

# Determining the Optimum Reaction Pathway from a Reaction Pathway Search Space: a Review

Jaimee Jugmohan <sup>a\*</sup>, Josias van der Merwe <sup>b</sup>

<sup>a</sup> Council for Scientific and Industrial Research, Future Production: Chemicals, Pharmaceutical Technologies, Meiring Naudé Road, Pretoria, South Africa

<sup>b</sup> School of Chemical and Metallurgical Engineering, University of the Witwatersrand, Johannesburg, South Africa  
[JJugmohan@csir.co.za](mailto:JJugmohan@csir.co.za)

The feasibility of a chemical plant is heavily reliant on the reaction system and the subsequent downstream processing (DSP) techniques needed to achieve a marketable purity. However, with the ever-increasing number of reaction pathways being developed for a single product, it has become increasingly difficult to identify the optimum pathway for industrial scale up. Variations to a single reaction could involve changing the catalyst, operating conditions, residence times, and so forth. It is impractical to critically analyze each of these reactive systems, warranting techniques and frameworks that can be applied to reduce a reaction pathway search space to only those exhibiting feasibility. This article provides a basic review of previous work conducted in finding the optimal reaction pathway, highlighting the gap in the field that could be addressed in future research ventures.

## 1. Introduction

A chemical process is defined as the conversion of raw materials into a final product, having monetary value or a specific use. When developing such processes, environmental feasibility, economic feasibility, and social impact are considered. Processes which lack environmental benefits, pay high environmental taxes, offsetting their potential profit margin, and may have trouble finding investors, due to the lack of a sustainable process. There are two main components that determine the feasibility of a process, namely the reactor system and the subsequent DSP techniques. However, it is important to note that these two components are often directly linked. For example, optimizing the reactor system can help to lower the amount of unreacted raw materials leaving the reactor system, thereby lowering the need and extent of the subsequent separation process. Furthermore, it is possible that when investigating potential reaction pathways, an alternative route may provide a better conversion under lower reaction conditions, reducing the need and cost of future optimization. It is therefore necessary that the best pathway be chosen during the early development of a chemical process.

## 2. The Core of a Chemical Process

The hierarchical approach to process design focuses on a sequential tactic. Optimization via this route is a local optimum, as the interaction between variables at different points in the process is not considered. Should a global optimum be required, the superstructure approach is utilized (Cremaschi, 2015).

The hierarchical approach can be represented using the 'onion diagram', where each of the onion layers is representative of a design area. This concept, developed by Smith and Linnhoff in 1988, shows that the core of any process is the reactor unit operation, with all other unit operations being dependent on this system. Therefore, once the reactor has been designed and optimized the focus is shifted to designing the unit operations required to achieve the necessary operating conditions, and the subsequent separation systems.

Due to the importance that is placed on reactor unit operations, a considerable amount of research has been placed into determining the optimum reaction pathway to be employed in any given system. This allows for the feasibility of the process to be at its peak and will aid in promoting investment into the potential chemical plant.

### 3. Thermodynamic Feasibility

Thermodynamics indicate the practicality and possibility of a reaction occurring, prior to designing the process. Research conducted in the 1970s, looked at the development of a framework to explore alternative reaction pathways towards a single product. This could potentially reduce DSP costs, improving economic feasibility. The framework accounted for two process variables, Gibbs free energy and temperature (Govind & Power, 1977). The concern, however, is that the use of only two variables limits the search into alternative pathways.

In the early 1980s, this framework was expanded to account for three process variables, further including heat of reaction, i.e., enthalpy. In this study, alternative reaction routes were noted to be extremely useful in any process development, exhibiting higher efficiencies, or the absence of limiting by-products (Rotstein et al., 1982). Conversely, alternative reaction pathways may produce by-products with monetary value, thereby increasing the economic feasibility of the desired process structure. Whilst a three variable system was able to achieve a more holistic view, the major concern was the large degree of freedom noted. The use of three variables resulted in infinite possibilities. This is impractical to work with for the designing engineer.

Furthermore, a common concern is the extent to which Gibbs free energy is utilized during the analysis procedure. These frameworks consider feasibility based on the spontaneity of a reaction. Therefore, spontaneous reactions ( $\Delta G < 0$ ) are considered as feasible. This does not account for other factors imperative in any design, such as the economic feasibility of reaching reaction conditions and the environmental impact.

To limit the infinite search space developed by the previous framework, research conducted in 1989 looked at the possibility of limiting the variable ranges. This resulted in a reduction in the degrees of freedom noted in the reactive system problem structure, thereby resulting in a more manageable workspace (Fornari, Rotstein, & Stephanopoulos, 1989). The feasible search space identified can be further reduced using the reaction stoichiometry, allowing for a more concise search space to be developed.

The concerns that were noted with this framework, however, lie in the lengthy time period needed to conduct this analysis, thereby reducing its practical applications. Furthermore, the thermodynamic feasibility was considered based on the energy flow entering and leaving the reactive system, determined by the stoichiometric ratio. Therefore, this assumes a complete conversion in the reactive system, which is highly unlikely in an industrial setting. This lowers the accuracy and usability of the development.

When considering temperature as a factor in feasibility, as with the thermodynamic models previously discussed, it is imperative that the cost of the unit operations needed to achieve this temperature also be considered, as this plays a vital role in the economic feasibility of the process. This would assist in calculating other economic factors such as the payback period, as well as securing potential investments in the plant's development. Unfortunately, this was not accounted for within the developed thermodynamic frameworks.

### 4. Extending the Framework Beyond Thermodynamic Feasibility

To address the concerns raised on the existing analysis frameworks a research study aimed to extend the procedures beyond thermodynamics. In 1994, screening factors were integrated into the developed frameworks, accounting for economics and process safety. This looked at economics from an input/output perspective (Fornari & Stephanopoulos, 1994). The concern with this work, however, was the extent to which economic feasibility was considered, not accounting for the cost of the unit operations required to achieve the operating conditions. It is likely that whilst the economic feasibility of an input-output structure may exhibit a profit, this profit may be insufficient to pay off the unit operations within meaningful timeframes. Alternatively, it is possible that a portion of the product may be lost during the separation process, resulting in losses to the production rate. The screening mechanism utilized here was a manual procedure, which can be lengthy, increase the risk of human error, and reduce the efficiency and practicality of using this analysis procedure.

In 1997, Buxton and colleagues looked at the integration of environmental criteria into the analysis framework. By doing so, this investigation aimed to minimize the waste exiting a process structure at an early stage in its design. Additionally, the framework developed here looked at the economic feasibility of the process structure as well, with the objective function being to find a draw-off between both environmental and economic gains offered by the process structure (Buxton, Livingston, & Pistikopoulos, 1997).

The environmental considerations within this framework focused on only the reactants and products (Buxton, Livingston, & Pistikopoulos, 1997). By not extending the bounds beyond that of the main process structure, the framework does not account for the environmental impact of the energy required to operate the necessary unit operations. The energy requirements of a chemical process can be very extensive, thereby playing a massive role in its economic and environmental feasibility. The extent of the economic feasibility analysis conducted within this framework only considered the profitability of a process structure from an input-output perspective. Additionally, the reactions considered in the framework developed by Buxton and colleagues, looked at reactant to product stoichiometry, not accounting for the conversion achieved in the reactive system.

This is a major limiting assumption as complete conversion is a rare occurrence in any chemical process, especially those that have been scaled up to commercial production rates, thereby limiting the practical application of the framework.

A framework developed by Li and colleagues in 2000, also exhibited similar shortcomings to that previously noted, with economic feasibility only being considered on an input-output basis. Also, this framework aimed to find alternative reaction routes to produce the same product, with the main objective function being to minimize the number of intermediates produced in the reactive system (Li et al., 2000).

Whilst this may appear beneficial at a first glance, it is possible that a reactant could be converted to a more reactive state before forming the product, thereby resulting in a more efficient process, or higher conversions, than what would have been noted using a direct synthesis route. Therefore, the use of such an objective function can eliminate a vast array of reaction routes which may exhibit higher feasibilities.

Also, in 2000, Li and co-workers developed a hierarchy design approach for reactive systems, accounting for the economic and thermodynamic feasibility of the reactive system. In this approach, pathways that exhibited economic feasibility, but were not thermodynamically feasible, were broken down into multiple intermediary reactions. The objective function when breaking down reaction pathways into intermediary reactions was to achieve a reactive system that exhibits an overall thermodynamic and kinetic feasibility (Li, et al., 2000).

This framework exhibits similar shortcomings to the previous developments, with the reactive system only being considered from a stoichiometric point of view, not accounting for conversion. Furthermore, the input-output economic feasibility does not consider the cost of unit operations. The hierarchy approach developed was a manual approach, necessitating that each reactive system be analysed individually. This is time consuming, and increases the risk of human error, especially when translating data between different calculation platforms.

## 5. Using the P-Graph in Determining Reaction Pathway Systems

The process graph, also known as P-graph, is a direct bipartite graph that can be utilized to represent process superstructures, with the optimum process configuration being a subset of the P-graph superstructure. The P-Graph (Figure 1) offers multiple advantages over its predecessors in that it contains two vertices allowing for users to distinguish between unit operations and material flow (Friedler, et al., 1992). Before the development of the P-Graph, processes were represented by digraphs and signal flow diagrams, containing only a single vertex, making it hard to distinguish between material flows and unit operations (Palmer & Chung, 2000).

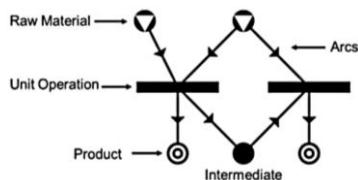


Figure 1: Diagrammatic representation of a basic P-Graph

Amongst its many applications, the P-graph has also been extended to reactive systems (Fan & Friedler, 1997). Optimizing a reaction pathway, in terms of its operating conditions, or even the comparison of multiple reaction pathways, as discussed in this article, requires knowledge of the reaction kinetics. Reaction kinetics are highly dependent on the reaction mechanism, i.e., the route taken to convert the reactant into the desired product.

In 2001, Fan and his colleagues utilized the P-graph to determine the possible reaction mechanisms for a catalytic reaction. The advantage of utilizing the P-graph in such an application is that it can allow for the user to account for all possible intermediaries that may be produced over the course of this reaction (Fan, et al., 2001). This investigation was verified later that year by Seo and his colleagues (Seo, et al., 2001).

In 2012, Barany and co-workers aimed to confirm the usefulness and ability of the P-graph to account for all possible reaction routes/mechanisms. During this investigation, linear algebraic approaches were utilized in conjunction with a reactive system, with the combinations and results being compared to that of the P-graph. This validated that the P-graph can produce a complete search space (Barany, et al., 2012).

An investigation conducted in 2018, utilized the P-graph as a means by which to generate all possible reaction mechanisms for the methanation of CO<sub>2</sub>. This research made use of the reaction block concept, whereby common intermediates that are not found in any other sub-reaction are grouped together, allowing these sub-reactions to be treated as a single reaction. In doing so, the workflow in the P-graph software is reduced, resulting in more efficient problem solving (Diaz-Alvarado, Miranda-Perez, & Grossmann, 2018).

The search space that was obtained from the P-graph was then compared with experimental data to find the commonalities in intermediates produced along the reaction routes, thereby allowing for the potential reaction mechanism search space to be reduced (Diaz-Alvarado, Miranda-Perez, & Grossmann, 2018).

The concern with this work, however, was that it focused on determining the reaction mechanism applicable to the system, rather than utilizing the P-graph in determining the optimum reaction pathway focused on the production of a single product, or a set of products. This limitation prevented the application of the P-graph to the development of new chemical plants, and the optimization of existing chemical plants.

The applications of the P-graph were furthered, by introducing the concept of feasibility and reaction startability into the superstructure. Reaction startability ensures that reactive systems are only considered as a possibility if they can proceed using only the starting materials available. This prevents intermediary reactions from being classified as an independent reactive system within the P-graph structure (Lakner, Bertok, & Friedler, 2018). Feasibility, on the other hand, was determined by the possibility of a reaction taking place, thereby not accounting for conversion, economic or environmental criteria. This is a major concern when looking at the practicality of a reactive system and its potential implementation in an industrial setting.

In 2022, Tapia and co-workers aimed to combine the P-graph framework with attainable region (AR) theory, to find optimal and near-optimal reaction pathways during process integration. The developed framework employed a heat, work and mole balance. To sufficiently account for the molar flow rates, reactants and products were broken up into their elemental compositions and represented in the P-graph (Tapia et al., 2022).

The developed P-graph was evaluated by means of the Solution Structure Generation (SSG) algorithm, to determine the number of possible pathways to attain the final product, with the optimal pathway being determined by the Accelerated Branch-and-Bound (ABB) algorithm. The advantage of pairing the AR theory with the P-graph framework is that the analysis can provide a more holistic insight, beyond that of the graphical approach typically taken by AR theory (Tapia et al., 2022).

However, the concern with this development lies in the scope considered, only accounting for feasibility in terms of the reaction pathway and its heat requirements. This development does not account for the cost of the unit operations before, and after, the reactor system, as well as the necessary separation systems. Furthermore, this framework does not consider economic benefits of the optimal reaction pathway – an important factor in determining the viability of the process. Additionally, this framework structure requires the user to physically draw out the P-graph maximal structure, opening the door to potential human error.

Another effort aimed at improving the usability and automation of the P-graph framework, looked at combining the P-graph with Python programming acting as an interface. Not only did this development aid in automation, but also allows for new algorithms to be incorporated into the P-graph framework, broadening its use and adaptability to different chemistry and engineering problems (Teng et al., 2022).

## 6. Determining the Optimum Reaction Pathway via Search Space Reduction Criteria

One possible methodology in which the previously defined frameworks could be expanded to incorporate the economic and environmental feasibility of the reactive system is using search space reduction criteria. This was employed in an investigation conducted by Al-Fadhli and his colleagues in 2018, where a multi-period network was considered using a feed stream of hydrogen, carbon dioxide, and oxygen. The advantage of multi-period process structures is that it can account for variations in the demand of certain products over different time periods throughout the year, thereby maximizing the potential profit (Al-Fadhli, et al., 2018).

This framework aimed to focus on the conversion of carbon dioxide to value added products, utilizing both environmental and economic criteria for the analysis of reactive systems (Al-Fadhli, et al., 2018). The shortcoming of this work, however, was that the framework can only be applied to analyse already existing chemical plants. The information required for this analysis encompassed the mass and energy balances of the chemical plant, as well as the costs and sizes of the associated unit operations.

When utilizing the aforementioned information, each scenario is analysed on a case-by-case basis. The major concern with this type of approach is that it cannot be utilized in the development of a new chemical plant, as much of this information would not be available. Furthermore, the manual nature of the framework can result in the analysis time being very lengthy, with a high risk of human error. When analysing scenarios on a case-by-case basis, it may become very difficult to amend the search space of reaction pathways, necessitating that the entire framework be restarted when including newly developed reactive systems.

In 2020, a systematic framework was developed by Jugmohan and colleagues determined the optimum reaction pathway through search space reduction. This framework aimed to address the shortcomings previously raised within this review article. The systematic framework developed employed a Reaction Pathway Database (RPD) and could focus on the production of a single product, or multiple products, with the advantage of being able to determine the optimum reaction pathway before extensive design procedures (Jugmohan, et al., 2020).

Additionally, the benefit of this systematic framework is that it considers both economic and environmental benefits, finding a draw off between these two criteria. The framework utilized a generic process flowsheet structure (Figure 2), allowing for the consideration of the conversion of each reactive system, the separation processes required, the unit operations needed to achieve the reaction and separation conditions, as well as a rough payback period for these units (Jugmohan, et al., 2020).

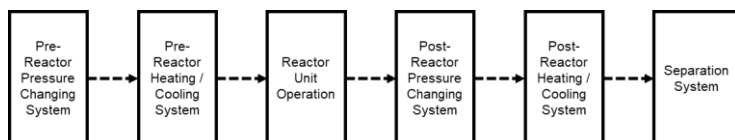


Figure 2: Generic process flow sheet structure utilized by Jugmohan, et al., (2020)

The shortcoming of the framework was that it utilized four different software platforms, namely Aspen Plus®, P-Graph Studio®, Microsoft® Excel and MATLAB®. This raises two main concerns. The first is the accessibility and affordability of these platforms, with software such as Aspen Plus® having high licensing costs. Secondly, the framework required the manual transfer of data between software platforms, leading to a high risk of human error and the framework being time-consuming. The manual transfer of data does not allow for changes to be made to the reactive systems, with any change resulting in the entire framework needing to be restarted.

Another concern noted was that the process design within Aspen Plus® was a manual procedure, increasing the likelihood of inconsistencies in the plant structure. Such inconsistencies would render comparisons inaccurate. The framework developed by Jugmohan, et al. (2020) utilized the costing and design of a single type of unit operation, with all units being constructed from stainless steel. This may not be advantageous, as it is likely that an alternative unit operation could provide the same functionality at a reduced cost.

In 2021, Jugmohan, et al. aimed to address these shortcomings by developing a novel, automated systematic synthesis framework tool (ASSF tool). This tool was coded into a single platform, eliminating the need for multiple software, or the manual transfer of data. Furthermore, the level of data required to operate the ASSF tool is low, in comparison to other software platforms such as Aspen Plus®. The ASSF tool simply requires the stoichiometric reaction equation, experimental conversions noted, operating conditions, feed stoichiometric ratios, and the catalyst (Jugmohan, Van der Merwe, & Bwalya, 2021). The uses of the ASSF tool are vast, encompassing quick chemical plant simulations, determining the optimum operating conditions for a reaction pathway using experimental data, analysing, designing, and reducing a reaction pathway search via economic and environmental criteria (Jugmohan, Van der Merwe, & Bwalya, 2021).

The ASSF tool allows for theoretically feasible reactive systems to be identified before any extensive design procedures, with the final search space being ranked in order of viability. This was applied to a 22-reactive system RPD developed by Jugmohan, et al. (2020). Whereas the manual analysis time required in 2020 was approximately 10 months, the ASSF tool was able to analyse this RPD within 5 hours, highlighting its efficacy. The advantage of such an automated tool is that all design procedures are coded into the background, with the user only needing to input the current economic data, specifications of unit operations, and the RPD. Should the specifications of the unit operations not be available the ASSF tool does contain default values. This reduces the prior training requirements associated with this tool, increasing its practicality and usability.

## 7. Conclusion & Future Work

In conclusion, multiple developments have been made in determining the optimal reaction pathway prior to extensive design procedures, with recent years focusing on employing an automated approach. Such approaches reduce the likelihood of human error in the design and optimization of new/existing chemical plants. Future work could potentially involve the integration of artificial intelligence into the frameworks, allowing for the latest reaction and technological developments to be extracted and implemented in real time. This allows for the RPD to remain up to date, increasing the accuracy of the analysis. Additionally, future developments should attempt to incorporate recycle streams into the generic process design. Whilst not found in every process, recycles can be imperative in improving the economic and environmental feasibility of a process structure.

## Acknowledgements

This work was supported by the Council for Scientific and Industrial Research (CSIR), South Africa, through special initiatives grant funding and Graduate in Training support for Jaimee Jugmohan.

## References

- Al-Fadhli, F. M., Mukherjee, R., Wang, W., & El-Halwagi, M. M. (2018). Design of Multiperiod C-H-O Symbiosis Networks. *ACS Sustainable Chemistry and Engineering*, 6(7), 9130-9136.
- Barany, M., Bertok, B., Imreh, C., Fan, L. T., & Friedler, F. (2012). On the equivalence of direct mechanisms and structurally minimal pathways. *Journal of Mathematical Chemistry*, 50(5), 1347-1361.
- Buxton, A., Livingston, A. G., & Pistikopoulos, E. N. (1997). Reaction Path Synthesis for Environmental Impact Minimization. *Computers & Chemical Engineering*, 21, S959-S964.
- Crevaschi, S. (2015). A perspective on process synthesis: Challenges and prospects. *Computers and Chemical Engineering*, 81, 130-137.
- Diaz-Alvarado, F. A., Miranda-Perez, J., & Grossmann, I. E. (2018). Search for reaction pathways with P-graphs and reaction blocks: Methanation of carbon dioxide with hydrogen. *Journal of Mathematical Chemistry*, 56, 1011-1102.
- Fan, L. T., & Friedler, F. (1997). *Reaction Pathway Analysis by a Network Synthesis Technique*. LA, USA.
- Fan, L. T., Bertok, B., Friedler, F., & Shafie, S. (2001). Mechanisms of ammonia-synthesis reaction revisited with the aid of a novel graph-theoretic method for determining candidate mechanisms in deriving the rate law of a catalytic reaction. *Hungarian Journal of Industrial Chemistry*, 29(1), 71-80.
- Fornari, T., & Stephanopoulos, G. (1994). Synthesis of Chemical Reaction Paths: Economic and Specification Constraints. *Chemical Engineering Communications*, 129(1), 159-182.
- Fornari, T., Rotstein, E., & Stephanopoulos, G. (1989). Studies on the synthesis of chemical and reaction paths - II Reaction schemes with two degrees of freedom. *Chemical Engineering Science*, 44(7), 1569-1579.
- Friedler, F., Tarjan, K., Huang, Y. W., & Fan, L. T. (1992). Graph-theoretic approach to process synthesis: Axioms and Theorems. *Chemical Engineering Science*, 47(8), 1973-1988.
- Govind, R., & Power, G. J. (1977). *A Chemical Engineering View of Reaction Pathway Synthesis*. ACS Symposium Series, 61.
- Jugmohan, J., Majazi, T., North, B., & Mukoma, P. (2020). *Systematic Synthesis Framework for the Generation of CO<sub>2</sub> and H<sub>2</sub> Sinks: The P-Graph Approach*. Johannesburg: University of the Witwatersrand.
- Jugmohan, J., Van der Merwe, J., & Bwalya, M. (2021). *Development of a Tool for Determining and Evaluating the Most Optimal Reaction Pathway Systems: Converting Carbon Dioxide to Methanol and Dimethyl Ether*. Johannesburg: University of the Witwatersrand.
- Lakner, R., Bertok, B., & Friedler, F. (2018). Synthesis of startable reaction pathways. *Chemical Engineering Transactions*, 70, 1129-1134.
- Li, M., Hu, S., Li, Y., & Shen, J. (2000). A Hierarchical Optimization Method for Reaction Path Synthesis. *Industrial & Engineering Chemistry Research*, 39, 4315-4319.
- Li, M., Hu, S., Li, Y., & Shen, J. (2000). Reaction path synthesis for a mass closed-cycle system. *Computers and Chemical Engineering*, 24, 1215-1221.
- Palmer, C., & Chung, P. W. (2000). Created Signed Directed Graph Models for Process Plants. *Industrial & Engineering Chemistry Research*, 39(7), 2548-2558.
- Rotstein, E., Resasco, D., & Stephanopoulos, G. (1982). Studies on the Synthesis of Chemical Reaction Paths - I: Reaction Characteristics in the (G,T) Space and a Primitive Synthesis Procedure. *Chemical Engineering Science*, 37(9), 1337-1352.
- Seo, H., Lee, D. Y., Park, S., Fan, L. T., Shafie, S., Bertok, B., & Friedler, F. (2001). Graph-Theoretical identification of pathways for biochemical reactions. *Biotechnology Letters*, 23, 1551-1557.
- Smith, R., & Linnhoff, B. (1988). The design of separators in the context of overall processes. *Chemical Engineering Research and Design*, 195-228.
- Chew K.H., Klemeš J.J., Wan Alwi S.R., Abdul Manan Z., 2013, Industrial implementation issues of Total Site Heat Integration, *Applied Thermal Engineering*, 61, 17–25.
- Klemeš J.J. (Ed), 2013, *Handbook of Process Integration (PI): Minimisation of Energy and Water Use, Waste and Emissions*, Woodhead Publishing Limited, Cambridge, UK.
- Klemeš J.J., Varbanov P., Lam H.L., 2009, Water Footprint, water recycling and Food Industry Supply Chain, Chapter In: K Waldron (Ed.), *Waste management and co-product recovery in food processing*, Vol 2, Woodhead Publishing Limited, Cambridge, UK, 134 – 168.
- Raissi K., 1994, *Total site integration*, PhD Thesis, University of Manchester Institute of Science and Technology, Manchester, UK.
- Tapia, J.F.D., Evangelista, D. G., Aviso, K.B., & Ran, R.R., P-graph Attainable Region Technique (PART) for Process Synthesis. *Chemical Engineering Transactions*, 94, 1159-1164
- Teng, S.Y., Orosz, A., How, B.S., Pimentel, J., Friedler, F., & Jansen, J.J. (2022). Framework to embed machine learning algorithms in P-graph: Communication from the chemical process perspectives. *Chemical Engineering Research and Design*, 188, 265-270.