Evolutionary Operation and Control of Chromatographic Processes

Deepak Nagrath, B. Wayne Bequette, and S. M. Cramer
Howard P. Isermann Dept. of Chemical Engineering, Rensselaer Polytechnic Institute, Troy, NY 12180

A novel generalized run-to-run control (GR2R) control strategy is presented for the optimization and control of nonlinear preparative chromatographic processes. The GR2R approach synergistically employs a hybrid (both physical and empirical) model to control chromatographic processes in the presence of sporadic and autocorrelated disturbances. First, parameters of the physical model through experiments are determined, and then the physical model is used to estimate initial parameters of the nonlinear empirical model (Hammerstein) using orthogonal forward regression. Parameters of the nonlinear empirical model are updated at the end of each run using a nonlinear recursive parameter estimation method. The updated empirical model is then used in the control algorithm (model predictive control) to estimate operating conditions for the next batch. Processes operating under fixed optimal conditions are compared with those operating with GR2R control for both gradient and displacement chromatography. The GR2R outperforms the fixed conditions in the presence of various disturbances (such as bed capacity, column efficiency, and feed load) and is an effective strategy for the optimization and control of complex chromatographic processes.

Introduction

Although preparative ion-exchange chromatography (IEC) is widely employed for protein purification, the choice of operating conditions has remained largely empirical (Felinger and Guiochon, 1994, 1996a,b; Luo and Hsu, 1997), resulting in a suboptimal performance of these separation systems. Concurrent advances in both the theory of protein nonlinear IEC and the run-to-run control algorithm sets the stage for the development of optimal and robust nonlinear gradient and displacement purification processes with minimal experiments. Chromatographic processes also have the lack of real-time data directly related to the product quality or productivity, thus making R2R control a viable strategy.

In this article we present a novel hybrid approach, generalized *run-to-run control* (GR2R) for the optimization and control of chromatographic processes. This approach synergistically uses a hybrid model (both an empirical and a physical model) for optimization (Siouffi and Phan-Tan-Luu, 2000) and control. The motivation for using both physical and empirical models is to complement the knowledge of physics from the physical model with the simplicity and low computational cost of the empirical model. The approach is based on the realization that the fixed parameter model based approaches will not give an optimal performance due to batch-to-batch variability and disturbances. The parameters of both the empirical and physical model can be updated in the approach to drive the models close to the actual process. Run-to-Run (R2R) control refers to a class of statistical process/quality control (SPC/SQC) techniques used to improve the operation of batch processes. R2R handles batch-to-batch variations and gives a reasonably good performance compared to the cases where control algorithms do not learn from batch-to-batch. There are several approaches for R2R control existing in the current literature. The R2R controller has two modes of operation: optimization and control. Optimization may be repeated periodically, if it is thought that additional opportunity for improvement exists or if the process has changed drastically. Once the process is optimized, the R2R maintains the process at the optimum conditions in the presence of disturbances (fluctuations in operating parameters from batch-to-batch).

The most common R2R approach is the Exponential Weighted Moving Average (EWMA) based approach. Sachs

Correspondence concerning this article should be addressed to S. M. Cramer.

et al. (1995) use EWMA for small drifts from the target (desired quality attribute) and call it an EWMA "Gradual Mode" R2R controller (GM). This approach uses a linear model of the process and the controller updates the model by weighting the past and the present batch data. This approach is not appropriate for processes that have strong autocorrelation between batches, and processes with physical or operational constraints on the inputs or outputs.

Hankinson et al. (1997) proposed a *Knowledge-based Interactive Run to Run controller*, which generates nonlinear response surfaces from experimental data using neural networks. Ning et al. (1996) have shown that this gives a better performance for a linear process than EWMA, but may fail to satisfactorily control nonlinear processes. A *Optimizing Adaptive Quality Controller* (OAQC) presented by Castillo and Yeh (1998) tries to keep adequate control even if the relation between the input and output parameters is severely nonlinear. The OAQC combines the model optimization step with the control step by using recursive least squares (RLS) to estimate the parameters of a Hammerstein model on-line and then optimizing the objective function to obtain the best control action. It is restricted to systems having second-order nonlinearities occurring only in the input. Golden and Ydstie (1989) proposed adaptive extremum control using approximate process models. The objective of an adaptive extremum control is to locate the steady-state optimum of a process and then continuously keep the process operating at its optimum despite inaccuracies in the model, drifts due to unmeasured process disturbances, and slow dynamical changes that result from changing parameters. Their strategy has not been applied to run-to-run control.

While R2R is currently being used extensively in semiconductor processes, a variant of R2R control was applied to chromatographic processes as early as 1990. Frey (1990) applied minimum variance control to preparative chromatography for maximizing the yield of a desired component, while maintaining a required level of product purity in the presence of measurement error and external disturbances. Furthermore, input-output models utilizing discrete variables (Frey, 1991) were developed for elution chromatography and used together with a control theory to investigate the correlation between output variables (such as yield, purity, and production rate) and input variables (such as cut point locations and feed slug size). However, there are several limitations to this work. The manipulated inputs were limited to cut point locations and feed size. In addition, the use of linear models limits the performance of the control strategy, particularly near an optimum production rate.

Over the past few years, R2R control has received considerable interest from the chemical process control community. There has been a surge of articles in the application of traditional process control algorithms (internal model control and model predictive control) for batch processes. We can classify and compare the current approaches based on two distinctive criterions. The first criterion for comparison deals with the issue of a modeling approach adopted for the batch process. Some of the approaches in literature use only a data based empirical model (Pan and Lee, 2000; Adivikolanu and Zafiriou, 2000; Sreenivasan et al., 2001; Gillet et al., 2001; Dorsey and Lee, 2000; Pan and Lee, 2000). On the contrary, some of the other approaches deal only with the fundamental models (Gattu et al., 1999). The approach presented in our article is the only one which deals with the implementation of nonlinear predictive control using hybrid models (both empirical and fundamental) for the control of batch processes. We would like to emphasize that, although Crowley et al. (2001) presented a hybrid modeling approach for batch-to-batch optimization of particle-size distributions in semi-batch emulsion polymerization, they have not implemented any control strategy. A second measure for comparison is based on the use of a linear or nonlinear model and/or controller design. Most approaches (for example, Adivikolanu and Zafiriou, 2000; Sreenivasan et al., 2001; Gillet et al., 2001) use a linear model and/or controller design. The approach presented by Pan and Lee (2000) could be extended to nonlinear models; however, their approach employs a linear recursive predictor. The GR2R approach presented makes use of the nonlinear recursive prediction error method developed by Hernandez and Arkun (1993) for continuous processes. We have been the first to apply a nonlinear recursive prediction error for model updating to a batch process. The use of linear updating scheme can limit the performance of the extremal control strategy. As previously described, there is an essential difference between our GR2R approach and the other R2R control approaches. These approaches do not deal with the issue of hybrid modeling (that is, coupling fundamental knowledge of process with the measurement data from the process). This is because most of the R2R control literature is based on the processes where fundamental or first principles model are not available or are very difficult to obtain. In addition, large numbers of off-line experiments are required for the generation of linear or nonlinear empirical model from experiments. The generation of nonlinear empirical model off-line (through experiments) for the chromatographic processes will entail a large number of preparative (large-scale) chromatographic experiments. However, this will not be feasible for the pharmaceutical industry, which employs chromatography for protein separations because these experiments can be extremely expensive. Hence, any way of reducing the number is welcome.

Generalized run-to-run control (GR2R) inherits the advantages of present run-to-run control formulations and overcomes the limitations and disadvantages of classical R2R. The motivation for the GR2R control is in optimizing and controlling at the optimum and making the chromatographic process insensitive to the effect of varied disturbances and changes in the operating conditions. *Generalized run-to-run control* (GR2R) synergistically uses both physical (first principles) and nonlinear empirical (input-output) models for optimization. Initial parameter identification for the physical and empirical model is carried out using linear gradient, unretained and a few preparative scale experiments. Parameters of the empirical and physical model can be updated with the data obtained from subsequent runs. However, we only update in this article the parameters of the empirical model. The empirical model is then used with the proposed control algorithm to obtain optimal operating conditions in the presence of measured and unmeasured disturbances.

The theory is provided for physical and empirical modeling, the detailed procedure is described for Generalized Run to Run Control, results and discussion are presented, and conclusions and suggestions are presented for future work.

Theory

Physical model

In this article, a *solid film linear driving force* model is employed in concert with the steric mass action (SMA) isotherm and appropriate Danckwert's boundary conditions to describe gradient and displacement separations. The solid film linear driving force model (Glueckauf and Coates, 1947; Phillips et al., 1988; Guiochon et al., 1994) falls under the broader category of transport-dispersive models. In this model, a linear driving force approximation describes the effects of mass transfer

$$\frac{\partial C_i}{\partial t} + \frac{1-\epsilon_t}{\epsilon_t}\frac{\partial Q_i}{\partial t} + u\frac{\partial C_i}{\partial x} = D_{ai}\frac{\partial^2 C_i}{\partial x^2} \tag{1}$$

$$\frac{\partial Q_i}{\partial t} = k_{m_i}\left(Q_i^{\text{equil}} - Q_i\right) \tag{2}$$

where Q_i^{equil} is the equilibrium stationary phase concentration of the ith component. In this model, D_a accounts for axial dispersion effects and k_m represents a lumped mass transport coefficient that accounts for film, pore, and/or surface diffusion effects (depending on the relative importance of these phenomena).

The SMA formalism (Brooks and Cramer, 1992) is used to describe multicomponent protein-salt equilibrium in ion-exchange systems. The stoichiometric exchange of protein and salt can be represented as

$$C_i + \nu_i\overline{Q}_1 \Leftrightarrow Q_i + \nu_i C_1 \tag{3}$$

where ν_i is the characteristic charge of protein, C_i and Q_i are the mobile and stationary phase concentration, respectively, and $\overline{Q}_1$ is the number of sites on the stationary phase available for exchange with the protein. The equilibrium constant K_{smai} is defined as

$$K_{smai} = \left(\frac{Q_i}{C_i}\right)\left(\frac{C_1}{\overline{Q}_1}\right)^{\nu_i}$$

Ion-exchange surface must maintain the electroneutrality condition. The electroneutrality condition is described by

$$\overline{Q}_1 = \Lambda - \sum_{i=2}^{N}(\nu_i + \sigma_i)Q_i \tag{4}$$

The finite difference technique is employed to solve Eqs. 1–4. As the SMA isotherm is implicit, a Newton-Raphson technique is used to solve for the equilibrium at each point. The temporal terms are discretized using forward differences, while the convection and diffusion terms are discretized using backward and central differences, respectively.

Empirical model

Input-output data can be used to develop an empirical model that may approximate the physical process in the given data range. In the GR2R approach, an empirical model is generated by making parametric changes in the manipulated inputs of the physical model. The use of the physical model for empirical model generation eliminates the need for many preparative experiments and, thus, makes the identification of model structure less cumbersome and more economical. Parametric simulations are used to generate n-dimensional response data, which relate the production rate, yield, and purity to the other parameters of the system (such as feed load, flow rate, salt gradient, and displacer concentration). Billings (1980) gives a survey of constructing a nonlinear model from input-output measurements.

Most applications of R2R have been limited to the use of linear models. These approaches have been used successfully on the processes where the "output," which is a product property or quality variable, is a monotonic function of an "input" variable. However, for extremum control, the desired variable (for example, productivity in chromatography) exhibits a maximum and it is necessary to operate as close to that maximum as possible. If linear models are used, then the desired output may exhibit oscillatory response close to the optimum, and optimum may never be achieved. Hence, a nonlinear model representation is needed for systems that have nonmonotonic relationships between inputs and outputs.

Various nonlinear empirical models share the form $y(k) = F[\phi(k),\theta]$, where F is a parameterization function that can be expanded using basis functions, and maps set of regressors ϕ to the output y with the parameters θ. Different model types can be obtained by using different sets of basis functions and regressors. The regressor set ϕ may include past inputs, past outputs, or their combination, thereby yielding different nonlinear models. There are various empirical nonlinear model structures for the representation of nonlinear systems. The theory for identification of nonlinear systems based on the Hammerstein model (the model studied in this article) is well established. In this article, nonlinear effects are modeled as an input dependent nonlinearity. The Hammerstein model is a simplified form obtained from a more general NARMAX form, and can be represented as

$$y(k) = f\left[y(k-1),\ldots y\left(k-n_y\right), u(k-1),\ldots,u(k-n_u), e(k-1)\ldots e(k-n_e)\right] + e(k) \tag{5}$$

where $f(.)$ is a nonlinear function. System outputs, inputs, and noise are denoted by $y(k)$, $u(k)$ and $e(k)$, respectively; n_y, n_u, and n_e are the maximum lags in the output, input and noise, respectively; $e(k)$ is assumed to be a white noise sequence and k denotes the batch index (it is to be noted that, in the real-time control literature, k denotes the sample time).

In the empirical model, outputs (production rate and yield) are nonlinearly related to current and previous batch inputs (gradient slope and flow rate for gradient chromatography; flow rate and displacer concentration for displacement chromatography), as shown in Figure 1.

The Hammerstein model is generated by orthogonal least squares (OLS) using the modified Gram-Schmidt method (Chen et al., 1990). The advantage of OLS is that structure determination is performed simultaneously with parameter estimation. Expanding $f_i(.)$ as a polynomial of degree L_i gives

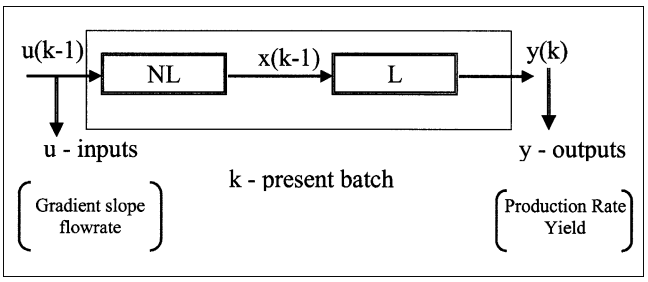

Figure 1. Hammerstein model.

the representation

$$y_i(k) + a_1 y_i(k-1) + \ldots a_n y_i(k-n) = \theta_0^i + \sum_{i_1=1}^{n} \theta_{i_1}^i u_{i1}(k) + \sum_{i_1=1}^{n} \theta_{i_1}^i \sum_{i_2=i_1}^{n} \theta_{i_2}^i u_{i1}(k) u_{i2}(k) \ldots + \sum_{i_1=1}^{n} \theta_{i_1}^i \ldots \sum_{i_L=i_{L-1}}^{n} \theta_{i_L}^i u_{i1}(k) \ldots u_{iL}(k) + e_i(k), \quad i = 1, \ldots m \quad (6)$$

where k denotes the present batch index. The coefficents a_i and θ_{ij} are derived by the orthogonal least-squares procedure.

In compact notation, Eq. 6 is written as

$$y(k) = \begin{bmatrix} y_1(k) \\ . \\ . \\ . \\ y_m(k) \end{bmatrix} \quad u(k) = \begin{bmatrix} u_1(k) \\ . \\ . \\ . \\ u_r(k) \end{bmatrix}$$

$$y_i(k) = \sum_{j=1}^{n_i} \theta_{ij} u_{ij}(k) + e_i(k), \quad i = 1, \ldots m \quad (7)$$

$$n_i = \sum_{j=0}^{L_i} n_{ij}, \; n_{i0} = 1, \; n_{ij} = \frac{n_{ij-1}\left[\sum_{k=1}^{m} n_{yk}^i + \sum_{k=1}^{r} n_{uk}^i + j - 1\right]}{j}, \quad j = 1, \ldots L$$

The Hammerstein model is then cast into a linear-regression form as

$$z(k) = \sum_{i=1}^{M} p_i(k)\theta_i + \xi(k), \; k = 1, \ldots N \quad (8)$$

where $z(k)$ is a dependent variable, $p_i(k)$ are regressors, $\xi(k)$ is the modeling error, and θ_i are unknown parameters. The regressor matrix P is defined as

$$P = \left[P^T(1) \ldots P^T(N) \right]^T$$

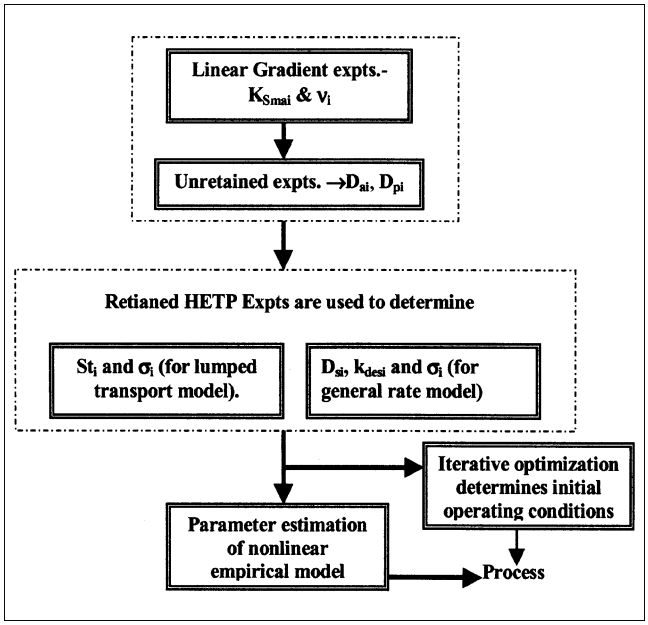

Figure 2. Initial parameter identification step for the generalized run-to-run control strategy.

where N is data length. Equation 8 is written in a general form as

$$Z = P\Theta + \Xi \quad (9)$$

where Ξ is a vector of modeling errors and Θ is a vector of unknown parameters. Steps for the Modified Gram Schmidt based identification are given in the appendix.

Procedure for Generalized Run to Run Control

The GR2R uses the physical model (lumped transport model) for iterative optimization and for generation of an empirical model. For the sake of clarity, GR2R is divided into two segments, a *parameter identification* step and *extremum control* step. The aim of the first step, parameter identification, is to estimate the parameters of the physical and empirical models. The second step, extremum control, addresses the requirement of maintaining the process at the current optimum conditions (and/or determining a new optimum when required) in the presence of disturbances (measured and unmeasured).

Preliminary experiments for building models

The first step in the parameter identification step of GR2R, as shown in Figure 2, is to generate a physical model using analytical experiments. The procedure for parameter estimation is described elsewhere (Natarajan and Cramer, 2000). Briefly, isotherm parameters (K_{smai}, ν_i) first are obtained by linear gradient experiments. The axial dispersion coefficient (D_{ai}) and pore diffusion coefficient (D_{pi}) are then obtained by unretained HETP experiments. Finally, the surface diffusion coefficient (D_{si}) and the steric factor σ_i are obtained by retained HETP experiments. These experiments provide us

with an initial set of parameters for the physical model. However, the parameters of the physical model estimated in GR2R can be updated at the end of each run.

Iterative optimization using physical model

We then employ the physical model with iterative optimization techniques (Gallant et al., 1996; Natarajan et al., 2000) to obtain optimal initial operating conditions.

Objective Function. The maximization of production rate is defined as the objective function in iterative optimization.

Decision Variables. The decision variables in the iterative optimization are the salt concentration and flow rate for linear gradient chromatographic systems. For displacement systems, the decision variables are feed load, $\Delta(Q_{Di}/C_{Di})$, flow rate, and initial salt concentration. The feed loads for the displacement and gradient simulations were arbitrarily set at 1 and 2 column volumes, respectively, to facilitate the simulations.

Constraints. The constraints are imposed on purity (purity of desired protein $\geq 95\%$), solubility (protein concentration < 5 mM), and yield (yield $> 87\%$ for gradient separation; yield $> 89\%$ for displacement).

For displacement, the first step in iterative optimization is to start with an initial guess for the flow rate F and Δ at their lowest bounds. The next step is to optimize the production rate with respect to the salt concentration. If yield constraints are not satisfied, then delta is increased. If satisfied, then flow rate is increased. If the production rate has not increased because of the last step, the flow rate is decreased. The next step is to increase the delta until the yield constraint is satisfied. This process is done in a loop wise fashion until the desired tolerances and convergence are achieved. Iterative optimization provides the optimal initial operating conditions. An analogous approach is employed for gradient systems. Natarajan et al. (2000) show that the results obtained from iterative optimization are comparable to that obtained using the rigorous optimization algorithm feasible sequential quadratic programming (FSQP). The computational time required by iterative optimization was substantially less than FSQP. Hence, iterative optimization can be effectively used in GR2R.

In the present work, this approach is employed to establish an initial guess of operating conditions.

Extremum control step

The approach is based on using the physical model to determine initial optimal operating conditions and the empirical model for controlling the process at those conditions. This approach is provided in Figure 3. The first step is to use the physical model to generate the optimal operating conditions using iterative optimization. The optimal output (production rate) obtained from the iterative optimization is defined as the target. The optimal set of inputs is then applied to the process.

After the completion of a preparative chromatographic run, the output data is then used in conjunction with the input data to update the parameters of the empirical model (appendix). In the ensuing step, the updated nonlinear empirical model is used in the nonlinear model predictive control formulation (indicated as control algorithm in Figure 3) to obtain a new optimal set of inputs. The new operating conditions attempt to maintain the process at the optimal output in the presence of measured and unmeasured disturbances. The new operating conditions obtained from the control algorithm are then applied to the process for the next run. The use of the nonlinear empirical model and nonlinear recursive parameter estimation and update makes GR2R appropriate for both linear and nonlinear processes. Moreover, insensitiveness to disturbances in the process is ensured, since the disturbance structure will be able to handle both measured and unmeasured disturbances.

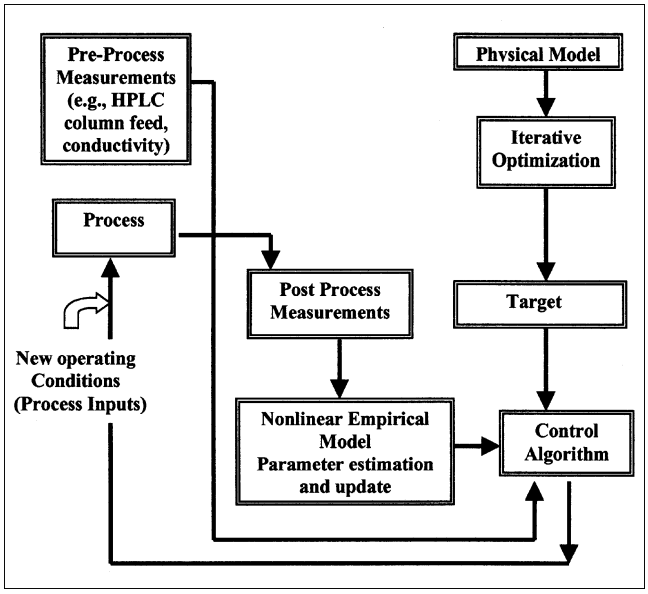

Figure 3. GR2R using physical and empirical model.

Control algorithm

Traditionally, minimum variance control (Castillo and Hurwitz, 1997; Clarke and Gawthrop, 1975) has been a popular algorithm for R2R control. In this work we used model predictive control (MPC). A review of MPC is presented by Garcia et al. (1989) which can handle constraints explicitly, and is well suited for multiinput, multioutput systems. A nonlinear model predictive control formulation (Fruzzetti et al., 1997; Henson, 1998; Hernandez and Arkun, 1993; Bequette, 1991; Sistu et al., 1993) was used to obtain the optimal inputs for the process. We have modified the MPC problem so that optimization is done over future batches instead of time steps. In the current formulation at the end of each batch, an optimization problem is solved which consists of the minimization of an objective function based on output predictions over a *prediction horizon* of P future batches. This is carried out by the selection of manipulated variable moves over a *control horizon* of M control moves over M future batches. Although M moves are optimized, only the first move is implemented. After the input $u(k)$ is implemented, the measurement at the end of the batch $y(k+1)$ is obtained. A new optimization problem is then solved, again, over a prediction horizon of P

future batches by adjusting M control moves. This approach is also known as receding horizon control.

The objective function in NPC used to obtain the optimal input sequence for future batches is

$$\min_{\bar{u}(k)\ldots\ldots\bar{u}(k+M+1)} \sum_{j=1}^{P} e_p(k+j)^T \delta^T e_p(k+j) + \sum_{j=1}^{P} \bar{u}(k+j-1)^T \Gamma^T \Gamma \bar{u}(k+j-1) + \sum_{j=1}^{M} \Delta\bar{u}(k+j-1)^T \beta^T \beta \Delta\bar{u}(k+j-1) \quad (10)$$

Here, k denotes the batch index and δ is the weight on the prediction error $[e_p(k) = \hat{y}(k) - y^{sp}(k)]$, and Γ, β are the weights on the magnitude of the input $\bar{u}$, and the change in the input $\Delta\bar{u}$, respectively. M and P denote the control and prediction horizon, respectively.

In GR2R, a physical model is used to obtain optimal operating conditions $[\bar{u}(k)]$ and the desired target $[y^{sp}(k)]$. The nonlinear model predictive control is then used to keep the system at the optimum in presence of measured and unmeasured disturbances (Figure 3).

Nonlinear recursive parameter estimation and model update

In chromatographic processes, it is quite possible that the process will suffer aberrations (because of changes in feed coming from upstream processes and external disturbances in process itself) and, hence, enter the region not previously observed by the model. Processes experiencing these anomalies will encounter a large process-model mismatch. Hence, it is required to essentially use a recursive parameter estimation and model update technique, in which parameters are updated from batch to batch. The recursive parameter estimation method (RPEM) developed by Hernandez and Arkun (1993) is adopted for this work. The parameters of the nonlinear empirical model are then updated using the nonlinear recursive prediction error method, as described in Appendix. Briefly, the error in the outputs from the current batch is used to update the parameters of the nonlinear empirical model using estimator gain matrix L (k). In RPEM, model parameters are augmented with the estimator gains.

Results and Discussion

In the current chromatographic applications, a common desired objective is to keep the production rate near the maximum by manipulating a variety of chromatographic parameters (such as for feed load, salt concentration, displacer concentration, and flow rate).

Figure 4 shows both the disturbances that can occur in a typical chromatographic process, as well as the manipulated and controlled variables. Disturbances can be either sporadic or autocorrelated. Sporadic disturbances can occur randomly and can vary from batch-to-batch, while autocorrelated disturbances tend to have a relationship between batches. As seen in the figure, sporadic disturbances can include changes

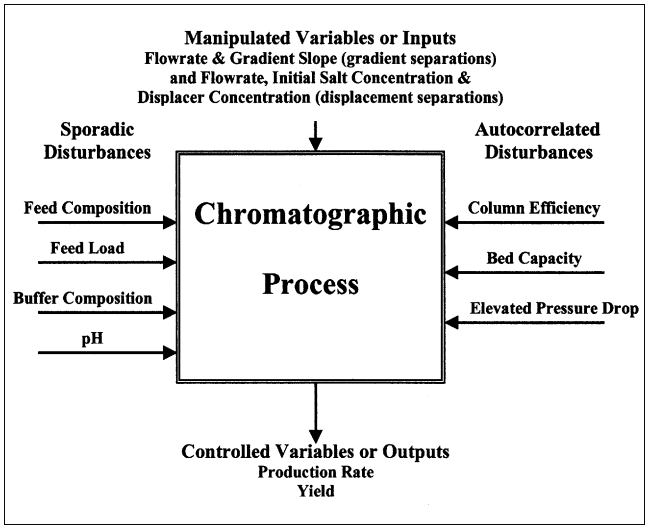

Figure 4. Various variables effecting displacement and linear gradient based chromatographic processes.

in the feed composition, feed load, buffer composition, and pH. Autocorrelated disturbances in chromatographic processes can include changes in bed capacity and column efficiency, which are indicative of column fouling, a major issue in bioprocessing.

The controlled variables (also known as outputs) in this work will be the production rate and the yield. Production rate is a measure of the amount of protein purified per unit time and per unit stationary phase volume. It is a strong function of the amount of material loaded onto the column. Production rate is defined as

$$\mathrm{PR} = \frac{C_f V_f Y}{t_{\mathrm{cyc}} V_{sp}} \quad (11)$$

where C_f denotes feed concentration, V_f denotes the feed volume, Y denotes the yield, t_{cyc} denotes the cycle time, and V_{sp} denotes the stationary phase volume. Yield is calculated as

$$Y = \frac{\int_{t_1}^{t_2} C d\tau}{C_f t_f} \quad (12)$$

where the cut times t_1 and t_2 are chosen to maximize the yield at a given purity.

The manipulated variables (also known as inputs) in the current work will be the gradient slope and flow rate (for gradient systems), and initial salt concentration, displacer concentration, and flow rate (for gradient systems). Constraints, which are addressed in this article, are purity, yield, and solubility limits.

In this article, the transport and kinetic parameters for the proteins α chymotrypsinogen A and ribonuclease A were obtained from our previous work (Natarajan et al., 2002), as

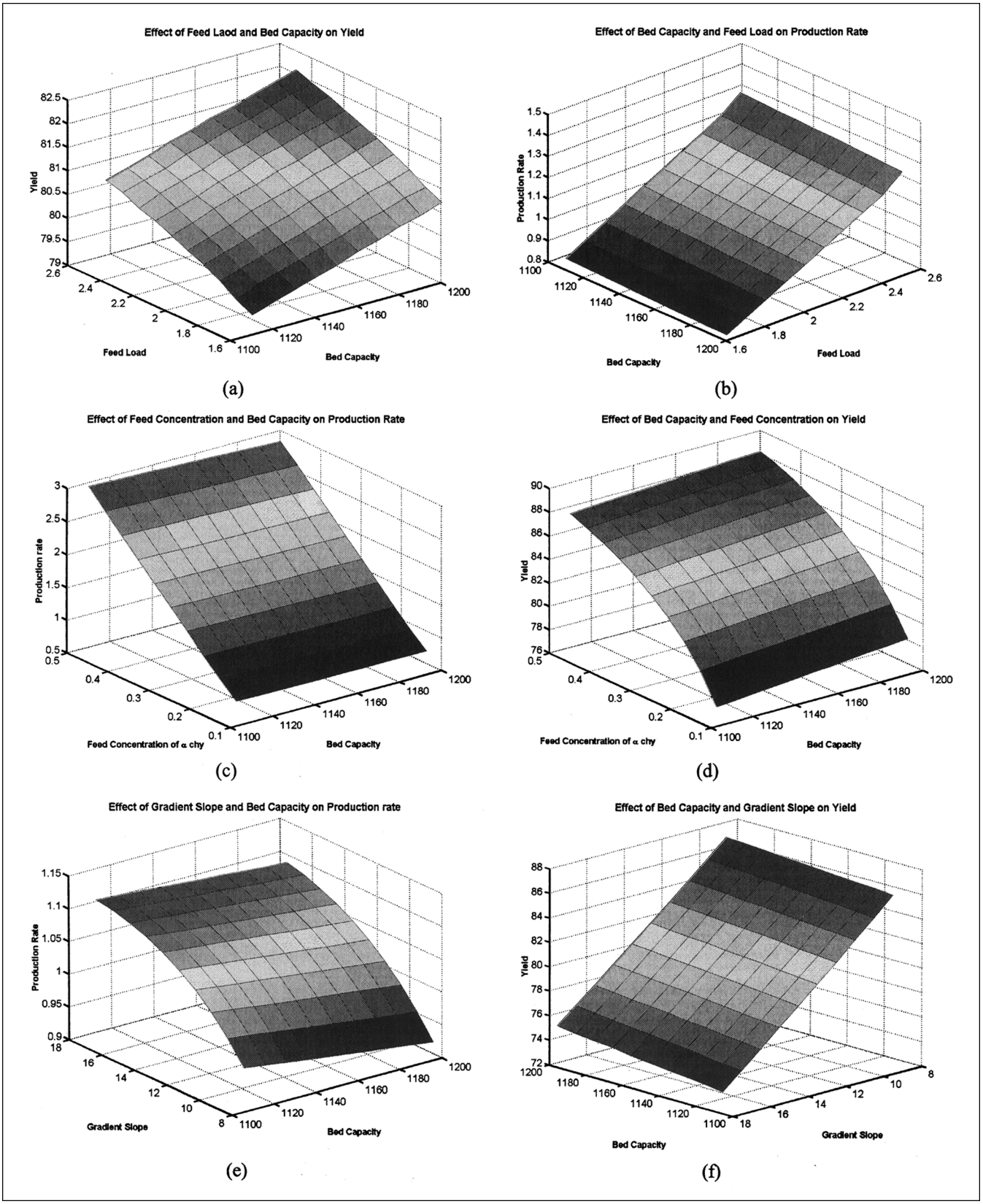

Figure 5. Parametric sensitivity of production rate and yield with respect to feed load and bed capacity, and the effect of manipulated variables and disturbances on production rate and yield.

Table 1. Column Parameters and Optimal Operating Conditions for Displacement Separation

Column:	1.6×10.5 cm
Stationary phase:	FF Sepharose SP resin
Flow rate:	2.0 mL·min^{-1}
Particle dia.:	90 μm
Feed composition:	1:1 (0.15 mM each)
Displacer conc.:	2.3 mM
Salt conc.:	170.3 mM
Feed load:	1.0 dimensionless column vol.

Table 2. Column Parameters and Optimal Operating Conditions for Linear Gradient Separation

Column:	0.5×10.5 cm
Stationary phase:	FF Sepharose SP resin
Flow rate:	0.6 mL min^{-1}
Particle dia.:	90 μm
Feed composition:	0.2 mM α chymotrypsinogen A 0.4 mM ribonuclease A
Initial salt conc.:	50 mM
Final salt conc.:	1,000 mM
Gradient slope:	12.6 mM/dimensionless volume
Feed load:	2.0 dimensionless column volume

described in Figure 2. In that article, it was demonstrated that the results obtained from the physical model corresponded well with the experiments. The parameters were then used to obtain initial optimum operating conditions using the iterative optimization algorithm. The resulting column parameters and initial optimum operating conditions are presented in Tables 1 and 2 for displacement and gradient separation, respectively.

In an industrial environment, there will be both measured and unmeasured disturbances. Certain disturbances (such as relative feed concentration and feed volume and buffer changes in pH and/or salt concentration) can be measured by various techniques (such as analytical chromatography and conductivity meter) before they affect the process. Other disturbances, such as bed capacity, will typically not be measured. The effect of these unmeasured disturbances is minimized in the current approach by having a stochastic component in the empirical model.

The effect of some of the disturbances such as feed load, bed capacity and feed concentration of α chymotrypsinogen A on the performance of gradient chromatography are illustrated in Figure 5. For these simulations, there are two proteins in the feed (ribonuclease A and α chymotrypsinogen A) and α chymotrypsinogen A is the more retained protein and the designated product. While the production rate is relatively insensitive to bed capacity over this range, it is highly sensitive to feed load (as shown in Figure 5a). The yield exhibits a nonlinear response to both bed capacity and feed load (Figure 5b). In addition, as seen in Figures 5c and 5d, a decrease in the feed concentration of α chymotrypsinogen A, results in a linear and nonlinear decrease in production rate and yield, respectively. The effect of the manipulated variables such as flow rate and gradient slope on production rate and yield is examined in Figures 5e and 5f. As expected, an increase in the gradient slope results in an increase in the production rate and a decrease in the yield. While these trends are to be expected, the purpose of presenting them here is to motivate the need for developing nonlinear control approaches to these complicated systems.

Once the initial parameters for the physical model are determined, the physical model is then used to determine the parameters of the nonlinear empirical model as described earlier. The nonlinear empirical model is determined separately for gradient and displacement separations. The input data is selected using a random Gaussian signal and the corresponding outputs are determined from the physical model. Once the empirical model is generated, the model is validated using input values not employed in the generation of the model. The measured and predicted output for a representative gradient validation data set is shown in Figure 6. As seen in Figure 6, the nonlinear empirical model has excellent predictive ability. Similar results were obtained for the validation set generated from displacement chromatography. Once the empirical model is generated, it is subsequently employed in the model predictive control algorithm to obtain a new set of optimal operating conditions. In the model predictive control (MPC) algorithm, the prediction (P) and control horizons (M) are chosen as 3 and 1, respectively, for both the displacement and gradient simulations. The penalty matrices on inputs and outputs are selected as the identity matrix.

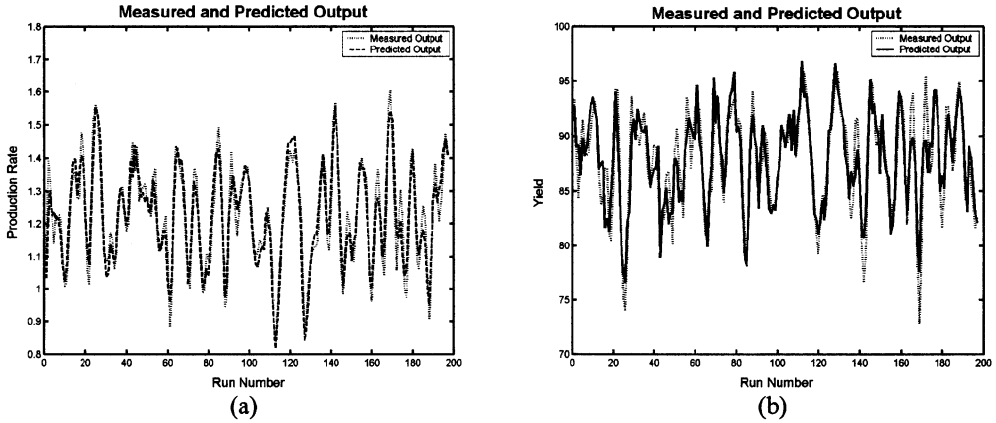

Figure 6. Measured vs. predicted output (yield and production rate) for linear gradient separation for a validation data.

The dotted line is the measured output in Figures 8a and 8b. The dashed (Figure 8a) and solid line (Figure 8b) is the predicted output.

Extremal control results for gradient chromatography

This section compares the performance of a gradient separation process operated with a GR2R controller to a process operating under fixed optimal conditions. We will examine first the performance of these systems in response to a step disturbance. At the start of a run, an unmeasured disturbance (step) is imposed in the feed load (from 2.0 to 1.9 column volumes). In addition, noise is added to the input signals to represent typical uncertainty in these values under actual operating conditions. The responses of the process operating under GR2R controller and fixed optimal conditions are presented in Figure 7. The process operating under GR2R controller compensates for the disturbance by taking suitable manipulated actions based on the error between the desired output variable and the measured output after each run. It can also be seen that the average production rate for the process operating with GR2R control is higher than that obtained with the fixed optimal conditions.

We will now compare the performance of the gradient process operating with GR2R control to that operated under fixed operating conditions, in the presence of both the unmeasured step (feed load) and the drift (bed capacity) disturbances (Figure 8). As seen in the Figure 8a, while the production rate continues to increase with the bed capacity for the process operating under fixed conditions, it remains essentially constant for the GR2R controlled process. The reason for this is shown in Figure 8b, where it can be seen that the yield in the fixed process tends to continuously decrease, eventually resulting in a violation of the yield constraint (87%). Clearly, this is unacceptable in a real manufacturing setting, where yield constraints in chromatography are considered as hard constraints due to significant economic incentives for high value biopharmaceuticals. The changes of inputs (run-to-run) computed by the control algorithm for this system will be presented in Figures 10c and 10d. These inputs are changing in response to both a step change in feed load at the beginning of the first run, as well as a continual decrease in bed capacity as described above.

In order to maintain the production rate at the desired target, while satisfying the constraints, the controller determined that the gradient slope should continuously decrease while the flow rate exhibited a minimal increase. As shown in the sensitivity analysis of Figure 6, the yield is much more sensitive to bed capacity changes than the production rate. Clearly, the yield constraint is the driving force in this process. Furthermore, as shown in Figure 8, control in this system is governed primarily by the gradient slope. This is not surprising, since, as the ion capacity decreases, the selectivity in these ion-exchange systems tends to decrease. This in turn necessitates a decrease in the gradient slope in order to satisfy the yield constraint. The flow rate change is relatively small, as compared to the gradient slope change, since the flow rate is more closely linked to mass transport effects. These results confirm that GR2R is indeed capable of handling both step and drift disturbances for gradient separation processes while satisfying process constraints.

Extremal control results for displacement chromatography

The performance of a displacement process using GR2R control in the presence of various disturbances was also investigated.

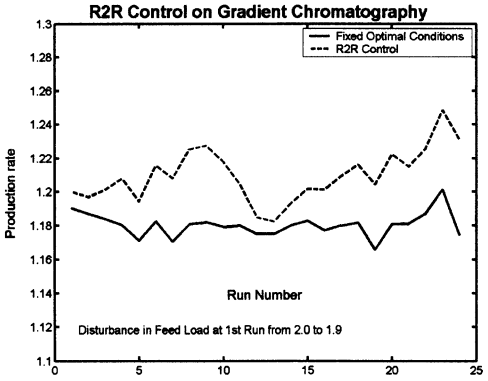

Figure 7. Production rate of gradient separation process operating with and without R2R control in the presence of unmeasured step disturbance in feed load at startup (from 2.0 to 1.9 column volumes).

The solid line is the fixed optimal condition result and the dotted line is the result obtained using GR2R.

The effect of an unmeasured step disturbance of feed load (at the 6th run from 1.0 to 0.95 column volume) and feed concentration of α chymotrypsinogen A (the 31st run from 0.15 to 0.14 mM) was examined. In addition, noise is added to the input signals to represent typical uncertainty in these values under actual operating conditions. As seen in Figure 9, the production rate for the process operating with GR2R2 control was always higher than the one operating with fixed operating conditions. Importantly, this result substantiates that GR2R can actually move the process to new optimal conditions in the presence of multiple disturbances.

We then examined the performance of these systems in the presence of multiple unmeasured and autocorrelated disturbances. An unmeasured disturbance in feed load (from 1.0 to 0.95 column volume) and a continuous decrease in bed capacity at the rate of 1.0 mM per run were examined (both occurring at the 6th run). The results in Figure 10 show that the GR2R controller was able to maintain the production rate at the optimal value after the disturbances occurred. On the other hand, the performance of the process operating with fixed optimal conditions deteriorated continuously. This is due to the fact that in the process operating with run to run control, a new feasible optima was found and corrective action was taken by changing the manipulated inputs resulting in an increased production rate.

The last example deals with the case of varying target specifications. While the examples given thus far in this article have used the production rate as the objective function, in this example both the production rate and yield are included in the objective function with a weighting ratio of 4 to 1, respectively. The specific objective function employed in this work was the minimization of the difference of production rate and yield with respect to their desired target values. Under these conditions, manipulated inputs have to be changed to achieve the desired attributes. In Figure 11, a case is presented in which several new targets are specified during the run. At the first run, the production rate target is increased from 15.6 to 17.0 and the yield is increased from 89 to 90%. At the 5th run, the desired production rate was decreased

from 17 to 15 (mM/min), while the desired yield was increased further from 90 to 94%. As seen in the figure, both the production rate and the yield were driven to the new targets, although the weighting of the production rate resulted in a more rapid adjustment. (Note: it would be straightforward to reformulate the GR2R controller to use alternative objective functions in order to improve the performance with respect to yield.) In order to achieve these new specifications, the controller determined that the manipulated variables (flow rate and displacer concentration) should change as shown in the figure. The displacer concentration was first decreased and the flow rate was increased in order to produce the initial increase in production rate and yield. After the 5th run, the displacer concentration was continuously decreased and the flow rate exhibited a sharp initial decrease in order to attempt to satisfy the new yield target of 94%. It turned out that this yield target was quite difficult for this particular system. The interplay between displacer concentration and flow rate determined by the controller for this particular case is not intuitively obvious, and will be the subject of a future investigation.

Conclusions

There is a pressing challenge in the biotechnological industry to develop effective nonlinear preparative chromatographic processes. In order to address this challenge, we have developed a novel GR2R technique that has the ability for simultaneous optimization and control of nonlinear chromatographic processes. The strategy presented can optimize and control the process in the presence of batch-to-batch and sporadic variations and can have a significant impact on the design and operation of more efficient preparative chromatographic processes. The results presented in this article demonstrate that the current practice of using fixed optimal conditions can lead to suboptimal performance in the pres-

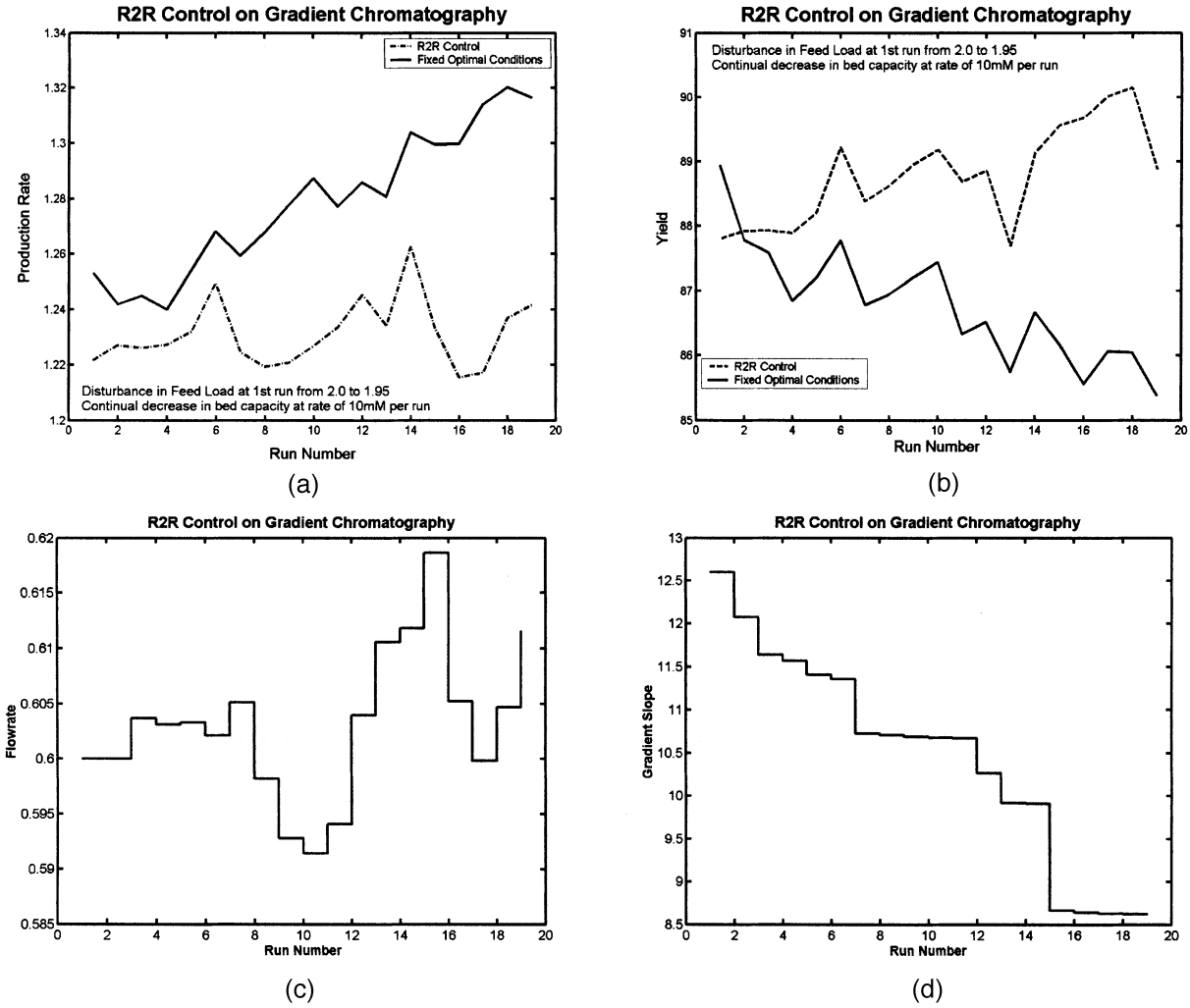

Figure 8. Production rate and yield of gradient separation process operating with and without R2R control in the presence of unmeasured step (feed load at start up from 2.0 to 1.95) and drift (continuous decrease in bed capacity at the rate of 10 mM per run from startup) disturbance.

(a) Change in production rate in each run; (b) change in yield in each run; (c) optimal change in flow rate at each run computed by GR2R; (d) optimal change in gradient slope at each run computed by GR2R. a and b the solid lines are the fixed optimal condition results, and the dotted lines are the result obtained using GR2R.

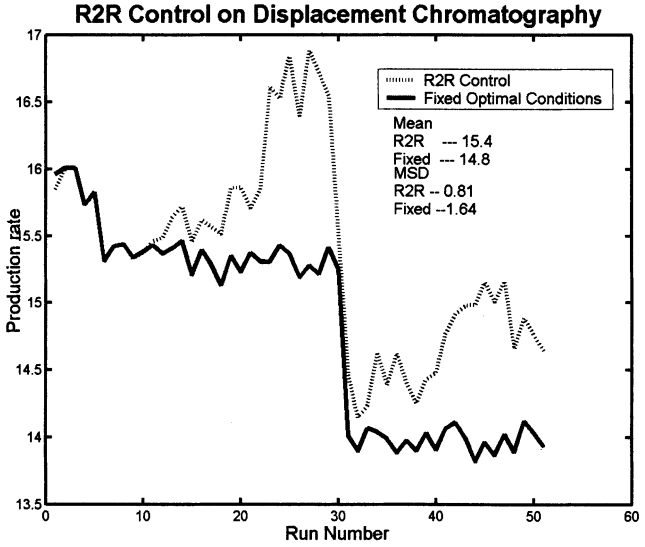

Figure 9. Production rate of displacement separation process operating with and without R2R control in the presence of unmeasured step disturbances of feed load (at 6th run from 1.0 to 0.95) and feed concentration (α chymotrypsinogen A at 31st run from 0.15 to 0.14 mM).

The solid line is the fixed optimal condition result and the dotted line is the result obtained using GR2R.

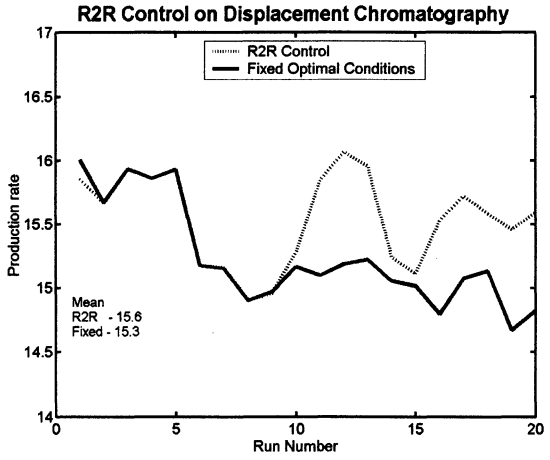

Figure 10. Production rate of displacement separation process in the presence of unmeasured (feed load at 6th run from 1.0 to 0.95) and autocorrelated (continuous decrease in bed capacity at the rate of 1.0 mM per run from 6th run) disturbances.

The solid line is the fixed optimal condition result and the dotted line is the result obtained using GR2R.

ence of measured and unmeasured disturbances. In contrast, processes using generalized run to run control can result in an improved performance in the presence of a variety of disturbances. The GR2R strategy is highly efficient in rejecting disturbances, as well as for target tracking.

We will validate this approach in future work with experimental results and will develop a protocol for updating the parameters of the physical model. For more complex systems, the increased nonlinearity in the empirical model will necessitate the use of rigorous nonlinear optimization algorithm. Further efforts will be made towards using dynamic programming methods (Cuthrell and Biegler, 1987) to decrease the computational cost involved in such complex nonlinear optimization. The GR2R control method presented in this article

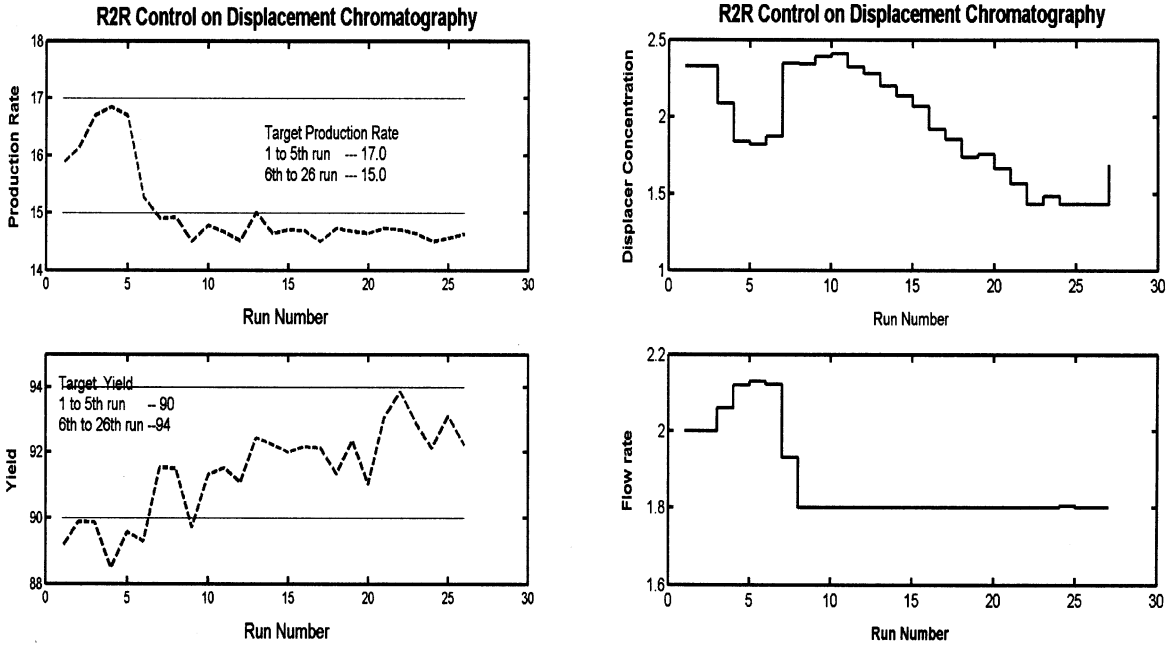

Figure 11. Varying target specifications: production rate changed from 17 to 15 at 6th run; yield changed from 90 to 9 at 6th run.

has significant potential for improving the performance of large-scale chromatographic processes.

Acknowledgments

The financial support of Amersham Pharmacia Biotech is gratefully acknowledged.

Notation

C_i = mobile phase concentration, mM
C_{fi} = feed concentration, mM
C_1 = mobile phase salt concentration, mM
D_{ai} = axial dispersion coefficient, cm^2/s
F = flow rate, mL/min
H_i = height equivalent to a theoretical plate, cm
k = run number
k_{mi} = lumped mass transport coefficient, s^{-1}
K_{Smai} = steric mass action isotherm equilibrium constant
L = length of column, cm
M = control horizon
P = prediction horizon
PR = production rate, mM/min
Q_i = stationary phase concentration, mM
$\bar{Q}_1$ = concentration of bound salt that is not sterically shielded, mM
Q_i^{equil} = equilibrium stationary phase concentration, mM
R = particle radius, cm
t_{cyc} = cycle time, min
t_f = feed time, min
u = superficial velocity, cm/s
V_f = feed volume, mL
V_{sp} = stationary phase volume, cm^3
x = axial distance, cm
Y = yield

Greek letters

β = weights on the magnitude of the change in the input $\Delta\bar{u}$
Γ = weights on the magnitude of the input $\bar{u}$
δ = weights on the prediction error in MPC
ϵ_t = total porosity
Λ = ionic capacity, mM
ν_i = characteristic charge for ith component
σ_i = steric factor

Literature Cited

Adivikolanu, S., and E. Zafiriou, "Extensions and Performances/Robustness Tradeoffs of the EWMA Run-to-Run Controller by Using the Internal Model Control Structure," *IEEE Trans. on Electronics Packaging Mftg.*, **23**, 56 (2000).

Bequette, B. W., "Nonlinear Control of Chemical Processes. A Review," *Ind. Eng. and Chemistry Res.*, **30**, 1391 (1991).

Billings, S. A., "Identification of Nonlinear Systems—a Survey," *IEE Proc. Pt. D.*, **127**, 272 (1980).

Brooks, C. A., and S. M. Cramer, "Steric Mass-Action Ion-Exchange: Displacement Profiles and Induced Salt Gradients," *AIChE J.*, **38**, 1969 (1992).

Castillo, E. D., and A. M. Hurwitz, "Run-to-Run Process Control: Literature Review and Extensions," *J. of Quality Technol.*, **29**, 184 (1997).

Castillo, E. D., and J. Y. Yeh, "An Adaptive Run-to-Run Optimizing Controller for Linear and Nonlinear Semiconductor Processes," *IEEE Trans. Semiconductor Mftg.*, **11**, 285 (1998).

Clarke, D. W., and P. J. Gawthrop, "Self tuning Controller," *Proc. Inst. Elect. Eng.*, **122**, 929 (1975).

Chen, S., S. A. Billings, C. F. N. Cowan, and P. M. Grant, "Practical Identification of NARMAX Models using Radial Basis Functions," *Int. J. Control*, **52**, 1327 (1990).

Crowley, T. J., C. A. Harrison, and F. J. Doyle III, "Batch-to-Batch Optimization of PSD in Emulsion Polymerization Using a Hybrid Model," *Proc. Amer. Control Conf.*, **2**, 981 (2001).

Cuthrell, J. E., and L. T. Biegler, "On the Optimization of Differential-Algebraic Process Systems," *AIChE J.*, **33**, 1257 (1987).

Dorsey, A. W., and J. H. Lee, "Subspace Identification for Batch Processes," *Proc. of American Control Conf.*, **3**, 2538 (1999).

Edgar, T. F., W. J. Campbell, and C. Bode, "Model-Based Control in Microelectronics Manufacturing," *Proc. Conf. on Decs. & Control*, 4185 (1999).

Felinger, A., and G. Guiochon, "Optimizing Experimental Conditions for Minimum Production Cost in Preparative Chromatography," *AIChE J.*, **40**, 594 (1994).

Felinger, A., and G. Guiochon, "Comparing the Optimum Performance of the Different Modes of Preparative Liquid Chromatography," *J. Chromatog.*, **752**, 31 (1996a).

Felinger, A., and G. Guiochon, "Optimizing Experimental Conditions in Overloaded Gradient Elution Chromatography," *Biotechnol. Prog.*, **12**, 638 (1996b).

Frey, D. D., "Minimum Variance Purity Control of Preparative Chromatography with Simultaneous Optimization of Yield. An On-line Species-Specific Detector," *ACS Symp. Ser. Anal. Biotechnol.; Capillary Electrophor. Chromatogr.*, **434**, 141 (1990).

Frey, D. D., "Feedback Regulation in Preparative Elution Chromatography," *Biotechnol. Prog.*, **7**, 213 (1991).

Fruzzetti, K. P., A. Palazoglu and K. A. McDonald, "Nonlinear Model Predictive Control Using Hammerstein Models," *J. Proc. Cont.*, **7**, 31 (1997).

Gallant, S. R., S. Vunnum and S. M. Cramer, "Optimization of Preparative Ion-Exchange Chromatography of Proteins: Linear Gradient Separations," *J. of Chromatog. A,* **725**, 295 (1996).

Garcia, C. E., D. M. Prett, and M. Morari, "Model Predictive Control: Theory and Practice—A Survey," *Automatica*, **25**, 335 (1989).

Gattu, G., and E. Zafiriou, "Methodology for On-line Setpoint Modification for Batch Reactor Control in the Presence of Modeling Error," *Chem. Eng. J.*, **75**, 21 (1999).

Gillet, D., O. D. Crisalle, and D. Bonvin, "Run-to-Run Control of DC-Sputtering Processes," *Proc. Amer. Control Conf.*, **3**, 1997 (2001).

Glueckauf, E., and J. I. Coates, "Theory of Chromatography: IV. The Influence of Incomplete Equilibrium on the Front Boundary of Chromatograms and on the Effectiveness of Separation," *J. Chem. Soc.*, 1315 (1947).

Golden, M. P., and B. E. Ydstie, "Adaptive Extremum Control Using Approximate Process Models," *AIChE J.*, **35**, 1157 (1989).

Guiochon, G., S. Golshan-Shirazi, and A. M. Katti, *Fundamentals of Preparative and Non-linear Chromatography*, Academic Press, New York (1994).

Hankinson, M., T. Vincent, K. Irani, and P. Khargonekar, "Integrated Real-Time and Run-to-Run Control of Etch Depth in Reactive Ion Etching," *IEEE Trans. Semiconductor Mftg.*, **10**, 121 (1997).

Henson, M. A., "Nonlinear Model Predictive Control: Current Status and Future Directions," *Comput. and Chem. Eng.*, **23**, 187 (1998).

Hernandez, E., and Y. Arkun, "Control of Nonlinear Systems Using Polynomial ARMA Models," *AIChE J.*, **39**, 446 (1993).

Lee, K. S., and J. H. Lee, "Convergence of Constrained Model-Based Predictive Control for Batch Processes," *IEEE Trans. Automatic Control*, **45**, 1928 (2000).

Luo, R. G., and J. T. Hsu, "Optimization of Gradient Profiles in Ion-Exchange Chromatography for Protein Purification," *Ind. Eng. and Chemistry Res.*, **36**, 444 (1997).

Natarajan, V., and S. M. Cramer, "A Methodology for the Characterization of Ion-Exchange Resins," *Sep. Sci. Technol.*, **35**, 1719 (2000).

Natarajan, V., B. W. Bequette, and S. M. Cramer, "Optimization of Ion-Exchange Displacement Separations I. Validation of an Iterative Scheme and Its Use as a Methods Development Tool," *J. of Chromatog. A.*, **876**, 51 (2000).

Natarajan, V., S. Ghose, and S. M. Cramer, *Biotechnol. Bioeng.*, in press (2002).

Ning, Z., J. R. Moyne, T. Smith, D. Boning, E. D. Castillo, J. Y. Yeh, and A. Hurwitz, "A Comparative Analysis of Run-to Run Control Algorithms in the Semiconductor Manufacturing Industry," *IEEE/SEMI Adv. Semiconductor Mftg. Conf.*, 375 (1996).

Pan, Y., and J. H. Lee, "Recursive Data-Based Prediction and Con-

trol of Product Quality for a Batch PMMA Reactor," *Proc. Amer. Control Conf.*, **3**, 1747 (2000).
Phillips, M. W., G. Subramanian, and S. M. Cramer, "Theoretical Optimization of Operating Parameters in Non-Ideal Displacement Chromatography," *J. of Chromatog.*, **454**, 1 (1988).
Sachs, E., A. Hu, and A. Ingolfsson, "Run by Run Process Control: Combining SPC and Feedback Control," *IEEE. Trans. Semiconductor. Mftg.*, **8**, 26 (1995).
Siouffi, A. M., and R. Phan-Tan-Luu,"Optimization Methods in Chromatography and Capillary Electrophoresis," *J. Chromatog. A*, **892**, 75 (2000).
Sistu, P. B., R. S. Gopinath, and B. W. Bequette, "Computational Issues in Nonlinear Predictive Control," *Comput. and Chem. Eng.*, **17**, 361 (1993).
Sreenivasan, R., T. Gougousi, Y. Xu, J. Kidder, Jr., E. Zafirioiu, and G. W. Rubloff, "Run to Run Control in Tungsten Chemical Vapor Deposition Using H2/WF6 at Low Pressures," *J. of Vacuum Sci. & Technol. B*, **19**, 1931 (2001).

Appendix

Steps for the Modified Gram Schmidt based identification

Regressor matrix P is factorized into an auxiliary matrix W and upper triangular matrix A as $P = WA$

- The first step is to estimate the upper triangular matrix A by
- $A = D^{-1}W^TP/W^TW$ where $D = W^TW$
- Then, an Auxiliary matrix W is estimated recursively by
- $W = P - W(A - I)$
- The third step is to compute the auxiliary parameter vector g using
- $g = D^{-1}W^TZ$
- Then, Θ is computed using
- $\hat{\Theta} = \hat{g} - (A - I)\hat{\Theta}$
- At each stage (kth in Eq. 13), the error reduction coefficient is computed using Modified Gram-Schmidt (MGS) procedure

$$[\text{err}]_k^i = \frac{\left(g_k^i\right)^2 \langle p_i^{k-1},\, z^{(k-1)}\rangle}{\langle z,z\rangle} \tag{A1}$$

The maximum error reduction column j is found and replaced with the kth column. MGS is again performed until the desired tolerance is reached.

Nonlinear recursive parameter estimation and model update

The nonlinear empirical model is then cast into a nonminimal state space realization using the delay coordinate method. The states are defined as

$$x_i^a(k) = \begin{bmatrix} y_1(k-i+1) \\ \cdot \\ \cdot \\ y_p(k-i+1) \end{bmatrix};\quad x_j^b(k) = \begin{bmatrix} u_1(k-j) \\ \cdot \\ \cdot \\ u_q(k-j) \end{bmatrix}$$

$$i = 1,.....n_y + 1; \qquad j = 1,.....n_u$$

where subscripts p and q denote the number of outputs and inputs, respectively. The state of the system $x(k)$ is defined as

$$x(k) = \left[x_1^a(k).....x_{n_y+1}^a(k)\, x_1^b(k).....x_{n_u}^b(k)\right]^T$$

The multiinput, multioutput empirical model can then be compactly written as

$$\begin{aligned} x(k+1) &= F[x(k),u(k)] \\ y(k) &= h[x(k)] \end{aligned} \tag{A2}$$

The estimator for this model can be designed as

$$\begin{aligned} \hat{x}(k+1|k) &= F[\hat{x}(k|k),u(k)] \\ \hat{x}(k|k) &= \hat{x}(k|k-1) + L(k)[\tilde{y}(k+1) - \hat{y}(k+1/k)] \\ \hat{y}(k) &= h[\hat{x}(k|k)] \end{aligned} \tag{A3}$$

where $k|k$ denotes the estimated value at kth batch knowing the information available at the kth batch.

The major Steps in RPEM are:

Time Update:

$$\hat{x}(k+1/k) = F[\hat{x}(k/k),u(k),\theta(k)]$$

Output Calculation:

$$\hat{y}(k+1/k) = h[\hat{x}(k+1/k)]$$

Error Calculation:

$$\epsilon(k+1/k) = \tilde{y}(k+1) - \hat{y}(k+1/k)$$

Measurement Update:

$$\hat{x}(k+1/k+1) = \hat{x}(k+1/k) + L(k)\epsilon(k+1/k)$$

Parameter Update:

$$\hat{\Psi}(k+1) = \begin{bmatrix} \hat{\theta}(k+1) \\ L(k+1) \end{bmatrix} = \hat{\Psi}(k) + \frac{P_c(k)\varphi(k)}{\lambda(k) + \varphi^T(k)P_c(k)\varphi(k)}\epsilon(k+1/k)$$

$\eta(k+1)$ Calculation:

$$\eta(k+1) = [I - L(k)C(k)]\frac{\partial F[\hat{x}(k/k),u(k),\theta(k)]}{\partial \hat{x}(k/k)}\eta(k) + \frac{\partial\{F[\hat{x}(k/k),u(k),\theta(k)] + L(k)\epsilon(k+1/k)\}}{\partial \hat{\Psi}(k/k)}$$

$P_C(k+1)$ Calculation:

$$P_C(k+1) = P_C(k) - \frac{P_C(k)\varphi(k)\varphi^T(k)P_C(k)}{\lambda(k) + \varphi^T(k)P_C(k)\varphi(k)} + \delta I$$

$\varphi(k+1)$ Calculation:

$$\varphi(k+1) = \eta^T(k+1)C_k^T$$

where $\lambda(k)$ denotes "forgetting factor," and δ is a regularization parameter selected to maintain $P_C(k)$ positive definite. The initial value of $\varphi(0)$ is selected as matrix of zeros and $P_C(0)$ is a diagonal matrix.

Manuscript received Feb. 22, 2002, and revision received July 11, 2002.