Safe Optimization of Potentially Runaway Reactions: from Fedbatch to Continuous Stirred Tank type reactor

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Abstract

A great variety of processes of both fine chemical and pharmaceutical industries are commonly carried out in semibatch reactors (SBRs). Most of such synthesises often involve strongly exothermic and very fast reactions where the control of the heat evolution is achieved thanks to the combined effect of a dedicated cooling system and the feeding of a "cold" (mostly, ambient temperature) co-reactant. For these types of process, the well known phenomenon of "thermal runaway" can take place. Accordingly to the ever increasing market requests, the desired goal of whatever enterprise is to increase the productivity of a certain product being sure of maintaining safe operating conditions during all the synthesis steps. This is a very hard task which can be performed by changing the reactor operating mode from semibatch to continuous. A continuous reactor can achieve the same productivity of a discontinuous reactor using significantly lower reaction volumes; this means that the intrinsic safety of the process is increased. In this work, the switch from a semibatch reactor to a series of continuous stirred tank reactors has been investigated using as a case study the nitration of N-(2-Phenoxyphenyl) methane sulphonamide. Particularly, after the determination of the most effective number of reactors in the series and their effective volumes, dynamical simulations have been carried out in order to guarantee that possible thermal instabilities are not generated during the synthesis in both the start up and the normal exercise phases.

Keywords: nitration reactions; shift to a continuous process; process intensification; runaway reactions; series of continuous reactors.

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1. Introduction

A wide variety of synthesis typical of both pharmaceutical and fine chemical industries involve fast and strongly exothermic reactions. This type of processes may lead to a well known hazardous phenomenon called “thermal runaway”, where the temperature control of the synthesis reactor is lost whenever the rate at which the cooling system is able to remove the heat generated by the synthesis reactions is lower than that at which the heat is released by the reactions themselves (Copelli et al., 2014a). Therefore, in order to mitigate the effects due to the high rate of heat release, these processes are typically carried out in fed discontinuous reactors, that is semibatch (SB) reactors, in which one of the reactants (the so-called co-reactant) is dosed on a previously loaded mixture (Maestri et al., 2009a). In this way, the combined effect related to both the slow addition of a “cold” inlet stream (the dosed reactant) and the presence of a dedicated cooling system allows to keep under control the reactor temperature.

Particularly, many studies concerning the identification of the so-called "runaway boundary" (that is, the set of design and operating parameters at which there is the triggering of a runaway phenomenon) have been carried out, since the first pioneering studies of Semenov (Varma et al., 1999) on isothermal BRs, on all the four classes of ideal reactor types.

Focusing on SBRs (which are the most used in fine chemical and pharma industry), all the works aimed at identifying explicitly and generally the runaway boundary dealt almost exclusively with SBRs operating in the isoperibolic temperature control mode, where a single reaction occurred (Hugo and Steinbach, 1985; Steensma and Westerterp, 1988; Van Woezik and Westerterp, 2001; Westerterp and Molga, 2004; Maestri and Rota, 2005; Copelli et al., 2010). The only criterion able to treat multireacting systems and different types of temperature control modes was the parametric sensitivity criterion (Morbidelli and Varma, 1988; Varma et al., 1999). The drawback of such a criterion was its implicitness; in fact, it is not possible to determine whether the system is in a runaway state by simply analyzing the value of its constitutive parameters. Later, it was developed a general method of thermal runaway detection: the divergence criterion (Copelli et al., 2014a; Zaldívar et al., 2003; Zaldívar et al., 2005), which stated that whether, during any time interval, the dynamic system of ordinary differential equations (ODEs) that describes the process exhibits a positive divergence, the system is operating under runaway conditions. Therefore, being note the constitutive parameters of the model, it is straightforward calculating the divergence.

Although these methods are very effective in the identification of the runaway boundary, they both share the problem of not being able to define operating conditions that are, at the same time, both safe and productive. This problem has been partially solved, for SBRs, using safe-optimization criteria, such as the topological criterion (Copelli et al., 2011) or the combined method of boundary and temperature diagrams (Maestri et al., 2009b); however, when a strong intensification of the process is required, such criteria can not be used successfully. In fact, as a response to the ever pressing market requests in terms of both productivity and competitiveness increase, process engineers have been pushed towards the exploration of the possibility of using reactors which were more performing than SB (Copelli et al., 2017).

Therefore, with the main aim of eliminating dead times (which are unavoidable in a discontinuous process), one of the simplest solutions is using a series of Continuous Stirred Tank Reactors (CSTRs). Such a choice possesses a number of practical advantages: first of all, the structure of the vessels is the same of a SBR; then, in a series of CSTRs, the desired product is produced continuously, allowing for increasing both the productivity and the product quality in terms of its reproducibility (as a matter of fact, production lots can not be identified); moreover, reaction rates in a CSTR are lower than those ones in a corresponding SB reactor.

The only drawbacks are: 1) the presence of death times during both start-up and shut-down with a consequent product lost; and, 2) safety problems during the start-up phase of an exothermic system, where liquid level fluctuations may trigger runaway phenomena because of an erroneous intervention of the temperature control system. Moreover, depending on the start up procedure,

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significantly higher reaction rates than during steady state operating conditions may be observed: this could be critical from a safety point of view.

Studies on the determination of the runaway boundaries for a CSTR are known since the early ‘40s: in fact, at that time, it was well known that a non-isothermal CSTR might exhibit steady-state multiplicity (that is, different steady-state temperatures according to different values of its constitutive parameters). In 1941, Zeldovich published some works containing the complete classification of both limit points and isolated branches for a CSTR referring to a temperature – conversion plane (Zeldovich, 1941; Zeldovich and Zysin, 1941): particularly, he identified the character of all the steady-state solutions in terms of thermal stability and he used it in order to determine critical conditions. In 1955, Bilous and Amundson published a work (Bilous and Amundson, 1955) where they investigated the thermal behavior of a CSTR basing entirely on steady-state multiplicity considerations. Particularly, only a few steady states are stable, i.e., such that small perturbations lead to small changes in the thermal response of the system, with a tendency to deplete perturbations carrying forward to the initial condition; other operating conditions are unstable, i.e., such that the result of a minimum disturbance is that the system tends to move away from the steady state.

Successively, the behavior of a potentially runaway CST system has been rationalized using both stability analysis and bifurcation theory for complex nonlinear systems (Chang and Schmitz, 1975; Wirges, 1980; Ball and Gray, 2013). The dynamic analysis of this type of systems has showed that, accordingly to small changes in the initial conditions, or in the constitutive parameters of the system, both cyclic and extremely rapid variations in the behavior of the system itself can be found. Recent studies (Pellegrini and Biardi, 1990; Perez and Albertos, 2004; Molnár et al., 2004) have also underlined the importance of a complete characterization of the thermal behavior of a CST system: particularly, they have developed and analyzed (using bifurcation theory) dynamical

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models for a controlled CSTR, identifying clearly runaway boundaries (testing both steady and unsteady state operating conditions).

Anyway, according to the authors' knowledge, no literature studies concerning both the complete thermal characterization of a series of complex controlled CSTRs during transient operating conditions and the safe intensification of a target process has been done.

Therefore, the main aim of this work was finding a suitable criterion to select the most effective operating conditions for the safe start-up of an effective configuration of CSTRs determined using a literature safe-optimization method (Copelli et al., 2017). The proposed procedure has been applied to a potentially runaway system, that is the synthesis of N-(4-nitro, 2-phenoxyphenyl) methane sulphonamide (also note as nimesulide, NIM).

Results showed that a considerable reduction of the production volumes (e.g., one order of magnitude) and, contextually, an increase of the productivity (in this case, doubling) can be achieved without compromising the process safety.

2. Proposed Methodology

A series of CSTRs can be considered a good compromise between both safety and productivity point of view. However, moving a process from discontinuous to continuous reactors requires:

1) selecting a suitable procedure to identify the optimal configuration of the CSTRs series (that is, the number of CSTRs in the series, the volume of each reactor and the dosing policy of the original SB co-reactant);

2) identifying safe and productive operating conditions (both for start-up and steady state phases) under which the potentially runaway synthesis can be safely run.

The last point is crucial because, dealing with a potentially runaway system, the complex interactions among dosing policy of co-reactant, reaction kinetics and temperature/reactor level control system can generate strong temperature oscillations during the start up phase.

2.1 Identification of the optimal configuration of CSTRs series

A procedure suitable to estimate the number of CSTRs in a series and the volume of each reactor as a function of a selected dosing policy has been already discussed elsewhere (Copelli et al., 2017); therefore, it is only briefly summarized in the following.

If a series of NR CSTRs where a single reaction of the type:

$$A \; + \; B \; \rightarrow products \tag{1a}$$

with:

$$r = k(T) \cdot [A]^a \cdot [B]^b \tag{1b}$$

is operated under the hypothesis of isothermal steady state conditions (this means that all the volumetric flow rates ($F_{out,n}$, $F_{in,n}$; see Figure 1) are equal to their set-point values), the reactor/jacket energy balance and all the control equations (temperature, level) can be neglected and, consequently, the only material balance can be used to derive the relative conversion of species A in each reactor *i* of the series ($\zeta_{A,i}$) as:

$$\begin{aligned} F_{out,0} \cdot [A]_0 \cdot \prod_{i=1}^{NR-1} (1-\zeta_{A,i}) = k \cdot \left(\frac{F_{out,0}}{F_{out,NR}} \cdot [A]_0 \cdot \prod_{i=1}^{NR} (1-\zeta_{A,i}) \right)^a \cdot \left(\frac{1}{F_{out,NR}} \cdot \prod_{i=1}^{NR} F_{in,i} \cdot [B]_{in,i} \cdot (1-\alpha_i \cdot \zeta_{A,i}) \right)^b \cdot V \\ + F_{out,0} \cdot [A]_0 \cdot \prod_{i=1}^{NR} (1-\zeta_{A,i}) \end{aligned} \tag{2}$$

where:

$$\alpha_i = \frac{F_{out,i-1} \cdot [A]_{i-1}}{\left(F_{out,i-1} \cdot [B]_{i-1} + F_{in,i} \cdot [B]_{in,i} \right)} \tag{2a}$$

represents the ratio between the molar flow rate of A (main reactant) and B (co-reactant) entering the i-th reactor (which depends on the dosing policy; in fact, superimposing different values at $F_{in,i}$, or $[B]_{in,i}$, different dosing policies can be realized – Copelli et al., 2017).

The global conversion (at the outlet of the last reactor) can be calculated as:

$$\zeta_{end} = 1 - \prod_{i=1}^{NR} (1-\zeta_{A,i}) \tag{3}$$

Analogously to the case of a SBR, we can define the productivity as:

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$$P = F_{out,0} \cdot [A]_0 - F_{out,NR} \cdot [A]_{NR} \tag{4}$$

The optimum number of CSTRs in the series (NR) and the volume of each reactor (V) can be determined iteratively by superimposing the following constraints:

1) $\zeta_{end} \geq \zeta_{\min}$ (5a)

2) $P = P_{set}$ (5b)

where $\zeta_{\min}$ is the minimum desired conversion to be obtained at the outlet of the reactors series and P_{set} is the desired productivity of the CSTRs series. In the optimization algorithm, the search for the minimum volume of the reactors is subjected to a condition: when two conversion values satisfy Eq.(5a), if there is a conversion corresponding to a slightly larger volume but a lower number of reactors in the series, such a value is automatically selected.

2.2 Identification of safe and productive operating conditions

Once a suitable configuration of the series of CSTRs is selected, it is necessary to define a safe start-up procedure. This calls for the development of an unsteady state model of the CSTRs series, which should be able to simulate the plant start up. Using such a model, the runaway boundaries can be determined using a suitable runaway criterion to verify whether a selected start-up procedure is safe or not.

Accordingly, in this work, the parametric sensitivity criterion, proposed by Morbidelli and Varma (Varma et al., 1999), has been used together with a corollary. The concept of parametric sensitivity was firstly introduced by Barkelew (1959) to characterize the behavior of a system extremely sensitive to small variations in its constitutive parameters. Unlike the concept of instability, in this case it is possible to unambiguously correlate the resulting offset to the entity of the assigned perturbation. Given a generic system described, in the simplest case, by a single equation as (6):

$$\frac{dy}{dt} = f(y, \phi, t) \tag{6}$$

where ϕ is the array containing m input parameters, t is time, f is a continuous differentially function and $y(\phi,t)$ is the system solution (which is unique under the previous hypothesis), continuous in ϕ and in time; it is possible to define the so-called objective normalized sensitivity through the following Eq. (7):

$$S(I,\phi_j)=\frac{\phi_j}{I}\cdot\frac{\partial I(t,\phi_j)}{\partial\phi_j} \tag{7}$$

where I is the objective function, that is a function of the system variables (y), such as the maximum temperature detected in a continuous reactor during the start-up phase.

According to the Varma and Morbidelli criterion (Varma et al., 1999), the boundary between the area of thermal explosion and that of the non-explosive behavior is located where the system becomes sensitive to small variations in the initial reactor temperature: the region of parametric sensitivity critical from the point of view of thermal runaway is that at which the modulus of the normalized sensitivity with respect to the maximum temperature reaches the maximum value. This criterion is also applicable to continuous stirred reactors, even in the case of a multiplicity of steady state solutions.

From the idea underlined in the criterion of Morbidelli and Varma, it is possible to derive an important consideration: if the parametric sensitivity of the maximum temperature of a system is equal to zero (in practical terms, it is minor than a very small value ε_j depending on the j-th parameter) for all NP values of the parameters considered in the analysis, the system operates in conditions intrinsically safe from the point of view of the thermal stability (Alós et al., 1998). This statement can be written as:

$$S(T_{\max},\phi_j)=\frac{\phi_j}{T_{\max}}\cdot\frac{\partial T_{\max}(t,\phi_j)}{\partial\phi_j}\leq\varepsilon_j \qquad for \qquad \forall j=1:NP \tag{8}$$

The physical meaning of Eq. (8) is that a relative change in the parameter ϕ_j would induce a relative change in the $T_{\max}$ value ε_j times lower:

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$$\frac{\Delta T_{\max}(t,\phi_j)}{T_{\max}} \le \varepsilon_j \cdot \frac{\Delta \phi_j}{\phi_j} \tag{9}$$

It is clear that when ε_j = 0, changes in the ϕ_j value are not able to induce any change in the $T_{\max}$ value. Provided that the value of $T_{\max}$ is acceptable (that is, $T_{\max}$ < MAT, where MAT is the Maximum Allowable Temperature – Maestri et al., 2006), the system is intrinsically safe.

In practical systems, ε_j is always larger than zero (in absolute value); however, relations (8) and (9) provide a guideline for selecting safe values for the parameters ϕ_j. In fact, on one side it is evident that the lower the ε_j value is, the safer the system will be; on the other hand, the value of ε_j for a given paramter ϕ_j can be used to decide whether a given relative variation can lead to dangerous situations. In fact, from Eq. (9) follows that:

$$\Delta T_{\max}(t,\phi_j) \le T_{\max} \cdot \varepsilon_j \cdot \frac{\Delta \phi_j}{\phi_j} \tag{10}$$

A given relative variation $\Delta\phi_j / \phi_j$ cannot lead to hazardous conditions as far as:

$$T_{\max} + \Delta T_{\max}(t,\phi_j) \le T_{\max}\left(1 + \varepsilon_j \cdot \frac{\Delta \phi_j}{\phi_j}\right) \le MAT \tag{11}$$

It is important to note that for the series of CSTRs considered in this work, such a set of operating conditions are not only safe but also optimal because the productivity of the system at the steady state has been set a priori through the procedure discussed in the previous section. It is therefore possible to use Eq. (11) to calculate a set of operating conditions to be used for the start-up procedure which is intrinsically safe.

3. Case study

Statistics show that nitrations are among the chemical processes most frequently involved in accidents (Cardillo, 1998). This occurs because, under certain conditions, nitric acid can oxidize most of the organic molecules with the development of large quantities of harmful gases. Generally, this behavior takes place at high temperatures and it is favored by the presence of an accumulation of nitric acid during the synthesis.

Among the several nitration processes described in the literature (Maestri et al., 2009b; Maestri et al., 2006; Zaldívar et al., 1995; Lunghi et al., 2002; Copelli et al., 2014b), in this work, the relevant case study of the nitration of N-(2-Phenoxyphenyl) methane sulphonamide (FAM) to N-(4-nitro, 2-phenoxyphenyl) methane sulphonamide (NIM) was considered as case study. Such a process is carried out industrially in an indirectly cooled SBR (with a typical nominal volume of 12.5 m^3) where a 65% w/w nitric acid aqueous solution is added to a 20% w/w acetic acid solution of FAM, previously loaded into the reactor (see Table 1 for a typical industrial recipe together with its target operating parameters).

The stoichiometry of the main reaction can be expressed as in Eq. (1), where species A is FAM and species B is the nitric acid; moreover, the reaction is supposed to occur in a homogeneous liquid phase. The most important process and thermochemical properties of this system are summarized in Table 2; more details can be found elsewhere (Maestri et al., 2006).

The reaction is usually carried out in isothermal temperature control mode (with a set-point temperature of about 80 °C), by dosing the nitric acid in a time equal to about 2 h in order to operate at least 20-30 °C below the Maximum Allowable Temperature (MAT) of the system. The MAT value can be assumed equal to the acetic acid boiling point (120 °C) because no decompositions of the final reacting mixture has been observed under 220 °C (Maestri et al., 2006). Moreover, reactor temperatures above 90-92 °C are highly undesirable because of the possible triggering of local nitric acid boiling and decomposition.

Using such operating conditions, a full conversion of FAM to NIM is achieved just after the end of the dosing period (see Figure 2A, where the conversion of FAM vs. time, as predicted by the SBR version of the mathematical model reported in Appendix, is shown). In spite of the presence of a control system that should keep the temperature close to 80 °C, an isoperibolic-like temperature

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profile can be noticed (see Figure 2B, where the reactor temperature is reported as a function of time): this behavior is due to the high reaction exothermicity which makes difficult the temperature control (see Figure 2C, where the jacket temperature is reported as a function of time). Anyway, the reactor temperature is always in a range of about ±5 °C and a desired productivity of about 215 kg_{NIM} h^{-1} (the total process time is about 400 min, considering also the dead times due to the reactor loading and unloading together with the cleaning operation) is achieved. Such temperature ranges, conversion and productivity values are in perfect agreement with those ones desired from an industrial point of view (see Table 1).

4. Results and discussion

Let us consider the occurrence of a new market request: "doubling of the original desired productivity (which was, 215 kg_{NIM} h^{-1})". One solution could be the switch to a continuous operating mode, while maintaining the same process set-point temperature to avoid both changes in the characteristics of the desired product and the triggering of secondary reactions. This would enhance the intrinsic safety of the process by reducing the reaction volumes (and therefore the reactants hold-up) and increasing the effectiveness of the heat exchange during the synthesis.

In the following, the results of the methodology proposed in section 2 applied to the selected case study are reported.

4.1 Identification of the optimal configuration of CSTRs series

The optimum number of CSTRs in the series (NR) and the volume of each reactor (V) can be determined iteratively by superimposing the following constraints (which correspond to the industrial desired values of process variables and productivity, see Table 1):

$$\zeta_{end} \geq 0.95 \tag{12a}$$

$$P = 2P_{SB} \approx 430 \quad kg \cdot h^{-1} \tag{12b}$$

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Since the basic idea is to mime the behavior of a SBR with a series of CSTRs, the post-dosing reaction time in the SBR can be recovered by eliminating the feed of the co-reactant B in the last CSTR of the series, which consequently behaves as a work-out reactor.

The result of this procedure is: $V = 0.25$ m^3 and $NR = 2$. Using such a configuration, under the hypothesis of isothermal CSTRs series (this means that the request on the desired reactor temperature range is automatically satisfied), the conversion at the outlet of the work-out reactor (ζ_{end}) is equal to 0.95; while the maximum relative conversion achieved in the first reactor of the series ($\zeta_{A,1}$) is 0.86.

In this case, as the optimal number of reactors in the series is equal to 2 and the second reactor is for work-out, the dosing policy of the co-reactant B is unimportant: all the nitric acid is dosed in the first reactor.

It is important to comment about the applicability of such a solution in terms of costs (both capital and operating/safety). Since a detailed analysis is beyond the aim of this work only a simple consideration will be provided. In general, the investment (initial fixed costs) for a discontinuous reactor is relatively low with respect to the continuous counterpart (comparable reactor size); there are, however, higher variable costs of operation and the automation is difficult and expensive to apply. This roughly means that, if a sufficient reduction of the volumes of the reactors in the continuous configuration is achieved (about one order of magnitude), a series of CSTRs could be more attractive than the corresponding SB counterpart.

4.2 Identification of safe start-up conditions

According to the procedure detailed in section 4.1, the previously determined configuration of the CSTRs series permits to shift from a SB to a continuous process without penalizing the desired degree of conversion and productivity; but no information about the thermal stability of the system under both steady and unsteady state operating conditions are available (as the system has been assumed isothermal). In order to identify the operating conditions under which the previously

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determined configuration of the CSTRs series is thermally stable (both start-up and steady state operations), a mathematical model able to simulate its dynamical behavior is required (see the Appendix for the details). Particularly, simple control loops for adjusting both the liquid level in the reactors and the reactor outlet flow rates, as well as a complex control loop for either the reactor or the jacket temperature control with the possibility to operate both under isothermal and isoperbolic temperature control mode were implemented in the model.

Therefore, such a model can be used to predict all the operational phases of the CSTR series, namely:

- the start-up mode, or Phase 1, which should minimize the time to make the plant operational by ensuring, at the same time, that it does not operate in unstable conditions (that is, guaranteeing the process safety);

- the steady state operation mode, or Phase 2, where a constant product quality is dispensed from the outlet of the last reactor of the series;

- the shutdown mode, or Phase 3, which is not critical in terms of safety but it is useful for analyzing the system shutdown times and the characteristics of the wastes to be safely stored while awaiting their disposal.

During Phase 1, to avoid long transients and / or the triggering of runaway phenomena (possibly caused by liquid level fluctuations within the reactors), the following operational procedure was investigated:

1- Filling the reactors one by one with the FAM solution at storage temperature (25 °C); open the outlet valve of each reactor to fill the next, or starting to empty the work-out reactor, only when the liquid level in a given reactor is at the 90% of its set-point value; during such a phase the preferred temperature control mode is the isoperibolic one with a set point temperature of the coolant equal to 80 °C;

2- when the set-point level is reached in the work-out reactor, shifting the temperature control mode to isothermal and waiting for the set-point temperature of each reactor to be reached;

3- activating the nitric acid supply (nitric acid is supplied only to the first reactor of the series, in a stoichiometric amount, with a volumetric flow rate increasing from 0 to its steady state value in a given time, t_{ramp}.

The mathematical model reported in Appendix can be used to perform a preliminary parametric sensitivity analysis on the optimal configuration of the CSTR series by perturbing the system parameters deemed most significant from the point of view of their possible influence on the thermal stability of the process, namely: ramp time of nitric acid (t_{ramp}), set-point temperature of the reactors (T_{set}), static gain (K_p) and reset time (K_i) of the temperature controllers, and global heat transfer coefficient (U).

The results of these analyses are summarized in Figure 3, where the objective normalized sensitivity of the maximum temperature observed in both reactor 1 and 2 with respect to the previous parameters is shown. Note that, only the maximum sensitivity coefficients were reported in the figure to better highlight which parameters are the most relevant. We can see that the most influencing parameters are the set-point temperature of each reactor and the dosing ramp time. This means that such parameters must be carefully selected to assure the thermal stability of the system.

As previously discussed, it is also necessary to select a set of operating parameters (ϕ_j) which satisfy Eq. (11) in order to find safe and productive operating conditions for the proposed reactors configuration.

Figures from 4A to 4E show the trends of the objective sensitivity coefficients with respect to the most deemed system parameters. Looking at Figure 4A, it is possible to notice that the sensitivity coefficients for both reactor 1 and 2 become lower than 5e-3 (in absolute value) when the dosing ramp time is larger than about 2400 s. This means that, considering the first reactor, even halving the ramp dosing time (that is, $\Delta t_{ramp}/t_{ramp} \approx$ -5e-1) leads to a $\Delta T_{\max,1}/T_{\max,1} \leq$ 2.5e-3, which is a

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$\Delta T_{\max,1}$ of the order of 1 K (analogously, it is possible to calculate $\Delta T_{\max,2}$ equal to about 2 K). Providing that $T_{\max,1}$ and $T_{\max,2}$ are far enough from the MAT, these conditions are expected to be quite robust with respect to small changes in the t_{ramp} value. On the contrary, if values of t_{ramp} lower than 1200 s are selected, dangerous situations can occur because sensitivity coefficients are relatively high and can induce significant $\Delta T_{\max,1}$ and $\Delta T_{\max,2}$. As the sake of example, shifting from a t_{ramp} value equal to 500 s to a value of 240 s, both $\Delta T_{\max,1}$ and $\Delta T_{\max,2}$ are about 13 K also providing $T_{\max,1}$ and $T_{\max,2}$ not far enough from the MAT: this means unsafe start-up conditions.

An ad hoc consideration is required for the set-point temperature of each reactor of the series. As shown in Figure 4B, the sensitivity coefficients increase continuously as the set-point temperature of the reactors increases in the range of operating temperatures which are eligible for this reaction. However, the changes in the value of the sensitivity coefficients are quite small, being always of the order of 2e-1. This means that a 5 K variation in the set-point temperature would lead to a $\Delta T_{\max,1}$ or $\Delta T_{\max,2}$ of 5 K. Therefore, the set-point temperature was set equal to that used in the discontinuous plant, that is 80 °C.

Observing Figure 4C (that one referring to the effects of the static gain of the temperature controller, K_p), it is possible to note that the sensitivity coefficients are always lower than 1.5e-2 (in absolute value). This means, according to Eq. (11), that even doubling the value of K_p (e.g. from 6 to 12) $\Delta T_{\max,1}$ is equal to about 1 K while $\Delta T_{\max,2}$ is equal to about 2 K. This confirms that the value typically used for the SB process (that is 6) can be used also for the CSTR series. Analogously, looking at Figure 4D (that one referring to the effects of the reset time of the temperature controller, K_i), it is possible to see that the sensitivity coefficients never exceed the value of 7e-3. This means that $\Delta T_{\max,2}$ is always lower than 0.25 K even halving the original K_i value of the SB process (which was 3600 s) while $\Delta T_{\max,1}$ is about 1 K. Therefore, K_i has been set equal to 3600 s as in the SB configuration. Finally, concerning Figure 4E (that one referring to the effects of the global heat transfer coefficient, U), the sensitivity coefficients are always lower than 3.5e-2. This imply that, whether a value of U higher than 500 W/(m^2 K) but lower than 1000 W/(m^2 K) is selected, the corresponding $\Delta T_{\max,1}$ is about 2 K while $\Delta T_{\max,2}$ is about 1 K.

Summarizing, from this analysis, it is possible to conclude that the most important operating parameter that can be manipulated in order to achieve safe start-up conditions is the dosing ramp time. Particularly, dosing ramp times higher than 2400 s can be considered intrinsically safe; below such a value, the system progressively starts to enter the runaway region (see Figure 4A). In section 4.3 and 4.4 two limiting cases, (a) no dosing ramp and (b) suitable dosing ramp on nitric acid are discussed, demonstrating that the proposed sensitivity analysis on the optimum continuous configuration of the CSTR series is suitable for a safe process intensification.

4.3 Start up policy 1: no dosing ramp on nitric acid

The trends of the main operating variables computed using a zero dosing ramp time are shown in Figures 5A to D. The durations of the different phases (see also the Appendix) are reported in Table 3: the start-up (1, step 1 to 4) and shut-down (3) phases are effectively those ones of the actual operation of the plant, while the duration of the steady state operation phase (2) has been reduced to 6 hours to facilitate its graphical representation.

From Figure 5A it is possible to observe that the liquid levels inside the reactors increase in steps 1 to 3, during which the reactors are loaded with a constant flow rate of FAM solution. The filling of the reactors is adjusted so that the exiting valve of each reactor is opened only when the liquid level reaches 90% of the set-point. The level remains constant during the dosing ramp of the second line reagent (step 4) and the steady state operating step (phase 2) while it decreases rapidly when, during the shut-down (phase 3), all the supply streams are closed and the exiting valves at the bottom of each reactor are opened.

Observing Figure 5B, it can be noted that maximum relative conversions of about 0.97 and 0.70 are reached, respectively, in the first and the second reactor of the series. Such conversion values lower to 0.84 and 0.26, respectively, under steady state conditions. This is due to the thermal behavior of the CSTRs series under this start up policy. In fact, the analyzed reaction is very fast and strongly exothermic, so that the reactors are equipped with an external cooling jacket whose control system manipulates the inlet coolant temperature for maintaining the set-point value. The control system maintains the jacket temperature constant (isoperibolic mode) during the start-up (steps 1-3) and shut-down; while, the dosing ramp of nitric acid (step 4) and the subsequent steady operation phase are controlled in isothermal mode.

It is possible to note from Figure 5C and D that the temperatures of the reactors and the cooling fluids remain constant throughout the steps from 1 to 3. At the beginning of step 4, the exothermic reaction starts and the temperatures inside the reactors increase sharply; consequently the control systems activate by reducing the inlet coolant temperatures (up to their saturation values: that is, an inlet coolant temperature equal to 15 °C - see Figure 5D), so as to bring back the temperature of each reactor to its set-point value. It is important to note that, for both reactors 1 and 2, it is not possible to keep the reactor temperature close to its set-point (80 °C) because of the huge reaction exothermicity (see Figure 5C). Particularly, the offset is so high (more than 30 °C) which can be considered too dangerous for an industrial synthesis of this type.

Such results are well confirmed by the fact that a zero dosing ramp time on nitric acid lies in the fully runaway region according to the sensitivity analysis performed in section 4.2.

4.4 Start up policy 2: suitable dosing ramp on nitric acid

Following the results obtained in paragraph 4.2, a dosing ramp time for nitric acid equal to 2400 s was selected.

During the synthesis the previously described phases and steps are maintained (see paragraph 4.3). The new durations of all the different phases are detailed in Table 4: even in this case, the start-up

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(1) and shut-down (3) phases are effectively those ones of the actual operation of the plant, while the duration of the steady state operation phase (2) was reduced to 6 hours to facilitate its graphical representation.

The trends of the main operating variables using these operating conditions are shown in Figures 6A to C.

From Figure 6A, it is possible to observe that the relative conversions inside each reactor rise sharply during the transient (that is, step 4) to reach their steady state values. Also in this case, the control system maintains the jacket temperature constant (isoperibolic mode) during the start-up (steps 1 to 3) and shut-down; while, the dosing ramp of nitric acid (step 4) and the subsequent steady operation phase are controlled using an isothermal mode. It is possible to note that the temperatures of the reactors and the inlet coolant remain constant throughout steps 1 to 3. At the beginning of step 4, because of the exothermic reaction triggering, the temperatures inside the reactors tend to increase; consequently the control systems activate by reducing the inlet coolant temperatures, so as to bring back the temperature of each reactor to its set-point value (that is, 80 °C). It is important to note that, for reactor 1 it is not possible to keep the reactor temperature at its set-point (80 °C) because of the huge reaction exothermicity. However, in this case, the offset is quite small (below 6 °C) and can be considered safe from an industrial point of view.

Therefore, it is possible to conclude that, using a suitable dosing ramp time – that is, 2400 s – found through a modified sensitivity analysis (see both section 2.2 and section 4.2), the reactors configuration selected using a simple steady state optimization procedure (reported in sections 2.1 and 4.1) can be used without penalizing neither the productivity nor the number of reactors in the series.

5. Conclusions

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The main aim of this work has been to discuss a criterion able to classify the intrinsic safety of a set of operating conditions (for continuous processes) already classified as optimal from the point of view of the desired productivity.

To this end, a dynamic model suitable to simulate the desired process on a full-plant scale has been implemented with an input-output logic for system variables management. Such a model has been proved to be particularly effective for the characterization of the role of the input parameters disturbances on the output variables.

A sensitivity analysis also allowed to determine the parameters that most influenced the maximum temperature inside the reactors.

The analysis revealed that the parameters that have the greatest impact on the process are the set point temperature of each reactor and the dosing ramp time. However, a selected continuous plant configuration can be made practically intrinsically stable by considering a suitable dosing ramp time that it can be easily determined using a corollary of the parametric sensitivity criterion (that is, Eq. (11)).

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Nomenclature

a	order of reaction for component A, -
A	generic reactant (main reactant)
ArH	Aromatic hydrocarbons
b	order of reaction for component B, -
B	generic reactant (co-reactant)
$\hat{c}_p$	specific heat capacity, kJ/(mol·K)
$CSTR$	Continuous Stirred Tank Reactor
D	reactor diameter, m
Da	$= k_{rif} \cdot \left([A]_0^{\,a-1} \cdot [B]_{in}^{\,b}\right)$, Damköhler number, -
FAM	N-(2-Phenoxyphenyl) methane sulphonamide
F	generic function / volumetric flowrate, m^3/s
I	generic objective function, see Eq. 7
K_I	reset time, s
K_P	Static gain, -
K	micro-kinetic constant, $m^3/(kmol \cdot s)$
K_∞	pre-exponential factor, $m^{3(a+b-1)}/\ (kmol^{(a+b-1)} \cdot s)$
k_{rif}	$= k_\infty \cdot \exp\left(-\frac{E_{att}}{RT_{rif}}\right)$,kinetic constant at T_{rif}, $m^{3(a+b-1)}/\ (kmol^{(a+b-1)} \cdot s)$
L	liquid level, m
l_i	$= \frac{L_i}{L_{set}}$ dimensionless liquid level of the i-th reator, -
MAT	Maximum Allowable Temperature, K
M	mass, kg
NIM	Nimesulide
NP	Number of parameters, -
NR	number of CSTR reactors in the series, -
NTU_j	$= \frac{U \cdot \pi D \cdot L_{set}}{\hat{\rho}_W \cdot \hat{c}_{p,W} \cdot V_j}$, Number of Transfer Units relative to the reactor jacket, -
N	number of moles, kmol
P	Productivity, mol/s
Q	Heat flowrate, W
R_{Hi}	$= \frac{\hat{\rho}_i \cdot \hat{c}_{p,i}}{\hat{\rho}_{i+1} \cdot \hat{c}_{p,i+1}}$, Heat capacity ratio for the i-th reactor, -
$R_{H,in,1}$	$= \frac{\hat{\rho}_{in} \cdot \hat{c}_{p,in}}{\hat{\rho}_1 \cdot \hat{c}_{p,1}}$, Heat capacity ratio for the nitric acid to the first reactor, -
S	objective normalized parametric sensitivity function
SBR	Semibatch reactor
T	time, s
T	temperature, K
U	overall heat transfer coefficient, $kW/(m^2K)$
V	volume, m^3

V	$= \dfrac{F_{out,i}}{F_{out,0}}$ dimensionless volumetric flow rate, -
Wt_i	$= \dfrac{4 \cdot U}{\hat{\rho}_1 \cdot \hat{c}_{p,1} \cdot D}$,Westertep number relative to the i-th reactor, -
Y	generic target function, see Eq. 6

Subscripts and superscripts

0	inlet to first reactor
1	first reactor
2	second reactor
A	component A/FAM (reactant)
Ad	Adiabatic
Cool	Coolant
End	end of the relative step
I	i-th reactor
In	inlet of reactor/jacket
J	jacket/ j-th parameter (see Eq. 7)
L	level, related to the controller parameters
Max	Maximum
Min	Minimum
NIM	Nimesulide
Out	outlet of reactor/jacket
ramp	ramp of temperature/flowrate
Rif	Reference
Rxn	Reaction
SB	Semibatch
Set	setpoint for a controlled variable
step	step of reaction (from step 1 to step 4)
T	temperature, related to the controller parameters
W	Water

Greek symbols

α	flowrate ratio of A/FAM and B/NIM
ε	generic small value,-
$\zeta_{A,i}$	$= \dfrac{F_{out,i-1} \cdot [A]_{i-1} - F_{out,i} \cdot [A]_i}{F_{out,i-1} \cdot [A]_{i-1}}$ conversion of FAM in the i-th reactor, -
θ_{set}	$= \dfrac{V_{set}}{F_{out,i}}$, inverse of the residence time, 1/s
κ_i	$= \exp\left(\dfrac{E_{att}}{RT_{rif}} \left(1 - \dfrac{1}{\tau_i} \right) \right)$, dimensionless rate constant for the i-th reactor, -

$\hat{\rho}$	molar density, kmol/m^3
ϕ	sensitivity parameters array
τ_i	$= \dfrac{T_i}{T_{rif}}$ dimensionless temperature of the i-th reactor, -

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Appendix

In the following all the material and energy balance equations, complemented by suitable control equations for level and temperature control, will be reported in order to simulate the nitration of FAM to NIM.

A.1 Liquid Level and Volumetric Flow Rates Control Equations

As previously detailed, the start up phase (Phase 1) of the CSTRs series comprises a number of steps aimed at fulfilling the reactors one by one until the desired dimensionless set-point level ($l_{set} = 1$) is reached in each of them. Such steps can be expressed using the following dimensionless global material balances (see dimensionless liquid levels in reactor 1, l_1, and 2, l_2) and outlet volumetric flow rates control equations (see $v_{out,1}$ and $v_{out,2}$ variables):

STEP 1 (Loading of Reactor 1)

$$\begin{cases} \dfrac{dl_1}{dt} = \dfrac{v_{out,0}}{\theta_{set}} \\ \dfrac{dl_2}{dt} = 0 \\ \dfrac{dv_{out,1}}{dt} = 0 \\ \dfrac{dv_{out,2}}{dt} = 0 \end{cases} \quad if \quad 0 \le t < t\left(l_1 = 0.9 \cdot l_{set}\right) = t_{end,step1} \tag{A1}$$

STEP 2 (Loading and unloading of Reactor 1, loading of Reactor 2)

$$\begin{cases} \dfrac{dl_1}{dt} = \dfrac{1}{\theta_{set}} \cdot \left(v_{out,0} - v_{out,1}\right) \\ \dfrac{dl_2}{dt} = \dfrac{v_{out,1}}{\theta_{set}} \\ \dfrac{dv_{out,1}}{dt} = K_{pL,set1} \cdot \left[\dfrac{dl_1}{dt} - \dfrac{1}{K_{iL}} \cdot \left(1 - l_1\right)\right] \\ \dfrac{dv_{out,2}}{dt} = 0 \end{cases} \quad if \quad t_{end,step1} \le t < t\left(l_2 = 0.9 \cdot l_{set}\right) = t_{end,step2} \tag{A2}$$

STEP 3 (Simultaneous loading and unloading of Reactor 1 and 2)

$$\begin{cases} \dfrac{dl_1}{dt} = \dfrac{1}{\theta_{set}} \cdot \left(v_{out,0} - v_{out,1} \right) \\ \dfrac{dl_2}{dt} = \dfrac{1}{\theta_{set}} \cdot \left(v_{out,1} - v_{out,2} \right) \\ \dfrac{dv_{out,1}}{dt} = K_{pL,set1} \cdot \left[\dfrac{dl_1}{dt} - \dfrac{1}{K_{iL}} \cdot \left(1 - l_1 \right) \right] \\ \dfrac{dv_{out,2}}{dt} = K_{pL,set1} \cdot \left[\dfrac{dl_2}{dt} - \dfrac{1}{K_{iL}} \cdot \left(1 - l_2 \right) \right] \end{cases} \quad if \quad t_{end,step2} \le t < t_{end,step3} \tag{A3}$$

The initial conditions for such equations are:

$$I.C. \qquad t = 0 \qquad l_1 = l_2 = v_{out,1} = v_{out,2} = 0$$

The meaning of all the symbols is reported in the Nomenclature section.

After step 3 is completed ($t = t_{end,step3}$) and the correct set-point temperature is reached in all the reactors of the series, the nitric acid (reactant B) dosing can start (step 4). In a real plant a certain time interval is always required in order to achieve the set-point value of whatever controlled variable; in this case, the time imposed to reach the set-point volumetric flow rate of reactant B was indicated as t_{ramp}.

Particularly, during step 4 the following equations must be used:

$$\begin{cases} \dfrac{dl_1}{dt} = \dfrac{1}{\theta_{set}} \cdot \left(\dfrac{\hat{\rho}_0}{\hat{\rho}_1} + \dfrac{\hat{\rho}_{in}}{\hat{\rho}_1} \cdot \dfrac{v_{in,set}}{t_{ramp}} \cdot \left(t - t_{end,step3} \right) - v_{out,1} \right) \\ \dfrac{dl_2}{dt} = \dfrac{1}{\theta_{set}} \cdot \left(\dfrac{\hat{\rho}_1}{\hat{\rho}_2} \cdot v_{out,1} - v_{out,2} \right) \\ \dfrac{dv_{out,1}}{dt} = K_{pL,set1} \cdot \left[\dfrac{dl_1}{dt} - \dfrac{1}{K_{iL}} \cdot \left(1 - l_1 \right) \right] \\ \dfrac{dv_{out,2}}{dt} = K_{pL,set1} \cdot \left[\dfrac{dl_2}{dt} - \dfrac{1}{K_{iL}} \cdot \left(1 - l_2 \right) \right] \end{cases} \quad if \quad t_{end,step3} \le t < t_{end,step4} \tag{A4}$$

It is possible to notice the activation of a dosing ramp for reactant B in reactor 1 (see the first equation of the series); the dimensionless volumetric flow rates control equations are unchanged.

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After the end of nitric acid ramp ($t = t_{end,step4}$), steady state conditions for liquid levels and volumetric flow rate exiting from the reactors of the series start. It is important to state that such conditions can not be considered the effectively steady state conditions of the CSTRs series: in fact, in order to reach the effective steady state, the global conversion of FAM must be checked. Simply, for times higher than $t_{end,step4}$, the following equations hold on:

$$\begin{cases} \dfrac{dl_1}{dt} = \dfrac{1}{\theta_{set}} \cdot \left(\dfrac{\hat{\rho}_0}{\hat{\rho}_1} + \dfrac{\hat{\rho}_{in}}{\hat{\rho}_1} \cdot v_{in,set} - v_{out,1} \right) \\ \dfrac{dl_2}{dt} = \dfrac{1}{\theta_{set}} \cdot \left(\dfrac{\hat{\rho}_1}{\hat{\rho}_2} \cdot v_{out,1} - v_{out,2} \right) \\ \dfrac{dv_{out,1}}{dt} = K_{pL,set1} \cdot \left[\dfrac{dl_1}{dt} - \dfrac{1}{K_{iL}} \cdot (1 - l_1) \right] \\ \dfrac{dv_{out,2}}{dt} = K_{pL,set1} \cdot \left[\dfrac{dl_2}{dt} - \dfrac{1}{K_{iL}} \cdot (1 - l_2) \right] \end{cases} \quad if \quad t_{end,step4} \le t < t_{shut-down} \qquad \text{(A5)}$$

Finally, when the series of CSTRs must be shut down, all the inlet stream must be stopped and the liquid level set-point value for each reactor must be set equal to zero; consequently:

$$\begin{cases} \dfrac{dl_1}{dt} = -\dfrac{v_{out,1}}{\theta_{set}} \\ \dfrac{dl_2}{dt} = -\dfrac{v_{out,2}}{\theta_{set}} \\ \dfrac{dv_{out,1}}{dt} = K_{pL,set1} \cdot \left[\dfrac{dl_1}{dt} + \dfrac{l_1}{K_{iL}} \right] \\ \dfrac{dv_{out,2}}{dt} = K_{pL,set1} \cdot \left[\dfrac{dl_2}{dt} + \dfrac{l_2}{K_{iL}} \right] \end{cases} \quad if \quad t \ge t_{shut-down} \qquad \text{(A6)}$$

4.2.2 Partial and Global Conversions of FAM

Concerning the determination of the partial conversion of FAM to NIM in the reactors of the series, during all the steps from 1 to 3 such a conversion is always zero, because the lack of the co-reactant supply. Therefore, it follows:

$$\begin{cases} \dfrac{d\zeta_{A,1}}{dt} = 0 \\ \dfrac{d\zeta_{A,2}}{dt} = 0 \end{cases} \quad if \quad 0 \le t < t_{end,step3} \tag{A7}$$

with the corresponding initial conditions:

$$I.C. \qquad t = 0 \quad \zeta_{A,1} = \zeta_{A,2} = 0$$

Just after the starting of step 4, due to the nitric acid supply in the first reactor of the series (activation of the corresponding dosing ramp), both the partial conversions of FAM ($\zeta_{A,1}$ and $\zeta_{A,2}$) in each reactor and the global one at the work-out outlet (ζ_{end}) start to change according to the following equations:

$$\begin{cases} \dfrac{d\zeta_{A,1}}{dt} = -\dfrac{1}{\theta_{set}} \cdot \dfrac{v_{out,1} \cdot \zeta_{A,1}}{l_1} - \dfrac{\left(1-\zeta_{A,1}\right)}{v_{out,1}} \cdot \dfrac{dv_{out,1}}{dt} + \dfrac{1}{l_1} \cdot \dfrac{dl_1}{dt} \cdot \left(1-\zeta_{A,1}\right) \\ + Da \cdot \kappa_1 \cdot \dfrac{\left(1-\zeta_{A,1}\right)^a}{v_{out,1}{}^{a-1}} \cdot \left(\dfrac{v_{in,set}}{v_{out,1}} \cdot \dfrac{\left(t - t_{end,step3}\right)}{t_{ramp}} \cdot \left(1 - \alpha_1 \cdot \zeta_{A,1}\right) \right)^b \\ \dfrac{d\zeta_{A,2}}{dt} = -\dfrac{1}{\theta_{set}} \cdot \dfrac{v_{out,2}}{l_2} \cdot \zeta_{A,2} + \dfrac{1}{l_2} \cdot \dfrac{dl_2}{dt} \cdot \left(1-\zeta_{A,2}\right) - \dfrac{\left(1-\zeta_{A,2}\right)}{v_{out,2}} \cdot \dfrac{dv_{out,2}}{dt} - \dfrac{d\zeta_{A,1}}{dt} \cdot \dfrac{\left(1-\zeta_{A,2}\right)}{\left(1-\zeta_{A,1}\right)} + \\ + Da \cdot \kappa_2 \cdot \dfrac{\left(1-\zeta_{A,1}\right)^{a-1} \cdot \left(1-\zeta_{A,2}\right)^a \cdot \left(1-\alpha_1 \cdot \zeta_{A,1}\right)^b \cdot \left(1-\alpha_2 \cdot \zeta_{A,2}\right)^b \cdot \left(v_{in,set} \cdot \dfrac{\left(t - t_{end,step3}\right)}{t_{ramp}} \right)^b}{v_{out,2}{}^{a+b-1}} \end{cases} \tag{A8}$$

$$if \quad t_{end,step3} \le t < t_{end,step4}$$

where:

$$\alpha_1 = \frac{[A]_0}{v_{in,set} \cdot \dfrac{\left(t - t_{end,step3}\right)}{t_{ramp}} \cdot [B]_{in}} \tag{A8a}$$

$$\alpha_2 = \frac{[A]_0 \cdot \left(1-\zeta_{A,1}\right)}{v_{in,set} \cdot \dfrac{\left(t - t_{end,step3}\right)}{t_{ramp}} \cdot [B]_{in} \cdot \left(1 - \alpha_1 \cdot \zeta_{A,1}\right)} \tag{A8b}$$

$$\zeta_{end} = 1 - \left(1-\zeta_{A,1}\right) \cdot \left(1-\zeta_{A,2}\right) \tag{A8c}$$

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Even in this case, the meaning of all the variables, dimensionless groups and constitutive parameters is reported in the Nomenclature section.

Of course, after the completion of the dosing ramp, Eq. (A8) simplify accordingly to the following:

$$\begin{cases} \dfrac{d\zeta_{A,1}}{dt} = -\dfrac{1}{\theta_{set}} \cdot \dfrac{v_{out,1} \cdot \zeta_{A,1}}{l_1} - \dfrac{\left(1-\zeta_{A,1}\right)}{v_{out,1}} \cdot \dfrac{dv_{out,1}}{dt} + \dfrac{1}{l_1} \cdot \dfrac{dl_1}{dt} \cdot \left(1-\zeta_{A,1}\right) \\ + Da \cdot \kappa_1 \cdot \dfrac{\left(1-\zeta_{A,1}\right)^a}{v_{out,1}{}^{a-1}} \cdot \left(\dfrac{v_{in,set}}{v_{out,1}} \cdot \left(1-\alpha_1 \cdot \zeta_{A,1}\right)\right)^b \\ \dfrac{d\zeta_{A,2}}{dt} = -\dfrac{1}{\theta_{set}} \cdot \dfrac{v_{out,2}}{l_2} \cdot \zeta_{A,2} + \dfrac{1}{l_2} \cdot \dfrac{dl_2}{dt} \cdot \left(1-\zeta_{A,2}\right) - \dfrac{\left(1-\zeta_{A,2}\right)}{v_{out,2}} \cdot \dfrac{dv_{out,2}}{dt} - \dfrac{d\zeta_{A,1}}{dt} \cdot \dfrac{\left(1-\zeta_{A,2}\right)}{\left(1-\zeta_{A,1}\right)} + \\ + Da \cdot \kappa_2 \cdot \dfrac{\left(1-\zeta_{A,1}\right)^{a-1} \cdot \left(1-\zeta_{A,2}\right)^a \cdot \left(1-\alpha_1 \cdot \zeta_{A,1}\right)^b \cdot \left(1-\alpha_2 \cdot \zeta_{A,2}\right)^b \cdot \left(v_{in,set}\right)^b}{v_{out,2}{}^{a+b-1}} \end{cases} \tag{A9}$$

$$if \quad t_{end,step4} \le t < t_{shut-down}$$

Finally, during the reactors unloading it is reasonable to suppose that conversion can not vary anymore, therefore it is possible to write:

$$\begin{cases} \dfrac{d\zeta_{A,1}}{dt} = 0 \\ \dfrac{d\zeta_{A,2}}{dt} = 0 \end{cases} \qquad if \quad t \ge t_{shut-down} \tag{A10}$$

4.2.3 Reactor and Jacket Energy Balance Equations and Temperature Control Equation

During all the steps from 1 to 3, the reactors loadings and unloadings are carried out under an isoperibolic temperature control mode. Consequently:

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$$\left\{\begin{aligned}
&\frac{d\tau_1}{dt}=\frac{1}{\theta_{set}}\cdot\frac{v_{out,0}}{l_1}\cdot\left(\tau_0-1\right)-\frac{1}{\theta_{set}}\cdot\frac{v_{out,1}}{l_1}\cdot\left(\tau_1-1\right)-Wt_1\cdot\left(\tau_1-\tau_{j,1}\right)-\frac{\tau_1}{l_1}\cdot\frac{dl_1}{dt}\\
&\frac{d\tau_2}{dt}=\frac{1}{\theta_{set}}\cdot\frac{v_{out,1}}{l_2}\cdot\left(\tau_1-1\right)-\frac{1}{\theta_{set}}\cdot\frac{v_{out,2}}{l_2}\cdot\left(\tau_2-1\right)-Wt_2\cdot\left(\tau_2-\tau_{j,2}\right)-\frac{\tau_2}{l_2}\cdot\frac{dl_2}{dt}\\
&\frac{d\tau_{j,1}}{dt}=\frac{1}{\theta_j}\cdot\left(\tau_{j,in,1}-\tau_{j,1}\right)+NTU_j\cdot l_1\cdot\left(\tau_1-\tau_{j,1}\right)\\
&\frac{d\tau_{j,2}}{dt}=\frac{1}{\theta_j}\cdot\left(\tau_{j,in,2}-\tau_{j,2}\right)+NTU_j\cdot l_2\cdot\left(\tau_2-\tau_{j,2}\right)\\
&\frac{d\tau_{j,in,1}}{dt}=-K_{pT}\cdot\left[\frac{d\tau_{j,1}}{dt}-\frac{1}{K_{iT}}\cdot\left(\tau_{j,set}-\tau_{j,1}\right)\right]\\
&\frac{d\tau_{j,in,2}}{dt}=-K_{pT}\cdot\left[\frac{d\tau_{j,2}}{dt}-\frac{1}{K_{iT}}\cdot\left(\tau_{j,set}-\tau_{j,2}\right)\right]
\end{aligned}\right. \qquad \text{(A11)}$$

$$if \quad 0\le t<t_{end,step3}$$

where the first and fourth equations express the reactor energy balance for the first and second reactor, respectively; the second and fifth equations express the jacket energy balance for the first and second reactor, respectively; and, the third and sixth equations express the reactor temperature control mode actually used.

Initial conditions are:

$$I.C. \qquad t=0 \quad \tau_1=\tau_2=\tau_0,\;\; \tau_{j,1}=\tau_{j,2}=\tau_{j,set},\;\; \tau_{j,in,1}=\tau_{j,in,2}=\tau_{j,set}$$

Starting from step 4, that is when the nitric acid dosing ramp is activated, the previous equations are modified accordingly to the following:

$$
\begin{cases}
\dfrac{d\tau_1}{dt} = \dfrac{R_{H,0}}{\theta_{set}} \cdot \dfrac{(\tau_0 - 1)}{l_1} + \dfrac{R_{H,in,1}}{\theta_{set,in}} \cdot \dfrac{(\tau_{in} - 1)}{l_1} - \dfrac{1}{\theta_{set,1}} \cdot \dfrac{(\tau_1 - 1)}{l_1} - \dfrac{\tau_1}{l_1} \cdot \dfrac{dl_1}{dt} + \dfrac{\Delta\tau_{ad,1}}{\theta_{set}} \cdot \dfrac{\zeta_{A,1}}{l_1} - \dfrac{\Delta\tau_{ad,1}}{l_1} \cdot \dfrac{dl_1}{dt} \cdot \dfrac{(1-\zeta_{A,1})}{v_{out,1}} + \\
+ \dfrac{\Delta\tau_{ad,1}}{v_{out,1}} \cdot \dfrac{d\zeta_{A,1}}{dt} + \Delta\tau_{ad,1} \cdot \dfrac{(1-\zeta_{A,1})}{(v_{out,1})^2} \cdot \dfrac{dv_{out,1}}{dt} - Wt_1 \cdot (\tau_1 - \tau_{j,1}) \\
\dfrac{d\tau_2}{dt} = \dfrac{R_{H,1}}{\theta_{set,1}} \cdot \dfrac{(\tau_1 - 1)}{l_2} - \dfrac{1}{\theta_{set,2}} \cdot \dfrac{(\tau_2 - 1)}{l_2} - \dfrac{\tau_2}{l_2} \cdot \dfrac{dl_2}{dt} + \dfrac{\Delta\tau_{ad,2}}{\theta_{set}} \cdot \dfrac{(1-\zeta_{A,1}) \cdot \zeta_{A,2}}{l_2} \\
- \dfrac{\Delta\tau_{ad,2}}{l_2} \cdot \dfrac{dl_2}{dt} \cdot \dfrac{(1-\zeta_{A,1}) \cdot (1-\zeta_{A,2})}{v_{out,2}} + \Delta\tau_{ad,2} \cdot \dfrac{(1-\zeta_{A,1}) \cdot (1-\zeta_{A,2})}{(v_{out,2})^2} \cdot \dfrac{dv_{out,2}}{dt} + \Delta\tau_{ad,2} \cdot \dfrac{(1-\zeta_{A,2})}{v_{out,2}} \cdot \dfrac{d\zeta_{A,1}}{dt} + \\
+ \Delta\tau_{ad,2} \cdot \dfrac{(1-\zeta_{A,1})}{v_{out,2}} \cdot \dfrac{d\zeta_{A,2}}{dt} - Wt_2 \cdot (\tau_2 - \tau_{j,2}) \\
\dfrac{d\tau_{j,1}}{dt} = \dfrac{1}{\theta_j} \cdot (\tau_{j,in,1} - \tau_{j,1}) + NTU_j \cdot l_1 \cdot (\tau_1 - \tau_{j,1}) \\
\dfrac{d\tau_{j,2}}{dt} = \dfrac{1}{\theta_j} \cdot (\tau_{j,in,2} - \tau_{j,2}) + NTU_j \cdot l_2 \cdot (\tau_2 - \tau_{j,2}) \\
\dfrac{d\tau_{j,in,1}}{dt} = -K_{pT} \cdot \left[\dfrac{d\tau_1}{dt} - \dfrac{1}{K_{iT}} \cdot (\tau_{set} - \tau_1) \right] \\
\dfrac{d\tau_{j,in,2}}{dt} = -K_{pT} \cdot \left[\dfrac{d\tau_2}{dt} - \dfrac{1}{K_{iT}} \cdot (\tau_{set} - \tau_2) \right]
\end{cases}
\qquad \text{(A12)}
$$

$$
if \quad t_{end,step3} \le t < t_{shut-down}
$$

Note that an isothermal temperature control mode is activated and the effects of the reaction exothermicity can be easily traced.

Finally, during the shut down phase, the isoperibolic temperature control mode is used again.

$$
\begin{cases}
\dfrac{d\tau_1}{dt} = -\dfrac{1}{\theta_{set}} \cdot \dfrac{v_{out,1}}{l_1} \cdot (\tau_1 - 1) - Wt_1 \cdot (\tau_1 - \tau_{j,1}) - \dfrac{\tau_1}{l_1} \cdot \dfrac{dl_1}{dt} \\
\dfrac{d\tau_2}{dt} = -\dfrac{1}{\theta_{set}} \cdot \dfrac{v_{out,2}}{l_2} \cdot (\tau_2 - 1) - Wt_2 \cdot (\tau_2 - \tau_{j,2}) - \dfrac{\tau_2}{l_2} \cdot \dfrac{dl_2}{dt} \\
\dfrac{d\tau_{j,1}}{dt} = \dfrac{1}{\theta_j} \cdot (\tau_{j,in,1} - \tau_{j,1}) + NTU_j \cdot l_1 \cdot (\tau_1 - \tau_{j,1}) \\
\dfrac{d\tau_{j,2}}{dt} = \dfrac{1}{\theta_j} \cdot (\tau_{j,in,2} - \tau_{j,2}) + NTU_j \cdot l_2 \cdot (\tau_2 - \tau_{j,2}) \\
\dfrac{d\tau_{j,in,1}}{dt} = -K_{pT} \cdot \left[\dfrac{d\tau_{j,1}}{dt} - \dfrac{1}{K_{iT}} \cdot (\tau_{j,set} - \tau_{j,1}) \right] \\
\dfrac{d\tau_{j,in,2}}{dt} = -K_{pT} \cdot \left[\dfrac{d\tau_{j,2}}{dt} - \dfrac{1}{K_{iT}} \cdot (\tau_{j,set} - \tau_{j,2}) \right]
\end{cases}
\quad if \quad t \ge t_{shut-down} \qquad \text{(A13)}
$$

As a consequence of the assumption made in Eq. (A10), the thermal effects due to the reaction can be neglected.