DE MONTFORT UNIVERSITY LEICESTER

Impedance Spectroscopy :

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

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TVIS Through Vial Impedance Spectroscopy

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PHARMACEUTICAL LYOPHILIZATION SUMMIT 2019

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Prague, Czech Republic

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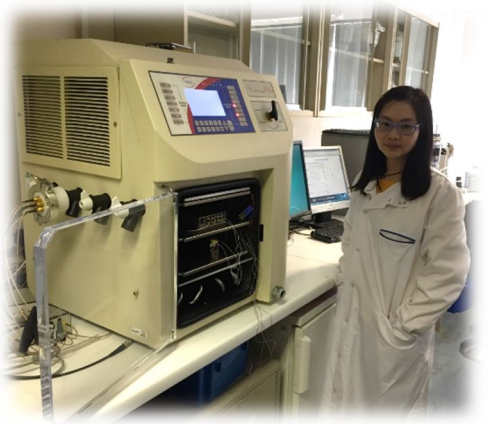
Introduction to the TVIS System

- Impedance spectroscopy characterizes the ability of materials to conduct electricity under an applied an oscillating voltage (of varying frequency)
- Impedance measurements across a vial rather than within the vial
- Hence **"Through Vial Impedance Spectroscopy"**

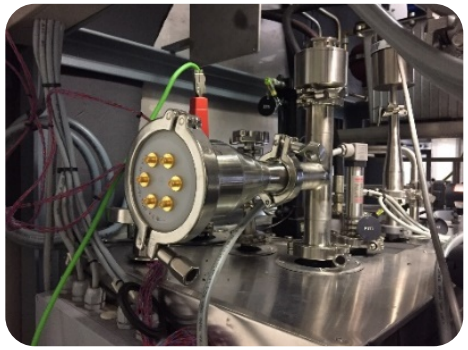
- Features
  - Single vial "non-product invasive"
  - Both freezing and drying characterised in a single technique
  - Non-perturbing to the packing of vials
  - Stopper mechanism unaffected

Outline of talk

- Introduction
  - Dielectric loss mechanisms
- TVIS Theory
  - What frequency for what process?
  - Observations on ice
- TVIS Applications
  - Ice nucleation
  - Ice growth
  - Solidification end point
- Acknowledgements
- Supplementary Slides
  - Description of measurement system
  - Applications in Brief



Yowwares Jeeraruangrattana
GPO Thailand



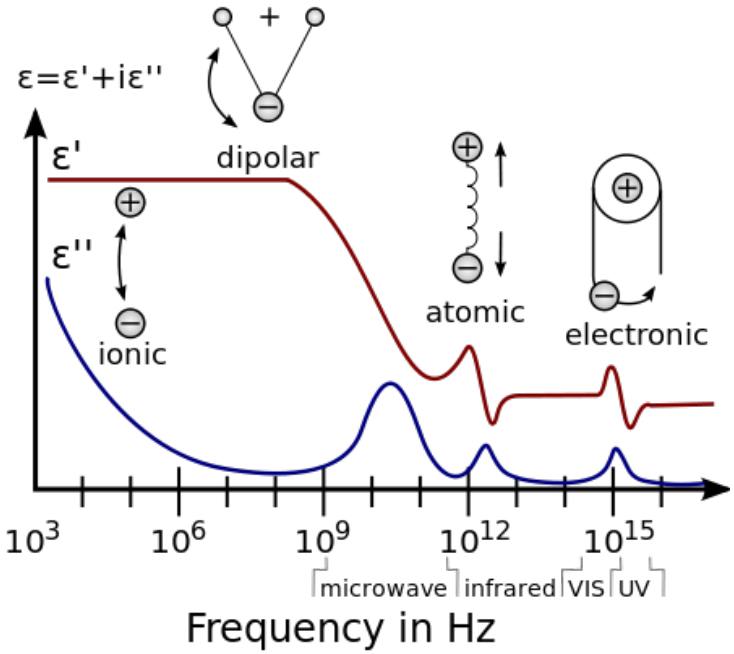
TVIS pass through on
GEA Lyophil dryer, Hurth, Cologne

Through Vial Impedance Spectroscopy (TVIS)

Dielectric Loss Mechanisms

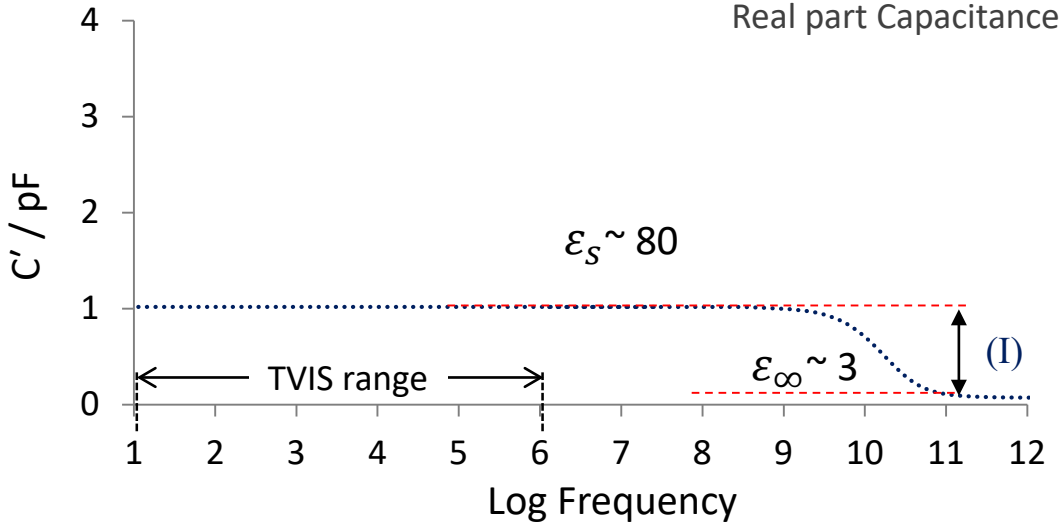
Dielectric Loss Mechanisms

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

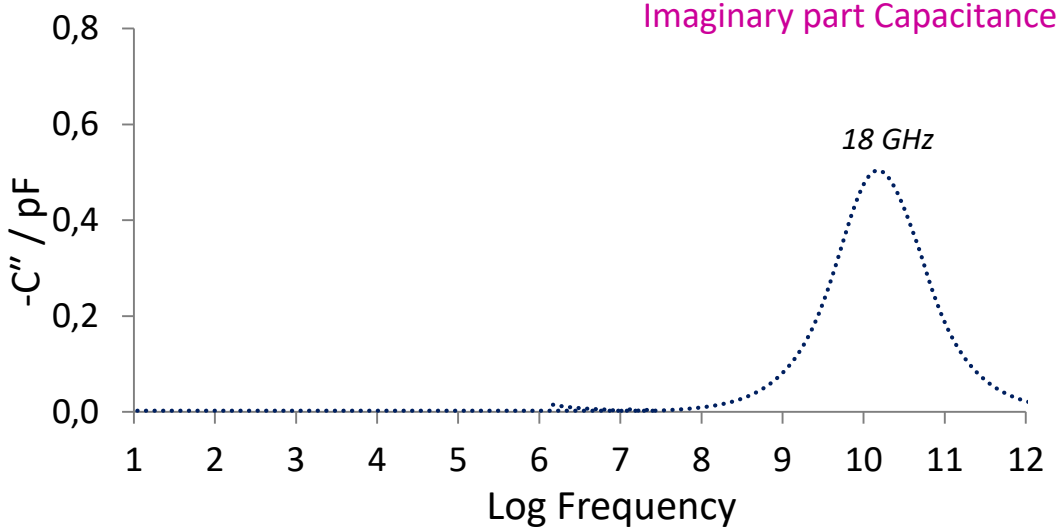


https://en.wikipedia.org/wiki/Permittivity

Real part Capacitance



Imaginary part Capacitance



Dielectric Loss Mechanisms

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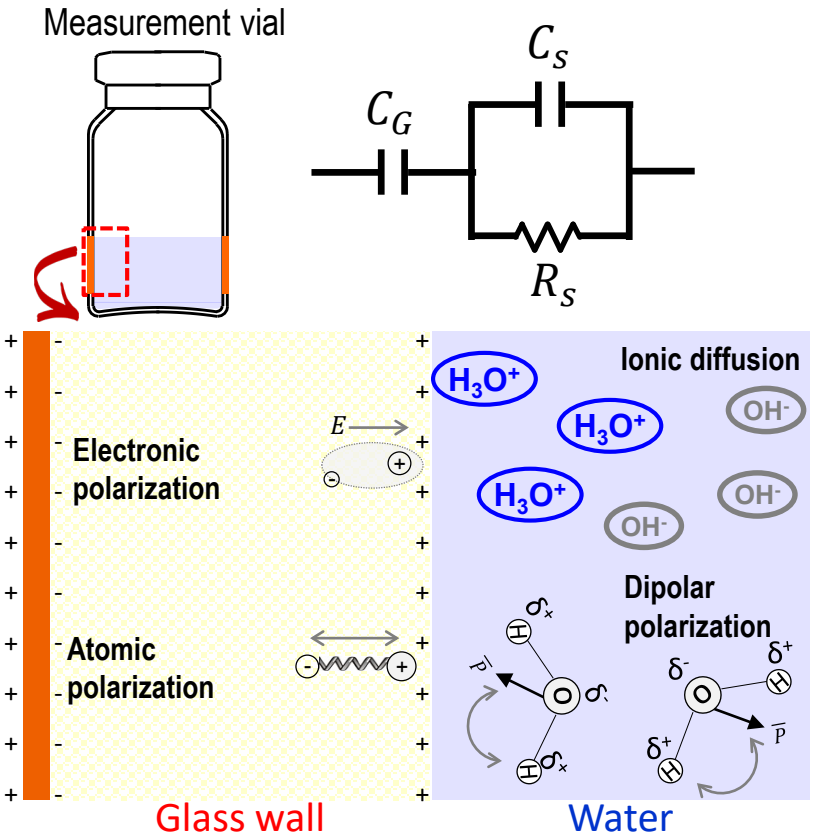

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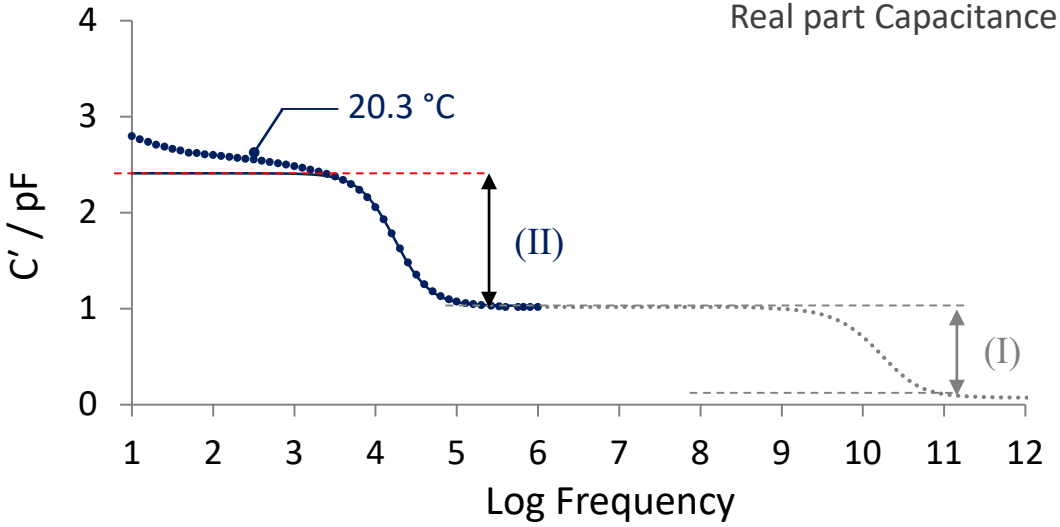

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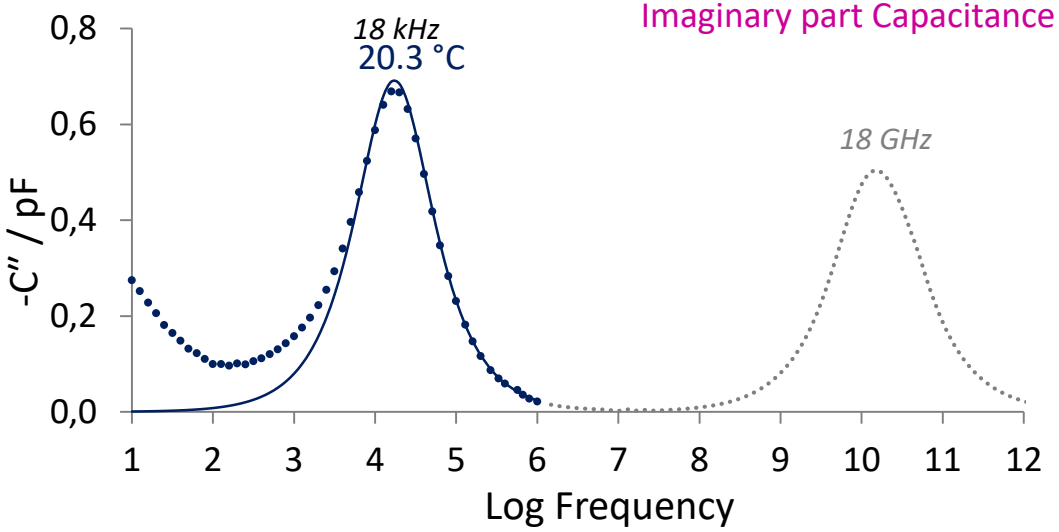

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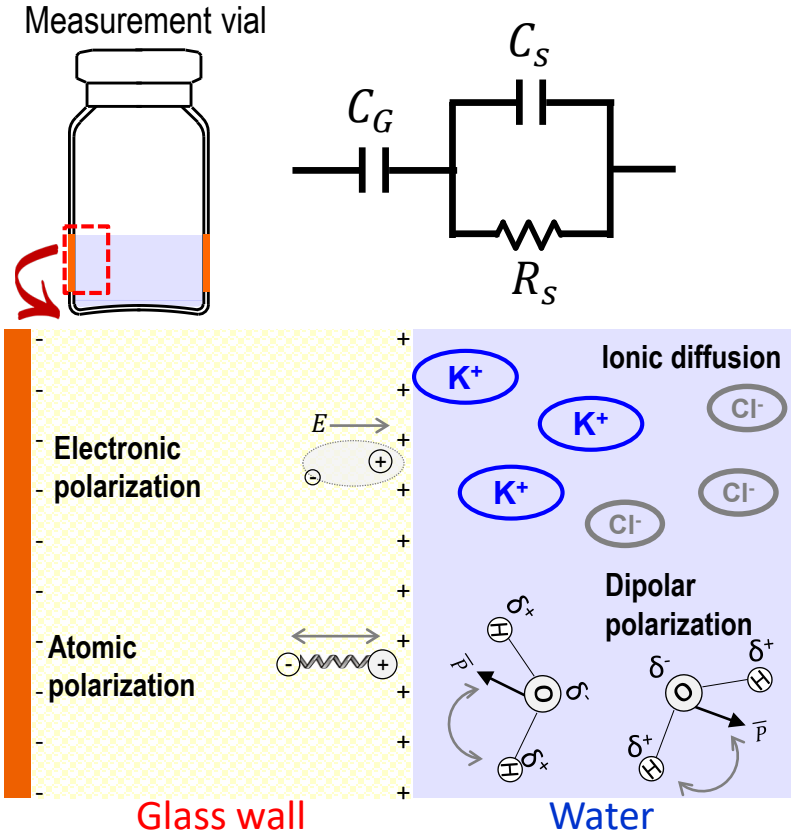
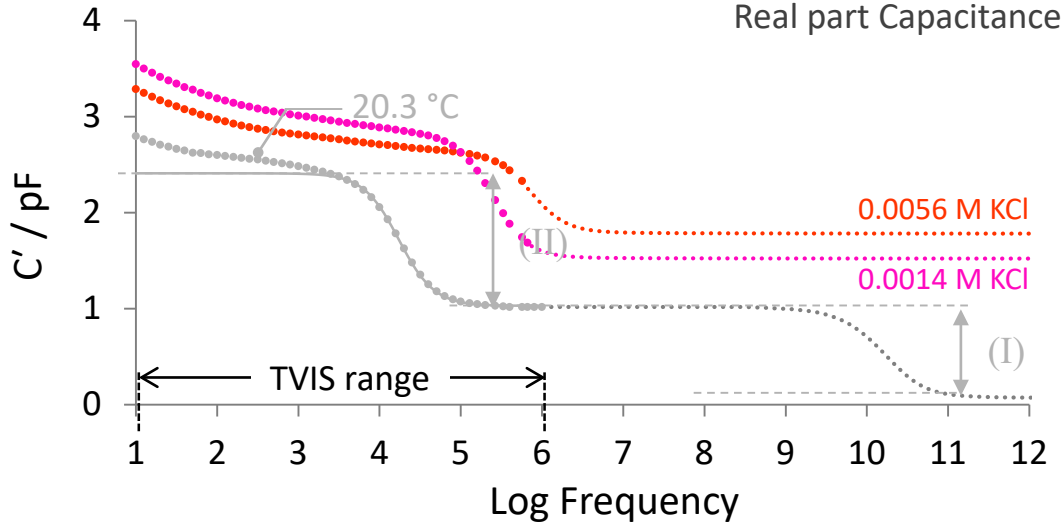
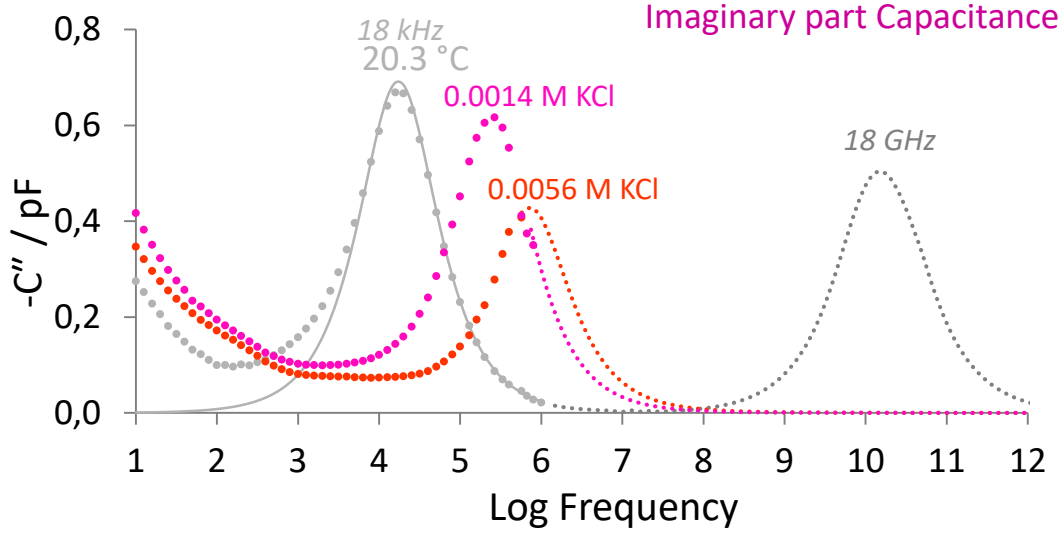
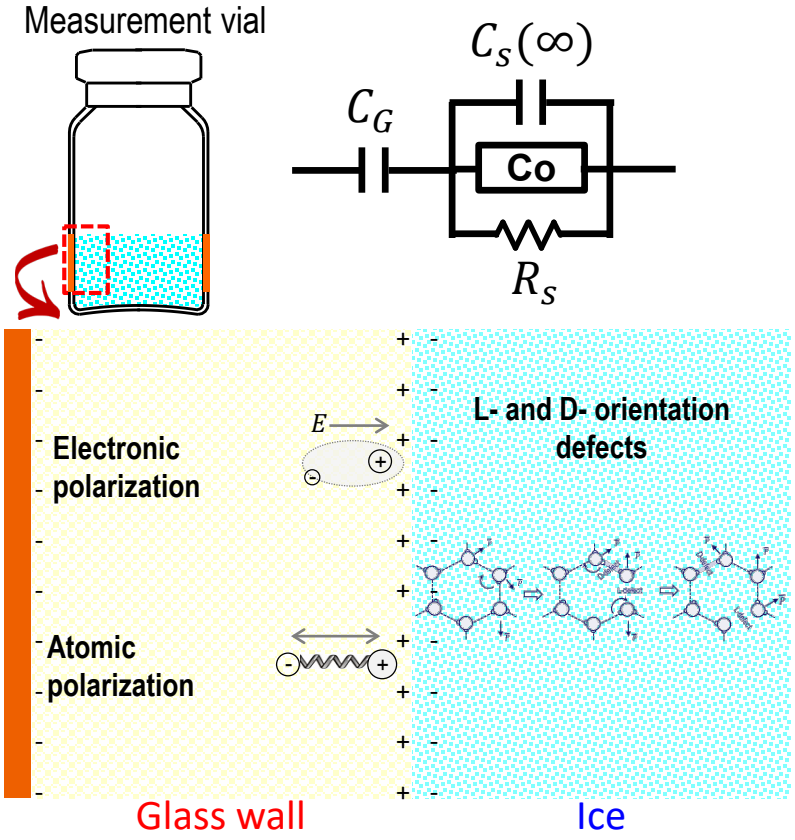


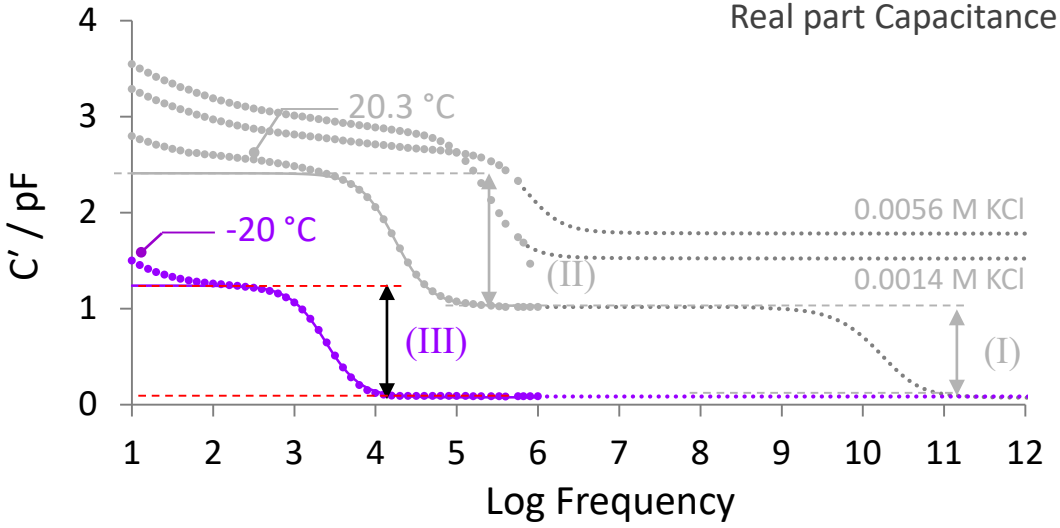


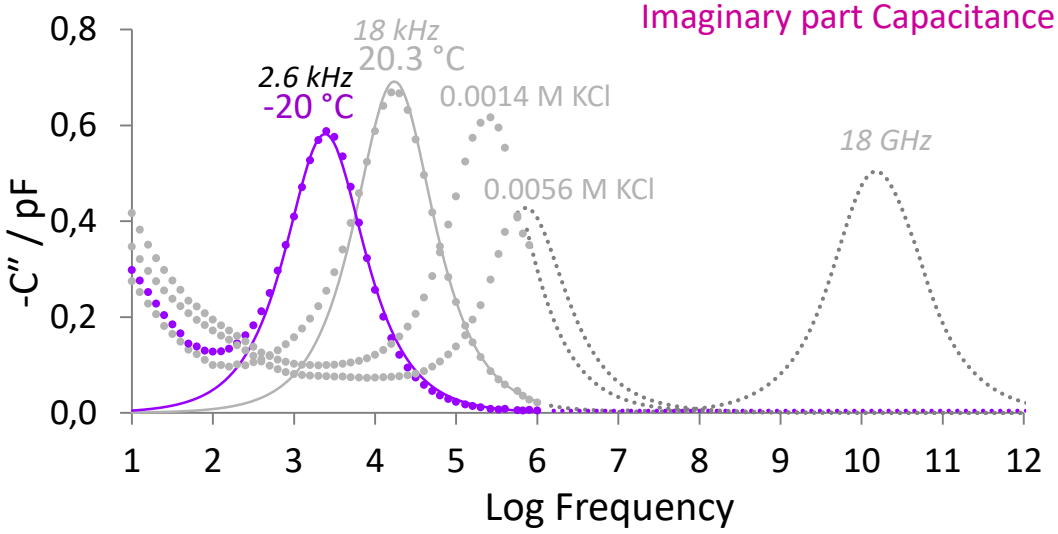


Dielectric Loss Mechanisms

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

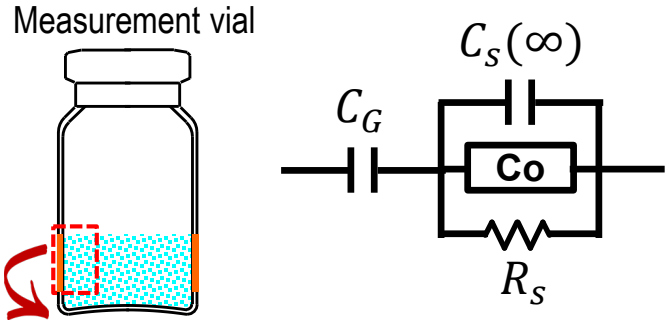


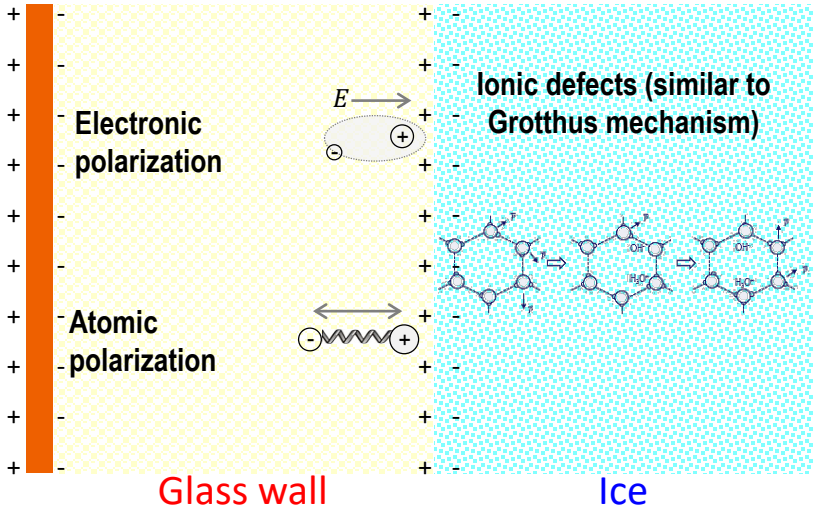


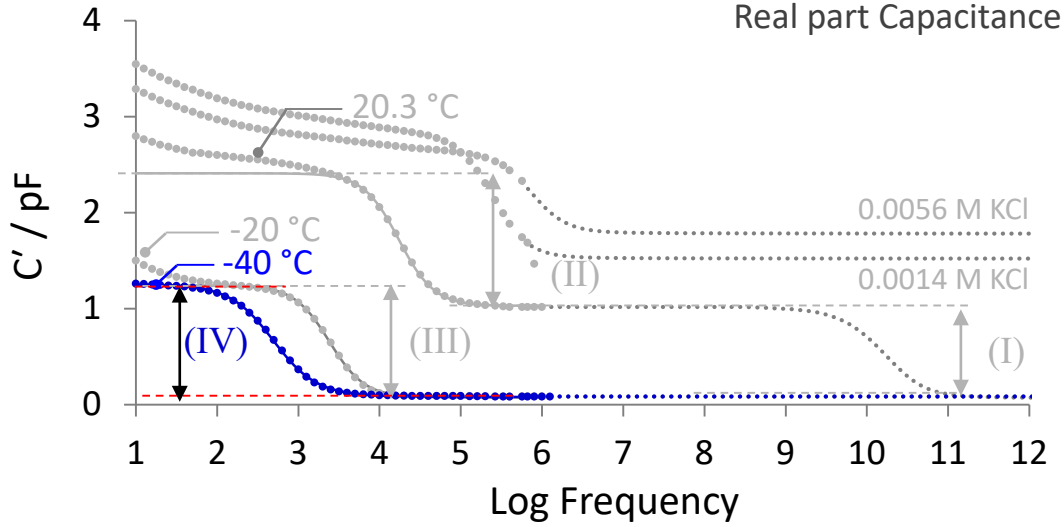


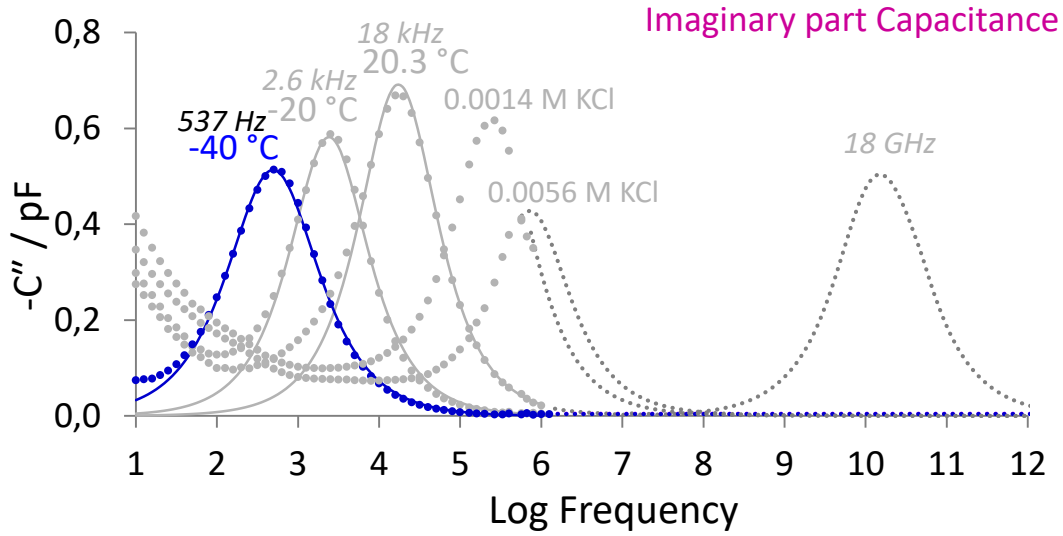
Dielectric Loss Mechanisms

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









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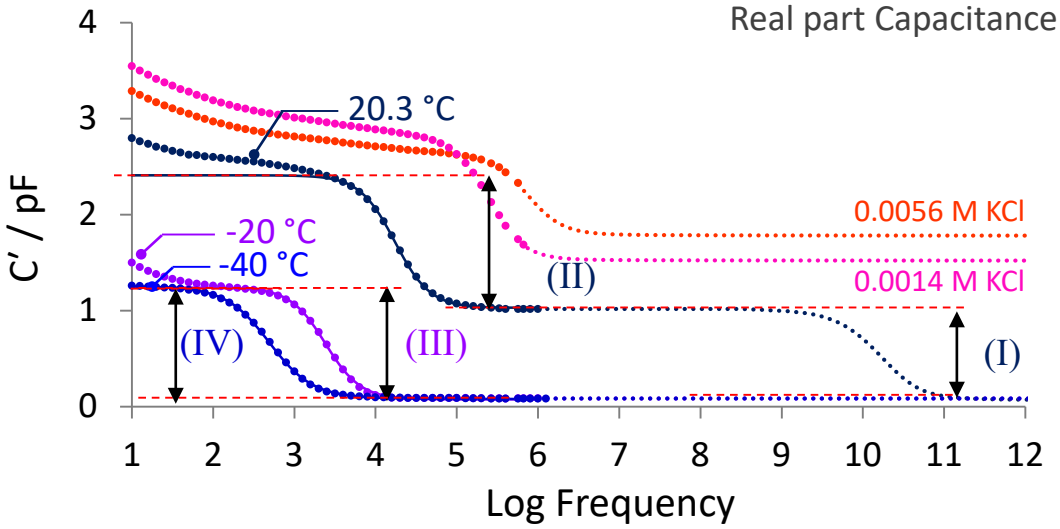
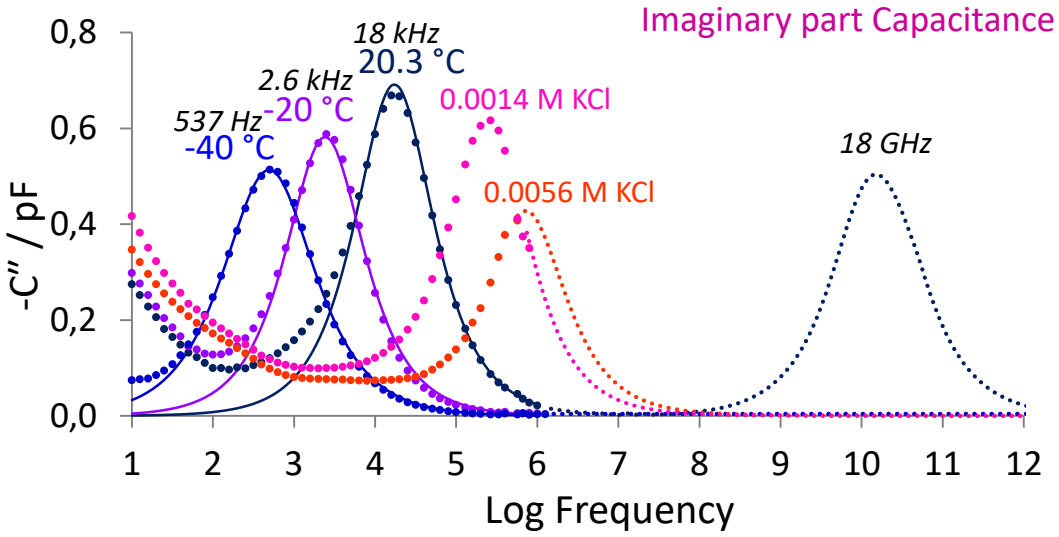


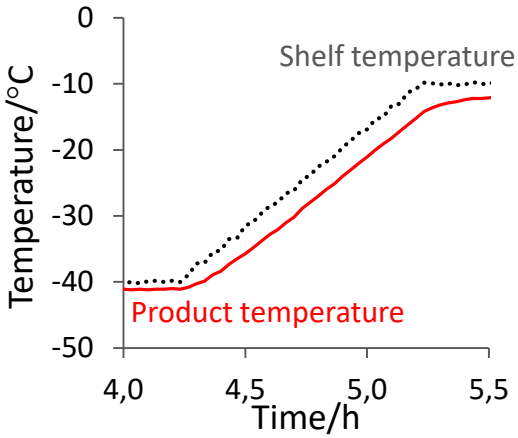


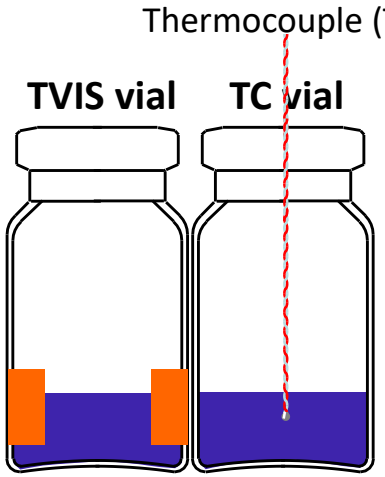
Through Vial Impedance Spectroscopy (TVIS)

What frequency for what process? Observations on Ice

Temperature Dependence of TVIS Parameters

Thermal cyclic of freeze drying process





TC in the nearest neighbour vial at a height equivalent to the mid point of the volume bounded by the electrodes

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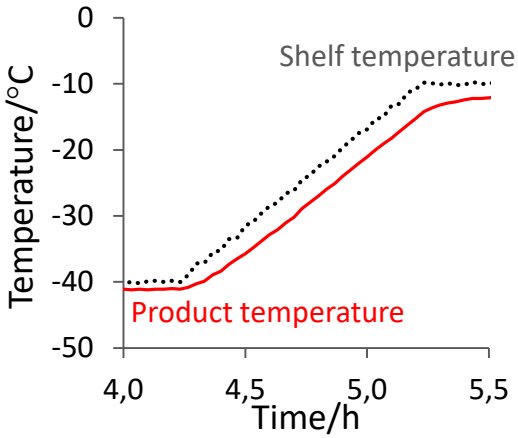

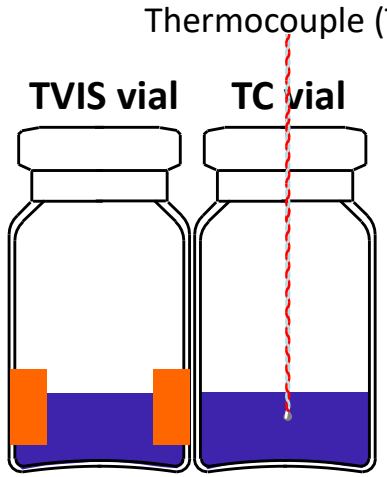

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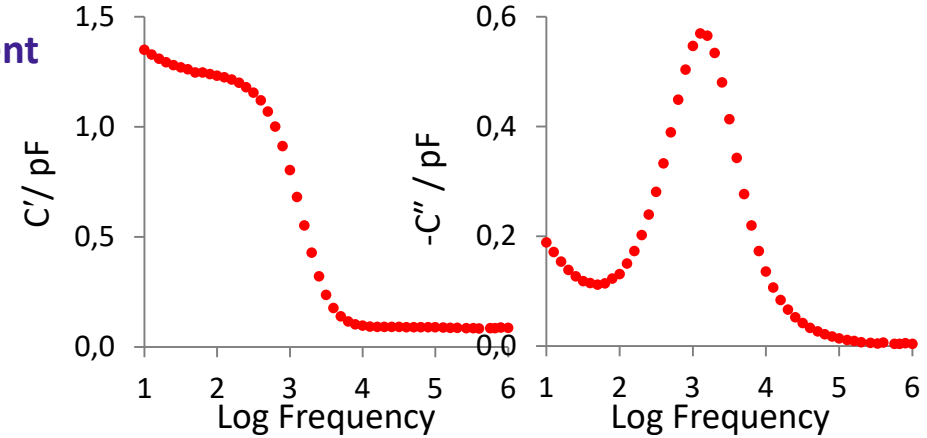
In-line TVIS measurement



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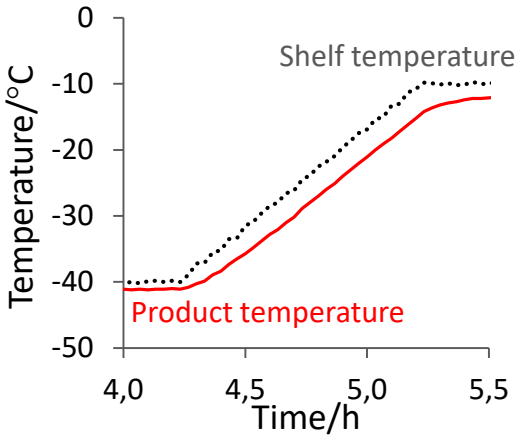

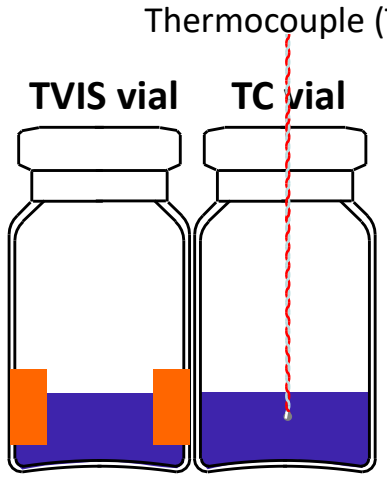

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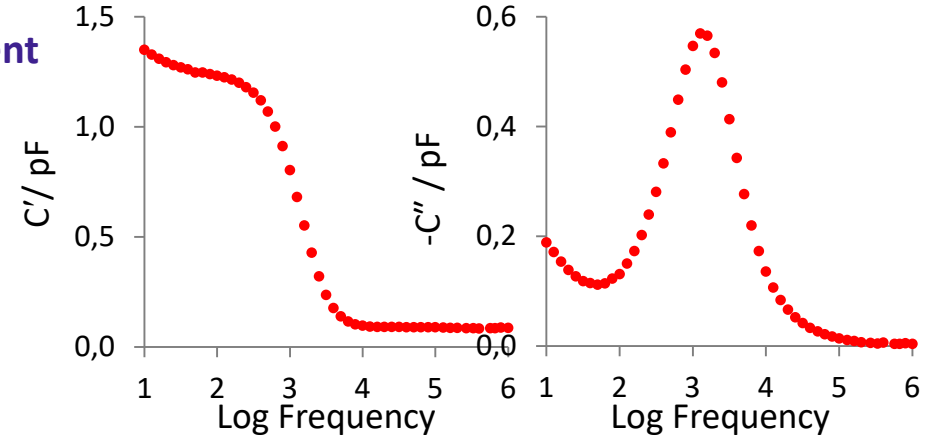
In-line TVIS measurement

Identifying TVIS parameters using LyoView software

(i.e. C''_{PEAK}, F_{PEAK}, C')



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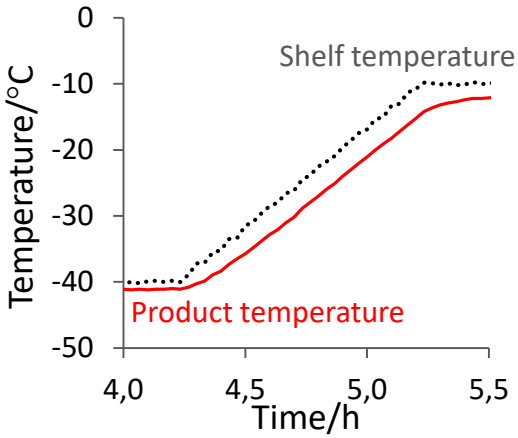

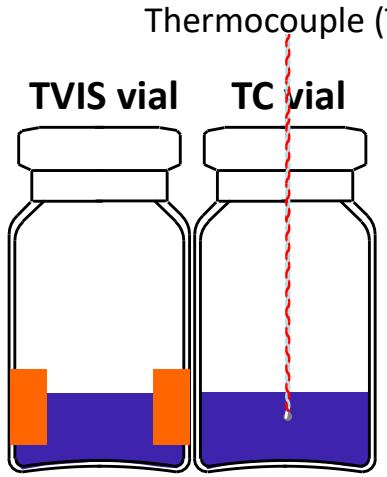

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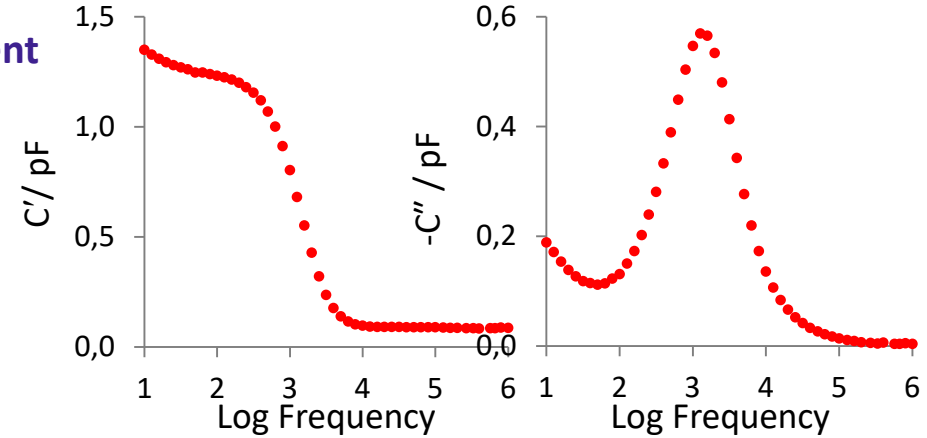
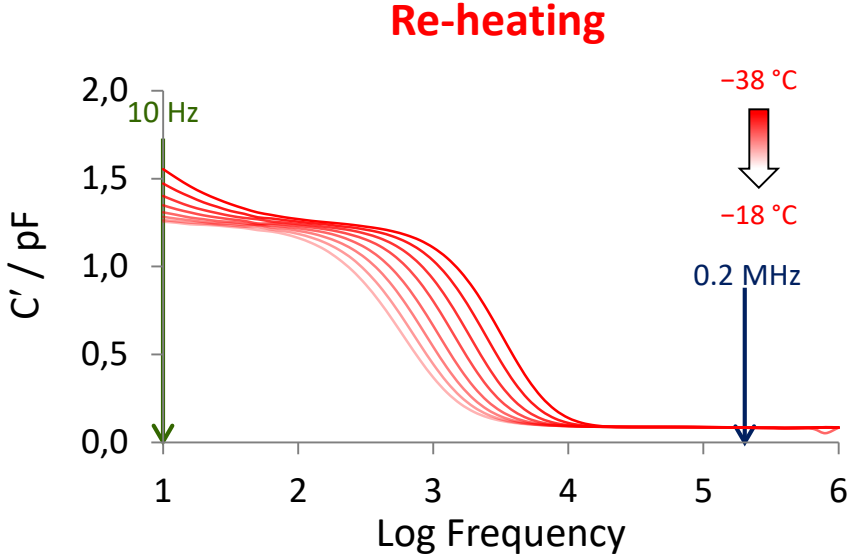
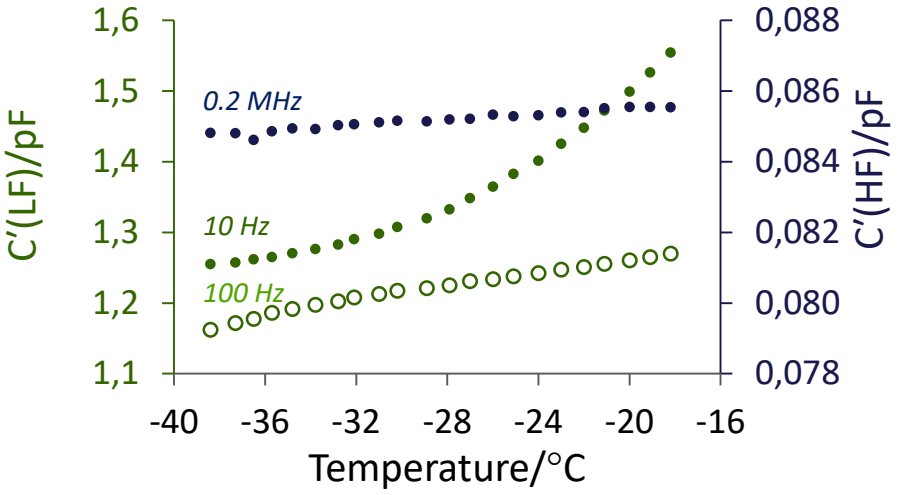
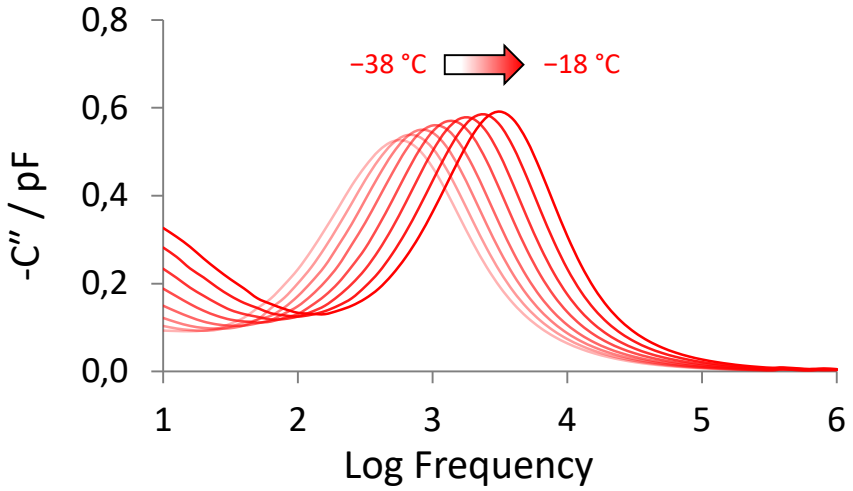


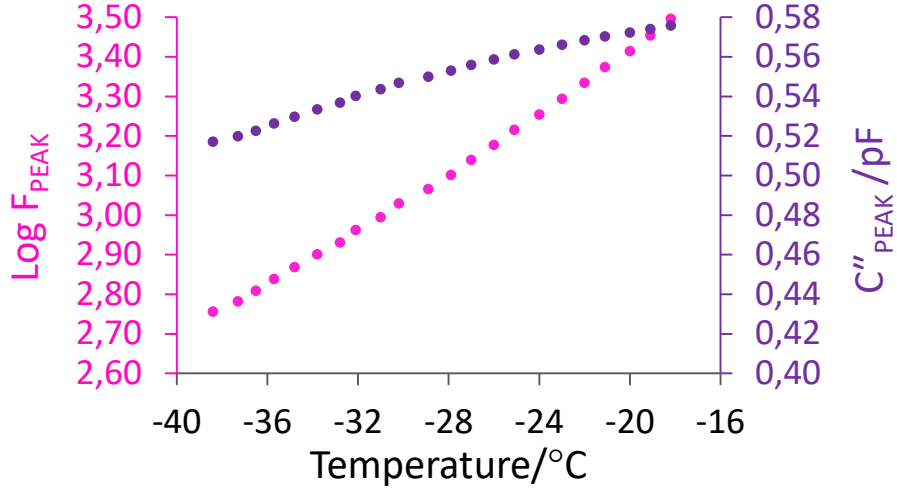
Temperature profile of TVIS parameters

Temperature Profile of Frozen Water









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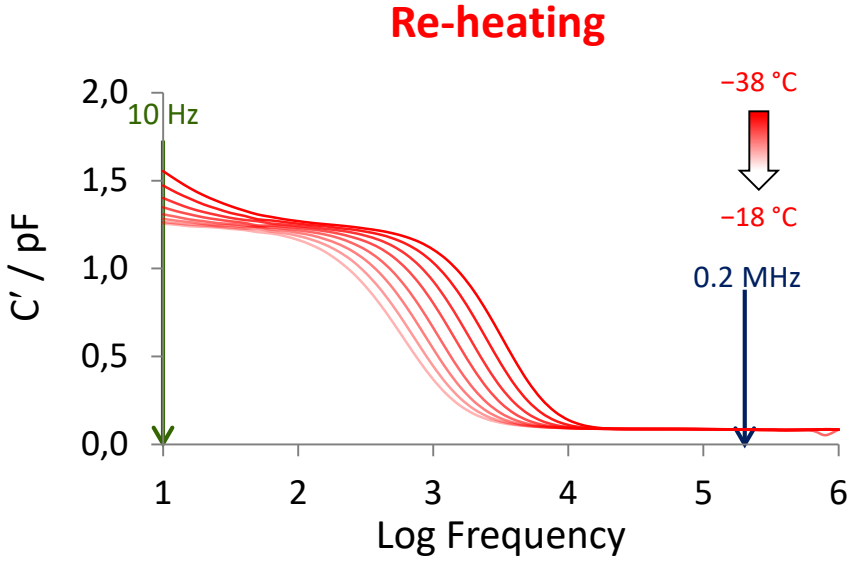
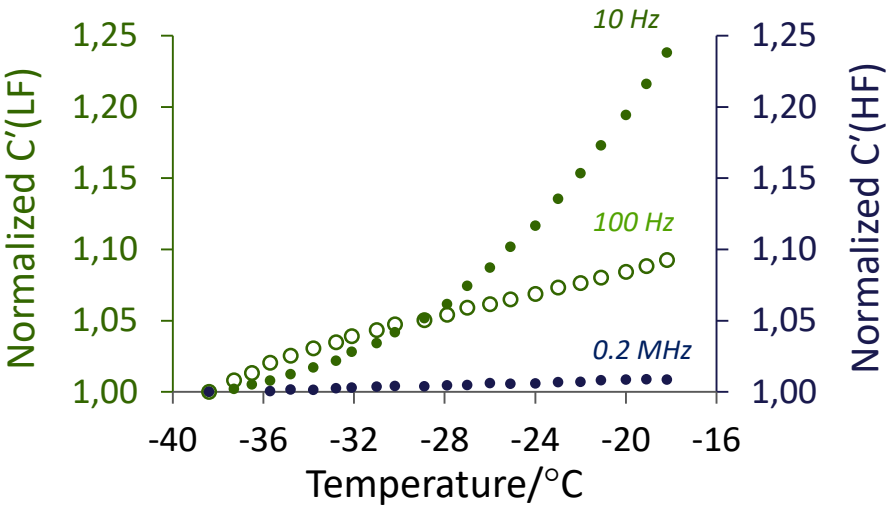
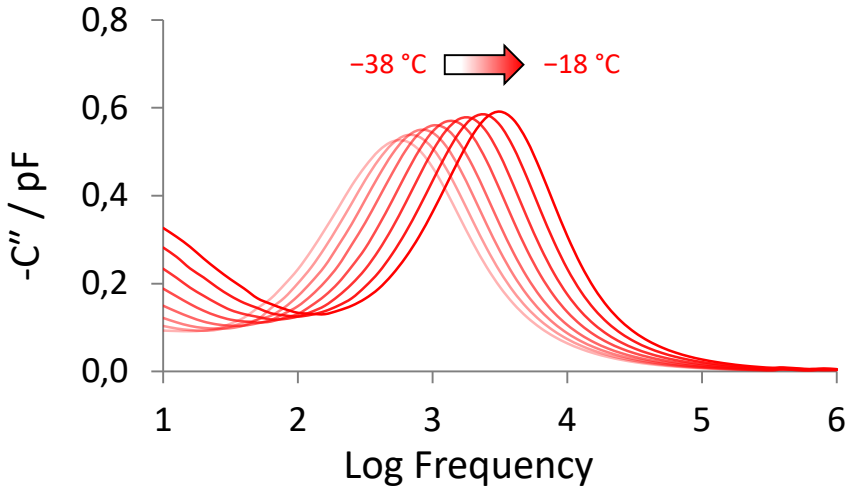
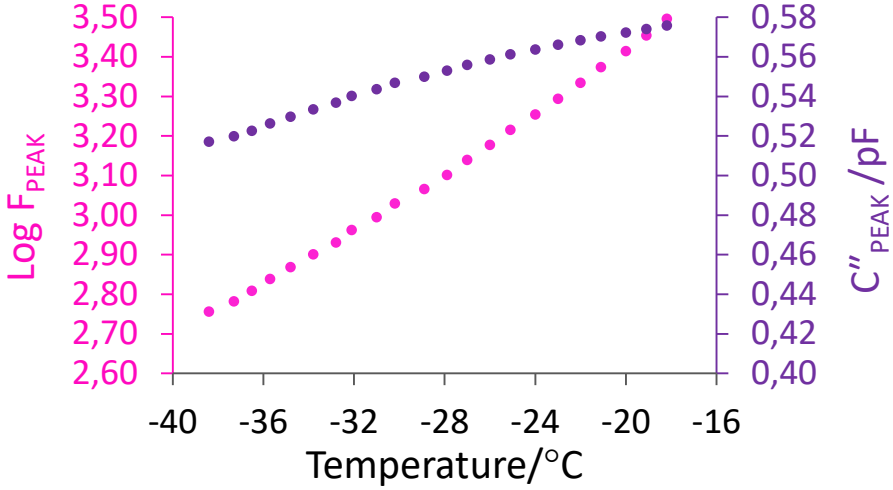




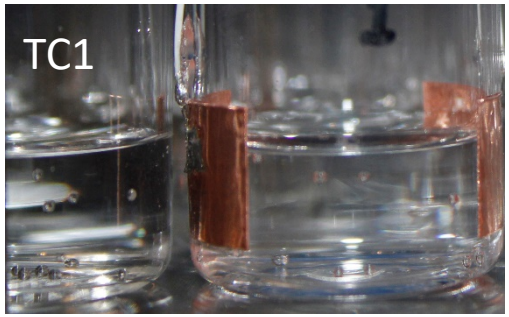


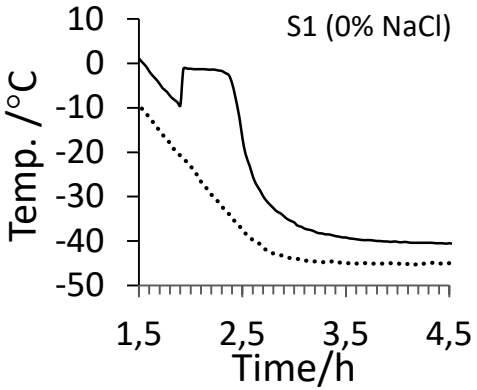


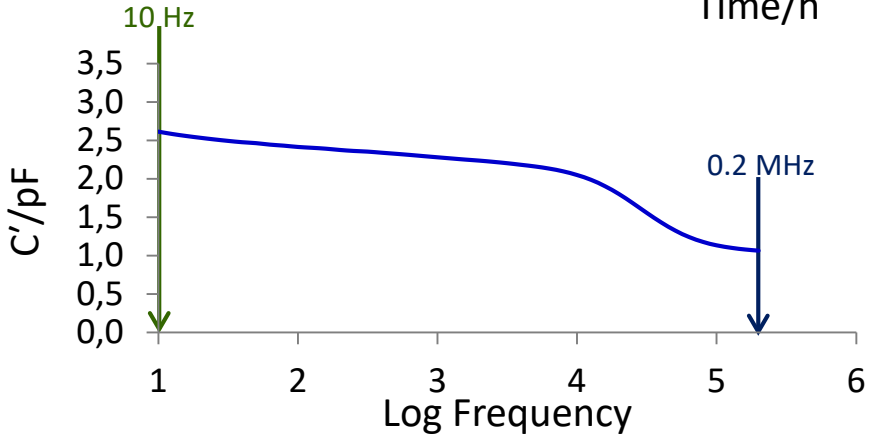
Through Vial Impedance Spectroscopy (TVIS)

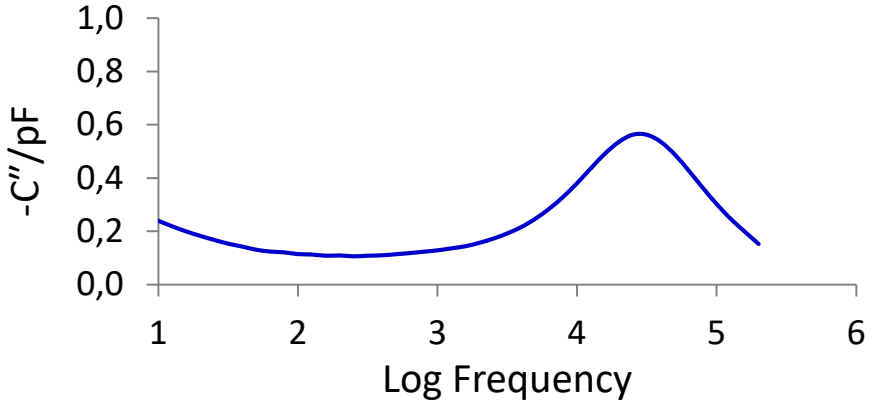
An example : 5% sucrose

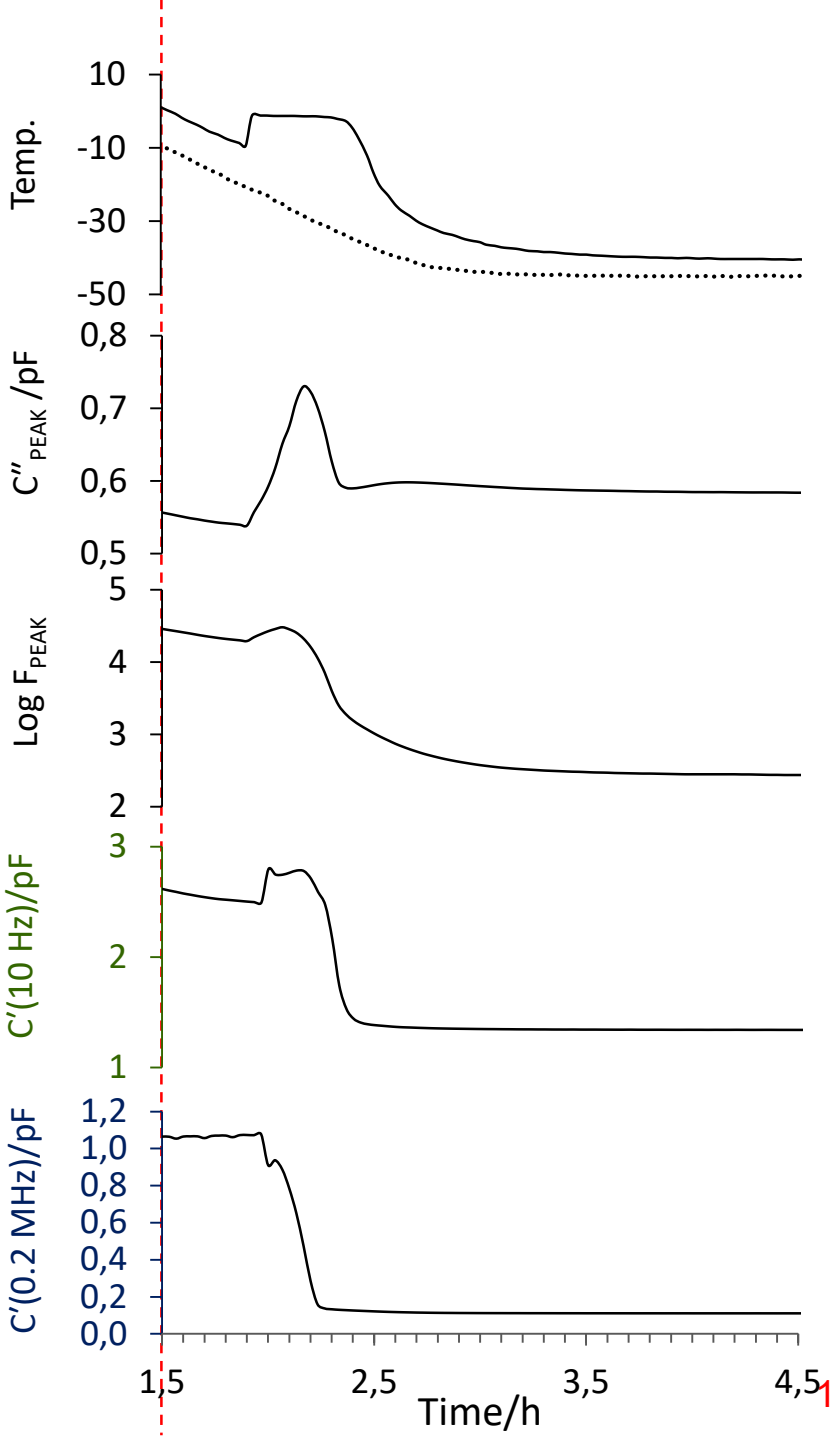
Freezing Step-5%Sucrose



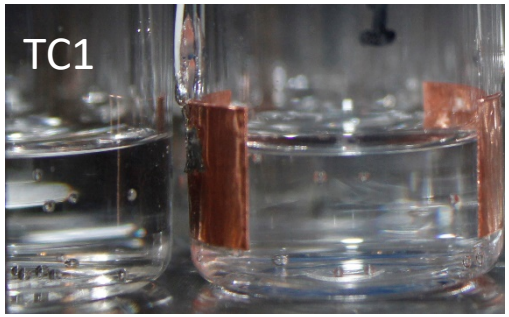


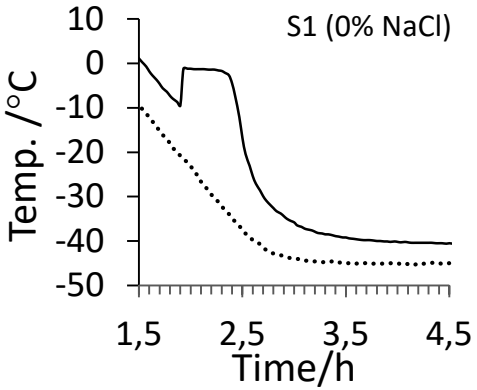


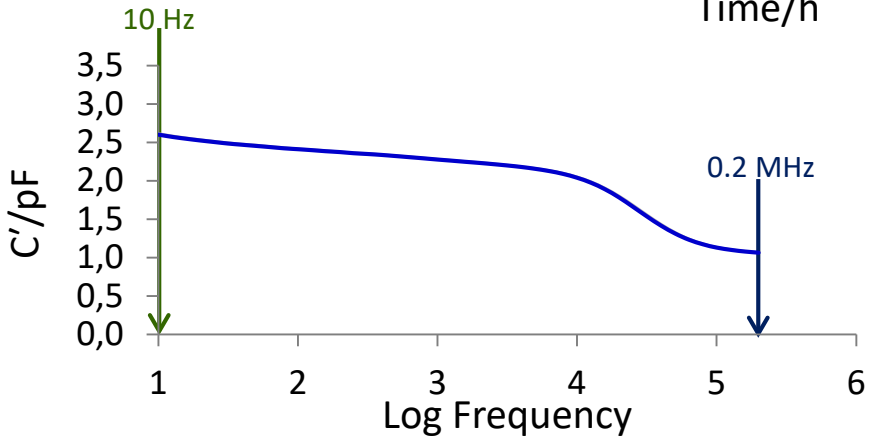


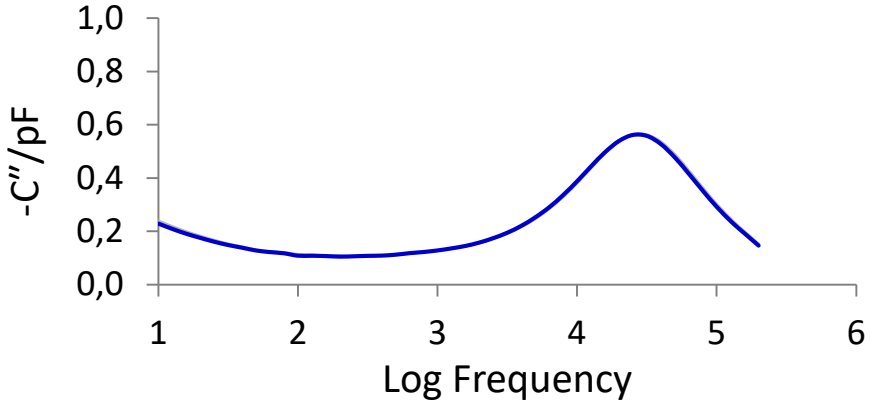


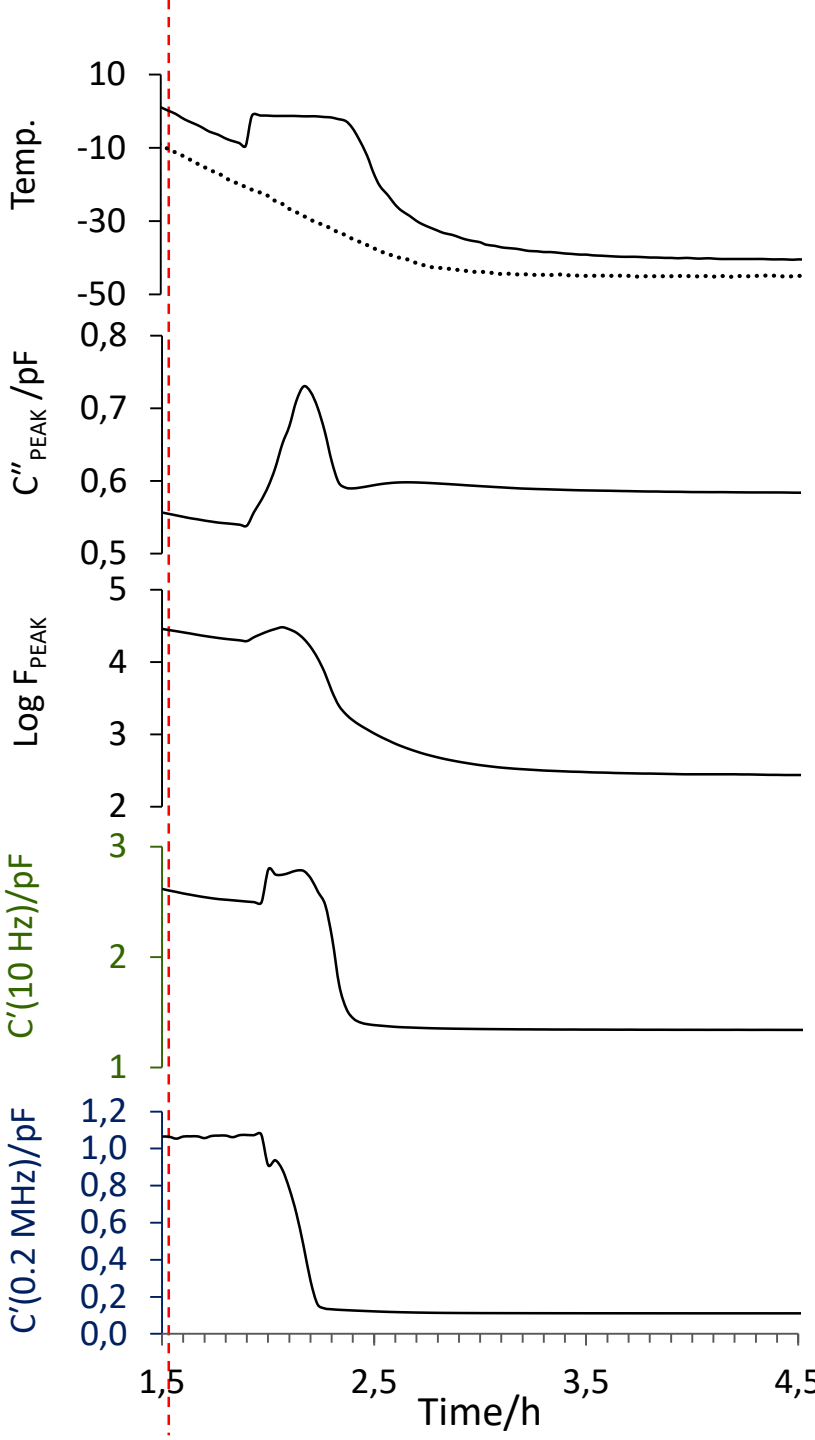
Freezing Step-5%Sucrose



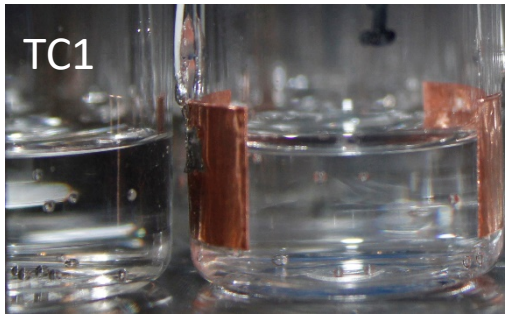


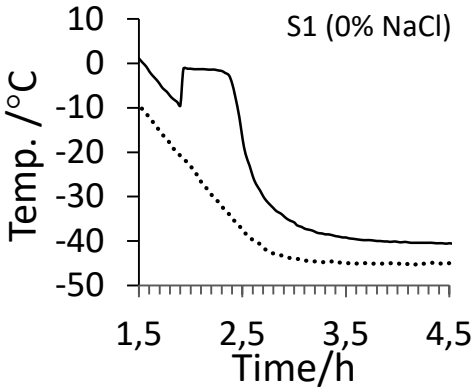


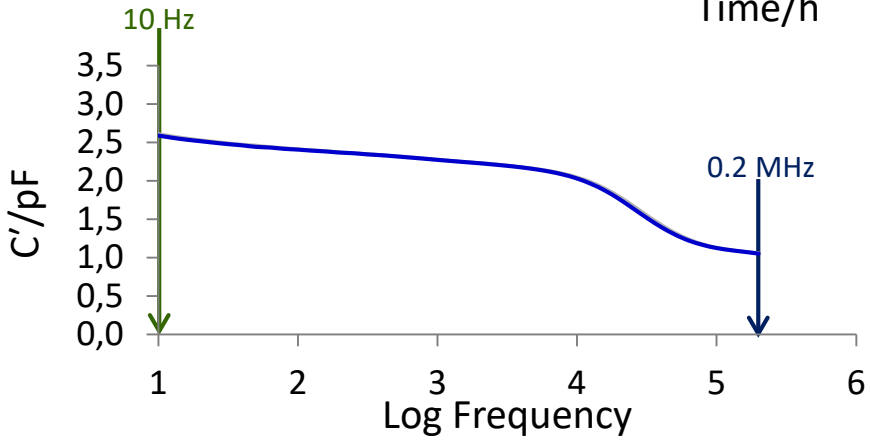


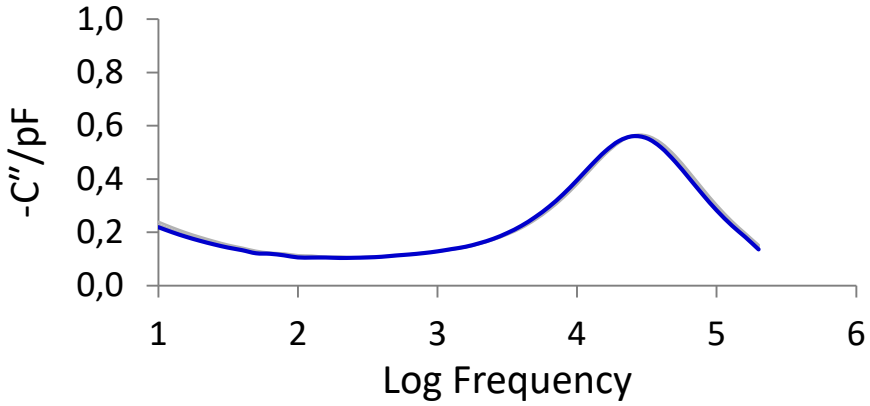


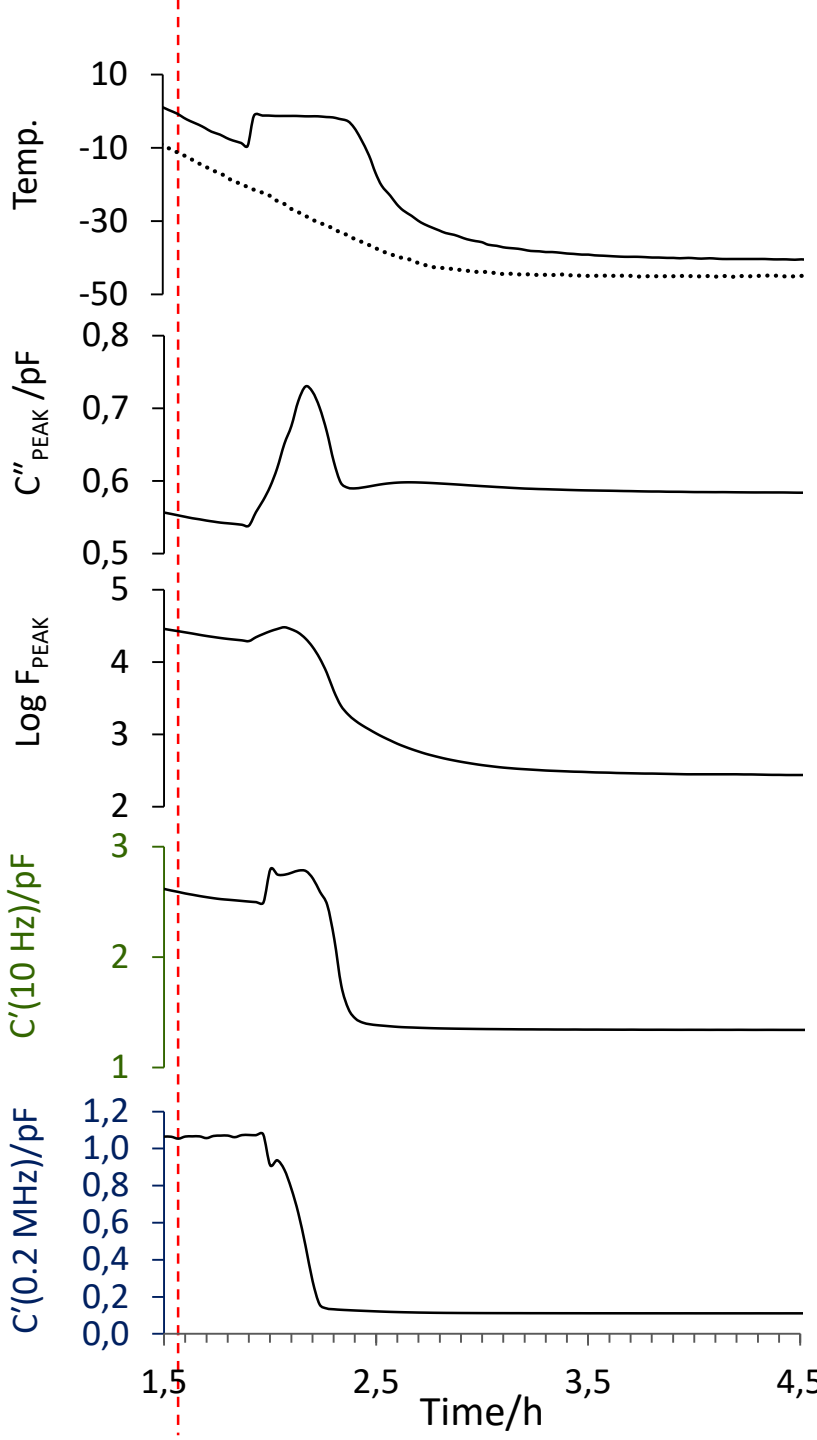
Freezing Step-5%Sucrose











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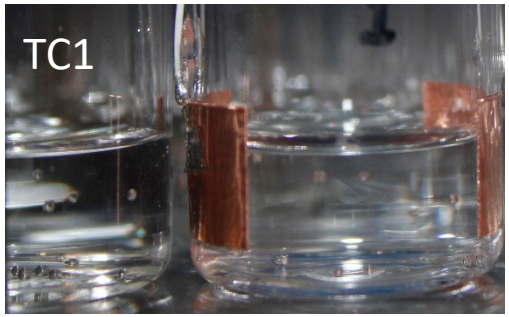

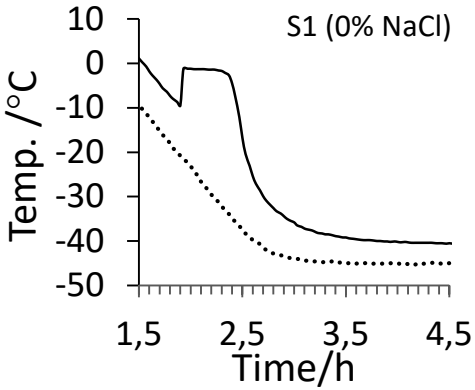

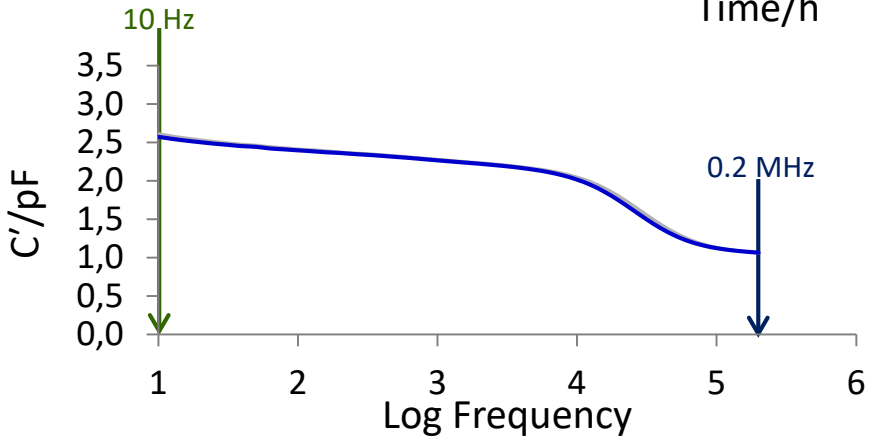

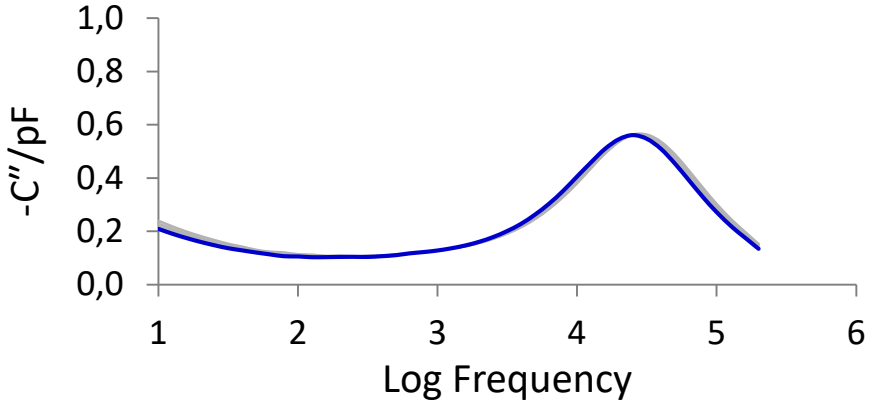

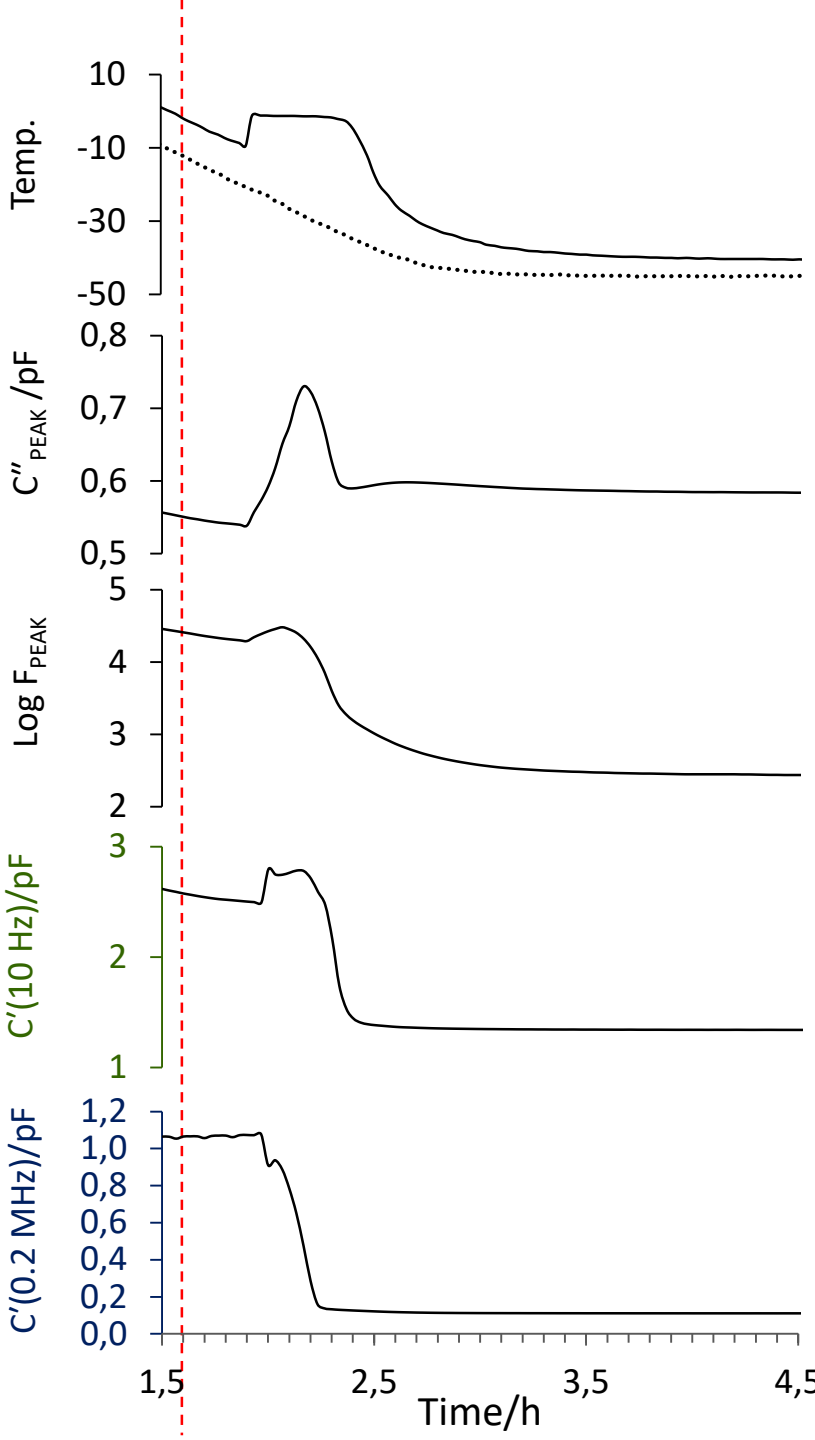

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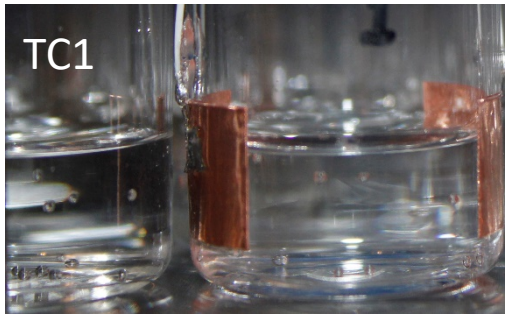

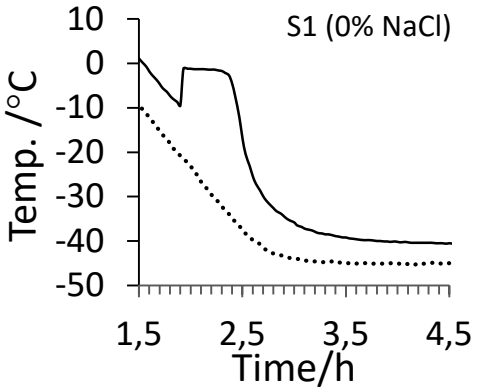

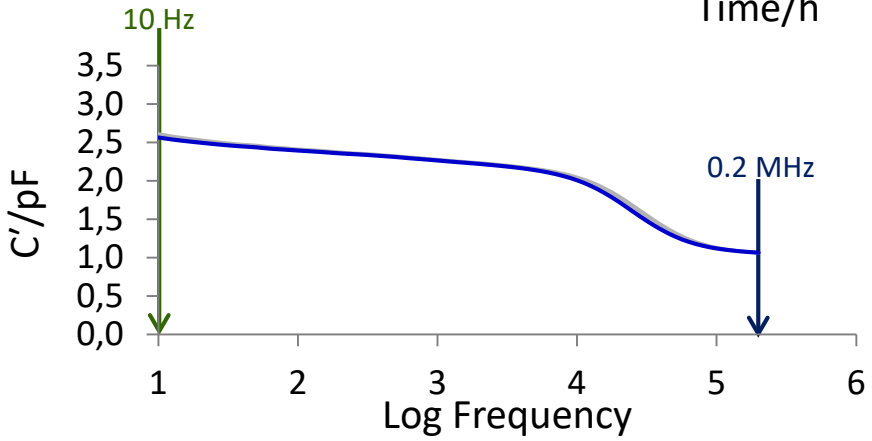

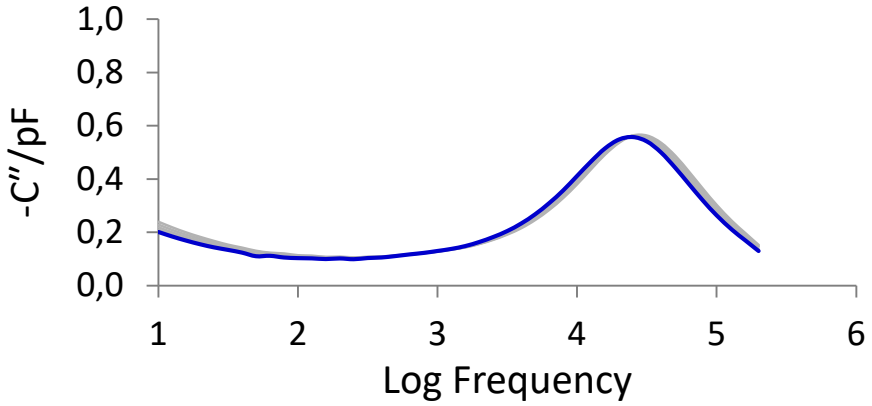

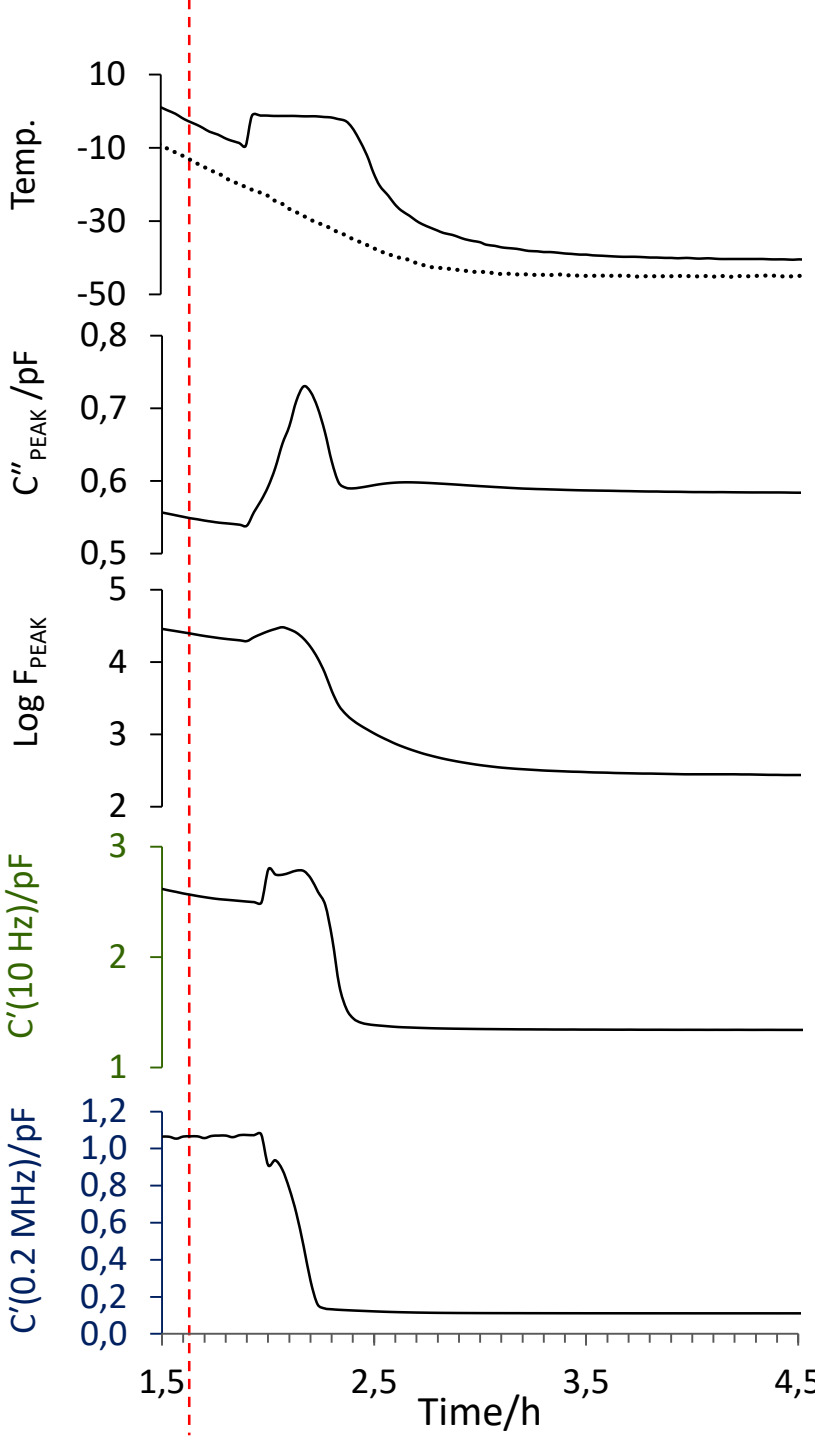

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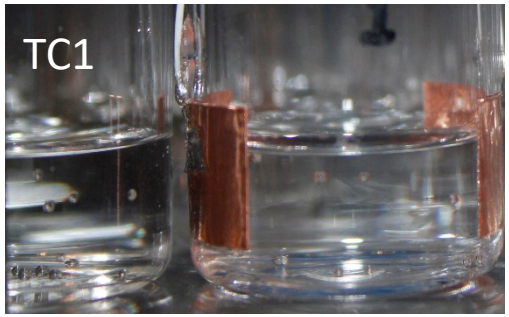

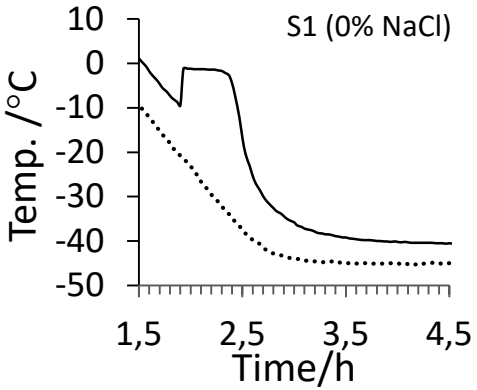

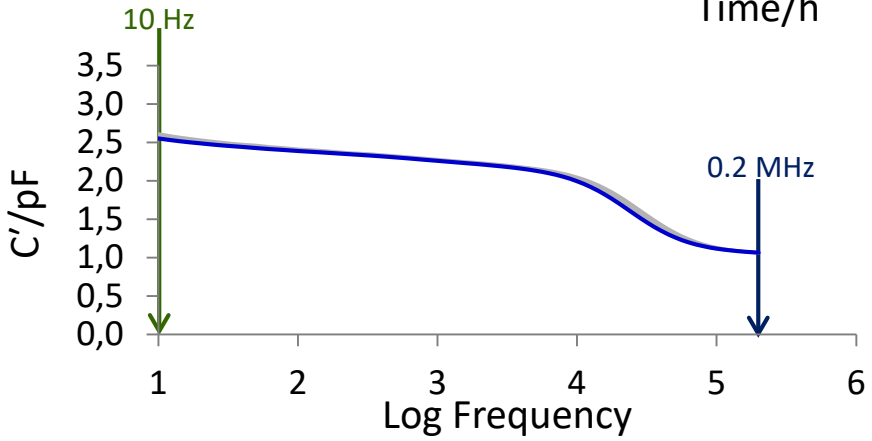

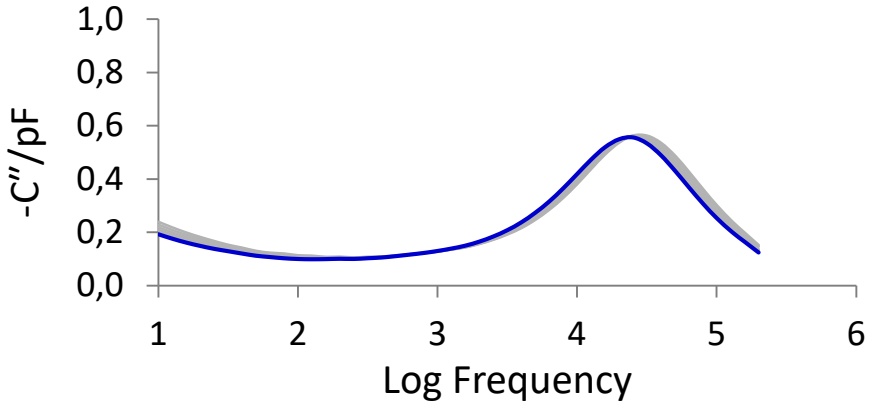

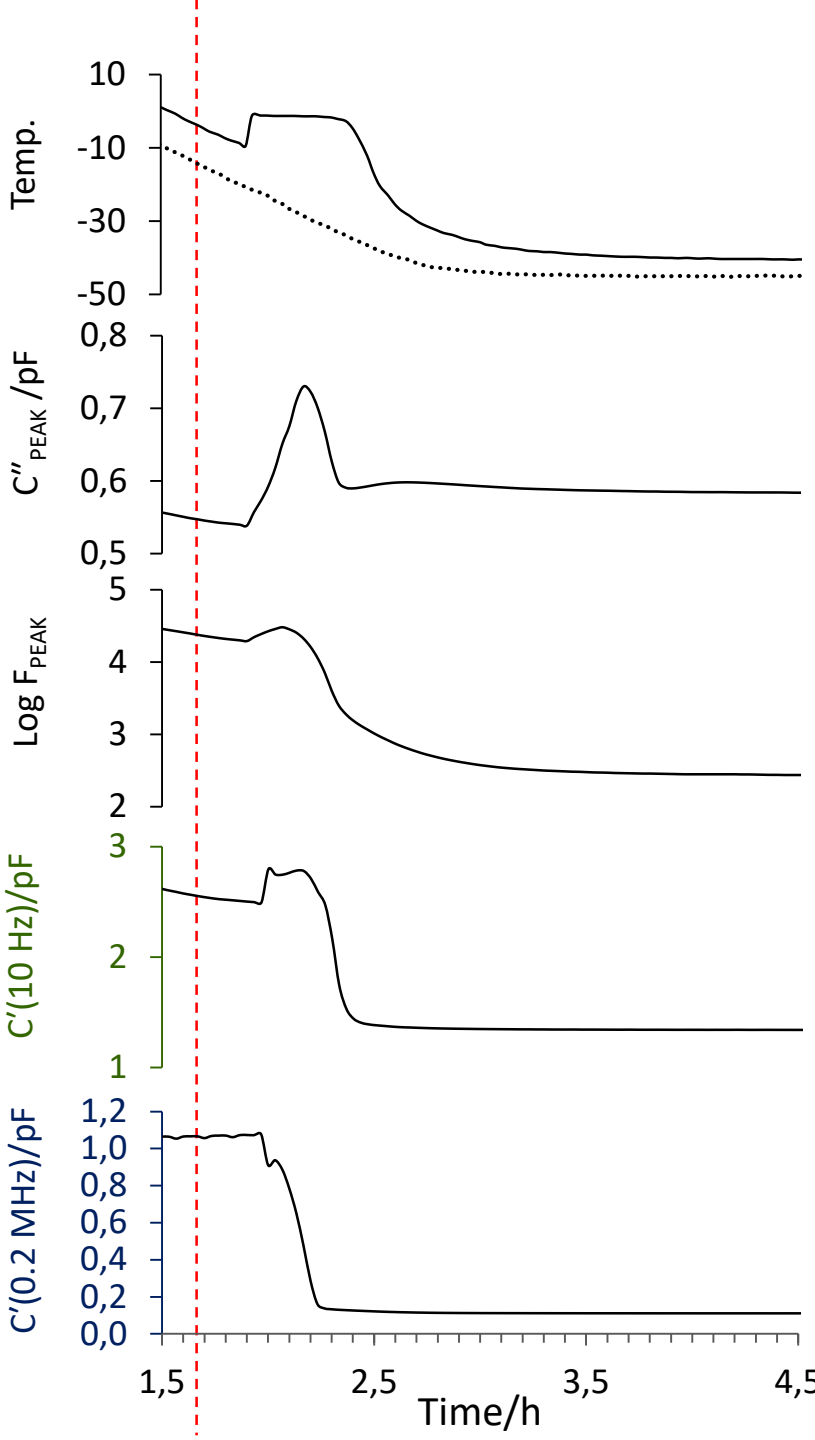

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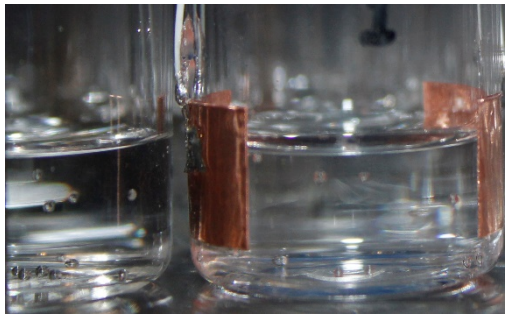

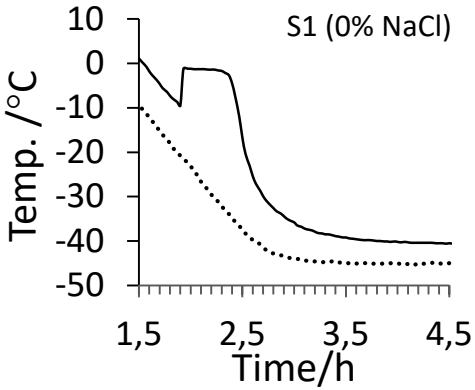

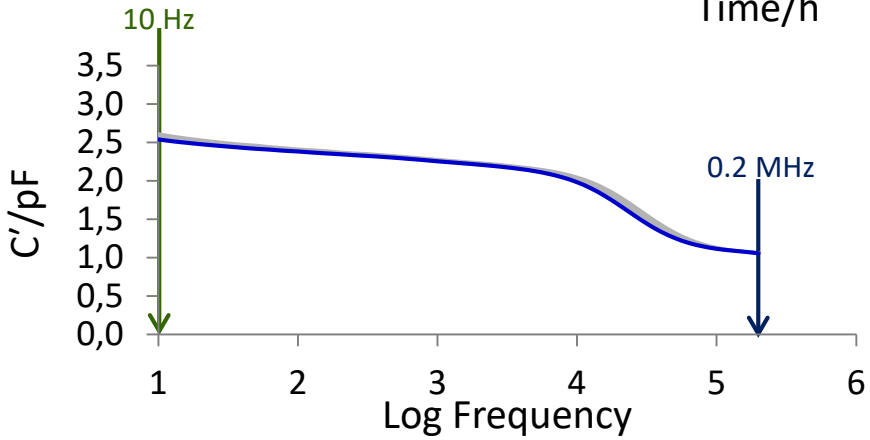

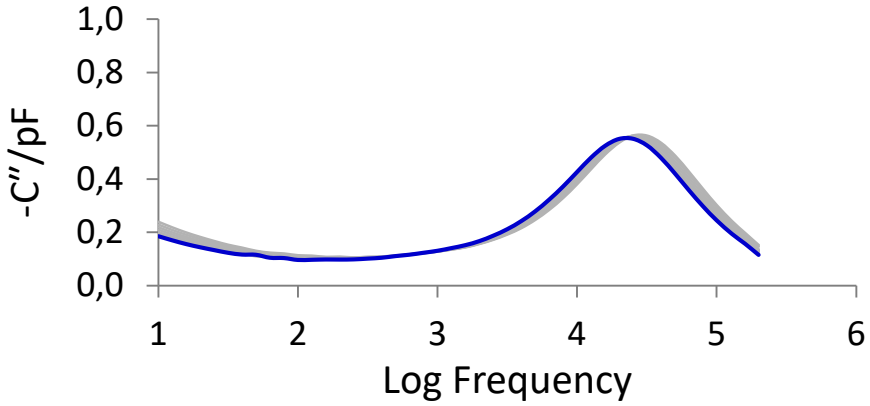

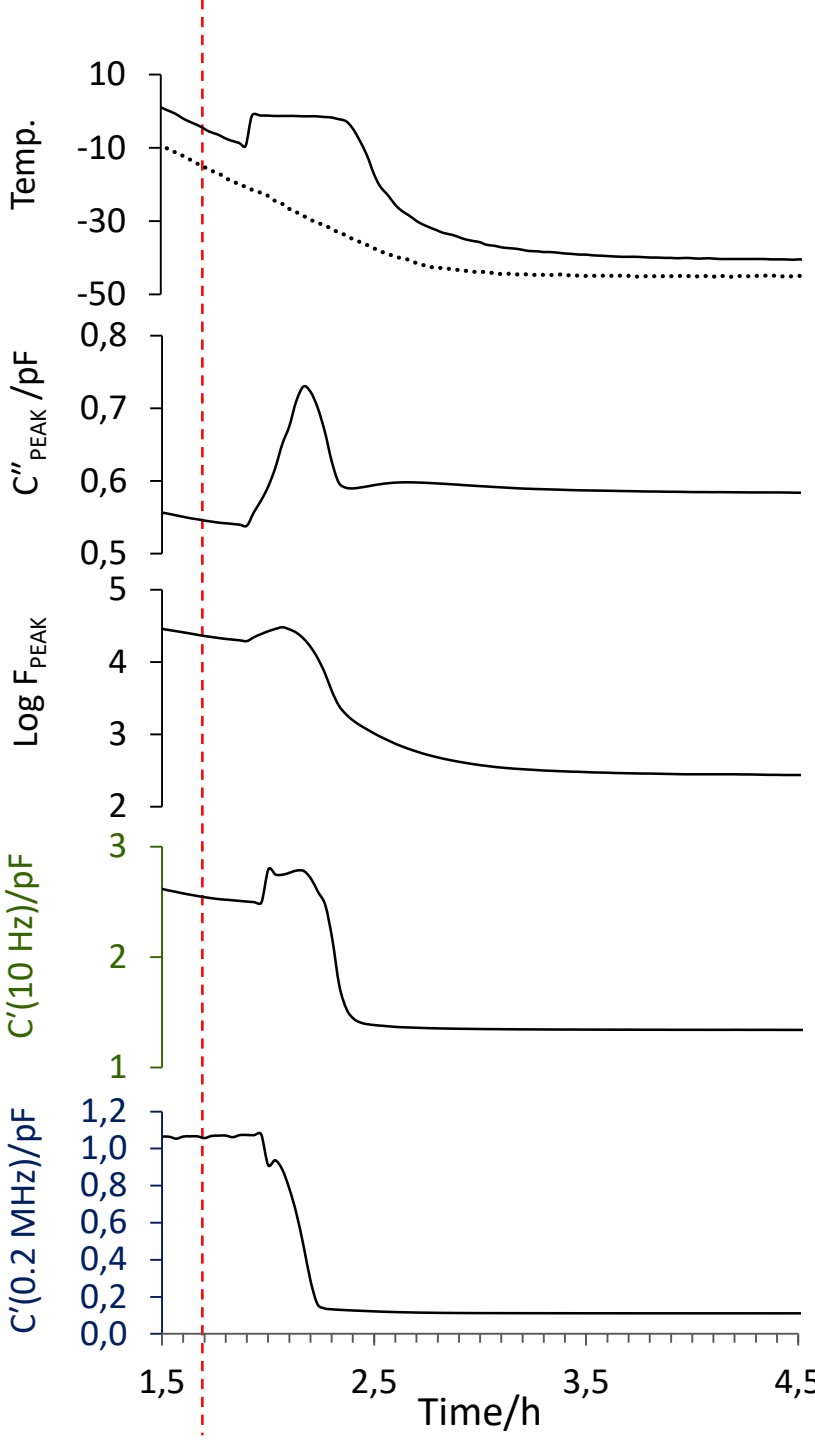

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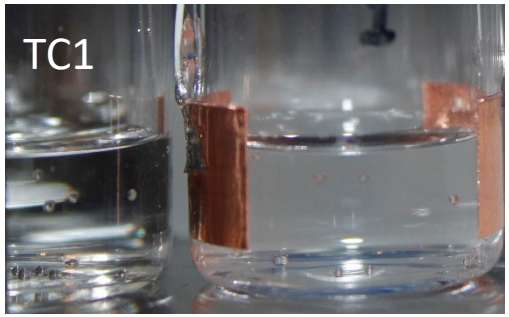

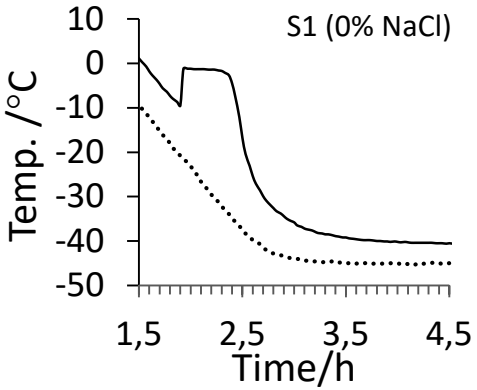

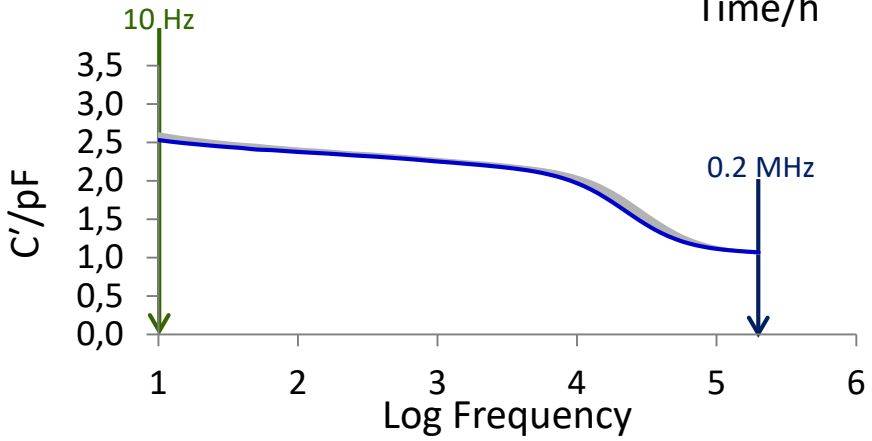

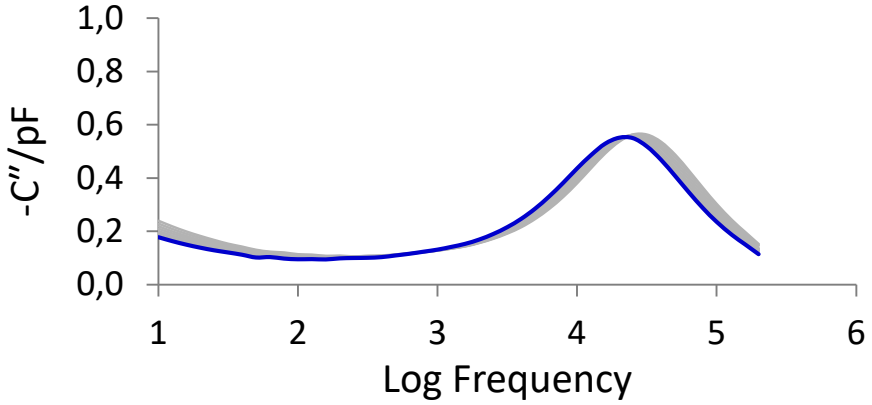

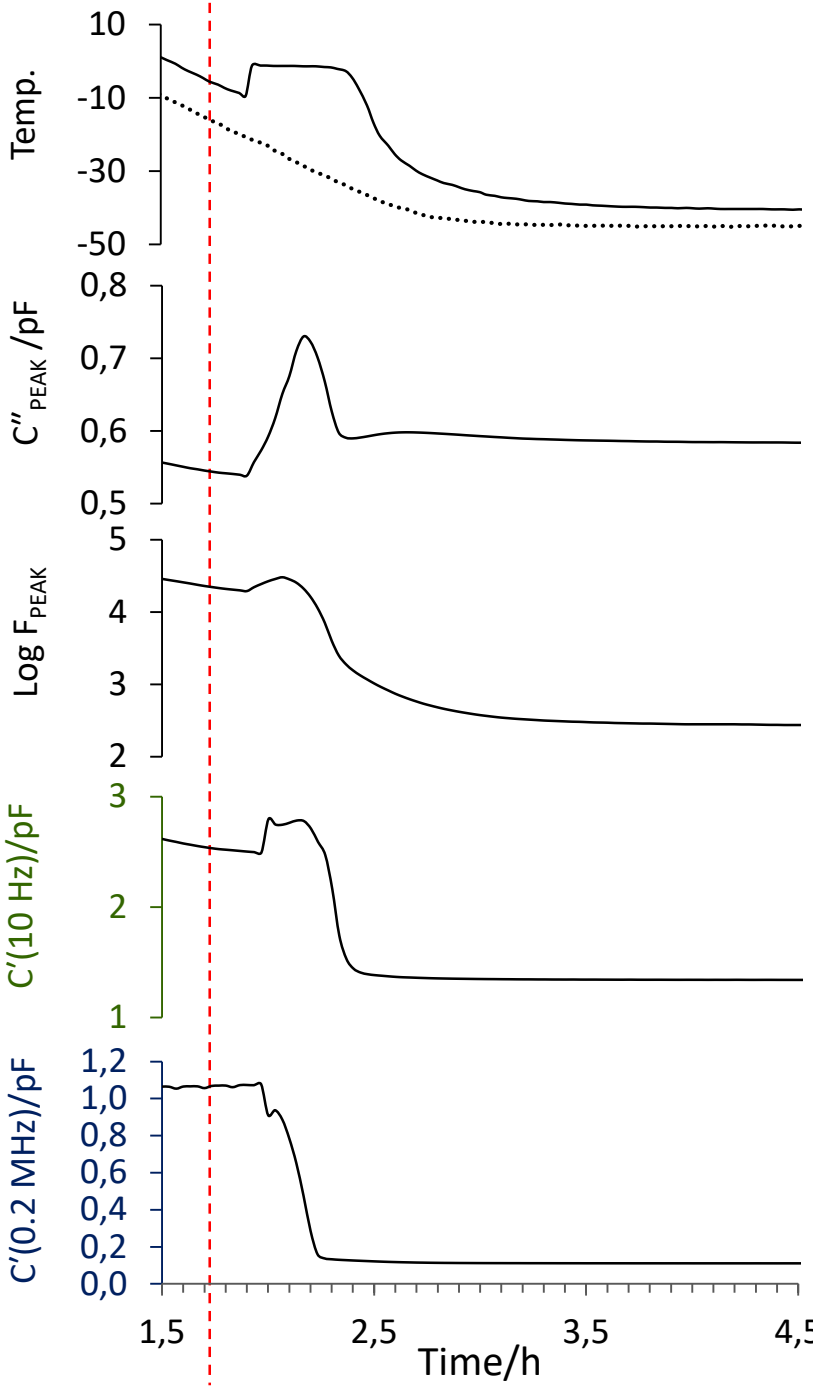

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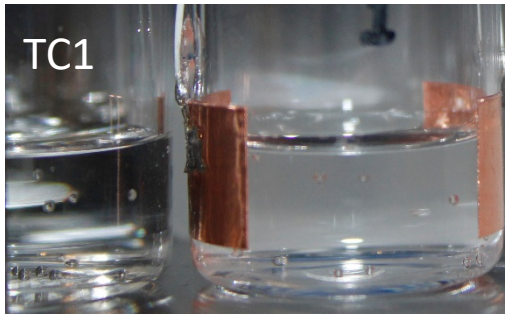

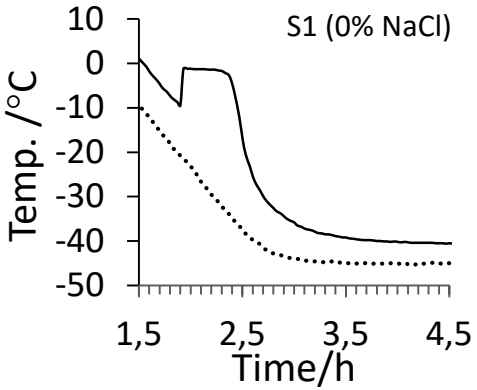

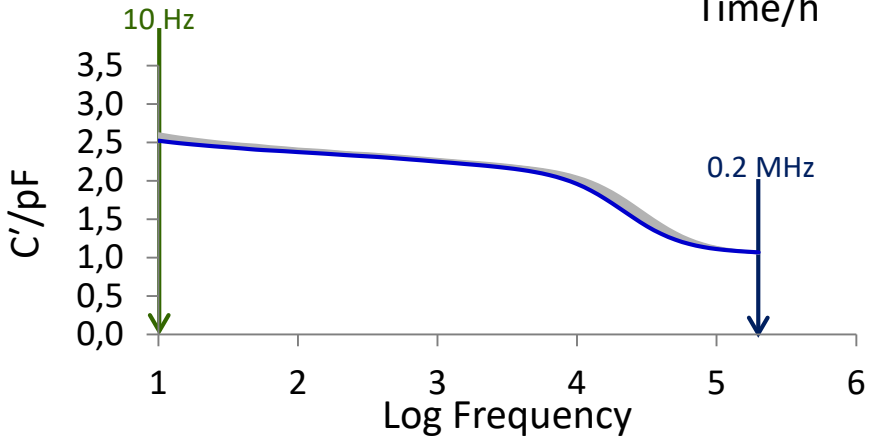

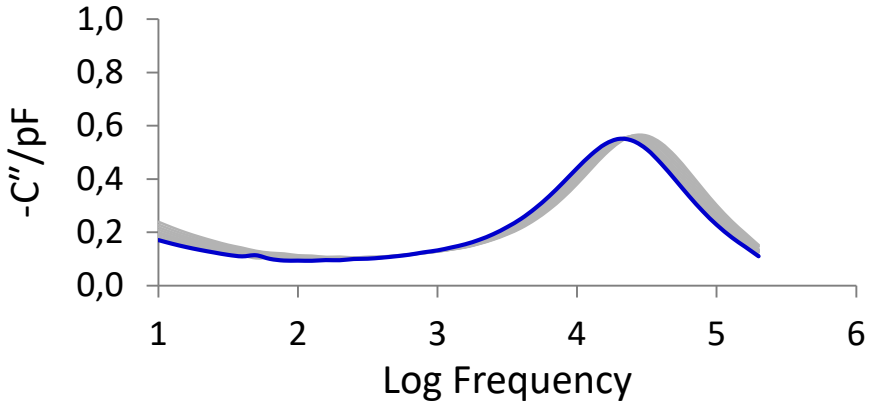

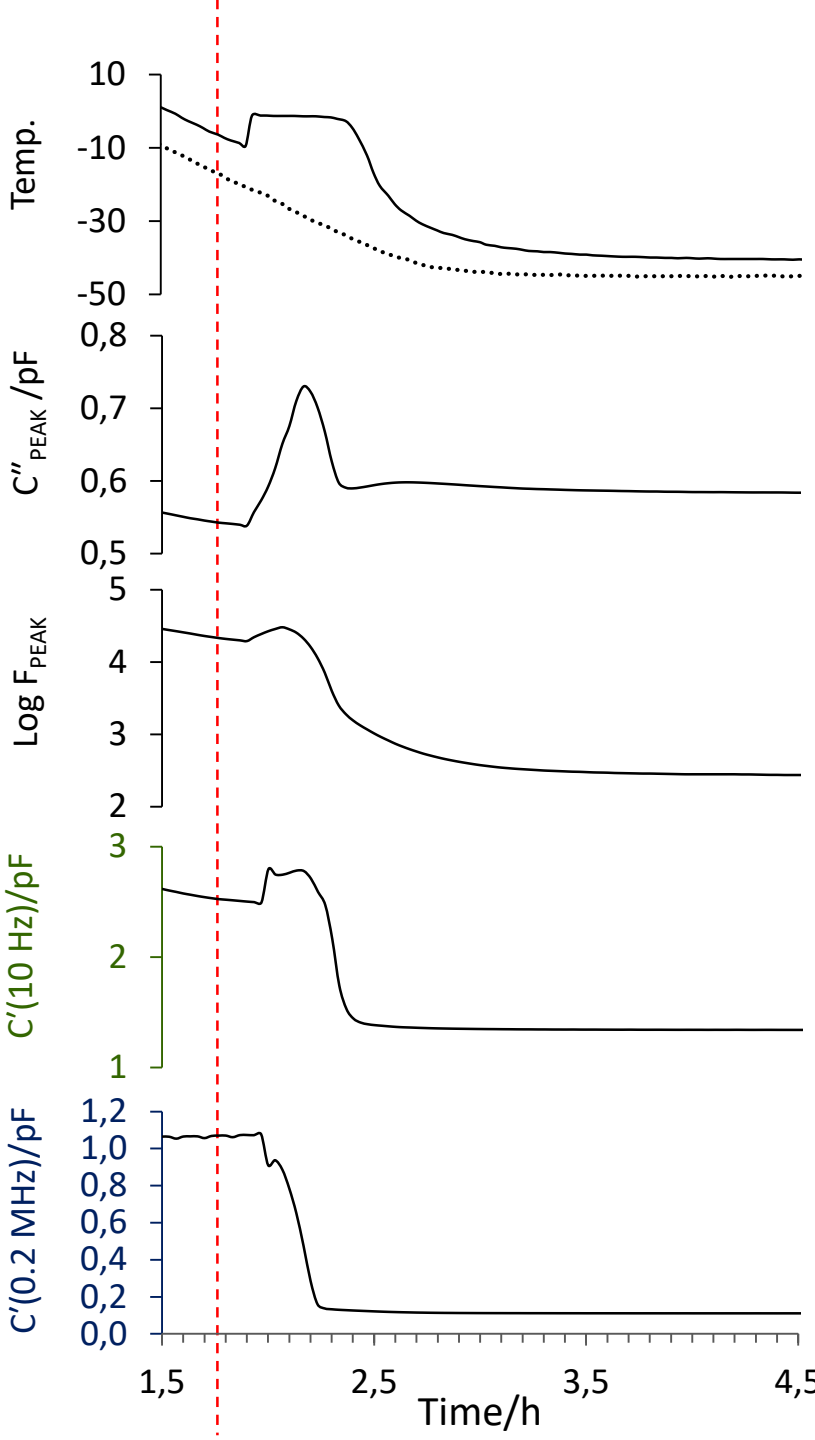

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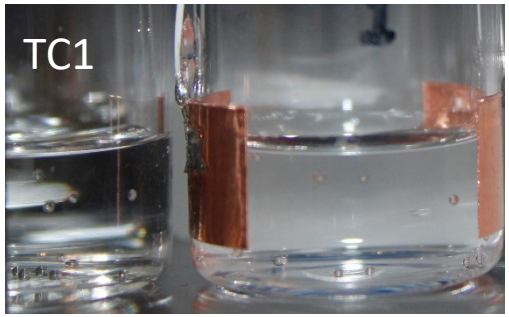

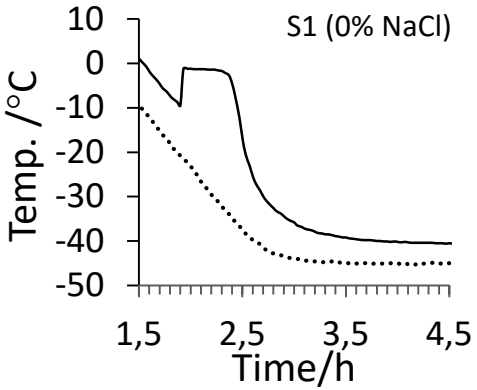

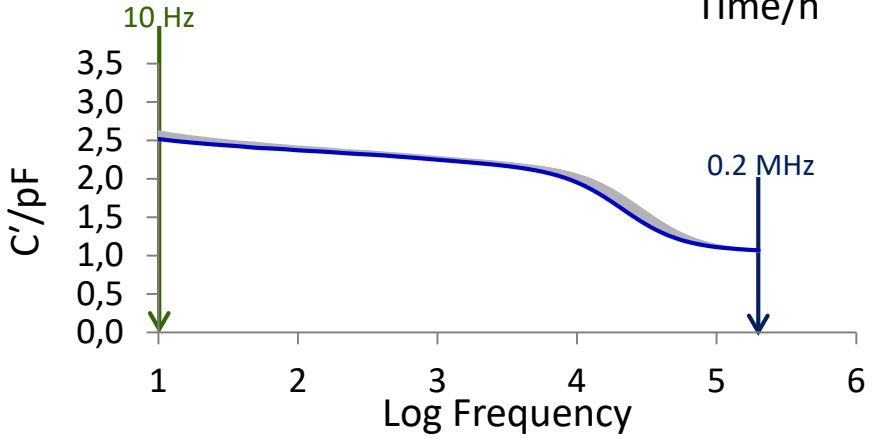

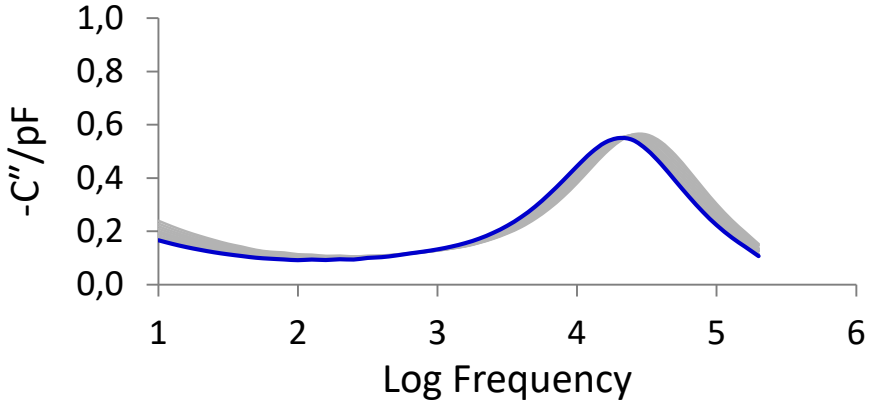

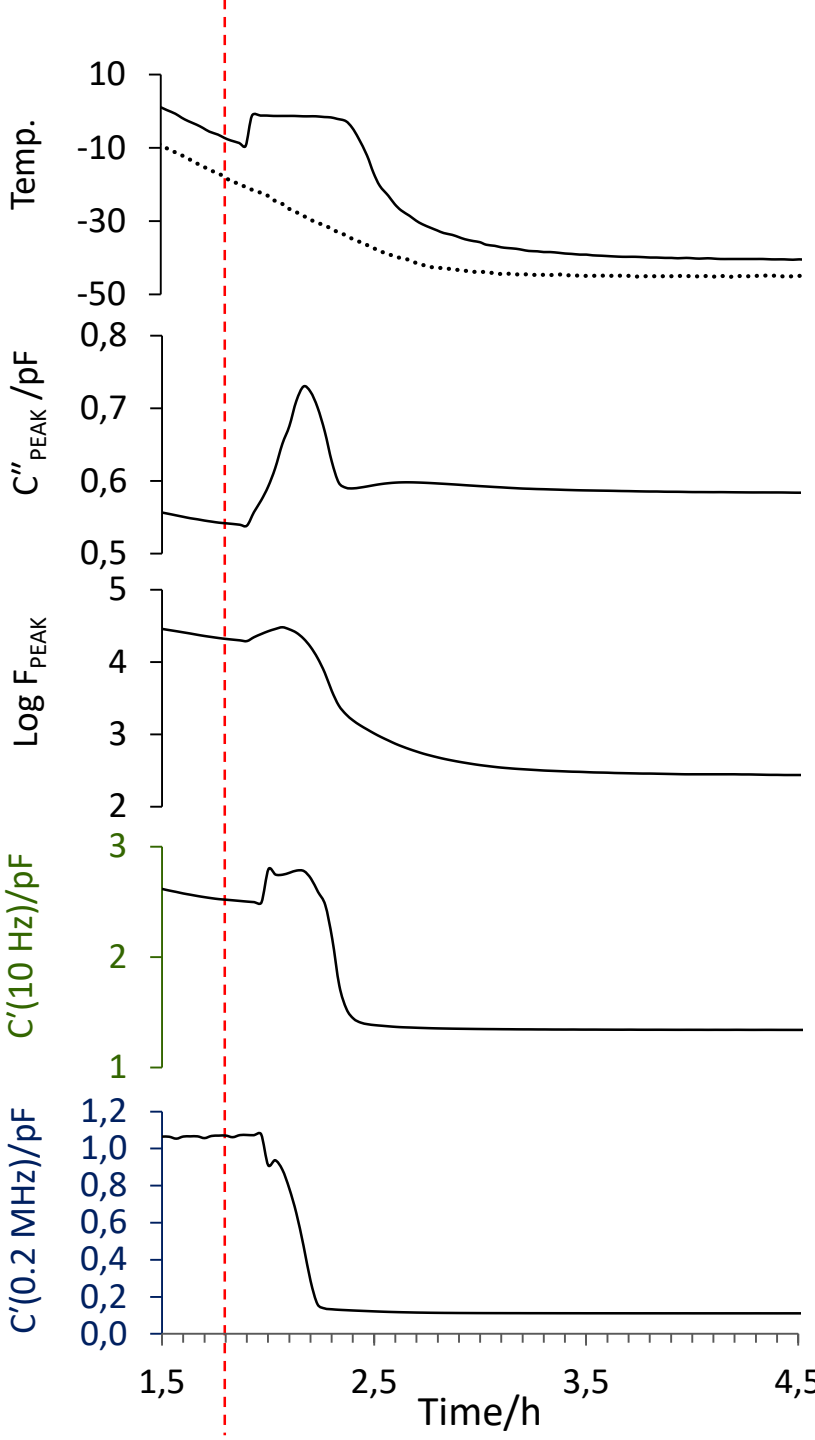

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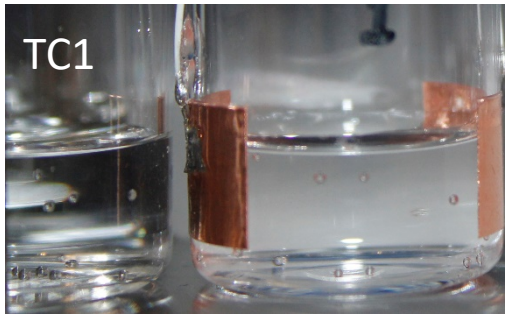

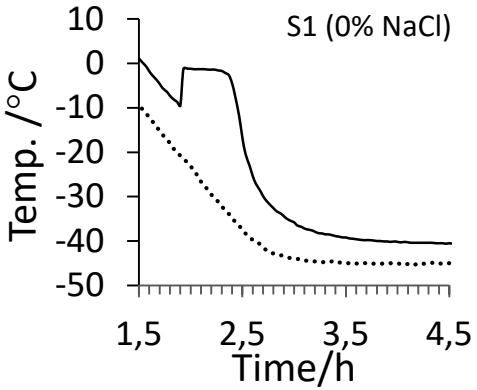

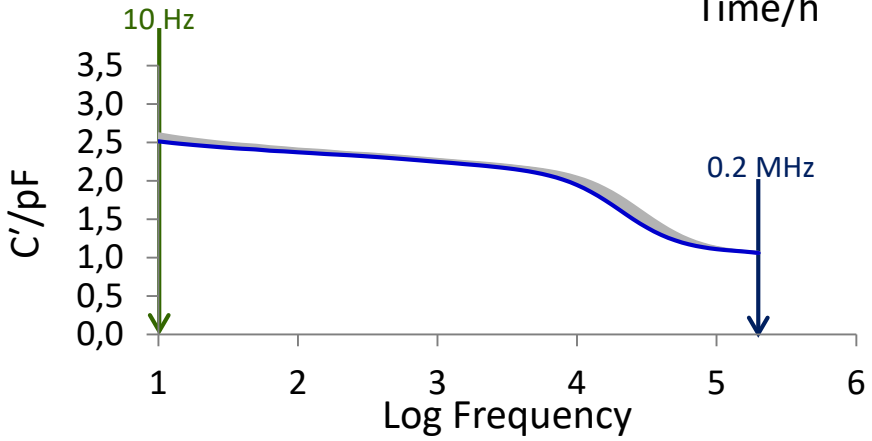

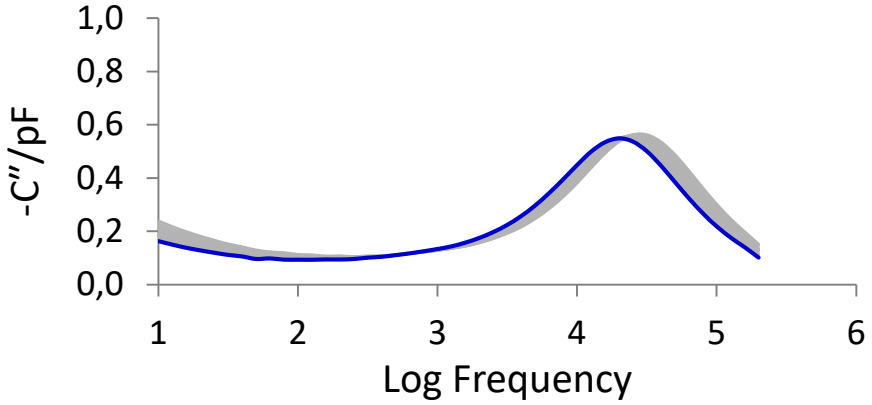

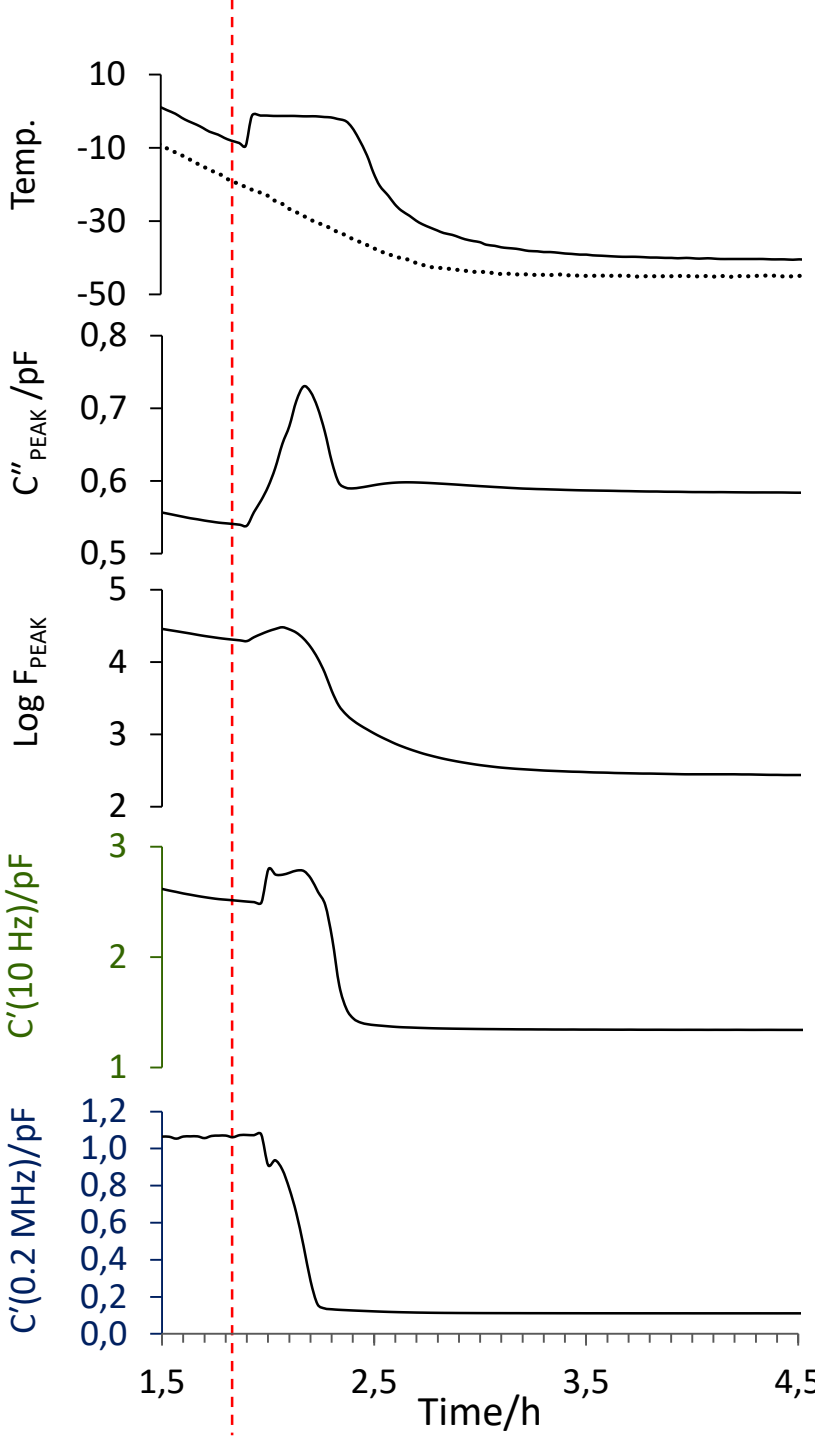

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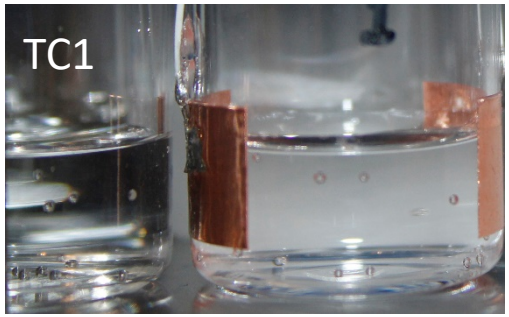

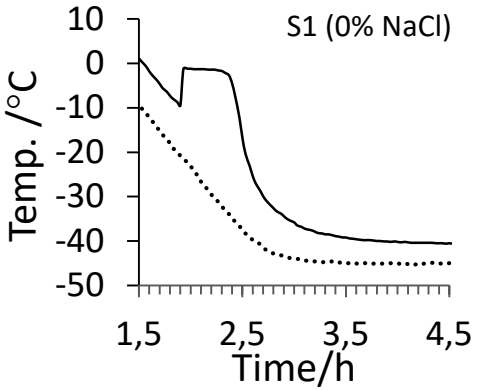

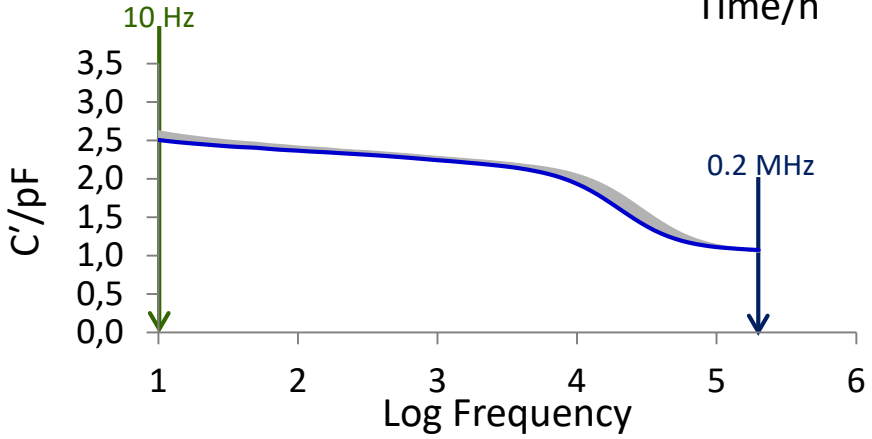

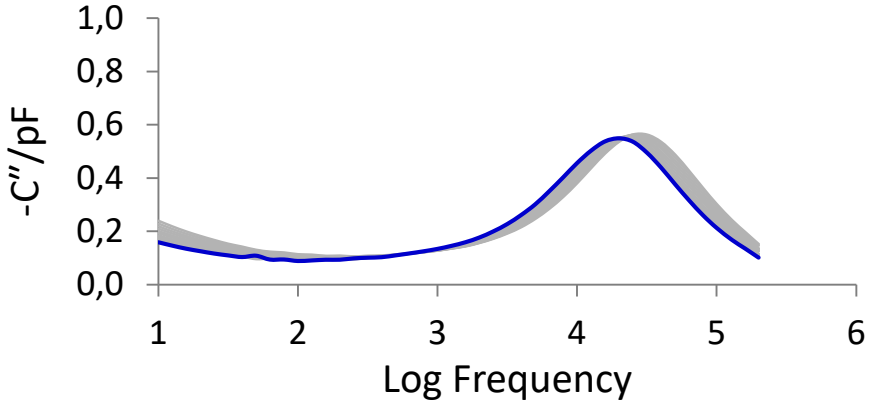

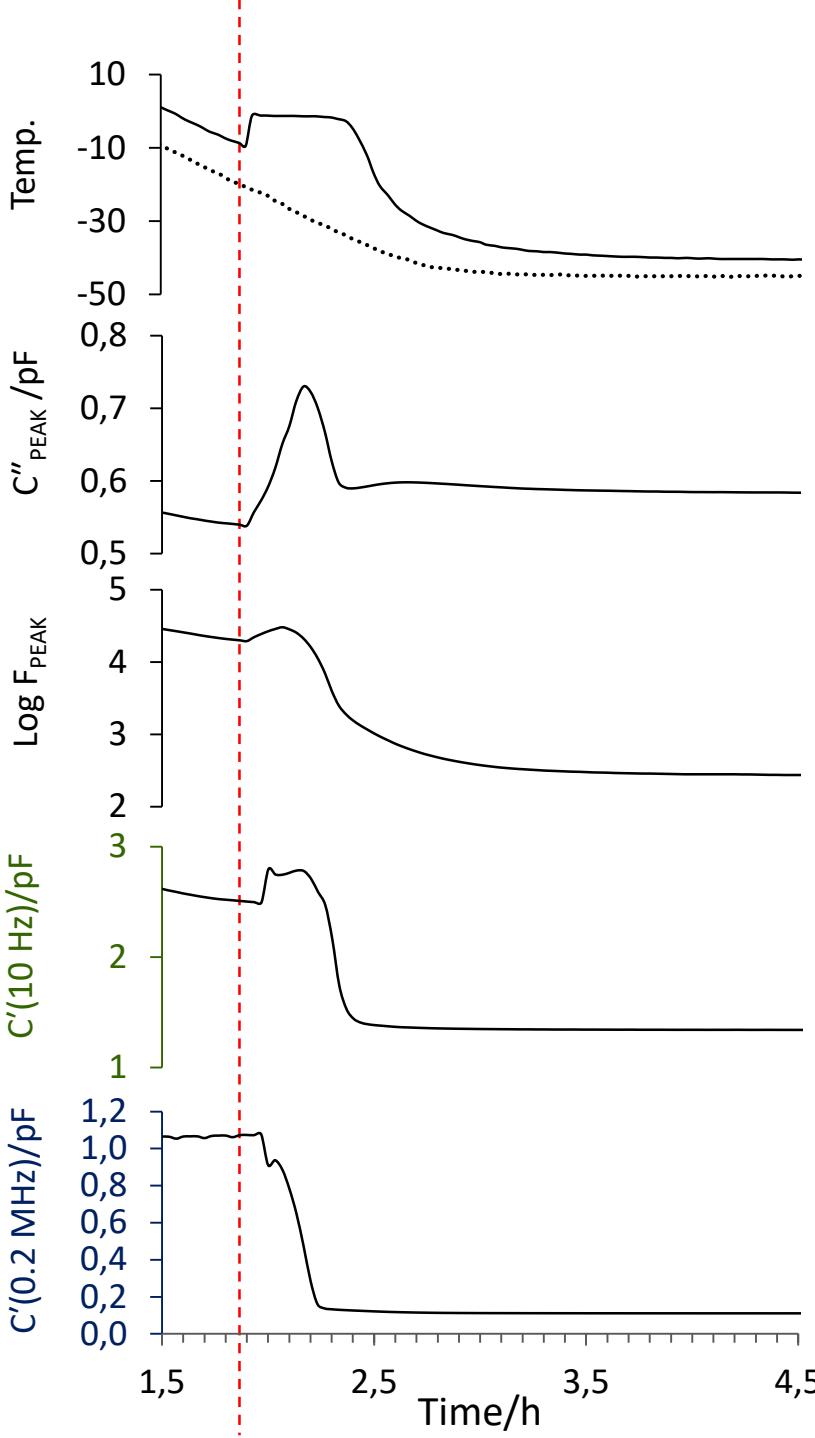

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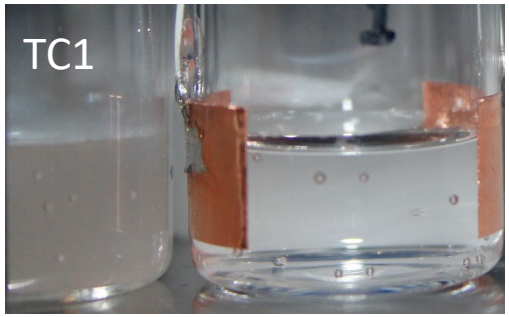

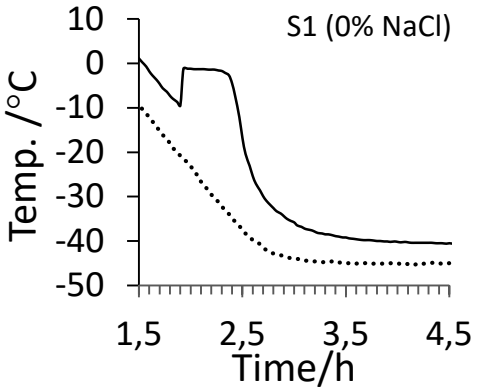

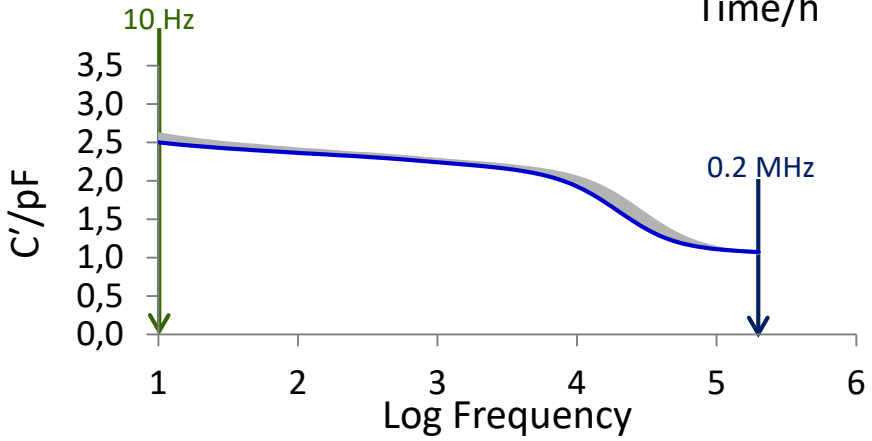

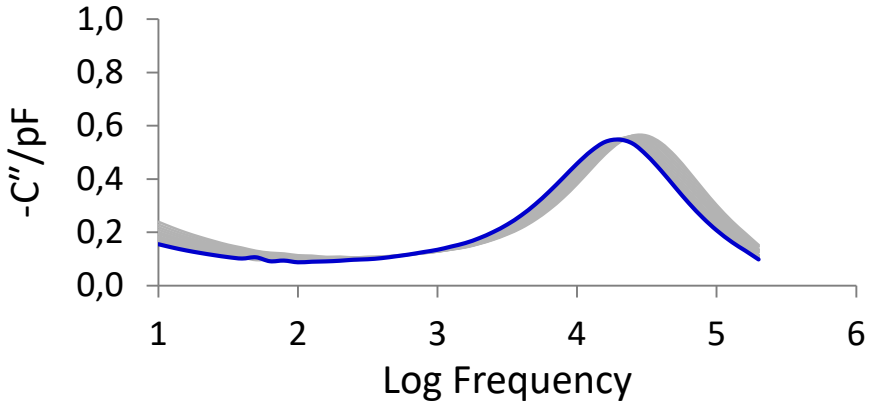

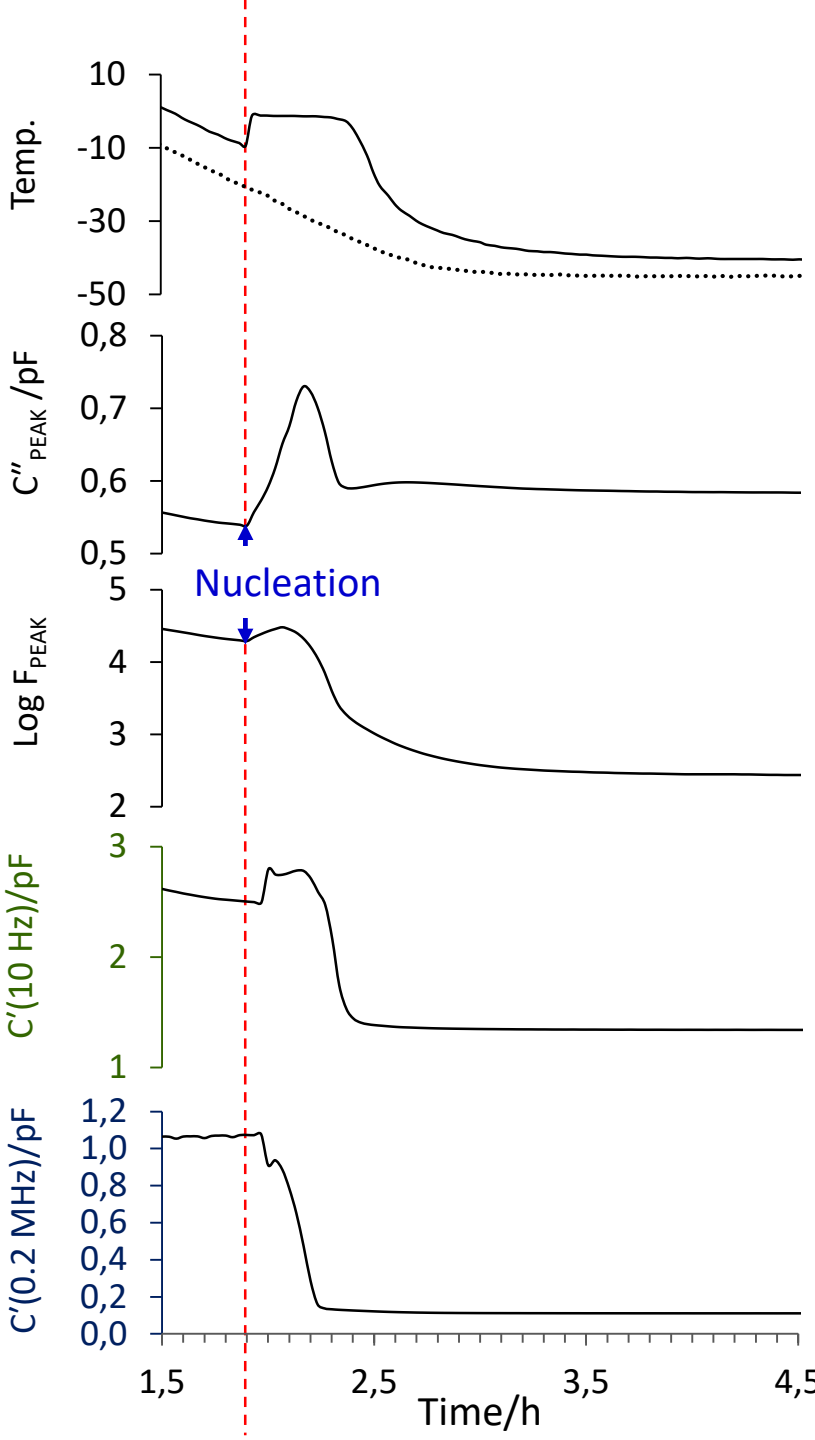

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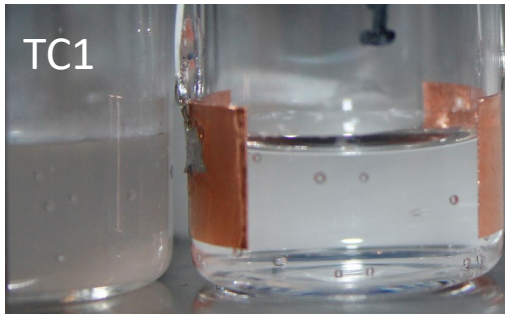

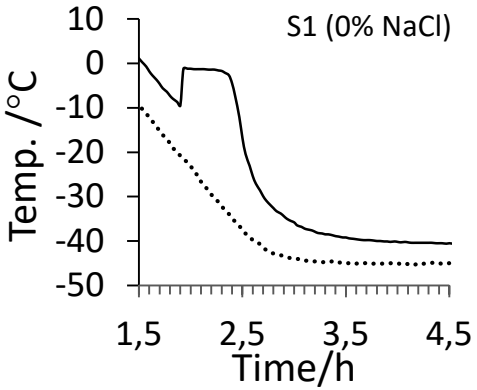

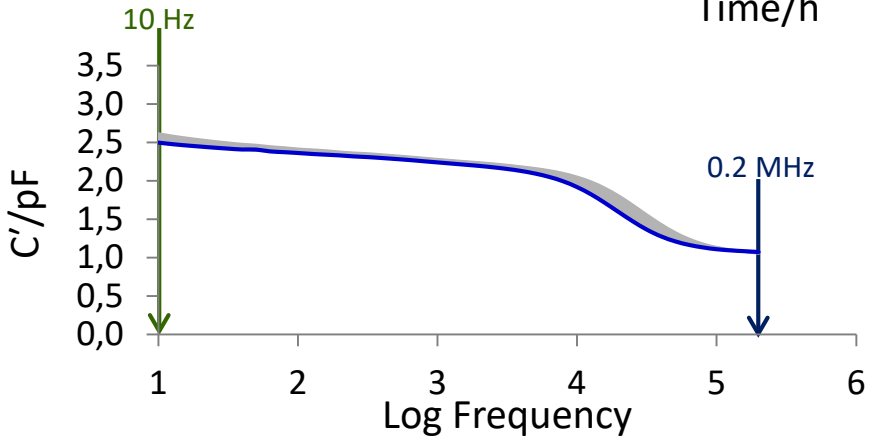

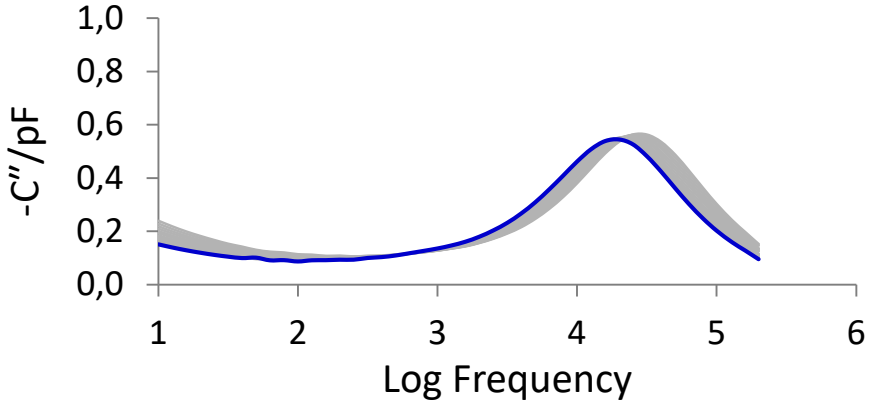

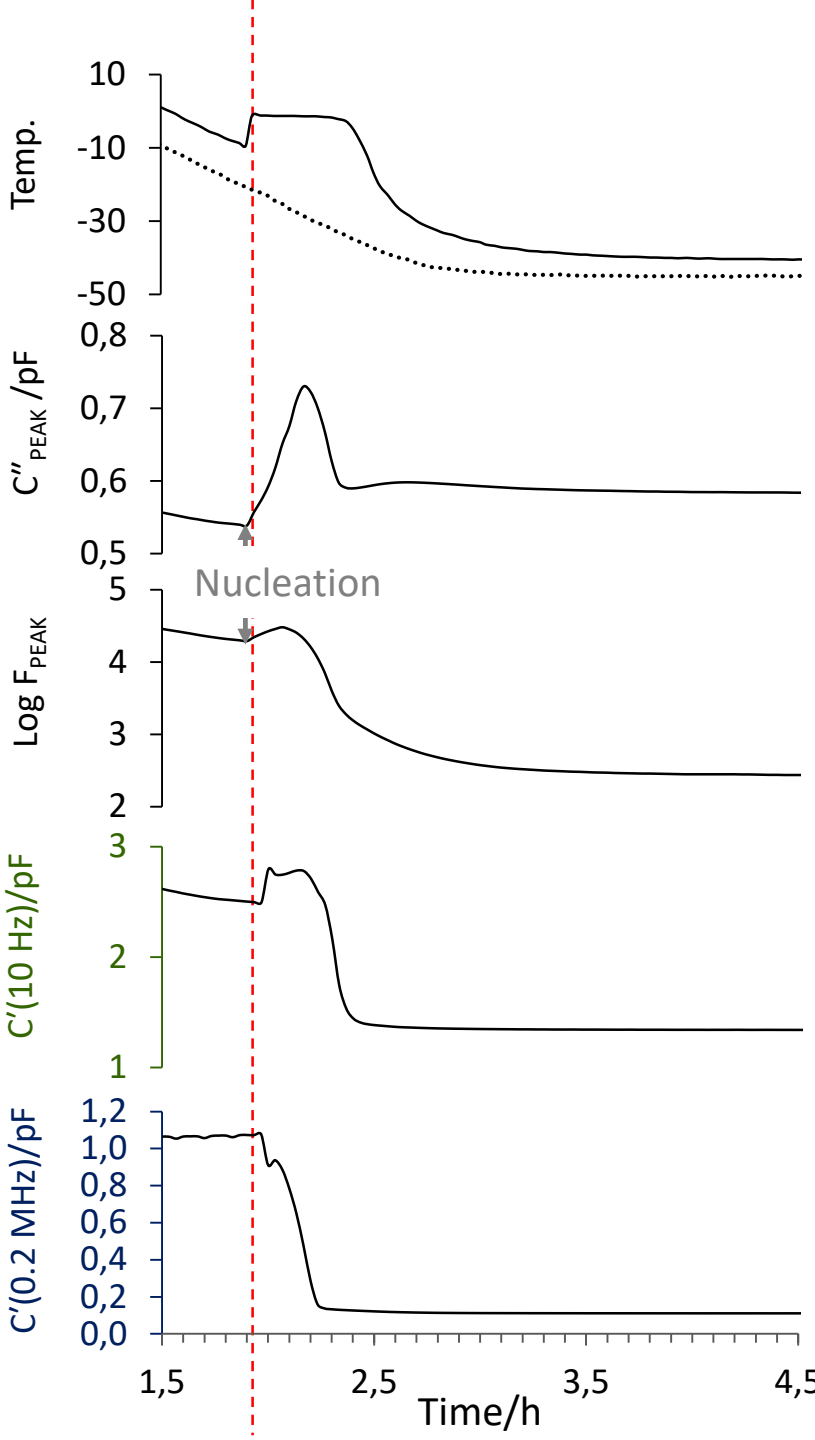

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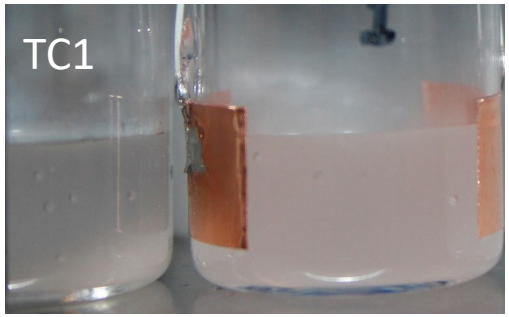

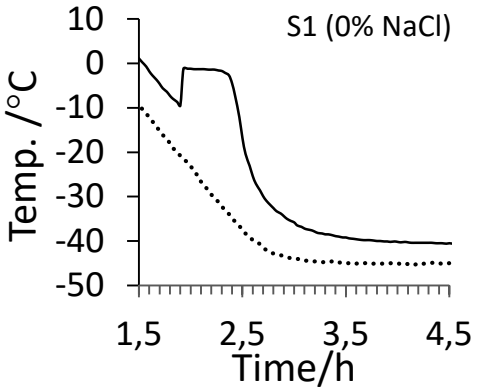

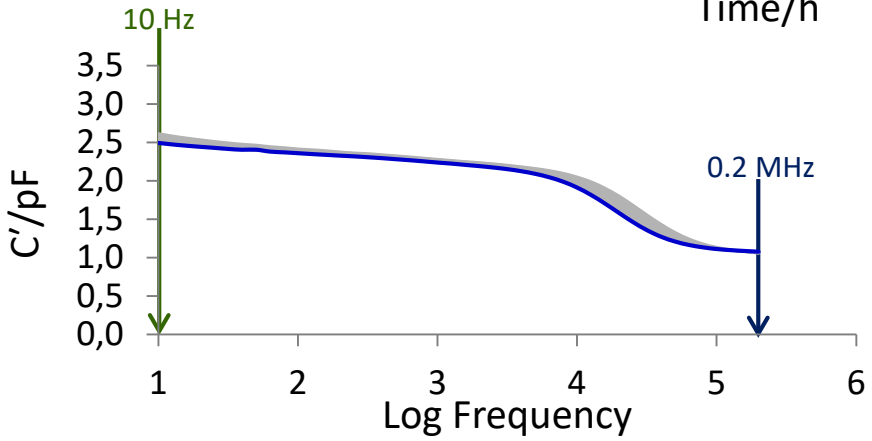

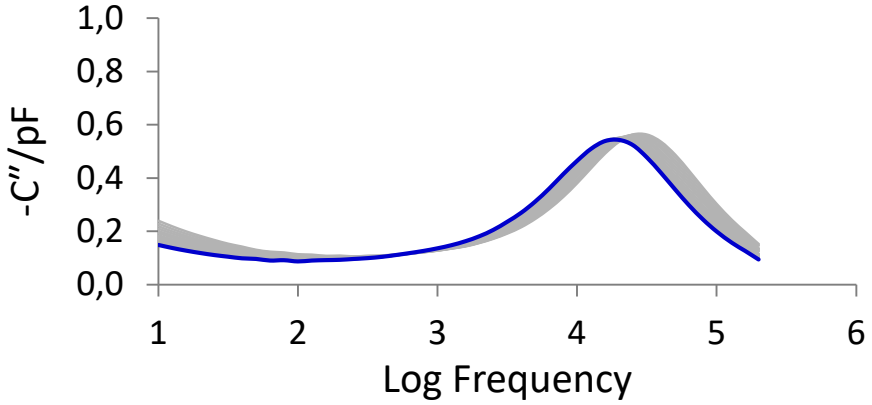

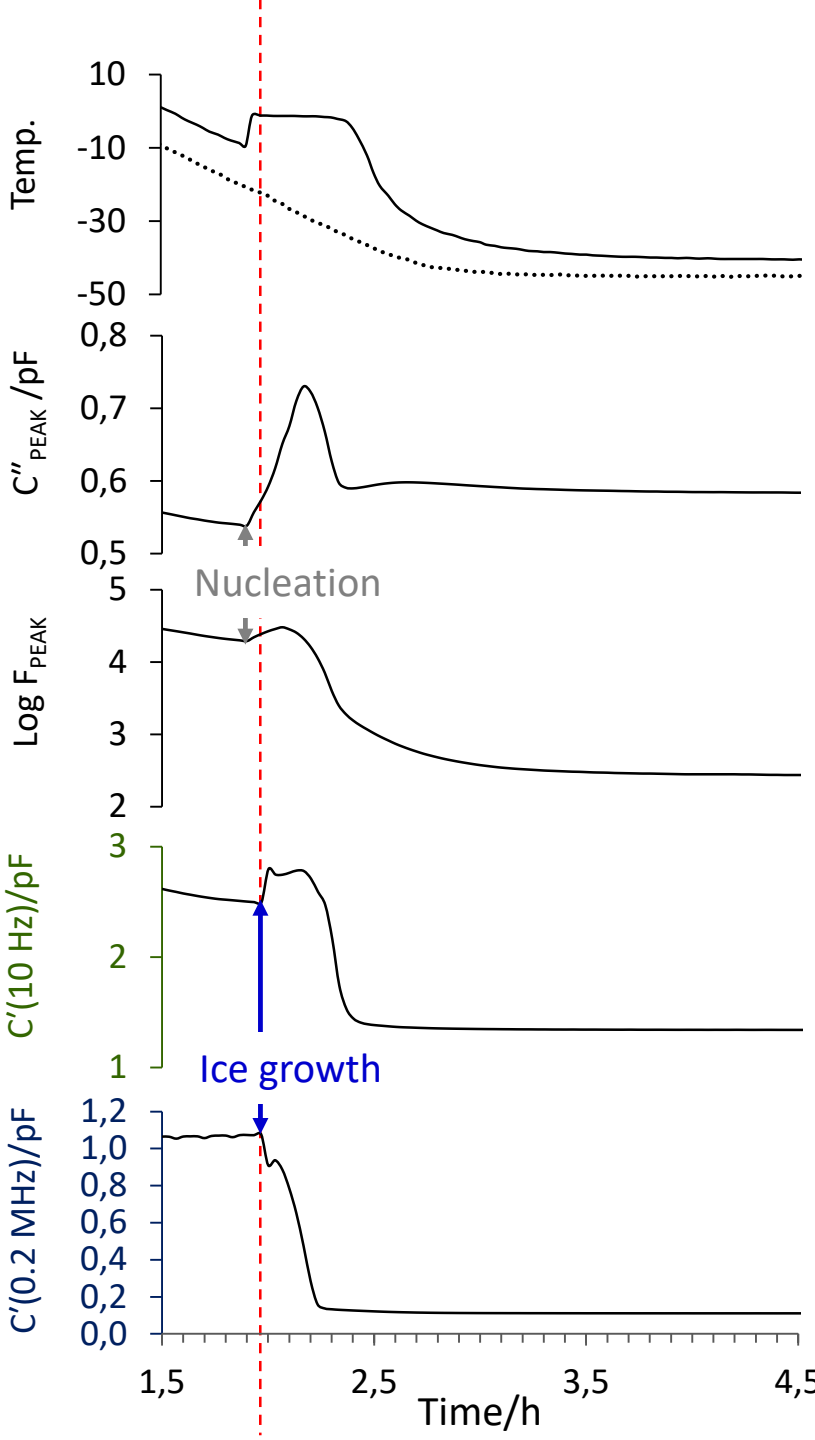

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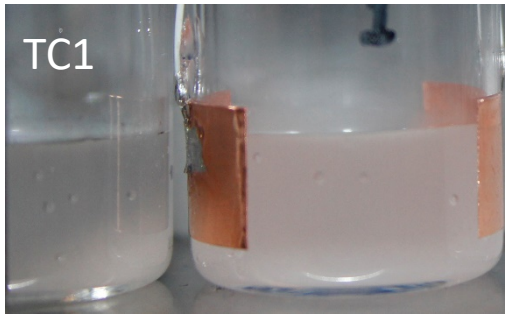

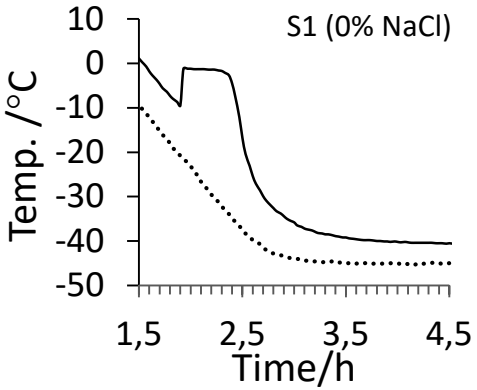

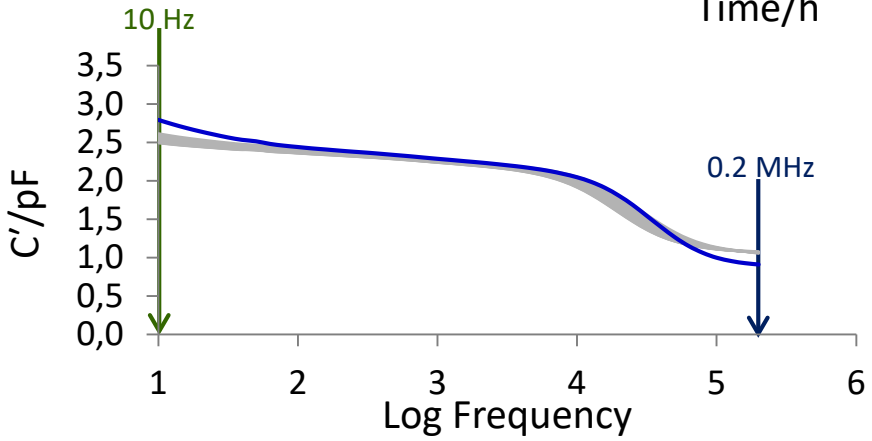

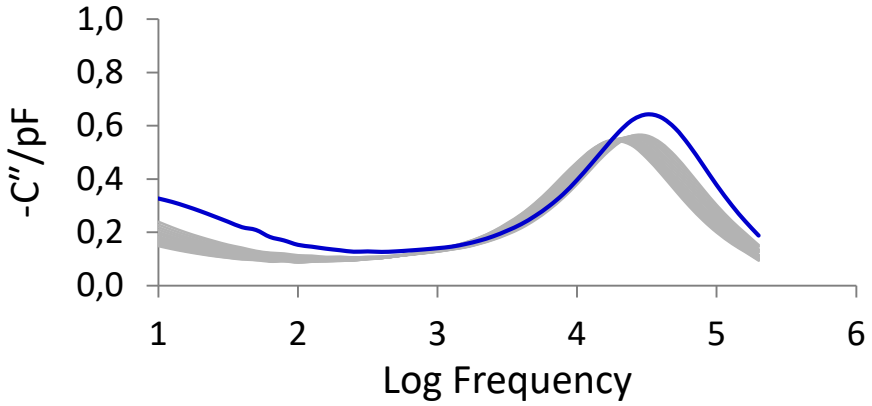

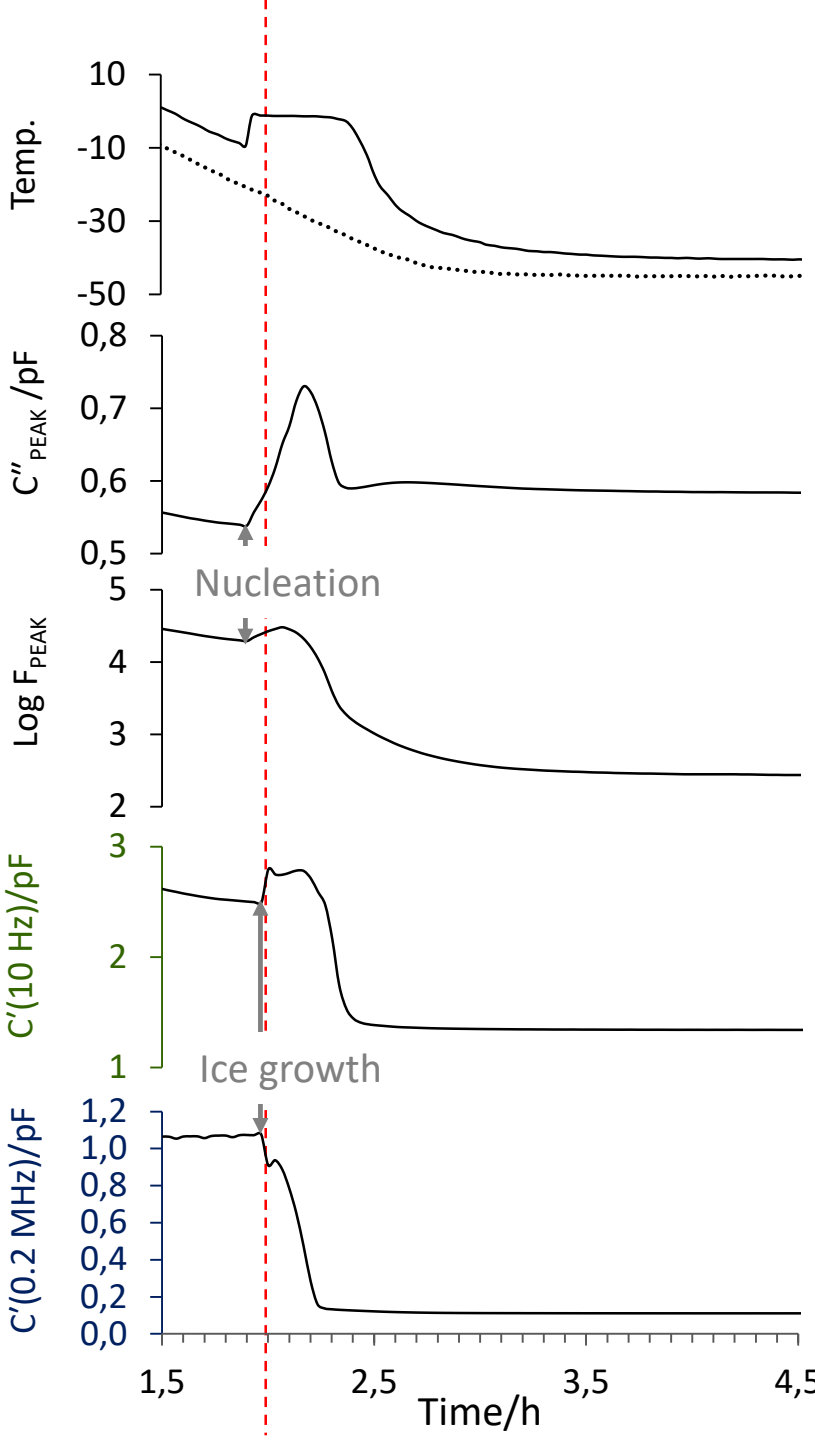

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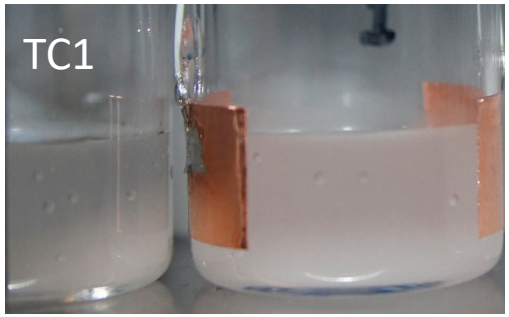

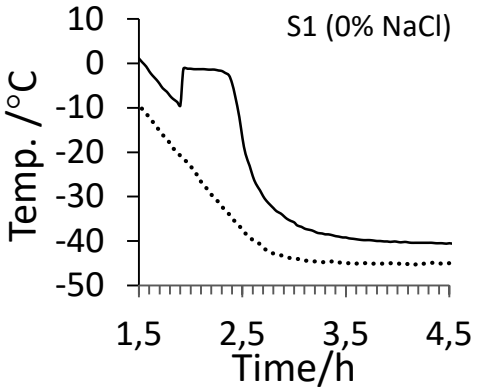

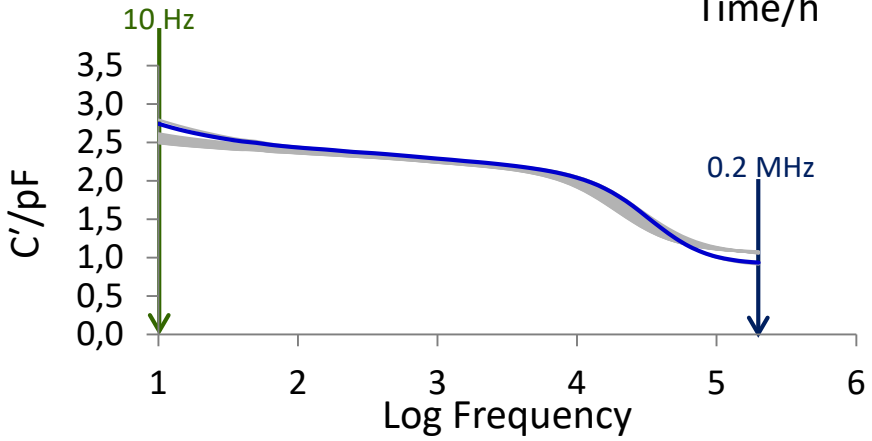

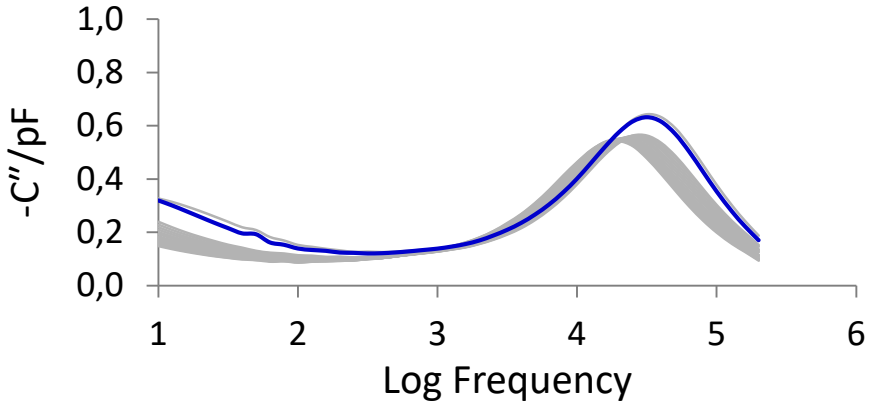

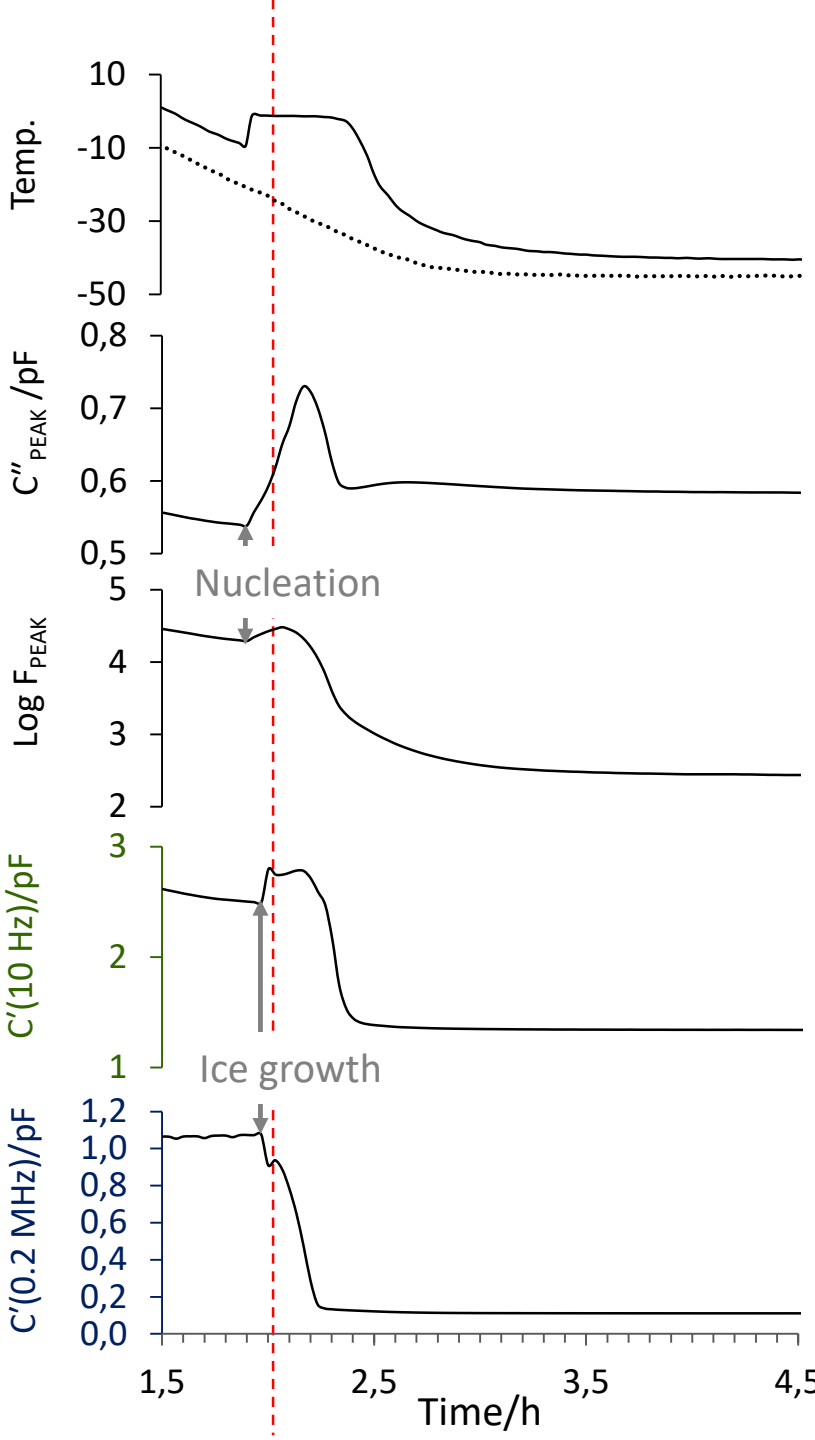

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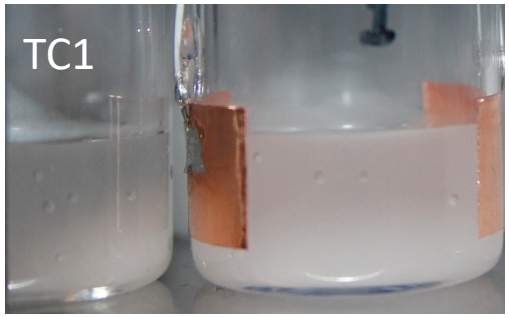

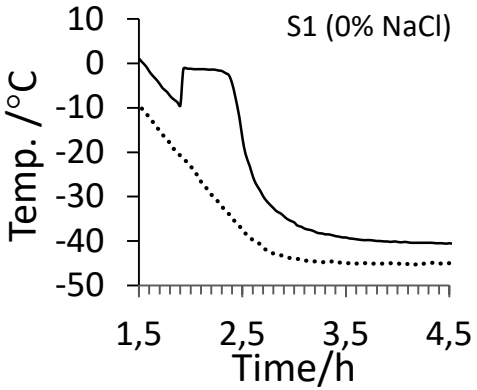

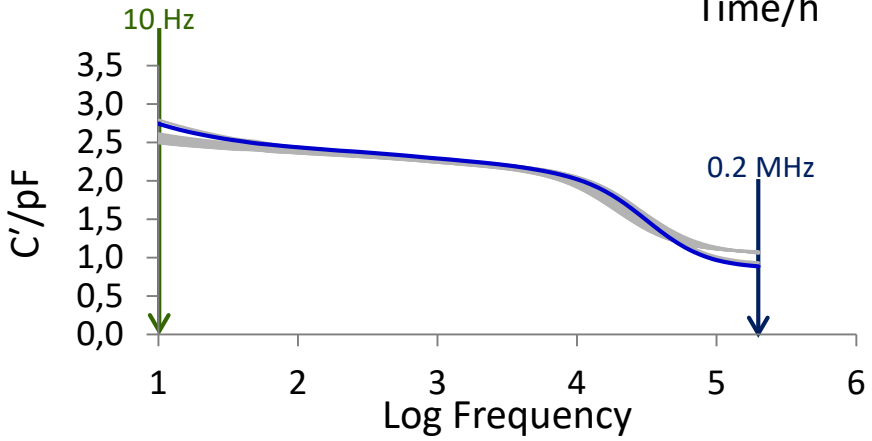

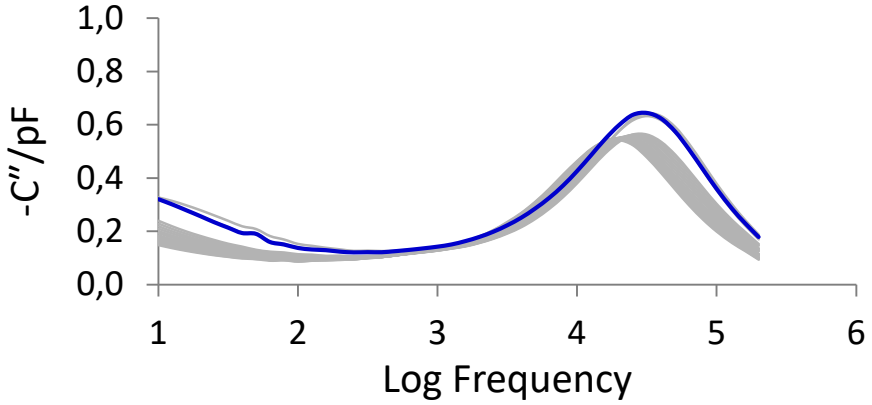

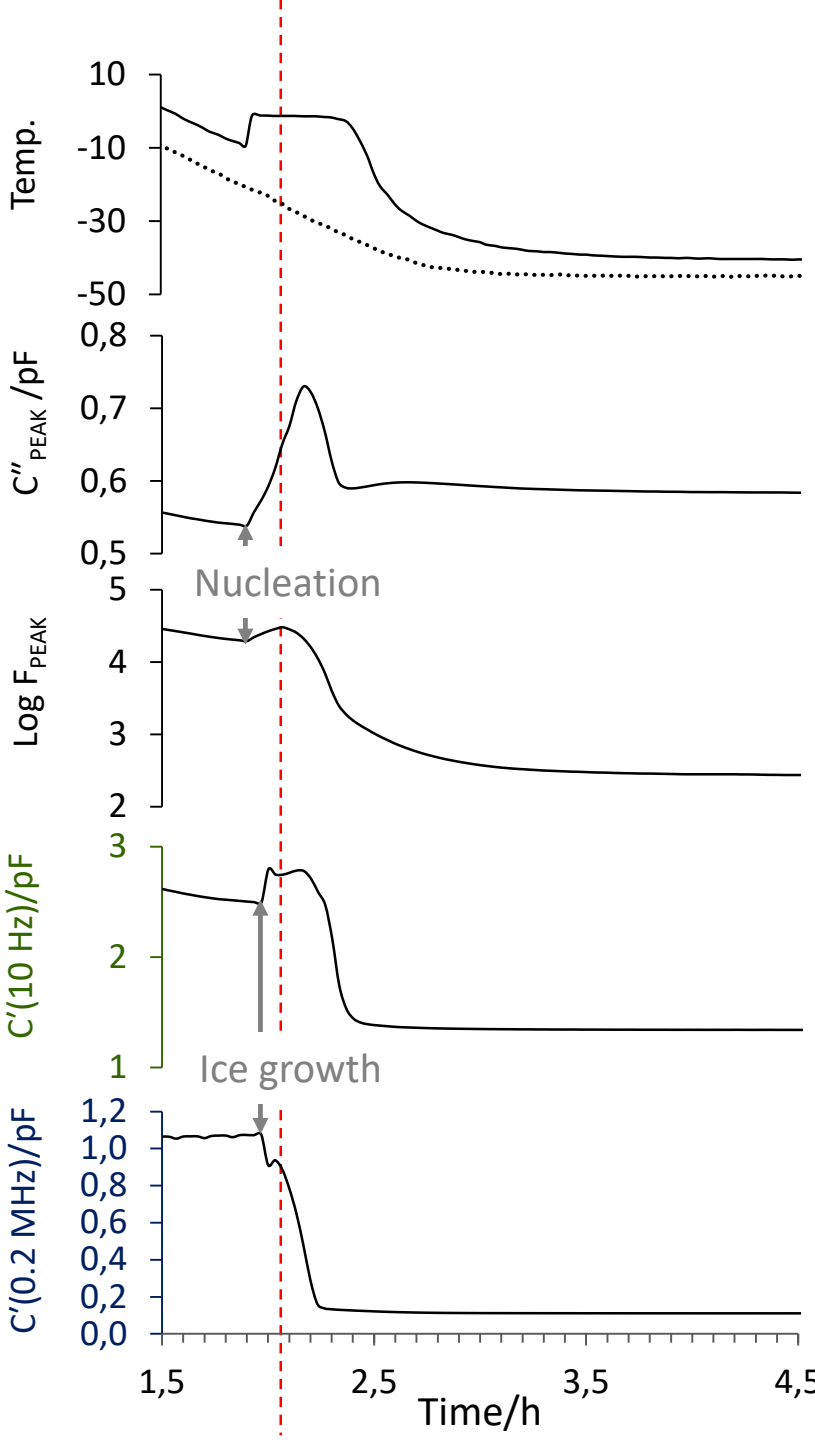

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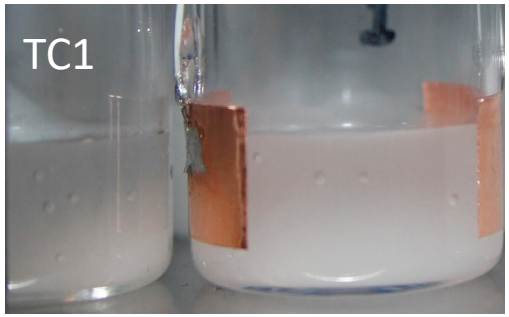

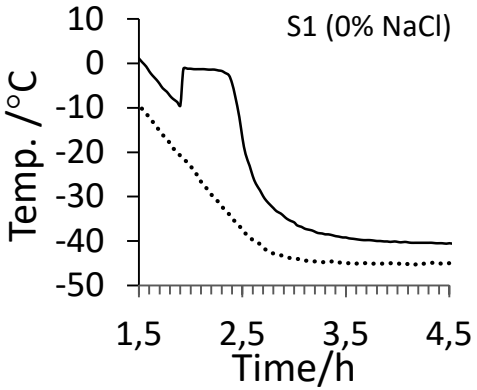

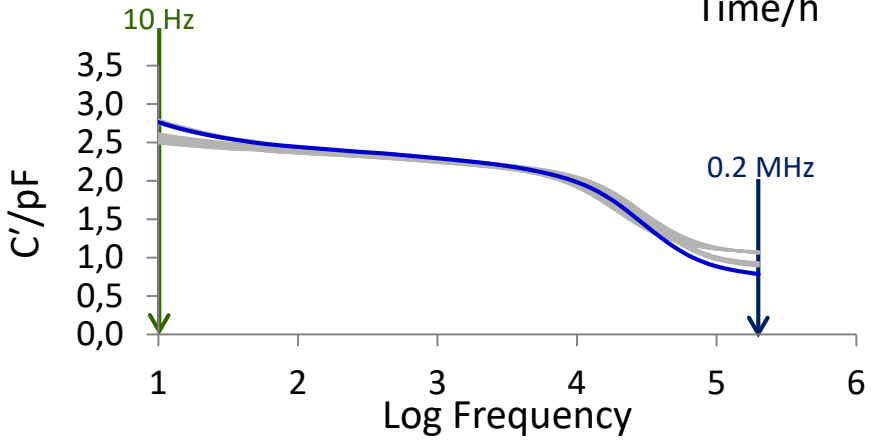

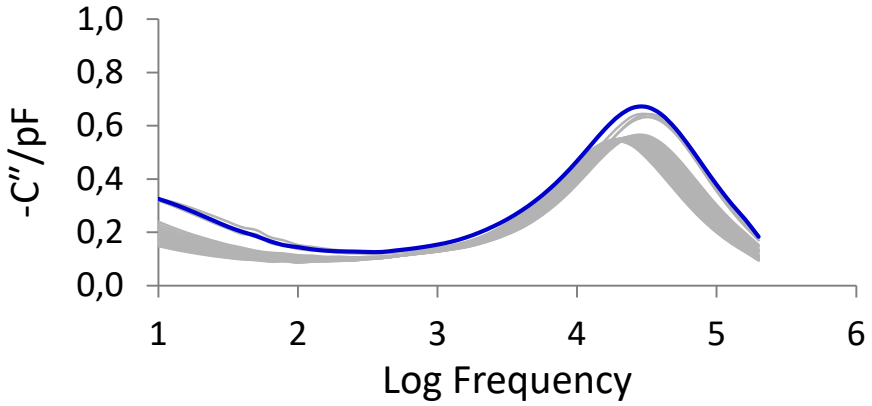

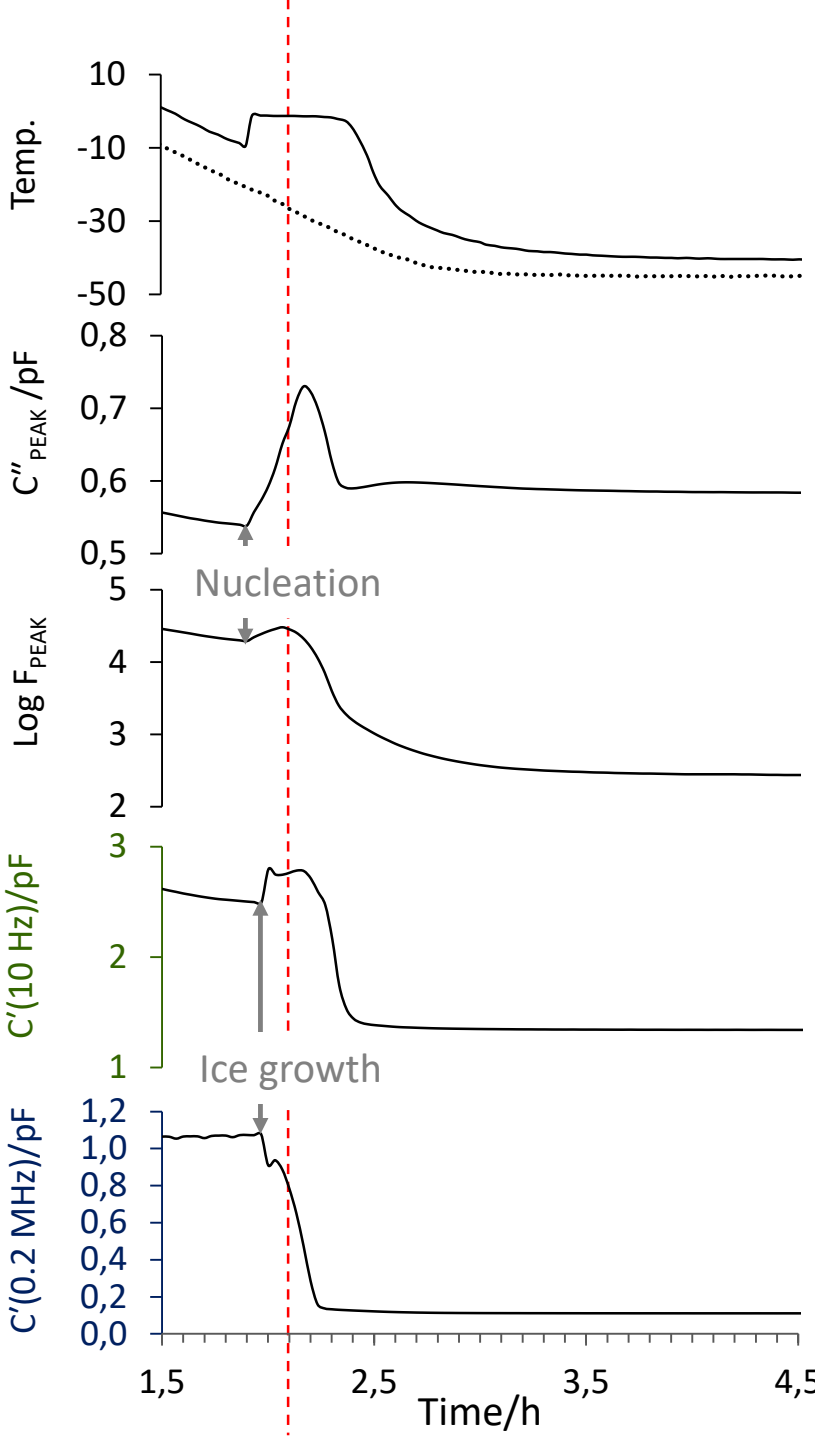

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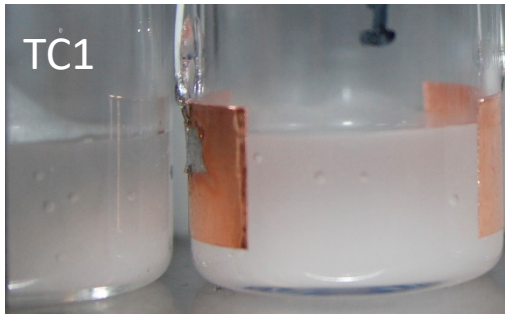

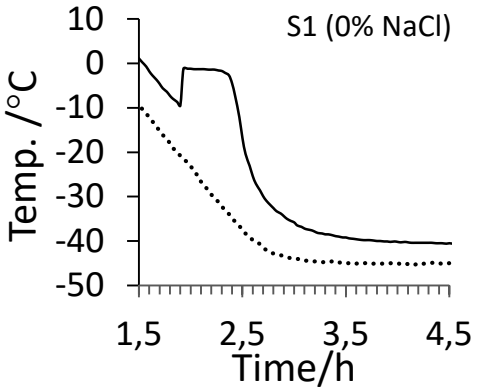

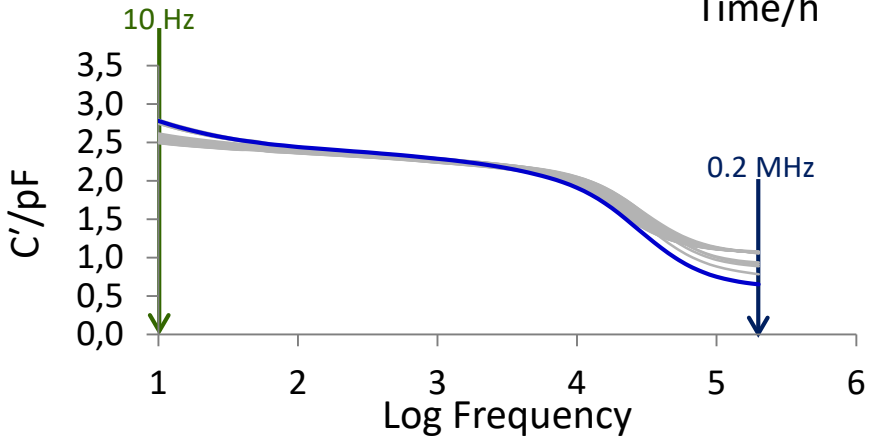

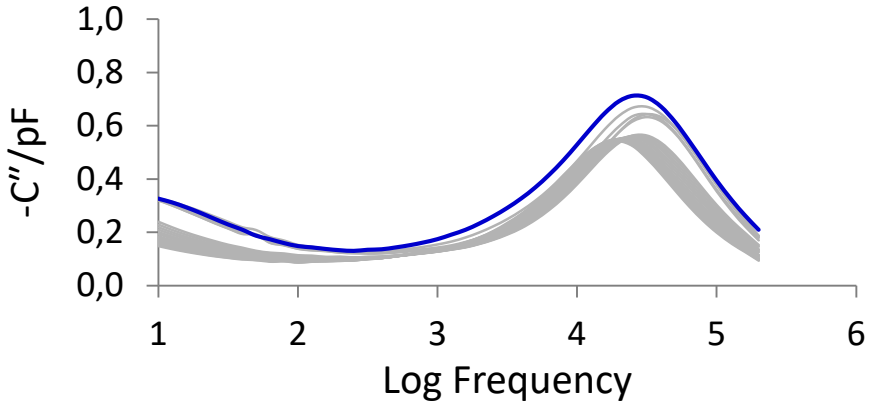

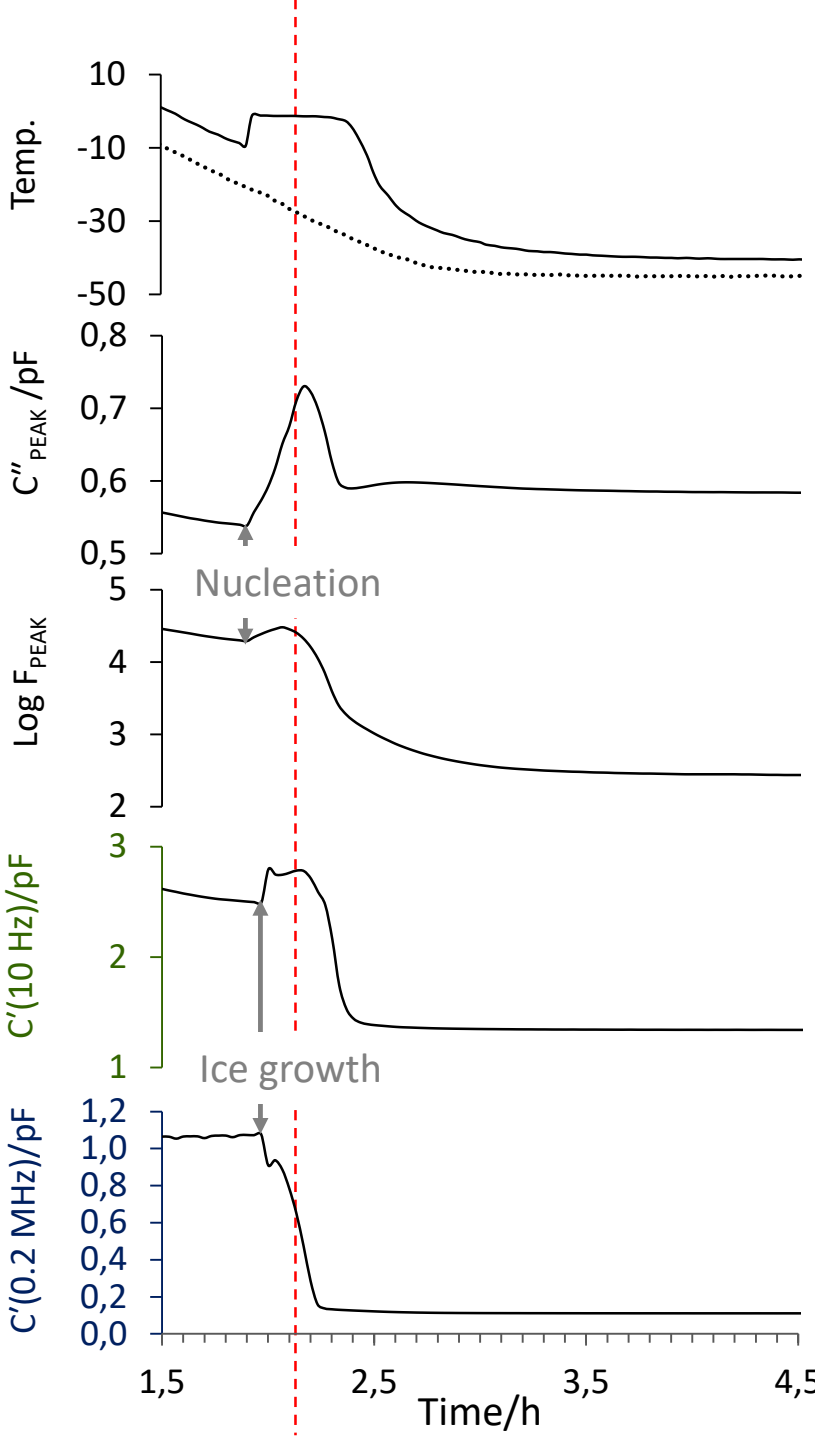

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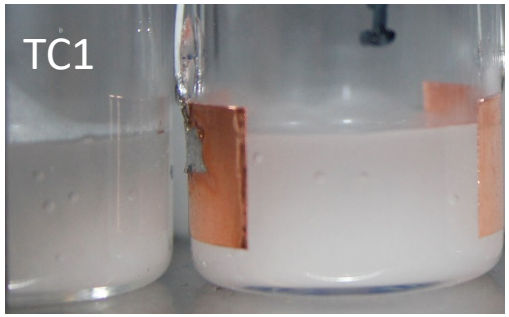

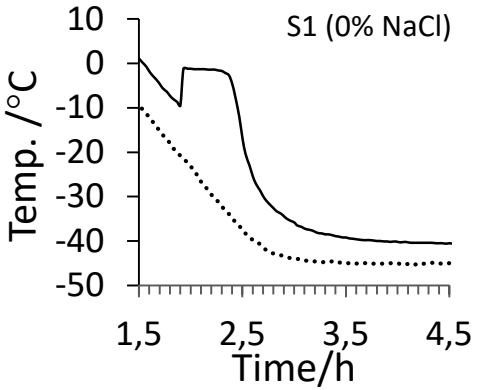

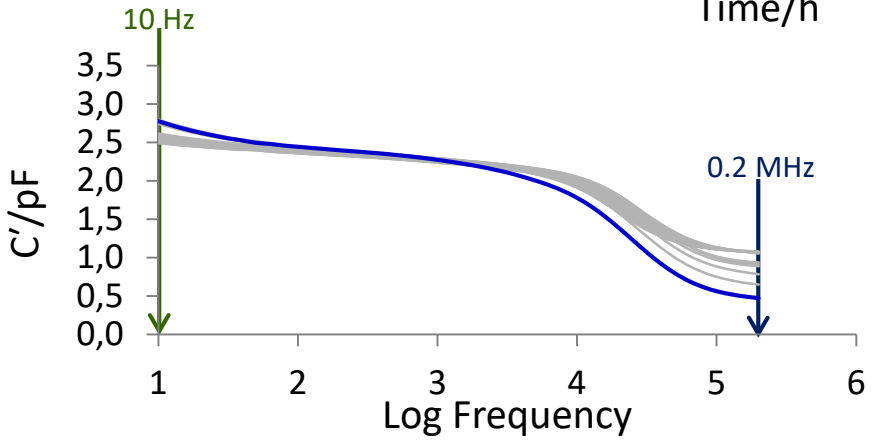

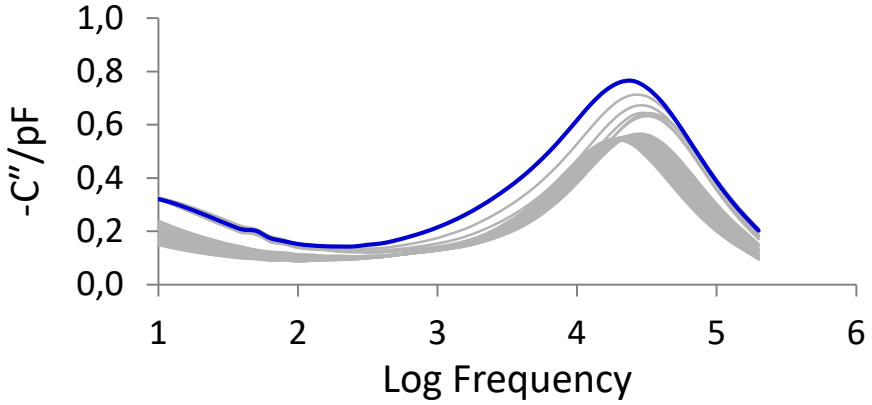

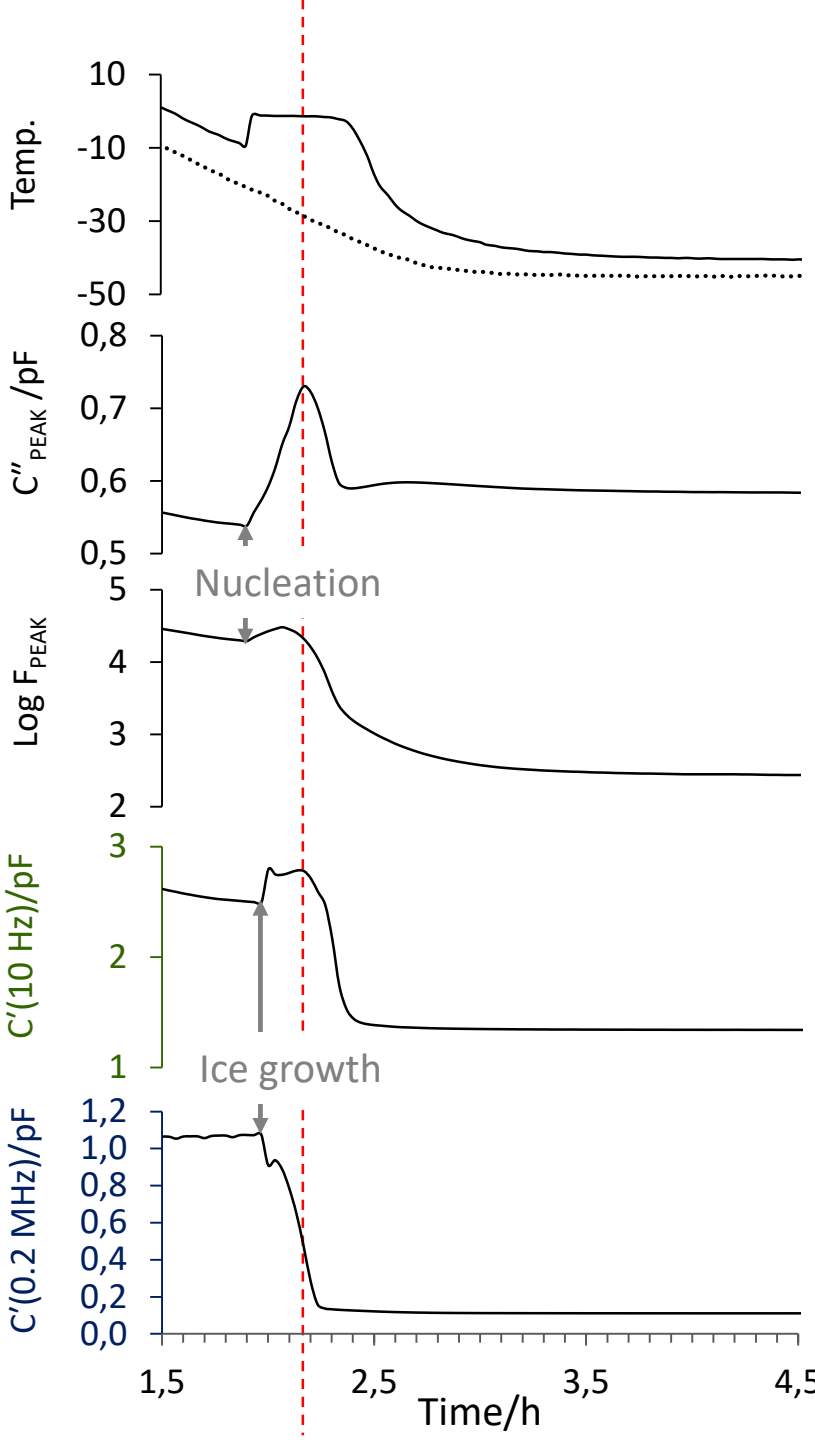

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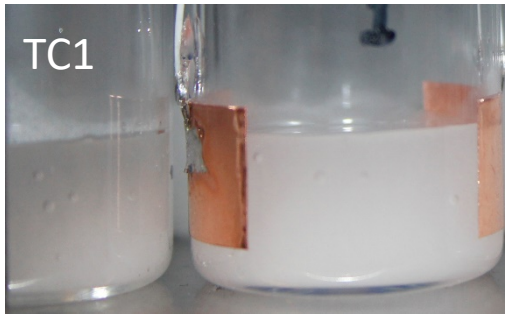

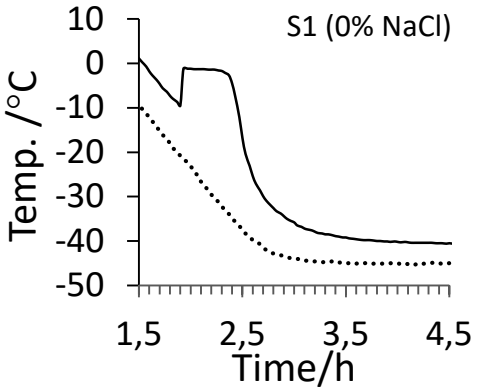

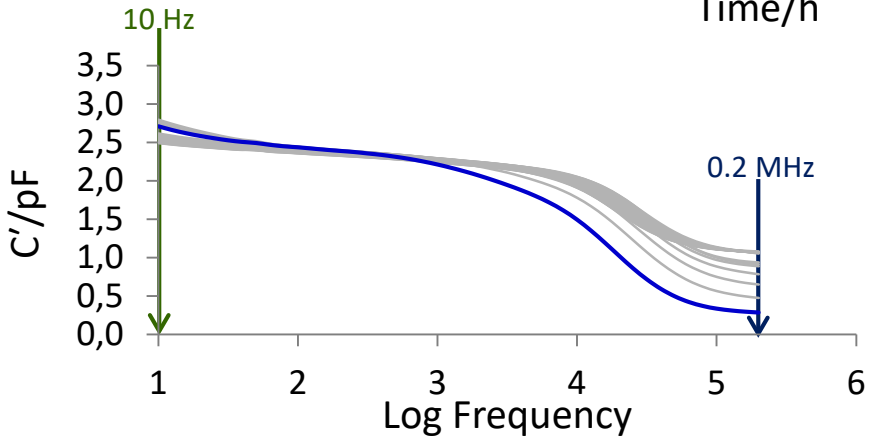

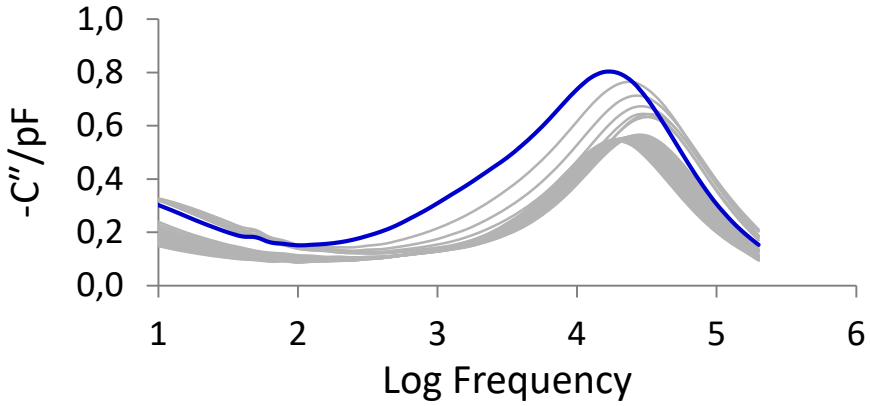

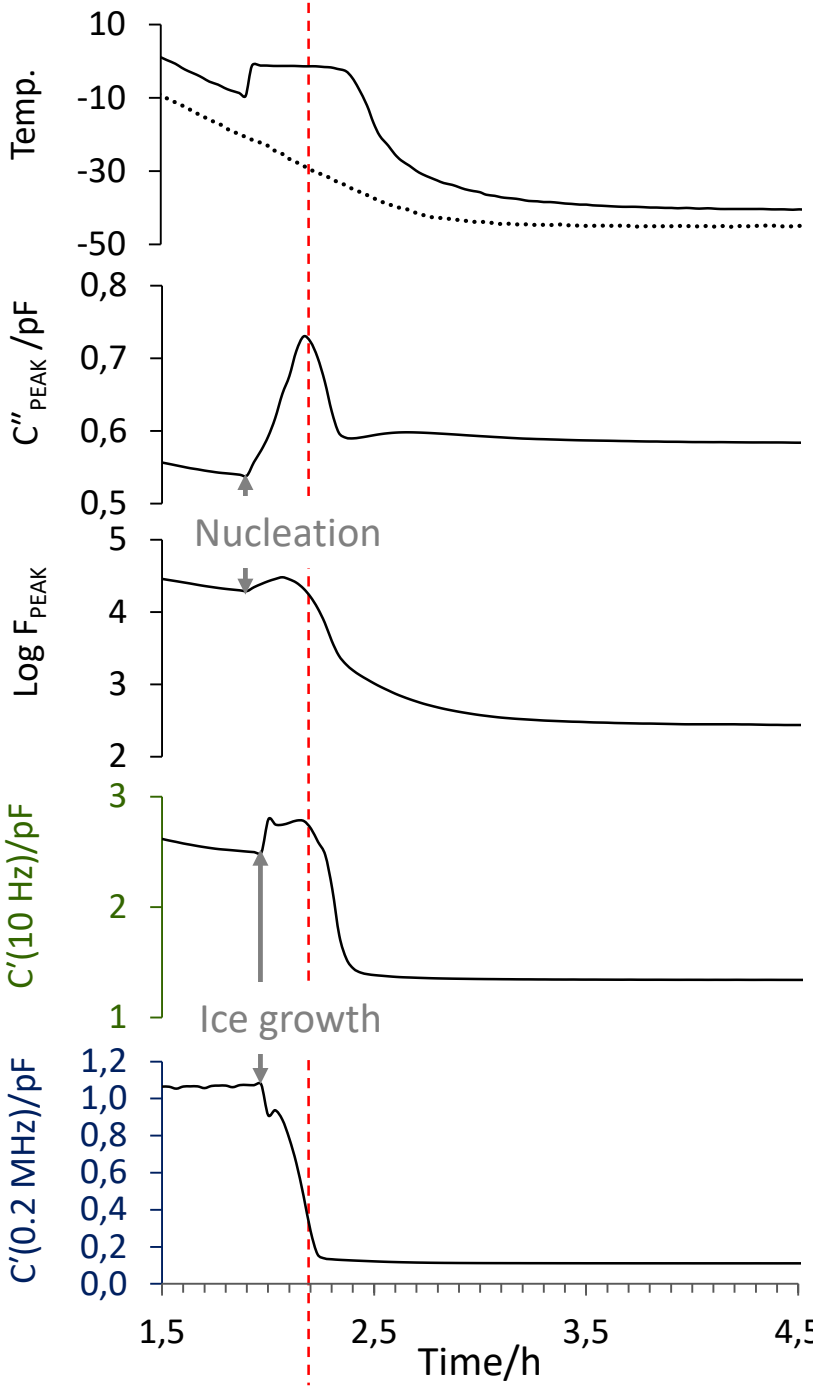

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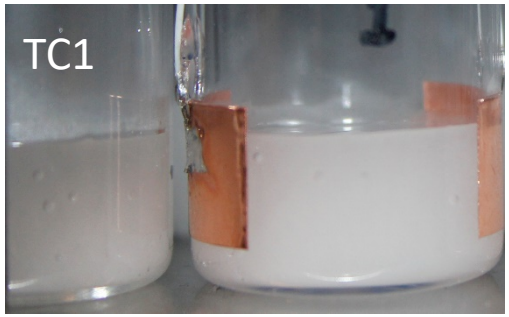

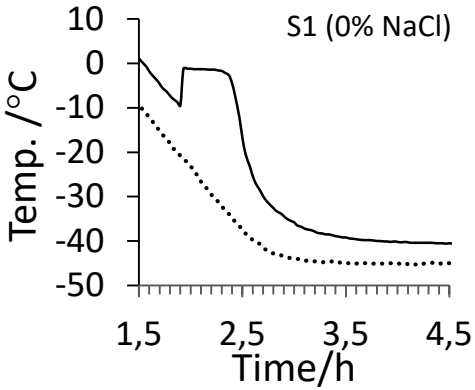

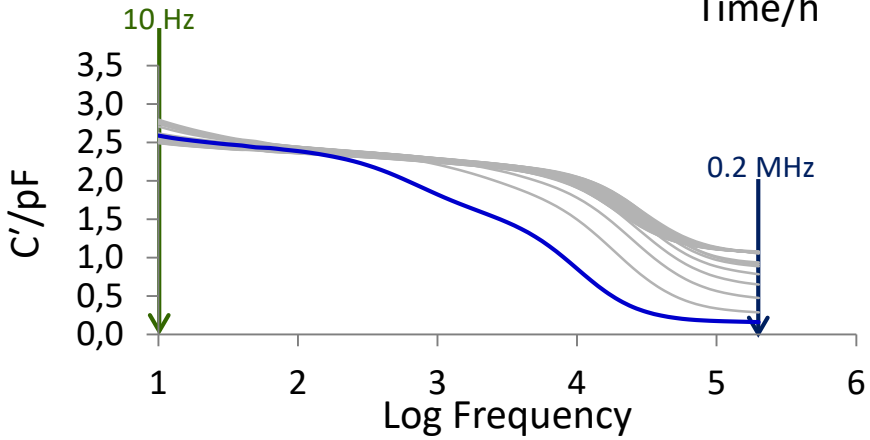

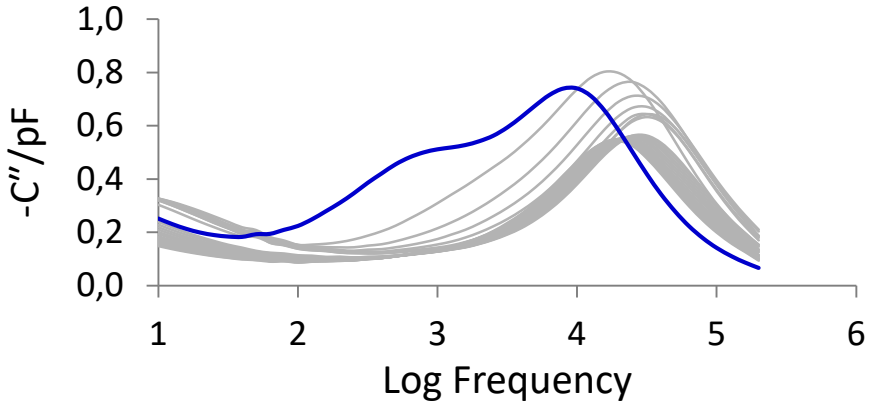

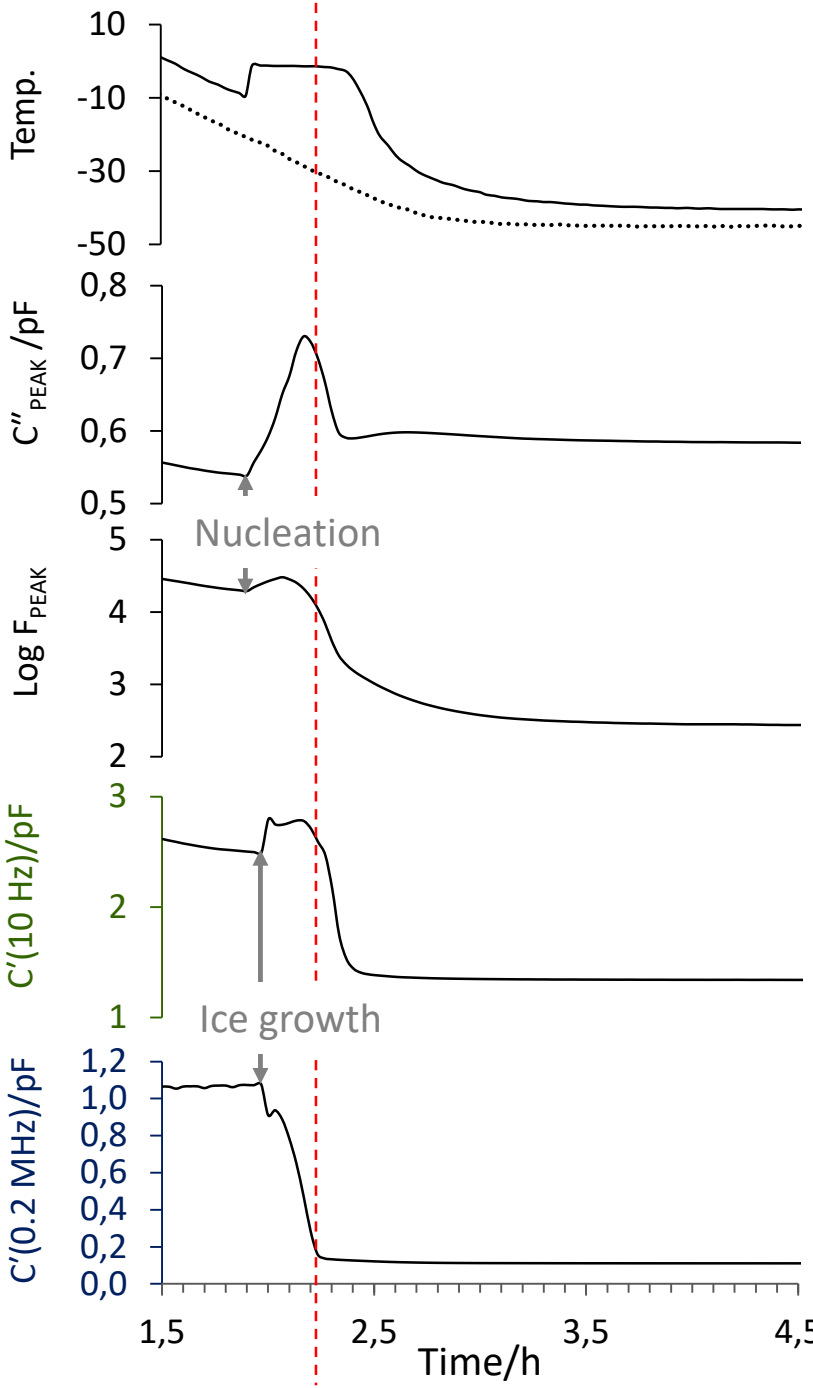

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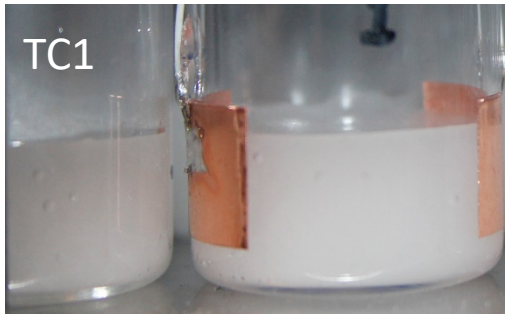

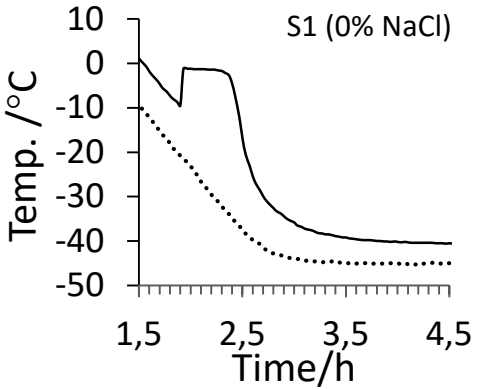

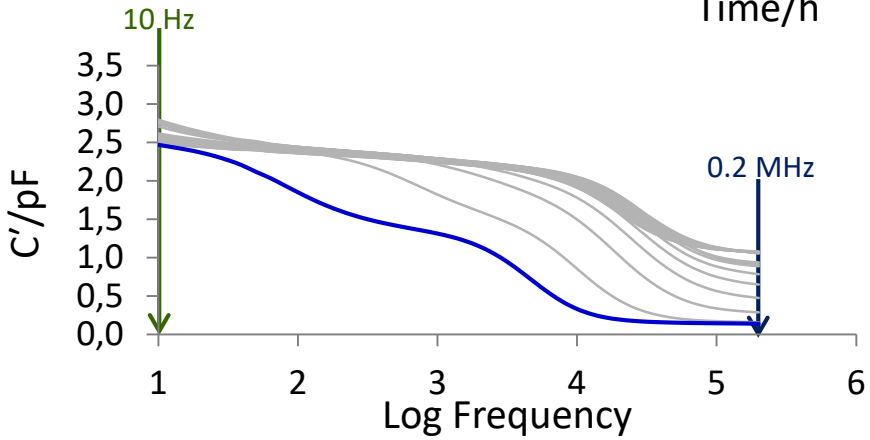

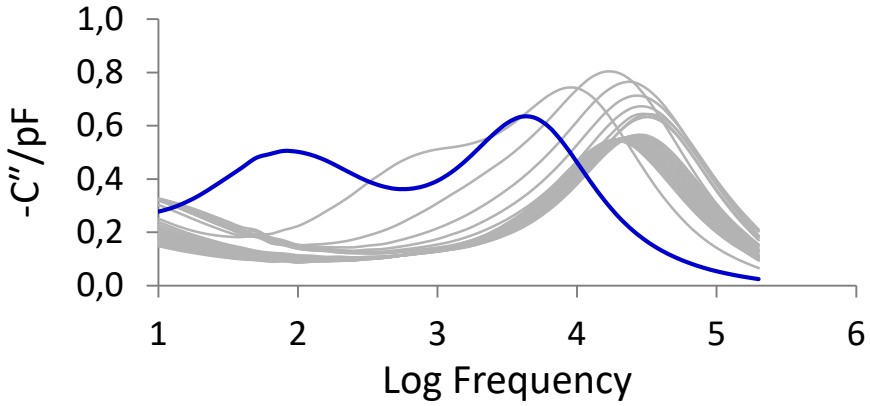

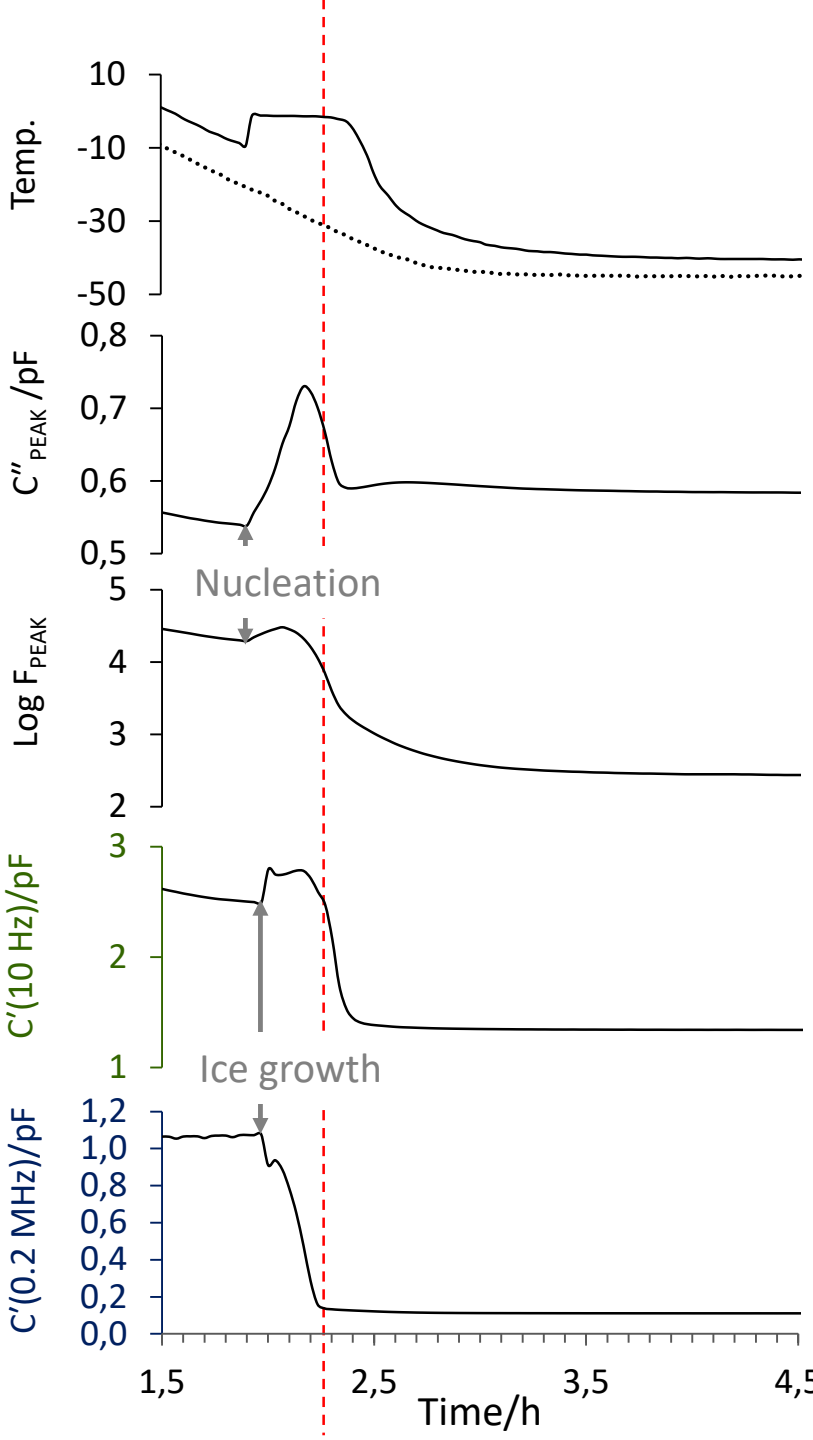

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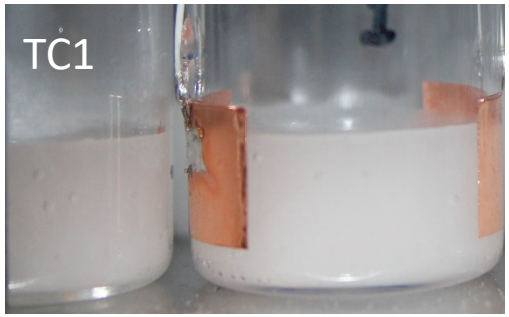

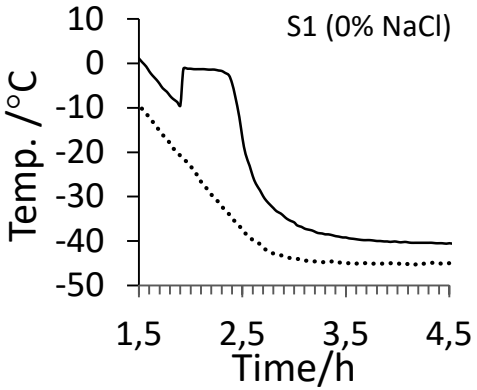

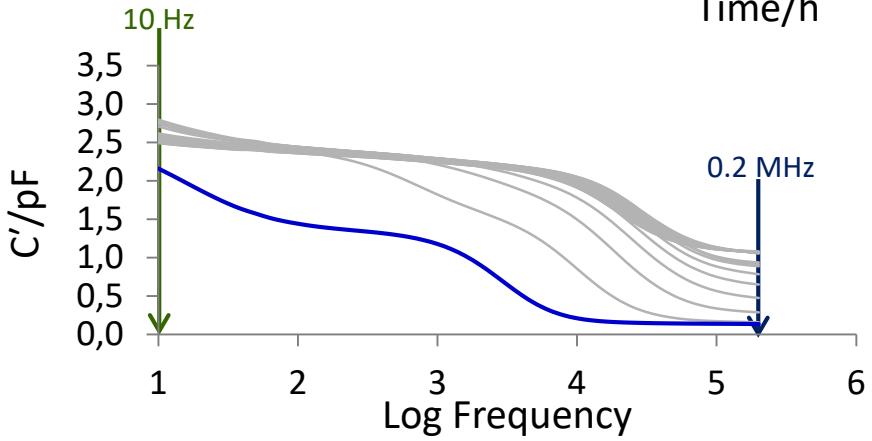

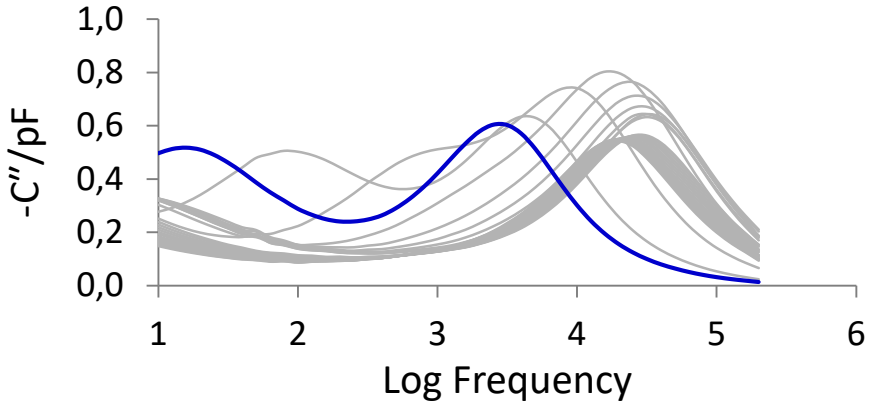

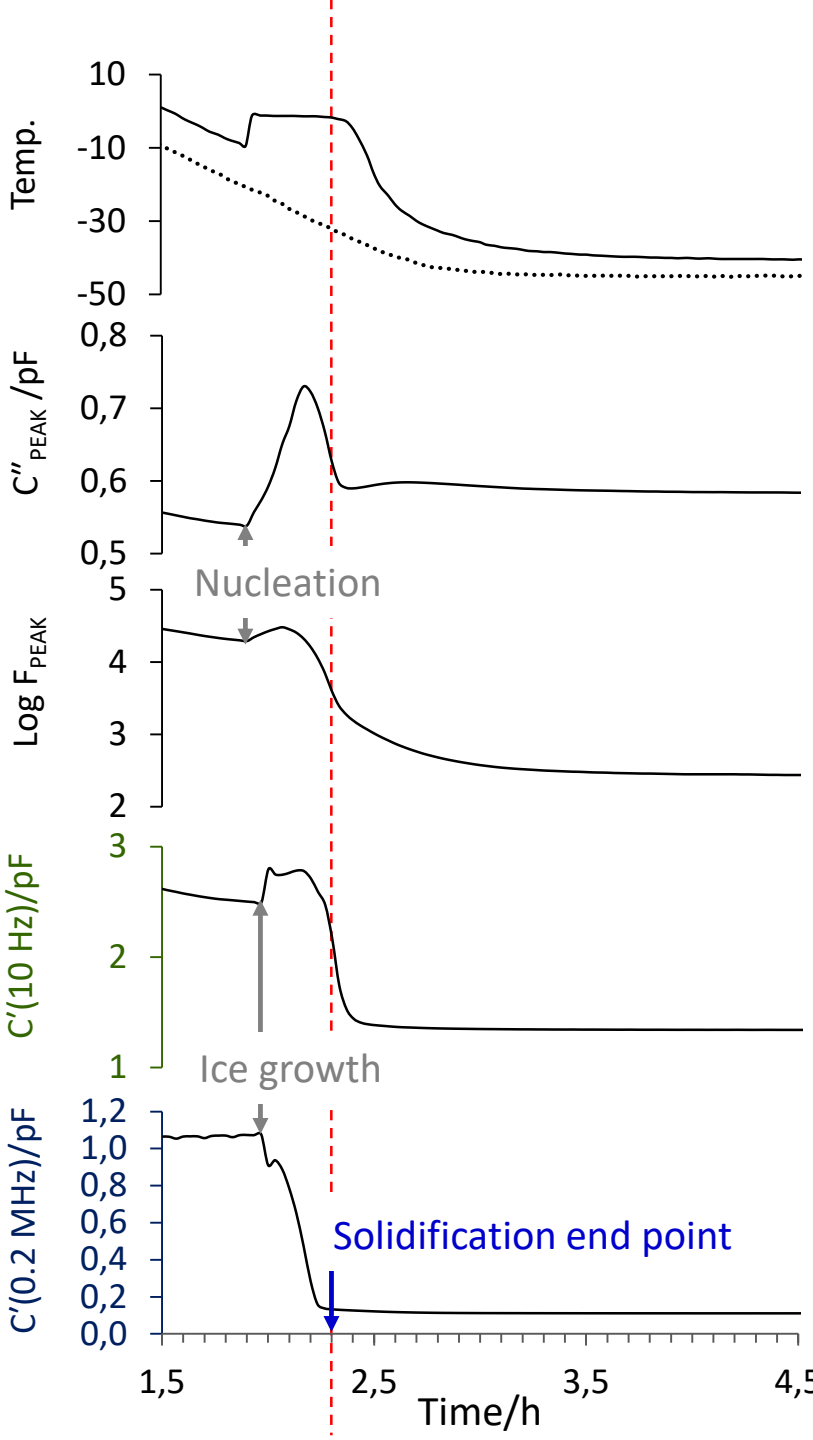

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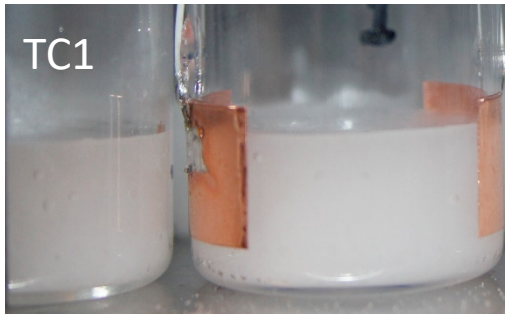

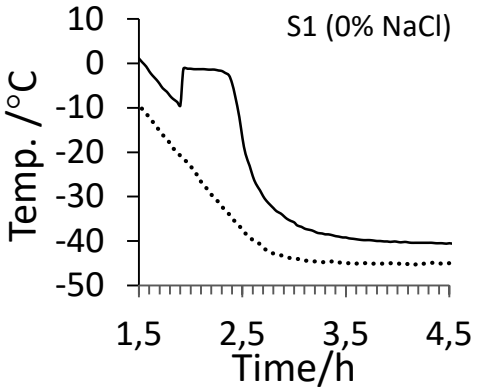

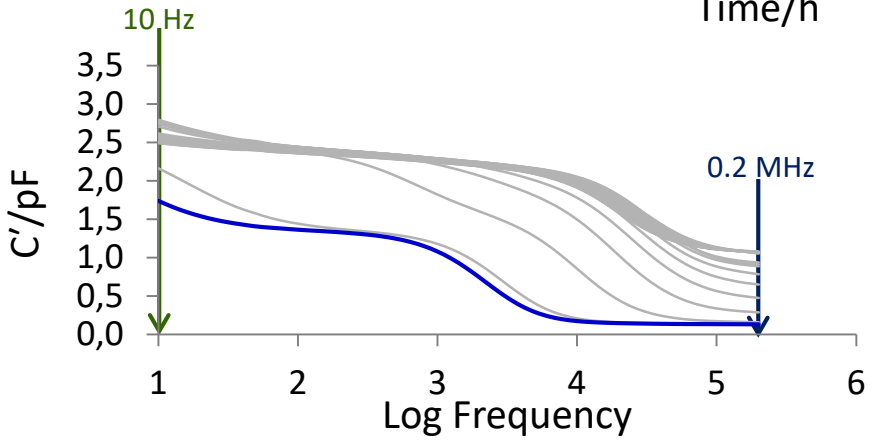

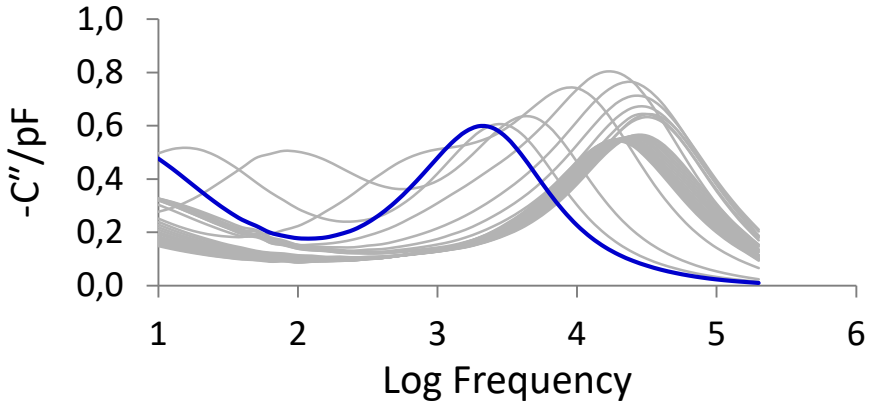

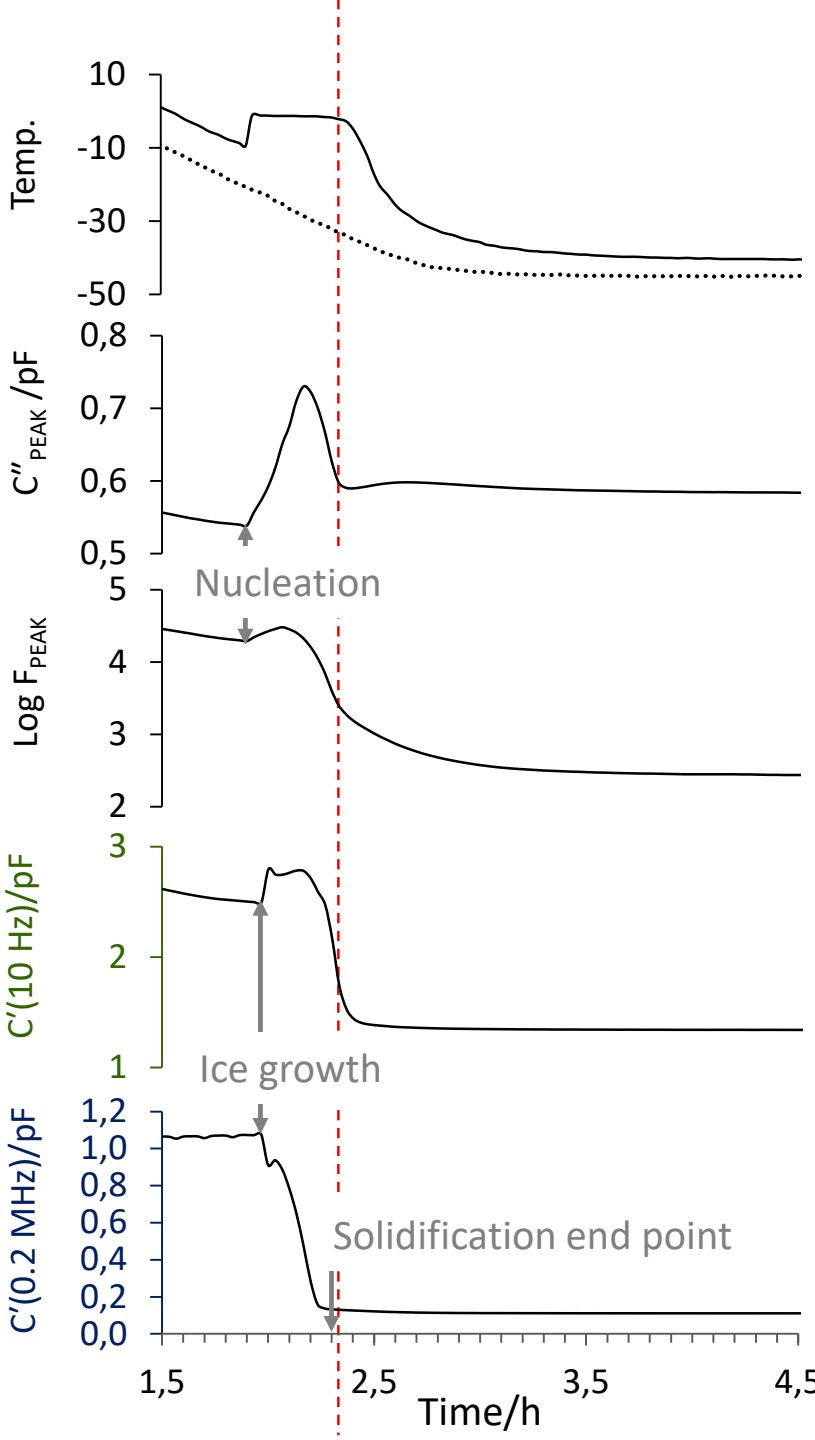

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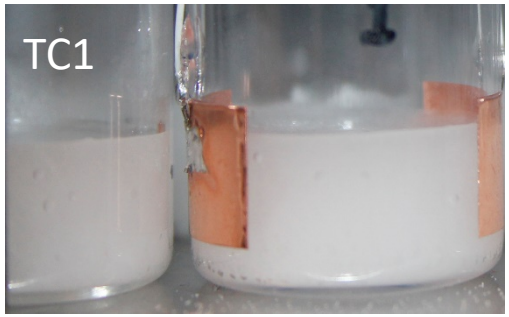

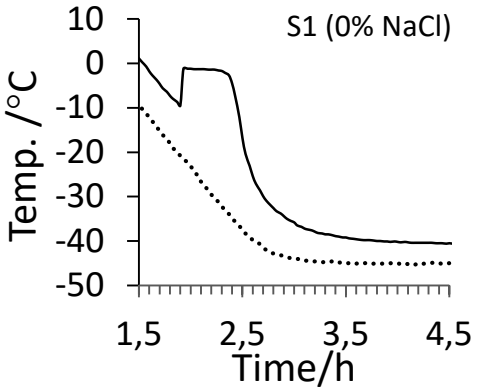

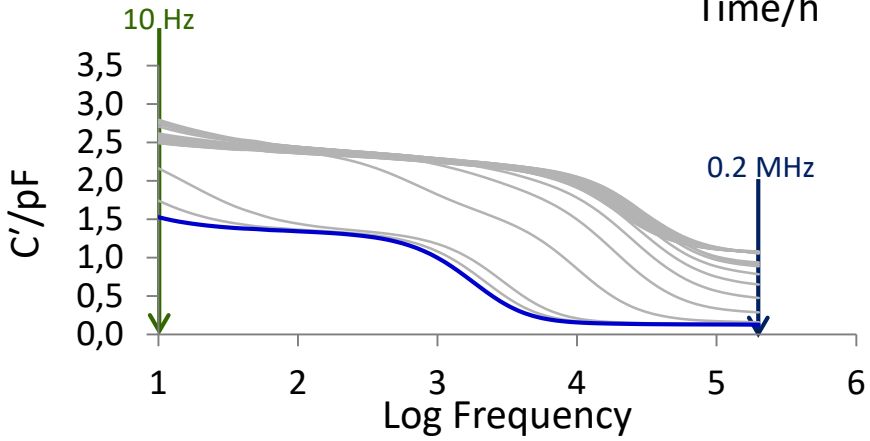

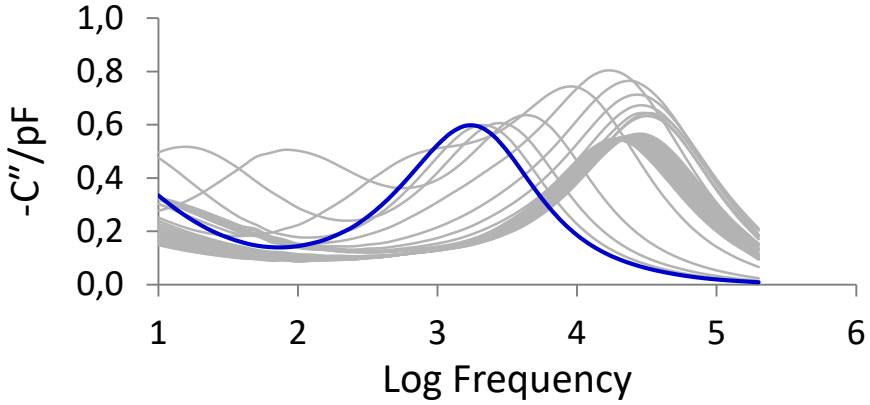

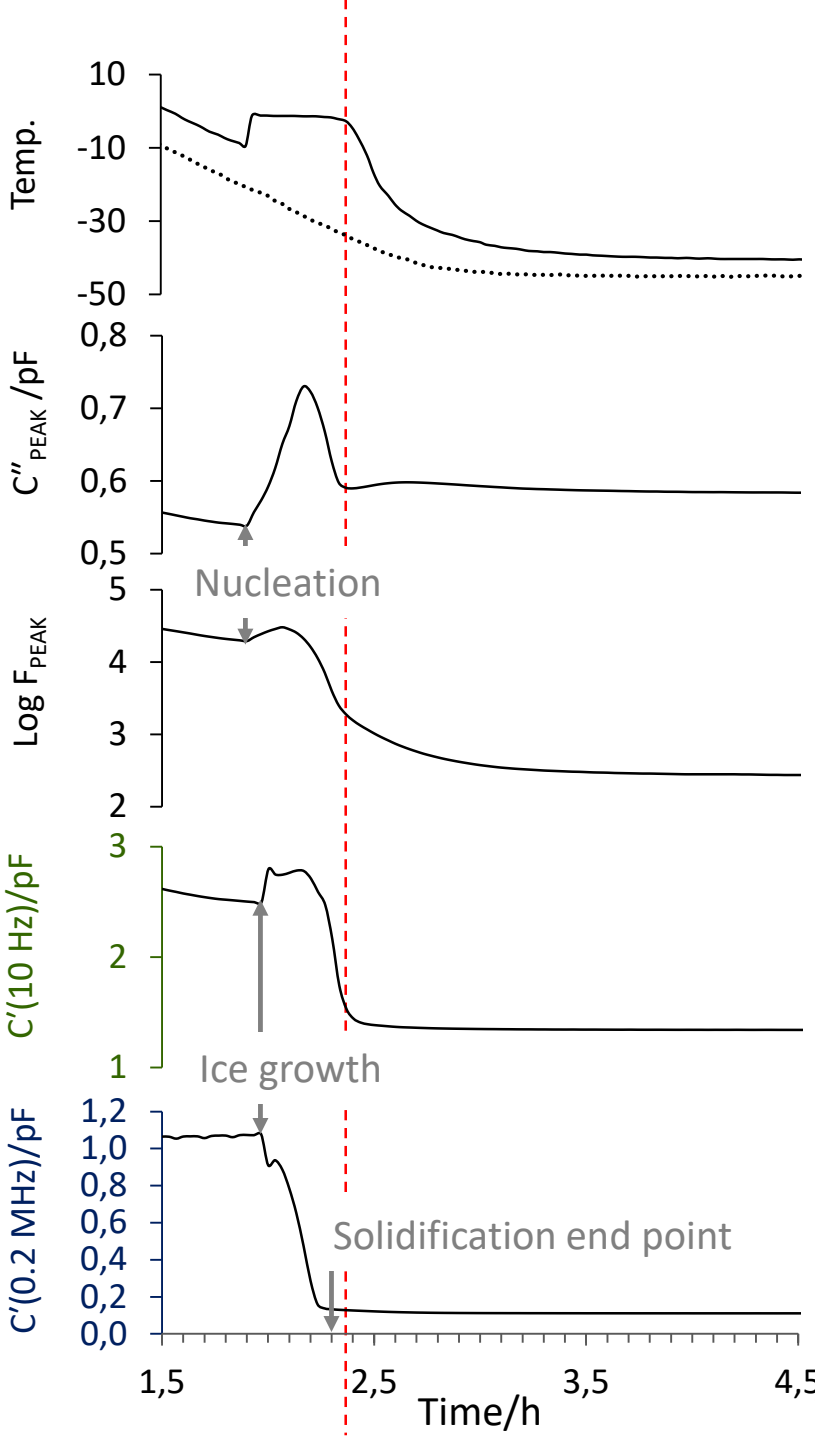

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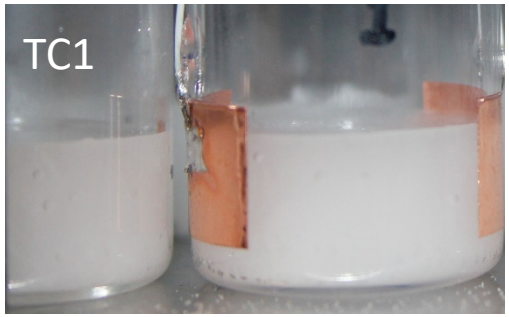

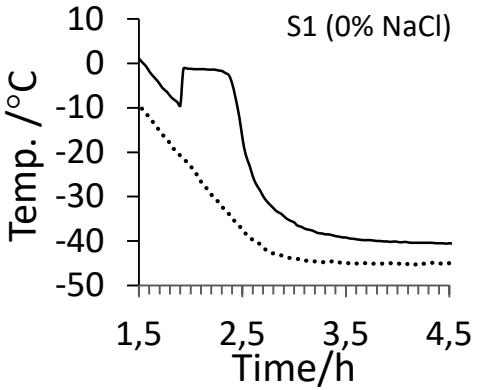

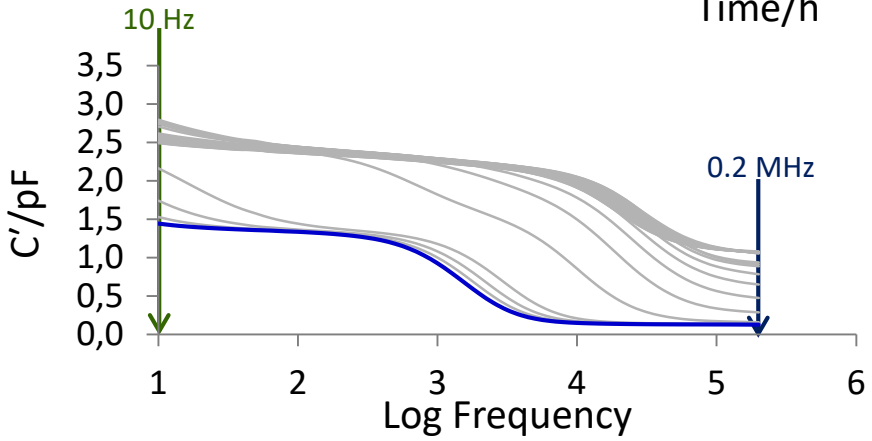

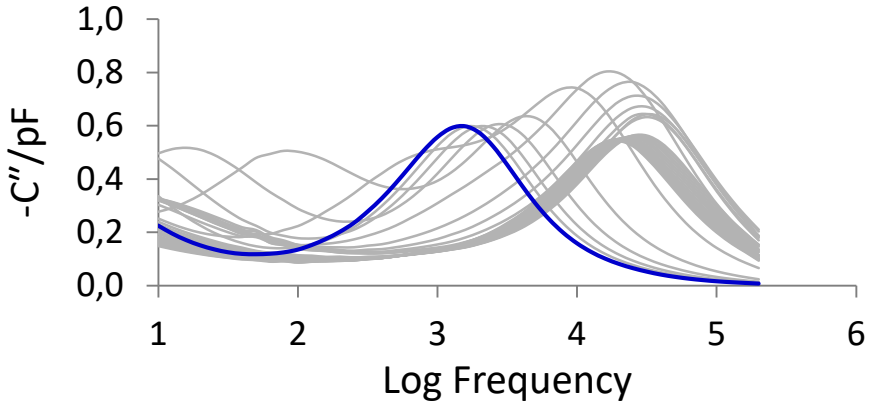

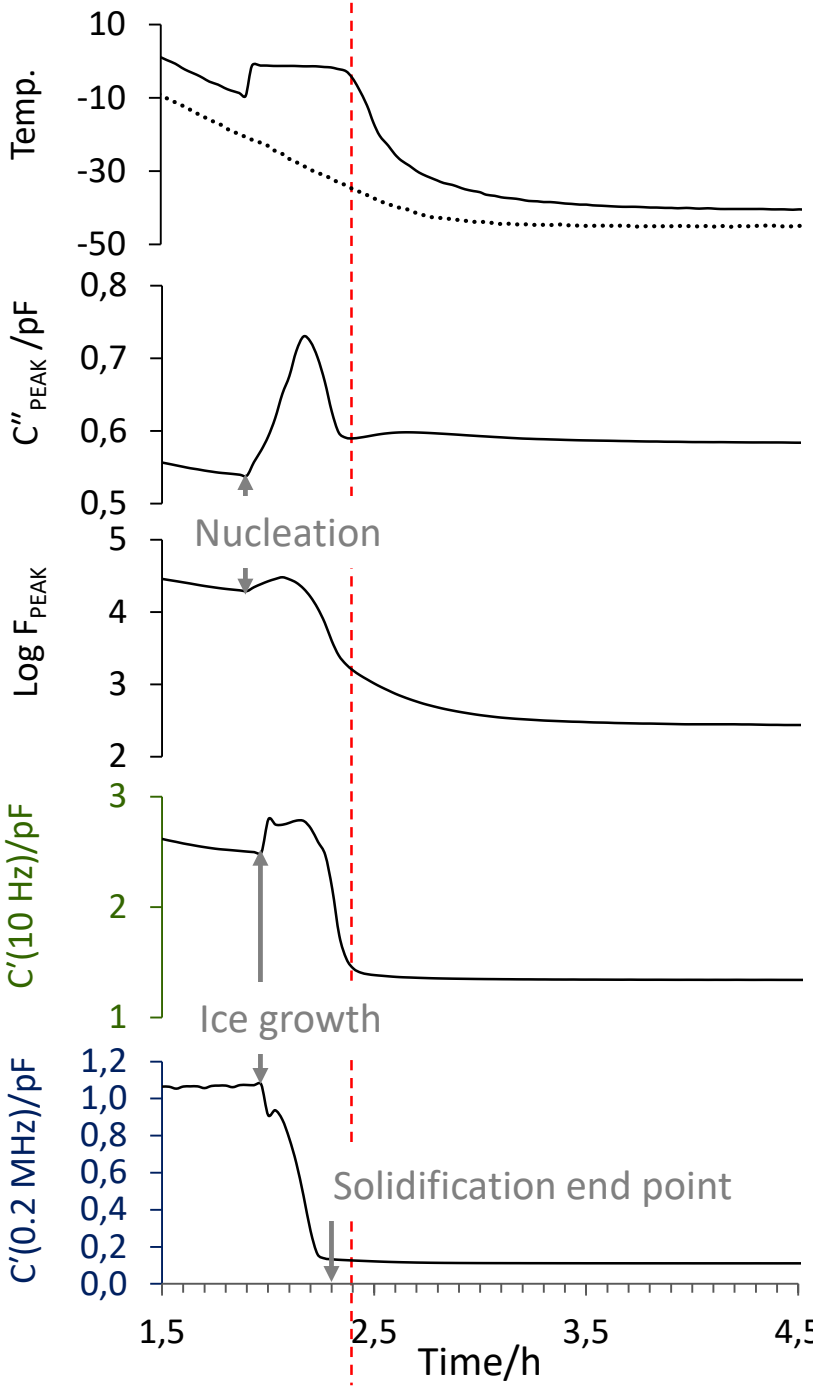

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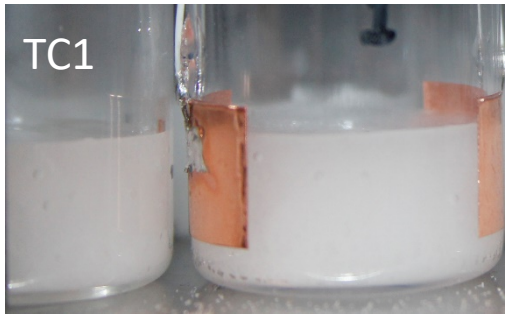

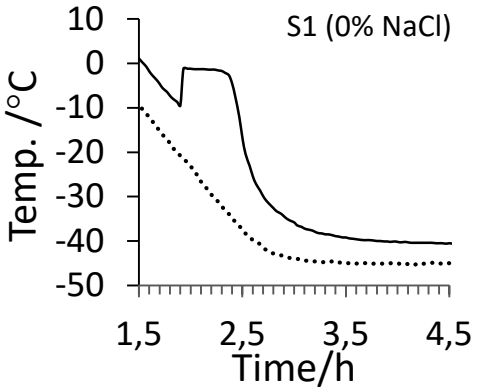

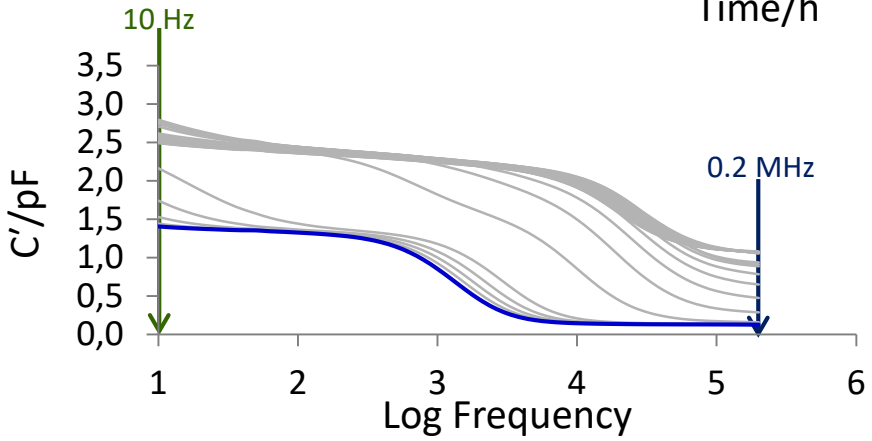

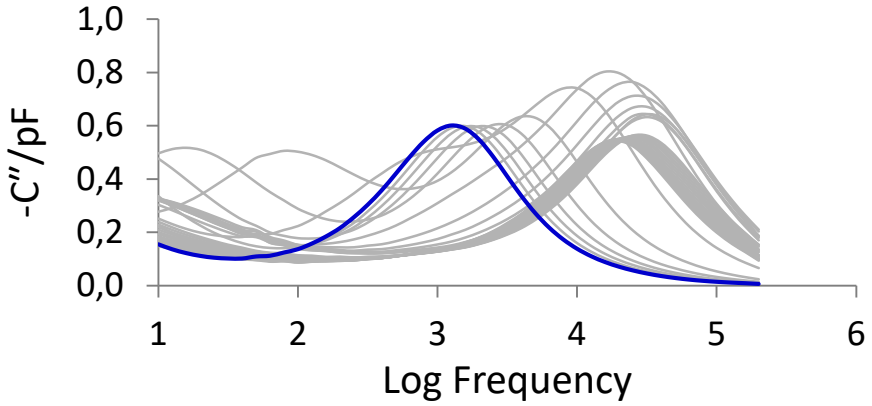

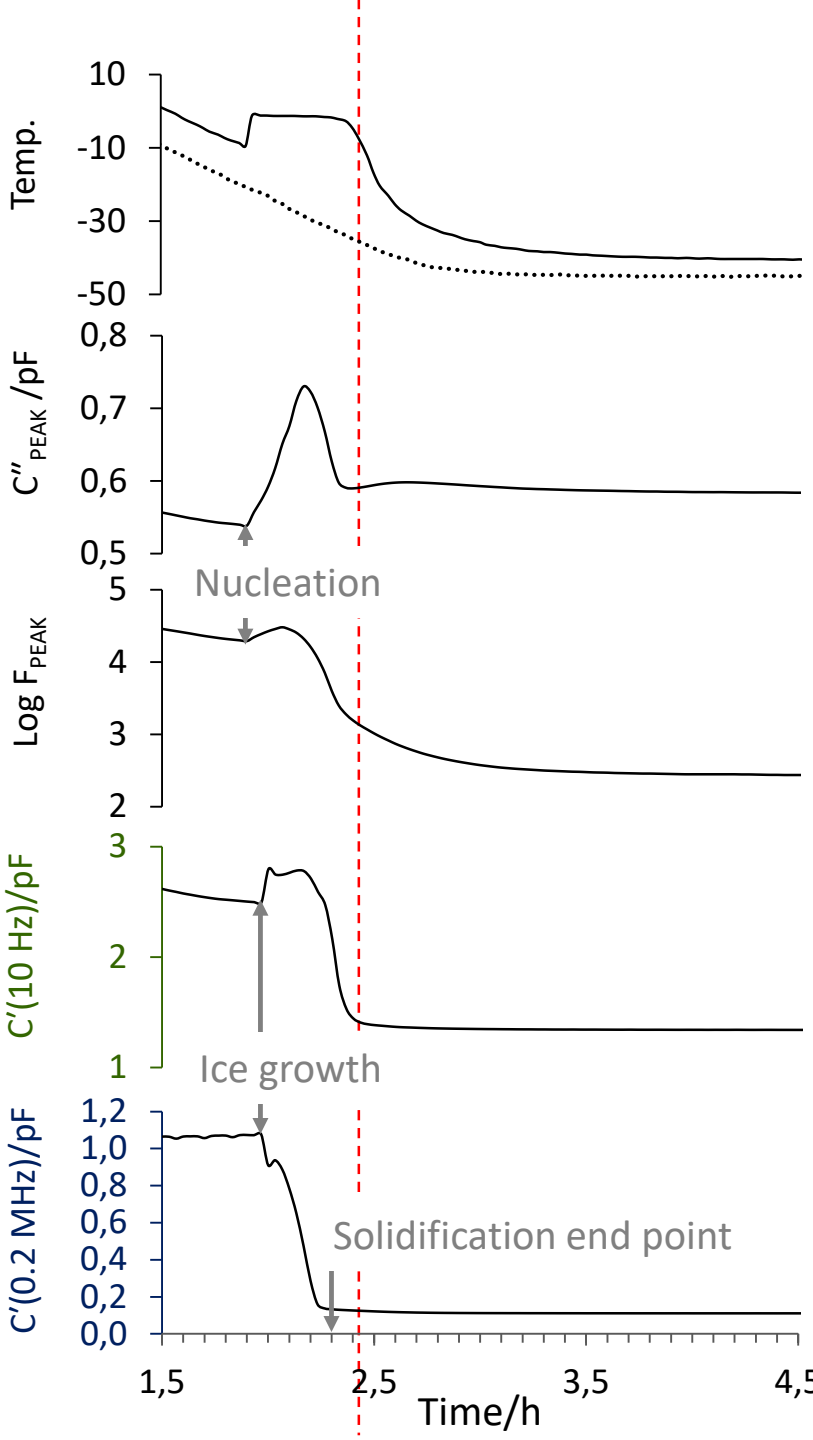

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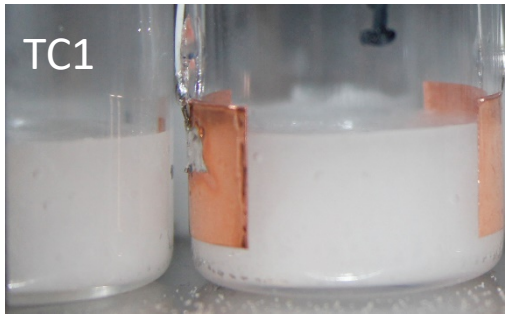

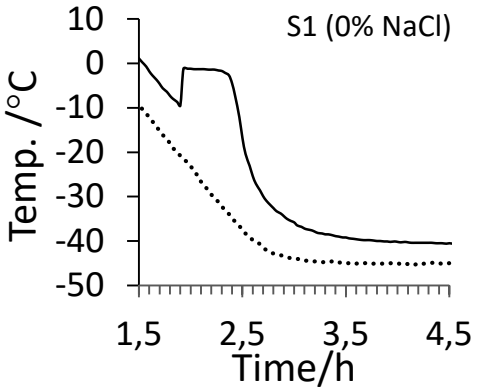

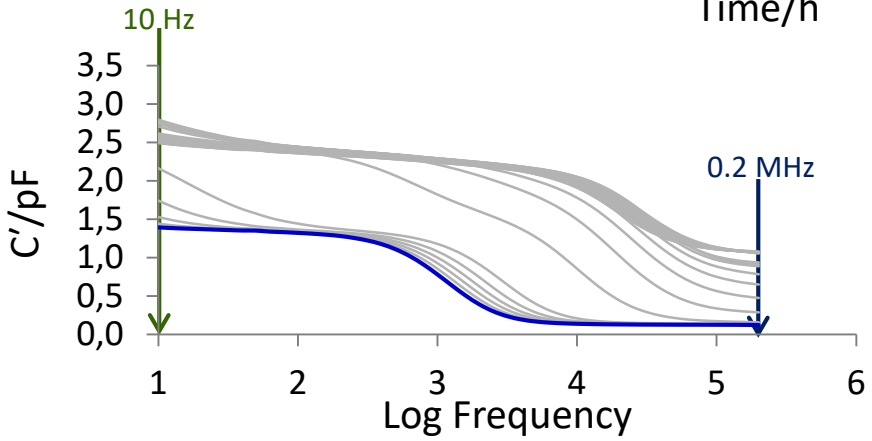

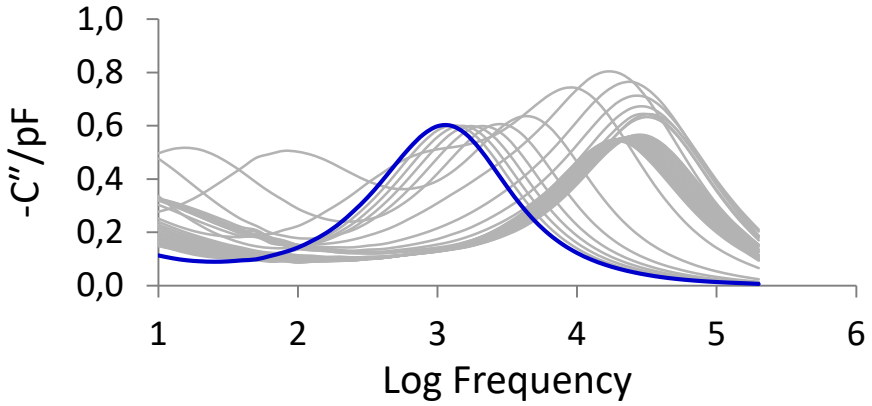

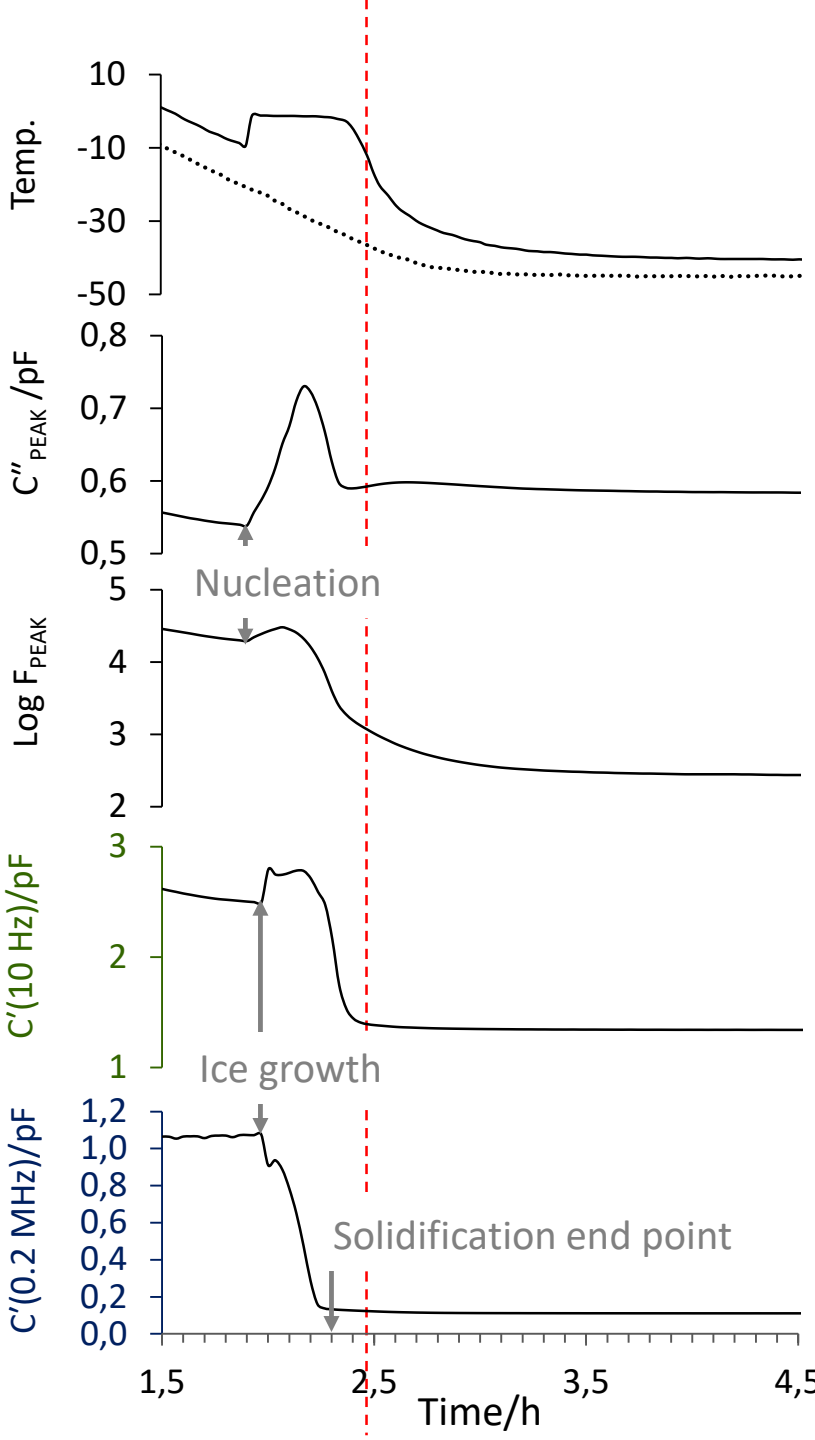

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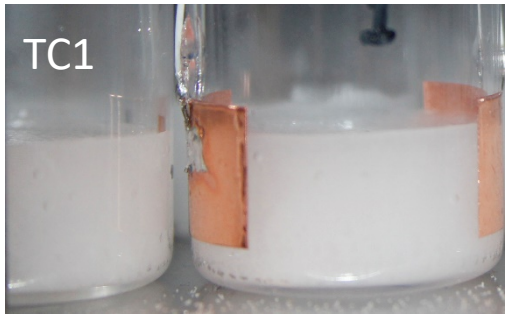

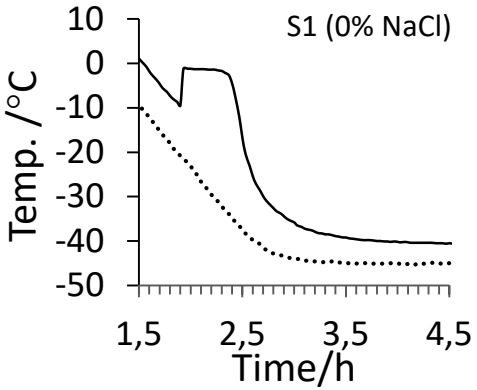

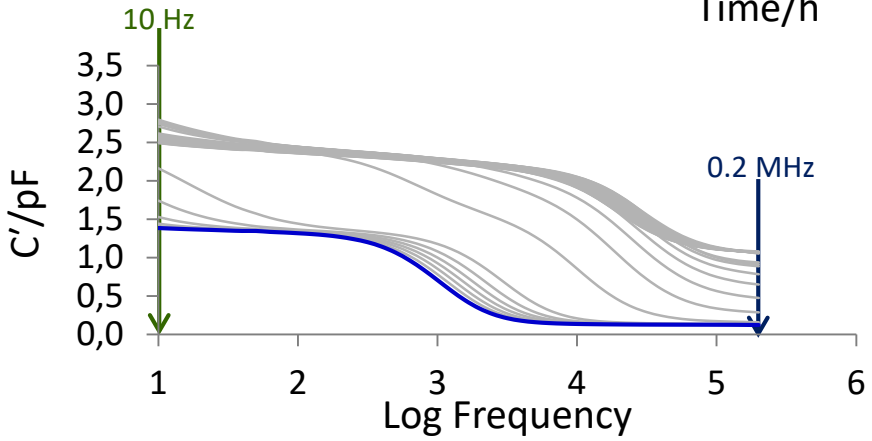

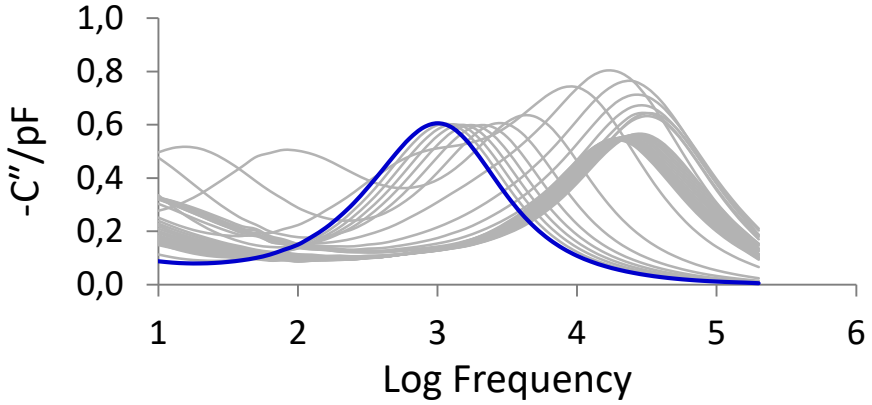

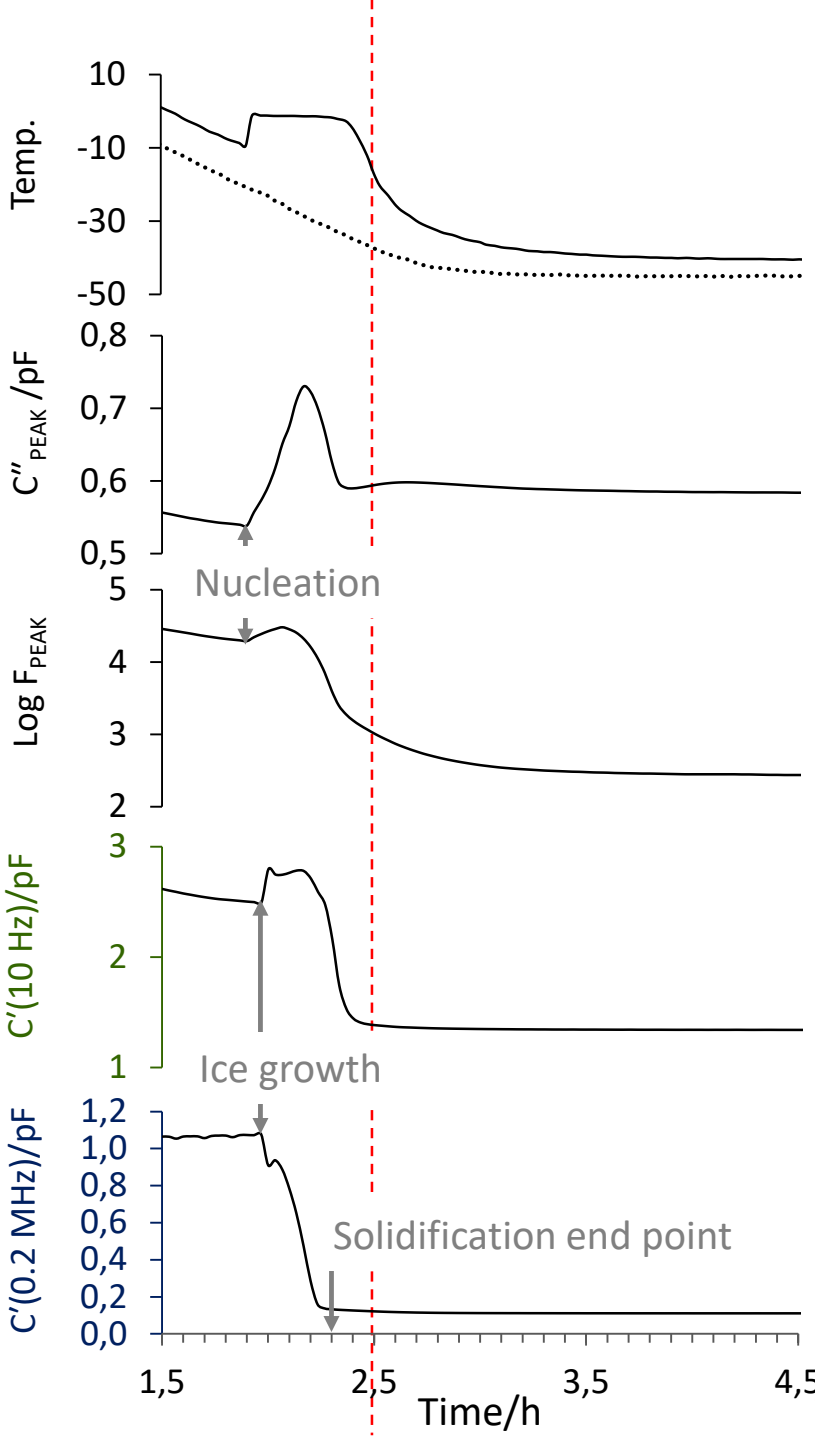

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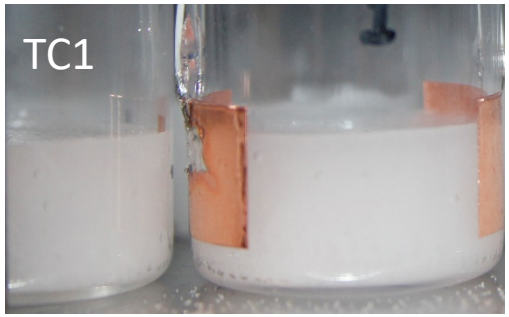

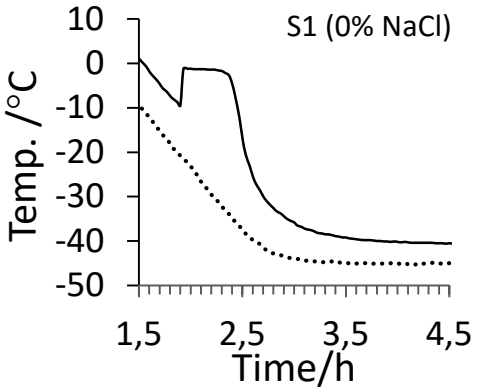

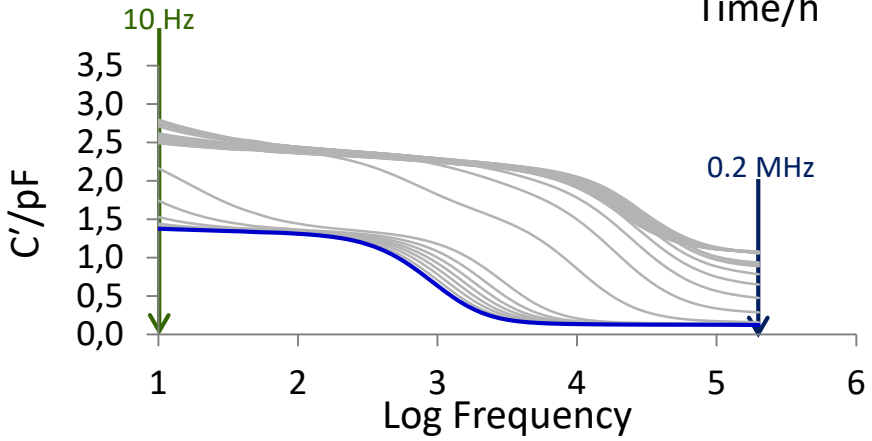

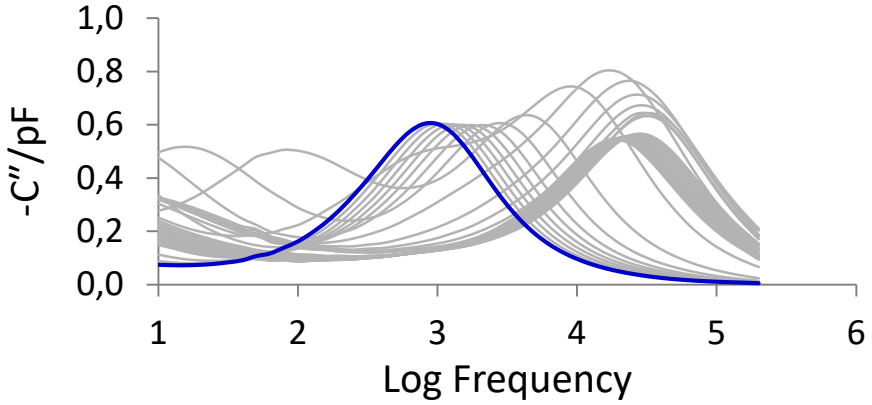

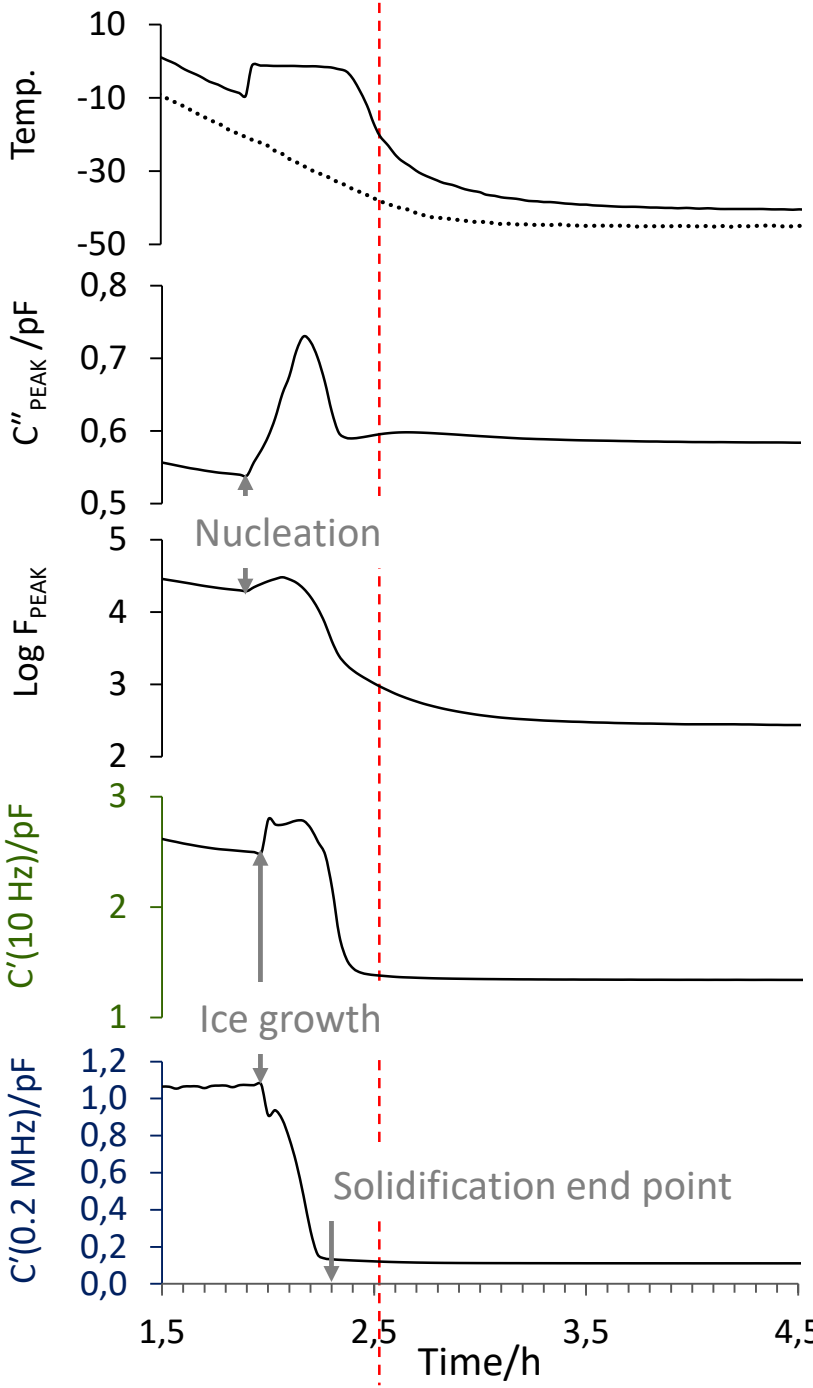

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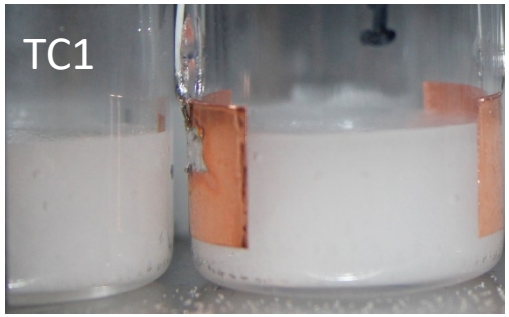

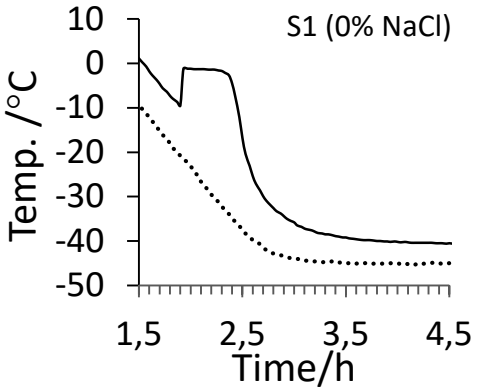

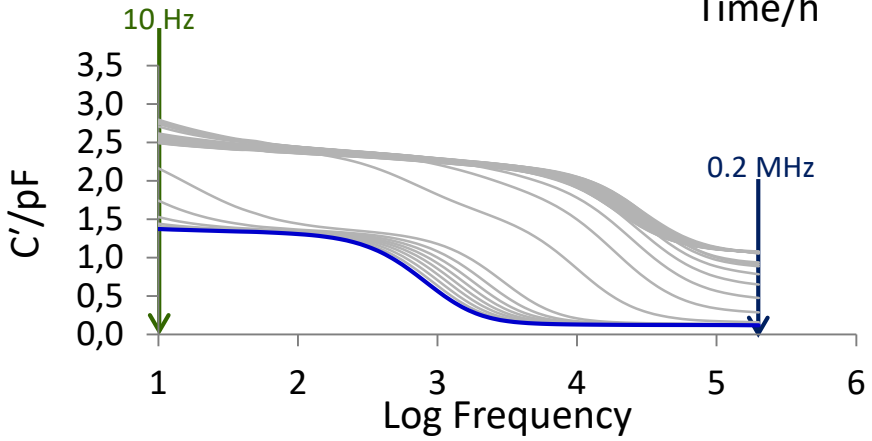

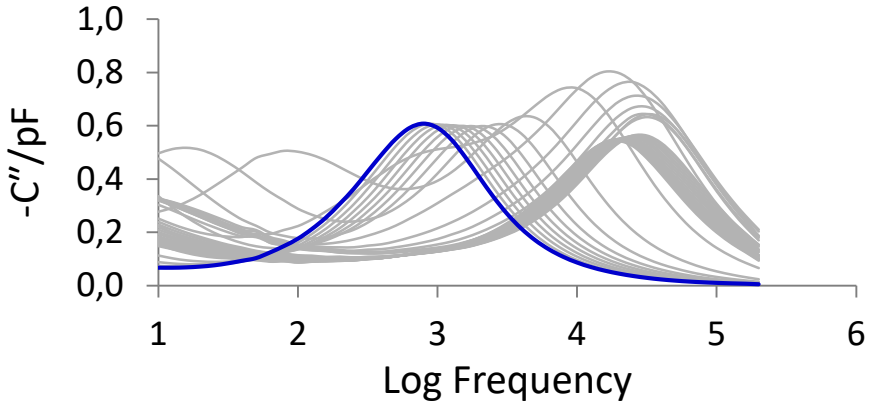

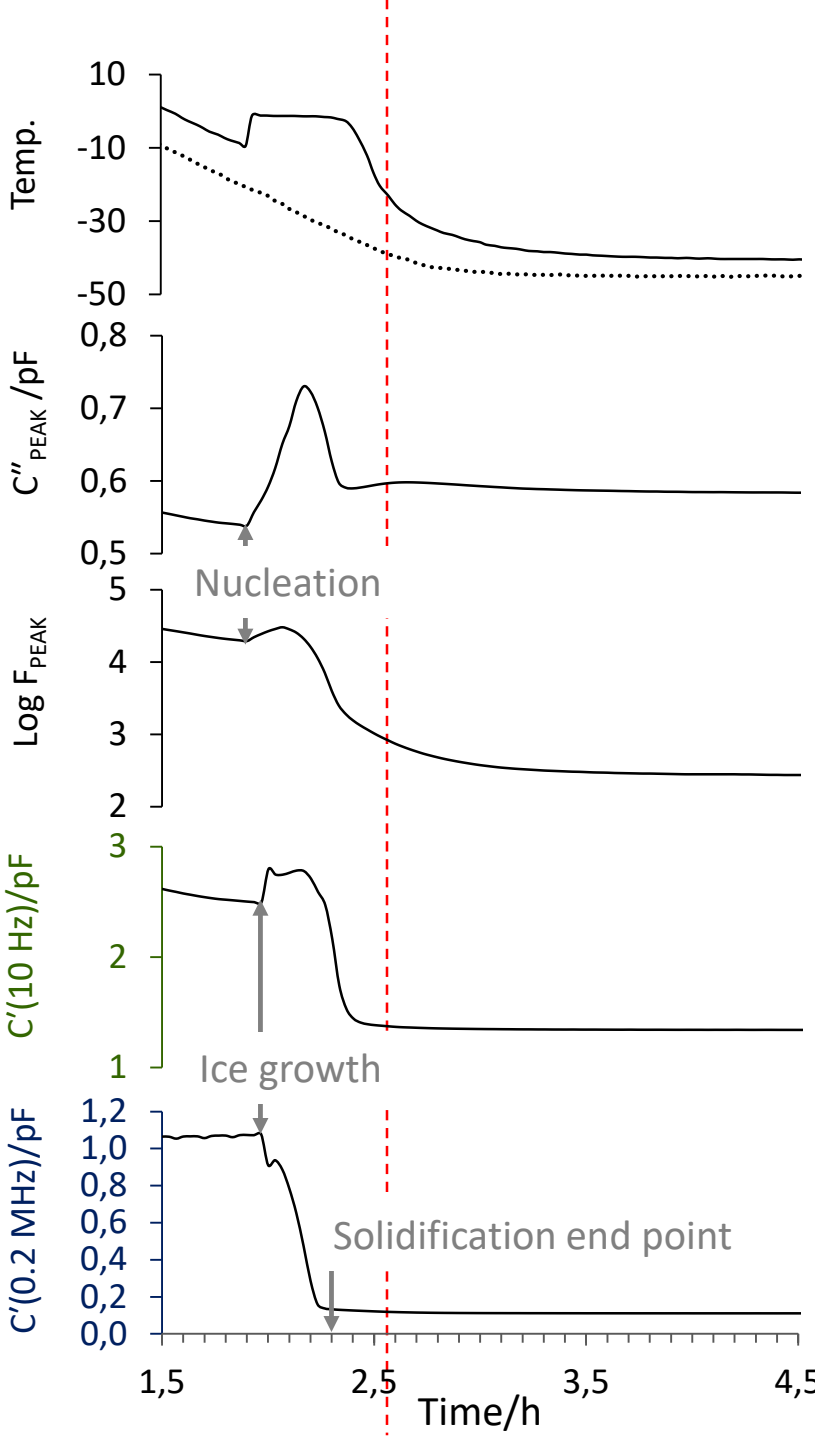

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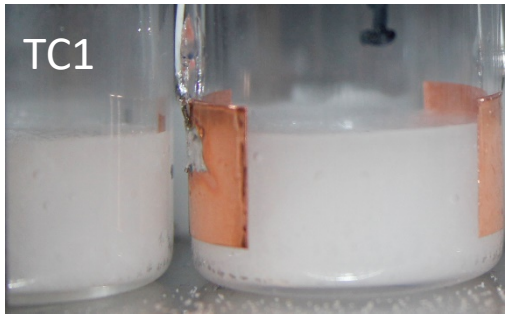

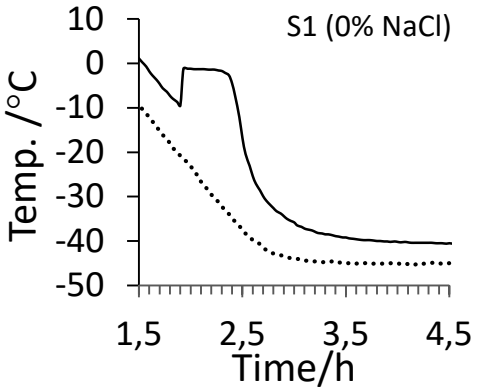

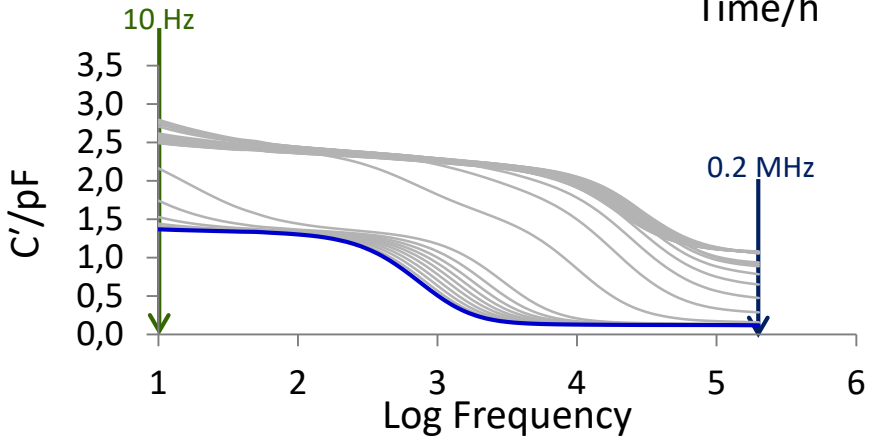

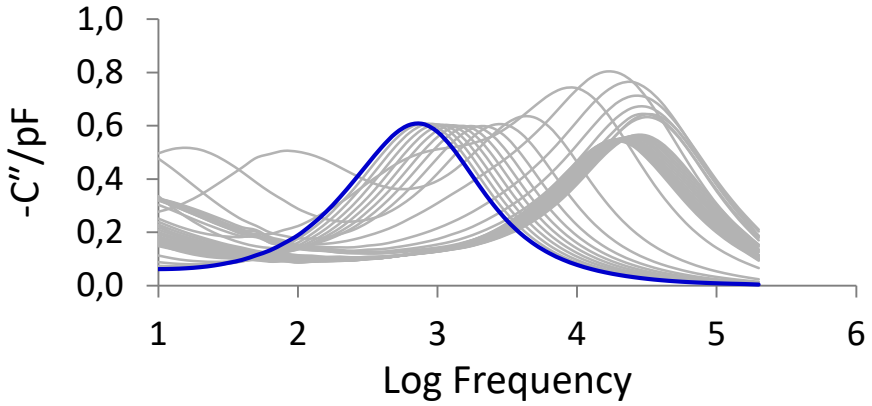

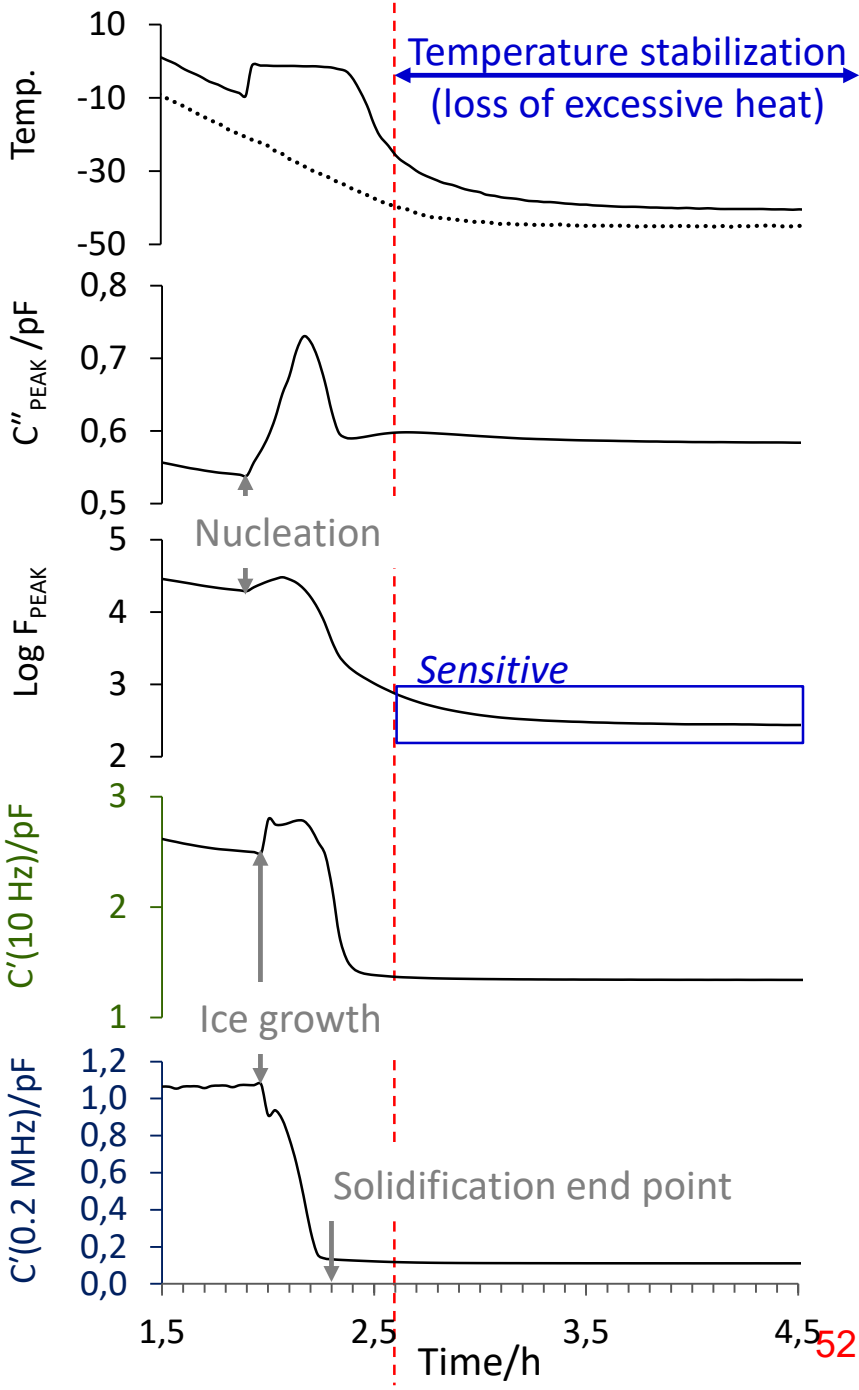

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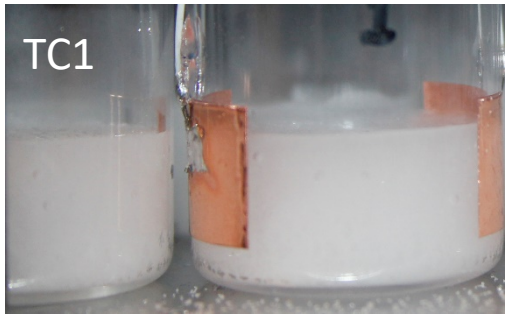

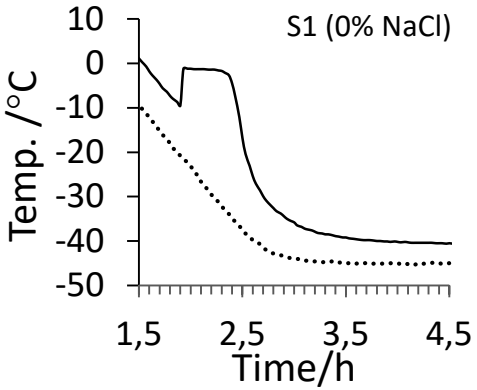

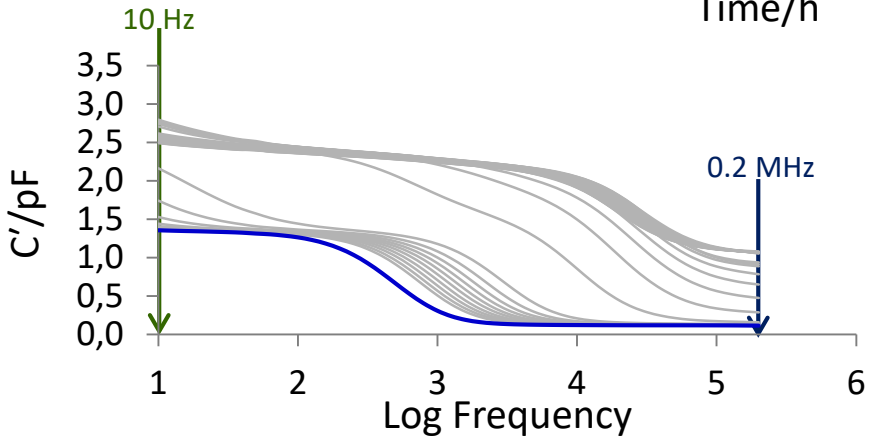

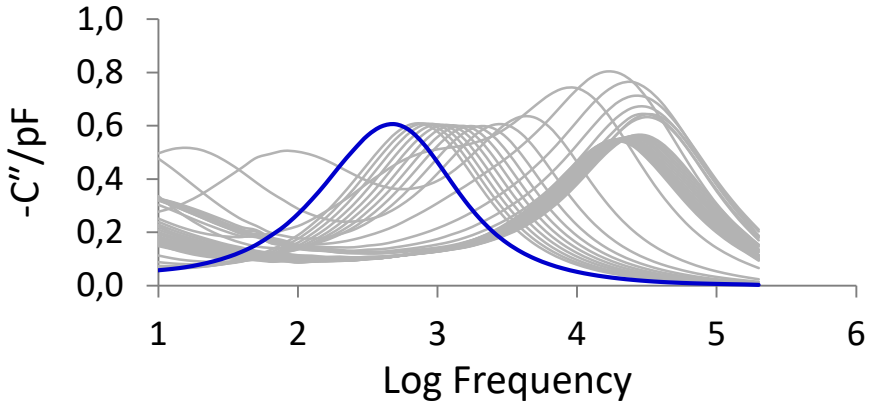

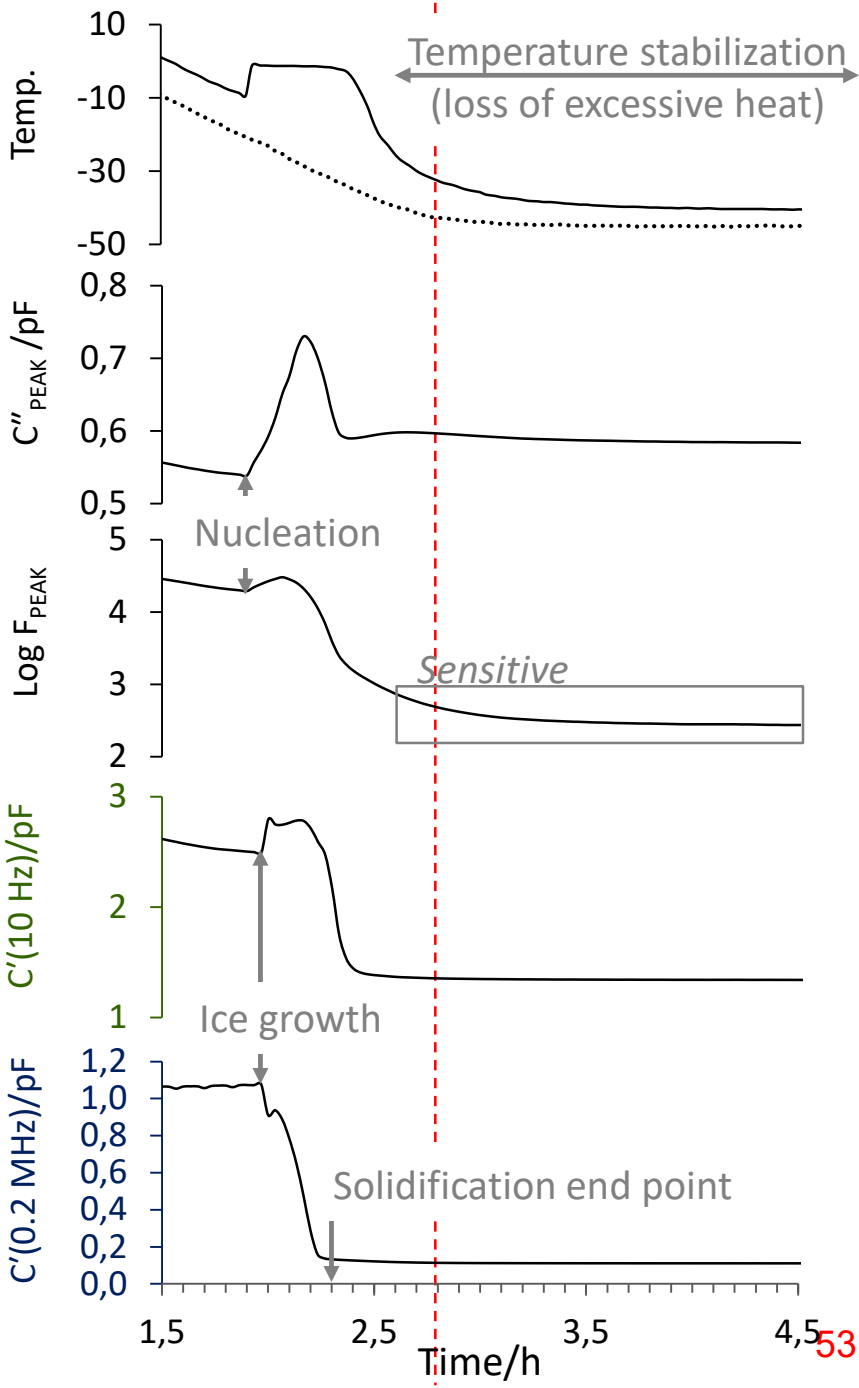

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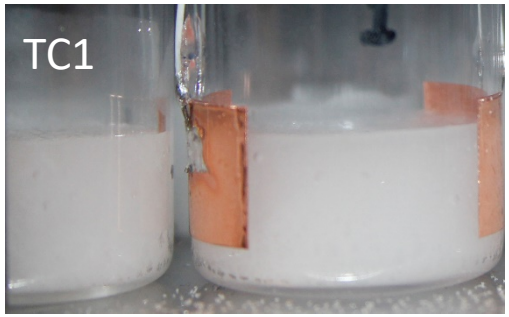
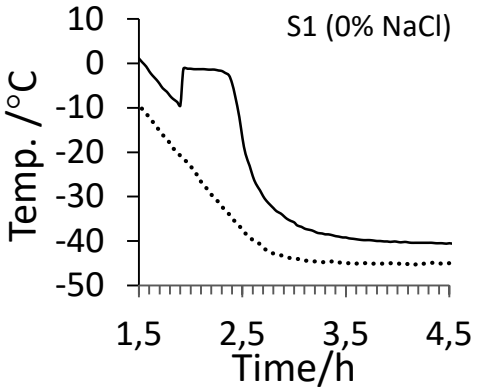
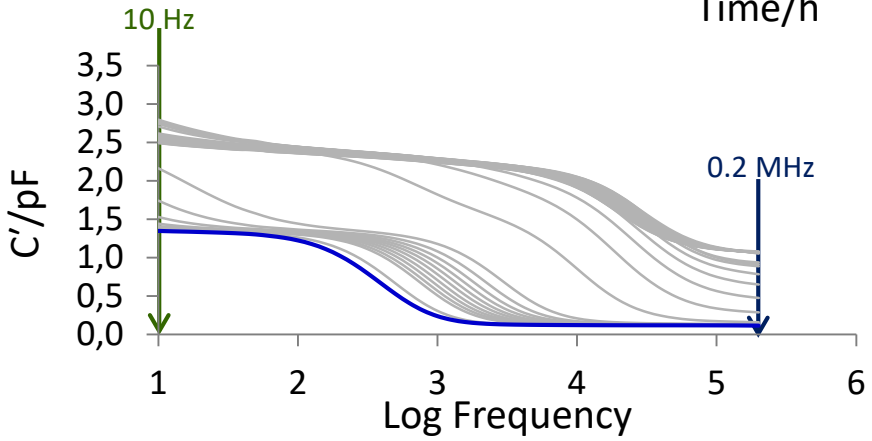
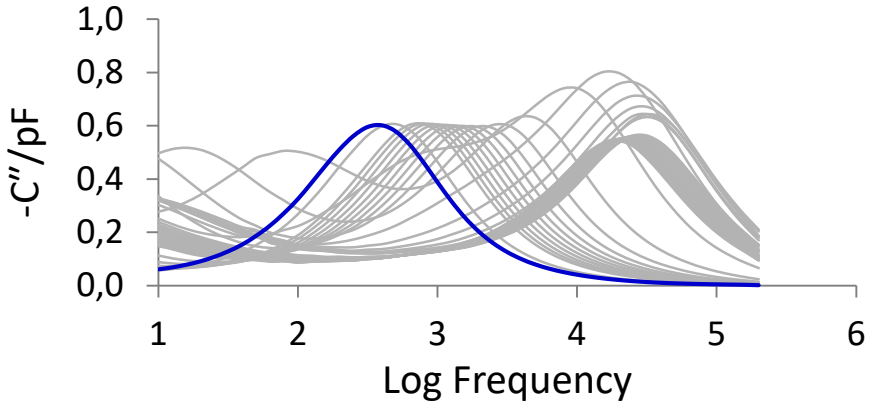
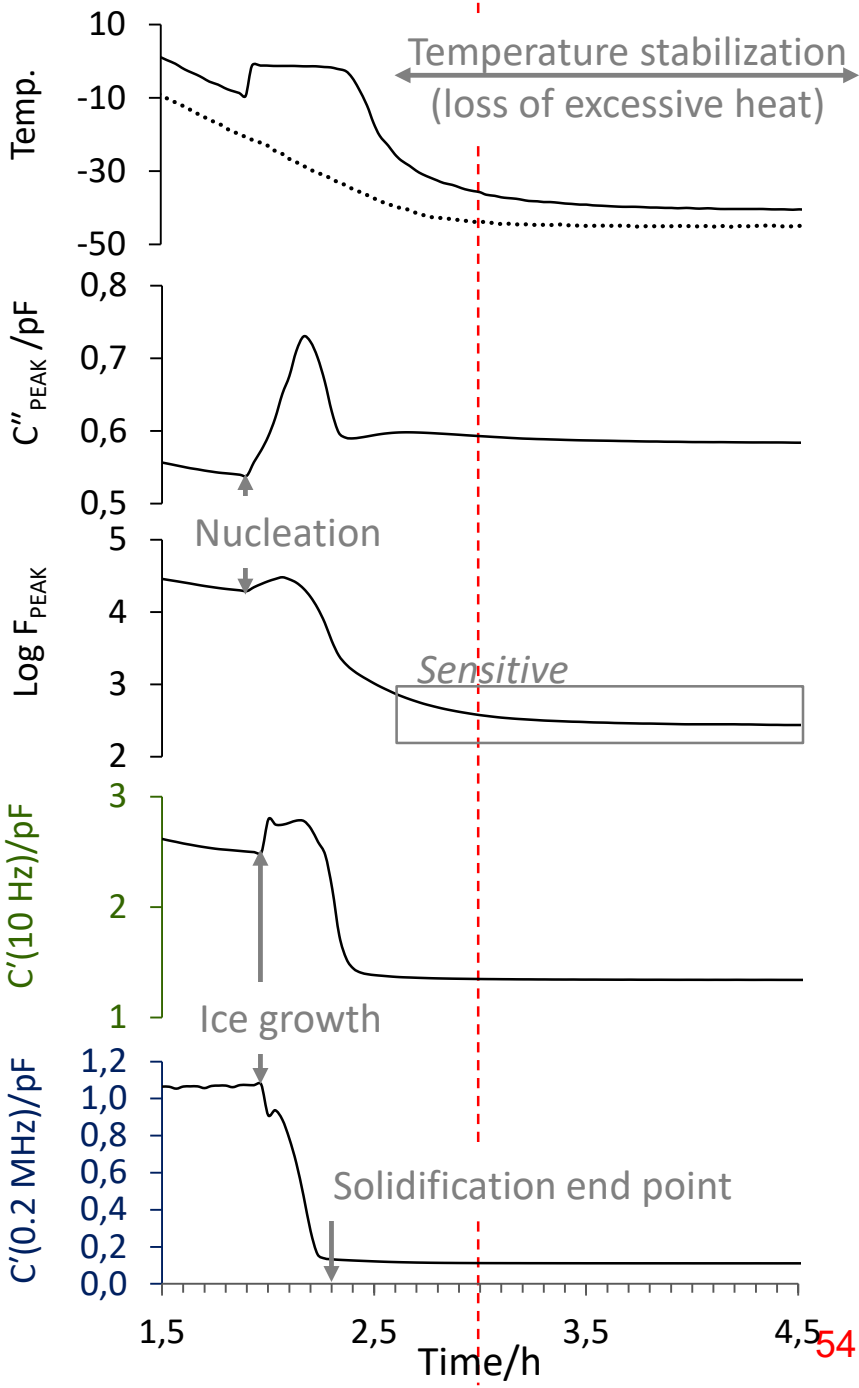


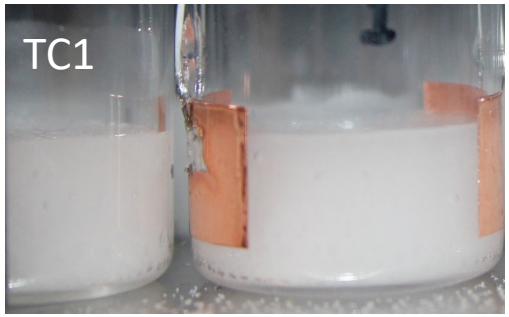


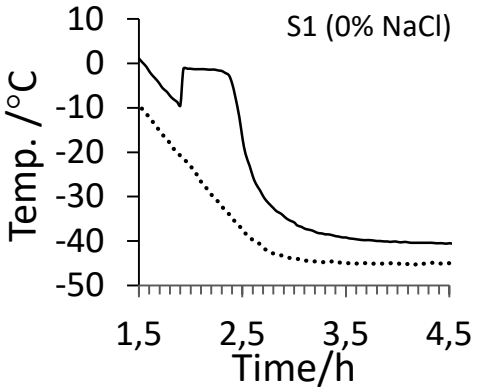


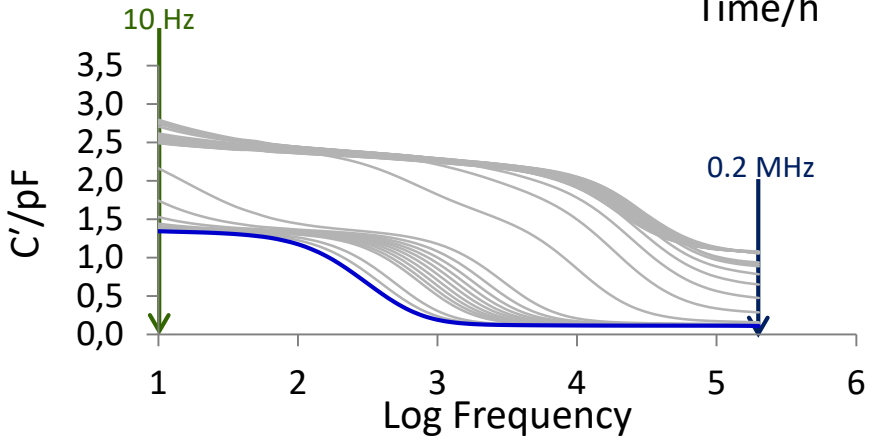


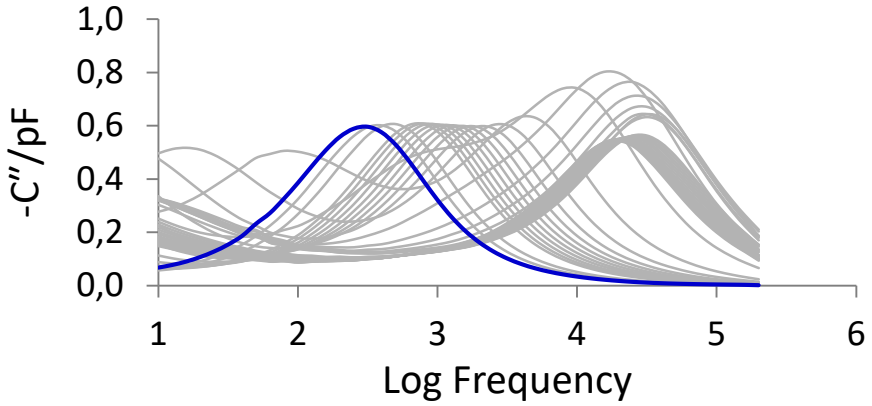


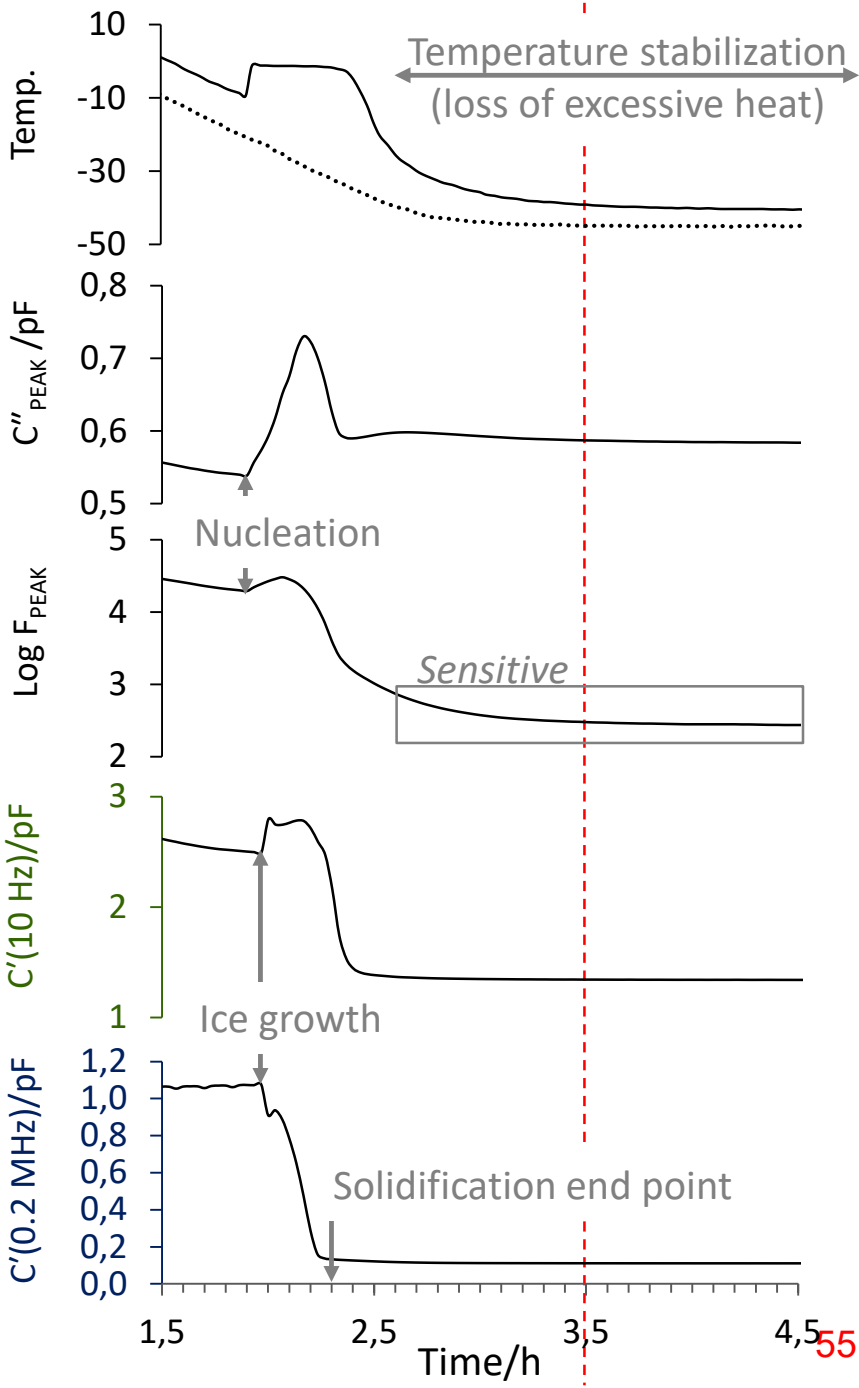
Freezing Step-5%Sucrose



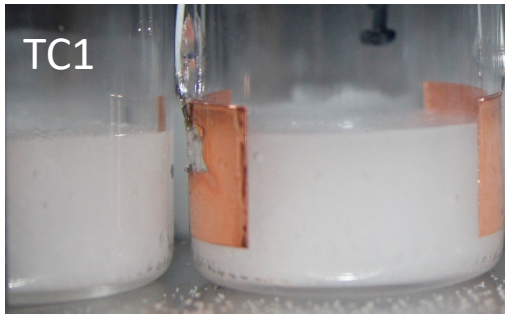


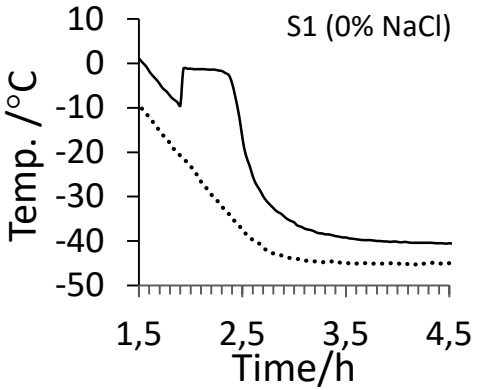


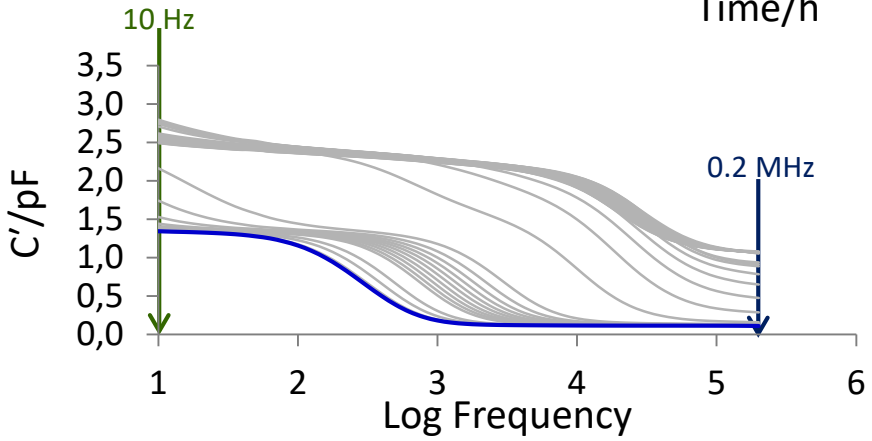


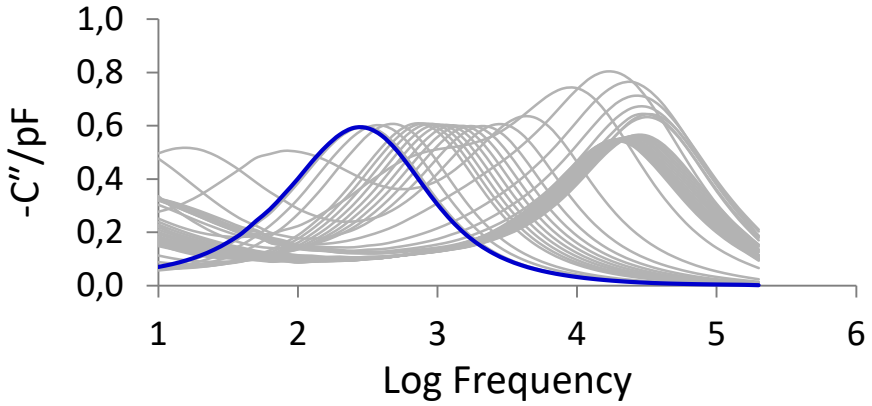


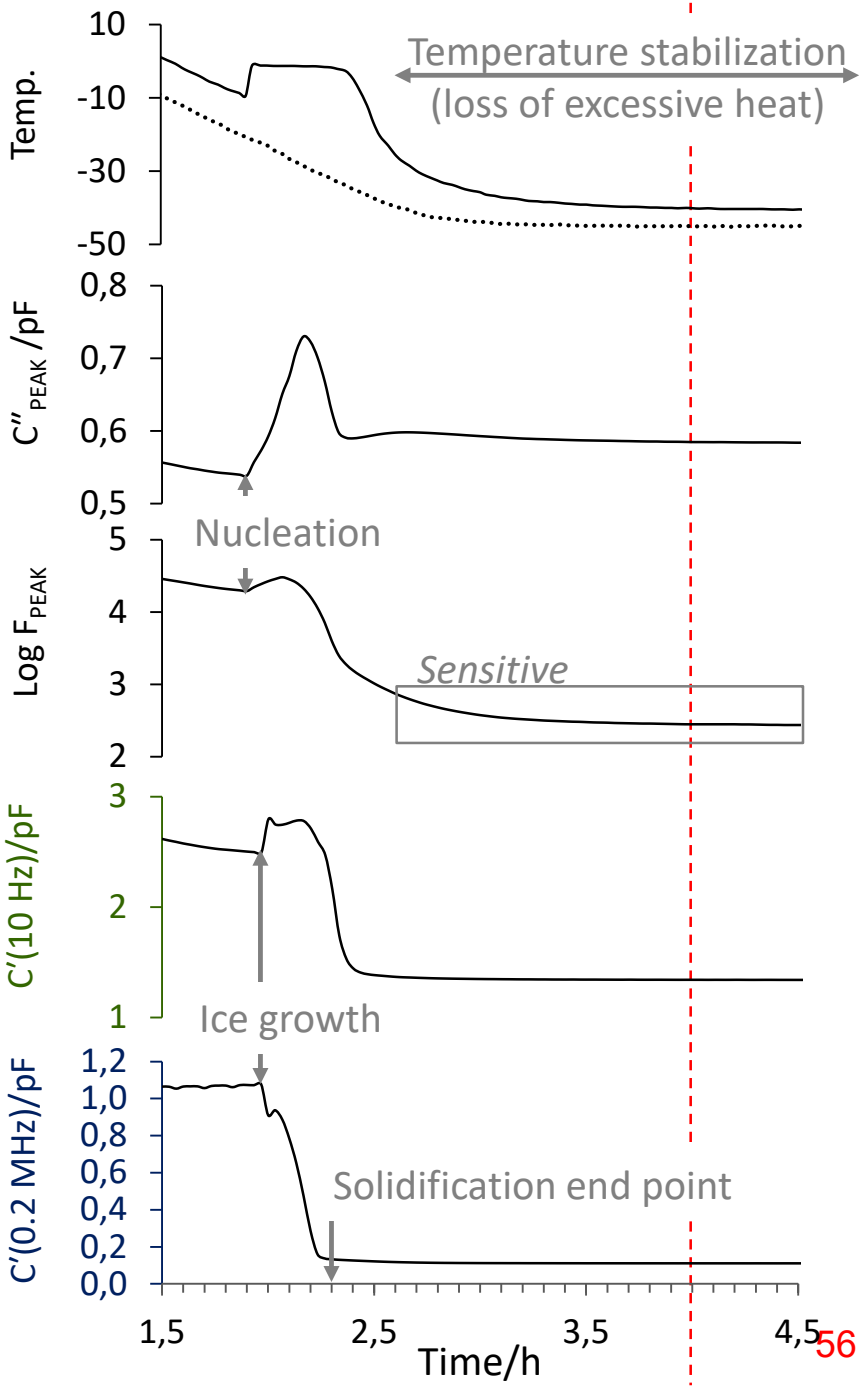
Freezing Step-5%Sucrose



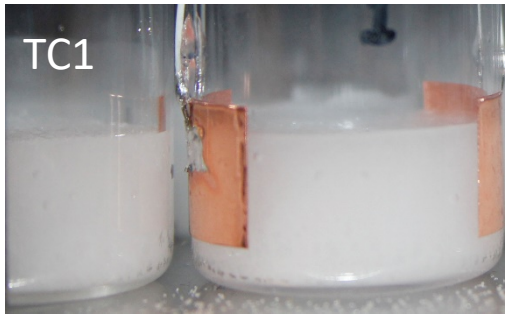


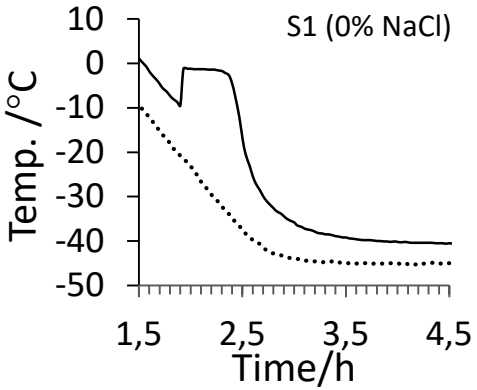


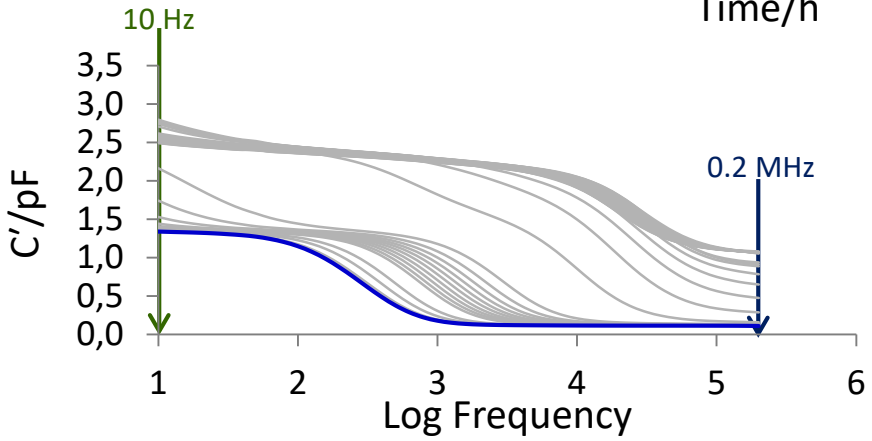


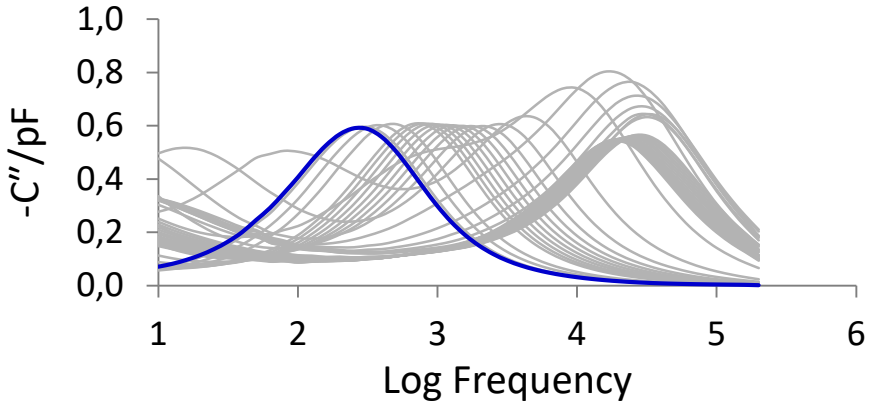


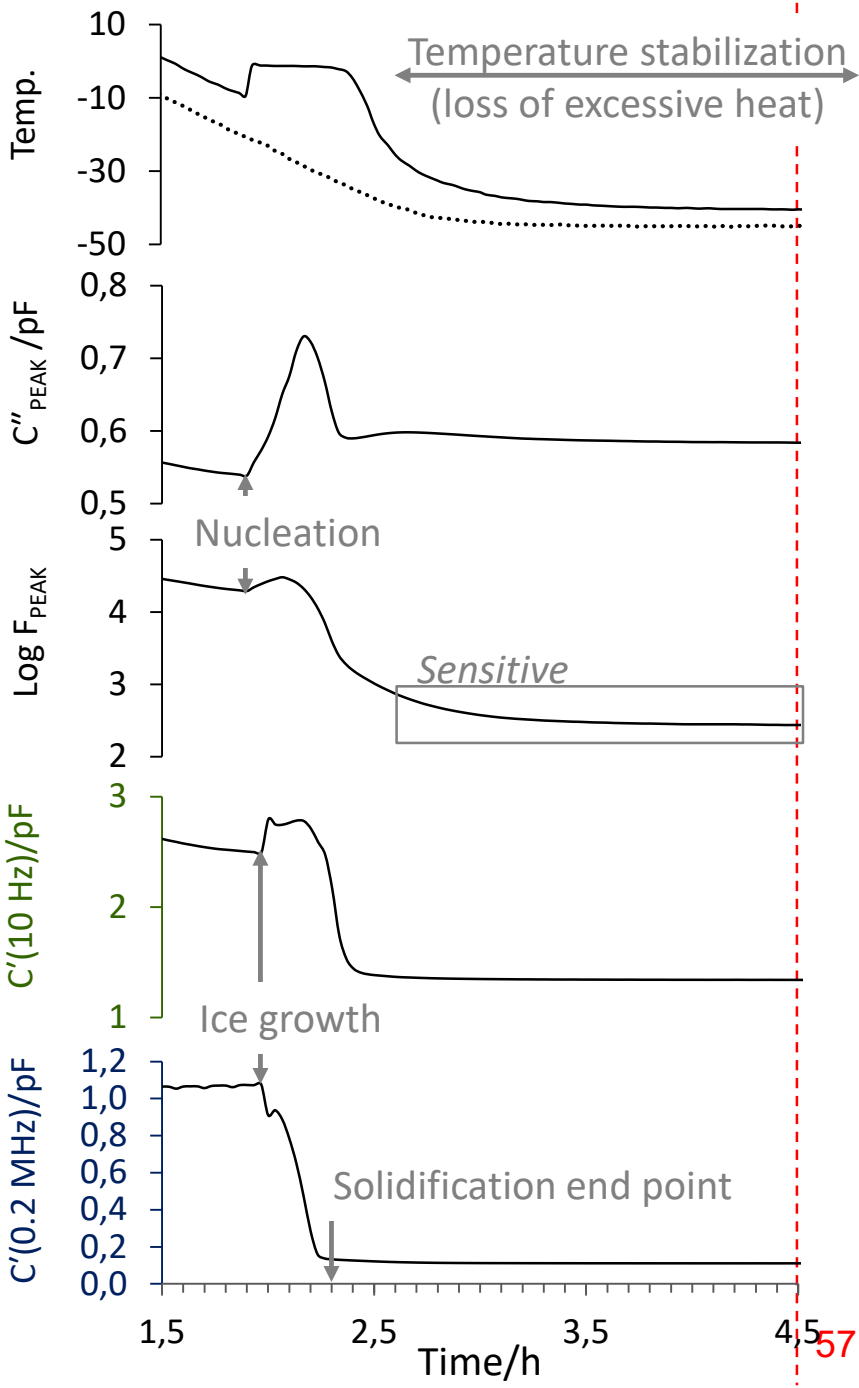
Freezing Step-5%Sucrose





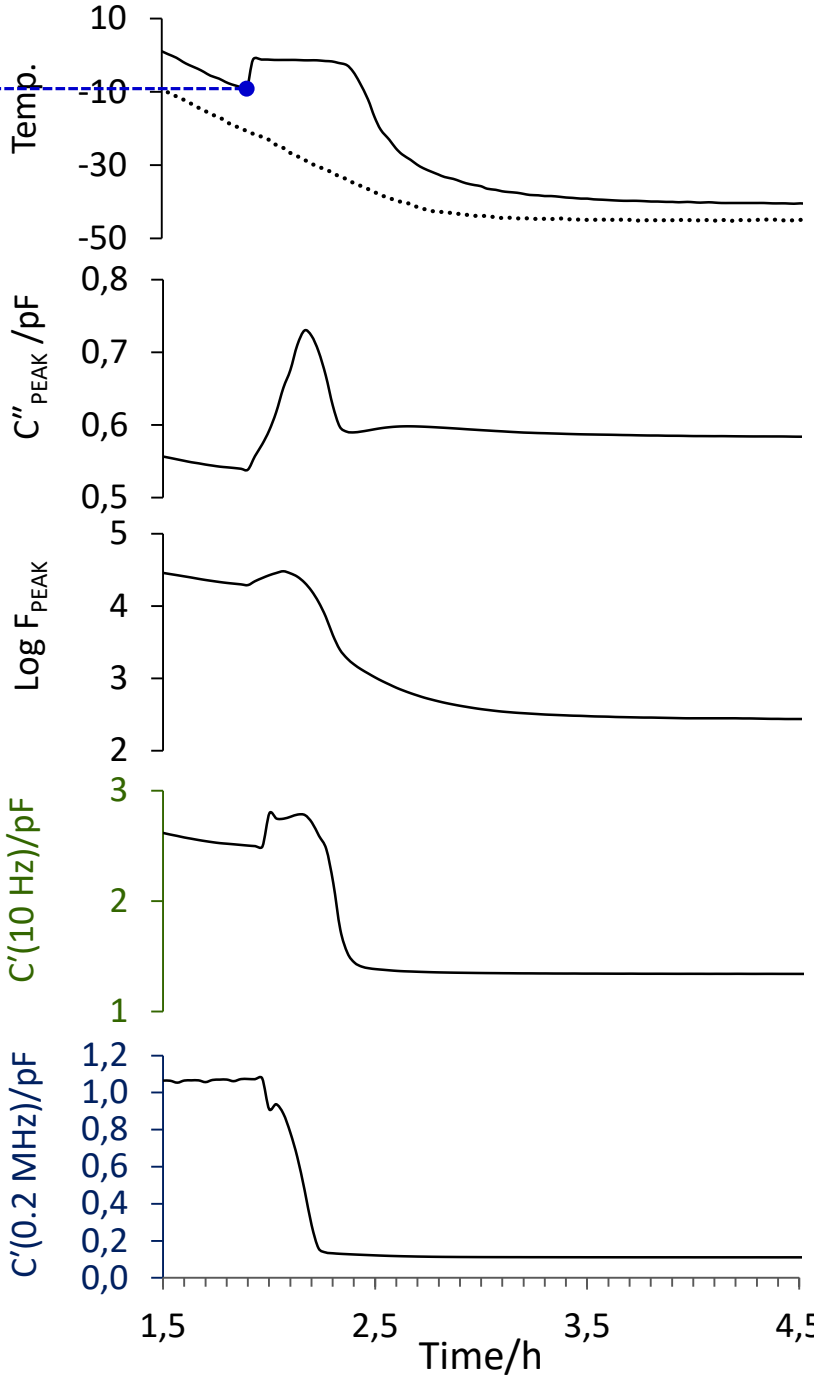






Freezing Step-5%Sucrose

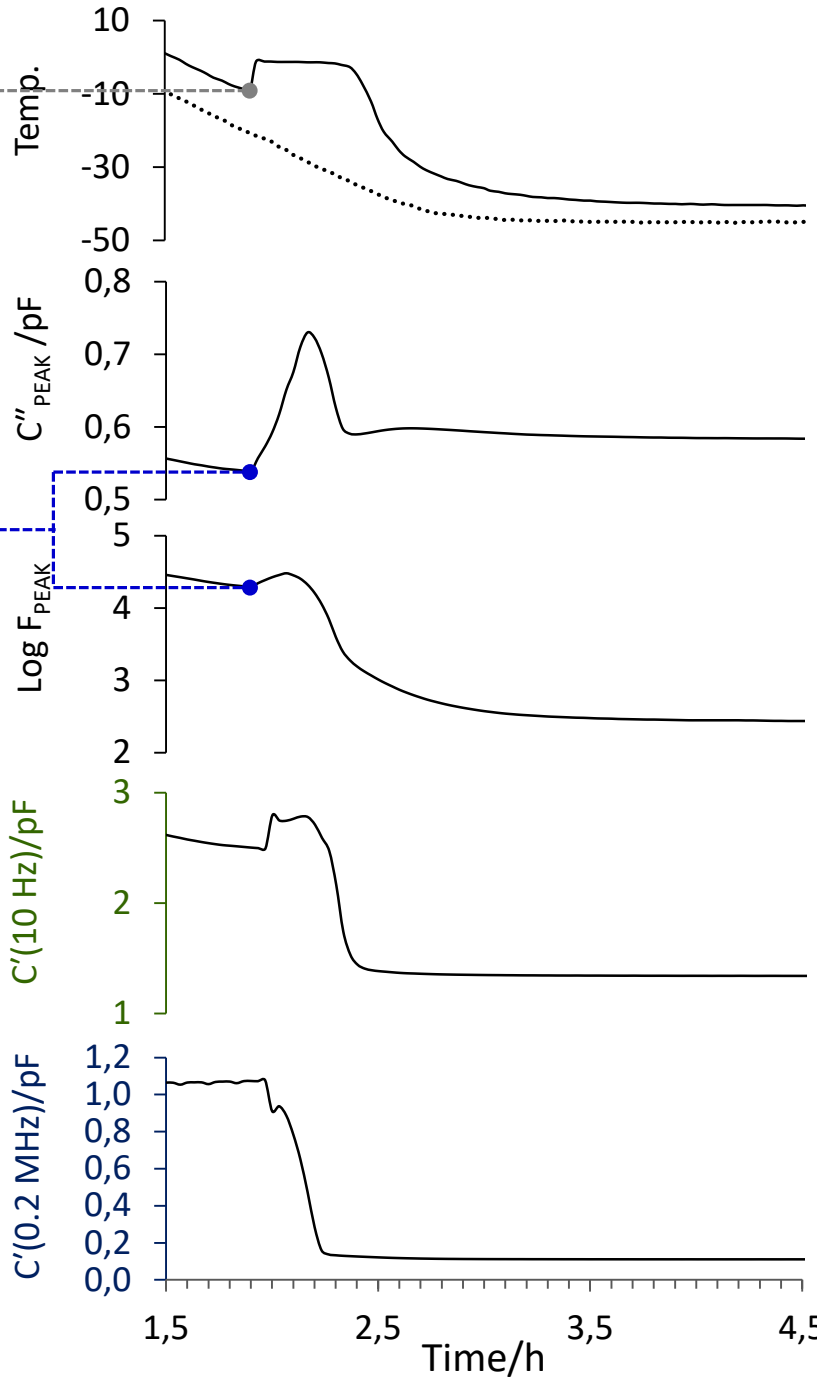
Nucleation point from TC



Freezing Step-5%Sucrose

Nucleation point from TC

Sensitive to nucleation

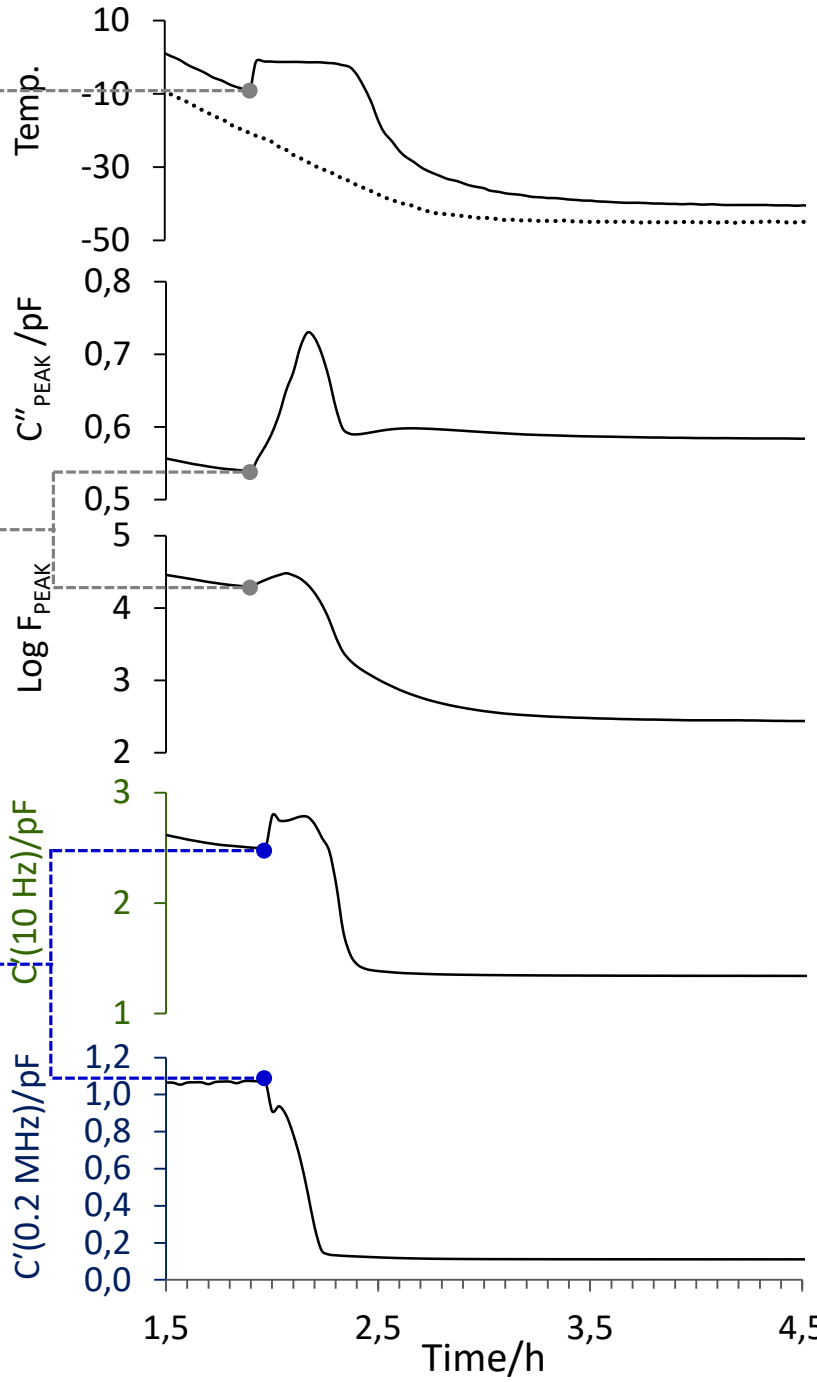


Freezing Step-5%Sucrose

Nucleation point from TC

Sensitive to nucleation

Sensitive to ice growth



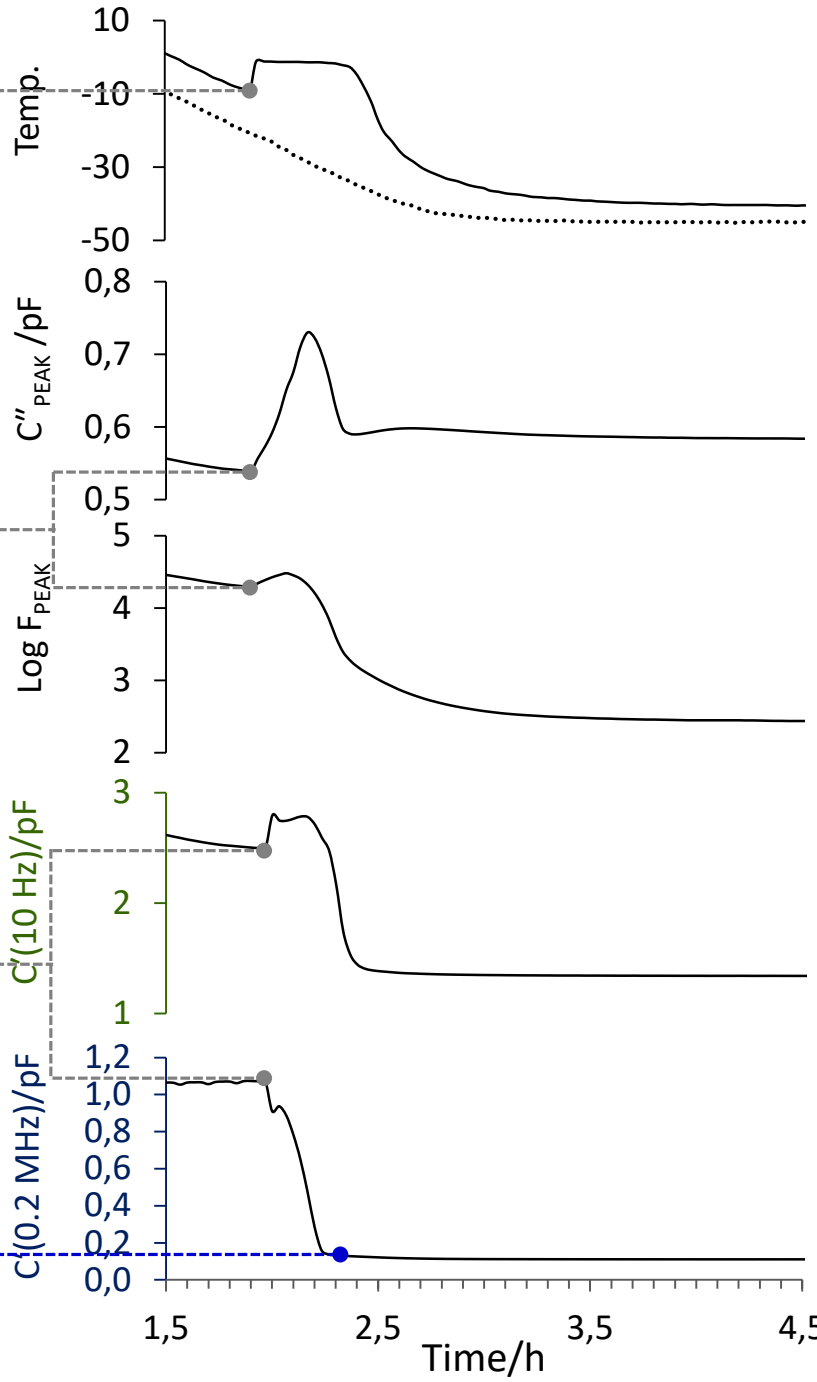
Freezing Step-5%Sucrose

Nucleation point from TC

Sensitive to nucleation

Sensitive to ice growth

Solidification



Freezing Step-5%Sucrose

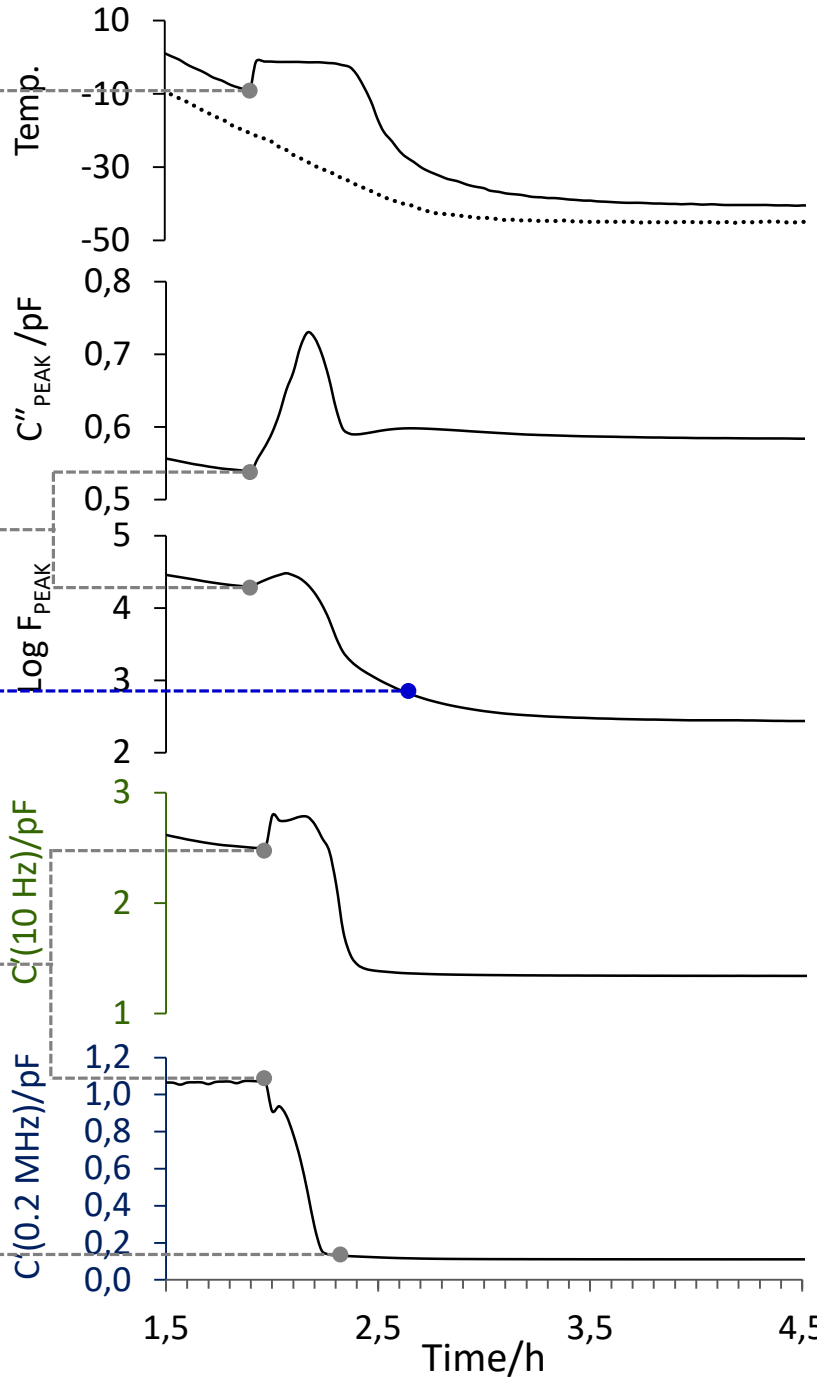
Nucleation point from TC

Sensitive to nucleation

Good indication for temperature

Sensitive to ice growth

Solidification



Freezing Step-5%Sucrose

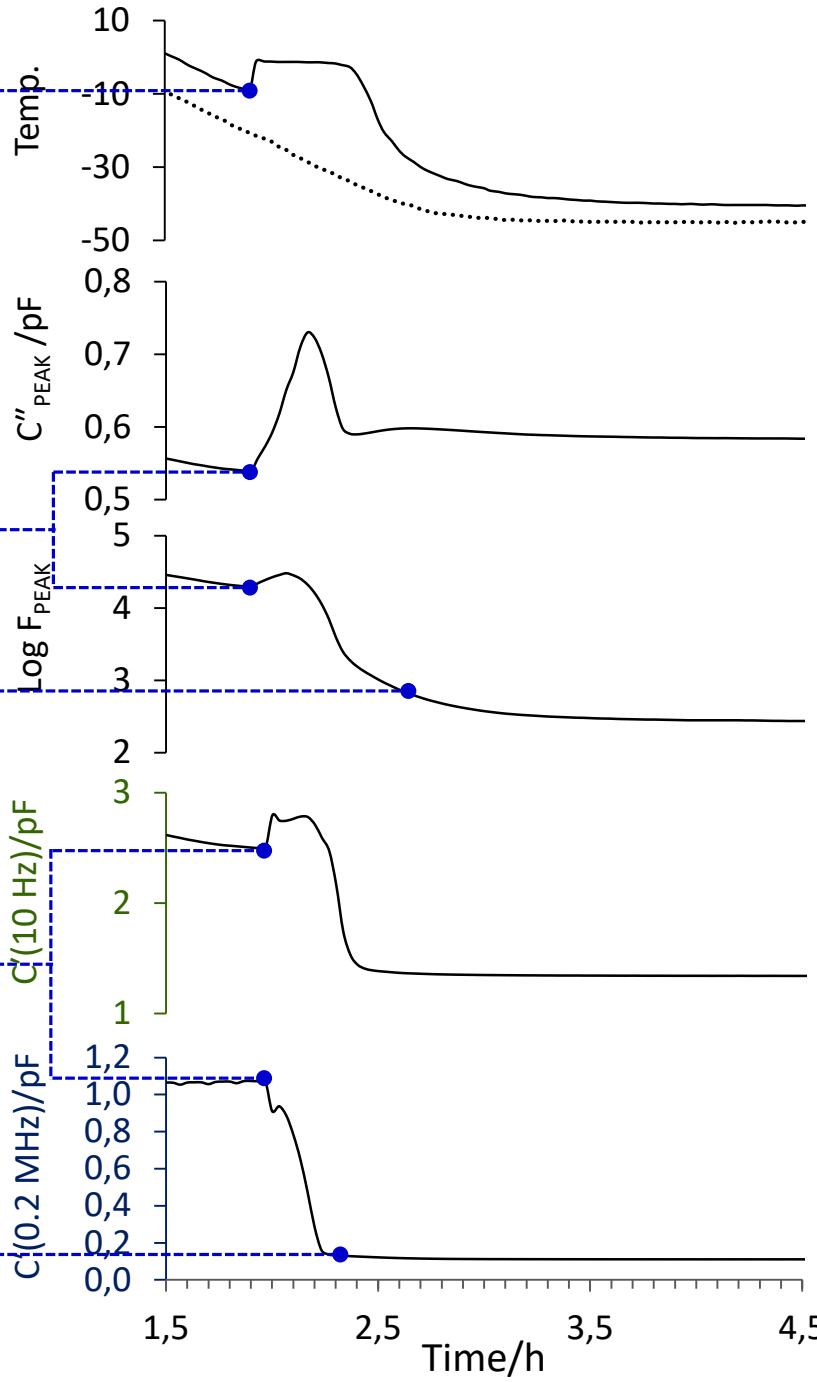
Nucleation point from TC

Sensitive to nucleation

Good indication for temperature

Sensitive to ice growth

Solidification

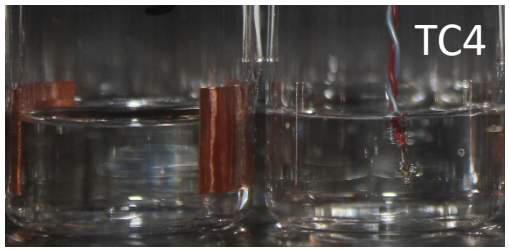


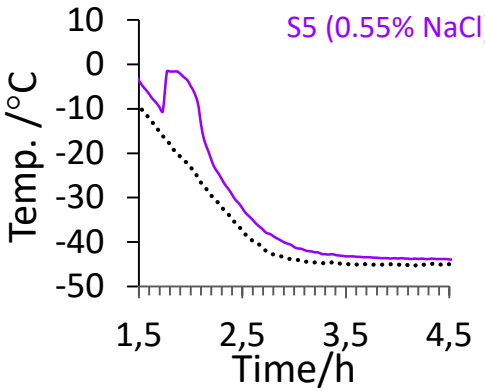
Jump to Ice Nucleation slide

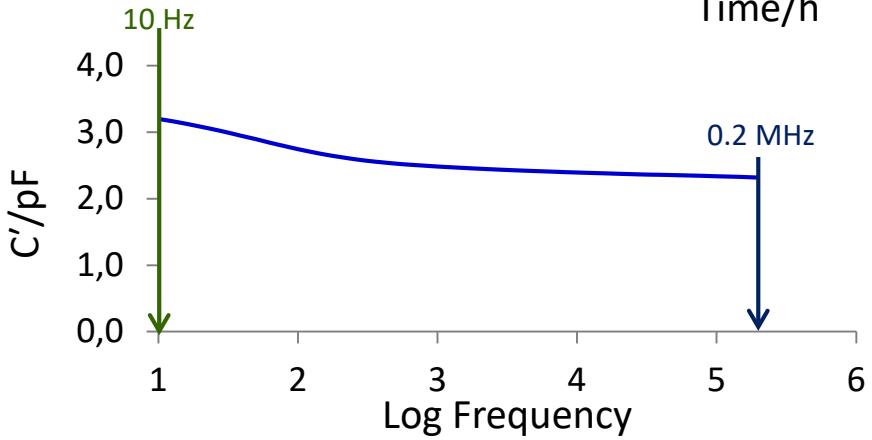
Through Vial Impedance Spectroscopy (TVIS)

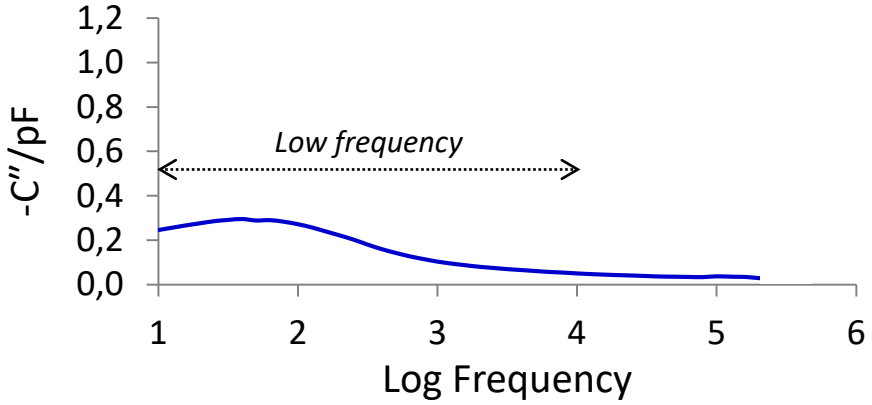
Another example : What if we add salt?

Freezing Step - 5%Sucrose+0.55%NaCl

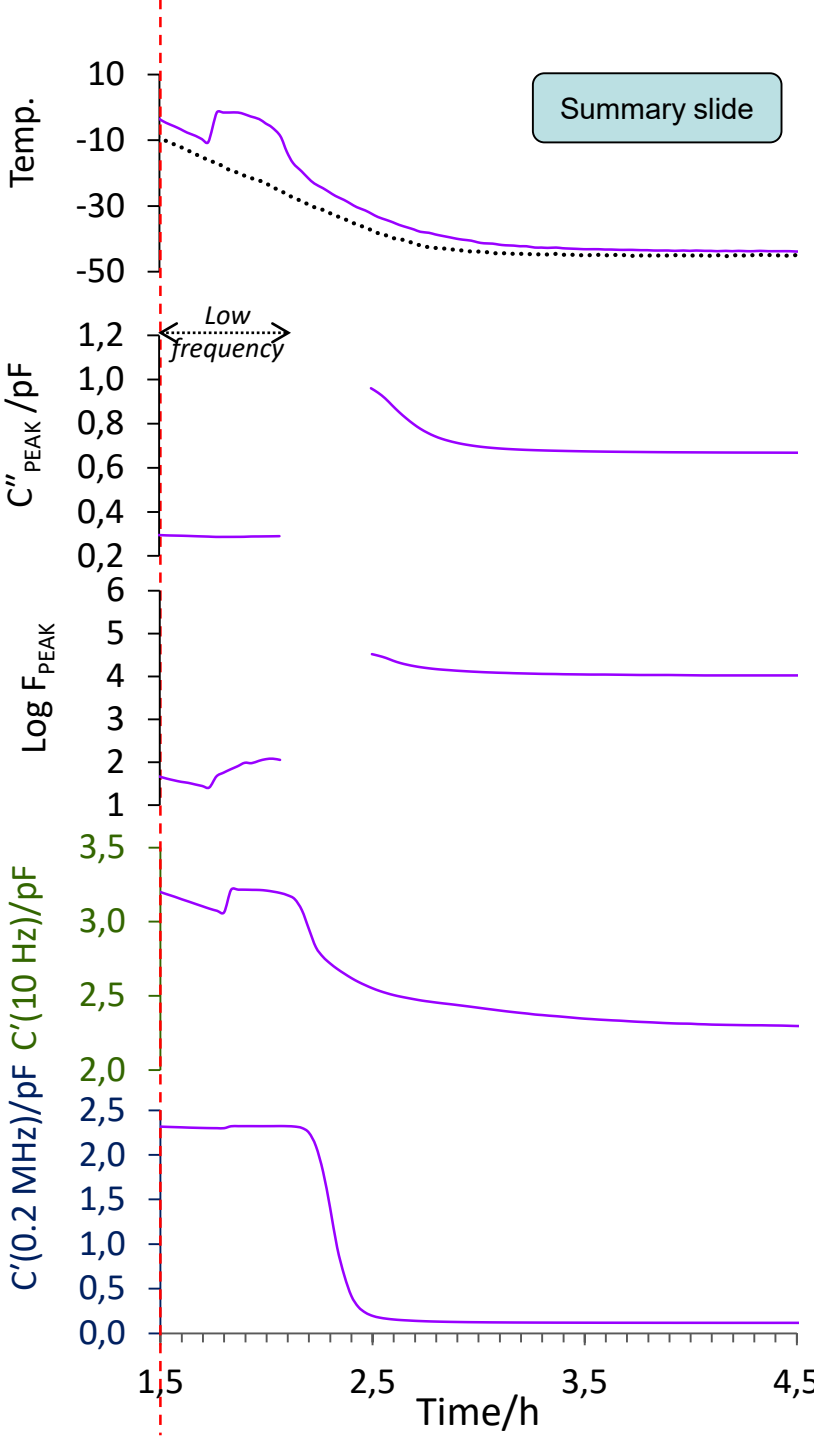




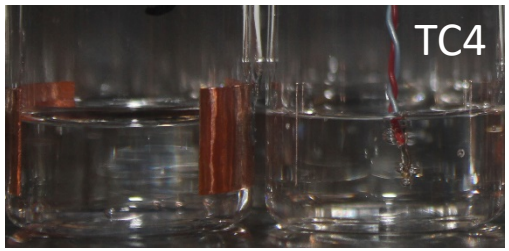


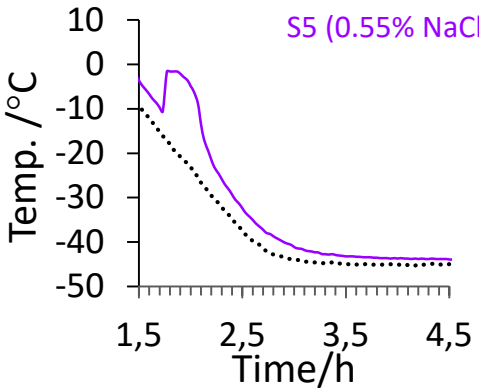


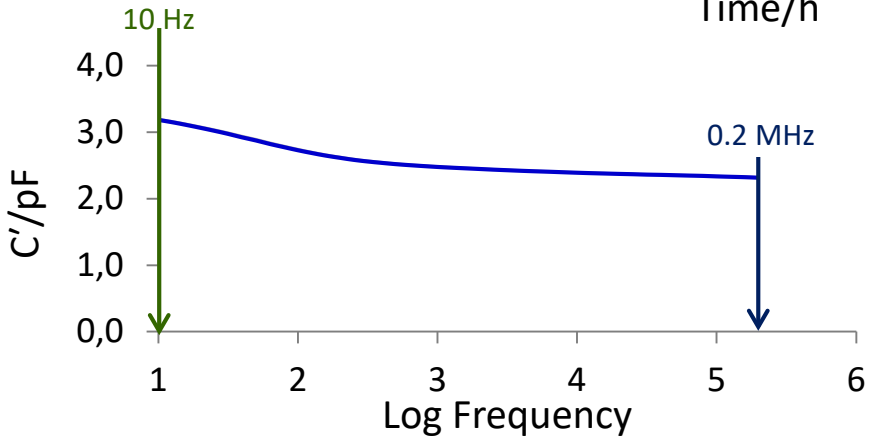
Summary slide

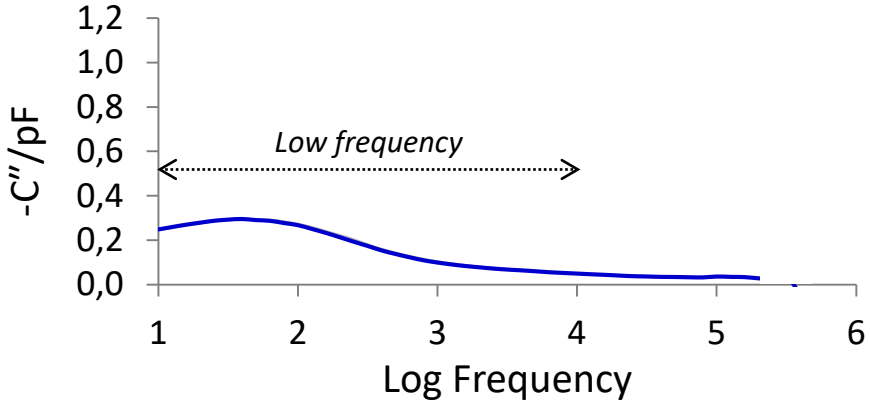


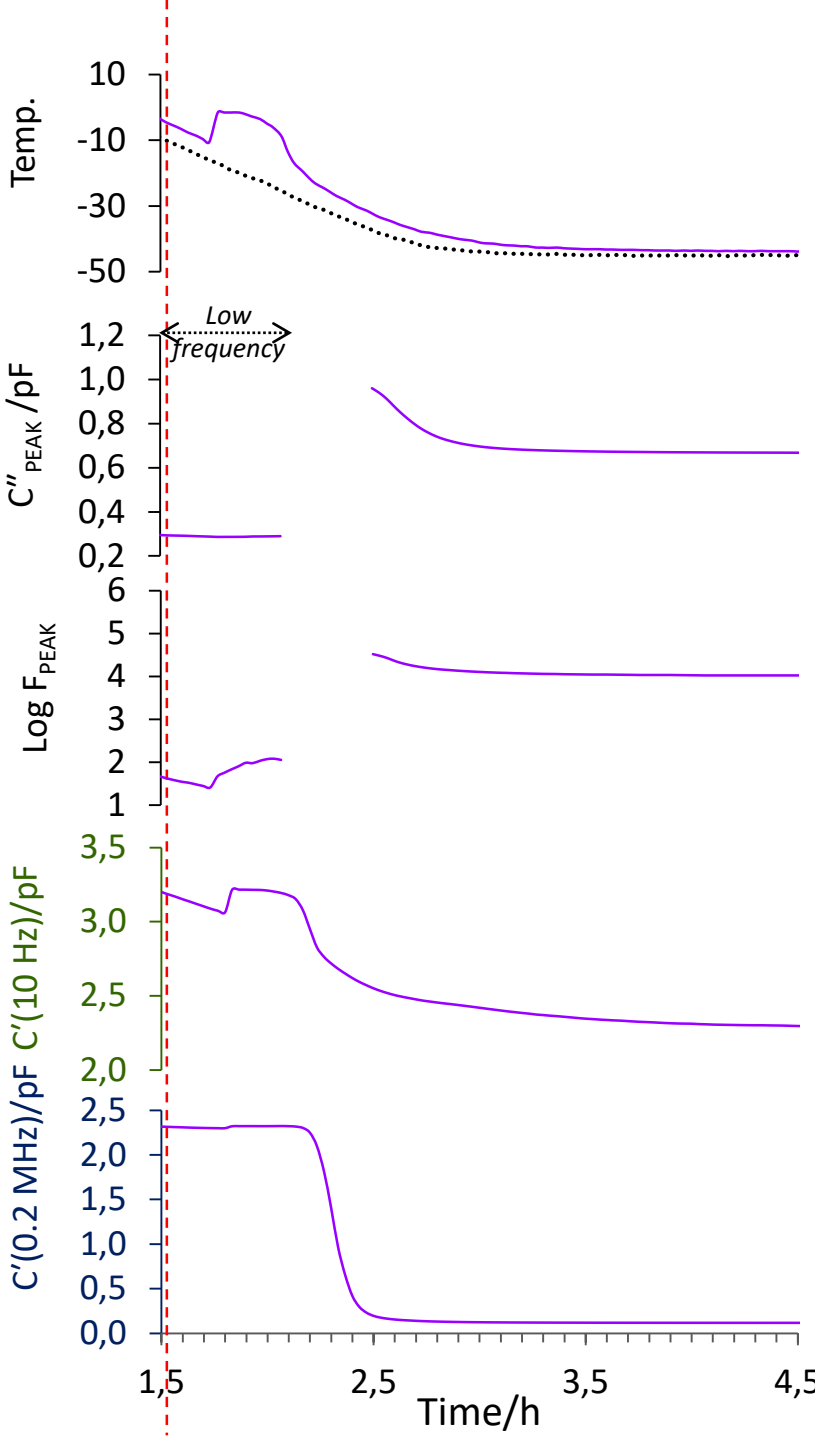
Freezing Step - 5%Sucrose+0.55%NaCl



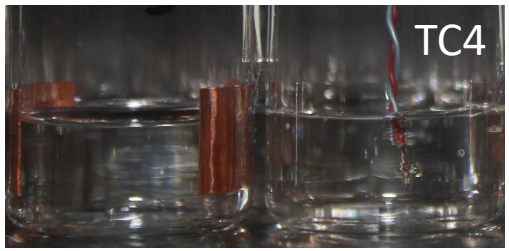


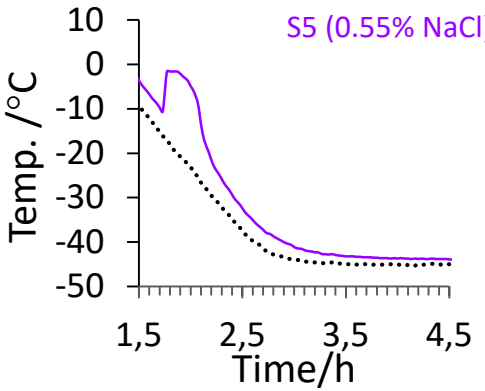


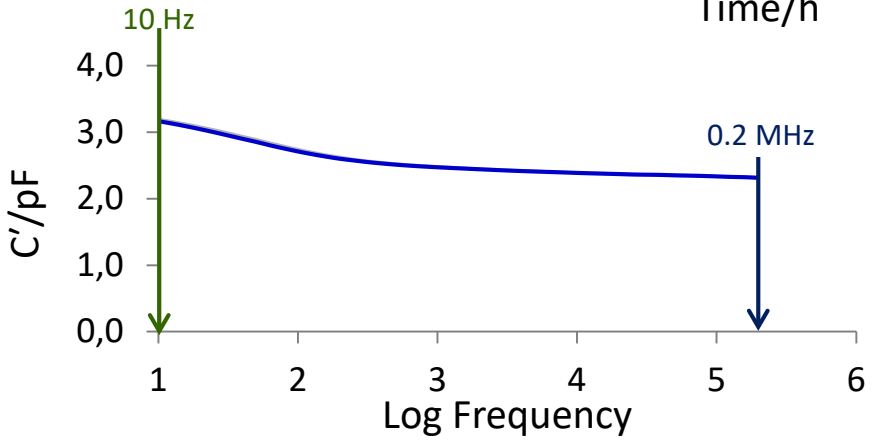


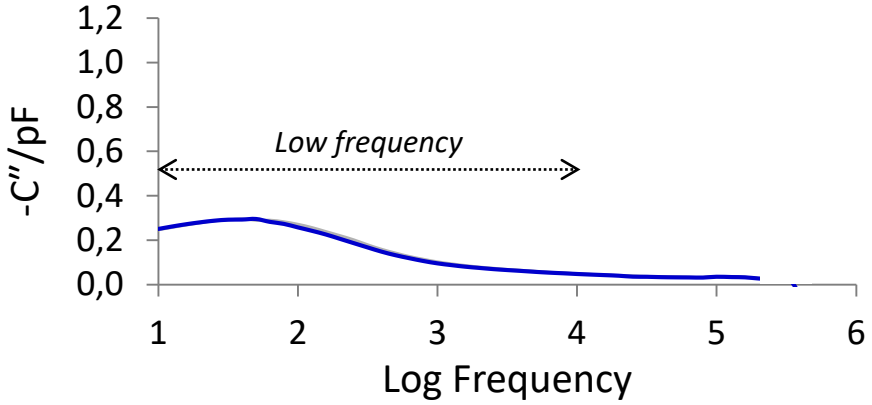


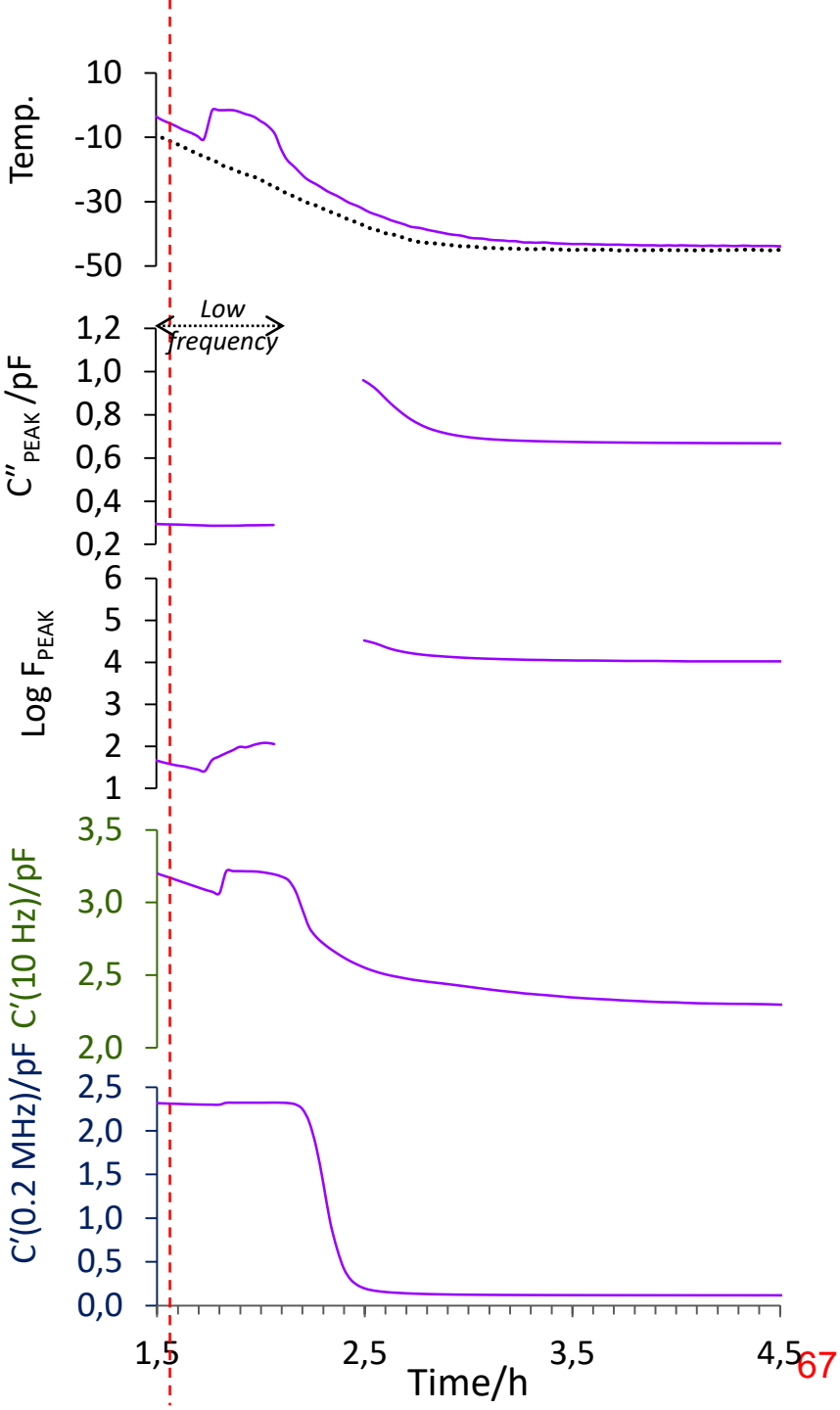
Freezing Step - 5%Sucrose+0.55%NaCl



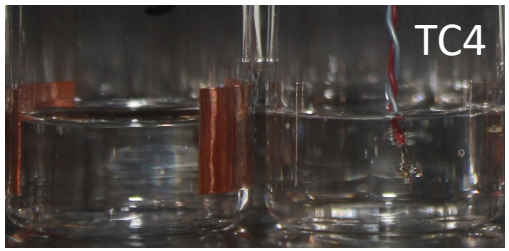


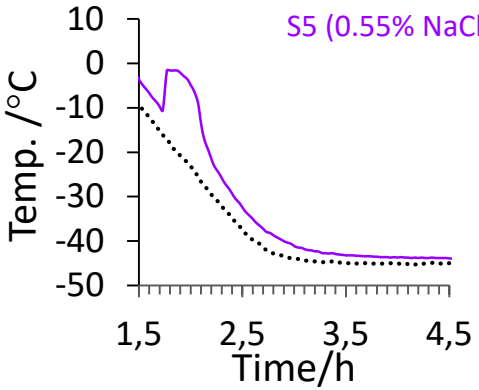


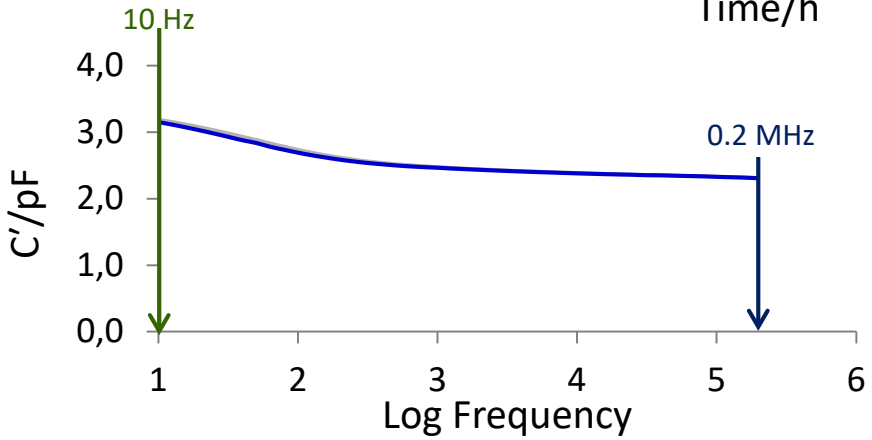


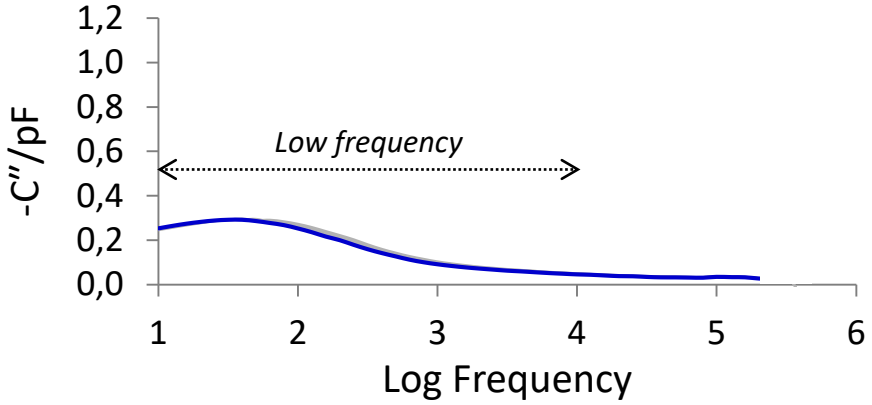


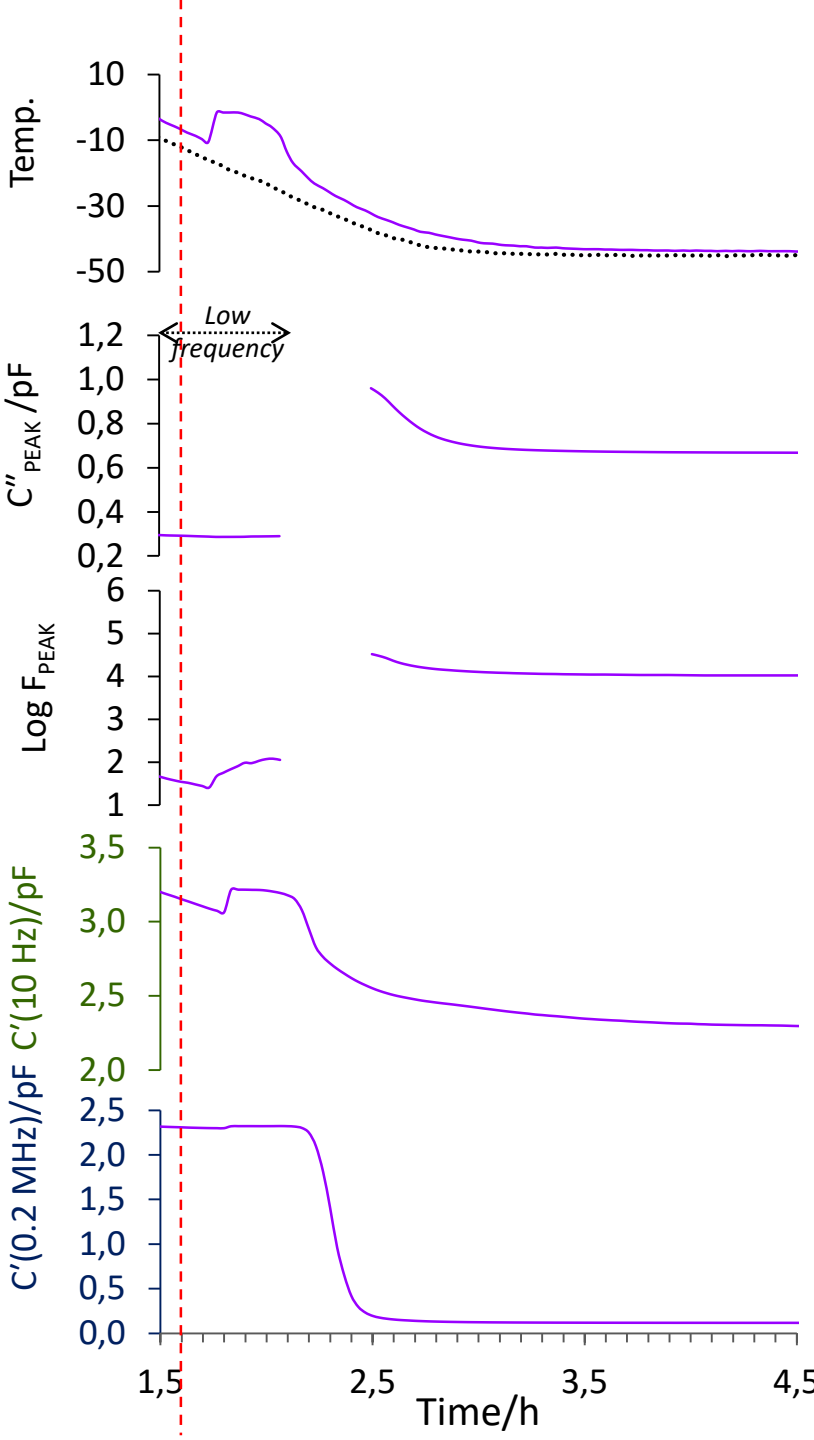
Freezing Step - 5%Sucrose+0.55%NaCl



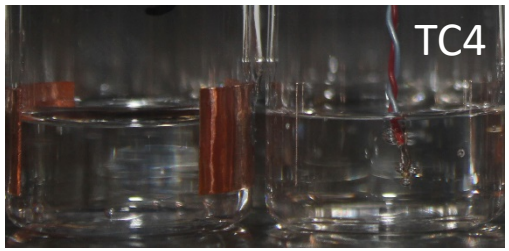


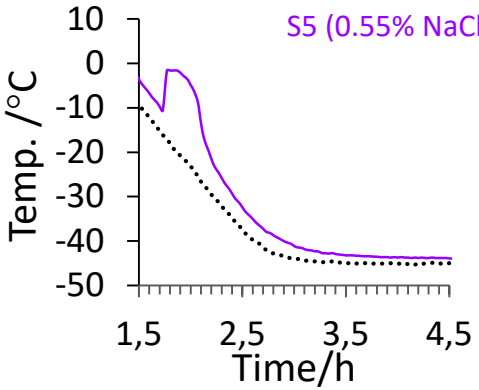


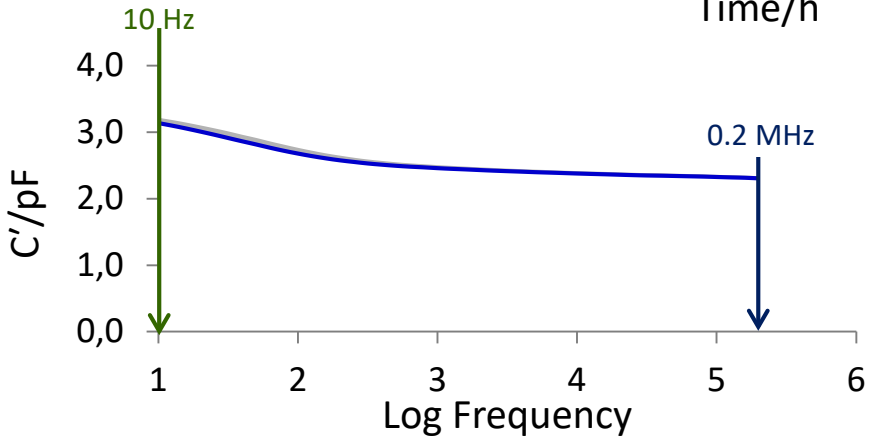


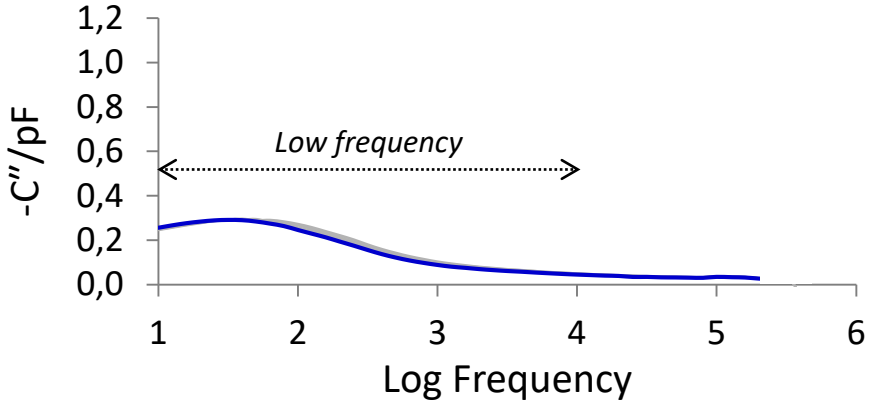


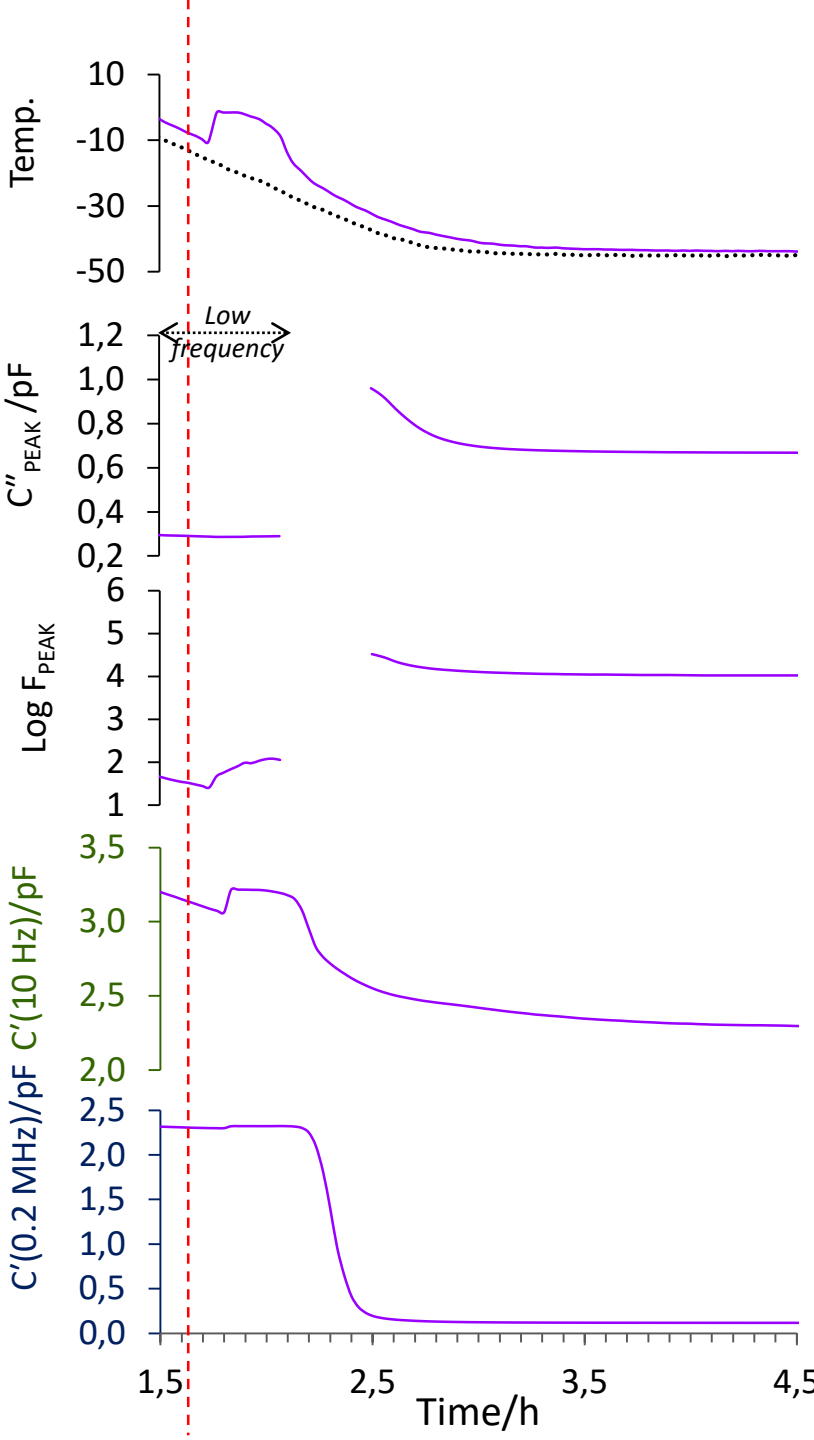
Freezing Step - 5%Sucrose+0.55%NaCl



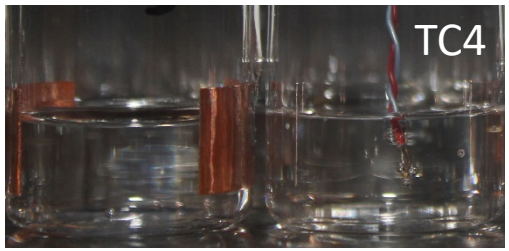


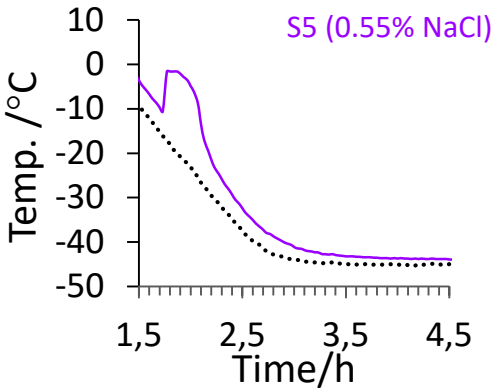


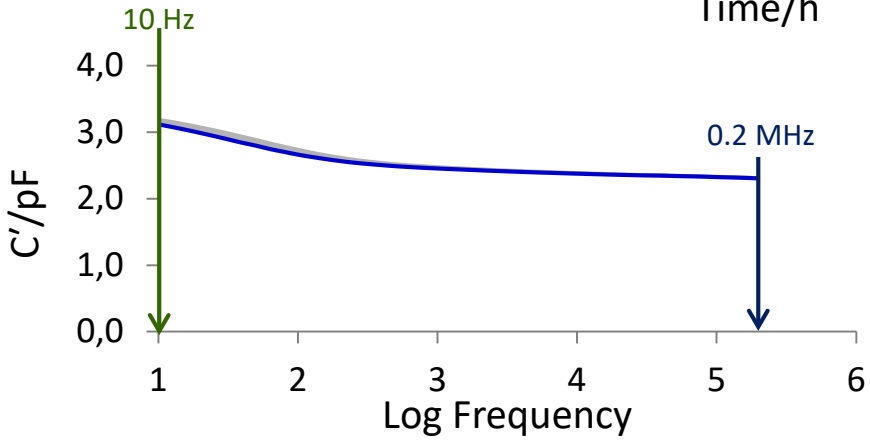


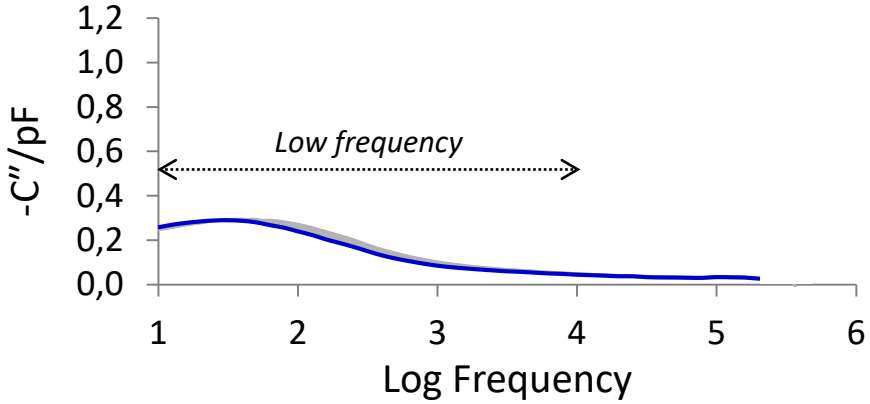


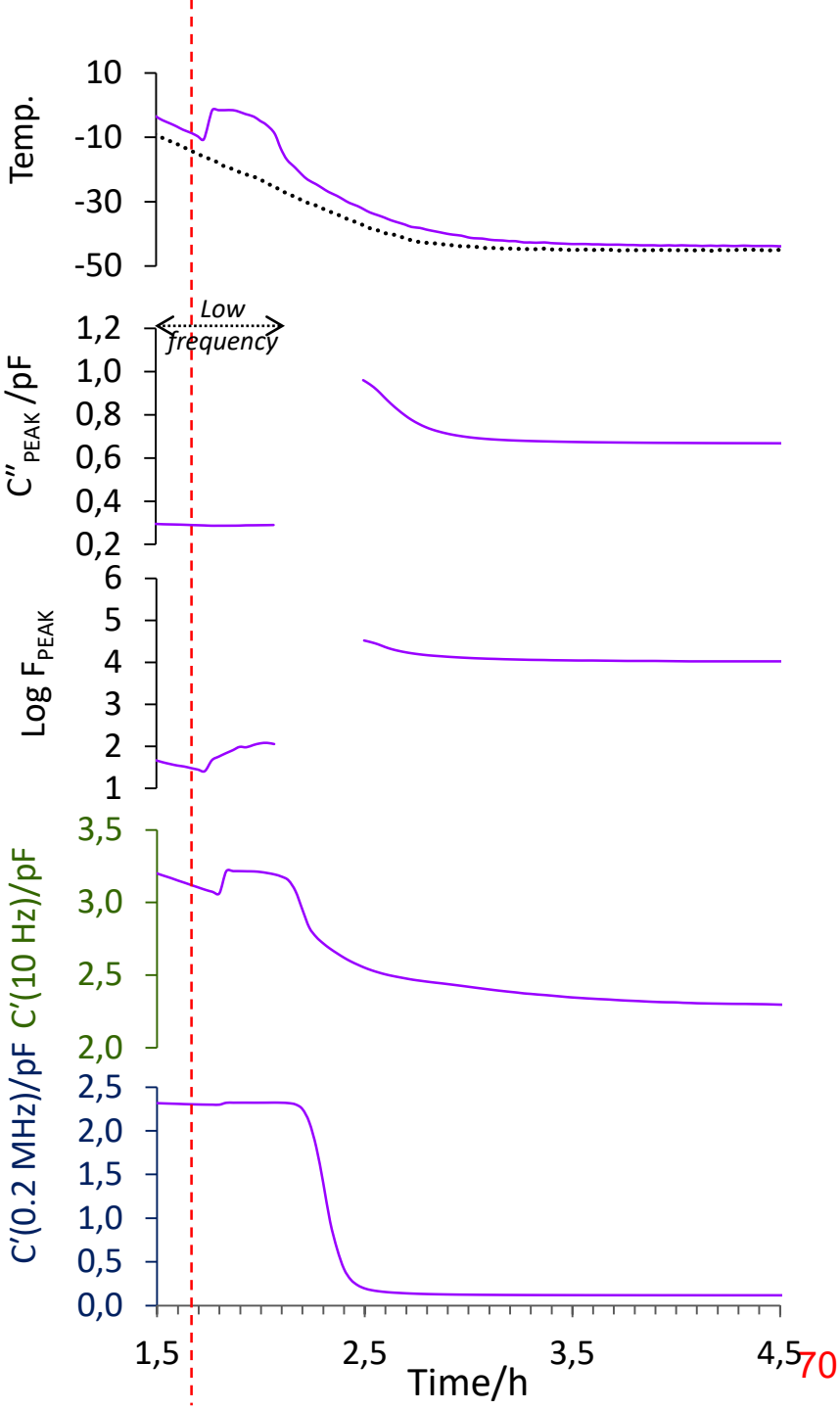
Freezing Step - 5%Sucrose+0.55%NaCl











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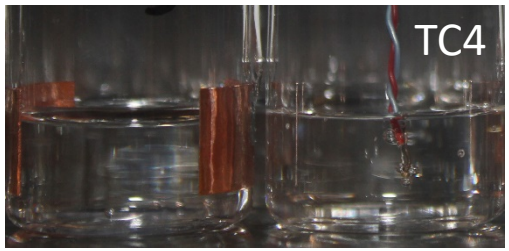

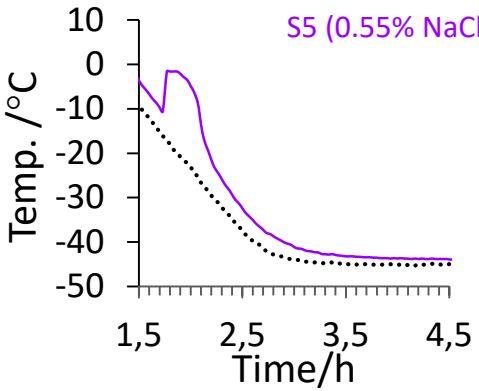

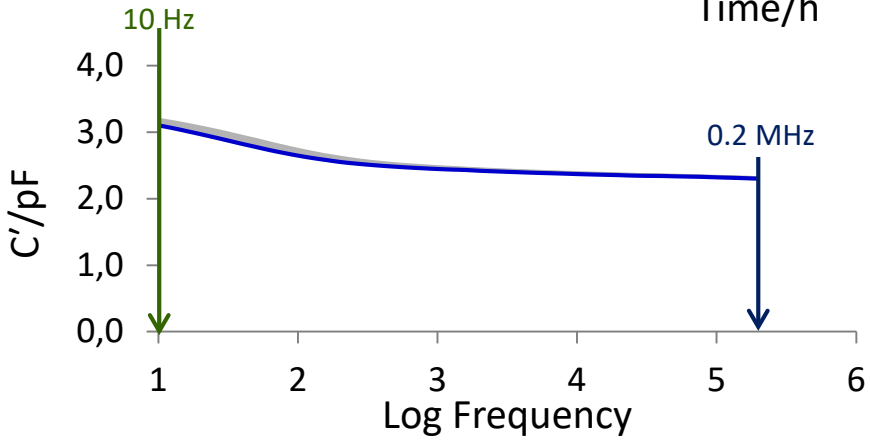

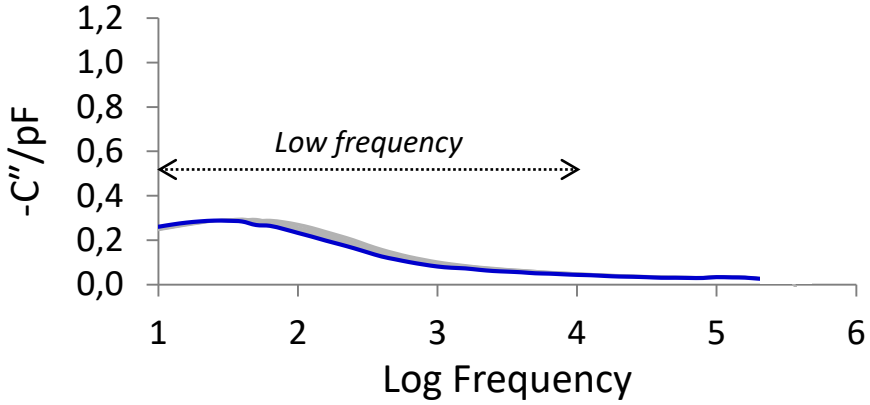

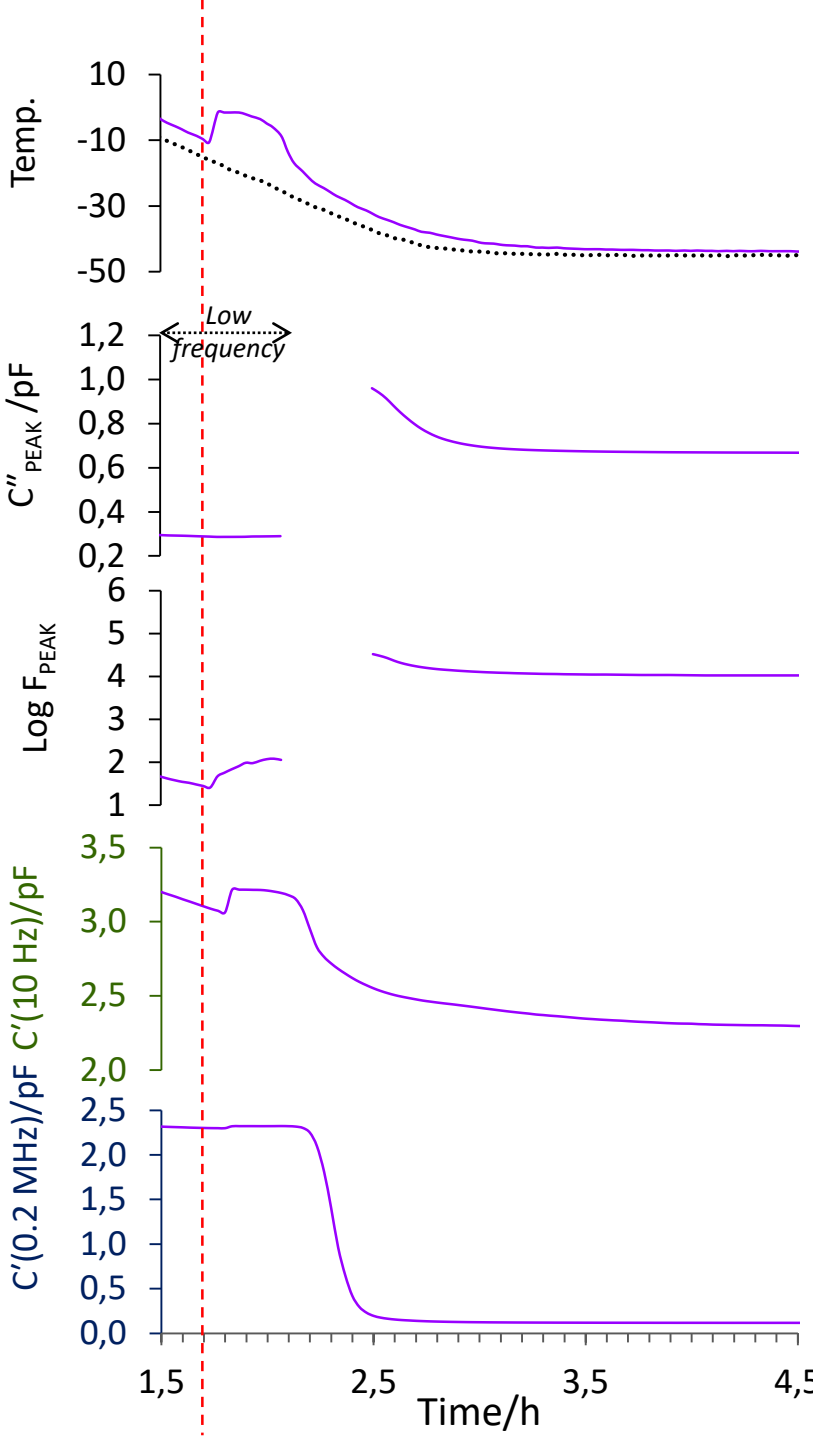

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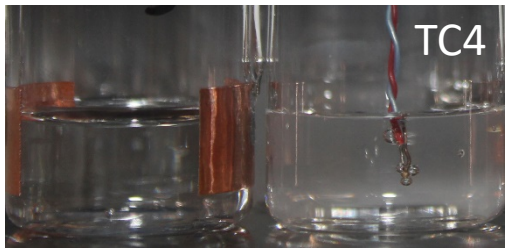

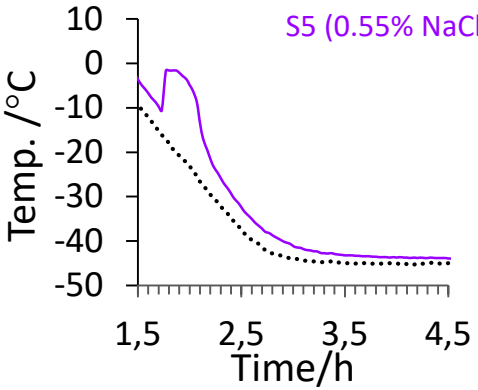

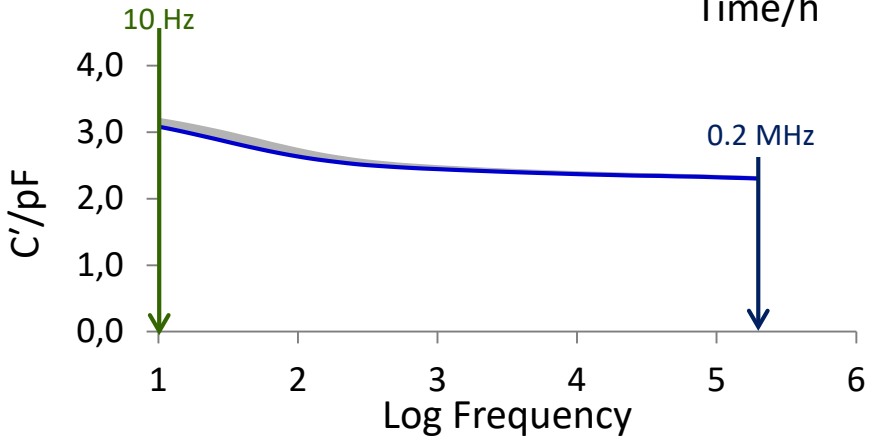

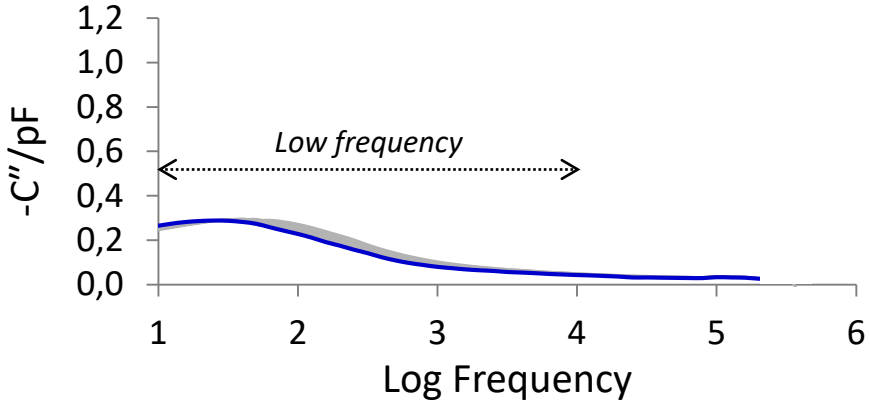

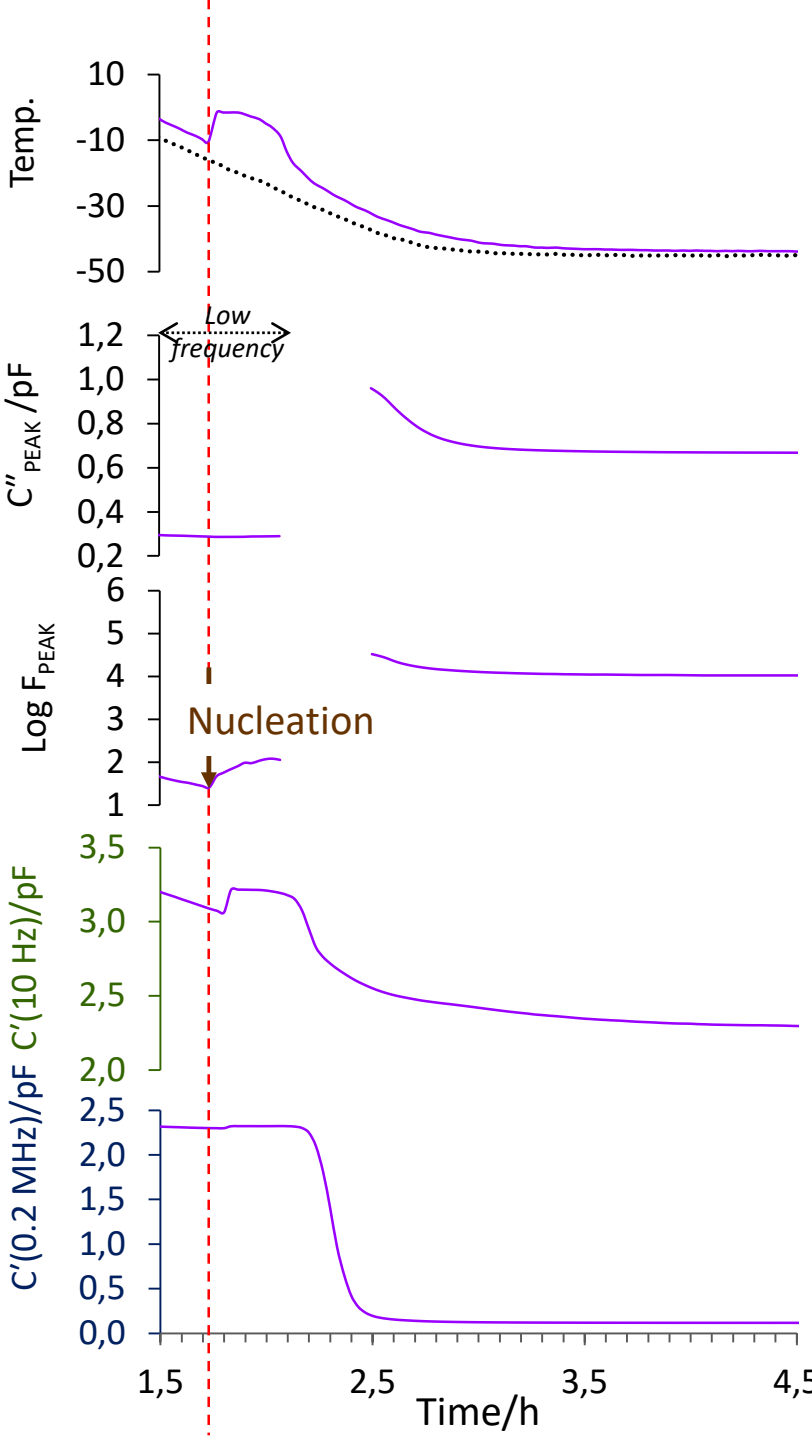

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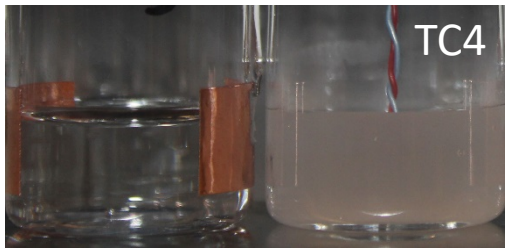

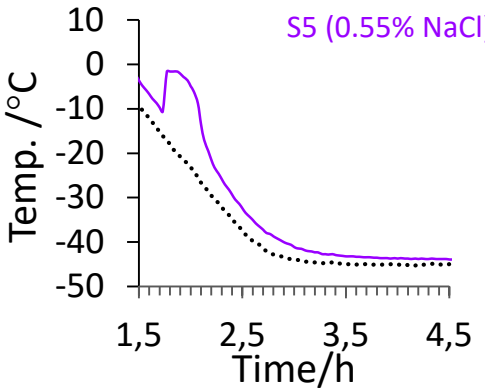

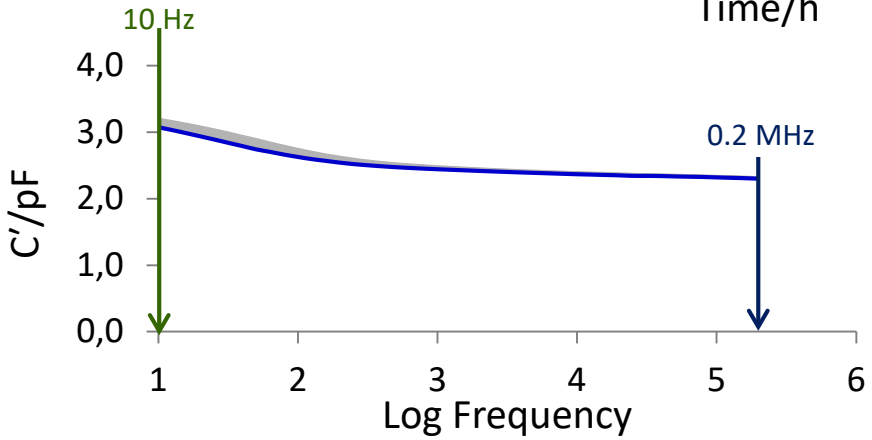

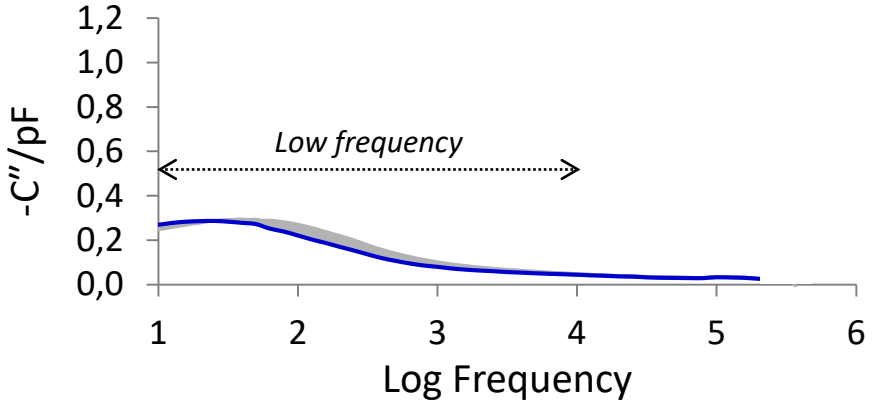

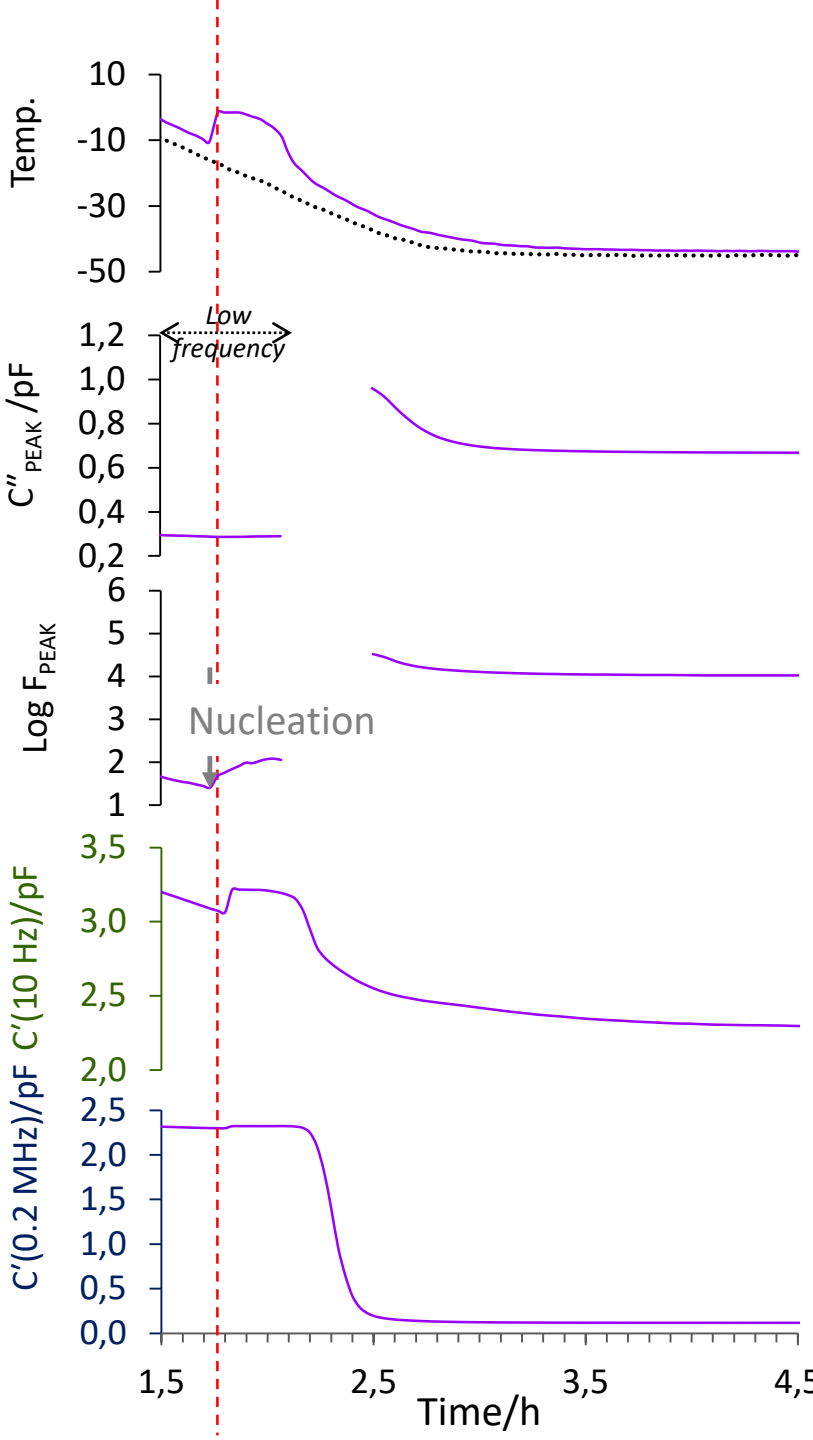

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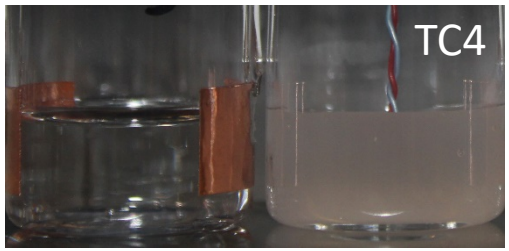

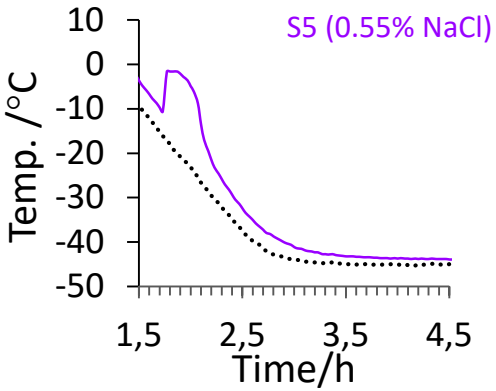

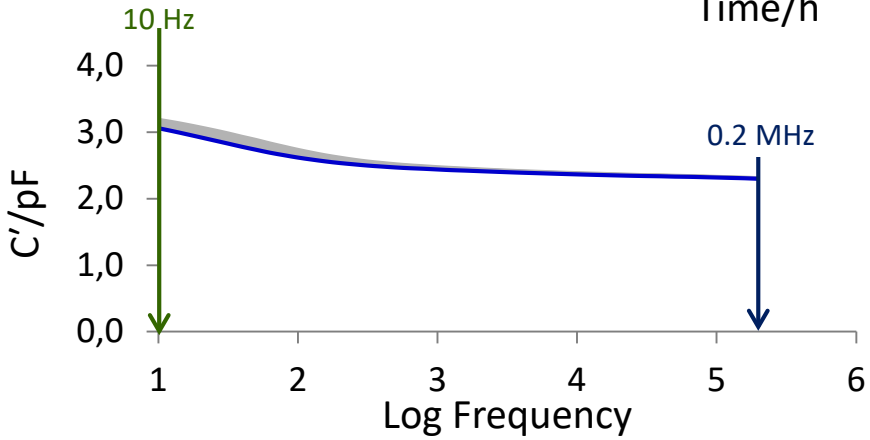

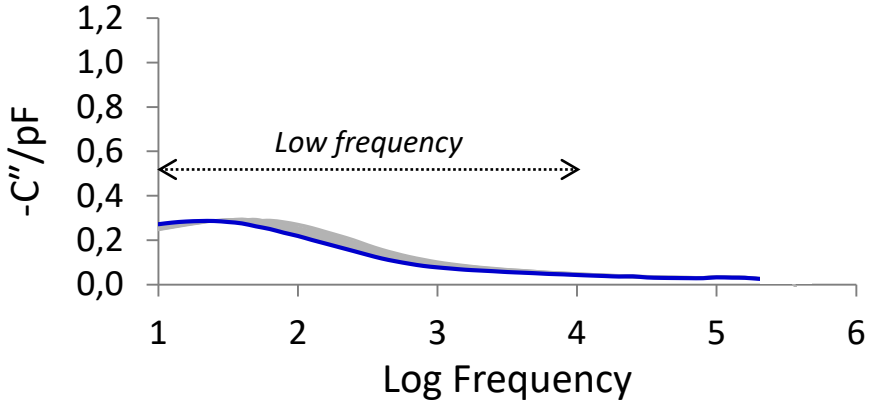

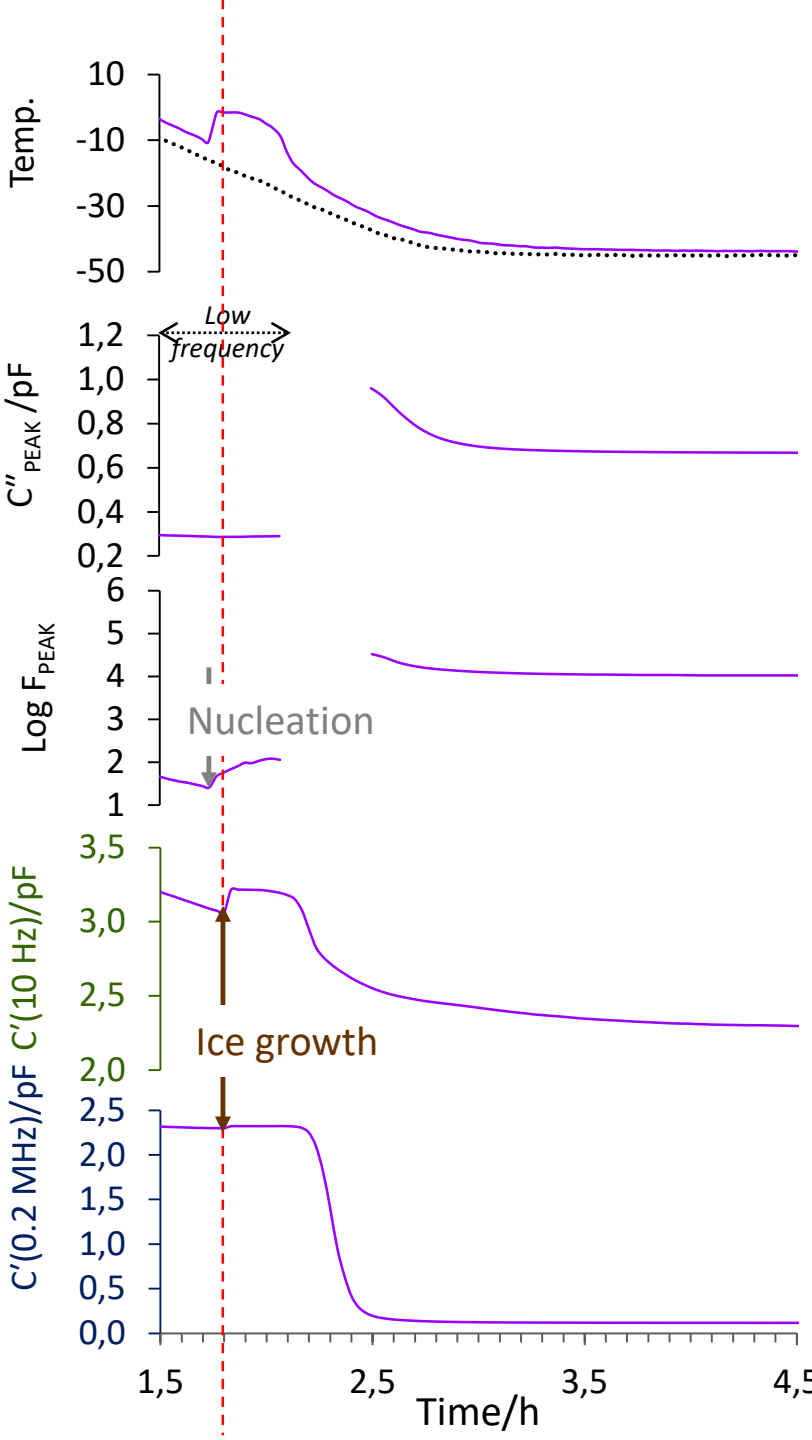

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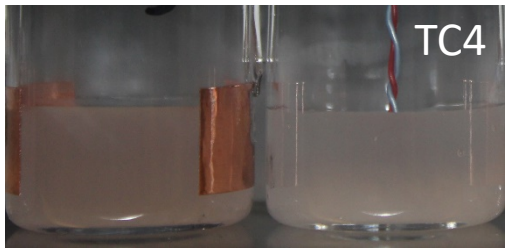

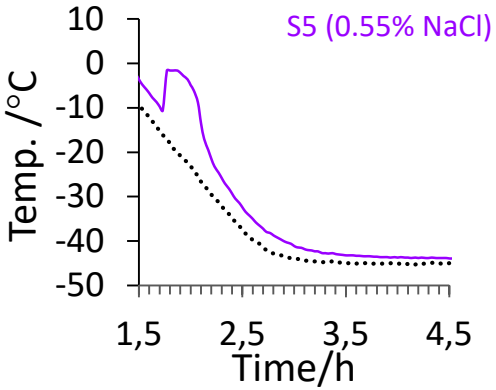

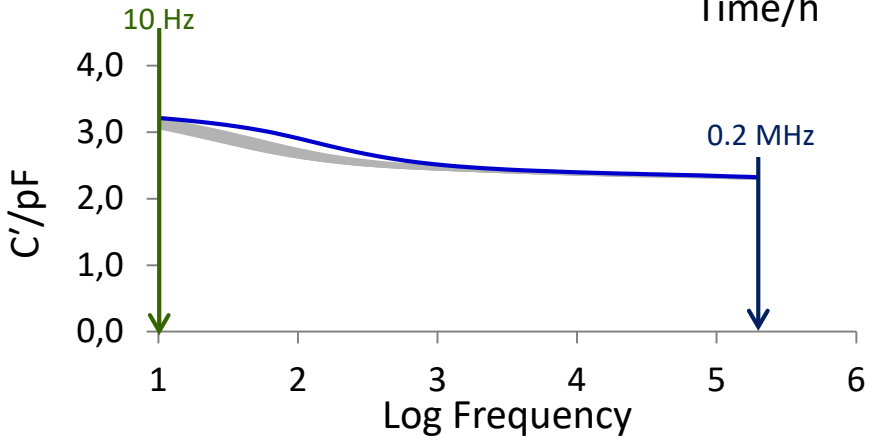

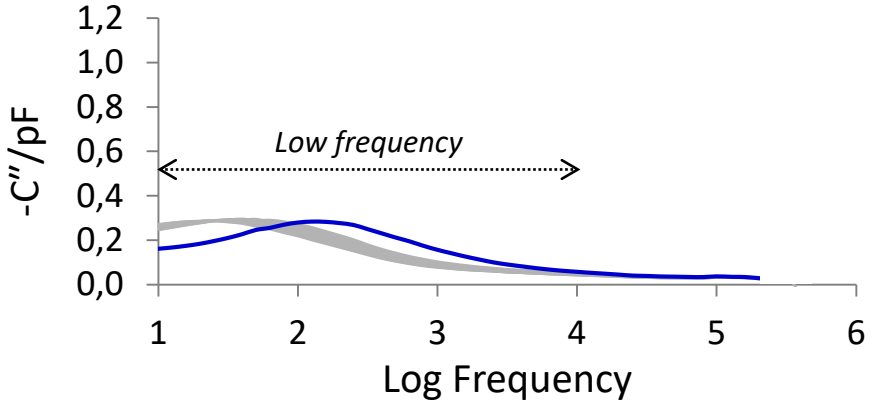

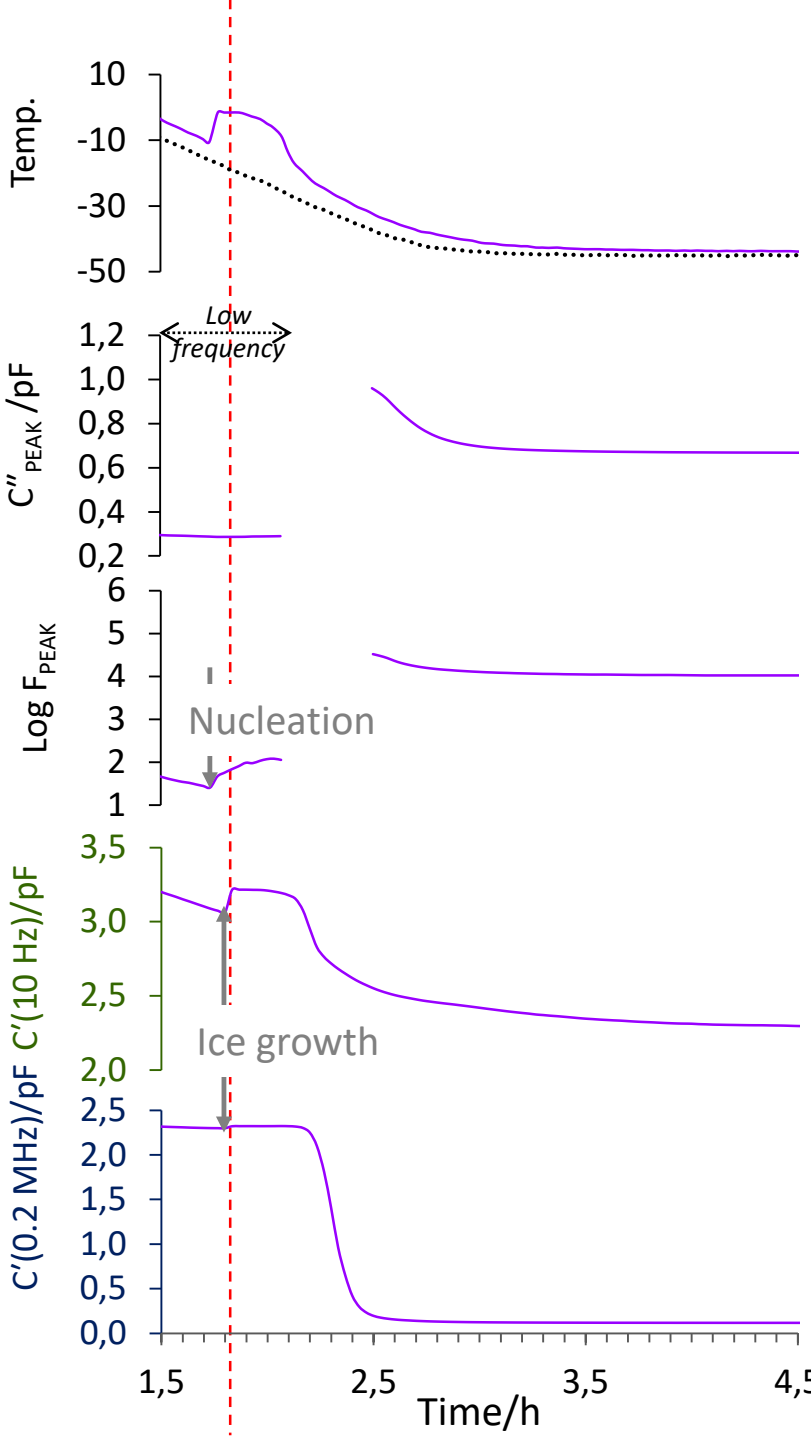

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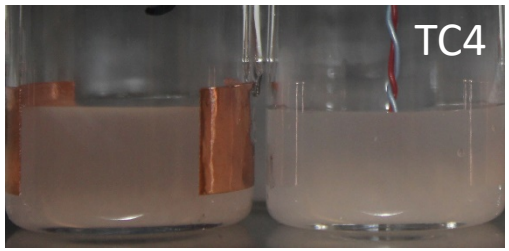

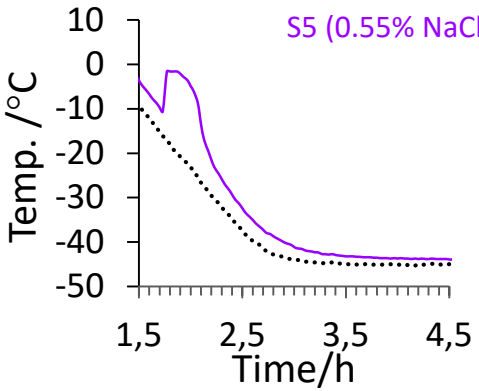

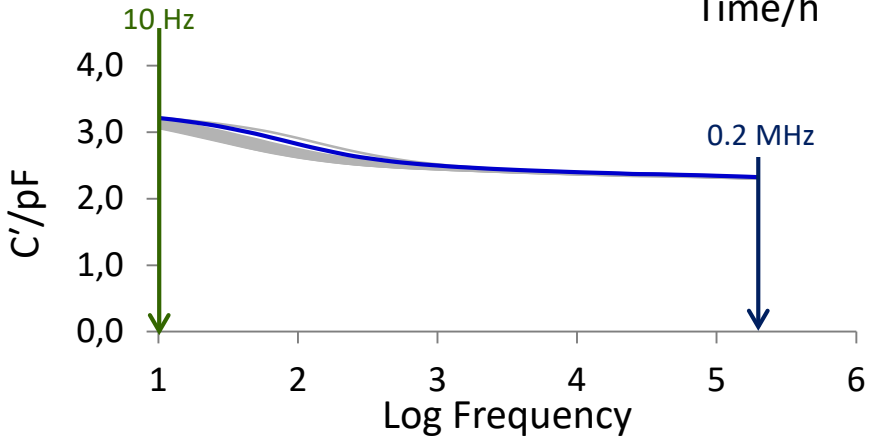

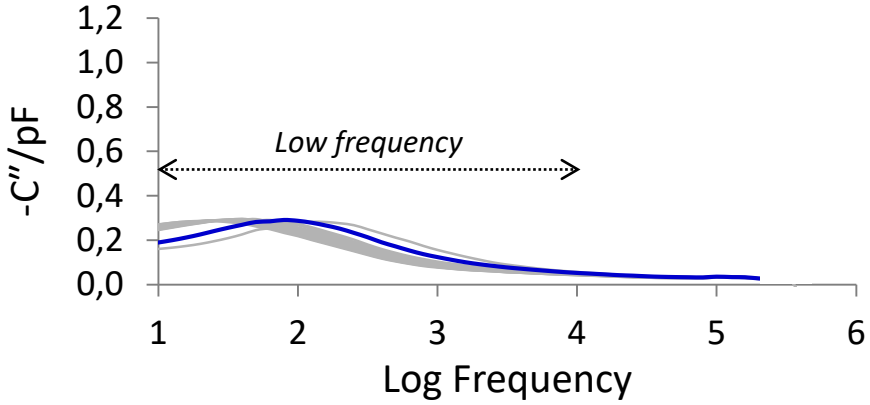

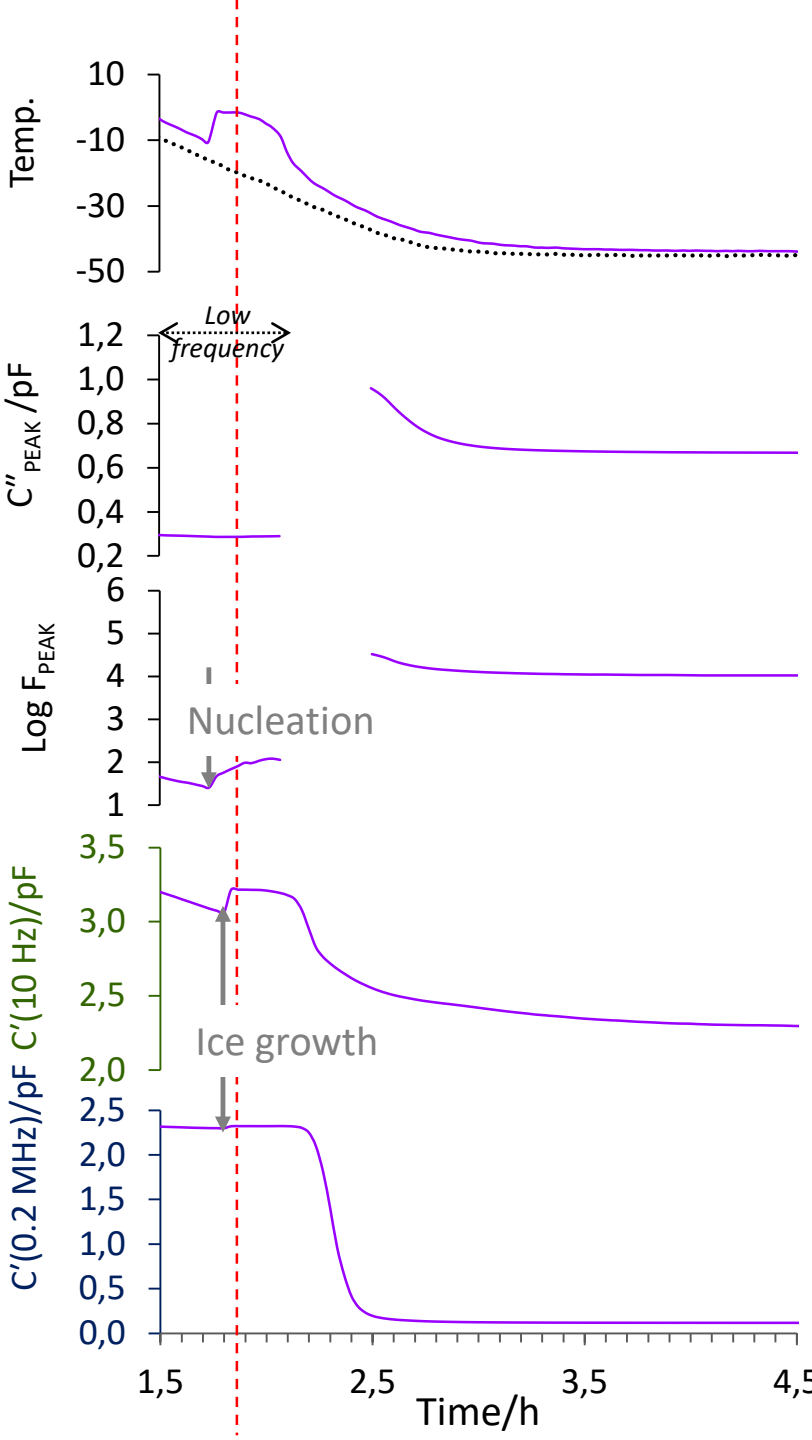

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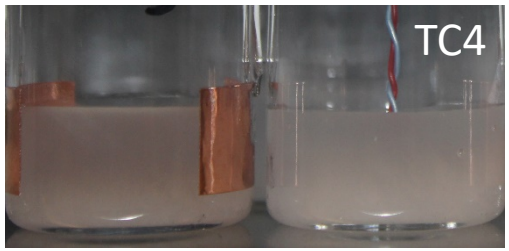

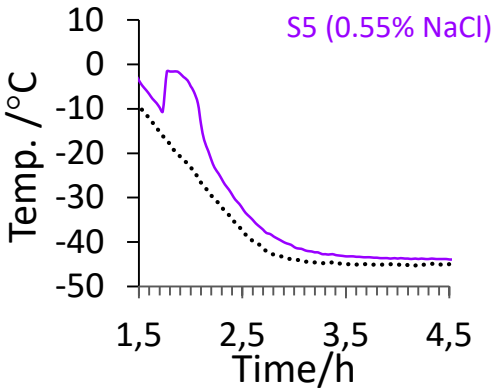

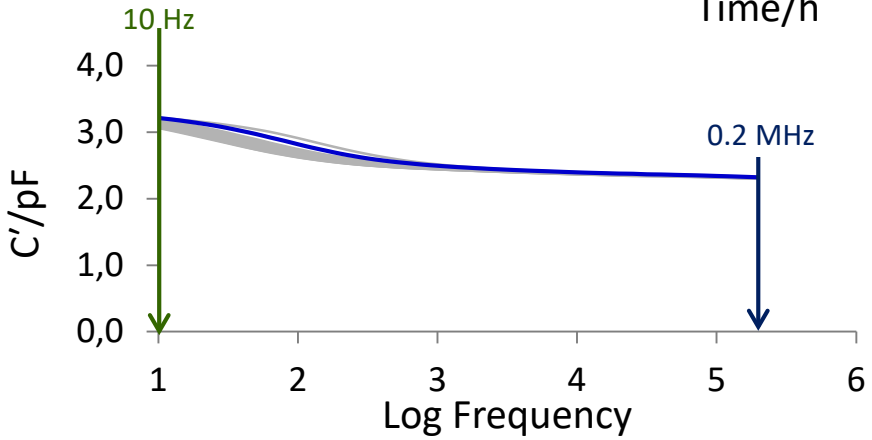

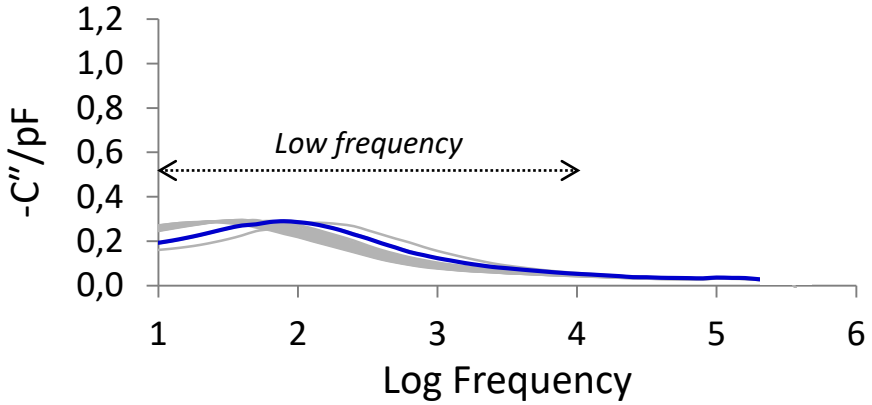

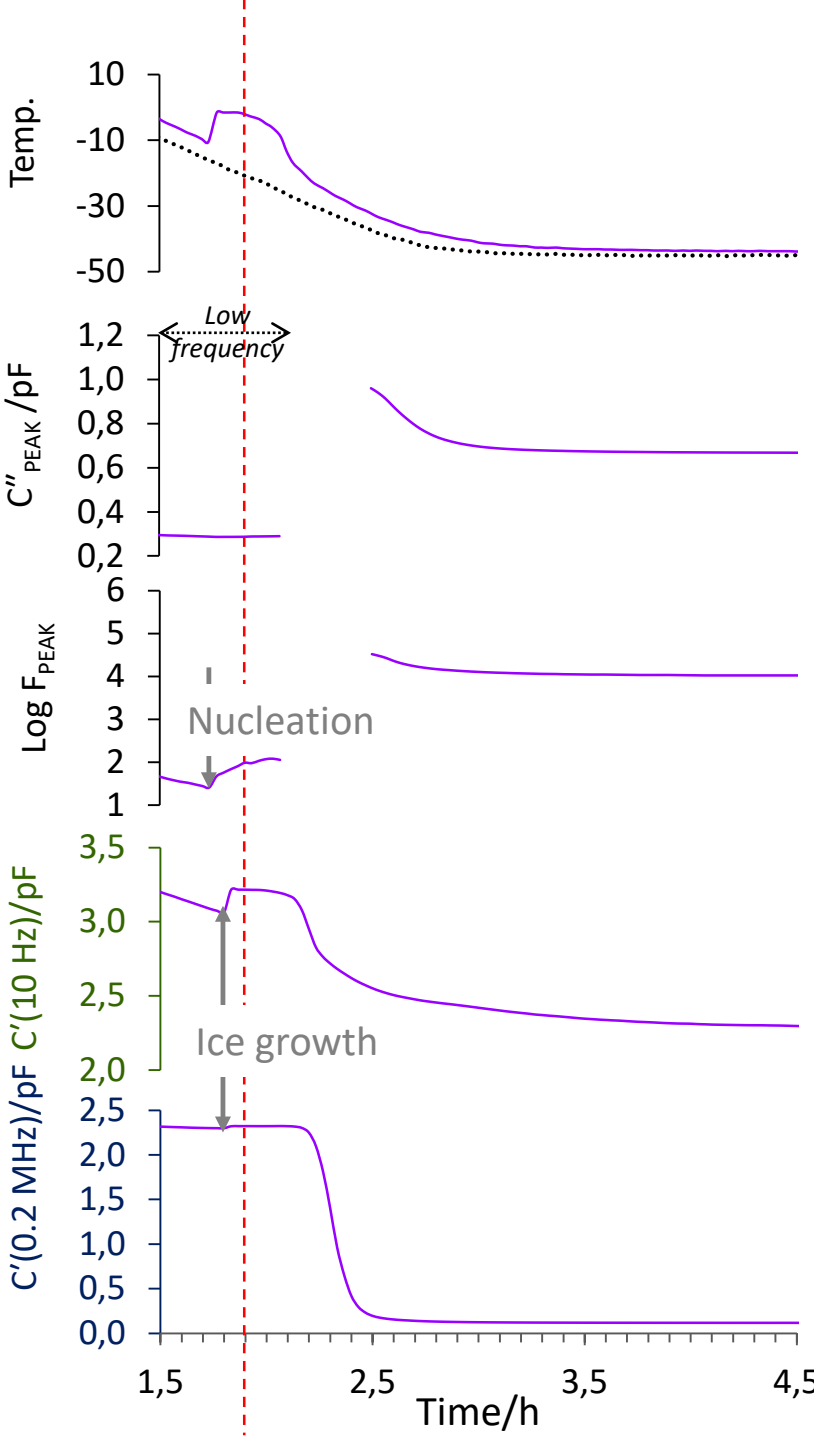

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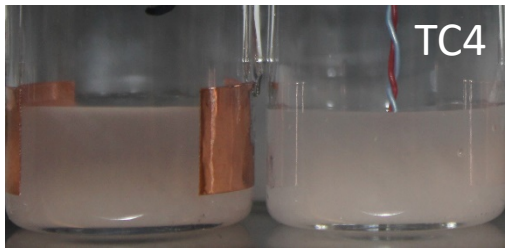

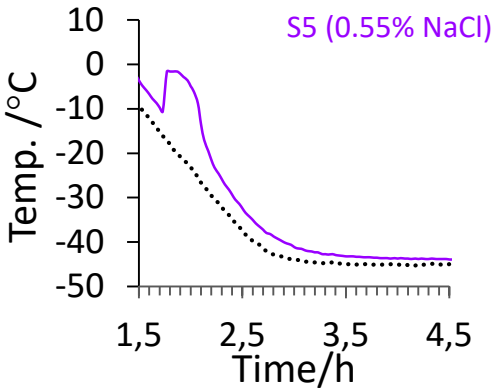

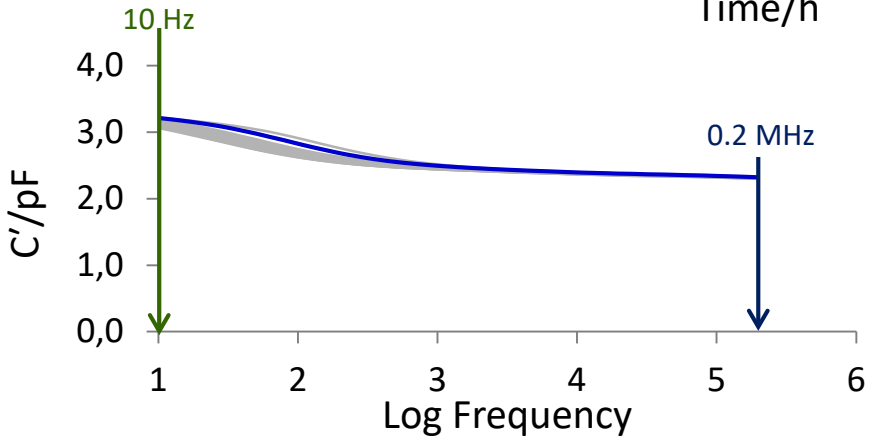

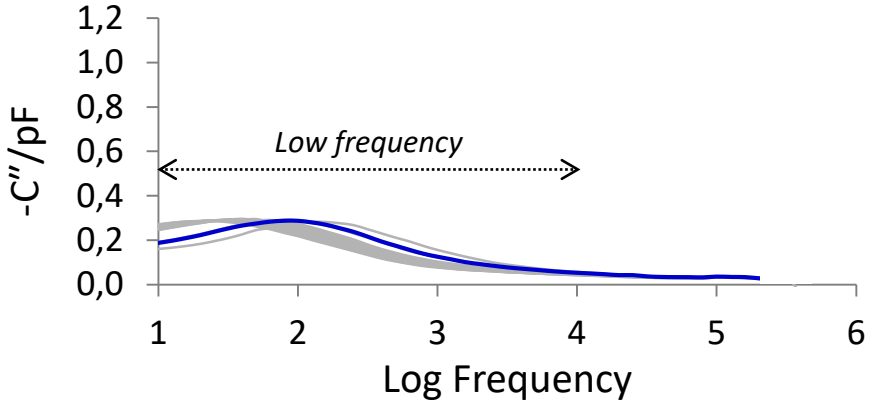

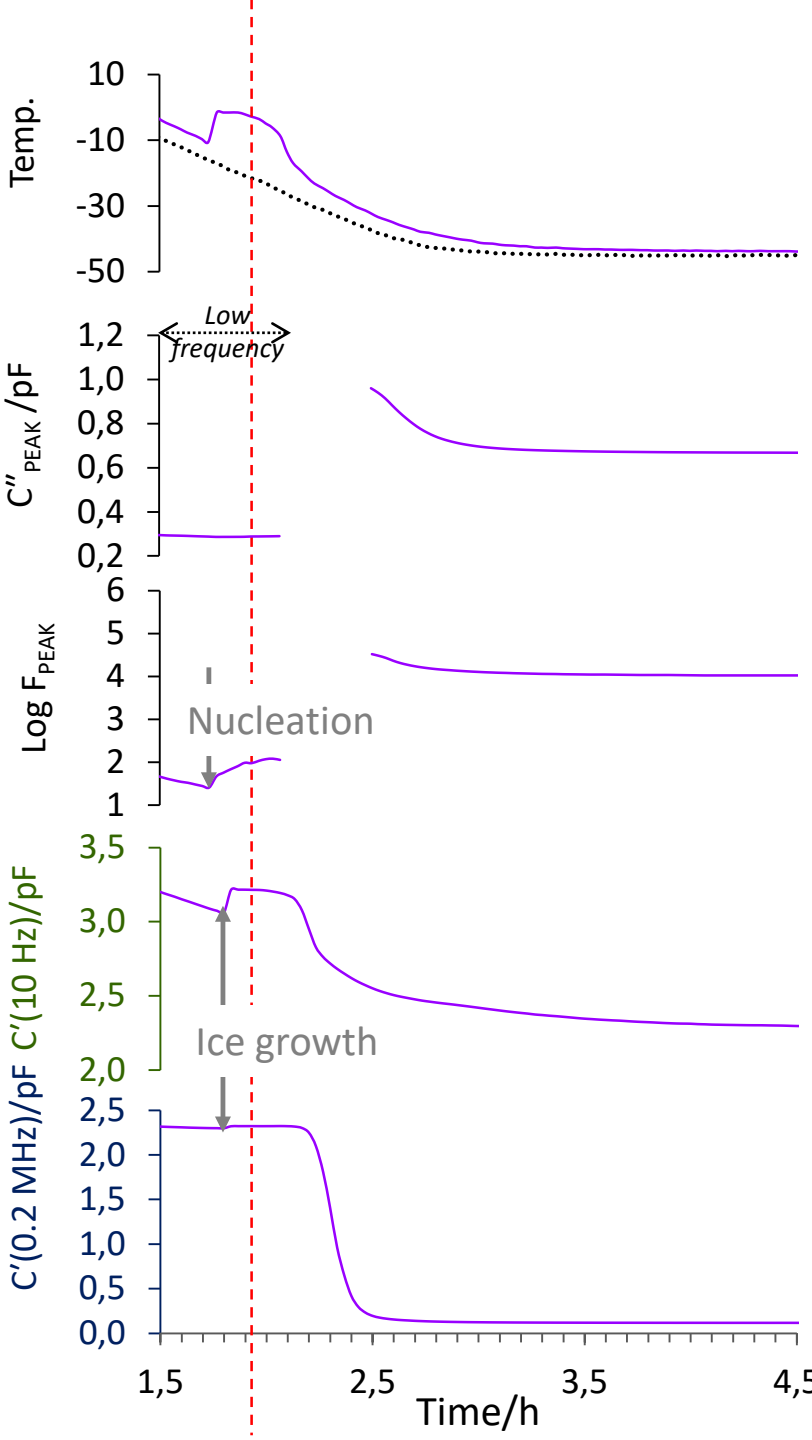

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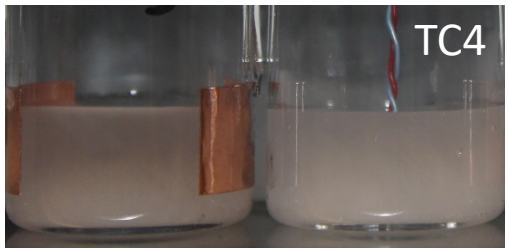

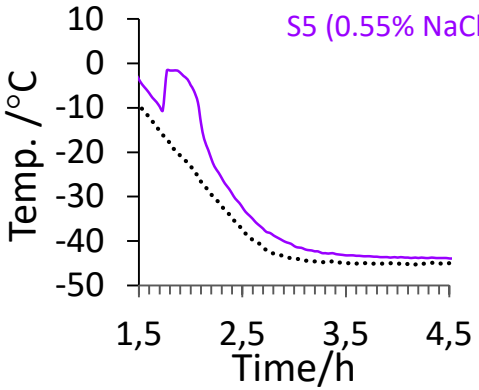

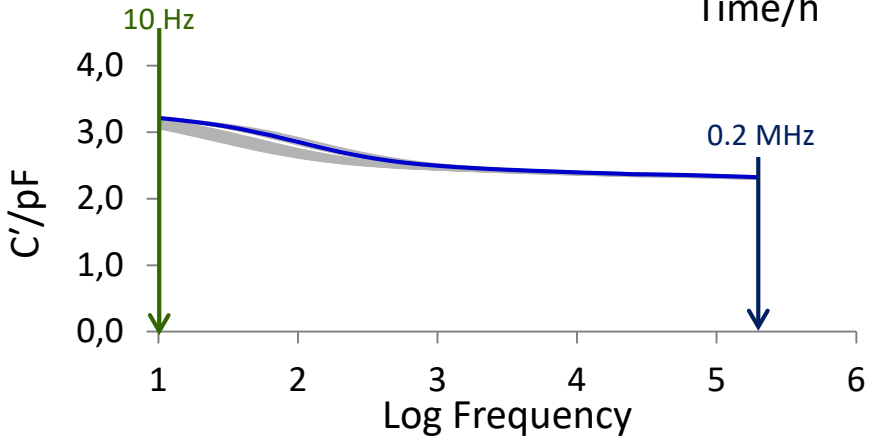

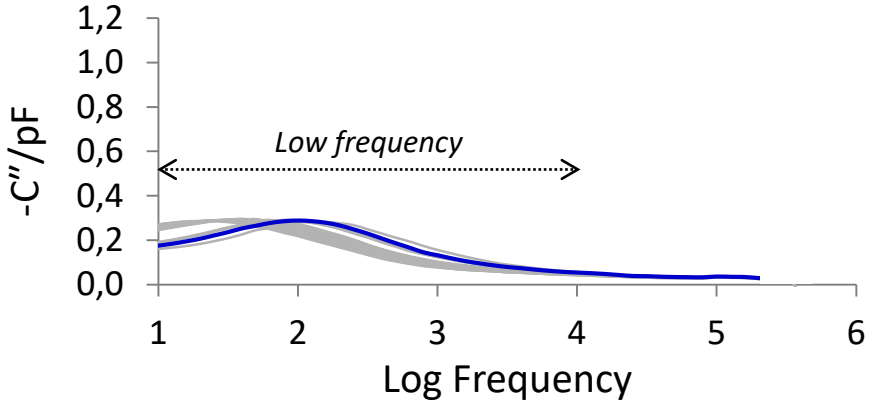

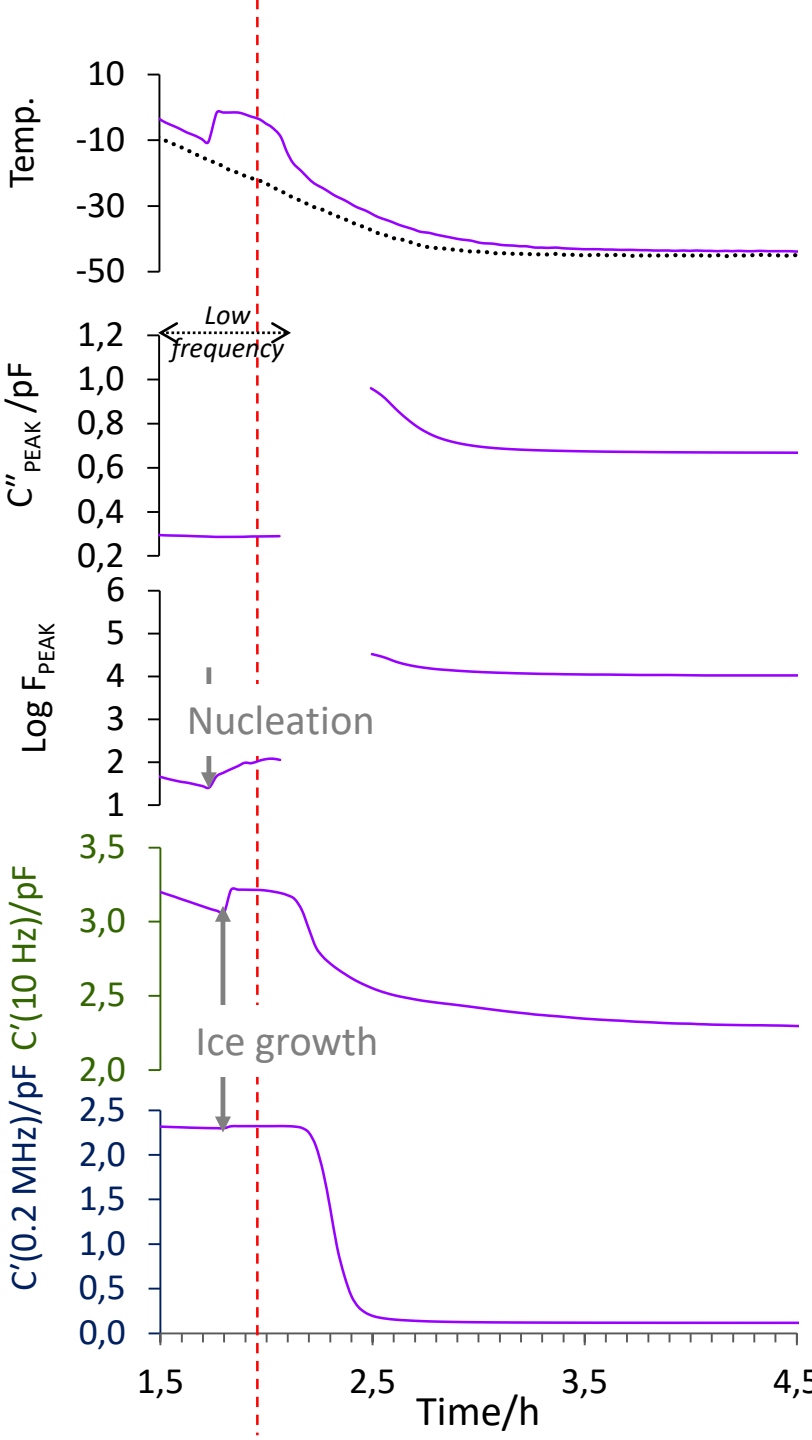

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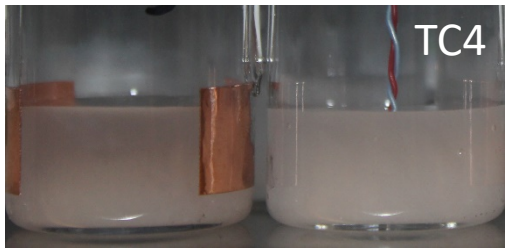

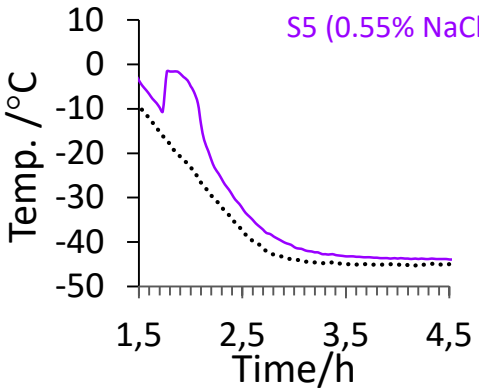

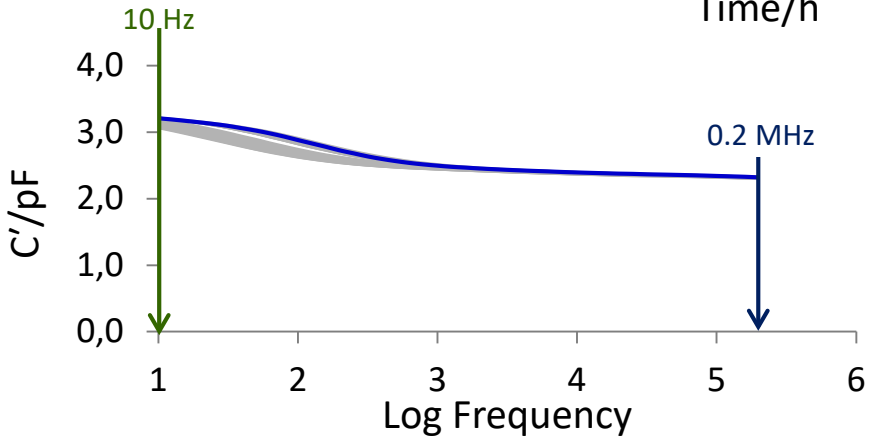

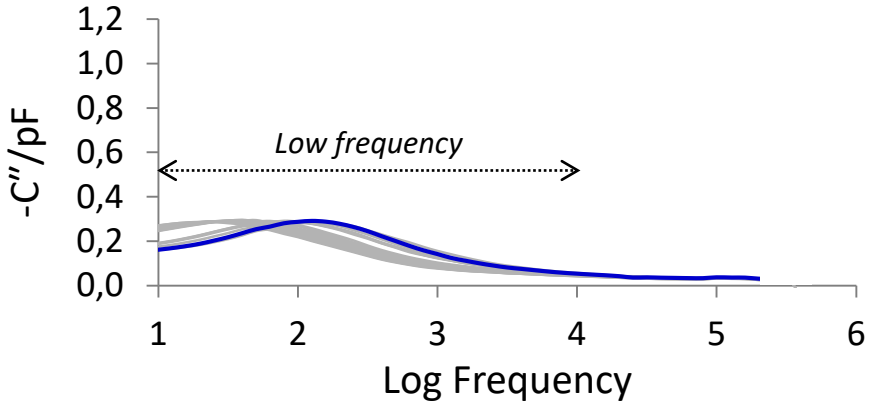

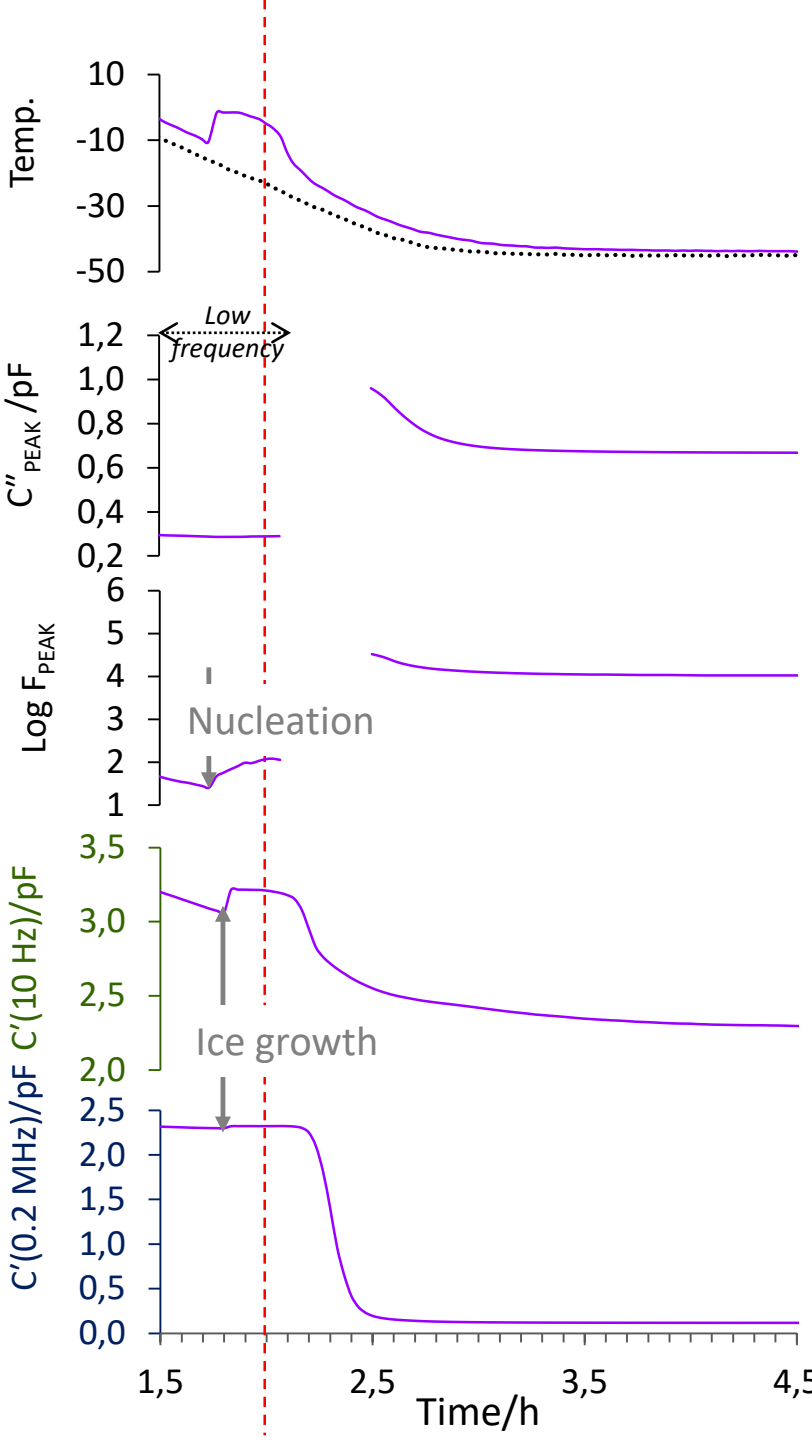

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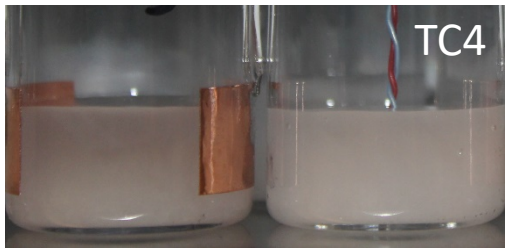

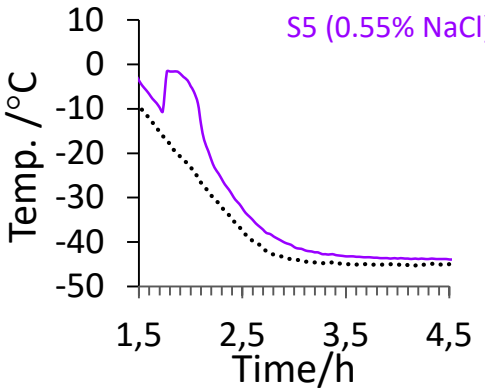

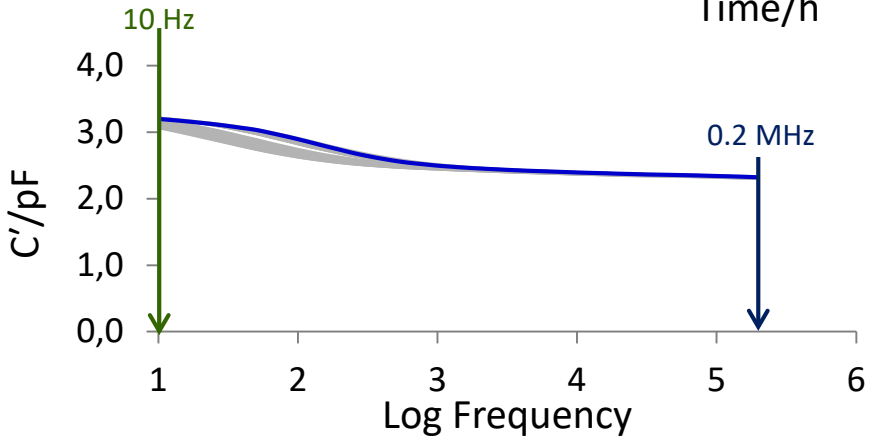

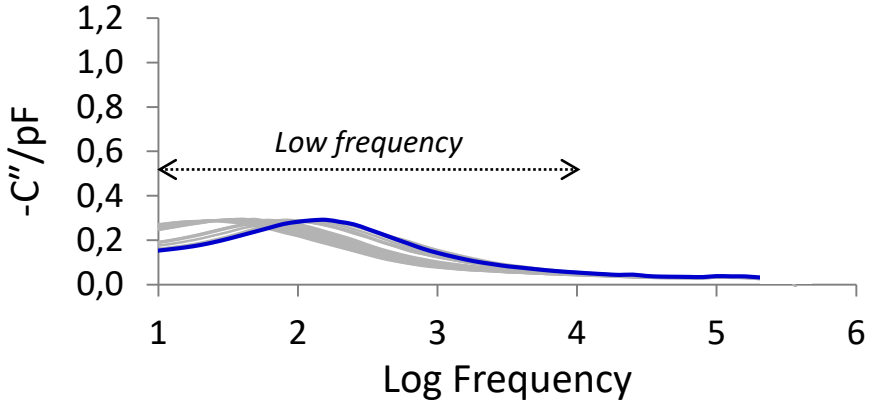

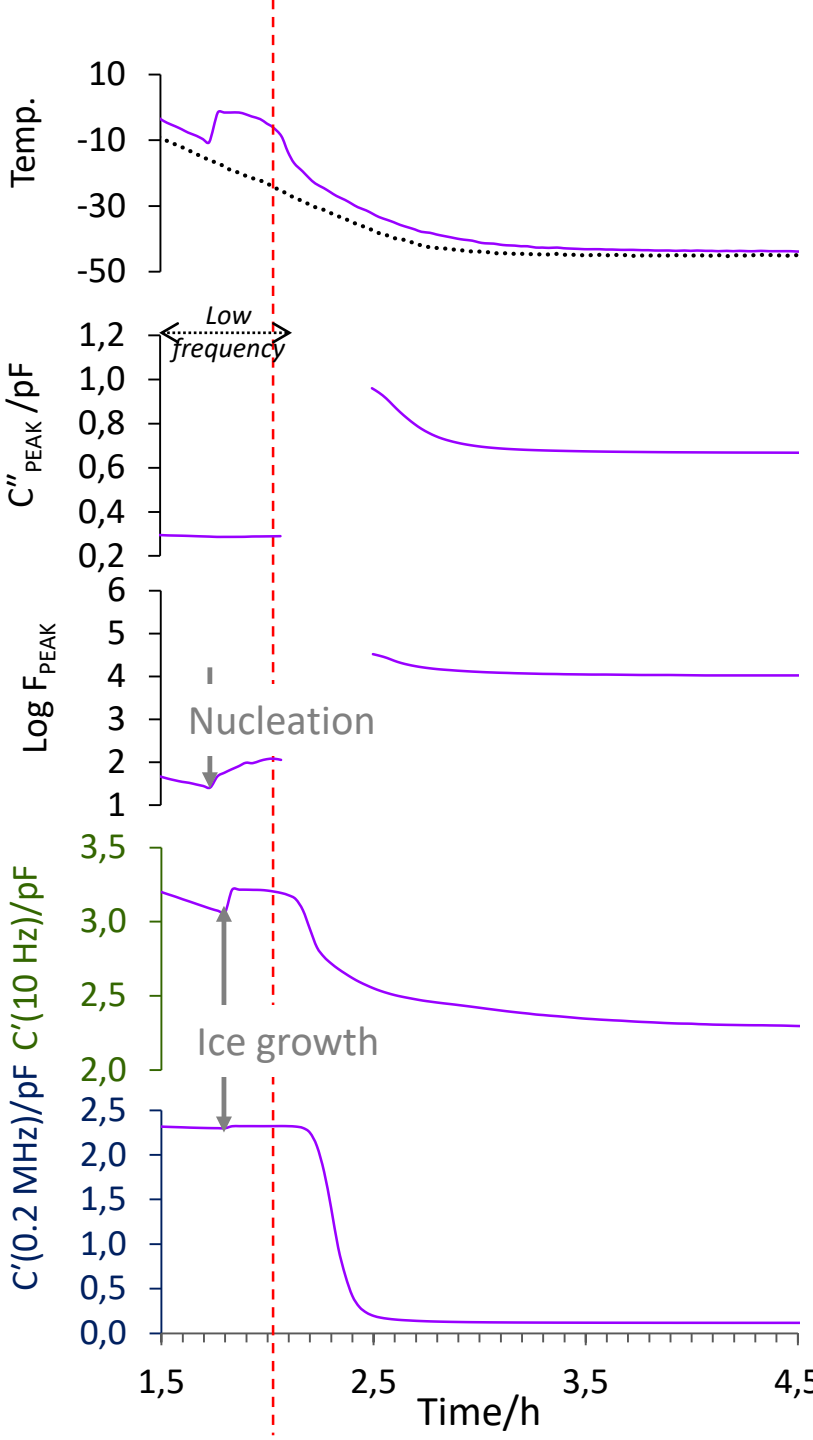

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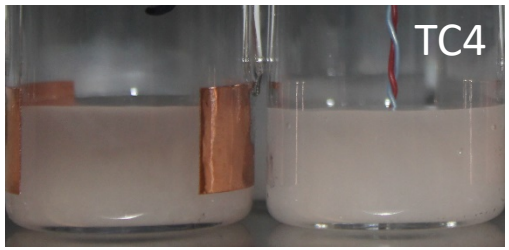

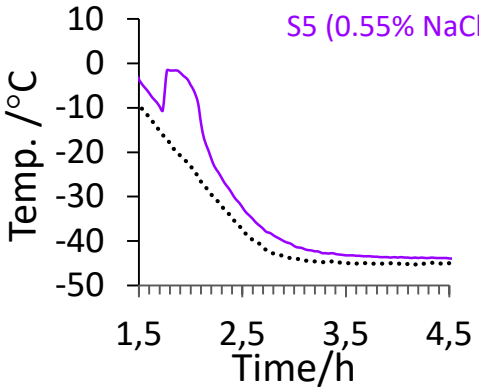

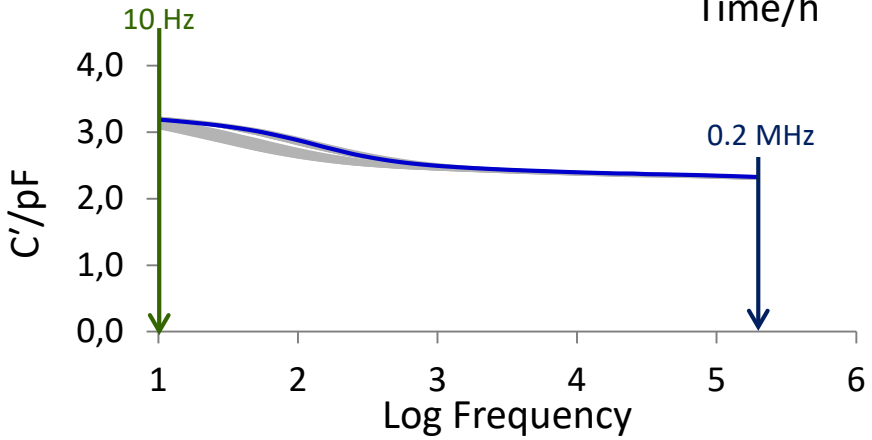

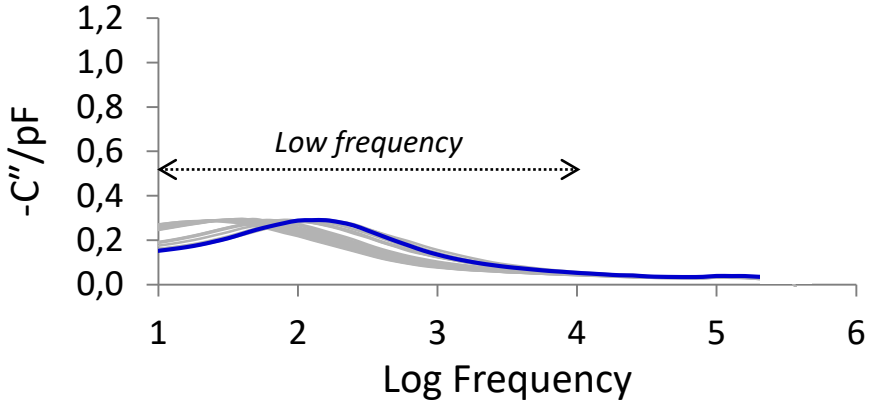

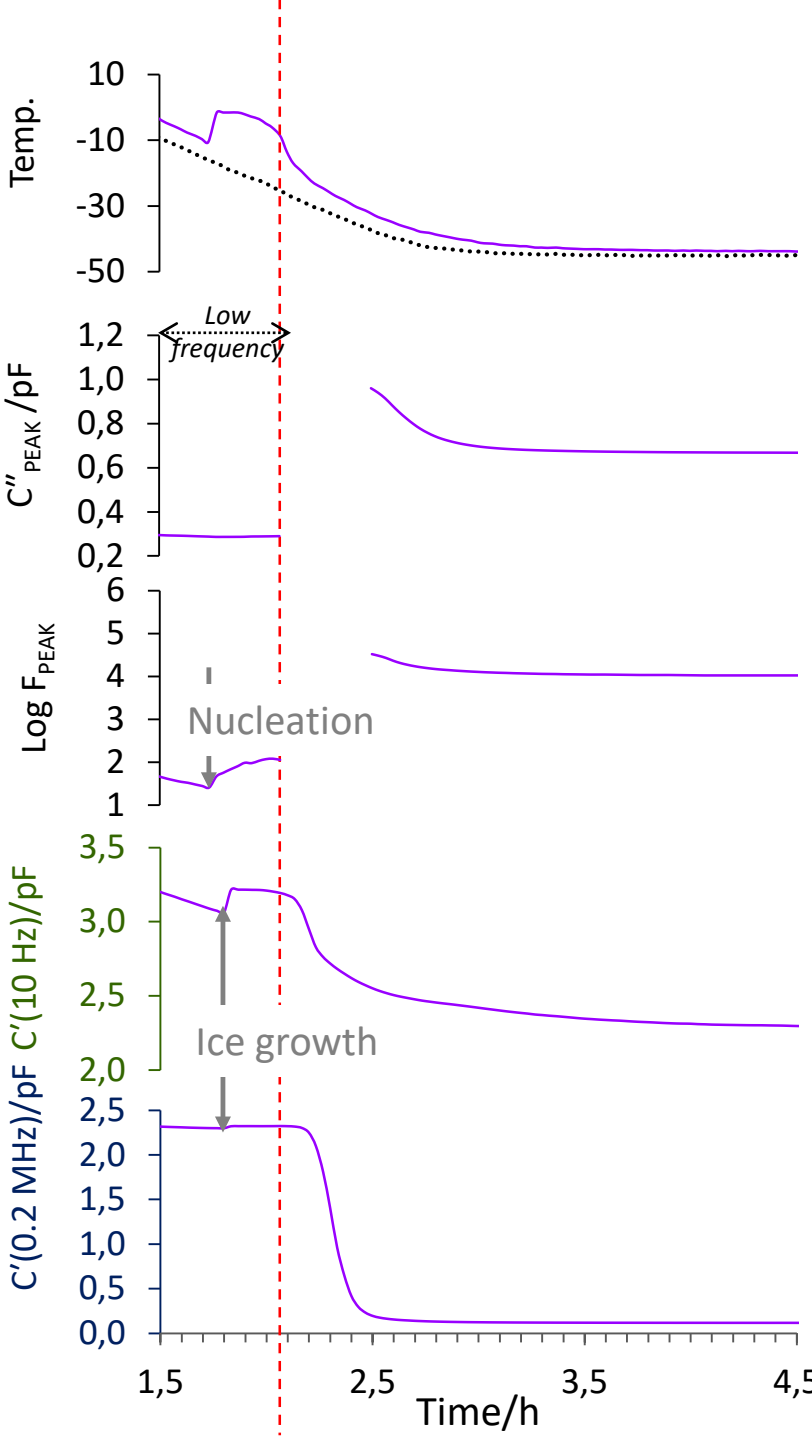

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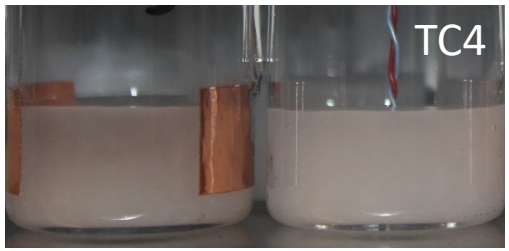

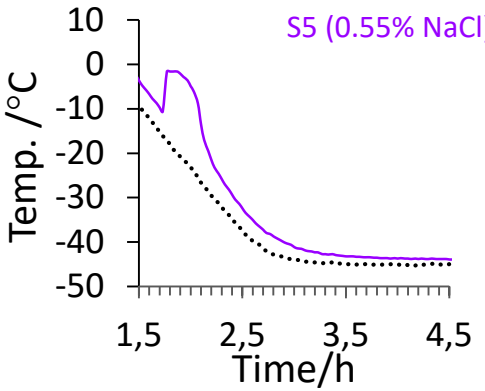

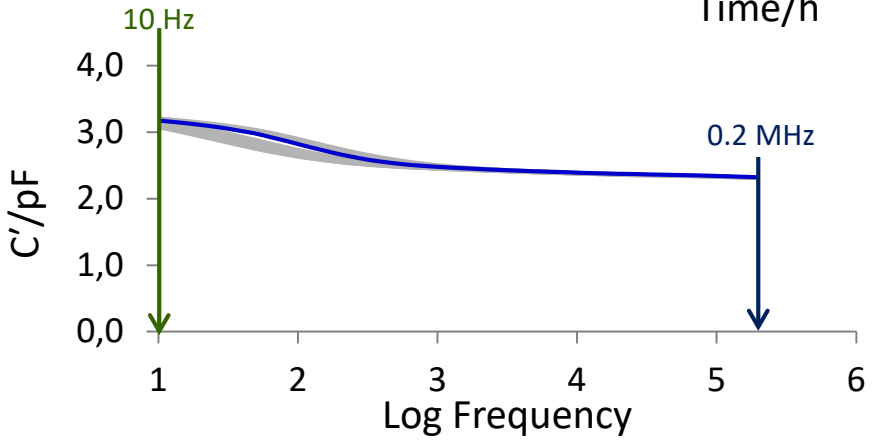

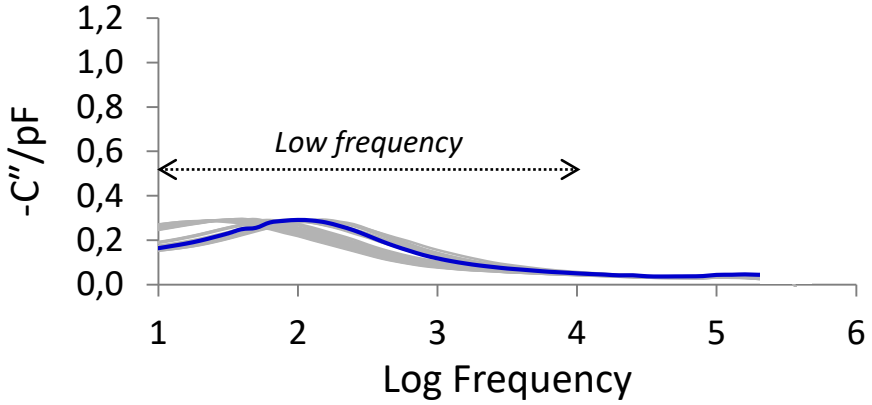

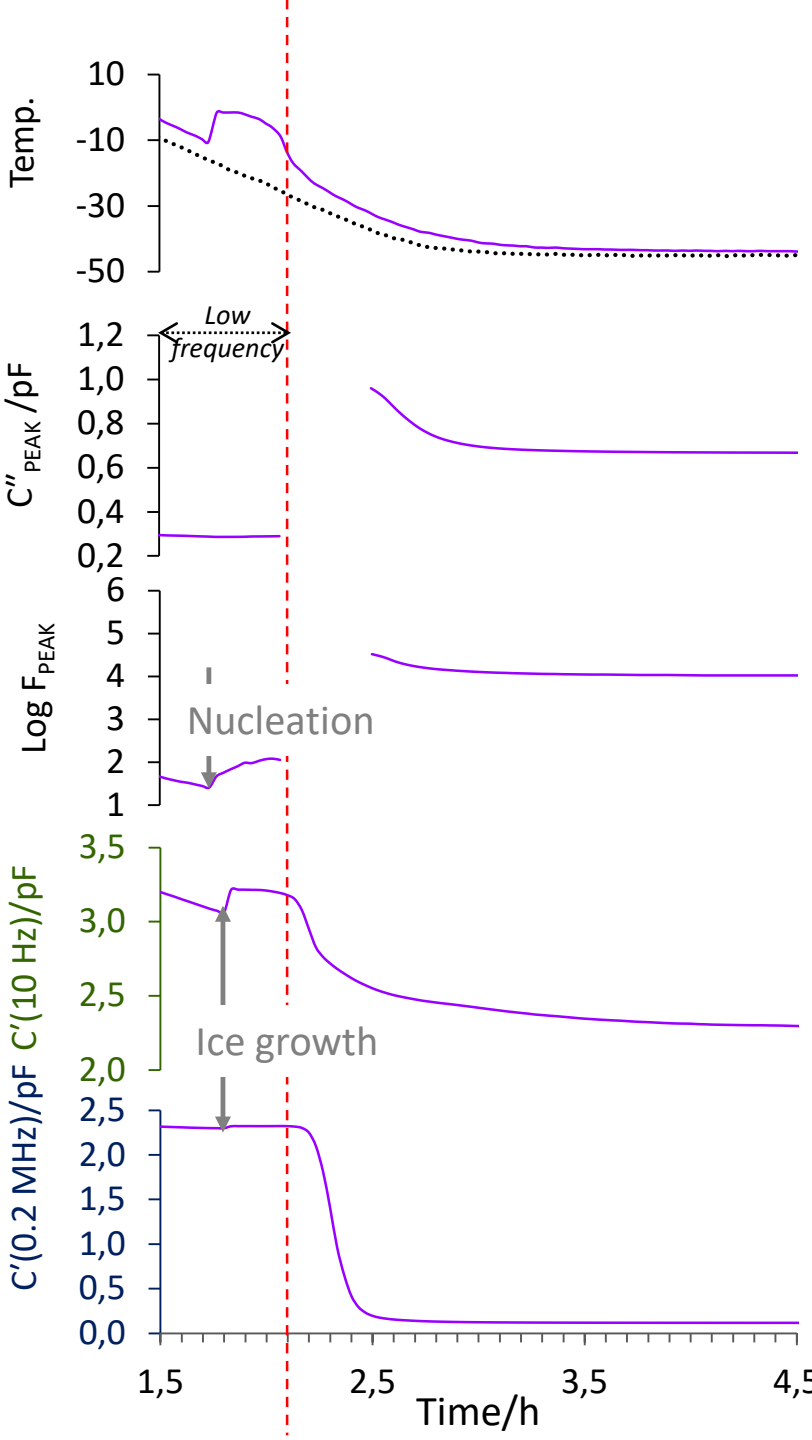

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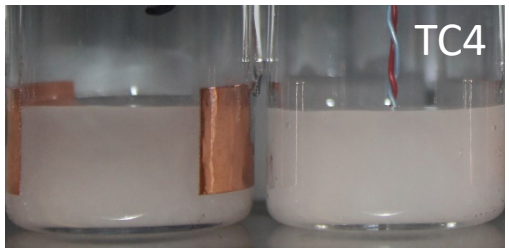

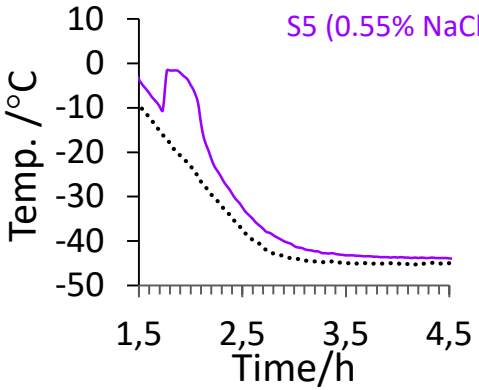

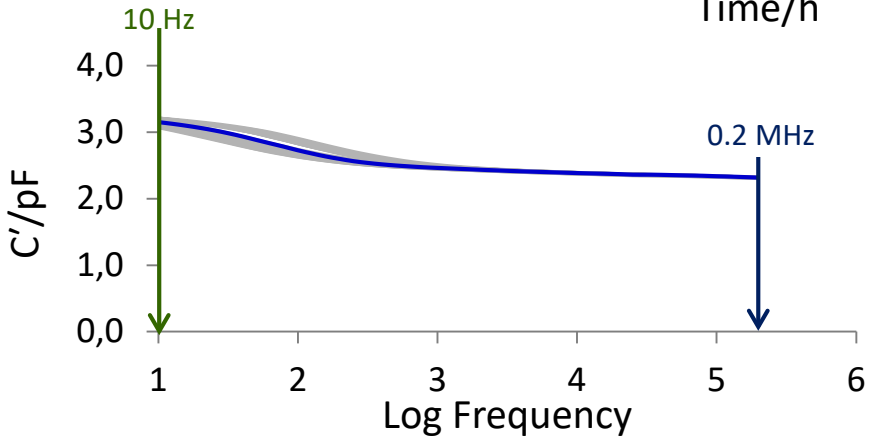

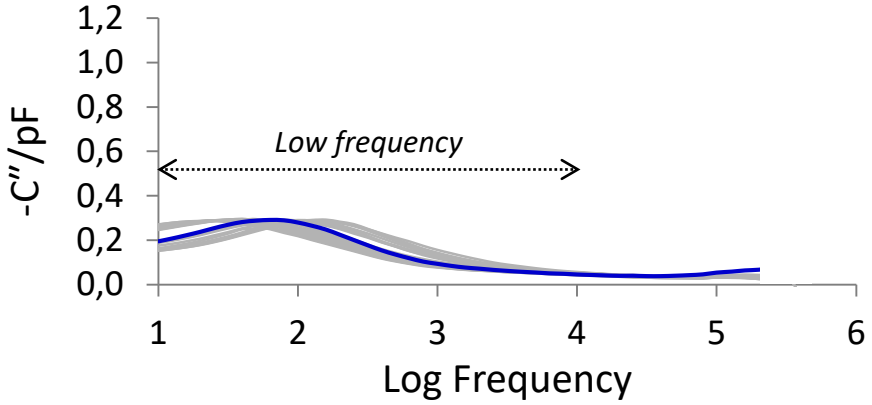

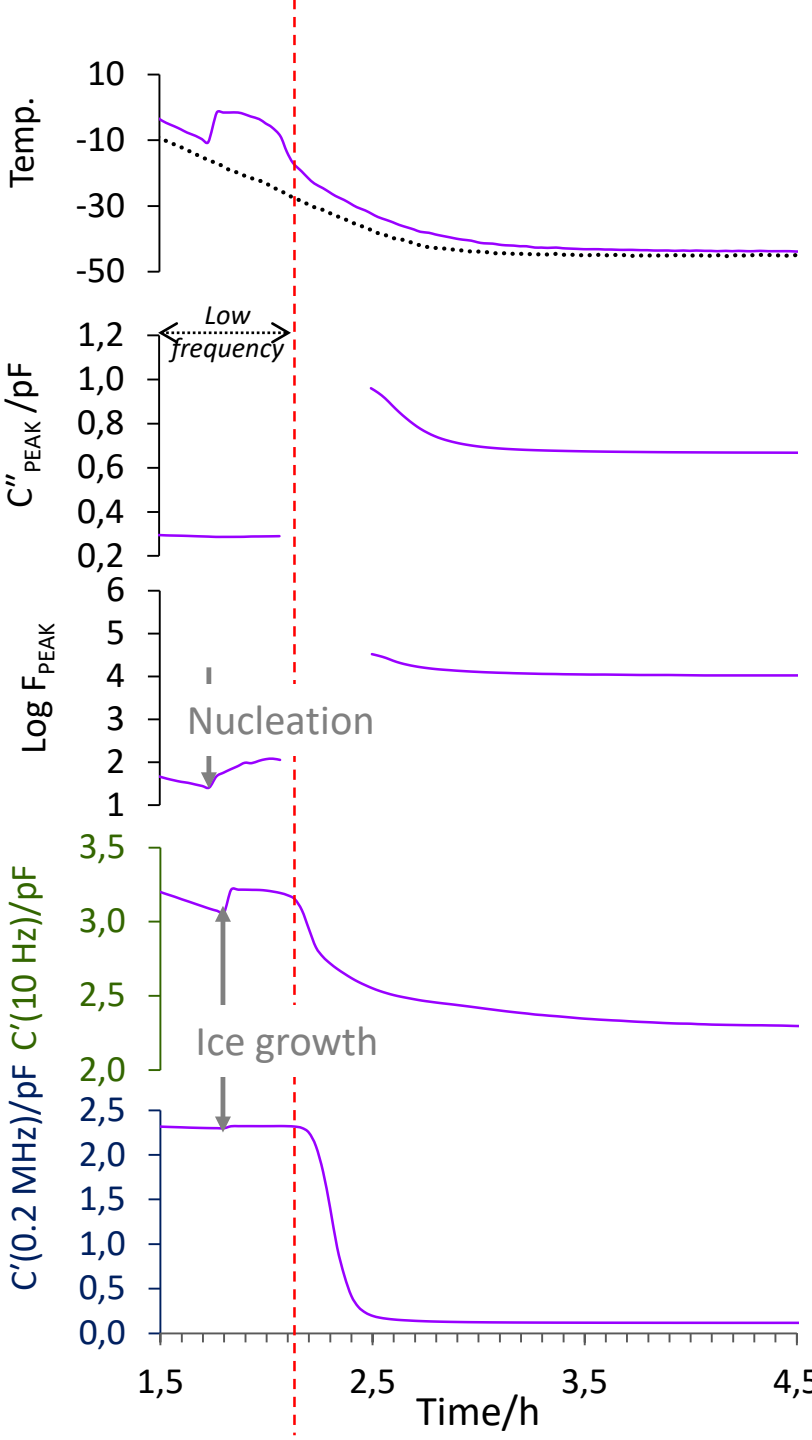

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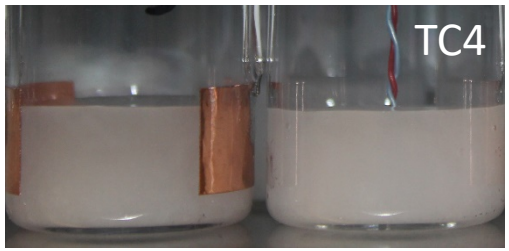

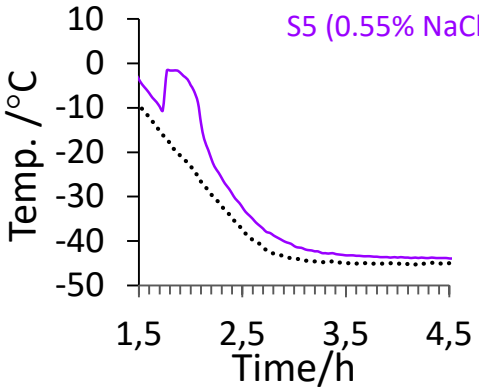

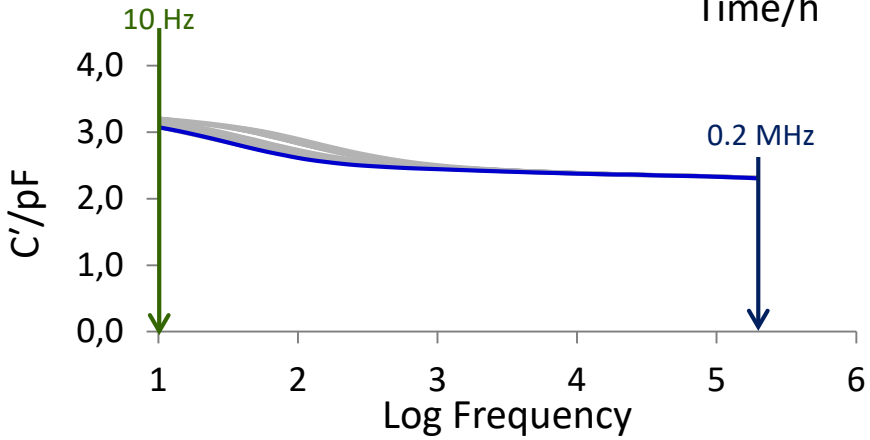

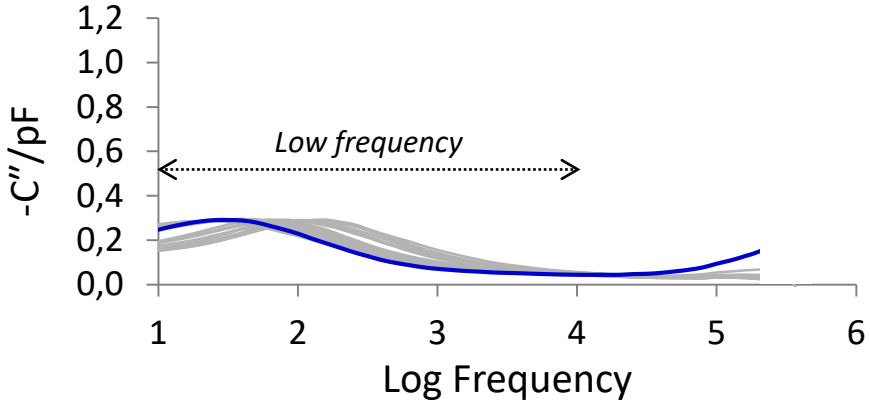

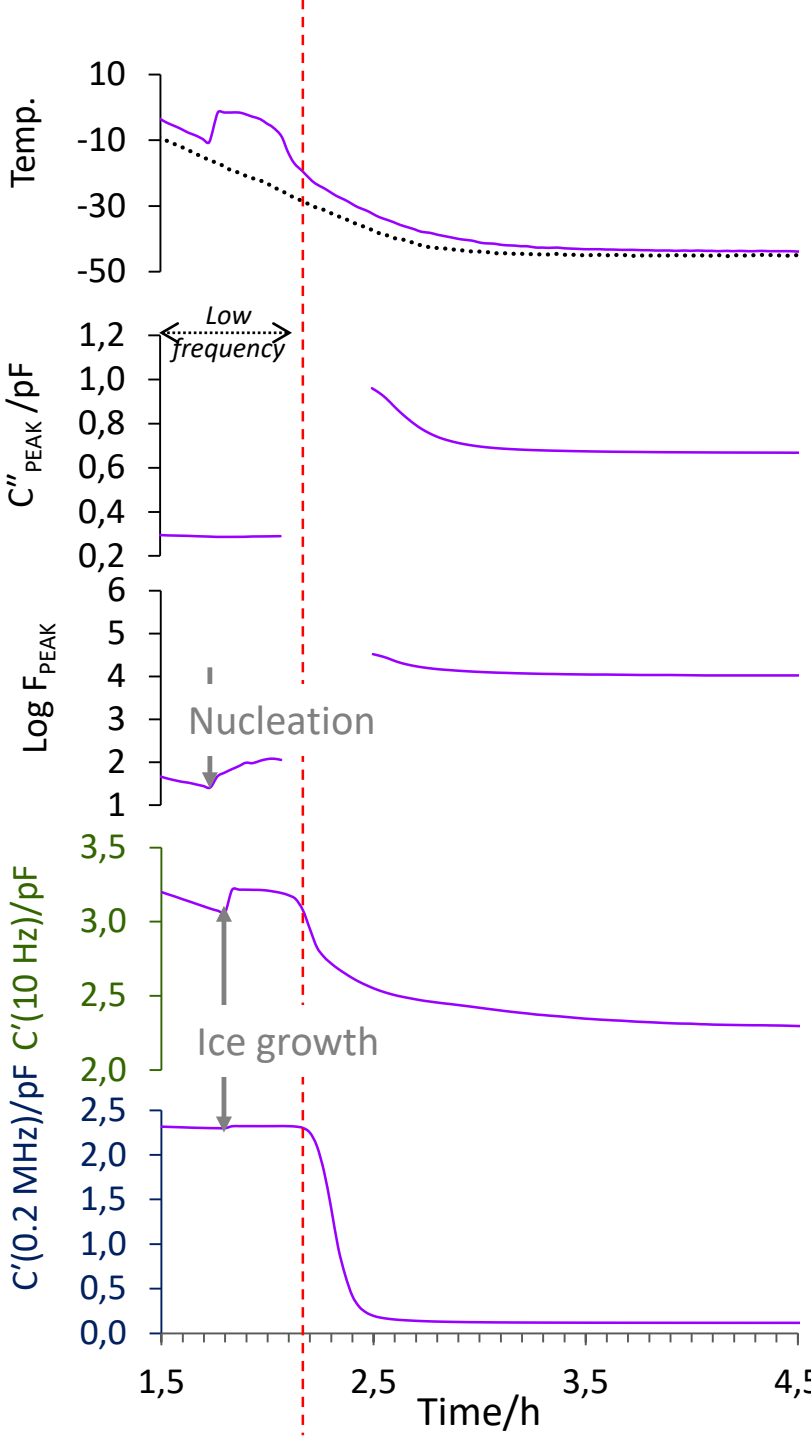

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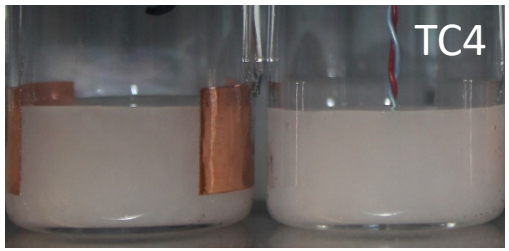

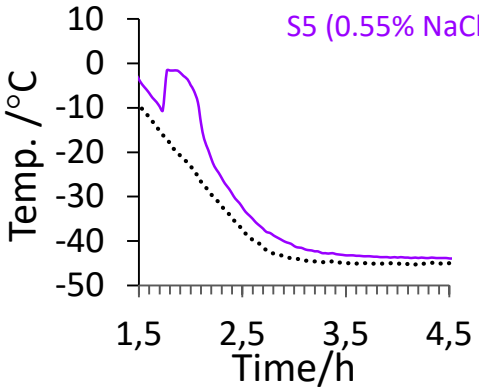

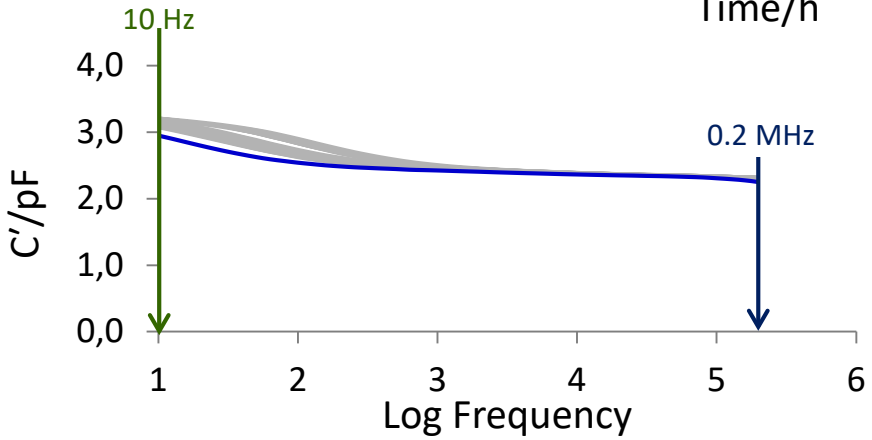

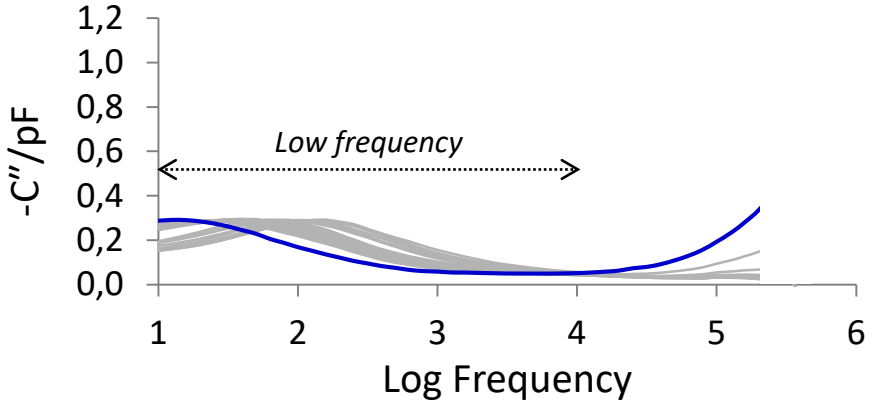

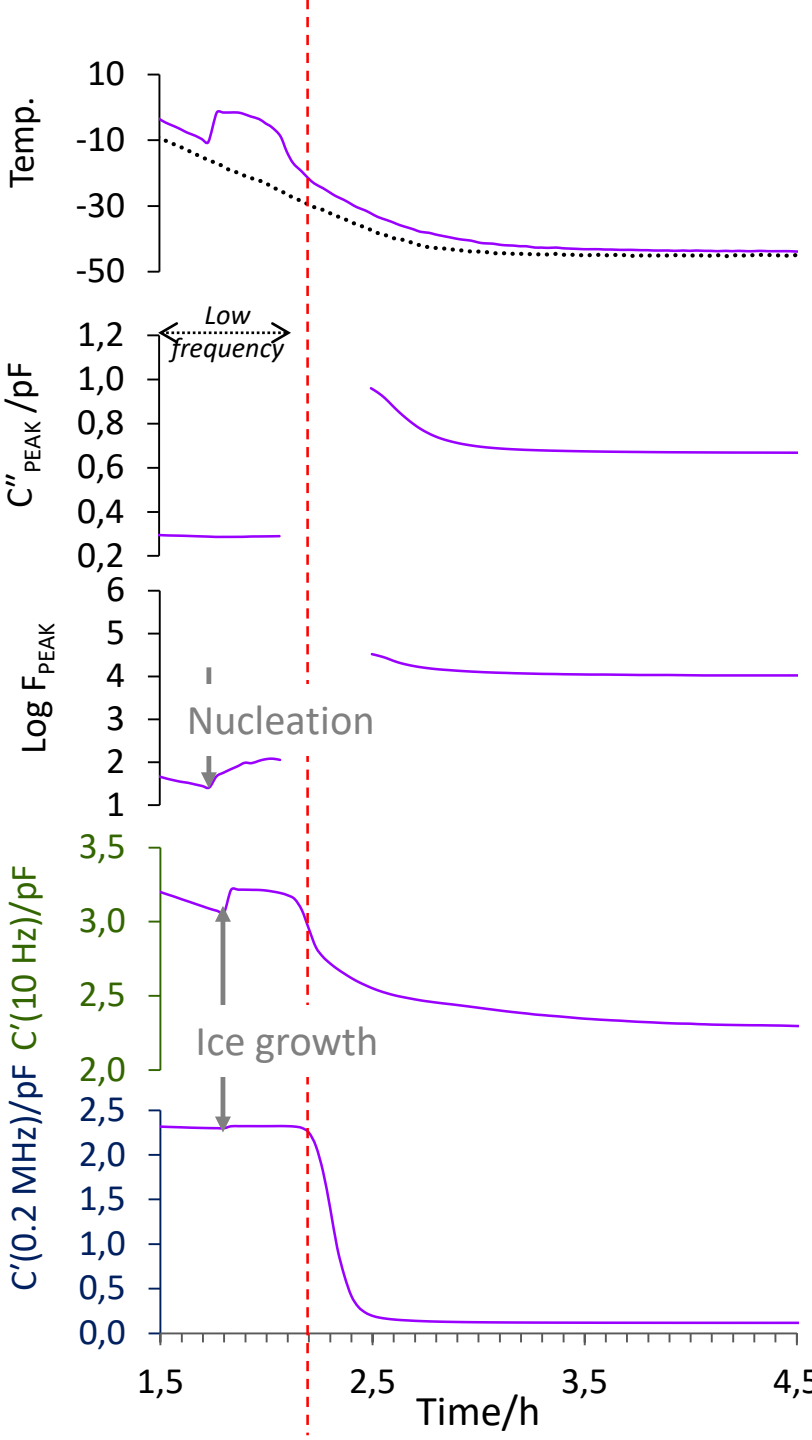

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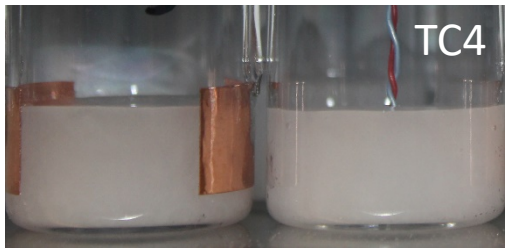

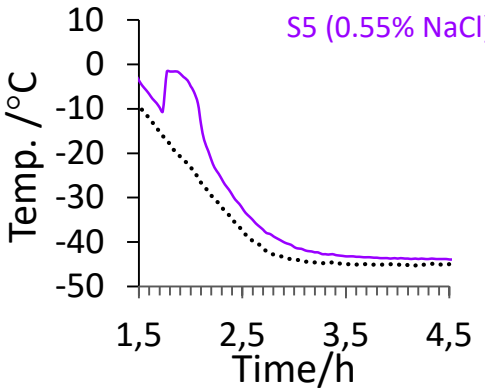

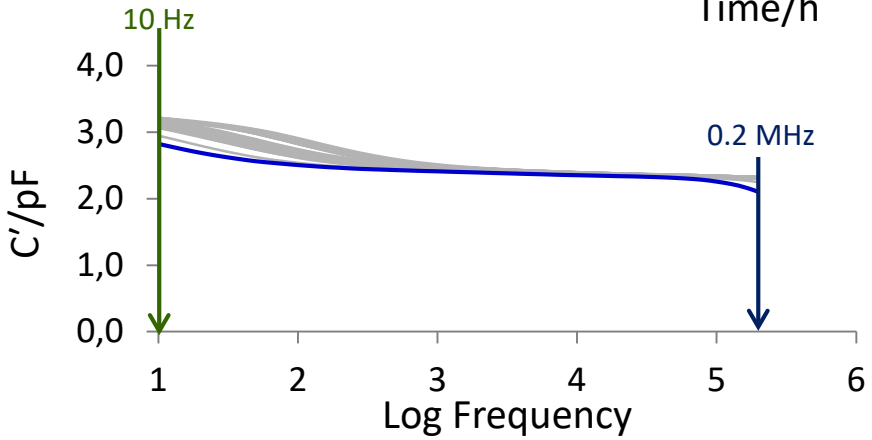

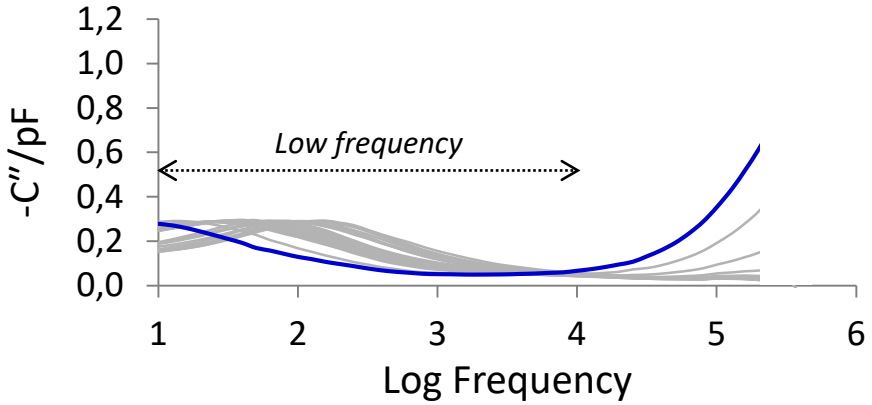

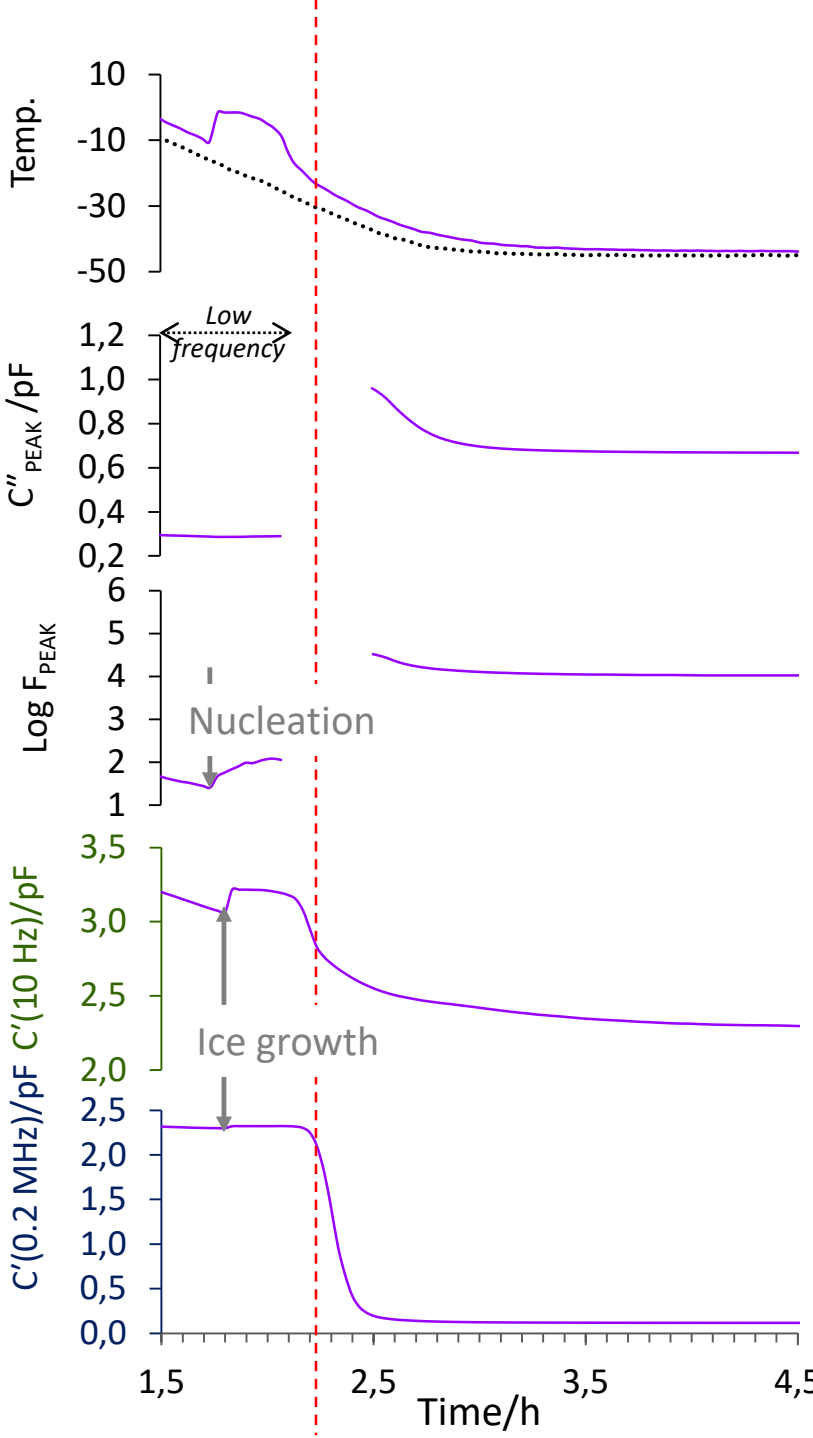

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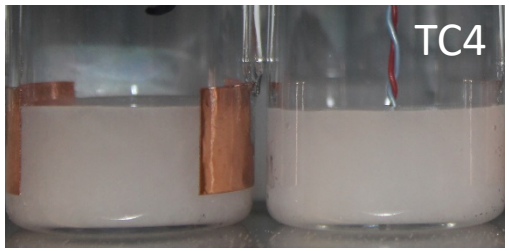

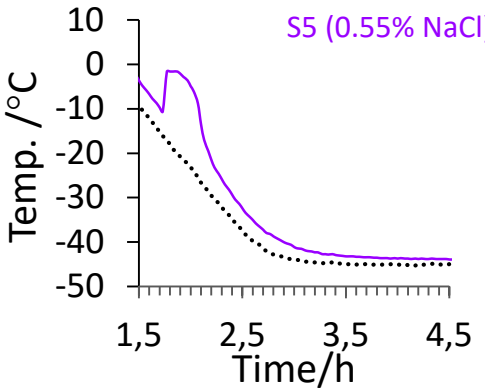

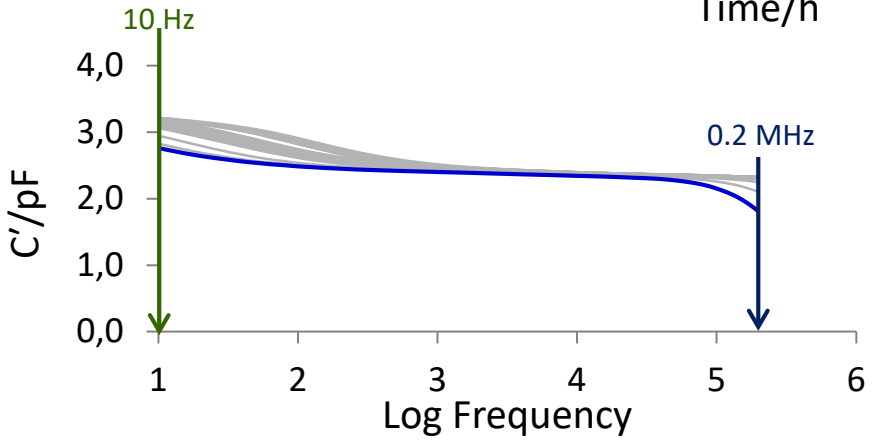

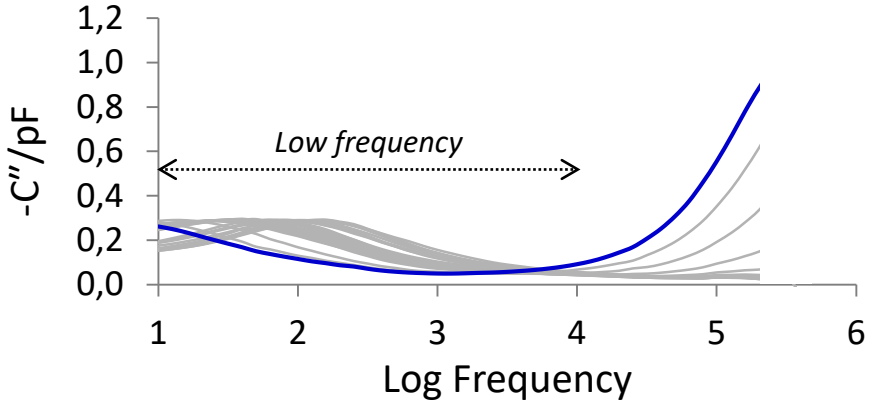

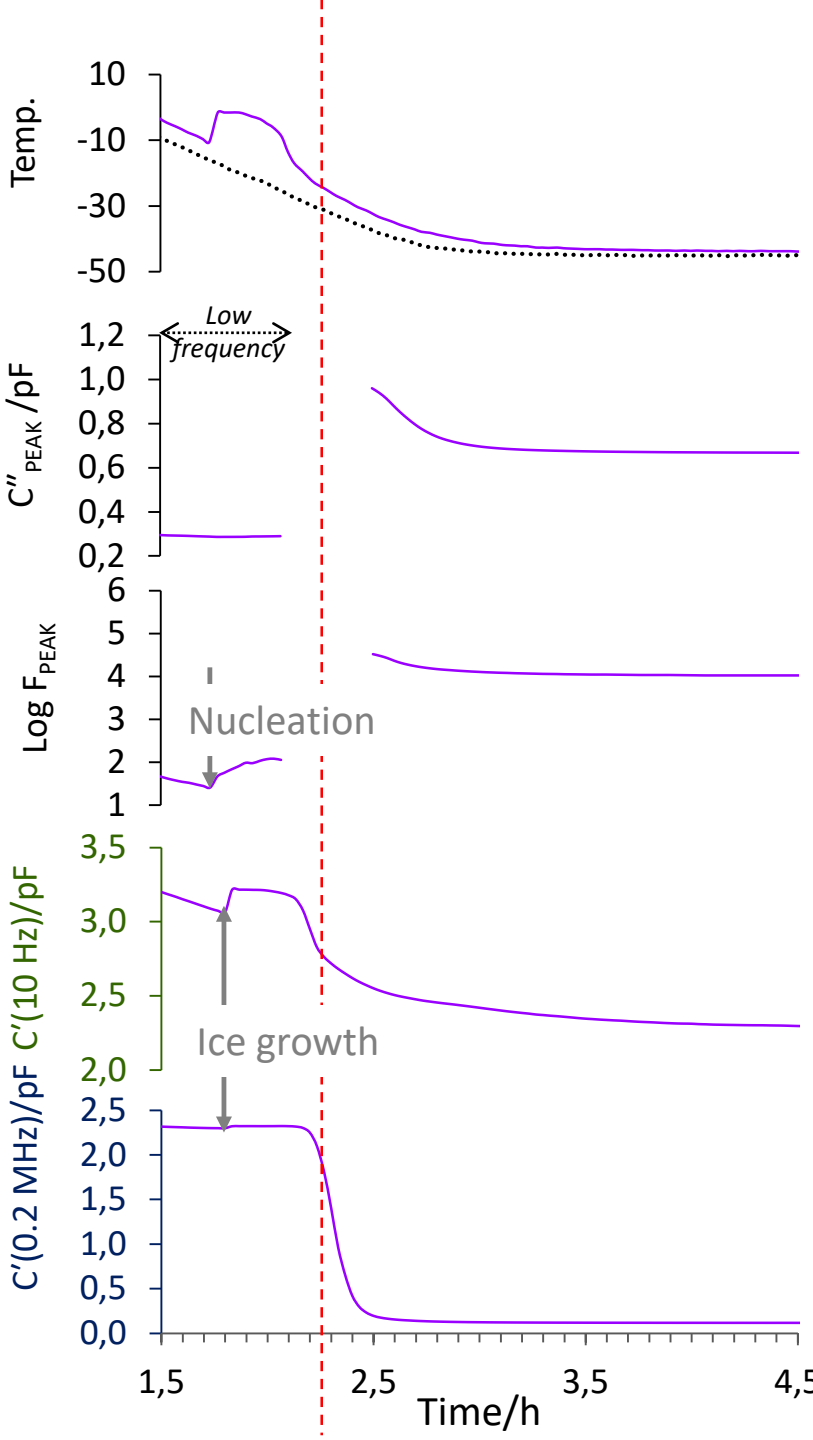

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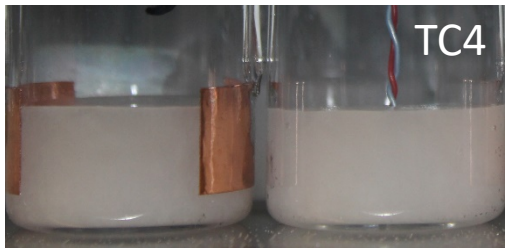

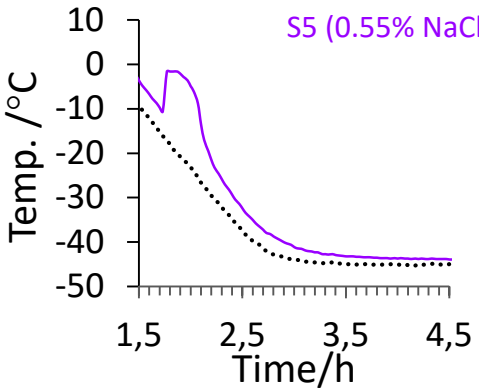

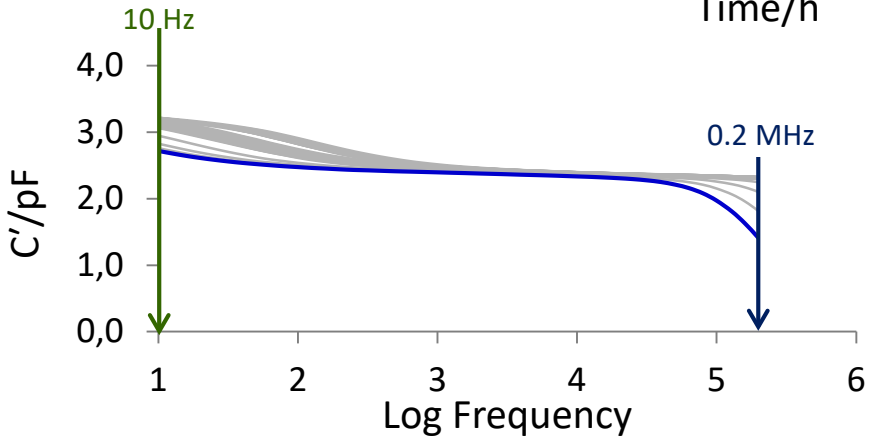

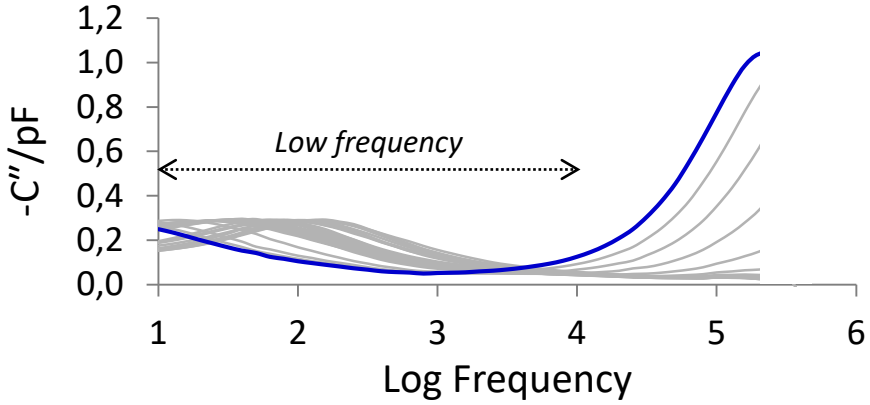

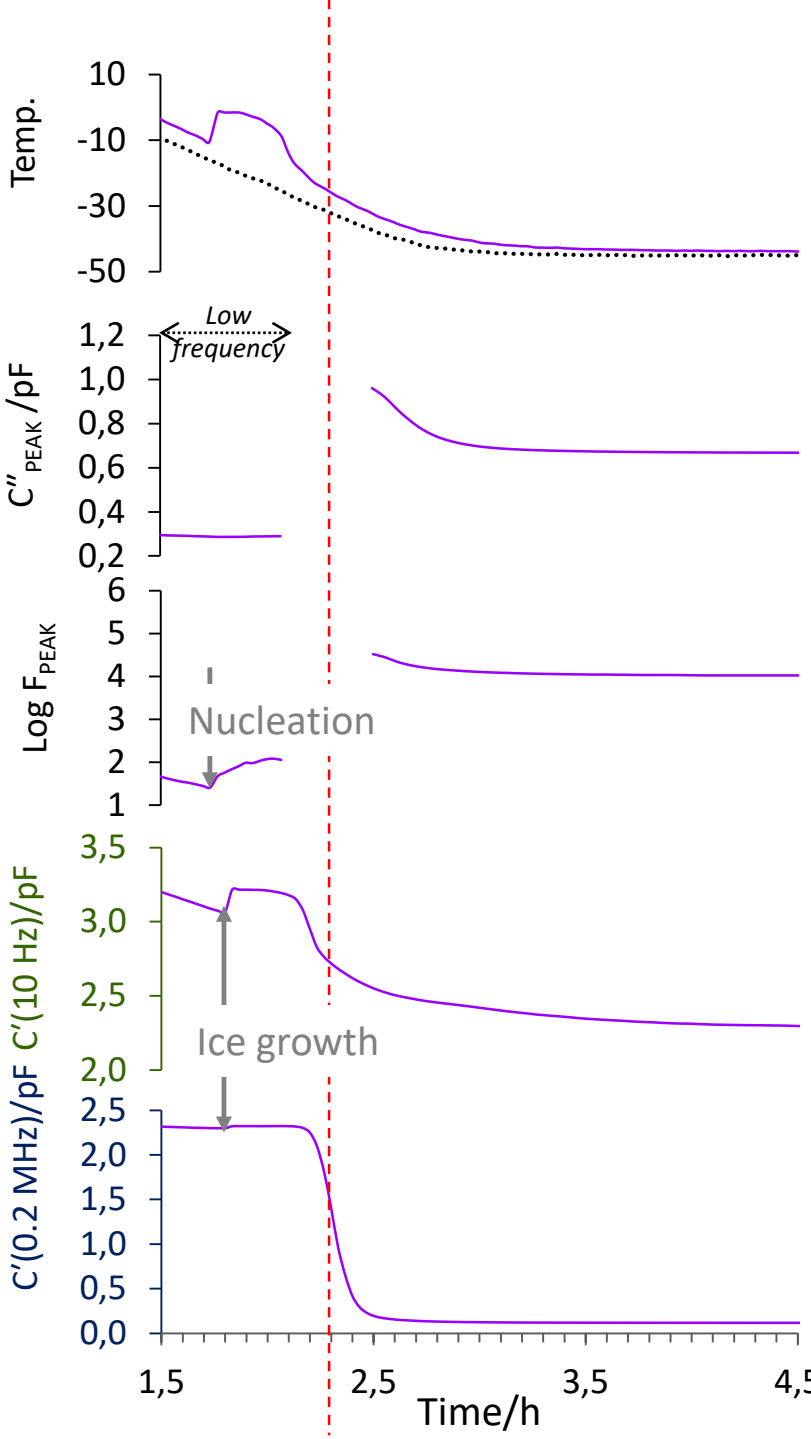

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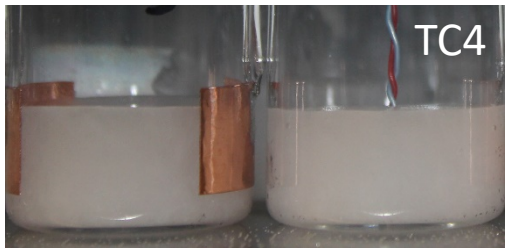

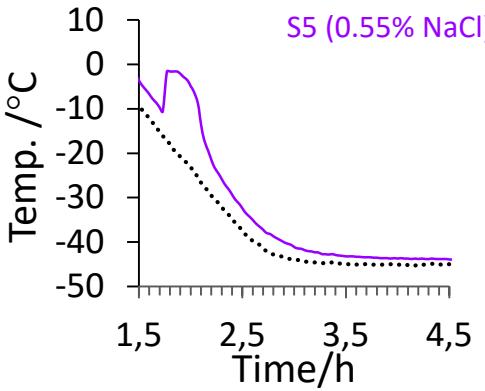

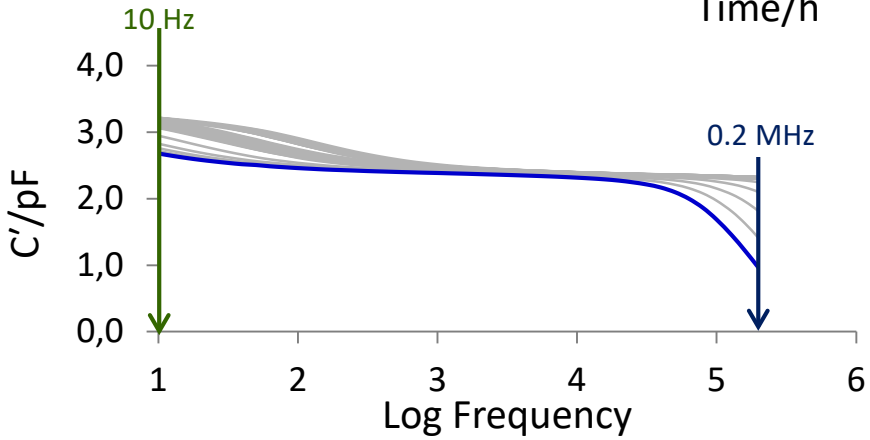

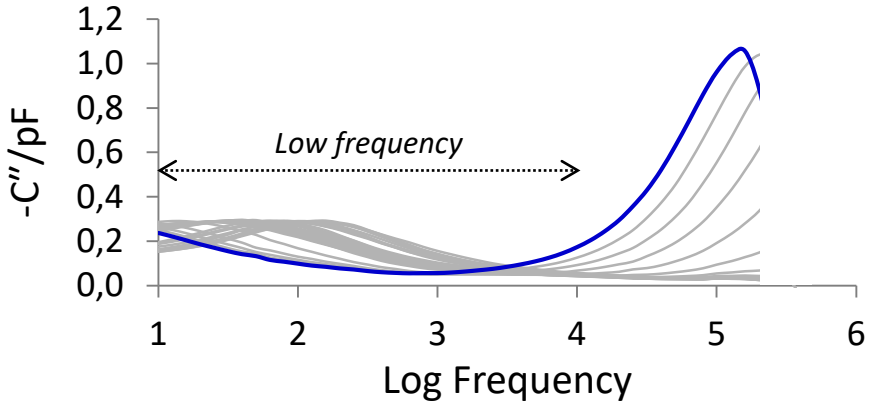

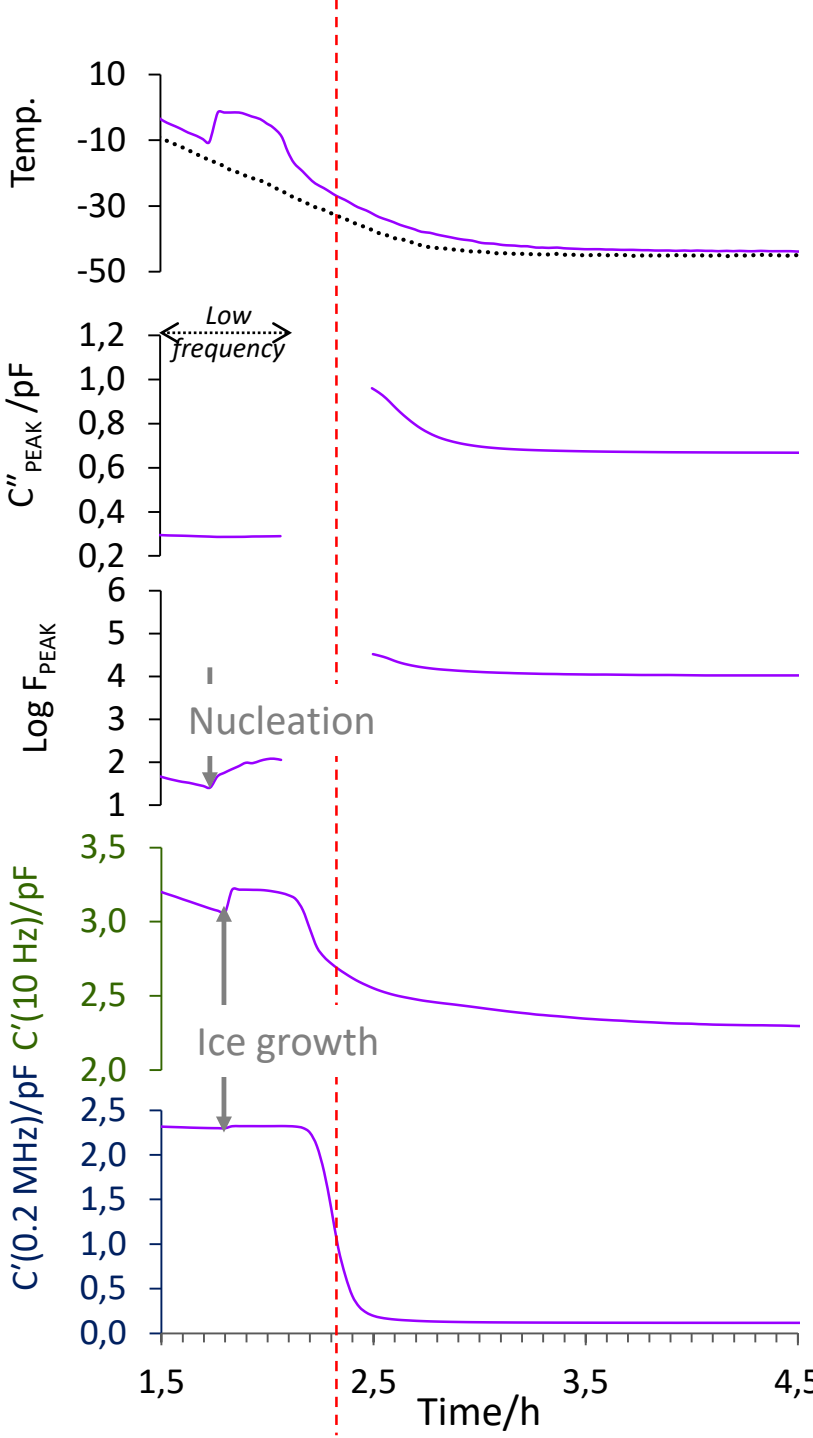

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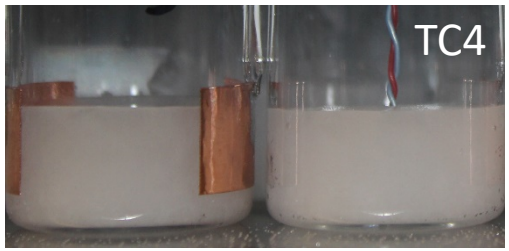

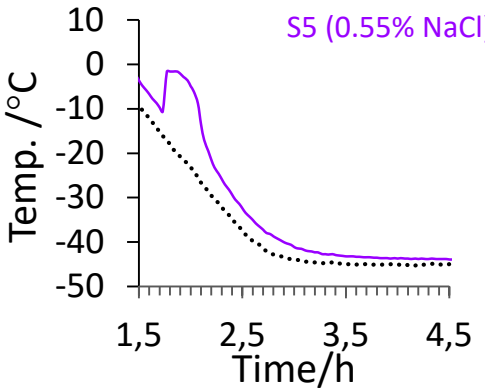

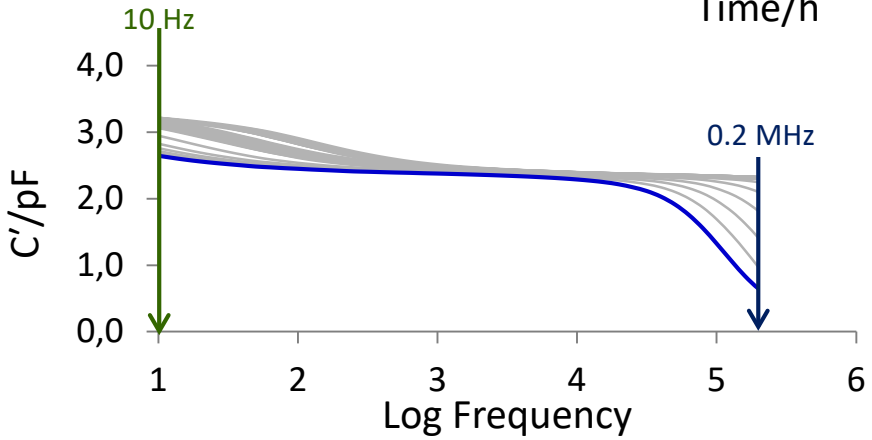

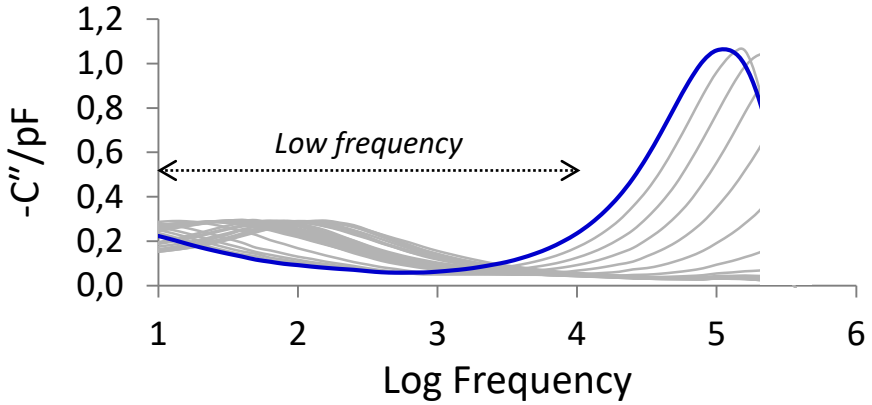

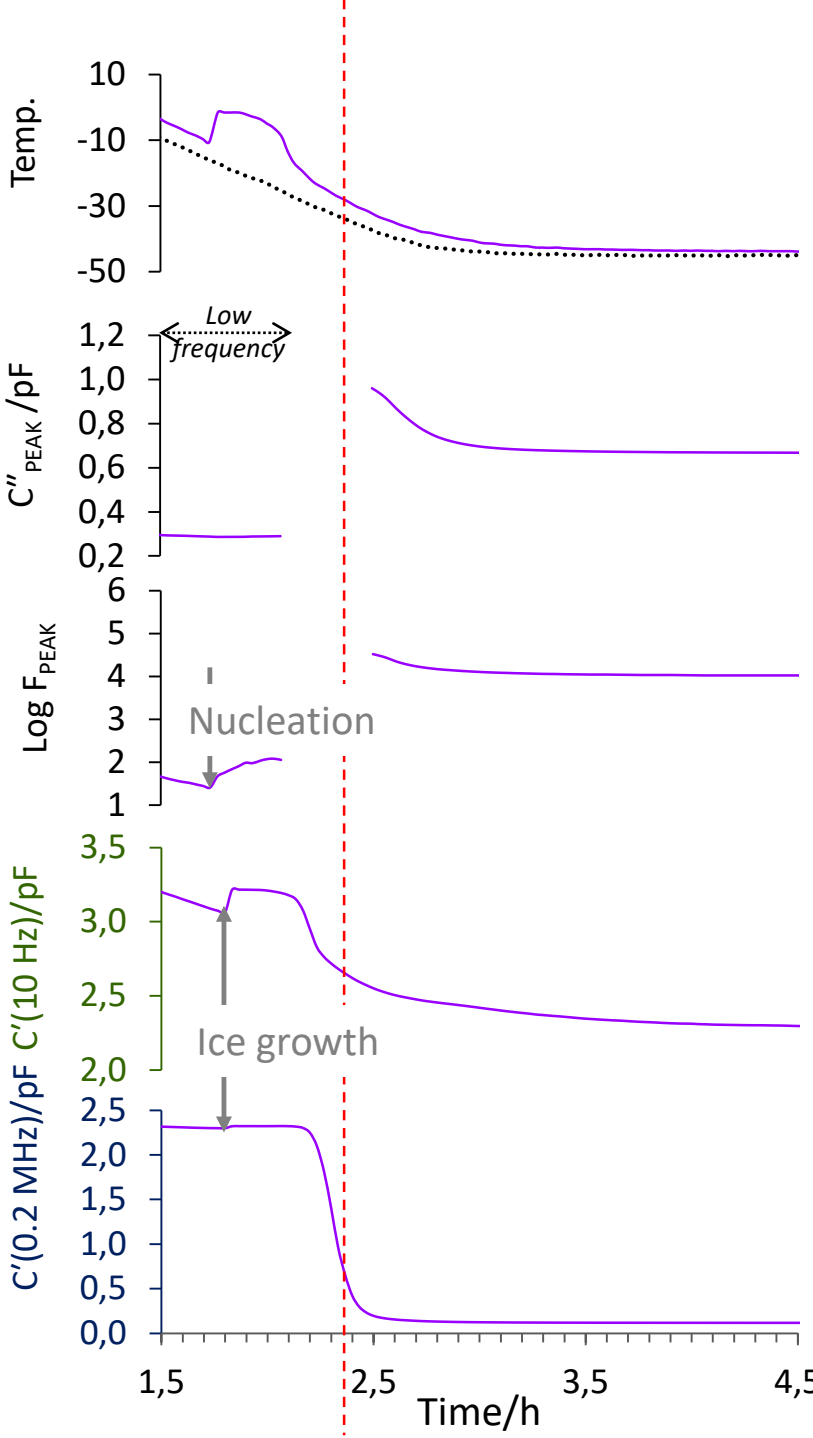

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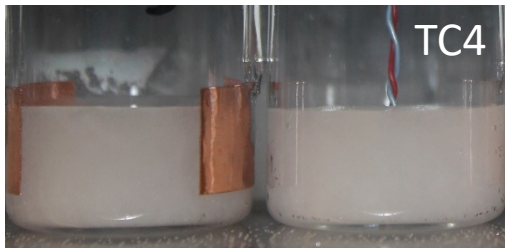

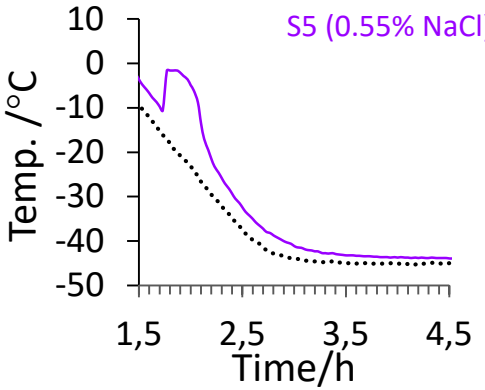

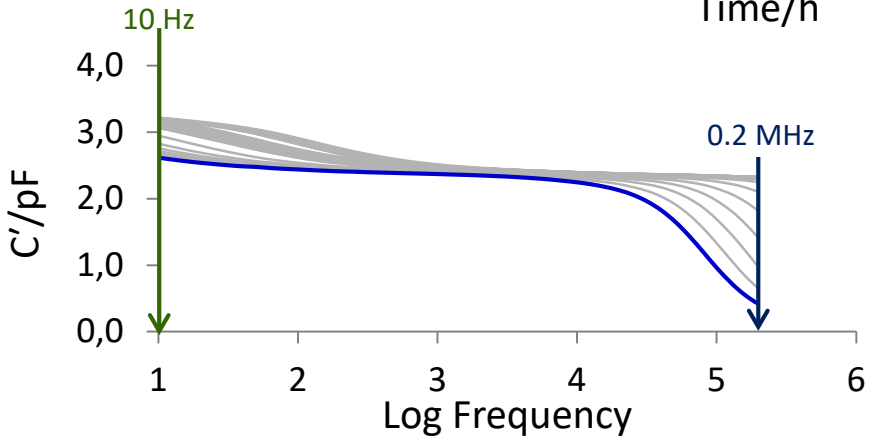

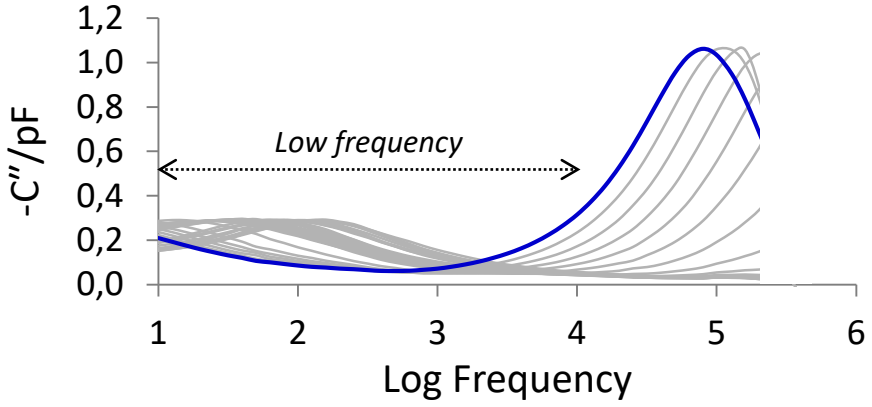

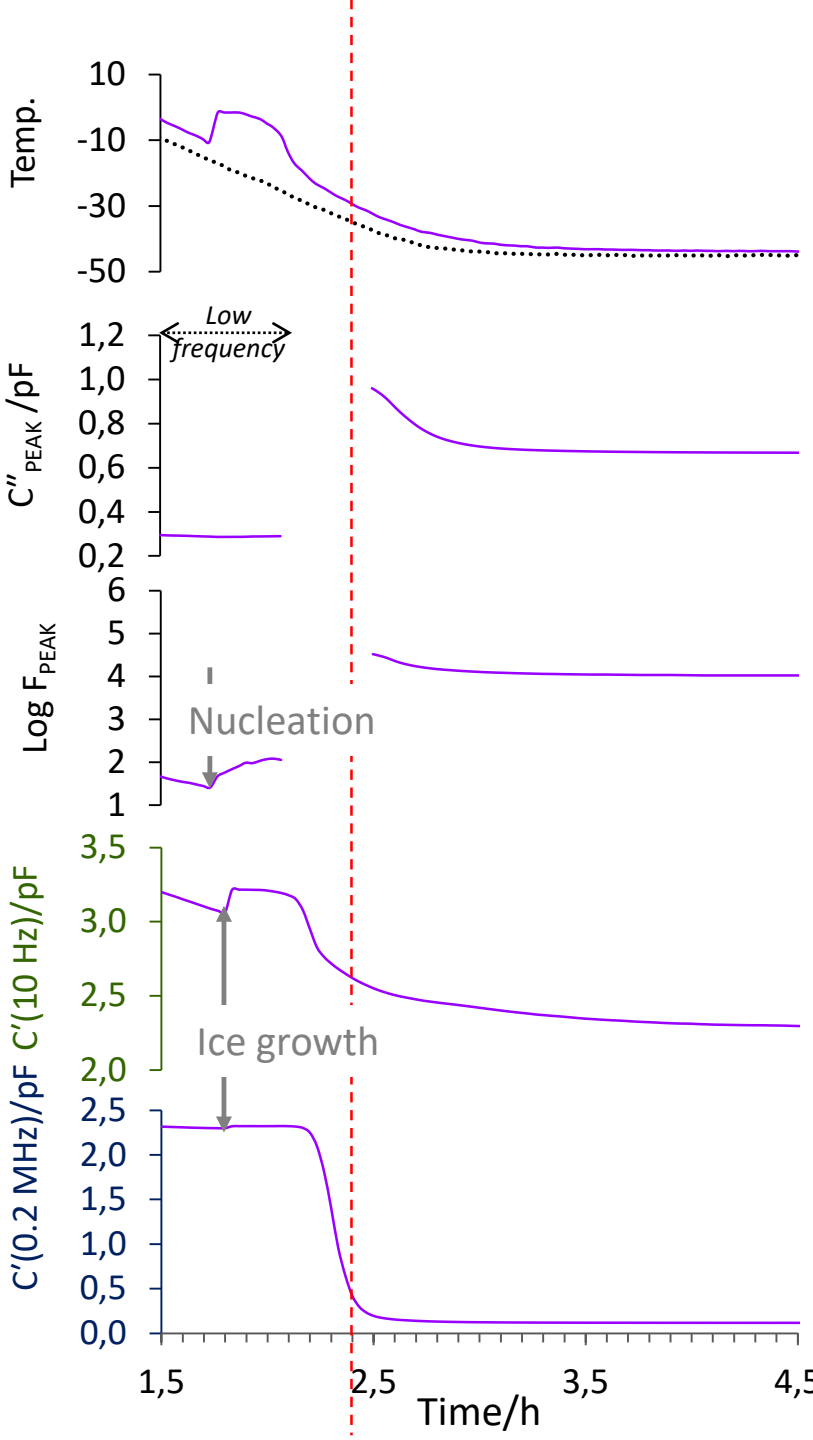

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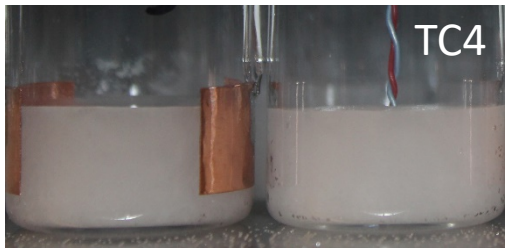

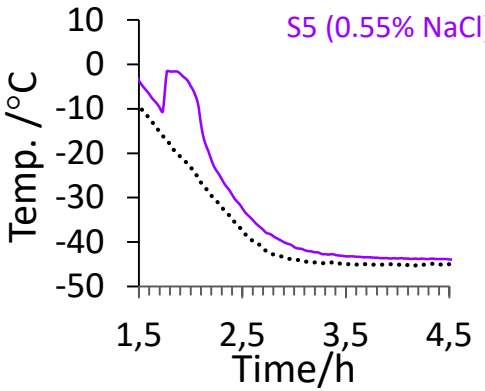

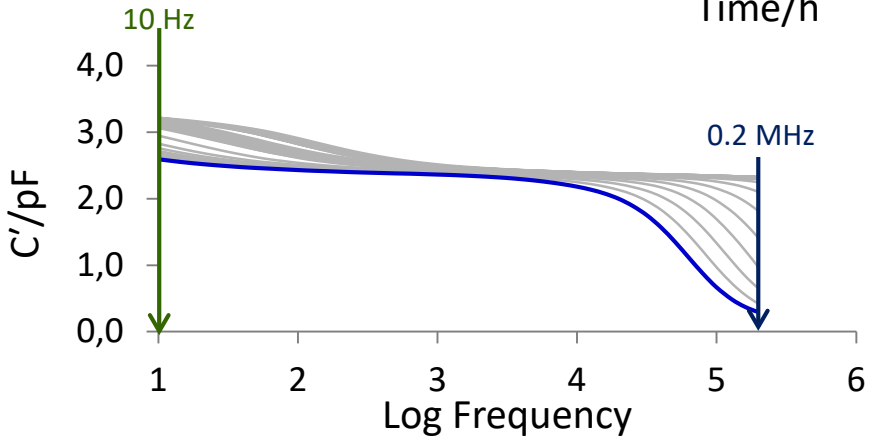

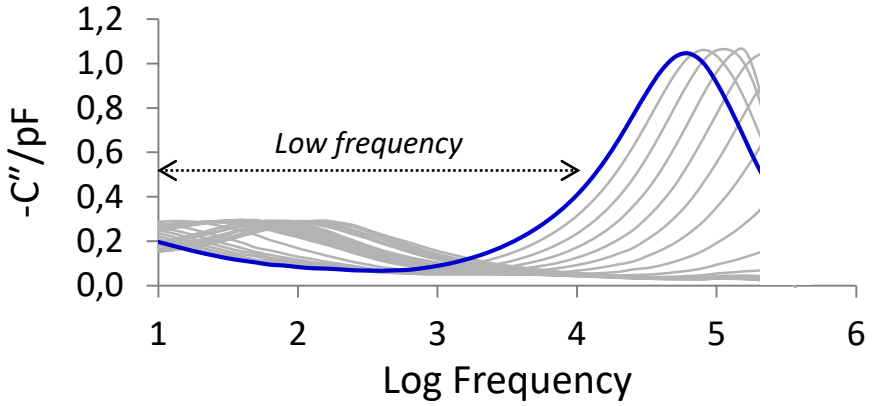

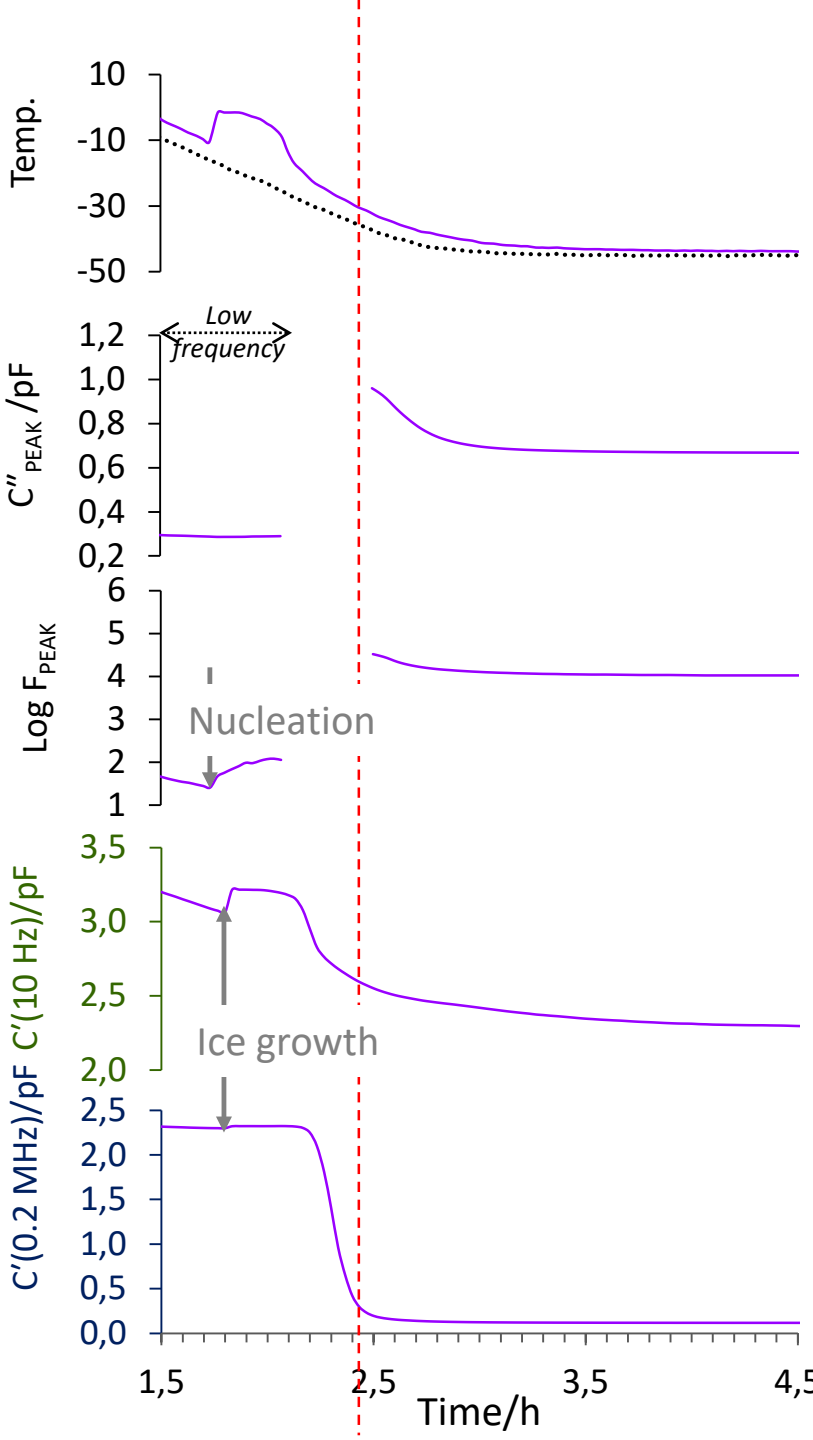

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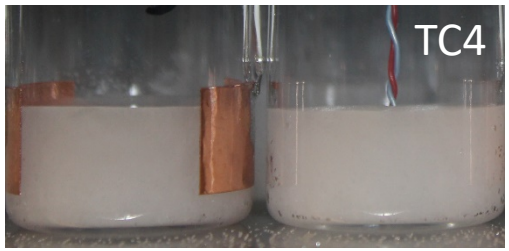

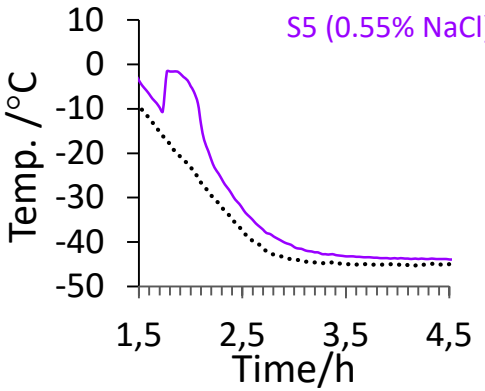

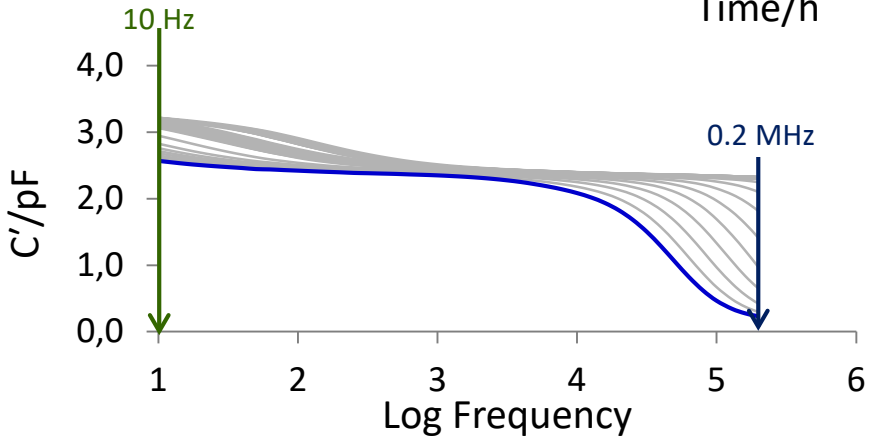

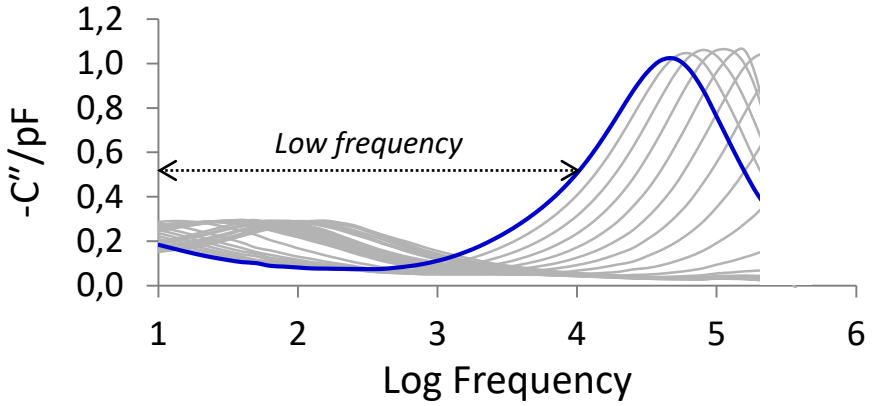

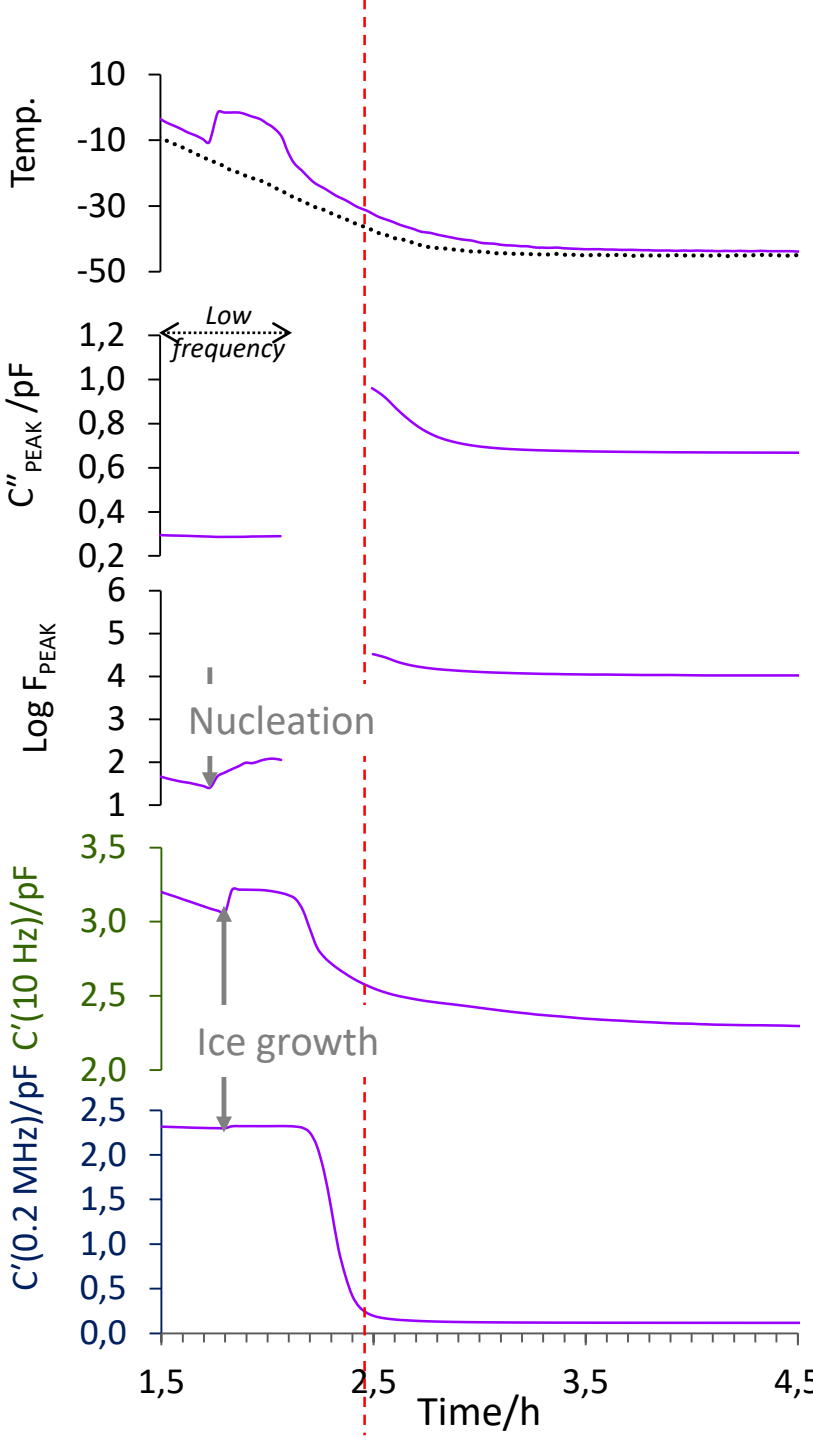

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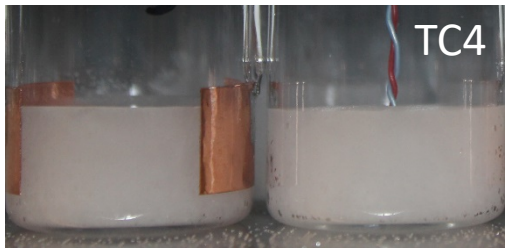

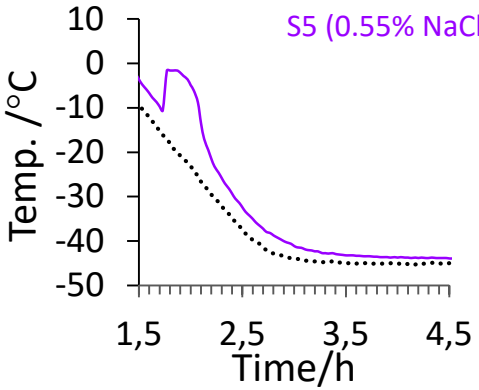

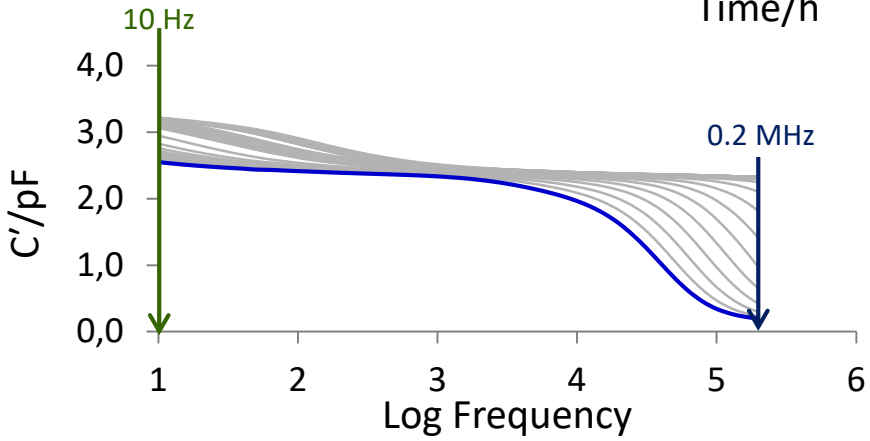

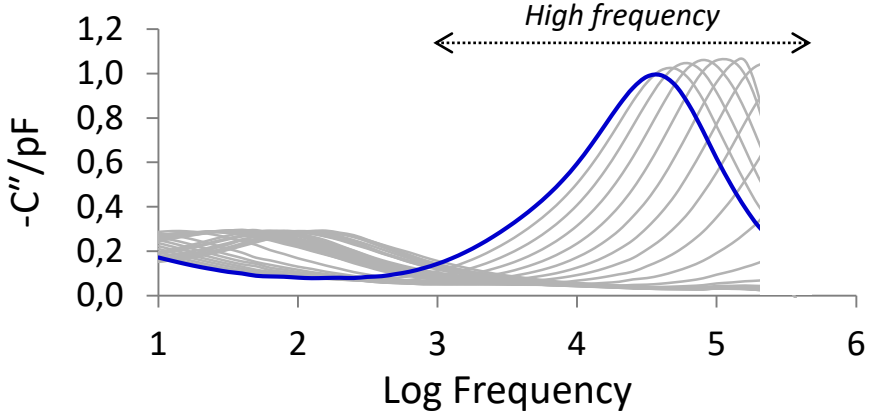

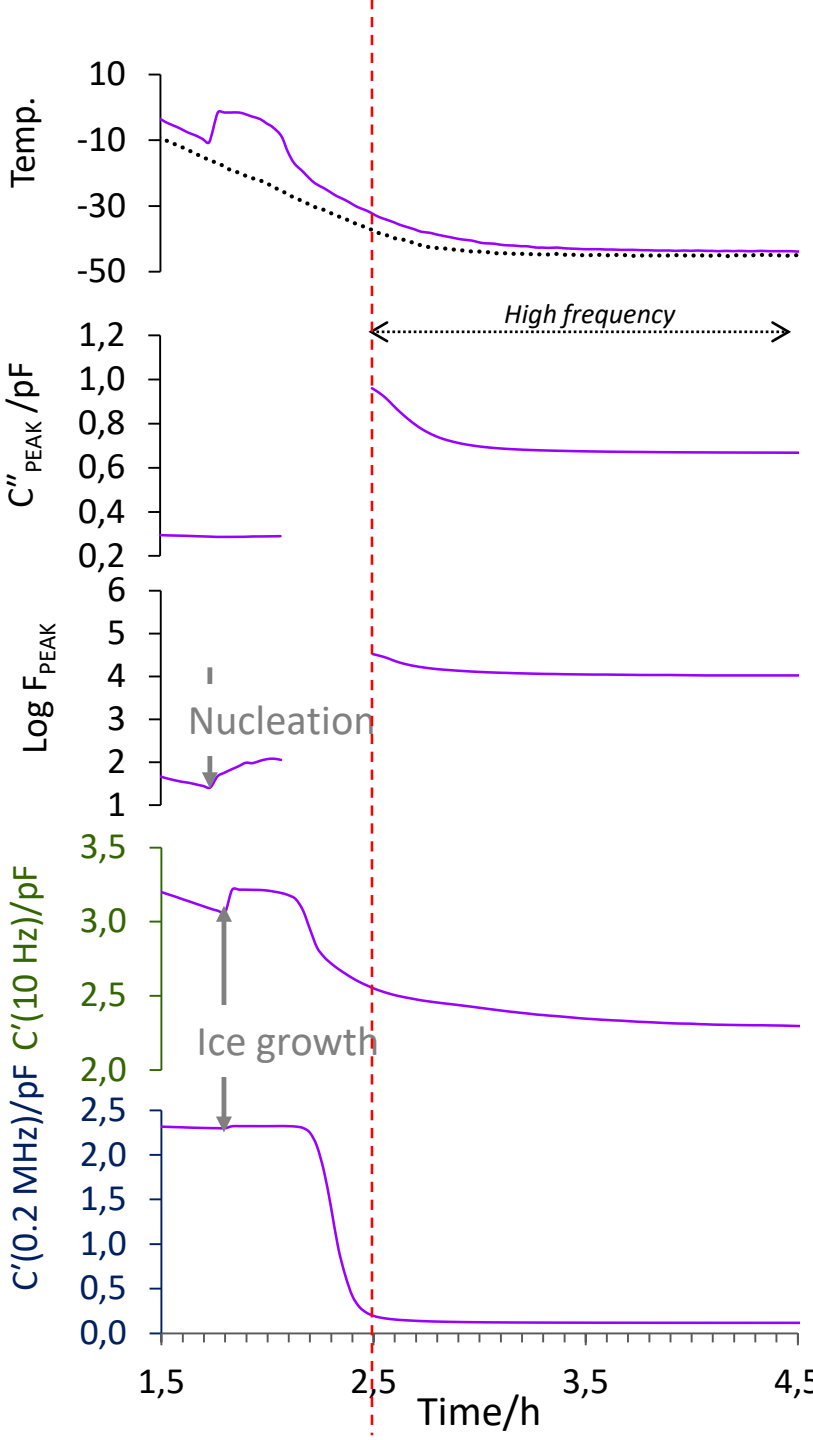

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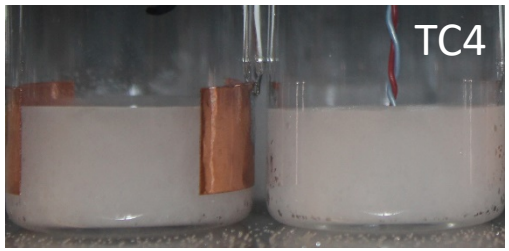

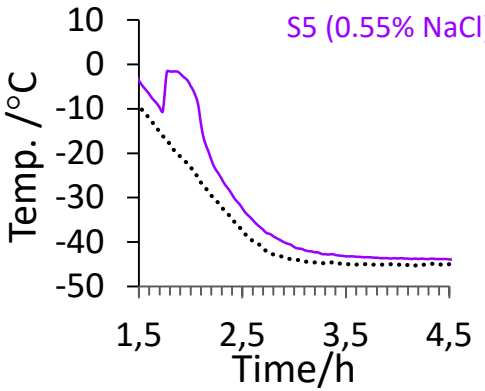

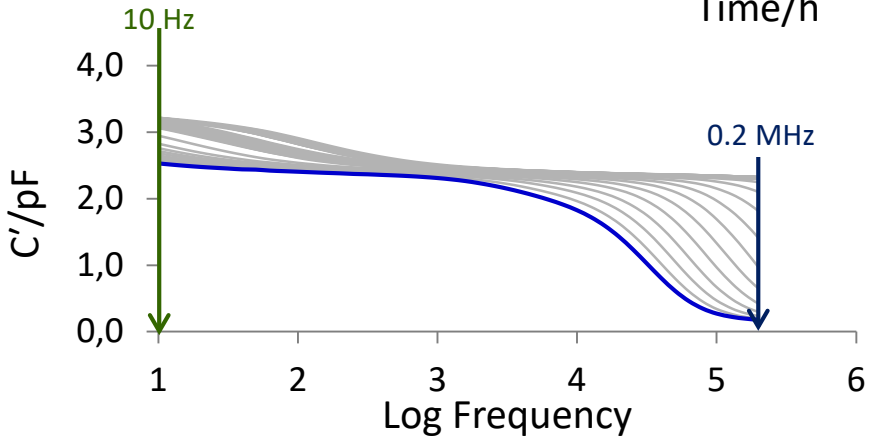

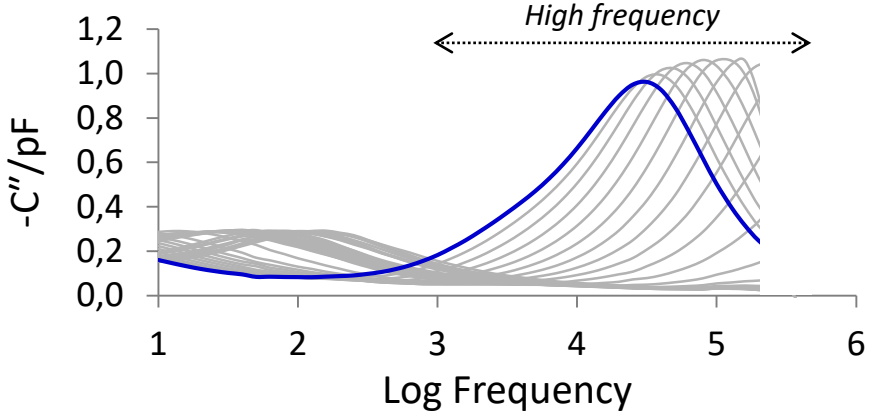

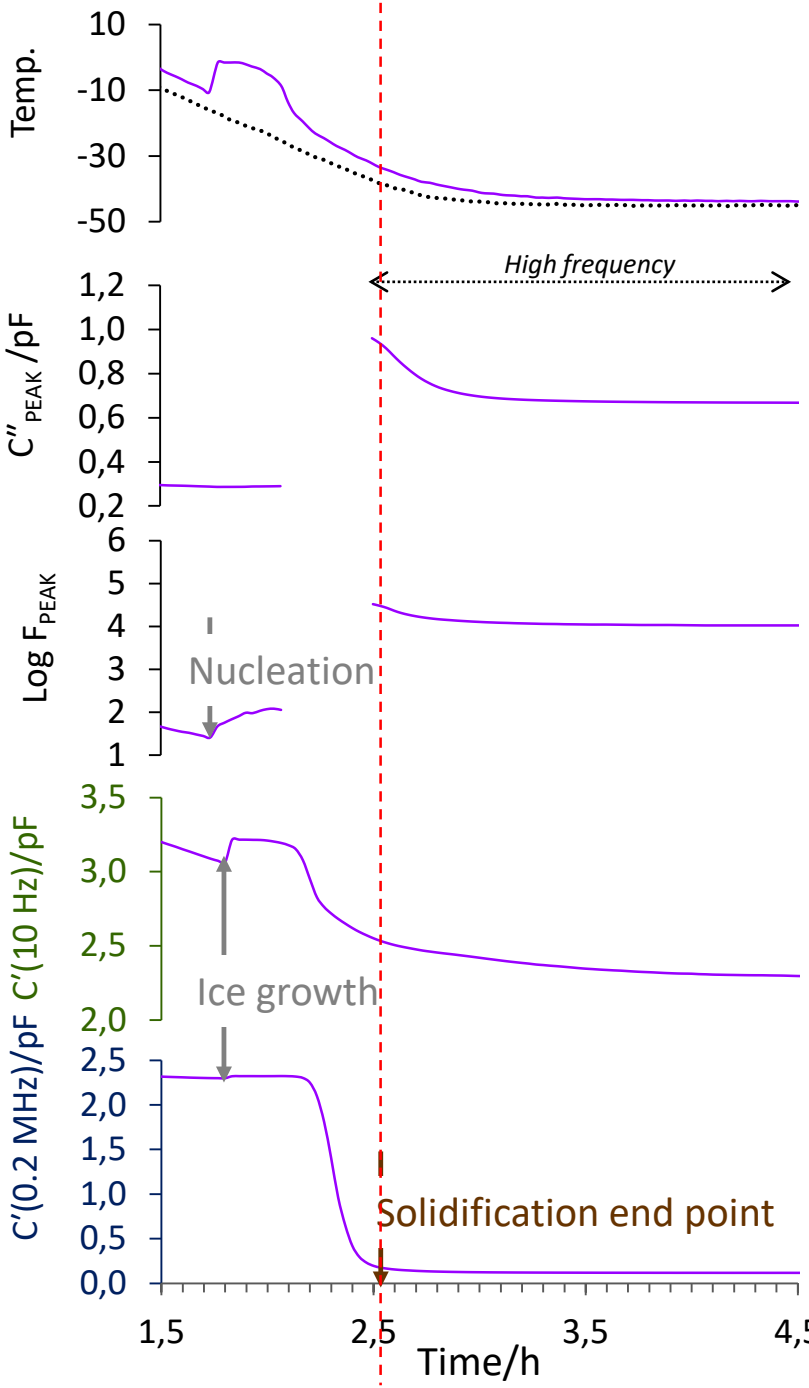

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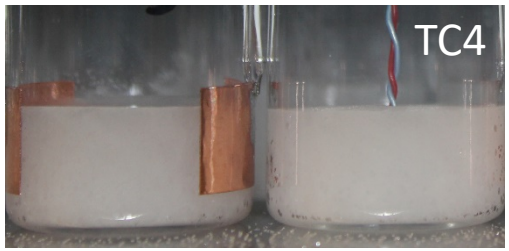

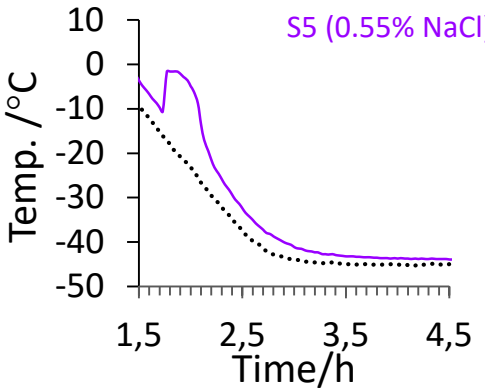

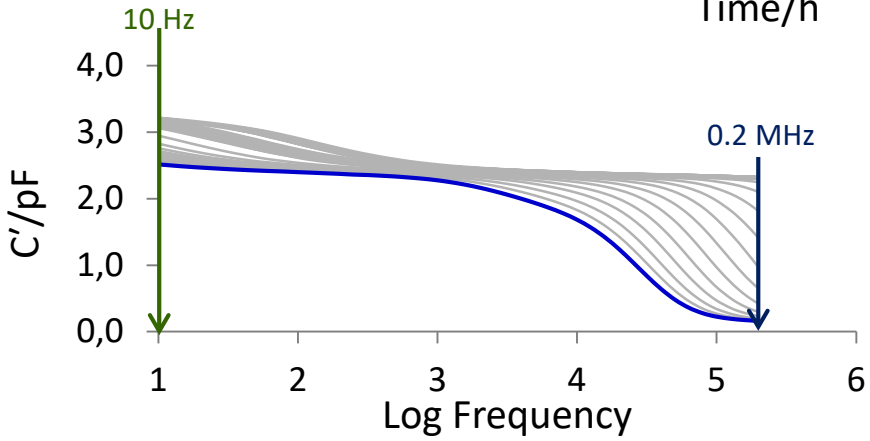

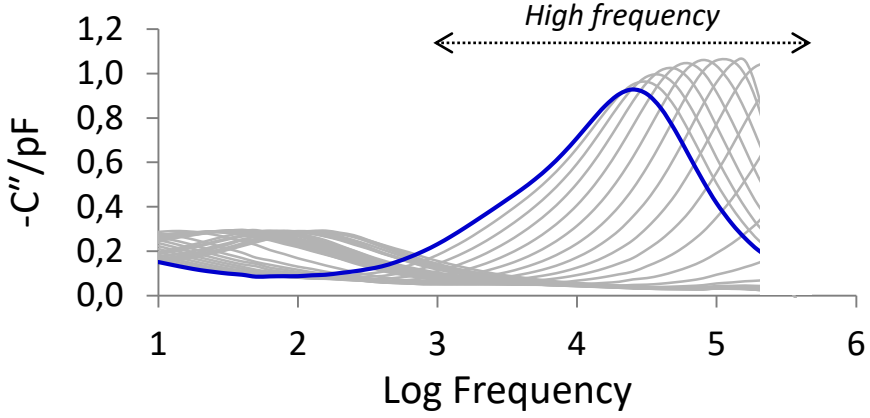

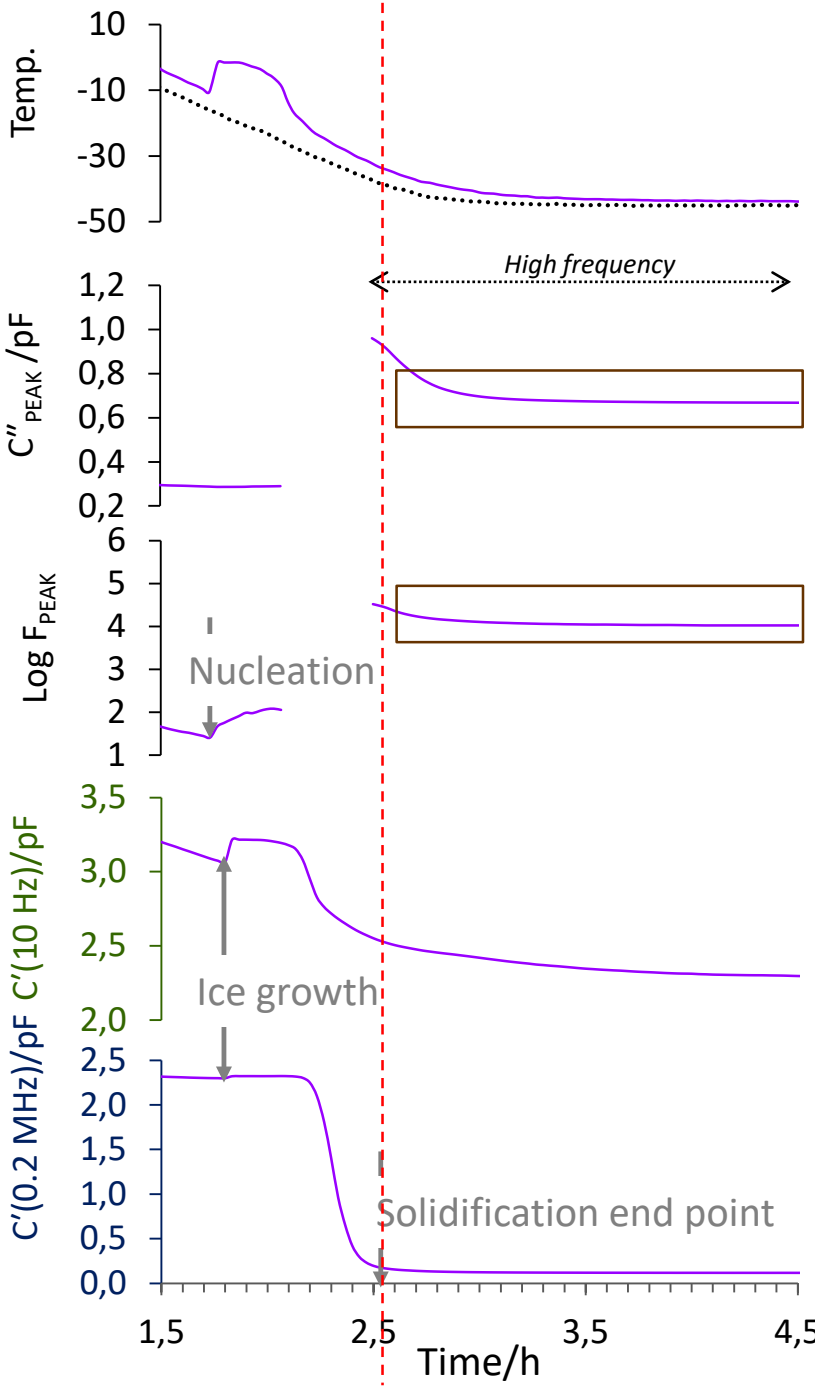

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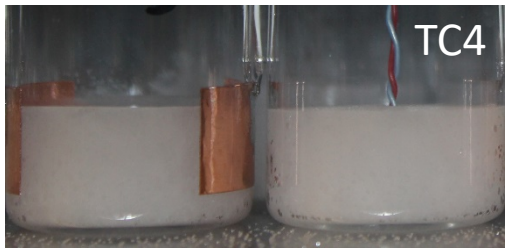

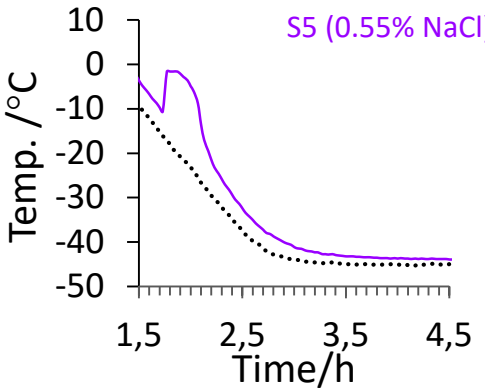

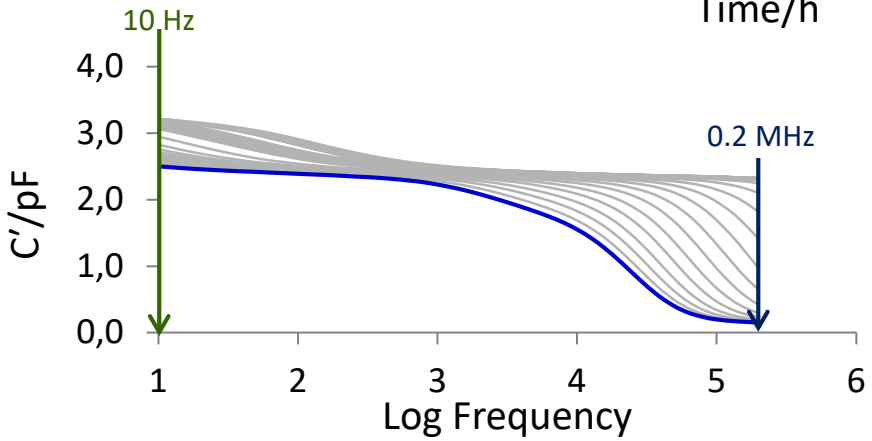

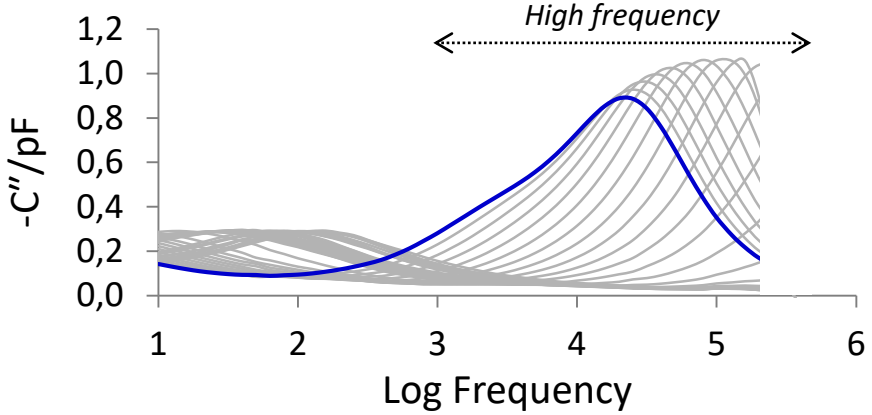

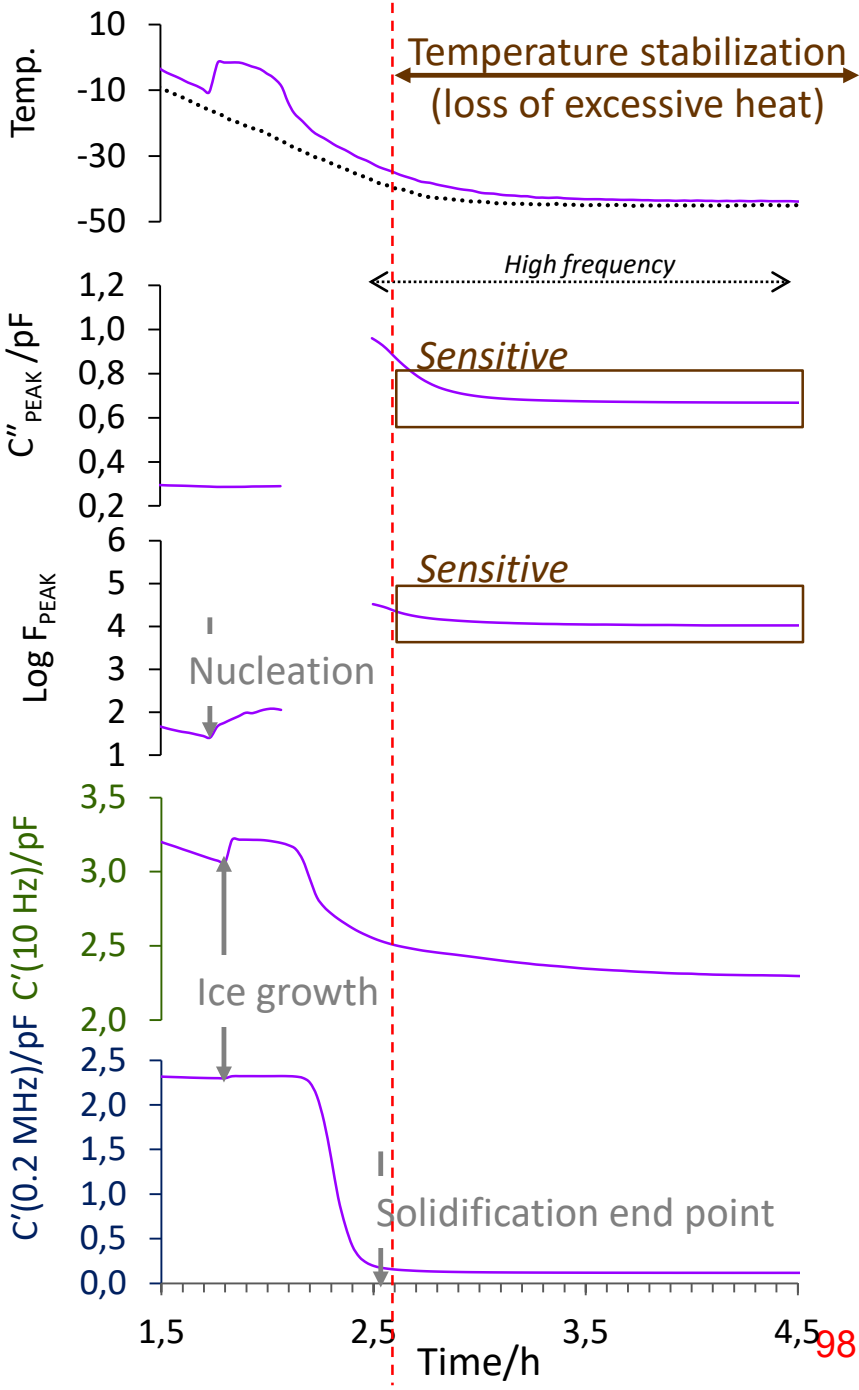

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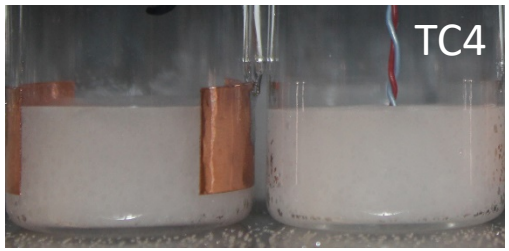

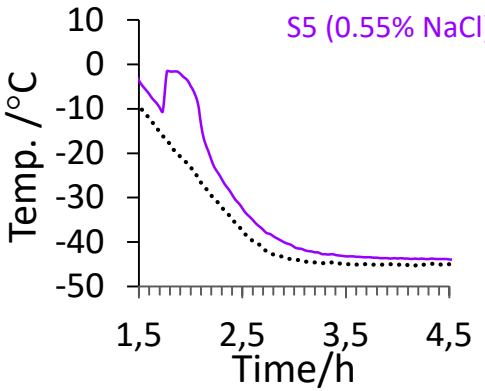

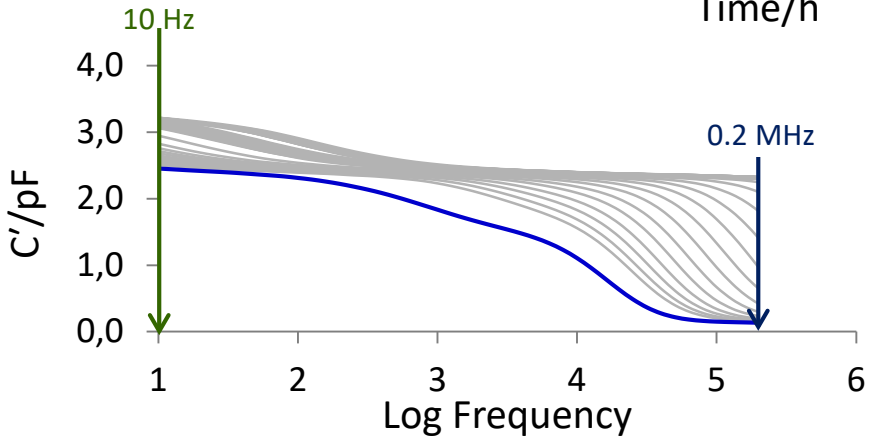

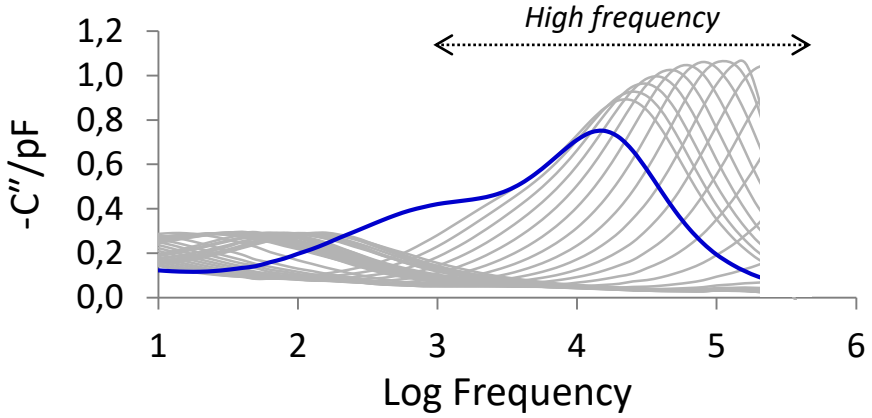

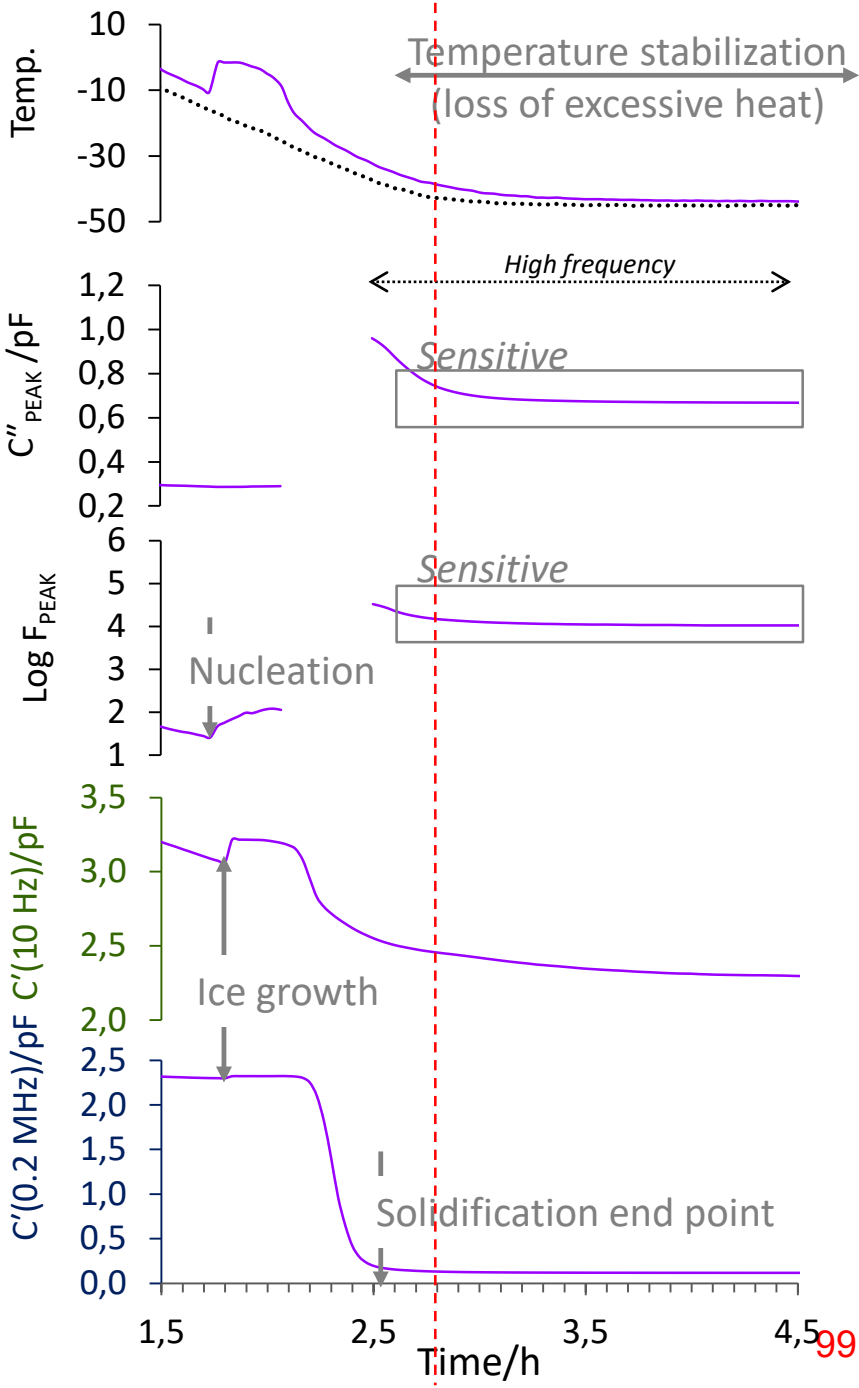

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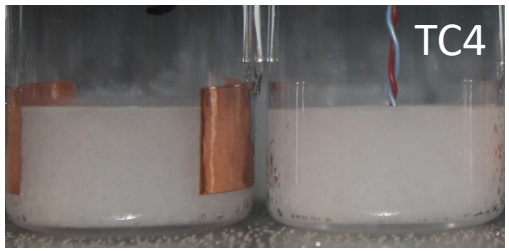

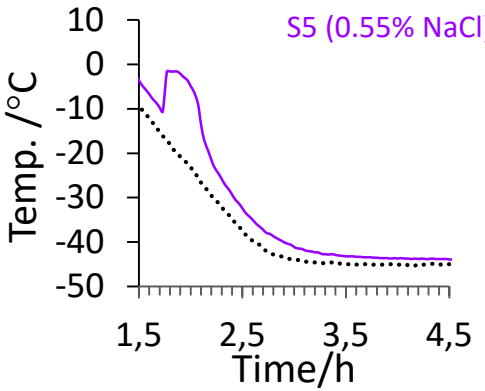

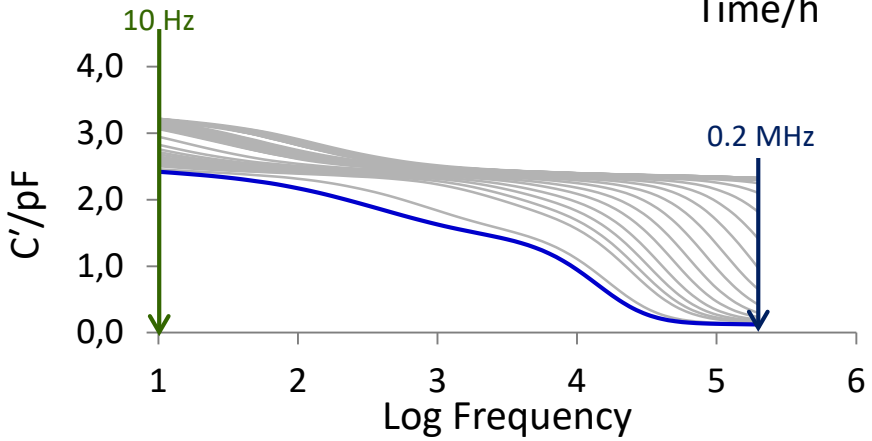

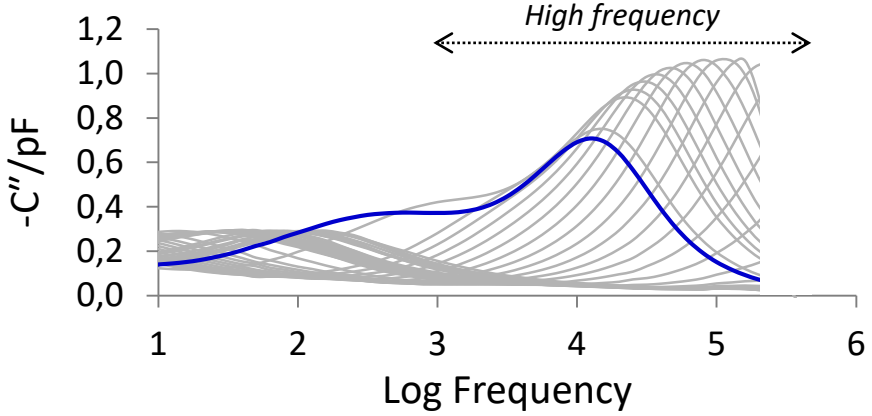

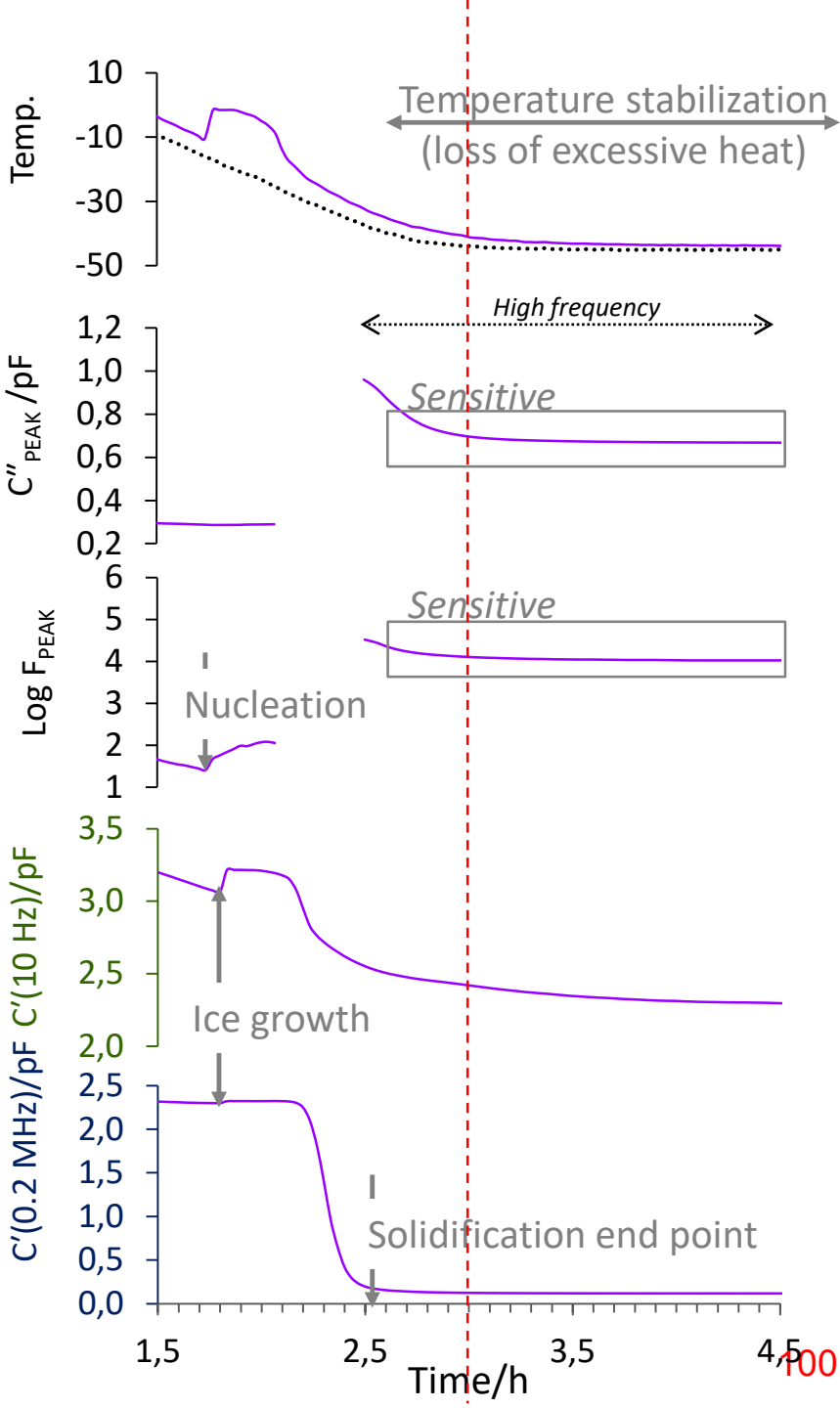

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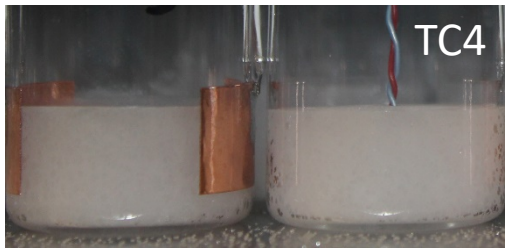

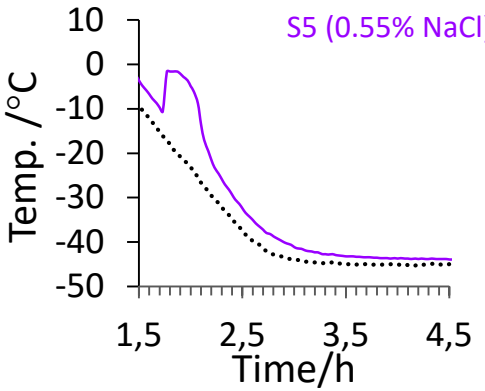

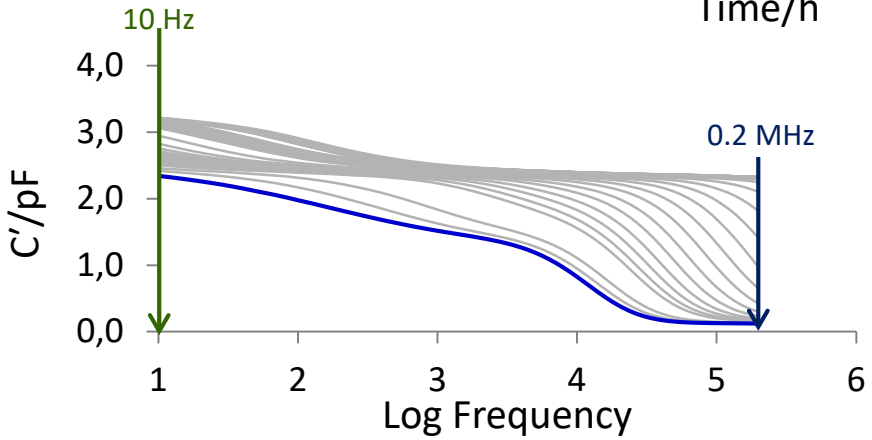

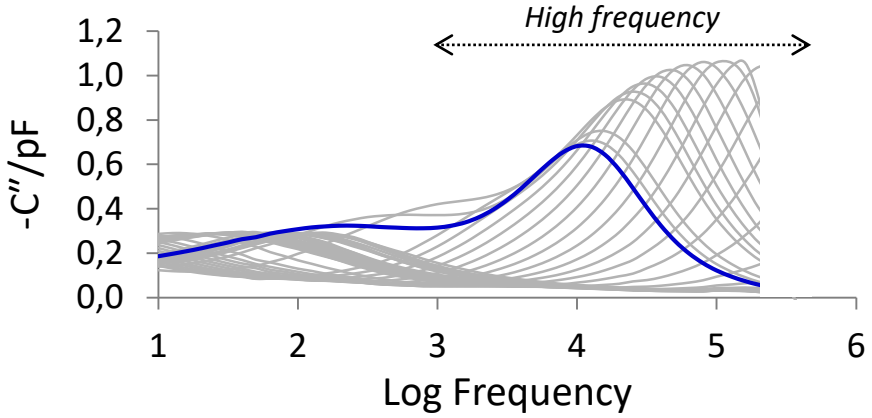

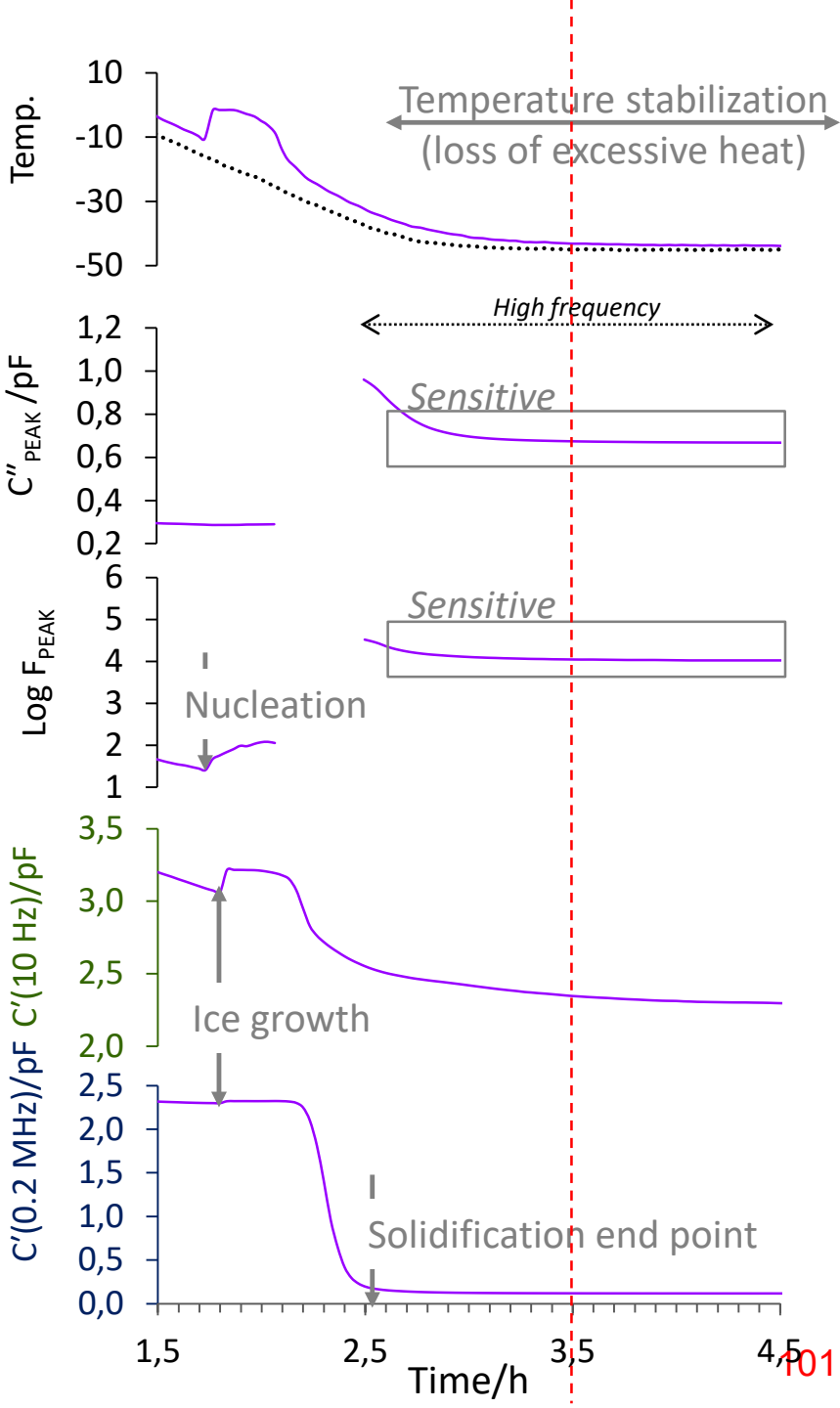

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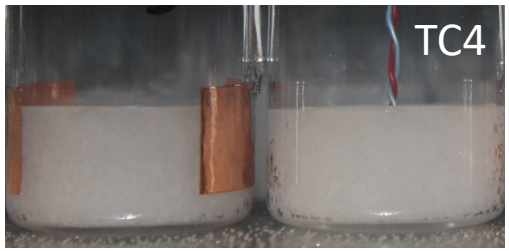
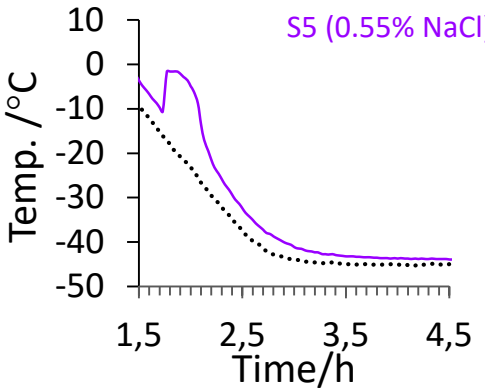
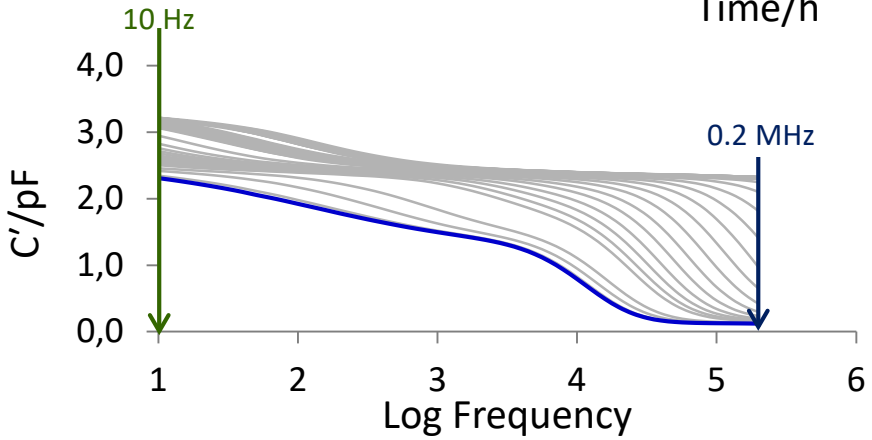
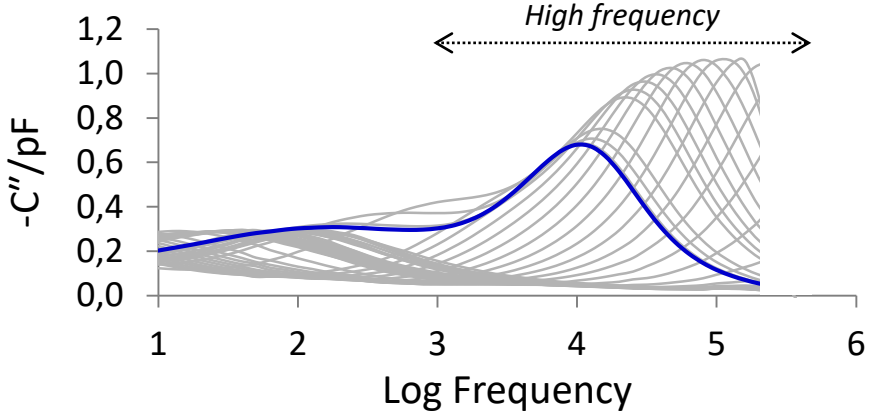
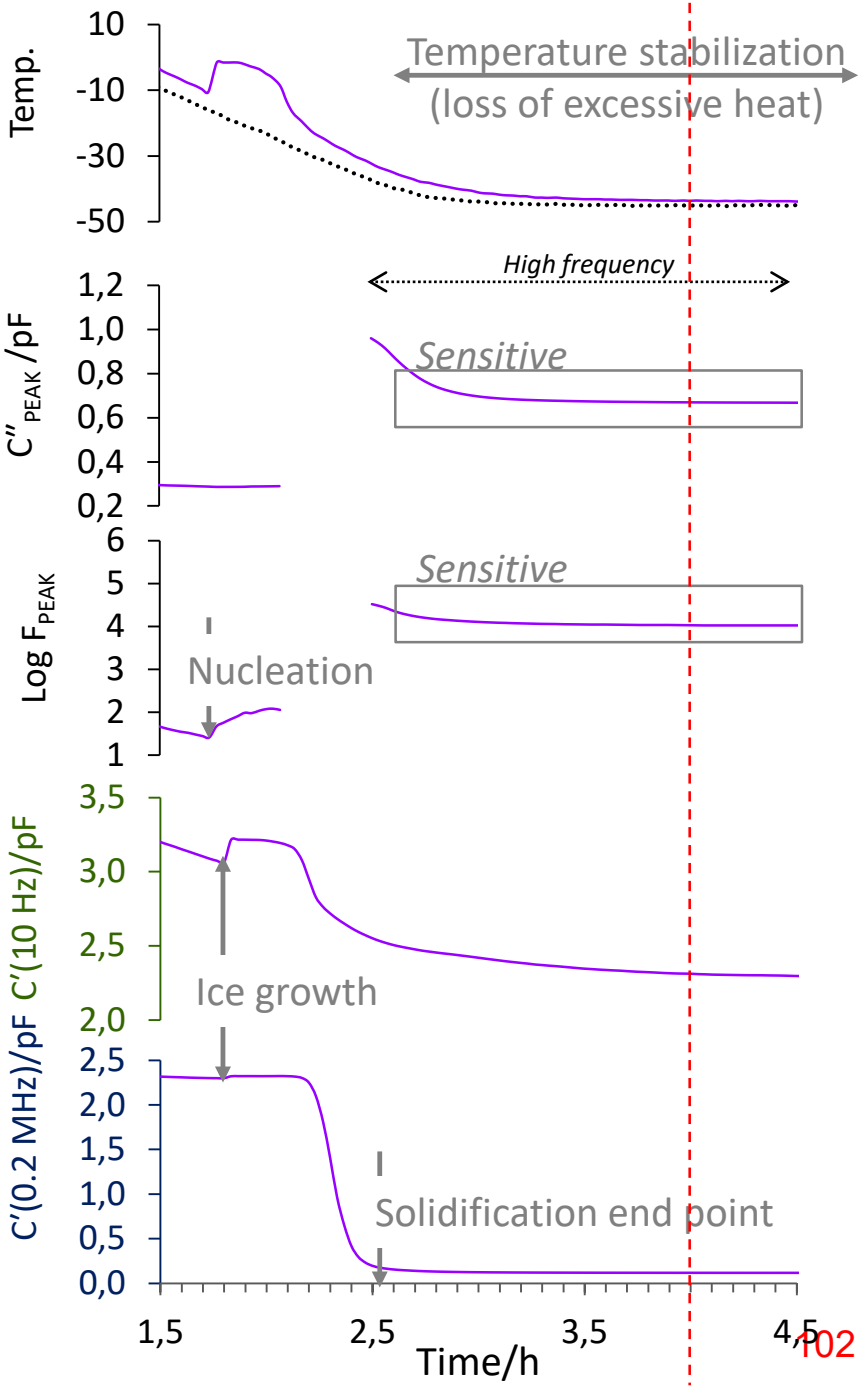


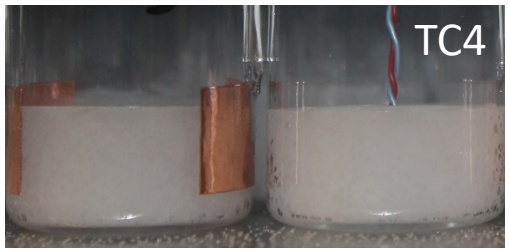


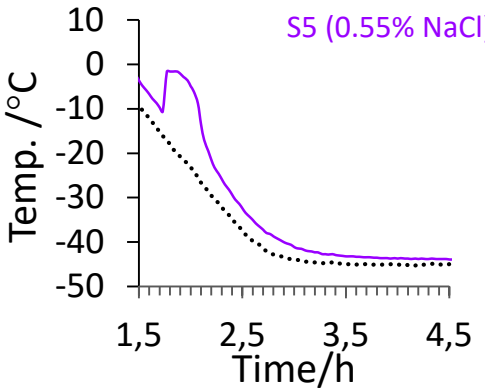


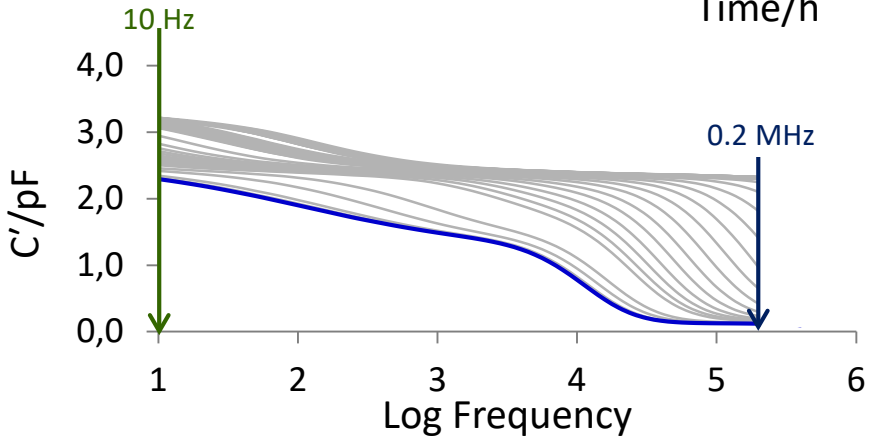


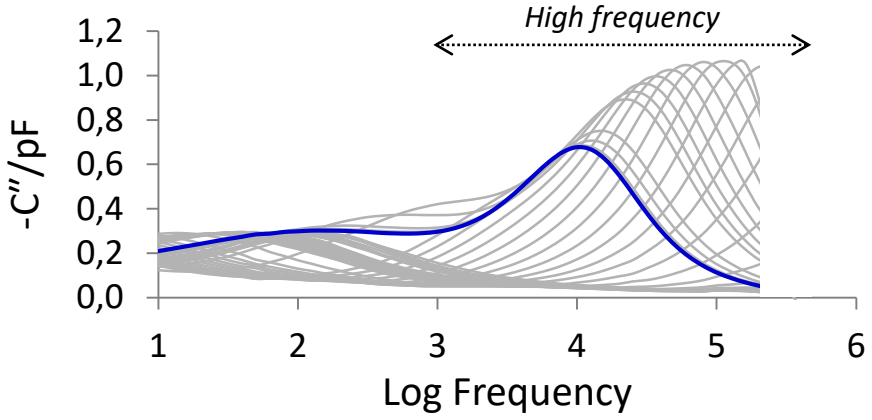


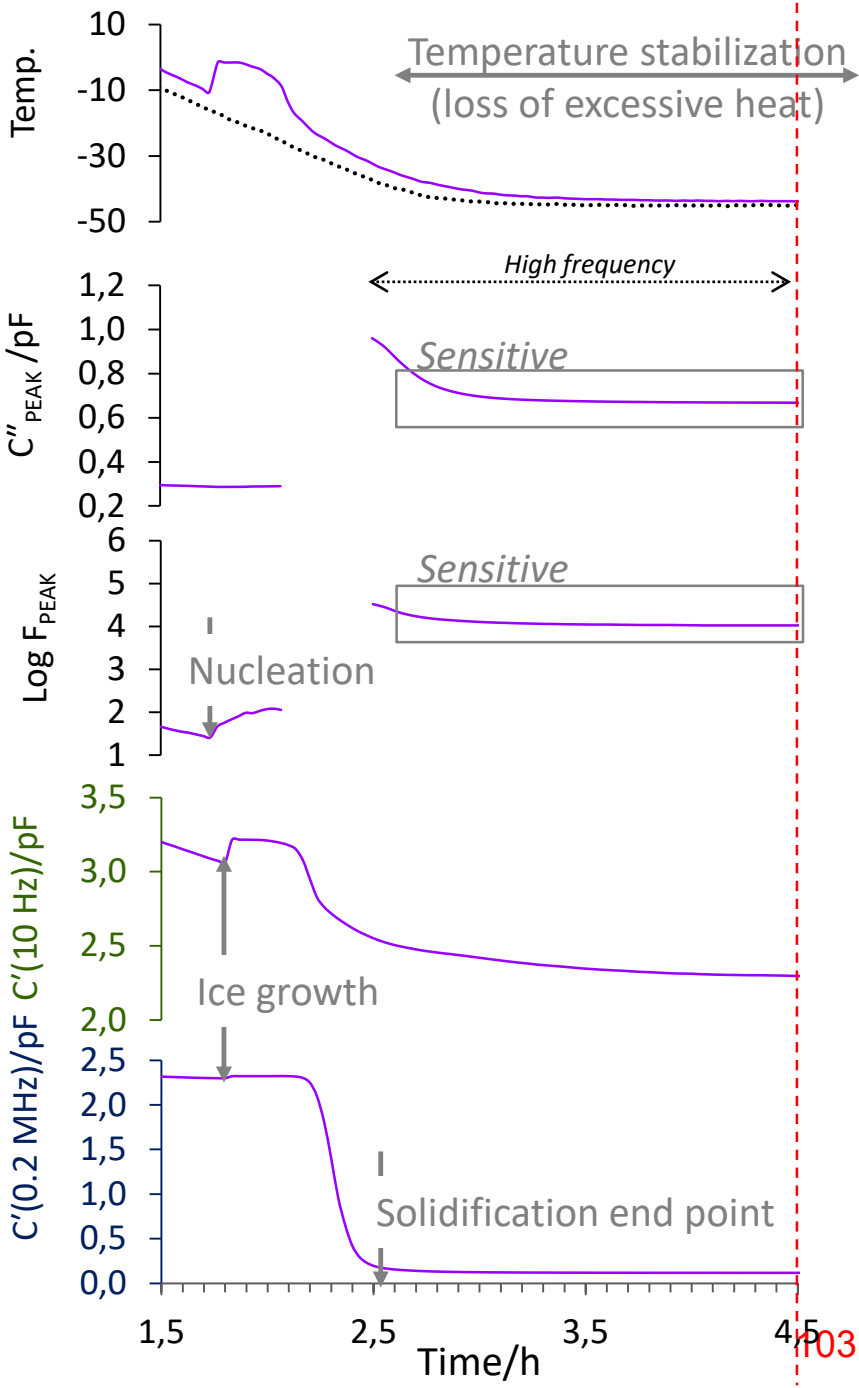
Freezing Step - 5%Sucrose+0.55%NaCl





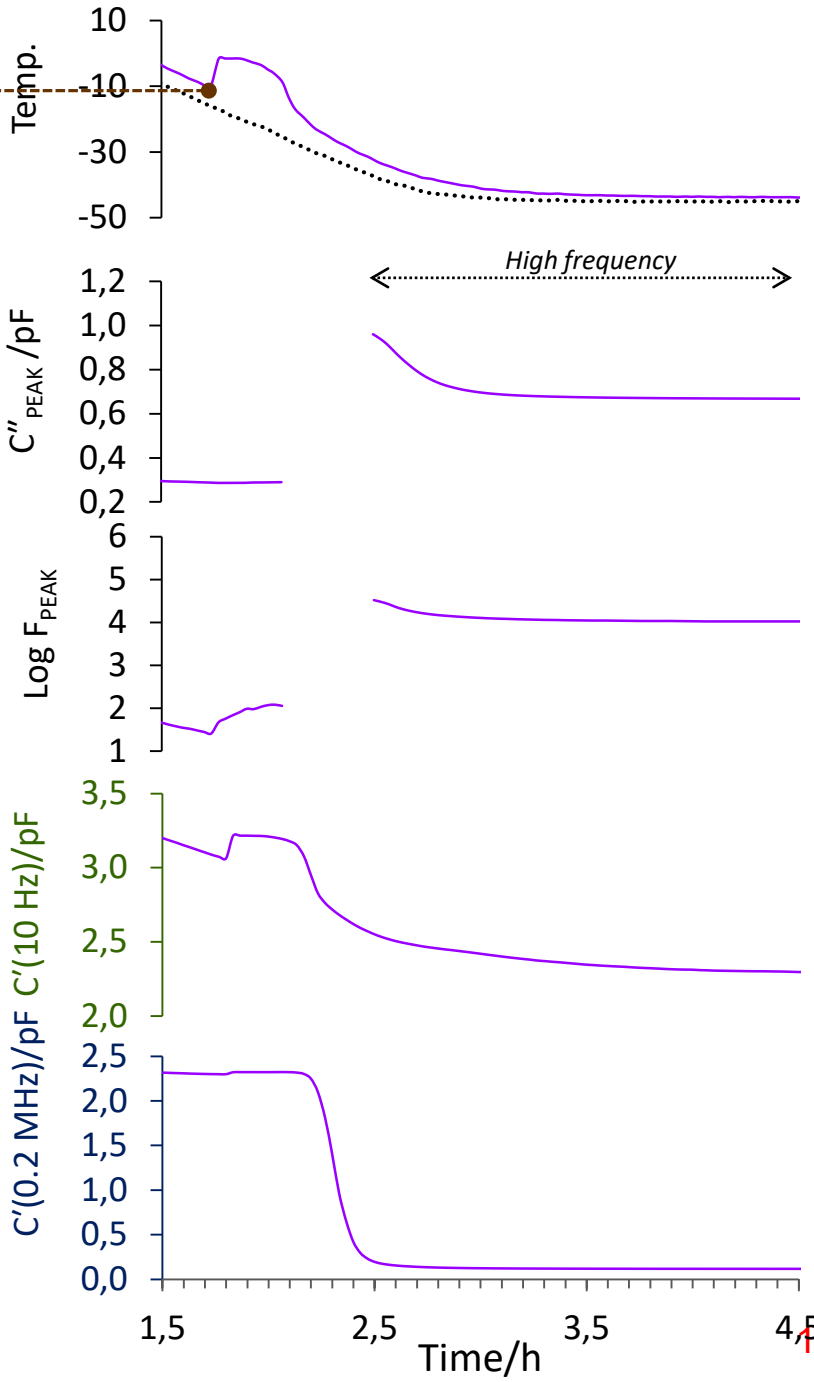






Freezing Step - 5%Sucrose+0.55%NaCl

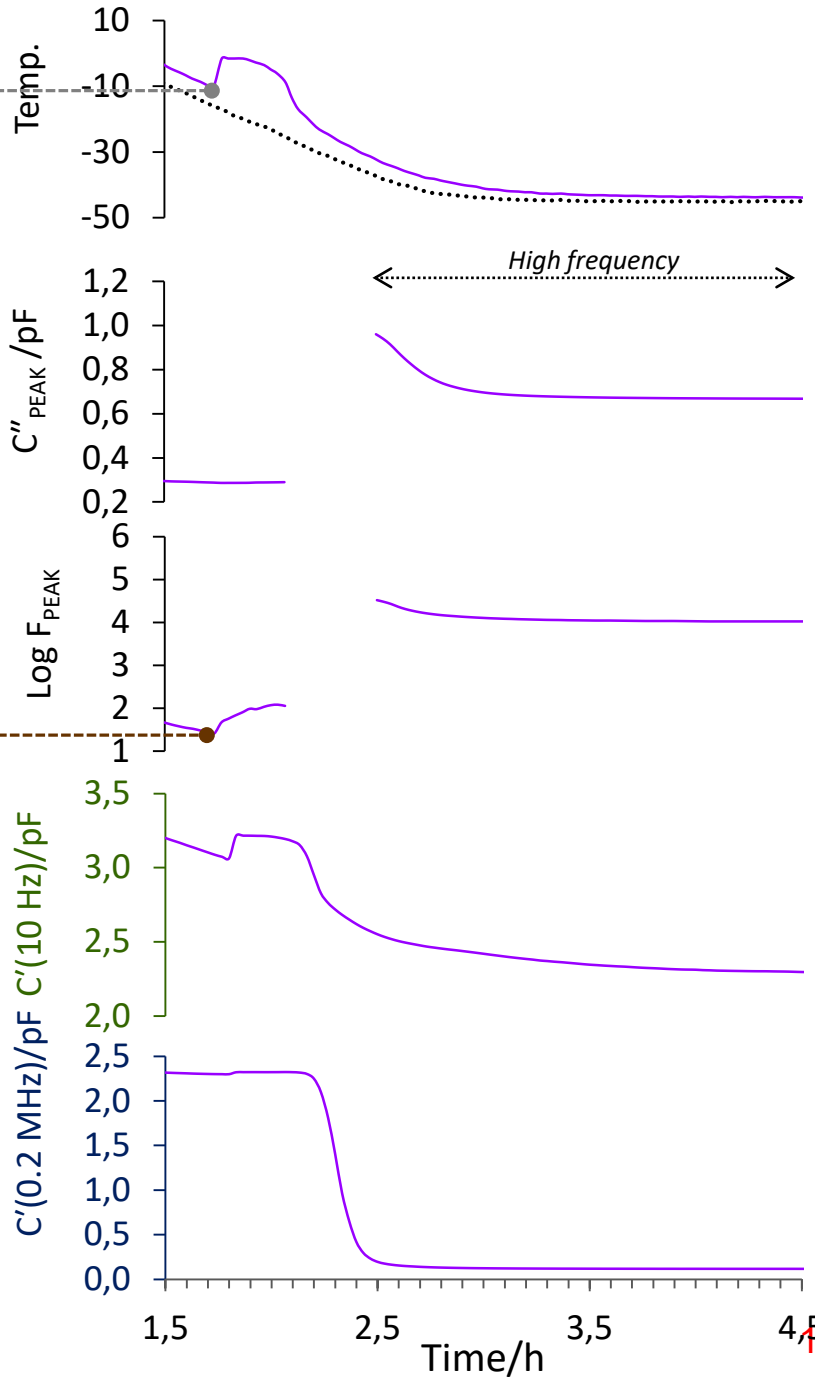
Nucleation point from TC



Freezing Step - 5%Sucrose+0.55%NaCl

Nucleation point from TC

Sensitive to nucleation

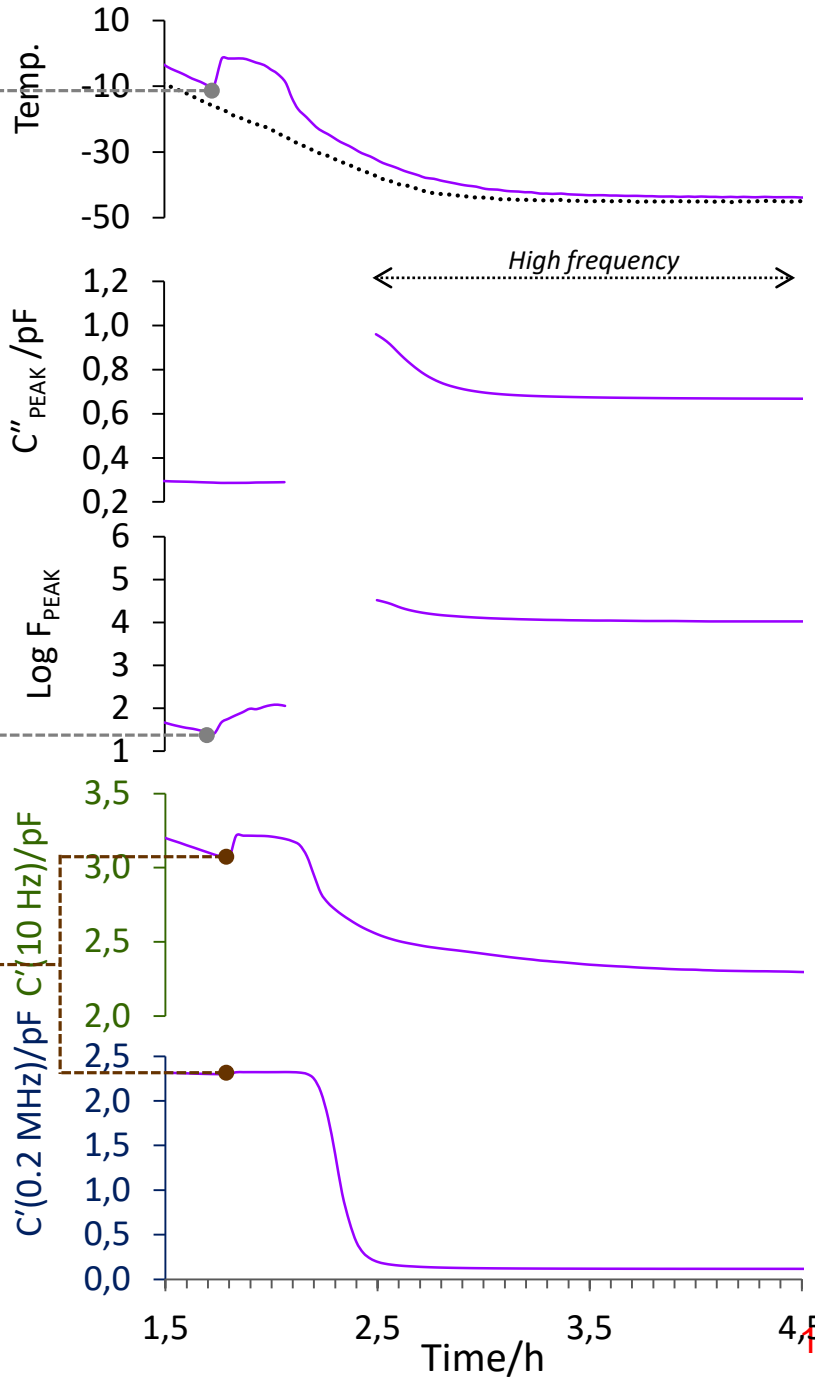


Freezing Step - 5%Sucrose+0.55%NaCl

Nucleation point from TC

Sensitive to nucleation

Sensitive to ice growth



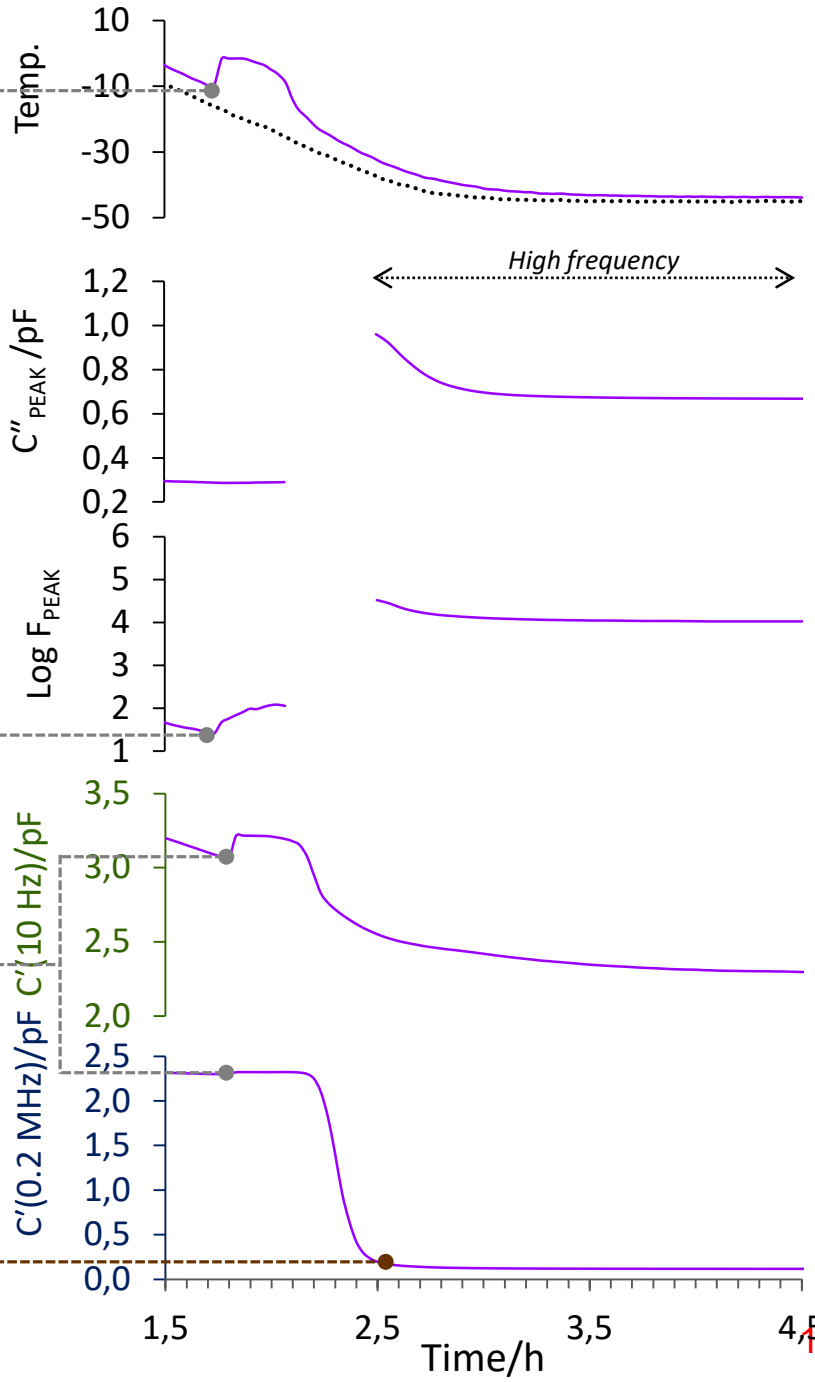
Freezing Step - 5%Sucrose+0.55%NaCl

Nucleation point from TC

Sensitive to nucleation

Sensitive to ice growth

Solidification



Freezing Step - 5%Sucrose+0.55%NaCl

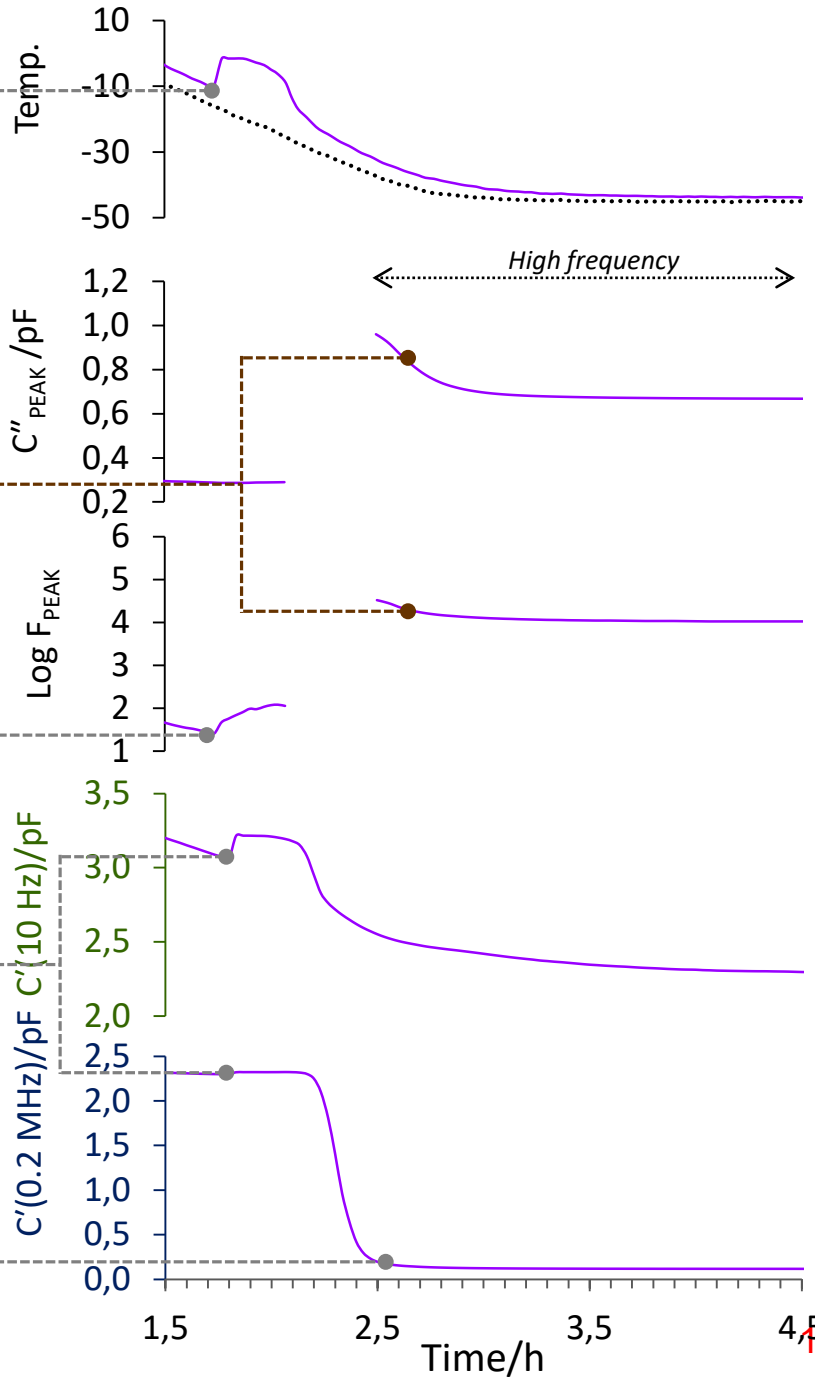
Nucleation point from TC

Good indication for temperature

Sensitive to nucleation

Sensitive to ice growth

Solidification



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Nucleation point from TC

Good indication for temperature

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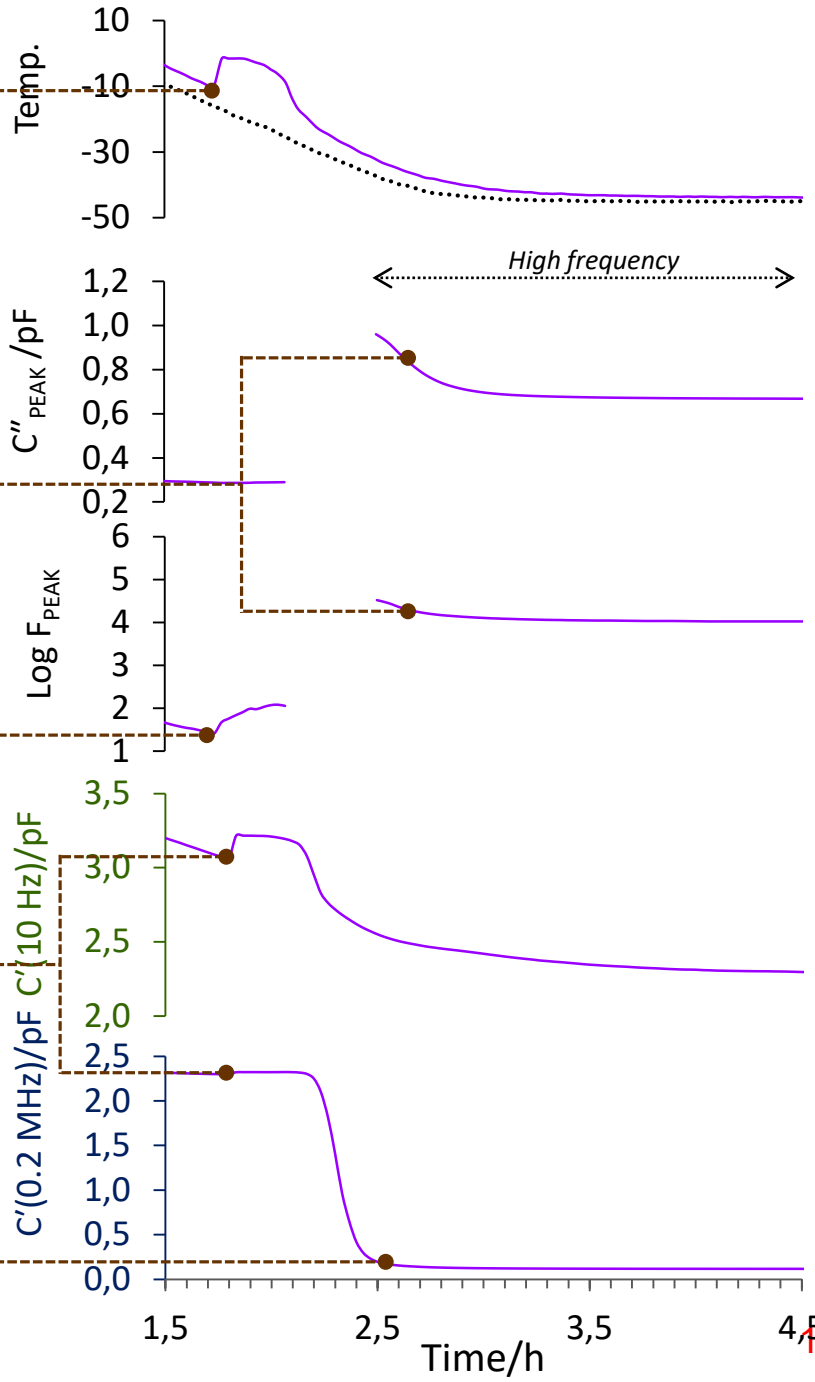
Solidification



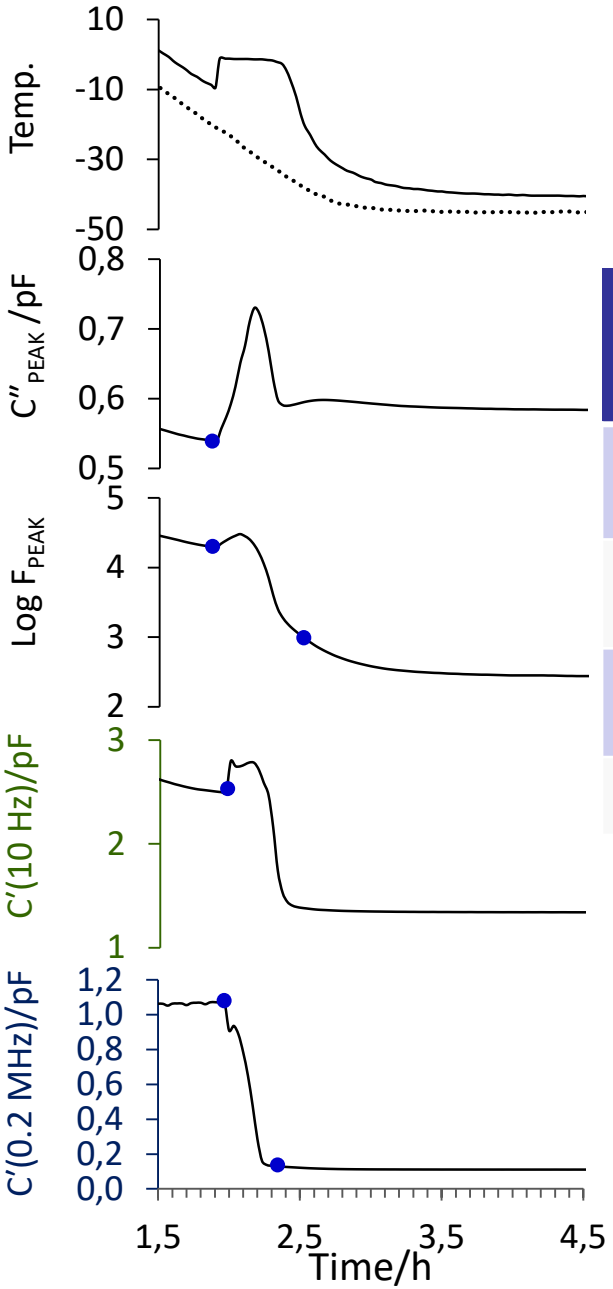
Jump to Ice Nucleation slide

Through Vial Impedance Spectroscopy (TVIS)

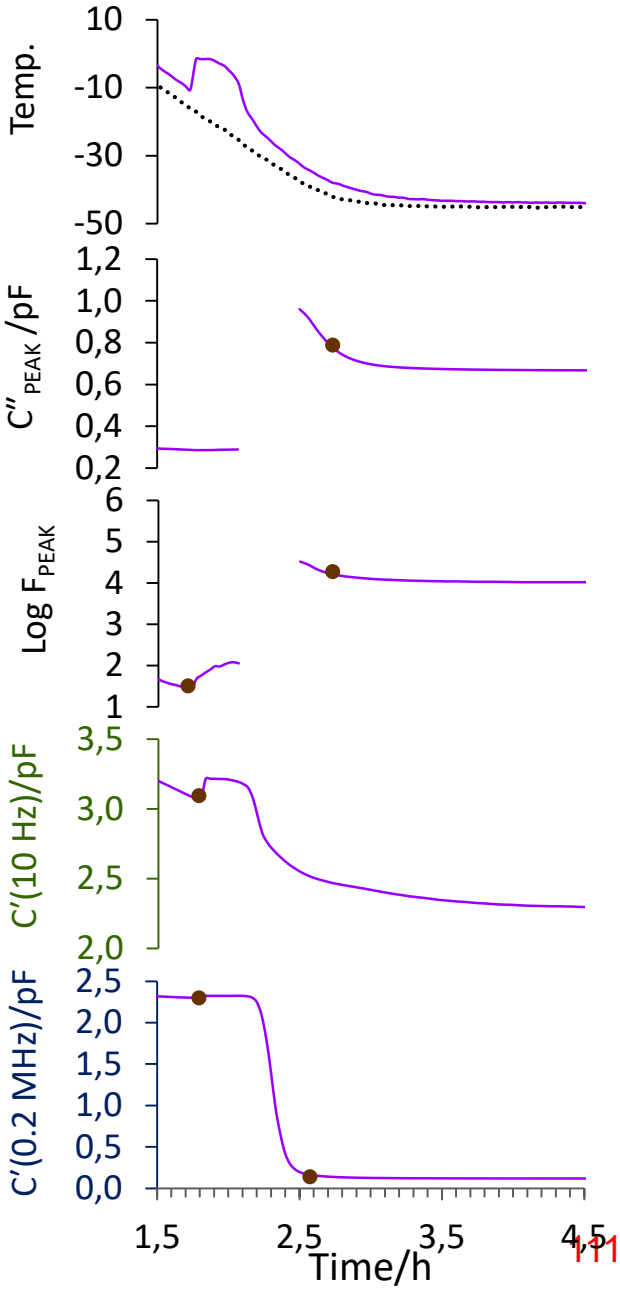
Contrast between low and high conductivity

Low conductive sample (LC)

High conductive sample (HC)



Stage	TVIS Parameters	
	LC	HC
Temperature indication	F_{PEAK}	C''_{PEAK} F_{PEAK}
Nucleation	C''_{PEAK} F_{PEAK}	F_{PEAK}
Ice growth	C'(10 Hz) C'(0.2MHz)	C'(10 Hz) C'(0.2MHz)
Solidification	C'(0.2MHz)	C'(0.2MHz)

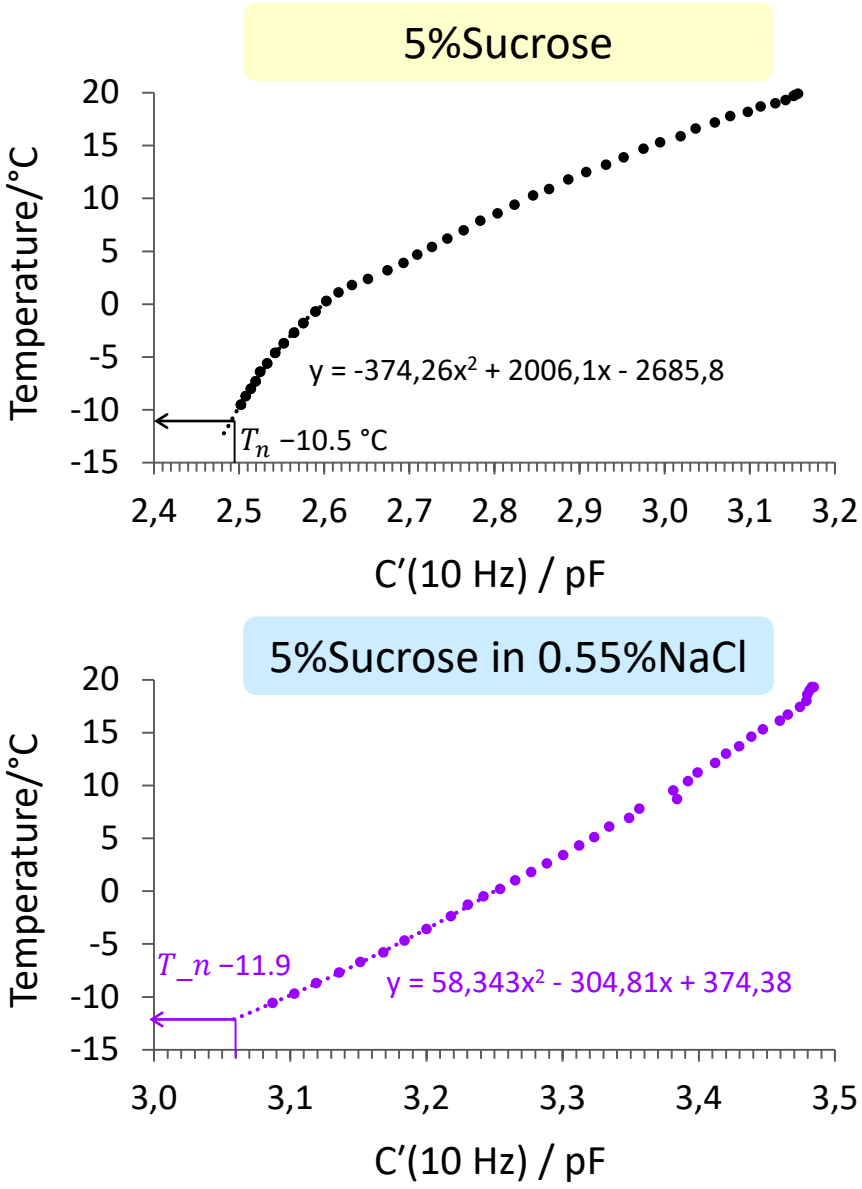


Through Vial Impedance Spectroscopy (TVIS)

Prediction of ice nucleation temperature

Ice Nucleation Temperature

- In case the TVIS vial nucleates before TC vial, the nucleation temperature in the TVIS vial can be inferred directly from TC temperatures in the nearest neighbor vials
- However, if TVIS vial nucleates later than TC vial, the nucleation temperature can be predicted by fitting a curve to the plot of the average temperature from thermocouple vials against TVIS parameter (i.e. $C'(10\ Hz)$)
- In this presentation, the ice nucleation temperature of both sample are extrapolate from fitting because TVIS vials form ice after TC vials



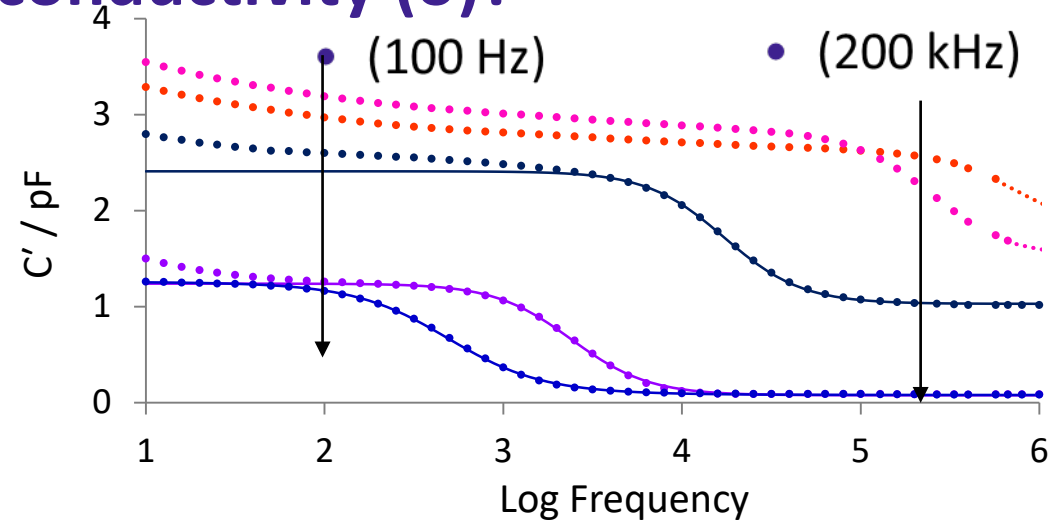
Jump to Ice Nucleation slide

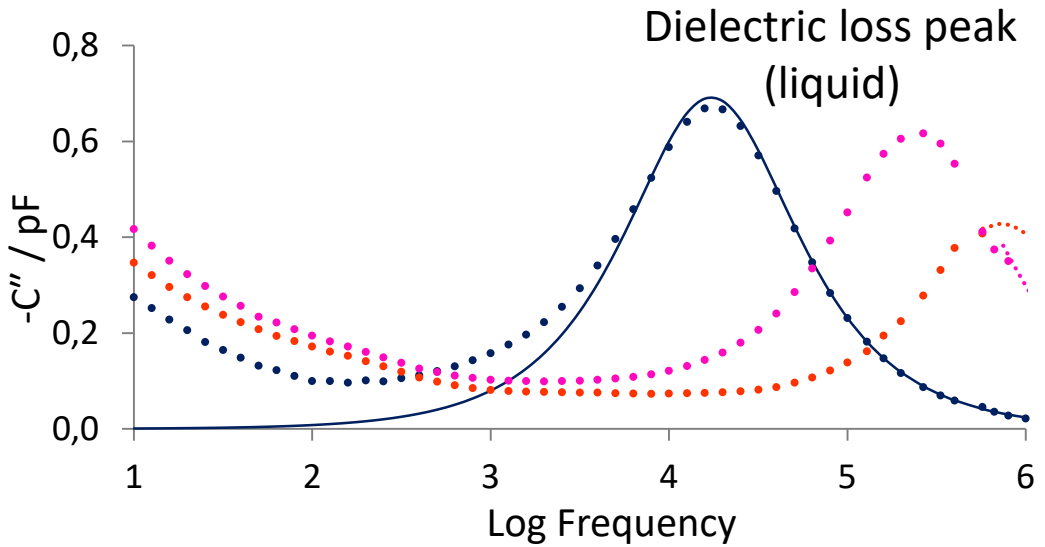
Through Vial Impedance Spectroscopy (TVIS)

Concluding remarks

What frequency & phase for what process & product conductivity (σ)?

- Low frequency (100 Hz) (real part)
  - Temperature spike from ice growth (any σ;)
- High frequency (200 kHz) (real part)
  - Solidification end point (any σ)
- Dielectric loss peak (imaginary part)
  - Ice nucleation (nano-seeding) MW for low σ; LFD for high σ





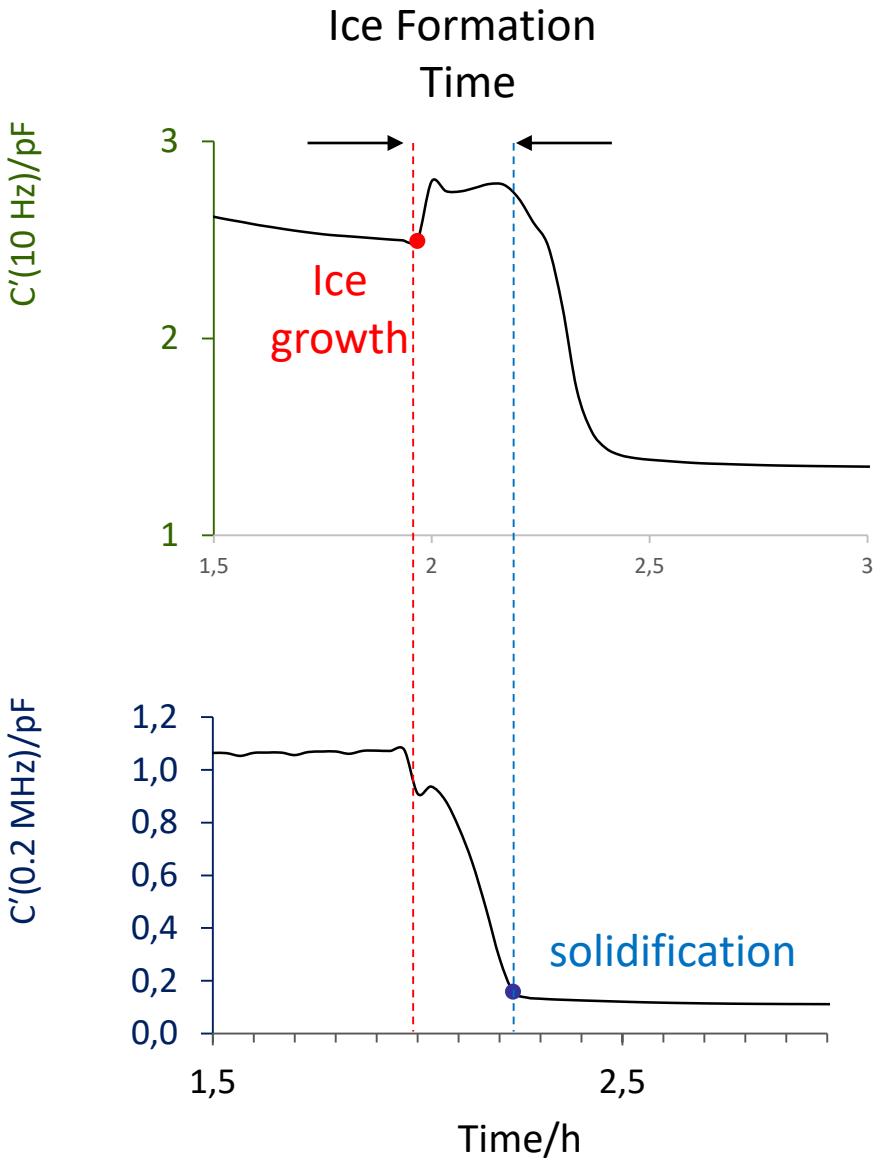
Design Space

- Nucleation temperature
  - A critical process parameter
  - As influences the rate of ice crystal growth which in turn impacts
  - Size crystal structure and hence dry layer resistance

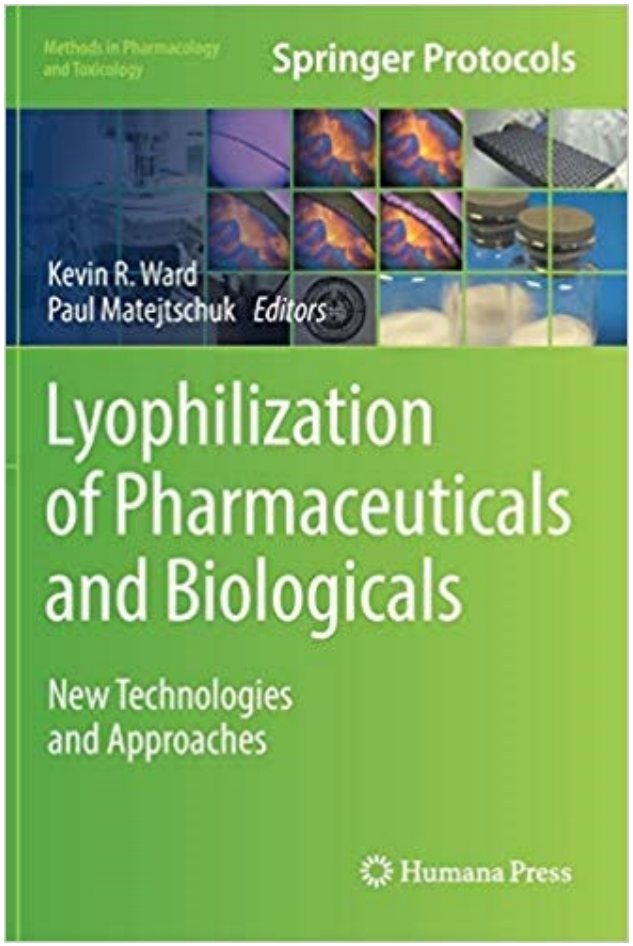
- Solidification end point
  - Also a critical process parameter?

QUESTION:

- Difference between solidification time and ice growth onset time – coupled to nucleation temperature – could help formulate the design space?



Further Reading



Link to this book

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

Acknowledgements, Recent Projects & Collaborators

- De Montfort University, School of Pharmacy
  - Evgeny Polygalov: co-inventor of TVIS instrument
  - Yowwares Jeeraruangrattana. PhD student
  - Bhaskar Pandya. PhD student
  - Irina Ermolina. Senior Lecturer

Our data

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Our WebPage

Innovate UK
Government Support for industry

LyoDEA
Lyophilization process analytics
By dielectric analysis

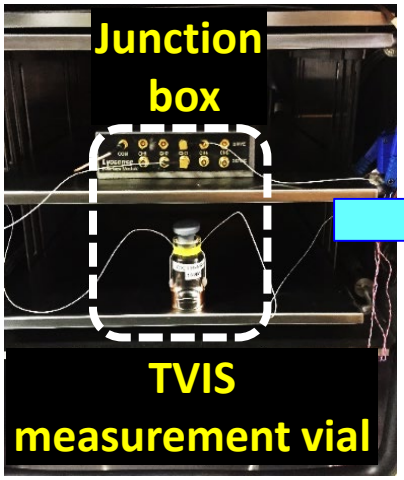
BIOSTART
Biopharmaceutical Stability at
Room Temperature

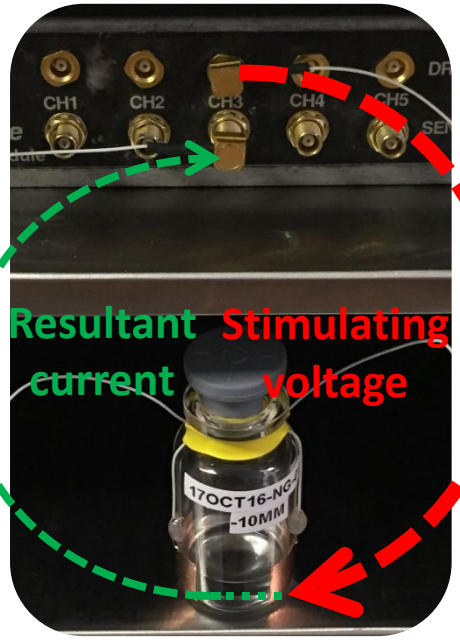
AtlasBio
Analytical Technologies for the
Stabilization of Biopharmaceuticals

Through Vial Impedance Spectroscopy (TVIS)

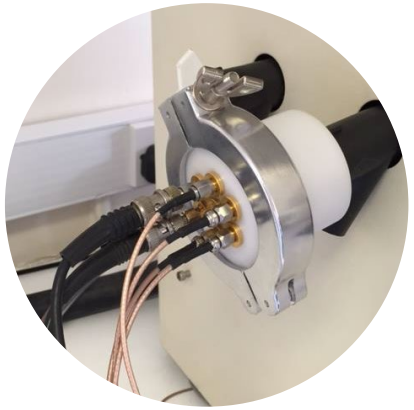
Description of Measurement System

Freeze drying chamber

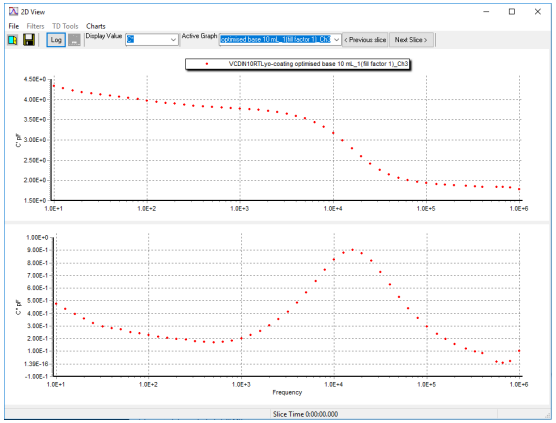




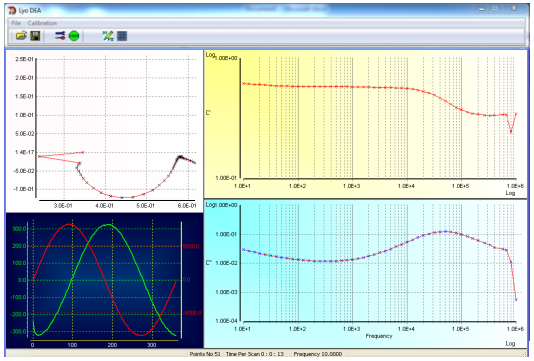
Pass-through



LyoView™ analysis software

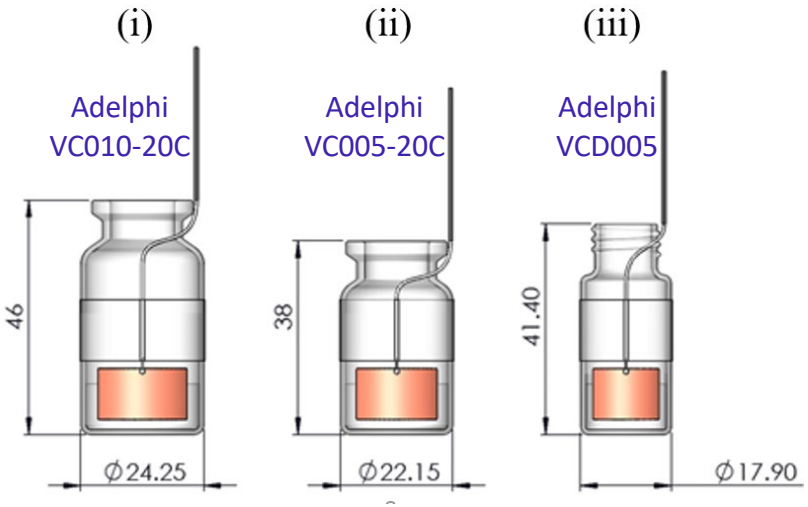


LyoDEA™ measurement software



TVIS system (I to V convertor)

TVIS Measurement System



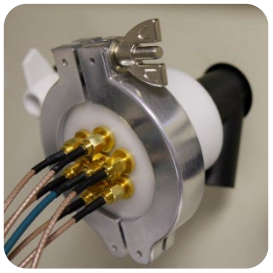
- The designs of various vials that have been modified with copper foil electrodes (10 mm in height and 3 mm from the base of each container

  i. 20 mm crimp-neck vial with 10 ml nominal capacity
  ii. 20 mm crimp-neck vial with 5 ml nominal capacity
  iii. screw-neck vial with 5 ml nominal capacity

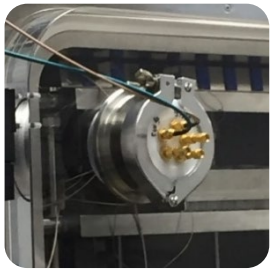
- The different styles of a bespoke pass-through for TVIS systems

  A. Connected via the manifold hose on the outside of the dryer
  B. Connected via the port on top left side of the door on the dryer
  C. Connected to a port on the top of the drying chamber

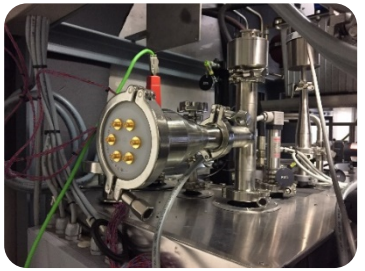
A



B



C



Through Vial Impedance Spectroscopy (TVIS)

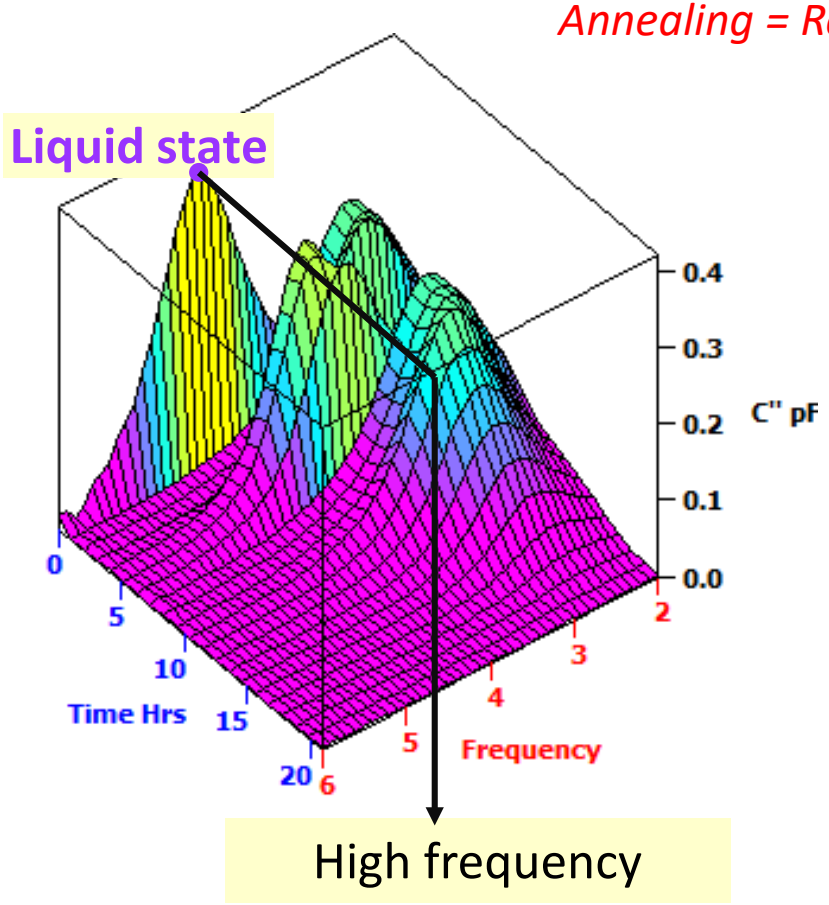
Supplementary Material

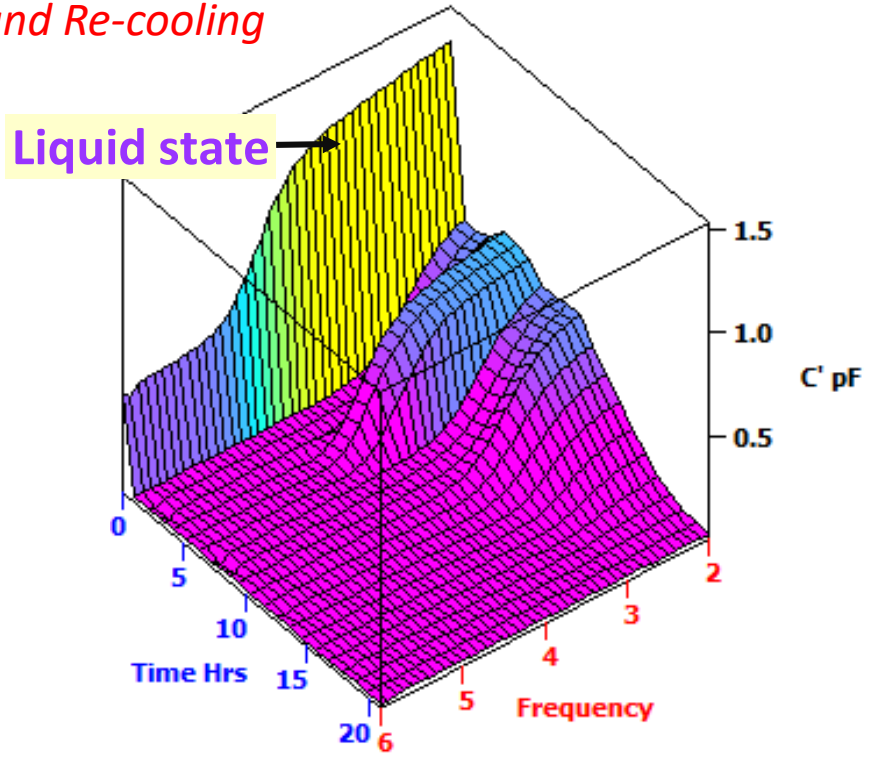
TVIS Response Surface (3D-Plot)

Imaginary Part of Capacitance

Real Part of Capacitance

Annealing = Re-heating and Re-cooling





TVIS Response Surface (3D-Plot)

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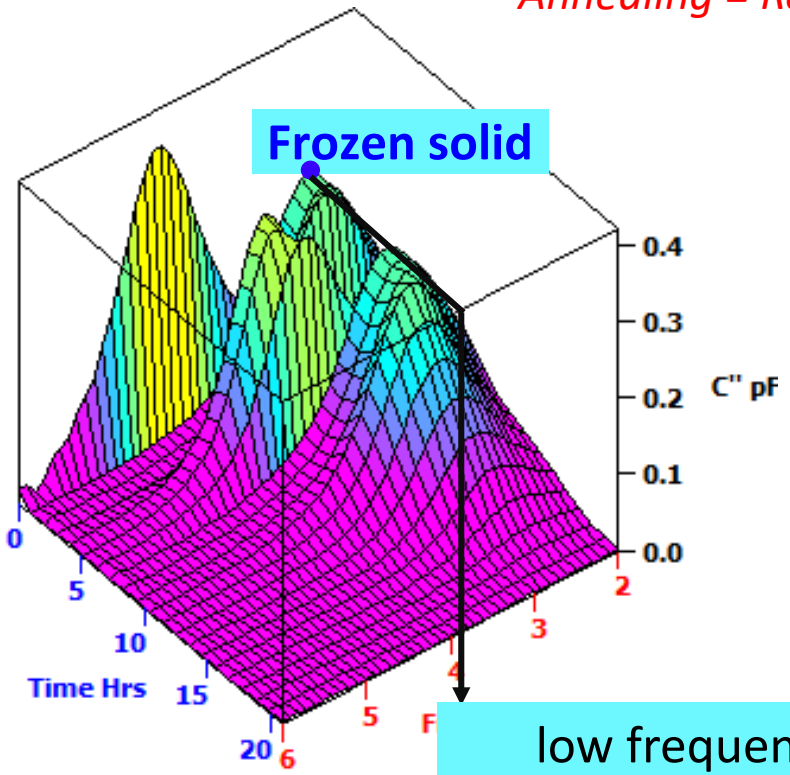
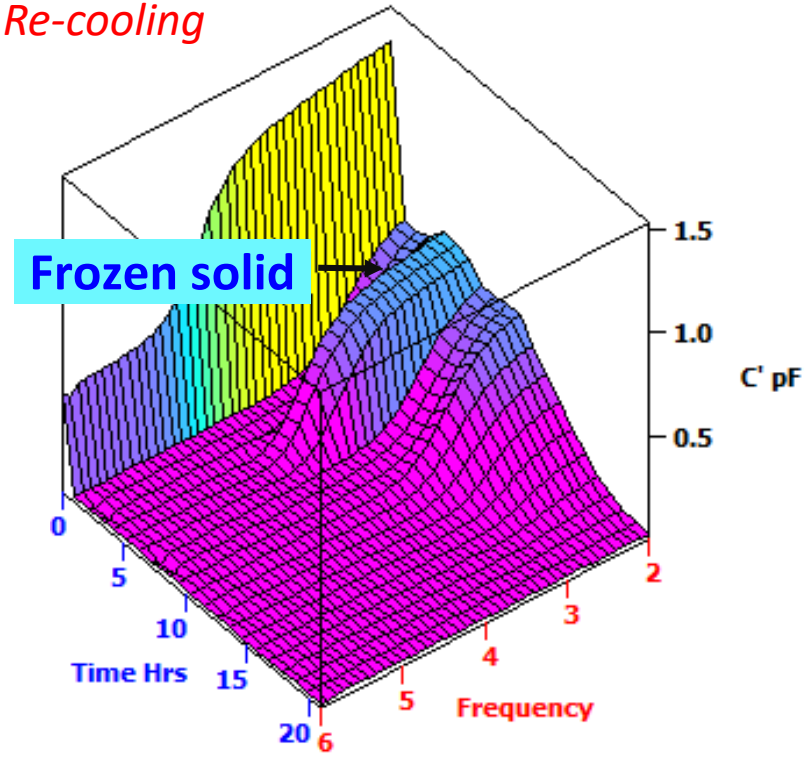


low frequency



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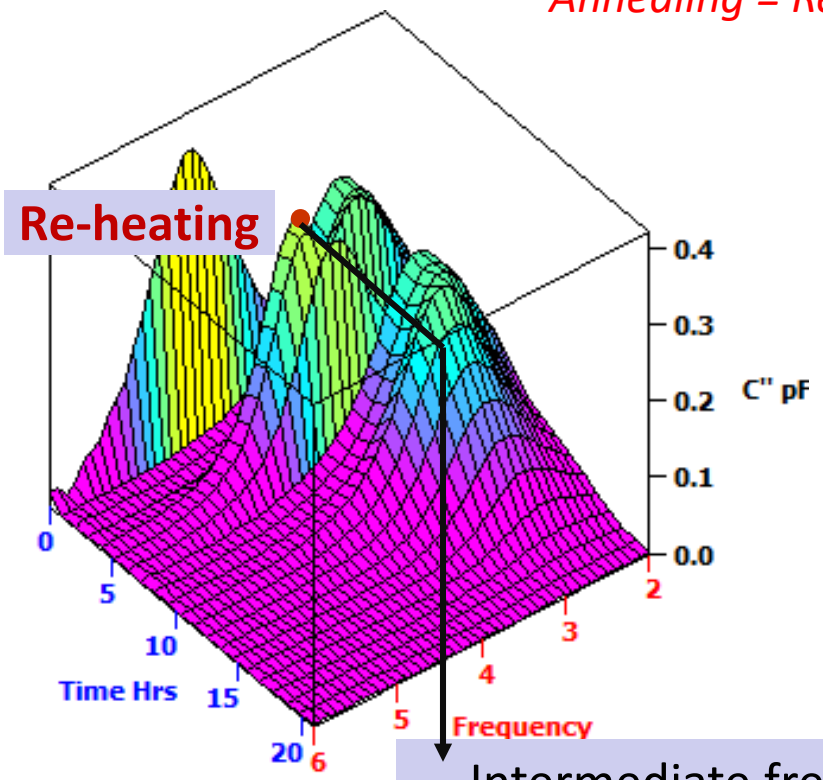
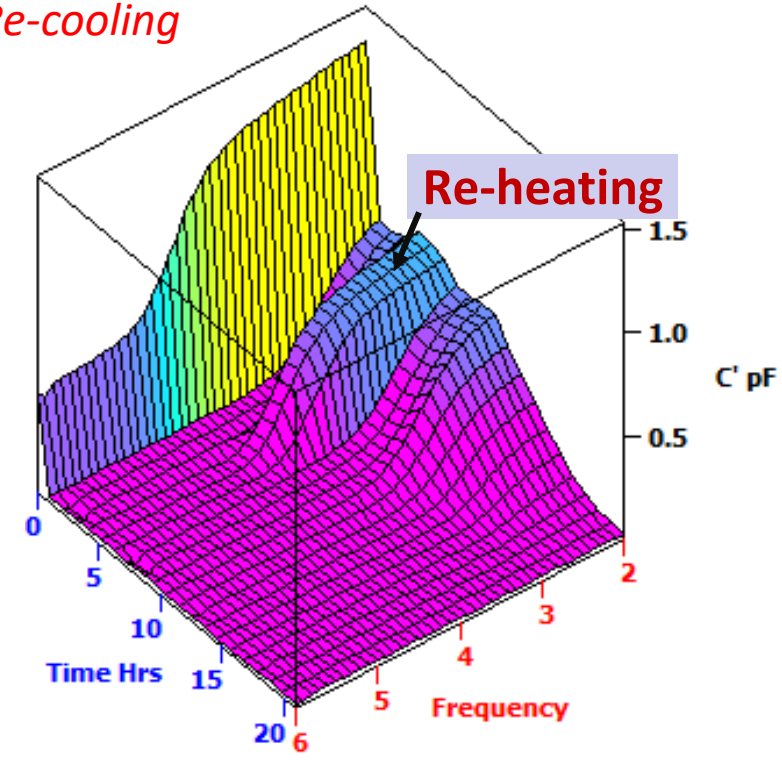


Intermediate frequency

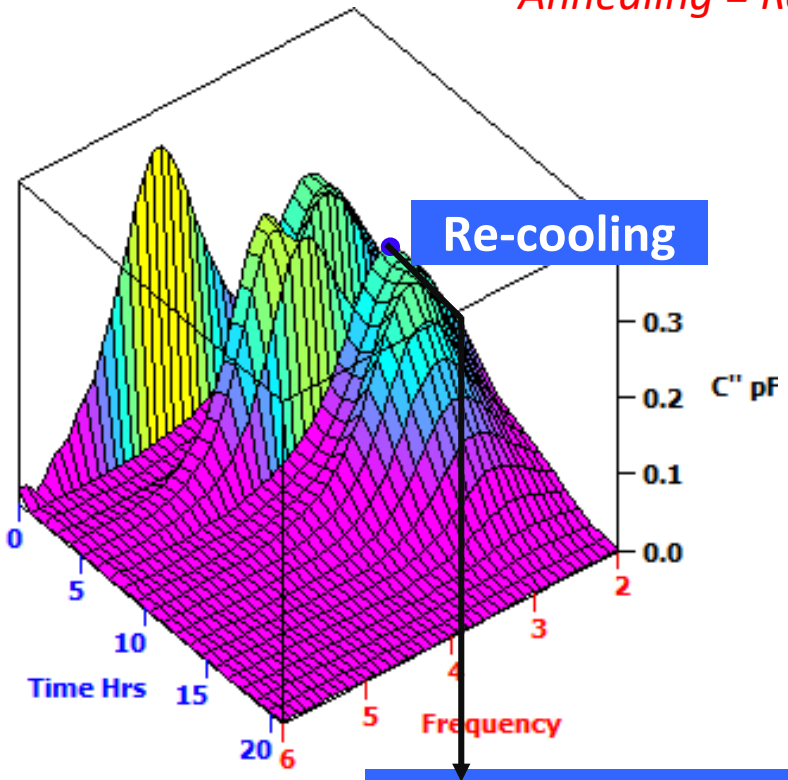


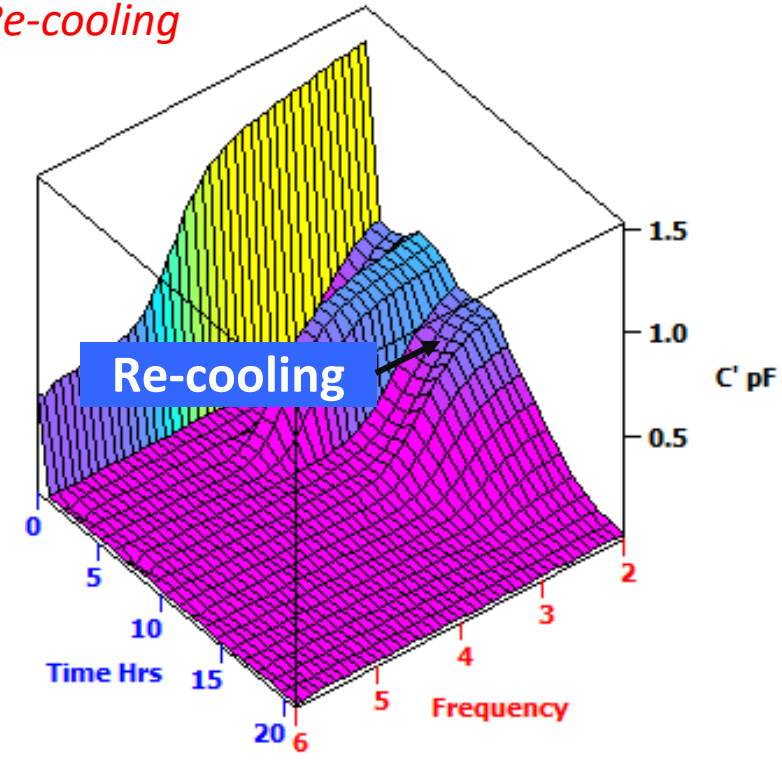
TVIS Response Surface (3D-Plot)

Imaginary Part of Capacitance

Real Part of Capacitance

Annealing = Re-heating and Re-cooling





TVIS Response Surface (3D-Plot)

Imaginary Part of Capacitance

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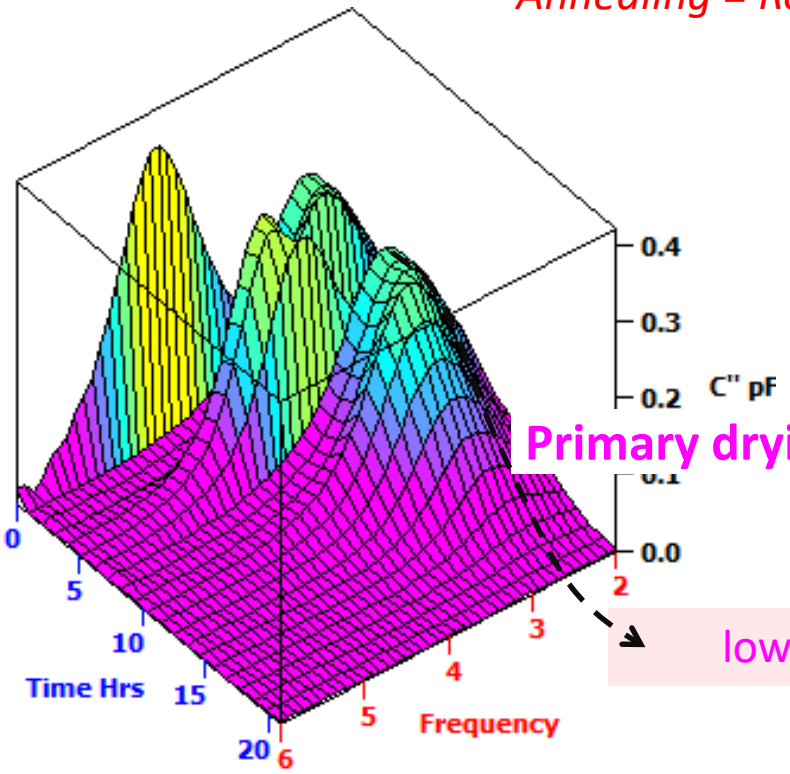
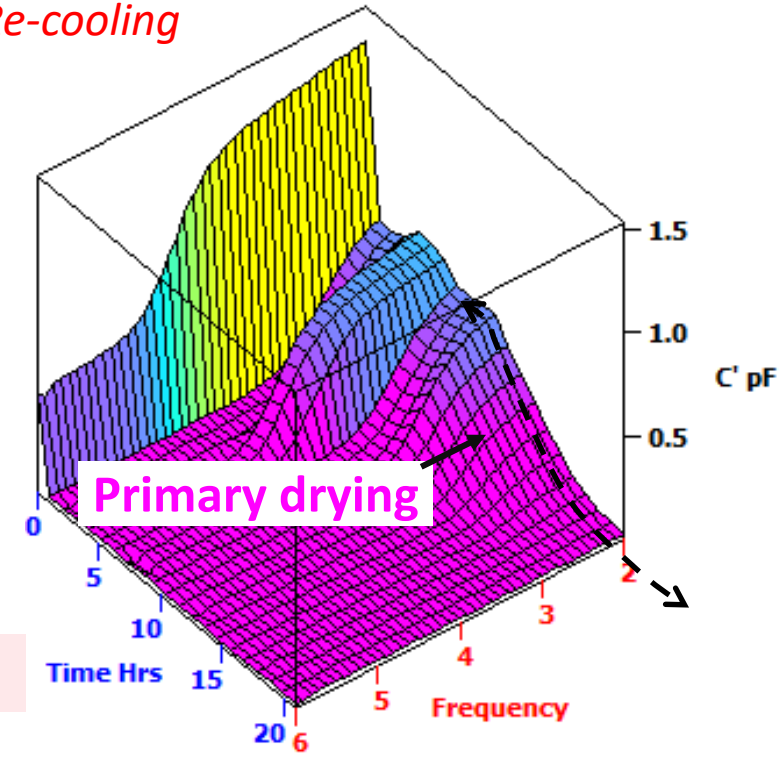


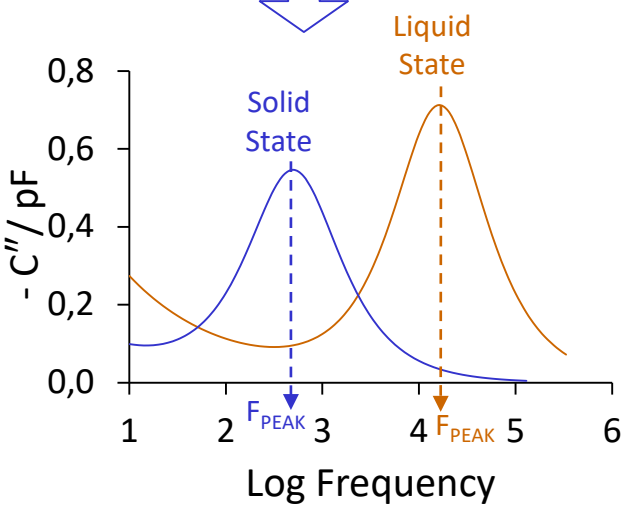


Through Vial Impedance Spectroscopy (TVIS)

Applications

Through Vial Impedance Spectroscopy (TVIS)

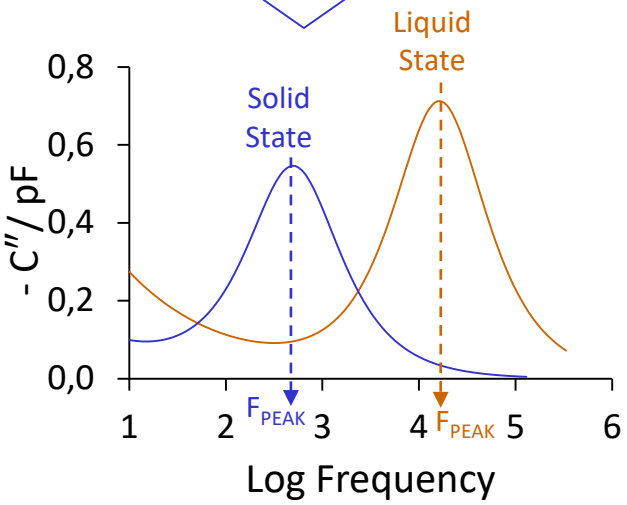
Monitoring **Phase Behaviour** (ice nucleation temperature and solidification end points by using F_{PEAK}

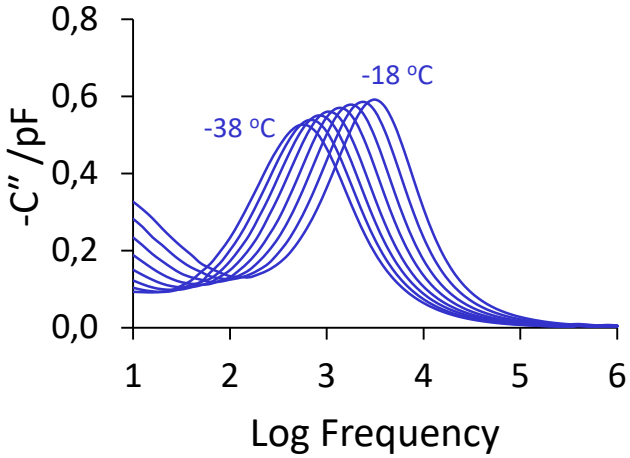


Through Vial Impedance Spectroscopy (TVIS)

Monitoring **Phase Behaviour** (ice nucleation temperature and solidification end points by using F_{PEAK}

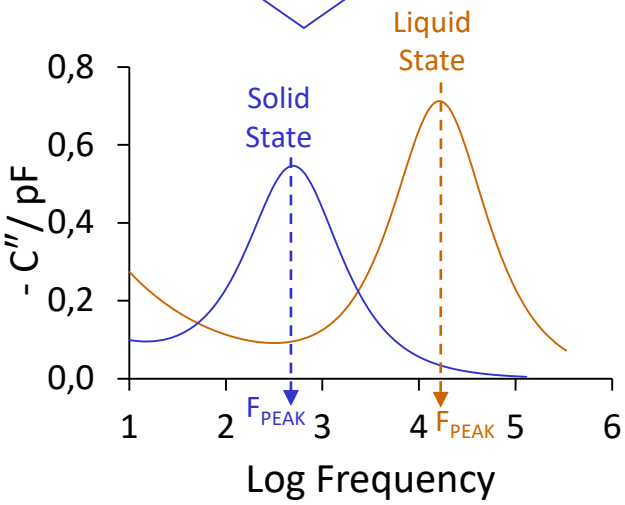
F_{PEAK} temperature calibration for **predicting temperature** of the product in primary drying



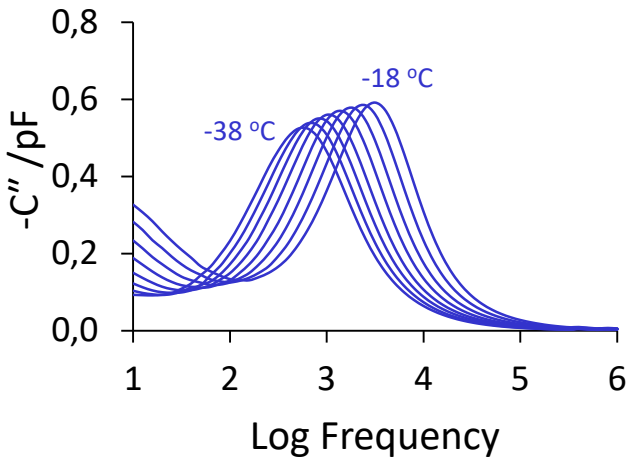


Through Vial Impedance Spectroscopy (TVIS)

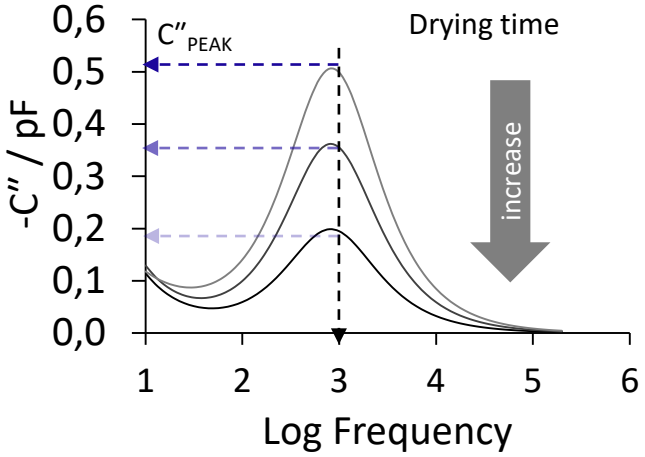
Monitoring **Phase Behaviour** (ice nucleation temperature and solidification end points by using F_{PEAK}



F_{PEAK} temperature calibration for **predicting temperature** of the product in primary drying



Surrogate **drying rate** (from $\frac{dC''_{PEAK}}{dt}$)

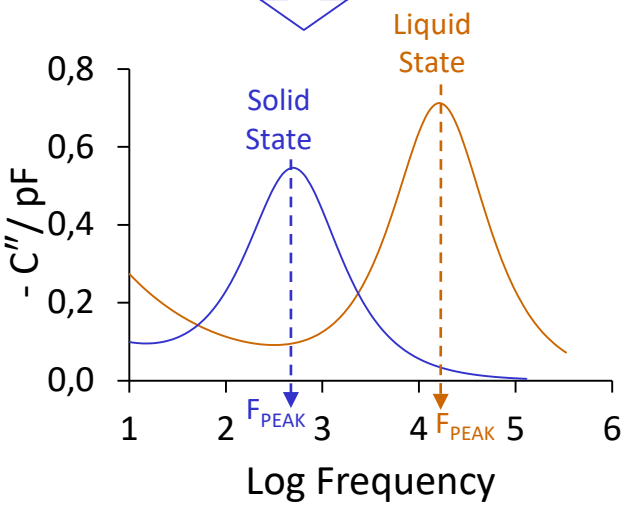


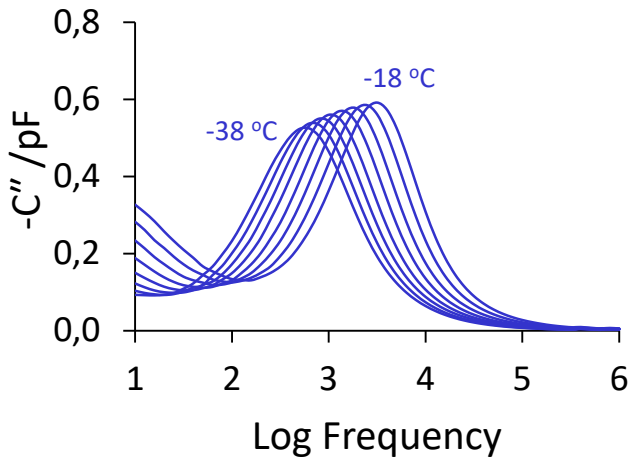
Through Vial Impedance Spectroscopy (TVIS)

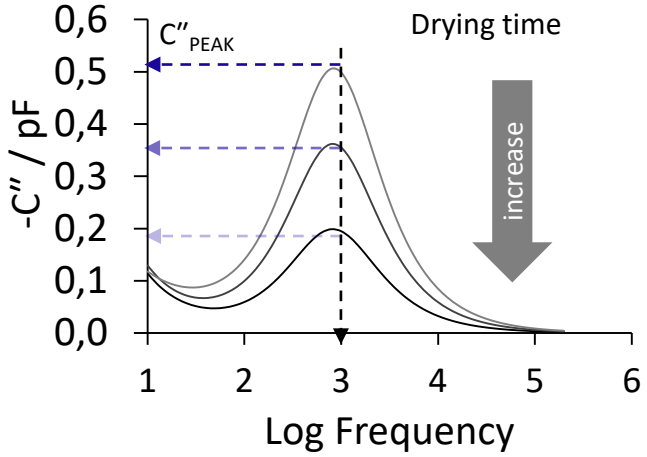
Monitoring **Phase Behaviour** (ice nucleation temperature and solidification end points by using F_{PEAK}

F_{PEAK} temperature calibration for **predicting temperature** of the product in primary drying

Surrogate **drying rate** (from $\frac{dC''_{PEAK}}{dt}$)







C'(~ 100 kHz) is highly sensitive to low ice volumes; therefore it could be used for determination **end point** of primary drying

Dielectric loss spectrum – liquid state

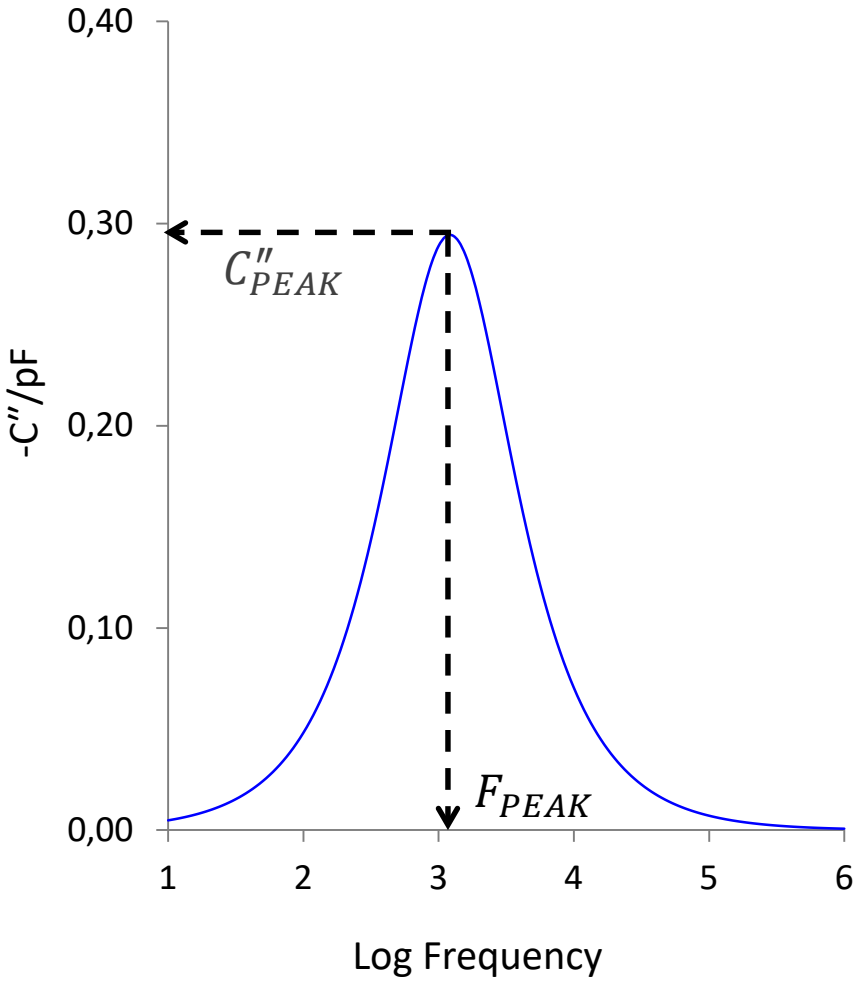
- *Data analysing software (LyoView ™) identifies the peak frequency (F_{PEAK}) and peak amplitude (C''_{PEAK}) in the imaginary part of the capacitance spectrum*

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

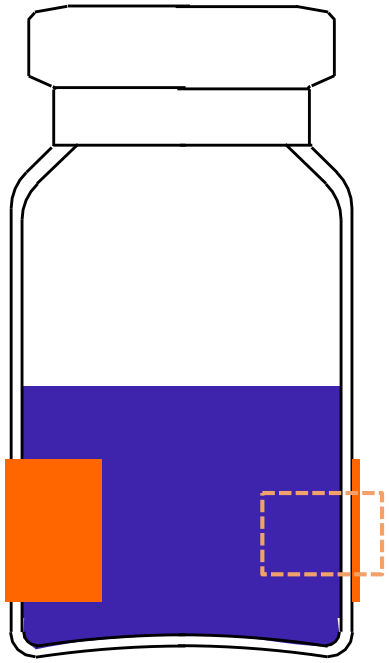
$$C''_{PEAK} = \frac{C_G^2}{2(C_s+C_G)}$$

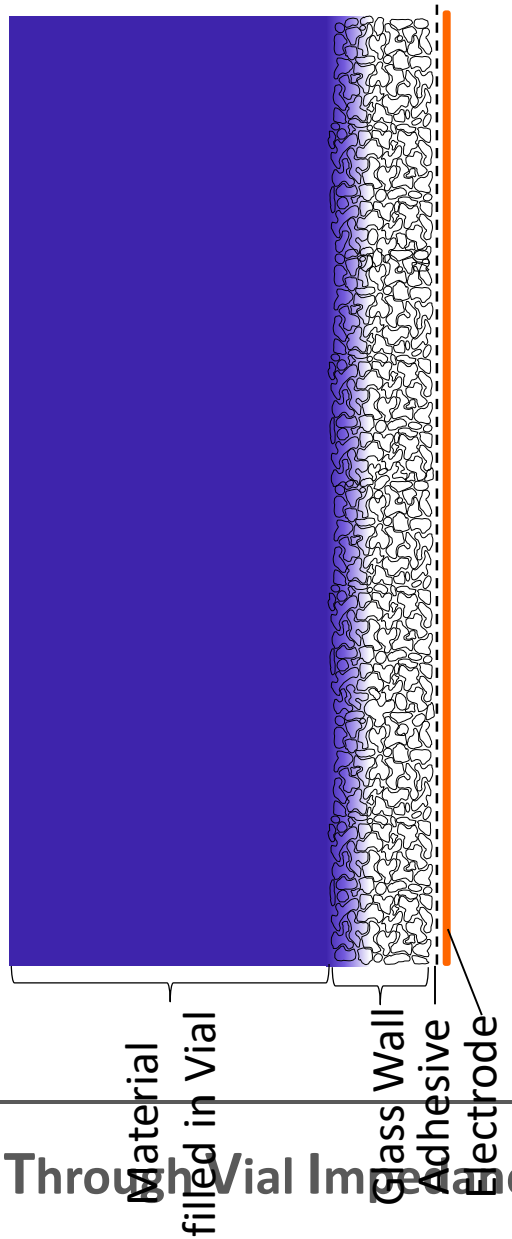
- A frequency of

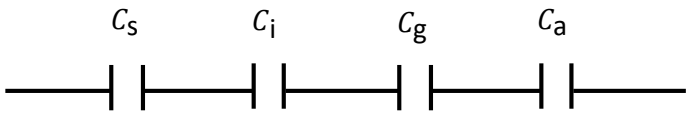
$$F_{PEAK} = \frac{1}{2\pi R_S(C_s + C_G)}$$



Glass-liquid Interface capacitance







C_s Capacitance of the sample

C_i Capacitance of the interfacial layer between the glass and the sample

C_g Capacitance of glass wall

C_a Capacitance of adhesive layer

$$\frac{1}{C_T} = \frac{1}{C_s} + \frac{1}{C_i} + \frac{1}{C_g} + \frac{1}{C_a}$$

$$C_T = \frac{C_s C_i C_g C_a}{(C_i C_g C_a) + (C_s C_g C_a) + (C_s C_i C_a) + (C_s C_i C_g)}$$

C_T Total capacitance in series of C_s, C_i, C_g and C_a