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# Monitoring of pharmaceutical processes with image analysis: direct and indirect approaches

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Image analysis (IA) is an effective and non-invasive tool for extracting useful information about depicted objects and scenes. It is widely used in many industrial applications including on-line process monitoring. From a pharmaceutical research and development perspective, the interest for image analytical applications is increasingly being recognized. One of the success stories for IA is particle analysis, giving quantitative estimation of geometrical and morphological properties (e.g. diameter, perimeter, area, roundness, etc.) of objects of interest as well as counting the objects.

A usual analytical procedure for particle analysis includes preprocessing to enhance image quality, segmentation and morphological operations with segmented binary masks. This procedure can be considered as a “direct measurement” of the objects of interest, and it can be efficiently implemented if objects are separated among each other and from the rest of scene, e.g. using threshold operation or edge detection.

In many cases however, segmentation can be a challenging step, especially if images are noisy and/or objects are partially overlapped or merged. In this case, using more sophisticated segmentation methods, e.g. a combination of traditional histogram based segmentation with demerging algorithms (e.g. watershed transformation) or shape detectors, can solve the problem. But for certain complicated cases, these methods do not work satisfactory and indirect approach can be considered as an alternative.

The idea of indirect approach is to calculate integral properties of an image (statistics of intensity or color distributions, textural properties, etc.) and use them as predictors in multivariate models from which the particle parameters can be inferred. Although, this approach does not allow estimation of the particle properties with high precision, an average estimation over the whole image can be obtained.

In the present study, crystallization of a needle shaped active pharmaceutical ingredient (API) was monitored using polarized light microscopy with both direct and indirect IA approaches. The methods were validated on crystallization simulated images. Because the needle shaped particle has poor flowability, the presence of this crystalline morphology can compromise further downstream processability. Hough and Radon transformations were employed for direct measurements, and Angle Measure Technique (AMT) was used for extracting textural properties for indirect measurements. Both techniques were applied to several sets of simulated and real images (video frames) of nucleation and crystal growth process of needle shaped particles, and their performance were estimated and compared.