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Model Predictive Control and Its Role in Biomedical Therapeutic Automation: A Brief Review

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Abstract: The reliable and effective automation of biomedical therapies is the need of the hour for medical professionals. A model predictive controller (MPC) has the ability to handle complex and dynamic systems involving multiple inputs/outputs, such as biomedical systems. This article firstly presents a literature review of MPCs followed by a survey of research reporting the MPC-enabled automation of some biomedical therapies. The review of MPCs includes their evolution, architectures, methodologies, advantages, limitations, categories and implementation software. The review of biomedical conditions (and the applications of MPC in some of the associated therapies) includes type 1 diabetes (including artificial pancreas), anaesthesia, fibromyalgia, HIV, oncolytic viral treatment (for cancer) and hyperthermia (for cancer). Closed-loop and hybrid cyber-physical healthcare systems involving MPC-led automated anaesthesia have been discussed in relatively greater detail. This study finds that much more research attention is required in the MPC-led automation of biomedical therapies to reduce the workload of medical personnel. In particular, many more investigations are required to explore the MPC-based automation of hyperthermia (cancer) and fibromyalgia therapies.

Keywords: model predictive controller; biomedical therapy automation; diabetes; anaesthesia; artificial pancreas; hyperthermia; fibromyalgia; HIV; cancer; cyber-physical healthcare

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1. Introduction

The idea of automated disease control is not new. Researchers have worked on it since the creation of the first analytical models between 1960 and the early 1970s [1]. These researchers' goal was to explore newer and more effective mathematical models to aid medical diagnostic procedures and therapeutic regimens. By nature, physiological systems are innately nonlinear and time-varying, making them difficult to predict. Therefore, some clinical researchers feel that a formal model-based approach is not suitable for effective application in medication and that open-loop control architecture is the way ahead in medicine administration. In spite of the fact that the assignment of mathematical model variables to human test subjects appears ambitious, the establishment of feedback loop for testing and controlling therapy is not only possible but also feasible. MPCs are a prominent control solution that has been employed in therapeutic automation.

The main goal of this study is to firstly review the background, evolution, methodology and salient features of MPCs followed by a review of MPC-led therapeutic automation in some important medical conditions. The motivation behind this study is to promote more research in this important field primarily because of two reasons—1. easing the routine workload of medical personnel and 2. the capability of MPCs to effectively deal with biomedical therapeutic closed-loop conditions. The first part of the literature search included the basic MPC domain keywords of 'model predictive control', 'model predictive controller', 'mpc', 'mpc control', 'mpc controller', 'mpc architecture' and 'mpc model'

individually and in conjunction with 'review' and 'survey'. The second part of the literature search included the MPC domain keywords in conjunction with application-specific keywords, such as 'biomedical', 'therapy', 'biomedical therapy', 'automation', 'biomedical therapy automation', 'therapeutic automation', 'automated disease control', 'diabetes', 'blood glucose level', 'BGL', 'anaesthesia', 'artificial pancreas', 'cancer', 'hyperthermia', 'fibromyalgia', 'HIV', 'AIDS', 'cyber physical healthcare' and 'cyber physical health system'. For the historical review of MPCs and MPC algorithms, landmark papers published from the 1960s to 1990s were considered. Papers published in the past two decades were primarily considered for the review of various MPC architectures, advantages, limitations and software. Although no specific time frame was decided upon to gather literature dealing with MPC in the selected biomedical conditions and therapies, more papers were found from the recent twenty years as compared to the previous decades. All papers were sourced from Scopus, Sciencedirect and Web of Science databases.

MPC refers to a group of control methods that are employed in single-input single-output (SISO) and multi-input multi-output (MIMO) systems. An MPC is capable of managing MIMO systems that share complex system information between their inputs and outputs [2]. Because of the complexity of these exchanges, it is extremely difficult to construct MIMO systems using standard controllers such as proportional–integral–derivative (PID) controllers. An MPC, on the other hand, is capable of controlling all of the outputs while allowing online process input-output exchanges simultaneously. An MPC is also capable of dealing with contradicting restrictions. The handling of constraints is important because breaking them could result in unintended consequences. An MPC has the ability to preview data and react accordingly. If the MPC controller is aware of set point changes in advance, it will be able to better react to those changes and increase its overall performance. An MPC fulfills the requirement of a dynamic process model to reduce the discrepancy between the expected and actual plant outputs. The earliest MPCs have been in use in process industries since the 1980s. MPCs can be applied to both basic and complex processes. Because of the rising computational capability of microprocessors, MPC applications have expanded to a variety of other disciplines, including the medical, automotive and aerospace sectors.

The layout of this paper is as follows. The following subsections present a brief overview of the background and evolution of MPC methodologies and algorithms, followed by the general MPC methodology, its advantages and limitations. The Section 2 throws light on the various types of MPCs in practice followed by information about some popular software used to implement these MPCs. The Section 3 presents a research review of MPC-enabled therapeutic automation in conditions such as type 1 diabetes, anaesthesia, artificial pancreas, fibromyalgia, HIV and cancer. The Section 4 presents conclusions and the future research scope. Table 1 shows the nomenclature of all the terms and acronyms used in this study.

Table 1. Nomenclature of terms and acronyms used in the paper.

Notation	Meaning	Notation	Meaning
AP	Artificial Pancreas	MPC	Model Predictive Control
BGL	Blood Glucose Level	NMPC	Nonlinear Model Predictive Control
BIS	Bispectral Index	OPC	Optimum Predictive Control
BMM	Bergman Minimal Model	OVT	Oncolytic Viral Therapy
CTLs	Cytotoxic T Lymphocytes	PCT	Predictive Control Technology
CPHS	Cyber-Physical Human System		
DMC	Dynamic Matrix Control	PEG	Polyethylene Glycol
DoA	Depth of Anesthesia	PI	Protease Inhibitors
EEG	Electroencephalogram	PID	Proportional-Integral Derivative
eMPC	Explicit Model Predictive Control	PWA	Piece-wise Affine Function
FM	Fibromyalgia	QP	Quadratic Programming

Table 1. *Cont.*

Notation	Meaning	Notation	Meaning
HAART	Highly Active Antiretroviral Therapy	RHM	Receding Horizon Technique
hEKF	Hybrid Extended Kalman Filter	RMPCT	Robust Model Predictive Control Technology
HIV	Human Immunodeficiency Virus	RPI	Robust Positively Invariant
ICU	Intensive Care Unit		
ICS	Impulsive Control System	RTI	Reverse Transcriptase Inhibitors
IDCOM	Identification and Command	SISO	Single-Input and Single-Output
iNMPC	Impulsive Nonlinear Model Predictive Control	SNAPL	Neuroscience and Pain Lab
LDN	Low-Dose Naltrexone	STIs	Structured Interruptions
LQR	Linear Quadratic Regulator	T1D	Type 1 Diabetes
LR	Long Range	T2D	Type 2 Diabetes
LRPC	Long-Range Predictive Control	TCI	Target Controlled Infusion
LRQP	Long-Range Quadratic Programming	TIVA	Total Intravenous Anesthesia
MIMO	Multi-Input Multi-Output	VL	Viral Load

1.1. Background of MPC

The term MPC refers to a category of computer control methods that generate explicit models of plant processes to effectively predict the concerned responses. It is an effective means of dealing with multivariable constrained control problems. MPC was first developed to control the transients of dynamic systems with multiple inputs and outputs subjected to constraints for chemical process applications.

Figure 1 depicts a few landmark articles marking the advancements in MPC research over the past decades. One of the founders of modern industrial control strategies was Kalman, who developed the linear quadratic regulator (LQR) in the early 1960s. The LQR was designed to minimize the unconstrained objective functions composed of multiple inputs and states. The LQR had powerful stabilising properties due to an infinite state horizon. However, the LQR did not result in widespread control applications in the process industries of that time. This was mostly due to the prevalent indifference of the industrial process control personnel of that time towards optimal control strategies. Moreover, the LQR did not have a suitable provision for constraints in its formulation and was not perceived as being capable of handling real-world nonlinear systems. Consequently, the early proponents of MPCs worked in isolation on sparse industrial applications [3]. A comparative study of self-adaptive long-range predictive control (LRPC) methods keeping focus on robustness with respect to unmodeled dynamics, parameter variations, process noise and varying dead-time was presented by Keyser et al. in 1988 [4]. Garcia et al. [3] published a survey article highlighting the design and implementations of linear quadratic MPC control structures. Scattolini and Bittanti (1990) [5] provided insights into the proper selection of the prediction horizon with regards to the impulse/plant step responses. Clarke and Scattolini [6] showed that general linear plants could be stabilized by optimizing quadratic functions over a costing horizon using constrained predictive control methodology. The authors found that computation was more complex for finite-horizon methods, which tended to be numerically sensitive. A summary of commercially existing MPC technology was presented by Qin and Badgwell [7]. Bemporad and Morari [8] compiled a summary of robustness in MPCs and suggested methods for constraint-handling, stability and performance. Sandoz et al. [9] proposed techniques of quadratic programming (QP), long range (LR) and long-range quadratic programming (LRQP) to effectively manage dynamic system constraints and the related constraint violations. The authors employed QP and LRQP to integrate output constraints and handle the input constraints, respectively. They also found that LR performance was robust, computationally efficient and reliable. Grim et al. [10] reported asymptotic instability in nonlinear systems due to the optimization algorithm managing constraints in shorter horizons. Warren and Thomas [11] formulated an MPC architecture that calculated closed-loop uncertainties of input constraints off-line to maintain steady-state input constraints, thus ensuring robust process outputs. Li et al. [12]

found that set-point tracking of controllers could be improved by employing infinite control horizons. They also discovered that steady-state constraints lead to set point offsets in controller responses. Other researchers reviewed robust MPC methodologies based on model and disturbance uncertainties [8] and compared different predictive controller performances [13].

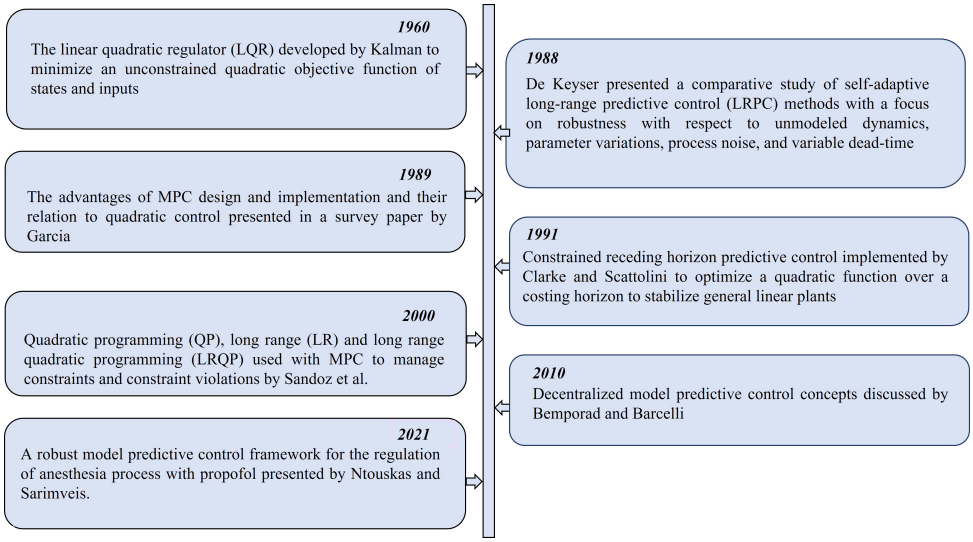

Figure 1. MPC development milestones [6,13–18].

1.2. Evolution of MPC Algorithms

MPC technology is presently used across a range of industries, such as aerospace, petrochemicals, automotive manufacturing, food processing, and many more. Figure 2 displays the evolution of the major industrial MPC algorithms since the 1960s. These evolutionary MPC algorithms are discussed below.

1. Linear quadratic Gaussian (LQG): The linear quadratic gaussian (LQG) approach determines appropriate control for a stochastic system that minimises a performance metric. LQG helps to address some of the most difficult control problems in stochastic systems. As a result, it can be viewed as the stochastic counterpart to the deterministic LQR problem. In order to apply the LQG formulation, it is prudent to first construct a solution to the deterministic LQR problem and then develop a Kalman filter to deal with the LQG stochastic problem [14,19].

2. Identification and command (IDCOM): This differs from the previous approach in that it analyses the plant's impulse response model, which includes linear inputs or internal variables. The model's performance objective is quadratic with respect to the input variables across a finite prediction horizon. A reference trajectory as well as input and output restrictions are included to the formulation to characterise future plant output behaviour. An iterative heuristic strategy (the polar opposite of identification) is used to calculate the ideal inputs [15,20].

3. Dynamic matrix control (DMC): A linear step response model for the plant is linked with a quadratic performance target across a finite prediction horizon in the DMC control strategy. The plant's future output behaviour is characterised by the plant's attempt to match the set point as closely as feasible in the future output behaviour. The least-squares problem is used to determine which inputs are the most effective/significant [16,21].

4. Quadratic dynamic matrix control (QDMC)- The original IDCOM and DMC algorithms were particularly effective in regulating non-limited multivariable processes. Constraint handling, on the other hand, remained unpredictable. The Shell Oil corporation solved this issue by applying a quadratic programming technique to achieve the DMC technique using well-defined input/output constraints in QDMC [22,23].

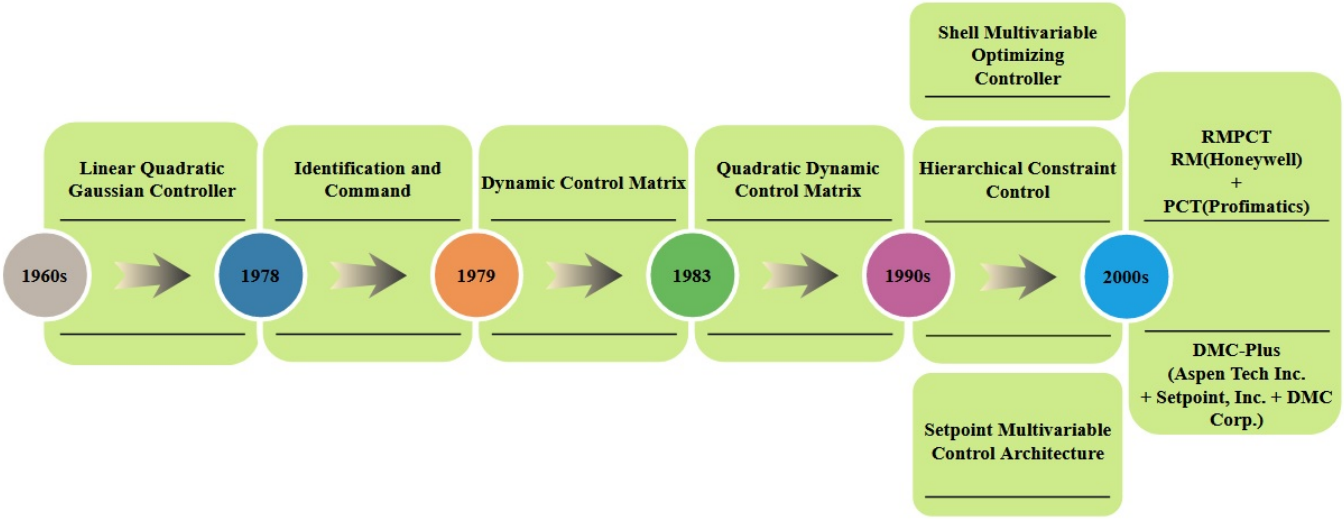

Figure 2. Industry-wide evolution of MPC algorithms.

5. IDCOM-M or hierarchical constraint (HIECON): The IDCOM-M algorithm, also known as the hierarchical constraint (HIECON) algorithm, differs from previous algorithms in that it employs two separate objective functions for determining outputs and inputs with higher degrees of freedom. Prior to minimising an output objective function, a strict set of input constraints is imposed. The inputs drive the outputs as close to the anticipated value as possible at the coincidence point [24].

6. Setpoint multivariable control architecture (SMCA): Setpoint's developers combined identification, simulation, configuration, and control technologies to create the setpoint multivariable control architecture (SMCA). This numerical solution engine automatically accommodated a large number of ranking objectives and constraints by solving a sequence of discrete steady-state goal optimizations.

7. Shell Multivariable Optimizing Controller (SMOC): In the late 1980s, engineers at Shell Research in France created the Shell multivariable optimizing controller (SMOC), presented as a bridge between state space and multivariable optimization approaches. The engineers merged MPC's constraint-handling capabilities with state-space methods' feedback architecture to attain better control characteristics [25,26].

8. Tech mergers and acquisitions—DMC-plus (dynamic matrix control-plus) and RMPCT (robust model predictive control technology): Increased competition among MPC manufacturers, as well as mergers of numerous MPC companies, resulted in significant changes in the industrial MPC ecosystem. Honeywell Hi-Spec Solutions was founded in 1995 as a result of Honeywell's acquisition of Profimatics, Inc. Eventually, Honeywell launched the RMPCT product, which is based on Honeywell's RMPC algorithm and Profimatics' PCT controller. In a similar fashion, Setpoint Inc. and the DMC Corporation were purchased by Aspen Technology Inc. in the first quarter of 1996. Thereafter, Aspen Technologies created the current DMC-plus product on the market by combining SMCA and DMC technologies. In a continuation of tech mergers, Treiber Controls was acquired by Aspen Technologies in 1998.

1.3. MPC Methodology

Expressed in its simplest form, the MPC predicts future output values based on current input and output values, as well as the future controller action and state variables (Figure 3). Every MPC is comprised of three interconnected elements: a process model, an objective function that employs the receding horizon technique (RHM), and a control rule.

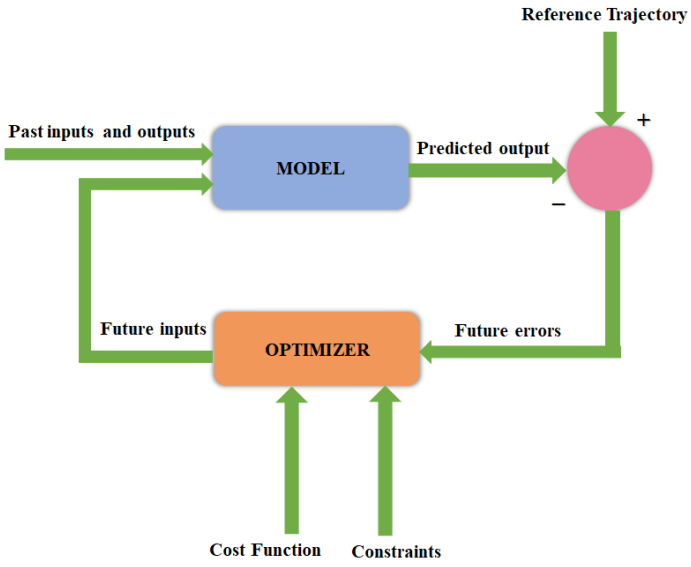

Figure 3. Basic structure of MPC.

The model of the process describes the dynamics of the inputs and outputs as they occur during the process. An MPC can employ feed-forward, feed-backward and disturbance models, among other techniques. The objective function is sometimes referred to as the cost function in some circles. Specifically, MPC methodology aims to achieve the following objectives [27]:

- Anticipate the outcome of a process over a future time horizon via the explicit application of a system model;
- Calculate and optimizate the control sequence;
- Implement a receding horizon strategy in which the horizon is moved towards the future at each step while applying the control sequence for that step.

The following steps (schematically depicted in Figure 4) broadly describe the generalized MPC tuning methodology followed to attain the above-listed objectives:

Step 1: In the first step, the initial process model is utilised to generate future outputs $y(t+k|t)$, $k = 1, \cdots, N$ (where N is the number of samples) at all time instants t within the prediction horizon. Future predictions of the system states are calculated considering the previous system inputs and corresponding outputs, the current output (initial condition) $y(t)$, and the required control signals $u(t+k|t)$ so that the desired output is reached/maintained.

Step 2: A control sequence is computed to maximise a performance objective, which is frequently updated to minimise the error between the reference trajectory and the expected process output. Typically, the effort required to maintain control is incorporated in the performance criterion.

Step 3: A single control signal $u(t|t)$ is transmitted to the process at this point in the process. After that, $y(t+1)$ is measured, and step 1 is repeated, with all sequences being brought up to date at the end of that sampling period. This is accomplished by employing the concept of a receding horizon, in which the prediction horizon is maintained at the same level but is step-wise incremented by one sample interval $u(t+1|t+1)$.

The receding horizon method (RHM) predicts the behaviour of a preset range or horizon by using a mathematical formula. Consideration is given to the present and future limitations, and calculations are made for all values occurring inside the horizon beginning at time t. Those values are then forwarded to the controller, which allows all values greater than t to be refused. The control law is a mathematical formula that is utilised by the controller to determine the objective functions and the process model. The controller monitors the value calculated for the horizon from the objective function and rejects all values other than those occurring at the specified time t in the objective function. Thereafter,

a signal is sent to the controlled variables, and the entire procedure is repeated, with new outputs calculated based on the newly introduced inputs, outputs, and restrictions. Subsequently, the controller rejects all values with the exception of those at time $t + 1$. Such repetitions/iterations are carried out until the end of the predetermined horizon has been reached. An objective function and constraints are used in the process model optimization process. Projected outputs are compared to the reference trajectories in order to reduce deviations/mistakes. Updated outputs are sent to the process, and in this way, the entire system process is repeated for each future output.

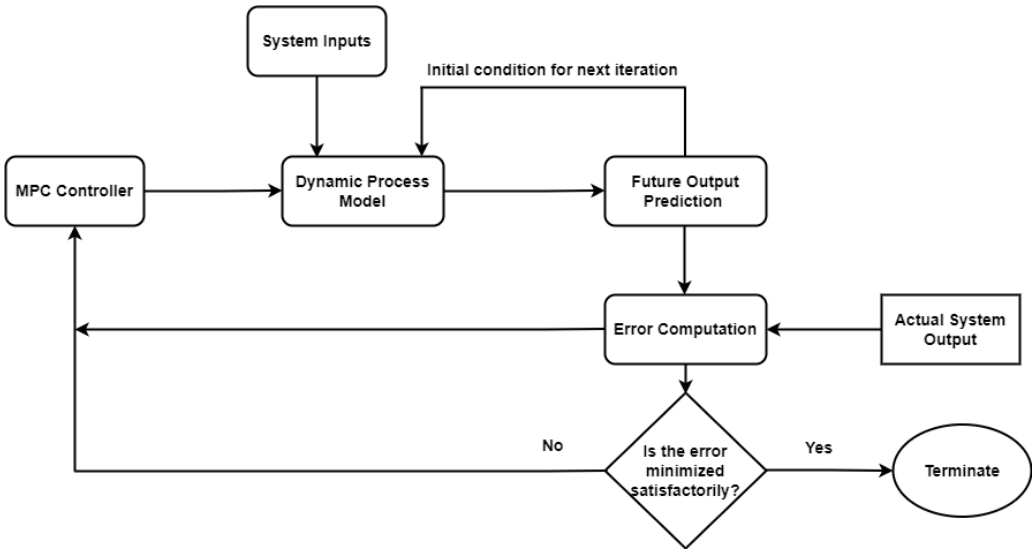

Figure 4. Generalized MPC tuning methodology.

1.4. Advantages and Limitations of MPC

The MPCs are now applicable to more dynamic processes instead of being restricted to slower and more stable processes because of advancements in the computation technologies. Aside from the fact that it handles constraints effectively, an MPC is also very easy to modify and customise. An MPC makes it possible to place constraints on the output of controlled processes (control variable) as well as on the control signals that are inputs to the controlled processes (manipulated variables). Input restrictions can also take the form of rate constraints, such as valves and other actuators with a limited range of slew rates. Model predictive control is also extremely adaptable, and it may be applied in practically any situation. An MPC is used to reduce the amount of error between the set-point and the actual trajectory. It also outperforms conventional controllers when the process has many constraints and/or nonlinear constraints. An MPC can also assist with optimization objectives, since the MPC cost function minimization serves as an optimization tool as well. Furthermore, an MPC is well suited for systems with dead time and slow dynamics since it automatically accounts for dead time. The following are some of the reasons why MPCs are being applied widely across various industries :

- Multi-variable control problems can be naturally handled by MPCs;
- Actuator limitations can be taken into account by MPCs;
- MPCs permit operations nearer to constraints, resulting in higher performance;
- Structural changes can be handled by MPCs;
- MPCs have sufficient capability for online calculations;
- Unstable processes and non-minimal phases can be handled by MPCs;
- MPCs can be easily tuned.

Despite the fact that there are numerous advantages to using MPCs, there are also a few limitations. Although MPCs can be employed when there are constraints in the system, the control rule is derived in a complex manner, and the difficulty of its derivation increases with the number of constraints in the system. This kind of process control may result

in suboptimal optimization, which is undesirable. As a result of the software package's objective to complete the optimization process as quickly as possible, the MPC may be forced to produce erroneous results. The final problem of the dynamic system modeling is its instability, which is caused by its dependence on time. As a result, while utilising MPCs, it may become difficult to maintain/ensure system stability.

2. MPC Implementation

MPC implementation demands current process data, its dynamic parameters, output setpoint targets as well as specified tolerances to estimate the upcoming deviations in the dependent variables [3,28]. An MPC corrects the parameters in accordance with the model constraints for both the dependent and the independent variables. It implements changes in independent variables for the current iteration before commencing calculations for the next set of changes. This section covers major varieties of MPCs employed for different applications followed by a note on the prominent software used in MPC implementation.

MPC models are intended to capture the behaviour of complex dynamical systems with reasonable accuracy. Hence, complex MPC control architectures are seldom required for basic systems for which the generic PID controllers prove to be sufficient. Setpoints (for pressure, flow, temperature, and other variables) and the final control element in a processing plant are generally independent parameters that the PID controller can manipulate (such as valves and dampers). On the other hand, changes in the independent variables result in related changes in the dependent variables of an MPC-controlled system. Disturbances are variables that are not controlled by the PID controller and cannot be changed by it. Large time delays and higher-order dynamics are two of the most common problems that PID controllers face when it comes to controlling dynamic characteristics. The following subsections give details of the major MPC architectures used in industries. Broadly, MPCs can be classified into two main categories: linear and nonlinear [29]. Other classes of MPCs include explicit and various kinds of robust MPC designs.

2.1. Linear MPC

Most of the real-world processes are nonlinear by nature. However, for a limited working range of values, they frequently resemble linear behaviour. Linear MPC techniques include corrections of independent variables on the basis of the feedback received regarding the mismatch between the predicted and actual process outputs. The influence of changes in a large number of independent variables can be integrated in order to forecast the response of the dependent variables in MPCs that are purely based on linear models. The control problem is thus reduced to a series of quick and dependable linear matrix algebra calculations. There are several approaches that can be used when linear models are insufficiently precise to describe real-world nonlinearities. For instance, some process variables can be corrected after generating the linear MPC model to account for the nonlinear system behaviors. On the other hand, nonlinear MPC models can be utilised to effectively control such processes directly. Such nonlinear MPC models could be based on energy and mass balance fundamentals, or they could be empirical relations based on the information/data available (e.g., artificial neural networks). Moreover, a nonlinear model can also be linearized to yield a linear MPC or a Kalman filter. Table 2 displays the basic differences between the linear and nonlinear MPC configurations.

Table 2. Linear and Non Linear MPCs.

Linear MPC	**Nonlinear MPC**
Uses linear model $x = Ax + Bu$	Nonlinear model—$x = f(x;u)$
Quadratic cost function $F = xTQx + uTRu$	Cost function can be nonquadratic $F = (x;u)$
Linear constraints $Hx + Gu < 0$	Nonlinear constraints $h(x;u) < 0$
Quadratic program	Nonlinear program

According to El-Gherwi et al. [30], following a dual-mode MPC approach can drastically reduce online calculations while maintaining performance comparable to the isolated implementation of the same algorithm. By utilising information exchange among dual controllers, the authors proposed an information-sharing-based parallel solution approach to effectively solve complex optimization problems.

2.2. Nonlinear MPC

Nonlinear techniques are unavoidable in complex systems because linear model predictive control applications do not always result in acceptable performance [31]. This is one of the reasons why nonlinear model predictive control (NMPC) has received a lot of attention in the last several decades, with many recent breakthroughs in both academia and industry. The term NMPC refers to MPCs that employ a nonlinear dynamic model and nonlinear constraints, resulting in increased complexity. Nonlinear model predictive control (NMPC) uses nonlinear system models to estimate the dynamic state of the plant. Nonlinear MPC, as with linear MPC, requires multiple iterations within the prescribed prediction horizon to arrive at optimal control parameters. Unlike linear MPCs, the control problems are not always convex in the case of nonlinear MPCs due to the way the nonlinear MPC solves them [32,33]. The NMPC usually employs Newton-like optimization methods to arrive at optimal solutions viz. direct collocation and direct single/multiple shooting. The NMPC algorithms are generally designed on the basis of the inherent similarity of the successive optimal control problems. The previously obtained optimal solution can be utilised to efficiently initialise the Newton-type solution technique, saving significant time in the computation process. As a result, path-following algorithms (also known as "real-time iterations") capitalise ever more on the similarity of subsequent problems. Thus, such algorithms do not directly iterate towards the convergence of the given optimization problem; instead, they iterate to solve recent problems before starting with the current NMPC problem with a more effectively selected initialization [34].

NMPC models have been typically implemented in the industrial processes involving slow sampling rates or distributed parameter systems. However, recent advancements in computational algorithms as well as in controller hardware have made it possible for large-scale implementations of NMPCs in high-sampling-rate applications such as the automotive manufacturing processes, or even when the states are distributed over a large space [35]. Recent applications of NMPC include optimal terrain path and obstacle avoidance trajectory following in varied real-time aerospace applications [36,37].

2.3. Explicit MPC

In contrast to online MPCs, some systems benefit from explicit MPCs (eMPCs), which allow for a more rapid evaluation of the control rule. In this method, the explicit MPC parametric programming configuration is preceded by an offline pre-computation of the optimization problem [38]. This offline pre-computed solution is represented by a piecewise affine function (PWA). The eMPC controller selectively saves the coefficients of the piecewise affine function for the state spaces wherein the said function is constant. The eMPC also saves the parametric coefficients of such state spaces for further processing.

Every state space region in a linear MPC is a geometrically convex polytope with each of its faces having a respective individual coefficient. All such linear MPC face-regions are firstly examined for their quantization accuracies [39]. The optimal control action is decided by initially selecting the state space area representing the current state and then evaluating PWA using the PWA coefficients that were previously saved for all state spaces. Unlike an online MPC, the eMPC implementation does not require a significant investment of computer resources for processes wherein the total number of state spaces is small, making it particularly well suited for control systems with a high dynamic range and speed [40]. However, in cases wherein the total number of control regions is huge, especially when a greater number of system parameters are considered, the eMPC demands much more memory for searching the current control region. In such

cases, the eMPC invariably becomes computationally intensive. An explicit MPC involves parametric programming that pre-computes solutions to the explicit control law expressed as optimization problem(s) (Figure 5). Bacic et al. [41] explored the role of pre-computed terminal sets in MPC interpolation. However, some researchers found that the prediction and optimization cycles of an MPC over a receding horizon yielded more optimal solutions as compared to the precomputed control regimes [42].

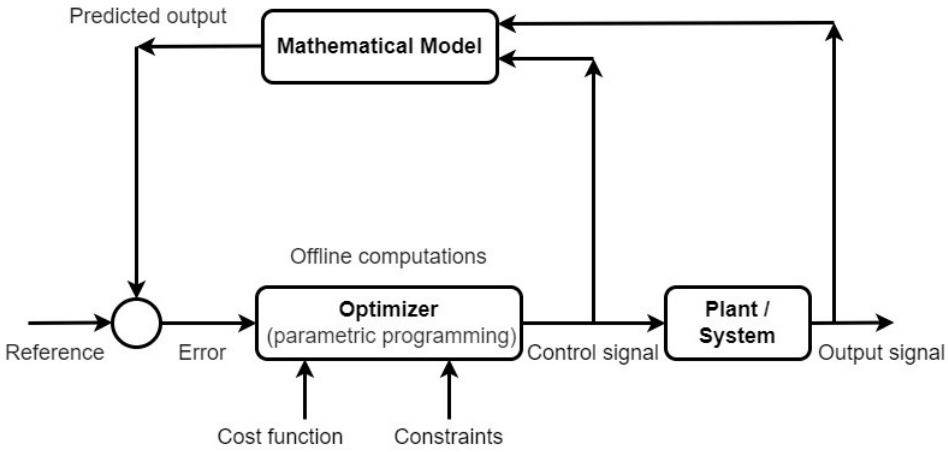

Figure 5. Explicit (pre-computed) MPC [43].

2.4. Robust MPC

MPC architectures can be specifically designed to ensure robust performances for set bounded disturbances within the expected state constraints [44]. The following are some of the most commonly used strategies for ensuring robust control performance:

- **Min-max:** The min/max MPC approach essentially converts a "min" optimization problem into "min-max" optimization by decreasing the worst-case objective functions and maximising them across all feasible points in the uncertainty set [45]. In this formulation, optimization is performed with respect to all possible disturbance evolutions. The min-max MPC has been proven to be the most effective for solving linear robust control applications. However, it is also relatively computationally expensive.
- **Constraint tightening:** In this approach, the state constraints are widened by a certain amount to ensure that a trajectory is discovered regardless of the disturbance evolution [46].
- **Tube:** The tube method employs a separate nominal system model and a feedback controller for converging the active state to the nominal state as quickly as possible [47]. This MPC collects all possible state deviations due to disturbances in a robust positively invariant (RPI) set, which are then used to determine the degree of separation of the states from the set of constraints.
- **Multi-stage:** The multi-stage approach accommodates different control decisions at every stage. It is non-conservative in nature due to the availability of measurement information at each time step in the forecast as well as the fact that it can be used to mitigate the effects of uncertainties. The inherent disadvantage of this strategy is that the complexity of the control problem increases as the number of uncertainties and the time between predictions increases [48,49].
- **Tube-enhanced multi-stage:** This approach combines the advantages of tube-based and multi-stage MPC architectures to furnish more options for optimality versus simplicity trade-offs. This method has been found to be quite useful in system forecasting using various control and uncertainty principles [50,51].

2.5. Other MPCs

- **Decentralized and distributed MPC:** Each controller in a decentralised and/or distributed control system simply monitors and regulates local outputs and inputs. Decentralization has profound benefits for controller implementation and maintenance. During maintenance, some functional aspects of the overall process are interrupted, but the remainder of the components continue to function uninterrupted with local controllers in a closed-loop, as against total shutdown in the case of centralised control architectures. Similarly, redesigning a part of the process does not imply complete remodeling of the entire controller architecture, as would happen in the case of centralised control. Under decentralization, it is important to specify the applicable conditions for which the local closed-loop controller laws are capable of keeping the entire system stabilized. In the process industries, MPC techniques are generally utilised to solve large-scale multivariable control problems. An MPC formulates the control problem in the form of an optimization problem in which several (possibly competing) goals and constraints (state- and control-related) can be specified. Due to scalability and model maintenance issues, a centralised MPC is typically inadequate for large-scale networked systems. In light of the above, it makes sense to envisage decentralised model predictive control (DeMPC) and distributed model predictive control (DMPC) algorithms, which involve compartmentalizing a big optimization objective into multiple smaller units that iterate independently (DeMPC) or cooperatively (DMPC) to ultimately attain the overall system objective. The primary distinction between "decentralised" and "distributed" is the way information is shared among control regions. In DeMPC, local controllers make independent decisions. Prior control choices and measurements can only be provided before and after a decision is made. Communication considerations such as network delays and packet loss have no effect on the decision-making time for local control actions. Figure 6 depicts a DeMPC architecture wherein five distinct control regions are controlled individually by local MPC controllers. On the other hand, Figure 7 shows a corresponding DMPC layout wherein candidate control decisions may be exchanged and iterated during the decision-making process until local controllers agree on a stopping condition [52].
- **Feedback and feedforward MPCs:** Feedback correction is an inherent feature of MPCs, along with rolling optimization and predictive modeling characteristics [18]. The combination of MPC and feedback linearization (FL) has been popular among researchers for many years due to the ease of controllability of FL plants using linear MPCs [53]. For instance, Parekh et al. [54] applied a state feedback linearization (SFL)-enabled MPC to effectively control a pharmaceutical coolant temperature application. However, some researchers [55] have supported MPC architectures inclusive of feedback as well as feedforward control signals. This architecture overcomes the inherent drawback of purely feedback control loops with regards to the detection of system deviations after they have occurred. The feedforward and feedback loops act together to eliminate all measured and unmeasured system disturbances (Figure 8). Kayacan et al. [55] also proposed linear MPC architectures with feedback as well as feedforward loops for multi-input and multi-output mobile robot systems. Sbarciog et al. [56] designed cascaded linearized feedback controllers to control animal cell concentrations and nutrients in a cultivation plant. Wang et al. [57] incorporated a feedforward-feedback regulation regime to effectively control disturbances in a multiple-effect falling film evaporator system. Zhao et al. [18] applied active feedback correction in a trajectory-tracking controller for an unmanned vehicle to overcome system interference and uncertainties. Table 3 furnishes a featured summary of the above-discussed MPC variants.

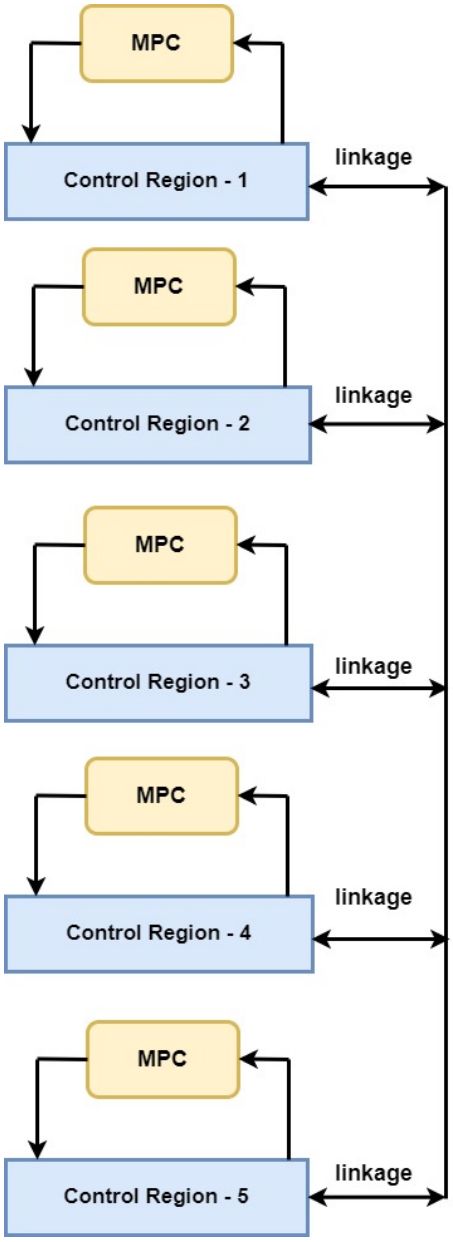

Figure 6. Decentralized MPC.

Table 3. Variations of MPC.

Class of MPC	Features
Linear MPC [30]	Corrects independent variables on the basis of the plant feedback
Nonlinear MPC [31]	Employs nonlinear dynamic model and nonlinear constraints, resulting in increased complexity
Explict MPC [38]	Allows for a more rapid evaluation of the control rule
Robust MPC [45]	Ensures viability and long-term stability
Decentralized and distributed MPC [52]	Monitors and regulates local outputs and inputs
Feedback and feedforward MPC [18]	Reduces contraction of the feasible solution region

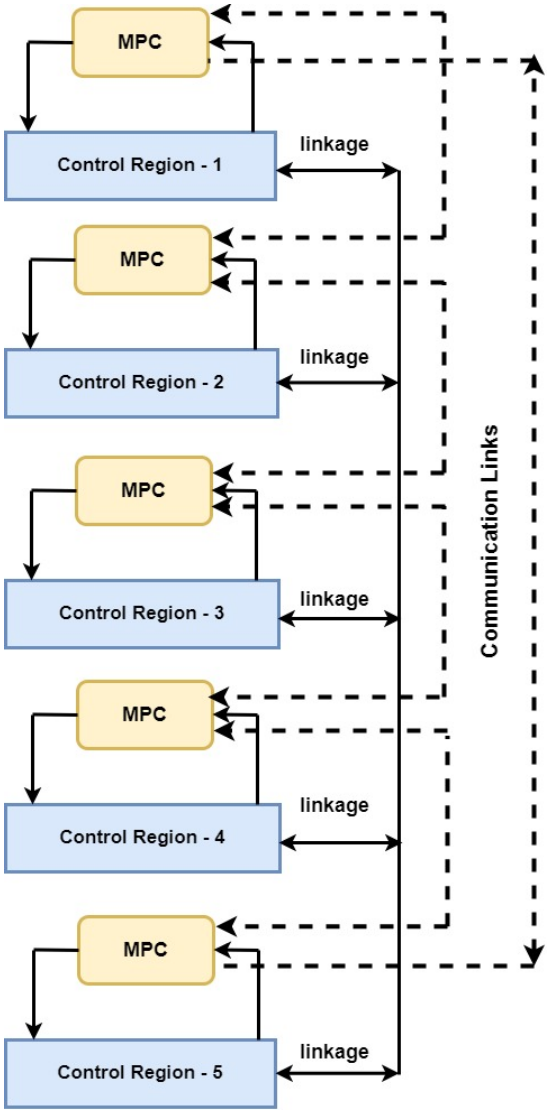

Figure 7. Distributed MPC.

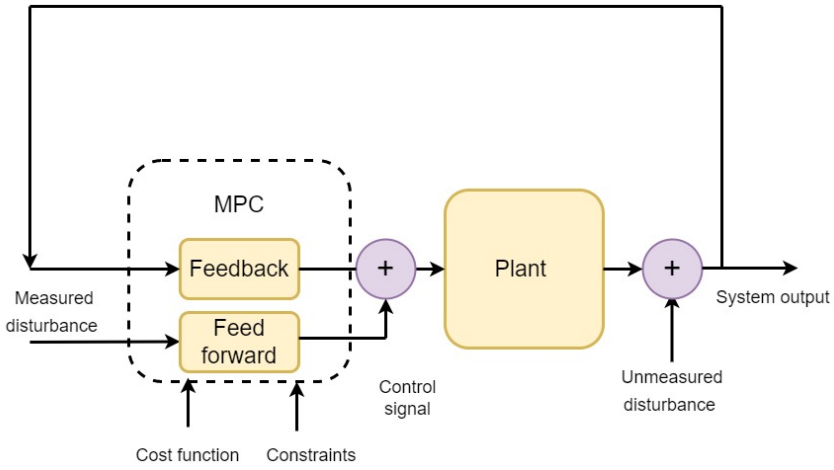

Figure 8. Feedback and feedforward MPC [55].

2.6. MPC Softwares

This subsection gives a brief introduction to some of the important software used to implement MPC architectures.

- **MATLAB:** The model predictive control toolbox of Matlab includes application, function and Simulink blocks for designing and simulating linear and nonlinear model predictive control (MPC) controllers [58]. This toolbox allows users to specify plant model parameters, horizons, constraints and weights. Closed-loop simulations can be used to assess controller performance. Controller weights and constraints can be changed during runtime to update output behaviour. In addition to deployable solvers, control designers can employ a custom optimizer from the toolbox. Nonlinear, gain-scheduled and adaptive MPCs can be used to control nonlinear plants. For applications with high sample rates, this toolbox can generate explicit MPCs from regular controllers to approximate feasible solutions.
- **Oravec's MUP:** This software uses the MATLAB/Simulink toolbox to implement a robust MPC in the LMI (linear matrix inequalities) framework online [59]. The MUP toolbox is a practical and user-friendly solution for MPC control engineering. It is also an excellent choice for educational purposes. The MUP package is provided "as is," with no warranties of any kind. YALMIP (yet another LMI parser and SeDuMi (self dual minimization)) are the required MUP dependencies, with Mosek as the recommended solver. These are not included in the MUP toolbox.
- **do-MPC:** do-MPC is an open-source toolbox used for moving horizon and parameter estimation to develop robust multi-stage MPC architectures. do-MPC includes specialized tools to deal with time discretization and system uncertainties. Its modular layout easily accommodates different combinations of control, estimation and simulation components in seamless integration for various applications. do-MPC is widely used for nonlinear system modeling, estimation and simulations. It supports differential algebraic equations as well [60].

Table 4 lists a summary representation of the above-discussed commercial MPC softwares, including a brief mention of their respective owners/creators, methodologies, model types, tuning and applications.

Table 4. MPC Commercial Softwares.

Software	**MATLAB**	**MUP**	**do-MPC**
Year	2004	2012	2017
Developed/created by	Mathworks	Bakosov'a, M. and Oravec, J	S. Lucia, A. Tatulea-Codrean, C. Schoppmeyer, and S. Engell
Methodology	–	MATLAB/Simulink toolbox for online robust MPC design in LMI-framework	Comprehensive open-source toolbox for robust model predictive control (MPC) and moving horizon estimation (MHE)
Model type	Continuous and discrete model	Linear matrix inequalities	Differential algebraic equations (DAE)
Approach	Calculates the sequence of control actions based on current state of the plant	Optimally and robustly stabilizes state-feedback control law	Efficient formulation and solution of control and estimation problems for nonlinear systems
Tuning	Prediction, control horizon, constraints	–	Horizon state and parameter estimation
Usage	Design of implicit, explicit, adaptive, and gain-scheduled MPC. For nonlinear problems, single and multi-stage nonlinear MPCs can be implemented	Practical and user-friendly solution for MPC control engineering; also an excellent choice for educational purposes.	Contains simulation, estimation and control components that can be easily extended and combined to fit many different applications

3. MPC in Biomedical Applications

Over the last several decades, control and system identification techniques have been applied in biological and biotechnological systems. As interest in the field of disease control grew in the 1960s–70s, researchers had a strong desire to develop mathematical frameworks for supporting medical operations and developing novel healing protocols [1]. Although control systems have been intertwined with medical applications for decades, their impact on medical devices and applications became apparent in the literature only recently [61]. Nowadays, ever more researchers are combining the principles of biomedical control engineering with the insights of molecular life sciences to solve modern problems through the measurement and modelling of biological systems. These researchers are developing biological-based/inspired technologies that will be useful in a variety of different industries, including manufacturing, defence, agriculture, and environmental and human health. From the point of view of the variety of issues being addressed and related real-time applications, the field of biological systems can still be considered to be in its infancy.

Hence, there is a vast scope to develop closed-loop controls for biomedical systems in a way that they can be translated into workable and scalable technologies. It is still a challenge in the design of control and sensor systems to translate meaningful clinical health results of the patient body into quantitative control parameters. In this scenario, the MPC's receding horizon control concepts are particularly suited for effective medication delivery control. Hence, MPCs are being used in medical applications, as these controllers have been useful in overcoming signal disturbances and generating robust performances [1,62]. The latest advances in MPC designs ensure robust and offset-free control definitions to address inherent vulnerabilities in the system models. The following subsections present MPC biomedical applications in therapies addressing type 1 diabetes (including artificial pancreas), anaesthesia, cancer (including hyperthermia and oncolytic viral treatments), fibromyalgia, and HIV.

3.1. Type-1 Diabetes

The blood glucose level (BGL) of a healthy person fluctuates within a healthy range of 70–110 mg/dL. The glucose-regulating process in the body is comprised of two regulating inputs, glucagon and insulin, which are used to control blood glucose output into the blood stream. BGL is reduced by insulin and increased by glucagon. Type 2 diabetes (T2D) and type 1 diabetes (T1D) are both caused by the failure of the pancreas to release insulin, either partially or completely. T1D is the most frequent of the four types of diabetes, and it is primarily caused by pancreatic dysfunction [63]. Long-term anxiety and stress, as well as a lack of physical activity, contribute to the development of type 1 diabetes. In these patients, long-term hyperglycaemia (deviation from the normal BGL to a higher value) leads to multiple complications, such as cardiovascular disease, kidney failure, neuropathy, and retinopathy. On the other hand, hypoglycaemia (deviation from the normal BGL to a lower value) causes complications such as tachycardia and nausea. Even coma (at BGL of 50–70 mg/dL) is a likely complication of disrupted BGL regulation [64–66]. Insulin injections (subcutaneous, intravenous, or intraperitoneal) are recommended as common therapy for pancreatic cell death in non-automated clinical procedures [65].

BGL regulation is a tough control task in T1D patients, complicated by severe non-linearities, complex dynamics and unexpected disruptions. Control algorithms for blood glucose control in type 1 diabetes patients should be capable of successfully dealing with fluctuations in everyday living. Furthermore, careful consideration must be given to the design of the controller in order to deliver insulin safely and avoid hypoglycemia. Hypoglycemia can arise as a result of fasting or excessive physical exercise. Overeating or being exposed to stressful situations contribute towards hyperglycemia. In general, physicians determine exogenous insulin dosage for a patient through an experimental procedure based on measured blood glucose levels. This procedure can be automated by designing a closed-loop automatic BGL control framework that determines the amount of applicable injectable insulin, taking into account various T1D condition parameters. Several researchers have

attempted to create dynamic models characterising the human blood glucose relationship in recent decades. Nath et al. [66] presented an overview of the major glucose-insulin models developed for type 1 diabetes. The well-known Bergman minimal model (BMM) has been reported to be the most preferred among BGL control researchers [67,68]. There are many options for dealing with type 1 diabetes when it comes to control methods. Herein, proportional–integral–derivative (PID) control is the most prevalent traditional control system. For BGL regulation, intelligent techniques such as artificial neural networks and metaheuristic algorithms [69] are frequently used. The backstepping technique and robust H control [70,71] have also been used in some studies [72,73].

Among all blood glucose control approaches, MPC is one of the most well-known and widely applied methods. MPC is an effective control algorithm for BGL regulation since it can readily combine the dynamics of glucose–insulin, meal information and insulin injection constraints. MPC is one of the most suited approaches for designing control systems that are subjected to a variety of restrictions, since constraints are intrinsically incorporated into the control design procedure [74]. Several studies have described MPC-based blood glucose regulation using both linear [75] and nonlinear techniques [76]. The nonlinear model predictive control (NMPC) technique is one of the most effective methods of dealing with disturbances in the modelling of a T1D patient and reaching/maintaining the ideal blood glucose level. An appropriate insulin pattern is generated using the NMPC algorithm in conjunction with essential injection restrictions as well as hyperglycemia and hypoglycemia constraints. The algorithm's goal is to minimise a quadratic function of blood glucose deviation from the normal range and insulin dosage. It has been demonstrated that the performance of the NMPC controller is relatively robust against random minor disturbances, such as exercise, stress and fatigue, among other conditions [63].

Artificial Pancreas

MPC is also used to operate artificial pancreas (AP) devices, which automatically deliver the appropriate amount of insulin dosage to type 1 diabetes patients in order to keep their blood glucose levels within acceptable limits [77,78]. Inside an AP, a control algorithm determines the appropriate dosage under a variety of different daily living conditions and for a variety of patient populations. Although linear MPC models yield computationally efficient control algorithms, such generalized models prove insufficient for effective control because physiological variables vary greatly between individuals and also dramatically within individuals over time. Customized and recursive identification algorithms can be used to overcome this limitation and better characterise the time-varying nonlinear dynamics of AP-related biological processes [79].

A study [79] presented a new adaptive MPC approach for modeling complex biological systems characterized by transient dynamics. This approach firstly involved the recursive system identification of metabolic process parameters associated with diabetes. Thereafter, the identified system model was employed to develop an adaptive MPC algorithm to control insulin delivery in the blood. Glucose levels were monitored using a feature extraction protocol in order to quickly react to deviations from the target setpoint caused by metabolic events. Subsequently, the constraints of the optimization problem were updated to negotiate between the controller's aggressiveness and robustness in order to recommend the appropriate amount of insulin to be delivered.

3.2. Anaesthesia

Anaesthesia is widely employed in various applications, particularly in the medical field, including in operations requiring incisions, dental surgeries and intensive care. The fundamental goal of anaesthesia is to provide a painless experience to a patient undergoing surgery by putting him or her into an unconscious condition. The entire functional scenario of anaesthesia can be divided into three temporal phases: induction, maintenance and emergence. The opioid drug propofol is commonly used in conjunction with other fast-acting opioids during the induction of general anaesthesia. An under-dosage

of anaesthetic medicines might result in the patient being aware of the operating situation or insufficient analgesia administration. On the other hand, a patient receiving more medication than necessary can also face detrimental effects. Therefore, the major concern in anaesthesia administration is to maintain the optimum level of sedation during and after induction, which is one of the most difficult tasks in the medical field. Complications may arise following surgery as a result of post-operative pain medication or due to the administration of insufficient intra-operative anaesthetics. Considering the large number of individuals who undergo surgeries every day around the globe, automated regulation of total intravenous anaesthesia (TIVA) is of paramount importance. A higher clinical workload, the wide variety of anaesthesia infusion practices to cater to large inter-patient variability (correlated with doctors' expertise) and the repeated use of a constant drug infusion rate (slightly over-dosing) are pertinent issues that need to be addressed. Recently, the pandemic outbreak of COVID-19 brought to light specific dangers such as acute cardiac damage and arrhythmia associated with infected patients that required special attention during anaesthesia [80].

The solution to the difficulties associated with anaesthesia is three-pronged: (i) robustness to disturbances (such as noise in the measured variables and nonreceptive stimuli); (ii) preventing overdosage by the minimization of the control effort; and (iii) dosage management to control pharmacokinetic and pharmacodynamic drug interactions. MPC is a proven methodology that can be used to deliver such multifaceted solution approaches. A wide range of hypnotic and analgesic medications, such as propofol and remifentanil, are suitable anaesthetic actuators. These medications can be delivered through computer-controlled automated perfusion syringes, which are suitable for intravenous anaesthesia and pain relief. There are several indicators available to measure the depth of anaesthesia, including the BIS index, EEG signal entropy measures, and auditory evoked potentials [81]. In [81], researchers designed a control loop based on an in situ model and used it for the delivery of an opioid analgesic (remifentanil) and an anaesthetic (propofol). The authors simulated the patients' bio-responses (in situ), such as heart rate, arterial pressure and bispectral index, using a pharmacokinetic-dynamic model. This methodology allowed for predicting the bio-responses of the patients as would occur in a real-life scenario. The authors' simulation of the induction phase of anaesthesia was successful in terms of obtaining a rapid and risk-free response from the patient. This was accomplished by designating the arterial pressure and the bispectral index as controlled variables, as well as by imposing appropriate bounds on the plasma concentration and the controlled variables. Overdosing and underdosing are both potentially dangerous outcomes during intravenous anaesthesia, so it is important to find the right pace of delivering anaesthetic medicines to the patients. The connection between the dose of anaesthetic given to a patient and the hypnotic effects it has on that patient has been studied by researchers using a pharmacokinetic–pharmacodynamic (PK/PD) model built specifically for this purpose [82]. In this study [82], the authors designed a linear MPC to control intravenous anaesthesia based on a single input (rate of propofol infusion) and single output (bispectral index). The effectiveness of the developed LMPC in tracking the BIS reference, while also accommodating for restrictions, disturbances, and noise in the measured variables, was investigated. Taking into account closed-loop time delays, the performance of this method in comparison to that of a traditional proportional–integral -derivative (PID) controller was evaluated. The results of the simulations demonstrated that the suggested linear MPC is superior to the standard PID controller in such applications.

Figure 9 shows an NMPC control loop architecture for anaesthetic applications. This NMPC attains and maintains the desired level of patient bispectral index (BIS). Anaesthetic dosage is administered to the patient by the control loop as follows. Initially, the state observer estimates the future state vector of the system (level of anaesthesia of the patient). The NMPC controller takes this state vector estimate as an input and computes the optimal anaesthetic dosage to be administered to the patient. In the subsequent time steps, the state observer advances the state vector estimate to the next horizon, which is followed

by the controller to compute and deliver optimal dosages to the patient at those discrete time instants [83]. Researchers [17] also attempted closed-loop modeling and control of volatile anaesthesia through a traditional online MPC as well as a multi-parametric MPC. A Kalman filter was employed to determine the dynamic status of anaesthesia on the basis of end-tidal concentrations measured by an online estimator integrated in the closed loop. The authors demonstrated simulations for anaesthetic induction as well as disturbances arising during the course of anaesthesia, along with online parameter estimation of an explicit MPC controller architecture [17]. In a similar work, Patel et al. [84] attempted automated anaesthesia using the BIS signal obtained from the electroencephalogram (EEG) to control the infusion of the hypnotic drug propofol during surgery in order to prevent adverse effects and reduce post-operative recovery duration. The authors found that the low quality of the EEG data caused interruptions in the BIS signals generated during the operation. Hence, they proposed a fault-tolerant MPC architecture to prevent faulty propofol dosages leading to intraoperative patient arousal due to breaks in the BIS signals received by the MPC.

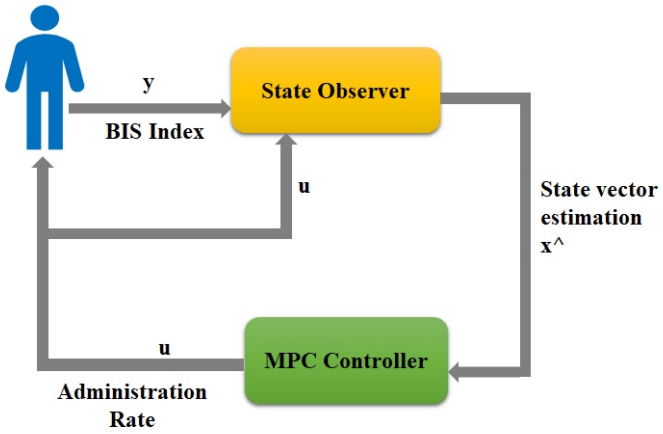

Figure 9. NMPC closed-loop structure in anaesthesia.

A patient undergoing ambulatory surgery must obtain the appropriate dose of anaesthetic medicines to reduce the likelihood of adverse responses after release. In order to create more effective anaesthesia, a hypnotic control system was developed by Sawaguchi et al. [85]. The authors measured EEG-derived BIS as an indicator of the patient's hypnotic state. Their system primarily consisted of three components: (1) an MPC-based feedback controller with a time-delay-handling functionality; (2) a function to estimate MPC parameters; and (3) a function to prevent intraoperative risks such as the overinfusion of the anaesthetic drug and/or patient agitation due to underdosage. Computer-controlled infusion systems play a vital role in maintaining the positive balance in such situations, wherein medicine and engineering work together to achieve the optimal results [86]. Medical specialists can concentrate on high-value jobs, while computer-based drug delivery manages regular tasks such as anaesthesia and heamodynamic maintenance. Patient safety is the driving force behind the wider implementation of automation in clinical anaesthetic delivery. The following are some of the multifaceted advantages of automated anaesthetic delivery systems:

- Optimization of drug dose regimen;
- Better efficiency as compared to manual control;
- Chances of unintended under- or over-dosing are reduced;
- Clinicians can receive early alerts in case a crucial event occurs with the patient, allowing the clinician to intervene as soon as possible;
- Decision support is provided to the anaesthesiologist in the form of a recommended optimal drug infusion determined using context-aware methods;

- Reduction of the workload of clinicians while increasing the effectiveness and vigilance of anesthesiologists. This allows the physician to devote more attention to decisions that demand human expertise;
- Effectiveness in terms of cost, including the avoidance of repetitive treatment and saving costs by achieving accurately targeted drug delivery.

Cyber Physical Human Systems

Figure 10 depicts a schematic representation of a cyber-physical-human system in healthcare. For the anaesthesiologist, an intelligent control architecture can be designed to avoid repetitive tasks, such as constantly monitoring the state of the patient or adhering to well-defined international standards. There are also new issues arising from the COVID-19 pandemic, such as sudden cardiac arrest and arrhythmias, which need to be addressed [87]. With the smart controllers handling routine anaesthesia tasks with satisfactory effectiveness, medical personnel have more time to attend to other vital obligations. In this way, the automation of general sedation regulation may be realised in operation theatres and intensive care units (ICU) alike. While administering anaesthesia, the patient's condition is constantly monitored, and the dosage of drug is adjusted accordingly. When it comes to administering medication by computer, open-loop target-controlled infusion systems (TCI) are used as a first step. Using pharmacokinetics principles, TCIs keep the anaesthetic infusion within predefined limits [88]. To be extra certain, the anaesthesiologist is made a part of the closed-loop control by setting the initial dosage set point targets and then manipulating them in accordance with the patient's state of anaesthesia and health parameters. Patients' responses to medications are predicted by doctors based on data from monitoring equipment, clinical judgement and prior experience. Closed-loop automated control systems, on the other hand, automatically adjust drug infusion rates based on measurements of anaesthesia depth taken from the patient directly. The controller receives constant feedback from the patient's measured bio-responses. This upgrades the role of anaesthesiologists to a higher level, such as the monitoring of patient-specific physiological parameters and/or responding to emergency situations for special drug delivery cases.

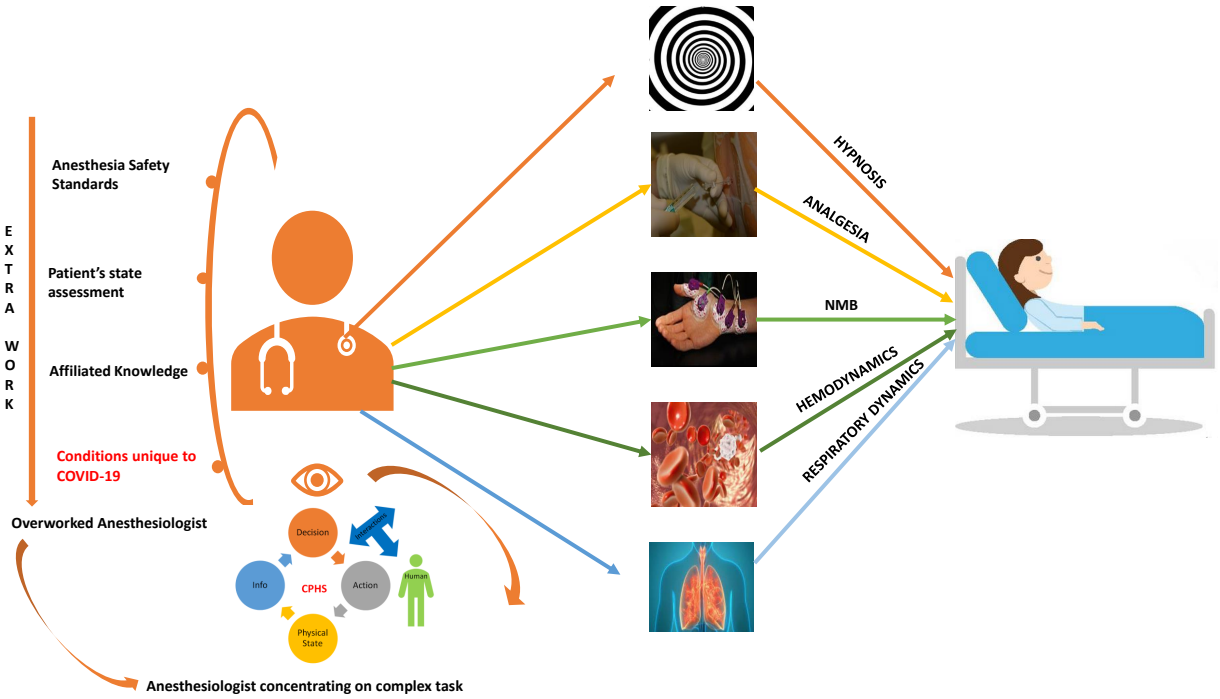

Figure 10. The potential of a cyber-physical-human system (CPHS) in anaesthesia [86].

Figure 11 presents an anaesthesia process schematic including manual as well as computerised closed-loop control and optimization. The automated closed-loop control system monitors the effect of the drug via measured bio-parameters (multi-outputs) of the patient and regulates multiple drug infusions (multi-inputs). By actively operating on patients as needed in order to keep medication delivery systems running well, anaesthesiologists have a direct impact on the system. Patient dynamics, surgeon's actions, anaesthetist actions, syringe pump outputs, sensor data collection, and syringe pump actuators are all components of the anaesthesia system that can be modelled in a control loop. Using these components, the entire process can be simulated, allowing surgeons and anaesthesiologists to better understand and control their patients' medical hypnosis. Clinical expertise and automatic closed-loop control and optimization can be interlinked to ensure optimal drug delivery to the patients.

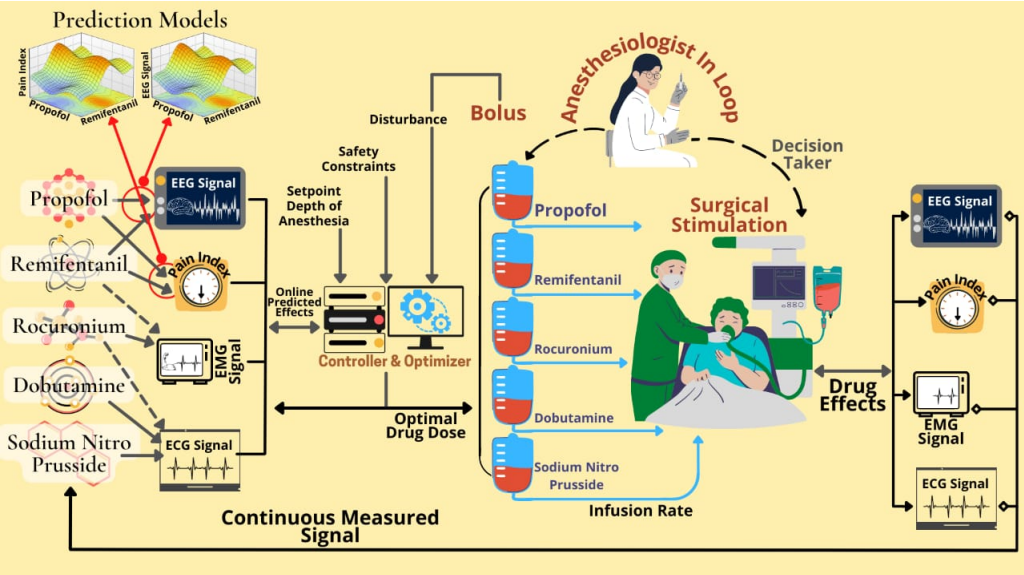

Figure 11. Closed-loop scheme for anesthesia automation in clinical practice [86].

3.3. Fibromyalgia

Fibromyalgia is a disorder characterized by widespread musculoskeletal pain accompanied by fatigue, bowel abnormalities, sleep irregularities, anxiety, mood swings and memory issues [89,90]. There seem to be no specific diagnostic tests to confirm fibromyalgia. Since the causes of fibromyalgia are yet to be precisely determined, it is difficult to process a specific treatment for the condition [91]. Naltrexone is one of the most tried and effective medications against fibromyalgia. This drug (in low dosages) acts in a neuroprotective capacity and is a tolerable and cost-effective solution [92–94]. Moreover, researchers have explored improvised techniques to deal with such chronic relapsing conditions [95]. In particular, adaptive interventions have been found to exhibit profound efficacy in these treatments. In adaptive interventions, the treatment dosage is modified in accordance with the current condition of the patient. In this regard, control system engineering helps to obtain optimal dosage solutions to maximise the efficacy of such strategies [96–99]. This approach also minimizes waste and overcomes the limitations of conventional therapies. Conventional treatments tend to be based on standard protocols devised for standard responses, which may not account for individual patient characteristics.

Hence, investigators implemented the MPC-led adaptive intervention-based treatment of fibromyalgia using naltrexone dosages [93,100]. Their studies included daily patient reports consisting of self-assessment of treatment outcomes. This self-assessment served as the framework for applying the MPC architecture to naltrexone dosage control. It consisted of overall feedback of the current level of fibromyalgia symptoms, followed by specific questions related to fatigue, stress, sadness, mood, pain, sleep and gastric

conditions. The study modeled these symptoms as system outputs. The drug dosage and the placebo were considered as the system inputs. In this way, the problem was identified from a systems and controls perspective, and system identification techniques were used to develop models from regular self-assessment reports of the participants. These dynamical systems models were used as the basis for applying model predictive algorithms to determine the dosage, taking the external disturbances into consideration. Hybrid model predictive control (HMPC) techniques were also explored due to the discrete nature of the dosage. Additionally, a multiple-degrees-of-freedom technique was used to tune the controller instead of conventional weight matrix tuning. This methodology enabled the independent alteration of set-point tracking as well as measured/unmeasured disturbance rejections in the closed-loop system [101,102].

3.4. HIV

Pharmaceutical treatment for HIV infection increases the patient's life expectancy and enhances the patient's overall quality of life. Research studies have explored therapy regimens that stimulate HIV-specific immune responses in order to avoid side effects and drug resistance associated with long-term drug administration [103]. With current medicines, it is almost impossible to completely eradicate the virus from the body because of the presence of hidden reservoirs of the virus that have a longer half-life (from months to years). For instance, a decrease in specific cytotoxic T lymphocytes (CTLs) has been linked to HIV progression; however, patients with slow disease progression exhibit high CTLs as compared to those with rapid disease progression. Reverse transcriptase and protease inhibitors are two types of highly active antiretroviral medications that restrict the formation of virions by blocking the creation of viral protein precursors and protease inhibitors. However, the effectiveness of such highly active antiretroviral therapy (HAART) has been found to be restricted. To mitigate the severe side effects and development of drug resistance associated with long-term medication administration, recent research efforts have focussed on designing therapy regimens that can increase HIV-specific immune responses [103,104]. Structured treatment interruptions (STIs) have been shown to be beneficial in enhancing HIV immunity in a number of clinical investigations, particularly when conducted immediately after infection [105]. STIs have been found in a number of studies to increase immunological responses to the HIV virus. STD (sexually transmitted disease) treatment is helpful when begun within the first few weeks of HIV infection but tends to be ineffective when begun later in infection [106–111]. The qualitative influence of medication side effects on HIV dynamics has also been detailed in a number of clinical investigations, establishing the significance of feedback control systems in such cases.

MPCs have emerged as one of the best solutions for the optimal control of STI among different control strategies, owing to their inherent resistance to noise, uncertainty in their model shape and their capacity to successfully deal with dynamic constraints. Appropriate model selection is of paramount importance in the development of an STI MPC application. Researchers have chosen the Wodarz and Nowak models [105,112,113] for this purpose since these models most closely resemble the natural evolution of HIV as hypothesised in [114]. Investigators have also proposed that two MPC algorithms be used to calculate the "optimal" doses of PI and RTI medications over a common prediction horizon. In this methodology, the simulation results of both algorithms are reviewed and compared to one another [110]. In this approach, all state variables were tested weekly, but only CD4+ T concentration and VL (virus level in the plasma) were measured once a month. CD4+ T helper cells are white blood cells that are an essential part of the human immune system. They are often referred to as CD4 cells, T-helper cells or T4 cells. Their main role is to send signals to other types of immune cells, including CD8 killer cells, which then destroy the infectious particle. Rather than employing a correction strategy in the presence of model flaws, the above-mentioned method maintained control variables within their prescribed ranges by augmenting the system states over successive iterations. As per [110], the HIV therapy can be adjusted using the MPC algorithm to produce the "safe" stable

state that exists even when no therapy is applied. Hence, the immune system can achieve a stable state even in the absence of therapy. However, the internal model is unable to reach a perfect stable state because it is unable to zero the last state-variable derivative. The traditional technique of calculating stage costs has been carried out in terms of departures from a steady-state; however, that method is not relevant in this case. Another feature of the model presented in this research is that it does not allow for the discontinuation of therapy permanently. This is supported by the fact that there is currently no definitive cure for HIV. In conclusion, the stage cost of the model presented by [110] is linear for drug uptake and quadratic for state variation when there are no output constraints considered. In order to incorporate the impact of medication uptake and output constraint breaches, a linear stage cost approach was employed in this study.

3.5. Cancer

3.5.1. Oncolytic Viral Therapy

Oncolytic viral therapy (OVT) is an emerging cancer treatment in which genetically modified viruses are employed to cure cancer in such a way that the healthy cells are not harmed or infected in any way [115,116]. To infect and kill cancer cells, the OVT either induces immunological responses against them or produces lysis, which involves rupturing cancer cell membranes by extensively replicating the oncolytic virus within them. Virus particles that are released as a result of OVT are disseminated to spread the infection to tumour cells that are vulnerable [115–117]. Considering its numerous positive effects on tumour reduction, OVT is widely recognised as an acceptable cancer therapy that can be safely applied in association with other treatments, such as surgeries. OVT treatment can also be applied on its own without any associated therapies to shrink tumors. However, a number of technical, biochemical, immunological, and clinical factors impede OVT performance. The process of selecting the most effective oncolytic virus for a certain malignancy, determining and controlling the virus dosage supplied to the cancer cells as well as developing suitable protocols is time-consuming and challenging. Progress in virus engineering has benefited OVT by furnishing newer variants of genetically modified oncolytic viruses to act against target tumor cells while remaining neutral against healthy cells [115,116]. Researchers have explored various modifications to boost virus survivability when confronted with the immune system. For instance, a study [116] reported that the ADPEGHER virus was generated by coating a naked adenovirus with a non-immunogenic polymer such as polyethylene glycol (PEG), together with the antibody herceptin. In comparison to the earlier version, this modified adenovirus improved infection, tumour regression, and caused no harm to healthy cells.

It is crucial to maximise the infectivity and anti-tumor activity of the oncolytic viruses. In order to reach this goal, OVT effectiveness enhancement has been investigated using mathematical modelling. Model-based investigations have revealed mechanistic insights into the multifarious cancer cell dynamics and oncolytic virus actions within the host, both in the presence and absence of immune responses [118–120]. Researchers [118] also studied the effects of OVT in mice using mathematical modeling. Their model provided an excellent fit to the temporal data of tumour given in a previous study [116]. A viable in silico platform and exact biological parameters were reported by other investigators [118], which can be used to further investigate potential OVT protocols.

Recent developments in the modelling of OVT dynamics and viral genetic engineering made it possible to estimate the ideal viral dosages that should be provided in order to maximise the efficacy of the therapeutic interventions. However, OVT has not been substantially investigated in the context of control theory. Particularly in the context of model predictive control (MPC), the ideal sequence of inputs is determined by minimising a cost function over the course of a prediction horizon while also meeting system limitations. The virus input and the positivity of states both serve as restrictions in OVT. Moreover, because the input is of limited duration in terms of sampling time, the OVT therapy may be considered as a form of impulsive control system (ICS) [121]. As a result, a continuous

or discrete virus injection estimate tends to be less accurate than a corresponding impulsive representation [121,122]. Impulsive control solutions have been developed for a variety of biomedical applications such as influenza [123,124], type 1 diabetes therapy [125], HIV [126] and many more. There have been several studies on ICS in the MPC environments [127]. In order to compensate for the effects of plant-model mismatch, researchers [128] created an impulsive offset-free MPC that was not dependent on the plant model. Figure 12 depicts a nonlinear MPC framework incroporating an impulsive control system for cancer tumor eradication using oncolytic virses.

Similar research [129] has explored such nonlinear modelling for real-time OVT estimation and control. This model represented virus injection in the form of an impulse. In order to correlate with the sampling time for tumour volume measurements, this impulse was initially generated every two days. The subject's state was estimated by feeding this discrete measurement into a hybrid extended Kalman filter (hEKF). This was followed by an impulsive nonlinear MPC (iNMPC) design to determine the optimal virus dosage for minimizing the number of tumour cells. The findings of this impulsive nonlinear MPC approach were compared to those obtained from prior studies [116,121]. To calculate optimal viral doses, the suggested system employed a mathematical model that produced better and faster tumour regression than previous protocols. This model's effectiveness was also examined under different system uncertainties, such as dynamic biological parameters. This technique provided individualised therapy that was resilient to parameter and modelling uncertainties.

The purpose of oncolytic virus treatment is to treat cancer by using viruses as therapeutic agents. There are several clinical difficulties that must be addressed before this potential therapy may be used, including dose issues, toxicity, and unknown tumour dynamics. In order to increase the knowledge of treatment outcomes and build better therapeutics, mathematical models can be employed to characterise the interactions between oncolytic viruses and cancer cells. As a result of the pressing need to enhance clinical results, a nonlinear estimate and control method based on impulsive control theory has been presented by the studies (discussed above) for determining the appropriate/optimal doses of viral injections.

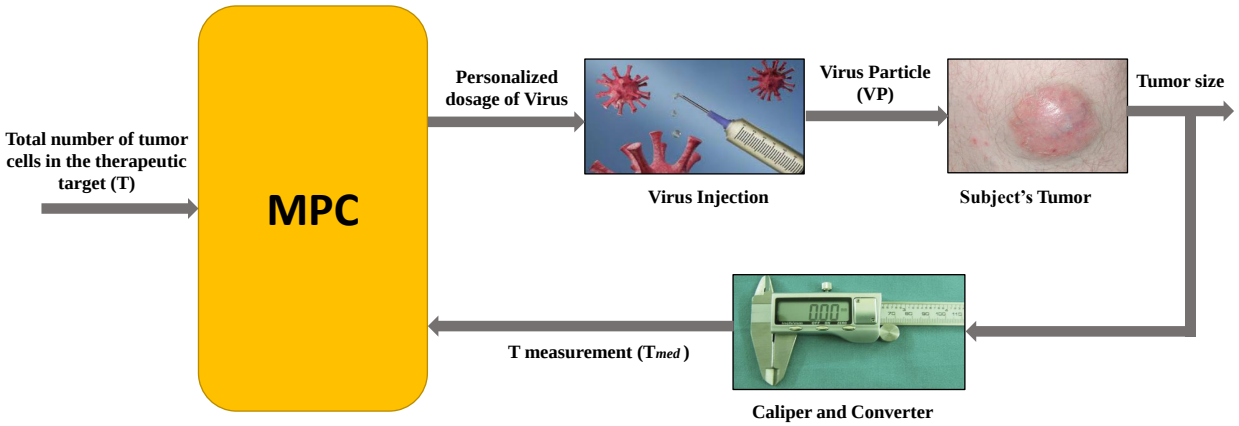

Figure 12. Tumor eradication by the employment of oncolytic viruses in conjunction with an impulsive nonlinear estimating and predictive control strategy.

3.5.2. Hyperthermia Therapy

Mild hyperthermia is a non-toxic therapy process for the treatment of cancer cells. The process involves heating specific targeted tissues of the body, usually consisting of the surroundings of the tumor cells, to temperatures of 39 to 45 degree Celsius for up to 90 min. The rest of the patient body is kept at the normal functioning temperature. Various research trials have established hyperthermia as an effective cancer therapy [130]. For instance, hyperthermal therapy displayed a complete response in cervical cancer-

diagnosed human subjects under randomized Phase III trials [131]. In fact, the results of these trials showed an approximately double complete-response rate in comparison to that of radiation therapy. Hyperthermia therapy has proven effective in attaining higher control of metastatic or recurrent malignant melanoma [132] and other tumors as well [133]. Hyperthermic treatment involves the temporal cumulative application of elevated temperatures on the target tissues. In this therapy, the relationship between time and temperatures is established using the relationship given by Arrhenius [134]. In-treatment temperatures are typically monitored using catheterized point-wise temperature sensors placed at certain discrete points of/around the tumor [135,136]. Non-invasive magnetic resonance temperature measurements are employed to obtain a more detailed spatial temperature distribution [13,137].

However, extended hyperthermic treatments cause patient discomfort, leading to non-sustained temperature levels. Moreover, during these treatments, maintaining the desired thermal dose is challenging due to unknown and altering body fluid rates and other various factors not taken into consideration. One of the solutions to these issues is to apply higher temperature (about 57 degree Celsius) for a shorter duration [138–141]. Such high-power, short-duration therapies include high-temperature hyperthermia, coagulation necrosis and thermal ablation therapy. Magnetic resonance-guided high-intensity focused ultrasound (MR- HIFU) is one of the most prominent technologies deployed for such treatments. Appropriate feedback controllers are needed to maintain the desired thermal distribution over the duration of the therapy despite unknown disturbances and plant-model mismatch. Therefore, MR-HIFU implementations include feedback controller-assisted temperature control schemes. These control schemes typically include binary strategies to regulate the sonic intensities and radiation durations using PID-based models. The major drawbacks associated with these controllers are their default constraints and incapacity to consider the future thermal behavior of the patient body. Hence, proportional, multipoint adaptive and linear quadratic regulator control systems have also been used for simulating temperature control during hyperthermia treatments [142]. However, these control systems are typically designed around standard hyperthermia treatments. In a real-life scenario, a tissue at a high temperature continues to acquire thermal dosage even after the radiation is switched off. This indicates an integral relationship between temperature and dose. Hence, the control mechanism should consider predicting future temperature values to prevent overdose.

In this regard, MPCs can provide optimum control in hyperthermal treatments. Researchers have suggested MPCs as a superior scheme to control thermal dose parameters while considering multiple heating locations and intensities simultaneously [130]. The contributing variables make it difficult to sustain a specified temperature in the spatial distribution of the target tissue. Hence, the solution to the problem is to reduce the number of control parameters using an MPC. Investigators [142] developed a model-based thermal dose controller for hyperthermia treatment explicitly based on a dynamic patient model that predicted the future thermal dosage. This model also computed optimum corrective actions to minimize output errors and control costs. Precise temperature control in the target tissue is the major factor affecting the quality of treatment in the case of local hyperthermia. Researchers [143] have explored an MPC algorithm providing voxel-level temperature control in MR-HIFU hyperthermal treatment. In this method, the system state variables, i.e., voxel temperatures, were measured at all sampling instants. Appropriate control actions were determined for the subsequent instants based on the system state variables of the previous instant. These control actions were aimed to minimize deviations from the desired temperatures of the target region voxels. More investigations are needed to further improve the efficacy of MPC-led automated hyperthermia therapies.

4. Conclusions and Future Scope

The present study presents a brief review of published research reporting MPC-led therapeutic automation in some biomedical conditions such as type 1 diabetes (including artificial pancreas), anaesthesia, fibromyalgia, HIV, and cancer (including oncolytic viral

treatment and hyperthermia). A detailed review of MPC evolution, architectures, methodology, advantages, limitations, categories, implementation and softwares has also been presented. Automated therapeutic systems are sorely needed by medical professionals worldwide for the following reasons:

- Better efficiency over manual monitoring and control;
- Automated and optimized drug delivery based on dynamic monitoring of therapeutic and patients' bio-parameters;
- Minimization of unintended under- or over-dosing;
- Real-time data-based decision support to medical personnel;
- Routine workload reduction of medical personnel;
- Cost effectiveness by minimizing repetitive treatments.

Patient safety is the driving force behind the need for the wider implementation of automation in clinical therapeutic delivery. Medical specialists can concentrate on high-value jobs while computer-based drug delivery can manage routine tasks.

Over the past few decades, researchers have explored MPC-led blood glucose level regulation, the automation of insulin delivery in blood, target controlled aneasthesia infusion, impulsive oncolytic viral therapy for treating cancer, structured treatment interruptions to increase immunological responses to HIV, and more. However, from the point of view of the variety of issues being addressed and related to real-time applications, the field of automated biological therapeutic systems is still in its infancy. Hence, there is a vast scope to develop closed-loop control for biomedical therapy systems in a way that they can be translated into workable and scalable technologies. In this scenario, the MPC's receding horizon control concepts are particularly suited for effective medication delivery control. In particular, there is a large research scope in the MPC-based effective automation of hyperthermia therapy for cancer treatment, as well as that of adaptive intervention therapy for fibromyalgia. Currently, there is very limited research literature available that addresses these niche topics. Hence, this future scope is open to all MPC and biomedical therapeutic automation researchers.

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