The nucleation of molecules in solution using shear flow

Debuysschère Robin

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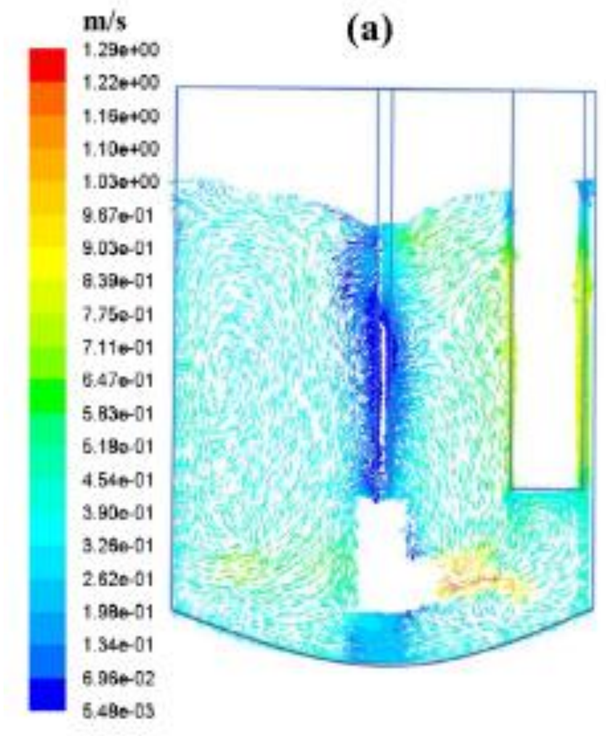
Flow conditions in industrial crystallization processes

CSTR (also true for MSMPR) [1]

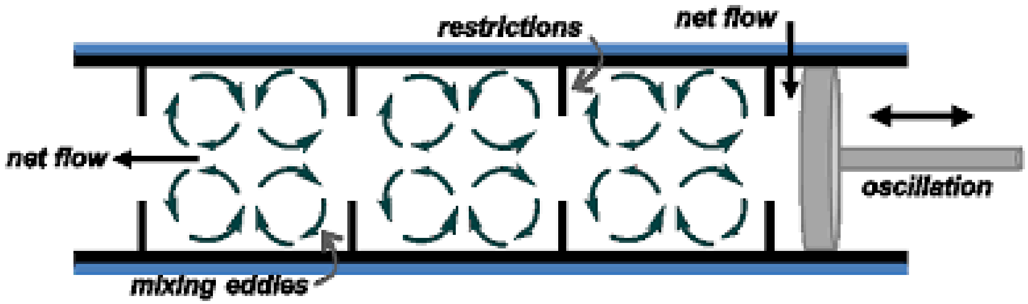


$\Rightarrow$ Inhomogeneous

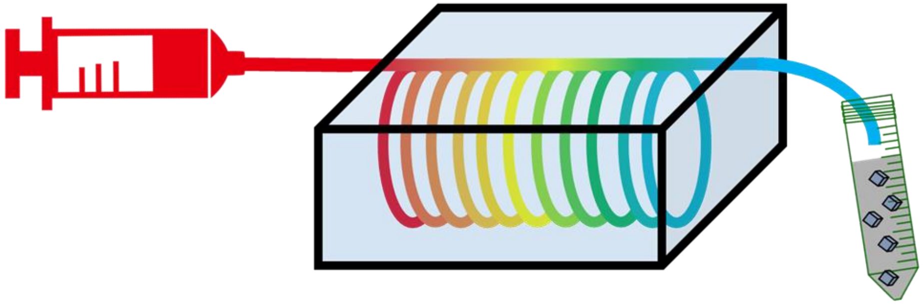
Homogenizing

Controlling

COBRC [2]



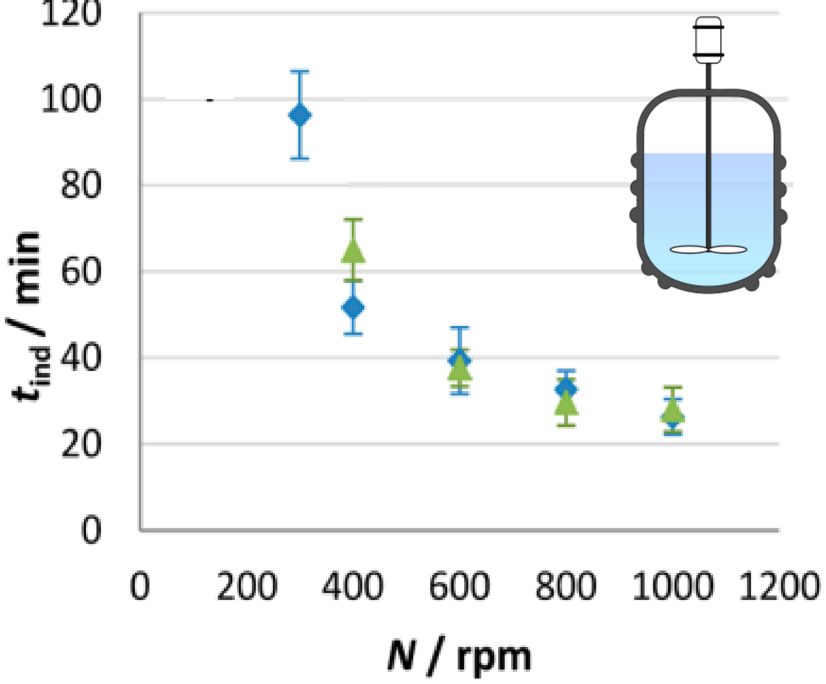
LFC



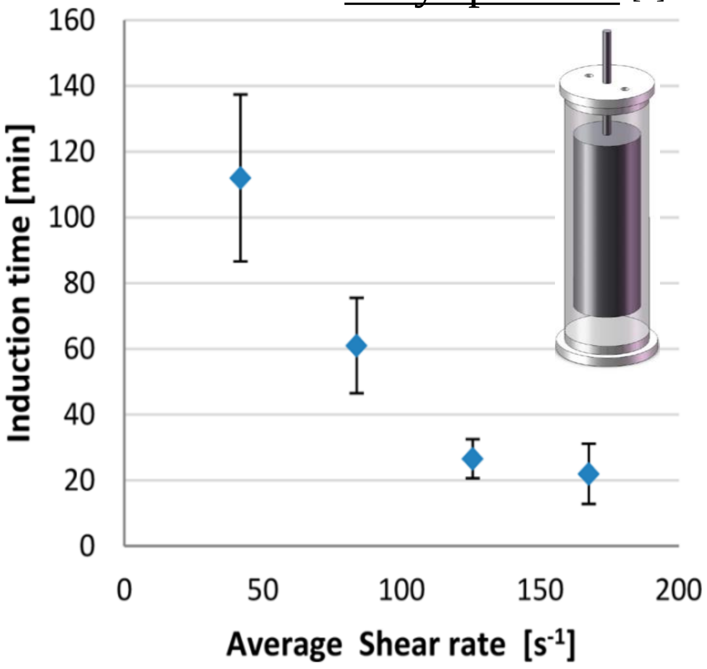
[1] Camacho Corzo, D. M., Ma, C. Y., Mahmud, T., & Roberts, K. J. (2020) *Organic Process Research & Development*, *24*(11), 2565-2582.
[2] McGlone, T., Briggs, N. E., Clark, C. A., Brown, C. J., Sefcik, J., & Florence, A. J. (2015). *Organic Process Research & Development*, *19*(9), 1186-1202.

Flow behaviour and crystallization

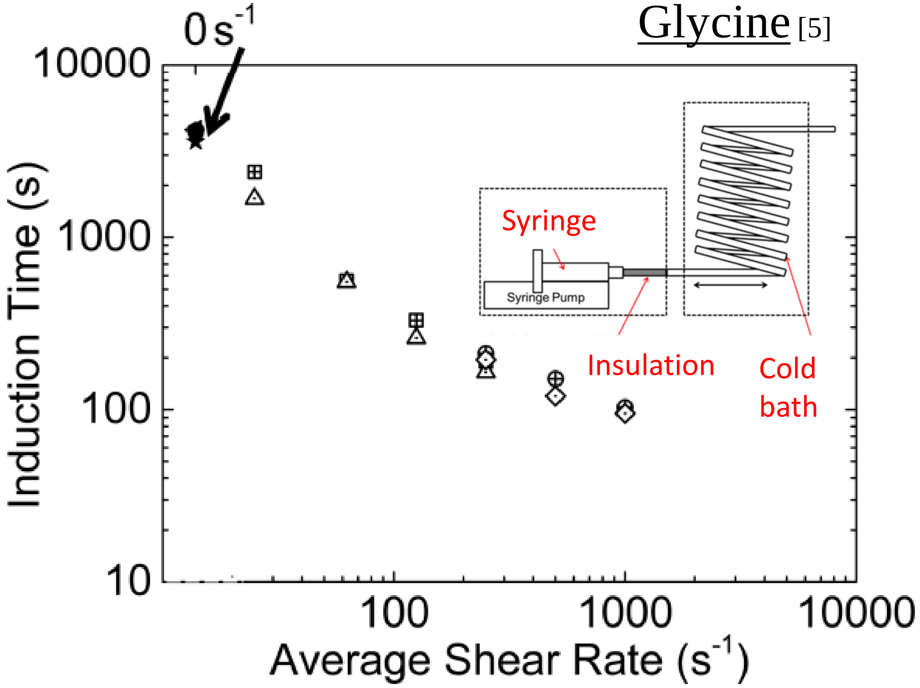
Butyl-paraben [3]



Butyl-paraben [4]

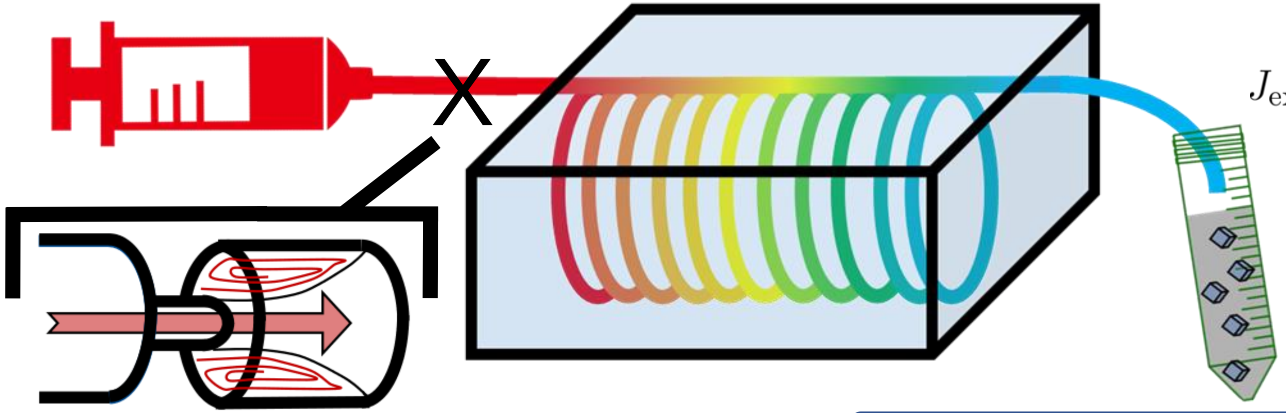


Glycine [5]

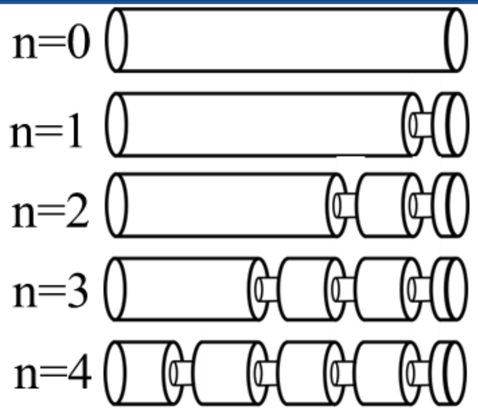


[3] Liu, J., Svard, M., & Rasmuson, Å. C. (2015). *Crystal Growth & Design*, *15*(9), 4177-4184.
[4] Liu, J., & Rasmuson, Å. C. (2013). *Crystal growth & design*, *13*(10), 4385-4394.
[5] Forsyth, C., Mulheran, P. A., Forsyth, C., Haw, M. D., Burns, I. S., & Sefcik, J. (2015). *Crystal Growth & Design*, *15*(1), 94-102.

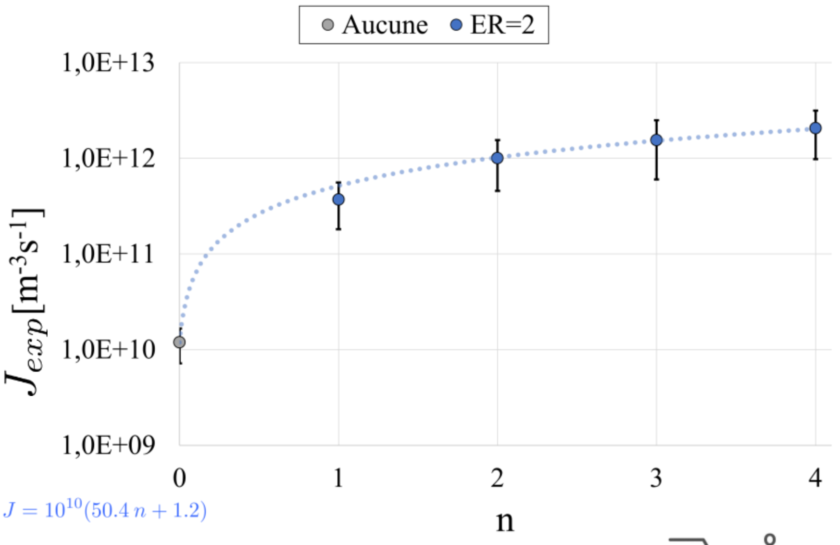
Introduction

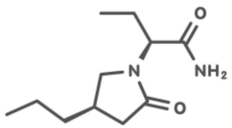


$$J_{\text{exp}} = \frac{C - C^*}{\rho_c V_c t^*} [m^{-3} s^{-1}]$$

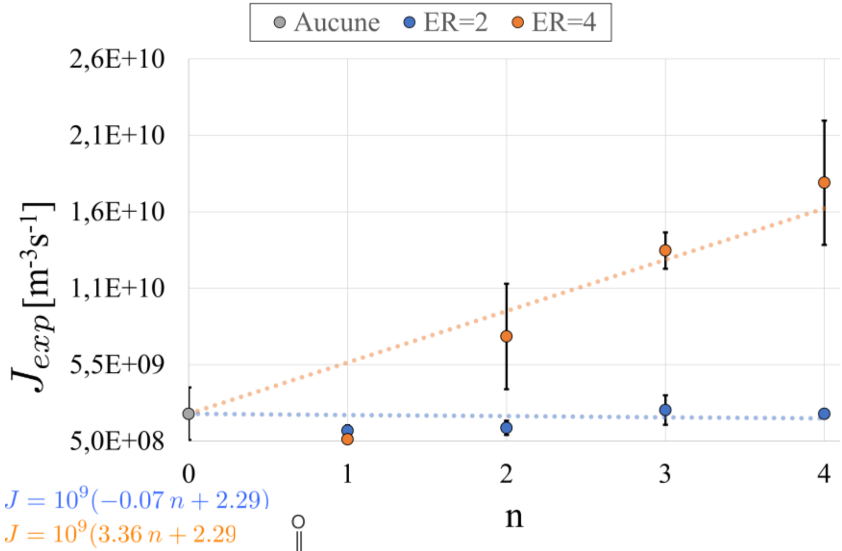


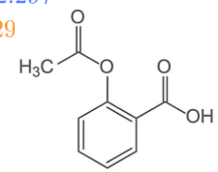
Brivaracetam [6]



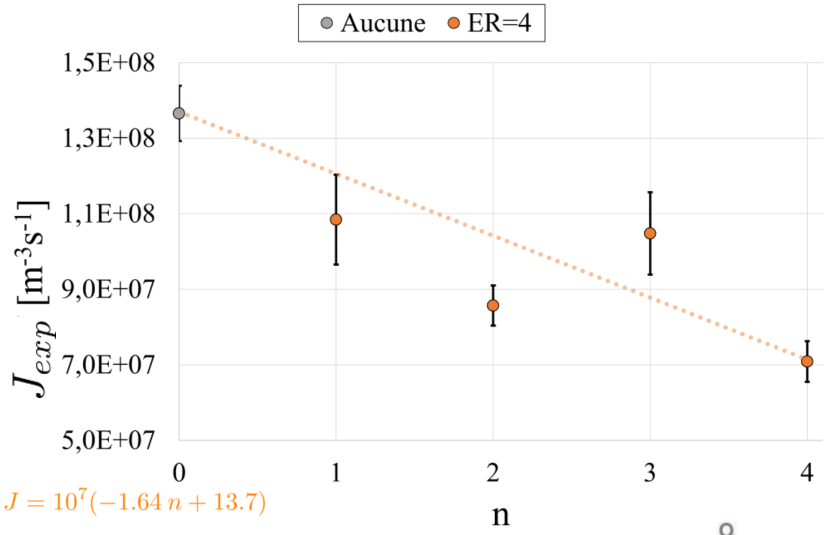


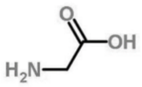
Aspirin [7]





Glycine [8]



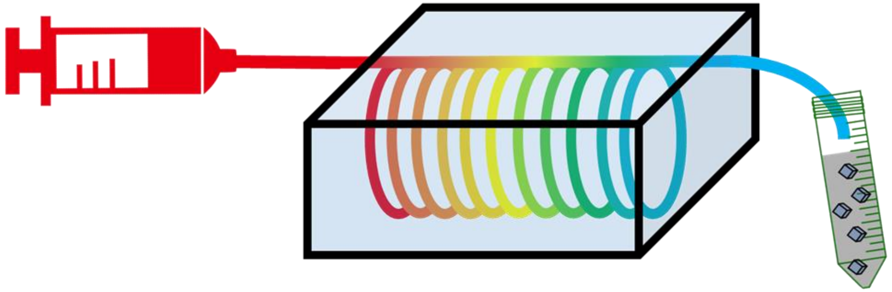


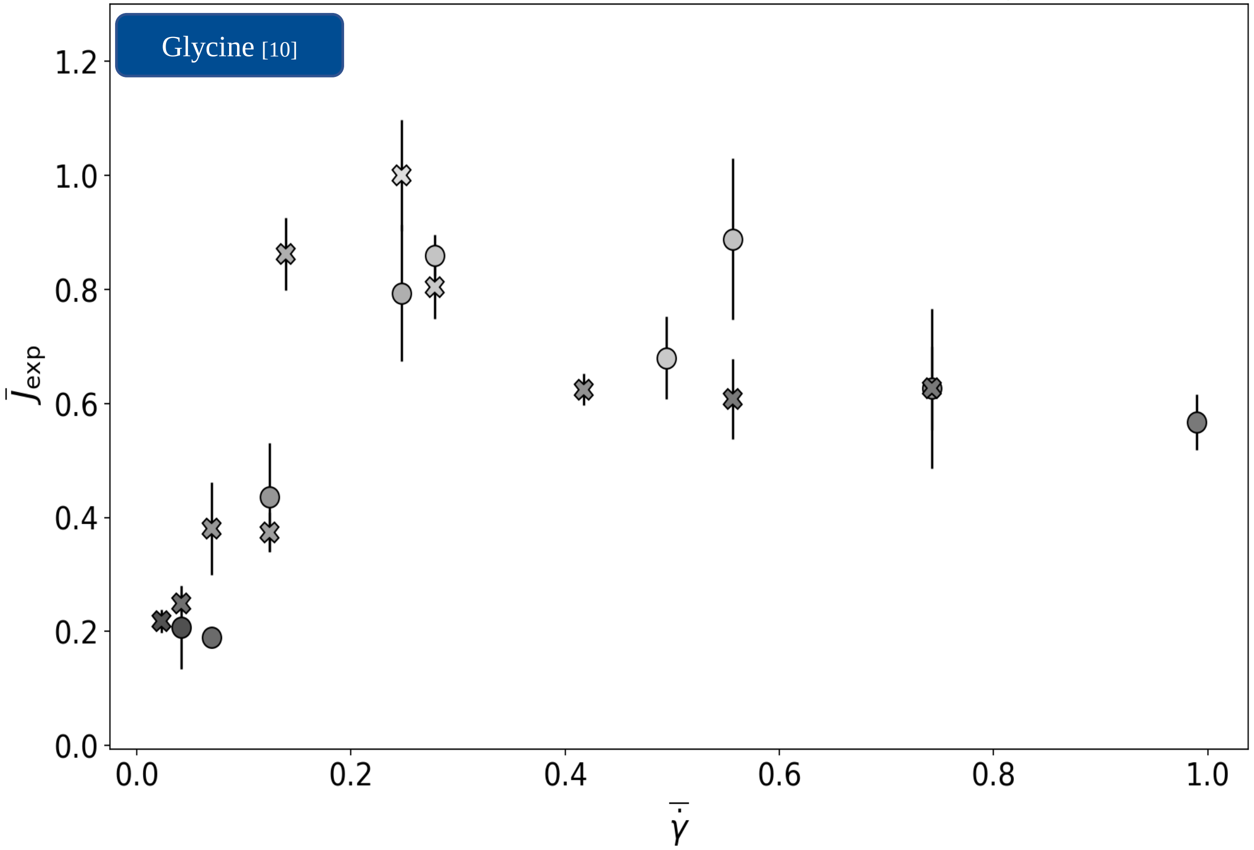
[6] Rimez, B., Debuysschère, R., Conté, J., Lecomte-Norrant, E., Gourdon, C., Cognet, P., & Scheid, B. (2018). *Crystal Growth & Design*, *18*(11), 6431-6439.

[7] Rimez, B., Debuysschère, R., & Scheid, B. (2020). *Journal of Flow Chemistry*, *10*(1), 241-249.

[8] Debuysschère, R. (2022) Doctoral dissertation - ULB

Experimental shear-rate analysis





In crystallizer **WITHOUT** diameter constriction, changing

- Q : flow rate
- r : internal radius

- L the length to keep the residence time constant

Shear rate :

$$\dot{\gamma} = \frac{4Q}{\pi r^3}$$

CNT with shear [9]

$$J = N_t j Z e^{-\frac{F(R^*)}{k_b T}} \; [m^{-3}s^{-1}]$$

$$J_{\mathrm{th}} = \frac{J}{N_t} = jZe^{-\frac{F(R^*)}{k_b T}} \; [s^{-1}]$$

[9] Mura, F., & Zaccone, A. (2016). *Physical Review E*, *93*(4), 042803.
[10] Debuysschère et al. (2023) *Crystal Growth & Design*. 2023, 23, 7, 4979−4989

Theoretical shear-rate analysis

$$J_{\text{th}} = \frac{J}{N_t} = jZe^{-\frac{F(R^*)}{k_b T}} \; [s^{-1}]$$

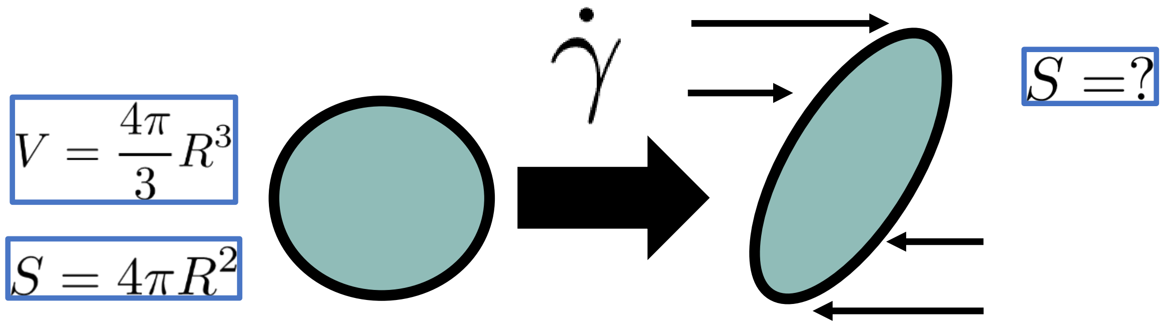
Free energy [9]

From the classical expression as spherical nucleus :

$$F(R) = -VF_v + S\nu$$

1) Shear induces an increase of the internal energy due to stretching

2) Volume is conserved but not the surface !



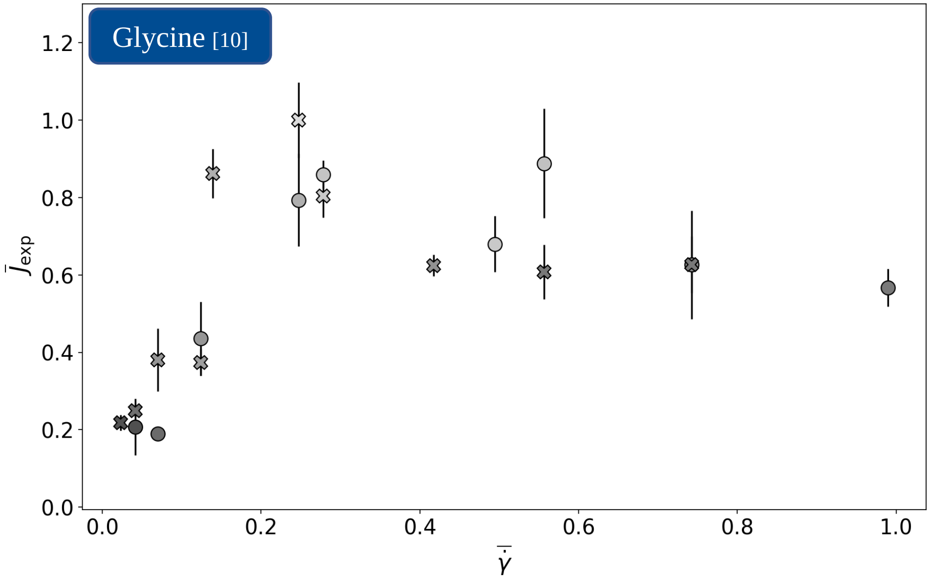
$F(R^*) \propto \dot{\gamma}$: Increase of the energy barrier with shear rate (unfavorable)

Successful aggregation rate [9]

$Zj \propto \dot{\gamma}$: Mass transfer enhancement with shear rate (favorable)

[9] Mura, F., & Zaccone, A. (2016). *Physical Review E*, *93*(4), 042803.

Theoretical shear-rate analysis

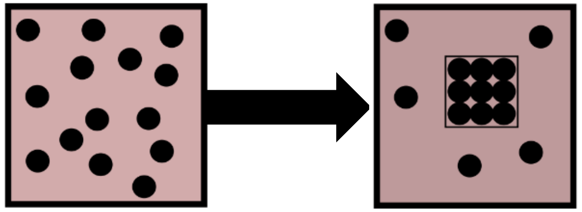


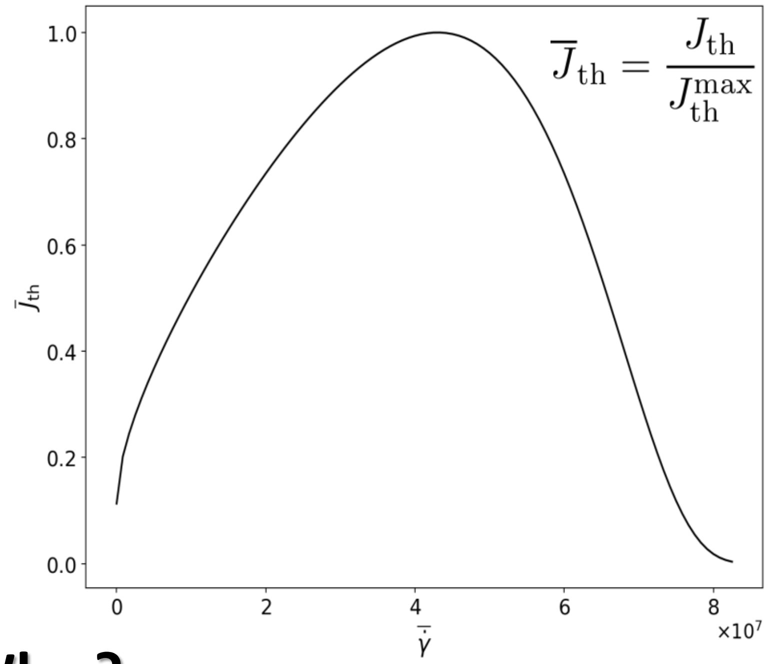
With :

$$\bar{J}_{\mathrm{exp}} = \frac{J_{\mathrm{exp}}}{J_{\mathrm{exp}}^{\mathrm{max}}}$$

and

$$\bar{\dot{\gamma}} = \frac{\dot{\gamma}}{\dot{\gamma}^{\mathrm{max}}}$$





For molecular aggregation

$\Rightarrow$ Not working [10]

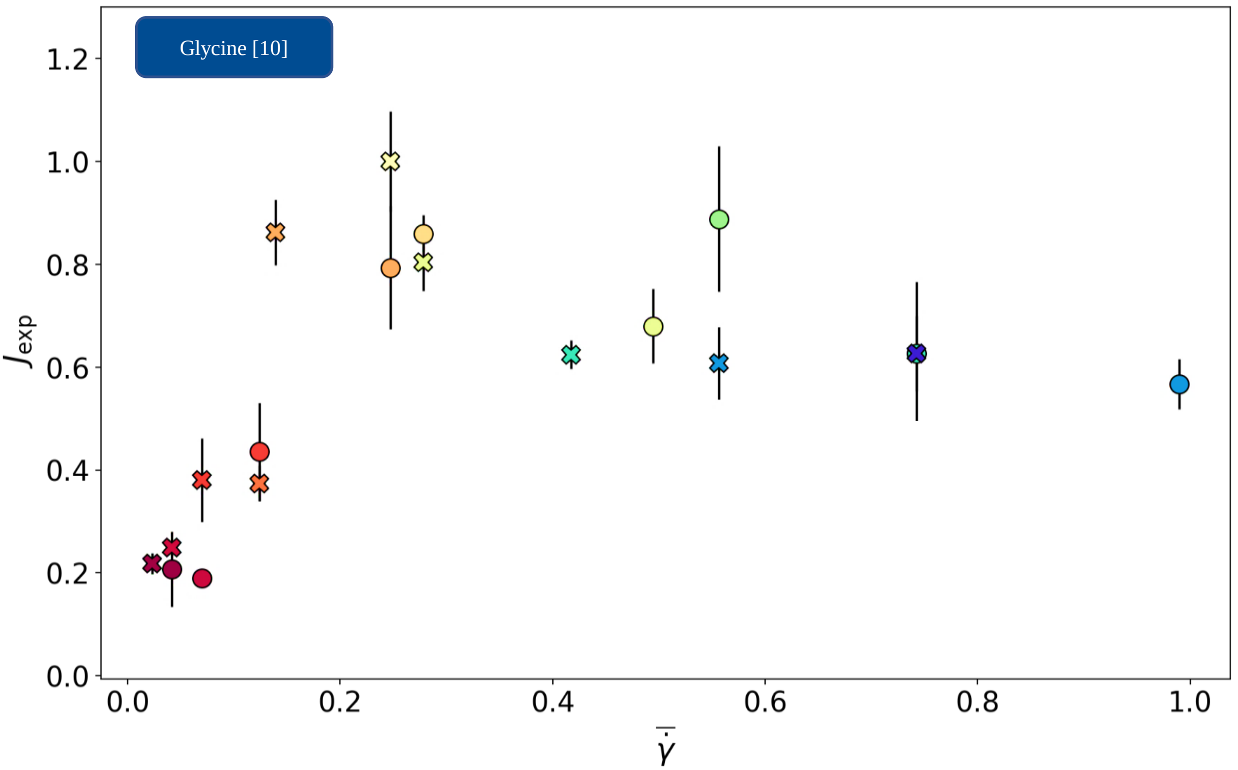
Why ?

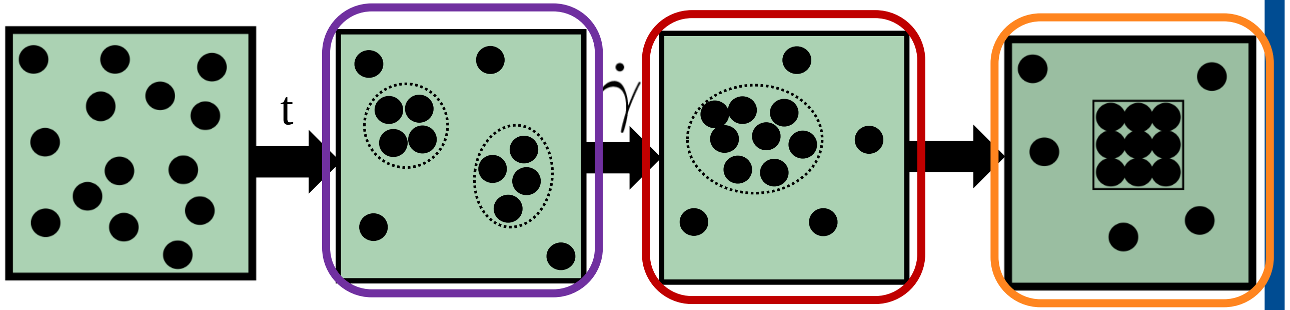
- Low nucleus scale (~ 1 nm [10])
- Rigid glycine nucleus (G ~10^{10} Pa [11])

$\Rightarrow$ Deformation effect << mass transfer effect

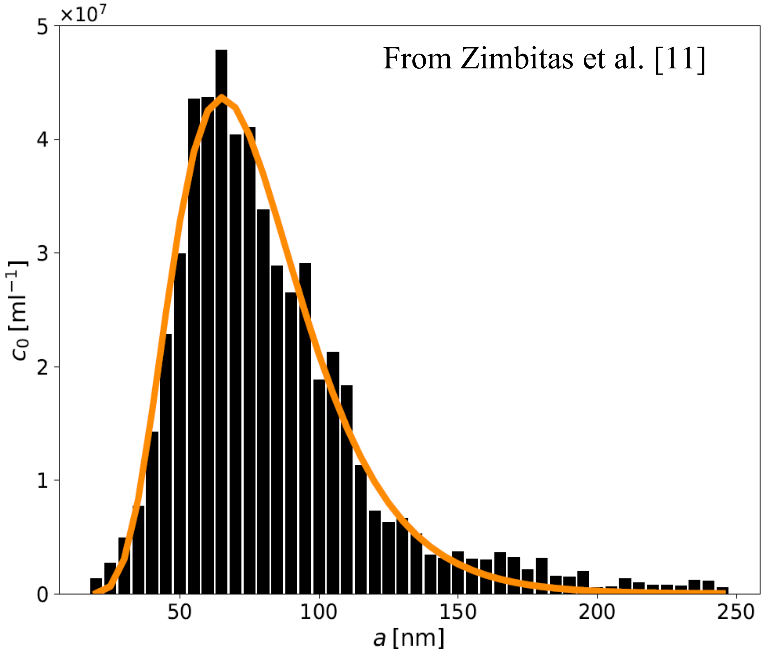
[10] Debuysschère et al. (2023) *Crystal Growth & Design*. 2023, 23, 7, 4979−4989

Theoretical shear-rate analysis





⇒ Molecular assemblies (clusters) exist in undersaturated conditions ! [11]



Distribution population nearly independent of the supersaturation :

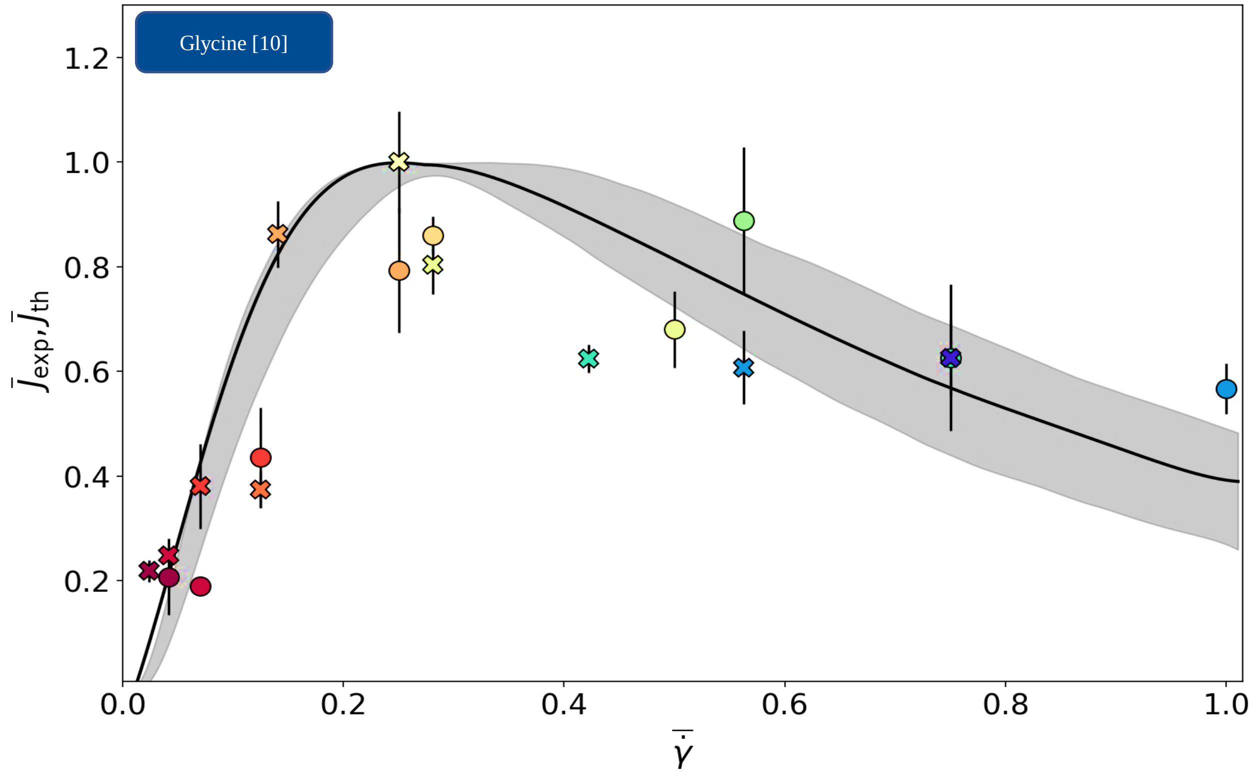
- Mean radius ~ 80 nm

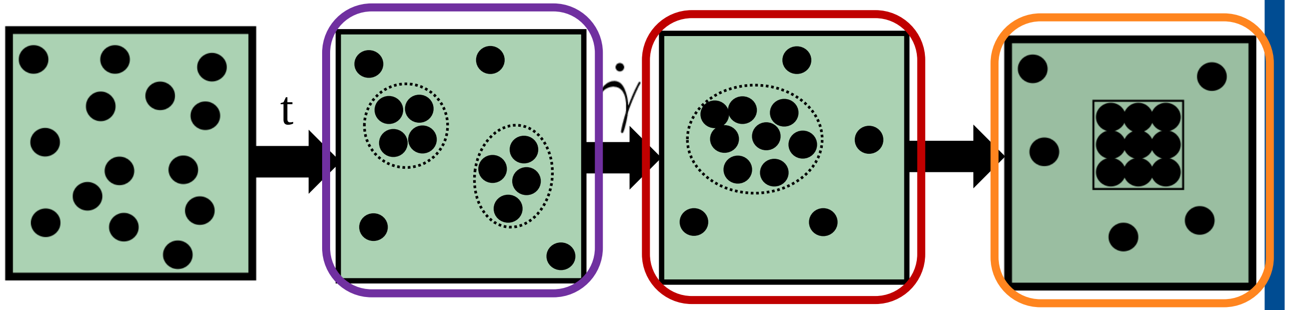
⇒ Under agitation conditions bigger cluster are created : radius >250 nm [12]

⇒ When big clusters are created, a huge decrease of the induction time is observed [12]

[10] Debuysschère et al. (2023) *Crystal Growth & Design*. 2023, 23, 7, 4979−4989
[11] Georgina ZIMBITAS et al. (2019). *Colloids and Surfaces A : Physicochemical and Engineering Aspects*, 579 p. 123633.
[12] Anna JAWOR-BACZYNSKA, Jan SEFCIK et Barry D MOORE (2013). *Crystal growth & design*, 13.2 p. 470-478.

Theoretical shear-rate analysis





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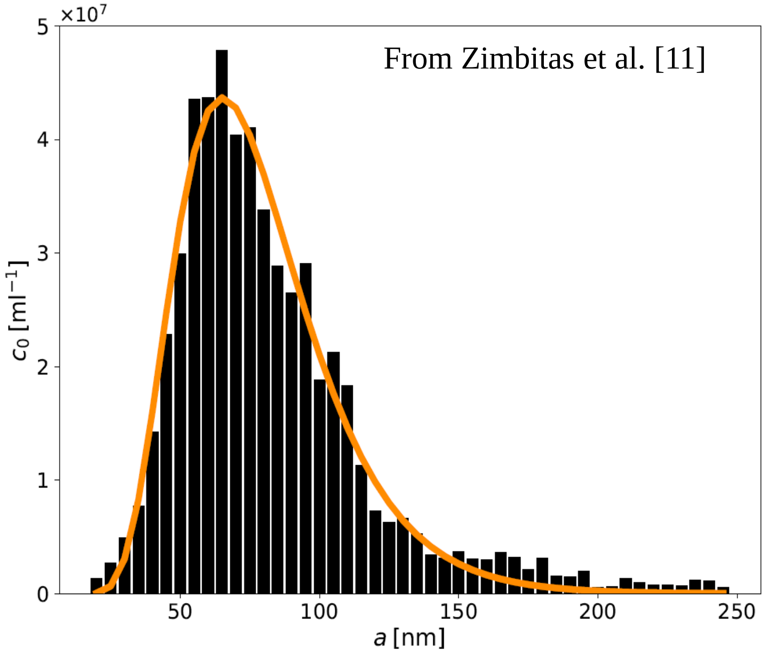

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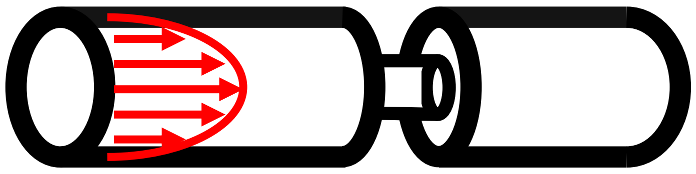
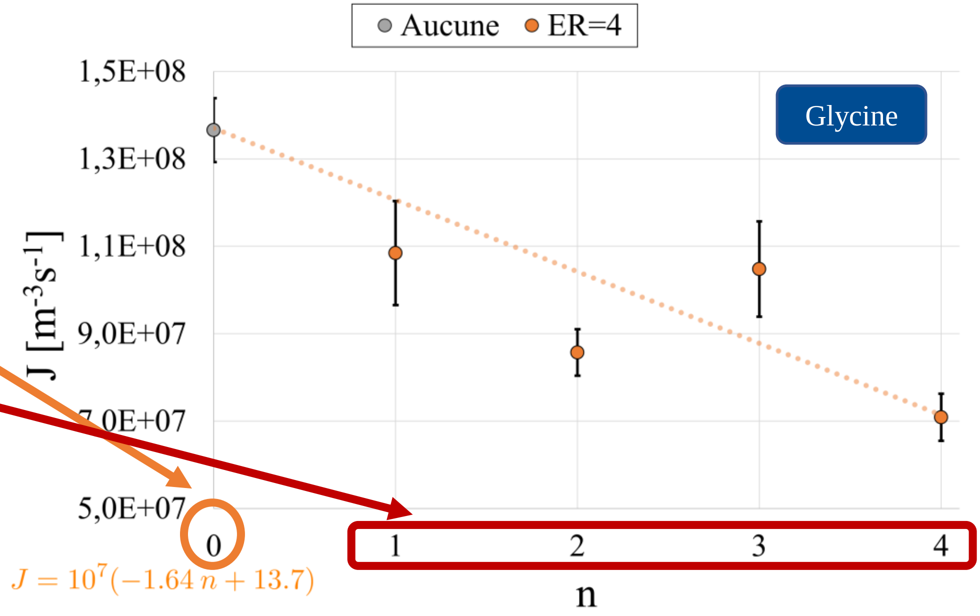
Conclusion



Initial point realized at
~ **5 000 [s^{-1}]**



- Adding supplementary shear through the constrictions

  $\Rightarrow$ drop of nucleation after **3 000 [s^{-1}]**

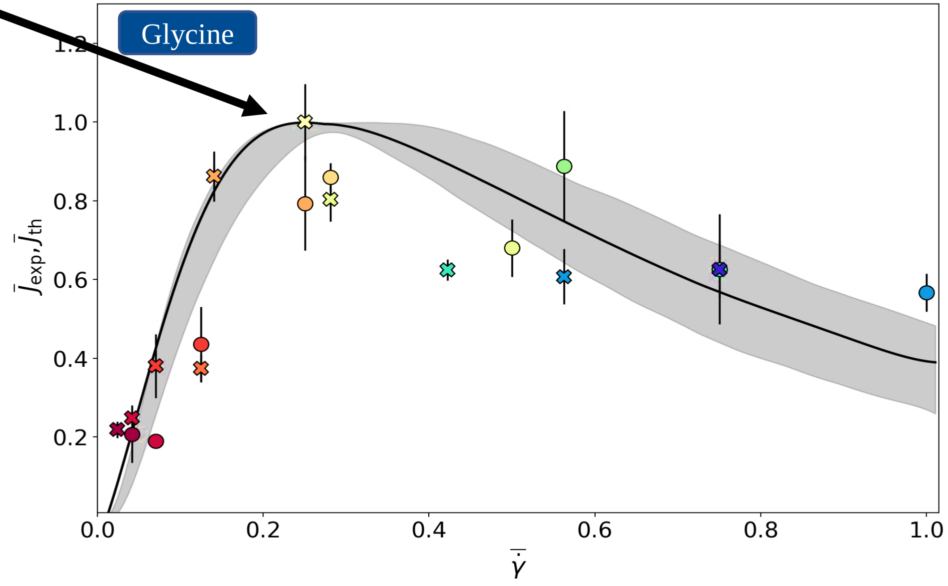
- Brivaracetam, similar structures already observed [13].

- What about Aspirin ?

- Brivaracetam $\neq$ Glycine $\neq$ Aspirin :

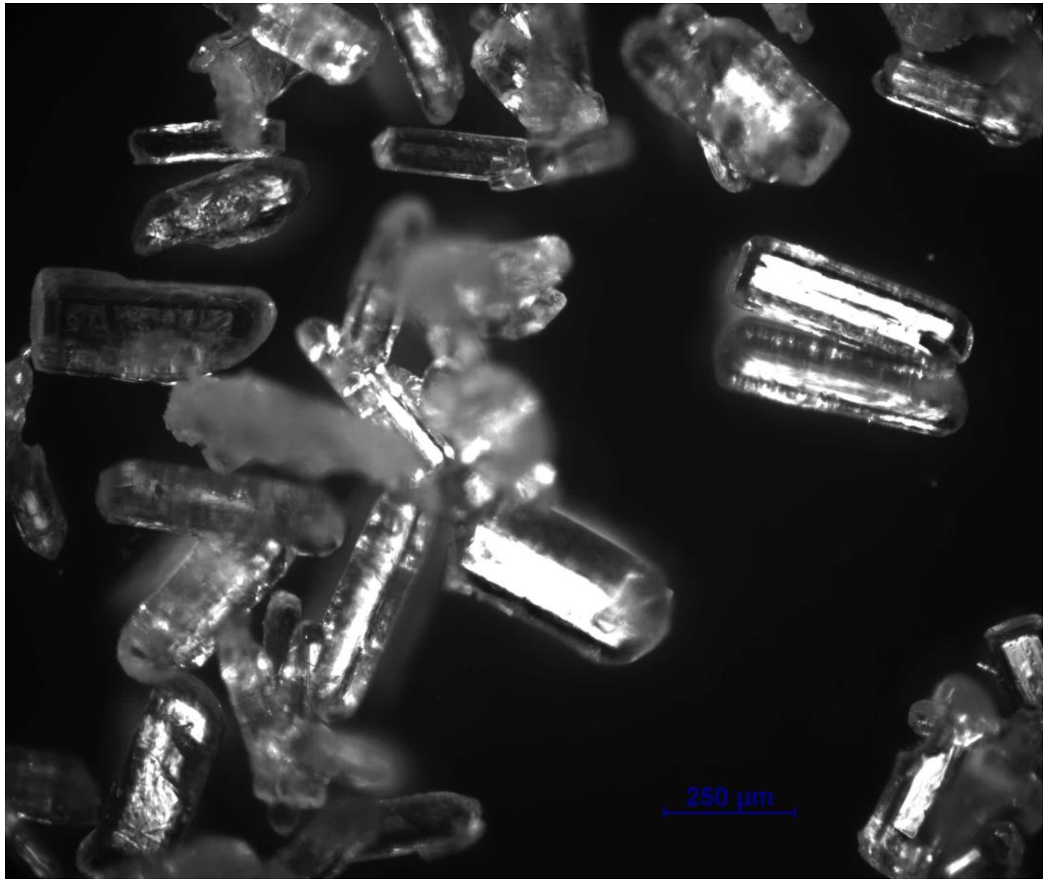
  Different physico-chemical properties (G, ν, Δμ) of the clusters

  $\Rightarrow$ change the position of the optimum ?



[13] Bart RIMEZ, Benoit HAUT et Benoit SCHEID (2014). *21st international workshop on Industrial Crystallization*..

Thanks !



Temperature verification