DE MONTFORT UNIVERSITY LEICESTER

Recent Advances in Through Vial Impedance Spectroscopy (TVIS) for Process Parameter Determination

Geoff Smith
Leicester School of Pharmacy, De Montfort University, United Kingdom

LyoTalk Dublin, May 22 2017

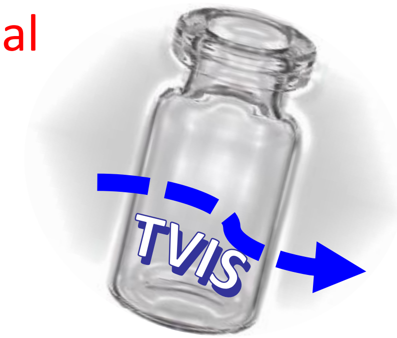
Outline

- Through Vial Impedance Spectroscopy (TVIS)
  - Description of Measurement System
- TVIS Application in Freezing
  - Ice Formation and phase separation
- TVIS Application in Annealing
  - Surrogate Temperature Calibration
- TVIS Application in Primary Drying
  - Drying Rate
  - Product Resistance (R_P)
  - Micro-collapse
- Acknowledgements

Through Vial Impedance Spectroscopy (TVIS)
Description of Measurement System

Introduction to the TVIS System

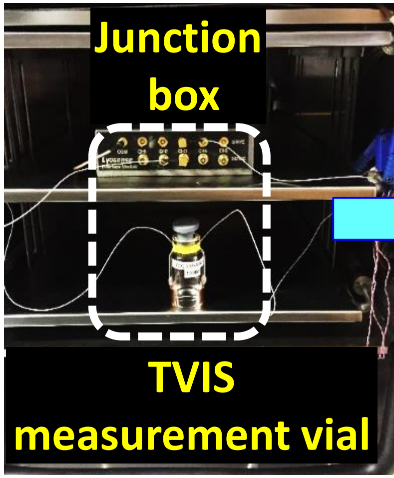
- Impedance measurements across a vial rather than within the vial
- Hence “**Through Vial Impedance Spectroscopy**”

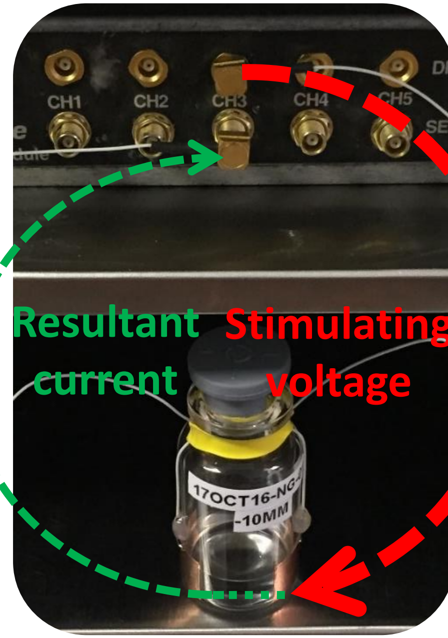


- Features
  - Single vial “non-product invasive”
  - Both freezing and drying characterised in a single technique
  - Non-perturbing to the packing of vials
  - Stopper mechanism unaffected

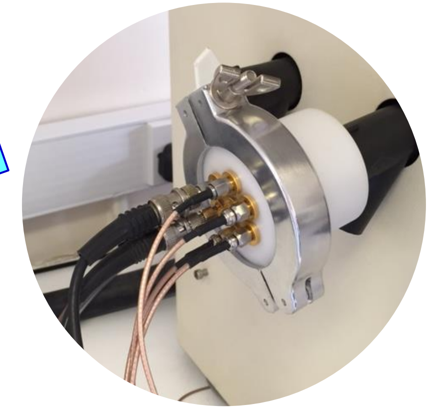
SV product temperature	
SV sublimation rate	
SV end point (At-Ap!)	

Freeze drying chamber

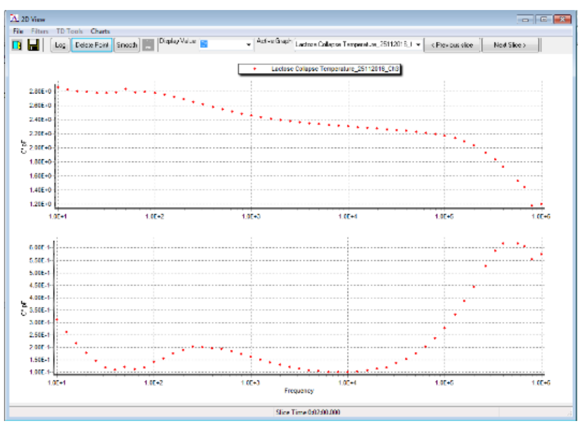




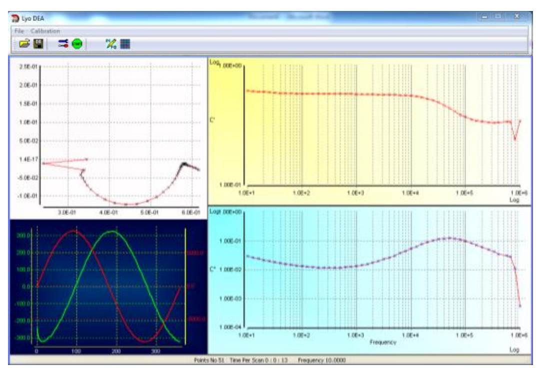
Pass through



LyoView™ analysis software



LyoDEA™ measurement software

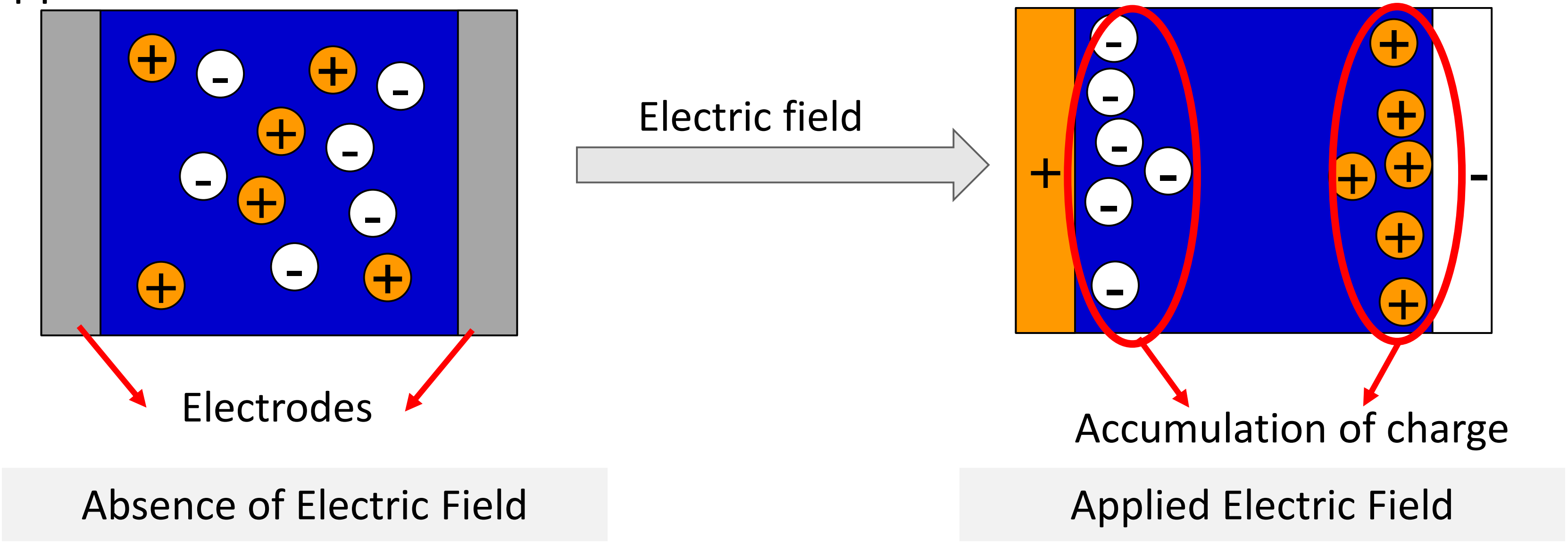


TVIS system (I to V convertor)

Through Vial Impedance Spectroscopy (TVIS)
Theory

Interfacial Polarization Phenomena

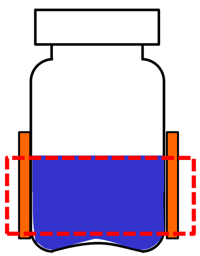
- Interfacial or space charge polarization is one type of dielectric polarization.
- It refers to the accumulation of charges at an interface between two dielectric materials or between two regions within a material when an external field applied.

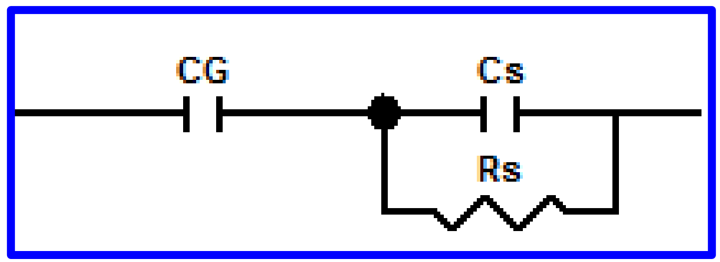


- This phenomenon occurs when an electric field is applied to a glass vial (a dielectric material) containing a liquid and/or solid (a dielectric material with some conductivity).

Equivalent electrical circuit model

- An equivalent electrical circuit model is created by combining the circuit elements which includes the solution resistance (R_s) and the the capacitances of the glass-solution interface (C_G) and the solution (C_s) in an appropriate configuration of series and parallel elements.





C_G is the capacitance of the glass-solution interface,
C_S and R_S are the capacitance and resistance of the solution

$$Z_{Total} = Z(C_G) + Z(R_s = C_s)$$

$$Z_{Total} = Z(C_G) + [\frac{1}{Z(R_s)} + \frac{1}{Z(C_s)}]$$

Dielectric loss spectrum

- As the frequency increase, C'' increases to maximum (C''_{max})

$$C''_{peak} = \frac{C_G^2}{2(C_S+C_G)}$$

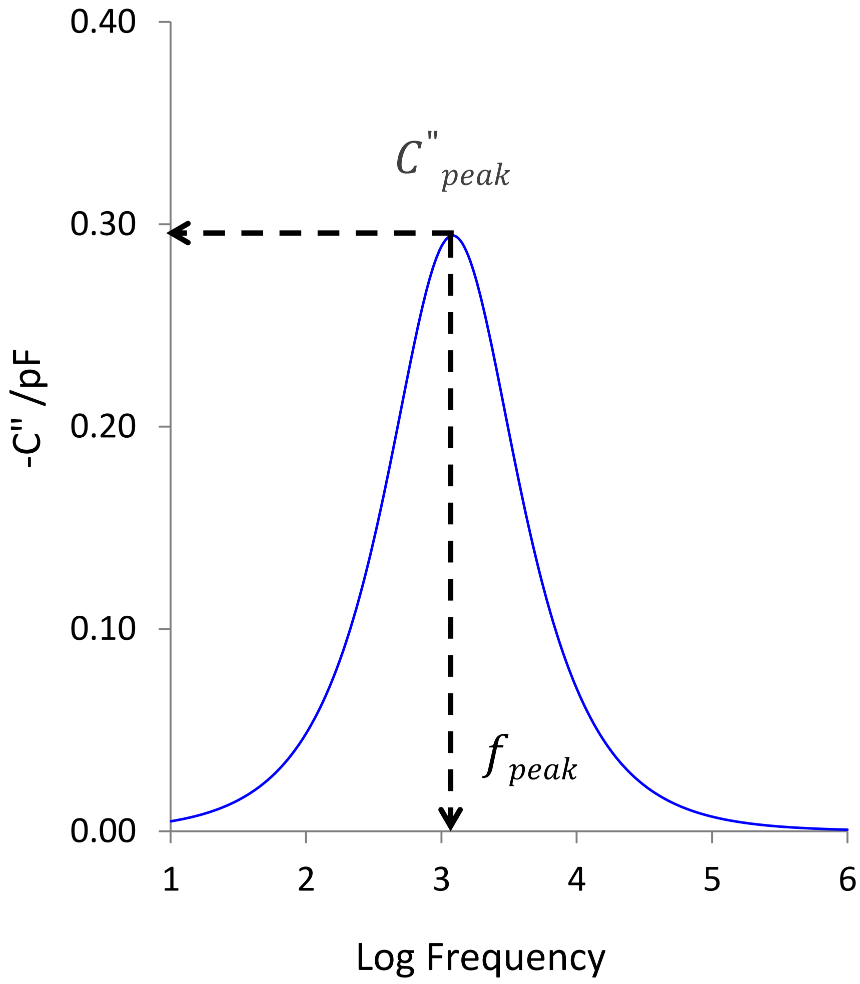
- a frequency of

$$F_{peak} = \frac{1}{2\pi R_S(C_S + C_G)}$$

- If C_G > C_S then

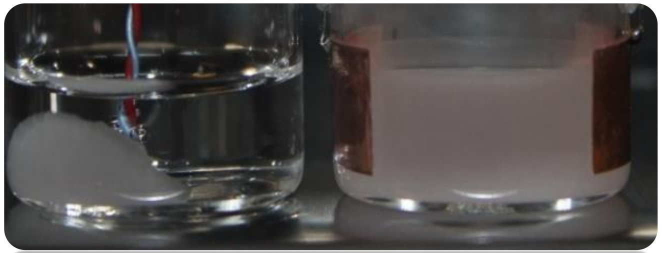
$$C''_{peak} \cong C_G$$

- Which explains the sensitivity of C''_{peak} to the height of the ice layer



TVIS Applications

Freezing, Annealing, Primary Drying

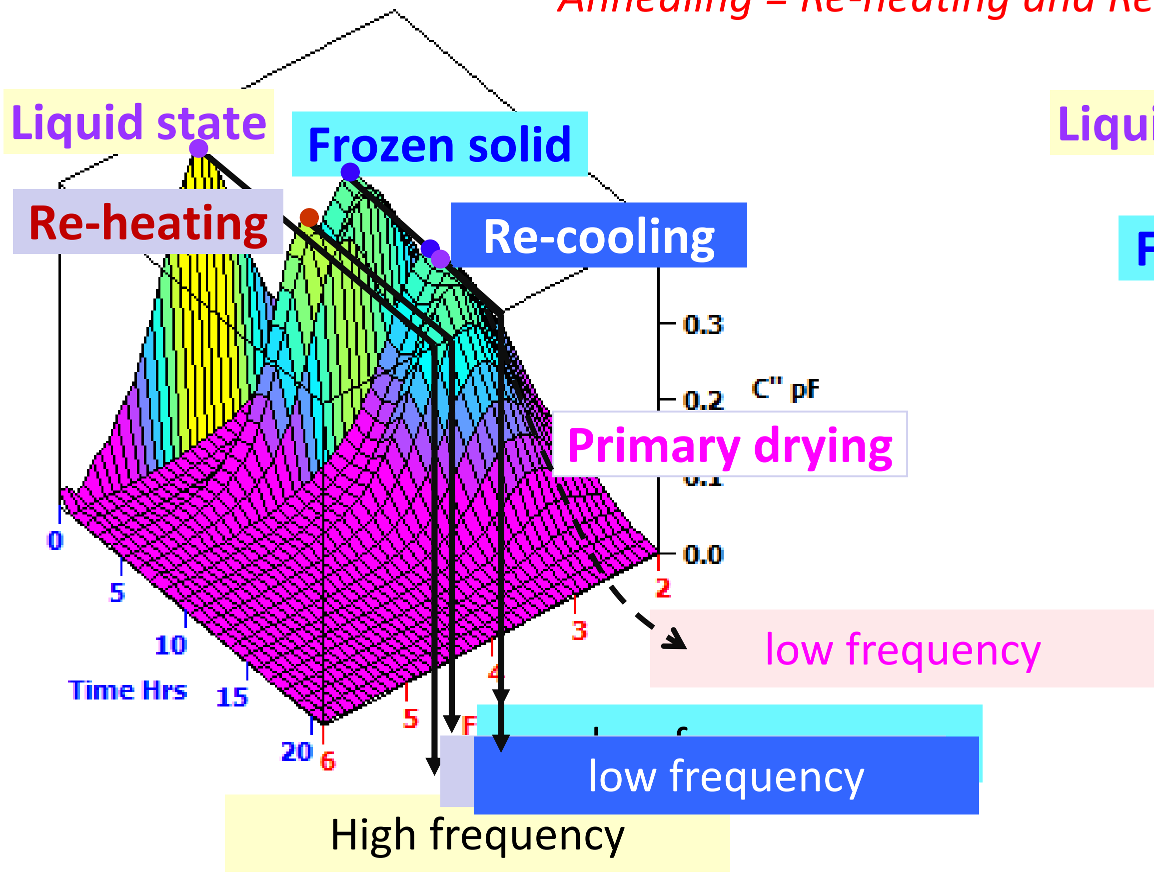


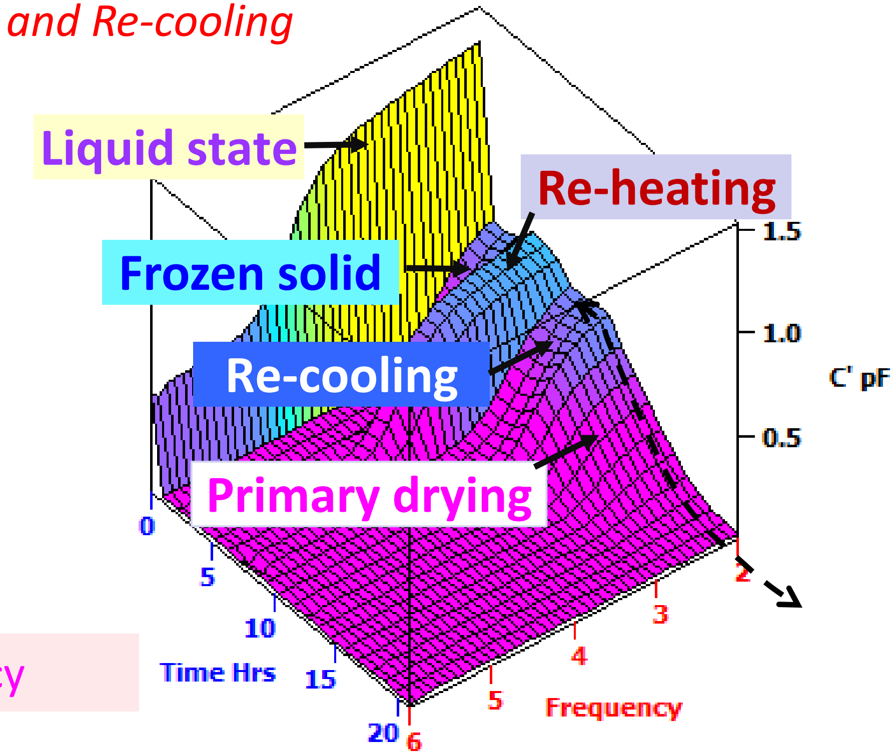
TVIS Response Surface

Imaginary Part of Capacitance

Real Part of Capacitance

Annealing = Re-heating and Re-cooling





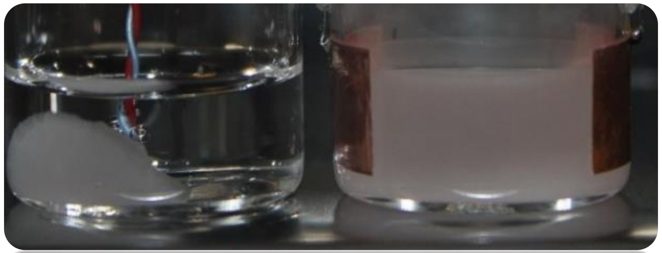
Through Vial Impedance Spectroscopy (TVIS)

- The capacitance spectrum depends on both the *electrical resistance and electrical capacitance of the vial contents.*
- Data viewing software (LyoView ™) identifies the peak frequency (F_{PEAK}) and peak amplitude (C''_{PEAK}) in the imaginary part of the capacitance spectrum from which various physical properties can be determined

TVIS parameter	**Application**	**Notes (requirements/assumptions)**
F_{PEAK}	**temperature & phase** (ice & eutectic formation, phase separation)	F_{PEAK} temperature calibration (annealing stage required)
$d\,C''_{PEAK}\,/dt$	**drying rate** surrogate	80% of 1º drying (assumes flat ice front)
C' (~ 100 kHz)	**end point** of 1º drying	C' (real part of the complex capacitance) is highly sensitive to low ice volumes

TVIS Application
Freezing Step

5%w/v Lactose in deionised water



The relationship between F_{PEAK} and Product Temperature/Phase Behaviour

- Both resistance and capacitance parameters impact the peak frequency

$$F_{peak} = \frac{1}{2\pi \boldsymbol{R}_S (C_S + C_G)}$$

- However the sample resistance ($\boldsymbol{R}_S$) has a greater temperature coefficient so the peak frequency is especially sensitive to the electrical resistance of the product.

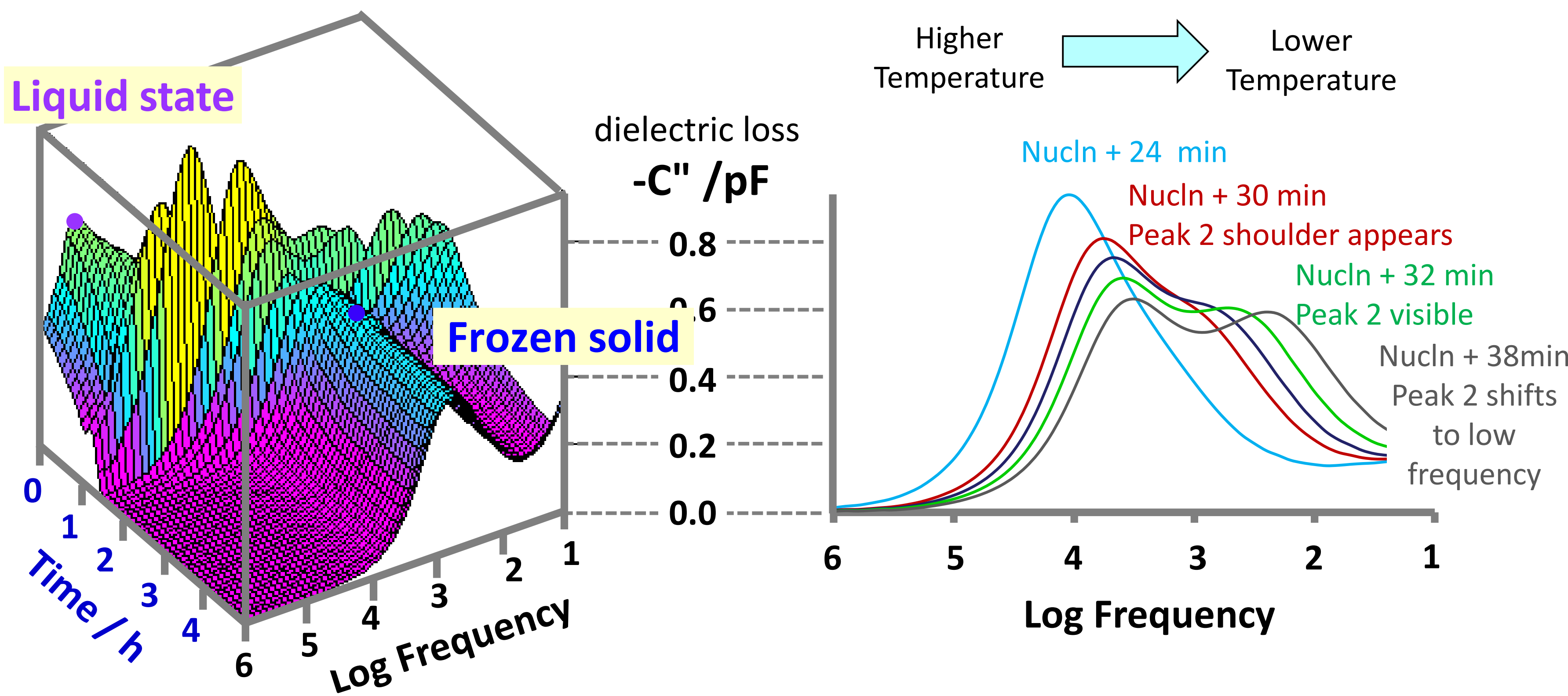
- It follows that F_{PEAK} can be used to monitor (i) the phase behaviour and (ii) the temperatures of both the liquid and solid states.

- During the solidification process the increased resistance of the frozen phase shifts the peak frequency (F_{PEAK}) by two orders of magnitude.

- During the annealing of the frozen phase, a temperature ramp of 40 ^{o}C can shift the peak frequency (F_{PEAK}) by one order of magnitude.

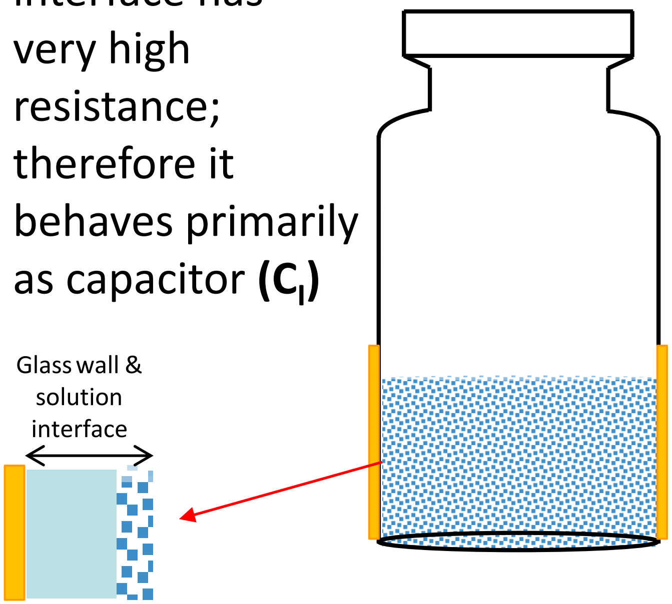
Phase separation

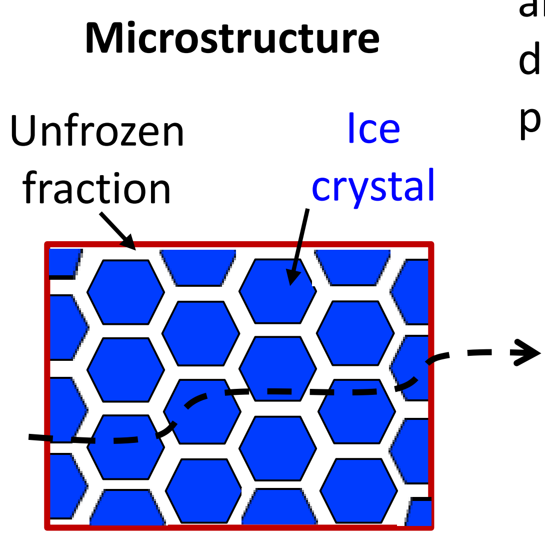
Freezing Step



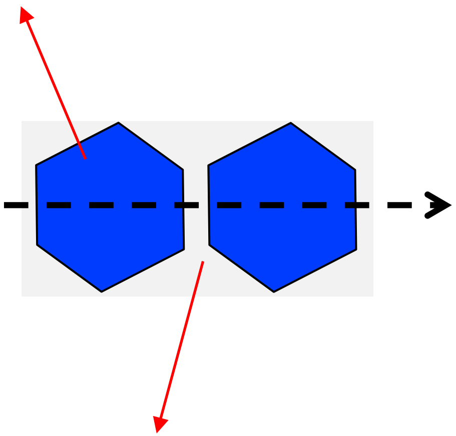
Ice and the unfrozen fraction

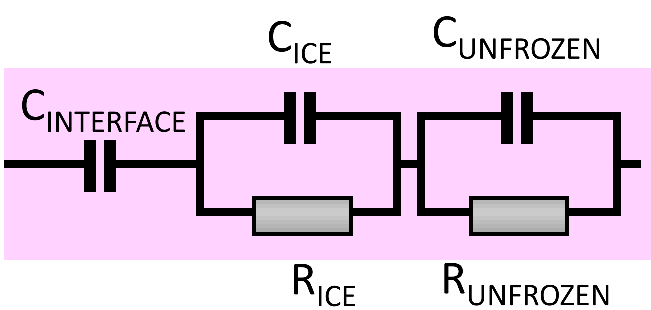
The glass interface has very high resistance; therefore it behaves primarily as capacitor **(C_I)**





Ice has a conductivity **(R_{ICE})** and dielectric constant **(C_{ICE})** due to the percolation of protons (H^+)

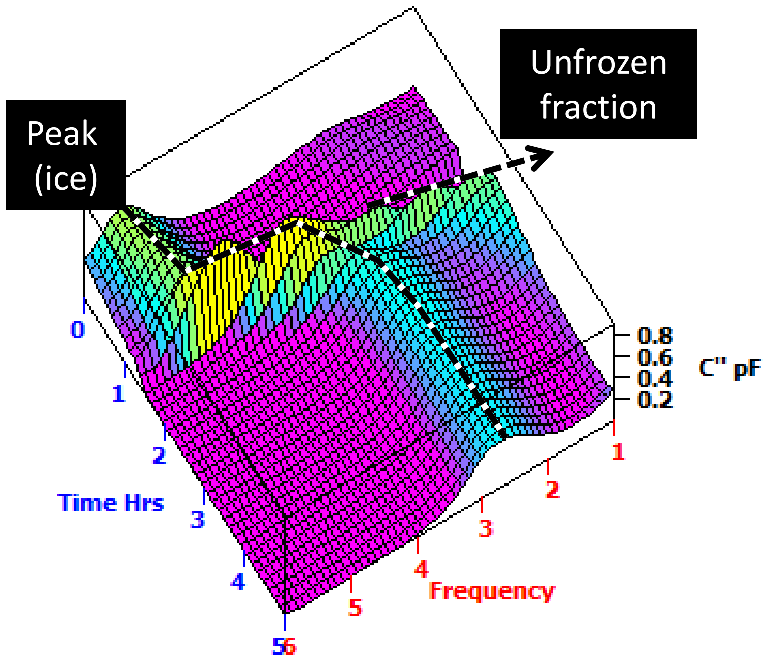


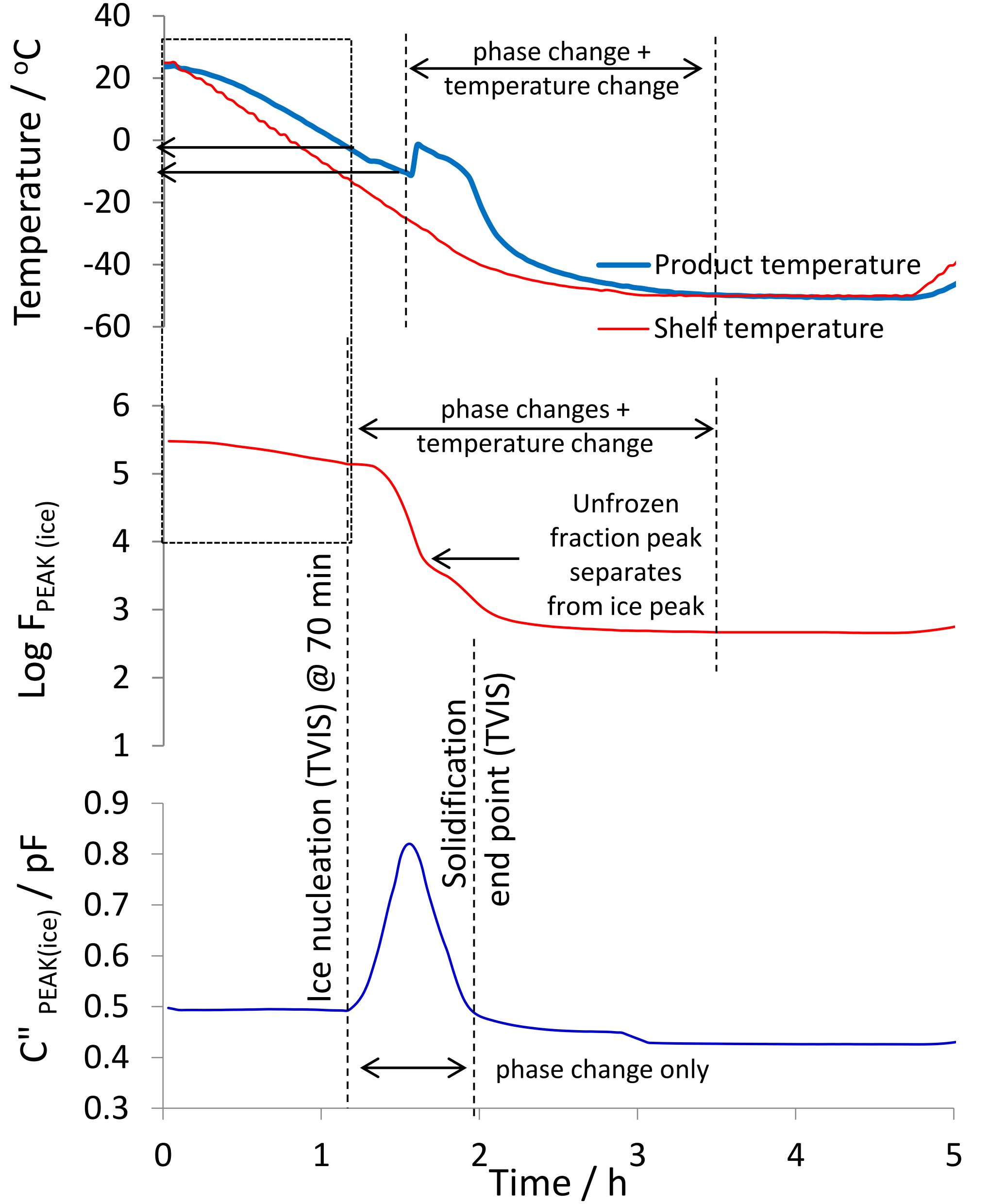


A layers of unfrozen fraction between the ice crystals have dielectric constants and a conductivities which are reflected in $C_{UNFROZEN}$ and $R_{UNFROZEN}$, respectively.

The latter is strongly dependent on mobile charge carriers and hence very sensitive to the viscosity (temperature and water content) of the unfrozen fraction .

Ice Formation

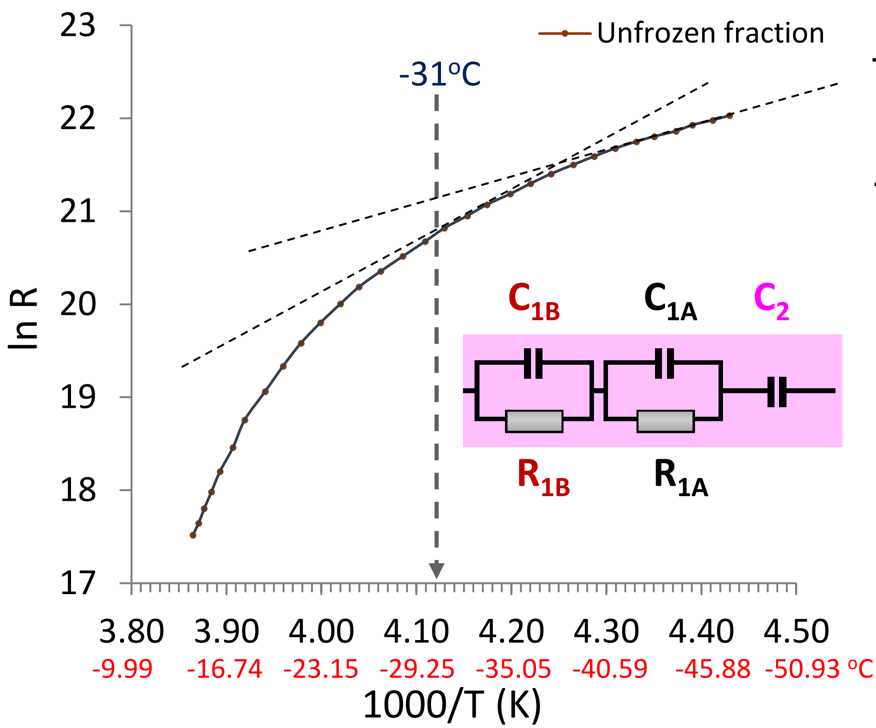


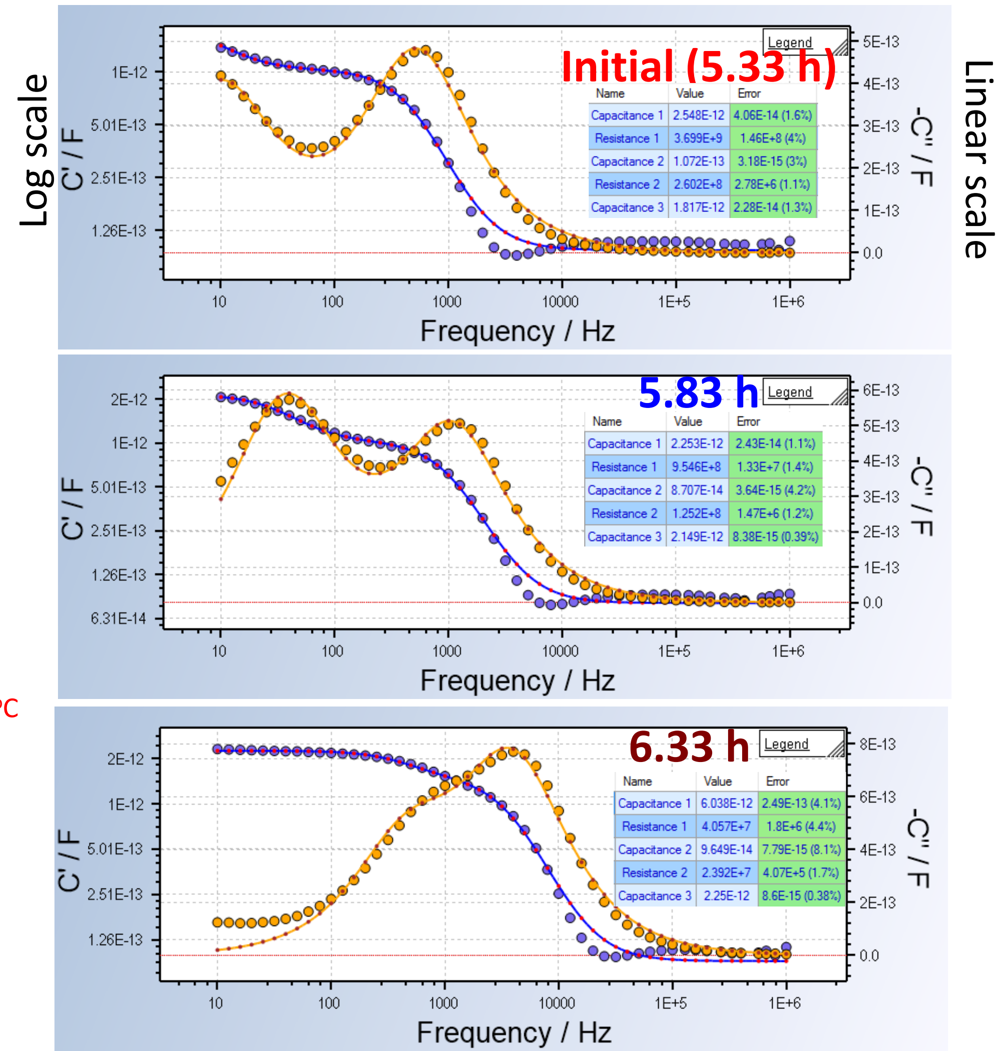


- The thermocouple vial nucleates later than the TVIS vial
- C''_{PEAK} may provide a more reliable end point for solidification

Glass Transition (T_g') Determination

5% w/v Lactose solution

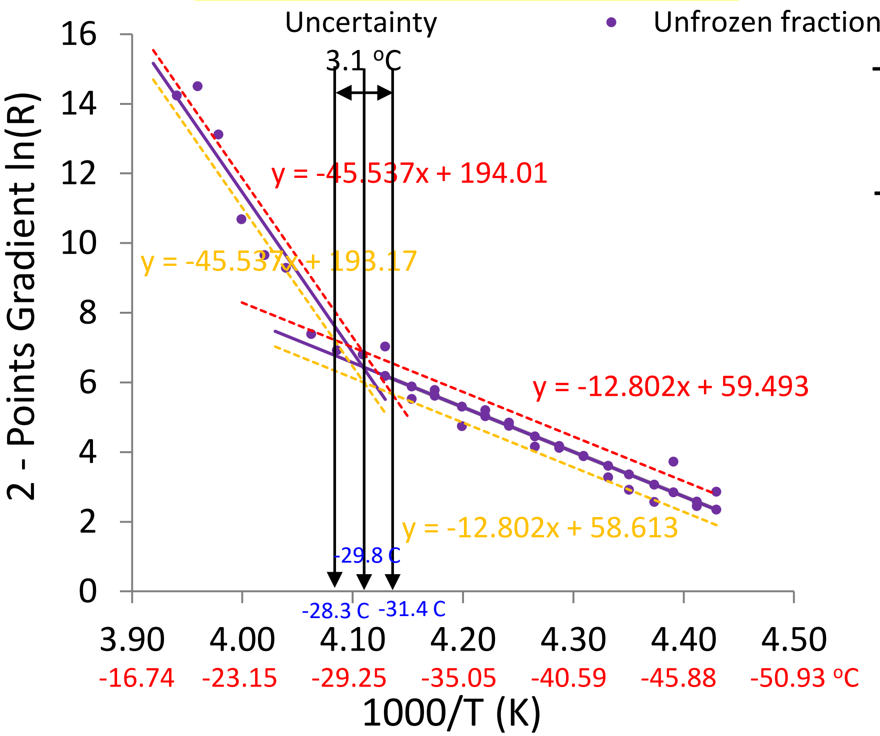


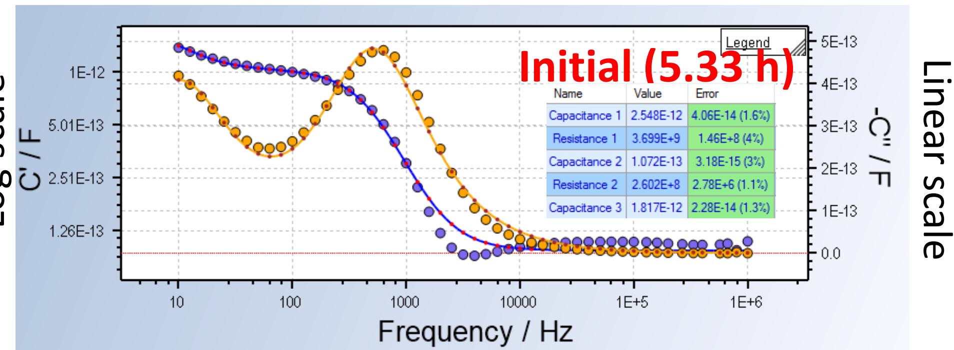


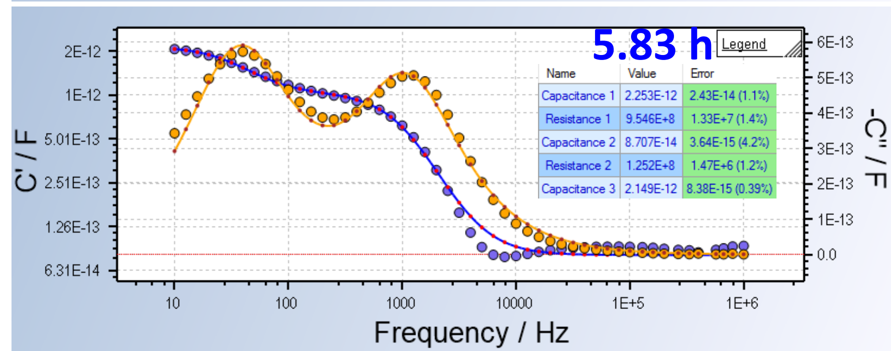
- Below T_g' the changes in product resistance follows Arrhenius
- Above T_g' VTF function models the resistance profile.

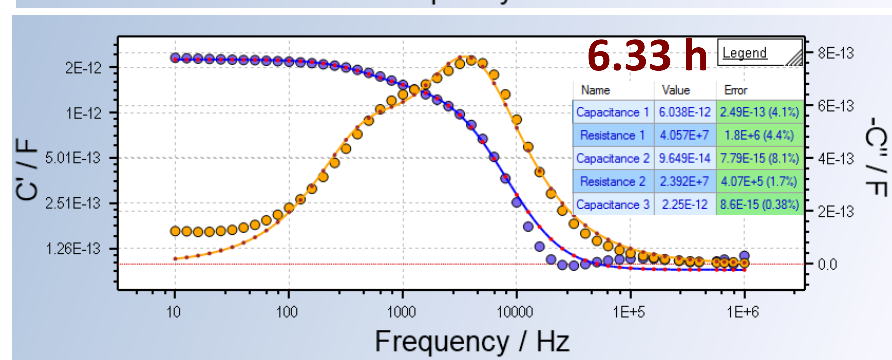
Glass Transition (T_g') Determination

5% w/v Lactose solution









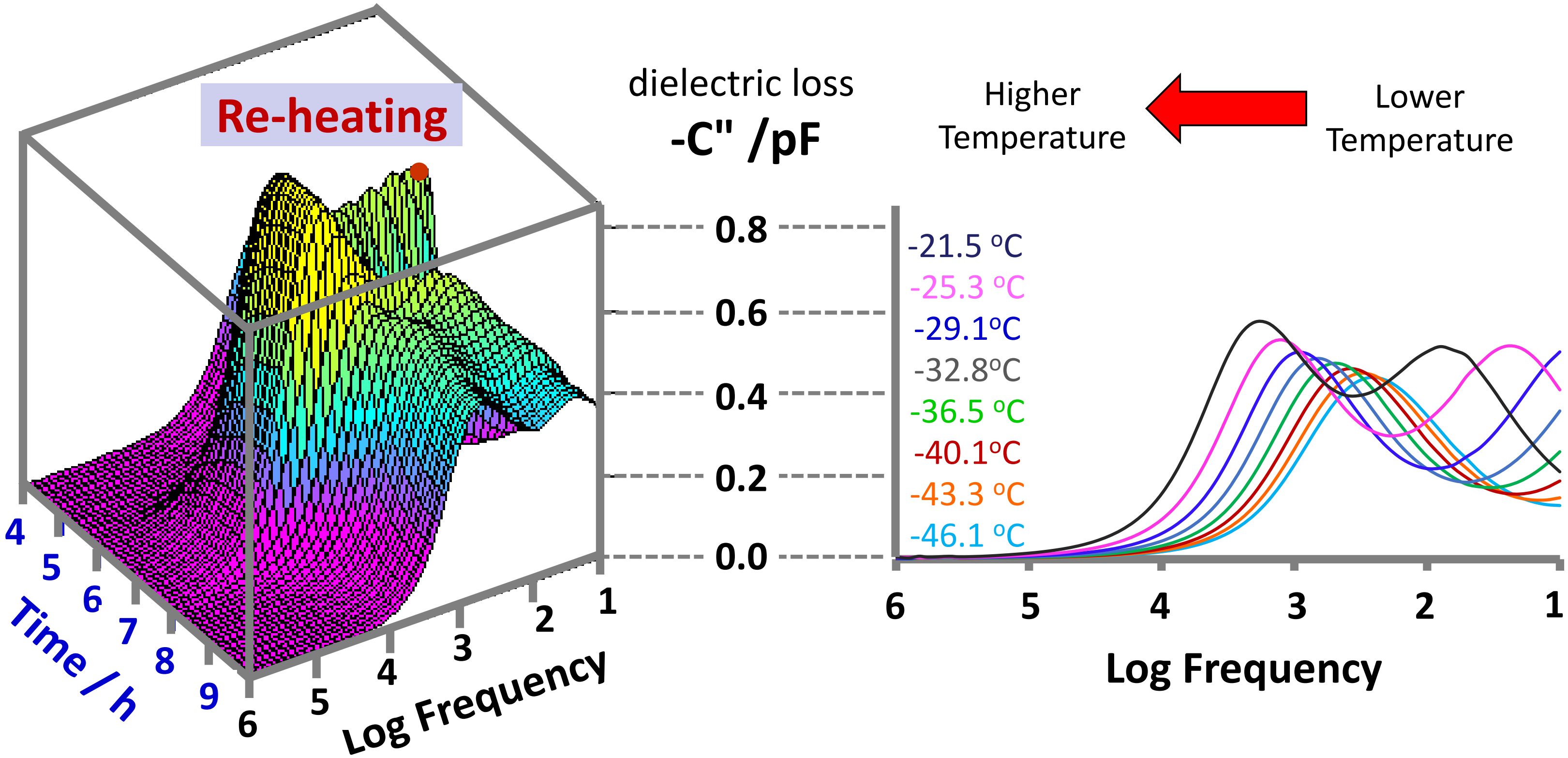
- Below T_g' the changes in product resistance follows Arrhenius
- Above T_g' VTF function models the resistance profile.

TVIS Application
Annealing for Temperature Calibration

5%w/v Lactose in deionised water

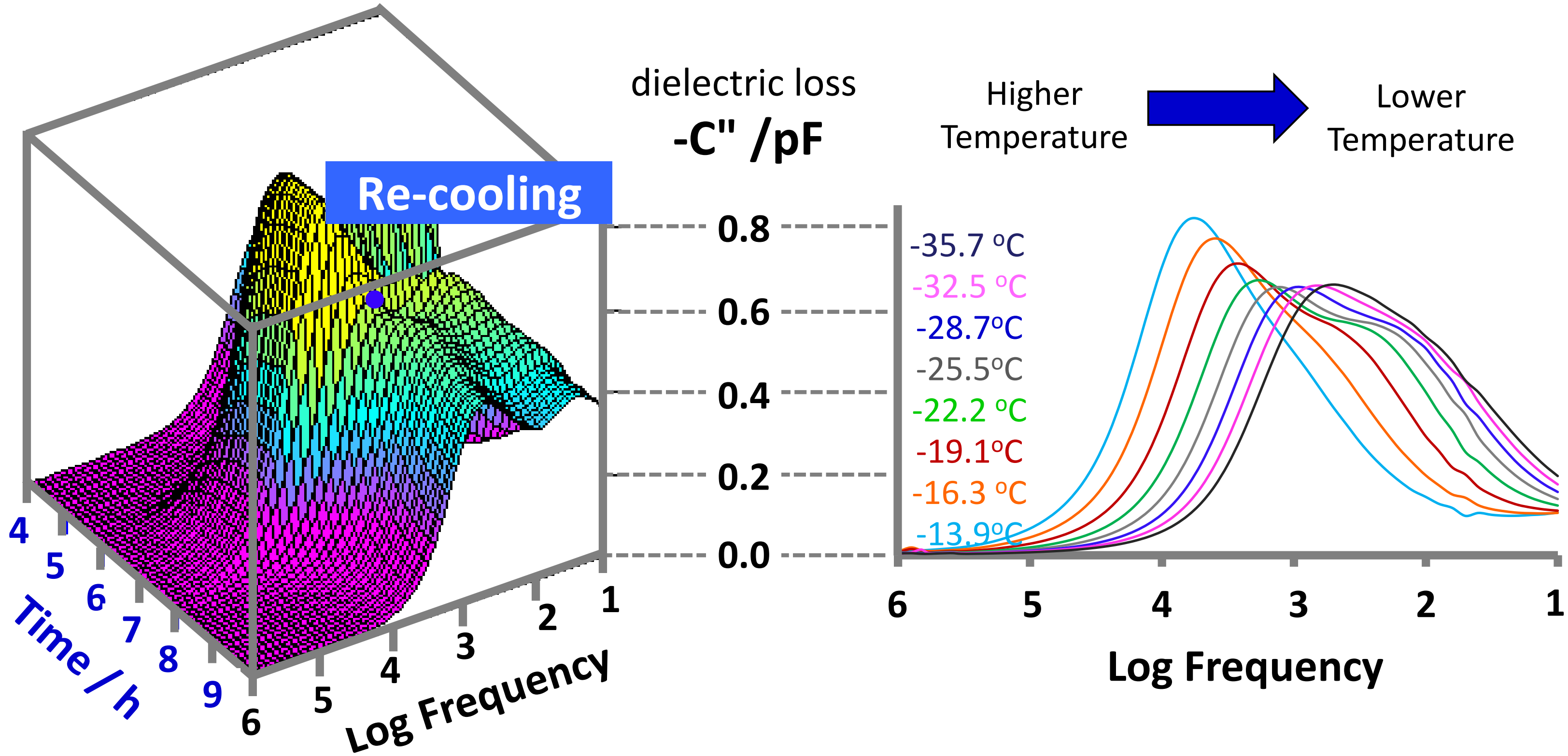
The relationship between F_{PEAK} and Product Temperature/Phase Transition

Re-heating

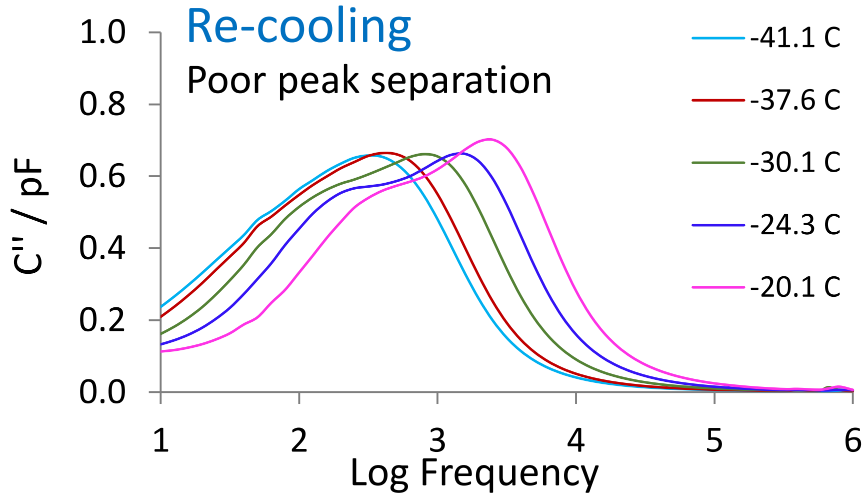


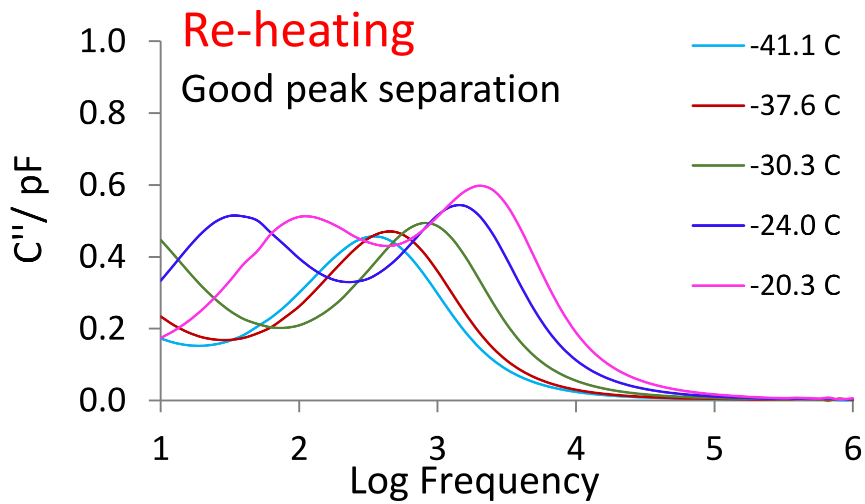
The relationship between F_{PEAK} and Product Temperature/Phase Transition

Re-cooling



Temperature  Calibration





Re-cooling

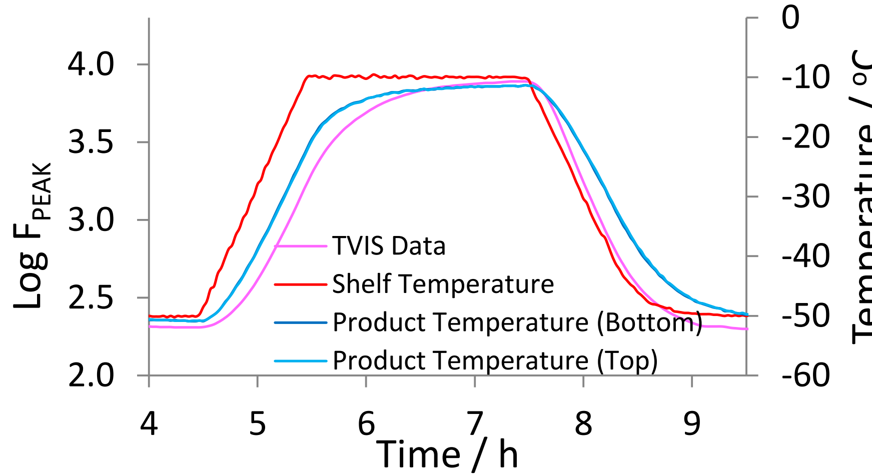
- At low temperatures, the two peaks are merged, forming one peak below –35 C.
- At higher temperatures > – 20 C the two curve separate to some degree

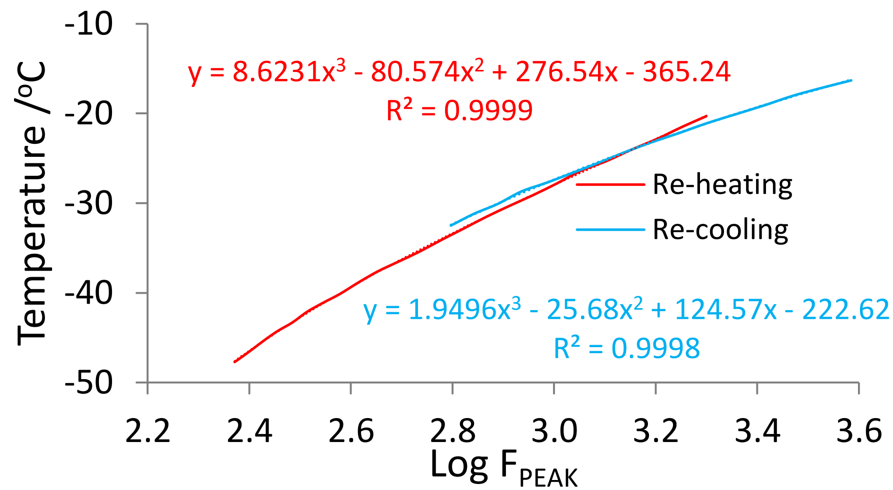
Re-heating

- The two peaks on re-heating are well separated at all temperatures between – 20 C and – 50 C

Temperature  Calibration

- Thermal homogeneity of the frozen solid demonstrated by two TCS (top and bottom)
- F_{PEAK} profile during annealing has 'similar' profile with product temperature.
- Assuming thermal equivalence between the TC and TVIS vial (?!!) then temperature calibration from annealing might be employed for the prediction of temperature during primary drying
- Re-heating curve selected because of the wider range of temperatures for the observation of a single peak

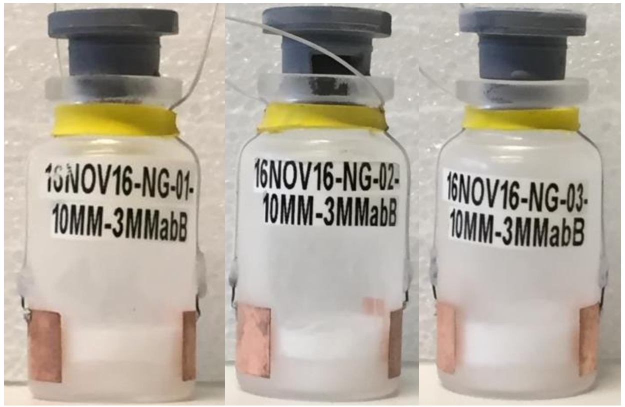




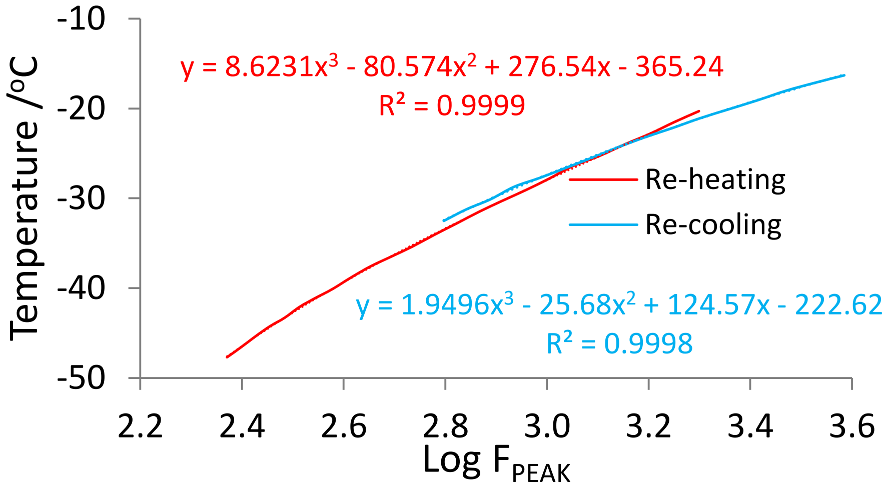
5%w/v Lactose in deionised water

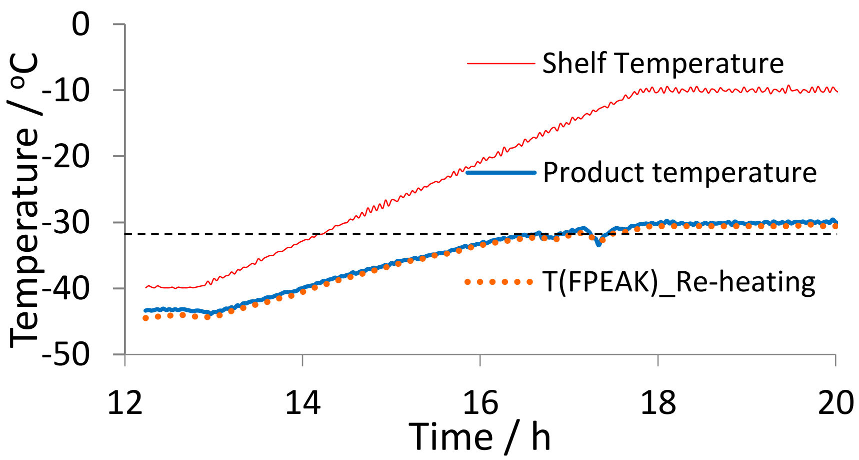
TVIS Application

Primary Drying (1) Product temperature prediction



Temperature Prediction in Primary Drying

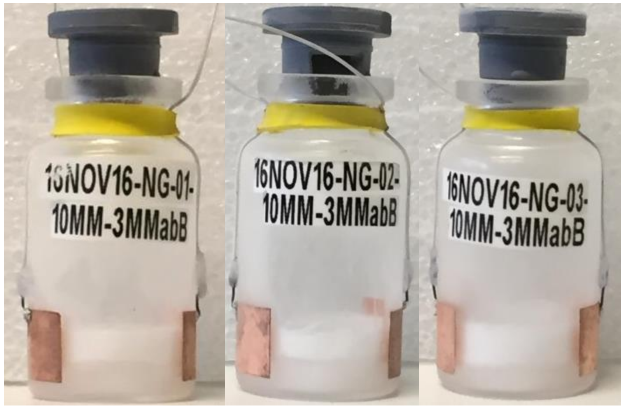




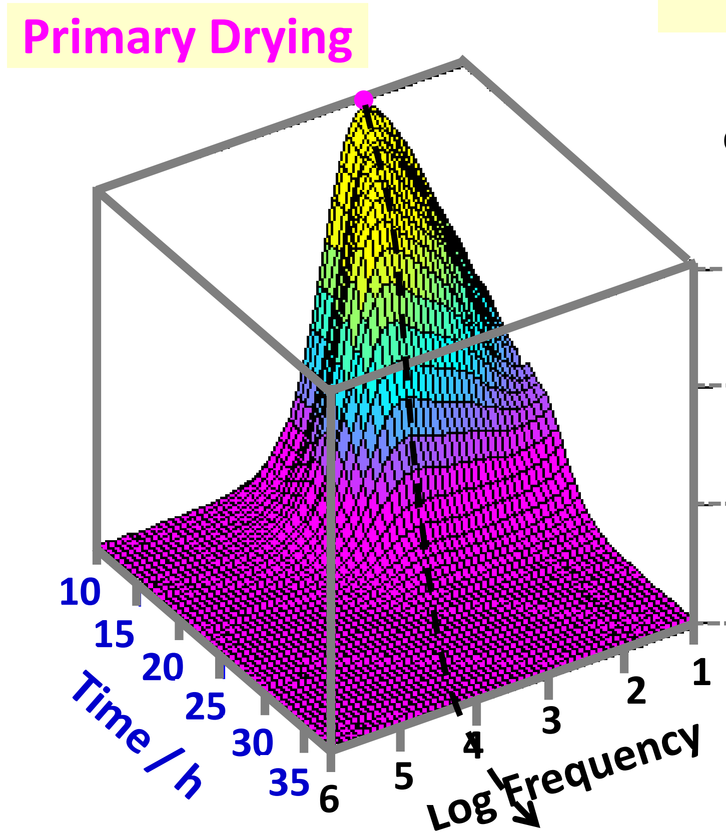
- Re-heating calibration curve selected for temperature prediction in primary drying : $T(F_{PEAK})$
- Good agreement between production temperature (by TC) and $T(F_{PEAK})$
- At approx. –32 °C (product collapse) the time profile of each parameter undergoes some instability

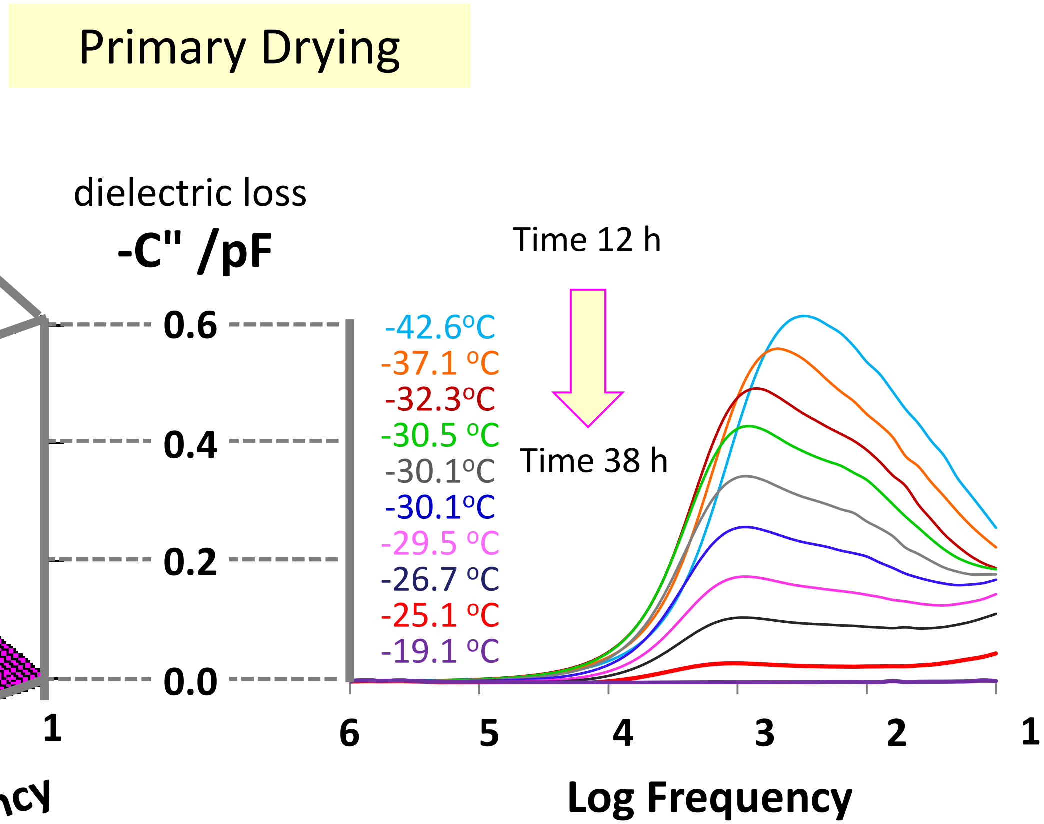
5%w/v Lactose in deionised water

TVIS Application
Primary Drying (2) Drying Rate Prediction



The relationship between F_{PEAK} and Product Temperature/Phase Transition





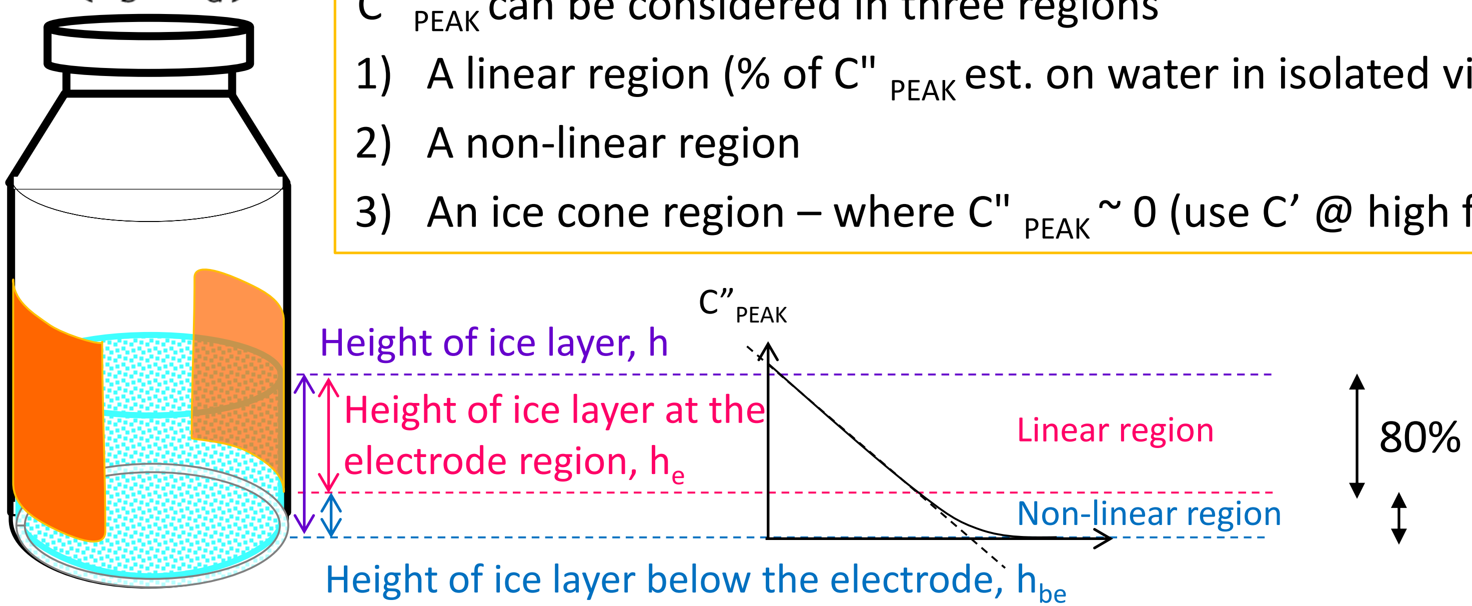
C" $_{PEAK}$ Criteria & Assumptions

- C" $_{PEAK}$ is proportional to the height of the ice cylinder bounded by the electrode region, through the value of C_G
- Drying rates are based on the assumption of a planar sublimation front
- Below the electrode C" $_{PEAK}$ loses sensitivity to ice layer height (non-linear)
- C" $_{PEAK}$ cannot be used for end point determination: use C' @ high freq. instead.

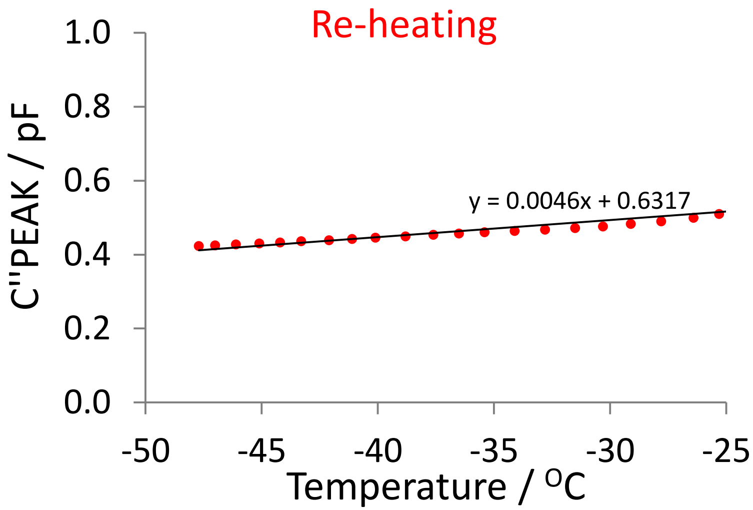
$$C''_{peak} = \frac{C_G^2}{2(C_S + C_G)}$$

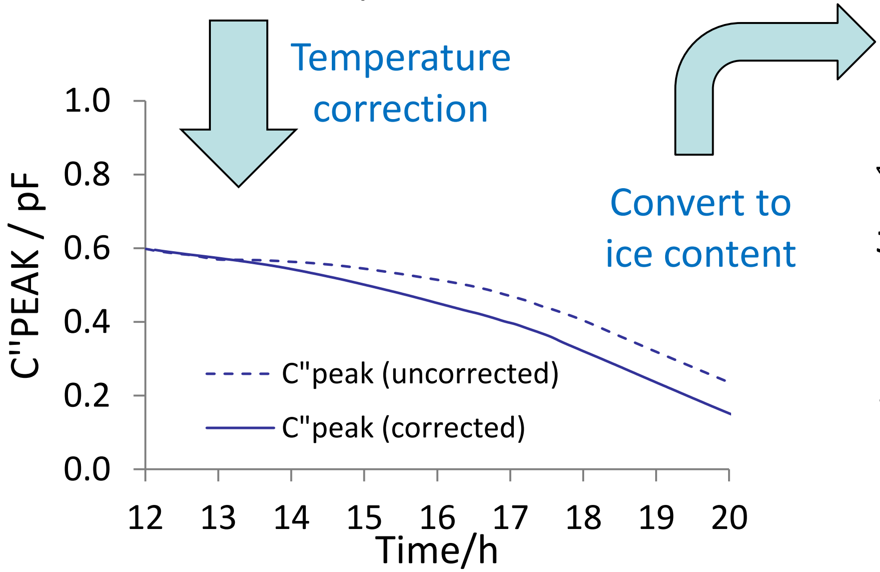
C" $_{PEAK}$ can be considered in three regions

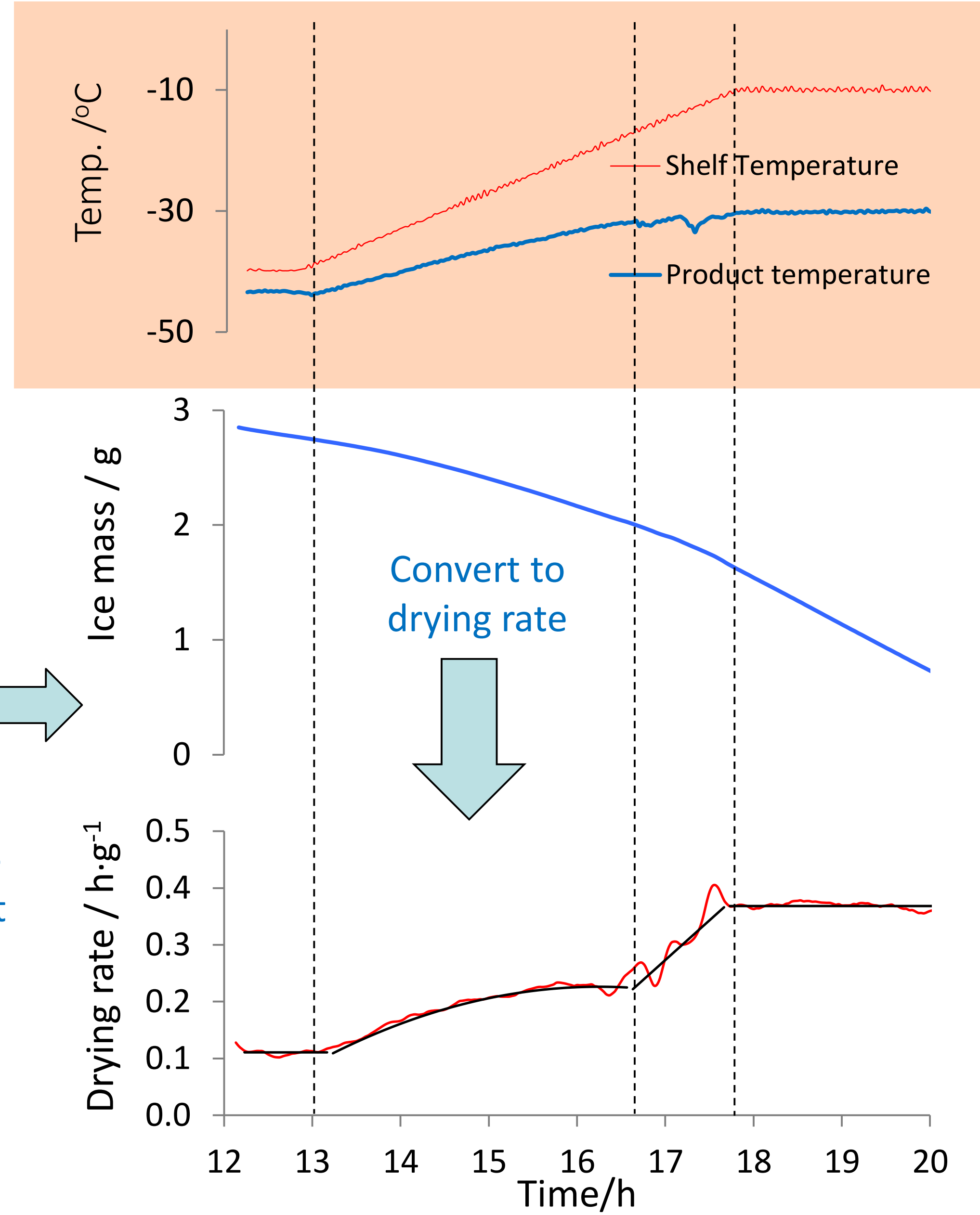
1) A linear region (% of C" $_{PEAK}$ est. on water in isolated vial)
2) A non-linear region
3) An ice cone region – where C" $_{PEAK}$ ~ 0 (use C' @ high freq.)



Drying Rate (*dm/dt*) Determination

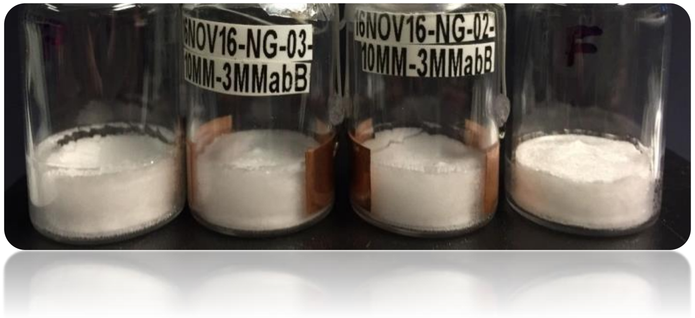






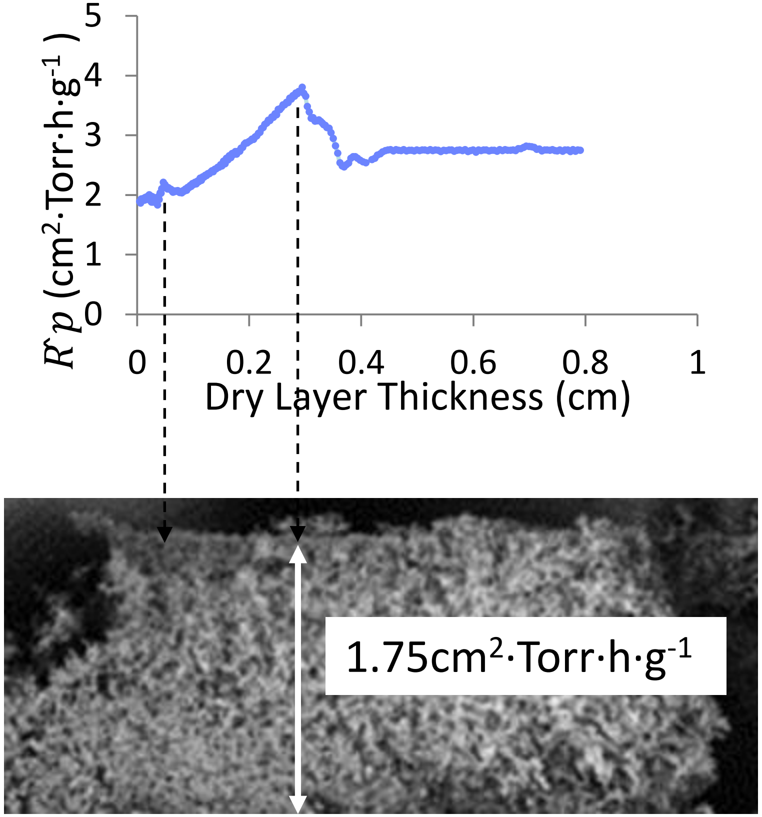
5%w/v Lactose in deionised water

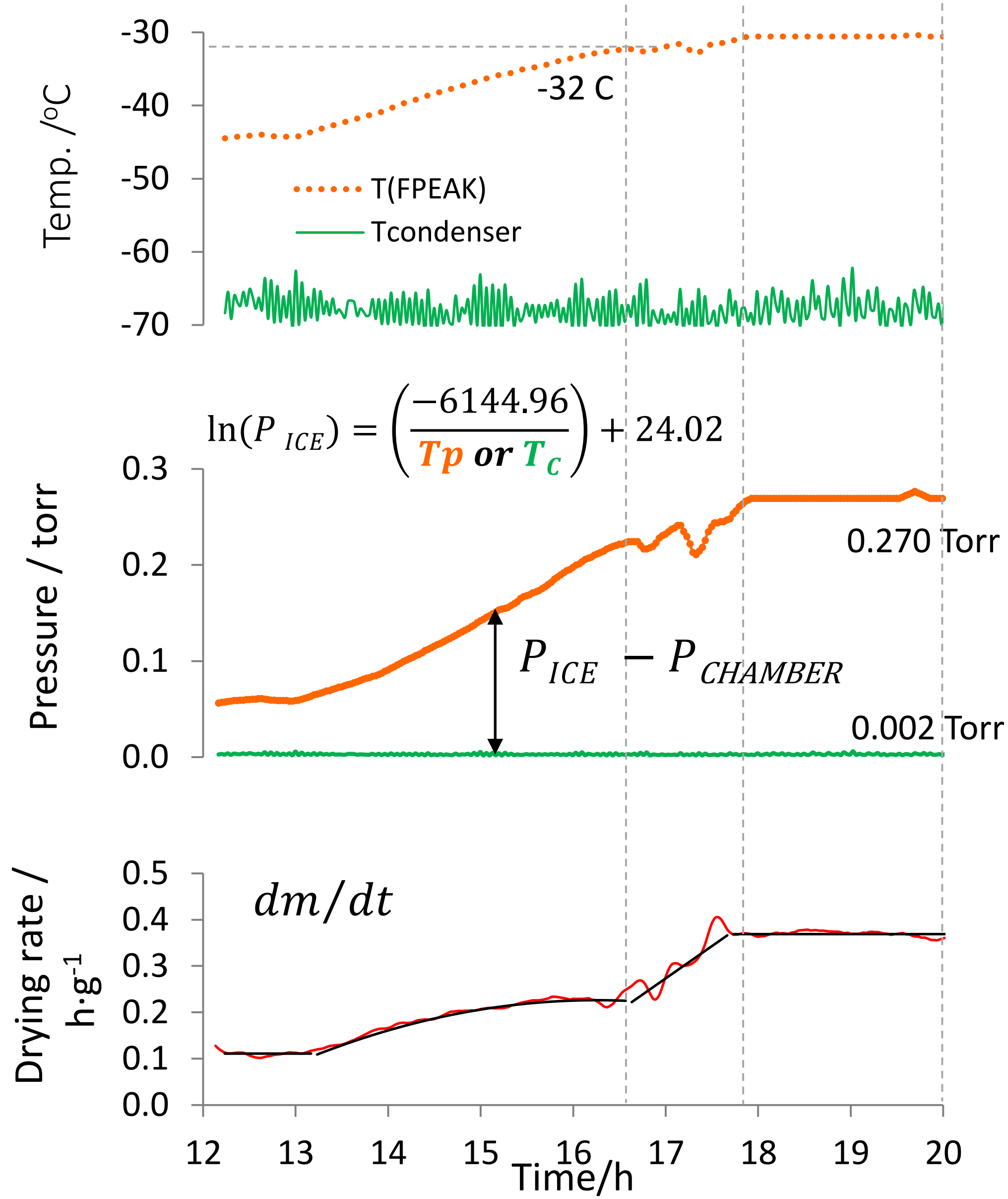
TVIS Application
Primary Drying: Rp determination



Lactose Dried Product Resistance (R_p)

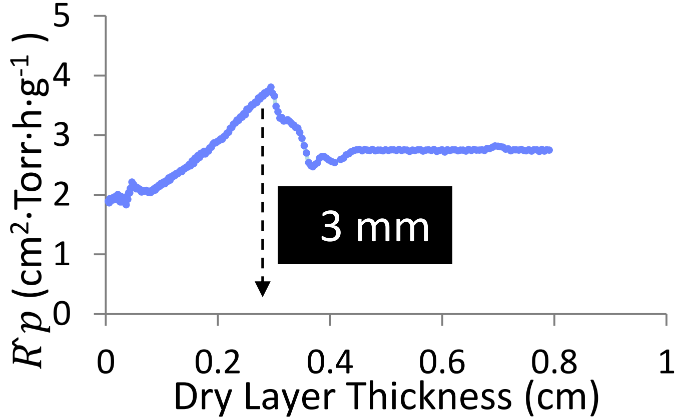
$$\hat{R}p = \left(\frac{P_{ICE} - P_{CHAMBER}}{dm/dt}\right) \cdot A_P$$

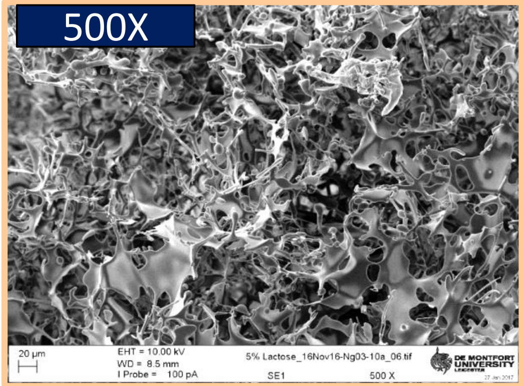




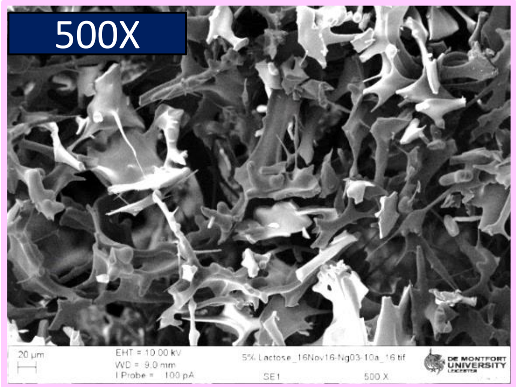
Lactose Dried Product Resistance (R_P)

$$\hat{R}p = \left(\frac{P_{ICE} - P_{CHAMBER}}{dm/dt}\right) \cdot A_P$$

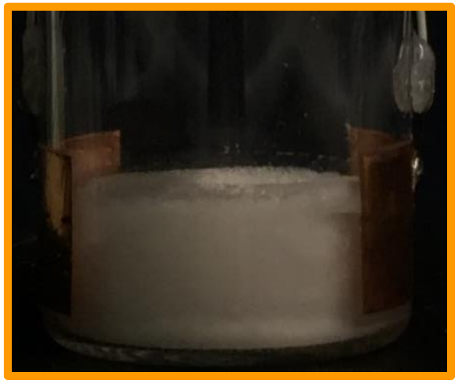


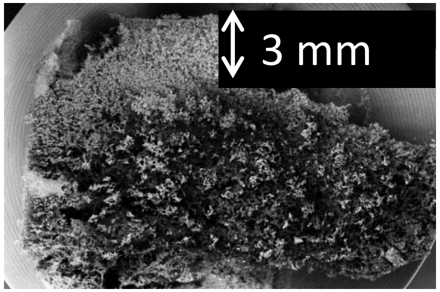


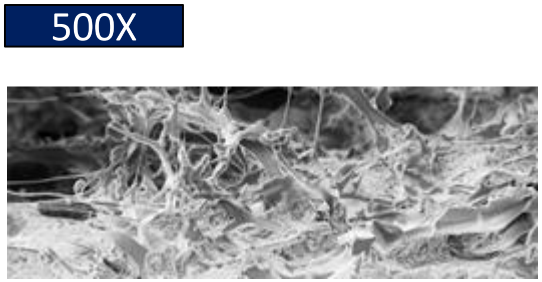
Top layer
Fine pores



Middle layer
Micro-collapse







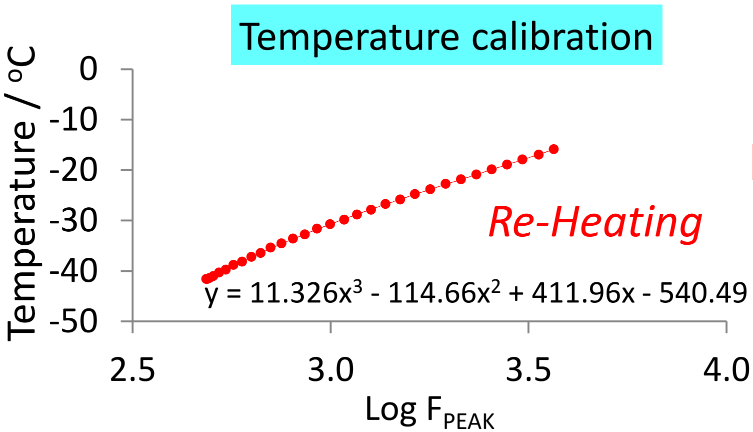
Bottom layer
Full collapse

TVIS Application

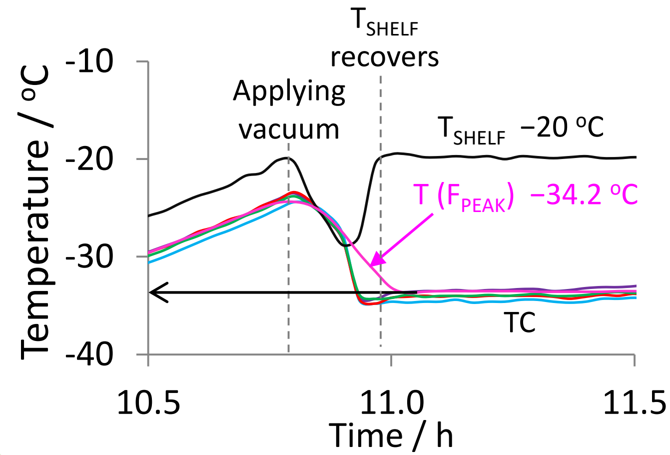
Primary Drying: Kv determination

Heat Transfer Coefficient (K_V) Determination

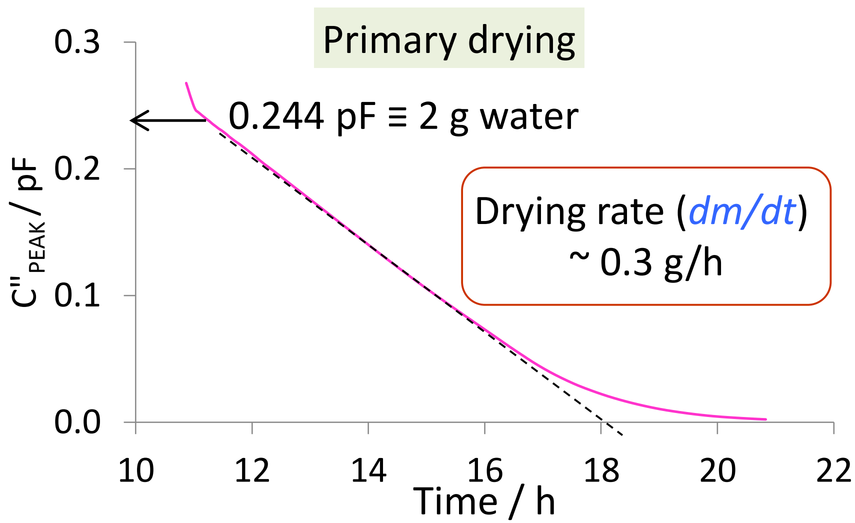
- The product temperature ($T_{PRODUCT}$), which derived by ***TVIS*** as $T(F_{PEAK})$ or *by thermocouple (TC),* is one of parameters needed for K_V determination



Calculate $T_{PRODUCT}$ from Log F_{PEAK} (TVIS)



- Sublimation rate (*dm/dt*) is estimated by ***TVIS***
- Test sample is 2 mL water filled in 10 mL vial



$T_{PRODUCT}$ and *dm/dt* from ***TVIS***

K_V determination

Heat Transfer Coefficient (K_V) Determination

- First convert dm/dt to dq/dt using the latent heat of sublimation
  (L = 2844 J g^{-1})

$$L\frac{dm}{dt} = \frac{dq}{dt}$$

dm/dt = 0.3 g/h

L = 2844 J g^{-1}

dq/dt = 853 J/h

$$\frac{dq}{dt} = A_V K_V (T_{SHELF} - T_{PRODUCT})$$

T_{SHELF} = – 20 °C

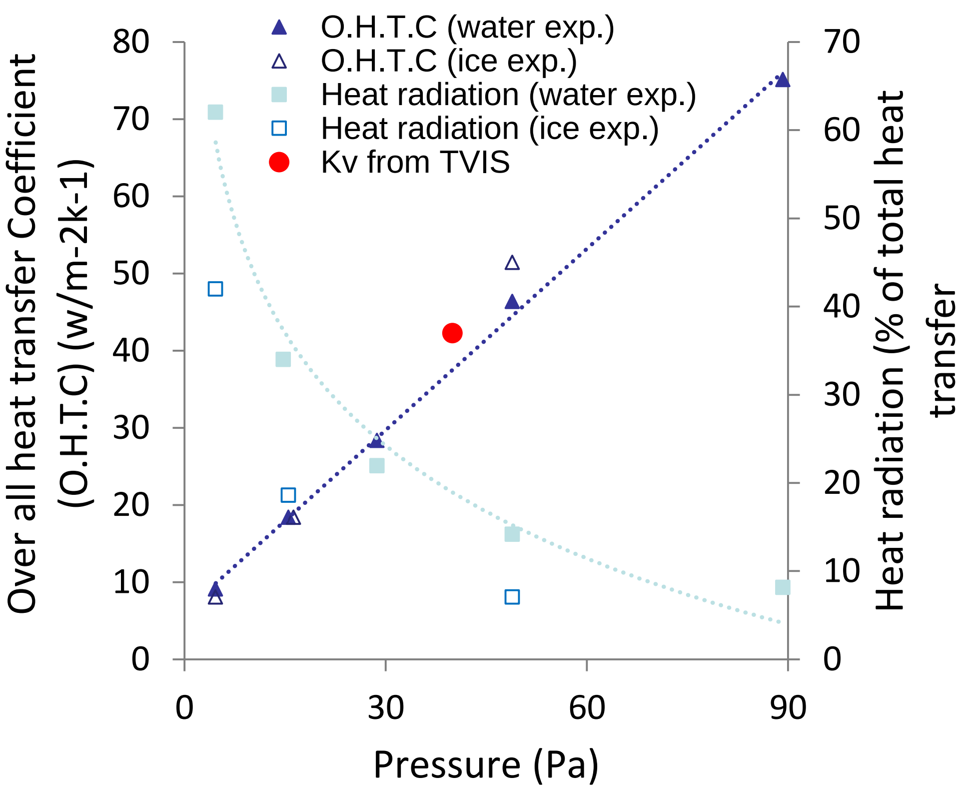
$T_{PRODUCT}$ = – 34.2 °C

A_v = 0.0045 m^2

(*Schott Type1 glass 10 ml tubing vial*)

K_v = 37 W m^{-2} K^{-1} [@ 40 Pa, 400 µBar]

K_v values for 10 mL tubing vials (2 mL fill volume)



Brülls, M., and Ramusson, A. (2002) Heat Transfer in Lyophilization. Int J Pharm 10;246(1-2):1-16.

Acknowledgements, Recent Projects & Collaborators

- De Montfort University
  - Evgeny Polygalov. Senior Research Fellow
  - Irina Ermolina. Senior Lecturer
  - Yowwares Jeerarunangrattana. PhD student
  - Bhaskar Pandya. PhD student
- GEA Process Engineering
  - Trevor Page & Julian Taylor
  - Daniela Buchmeyer & Thomas Beutler
- BlueFrog : Chris Samwell Ben Irvin
- NIBSC : Paul Matejtschuk
- Sanofi : Tim McCoy

BIOSTART

AtlasBio

GEA Pharma Systems

bluefrog design

NIBSC Confidence in Biological Medicines

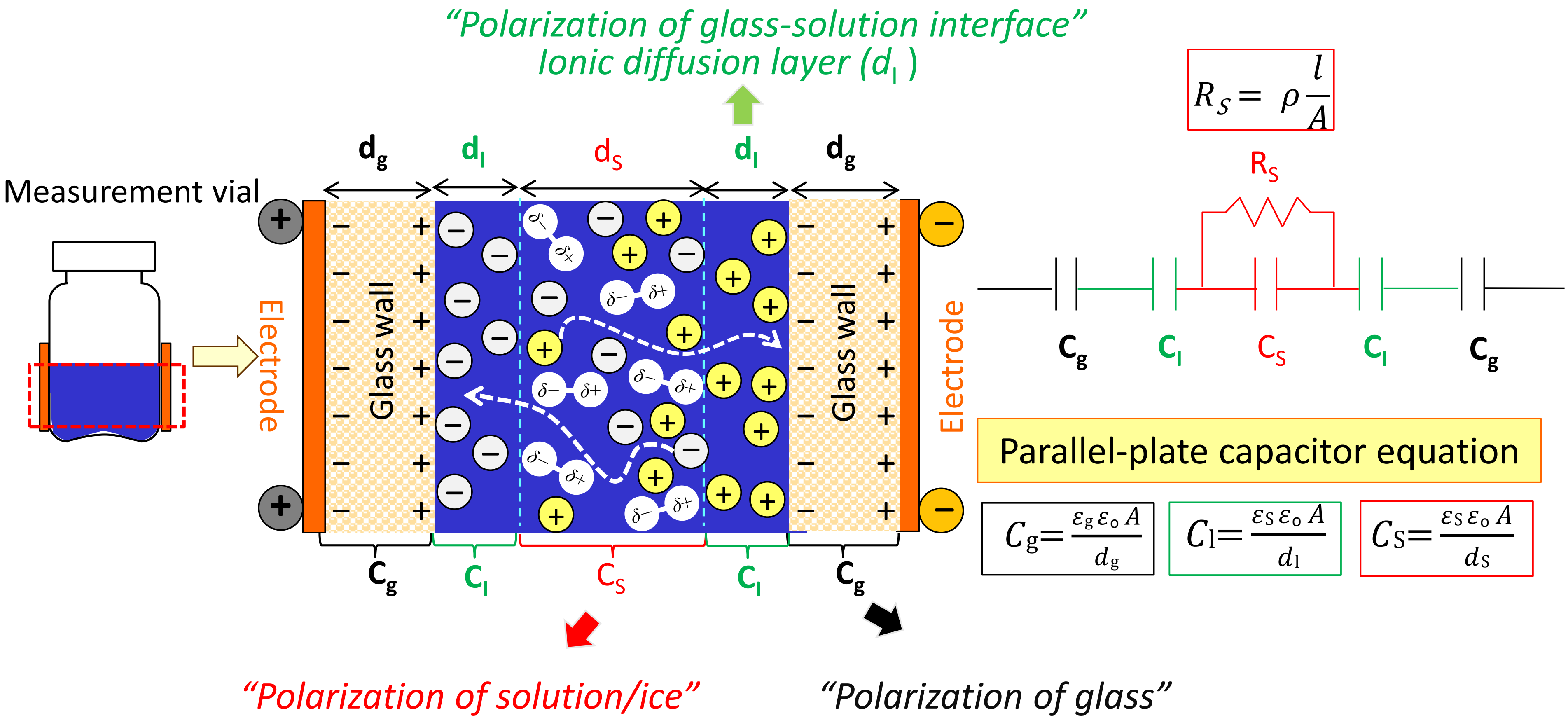
SANOFI

Innovate UK

Thank you

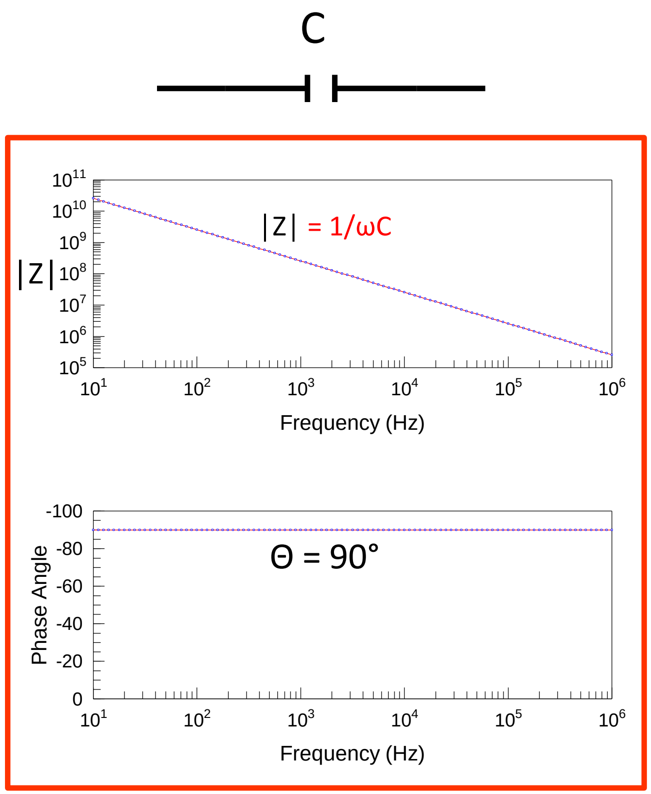
Annex : TVIS Theory

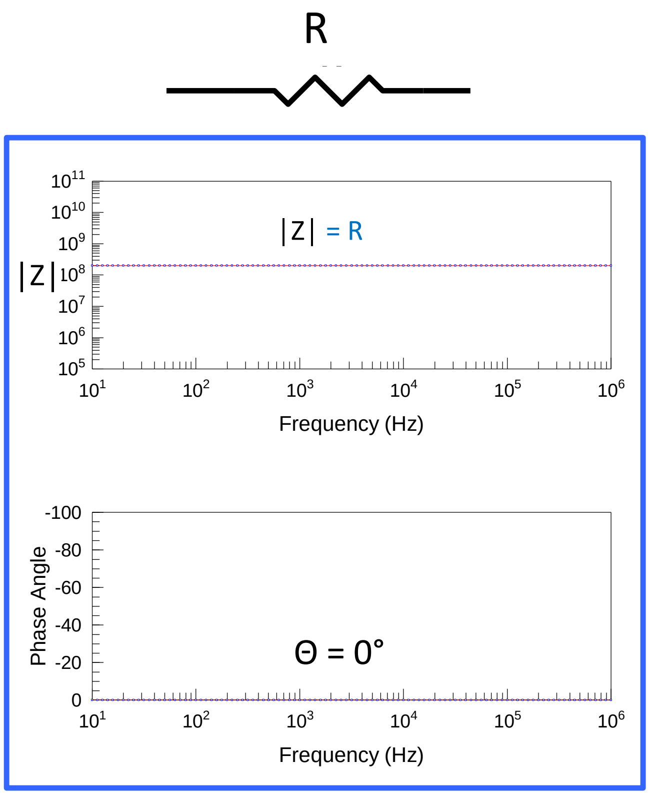
Equivalent circuit model



Impedance Spectroscopy

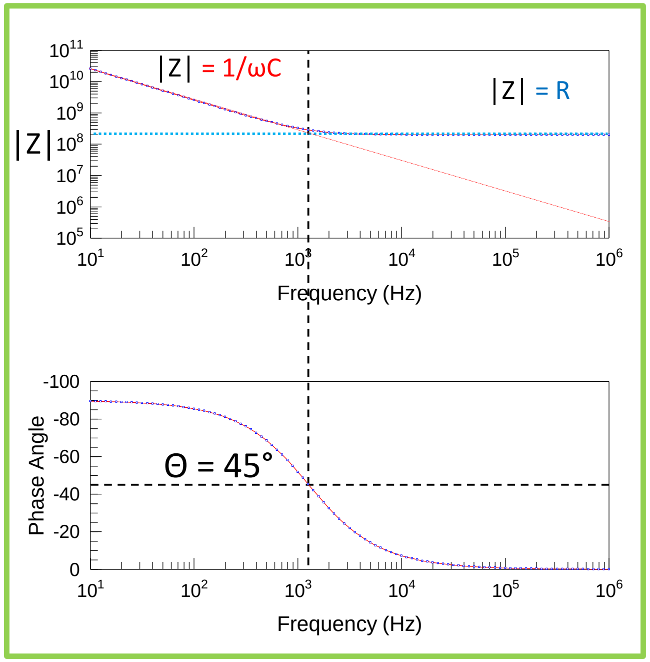
- Impedance is a frequency dependent parameter largely because the impedance of a capacitance is dependent on the frequency of the applied field, whereas an ideal resistor has zero frequency dependence





Impedance Spectroscopy

- In the case of a composite object that has both capacitance and resistance then the impedance spectrum that results will be dominated by one or the other element.



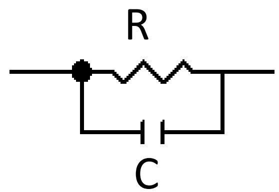
In a series circuit

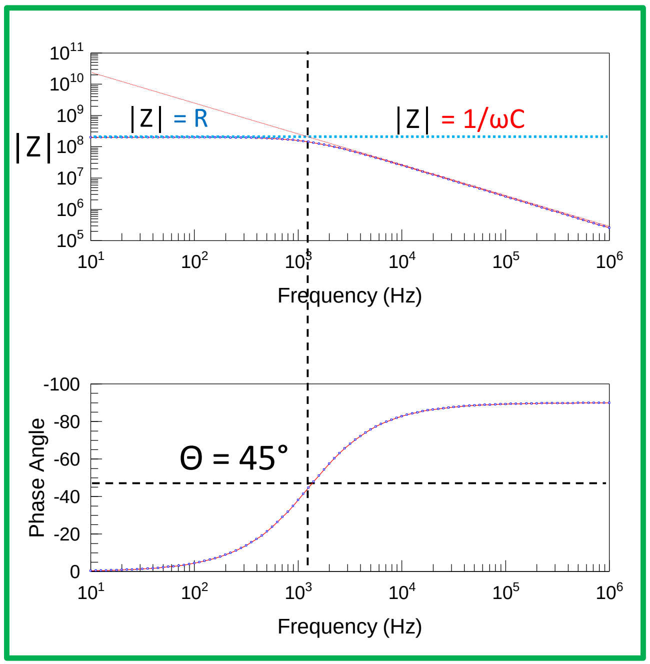
@ low frequency the capacitor dominates the spectrum because the impedance of the capacitance is so high that the capacitor effectively controls the current that flows through the circuit

@ high frequency the resistor dominates the spectrum because the impedance of the capacitor has fallen below that of the resistor such that the resistor effectively controls the current that flows through the circuit

Impedance Spectroscopy

- In the case of a composite object that has both capacitance and resistance then the impedance spectrum that results will be dominated by one or the other element.





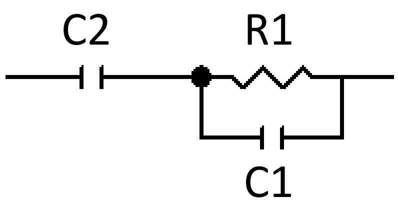
In a parallel circuit

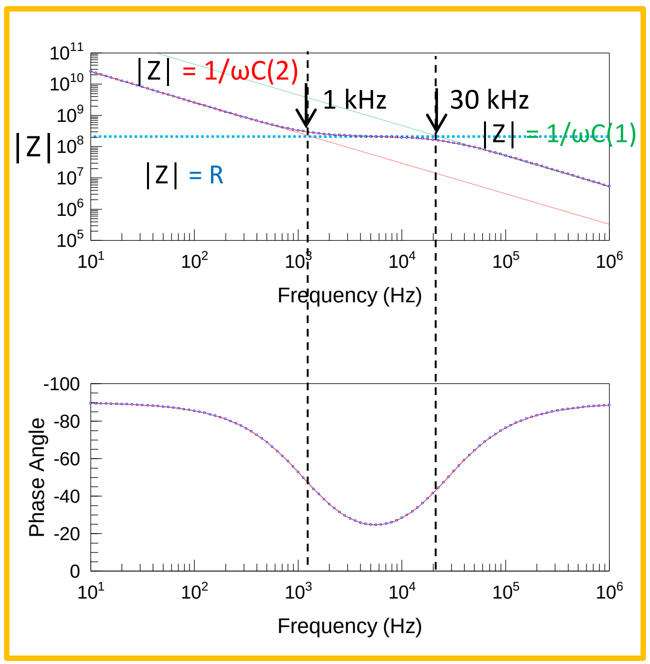
@ low frequency the resistor dominates the spectrum because the impedance of the capacitance is so high that all the current flows through the resistor.

@ high frequency the capacitor dominates the spectrum because the impedance of the capacitance is now lower than the resistor such that all the current now flows through the capacitor.

Impedance Spectroscopy

- More complex composite objects can be considered as combinations of impedances. Again, the impedance spectrum that results will be dominated by one or the other impedance.





In a complex circuit

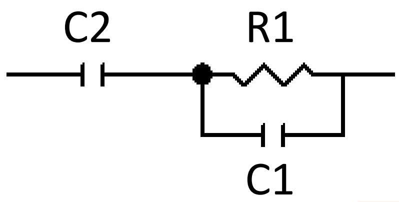
@ low frequency (<1 kHz) the resistor R1 dominates the impedance of the R1C1 circuit, but because this circuit is in series with a capacitor , C2 (which has a high impedance at low frequency) then C2 effectively controls the current that flows through the entire circuit

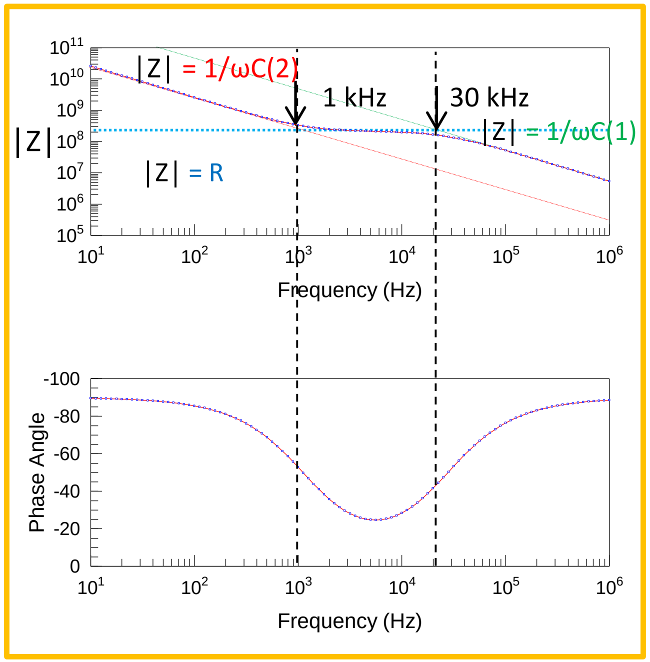
@ intermediate frequency (1-30 kHz) the impedance of C2 drops below that of the resistor, such that the resistor begins to dominate the impedance and therefore the phase angle tends to increase from -90 to zero

@ high frequency (>30 kHz**)** the impedance of the capacitor, C1, which is in parallel with the resistor, decreases below that of the resistor such that the resistor no longer dominates the impedance of the parallel RC circuit so then the circuit behaves like two capacitors in series but with C1 dominating the spectrum

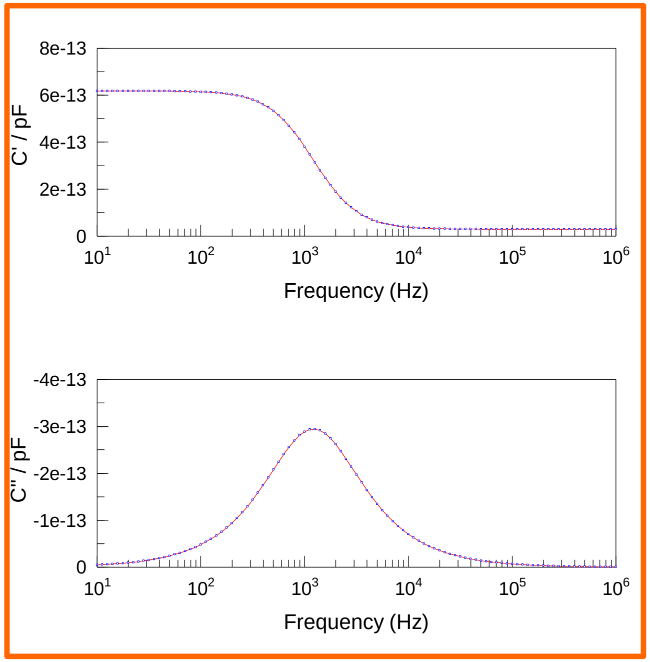
Impedance Spectroscopy

- The impedance spectrum of complex element can be presented as the capacitance spectrum





Impedance Spectrum



Capacitance Spectrum

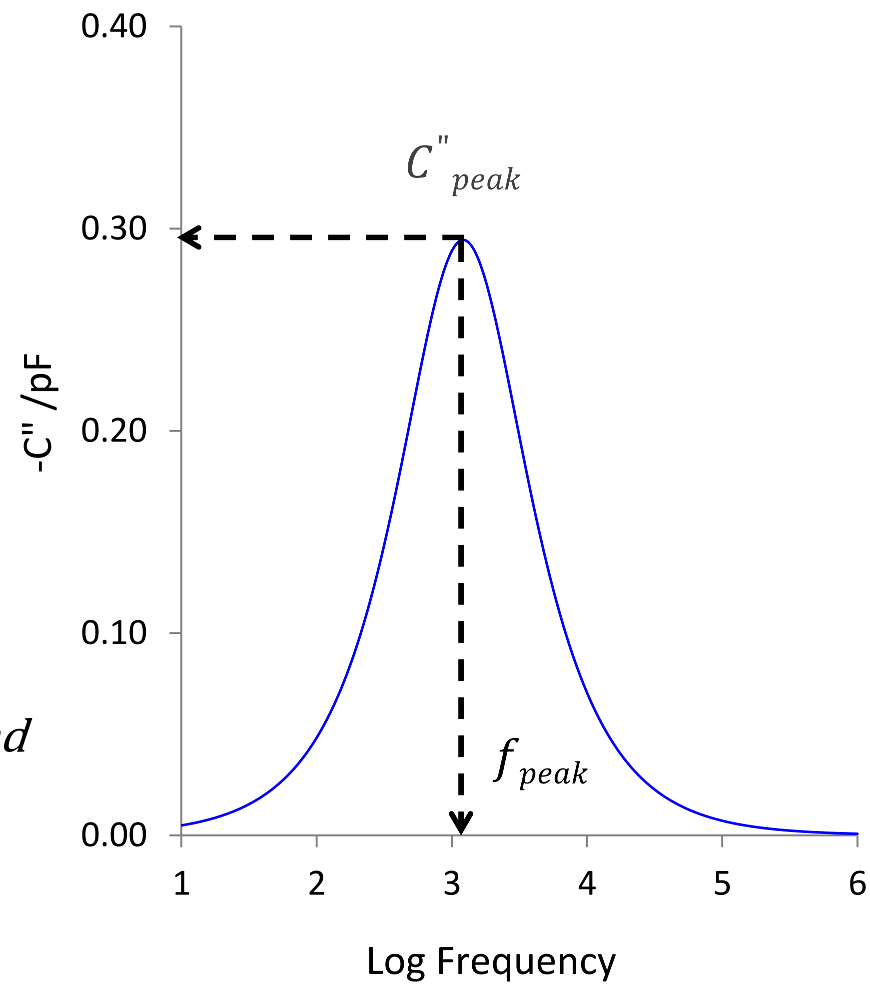
Interfacial Polarization Characteristic

- At ω→0, $C^{"} = 0$
- As the frequency increase, $C^{"}$ increases to maximum ($C^{"}_{max}$)then decreases to zero as the frequency ω→∞
- At a frequency of

$$\omega_{max} = \frac{1}{R_S(C_S + C_G)} \ in\ radians$$

$$f_{peak} = \frac{1}{2\pi R_S(C_S + C_G)} \ in\ cycles\ per\ second$$

$$C''_{peak} = \frac{C_G^2}{2(C_S+C_G)}$$



Interfacial Polarization Characteristic

- The impedance of the model can be calculated from the following equation

$$Z^*_{\text{Total}} = Z^*(C_G) + [\frac{1}{Z^*(R_S)} + \frac{1}{Z^*(C_S)}]$$

$$Z^*_{\text{Total}} = \frac{1}{i\omega C_G} + \frac{R_S}{1 + i\omega R_S C_S}$$

which re-arranges to

$$Z^*_{\text{Total}} = \frac{1 + i\omega R_S(C_G + C_S)}{i\omega C_G + i\omega^2 R_S C_G C_S}$$

- Impedance can be expressed in terms of a complex capacitance

$$C^*_{\text{Total}} = \frac{1}{i\omega Z^*_{\text{Total}}} = \frac{C_G + i\omega R_S C_G C_S}{1 + i\omega R_S(C_G + C_S)}$$

- The complex capacitance can also be expressed in form of real part and imaginary part

$$C^* = C' + iC''$$

- From the complex capacitance formula, the expressions for real and imaginary capacitance can be calculated to explain the origin of interfacial polarization peak. This achieved by multiplying the nominator and denominator by the complex conjugate of the denominator and by grouping the real (C') and imaginary (C'') parts

$$C' = \frac{C_G + \omega^2 R_S^2 C_G C_S (C_S + C_G)}{1 + \left(\omega R_S\left((C_S + C_G)\right)\right)^2}$$ and $$C'' = -\frac{\omega R_S C_G^2}{1 + (\omega R_S((C_S + C_G))^2}$$