Simulating the Extra Cellular Matrix Calculations and data from atom to animal

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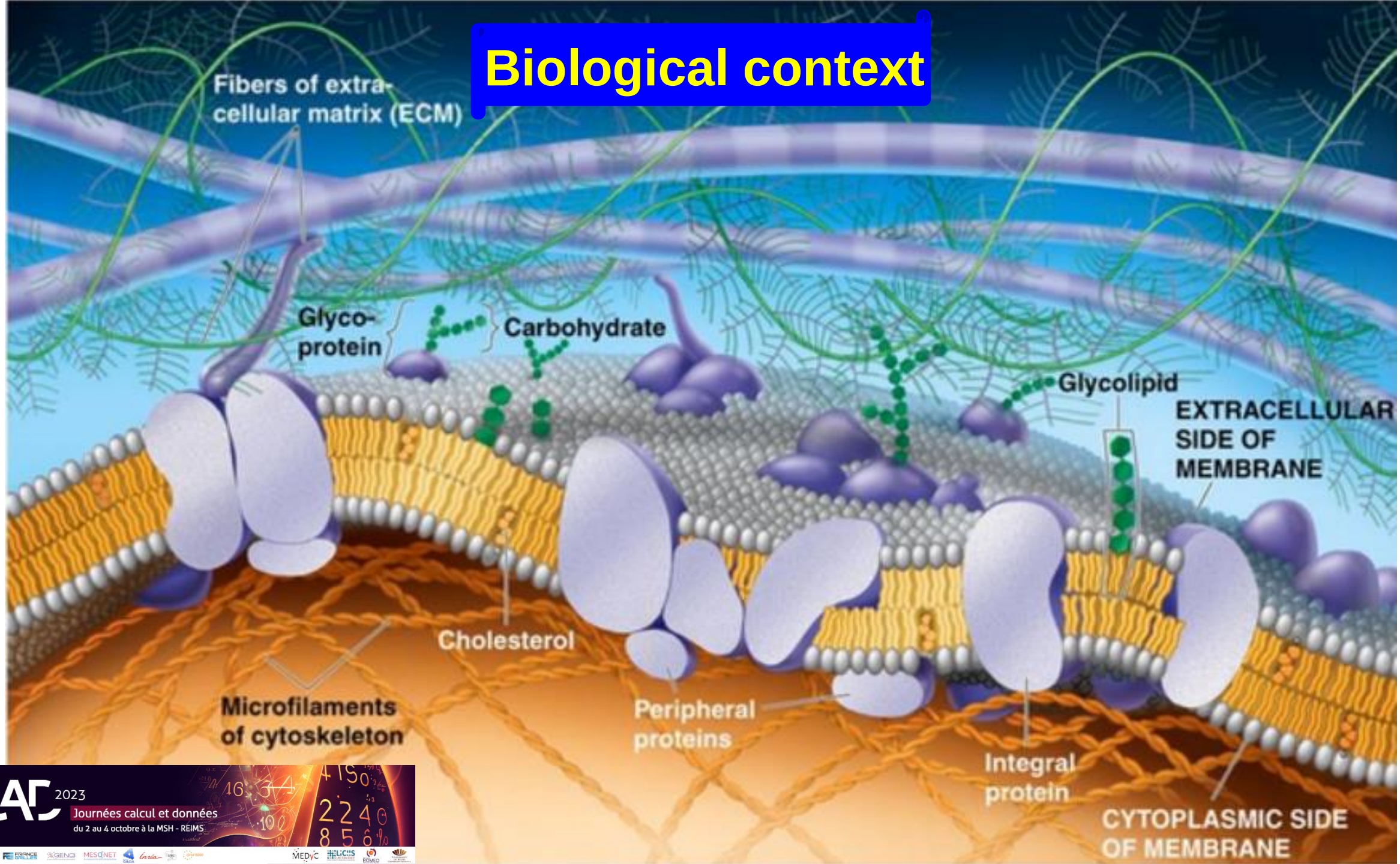
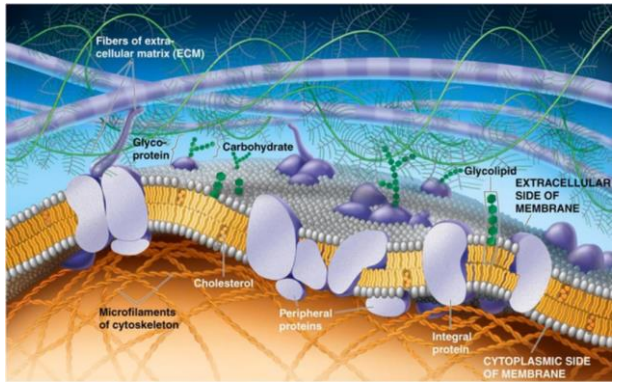
JCAD 2023 Journées calcul et données du 2 au 4 octobre à la MSH - REIMS

Biological context



Biological context



Diversity

Structural proteins forming fibers

Protein polysaccharide complexes

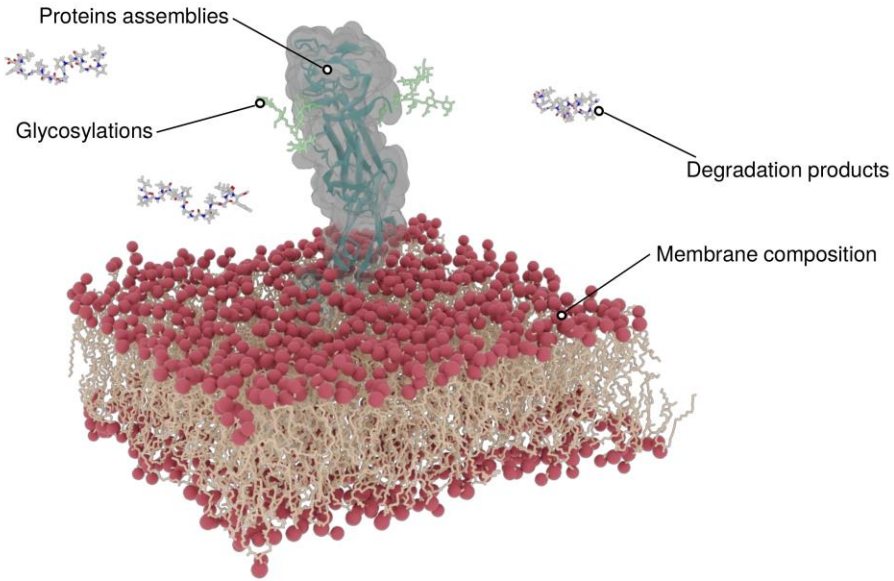
Adhesive glycoprotein

Maintenance and cohesion of tissues

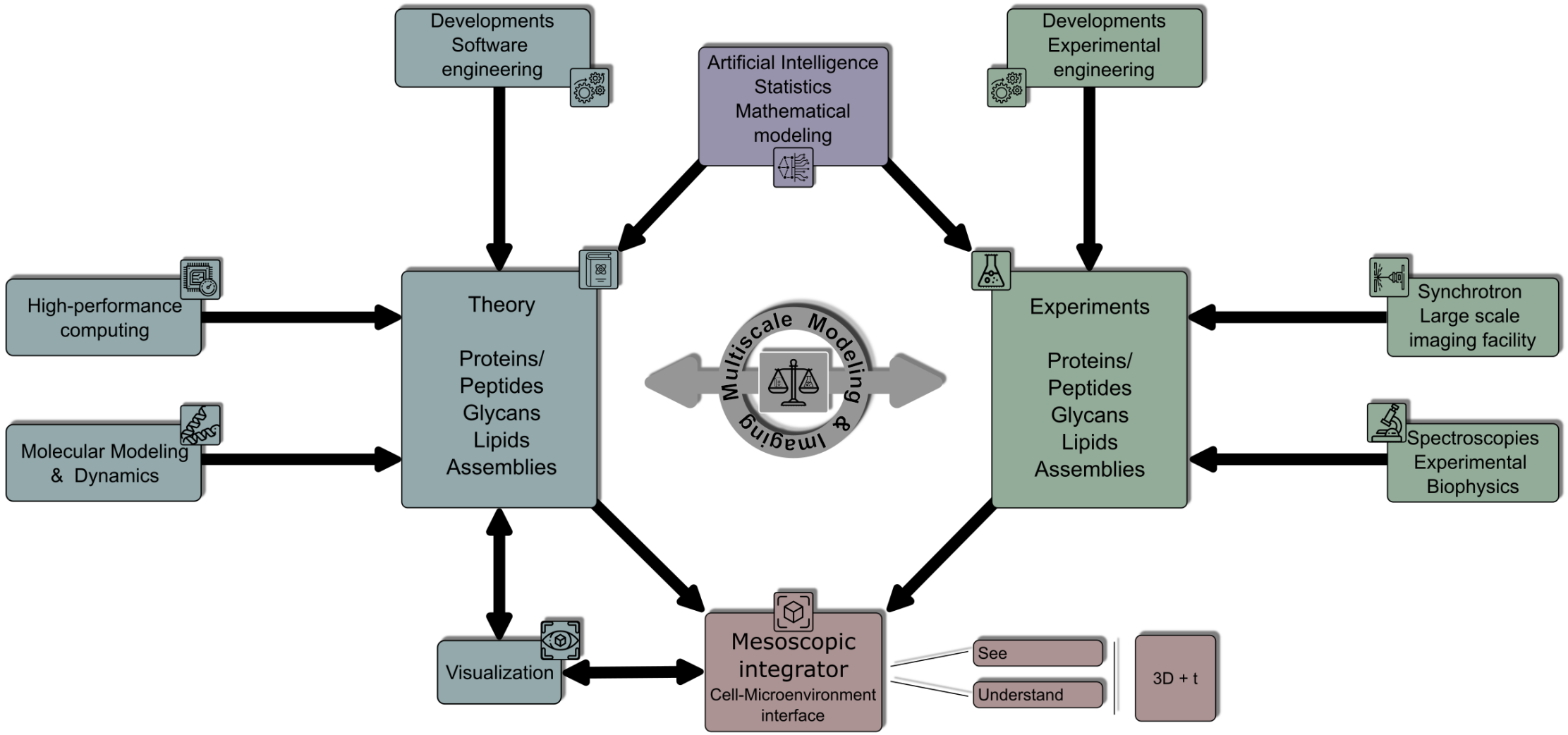
Growth factors reservoir

Cellular regulation

Source of matrikines



MIME Team



- **Unravel how a cell interacts at the interface of its matrix microenvironment.**

Molecular modelling

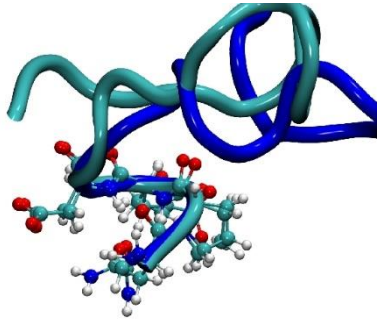
A dedicated tool for structural bioinformatics

What contribution(s) for biologists and biochemists ?

Computational Microscope

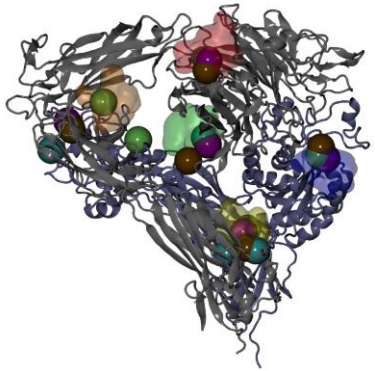
Atomic and molecular insight

Axis 1 Structural characterization – Structure activity relationship



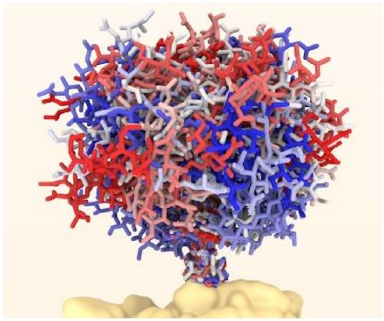
Molecular Dynamics
Energy minimization
Normal mode analysis

Homology modelling
Molecular Dynamics
Molecular docking



Axis 2 Interactions between matrikines and ECM proteins

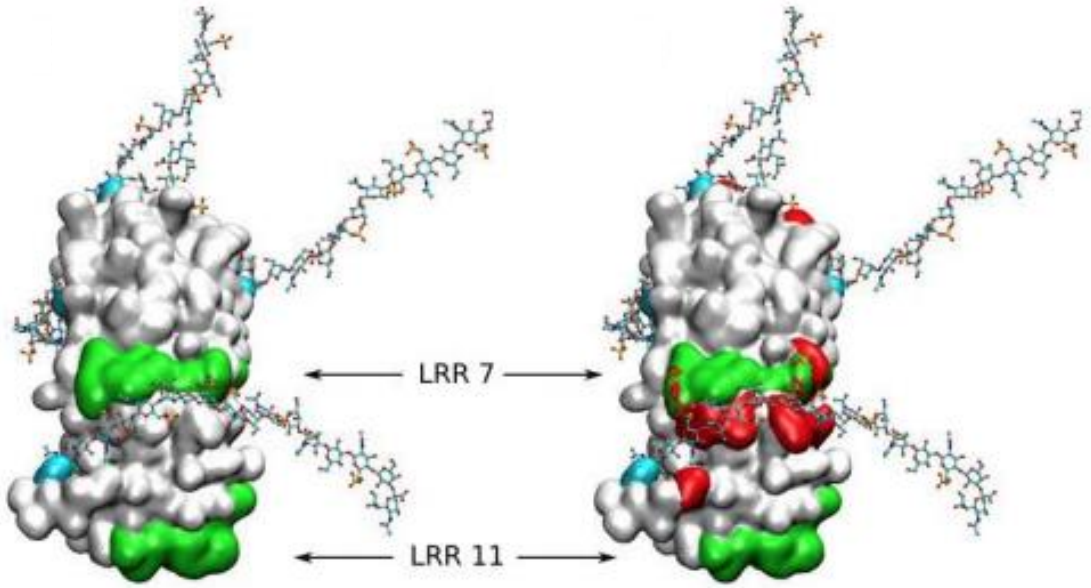
Axis 3 Methodological developments



Computationnal distributions
New methods of analysis and representation

Discussion with experimentalists / needs analysis / choice of methods and models

HPC contribution

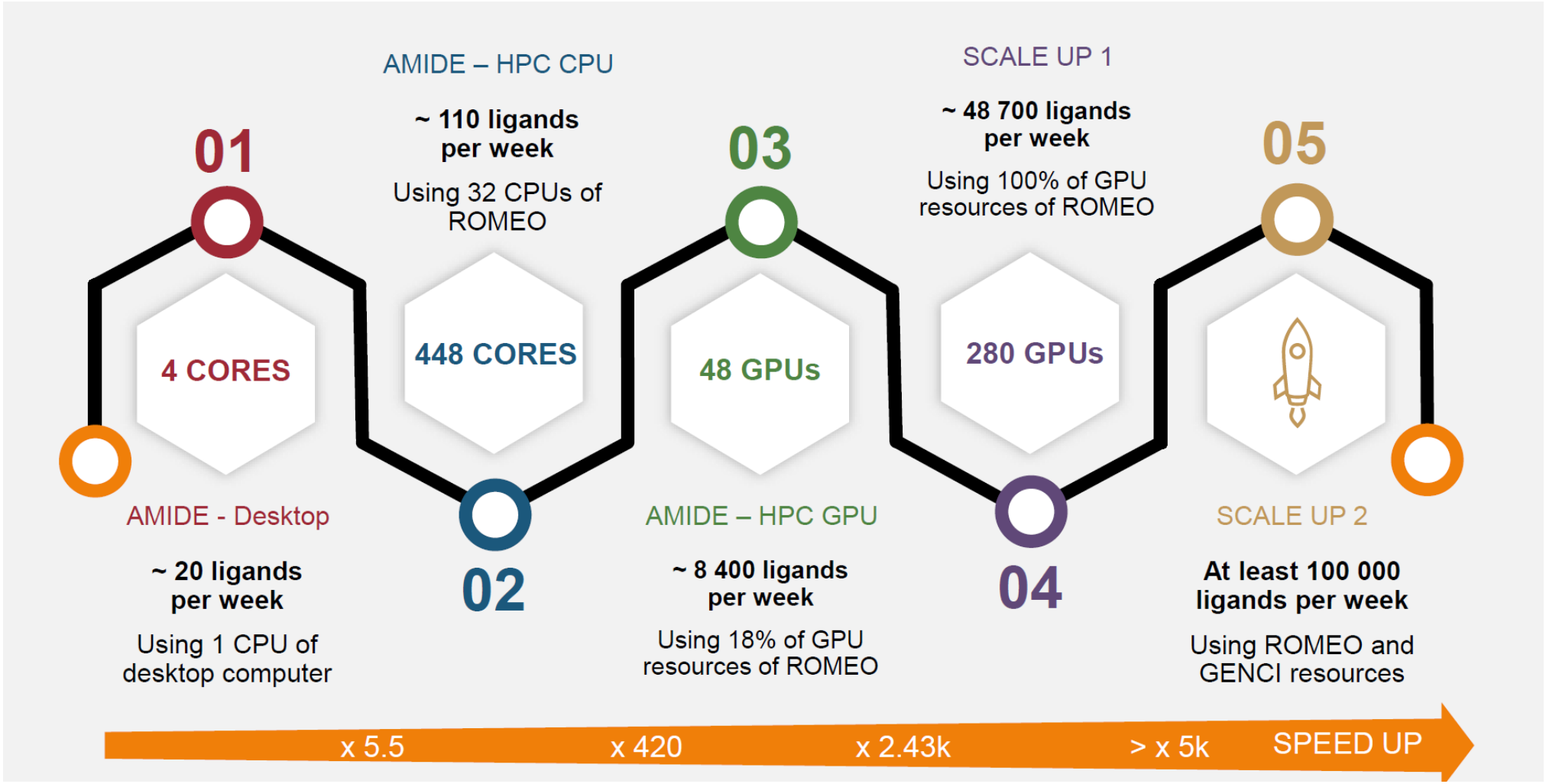


Glycosylated FMOD

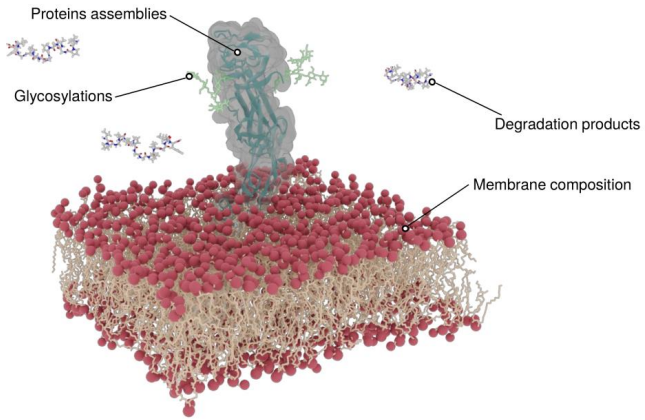
System consisting of 258,934 atoms in a truncated octahedron PBC box. Protein described by Amber-sb14 force field; glycans described by GLYCAM-06 force field.

Time of simulation (ns)	CPU core time (in hours/MPI process)	Remarks
63	2304	On ROMEO-2018 HPC; 8 hours for 288 MPI processes
200	7,084	Cost for simulation of a single replicate
2400	84,960	Cost for 12 simulations
180	6,400	Cost for calculation of binding energy for FMOD-Collagen II complex under different glycosylation conditions (9 simulations of 20ns each)

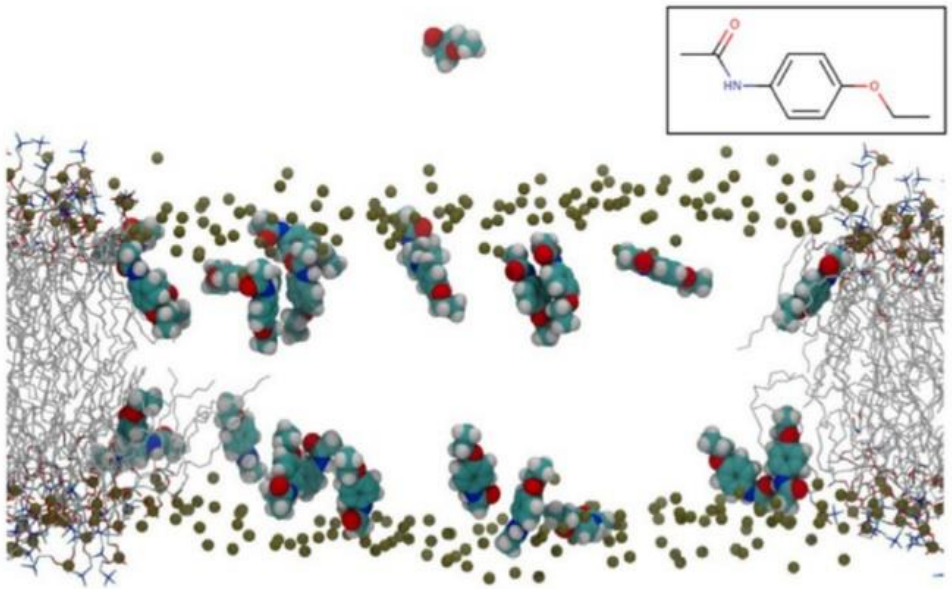
HPC contribution

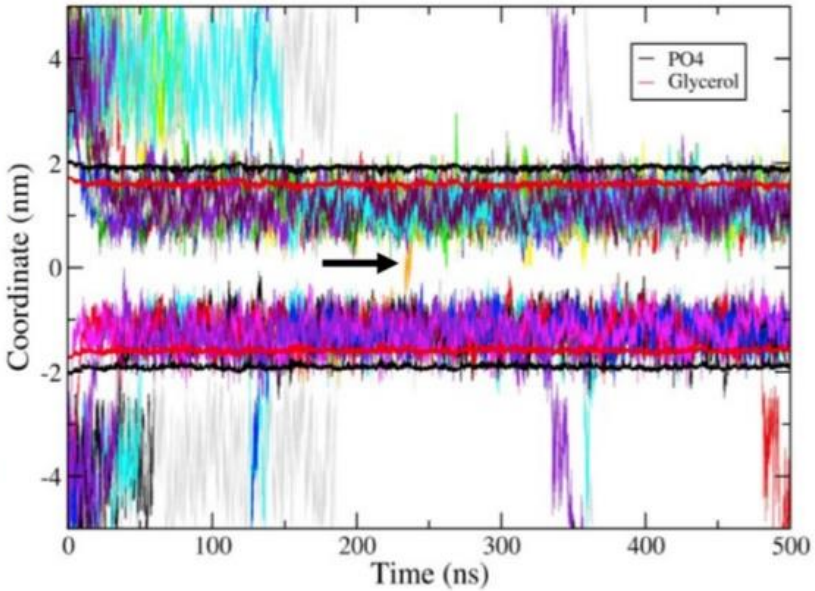


Description of molecular dynamics and interactions



Interaction at the membrane





	POPC	DPPC	DPPC:CHOL (90:10)
COC – CON	0.12	0.06	0.08
CON – CON	3.39	2.96	4.97
CON – Phosphate	8.66	7.64	5.61
CON – Glycerol	21.37	23.77	23.30
COC – Cholesterol			0.45
CON – Cholesterol			1.00
CON – water	127.88	112.94	106.20
COC – water	14.94	9.73	6.19

Insertion and interaction of phenacetin molecules with the lipid bilayer

Phenacetin molecule is able to cross the lipid bilayer

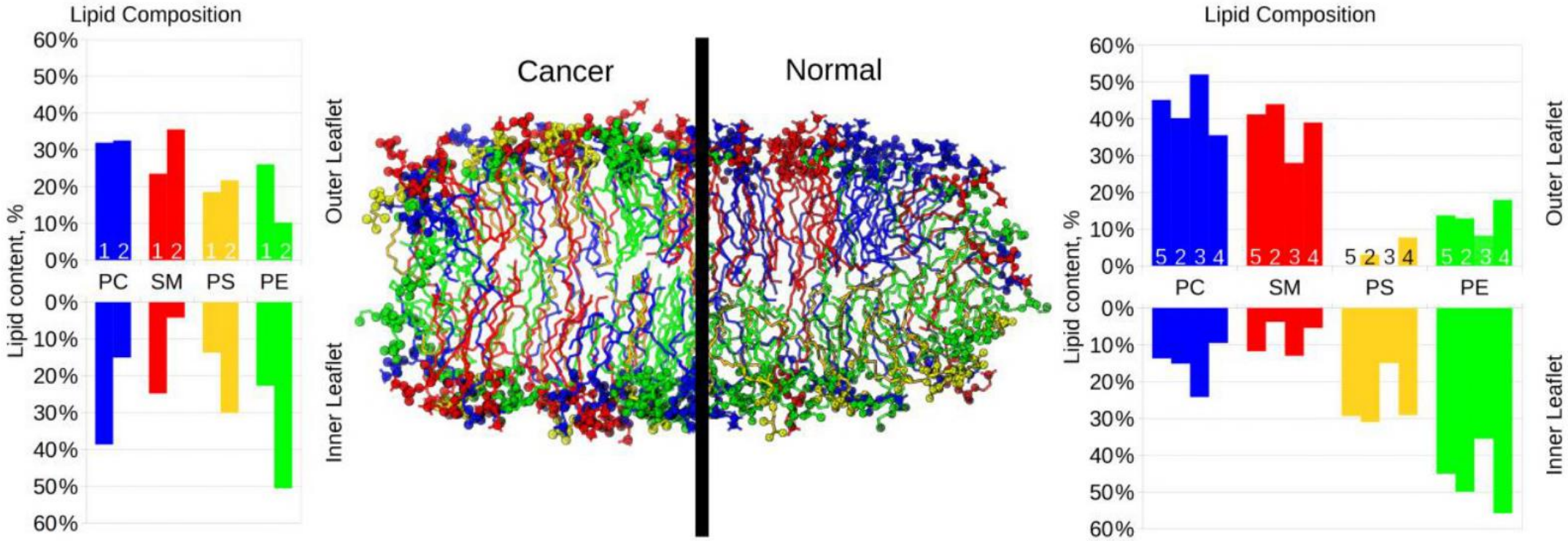
Phenacetin molecule adopted a specific orientation in the membrane

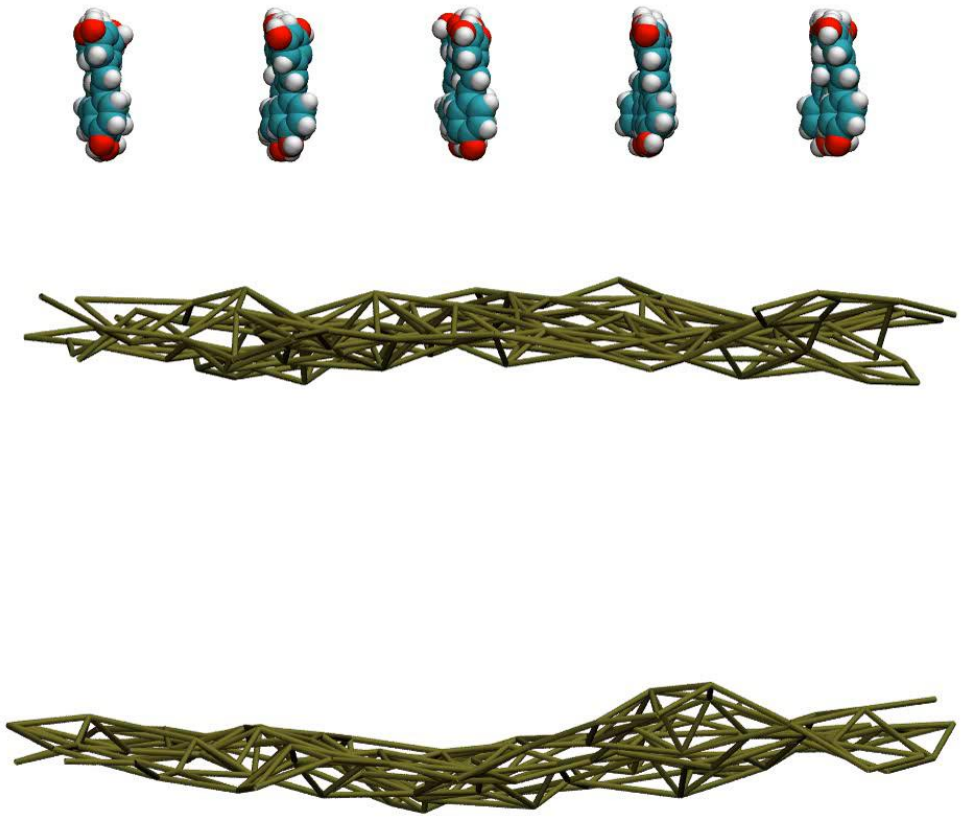
Phenacetin molecule formed hydrogen bonds

Fuselier et al. *Low-diluted Phenacetinum disrupted the melanoma cancer cell.* **Scientific Reports 9:9109 (2019)**

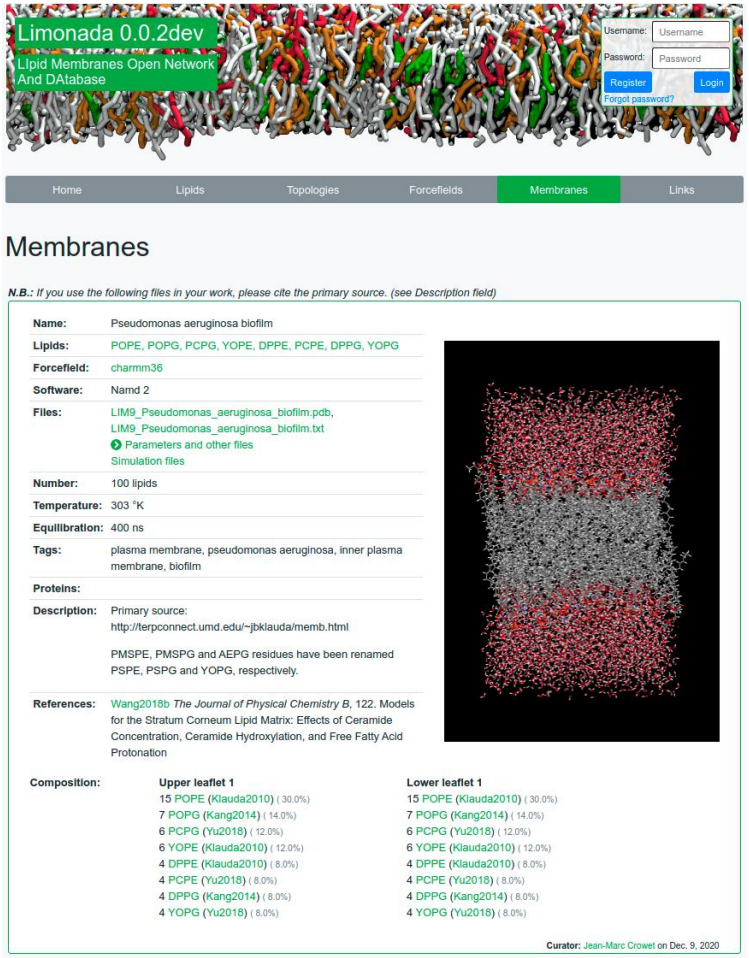
Membrane composition

Knowledge of the membrane environment → better understanding of membrane-residing protein behavior.





Elaboration of specific databases

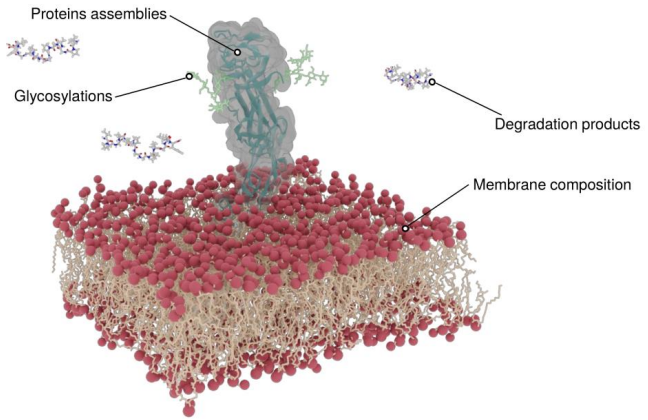


LIMONADA database
Lipid **M**embrane **O**pen **N**etwork **A**nd **Da**tabase
(https://limonada.univ-reims.fr/)

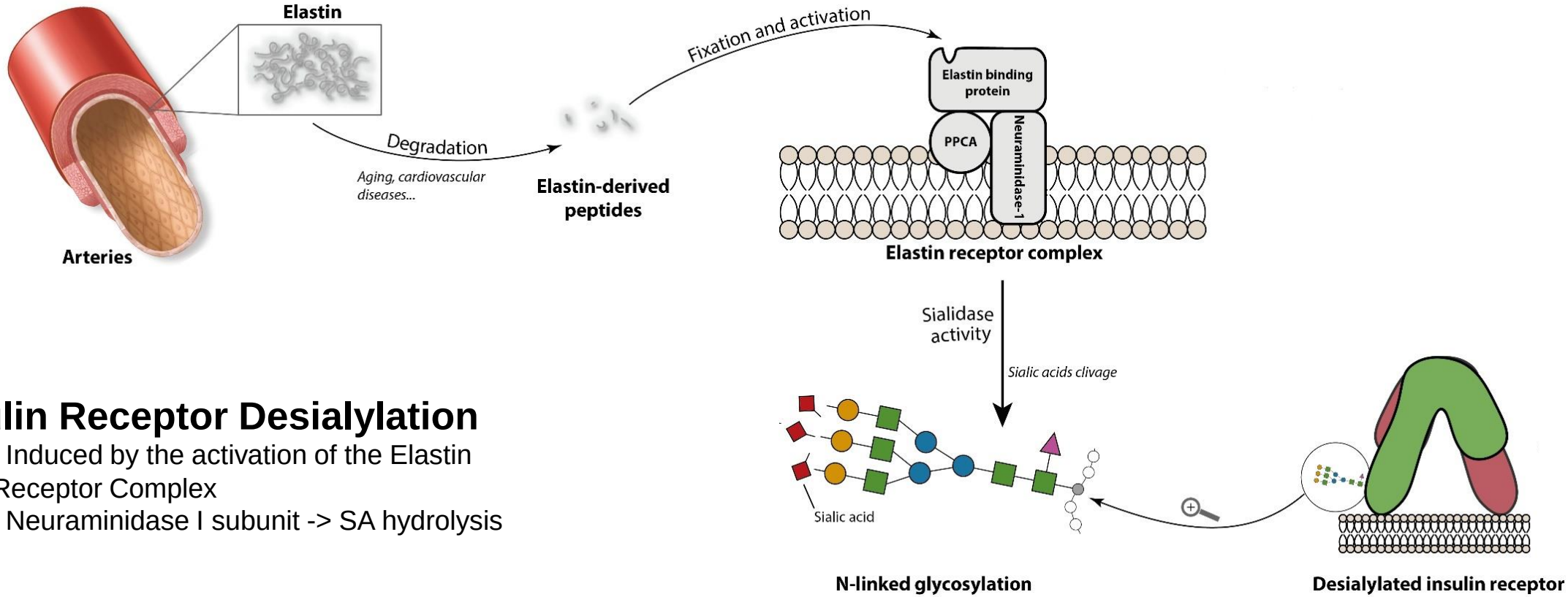
Gathers published membrane patches and simulation files associated to cellular membrane models

Crowet et al. *LIMONADA: a database dedicated to the simulation of biological membranes.* **Journal of Computational Chemistry 42(14):1028-1033 (2021)**.

Effect of post translational modifications



Ageing and consequences



Insulin Receptor Desialylation

· Induced by the activation of the Elastin Receptor Complex

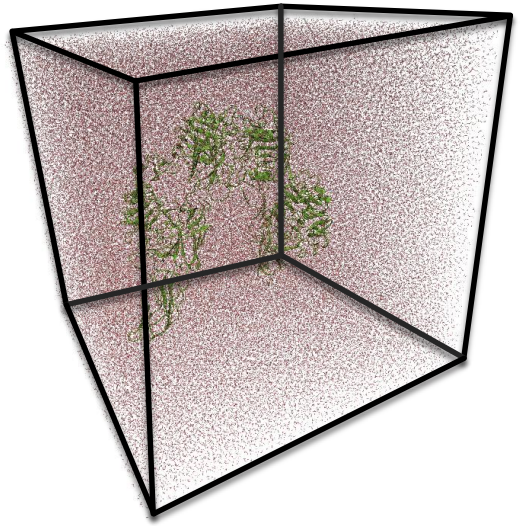
· Neuraminidase I subunit -> SA hydrolysis

Blaise S. et al., *Elastin-derived peptides, new regulators of insulin resistance development in mice.* **Diabetes 62, 3807-16 (2013).**

INSULINORESISTANCE (Type 2 diabetes)

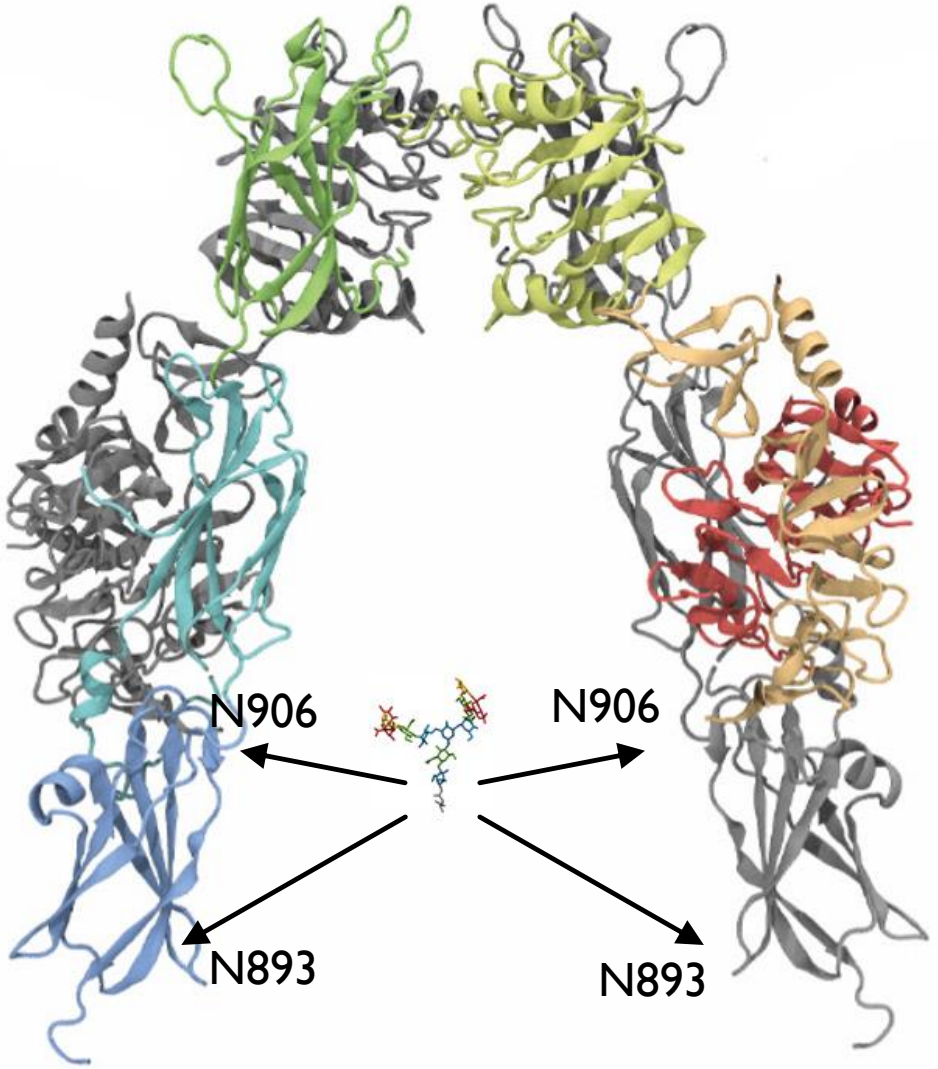
Minimum size to be studied

Ng-c

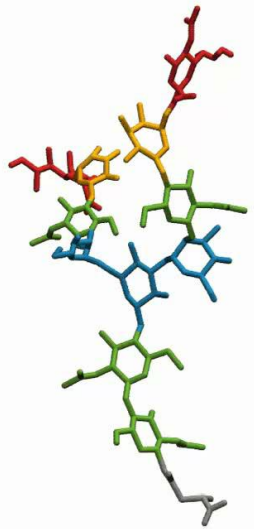


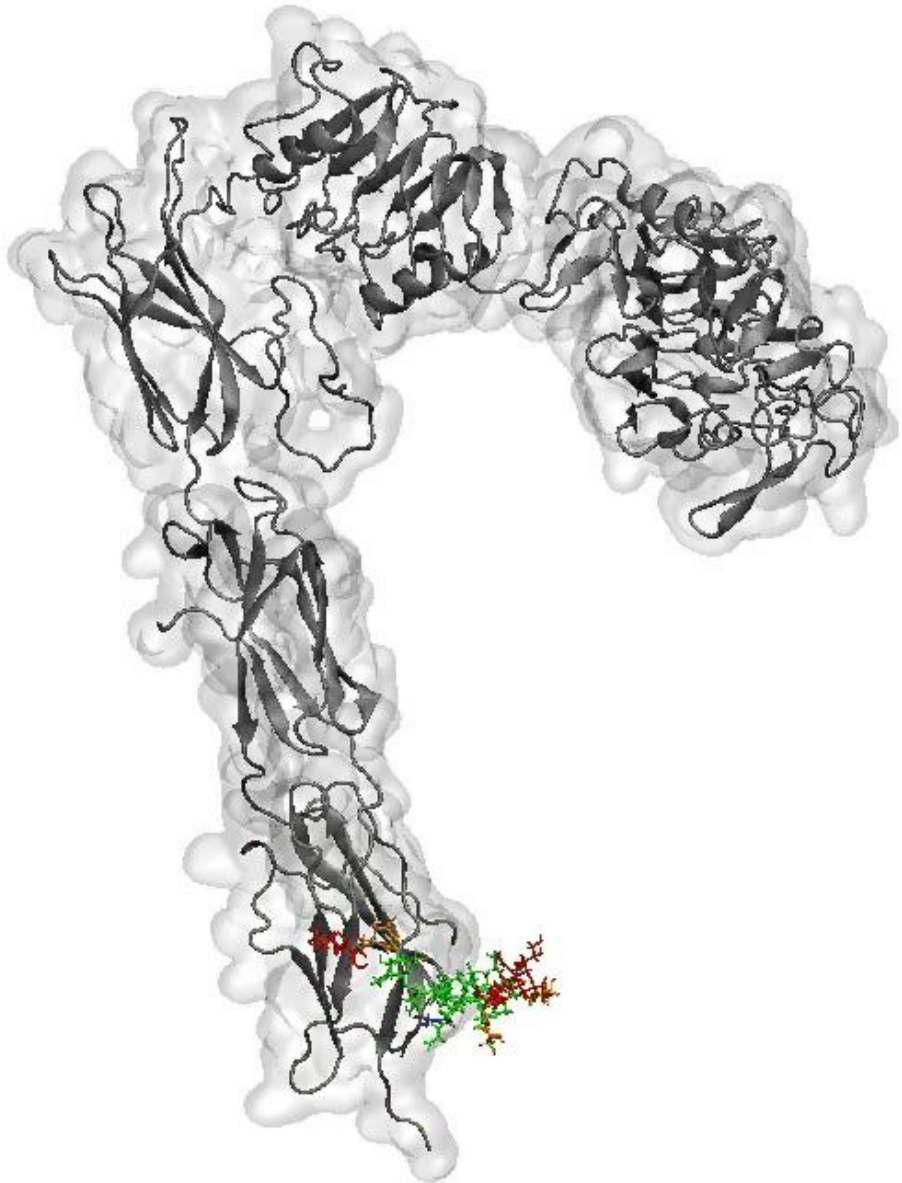
Ng-c + RI

620 000 atoms
320 CPU
500 ns ↔130 h

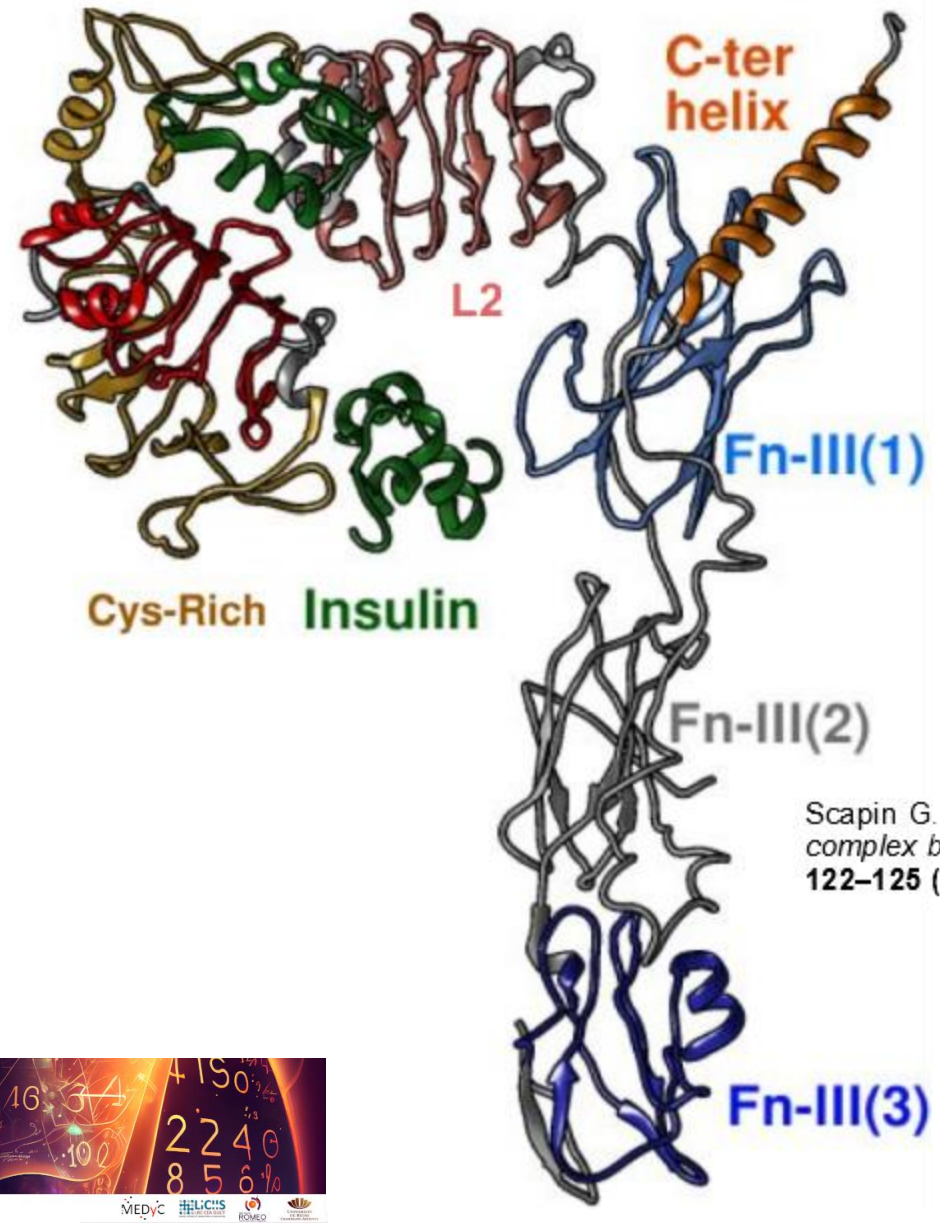


Minimum size to be studied





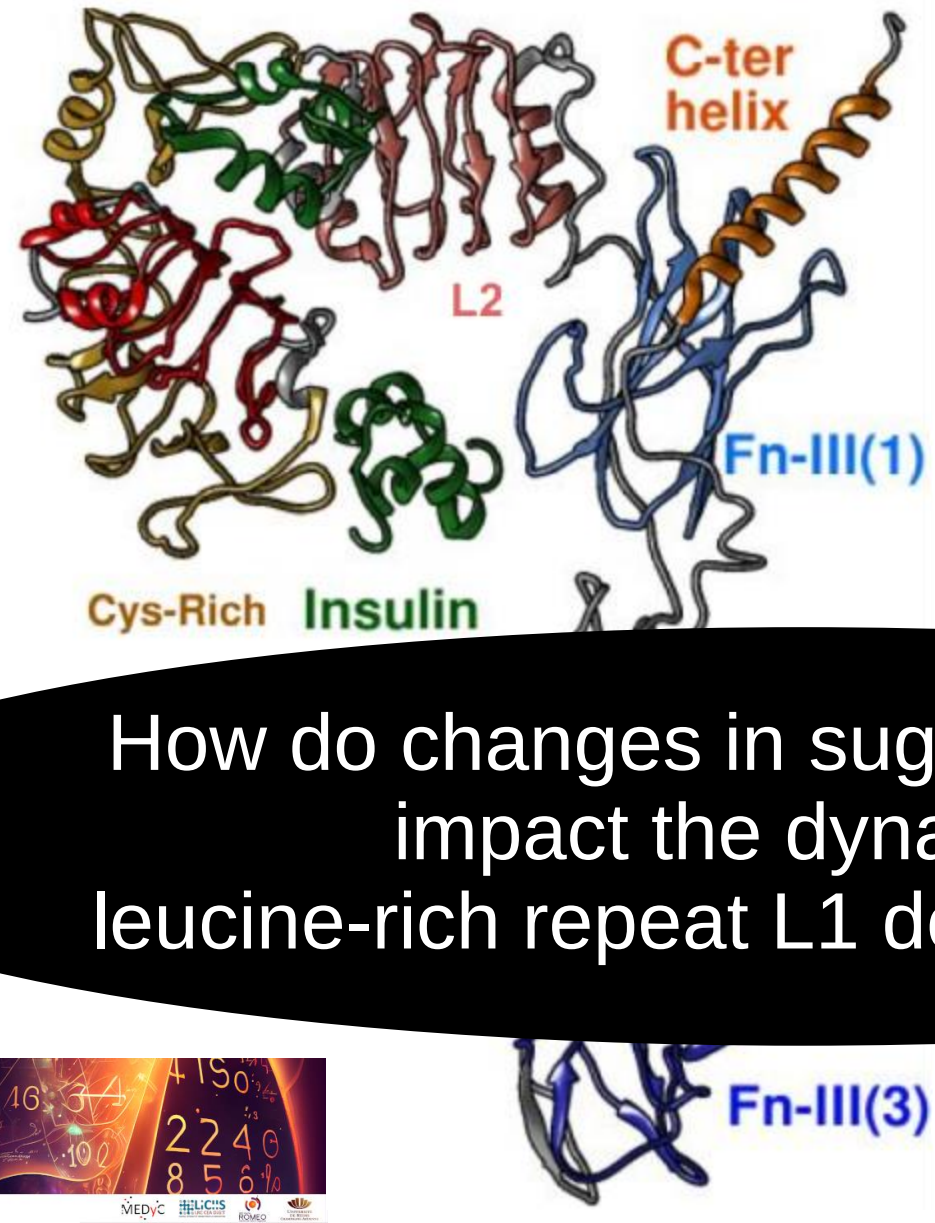
Desialylation of the Insulin Receptor



Human IR Ectodomain
(PDB:6SOF)

Scapin G. et al., *Structure of the insulin receptor–insulin complex by single-particle cryo-EM analysis*. **Nature 556, 122–125 (2018)**.

Desialylation of the Insulin Receptor



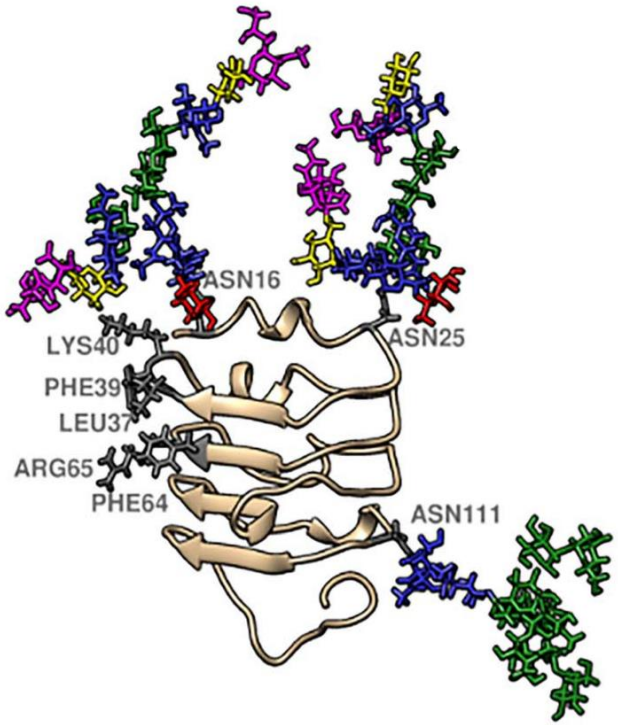
Human IR Ectodomain
(PDB:6SOF)

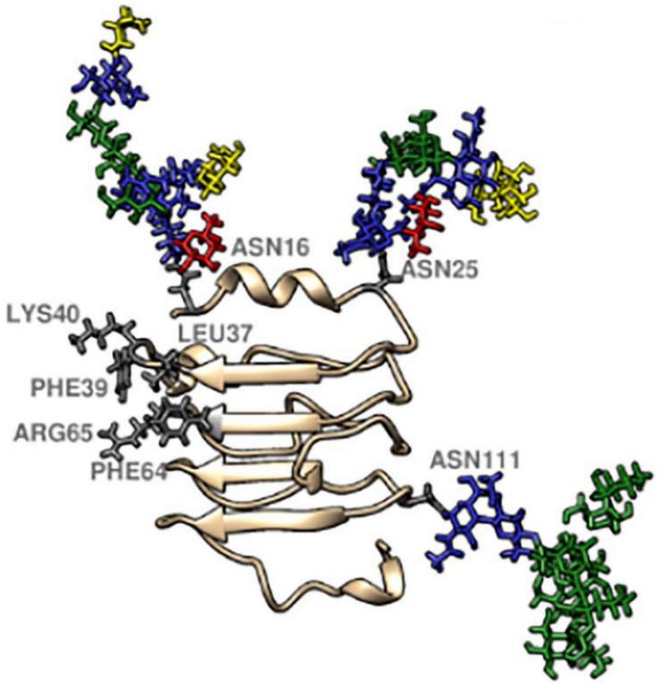
How do changes in sugars composition
impact the dynamics of
leucine-rich repeat L1 domain of the IR?

Desialylation of the Insulin Receptor

IR L1 domain

Glycosylated asparagines, along with insulin-binding residues, as identified from cryo-EM studies are represented





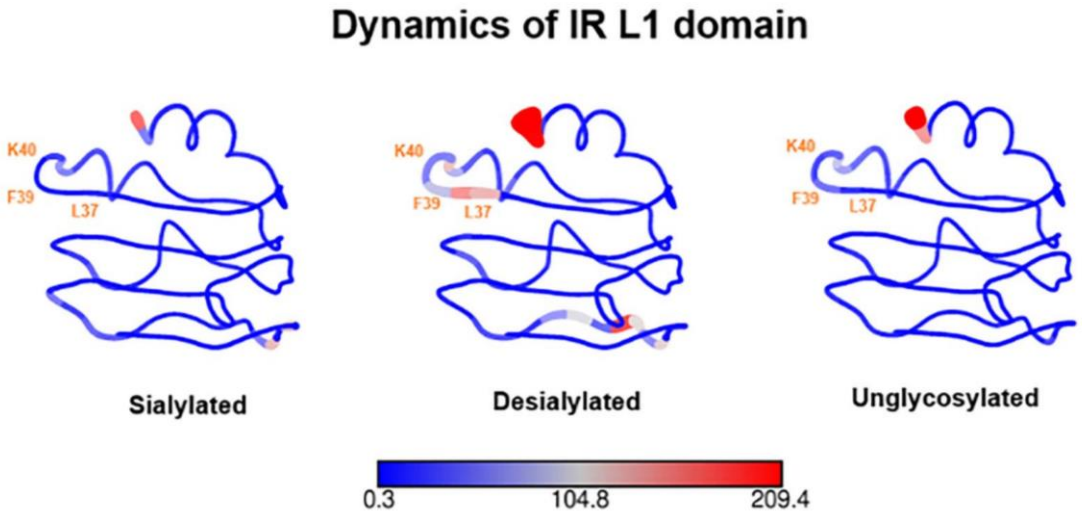
MD experiments

Gromacs MD simulation package
Charmm36 force field
NPT Simulations (T = 303 K, P = 1 bar)
TIP3P explicit water model
Human IR L1 domain (PDB: 4ZXB)
→ L1+Sialylated glycans (1µs);
→ L1+desialylated glycans (1µs);
→ unglycosylated L1 domain (1µs)

Scapin G. et al., *Structure of the insulin receptor–insulin complex by single-particle cryo-EM analysis*. **Nature 556, 122–125 (2018)**.

Croll TI. Et al., *Higher-resolution structure of the human insulin receptor ectodomain: multi-modal inclusion of the insert domain.* **Structure 24, 469–476 (2016)**.

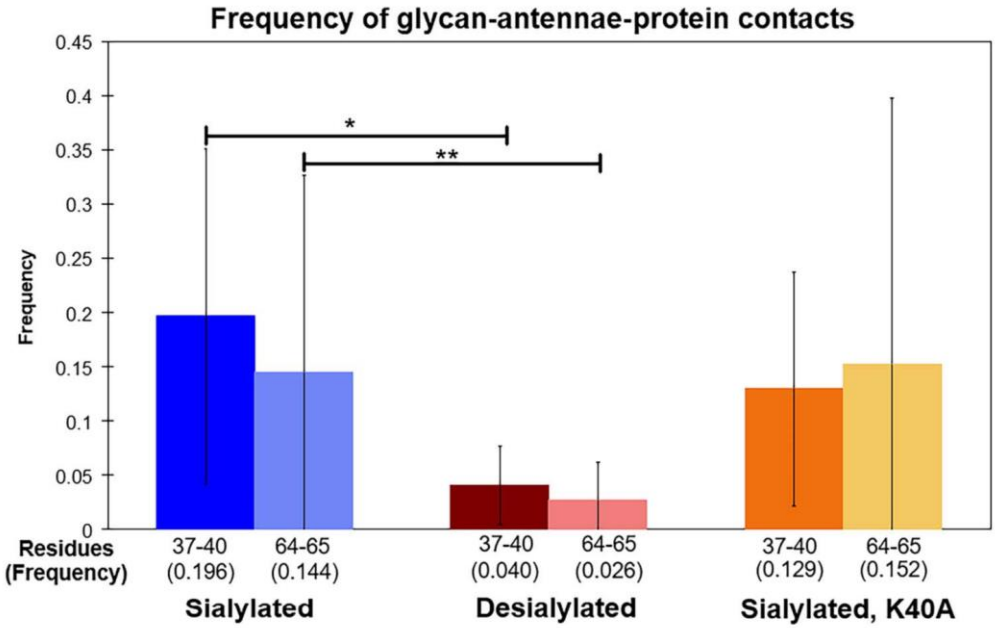
Impact of the desialylation on L1 domain



Analyses of protein dynamics by PCA

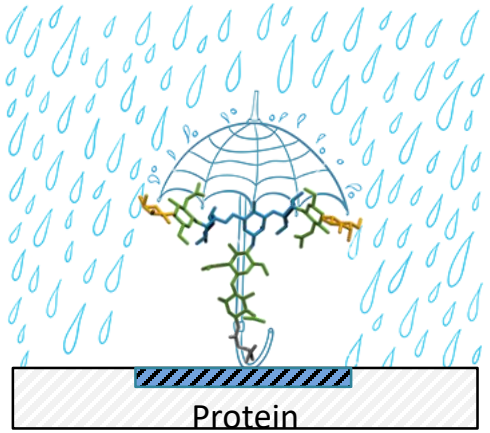
Upon desialylation, insulin binding residues are perturbed in a dynamic way

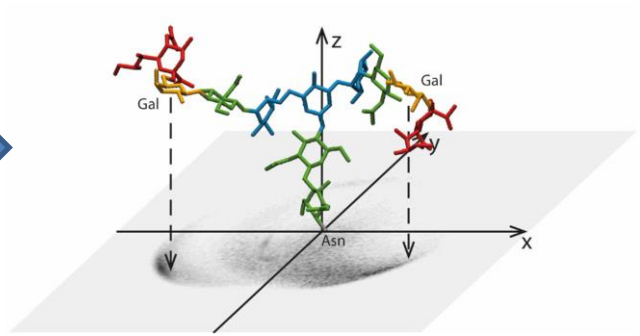
Glycan-protein interactions are modified



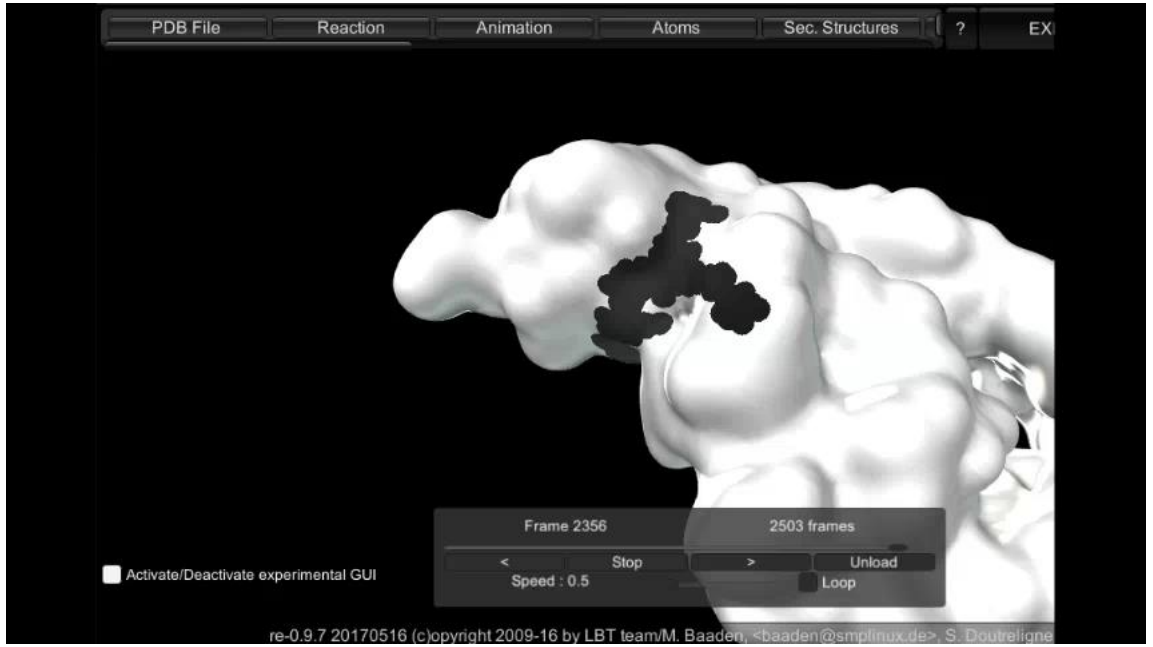
Rao R., et al., *Effects of changes in glycan composition on glycoprotein dynamics: Example of N-glycans on insulin receptor.* **Glycobiology 31(9), 1121-1133 (2021).**

Desialylation and protein accessibility





Lack of tools dedicated to the study of glycosylations

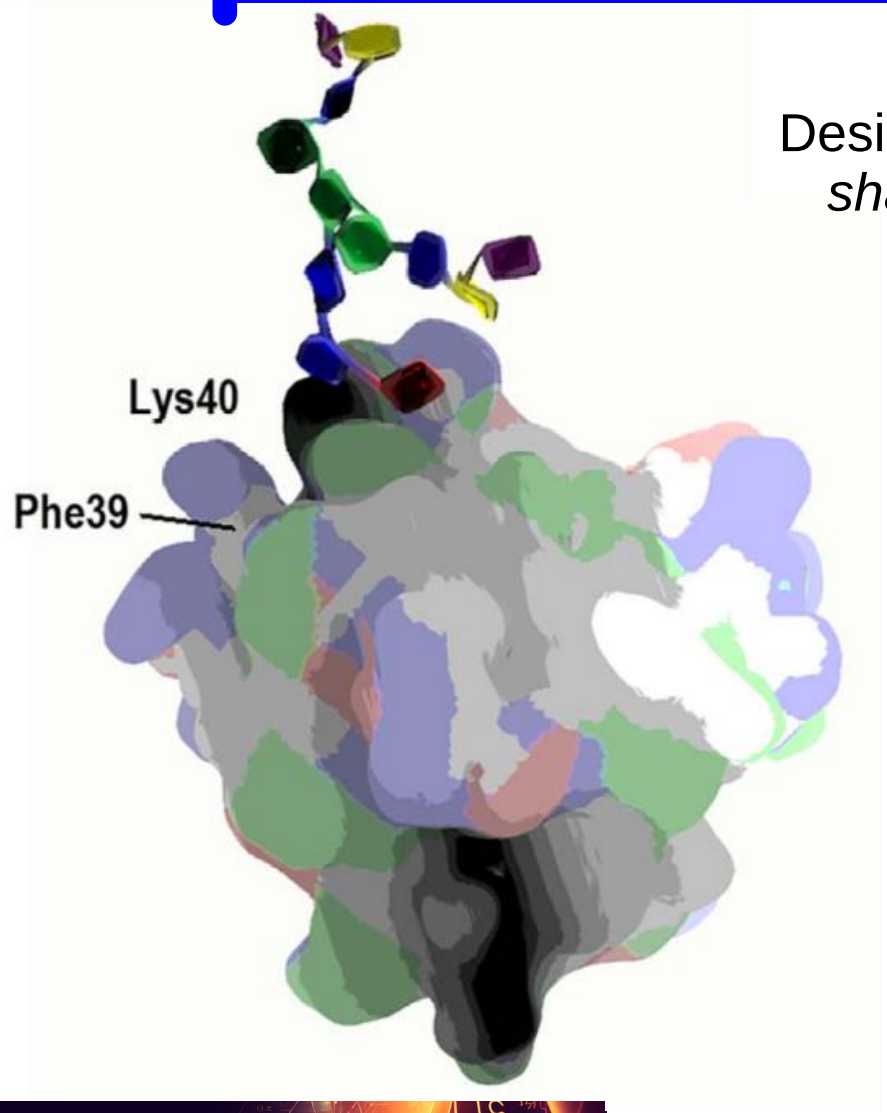


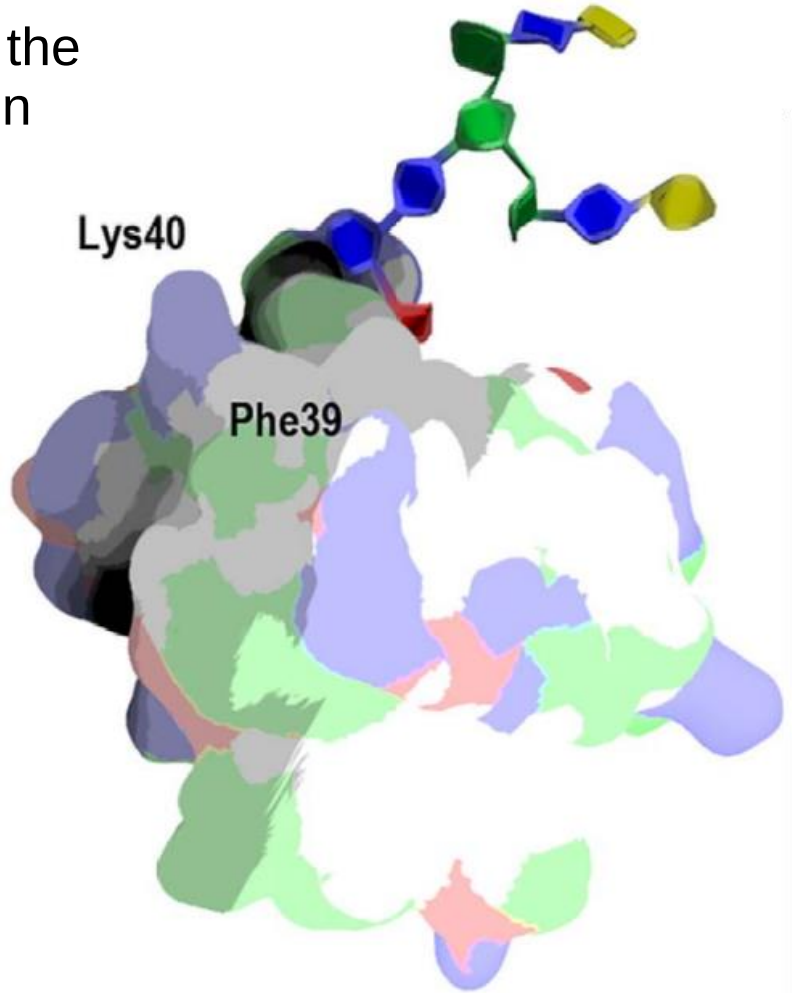
Besançon C. et al., *New visualization of dynamical flexibility of N-Glycans : Umbrella Visualization in UnityMol*. **IEEE International Conference on Bioinformatics and Biomedicine (BIBM), 291-298 (2019)**

Besançon C. et al., *Umbrella Visualization: a method of analysis dedicated to glycan flexibility with UnityMol*. **Methods 173, 94-104 (2020)**

Impact of the desialylation on L1 domain

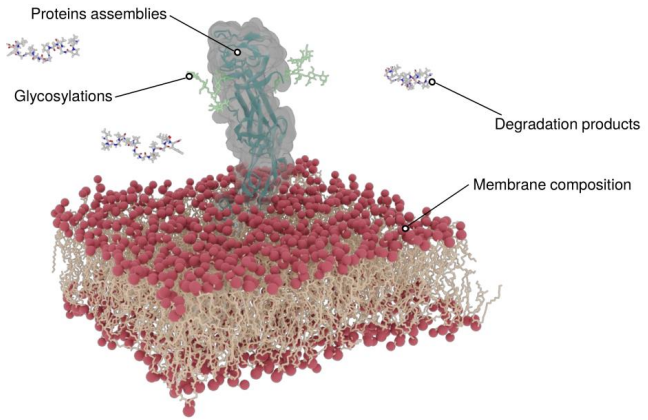
Desialylation modifies the *shadowed* L1 domain





Rao R., et al., *Effects of changes in glycan composition on glycoprotein dynamics: Example of N-glycans on insulin receptor.* **Glycobiology 31(9), 1121-1133 (2021).**

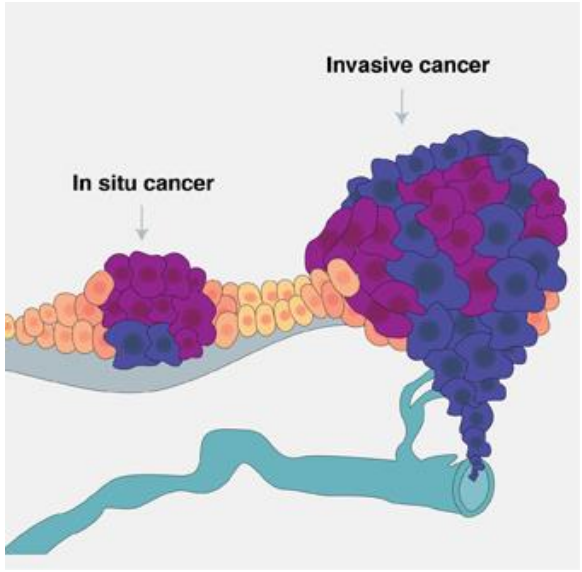
Towards the mesoscopic description scale



Basement membrane

Basement membrane is part of the ECM

Connection of the cells to the matrix



Basement membrane → hard to study
Composed of molecules that are in the mesoscopic scale

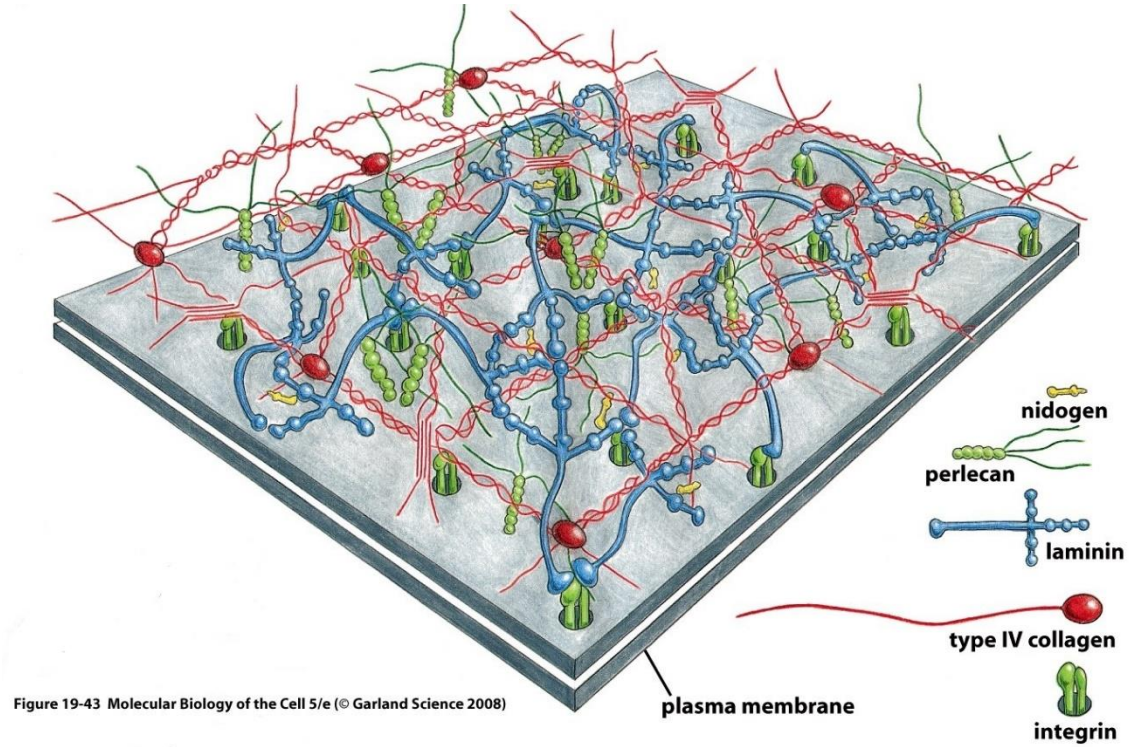
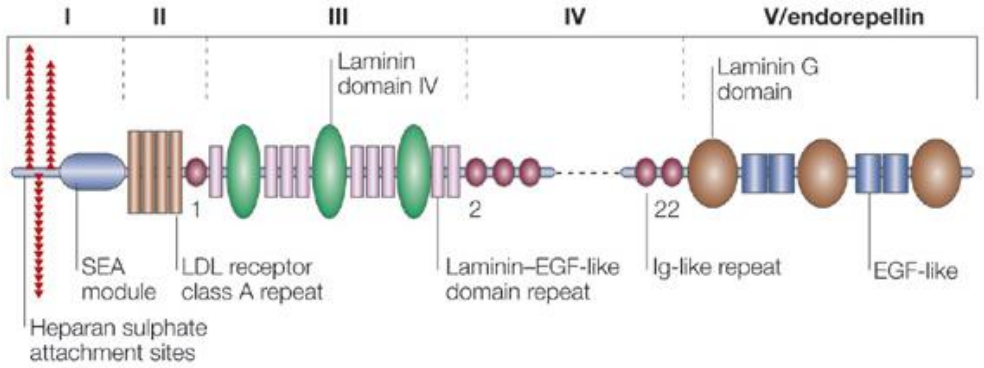


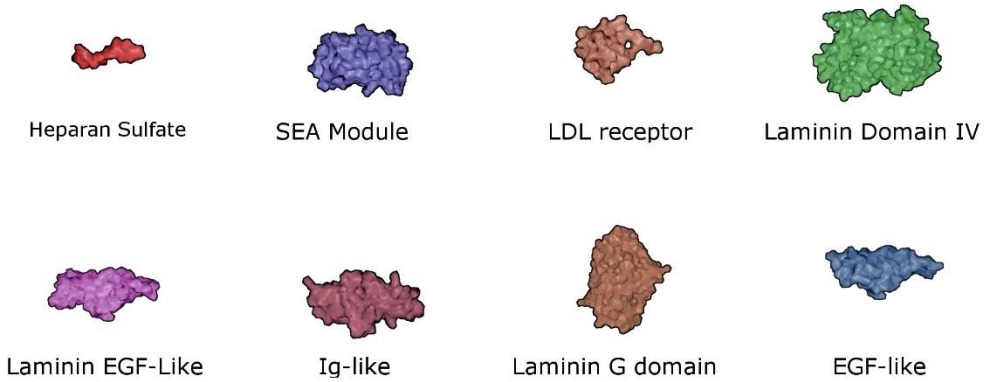
Figure 19-43 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Building of molecules

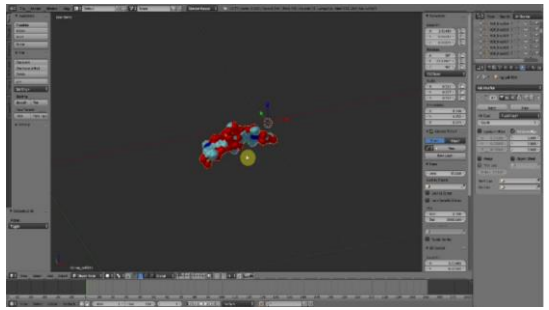
Mesoscales objects are too small to be seen with a microscope but are still too big to be resolved using techniques like crystallography



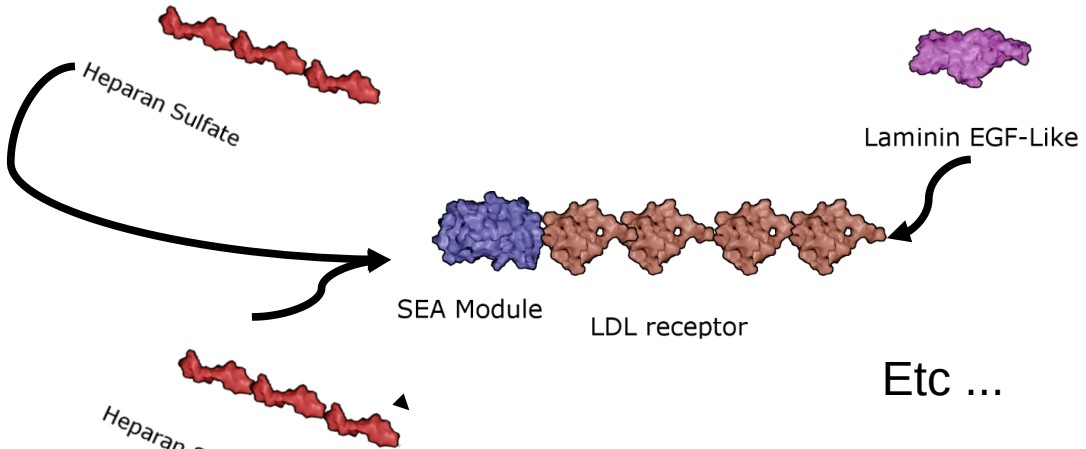
Schematic molecular sructure of perlecan



The different domains have been resolved experimentally

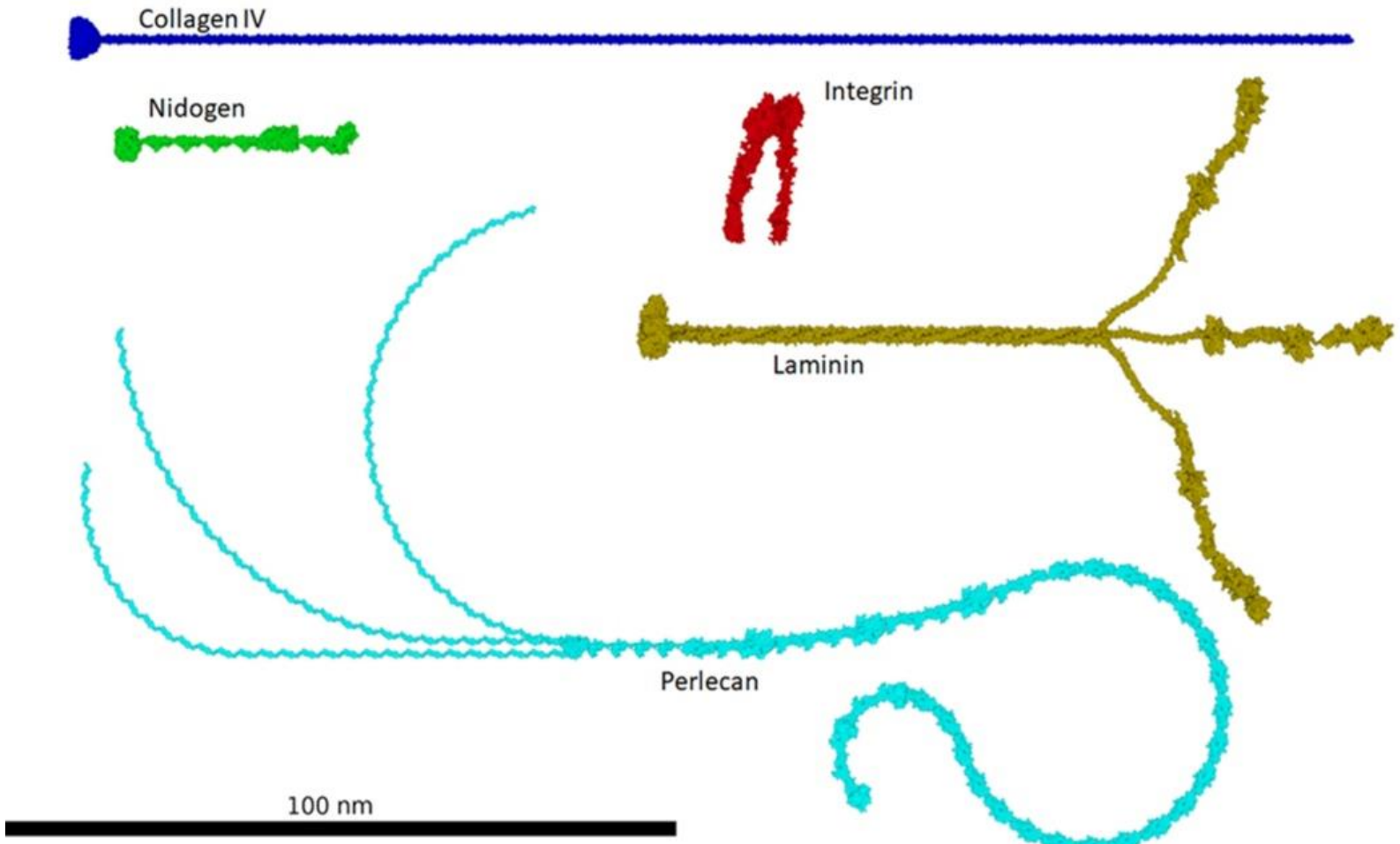


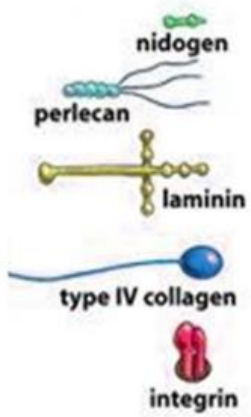
www.blender.org

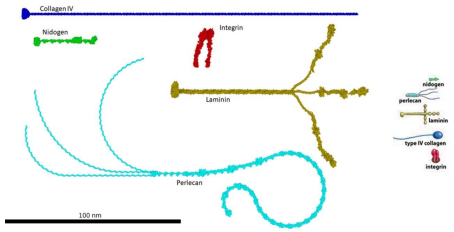


Etc ...

Glimpse at the dynamics



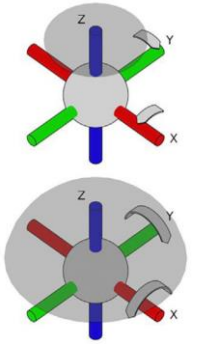




Glimpse at the dynamics

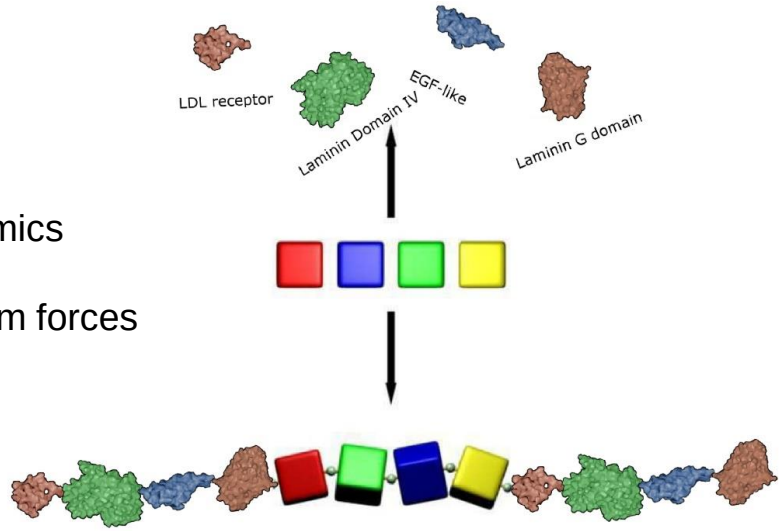
Rigid body dynamics

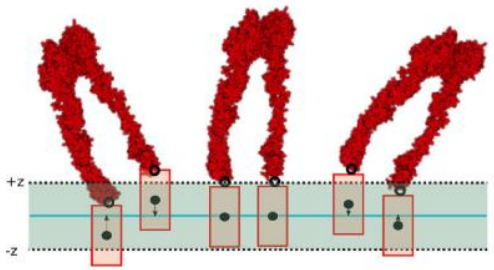
Link together rigid molecular ingredients
to form dynamic body chains



Universal joint
rotational constraint

Langevin dynamics
=
Viscosity and random forces

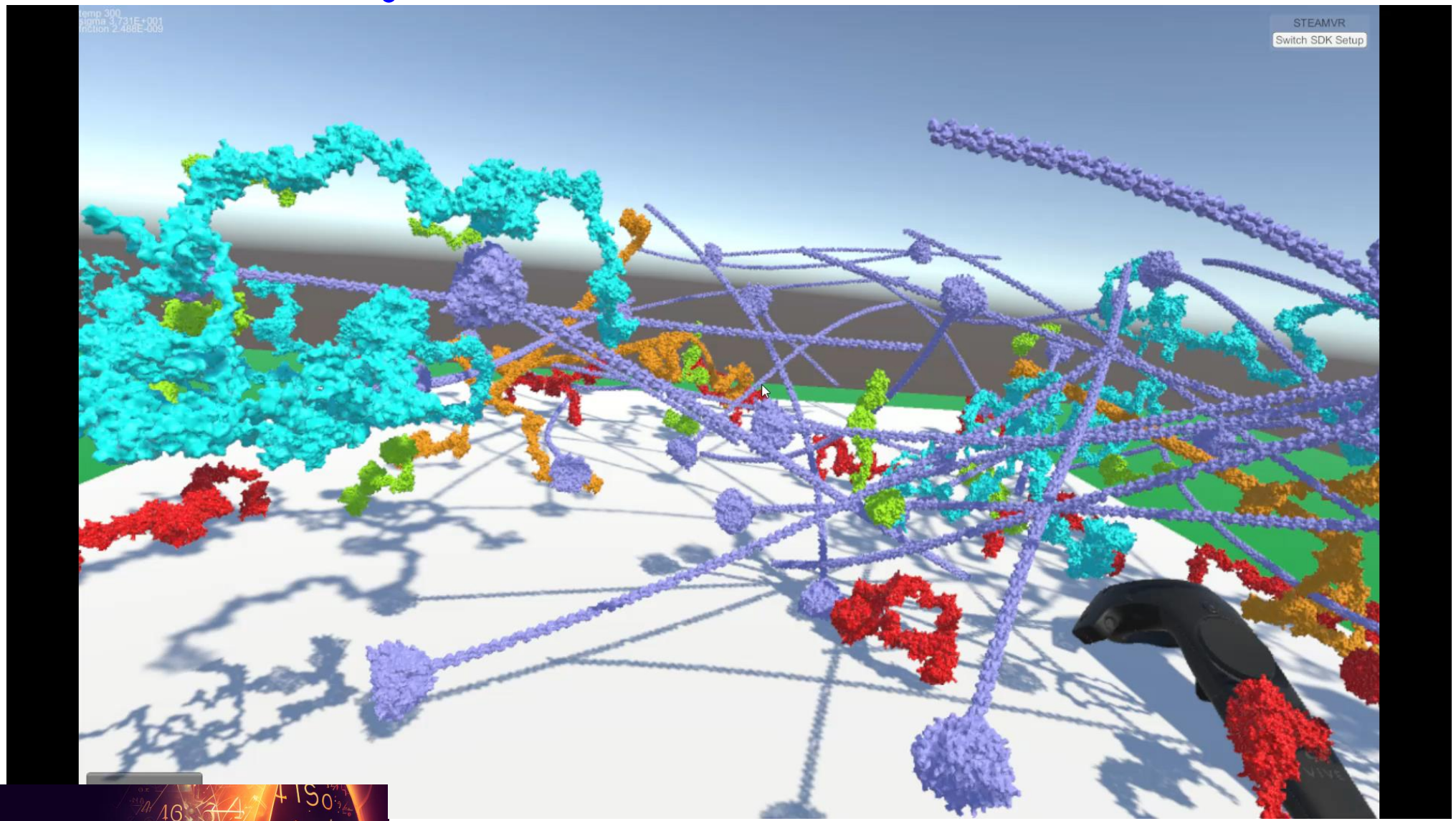




$$C_z = 0.5 - \frac{1}{1 + e^{\alpha(|z|-z_0)}}$$

restraint field based on IMPALA (Integral Membrane Proteins and Lipids Association) implemented

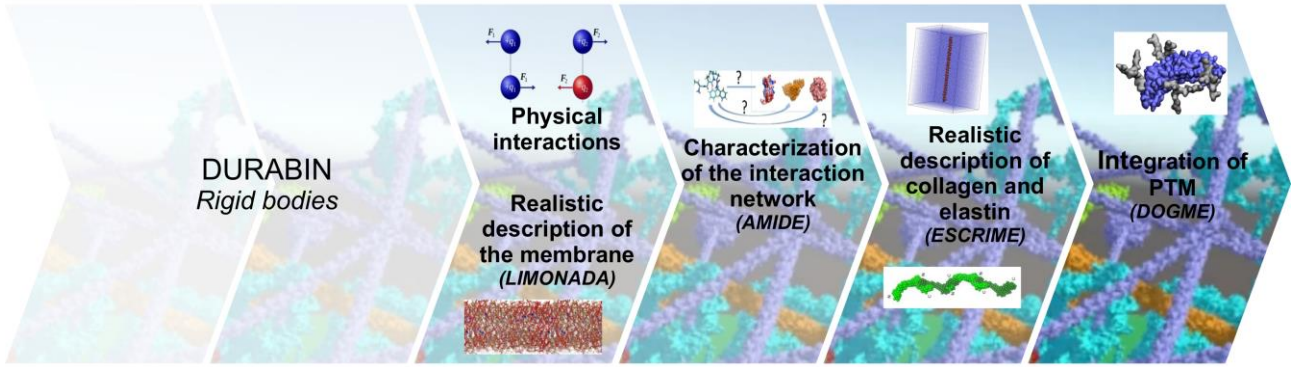
Immersion in the ECM



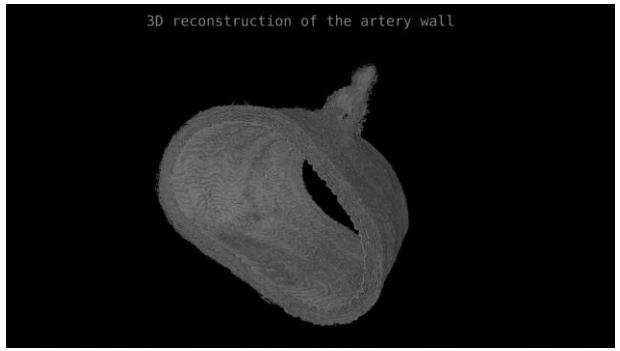
Wong H., et al., *Mesoscopic rigid body modeling of the extracellular matrix self-assembly*. **Journal of Integrative Bioinformatics 15(2) (2018).**
Wong H., et al., *Multiscale modelling of the extracellular matrix.* **Matrix Biology Plus 13, 100096 (2022).**

Conclusion and perspectives

Modeling offers a wide spectrum of techniques allowing scientists to decipher and improve understanding of biological behavior at different scales (from the electronic scale to the mesoscopic scale). *In silico* approaches are of utmost interest to encompass the ECM environement.



Reliable model if it integrates the relevant observables from each of the descriptive scales



A wide range of knowledge associated to atomic and molecular data collected at different scales can be integrated into the DURABIN simulation engine and will thus contribute to improving its reliability provided that the relevant observables are collected for each of the descriptive scales.

Aknowledgements

MEDyC

Université de Reims Champagne-Ardenne

cnrs dépasser les frontières

MAgICS

Maison de la Simulation de Champagne-Ardenne

Centre de Calcul régional Roméo
https://romeo.univ-reims.fr/

Centre Image
http://crestic.univ-reims.fr/centreimage/

Plateau de modélisation moléculaire
https://p3m.univ-reims.fr/

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