UNIVERSIDADE FEDERAL DE SANTA CATARINA
CENTRO TECNOLÓGICO
PROGRAMA DE PÓS-GRADUAÇÃO EM ENGENHARIA QUÍMICA

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REACTIVITY RATIOS ESTIMATION OF THE FREE-RADICAL COPOLYMERIZATION OF ITACONIC ACID AND N-VINYL-2-PYRROLIDONE BY A NON-LINEAR REGRESSION TECHNIQUE USING THE ERROR-IN-VARIABLES METHODOLOGY

Florianópolis
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Dissertação submetida ao Programa de Pós-graduação em Engenharia Química da Universidade Federal de Santa Catarina para a obtenção do título de Mestre em Engenharia Química
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Florianópolis
2020

Ficha de identificação da obra elaborada pelo autor, através do Programa de Geração Automática da Biblioteca Universitária da UFSC.

Krieger, Bruno Vasconcellos
Reactivity ratios estimation of the free-radical copolymerization of itaconic acid and n-vinyl-2-pyrrolidone by a non-linear regression technique using the error-in-variables methodology / Bruno Vasconcellos Krieger; orientadora, Claudia Sayer, coorientador, Pedro Henrique Hermes de Araújo, 2020.
68 p.

Dissertação (mestrado) - Universidade Federal de Santa Catarina, Centro Tecnológico, Programa de Pós-Graduação em Engenharia Química, Florianópolis, 2020.

Inclui referências.

1. Engenharia Química. 2. Copolimerização. 3. Regressão não linear. 4. Metodologia dos erros nas variáveis. I. Sayer, Claudia. II. Hermes de Araújo, Pedro Henrique. III.Universidade Federal de Santa Catarina. Programa de Pós Graduação em Engenharia Química. IV. Título.

Bruno Vasconcellos Krieger

Reactivity ratios estimation of the free-radical copolymerization of itaconic acid and n-vinyl-2-pyrrolidone by a non-linear regression technique using the error-in-variables methodology

O presente trabalho em nível de mestrado foi avaliado e aprovado por banca examinadora composta pelos seguintes membros:

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Documento assinado digitalmente
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Data: 31/08/2020 13:09:32-0300
CPF: 728.453.929-15

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CPF: 002.697.897-07

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Florianópolis, 02 de julho de 2020.

ACKNOWLEDGEMENTS

First and foremost I would like to thank my family for all the unconditioned emotional and financial support given me throughout all these long years of my academical formation, especially my mother who always stood by and supported my every decision, even when some of those proved to be completely misguided.

I would also like to thank my laboratory colleagues for all the time spent together, the laughs, the everyday drama, all the things that make our everyday work life better and worthwhile. A special thanks to Diego, Vinícius, Thiago O., Jeovandro and Arthur for the constant companionship. A most special thanks to Thiago Neubauer, who had to move away for his own PhD, but who provided months of friendship and guidance for the earlier stages of this work.

I would also like to extend a few words of thanks to my academic advisors Dr. Claudia Sayer and Dr. Pedro Henrique Hermes de Araújo, who shared with me their expert knowledge, know-how and guidance. Because of them this work became possible.

A final thanks to these institutions, the Universidade Federal de Santa Catarina (UFSC) and the Laboratório de Controle de Processos de Polimerização (LCP) for the opportunity, infrastructure and resources that made this work possible, and also to the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and the Conselho Nacional de Desenvolvimento Cientifico e Tecnológico (CNPq) for the direct and indirect financial support.

‘You may have a fresh start any moment you choose, for this thing that we call "failure" is not the falling down, but the staying down.’

(Mary Pickford, 1936)

RESUMO

Copolímeros ocupam um espaço crítico como materiais modernos devido a sua versatilidade, o que permite que suas propriedades físicas sejam projetadas para terem uma função especifica ou ocuparem um nicho de mercado particular. Porém, isso requer um entendimento profundo de como estes copolímeros devem ser produzidos em respeito a suas condições de processamento e cinética de reação. Um dos parâmetros que se deve ter para produzir um copolímero com distribuição monomérica e propriedades físicas conhecidas é a reatividade relativa do par monomérico, e dessa forma, o uso de técnicas de regressão apropriadas que podem extrair essa informação de dados experimentais é essencial para a produção desses copolímeros. Esses métodos, porém, ainda não são muito utilizados devido a sua complexidade e baixa acessibilidade. Portanto, para obter-se esses parâmetros, foi escrita uma implementação da técnica dos erros nas variáveis, descrita previamente na literatura. Desenvolveu-se também uma metodologia de HPLC de passo único para a aquisição dos dados cinéticos requeridos para a regressão dos parâmetros do sistema de polimerização por radicais livre ácido itacônico/ n-vinil-2-pirrolidona. O PVPIA é um copolímero altamente hidrofílico e biocompatível que pode ser utilizado como removedor de metais pesados de águas residuais, na liberação controlada de fármacos, entre outros. Dos dados adquiridos foi observado que altas frações de ácido itacônico no meio reacional alteram a cinética da reação ao ponto de impedir a realização da regressão dos parâmetros. Esse efeito, no entanto, não foi observado para frações molares de ácido itacônico abaixo de 10%, o que permitiu a realização da regressão paramétrica. A performance do algoritmo desenvolvido foi satisfatória, com uma diferença de até 5% quando comparado com dados da literatura que utilizaram o mesmo método. Os valores dos parâmetros adquiridos para o sistema sob estudo com o algoritmo desenvolvido foram $r_1 = 0{,}3046$ e $r_2 = 0{,}0170$, tendo ácido itacônico como composto 1. Um pequeno desvio foi observado para r_1 devido a um espalhamento dos dados cinéticos a frações baixas de IA e a baixas conversões que são causadas pelas taxas de reação elevadas desse monômero e incertezas na detecção do HPLC a concentrações muito baixas. Sistemas com altas frações de IA também foram estudados, mas eles não se conformaram a equação de copolimerização utilizada, o sistema com maior concentração atingiu um platô de conversão.

Palavras-chave: Método dos erros nas variáveis. Copolimerização. Regressão não linear.

RESUMO EXPANDIDO

Introdução

A ciência dos materiais ocupa uma área crítica no desenvolvimento a na manutenção de nossa sociedade moderna, criando e produzindo os diversos materiais utilizados em todos os níveis do conhecimento humano. Dentre esses materiais os polímeros sintéticos têm um papel singular, considerando que suas propriedades e características físicas podem ser livremente modificadas pela alteração das suas condições de produção, constituintes iniciais e suas proporções e outras variáveis de processo. A polimerização multicomponente em especial, é utilizada para produzir diversos polímeros comerciais utilizados em nosso dia-a-dia que possuem propriedades muito diferentes quando comparados aos homopolímeros formados pelos seus monômeros individuais. Essas características são dependentes de como esses diferentes monômeros estão organizados na cadeia polimérica e, portanto, o entendimento de como eles são adicionados a cadeia é de importância crítica quando se deseja produzir um polímero com propriedades bem definidas. A maneira mais comum com a qual um processo de copolimerização pode ser descrito é através da razão de reatividade relativa dos monômeros da reação. Historicamente, a maneira pela a qual essas razões são calculadas é pela regressão linear de algum tipo de linearização da equação de Mayo-Lewis, a equação de copolimerização instantânea. Essas linearizações, no entanto, são consideradas errôneas já que elas causam modificações significantes a estrutura dos erros dos dados utilizados. Esse problema de regressão já se encontra resolvido com o emprego de técnicas de regressão não linear que infelizmente, devido a sua dificuldade de implementação quando comparada a técnicas tradicionais, ainda não se encontram bem disseminadas. Esse trabalho tem o intuito de abater ou ao menos reduzir a falta de disponibilidade da implementação de uma dessas técnicas, a metodologia de erros nas variáveis (Error-in-Variables Method, EVM).

Objetivos

Em vista da extrema importância que as reatividades relativas têm na descrição do comportamento de reações de copolimerização, a utilização de metodologias estatisticamente corretas para obtenção desses valores é de extrema importância. Especialmente quando a maioria dos cientistas da área ainda fazem uso de metodologias que são limitadas a regiões de baixa conversão e que, portanto, ignoram os desvios de composição associados a regiões de alta conversão encontrados em muitos dos sistemas utilizados industrialmente. Com isso o objetivo principal desse trabalho é implementar e utilizar a metodologia dos erros nas variáveis para a estimação das razões de reatividade relativa do par monomérico ácido itacônico/n-vinil-2-pirrolidona na reação de polimerização por radicais livres do poli[(ácido itacônico)-co-(n-vinil-2-pirrolidona)] em solução de álcool isopropílico. Como objetivo secundário tem-se a reprodução e disponibilização pública de uma implementação da técnica EVM para a regressão paramétrica no ambiente MATLAB; implementação da equação de Skeist no sistema EVM para a regressão de reatividades relativas de sistemas copoliméricos; desenvolvimento e descrição de uma metodologia de passo único para a aquisição de dados de reações de copolimerização através de técnicas de HPLC; e por fim estimar as reatividades relativas do par IA/NVP utilizando as técnicas desenvolvidas.

Metodologia

Reações em 2-propanol foram realizadas em um balão de duas bocas de 250 ml com adaptador de Schlenck e septo de borracha. As reações ocorreram a 55 °C ou 65 °C dependendo da formulação e a concentração total de monômeros inicial foi 0,55 M, a razão monômero inicial para iniciador foi de 112,5 mol/mol. A variável ajustada entre as reações foi a fração molar

inicial dos monômeros em relação a quantidade de monômero total. A temperatura de 55 °C foi utilizada quando a taxa de reação se mostrou elevada demais para a aquisição de dados cinéticos. As diferentes frações molares de ácido itacônico utilizado variaram de 0,03 a 0,70, escolhidos devido a detectabilidade e limitações de solubilidade e alterações cinéticas quando usado em altas proporções. O polímero resultante foi isolado por precipitação em dietil éter a partir de solução em metanol, esse foi então separado por filtração ou centrifugação e seco. Aquisição dos dados de fração molar inicial, conversão e composição copolimérica cumulativa foi realizada por HPLC. Amostras do reator foram diluídas em solução 1:9 (vol/vol) de metanol/água tamponada (pH 6,8 50 mM fosfato de hidrogênio monobásico/fosfato de hidrogênio bibásico) em um fator de diluição de 27,5. O cromatógrafo (Shimadzu série 20A) foi operado a 216 nm e 254 nm para a leitura do IA (eluição a 2,9 min) e a 258 nm e 271 nm para NVP (eluição a 8 min), seguindo um gradiente de fase móvel, fases utilizadas foram metanol, acetonitrila e solução tampão. A coluna utilizada foi uma Supelcosil LC-18 de 250 mm x 4,6 mm e 5 μm de tamanho de poro. Temperatura de análise foi de 40 °C com corridas de 20 min. Para adquirir as concentrações foram construídas quatro curvas de calibração, duas para o IA, uma para concentrações baixas utilizando o menor dos dois comprimentos de onda e uma para baixas concentrações utilizando o outro comprimento; o mesmo foi feito para a NVP. As razões de reatividade relativa foram calculadas a partir da implementação da técnica de EVM utilizando integração numérica direta no loop interno e programação quadrática sequencial (SQP) e evolução complexa embaralhada (SCE) para o loop externo. O EVM considera que todos os dados adquiridos em um experimento são compostos de um valor real intrínseco e um erro associado e que não existe diferenciação entre variáveis dependentes e independentes. Os valores reais das variáveis são relacionados aos valores dos parâmetros do problema (nesse caso as reatividades relativas dos monômeros) através de uma função erro que é minimizada no loop interno do algoritmo, que então retorna o valor real das variáveis atualizados bem como o novo valor da função objetivo do loop externo. O loop externo então altera o valor dos parâmetros e o loop interno é rodado novamente com os novos valores, esse procedimento é repetido até que o valor da função objetivo seja minimizado.

Resultados e Discussão

Análise dos dados cinéticos de conversão das reações, permitiu o direcionamento do processo de seleção de dados a serem considerados para a determinação das razões de reatividade. Observou-se que as taxas de reação do IA e da NVP aumentaram com a concentração inicial da IA utilizado até 20% molar, a partir do qual as taxas começaram a diminuir e inclusive, para o caso limitante de 70% molar de IA, um platô de conversão foi observado. Isso apontou para uma mudança na cinética reacional que não permite a aplicação da equação de Mayo-Lewis para descrever a copolimerização do sistema. Esse comportamento anormal, no entanto, não foi observado ao se utilizar frações de IA abaixo de 0,1, e essas concentrações foram usadas para calcular as razões relativas. A implementação da metodologia EVM não pode ser aplicada na sua forma mais otimizada como apresentado na literatura, ao fazer a consideração de estrutura de erros multiplicativos, observou-se que o algoritmo diverge. Dessa forma, erro aditivo foi considerado ao se realizar as análises. Essa determinação altera apenas o tamanho da região de confiança conjunta, não alterando o valor das razões de reatividade em si, o erro multiplicativo apresenta menos incerteza de forma geral. Diferentes conjuntos de dados da literatura foram utilizados para comparar os resultados da implementação com aqueles já publicados e observou-se uma diferença menor de 5% para a maioria dos casos analisados. Regiões de confiança conjunta não foram comparadas devido ao uso de estruturas de erro diferentes. Para determinar as razões de reatividade relativa, dados reacionais de três composições diferentes foram usados, todos abaixo de 10% molar de IA. O cálculo foi realizado utilizando primeiro SCE para determinar uma aproximação inicial que foi então alimentada na implementação SQP

para refinamento e plotagem da região de confiança. Os valores das razões de reatividade adquiridos foram $r_1 = 0{,}3046$ e $r_2 = 0{,}0170$ em que o composto 1 é o IA. A região de confiança apresentou espalhamento no eixo do r_1 devido a discrepâncias entre dados e modelos nas regiões de baixa conversão, causado pelas baixas concentrações de IA utilizadas e incertezas experimentais nas medidas de HPLC para baixas concentrações. Um ponto azeotrópico foi observado nesse sistema em f_{10} = 0.5857. Experimentos com altas proporções de IA (maior de 10% molar) apresentaram discrepância quase total do esperado pelo modelo mesmo quando consideradas separadamente.

Considerações Finais

Com o trabalho conduzido, a metodologia de erro nas variáveis foi implementada de forma satisfatória no ambiente de programação do MATLAB e foi utilizada na regressão não linear dos parâmetros de razão de reatividade relativa do sistema de copolimerização por radicais livres do par monomérico ácido itacônico/n-vinil-2-pirrolidona, fornecendo também uma estimativa do seu erro. A metodologia em passo único em HPLC desenvolvida também proveu, de forma viável e simples, a aquisição dados cinéticos de copolimerização. O método permitiu a determinação de conversões parciais, total e composição cumulativa copolimérica sem a necessidade das etapas de purificação destrutivas normalmente associadas a esse tipo de dado e que também requerem reações em escala maior para serem realizadas.

Palavras-chave: Método dos erros nas variáveis. Copolimerização. Regressão não linear.

ABSTRACT

Copolymers occupy a critical role as modern building materials due their versatility that permit them to have their physical properties designed to serve a specific function or market niche. This, however, requires a deep understanding of how these copolymers must be produced in respect to their processing conditions and kinetics. One of the parameters one must have to produce a copolymer with known moiety distribution and physical properties is the relative reactivity ratios of the monomer pair, and as such, the employment of a proper regression technique that can extract this data from experiment is essential for the production of these copolymers, though these methods are still seldom employed due to their complexity and lack of availability. Therefore, in order to obtain these parameters, an implementation of the error-in-variables method previously described in the literature was written and made fully publicly available for use and further development, along with a single step HPLC methodology for the acquisition of the required kinetic data for the regression analysis of the itaconic acid/n-vynil-2-pyrrolidone free-radical polymerization system under study. PVPIA is a highly hydrophilic and biocompatible copolymer that can be used in heavy metal removal, as a medium for the controlled release of drugs, and other uses. From the acquired kinetic data it was observed that higher initial mole fractions of itaconic acid in the reaction medium would change the reaction kinetics in such a way as to prevent the regression analysis from being performed, as it makes use of a non-linear equation that must describe the data. This effect, however, was not observed at molar fractions below 10%, which enabled the regression to be performed and the parameters estimated. The performance of the developed algorithm was found to be satisfactory, and within less than 5% error when applied to the same data and method found in the literature. The values of the parameters for the system under study were estimated by the algorithm as being $r_1 = 0.3046$ and $r_2 = 0.0170$, with itaconic acid as compound 1. A small deviation was observed for r_1 due to a high spread in the kinetic data at very low itaconic acid fractions and low conversions that is caused by the very fast reaction rate of this monomer and uncertainties of HPLC detection at low concentrations. Systems with very large molar fractions of itaconic acid were also studied but they did not conform to the expected copolymerization equation with the high limiting case even reaching a conversion plateau at the later reaction stages.

Keywords: Error-in-variables Methodology. Copolymerization. Non-linear regression.

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LIST OF ABREVIATIONS AND SYMBOLS

CC – Calibration concentration (g/ml)

RC – Real concentration (g/ml)

DF – Dilution factor

X_i^P – Partial molar conversion of monomer i

MM_i – Molar mass of compound i

X – Total molar conversion

f_1 – Mole fraction of monomer 1 at time t

$f_{1,0}$ – Initial mole fraction of monomer 1

$\overline{F_1}$ – Cumulative copolymer composition (molar fraction of monomer 1 in the polymer chains)

M – Monomer species

PVPIA – poly[(n-vinyl-2-pyrrolidone)-co-(itaconic acid)]

IA – Itaconic Acid

NVP – N-vinyl-2-pyrrolidone

DNI – Direct numerical integration

EVM – Error-in-variables model

JCR – Joint confidence region

k – Specific rate of reaction

r – Monomer reactivity ratio

p – Number of problem parameters

V – Variance-Covariance matrix

B – Matrix of partial derivatives of g with respect to the true variables

G – Information matrix or hessian

^ – Most recently estimated variable value

Subscripts

0 – initial

1 – Chemical species 1

2 – Chemical species 2

i – Compound i

j – Compound j where j ≠ i

Superscripts

P – Partial

* – Denotes true value of a variable

Greek letters

α – Calibration curve linear coefficient (AU)

β – Calibration curve angular coefficient (ml/g)

ξ – Real value of a measurement

ε – Measurement associated error

υ – Number of problem variables

θ – Problem parameters

ϕ – Objective function value

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1 INTRODUCTION

Materials science occupies a critical role in the development and maintenance of modern society, creating and producing materials that are used in all levels of human endeavor, from the construction of our buildings to the weaving of our clothes (DOBRZAŃSKI (2006)). Among these materials, synthetic polymers have an extremely versatile role as their physical characteristics can be fully modified by altering the conditions in which they are processed, their starting constituents and proportions, and a plethora of other process variables (JASSO-GASTINEL; KENNY (2017)).

Multicomponent polymerizations, those polymerizations with two or more starting monomers, have numerous industrial applications and are used to produce several commercially available polymers that usually have very different physical properties when compared to their homopolymeric counterparts, properties that can behave in distinct manners depending on how much of each monomer is in the polymer chain and how these individual units are arranged in relation to one another in the chain (ODIAN (2004)). Therefore, understanding how these monomers are added to the chain and at what rate is of critical importance if one intends to construct a specific polymer with well-defined properties.

The manner with which to describe this copolymerization pathway is with the use of monomer reactivity ratio values. These values relate the ease with which each monomer tends to homopolymerize instead of copolymerizing, and with such values known a process engineer could devise a specific methodology to produce a copolymer with known moiety distribution (SALDIVAR-GUERRA; VIVALDO-LIMA (2013), ARZAMENDI; ASUA (1989), CHEN; LEE (1987), RAY; GALL (1969)).

Historically, the most commonly used method for determining the reactivity ratios of a copolymerization reaction is by linearization of the Mayo-Lewis equation, such as those first pioneered by Fineman and Ross (FINEMAN; ROSS (1950)) and Kelen and Tudos (KELEN; TUDOS (1975)) and later extended by other authors. Such methods, however, have been found to alter the error structure of the collected data, thus arriving at statistically incorrect results (TIDWELL; MORTIMER (1965)), and are still being employed by researchers to this day (KADIMI ET AL. (2019), KIM ET AL. (2019), MITSONI ET AL. (2019), STIERNET ET AL. (2019), WANG ET AL. (2020), ZOUGANELIS ET AL. (2019)). This problem was later solved

by other authors using non-linear parameter estimation techniques, such as the error-in-variables method (EVM), which are based on sound statistical theory (Bayesian approach) and return parameter estimates with joint confidence regions (REILLY; PATINO-LEAL (1981), PARK M. REILLY, S.E. KEELER (1993)).

Part of the reason for why methods such as Fineman-Ross and Kelen-Tudos are still used to this day is not only because of their simplicity, ease of use and traditional weight, but also because of an extreme lack of widespread and publicly available alternatives that can be used and modified freely to tackle specific problems. For example, when reported on the literature, the use of EVM for copolymerization parameter estimation is confined to a few groups who either worked on its initial development (HAUCH ET AL. (2008), KAZEMI ET AL. (2011), MCMANUS ET AL. (1999), O'DRISCOLL ET AL. (1984)) or later worked on their own implementations (BHAWAL ET AL. (2003), GIZ (1998), SANTOS ET AL. (2020)). This work seeks abate or at least lessen the lack of availability of these more statistically sound methods so that others can use and further contribute to their development in a free environment.

Also, of significative relevance to the work is the application of the developed methodology to a previously unexplored system. For this reason the copolymer of N-vynil-2-pyrrolidone and itaconic acid, PVPIA, was chosen. It is a highly hydrophilic polymer with applications in water treatment and the controlled release of drugs whose free radical chain polymerization is poorly described in the literature and with no published relative reactivity ratios.

1.2 OBJECTIVES

In view of the extreme importance reactivity ratios have on describing the behavior of copolymeric reaction systems, used expansively in both the laboratory and in industry, the use of appropriate and statistically sound methods for the estimation of such critical values is of utmost relevance. Even more so when most polymer scientists still use statistically incorrect methods that, by focusing only on the low conversion region of a polymerization reaction, ignore the compositional drift that can be found on many systems used in industry that reach complete or near-complete conversion, and that in turn, gives rise to values that do not correctly describe or only partially describe such systems.

1.2.1 Main objective

Implementing and employing the Error-in-Variables Method for the estimation of the monomer reactivity ratios of the radical chain polymerized system Itaconic Acid/N-Vinyl-2-pyrrolidone (IA/NVP) on isopropyl alcohol solution.

1.2.2 Specific objectives

- Reproduce a generic EVM implementation for non-linear equation parameter regression on the MATLAB scripting environment;
- Implement the Skeist cumulative polymerization equation under the EVM framework for the regression of monomer reactivity ratios of a generic system on a publicly accessible .m MATLAB program file;
- Develop and describe a method for the acquisition of copolymerization data such as initial mole fraction, conversion and cumulative copolymer composition of the IA/NVP system by use of a single-step HPLC methodology;
- Estimate the reactivity ratios for the IA/NVP system using the implemented method and acquired data.

2 LITERATURE REVIEW

In the sections that follow a general overview will be given on the most relevant topics used in this work along with the rationale behind their use and how they are to be applied. First, using the terminal model of polymeric propagation, the Mayo-Lewis equation will be derived, and from it the concept of relative reactivity ratios will be presented, followed by the derivation of the cumulative copolymer equation.

Following it, the manner in which reactivity ratios can be estimated from copolymerization reaction data will be shown and the Error-in-Variables Methodology will be explained in detail along with its general algorithm and the concept of Joint-Confidence-Regions for error visualization.

Finally, a brief literature review of the current state of the art for the copolymer used in this work, poly[(n-vinyl-2-pyrrolidone)-co-(itaconic acid)] (PVPIA), will be given as well as an overview of its physical properties.

2.1 COPOLYMERIZATION KINETICS AND MODELING

2.1.1 The instantaneous copolymer composition equation

A copolymerization is defined as a polymerization reaction in which the final polymer product is derived from two or more distinct monomers, and its product is termed a copolymer (IUPAC (1997)). A simplified representation of this process involving two monomers can be visualized in Figure 1 below.

Figure 1 - Simplified representation of a copolymerization reaction.

$$M_1 + M_2 \longrightarrow \quad -M_1M_2M_2M_1M_2M_1M_1M_2M_1M_2M_1M_2-$$

Source: Adapted from ODIAN (2004)

The overall copolymer composition and microstructure, for batch reactions, will depend on the monomers' initial feed concentrations as well as on their relative concentrations.

For the objectives of the present research, the only relevant polymerization stage is that of propagation since, by the long chain approximation, the processes of initiation and termination normally occur at rates that are orders of magnitude smaller than propagation for

most free radical chain polymerizations (GAVALAS (1966)), and the model used to describe this propagation step is called the Terminal Model of Copolymerization. This model considers that propagation of the polymeric chain is dependent only on the monomer at the end of the chain, the preceding monomeric units being considered irrelevant to this growing process.

The copolymerization of two monomers, named here M_1 and M_2, can give rise to two kinds of propagating species, M_1^* and M_2^*, i.e. a reactive species with an M_1 and one with an M_2 at the chain end, where the * can represent a reaction propagating by means of cationic, anionic or radical mechanism. This gives rise to four possible propagation reactions, shown in the equations below.

$$M_1^* + M_1 \xrightarrow{k_{11}} M_1M_1^* \tag{1}$$

$$M_1^* + M_2 \xrightarrow{k_{12}} M_1M_2^* \tag{2}$$

$$M_2^* + M_1 \xrightarrow{k_{21}} M_2M_1^* \tag{3}$$

$$M_2^* + M_2 \xrightarrow{k_{22}} M_2M_2^* \tag{4}$$

where k_{11} is the specific rate of reaction with which a propagating chain ending with M_1 adds another M_1 species, k_{12} is the specific rate of reaction for a propagating chain ending with M_1 adding an M_2, and so forth. An assumption made at this point is that these reactions are irreversible, or that at least further propagation is orders of magnitude faster than the reverse reaction.

Given equations (1)-(4) a mass balance for species 1 and 2 can be performed and their rates of disappearance from the reaction medium can be construed, assuming long chain approximation, as following

$$-\frac{d[M_1]}{dt} = k_{11}[M_1^*][M_1] + k_{21}[M_2^*][M_1] \tag{5}$$

$$-\frac{d[M_2]}{dt} = k_{12}[M_1^*][M_2] + k_{22}[M_2^*][M_2] \quad (6)$$

Dividing equation (5) by (6) one is left with the ratio of monomer incorporation rate in the copolymeric chain or copolymer composition

$$\frac{d[M_1]}{d[M_2]} = \frac{k_{11}[M_1^*][M_1] + k_{21}[M_2^*][M_1]}{k_{12}[M_1^*][M_2] + k_{22}[M_2^*][M_2]} \quad (7)$$

It is possible to remove the reactive species M_i^* from equation (7) by considering that, due to the pseudo-steady-state assumption (radical concentration doesn't change with time when compared to the change in monomer concentration (MARK (2002)) their concentrations are in steady-state and their rate of interconversion are equal, that is

$$k_{12}[M_1^*][M_2] = k_{21}[M_2^*][M_1] \quad (8)$$

Equation (8) can then be combined with equation (7), rearranged and simplified into the form bellow.

$$\frac{d[M_1]}{d[M_2]} = \frac{[M_1]\left(\frac{k_{11}}{k_{12}}[M_1] + [M_2]\right)}{[M_2]\left([M_1] + \frac{k_{22}}{k_{21}}[M_2]\right)} \quad (9)$$

From there two parameters r_1 and r_2, the monomer reactivity ratios, can be defined and replaced in equation (9). These parameters relate the tendency a monomer has of homopolymerizing or copolymerizing, the higher the value, the higher the probability a monomer has of being added to a polymeric chain in which it already is the end species.

$$r_1 = \frac{k_{11}}{k_{12}} \quad \text{and} \quad r_2 = \frac{k_{22}}{k_{21}} \quad (10)$$

$$\frac{d[M_1]}{d[M_2]} = \frac{[M_1](r_1[M_1] + [M_2])}{[M_2]([M_1] + r_2[M_2])} \quad (11)$$

Equation (11) is called the instantaneous copolymer composition equation. This expression can also be written more simply, in the form of mole fractions rather than concentrations by using the following definitions

$$f_1 = 1 - f_2 = \frac{[M_1]}{[M_1] + [M_2]} \tag{12}$$

$$F_1 = 1 - F_2 = \frac{d[M_1]}{d[M_1] + d[M_2]} \tag{13}$$

Where f_1 is the mole fraction of species 1 in the reactor feed at a specific time, and F_1 is the instantaneous copolymer composition of species 1 in the copolymer or the mole fraction of species 1 incorporated into the copolymer in that instant.

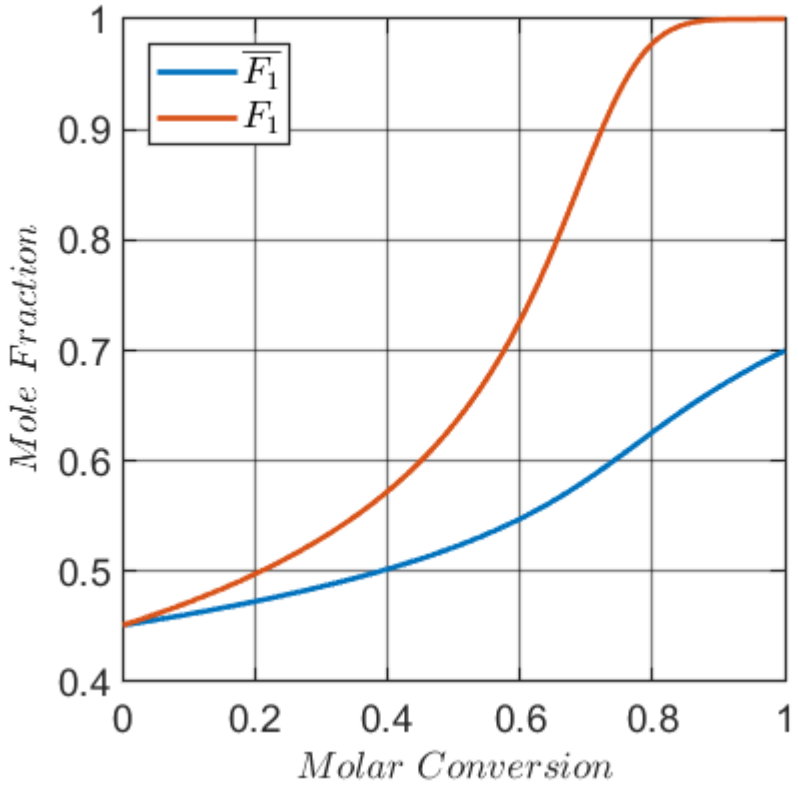
Substituting the above definitions into equation (11) yields the final form of the instantaneous copolymer composition equation, also called the Mayo-Lewis equation (MAYO; LEWIS (1944)).

$$F_1 = \frac{r_1 f_1^2 + f_1(1 - f_1)}{r_1 f_1^2 + 2f_1(1 - f_1) + r_2(1 - f_1)^2} \tag{14}$$

2.1.2 The cumulative copolymer composition equation

The Mayo-Lewis equation can only be used effectively when performing polymerization processes at low conversions since, for most systems, as conversion increases significant compositional drift can be observed. Thus the instantaneous composition is only equal to the composition of the whole chain (i.e. the cumulative composition that is usually the measured variable) during the initial stages of the polymerization.

Figure 2 - Instantaneous (F_1) and cumulative ($\overline{F_1}$) compositions comparison for a simulated system with $f_{10} = 0.7$ and $r_1 = 0.15$ and $r_2 = 1.5$.



Source: Author (2020).

This effect can be seen in Figure 2, shown above, that makes a direct comparison between the instantaneous copolymer composition F_1 and the cumulative one $\overline{F_1}$ using simulated data. In this situation, the initial mole fraction of species 1 in the feed, f_{10}, is 0.7 and the reactivity ratios, r_1 and r_2 are 0.15 and 1.5 respectively, that is, species 1 tends to preferentially copolymerize while species 2 tends to homopolymerize. As the copolymerization starts both instantaneous and cumulative compositions are the same because feed conditions are not yet sufficiently altered to change the rate at which monomers are added to the chains, however, as the process proceeds and the reaction medium becomes poorer in species 2 (as it is added at a faster pace) this rate changes significantly and the total amount of both species in the copolymer is altered.

As such, for one interested in acquiring the relative reactivity parameters from data taken over the entire conversion trajectory, the use of a cumulative composition model is of great relevance.

By writing the mole balance of monomer 1 for the whole extent of the reaction an expression that relates the amount of monomer measured at two different points in time to the total amount of that monomer on the polymeric chain can be written

$$amount\ of\ monomer\ 1\ at\ time\ 0 - amount\ of\ monomer\ 1\ at\ time\ t = amount\ of\ monomer\ 1\ on\ the\ polymer\ at\ time\ t \quad (15)$$

$$[M_0]f_{10} - f_1[M_0](1 - X) = \bar{F_1}[M_0]X \quad (16)$$

Where X is the total molar conversion and $[M_0]$ is the total monomer concentration at time 0, rearranging and simplifying results in the following equation (17)

$$\bar{F_1} = \frac{f_{10} - f_1(1 - X)}{X} \quad (17)$$

Which is known as the Skeist equation (SKEIST, 1946). An expression for f_1, the monomer mole fraction at time t, can be found by performing a differential mole balance on monomer 1, and manipulating it until arriving at the differential copolymer composition equation

$$\frac{df_1}{dX} = \frac{f_1 - F_1}{1 - X} \quad (18)$$

This equation can be solved numerically with the initial condition $f_1 = f_{10}$ at $X = 0$. F_1, in turn, can be calculated using the Mayo-Lewis equation (14).

The use of equations (14), (17) and (18) to relate initial feed mole fraction, feed mole fraction at an arbitrary time and cumulative composition is termed the Direct Numerical Integration approach or DNI. This methodology is somewhat more computationally intensive but is preferred to the alternative, which is to analytically integrate the Mayo-Lewis equation into the Meyer-Lowry solution, a transformation that alters the error structure (i.e. magnitude, distribution, type of error and correlation) of the problem and limits the conversion range that

can be used to 25-30% maximum due to numerical instabilities that arise when using it at higher conversions (KAZEMI ET AL., (2011).

2.2 THE ESTIMATION OF REACTIVITY RATIOS FROM COPOLYMER COMPOSITION EQUATIONS

With models that describe them, it is now possible to estimate the reactivity ratios of copolymerization systems using regression techniques and experimental data. The first methods found in the literature, and to this day the ones most commonly used, are linearizations of the Mayo-Lewis equation. These were spearheaded principally by Fineman and Ross (1950) and Kelen and Tudos (1975), and later followed by others. They have, however, been known to be awfully unsuitable and statistically incorrect for the estimation of reactivity ratios for a significant time now. (BEHNKEN (1964),TIDWELL AND MORTIMER (1965)). The main issue presented by this methodology is that linearizations alter the error structure of the employed equations and violate basic assumptions of linear regression, such as imperfectly known independent variables, errors with a non-zero mean, variable variance and correlation between errors on the dependent and independent variables. (O'DRISCOLL; REILLY (1987), POLIC ET AL. (1998), KAZEMI (2010))

An alternative to linearization methods is the use of nonlinear regression methodologies, nonlinear least squares (NLLS) and its variants being the foremost among these. However, NLLS assumes the error in the independent variable to be negligible. In batch copolymerizations the independent variable is the initial comonomer feed compositions, set by the experimenter, bound to material purity and analytical balances' accuracies and calibration, and thus accompanied by noticeable error.

To avoid this inconsistency and estimate parameters as accurately as possible alternative methods may be employed. The error-in-variables-model (EVM) methodology can handle linear and nonlinear explicit or implicit models, single and multi-response problems, considers there are errors in both dependent and independent variables all the while outputting statistically sound values for the estimated parameters along with an estimation of its errors. As such it was selected as the main technique to be used in this work.

2.2.1 The error-in-variables-model (EVM)

The approach to EVM taken in this work is the one developed by Reilly and Patino-Leal (1981), whose implementation was further expounded upon by Reilly et al. (1993) and later solidified in Kazemi (2010) and Kazemi (2014).

2.2.1.1 EVM interpretation

The EVM method considers that all measurements taken are composed of two parts, the real value of the variable, and an associated error as shown in the equation below.

$$\underline{x_i} = \underline{\xi_i} + \underline{\varepsilon_i} \tag{19}$$

Where, $\underline{x_i}$ is the vector of measured variables, $\underline{\xi_i}$ is the vector of the real values of the measurements and $\underline{\varepsilon_i}$ is the vector of the associated errors. The under bar represents a vector, and the subscript i is the trial number that can vary from 1 to the total number of trials n. The error vector is assumed to be normally distributed with a mean of 0, and to have a known or unknown positive definite non-singular variance-covariance matrix $\underline{V}$ (KEELER AND REILLY (1991), REILLY AND PATINO-LEAL (1981)). $\underline{V}$ is also a square matrix of size υ by υ where υ is the number of variables in the problem.

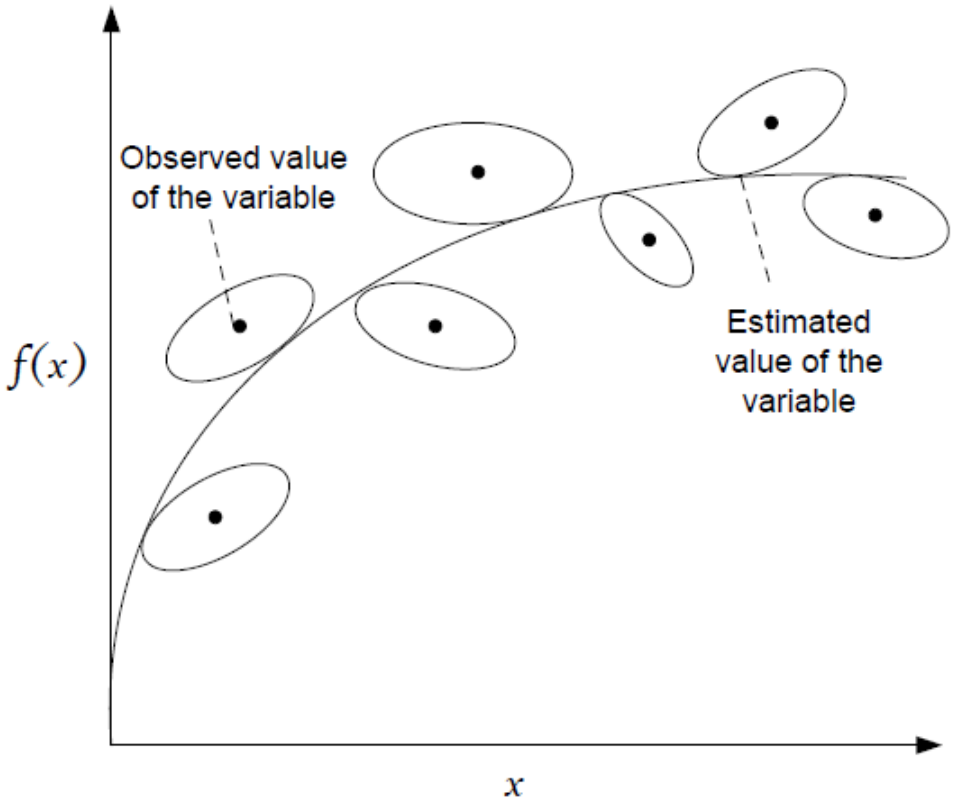
The true values of the variables can be related to parameters by the following equation

$$\underline{g}\left(\underline{\xi_i}, \underline{\theta^*}\right) = 0, \tag{20}$$

where $\underline{\theta^*}$ is the p by 1 vector of the real values of the parameters to be estimated, and p is the number of parameters in the problem.

For linear or nonlinear least-squares an optimization procedure attempts to find the model parameters such that these minimize the vertical distances between the observed values and the ones given by the model. For EVM however, there's no independent variable, thus vertical distances cannot be used, and an appropriate procedure would be the one shown in Figure 3 for a two-dimensional case.

Figure 3 - Visual interpretation of EVM.



Source: Kazemi (2014).

The EVM algorithm attempts to minimize the area of the ellipses, each centered on the measured value with the estimated true value being tangent to the model. The model, in turn, is constructed with estimated values of the parameters, as these are changed the "shape" of the model changes, and the areas are recalculated and eventually minimized. The objective function that represents this process is given by equation (21) below

$$\phi = \frac{1}{2}\sum_{i=1}^{n}\left(\underline{x_i} - \underline{\hat{\xi}_i}\right)' \underline{V}^{-1}\left(\underline{x_i} - \underline{\hat{\xi}_i}\right), \tag{21}$$

where $\underline{\hat{\xi}_i}$ is the vector of estimated values of the true variables.

2.2.1.2 Error structure and the variance-covariance matrix

For proper parameter estimation, knowledge of the error structure is of critical importance, this is doubly true for the EVM methodology since it requires that this information

be stated explicitly. Error structure in this context refers to the magnitude of the error for each variable considered, the distribution of the error, the type of error (additive or multiplicative), and for multi-response problems, whether the measurements are independent or correlated.

For the case of magnitude, the proper approach would be to estimate them using replicated measurements, however, that is not always feasible as a great number of experiments would have to be performed and copolymerization experiments tend to be costly and time-consuming. An alternative that is commonly used is to assign the values of the covariance matrix to the accuracy of the measuring devices (KIM ET AL., 1990), in this case the intercorrelation between measurements would be considered to be negligible, otherwise it is acquired along with error magnitude in replicated trials. The distribution of the error is unknown but is generally assumed to be normal, deviations from the normal distribution, if there are any, affect results in a negligible manner (KEELER; REILLY (1991)). Finally, the type of error can be additive (equation (22)) or multiplicative (equation (23)).

$$x = \xi + k\varepsilon \tag{22}$$

$$x = \xi(1 + k\varepsilon) \tag{23}$$

In these equations x is the observed variable, ξ its true and unknown value, k is a constant reflective of the uncertainty in the variables and may vary between different variables, and ε is a random error term, usually normally distributed in the interval from -1 to 1. For the multiplicative case a log transformation is necessary to make the error additive again

$$ln(x) = ln(\xi) + ln(1 + k\varepsilon) \longrightarrow ln(x) \cong ln(\xi) + k\varepsilon, \tag{24}$$

the above equation is valid so long as the as the magnitude of the error is below 10%, i.e. $k < 0.1$.

With equations (22) and (24) it becomes possible to calculate the variance for the case of normally distributed error in the interval from -1 to 1 with $k < 0.1$

$$V\big(ln(x)\big) = V(ln(\xi) + k\varepsilon) = k^2V(\varepsilon)$$
$$V(x) = V(\xi + k\varepsilon) = k^2V(\varepsilon) \tag{25}$$
$$V(\varepsilon) = \int_{-1}^{1} \frac{\varepsilon^2}{2} d\varepsilon = \frac{1}{3}$$

$$V\big(ln(x)\big) = V(x) = \frac{k^2}{3} \tag{26}$$

In which $V(x)$ represents a diagonal term of the variance-covariance matrix, a square matrix of side equal to the number of variables in the problem. By equation (26) we see that regardless of the error structure used, the variance-covariance matrix can be estimated with the same expression.

2.2.1.3 The EVM algorithm

The EVM algorithm developed for this work is based on the method described by Reilly and Patino-Leal (1981) and implemented in Reilly et al. (1993) and is made available on appendix B. It is noted here, however, that full implementation of the algorithm as published in Reilly et al. (1993) (available on the journal's website (PARK M. REILLY, S.E. KEELER (1993))) was only discovered by this author after the code had already been independently written.

The algorithm is composed of two iteration loops, the outer loop searches for the optimal value of the parameters (r_1 and r_2 in the copolymerization case), and for each pair of parameters tried, an internal loop estimates the true value of the variables using the given parameters and model equation, it then calculates the value of the objective function (through a form of equation (21)) and returns it to the outer loop. The process is repeated until the objective function value reaches a minimum value as defined by a stopping criterion.

The optimization process starts by defining initial parameter estimates and initial values for the true variables, $\underline{\theta}^{(0)}$ and $\underline{\xi_i}^{(0)}$ respectively. $\underline{\theta}^{(0)}$ can be taken from the literature or estimated by a Mayo-Lewis linearization of low conversion data, and $\underline{\xi_i}^{(0)}$ can be defined as the measured variables $\underline{x_i}$. Depending on the optimization technique used for the outer loop, upper and lower bounds on the parameter values can also be inputted at this point.

The inner loop then calculates the true value of the variables for the next step using the equations below

$$\underline{\xi_i}^{(k+1)} = \underline{x_i} - \underline{V}\underline{B_i}' \left(\underline{B_i}\underline{V}\underline{B_i}'\right)^{-1} \left[\underline{g}\left(\underline{\xi_i}^{(k)}, \underline{\theta}\right) + \underline{B_i}\left(\underline{x_i} - \underline{\xi_i}^{(k)}\right)\right] \tag{27}$$

$$\underline{B_i} = \left[\frac{\partial \underline{g}\left(\underline{\xi_i}^{(k)}, \underline{\theta}\right)}{\partial \underline{\xi_i}^{(k)}}\right] \tag{28}$$

where k represents the iteration step, and $\underline{B_i}$ is the matrix of partial derivatives of $\underline{g}$ with respect to the true variables calculated at the current iteration point.

Equation (27) is rather unwieldy and computationally expensive to calculate, mostly due to the matrix inversion step, however, it can be simplified by applying Cholesky decomposition (PLACKETT (1968))

$$\begin{aligned}
&\underline{S_i}'\left[\underline{S_i} \vdots \underline{h_i}\right] = \left[\underline{B_i}\underline{V}\underline{B_i}' \vdots \underline{g}\left(\underline{\xi_i}^{(k)}, \underline{\theta}\right) + \underline{B_i}\left(\underline{x_i} - \underline{\xi_i}^{(k)}\right)\right] \\
&\underline{S_i}'\left[\underline{S_i} \vdots \underline{h_i}\right] = \left[\underline{C_i} \vdots \underline{b_i}\right] \\
&\underline{S_i} = chol(\underline{C_i}) \\
&\underline{h_i} = \underline{S_i}' \backslash \underline{b_i} \\
&\underline{t_i} = \underline{S_i} \backslash \underline{h_i}
\end{aligned} \tag{29}$$

$$\underline{\xi_i}^{(k+1)} = \underline{x_i} - \underline{V}\underline{B_i}'\underline{t_i} \tag{30}$$

In lieu of this procedure, the objective function, equation (21), may be rewritten and calculated as

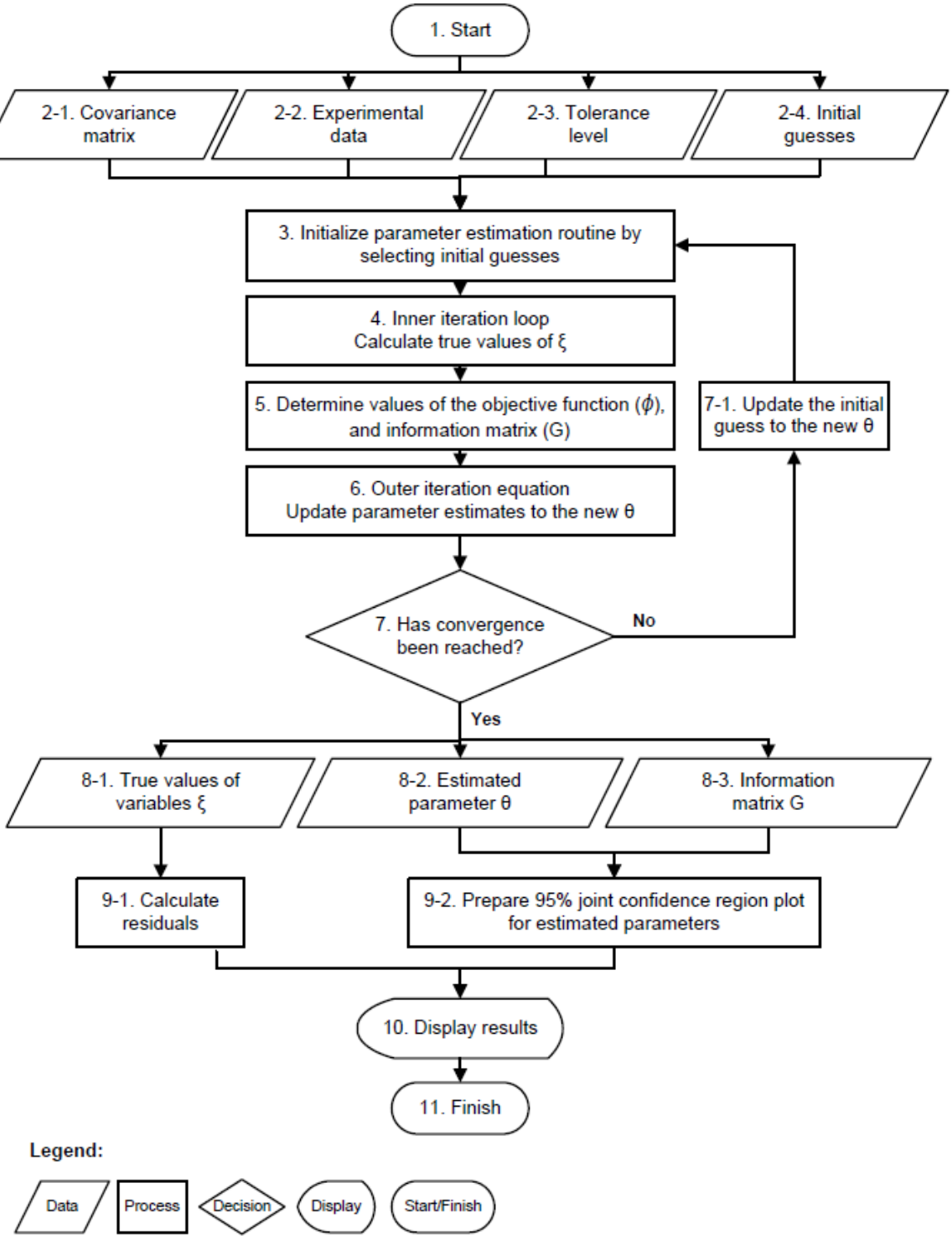
$$\phi = \frac{1}{2}\sum_{i=1}^{n} \underline{\hat{h}_i}' \underline{\hat{h}_i}, \tag{31}$$

where $\underline{\hat{h}_i}$ is the vector of h_i values reached by the decomposition and back-substitution after inner loop convergence.

For outer loop implementation, any kind of optimization algorithm can be utilized. Reilly and Patino-Leal (1981) utilized Newton's method, as did Kazemi (2014). Kazemi also recommended and compared the use of build-in MATLAB functions such as sequential quadratic programming (SQP) in the form of the fmincon function, and generalized pattern search (GPS) in the form of the patternsearch function. Kazemi also recommended the use of shuffled complex evolutionary (SCE) method as published by Donckels (2012), the link provided was not working by the time this document was published however. Thus, Duan's et al. (1993) implementation was used as it was publicly and readily available (DUAN (2005)) needing only a few modifications in order for the code to work. Comparisons between these different techniques is out of the scope of this dissertation and the reader is referred to Kazemi (2014) for details. For the most part this author used MATLAB's built-in fmincon function for outer loop optimization as it converges relatively quickly (seconds) given appropriate starting parameter estimates, allows for the limitation of parameter values with lower and upper bounds, and calculates hessians (estimated information matrices) internally.

The flowchart in Figure 4 gives a general overview of the procedure.

Figure 4 - EVM algorithm flowchart.



Source: Adapted from Kazemi (2014).

2.2.1.4 Joint confidence regions and evaluation of results

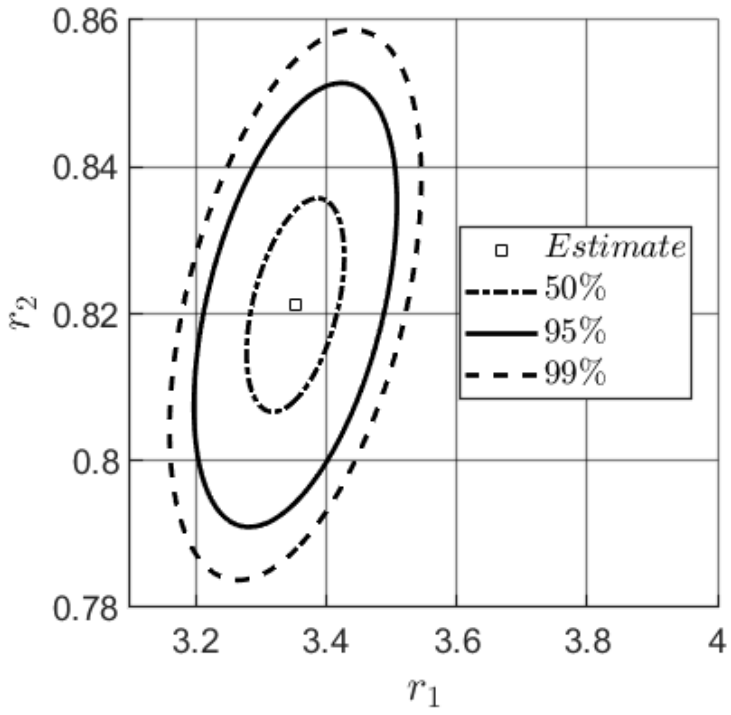
Once model parameters are calculated it becomes important to analyze the error ingrained in their estimation. For one-parameter models, confidence intervals are a common method of visualizing these uncertainties, in a bidimensional case, such as for copolymerization, joint confidence regions (JCRs) can be used. The JCR is a contour plotted around the parameters point estimate and they encircle, for a given confidence level, the possible values the parameters can have as shown in Figure 5.

According to Keeler (1989) the JCRs can be constructed according to the equation below, where $\underline{G}$ is the approximate information matrix or hessian of the objective function and $\chi^2_{(p,1-\alpha)}$ is the value of the chi-squared distribution for p parameters and α confidence level.

$$\left(\underline{\theta} - \underline{\hat{\theta}}\right)' \underline{G} \left(\underline{\theta} - \underline{\hat{\theta}}\right) \leq \chi^2_{(p,1-\alpha)} \tag{32}$$

The error_ellipse MATLAB code (JOHNSON (2004)) was used to perform the calculations and plot the contours in this work.

Figure 5 - JCRs example with simulated data for illustration purposes.

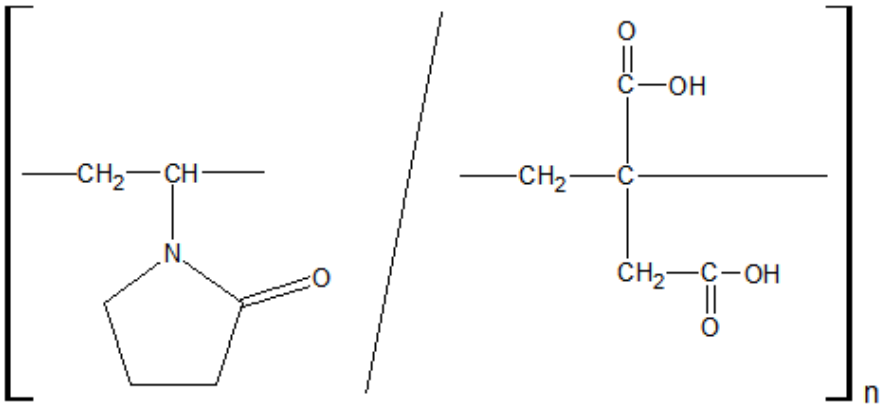


Source: Author (2020).

2.3 POLY[(ITACONIC ACID)-CO-(N-VINYL-2-PYRROLIDONE)]

Poly[(itaconic acid)-co-(n-vinyl-2-pyrrolidone)] (PVPIA) was the copolymer studied in this work, it can be formed by the copolymerization of itaconic acid and n-vinyl-2-pyrrolidone and has a general structure as shown in Figure 6.

Figure 6 - Basic PVPIA structure.



Source: Author (2020).

PVPIA is reported by as being a hydrophilic, highly biocompatible polymer (KARADAĞ ET AL. (1994)) that, when synthetized in the presence of a cross-linker or through UV or gamma-ray irradiation, produces a crosslinked hydrogel that may present swelling rates of up to 1500% (CHEN ET AL. (2005)). It can be used as a heavy metal ion remover (EVREN ET AL. (2014); PIZARRO ET AL. (2008)) in waste-water treatment, as an enzyme immobilization support structure (TÜMTÜRK ET AL. (1999)), and as a medium for the controlled release of drugs (ŞEN; GÜVEN (1999)).

However, reports of the copolymer when prepared through free radical chain polymerization are severely limited and so are descriptions of its physical properties and possible applications. As such, the development of a methodology that enables the synthesis of PVPIA with a controlled microstructure should be of assistance in that future undertaking.

3 MATERIALS AND METHODS

3.1 MATERIALS

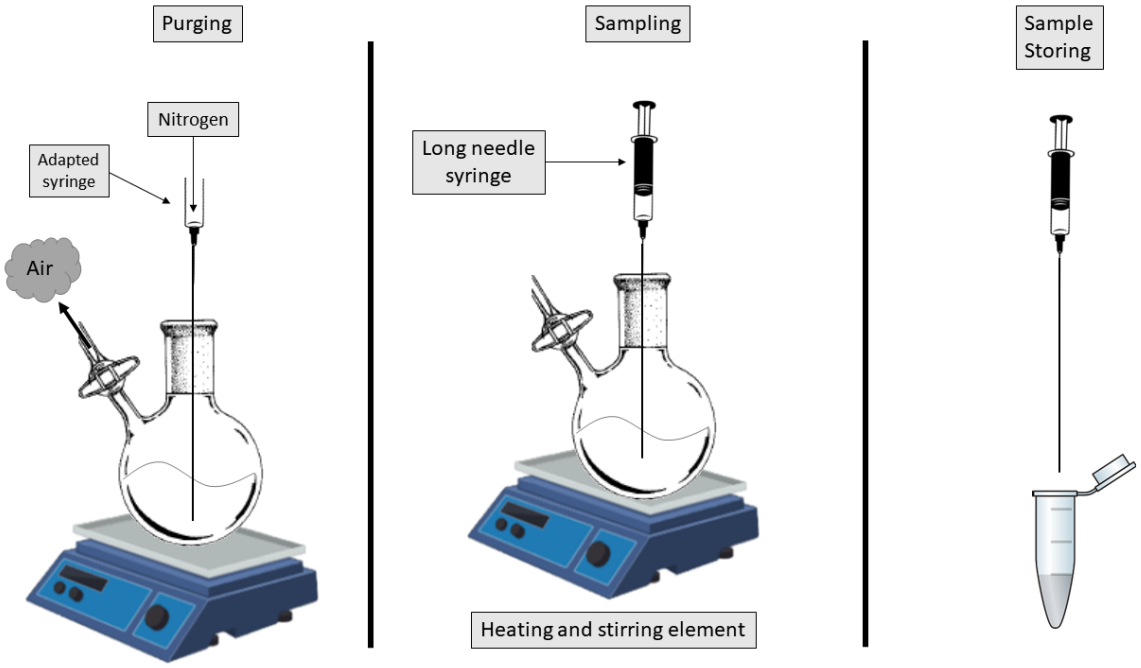
The monomers utilized for the copolymerization reactions were N-vinyl-2-pyrrolidone (NVP), kindly donated by Termotécnica Ltda. (Joinville, SC) with 99% purity and inhibited with sodium hydroxide (20 ppm), and Itaconic acid (IA), acquired from Sigma-Aldrich also with 99% purity. The initiator employed was Tert-butyl peroxypivalate diluted at 75% mass concentration on a C7 to C12 hydrocarbon fraction (odorless mineral spirits) with 9.18% active oxygen content and commercialized as Trigonox 25-C75 by AkzoNobel, it was also donated by Termotécnica Ltda. 2-propanol, used as the reaction solvent, was acquired from Neon Comercial Ltda. at 99.5% purity. All reagents were used as received apart from NVP which was distilled under high vacuum and stored under refrigeration and Itaconic acid, which was first dissolved in acetone, hot filtrated, and twice recrystallized from 2-propanol.

Polymer purification used diethyl ether and methanol both acquired from Neon Comercial Ltda. at 99.5% purity. Hydroquinone was acquired from Nuclear at 99% purity and was recrystallized from 2-propanol due to yellowing. Deionized water was produced locally from a reverse osmosis Q342-230 Quimis Ltda. deionizer.

3.2 COPOLYMERIZATION REACTIONS

The reactions were carried out based on a methodology heavily adapted from previous work done by our research group based on NVP homopolymerization (NEUBAUER (2017)), more specifically, reaction temperature and monomer to initiator ratio settings were taken from it. The general reaction scheme can be observed on Figure 7. Copolymerization reactions in 2-propanol were carried out in a 250 ml 2-necked round-bottomed flask into which a Schlenk adapter and rubber septum were fitted. Reactions were carried out at 65 °C or 55 °C depending on the formulation, and the reaction volume was targeted to be 250 ml at that temperature, comonomers were weighted so as to keep their total initial concentration at 0.55 M. Initial monomer to initiator ratio was also kept constant at 112.5 mol/mol. The adjusted variable between different reactions was the initial IA and NVP mole fractions with respect to the total monomer amount. The lower 55 °C temperature was employed when the reaction rate was too fast for proper sampling and collection of kinetic data.

Figure 7 - General reaction Scheme.



Source: Author (2020).

Once the material amounts were calculated they were weighted on a Marte AL-500 analytical balance, an oval magnetic stirrer was then placed in the vessel, and the system closed with the Schlenk adapter and rubber septum. The reactor was placed on a heater plate with magnetic stirring and temperature control for temperature stabilization (IKA C-MAG HS7 magnetic stirrer and heater and IKA ETS-D5 thermo-controller). Once the reactor reached the desired temperature the Schlenk stopcock was opened and a long needle inserted through the rubber septum. Industrial grade nitrogen gas was then bubbled through the reaction medium for 5 min to displace the overhead atmosphere and dissolved oxygen. After the system was closed and the needle removed, the initiator solution was weighted on a Shimadzu AY220 analytical balance using a nitrogen purged syringe. The initiator was then injected into the reactor and the reaction timer started.

An overview of the performed reactions and their conditions is shown in Table 1. The f_I values used were decided upon based on system limitations that are discussed further in the text and on the practical applications of the copolymer, which tend to use small amounts of itaconic acid, but basically, f_I is limited on the lower end due to detectability, and on the higher

end due to its solubility of itaconic acid on the solvent, 2-propanol, and also on changes to its kinetic behavior at higher molar fractions.

Table 1 - Reaction conditions overview.

Reaction	$f_{1,0}$	Temp. (°C)	Total Conc. (mol/L)	[M]/[I]
R-1	0.03	55	0.55	112.5
R-2	0.06	55	0.55	112.5
R-3	0.10	65	0.55	112.5
R-4	0.20	65	0.55	112.5
R-5	0.30	65	0.55	112.5
R-6	0.40	65	0.55	112.5
R-7	0.70	65	0.55	112.5

$f_{1,0}$: initial molar fraction of itaconic acid in feed. [M]/[I]: monomer to initiator ratio.

Source: Author (2020).

3.2.1 Reaction sampling

Concurrently with initiator injection, a second nitrogen purged syringe was inserted into the reactor and a sample of 1.5 ml was extracted from the reaction medium, this sample was then transferred to a 2 ml Eppendorf vial containing about 0.05 ml of a 4% (m/m) hydroquinone solution in 2-propanol that acted as a free radical acceptor, thus stopping the reaction. The vial was then set aside in a refrigerator for further analysis. The syringe and needle were cleaned with deionized water, dried with compressed air and purged with nitrogen in preparation for the next sampling. This process was then repeated for all sampled points, the time at which the sampling was done was also noted. Each reaction was sampled 15 to 20 times.

3.2.2 Final polymer isolation

Once the last sampling point was taken heating was turned off, the reactor opened and injected with about 10 ml of the hydroquinone solution. The reaction medium was then transferred to a 500 ml round-bottomed flask and rotary-evaporated at 60 °C and 160 mbar to remove the isopropyl alcohol. The remaining solids were dissolved in a minimal amount of methanol (about 50 ml), poured into a burette and drop-wise precipitated into cold diethyl ether under strong agitation in a 1:4 proportion. The precipitated solution was then either transferred to 13 ml round-bottomed cylindrical falcon tubes and centrifuged on a Centrebio centrifuge

model 80-2B for 15 minutes at 4000 RPM or directly filtered on a sintered glass filter depending on the reaction. If centrifuged, solvent from the tubes was removed, and additional clean diethyl ether was added. To assist with washing the polymer cake, the tubes were vortexed until the cake was fully broken. The tubes were then recentrifuged under the same conditions. Solvent was removed from the tubes and these were placed on a forced convection stove at 60 °C until dry. The polymer was then transferred into a mortar, ground into a fine powder and finally collected and stored. If filtered through a fritted glass disk the resulting polymer cake was washed with cold diethyl ether, collected into a petri dish, dried and ground as described previously.

3.3 CONVERSION, INITIAL MONOMER FRACTION AND CUMULATIVE COPOLYMER FRACTION ANALYSIS

For calculating monomer conversion, initial real molar fraction and cumulative copolymer composition, analysis of remaining monomer in the sampling vials was required. For this purpose, use of High-Performance Liquid Chromatography (HPLC) was of paramount importance.

3.3.1 Sample dissolution

Before being injected into the HPLC samples needed to be properly conditioned. An adapted version of the method used by Neubauer (2017) was employed. A sample aliquot of 0.2 ml was transferred to a 10 ml beaker and 5.12 ml of a 1:9 (vol/vol) methanol/water buffered solution was added to target a 27.5 dilution factor (DF) with the DF of hydroquinone solution from the previous step already factored in. The methanol/water solution was chosen to ease polymer dissolution as pure water was tested and found to give inconsistent results. This solution was then collected (about 4 ml) with a syringe and passed through an Allcrom 0.45 μm nylon syringe filter directly into a 2 ml HPLC vial.

3.3.2 HPLC methodology

20 µl of each sample were injected into the chromatography column through a SIL-20A auto-sampler, the mobile phase was pumped at a rate of 1 ml/min by an LC-20AD pump. The chromatograph was equipped with a Supelcosil LC-18 (20 mm x 4 mm, 5 µm, Supelco) pre-column and a Supelcosil LC-18 (250 mm x 4.6 mm, 5 µm, Supelco) column. A CTO-20A oven kept the column temperature at a constant 40 °C. The UV detector SDP-20A was operated in dual wavelength mode at 258 nm and 271 nm for NVP measurements and 216 nm and 254 nm for IA measurements with cell temperature also at 40 °C. Sample run-time was of 20 min. Peaks were visualized and manually integrated using Shimadzu's LCSolution software version 1.24 SP1. All HPLC modules were manufactured by Shimadzu. The system was operated in low-pressure gradient mode and each injection followed the programmed steps shown in Table 2.

All mobile phase transitions presented in Table 2 were performed as step changes and not gradients, Phase A is pure methanol, Phase C is pure acetonitrile, and Phase B is a pH 6.8 50 mM sodium dihydrogen phosphate/disodium hydrogen phosphate buffered water solution. Itaconic acid eluted around 2.9 min and NVP around 8.0 min.

The wavelengths employed were chosen by running monomeric solutions at different concentrations through the column, stopping the pump at peak maxima and then running the detector in spectrum scan mode. The resulting data enable linearity and monomer detector response to be analyzed by wavelength.

Table 2 - Programed steps during HPLC analysis.

Time (min)	Action	Value
Pre-injection	Phase A	90%
Pre-injection	Phase B	10%
0	Phase A	42%
0	Phase B	50%
0	Phase C	8%
5	Wavelength ch.1	258 nm
5	Wavelength ch.2	271 nm
6	Phase A	90%
6	Phase B	10%
20	Stop data acquisition	

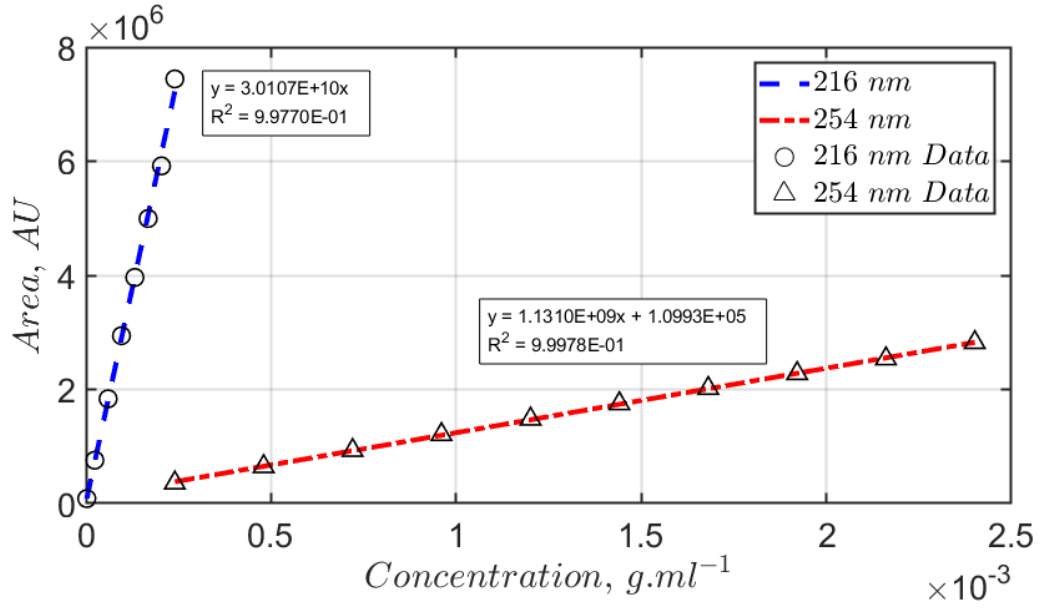
Source: Author (2020).

3.3.3 Calculations of monomer concentrations, conversions, initial mole fractions and cumulative copolymer composition

For quantifying the amount of monomer left in the sampling vials, calibration curves were constructed by dissolving known amounts of IA and NVP into a 1:9 (vol/vol) methanol/ buffered water solution, injecting it in the HPLC and integrating the resulting peaks at the appropriate wavelengths.

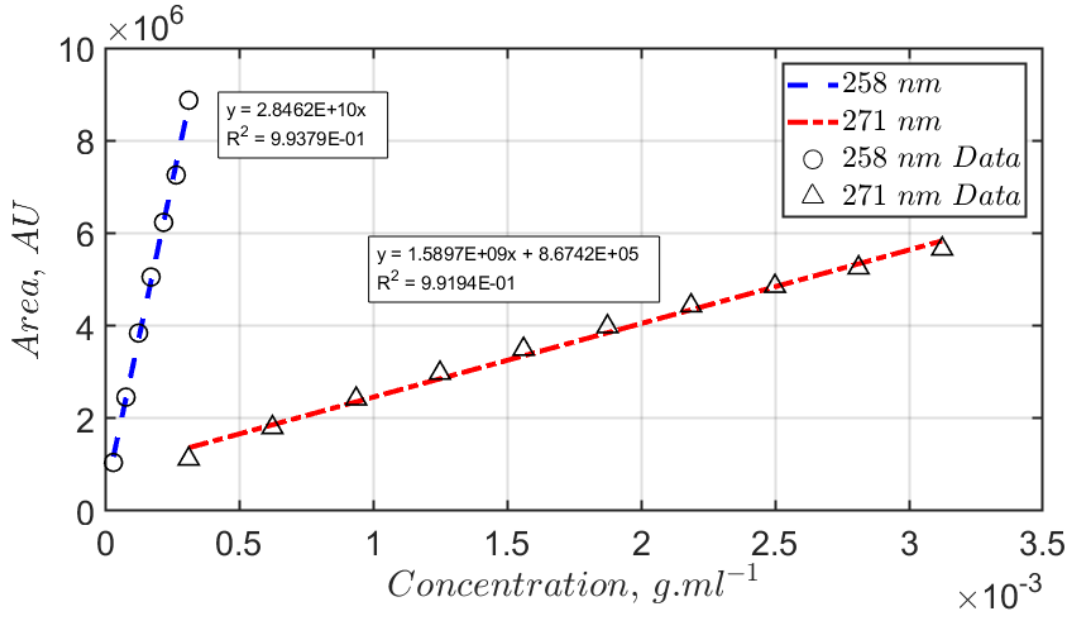
The curves are shown below in Figure 8 and Figure 9 along with their respective equations and R^2. Both IA and NVP have two calibration curves, one for each of two different concentration ranges, measured at different wavelengths that were chosen based on linearity and good detector response.

Figure 8 - Itaconic acid calibration curves.



Source: Author (2020).

Figure 9 - N-vinyl-2-pyrrolidone calibration curves.



Source: Author (2020).

With the calibration curve done, the procedures described in sections 3.3.1 and 3.3.2 were performed and the respective peak areas for each sample were collected.

With peak areas in hand, conversions, initial mole fractions and cumulative copolymer compositions were calculated as described below.

$$CC = \frac{(Area - \alpha)}{\beta} \tag{33}$$

where CC is the concentration given by the calibration curve in g/ml, $Area$ is the numerical value in arbitrary units acquired for each measured point by peak integration, α is the calibration curve linear coefficient given in arbitrary units, and β is the calibration curve angular coefficient in ml/g.

$$RC = CC.DF \tag{34}$$

where RC is the real concentration in g/ml, and DF is the dimensionless dilution factor used to prepare the samples for analysis.

$$X_i^P = \frac{\left(\frac{RC_{i,0}}{MM_i} - \frac{RC_i}{MM_i}\right)}{\frac{RC_0}{MM_i}} \tag{35}$$

where X_i^P is the partial molar conversion of compound i, $RC_{i,0}$ is the initial real concentration of compound i, and MM_i the molar mass of compound i.

$$X = \frac{\left(\frac{(RC_{0,IA} - RC_{IA})}{MM_{IA}} + \frac{(RC_{0,NVP} - RC_{NVP})}{MM_{NVP}}\right)}{\left(\frac{RC_{0,IA}}{MM_{IA}} + \frac{RC_{0,NVP}}{MM_{NVP}}\right)} \tag{36}$$

X is the total molar monomer conversion.

$$f_{1,0} = \frac{\frac{RC_{0,IA}}{MM_{IA}}}{\left(\frac{RC_{0,IA}}{MM_{IA}} + \frac{RC_{0,NVP}}{MM_{NVP}}\right)} \tag{37}$$

$f_{1,0}$ is the initial mole fraction of itaconic acid inside the reactor, and $\bar{F}_1$ below is the cumulative copolymer composition for the itaconic acid.

$$\bar{F}_1 = \frac{\frac{(RC_{0,IA} - RC_{IA})}{MM_{IA}}}{\left(\frac{(RC_{0,IA} - RC_{IA})}{MM_{IA}} + \frac{(RC_{0,NVP} - RC_{NVP})}{MM_{NVP}}\right)} \tag{38}$$

The abbreviations used in each of the formulas can also be found on the abbreviations list.

3.4 RELATIVE REACTIVITY RATIO CALCULATION

Calculating the reactivity ratios by use of the algorithm presented in section 2.2.1.3 requires that the equations presented be combined with the ones given in section 2.1.2.

For the case of Direct Numerical Integration (DNI) only a single EVM variable is considered, since f_{10} and X are utilized during the numerical solution of f_1 (equation (18) they cannot be EVM variables and only the cumulative copolymer composition, $\overline{F_1}$ is considered as such. In lieu of this, equations (22) and (24), which describe the error structure used (either additive or multiplicative respectively) can be rewritten as

$$\overline{F_1} = \overline{F}_1^* + k\varepsilon \tag{39}$$

$$ln(\overline{F_1}) = ln\left(\overline{F}_1^*\right) + k\varepsilon \tag{40}$$

where * represents the true value of the variable.

The variance-covariance matrix is a square matrix of size equal to the number of variables in the problem, in this case it has a single element as shown below

$$V(\overline{F_1}) = \frac{k^2}{3} \tag{41}$$

and is the same for both additive and multiplicative error as show in section 2.2.1.2.

The error function used in the EVM procedure, $\underline{g}\left(\underline{\xi_i}, \underline{\theta^*}\right)$ is given below

$$\underline{g}\left(\underline{\xi_i}, \underline{\theta^*}\right) = \underline{\overline{F}_{1,i}^*} - \frac{f_{10} - \underline{f_{1,i}}\left(1 - \underline{X_i}\right)}{\underline{X_i}} \tag{42}$$

it relates the true value of the variable, either estimated through measurements during the first step or calculated in a previous inner loop step with equation (30), to the theoretical values calculated by the model equations (17), (18) and (14).

The vector of partial derivatives of $\underline{g}$, $\underline{B_i}$ is given below and has two forms depending on the error structure used. Equation (43) is used for additive error and equation (44) for multiplicative error. Since multiplicative error considers the natural logarithm of $\overline{F_1}$ to be the

EVM variable, the derivative of $\underline{g}$ must be taken with respect to the $ln(\overline{F}_1)$, an expansion of the derivative is thus necessary.

$$\underline{B_i} = \left[\frac{\partial \underline{g}\left(\underline{\xi_i}^{(k)}, \underline{\theta}\right)}{\partial \underline{\xi_i}^{(k)}}\right] = 1 \tag{43}$$

$$\begin{aligned}\underline{B_i} = \left[\frac{\partial \underline{g}\left(\underline{\xi_i}^{(k)}, \underline{\theta}\right)}{\partial ln\left(\underline{\xi_i}^{(k)}\right)}\right] &= \left[\frac{\partial \underline{g}\left(\underline{\xi_i}^{(k)}, \underline{\theta}\right)}{\partial \underline{\xi_i}^{(k)}}\right]\left[\frac{\partial \underline{\xi_i}^{(k)}}{\partial ln\left(\underline{\xi_i}^{(k)}\right)}\right] = \underline{\xi_i}^{(k)}\left[\frac{\partial \underline{g}\left(\underline{\xi_i}^{(k)}, \underline{\theta}\right)}{\partial \underline{\xi_i}^{(k)}}\right] \\ &= \underline{\xi_i}^{(k)} = \underline{\overline{F}_{1,i}}\end{aligned} \tag{44}$$

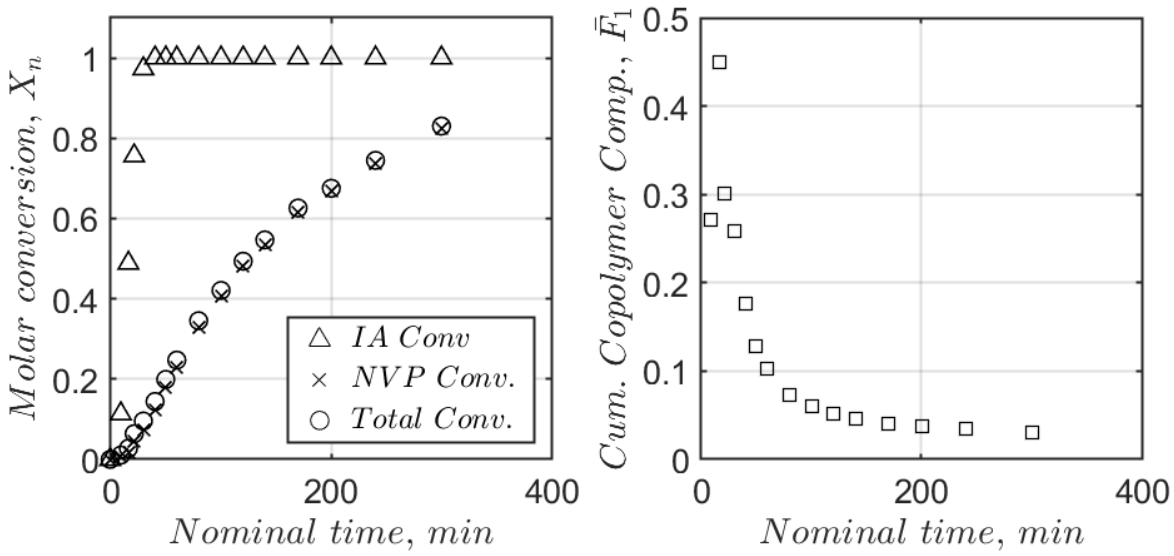
4 RESULTS AND DISCUSSION

4.1 REACTION KINETICS

It is out of the scope of this work to develop a detailed kinetic description of the system under study; however, analysis of the comonomer conversion curves gives insight on certain system characteristics that can help guide the data selection procedure, especially with regards to limitations to the feasible experimental region, i.e. limit feed compositions.

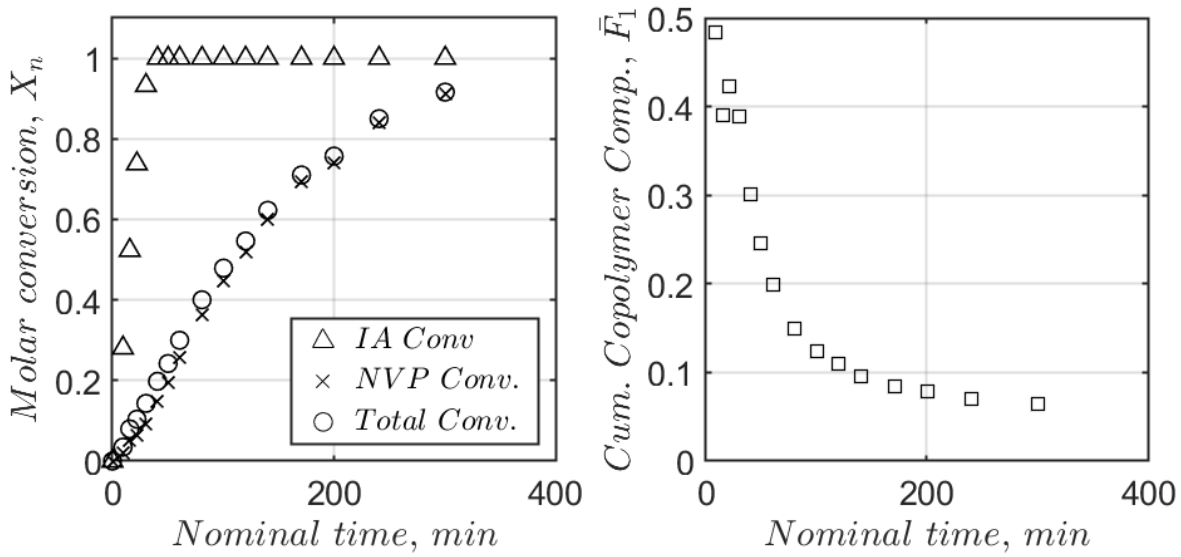
The data collected in experiments at 7 different initial feed compositions are represented in graphical form in Figure 10 through Figure 16. They show itaconic acid partial conversion, N-vynil-2-pyrrolidone partial conversion, total conversion and the cumulative copolymer composition for the itaconic acid as a function of reaction time.

Figure 10 – Experimental results of IA and NVP copolymerization for $f_1 = 0.0254$ and T = 55 °C. a) Molar conversion and b) Cumulative copolymer composition.



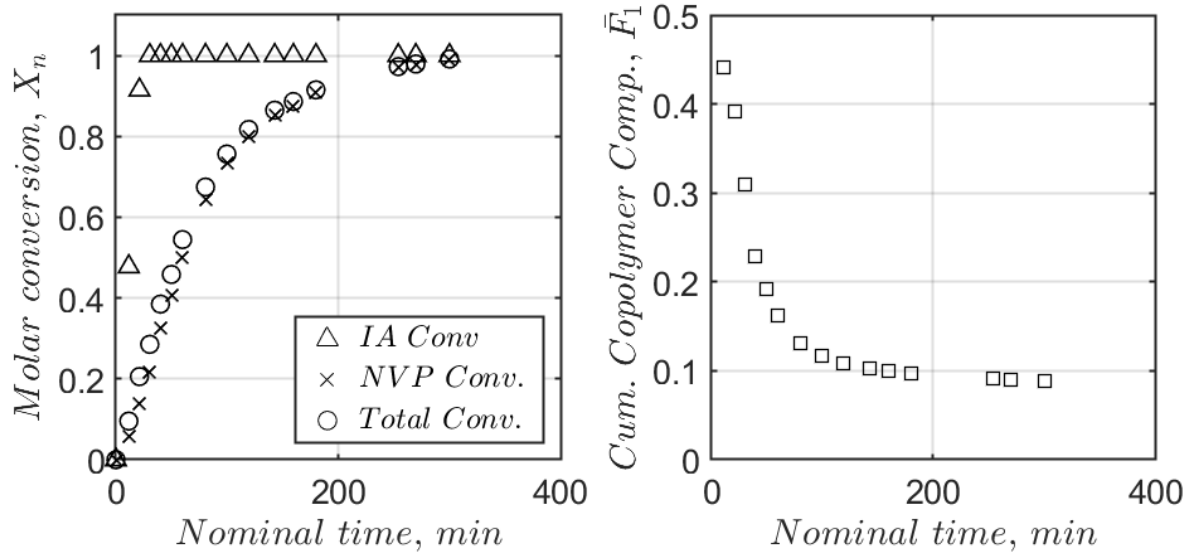
Source: Author (2020).

Figure 11 – Experimental results of IA and NVP copolymerization for $f_1 = 0.0596$ and T = 55 °C. a) Molar conversion and b) Cumulative copolymer composition.



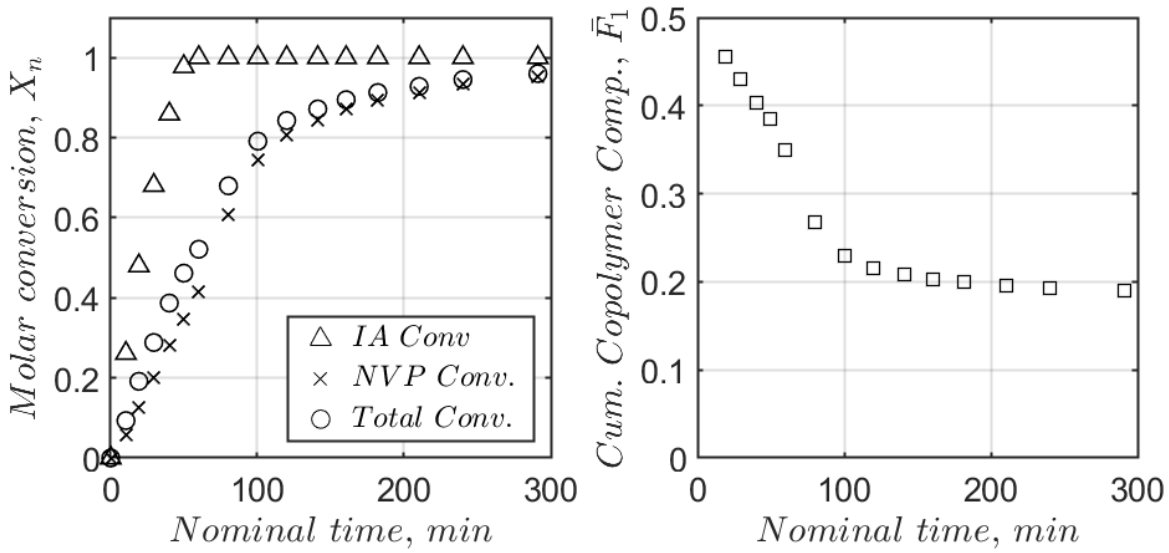
Source: Author (2020).

Figure 12 – Experimental results of IA and NVP copolymerization for $f_1 = 0.0882$ and T = 65 °C. a) Molar conversion and b) Cumulative copolymer composition.



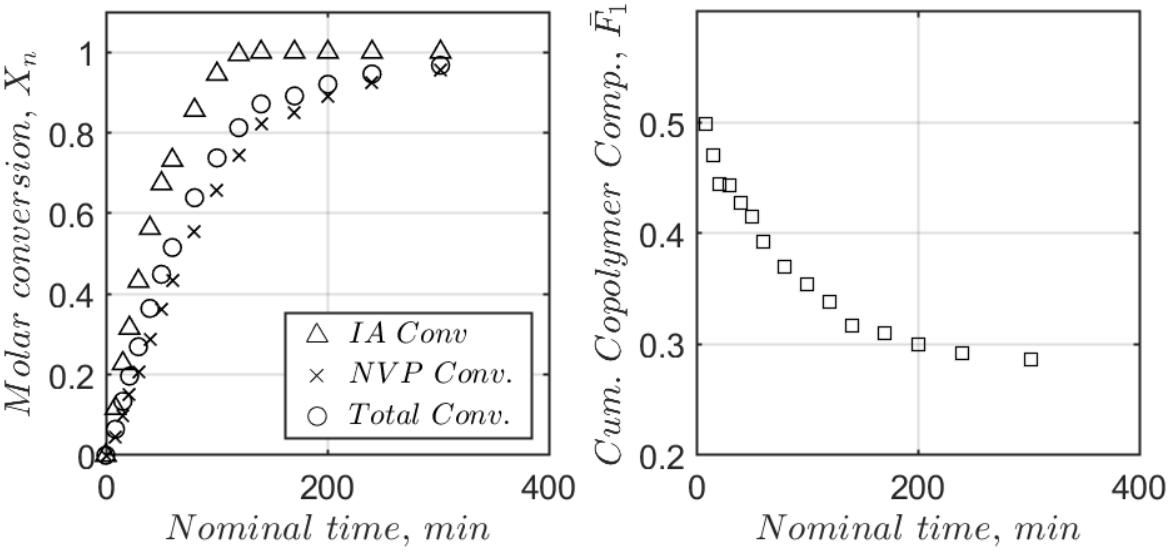
Source: Author (2020).

Figure 13 – Experimental results of IA and NVP copolymerization for $f_1 = 0.1819$ and T = 65 °C. a) Molar conversion and b) Cumulative copolymer composition.



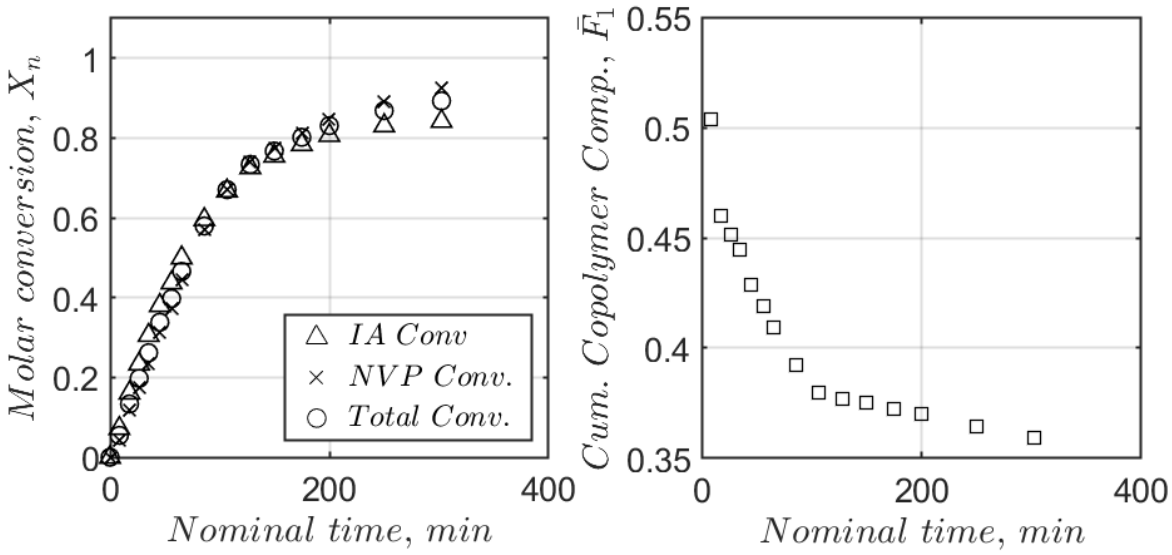
Source: Author (2020).

Figure 14 – Experimental results of IA and NVP copolymerization for $f_1 = 0.2765$ and T = 65 °C. a) Molar conversion and b) Cumulative copolymer composition.



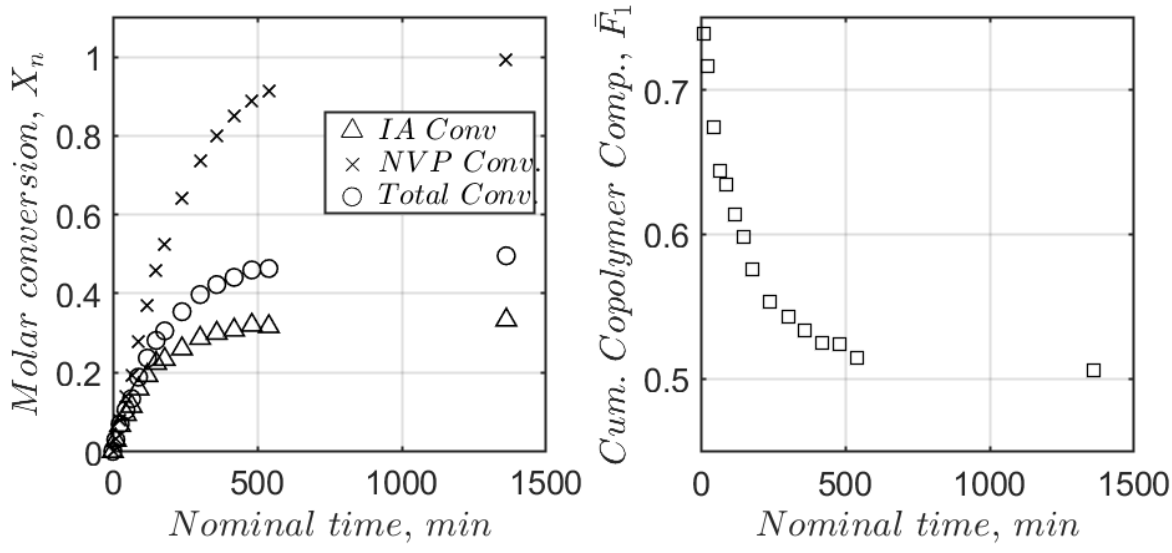
Source: Author (2020).

Figure 15 – Experimental results of IA and NVP copolymerization for f_1 = 0.3812 and T = 65 °C. a) Molar conversion and b) Cumulative copolymer composition.



Source: Author (2020).

Figure 16 – Experimental results of IA and NVP copolymerization for f_1 = 0.7535 and T = 65 °C. a) Molar conversion and b) Cumulative copolymer composition.



Source: Author (2020).

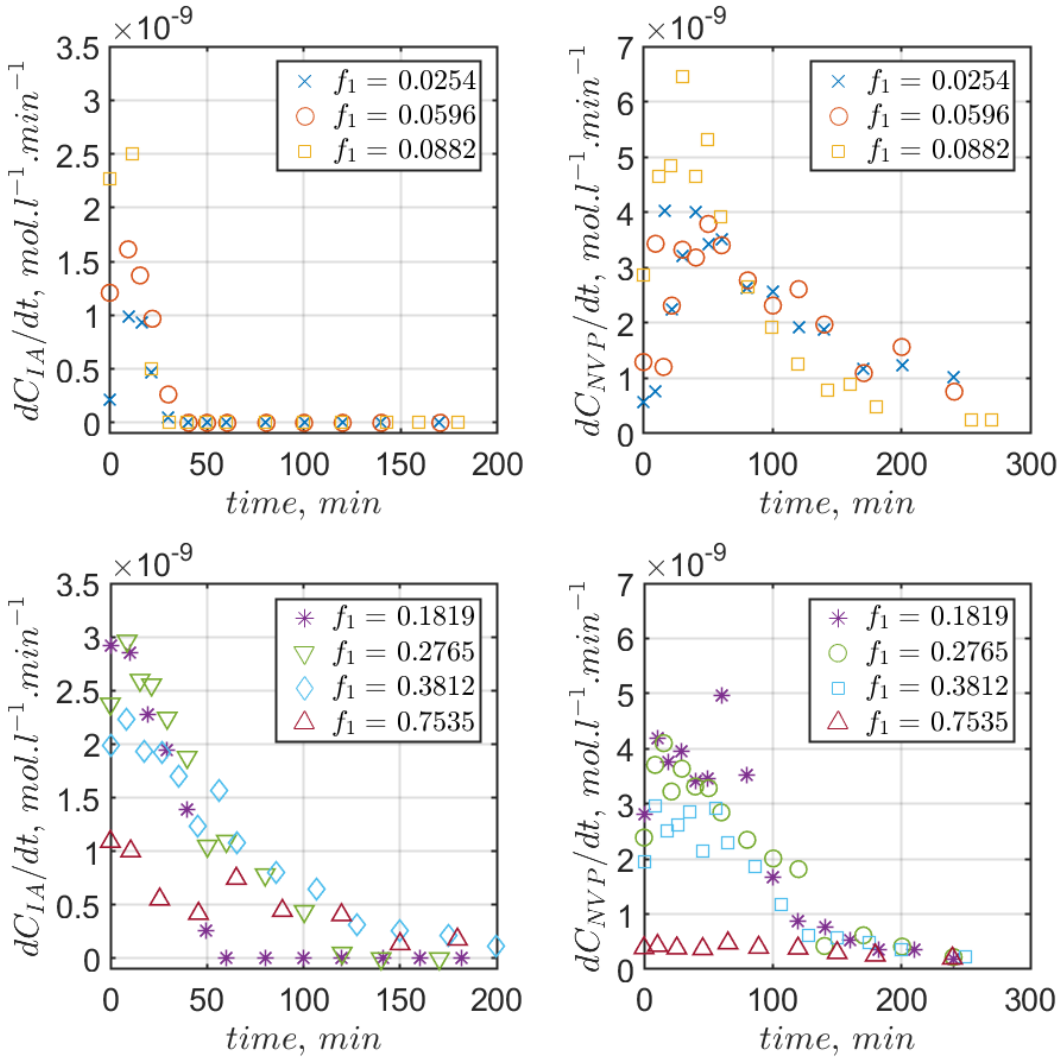
Figure 17 displays the reaction rates of IA and NVP. From them, it can be observed that the reaction rates of IA and NVP increase with the increase of initial IA feed concentration

up to, respectively, f_1 = 0.1819 and f_1= 0.0882. For higher f_1 values the reaction rates start to decrease and for the limiting cases of higher IA concentration, IA conversion reaches a plateau, as can be observed in Figure 15 and more pronouncedly in Figure 16. This effect of decreasing reaction rates has also been observed by other authors using different itaconic acid copolymerization systems (BARNER-KOWOLLIK ET AL. (2001) AND REZA MAHDAVIAN; ABDOLLAHI (2007)). This behavior is expected due to the well-known difficulty in polymerizing itaconic acid (MARVEL; SHEPHERD (1959)), and for the reactions with higher initial IA composition, as NVP is consumed and the reaction becomes richer in IA this effect becomes more evident.

This points to an apparent change in reaction kinetics such that the Mayo-Lewis equation cannot be applied to properly describe the copolymerization reaction. This is eminently evident when observing the cumulative copolymer composition, $\bar{F}_1$, in Figure 16. By the end of the reaction $\bar{F}_1$ is expected to reach the same value as the initial feed composition, in this case f_1 = 0.7535, but it reaches a value that is much lower, about 0.5 at 50% conversion. Could the IA be made to react further, the cumulative copolymer composition graph would rebound upwards, which according to the kinetics developed in sections 2.1.1 and 2.1.2 should not be possible.

This abnormal behavior is not observed in any of the other data sets, especially those below 10% IA feed, but those between 10% and 75% feed composition present other inconsistencies that will be expounded on further in the text. In purview of these limitations, the relative reactivity ratios for the system under study were calculated based solely on the data acquired under 10% molar initial itaconic acid feed composition, which is a particularly fortunate predicament since most applications of this copolymer use very small quantities of itaconic acid in their compositions (CHEN ET AL. (2005); ŞEN; GÜVEN (1999) AND TÜMTÜRK ET AL. (1999)).

Figure 17 - Estimated reaction rates of Itaconic acid and N-vinyl-2-pyrrolidone.



Source: Author (2020).

4.2 ERROR-IN-VARIABLES METHODOLOGY PERFORMANCE

Before the reactivity ratio results are discussed, a general overview of the algorithm performance should be presented, and the method validated.

It should be noted here first that this it was not possible to implement the EVM strategy with multiplicative error as described by Kazemi (2014), the inner loop of the algorithm was found to diverge when utilizing Equation (44). As such, the only manner with which to validate

and make use of the implementation was by considering the error structure to be additive in nature (i.e. using equation (43)).

The use of additive error is only partially detrimental to the regression procedure. Kazemi notes that full clarification on the matter of error structure for a specific measuring methodology can only be achieved using extensive replicated experiments, which would nullify one of the justifications in employing EVM in the first place, which is the reduced number of experiments required to acquire useful results. Hauch (2005) concluded that for compositional data, such as the ones used in this work, the choice of error structure does not significantly alter the estimated values of the reactivity ratios, affecting only the size of the joint confidence regions, multiplicative error generally having a smaller JCR area and thus less uncertainty.

Table 3 shows the point estimate comparisons of 5 different data sets between this work and as calculated by two other authors. Both Hauch and Kazemi used the same EVM implementation with multiplicative error structure, difference between estimated values remained generally below 5% for most cases. Joint confidence regions were not compared due to the use of different error structures.

Table 3 - Point estimates comparison.

	O'Driscoll (1984)		Rossignoli (1993)		Shawki (1979)	
	STY-MMA		STY-MMA		AAc-AA	
	r1	r2	r1	r2	r1	r2
Hauch (2005)	0.4403	0.4385	0.3986	0.4273	1.4808	0.5685
This work	0.4319	0.4215	0.4200	0.4397	1.4564	0.5708
Error %	-1.94	-4.03	5.10	2.82	-1.68	0.40
	O'Driscoll (1984)		Madruga et al (1995)		Haque (2010)	
	STY-MMA		DBI-MMA		AAc-AA	
	r1	r2	r1	r2	r1	r2
Kazemi (2011)	0.4402	0.4385	0.6798	1.2380	1.3157	0.2475
This work	0.4319	0.4215	0.7127	1.2807	1.3046	0.2406
Error %	-1.92	-4.03	4.62	3.33	-0.85	-2.87

(a) Kazemi and Hauch used multiplicative error structure for the regression procedure, this work used additive.

(b) Hauch did not present values in table form, values were extracted from graph.

STY: Styrene; MMA: Methyl Methacrylate; AAc: Acrylic Acid; AA: Acrylamide; DBI: Di-n-Butyl Itaconate.

Source: Author (2020).

4.3 REACTIVITY RATIO ESTIMATES

Table 4 shows the data set used for estimating the reactivity ratio of the IA/NVP system, and as explained in section 4.1 only the data below 0.1 IA mole fraction were selected for the calculation.

Table 4 - Initial mole fraction, total mass conversion, and cumulative copolymer composition data used for reactivity ratio estimation of the itaconic acid/N-vinylpyrrolidone system.

f_{10}	X_w	$\bar{F}_1$	f_{10}	X_w	$\bar{F}_1$	f_{10}	X_w	$\bar{F}_1$
0.0254	0.0111	0.2711	0.0596	0.0371	0.4832	0.0882	0.1012	0.4410
0.0254	0.0296	0.4504	0.0596	0.0843	0.3907	0.0882	0.2164	0.3922
0.0254	0.0669	0.3009	0.0596	0.1102	0.4234	0.0882	0.2961	0.3091
0.0254	0.0995	0.2586	0.0596	0.1511	0.3882	0.0882	0.3943	0.2291
0.0254	0.1480	0.1762	0.0596	0.2061	0.3009	0.0882	0.4664	0.1925
0.0254	0.2026	0.1277	0.0596	0.2499	0.2460	0.0882	0.5514	0.1620
0.0254	0.2506	0.1028	0.0596	0.3070	0.1987	0.0882	0.6795	0.1308
0.0254	0.3482	0.0736	0.0596	0.4064	0.1488	0.0882	0.7600	0.1167
0.0254	0.4233	0.0604	0.0596	0.4842	0.1244	0.0882	0.8198	0.1080
0.0254	0.4958	0.0515	0.0596	0.5509	0.1091	0.0882	0.8667	0.1021
0.0254	0.5486	0.0465	0.0596	0.6263	0.0957	0.0882	0.8878	0.0996
0.0254	0.6276	0.0406	0.0596	0.7131	0.0839	0.0882	0.9163	0.0964
0.0254	0.6767	0.0377	0.0596	0.7594	0.0787	0.0882	0.9729	0.0907
0.0254	0.7459	0.0341	0.0596	0.8514	0.0701	0.0882	0.9794	0.0901
0.0254	0.8309	0.0306	0.0596	0.9168	0.0651	0.0882	0.9914	0.0890

Source: Author (2020).

Figure 18 and Figure 19 present, respectively, the cumulative copolymer profiles for the selected data along with the data points themselves, and also the calculated point estimates for reactivity ratios along with the approximated joint confidence region as calculated by MATLAB's fmincon implementation of the SQP methodology.

A distinction is made between the JCRs acquired when using SQP and Duan's Shuffled Complex Evolution (SCE) methods. As described in section 2.2.1.3 the JCR needs an estimated information matrix (hessian of the objective function) to be drawn, SQP has the advantage of returning an estimated hessian when requested as it is used internally by the program in its calculations (MathWorks (2020)) even if it can be, at times, considered inaccurate due to the quasi-Newton nature of the method. SCE on the other hand does not

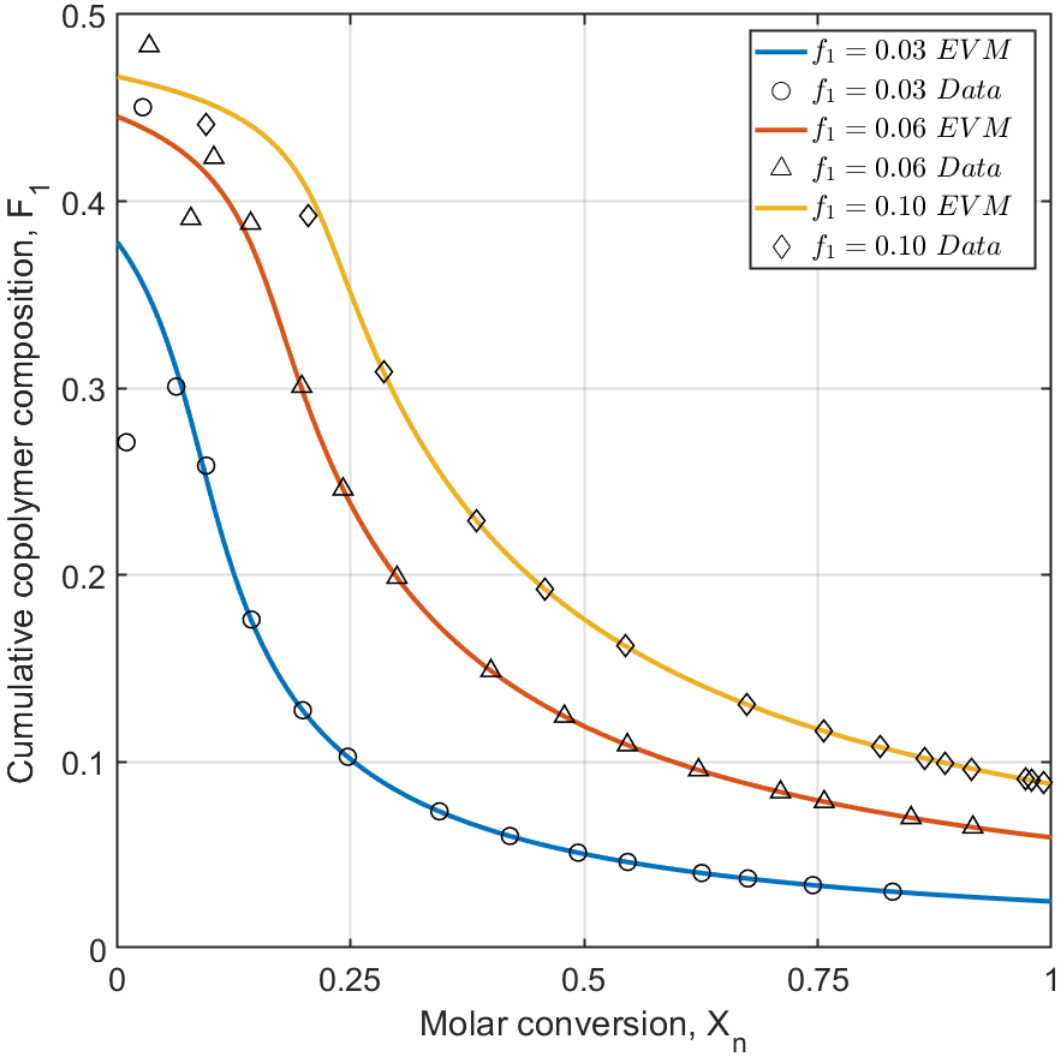
provide the estimated hessian, which must then be estimated by other means. In this case, an adaptation of John D'Errico's DERIVEST toolbox (D'ERRICO (2020)) was used.

The JCRs presented here were drawn using SQP's approximated hessian. According to Kazemi (2014) fmincon makes a smaller number of function evaluations, performs about 6 times more iterations to reach convergence and can handle larger systems with multiple optimal points more quickly, SCE however, has a lesser dependency on the initial parameter guesses given to start calculations, and is thus more beneficial for studying new systems. This work used SCE to initially calculate a starting point for the SQP implementation which then also enables the estimation of the hessian and the drawing of the joint confidence regions.

The estimated values for the reactivities ratios are $r_1 = 0.3046$ and $r_2 = 0.0170$, and as can be seen in Figure 18 the values fit the data quite well, especially the regions of moderate to high conversion. The slight spread present in the low conversion data is likely caused by the fast rate of conversion of the itaconic acid during the initial stages of the polymerization along with the uncertainties in the HPLC measurements at the low IA concentrations of these reactions. Since both reactivities ratios are below 1 this system forms an azeotrope at $f_{10} = 0.5857$.

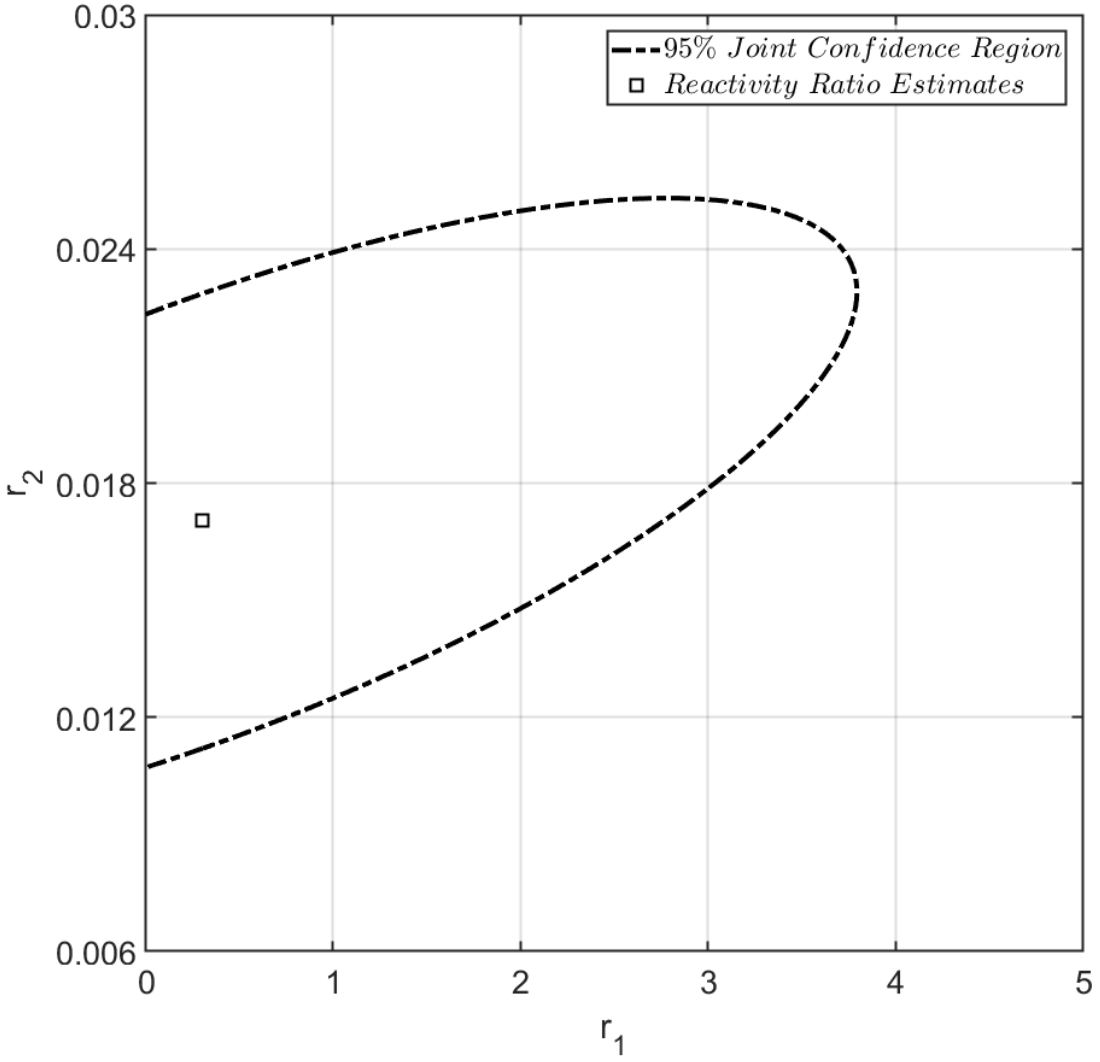
The small discrepancies between model and data for low conversions can also explain the large uncertainty range observed for r_1 when compared to r_2 in the JCR of Figure 19, this uncertainty can only be reduced, however, by either increasing sampling at the beginning, which would likely require automated sampling strategies or inline monitoring of the system. Further reduction in reaction temperature is not recommended due to possible changes to the reaction ratios.

Figure 18 - Cumulative copolymer profiles for data below 0.1 IA mole fraction.



Source: Author (2020).

Figure 19 - Reactivity Ratio Estimate and JCR for data below 0.1 IA mole fraction.

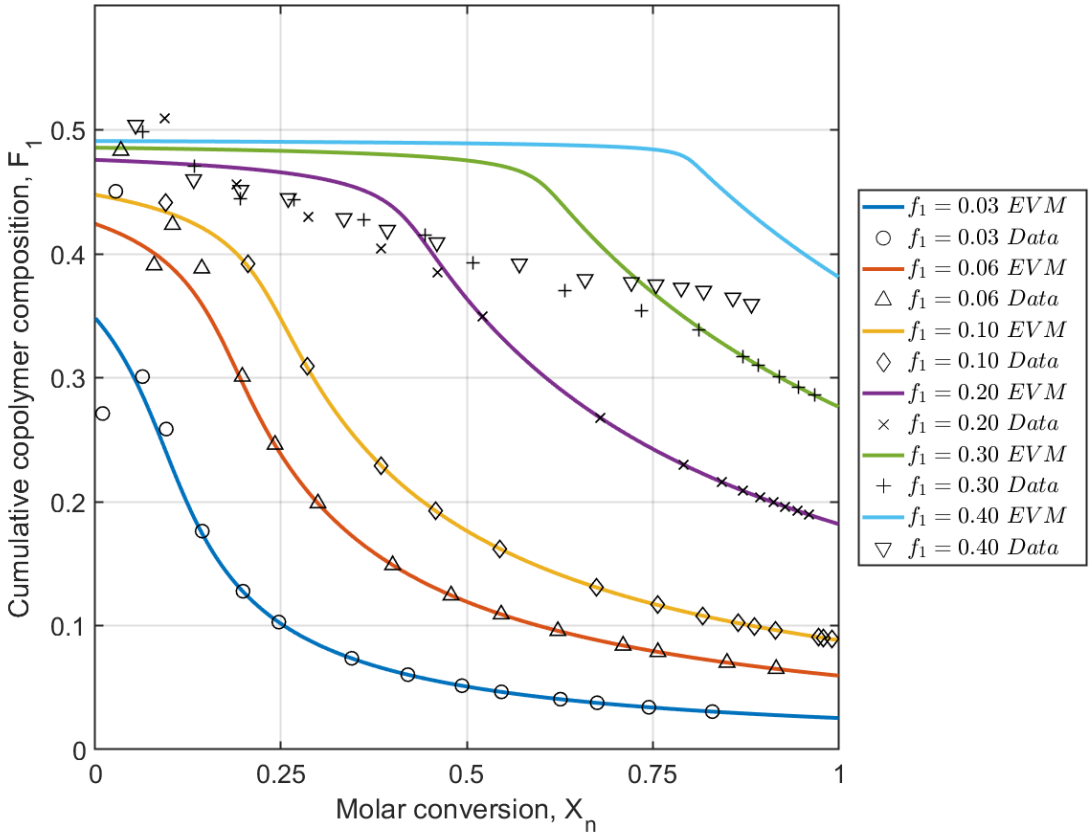


Source: Author (2020).

4.4 REACTIVITY RATIO ESMTIMATES FOR SYSTEMS OF HIGHER ITACONIC ACID COMPOSITION

As stated in section 4.1, the use of reaction systems with higher IA compositions is not recommended when using the Mayo-Lewis equation for describing the IA-NVP copolymerization system. In that section the use of partial conversion profiles was used to justify that recommendation and here EVM model fitting can be employed to strengthen that recommendation.

Figure 20 - Cumulative copolymer profiles for data below 0.75 IA mole fraction.

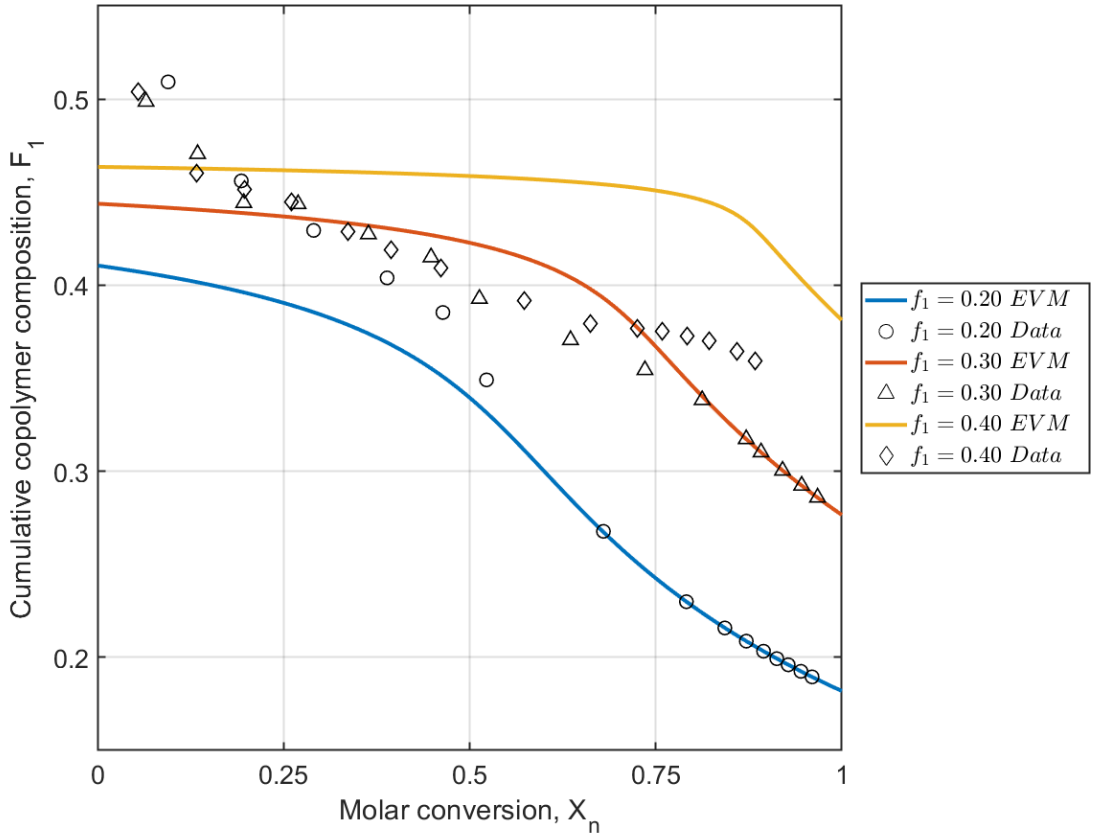


Source: Author (2020).

As can be seen in Figure 20, increased levels of IA on initial reaction composition greatly alter the behavior in which this IA is added to the polymeric chain such that for all compositions above $f_1 = 0.1$ the fitting of the data to the model is extremely poor, a decent fit being observed only for $f_1 = 0.2$ beyond 40% conversion and for $f_1 = 0.3$ beyond 75% conversion. $f_1 = 0.4$ observed no fit at all.

Even when determining the reactivity ratios using only these higher composition data sets the general fit remains poor as can be seen in Figure 21.

Figure 21 - Cumulative copolymer profiles for data above 0.2 IA mole fraction.



Source: Author (2020).

5 CONCLUSION

With the work conducted throughout this dissertation we were able to successfully implement the Error-in-Variables methodology for the parameter regression of non-linear equations under the MATLAB programming environment, apply it to the Mayo-Lewis and Skeist copolymerization equations and use it to estimate the monomer reactivity ratios of the novel, radical-chain polymerized, Itaconic Acid/N-Vynil-2-Pyrrolidone system along with an estimative of its error.

The developed single-step HPLC methodology also provided a viable and easy to use process for acquiring kinetic data. The traditional methods required conversion to be calculated gravimetrically and cumulative copolymer composition to be acquired by elemental analysis of previously purified polymer from reaction samples. The single step method allowed partial and total conversion to be calculated along with cumulative composition without the need for an extraneous and costly purification step of samples that can sometimes be very small, especially in the low conversion regions of a polymerization reaction, which in turn also allowed the experiments to be performed on a smaller scale.

As recommendations for future work, the entire EVM framework could not be implemented in this work, only the Direct Numerical Integration strategy was implemented, and much could be learned from comparing results directly with the Mayo-Lewis equation and the analytically integrated Meyer-Lowry equation. On another front, the multiplicative error structure of EVM could also not be applied, and since it is known to arrive at more precise results, its application should be sought out. Further work is also necessary to implement the design of experiments part of the EVM framework since it allows for the calculation of initial compositions that lead to more statistically meaningful experiments, i.e. initial monomer concentrations that allow the elliptical area of JCRs to be reduced optimally with each subsequent performed experiment.

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APPENDIX A – Full data collected for the IA/NVP system

Table A-1 - Full collected data for the IA/NVP copolymer system.

f_{10}	X_w	$\overline{F_1}$	f_{10}	X_w	$\overline{F_1}$	f_{10}	X_w	$\overline{F_1}$
0.0254	0.0111	0.2711	0.0596	0.0371	0.4832	0.0882	0.1012	0.4410
0.0254	0.0296	0.4504	0.0596	0.0843	0.3907	0.0882	0.2164	0.3922
0.0254	0.0669	0.3009	0.0596	0.1102	0.4234	0.0882	0.2961	0.3091
0.0254	0.0995	0.2586	0.0596	0.1511	0.3882	0.0882	0.3943	0.2291
0.0254	0.1480	0.1762	0.0596	0.2061	0.3009	0.0882	0.4664	0.1925
0.0254	0.2026	0.1277	0.0596	0.2499	0.2460	0.0882	0.5514	0.1620
0.0254	0.2506	0.1028	0.0596	0.3070	0.1987	0.0882	0.6795	0.1308
0.0254	0.3482	0.0736	0.0596	0.4064	0.1488	0.0882	0.7600	0.1167
0.0254	0.4233	0.0604	0.0596	0.4842	0.1244	0.0882	0.8198	0.1080
0.0254	0.4958	0.0515	0.0596	0.5509	0.1091	0.0882	0.8667	0.1021
0.0254	0.5486	0.0465	0.0596	0.6263	0.0957	0.0882	0.8878	0.0996
0.0254	0.6276	0.0406	0.0596	0.7131	0.0839	0.0882	0.9163	0.0964
0.0254	0.6767	0.0377	0.0596	0.7594	0.0787	0.0882	0.9729	0.0907
0.0254	0.7459	0.0341	0.0596	0.8514	0.0701	0.0882	0.9794	0.0901
0.0254	0.8309	0.0306	0.0596	0.9168	0.0651	0.0882	0.9914	0.0890
f_{10}	X_w	$\overline{F_1}$	f_{10}	X_w	$\overline{F_1}$	f_{10}	X_w	$\overline{F_1}$
0.1819	0.0984	0.5092	0.2765	0.0670	0.4986	0.3812	0.0558	0.5039
0.1819	0.2001	0.4560	0.2765	0.1381	0.4705	0.3812	0.1352	0.4600
0.1819	0.3002	0.4294	0.2765	0.2017	0.4442	0.3812	0.1997	0.4514
0.1819	0.4011	0.4039	0.2765	0.2765	0.4436	0.3812	0.2645	0.4447
0.1819	0.4770	0.3853	0.2765	0.3732	0.4274	0.3812	0.3408	0.4286
0.1819	0.5356	0.3491	0.2765	0.4591	0.4150	0.3812	0.4001	0.4191
0.1819	0.6893	0.2677	0.2765	0.5252	0.3927	0.3812	0.4678	0.4091
0.1819	0.7974	0.2299	0.2765	0.6487	0.3705	0.3812	0.5805	0.3919
0.1819	0.8475	0.2158	0.2765	0.7470	0.3544	0.3812	0.6703	0.3794
0.1819	0.8755	0.2087	0.2765	0.8208	0.3383	0.3812	0.7334	0.3770
0.1819	0.8979	0.2033	0.2765	0.8773	0.3173	0.3812	0.7667	0.3751
0.1819	0.9152	0.1993	0.2765	0.8963	0.3102	0.3812	0.8008	0.3725
0.1819	0.9301	0.1960	0.2765	0.9239	0.3004	0.3812	0.8296	0.3700
0.1819	0.9466	0.1925	0.2765	0.9484	0.2923	0.3812	0.8665	0.3645
0.1819	0.9612	0.1895	0.2765	0.9688	0.2859	0.3812	0.8899	0.3594

Source: Author (2020).

Table A-1 - Full collected data for the IA/NVP copolymer system. Continued.

f_{10}	X_w	$\overline{F_1}$
0.7535	0.0290	0.7386
0.7535	0.0691	0.7167
0.7535	0.1034	0.6743
0.7535	0.1315	0.6435
0.7535	0.1848	0.6345
0.7535	0.2315	0.6134
0.7535	0.2747	0.5982
0.7535	0.2972	0.5756
0.7535	0.3433	0.5535
0.7535	0.3849	0.5433
0.7535	0.4088	0.5337
0.7535	0.4259	0.5252
0.7535	0.4440	0.5242
0.7535	0.4469	0.5143
0.7535	0.4772	0.5062

Source: Author (2020).

APPENDIX B – Developed algorithm for the determination of reactivity ratios

In this appendix are collected the two MATLAB functions developed for this work for the determination of the relative reactivity ratios of a copolymerization system, EVM.m and EVM_Inner.m. They are to be used in conjunction, with themselves, and with other functions, internal and external to MATLAB, that have been mentioned elsewhere in this text. Those adapted functions that are external to MATLAB will not be published here but will be made available alongside this text in the appropriate formats, upon request or on the author's personal Github page.

```
function out_data = EVM(Data,Mw,theta,e,s,m,lb,ub)

% Written by Bruno V. Krieger 2019/2020
% bv.krieger at gmail.com
% Data must be a MATLAB structure containing:
%   f10 = [0.1; 0.1; 0.3; 0.3]; Column vector containing the initial mole fraction of each
%                               data set. The value repeats for every data point in each
%                               set
%   Xw = [0.01; 0.02; 0.03; 0.04]; Column vector containing the degree of mass conversion
%                                  for every data point for each data set
%   F1 = [0.23; 0.22; 0.41; 0.42]; Column vector containing the cumulative copolymer
%                                  compositions of all data sets by order of initial mole
%                                  fraction followed by order of conversion
%   Data example:
%    f10 = [0.0254;   Xw =  [0.0111;    F1 = [0.2711;
%           0.0254;          0.0296;          0.4504;
%           0.0254;          0.0669;          0.3009;
%           0.0254;          0.0995;          0.2586;
%           0.0254;          0.1480;          0.1762;
%           0.0596;          0.0371;          0.4832;
%           0.0596;          0.0843;          0.3907;
%           0.0596;          0.1102;          0.4234;
%           0.0596;          0.1511;          0.3882;
%           0.0596;          0.2061;          0.3009;
%           0.0882;          0.1012;          0.4410;
%           0.0882;          0.2164;          0.3922;
%           0.0882;          0.2961;          0.3091;
%           0.0882;          0.3943;          0.2291;
%           0.0882];         0.4664];         0.1925];
% In this example there are 3 f10 levels 0.0254, 0.0596, and 0.0882, these correspond to
% three experiments with different monomer 1 concentrations. For each experiment the
% different lines represent a diferent mass conversion level with an associated cumulative
% copolymer composition, these must be placed in order inside each inital mole fraction
% group.
%
% Other input arguments:
% Mw = [Monomer_1_Mw Monomer_2_Mw]; Line vector containing monomer molecular weights
% e = [e_F; e_f; e_X]; Column vector of associated measurement errors.
% theta = [.01 .3]; Line vector containing the initial reactivity ratio estimates.
```

```
% s = [15 15 15]; Line vector containing the number of data sets and how many measurements
%                 there are in each one. In the example given we have 3 data sets, each
%                 level has 15 data points.
% m = 1; Method code, can either be 1 for fmincon or 2 for SCE
% lb = 0*ones(size(theta,2),1)'; Lower bound line vector containing the lower bound
%                                values for each theta used
% ub = 5*ones(size(theta,2),1)'; Upper bound line vector containing the upper bound
%                                values for each theta used
%
% Output data: Is a MATLAB structure contaning the relevant output result
% data. It contains: the final parameter estimate, f_theta; minimized
% objective function value, phi; the true value of the inputed variables,
% xi; values of the error function g, and its derivative B; and finally the
% corrected conversion values, Xn.
%
% This function uses global variables internally.
%

clear global
% Setting global variable spaces for result estimates and internal values:
global ests ints
ests.phi = [];
ests.theta = [];
ints.g = [];
ints.xi = [];
ints.B = [];

% Variable reallocation:
F1 = Data.F1;
f10 = Data.f10;
Xw = Data.Xw;
% Variance co-variance matrix:
V = (diag(e)^2)/3;
% Number of f10 levels in the data:
c = size(s,2);

%  Inner loop call:
switch m
    case 1
        % Using fmincon:
        options = optimoptions('fmincon');
        options = optimoptions(options,'Display', 'iter');
        options = optimoptions(options,'FunValCheck', 'off');
        options = optimoptions(options,'Algorithm', 'sqp');
        options = optimoptions(options,'FiniteDifferenceType', 'central');
        options = optimoptions(options,'UseParallel', false);
        options = optimoptions(options,'StepTolerance', 1e-10);
        options = optimoptions(options,'OptimalityTolerance', 1e-8);
        options = optimoptions(options,'MaxFunctionEvaluations', 1000);
        A = [];
        b = [];
        [theta(2,:),phi,~,output,~,grad,hessian] = fmincon(@(theta) ...
            EVM_Inner(theta,F1,f10,Xw,s,Mw,V,c),theta,A,b,[],[],lb,ub,[],options);
```

```
    case 2
        % Using SCE:
        maxn=10000;
        kstop=10;
        pcento=0.1;
        peps=0.001;
        iseed=-1;
        iniflg=0;
        ngs = 20;
        [theta(2,:),phi] = sceua_n(theta,lb,ub,maxn,kstop,pcento,peps,ngs,iseed, ...
                                   iniflg,F1,f10,Xw,s,Mw,V,c);
        hessian = [];
    otherwise
        error('Method code must be between 1 for fmincon or 2 for SCE.')
end

min_phi = phi;
min_index = find(min_phi==ests.phi); % Finds the index of min phi
g = ints.g(:,:,:,min_index); % Uses min phi index to find the correct g
xi = ints.xi(:,:,:,min_index); % Uses min phi index to find the correct xi
B = ints.B(:,:,:,min_index); % Uses min phi index to find the correct B
Xn = Xw.*(Mw(1)*f10+(1-f10)*Mw(2))./(Mw(1)*(xi(:,:,end))+(1-(xi(:,:,end)))*Mw(2));

ODEoptions = odeset('RelTol',1e-10,'AbsTol',1e-12);
for i = 1:c
    [iXn,f1(:,i)] = ode45(@(Xn_,f1_) odefun(Xn_,f1_,theta(2,:)), ...
                                            linspace(0,.9999,1000), ...
                                            f10(1+sum(s(1,1:i-1),2),1),ODEoptions);
    F1_ctot(:,i) = (f1(1,i)-f1(:,i).*(1-iXn))./iXn;
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%% JCR plotting sub-fuction %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
p = input('Would you like to plot the Joint Confidence Regions? (y/n) \n','s');
isOK = false;
while ~isOK
    switch p
        case 'y'
            isOK = true;
            if isempty(hessian)
                hessian = hessian_n_alt(@(theta) EVM_Inner(theta,F1,f10,Xw,s,Mw, ...
                                                           V,c),theta(2,:));
            end
            JCR = error_ellipse(inv(hessian),theta(2,:),'conf',0.95);
            hold on
            grid on
            set(JCR,'LineStyle','-.','Color','k')
            sct = scatter(theta(2,1),theta(2,2),'s','MarkerEdgeColor','k','Marker', ...
                          'square');
            out_data.JCR = JCR;
        case 'n'
            isOK =true;
        otherwise
            p =  input('Anwser must be either y or n. \n','s');
    end
end

% Outputting:
```

```
out_data.f_theta = theta(2,:);
out_data.phi = phi;
out_data.g = g;
out_data.xi = xi;
out_data.B = B;
out_data.Xn = Xn;
if ~isempty(hessian)
    out_data.hessian = hessian;
else
    hessian = hessian_n_alt(@(theta) EVM_Inner(theta,F1,f10,Xw,s,Mw,V,c),theta(2,:));
    out_data.hessian = hessian;
end

clear global
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%% Mayo-Lewis equation sub-function %%%%%%%%%%%%%%%%%%%%%%%%%%%%
function df1dXn = odefun(x,y,theta)
r1 = theta(1);
r2 = theta(2);
f1 = y;
f2 = 1-f1;
Xn = x;
F11 = ( r1*f1^2 + f1*f2 )/( r1*f1^2 + 2*f1*f2 + r2*f2^2 );
% Vector of equations:
df1dXn = (f1-F11)/(1-Xn);
end
```

```
function phi = EVM_Inner(theta,F1,f10,Xw,s,Mw,V,c)

% Written by Bruno V. Krieger 2019/2020
% Should be used alongside EVM.m for the calculation of the objetive
% function values for the estimation of the reactivity ratios in a
% copolymerization problem. Uses global variables.

global ests ints
xi = (F1);
tol = 1e-6;

ODEoptions = odeset('RelTol',1e-10,'AbsTol',1e-12);
k = 1;
intp = 1000;

Xn = Xw.*(Mw(1)*f10+(1-f10)*Mw(2))./(Mw(1)*(F1(:,1,end))+(1-(F1(:,1,end)))*Mw(2));

for i = 1:c
    sol(i) = ode45(@(Xn_,f1_) odefun(Xn_,f1_,theta),linspace(0,.9999,intp), ...
                                    f10(1+sum(s(1,1:i-1),2),1),ODEoptions);
end
```

```
while 1
    clearvars F1_c f1
    F1_c = zeros(size(F1,1),1);
    f1 = zeros(size(f10,1),1);
    for i = 1:c
        idx = (1+sum(s(1,1:i-1),2):sum(s(1,1:i),2));
        f1(idx,1) = deval(sol(i),Xn(idx,1))';
        Xn_ = Xn(idx,1);
        F1_c(idx,1) = (f10(1+sum(s(1,1:i-1),2),1)-f1(idx,1).*(1-Xn_))./Xn_;
    end

    clearvars g B Xn_
    for i = 1:size(F1,1)
        g(:,:,i) = ((xi(i,1,end)) - (F1_c(i,1)));
%         B(:,:,i) = (xi(i,1,end)); % B vector for multiplicative error
        B(:,:,i) = 1; % B vector for additive error
    end

    for i = 1:size(F1,1)
        C(:,:,i) = B(:,:,i)*V*B(:,:,i)';
        b(:,:,i) = (g(:,1,i)+B(:,:,i)*((F1(i,:))-(xi(i,:,k)))');
        S(:,:,i) = chol(C(:,:,i));
        h(:,:,i) = S(:,:,i)'\b(:,:,i);
        t(:,:,i) = S(:,:,i)\h(:,:,i);
        xi(i,:,k+1) = ((F1(i,:)) - (V*B(:,:,i)'*t(:,:,i))');
        phi(1,i) = h(:,:,i)'*h(:,:,i)/2;
    end

    if abs(xi(:,:,k+1)-xi(:,:,k)) < tol
        Xn = Xw.*(Mw(1)*f10+(1-f10)*Mw(2))./(Mw(1)*(xi(:,1,end))+(1-(xi(:,1,end)))*Mw(2));
        break
    end

    Xn = Xw.*(Mw(1)*f10+(1-f10)*Mw(2))./(Mw(1)*(xi(:,1,end))+(1-(xi(:,1,end)))*Mw(2));
    k = k+1;
end

phi = sum(phi);
ests.phi = cat(1,ests.phi,phi);
ests.theta = cat(1,ests.theta,theta);
ints.g = cat(4,ints.g,g);
ints.xi = cat(4,ints.xi,(xi(:,:,end)));
ints.B = cat(4,ints.B,B);
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%% Mayo-Lewis equation sub-function %%%%%%%%%%%%%%%%%%%%%%%%%%%%
function df1dXn = odefun(x,y,theta)
r1 = theta(1);
r2 = theta(2);
f1 = y;
f2 = 1-f1;
Xn = x;
F11 = ( r1*f1^2 + f1*f2 )/( r1*f1^2 + 2*f1*f2 + r2*f2^2 );
% Vector of equations:
df1dXn = (f1-F11)/(1-Xn);
end
```