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Investigating the Role of Thermal Interactions during Freezing on the Morphology of Freeze-Dried Products

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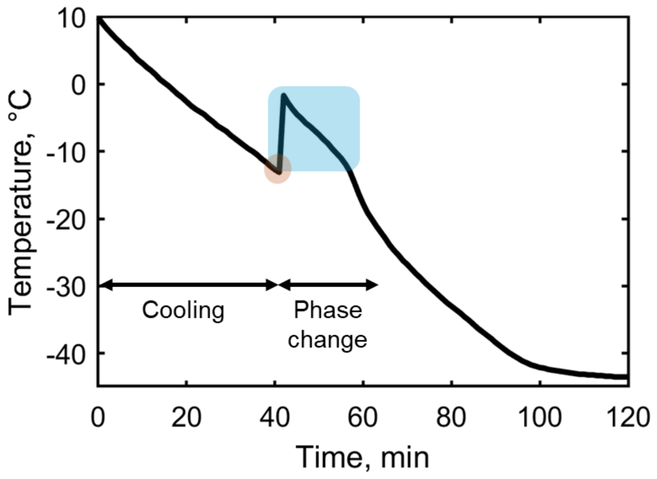
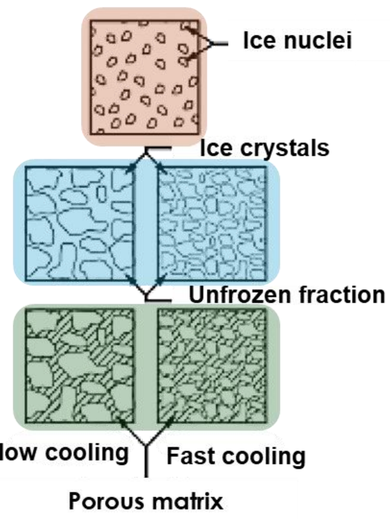
Introduction

- The freezing process takes place in two different steps: a cooling phase, where the solution remains in a liquid state, and the solidification phase, during which the phase change occurs.



- The phase change is initiated by a stochastic phenomenon called nucleation, i.e. the formation of the first stable nuclei.
- These nuclei lead to the formation of ice crystals that continue to grow until the entire solution is frozen.
- The thermal history during freezing strongly affects the morphology of freeze-dried products.



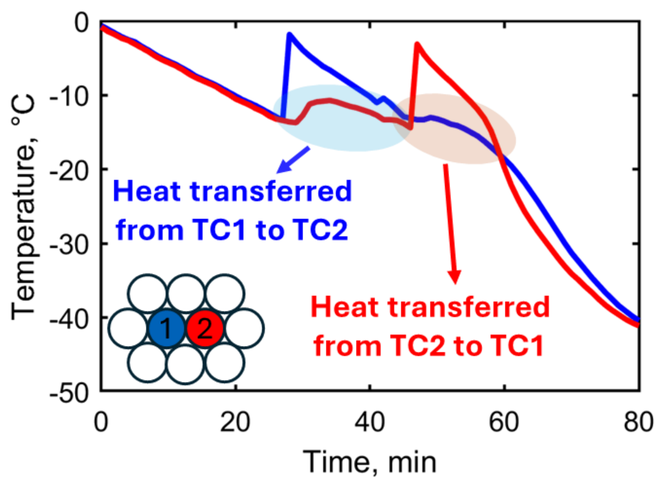
- Since the phase change is an exothermic process, the heat released by nucleation in a vial can be transferred to neighbouring ones.
- The stochasticity of nucleation and the release of the latent heat of solidification causes each vial to have a unique thermal profile.
- Thermal interactions during freezing may increase the vial-to-vial variability.

Materials and Methods

A 5% sucrose-mannitol (1:1) solution was freeze-dried in different loading conditions:

The interacting configuration, in which vials were highly packed to maximise thermal interactions.

The non-interacting configuration, where vials were separated to suppress thermal interactions.



- Thermocouples were used to observe the effect of the phase change in a vial on the thermal profile of the neighbouring ones.
- These profiles were used to estimate the heat exchanged due to thermal interactions ($\hat{Q}_{int}$).
- Two video cameras were positioned above the shelf to capture the nucleation time of each vial.
- $\hat{Q}_{int}$ and the map of nucleation time were used as input data for the 1D mathematical model.
- The thermal profiles of each vial were obtained by numerically solving an energy balance:

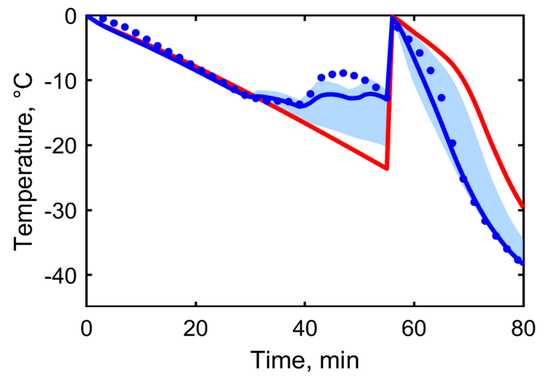
$$\rho_{sol} c_{p,sol} \frac{\partial T}{\partial t} = \nabla \cdot (k_{sol} \nabla T) + \hat{Q}_{int} + \hat{Q}_c$$

- The model outputs are the thermal profiles of each vial in the batch, from which it extracts information on the product morphology and the resulting drying times.

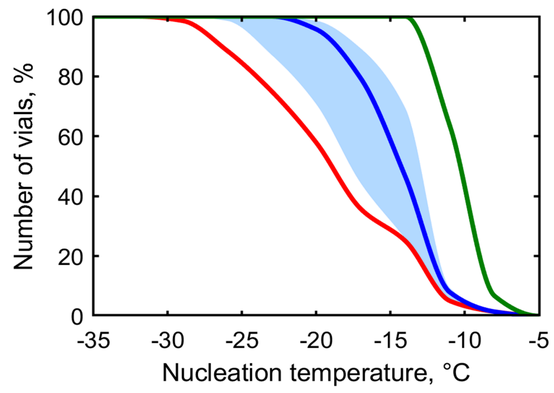
Results

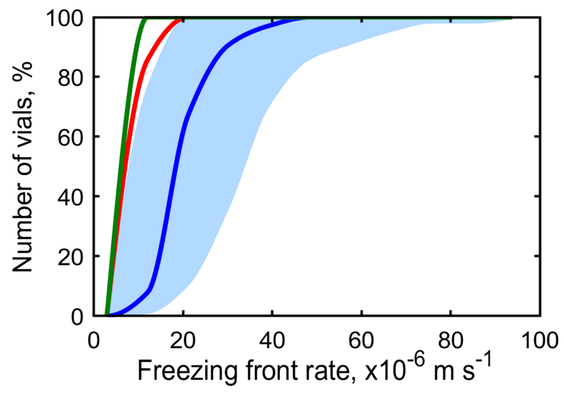
The outputs of the model suggested that thermal interactions affect nucleation temperature (T_n) and freezing rate (v_f).

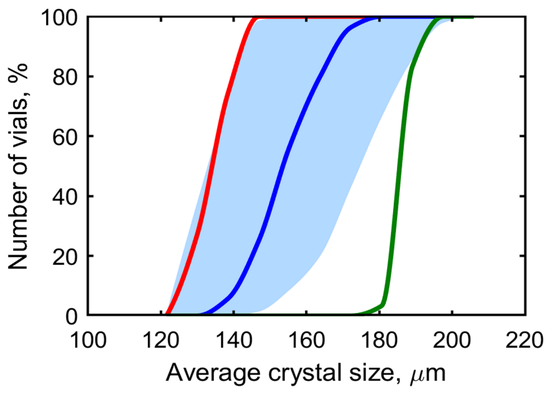
- Neglecting thermal interactions led to an underestimation of both T_n and v_f.
- The agreement with experimental data improved when thermal interactions were included in the thermal balance.
- The complexity of the phenomenon resulted in high uncertainty in the prediction of the thermal profile.



By extracting T_n and v_f from the thermal profiles of each vial, it is possible to assess their variability within the batch and estimate the crystal size distribution.

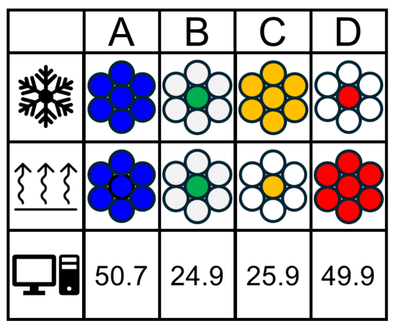


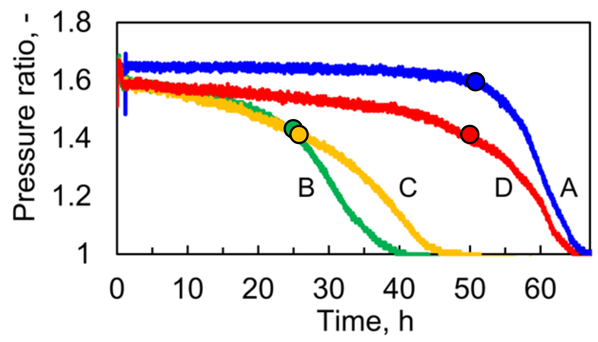




- The higher T_n and the lower v_f caused the formation of larger crystals. Uniform freezing conditions led to a narrower distribution.
- The perturbations caused by thermal interactions decreased the average crystal size and increased the batch variability.
- Neglecting interactions underestimated the average crystal size and its variability.

To evaluate the effect of thermal interactions on the drying times, the product was freeze-dried in four different loading conditions.





- The smaller and more irregular pores generated by interacting freezing resulted in longer drying times.
- The results of the model are in good agreement with experimental data, giving a qualitative estimation of the onset of the Pirani/Baratron pressure ratio.

Conclusions

- Thermal interactions alter the thermal profile of the product during freezing.
- Each vial experience a unique thermal history which causes a vial-to-vial variability.
- The morphology of the dryied product and its drying times are affected by the product morphology during freezing.
- These results highlight the importance of considering vial-to-vial interactions in the design and optimisation of the lyophilisation process.

References

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