qepler

PHARMACEUTICAL LYOPHILIZATION SUMMIT 2021

An introduction to TVIS PAT

Through-Vial Impedance Spectroscopy

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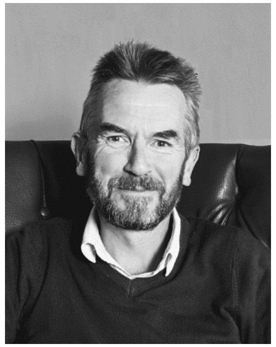
July 29 | 1st DAY

Central European Summer Time (CEST, Prague, UTC/GMT +2 hours)

In collaboration with

NIBSC Confidence in Biological Medicines



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Overview

Process analytical technologies (PAT)
Single vial and Batch

Measurement instrumentation

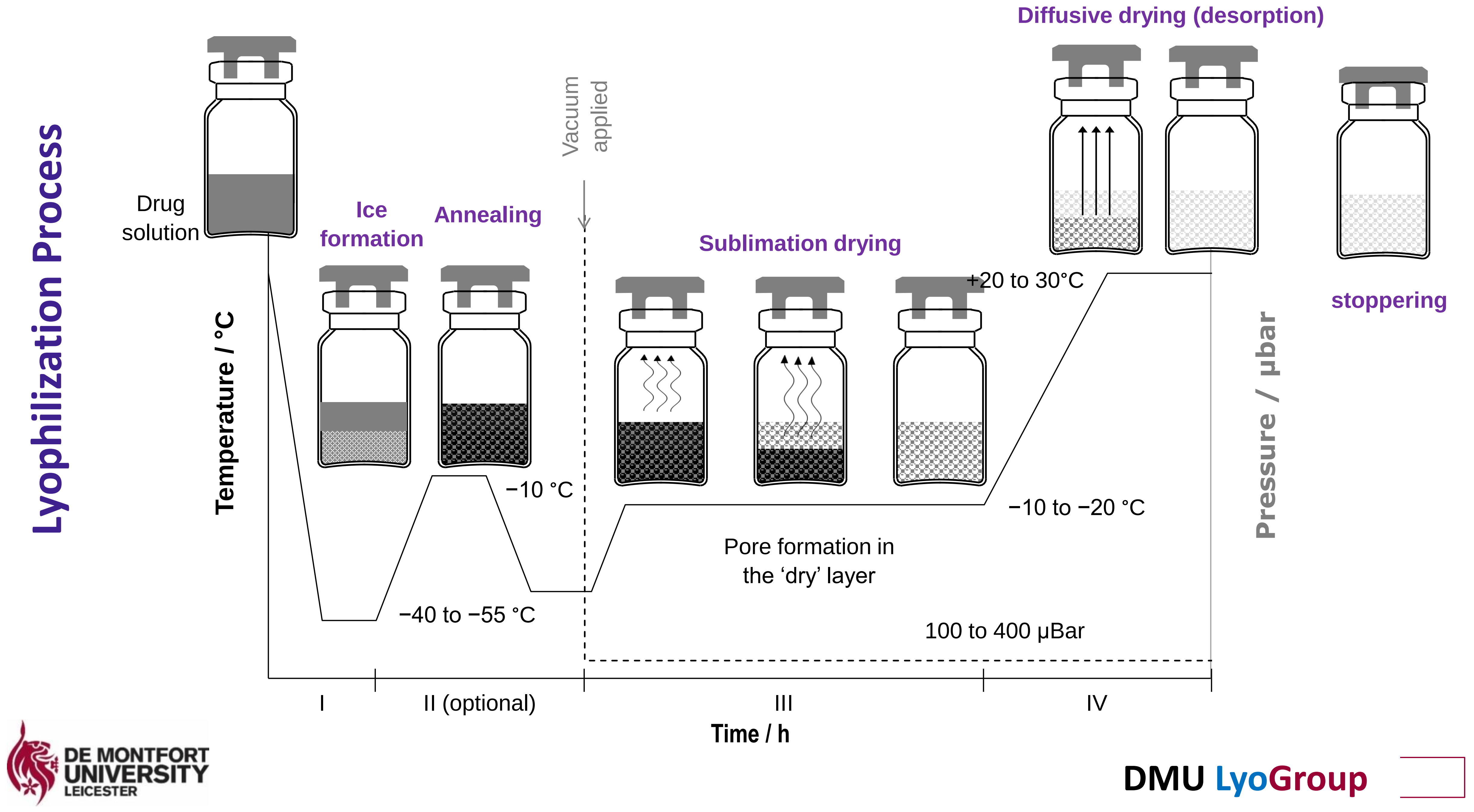
- Electro-thermal analysis (Lyotherm)
- Broad band dielectric spectroscopy
- Through-vial impedance spectroscopy (TVIS)

Fundamentals

- Dielectric properties of water and solutions
- Dielectric properties of ice and frozen solutions

Applications

- Temperature calibration
- Ice nucleation and solidification
- Sublimation end point
- Shape of ice mass



Lyophilization Process
Drug solution
Ice formation
Annealing
Vacuum applied
Sublimation drying
Diffusive drying (desorption)
stoppering
Temperature / °C
Pressure / µbar
−10 °C
+20 to 30°C
−10 to −20 °C
−40 to −55 °C
Pore formation in the ‘dry’ layer
100 to 400 µBar
I
II (optional)
III
IV
Time / h
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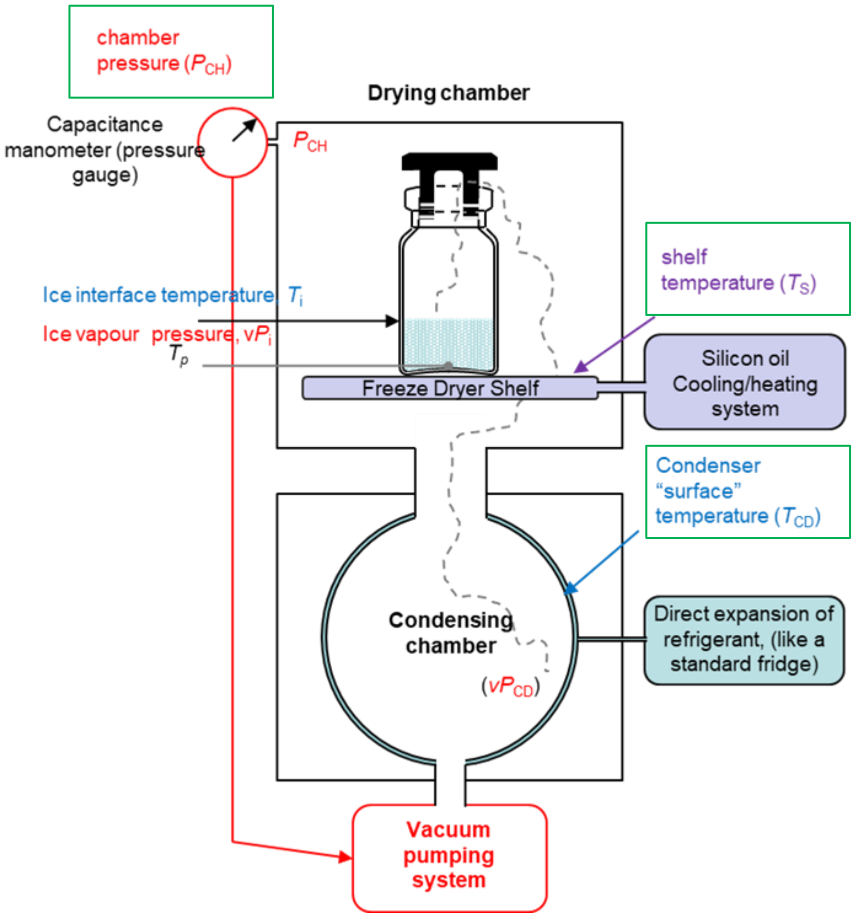
Lyophilization Process



Operating parameters :

(A) shelf temperature (ramp)

(B) chamber pressure

(C) condenser temperature

Critical process parameters:

- Ice nucleation temperature (T_n)
- Rate of change of the product temperature (dT_p/dt):
- Phase behaviour of solid/solute fraction
- Critical temperature (e.g. collapse), T_c
- Vial heat transfer coefficient
- Porosity of the 'dry' fraction of the product that develops during primary drying (R_p = 1/ Porosity)
- Ice interface temperature (T_i) < T_c
- Primary and secondary drying end points

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Process analytical technologies (PAT) for freeze-drying

Process Analytical Technology (PAT)

PAT, as defined by the ICH, is "a system for **designing, analysing and controlling** the manufacturing through timely measurement (during the process) of critical quality and performance attributes of raw and in-process materials and the process with the goal of ensuring final product quality"

ICH, 2009. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Topic Q8(R2): Pharmaceutical Development.

Single vial techniques

- Temperature probes
  - TC, RTD
  - Wireless : Tempris®; TrackSense®
- Microbalance (CHRIST GmbH)
- Heat flux transducers (MicroFD, Millrock)

Batch techniques

- Pressure rise test (PRT)
- Comparative pressure measurement (CPM)

→ Primary drying end point

- Manometric temperature measurement (MTM)
- Time domain laser absorption spectroscopy (TDLAS)

→ Predictions of product temperature, drying rate

Louis Rey 1960s

STUDY OF THE FREEZING AND DRYING OF TISSUES AT VERY LOW TEMPERATURES

L. R. Rey

Laboratoire de Zoologie-Physiologie, Ecole Normale Supérieure, Paris

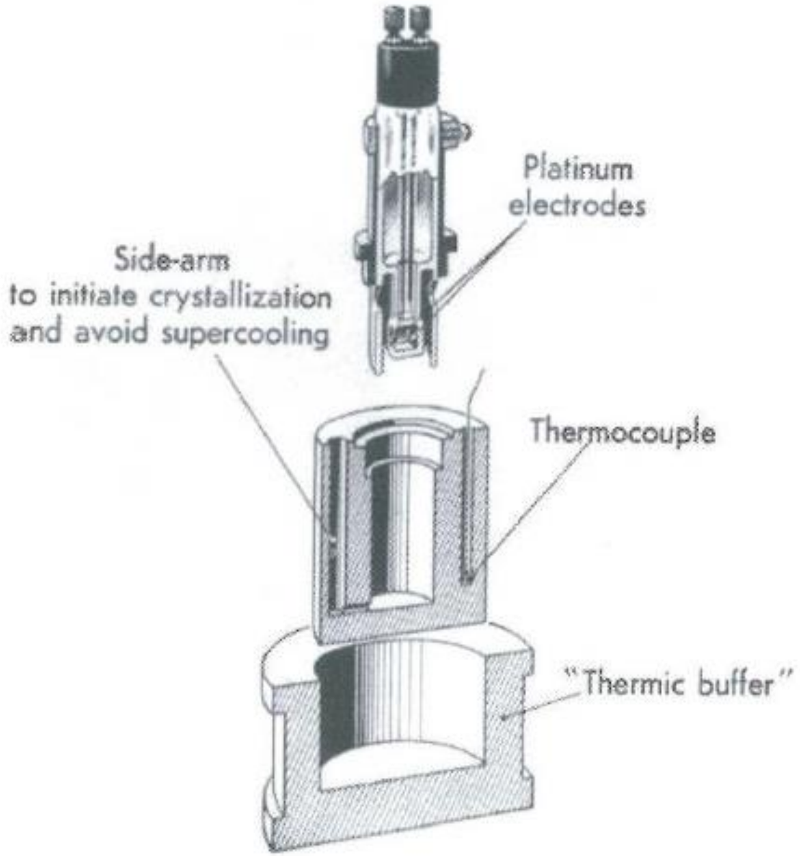
The outstanding interest of the freeze-drying technique is that it provides a possibility for long-term preservation of highly alterable structures. The method has had a great number of applications in the field of histology and histochemistry since the pioneer work of Altmann (1890) and Gersh (1932).

Many authors have thought, too, that it would be possible to try to preserve life in frozen and dried animal tissues. It has been shown long ago, by Becquerel (1936) that, as far as the cells of certain plants and lower animals are concerned, highly dehydrated material could be kept over very long periods of time and would resist extreme conditions of temperature.

Unfortunately, animal cells are not very resistant and they are not able to loose a great amount of water. Luyet and Hartung (1941), Rostand (1946), Parkes (1951) and Polge, Smith and Parkes (1949), have shown that different chemical substances and especially glycerol offer very good protection against cold injury. We have done similar experiments in our laboratory, and we have studied the protective action of glycerol by the use of tissue-culture and organ-culture techniques (Rey, 1957, b and d).

In a second group of researches, our intention was to find out the conditions of lyophilization which would be able to give the best preservation of the fine cytological structures of the tissue-cells, and which, if possible, would preserve life.

At first, and according to what we said in 1957 at the Royal Society, the freezing must be done in a very precise way, because there is no use drying with great care a tissue which has undergone denaturation in the course of freezing. It is likely that a glycerol preimpregnation would be necessary. However, we have had much evidence in our work (1957 d) and we agree perfectly well with Meryman (1957) that the most harmful period of the action of low temperatures on living tissues is during thawing. One could think then, that, if we avoid thawing by previous drying, it would be possible not to use glycerol impregnation, provided that the freezing period is short. This is a theoretical point of view, compromise solutions are not excluded and we can reasonably



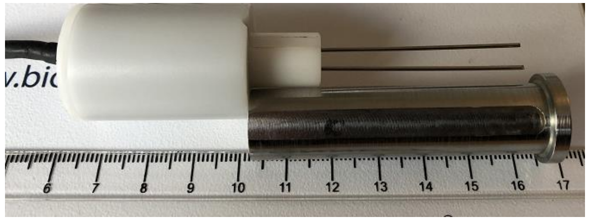
Rey (1960) Study of freezing and drying of tissues at very low temperatures. In Parkes and Audrey eds. Recent research in freezing and drying, Blackwell, Oxford.

Lyotherm

Biopharma Process Systems

Impedance analysis (Zsinϕ) at a single frequency (1 kHz) with differential thermal analysis (DTA)

- Pin electrode (pair)



- Integrated within cryostat

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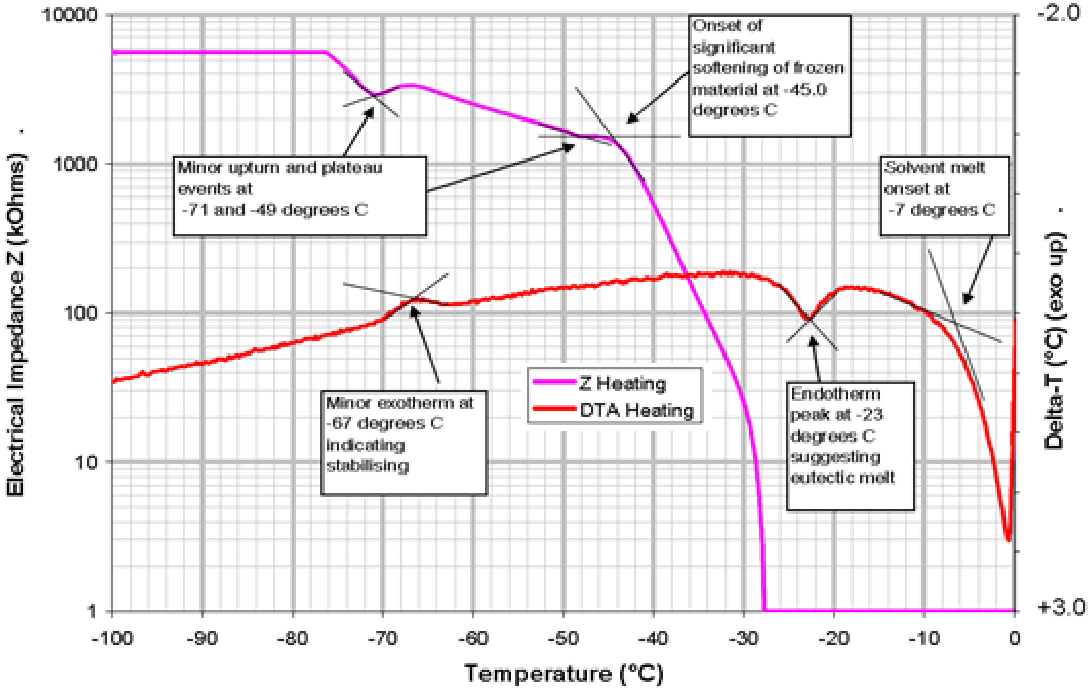
Designed to measure temperatures relevant to freeze-dried formulations

- glass transition (T_G')
- ice melting (T_M) and eutectic (T_{EU})



Ward & Matejtschuk , 2010 *in Freeze Drying/ Lyophilization of Pharmaceutical & Biological Products* 3rd ed. Rey,L & May JC eds, Informa Press, New York

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Measurement within glass vials

Freeze-thawing and freeze-drying

Spectroscopy Systems (sub Hz to 10 MHz)

Alpha-series dielectric spectrometer

Temperature controller

ZGS active sample Cell

2-electrode sample cell

TVIS vial on new cradle to be placed in the cryostat of Novocontrol BDS

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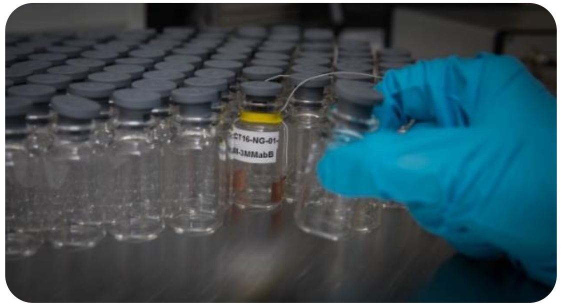
Non-invasive measurements: Lyosense ….. LyoDEA …… TVIS

Individual vials

In process

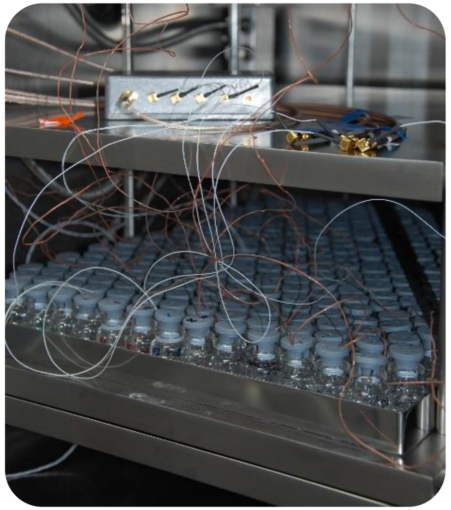
Through Vial Impedance Spectroscopy

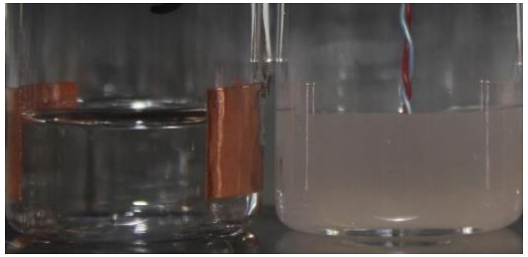
Non- perturbing to packing of vials



Thin flexible cables (0.533 mm)

- Stoppering unaffected





Non-sample invasive

- no impact on ice nucleation

Low thermal mass of electrodes

- no interference with heat transfer & drying rates

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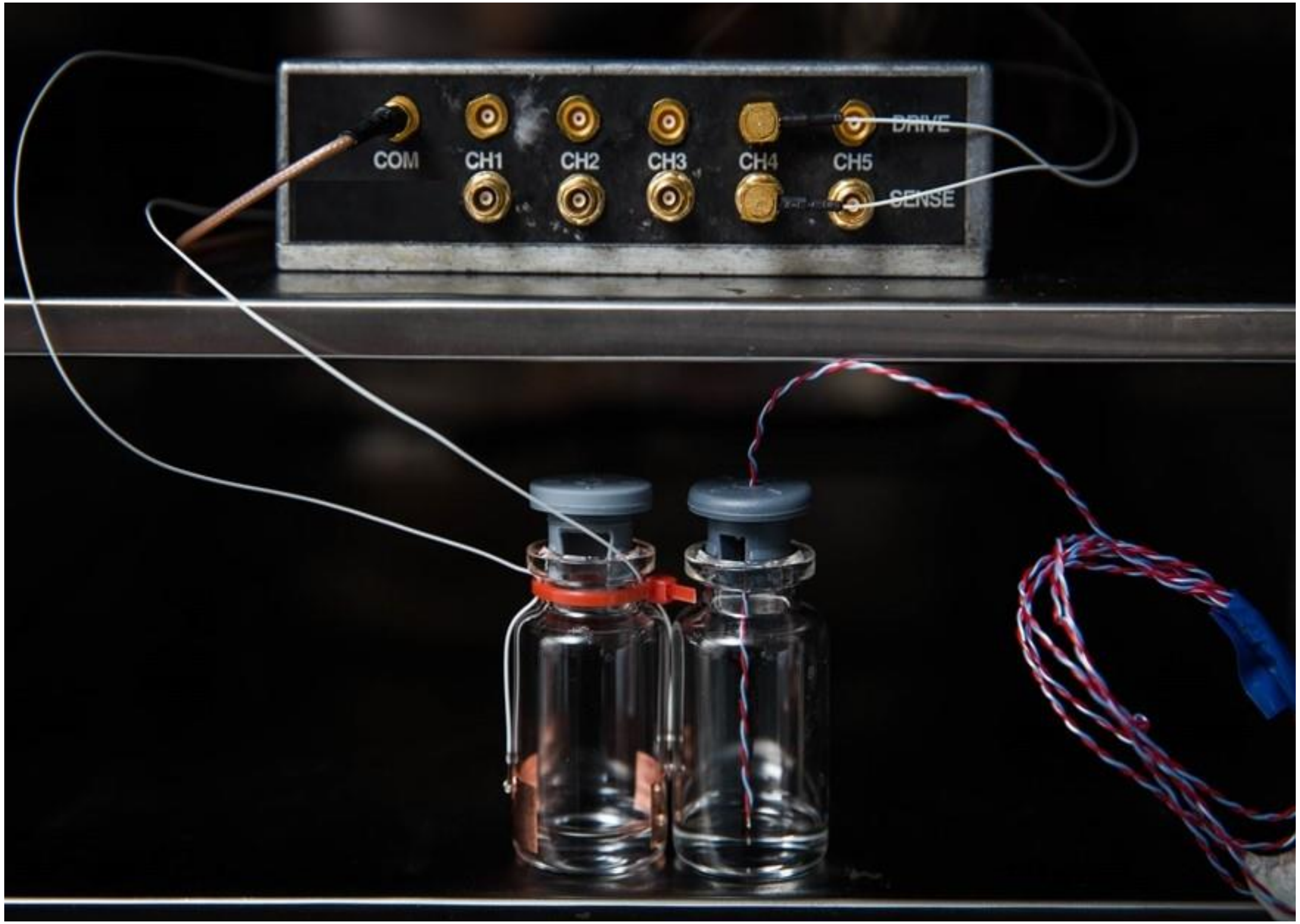
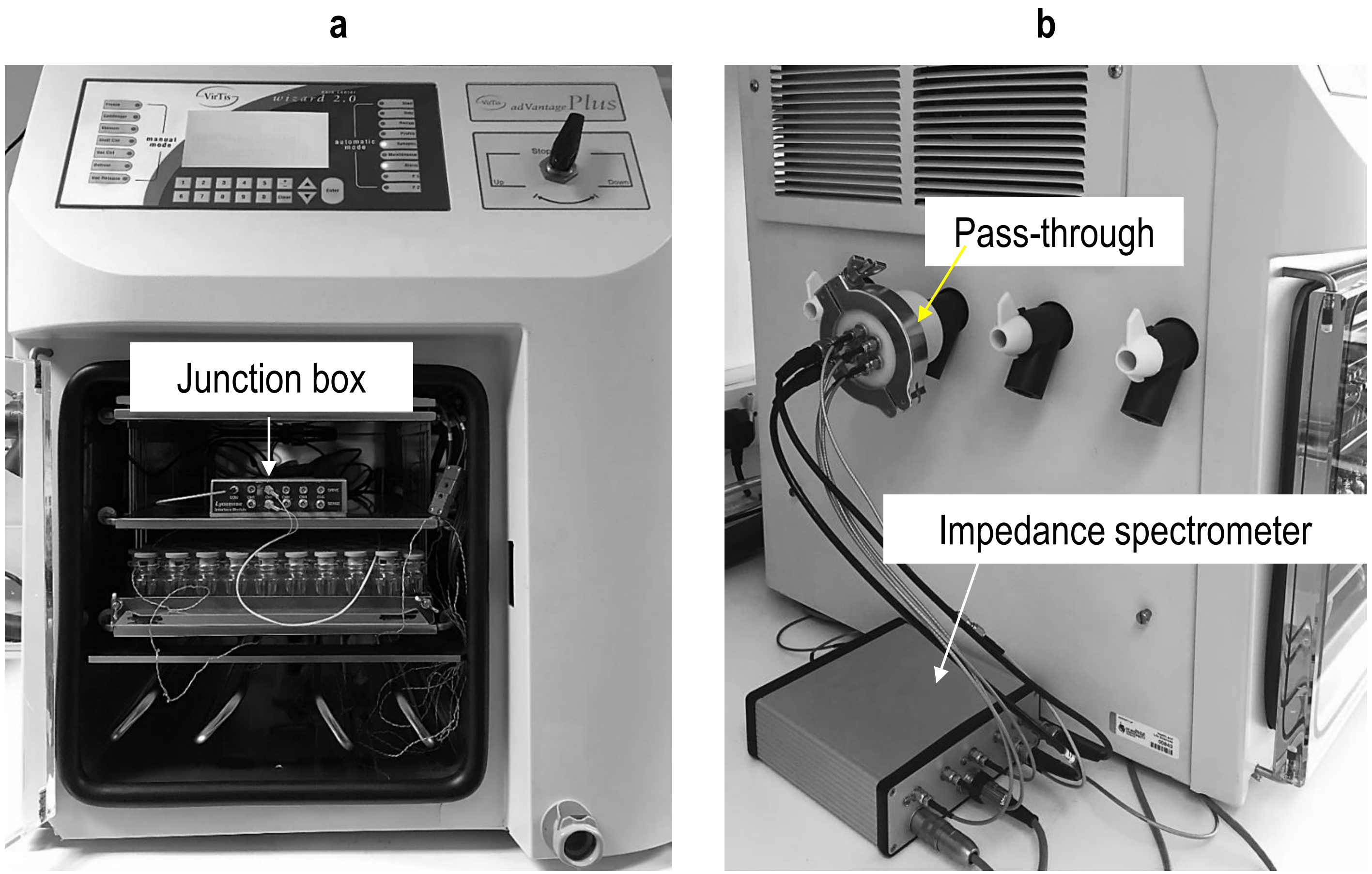
Junction box

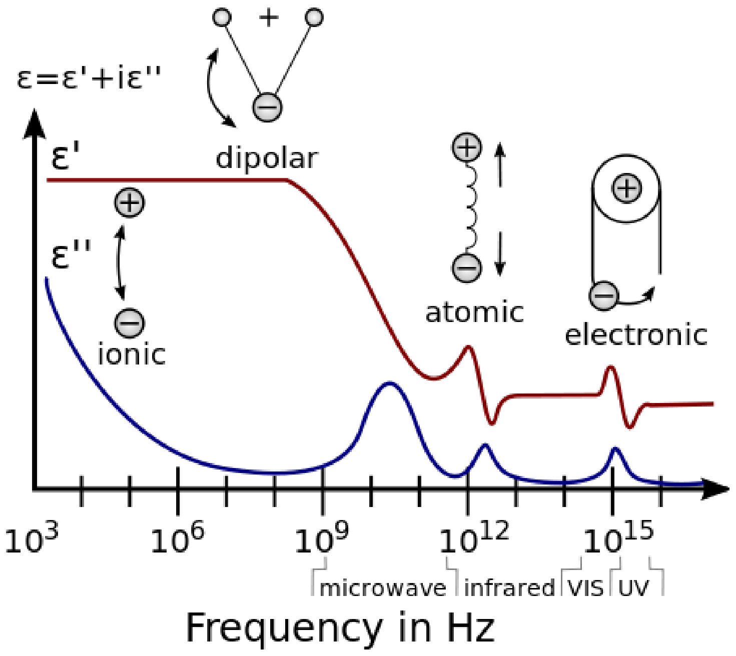


System configuration

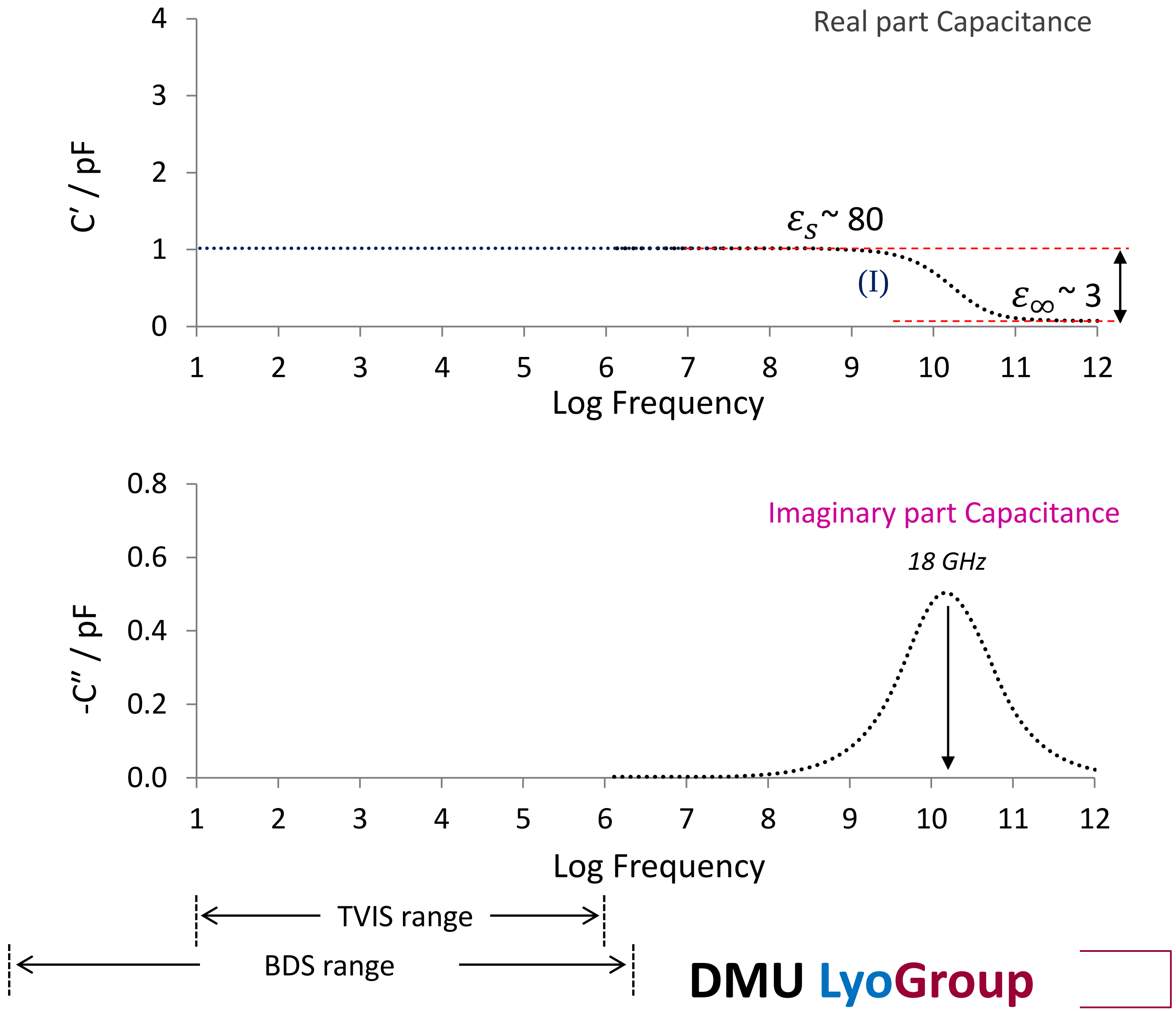


Dielectric Loss Mechanisms :

I. The polarization of the water dipole in liquid water at 20 ˚C, with a dielectric loss peak frequency of ~ 18 GHz



https://en.wikipedia.org/wiki/Permittivity



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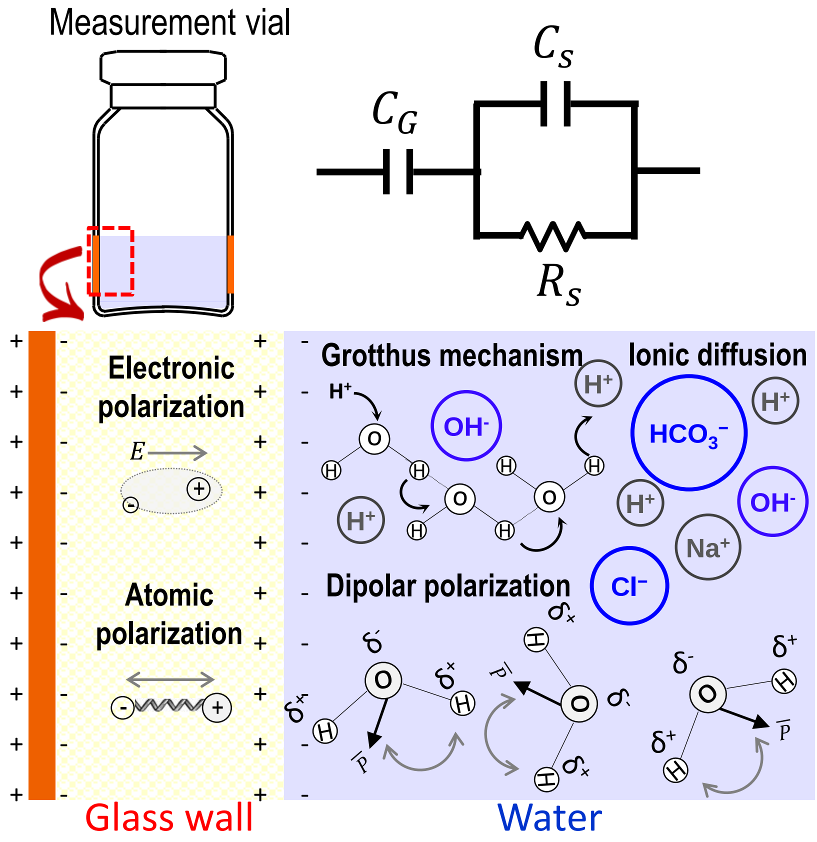
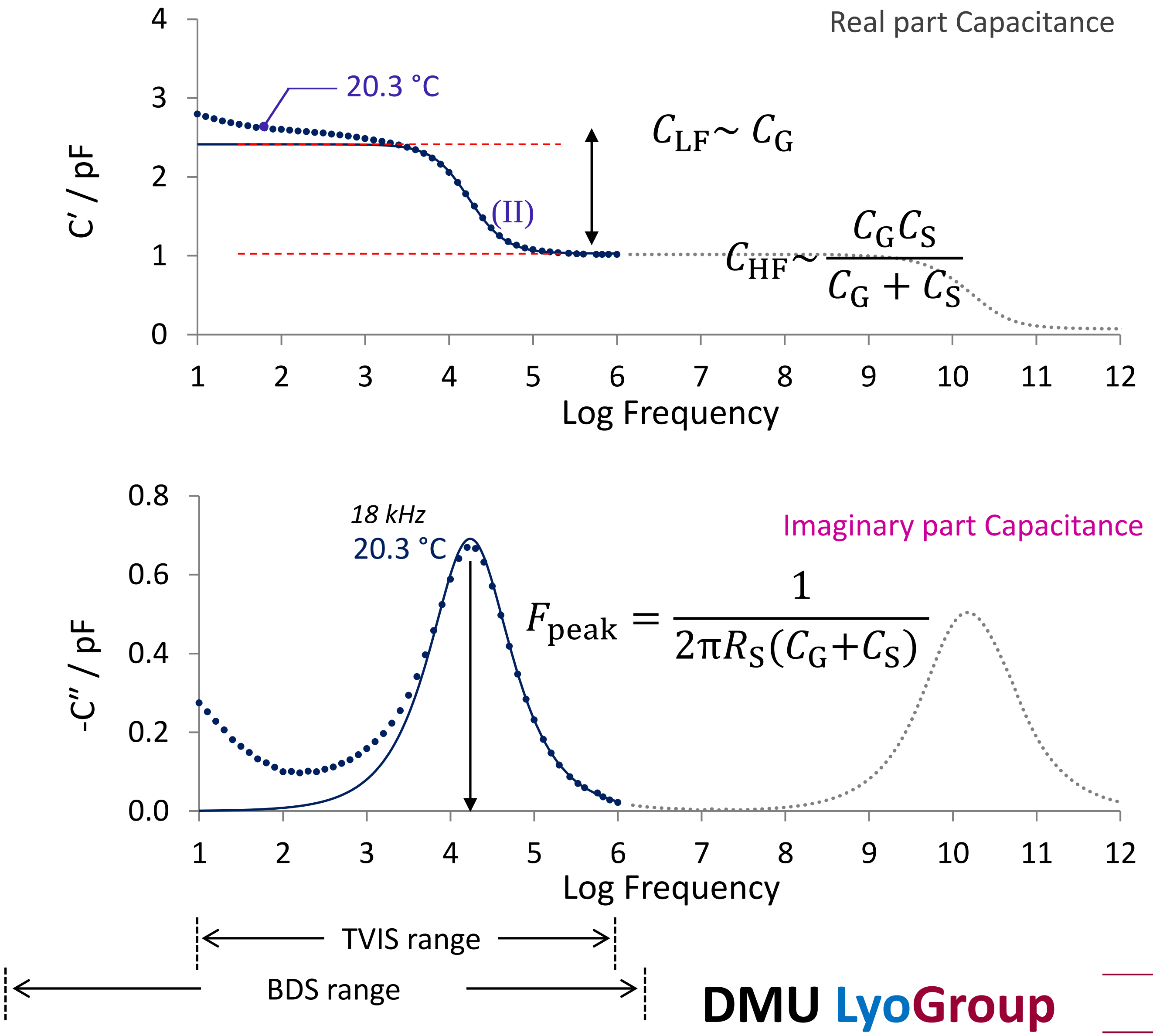
Dielectric Loss Mechanisms : Glass vial containing water

II. Maxwell-Wagner (MW)* polarization of the glass wall of the TVIS vial at +20 ˚C, with a dielectric loss peak frequency of 17.8 kHz





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* Interfacial or space charge

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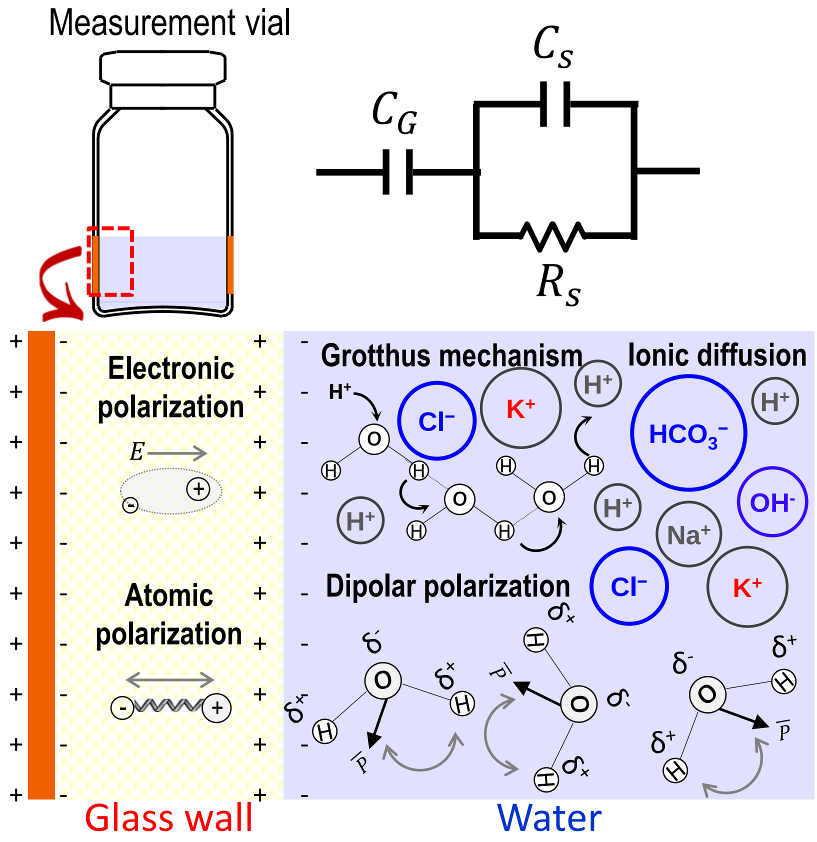
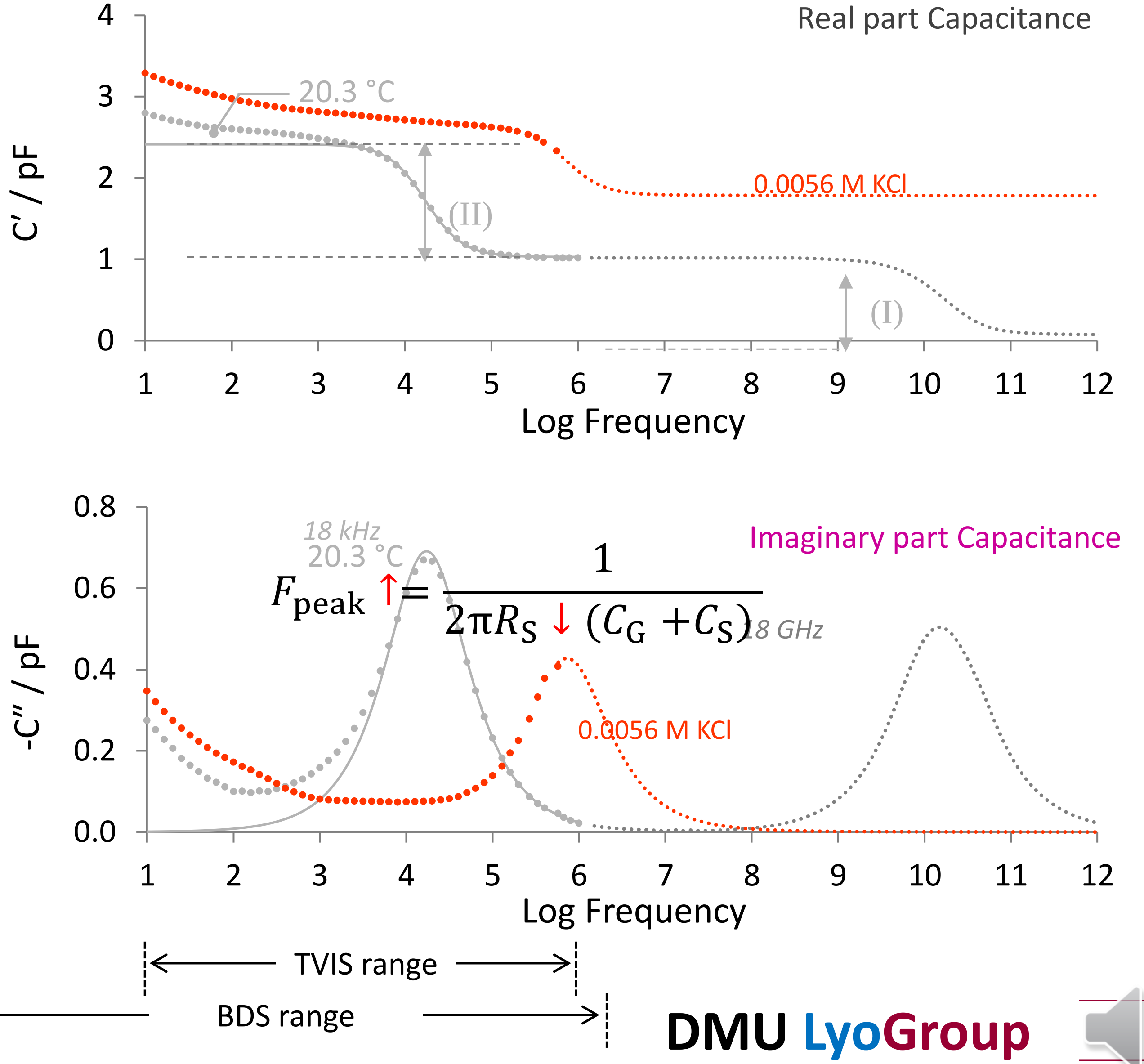
Dielectric Loss Mechanisms

II. Maxwell-Wagner (MW) polarization of the glass wall of the TVIS vial at +20 ˚C, with a dielectric loss peak frequency of 17.8 kHz





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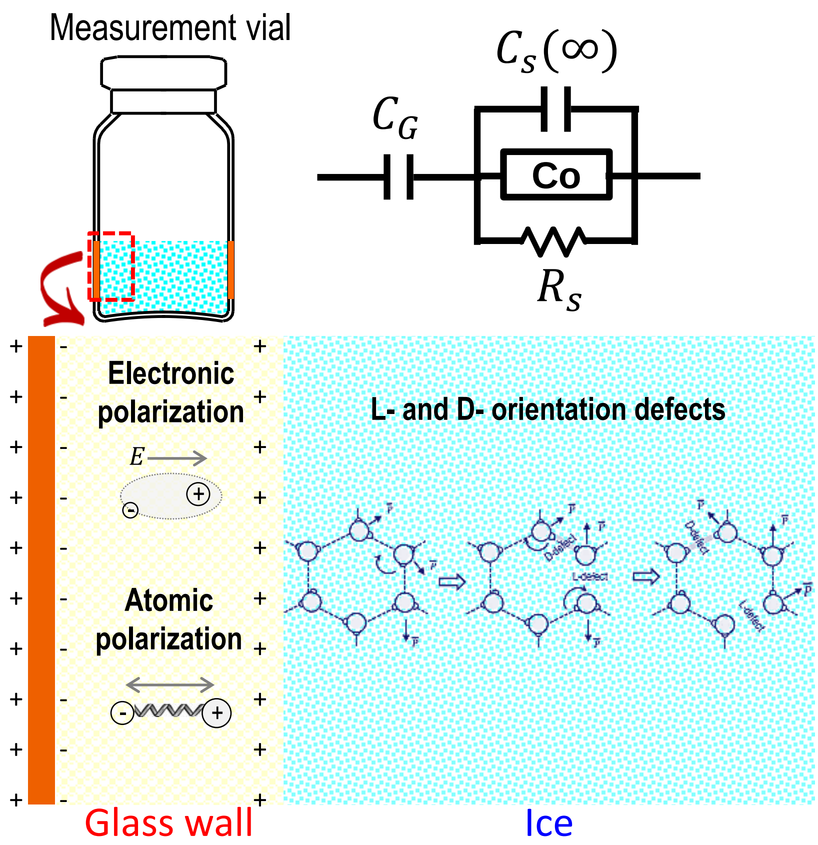
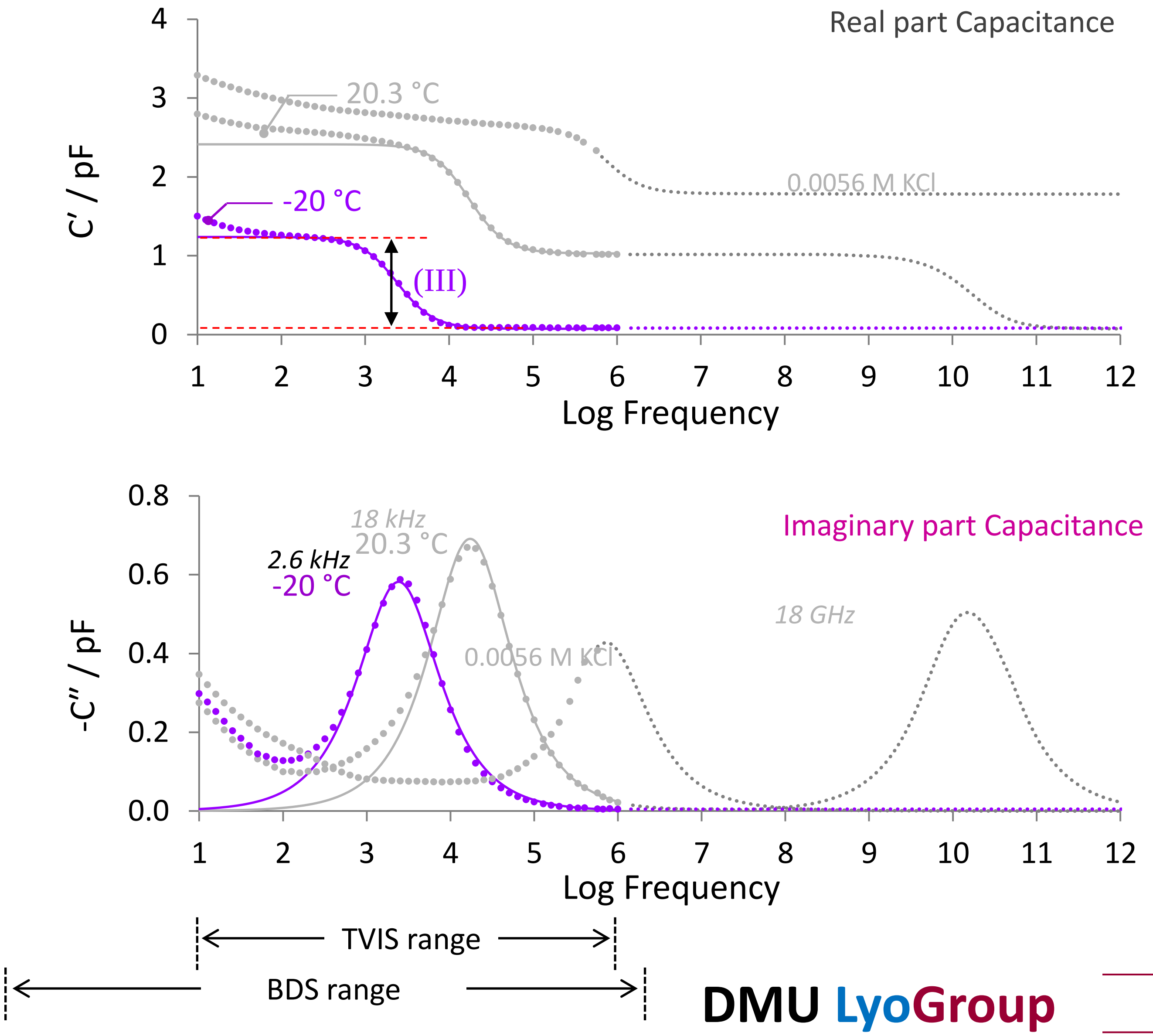
Dielectric properties of ice

Dielectric Loss Mechanisms

III. The dielectric polarization of ice at −20 ˚C, with a dielectric loss peak frequencies of 2.57 kHz





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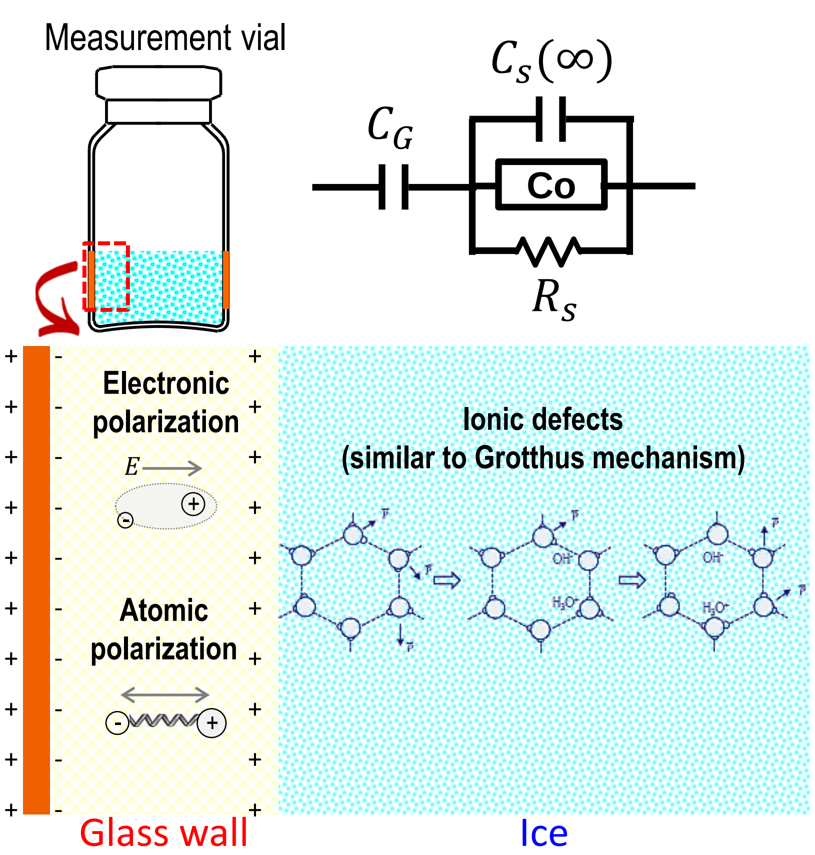
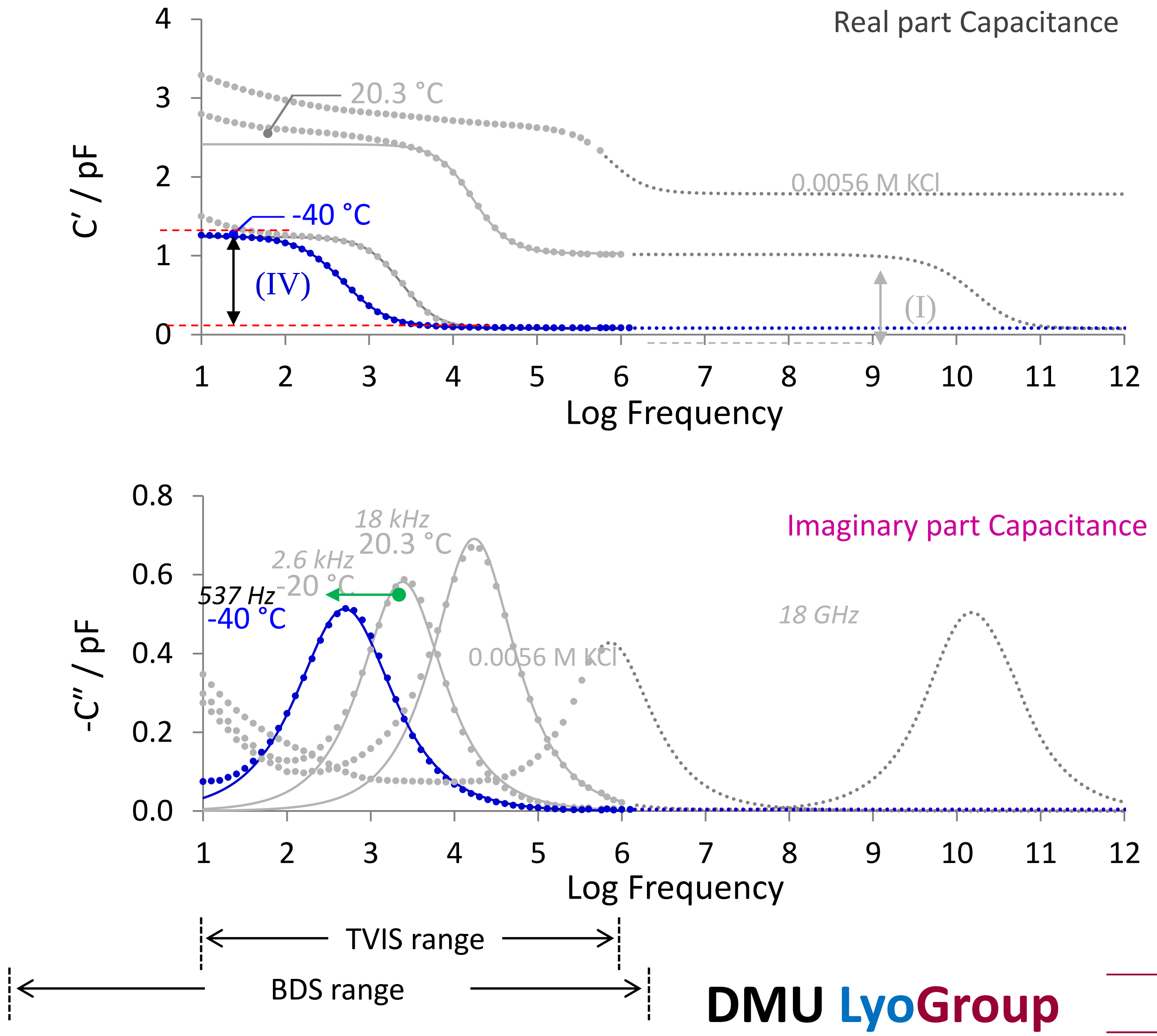
Dielectric Loss Mechanisms

IV. The dielectric polarization of ice at −40 ˚C with a dielectric loss peak frequencies of 537 Hz.





TVIS Applications

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CASE STUDY 1

TVIS temperature calibration

Method 1 : Triangulation

Mehod 2 : Tempris®

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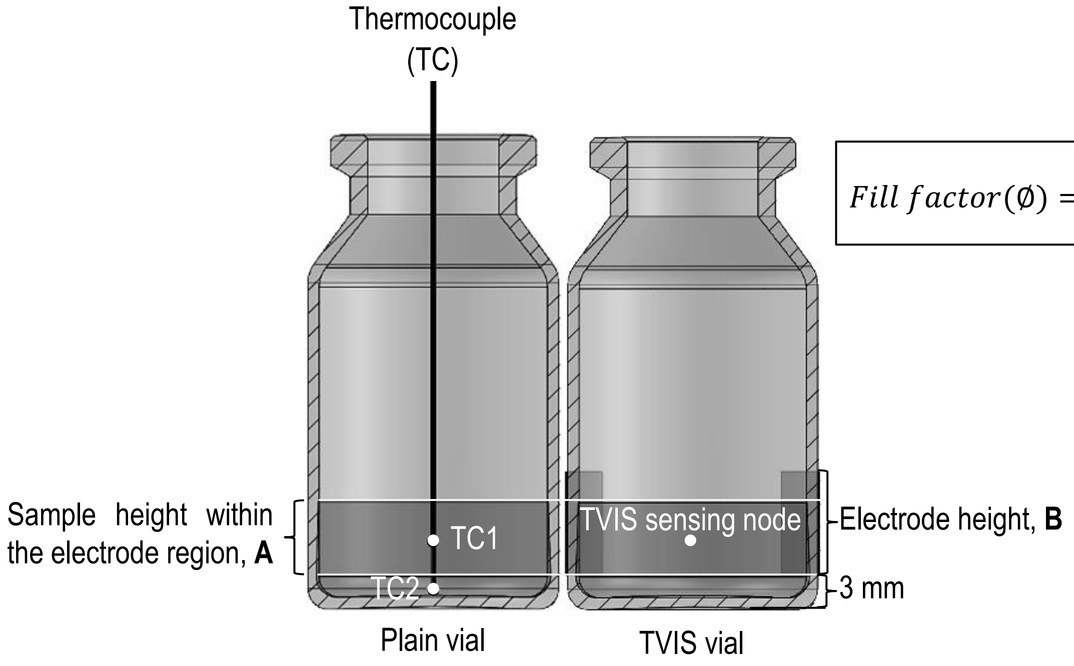
1. Triangulation method

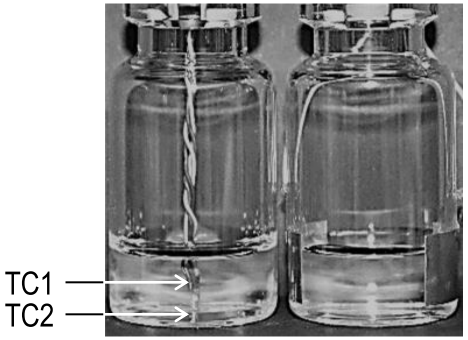
Placing a thermocouple at the TVIS sensing node allows for the calibration of the temperature inside the TVIS vial to a precision of +/- 0.4 C

(see next two slides)

TC in nearest neighbour vial



$$Fill\ factor(\emptyset) = \frac{A}{B}$$



Jeeraruangrattana (2020) PhD Thesis https://dora.dmu.ac.uk/handle/2086/20278

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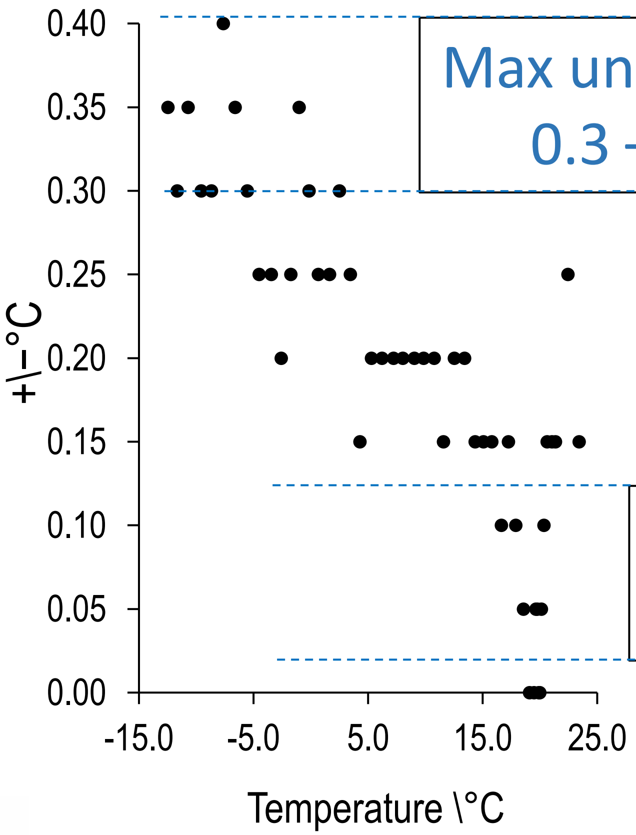
1. Triangulation method

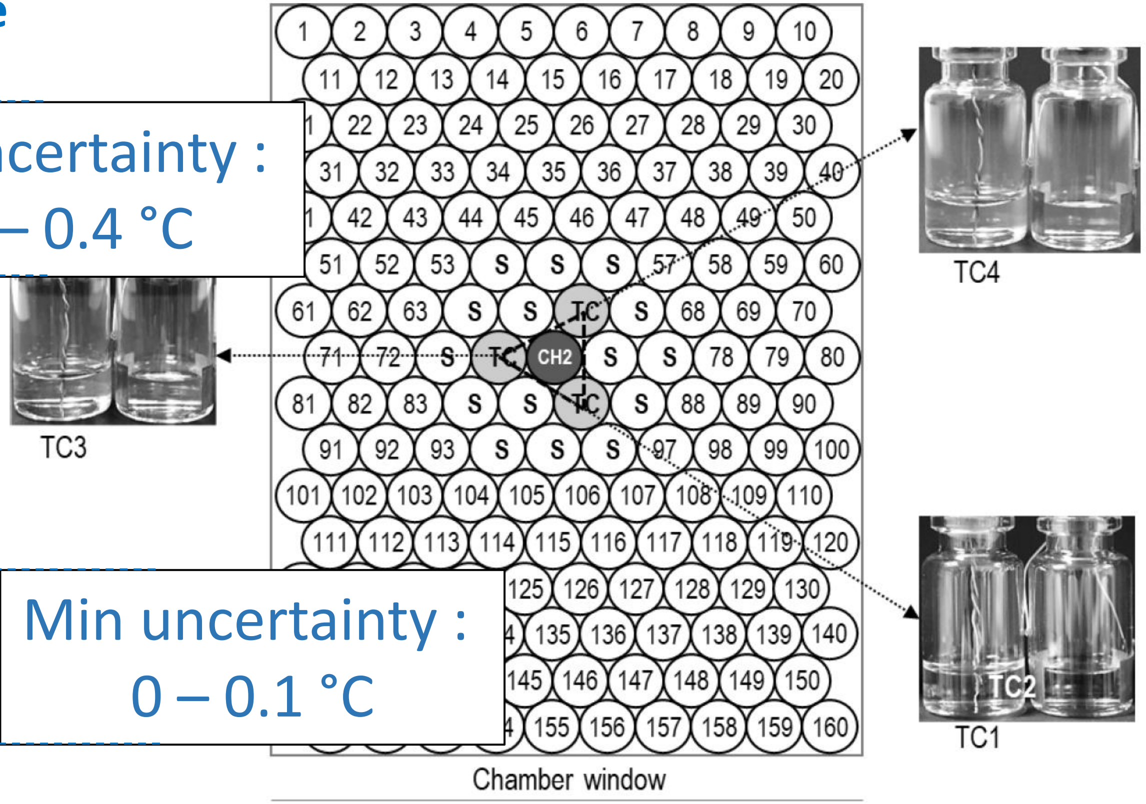
Temperature uncertainty during freezing phase



Max uncertainty : 0.3 – 0.4 °C

Min uncertainty : 0 – 0.1 °C

TC in nearest 3 neighbour vials



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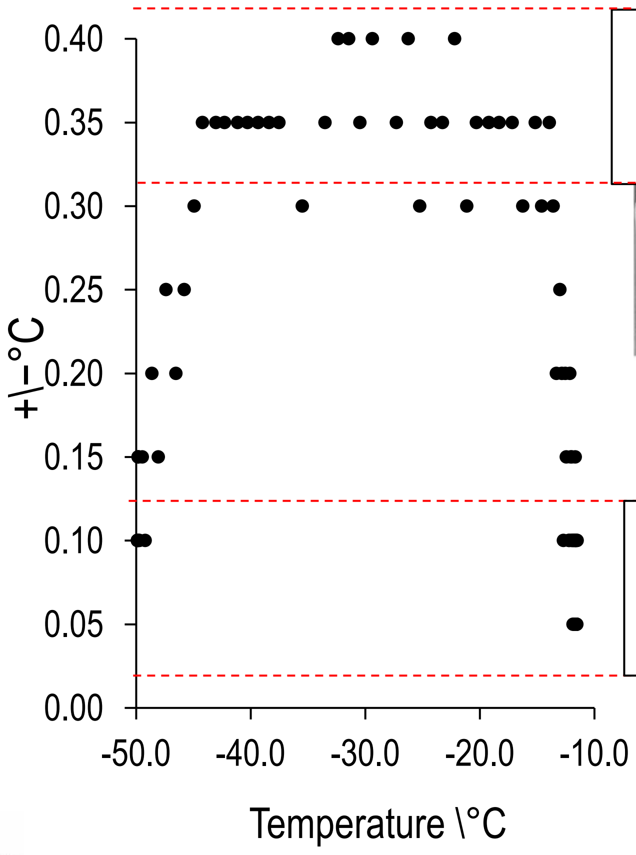
Temperature calibration for the TVIS vial:
1. Triangulation method

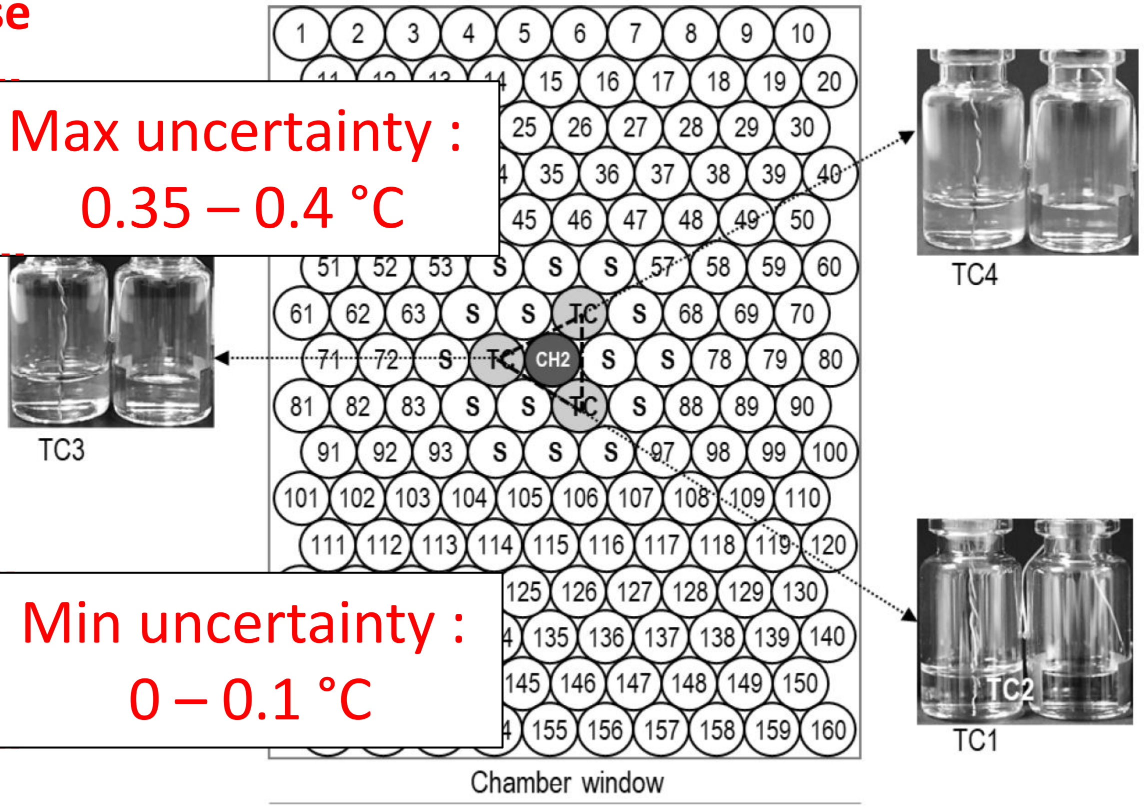
Temperature uncertainty during re-heating phase



Max uncertainty : 0.35 – 0.4 °C

Min uncertainty : 0 – 0.1 °C

TC in nearest 3 neighbour vials



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Temperature calibration for the TVIS vial: 2. Tempris® method

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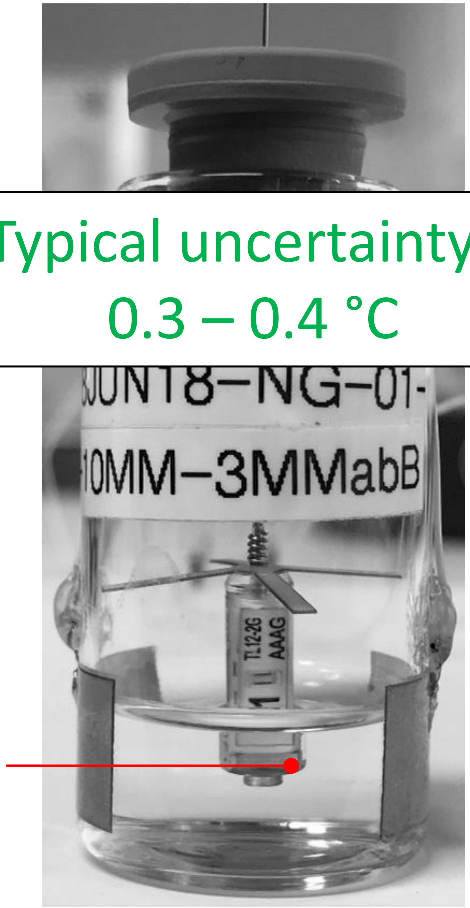
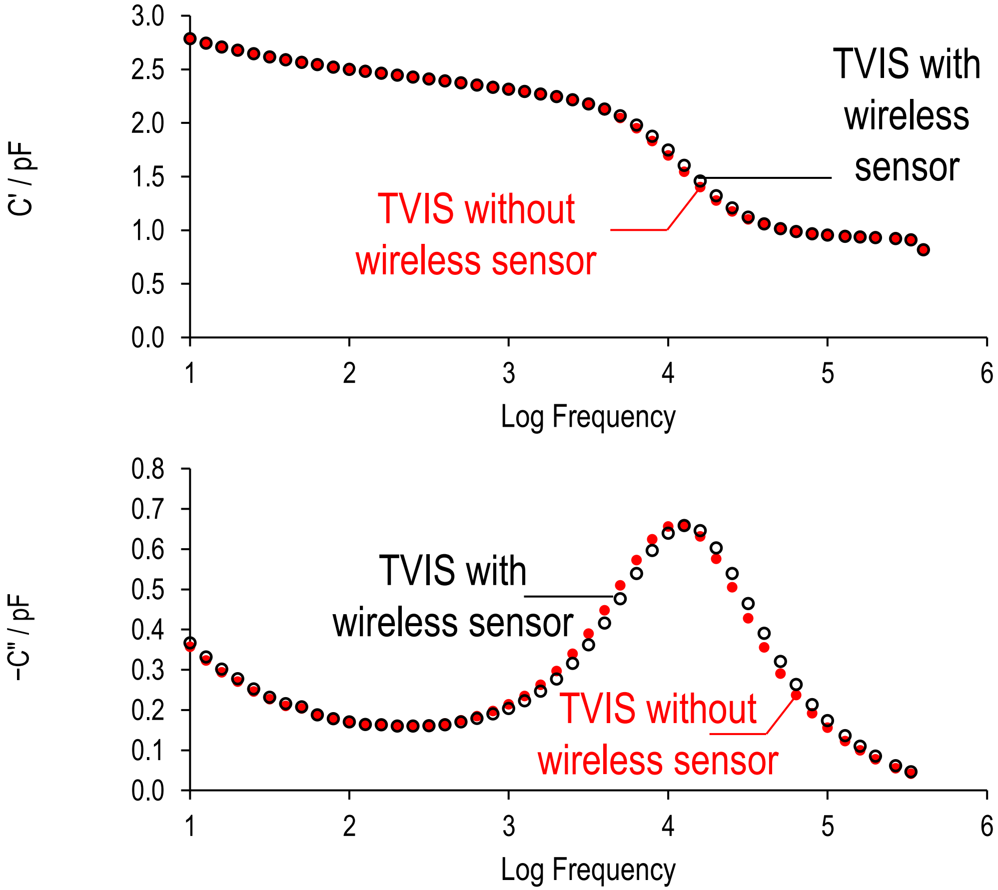


Typical uncertainty : 0.3 – 0.4 °C

TVIS spectra



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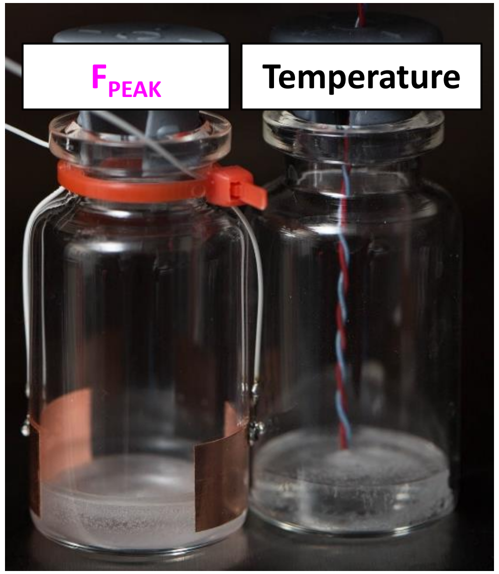
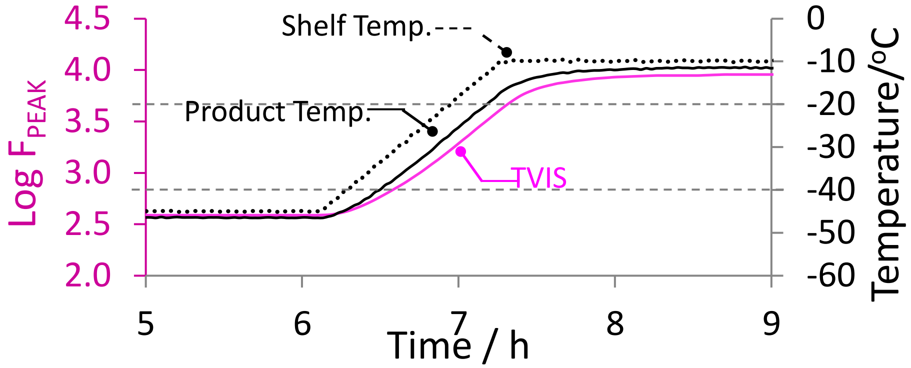
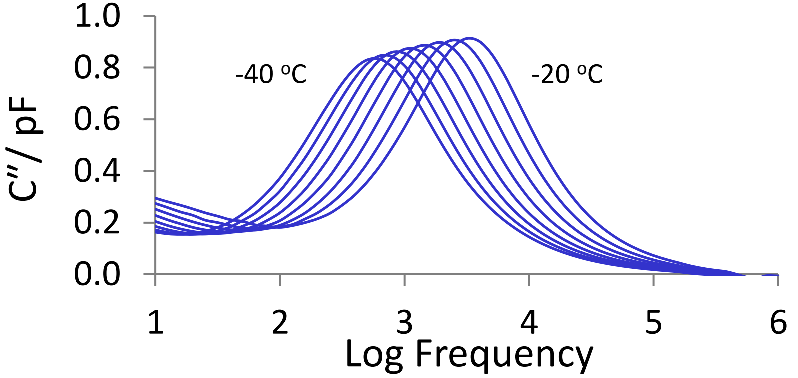
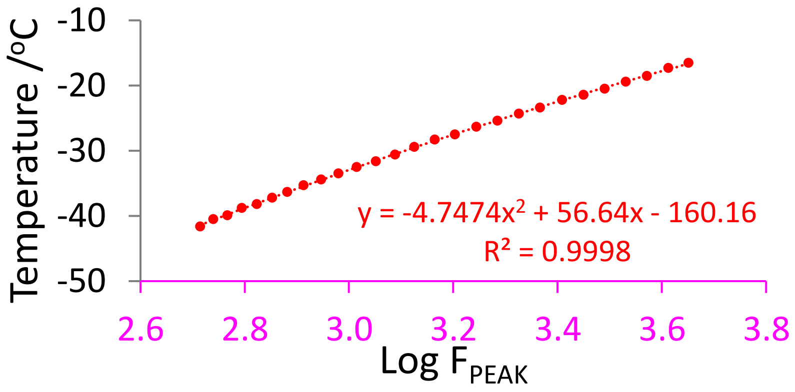
Temperature Calibration

- F_{PEAK} profile during annealing has 'similar' profile with product temperature.
- Assuming thermal equivalence between the thermocouple (TC) vial and TVIS vial, then the temperature calibration from annealing might be employed for the prediction of temperature during primary drying









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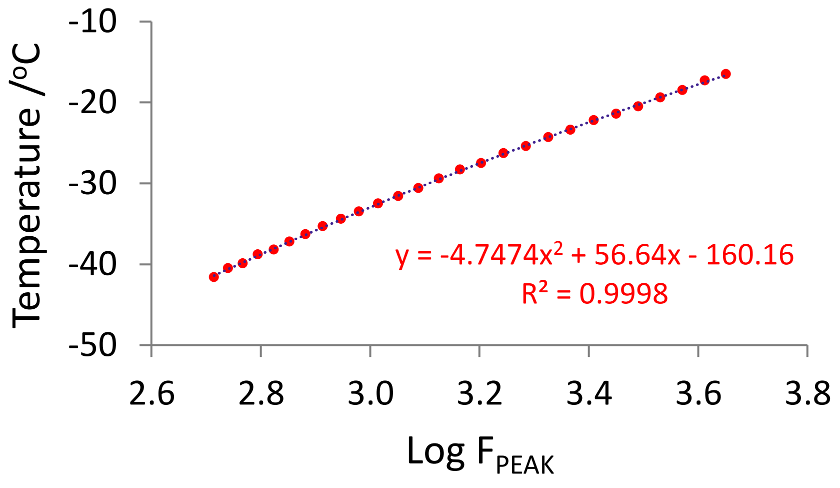
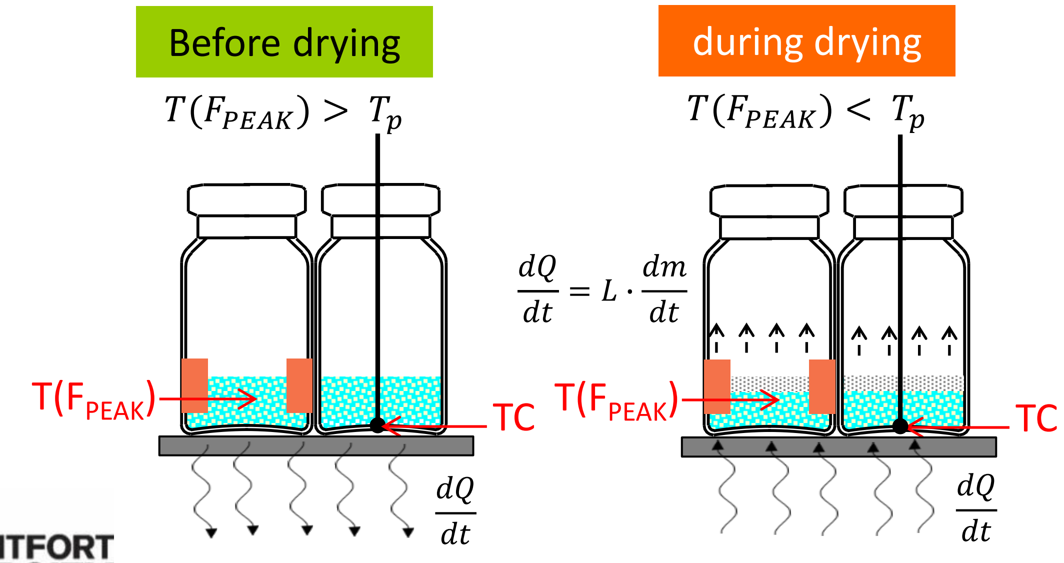
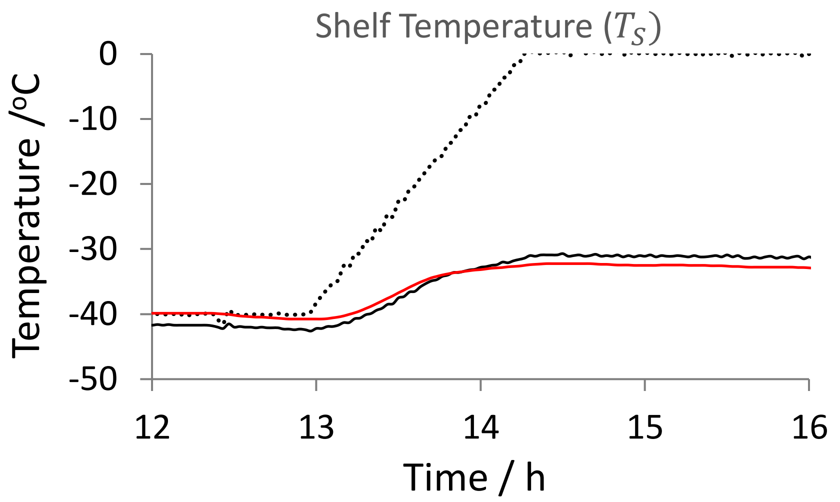
Temperature Prediction in Primary Drying

- Temperature calibration curve selected for temperature prediction in primary drying : $T(F_{PEAK})$
- Good agreement between product temperature (by TC) and $T(F_{PEAK})$







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CASE STUDY 2

Ice solidification end point

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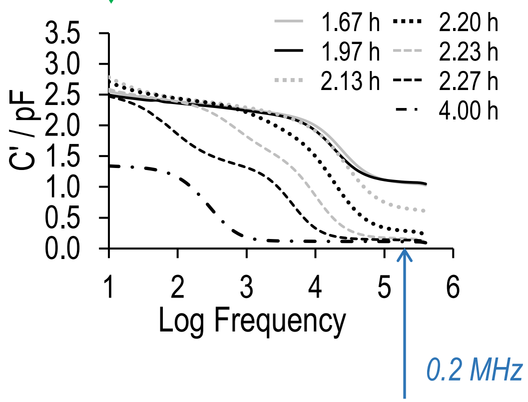
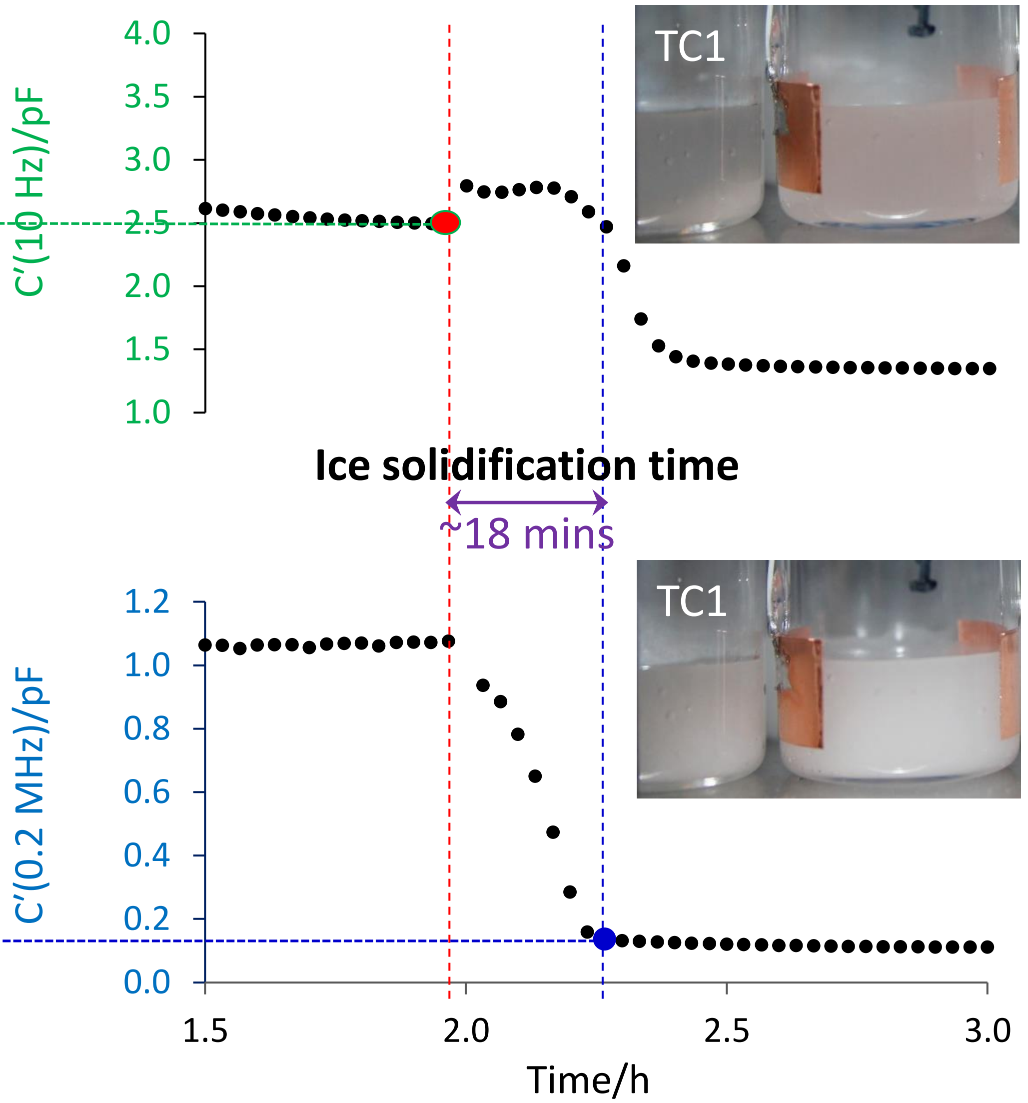
Solidification period

Ice nucleation

10 Hz

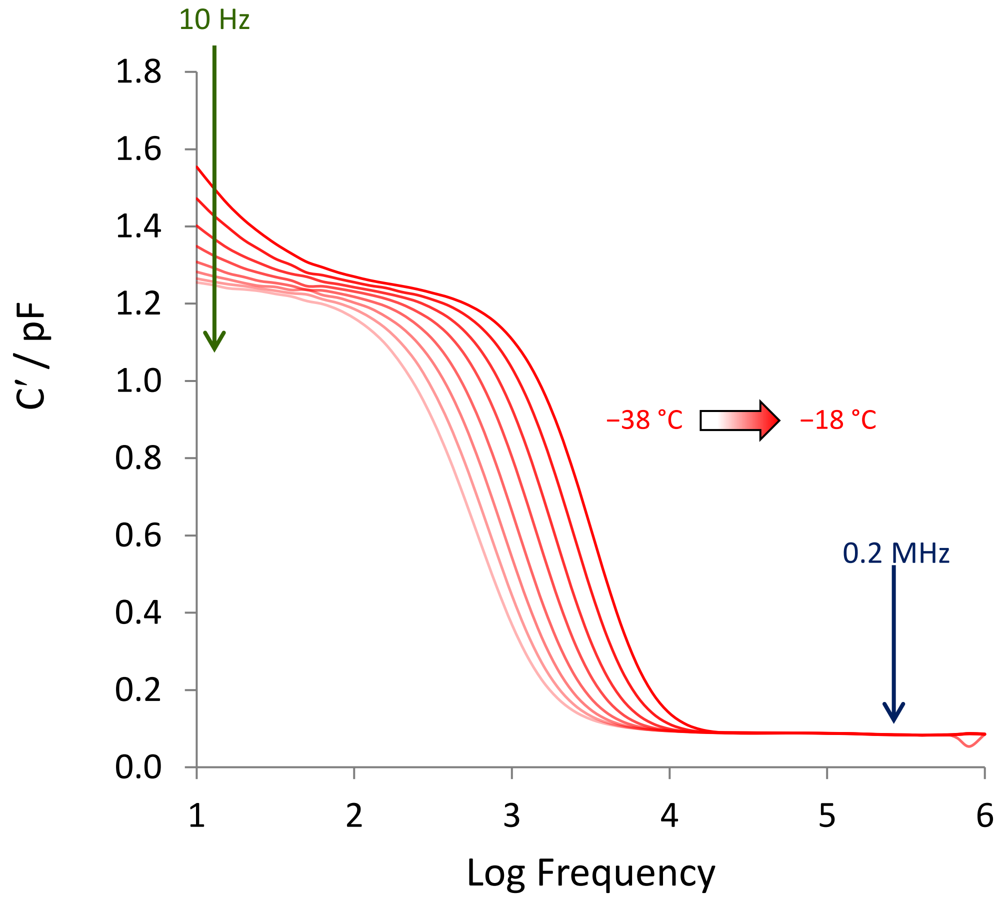


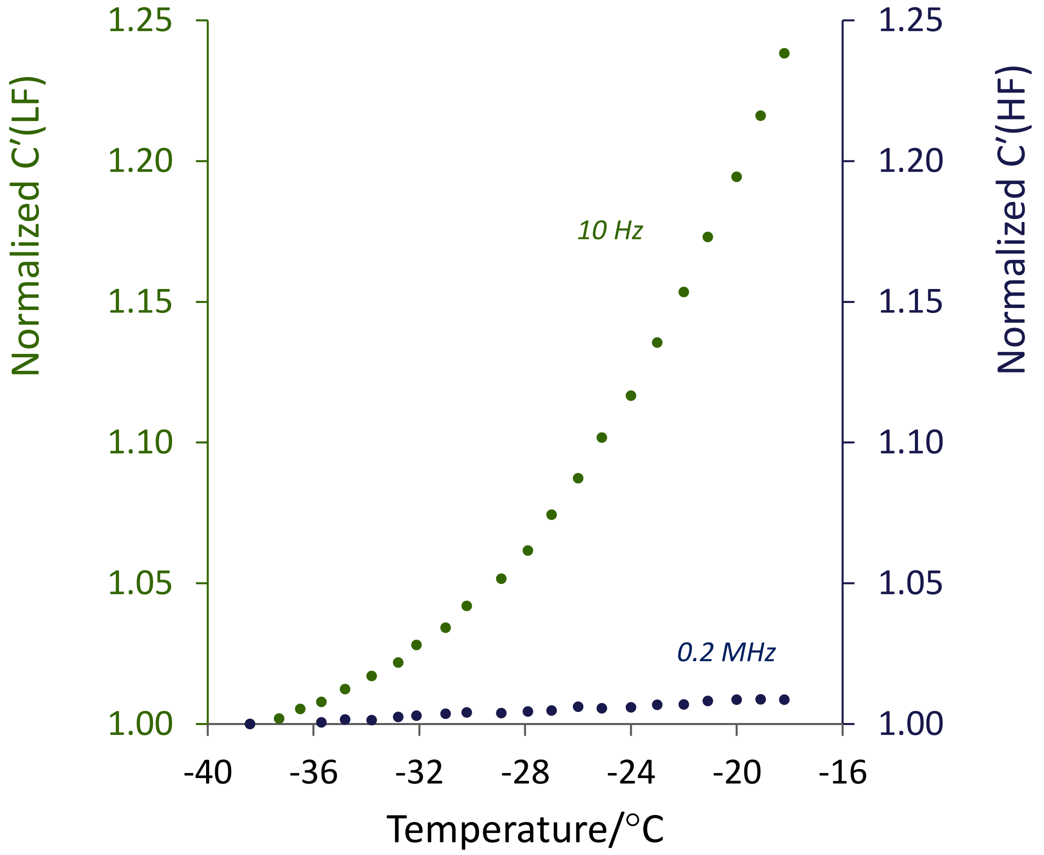
- The difference between these two times if the ice solidification time
- Knowing the height of the product in the vial one can then estimate an average solidification rate



Solidification end point

Temperature Profile of Frozen Water





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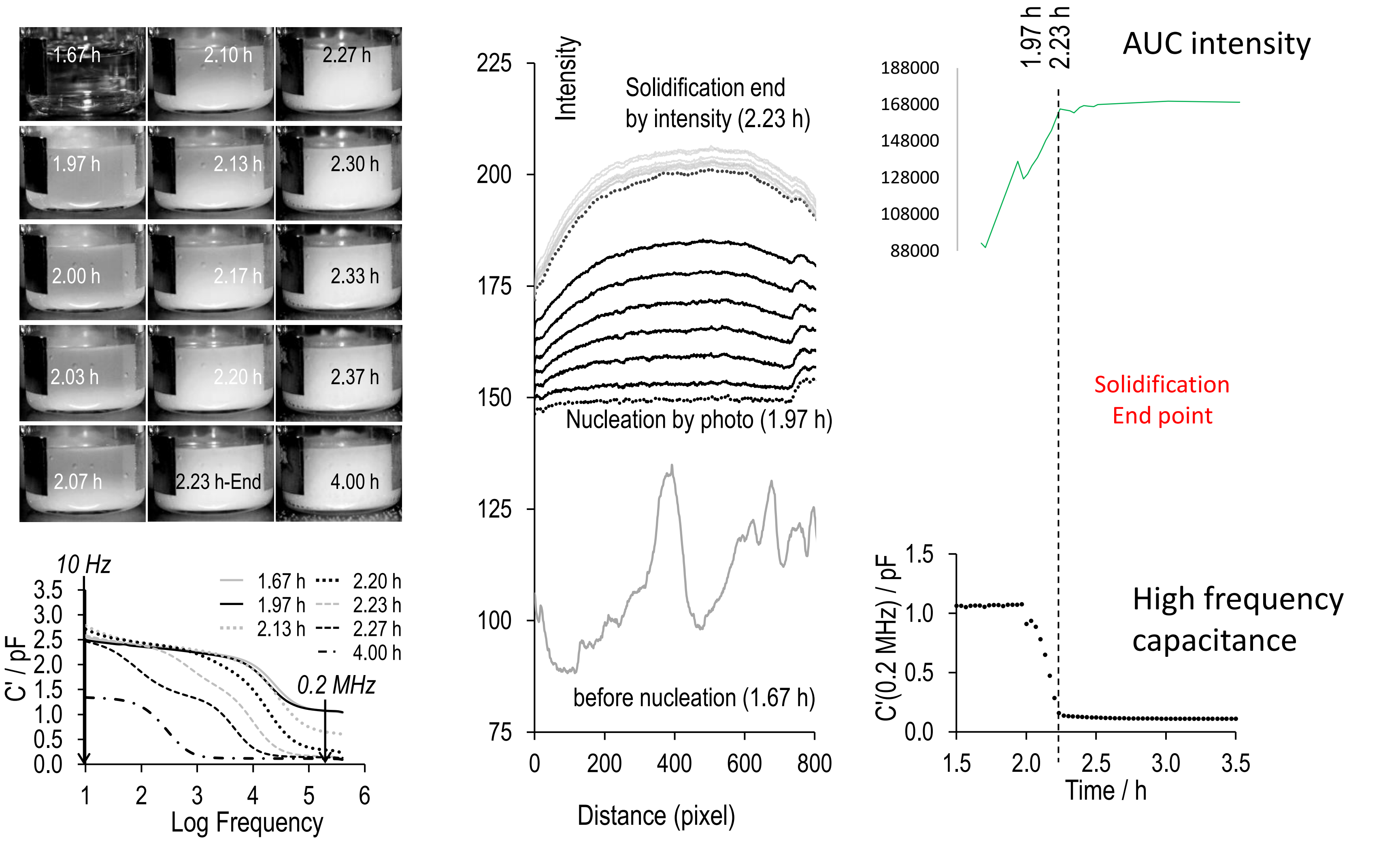
Solidification end point 5% sucrose



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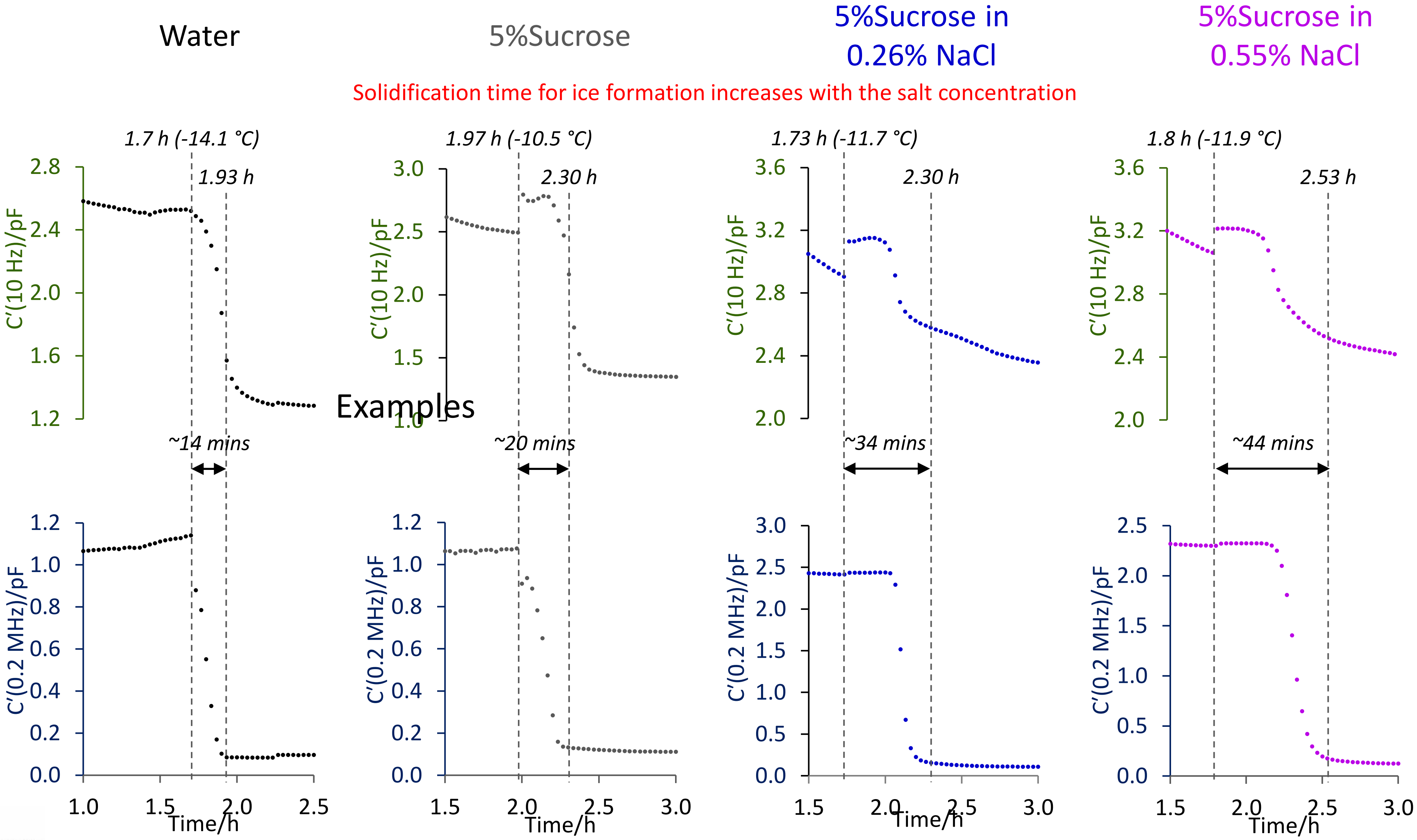

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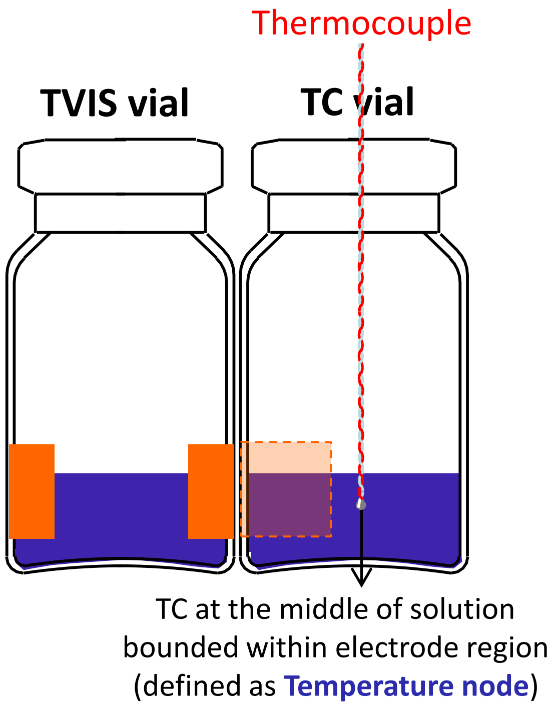
CASE STUDY 3

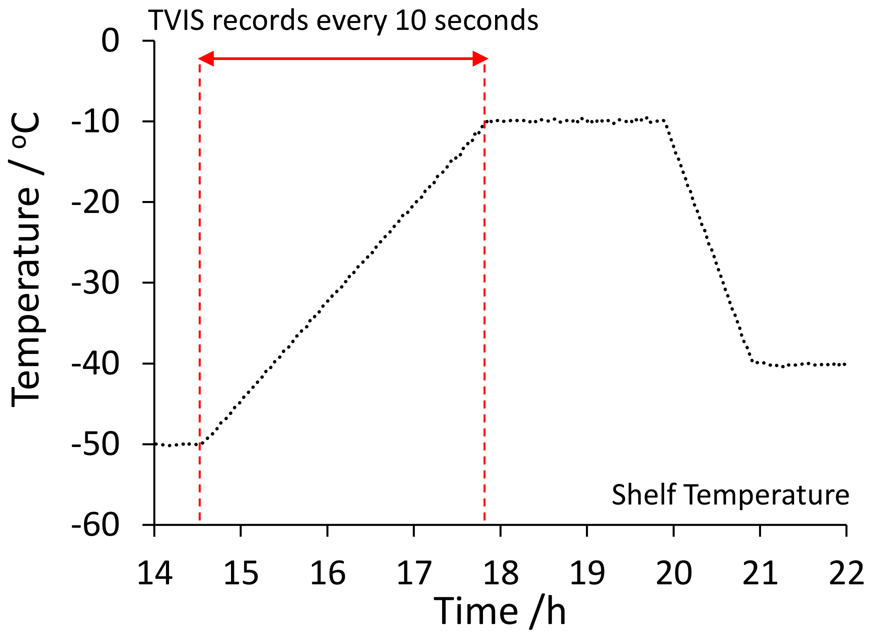
Determination of in-vial Glass Transition temperature (T_g')

Glass Transition Temperature



Thermocouple position

Annealing



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

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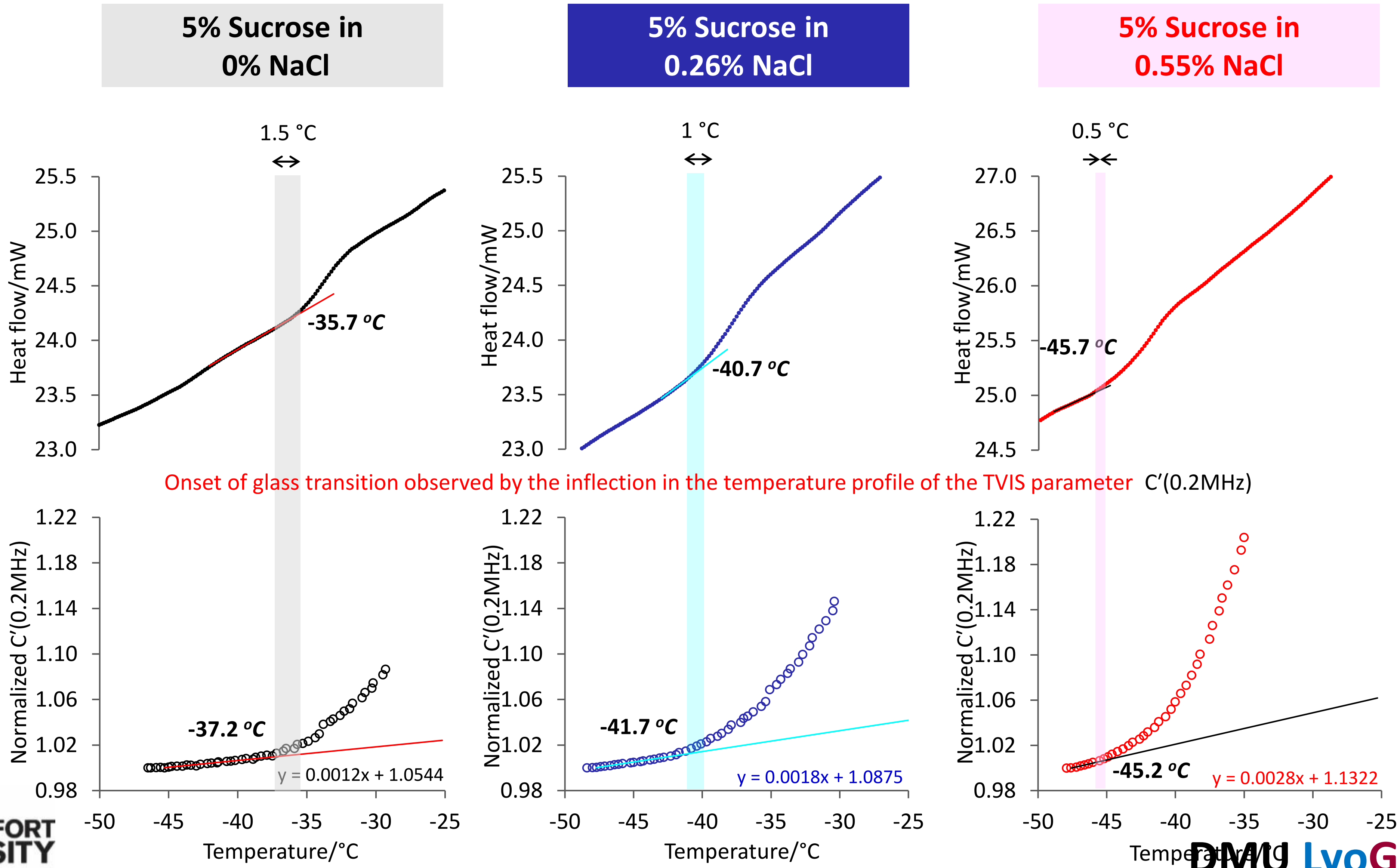
$C'(0.2\ MHz)$ during Re-heating



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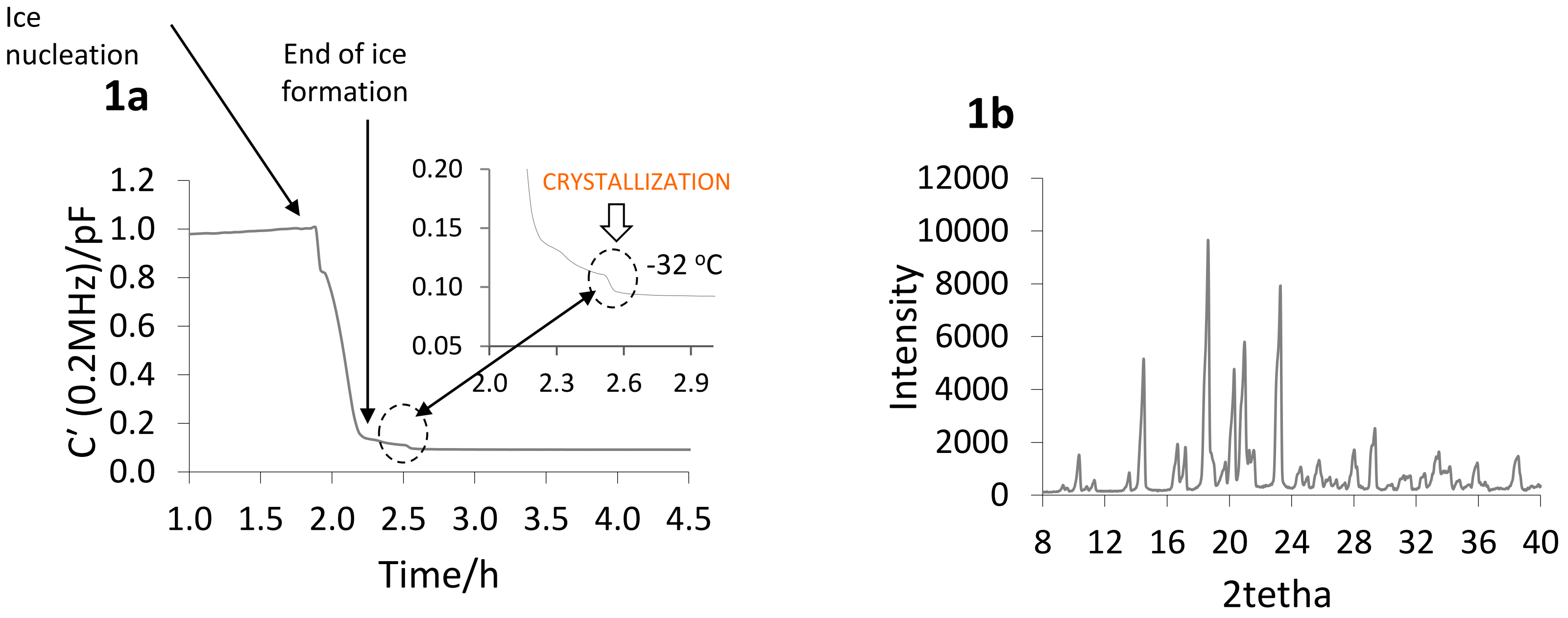
CASE STUDY 4

Freezing and annealing of mannitol solution

- Freezing mannitol solution
- Crystallization in mannitol formulations
- Re-crystallization events
- Change in crystal structures

Crystallization events at freezing step for 5% mannitol



TVIS and XRD results for solution of 5% mannitol showing crystallization detected by TVIS

Ogugua (2021) PhD Thesis https://dora.dmu.ac.uk/handle/2086/20993

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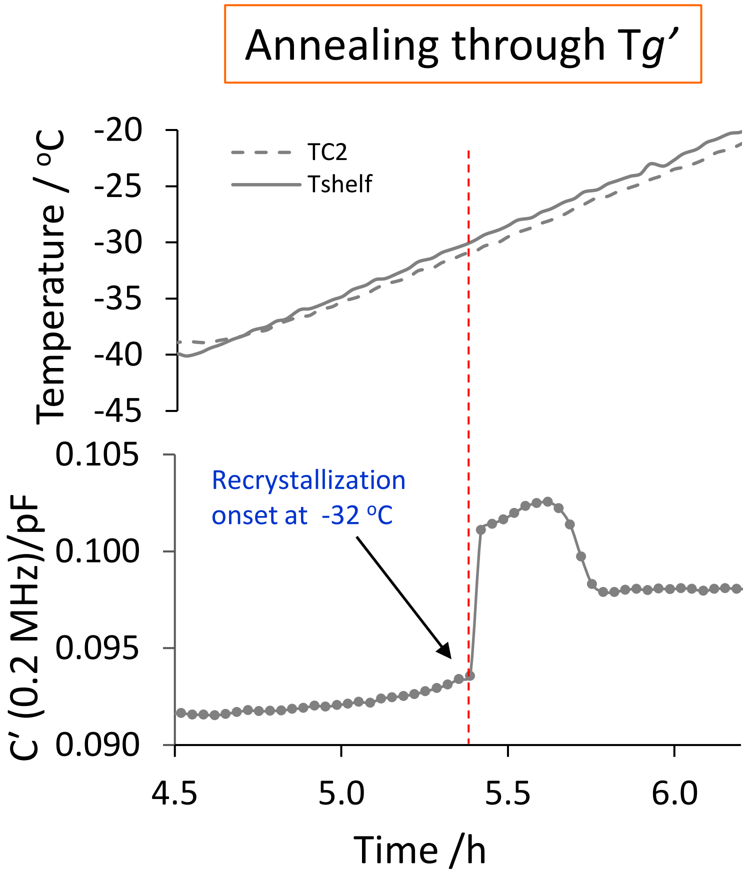
BACK to Drying

Recrstallization (dehydration) and de-vitrification? on annealing of 5% mannitol



On annealing to −20 °C $C'(0.2MHz)$ shows mannitol recrystallization with onset at – 32 °C

A devitrification end point at – 25 °C

Ogugua (2021) PhD Thesis https://dora.dmu.ac.uk/handle/2086/20993

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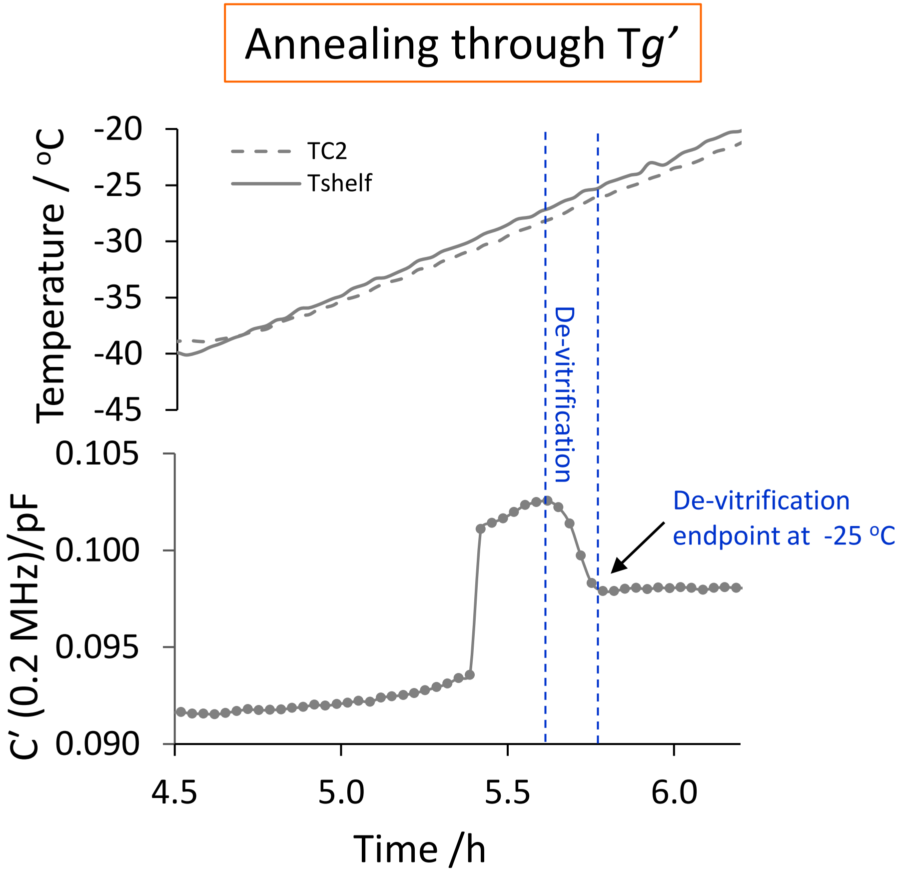
Recrstallization (dehydration) and de-vitrification? on annealing of 5% mannitol



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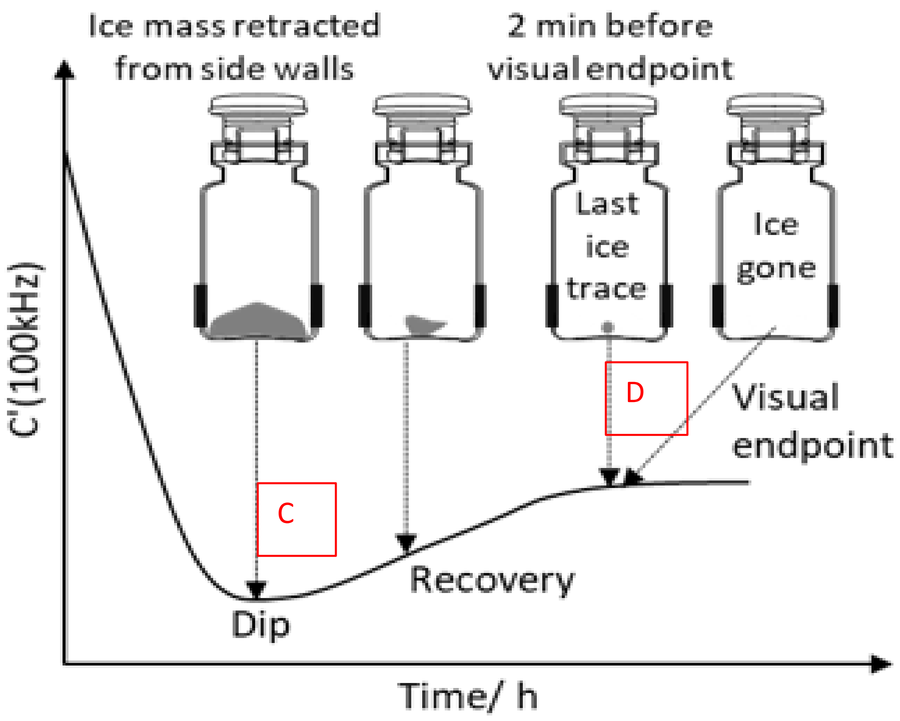
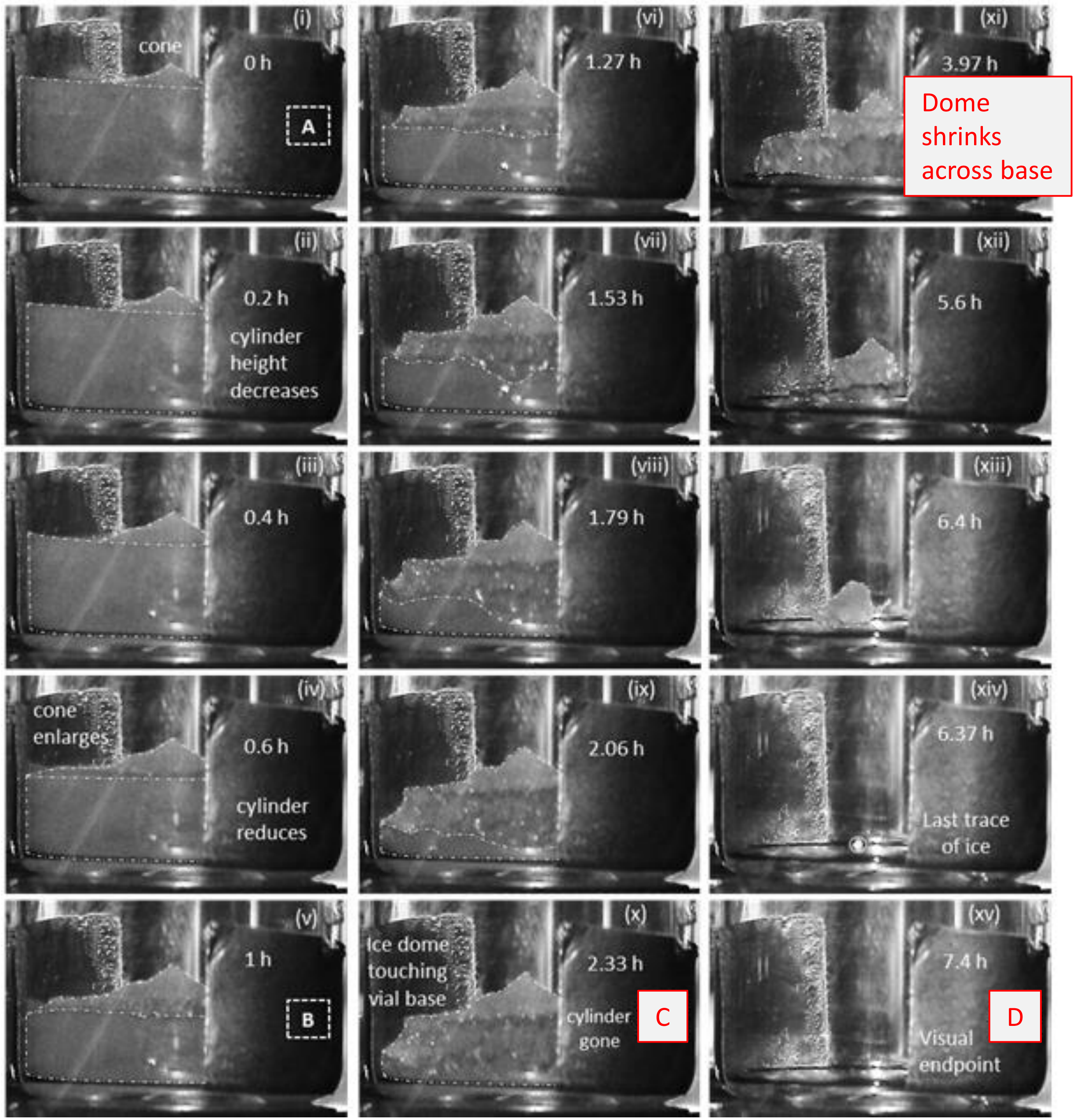
CASE STUDY 5

Sublimation end point

Sublimation end point





Pandya (2020) PhD Thesis https://dora.dmu.ac.uk/handle/2086/19997

CASE STUDY 6

Primary drying rate models

Assumptions of a planar ice interface

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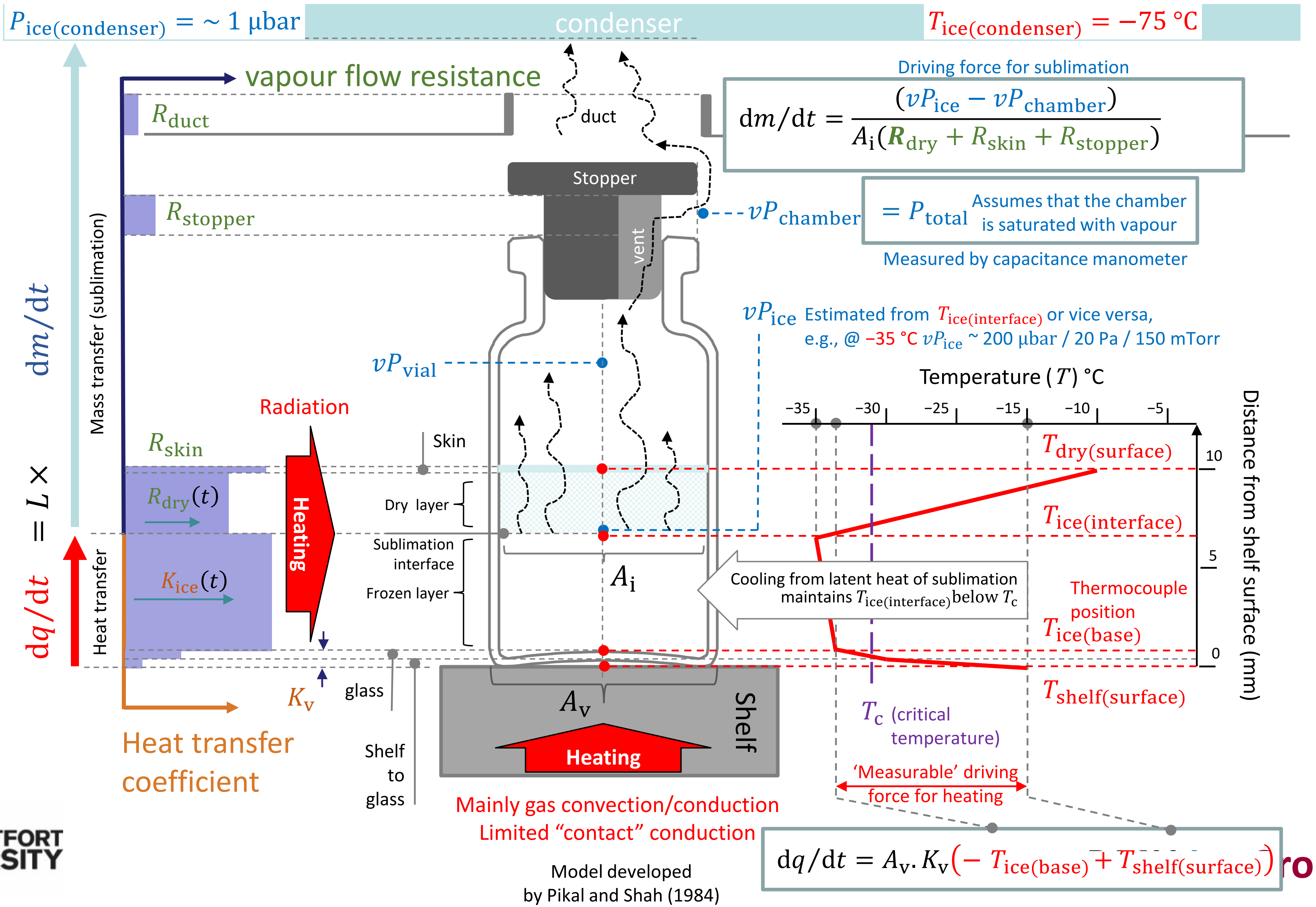

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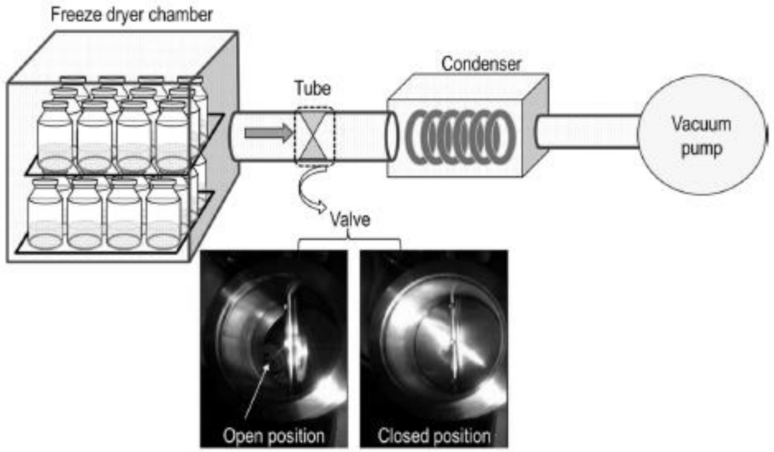
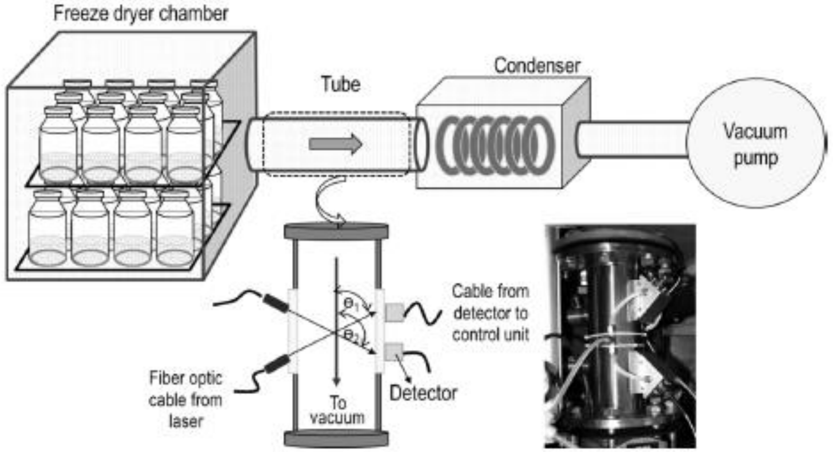
Drying rate based on vapour pressure measurement

MTM



TDLAS



- Increase the pressure in the freeze dryer (same as PRT)
- MTM combines the pressure rise data with a mathematical equation to predict drying rates

- Laser assembly tube is connected between chamber and condenser
- Drying rate determined from
  - Laser light absorbed is proportional to the concentration of gas/water vapour
  - Doppler effect used to determine velocity of the vapour

From drying rate calculate:

(i) heat transfer coefficient; (ii) batch 'average' temperatures (@ ice front & ice base), (iii) drying endpoints, (iv) dry layer resistance

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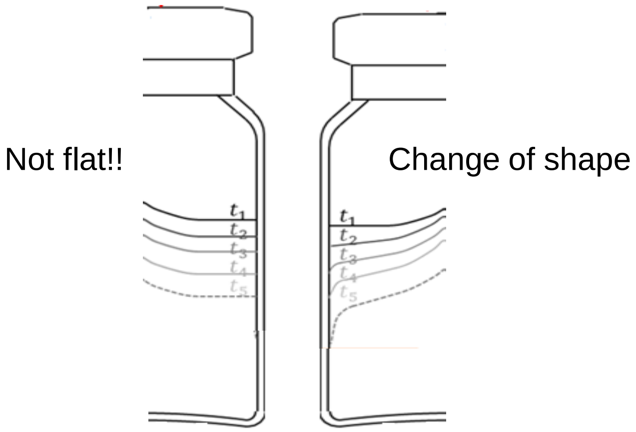
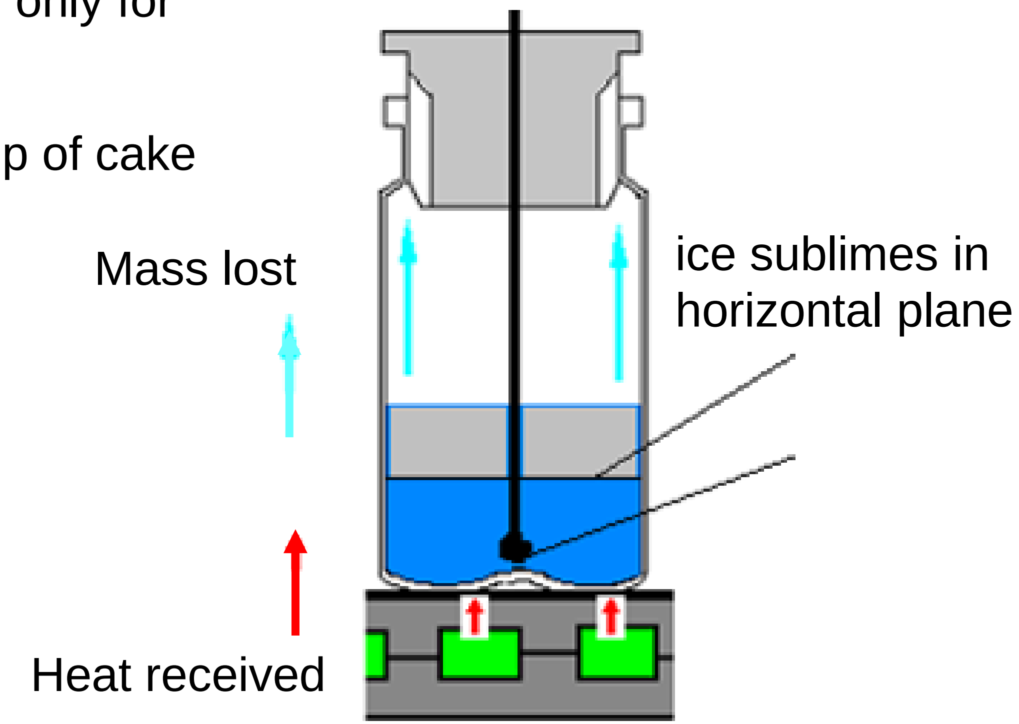
Heat and Mass Balance: Assumptions

1. All heat received by product is used only for sublimation of water.
2. Sublimation front moves from the top of cake parallel to the vial bottom

Reality:





3. The contribution of radiation component to the vial heat transfer coefficient is constant within entire operation temperature range

Pikal et al. (1984) J Pharm Sci 73:1224
Temperature measurements have to be completed before 15% of the ice mass is removed before the assumption of a planar ice-surface interface is seriously violated

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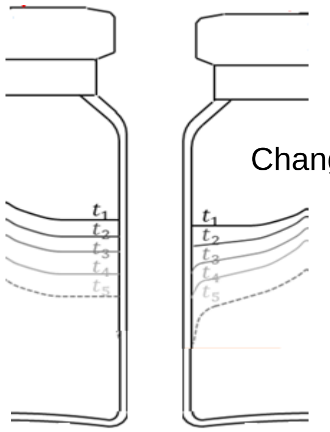

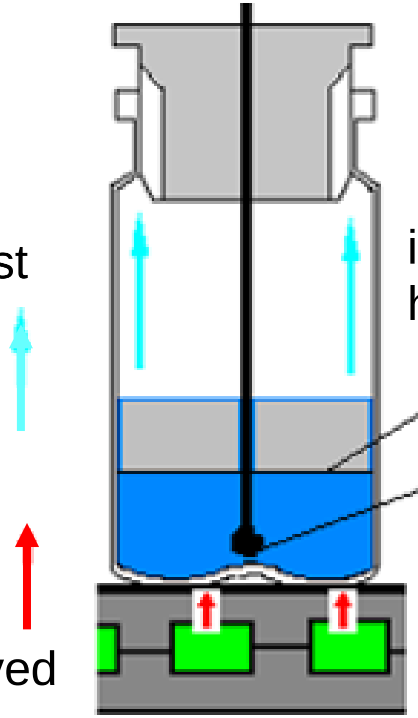

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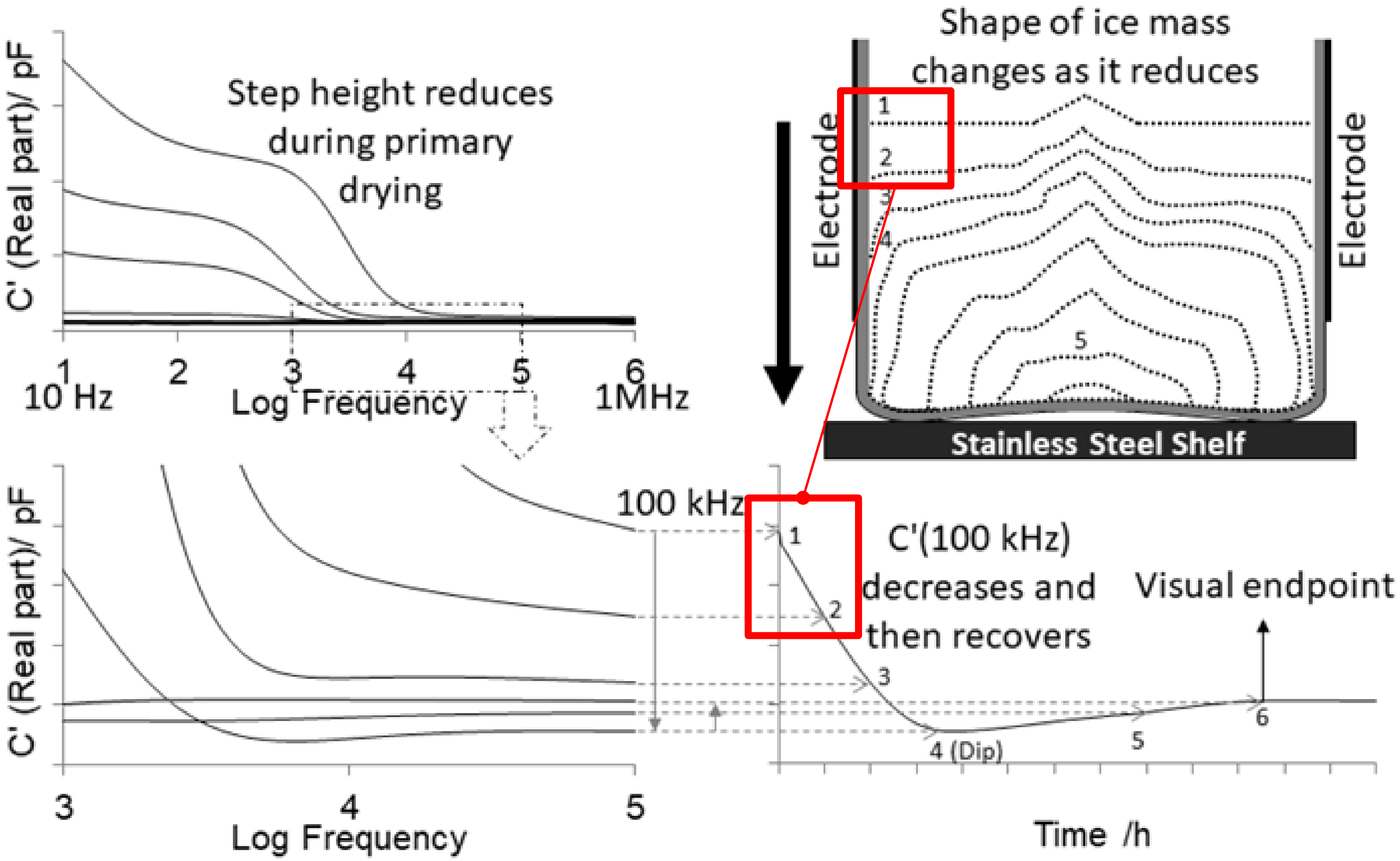
TVIS application in studying ice mass shape



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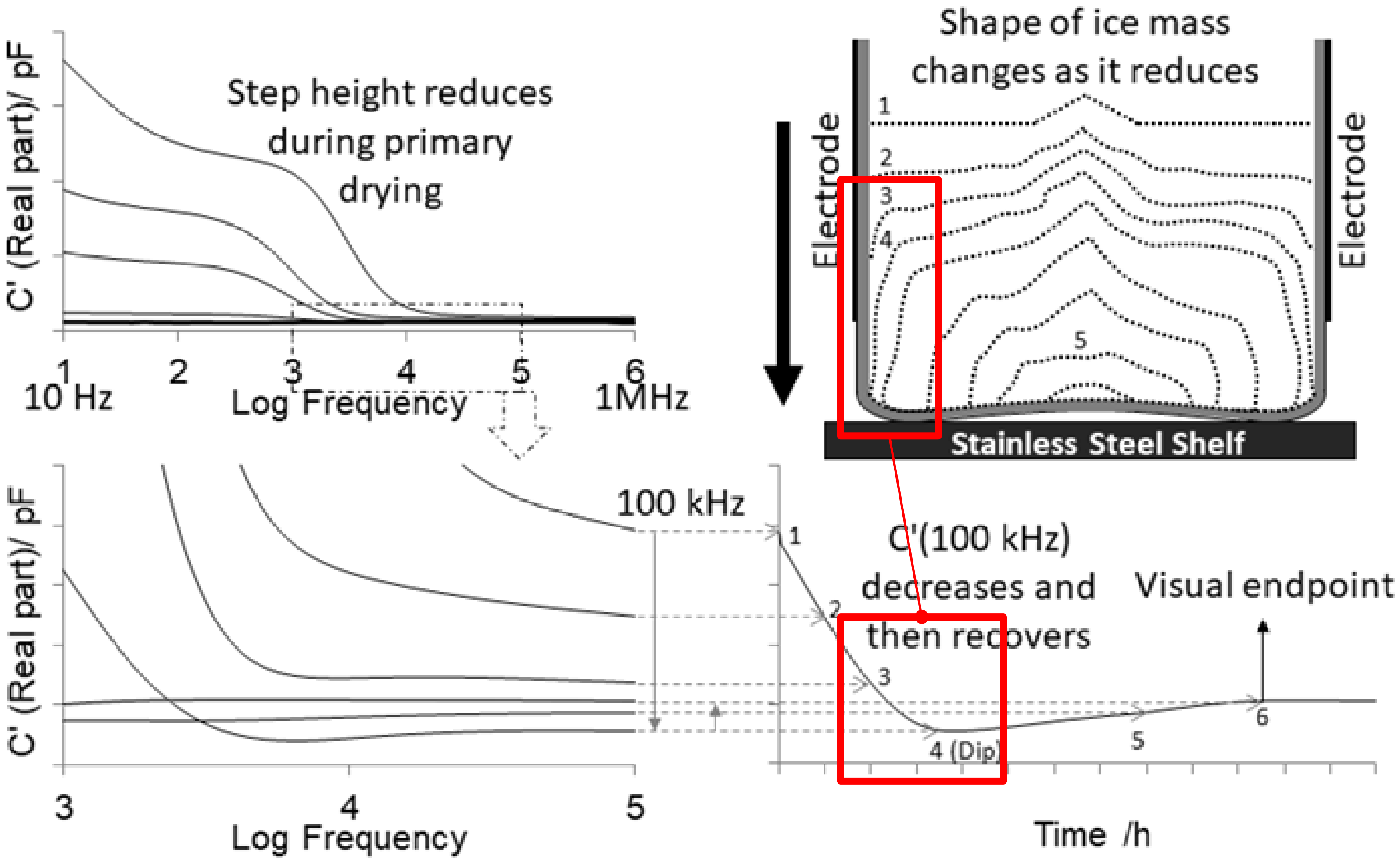

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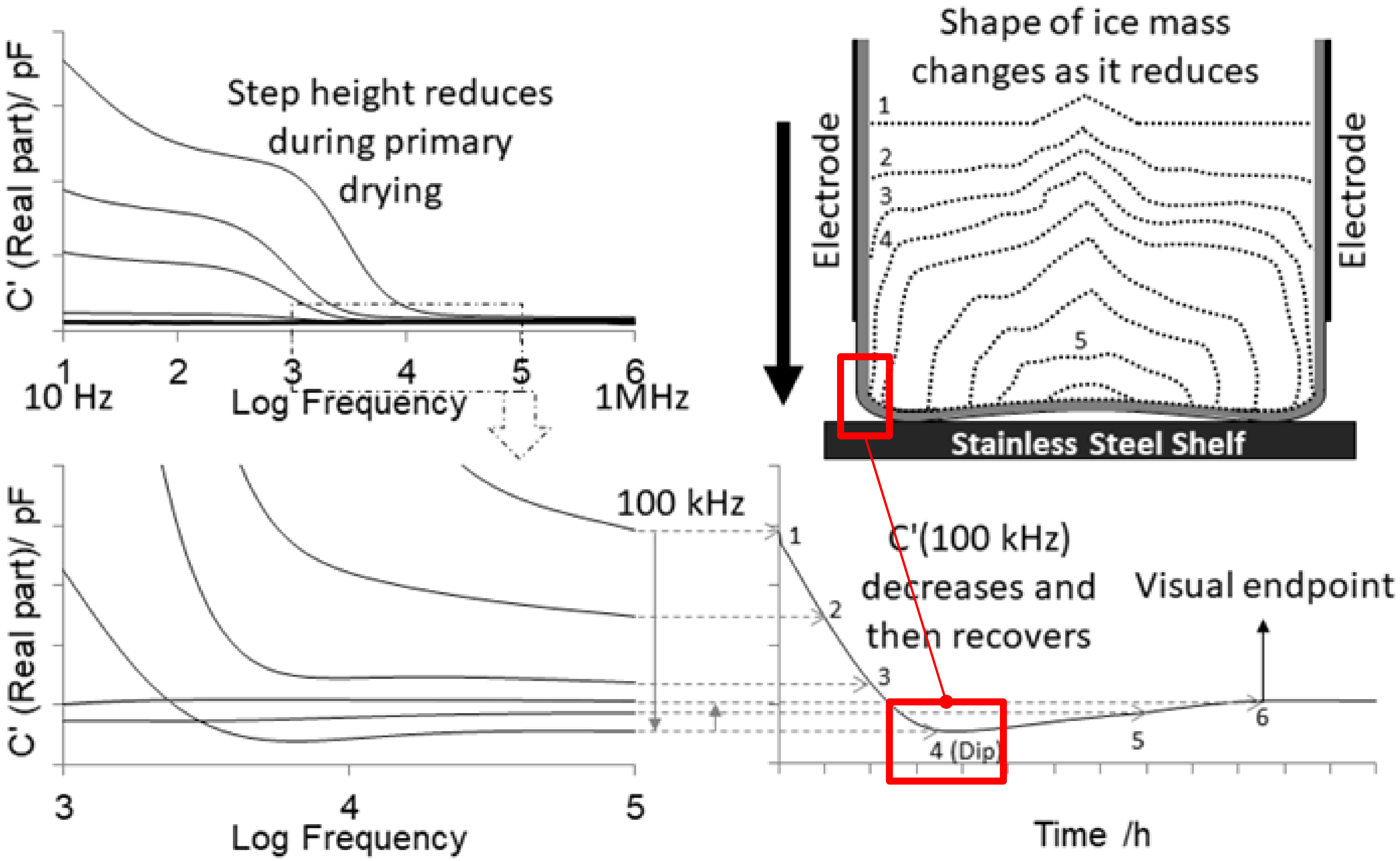

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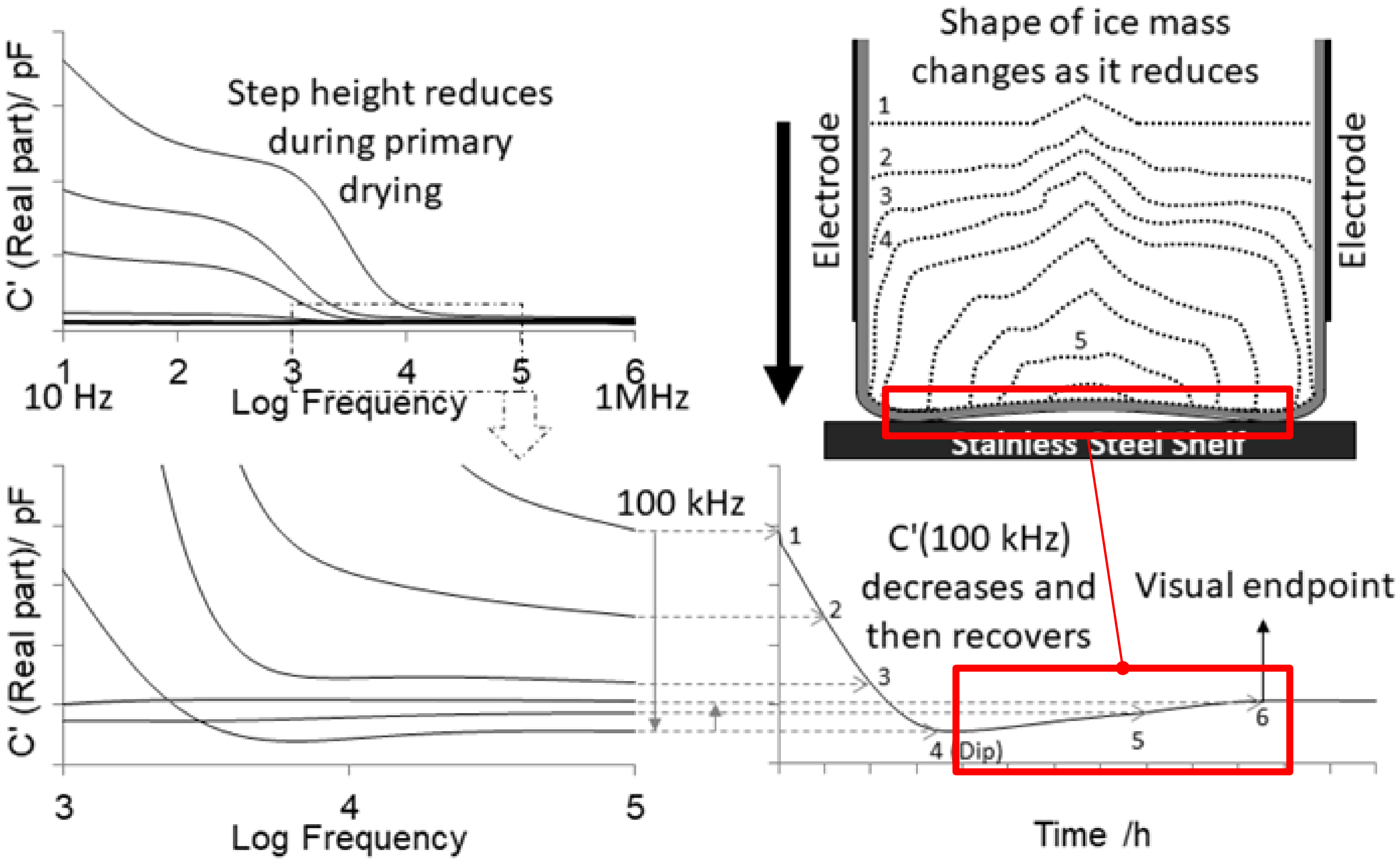

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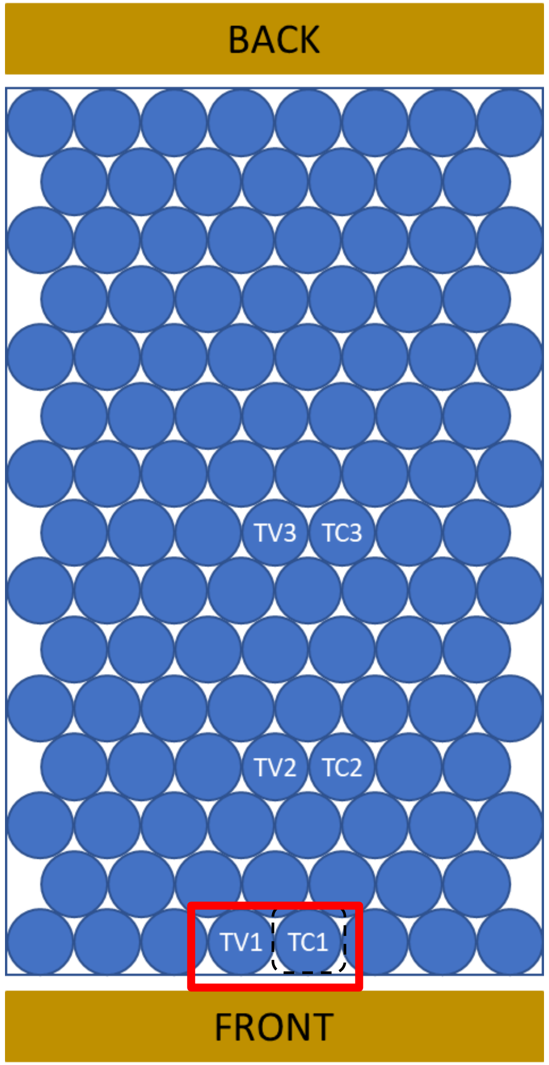
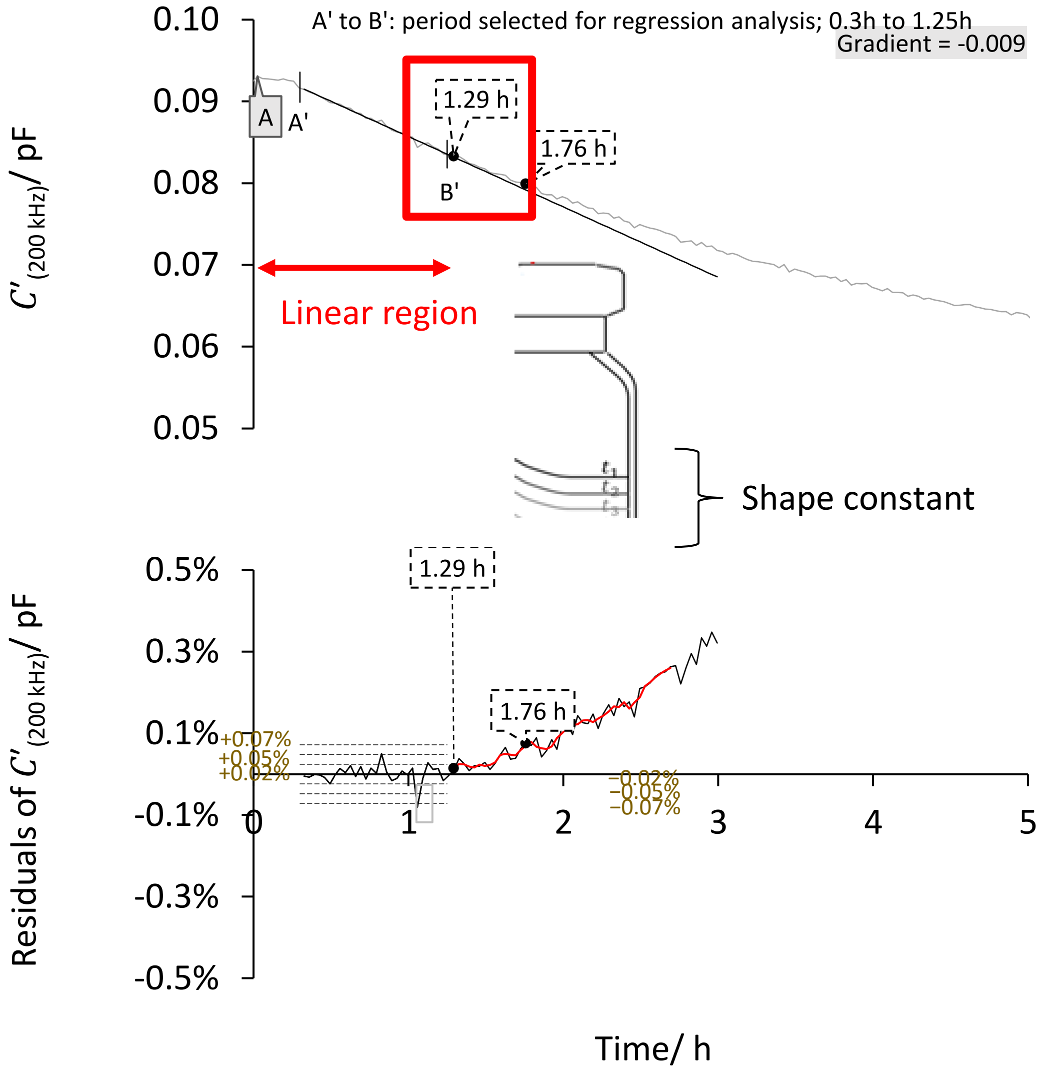
Front of shelf: linear for 1.29 h





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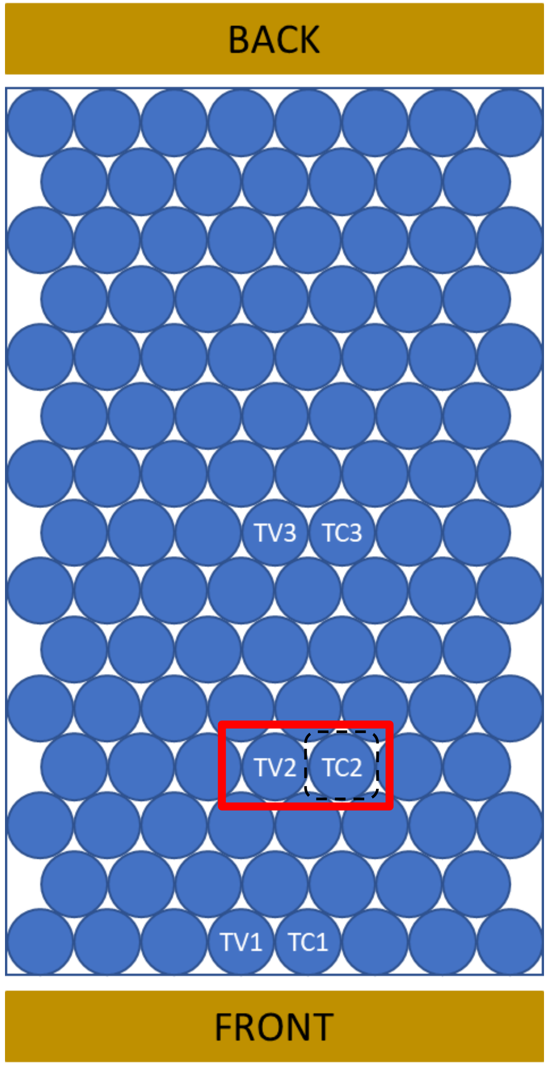
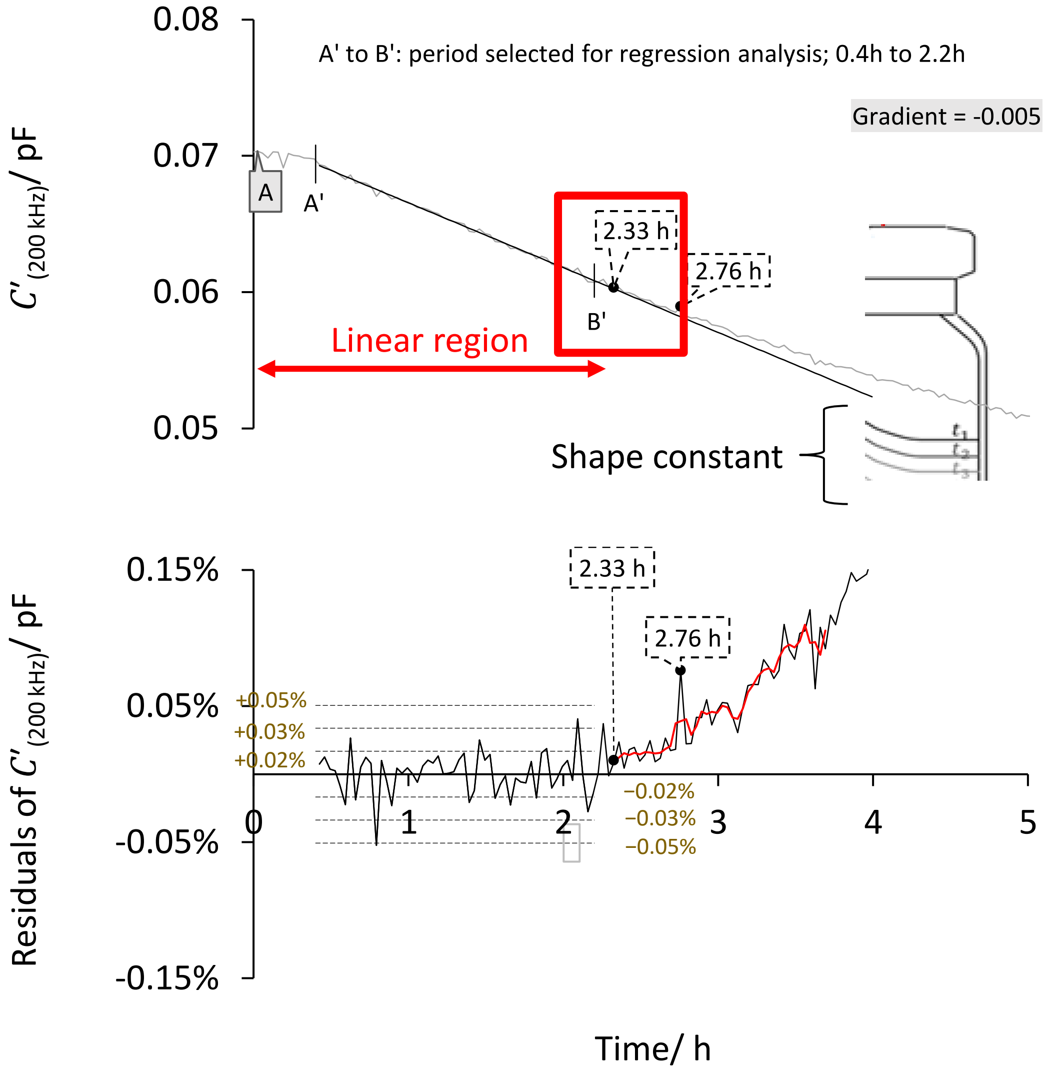
Mid-way to the centre : linear for 2.33 h





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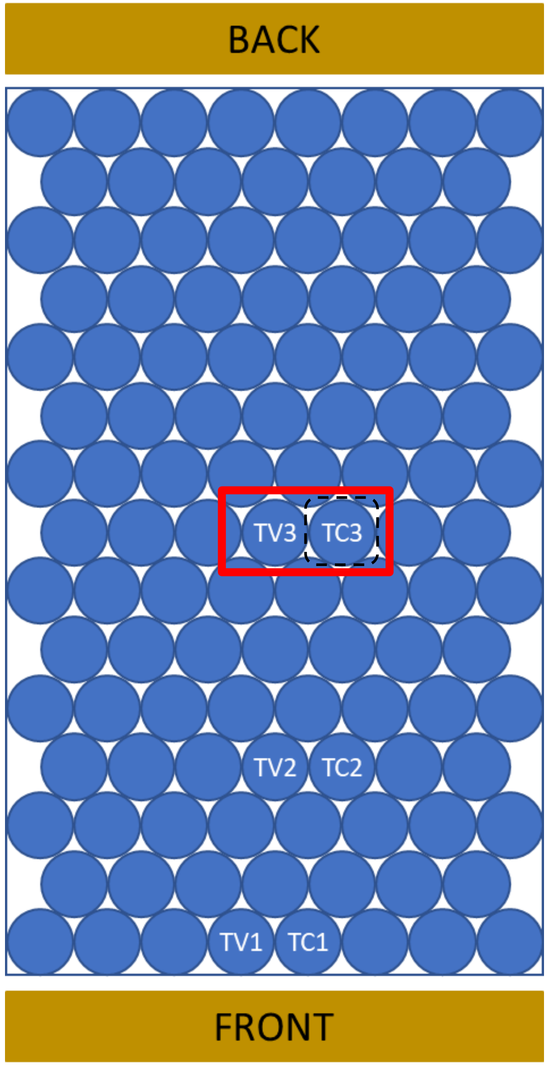
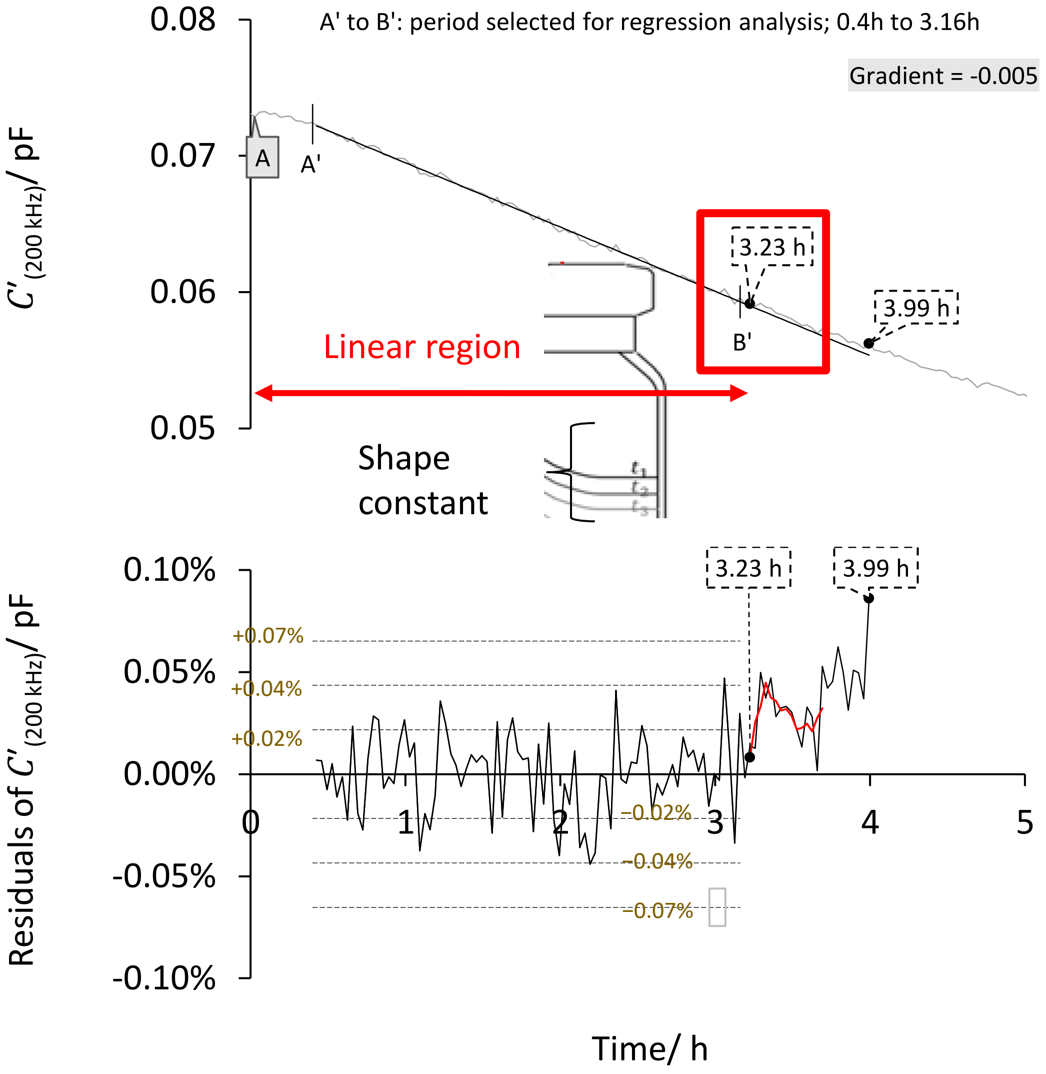
Centre of the shelf : linear for 3.23 h





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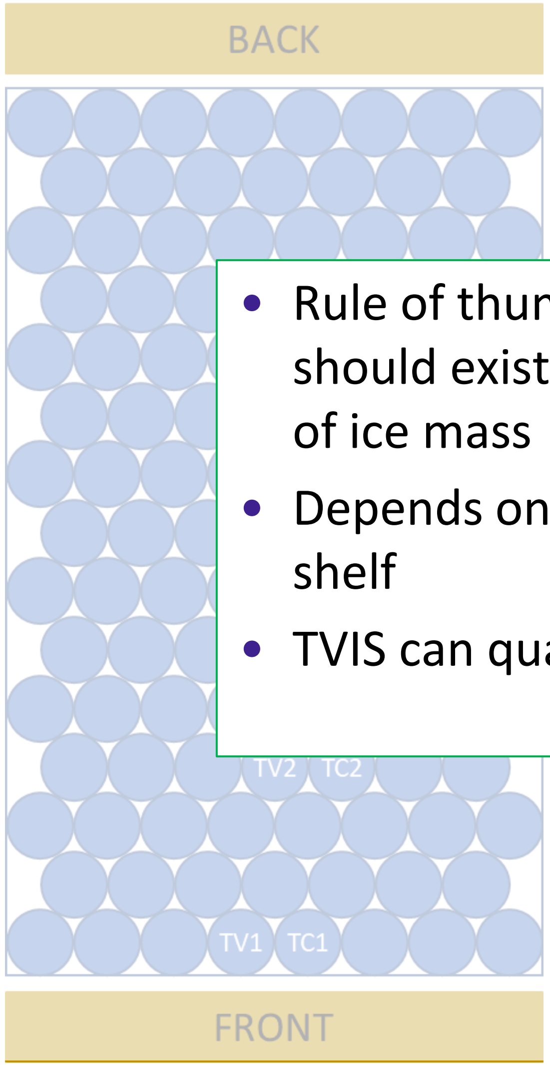

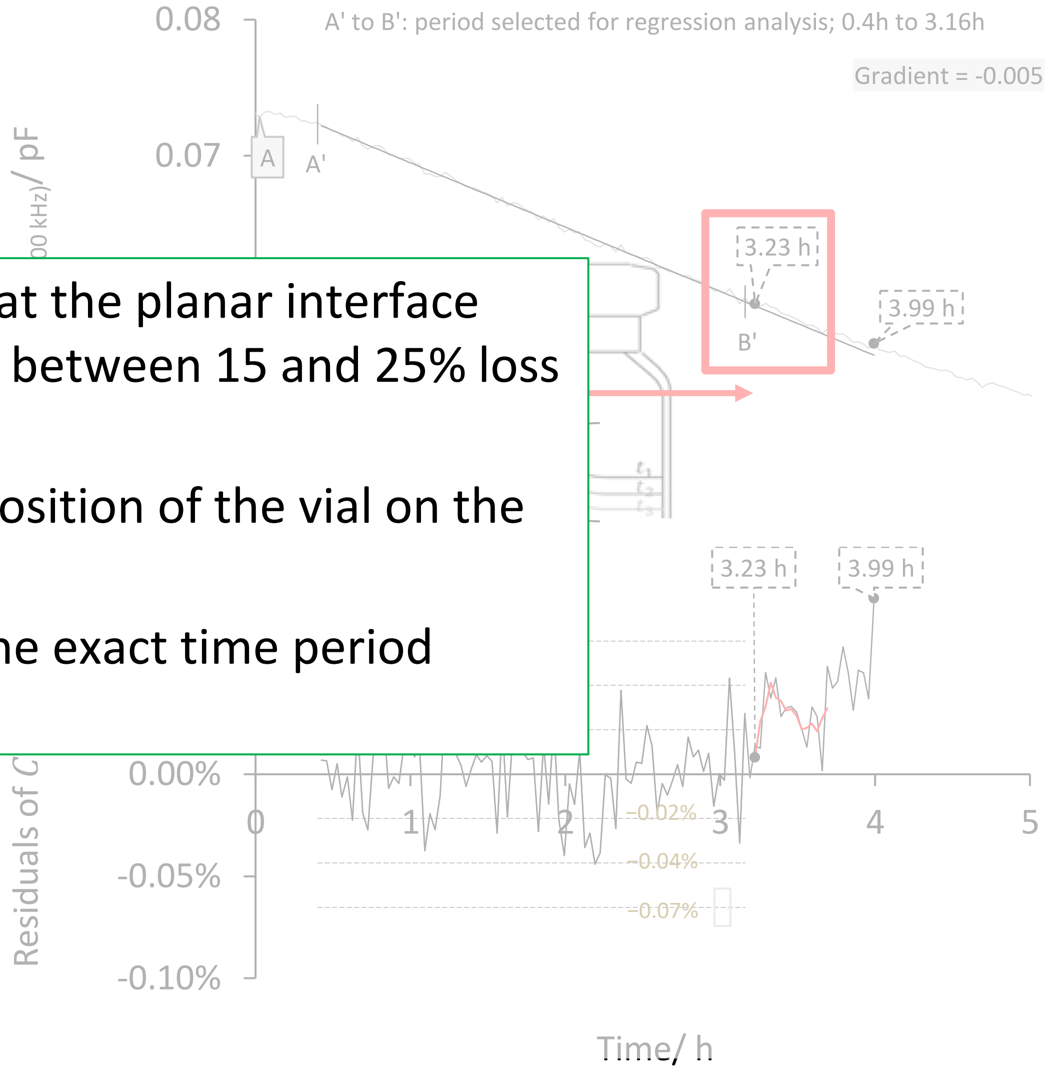

- Rule of thumb, that the planar interface should exist up to between 15 and 25% loss of ice mass
- Depends on the position of the vial on the shelf
- TVIS can qualify the exact time period

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Take home messages from this talk

TVIS provides ….

- Temperature prediction for primary drying
- Non-invasive determination of ice nucleation temperature (and ice solidification end point)
- Identification of primary drying end point
- Qualification of batch process models (MTM, TDLAS) in terms of the assumptions in the model (planar ice interface)

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

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Acknowledgements

Evgeny Polygalov
Physicist and Inventor of TVIS
1952-2020

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Dr Paul Matejtschuk
Head of Standardization
Science in the Analytical &
Biological Sciences Division

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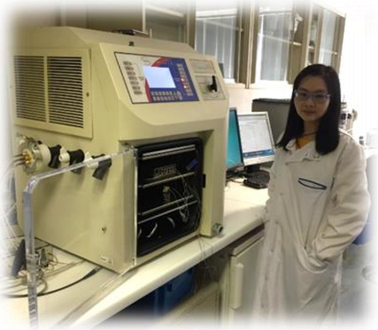
Acknowledgements

Dr Yowwares Jeeraruangrattana
Government Pharmaceutical Organization, Bangkok, Thailand



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Biopharma, Winchester

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De Montfort University Leicester

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References

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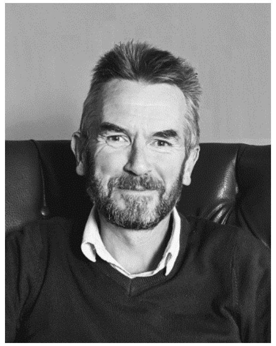
Thank you for listening!



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