# INSIGHT ON AGEING PROCESSES EFFECTS IN COLLAGEN I USING MOLECULAR DYNAMICS

JCAD 2023
03/10/23

Zara MSOILI, PhD student

Matrice Extracellulaire et Dynamique Cellulaire (MEDyC)

UNIVERSITÉ DE REIMS CHAMPAGNE-ARDENNE

cnrs

MEDyC

A WORLDWIDE AGEING PROSPECT

2015

2050

■	0-9%
■	10-19%
■	20-24%
■	25-29%
■	30+%
■	No data
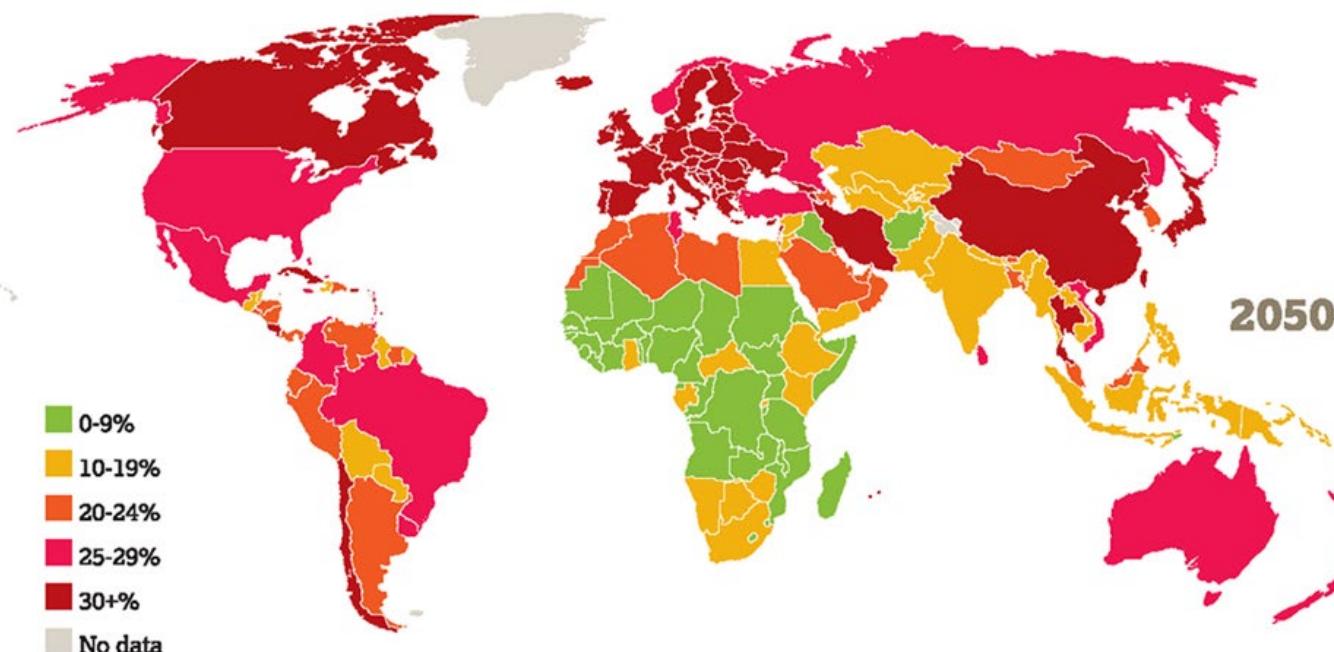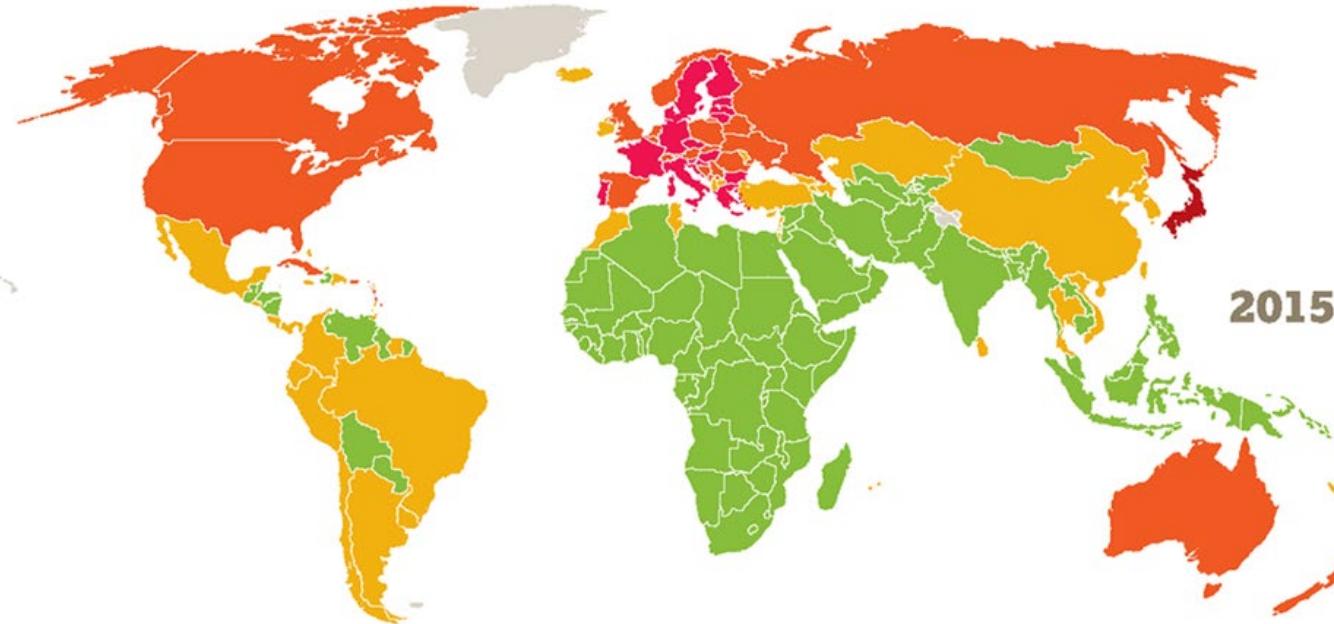
Source: UNDESA Population division, World population prospects: the 2015 revision, DVD Edition, 2015.
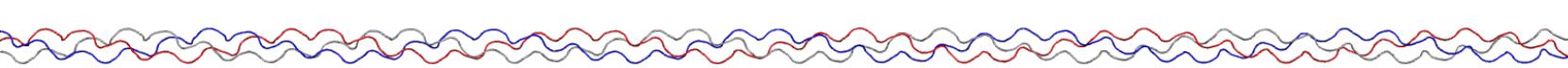
DEFINING AGEING

Ageing

The process of growing old or developing the appearance and characteristics of old age (Collins Concise English Dictionary)

Biological ageing

Accumulation of molecular and cellular damage

3

COLLAGENS, CARBAMOYLATION AND AGEING
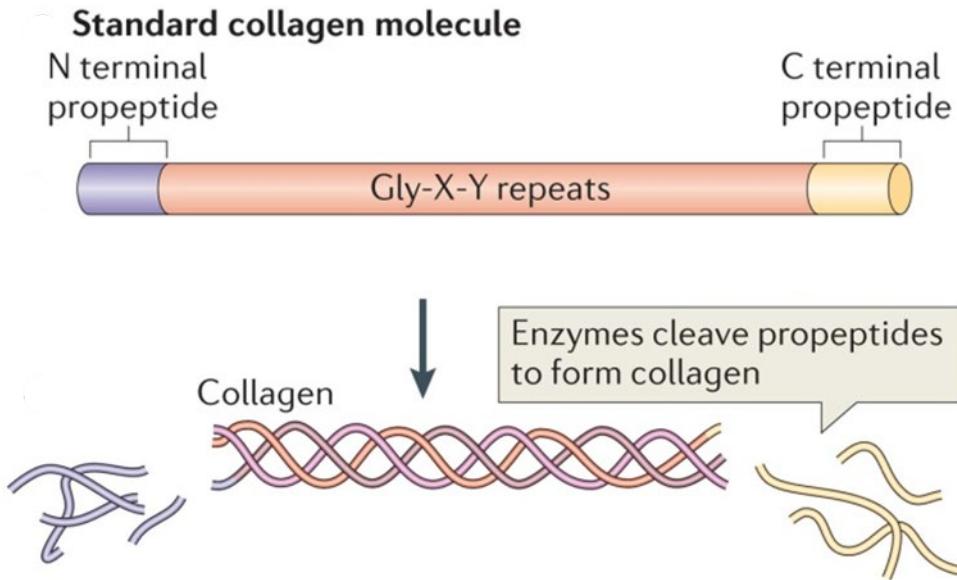
Mouw et al. , *Nat Rev Mol Cell Biol*, 2014
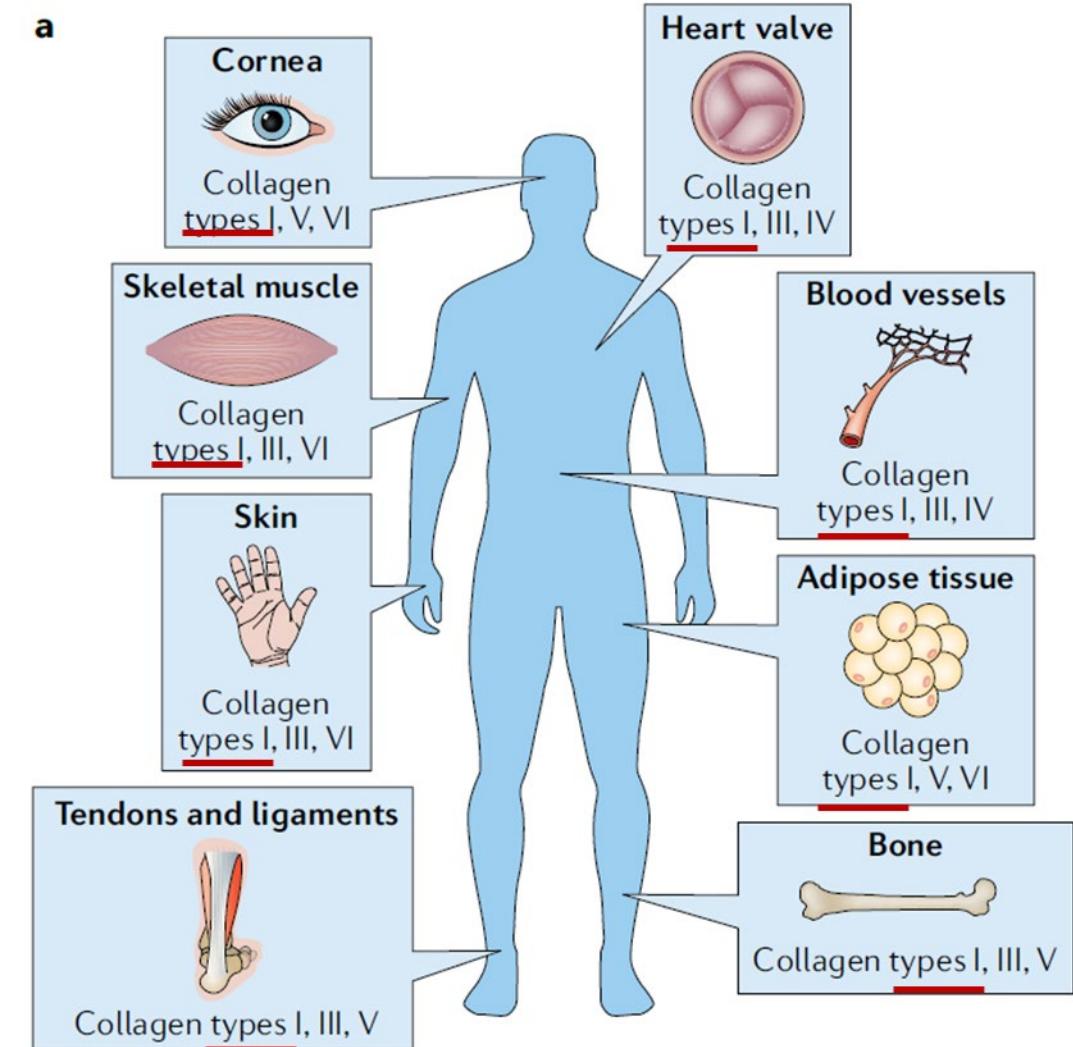
Bielajew *et al.* , *Nat Rev Mats*, 2020

# POST-TRANSLATIONAL MODIFICATIONS (PTM) ALLOW PROTEIN DIVERSITY/VARIABILITY

Definition

Biochemical modification occurring on one or more amino acids after the translation *(Guide to Research Techniques in Neuroscience (Second Edition), 2015)*

Implication

- Protein diversity

- Enzymatic or nonenzymatic

- Alteration of structure and function

- Reversible or irreversible

- Exemples : glycation, phosphorylation, acetylation…

COLLAGENS, CARBAMOYLATION AND AGEING

Lysine

Homocitrulline
(Hct)

Jaisson *et al.* , *Clinical Chemistry*, 2011
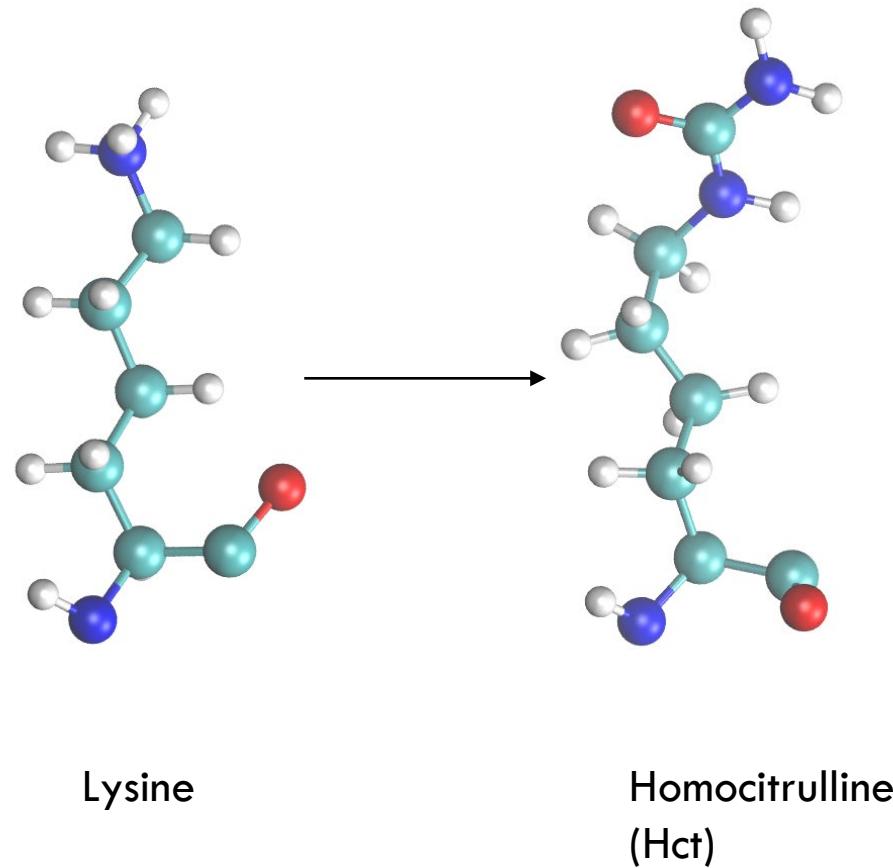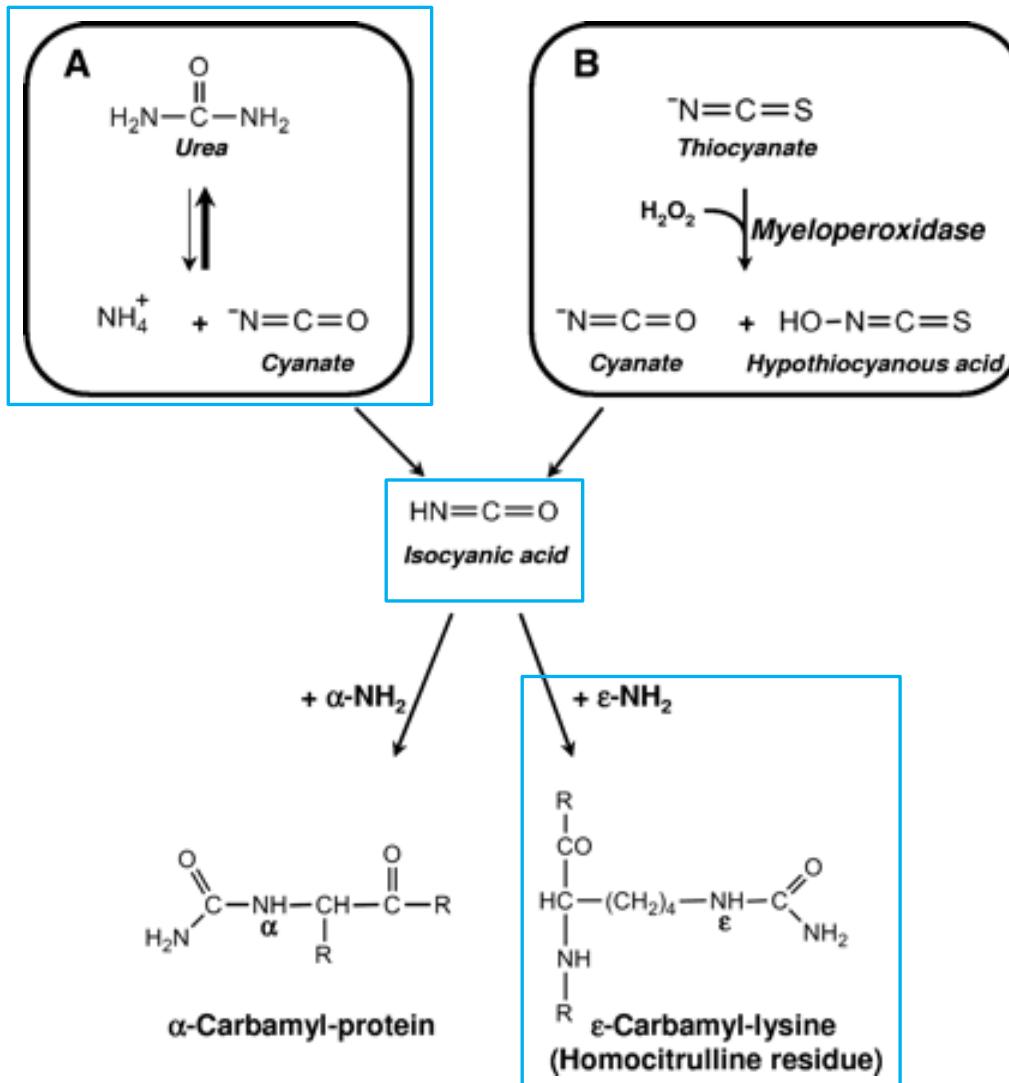
MOLECULAR MODELLING OF COLLAGEN I TRIPLE HELIX

- **Interactive Triple-Helical collagen Building Script** (THeBuScr)[1] and SIDEpro[2]

- FASTA sequences of human COL1A1 and COL1A2 (UniProtKB code: P02452 and P08123).

- Chaînes A (α1) and C (α1) : residues 179-1192

- Chaîne B (α2) : residues 91-1104

2898 Å
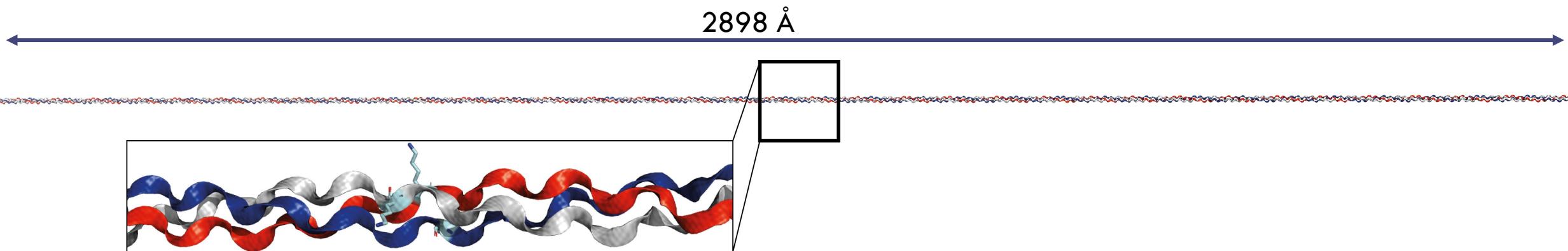
[1] J.K. Rainey et al., *Bioinformatics*, 2004.
[2] Nagata et al. , *Proteins*, 2012

Ace-HCT-Nme structure
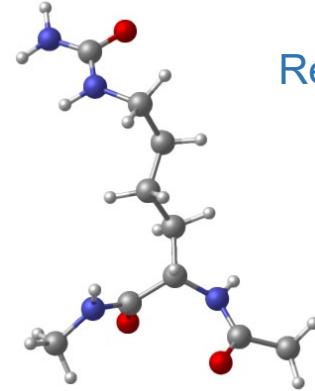
Calculation of the
Restrained Electrostatic Potential (RESP)
&
Bonded and Non-bonded parameters
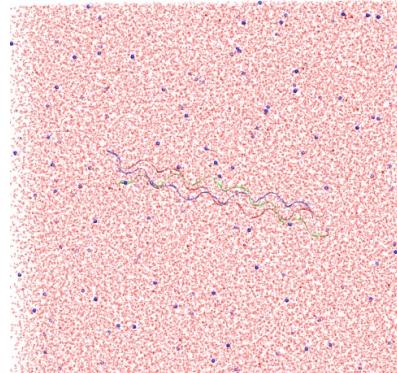
Solvated region of collagen
based on Gorisse's paper

Molecular Dynamics (MD)
Simulations

(a)
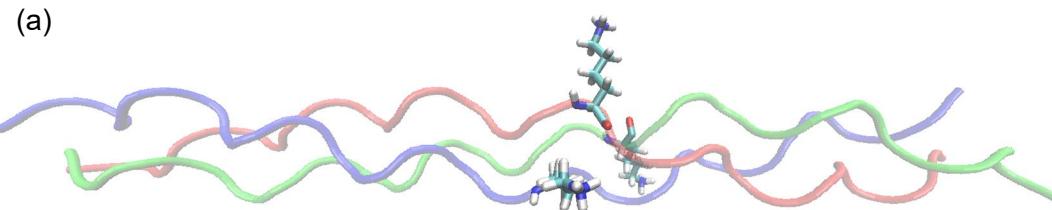
Transverse view of carbamoylation sites

(b)　　　　　　　(c)　　　　　　　(d)
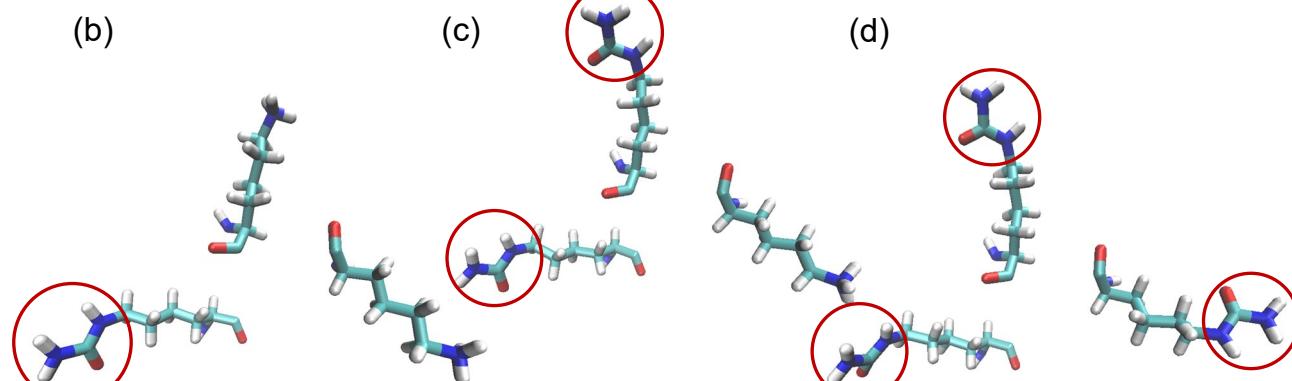
Chains A (blue) and C (green) sequence :
GARGQAGVMGFOGP**K**GAAGEOGKAGER
Chain B (red) sequence : GARGEPGNIGFPGP**K**GPTGDPGKNGDK

Simulation Details
Software : Gromacs 2020.4
Forcefield : AMBER99SB-ILDNP*
Time : 200 ns each system
Temperature / Pressure : 310 K / 1 bar
Salt : 0,154 M NaCl

Legend:
(a):Control with no carbamoylation
(b):System 1 1HCT on chain A
(c):System 2 2HCT on chain A and B
(d):System 3 3HCT on all chains

LOCAL MACHINE VS ROMEO2018 COMPARISON

Model : Dell Precision 7920

Graphic card: NVIDIA Quadro RTX 4000

Software : Gromacs 2020.4

Resources : 4 MPI tasks, 7 OpenMP threads per MPI task

Model : BullSequana X1000

Graphic card: Nvidia P100 SXM2

Module : _2020.4_spack2021_gcc-9.3.0-cuda-42nm

Resources : 1 node, 4 MPI tasks, 7 OpenMP threads per MPI task, 4 GPUs per node

**Gromacs 2020.4, selected region of collagen in water, ~120 K atoms**

Biologic systems (y-axis)
- System 3: 154,45 / 23,504
- System 2: 153,781 / 24,166
- System 1: 134,392 / 23,584
- System 0: 133,653 / 22,205

Performance, ns/day (x-axis): 0, 50, 100, 150, 200

■ HPC
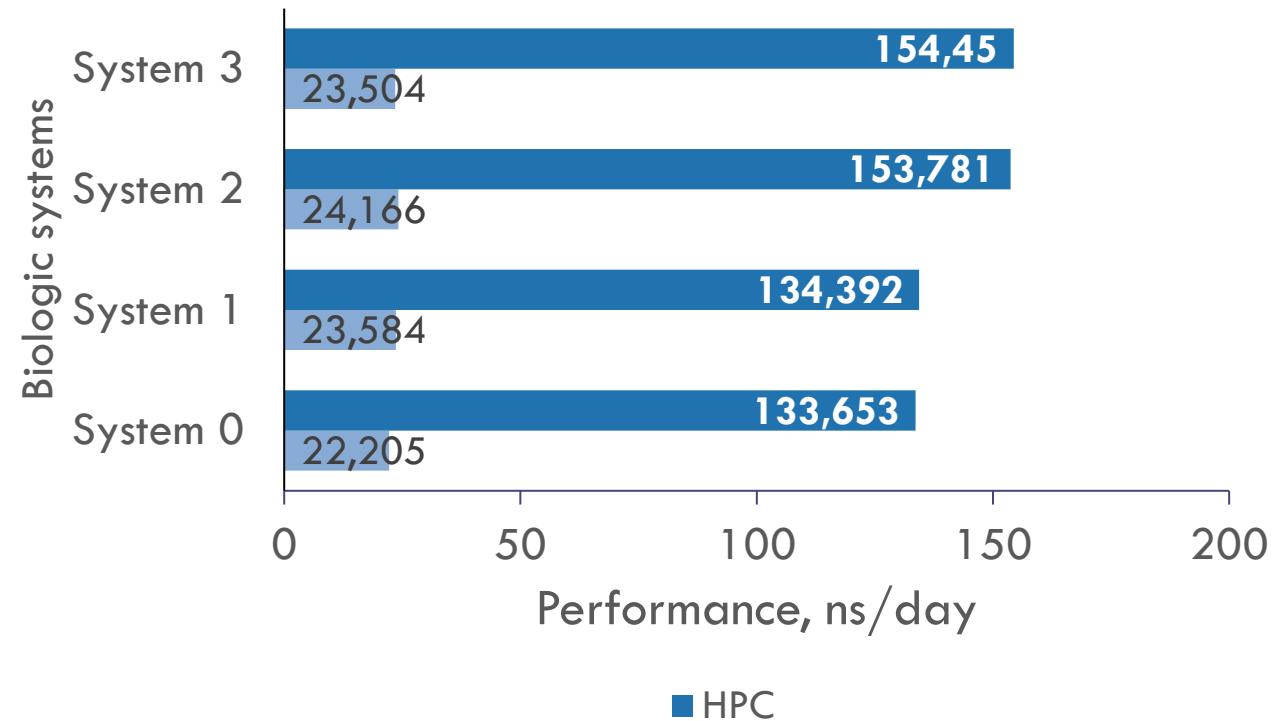
HCT HAS AN ELECTRON WITHDRAWING EFFECT

System 0
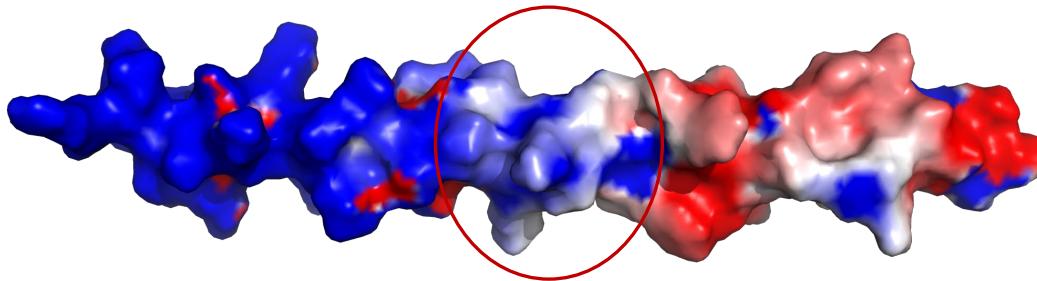
System 1
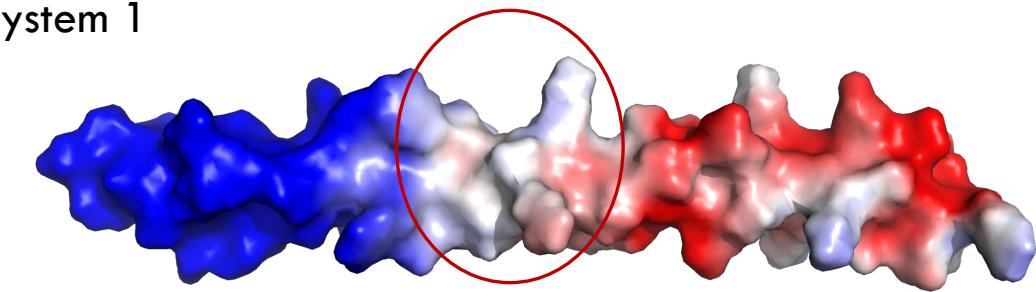
Negative   Positive

−3.000   3.000
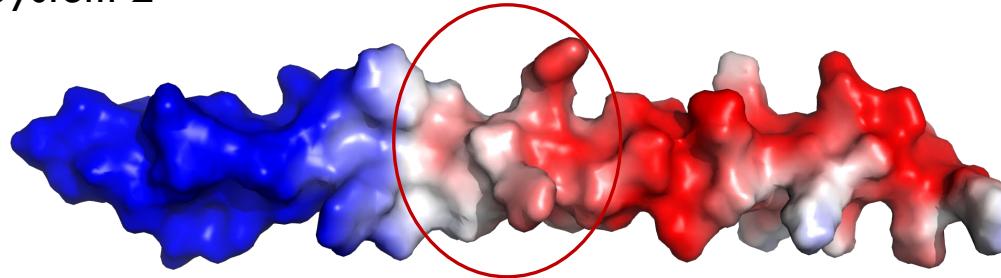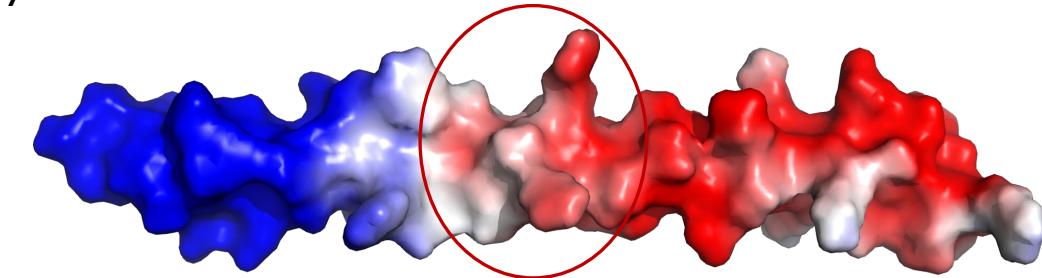
System 2

System 3

SOME SIMULATIONS MOVIES

System 0
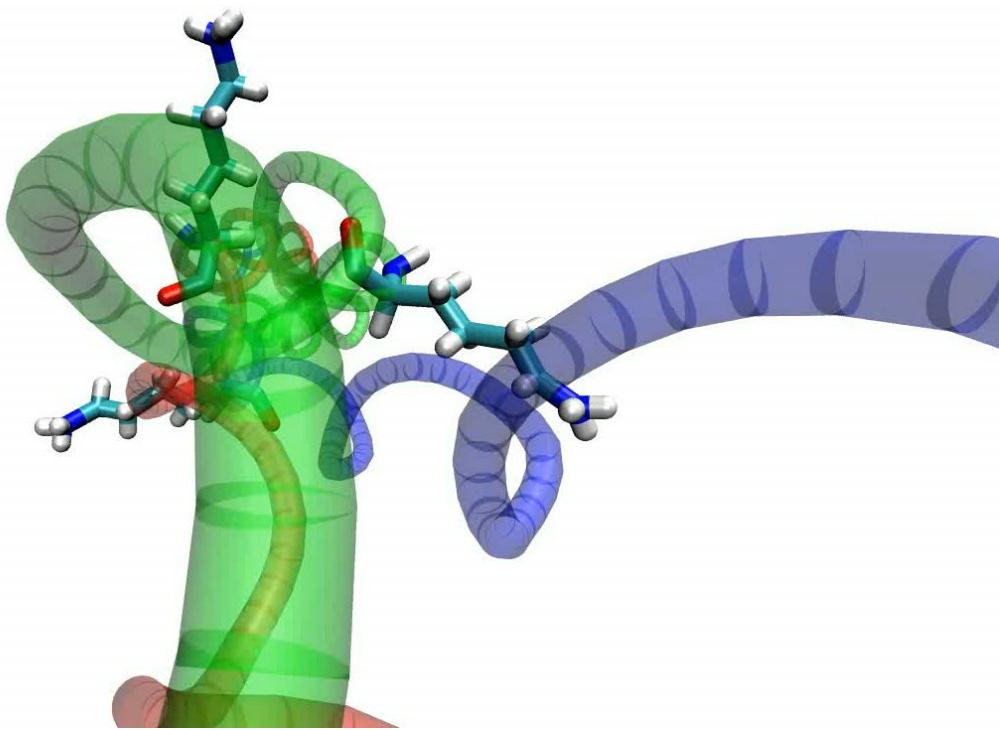
System 1
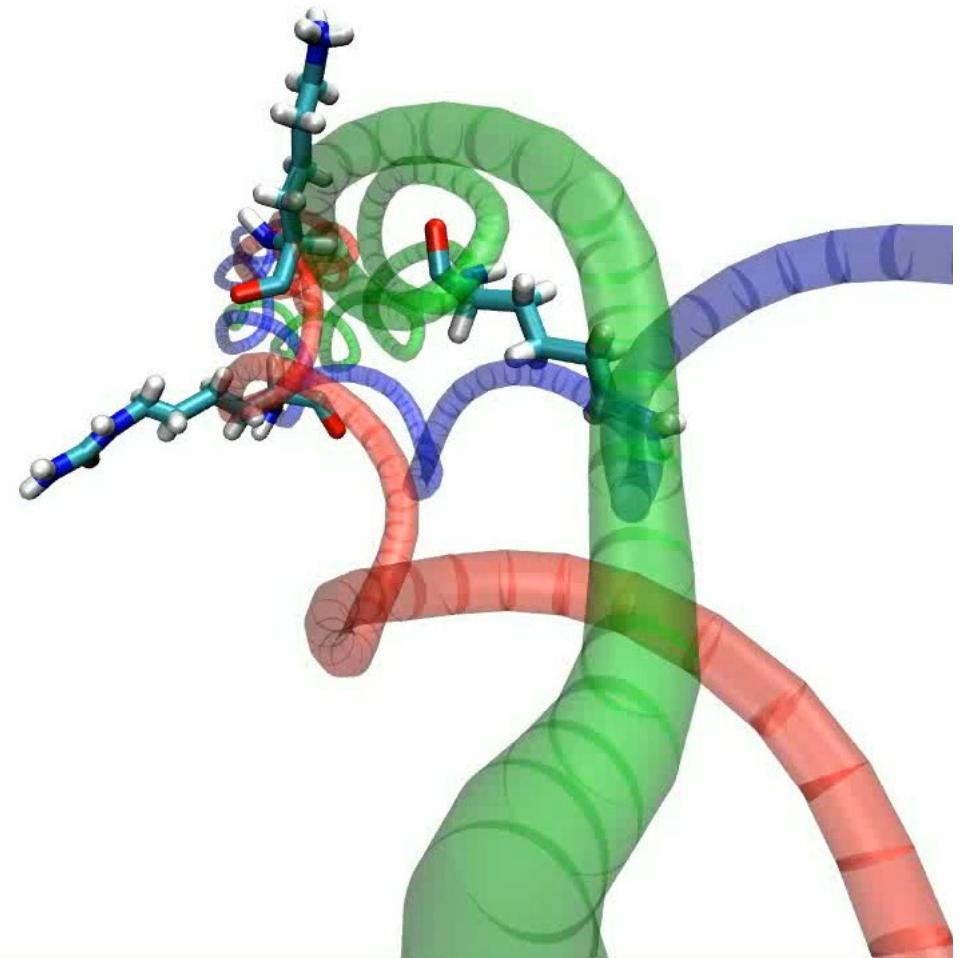
DIHEDRAL ANGLE PRINCIPAL COMPONENT ANALYSIS
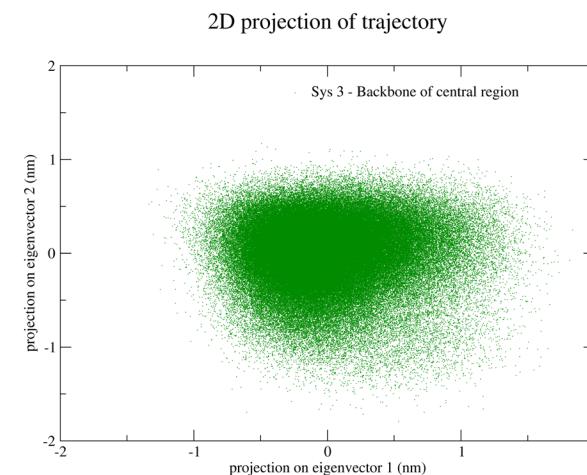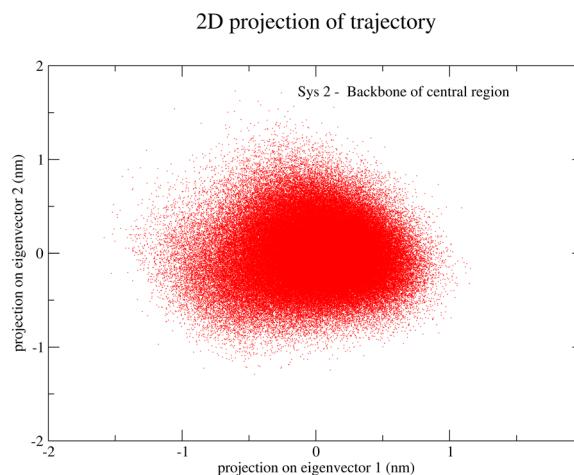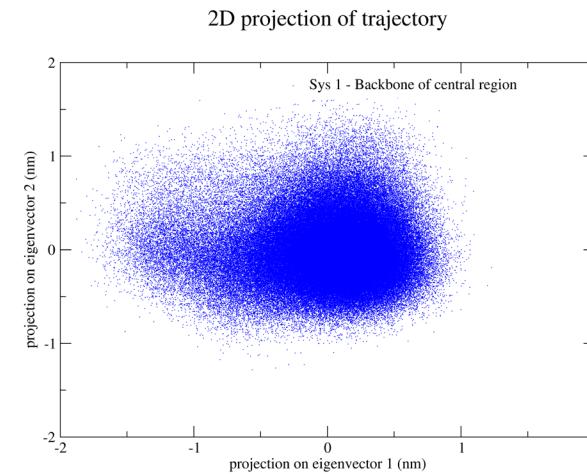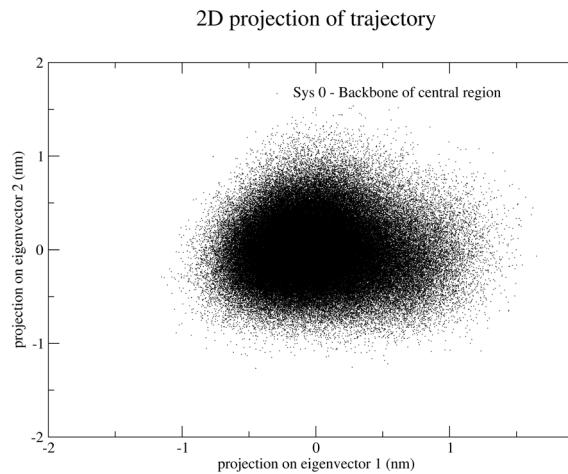
Globally the presence of HCT has little impact on the backbone of protein.

DIHEDRAL CONFORMATIONAL ANALYSIS
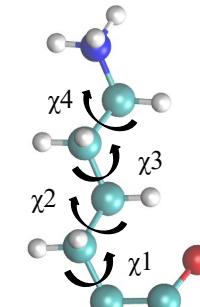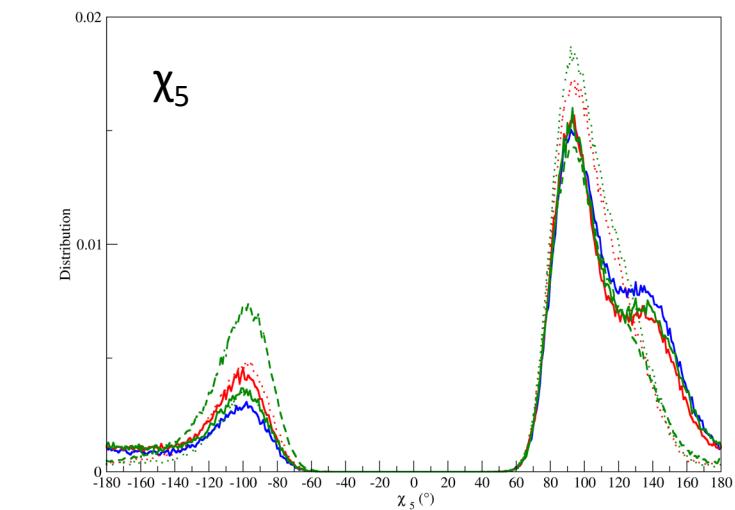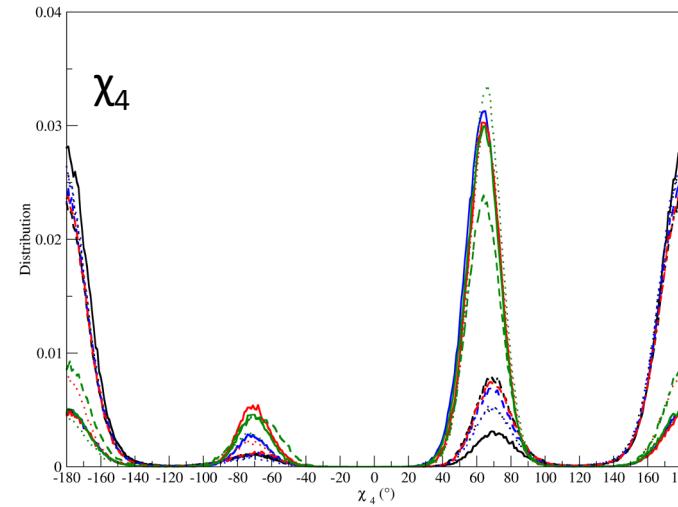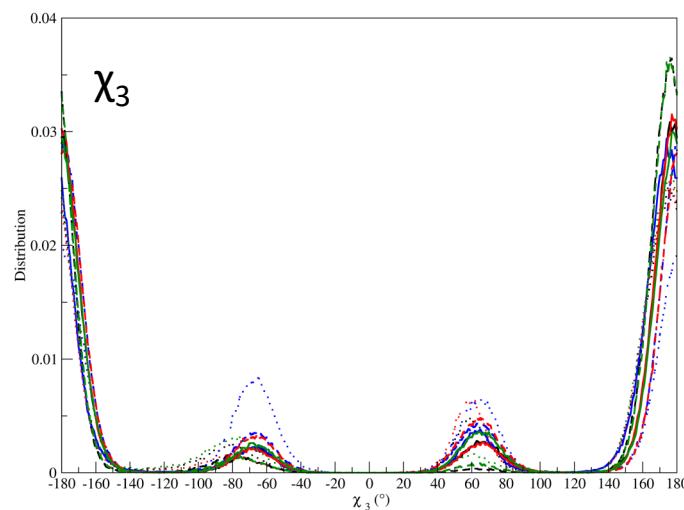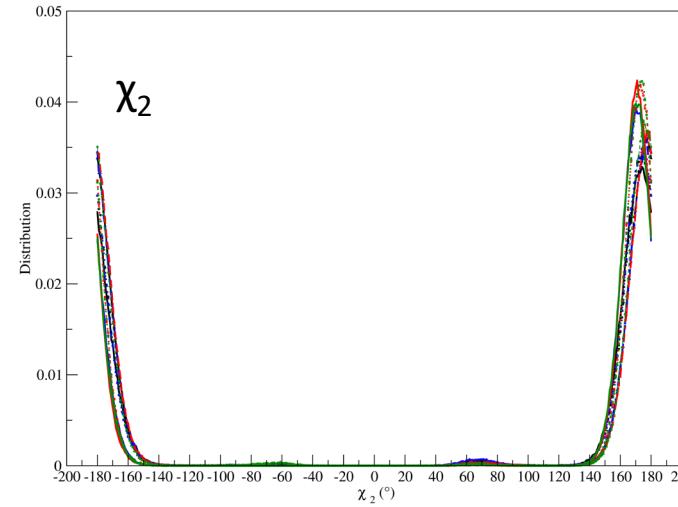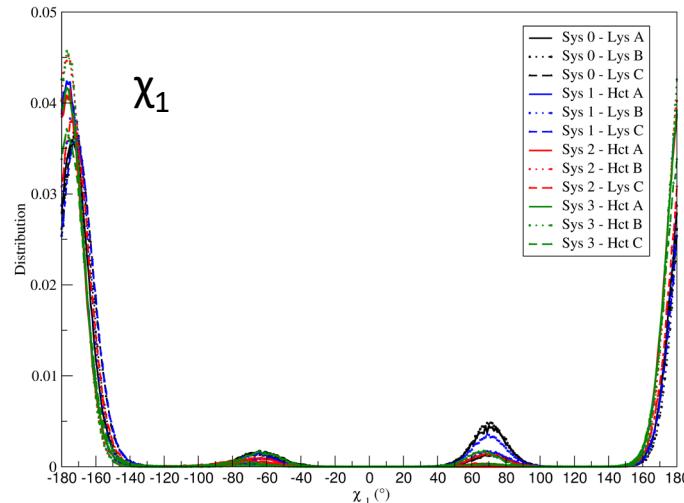

Lysine
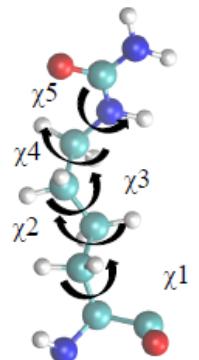
Homocitrulline

$\chi 4$: trans

$\chi 4$: gauche (+)

The introduction of at least one carbamoylation modifies the proportion at χ_3. A conformational change occurs at χ_4.
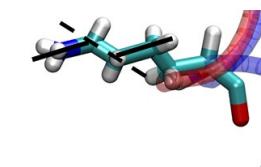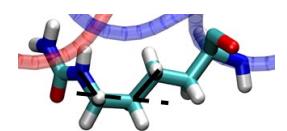
ADDITION OF CARBAMOYL CHANGE THE LOCAL CONFORMATION

Lysine

Homocitrulline
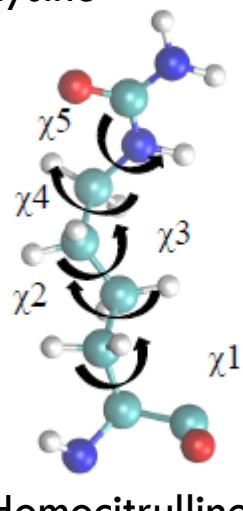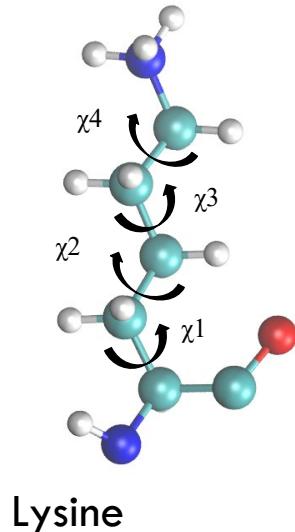
|	χ^1	χ^2	χ^3	χ^4	χ^5
S0 LYSA	83,97% trans	98,86% trans	55,52% trans	87,08% trans	
S0 LYSB	84,18% trans	98,91% trans	76,34% trans	81,90% trans	
S0 LYSC	92,85% trans	98,00% trans	85,94% trans	74,15% trans	
S1 HCTA	98.52% trans	99.54% trans	78.77% trans	78.56% gauche (+)	52.48% gauche (+)
S2 HCTA	96,34% trans	99,62% trans	83,26% trans	72,72% gauche (+)	51,56% gauche (+)
S2 HCTB	98,11% trans	99,62% trans	93,34% trans	71,48% gauche (+)	61,74% gauche (+)
S3 HCTA	97,38% trans	99,52% trans	78,72% trans	73,61% gauche (+)	51,94% gauche (+)
S3 HCTB	98,79% trans	99,40% trans	93,73% trans	79,54% gauche (+)	66,08% gauche (+)
S3 HCTC	91,48% trans	98,71% trans	83,57% trans	59,50% gauche (+)	50,92% gauche (+)

Angle classification[1,2]:
-120°<gauche(-)<0°
0°<gauche(+)<120°
120°<trans≤180°
-180°≤trans<-120°

[1]Dunbrack and Karplus, *JMB*, 1993
[2]Shapalov and Dunbrack, *Structure*, 2011

$\chi4$: trans

$\chi4$: gauche (+)
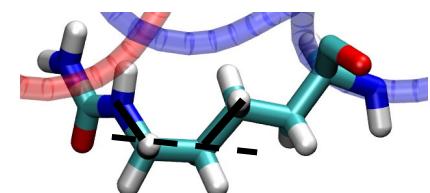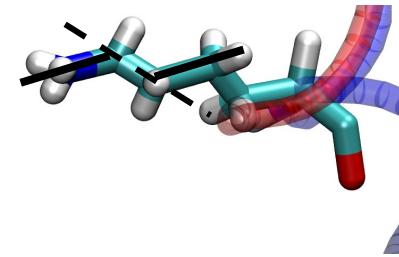
LINK WITH BIOLOGY

Salt bridge disruption
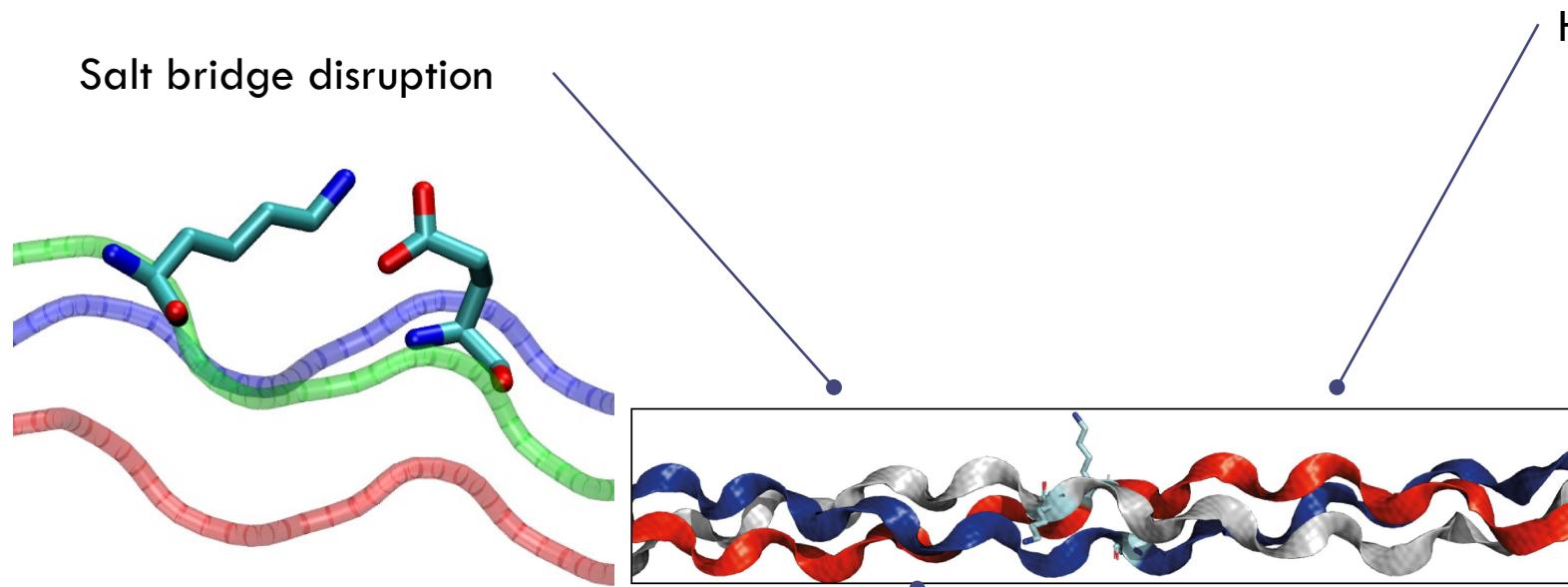
H-bonds increase
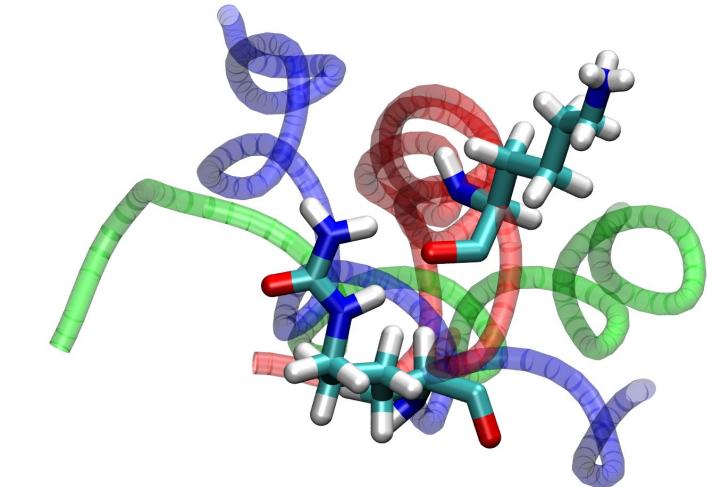
Impact on protein protein interaction

collagen trimer

slow
proteolysis
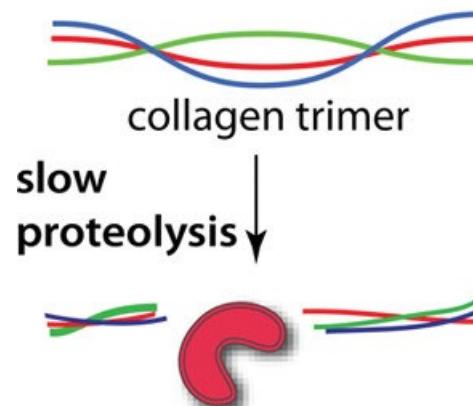
Impact on fiber integrity

a Fibrillar collagen
Procollagen

Procollagen
peptidase

Collagen

Fibril
formation

Microfibril

Fibril

Fibre

Fibre bundle (subfascicle)

Adhikari *et al.*, *JACS*, 2011
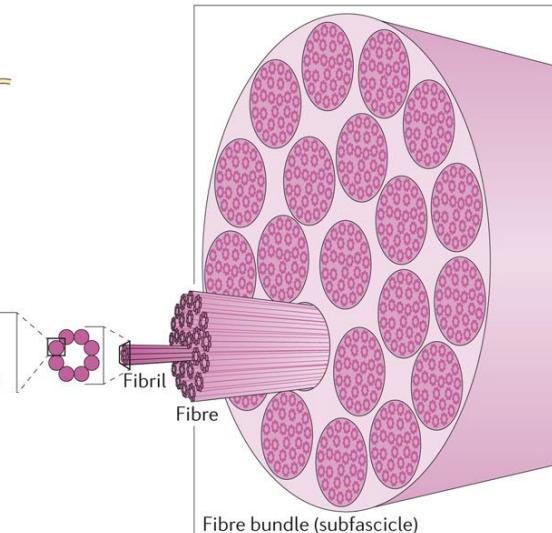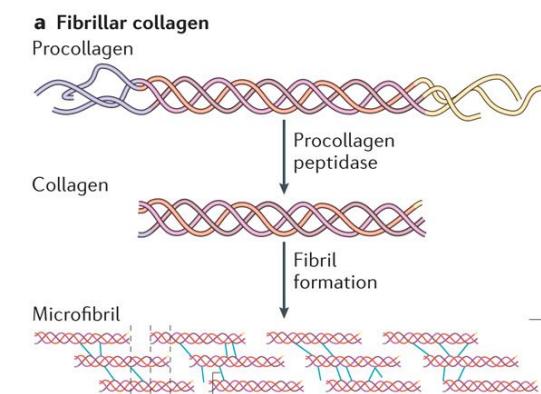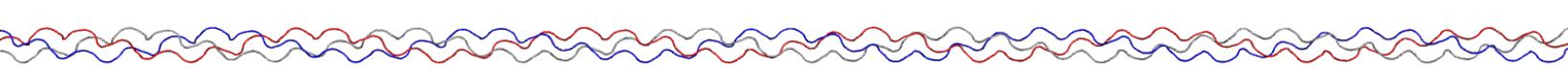
CONCLUSION

- Carbamoylation of collagen modify charge repartition in protein.

- The presence of HCT has little impact on protein backbone.

- Local side chain conformational transition of $\chi 4$ from trans to gauche(+).

# PROSPECT

- Suspicion of a collective effect of HCTs → Increasing the number of carbamylations

- Increase chain length

- Simulate systems **closer** to biological reality = create an interaction between 2 (or more) triple helices

Triple Helix — 1.4 nm

300 nm

Collagen Fibril — D = 67 nm — Lysyl oxidase crosslinking

Collagen Fiber — 300 nm - 1 μm — D = 67 nm
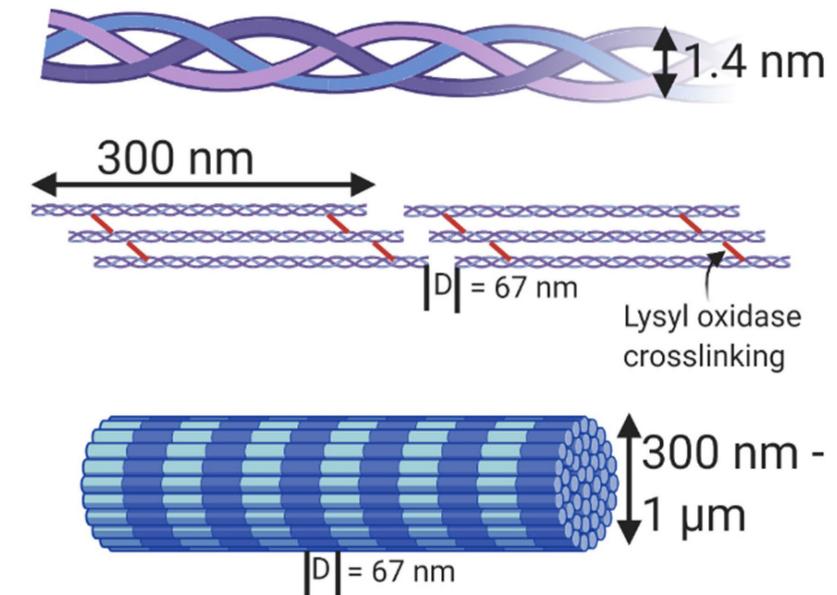
Walimbe and Panitch, *Bioengineering*, 2020

THANK YOU !

Équipe Modélisation et
Imagerie Multi-Echelle

Supervisors:
Pr. Stéphanie Baud
Dr. Hua Wong

Post-doc :
Zeynep Pinar Haslak