



Diffusive mixing in antisolvent crystallisation.

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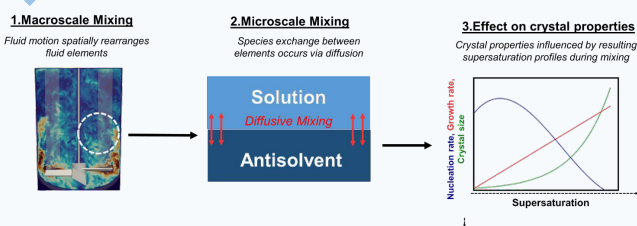
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Projects aims

- To model diffusive mixing in multicomponent in highly non-ideal antisolvent crystallisation processes using physically correct driving forces
- Implement model to gain insight into the effect of both non-ideality and antisolvent choice on crystallisation outcomes
- Investigate the occurrence of liquid-liquid phase separation during the diffusive mixing process

Background Theory

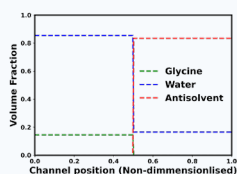
- ❖ Driving force for crystallisation is supersaturation
- ❖ Addition of antisolvent generates supersaturation by lowering local solute solubility in solvent mixture
- ❖ Macro-mixing can be described by two sequential processes: bulk rearrangement of fluid elements & diffusive mixing



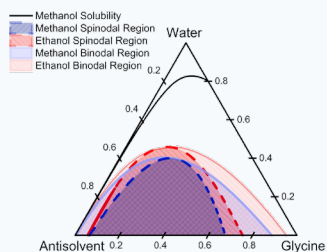
- ❖ At low length scales mixing becomes important consideration
- ❖ Antisolvent choice can impact diffusive mixing profiles and the resulting supersaturation profiles in strongly non-ideal solvent mixtures
- ❖ Crystallisation outcomes strongly influenced by supersaturation profiles [2]

Methods

Water/Antisolvent/Glycine ternary system



Initial volume fraction profile



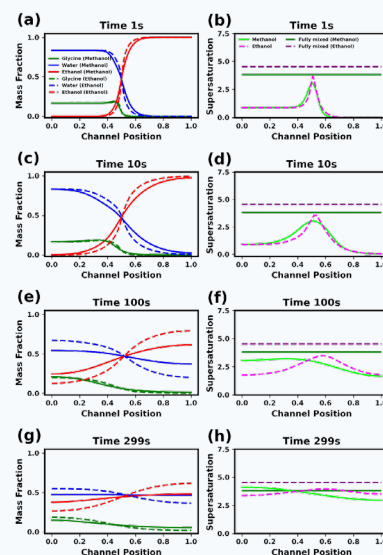
Predicted phase diagram

- ❖ Interdiffusion between fluid elements modelled as 'channel' filled with Aqueous glycine solution and antisolvent.
- ❖ Mixing modelled using the ternary component Maxwell-Stefan diffusion equation [3]
- ❖ Equations solved using finite volume approach
- ❖ Two antisolvents compared – methanol and ethanol
- ❖ Thermodynamic non-ideality predicted via Scatchard-Hildebrand approach [4]
- ❖ Activity model allows for calculation of phase diagram and correct driving force for diffusion based on activity gradients instead of concentration gradients

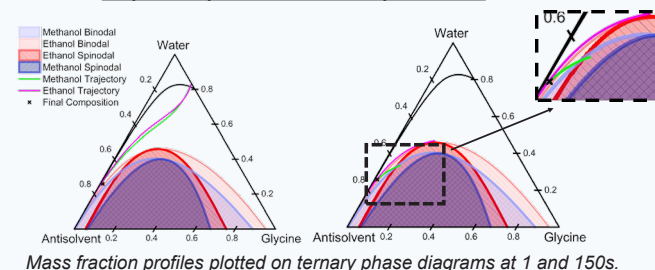
Results

Comparison of mixing profiles

- ❖ Comparison of mass fraction and supersaturation profiles for methanol/ethanol antisolvent systems
- ❖ Solid lines indicate methanol, Dashed depict ethanol
- ❖ Methanol system mixes quicker due to higher diffusivity
- ❖ Composition at peak supersaturation varies between systems
- ❖ Solute-solvent interactions effect crystal properties, such as morphology or shape



Liquid-liquid Phase Separation



- ❖ Localised liquid-Liquid phase (LLPS) separation spontaneously occurs when local solution composition enters spinodal region
- ❖ Complicates nucleation as co-existing phases have different solute concentrations, significantly affects crystal growth and nucleation
- ❖ Antisolvent choice influences occurrence of LLPS
- ❖ Composition profiles across channel shown below for the two antisolvent systems. 'channel' filled with 80% antisolvent and 20% aqueous glycine solution and pure antisolvent was used.
- ❖ Ethanol antisolvent results in local LLPS, as local composition enters spinodal region. LLPS does not occur in methanol system

Conclusions

- ❖ Diffusive mixing simulated for aqueous glycine solution with two different antisolvents with thermodynamically correct driving force for diffusion based on activity
- ❖ Supersaturation overshoots are artefacts of ideal Fickian diffusion models and do not occur in real non-ideal mixtures in antisolvent crystallisation
- ❖ The prediction of LLPS is influenced by antisolvent selection and offers a novel explanation for effects of various antisolvents on crystallisation outcomes

References: [1] Miller, R.; Sefcik, J.; Lue, L. Modelling diffusive mixing in antisolvent crystallization. *Cryst. Growth Des.* 2022, 22, 2192-2207
 [2] Mullin, J. W. J. W. Crystallization; Butterworth-Heinemann: Oxford, UK, 2001; p 594 [3] Krishna, R. Uphill diffusion in multicomponent mixtures. *Chem. Soc. Rev.* 2015, 44, 2812-2836.
 [4] Wilhelm, E. Mitigating Complexity: Cohesion Parameters and Related Topics. I: The Hildebrand Solubility Parameter. *J. Solution Chem.* 2018, 47, 1626-1709

