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Adaptive blood pressure control using nitroglycerin

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Eindhoven University of Technology
Faculty of Electrical Engineering
Division of Medical Electrical Engineering

ADAPTIVE BLOOD PRESSURE CONTROL
USING NITROGLYCERIN

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Report of the graduation work
performed from december 1991 until september 1992
Under the supervision of Dr. ir. J.A. Blom and Dr. J.J. Schreuder

The faculty of Electrical Engineering of the Eindhoven University of Technology declines all responsibility for the contents of graduation and trainee reports.
Summary

During coronary artery surgery, patients often have their blood pressure artificially lowered by a continuous infusion of a pressure lowering drug. The drug Nitroglycerin is often used for this purpose. Maintaining the pressure at a certain level requires a continuous observation of the pressure and adjustment of the flow rate. To relieve the anaesthetist from this time consuming task, automatic control can be applied. Since there is no a priori knowledge of the patient sensitivity to the pressure lowering drug, the use of an adaptive robust controller is inevitable.

The controller is monitored by an expert system. The knowledge base is used to implement additional medical knowledge, which is difficult to express in control engineering terms. The medical knowledge of the expert, in this case the anaesthetist, is used to adapt or overrule the controller when necessary. The controller has been clinically tested during twenty cases of coronary artery surgery at the Academic Hospital of Maastricht.

The clinical tests were successful: It was never found necessary to adjust the flow rate manually. Regulating the pressure with the aid of the controller never caused a dangerous clinical situation. The time necessary to reach the setpoint was in all cases more than acceptable for the anaesthetist. The stability of the pressure, after reaching the setpoint, was in all cases adequate and in half of the cases remarkable.

During the last tests an interesting phenomenon was observed: After the pressure was stabilized around the setpoint for 5 to 10 minutes, the patient was able to maintain the pressure at this setpoint without the further aid of the controller. A possible explanation is that the baroreceptor function, which is disturbed by the anaesthesia, can be reset and resume its control task. This implies that the controller’s task could be reduced; to regulate the pressure towards the setpoint and stabilize the pressure around this setpoint for 5 to 10 minutes, thus resetting the baroreceptor function.
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Introduction

The main task of an anaesthetist is to bring the patient into an optimal condition for surgery. This includes, among others, tasks like sedation, suppression of pain, prevention of muscle reflexes and regulation of the blood pressure. During coronary artery surgery, hypertension can give rise to several problems: The excessive bleeding caused by the hypertension blocks the surgical view and increases the amount of blood lost during the operation. Furthermore hypertension enlarges the chance of intra-operative myocardial infarction. Although many of the applied drugs already lower the blood pressure, additional lowering of the pressure is often required.

Usually the drugs Sodium Nitroprusside (SNP) or Nitroglycerin (NTG) are used for this purpose. The patient's response to these drugs is fast so that regulation and stabilization of the pressure is possible by varying the infusion flow rate of the drug. Manually controlling the infusion rate requires continuous monitoring of the pressure and adjustment of the flow rate. To relieve the anaesthetist from this time consuming task, an automatic controller can be applied. In this case the controller calculates the infusion flow rate based on measurements of the mean arterial pressure. If we connect the controller to an infusion pump, the anaesthetist's task is reduced to selecting a desired mean arterial pressure and switching on the controller.

There are some restrictions that prevent the use of a classic controller. Prior to the operation the patient sensitivity to the applied drug is unknown. Since this can differ considerably among patients, some sort of gain adaptation is inevitable. Also system identification, and thus a well tuned controller, is impossible due to a pressure signal, which is influenced by many other factors besides the infusion flow rate.

Although most automatic control methods fail, the anaesthetist is able to regulate the pressure safely. Thus it seems necessary that some sort of medical knowledge must be incorporated into a successful controller. This led to the development of a robust PI controller monitored by a medical knowledge base, which overrules or adapts the controller. The knowledge based pressure controller is implemented with
the Simplexys toolbox which supports the design of real time expert systems [Blom, 1990].

The controller and the expert system were initially designed for the use of the drug Sodium Nitroprusside. After various simulations, the system was introduced and clinically evaluated during thirty cases of heart surgery [Zwart, 1990]. The safety mechanisms incorporated in the knowledge base worked well, but the control speed was often limited by these safety mechanisms. Although the results of this clinical evaluation were promising, it was clear that, in this type of surgery, the controller was not yet able to successfully relieve the anaesthetist from his control task. By combining the recommendations, which resulted from the first clinical evaluation [Lammers, 1990; Zwart, 1990], with some new ideas, an adjusted rule base has been developed.

The Academic Hospital of Maastricht was kind enough to offer us the possibility to clinically test this adjusted rule base during open heart surgery. However, the Academic Hospital of Maastricht uses the drug Nitroglycerin, instead of Sodium Nitroprusside, to lower the blood pressure. As a result this research is twofold; first, the adjustments made to the rule base can be evaluated, then the difference between the use of Sodium Nitroprusside and Nitroglycerin during automated pressure control can be evaluated.

This report describes the results of this twofold research. First, all the features of the blood pressure controller will be described. Special attention will be given to the adjustments made after the evaluation of the existing SNP based controller. Then, the results of the clinical tests on twenty patients undergoing open heart surgery will be given and interpreted. Finally, a comparison between the original and the adjusted blood pressure controller will be made, which will result in conclusions and recommendations for further research.
1 Automated blood pressure control

To successfully relieve the anaesthetist from his blood pressure control task, a blood pressure controller has to be fast enough, insensitive to disturbances and safe under all circumstances. The requirements necessary to meet these demands will be discussed in the first part of this chapter. The second part of this chapter gives arguments in favour of the chosen design of the blood pressure controller.

1.1 Requirements of an automatic blood pressure controller

Previously designed controllers are able to control the blood pressure of most patients, but there still remains a small group of patients for which these controllers are not suitable. The aim of our controller is to be applicable for all kind of patients. Therefore a controller that can deal with a wide variety of patient characteristics is required. Furthermore, the controller must respond safely in all circumstances. This means that disturbances caused by other drugs or surgical interferences should not result in an unstable control. These are the reasons why we should design a robust controller, which can handle a wide variety of patient characteristics and ensures a stable control under all circumstances.

The pressure measurement is sometimes unreliable or not available, e.g. during the taking of blood samples. The controller should not react to these erroneous measurements; consequently some sort of validation of the blood pressure signal is necessary. If the blood pressure signal is invalid for a longer time, the controller should issue a warning and switch to manual control.

A transient is defined as an unexpected, temporary, large pressure increase or decrease. Because the pressure change during a transient is too fast for the controller to respond accurately, transients need to be detected. When a transient has been detected, the controller should not attempt to regulate the pressure. Instead the flow should be frozen or shut off.

The control speed, this is the time necessary to bring the pressure towards the desired level, should approximate the control speed of the anaesthetist, who
regulates the pressure manually. To have a notion of the required control speed, the following example can be illustrative: When using Nitroglycerin as a pressure lowering drug, a typical situation is one in which the anaesthetist regulates the pressure from 110 mm Hg towards 70 mm Hg within five to ten minutes, and with a maximum pressure undershoot of 5 mm Hg. Our controller should at least match this performance, without causing unacceptable pressure overshoot for extremely sensitive patients or slow control speed for insensitive patients.

1.2 The use of an expert system to adapt or overrule the controller

Though hopeful results have been achieved using adaptive robust controllers [Colvin, 1989; O'Hara, 1992; Sheppard, 1975; Slate, 1980], a controller that can deal with all varieties of the patient characteristics has not been developed yet. To improve the performance of a blood pressure controller three strategies should be considered.

First we can improve the mathematical model of the patient's response by extending our knowledge of the dynamic response to the applied drug, and then use this improved model to design a better tuned controller. Since a priori knowledge of the patient characteristics is not available, we would have to obtain this knowledge gradually during the operation and adapt the controller accordingly. This method holds two major drawbacks: As long as there is no knowledge derived from the patient's response the performance of the controller will be very poor, i.e. slow and overcautious. Moreover, it is difficult for the controller to make a distinction between pressure changes caused by a change of infusion flow rate and changes caused by other drugs, surgical interferences or noise.

The second alternative is to make the controller more robust so that it can handle a wide variety of patient characteristics. It is obvious that this method will work at the expense of the control speed, and is therefore not suited for this application which requires a fast control speed.

But why is an anaesthetist able to control the pressure satisfactorily? The answer is obvious: The anaesthetist also uses his medical knowledge when controlling the
pressure. Consequently, our third alternative is to design a controller which is being monitored by a medical knowledge based expert system. An expert system is a rule based structure, which implements expert knowledge into a program.

Because of measurement limitations, we cannot incorporate all medical knowledge in this knowledge base, i.e. we cannot inform the system when another drug that also influences the pressure is administered, or when the surgeon makes an incision. Nevertheless there remains enough medical knowledge to build a knowledge base: With the aid of the knowledge base we can detect transients and add additional knowledge of the non-linear response to the pressure lowering drug. Furthermore we can use the expert system to observe the progress of the pressure signal towards the setpoint, and adapt the control gain when the progress is too fast or too slow.

![Diagram of blood pressure control system](image)

**Figure 1.1: The blood pressure control system**

The SNP based controller uses for this purpose Simplexs, a real time expert system developed by the Medical Electrical Engineering division of the Eindhoven University of Technology [Blom, 1990]. The Expert system adapts or overrules the controller when the patient's blood pressure reacts unexpectedly. Because this is
the most promising alternative, the same design has been chosen for the blood pressure controller using Nitroglycerin (see figure 1.1).

1.3 The functional units of the blood pressure controller

This paragraph gives the functional units of the blood pressure controller. Referring to figure 1.1 and the requirements described in paragraph 1.1 the blood pressure controller can be divided in the control loop, the knowledge base and the user interface.

1.3.1 The control loop

The analog pressure signal is taken from the instrument panel of the operating room. It is sampled with an Analog to Digital convertor (Labmaster [Scientific Solutions, 1990]). Every 20 millisecond a new value is sampled. The samples are stored in the internal (FIFO) buffer of the Labmaster. Every cycle the validation algorithm waits until 250 samples have been read from the buffer. Thus the timing of the controller is provided by the Labmaster. The algorithm validates the pressure samples and extracts (if the pressure signal is valid) the average mean arterial pressure over 5 seconds. If there are too many invalid periods the knowledge base will overrule the controller and switch to manual. Based on the mean arterial pressure a PID-controller calculates a new flow rate. This flow rate is sent to the infusion pump which infuses the calculated flow rate.

The routine controlling the Analog to Digital Convertor has been rewritten because a new version of the Analog to Digital Convertor became available (chapter 6.1). The pump communication routine is identical to the routine used in the SNP system and has not been adjusted. The control parameters of the PID-controller have been changed because a new drug (NTG instead of SNP) has been used. In chapter two a NTG patient model is derived and, based on this model, the robust controller is tuned. The validation algorithm used in the SNP based system had some deficiencies, which sometimes caused the controller to improperly return to manual
mode. To improve the algorithm some adjustments have been made to it. These will be discussed in chapter three.

1.3.2 The knowledge base

The knowledge base observes the pressure and flow rate signal and adapts or overrules the controller when necessary. All the adaptation mechanism are described in chapters two and four. An important adaptation mechanism is the adaptation of the gain of the PID-controller. The gain is increased if the progress of the pressure signal towards the setpoint is too slow, whereas the gain is decreased when unstable control has been detected. An indication of unstable control is either a too rapidly changing pressure towards the setpoint or a detection of an oscillation. The pressure progress testing algorithm of the SNP system does not give an indication of the progress with each new pressure value. A new pressure progress testing algorithm has therefore been developed (chapter 5) which solves this problem. The oscillation detection mechanism has been extended (chapter 5) and can now also detect oscillation at low flow rates.

In a situation of ineffective control a flow rate increase does not result in the expected pressure decrease. This suggests that the user has chosen a setpoint which cannot be reached by the controller. During a situation of ineffective control the knowledge base notifies the user and freezes all gain adaptations. The rules which detect ineffective control are similar to the ones used in the SNP system (chapter 4).

Another adaptation mechanism is the transient detection mechanism. A transient is defined as a fast, unexpected, pressure increase or decrease. When a transient has been detected the knowledge base will freeze (if the pressure increases during the transient) or shut down (if the pressure decreases during the transient) the flow rate. The transient detection mechanism used in the SNP system worked well and is therefore not adjusted.
1.3.3 The user interface

The user interface provides all communication with the outside world. It stores the operation data on disk, builds the graphic display and checks the keyboard for user input. The user interface of the SNP system worked well and has therefore not been changed. Only the name 'SNP' on the display has been replaced by 'NTG'.

To give an indication of the usage of the controller during surgery, the function keys of the system will be summarized below (see also [Lammers, 1990]):

- **To Auto:** Switches the controller to automatic mode. The controller will now start to regulate the pressure towards the setpoint.

- **To Manual:** Switches the controller to manual mode. The last calculated flow rate is maintained.

- **Setpoint Up:** Increases the setpoint, i.e. the desired pressure level.

- **Setpoint Down:** Decreases the setpoint.

- **To perfusion:** Switch the validation algorithm to perfusion validation.

- **Flow Up:** Increases the flow rate (only possible in manual mode).

- **Flow Down:** Decreases the flow rate (only possible in manual mode).

- **Flow Zero:** The flow rate is shut off immediately and the controller returns to manual mode.

- **From Perfusion:** Switch the validation algorithm to normal validation.

- **Quit:** The flow rate is shut off and the system is shut down. Only works in manual mode.
2 Designing a robust controller

As mentioned before, we will not attempt to establish an accurate description of the patient’s response to the applied pressure lowering drug. Nevertheless, a rough description of the patient’s response is necessary to tune the robust controller. In this chapter a patient model will be derived. The remainder of this chapter describes the tuning of the robust controller, based on the patient model and the desired performance of the controller.

2.1 Modelling the patient’s response

There is no accurate description of the patient’s response to Nitroglycerin available. We therefore have to derive a model of the patient’s response which approximates the reality as closely as possible. The patient model consist of two parts. The first part is a mathematical description of the expected pressure change caused by a change of flow rate. The second part takes into account the expected non-linearities of the patient’s response. The knowledge of these non-linearities is implemented in the knowledge base, thus enabling the expert system to adapt or overrule the controller when the mathematical model does not approximate the reality.

The first part of the patient model is the mathematical model. We assume that all non-linearities of the patient model are covered by the knowledge implemented in the rule base. A new flow value is calculated every 5 seconds. We can model this by a Hold circuit [Ven van de, 1986] (or a Digital to Analog convertor). The influence of this hold circuit can be neglected since the sampling time (5 seconds) is small compared with the time constant of the patient model (approximately 175 seconds). The average mean arterial pressure is calculated over 5 seconds. We assume that a sample of the mean arterial pressure is taken every 5 seconds. Figure 2.1 shows the resulting system.

We estimate the patient’s response by a first order model. There are several reasons why a first order model is the most promising model to approximate the patient’s response: The SNP based controller successfully modelled the response with a first order model. A first order approximation provides sufficient parameters to
satisfactorily tune the robust PID-controller (see paragraph 2.2). The equation of a first order model describes the first terms of the power series which describes the true patient's response.

Thus a first order model with time delay is used to represent the patient's response to a change of flow rate. Figure 2.2 shows the important quantities in the step response of the first order system with time delay. The time-discrete response of this model is given by [1] (see also [Lammers, 1990; Zwart, 1990]). The time constant (tau) and the delay time (T\_delay) of the first order model are the values which will minimize the error of the approximation.

\[
P(n+1) = P_0 + K (1-a_1) F(n - T\_delay/T\_sample) + a_1 (P(n) - P_0) \tag{1}
\]

\(P(n)\) denotes the pressure after \(n\*T\_sample\) seconds, and \(F(n)\) the flow rate after \(n\*T\_sample\) seconds. \(P_0\) is the initial pressure (flow rate equals zero), and \(a_1\) is a constant coefficient; \(a_1 = \tau/(T\_sample + \tau)\)
Now we can describe the different parameters of the patient model. The delay time is the time it takes before the effect of a change of flow rate is visible. When using the drugs NTG or SNP, the delay time mainly consists of the time required for the drug to reach all arteries. Since this time is independent of the drug used, the chosen delay time of the NTG model is approximately the same as the delay time used in the SNP model.

The sensitivity (K) is the final change of pressure after the flow rate changed by one unit. There have been several studies on the pressure change caused by the infusion of NTG, e.g. [Kaplan, 1976; Kaplan, 1979; Hempelman, 1976; Bernstein, 1966; Christensson, 1969; Guggiari, 1985]. The highest reported sensitivity is 50 mm Hg/μg/kg/min, whereas the lowest reported sensitivity is 9 mm Hg/μg/kg/min.

The time constant (tau) is the time it takes, after the delay time, for the pressure to move by 63% towards its final value. It is not likely to have any physical meaning, i.e. it is not necessarily a time constant of the real process. Because this constant is of less value to the anaesthetist, who is more interested in the final pressure change, the literature on the dynamic response to Nitroglycerin is poor. Based on the research done by Hempelman [Hempelman, 1976], a nominal time constant of
175 seconds is chosen. It has become clear from the studied reports, that this time constant can vary strongly among patients, see among others [Fahmy, 1978]. Therefore, the time constant is expected to vary between 100 and 400 seconds.

Table 2.1 summarizes the chosen parameters of the patient model; the parameters used for the SNP model are placed between brackets.

<table>
<thead>
<tr>
<th>parameter</th>
<th>nominal</th>
<th>minimal</th>
<th>maximal</th>
<th>unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>sensitivity</td>
<td>21 (25)</td>
<td>5 (2.8)</td>
<td>90 (225)</td>
<td>mmHg/μg/kg/min</td>
</tr>
<tr>
<td>delay time</td>
<td>45 (50)</td>
<td>30 (35)</td>
<td>60 (60)</td>
<td>seconds</td>
</tr>
<tr>
<td>time constant</td>
<td>175 (60)</td>
<td>100 (40)</td>
<td>400 (90)</td>
<td>seconds</td>
</tr>
</tbody>
</table>

Table 2.1: Patient parameters of the first order model using NTG, and using SNP (between brackets)

The second part of the patient model describes the expected non-linearities of the patient's response. The linearities will be summarized below. The implementation of these non-linearities in the knowledge base will be discussed in chapter 4.

The patient sensitivity to SNP decreases at high flow rates due to a non-linear response [Blom, 1990]. Though no evidence for this phenomenon, when using NTG, could be found in the studied literature, out of a safety precaution we assume the same property for NTG. This decreasing sensitivity at high flow rates suggests that when a large decrease of the flow rate is expected the gain of the controller should be decreased.

The sensitivity to SNP can differ strongly among patients; the assumed variation in the sensitivity to SNP is more than 80 fold. Though the range of sensitivity is smaller when using NTG, the difference between most sensitive and least sensitive is still large. The robust controller itself cannot cope with the complete range of sensitivity. Therefore some sort of adaptive amplification of the control gain is necessary (see paragraph 2.2).
The hypotension which can be reached by the infusion of a pressure lowering drug is limited. This means that a situation can exist in which an increase of the flow rate does not result in a decrease of the blood pressure. This situation should be detected because the controller, which is still expecting the patient to respond to the increase of the flow rate, will assume wrongly that the patient is less sensitive than expected, and will increase the control gain unnecessarily.

Although Nitroglycerin, unlike SNP, has no toxic properties a limitation of the flow rate is desirable. If this upper flow rate is reached, the anaesthetist can decide to change the setpoint or lower the pressure with additional drugs. The upper limit set to the infusion flow rate is 3 μg/kg/min in automatic mode and 5 μg/kg/min in manual mode. Because Nitroglycerin has no toxic properties, a maximum of the total infused amount of Nitroglycerin is not necessary.

An obvious but very important property is, that we cannot infuse a negative flow rate. In other words the controller is only able to increase the pressure by decreasing the flow rate. If the flow rate reaches zero the controller will not be able to regulate the pressure. As a result we can expect a poor control performance if the flow rate is around zero, because the controller still expects the patient to respond according to a first order model, even with a negative flow rate.

Nitroglycerin is known to predominantly produce relaxation of the venous bed. Thus, left ventricular end-diastolic pressure and volume will be diminished strongly when using Nitroglycerin, this in contrast to the agent’s lack of effect on the total systemic vascular resistance, whereas Sodium Nitroprusside causes similar degrees of dilation of both the resistance and capacitance beds, see for example [Miller et al; 1976; Kaplan, 1979]. During perfusion, the venous blood is gathered by the heart-lung machine and injected at the arterial side. The relaxation of the venous bed, caused by the infusion of Nitroglycerin, will therefore only effect the mean arterial pressure if the total amount of blood inside the patient is kept constant. During a non iso-volemic perfusion only the drug Sodium Nitroprusside will satisfactorily decrease the mean arterial pressure.

All patient parameters are expected to vary among patients and change slowly in time. According to the studied literature [Fahmy, 1978] the patient sensitivity to
Nitroglycerin does not change in time, this in contrast with the sensitivity to Sodium Nitroprusside. But because we are not completely certain, as a safety precaution we still expect the sensitivity to vary slowly in time. Therefore continuous estimation of the patient parameters remains vital.

2.2 Control strategy

As a controller a PIO controller is chosen. PIO controllers offer a lot of advantages: They are easy to describe, easy to implement and easy to tune. Moreover an accurately tuned PIO controller is stable over a wide range of system characteristics.

<table>
<thead>
<tr>
<th>extremely sensitive</th>
<th>sensitive</th>
<th>nominal sensitive</th>
<th>insensitive</th>
<th>extremely insensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 - 9</td>
<td>9 - 16</td>
<td>16 - 29</td>
<td>29 - 50</td>
<td>50 - 90 [mmHg/\mu g/kg/min]</td>
</tr>
<tr>
<td>1/3.24</td>
<td>1/1.8</td>
<td>1</td>
<td>1.8</td>
<td>3.24 control gain</td>
</tr>
</tbody>
</table>

Table 2.2: Five sensitivity categories and the required control gain

The range of sensitivity is too large for the basic controller to handle. Therefore the gain of the controller is adapted by the expert system. The range of sensitivity is spread over five categories (see table 2.2). The three middle categories cover the complete expected range of sensitivity (9 to 50 mm Hg/\mu g/kg/min). The two outside categories have been added to ensure that also the extremely sensitive and extremely insensitive patients are categorized correctly, even though such patients have not been reported.

The classification of the patient in a category is controlled by the expert system. Assuming perfect classification, the robust controller only needs to be stable for all patient characteristics within one sensitivity class. For example the control gain used for extremely sensitive patients is suitable for patients with a sensitivity between 50 and 90 mm Hg/\mu g/kg/min.
After the first clinical tests of the SNP based system, the random fluctuation of the mean arterial pressure proved to be unexpectedly high. As a result the flow variation calculated by the derivative term (D-term) of the PID controller did not improve the control performance. This is the reason why the derivative term is chosen to be zero in both the SNP and the NTG based controller.

The SNP based controller made a distinction between the regulation and the stabilization task of the controller. Two pairs of PI parameters were defined, one for the regulation and one for the stabilization. The actual PI parameter depended on the distance between the pressure and the setpoint. In reality it turned out that the difference between pressure and setpoint was constant most of the time. As a result the variation in the PI parameters was negligible. Because of these small variations in the PI parameters, the NTG based controller uses the same PI parameters for stabilization and regulation.

Moreover any limitation of the control gain, and thus the flow rate, which is dependent on the current difference between the pressure and the setpoint, deteriorates the control performance. If the controller has stabilized the pressure, a flow rate change caused by a pressure disturbance away from the setpoint should be equal to the flow rate change caused by the return of the pressure to the setpoint. If however the change of flow rate depends on the difference between the pressure and the setpoint, then the flow rate will not return to the same value as before the disturbance, because the difference from the setpoint is different, and consequently the flow rate change is different. This will result in a drift of the pressure a few minutes later. This is illustrated in figure 2.3.
The PI parameters have been determined through various simulations. Using simulation results to determine the optimal PI parameters offers several advantages. It is easy to add features to the controller and the patient model. For example, a limitation of the flow rate slope, and a non-linear extension of the patient model will be easy to add. In order to prevent unlimited growth of the integration term (I-term) when the control signal is limited for a certain period, the dog lead principle is applied for the implementation of the PI-controller:

\[ F(n) = F(n-1) + G \left[ K_i \left( P(n) - T(n) \right) + K_p \left( P(n) - P(n-1) \right) \right] \]  \[2\]

G represents the control Gain, and T represents the setpoint (or target level), F denotes the flow rate, P denotes the mean arterial pressure and \( K_i \) and \( K_p \) represent the PI-parameters.

The optimal PI parameter set is defined as the set providing the fastest response time after a setpoint change, without causing any overshoot in the pressure and without causing more than 5% overshoot in the flow. The response time is the time necessary to cross 80% of the initial difference between the setpoint and the
pressure. With the aid of the patient model (\(\tau = 175\); delay time = 45; control gain 1; sensitivity = 21) a program has been written, which searches for this optimal PI parameter set by comparing the results from various simulations each with different PI parameters. The user only needs to define the minimum and maximum values of the PI parameters, and the desired accuracy. If we execute the program several times we can decrease the difference between the minimum and maximum PI-values and at the same time increase the accuracy. Appendix III gives the simulation program used to tune the PI controller.

<table>
<thead>
<tr>
<th>sensitivity (in one category)</th>
<th>response time [min : sec]</th>
<th>flow overshoot</th>
<th>pressure overshoot</th>
</tr>
</thead>
<tbody>
<tr>
<td>minimal</td>
<td>7:00</td>
<td>0 %</td>
<td>0 %</td>
</tr>
<tr>
<td>average</td>
<td>6:10</td>
<td>5 %</td>
<td>0 %</td>
</tr>
<tr>
<td>maximal</td>
<td>5:45</td>
<td>20 %</td>
<td>0 %</td>
</tr>
</tbody>
</table>

Table 2.3: Controller's performance within one sensitivity category (time constant = 175 seconds, delay time = 45 seconds)

With the aid of the simulation program the PI parameters have been determined. The found PI parameters provide a stable control for all combinations of the patient parameters. Figure 2.4 shows the simulation result of the most critical situation (the time constant is minimal and the delay time is maximal). In reality this situation will not occur because the high pressure slope at the beginning will trigger the gain adaptation mechanism to decrease the control gain (chapter 4). The controller is still stable even when the control gain chosen is too high or too low (see figure 5.4).

If the pressure changes fast, the flow rate will consequently change fast as well. The flow rate slope is limited at 0.2 \(\mu g/kg/min\) per five seconds, to ensure that the patient has sufficient time to respond to this fast changing flow rate before the flow rate is too high. This limitation does not interfere with the controller's stabilization task, because it only limits the flow rate change when the pressure changes fast.

As mentioned before, the controller can only increase the pressure by decreasing the flow rate. When the average flow rate is around zero, random pressure
fluctuations can still cause the controller to increase the flow rate. Because the flow rate cannot be negative, the positive flow rate fluctuations are not compensated. Consequently will the pressure signal show a negative offset away from the setpoint. To overcome this problem the actual (infused) flow rate is zero as long as the flow rate is below 0.15 \( \mu g/kg/min \). When the suggested flow rate crosses the \( 0.15 \mu g/kg/min \) border the actual flow rate is increased. Because a negative offset in the pressure only forms a problem when the pressure is around or under the setpoint, this mechanism is only active as long as the pressure is under the setpoint or not more than 5 mm Hg above the setpoint. This mechanism does not work satisfactorily for extremely sensitive and extremely insensitive patients. Because the \( 0.15 \mu g/kg/min \) border is respectively too low or too high.
3 Validation of the blood pressure signal

Many disturbances can cause the pressure signal not to reflect the true blood pressure; such as blood clotting, air bubbles in the line, flushing of the arterial line, sampling of blood, electrocautery etc. Because these disturbances can cause an incorrect computation of the mean arterial pressure, some sort of validation of the pressure signal is inevitable. The blood pressure validation algorithm is based on the validation algorithm, used in the SNP based controller [Blom, 1990; Zwart, 1990; Goossens, 1986]. This chapter describes the main outline of the existing algorithm and the adjustments made to it.

The validation algorithm is based on the assumption that almost identical blood pressure periods follow each other. The algorithm extracts several features from one period of the arterial pressure and compares them with the features of a signal model. This model is built by averaging the features of the most recent validated periods. To characterize one period of the arterial pressure, the following features have been chosen, see also figure 3.1:

- the diastolic pressure, MI
- the systolic pressure, MA
- the upslope pulse pressure, D1
- the downslope pulse pressure, D2
- the systolic pressure slope, H1
- the pulse period, HP
- the average of the blood pressure over a full period, PG

Because the sampling rate is only 50 Hz, it is most likely that some of the features of the pressure signal will not be sampled. To limit the resulting fluctuations in the systolic pressure parameter MA, the systolic pressure is defined as the maximum average of three adjoining samples. It is not necessary to adjust the diastolic pressure parameter similarly: The slow changing pressure around the diastolic pressure will ensure that the samples taken are all close to the diastolic pressure value.
To track the pressure signal in the time domain, six different states have been defined. A state transition is performed when the pressure signal crosses a certain level, i.e. 25, 50 or 75 percent. Figure 3.1 shows the different states and the features used to describe one period of the pressure signal. With the aid of this figure the state transitions can be defined:

The backwards state transitions are necessary because the dip in the middle of the pressure signal can be mistaken for the diastolic pressure and trigger an incorrect state transition. To ensure that the middle dip is not confused with the diastolic pressure, the value of the diastolic pressure is reset after the backward state transition from F2 to F1, see figure 3.3. The updating and resetting of the
parameters during a period depend on the current state or state transition. Table 3.1 summarizes the actions taken during each state or state transition.

<table>
<thead>
<tr>
<th>feature</th>
<th>actualize</th>
<th>reset</th>
</tr>
</thead>
<tbody>
<tr>
<td>the diastolic pressure</td>
<td>F1</td>
<td>F4 = &gt; F5, F2 = &gt; F1</td>
</tr>
<tr>
<td>the systolic pressure</td>
<td>F4</td>
<td>F6 = &gt; F1</td>
</tr>
<tr>
<td>the upslope pulse pressure</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>the downslope pulse pressure</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>the systolic pressure slope</td>
<td>F2, F3</td>
<td>F3 = &gt; F4</td>
</tr>
<tr>
<td>the pulse period</td>
<td>F1, ..., F6</td>
<td>F3 = &gt; F4</td>
</tr>
<tr>
<td>the average of the pressure</td>
<td>F1, ..., F6</td>
<td>F3 = &gt; F4</td>
</tr>
</tbody>
</table>

Table 3.1: Updating and resetting of the features

The actual validation takes place by comparing the extracted features from one period of the pressure signal with the features extracted from the previous periods. If a period has been validated, the signal model is updated with this newly validated period. The algorithm provides the expert system with a new valid mean arterial pressure value every five seconds, if at least two periods have been validated within the last five seconds. The validation boundaries (this is the allowed deviation from the signal model) differ from the validation boundaries used for the SNP based
controller. The new validation boundaries have been determined by examining the variation in the features extracted from the sampled data taken during the SNP test phase.

<table>
<thead>
<tr>
<th></th>
<th>deviation from previous periods</th>
<th>minimal value</th>
<th>maximal value</th>
<th>units</th>
</tr>
</thead>
<tbody>
<tr>
<td>diastolic pressure</td>
<td>7 (5)</td>
<td>20 (20)</td>
<td>200 (200)</td>
<td>mmHg</td>
</tr>
<tr>
<td>systolic pressure</td>
<td>7 (6)</td>
<td>40 (40)</td>
<td>270 (270)</td>
<td>mmHg</td>
</tr>
<tr>
<td>upslope pulse pres.</td>
<td>8 (6)</td>
<td>10 (10)</td>
<td>150 (150)</td>
<td>mmHg</td>
</tr>
<tr>
<td>downslope pulse pres.</td>
<td>6 (6)</td>
<td>10 (10)</td>
<td>150 (150)</td>
<td>mmHg</td>
</tr>
<tr>
<td>systolic pressure slope</td>
<td>20 (20)</td>
<td>1 (1)</td>
<td>100 (100)</td>
<td>0.02 sec.</td>
</tr>
<tr>
<td>pulse period</td>
<td>6 (6)</td>
<td>10 (10)</td>
<td>100 (100)</td>
<td>0.02 sec.</td>
</tr>
<tr>
<td>average pressure</td>
<td>10 (6)</td>
<td>30 (30)</td>
<td>280 (280)</td>
<td>mmHg</td>
</tr>
</tbody>
</table>

Table 3.2: The validation boundaries (the SNP values are placed between brackets)

Summarizing the new validation algorithm has; adjusted validation boundaries, the actions during backwards state transitions have been improved and the definition of the systolic pressure feature has been changed. After these adjustments the validation algorithm has been compared with the old validation algorithm, using the sampled data taken during the SNP test phase. It turned out that the adjusted algorithm validates more periods correctly than the old validation algorithm, especially the periods, which had a middle dip with a lower pressure than the diastolic pressure were validated correctly.
4 Rules incorporated in the knowledge base

Simplexys is an analysis type of expert system. The goal is the analysis of one specific situation, process state, only. This in contrary to planning systems which search for the best path between a current and a desired state. The knowledge base consists of conditional rules containing the expert’s knowledge. This paragraph describes the rules, which adapt and overrule the controller. These rules can be divided into the following categories (see also [Lammers, 1990]):

- Gain up adaptation
- Gain down adaptation1; large pressure change up
- Gain down adaptation2; large change of flow rate
- Gain down adaptation3; pressure changes fast
- Gain down adaptation4; oscillation detection
- Actions in case of large pressure fluctuations
- Ineffective control

The rules implemented in the NTG base controller will be discussed in this chapter. They are similar to the rules implemented in the SNP based system. Only gain down adaptation mechanism 2 (large change of flow rate) is not implemented, since this rule did not work satisfactorily in the SNP system (see paragraph 4.2.2).

4.1 Transient detection

A transient is defined as an unexpected, temporary, large pressure increase or decrease. An unexpected pressure increase can be interpreted as pain, whereas a unexpected pressure decrease can be an indication of shock. Even fast pressure changes caused be surgical interferences or infusion of additional pressure influencing drugs are regarded by the system as a transient. Because the system has no other information than the pressure signal, it must therefore always assume the worst case. The pressure change during a transient is too fast for the controller to respond accurately. Moreover we know that the disturbance is temporary and the pressure will return to its pre-transient value. Thus the controller should not attempt to regulate the pressure when a transient has been detected.
If the pressure increases during a transient, the correct strategy is to keep the flow constant until the pressure returns to its pre-transient value or the pressure increase turns out to be permanent. Nevertheless, this is not the best strategy when the pressure decreases during a transient, since we are never sure if the pressure decrease is a transient or a permanent pressure decrease. To guarantee the patient’s safety the best strategy is to assume the worst. The flow should be shut off when the pressure drops quickly, and should be resumed at its pre-transient value when the pressure decrease turns out to be temporary after all.

Since the transient detection mechanism used with the SNP base controller worked well, the same structure has been used for the NTG based controller.

4.2 Gain adaptations

The complete range of patient sensitivity is too wide for the controller to handle, therefore the gain of the controller should be adapted to the sensitivity of the patient. At start up the patient is categorized in the second sensitivity class. The control gain is increased when the pressure changes too fast, whereas the control gain is decreased when the pressure changes too slow or an unstable control has been detected. The rules which increase and decrease the control gain are described in this paragraph.

4.2.1 Gain up adaptation

If after a certain time the progress of the pressure towards the setpoint is not as fast as expected, then it is likely that the gain of the controller is too low compared with the patient sensitivity, and an increase of the control gain is required. The rule base is allowed to increase the control gain in case of a too slow progress of the pressure signal. Because during a situation of ineffective control (see paragraph 4.3) or during a transient the progress of the pressure has no relation with the control gain, the rule base is not allowed to change the controller gain when a transient or a situation of ineffective control has been detected. To prevent too many gain changes in a short period of time, the control gain is only changed, if it
has been constant for 200 seconds. Because a gain change is of no use when the flow rate is limited, the gain is only increased if the flow rate has not been more than 95% of its maximum value within the last 60 seconds.

4.2.2 Gain down adaptation

The rule base decreases the gain when unstable control has been detected. An indication for unstable control is either a rapid pressure change towards the setpoint or a detection of an oscillation. Though the controller is designed in such a way that an oscillation should not occur, detection of it remains vital especially for extremely sensitive patients. As a result, a gain down request is issued after a fast changing pressure or a detection of oscillation.

Due to the assumed non-linear response, the patient sensitivity decreases at high flow rates (see paragraph 2.1). After a large setpoint change up, a large decrease of the flow rate is expected. Thus we can expect an increased sensitivity after a large setpoint change up. In order to compensate for the changed sensitivity, the control gain should be decreased after a large setpoint change up. During the clinical testing of both the SNP and the NTG based controller, such a large change of setpoint never occurred.

The designers of the SNP based controller [e.g. Zwart, 1990] also made the assumption that a relatively large change of the flow rate in a short time is caused by a too high control gain. Consequently a continuously high flow slope should result in a gain down request. There are several reasons why this rule is not feasible and therefore not implemented in the NTG based controller: It is obvious that insensitive patients cause a higher flow slope then sensitive patients. Moreover the relative change of the flow rate is used to detect a too high flow slope, and this measure is dependent on the absolute flow rate, and consequently on the chosen setpoint. Furthermore Lammers [Lammers, 1990] concluded that this rule often slowed down the control speed unnecessarily. And finally we cannot determine the sensitivity by observing the flow rate, we also have to observe the pressure change caused by this flow rate.
Similarly to the gain up adaptation, the expert system is allowed to decrease the gain only when certain conditions hold: The gain has not been changed within the last 50 seconds and no transient has been detected. Because a decrease of the control gain is useless when the flow rate is limited, the control gain is not decreased if the flow rate has been less than 2% percent of its maximum value within the last 30 seconds.

4.3 Ineffective control

Control is ineffective if a further change of the flow rate is not possible or does not bring the pressure closer to the desired level. This suggests that in a situation of ineffective control the user has chosen a setpoint, which cannot be reached by the controller. Infusion of an additional drug is necessary to reach the desired setpoint. During a situation of ineffective control, the expert system notifies the user and freezes all gain adaptations.

Ineffective control is detected when the pressure is showing no progress and is not close to the setpoint. Furthermore ineffective control is detected when the flow rate has been more than 95% or less than 2% of the maximal flow rate longer than 60 seconds. Finally a gain up request, while the gain is already at its maximum level, is also regarded as a symptom of ineffective control.
5 Tracking the pressure signal

The rules in the rule base observe the pressure signal and adapt or overrule the controller when necessary. To perform its task correctly, the rule base needs some measure of progress of the pressure signal. Furthermore, the rule base has to be notified when an oscillation has been detected. The methods used to determine the progress of the pressure signal and the presence of oscillation will be described in this chapter.

5.1 Oscillation detection

When the system is oscillating the pressure signal is alternately higher and lower than the setpoint. Thus the number of setpoint crossings per unit of time can be used as a measure of oscillation. To limit the influence of random fluctuations around the setpoint, a hysteresis above and under the setpoint is taken into account, see figure 5.1. The counter, which contains the number of setpoint crossings, is incremented every time the pressure signal travels from the lower hysteresis border to the upper hysteresis border, or visa versa. Oscillation is detected when too many border crossings have been counted in a short period of time. To ensure that only too many border crossings following each other in a short period of time are regarded as an oscillation, the counter is decremented every 250 seconds. The counter is limited at zero. Because a setpoint change and a transient can cause the border cross counter to be incremented incorrectly the counter is decremented after a setpoint change, and is set to zero when a transient has been detected.

This mechanism detects oscillation correctly as long as the oscillation centers around the setpoint. There exists however one situation in which the oscillation does not center around the setpoint, see figure 5.2. Because it is not possible to administer a negative flow rate (and because the controller does not calculate with a negative flow rate), an oscillation at a low flow rate will cause a pressure oscillation with a negative offset. Due to this offset the pressure oscillation detection
mechanism, which expects an oscillation around the setpoint, fails. The oscillation detection mechanism has therefore been extended in order to deal with this form of oscillation correctly.

Therefore, similarly to the detection of a pressure oscillation, a counter is incremented every time the flow rate crosses the flow detection border, see figure 5.2. To limit the influence of random fluctuations, a filtered version of the flow rate is being used for this purpose. Currently the value of the flow oscillation detection border is set at 0.5 μg/kg/min. It is advisable to decrease this value, because an extremely sensitive patient can still cause an oscillation with a flow rate amplitude lower than 0.5 μg/kg/min.

To prevent incorrect detection during transients and after a setpoint change, the counter is decremented after a setpoint change and set to zero during transients. If too many crossings of the flow oscillation border are counted in a short period of time, oscillation is detected. Table 5.1 summarizes all the situations which influence the counters used to detect oscillation.
Figure 5.2: Oscillation at low flow rates

Table 5.1: The oscillation detection mechanisms
The numeric values of table 5.1 are motivated as follows. Because of the values of the dynamic model parameters, it is unlikely for an oscillation to occur with a cycle period of more than 250 seconds. During one cycle period 2 border crossings occur, which will increase the counter by 4, this counts both for flow and pressure oscillation. After one and a half cycle the counter is increased by 6 and decreased by at most 2, because one and a half cycle takes less than 500 seconds. Oscillation is therefore detected within 2 cycle periods under the condition that the cycle period is less than 4 minutes.

5.2 Testing the progress of the pressure signal

To test the progress of the pressure signal, necessary for the gain adaptations rules and the testing of ineffective control, some measure of the progress of the pressure towards the setpoint is required. A simple derivative of the pressure signal will not suffice, because this measure is very sensitive to noise and pressure fluctuations. To overcome this problem the SNP based controller defined 11 regions around the setpoint (see figure 5.3). The width of the different regions is chosen such that if the control gain is correct, the pressure stays in each region for about 2 minutes. To prevent the MAP from travelling repetitiously from one region to another and back due to small spontaneous pressure variations, the pressure is filtered and the region borders have a hysteresis.

If the pressure stays in one region (except region #5) longer than 4 minutes, the control gain is increased, whereas if the pressure stays in one region shorter than 1 minute the control gain is decreased. Ineffective control is detected when the pressure stays in one region longer than 8 to 9 minutes. This time depends on the region the pressure is in.

However the above described system has some deficiencies, which caused the gain adaptation mechanism to slow down control speed unnecessarily: A too fast progress of the pressure signal towards the setpoint is only detected when the pressure crosses a region border. This implies that during the time the pressure stays between two region borders no knowledge of the progress is available. Also the region the pressure settles in after a setpoint change will have no contribution to
the progress testing, because all timing parameters are based on the time
necessary to cross a whole region. Thus the actual progress testing starts after the
pressure signal crosses the first region border.

To improve the progress testing mechanism, an estimation of the progress of the
pressure signal should be available after every sample. Lammers [Lammers, 1990]
proposes the use of the integral of the pressure minus the setpoint as another
measure of progress. This method holds two major drawbacks: The detection of a
fast changing pressure is delayed due to the time delaying properties of the
integral. And the measure of progress is defined by the integral and not the
expected pressure progress. For example, using an integral an offset will have half
the contribution to the measure of progress as twice that offset. In other words,
when using an integral we will not be able to take the expected control performance
fully into account.

Thus the best alternative is to use the region structure, but to increase the number
of regions used. This led to the following algorithm: To detect a too fast pressure
change, we compare the largest pressure change over the last 6 pressure values
with the maximum allowed pressure change. To detect a too slow pressure change
we compare the maximal pressure change over the last 31 pressure values, with the minimal expected pressure change. No progress of the pressure signal is detected in a similar way, but now 51 samples are taken into account instead of 31. In this manner the expected pressure progress is fully used, when judging the progress of the pressure signal.

The minimal and maximal allowed pressure change are both a function of the distance between the current pressure and the setpoint. Simulation results have been used to observe the pressure change caused by a setpoint change. The nominal patient parameters have been used (i.e. time constant = 175 seconds; delay time = 45 seconds). To determine the maximum expected pressure change the highest sensitivity within one category is chosen (e.g. control gain = 1; sensitivity = 28). The highest pressure change is then 21% (i.e. 100% * pressure change over 6 samples divided by the most recent pressure of the 6 samples). To determine the minimum expected pressure change the lowest sensitivity within one category is chosen (e.g. control gain = 1; sensitivity = 15.6). The pressure change is the slowest just after the setpoint has been changed. We should take into account the delay time (9 samples) and the time necessary to obtain the samples necessary for the too slow progress detection (31 samples). The minimum expected pressure change is then 50% (100% * (P[40]-P[10])/P[40]). To detect no progress of the pressure signal a minimum pressure change of 15% over 51 samples has been chosen. The progress of the pressure signal is not tested if the difference between the pressure and the setpoint is smaller than 7 mm Hg. The percentages 21%, 50% and 15% have been used as a guideline to determine the expected pressure change for each error value. The progress testing methods are implemented in a Pascal-like structure as follows:
error := abs ( pressure- setpoint );

Region_Fast : array [7..200] of integer; {contains the maximum allowed pressure change over 6 samples}
Region_Slow : array [7..200] of integer; {contains the minimum allowed pressure change over 30 samples}
Region_NoProg : array [7..200] of integer; {contains the minimum allowed pressure change over 50 samples}

If MaxError_Last_6 > Region_Fast[ round(error) ] then TooFast := true;
If MaxError_Last_31 < Region_Slow[ round(error) ] then TooSlow := true;
If MaxError_Last_51 < Region_NoProg[ round(error) ] then NoProg := true;

To take into account the time during which the patient shows no response to the Nitroglycerin, the progress testing is disabled by the rule base for a certain time, after switching to automatic control. This delay time together with the time necessary to obtain all the samples used to detect the progress, either 6, 31 or 51 samples, determine the time the progress testing is disabled after switching to automatic control. The too fast progress detection is therefore enabled after 45 seconds; 9 samples are taken during this time, after switching to automatic control. The too slow progress detection is enabled after 205 seconds, and the no progress detection is enabled after 255 seconds. Similarly, the progress detection mechanisms are also disabled during the same time after a setpoint change or a setpoint crossing of the pressure signal. To guarantee the patient’s safety the invalid measurements are also considered when testing for too fast pressure changes.

In principle this method is similar to the method used in the SNP based controller, only now every discrete pressure value has a region assigned to it. With the new progress testing algorithm, we are now able to give an indication of the progress with each new pressure value. This new progress testing algorithm has been tested during several simulations, see figure 5.4. It turned out that the new gain adaptation algorithm is fast enough to guarantee stable control, even if the initial gain has been chosen too high. Because the gain adaptation mechanism is fast enough, we can safely assume at start up that the patient is of the second sensitivity category, i.e. sensitive and not extremely sensitive.
Figure 5.4: Simulation result with the new progress testing algorithm. The sensitivity is respectively two categories too high, correct and two categories too low.

As mentioned in chapter two, patients with a sensitivity in the lower and the higher sensitivity category are not likely to exist. Since the progress testing algorithm proved to be fast enough to correct an erroneous sensitivity categorization, we can safely change the classification of the patients in the highest and lowest category after a period of stable control. Thus a gain up request is issued when the gain is minimal and the pressure has been close to the setpoint for more then 300 seconds. And similarly, a gain down request is issued when the gain is maximal and the pressure has been close to the setpoint for more then 300 seconds.
6 Preparing the clinical tests

The blood pressure control system has been tested during cardiac surgery procedures at the Academic Hospital of Maastricht, after approval by the Medical Ethics Committee and with informed consent of the patients. The set up of the blood pressure control system, used during these clinical tests, will be discussed in this chapter.

6.1 Set up of the blood pressure controller

Figure 6.1 shows the complete blood pressure control system. The patient's blood pressure is sampled with an Analog to Digital Converter and, after validation, the mean arterial pressure is determined. Based on the mean arterial pressure the controller calculates the required flow rate, necessary to bring the pressure towards the setpoint. The infusion pump administers the calculated flow rate to the patient.

After implementation of the rule base, with the aid of the Simplexys designers toolbox [Blom, 1990] version 4.0. The rule base and the units have been compiled
using Turbo Pascal, version 6.0. Besides the actual controller, as described in the previous chapters, there are several functional units which provide the communication with the outside world. These units will be discussed briefly below:

The pressure signal is taken from the instrument panel of the operation room. To import this signal into the rule base the signal is sampled at a sampling rate of 50 Hz. To reduce the influence of measurement noise the signal is filtered before sampling, with a low pass anti-aliasing filter with a cut off frequency at 25 Hz. The blood pressure samples are stored in the FIFO buffer of the Labmaster [Scientific Solutions, 1990]. This buffer can store up to 1024 (12 bit) samples. Using a sampling rate of 50 Hz the buffer needs to be emptied every 20 seconds. This provides enough time for the controller to handle all pump communications, user input and other calculations. The programmable gain of the Labmaster can be used to improve the measurement accuracy. A gain amplification of a factor 4 improves the resolution to 0.05 mm Hg.

Since the development of the SNP based controller a new version of the ADC convertor had become available. Therefore the unit controlling the Labmaster needed to be adjusted. This resulted in the unit LabFiFo, which initializes and controls the ADC convertor. After sampling and filtering, the pressure signal is validated as described in chapter three. The validation algorithm is implemented in the unit MapVal, which provides the expert system with a new pressure value every five seconds.

The unit BibPump establishes the contact with the infusion pump, an Imed 929. When no pump failure occurs, the infusion pump accepts the calculated flow rate and administers it to the patient. The resolution of the infusion pump is 1 ml/hr. For a patient who weights 60 kilogram we still have a resolution of 0.01 μg/kg/min. Assuming the highest sensitivity we are still able to regulate the pressure with an accuracy of 1 mm Hg. Pump failures can occur due to a computer/pump communication error, an occlusion of the infusion line, air in the line, an exhausted battery or an empty infusion bag. During a pump failure the unit BibPump alerts the expert system and warns the user.
Finally there are several units which take care of the communication between the user and the system. These units build the graphic display, check the keyboard for user's input and update the files, which are used to store the operation's data. I will not describe these units, since there have been no fundamental changes, compared with the SNP based controller [Zwart, 1990; Blom, 1990; Lammers, 1990].

6.2 Program flow of the complete system

The different features of the blood pressure controller have been described throughout this report. This paragraph will give a summation of the program flow of the complete system:

INITIALIZATION

- Enter patient's weight
- Initialize Analog to Digital convertor, pump communication, display

MAIN LOOP

- Import the pressure measurement: Empty the FiFo buffer and calculate the mean arterial pressure. This routine provides the timing of the main loop, since it waits until 250 samples are taken, i.e. 5 seconds (the sampling rate equals 50 Hz). If the pressure measurement is not valid the previous pressure value is taken as the current pressure.

- Test for and serve the user input (such as setpoint changes).

- Calculate the output of the PI-controller: The output is only calculated when the controller is in automatic mode.
- The major part of the main loop consists of the knowledge base. These rules define the actions concerning the non-linearities of the patient model, gain adaptations, oscillation, ineffective control and transients. All these rules are described in chapter 2, 4 and 5. The rules which detect transients are described by Lammers [Lammers, 1990].

- Store data on disk
- Send current flow rate to pump
- Update graphic display

CLOSE DOWN

- Close Analog to Digital convertor, pump communication, display, output files.

6.3 The procedure followed during tests

The infusion fluid had a concentration of 40 microgram Nitroglycerin per milliliter. After preparation of the infusion fluid, the infusion bag was connected to the infusion pump. The infusion line was connected to a 7 F. pulmonary catheter.

The pressure signal was obtained using a radial artery catheter cannula (20-gauge).

After these preparations the controller is ready to start. At start up the user is asked to enter the patient's weight. The system is entered in manual mode. When no pump failures or invalid measurements occur, the system can be switched to automatic mode and start its control task.

To get some insight into the use of the controller during the operation, a brief description of the different stages during cardiac surgery is necessary. Cardiac surgery has three stages. During the first stage access to the heart is made. The opening of the chest can cause a large increase of the blood pressure. During the second stage the heart is inoperative and blood circulation and oxygenation is provided by a heart-lung machine. The pressure validation is now in perfusion mode.
since there is no heart cycle. During this stage the pressure is mostly controlled by the heart lung machine and hypertension seldom forms a problem. During the third stage the heart is reactivated and the chest is closed.

In most cases the controller was switched to automatic control after the opening of the patient’s chest. There remained approximately 20 to 60 minutes before the patient was connected to the heart lung machine. In most cases additional lowering of the blood pressure during the perfusion was not required. After the reactivation of the heart the controller was allowed to regulate the pressure again. The greatest demand on the controller was made just after the opening of the chest, because the hypertension during this stage was the largest and pressure fluctuations were large as well.

6.4 The patients

<table>
<thead>
<tr>
<th>Test</th>
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<th>Surgery</th>
</tr>
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<tbody>
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<td>82</td>
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</tr>
<tr>
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<td>69</td>
<td>68</td>
<td>Bypass</td>
</tr>
<tr>
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<td>M</td>
<td>71</td>
<td>55</td>
<td>Bypass</td>
</tr>
<tr>
<td>#14</td>
<td>M</td>
<td>72</td>
<td>85</td>
<td>Valve</td>
</tr>
<tr>
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<td>M</td>
<td>71</td>
<td>87</td>
<td>Bypass</td>
</tr>
<tr>
<td>#16</td>
<td>F</td>
<td>61</td>
<td>70</td>
<td>Bypass + Valve</td>
</tr>
<tr>
<td>#17</td>
<td>M</td>
<td>47</td>
<td>85</td>
<td>Bypass</td>
</tr>
<tr>
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<td>F</td>
<td>74</td>
<td>70</td>
<td>Valve</td>
</tr>
<tr>
<td>#19</td>
<td>M</td>
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</tr>
<tr>
<td>#20</td>
<td>M</td>
<td>62</td>
<td>85</td>
<td>Valve</td>
</tr>
</tbody>
</table>

Table 6.1: The patients’ data
The blood pressure control system has been tested on twenty patients undergoing open heart surgery, either valve replacement or coronary artery bypass surgery. During the first test case the calculated flow rate was suggested by the computer and infused by the anaesthetist. During the other 19 test cases the control loop was closed, and the calculated flow rate was infused by the infusion pump. The control system’s behaviour was closely supervised at all times.

A standard technique of anaesthesia was employed for all patients. All patients received Lorazepam as oral pre-medication. Anaesthesia was induced and maintained with Sufentanil. After the perfusion patients undergoing coronary artery bypass surgery received a continuous flow of Nitroglycerin, 0.5 \( \mu g/kg/min \). When necessary, additional lowering of the blood pressure was obtained with the aid of the blood pressure control system.

Most patients were male (14 out of 20). The average age of the patients was 61 years (37 to 75 years). The average weight of the patients was 77 kg (55 to 102 kg). Table 6.1 summarizes all patients’ data.

### 6.5 Changes made to the rule base between tests

The knowledge base had to be slightly changed during the tests. Adjustment of the knowledge base was found necessary, because the control performance at low flow rates was not as expected. At low flow rates the pressure showed a negative offset away from the setpoint which disabled the oscillation detection mechanism. Starting from test #8 the flow oscillation detection mechanism (as described in chapter 5) has been added to the rule base. To prevent the offset at low flow rates the flow rate limitation mechanism (as described in chapter 2) has been added at the same time.
7 The clinical tests

Before summarizing the results of the clinical tests, I want to stress that it is not always possible to distinguish between the effect of the infused Nitroglycerin on the mean arterial pressure and the pressure disturbances caused by other drugs, the surgeon’s manipulations or the natural tendency of the pressure to in- or decrease. We should always bear this in mind when interpreting the numeric results given in this chapter. The numeric data of test #13 has not been available due to a disk malfunction, and is therefore not given.

7.1 The control performance

<table>
<thead>
<tr>
<th>case</th>
<th>first pressure</th>
<th>to auto pressure</th>
<th>setpoint</th>
<th>settling time</th>
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<tbody>
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<td>#1</td>
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<td>119</td>
<td>90</td>
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<td>#9</td>
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<td>80</td>
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<td>7:15</td>
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<td>#20</td>
<td>68</td>
<td>99</td>
<td>80</td>
<td>8:15</td>
</tr>
</tbody>
</table>

Table 7.1: Initial pressures (MA filtered) and settling time of each test. The settling time is the time necessary, after switching to automatic control, to reach a pressure value within 5 mm Hg of the setpoint.

The controller was generally switched to automatic control after the opening of the chest. A good measure of the control performance is the settling time. The settling
time is defined as the time necessary, after switching to the automatic mode, to reach a pressure value within 5 mm Hg of the setpoint. This settling time varied between 1 and 15 minutes (average 7 minutes and 12 seconds). Table 7.1 shows the initial pressures and the settling time of each test. To reduce the influence of random fluctuations, the pressure measurements are filtered with a Moving Average filter ($P_{\text{avg\_new}} = 0.8 \times P_{\text{avg\_old}} + 0.2 \times P$). This filter is strong enough to reduce the influence of noise and follows the unfiltered pressure signal close enough in time.

The controller remained in automatic mode until the perfusion commenced. During none of the tests it was found necessary to adjust the flow rate manually (this was sometimes necessary during the tests of the SNP based controller). Test #5 showed that the oscillation detection mechanism was not yet complete. At low flow rates the pressure has an offset away from the setpoint. Due to this offset the pressure oscillation detection mechanism fails to detect oscillation correctly (see paragraph 5.1). Though this situation did not result in unstable control, adding the flow oscillation detection to the oscillation detection mechanism was found necessary.

<table>
<thead>
<tr>
<th>offset band</th>
<th>5</th>
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<th>20 [mmHg]</th>
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<td>5</td>
<td>34</td>
<td>71</td>
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<td>99</td>
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<td>#19</td>
<td>34</td>
<td>65</td>
<td>83</td>
<td>90</td>
</tr>
</tbody>
</table>

Table 7.2: Distribution of the offset over time (in percentages) in zero-centered bands around the setpoint.
The stabilization performance of the controller can be judged by measuring the offset, the difference between the pressure and the setpoint, over time. Figure 7.1 shows the cumulative distribution of this offset. The average deviation from the setpoint was 7.0 mm Hg. All the values during which the controller was in the automatic mode (not during the perfusion) are considered. Table 7.2 gives the offset over time in zero centered bands around the setpoint for each test. Table 7.3 compares the average offset with the performance of the SNP system. When interpreting figure 7.1 and tables 7.2 and 7.3 we should bear in mind that the measurements during transients, periods of ineffective control and the time necessary to reach the setpoint, are also included. Table 7.3 shows clearly that the stabilization performance of the controller is better than the SNP based controller.

<table>
<thead>
<tr>
<th>offset band</th>
<th>NTG</th>
<th>SNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>± 5 mm Hg</td>
<td>52%</td>
<td>33%</td>
</tr>
<tr>
<td>± 10 mm Hg</td>
<td>79%</td>
<td>61%</td>
</tr>
<tr>
<td>± 15 mm Hg</td>
<td>90%</td>
<td>78%</td>
</tr>
<tr>
<td>± 20 mm Hg</td>
<td>95%</td>
<td>86%</td>
</tr>
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</table>

Table 7.3: Percentages of the offset over time in zero-centered bands in automatic control of both the NTG and the SNP system.
7.2 Verification of the patient model

It is difficult to give a good estimation of the patient parameters, because all the flow rate changes during automatic control are gradual. Also the noisy environment makes system identification impossible. In some cases the flow rate change after
switching to automatic control can be approximated by a step-wise flow adjustment. A condition is that after switching to automatic control the flow rate should increase quickly and then remain at a stable level. By observing the pressure change in these cases it is possible to give an estimation of the patient parameters (we assume the patient parameters do not change in time). To reduce the influence of noise and random fluctuations a Moving Average filter is used to filter the pressure and flow signal (see also paragraph 7.1). The difference between the pressure (after switching to automatic control) and the setpoint is the total pressure change caused by the step wise flow rate adjustment. The flow rate value after the pressure changed by 63% (of the total pressure change) towards the setpoint is regarded as the flow rate step size. The sensitivity is now defined as the total pressure change divided by the flow rate after 63%. The pressure signal was too disturbed to give a good estimation of the delay time; a rough estimation is that the delay time is approximately 50 seconds. The time constant is defined as the difference between the time necessary to reach 63% of the total pressure change and the time the first pressure decrease after switching to automatic control is visible. In two cases (test #8 and #16) the pressure did not initially stabilize around the setpoint. To determine the patient parameters correctly in those situations (#8 and #16) the total pressure change is defined as the pressure after switching to automatic control minus the value the pressure stabilized at. Table 7.4 shows the results of these calculations. From table 7.4 it follows that the sensitivity varied between 8 and 38 mm Hg/μg/kg/min, average 21 mm Hg/μg/kg/min. The time constant varied between 3 minutes and 20 seconds and 7 minutes and 40 seconds, average 4 minutes and 47 seconds.

We are now able to compare the measured patient parameters with the assumptions made in chapter two (see table 2.1). The average sensitivity was well chosen. But there were more extremely insensitive patients than assumed. The average time constant turns out be larger than expected (287 instead of 175 seconds). But this can very well be the result of the approximation of the flow rate by a step wise flow adjustment, because the pressure already starts to decrease before the flow rate reaches a stable level.
7.3 Gain adaptations

The new gain adaptation algorithm worked well. It was fast enough to ensure a fast settling time, even for extremely insensitive patients. And it was safe enough to decrease a too high control gain before the flow rate change was too large. For each data file the gain, which has been used most of the time, has been determined. The distribution of the control gain around the most used gain of each data file is shown in figure 7.2.

![Figure 7.2: Distribution around most used gain. There have been a total of 102 gain changes](image)

Table 7.5 shows the relation between the most used gain of each test and the estimated sensitivity (see also table 7.4). It is clear from this table that the correlation between the selected control gain and the patient sensitivity is not large. The most likely explanation is that the control gain is adapted quite fast and reflects more the gain necessary to reach the chosen setpoint within an acceptable settling time than the sensitivity. Another explanation is that our assumption that the sensitivity does not change with the time is wrong. This implies that we have only determined the sensitivity for one time interval, and that this is not necessarily the sensitivity at all times.
Table 7.5: Relation between the estimated sensitivity and the most used control gain.

<table>
<thead>
<tr>
<th></th>
<th>sensitivity</th>
<th>sensitivity</th>
<th>most used</th>
<th>number of categories too high/low</th>
</tr>
</thead>
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<td>2</td>
</tr>
<tr>
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<td>III</td>
<td>V</td>
<td>2</td>
</tr>
<tr>
<td>#7</td>
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<td>I</td>
<td>II</td>
<td>1</td>
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<td>0</td>
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<td>II</td>
<td>1</td>
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<td>#20</td>
<td>16</td>
<td>III</td>
<td>III</td>
<td>0</td>
</tr>
</tbody>
</table>

The rule base does not allow to change the control gain if the gain has been changed recently. After examining the data of the operations it became clear that this rule limits the gain down mechanism. If the pressure signal shows no progress the gain is increased; if however the pressure drops quickly within 50 seconds after this gain increase, the rule base is not allowed to decrease the too high control gain. It should be considered to have two separate counters, instead of one, which count the time since the gain has been changed, one for gain up adaptations and one for gain down adaptations. In this way the rule base is allowed to decrease the control gain if the pressure drops quickly just after a gain up adaptation.

7.4 Validation

The changes made to the validation algorithm were successful; the controller never improperly returned to manual mode. With the aid of the validation parameters obtained during the operation, a distribution of the validation boundaries has been calculated. Figures A1 to A7, see Appendix I, show the results. The chosen validation boundaries, see table 3.2, can be adjusted with the aid of these figures.
7.5 The oscillation detection mechanisms

After adding the flow oscillation detection, the oscillation detection mechanism worked well. In some cases a flow oscillation was detected incorrectly, because there were random flow fluctuations around the flow oscillation detection border. This can be prevented if a hysteresis is taken into account with the flow oscillation detection border. The flow oscillation counter should only be increased if the flow signal crosses first the lower and then the upper border, or vice versa.

7.6 The controller during perfusion

Nitroglycerin does not lower the mean arterial pressure satisfactorily during perfusion (see paragraph 2.1). This has been verified during the first operations. After the first operations the controller was switched to manual just before the perfusion commenced. However, one thing could be deduced from the operations, during which the controller remained in automatic mode pending the perfusion. The temporary pressure increase, which is sometimes caused by the activation of the heart-lung machine, is not always detected as a transient. As a result the flow rate sometimes increased unnecessarily. A better strategy therefore, is to freeze or shut down the flow after the controller’s validation has been switched to the perfusion validation, and to resume controlling the pressure after the pressure has stabilized again.

7.7 Influence of the baroreceptor

In the last few tests an interesting phenomenon was observed. After the controller had stabilized the mean arterial pressure around the setpoint for 5 to 10 minutes, the infusion flow was shut off. This did not result however in the expected pressure increase a few minutes later. The patient was able to maintain the same pressure level until the perfusion commenced. This was observed clearly during 4 cases, see also figure 7.4a and 7.4b. One possible hypothesis is that the patient’s pressure regulation system can be reset by regulating the pressure close around a setpoint.
for a certain time, and that after this time the patient is able to maintain the same pressure level without the aid of the controller.

It has been reported before that the disturbance of the baroreceptor function, caused by among others the used anaesthesia, can lead to a hemodynamic lability with a transitory hypertension elicited by relatively minor external stimuli, [Berne, 1979; Vatner, 1971]. In this view, the hypertension after the opening of the chest, is mainly caused by a disturbance of the baroreceptor function. It is possible that the baroreceptors can be reset with the aid of the controller, and resume their stabilization task. The patient model should therefore be extended, and also take the baroreceptor function into account. More tests are required before the controller is adapted in this manner.
Figure 7.4a: The perfusion starts 43.5 minutes after the starting of the test. The pressure decrease after 30 minutes is caused by a direct injection of papaverine. Patient: male, 60 years old, 80 kg, bypass surgery.

Figure 7.4b: Perfusion starts 37 minutes, after the start of the test. Patient: male, 62 years old, 85 kg, Valve replacement.
8 Conclusions and recommendations

The clinical evaluation of the blood pressure controller has been successful. The controller never caused a dangerous clinical situation. The new gain adaptation algorithm worked well and provided an acceptable settling time for all patients. Also manual adjustment of the flow rate was never found necessary. The stabilization performance of the controller showed an improvement compared with the SNP system. The offset from the setpoint was considerably smaller than during the SNP test phase (see table 7.3). The changes made to the validation algorithm proved to be correct; the controller never improperly returned to manual mode due to invalid measurements. The chosen control strategy, a robust controller monitored by a knowledge based expert system, proved to be a successful one.

Due to a deficiency of the flow oscillation detection mechanism some unnecessary gain down requests were issued. Paragraphs 5.1 and 7.5 give a suggestion to solve this problem.

All patient parameters were within the expected range, though more patients were extremely insensitive than expected. Also the average time constant is perhaps larger than expected. More knowledge of the response to Nitroglycerin is needed if we want to adjust the patient model and thus tune the robust controller more accurately. But another application may be required to study this aspect satisfactorily.

Beside the control performances, it is now possible to make a comparison between the use of Nitroglycerin and Sodium Nitroprusside during automated blood pressure control. According to the studied literature [Fahmy, 1978; Kaplan, 1976, Kaplan, 1979] Nitroglycerin produces less pressure fluctuations than Sodium Nitroprusside. However, the patient's response to Nitroglycerin is slower than the response to Sodium Nitroprusside. Furthermore, Nitroglycerin does not work satisfactorily during perfusion. This is not a great problem since hypertension seldom is a problem during perfusion. The main advantage of Nitroglycerin is that it has no toxic properties. This offers a lot of freedom during the introduction phase of the system.
Because the control gain is adapted quite fast, the control gain reflects more the gain necessary for the pressure to reach the desired level than the patient sensitivity. Consequently the chance exists that the control gain is sometimes too high or too low for the patient sensitivity. This problem is unavoidable; it is impossible to extract the patient sensitivity from the disturbed pressure signal within the short time available. Further research should therefore concentrate on the consequences of a mismatch between the control gain and the patient sensitivity, and not on the estimation of the patient sensitivity. A start in this direction has already been made by improving the progress and the oscillation detection mechanisms. For other types of surgery, which have less pressure disturbances and more time available to regulate the pressure towards the setpoint, e.g. in an intensive care unit, a control strategy based on the estimation of the patient sensitivity could be more successful.

The control performance is poor when flow rate is around zero. It should be investigated if we can allow the robust controller to calculate (partially) with a negative flow rate (though we cannot administer a negative flow rate). This can perhaps replace the flow rate limitation at low flow rates (chapter 2), and avoid the necessity of a flow oscillation detection mechanism (chapter 5).

Due to the assumed possibility to reset the baroreceptor function, the patient model needs to be extended. After maintaining a stable pressure for a few minutes, it should be tested if the patient can maintain the same pressure level without the aid of the controller. More research into the baroreceptor function is necessary, before the rule base is adapted in this manner.

To involve the anaesthetist more in the development of the knowledge base, a stricter separation between control and medical knowledge is necessary. In the ideal situation the knowledge base should only contain medical knowledge, which can be easily updated without interfering with the technical and control knowledge. This separation offers the advantage that the system is more accessible for both control engineers and anaesthetist. Appendix II gives an overview of the suggested separation.
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Appendix I: The validation boundaries

Figure A1: Distribution of the validation parameter, D1.

Figure A2: Distribution of the validation parameter, D2.
Figure A3: Distribution of the validation parameter, Mi

Figure A4: Distribution of the validation parameter, Ma
Figure A5: Distribution of the validation parameter, H1

Figure A6: Distribution of the validation parameter, H_P
Figure A7: Distribution of the validation parameter, $P_g$
Appendix II: A stricter separation between control and medical knowledge

The following gives a schematic overview of the suggested separation between control engineering and medical knowledge. The medical knowledge should be expressed in simple boolean like statements. The control engineering part should contain the calculations and routines which are of no interest to the medical expert. The communication between both parts should be simple and straightforward.

MEDICAL KNOWLEDGE:

Actions in case of transients
Actions in case of too slow or too fast progress
Actions in case of ineffective control

COMMUNICATION:

medical to control          control to medical
- freeze flow             - transient up detected
- shut down flow          - transient down detected
- gain up request         - ineffective control detected
- gain down request       - too slow progress detected
- switch to manual        - too fast progress detected
                          - gain change request acknowledged
                          - flow reached minimal/maximal level
                          - validation normal/perfusion
                          - invalid measurements
                          - setpoint reached
CONTROL ENGINEERING KNOWLEDGE:

User interface
Pump control
Pressure validation
Progress testing
Oscillation detection
Ineffective control detection
Enable or disable gain change requests
Transient detection
The robust PI controller
Appendix III: Program used to tune the robust PI-controller

{This program calculates the (simulated) patient’s and controller’s response to a step wise change of the setpoint. The program returns the optimal pi set; between (p_min, I_min) and (p_max, I_max). The accuracy is p_step and I_step.}

procedure CalcFlow; {calculate control output}

begin {CalcFlow}
  d_flow := l * error + p * (error - prev_error);
  flow := flow + d_flow;
end; {CalcFlow}

procedure CalcPressure; {calculate the patient’s response}

    var a1, G: real;

begin {CalcPressure}
  a1 := (time_constant/sampletime)/(1 + time_constant/sampletime);
  for c := 30 downto 0 do flow_array[c+1] := flow_array[c];
  flow_array[0] := flow;
  G := sensitivity * (1-a1);
  pressure := first_pres + G * flow_array[round(delay_time/sampletime)] +
              a1 * (pressure_old-first_pres);
  pressure_old := pressure;
end; {CalcPressure}

Procedure Init;

begin {Init}
  for i := 0 to 30 do flow_array[i] := 0;
  flow := 0;
  pressure := first_pres;
  pres_old := first_pres;
  n := 0;
end; {Init}

begin {main}
  p := p_min
  Repeat
    i := i_min;

Repeat
  Init;  {initialize all parameters}
  Repeat
    Inc(n);  {increase time counter}
    CalcFlow;  {calculate control output}
    CalcPressure;  {calculate patient’s pressure}

    If abs( (pressure - setpoint) / (first_pressure - setpoint) ) > 0.2 then n20:= n;
    {n20 stores the time necessary for the pressure to change by 80% towards the setpoint}
  Until (n > time_out) or Pres_osc or Flow_osc;

  if not Pres_osc and not Flow_osc and (n20 < n20_best) then begin
    p_best:= p;
    I_best:= l;
    n20_best:= n20;
  end;
  I:= I + I_step;
  Until I > I_max;
  p:= p + p_step;
  Until p > p_max;
  writeln('Best pi set: ',p_best,':',l_best);
end;  {main}