Supplementary Information: Rusli, W., Naraharisetti, P.K., Chew, W., Calibration Methods to Circumvent Unknown Component Spectra for Quantitative in situ Raman Monitoring of Co-polymerisation Reaction

Experimental Measurements

1. Perform inline Raman monitoring of styrene and butyl acrylate (St-BA) co-polymerisation. Each Raman spectrum in this time-series, $\vec{r}_{1 \times v}^{mix}$, measures a mixture of the three components, St, BA and co-polymer (Cp). For a particular reaction run, m number of reaction mixture spectra is collated into a spectral matrix $R_{m \times v}$.

2. Take hourly offline NMR measurements of St and BA for multivariate calibration using PLSR, MMRS, or BTEM-MLR. For each NMR measurement dataset used for calibration, $C_{k \times s}^{cal}$, its corresponding inline Raman spectral is $R_{k \times v}^{cal}$.

3. Measure the known Raman spectra of monomers St ($\vec{r}_{1 \times v}^{St}$), and BA ($\vec{r}_{1 \times v}^{BA}$) in the solvent 1,4 dioxane. This will be used in the MMSR calibration algorithm.

PLSR Calibration

1. Respective NMR measurements of each monomer (St or BA), $C_{k \times s}^{cal}$, and its corresponding Raman calibration data, $R_{k \times v}^{cal}$, are entered into a PLSR software package (e.g. Unscrambler). <Eqs. 3a & 3b>

2. Latent variables, $\hat{L}_{v \times s}$, will be generated from the PLSR software (running NIPALS, SIMPLS or Kernel algorithms). Judiciously decide the number of latent variables to use for each monomer calibration. <Eq. 4>

3. Using the reaction monitored spectral data $R_{m \times v}$, the PLS software would estimate the concentrations of monomers, $\hat{C}_{m \times s}$. <Eq. 5>

MMSR Calibration

1. MMSR utilizes a novel spectral residual minimization algorithm to achieve the optimal residual spectra, $\vec{\hat{e}}_{1 \times v}^{Cp}$. <Eq. 8b>

2. The MMSR algorithm calculates towards optimal estimates of St and BA concentrations, $\hat{c}_{St}^{t}$ and $\hat{c}_{BA}^{t}$, with positive concentration constraint to obtain minimized $\hat{\vec{e}}_{1 \times v}^{Cp}$ spectrum for each NMR calibration value. <Eq. 9>

3. The optimal residual spectra, $\hat{\vec{e}}_{1 \times v}^{Cp}$, in this St-BA co-polymerisation corresponds to the co-polymer (Cp) spectra. <Eq. 10>

4. Using the hourly NMR offline St and BA monomer concentrations ($\hat{\vec{c}}_{St}^{NMR}$ and $\hat{\vec{c}}_{BA}^{NMR}$), the respective linear calibrations for $\hat{c}_{St}^{t}$ and $\hat{c}_{BA}^{t}$ obtained from MMSR can be validated by plotting $\hat{c}_{St}^{t}$ and $\hat{\vec{c}}_{St}^{NMR}$ for St and $\hat{c}_{St}^{t}$ and $\hat{\vec{c}}_{St}^{NMR}$ for BA . <Eqs. 11a & 11b>

BTEM-MLR Calibration

1. Perform BTEM self-modeling multivariate curve resolution on $R_{m \times v}$ to elucidate s number of significant component spectra corresponding to reactants, intermediates or products. For this work, St, BA and Cp spectra were reconstructed via BTEM.

2. Calculate the relative concentration, $\hat{C}_{m \times s}^{rel}$, by performing multi-linear regression (MLR) using the BTEM elucidated component spectra, $\hat{r}_{s \times v}^{norm}$, on the reaction Raman data $R_{m \times v}$. <Eq. 12>

3. For each significant Raman component with a series of measured offline calibration NMR concentration values in $C_{k \times s}^{cal}$ (e.g. for styrene, $\hat{\vec{c}}_{St}^{NMR}$), perform a linear regression to estimate its slope and intercept values (e.g. m_{St} and y_{St}) to correlate with MLR relative concentration (e.g. $\hat{\vec{c}}_{St}^{rel}$). Use this slope and intercept to obtain properly scaled chemical component inline concentrations (e.g. $\vec{c}_{St}$). <Eq. 13>