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AUTOMATION AND CONTROL ISSUES IN THE DESIGN OF A PHARMACEUTICAL PILOT PLANT

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Abstract: The role of process design and automation for a pilot plant facility in the pharmaceutical industry is discussed. Vessels range from 80 to 5000 liters, with various materials of fabrication. A simulator was developed to predict limitations to operating performance. Challenges to operation and control of vessels in this facility are discussed, and illustrative simulation results are presented. *Copyright © 2002 IFAC*

Keywords: chemical process, batch reactor, process control, simulation, design.

1. MOTIVATION

Pilot plant studies are critical to the successful development of a drug manufacturing process, as these form the bridge between laboratory bench scale studies and full-scale manufacturing. In addition to performing process validation and setting the standards for good manufacturing practices (GMP), pilot plants often produce significant amounts of a drug for clinical trials. Because of the wide variety of possible processes that may need pilot plant studies at any one time, many vessels with different volumes and fabrication materials must be available. Also, operation over a wide range to reactor temperatures is often required (roughly –70 to 150 ^{o}C) placing severe demands on the process equipment and automation system design. The dynamic nature of batch (and semi-batch) processing places performance limitations that would not be detected from solely a quasi-steady-state analysis.

In this paper we discuss important issues in the design of a multiple scale organic chemicals pilot plant for a major pharmaceutical R&D facility. We begin with a review of batch process operation and pharmaceutical research, followed by a description of a process in the pilot plant. Specifications for the automation system are presented, followed by a model and simulator developed to understand possible performance limitations to the proposed process/control design. The effect of reactor type and heat transfer fluid on the vessel heat transfer capability is presented. Dynamic performance limitations are also presented.

2. BACKGROUND

Batch processes present challenging control problems due to the time-varying nature of operation. Chylla and Haase (1993) present a detailed example of a batch reactor problem in the polymer products industry. This reactor has an overall heat transfer coefficient that decreases from batch-to-batch, due to fouling of the heat transfer surface inside the reactor. Bonvin (1998) discusses a number of important topics in batch processing, including safety, product quality and scale-up.

Bequette (1998) discusses the effect of process scale-up on batch reactor operability. Information obtained from a reaction calorimeter can be used to help decide the proper vessel and operating conditions for a pilot plant study. Procedures for estimating parameters in a pilot plant reactor and a comparison between model and experiment are presented.

LeLann *et al*. (1999) discuss tendency modeling (using approximate stoichiometric and kinetic models for a reaction), and the use of model predictive control (linear and nonlinear) in batch reactor operation. Studies of a hybrid heating-cooling system on a 16 liter pilot plant are presented.

Anderson (2000) presents a wide-range of topics on pharmaceutical process development, including a number of different problems related to process scale-up. It is clear that a process chemist's view of "in-process controls" is much broader than the view of a typical control systems engineer.

Pisano (1997) discusses the management of process development projects in the pharmaceutical industry. Case studies are used to illustrate the effect of resource allocation decisions at different stages of a project.

3. PROCESS DESCRIPTION

The pilot plant, currently at completion of the design phase, has vessels that range from 80 to 5000 liters, some constructed of alloy and others that are glass-lined. In addition some vessels have half-pipe coils for heat transfer, while others have jackets with agitation nozzles. The facility has two heat transfer fluid systems (hot and cold syltherm) that are used for most of the heating and cooling needs. Each jacketed vessel has a recirculating heat transfer system with feed and exit valving for the hot and cold fluids. In addition, some vessels have nitrogen coolers for cryogenic operation.

A simplified schematic for a non-cryogenic heat transfer service is shown in Figure 1. Two items are distinctive to note: (i) there is a single control valve, and (ii) it is placed on the heat transfer fluid return stream. One reason for the single control valve is to reduce the capital and maintenance costs. On-off valves are used to provide fluid from either the cold or hot heat transfer fluid header; similarly, on-off valves return fluid to the appropriate distribution system. It is somewhat counter-intuitive that the control valve is placed on the fluid return stream, rather than the inlet stream. The reason for this is that a valve placed on the inlet stream would have a potentially large differential in temperature, since cold syltherm (at -25^oC) could be entering the jacket recirculation header at a relatively warm temperature (100 ^oC or more). Placing the valve on the fluid return stream minimizes these temperature differentials. It is clearly important to switch between the hot and cold heat transfer system, depending on the condition of the jacket temperature. Although not absolutely necessary, it makes sense to have the on-off valves for entering and exiting fluid to be set to the same position (i.e. both hot valves open simultaneously, etc.).

During cryogenic service the recirculating heat transfer fluid passes through a liquid nitrogen exchanger.

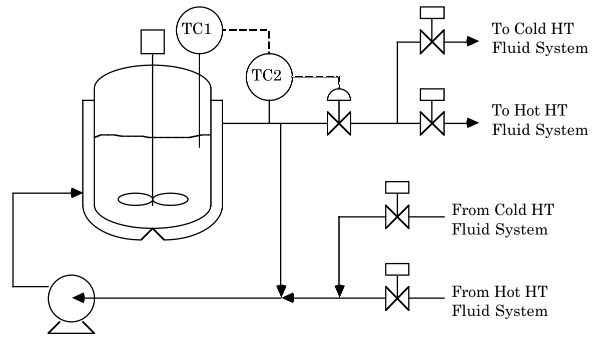

Fig. 1. Characteristic Pilot Plant Vessel Control Strategy. Slave controller based on jacket outlet temperature shown. Alternative is jacket inlet temperature.

4. AUTOMATION SYSTEM SPECIFICATIONS

This is a continuous-discrete (hybrid) system, since the temperature control strategy is continuous, but there are discrete switches made depending on the operating condition. There are a number of important safety-related constraints. Many of these vessels are glass-lined, placing constraints on temperature differences and rates of temperature changes allowed. These constraints include

- a maximum temperature difference between the vessel and jacket
- a maximum rate-of-change of jacket temperature

Although the heat transfer fluid can be used over a wide range of temperatures, the film heat transfer coefficient is a strong function of temperature due to viscosity effects. The "cooling time" of a large reactor operating at a low temperature can be substantially longer than that of a small reactor operating at a high temperature, due to this strong temperature effect. A simulator was developed to:

- understand possible performance limitations due to scale and operating conditions
- detect possible problems with the unique circulating heat transfer fluid system
- test the effect of specified temperature gradient constraints
- assist with controller design and selection of tuning parameters for system start-up

One finding with the current pilot plant is that operators often do not use the cascade temperature control strategy, preferring to manipulate the jacket temperature setpoint, thus serving as the "outer-loop" controller themselves. A goal with the new facility is be able to have better tuning parameters on the reactor temperature controller, resulting in fully closed-loop control.

5. MODELING AND SIMULATION

5.1 Modeling Assumptions (Appendix)

It is assumed that the reactor and jacket are well-mixed, resulting in differential equations for the material and energy balances. The reactor shell (including a glass lining, if used), and reactor internals (agitator and baffles) are at the same temperature as the reactor, so their "thermal mass" is including in the reactor energy balance. Similarly, the jacket shell is at the jacket temperature, with an associated thermal mass. The heat transfer area is proportional to the reactor liquid level (between a minimum and maximum heat transfer volume); also, the reactor shell thermal mass varies linearly with the liquid level. Heat transfer coefficients are calculated using well-known correlations; see Garvin (1999) or Dream (1999) for examples. Parameters, viscosity in particular, are a function of temperature.

Steady-state energy balances are used for the recirculating heat transfer system, however small lags are used for realism and to eliminate problems with algebraic loops in solving the differential equations. Also, there is a 0.2 ^{o}C increase across the pump in the recirculation loop.

5.2 Linear Analysis

A linear state-space reactor model is developed to ease the control system design and tuning. The model is realistic when simple heating and cooling is being performed. It also approximates the behavior quite well when a feed-limited reaction is occuring in semi-batch mode. If jacket inlet temperature is considered the input (this is appropriate when the reactor temperature controller output is the setpoint for the jacket inlet temperature controller), the linear model is

$$\begin{bmatrix} \frac{dT}{dt} \\ \frac{dT_j}{dt} \end{bmatrix} = \begin{bmatrix} -\frac{UA}{\left(mc_p\right)_r} & \frac{UA}{\left(mc_p\right)_r} \\ \frac{UA}{\left(mc_p\right)_j} & -\frac{\left(\dot{m}_j c_{pj} + UA\right)}{\left(mc_p\right)_j} \end{bmatrix} \begin{bmatrix} T \\ T_j \end{bmatrix} + \begin{bmatrix} 0 \\ \frac{\dot{m}_j c_{pj}}{\left(mc_p\right)_j} \end{bmatrix} T_{jin} + \begin{bmatrix} \frac{1}{\left(mc_p\right)_r} \\ 0 \end{bmatrix} q_{gen}$$

$$T = \begin{bmatrix} 1 & 0 \end{bmatrix} \begin{bmatrix} T \\ T_j \end{bmatrix}$$

The resulting input-output transfer function model is

$$T(s) = \frac{k_p}{\tau^2 s^2 + 2\zeta\tau s + 1} T_{jin}(s) + \frac{k_d\left(\tau_n s + 1\right)}{\tau^2 s^2 + 2\zeta\tau s + 1} q_{gen}(s)$$

$$k_p = 1, \qquad \tau^2 = \frac{\left(mc_p\right)_j \left(mc_p\right)_r}{\left(\dot{m}_j c_{pj}\right) UA}$$

$$2\zeta\tau = \frac{UA\left[\left(mc_p\right)_j + \left(mc_p\right)_r\right] + \left(\dot{m}_j c_{pj}\right)\left(mc_p\right)_r}{\left(\dot{m}_j c_{pj}\right) UA}$$

IMC-based PID Tuning Parameters. Using IMC-based PID tuning rules (Morari and Zafiriou, 1989; Bequette, 2002), with a desired first-order closed-loop response with a time constant of λ, we find

$$k_c = \frac{2\zeta\tau}{k_p \lambda}, \quad \tau_I = 2\zeta\tau, \quad \tau_D = \frac{\tau^2}{2\zeta\tau}$$

We can also use the following order of magnitude analysis to reduce the expressions

$$\dot{m}_j c_{pj} >> \left(mc_p\right)_r \approx \left(mc_p\right)_j$$

so,

$$\tau_I = 2\zeta\tau \approx \frac{\left(mc_p\right)_r}{UA}$$

$$\tau_D = \frac{\tau^2}{2\zeta\tau} \approx \frac{\left(mc_p\right)_j}{\dot{m}_j c_{pj}}$$

$$k_c = \frac{2\zeta\tau}{k_p \lambda} = \frac{\tau_I}{\lambda} \approx \frac{\left(mc_p\right)_r / UA}{\lambda}$$

Notice that the controller tuning parameters are clear functions of the natural reactor/jacket physical parameters. The "cooling time" (reactor heat transfer time constant) is the dominant reactor time constant. These values indicate how tuning parameters can be expected to vary with process scale. Although these relationships are best for step setpoint (or output disturbance) changes, the tuning parameters for ramp setpoints and input disturbances vary similarly with scale and parameter values.

5.3 Simulation Using MATLAB/SIMULINK

The simulator was developed in the MATLAB/SIMULINK programming environment, because of ease of development and flexibility for control system design and analysis. The reactor and heat transfer system models were verified based on agreement with previous pilot plant experimental studies (using a different heat transfer fluid). Note that this is a hybrid discrete/continuous simulation, due to switching decisions that are made as a function of the operating condition. Discrete switches can occur, for example, due to imposed constraints on reactor vessel-jacket temperature differences, as well as limits on the rate-of-change of jacket temperature. Effects of valve hysteresis and finite resolution (valve stiction) are also included.

6. ILLUSTRATIVE RESULTS

In this section we focus on the effect of reactor size and material of construction on the expected dynamic behavior of the reactors.

6.1 Heat Transfer Studies

Here we present examples of how the reactor type and heat transfer fluid affect the heat transfer coefficient.

Effect of Reactor Type. Figure 2 shows that the overall heat transfer coefficient is much higher for an alloy reactor/half-pipe jacket than for a glass-lined carbon steel reactor/agitation nozzle jacket.

Effect of Heat Transfer Fluid. An existing pilot plant uses an ethylene glycol mixture as the heat transfer fluid. Figure 3 indicates that a similar reactor in the new pilot plant facility using Syltherm would be expected to have a significantly lower heat transfer coefficient, but be capable of operating over a wider range of temperatures.

6.2 Control: Batch Heat-up/Cool-down

The reactor temperature output is similar to a split-range set-up, as shown in Figure 4. Figure 5 illustrates that a vessel can have significantly different dynamic behavior depending on whether it is being heated or cooled. The increase in reactor temperature results in a much faster response than a decrease for two reasons: (i) the jacket heat transfer fluid has a much higher viscosity (resulting in a lower overall heat transfer coefficient) at low temperatures, and (ii) the fluid flowrate/jacket temperature gain is proportional to the difference between the jacket temperature and make-up fluid temperature (-25 ^{o}C), which becomes small at low jacket temperatures. Notice that the initial response for the temperature increase is constrained by the ramp limit of 5^{o}C/min on the jacket temperature. Figure 6 shows that the jacket temperature controller output is saturated for the setpoint decrease, but not the increase. The temperature response of an organic solvent is much faster than water because of the heat capacity difference, as shown in Figure 7.

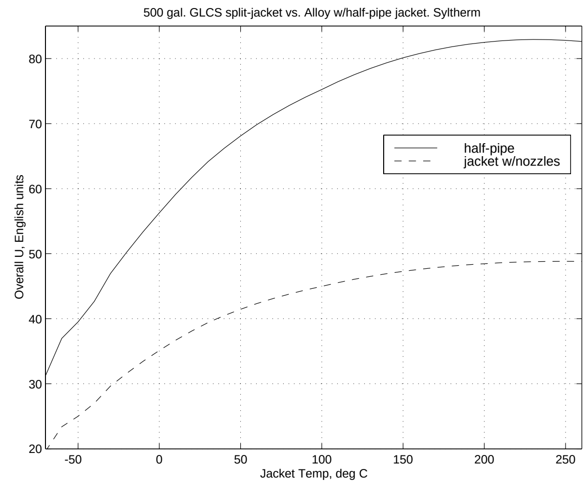

Fig. 2. Overall heat transfer coefficient for 500 gallon reactors. Comparison of alloy-half pipe with Glass-Lined Carbon Steel (GLCS).

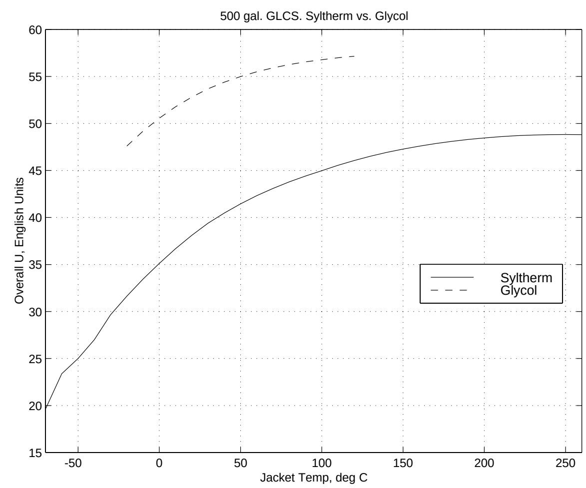

Fig. 3. Overall heat transfer coefficient for 500 gallon GLCS reactor. Comparison of Syltherm with Glycol.

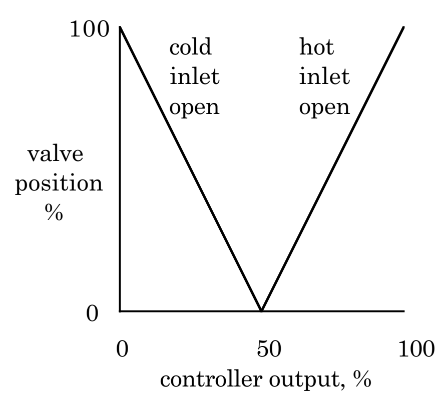

Fig 4. Reactor temperature controller output.

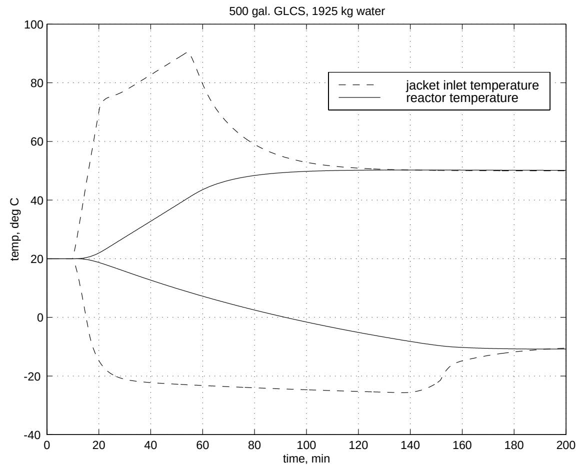

Fig. 5. Comparison of responses for ± 30 °C reactor temperature setpoint Changes at t = 10 min. 500 gal. GLCS filled with water (1925 kg).

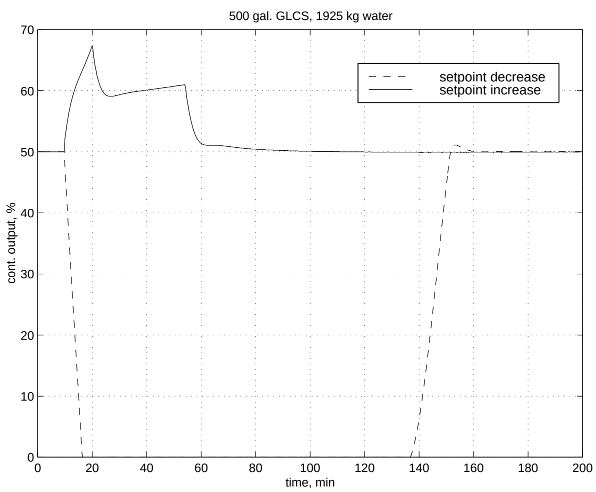

Fig. 6. Controller outputs for ± 30 °C reactor temperature setpoint changes. 500 gal. GLCS filled with water (1925 kg).

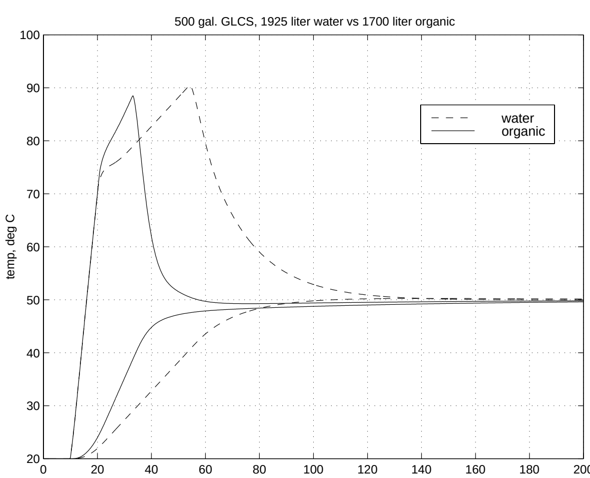

Fig. 7. Comparison of temperature responses for a 30 °C batch setpoint change. 500 gal. GLCS, water (1925 liters) vs. organic (1700 liters).

6.3 Control: Semibatch Reaction

The previous plots were for simple heating/cooling applications. Here we consider a feed-limited semi-batch reaction. The feed and heat flow profiles are shown in Figure 8, and the temperature profiles are shown in Figure 9. Notice that the temperature control performance is better immediately after the feed is initiated, than it is when the flow is stopped. When the flow (and reaction) is stopped, the temperature decreases because of the jacket thermal capacity. The liquid nitrogen flow is stopped (Figure 10), but the reactor takes some time to heat because the only heat flow into the system is due to the pump in the heat transfer loop.

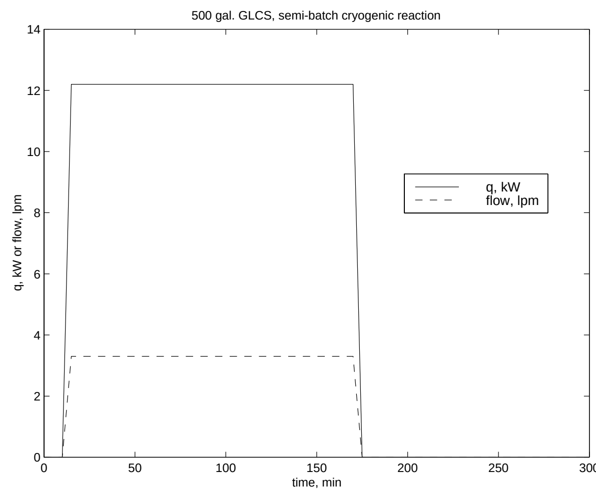

Fig. 8. Reaction heat flow and feed flowrate for semibatch reaction.

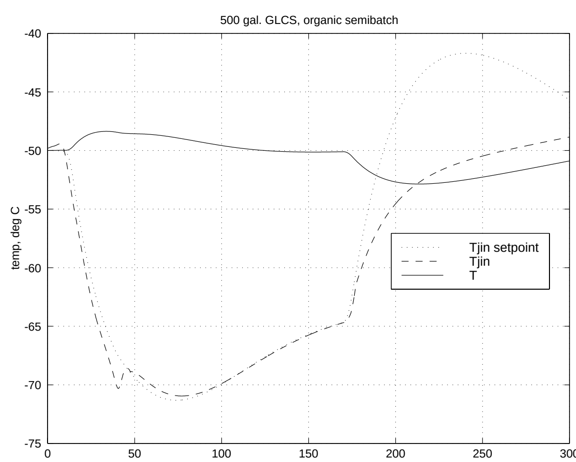

Fig. 9. Temperature response for a semibatch reaction. 500 gal. GLCS, organic solvent with 1147 liter initial volume.

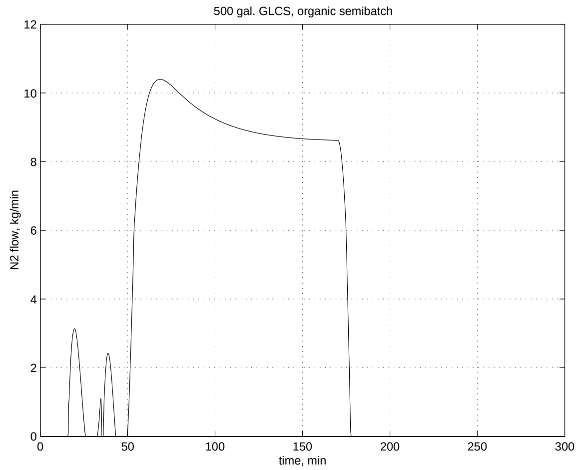

Fig. 10. Nitrogen flow response for a semibatch reaction. 500 gal. GLCS, organic solvent with 1147 liter initial volume.

6.4 Control: Other Issues

Although the results are not shown here, it is important to have external reset windup protection on the reactor temperature controller, since the actual jacket temperature will not necessary match the jacket temperature setpoint. Also, the secondary process gain is low at very high or low temperatures, so gain scheduling can be used for more effective control. A concern, before the simulation studies were conducted, was that significant *chattering* of the make-up valve could occur when the reactor temperature controller was close to mid-range (50%); this does not appear to be a problem even with significant valve stiction.

7. SUMMARY

The importance of flexibility sets limits on the type of control system that can be used. In the presentation we will provide simulations to show the additional performance achievable when model predictive control is used, compared to the (more or less) classical PID strategies implemented in the pilot plant control system.

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APPENDIX. Modeling Equations

$$\frac{dV}{dt} = F$$

$$\frac{dN_A}{dt} = FC_{Af} - Vr_A$$

$$\frac{dT}{dt} = \left[F\rho_f c_{pf}\left(T_f - T\right) + \left(-\Delta H_{rxn}\right)Vr_A\right] \Big/ \left(mc_p\right)_r$$

$$+ \left[-UA\left(T - T_j\right) + q_{gen}\right] \Big/ \left(mc_p\right)_r$$

$$\frac{dT_j}{dt} = \dot{m}_j c_{pj}\left(T_{jin} - T_j\right) + UA\left(T - T_j\right) \Big/ \left(mc_p\right)_j$$

$$T_{jin} = T_j + \frac{\dot{m}_{jf}}{\dot{m}_j}\left(T_{jf} - T_j\right)$$

where

$$r_A = k_0 \exp\left(-E/RT\right) N_A/V$$

$$q_{gen} = \left(-\Delta H\right)Vr_A$$

$$A = A_{\min} + \left(A_{\max} - A_{\min}\right)f$$

$$M_m = M_{\min} + \left(M_{\max} - M_{\min}\right)f$$

$$M_{mj} = M_{mj1} + M_{mj2}$$

$$\left(mc_p\right)_r = V\rho c_p + M_m c_{pm}$$

$$\left(mc_p\right)_j = V_j \rho_j c_{pj} + M_{mj} c_{pm}$$

$$f = \frac{V - V_{\min}}{V_{\max} - V_{\min}}$$

$$0 \le f \le 1$$