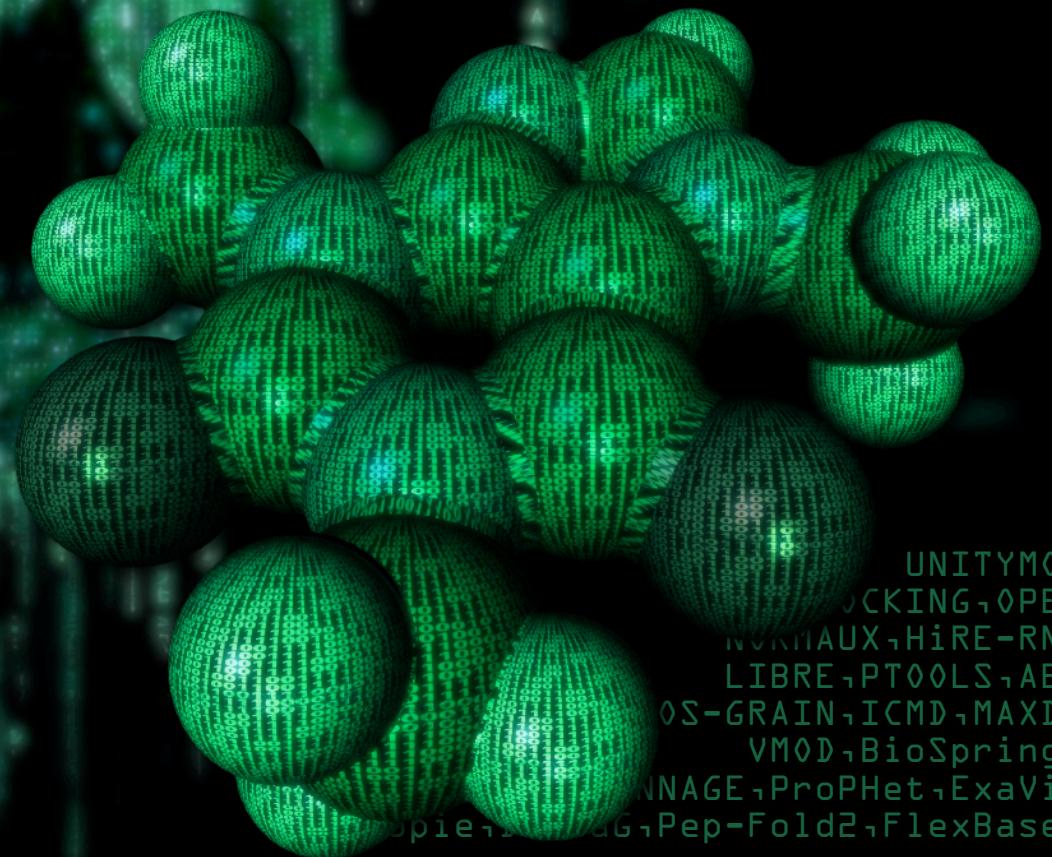


Interactive simulation and
visualisation to characterize

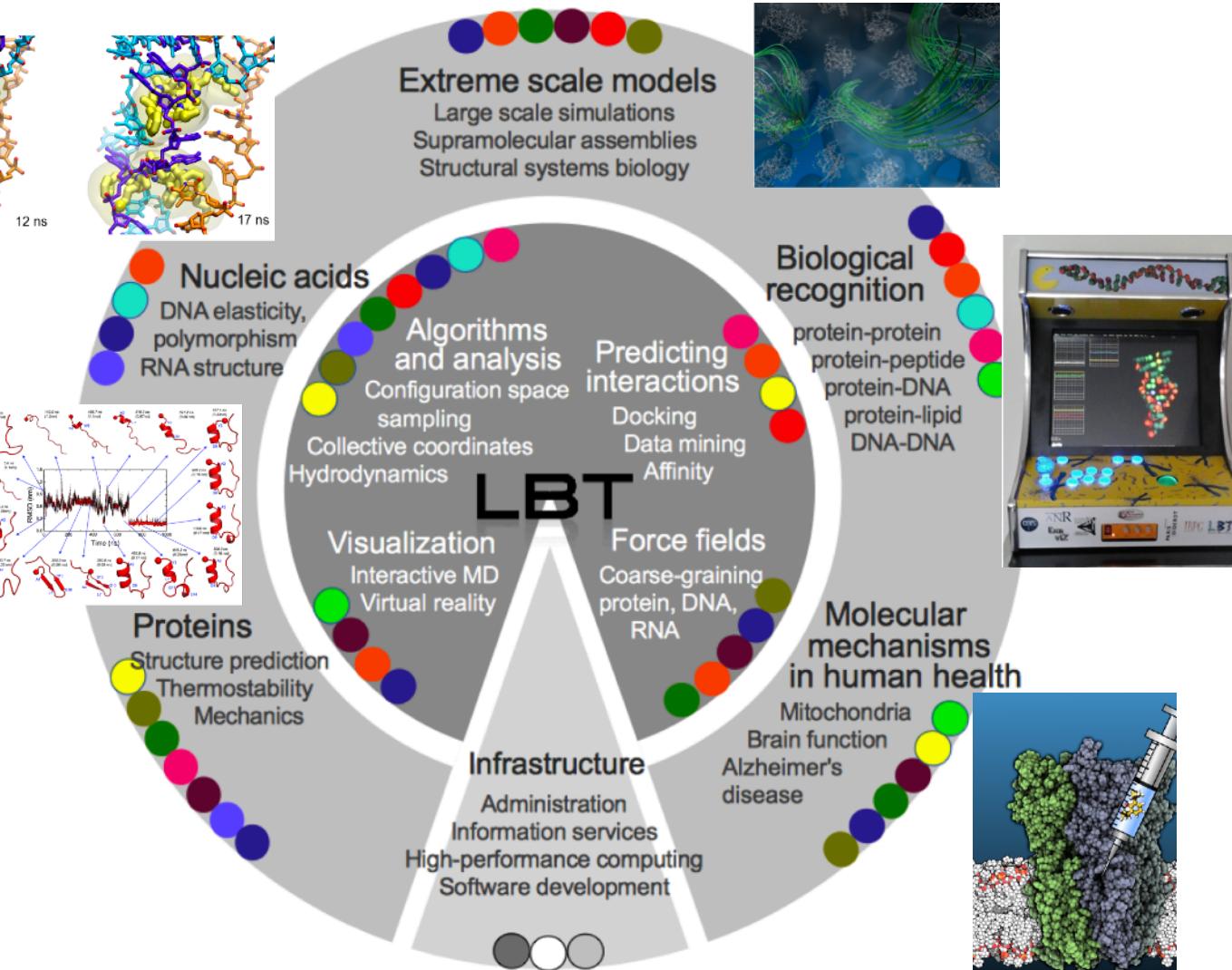
Macromolecular structures and interactions



Laboratory of Theoretical Biochemistry

CNRS UPR 9080

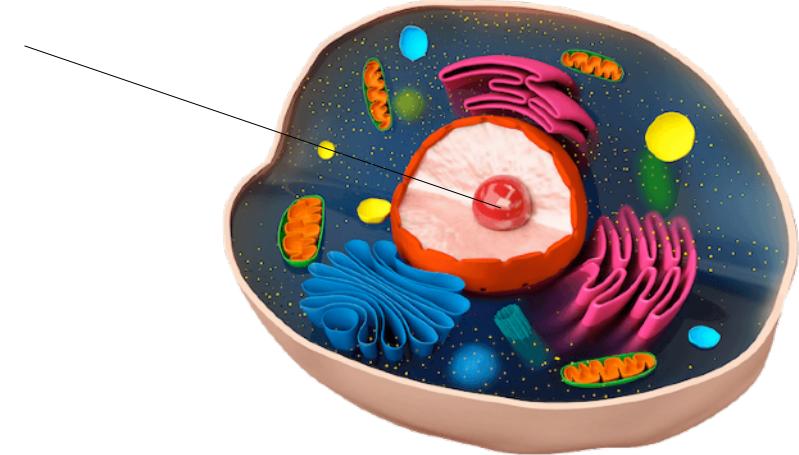
CoNRS/CNU HDR			
Baaden	DR2	13, 51	•
Derreumaux	PREX UP7	64	•
Hénin	CR1	13	•
Mazur	CR1	13	•
Nguyen	CR1	13, 51	•
Prévost	CR1	16	•
Robert	DR2	20	•
Sacquin-Mora	CR1	13	•
Sterpone	CR1	16	•
Stirnemann	CR1	13	•
Taly	CR1	16	•
Letessier	IE		
Santuz	IE		
Terziyan	TCH		



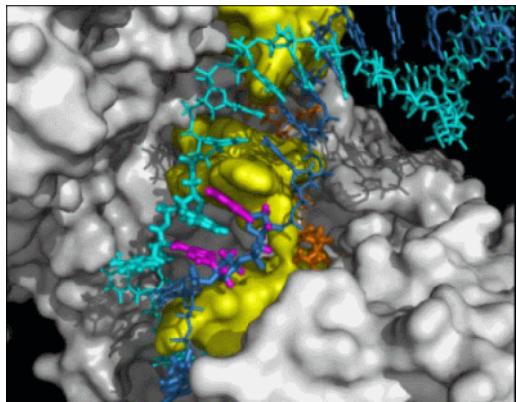
Research directions

Looking inside the cell: a variety of topics

The nucleic-acid lovers



homologous recombination: RecA/DNA

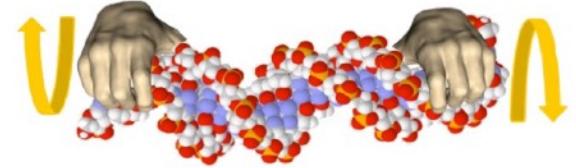


Chantal



Alexey

DNA flexibility/assembly



Looking inside the cell: a variety of topics

Those who care about protein stability



Fabio



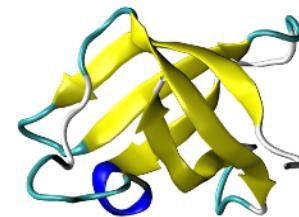
Guillaume



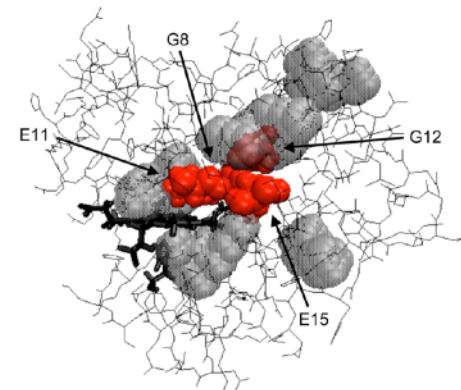
mechanical stability



thermophilicity



how local mechanics relates to protein properties and reactivity

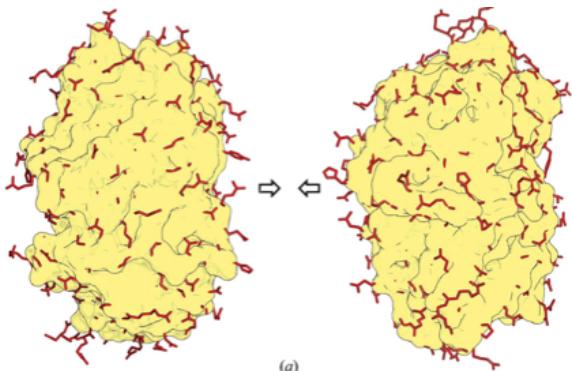


Sophie

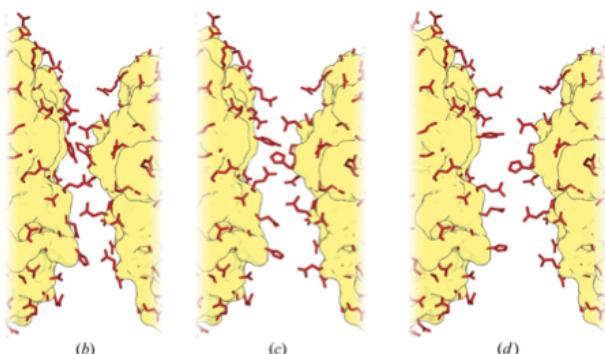
Looking inside the cell: a variety of topics

They study protein love stories

conformational changes upon
protein-protein interactions



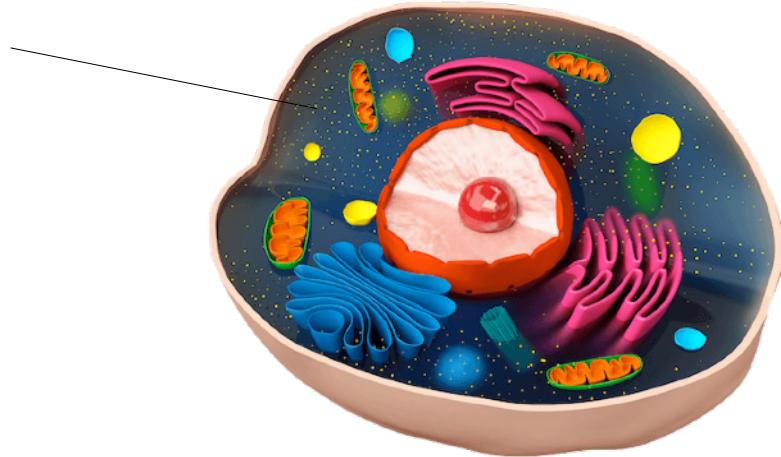
Charles



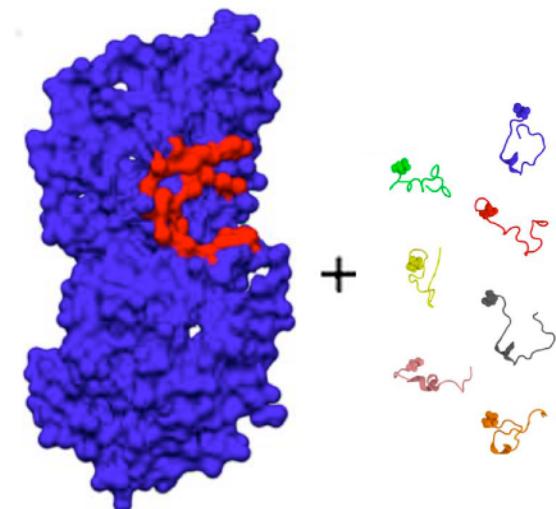
Chantal



Sophie



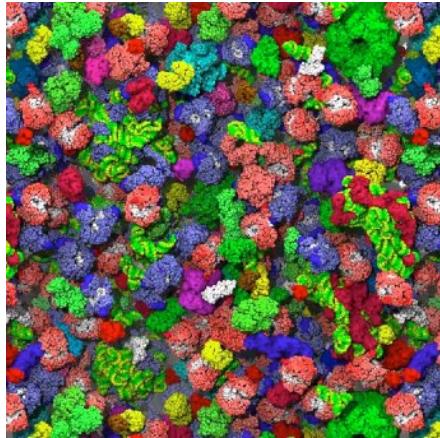
peptide - α,β tubulin interaction



Pushing the limits: towards mesoscopic simulations

They simulate the cell cytoplasm

effect of hydrodynamic interactions



Fabio Philippe



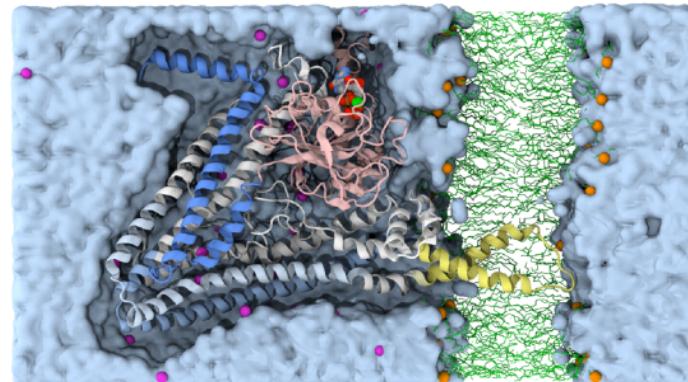
They look at mitochondrial membrane fusion



Antoine

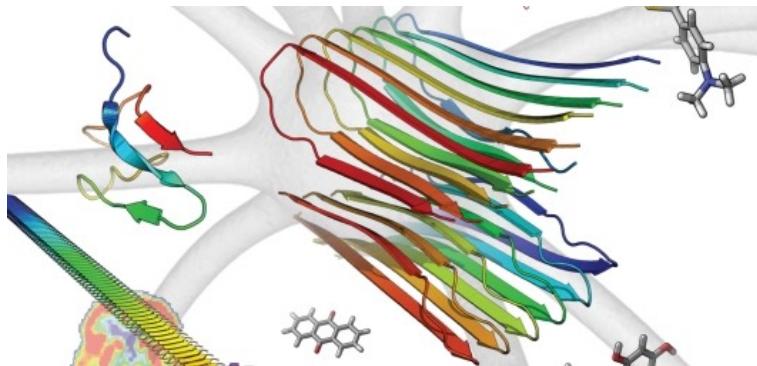
Jérôme

Marc



The neuron: degenerative diseases, synapses

Amyloid aggregation



Philippe

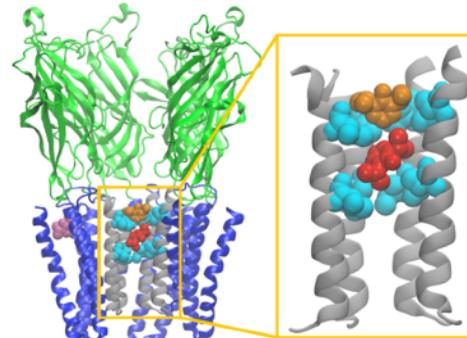
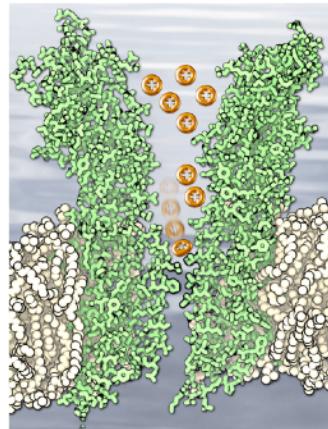
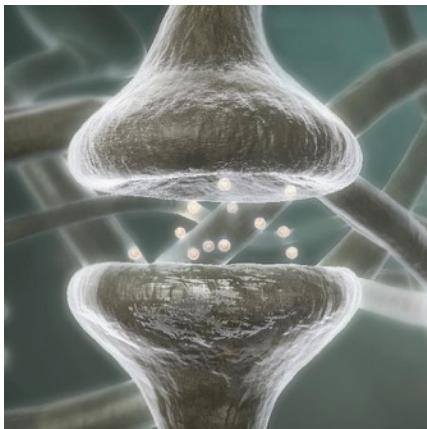


Phuong



Fabio

Pentameric ligand-gated channels in synapses



Jérôme



Marc



Antoine

Toward more efficient simulation approaches

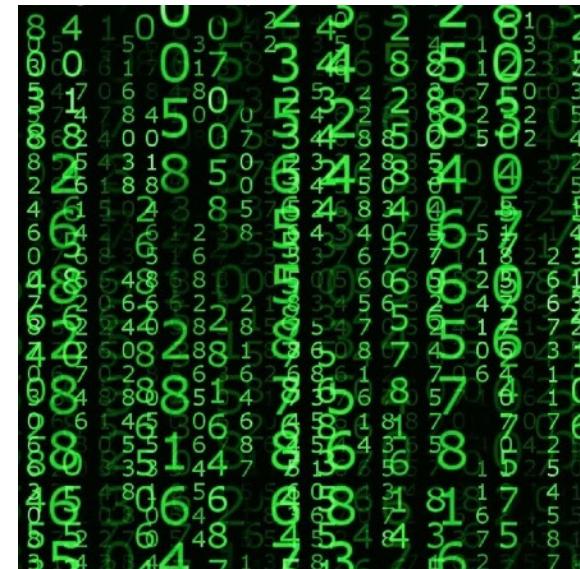
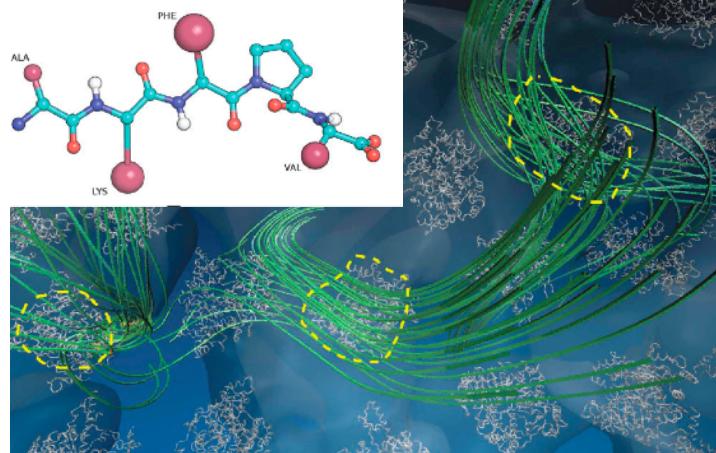
development of sophisticated “coarse-grain” representations

OPEP proteins



HiRE DNA/RNA

MUPHY: toward simulating the cytoplasm



guiding simulations, making them faster: enhanced sampling



Toward more efficient simulation approaches

How to generate a trajectory?

(we try not to generate random numbers)

development of sophisticated “coarse-grain” representations

OPEP proteins



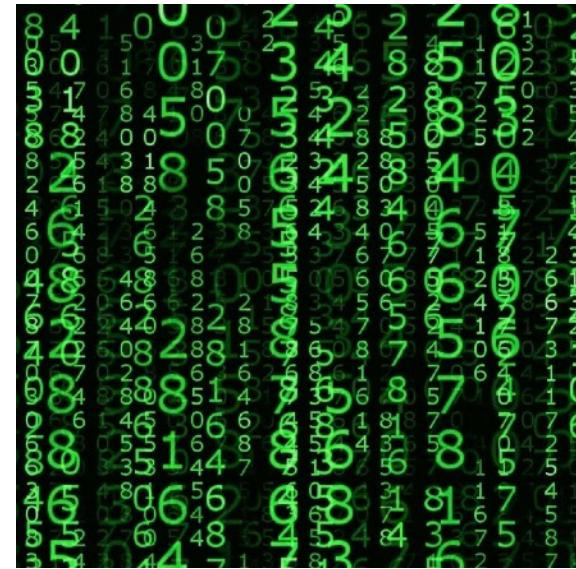
Phuong

Fabio

Philippe

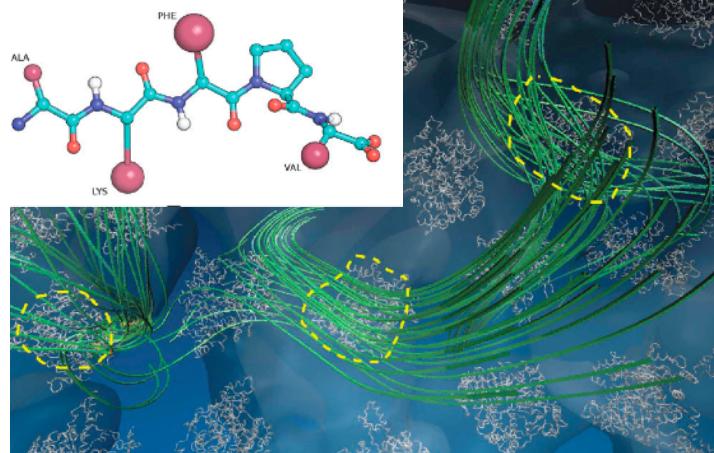


Sophie



HiRE DNA/RNA

MUPHY: toward simulating the cytoplasm



guiding simulations, making them faster: enhanced sampling



Fabio

Guillaume

Charles

Jérôme

Sampling and analyzing high dimensional configurational spaces

Charles Robert and Frédéric Cazals (Inria)

- Global optimization method: hybridize two strategies

1) T-RRT: Voronoï bias (taboo-ish)

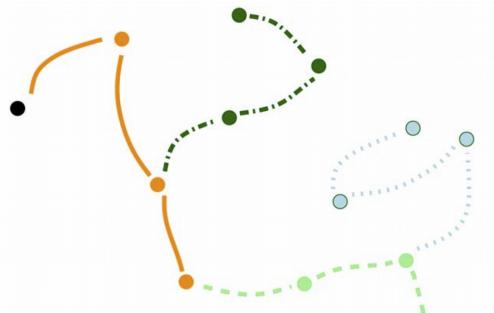
Rapidly-expanding Random Tree with Temperature control

Jaillet, Corcho, Pérez & Cortés (2011) J Comp Chem

+

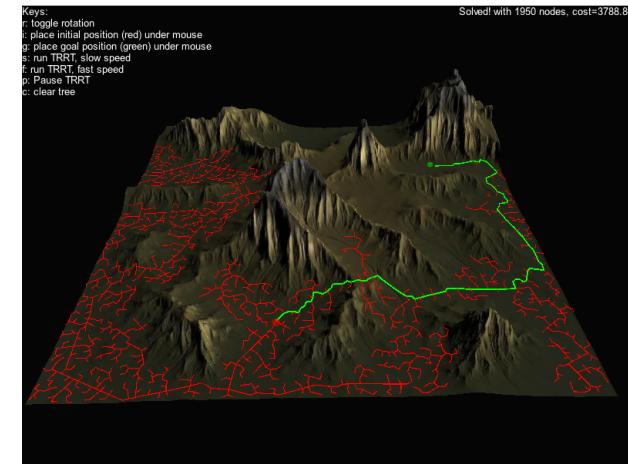
2) Monte Carlo with minimization (Basin Hopping)

Li & Scheraga (1987) PNAS

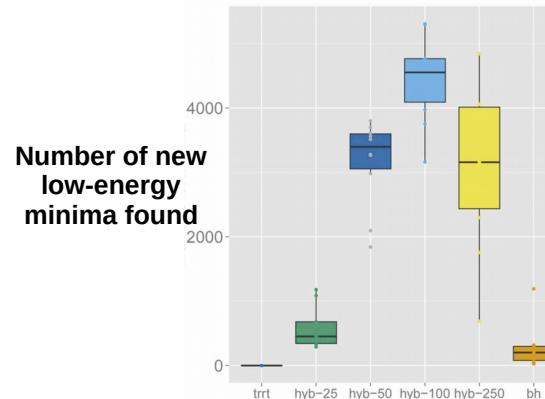
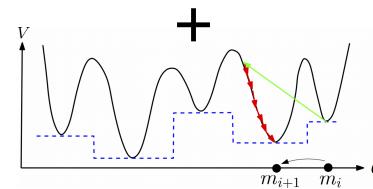


Hybrid algorithm: T-RRT + BH threads

- Targets: frustrated, multifunnel macromolecular systems
 - (here BLN69 beta-barrel model system)
- Energy Landscape analysis and comparison methods



Courtesy J. Cortés



More T-RRT-like More basin-hopping-like

Synergy:
exploration
and
exploitation

Cazals et al (2015) J Comp Chem
Roth et al (2016) J Comp Chem

Toward more efficient simulation approaches



What to do with all these numbers?



high-level visualization and user interaction
innovative education approaches



Marc

Antoine



projection onto relevant reaction coordinates

$$\{\vec{X}_i\}_{i=1,\dots} \rightarrow \vec{R}$$

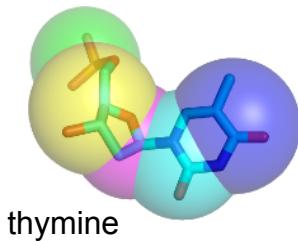
everyone...

A few software developments..

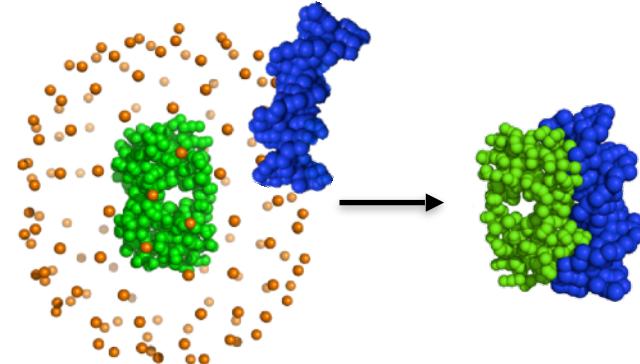
Nom	Auteur	Objectif	Distribution	Dissémination
BioSpring	MB	réseau élastique augmenté interactif	(interne) ...	
CG-FA	SP, PhD	reconstruction acides nucléiques	interne	
colvars module	JH	biais sur variables collectives en MD	licence libre	NAMD, LAMMPS
FlexBase	CHR	analyse des complexes protéiques	(interne) ...	
FvNano	MB	laboratoire virtuel	licence libre	
HiRe-RNA	SP, PhD	modèle GG acides nuc. (ARN+ADN)	interne	
HyperBalls	MB	visualisation moléculaire sur GPU	licence libre	
ICMD	AM	MD en coordonnées internes	sur demande	
MAXDo	SSM	partenaires d'interactions protéiques		IBM WC GRID
MDDriver	MB	API pour simulations interactives	licence libre	
Pep-Fold2	PhD	prédiction de structures peptidiques	web	
ProPHet	SSM	propriétés mécaniques de protéines	sur demande	
PTools/ADN	CP	édition/manipulation de l'ADN	(interne) ...	
PTools/Helgeom	CP	auto-assemblages par vissage	(interne) ...	
PTools/PyAttract	CP	docking gros grains protéine/ADN	licence libre	
UnityMol	MB	visualisation moléculaire et illustrative	(interne) ...	
VMOD	CHR	contrainte sur modes normaux		CHARMM
:	:	:	:	:

A few software developments..

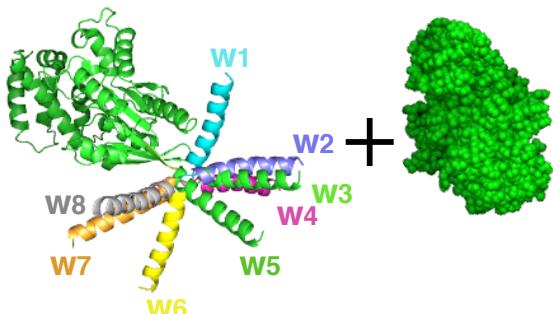
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BioSpring	MB	réseau élastique augmenté interactif	(interne) ...	
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MDDriver	MB	API pour simulations interactives	licence libre	
Pep-Fold2	PhD	prédiction de structures peptidiques	web	
ProPHet	SSM	propriétés mécaniques de protéines	sur demande	
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PTools/Helgeom	CP	auto-assemblages par vissage	(interne) ...	
PTools/PyAttract	CP	docking gros grains protéine/ADN	licence libre	
UnityMol	MB	visualisation moléculaire et illustrative	(interne) ...	
VMOD	CHR	contrainte sur modes normaux		CHARMM
:	:	:	:	:



coarse-grain/atomic resolution



docking with ATTRACT



flexible docking
multi-copy/mean field method

PTools

Py/C++ library for
macromolecule manipulation

<https://github.com/ptools/ptools>

Force fields

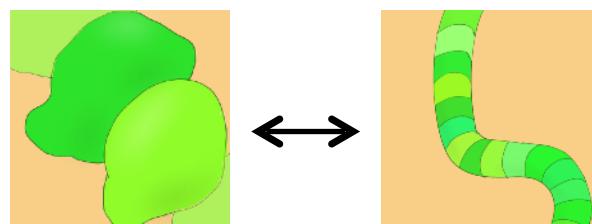
ATTRACT1

protein-protein
protein-DNA

ATTRACT2

Scorpion

[add your own...]



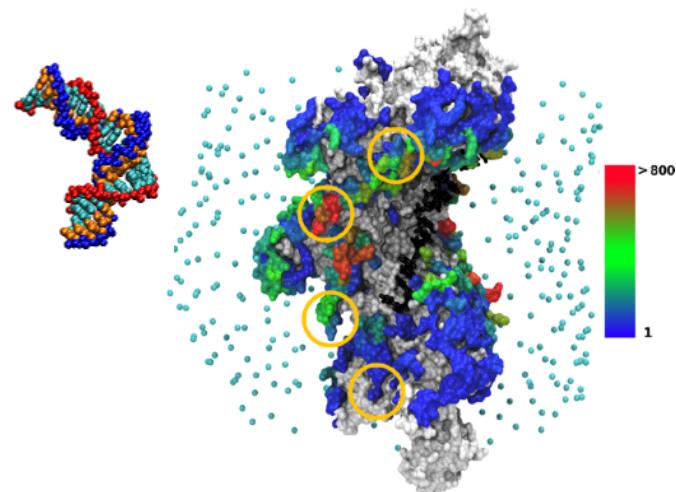
helgeom module

Development team
Adrien Saladin
Chantal Prévost
Pierre Poulain
Benjamin Boyer
Benoist Laurent
Martin Zacharias
Tâp Ha Duong
Nathalie Basdevant
Sébastien Fiorucci

PTools applications

PTools/docking applications

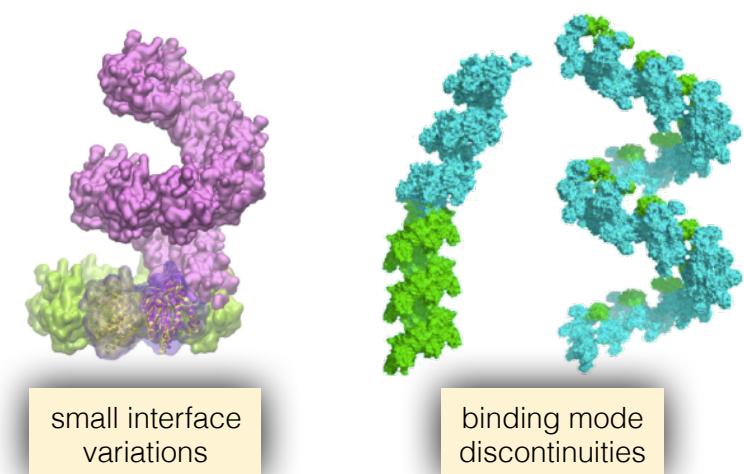
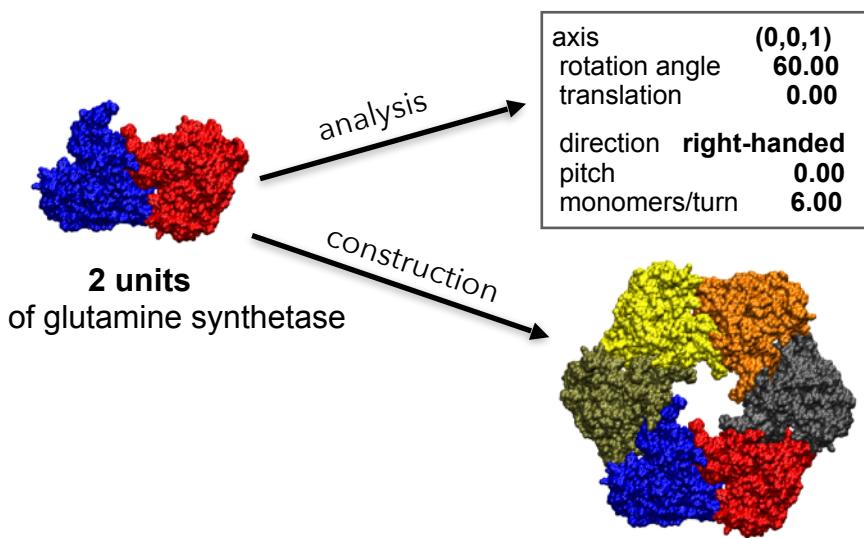
- ▷ mapping the interface : residues that best interact
- ▷ docking analysis : fNAT, fIR, iRMSD
- ▷ interfaces comparison



Saladin et al. Nucleic Acids Res 2010 38:2313

PTools/Heligeom applications

- ▷ analysis
- ▷ construction
- ▷ prediction when coupled with docking



Boyer et al. PLoS ONE 2015 10 (3): e0116414

unity



mol

mol

mol

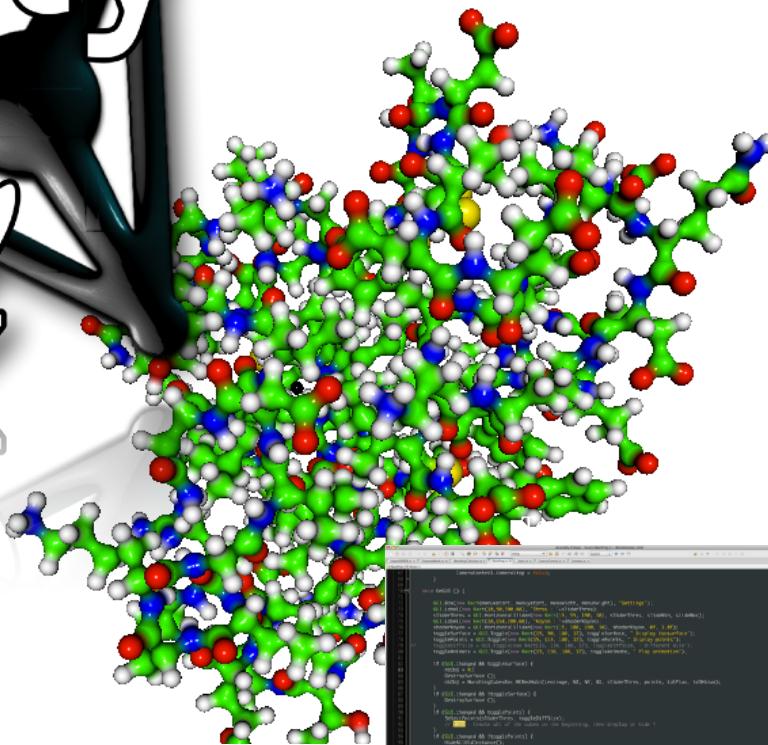
mol

mol

mol

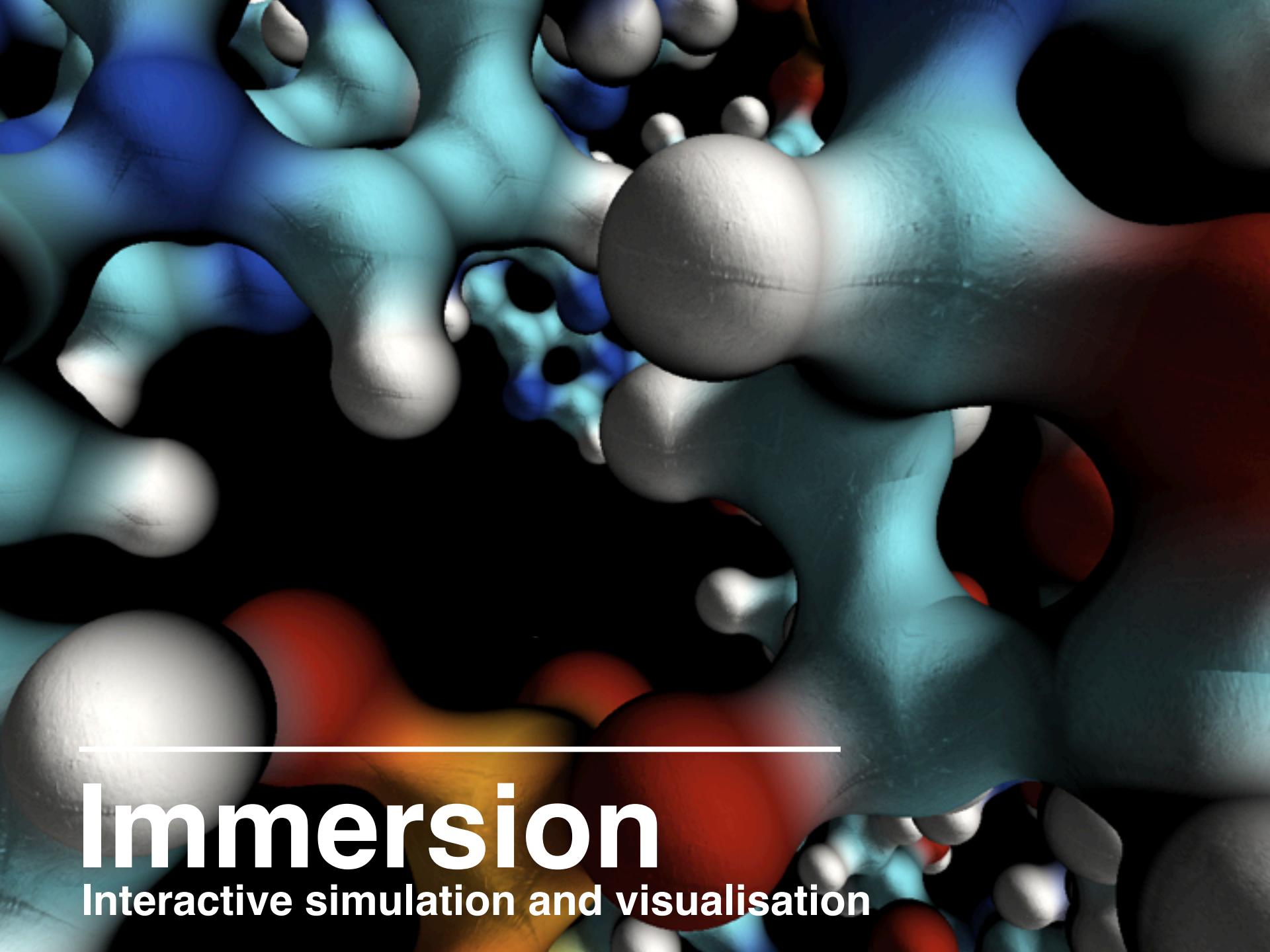
mol

6 years
9500 downloads



- Full 3D development platform
- Advanced graphics engine
- Portable, intuitive to use
- 3 languages : C#, Boo, Javascript

- Export to multiple platforms : OSX, Windows, Linux, Android, iOS, .. WebGL ..



Immersion

Interactive simulation and visualisation

Immersion

- be an **actor** and "**manipulate**" molecules (or data in general)
 - for example «serious games» such as FoldIt
- immersion into the structural world of molecules
 - view in 3 dimensions
 - apprehend spatial architecture

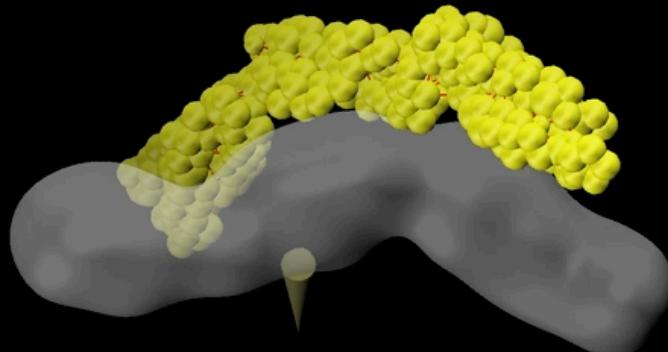


Interactive refinement

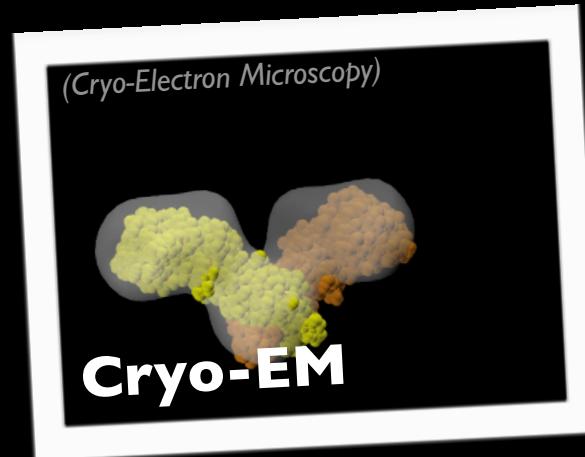
**Integrative
Biology**

Experimental data
+
Interaction & human expertise
+
Physical model

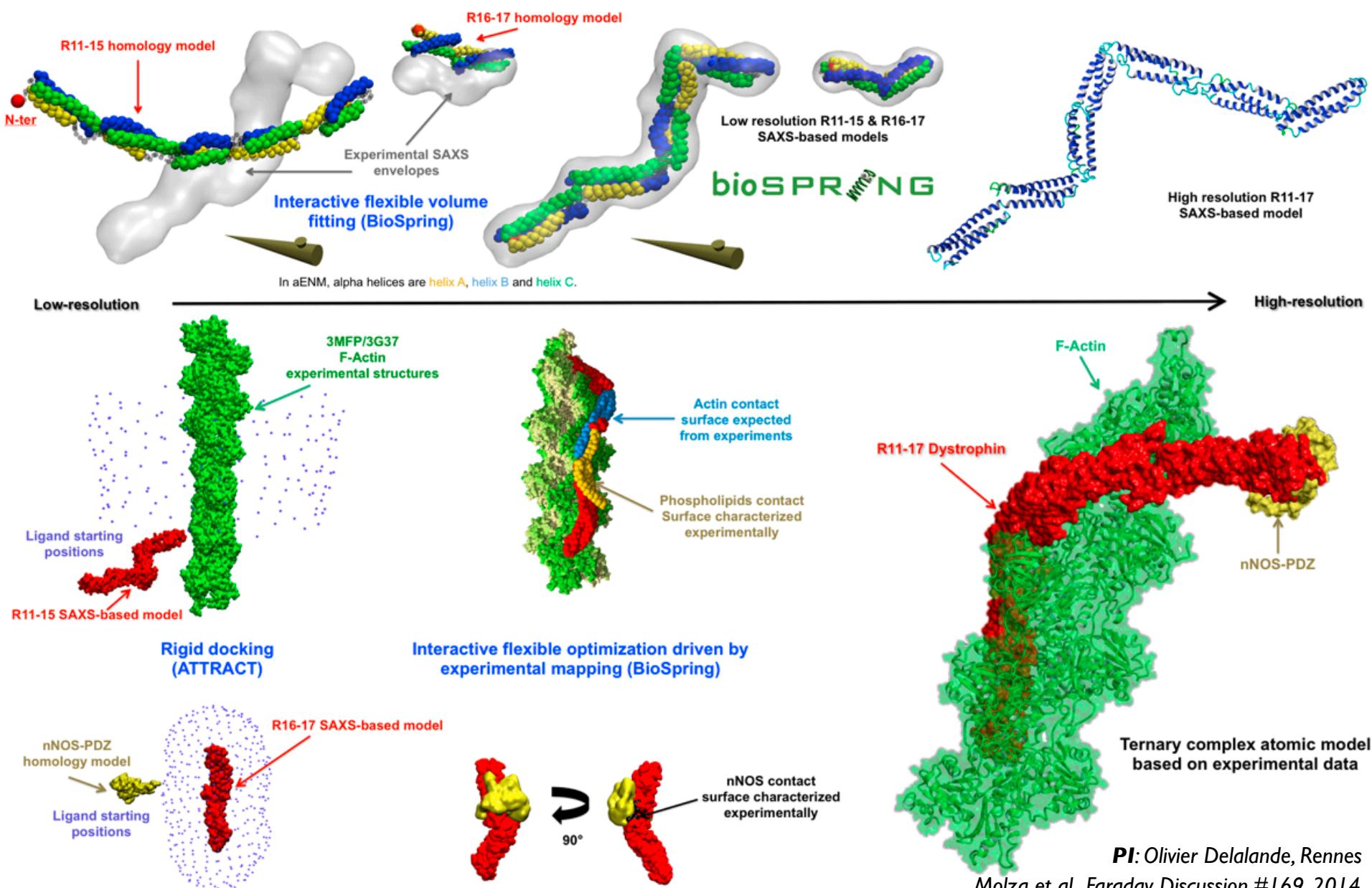
Dystrophin filament

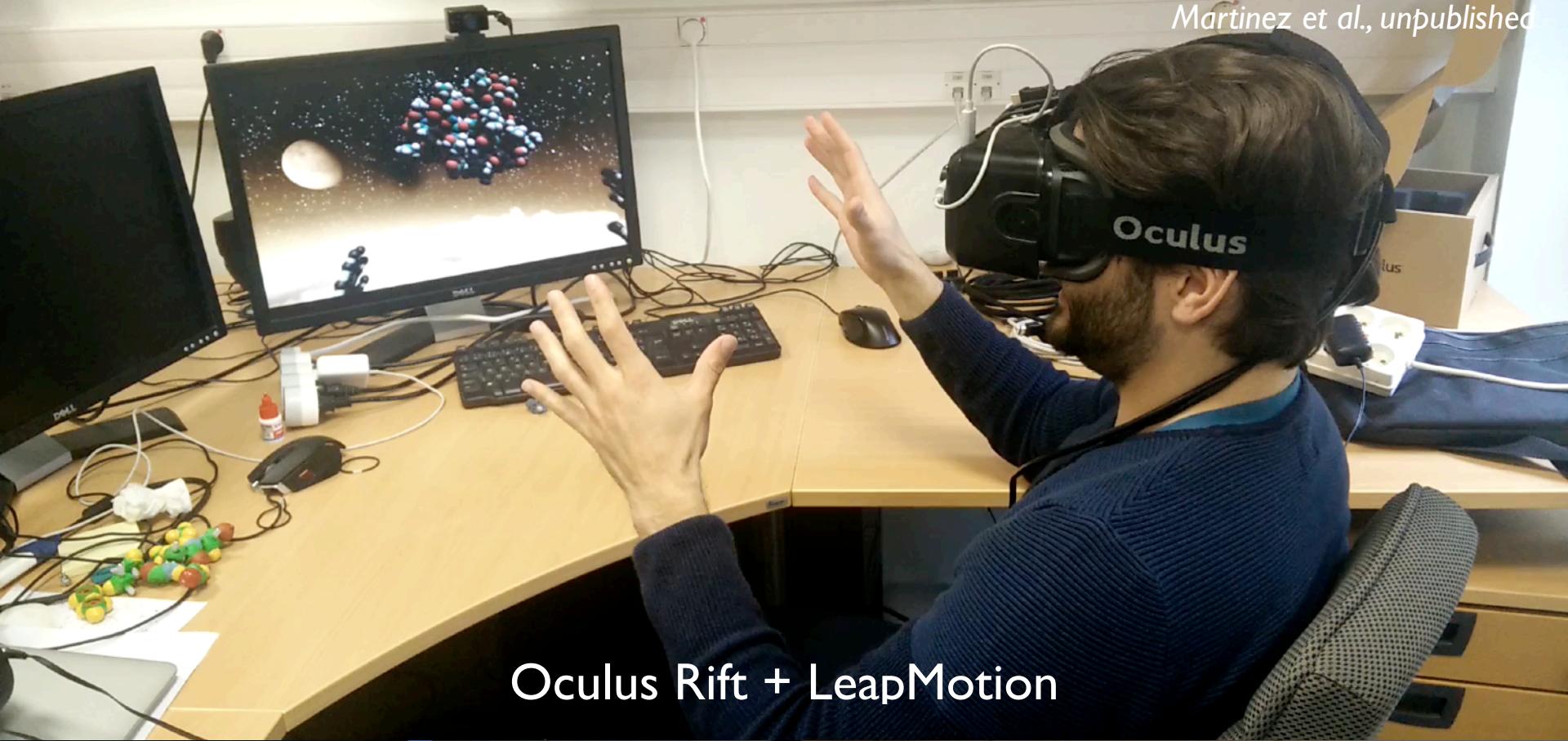


SAXS (Small Angle X-ray Scattering)



Building a dystrophin filament model





Oculus Rift + LeapMotion



HTC Vive



HoloLens

A computational microscope @IBPC

Centre for the Analysis of
Complex Systems In
Complex Environments



- 8 m²
- 7680 x 3240
- 25 MPixels
- 4,4 m x 2 m
- 3D stereo
- pixel 0.58 mm



A computational microscope @IBPC

Centre for the Analysis of
Complex Systems In
Complex Environments



What is a visualization wall??

- a large (several meters x several meters) tiled display screen
- to display single images at (very) high resolution
- for collaboration in small groups with shared access
- to compare and explore multiple views
- powered by high-performance computers for data treatment

- 8 m²
- 7680 x 3240
- 25 MPixels
- 4,4 m x 2 m
- 3D stereo
- pixel 0.58 mm



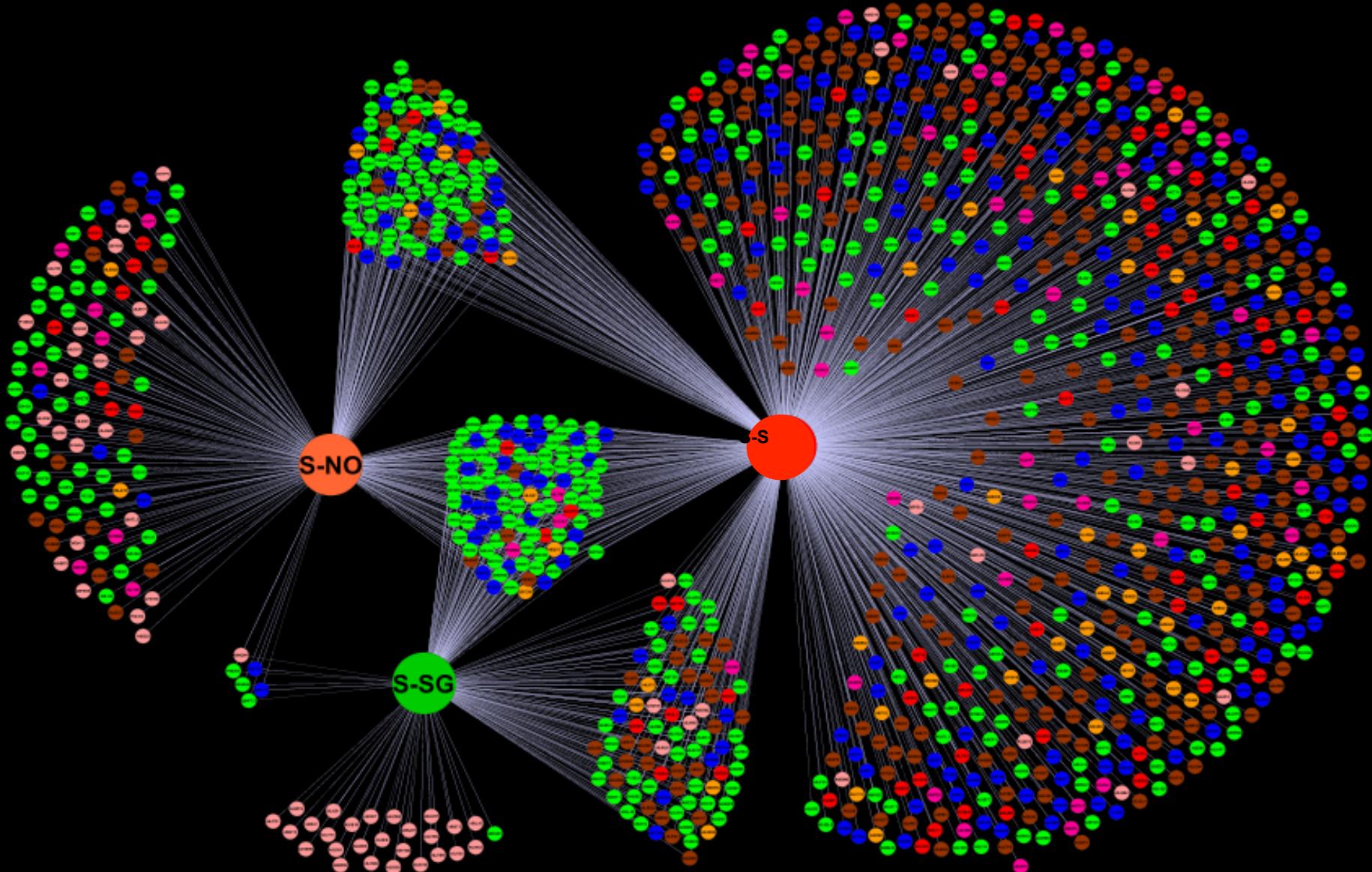
A computational microscope @IBPC



- modular display wall
- up to 15 people
- immediately functional!
- 12 retro-projected modules full HD (1920 x 1080)
- active 3D stereo
- very high contrast ratio
- vivid colours
- exceptionnal image quality



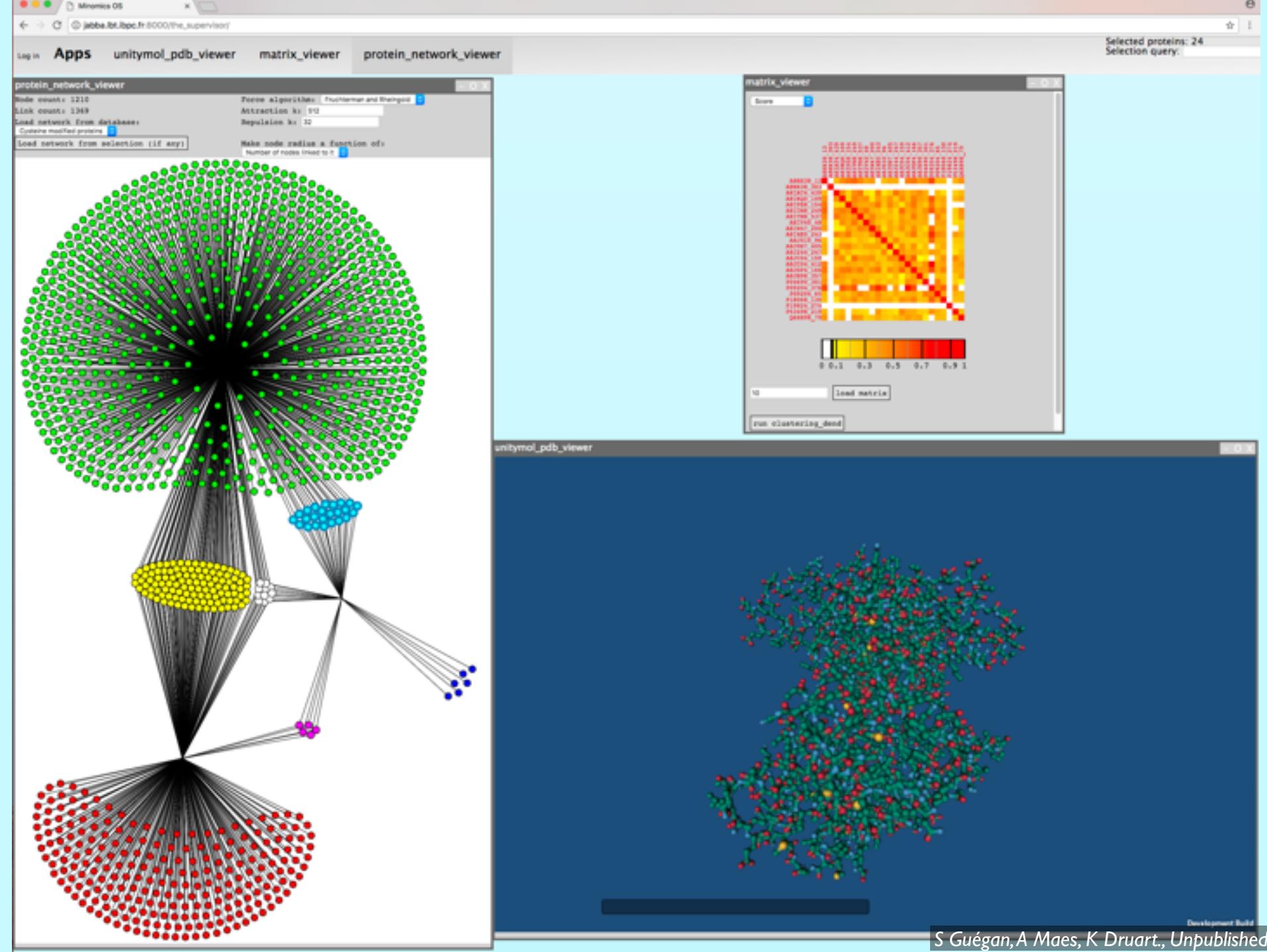
Example network of post-translational modifications

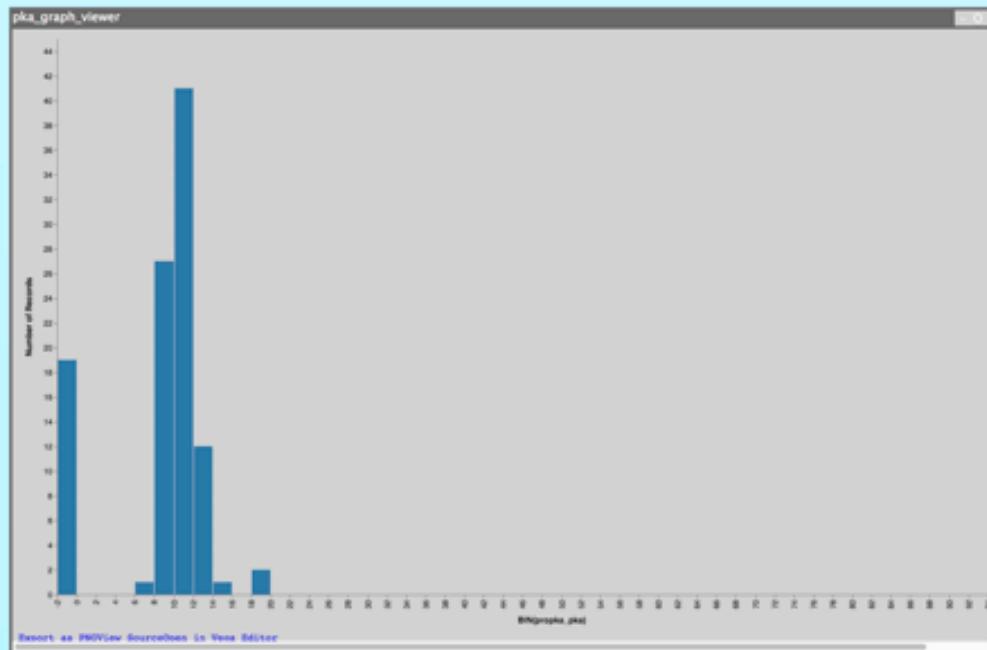
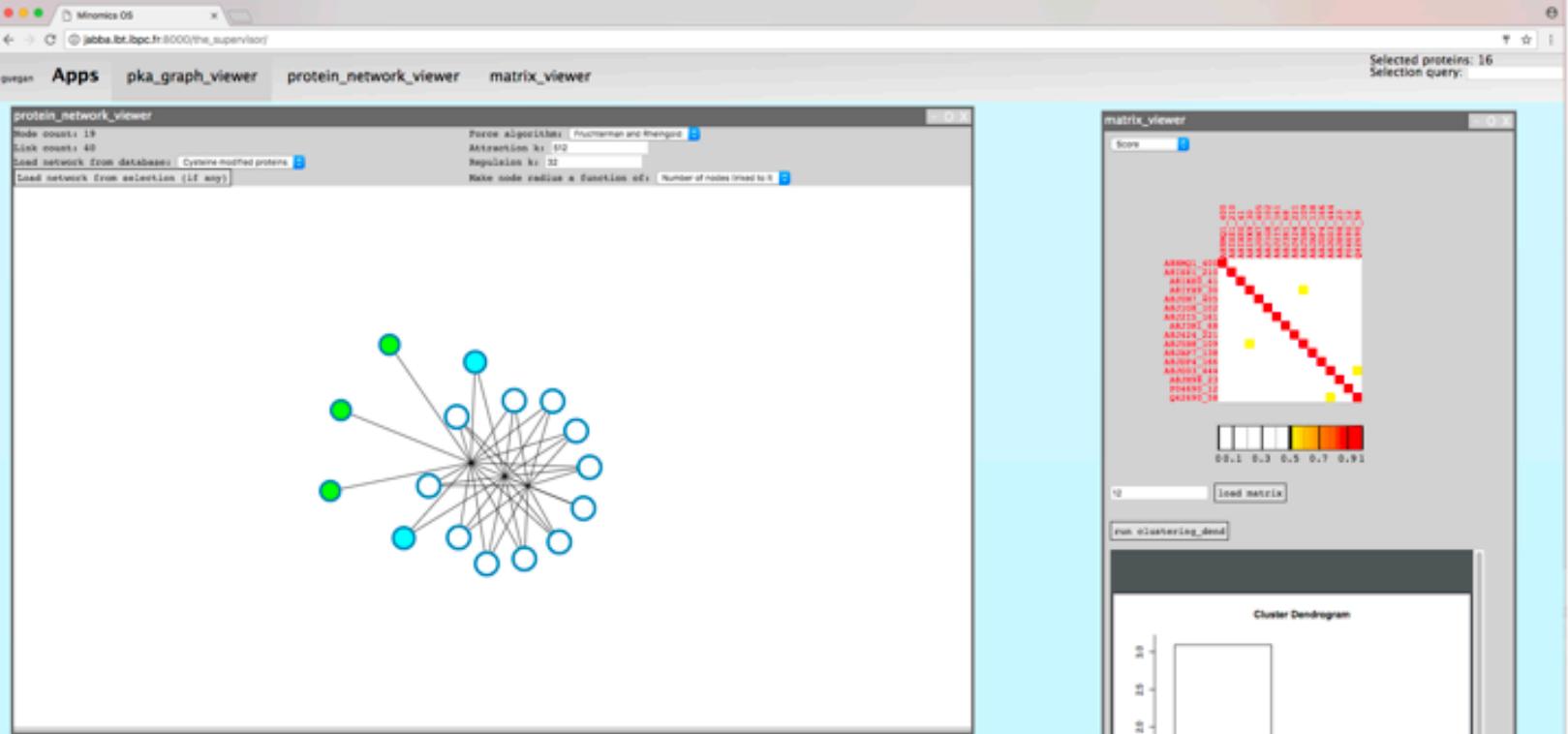


Courtesy Stéphane Lemaire

Example network of post-translational modifications

- Visualize and explore mass spec data $f(t)$ & conditions ($T, pH, ..$) at proteome level
- Zoom in on structural models of each protein
- Explore MD of each protein
- Make cross-analysis and establish correlations





Laboratory of Theoretical Biochemistry says

A collage of "thank you" and "merci" in various languages, including English, French, Spanish, Italian, German, Portuguese, Dutch, Polish, Russian, Chinese, Japanese, Korean, and many others.

Key words in the center include:

- merci (French)
- thank you (English)
- gracias (Spanish)
- dank je (Dutch)
- obrigado (Portuguese)
- grazie (Italian)
- danke (German)
- go raibh maith agat (Irish)
- спасибо (Russian)
- murakoze (Japanese)



The end

Uses



- Understanding ; hypothesis generation
- **Collaborations** and exchange with visual support
examples: work meeting, project review, presentation ..
- Visualisation in **high resolution** and/or on a **large surface**
ex: sequence alignments, phylogeny, DNA arrays, ..
- Visualisation in **3D active stereo** for complex data
ex: bridging multiple scales from atomic structures (xtal) to the cellular level (tomograms)
- Mining and comparison of **multiple data**
*ex: *in silico* screening – comparing docked molecules*
- **Treatment** of massive datasets ("big data")
computing power, memory and storage capacities

: : : : : :

IT: meso-center for computation, technical support

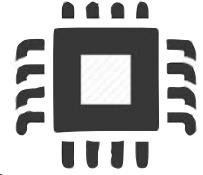


Geoffrey

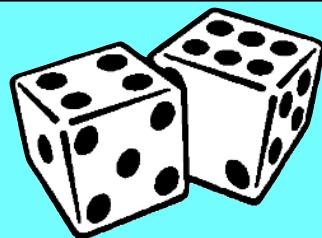


Typical MD workflow

Super-computer

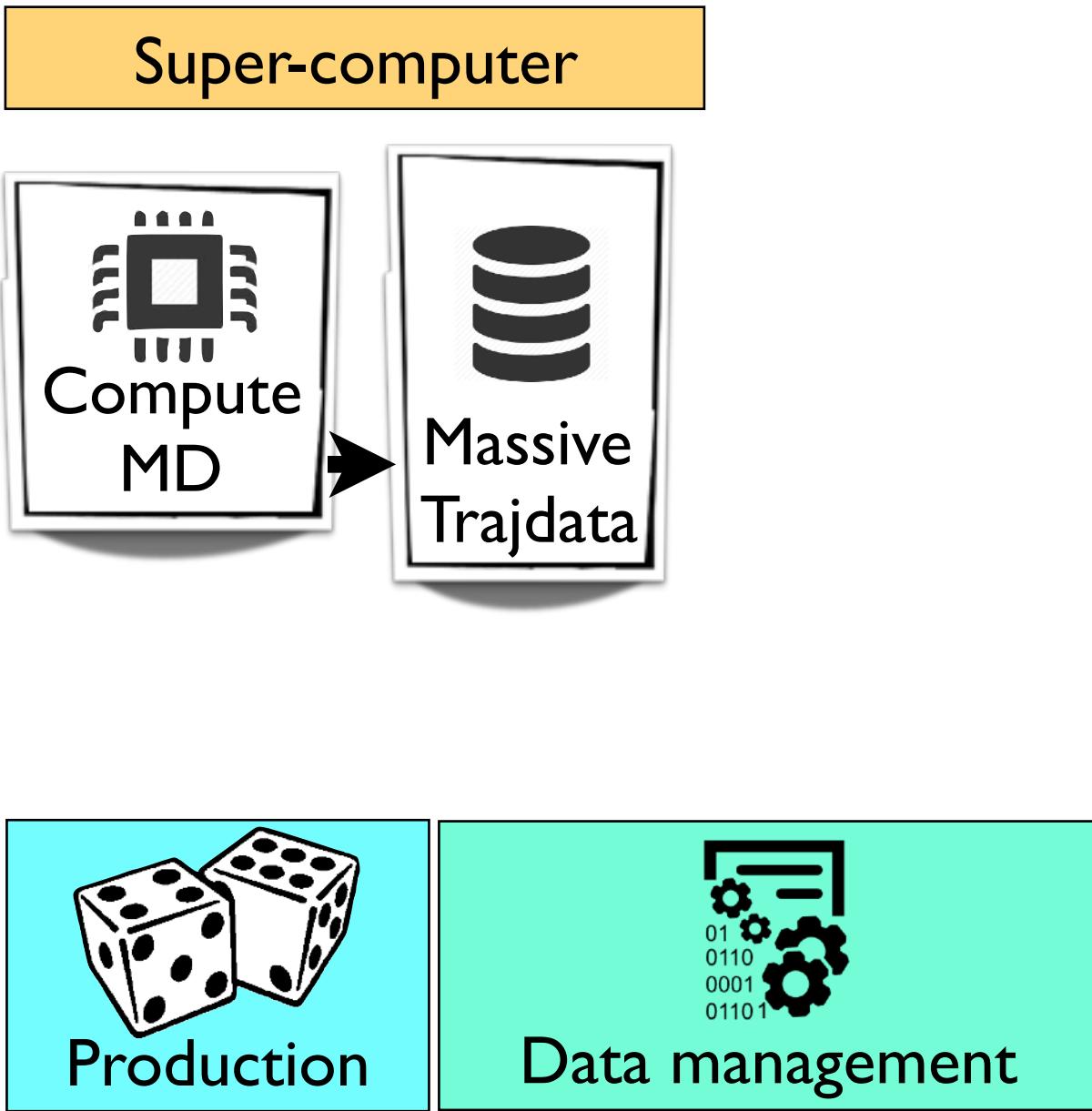


Compute
MD

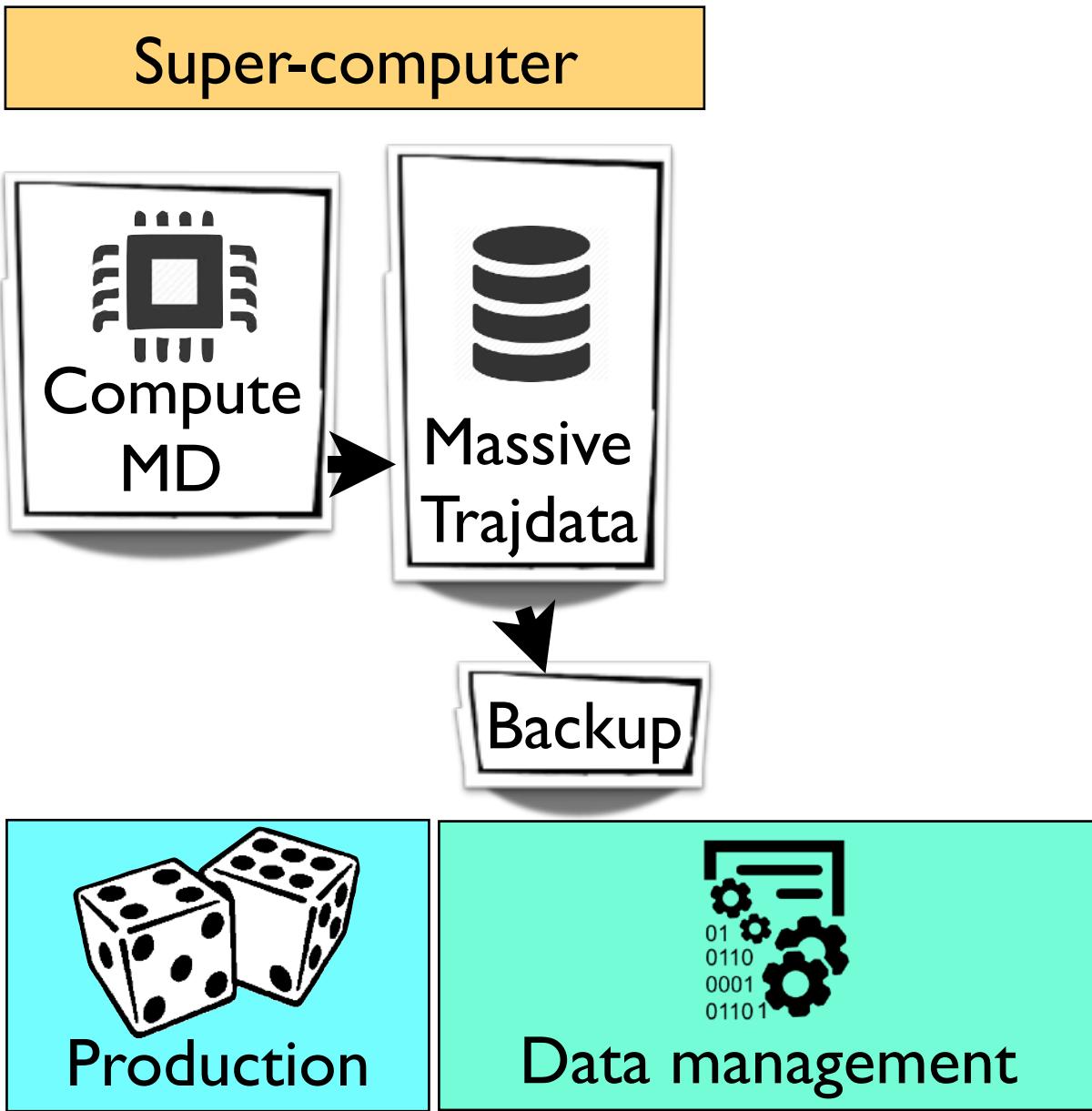


Production

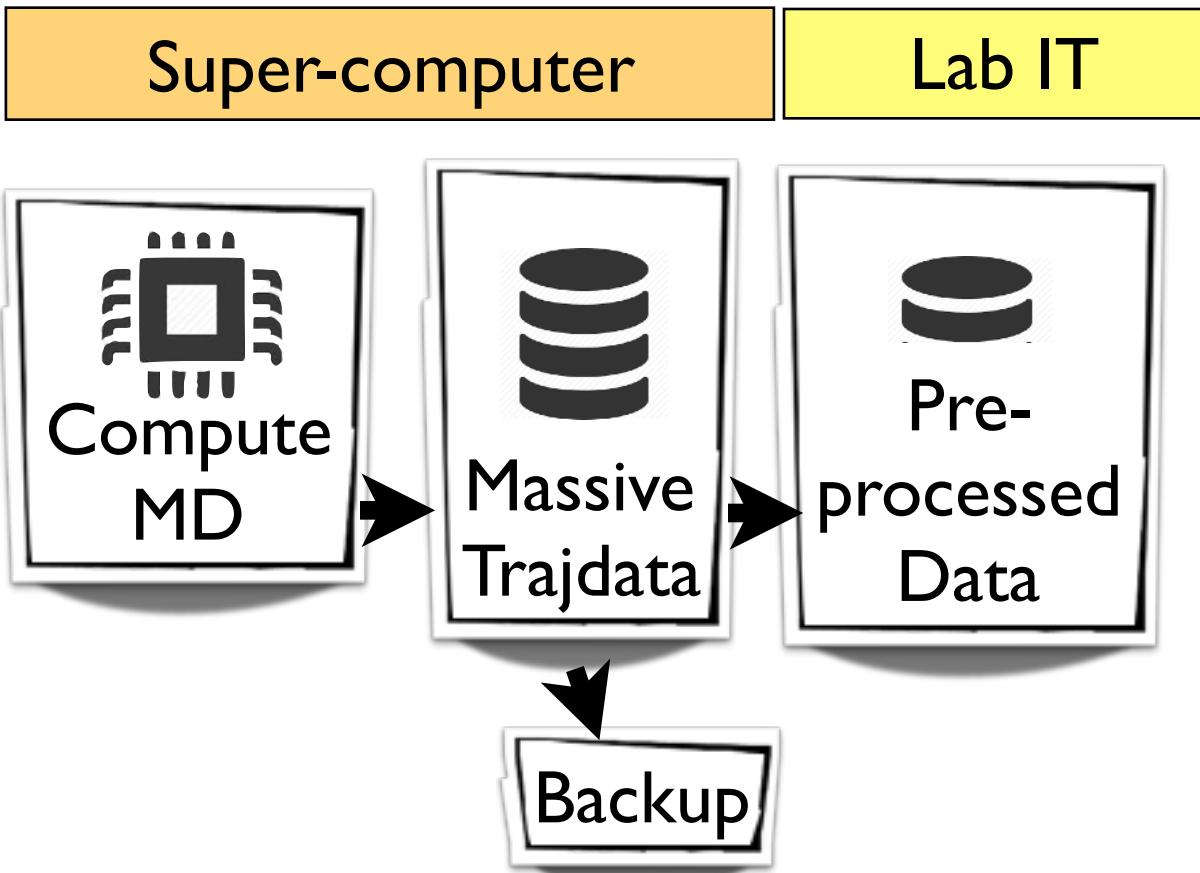
Typical MD workflow



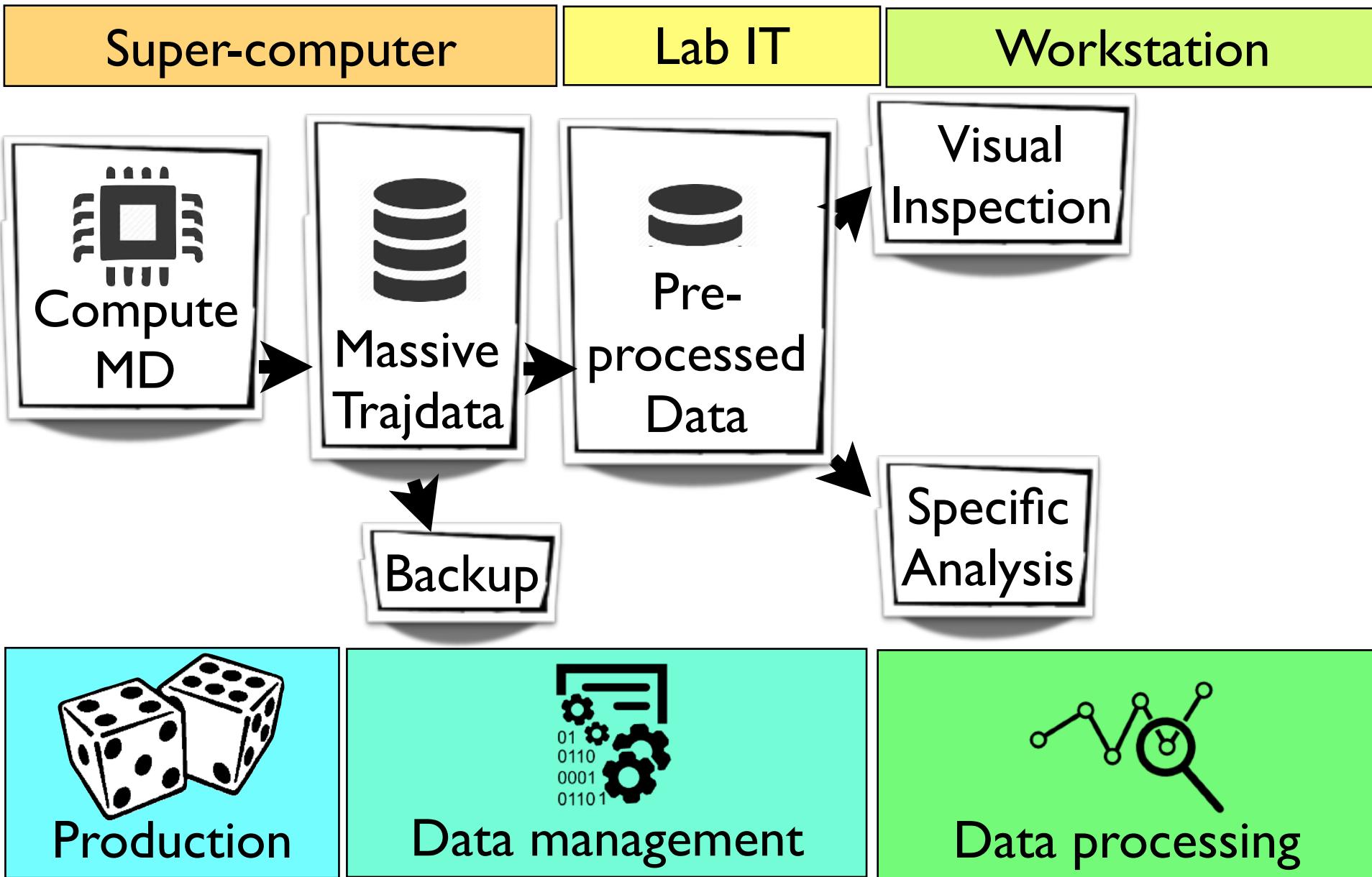
Typical MD workflow



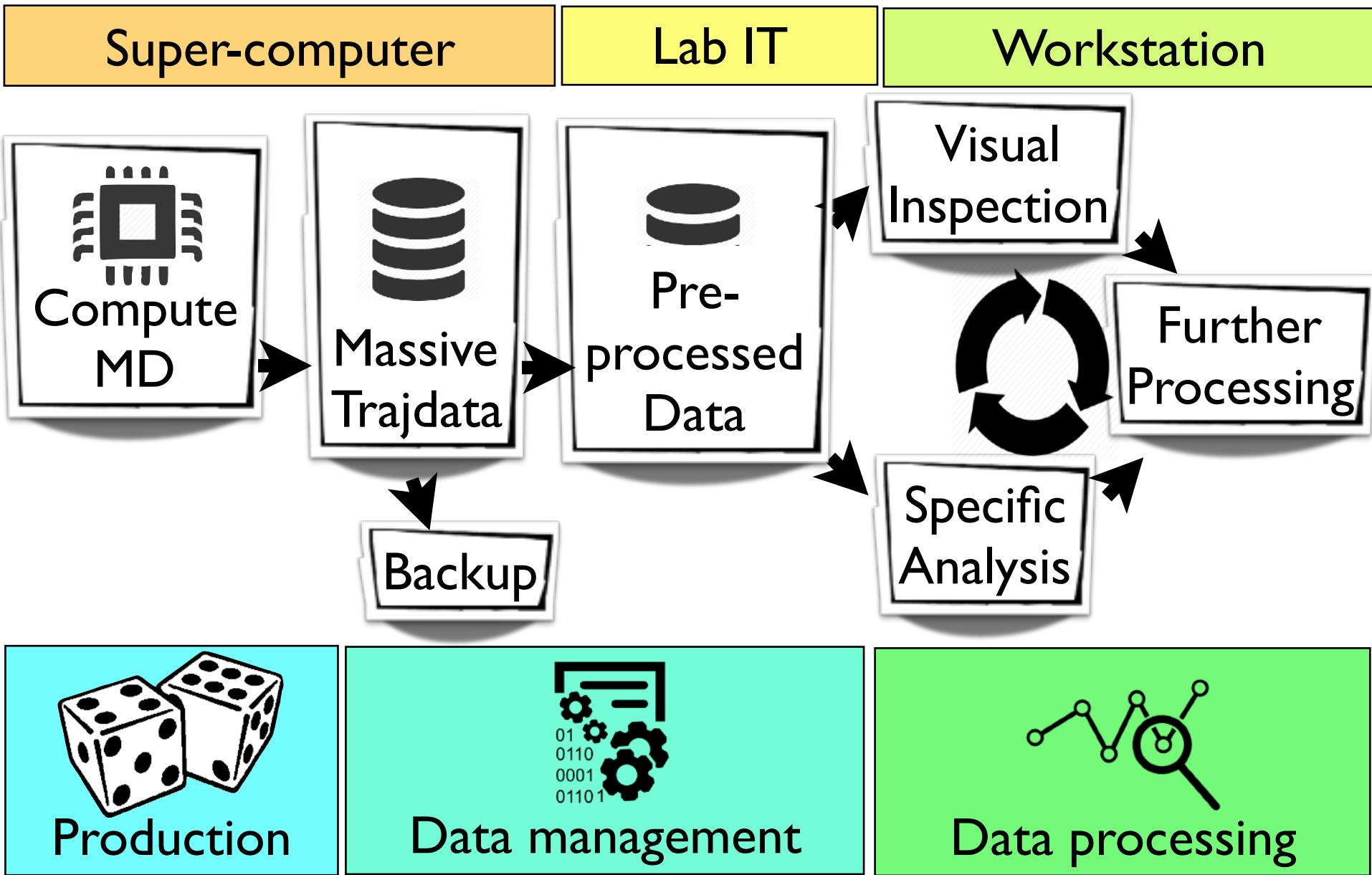
Typical MD workflow



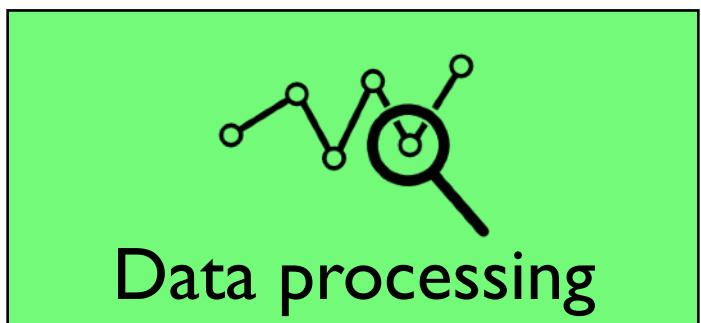
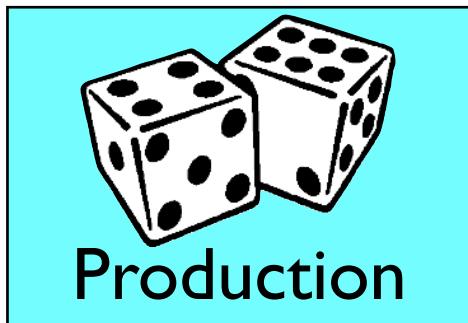
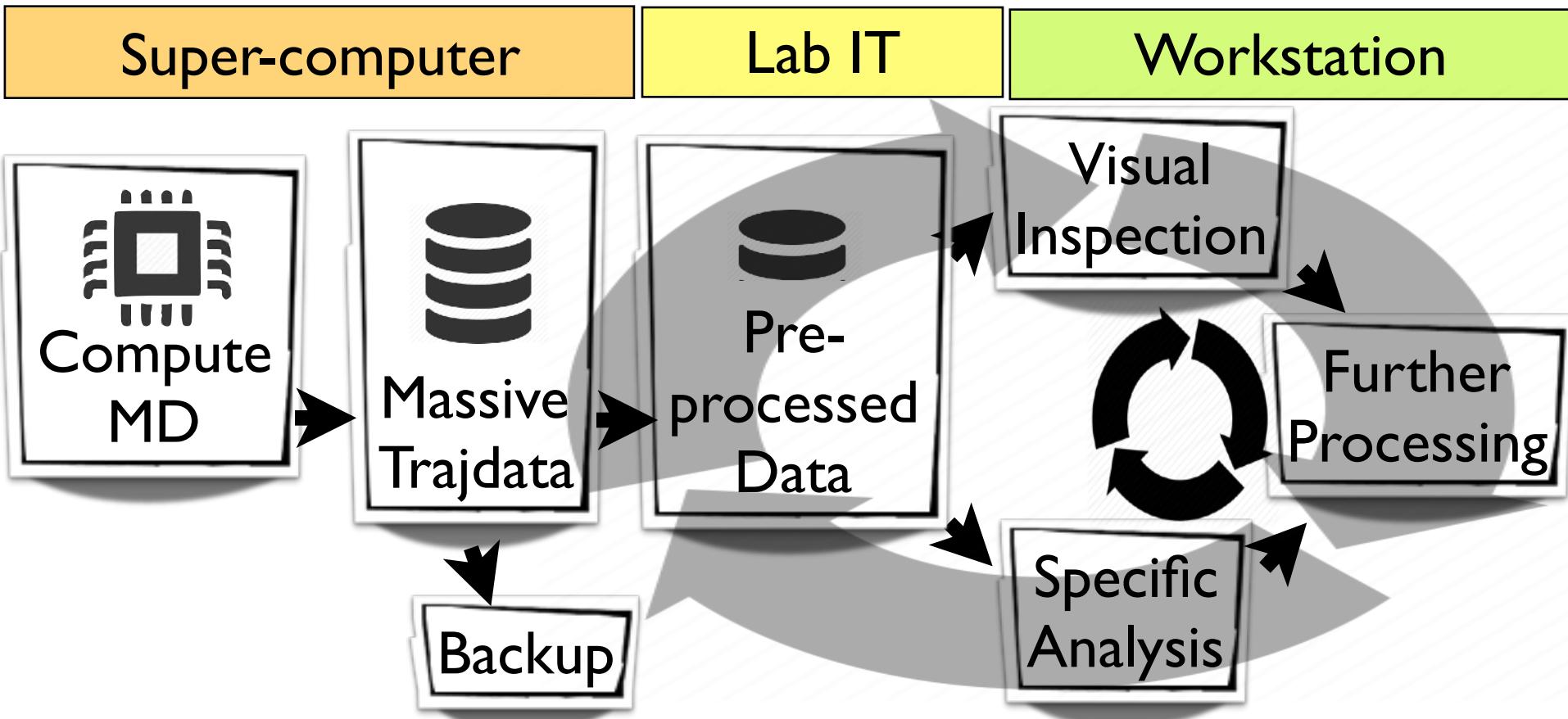
Typical MD workflow



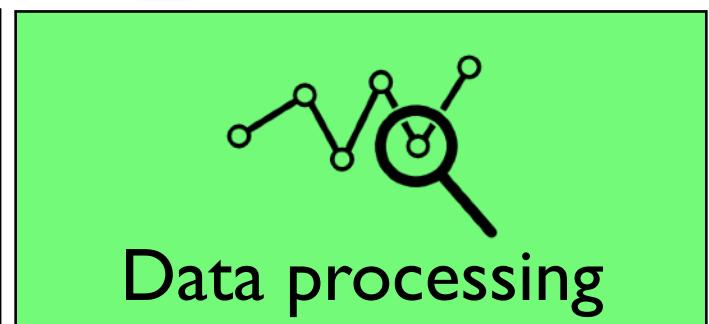
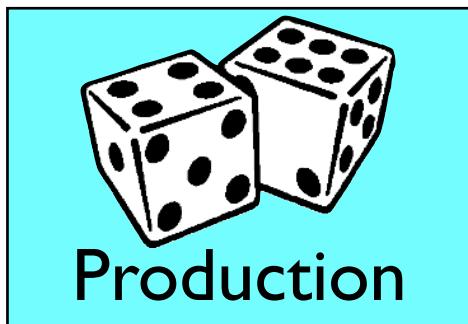
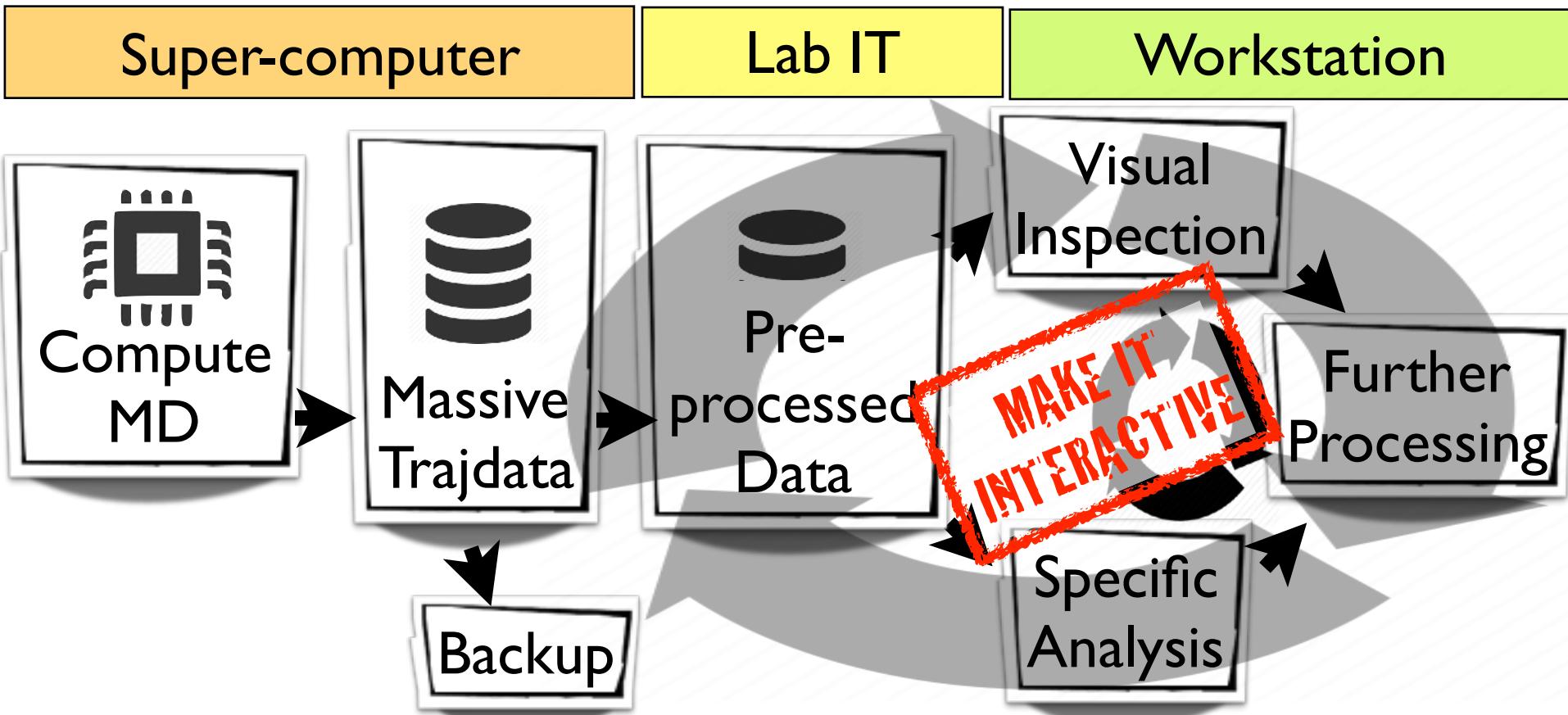
Typical MD workflow



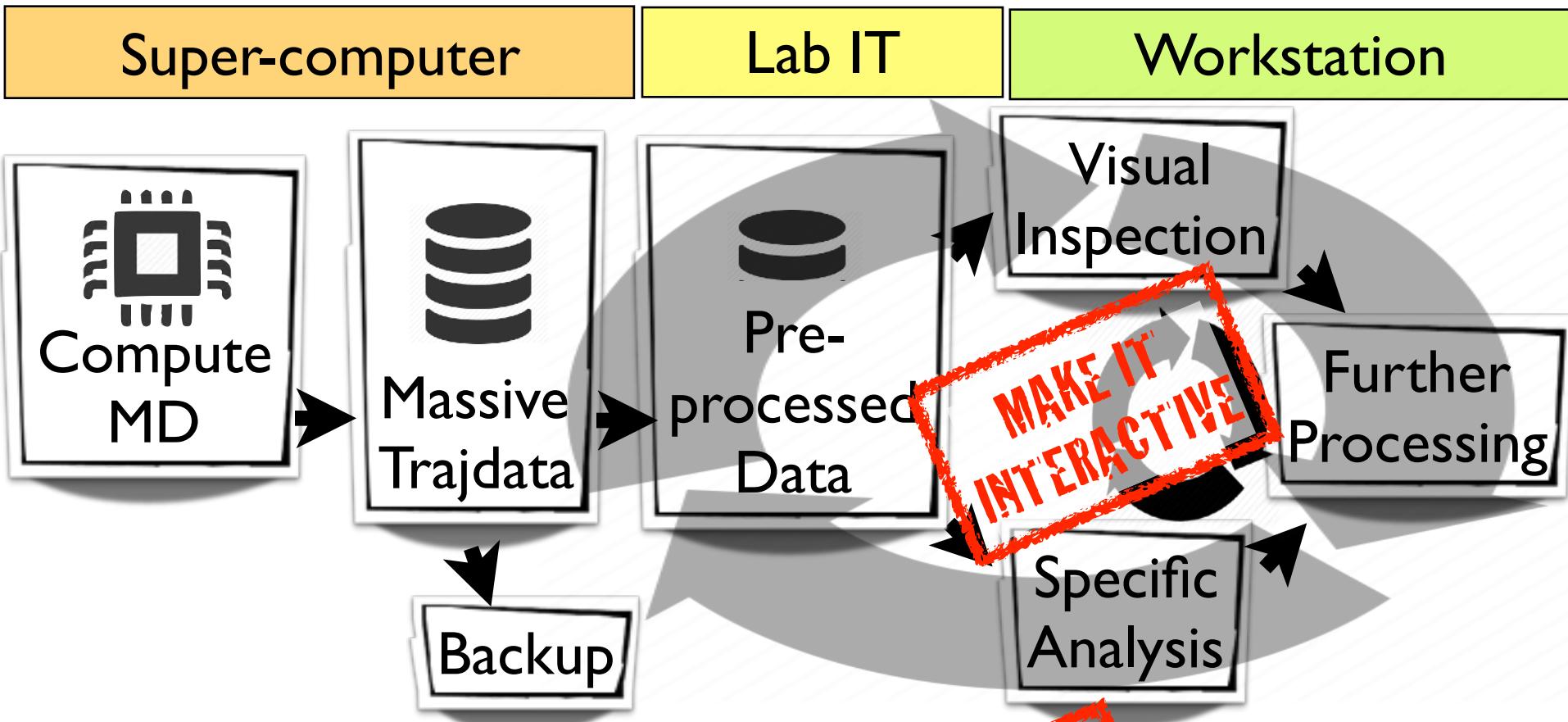
Typical MD workflow



Typical MD workflow



Typical MD workflow



Typical MD workflow

