SIMULACIÓN Y EXPERIMENTOS EN FÍSICA MACROMOLECULAR

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BREVE HISTORIA DEL GRUPO BIOPHYM

ESTRUCTURA DE MEMBRANAS CELULARES-DISTORSIONES POR PROTEÍNAS

1976-1994

morphology/structure vs. Physical properties (solid)

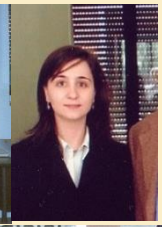



1996-2004

molecular architecture vs. physical properties melt

Computational chemistry (MM and QM, DFT)





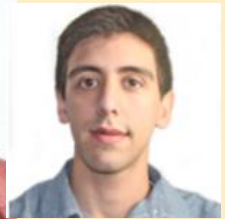
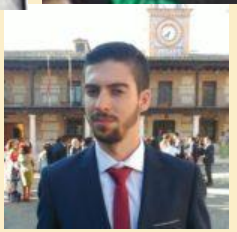

2004 - 2008

Macromolecular simulation (MC, MD): crystallization + melt

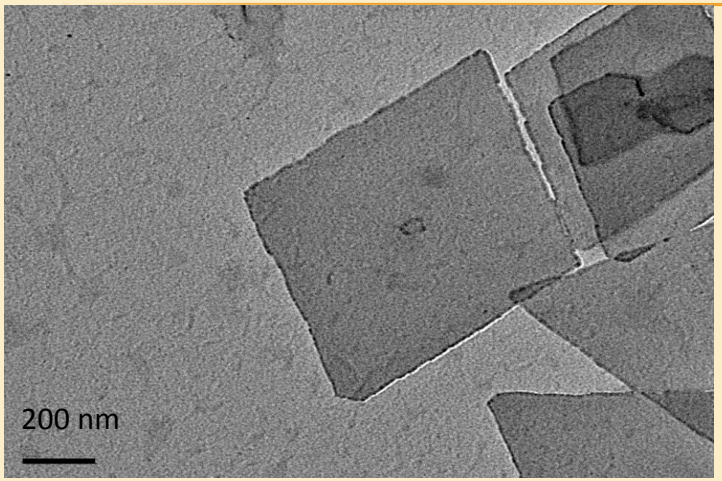



2008 - 2018

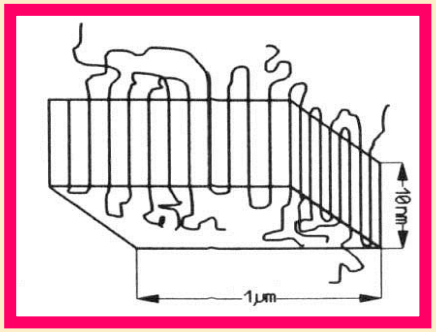
Macromolecular/ BIO

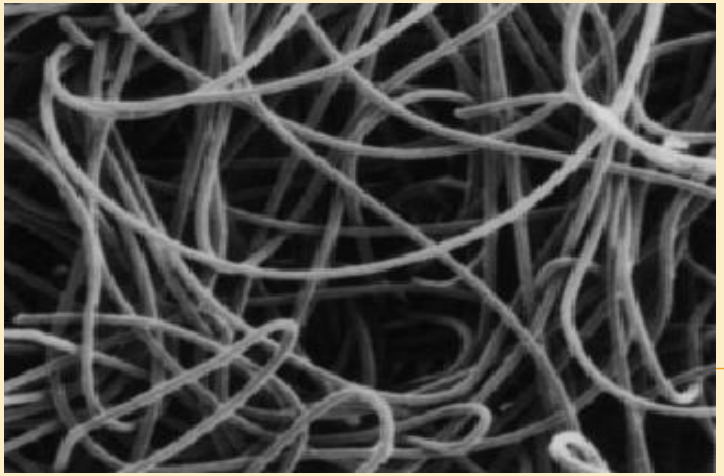





Las macromoléculas adoptan conformaciones extremas



plegada → laminas

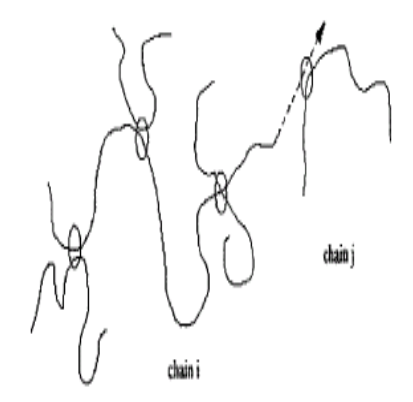


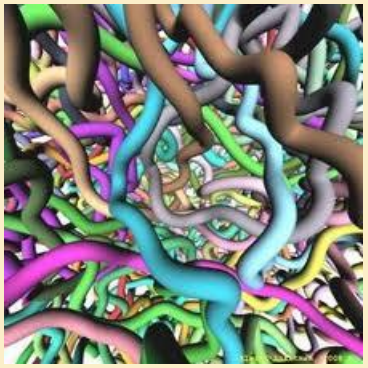


extendida → fibras

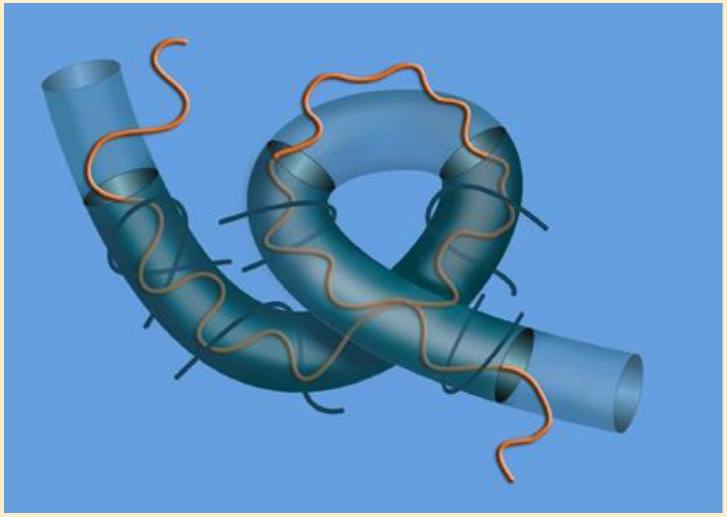
FORMAN UNA RED COOPERATIVA CON EFECTOS NO LINEALES

UNO AFECTA A TODOS





Las macromoléculas forman un sistema (red de entrecruzamientos) en la que cada elemento (molécula) repta en un tubo cuyo contorno queda fijado por el resto



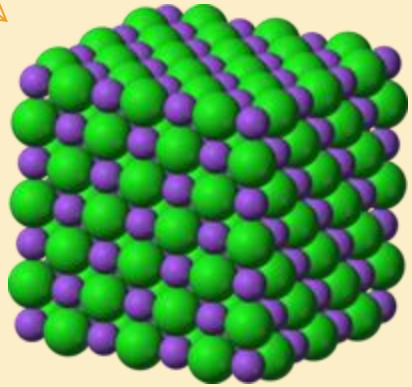
Se manifiestan fenómenos cooperativos (sistemas altamente correlacionados)

El sistema es más que la suma de sus elementos (estructuras complejas)

Cristal NaCl

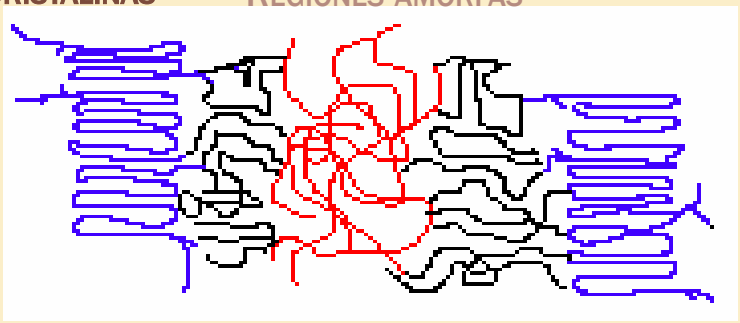
Na^+

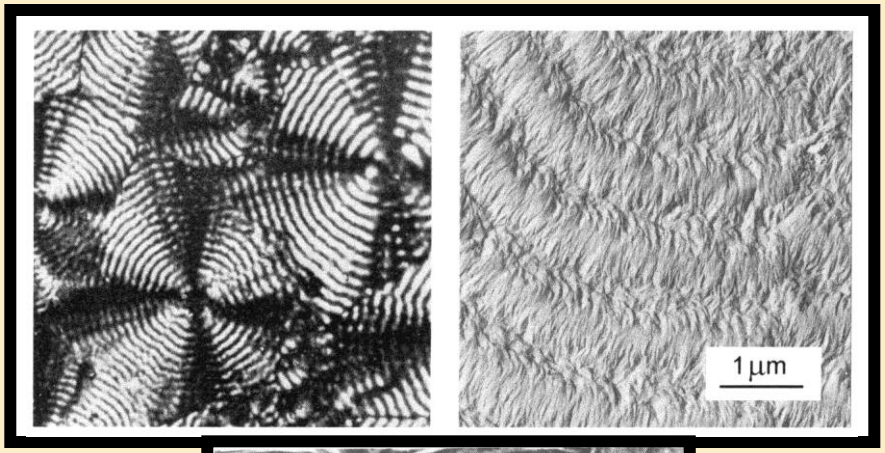
Cl^-

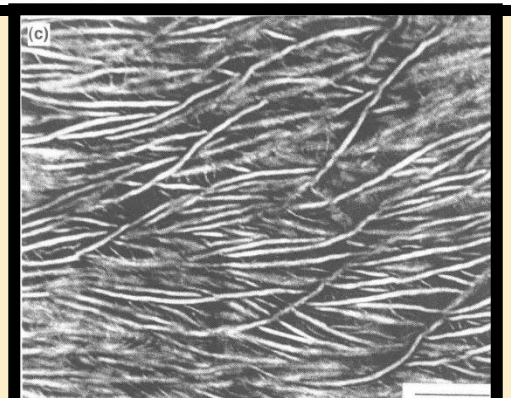


Polimeros semicristalinos

Regiones Cristalinas Regiones amorfas







¿POR QUÉ HACER SIMULACIÓN COMPUTACIONAL?

- TRATAMOS CON SISTEMAS MULTICOMPONENTES EN EL QUE SUS ELEMENTOS SE ORGANIZAN ESTRUCTURALMENTE DANDO LUGAR A FENÓMENOS NO PREDECIBLES POR LAS TEORIAS EXISTENTES

- LIMITACIONES EN LA OBTENCIÓN DE SEÑALES EXPERIMENTALES

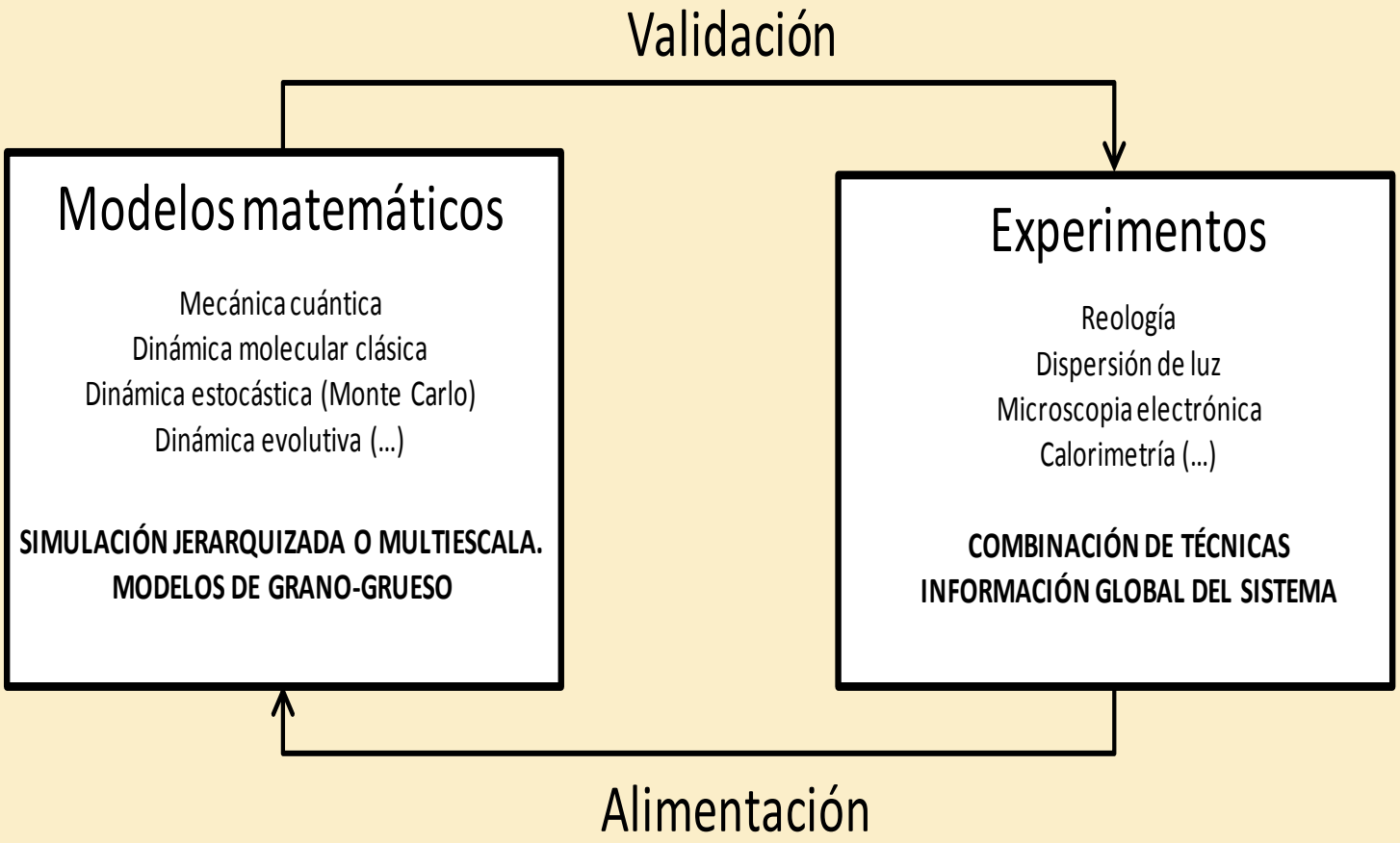
MUCHAS PREGUNTAS BÁSICAS SIN RESPUESTA

¿Cómo solidifican los polímeros?
teorías actuales no explican muchos resultados experimentales

¿PARADIGMA INVÁLIDO?

¿Como se forman las fases en el fundido?
la termodinámica no da respuestas concluyentes

APROXIMACIÓN SISTÉMICA A LOS PROCESOS DE ENSAMBLAJE Y SEÑALIZACIÓN EN MACROMOLÉCULAS.



ESTABLECIENDO SINERGIAS ENTRE EXPERIMENTOS Y SIMULACIÓN

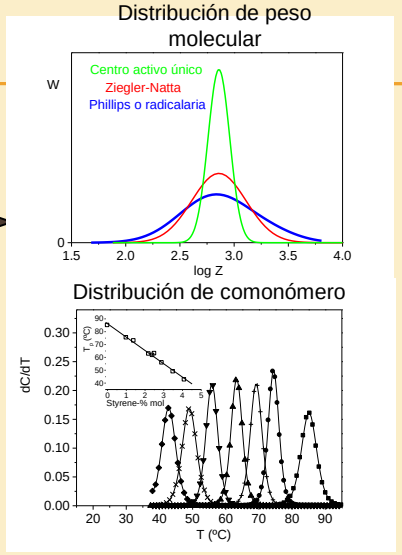
Problema en un Sistema Real

Abstracción

Simplificación

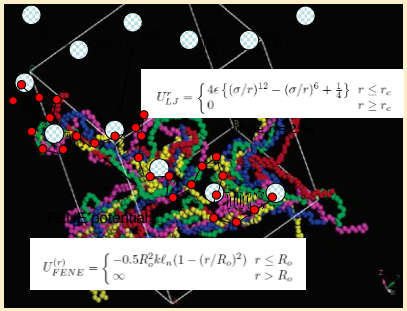
Experimentos

Resultados experimentales



Modificación del modelo

Modelo valido



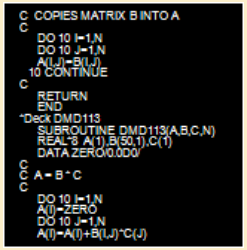
Modelos

Parametrización

Abstracción

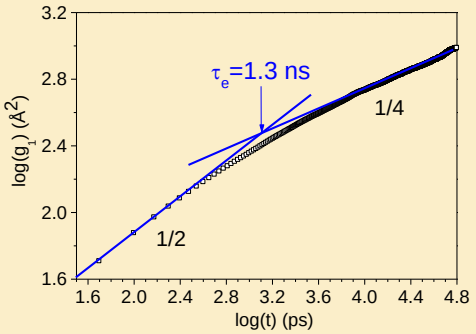
Implementación

+



Métodos computacionales

Force Field	$\langle R^2 \rangle$ (Å^2)	$\langle R_g^2 \rangle$ (Å^2)	$\langle R^2 \rangle / \langle R_g^2 \rangle$	C_∞[c]	l_p (Å)[d]	M_e (kg/mol)[e]
Trappe-UA[a]	19805 ± 50	3299 ± 6	6.00 ± 0.03	8.34 ± 0.01	9.22 ± 0.02	0.71 ± 0.01
Karayiannis et al.[b]	19335 ± 56	3187 ± 6	6.07 ± 0.03	8.06 ± 0.01	9.54 ± 0.02	0.79 ± 0.01



El concepto de multiescala

Investigar y diseñar nuevos materiales desde la síntesis a su aplicación.

Química Cuántica (DFT)

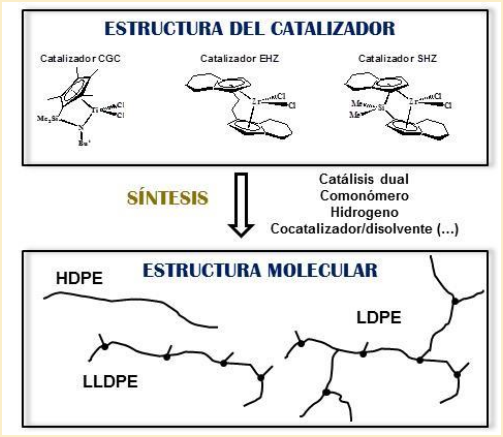
Electrones explícitos.

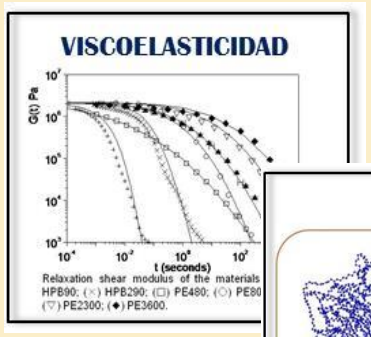
Modelos atómisticos

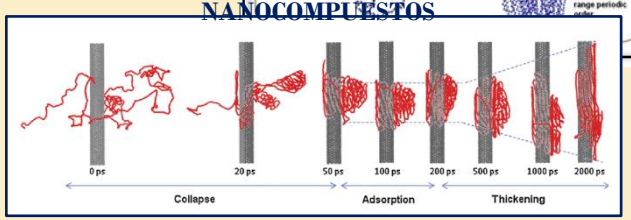
Física clásica con "force field" atomísticos (dinámica molecular y Monte Carlo).

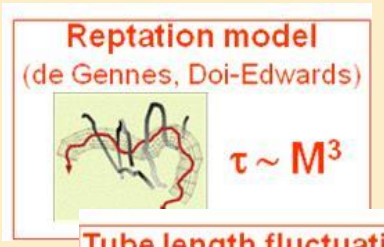
Modelos mesoscópicos

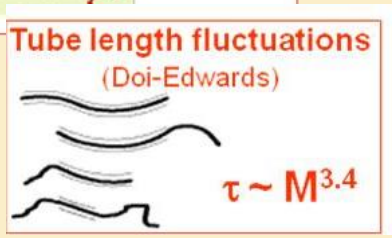
Grano-grueso (CG) o modelos moleculares. Potenciales efectivos.









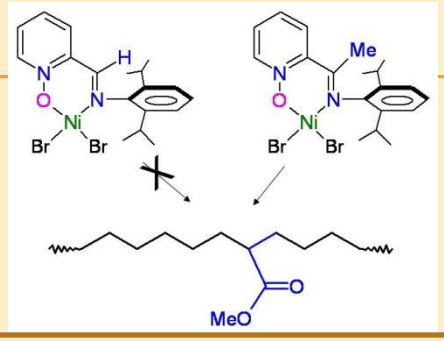


Escala espacial

Escala temporal

SIMULACIÓN Y EXPERIMENTOS EN FÍSICA MACROMOLECULAR.

Modelización de las reacciones de polimerización mediante catalizadores organometálicos.

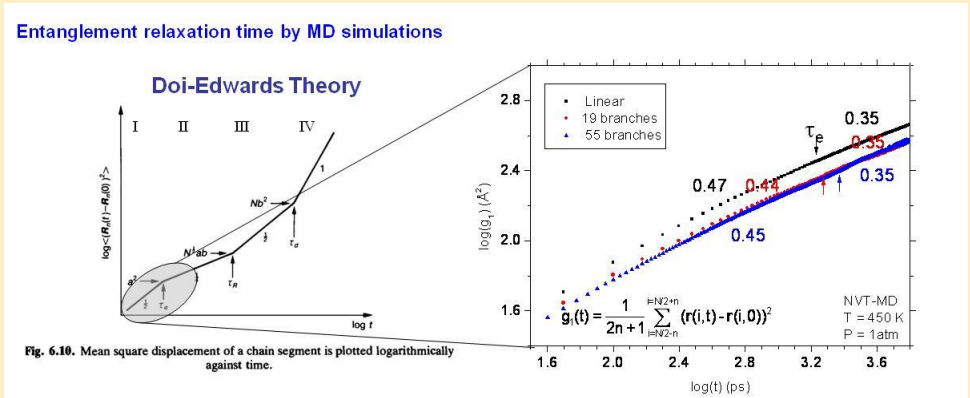


Copolimeros de etileno y metacrilato. Biocompatibilidad

J. Ramos, S. Martínez, V.L. Cruz and J. Martínez-Salazar, J. Molecuar Mod. (**2011**)
J. Ramos, V. L. Cruz, J. Martínez-Salazar, M. Brasse, P. Palma and J. Campora J Pol Sci: Pol Chem **(2010)**

Comportamiento viscoelástico y dinámica molecular de polímeros sintéticos

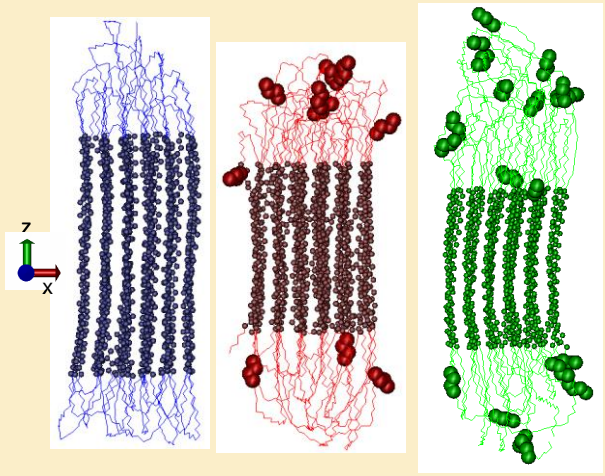
Procesabilidad Viscoelasticidad



J.F. Vega, J.Ramos and J. Martínez-Salazar, Rheologica Acta **(2011)**
J. Ramos, J.F. Vega, D.N. Theodorou and J. Martínez-Salazar, Macromolecules **(2008)**

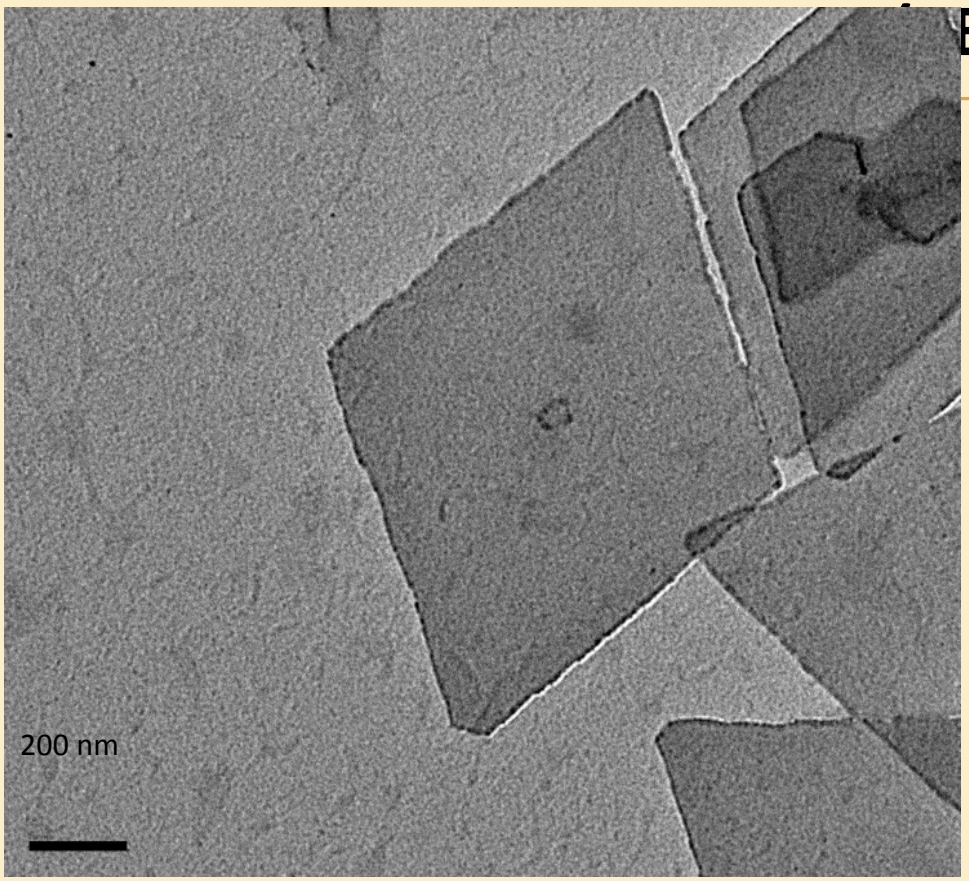
Cristalización de polímeros en disolución. Efecto de la arquitectura molecular

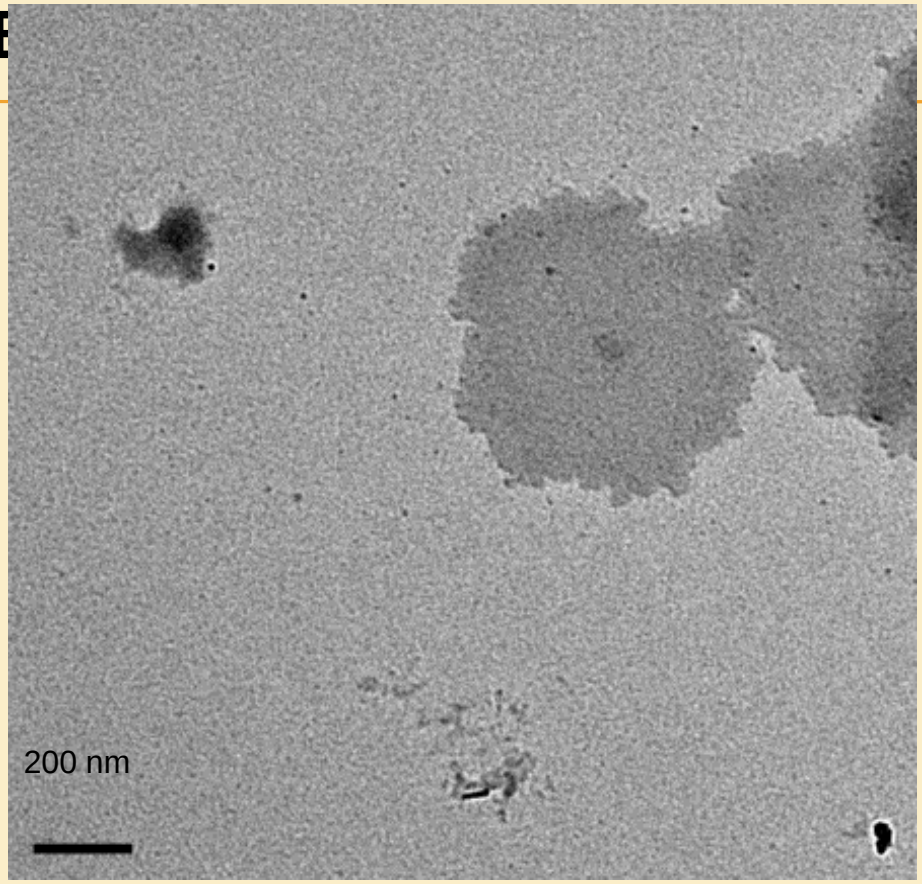
Teorías de cristalización Propiedades mecánicas



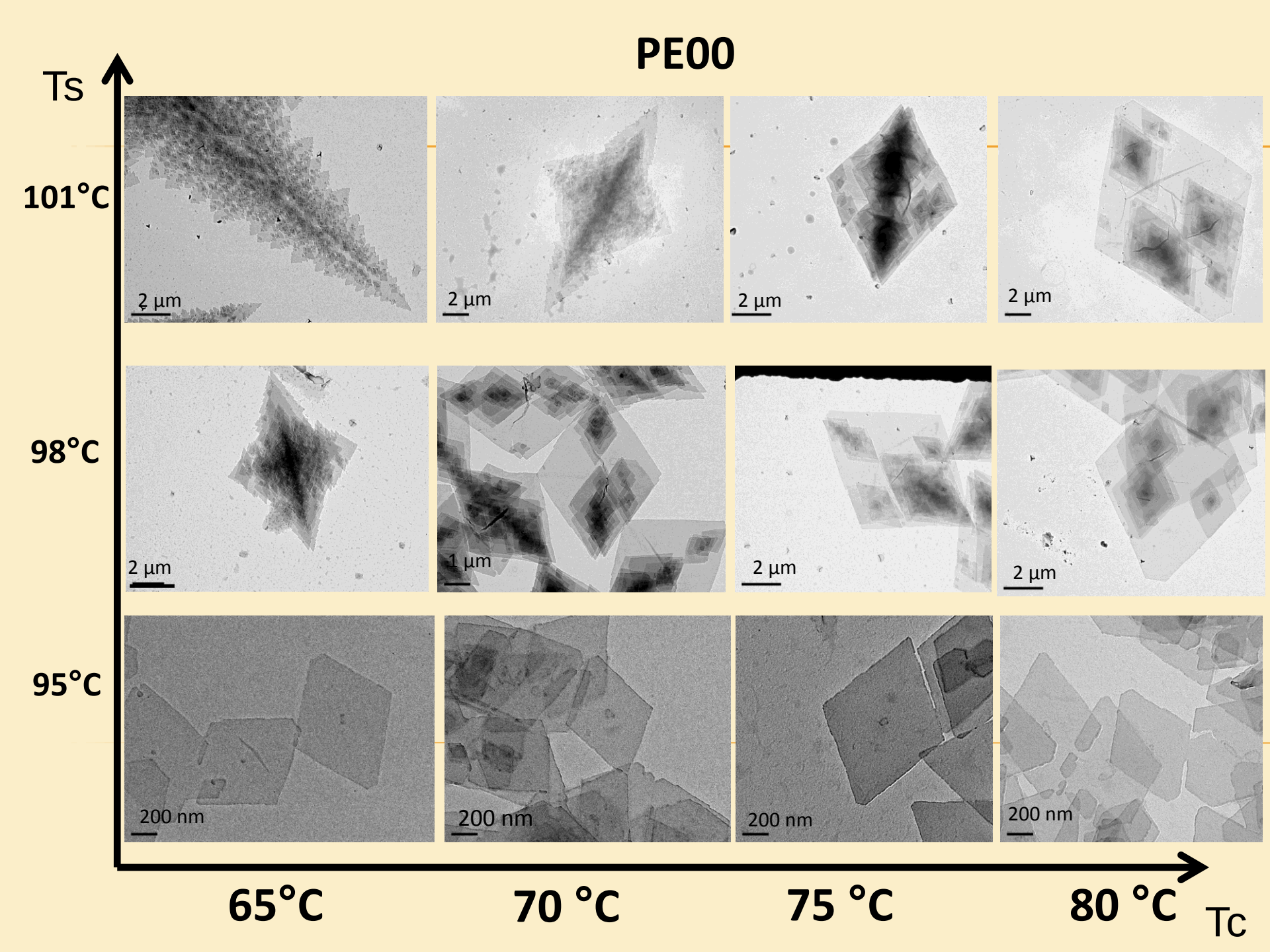
S. Sanmartín, J. Ramos and J. Martínez-Salazar Macromolecular Symposia (**2011**)
J. Ramos and J. Martínez-Salazar J Pol Sci: Pol Phys (**2011**)

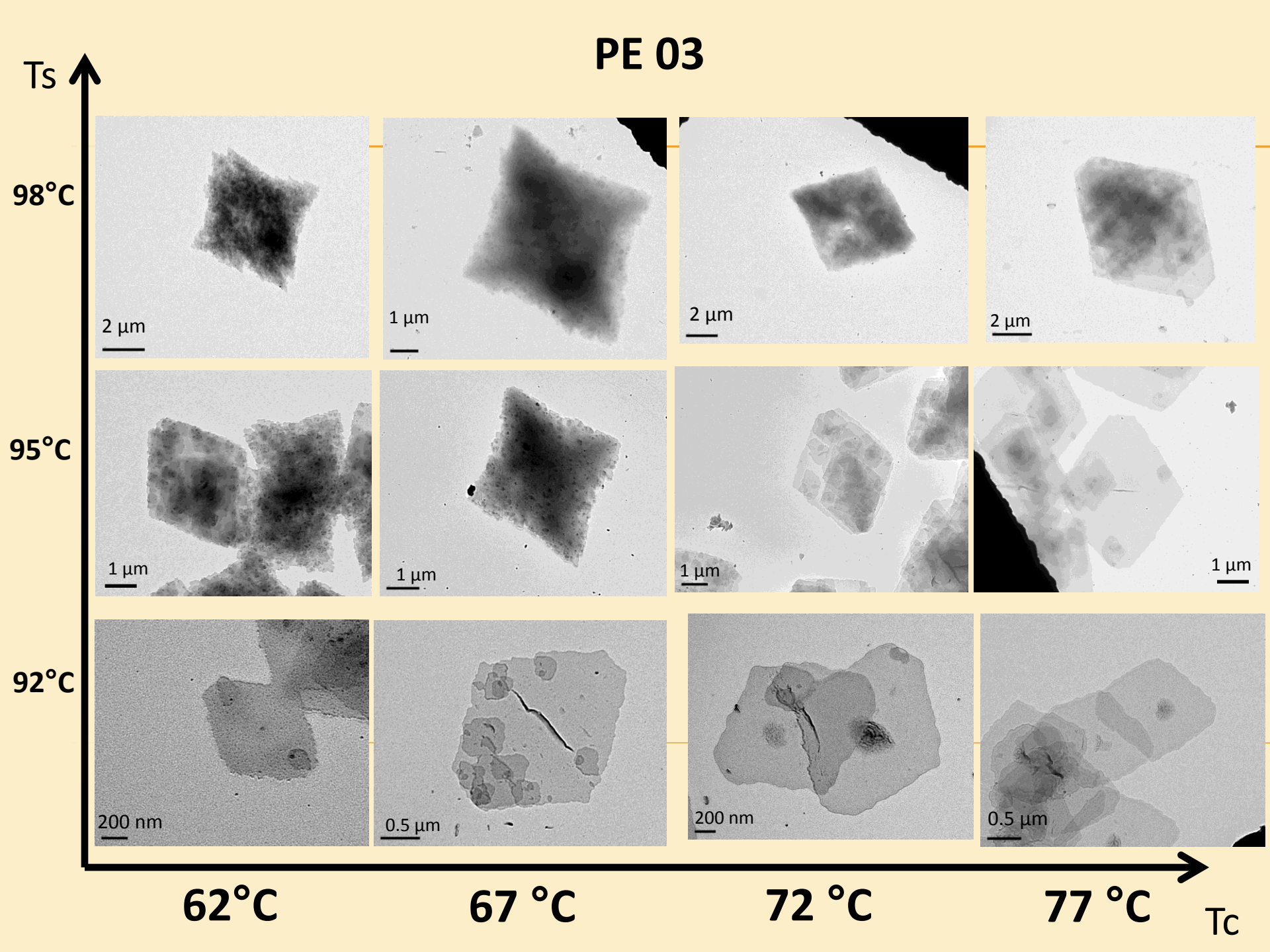
EXPERIMENTAL MORFOLOGIA MONOCRISTALES

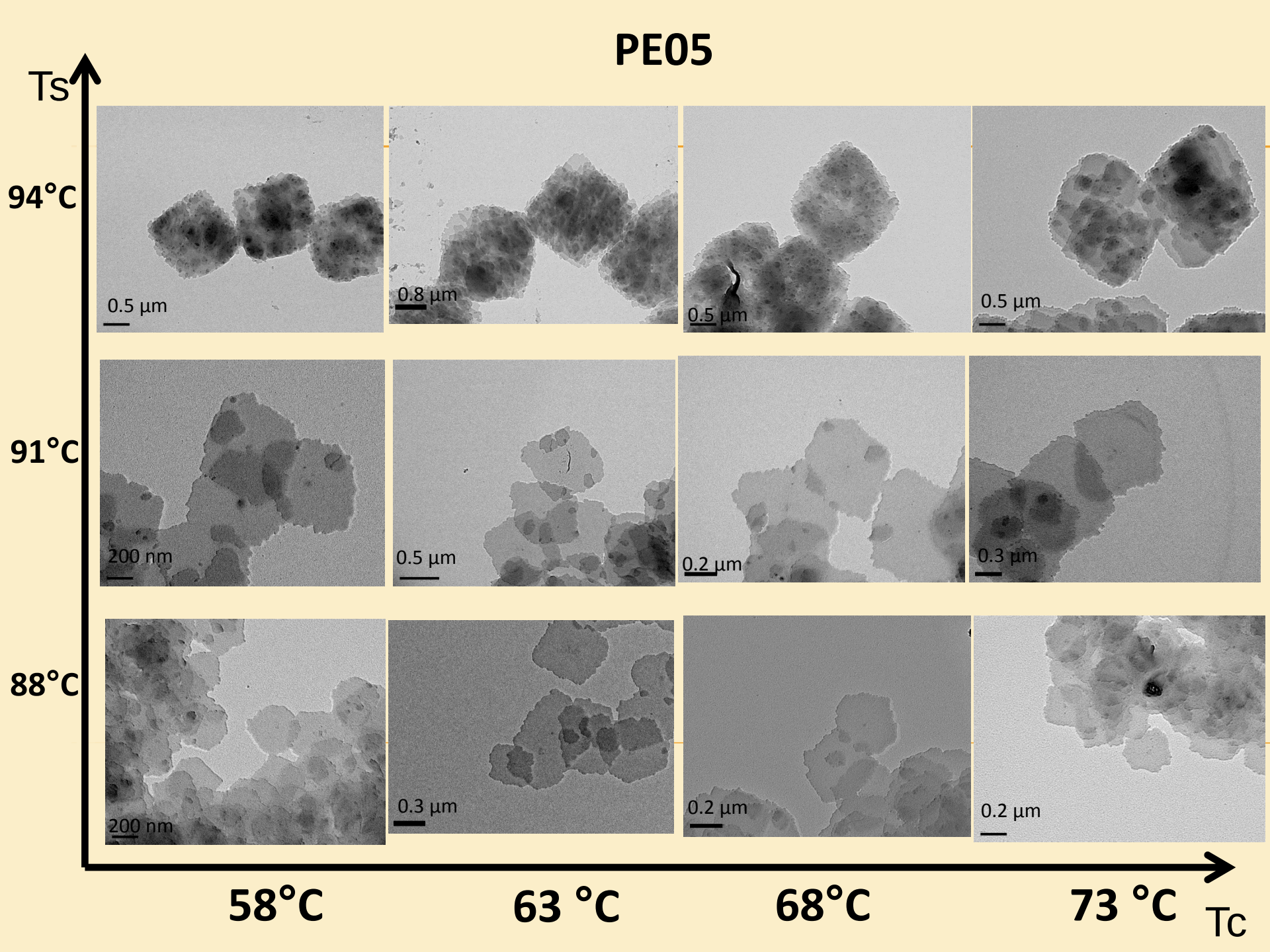


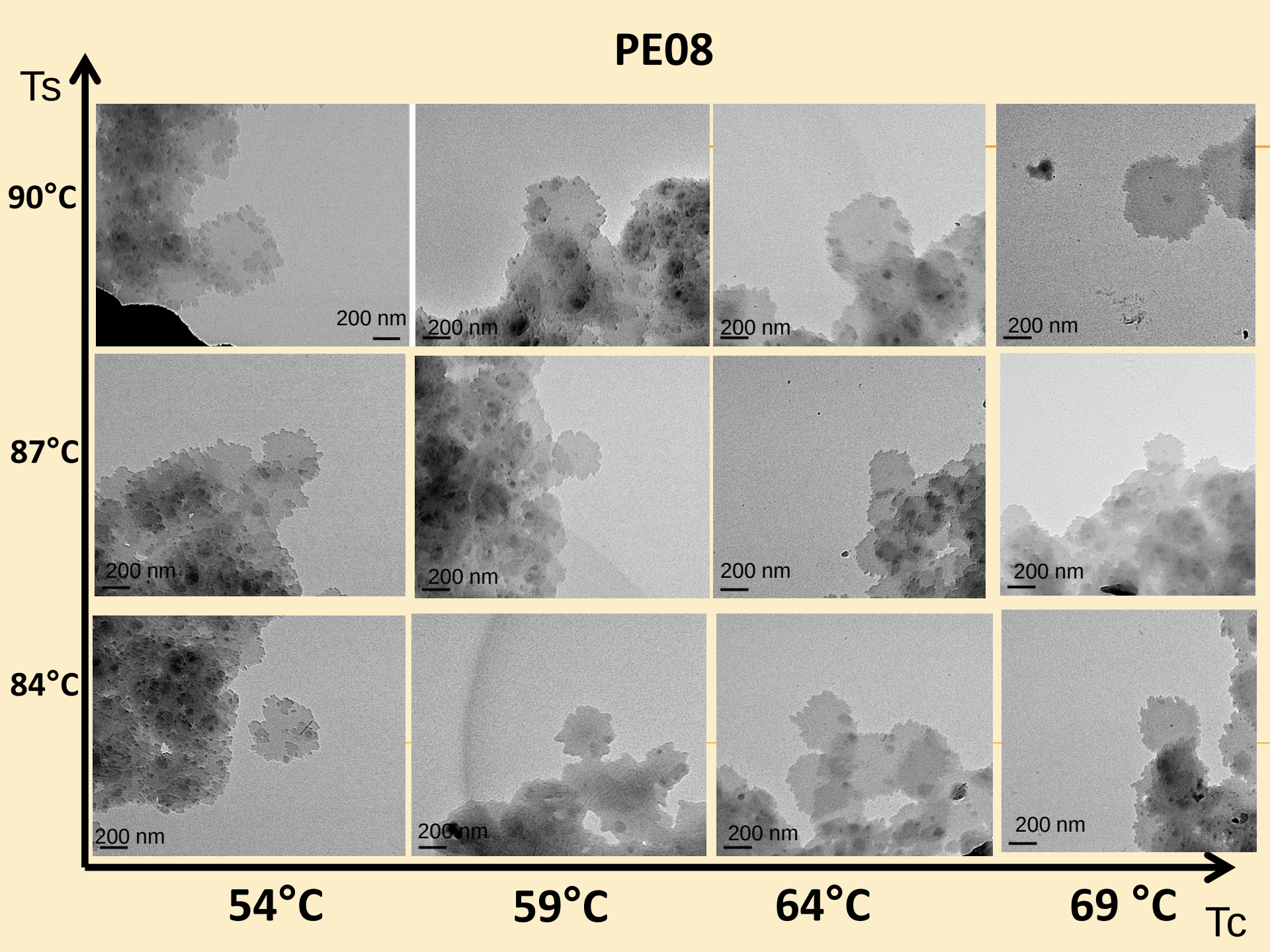


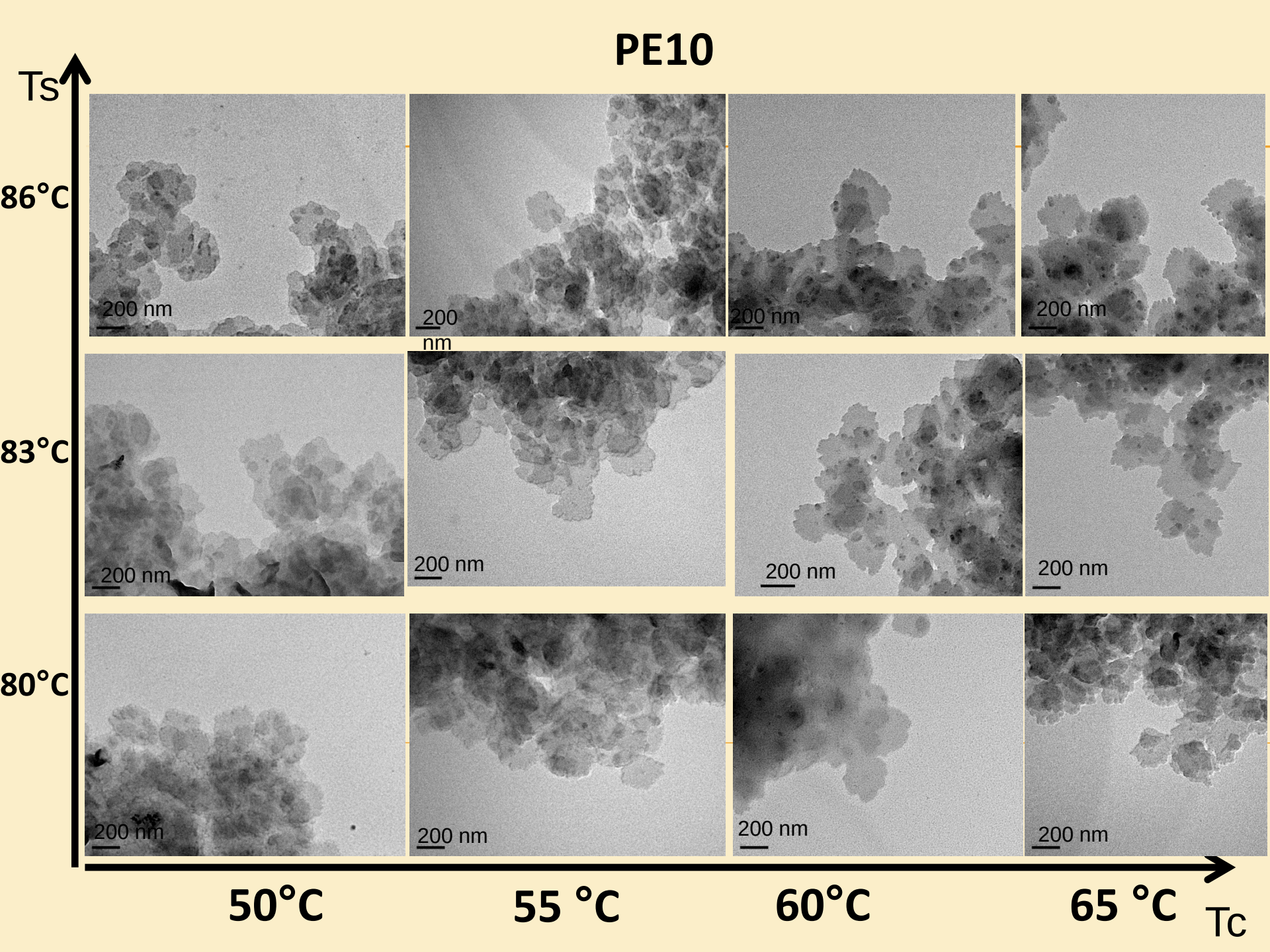
Tc


PE00
Ts
101°C
98°C
95°C
2 µm
2 µm
2 µm
2 µm
2 µm
1 µm
2 µm
2 µm
200 nm
200 nm
200 nm
200 nm
65°C
70 °C
75 °C
80 °C
Tc

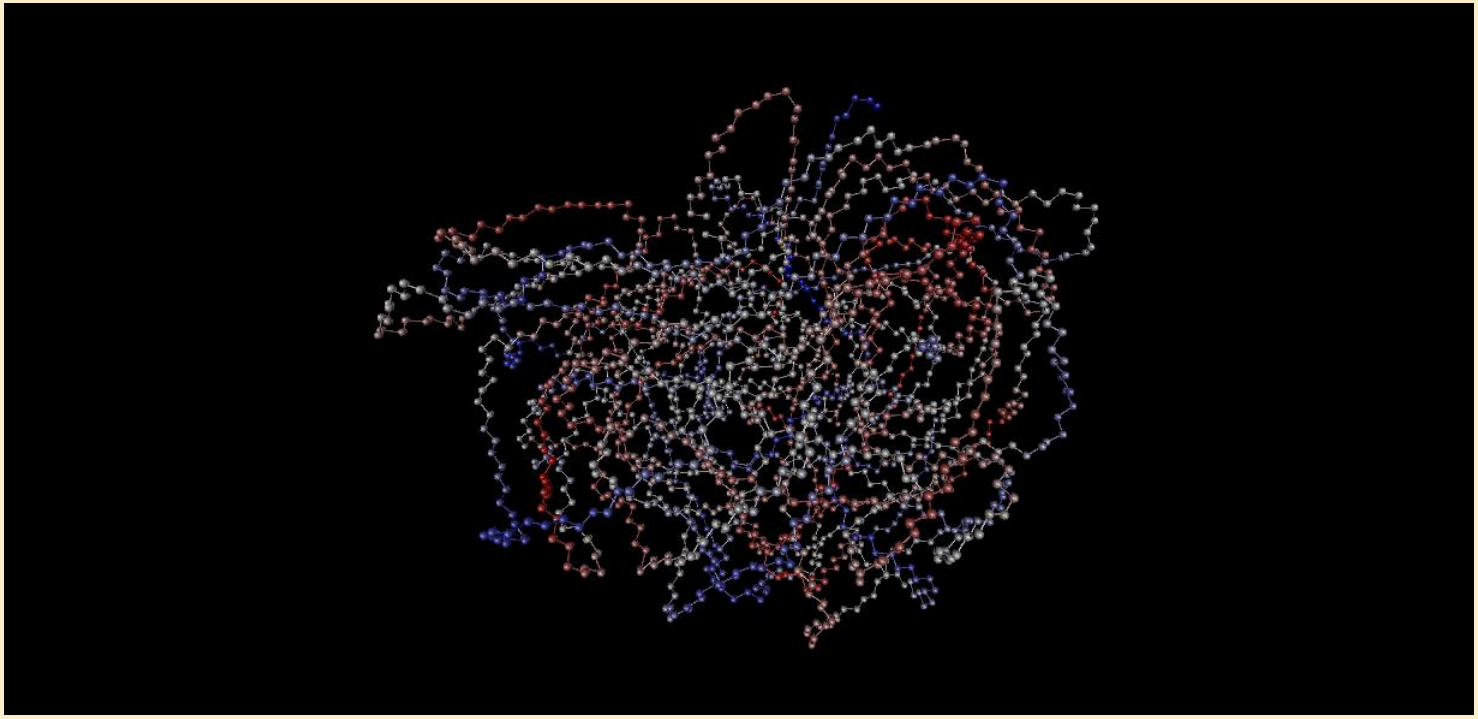

PE 03
Ts
98°C
95°C
92°C
2 µm
1 µm
2 µm
2 µm
1 µm
1 µm
1 µm
1 µm
200 nm
0.5 µm
200 nm
0.5 µm
62°C
67 °C
72 °C
77 °C
Tc


PE05
Ts
94°C
91°C
88°C
0.5 µm
0.8 µm
0.5 µm
0.5 µm
200 nm
0.5 µm
0.2 µm
0.3 µm
200 nm
0.3 µm
0.2 µm
0.2 µm
58°C
63 °C
68°C
73 °C
Tc


PE08
Ts
90°C
87°C
84°C
200 nm
54°C
59°C
64°C
69 °C
Tc


PE10
Ts
86°C
83°C
80°C
200 nm
200 nm
200 nm
200 nm
200 nm
200 nm
200 nm
200 nm
200 nm
200 nm
200 nm
200 nm
50°C
55 °C
60°C
65 °C
Tc

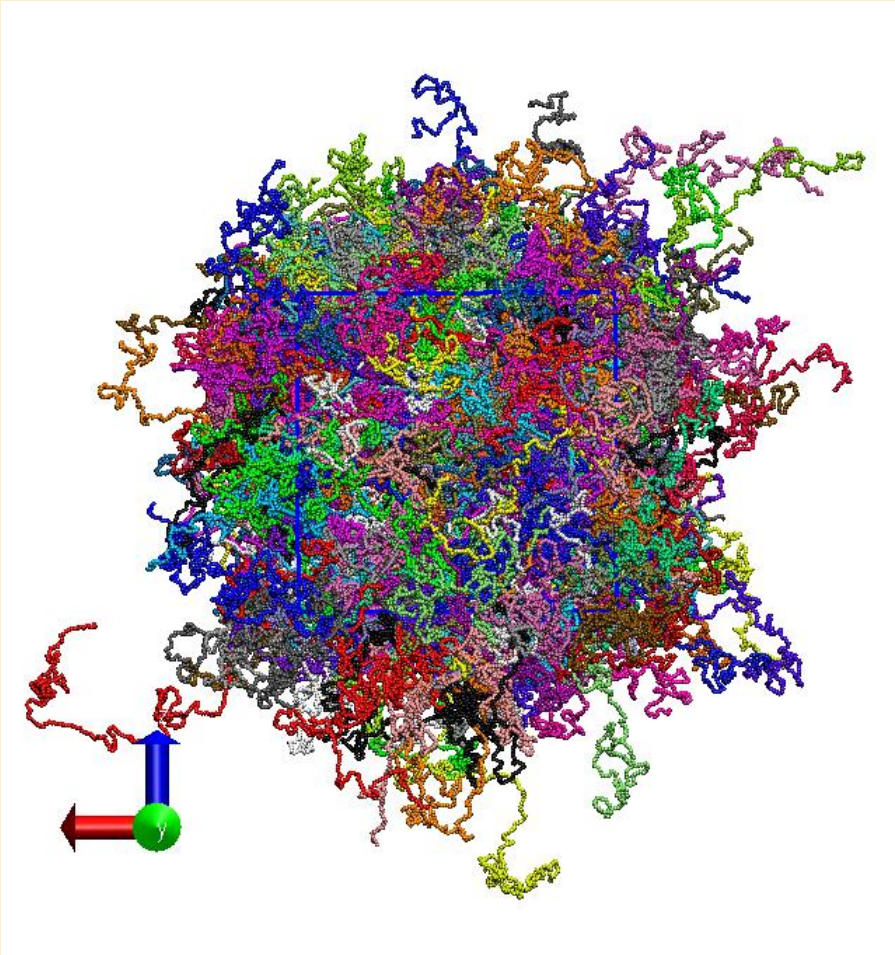
Plegamiento de una macromolécula

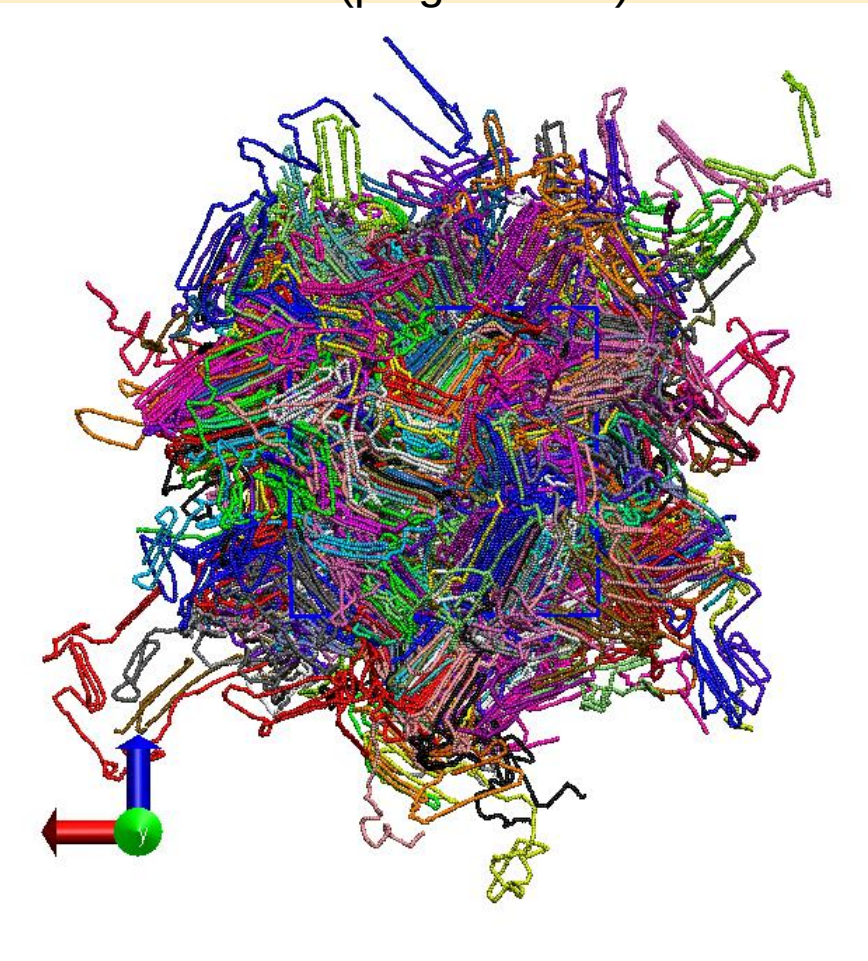


T* = 1
(fundido)

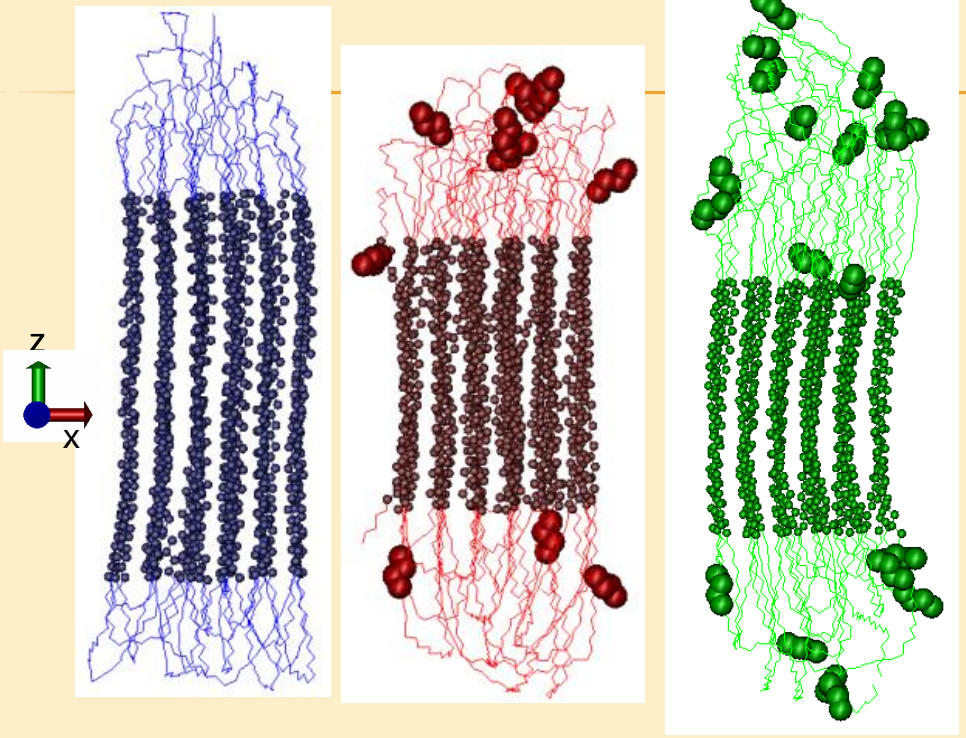
tiempo

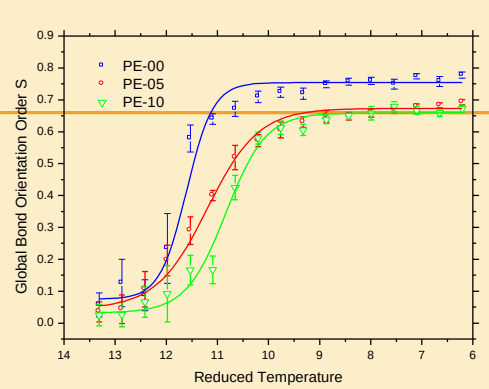
T* = 0.5
(plegamiento)

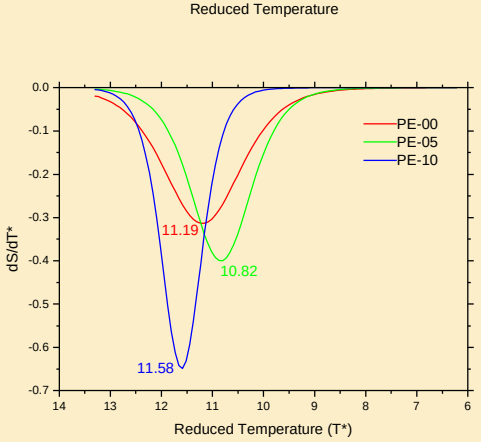




SIMULACION Y EXPERIMENTOS EN MONOCRISTALES







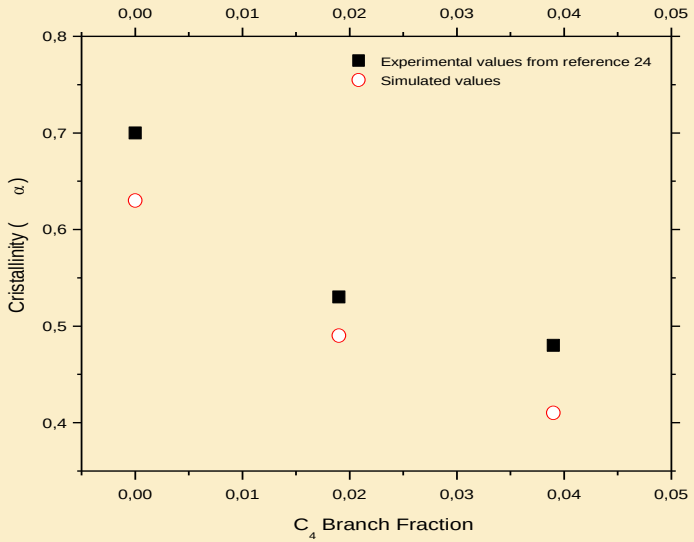


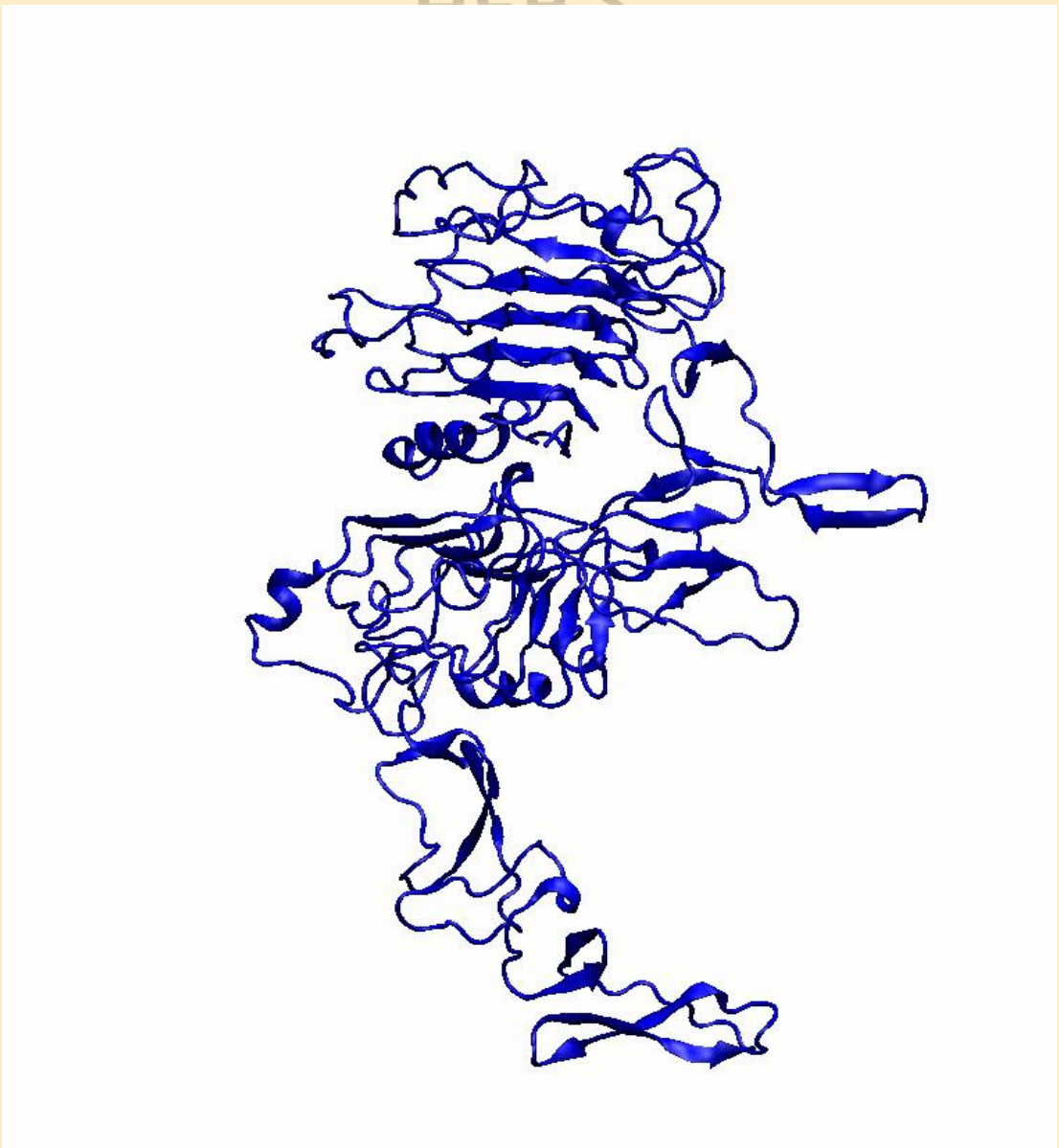
Table 2: Simulated densities as a function of the degree of branching.

	PE-00	**PE-05**	**PE-10**
Crystallyne(ρ_c)	0.933	0.917	0.915
Amorphous(ρ_a)	0.858	0.863	0.860
Amorphous experimental[25]	*0.861*		
Total(ρ)[a]	0.906	0.889	0.882
Total Experimental[25]	*0.952*	*0.931*	*0.922*

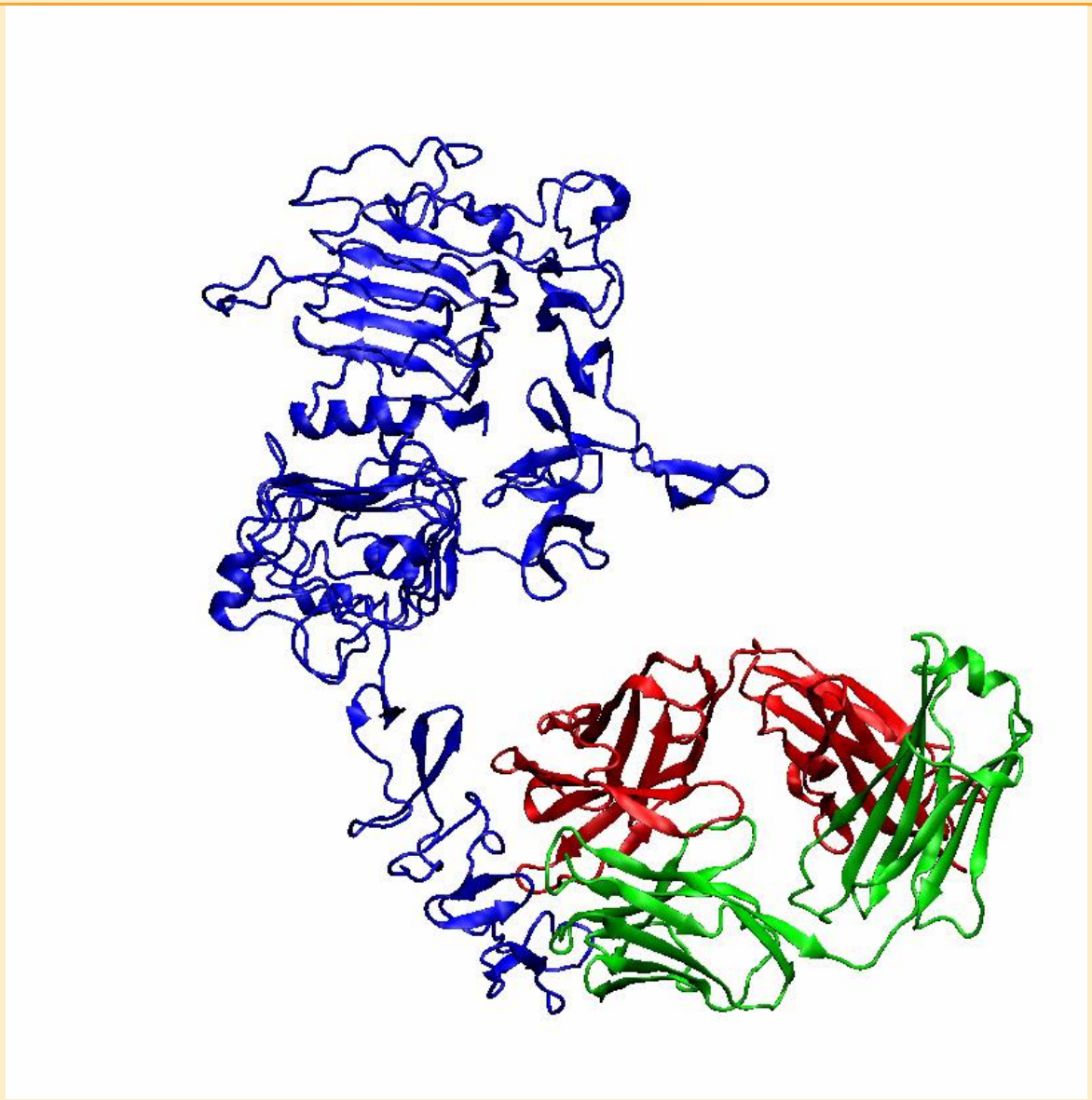
[a] Calculated as: $\rho_c = \alpha\rho_c + (1-\alpha)\rho_a$ where α is the simulated crystallinity reported in Fig 8. Experimental values are in italics style. Units are given in g/cm^3.

PROPIEDADES HIDRODINÁMICAS DEL COMPLEJO HER2/TZM

HER2



HER2 / TZM



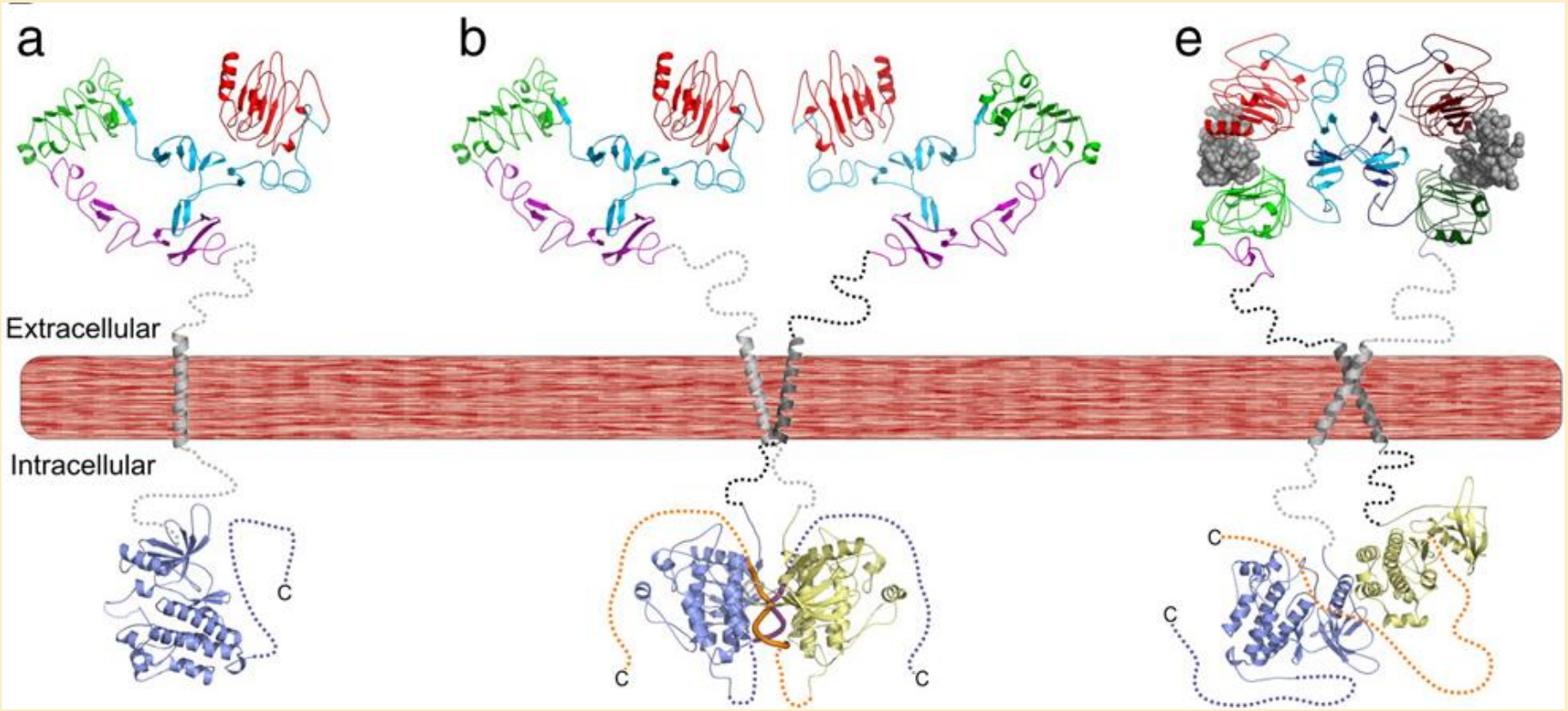
- HER2 pertenece a una familia de receptores que son potentes mediadores en el crecimiento y desarrollo celular

Nature Review 9 (2009) 463-475
Advances In Protein Chemistry 68 (2004) 1-27

Receptor	Enfermedad	Estrategias
HER2 Se sobre-expresa	Cáncer de mama Cáncer gastrico Cáncer de ovario Cáncer pulmonar	Inhibidores tirosina- kinasa, proteínas de choque térmico, inhibidores de dimerización y conjugación entre anticuerpos-quimioterapia.
	Tratamiento actual	Anticuerpos monoclonales especificos

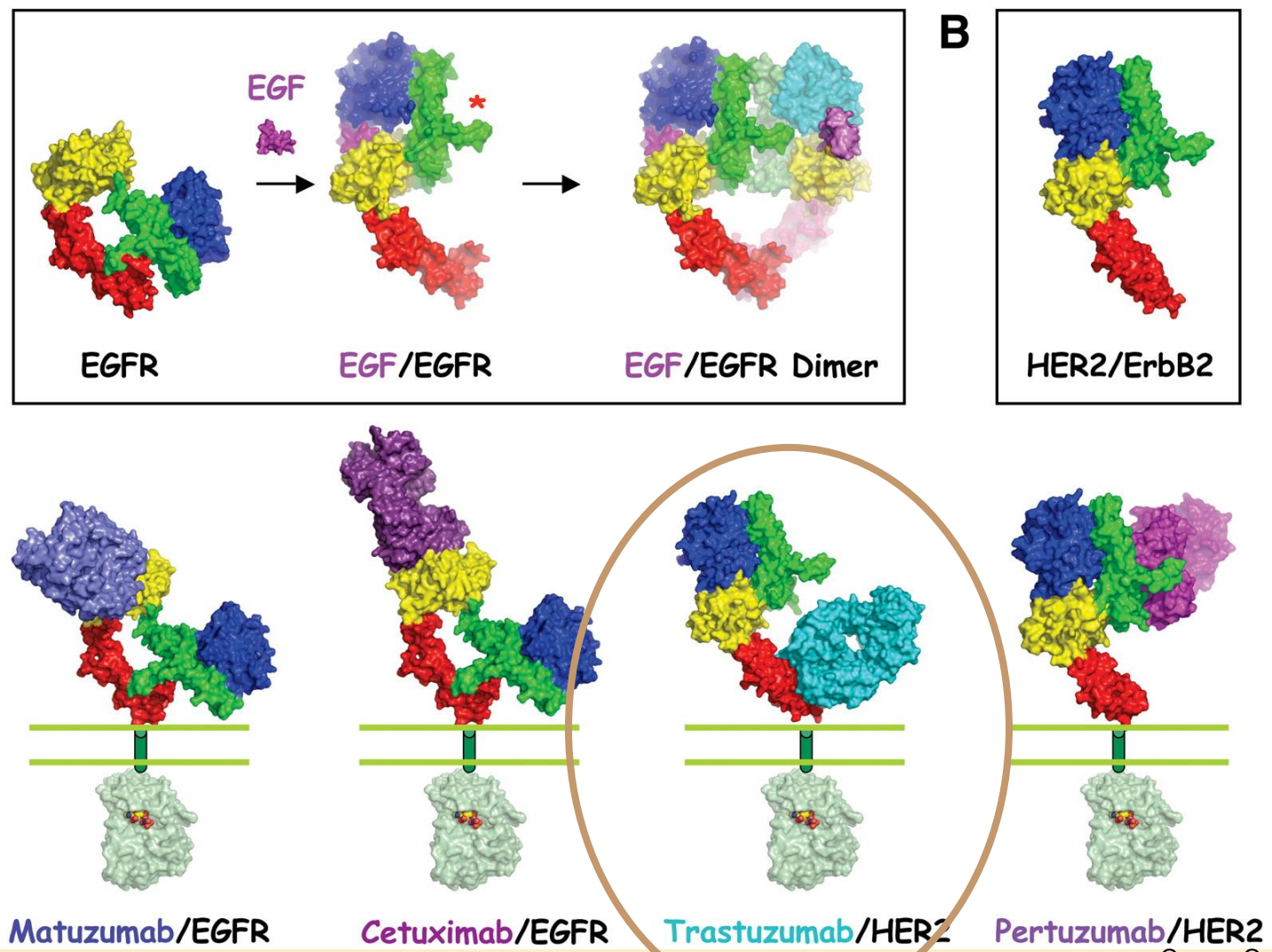
MECANISMOS DE TRANSFERENCIA:

Dimerización



Biochimica et Biophysica Acta 178 (2008) 12-13
Advances in Protein Chemistry 68 (2004) 1-17
Structure 15 (2007) 942-954

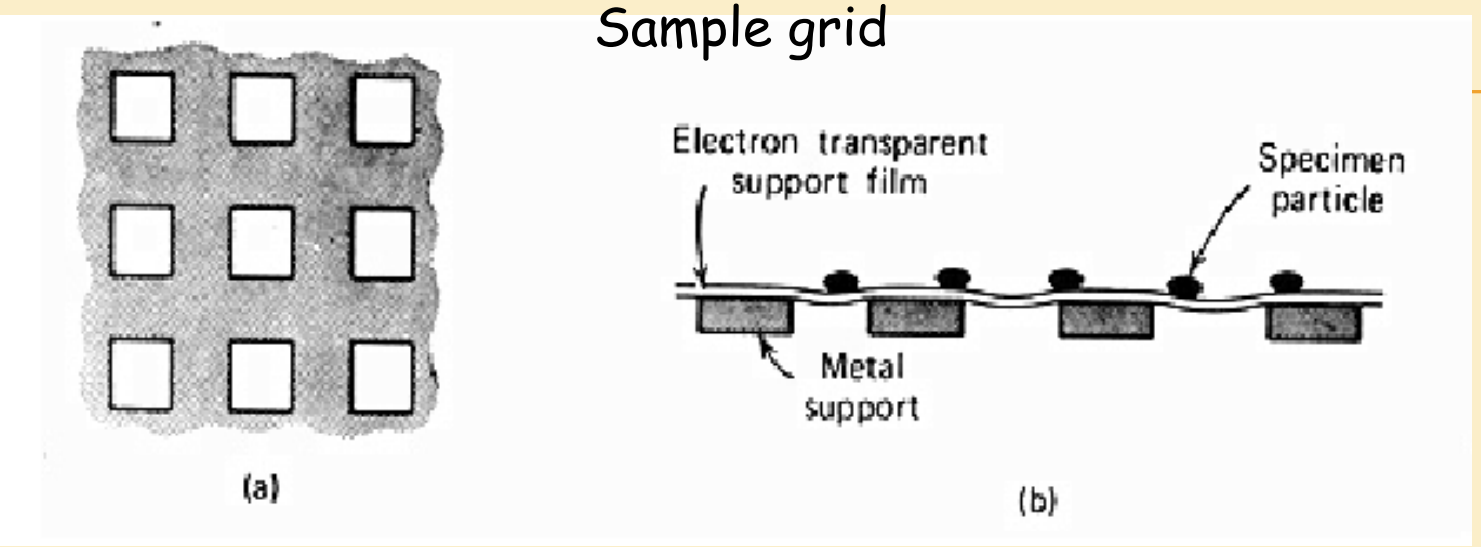
Interacción anticuerpo ErbB



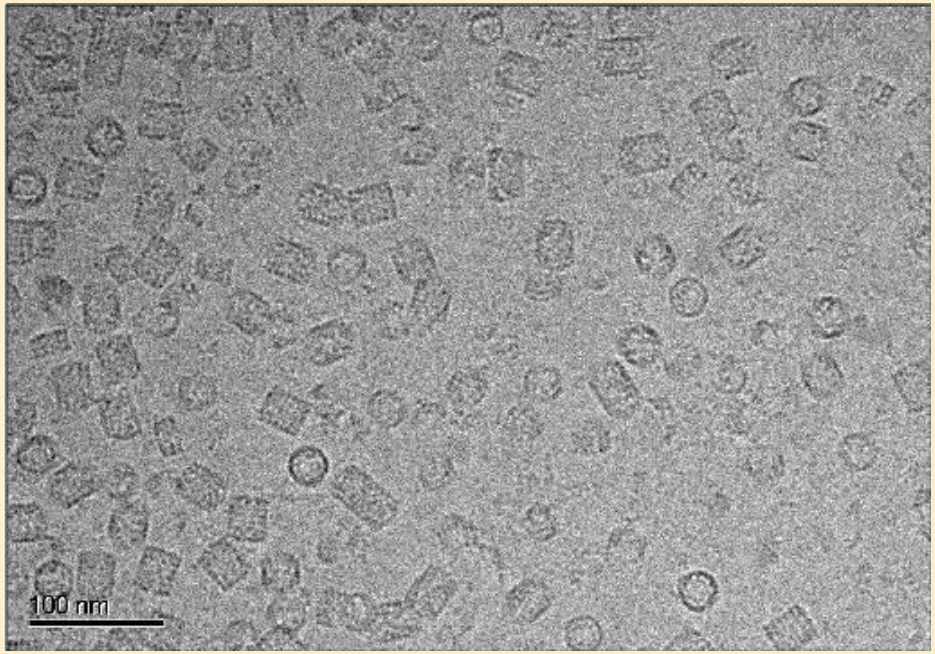
Cancer Cell 13 (2008) 291
PNAS 105 (2008) 6109
BMC Systems Biology 3:1 (2009) 1

Transmission Electron Microscopy

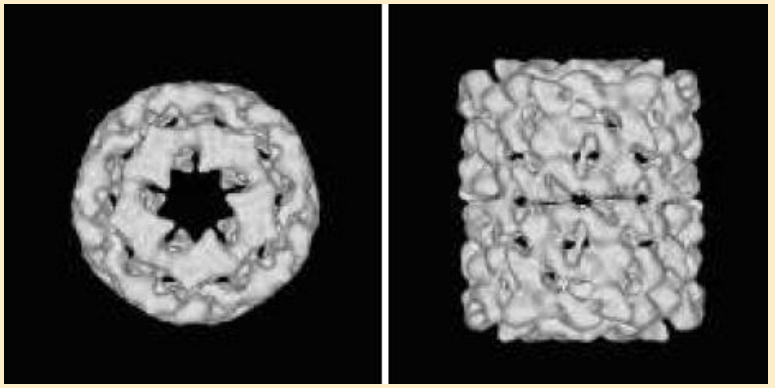
Sample grid



Image

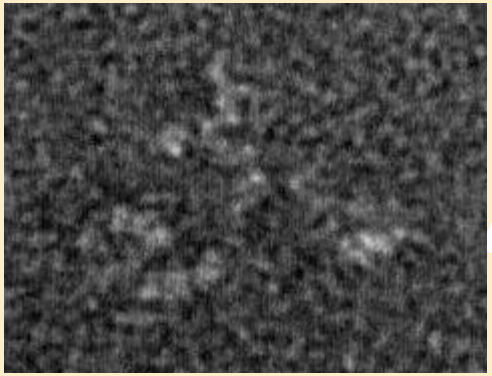


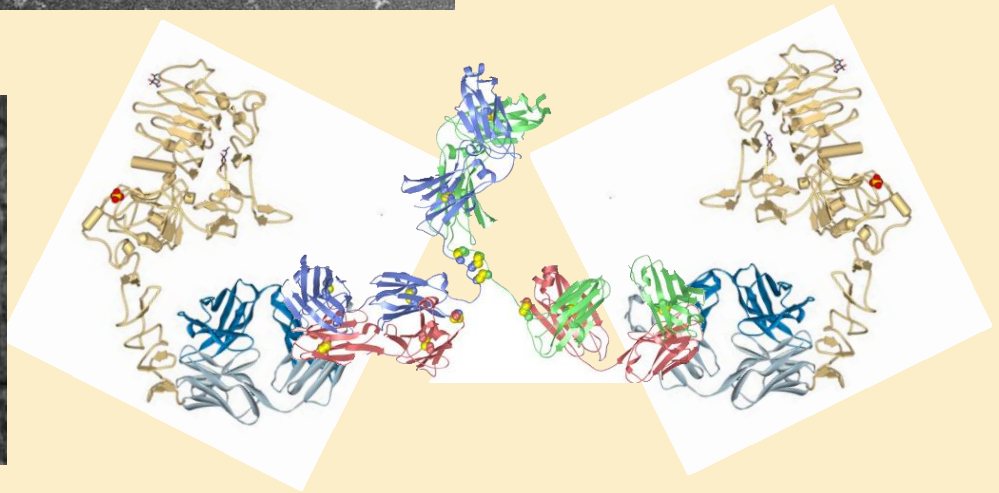
Reconstruction



360 kDa

HER2/TZM (C2)



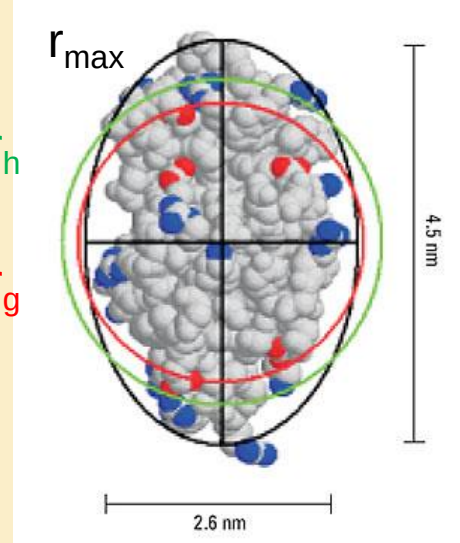


Dynamic Light Scattering
Diffusion Coefficient

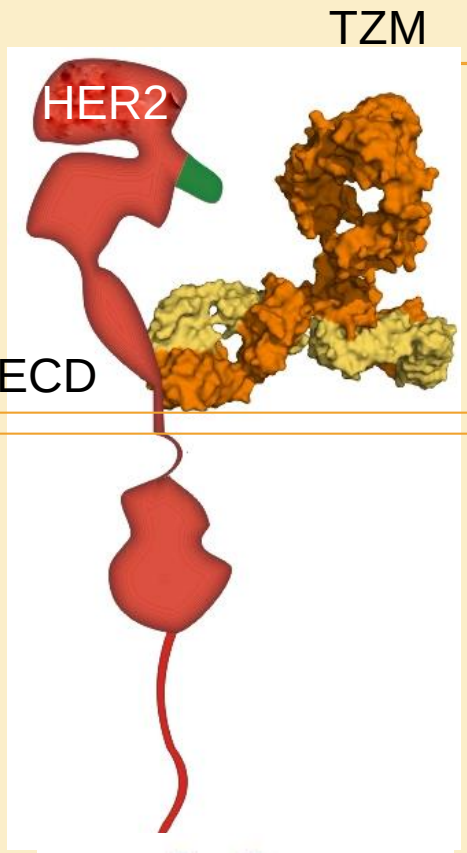
Stokes-Einstein relation

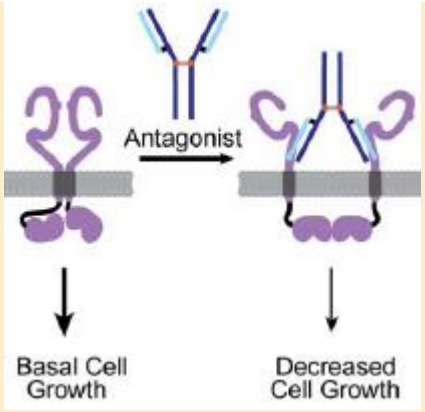
- D = Diffusion coefficient
- k = Boltzmann's coefficient
- T = Temperature
- η = Viscosity
- R = hydrodynamic radius

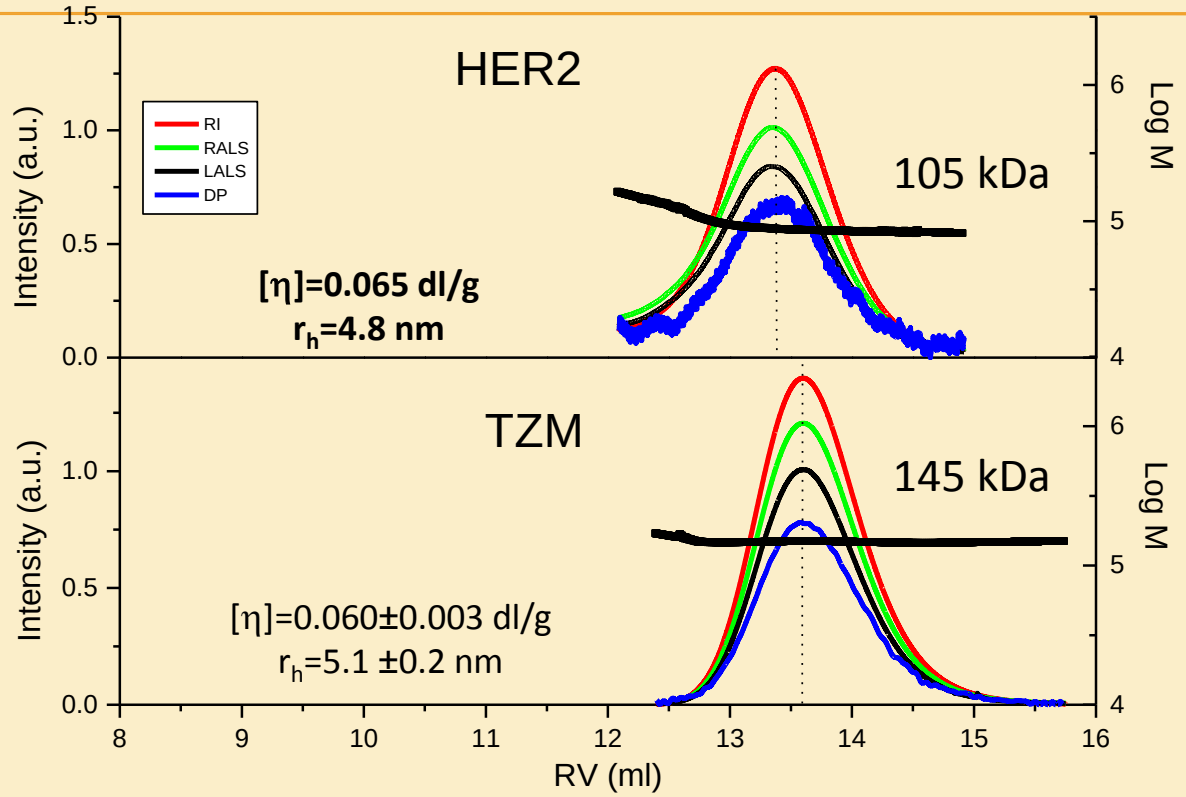
$$D = \frac{kT}{6\pi\eta R}$$



HER2/TZM







Calibration

BSA
[η]=0.038±0.002 dl/g
r_h=3.42 ±0.06 nm

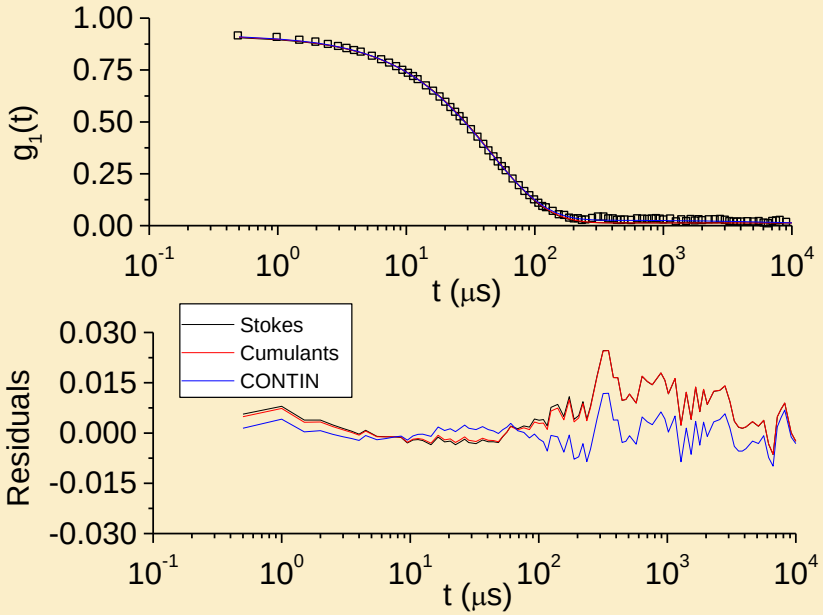
BSA Literature
[η]=0.033-0.042 dl/g
r_h=3.27-3.54 nm

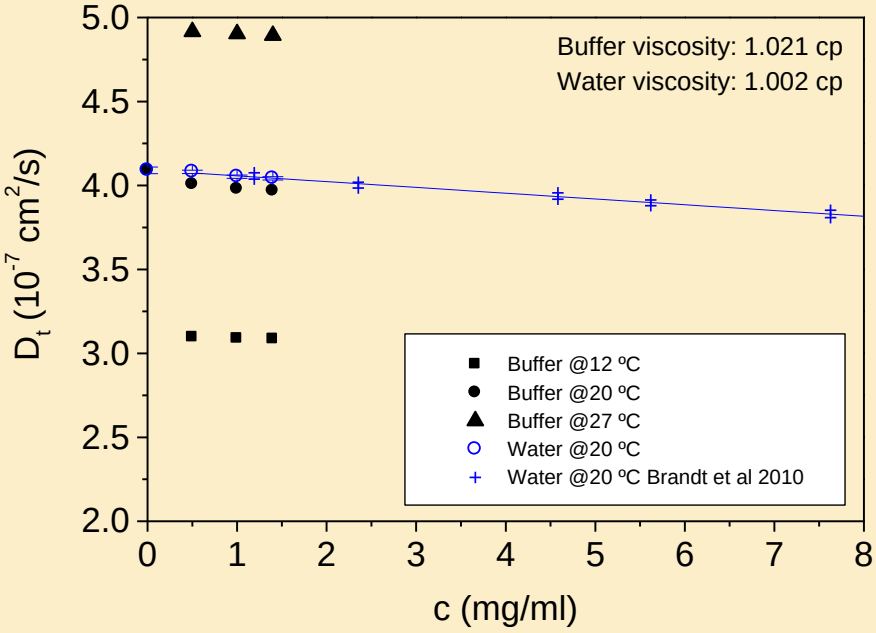
TZM (Literature)

[η]=0.064±0.002 dl/g
r_h=5.3 ±0.1 nm
M_w~150 kDa

Diffusion Coefficient and Size

TZM (monodisperse)

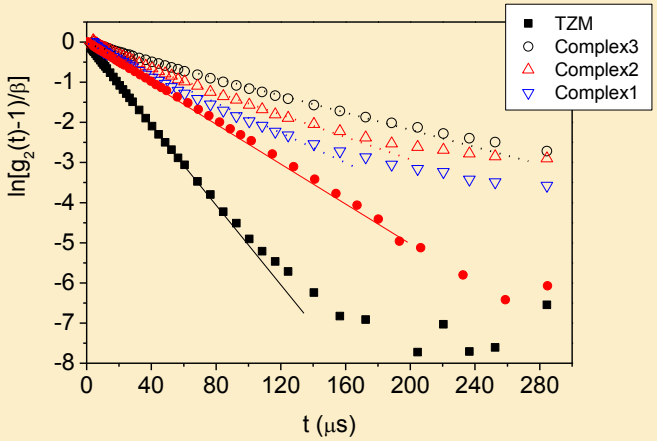


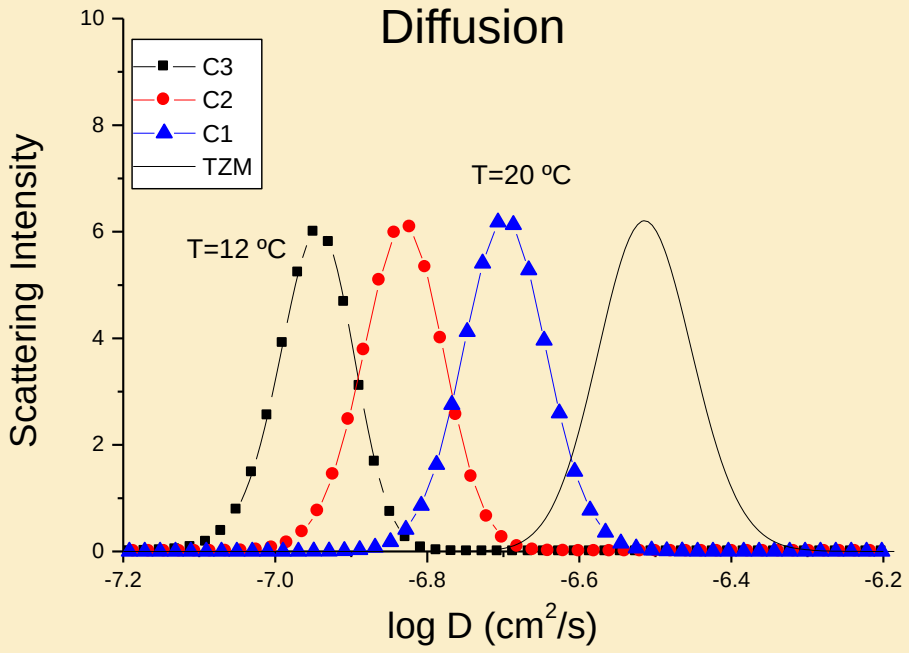


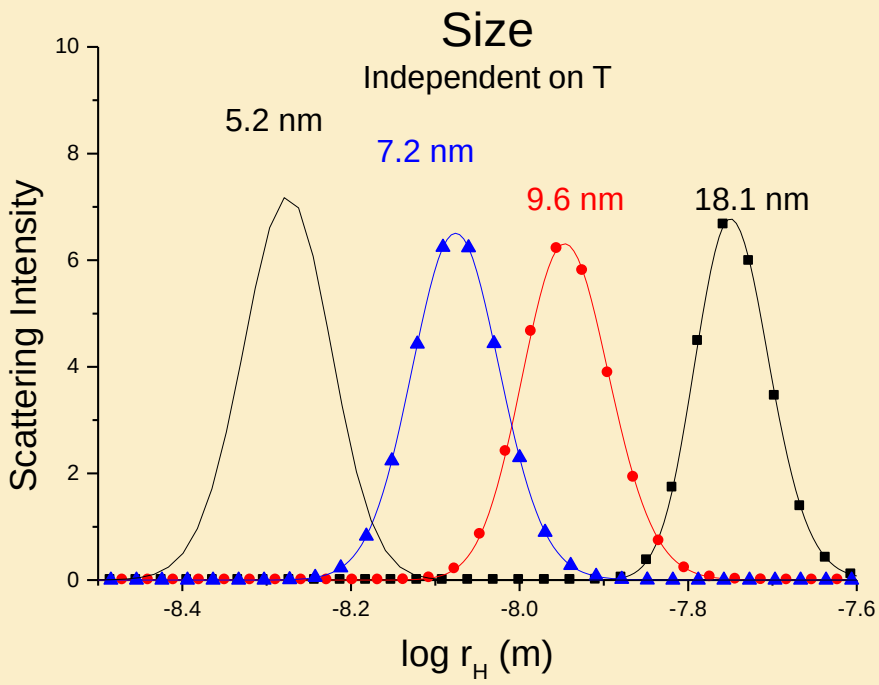
D_t (Buffer @20 ºC) = 4.01 10^{-7} cm^2/s
D_t (Water @20 ºC) = 4.09 10^{-7} cm^2/s

r_h (Stokes-Einstein)=5.23 nm
r_h (TDA-SEC)=5.16 nm

Diffusion Coefficient and Size
Complexes

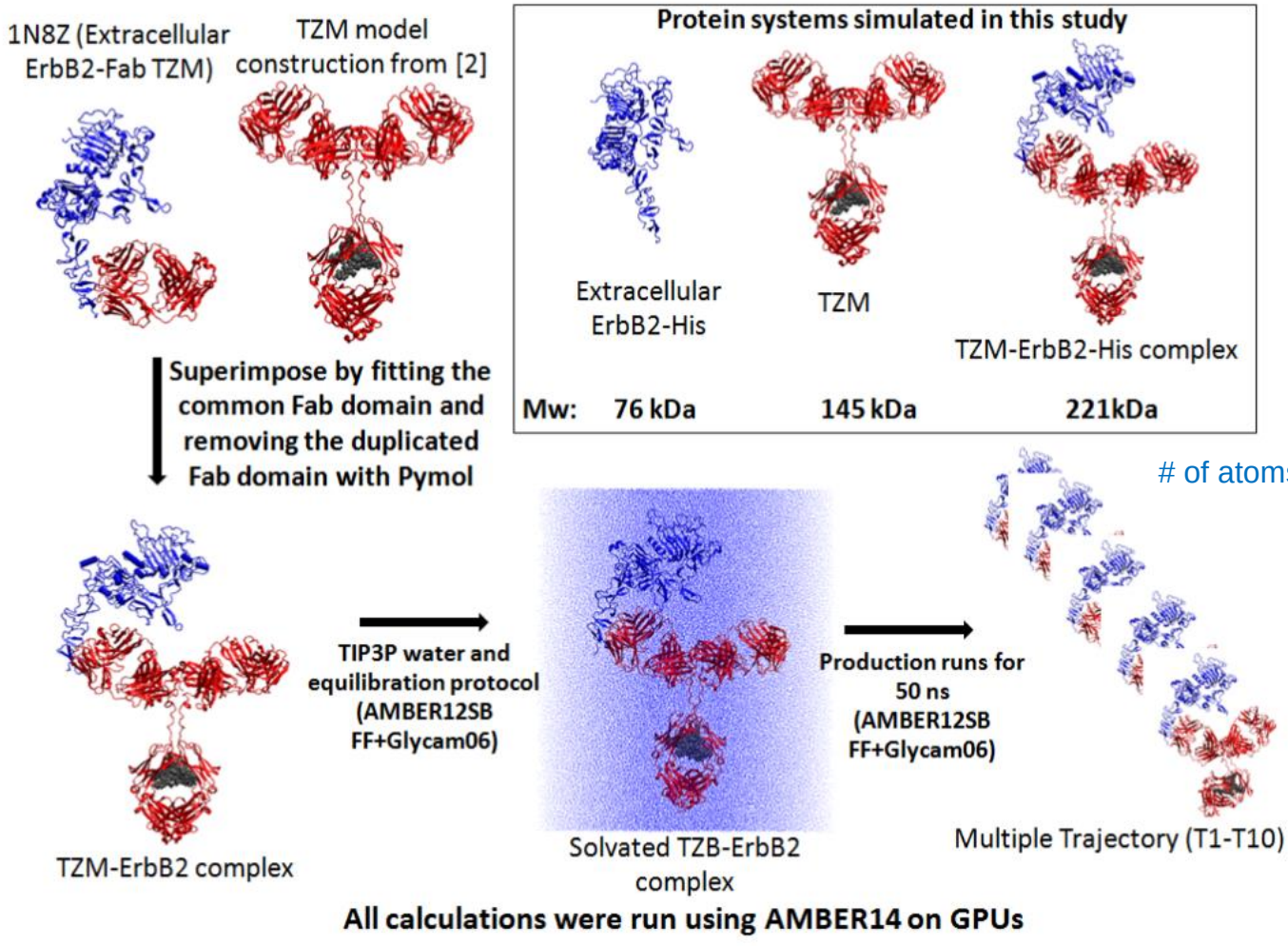


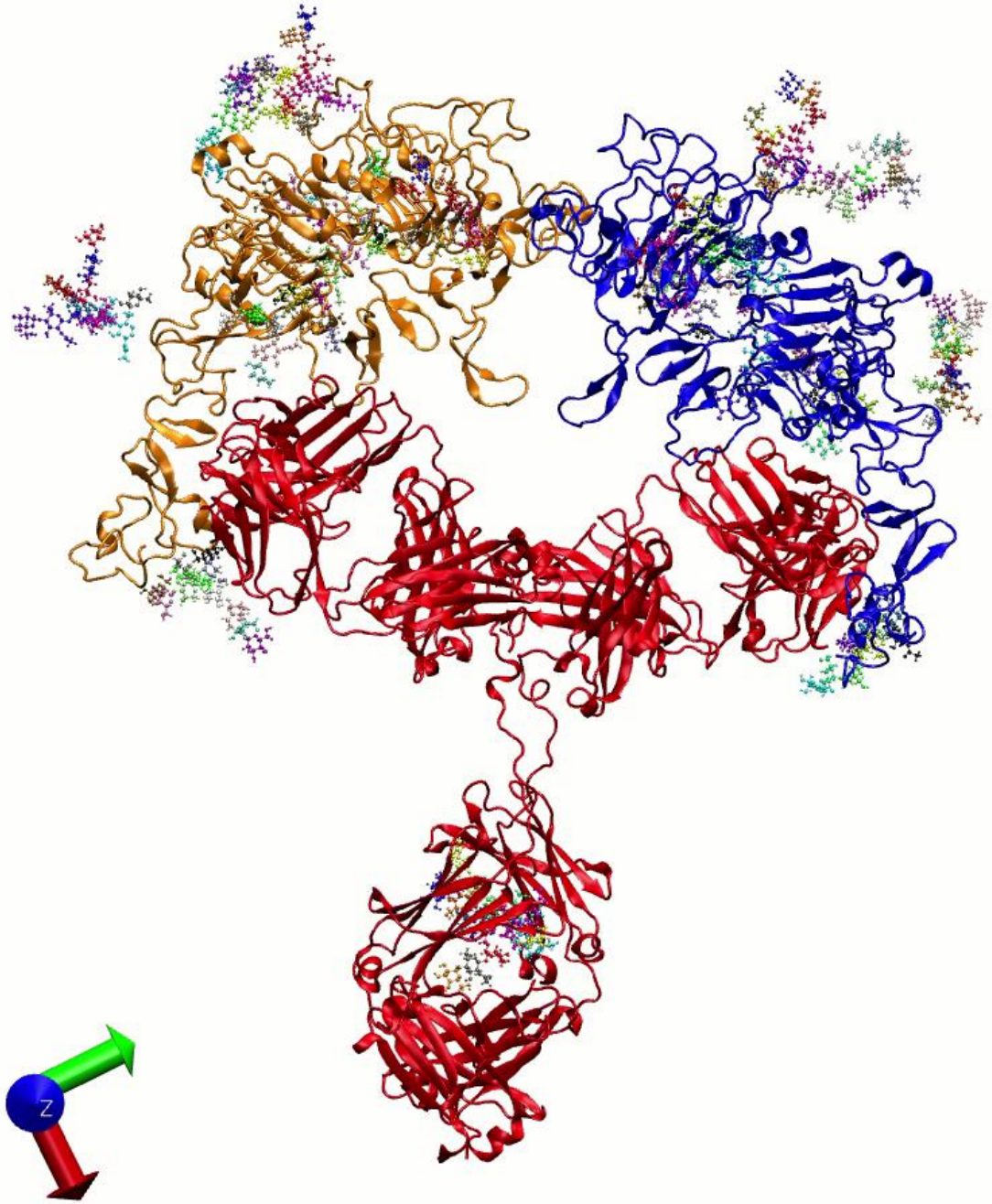




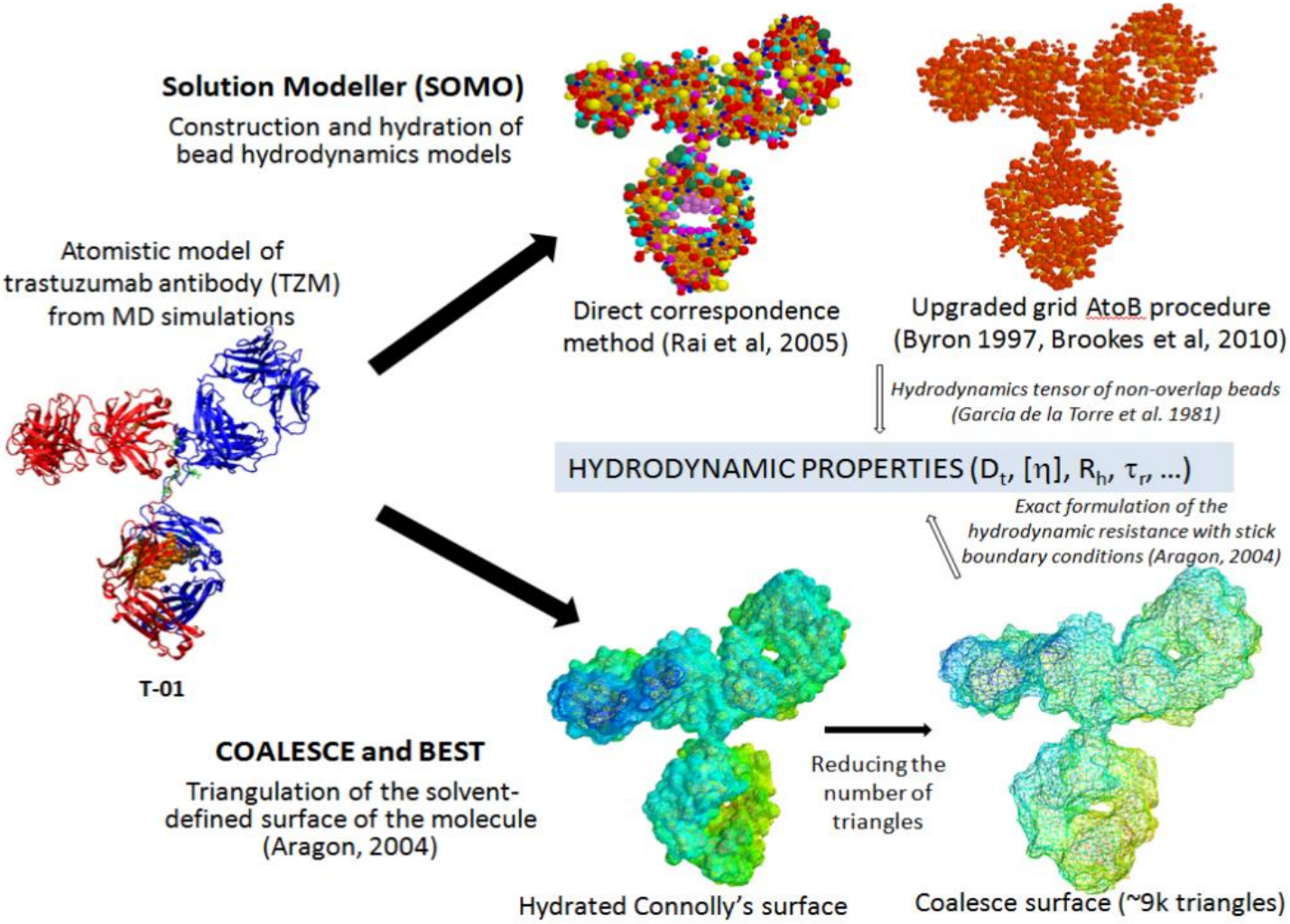
Study of the interaction in extracellular domain ErbB2-Transtuzumab complexes by hydrodynamic properties and computational models

Generating atomistic structures from MD simulations




Z

Study of the interaction in extracellular domain ErbB2-Transtuzumab complexes by hydrodynamic properties and computational models



Study of the interaction in extracellular domain HER2-Transtuzumab complexes by hydrodynamic properties and computational models

Table 3. *Comparison of experimental and calculated hydrodynamic results for the structures studied, including the TZM as model case, at T = 293 K*

Sample	[η] ($cm^3 \cdot g^{-1}$) SEC	[η] ($cm^3 \cdot g^{-1}$) SIM	D×10^7 ($cm^2 \cdot s^{-1}$)[a] DLS	D×10^7 ($cm^2 \cdot s^{-1}$)[a] SIM
TZM	6.5 ± 0.1	**6.6 ± 0.2**	4.09 ± 0.02 (5.2 nm)	**3.95 ± 0.03 (5.3 nm)**
eHER2	n.d.	**5.7 ± 0.2**	n.d.	**5.32 ± 0.04 (4.0 nm)**
g-eHER2	6.4 ± 0.2	**6.5 ± 0.2**	4.56 ± 0.02 (4.7 nm)	**4.77 ± 0.04 (4.5 nm)**
g-eHER2 dimer	6.9 ± 0.5[a]	**6.9 ± 0.2**	3.57 ± 0.02 (6.0 nm)	**3.71± 0.02 (5.8 nm)**
Complex 1:1 (TZB-erbb2)	7.4± 0.2	**7.9 ± 0.2**	3.16± 0.02 (6.8 nm)	**3.20 ± 0.02 (6.7 nm)**
Complex 1:2 (TZB-erbb2)$_2$	8.6± 0.2	**8.4 ± 0.2**	2.38± 0.02 (9.0 nm)	**2.80 ± 0.02 (7.6 nm)**

[a] In parentheses the corresponding value of r_h obtained from Eq. 6 in water at T = 293 K.

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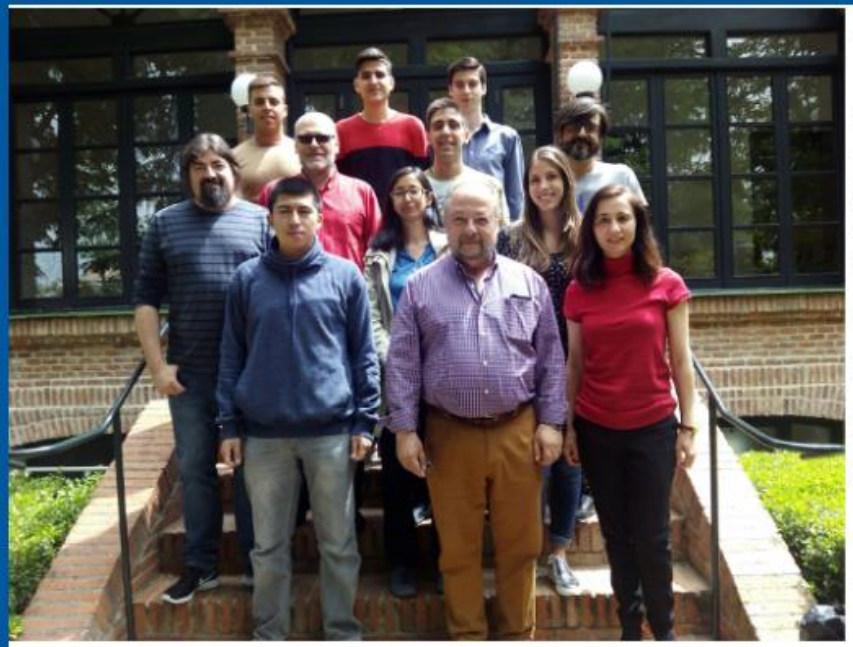

Group members (left to right): *Top*: Mr. Rubén Casas, Mr. Alejandro Clemente, Mr. Guillermo Juárez. *Middle*: Dr. Javier Ramos, Dr. Victor Cruz, Dra. Virginia Souza-Egipsy, Mr. Eduardo Sanchez, Mrs. Anna Espasa, Dr. Juan Francisco Vega. *Bottom*: Mr. Alexis Julián Amagua, Prof. Javier Martínez-Salazar, Dra. Sonia Martínez.

BIOPHYM is a group devoted to experimental and computational research activities related to the fundamental physical properties of macromolecular systems: molecular dynamics, assembling and functionality of synthetic polymers and biomacromolecular systems.

BIOPHYM is particularly concerned on maintaining a constant link with the industrial sector. The formation of doctoral students is also an important task for this group.

THE END

MUCHAS GRACIAS POR VUESTRA ATENCIÓN
OS ESPERAMOS ESTA TARDE