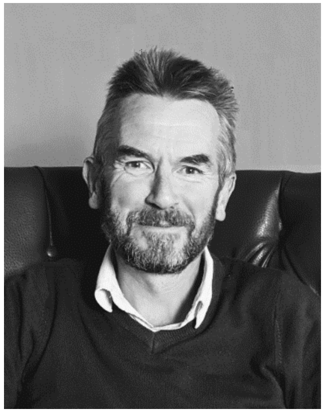
Impedance Spectroscopy

Recent Developments as a Process Analytical Technology for Pharmaceutical Freeze-Drying

Geoff Smith, PhD
Prof. of Pharmaceutical Process Analytical Technology
School of Pharmacy



Recording: Smith (2020) Biomanufacturing Congress July 9th

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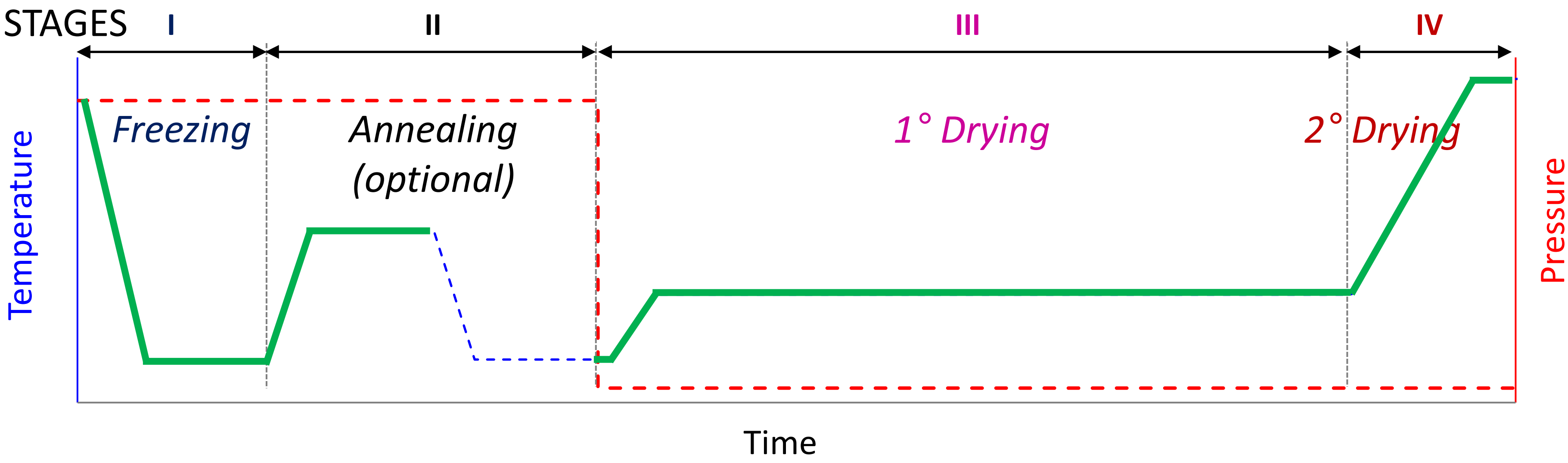
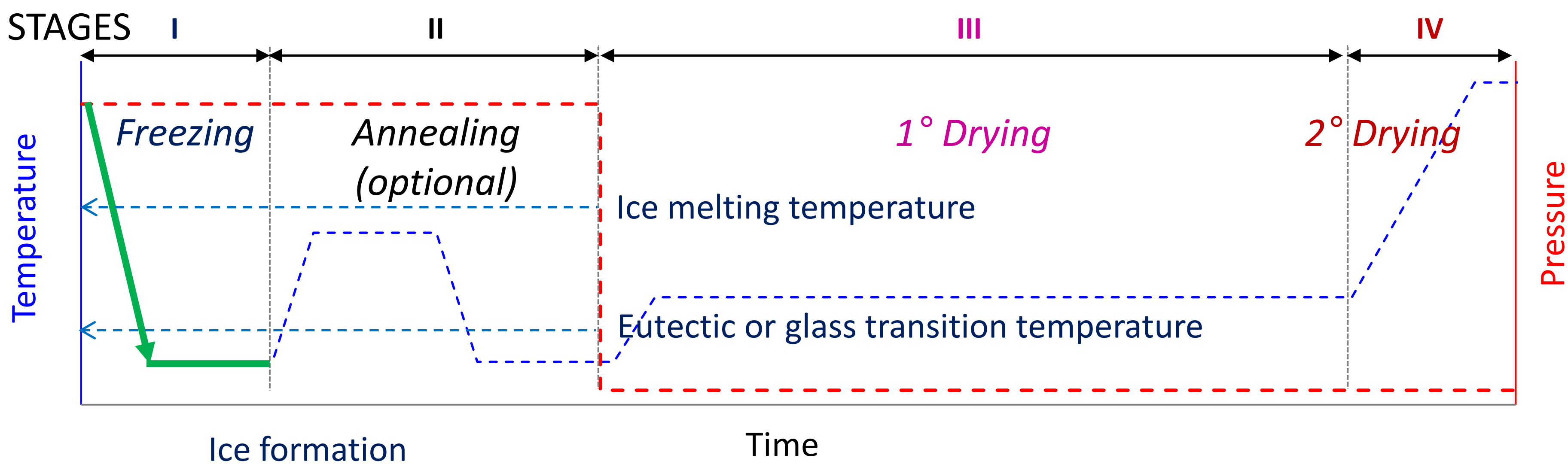
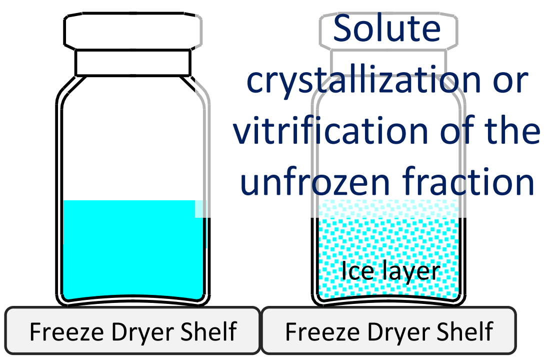
Freeze-drying (lyophilization)



Freezing

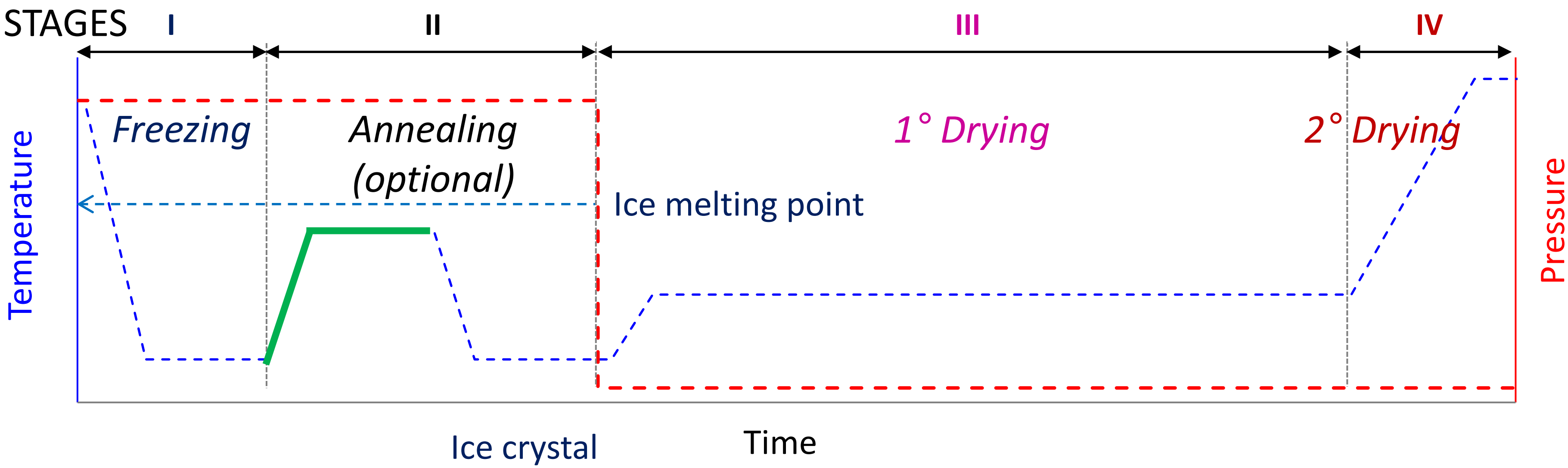


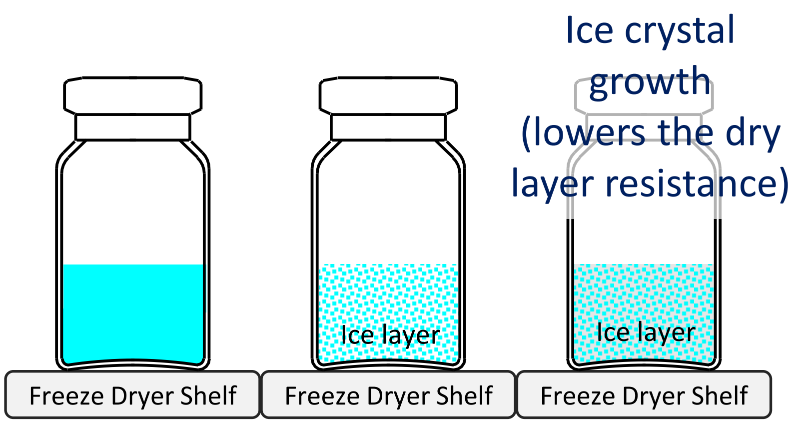
Ice formation



Product ⇨ Freeze

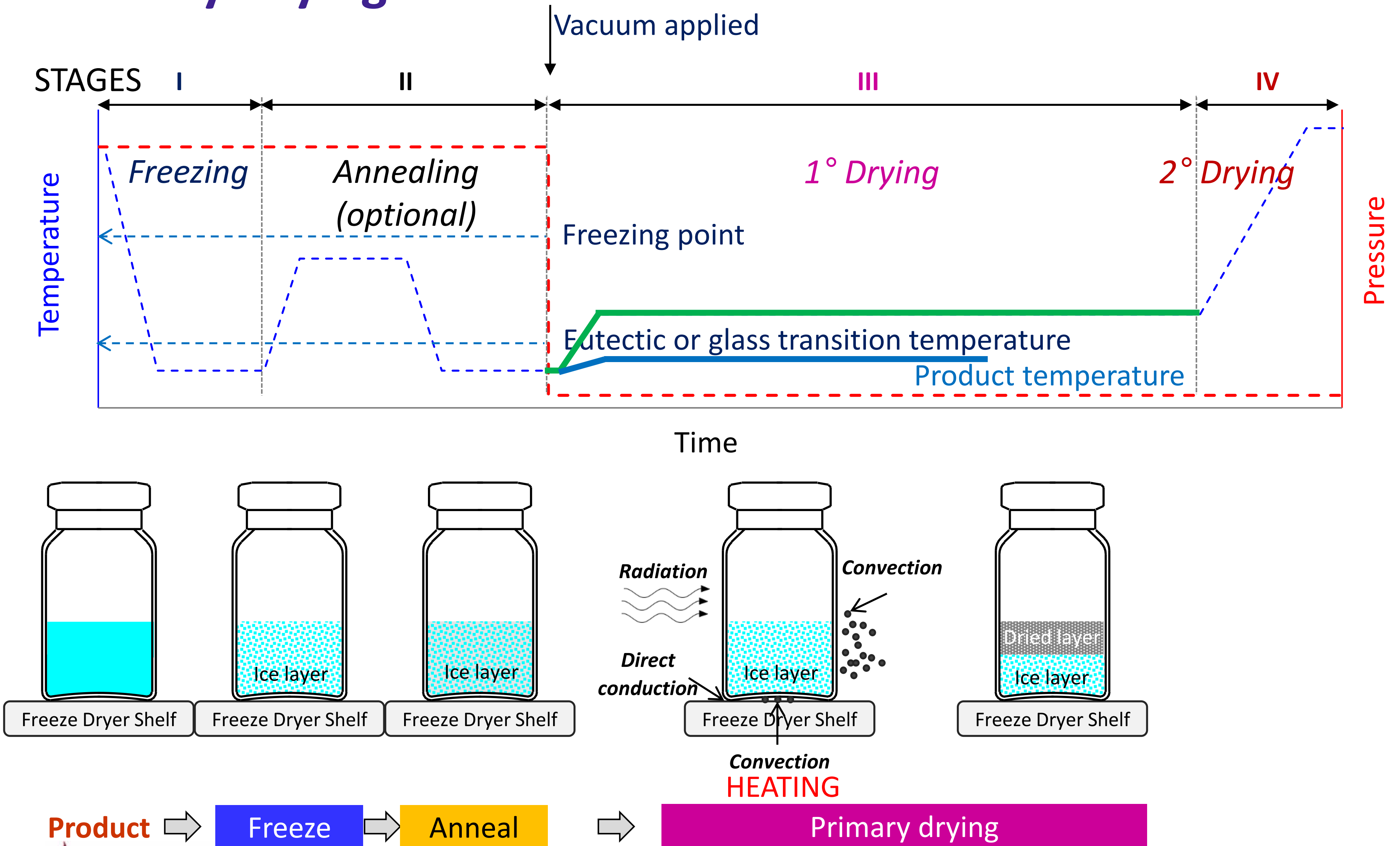
Annealing



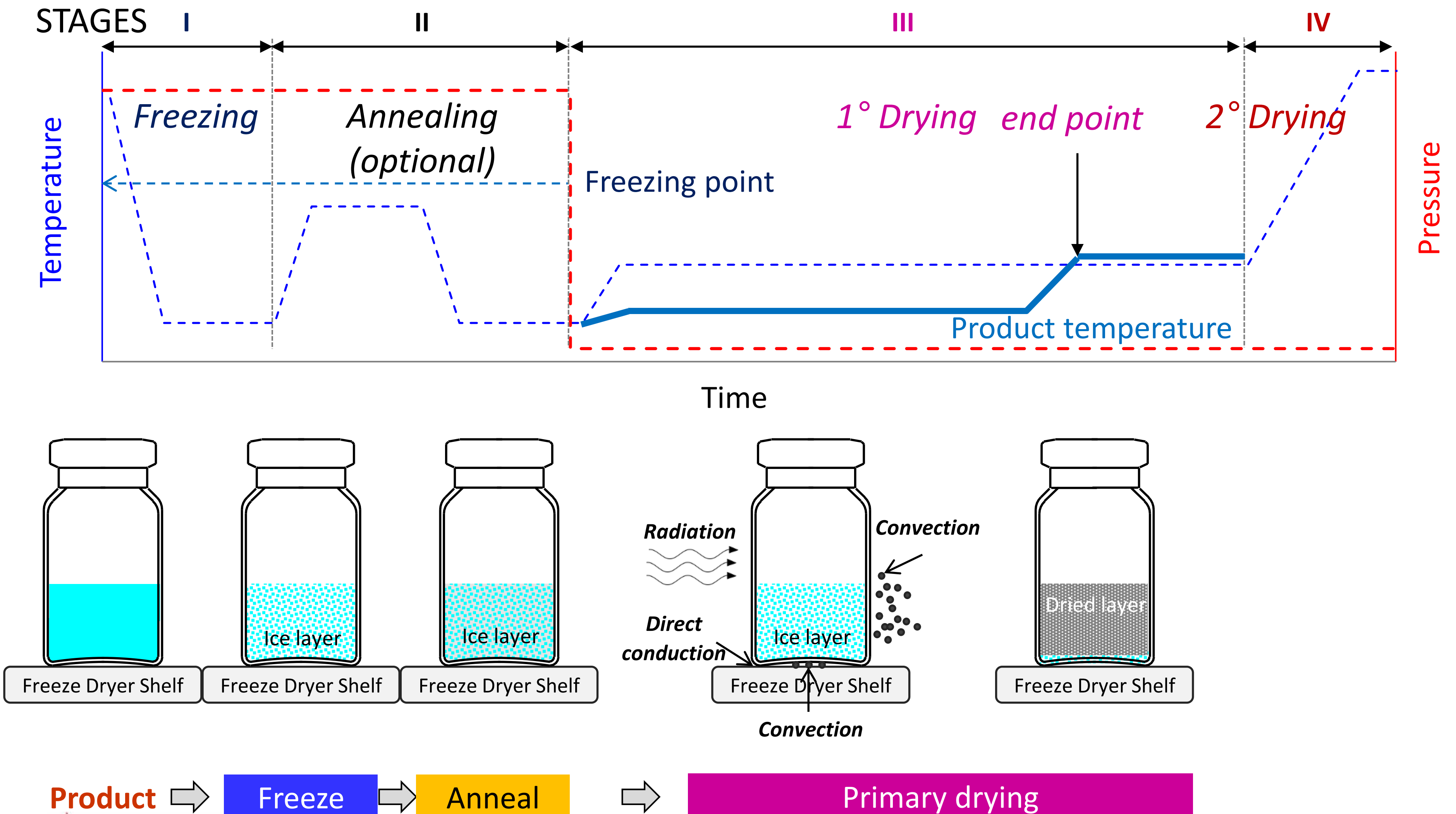


Product ⇨ Freeze ⇨ Anneal

Primary-drying



End of Primary-drying



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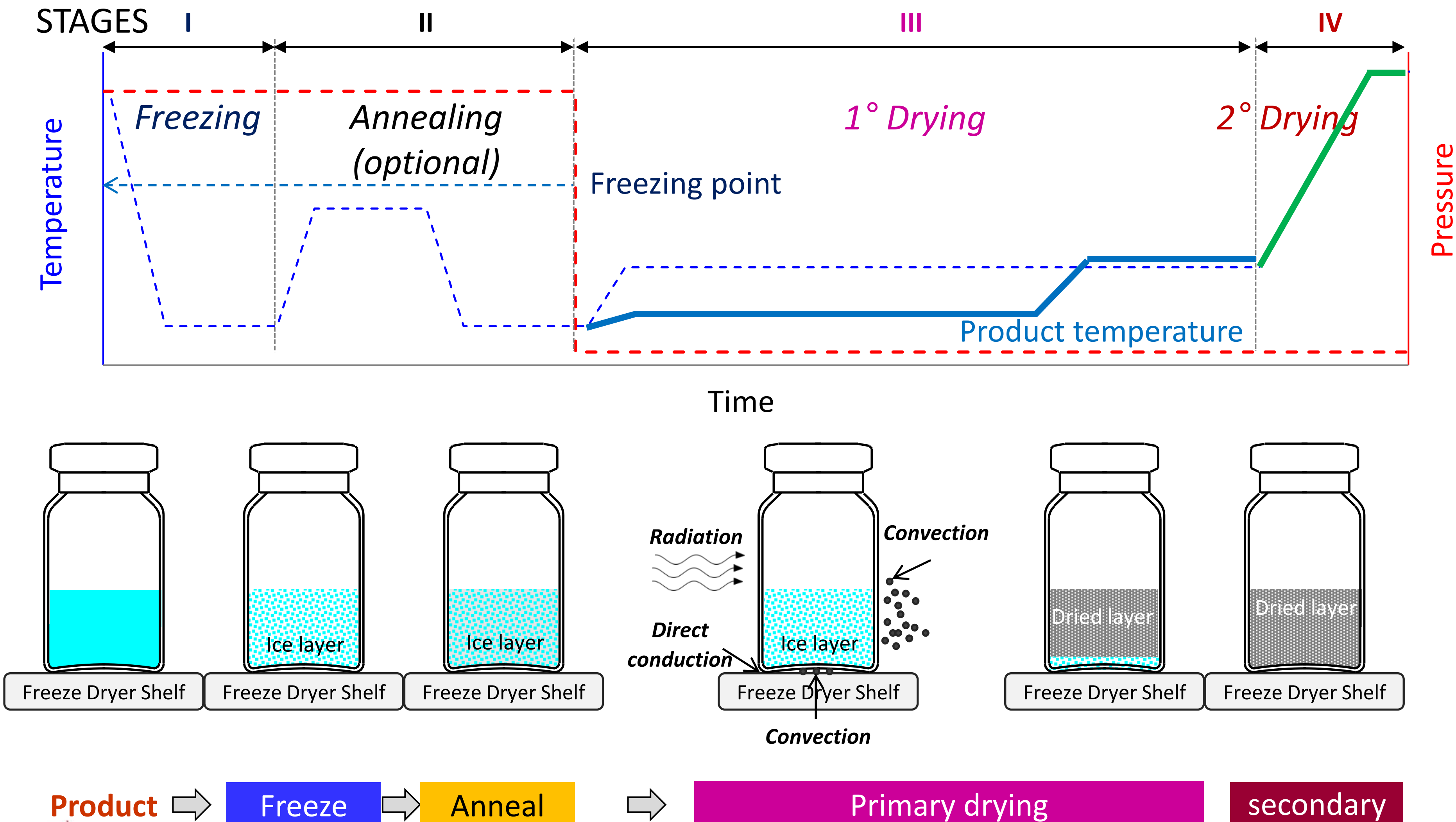

Design space

Product Design : Formulation

- Stability (chemical & physical) and packaging compatibility
- Critical product temperature T_c (~T_g' and/or T_{eu})

Process Design : Lyophilization

Freezing	Annealing	1° Drying	2° Drying
T_n ↓ Structure of frozen product	Maximize crystallization & ice crystal size ↓ Modification of frozen structure	$K_v(P_C)$ & R_p ↓ Set T_S & P_C ↓ - Product Temp. - Drying rate	Moisture content

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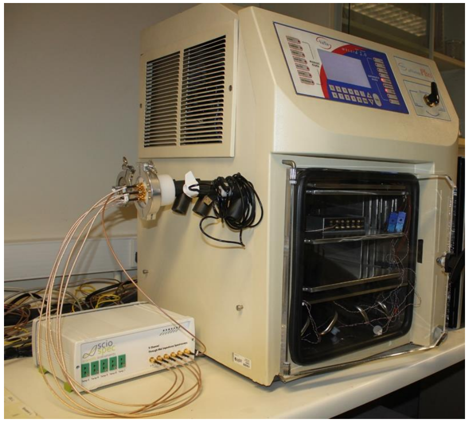
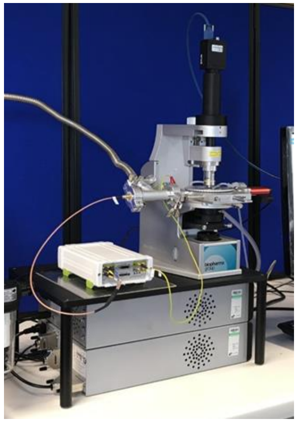
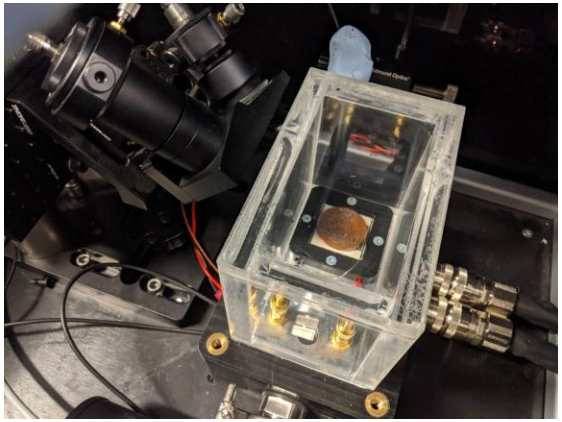
Dryers with Multiplexed PAT



Bench top 160 vial dryer enabled with Through-Vial Impedance Spectroscopy **TVIS**



Impedance enhanced Freeze-Drying Microscopy **Z-FDM**



Peltier-cooled **single vial dryer** enabled with **Raman**, **TVIS** and **laser speckle**

35 vial dryer enabled with
dew point sensor,
laser absorption, and
THz spectroscopy
for vapour pressure

and **TVIS**
for in-vial behaviour

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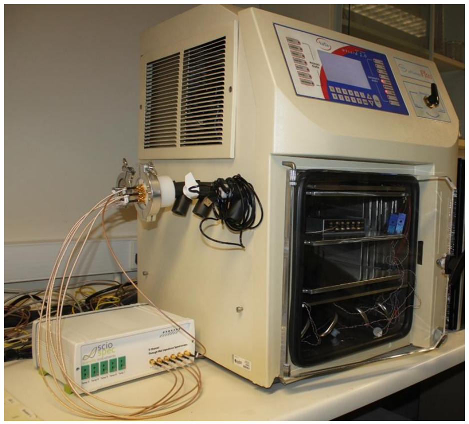
Dryers with Multiplexed PAT



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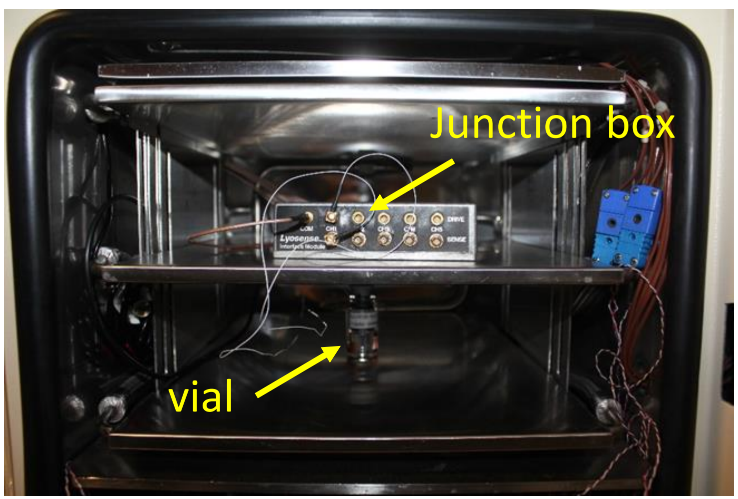
Spectroscopy Systems : TVIS

Modified glass vial

Electrode system

Placed within the dryer



TVIS (Through-Vial Impedance Spectroscopy)

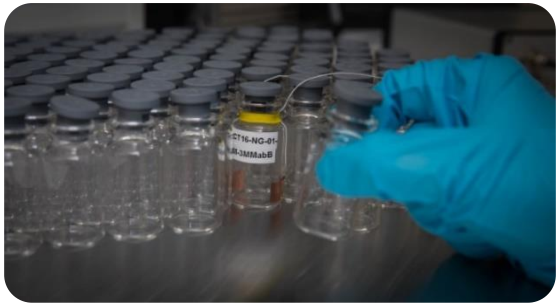
spectrometer

Through-Vial Impedance Spectroscopy

Single-vial PAT

Multichannel (5)

Non- perturbing to packing of vials



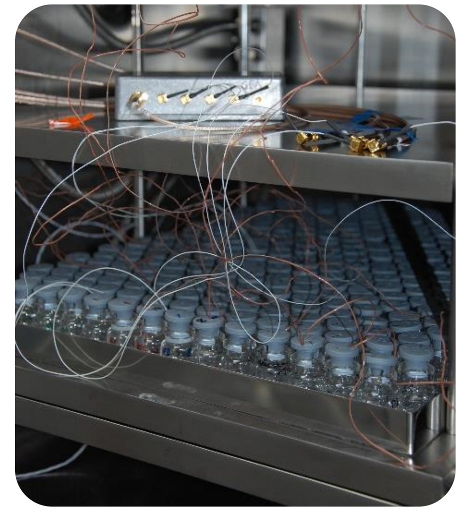
Through-Vial Impedance Spectroscopy

Single-vial PAT

Multichannel (5)

Non- perturbing to packing of vials

Thin (0.533 mm)
flexible cables
(0.5 - 2 m length)
Stoppering unaffected



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electrodes
no interference with heat
transfer & drying rates

plain TVIS TC vial

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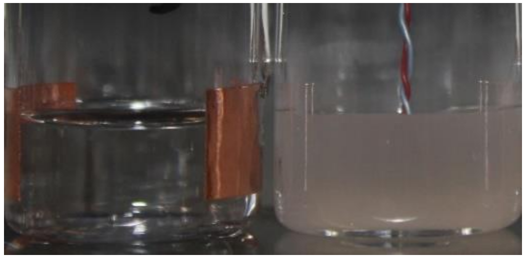

Non-sample invasive
no impact on ice nucleation

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Through-Vial Impedance Spectroscopy

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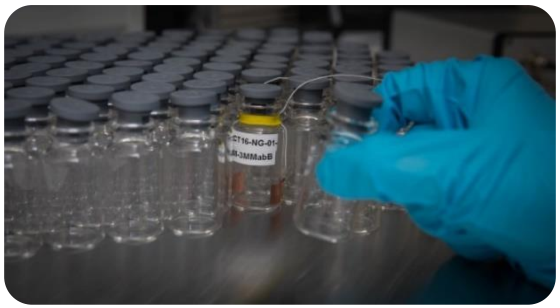

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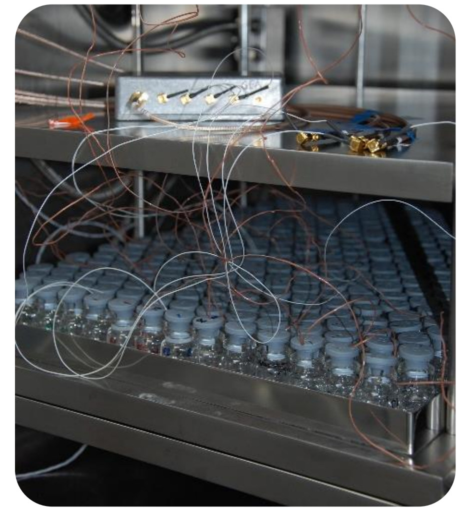

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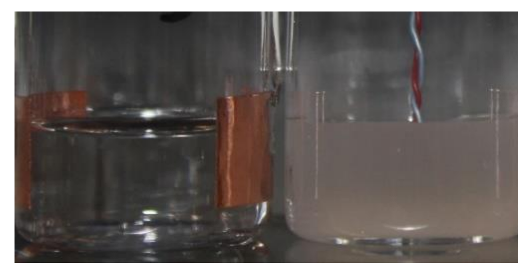

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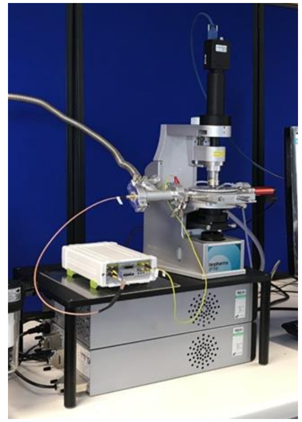
Dryers with Multiplexed PAT

Bench top 160 vial dryer enabled with Through-Vial Impedance Spectroscopy TVIS



Impedance enhanced Freeze-Drying Microscopy Z-FDM

Peltier-cooled single vial dryer enabled with Raman, TVIS and laser speckle

35 vial dryer enabled with
dew point sensor,
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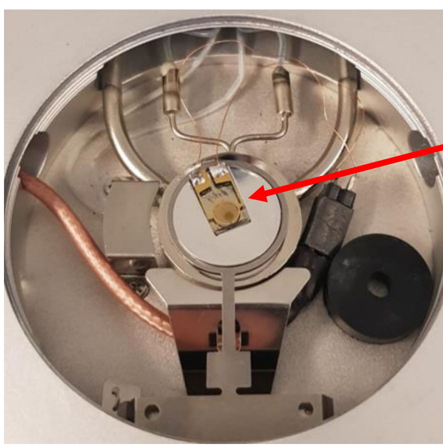
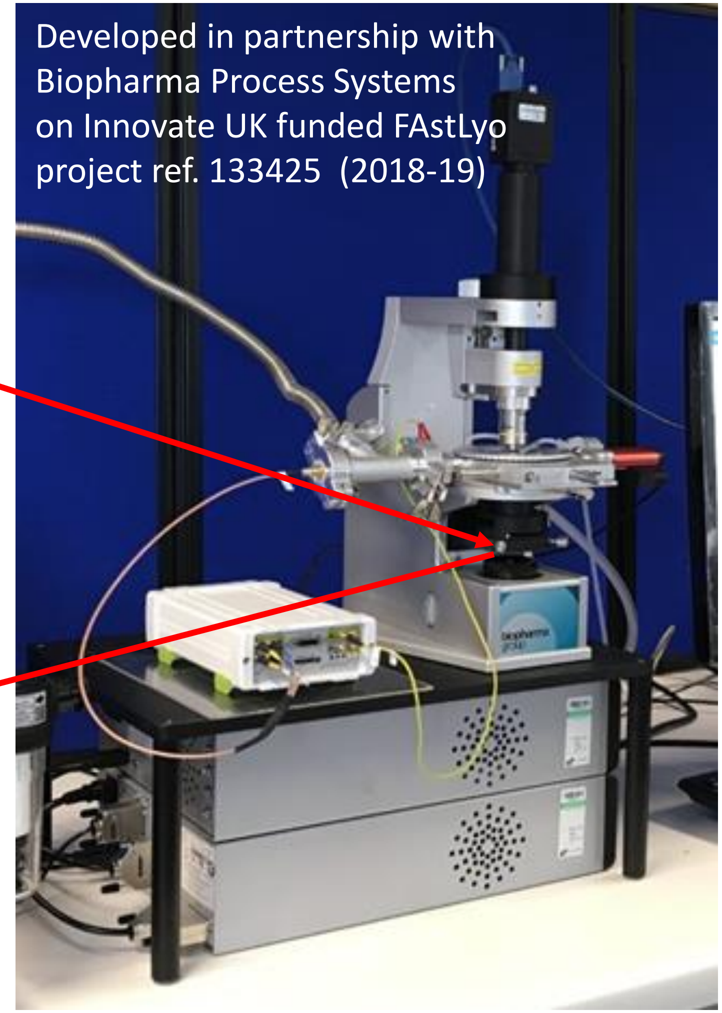
Impedance-enabled (Z-) Freeze drying microscopy (FDM)

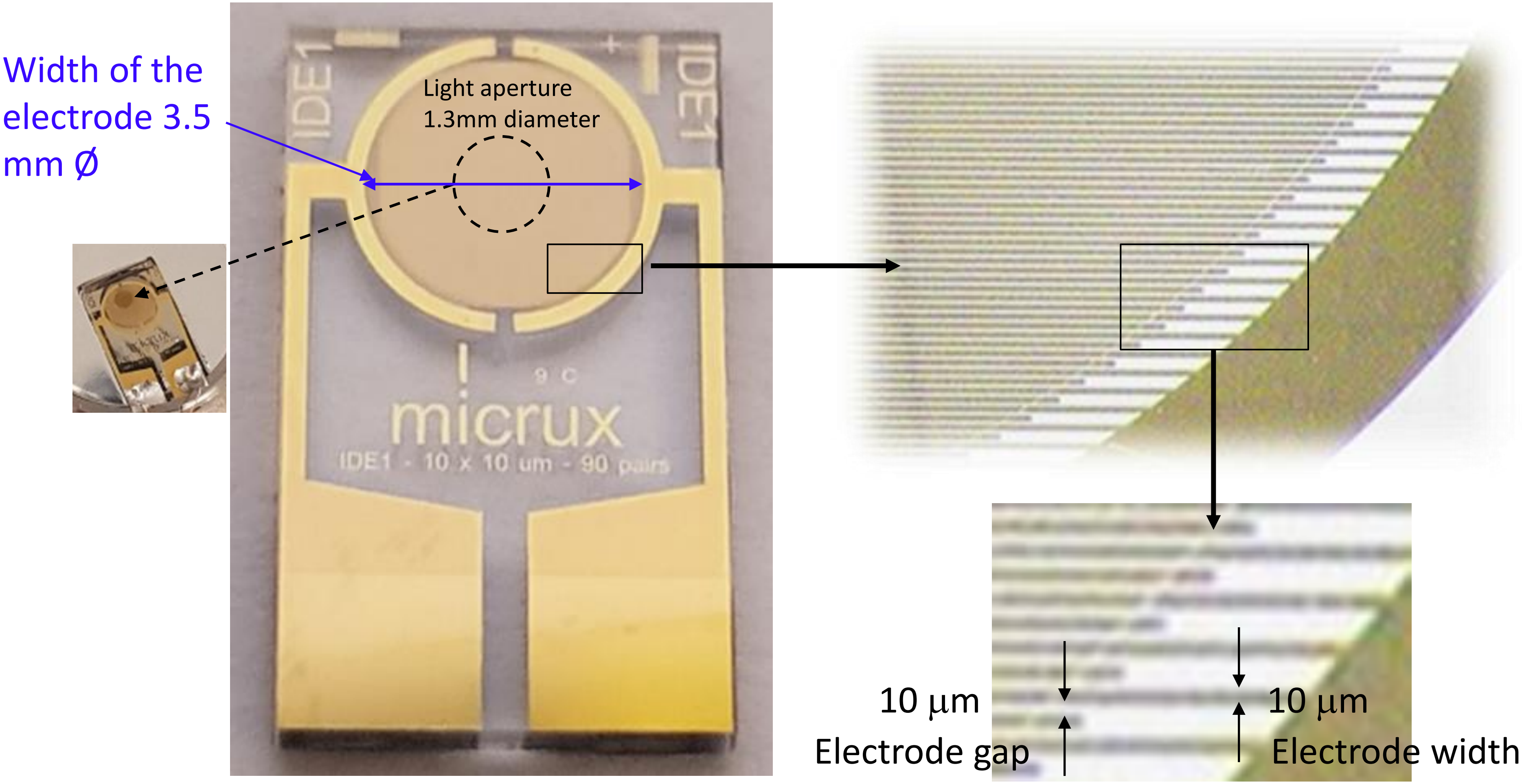
Inter-digitated electrode

Integrated within the FDM stage





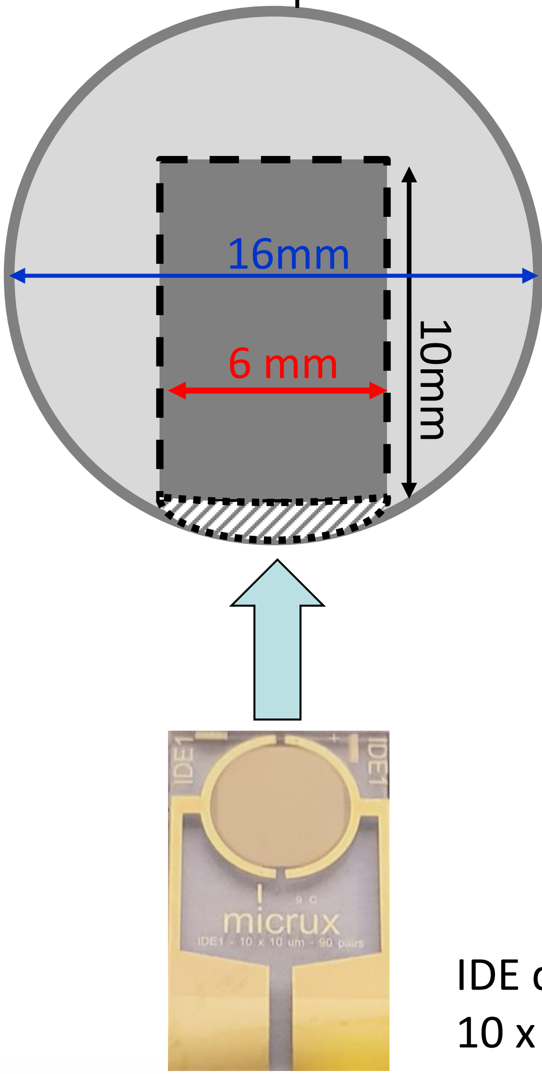
Example interdigitated electrode (gold on glass)



Commercial IDE – Micrux™

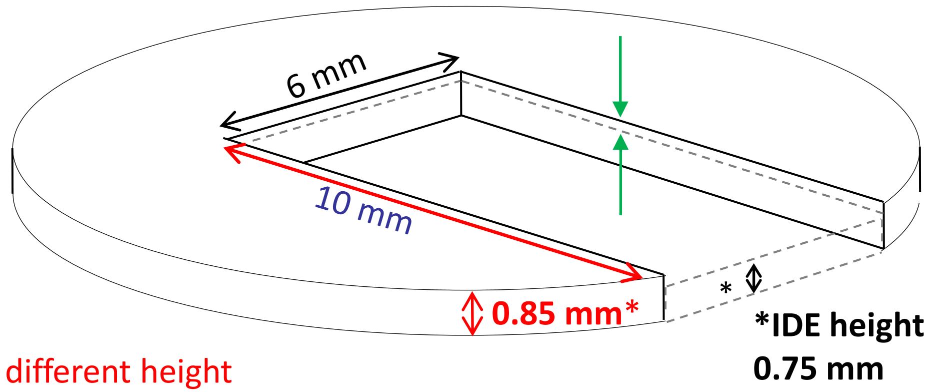
Design of IDE holder

Top view



IDE dimensions:
10 x 6 x 0.75 mm

Theoretical sample height



* different height of IDE adaptors used for initial assessment:

- 0.85 mm
- 0.90 mm
- 0.95 mm
- 1.00 mm

IDE is lower than the adapter and sample height derived between difference between then IDE adaptor size

Dryers with Multiplexed PAT

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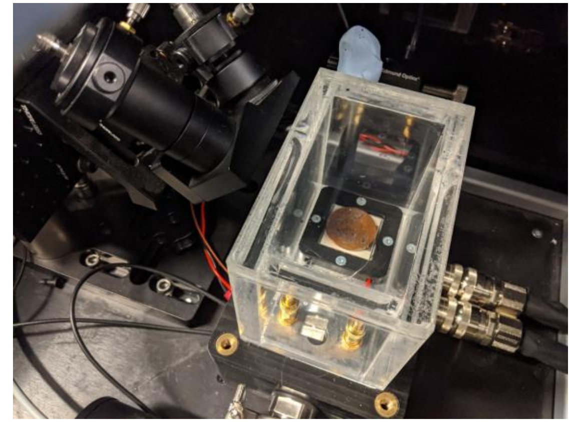
Impedance enhanced Freeze-Drying Microscopy Z-FDM



Peltier-cooled single vial dryer enabled with Raman, TVIS and laser speckle

is-instruments
Tonbridge, Kent, UK

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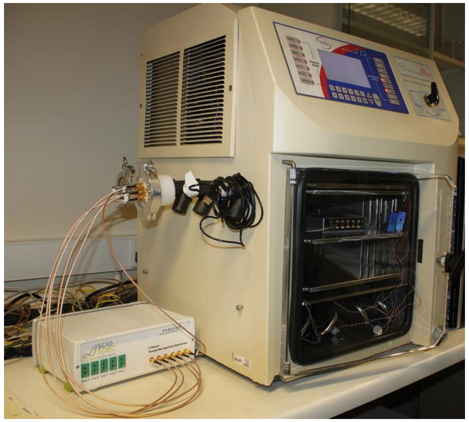

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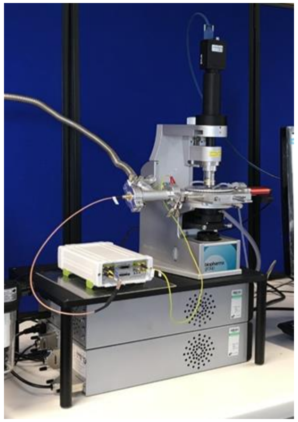

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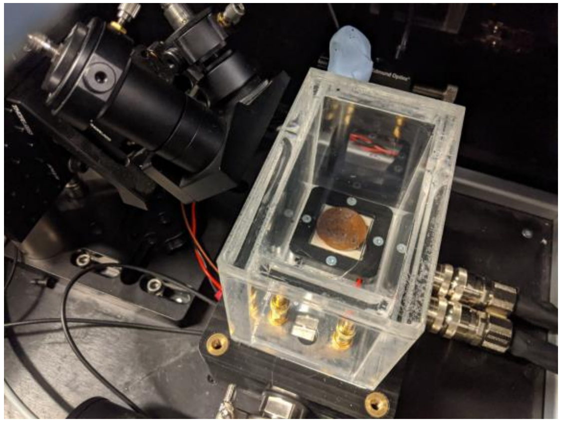

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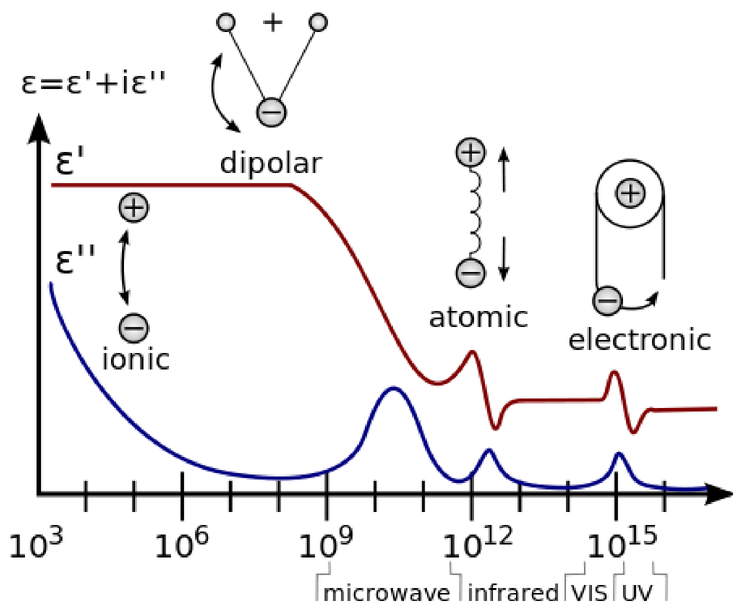
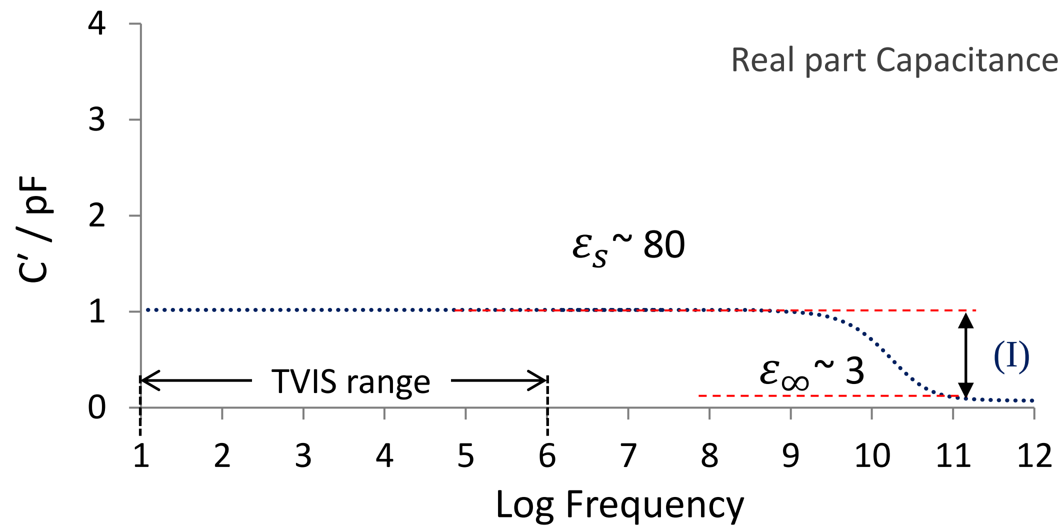
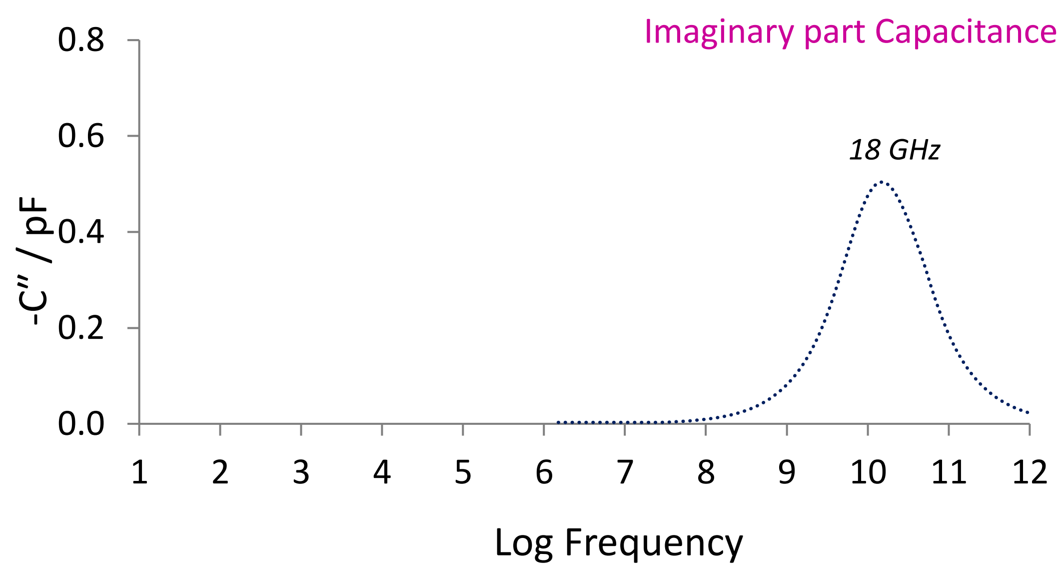
Dielectric Loss Mechanisms

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



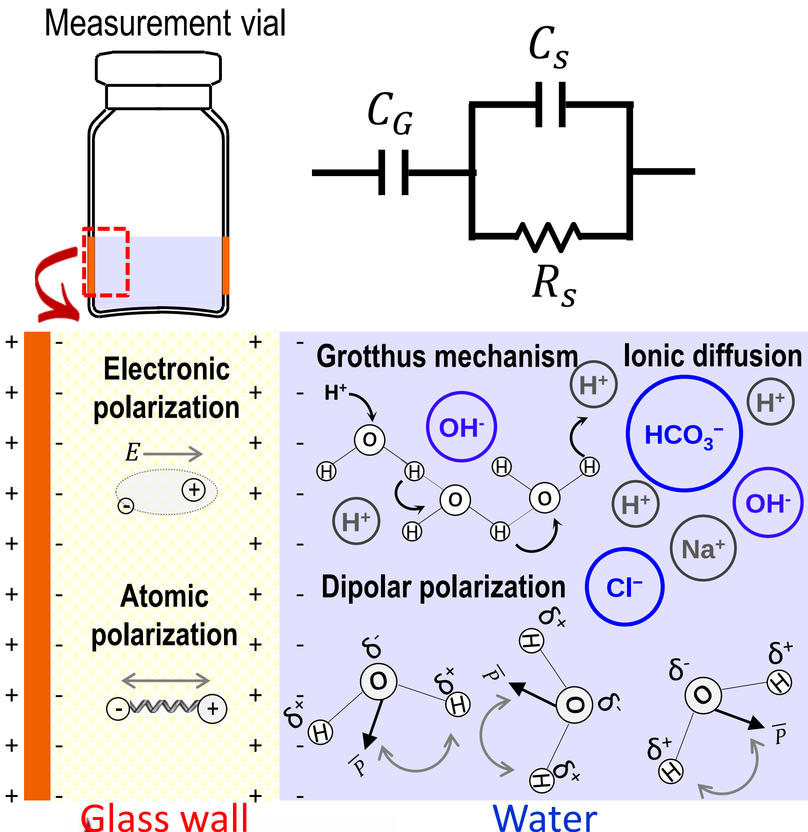
https://en.wikipedia.org/wiki/Permittivity

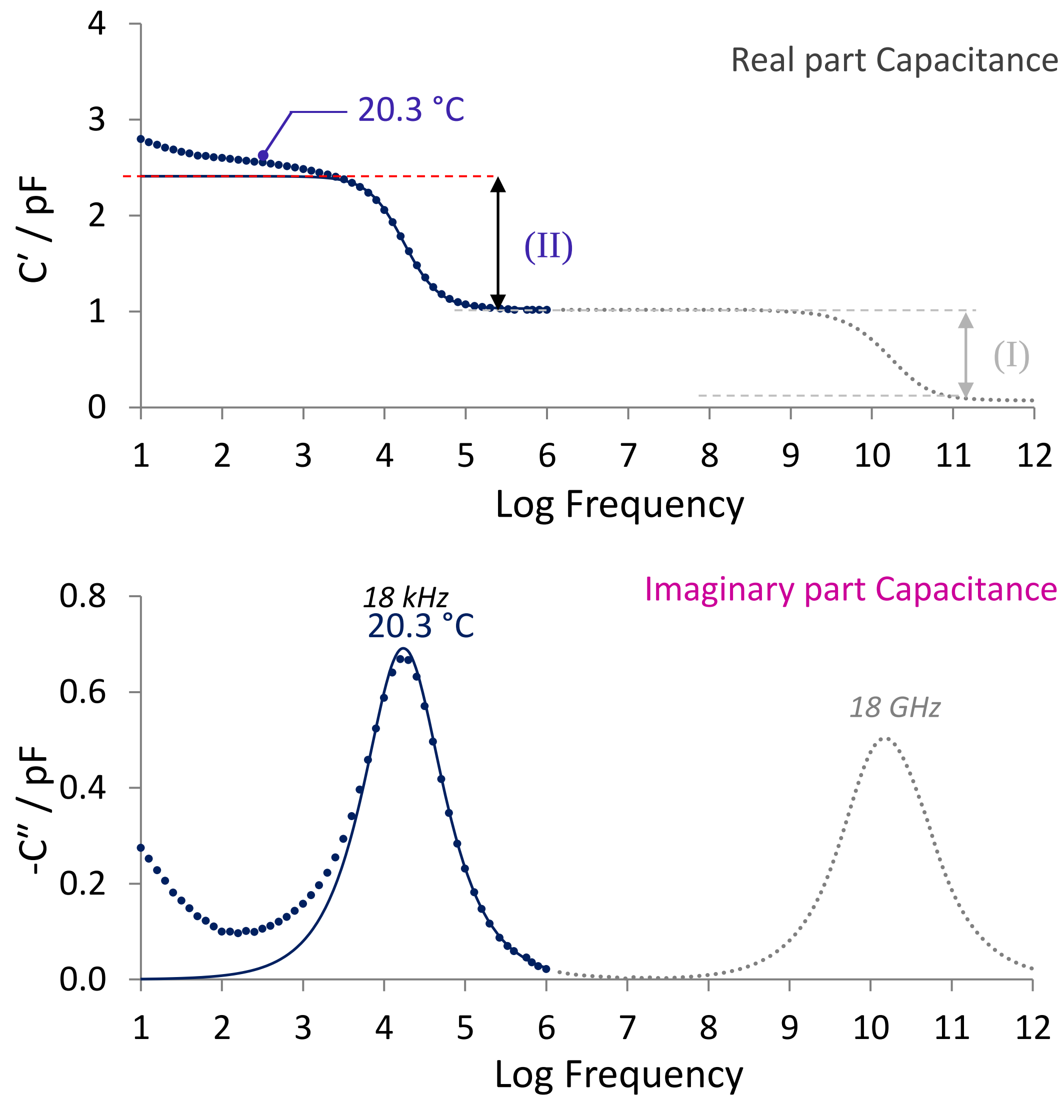




Dielectric Loss Mechanisms

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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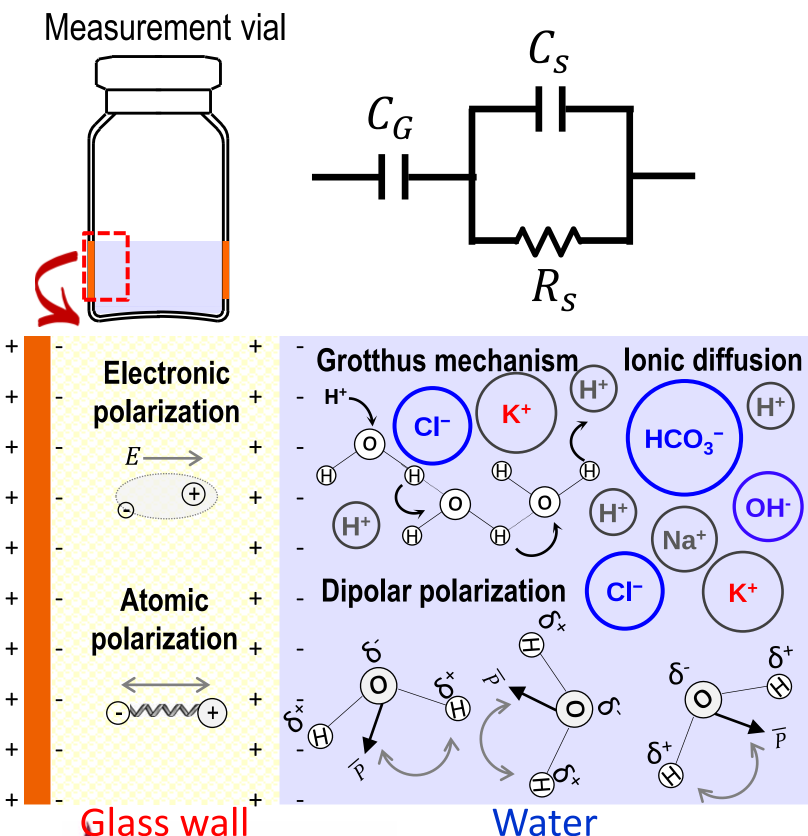
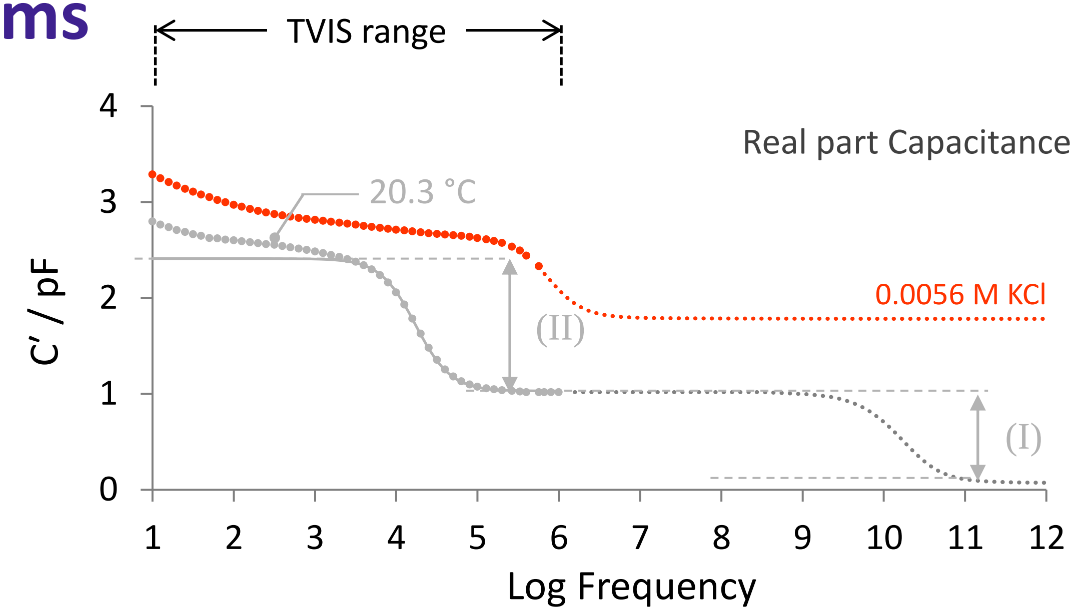
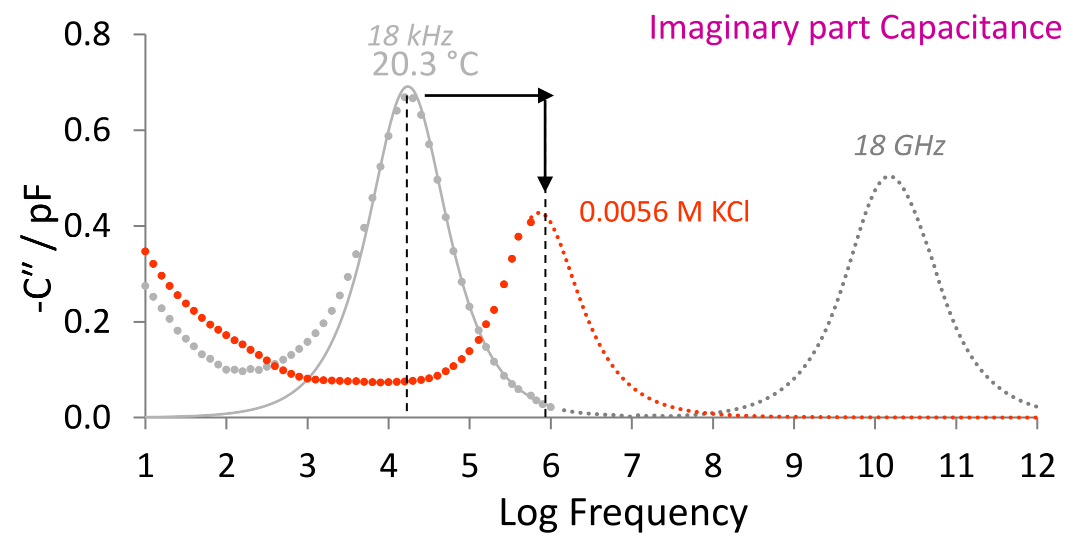
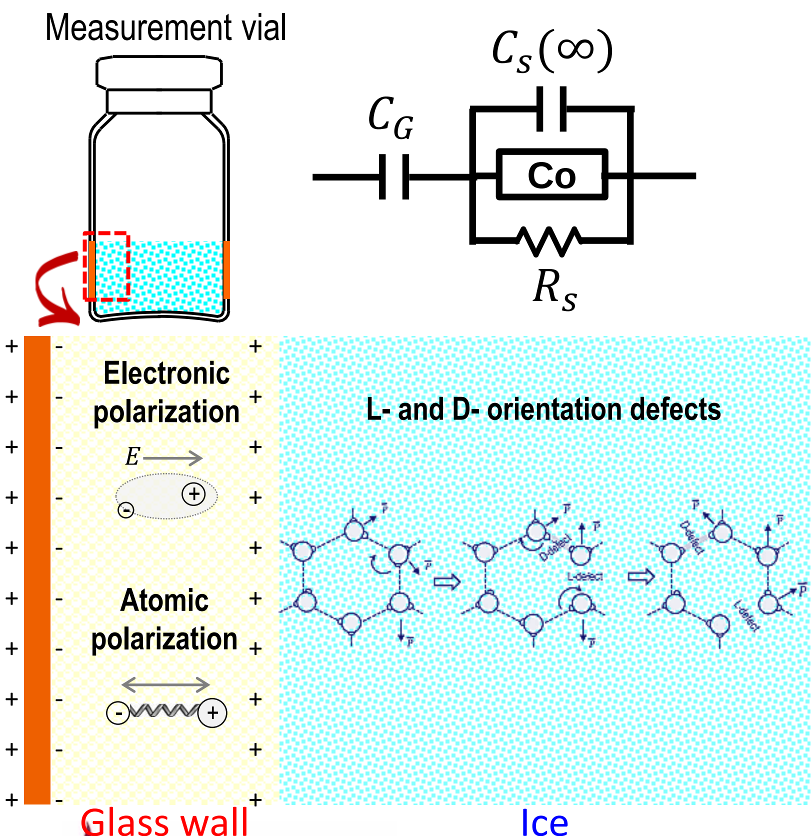


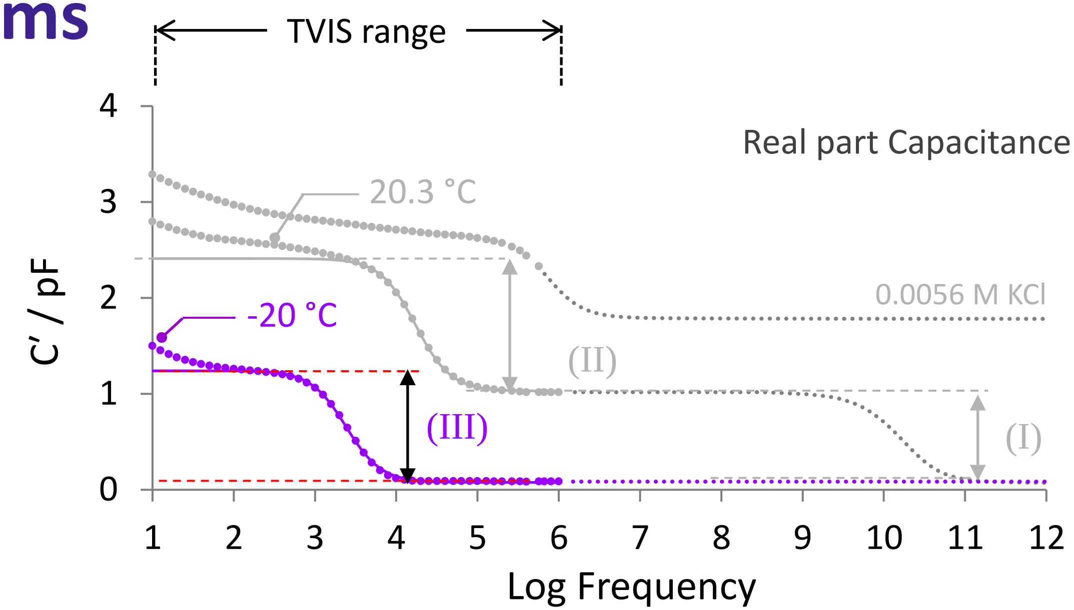


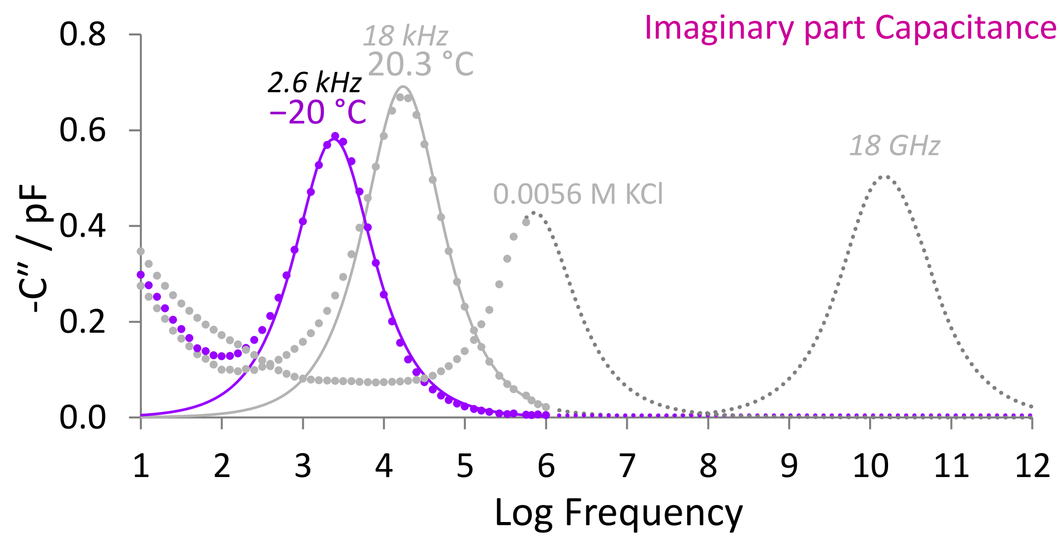


Dielectric Loss Mechanisms

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

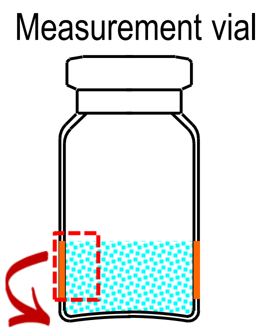


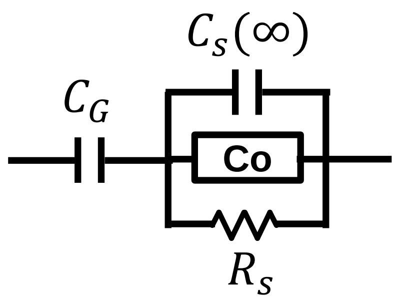


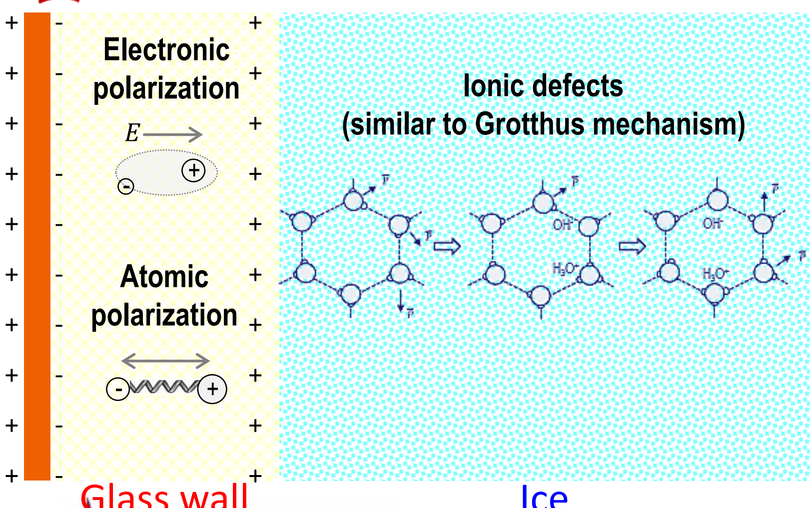


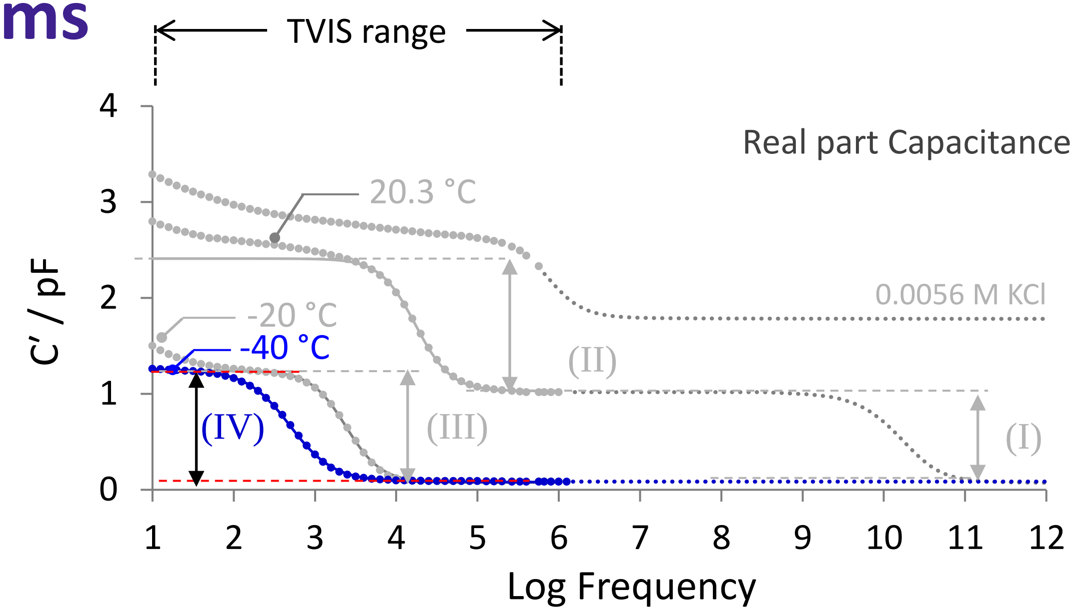
Dielectric Loss Mechanisms

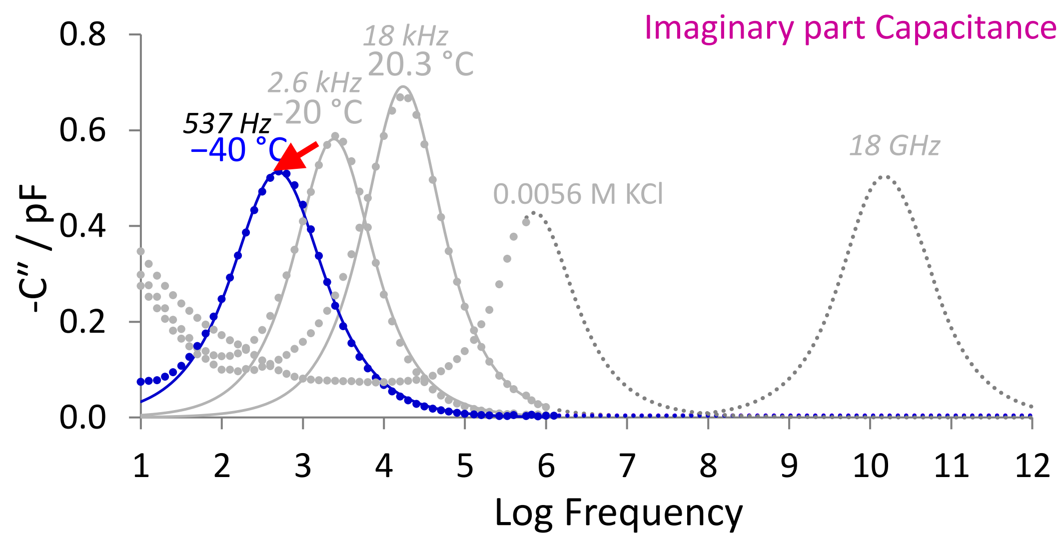
IV. The dielectric polarization of ice at −40 ˚C with a dielectric loss peak frequencies of 537 Hz.











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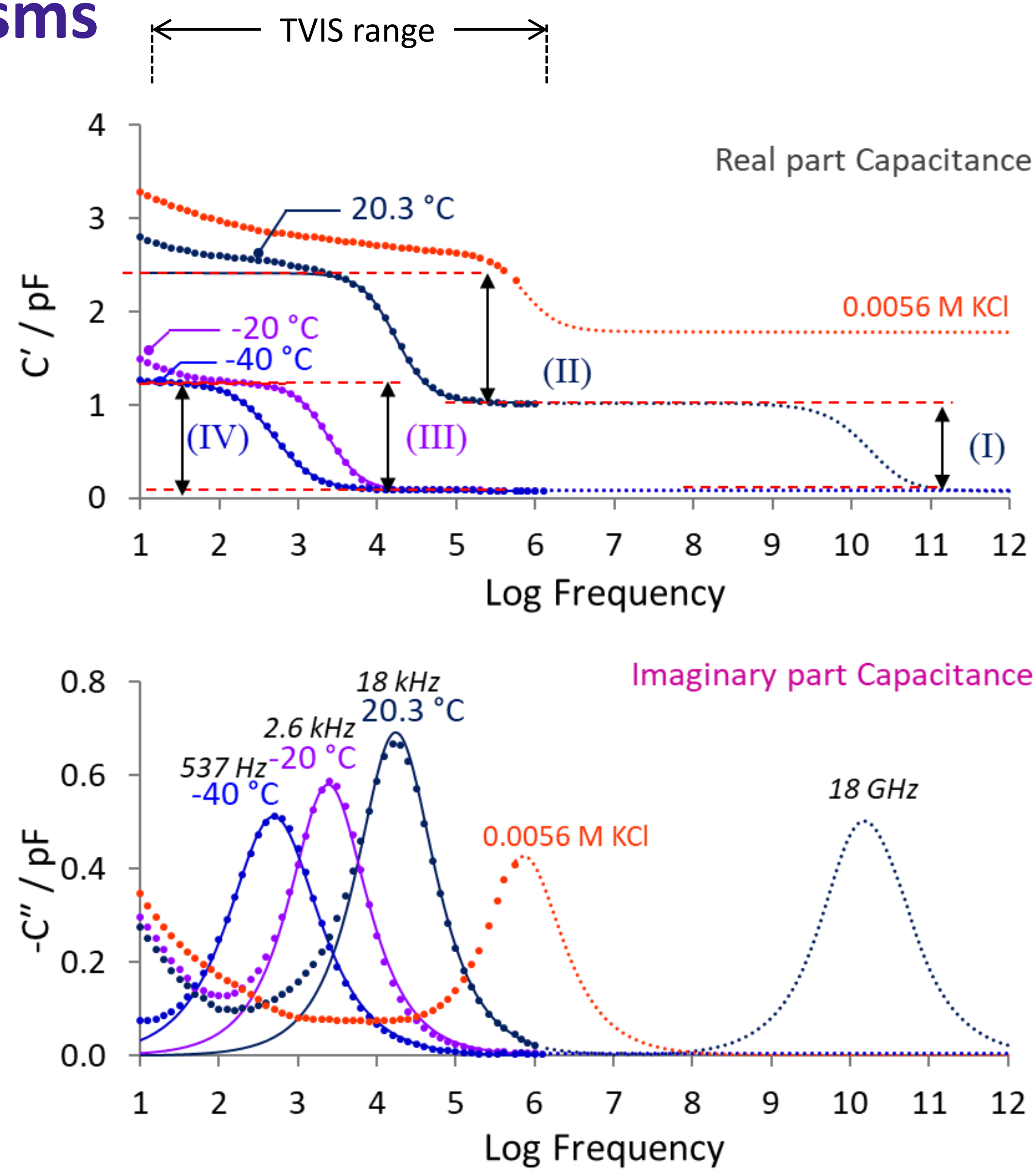
IV. The dielectric polarization of ice at −40 ˚C with a dielectric loss peak frequencies of 537 Hz.

Note: Process II only seen in TVIS vial; in Z-FDM process II is replaced by electrode polarization impedance)



TVIS publications suggestive of Z-FDM applications

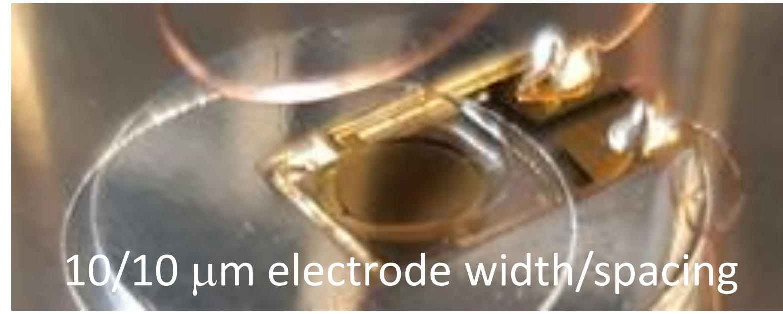
- Smith, G. & Jeeraruangrattana, Y. 2019, "Chapter 5 Through-Vial Impedance Spectroscopy (TVIS): A New Method for Determining the Ice **Nucleation Temperature and the Solidification End Point** n Freeze Drying of Pharmaceutical Products, eds. D. Fissore, R. Pisano & A. Barresi, 1st edn, CRC Press, Florida, United States
- Jeeraruangrattana, Y., Smith, G., Polygalov, E. and Ermolina, I. (2020) Determination of ice interface temperature, sublimation rate and **the dried product resistance**, and its application in the assessment of microcollapse using through-vial impedance spectroscopy. European Journal of Pharmaceutics and Biopharmaceutics, 152, pp. 144-163
- Smith, G., Jeeraruangrattana, Y., Ermolina, I. (2018). The application of dual-electrode through vial impedance
-

Freeze-Drying Cycle Development: Applications for Through-Vial Impedance Spectroscopy (TVIS) in Mini-pilot Studies. Journal of Pharmaceutical Innovation, 12 (1), pp. 26-40 **Key observation was the potential to measure temperature non-invasively**

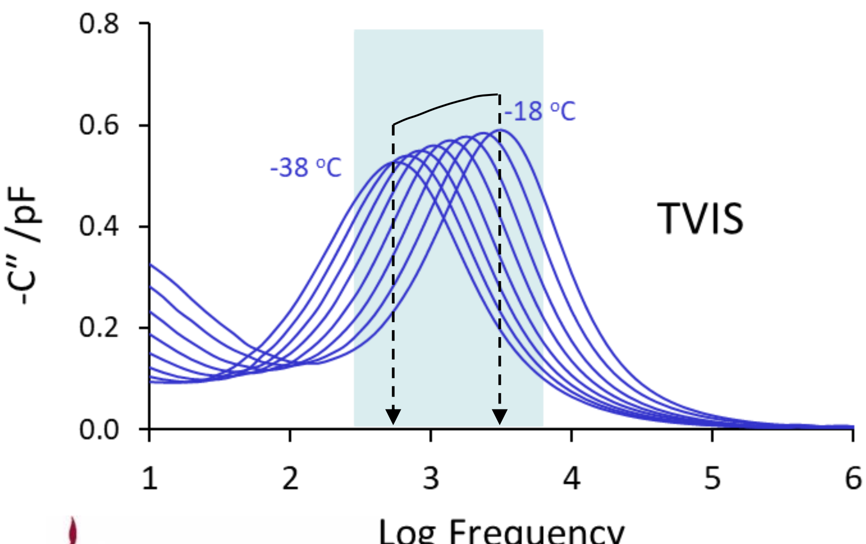
- Arshad, M.S., Smith, G., Polygalov, E., Ermolina, I. (2014). Through-vial impedance spectroscopy of critical events during the freezing stage of the lyophilization cycle: The example of the impact of sucrose on the **crystallization of mannitol**. European Journal of Pharmaceutics and Biopharmaceutics, 87 (3), pp. 598-605
- Smith, G., Arshad, M.S., Polygalov, E., Ermolina, I. (2014). Through-Vial Impedance Spectroscopy of the **Mechanisms of Annealing** in the Freeze-Drying of Maltodextrin: The Impact of Annealing Hold Time and Temperature on the Primary Drying Rate. Journal of Pharmaceutical Sciences, 103 (6), pp. 1799-1810
- Smith, G., Arshad, M.S., Polygalov, E. and Ermolina, I. (2013) An application for impedance spectroscopy in the characterisation of the **glass transition** during the lyophilization cycle: The example of a 10% w/v maltodextrin solution. European Journal of Pharmaceutics and Biopharmaceutics, 86 (3 Part B), pp. 1130-1140.

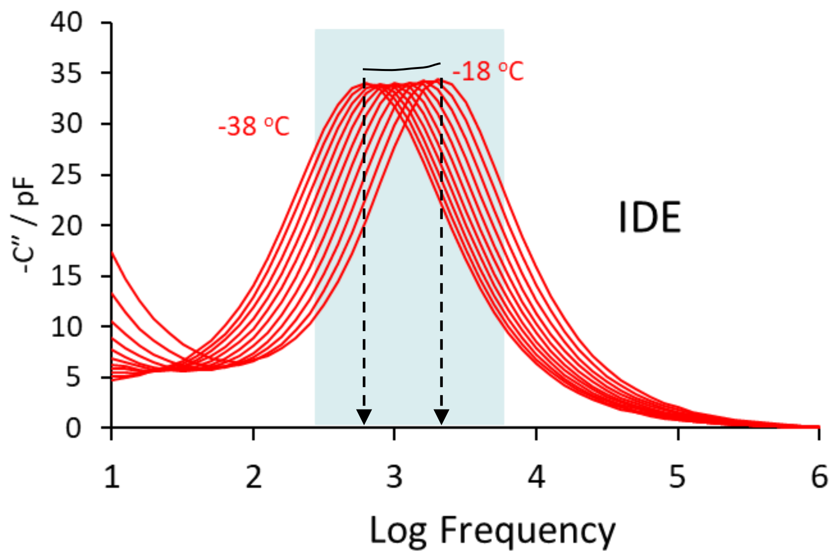
Dielectric relaxation of ice

5 mL water in
10 mL glass TVIS vial
(1 pair of 10/19 mm
height/width electrodes)



2 µL water over IDE
(90 pairs of gold interdigitated electrodes)





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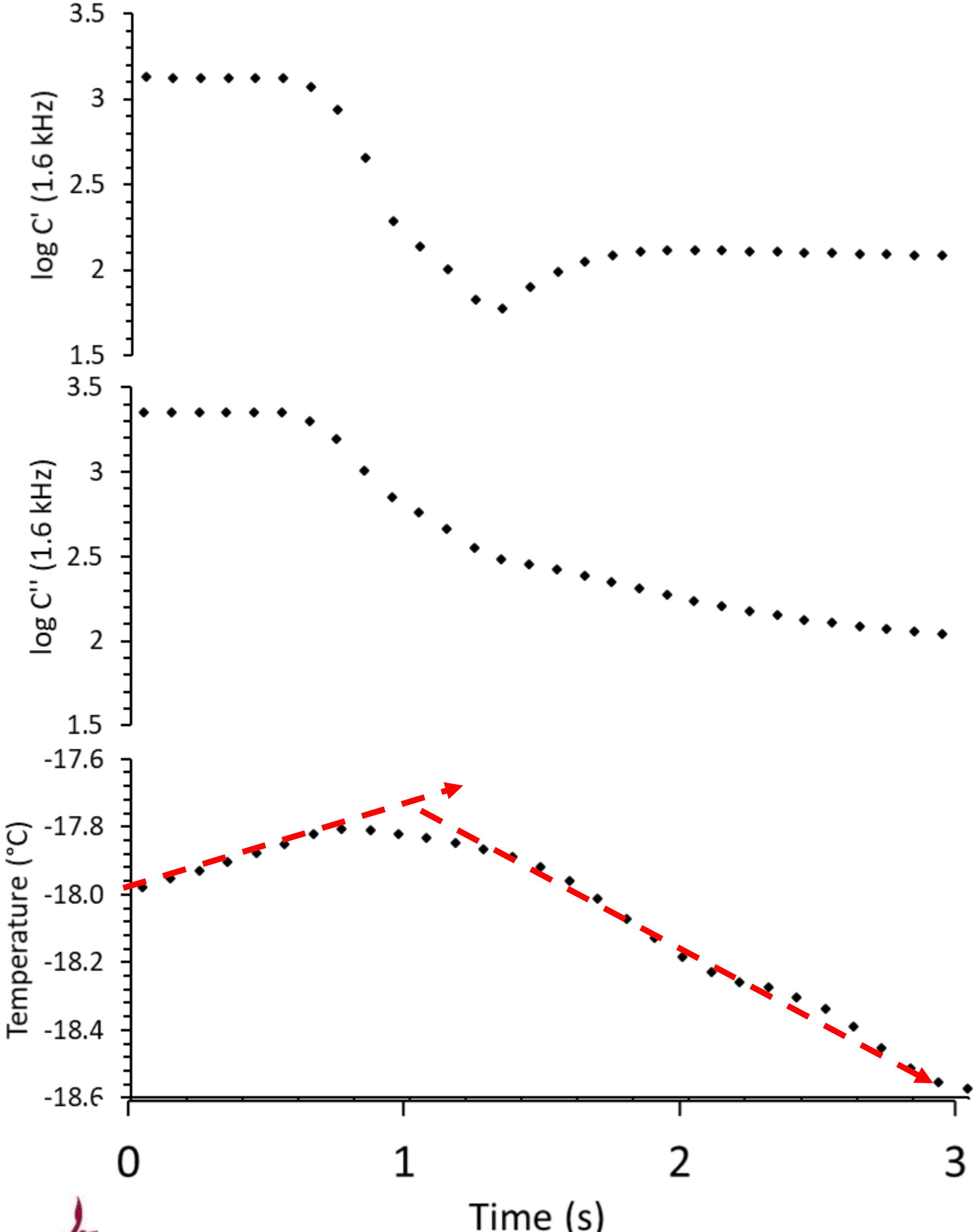
Applications in freezing (nucleation temperature, ice growth rates, solidification end point)

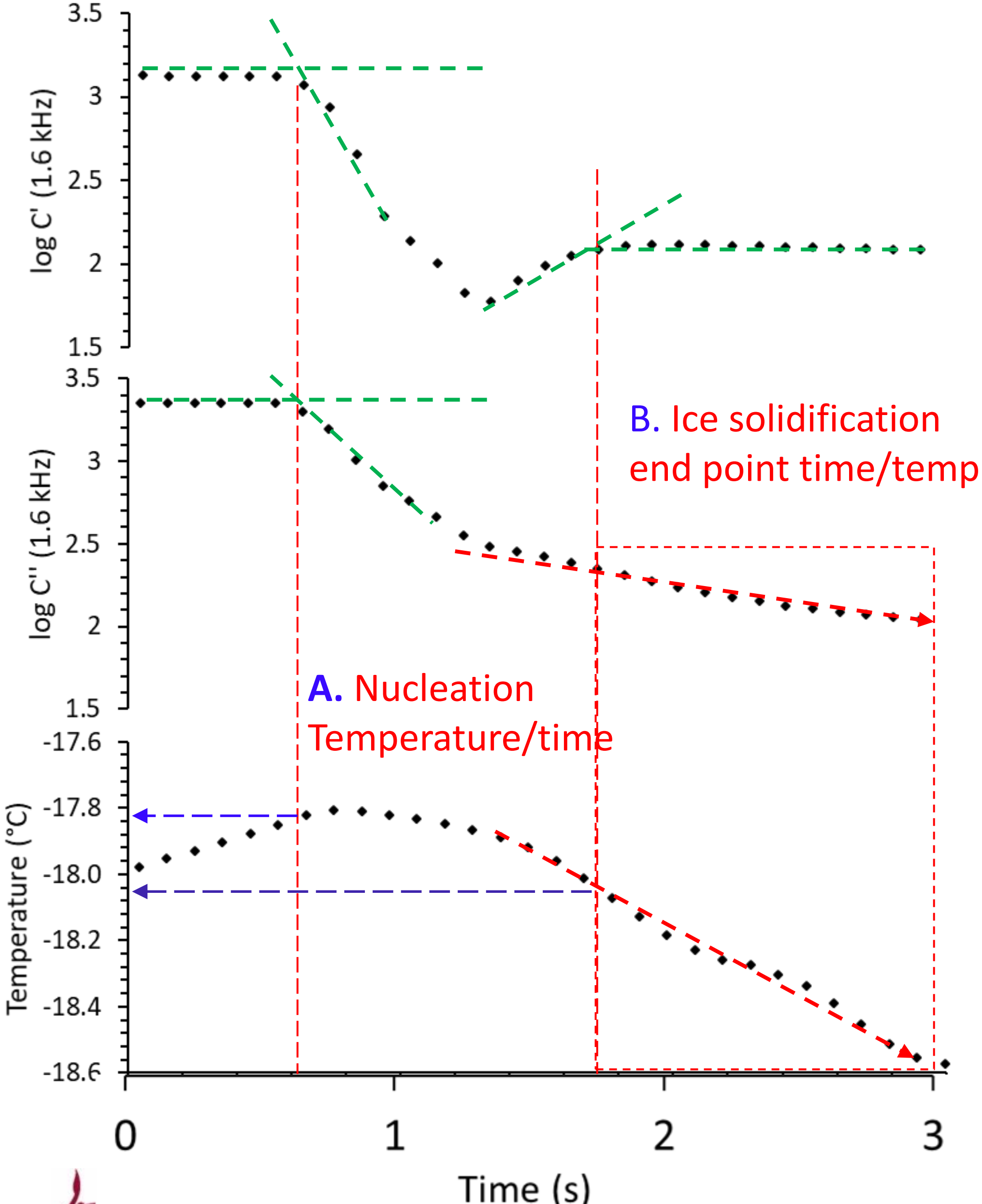
Observations on Sample Size

Case study of 5% w/v Sucrose Solution

Nucleation of 0.5µL of 5% Sucrose



Nucleation of 0.5µL of 5% Sucrose



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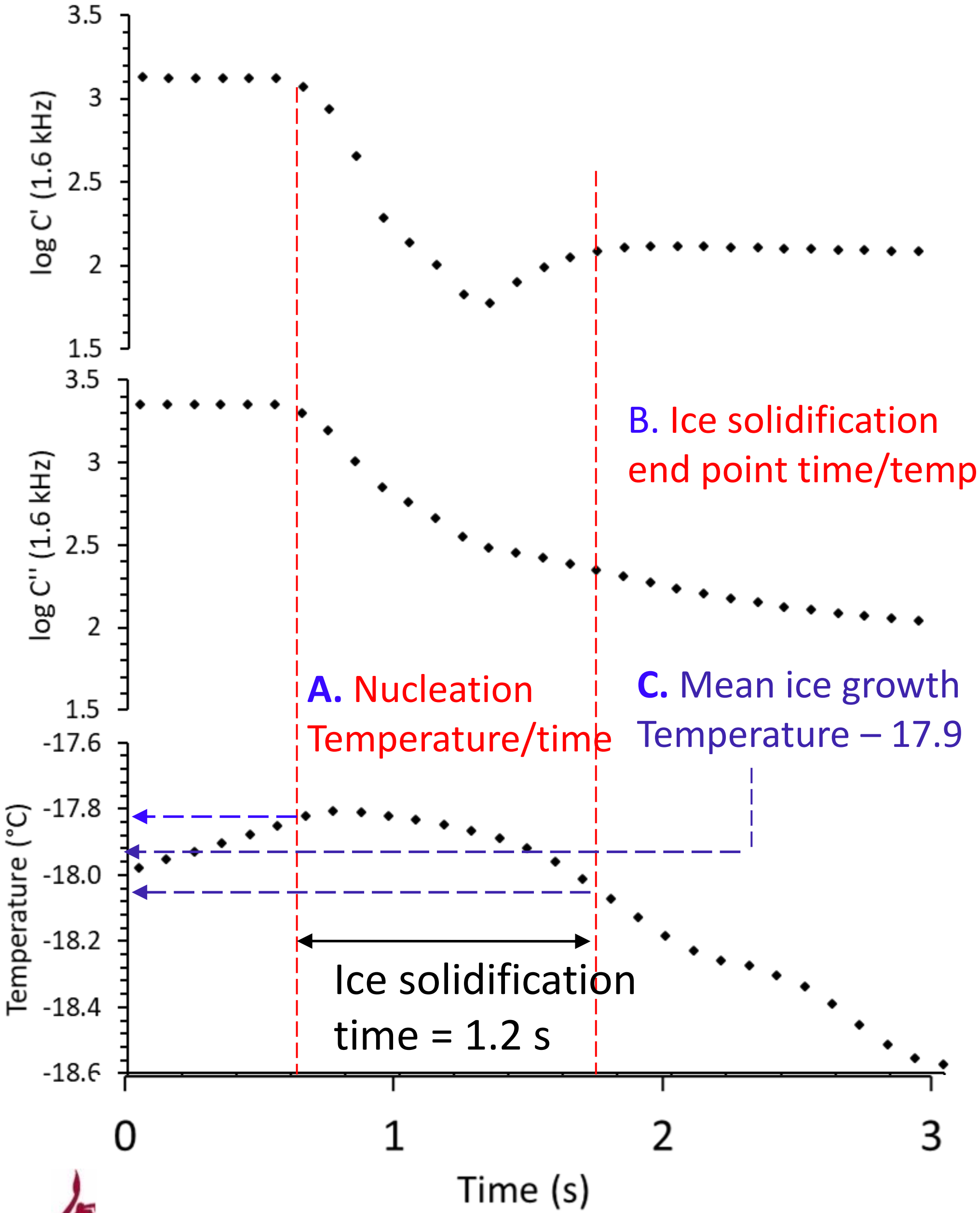
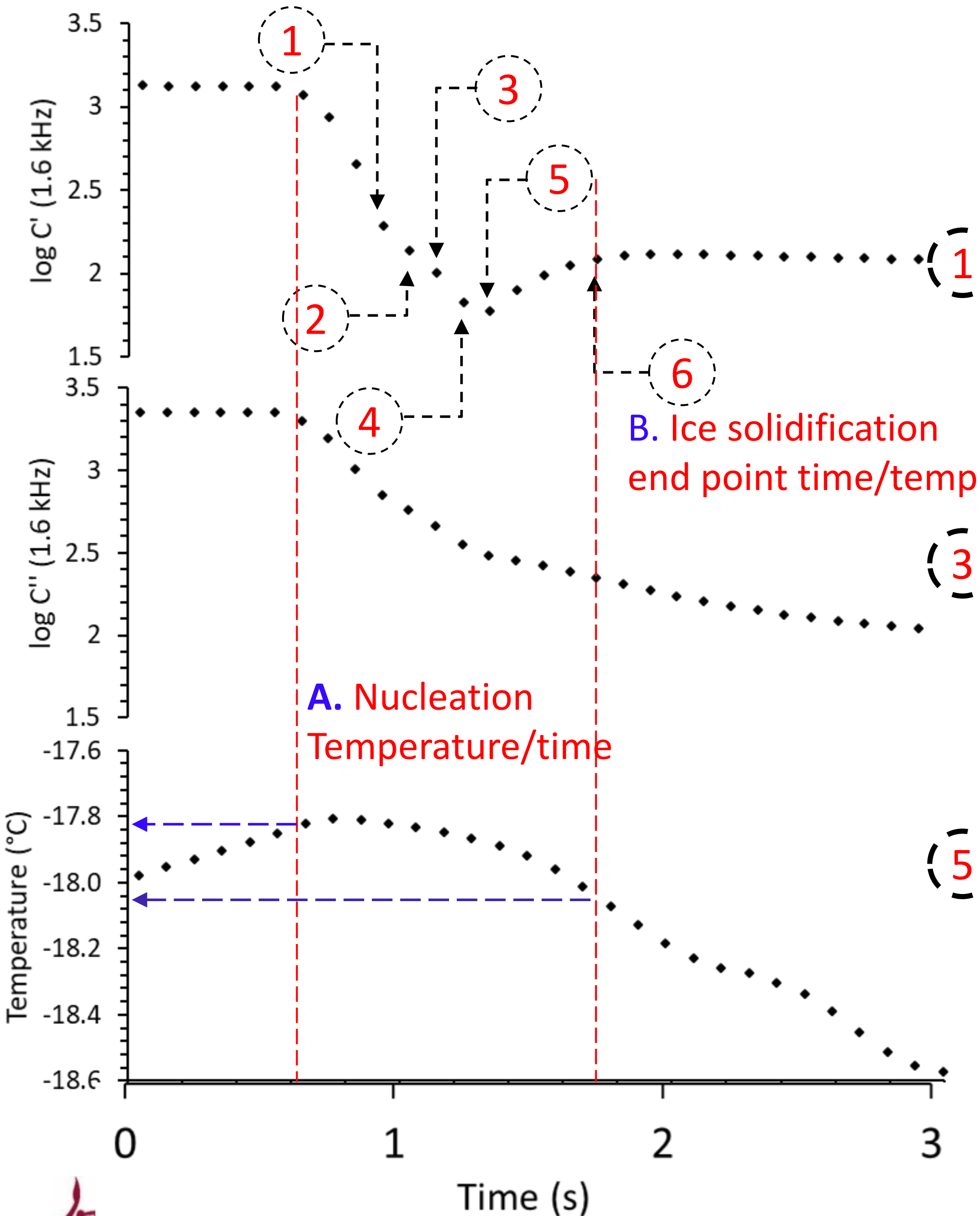
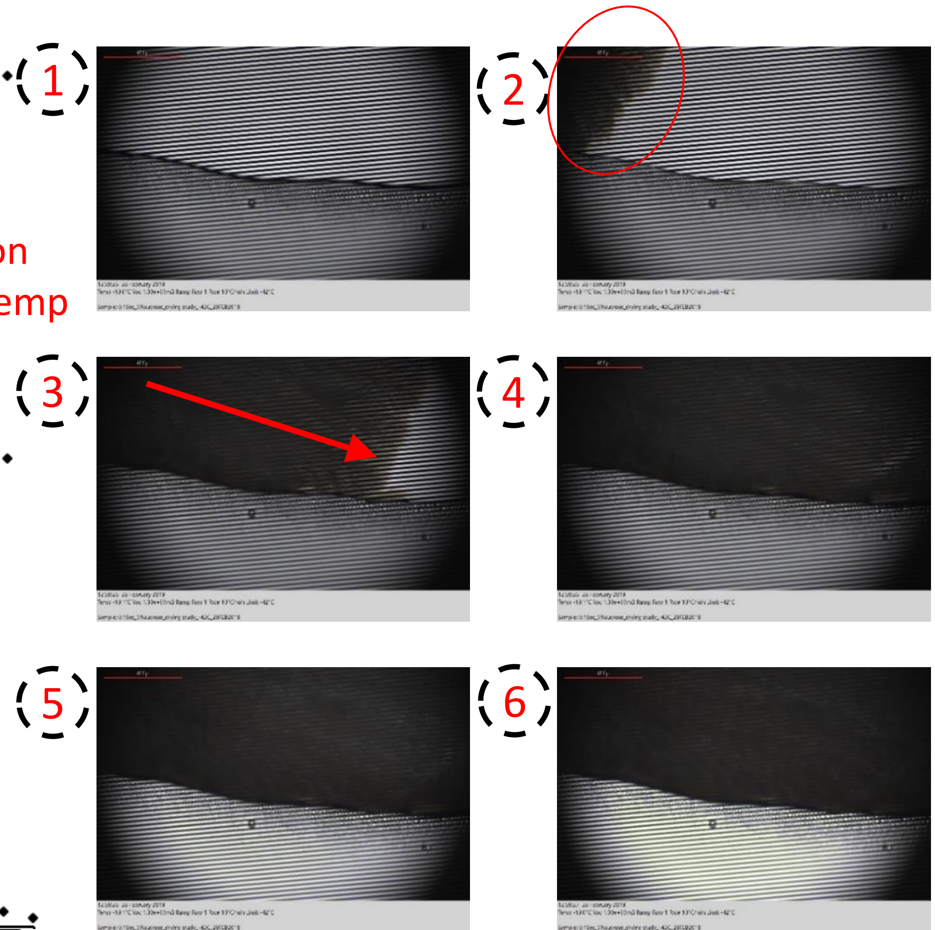
Nucleation of 0.5µL of 5% Sucrose



Time difference between time points A and B is the ice solidification time and hence provides an opportunity to measure ice growth rates at the mean ice growth temperature (C)

Nucleation of 0.5µL of 5% Sucrose





Ice growth rates

- Assumption: unfrozen fraction comprises 80:20 ratio of sucrose to water
- 1 mL of 5% w/w sucrose has 0.95 g water
- It follows that 0.0125 g (0.05 x 20/80) is bound and produces 0.9375 g ice

Estimated from:

0.5 µL of 5% sucrose (produces 4.688E-04 g ice)

- Ice formation time = 1.2 s (12 data points)
- Ice growth rate: 4.688E-04 / 1.2 = 0.39 mg/s

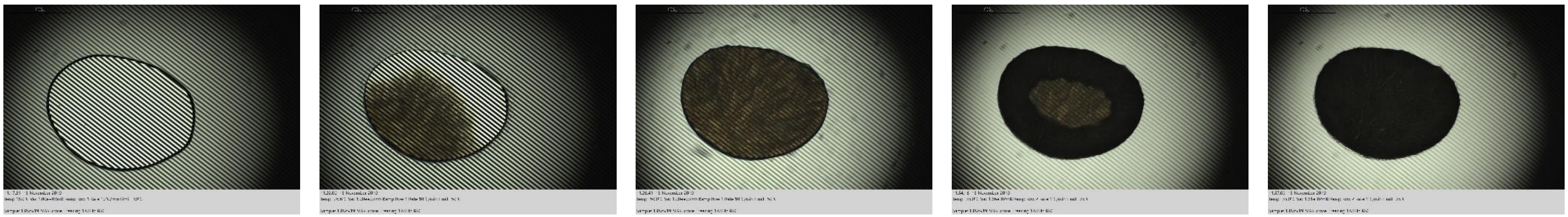
Relevance in formation design :
ice crystal size? Dry layer resistance Rp and drying rates

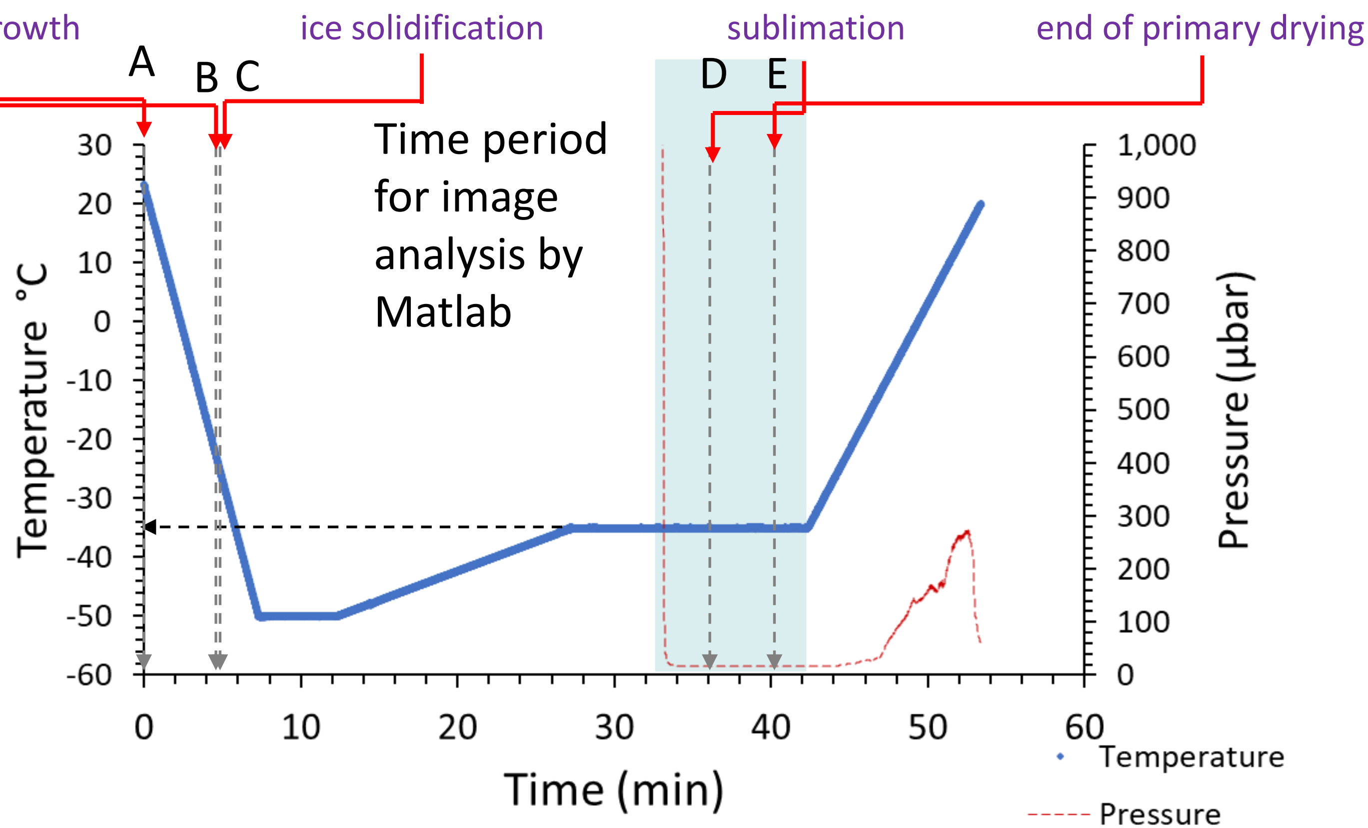
Applications in primary drying
(drying rate, product collapse)

Freeze drying of 5% sucrose (0.05µL)

Studied by Image analysis

FDM protocol





set temperature for the FDM stage

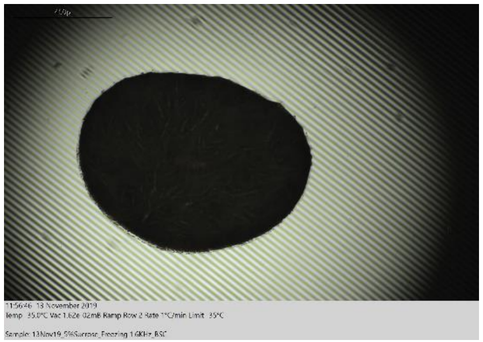
FDM freeze-drying of 5% sucrose solution (0.05 µL)

NB: Temperature and pressure measured on FDM every 100 ms

MATLAB® Image analysis (pixel counting)

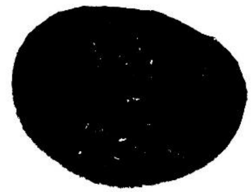
FDM primary-drying of 5% sucrose soln (0.05 µL) at -35˚C

1. **Global templet generation** – dried product image



Dried product image

MATLAB®



Global pixel : 527515

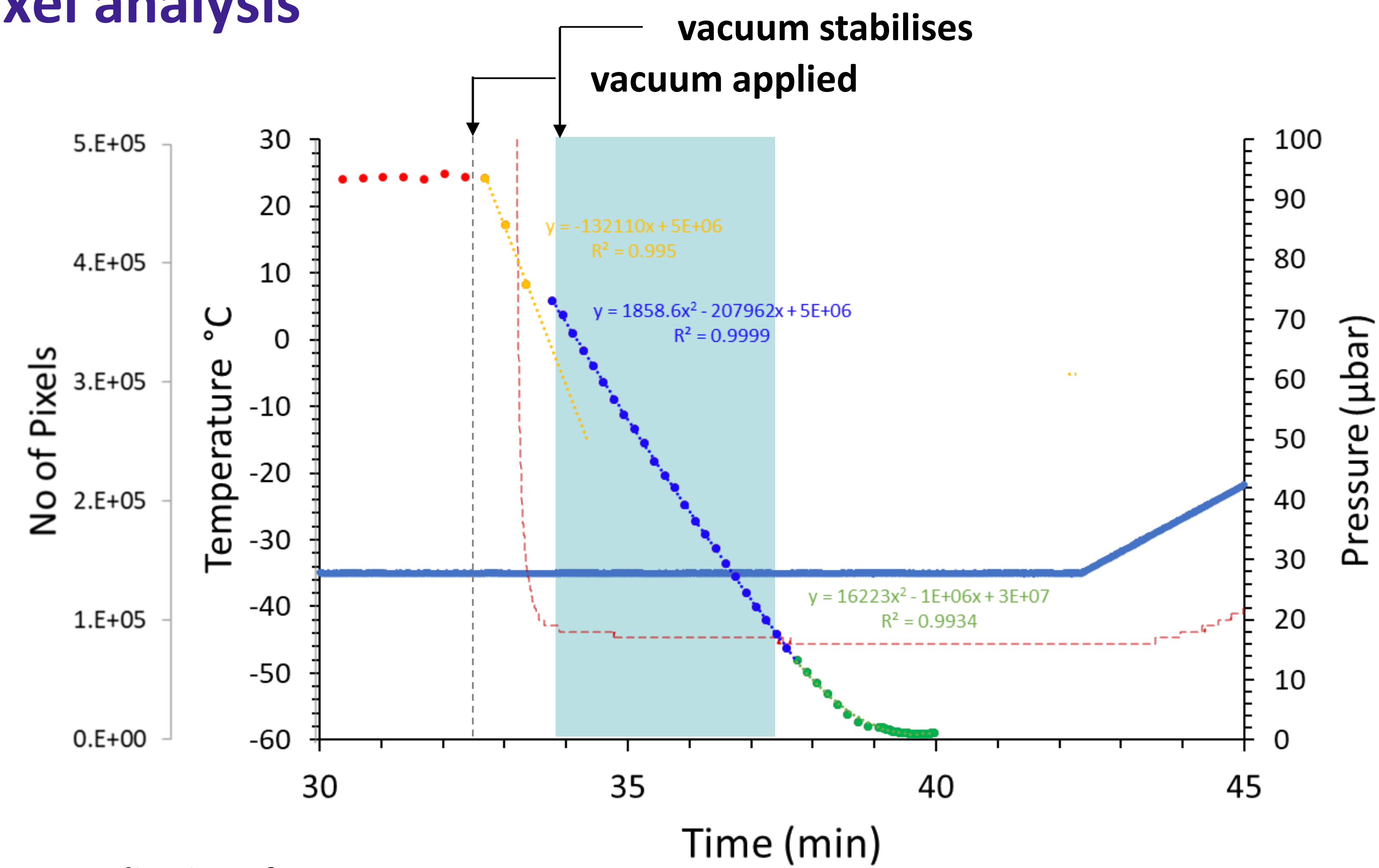
2. **Threshold test image** – frozen image or drying stage image

Product during drying

MATLAB®

Pixel for central area: 86317

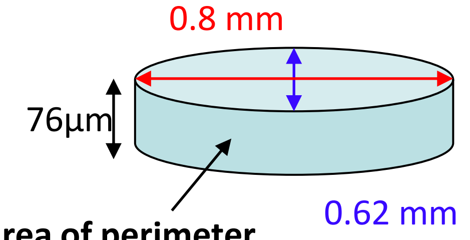
Pixel analysis



A: Application of vacuum

NB: Temperature and pressure measured every 100 ms

Drying rate determination



Weight fraction of sucrose	0.05	(5% Sucrose)
Weight fraction of water	0.95	i.e. 95 % water
Weight fraction of bound water (1)	0.0125	
Weight fraction of freezable water	0.9375	

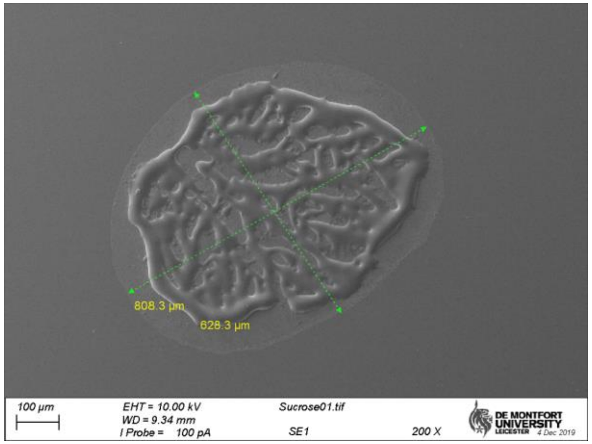
(1) based on 80:20 ratio of sugar to water in freeze-concentrated solution

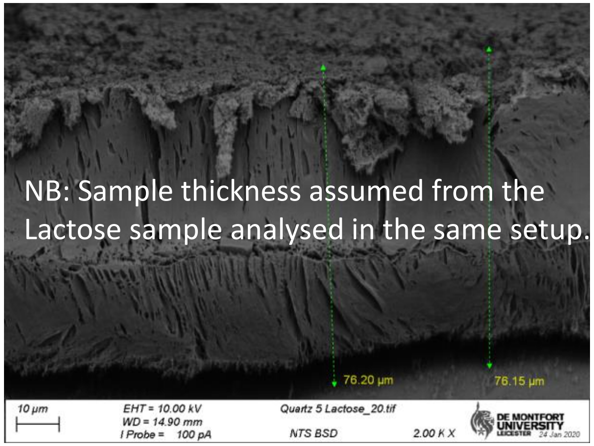
Sample volume	0.05	µL
Freezable water	0.0469	µL
Freezable water in mg	0.0469	mg of ice

Total pix before drying starts	466873	
1 pixel (a)	1.004E-07	mg of ice

Gradient of linear part (b)	132110	pixel per min (yellow line)
Drying rate (a x b)	0.0133	mg min^{-1}
Drying rate (B)	**0.00080**	**g h^{-1}**

Area of perimeter of sample (A)	0.00342	cm^2
Specific drying rate (B/A)	**0.233**	**g h^{-1} cm^{-2}**





Example drying rate from a 10 mL glass tubing vial is 0.25 g h^{-1}

Vial diameter : 22 mm Internal area : 3.8 cm^{-1}

Specific drying rate : 0.065 g h^{-1} cm^{-2}

Difference due to differences in heat transfer etc.

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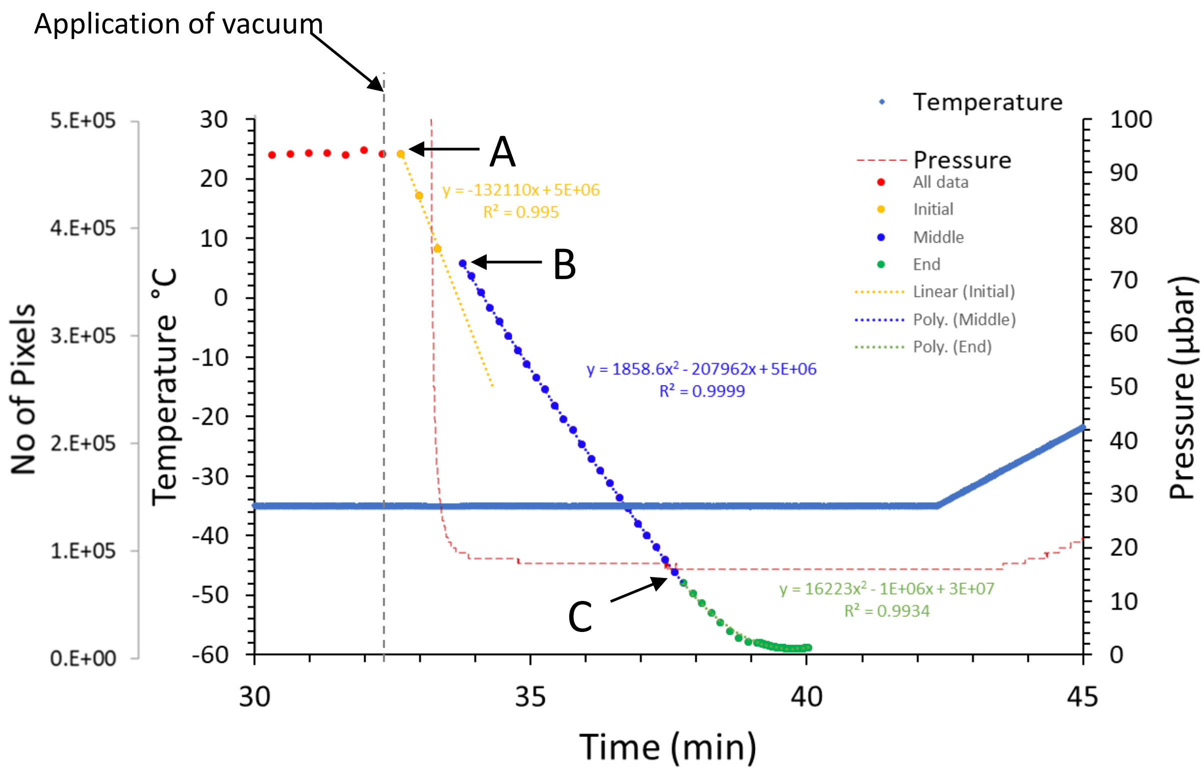
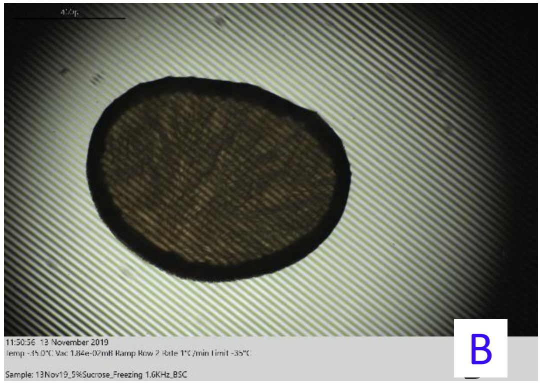
Drying rate at different gradient





NB: Temperature and pressure measured every 100 ms

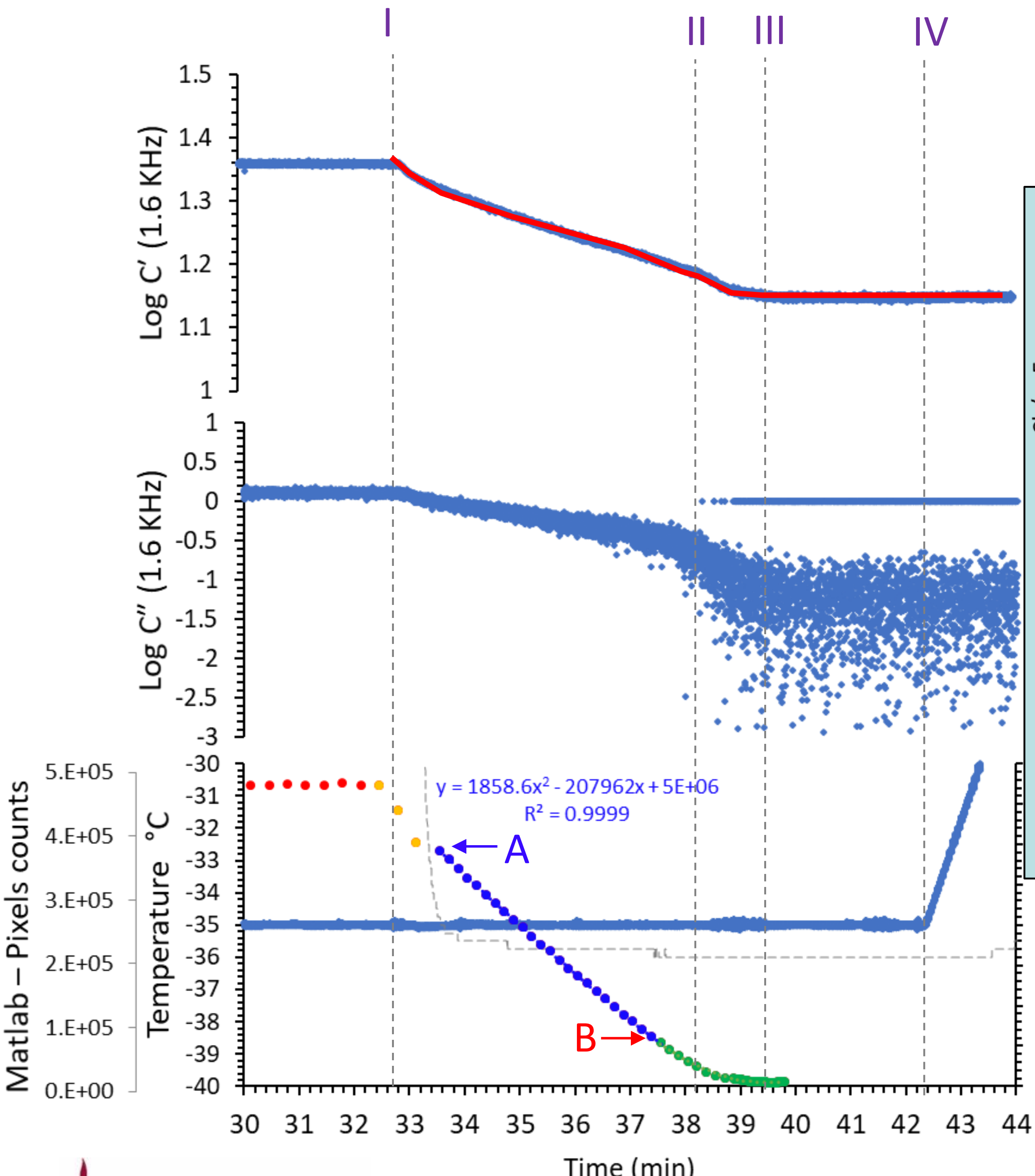
Drying Rates

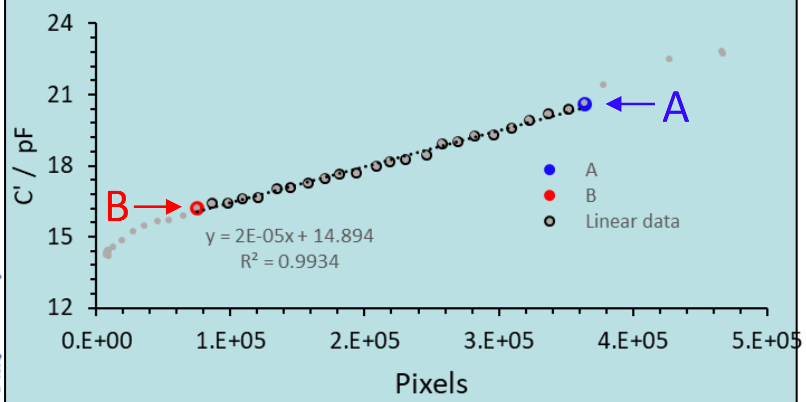
- At A Initial – 0.00080g h^{-1}
- At B: Middle – 0.00050 g h^{-1}
- At C: Middle – 0.00041 g h^{-1}

Freeze drying of 5% sucrose (0.05µL)

Studied by Z-FDM

Drying: Image analysis vs Capacitance during drying of 0.05 µL 5%sucrose





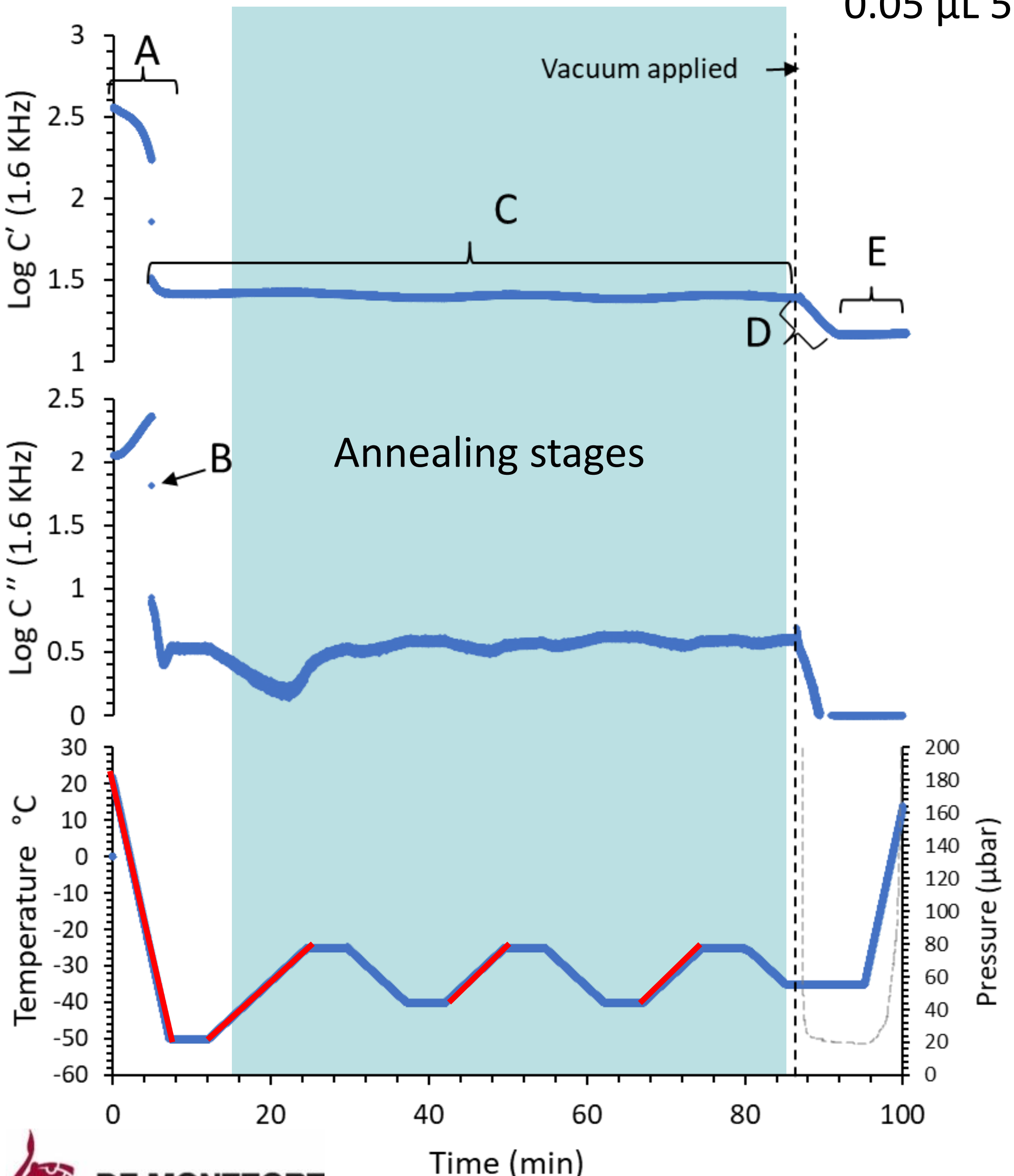
Linear relationship between real part capacitance C' and pixel count (ice content) confirms the opportunity to use Z-FDM for drying rate estimation

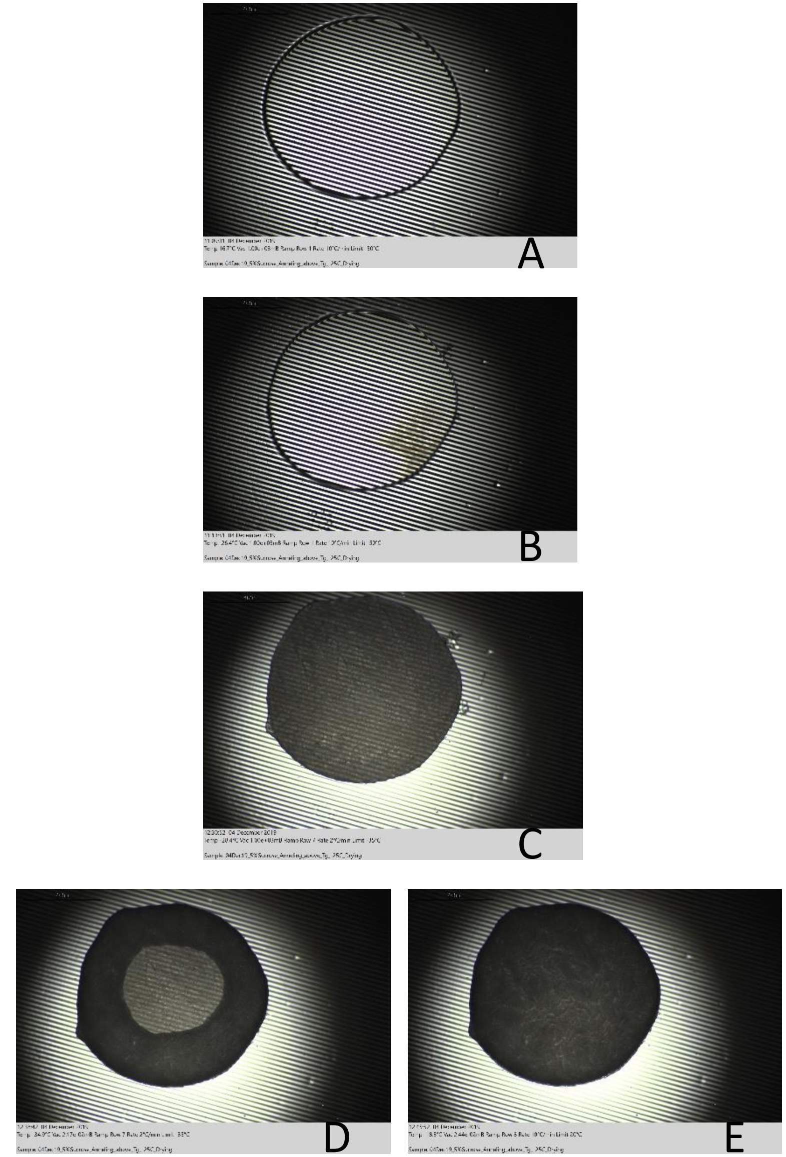
I: Application of vacuum. Primary drying starts
II: Both gradients of imaginary and real part capacitance change towards the end of drying
II : end of primary drying
IV: Ramped to RT and capacitance remains unchanged with temperature

Annealing of 5% sucrose (0.05µL)

Studied by Z-FDM

0.05 µL 5%sucrose **Full process**



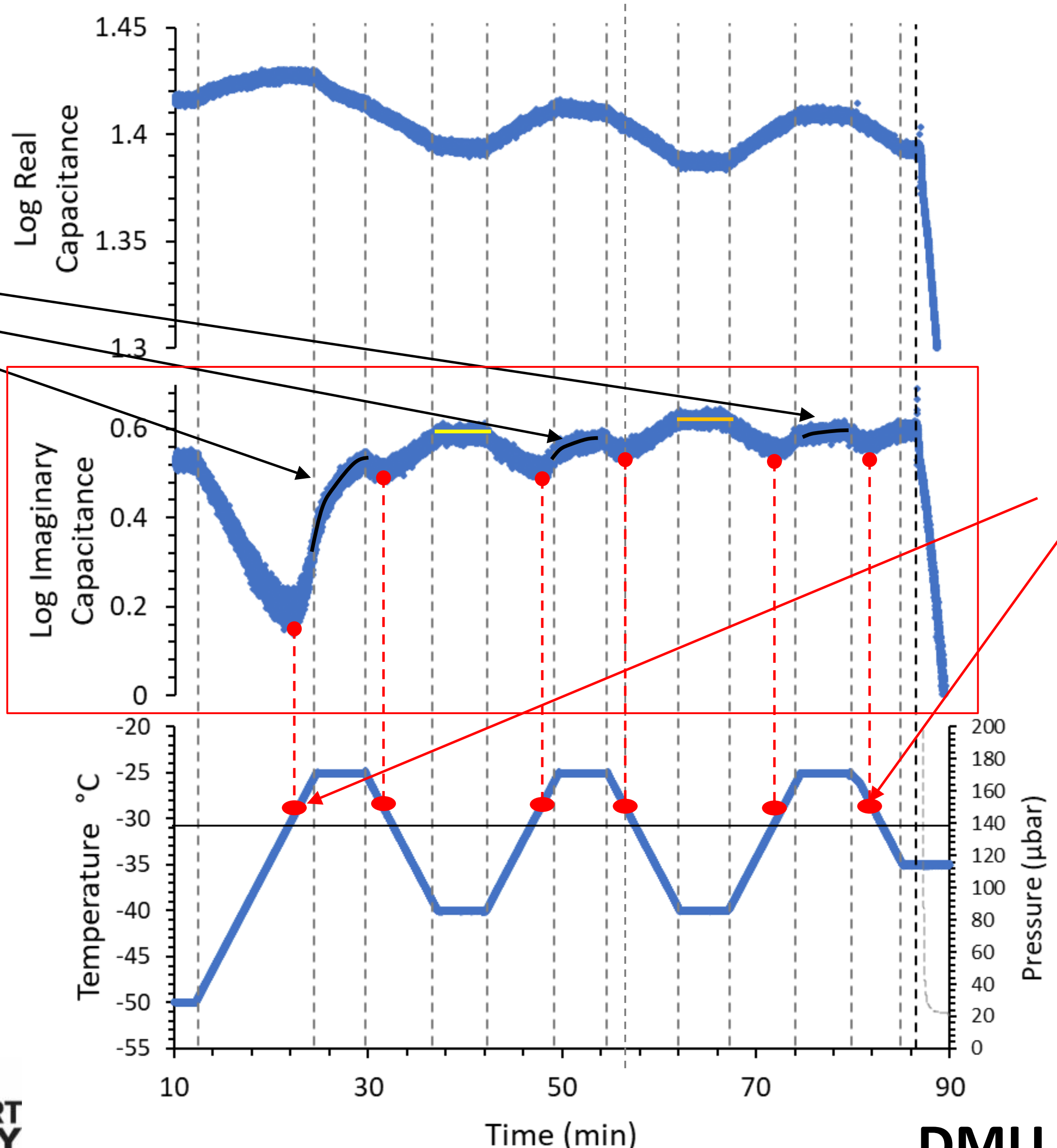


Capacitance data measured at 1.6KHz

Annealing (1.6KHz)

0.05 µL 5%sucrose

Structural changes on re-heating decrease with each annealing



Excursions in temperature just above the glass transition

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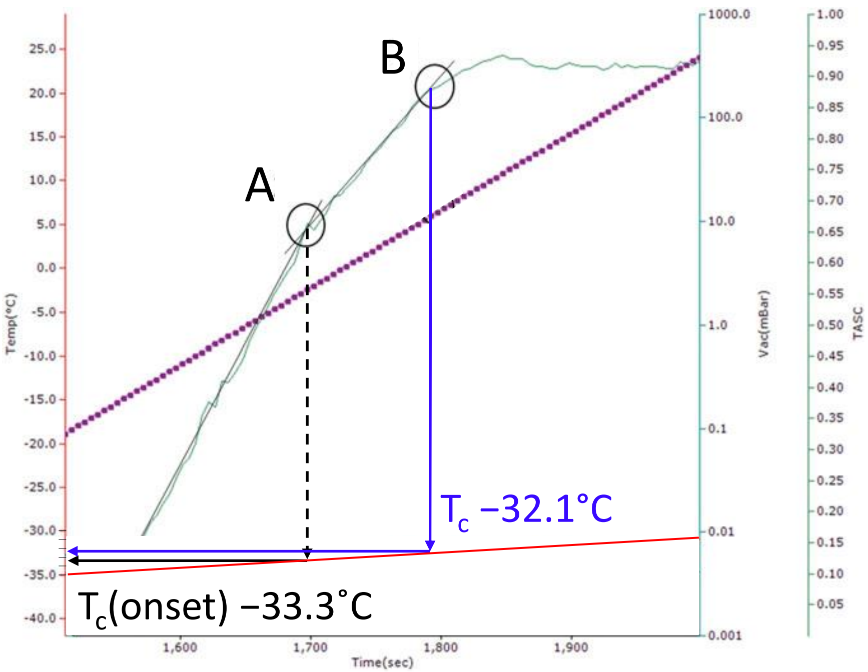
Applications in primary drying : product collapse

Collapse of 5% sucrose (0.5 µL)

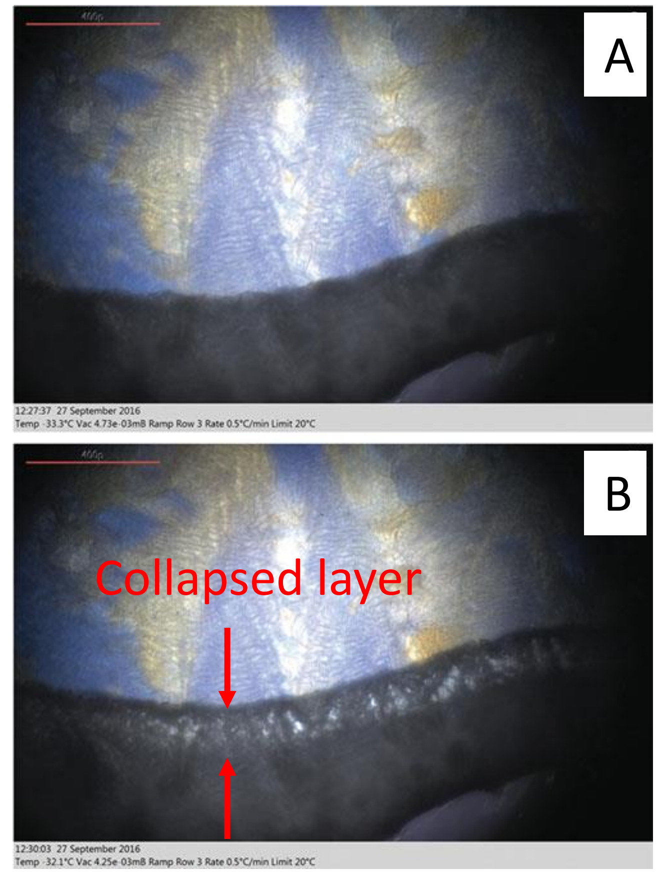
Studied by Z-FDM

TASC – image analysis of sucrose solution

Reduces operator error in the analysis of the collapse temperature and can use for drying rate.

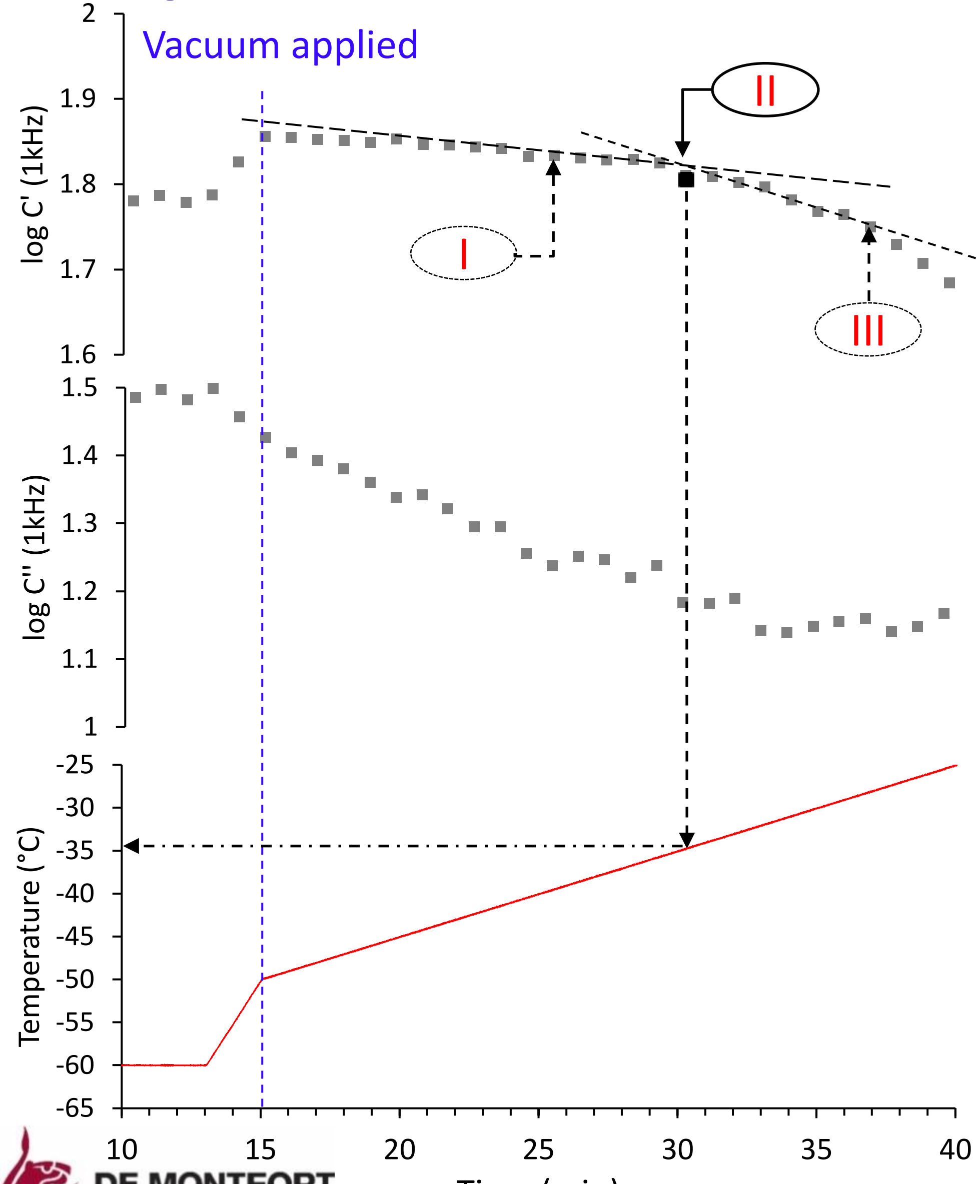


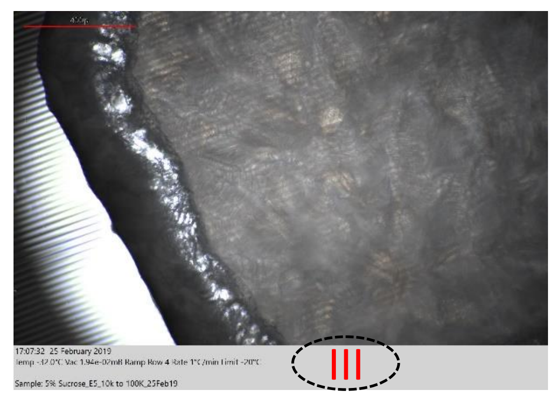
Adapted from: Ward, K. and Matejtschuk, P., 2019. Chapter 1 Characterization of Formulations for Freeze-Drying In: K. R. WARD and P. MATEJTSCHUK, eds, Lyophilization of Pharmaceuticals and Biologicals: New Technologies and Approaches. 1 edn. New York: Humana Press, pp. 1-33.



Images coinciding with TASC features
(A) onset of collapse at −33.3°C, and
(B) full collapse occurring at −32.1°C

Collapse Observation at 1 kHz





NB: 0.5 µl of 5% Sucrose soluiton

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Take home messages (from measurements at 1.6 KHz)

- Real and imaginary part capacitances can be used for the determination of ice nucleation and ice growth rates
- Pixel analysis works for drying rate determination
- Real capacitance has a linear relationship with pixel count, and hence ice mass, so can be used for drying rate determination
- Imaginary part capacitance can be used to study the annealing process but requires further work in order to be able to determine the glass transition temperature.
  - Selection of a higher measurement frequency is likely to provide the answer to the glass transition temperature assessment
- Step changes in drying rate (observed from real part capacitance) can be used to determine the collapse temperature

Acknowledgements

Evgeny Polygalov
TVIS technology development

Dr Yowwares Jeeraruangrattana
Thai Government Pharmaceutical Organization

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Oncolytika

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UCL UKRI Engineering and Physical Sciences Research Council

Prof. Paul Dalby

Thank you for listening

Any questions?

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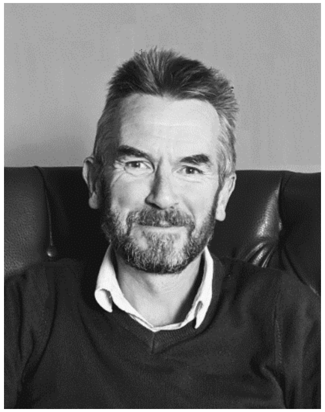
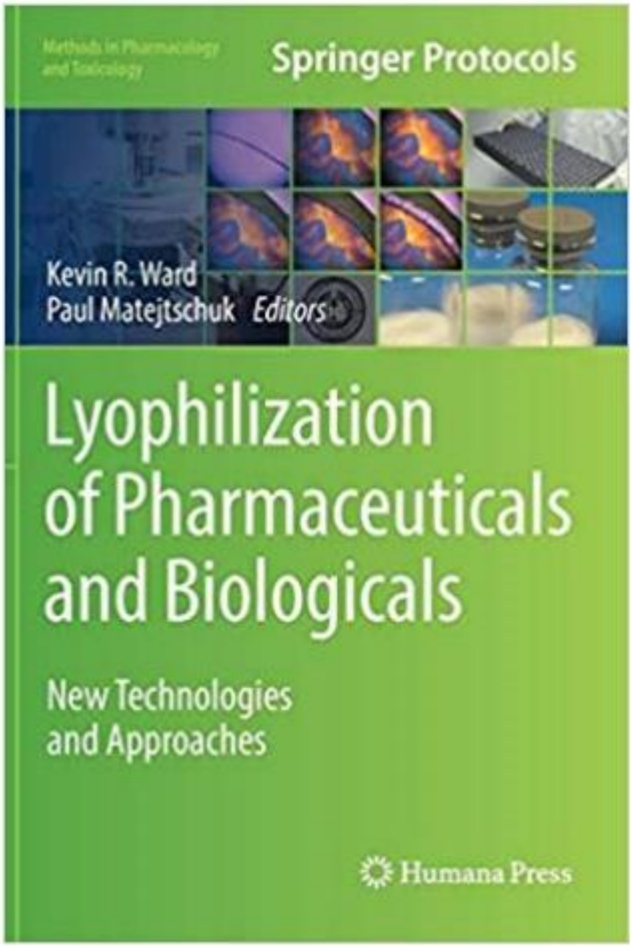


Publications



Chapter 11

Through Vial Impedance Spectroscopy (TVIS): A Novel Approach to Process Understanding for Freeze-Drying Cycle Development

Geoff Smith and Evgeny Polygalov

Abstract

Through vial impedance spectroscopy (TVIS) provides a new process analytical technology for monitoring a development scale lyophilization process, which exploits the changes in the bulk electrical properties that occur on freezing and subsequent drying of a drug solution. Unlike the majority of uses of impedance spectroscopy, for freeze-drying process development, the electrodes do not contact the product but are attached to the outside of the glass vial which is used to contain the product to provide a non-sample-invasive monitoring technology. Impedance spectra (in frequency range 10 Hz to 1 MHz) are generated throughout the drying cycle by a specially designed impedance spectrometer based on a 1 GΩ trans-impedance amplifier and then displayed in terms of complex capacitance. Typical capacitance spectra have one or two peaks in the imaginary capacitance (i.e., the dielectric loss) and the same number of steps in the real part capacitance (i.e., the dielectric permittivity). This chapter explores the underlying mechanisms that are responsible for these dielectric processes, i.e., the Maxwell-Wagner (space charge) polarization of the glass wall of the vial through the contents of the vial when in the liquid state, and the dielectric relaxation of ice when in the frozen state. In future work, it will be demonstrated how to measure product temperature and drying rates within single vials and multiple (clusters) of vials, from which other critical process parameters, such as heat transfer coefficient and dry layer resistance, may be determined.

Key words Impedance spectroscopy, Process-analytical-technology, PAT, Freeze-drying, Lyophilization, Maxwell-Wagner, Polarization, Dielectric relaxation, Ice

Abbreviations

ADC	Analog digital converter
AWG	American wire gauge
BDS	Broadband dielectric spectroscopy
DAQ	Data acquisition card
DSC	Differential scanning calorimetry
DTA	Differential thermal analysis
ER	Electrical resistivity measurements

Kevin R. Ward and Paul Matejtschuk (eds.), *Lyophilization of Pharmaceuticals and Biologicals: New Technologies and Approaches*, Methods in Pharmacology and Toxicology, https://doi.org/10.1007/978-1-4939-8928-7_11,

241

Global Sales of Top 10 Lyophilized Drug Products

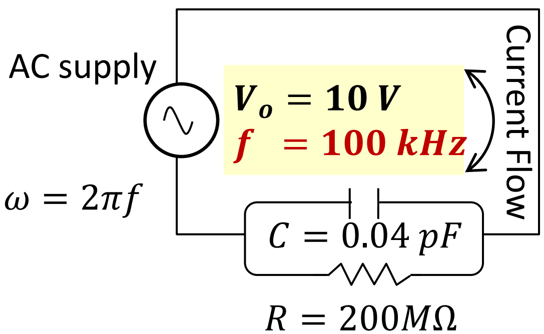
The prevalence of stability challenges for complex APIs and biologics has resulted in more pharmaceutical and biotech manufacturers turning to lyophilization resulting in 13.5% annual growth in freeze-drying over the last five years.

Product Name	API	Indication	Owner	Estimated 2018 Product Sales
Herceptin IV	Trastuzumab	Cancer	Genentech	$7.2B
Keytruda	Pembrolizumab	Cancer	Merck and Co.	$7.2B
Remicade	Infliximab	Rheumatoid Arthritis, Crohn's Disease	Janssen Biotech	$6.4B
Botox	Daxibotulinumtoxin A	Various	Allergan	$3.6B
Carimune NF	Immunoglobulin	Immunodeficiency	CSL Behring	$3.3B
Xolair	Omalizumab	Asthma	Genentech	$3B
Orencia	Abatacept	Rheumatoid Arthritis	Bristol-Myers Squibb	$2.9B
Cosentyx	Secukinumab	Plaque Psoriasis	Novartis AG	$2.8B
Avonex	Interferon beta-1a	Relapsing MS	Biogen	$2.4B
Velcade	Bortezomib	Cancer	Takeda	$2.3B

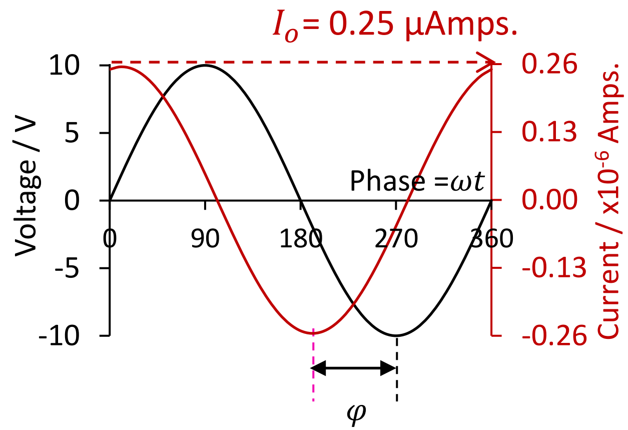
https://lubrizolcdmo.com/blog/lyophilization-of-pharmaceuticals-an-overview/

Impedance Spectroscopy

Oscillating voltage $V(t)$ of fixed angular frequency ω applied to the test object



Resultant current $I(t)$ and phase shift φ measured



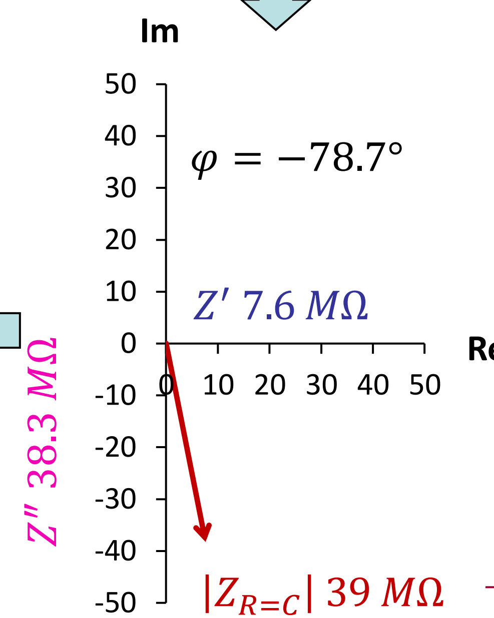
Complex impedance ($\mathbf{Z}$) determined as the ratio of the voltage vector $V(t)$ to the current vector $I(t)$

$$|\boldsymbol{Z}_{\boldsymbol{R=C}}| = \sqrt{(Z')^2 + (Z'')^2}$$

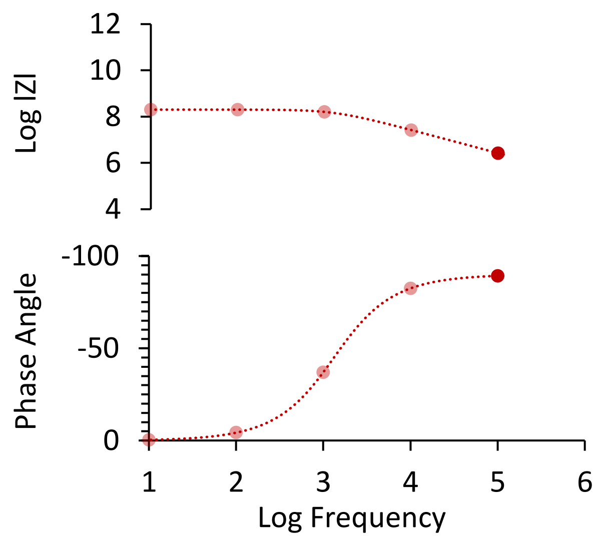
$$Z' = \frac{RX_C^2}{R^2 + X_C^2} \qquad Z'' = \frac{R^2 X_C i}{R^2 + X_C^2}$$

$$|\boldsymbol{Z}_{\boldsymbol{R=C}}| = \sqrt{(7.6)^2 + (38.3)^2}$$

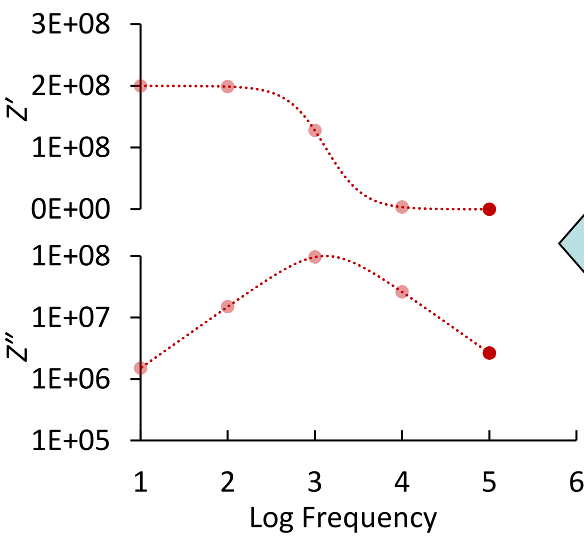
$$= 39\ \mathrm{M\Omega}$$



Argand diagram



$\boldsymbol{f = 100\ kHz}$



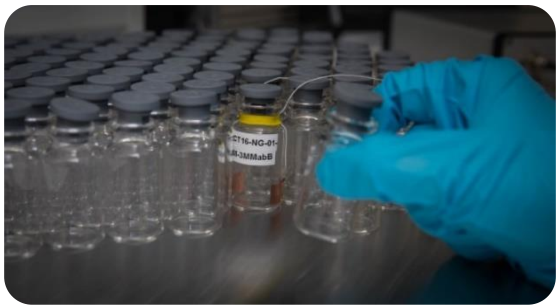
$\boldsymbol{f = 100\ kHz}$

Through-Vial Impedance Spectroscopy

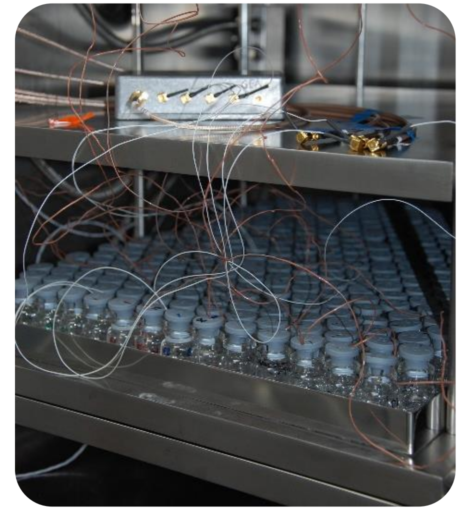
Single-vial PAT

Multichannel (5)

Non- perturbing to packing of vials



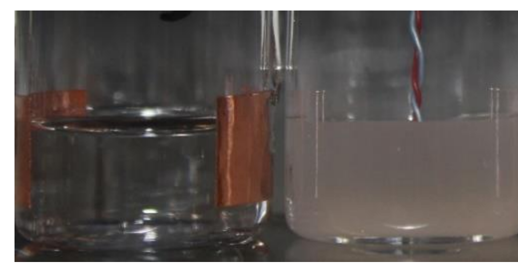
Thin (0.533 mm)
flexible cables
(0.5 - 2 m length)
Stoppering unaffected



Temperature calibration
using nearest neighbour vial(s)

Low thermal mass
electrodes
no interference with heat
transfer & drying rates

plain TVIS TC vial



Non-sample invasive
no impact on ice nucleation

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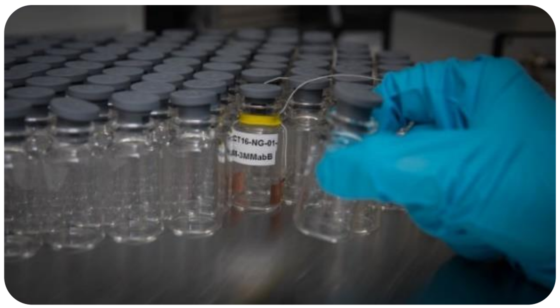
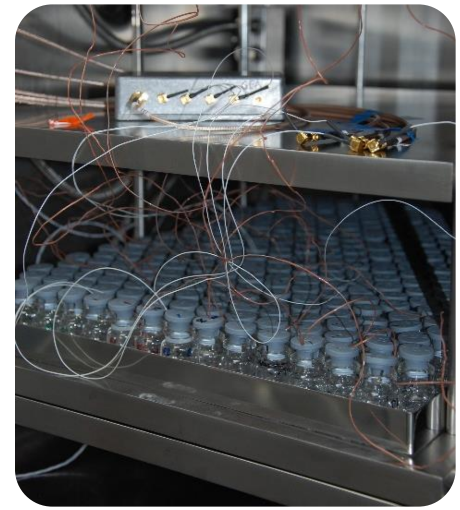
Through-Vial Impedance Spectroscopy

Single-vial PAT

Multichannel (5)

Non- perturbing to packing of vials





Thin (0.533 mm)
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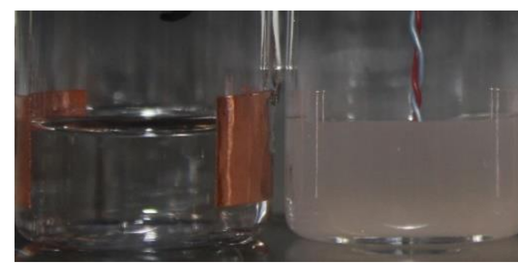
Temperature calibration
using nearest neighbour vial(s)

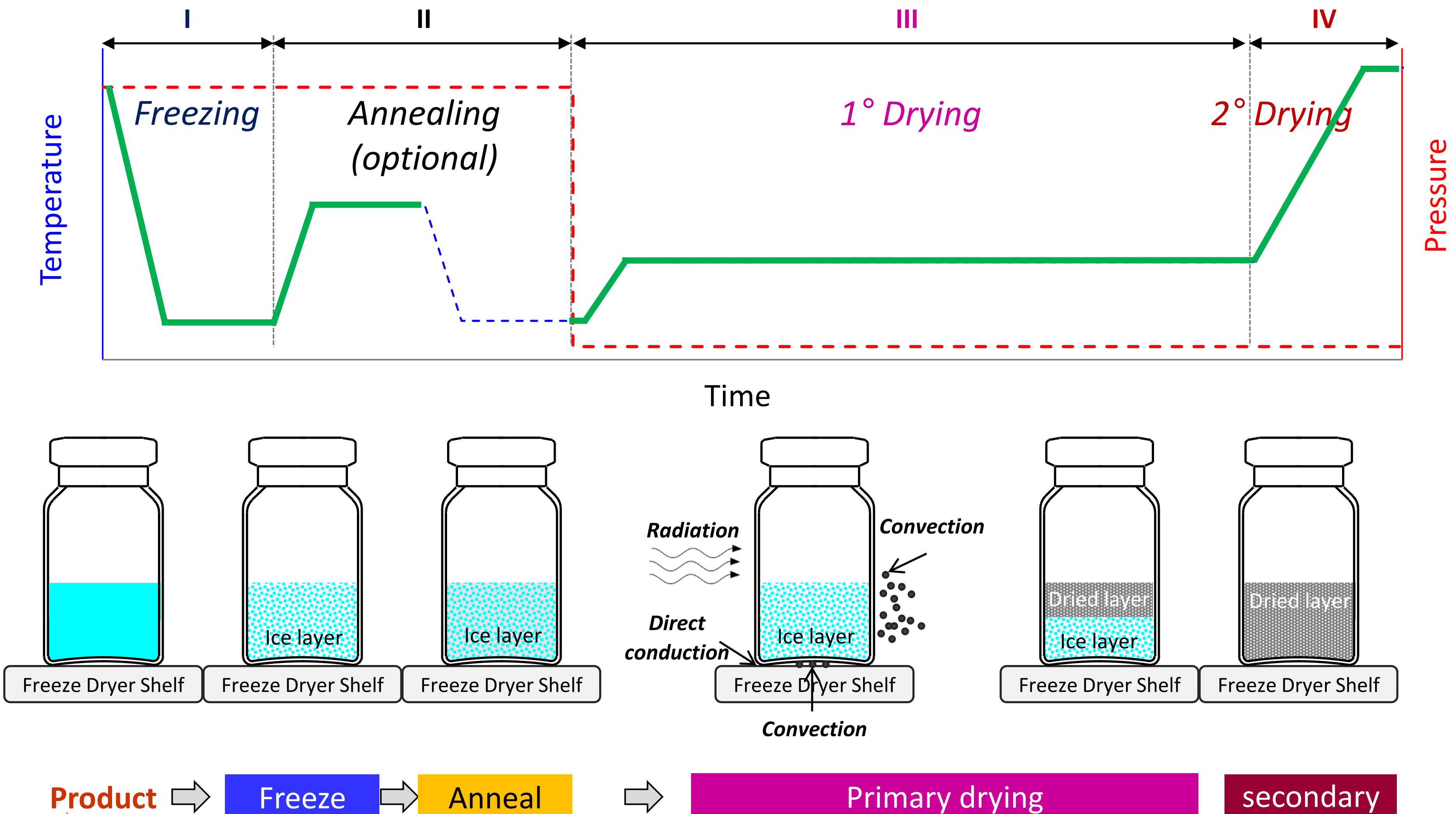


Non-sample invasive
no impact on ice nucleation

Low thermal mass
electrodes
no interference with heat
transfer & drying rates

plain TVIS TC vial

Freeze-drying

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