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IUPAC recommended experimental methods and data evaluation procedures for the determination of radical copolymerization reactivity ratios from composition data†

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The IUPAC working group on "Experimental Methods and Data Evaluation Procedures for the Determination of Radical Copolymerization Reactivity Ratios" recommends a robust method to determine reactivity ratios from copolymer composition data using the terminal model for copolymerization. The method is based on measuring conversion (X) and copolymer composition (F) of three or more copolymerization reactions at different initial monomer compositions (f_0). Both low and high conversion experiments can be combined, or alternatively only low conversion experiments can be used. The method provides parameter estimates, but can also reveal deviations from the terminal model and the presence of systematic errors in the measurements. Special attention is given to error estimation in F and construction of the joint confidence interval for reactivity ratios. Previous experiments measuring $f_0 - F$ or $f - X$ can also be analyzed with the IUPAC recommended method. The influence of systematic errors in the measurements on the reactivity ratio determinations is investigated, including ways to identify and mitigate such errors.

Introduction of the method

There are several kinetic models describing the incorporation of monomers into polymer chains during radical copolymerizations,[1] of which the terminal model, where only the last unit in the chain affects the reactivity of a chain-end radical, is the most widely applied for copolymer composition. Other models include the penultimate model,[2] in which the penultimate unit also affects the reactivities, and the non-terminal model, where the chain ends do not affect reactivities. The non-terminal model only applies to the special case of ideal copolymerization, where there is no difference in reactivity for the monomers towards the propagating species.[3] Then there are several models to cater for complexation between monomers (the complex participation model) or complexation between monomer and polymer chain end (the bootstrap model).[4] Copolymerization models serve to create mechanistic understanding of copolymerization reactions, but are ultimately most important in modelling of composition in manufacturing of copolymers. A high conversion is typically pursued for commercial manufacturing of copolymers. For batch reactions, or reactions conducted in a plug-flow reactor, high conversion almost inevitably leads to composition drift, *i.e.* the shift in monomer and copolymer composition due to different monomer consumption rates. In conventional radical copolymerizations, composition drift results in heterogeneous copolymers. In reversible-deactivation radical polymerizations, however, drift in monomer composition results in a gradient in the composition of all the growing polymer chains, which can be a desirable feature for generating gradient copolymers.[5]

The core assumption of the terminal copolymerization model is that the reactivity of the growing chains is entirely

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determined by their final monomer unit. Thus a copolymerization of two monomers, M_1 and M_2, contains two types of growing chains, and a total of four propagation reactions, as shown in Scheme 1.[6] Reactivity ratios,[1] r_i are defined as the ratio of the rate coefficients of propagation k_{ii} and k_{ij}, corresponding to homopropagation and crosspropagation of chains containing a terminal unit M_i.

Defining f_i as the mole fraction of M_i in the comonomer mixture ($f_i = [M_i]/([M_1] + [M_2])$), and and F_i^{inst} as the mole fraction of M_i that is instantaneously being incorporated into the copolymer ($F_i^{\text{inst}} = d[M_i]/d([M_1] + [M_2])$), gives the well-known Mayo–Lewis[7] copolymer composition equation (eqn (1)):

$$F_1^{\text{inst}} = \frac{r_1 f_1^2 + f_1 f_2}{r_1 f_1^2 + 2 f_1 f_2 + r_2 f_2^2} \tag{1}$$

Differentiating f_1 with respect to the total monomer concentration (eqn (2)) and integration after separation of variables leads to the Skeist equation[8] (eqn (3)) relating total monomer conversion, X, to the change in monomer composition:

$$\begin{aligned}\frac{\mathrm{d}f_1}{d[M]} &= \frac{d}{d[M]}\left(\frac{[M_1]}{[M]}\right) = \frac{1}{[M]}\left(\frac{d[M_1]}{d[M]} - \frac{[M_1]}{[M]}\right) \\ &= \frac{1}{[M]}\left(F_1^{\text{inst}} - f_1\right)\end{aligned} \tag{2}$$

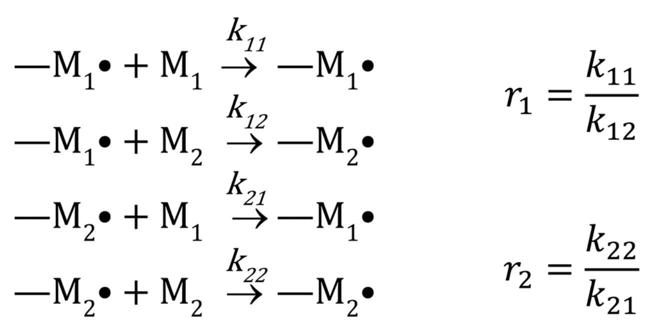
$$\ln(1 - X) = \int_{f_{10}}^{f_1} \frac{1}{F_1^{\text{inst}} - f_1}\,\mathrm{d}f_1 \tag{3}$$

The Skeist equation may be solved numerically. Alternatively, an analytical solution to this equation was provided by Meyer and Lowry[9] (eqn (4)) which relates X to the current monomer composition f_i and the initial monomer composition f_{i0}.

$$1 - X = \left(\frac{f_1}{f_{10}}\right)^{\alpha}\left(\frac{f_2}{f_{20}}\right)^{\beta}\left(\frac{f_{10} - \delta}{f_1 - \delta}\right)^{\gamma} \tag{4}$$

$$\alpha = \frac{r_2}{1 - r_2},\ \beta = \frac{r_1}{1 - r_1},\ \gamma = \frac{1 - r_1 r_2}{(1 - r_1)(1 - r_2)},\ \delta = \frac{1 - r_2}{2 - r_1 - r_2}$$

It should be noted that this equation contains singularities at $r_1 = 1$, $r_2 = 1$ and $r_1 + r_2 = 2$ and these can complicate its utilization (for specific solutions at the singularities see ESI-1†).



Scheme 1 Terminal model for copolymerization of two monomers M_1 and M_2.

Finally, the cumulative monomer composition, F_1^{cum} can be obtained from eqn (5).

$$F_1^{\text{cum}} = \frac{f_{10} - (1 - X) f_1}{X} \tag{5}$$

If we isolate a copolymer sample during a copolymerization and analyze the copolymer composition, we always deal with the cumulative copolymer composition, which from now on will be denoted as F.

Reactivity ratios play a central role in eqn (1)–(4), but as the equations are non-linear in nature, it is not immediately evident how to determine these reactivity ratios from experimental data. Several methods have been proposed over the last 75 years, many of which involve linearization of the copolymer composition equation. Widely used linearized methods such as Fineman–Ross[10] and Kelen–Tüdős[11] distort the error structure of the experimental data, however, and can lead to biased and imprecise results. For this reason, non-linear least squares fitting (NLLS) is greatly preferred. Further problems are encountered when the assumptions of the models are violated: for example, by applying eqn (1) to copolymerizations with non-negligible conversion, where eqn (4) would be more appropriate. These incorrect procedures can lead to significant errors in the estimation of reactivity ratios.

One of the early advocates of establishing methods for determining reactivity ratios more correctly was Prof. Ken O'Driscoll. In a recent paper on his work[6] we presented his insights, which we fully support and which formed the basis of this present work of our IUPAC working group on "Methods and Data Evaluation Procedures for the Determination of Radical Copolymerization Reactivity Ratios".

From ref. 6 we repeat the eight key insights:

1. Model discrimination and parameter estimation normally require two different sets of experiments.
2. To apply the instantaneous copolymer composition equation (eqn (1)), low conversion data needs to be used (O'Driscoll indicates < 5% conversion).
3. The outcome of the statistical method applied should not depend on the indexing of the monomers (*i.e.*, whether a monomer is designated M_1 or M_2) (many workers do not realise that this is commonly a problem).
4. The starting point of the calculation should not affect the estimates (this is in reference to the use of iterative methods to find the optimal values).
5. Linearized methods cannot be expected to give good estimates of the reactivity ratios due to distortion of the error structure by the linearization process.
6. Correct design of experiments is of great importance.
7. Results should be reported as a point estimate together with a joint confidence interval (JCI).
8. If there is also an error in the monomer composition (f_i), the errors in (all) variables method (EVM) should be used, and this is especially relevant for the determination of reactivity ratios from conversion dependent data using the integrated copolymerization equation (eqn (4)).

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O'Driscoll also pointed out that the ease of doing the calculation plays an important role in the choice of the method, writing "The ease criterion was, even in 1970, satisfied by the "advent of the digital computer" (unfortunately, the subsequent advent of the pocket calculator with its *linear* least squares button has made the Fineman-Ross and related techniques seem more convenient)".[12] The unavailability of a simple-to-use NLLS computer program likely contributed to the continued use of linearized methods by many researchers. In the early 1990s O'Driscoll therefore worked with Reilly and others at the University of Waterloo to develop a microcomputer program, RREVM, based on the errors in all variables method (EVM) in order to alleviate this issue.[13]

In 1995 van Herk attempted to simplify NLLS fitting through visualization of the sum of squares space (VSSS), a method that can be easily implemented by scientists themselves in Visual Basic, Python or any other computer language.[14] The VSSS method maps the weighted sum of squares of residuals in a large parameter space (a grid of r_1 and r_2) and simply finds the lowest value (the minimum) to be the optimal parameter set for the reactivity ratios.[14] It was also stressed that proper weighing of the data (with their individual errors) is important to obtain correct reactivity ratios and joint confidence intervals.[14–16] Until recently this was the only rigorous approach to obtain unbiased estimates and unbiased errors for arbitrary non-linear models.[17]

However last year a new correct method was introduced using a Bayesian hierarchical approach addressing the issue of a non-Gaussian structure of the error estimates that is a consequence of the nonlinearity of the copolymerization model.[17]

Unfortunately, today many researchers still use linearized methods. In 2023 alone, more than 400 papers using the Finemann–Ross method[10] were reported. Furthermore, several papers were published using copolymer compositions determined at too high conversions, where composition drift will be significant, and eqn (1) cannot be used. Another issue is that some works report incorrect joint confidence intervals (see ref. 18 for a re-evaluation of a collection of published data). Even worse, many works report no uncertainty or JCI at all.

In this paper we present an example of the application of NLLS using the VSSS method keeping in mind the eight core insights of O'Driscoll.

Data collection

Polymer composition *vs.* comonomer composition at low conversion ($f_0 - F$). The most common method for determination of reactivity ratios involves collecting copolymer composition data (F) at low conversion across a range of initial comonomer mixture ratios (f_0). At sufficiently low conversion, the change in monomer composition (f) during polymerization is negligible, and the cumulative and instantaneous copolymer compositions can be assumed to be equivalent, allowing direct fitting of the Mayo–Lewis equation (eqn (1)).

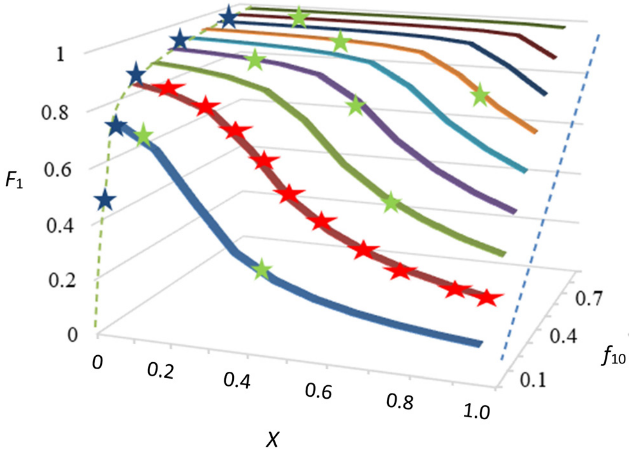

Fig. 1 Cumulative copolymer composition (F_1) *versus* conversion (X) at different monomer-1 starting fractions (f_{10}). The blue dotted line represent the cumulative copolymer composition at 100% conversion, which equals f_{10}. These data have been calculated using r_1 = 23 and r_2 = 0.02, as these exemplify well the discussed ideas. Indicated in the graph: low conversion experiments (blue stars, $f_0 - F$) with the $f_0 - F$ curve in dotted green, which is method (a) of the text; following conversion and f (red stars, $f_0 - f - X$), (f not shown in graph), which is method (b); IUPAC method, starting from several f_0 values and monitoring the copolymer composition with conversion (green stars, $f_0 - X - F$), method (c).

There is, however, no unique interpretation of "low conversion" in the $f_0 - F$ method, as with unfavorable reactivity ratios, strong composition drift can occur even at conversions below 5%. This may introduce significant errors in F (point 2 of O'Driscoll and see Fig. 1).

We therefore investigated several methods to correct for shifts in F at lower conversions. This includes, amongst others, using the average monomer composition over the conversion range instead of f_0. However, all of these approximate correction strategies require knowledge of the conversion, suggesting that direct application of an integrated form of the copolymer equation such as the Meyer–Lowry equation (eqn (4)) is then possible. In such a case application of the integrated expression is preferable.

Conversion *vs.* monomer composition ($f_0 - f - X$). An alternative approach is to measure the change in monomer composition across a range of conversions. The Meyer–Lowry equation (eqn (4)) relates the conversion X to the monomer composition f and therefore one most commonly fits X *vs.* f and not *vice versa*. This is how historically most fits are done, making X the dependent variable. This approach lends itself to online monitoring (for example with NMR), and in principle would allow determination of both reactivity ratios from a single copolymerization, monitored from low to high conversion. In practice, however, use of a single copolymerization is highly susceptible to systematic errors, for example resulting from errors in the initial monomer composition, and furthermore it is generally not possible to find a single initial monomer composition that gives accurate estimates of both reactivity ratios. These problems can be alleviated by carrying out multiple $f_0 - f - X$ experiments starting from different initial monomer mixture ratios. Random errors are also likely to be high as changes in f are small and relatively insensitive to the copolymer composition at low conversions, while at

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high conversions, little monomer remains to be measured, leading to a low signal to noise ratio. Very accurate measurements are thus required in order to obtain estimates of reactivity ratios of useful precision.

Copolymer composition *vs.* comonomer composition, while monitoring the conversion ($f_0 - X - F$). The recommended approach by the authors of this paper for data collection is to measure both cumulative copolymer composition and global monomer conversion, starting from multiple initial comonomer compositions. The resulting dataset can be fitted using an integrated form of the copolymer composition equation (eqn (4)). One of the first reports on this approach was in 1979 by the group of Hamielec.[19]

The way copolymerization experiments are performed does not change with this approach, but the measured conversion is now taken explicitly into account.

This also means that there is no longer any real difference between low and high conversion experiments, as in both cases copolymer composition and conversion are measured, starting from a particular f_0. Low and higher conversion data may be mixed to calculate reactivity ratios. This is illustrated in Fig. 1, where data points are fitted on a f_0, X, F surface. Other methods using low conversion data or measuring $f - X$ data from a single f_0 can still be seen as special cases of this more general preferred method of performing several experiments starting with different f_0 values. It is also very important to have error estimates for the F value, either directly measured or calculated from changes in monomer concentrations.[15,16] Note that the error in F is very different depending on whether it was measured directly or calculated from changes in f.

In this approach, both F and X may be expected to be subject to experimental errors, and as such the error in variables method (EVM) is preferred. However, in many cases it is likely that errors in determination of X will be small relative to errors in determination of F, as the measurement of X is more straightforward. In these cases, X can be treated as the error-free independent variable for the purposes of fitting.

It is also important to weight data appropriately. For example, if the experimentally obtained data is copolymer composition (F) and conversion (X), but the data is fitted using the Meyer–Lowry equation (eqn (4)), which relates the comonomer composition (f) and conversion (X), calculated f values should be weighted using Gaussian propagation of errors, as follows (note, an error in f_0 is not taken into account in this equation):

$$\Delta f_1 \approx \sqrt{\left(\Delta F_1 \frac{\partial f_1}{\partial F_1}\right)^2 + \left(\Delta X \frac{\partial f_1}{\partial X}\right)^2} = \sqrt{\left(\frac{X \Delta F_1}{1-X}\right)^2 + \left(\frac{(f_{10} - F_1)\Delta X}{(1-X)^2}\right)^2} \tag{6}$$

In the current approach we use $f_0 - X - F$ data and make the physically reasonable assumption that the major error is in F. Besides comparing the errors per datapoint, the overall error estimated by the user and the overall error obtained from the fit (s_F) can also be compared using a Fisher test (see for example ESI-Tables 4 and 5†).

$$s_F = \sqrt{\frac{\mathrm{ss}_{\min}(r_1, r_2)}{n-2}} \tag{7}$$

where $\mathrm{ss}_{\min}(r_1, r_2)$ is the sum of squares of the residuals at the minimum and n the number of datapoints.

In the case where f is monitored as a function of conversion (for example with *in situ* NMR[20]), these values can easily be converted to $f_0 - X - F$ data *via* the mass balance (eqn (5)). As O'Driscoll highlighted in point 8, a non-negligible error in f_0 or f should be taken into account. In the conversion, the errors assumed in f and X are then converted to errors in F through Gaussian error propagation (note, an error in f_0 is not included in this equation):

$$\Delta F_1 \approx \sqrt{\left(\Delta f_1 \frac{\partial F_1}{\partial f_1}\right)^2 + \left(\Delta X \frac{\partial F_1}{\partial X}\right)^2} = \sqrt{\left(\frac{(1-X)\Delta f_1}{X}\right)^2 + \left(\frac{(f_1 - f_{1,0})\Delta X}{X^2}\right)^2} \tag{8}$$

We believe the best option is to do the calculations with $f_0 - X - F$ data and not directly with the $f_0 - f - X$ data, because in the end we are interested in the best values for the reactivity ratios for predicting copolymer compositions. In the $f_0 - f - X$ approach a potential problem is that some of the monomer can evaporate if the reactor is not a closed system, so even if f data are converted into F data it is advised to measure at least the final average composition of the copolymer to check for internal consistency.

It is likely that the analysis of $f_0 - f - X$ data and the analysis of those data converted into $f_0 - X - F$ might give slightly different results (see ESI-Tables 7–9†) if EVM is not used. This is due to the fact that in the $f_0 - f - X$ approach fitting is of the conversion data, X, while in the $f_0 - X - F$ approach, fitting is on the composition data, F. The latter is the more robust approach and furthermore the desired application of the reactivity ratios is to predict the composition of the copolymer. Another advantage is that in the conversion from $f_0 - f - X$ to $f_0 - X - F$ both the errors in f (and if needed f_0) and in X can be taken into account and through error propagation this gives a well estimated error in the calculated F (eqn (8)). This should also result in more realistic errors for the reactivity ratios. Note that this is not a full errors-in-variables method as the result is only optimized on the copolymer composition F. Proper weighting of those data can however take place.[14,15]

Advantages of the IUPAC recommended method

We will now address key insights made by O'Driscoll in the light of our preferred method.

1. Model discrimination and parameter estimation normally require two different sets of experiments.

Model discrimination should select those experiments that distinguish the different models in the best way. For example, if we compare the terminal model with the complex participation model[21] we should maximize the range of monomer

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concentrations and monomer fractions. In case of interactions between the comonomers and the formed copolymers we should also investigate the influence of conversion. For parameter estimation the best experiments are those that are most sensitive to parameter variation, for example according to the well-known criteria of Tidwell and Mortimer for the terminal model at low conversion.[22]

In the IUPAC recommended method variation in initial monomer fractions (f_0) as well as conversion (X) is highly advised, as this variation may be sufficient in itself to reveal deviations from the terminal model[6] and systematic errors in the measurements. Looking at the individual fit residuals (calculated F minus measured F *i.e.* $F_{\text{calculated}} - F_{\text{measured}}$) it is possible to detect trends (*e.g.* deviations at high conversion, deviations at low or high f_0).

In principle, we have combined parameter estimation with some investigating whether the (terminal) model is adequate for compositional data in this IUPAC recommended method.

As an example of an alternative model, the penultimate model might be required for describing propagation rate coefficients as a function of monomer composition,[23,24] but could also be applicable to compositional data.

2. To apply the instantaneous copolymer composition equation, low conversion data is required (O'Driscoll indicates < 5% conversion).

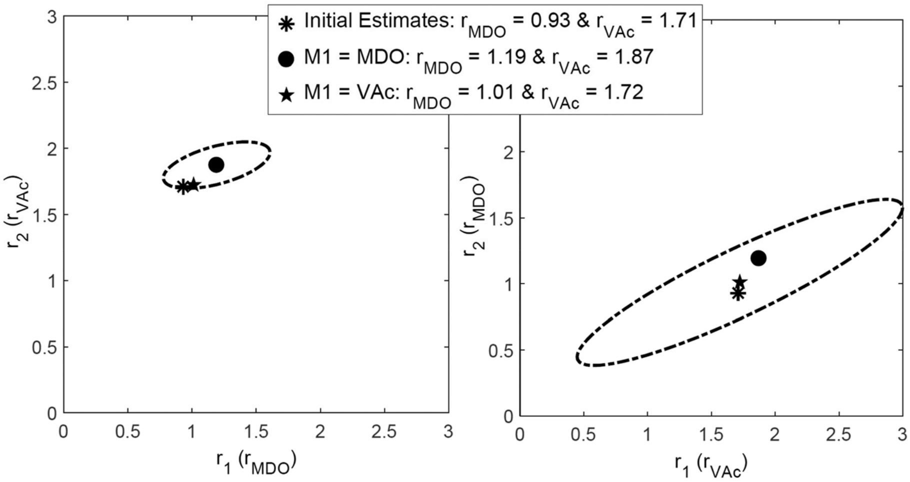
This is a very important point, but in practice a threshold of 5% is not always sufficient, and for cases of strong composition drift (*e.g.* see low f_{10} values in Fig. 1) even 5% conversion might already introduce a significant change in F.

Our working group initially looked at methods to correct for conversion (at relatively low levels) but it turned out that if the conversion is known, it is simpler to take it into account explicitly through the use of the integrated copolymerization equation. This also opens the possibility to no longer be restricted by a threshold conversion but instead use data at any conversion. Including data at higher conversion has the additional benefit that any influence of the presence of formed copolymer on reactivity ratios might be revealed, which then would show up as a systematic error at higher conversions (see point 1). A prerequisite is of course that the conversion is measured for each experiment, which largely improves on the quality of the data in all cases. In the case that only low conversion data is used, it is again important to carefully compare the estimated errors in F with the fit residuals (looking at individual datapoints and also utilizing the Fisher-test described in eqn (8)). In case of doubt the $f_0 - X - F$ method should be used.

3. The outcome of the statistical method applied should not depend on the indexing of the monomers.

The model used to fit the data should be identical, regardless of the way in which the monomers are numbered. This is the case for the Mayo–Lewis and Meyer–Lowry equations (1 and 4 respectively), but not for the linearized Fineman–Ross method, which will give different values of r_1 and r_2 depending on the indexing.[10,11] In addition to the model itself, the weight given to each result should also be independent of the indexing. While the simplest assumption is to give equal absolute weight to all experimental data points, this assumption is not always correct. An incorrect alternative approach of using equal relative weightings (*e.g.* assuming an uncertainty of 10% in all experimental data) will lead to weights that depend on indexing. For example, $f_1 = 0.1$ can be equivalently expressed as $f_2 = 0.9$, but the uncertainties, assuming a constant relative error of 10%, will be ±0.01 in the first case and ±0.09 in the second. This can lead to parameter estimates and joint confidence intervals that differ depending on the monomer indexing, even when the underlying model is symmetrical with respect to indexing.

For the copolymerization of 2-methylene-1,3-dioxepane (MDO) and vinyl acetate (VAc), using the RREVM program (see above), Scott *et al.* found slightly different reactivity ratios and joint confidence intervals (JCIs) when the indexing was switched, as shown in Fig. 2.[25] The origin of this discrepancy lies in the assumption of constant relative errors, as pointed out above.



(a) (b)

Fig. 2 Influence of indexing the monomers on reactivity ratios and 95% JCI, reproduced from ref. 25 with permission.

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To avoid such mistakes entirely in the future we recommend that errors in the measurements be expressed in absolute numbers. If we take the absolute numbers based on the 10% error in *F* for the dataset of ref. 25 and, switch the index but use the same absolute errors for *F*, we get identical reactivity ratios and identical JCIs (see ESI-Fig. 1 and 2†).

Related to the indexing issue (see above) is how the estimation of the errors in the dependent variable is done and we will see that this in turn can influence the size of the JCI.

We would like to emphasize the importance of some knowledge of the error (structure) in the measured data. If there is a large variation in the size of the error within a dataset, the error can be used to weight the data in the fit.[16]

In many cases, monomer mixture composition data is obtained by integrating NMR spectra of the reaction mixture. In this situation, the intensity of the signals due to monomer decreases as the conversion increases, and an appropriate weighting function is given by eqn (9):[26]

$$\Delta f_1 = \Delta(1-f_1) \propto \sqrt{\frac{1+(1-2f_1)^2}{4(1-X)^2}} \qquad (9)$$

This function will be appropriate to other methods of determining monomer composition as a function of conversion in which the intensity of a signal is directly proportional to the amount of monomer present and so eqn (9) can be generally recommended for use.

In the event that the errors are known, for example through an error propagation exercise or through replicate measurements, the errors can be used to construct the joint confidence interval using the χ^2 distribution[27] with $\mathrm{ss}(r_1,r_2)_z$ the boundary of the JCI at level z (for example a 95% probability):

$$\mathrm{ss}(r_1,r_2)_z \ \le\ \mathrm{ss}_{\min}(r_1,r_2)+\sigma^2\chi^2{}_z(p) \qquad (10)$$

Here σ^2 corresponds to the average absolute variance of the dependent variable (in this case *F*) and is calculated from the known errors as entered by the user. $\mathrm{ss}_{\min}(r_1,r_2)$ is the sum of squares of residuals at the minimum and with *p* degrees of freedom (*p* equals two in the present cases).

4. The starting point of the calculation should not affect the estimates (this is in reference to the use of iterative methods to find the optimal values).

In general, in iterative methods the values of the optimum depend slightly on the starting point of the calculation.[12] Luckily for determinations of reactivity ratios from the terminal copolymerization model there are no false minima. The VSSS method is not an iterative method, which means that even upon expansion to more complex models, falls minima will not be an issue.

5. Distortion of the error structure by linearization methods cannot be expected to give good estimates of the reactivity ratios.

While the copolymerization equation can be linearized using the Fineman–Ross,[10] Kelen–Tüdős[11] and other methods, doing so introduces bias into the results. In addition, these methods can only be used for low conversion data. We therefore strongly recommended to use NLLS, which provides an estimate of the reactivity ratios which is not biased by linearization.

In Fig. 3 we show the differences in output using the Fineman–Ross (F–R),[10] Kelen–Tüdős (K–T)[11] and NLLS[14] methods applied to simulated data with noise. It can be seen that the F–R method is always liable to give poor results (compared to the true values), NLLS always gives good results, and the K–T is sometimes OK (left-hand figure), other times not (right).

As the NLLS method does not involve any linearization, distorting the error structure is not an issue. However, it is important to stress that some knowledge of the errors in the measurements (error in copolymer composition *F*) is needed.

In the case that the errors are exactly known, the errors are also used to construct the JCI (eqn (10)). If the errors are only estimates (which is often the case), the JCI at level z is constructed through the following equation:

$$\mathrm{ss}(r_1,r_2)_z \ \le\ \mathrm{ss}_{\min}(r_1,r_2)(1+p/(n-p)F_z(p,n-p)) \qquad (11)$$

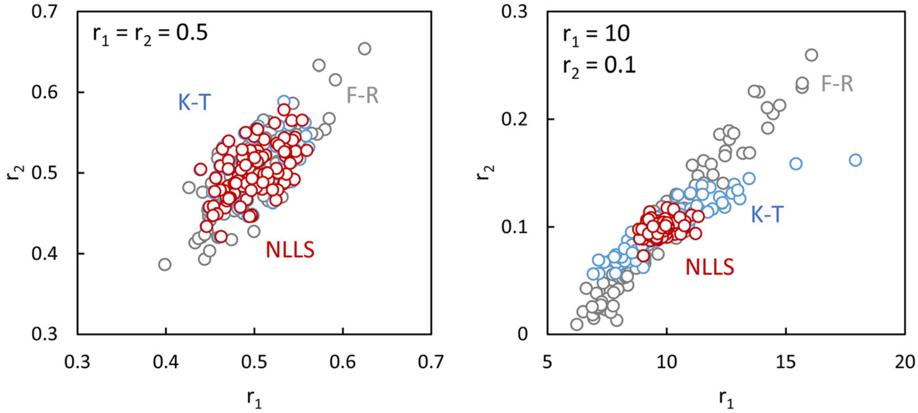

Fig. 3 Differences using Fineman–Ross (F–R)[10] and Kelen–Tüdős (K–T)[11] and NLLS methods applied to simulated data with noise, where the true values are given in the upper left of each figure, and the circles are the values obtained from each analysis of simulated composition data with different noise (more details see ESI-Tables 1–3†).

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where $F_z(p,n-p)$ represents a value from the Fisher-distribution at level z (for example at 90 or 95% probability) with p and $n-p$ degrees of freedom (p equals two in these cases), n data points and $\text{ss}_{\min}(r_1,r_2)$ sum of squares of residuals at the minimum.

Another aspect that needs to be discussed with respect to errors is that statistics can only deal with random errors. As soon as systematic errors appear, the JCI will no longer give a useful reflection of reality. For example, if through a weighing error the true f_0 is significantly different from the reported value, all the data from that experiment are systematically biased. For this reason, it is recommended that several different starting values for f_0 are used (see also point 6). If each of these f_0 sets (*e.g.* the different curves in Fig. 1) have different systematic errors, the overall fit with all the different f_0 values and associated systematic errors is more likely to transpose to a random error. After all, if the source of the systematic error is for example a weighing error for f_0, it might be expected that these weighing errors across the different f_0 values are again randomly distributed. The sum of squares of residuals at the minimum will be larger than for the individual f_0 sets and $\text{ss}_{\min}(r_1,r_2)$, through eqn (10) or (11) will increase the size of the JCI. We will address this issue in more detail in the paragraphs on systematic errors.

6. Correct design of experiments is of great importance.

Design of experiments can also be applied on the IUPAC recommended method. In the case of low conversion data, we recommend use of at least three different f_0 values, where two of them can be chosen through the Tidwell–Mortimer D-optimal design criteria.[22] Some estimate of the reactivity ratios is needed. We realize that the Tidwell–Mortimer approach is only applicable to low conversion experiments and cannot be extended to higher conversions. We are currently working on developing appropriate criteria for high conversion experiments. The third value (and other values) can be chosen on the basis of potential complications (*e.g.* complex formation between monomer and polymer, influence of high conversion).

7. Results should be reported as a point estimate together with a joint confidence interval.

Because we calculate the full sum of squares space in the VSSS approach, the unbiased joint confidence interval with exact shape for the parameter estimates is given as a contour line in the sum of squares space using eqn (10) or (11). Some software report the approximate JCI estimate in the form of an ellipse, see for example Fig. 2 and compare to ESI-Fig. 2 and 3† for unbiased joint confidence intervals (see ref. 15 for an extensive discussion on this topic). Reporting the JCI in some form is strongly recommended.

8. If there is also an error in the monomer composition (f_i), the errors in (all) variables method (EVM) should be used, and this is especially relevant for the determination of reactivity ratios from conversion dependent data using the integrated copolymerization equation.

In the IUPAC recommended method ($f_0 - X - F$) we measure the copolymer composition (or the monomer composition which is then converted into a copolymer composition using the mass balance in eqn (5)) and estimate the error in F. The error in X can either be transposed into an error in F (see for example ref. 16) or taken into account *via* the EVM.[25] In the VSSS method, the EVM can also be applied.[26]. The errors in f_0 have been discussed already with point 3.

The errors are important in three ways: (1) they can be used to weigh the data; (2) They determine the size of the JCI (in case of known errors and applying eqn (10); and (3) They can be used to determine whether the fit is adequate by comparing the actual fitting residues with the estimated errors (eqn (7)).

Besides these eight points, O'Driscoll also highlighted the "ease criterion". The easier it is for the polymer chemist to apply a method to obtain reactivity ratios, the more likely it is that the method will be used. This is why our working group undertook to make free software available for applying the IUPAC recommended method as a stand-alone program (Contour),[28] as open source Python code[29] and as an Excel workbook with macro,[30] all containing the VSSS method for $f_0 - X - F$ data. We recommend that either $f_0 - X - F$ (either directly measured F-values or converted from f) or (very) low conversion ($f_0 - F$) data may be used.

Application of the IUPAC recommended method

We implemented the IUPAC method in the existing freeware Contour.[14–16] There we used the VSSS method and f_0, X, F, ΔF (absolute error in F) data. The software carries out numerical integration of the copolymerization equation during the parameter estimation process. This means that software issues due to singularities are minimized, but that calculation time can be a couple of seconds up to a few minutes. A JCI is generated, as well as a graphical display of the residuals in the 3-dimensional $f_0 - X - F$ plot. It is determined whether the fit is adequate by comparing the actual fitting residues with the estimated errors through a Fisher test (eqn (7)).

We first generated a dataset with random noise (±0.005 on X and F) and original reactivity ratios of $r_1 = 0.4$ and $r_2 = 0.6$ (exact values), (see ESI-table 4†).

The resulting reactivity ratios are $r_1 = 0.401 \pm 0.003$ and $r_2 = 0.601 \pm 0.003$ (ESI-Table 4 and for the JCI SI-Fig. 3†).

We see that the residuals space (Fig. 4a) shows an even distribution of positive, negative and even close to zero residuals. Of course, because this is a dataset with limited random errors added, this result is as expected.

We also used an experimental dataset from the group of Schmidt-Naake[31] which is shown in Table 1:

We selected this experimental dataset because the necessary $f_0 - X - F$ data are directly available (not indirectly through f measurements) and this system might not behave according to the regular terminal model as acid–base interactions are expected between the APSA and the VIm.[31]

With the IUPAC method the obtained reactivity ratios are 0.40 for r_1 and 0.022 for r_2 (see ESI-Table 5†) whereas in the original paper values of 0.31 for r_1 and 0.026 for r_2 were reported using a slightly different fitting procedure.[31] Based on comparison of the estimated errors in F (0.030) with the

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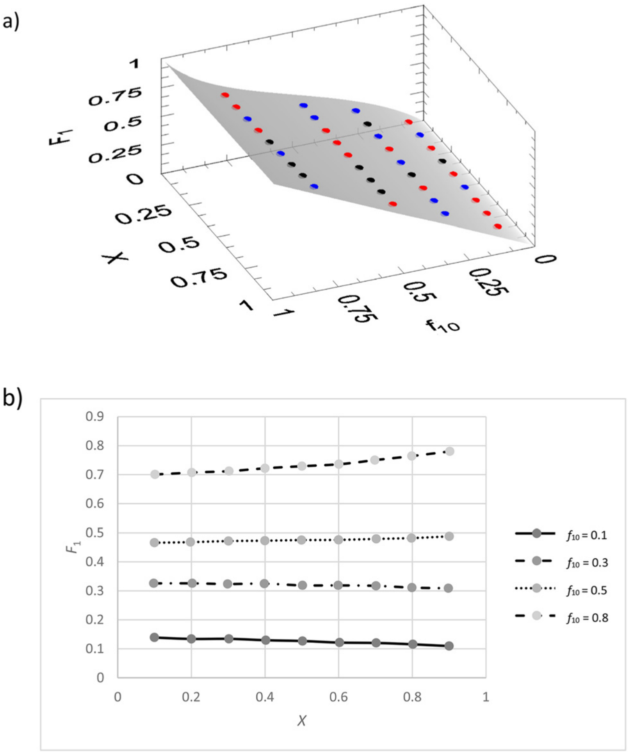

Fig. 4 (a) Plot of f_{10}, X, F_1 data for a simulated copolymerization with reactivity ratios r_1 = 0.4 and r_2 = 0.6. Points in red are indicating a positive fit residue and in blue a negative fit residue, black are residues less than 10% of the estimated error. (b) Individual $X - F_1$ plots for different values of f_{10} (f_0 for monomer 1).

actual fit residues it is determined that the terminal model gives an adequate fit to the data (ESI-Table 5†). The JCI is shown in Fig. 5.

As in this case it is expected that complexation between the two monomers will occur, some systematic trend in the residuals is expected. Schmidt-Naake *et al.*[31] report that maximum complexation between the two monomers takes place at f_{10} of 0.5. We see that in the middle region most residuals are negative whereas at low f_{10} values most residuals are positive, indicating some systematic deviations (Fig. 6). Also it has to be noted that at low f_{10} values monomer 1 is depleted at higher conversions.

The best way to investigate this further is by deleting some data structurally (*e.g.*, take out low f_0 values or high conversion data) from the set and see whether the reactivity ratios change. For example, if we take out the f_{10} = 0.05 and f_{10} = 0.1 data, we obtain 0.42 and 0.058 (ESI-Table 6†) for r_1 and r_2 respectively, more than doubling the value of r_2.

Table 1 f_{10}, X, F_1, ΔF_1 data[a] for the copolymerization of 2-acrylamido-2-methyl-1-propanesulfonic acid (APSA, monomer 1) and 1-vinylimidazole (Vim, monomer 2)[31]

f_{10}	X	F_1	ΔF_1
0.05	0.04	0.404	0.030
0.05	0.093	0.381	0.030
0.05	0.209	0.316	0.030
0.05	0.195	0.282	0.030
0.05	0.279	0.227	0.030
0.05	0.434	0.146	0.030
0.1	0.1	0.458	0.030
0.1	0.182	0.457	0.030
0.1	0.194	0.407	0.030
0.1	0.301	0.396	0.030
0.1	0.389	0.347	0.030
0.1	0.474	0.235	0.030
0.3	0.109	0.547	0.030
0.3	0.168	0.491	0.030
0.3	0.201	0.484	0.030
0.3	0.383	0.486	0.030
0.3	0.456	0.488	0.030
0.3	0.731	0.467	0.030
0.7	0.068	0.658	0.030
0.7	0.186	0.654	0.030
0.7	0.274	0.677	0.030
0.7	0.332	0.642	0.030
0.7	0.482	0.635	0.030
0.7	0.577	0.649	0.030
0.7	0.739	0.658	0.030
0.9	0.13	0.872	0.030
0.9	0.273	0.856	0.030
0.9	0.43	0.83	0.030
0.9	0.585	0.915	0.030
0.9	0.71	0.91	0.030
0.9	0.82	0.88	0.030

[a] f_{10} initial ratio of APSA in the monomer mixture, X overall monomer conversion, F_1 the content of APSA in the copolymer.

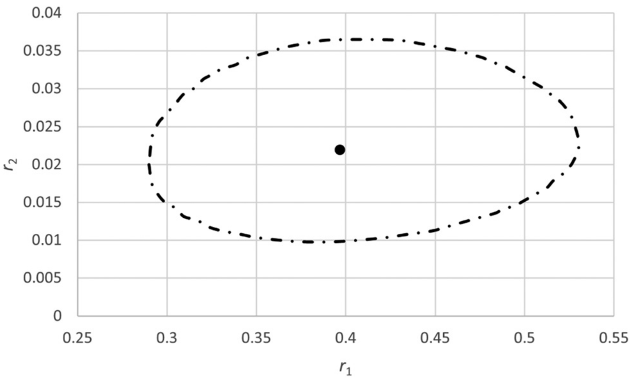

Fig. 5 95% Joint confidence interval based on eqn (11) for the reactivity ratios of copolymerization of 2-acrylamido-2-methyl-1-propanesulfonic acid (APSA, monomer 1) and 1-vinylimidazole (Vim, monomer 2).[29]

Effect of systematic errors in the initial monomer fraction in copolymerization experiments

In order to investigate how sensitive an analysis of an $f_0 - X - F$ dataset is in errors in f_0 we generated a dataset with little composition drift from reactivity ratios of r_1 = 0.40 and r_2 = 0.60 respectively and with initial monomer fraction (f_{10}) of 0.1, 0.3, 0.5 and 0.8. We superimposed an absolute random error on both conversion (X) and cumulative copolymer composition (F_1) of ± 0.005 each.

In Fig. 7 the original reactivity ratios (triangle) and the fitted reactivity ratios with the noisy data (circle) are shown (r_1 = 0.396 and r_2 = 0.595) as well as the corresponding JCI's.

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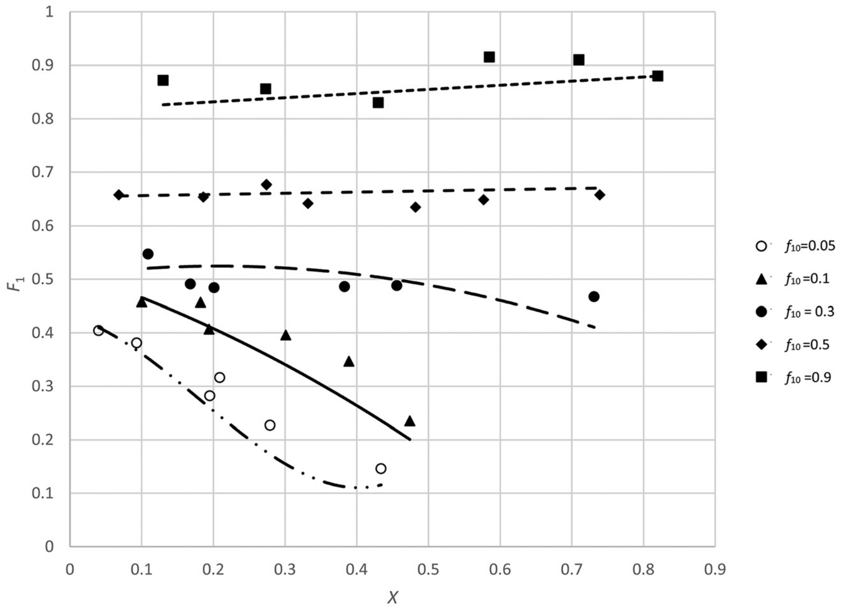

Fig. 6 Plots of X, F_1 data for the copolymerization of 2-acrylamido-2-methyl-1-propanesulfonic acid (APSA, monomer 1) and 1-vinylimidazole (Vim, monomer 2).

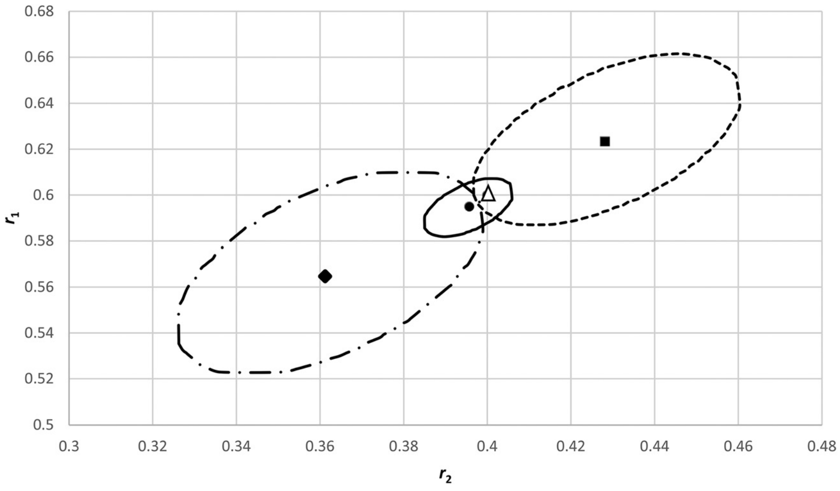

Fig. 7 95% JCI's based on eqn (11) for original reactivity ratios r_1 = 0.6 and r_2 = 0.4 (Δ), with random errors added but without systematic errors in f_{10} (—) and with systematic errors in f_{10}, modification 1 is adding/subtracting 0.01 with signs +−+− (----), modification 2 is −+−+(— -).

Now we alternatingly added and subtracted 0.01 to the four f_{10} values given above (in modification 1 we added first, in modification 2 we subtracted first) to create a systematic error in each experiment starting from a (incorrectly determined) f_{10} value only. All the other measurements are assumed to only have a random error. With these new data the fit is obviously worse and the JCI is much larger (see Fig. 7), due to the poor fit and thus the sum of squares of residuals at the minimum increases (we used the Fisher-distribution for the JCI).

It is important to note that the minima can shift considerably and differently, depending on the systematic errors introduced on the original f_{10} values. Although the 95% JCI's are much bigger, they barely touch the correct values. The systematic errors introduced in f_{10} in the individual experiments, overall seen over the different f_{10} values, are more or less random (2 × +0.01, and 2 × −0.01), but it makes a difference how we apply them (modification 1 *vs.* modification 2).

We plotted the residuals for the data (modification 1 in Fig. 7), which clearly indicate systematic deviations per experiment (see ESI- Fig. 6†).

This means that particular care has to be taken to avoid an error in the f_{10} values, but a residuals plot (like Fig. 4a) can be used to identify such issues. However, if we only take a single experiment with the systematic errors included, we obtain reactivity ratios diverging significantly from the true values with very large JCI's. It is an option to vary f_{10} values in a

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single experiment and see how the quality of the fit improves. This approach is recommended as very small variations in f_{10} have a major influence on the SSR and on the obtained reactivity ratios in for example X *vs.* f data (see ESI-Fig. 8†).

We also investigated a system with more composition drift and reactivity ratios of $r_1 = 13$ and $r_2 = 0.3$ (ESI-Fig. 5–7†). Applying systematic errors in f_{10} again, like we did before, there is hardly any overlap of the JCI's (ESI-Fig. 7†). If we use a single experiment (one f_{10}) with systematic error, hugely incorrect reactivity ratios are likely to be obtained. However, by taking a series of different f_{10} experiments we can still obtain reasonable estimates for the reactivity ratios. However, the JCI's with systematic errors seem to be not large enough to overlap with the true reactivity ratios (ESI-Fig. 7†). The increase in JCI due to a larger sum of squares of residuals at the minimum is not sufficient to reflect the increased error in the reactivity ratios. One of the assumptions in the non-linear least squares method is that the errors are independent, which is obviously violated here within a single experiment starting from a wrong f_{10} value.

The conclusion is that errors in the value of f_{10} should be avoided at all costs. One option is to investigate the residuals space and see whether there is a systematic pattern in one or more of the experiments starting from a particular f_{10}. If that is the case, an error in f_{10} could be assumed and a correction could be made by varying f_{10} and looking for the best value (see ESI-Fig. 8†). These variations in f_{10} could be as small as ±0.002, so usually well within the estimated error range for f. This option is available in Contour, with the optimized f_{10} value suggested by the software then used to see if the overall fit improves.

Recommendations

-Use only non-linear regression or VSSS methods.

-Either use low conversion $f_0 - F$ data or conversion dependent data in the form of $f_0 - f - X$ or $f_0 - X - F$, in all cases with at least three different starting monomer compositions f_0.

-If using low conversion $f_0 - F$ data, check that no significant (more than the expected random error) change in F has occurred due to composition drift. Once the reactivity ratios are estimated, the predicted change in F with conversion should then be calculated. If this indicates too much composition drift over the range of X used experimentally, then one should go back and use the $f_0 - X - F$ method instead.

-Obtain the best possible information about the errors in the measurements, and utilize weighting according to the errors in the dependent variable (in most cases F).

-If the independent variable (usually f) has considerable error, use EVM.

-If using $f_0 - f - X$ data without EVM, convert the $f_0 - f - X$ data into $f_0 - X - F$ with proper error propagation, taking errors in f (also f_0 if needed) and X into account.

-Be aware of errors in f_0, especially in conversion dependent experiments.

-Mitigate errors in f_0 through (1) measuring f_0 (*e.g.* through NMR), and/or (2) investigating limited variations in f_0 though fitting $f_0 - f - X$ single experiments, and/or (3) looking at the residuals in a set of experiments and detecting systematic patterns (if so, vary f_{10} again).

-Analyse the residuals and compare the fit residuals with the estimated errors.

-Investigate if fit residuals exceed the expected errors; if they do, this usually indicates either that the terminal model is not valid for the copolymerization system under investigation and/or that systematic errors are present.

-The obtained reactivity ratios should be reported with the correct number of significant digits (typically 2) and a measure of the uncertainty in those values (preferably a joint confidence interval).

Conclusion

The IUPAC working group on "Experimental Methods and Data Evaluation Procedures for the Determination of Radical Copolymerization Reactivity Ratios" has established a robust method to determine reactivity ratios from composition data following the terminal model. The method is based on measuring conversion (X) and (cumulative) copolymer composition (F) in a few copolymerization reactions at different starting monomer compositions (f_0), although a set with only low conversion can also be used ($f_0 - F$). Importantly, we make freely available the analysis software for this method, and we strongly recommend that it be used for reactivity ratio determination. The method not only provides parameter estimates but can also reveal deviations from the terminal model and systematic errors in the dataset. It is shown that error estimation for the F-values is important for weighing the data, determining the size of the joint confidence interval (in case of accurately known errors) and discerning whether the fit with the terminal model is adequate. In principle previous experiments measuring $f_0 - F$ (if conversion is known or sufficiently low) can still be analyzed with the IUPAC recommended method. Some examples have been given of reactivity ratio determinations, both with experimental data as well as simulated data. Special attention has been given to the occurrence of systematic errors in the $f_0 - X - F$ and $f_0 - f - X$ experiments. It is shown that the current statistical treatment is not able to properly accommodate systematic errors occurring within such experiments. However, with the analysis of the residuals space ($f_0 - X - F$) these errors can be identified and where possible corrected through optimization of f_0 as a third parameter.

The design of experiments procedure for the recommended method is under development.

Author contributions

Anton A. A. Autzen: investigation, methodology, writing – review & editing; Sabine Beuermann: investigation, method-

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ology, writing – review & editing; Marco Drache: investigation, methodology, writing – review & editing; Christopher M. Fellows: investigation, methodology, writing – review & editing; Simon Harrisson: investigation, methodology, project administration, writing – review & editing, software, formal analysis, funding acquisition; Robin A. Hutchinson: investigation, methodology, writing – review & editing; Atsushi Kajiwara: investigation, methodology, writing – review & editing; Daniel J. Keddie: investigation, methodology, writing – review & editing; Bert Klumperman: investigation, methodology, writing – review & editing, software; Gregory T. Russell: conceptualization, investigation, methodology, writing – review & editing; Alex M. van Herk: investigation, methodology, project administration, writing – original draft, software, formal analysis, funding acquisition.

Conflicts of interest

No conflicts of interest.

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References

1 S. Penczek and G. Moad, *Pure Appl. Chem.*, 2008, **80**, 2163–2193.
2 J. P. A. Heuts, R. G. Gilbert and I. A. Maxwell, *Macromolecules*, 1997, **30**, 726–736.
3 B. S. Beckingham, G. E. Sanoja and N. A. Lynd, *Macromolecules*, 2015, **48**, 6922–6930.
4 G. E. Roberts, M. L. Coote, J. P. A. Heuts, L. M. Morris and T. P. Davis, *Macromolecules*, 1999, **32**, 1332–1340.
5 J. Zhang, B. Farias-Mancilla, M. Destarac, U. S. Schubert, D. J. Keddie, C. Guerrero-Sanchez and S. Harrisson, *Macromol. Rapid. Commun.*, 2018, **39**, 1800357.
6 R. A. Hutchinson, B. Klumperman, G. T. Russell and A. M. Van Herk, *Can. J. Chem. Eng.*, 2022, **100**, 680–688.
7 F. R. Mayo and F. Lewis, *J. Am. Chem. Soc.*, 1944, **66**, 1594–1601.
8 I. Skeist, *J. Am. Chem. Soc.*, 1946, **68**, 1781–1784.
9 V. E. Meyer and G. G. Lowry, *J. Polym. Sci., Part A: Gen. Pap.*, 1965, **3**, 2843–2851.
10 M. Fineman and S. D. Ross, *J. Polym. Sci.*, 1950, **5**, 259–265.
11 T. Kelen and F. Tüdős, *React. Kinet. Catal. Lett.*, 1974, **1**, 487–492.
12 K. F. O'Driscoll and P. M. Reilly, *Makromol. Chem., Macromol. Symp.*, 1987, **10/11**, 355–374.
13 M. Dube, R. Amin Sanayei, A. Penlidis, K. F. O'Driscoll and P. M. Reilly, *J. Polym. Sci., Part A: Polym. Chem.*, 1991, **29**, 703–707.
14 A. M. van Herk, *J. Chem. Educ.*, 1995, **72**, 138–140.
15 A. M. van Herk and T. Dröge, *Macromol. Theory Simul.*, 1997, **6**, 1263–1276.
16 M. Buback, T. Dröge, A. M. van Herk and F. O. Mähling, *Macromol. Chem. Phys.*, 1996, **197**, 4119–4134.
17 R. Reischke, *Macromol. Theory Simul.*, 2023, **32**, 202200063.
18 J. B. Lena and A. M. van Herk, *Ind. Chem. Eng. Res.*, 2019, **58**, 20923–20931.
19 S. M. Shawki and A. E. Hamielec, *J. Appl. Polym. Sci.*, 1979, **23**, 3155–3166.
20 C. Preusser and R. A. Hutchinson, *Macromol. Symp.*, 2013, **333**, 122–137.
21 R. E. Cais, R. G. Farmer, D. J. T. Hill and J. H. O'Donnell, *Macromolecules*, 1979, **12**(5), 835–839.
22 P. W. Tidwell and G. A. Mortimer, *J. Polym. Sci., Part A: Gen. Pap.*, 1965, **3**, 369–387.
23 R. A. Sanayei, K. F. O'Driscoll and B. Klumperman, *Macromolecules*, 1994, **27**, 5577–5582.
24 S. K. Fierens, P. H. M. Van Steenberge, M.-F. Reyniers, D. R. D'hooge and G. B. Marin, *React. Chem. Eng.*, 2018, **3**, 128–145.
25 A. J. Scott and A. Penlidis, *Processes*, 2018, **6**, 8, DOI: 10.3390/pr6010008.
26 M. van den Brink, A. M. van Herk and A. L. German, *J. Polym. Sci., Part A: Polym. Chem.*, 1999, **37**, 3793–3803.
27 P. J. Rossignoli and T. A. Duever, *Polym. React. Eng.*, 1995, **3**(4), 361–395.
28 A. M. van Herk, *Software package Contour issue 2.4.0*, accessed 03/04/2024 Contour 2.4.0.
29 Code in Python for the VSSS method applied on $f_0 - X - F$ data, accessed 02/04/2024 Pythoncode.
30 Code in Excel (via VB) for the VSSS method applied on f_0-X-F data, accessed 02/04/2024 Excel application.
31 C. Schmidt, F. Merz, S. Jiang, M. Drache and G. Schmidt-Naake, *Macromol. Mater. Eng.*, 2007, **292**, 428–436.
32 IUPAC project site, last accessed 03/03/2024 https://iupac.org/project/2019-023-1-400/.