CFD modeling of precipitation of nanoparticles in Confined Impinging Jet Reactors

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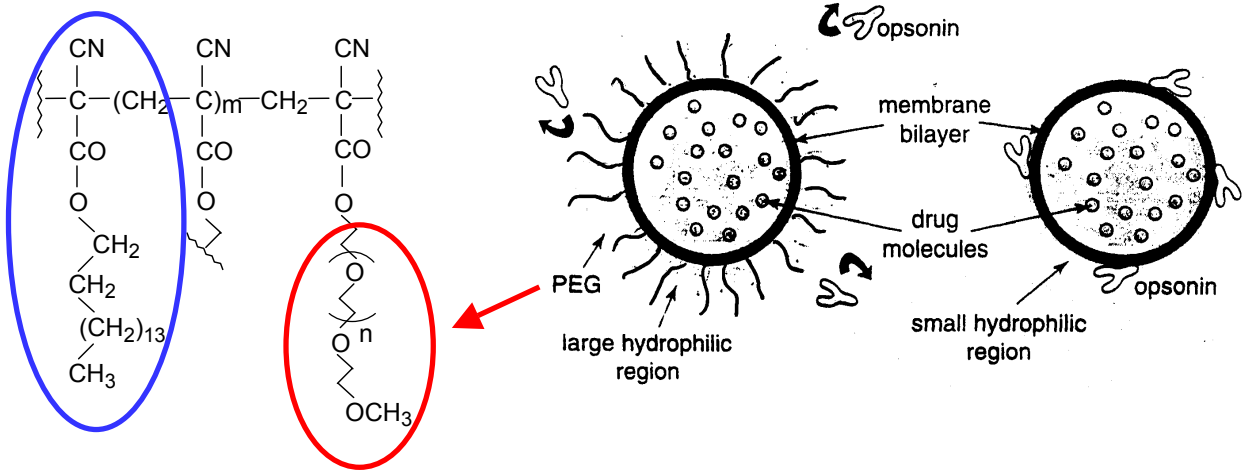
Motivation and goals

- Organic actives are often dispersed in polymer structures forming nano-spheres and nano-capsules
- The main advantages of these particulate systems are:
  - Possibility of release of actives insoluble in water
  - Controlled drug-delivery
  - Passive and active targeting
  - Increased lifetime in bloodstream
- The polymer usually has to be hydrophilic, flexible and non-ionic

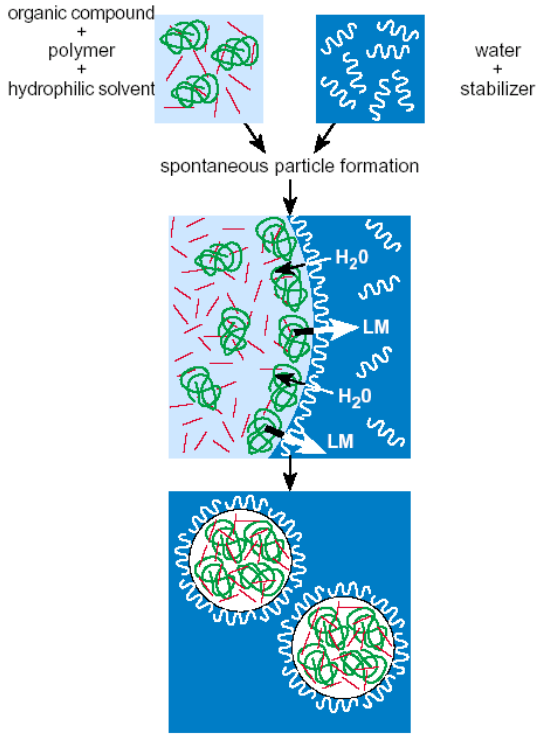
Motivation and goals

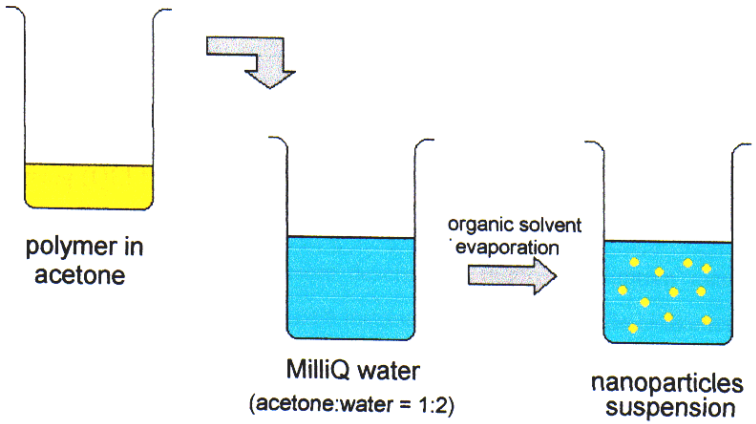
- Very often block co-polymers are used: poly(MePEGCA-co-HDCA) poly (methoxypolyethyleneglycole cyanoacrylate – *co* – hexadecyl cyanoacrylate)
- HDCA chains (hydrophobic) are inserted in the organic active core
- PEG chains (hydrophylic) are oriented towards the water phase, forming a flexible protective layer that reduces the absorption of plasmatic proteins



Preparation

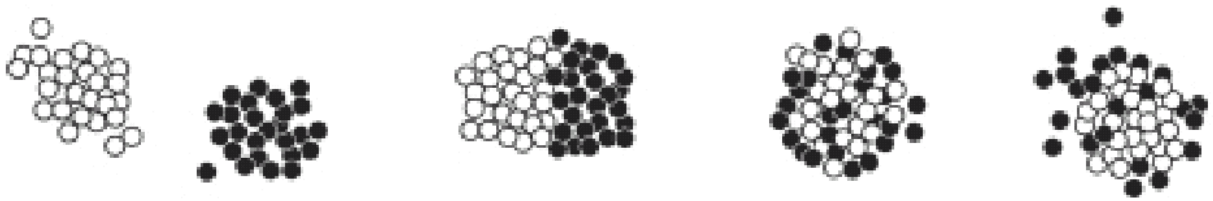
- Nano-particles are produced by precipitation (solvent displacement)





Effect of mixing

- Mixing controls nucleation, molecular growth (and aggregation) rates and therefore controls the particle size distribution
- Mixing (and cohesion forces) control the mass ratio of organic active/polymer in each particle

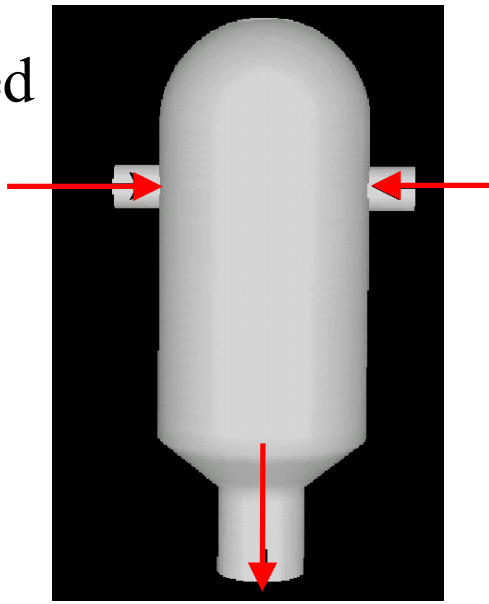


- Generally speaking good product quality is obtained with very high mixing rates

Aim of this work

- Design, optimization and scale-up of a continuous process to produce significant amounts of particles with a certain size range (≅200 nm) and with a specific active-to-polymer ratio
- CFD is used to simulate the precipitation process and its interaction with turbulent mixing
- Reactor configuration: confined impinging jet reactor (CIJR)
- Reacting systems:
  - parallel reaction scheme
  - barium sulphate precipitation
- Real system: acetone-PEG-doxorubicine + water

Confined Impinging Jet Reactor



- The flow regimes in the reactor are characterized by the jet Reynolds number
- In this work we investigated 300<Re<3000 for d=1mm/D=4.76 mm
- Flow field simulations were run with LES and RANS approaches in Fluent 6.1.22
- Different three dimensional unstructured grids were tested in order to find a grid independent solution
- LES: ≈ 500,000 cells for the full geometry
- RANS: ≈ 100,000 cells (with finer resolution near the walls)

Large Eddy Simulation

- Fluent: box filter with bandwidth Δ equal to the cell size

$$\frac{\partial \overline{U}_i}{\partial t} + \frac{\partial \overline{U}_i \overline{U}_j}{\partial x_j} = \nu \frac{\partial^2 \overline{U}_i}{\partial x_i \partial x_i} - \frac{1}{\rho}\frac{\partial \overline{p}}{\partial x_i} - \frac{\partial \tau_{ij}^r}{\partial x_j}$$

- The residual stresses are closed by using the Smagorinsky model

$$\tau_{ij}^r = -2\nu_r \overline{S}_{ij}$$

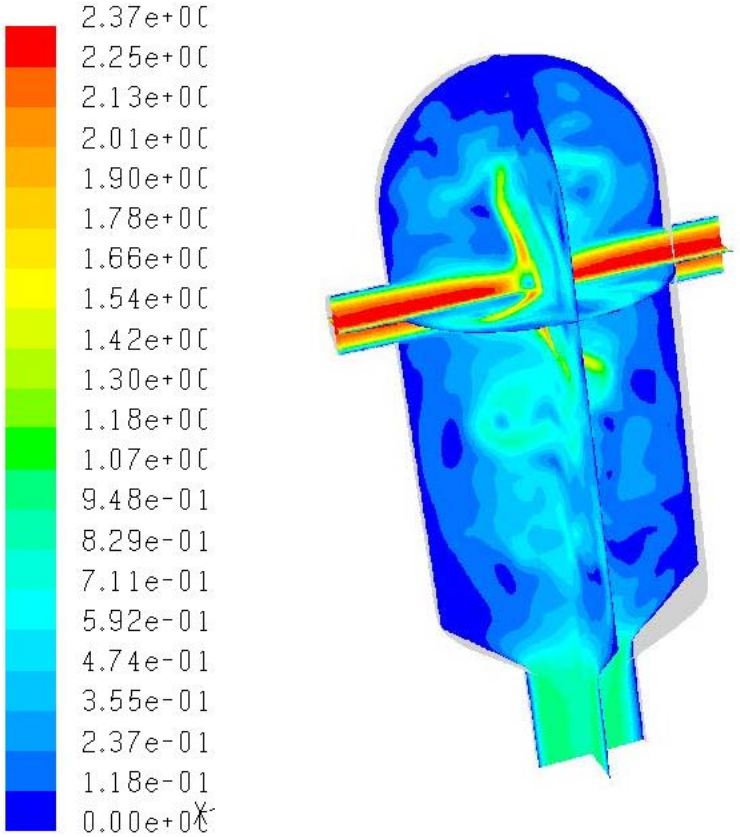
filtered Strain rate

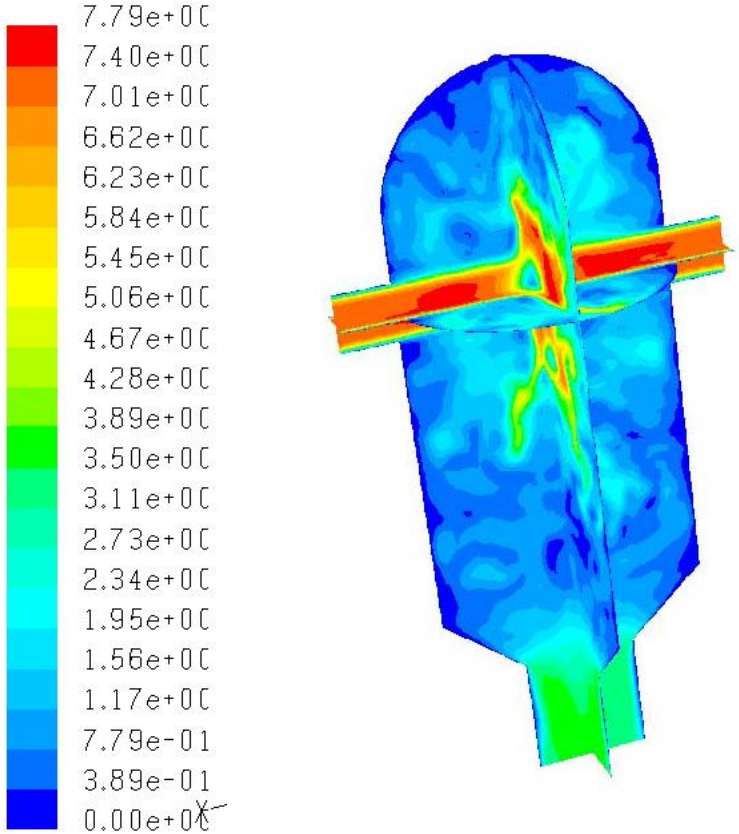
$$\nu_r = (C_S \Delta)^2 \overline{S} \qquad C_s = 0.08 - \boxed{0.10} - 0.12$$

- Next steps: implementation of a dynamic SGS model
- Cluster: 6 Xeon bi-processors 2400 (MHz)

Large Eddy Simulation

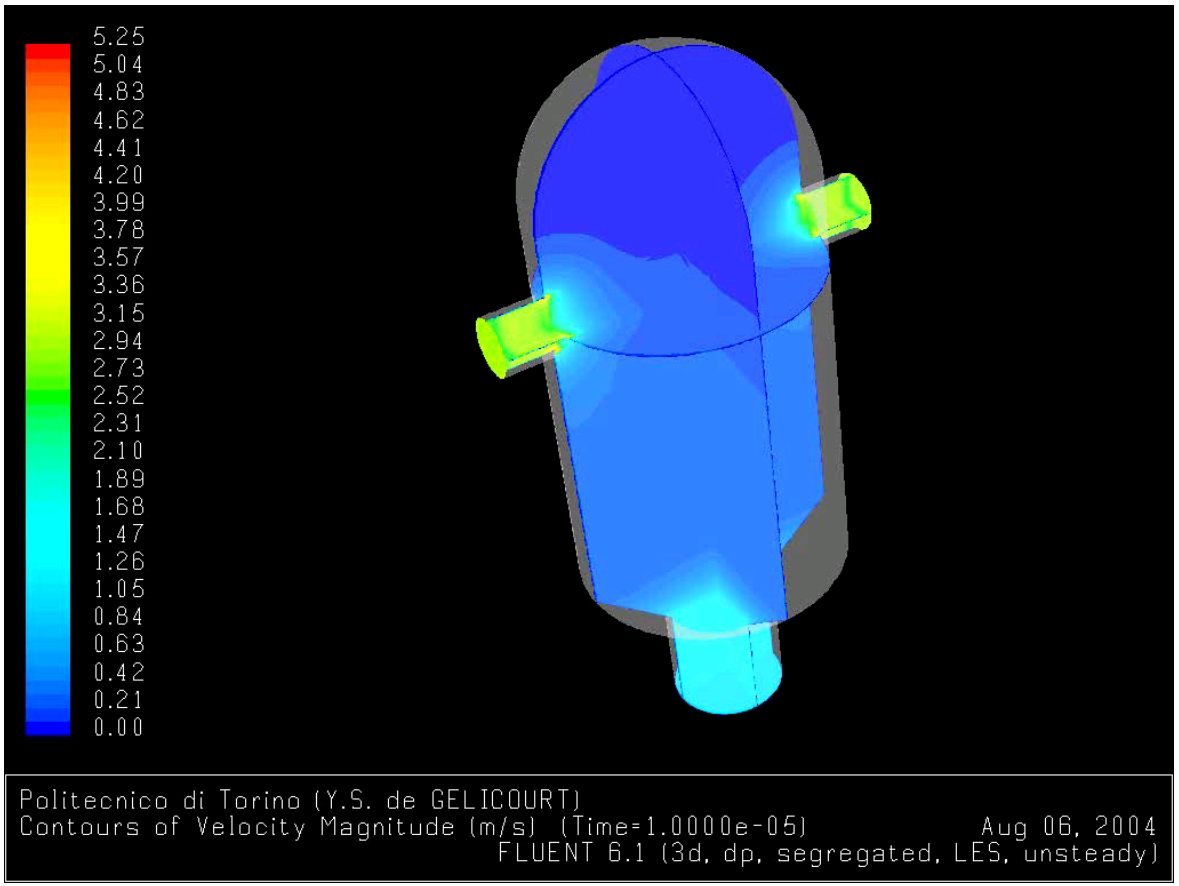
- Laminar inlet conditions (parabolic profile)
- Instantaneous velocity magnitude for Re= 704 and Re=2696





Large Eddy Simulation

- Velocity magnitude for Re=3000



RANS

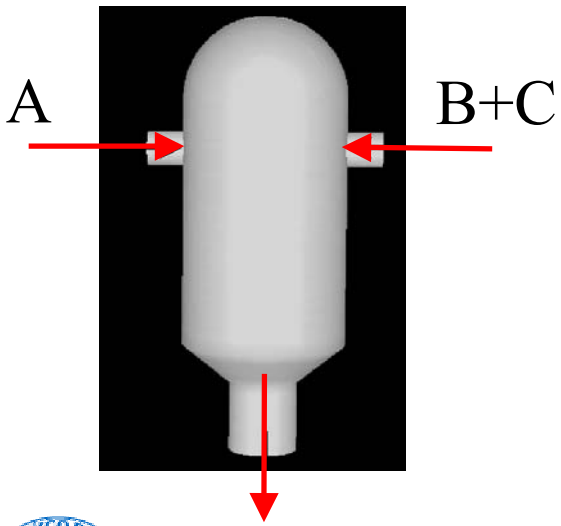
- Different turbulence models have been tested: k-ε, RNG k-ε, relizable k-ε, k-ω, RSM
- Different near wall treatments have been tested: standard wall function, non-equilibrium wall function, enhanced wall treatment
- Results show that RSM with enhanced wall treatment gives the best agreement with time-averaged LES velocities
- Further analysis needs experimental data or DNS data (Alfredo Soldati, University of Udine)

Step 1: Parallel chemical reaction

- In order to test mixing efficiency in the confined impinging jet reactor a parallel reaction has been used

$$A + B \rightarrow R \qquad A + C \rightarrow S + (A)$$

- The system can be described with mixture fraction and progress reaction variables



$$\frac{c_A}{c_{Ao}} = \xi - \xi_{s1} Y_1 \qquad \xi_{s1} = \frac{c_{Bo}}{c_{Ao} + c_{Bo}}$$

$$\frac{c_B}{c_{Bo}} = 1 - \xi - (1 - \xi_{s1}) Y_1 \qquad \xi_{s2} = \frac{c_{Co}}{c_{Ao} + c_{Co}}$$

$$\frac{c_C}{c_{Co}} = 1 - \xi - (1 - \xi_{s2}) Y_2$$

Step 1: Parallel chemical reaction

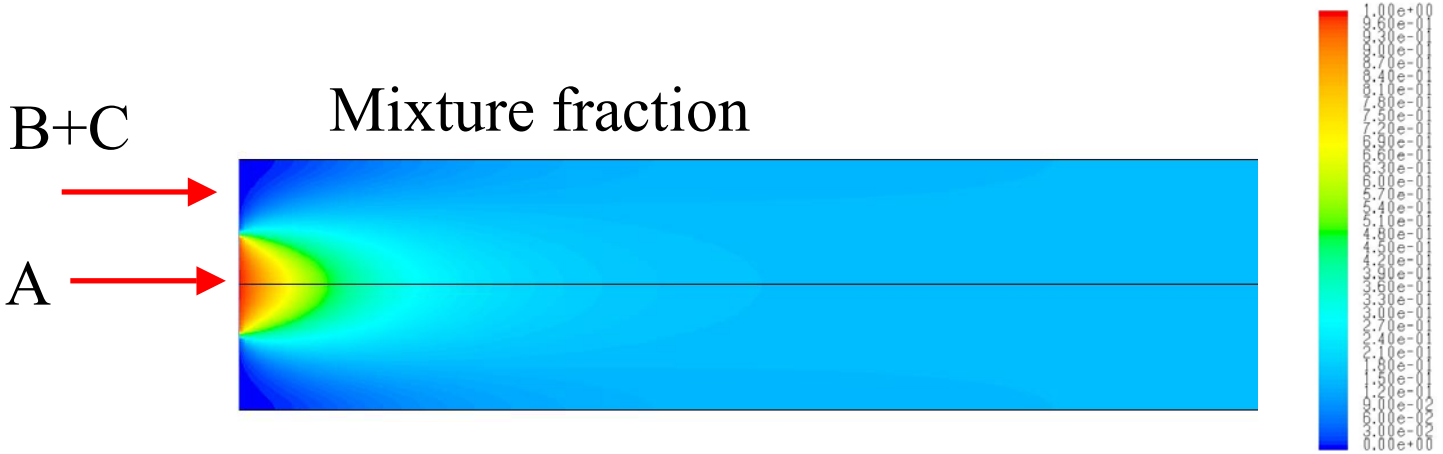
- Micro-mixing is modeled with the DQMOM-IEM model
- Functional form of the Probability Density Function:

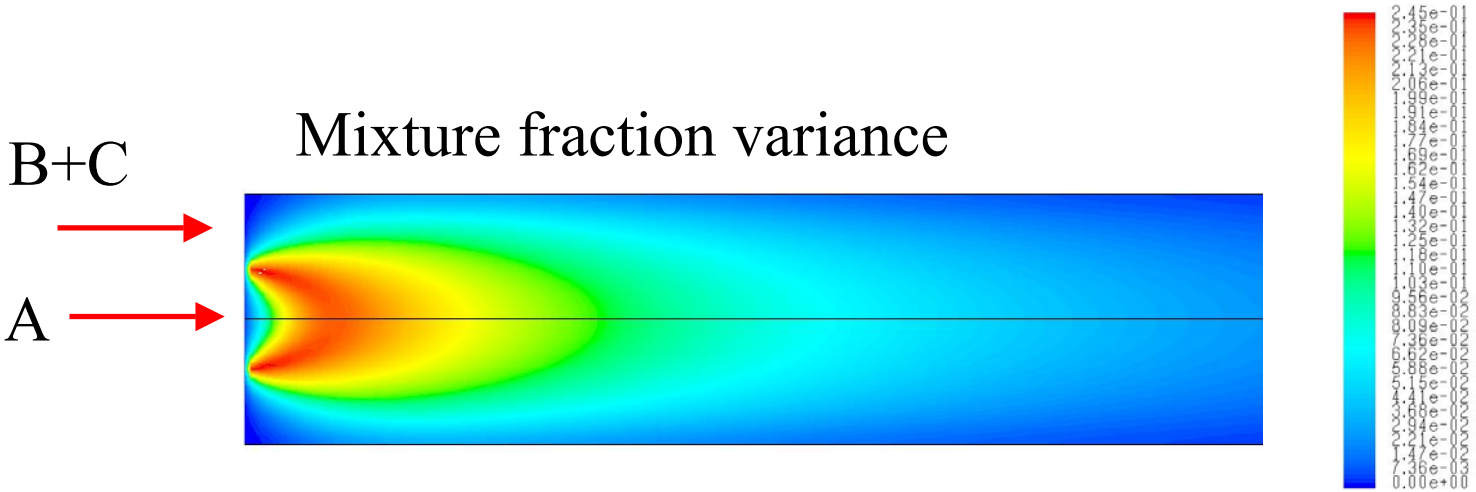
$$f(\xi;\mathbf{x},t)=\sum_{\alpha=1}^{N} p_\alpha(\mathbf{x},t)\,\delta[\xi-\xi_\alpha(\mathbf{x},t)]$$

- … where weights w_α and weighted abscissas $w_\alpha\xi_\alpha$ are calculated by solving their corresponding transport equations and forcing the moments of the PDF to be correctly predicted
- With two nodes ($N=2$)

$$m_0(\mathbf{x},t)=p_1+p_2 \qquad m_2(\mathbf{x},t)=p_1\xi_1^2+p_2\xi_2^2$$
$$m_1(\mathbf{x},t)=p_1\xi_1+p_2\xi_2 \qquad m_3(\mathbf{x},t)=p_1\xi_1^3+p_2\xi_2^3$$

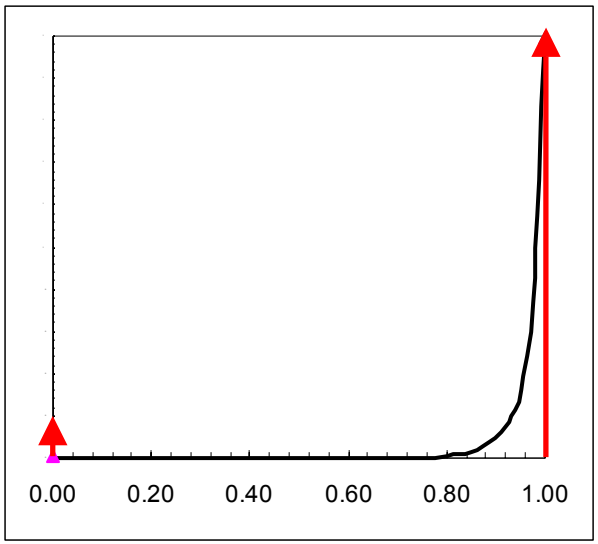
Step 1: Parallel chemical reaction

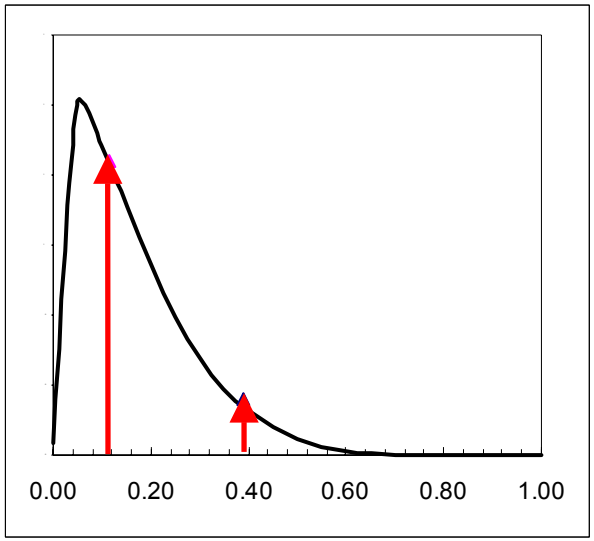


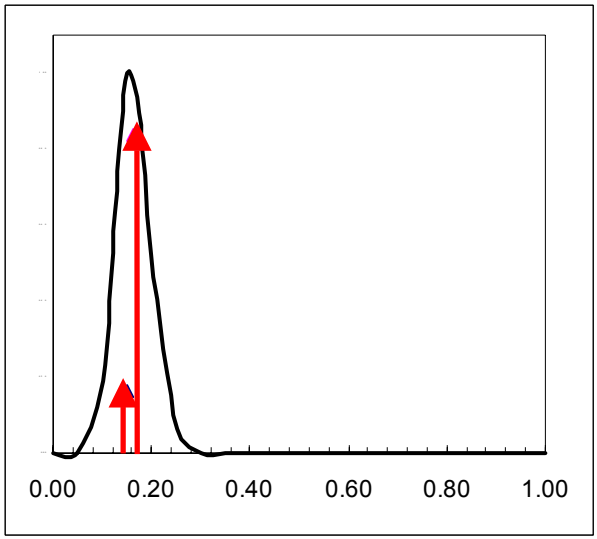


Step 1: Parallel chemical reaction

- Comparison between DQMOM-IEM and beta-PDF for the mixture fraction PDF







Step 1: Parallel chemical reaction

- Transport equations for weights and weighted abscissas

$$\frac{\partial p_1}{\partial t} + \langle u_i \rangle \frac{\partial p_1}{\partial x_i} - \frac{\partial}{\partial x_i}\left[(\Gamma + \Gamma_t) \frac{\partial p_1}{\partial x_i} \right] = 0 \qquad p_2 = 1 - p_1$$

$$\frac{\partial (p_1 \xi_1)}{\partial t} + \langle u_i \rangle \frac{\partial (p_1 \xi_1)}{\partial x_i} - \frac{\partial}{\partial x_i}\left[(\Gamma + \Gamma_t) \frac{\partial (p_1 \xi_1)}{\partial x_i} \right] = \gamma p_1 p_2 (\xi_2 - \xi_1) + \frac{p_1 c_1 + p_2 c_2}{\xi_1 - \xi_2}$$

$$\gamma = \frac{C_\phi}{2} \frac{k}{\varepsilon}$$

$$c_1 = \Gamma_t \left(\frac{\partial \xi_1}{\partial x_i} \frac{\partial \xi_1}{\partial x_i} \right)$$

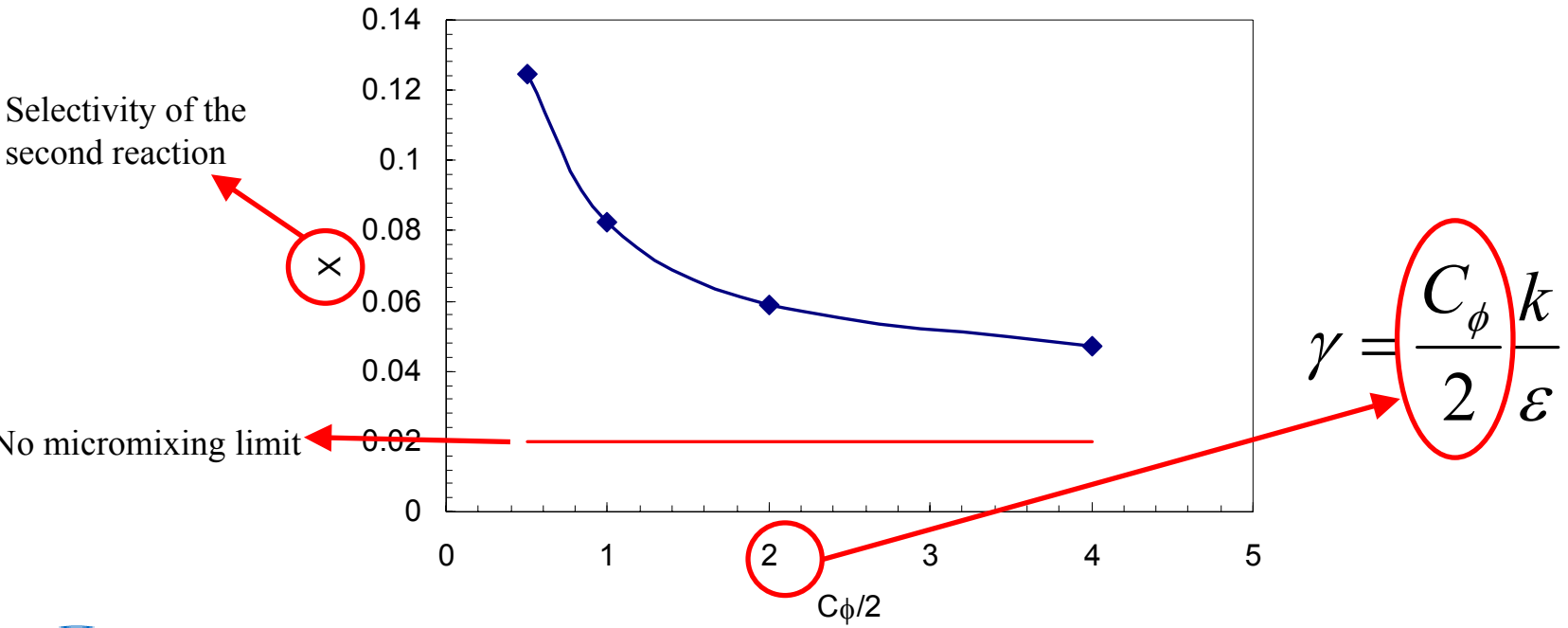
$$c_2 = \Gamma_t \left(\frac{\partial \xi_2}{\partial x_i} \frac{\partial \xi_2}{\partial x_i} \right)$$

Step 1: Parallel chemical reaction

- The reacting system is described by transport equations for:

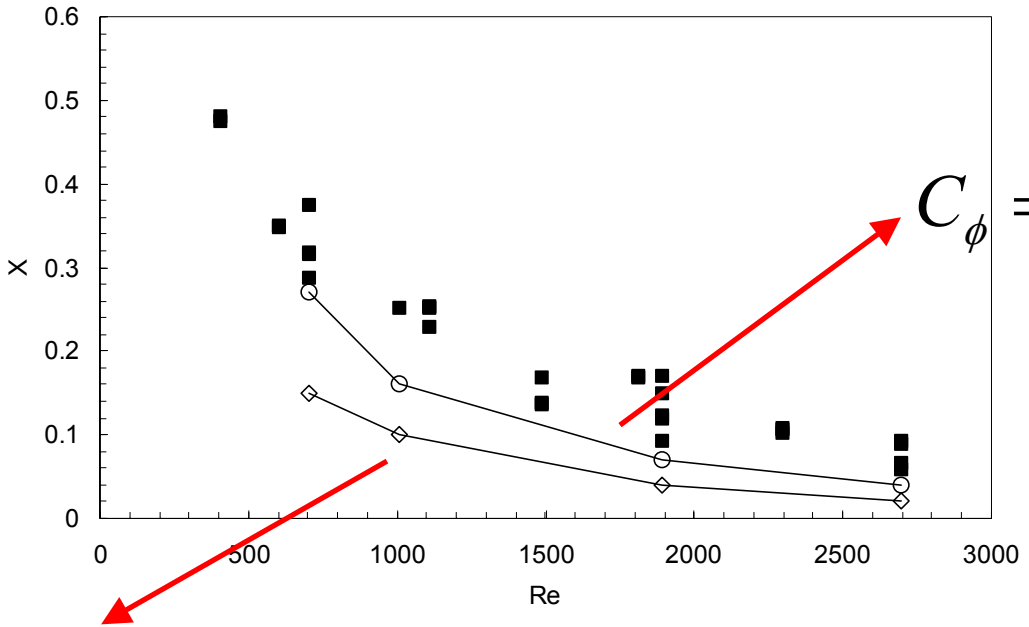
$$p_1 \quad p_1\xi_1 \quad p_2\xi_2 \quad p_1Y_{2,1} \quad p_2Y_{2,2}$$

- … and algebraic equations for: $p_2 = 1 - p_1$ $Y_{1,1}^{\infty}$ $Y_{1,2}^{\infty}$



Step 1: Parallel chemical reaction

- Comparison with experimental data from Johnson & Prud'homme (2003) for the CIJR



$C_\phi = 0.2$

$C_\phi = 2$

$C_\phi = f(\mathrm{Re}_1)$

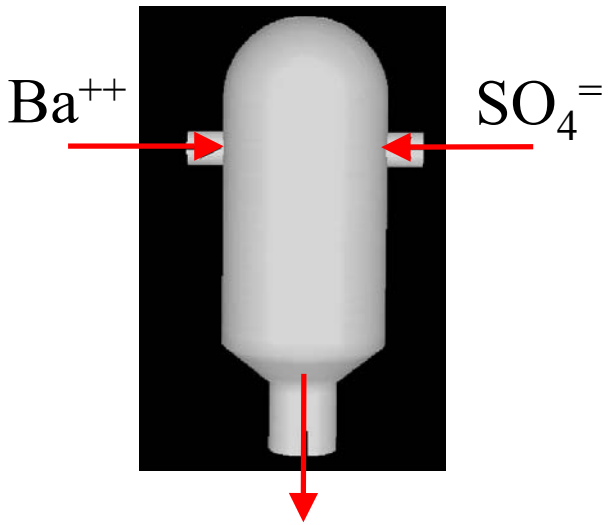
R.O. Fox & Y. Liu (2005) *AIChE J.*

Step 2: barium sulphate precipitation

- Different jet Reynolds numbers (80<Re<2500)
- Different reactant concentration (Ba^{++}, $SO_4^{=}$)
- Different reactant concentration ratio ($Ba^{++}/SO_4^{=}$)

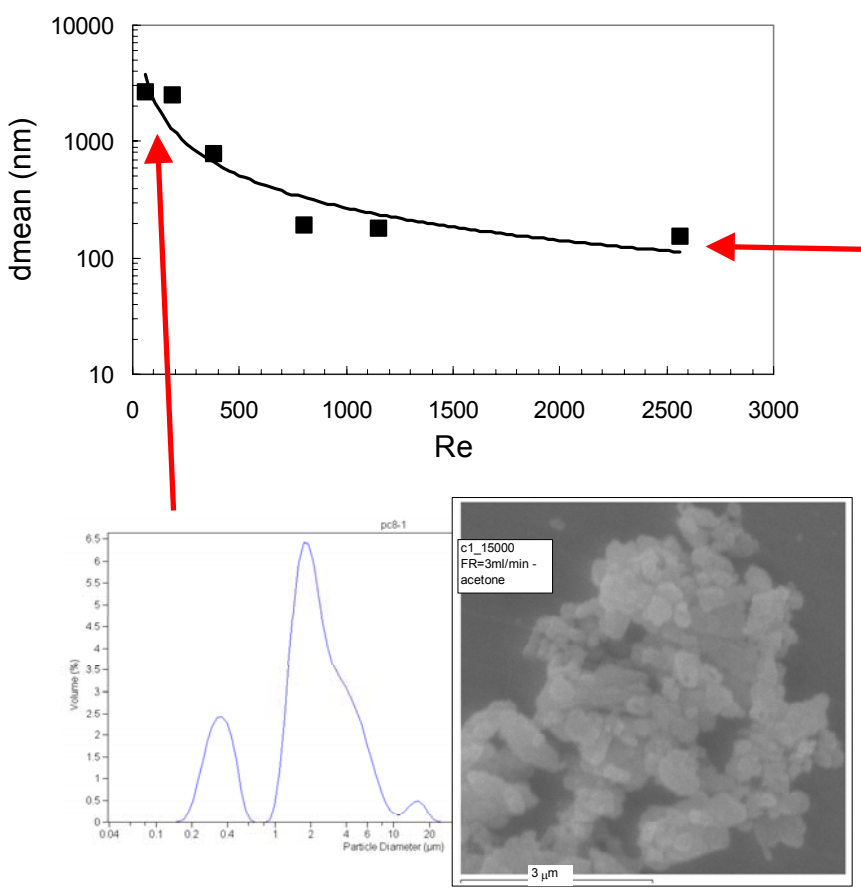
$$Ba^{++} + SO_4^{=} \rightarrow BaSO_4$$

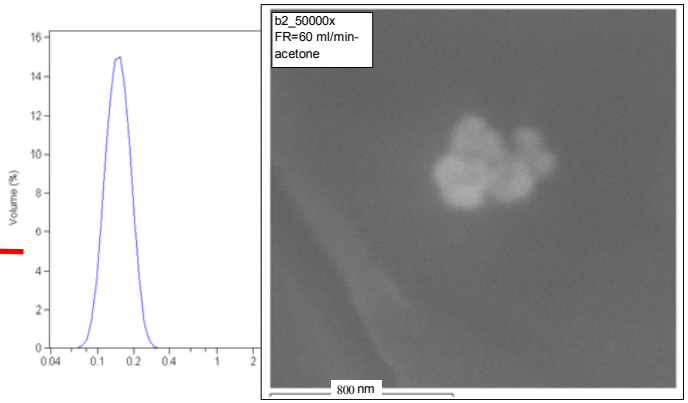
- The reaction is very fast and mixing sensitive
- Relevant phenomena involved: nucleation, molecular growth and aggregation



Step 2: barium sulphate precipitation

- Effect of Reynolds number Ba^{++}:800 $SO_4^{=}$:100 mol/m^3





Step 2: barium sulphate precipitation

- The CFD model uses the DQMOM-IEM (N=2) for micromixing
- Standard kinetic expressions for nucleation and growth

$$B_{\text{hom}} = 1.5 D_{AB} \left(\sqrt{k_{ps}} S N_A \right)^{7/3} \sqrt{\frac{\gamma_{CL}}{k_B T}} V_m \exp\left(-\frac{16\pi}{3} \left(\frac{\gamma_{CL}}{k_B T} \right)^3 \frac{V_m^2}{(\nu \ln S)^2} \right)$$

$$G = 2 \frac{Sh D_{AB} \sqrt{k_{ps}} M}{\rho} \frac{S-1}{L}$$

$$S = \gamma_{\pm} \sqrt{\frac{c_A c_B}{k_{ps}}}$$

- Brownian aggregation kernel

$$\beta = \frac{2 k_B T}{3 \mu} (L_1 + L_2) \left(\frac{1}{L_1} + \frac{1}{L_2} \right) \alpha$$

Step 2: barium sulphate precipitation

- The population balance equation is solved by using the QMOM (for the two reacting environments)
- The Particle Size Distribution is computed through the moments of the distribution (k=0,…,3)

$$m_k(\mathbf{x},t) = \int_0^{+\infty} n(L;\mathbf{x},t)\,L^k\,dL \approx \sum_{i=1}^{N} w_i L_i^k$$

$$\frac{\partial m_k(\mathbf{x},t)}{\partial t} + \frac{\partial}{\partial x_i}\left(\langle u_i \rangle m_k(\mathbf{x},t)\right) - \frac{\partial}{\partial x_i}\left(\Gamma_t \frac{\partial m_k(\mathbf{x},t)}{\partial x_i}\right) = 0^k\, J(\mathbf{x},t)$$

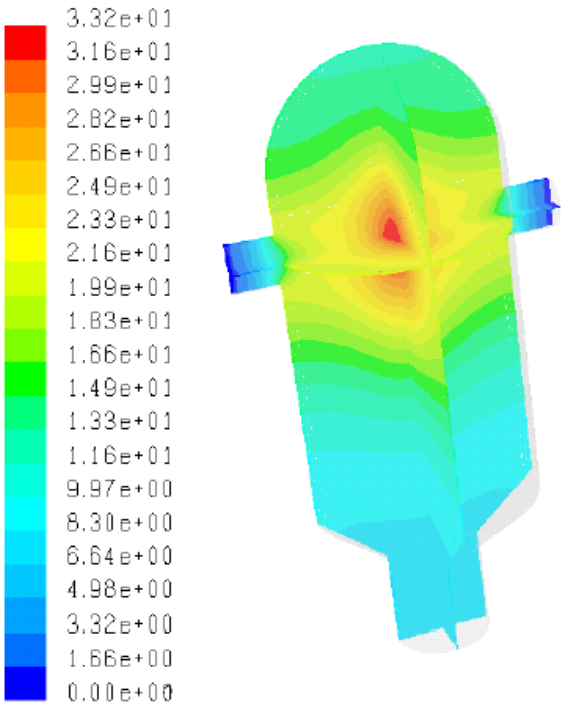
$$+ k\sum_{i=1}^{N} G(L_i) w_i L_i^{k-1} + \sum_{i=1}^{N} w_i \sum_{j=1}^{N} w_j \left(L_i^3 + L_j^3\right)^{k/3} \beta(L_i,L_j) - \sum_{i=1}^{N} w_i L_i^k \sum_{j=1}^{N} w_j \beta(L_i,L_j)\,.$$

Step 2: barium sulphate precipitation

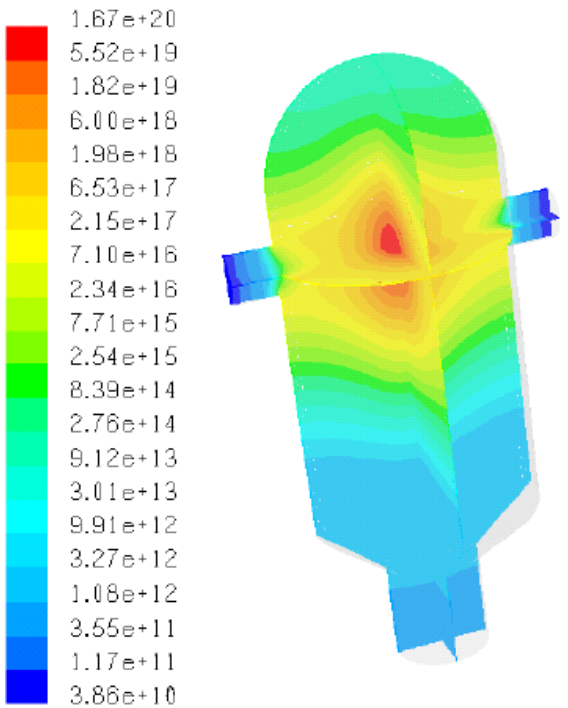
Re=2696

$c_{A0}=c_{B0}=100$ mol/m^3

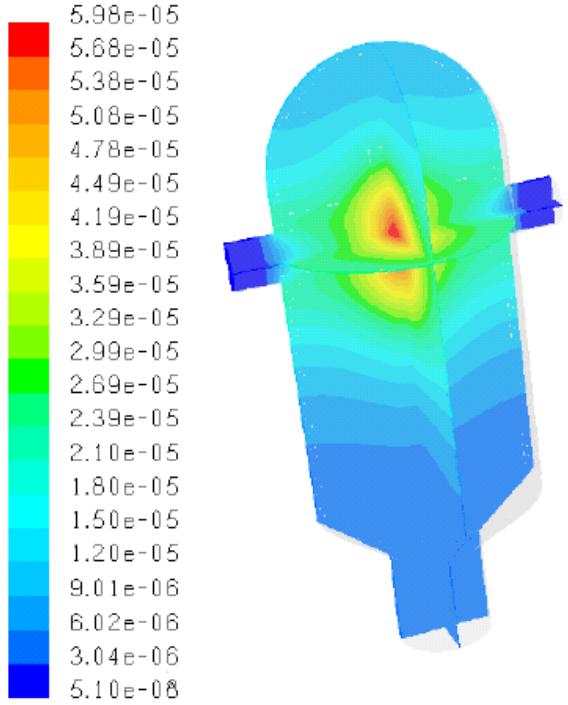
Supersaturation



Nucleation rate (1/m^{3}s)

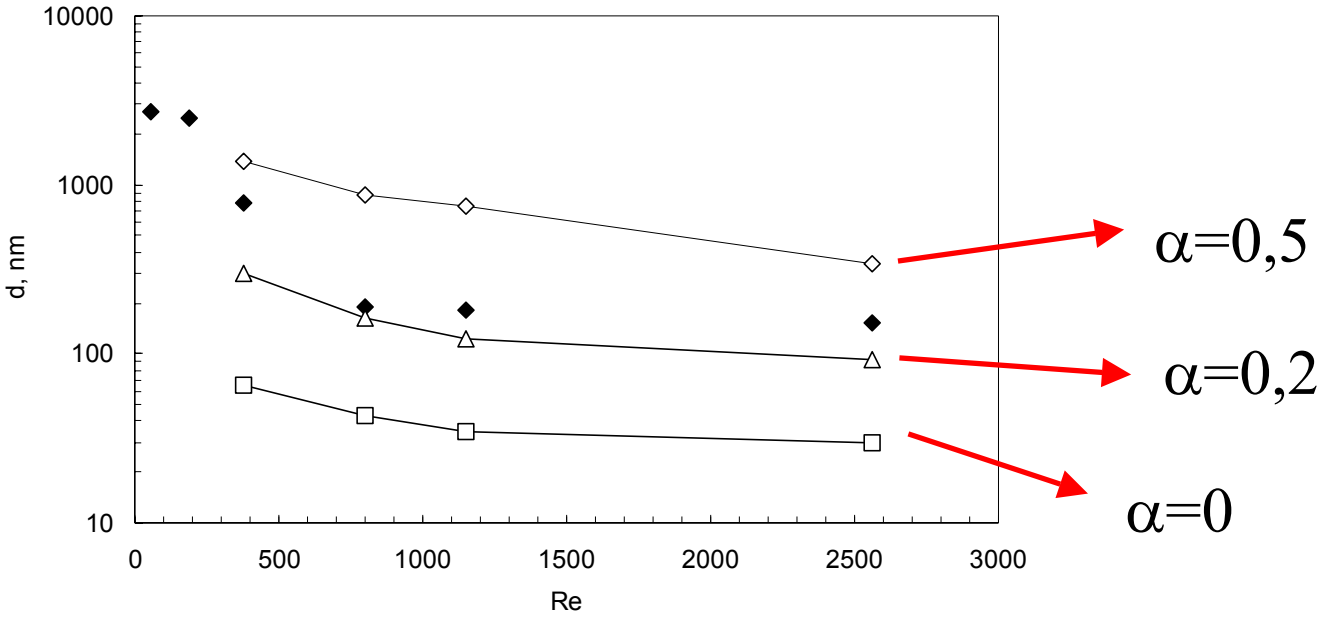


Growth rate (m/s)



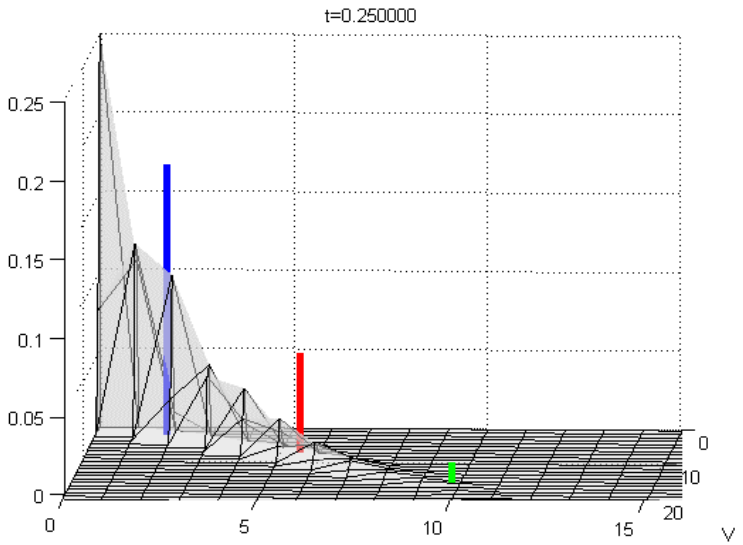
Step 2: barium sulphate precipitation

- Effect of the aggregation efficiency on the final mean particle size
- Crystallite size from X-ray measurements ≈20-40 nm



Step 3: acetone-PEG-doxorubicine/water

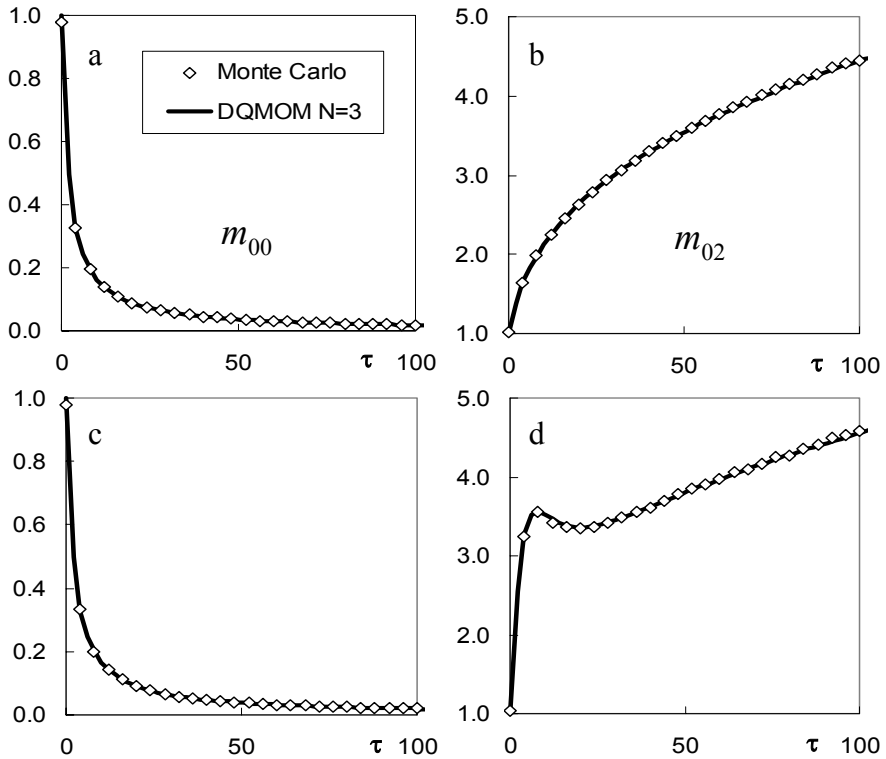
- Thermodynamics data concerning polymer and active solubility
- Bivariate population balance equation: DQMOM
- Validation by comparison with Monte Carlo simulations



$$m_{k,l} = \int_0^\infty \int_0^\infty n(\xi_1, \xi_2) \xi_1^k \xi_2^l d\xi_1 d\xi_2$$

Step 3: acetone-PEG-doxorubicine/water

- Validation by comparison with Monte Carlo simulations



$$m_{k,l} = \int_0^\infty \int_0^\infty n(\xi_1, \xi_2) \xi_1^k \xi_2^l d\xi_1 d\xi_2$$

Coalescence

Aggregation and restructuring

$$\tau = t\, \beta(0) m_{00}(0)$$

Conclusions and next steps

- The flow field in the confined impinging jet reactor has been modeled with RANS and LES (further validation with DNS data)
- Micromixing is taken into account with the DQMOM-IEM model and validation is carried out by comparison with experimental data from literature
- The population balance is described with QMOM (monovariate) and DQMOM (bivariate) resulting in a small number of additional scalars (4-8)
- Simulation of the real process will be carried out when thermodynamic and kinetic expressions will be available

Acknowledgements

- Liliana Rivautella (BaSO4 precipitation experiments)
- Emmanuela Gavi (CIJR simulations)
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