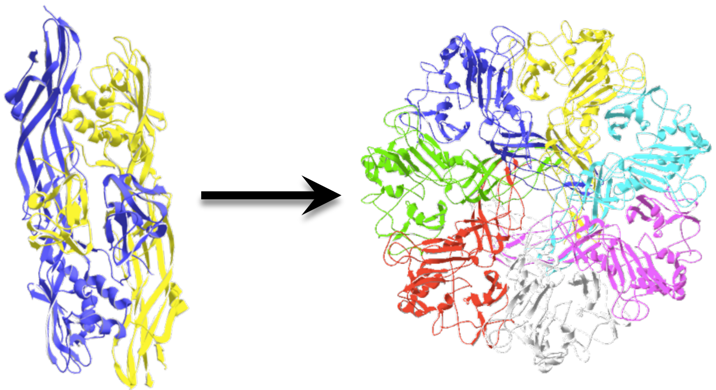
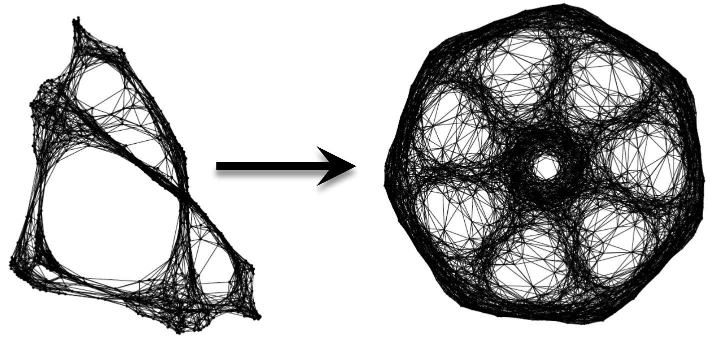
Proteins: design spatially optimized to build a durable system

Claire Lesieur
IXXI-ENS Lyon & Ampere Laboratory





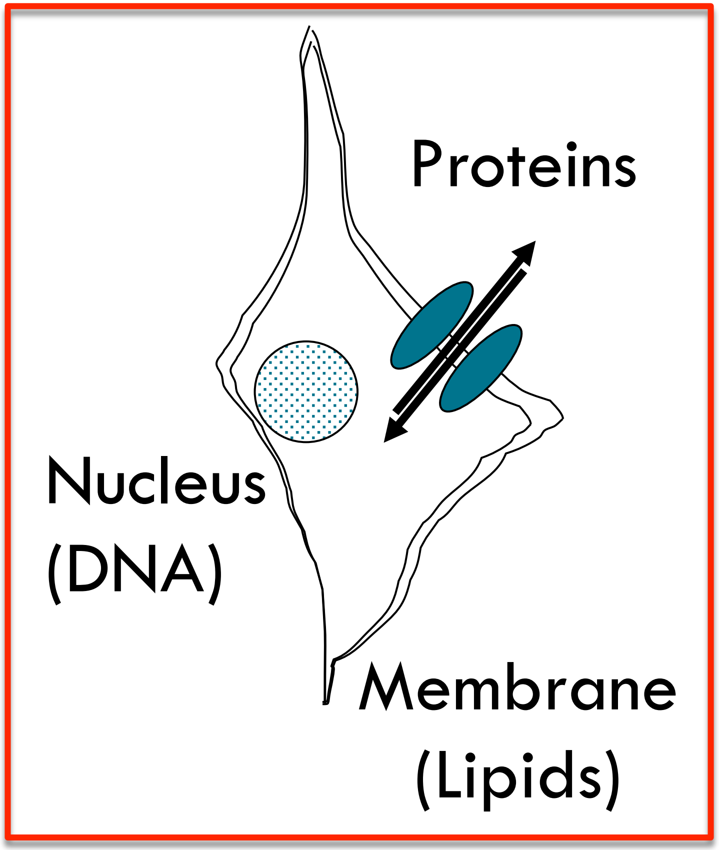
Content

- Background on Proteins
- Mechanisms of durability
- Analogy with urbanism
- Conclusions
- Open questions and Perspectives

Life organization

Macro

Micro



Nano

Proteins History

- **Proteins/Nucleic Acids/Amino acids/Fat: 3,8 billion years**
- Bacteria/archeobacteria/Eurkarotic: 3,5-2,7 billion years
- Homo Sapiens: 200 000 years ago

- **Half-life[1]: minutes, hours, days, years**

1-Toyama, B.H. and Hetzer, M.W (2013) Protein homeostasis: live long won't prosper. ***Nature Rev Mol Cell Biol*** 14:55-61.

Protein durability: implications

Protein maintain function throughout time and conditions

- Response to perturbations
  - Robustness
  - Adaptability
  - Low fragility
  - Error correction

- Control over
  - Construction
  - Function

Responses to perturbations

Perturbation

Protein

P1 **P2**

Robust Fragile

↓ **P2**

Robust

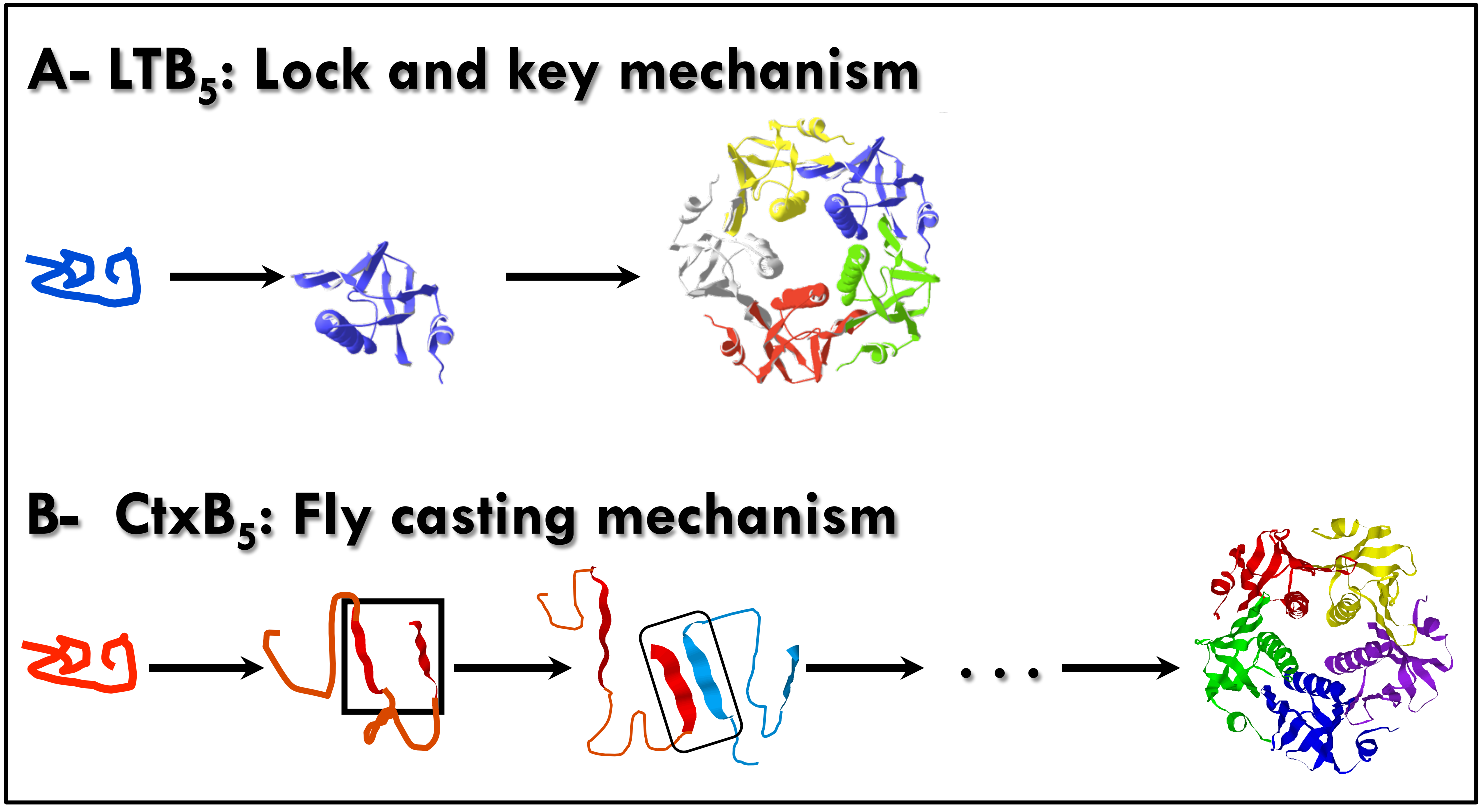
P1, P2 individually ≠ P1+P2

Genetic backgrounds and error correction

Adaptability

Control over construction

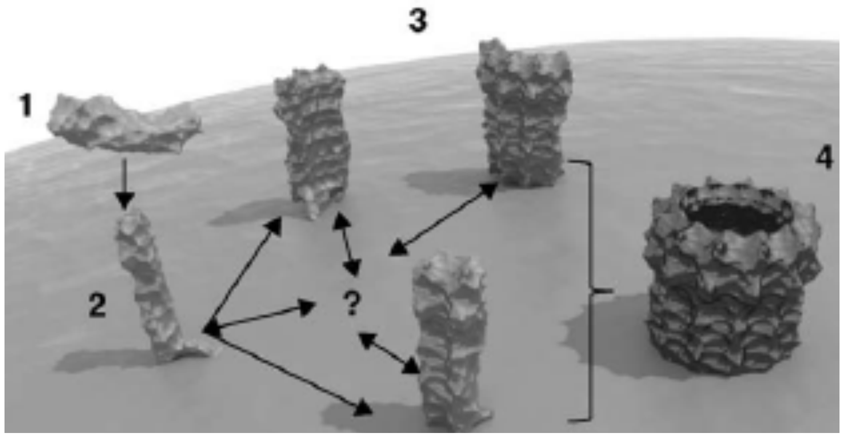
Experimental results

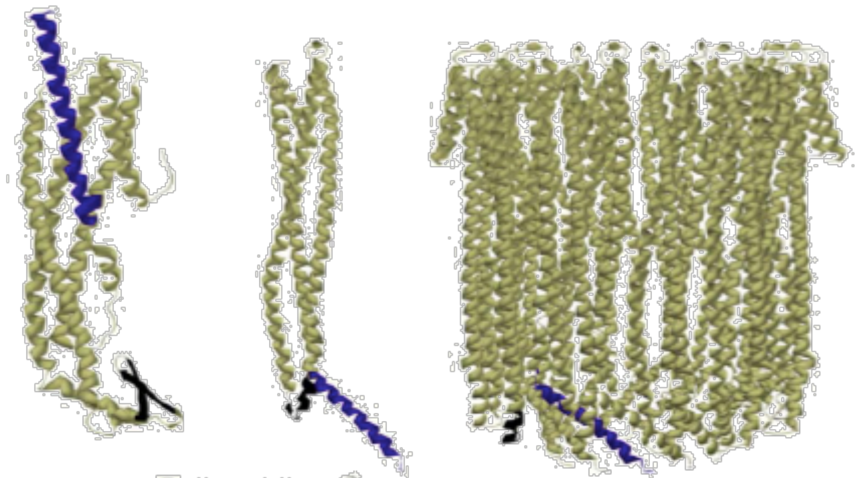


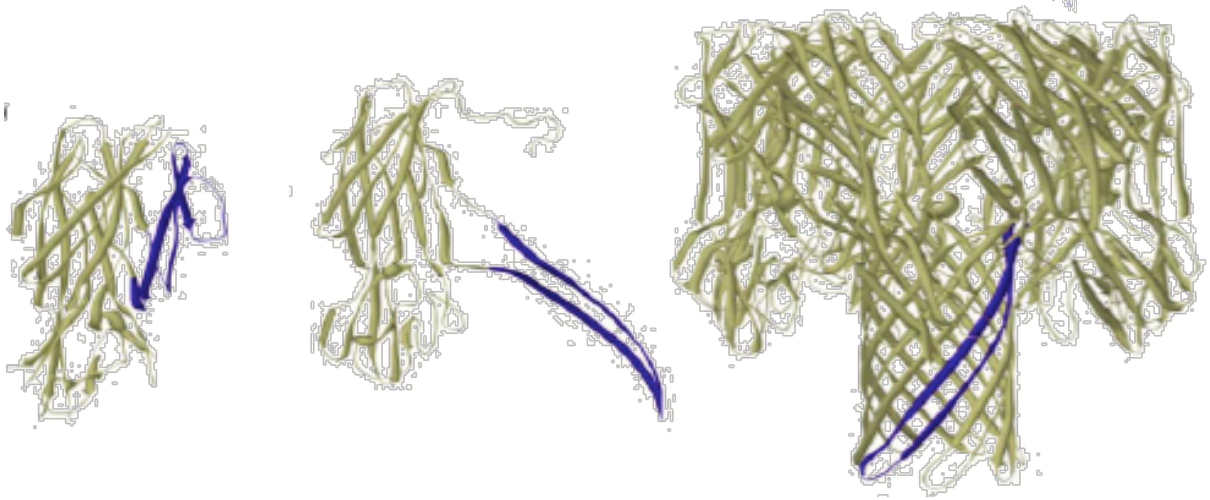
Ruddock et al, 1995

Lesieur et al, 2002; 2010

Control over function







Ioan Iacovache, Mirko Bischofberger and F Gisou van der Goot. Structure and assembly of pore-forming proteins. Current Opinion in Structural Biology 2010, 20:241–246

Protein durability: mechanisms?

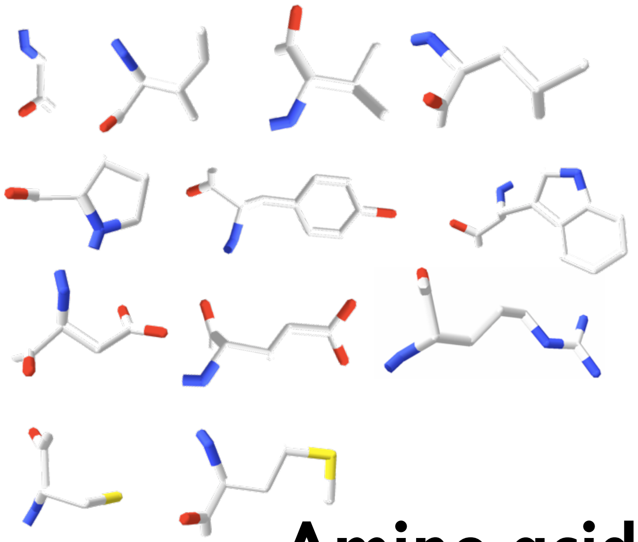
How proteins respond to perturbations?
How proteins control their shape flexbility?

ATOMIC MOTIONS
To
Large Scale motions

Proteins: Spatial-scale constraints

CHON: atoms

Interactions
Forces



Amino acids

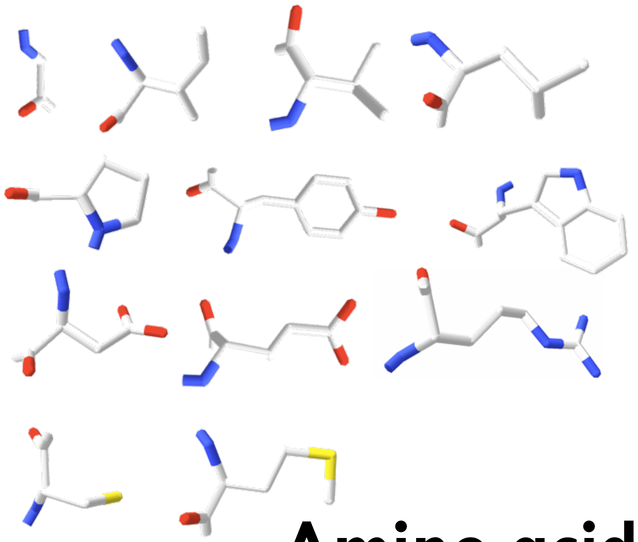
Geometrical & Chemical local constraints

1- Rackham, O. J. *et al*. The evolution and structure prediction of coiled coils across all genomes. *J Mol Biol* **403**, 480–93 (2010).

Proteins: Spatial-scale constraints

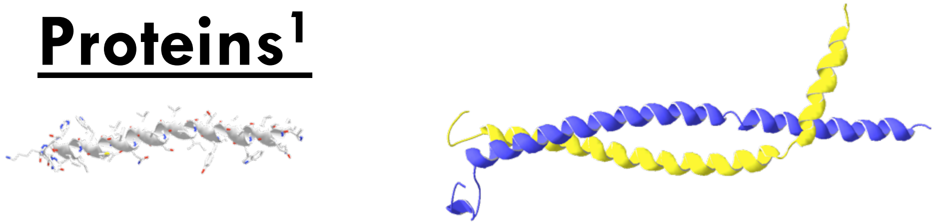
CHON: Atoms

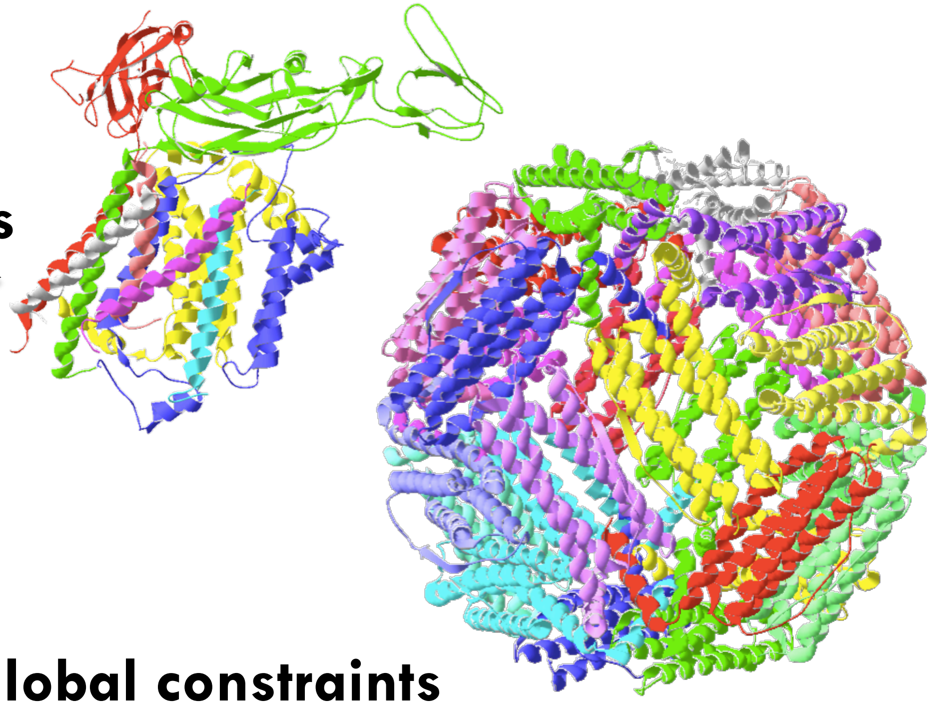
Interactions
Forces



Interactions
Forces

Proteins[1]





Amino acids

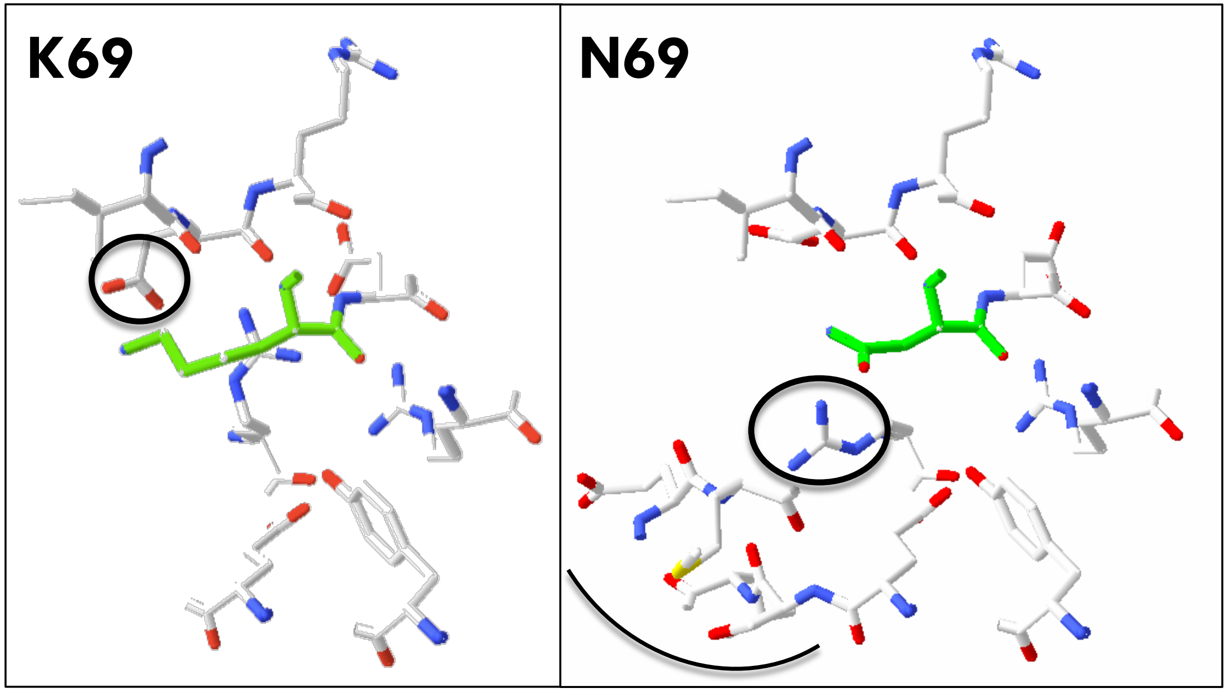
Geometrical & Chemical local and global constraints

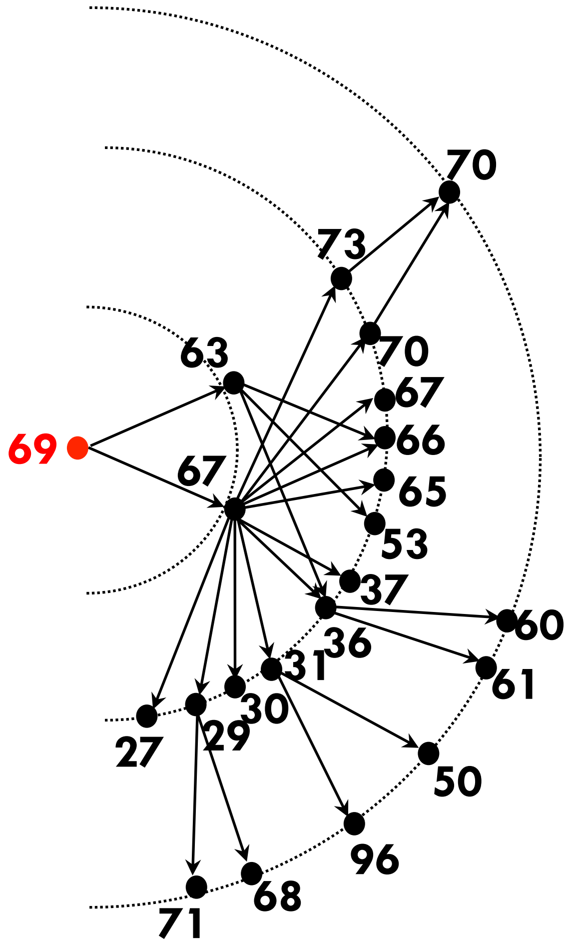
1- Rackham, O. J. *et al*. The evolution and structure prediction of coiled coils across all genomes. *J Mol Biol* **403**, 480–93 (2010).

Responses to perturbation

ATOMIC MOTIONS

- Local to global perturbation

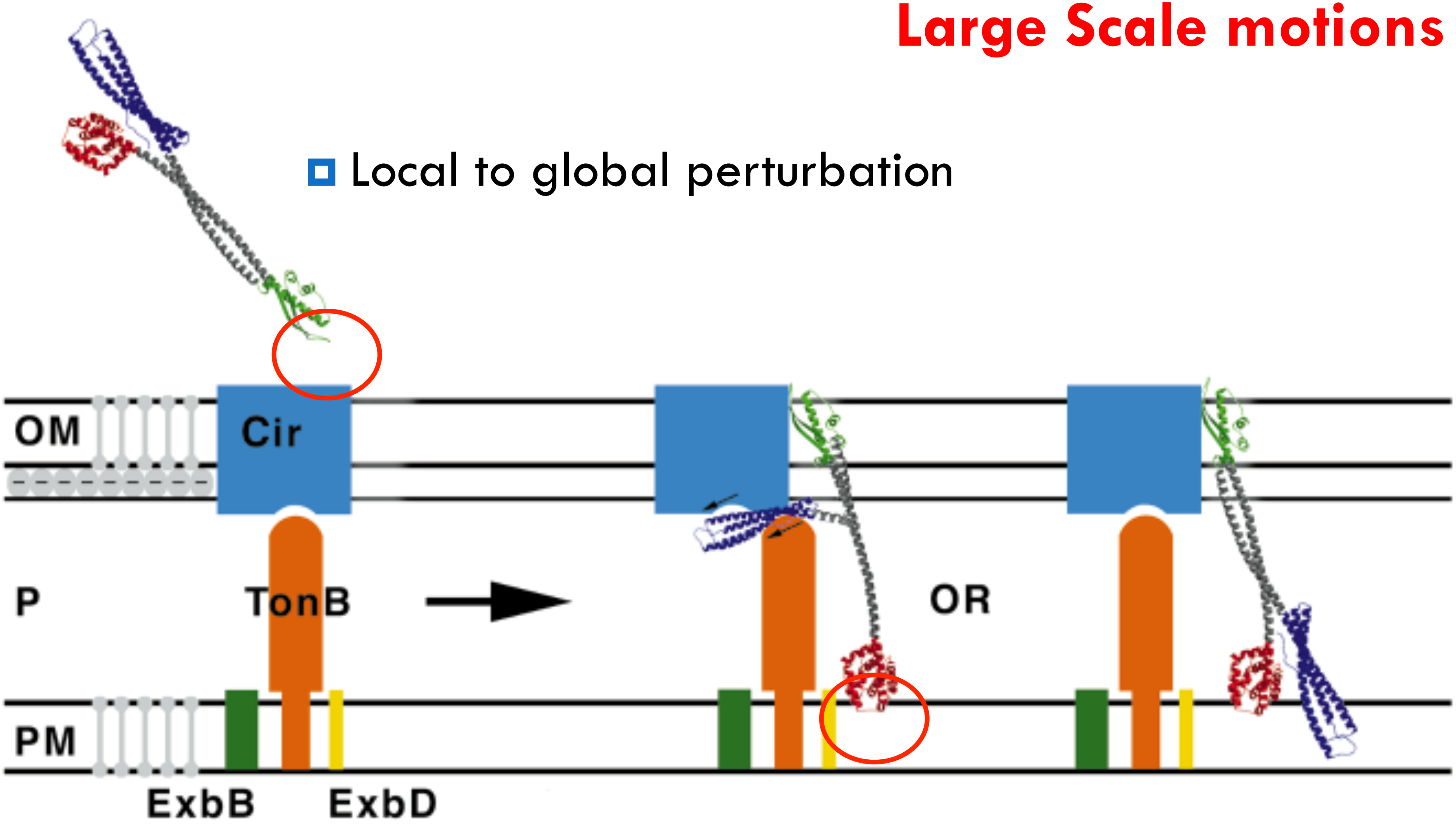




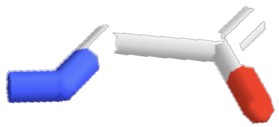
Responses to perturbation

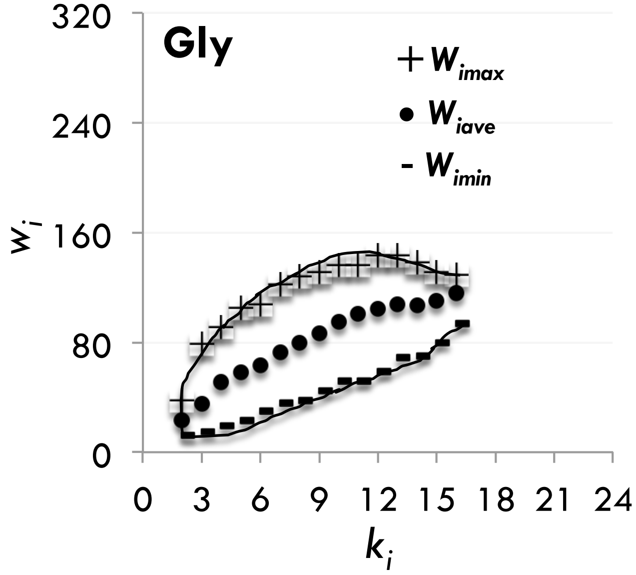
Large Scale motions

- Local to global perturbation



Any position

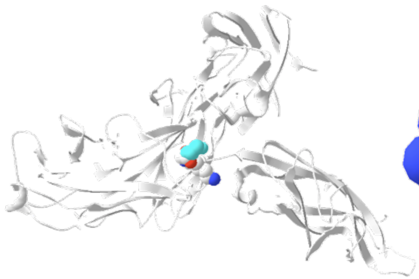


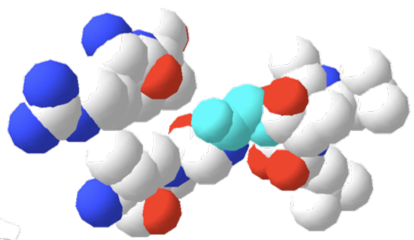


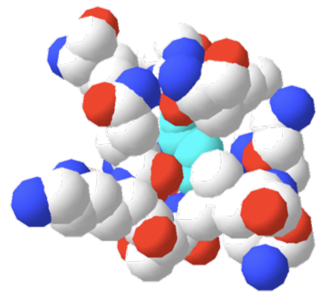
2UY6 B69, ki=2

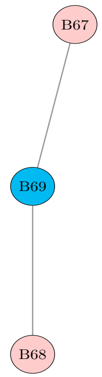
1IOK F374, ki=10

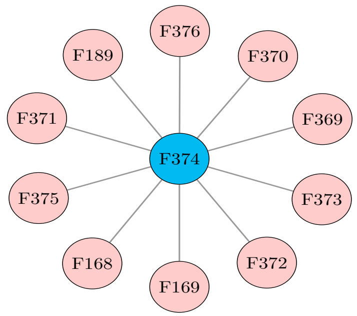
1V7Z C80, ki=16

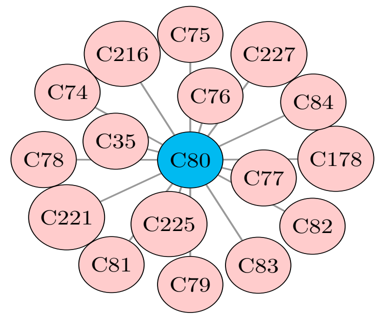




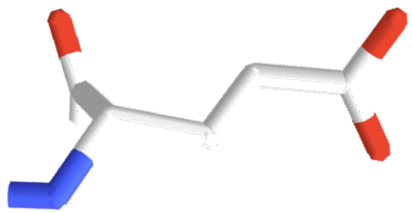


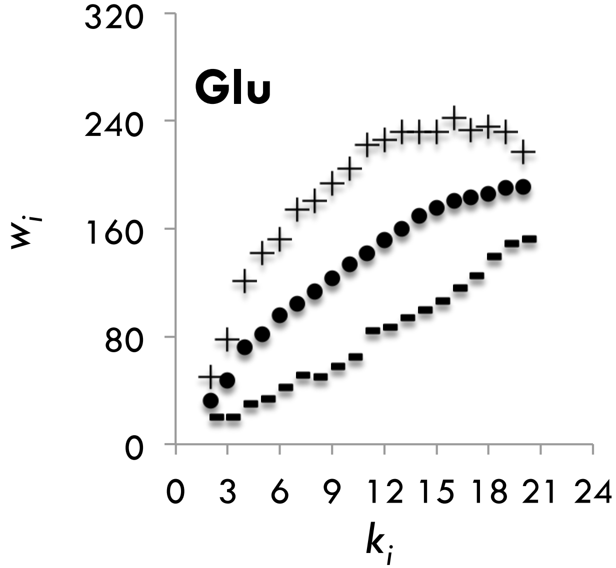




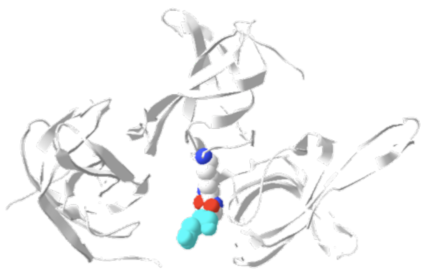


Any type

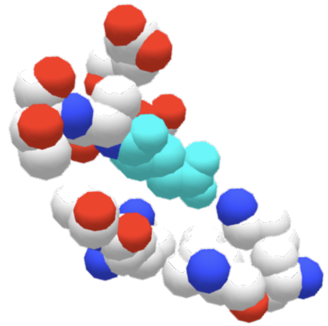




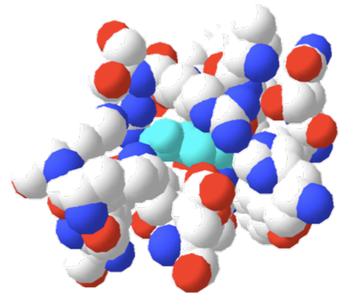
3DM3 C101
ki=2

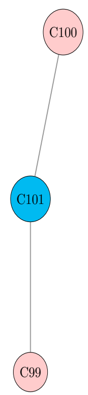


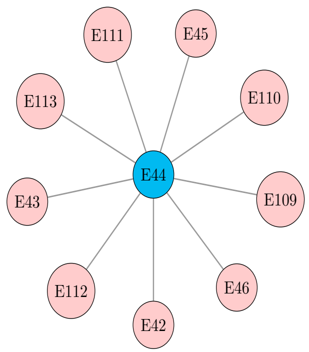
1OYP E44,
ki=9

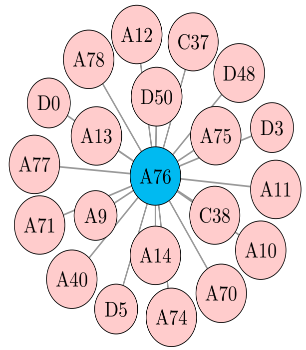


1VQ3 A76
ki=20

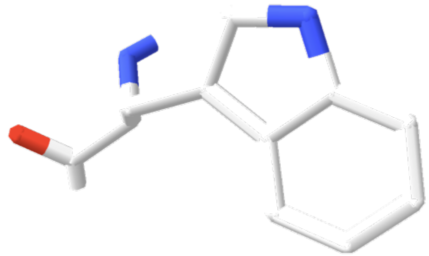


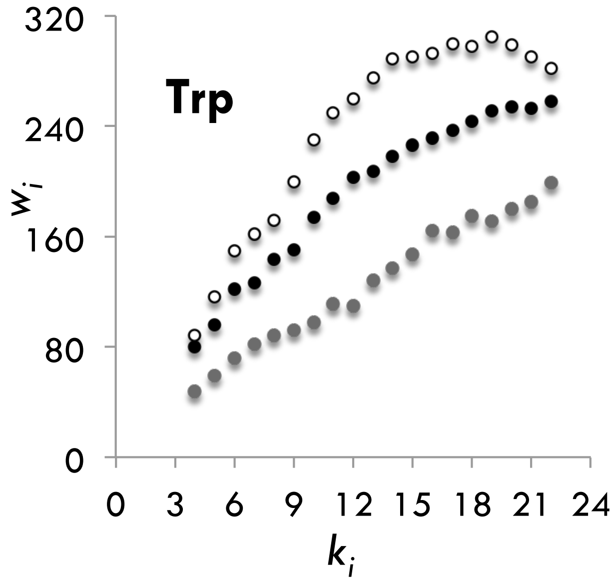






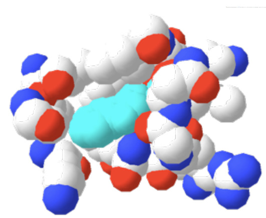
Any position



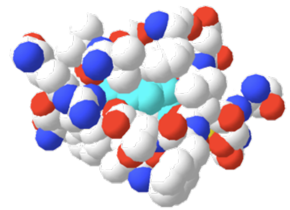


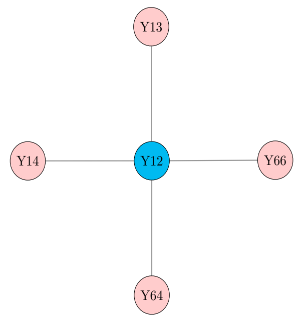
2CG9
Y12, ki=4

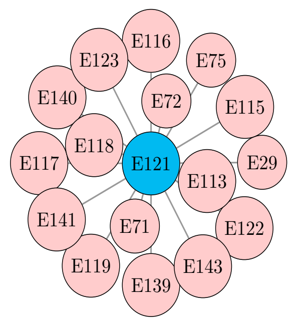
3D6X E121
ki=16

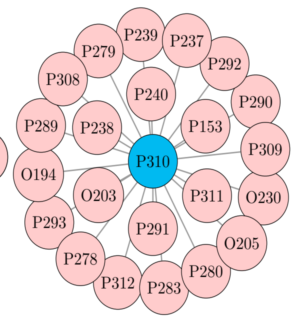


1GAD P310
ki=22

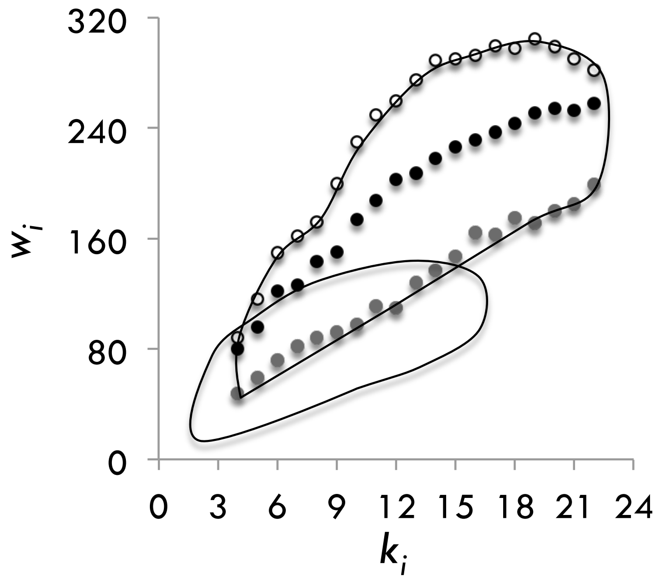


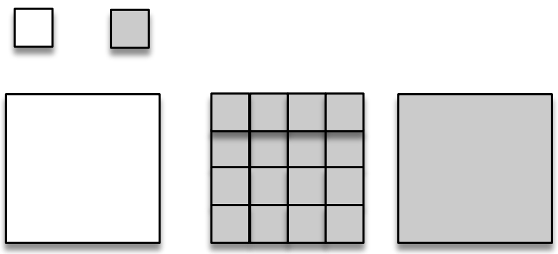




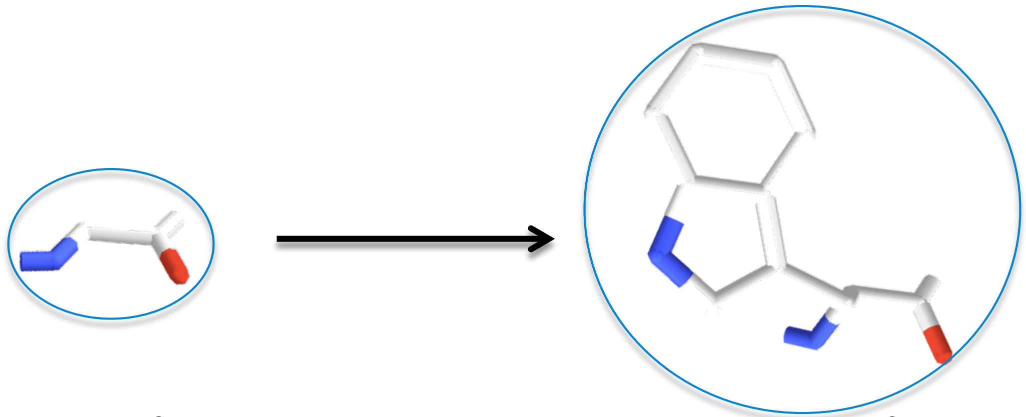


Any position any type





Gly Trp



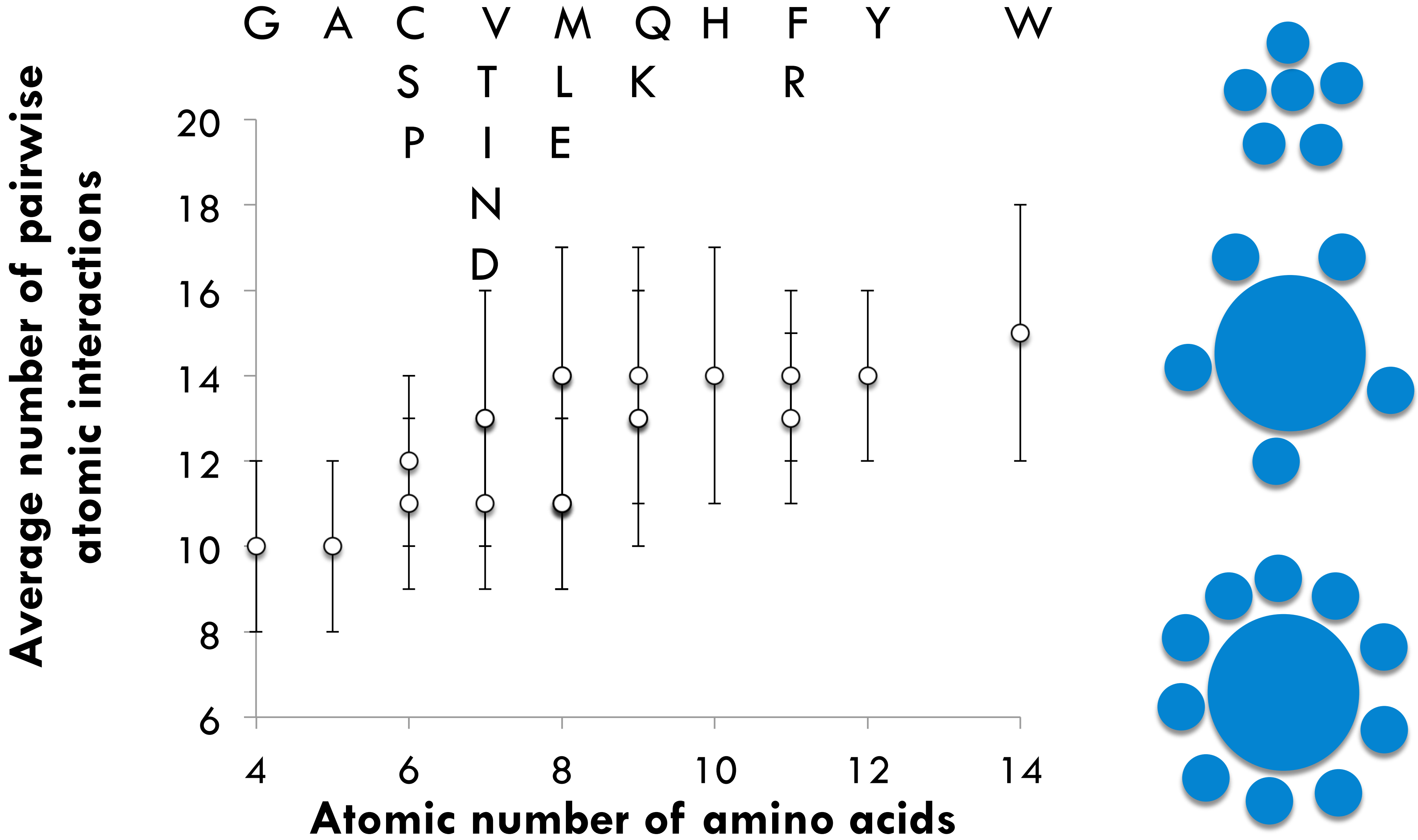
$r = 1 Å$ $r = 4 Å$

$r^2 = 1 Å^2$ $r^2 = 16 Å^2$

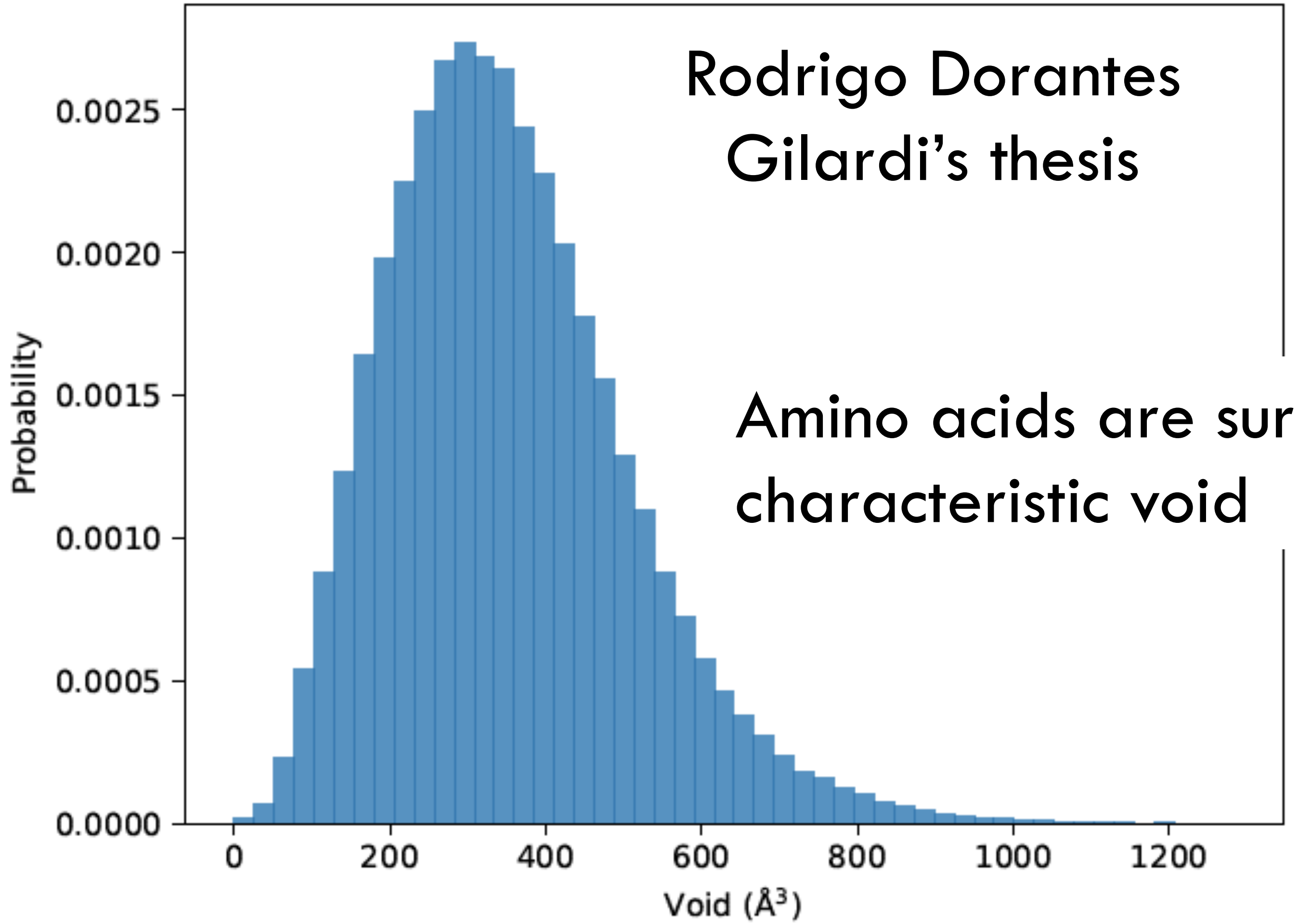
Any position any type because the amino acids adjust their neighbors to them

The Goldilocks principle

50/5
100/10



The local void measured by the Delaunay method

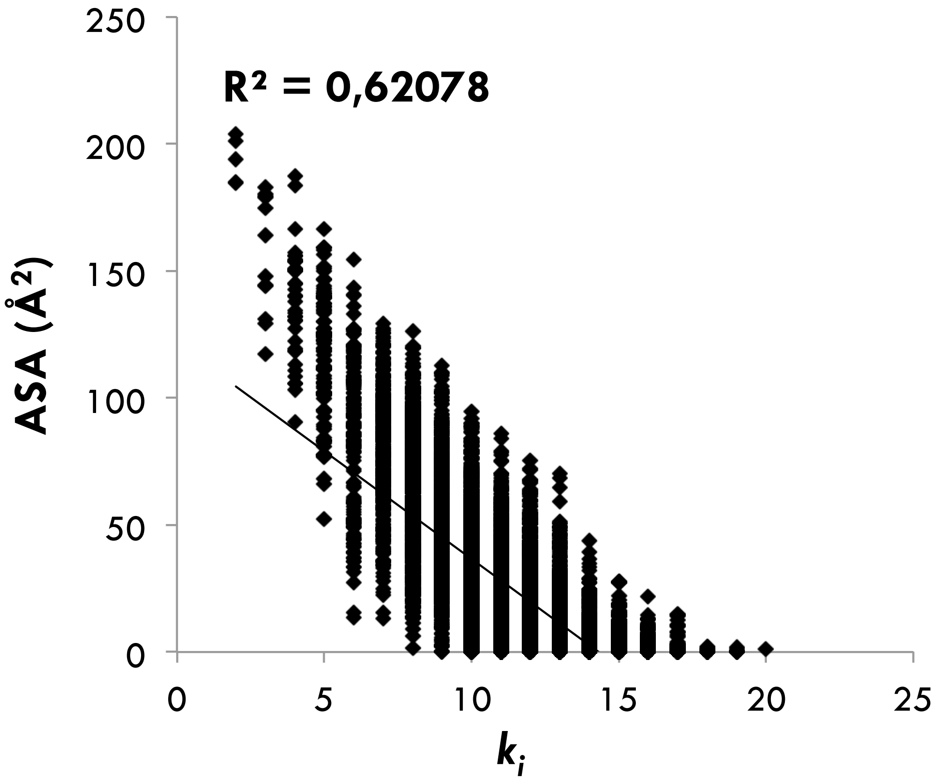


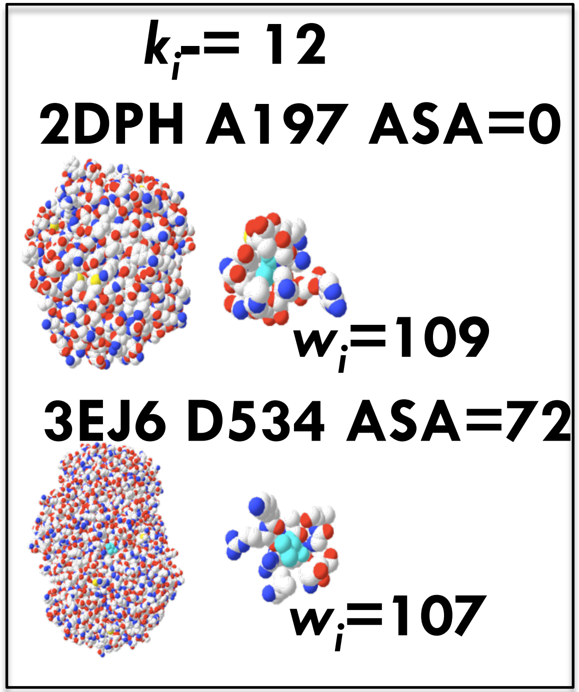
Rodrigo Dorantes Gilardi's thesis

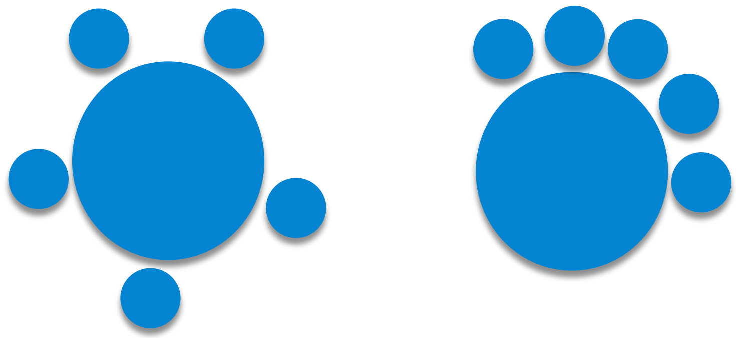
Amino acids are surrounded by a characteristic void

Figure 5.14: The distribution of voids over 250 proteins and 230522 residues.

Void Distribution







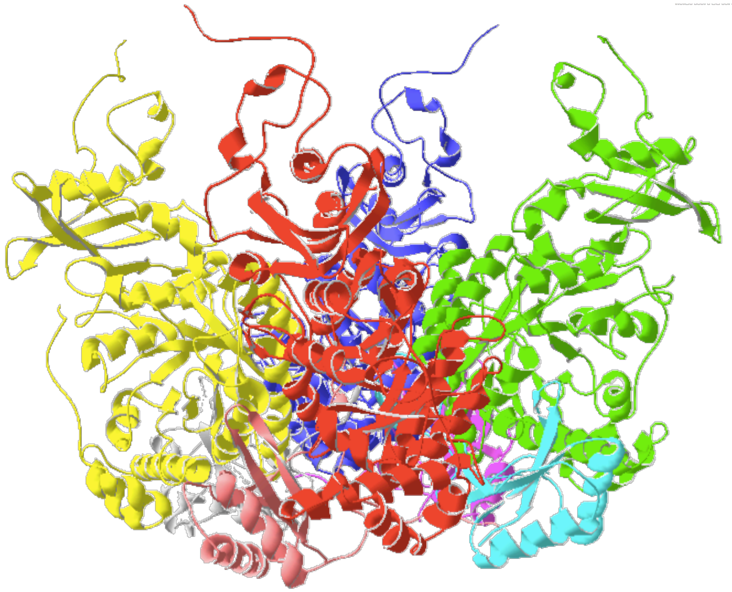
Design spatially optimized

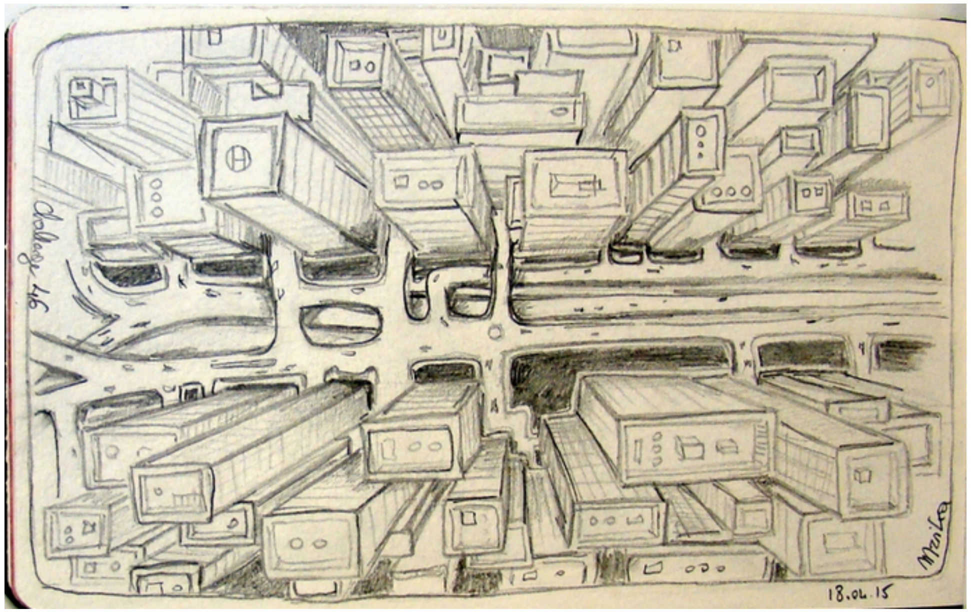
The Goldilocks principle

- Moderate surface density on average:
  - Cope with perturbations: local void
- Void distribution
  - Flexibility and Mobility regulation space dependent
- => Is there a Goldilocks principle in cities?

Analogy with urbanism

- Global spatial contraints



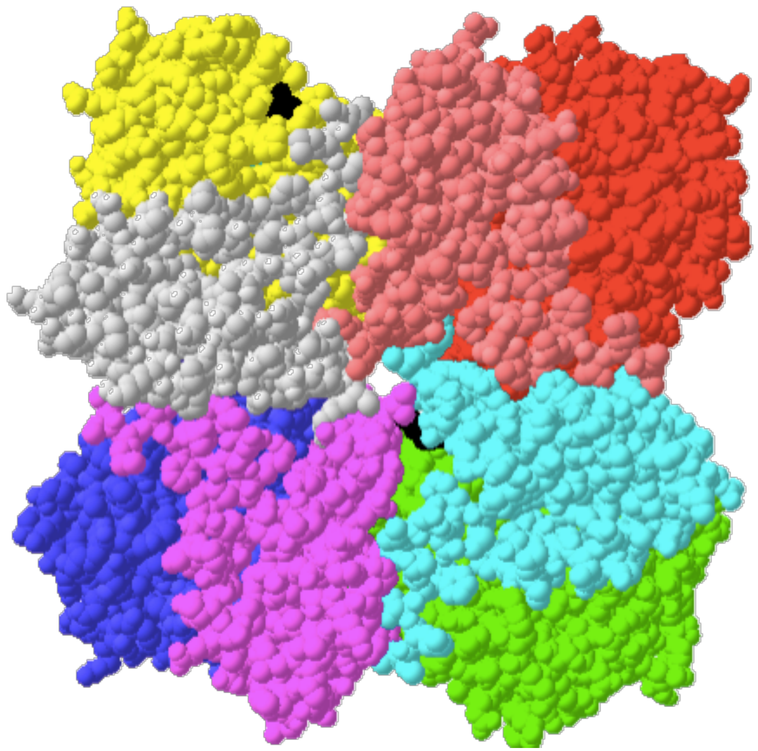


$4\text{-}20\ 10^{-9}$ m

100 m

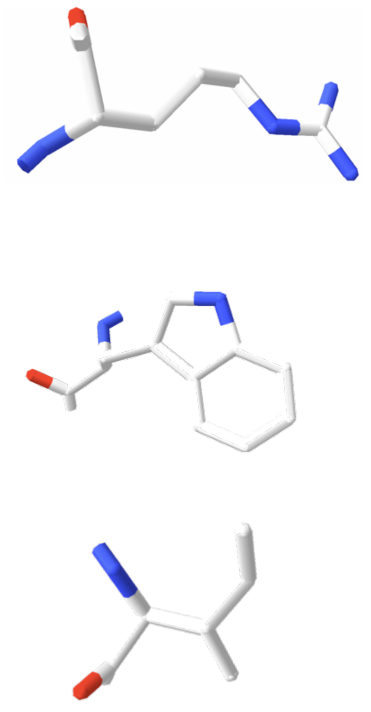
Analogy with urbanism

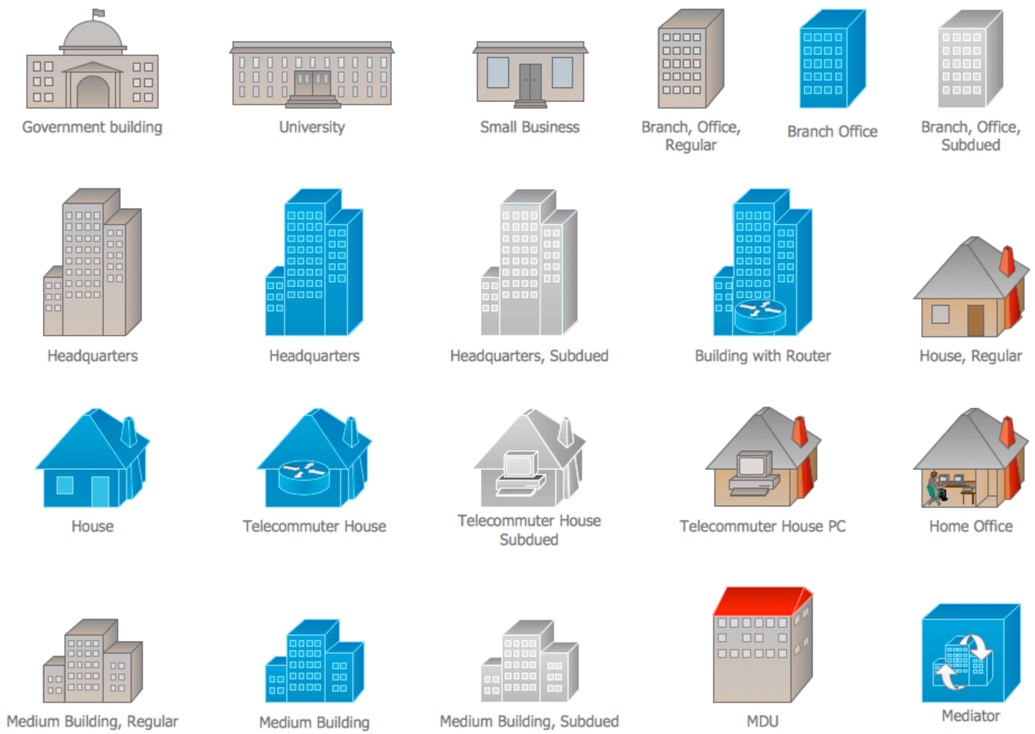
- Periphery versus Center: Position/density/neighborhood



Analogy with urbanism

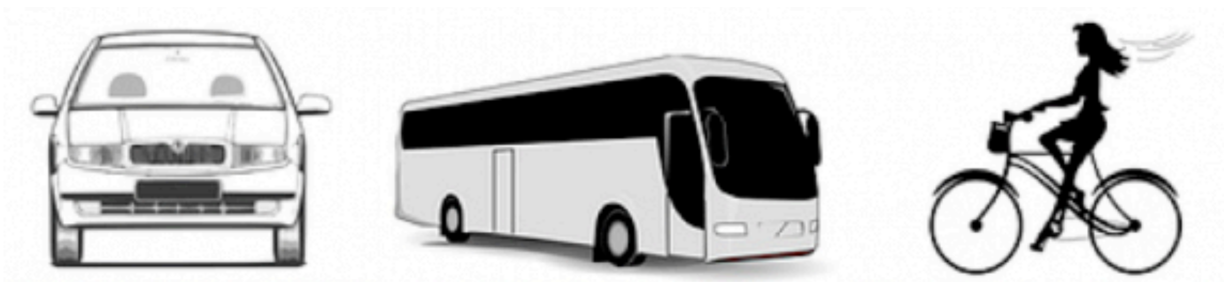
- Local spatial contraints

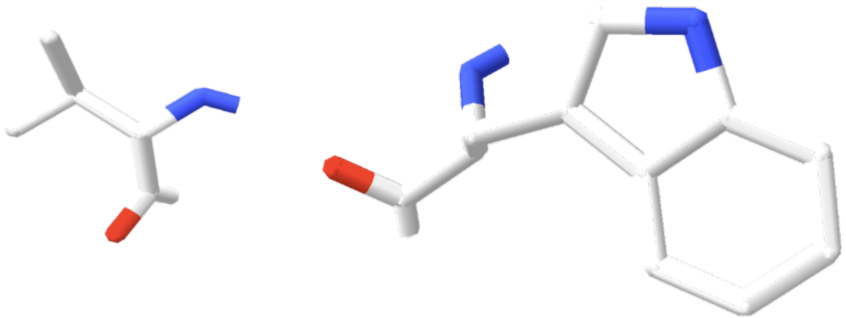




Analogy with urbanism

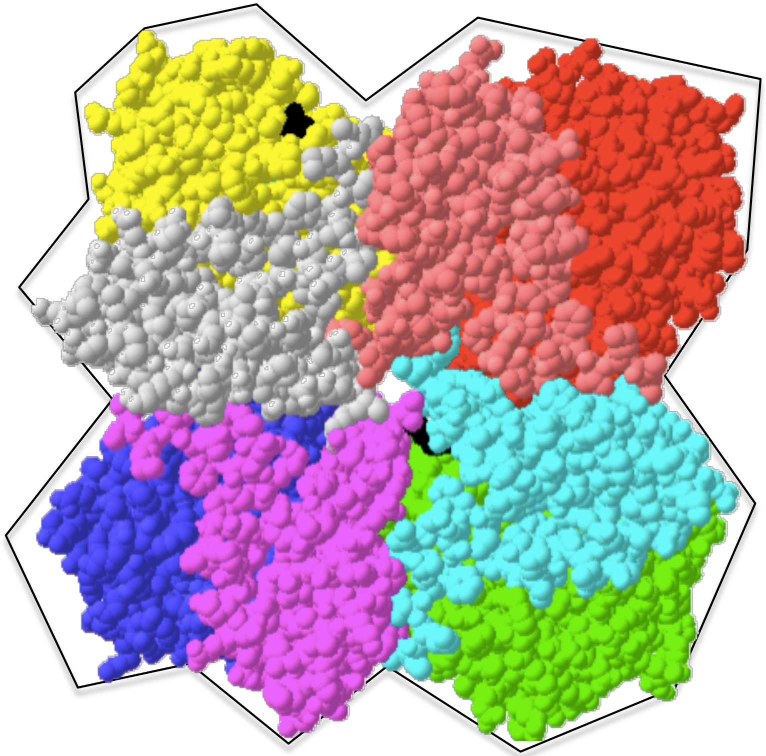
- Local spatial contraints

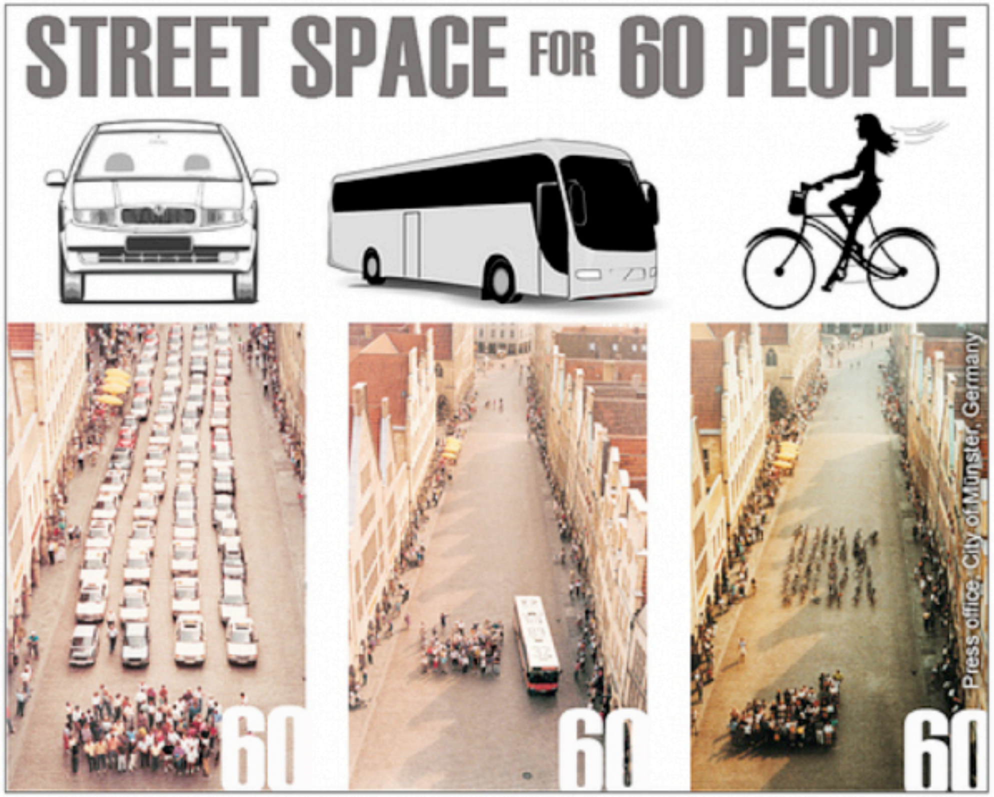




Analogy with urbanism

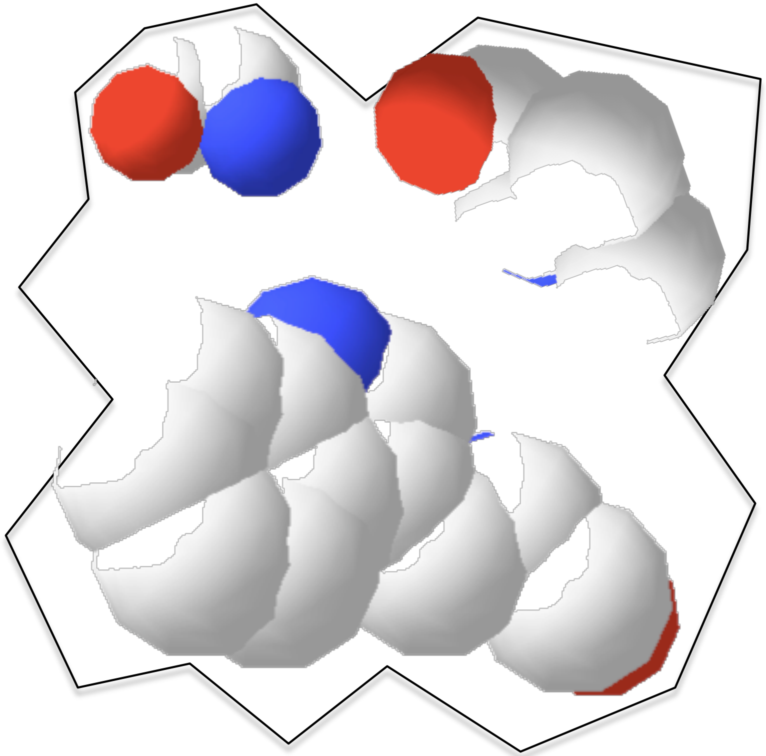
- Space occupancy

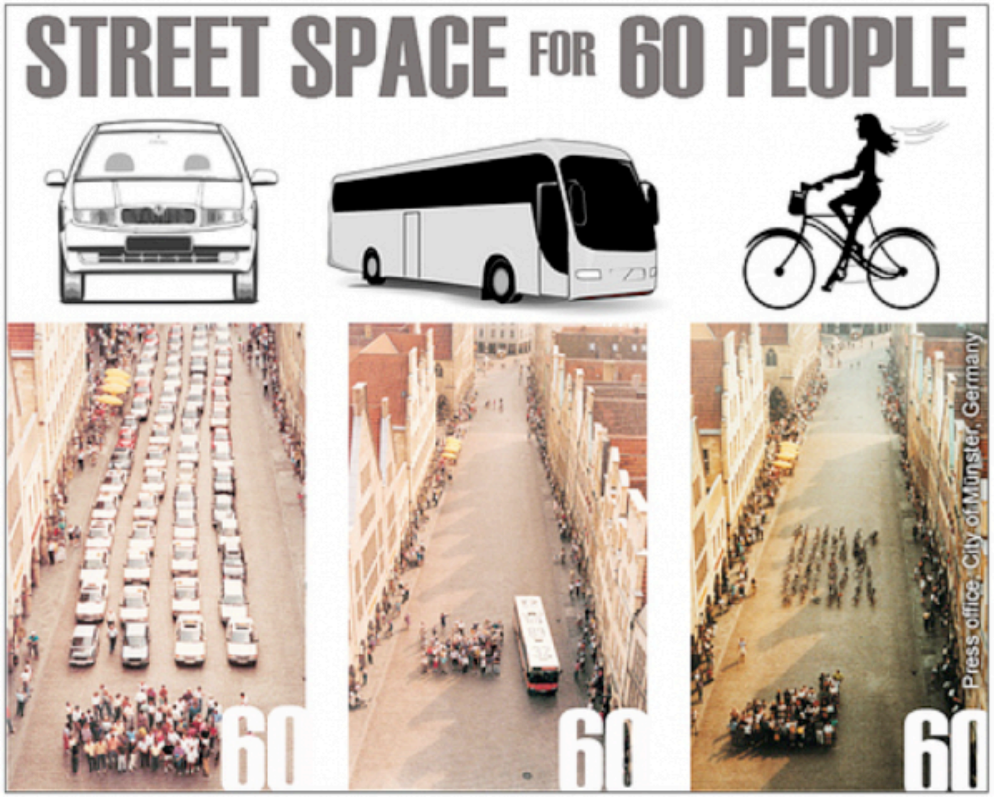




Analogy with urbanism

- Space occupancy





Thanks

- Laurent Vuillon
- Rodrigo Dorantes-Gilardi
- Mounia Achoch
- Giovanni Feverati
- Kave Salamatian