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TOPICAL REVIEW

Developments in control systems for rotary left ventricular assist devices for heart failure patients: a review

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Abstract
From the moment of creation to the moment of death, the heart works tirelessly to circulate blood, being a critical organ to sustain life. As a non-stopping pumping machine, it operates continuously to pump blood through our bodies to supply all cells with oxygen and necessary nutrients. When the heart fails, the supplement of blood to the body’s organs to meet metabolic demands will deteriorate. The treatment of the participating causes is the ideal approach to treat heart failure (HF). As this often cannot be done effectively, the medical management of HF is a difficult challenge. Implantable rotary blood pumps (IRBP) have the potential to become a viable long-term treatment option for bridging to heart transplantation or destination therapy. This increases the potential for the patients to leave the hospital and resume normal lives. Control of IRBP is one of the most important design goals in providing long-term alternative treatment for HF patients. Over the years, many control algorithms including invasive and non-invasive techniques have been developed in the hope of physiologically and adaptively controlling left ventricular assist devices and...
thus avoiding such undesired pumping states as left ventricular collapse caused by suction. In this paper, we aim to provide a comprehensive review of the developments of control systems and techniques that have been applied to control IRBPs.

Keywords: rotary blood pumps, ventricular assist devices, rotary blood pump control, pumping states, left ventricular assist devices control, abnormal pumping states, deadbeat control, model predictive control, heart failure, and abnormal pumping states

1. Introduction

Heart failure (HF), also known as a cardiac or myocardial failure is an abnormal health condition characterized by inability of the heart to supply sufficient blood-borne nutrients to meet the body’s metabolic demands. End-stage HF is the leading cause of mortality, morbidity and disability worldwide. For example, HF is the third largest cause of death in Australia accounting for 43% among males and 41.5% among females. It is estimated that at least 300,000 Australians (over 45 years of age) have chronic HF; with 300,000 new cases diagnosed every year (AIHW 2011). As the diagnosis is commonly missed in mild cases, the actual numbers could be as high as twice of these estimates (AIHW 2011). In the USA, HF was mentioned on more than 280,000 death certificates in 2010 with data indicating that, in both sexes, the prevalence of HF was 5.8 million Americans with associated direct and indirect treatment costs of $39.2 billion (Lloyd-Jones et al 2010). Moreover, in 2009, data for the UK indicated that there were more than 145,000 cases of HF each year with an estimate for the cost of prescriptions used in the treatment of £54.08 million (BHFSW 2000, 2010).

HF is caused by both heart-related factors, such as valve deformity, progressive coronary artery diseases, congenital defects diseases, myocardial infarction and cardiomyopathy, or external factors, such as hypertension, increased cardiac demands or increased volume load, which add extra load and demands on the heart muscle. Reduced myocyte function is the main precipitating cause of most forms of HF (Mohrman and Heller 2006). In steady cardiovascular states, the outputs of right and left ventricles of the heart are synchronized by Starling response in which the response of heart muscle to increase the force of contraction is achieved by increasing the preload. During HF, regardless of the cause, the Starling mechanism is degraded. Depressed cardiac output (CO) characterized by a lower than normal cardiac function curve, and thus lowered arterial pressure are the primary perturbations in acute or chronic systolic HF (Mohrman and Heller 2006, Guyton and Hall 1996).

Whilst surgical and medical management of HF continues to improve, the optimal treatment for end-stage HF remains heart transplantation. The lack of donor organs and the deficiencies of donor hearts for transplantation have made this therapy available only for a small minority of HF patients. For example, in the USA alone, the number of heart transplants per annum increased to a peak in 1995 of 2363 and then reached a plateau in 1998. Since then it has declined to a level of 2055 in 2003 while the prevalence of HF has reached 500,000 new patients each year (Barr et al 2005). Worldwide, reports have shown that the number of transplants performed plateaued at less than 4000 (Hosenpud et al 2001). This has necessitated the development of a range of mechanical assistance devices for the most critically ill HF patients. Left ventricular assist devices (LVADs) are mechanical pumps used...
to support a failing left ventricle (LV), whilst the patient awaits a heart transplant. Implantable rotary blood pumps (IRBPs) are continuous flow VADs, whose popularity has been increasing due to their minimal blood trauma, smaller sizes and lighter weight, and therefore easier implantation. Most commercially available LVADs operate at a fixed speed adjusted by the clinician according to the patient’s activity level or current condition. Due to the low preload sensitivity of IRBPs when compared to the native heart (Salamonsen et al. 2011), operation at constant speed increases the risk of over-pumping or under-pumping during changes in the patient’s circulatory state. Regular monitoring by clinicians is required to ensure that the pump speed is appropriate for the patient’s condition.

IRBPs (for clinical review of LVADs, see Timms (2011) and the references therein) are of a simple and reliable design that can be manufactured easily with several desirable advantages. Small size and light weight are the most important design aspects which make the second and third generation of IRBPs easily implanted inside the patient’s body and thus reduce the surgical efforts and damage to the myocardium as they require a smaller orifice inflow conduit. As heart valves are not incorporated in the IRBPs, the possibilities for thrombus and blood trauma formation are minimal. Also, as there is only one moving part for the blood-pumping action, the use of durable components for this moving part will result in a durable system (Nosé et al. 1996, 2000, Ichikawa and Nosé 2002, Kumpati et al. 2001, Nosé 2004, Ichikawa et al. 2002). RBPs have been shown to be associated with improved patient health outcomes when compared to the pneumatically driven first generation pulsatile pumps (Slaughter et al. 2009). Many RBPs have been introduced clinically for different applications such as a bridge to transplant and recovery (Nosé et al. 2000, Nosé 2004, Ichikawa et al. 2002, Matoba et al. 2004, Nosé and Motomura 2005), bridge to drug therapies (Kumpati et al. 2001, Ichikawa and Nosé 2002, Nosé 2008b), blood purification (Nosé et al. 2010, Ichikawa and Nosé 2002, Ichikawa et al. 2002, Nosé 2008a, 2008b), cellular implants (Kumpati et al. 2001, Nosé et al. 2010, Nosé 2008, Nosé 2009a) and myocardial repair by combination therapy (Nosé 2008a, 2008b, Nosé 2009b). Most importantly, RBPs are also used as a bridge to myocardial repair including two-week pump (125 000 patients/year in the USA) with device cost of US $3000, RBPs for longer than 12 months (70 000 patients/year in the USA) with device cost of US $75 000, and minimally invasive RBPs (500 000 patients/year) with system cost of US $35 000 (Nosé et al. 2010, Nosé 2008b).

The goal of long-term LVAD therapy, however, is to reduce patient dependence on clinical management of their device, allowing them to return home and improve their quality of life. Ideally this requires the implementation of an automatic, adaptive and robust physiological control system whose aim is to automatically adjust pump output with changes in a patient’s state. This task requires modelling the haemodynamic variables and using these models to design a controller that is able to automatically adapt according to patients’ bodies physiological demands. To achieve such control system, research has also been carried out to estimate the pump parameters such as pump flow and differential pressure (head). The implantation of additional sensors is not desirable as they result in thrombus formation, system reliability reduction; increase the system cost and regular calibration requirements due to measurement drifts. This makes the long-term implantation of such LVADs problematic. Also, the selection of suitable sensors that detect the changes in the body’s metabolic demands is one of the important goals in designing LVADs control system. Such sensors may include invasive and non-invasive sensors.

This paper aims to review the techniques that have been utilized in the past to develop control systems for LVADs. Section 2 summarizes the available non-invasive estimation models of pump flow and head in IRBPs. Finally, section 3 details and reviews the existing invasive and non-invasive control strategies developed to control IRBPs.
2. Estimation of pump flow and head in RBPs

Control of IRBPs requires knowledge of pump outputs i.e. differential pressure and flow. As stated earlier, the implantation of additional sensors is not desirable as they result in thrombus formation, system reliability reduction; increase the system cost and regular calibration requirements due to measurement drifts. This has led various research groups to develop methods to non-invasively measure pump and haemodynamic variables. This is crucial in designing an automatic, robust and responsive control system that effectively controls the blood flow according to the body’s physiological needs and perturbations (Wakisaka et al 1997, 1998, Khalil et al 2008, Oshikawa et al 2000). Various groups have shown that such controllers are important to avoid and detect pumping states associated with abnormal flow conditions (Karantonis et al 2006, Ohuchi et al 2001, Amin et al 1997, Yuhki et al 1999, Endo et al 2001, Voigt et al 2005, Vollkron et al 2005, 2004, 2006, Fonseca et al 2008, Lee et al 2003).

The invasive monitoring and non-invasive estimation of pump flow and head have been tackled by many research groups. For review, see Bertram (2005) and the references therein. To summarize, it has been shown that flow rate and head can be accurately estimated under steady-state conditions (Malagutti et al 2007, Ayre et al 2000 and 2003, Funakubo et al 2002, Kitamura et al 2000, Tsukiya et al 1997, Iijima et al 1997, Kikugawa 2000, Nakata et al 2000a, 2000b, Wong et al 2002). However, due to numerous factors that need to be taken into consideration, non-invasive instantaneous estimation of pulsatile flow and head in IRBPs has been much less frequently studied. Such factors, for example, may include the use of characteristic curves of the pump, where these curves are sensitive to many physiological and mechanical parameters, such as changing blood viscosity, native heart interaction, mechanical friction and impeller inertia of the pump. In addition to their contribution to the nature of the dynamical estimation approach that should be followed, these factors are also important to reach a valid and stable model to estimate the instantaneous flow and head of the pump. Also, the design characteristics for each pump can contribute to the proposed estimation algorithms; this means that for each different pump, different unique equations can be obtained (Wakisaka et al 1997, Endo et al 2001, Yoshizawa et al 2002). It is shown, in the VentrAssist™ LVAD (Ventracor Pty. Ltd, Sydney, Australia), that even within the same pump, a small change in the impeller design can result in significant modifications between the motor power, speed and flow relationships (Ayre et al 2000).

Instantaneous flow and head estimation were examined by Tsukiya et al (1997, 2001) when they employed pump power and pump speed to estimate the dimensionless flow rate. Results showed that their non-pulsatile flow rate estimator was able to monitor the values of flow with a mean flow rate error of 1.0 L min$^{-1}$. In addition to data obtained from chronic and acute sheep experiments, Ayre et al (2003) have used static, non-pulsatile and pulsatile mock loops with aqueous glycerol solutions and ovine blood to derive average flow estimator algorithms. Results obtained in this study provided high values of correlation coefficients for in vitro (0.997) and in vivo (0.986) experiments.

Non-invasive measurements of power and speed were used by Yoshizawa et al (2002) to estimate the instantaneous flow and head values using an autoregressive with exogenous inputs (ARX) model where the current and past values of power and speed were used as inputs to another ARX model to estimate a variable $K$ which was assumed to provide information about blood viscosity fluctuations. For flow estimation, a mean absolute error of 1.66 L min$^{-1}$ and a correlation coefficient of 0.85 were reported, while for head, a mean absolute error of 12.8 mmHg and a correlation coefficient of 0.906 were obtained. Their method was tested in vitro and using animal experiments (Tanaka et al 2003). They obtained
an estimation error of 0.27 L min\(^{-1}\) and a correlation coefficient of 0.875 for flow, as well as an estimation error of 6.77 mmHg and a correlation coefficient of 0.775 for pressure. Also, Ogawa et al (2006) have conducted a single chronic animal experiment to evaluate the flow estimation method proposed by Yoshizawa et al (2002) where a mean square error of 0.80 L min\(^{-1}\) and a correlation coefficient of 0.964 were obtained.

Although previous studies produced acceptable results when applied to estimate the pulsatile flow and head, some of these studies have used higher order input/output system models (Yoshizawa et al 2002, Ogawa et al 2006, Tanaka et al 2003) in which they did not study the stability of the transient response of the pump flow. Moreover, other researchers have assumed the system to be stable (Kitamura et al 2000).

In our laboratory, non-invasive feedback measurements of the rotational speed and power were used to estimate the instantaneous pump flow in a pulsatile environment using a new and novel nonlinear dynamical model (AlOmari et al 2009). When operated in steady state conditions, our instantaneous pulsatile flow estimation model can provide an accurate estimate of the pump flow which agrees with those obtained from the static model developed previously in our laboratory under non-pulsatile conditions by Malagutti et al (2007). The set of steady-state solutions of our dynamical flow model coincides with the set of solutions of the static equation derived by Malagutti et al (2007). Then, we used the estimated pulsatile flow values together with pump rotational speed to estimate the instantaneous head in a LVAD.

Other practically important requirements for our dynamical models for pulsatile flow and head estimation are their stability. The proposed models were verified using data obtained from pulsatile circulatory mock loop (AlOmari et al 2009) and animal experiments (AlOmari et al 2009, Zhang et al 2010). The models developed by our research group produced superior results in the pulsatile mock loop settings. For pulsatile flow estimation, it resulted in a high correlation coefficient of 0.982 with a mean absolute error of 0.323 L min\(^{-1}\) while for head, a correlation coefficient of 0.933 and mean absolute error of 7.682 mmHg were obtained. The pulsatile flow estimation model was also validated using ex vivo pig experiments (N = 6) which resulted in a correlation coefficient of 0.849 and mean absolute error of 0.584 L min\(^{-1}\). Recently, the performance of both models showed superior results when evaluated using in vivo experimental data obtained from greyhound dogs (N = 5) (Zhang et al 2010). Linear regression analysis between estimated and measured pulsatile flows resulted in a highly significant correlation coefficient of 0.916 and a mean absolute error of 0.13 mmHg were obtained.

The model proposed by our research group were inherently stable models where this have allowed us to accurately study and estimate the transient response and the dynamics of the pulsatile flow and head. It also performed a milestone in designing an automatic control algorithm for continuous and pulsatile pump flow, which is discussed later in this paper. Furthermore, the developed models were relatively simple and elegant which made the corresponding control design problems more tractable.

3. LVAD control systems

A number of physiological control strategies have been proposed for LVADs. In the following subsections, we will review the existing control systems available for LVADs.

3.1. Proportional, integral, proportional-integral and proportional integral derivative control

To mimic a Starling-type response in an air driven diaphragm pumps, McInnis et al (1985) have developed a feedback controller based on an auto-regressive moving average (ARMA)
model. The proposed ARMA model was then used in a self-tuning adaptive proportional integral derivative (PID) control algorithm to maintain constant systemic resistance, left arterial pressure during changes in heart rate and LV contractility. Similarly, Kitamura (1990) and Shimooka et al. (1991) have also used the auto-regressive modelling approaches to control atrial pressure in the pulsatile pumps.

Parnis et al. (1997) have used a proportional controller for the Javrik 2000 VAD. Heart rate was obtained from the fundamental frequency of the motor current ($I$) waveform and set as a linear function with the pump rotational speed ($\omega$). The proposed method was tested using treadmill exercise and heart pacing studies on a calf with the Javrik 2000 VAD for 26 weeks and no deleterious effects were noticed. One limitation in this approach is the assumption of a linear function between the heart rate and $\omega$. In addition to the heart rate, contractility and peripheral circulation are other factors that determine the CO in adults.

It is hypothesized that the physiological perfusion is achieved when the blood pump is controlled to maintain an instantaneous average pressure difference ($\Delta P$) between the LV and the aorta close to a reference pressure ($\Delta P_r$) (Giridharan and Skliar 2002, 2003). Here, the whole idea of the control problem can be summarized as the design of the feedback control algorithm that regulates $\omega$ within physiologically acceptable limits while minimizing the difference between $\Delta P_r$ and $\Delta P$. To increase the pump life and keep the patients comfort, it is necessary to keep oscillations of $\omega$ as low as possible (Giridharan and Skliar 2002). Electrical current of the pump ($I$) is used as a control input subject to inequality constraints $\omega_{\text{min}} \leq \omega(I) \leq \omega_{\text{max}}$ such that the quadratic objective function,

$$ J = \int_0^t [(\Delta P_r - \Delta P)^2 + r\dot{\omega}^2] \, dt, $$

is minimized. Here, $\omega_{\text{min}}$-$\omega_{\text{max}}$ are functions of the blood volume in LV, $\dot{\omega}$ is the rate of change of $\omega$ where this should satisfy the system of nonlinear hybrid equations which describes the circulatory system assisted by RBP (Giridharan et al. 2002). To maintain $\Delta P_r$, an optimal controller with the structure of a proportional integral controller was selected to manipulate $I$ according to the following control law:

$$ I = K_p(\Delta P_r - \Delta P) + K_i \int_0^t (\Delta P_r - \Delta P) \, dt, $$

where $\Delta P$ is the measured head pressure. The proportional ($K_p$) and integral ($K_i$) constants were selected using an exhaustive direct numerical search to minimize $J$ for different weighting, $r$, until the desired trade-off between the aggressiveness of the controller and oscillations of $\omega$ was reached. Values of $K_p$ and $K_i$ that minimized $J$ were obtained for two different types of RBPs. For the axial flow pump, $K_p = K_i = 0.005$ was obtained, while for the centrifugal one, the tuning procedure resulted in $K_p = K_i = 0.1$.

The designed proportional integral controller with the LVAD was tested under different physiological conditions using computer simulations. Results showed that maintaining a constant average pressure difference between the LV and aorta resulted in physiological perfusion over a wide range of physiological conditions including rest, light and strenuous exercise levels. The results proposed by Giridharan and Skliar (2002) and (2003) showed that the maintaining of a constant pressure difference between the LV and aorta, with either an axial or a centrifugal RBP, was able to achieve a CO close to the physiological cardiac demand irrespective of the heart condition.

Despite simplicity and ease of clinical implementation of the proposed controller, it requires the implementation of two pressure sensors to measure the pressure difference between the LV and aorta. Clinically, the invasive continuous measurements of blood pressure are not desirable for long-term settings due to thrombus formation and induction of septicaemia in
patients (Kitamura et al 2000). To eliminate the need for implantable sensors, Giridharan and Skliar (2006) have proposed a model-based method for estimation of $\Delta P$ where readily available measurements of the intrinsic pump parameters, such as $I$, voltage ($V$) and $\omega$ were utilized. In their studies, two approaches for estimation of $\Delta P$ were examined. First, a method that estimates $\Delta P$ based on the measurements of the intrinsic pump parameters and the flow rate ($F_p$) generated by VAD was proposed. Second, estimation of $\Delta P$ based only on the measurements of intrinsic pump parameters. It was shown that the extended Kalman filter (EKF) (Picard 1991, Petersen and Savkin 1999) can be used to accurately estimate $\Delta P$ across the pump when measurements of $F_p$ are available, while the quality of estimation deteriorated significantly without measurements of $F_p$. To solve this problem, a model-based estimation method of $F_p$ based on $I$ and $\omega$ was proposed where results used as input to the EKF as if it were the measured value of $F_p$. The estimation algorithm was referred to as a soft flow sensor to show the use of the estimated $F_p$ instead of measured one. Simulation results showed that there were virtually no performance degradations with the sensorless estimator-controller system compared with the case where $\Delta P$ was invasively obtained using two pressure sensors. Although the performance of the combined estimator-VAD controller system was tested for a wide range of physical activities and varying heart conditions, assumptions including Newtonian flow, instantaneous valves closing and no inertia or gravity still need further investigations.

In another study by Giridharan et al (2004), they compared the performance of the control strategy of maintaining a constant $\Delta P$ with the results obtained when a constant average pressure difference between the pulmonary vein and the aorta ($\Delta P_a$) is maintained. Using an in vitro mock circulatory system previously described in Pantalos et al (2004) and Giridharan et al (2004), the comparison was made for normal, failing and asystolic left heart during rest and at light exercise. Results indicated that the $\Delta P_a$ control approach adapted to the changing exercise and clinical perturbations better than the constant $\omega$ and $\Delta P$ control strategies (Giridharan et al 2004). Results also showed that the $\Delta P_a$ control strategy was able to maintain and restore the total flow rate to its physiologically normal limits during rest ($3.8 \text{ L min}^{-1}$) and light exercise ($5.4 \text{ L min}^{-1}$) conditions. Another limitation on the proposed proportional integral controller is that the time-varying coefficients of the controller were obtained from offline numerical searches to minimize the weighting function. Thus, whenever the cardiovascular conditions are different from those used in the numerical searches, the optimality of the controller may deteriorate.

In a similar fashion, to adjust the motor speed and maintain a reference differential pressure across a VAD when changes occur in the natural heart, Waters et al (1999) have proposed another proportional integral controller for an LVAD using the pump head as a single feedback signal. With the beating of the natural heart oversimplified as a sinusoidal disturbance, simulations showed that the proposed controller was able to effectively maintain head. However, values of pump flow and $\omega$ varied beyond their normal operating limits when systemic resistance was changed dramatically.

Bullister et al (2002) have developed hierarchical algorithms to physiologically control and monitor of blood pumps using pressure inputs measured by APEX pressure sensors (APSs) (APEX Medical Inc., Walpole, MA, USA) at pump inlet and outlet. The APS pressure sensor uses a pressure-sensing diaphragm that can be built into the wall of any titanium pump or inlet cannula (Bullister et al 2001). APS are designed for long-term implantation and for control of VADs and heart pumps. Two level control algorithms to adapt to various left ventricular diastolic filling pressure (LVDFP) is proposed. The proposed control system consisted of two levels of control algorithms. The main goal of level 1 controller is to keep the LVDFP within a physician-programmable range. This was done using an integral control algorithm
implemented with pump inlet pressure ($P_{\text{in}}$) where this was used as an input and the pump speed control signal as the output. Also, the level 1 outer loop control is based on maintaining the arterial pressure within programmed limits and has a slower response time than the LVDFP inner control loop. The outer loop changes the effective desired LVDFP set point of the nested inner loop when the arterial pressure reaches the programmed limit values.

The level 1 controller effectively controls the LVDFP within a programmed range whenever the arterial pressure reaches a programmed limit and controls the LVDFP value to a reference value when the arterial pressure is within limits. Therefore, the resultant LVDFP value has been optimized because it meets the conditions of both the inner and outer control loops. The level 2 control algorithm was implemented as an outer control loop around the inner level 1 control loop. Outlet pressure ($P_{\text{out}}$) was used as a control input to level 2 while the modified target LVDFP as a control output sent to the level 1 control loop (Bullister et al 2002). Finally, when level 2 is active and the pulse rate is above a certain threshold, the desired target value for LVDFP is continuously updated to provide the feedback control for the target arterial pressures. Thus, the level 2 mean arterial pressure is controlled through the intermediate mechanism of actively adjusting the level 1 effective target value of the LVDFP within its programmed ranges. It is worthy to point out that Bullister’s control strategy is the only sensor-based strategy that actually uses a sensor that their group has developed.

To prevent collapse of the LV which is an inherent problem for continuous LVADs, Wu et al (2003) have proposed an optimal proportional integral controller to minimize the sum of the aortic pressure tracking error ($e_{\text{aorta}}$) and weighted head tracking error ($e_{\text{diff}}$),

$$J = \int_0^\infty (|e_{\text{aorta}}| + w(e_{\text{diff}}) \times e_{\text{diff}})^2 \times Q + u^2 \times R) \, dt.$$  \hspace{1cm} (3)

where

$$w(e_{\text{diff}}) = \begin{cases} 0 & |e_{\text{diff}}| < \eta \\ k|e_{\text{diff}}| & |e_{\text{diff}}| > \eta \end{cases}$$  \hspace{1cm} (4)

is a typical dead zone nonlinear weighting function for the tracking error of head ($P_{\text{diff}}$) across a LVAD, $\eta$ and $k$ are parameters which may be refined, $Q$ is the weighting factor for the sum of the aortic pressure tracking error and weighted differential pressure tracking error, and $R$ is the weighting factor for $u$. Note that the ratio $Q/R$ determines the controller parameters $K$ and $K_I$. The motivations for this controller arose from that, during heart cycle, aortic pressure should be maintained relatively constant. However, during dramatic physiological disturbances such as a sudden change from rest to exercise, the left ventricular collapse may occur while aortic pressure was maintained as uniform as possible. When ventricular collapse occurs, the pressure and blood volume in the LV decreases; thus the onset of the ventricular collapse could be detected from the elevated $P_{\text{diff}}$ across LVAD. This explains the necessity of controlling both the aortic pressure and $P_{\text{diff}}$.

Simulation results showed that the designed controller can produce the desired CO and maintain the left arterial pressure within safe ranges. It is also shown that the designed optimal controller has maintained the aortic pressure in the presence of disturbances and in moderate exercise. Moreover, results showed that the addition of $w(e_{\text{diff}})$ was contributed in preventing the left ventricular collapse. In simulations performed by Wu et al (2003), values of $\eta$ and $k$ were set as 25 mmHg and 180 which means that the physiological controller waives the small variations in $P_{\text{diff}}$ tracking errors within 25 mmHg; however, it retains high sensitivity to large values of that error caused by impending left ventricular collapse. In order to contribute to the control output, $e_{\text{diff}}$ should reach values above the dead zone of $w(e_{\text{diff}})$; otherwise, the control output ($u$) is determined only by $e_{\text{aorta}}$. This means that the proposed controller is able to track and maintain the aortic pressure as long as left ventricular collapse is not impending.
To test the performance of the proposed controller, three activities including rest, sleep and exercise were simulated by varying the heart rate, the driving air pressure, the vacuum pressure of the cardiac simulator, the total peripheral resistance (TPR) and the pulmonary resistance element in a mock human circulatory loop. The controller was also tested using simulated different pathological levels of left ventricular failure. In the experimental settings, sensors were implanted to obtain $P_{\text{diff}}$ across the LV AD and $I$ signals which were used as feedback signals. Results showed that the controller was able to restore desired LV end-diastolic pressure to within safe ranges, provide the reference total peripheral flow, and elevate the mean arterial pressure in the presence of different heart contractilities. Also, left ventricular suction was detected and thus rapidly reversed by the controller (Wu et al. 2004). In a mock loop setting, the overall performance of the controller was acceptable despite the elevated values of the estimation error of aortic pressure ($-12$ mmHg). This is due to the corrective properties of $w(e_{\text{diff}})$ on the control system. As we may notice from equations (3), (4), $w(e_{\text{diff}})$ allows the reference pressure for the estimated aortic pressure to vary, thus having some corrective effects on the aortic pressure estimation error. These results mean that the use of adaptive techniques to estimate the aortic pressure may avoid the effects of patients’ activities and pathological levels on estimation accuracy, thus improve the performance of the proposed controller. To achieve these goals, parameters of $w(e_{\text{diff}})$ was explored more and related to the trajectories of haemodynamic parameters (Wu et al. 2007, Wu 2009).

During exercise conditions, simulations showed that the CO has been increased by the LVAD to within desired limits ($7$–$13$ L min$^{-1}$), while the aortic pressure dropped compared with resting conditions. The reason for such a drop is the trend to develop collapse by the LV where this is indicated by the drop of the left arterial pressure. The proposed proportional integral controller then adjusts the tracking performance of the aortic pressure a little to avoid the LV pressure collapse (Wu et al. 2004). The drop of aortic pressure may not happen in real clinical settings due to the interaction of the muscle pump during exercise conditions which is ignored during simulations. This has necessitated another study by Wu and Lim (2008) where a numerical model of the human circulatory system, incorporating the muscle pump in dynamic exercise, was proposed. Simulation results demonstrated that the incorporation of muscle pump has changed the response of haemodynamic variables and LVAD parameters. Also, in the same study, the performance of RBPs and their physiological controllers have been verified with the muscle pump effects taken into consideration.

One common limitation of the control algorithms described was that the estimation of either differential pressure or pump flow were performed based on steady state or model-based modelling of the pump (Giridharan et al. 2004, 2005), which had not been validated during transient changes. By accurately estimating the transient response of the pump, one is able to avoid dangerous or undesirable situations caused by sudden perturbations in the cardiovascular system during pump operation. A limitation of some of these strategies is that they require the implantation of an additional sensor (Bullister et al. 2002) or perhaps two (Giridharan and Skliar 2002, Wu et al. 2003, 2004) to provide measurements of parameters used as inputs to their control algorithms. Also, for sensor-based PID control, the gain selection is not immediately intuitive, and may require gain scheduling to be appropriate for all patients.

### 3.2. Fuzzy logic control

The ability to control nonlinear and uncertain systems even without the existence of mathematical model has encouraged many researchers to use fuzzy logic to control the operation of RBPs. Fuzzy logic controllers can provide a systematic approach to organize and incorporate human experience into the controller. To detect and monitor the malfunction
of a LVAD, Yoshizawa et al (1994) have proposed an expert system realized by fuzzy logic algorithms. In 1995, Kaufmann et al have developed a sensorless fuzzy controller to maintain the pump flow rate according to the body perfusion demands by detecting the left pump chamber filling in a total artificial heart (Kaufmann et al 1995). In another study, Kaufmann et al (1997) have also implemented a sensorless fuzzy controller for a pulsatile LVAD to achieve active adaptation by detecting preload and afterload induced effects at the pump motor current inputs.

A sensorless fuzzy logic controller utilizing pump motor speed and current without any invasive measurement is proposed by Fu and Xu (2000). The controller was employed to regulate the LVAD flow to track a desired rate by allowing the fuzzy logic based controller to adjust the motor input so that the pump output can reach the desired flow. The LVAD flow was estimated from the electric motor current and speed, while the required output flow was chosen based on the heart rate. The controller was evaluated using a computer simulation model of haemodynamics of the circulatory system under LVAD assist (Xu and Fu 1999, 2000). Although results indicated that the proposed controller can achieve the required pump flow, the assumption made included the proportionality of the pump flow to heart rate has ignored the influence of heart contractility, and most relevantly, the effects of the peripheral circulation on the desired flow rate (Guyton and Hall 1996, Mohrman and Heller 2006). In many HF patients, the native heart continues to provide residual contractility during LVAD support, even though the resulting CO is not sufficient to meet the patient’s metabolic demands. In these cases, aortic pressure, aortic flow and LV pressure may exhibit varying levels of pulsatility when LVAD is used. Also, the pump flow and motor current are pulsatile due to the pulsatile load conditions (Boston et al 2003). Pulsatility of the pump flow signal can be used to introduce a pulsatility index ($P_{ind}$) (Choi et al 2005). To optimize the delivery of blood flow without inducing LV suction, Choi et al (2001) have implemented a proportional integral-type fuzzy logic controller for RBP. The controller is based on the pulsatility of pump flow and assumes that the natural heart is still providing pumping action. A reference pulsatility level of 15 mL s$^{-1}$ was chosen to allow the natural heart to produce some SV (stroke volume) without introducing suction in LV. To avoid the use of flow sensors, the controller estimates the pump flow using a model of the assist device (Yu et al 1998).

The proposed controller was tested using computer simulations, a mock circulatory system and in animal experiments. Simulations results show that the fuzzy logic controller is more robust to parameter variations than the traditional proportional integral controller, while experimental results in animals showed that the proposed controller is able to provide satisfactory flows at adequate pressures without developing suction in the LV. However, the constant setting of the reference pulsatility may be not physiologically practical as the controller may fail to cope for patients with different heart conditions or varying failure level of the natural ventricle during the long period of LVAD support in the same patient where those can result in different abilities to generate flow rate pulsatility. Also, the relationship between pulsatility and speed is not a monotonic function as for speeds (flows) below the optimal range, an increase in speed will cause a drop in pulsatility due to the unloading of the ventricle. For values above the optimal speed, a further increase in speed may cause an increase in pulsatility due to instability caused by intermittent suction. Moreover, it is not easy to assign a unique pulsatility value which guarantees adequate unloading, perfusion and safety from suction.

To overcome these control problems and limitations, Choi et al (2007) have described another fuzzy logic controller which utilized the pulsatility ratio of the pump flow and pressure head as a control index and adjusts the pump speed according to a reference pulsatility ratio under different operating conditions. Using computer simulations, authors demonstrated that
the controller was able to adjust the pump speed safely with varying body physiological demands of patients under different simulated physiological conditions and perturbations. Again, one limitation on this controller is that the pump flow and pressure head were assumed to be measurable during simulations. Another limitation is that the proposed controller basically just ramps up pump speed until suction occurs, then backs the speed off a little bit allowing the pump to operate at the maximum possible flow rate and lowest possible ventricular volume.

Ferreira et al (2009) have combined a suction detector and a fuzzy logic controller to control the operation of rotary ventricular assist devices. Using a discriminant analysis model which combines the indices obtained from the pump flow signal to classify the pump status as one of the following: no suction, moderate or severe suction, the suction detector can classify pump flow patterns. The output of the suction detector, which is the discriminant scores, were used as inputs to the fuzzy logic controller where the controller, based on this information, updates the pump speed to provide the required flow and pressure perfusion to the patient. To evaluate the behaviour of the control system, a sixth-order nonlinear time-varying lumped parameter model of the circulatory system coupled with a LVAD is used (Simaan et al 2009). Simulation studies over a wide range of physiological conditions, including exercise, strenuous exercising, and hypertension for healthy, sick and severe sick hearts were performed and showed that the fuzzy logic control system was able to maintain CO and mean arterial pressure within acceptable physiologic ranges, while suction was avoided.

Casas et al (2004) used a fuzzy logic controller to maintain constant flow between 5.5 and 6.5 L min$^{-1}$ in a pulmonary bypass rotary blood pump. Pressure head and pump rotational speed were used as feedback inputs where these were also used to calculate the estimated pump flow. Simulations suggested that the proposed fuzzy controller was able to maintain a set point of 6 $\pm$ 0.5 L min$^{-1}$ when presented with pressure disturbances over range of $\pm$50 mmHg from baseline of 100 mmHg.

3.3. Optimal control

Here, the controllers were designed to minimize predefined penalty functions. In 1998, Boston et al have described a control algorithm for heart assist devices which uses a multi-objective optimization to satisfy a set of system constraints. These constraints include: (i) CO should be above the minimum value required to support the activity level of the patient, (ii) left atrial pressure should be maintained approximately below 10–15 mmHg to avoid pulmonary edema and above approximately 0 mmHg to avoid suction, and (iii) the systolic arterial pressure should be maintained between patient-specific limits to reduce sensitivity to afterload. Also, the controller consisted of three types of algorithms: a model-based adaptive algorithm which uses a systemic circulation model to determine the required CO for a given activity in patients, two heuristic algorithms that rely only on the device characteristics to adjust the CO to changes in demand without previous knowledge of patient’s conditions, and a default algorithm which provides a fixed speed operation which can be used in case of system and/or sensors failure.

As clinicians always seek the VAD controller to satisfy several objectives and they express these objectives as constraints, the proposed control approach (Boston et al 1998) was modified to a more complex multi-objective optimal controller where the constraints can be expressed through penalty functions based on clinical experience and observation (Baloo et al 2000, Antaki et al 2003, Boston et al 2000b). For example, Baloo et al (2000) have developed algorithms to measure changes in three indices to detect the occurrence of suction in RBP. Those include the waveform pulsatility, the derivative of mean flow with respect to speed and the harmonic power ratio of the motor current waveform. The proposed algorithms can be used to determine the pump operating speed just below the point that induces suction.
On the other hand, a hierarchical feedback controller which combines both heuristic and optimal approaches is developed (Antaki et al 2003, Boston et al 2000a). In the proposed controller, evaluation of the available estimates of haemodynamic variables, reliability of a patient model, past history of the patient and validity of the information available were continuously monitored by a supervisor included in the hierarchy. Based on these assessments, the supervisor then uses heuristic approach, multi-objective optimization, a combination of both, or a default algorithm to operate the device and to determine the pump desired speed. Also, another objective of the proposed controllers was to minimize a multi-objective penalty function of the form (Boston et al 1998, 2000, Antaki et al 2003, Balboa et al 2000)

\[ J(\omega) = \sum_{i=1}^{3} \mu_i J_i(\omega), \]

where \( J_i(\omega) \) was the penalty function of CO, arterial pressure and left atrial pressure, respectively, and \( \mu_i > 0 \) with \( \sum_{i=1}^{3} \mu_i = 1 \). The LVAD speed was used as the feedback signal. Although the controller showed a superior result when validated using in vitro circulatory mock loop (Gwak et al 2005), simple and accurate predetermined mathematical models of CO, arterial pressure and left atrial pressure with respect to the pump motor speed are always needed for the multi-objective optimization described in (5). This may perform limitations on the applicability of this controller in clinical settings.

In another study, He et al (2005) have described a general framework for designing an optimum control strategy for the Hemopump which is a continuous-flow axial pump. The objective function included four haemodynamic variables with suitable weighting factors (stroke volume, mean left atrial pressure, mean pump speed and aortic diastolic pressure) that were firstly defined. Then, the concept of a membership function used in fuzzy logic was utilized. Next, the pump was allowed to operate at either a constant speed or two different speeds during a cardiac cycle where the goal was to maximize the objective function by varying the magnitude and timing of the pump speed. Simulation results demonstrated that, in general, different heart conditions or different clinical objectives require different operation parameters. For example, in a LV with minor ischemia was simulated, and the main objective function was to increase the stroke volume, the objective function was maximized, from a value of 0.877 when the Hemopump was off, to 0.946 when the pump was operated at 18 500 rpm. Also, for a severely ischemic heart, the optimum pump speed became 20 000 rpm, which maximized the objective function to 0.943 from 0.707 when the pump was off. Moreover, results also suggest that it is more beneficial to operate the Hemopump at two different speeds during a cardiac cycle (a higher speed during systole and early diastole, and a lower speed during late diastole) than to maintain a constant speed throughout the heart cycle.

### 3.4. Adaptive control

It is well known that parameters fluctuations and the existence of unidirectional valves make the cardiovascular system a time-varying system. To control a LVAD, Wu et al (2002) have described that an adaptive controller with a control objective was set to track the reference artery pressure. Self-adaptability of controller parameters has made the adaptive controllers more preferable than fixed controllers. Simulation results showed that adaptive controller can adapt control gain vector according to system parameter variation and achieve a superior tracking performance.

Most recently, Chang et al (2011) have designed a model-free adaptive controller for an intra-aortic blood pump. The heart rate is chosen as the controlled variable with the aim of the controller is to force the output of the system to track the desired value of heart
rate; therefore, a weighted one-step-ahead control input criterion function and a parameter estimation criterion function are designed to calculate the control law. The proposed control strategy does not need the model for the controlled plant rather it can iteratively establish the model of the control system using the input/output data derived from implanted sensors. Simulation studies demonstrated that the proposed model-free adaptive controller was able to keep the heart rate stable. Also, no matter the peripheral resistance disturbance or the change of the desired heart rate, the controller was able to derive the system states to their desired values within minimum time and without overshoot or static error. However, it is clear that the reported controller is not fit for the patients with severe arrhythmia as the regulation mechanism of heart rate is abnormal in those patients (Borchard 2001). To overcome this, it is possibly important to incorporate a heart rate analyzer system with the controller to decide whether the heart rate measured from patients is normal.

3.5. Extremum seeking control

Extremum seeking control (ESC) (Åström and Wittenmark 1995, Ariyur and Krstić 2003) is a method of adaptive control but it does not fit into the classical paradigm of model reference and related schemes which deal with the problem of stabilization of a known reference trajectory or set point (Ariyur and Krstić 2003, Krstić and Wang 1997). Another distinction between classical adaptive control and ESC is that the latter is not model based. This property made ESC applicable in fluid flow, combustion processes (for IC engines, steam generating plants and gas furnaces) and biomedical systems which are all characterized by complex and unreliable models. Other applications of ESC include grinding processes, solar cell and radio telescope antenna adjustment to maximize the received signals, blade adjustment in water turbines, wind mills to maximize the generated power and anti-lock braking systems (Wang et al 2000, Drakunov et al 1995).

ESC is applicable when there exists nonlinearity in the control problem, and the nonlinearity has a local minimum or a maximum. The nonlinearity may result from physical nonlinearities in the plant itself, or it may be in the control objective which is added to the system through a cost functional of optimization problem. Therefore, ESC can be applied to tune a set point to achieve an optimal value of the output, and/or for tuning parameters of a feedback law (Ariyur and Krstić 2003). In other words, the problem is to keep the plant output at an extreme value by seeking a suitable operating point. However, extremum occurrence is not known and may move with variable plant parameters. LVAD is one example of this kind of plants in which the pump flow reach a maximum at a given rotational pump speed; thus the goal is to control the pump speed so that the pump flow is maintained at maximum level with suction avoided. To approach this problem, Chen et al (2005) used a feedback mechanism combined from ESC and a gradient method applied to mean pump flow and minimum pump flow (diastolic) to control the pump speed. The objective of the controller was to optimize the pump flow while suction was avoided. The optimum pump speed is achieved by minimizing the gradient of blood flow with respect to speed in real time. Simulation results demonstrated the responsiveness and robustness of the proposed control algorithm when tested using a state-space model of cardiovascular system combined with a rotary blood pump proposed by Ferreira et al (2005). Results also showed that a controller based on the gradient of diastolic pump flow demonstrated better performance than that applied on mean pump flow.

Also, Gwak (2007) employed an ESC algorithm and a slope seeking control (SSC) algorithm to obtain an adaptive pump speed controller to provide maximum cardiac perfusion while avoiding left ventricular suction. In the proposed novel approach, the adaptive controller was able to find and track unknown and moving peak points of a prescribed cost function.
ESC was employed to track the point where the gradient of minimum pump flow with respect to changes in pump speed approaches zero while SSC algorithm was used to maintain the operating point of the pump near the minimum pump flow to avoid the verge of suction. The proposed controller was validated with in vivo data using time-averaged diastolic pump flow as the cost function for the controller. The suboptimal point of the SSC algorithm is determined by the choice of the reference slope. Although results demonstrated the successful application of ESC/SSC controller as a physiologic pump speed controller, a systematic way to select the reference slope is not identified and requires further investigations in clinical settings as the shape of the cost function may vary from patient to patient and may depend on the therapeutic objectives of the physician. Also, due to the nature of ESC, the pump speed exhibited overshoot and the operating point ventured into the suction region where this should be avoided by the controller. To overcome these limitations, Gwak et al (2011) have proposed a safety-enhanced optimal (SEO) control algorithm based on their existing ESC/SSC control algorithm. Based on the analysis of in vivo experimental data, it is found that the peaks of the gradient of pulsatility of pump pressure head with respect to pump speed and the gradient of minimum pump flow should be within proximity to the suction point but not at the exact suction point. Also, two new in vivo cost functions to secure safety and robustness were proposed and validated using computer simulations. Results showed that the SEO operating point was successfully found and tracked in both fixed and varying haemodynamic scenarios using the proposed control indices without resorting to a SSC algorithm in which the reference slope must be supplied.

Another successful story of the application of ESC has been heralded by Berlin Heart®-R&D (Berlin, Germany) when Arndt et al (2008) and (2010) proposed a pulsatility index (PI)-based control strategy to control the operation of INCOR® axial RBP. In their study, PI was calculated from the pressure difference while the gradient of PI with respect to pump speed (GPI) was estimated via online system identification. In the proposed cascaded controller, consisting of outer and inner loops, ESC algorithm (outer loop) was used to regulate GPI to a reference value satisfying the selected control objective which include full assist before suction (minimum GPI), or at the boundary between partial assist and full assist (GPI equals to a predefined small value). The inner loop of the controller controls the PI to a reference value set by the ESC. When tested using a lumped-parameter computer model of the assisted circulation, the proposed controller was able to meet different control objectives including variations of ventricular contractility, pulmonary venous return pressure and aortic pressure. The risk of over-perfusion and the difficulty to choose the appropriate values for GPI represent two main limitations of the proposed ESC algorithm.

3.6. Abnormal pumping states limit control

Non-pulsatile RBPs include the axial or centrifugal run continuously to draw blood out of the ventricle and supply to the rest of the body through the circulation. Due to the lack of the overall sensitivity and unphysiological responses of the RBPs to changes in preload (Salamonsen et al 2011), a major design goal of a control strategy for RBPs is the ability to reliably and accurately detect pumping states which cause harmful consequences such as ventricular collapse due to over-pumping (suction), or pump back flow (regurgitation) as a result of under-pumping (Schima et al 1992, Konishi et al 2001). Of these, suction is the most dangerous state that must be detected instantly and the pump rotational speed should be reduced before the cardiac muscle is collapsed and thus damaged (Boston et al 2003).

To ensure safe operation of RBPs and thus patient’s safety and comfort, successful long-term implantation and to eliminate the need for a physician monitoring, undesired pumping states should be detected thus a control system will effectively avoid their occurrences,
the control strategy for LVADs must be able to cope with varying CO to meet body’s metabolic demands, maintain systolic arterial pressure within a physiological range to avoid over perfusion or under perfusion, and to maintain left arterial pressure within a normal physiological range to avoid pulmonary congestion and suction (Boston et al 1998, 2003). Also, pump parameters including voltage and current should be used to the greatest extent to non-invasively estimate the haemodynamic states necessary to control the operation of RBPs as the available pressure and flow sensors are not reliable for long-term clinical implementation.

Although the control algorithms reviewed in previous subsections have tackled the task of detecting and thus avoiding suction, here, in this subsection, we will review various physiological control strategies, heuristic algorithms, and combination of multiple indicators that only utilized to aid in detecting, preventing and thus managing abnormal pumping states in LVADs. Previously, various research groups have investigated the experimentation in the transition of pumping states (Amin et al 1997, Baloa et al 2000, Boston et al 2000a, 2000b, Endo et al 2001, 2002, Oshikawa et al 2000, Tanaka et al 2005, Voigt et al 2005, Vollkron et al 2004, 2005, 2006, Yuhki et al 1999, Olegario et al 2003, Ayre et al 2001). To aid in this task, invasive transducers were employed to measure the pump flow (e.g. Vollkron et al 2004 and Iijima et al 1997); however, it is highly desirable to avoid their use due to a significant reduction in system reliability and increased cost. To overcome this, research approaches have thus concentrated on the waveform analysis of the sensorless pump motor feedback signals including current or rotational speed from which a vital heuristic indicators of abnormal pumping states have been derived (Baloa et al 2000, Boston et al 2000b, Endo et al 2001, 2002, 2003, Oshikawa et al 2000, Tanaka et al 2005, Voigt et al 2005, Vollkron et al 2002, 2006, Yuhki et al 1999, Nakata et al 2000a, 2000b, Takami et al 1997).

Methods of pumping state discrimination based on the proposed indicators vary from simple threshold analysis (Endo et al 2001, 2002, 2003, Tanaka et al 2005, Yuhki et al 1999, Oshikawa et al 2000, Ohuchi et al 2001), to more complicated approaches such as Bayesian methods (Boston et al 2000), fuzzy logic (Boston et al 2000a, 2000b, Ferreira et al 2009), Dempster–Shafer theory (Boston et al 2000a), artificial neural networks (Stöcklmayer et al 1995) and multiple discriminant criteria (Ferreira et al 2006). Results obtained by Endo et al (2001, 2002, 2003) showed that the index of motor current amplitude (ICA) has feasibility in continuous flow VAD control. They showed that ICA can demonstrate the safe range of pump speed, which exists between the starting point of total assistance and the starting point of sucking.

Similarly, Oshikawa et al (2000) have investigated the use of symmetry in the current amplitude in a LVAD whereas Voigt et al (2005) also used the amplified, differential current signal as indicators to detect transition from partial to total assist and to detect suction, respectively. For fine-tuning of the pump speed, Ohuchi et al (2001) have employed the power spectral density of the motor current waveform and calculated the ratio of the fundamental to the higher order components. To determine the target speed, they used the relation between the native heart rate and CO.

Considering a waveform deformation index based on a spectral density analysis of the motor current waveform, Yuhki et al (1999) have developed a detection algorithm for suction and regurgitation of the centrifugal LVAD during left heart bypass without relying on external flow or pressure sensors. Seeking for another indicator, Nakata et al (2000a) have also shown that there was an association between the required current and pump flow waves. When compared with normal pumping conditions, the values of differentiated and the power of the differentiated motor current was increased 500 times during abnormal pump operating conditions.
On the other hand, Vollkron et al (2005) have developed a reliable suction detection algorithm (the proposed algorithm equipped with an expert system that continuously checks the flow signal for any indication of suction). The desired flow level of their control algorithm was derived from the measured patient’s heart rate. The response of the developed control system together with the suction detection algorithm was robust, stable and safe when tested under a wide range of in vitro mock circulatory loop and clinical studies. To obtain a mathematical model of ventricular suction, Yu and Porter (2006) have identified a nonlinear resistance as a function of the LV pressure, the absolute value of the LV pressure derivative and the pump inlet pressure. In 2008, Mason et al have investigated the clinical performance of seven expertly selected time domain indices of suction based on the observed positive spike induced in the RBP impeller speed waveform (Mason et al 2008). Results showed that the combination of only three index threshold settings was able to give a suction detector with high clinical utility.

To provide an indication of LV function using the Mag-Lev magnetically levitated centrifugal blood pump, Hoshi et al (2006) observed that the impeller rotor oscillated and that oscillation was synchronized with the native heart pulsation. It was then stated that this phenomenon could be used to provide an indication of LV function. However, it was only validated using a simple left-heart circulation loop. This method is invasive and requires position sensors so that the impeller position can be monitored in real time.

To control and estimate the backflow using only the electrical current in a Gyro C1E3 centrifugal blood pump, results obtained by Nakata et al (1999) have suggested that the ratio of the systolic current to the diastolic current was not influenced by the pump flow rate. However, the same ratio was changed when the pump was in a backflow conditions. In another study performed by Vandenberghe et al (2002), a mathematical model to study the influence of backflow through a failing rotary blood pump was obtained. The model consisted of a validated cardiac and arterial modules and a pump module from which the influence of pump failure with mechanoenergetic parameters and wall stress obtained from model output could be evaluated. Because of pump failure, results showed that stroke volume, aortic flow and stress time integral increased significantly. However, total systemic flow and arterial pressure were not altered by backflow.

Most recently, Saito et al (2010) developed a suction release control algorithm for a ventricular assist device by monitoring the inflow cannula pressure using an implantable pressure sensor mounted on the pump. With their control method, the flow assist can be increased more than 15% and suction episodes significantly decreased. Moreover, they claimed that the inflow cannula pressure monitoring was useful not only for the suction detection but also for synchronization with the natural heartbeat. Also, to continuously monitor the cardiac function and contractility in patients supported by RBPs, Naiyanetr et al (2010) have proposed a novel index ($I_Q$) which is defined as the slope of a linear regression between the maximum derivative of the pump flow and its peak-to-peak value. In vivo and simulation studies showed that the $I_Q$ index to be sensitive to changes in cardiac contractility. For in vivo studies using a MicroMed-DeBakey VAD implanted in seven sheep, $I_Q$ decreased when the heart contractility was reduced. The variation of $I_Q$ index was only marginally influenced by pre-load and after-load changes in computer simulations.

Although numerous number of algorithms and controllers have been developed to detect and thus avoid abnormal significant pumping states, most research groups fall short of developing algorithms to automate the classification and detection of these abnormal pumping states, and thus do not provide a statistical assessment of the ability of their approaches (e.g. Endo et al 2001, 2002, 2003, Oshikawa et al 2000, Tanaka et al 2005, Yuhki et al 1999). However, other studies have reported numerical results which provide a valuable platform for
3.7. Non-invasive classification of physiologically significant pumping states in IRBPs

In our laboratory, a non-invasive algorithm for state transition detection is proposed by Ayre et al. (2001). The proposed algorithm uses the non-invasive parameter of instantaneous impeller rotational speed. A state transition index (STI) derived originally from in vitro mock loop setup by considering the maximum instantaneous speed ($N_{\text{max}}(n)$) and the RMS of instantaneous speed ($N_{\text{rms}}(n)$) for the $(n-1)$th and $n$th cardiac cycle relative to the change in speed set point. The state transition was investigated in an ovine experimental model ($N = 3$). The cardiovascular system of the animal was perturbed by pharmacological intervention or exsanguinations where a total of six pump speed set point changes that caused physiological state transitions from the normal ventricular ejection (VE) to a state where the aortic valve remains closed (AC) were examined. Results also showed that STI was found to be directly applicable in the in vivo studies and demonstrated statistically significant ($p < 0.0005$) reliability in differentiating between no change and change in state.

In similar fashion, Karantonis et al. (2006) have used only the non-invasive measure of instantaneous pump impeller rotational speed to assess flow dynamics to automatically detect a range of pumping states including regurgitant pump flow (state PR), ventricular ejection (state VE), aortic valve not opening over the entire cardiac cycle (state ANO), partial intermittent collapse of the ventricle wall during the cardiac cycle (state PVC-I) and continuous ventricle collapse (state PVC-C). Seven indices, derived from the speed waveform, were used to classify pumping states. These indices including the speed pulsatility index ($N_{\text{pp}}$) which refers to the difference between the maximum and minimum speed over a speed cycle, the change in $N_{\text{pp}}$ ($\Delta N_{\text{pp}}$) refers to the difference in consecutive $N_{\text{pp}}$ values. The change in maximum speed value for the consecutive speed cycle ($\Delta N_{\text{max}}$), $N_{\text{profile}}$ which provides a measure of speed amplitude symmetry, change in $N_{\text{profile}}$ ($\Delta N_{\text{profile}}$) refers to the difference in consecutive $N_{\text{profile}}$ values, $N_{\text{freq}}$ refers to the number of samples between successive crossing of the filtered and averaged speed signal, and finally the second-order change in the speed signal ($\Delta N_2$) which was also noticed to be a valuable index of suction detection. The proposed strategy was validated using ex vivo porcine experiments ($N = 6$). Employing a classification and regression tree (CART), the proposed strategy was able to detect pumping states with a high degree of sensitivity and specificity.

The proposed strategy showed marked improvements in detecting pumping states when animal data containing arrhythmia events, obtained from sheep, were incorporated into the CART model (Karantonis et al. 2007a). Moreover, the proposed methodology yielded a peak sensitivity (99.11%) and specificity (98.76%) when validated on 12 990 segments of unseen data obtained from ten human pump recipients (Karantonis et al. 2007b). The results presented suggest that the proposed non-invasive techniques for pumping states classification and detection are robust, accurate and thus applicable in the clinical settings. It also highlights the important and feasibility of using combination of different indicators to successfully classify and clinically detect pumping states. Another advantage of the proposed strategy is that it can be easily included into linear or nonlinear IRBP control system.

Also, a demand-responsive multi-objective control algorithm for a centrifugal RBP based on a non-invasive indicator of the implant recipient’s activity level has been developed in our laboratory. A novel control variable referred to as the activity level index (ALI) is employed by Karantonis et al. (2010). ALI is based on a non-invasive estimate of heart rate and acceleration of a moving object using tri-axial accelerometers which are two non-invasive parameters.
Pump rotational speed is then varied linearly according to the ALI within a defined range. The ALI-based controller operated within a hierarchical multiobjective framework, which imposes several constraints on the operating region, such as minimum flow and minimum speed amplitude thresholds. The proposed control algorithm exhibited the effective intervention of each constraint, resulting in an improved flow response and maintenance of a safe operating state when evaluated using a software model of the human cardiovascular system combined with IRBP, previously developed and validated in our laboratory (Lim et al. 2008, 2010), in which three class IV HF cases of varying severity were simulated under rest and exercise conditions.

3.8. Non-invasive deadbeat control of IRBPs

3.8.1. Pump flow control. A number of clinical advantages of pulsatile perfusion have been hypothesized or proven throughout the years under clinical or animal settings (Undar 2004, Klotz et al. 2004), mostly during cardiopulmonary bypass procedures. Among the advantages include less vital organ injury and systemic inflammation (Alkan et al. 2007), beneficial exercising of the aortic valve, higher regional and global myocardial blood flow (leading to increased coronary perfusion), greater degree of left ventricular (LV) pressure and volume unloading (leading to better myocardial recovery) (Klotz et al. 2004), reduced risk of ventricular suction (Bourque et al. 2006) as well as beneficial effects on the vascular properties and microcirculation (Hornick et al. 1997).

Despite these findings, few researches have looked into the area of pulsatile flow control of an IRBP. Vandenberghe et al. (2003, 2005) studied the effect of various pulsatile mode support strategies on pressures and flows in a mock loop, while Korakianitis and Shi (2007) performed computer simulations to study the effect of counterpulsation flow control on the haemodynamic response using their mathematical model. Nevertheless, we are not aware of any studies which evaluate the performance of a pulsatile flow controller during transient changes of reference input or model parameters using only non-invasive measurements.

Using the non-invasive measurements of pump speed and current, a novel deadbeat controller, shown in figure 1, for the control of pulsatile pump flow in the IRBP is proposed by our research group (Lim et al. 2011). A deadbeat controller is a digital controller which drives the system error to zero after a minimum possible sampling period and exhibits no inter-sampling ripples after the steady state is reached (Ogata 1995, Åström and Wittenmark 1997). The ability to respond quickly to sudden perturbations in the cardiovascular system

Figure 1. Block diagram of the control system developed to control the rotary blood pump flow using non-invasive measurements of pump power and rotational speed.
(CVS) and adjust pump flow accordingly is highly desirable due to the fact that sudden changes in afterload or preload may cause undesirable effects on the CVS, such as ventricular collapse, if the pump control does not react fast enough.

The proposed controller was tested using a parameter-optimized model of cardiovascular-rotary blood pump (Lim et al 2010), in combination with the stable dynamical models of pulsatile flow and head estimation for the IRBP developed and validated in our laboratory (AlOmari et al 2009). The models have been developed and validated previously in our laboratory against *in vitro* mock loop data and *in vivo* animal experimental measurements (AlOmari et al 2009, Zhang et al 2010). When tested using both constant and sinusoidal reference pump flow as input to the CVS model, results showed that the control algorithm was able to track the reference input with minimal error in the presence of model uncertainty. Also, pump flow was shown to settle to the desired reference value within a finite number of sampling periods. Moreover, we simulated the effect of varying LVAD pump flow, systemic peripheral resistance, total blood volume and heart contractility on the CVS in terms of total CO, mean aortic pressure and left atrial pressure, under continuous and pulsatile model conditions (Lim et al 2011). Our results indicated that counterpulsation is most beneficial for myocardial recovery as it decreases LV external work and oxygen consumption. On the other hand, co-pulsation provides a higher degree of pulsatility compared with counterpulsation control.

3.8.2. Inlet pressure control. In HF patients with a LV assisted by an IRBP, when the volume in the LV is low, pump inlet pressure will automatically decrease. This may cause suction if the same target speed was maintained. By applying inlet pressure control, target speed will be reduced to allow the inlet pressure to increase and thus avoid suction. In the VentrAssist™ (Ventracor Pty. Ltd, Sydney, Australia) LVAD, during total obstruction of the inlet cannula, the diastolic inlet pressure may be as low as −160 mmHg, whereas it normally varies between ±10 mmHg during normal pump operation. This is one example that illustrates the benefit of non-invasive estimation and control of inlet pressure during the diastolic period. Also, estimated inlet pressure could be used to provide a definitive input to a controller to prevent highly negative pressure in the LV and thus auto regulates the pump speed to avoid suction. The second major advantage of inlet pressure monitoring is its great value in the regulation of pump flow. During normal diastole, the inlet pressure and left ventricular end diastolic pressure are closely related. At the end of diastole, this pressure equates to left ventricular preload. For a fixed inotropic heart state, this pressure and the associated ventricular volume are the most important factors regulating the force of ventricular contraction and the consequent stroke volume.

The precise relationship between ventricular preload and stroke work is defined as the Frank–Starling law (Guyton and Hall 1996). This is the major mechanism underlying the synchronization of left and right heart outputs which in steady state is mandatory (Mohrman and Heller 2006). Lack of this synchronization as in IRBPs, which do not have an inherent Starling characteristic can give rise to a number of consequences, the most serious being ventricular suction. Non-invasive estimation and control of inlet pressure during diastole is thus of considerable benefit. It facilitates the design of preload controllers of varying sophistication, the simplest being the maintenance of a set end-diastolic pressure. A more sophisticated alternative is to control the pump flow so that its output relates to the end-diastolic pressure as defined by the Frank–Starling mechanism. This would allow the pump to achieve a range of flows and left ventricular preloads in dynamic equilibrium with other changes in the patient’s haemodynamic state. Suction would be avoided with both these strategies.
For the first time, in our laboratory, we used non-invasive measurements of $\omega$, $P$, together with the pulse-width modulation signal (PWM) as inputs to a novel dynamical ARX model to estimate average inlet pressure during the diastolic period (AlOmari et al 2010, 2011a). The resulting model is stable and simple, thus offering a tractable control design solution. The average diastolic inlet pressure estimation model was validated using in vivo animal data obtained from acute implantation of a VentrAssist™ LVAD in greyhound dogs ($N = 3$) under wide ranges of speed ramp studies performed under different operating conditions which includes healthy, variations in heart contractility by administration of a beta blocker (metoprolol), systemic vascular resistance by administration of metaraminol or sodium nitroprusside, and by varying the total blood volume. The developed inlet pressure estimation model was then used by way of computer simulations to test the response of a deadbeat controller for control and regulation of the mean inlet pressure during the diastolic period. Results showed that the controller was able to regulate the diastolic mean inlet pressure of the pump within a predefined physiologically reasonable limit. Also, it was able to track and settle to the desired input within a finite number of sampling periods and minimal error (figure 2).

3.9. Model predictive control

Model predictive control (MPC) is a type of control in which the current control action is obtained by solving on-line, at each sampling instant, a finite horizon open-loop optimal control problem using the current state of the plant as the initial state where the optimization results in an optimal control sequence where the first control in this sequence is applied to the plant. In the application of modern control, MPC has actually been a major success story. In literature, more than 2000 applications of MPC method have been reported including, for example, petrochemical and electromechanical areas (Goodwin et al 2001). Recently, MPC is being increasingly used in biomedical engineering control problems such as those carried out in our laboratory (Javed et al 2011, Su et al 2010).

In another study performed by our research group to control the operation of the VentrAssist® IRBP (AlOmari et al 2011b), we firstly proposed a novel linear time-variant (LTV) state-space system to estimate the mean pulsatile flow ($Q_p$) in the pump. Non-invasive measurement of mean pulse-width modulation (PWM) signal acquired from the pump controller was used as an input to estimate the mean pulsatility index of pump rotational
speed ($\omega$), with this subsequently used to estimate ($Q_p$). Secondly, the proposed LTV model was used to develop a controller to regulate and track the variations ($Q_p$) and ($\omega$). We used a MPC approach to develop the controller where this allowed us to explicitly apply pre-defined practical constraints to control input PWM as well as the output and the states of the system including ($Q_p$) and ($\omega$). The model and the controller were tested using a parameter-optimized model of the CVS–RBP (Lim et al 2010) under wide ranges of speed ramp experiments carried out under different operating conditions such as variations in afterload, preload and heart contractility. A recursive least-squares method (Ljung 1999) was used to estimate the system parameters. Specifically, the time-varying parameters of the proposed state-space model were tracked on-line using a constant forgetting factor ($\lambda = 0.98$) approach. This approach suits our experimental design where contractility, preload and afterload were gradually changed causing sufficiently low variations in the system parameters. Sudden changes of venous return resulted from the change of body posture and when straining or coughing require other time-varying forgetting factor approaches to allow fast tracking of system parameters such as those proposed in Arndt et al (2008, 2010).

In the presence of model uncertainty and sudden changes in the system parameters, our results showed that the proposed MPC-based controller was able to non-invasively adapt and track the changes of ($Q_p$) and ($\omega$), with stable transient response, during different operating conditions (different reference trajectories) including sudden perturbations and variations in afterload and heart contractility, respectively (results not shown). Also, responses of the proposed non-invasive model and controller were tested during varying levels of preload induced by varying total blood volume. Results (not shown in this paper) showed that the non-invasive MPC controller was able to regulate and track desired reference trajectories with stable transient responses in the presence of sudden system perturbation, uncertainties and changes in the model parameters.

3.10. Starling-like controller

Most recently, Salamonsen et al (2012) have proposed a linear Starling-like controller for RBPs which emulated the response of the natural LV to changes in preload using pump flow pulsatility as the feedback variable. Such clinically intuitive physiologic controller is highly desired to improve the interaction between IRBP and the CVS. Moreover, this controller is crucial to restore the Starling mechanism of the heart, thus preventing over-pumping and under-pumping scenarios which are main obstacles facing the implementation of LVADs.

4. Conclusions and future work

Over the years, many physiological control systems have been developed aiming to control the operation of LVADs. Of all these proposed control systems, non-invasive control of IRBPs is one of the most important and desirable design goals in providing long-term alternative treatment for HF patient as the implantation of additional sensors may result in reliability, cost, system complexity and thrombus formation issues. The clinical implementation of such control strategies critically requires information regarding the cardiovascular system of the HF patient. For example, in order to use the MPC or the multiobjective optimization techniques, models of the patient’s CVS and the LVAD must be known. As the HF patient’s CVS status can be changed over time or varies from patient to another, the proposed control strategy must be able to update the model parameters and react rapidly to potential disturbances and perturbations.

Also, the LVAD and patient CVS models can be used to derive and determine, for example, the reference pump speed, flow or head of the proposed control algorithm. However, lack of
information to identify the models in real time results in a significant challenge in clinical settings. Therefore, most of the previously proposed LVAD controllers were not studied in possible pathophysiological states which may appear during permanent implantation of RBPs. The development of robust, effective and adaptive control system which takes into account the issues of estimators, sensors, suction prevention, Frank–Starling mechanism and thus robust performance in variable clinical and physiological situations is still in demand for LVADs.

On-going work in our laboratory includes testing the proposed model and controller responses to changes in physiological parameters associated with varying levels of simulated HF. Also, future work will include the testing of the proposed model and controller using a circulatory mock loop and in vivo animal experiments. Moreover, another direction of future research is to apply methods of modern robust control and filtering such as in Petersen and Savkin (1999), Petersen et al (2000), and Savkin and Evans (2002).

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