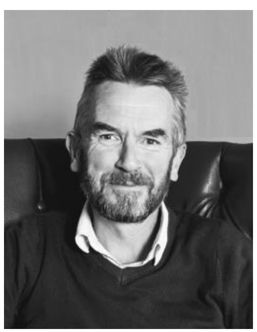
Applications for Electrical Impedance Spectroscopy Process Analytical Technology (EIS-PAT) in Lyophilization Process Development



Prof. Geoff Smith
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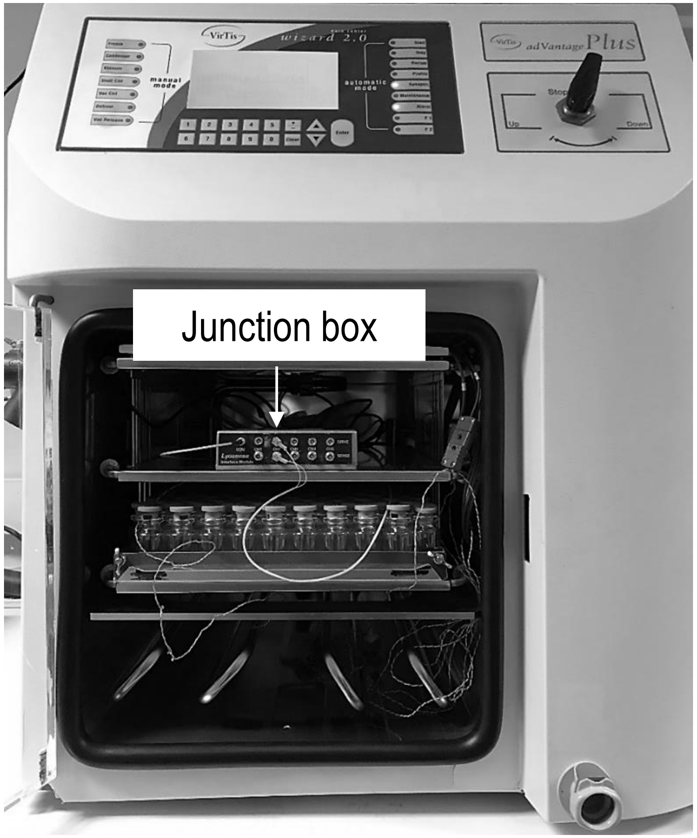
Overview

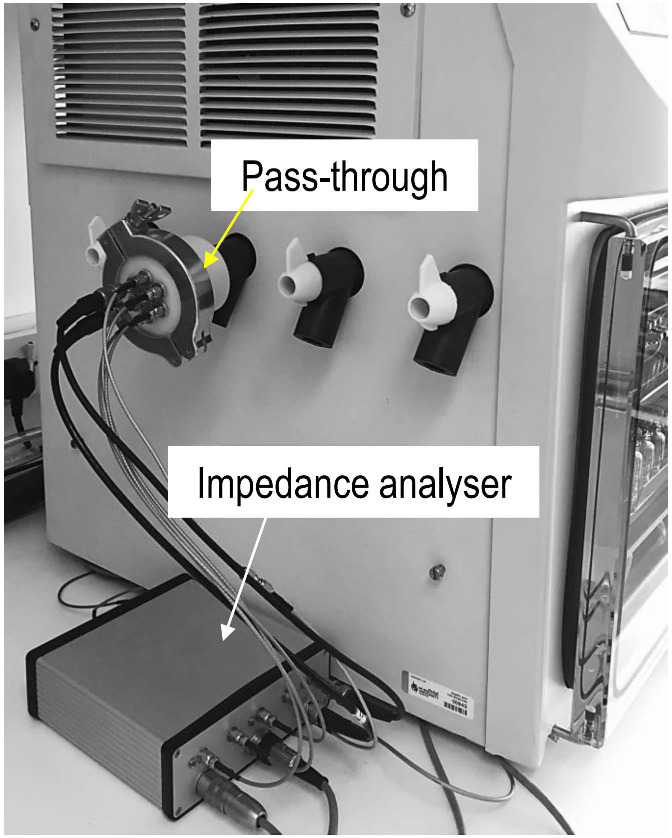
- System configuration: non-invasive measurements
- Electrical impedance and material attributes
- Methods for temperature calibration
  - Triangulation of thermocouple temperatures
  - Tempris
- LF and HF dielectric constant for
  - Nucleation temperature and solidification end point
  - Glass transition
  - Sublimation end point
- Dielectric loss peak
  - quantification of ice mass and drying rate
  - ice interface temperatures

System configuration

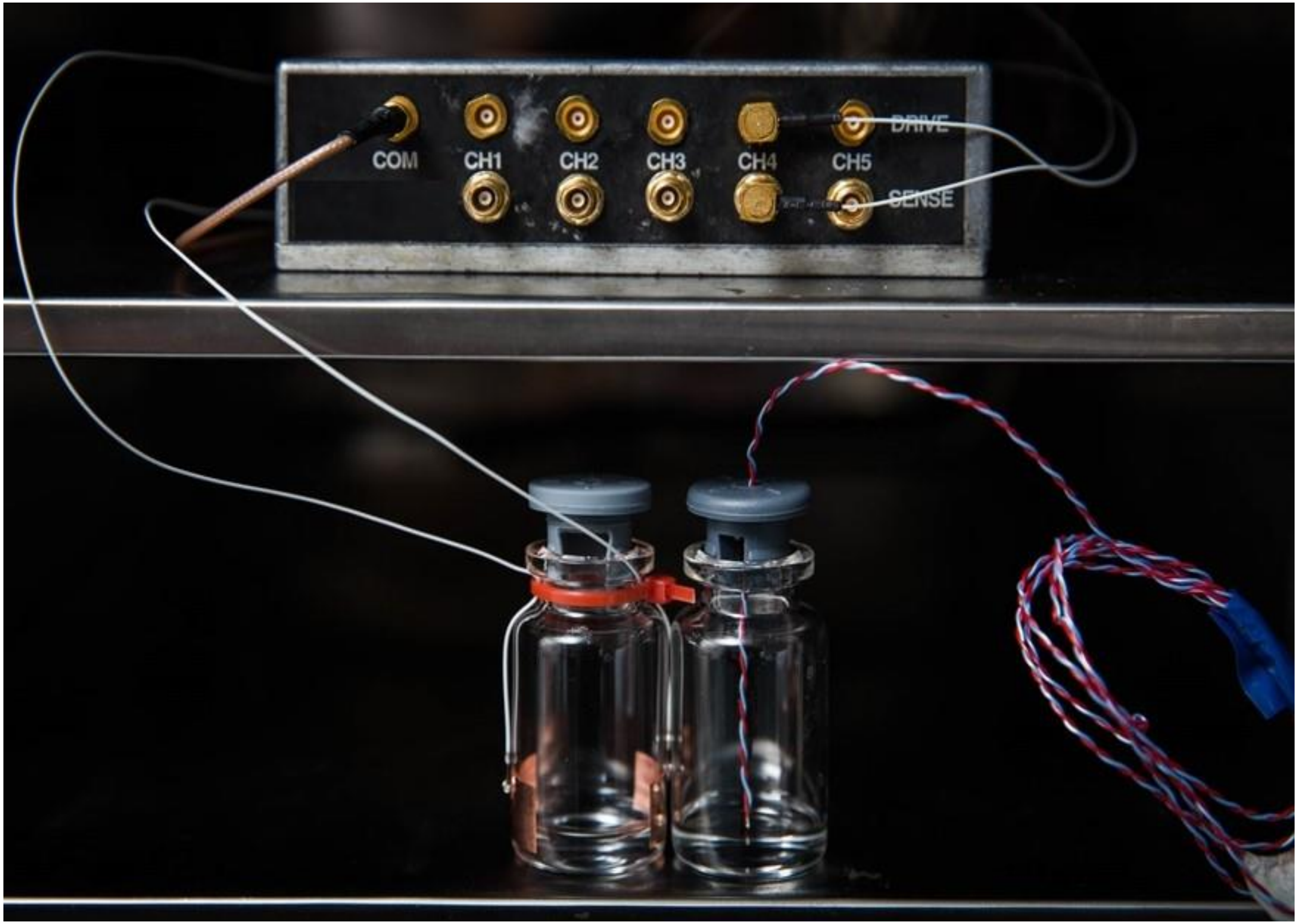
a



b



Junction box



Non-invasive measurements

Individual vials

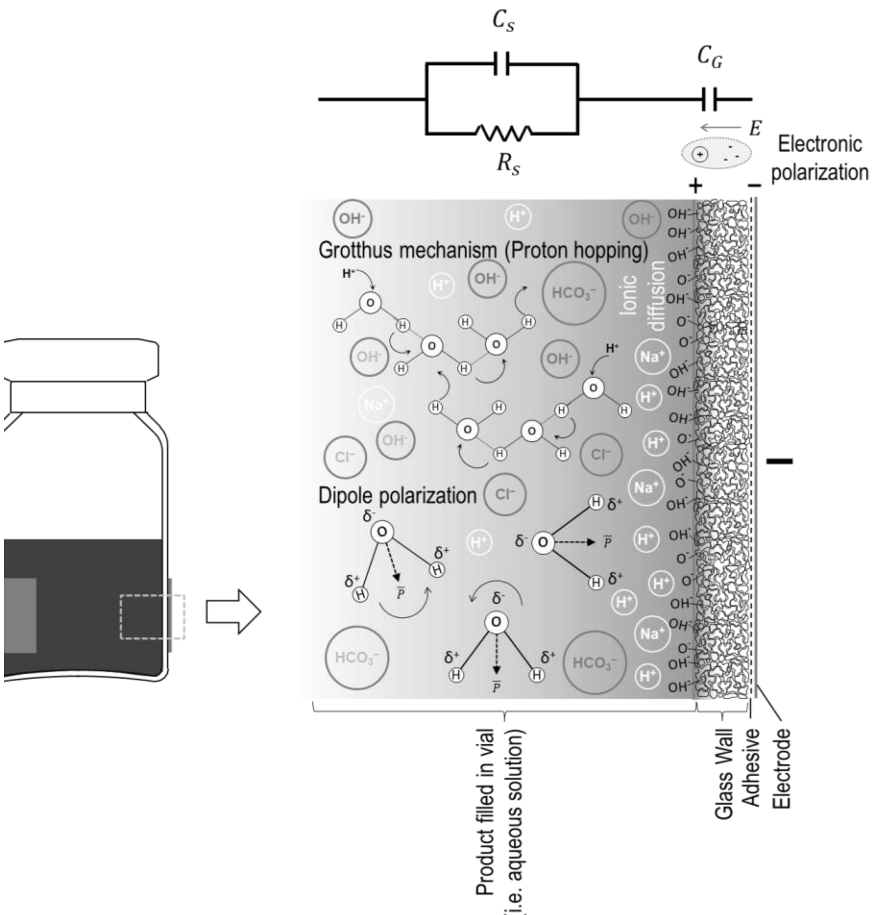
Electrodes on outside of vial

In process

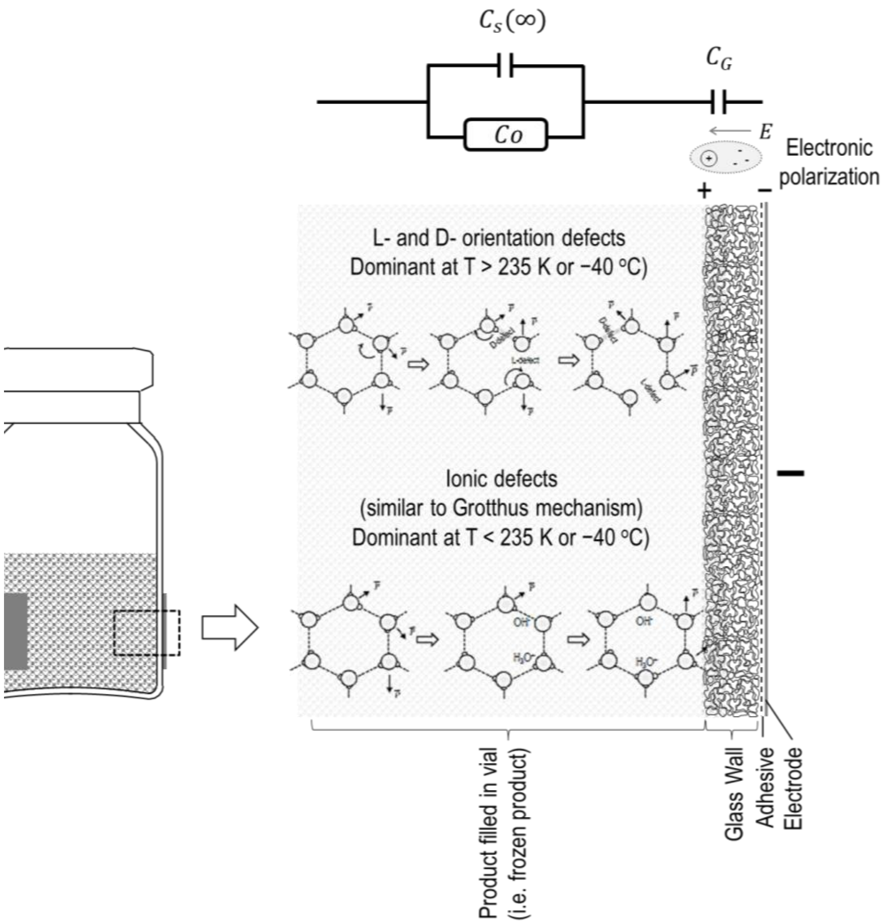
Allows for regular packing of vials

Electrical impedance and material attributes

Liquid state (Maxwell-Wagner)



Frozen state (dielectric relaxation)



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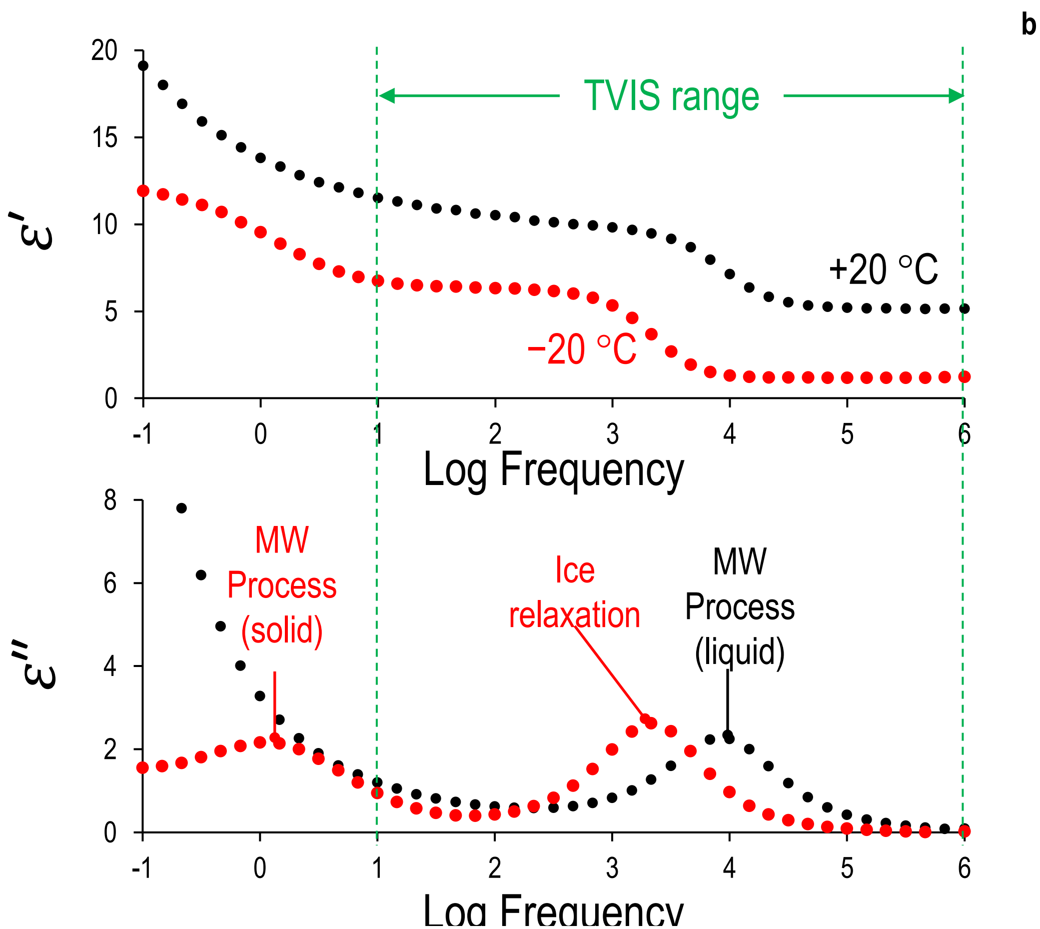
Electrical impedance and material attributes

Maxwell-Wagner & ice relaxation



TVIS vial on cradle

To be placed in the cryostat

of Novocontrol BDS

TVIS Applications

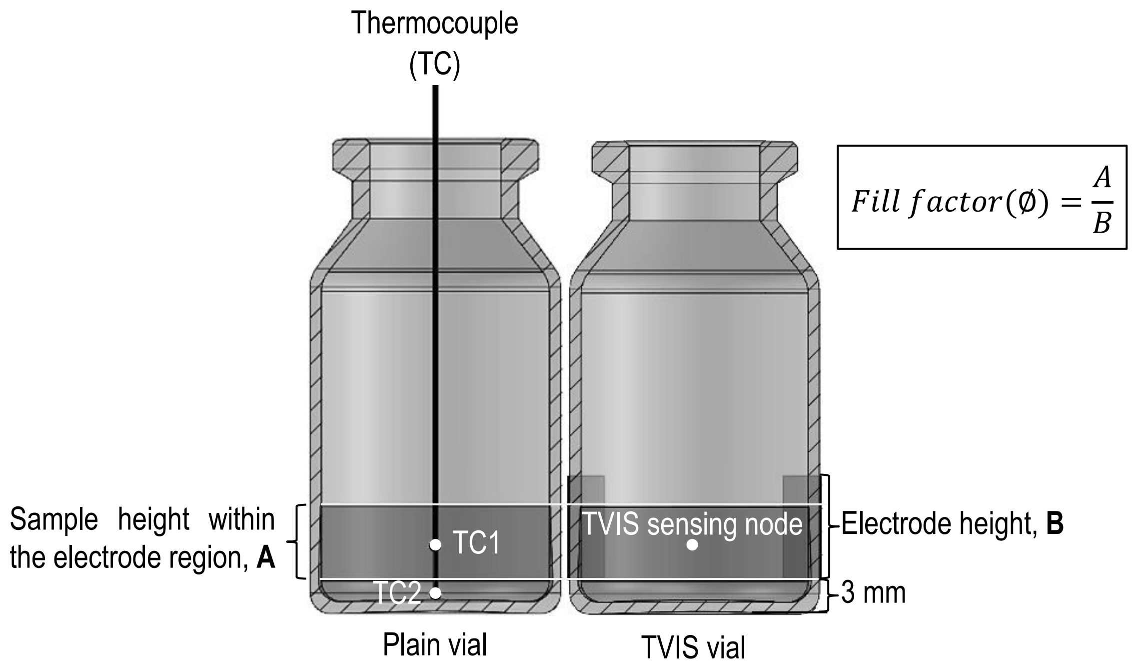
Temperature Calibration

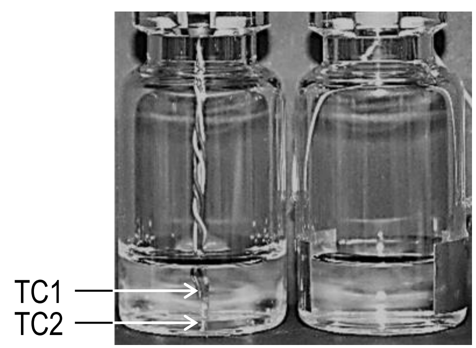
1. Triangulation method

Placing a thermocouple at the TVIS sensing node allows for the calibration of the temperature inside the TVIS vial to a precision of +/- 0.4 C

(see next two slides)

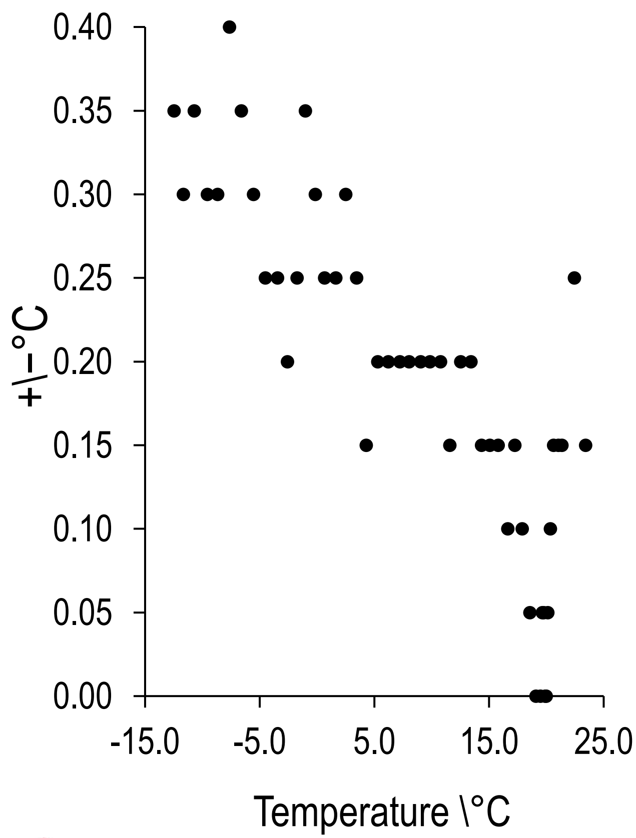
TC in nearest neighbour vial



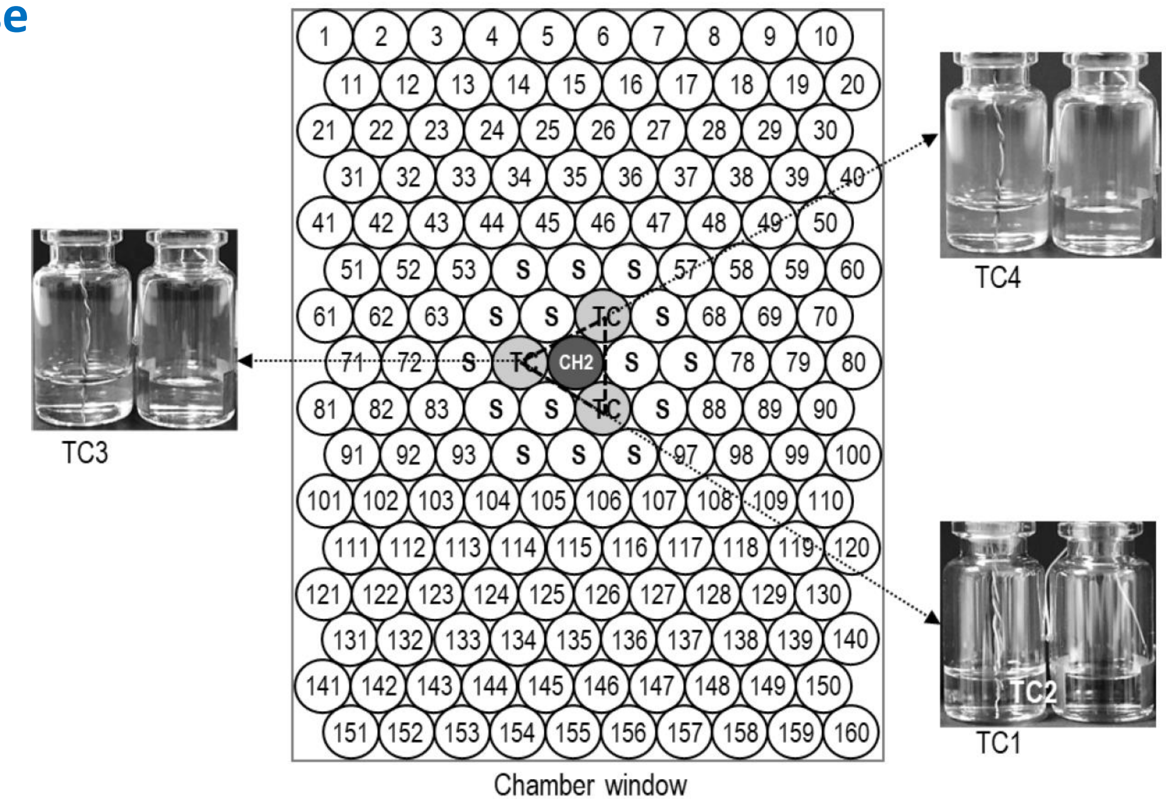


1. Triangulation method

Temperature uncertainty during freezing phase



TC in nearest 3 neighbour vials



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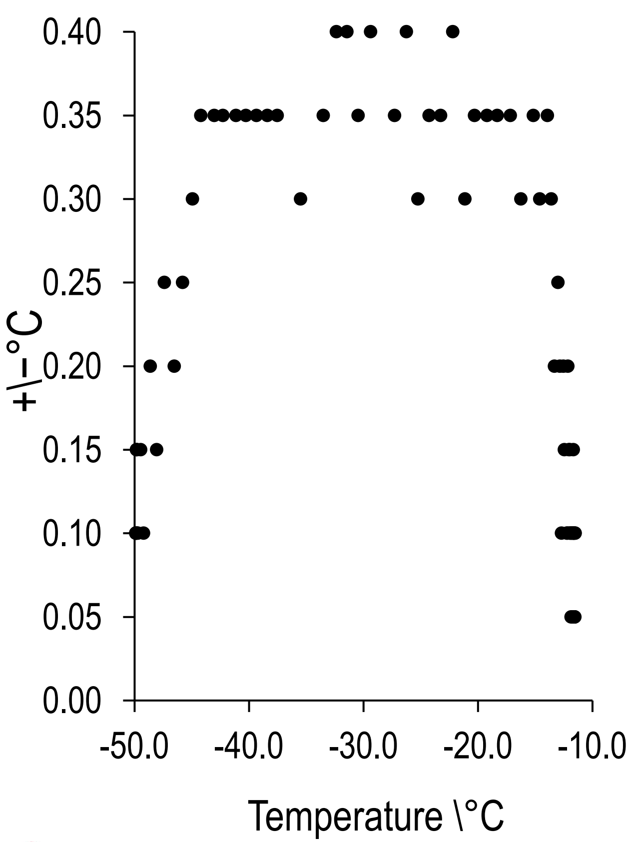
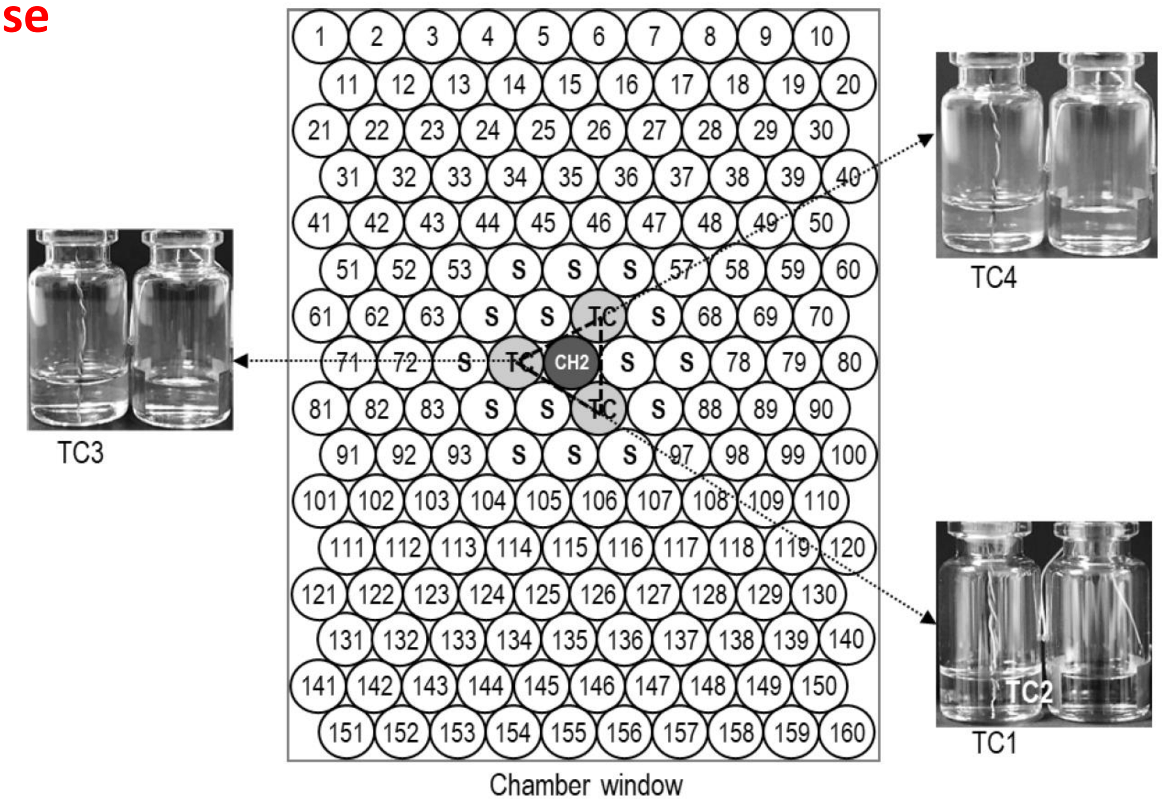
Temperature calibration for the TVIS vial: 1. Triangulation method

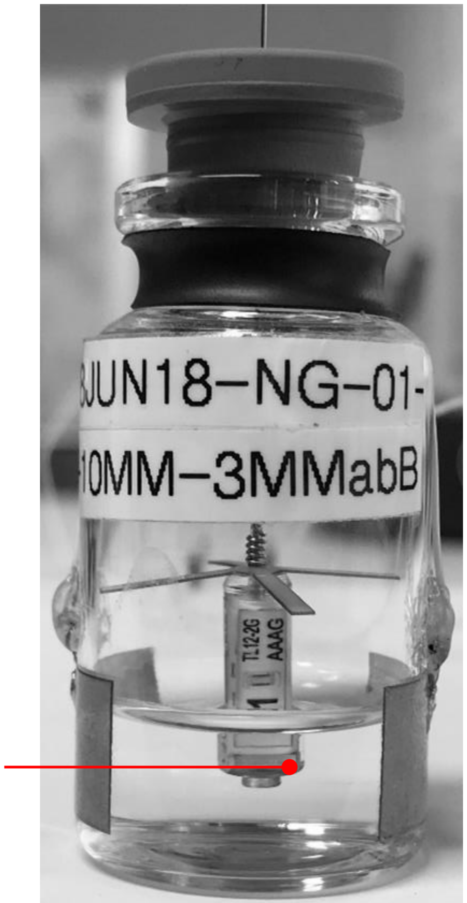
Temperature uncertainty during re-heating phase



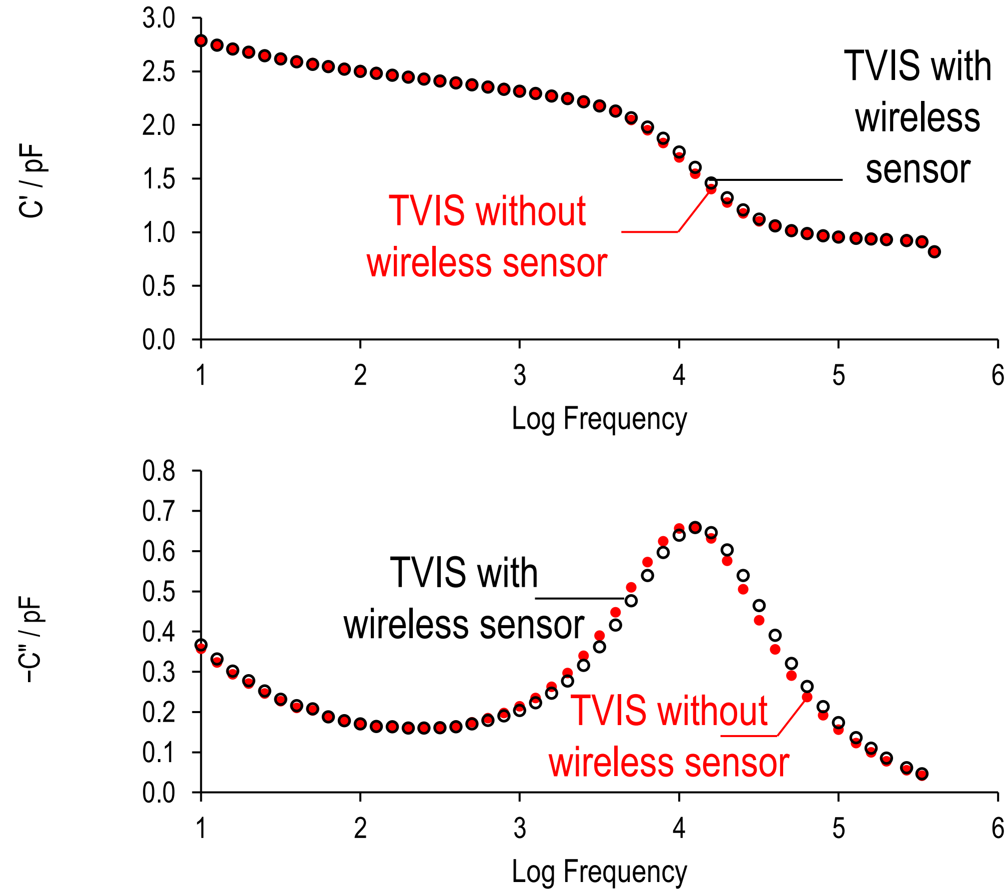
TC in nearest 3 neighbour vials



2. Tempris method

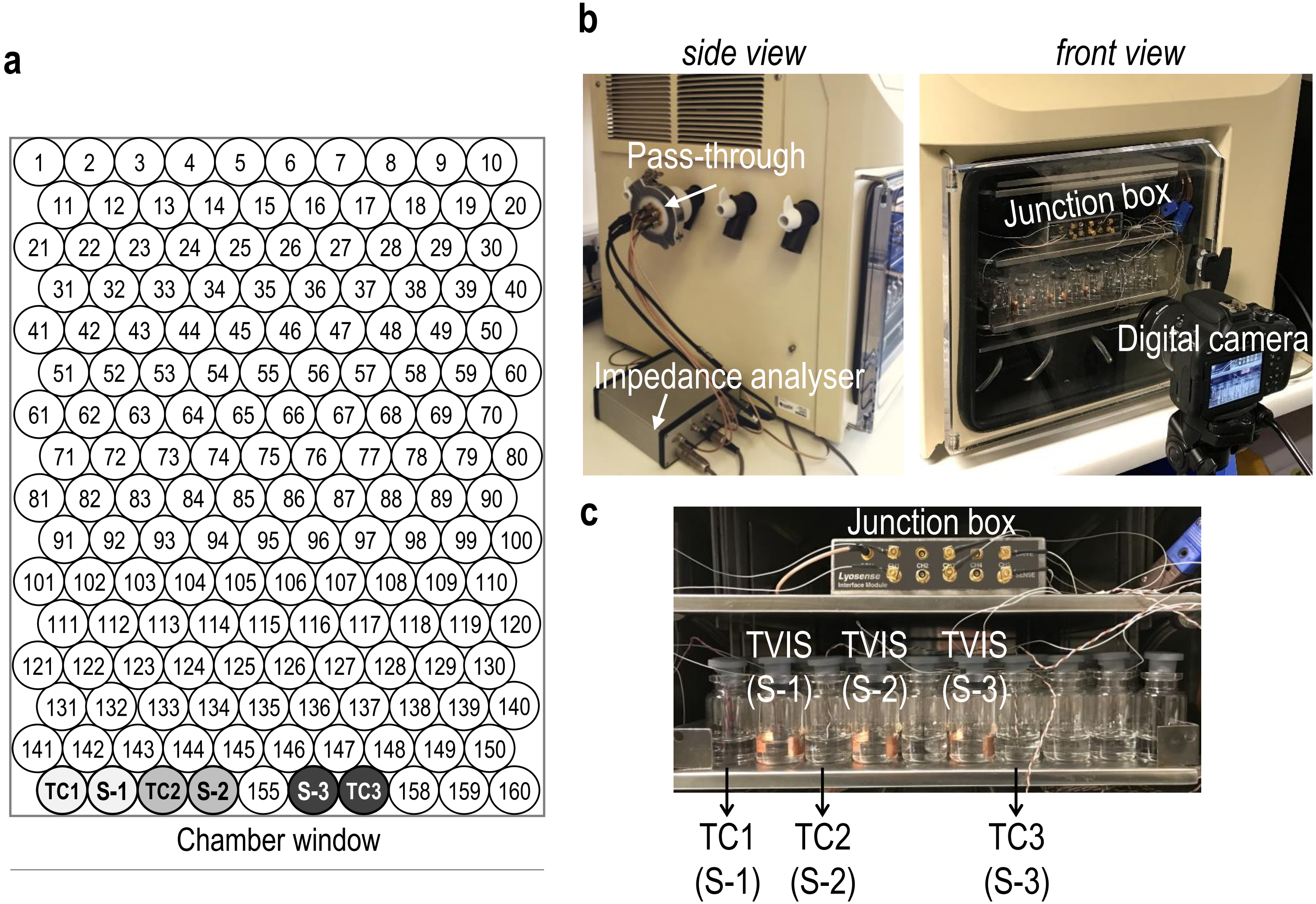


TVIS spectra



tempris® sensor technology

Typical experimental set-up



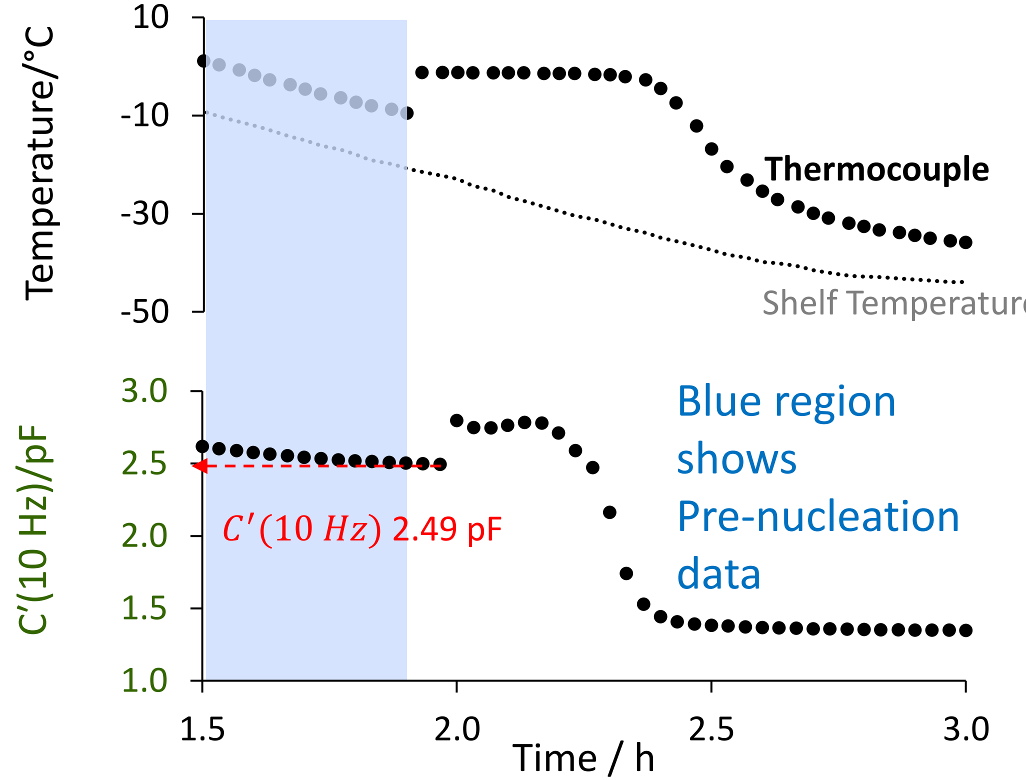
Jeeraruangrattana (2000). PhD Thesis. De Montfort University, Fig. 71

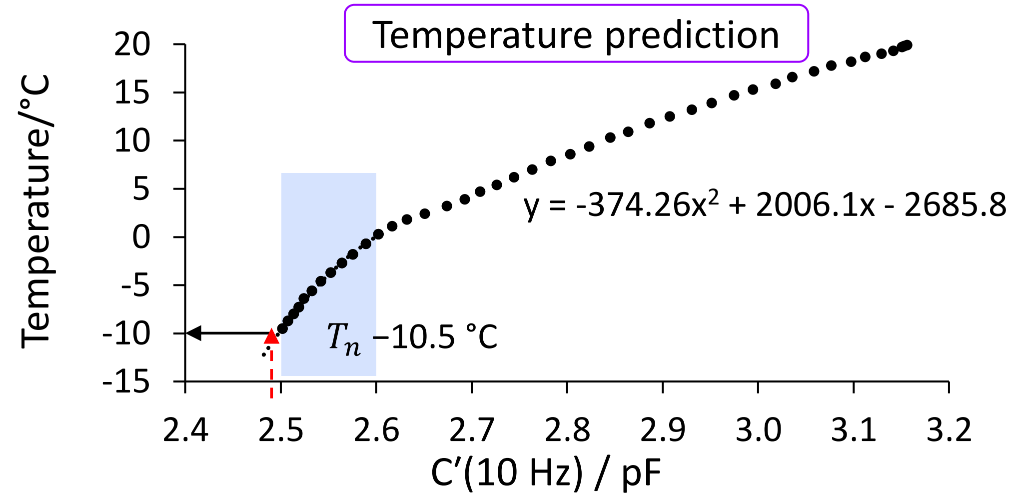
TVIS Applications

Nucleation temperature

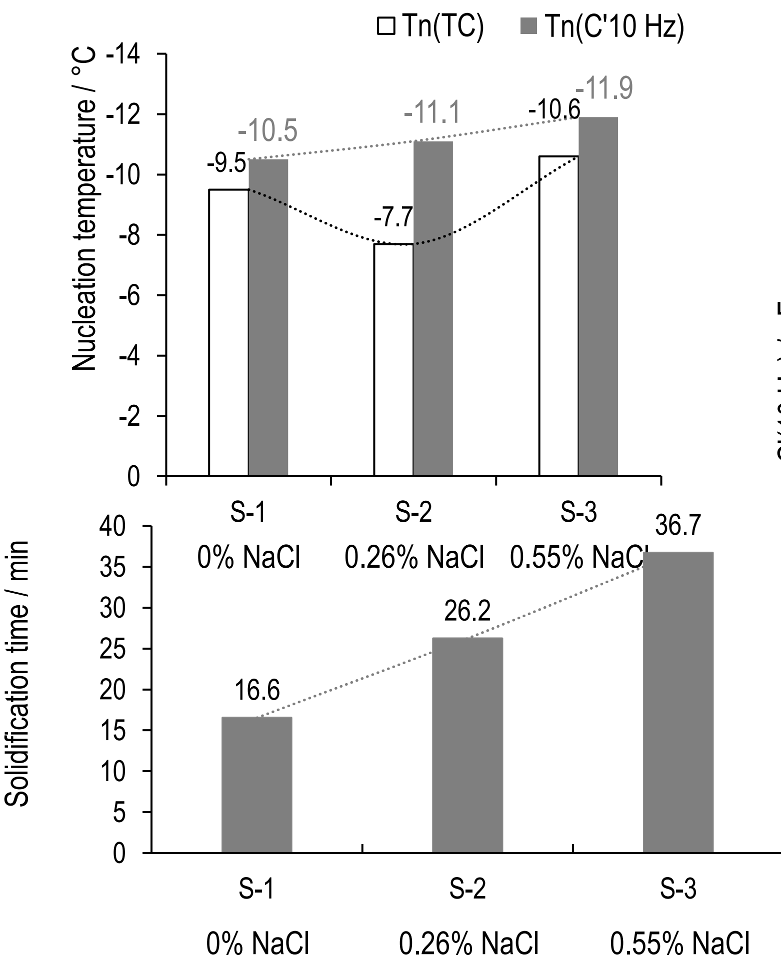
Nucleation Temperature

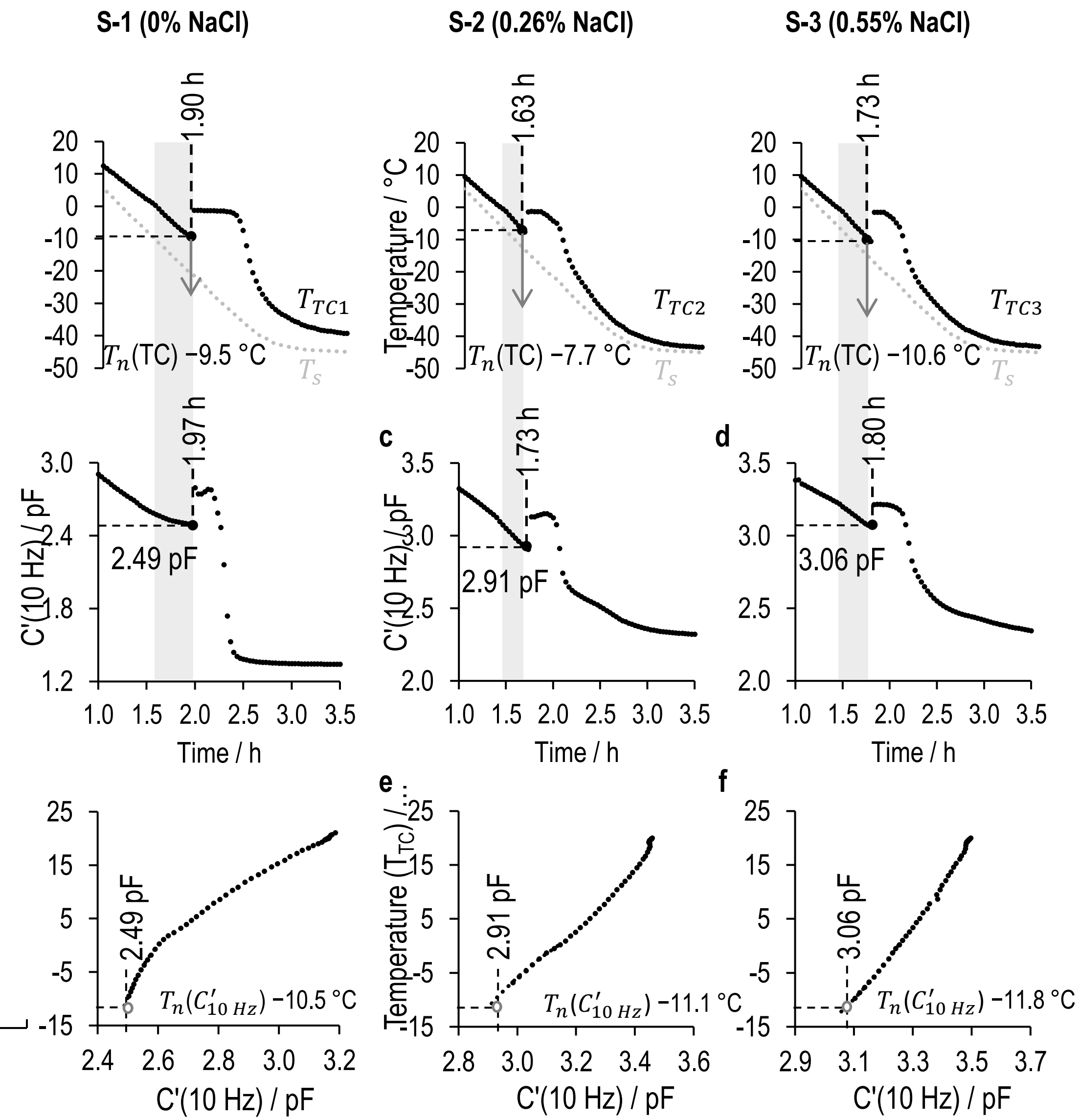
- In case the TVIS vial nucleates before TC vial, the nucleation temperature in the TVIS vial can be inferred directly from TC temperatures in the nearest neighbor vials
- However, if TVIS vial nucleates later than TC vial, the nucleation temperature can be predicted by fitting a curve to the plot of the average temperature from thermocouple vials against TVIS parameter (i.e. $C'(10\ Hz)$)
- The ice nucleation temperature of sample (5 %w/v sucrose) was found to be -10.5 C in the case of this particular TVIS vial (other vials will differ owing to the stochastic nature of ice formation.





Nucleation temperature





TVIS Applications

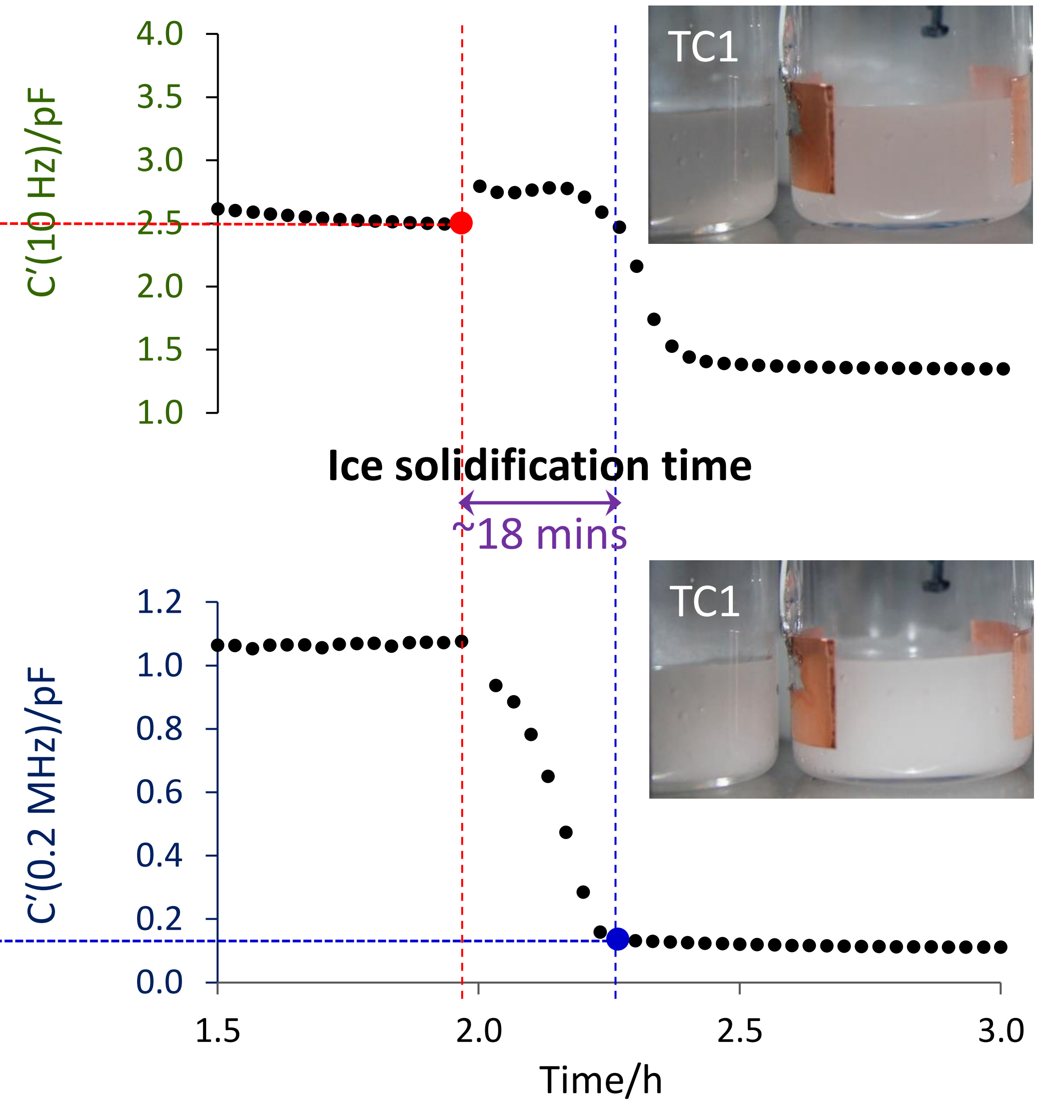
Solidification end point

Solidification period

Ice nucleation

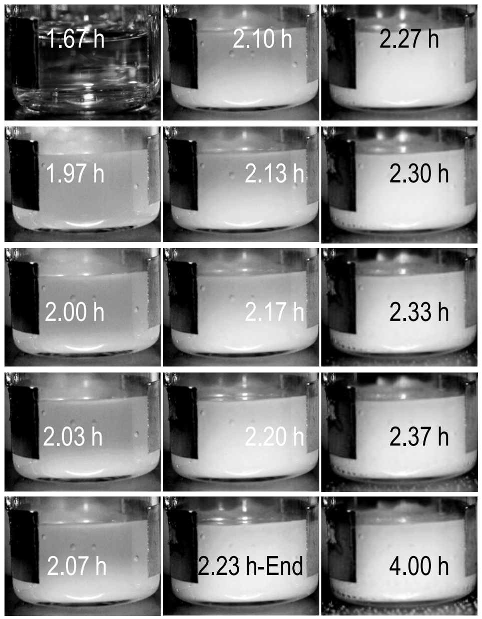
- The difference between these two times if the ice solidification time
- Knowing the height of the product in the vial one can then estimate an average solidification rate

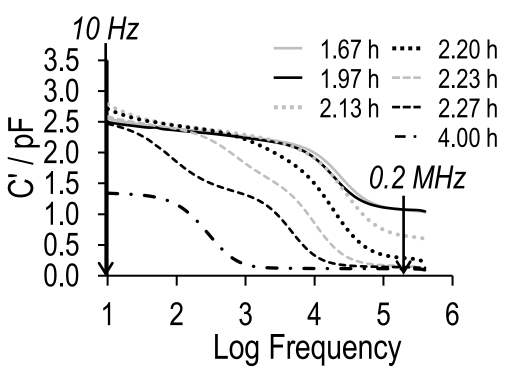
Solidification end point

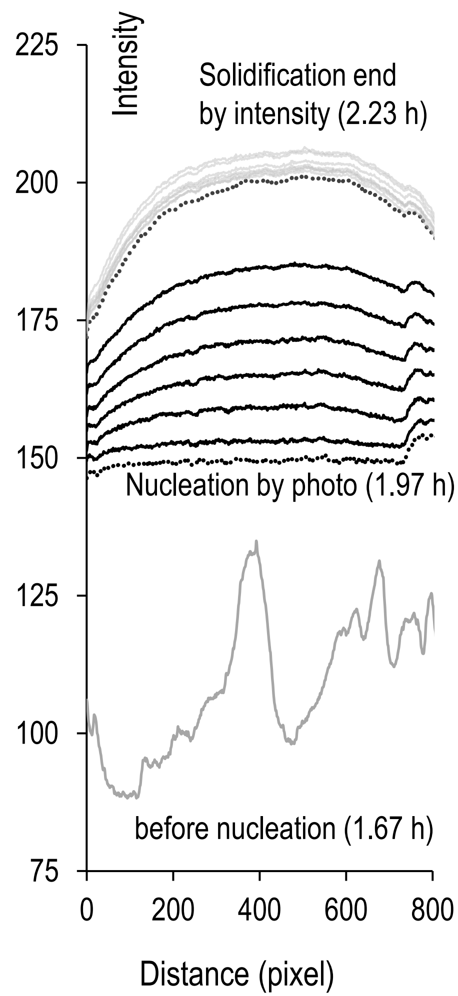


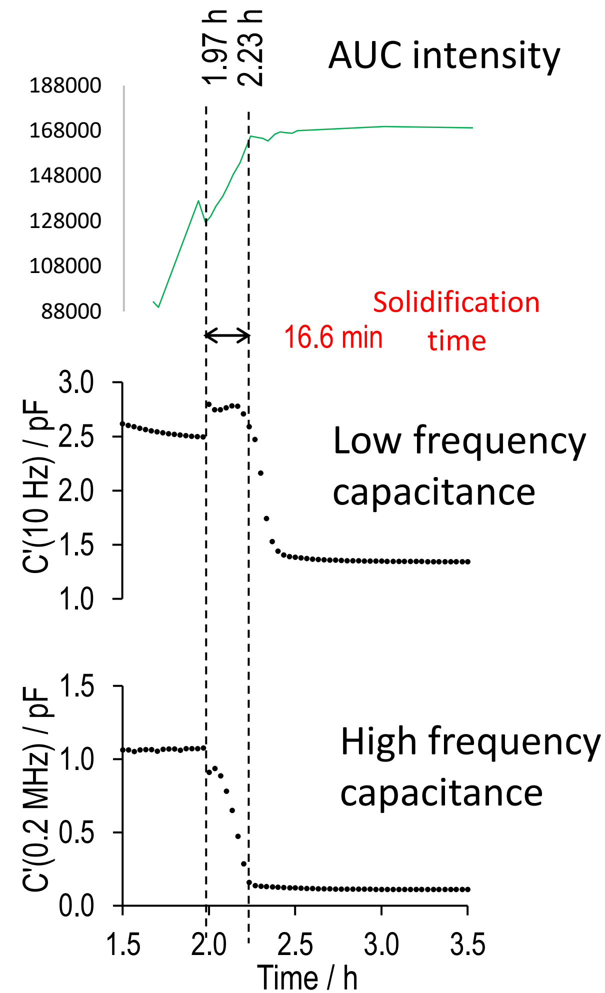
$$Average\ solidification\ rate\ (R_{av}) = \frac{Ice\ height\ (L)}{solidification\ time\ \Delta t}$$

Solidification end point 5% sucrose





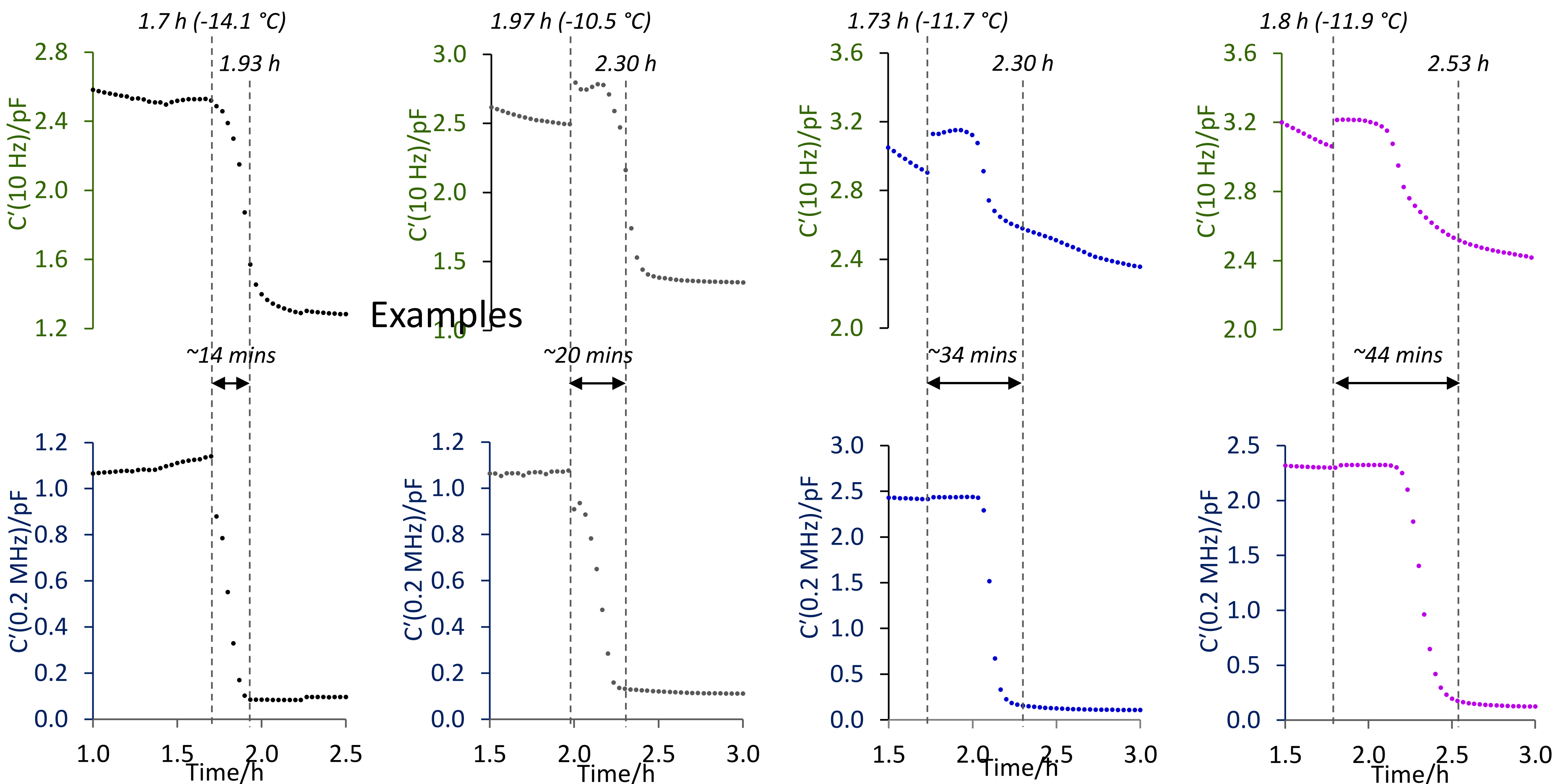




Water | 5%Sucrose | 5%Sucrose in 0.26% NaCl | 5%Sucrose in 0.55% NaCl

Solidification time for ice formation increases with the salt concentration

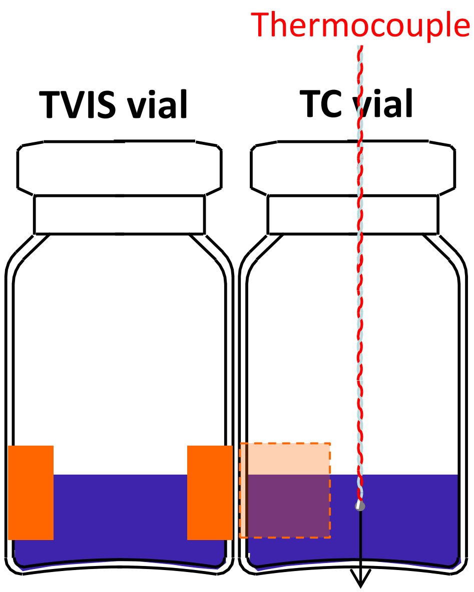
Examples



TVIS Applications

Determination of in-vial Glass Transition temperature (T_g')

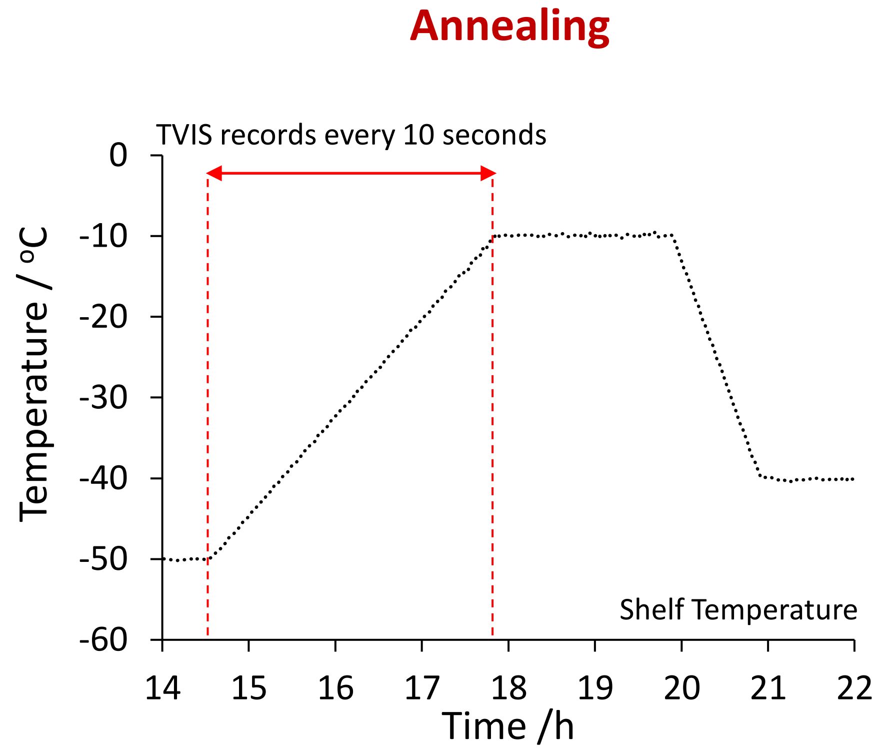
Glass Transition Temperature



TC at the middle of solution bounded within electrode region (defined as **Temperature node**)

Thermocouple position

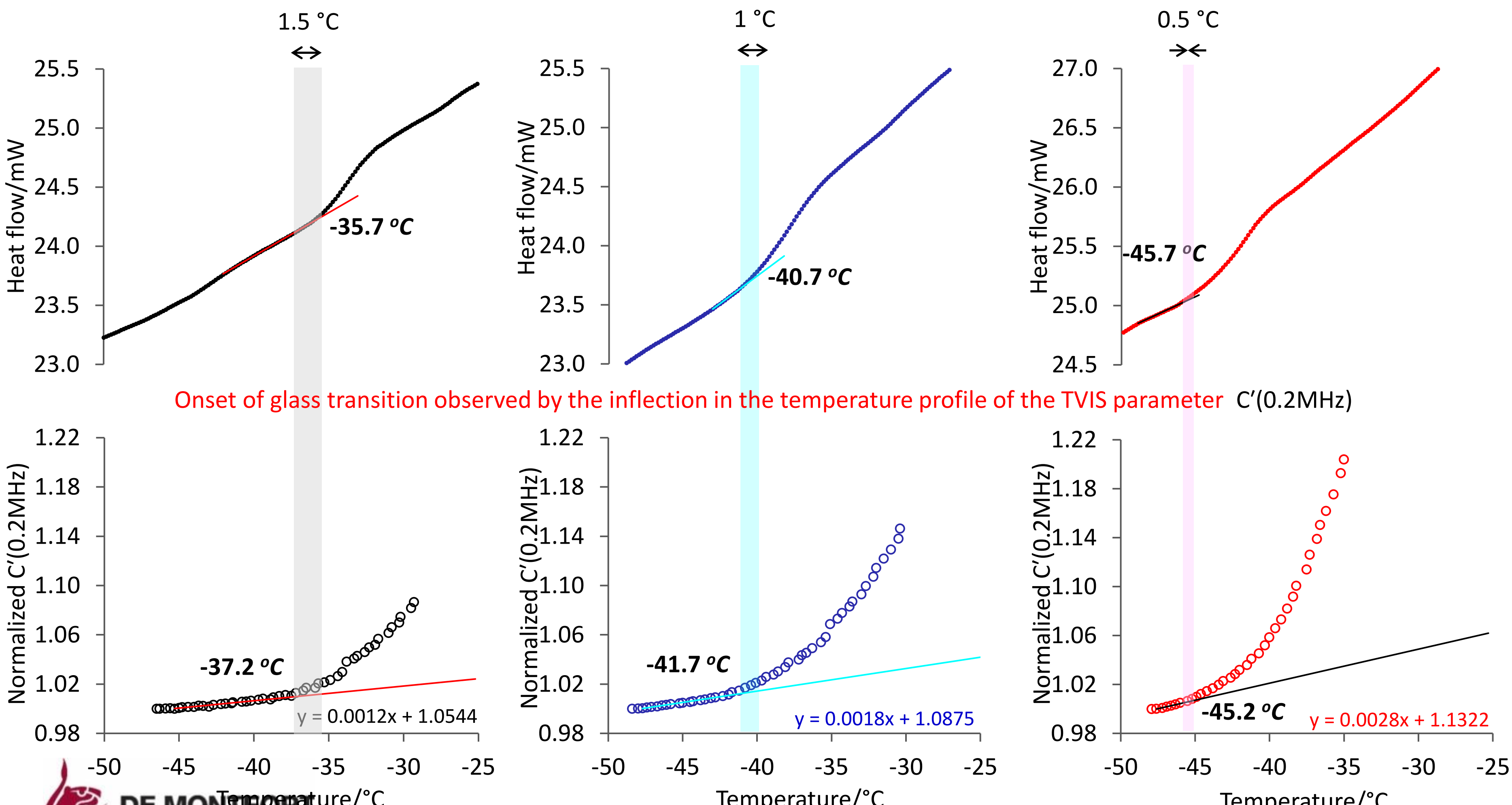
Annealing



Ramp from -50 °C to -10 °C with 0.2 /min

$C'(0.2\ MHz)$ during Re-heating

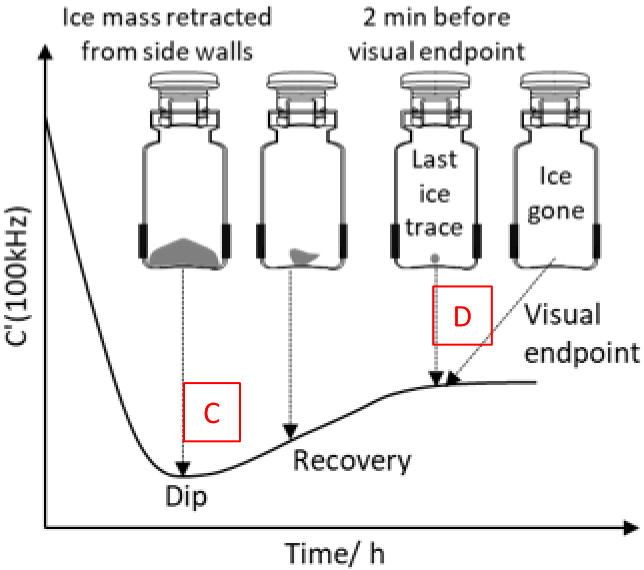
5% Sucrose in 0% NaCl	5% Sucrose in 0.26% NaCl	5% Sucrose in 0.55% NaCl

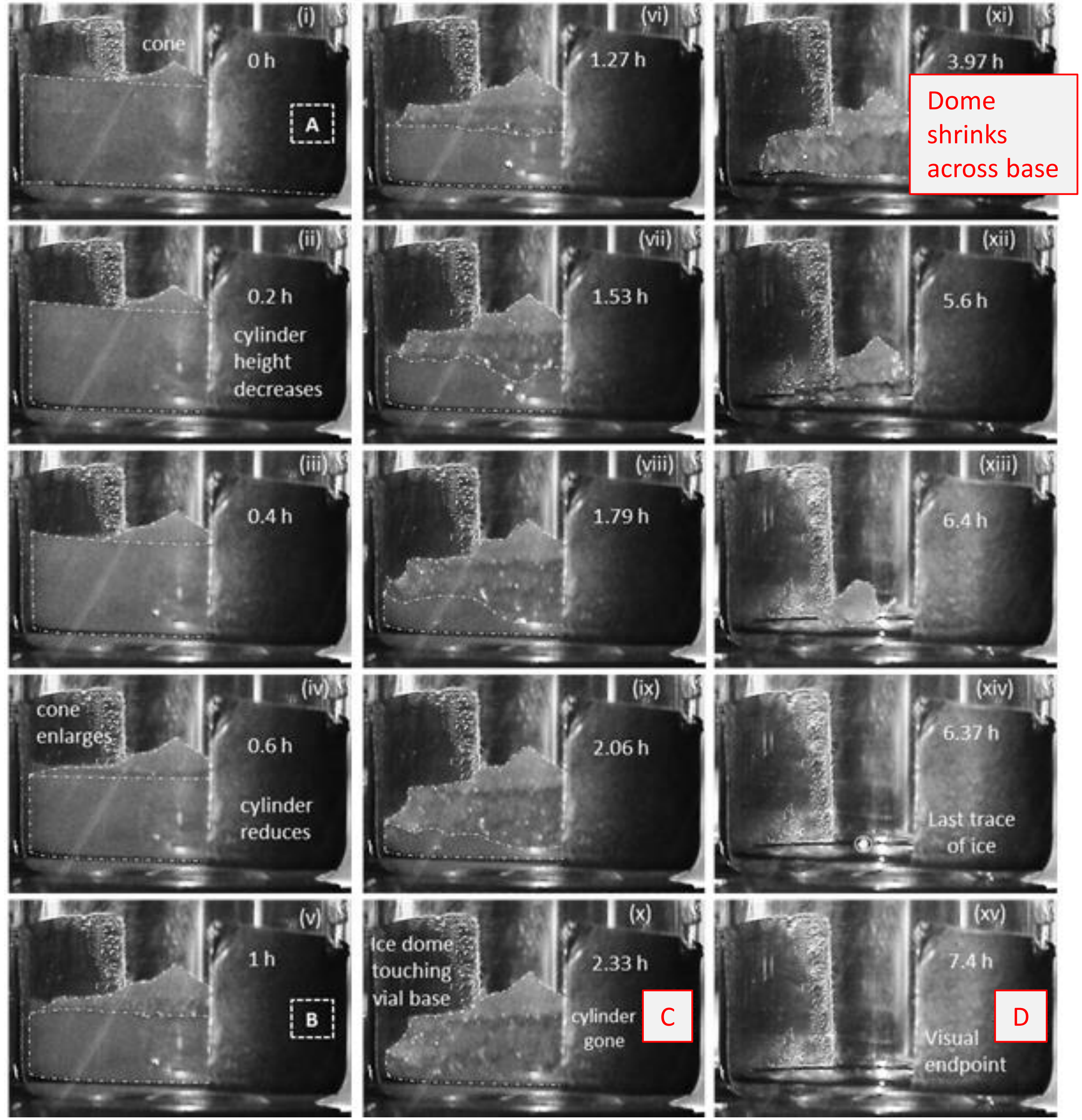


TVIS Applications

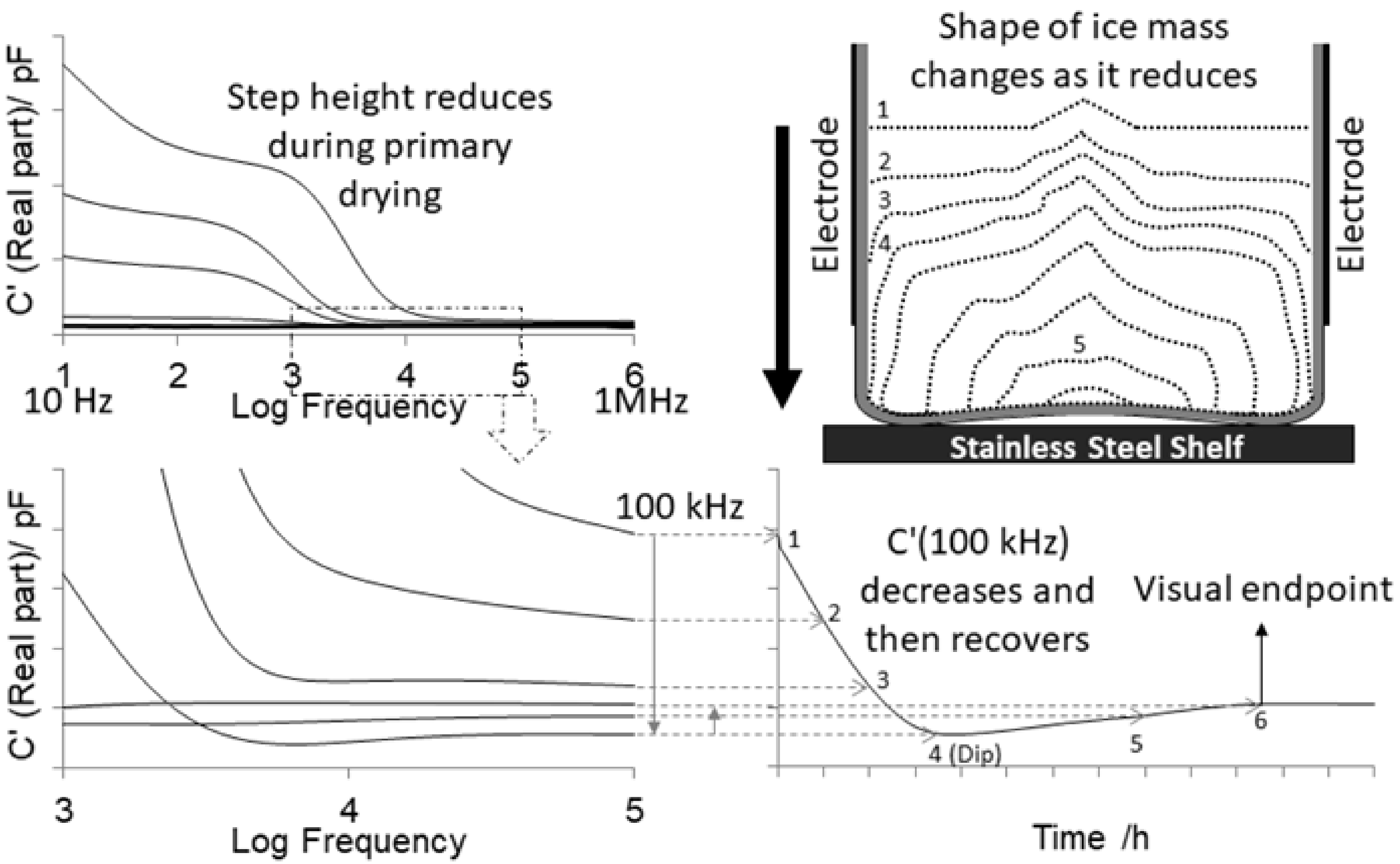
Sublimation end point

Sublimation end point





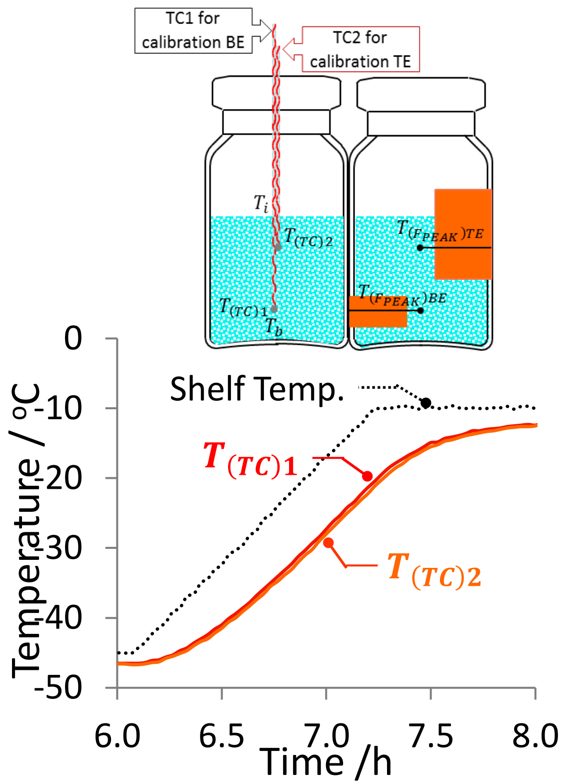
Sublimation end point

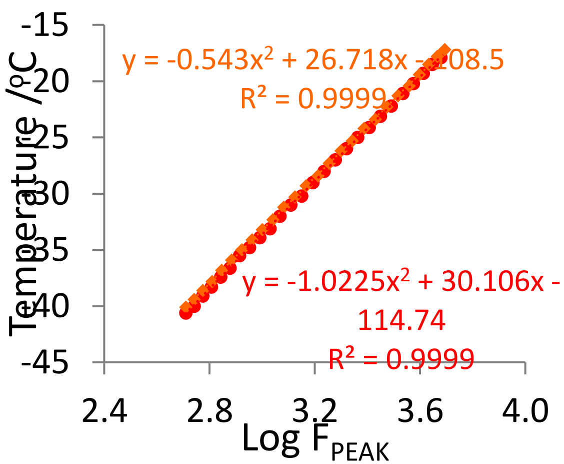


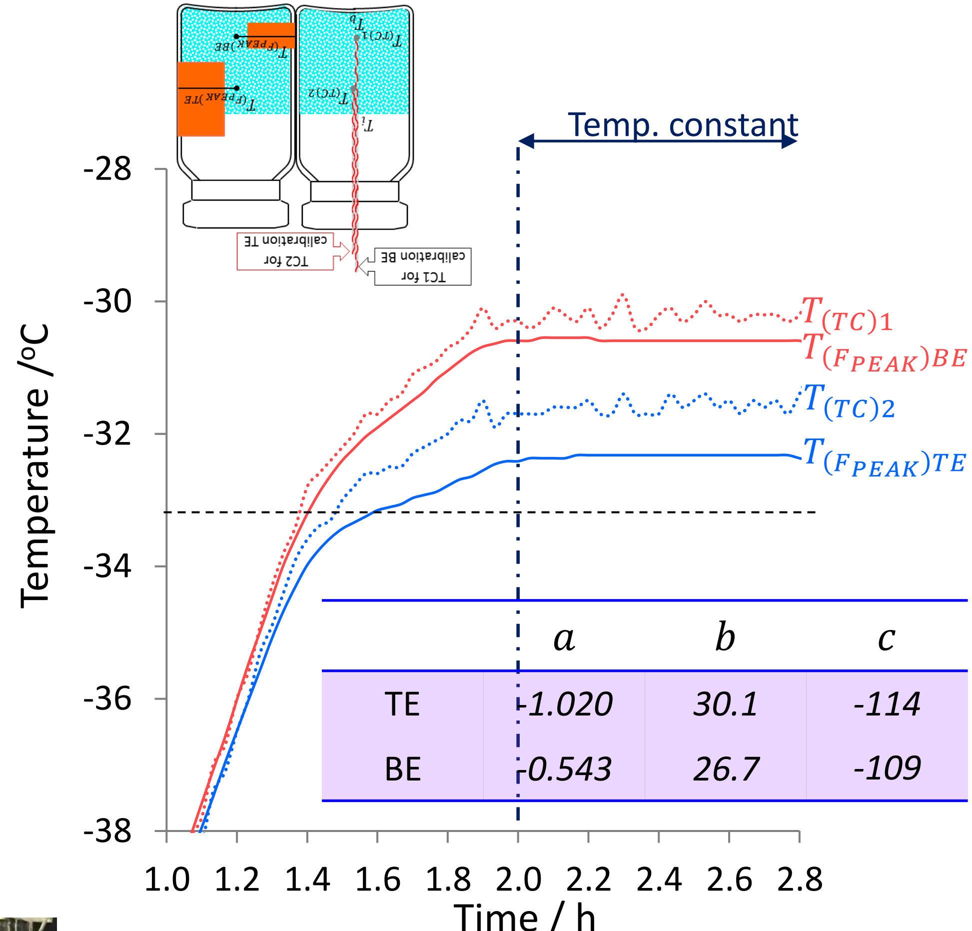
Primary drying

Product temperature → Sublimation rate → K_v → Primary drying endpoint → R_p → Collapse event

Product temperature prediction



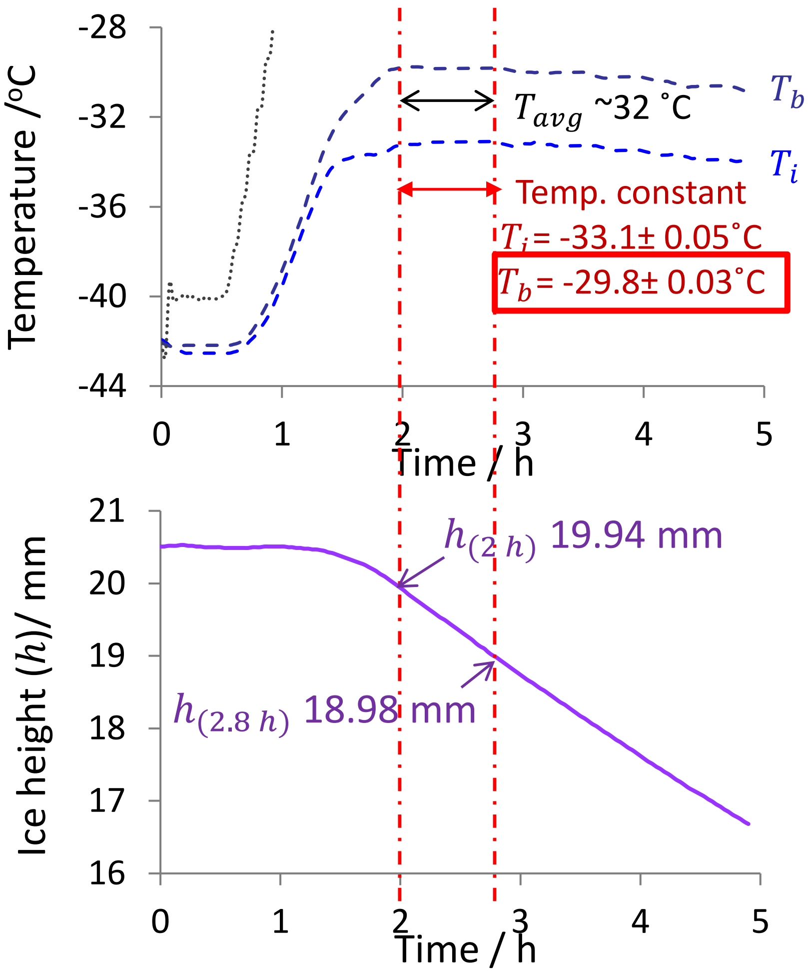




	a	*b*	*c*
TE	*-1.020*	*30.1*	*-114*
BE	*-0.543*	*26.7*	*-109*

The product temperature predicted by TVIS can demonstrate the temperature gradient across ice cylinder height

Drying Rate Estimation Pure ice



- Drying rate during the steady state

$$Drying\ rate\ (\frac{\Delta m}{\Delta t}) = \rho_i \cdot A \cdot \frac{h_{(t1)} - h_{(t2)}}{t_2 - t_1}$$

Ice density (ρ_i) at -32˚C = 0.920 g·cm^{-3}

(Calculated ice temperature between T_i & T_b)

Internal vial diameter (VC010-20C) = 2.21 cm

Cross-section area (A) = 3.80 cm^2

Ice height at 2 h ($h_{(2\ h)}$) = 19.94 mm

Ice height at 2.8 h ($h_{(2.8\ h)}$) = 18.98 mm

TVIS parameters used for determination:

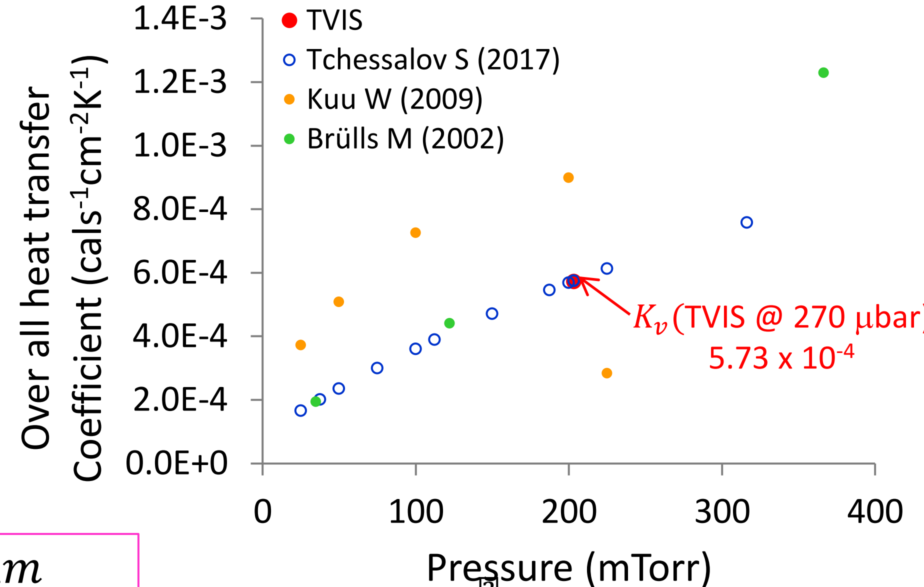
$\frac{\Delta m}{\Delta t}$ = 0.42 g·h^{-1}

T_b= -29.8˚C

$$Drying\ rate\ = 0.920\ g \cdot cm^{-3} \times 3.80\ cm^2 \times \frac{(19.94 - 18.98) \times 10^{-1} cm}{(2.8 - 2.0)\ h}$$

$$\mathbf{= 0.42\ g \cdot h^{-1}}$$

Parameters	TVIS
Drying rate at steady state (g/h) (2-2.8 h into primary drying)	0.42
Shelf Temperature, T_s (K)	273.3
Vial's base Temperature, T_b(K)	243.3



$$L\frac{\Delta m}{\Delta t} = A_e K_v (T_s - T_b) \Rightarrow K_v = \frac{L\frac{\Delta m}{\Delta t}}{A_e(T_s - T_b)}$$

L is the latent heat of sublimation of ice (2844 $J \cdot g^{-1}$ or 679.7 cal $\cdot g^{-1}$) and A_e is external cross-sectional area of the base of the TVIS vial (4.62 cm^2)

$$K_v(270\quad bar) = \frac{L\frac{\Delta m}{\Delta t}}{A_e(T_s - T_b)}$$

$$= \frac{679.7\ cal \cdot g^{-1} \times 0.42\ g \cdot h^{-1}}{4.62\ cm^2 \times (273.3 - 243.3)K}$$

$$= 2.06\ cal \cdot h^{-1} \cdot cm^{-2} \cdot K^{-1}$$

$$= 5.73 \times 10^{-4} cal \cdot s^{-1} \cdot cm^{-2} \cdot K^{-1}$$

$$K_v(270\ \mu bar) = 5.73 \times 10^{-4} cal \cdot s^{-1} \cdot cm^{-2} \cdot K^{-1}$$

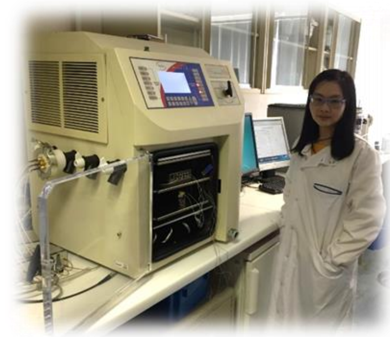
Summary

Dielectric loss peak		Dielectric constant	
Log peak frequency (F_{PEAK})	Temperature calibration (ice phase) Spatial measurements of ice temperature possible with multiple nodes	**Low frequency (100 Hz)**	Ice nucleation onset time and temperature
Peak amplitude (C''_{PEAK})	Ice mass & sublimation rate Annealing end-point	**High frequency (100 kHz)**	Ice solidification end point Glass transition temperature Devitrification Sublimation end point

Items in red not covered in talk

Acknowledgements

Dr Yowwares Jeeraruangrattana
Government Pharmaceutical Organization, Bangkok, Thailand



Evgeny Polygalov
Physicist and Inventor of TVIS
1952-2020

Dr Bhaskar Pandya
Biopharma, Winchester

References

Jeeraruangrattana, Y. (2020) Applications for Through-Vial Impedance Spectroscopy (TVIS) in the Development of Pharmaceutical Freeze-Drying Processes. PhD Thesis. De Montfort University. https://dora.dmu.ac.uk/handle/2086/20278

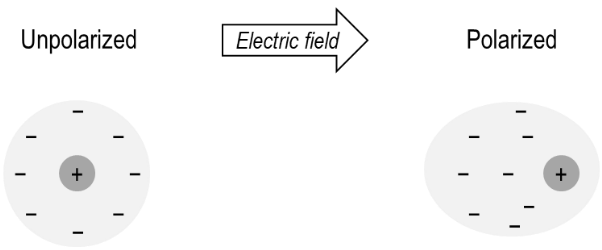
Pandya, B. (2020) Single Vial Monitoring of Pharmaceutical Freeze-Drying Processes using Through Vial Impedance Spectroscopy. PhD Thesis. De Montfort University. https://dora.dmu.ac.uk/handle/2086/19997

Appendix

Electrical impedance and material properties

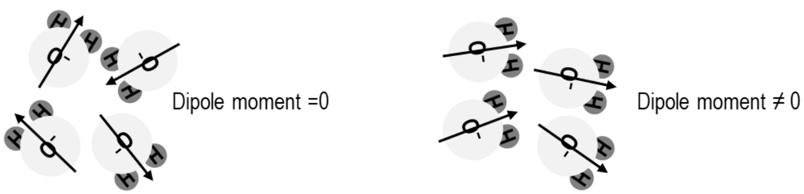
Material properties contributing to the permittivity

Electronic polarization (induced dipoles)



- Instantaneous relative to period of oscillating field

Orientation polarization (fixed dipoles)



- Relative dependence on period of oscillating field
- Relaxation as frequency increases

Material property:

Permittivity, ϵ

(dielectric constant)

Circuit element:

Capacitor, C

$$C = \epsilon_o \epsilon A/L$$

Impedance:

Reactance, X_c

$$X_c = 1/\omega C$$

Electrical impedance and material properties

Material property:

Resistivity, ρ

Conductivity, σ

$$\sigma = 1/\rho$$

Circuit element:

Resistor, R

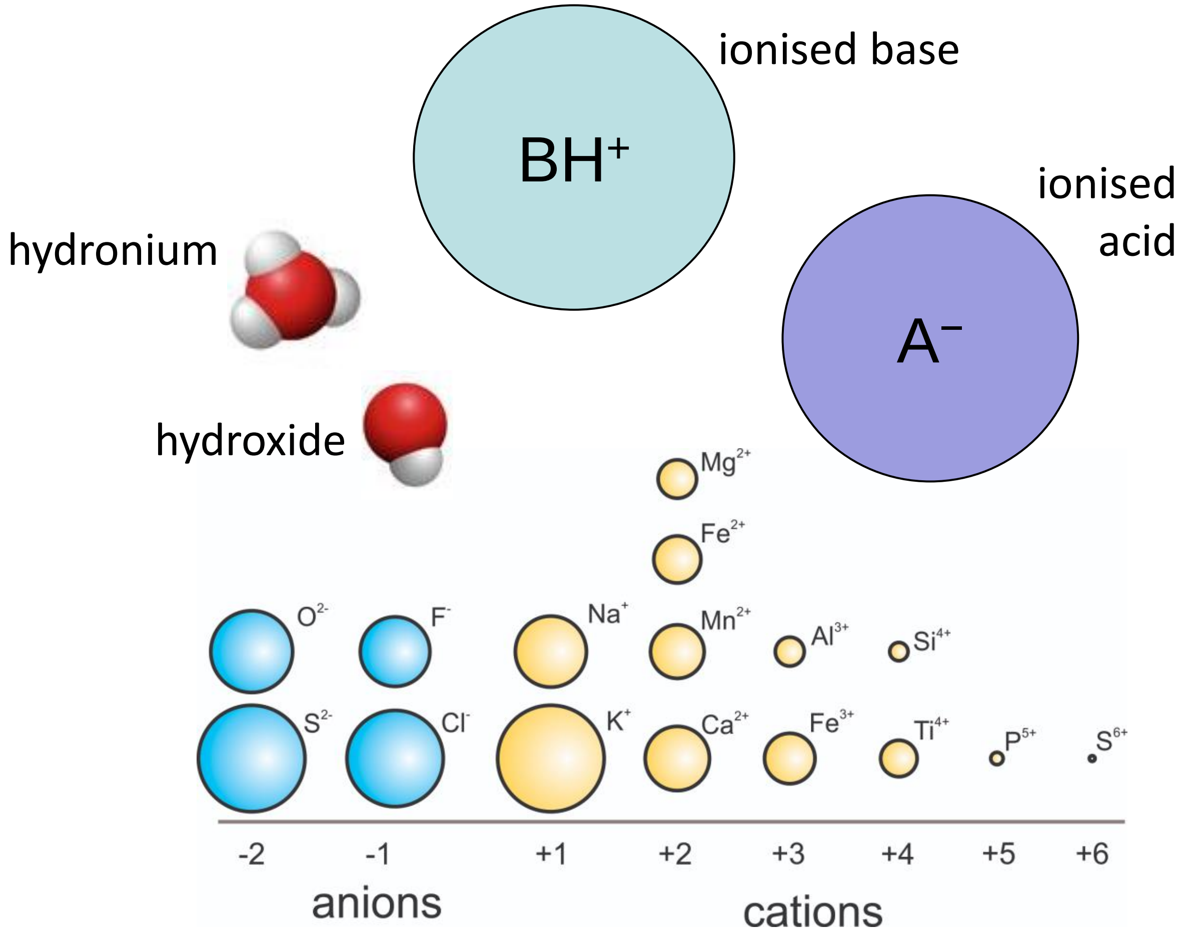
$$R = \rho L/A$$

Conductor, G

$$G = \sigma A/L$$

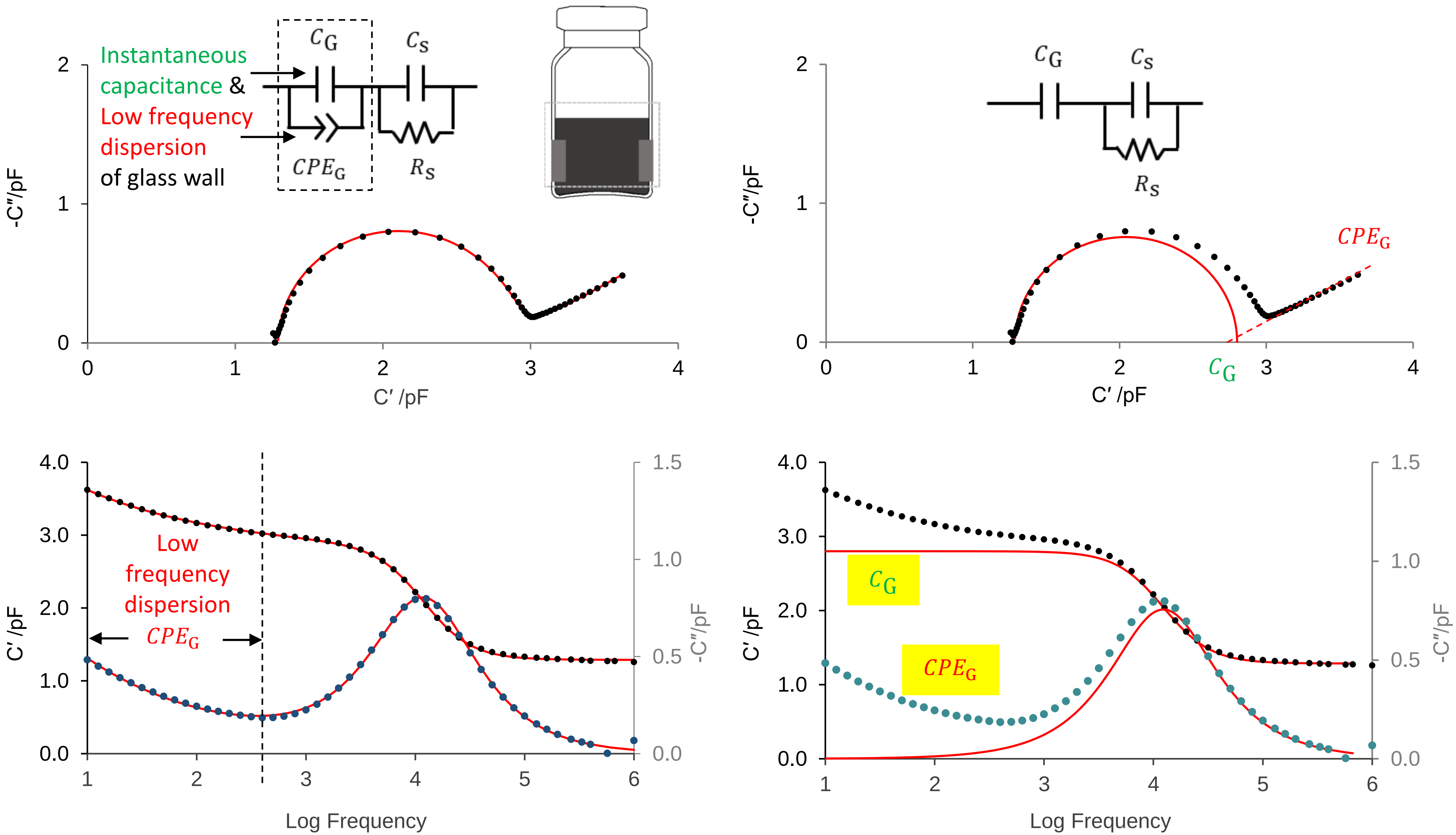
Impedance property:

Resistance, R

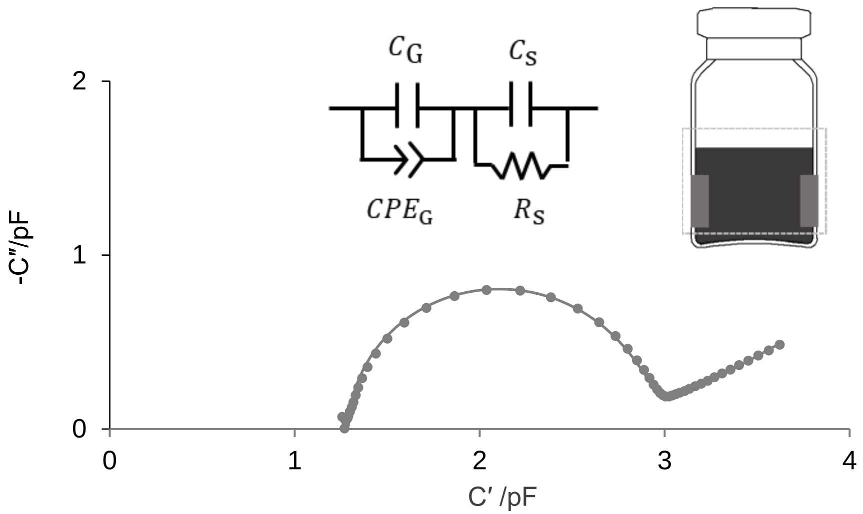


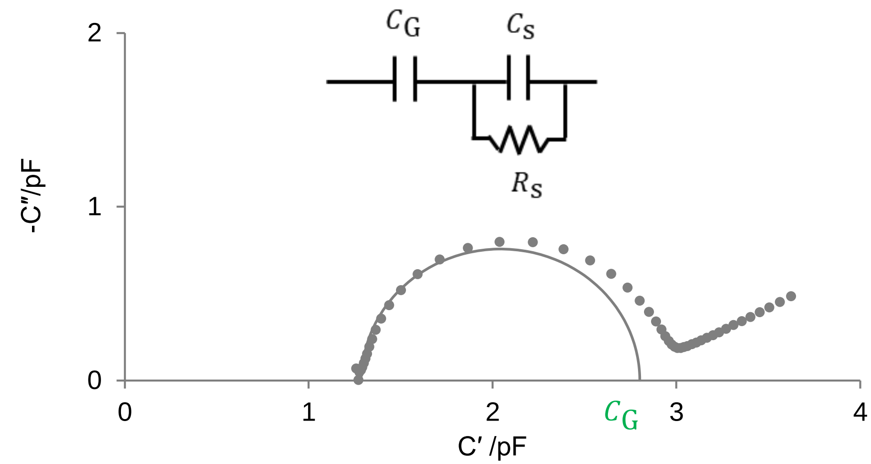
Metal ions, hydronium and hydroxide ions and ionised drugs in aqueous solution

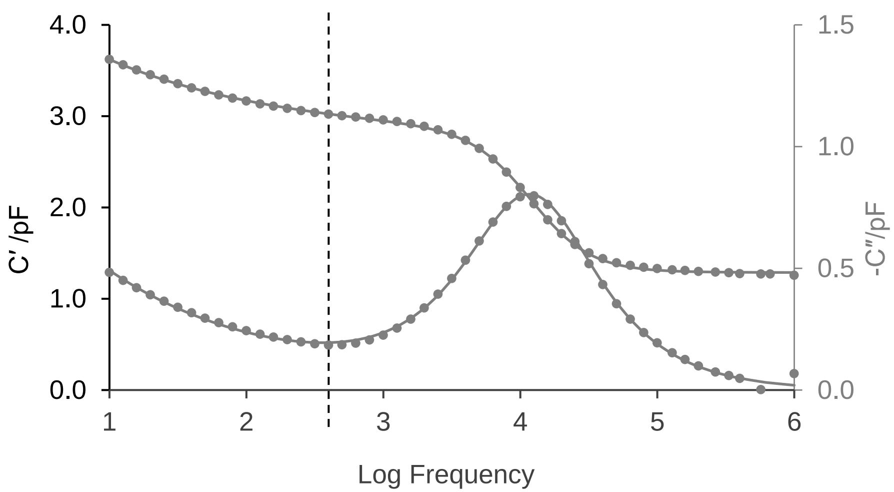
Liquid state: glass wall controls low frequency response

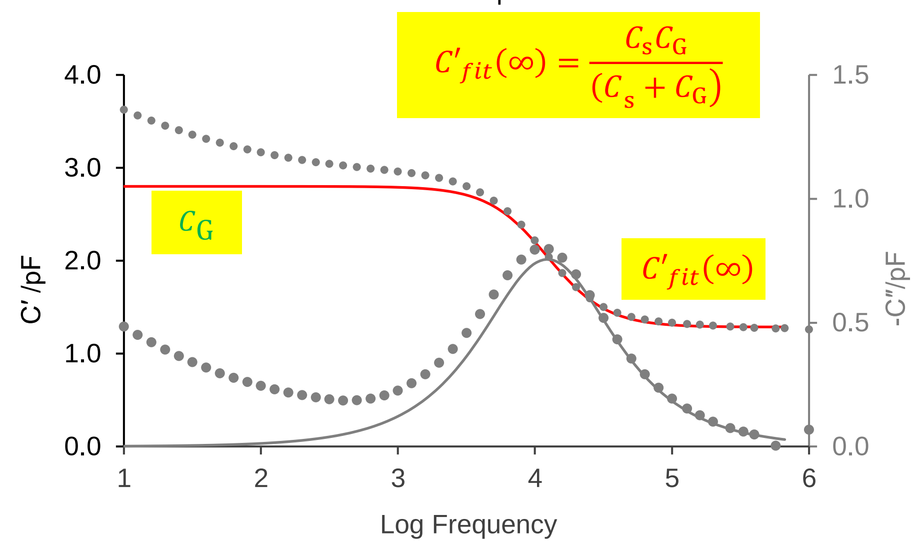


Liquid state: Charging of capacitances through solution

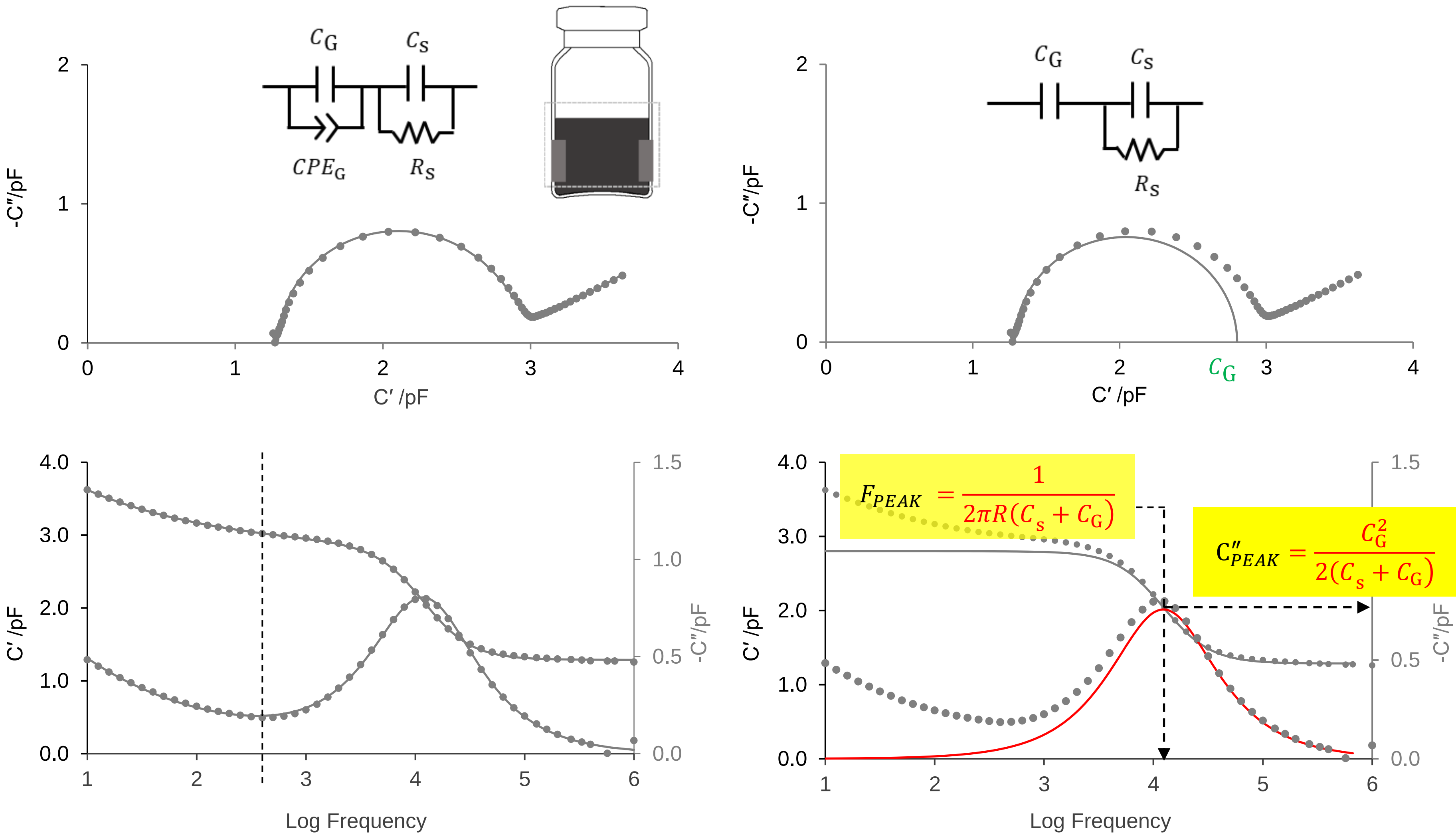






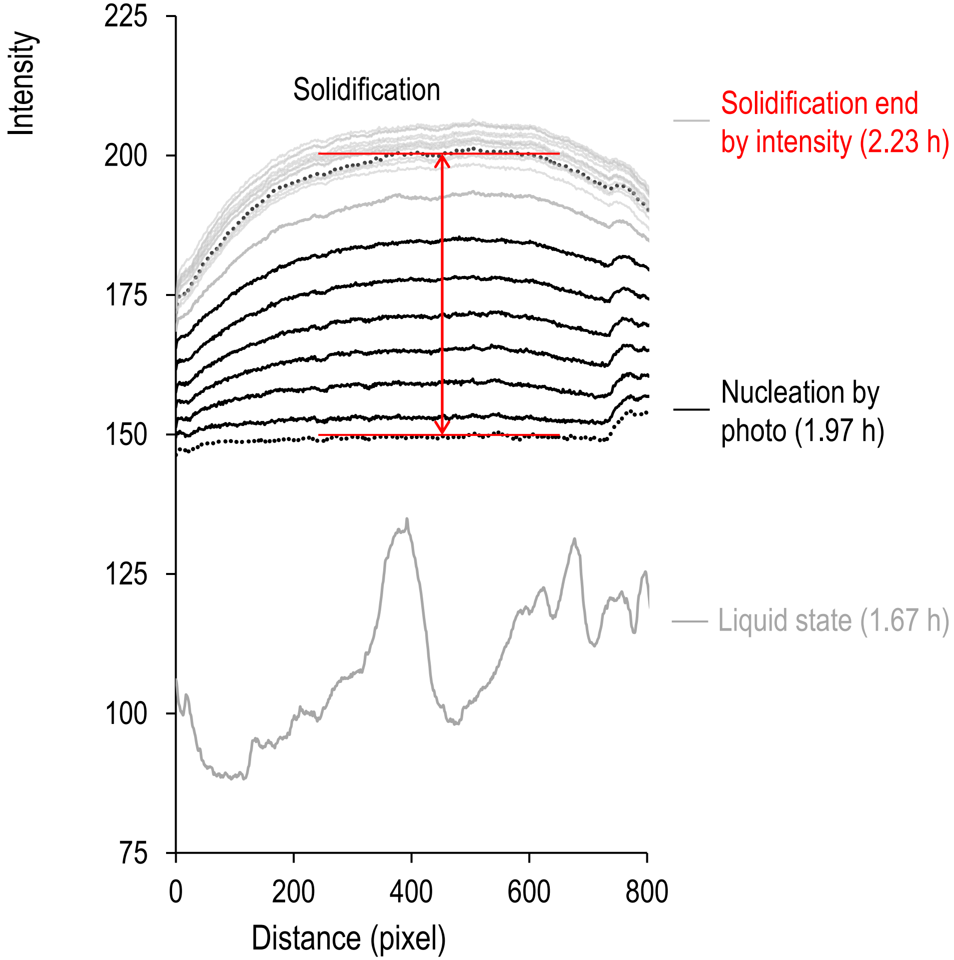


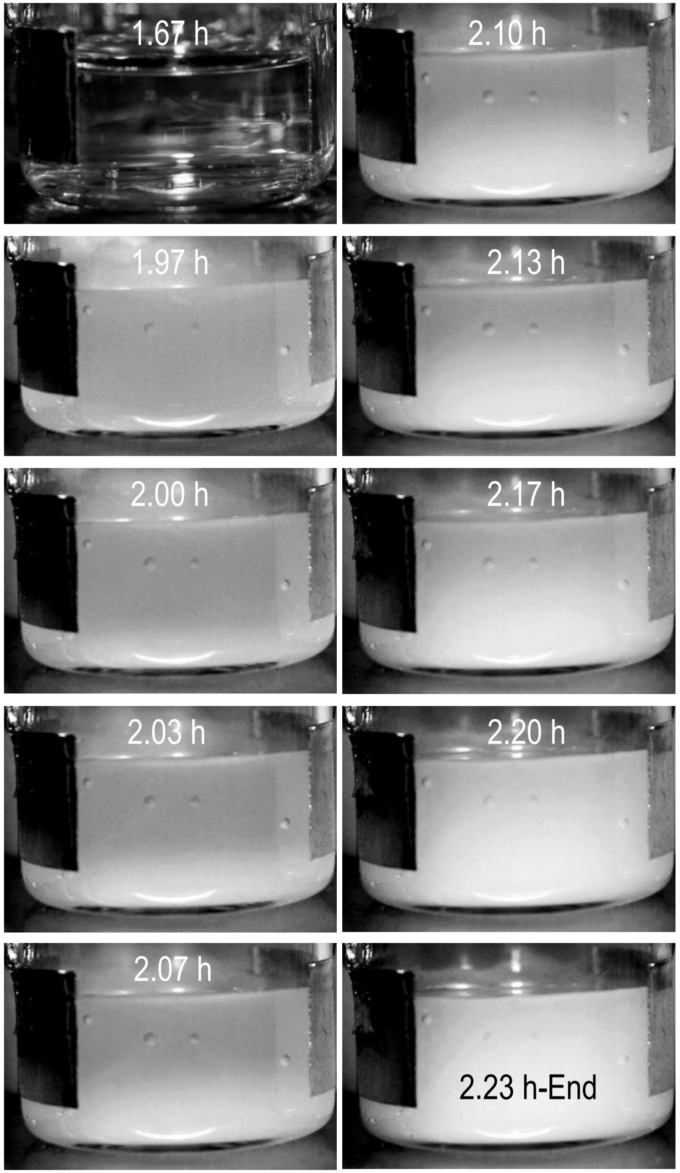
Liquid state: MW loss peak



Solidification end point

Image analysis





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