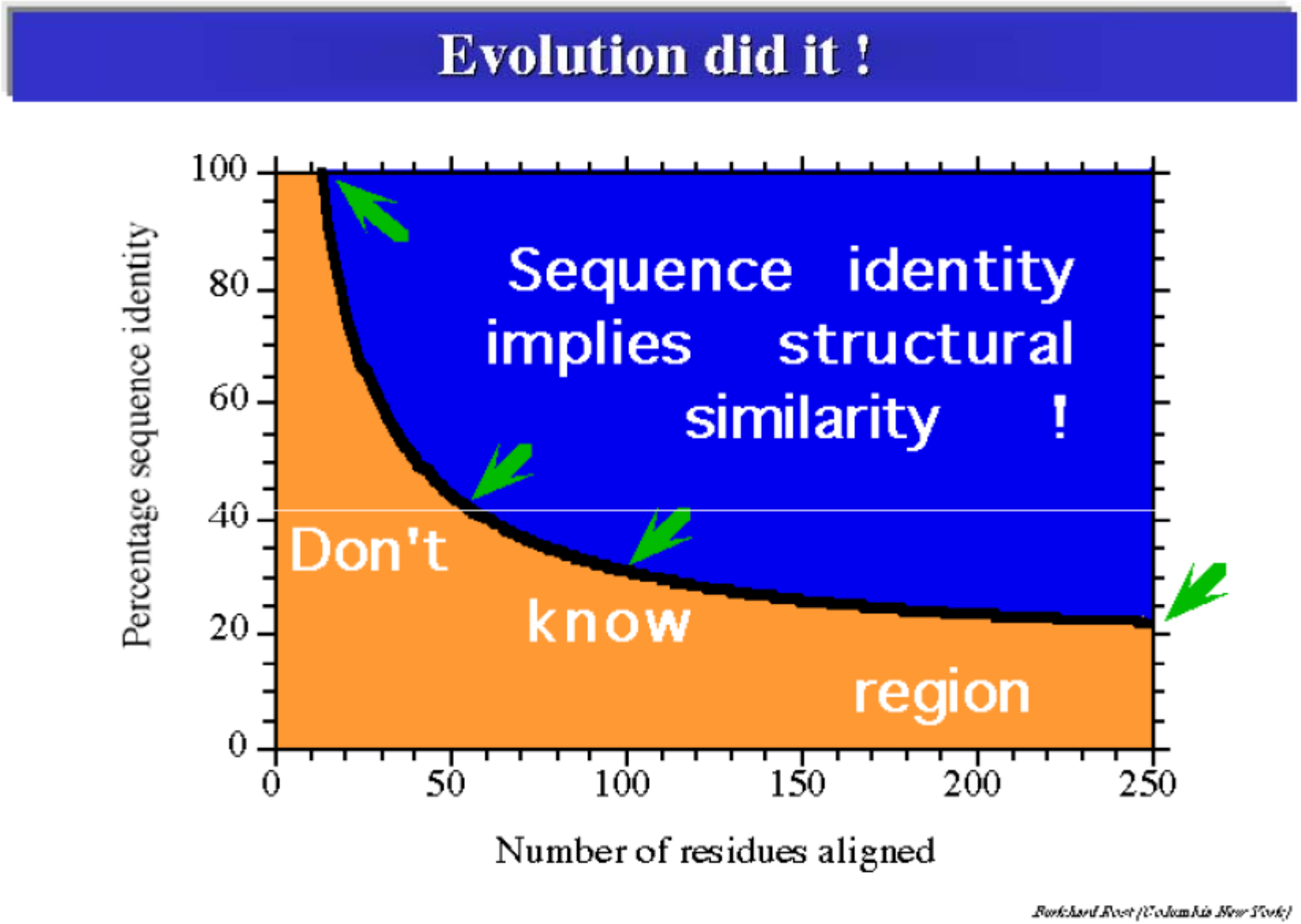
In search of distantly related homologs….



Distantly related proteins:

proteins with conserved function, putatively conserved structure (or functional domain) whose sequence is below the significance threshold of any alignment method

Structural Bioinformatics

To which extent protein structures change through evolution?

Multiple structural alignment of three trypsins from *Bos taurus* (5ptp), *Rattus rattus* (1bra) and *Streptomyces griseus* (1sgt, 2sga)

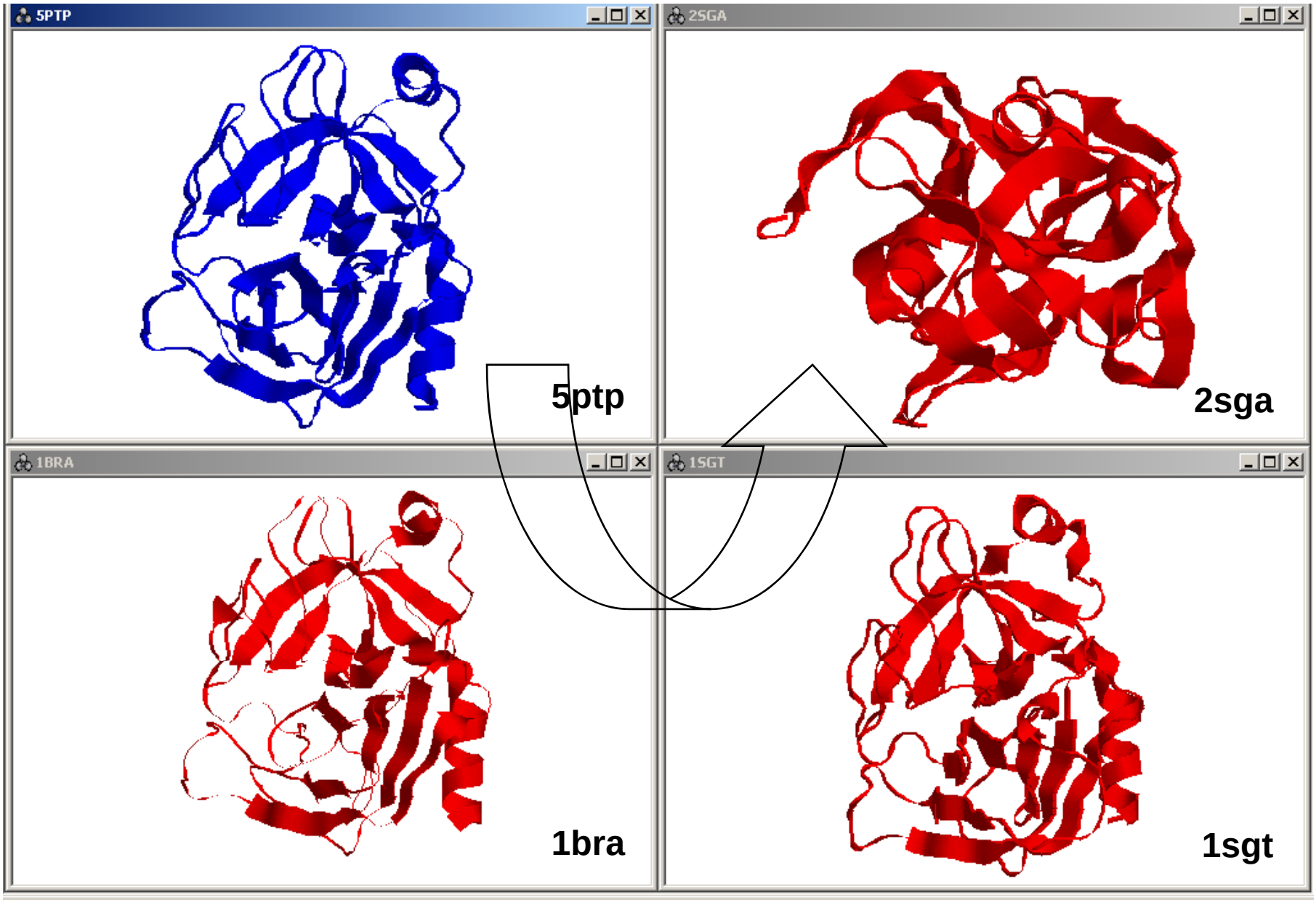
Sequence Identity

5PTP - 1BRA 72.6%

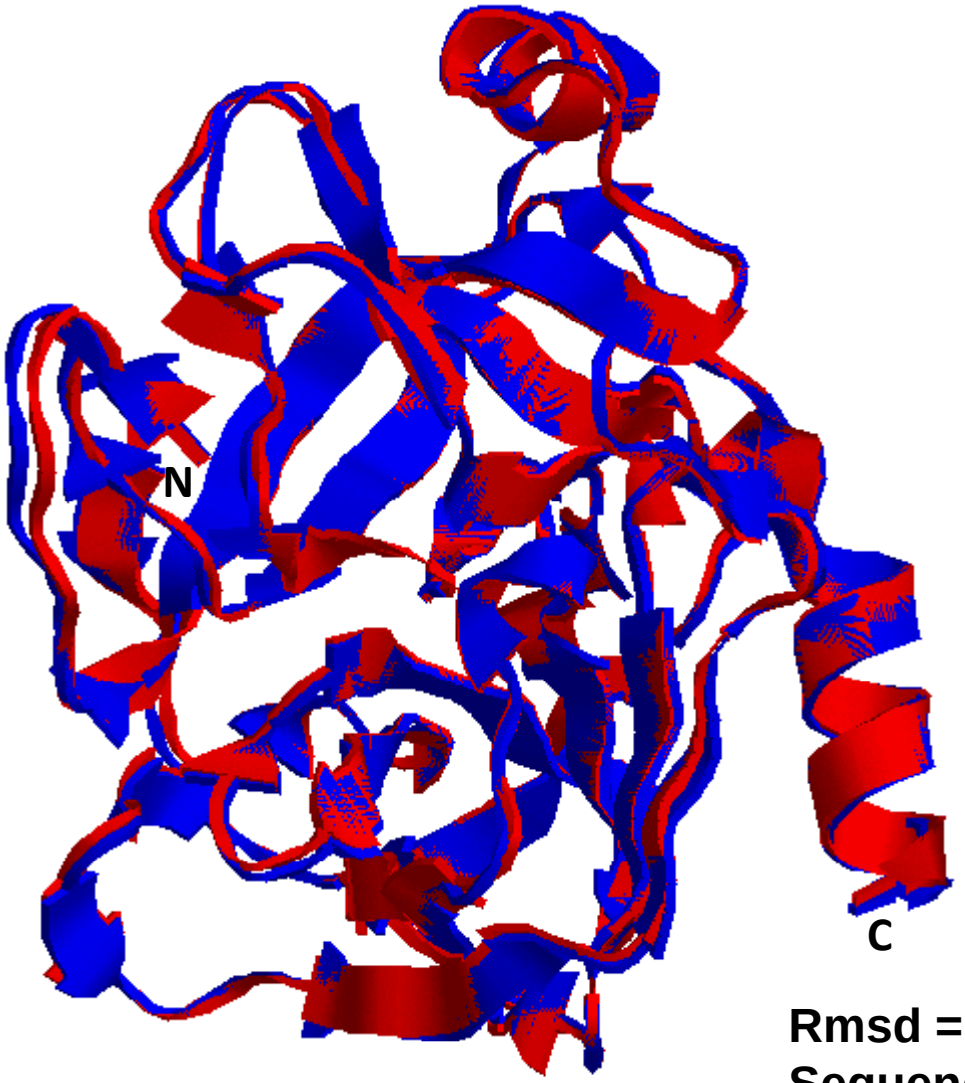
5PTP - 1SGT 33.5%

5PTP - 2SGA 21.9%

3D structures of trypsins from Bos taurus (5ptp), Rattus rattus (1bra), Streptomyces griseus (1sgt, 2sga)

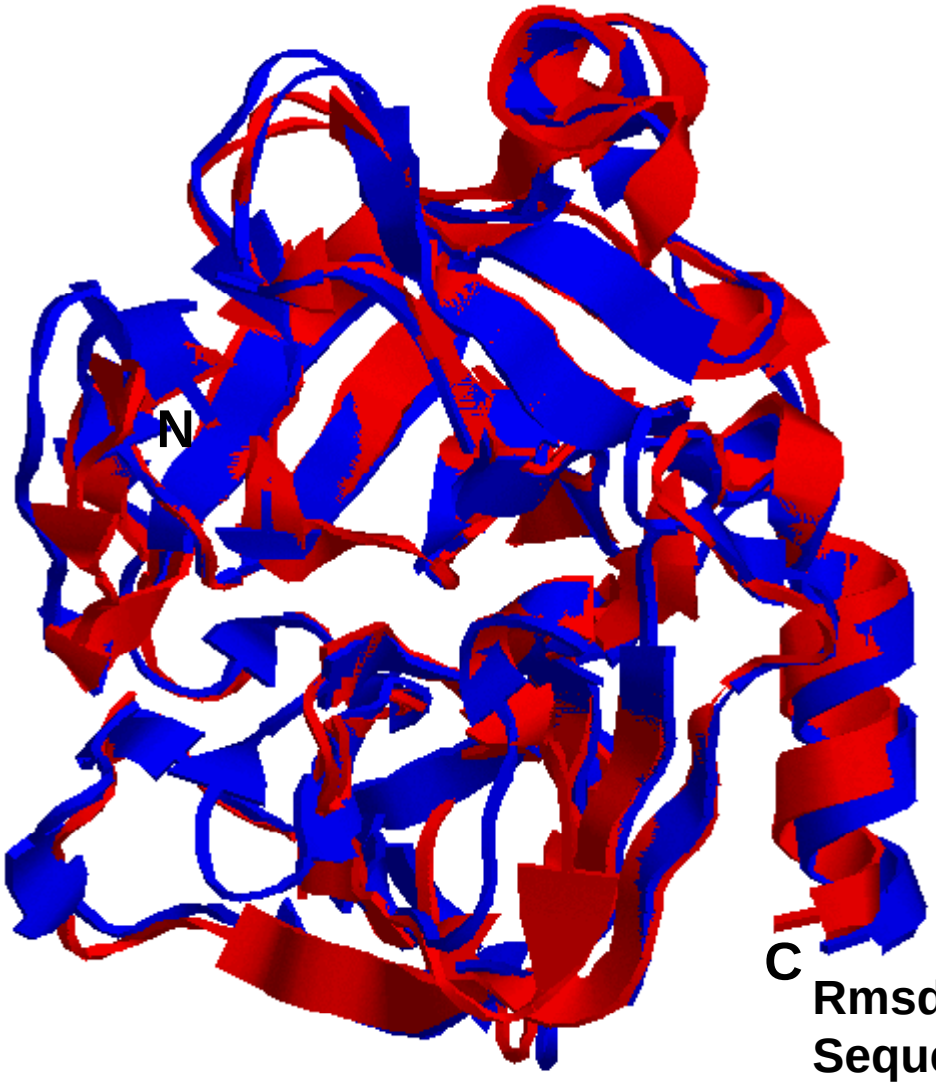


Structural superimposition of Bos taurus trypsin (5ptp) vs Rattus rattus trypsin (1bra)



Rmsd = 0.4Å Z-Score = 7.5
Sequence identity = 72.6%
Aligned/gap positions = 223/0

Structural superimposition of Bovin trypsin (5ptp) vs S.griseus trypsin (1sgt)



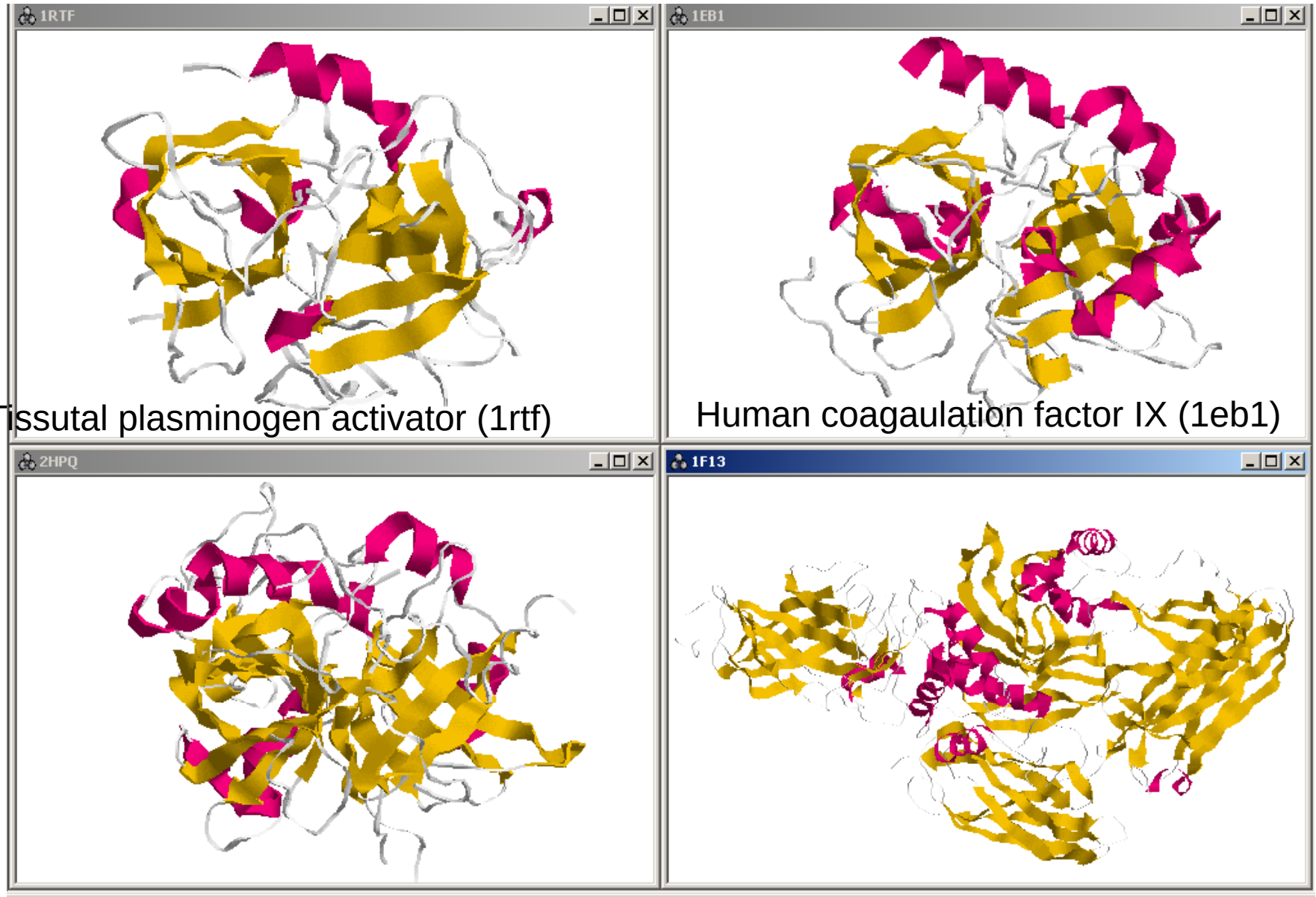
Rmsd = 1.5Å Z-Score = 6.9
Sequence identity = 34.1%
Aligned/gap positions = 221/24

Structural superimpostion of Bovin trypsin (5ptp) vs S.griseus protease A (2sga)

Rmsd = 3.0Å Z-Score = 4.9
Sequence identity = 17.5%
Aligned/gap positions = 154/75

When we compare other structures and sequences it gets more complicated ….

Can we understand what these proteins have in common?



Tissutal plasminogen activator (1rtf)

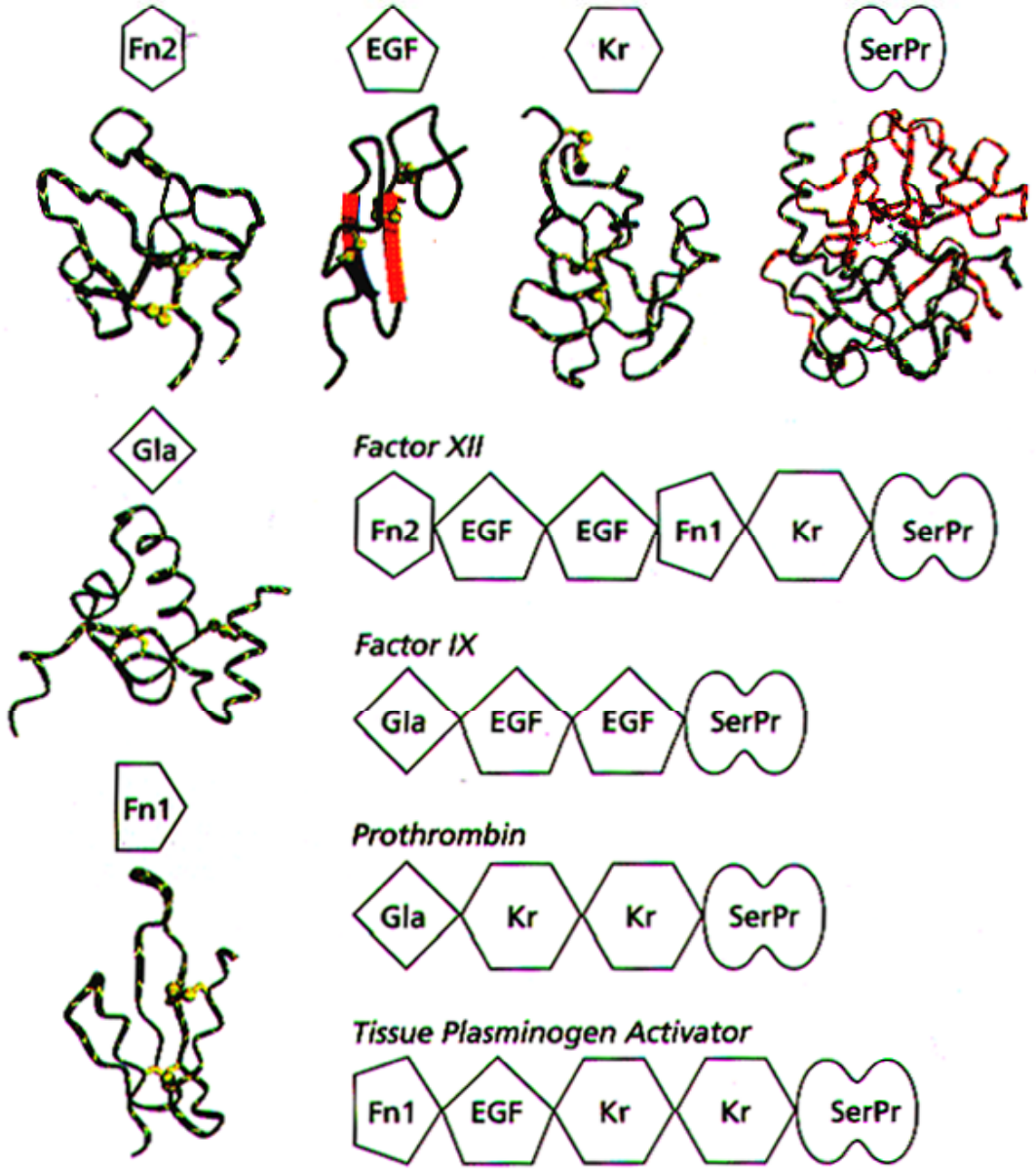
Human coagaulation factor IX (1eb1)

Human Protrombin (2hpq)

Human coagulation factor XIII (1f13)

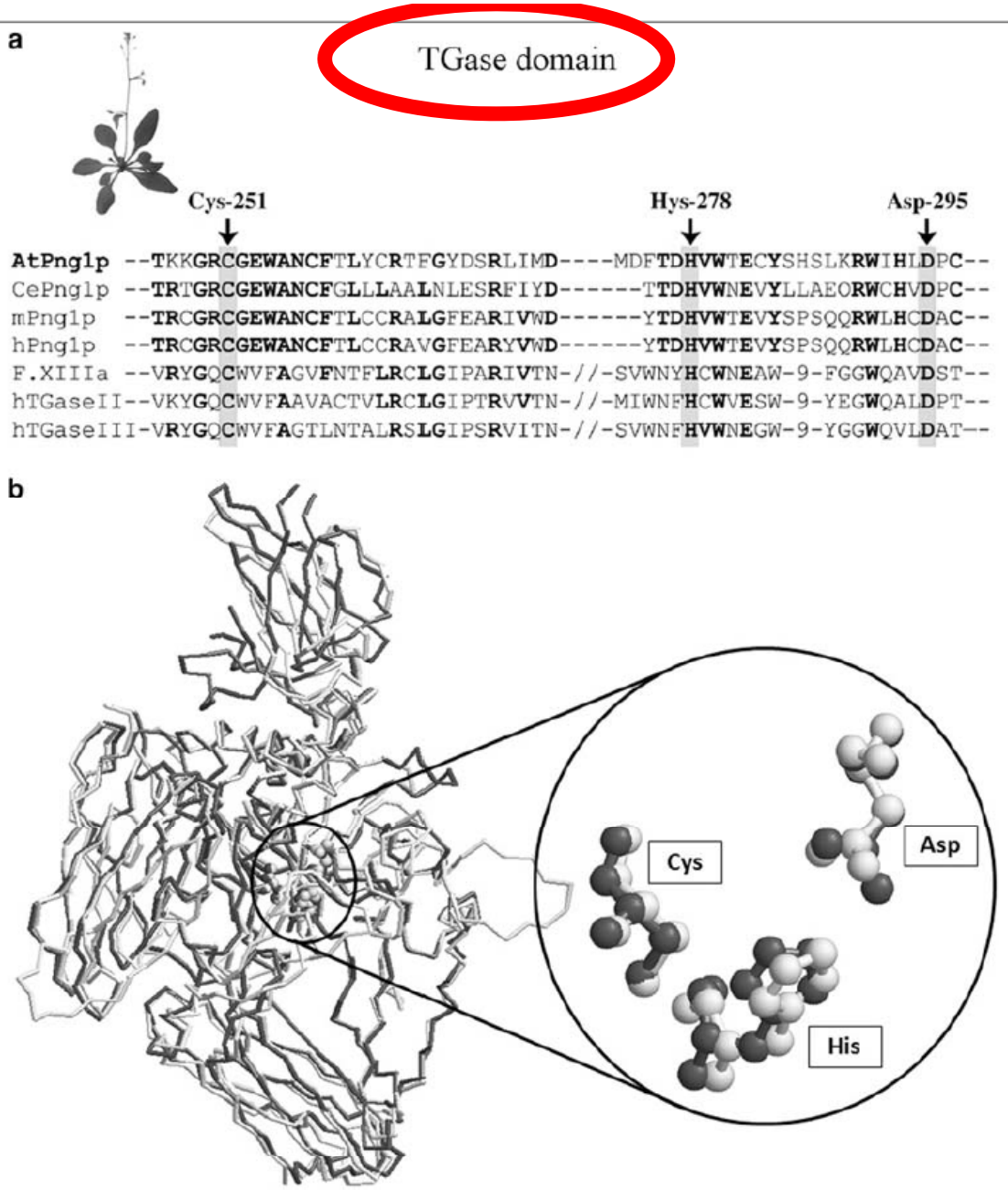
Many proteins share functional/structural domains

Blood Coagulation



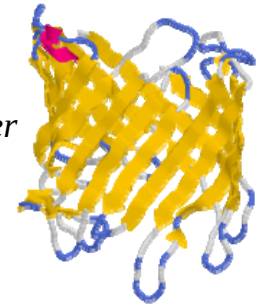
These ideas can be cast in threading approaches to model proteins provided that function is conserved

Fig. 3 a Alignment of the TGase domain of AtPng1p with that of some peptide glycanases and TGases of animal cells showing the typical catalytic triad (Cys, Hys, Asp) (from Della Mea et al. 2004a). b 3D superimposition provided by the Multiprot alghorithm (Shatsky et al. 2004) of Human Tissue Tranglutaminase 2 (pdb code 1KV3, the template) and of the AtPng1P (3D model, the target), represented in *dark and light grey*, respectively. The backbone root mean square deviation (RMSD) is equal to 0.115 nm (this value is similar to that of C–C bond length). In evidence, the superimposition of the TGase catalytic triad of the target and of the template



Serafini-Fracassini et al Amino Acids (2009) 36:643–657

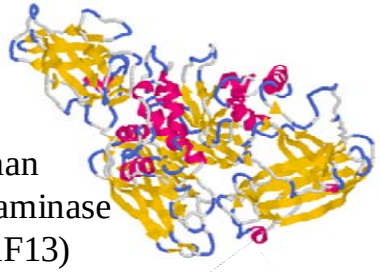
Membrane proteins



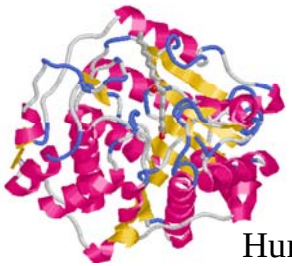
VDAC
D.melanogaster
(15%,2OMF)

Bovin OGC carrier
(20%,1OKC)

Globular proteins



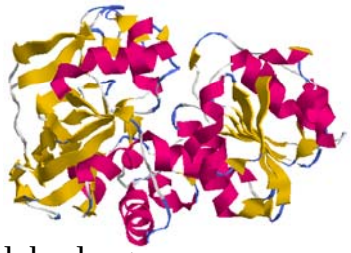
Human
Transglutaminase
(34%,1F13)



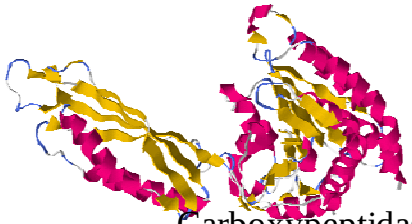
Human HDAC
(32%,1C3R)

Human Nectin1
(30%,1NEU)

Human Integrin β3
(20%.)



Alcohol dehydrogenase
S. solfataricus (24%,2OHX)



Carboxypeptidase
S. solfataricus (21%,1OBR)

Different models obatained with a knoweledge based procedure at the Biocomputing Group

Casadio et al., Methods Mol Biol. 2007;350:305-20.

Back to PFAM data base ::::

The Pfam database is a large collection of protein families, each represented by *multiple sequence alignments* and *hidden Markov models (HMMs)*.

Can we model a functional domain? How?

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Crystal structure of recombinant Kunitz Type serine protease Inhibitor-1 from the Carribean sea anemone stichodactyla helianthus

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DOI: 10.2210/pdb3ofw/pdb

Primary Citation

Structure of the recombinant BPTI/Kunitz-type inhibitor rShPI-1A from th Stichodactyla helianthus.

Garcia-Fernandez, R., Pons, T., Meyer, A., Perbandt, M., Gonzalez D., de los Angeles Chavez, M., Betzel, C., Redecke, L.

Journal: (2012) Acta Crystallogr.,Sect.F **68:** 1289-1293

PubMed: 23143234
PubMedCentral: PMC3515366
DOI: 10.1107/S1744309112039085
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PubMed Abstract:

The BPTI/Kunitz-type inhibitor family includes several extremely potent serine the inhibitory mechanisms have only been studied for mammalian inhibitors. of a BPTI/Kunitz-type inhibitor from a marine invertebrate (rShPI-1A) is repor

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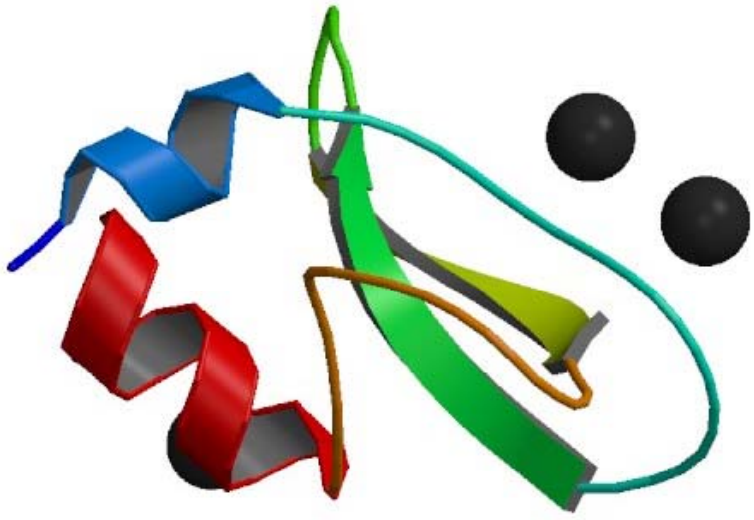
Molecular Description

Classification: Hydrolase/hydrolase Inhibitor
Structure Weight: 6730.90



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Kunitz domains are the active domains of proteins that inhibit the function of protein degrading enzymes or, more specifically, domains of Kunitz-type protease inhibitors. They are relatively small with a length of about 50 to 60 amino acids and a molecular weight of 6 kDa.

The structure is a disulfide rich alpha+beta fold

Examples of Kunitz-type protease inhibitors are aprotinin (bovine pancreatic trypsin inhibitor, BPTI), Alzheimer's amyloid precursor protein (APP), and tissue factor pathway inhibitor (TFPI).

Standalone Kunitz domains are used as a framework for the development of new pharmaceutical drugs

To which extent is it conserved?