On-Line Optimization of a Batch Reaction – Development and Experimental Demonstration

S. Samir Alam, R. Russell Rhinehart, Karen A. High, and Paul J. Gemperline

Abstract — **The approach is to observe the batch progress and use in-situ spectroscopic measurements to adjust values of model coefficients of the reaction system on-line, then to use the up-dated model to determine an optimum recipe for the remainder of the batch process. The methodology is illustrated using experimental and simulated semi-batch reactor data.**

I. INTRODUCTION

Batch and semi-batch modes of processing are of great importance to the chemical industry due to their low volume yet high value products - especially pharmaceutical products, polymers, cosmetics, specialty chemicals, and bio-materials. Batch processes are typically used when the production volumes are low, when isolation is required for reasons of sterility or safety, and when the materials involved are difficult to handle (Srinivasan *et al*., 2002), and optimization of batch processes has been the focus of many studies (Love, 1988, Bonvin, 1998). Many optimization studies on batch processes, especially fermentation and polymerization, are based on the use of process models (Johnson, 1998).

The traditional way of operating a reactor in a batch or semi batch mode is to follow a predefined recipe and to control manipulated variables such as temperature, pressure, and or pH along predetermined trajectories; and only at the end of the batch is it determined if the product has the required qualities. Often disturbances or natural variations in loading conditions or the change in operating conditions can go undetected and cause the batch to vary from the optimum, even when the recipe is adhered to, which may adversely affect product quality. Therefore, an optimization and monitoring system that can acquire composition information in real-time and track the evolution of a batch, detect variations and revise the optimal recipe on-line is needed to allow corrective measures to be taken early in the batch and to ensure safe operation and required product quality.

Techniques for batch-to-batch recipe optimization have been shown to work in maintaining product quality (Dong, *et al.* 1996). However, since all deviations that might occur cannot be predicted before the beginning of a batch, corrective action cannot be taken while the batch progresses, thus this technique cannot be used to improve the current batch.

Chemical information is obtained mostly by off-line analyses, and in many cases the time for analysis exceeds the batch time. Therefore, chemical analysis can only be used after the batch is complete, which is too late for any corrective action to be taken on previous batch and only the subsequent batches can benefit from the information.

Many have investigated on-line batch optimization using traditional process measurements (Eaton and Rawlings, 1990, Soroush and Kravaris, 1992, Choi *et al*., 1997, Ruppen *et al*., 1998, Dhir *et al.*). By contrast, in-situ spectroscopic measurements as a non-invasive on-line method for extracting chemical information has received significant attention (Gemperline *et al.*, 1999, Quinn *et al.*, 1999, Bijlsma *et al*., 2000, Bezemer *et al.*, 2002). An early report of an algorithm which uses spectrometric data along with a chemical model to obtain time-dependant chemical composition profile was shown to work successfully on laboratory data (Maeder *et al*., 1990). The algorithm described here, which uses non-linear estimation of model parameters, uses a similar approach.

In one experimental optimization of a batch process, the parameters of a simple phenomenological model were progressively adjusted to maintain an accurate representation of the process (Iyer *et al.* 1999). Once the model parameters were adjusted, the remaining recipe was re-optimized. Inaccuracies in the model were taken care of by on-line data reconciliation and model parameter adjustment. Although that work focused on a fed-batch fermenter, the approach is perfectly general and is easily applicable to any batch process that can be modeled.

We believe the combination of these two

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methodologies (Bijlsma *et al.* and Iyer, *et al.*) can develop a generic approach to optimizing batch processes. This work demonstrates the approach.

The idea, here, is to show that volume of reagent needed to reach batch end-point can be predicted on-line, in time for implementation. By monitoring the reactor's time-dependent spectroscopic response, after a few small additions of one of the reacting reagents, the kinetic and material models will be adjusted online. The adjusted model will be then used to forecast the residual reagent needed. Large reagent additions of the right amount can then be confidently/safely made to reach the endpoint rapidly, thereby shortening the batch time without wasting reagent, improving yields and reducing impurities.

II. Experimentation

The batch reaction here is the production of aspirin (acetylsalicylic acid, ASA). The process is illustrated in Figure 1. The reactor system consists of a 50 ml reactor vessel that fits in a glass jacket. The cooling jacket and the heating coil are used to maintain isothermal conditions, and the stirrer for uniform composition. Batch monitoring is done by the use of fiber optic UV/visible attenuated total reflectance (ATR) probe.

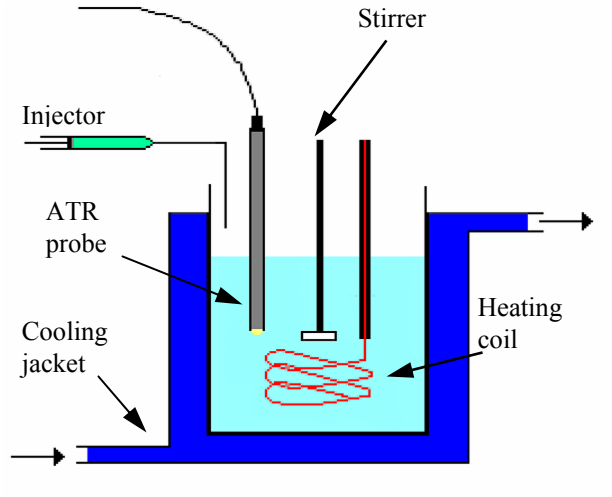


Fig. 1. Schematic of the reactor setup

The reaction used is the esterification of salicylic acid (SA) to form acetylsalicylic acid (ASA). This reaction system was chosen as it is well known, and is widely used industrially.

$$SA + AA \leftrightarrow ASA + HA \quad (k_{1f}, k_{1r}) \qquad (R1)$$

$$W + AA \rightarrow 2HA \quad (k_2) \qquad (R2)$$

In Reaction 1, SA reacts with AA to give, ASA and acetic acid (HA). Reaction 2 is an undesired side reaction, which occurs between the water (W), present in the solvent, and the AA being added and gives HA.

After the Reactor is filled with acetonitrile (solvent of choice), a measured amount of salicylic acid (SA) is added and allowed time to mix. Then a quantity of acetic anhydride (AA) is injected. One of the reactants, SA, and one of the products, ASA, are the only reagents in this system that show unique UV/Visible absorbance.

III. Model Development

Model equations were developed based on traditional mass balance and given below. The experiment is conducted isothermally; therefore, the temperature dependence of reaction rates is not modeled.

$$\frac{d}{dt}C_{SA} = -\frac{C_{SA}}{V}F_{AA} - r_1 \quad \text{.....(1)}$$

$$\frac{d}{dt}C_{W} = -\frac{C_{W}}{V}F_{AA} - r_2 \quad \text{.....(2)}$$

$$\frac{d}{dt}C_{HA} = -\frac{C_{HA}}{V}F_{AA} + r_1 + 2r_2 \quad \text{.....(3)}$$

$$\frac{d}{dt}C_{ASA} = -\frac{C_{ASA}}{V}F_{AA} + r_1 \quad \text{.....(4)}$$

$$\frac{d}{dt}C_{AA} = -\frac{C_{AAin} - C_{AA}}{V}F_{AA} - r_1 - r_2 \quad \text{.....(5)}$$

$$\frac{d}{dt}V = F_{AA} \quad \text{.....(6)}$$

$$r_1 = k_{1f}C_{SA}^{\alpha}C_{AA}^{\beta} - k_{1r}C_{SA}^{\gamma}C_{AA}^{\eta} \quad \text{.....(7)}$$

$$r_2 = k_2 C_{AA} C_W \quad \text{.....(8)}$$

where

$C \equiv$ concentration

$F \equiv$ flowrate of injection

$V \equiv$ volume of the reactor

$k_{1f} \equiv$ kinetic constant for forward R1

$k_{1r} \equiv$ kinetic constant for reverse R1

$k_2 \equiv$ kinetic constant for R2

$\alpha, \beta, \gamma, \eta \equiv$ order governing coefficients

IV. Process Simulator

The simulations developed are based on the experimental system described above. They use the model equations to generate composition profiles, and from them, generate absorbance spectra. Model parameters are chosen such that the spectra obtained would be similar to experimental spectra. And, also because the exact parameters are known and the algorithm under consideration may be tested

V. Spectroscopy

According to the Beer-Lambert law, there is a linear relationship between the concentration of a species and its molar absorbtivity which can be described by

$$a_\lambda = c_1 \times e_{1\lambda} + c_2 \times e_{2\lambda} + \ldots + c_n \times e_{n\lambda} \quad (9)$$

$$\Rightarrow a_\lambda = \sum_j^n c_j e_{j\lambda} \quad (10)$$

written in matrix notation

$$\Rightarrow A(m \times t) = K(m \times i) \bullet E^T(i \times t) \quad (11)$$

where

$\lambda \equiv$ wavelength

$a_\lambda \equiv$ overall absorbance at wavelength λ

$c_j \equiv$ concentration of specie j

$e_{j\lambda} \equiv$ molar absorbtivity of specie j at wavelength λ

$n \equiv$ total number of absorbing species

$A \equiv$ matrix of absorbtion as a function of reaction time

$K \equiv$ matrix of concentration as a function of reaction time

$E \equiv$ matrix of pure species spectra

$m \equiv$ total # of wavelenghts

$t \equiv$ total # of equidistant time points

$i \equiv$ total # of absorbing species

VI. Algorithm

The relationship between the data received from the probe (matrix A) and the time dependant concentration profile is given by Equation 10. If **E,** the pure species spectra matrix, is known, then **K,** the concentration profile matrix, can be easily calculated. But, to find **E** the probe needs to be calibrated with standard solutions such that their concentration match the initial concentration of the absorbing reactants and the final concentration of the absorbing products of every batch experiment to be performed, which is impractical. Without **E**, **K** cannot be determined straight away.

According to the CCR method, model parameters (e.g. initial concentrations and kinetic constants) are assumed and the concentration profiles (**K**) are generated. From **A** (from the probe) and **K**, **E** can be estimated according to Equation 12.

$$\mathbf{E}_{est}^T = \mathbf{K}^+ \bullet \mathbf{A} \quad (12)$$

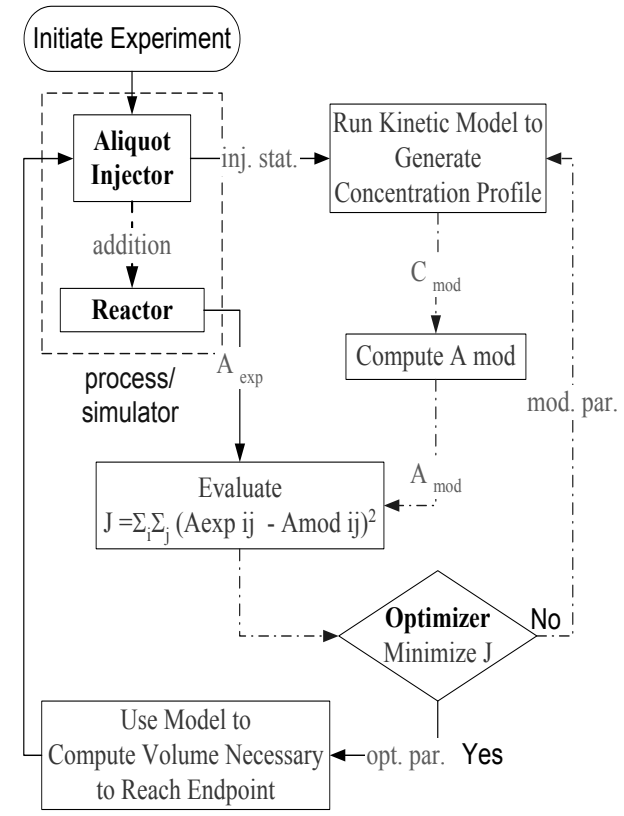
And from $\mathbf{E}_{est}$, $\mathbf{A}$ can be estimated by

$$\mathbf{A}_{est} = \mathbf{K} \bullet \mathbf{E}_{est}^T \quad (13)$$

where

$\mathbf{K}^+ \equiv$ *pseudo inverse of* $\mathbf{K}$

Now, to get the true concentration profile, the sum of the squared error between corresponding elements of **A** and $\mathbf{A}_{est}$ is minimized by changing the model parameters. In this case "fminsearch" a built-in MATLAB function, which is a Nelder-Mead type simplex search method (Lagarias *et al.,* 1998), was the optimizer. After the parameter values are found, the kinetic model is used to generate concentration profiles. Then with a few simple algebraic equations, the reactant volume required to reach end-point can be obtained. The command flow diagram that shows this technique as an on-line implementation tool can be seen in Fig. 2.



Amod: model generated spectra

Aexp: spectra obtained experimentally

Fig. 2. Command Flow Diagram

VII. Results and Discussion

A. Simulation

For simulation experiments, spectra (**A**) was generated by using Equation 13 with true species spectra (**E**) obtained experimentally and concentration profile (**K**) generated by the kinetic model with known parameter values. Only **A** was used as the input to the algorithm described above. **E** or **K,** which were used to create **A,** were treated as unknowns since they are not known in actual experiments.

1) Simulation 1

This simulation experiment was designed to show that the technique described in this paper can be used to determine the volume of the reactant and the time required to reach the end-point while the reaction rate law, reaction rate constants, reaction order and initial concentration of the reactants are not known, in fact all the unknowns can be exactly determined.

Seven out of the ten possible kinetic model parameters were chosen for the minimization routine, the rest were set constant at the known values. The chosen parameters were k_{1f}, k_{1r}, C_{SAo} (initial SA concentration), α, β, γ, and η. As shown in Table I, all parameter values, except values for γ and η, exactly match the known values. γ and η values do not match exactly because they represent excess degree of freedom. Although they do not match the known values; V_{req} is always (considering similar simulation results) correct.

TABLE I
KNOWN AND ALGORITHM DETERMINED PARAMETER VALUES FOR SIMULATION

Parameter	Known Value	Algorithm Determined
k_{1f} [L / (mol * min)]	0.1	0.1000
k_{1r} [L / (mol * min)]	0.001	0.0010
k_2 [L / (mol * min)]	0	Set Const.
C_{wo} [M]	0	Set Const.
C_{AAin} [M]	10	Set Const.
C_{SAo} [M]	2	2.0000
α [unit less]	1	1.0000
β [unit less]	1	1.0000
γ [unit less]	1	1.0326
η [unit less]	1	0.9674
V_{req} [mL]	2.9967	2.9967
t_{req} [min]	unknown	39.9622

2) Simulation 2

In the second simulation, four parameters, k_{1f}, k_2, C_{Wo} (initial water concentration) and C_{SAo}, were adjusted in the minimization routine. The rest were set constant at the known values. This simulation was mainly designed to show that the technique can be used to determine the volume of the reactant and the time required to reach the end-point while a side reaction is occurring that consumes one of the reactants. Also rate constants and initial concentration of one of the reactants and the initial concentration of the impurity are unknown.

TABLE II
KNOWN AND ALGORITHM DETERMINED PARAMETER VALUES FOR SIMULATION

Parameter	Known Value	Algorithm Determined
k_{1f} [L / (mol * min)]	0.1	0.1000
k_{1r} [L / (mol * min)]	0	Set Const.
k_2 [L / (mol * min)]	1	1.0000
C_{wo} [M]	0.25	0.2500
C_{AAin} [M]	10	Set Const.
C_{SAo} [M]	2	2.0000
α [unit less]	1	Set Const.
β [unit less]	1	Set Const.
γ [unit less]	1	Set Const.
η [unit less]	1	Set Const.
V_{req} [mL]	3.5	3.5000
t_{req} [min]	unknown	37.4208

In this simulation water was present as an impurity that reacts with AA at a rate that is ten times faster than the rate of reaction between AA and SA. As can be seen in Table II all parameter values found by the minimization routine exactly match the known values as well as V_{req}.

3) Simulation 3

To evaluate the sensitivity of the Algorithm to noise, similar simulation experiments as discussed above were performed, with the only difference being random noise added to the simulated spectra. These experiments indicated the magnitude of percent error, between V_{req} known and V_{req} determined by the Algorithm was, dependent on the level of noise, the higher the noise level the higher was the error.

Noise with magnitude close to what is observed experimentally was simply added to the spectra matrix obtained in Simulation 1 to represent experimentally obtained spectra. The same experiment as described above was repeated to see the sensitivity of the Algorithm to noise. Typically, an error of ±0.5 % (0.019 mL) between V_{req} known and V_{req} determined by the Algorithm was seen. This shows applicability of the Algorithm, as a tool to determine volume required to reach the end-point in

actual experiments.

Further research is needed to determine the consequence of this uncertainty, to find ways to compensate for it, and to determine the magnitude of accuracy acceptable for this type of operation.

4) Simulation 4

Simulations were designed to show the applicability of the Algorithm in the presence of structural mismatch and the inability to account for all natural changes which in actual experiments may be caused due to slight variations in operating condition such as variations in temperature, pressure and etc. For simplicity a variation in the kinetic constant was used to generate spectra which was not accounted for the in the model equations used by the Algorithm. This was done to create mismatch between the model and the simulated experiment.

The simulation was setup such that the kinetic parameter would slightly change after every addition of the aliquot. The results indicated that the Algorithm worked poorly if a few additions were made and then the Algorithm used. But the Algorithm worked well when after every addition the Algorithm was run using only the most recent spectra information and not all the previously collected spectra (i.e. only after the last addition) was used. This indicates that even with a model mismatch, such as variation in the kinetic constant which may be caused by indeterminable reasons, this Algorithm with model re-parameterization after every addition can be used to determine V_{req}. In the case of this simulation it was known that the variation in the kinetic constant occurs in every addition therefore re-parameterization was done after every addition, for actual experiments in which the variation may be undetectable re-parameterization can be done at short intervals of time to maintain a good match between the model and the process.

Further research is required to determine the confidence level of these results and also a method is needed to determine when there is enough information in the collected spectra (i.e. collection time) that would yield high-quality results.

B. Experimental

Two 1 ml additions of AA (Acetic Anhydride) separated by about thirty minutes were made at a flow rate of 0.5 ml per minute to the reaction mixture. Four parameters, k_{1f}, k_2, C_{Wo} (initial water concentration) and C_{SAo}, were used in the minimization routine with spectra (R.H.S. plot Figure 4) acquired by the ATR probe, placed in side the reactor, as the input to the algorithm.

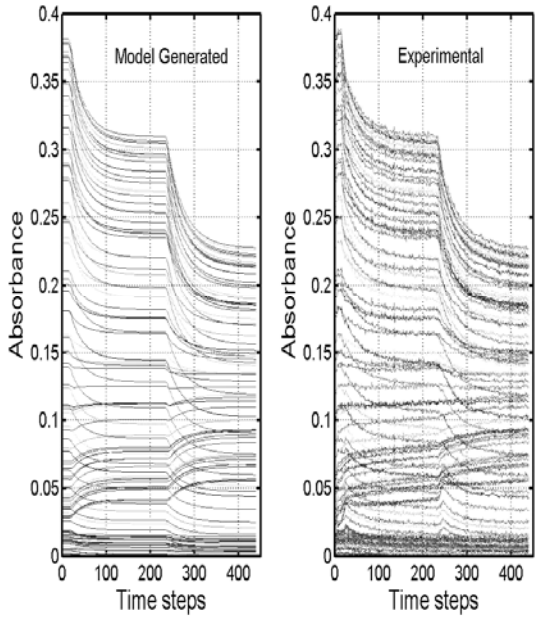


Fig. 4. Plot of Absorbance as a function of time steps (1time step = 6 sec)

Figure 4 shows the absorbance vs. time plots of spectra obtained experimentally and spectra generated by the model, and reveals that the model generated spectra closely resembles the experimentally obtained spectra. Figure 5 shows the model generated concentration profiles, of all reacting species in the system, which was developed by using the model parameters found by the algorithm. A small amount of water is shown to be present in the beginning, but soon disappears as AA is added.

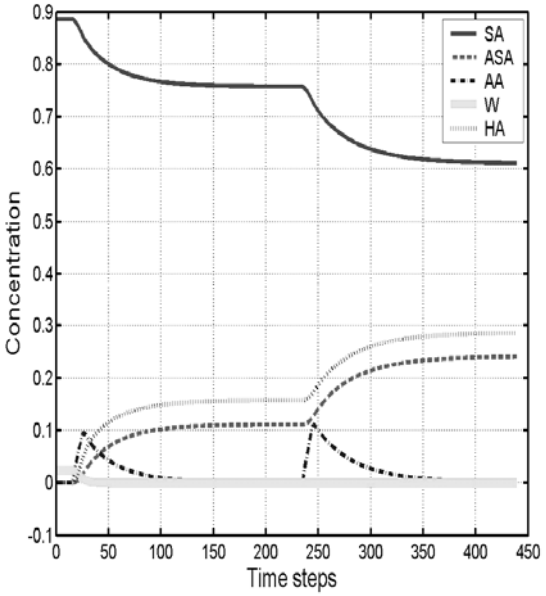


Fig. 5. Plot of Model Generated Concentration Profiles as a function of time steps (1time step = 6 sec)

V_{req} came out to be 2.3121 ml which is 0.22 ml more than prescribed by stoichiometry (2.09277 ml). The reason for this mismatch, although very small, is that the stoichiometric calculations were based only on the 1:1 mole ratio of SA to AA and did not (and could not) account for the presence of un-quantified water in the system. The amount of water cannot be determined by any non-invasive method.

Comment: The initial concentration of neither of the two reactants is required to find the correct V_{req} value. Dimensional analysis of the kinetic model reveals that only the ratio C_{SAo} / C_{AAin} is required to find the correct V_{req}. Therefore, either one of the parameters (C_{SAo} or C_{AAin}) can be arbitrarily set to a constant value, and the other could be searched for by the minimization routine. But, this method only yields the correct V_{req} value, not necessarily the correct values of the other parameters as they are related to the initial concentration of the reactants.

TABLE III
EXPERIMENTAL RESULTS

RUN #	CSAo [M]	CAAin [M]	CSAo/CAAin	Vreq [mL]
1	**1.0000**	7.7498	0.1290	2.3121
2	**0.8830**	6.8523	0.1289	2.3121
3	1.3652	**10.5800**	0.1290	2.3121

Bold represent fixed values

It can be seen in the fourth column of Table III that the ratio C_{SAo} / C_{AAin} and Vreq comes is the same for different constant values of C_{SAo} or C_{AAin} which further validates the dimensional analysis results.

Comment: Care was required to eliminate base-line drifts in the experimental data so that the Algorithm did not have to compensate.

VIII. CONCLUSIONS

By monitoring the reactor's time-dependent spectroscopic response, after a few small additions of one of the reacting reagents, the kinetic model can be adjusted online. The adjusted model can be then used to forecast the location of the batch endpoint. Large reagent additions can then be confidently made to reach the endpoint rapidly, thereby shortening the batch time, minimizing reagent consumption, improving yield, and reducing impurities in finished batches.

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