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ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

# Modelling pharmaceutical crystallisation processes using a coupled CFD-population balance approach

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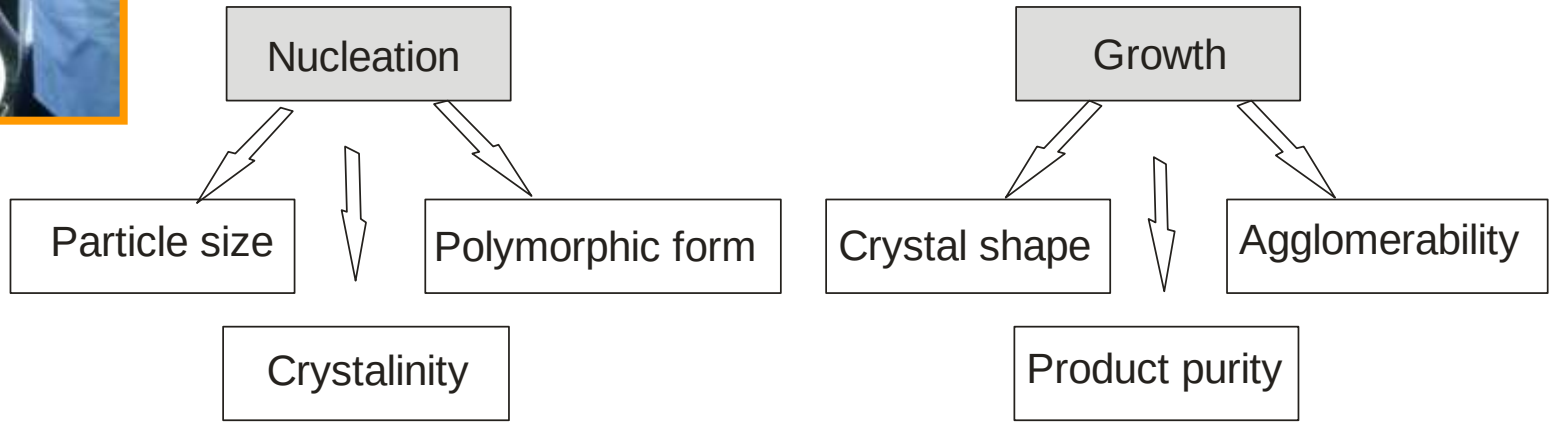
# Particle Formation Via Crystallisation



- Crystallisation is an essential process for the isolation & purification of APIs
- Process is driven by supersaturation involving two key steps, which affect the design of particles formed: nucleation & crystal growth




- Controlling competing demands for supersaturation by nucleation & growth is key issue for both particle design & process scale up

# Modelling Approach Context



- Crystallisation generally performed in glass-lined jacketed stirred crystallisers with different configurations
- Stirred tanks are inhomogeneous fluid mechanical environment

To this issue add

- Common crystallisation models assume perfectly mixed volume
- Incorrect estimation of nucleation, growth & agglomeration rates results in errors in predicted particle size & shape distributions
- Limited applicability of existing models in extrapolation to other scales of operations or other geometries
- Available models still are input-output which are tuned for a single configuration

- Robust process development & scale up requires detail knowledge of solid concentration distribution, supersaturation distribution, local velocities, shear rates, energy dissipation rates ….

- Design of a crystalliser & selection of operating conditions are vital for obtaining crystals with the required physical properties. e.g. crystal size distribution (CSD), morphology & purity
- Modelling approach coupling computational fluid dynamics (CFD) & population balance model (PBM)

# Holistic Framework for Modelling Crystallisation Processes



Morphological Population Balance (MPBM)/Poster (30)

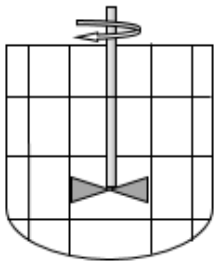
Fully Couple CFD -1D Population Balance (PBM)

UDF

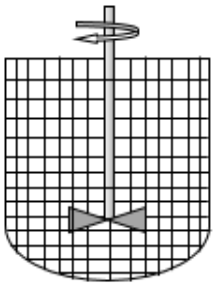
Solubility, Nucleation & Growth Kinetics Models

Library of CFD Database for Design & Scale-up of Crystallisation Processes

Scale-up Correlations



Network of Well-mixed Zones



Solubility, Nucleation & Growth Kinetics Data

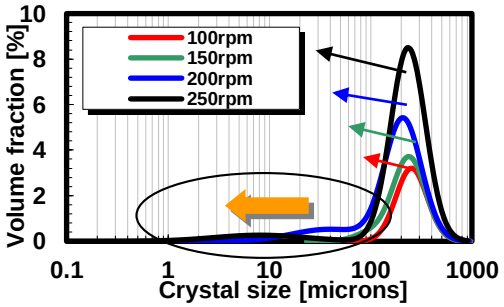
SOP's to Estimate Key Kinetics Parameters Using gCRYSTAL Parameters Estimation Tool

Zonal Process Model gCRYSTAL

Strategy Define "Well Mixed" Zones

Developed CFD Methodology

CFD Fluent Hydrodynamics/ Mixing/Heat Transfer




Crystallisation Process Data for Model Validation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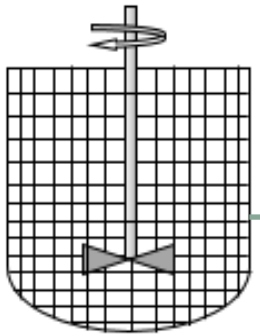
# Interactions Between CFD and gCRYSTAL



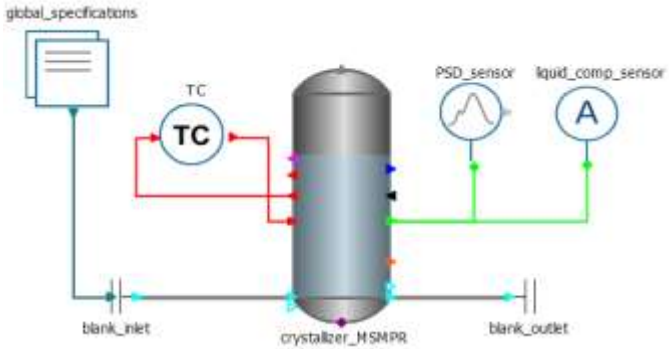
## 1.1. Coupling with single well-mixed zone system



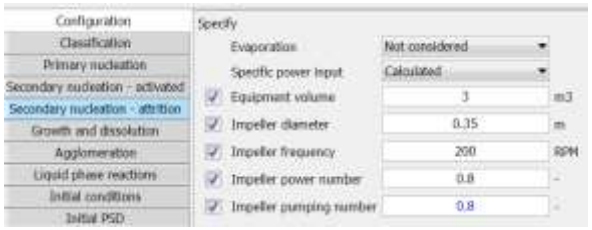
CFD Fluent Hydrodynamics/mixing/ heat transfer

**Lumped hydrodynamics parameters**

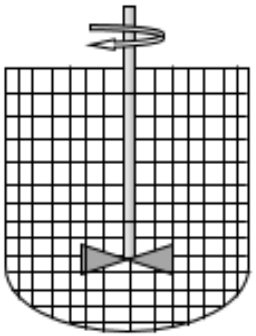
- Impeller power number
- Impeller pumping number
- Pumping efficiency
- Secondary circulation flow




gCRYSTAL Single well mixed zone



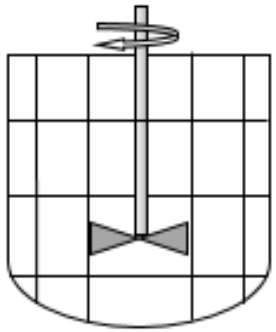

## 1.2. Coupling with Multi-zonal model



CFD Fluent Hydrodynamics/mixing/ heat transfer

**Inter-zone mass flow rates**

- Mass & momentum balances (velocities, solute concentration & Temperature distribution)
- Identify well mixed zones
- Coordinates centre each zone



Network of Well-mixed Zones

Zonal process Model gCRYSTAL



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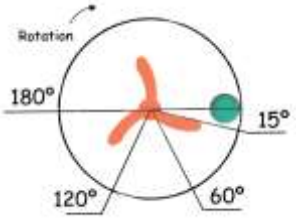
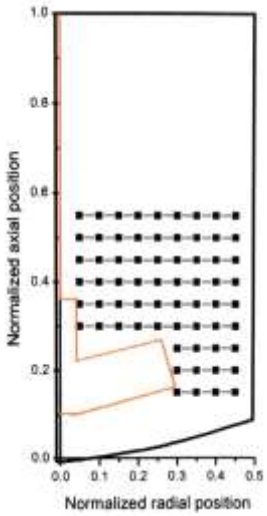
# Development & Validation of CFD Methodology: Single Phase



- CBBII project: 20 L single Beavertail baffle reactor with a retreat curve impeller




**Mesh: Tetrahedrons, Cells 597.801, Nodes 133.153**

**Different impeller speeds: 100, 150, 200 &250 rpm**

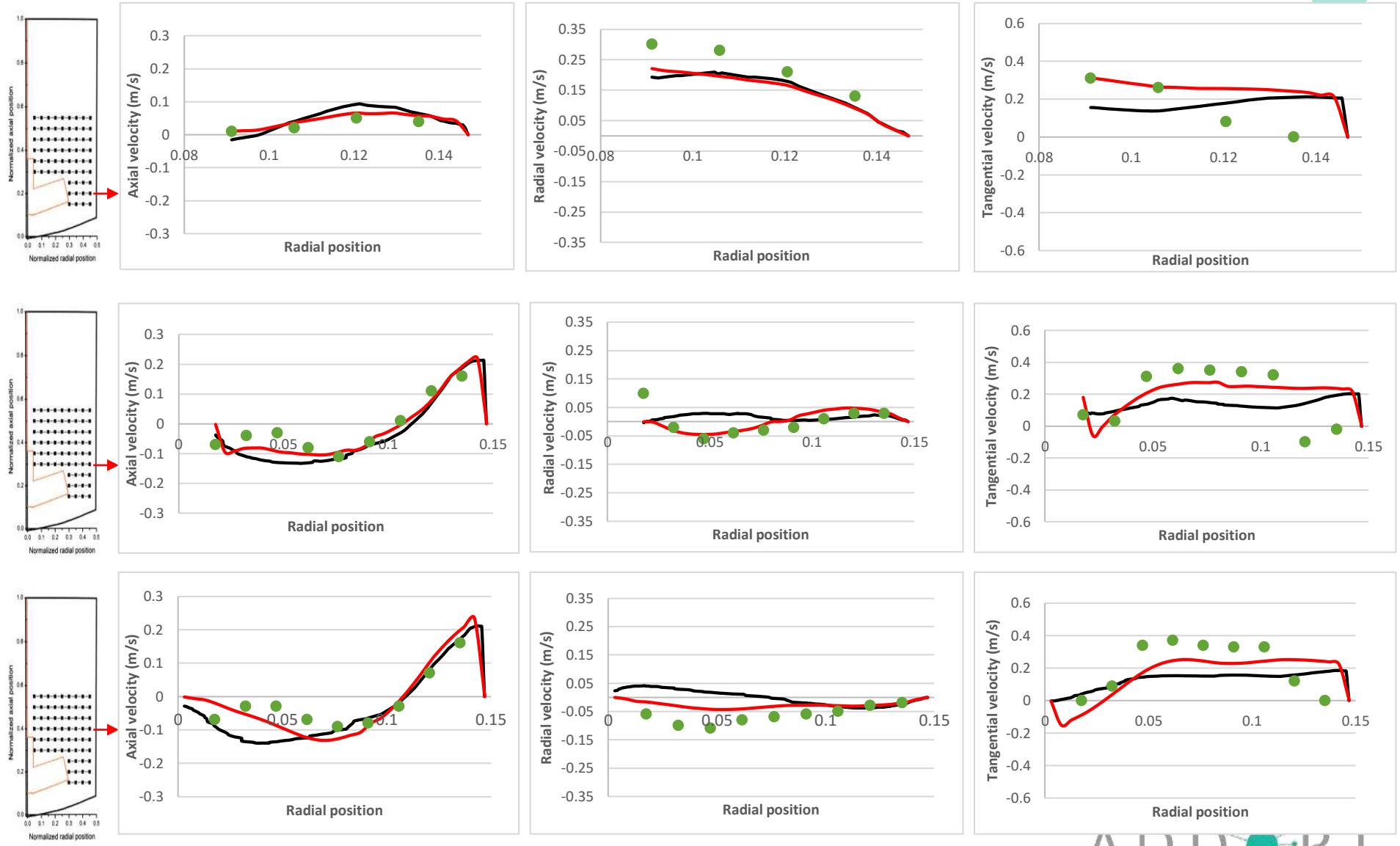
**Obtain prediction of velocity components as well as capture vortex profile**

- **CFD analysis for different turbulence models including: Shear Stress Transport (SST) & Reynold Stress Transport (RST) both for flat & free surface (coupled with Volume of Fluid (VOF) model). RST including Scalable Wall Functions (SWF)**

[1] Li, M., Graeme White, G., Wilkinson, D., Roberts, K.J., 2004. LDA measurements and CFD modelling of a stirred vessel with a Retreat curve impeller, *Ind. Eng. Chem. Res.,* 43, 6534-6547

# Development & Validation of CFD Methodology: Velocity Components at 100 rpm



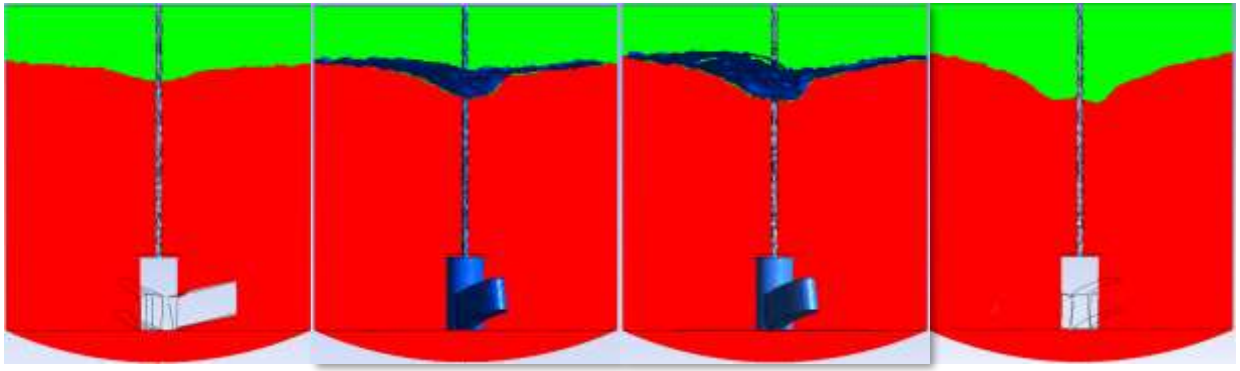



LDA
RST SWF
RST SWF VOF

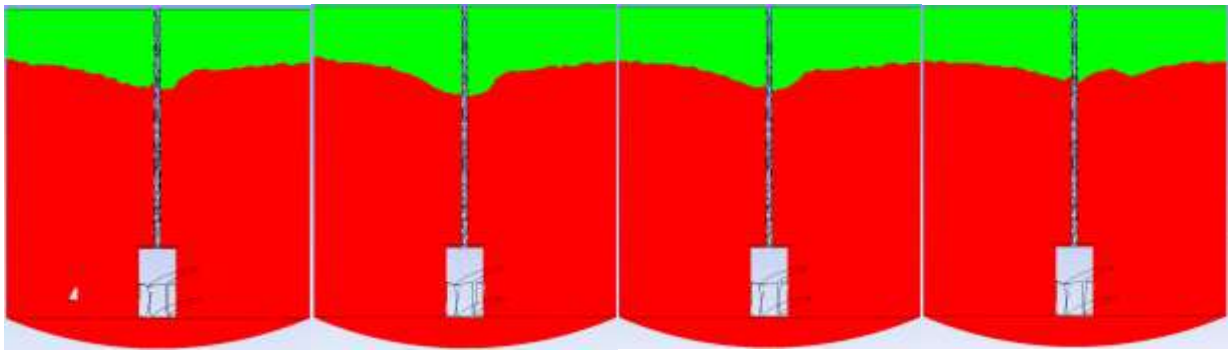
RST: Reynold stress transport
SWF: Scalable wall functions
VOF: Volume of fluid model

# Development & Validation of CFD Methodology: Vortex Profile





90 deg plane_100, 150,200 & 250 rpm



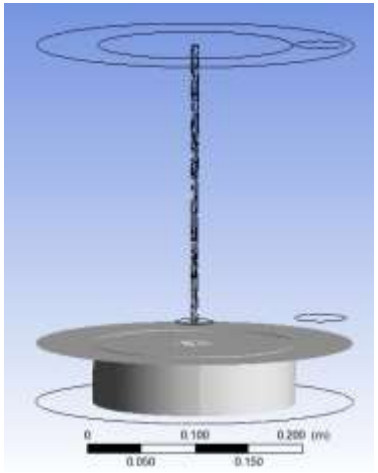
- ❑ Water turbulent
- ❑ Turbulent
- ❑ Transitional SST VOF
- ❑ Laminar
- ❑ Water/glycerine

90 deg plane_ 150 rpm, vis_0.001_0.0037, 0.0108, 0.0601

- ❑ Single baffle does not suppress vortex
- ❑ Volume of Fluid (VOF) model needed to assess hydrodynamics
- ❑ Effect of impeller speed & viscosity on vortex depth

# Development & Validation of CFD Methodology: Hydrodynamic Macro-parameters





- **Power number**

$$P = \omega \int_A r(\tau dA) \quad N_p = \frac{P}{\rho N^3 D^5}$$

- **Pumping efficiency: Pumping capability per unit of power consumed**

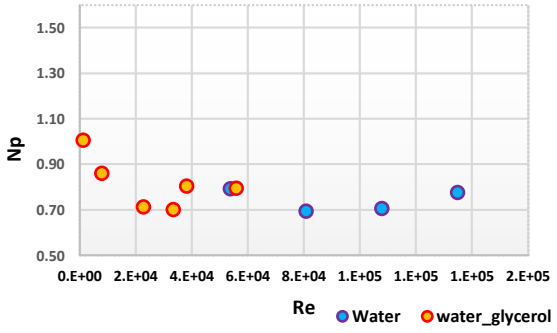
$$\eta = \frac{N_d}{N_p}$$

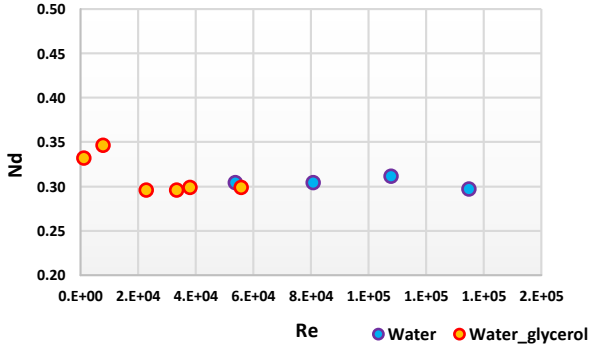
- **Pumping capacity (discharge flow)**

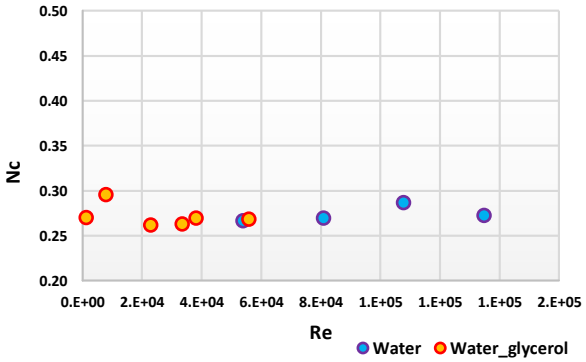
$$w_d = \int_{zb}^{zt} 2\pi\rho R_b v_r dz \quad N_d = \frac{w_d}{\rho N D^3}$$

- **Secondary circulation flow**

$$w_{up} = \int_{A+} \rho v_z dA_z \quad N_c = \frac{w_{up}}{\rho N D^3}$$

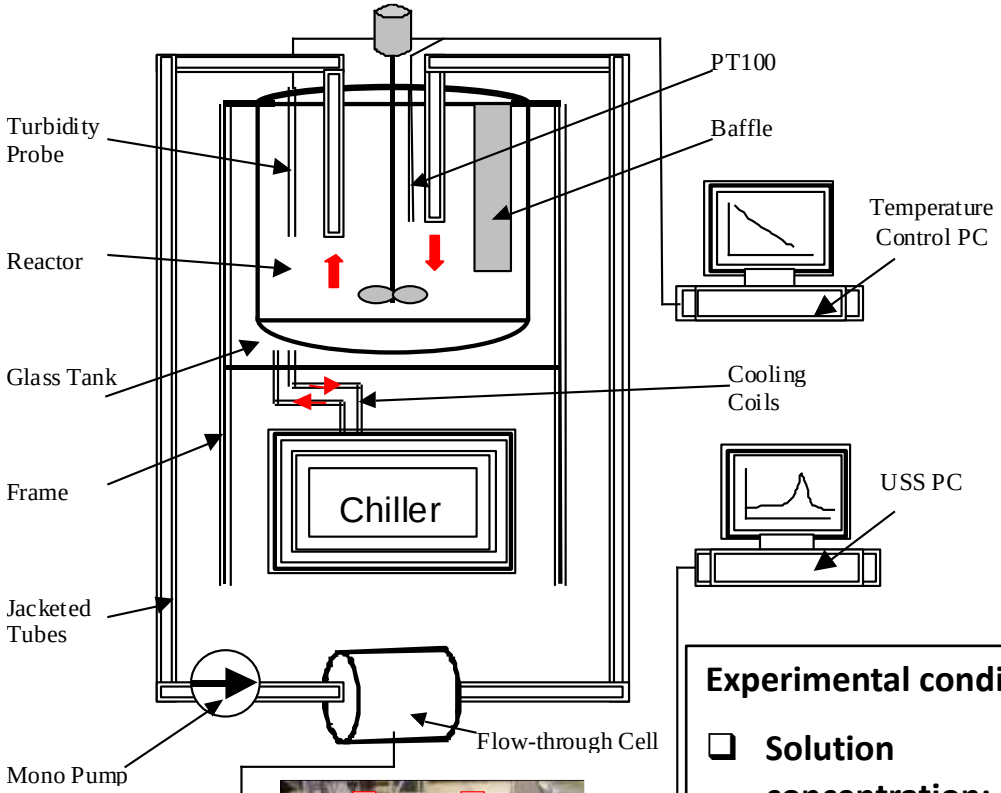


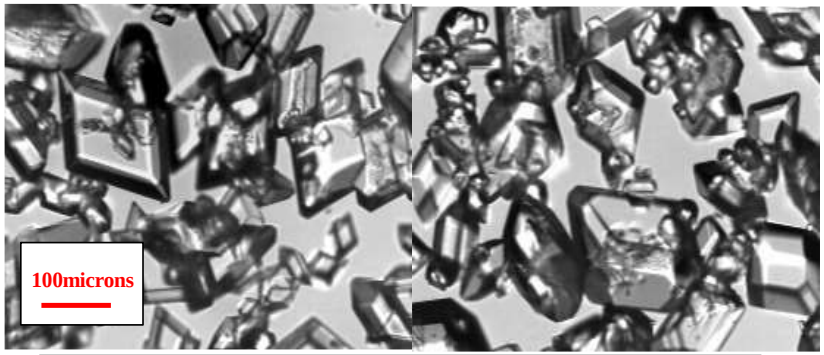



# Cooling Crystallisation of L-Glutamic Acid (LGA) α-form in Aqueous Solution: Measuring Crystal Size Distribution (CSD)





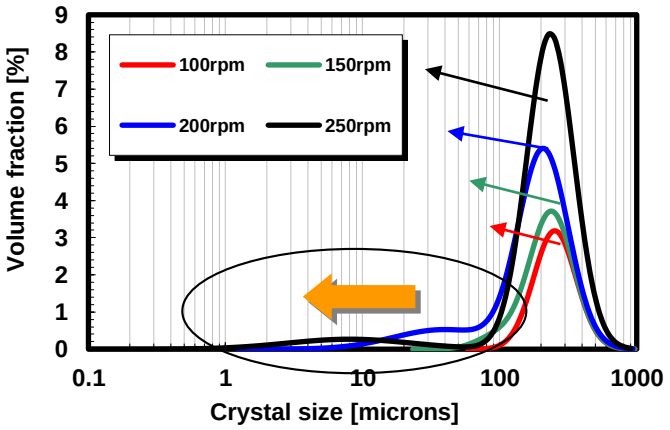

On-line ultrasonic spectrometer




Microscopic images of α-form L-glutamic acid crystals obtained at the end of batch cooling crystallisation from aqueous solution at 200rpm

**Experimental conditions:**

- Solution concentration: 45g/100g
- Cooling rate: 0.6 deg/min
- Stirrer speed: 100, 150, 200 & 250 rpm




2. K. Liang, Process Scale Dependence of L-glutamic Acid Batch Crystallised from Aqueous Solution in relation to Reactor Internals, Reactant Mixing and Process Conditions, Department of Chemical Engineering, Heriot-Watt University, Edinburgh, 2002.

# Modelling Methodology: Multiphase CFD Coupled with Population Balance Model (PBM)



**Continuity**

$$\frac{1}{\rho_{rq}}\left(\frac{\partial}{\partial t}(\alpha_q\rho_q)+\nabla.(\alpha_q\rho_q\overrightarrow{v_q})=\sum_{p=1}^{n}(\dot{m}_{pq}-\dot{m}_{qp})\right)$$

**Fluid-Solid momentum**

$$\frac{\partial}{\partial t}(\alpha_s\rho_s\vec{v}_s)+\nabla.(\alpha_s\rho_s\overrightarrow{v_s}\,\vec{v}_s)$$
$$=-\alpha_s\nabla p-\nabla p_s+\nabla.\bar{\bar{\tau}}_q+\alpha_s\rho_s\vec{g}+\sum_{p=1}^{N}(K_{ls}(\vec{v}_l-\vec{v}_s)+\dot{m}_{ls}\vec{v}_{ls}-\dot{m}_{sl}\vec{v}_{sl})+(\vec{F}_s+\vec{F}_{lift,s}+\vec{F}_{vm,s}+\vec{F}_{td,s})$$

$$K_{sl}=\frac{\alpha_s\rho_s f}{\tau_s}\qquad \tau_s=\frac{\rho_s d_s^2}{18\mu_l}\qquad d_s=\frac{\sum N_i L_i^3}{\sum N_i L_i^2}$$

**Species transport**

$$\frac{\partial}{\partial t}(\rho^q\alpha^q Y_i^q)+\nabla.(\rho^q\alpha^q\vec{v}^q Y_i^q)=-\nabla.\alpha^q\vec{J}_i^q+\alpha^q R_i^q+\alpha^q S_i^q+\sum_{p=1}^{n}(\dot{m}_{p^i q^j}-\dot{m}_{q^j p^i})+\mathcal{R}$$

**PBM**

$$\frac{\partial}{\partial t}(\rho_s\alpha_i)+\nabla.(\rho_s u_i\alpha_i)+\frac{\partial}{\partial V}\left(\frac{G_v\rho_s\alpha_i}{V}\right)=\rho_s V_i(B_{ag,i}-D_{ag,i}+B_{br,i}-D_{b,i})+O^i\rho_s V_0\dot{n}_0$$

**Transport equation for the discrete bin fraction $f_i$**

$$\frac{\partial}{\partial t}(\rho\alpha f_i)+\nabla.(\vec{u}_p\alpha f_i)=S_{b_i}$$

$$f_i=\frac{\alpha_i}{\alpha}$$

# Population Balance Model for Cooling Crystallisation of LGA in Aqueous Solution



- One-dimensional (1D) population balance model for a well mixed reactor. Disregarding agglomeration & breakage

$$\frac{\partial}{\partial t}(\rho_s \alpha_i) + \nabla.(\rho_s u_i \alpha_i) + \frac{\partial}{\partial V}\left(\frac{G_v \rho_s \alpha_i}{V}\right) = \rho_s V_i\left(B_{ag,i} - D_{ag,i} + B_{br,i} - D_{b,i}\right) + \rho_s V_0 \dot{n}_0$$

$$\frac{\partial}{\partial t}(\rho_s \alpha_i) + \nabla.(\rho_s u_i \alpha_i) + \frac{\partial}{\partial V}\left(\frac{G_v \rho_s \alpha_i}{V}\right) = \rho_s V_0 \dot{n}_0$$

$$G = k_G(\sigma)^n \qquad J = k_B(\sigma)^b$$

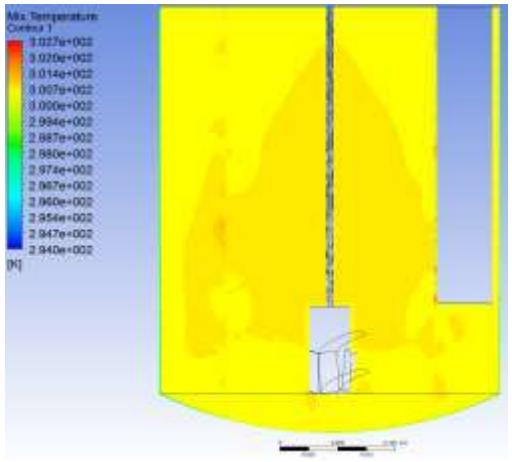
$$k_G = 9.76\ x\ 10^{-08} \qquad k_J = 4.02\ x\ 10^{6}$$

$$n = 2.34 \qquad b = 1.87$$

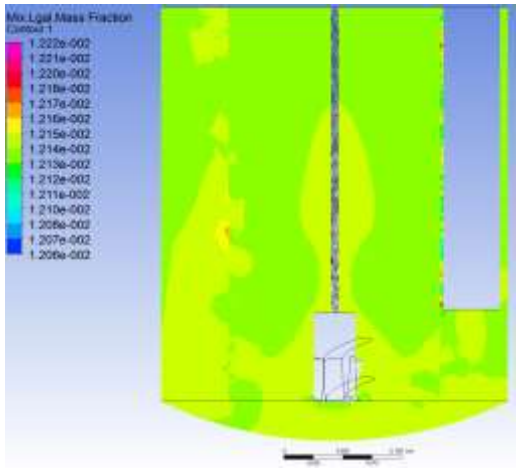
[3] Y. Clifford, W.L. Shei, 1992. Crystallisation kinetics and product purity of alpha-glutamic acid crystal, Chem. Eng. Comm., 120, 139-152

# Contours for Cooling Crystallisation of LGA in Aqueous Solution: Cooling from 70 to 25 deg C at 100 rpm

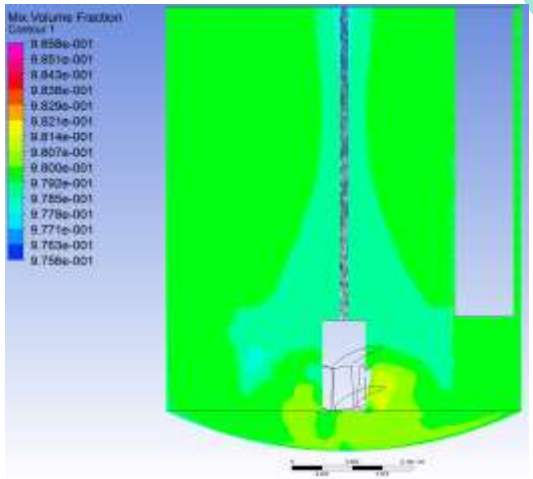




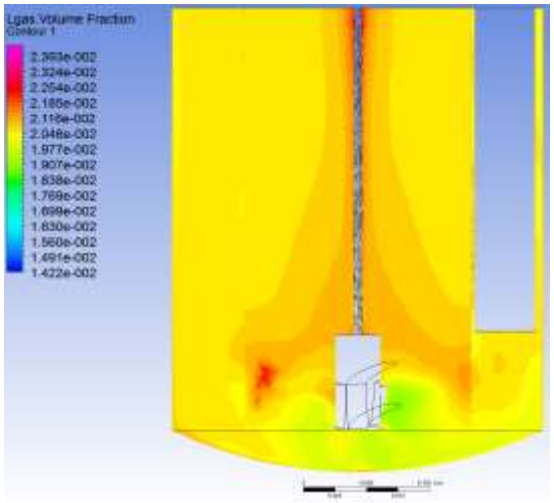
- Temperature distribution



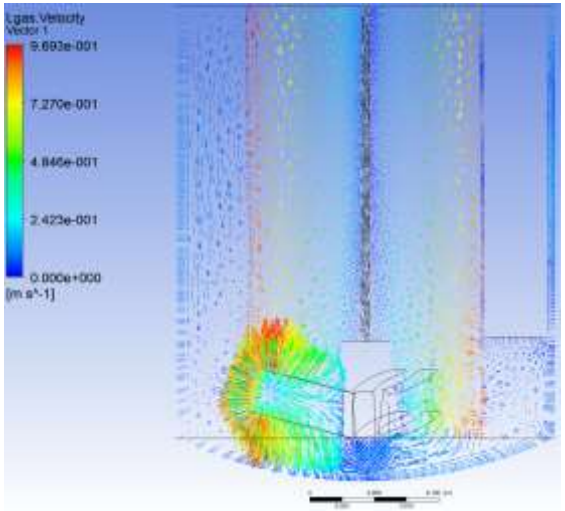
- Mass fraction of LGA



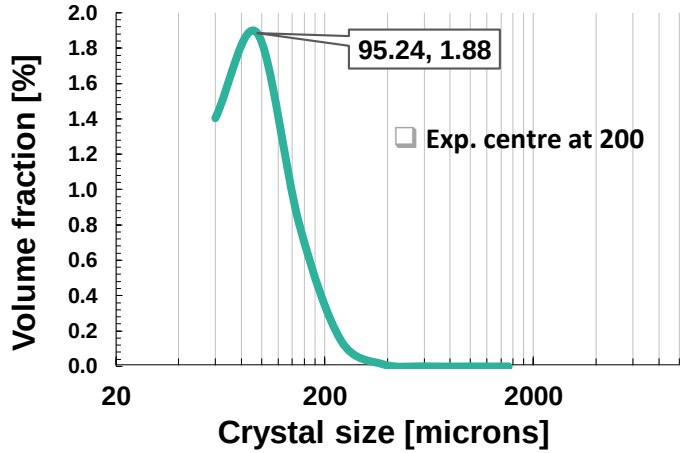
- Volume fraction of liquid phase



- Volume fraction of solid phase

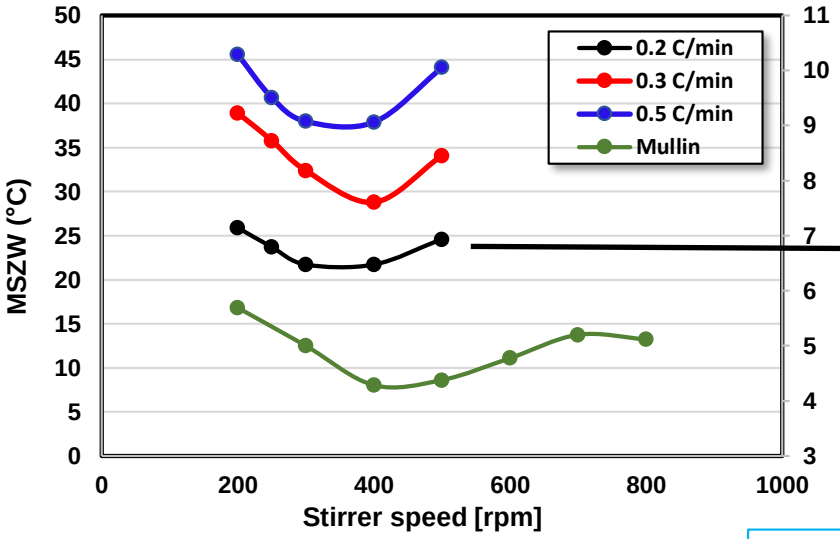


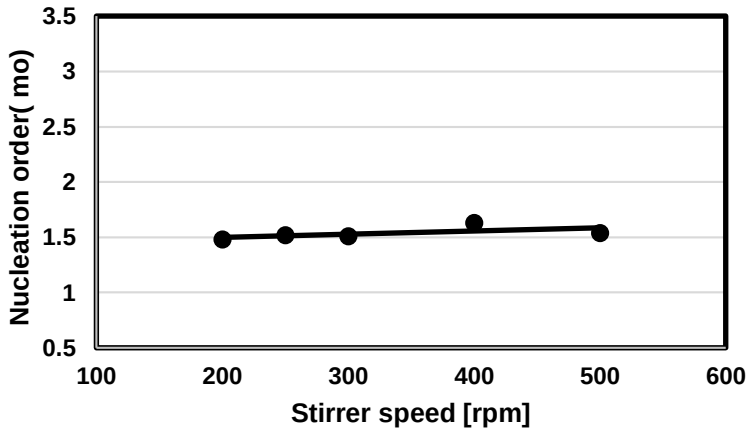
- Velocity vectors



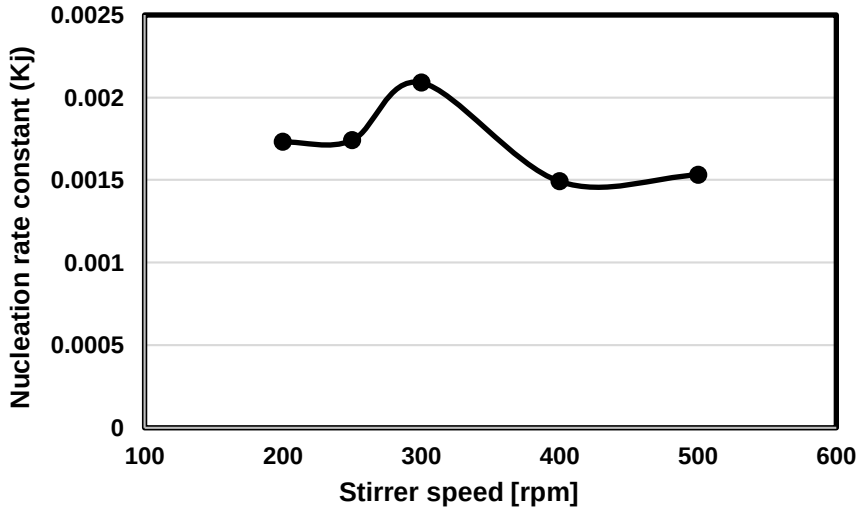
# Influence of Hydrodynamics on Nucleation Kinetics & CSD of L-GA Aqueous: Solutions 450 ml reactor/Nyvlt Approach

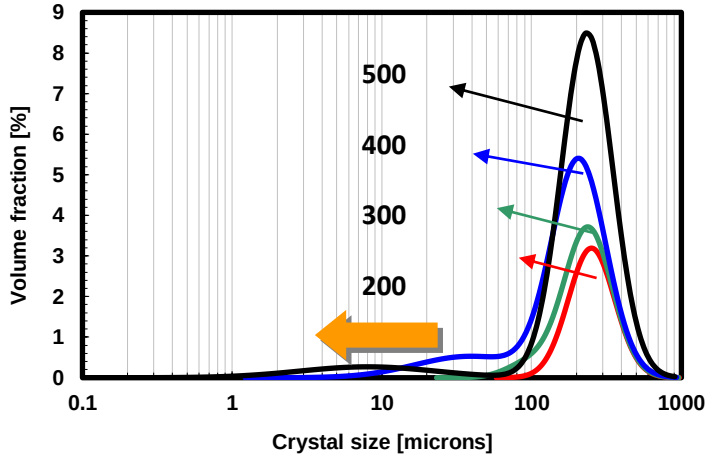





$$J = k_j(\Delta C_{max})^{m_0}$$

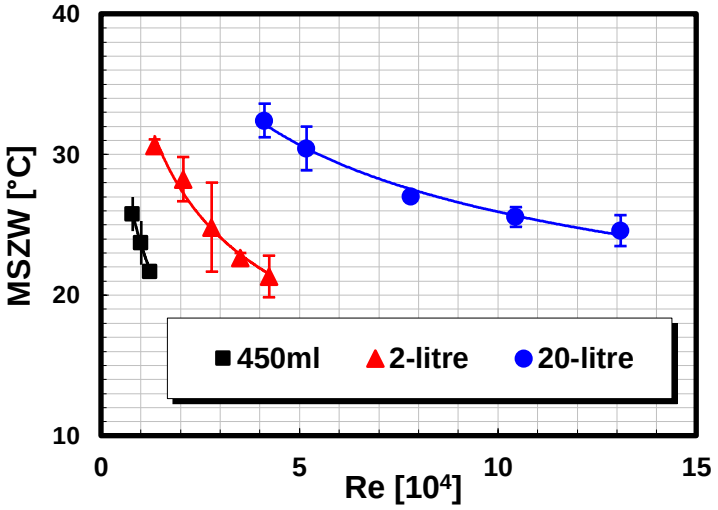


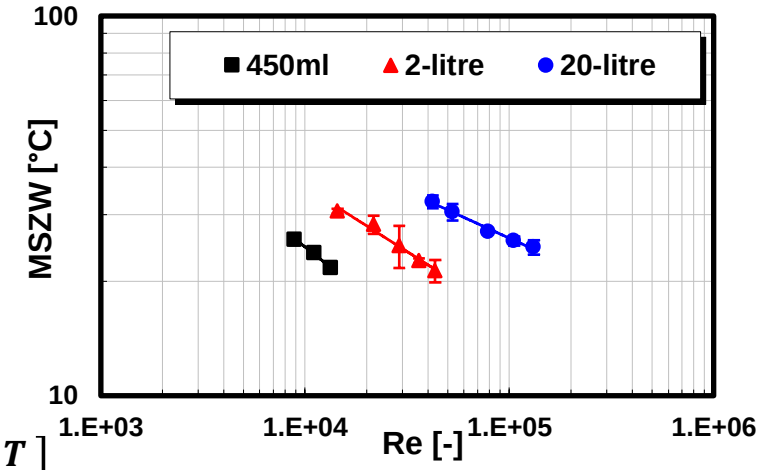




[2] K. Liang, Process Scale Dependence of L-glutamic Acid Batch Crystallised from Aqueous Solution in relation to Reactor Internals, Reactant Mixing and Process Conditions, Department of Chemical Engineering, Heriot-Watt University, Edinburgh, 2002.

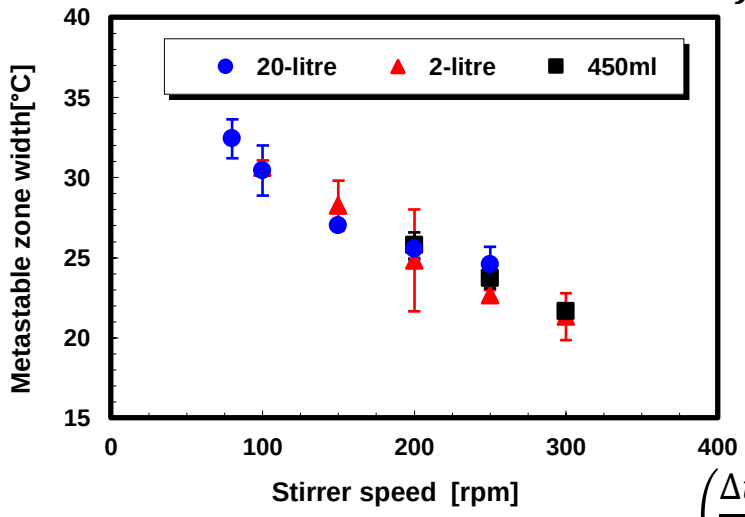
# Scale-up Model for Batch Cooling Crystallisation of LGA Aqueous Solutions : Cooling Rate 0.2 ℃/min

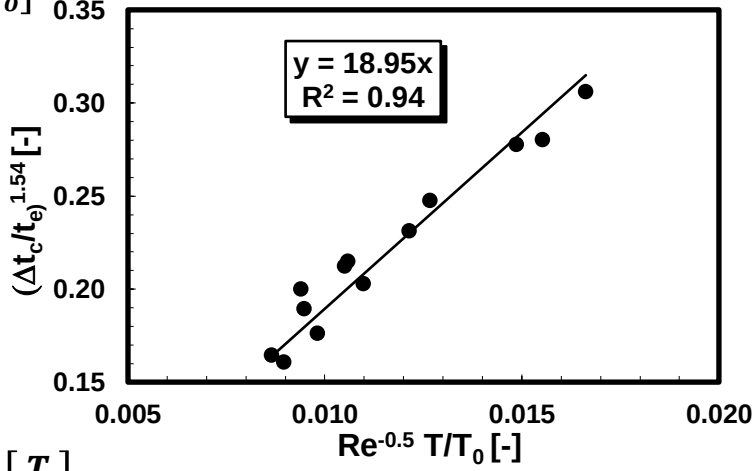





$$J \propto \left(\frac{\Delta t_c}{t_e}\right)^m = a\, R_e^b \left[\frac{T}{T_o}\right]$$




$$\left(\frac{\Delta t_c}{t_e}\right)^{1.54} = 18.95 R_e^{-0.5} \left[\frac{T}{T_o}\right]$$

$$\Delta t_c = -0.05N + 35.1$$

**t is temperature**

**T is reactor diameter**

**To laboratory reactor diameter**

[4] K. Liang, G White, D Wilkinson, L J Ford, K J Roberts, W M L Wood, 2004. Examination of the process scale dependence of L-glutamic acid batch crystallised from supersaturated aqueous solution in relation to reactor hydrodynamics, Ind. Eng. Chem. Res., 43, 1227-1234

# Concluding Remarks and Future work



- CFD methodology developed for improved predictions of velocity components
- Assessment of 20 L reactor hydrodynamics as a function of impeller speed, viscosity & density

- ***Ongoing work: modelling batch cooling crystallisation of LGA in 20 L reactor: CFD & 1D-PBM for different impeller speeds (100, 150, 200 &250 rpm). Power laws for nucleation & growth kinetics are used within 1D-PBM incorporated through user defined function (UDFs)***

- Short term future work will include:

**1. Assessment of first principles primary/secondary nucleation & growth kinetic models that can be used with 1D-PBM for improved predictions of CSD**

↓

**Incorporation of models through UDFs**

**2. Application of the developed CFD & 1D-PBM methodology to model batch cooling crystallisation, for a selected solution system, for laboratory & pilot scale reactors**

↓

**Development of scale-up correlations**