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

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Through Vial Impedance Spectroscopy

# 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*

# Conclusions : PAT for freeze-drying production

| | Product Temperature | Sublimation Rate | End Point |
|---|---|---|---|
| **Single vial** | | | |
| Product Probes | | | |
| Sample Thief | | | |
| Weight Loss | | | |
| NIR | | | |
| **Endpoint check** | | | |
| PRT | | | |
| Others | | | |
| **Batch** | | | |
| Windmill | | | |
| Moisture | | | |
| MS | | | |
| Vacuum gauge | | | |
| MTM | | | |
| TDLAS | | | |

**No perfect method available**

# YET!!!

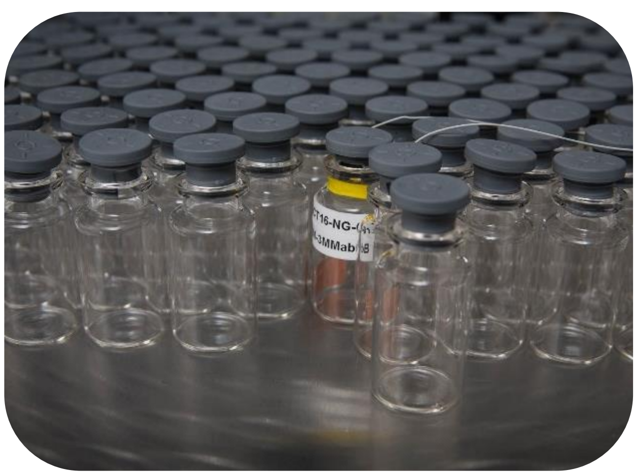
Kevin Murgatroyd, ISLFD workshop April 25th 2017

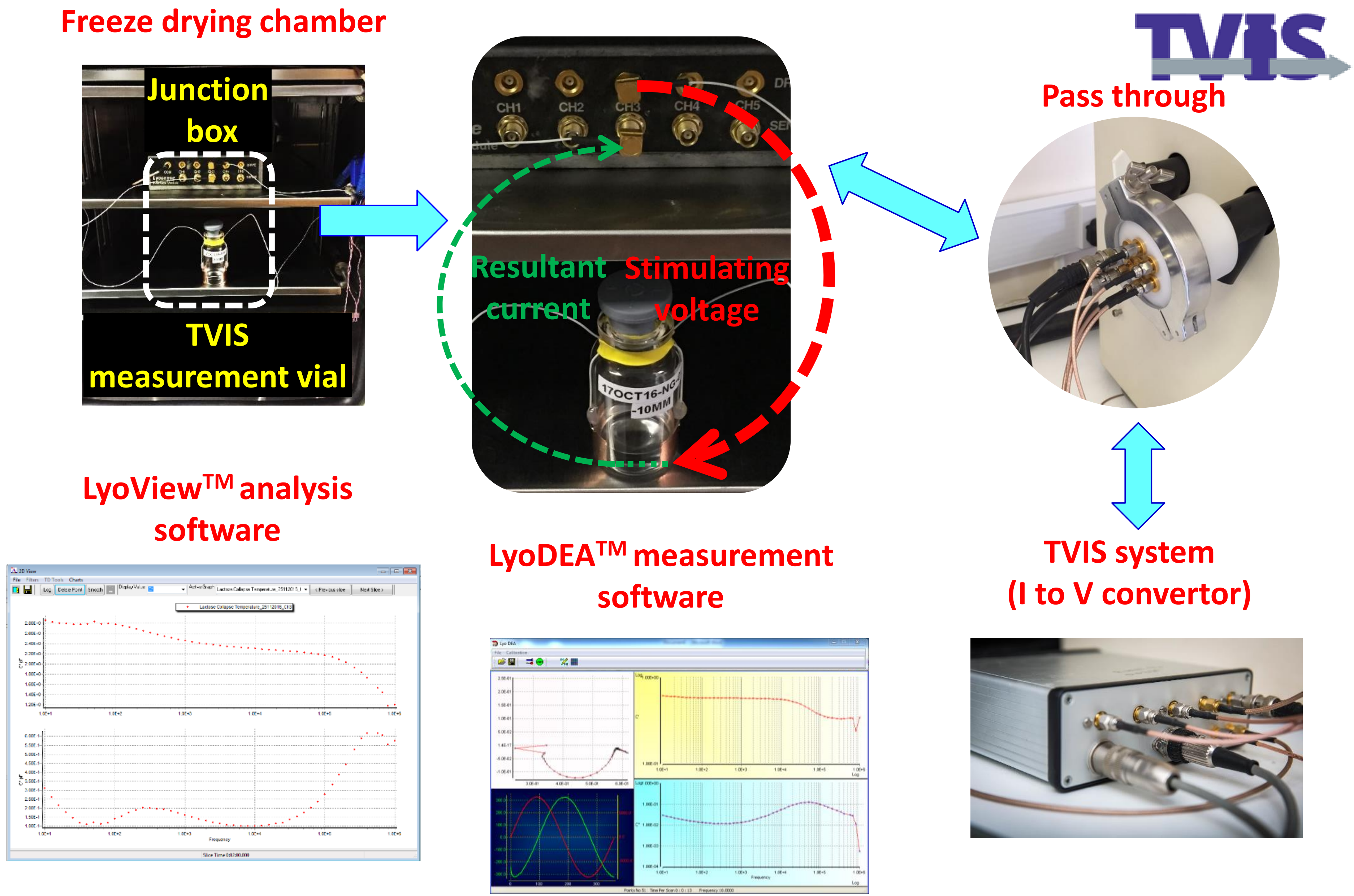
# Introduction to the TVIS System

- 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!)** | |

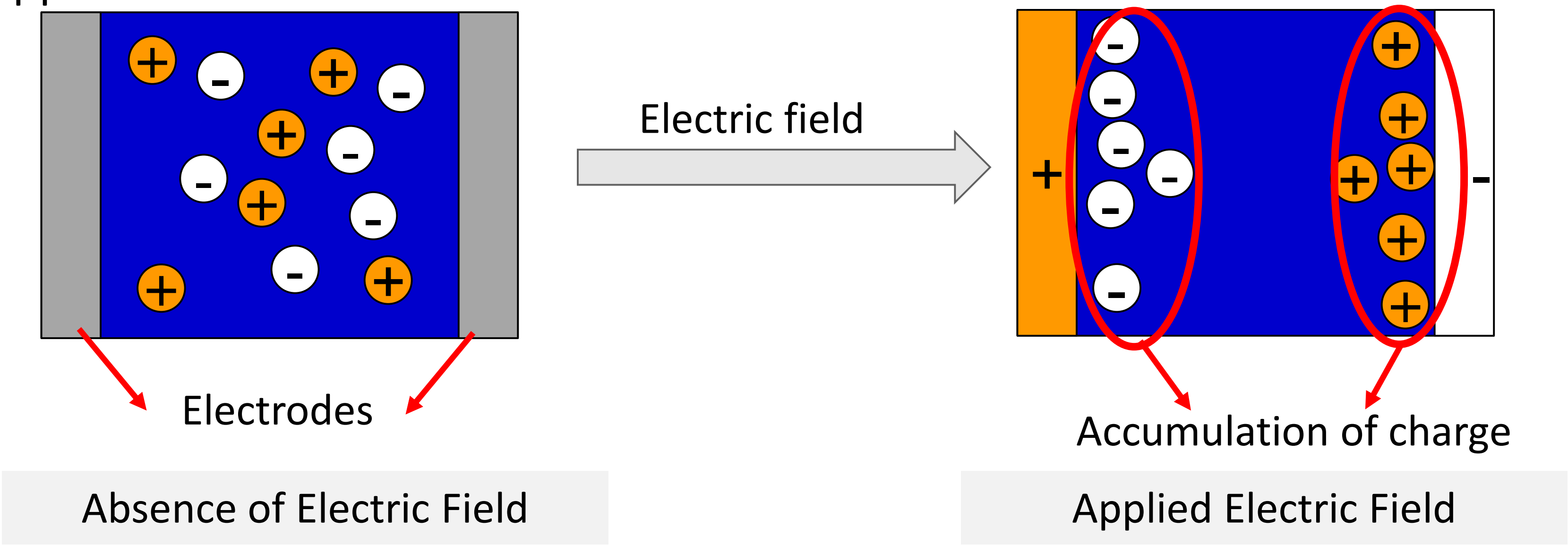



Freeze drying chamber
Junction box
TVIS measurement vial
Resultant current
Stimulating voltage
CH1
CH2
CH3
CH4
CH5
17OCT16-NG-
-10MM
TVIS
Pass through
LyoView™ analysis software
LyoDEA™ measurement software
TVIS system
(I to V convertor)

# Through Vial Impedance Spectroscopy (TVIS)
*Theory*

# Interfacial Polarization Phenomena

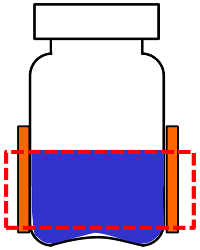
- Interfacial or space charge polarization is one type of dielectric polarization.
- It refers to the accumulation of charges at an interface between two dielectric materials or between two regions within a material when an external field applied.

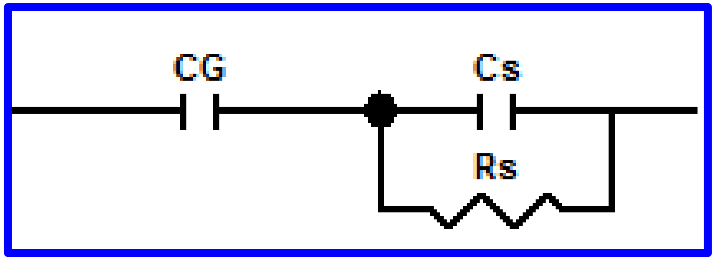



- This phenomenon occurs when an electric field is applied to a glass vial (a dielectric material) containing a liquid and/or solid (a dielectric material with some conductivity).

# 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 ($C^{"}_{max}$)

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

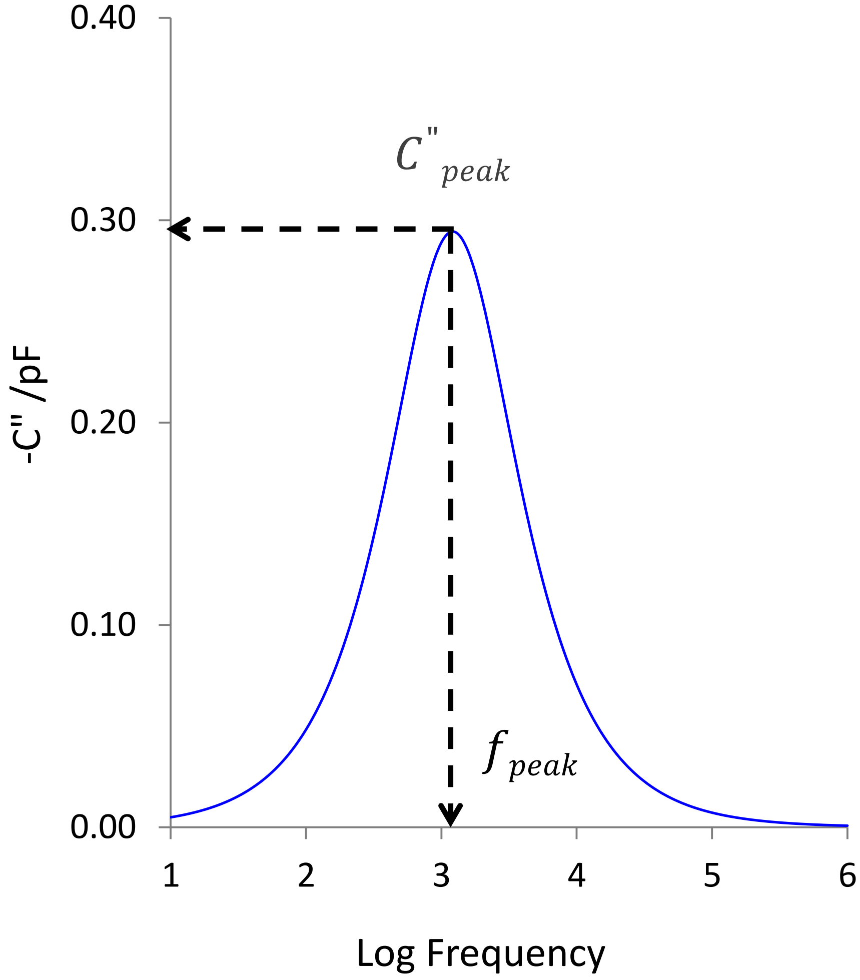
- a frequency of

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

- If $C_G$ > $C_S$ then

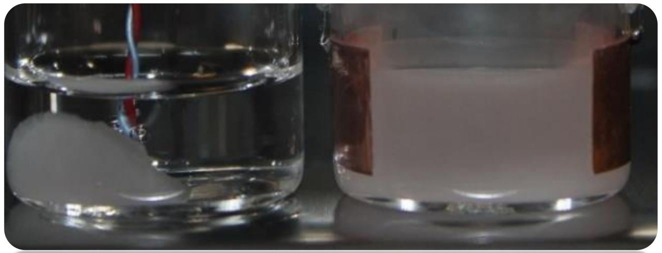
$$C''_{peak} \cong C_G$$

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



# TVIS Applications

## *Freezing, Annealing, Primary Drying*

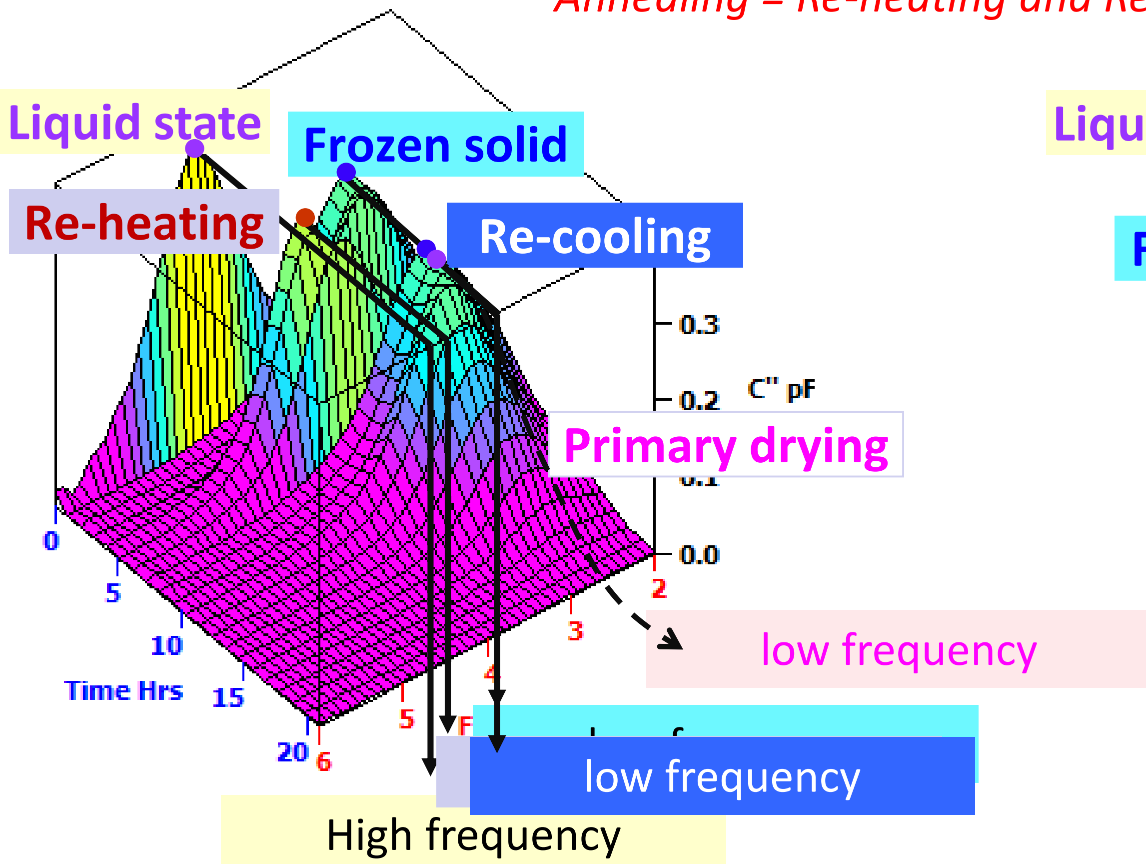


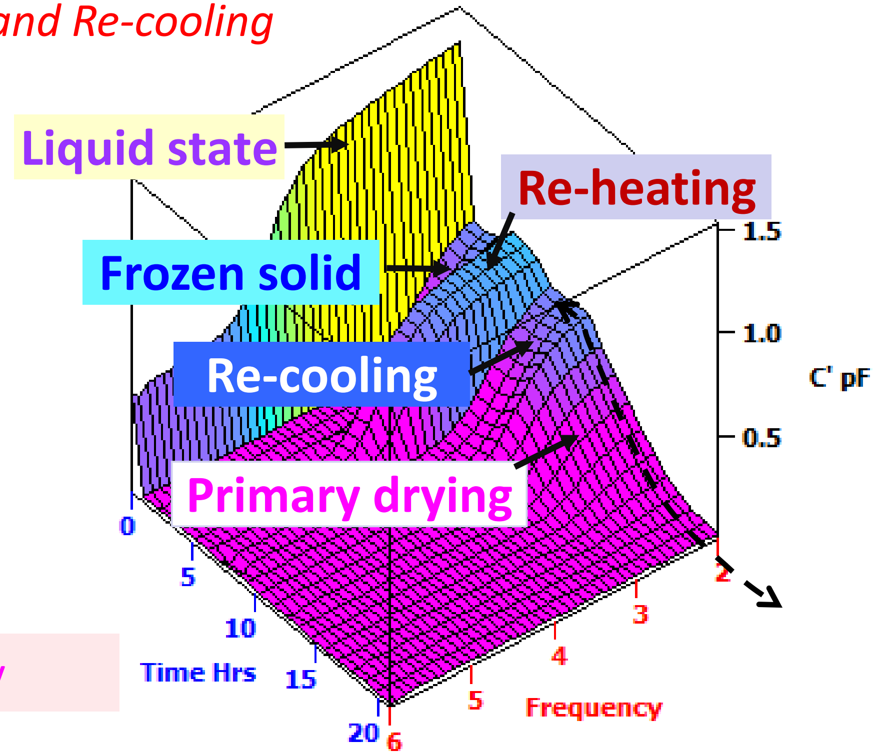
# TVIS Response Surface

Imaginary Part of Capacitance

Real Part of Capacitance

*Annealing = Re-heating and Re-cooling*



# Through Vial Impedance Spectroscopy (TVIS)

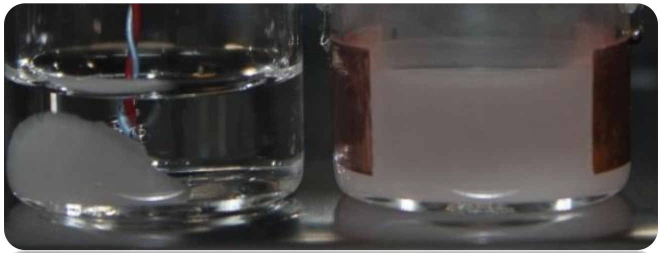
- The capacitance spectrum depends on both the *electrical resistance and electrical capacitance of the vial contents.*
- Data viewing software (LyoView ™) identifies the peak frequency ($F_{PEAK}$) and peak amplitude ($C''_{PEAK}$) in the imaginary part of the capacitance spectrum from which various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

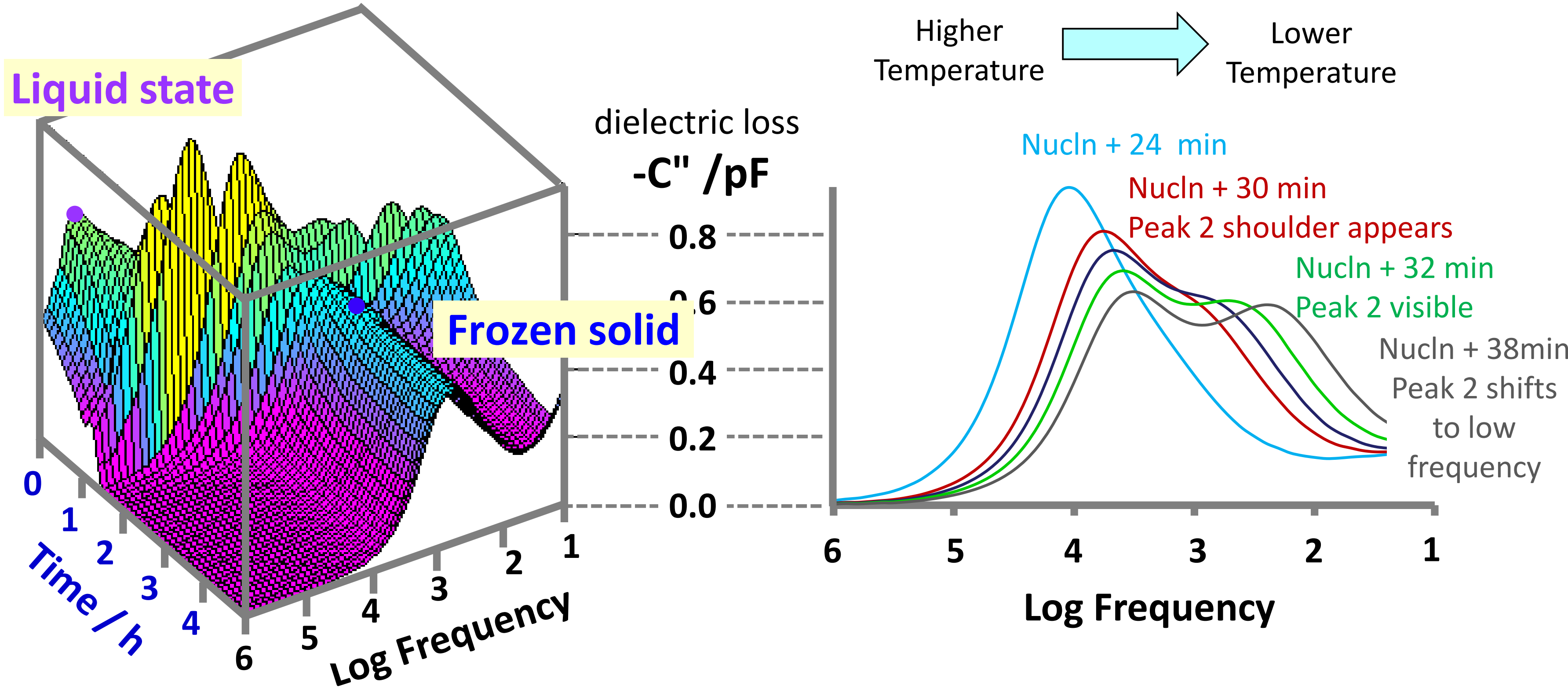
- It follows that $F_{PEAK}$ can be used to monitor (i) the phase behaviour and (ii) the temperatures of both the liquid and solid states.

- 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.

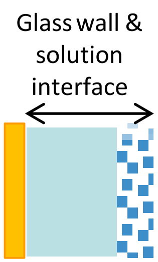
# Phase separation

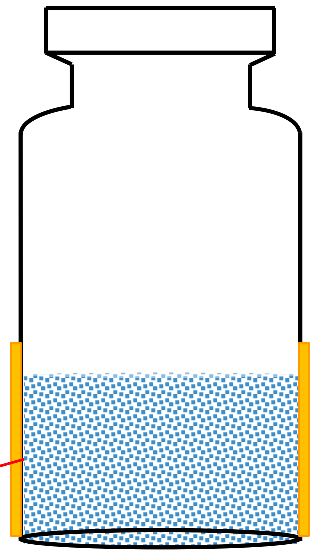
Freezing Step

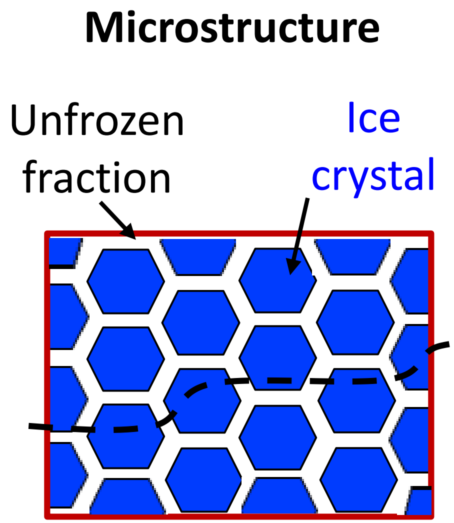


# Ice and the unfrozen fraction

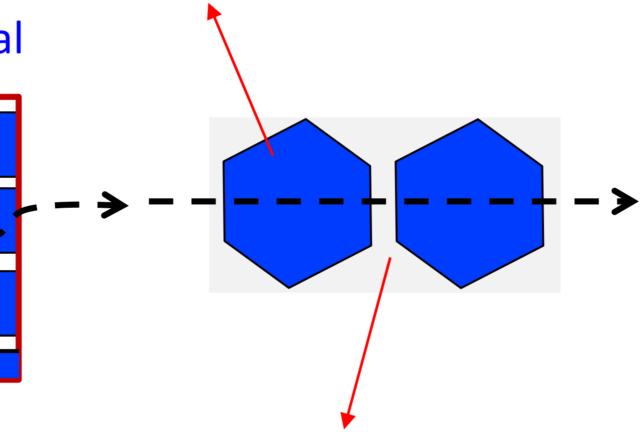
The glass interface has very high resistance; therefore it behaves primarily as capacitor **($C_I$)**

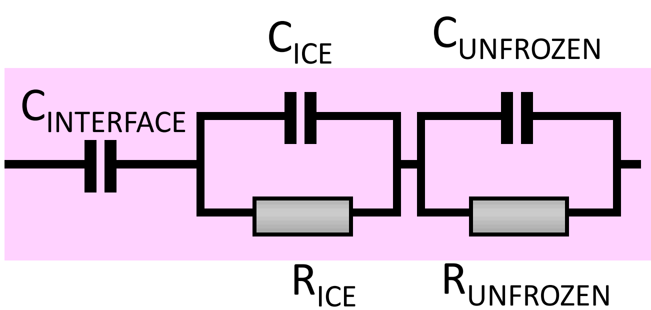





Ice has a conductivity **($R_{ICE}$)** and dielectric constant **($C_{ICE}$)** due to the percolation of protons ($H^+$)

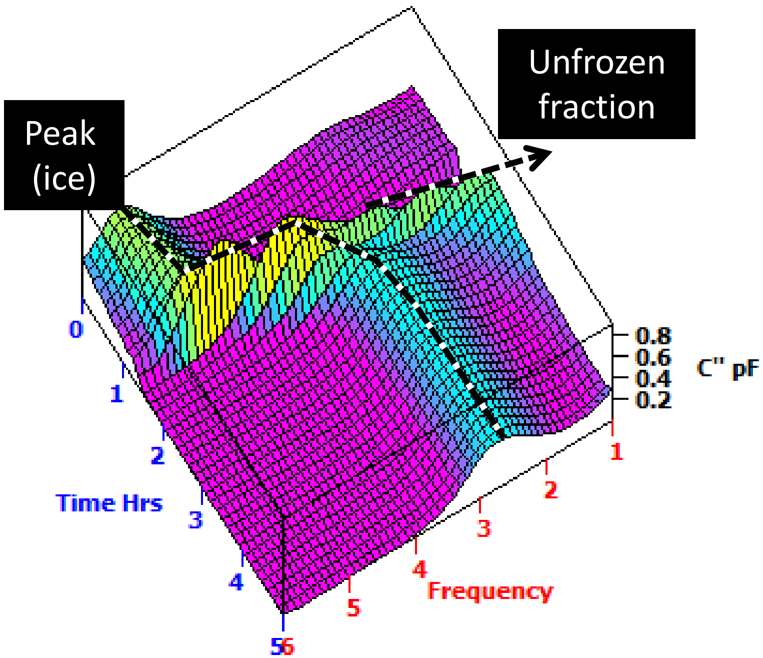




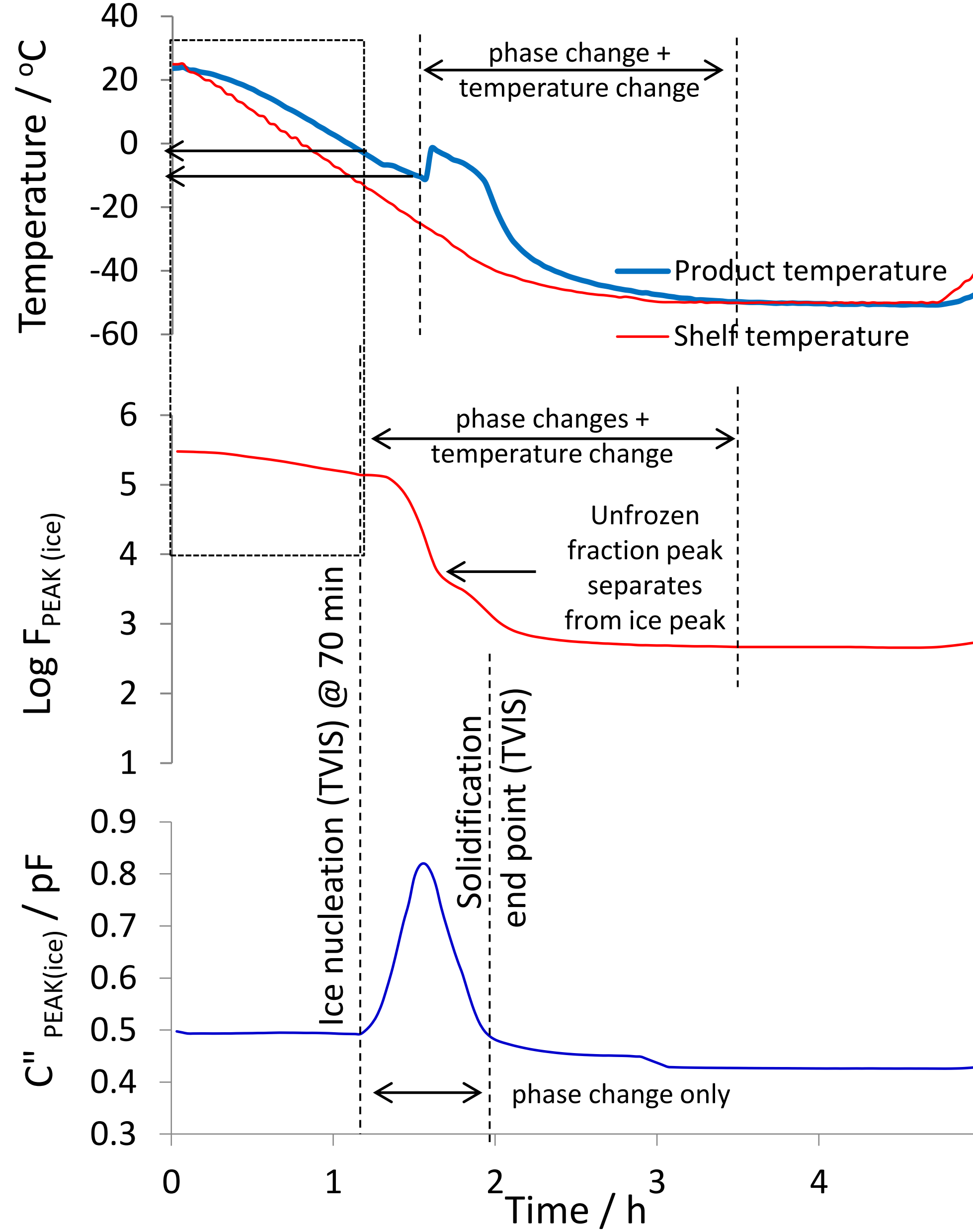

A layers of unfrozen fraction between the ice crystals have dielectric constants and a conductivities which are reflected in $C_{UNFROZEN}$ and $R_{UNFROZEN}$, respectively.

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

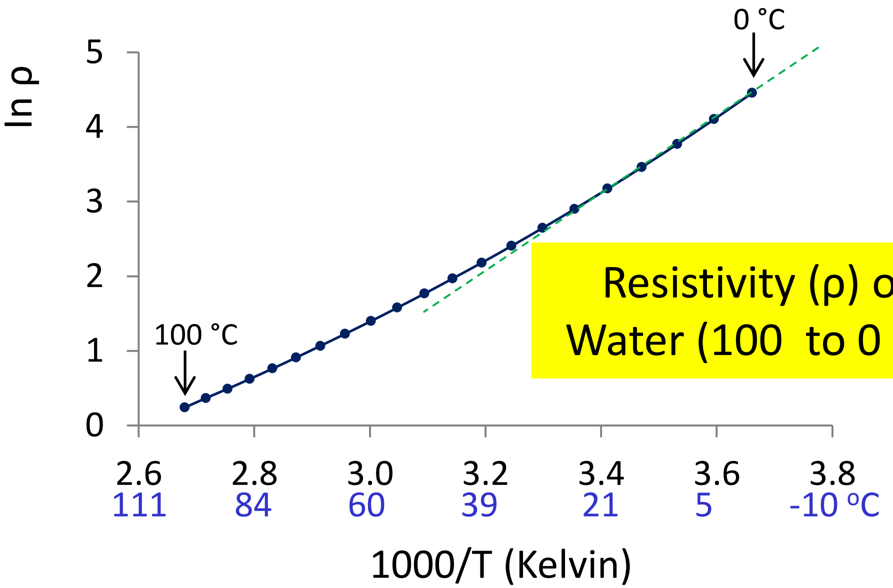


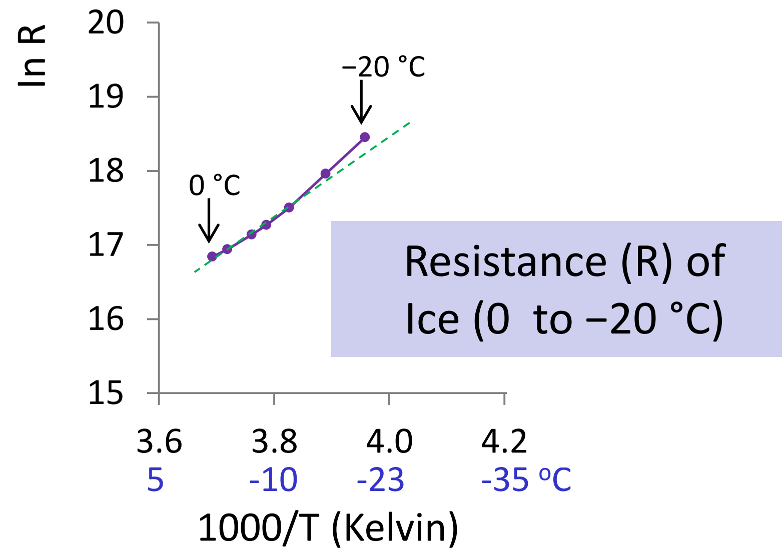

- The thermocouple vial nucleates later than the TVIS vial
- $C''_{PEAK}$ may provide a more reliable end point for solidification



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

The resistance/resistivity of liquid water and ice are both inversely proportional to temperature,




Light et al. (2005) The fundamental conductivity and resistivity of water. *Electrochemical and Solid-State Letters,* 8 (1), pp. E16-E19

Petrenko, V. F. (1993). *Electrical properties of ice* (No. CRREL-SR-93-20). Cold Regions Research and Engineering Lab Hanover NH.

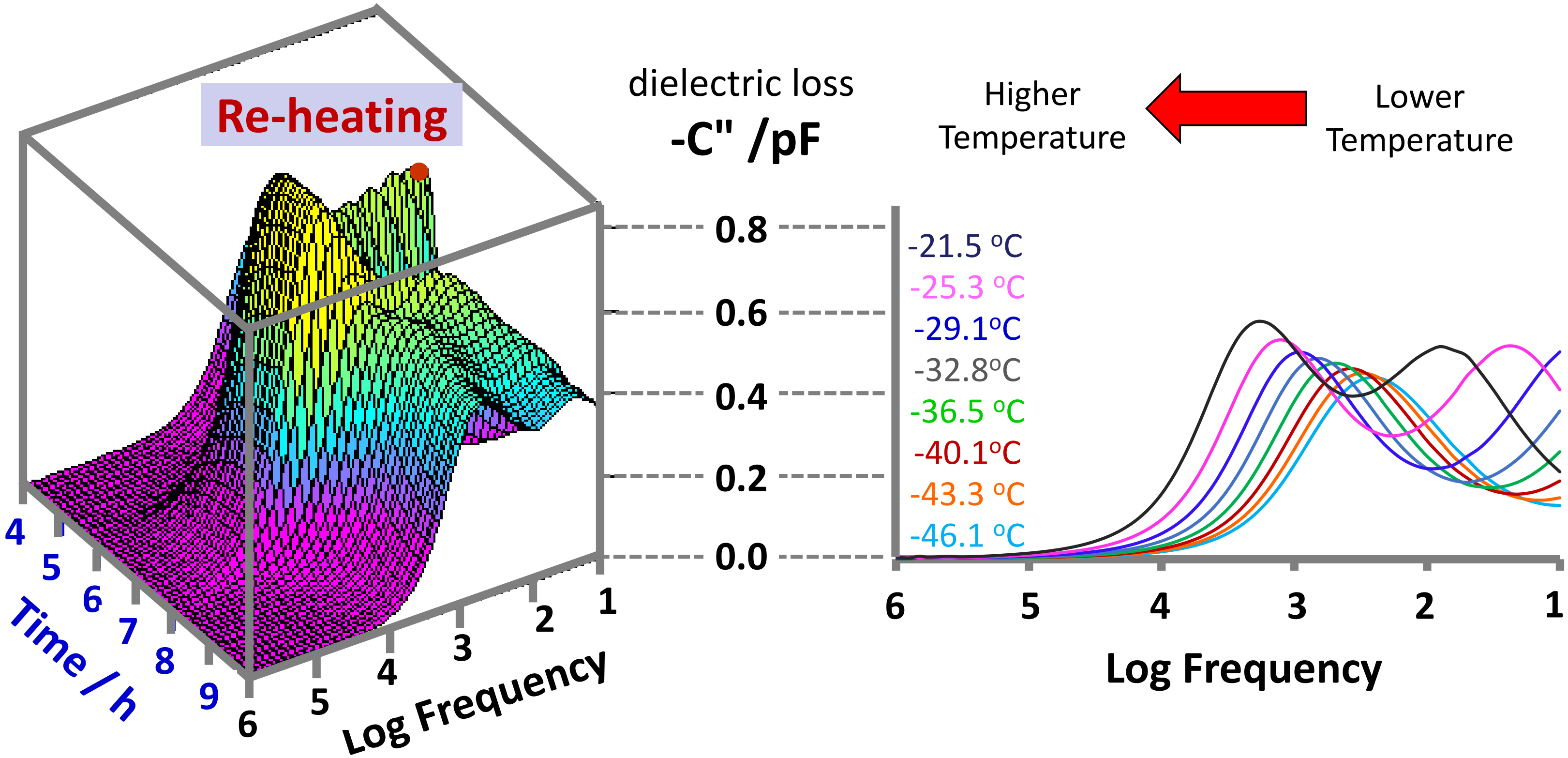
and so in the case of an aqueous solution, the resistivity/resistance will also decrease as the temperature increases

## TVIS Application
## *Annealing for Temperature Calibration*

**5%w/v Lactose in deionised water**

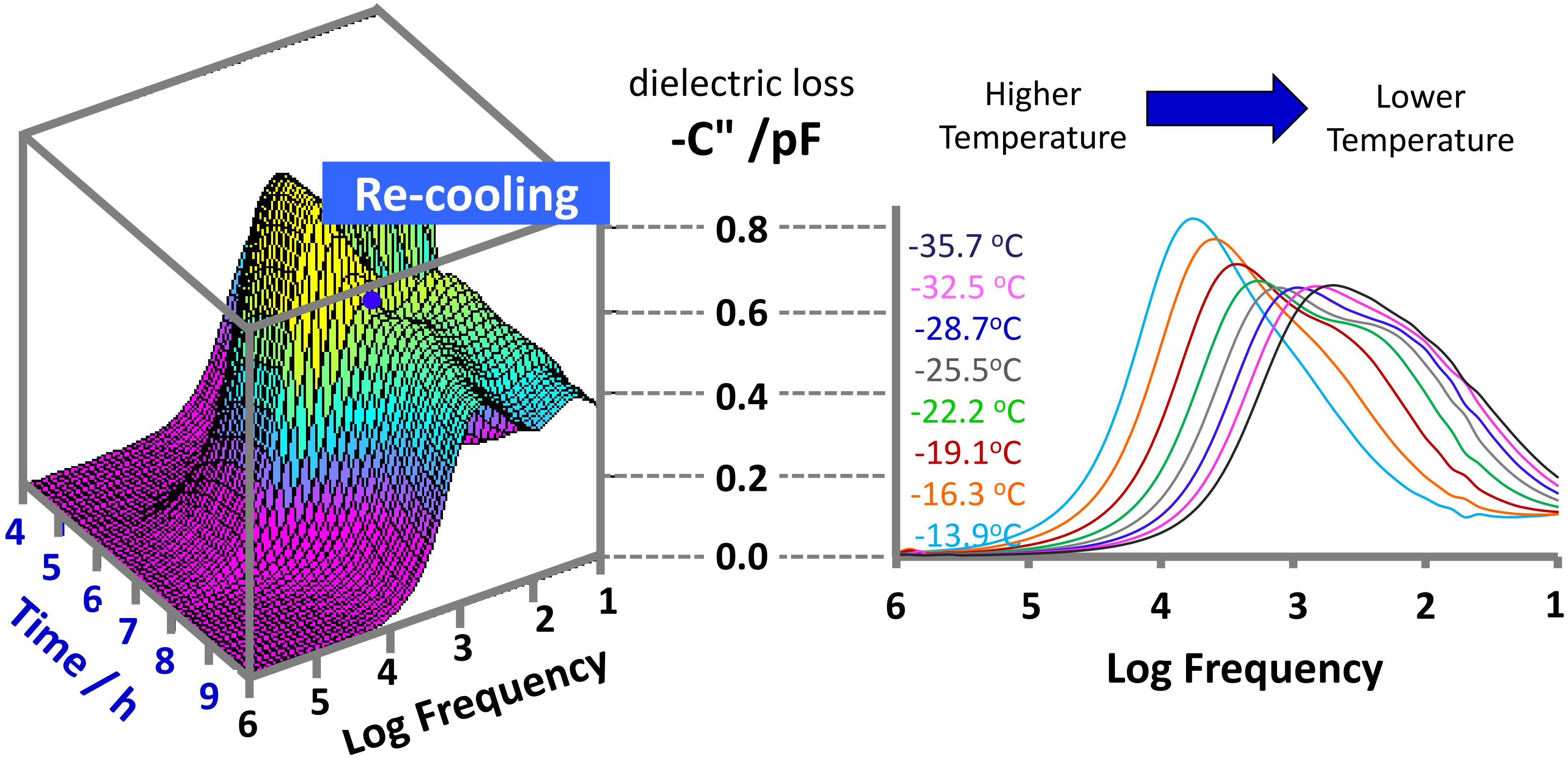
# The relationship between $F_{PEAK}$ and Product Temperature/Phase Transition

Re-heating

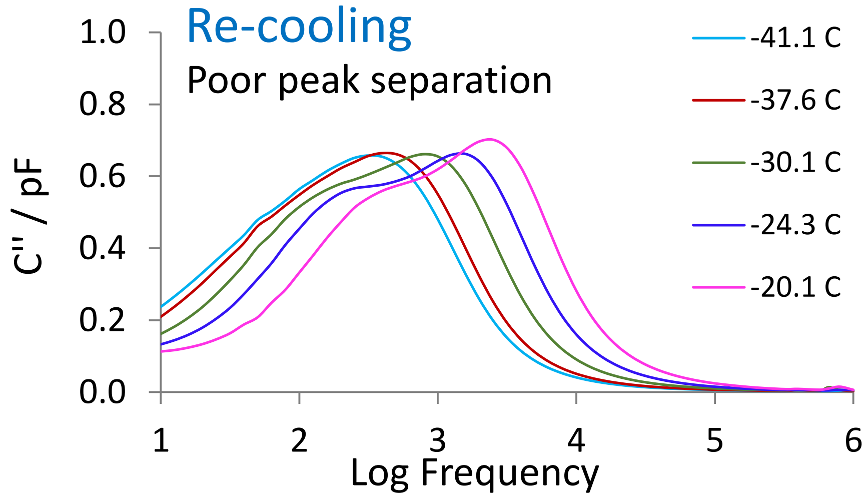


# The relationship between $F_{PEAK}$ and Product Temperature/Phase Transition

Re-cooling

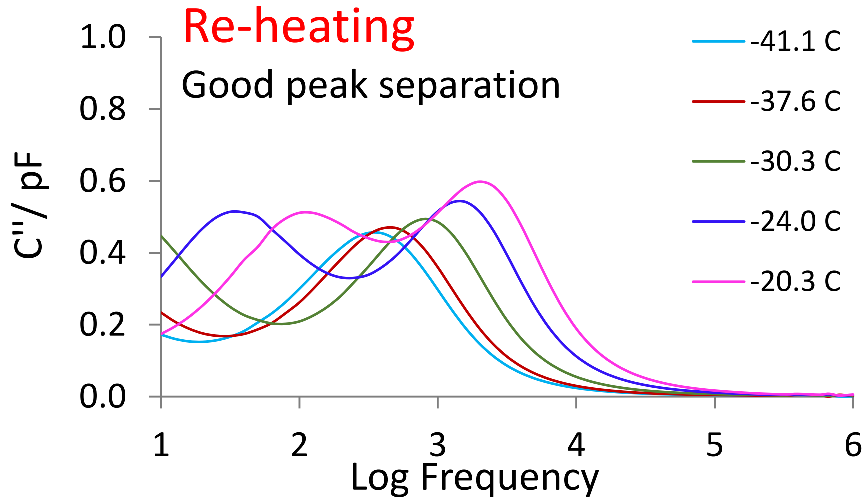


# Temperature  Calibration




## 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

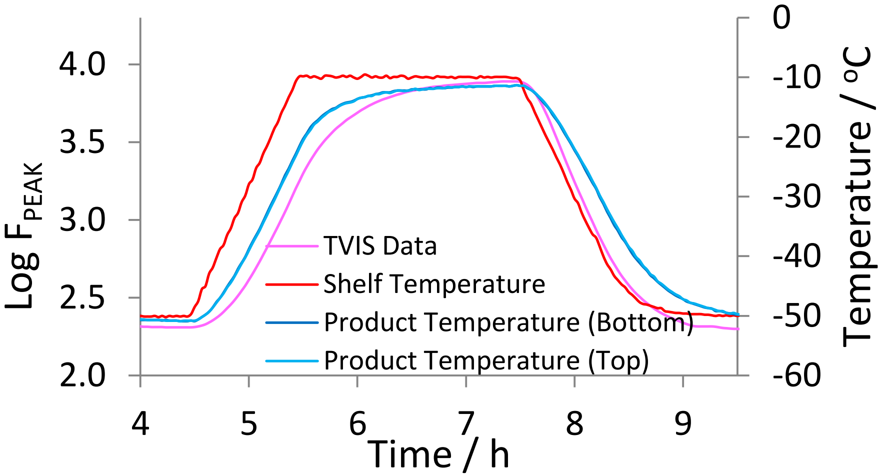


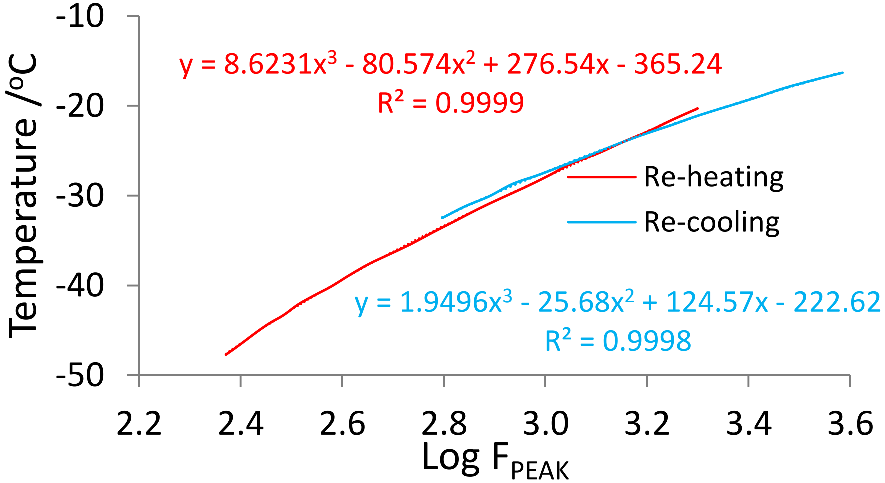

## Re-heating

- 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

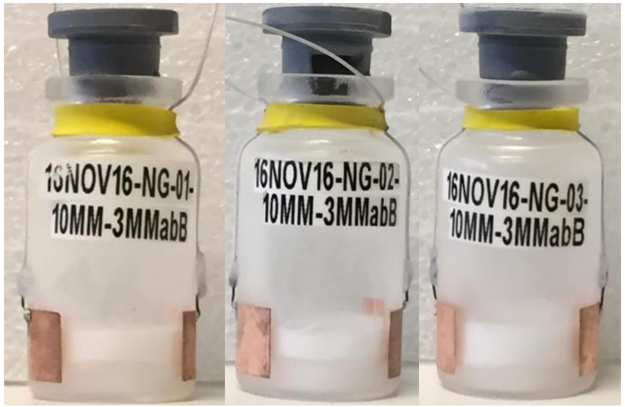


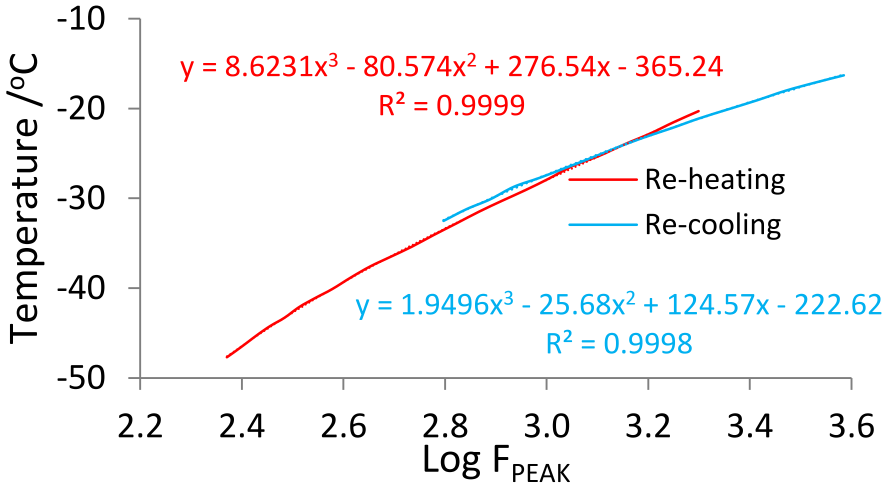
**5%w/v Lactose in deionised water**

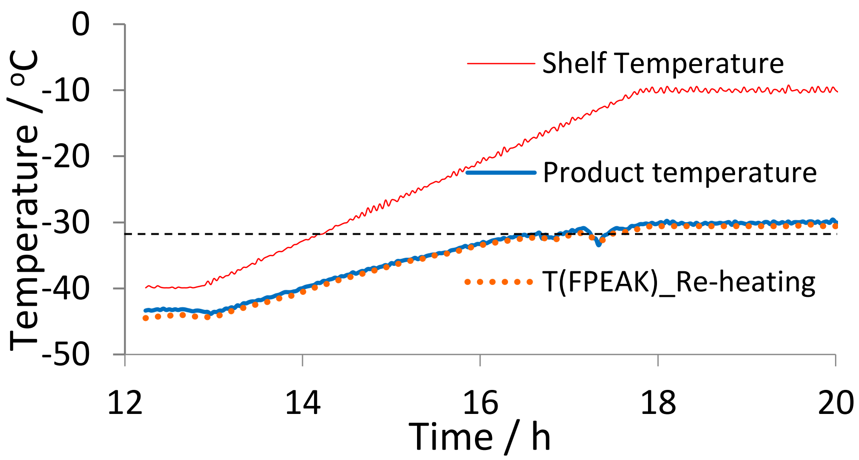
# TVIS Application

## *Primary Drying (1) Product temperature prediction*



# Temperature Prediction in Primary Drying



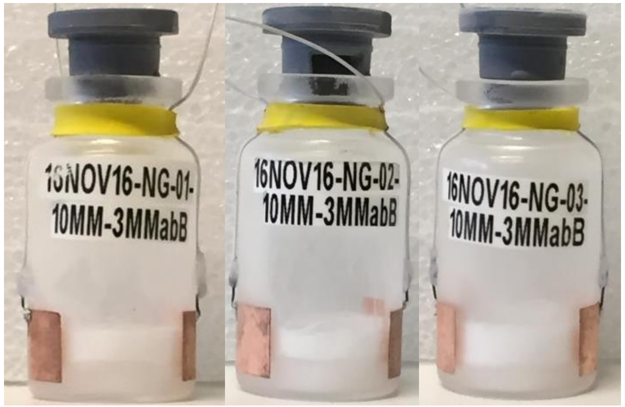




- Re-heating calibration curve selected for temperature prediction in primary drying : $T(F_{PEAK})$
- Good agreement between production temperature (by TC) and $T(F_{PEAK})$
- At approx. –32 $^oC$ (product collapse) the time profile of each parameter undergoes some instability

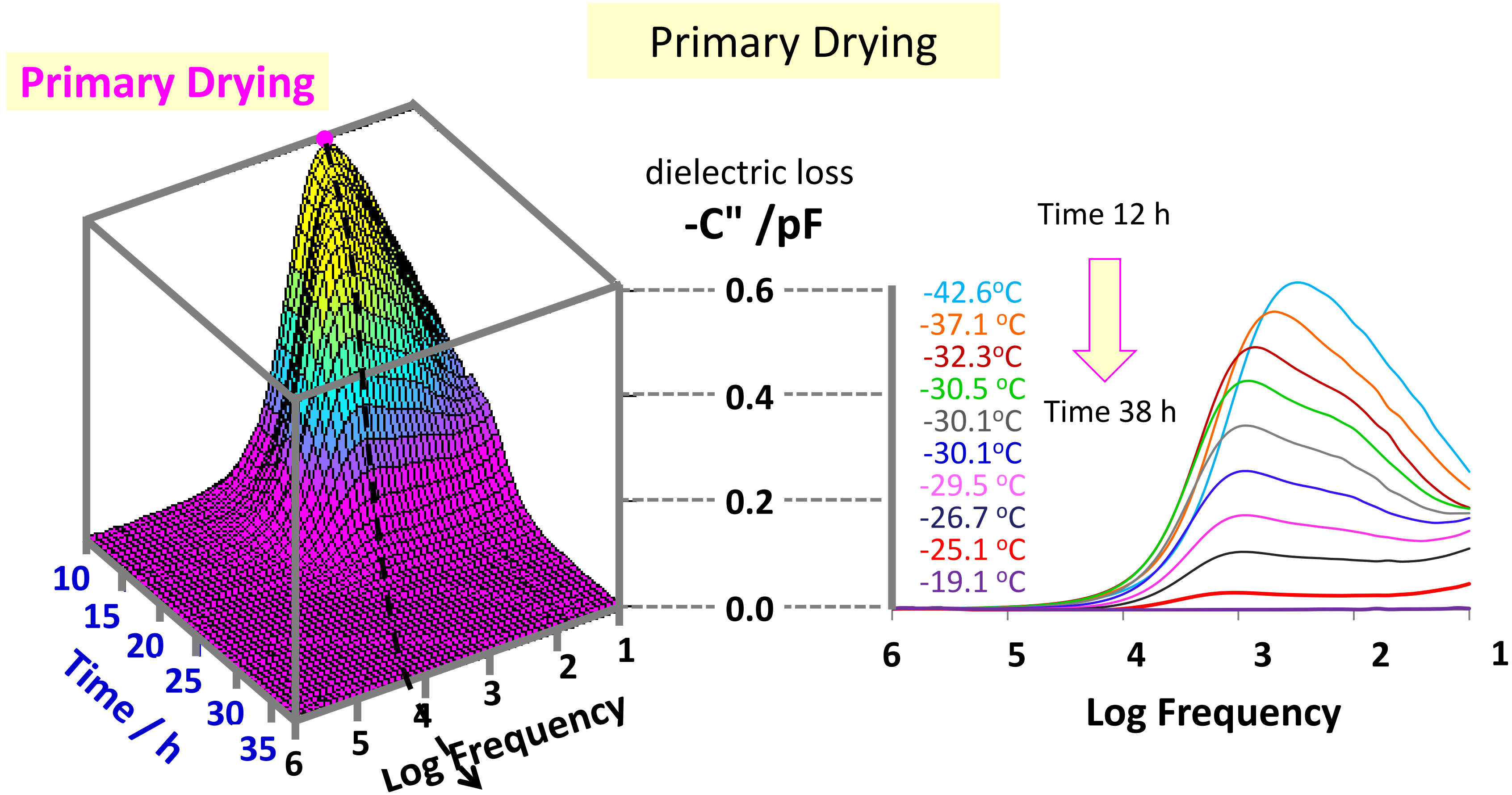
**5%w/v Lactose in deionised water**

# TVIS Application

*Primary Drying (2) Drying Rate Prediction*



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



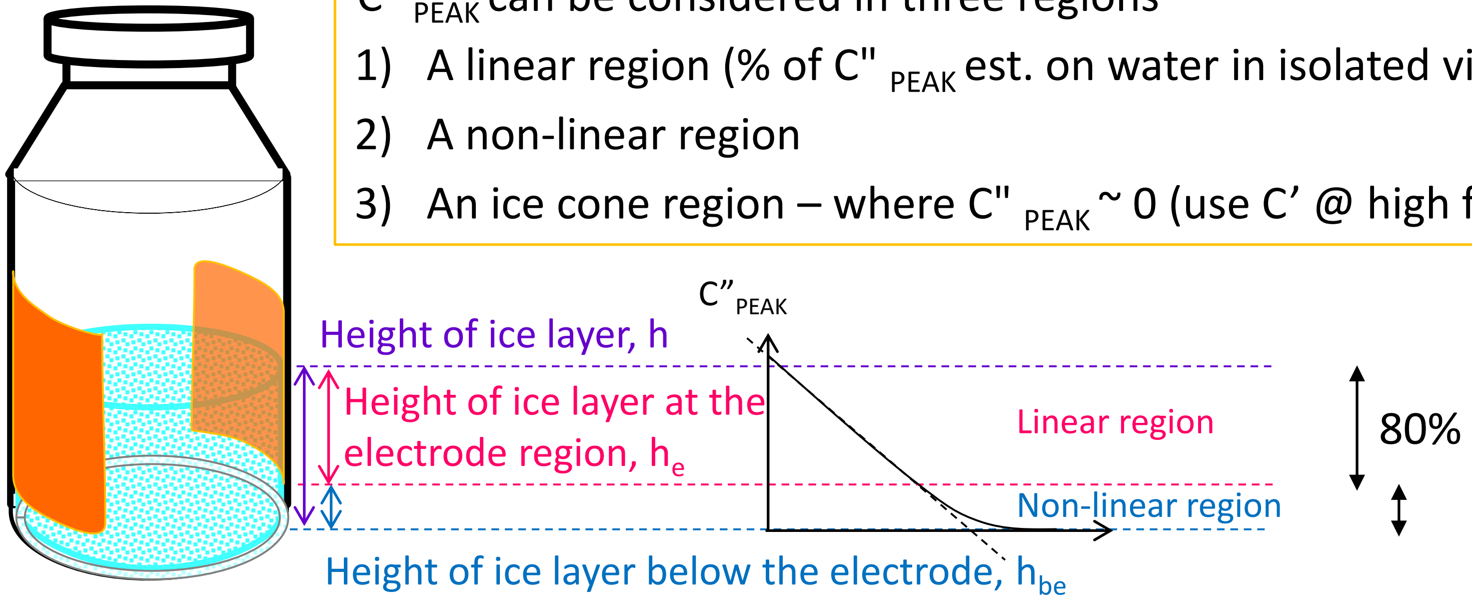
# C" $_{PEAK}$ Criteria & Assumptions

- 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.

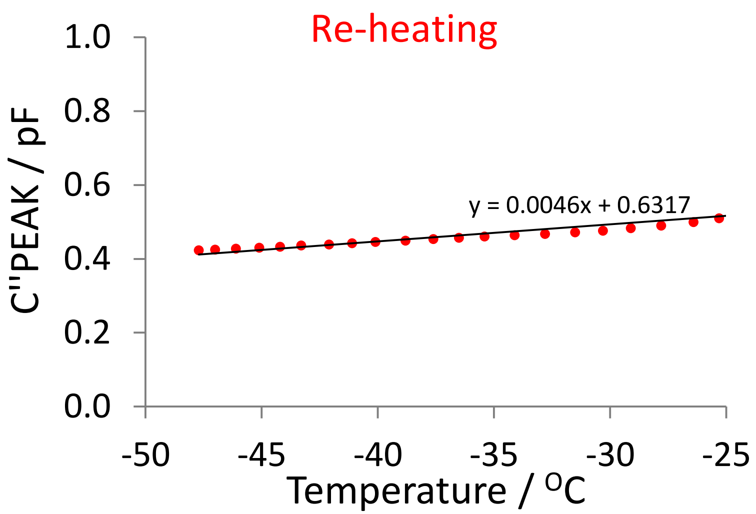
$$C''_{peak} = \frac{C_G^2}{2(C_S+C_G)}$$

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

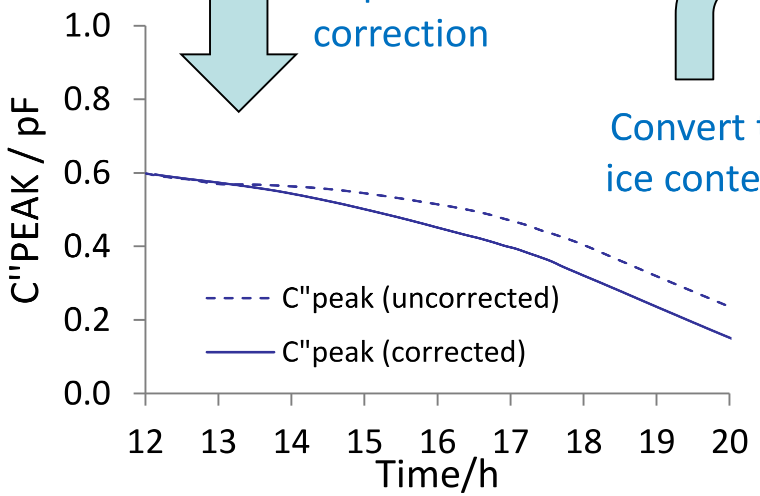
1) A linear region (% of C" $_{PEAK}$ est. on water in isolated vial)
2) A non-linear region
3) An ice cone region – where C" $_{PEAK}$ ~ 0 (use C’ @ high freq.)



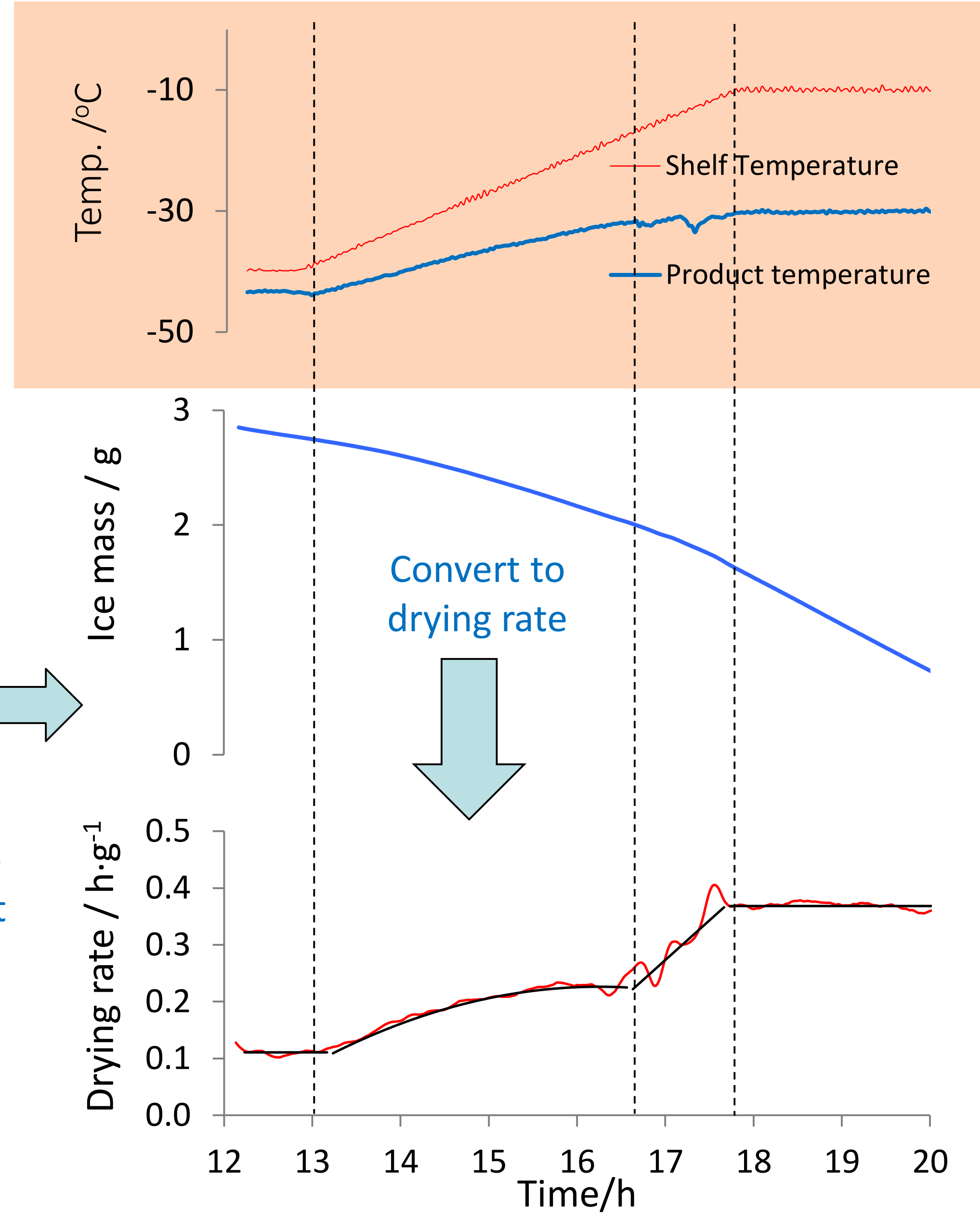
# Drying Rate (*dm/dt*) Determination




Temperature correction



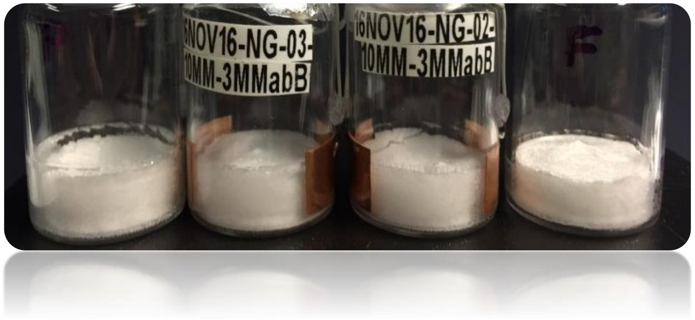

Convert to ice content



## 5%w/v Lactose in deionised water

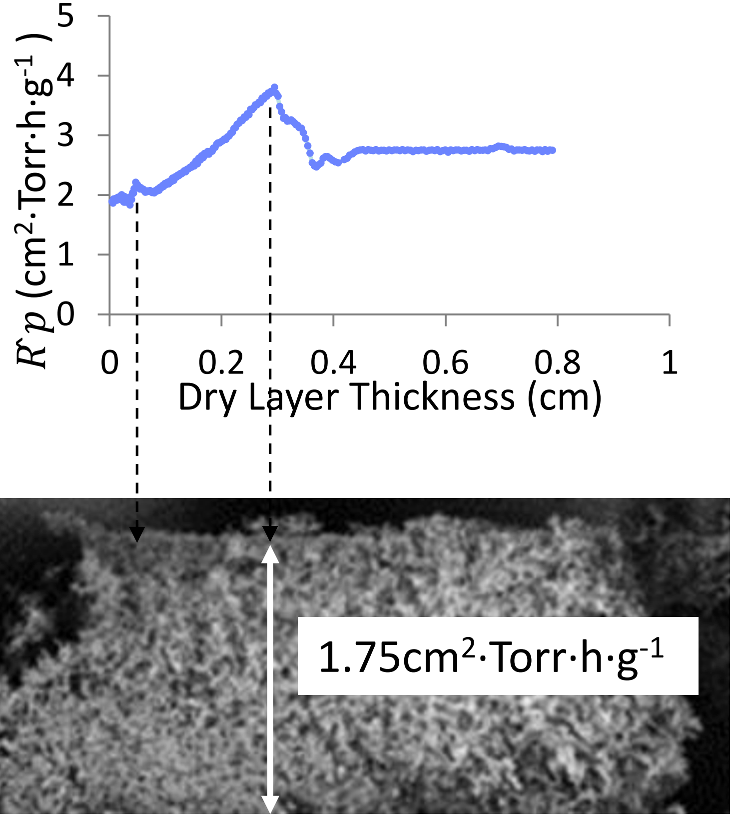
# TVIS Application

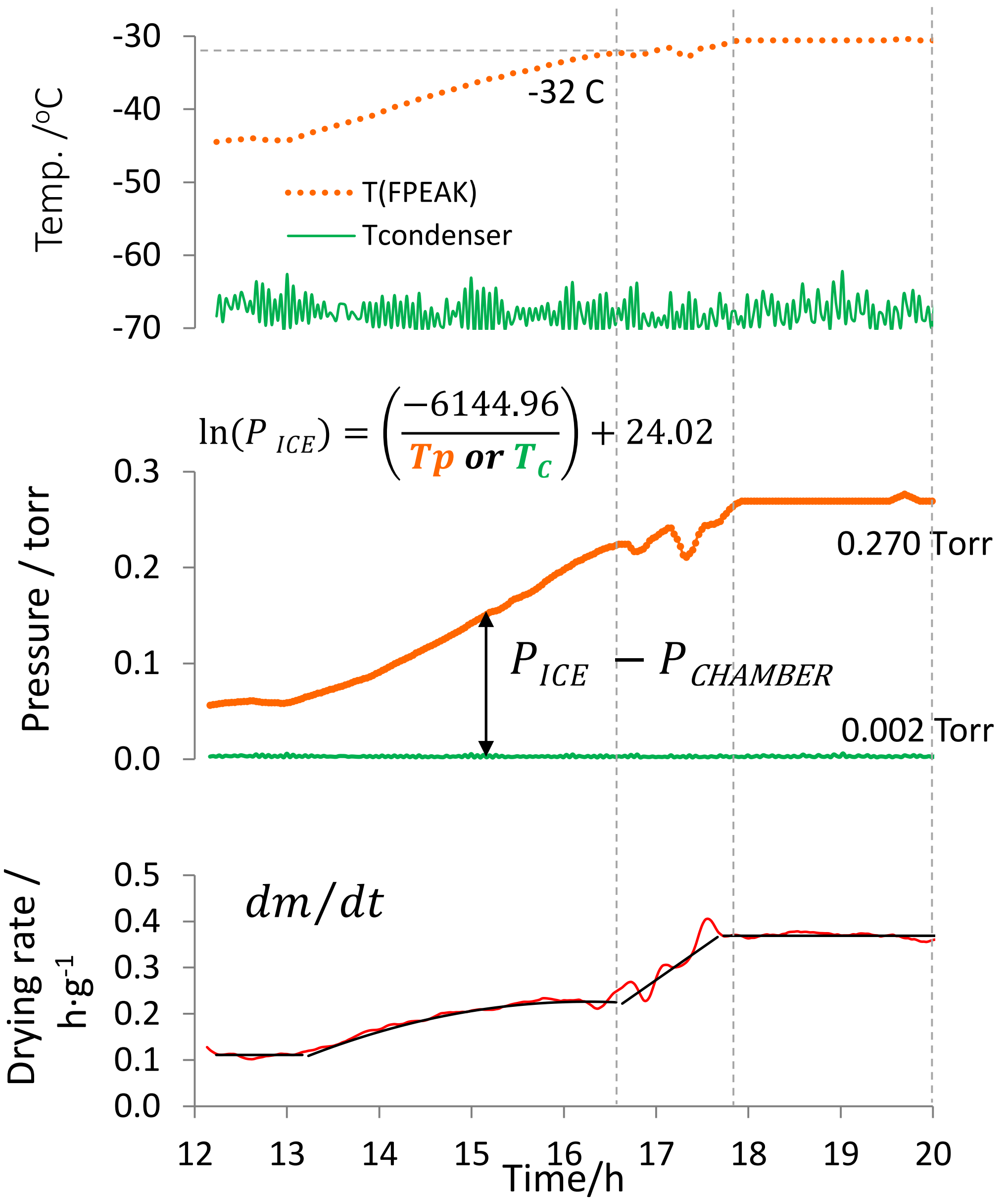
*Primary Drying: Rp determination*



# Lactose Dried Product Resistance ($R_p$)

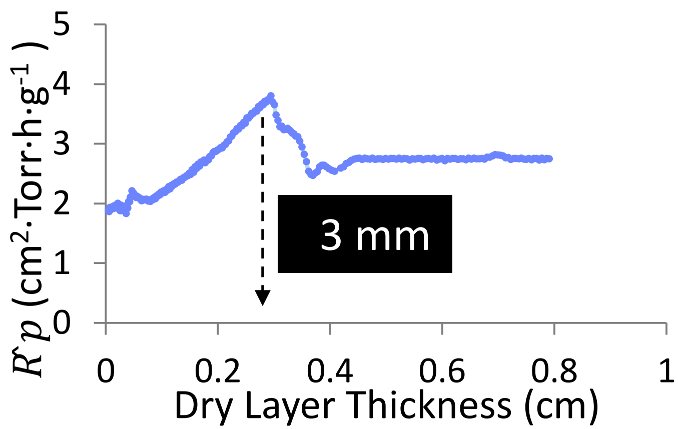
$$\hat{R}p = \left(\frac{P_{ICE} - P_{CHAMBER}}{dm/dt}\right) \cdot A_P$$

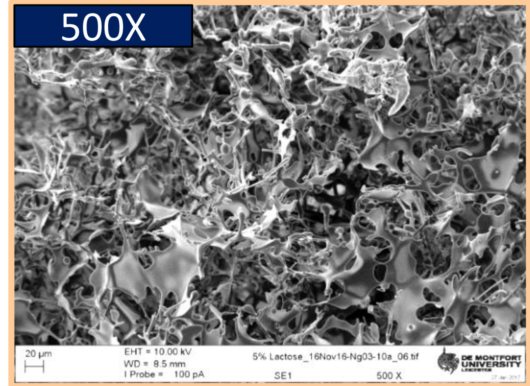


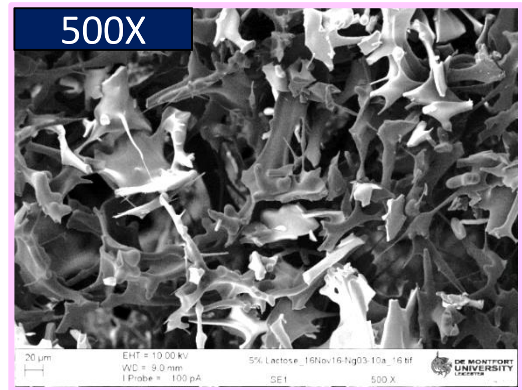
# Lactose Dry Layer Product Resistance ($R_P$)

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

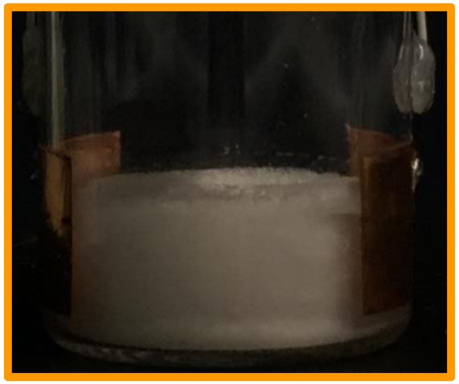


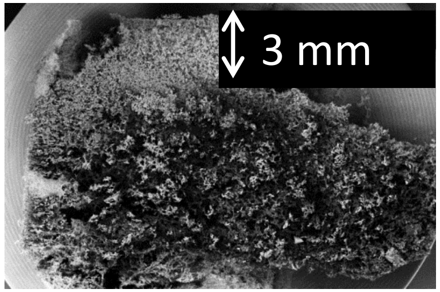



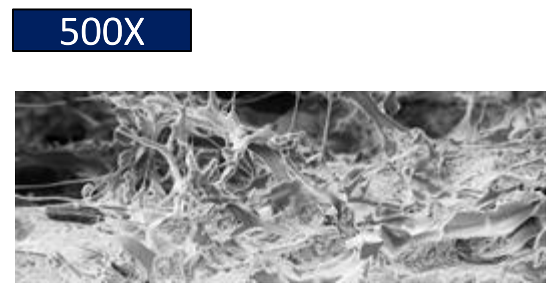

Top layer
Fine pores




Middle layer
Micro-collapse






Bottom layer
Full collapse

# Acknowledgements, Recent Projects & Collaborators

- De Montfort University
  - Evgeny Polygalov. Senior Research Fellow
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  - Yowwares Jeerarunangrattana. PhD student
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  - Trevor Page & Julian Taylor
  - Daniela Buchmeyer & Thomas Beutler
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- NIBSC : Paul Matejtschuk
- Sanofi : Tim McCoy

BIOSTART

AtlasBio

GEA Pharma Systems

bluefrog design

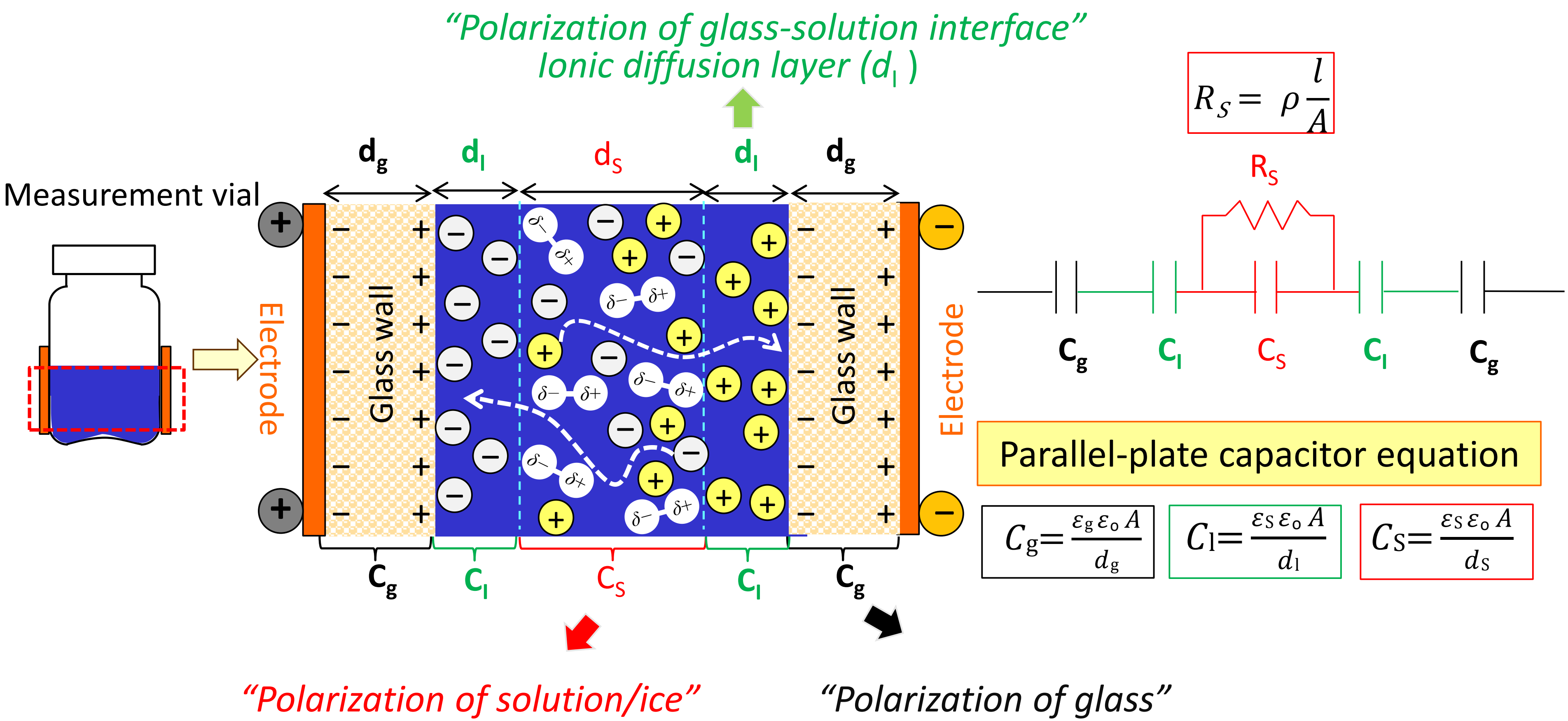
NIBSC Confidence in Biological Medicines

SANOFI

Innovate UK

# Annex : TVIS Theory

# Equivalent circuit model




$$R_S = \rho \frac{l}{A}$$

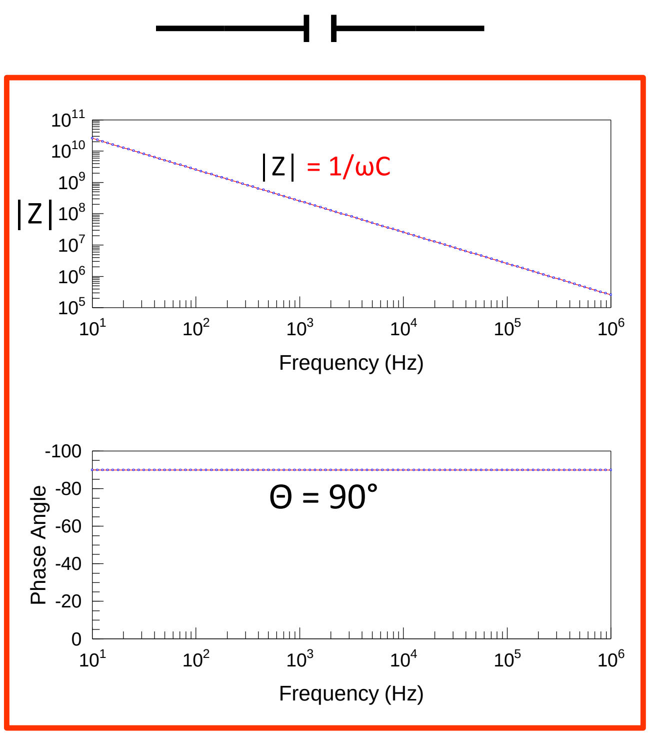
Parallel-plate capacitor equation

$$C_g = \frac{\varepsilon_g \varepsilon_o A}{d_g} \qquad C_l = \frac{\varepsilon_S \varepsilon_o A}{d_l} \qquad C_S = \frac{\varepsilon_S \varepsilon_o A}{d_S}$$

# 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

C

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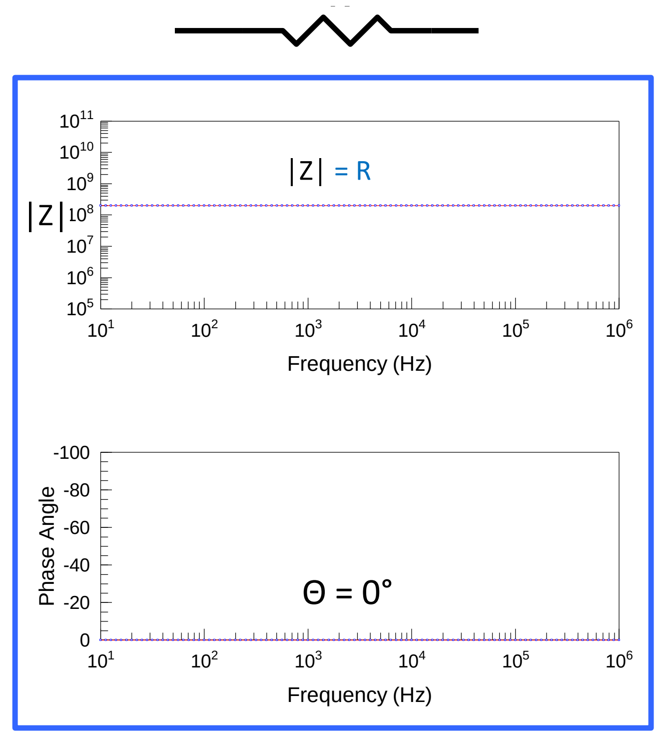
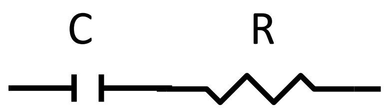
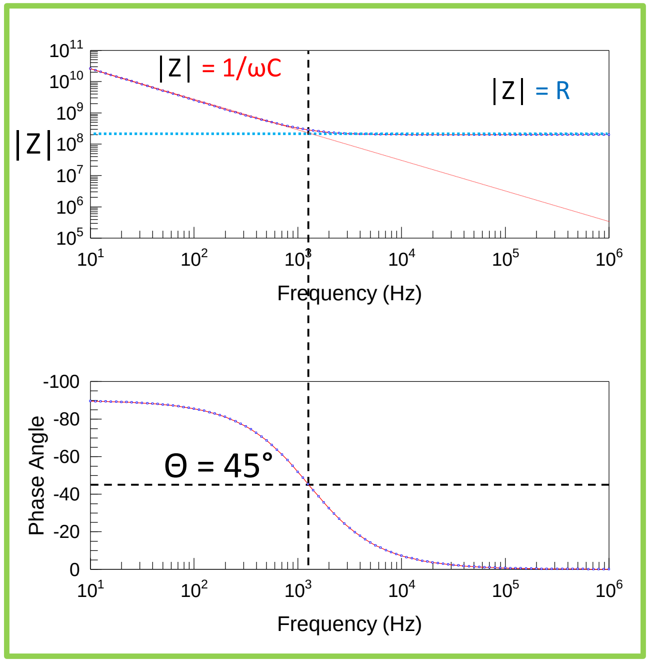


# Impedance Spectroscopy

- 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.



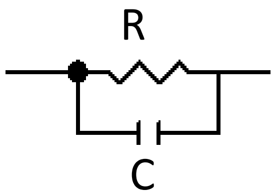

**In a series circuit**

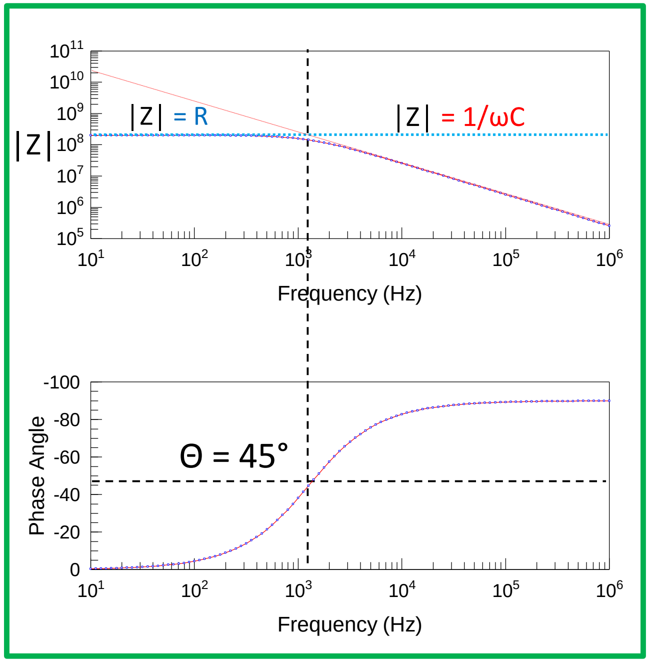
@ low frequency the capacitor dominates the spectrum because the impedance of the capacitance is so high that the capacitor effectively controls the current that flows through the circuit

@ 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.

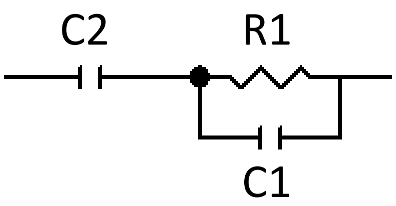


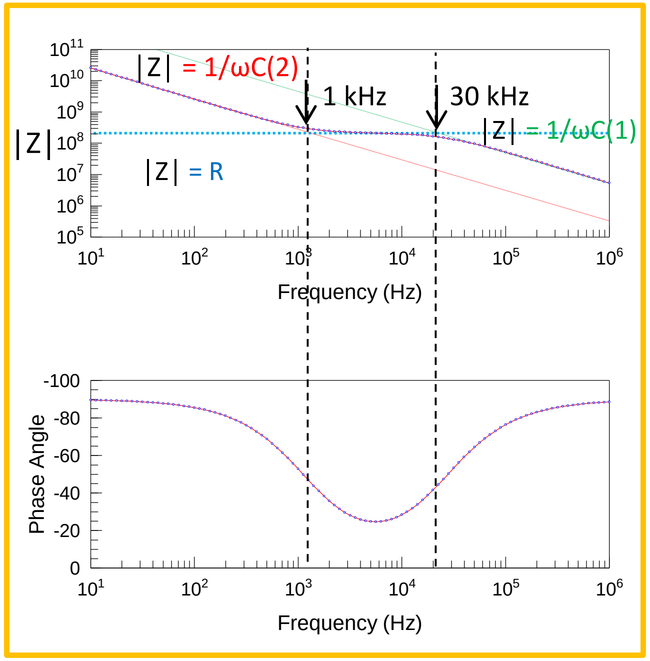




**In a parallel circuit**
@ low frequency the resistor dominates the spectrum because the impedance of the capacitance is so high that all the current flows through the resistor.
@ high frequency the capacitor dominates the spectrum because the impedance of the capacitance is now lower than the resistor 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.

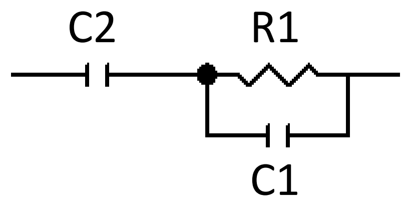


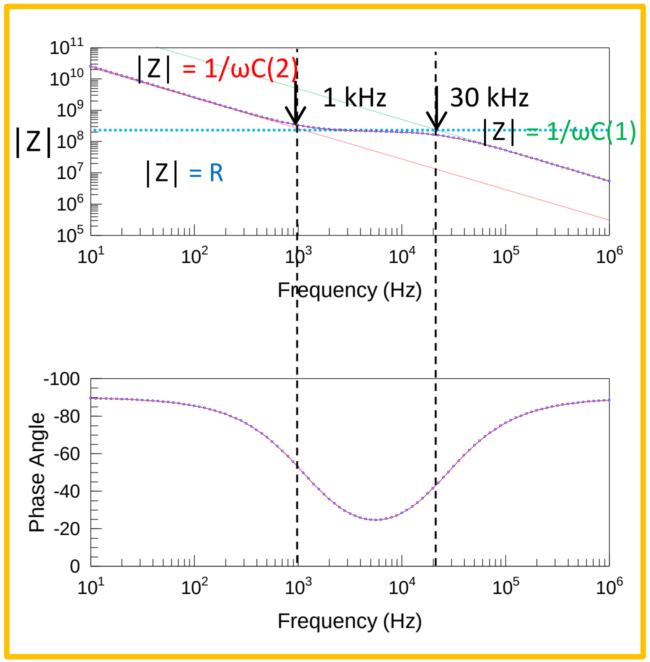



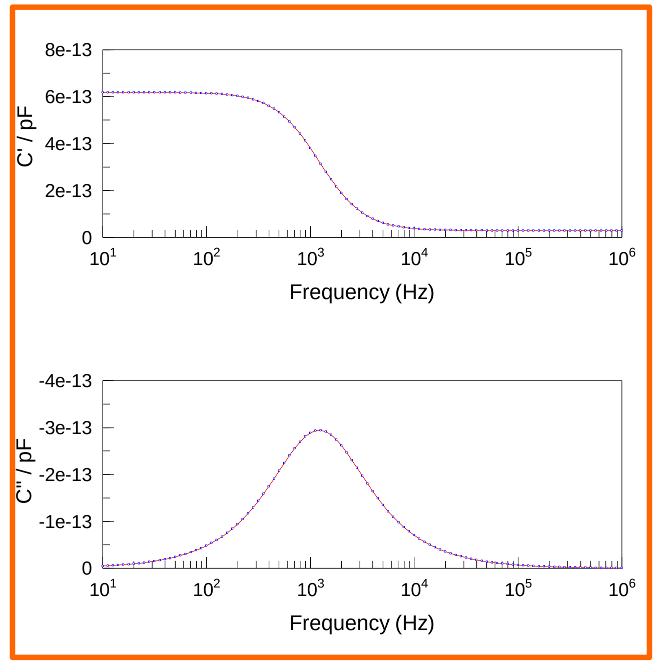

**In a complex circuit**
**@ low frequency** (<1 kHz) the resistor R1 dominates the impedance of the R1C1 circuit, but because this circuit is in series with a capacitor , C2 (which has a high impedance at low frequency) then C2 effectively controls the current that flows through the entire circuit
**@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

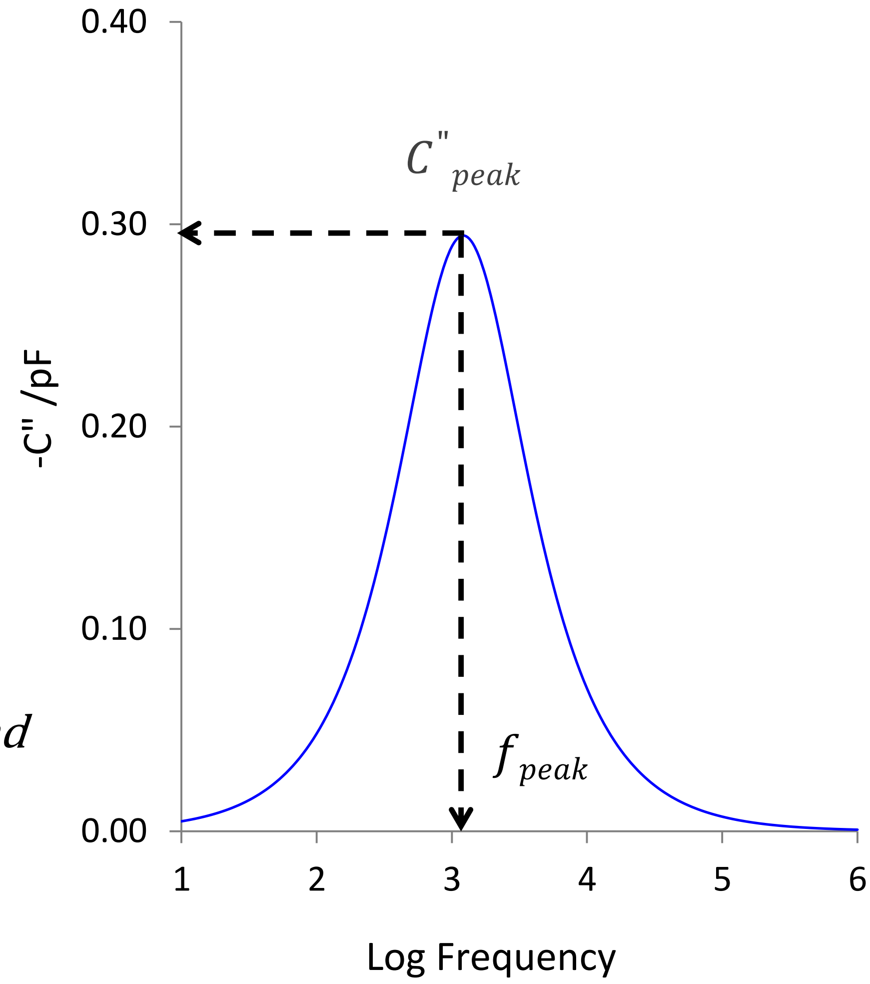
# Interfacial Polarization Characteristic

- 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

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

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

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



# Interfacial Polarization Characteristic

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

$$Z^*{}_{\text{Total}} = Z^*(C_{\text{G}}) + \left[\frac{1}{Z^*(R_{\text{S}})} + \frac{1}{Z^*(C_{\text{S}})}\right]$$

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

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