A large, white, cylindrical industrial reactor vessel is the central focus, surrounded by a dense network of pipes, scaffolding, and walkways. The structure is set against a clear blue sky with some light clouds. The reactor has several vertical pipes extending from its base and top. The overall scene is an industrial facility, likely a chemical or petrochemical plant.

*Computer-aided
Process Optimisation
2nd Symposium
Hürth, 2009*

CRYOGENIC BATCH REACTOR OPTIMISATION

John E Edwards
P&I Design Ltd
Teesside, UK

CRYOGENIC BATCH REACTOR OPTIMISATION ABSTRACT

There is an increasing requirement in drug manufacturing to carry out chiral reactions at low temperatures. This is due to Federal Drug Administration (FDA) directives requiring drugs to be developed as single enantiomers, which are chiral molecules that cannot be superposed on their mirror image. Two enantiomeric forms can display dramatically different biological activities where one can be an active drug and the other exhibit fatal toxicity. Enantiomers can be separated by using chromatography, crystallisation, chemical or biological synthesis.

The chemical synthesis approach has driven the requirement for low temperature reactions, where typically a temperature reduction of $\Delta T \downarrow 10^\circ\text{C}$ will result in a reaction rate $\Delta H_R \downarrow 50\%$, which allows for exploitation of the following:

1. Reduction of competing mechanisms and reactions
2. Entropy variance can be exploited, $\Delta G = \Delta H_R - T\Delta S$ when low T
3. Varying reaction rates for diastereoisomers
4. Stability and variation of energy levels of transition states
5. Reduced intra-molecular rearrangements
6. Stability of chiral starting materials and intermediates

A pharmaceutical manufacturer is considering investing in a multi-purpose batch reactor facility to carry out chiral reactions. This study is to establish the "proof of concept" for controlling chiral reactions, in a 2300L Hastelloy reactor using a heat transfer fluid, cooled by a multi-stage refrigeration facility. Reactions will be performed at temperatures below -70°C , with reaction rates ΔH_R not exceeding -10 kW . The economics of cooling with liquid nitrogen are also to be considered.

The design and operational parameters were optimised using dynamic modelling techniques based on CHEMCAD simulation software. The dynamic models allowed detailed study of the process flow and heat transfer characteristics as fluid physical properties changed with temperature. The Excel interface capabilities allowed operating strategies to be developed and hydraulic and heat transfer parameters to be calculated, validated and tested.

The design and its optimisation took the following into consideration:

1. Selection of heat transfer fluid with suitable flow characteristics
2. Optimum sizing of the refrigeration plant, allowing spare capacity for future dual reactor capability
3. Minimise the heat transfer fluid system volume consistent with stable operation
4. Minimise circulation flow rates consistent with acceptable heat transfer conditions
5. Sizing of balance tanks to protect evaporator from transient high temperature
6. Minimise ambient and pumping heat gain
7. Minimise capital expenditure (CapEx)

Operational optimisation considered the following criteria:

1. Minimise process cycle times
2. Study of optimum temperature for switching utility streams
3. Optimise balance tank weir cold side to hot side flow rate
4. Establish standby mode operating conditions

The key features of the CHEMCAD dynamic model included:

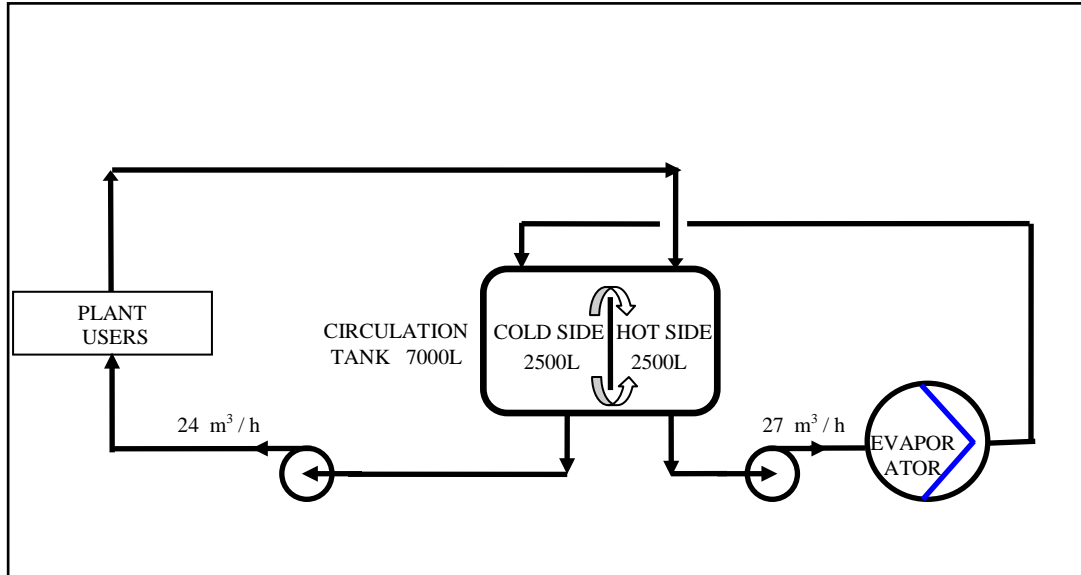
1. Adjustment and balancing of circulation flows
2. Transient heat transfer behaviour
3. Temperature set point ramping during cool down and heat up
4. Reactor half coil pressure drop prediction using dynamic friction factor
5. Reaction scheduling and rate control
6. Control of evaporator and heater duties

The design and optimisation study confirmed the suitability of Syltherm XLT, as the heat transfer fluid, and the requirement for a multi-stage refrigeration plant duty of 60 kW. It was demonstrated that chiral reactions could be performed in a 2300L Hastelloy reactor at temperatures below -70°C , with a reaction rate ΔH_R of -10 kW .

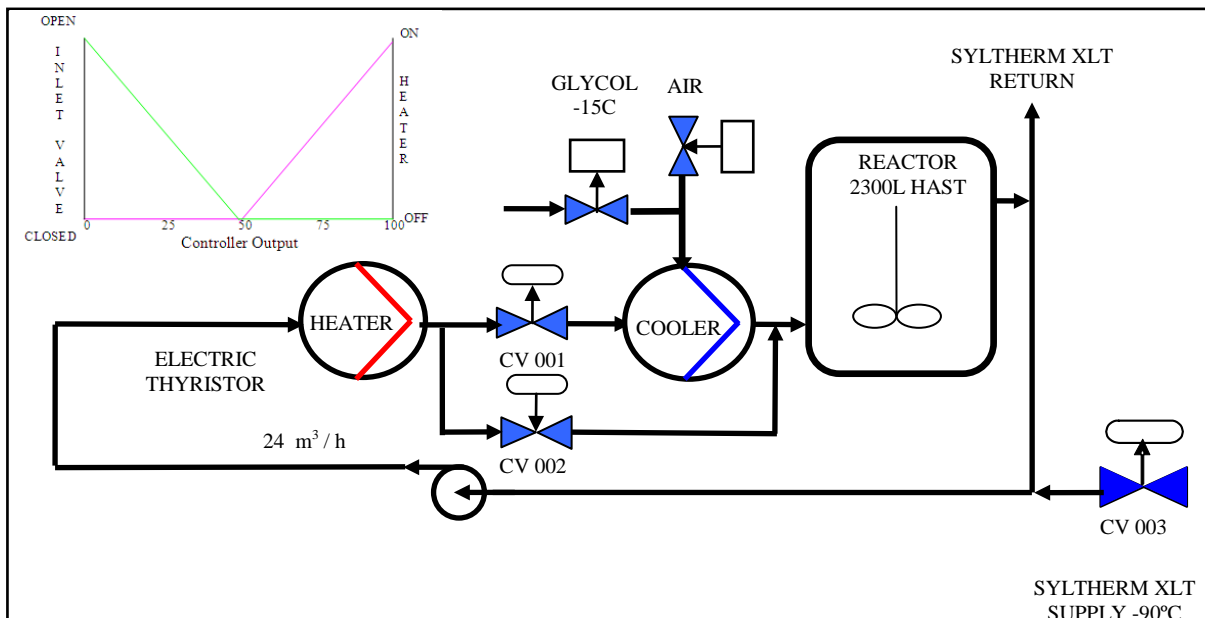
The study demonstrates the benefits of using dynamic simulation, when applied to batch processes, in simulating real transient behaviour to obtain an optimal design solution and in testing operational strategies.

CRYOGENIC BATCH REACTOR SYSTEM DESCRIPTION

The proposed scheme uses Syltherm XLT heat transfer fluid which is circulated through a refrigeration plant evaporator at a flowrate of 27 m³/h, with an off coil temperature of -90°C. The flowrate to plant is variable depending on the demand, with a maximum of 24 m³/h. The refrigeration plant compressors have variable speed drives to provide enhanced turn down capability and energy saving. The refrigeration plant uses a circulation tank fitted with a baffle allowing overflow and underflow from the cold side to the hot side, as shown in the schematic. This arrangement provides a cold reservoir of Syltherm XLT to minimise the impact of hot process return temperatures on the refrigeration unit performance and provides a nominal cold to hot side weir flowrate of 3 m³/h.



The reactor temperature control module consists of a thyristor controlled electric heater, instead of steam, to avoid freezing problems, and cooler with a service of 50% ethylene glycol / water at -15°C. Syltherm XLT is circulated through the reactor jacket and half-coils in series at a constant flow rate in the range 24-30 m³/h to ensure acceptable velocity for heat transfer. All pumps are fitted with variable speed drives to allow minimisation of energy input to the pumped fluids.



In normal mode, the calibrated temperature range is -15°C to 175°C. Cooling valve CV-001 and bypass valve CV-002 are modulated in split range for a controller output 0 to 50%. The heater is modulated for a controller output 50 to 100% with the cooler bypassed.

In cryogenic mode, the calibrated temperature range is -100°C to -10°C. Jacket circulation is routed through the heater and bypasses the cooler. The heater thyristor controls and the Syltherm inlet control valve CV-003 valve are operated in split range as shown.

CHEMCAD DYNAMIC MODEL

The spreadsheet, below, controls the initialisation of the chemical reaction and the rate of reaction. The model operating volume, calculated liquid level, stirrer speed and reaction frequency factor are fed back to confirm correct data transfer.

CHEMCAD Simulation Control Spreadsheet for Exothermic Reactions						
Reactor Details			Reaction Parameters and Conditions		Simulation Results	
Working Volume	2.50 m ³	Manual Entry to CCD	Total Charge	2050.0 kg	Batch Time	3.58 h
Inside Diameter	1.56 m	Manual Entry to CCD	Molecular Weight	72.11 kg/kmol	Contents Temperature (Tc)	-70.37 °C
Wall Thickness	0.00953 m	←	Total Moles	28430.0 mol	Frequency Factor (Start Rx at Tc -70°C)	8.02 mol/m ³ m
Dished End Volume	0.38 m ³		Liquid Density	967.85 kg/m ³	Jacket Temperature	-86.06 °C
Dished End Height	0.458 m		Volume	2.12 m ³	Calculated Volume	2.16 m ³
Straight Side Height	0.33 m					
Dished End Area (Half coil)	2.08 m ²		Level Straight	0.91 m		
Maximum Area	6.11 m ²		Total Level	1.37 m	Calculated Liquid Level	1.33 m
Turbine Impellor Diameter	0.99 m	Manual Entry to CCD				
Agitator Speed	2.0 rps	←	Side Area (Baffled Jacket)	4.03 m ²	Impellor Speed	2.00 rps
Wall Density	8690 kg/m ³		Total	6.11 m ²		
Wall Specific Heat	0.423 kJ/kg-K					
Wall Thermal Conductivity	11.1 W/m-K		Reactant Charge	250.0 kg	Cell Colour Key	
Reactor Weight	3300 kg		Molecular Weight	72.11 kg/kmol	Calculated Data	
			Reactant Charge	3467.1 mol	Data to CCD	
					Data from CCD	
		Manual Entry to CCD	Heat of Reaction	-25.00 kJ/mol	CCD Validation Data	
			Total Heat of Reaction	-86676.7 kJ		
				-86.68 MJ	Calculated Overall Heat of Reaction	-6.99 kWh
			Reaction Time	3.40 h		
Conversion (mol/m) = FF(mol/m ³ m) * Rx Volume (m ³)			Conversion Rate	17.00 mol/m	Frequency Factor Validation	8.02 mol/m ³ m
Total H (MJ) = Total Conversion (mol/m) * dH (MJ/mol) * Reaction Time(m)			Theo Frequency Factor	8.02 mol/m ³ m	Calculated Heat Rate of Reaction	-10.00 kW
Self Heat Rate(kW) = (Corr SHR(degC/m)/60*Heat Cap(J/kgK)*Charge(kg))/1000			Heat Rate	-7.1 kW	Calculated Reactor Heat Duty	-13.2 kW

The horizontal 'split baffle' balance tank was simulated using two dynamic vessels, capacity 3.5 m³ each, to represent the hot and cold sides. A total Syltherm XLT charge of 5m³ was used, giving a nominal retention time of ~5 minutes for each side. This volume could be adjusted to test the temperature sensitivity to different start up conditions, see later.

The reactor was charged with 2050L tetrahydrofuran giving an initial heat transfer area of 6.1 m².

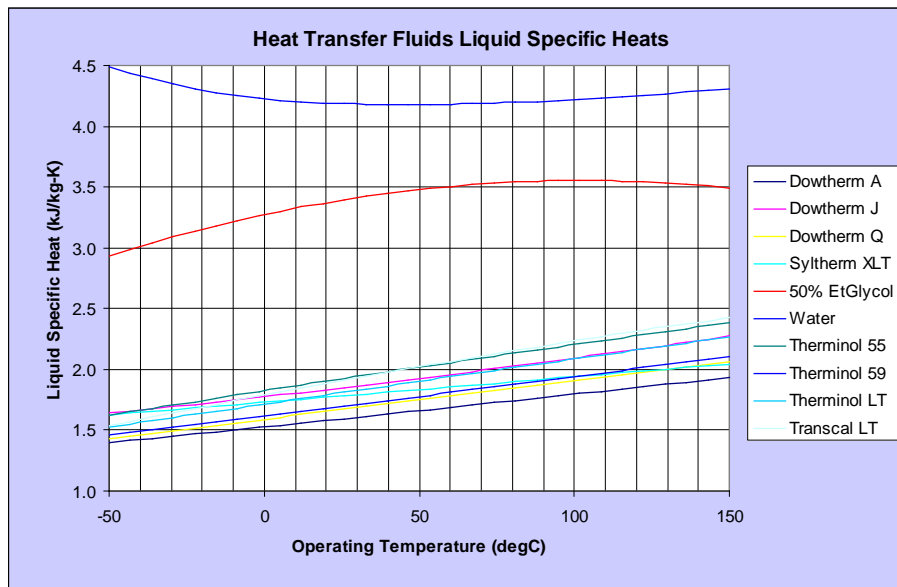
The proposed start up strategy involved cooling the heat transfer fluid and reactor contents to -10°C, by circulating through the reactor jacket heat exchanger, using a -15°C ethylene glycol / water service. The circulation tank contents were then cooled to -90°C via the refrigeration system prior to continuing the reactor cool down process. This strategy was tested and found to be acceptable.

The refrigeration plant recirculation flowrate strategy was based on minimising the plant circulation return flow at the end of the supply header. This results in an increase in the cold to hot side flowrate for a constant evaporator flow rate, which has the effect of minimising the temperature swings on the evaporator inlet.

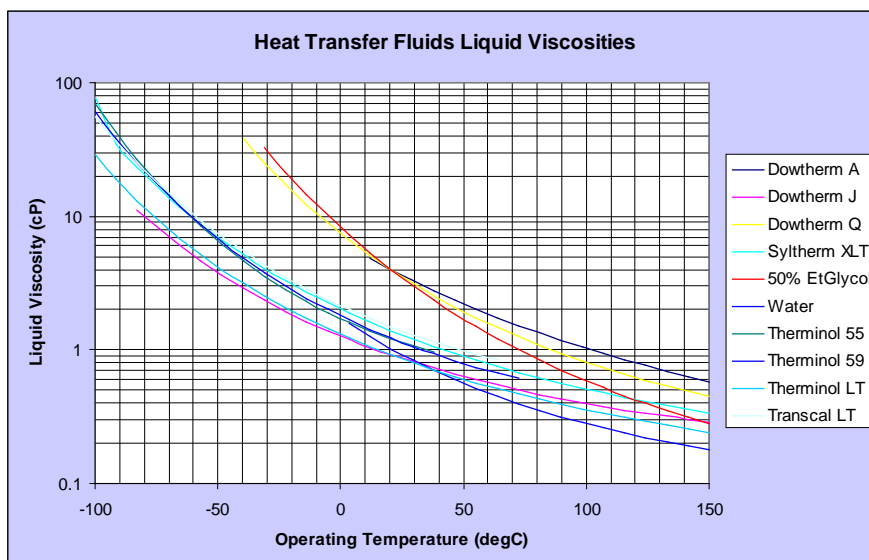
DESIGN AND OPTIMISATION

Heat Transfer Fluid Selection

A key consideration, in the process design of batch reactor control systems, is the operating temperature range, as this drives the heat transfer fluid selection based on acceptable physical properties. Liquid specific heats vary significantly for water based and organic thermal fluids, with the heat removal capacity of water being greater than that for organic fluids. The higher liquid specific heat allows a lower circulation flow to be used for the same heat removal capability.



The freezing point and liquid viscosity are key parameters for low temperature operation. Heat transfer fluid viscosity effects can become limiting resulting in low jacket / coil side heat transfer film coefficients and high pressure drops. Selection of a heat transfer fluid with reasonable viscosity characteristics and acceptable freeze point will allow operation down to -90°C.



Advantages of heat transfer fluids:

- Liquid phase throughout operating temperature range simplifies control system, equipment and operation.
- Fluid properties are stable over a wide temperature operating range.
- Heat transfer surface corrosion and erosion minimised.

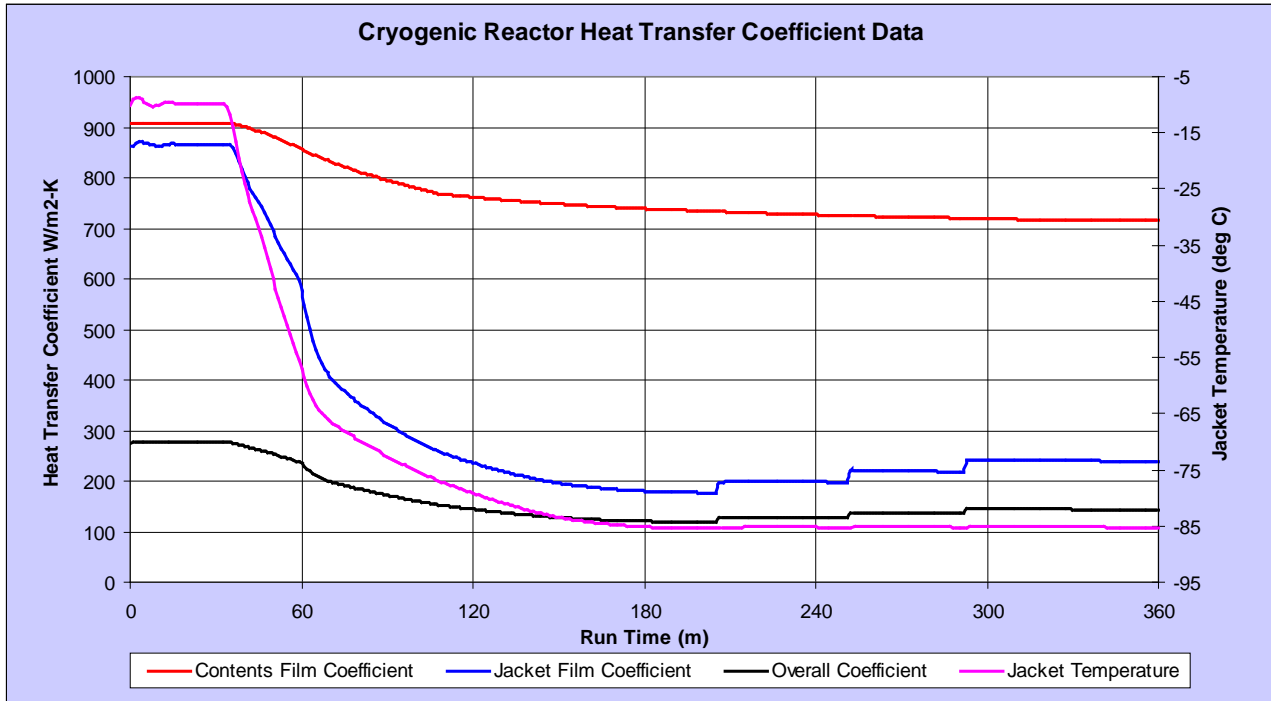
Disadvantages of heat transfer fluids:

- Lower thermal efficiency than systems based on water.
- More rigorous equipment and piping specification resulting in higher equipment and installation costs.
- High cost of initial fluid charge.
- Special commissioning, operational and maintenance procedures with longer downtimes on equipment failure.
- Flammability, toxicity, odour and GMP issues to consider.

DESIGN AND OPTIMISATION

Circulation Flowrates and Refrigeration Unit Sizing

Thermal design was based on the CHEMCAD predicted heat transfer coefficients with a jacket temperature set at -85°C as detailed in the plots and tables below. Plots show the impact on jacket side film coefficient for varying circulation rates.



Heat Transfer Coefficient Prediction with Jacket Temperature at -85°C and stirrer 1.5 rps			
Jacket Circulation	Jacket Pressure Drop	Jacket Film Coefficient	Overall Coefficient
m ³ /h	bar	W/m ² -°K	W/m ² -°K
24	0.172	207.9	130.0
26	0.197	220.9	135.0
28	0.223	233.1	139.5
30	0.252	244.8	143.7

Steady State Heat Duties with Reactor Contents at -70 °C / Jacket -90 °C / Ambient 20°C				
Description	OHTC	Area	ΔT	Duty
	kW/m ² -°K	m ²	°K	kW
Reactor Contents	0.130	6.3	20	16.4
Ambient Heat	0.0029	15.0	110	4.8
Pumping Energy	3 Pumps at 11 kW basis 80% transferred to process			26.4
Maximum Heat Duty under Steady State Conditions				51.7
Unsteady State Heat Duties System Starting at -10 °C cooling down to -70 °C / -90 °C				
Description	Mass	Specific Heat	Time	Duty
	kg	kJ/kg °K	h	kW
Reactor Contents	2050	1.69	4	14.4
Reactor Metal	3300	0.423	4	5.8
Heat Transfer Fluid	5130	1.65	4	47.0
Maximum Heat Duty for coincident cooling of heat transfer fluid and reactor				67.2

A refrigeration plant duty of 60 kW was considered acceptable, provided a high standard of thermal insulation is used and variable speed drives are fitted to all the pumps to minimise the energy input to process. This evaporator duty equates to a Syltherm XLT flow of 27 m³/h for a -85°C inlet and -90°C outlet. Overall heat transfer coefficients of ~150 W/m²-°K are achievable using a jacket circulation rate of 30 m³/h and an agitator speed of 2 rps.

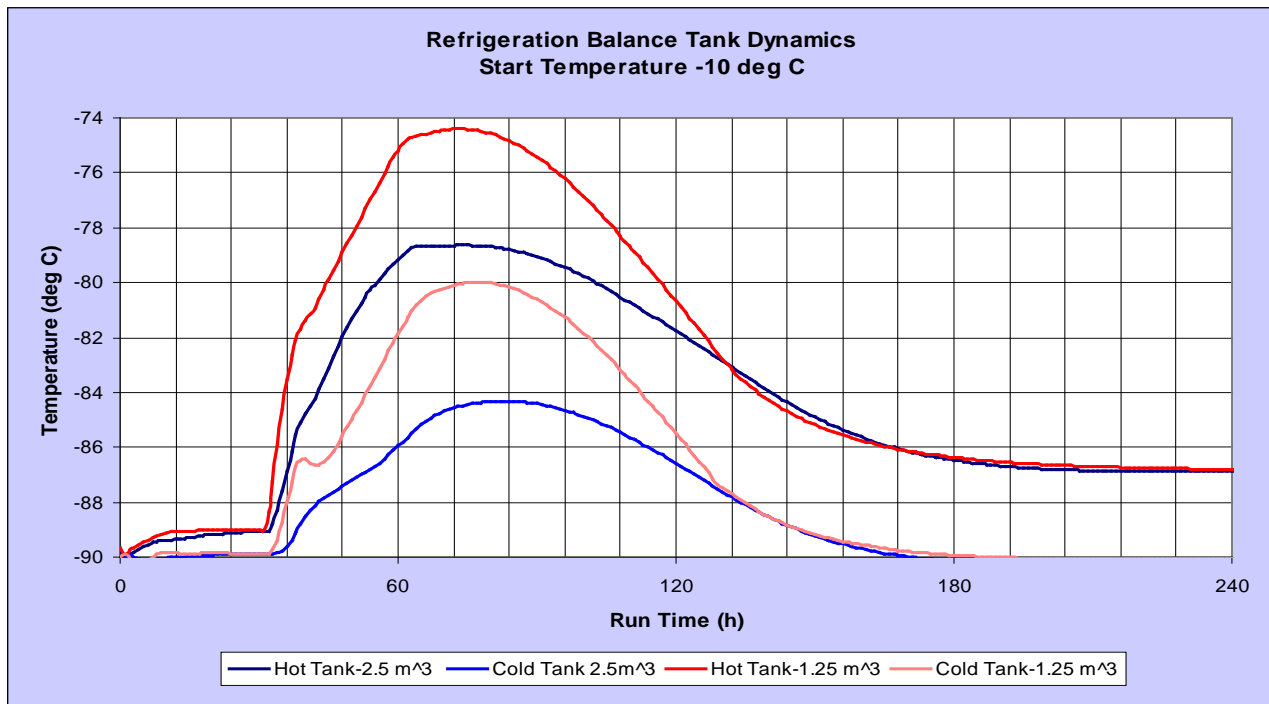
DESIGN AND OPTIMISATION

Hot-Cold Balance Tank Sizing

The function of the horizontal split balance tank is to provide separation of the heat transfer fluid cold supply from the hot return and to provide a permanent overflow from the cold side to the hot side. The tank volume should be able to hold the heat transfer fluid drain back under shutdown conditions and protect the evaporator from excessive inlet temperatures.

The result of simulations for varying volumes are shown in the plots following. The evaporator design point is for an inlet of -85°C and outlet of -90°C at $27\text{ m}^3/\text{h}$ which is equivalent to 60 kW . The 2.5 m^3 heat transfer fluid volume for each side satisfies this requirement under worst case conditions.

A balance tank volume of 7.0 m^3 was selected which provided adequate free volume and an acceptable retention time of ~ 5 minutes.



Source of Cooling

The low temperature cooling source can be refrigeration or liquid nitrogen. Cooling with liquid nitrogen, at -195°C , requires a design that avoids the freezing of Syltherm XLT, freezing point of -111°C . A heat exchanger consisting of a spiral coil mounted in a shell, such as the Graham Heliflow Heat Exchanger, has been proved in this application, with the heat transfer fluid being on the shell side. The maximum nitrogen flow achievable, before the onset of freezing, is determined by the heat transfer fluid flowrate to give an adequate velocity for turbulence. Also controlling the nitrogen outlet temperature, to within -4°C of the heat transfer fluid outlet temperature, will avoid freezing.

The CapEx for the refrigeration plant installation is more expensive, typically by factors in the range 3 to 4, due to the significant amount of additional equipment being required. Liquid nitrogen storage facilities are normally hired, which will give rise to a quarterly charge in the range 1 to 2% of the refrigeration plant CapEx.

Typical cascade cycle refrigeration plant efficiency η is in the range 0.3 to 0.5 where η = refrigerant duty/energy supplied.

A refrigeration cooling duty of 1.0 kWh requires a power input of 3.33 kWh and with a cost of $\text{£}0.1/\text{kWh}$ gives $\text{£}0.33/\text{kWh}$.

A liquid nitrogen cooling duty of 1.0 kWh requires 10.0 kg of nitrogen, and with a cost of $\text{£}0.193/\text{kg}$, gives $\text{£}1.93/\text{kWh}$. When using liquid nitrogen an increase in cooling cost per batch of ~ 6 can be expected.

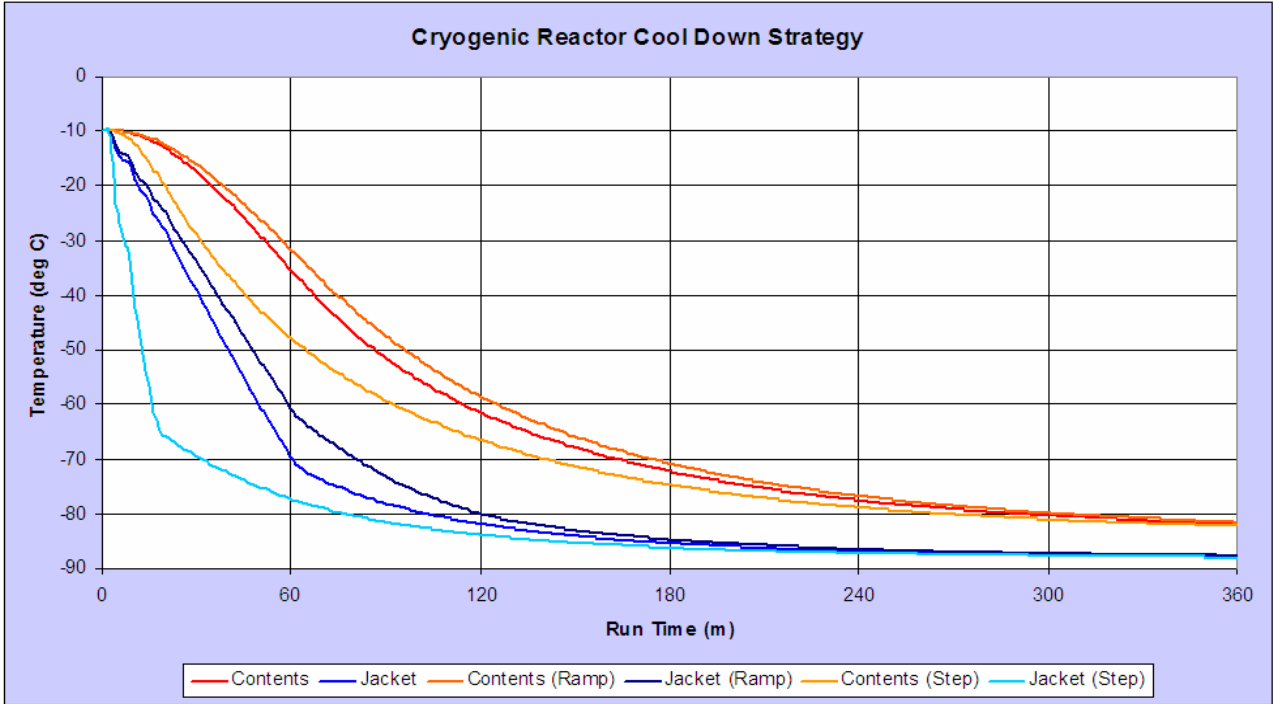
The liquid nitrogen option is, typically, applied to single reactor installations and to pilot plant facilities. The refrigeration option is more flexible in that the cooled heat transfer fluid can be used in multiple reactor installations and on other applications in the plant, such as low temperature condensation for VOC reduction.

The method selected will be driven by CapEx financing arrangements, site specific requirements, the number and frequency of batches.

DESIGN AND OPTIMISATION

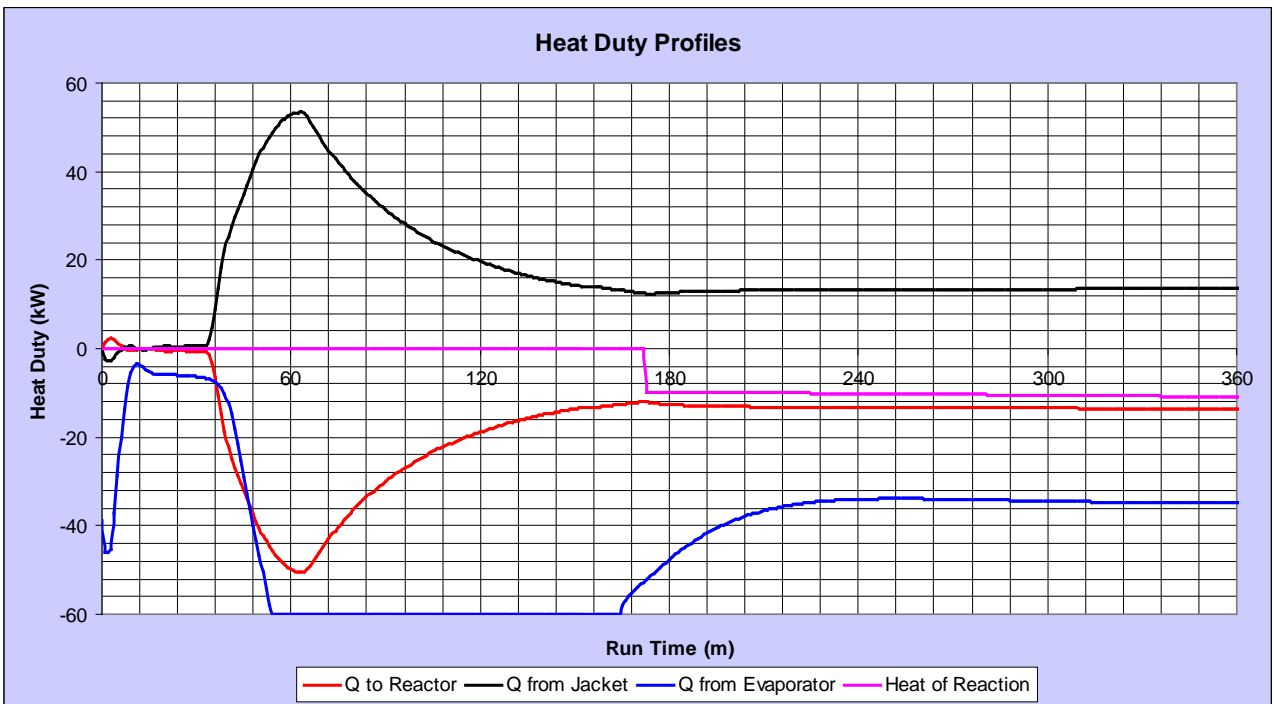
Cool Down Strategy

Three cool down strategies were tested as shown in the graphs below. It can be seen that the step change strategy, in which maximum cooling is applied throughout, reaches the reaction temperature of -70°C about 30 minutes earlier. It demonstrates that the controlling factor is the temperature difference driving force which compensates for the reduction in jacket side film heat transfer coefficient due to the viscosity increase.



Heat Gain from Environment and Pumping Energy

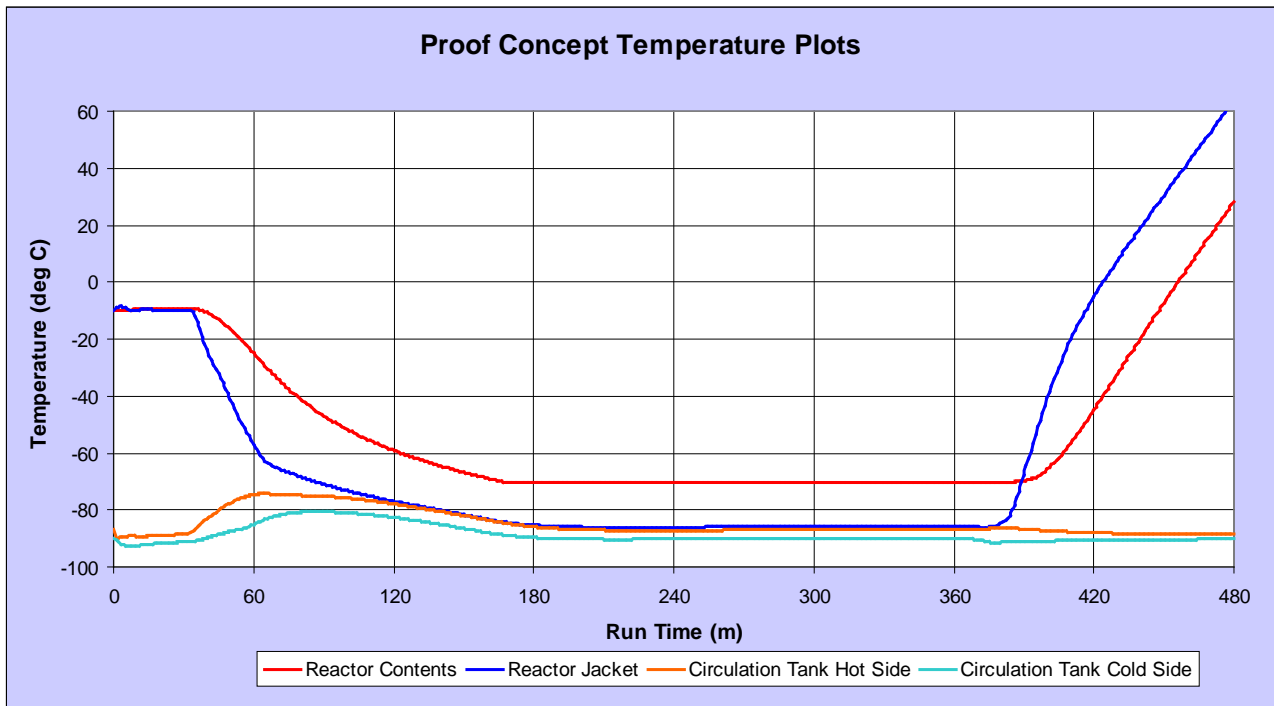
The heat gain from ambient, at a temperature of 20°C and the process at -90°C, has been based on an overall heat transfer coefficient of 2.91 W/m²·°K. It is estimated that the heat gain will be ~4 kW, when using a high quality insulation system. Pittsburgh Corning Foamglas®, with insulation thicknesses of 200mm on the tanks and 100mm on the piping was installed. Refrigeration unit suppliers assume 80% of rated motor power is transferred, as heat, to the pumped fluid. To minimise heat input from this source the design included for variable speed drives on all pumps.



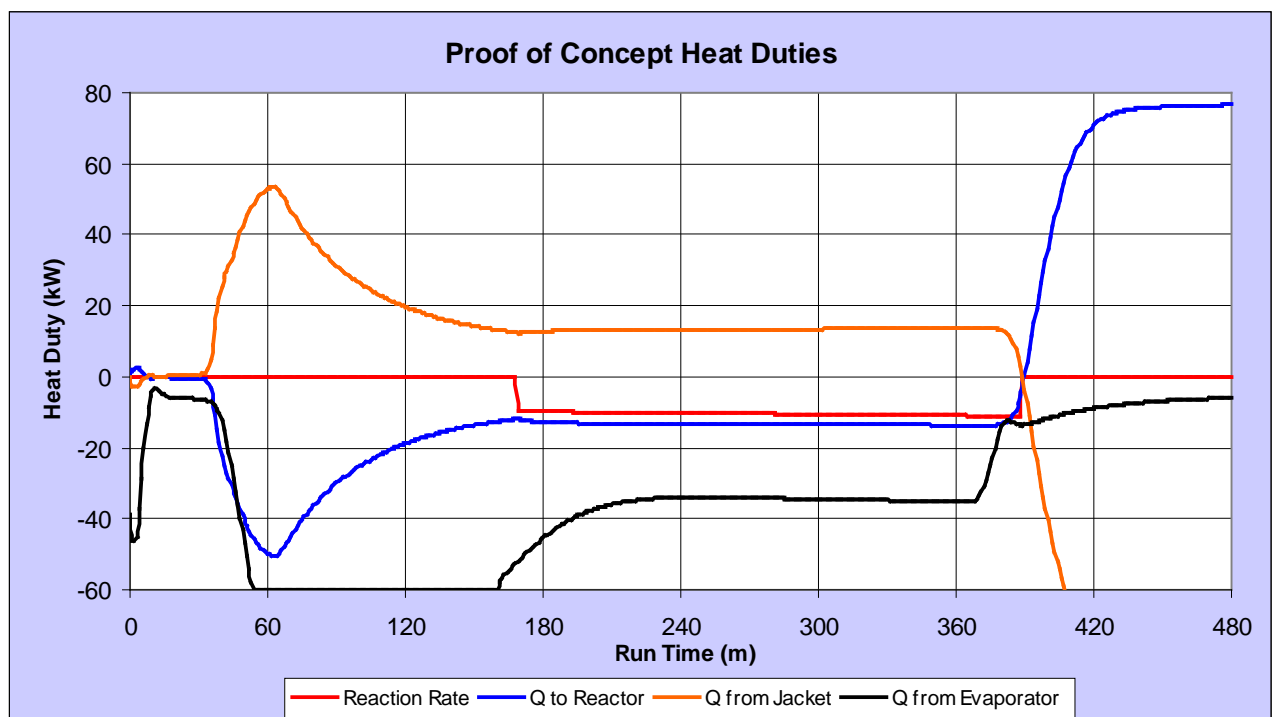
PROOF OF CONCEPT

Chiral reactions are to be performed in a 2300L Hastelloy reactor using a heat transfer fluid cooled by a multi-stage refrigeration facility at temperatures below -70°C, with a reaction rate ΔH_R not exceeding -10 kW. The design and optimisation study has confirmed the suitability of Syltherm XLT, as the heat transfer fluid, and a refrigeration plant duty of 60 kW.

The dynamic plots show the system behaviour when the reactor and contents, have been cooled to -10°C and the refrigeration system has been cooled to -90°C prior to supplying the jacket circulation loop. A reaction rate ΔH_R -10 kW is initiated when the reactor temperature is below -70°C and stable control is demonstrably achieved. At the end of the reaction the refrigeration supply is closed and heat up is achieved by circulation through the 100kW heater.



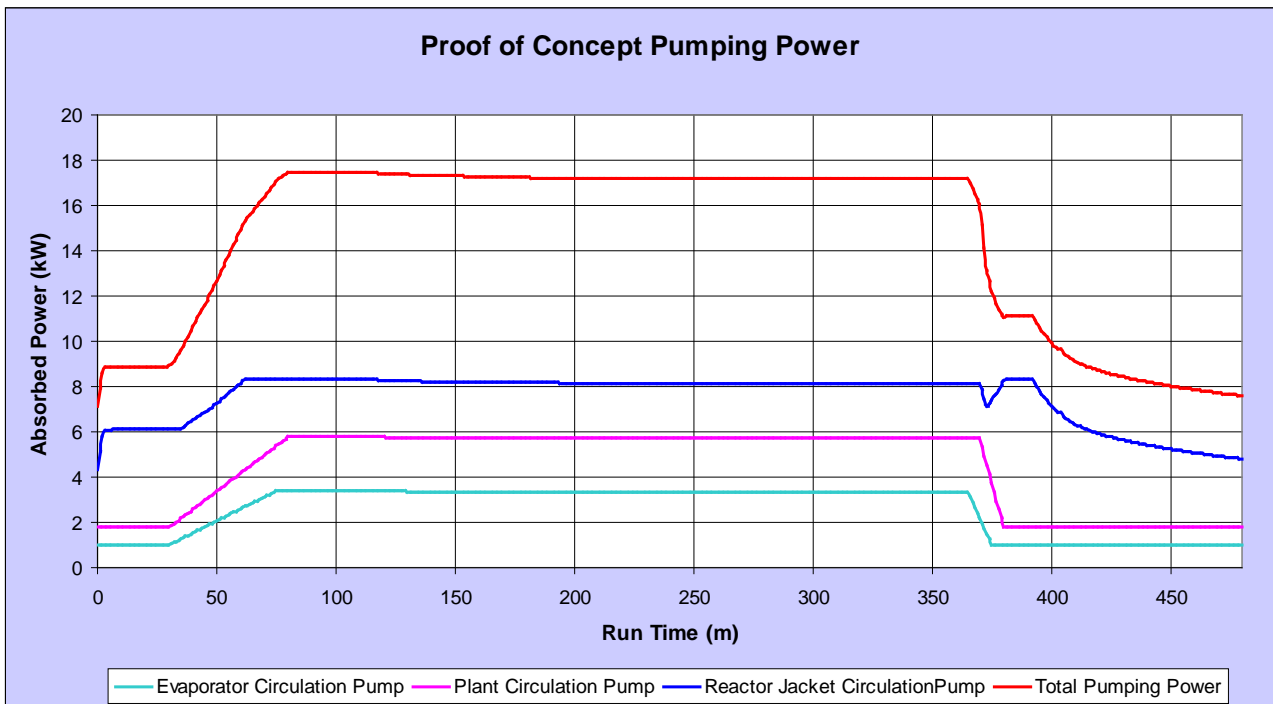
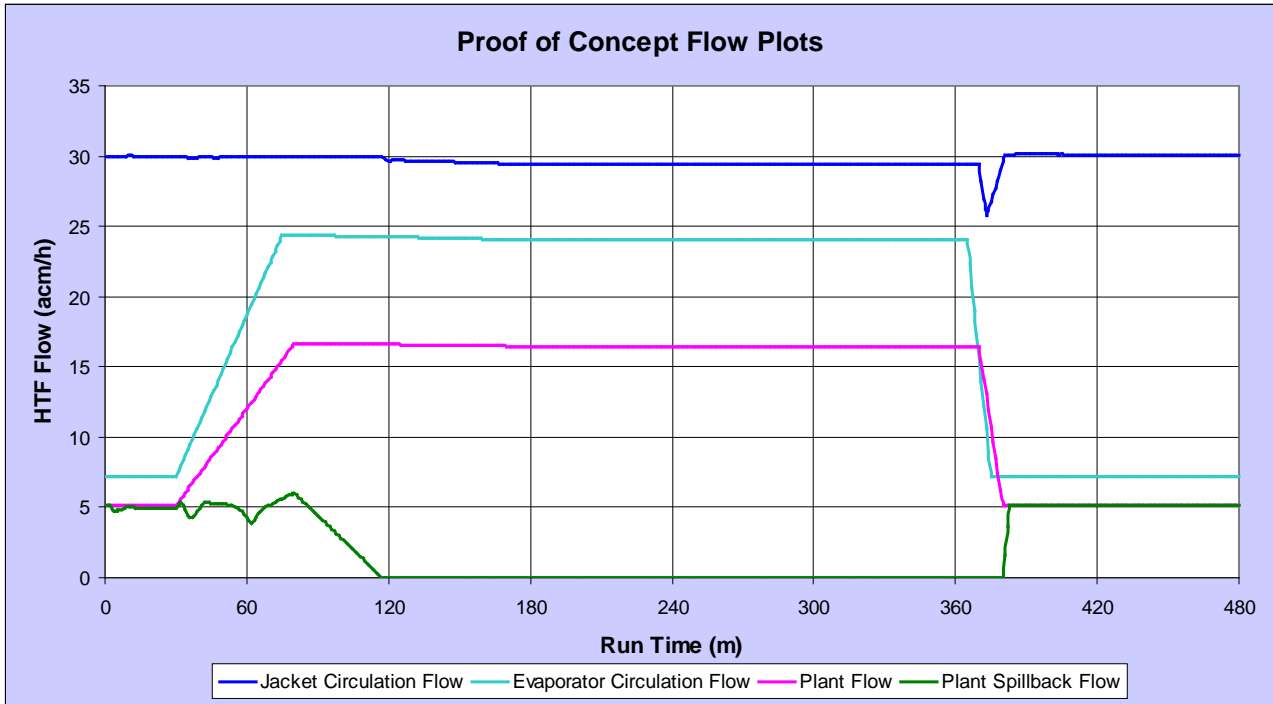
The heat duty plots indicate that the refrigeration plant is on full capacity for 2h during the reactor cool down period and then stabilises at 30 kW during reaction. This demonstrates that there is spare capacity to allow for other process applications during the reaction phase.



PROOF OF CONCEPT

Heat Gain from Pumping

The power input (P) to a pump shaft is work to provide pump head (H) due to Bernoulli's equation. In a closed system, involving recirculation, H will be converted to heat as a result of pipe friction. A pump will transfer heat to a pumped fluid equal to $P(1 - \eta)$. In consequence P is ultimately converted to heat but not all at the pump. Refrigeration practice "Rule of Thumb" assumes that ~80% of rated motor power will end up as heat transferred to the fluid e.g. for 11 kW motor we will have ~8.8 kW. In this design we have 3x11kW pumps giving a potential heat input of 26.4 kW which, with heat gain from the ambient, represents ~50% of refrigeration plant duty! Variable speed drives were fitted to all pumps. The system flowrates were adjusted to suit process requirements and to minimise power absorbed, as shown in the flow and power plots below.



ACTUAL PLANT DATA

Initial start up plant data plots are shown below for a tetrahydrofuran charge of 670L. The results from a dynamic simulation indicate similar cool down behaviour.

