A multiscale approach to simulate vacuum drying of a packed bed of spray-frozen particles

Munich - 27/10/2023

COMSOL CONFERENCE 2023 MUNICH

POLITECNICO DI TORINO

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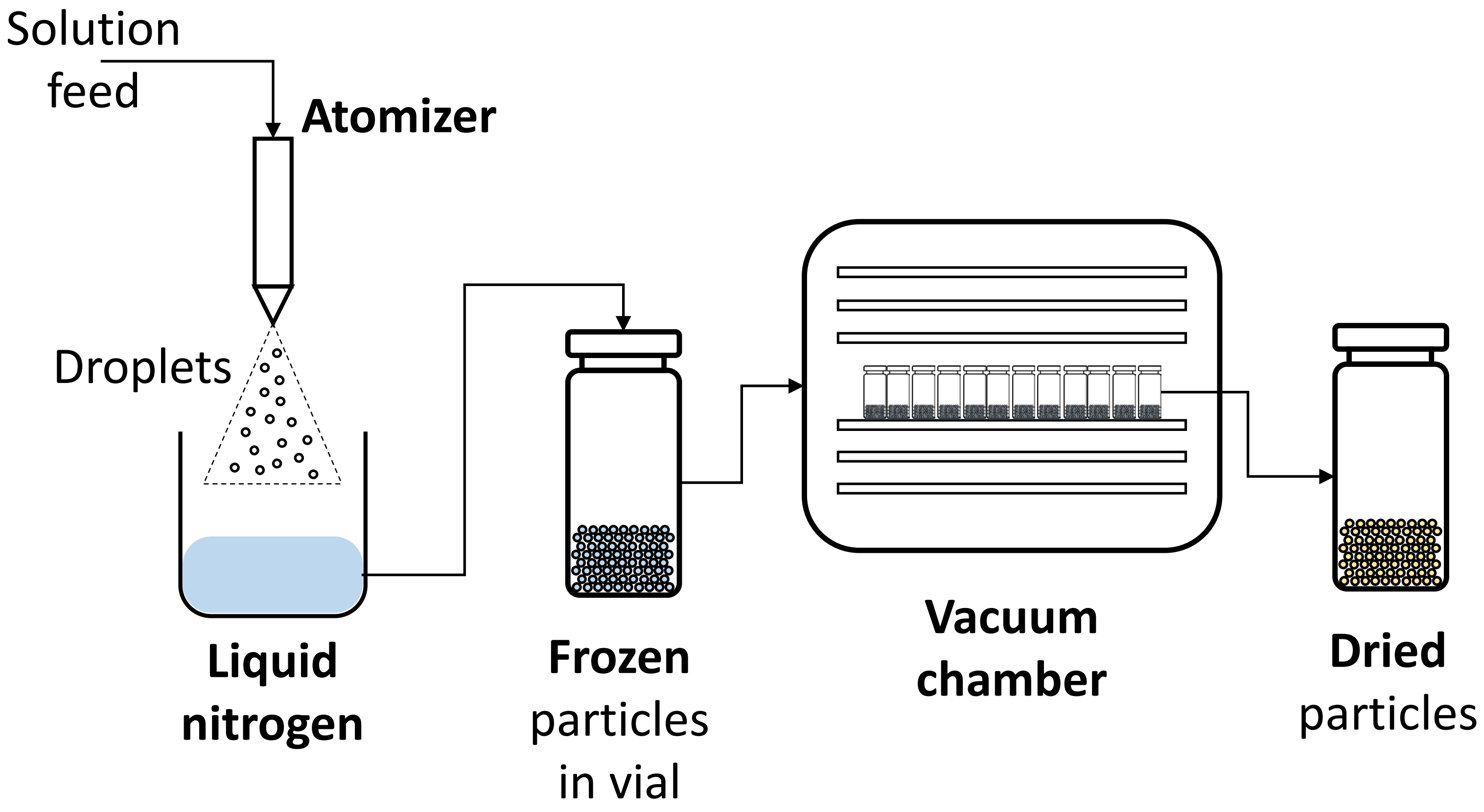
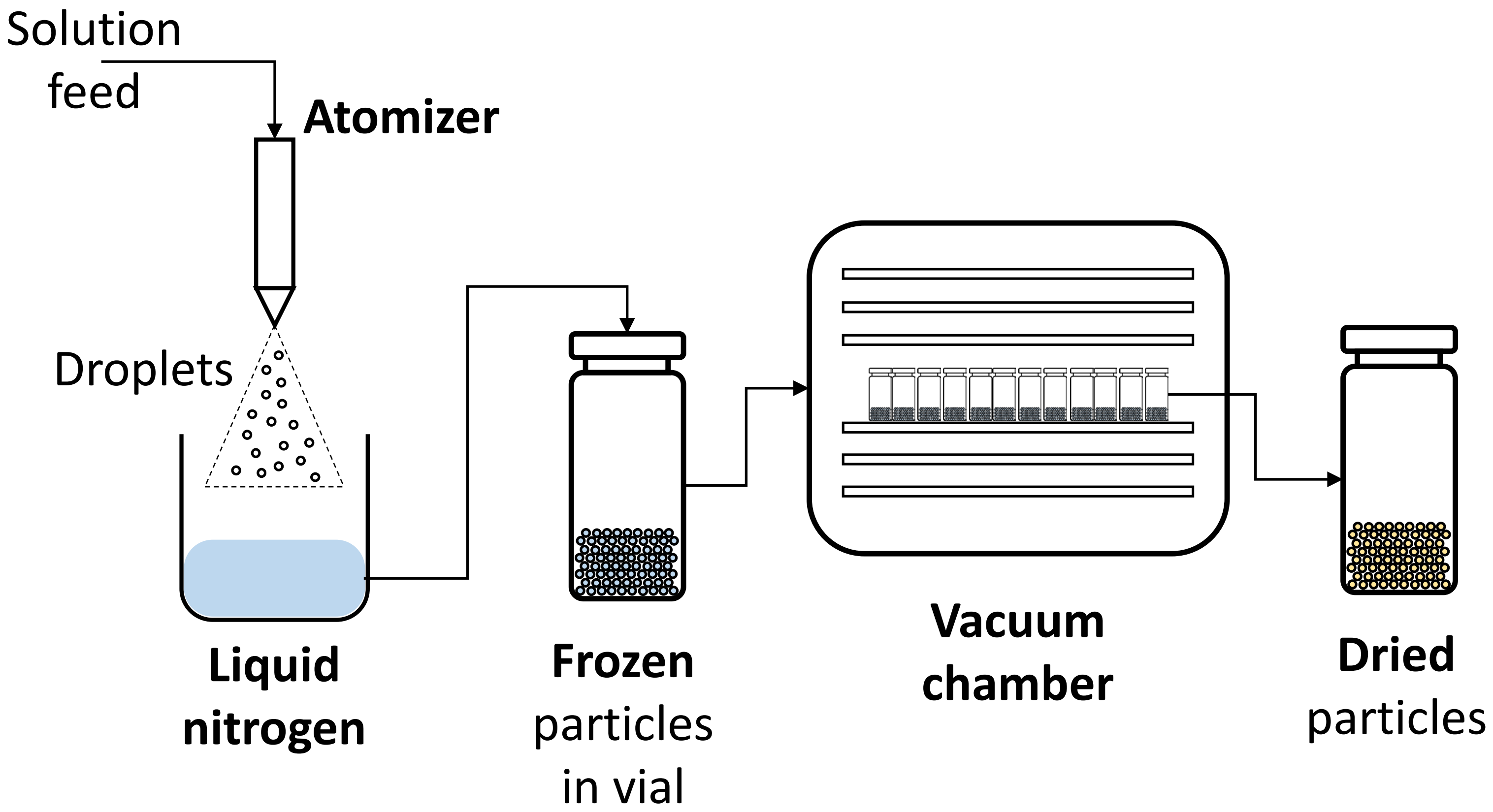
PhD Program in Chemical Engineering

Introduction

What is spray freeze-drying?



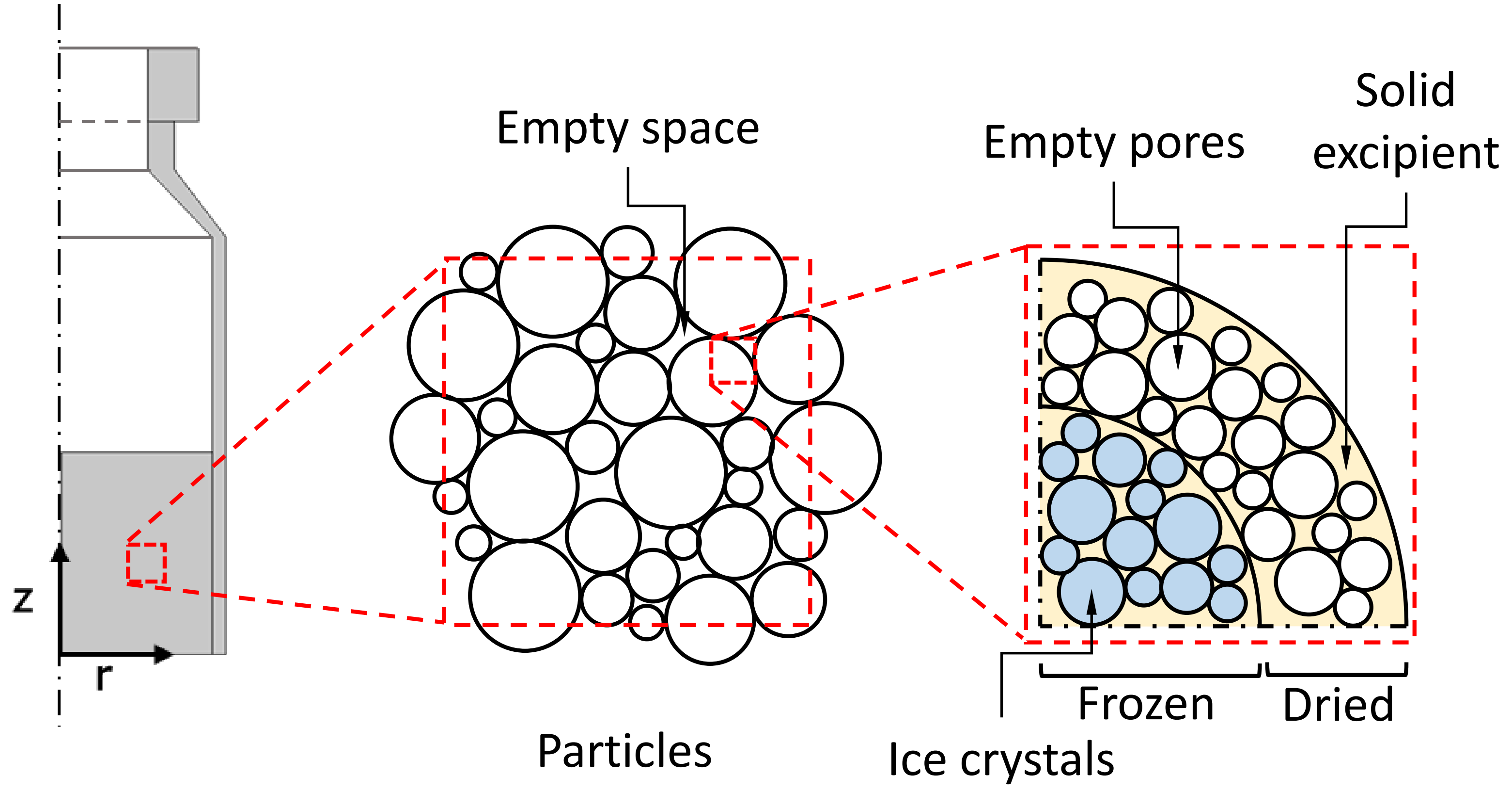
What is spray freeze-drying?



Why?

To **increase the shelf life** of (biopharmaceutical) products that are:

- **Unstable** in **liquid** solution
- Sensitive to **high temperatures**



Multiphysic

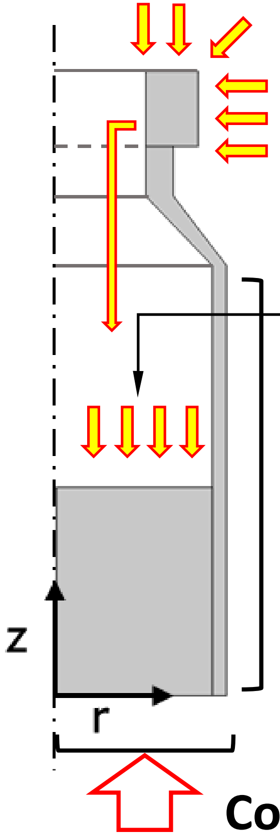
Heat transfer
Mass transport
Phase change

Scale	**Interface**
Micro	Yes
Macro	No

Solution ⇨ **Pseudo-homogeneous** model with **diffused interface**

Modelling

2D - axisymmetric



Radiation from shelf above

Surface-to-Ambient Radiation

$$-\mathbf{n}\cdot(-k_{bed}\nabla T_{bed}) = \sigma(\varepsilon_{vial,rad}T_{vial}^4 - \varepsilon_{bed,rad}T_{bed}^4)$$

Cascade **radiation** from vial top

Insulation

$$\nabla T = 0$$

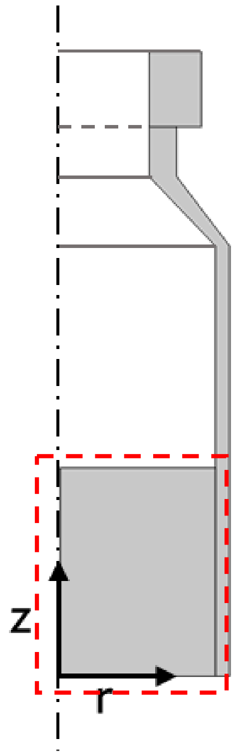
Conduction from shelf below

$$-\mathbf{n}\cdot(-k_{bed}\Delta T_{bed}) = K_v'(T_{shelf} - T_{bed})$$

$$K_v' = A_1 + \frac{A_2 P_c}{1 + A_3 P_c}$$

Heat transfer

2D - axisymmetric



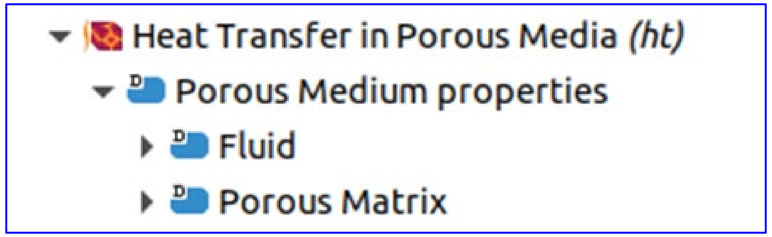
Heat transfer

Accumulation | **Conduction** | **Convection** | **Generation**

$$\rho_{bed} c_{p,bed} \frac{\partial T_{bed}}{\partial t} = \nabla(k_{bed} \nabla T_{bed}) - c_{p,gas}\left(\nabla(\mathbf{N}_t T_{bed})\right) + \dot{Q}$$

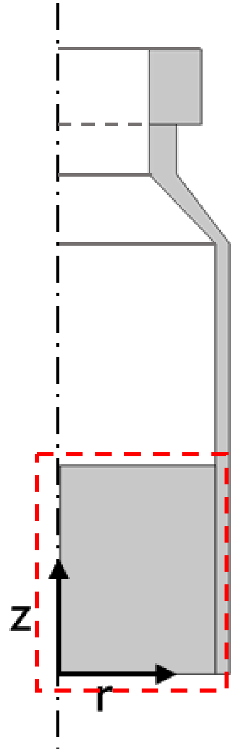
$c_{p,bed}$ → Linear combination of **frozen, dried and empty** domains

$\mathbf{N}_t$ → Total **mass flow** (inert + water vapor)



Modelling – Macroscale

2D - axisymmetric



Heat transfer

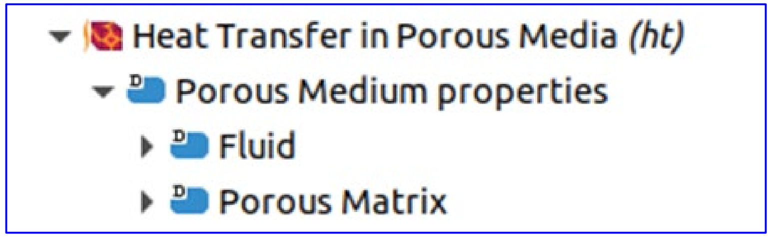
Accumulation	Conduction	Convection	Generation

$$\rho_{bed} c_{p,bed} \frac{\partial T_{bed}}{\partial t} = \nabla(k_{bed} \nabla T_{bed}) - c_{p,gas}\left(\nabla(\mathbf{N}_t T_{bed})\right) + \dot{Q}$$

- $c_{p,bed}$: Linear combination of **frozen, dried and empty** domains
- $\mathbf{N}_t$: Total **mass flow** (inert + water vapor)
- $\dot{Q}$: Heat source

$$\dot{Q} = -G_w \Delta H_s M_w$$

- G_w: **Sublimation rate**
- ΔH_s: **Latent heat** of sublimation
- M_w: Water molecular weight



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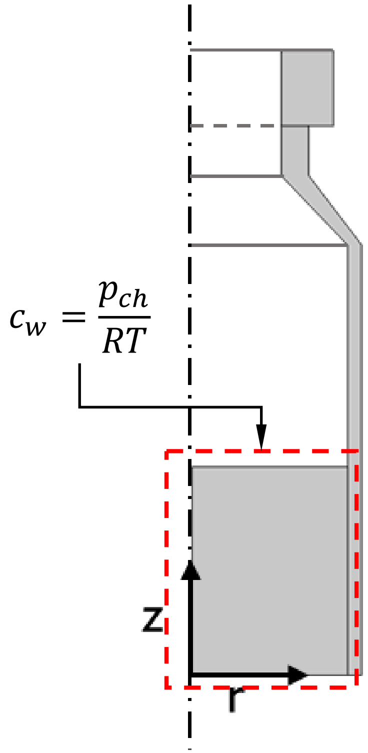
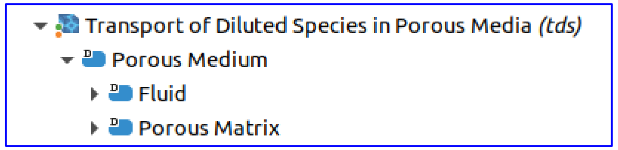
2D - axisymmetric



Mass transport



Accumulation | **Convection** | **Generation**

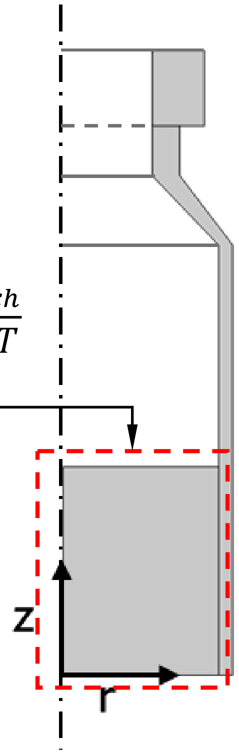
$$\frac{\partial(\varepsilon_{res} C_w)}{\partial t} = -\nabla \mathbf{N}_w + G_w$$

2D - axisymmetric

Mass transport

- Transport of Diluted Species in Porous Media (*tds*)
  - Porous Medium
    - Fluid
    - Porous Matrix

$$c_w = \frac{p_{ch}}{RT}$$



Accumulation **Generation**

$$\frac{\partial(\varepsilon_{res} C_w)}{\partial t} = -\nabla \mathbf{N}_w + G_w$$

Convection

$$G_w = \left(\frac{p^0_{ice}(T)}{RT} - C_w\right) v$$

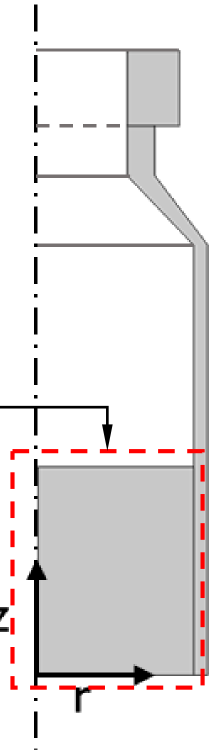
Species Source

Equilibrium concentration

Instantaneous concentration

Kinetic parameter

2D - axisymmetric



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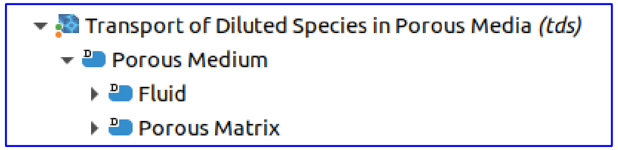

Mass transport

Accumulation **Convection** **Generation**

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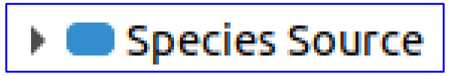


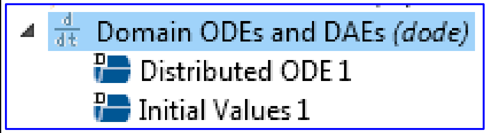
Equilibrium concentration

Instantaneous concentration

Kinetic parameter

The **integral** of the sublimation rate gives the total **sublimated ice**

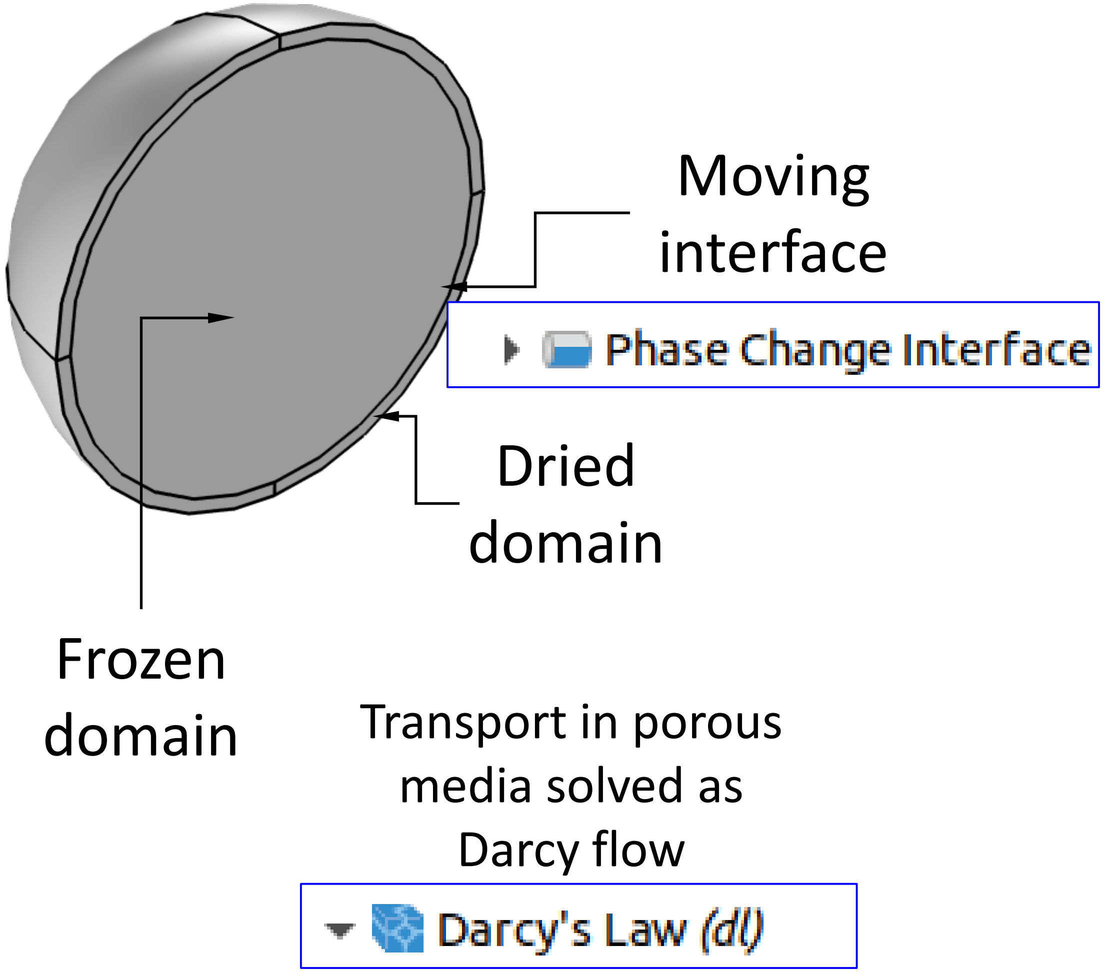
$$C_{ice,sub} = \int_0^t G_w dt$$



$$S = 1 - \frac{C_{ice,sub}}{C_{ice,0}}$$

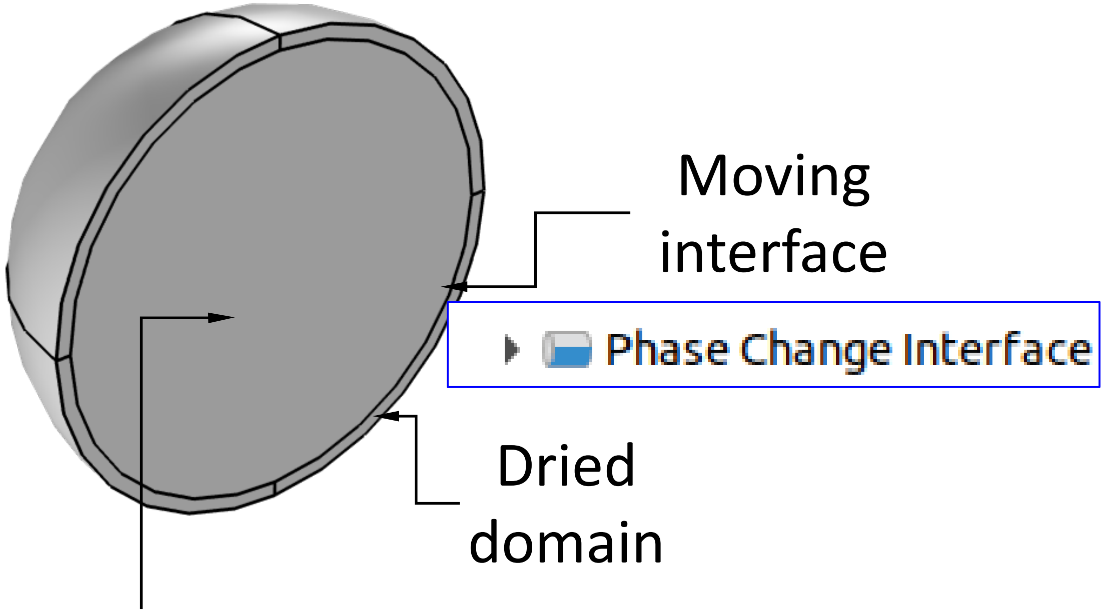
Ice saturation

Index of drying progression



To calculate the kinetic parameter:

Single-particle simulation



Frozen
domain

Transport in porous media solved as Darcy flow

Darcy's Law *(dl)*

To calculate the kinetic parameter:

Single-particle simulation

Sublimation flux over the whole interface

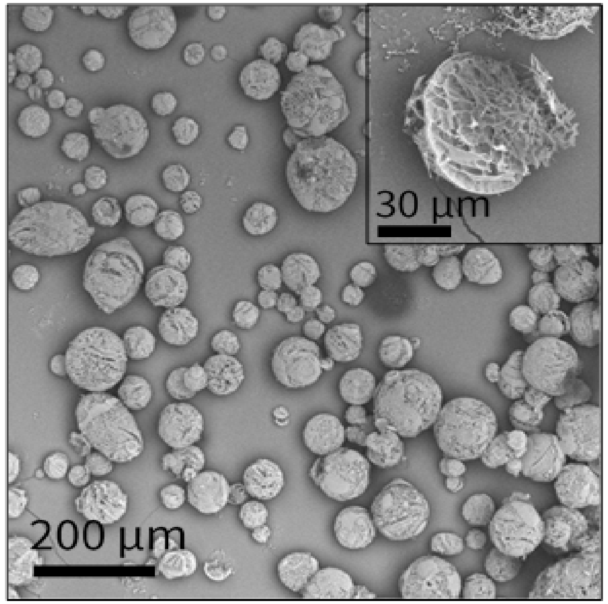
$$v_s = \frac{\oiint \mathbf{n}_{int} \cdot \mathbf{N}_{w,int} dS_{int}}{\left(\frac{p_{int}}{RT_{int}} - \frac{P_c}{RT_{r=R_0}}\right) M_w V_{ref}}$$

Water concentration at the **interface**

Water concentration **outside** the particle

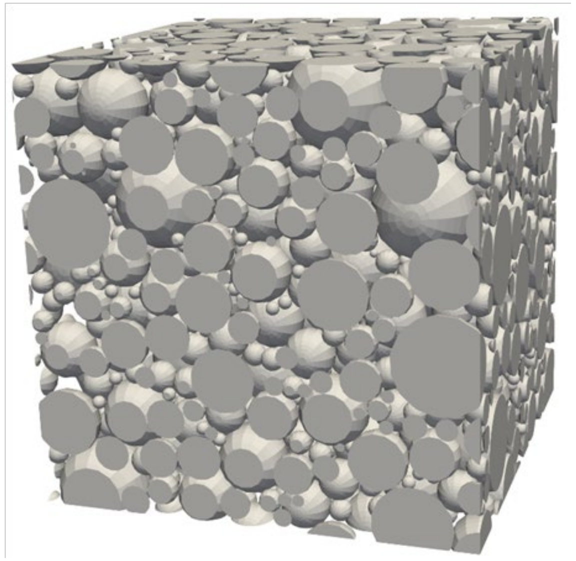
Reference volume

Experiments



From **SEM** images, obtain the **particle size distribution**

Generation of **packed bed geometry**

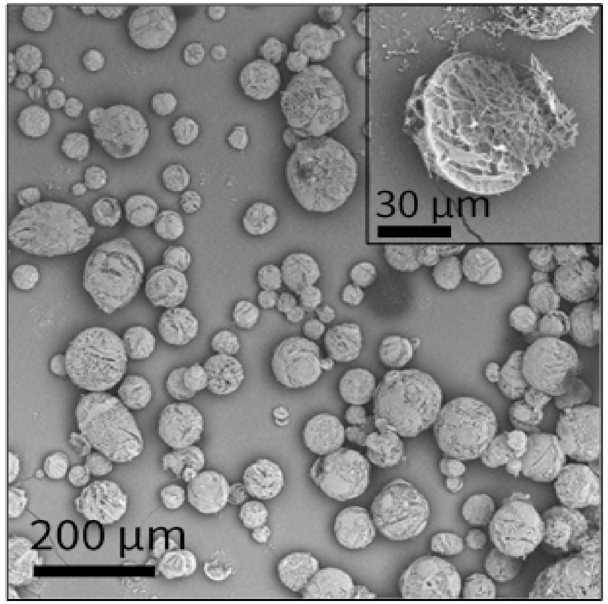


From **simulations** of the packed bed, obtain the **bed descriptors**

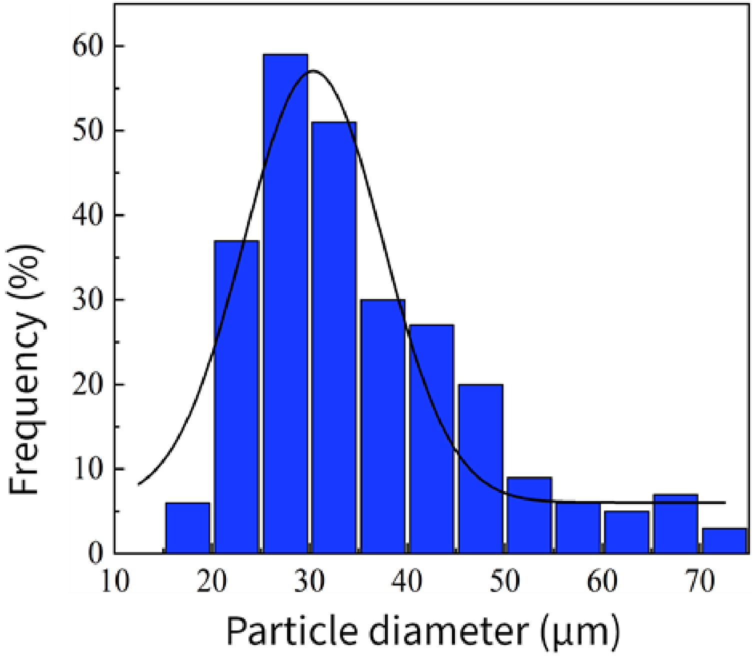
Simulations

To obtain:

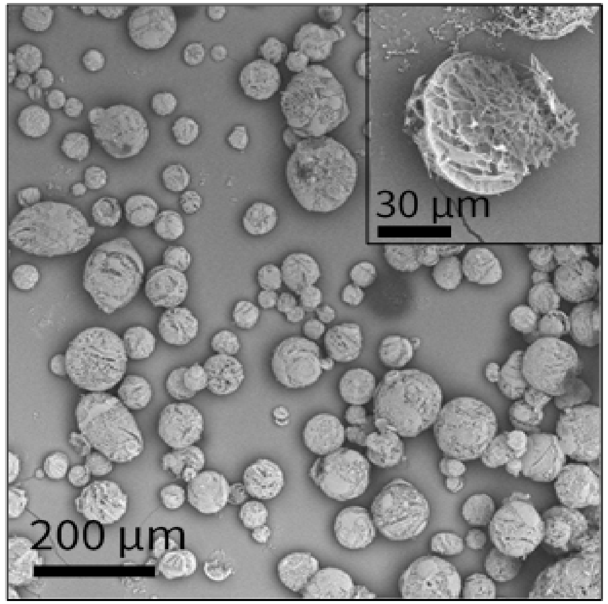
- Porosity
- Tortuosity
- Permeability
- Pore size



5% mannitol solution
60kHz ultrasonic atomizer
Feed: 5ml/min



- ε_{bed} = **0.39 -**
- τ = **1.33 -**
- $B_{0,b}$ = **$1.12 \cdot 10^{-11}$ m^2**
- $d_{pore,b}$= **19.5 µm**



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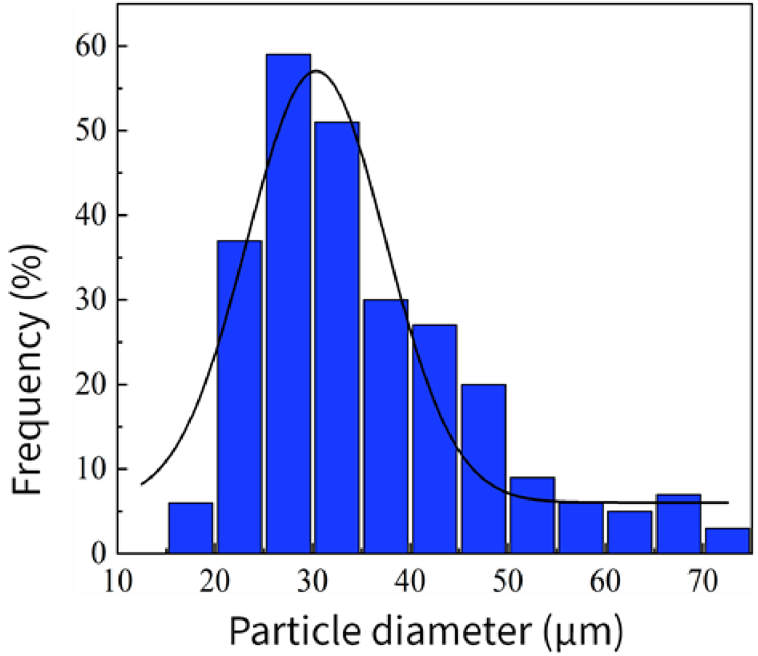

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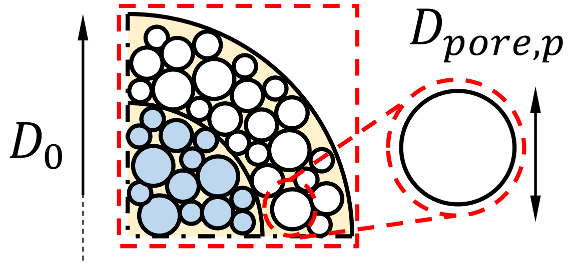


Plus one additional parameter:

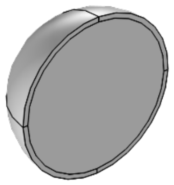
$$X = \frac{D_0}{D_{pore,p}}$$

Particle diameter

Pore diameter (in the particles)

X = 30-100-1000

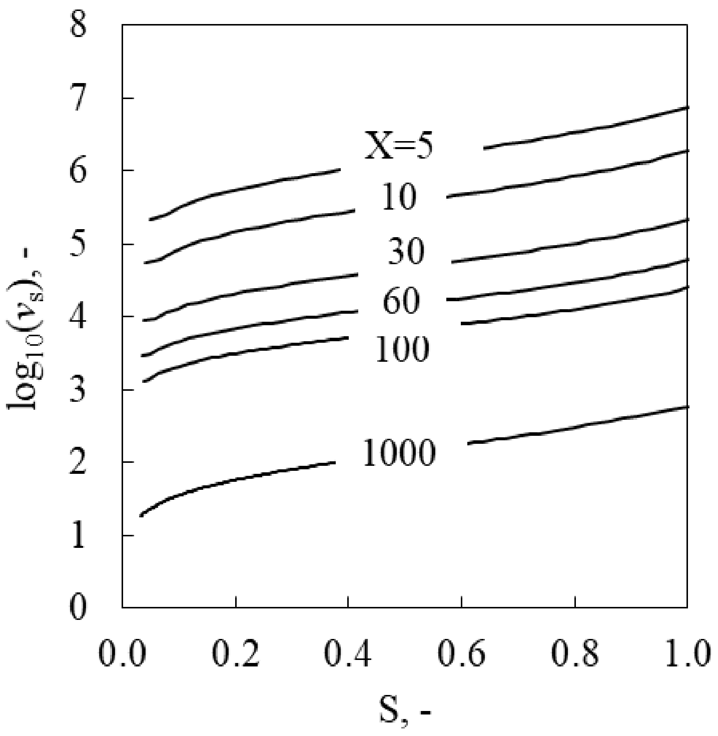
Results



$X \Downarrow$

$=$

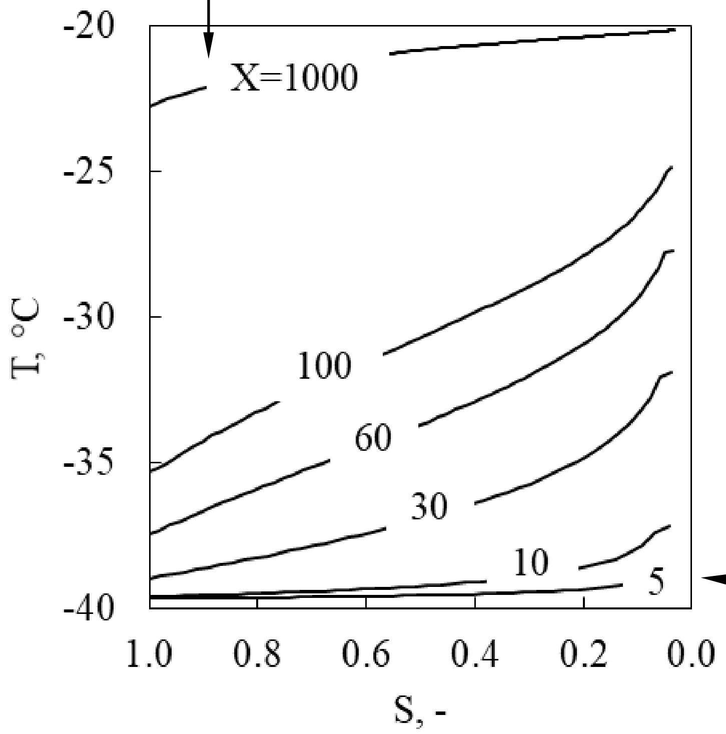
$v_s \Uparrow$



Large pores in the particles
allow **large sublimation rates**

Mass transport controls
the sublimation rate

$T = T_{shelf}$

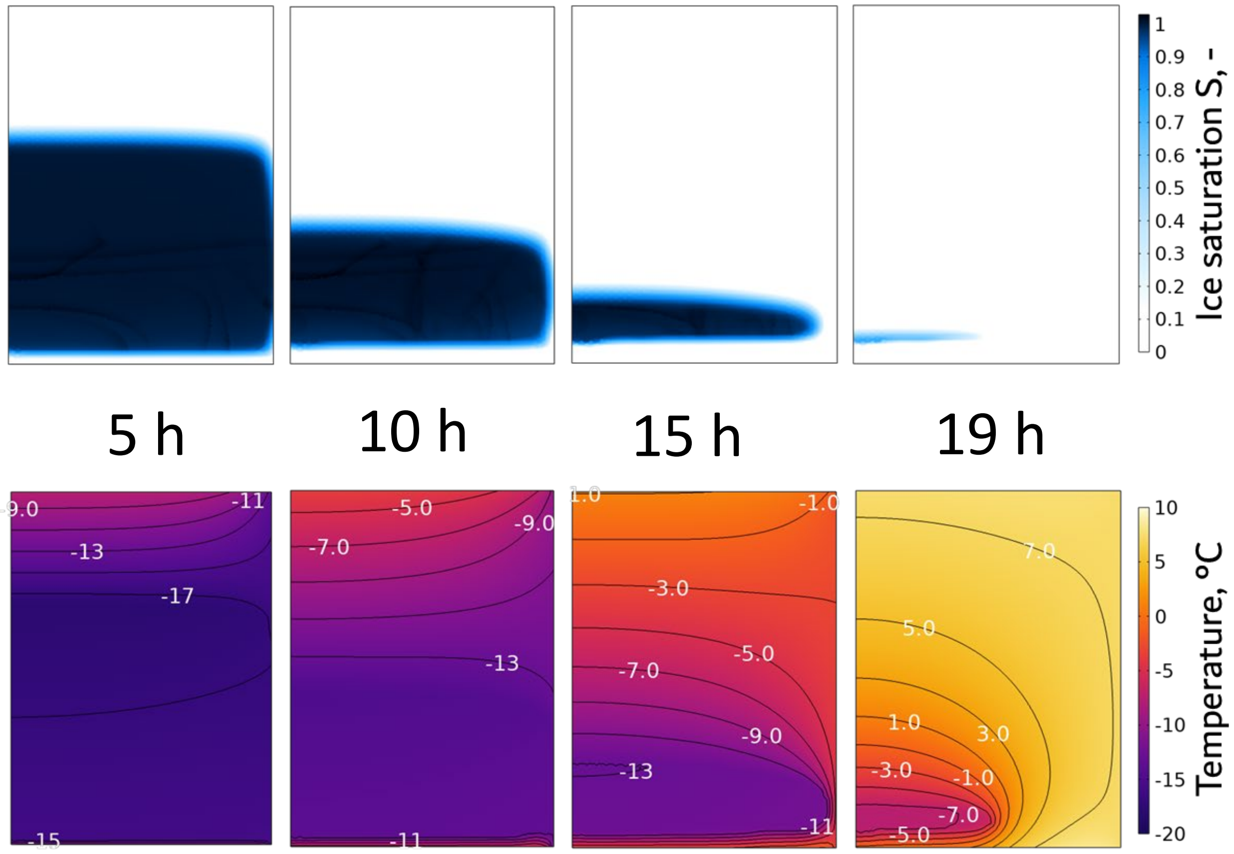


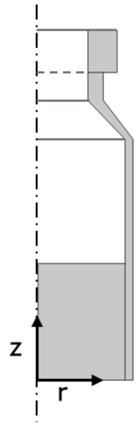
$T = T_{eq}(p_{ch})$

Heat transfer controls
the sublimation rate

Packed bed domain

$X = 100$





From the gradient in the Ice Saturation

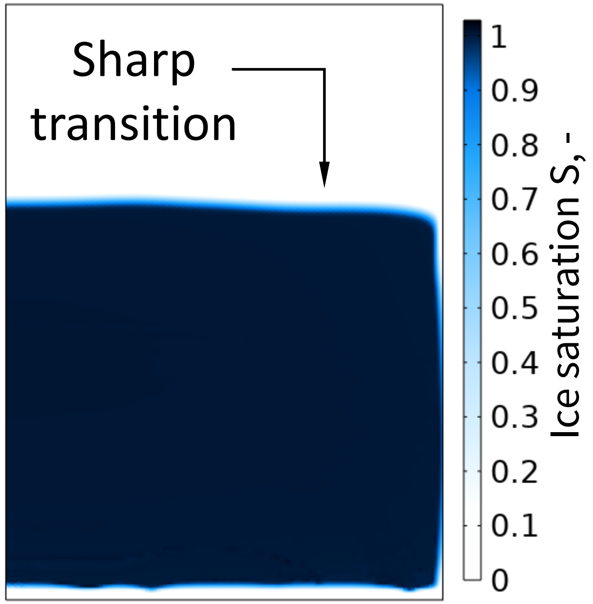
Detection of **sublimation fronts**

Three distinct **sublimation fronts** emerge

Bottom	Top	Side
Slow	Fast	Slow

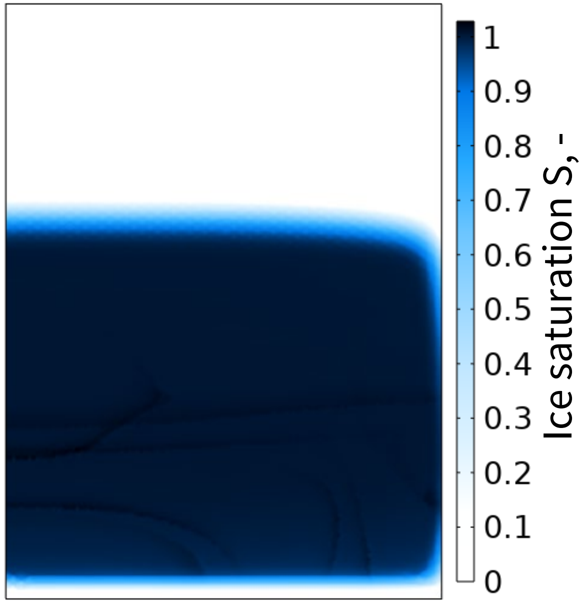
Drying time = 5 h

$X = 30$



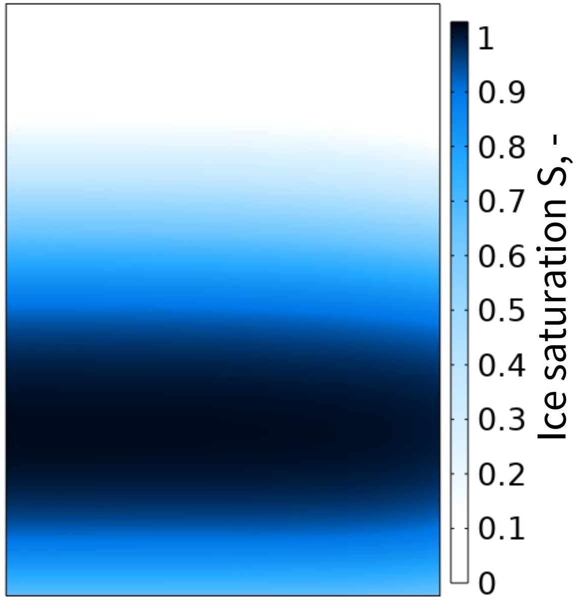
Bed porosity is **controlling**

$X = 100$



Intermediate

$X = 1000$



Particle porosity is **controlling**

Diffused interface within the whole domain

The whole bed dries at the same time

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A diffused-interface model for the lyophilization of a packed bed of spray-frozen particles

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Diffused interface
Multiscale
Particles

ABSTRACT

Spray freeze-drying is particularly suitable for the preservation of biopharmaceuticals as it involves gentle drying and can easily be integrated with continuous manufacturing strategies. This process is still an evolving application, and its potential is often being explored experimentally. However, experimental methods are expensive and time-consuming. Therefore, much effort is currently focused on the development of mathematical models to understand the basic mechanisms and hence lay the foundation for analysis and experimentation. Even though a few models were proposed in the past, all of them presented various flaws and failed in describing the process behavior. We propose a multiscale approach, which is able to reproduce the structure of a packing of spray-frozen particles and extract detailed pore-scale geometrical features, informing the final vial-scale drying and heat transfer simulation. This latter step is the main innovation here presented, a new model that is based on the concept of a diffused interface and describes the process in a more accurate way.

Thanks to my co-authors :

Merve B. Adali

Antonello A. Barresi

Gianluca Boccardo

Agnese Marcato

Raffaele Tuccinardi

Roberto Pisano

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Thank you for the attention

Any comments or questions?