural biologists quickly embraced the advantages that these models bring (Perrakis & Sixma, 2021), including insights into improved construct design, the generation of compelling hypotheses about interacting proteins or domains, and the acceleration of structure solution by molecular replacement (Millán *et al.*, 2021) for crystallography or docking for electron cryo-microscopy (cryo-EM). A particularly notable example was integrative modelling of the nuclear pore complex by combining *AlphaFold* (Jumper *et al.*, 2021) and *RoseTTAFold* (Baek *et al.*, 2021) models with cryo-electron tomography and complementary data (Mosalaganti *et al.*, 2022).

Most structural biologists are aware that the models are not actually as accurate as experimental structures. The backbone accuracy measured in CASP does not ensure the accuracy of all coordinates including side chains. An objective evaluation of how well different models explain experimental diffraction data showed that experimental structures from alternative crystal forms (in spite of different crystal-packing interactions) are generally better than *AlphaFold* models (Terwilliger *et al.*, 2023). It has also been reported that *AlphaFold* models perform less well than experimental structures as targets for the computational docking algorithms used in drug design (Karelina *et al.*, 2023).

Protein data bank (PDB)

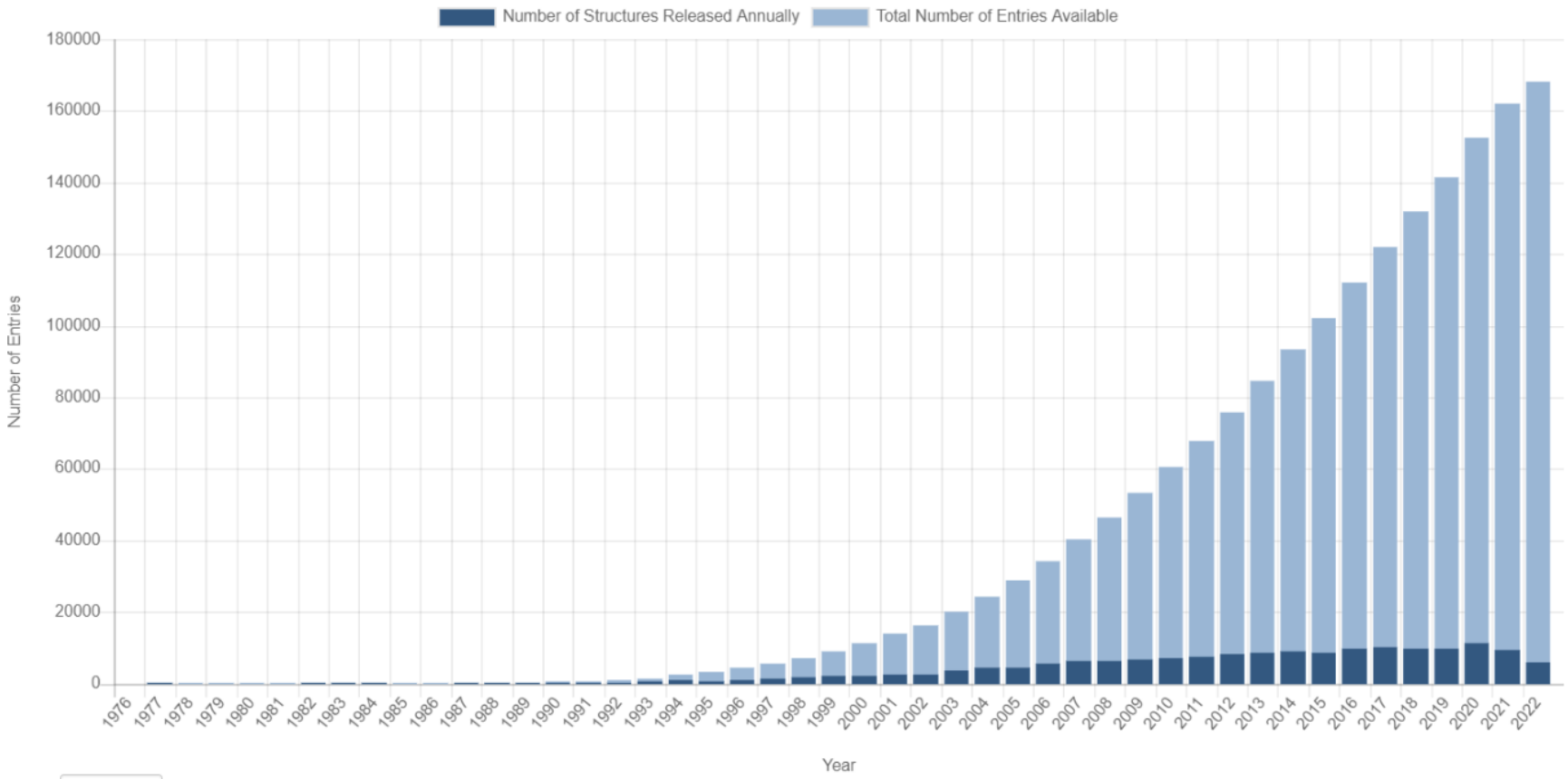


https://www.rcsb.org/stats/growth/growth-released-structures

Protein data bank (PDB)

PDB Statistics: Growth of Structures from X-ray Crystallography Experiments Released per Year

Experimental methods such as X-ray crystallography, NMR spectroscopy, and 3D electron microscopy are used to determine the location of each atom relative to each other in the molecule.



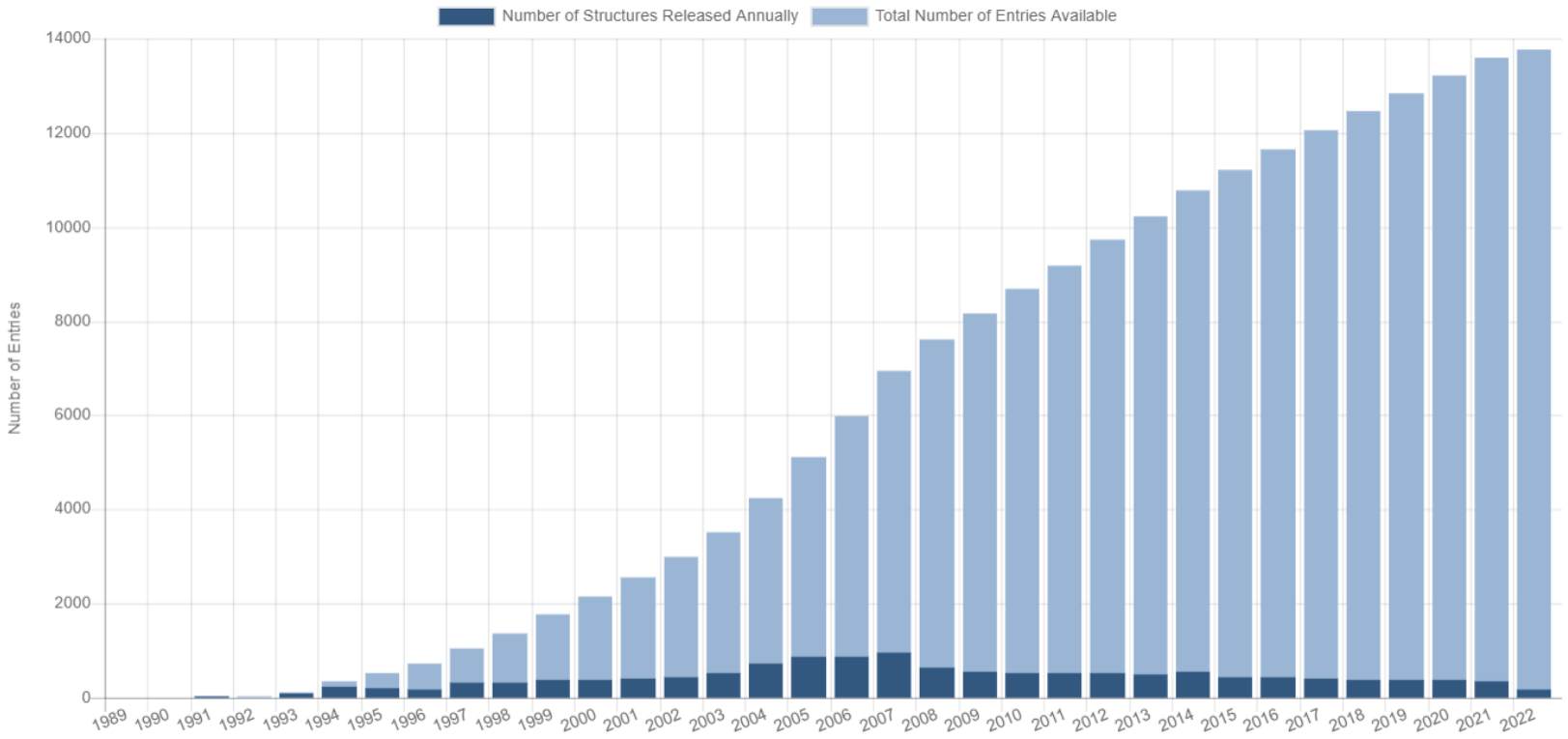
https://www.rcsb.org/stats/growth/growth-released-structures

Protein data bank (PDB)

All Statistics

PDB Statistics: Growth of Structures from NMR Experiments Released per Year

Experimental methods such as X-ray crystallography, NMR spectroscopy, and 3D electron microscopy are used to determine the location of each atom relative to each other in the molecule.



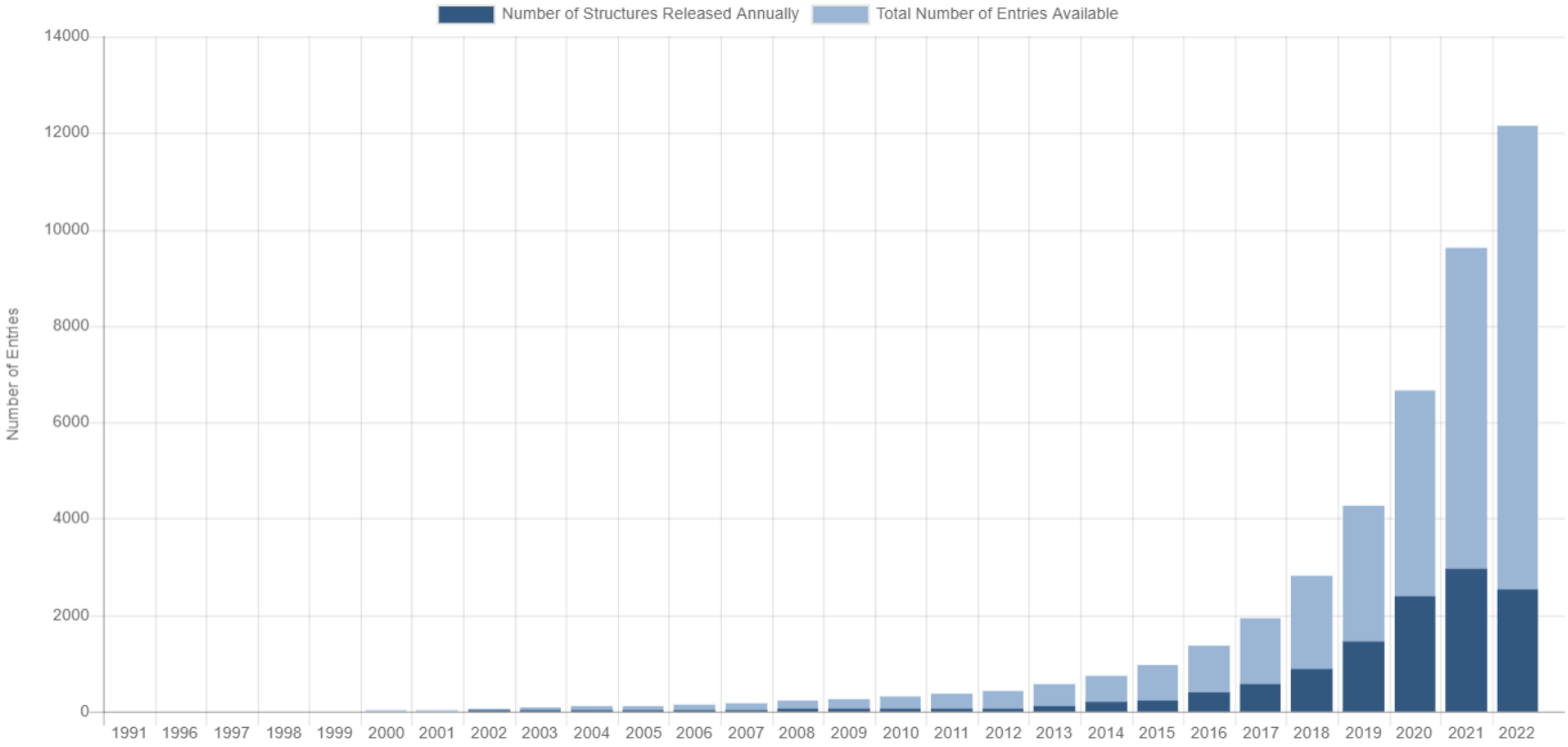
https://www.rcsb.org/stats/growth/growth-released-structures

Protein data bank (PDB)

All Statistics

PDB Statistics: Growth of Structures from 3DEM Experiments Released per Year

Experimental methods such as X-ray crystallography, NMR spectroscopy, and 3D electron microscopy are used to determine the location of each atom relative to each other in the molecule.



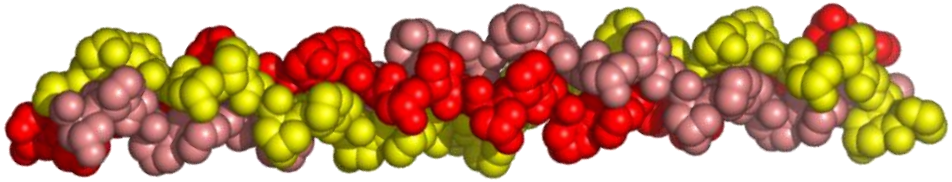
https://www.rcsb.org/stats/growth/growth-released-structures

Classificação de Proteínas por Função

- **CATALÍTICA:** enzimas
- **ARMAZENAMENTO:** ovalbumina (ovos), caseína (leite), zeína (milho)
- **TRANSPORTE:** hemoglobina
- **COMUNICAÇÃO:** hormônios (insulina) e neurotransmissores
- **CONTRÁTEIS:** actina, miosina
- **PROTEÇÃO:** imunoglobulina, fibrinogênio, fatores de coagulação do sangue
- **TOXINAS:** veneno de serpente
- **ESTRUTURAL:** queratina (cabelo), colágeno

Proteínas Fibrosas

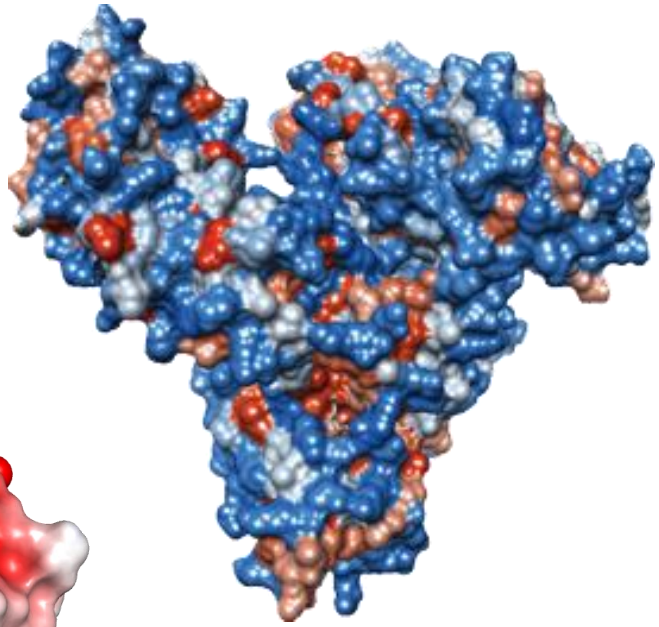
- Proteínas Estruturais: Tendões, ligamentos, coágulos de sangue (e.g., colágeno e queratina)

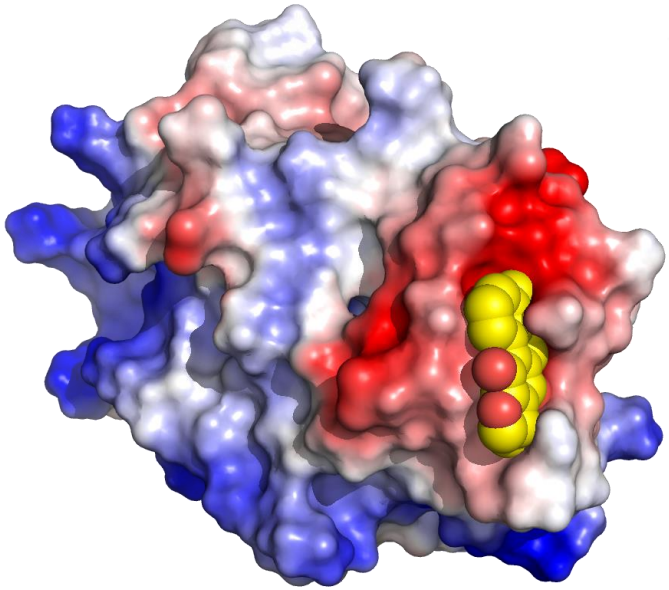


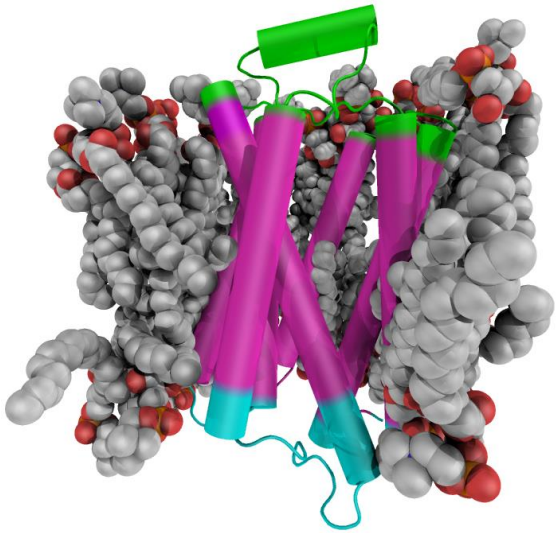
- Proteínas Contráteis: Músculos, microtúbulos (e.g., citoesqueleto, fuso mitótico, cílios, flagelos)

Proteinas Globulares

- Proteínas de armazenamento (e.g., albumina)







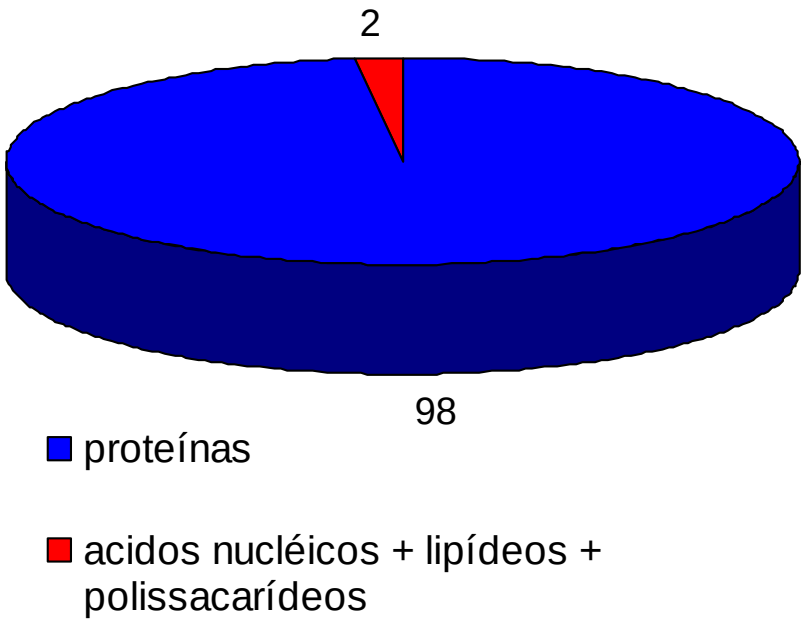
- Proteínas catalíticas, transporte, proteção: enzimas, hemoglobina, imunoglobulinas, receptores de membrana

Alvos Moleculares para Fármacos

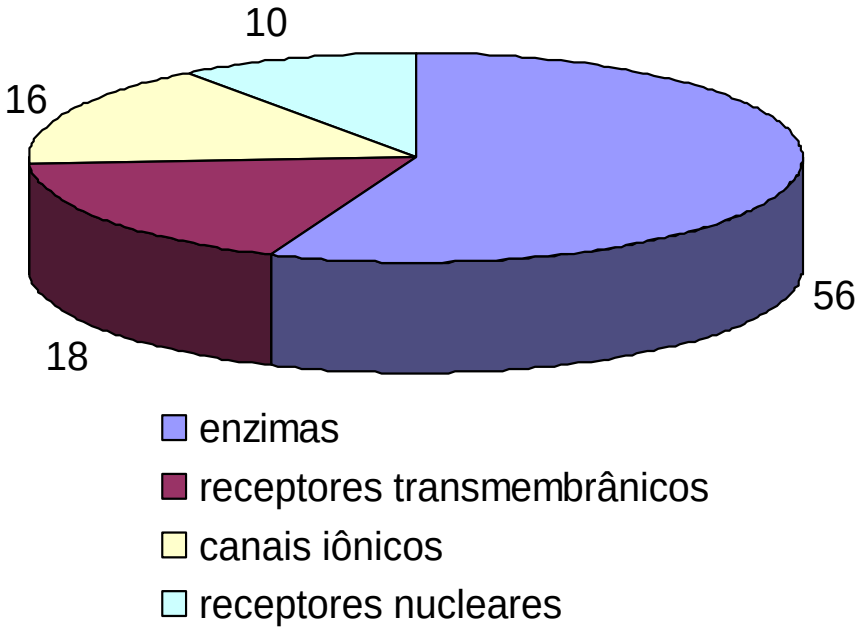
Alvos para fármacos

Principais Alvos Biológicos

1.357 fármacos em uso terapêutico



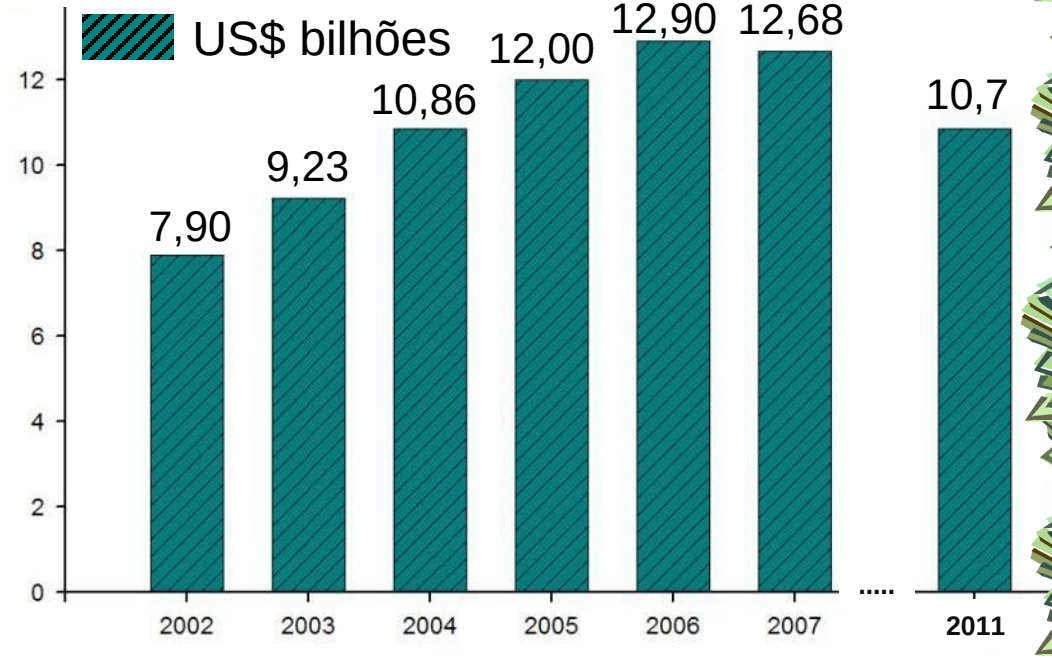
Considerando os 100 fármacos de maior sucesso no mundo tem-se:

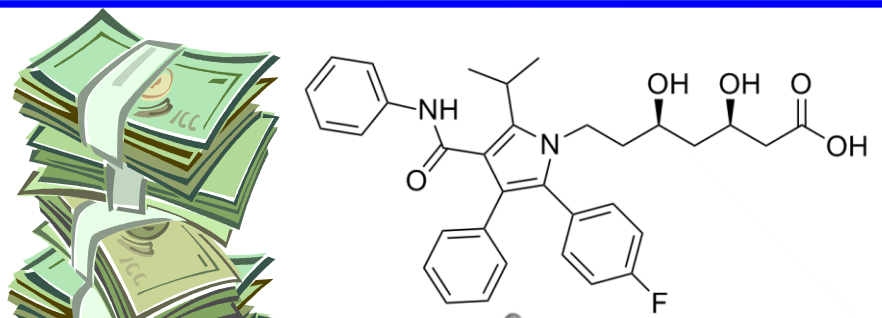


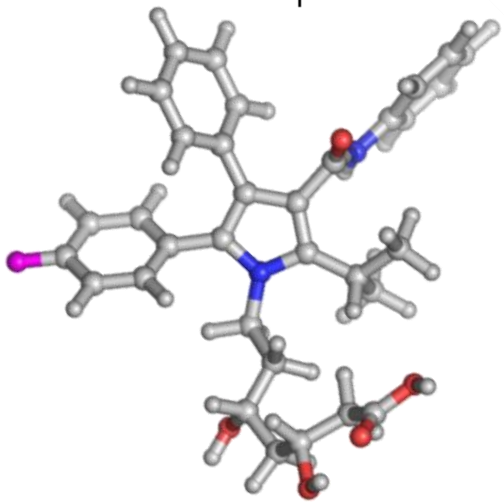
O fármaco mais bem sucedido da história

Lípitor®
atorvastatina cálcica

- **Redutor de colesterol;**
- O maior sucesso de vendas da história







$C_{33}H_{35}FN_2O_5$ = 76 átomos

US$ 140,79 milhões/átomo!!!

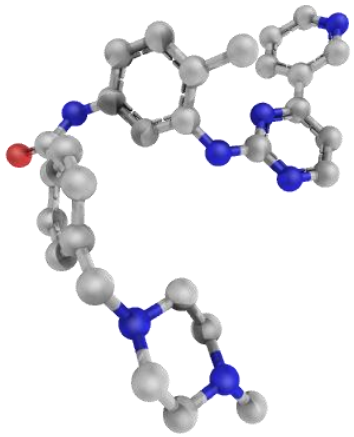
Glivec (Imatinib)

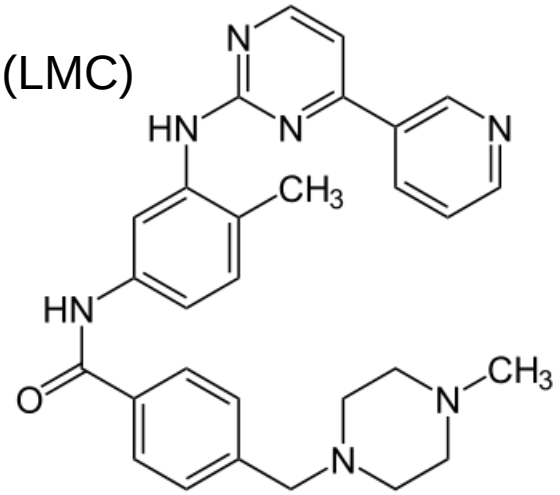
NOVARTIS

Gleevec/Glivec®
mesilato de imatinib

Anticâncer (Via Oral)

- leucemia mieloide crônica (LMC)
- tumores gastrointestinais

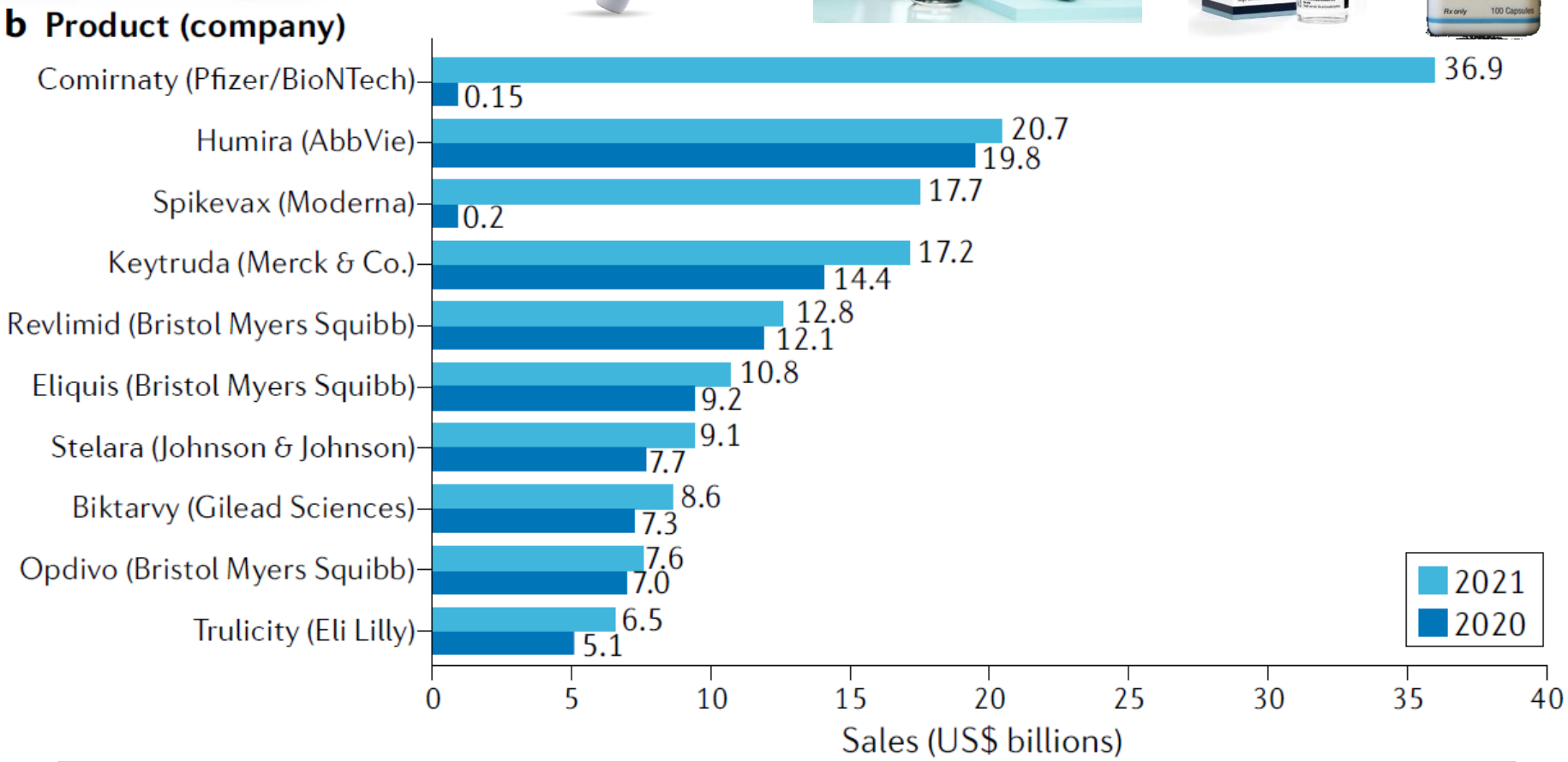




ANO	VENDAS (US$ BILHÕES)
2007	3,05
2008	3,67
2009	3,94
2010	4,30
2012	1,70

R$ 15.835,52 / 30 cprs.

Top 10 fármacos/vacinas em 2021



https://doi.org/10.1038/d41573-022-00047-9

Por que estudamos proteínas?

Talvez a melhor resposta que possa ser dada seja porque as proteínas sustentam todos os aspectos da atividade biológica.

- As proteína são essenciais para os organismos
- As proteínas constituem, em média, 15% da massa corporal
  - ✓ Grande parte do tecido do nosso corpo é constituído de proteína.
  - ✓ Proteínas desempenham funções vitais que mantém o organismo funcionando adequadamente
- Algumas proteínas são economicamente atrativas