An Automated Ambulatory Duodopa Pump: A Sliding Mode Control Approach

Pravika Malangandi (pravika.m@gmail.com)
Calicut Regional Engineering College: National Institute of Technology Calicut
JEEVAMMA JACOB
Calicut Regional Engineering College: National Institute of Technology Calicut
PAUL JOSEPH Kunnel
Calicut Regional Engineering College: National Institute of Technology Calicut

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AN AUTOMATED AMBULATORY DUODOPA PUMP: A SLIDING MODE CONTROL APPROACH

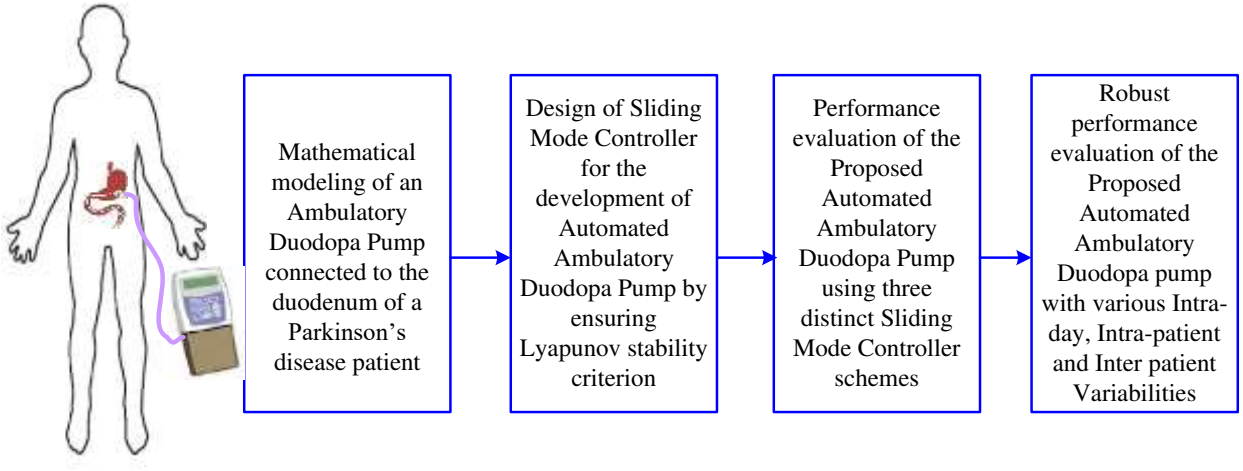
Pravika. Malangandi*, Jeevamma Jacob, Paul Joseph Kunnel

Department of Electrical Engineering, National Institute of Technology, Calicut, Kerala 673601, India

Email: *pravika.m@gmail.com

Abstract- Around ten million people in the world are affected by Parkinson's disease (PD), accounting for about less than 1% of the global population. The rising prevalence of PD draws attention to the growing individual and social cost, as well as the urgent need for efforts to enhance the quality of life of the patient. The automation of the conventional ambulatory Duodopa pump (ADP) is the most challenging aspect of dopamine therapy for PD due to a range of unanticipated external events. In this regard, the goal of this paper is to develop a robust control strategy specifically, a sliding mode controller (SMC) scheme for a newly designed ADP to ensure optimal drug therapy. The proposed ADP is modeled by cascading the mathematical model of linear electromechanical actuator (EMA), drug infusing syringe pump in tandem with the dose-effect relationship of Levodopa and continuous dopamine sensor (CDS). While traditional SMC is liable to induce numerical chattering, smooth SMC (SSMC) and an integral SMC (ISMC) are designed to minimize chattering by maintaining accuracy in set-point tracking of plasma dopamine concentration. The *in-silico* results described in this paper persuasively confirm that the SSMC and ISMC supersede the traditional one in numerous key ways: chattering in the control input is nearly non-existent, fast-tracking performance, and good transient response. A robust stability evaluation with ISMC reveals that it can accommodate only a small cohort with less inter-patient variability, but its overall performance in terms of chattering reduction and set-point tracking is superior to that of traditional SMC and SSMC.

Graphical Abstract



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Abbreviations

ADP	Ambulatory Duodopa pump
CDS	Continuous dopamine sensor
CNS	Central nervous system
COMT	Catechol-O-Methyltransferase
DDC	DOPA decarboxylase
EMA	Electromechanical actuator
IAE	Integral absolute error
ISE	Integral square error
ISMC	Integral sliding mode controller
MAO-B	Monoamine Oxidase Type B
MRA	Model reference adaptive
PA	Pharmacological activation
PD	Parkinson's disease
PDs	Pharmacodynamics
PDP	Portable Duodopa pump
PEG	Percutaneous endoscopic gastrostomy
PKs	Pharmacokinetics
PSD	Power spectral density
PSO	Particle swarm optimization
RMSE	Root mean square error
SMC	Sliding mode controller
SSMC	Smooth sliding mode controller

1. Introduction

Parkinson’s disease is a chronic degenerative, heterogeneous disease that causes deterioration of the central nervous system (CNS) specifically basal ganglia, and consequently requires constant and adequate treatment throughout life. PD disturbs many neurotransmitter systems in addition to several complex brain circuitry involving multiple hoops and inhibitory networks, and exhibiting a wide spectrum of motor and non-motor symptoms [1,2]. Over the past few decades, the attention of pathological study of PD has been focused on the neuronal deficit in the nigrostriatal

dopamine alleyway. Research on this complex disease has thrived and brought out epic improvements in understanding the biochemistry, anatomy, and physiology of basal ganglia as well as pharmacology of the dopaminergic system paving way for the treatment of PD [3,4].

After years of research and development, it is found that Levodopa is still the gold standard in PD treatment, and it can temporarily top-up the dopamine hoard in the nigrostriatal pathway [5]. However, there are a variety of different medicines available, each with its own set of side effects, contraindications, and problems. Over 99% of orally administered Levodopa is metabolized peripherally without crossing the blood-brain barrier and the resulting high peripheral concentrations of dopamine consequences opposing effects comprising vomiting, nausea, hypotension, and cardiac dysrhythmias. Thus, Levodopa is always used in amalgamation with DOPA decarboxylase (DDC) inhibitors and or Catechol-O-Methyltransferase (COMT) inhibitors to increase its bioavailability, which in turn results in elevated brain dopamine concentration rather than in the periphery. However, the patient who has been steadied on a therapeutic regimen may experience a recurrence of symptoms within 5 years due to the wearing-off phenomenon of pharmacological effect among doses [6]. The reemergence of symptoms may not be recognized in the beginning, which unnecessarily delays the implementation of an efficient pharmacotherapy for effectively managing the symptoms. Dystonia and dyskinesia are the two treatments related to motor complications that occur due to a high concentration of Levodopa, quite above the maximum safe level.

Numerous treatment-allied non-motor manifestations are also associated with PD, which are categorized as autonomic, cognitive/neuropsychiatric and sensory, where the frequency of further symptoms is interconnected with the progression of the disease. However, the non-motor symptoms are less frequently linked to the phenomenon of wearing off. Viable pharmacologic strategies used for handling wearing-off symptoms may comprise the addition of Monoamine Oxidase Type B (MAO-B) inhibitors, dopamine agonists, and COMT inhibitors [7]. These strategies can uphold continuous dopamine stimulation in an extended period by delaying the breakdown of dopamine in the brain, by providing a longer half-life than Levodopa, or by increasing the concentration of Levodopa inside the CNS. However, adverse effects related to these strategies are severe and necessitate a new approach for increasing dopamine concentration in the brain by continuous controlled release of the drug.

There are enhanced treatment options such as transdermal infusion of Levodopa [8], subcutaneous or intravenous infusion of Apomorphine [9,10], intraduodenal infusion of Duodopa [11] as well as deep brain stimulation (DBS) [12]. It is evident from the previously reported clinical studies and *in-silico* evaluations that a conceding equilibrium is possible between the optimum symptom relief and least side effects in intraduodenal infusion compared to the other methods in terms of bioavailability, absorption time, peak time, risk factors, and the opportunity for continuous accurate drug supply [13,14]. The beneficial effect offered by intraduodenal infusion of Duodopa demands a surgical procedure known as percutaneous endoscopic gastrostomy (PEG) [15].

Nowadays, the monotherapy with Duodopa has eased continuous duodenal infusion through PEG-Jejunal (PEG-J) tube by a portable Duodopa pump (PDP) for which the sanction has been accorded by the food and drug administration (FDA) in 2015. This procedure results in less variability in Levodopa level, lesser motor instabilities, and dyskinesia as compared to previously reported pharmacological strategies[16]. Nevertheless, the traditional open-loop PDP has certain downsides such as a precise amount of Duodopa infusion before physical activity, high

protein meals and disease progression is a burden as far as the patient is concerned, even though ambulatory medical therapy has been facilitated. In this situation, an 'artificial substancianigra', known as closed-loop control of dopamine in PD, is a good remedy, which requires three basic components namely CDS, controller, and Duodopa infusion pump [14]. A subcutaneous closed-loop control of Levodopa for maintaining steady plasma Levodopa concentration has already been reported in [17]. However, controlling plasma dopamine concentration instead of plasma Levodopa concentration can provide superior performance as presented in [18], where the drug infusion rate varies according to the current plasma dopamine level. This is promising, since many publications report that certain strong correlations exist between neurochemicals like dopamine in blood plasma and the brain [19–21]; but the empirical relationship is unknown.

An automated ambulatory Duodopa pump is already proposed with a PID controller which suppresses most of the hitches related to conventional one. Even though PID controller offers optimal drug delivery as well as adequate robustness, unacceptable under/overshoots and inadequate settling times are existing in the response under various disturbances. Therefore, to overcome this difficulty, a model reference adaptive-PID (MRA-PID) controller utilizing MIT rule is employed in [22], which offers superiority in terms of steady-state error as well as undershoots. Additionally, a positive displacement piston type drug dispensing syringe connected to the duodenum of the PD patient thru a PEG-J tube has been modeled by using Hagen-Poiseuille law and Bernoulli's equation. The precise and accurate operation of the actuator has a significant impact on the safety and longevity of an automated pump. As a result, the mathematical modeling of linear EMA in combination with a piston-type syringe pump has already been accomplished [23]. Although the MRA-PID controller's overall performance is higher in terms of over/undershoots and settling time, the study identifies areas for improvement for the total eradication of disturbance effects. As a result, the current study proposes SMC due to its efficiency in handling bounded and matched disturbances. In the presence of bounded disturbance, SMC drives the state variables to a predesigned sliding surface in a finite period and then maintains them there. As a result, the closed-loop response is completely insensitive to a certain class of uncertainty, such as external disturbances, parametric variations, and unmodeled dynamics. This invariance property obviously qualifies the methodology as suitable for robust control. Therefore, SMC has attracted immense research interests for a range of applications, including robotics [24], servo tracking systems [25], motor speed control [26], unmanned aerial vehicles [27], and artificial pancreas [28], etc.

This paper is novel in two respects: first, a completely automated ADP has been modeled by cascading the mathematical model of linear EMA, drug dispensing syringe pump in tandem with the dose-effect relationship of Levodopa and dopamine sensor. Second, SMC is proposed for the system to achieve robust performance. In the first contribution, the entire system under control is represented in state-space form. As the succeeding contribution, this paper evaluates the performance of an automated ADP using three distinct SMC schemes: traditional SMC, SSMC, and ISMC. The SSMC approach uses a saturation function instead of signum function in the control algorithm for reducing chattering, which is prevalent with traditional SMC. In ISMC, an integral dynamics is added to the traditional sliding surface while tracking a reference signal to reduce chattering as well as steady-state errors. To ensure the stability of the closed-loop system, the Lyapunov criteria are followed. The robust performances of the

automated ADP are evaluated against intra-day, intra-patient and inter patient variability with three different SMC schemes.

This paper is prepared as follows. In Section 2, the proposed methodology, dynamics of proposed ADP, and the design of three SMC schemes are presented. Section 3 is dedicated to the results and discussion: the *in-silico* analysis of open-loop system, closed-loop control system under intra-day, intra-patient, inter-patient variability. In Section 4, the conclusion brings this paper to an end.

2. Materials and Methods

2.1 Methodology

The configuration incorporating the key components of a closed-loop medication delivery system for the treatment of PD is depicted in Fig.1. A CDS in the feedback pathway of an automated ADP serves an essential function in monitoring the plasma level of dopamine. However, since CDS is not commercially available for real-time measurement, its implantation in the patient's body is still a major challenge. The SMC connects the CDS to the drug infusion mechanism and estimates the required medicine concentration based on the patient's current physiological condition. The proper control signal then activates the linear EMA, which forces the drug infusion pump to administer the required quantity of medication to the duodenum until the error is zero. The critical challenge for an automated ADP is to offer effective control in the face of various perturbations, such as patient sensitivity variations, external disturbances, time delays, and noise. The virtual physiological model of the patient comprises Levodopa's pharmacokinetics (PKs), pharmacological activation (PA), and pharmacodynamics (PDs). The drug delivery pump as well as the PKs and PA of Levodopa are all part of a larger system that must be kept under control. The smartphone appears to be an excellent candidate for implementing a control system due to its wireless capabilities.

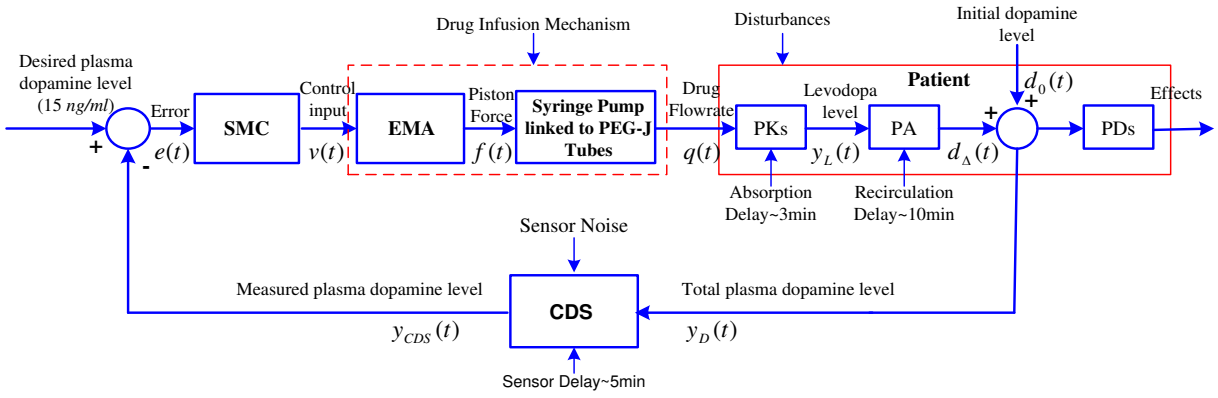

Fig.1 Block diagram of closed-loop dopamine control scheme in PD treatment

2.2. Mathematical modeling of ADP

The mathematical model of the system includes the dynamics of linear EMA [23], dynamics of the drug dispensing syringe connected to the duodenum through PEG-J tubes [22], virtual physiological model of PD patient and the

dynamics of CDS [18], as shown in Fig.1. The overall system under control consideration is linear time-invariant (LTI) in nature and is represented in state space form as,

$$\dot{x_1}(t) = (K_{CDS} y_D(t-\tau_3) - x_1(t))/T_{CDS}$$

$$\dot{x_2}(t) = x_3(t)$$

$$\dot{x_3}(t) = (q(t-\tau_1)K_{PK} - x_2(t) - 0.66203\, x_3(t))/0.03324 \quad (1)$$

$$\dot{x_4}(t) = 7.8x_5(t)$$

$$\dot{x_5}(t) = 7.8x_6(t)$$

$$\dot{x_6}(t) = 795.84v(t) - 9.59 \times 10^{-5}x_4(t) - 47.38x_5(t) - 35.12x_6(t)$$

$$d_\Delta(t) = K y_L(t-\tau_2) \quad (2)$$

$$y_D(t) = d_\Delta(t) + d_0 \quad (3)$$

$$q(t) = \left(\frac{\pi(D_1)^4}{8\mu L A_1}\right) f(t) \quad (4)$$

$$f(t) = \eta\left(\frac{2\pi}{l}\right) t_L(t) \quad (5)$$

$$t_L(t) = 4.04 \times 10^{-9}x_4(t) + 8.08 \times 10^{-4}x_5(t) + 6.08 \times 10^{-5}x_6(t) \quad (6)$$

The resulting system parameters/variables and their descriptions are listed in Table 1. The state variables x_1, x_2, x_3, x_4, x_5 and x_6 represent $y_{CDS}, y_L, \dot{y_L}, \theta_L, \dot{\theta_L}$ and $\ddot{\theta_L}$ respectively. In the current work, the intra-duodenal pressure as well as the total pressure loss inside the dispensing system is assumed to be zero.

Table 1 Description of proposed ADP model parameters/variables

Variables/ Parameters	Description	Typical Values	Unit
$\boldsymbol{y_L(t)}$	Plasma level of Levodopa	-	ng/ml
$\boldsymbol{y_D(t)}$	Total plasma level of dopamine	-	ng/ml
$\boldsymbol{y_{CDS}(t)}$	Sensor dopamine	-	ng/ml
$\boldsymbol{d_0(t)}$	Natural plasma dopamine level in PD case	0-10	ng/ml
$\boldsymbol{d_\Delta(t)}$	Change in dopamine level due to drug infusion	-	ng/ml
$\boldsymbol{T_{CDS}}$	Time constant of the sensor	0.01	min
$\boldsymbol{K_{CDS}}$	Gain of the sensor	1	-
K_{PK}	Pharmacokinetics model gain	1418	-
$\boldsymbol{K}$	Levodopa to dopamine conversion factor	0.004	-
$\boldsymbol{\tau_1}$	Absorption time delay	3	min
$\boldsymbol{\tau_2}$	Recirculation time delay	10	min
$\boldsymbol{\tau_3}$	Sensor time delay	5	min
$\boldsymbol{L}$	Length of the conduit	0.95	m
$\boldsymbol{\mu}$	Dynamic viscosity of the drug	1.753×10^{-5}	$Pa.min$
$\boldsymbol{D_1}$	Diameter of the syringe	0.036	m
$\boldsymbol{A_1}$	Area of the cross-section of the syringe	9.949×10^{-4}	m^2
$\boldsymbol{f(t)}$	Axial force applied on the piston	-	N
$\boldsymbol{q(t)}$	Flow rate of the drug	-	mg
$\boldsymbol{l}$	Lead of the screw	0.03	m

η	Efficiency of the screw	38.32	-
$\boldsymbol{t_L(t)}$	Load torque in the EMA	-	Nm
$\boldsymbol{v(t)}$	Actuator input voltage	-	V
$\boldsymbol{\theta_L(t)}$	Angular displacements of the lead screw	-	rad

2.3 Design of SMC

The SMC premised on discontinuous control law is one of the most successful and robust approaches for controlling dynamical systems with bounded and matched disturbances. From a design standpoint, the ability to directly specify performance makes the SMC desirable. This section discusses three different SMC schemes: traditional SMC, SSMC, and ISMC, as well as their design and closed-loop performances.

2.3.1 SMC

In the context of SMC [29], there are two sequential modes in control dynamics: reaching mode and sliding mode. Therefore mainly two phases are involved in the design of SMC such as,

(1) Design of sliding surface such that the system trajectory exhibits desirable characteristics when confined to it.

(2) Design of discontinuous feedback gains such that the system trajectory intersects and stays on the sliding manifold.

In the current work, the output, the plasma dopamine concentration is to be maintained at a predefined value in the presence of various unexpected external disruptions such as unannounced meals, physical activity, mood fluctuations, various drug interactions, drug sensitivity variations, and progression of PD. Any deviation causes an error, which should be driven to zero.

Therefore, the sliding manifold designed for SMC in the current work is given by,

$$S_T(e,t) = c_1 e(t) + c_2 \dot{e}(t) + c_3 \ddot{e}(t) + \dddot{e}(t) \tag{7}$$

Where c_1, c_2 and c_3 must satisfy the Hurwitz condition and $e(t)$ denotes the tracking error. In this work, the set-point value of plasma dopamine concentration is $15 ng/ml$. Therefore, the tracking error is given by,

$$e(t) = 15 - y_{CDS}(t) \tag{8}$$

The existence condition of SMC requires that the state trajectory should be driven to the sliding manifold $s_T(e,t) = 0$; or at least in the neighborhood of sliding manifold. Specifically, the system trajectory must approach the sliding manifold asymptotically. The reaching condition of SMC is denoted as;

$$\lim_{s_T \to 0^+} \dot{s_T} < 0, \lim_{s_T \to 0^-} \dot{s_T} > 0, i.e., s_T \dot{s_T} < 0, \tag{9}$$

In order to ensure the arrival within finite time and to avoid asymptotic approximation, Eq. (9) can be modified as,

$$\begin{cases} \dot{s_T} > \varepsilon, s_T < 0 \\ \dot{s_T} < \varepsilon, s_T > 0 \end{cases}, \quad i.e., s_T \dot{s_T} < -\varepsilon |s_T| \tag{10}$$

where, $\varepsilon > 0$ which is a neighborhood of the sliding manifold. The smaller the value of ε, the state is more constrained to the actual sliding manifold, which enables the system state point to reach the sliding manifold in finite time. Therefore, the existence problem can be seen as a generalized stability problem. In order to ensure the stability

of the system, the second method of Lyapunov has been used. For that, consider a positive definite Lyapunov function as given by,

$$V_T(e,t,s_T) = \frac{1}{2}{s_T}^2 \tag{11}$$

Therefore, $\dot{V}_T(e,t,s_T)$ can be derived as;

$$\dot{V}_T(e,t,s_T) = s_T\left[c_1\dot{e}(t) + c_2\ddot{e}(t) + c_3\dddot{e}(t) + \left[\frac{\ddot{x}_1 - \frac{K_{CDS}}{0.033}K\left[K_{PK}\left(\frac{\pi(D_1)^4}{8\mu LA_1}\right)\left(\eta\left(\frac{2\pi}{l}\right)\right)\left[4.04\times10^{-9}[795.8v(t)+z_1(t)]+z_2(t)\right]+z_3(t)\right]}{T_{CDS}}\right]\right] \tag{12}$$

where $z_1(t) = -9.59\times10^{-5}x_4(t) - 47.38x_5(t) - 35.12x_6(t)$, $z_2(t) = 8.08\times10^{-4}\dot{x}_5(t) + 6.08\times10^{-5}\dot{x}_6(t)$ and $z_3(t) = -\dot{x}_2(t) - 0.66203\dot{x}_3(t)$.

Where the control law, $v(t)$ incorporates two components such that,

$$v(t) = v_{eq}(t) + v_r \tag{13}$$

where v_r is the reaching control law, which is used to drive the system states to the sliding manifold and $v_{eq}(t)$ is the equivalent control law that is desirable to keep the system states on the sliding manifold even in the presence of various uncertainties.

In the current work, an exponential reaching law [26] is used and it is given by,

$$\dot{s}_T(e,t) = -\varepsilon sgn\ s_T(e,t) - ks_T(e,t), \quad \varepsilon > 0, k > 0 \tag{14}$$

Now, $v(t)$ can be derived by equating Eq. (14) with first derivative of Eq.(7) and it is obtained as,

$$v(t) = \frac{T_{CDS}[\varepsilon_1 sgn\ s_T(e,t)+ks_T(e,t)+c_1\dot{e}(t)+c_2\ddot{e}(t)+c_3\dddot{e}(t)]+\ddot{x}_1-\frac{K_{CDS}}{0.033}K\left[K_{PK}\left(\frac{\pi(D_1)^4}{8\mu LA_1}\right)\left(\eta\left(\frac{2\pi}{l}\right)\right)\left[4.04\times10^{-9}[z_1(t)]+z_2(t)\right]+z_3(t)\right]}{K_{PK}K\left(\frac{K_{CDS}}{0.033}\right)\left(\frac{\pi(D_1)^4}{8\mu LA_1}\right)\left(\eta\left(\frac{2\pi}{l}\right)\right)(4.04\times10^{-9}\times795.8)} \tag{15}$$

Substituting Eq. (15) in Eq.(12) gives,

$$\dot{V}_T(e,t,s_T) = s_T[-\varepsilon sgn\ s_T(e,t) - ks_T(e,t)] \tag{16}$$

$$= -\varepsilon|s_T| - k{s_T}^2 < 0$$

This condition together with Eq.(10) guarantees that every state trajectory converges to the sliding manifold with in finite time, and thus the tracking error approaches zero, or at least close to zero.

Despite the benefits of SMC, one of the most well-known problems is the chattering phenomenon that has been mentioned in literature. The chattering present in SMC when used in automated ADP may affect the performance of linear-EMA, resulting in low control precision, severe wearing off of moving components, and large heat losses in power circuits. Many variants of chattering alleviation techniques for the SMC are discussed in [30,31]. SSMC and ISMC are the most straightforward designs among them.

2.3.2 SSMC

By replacing the standard signum function with a saturation function in the control strategy, SSMC can effectively suppress the chattering phenomenon and can keep the system states inside a preset range, Δ in the vicinity of the sliding manifold $s_T = 0$. The usage of switching control exterior to the boundary layer and typical feedback control within the boundary layer distinguishes a saturation function, which is exposed in Eq. (17). As a result, the problem of buffering may be efficiently managed.

$$sat(s_T) = \begin{cases} 1 & s_T > \Delta \\ k_s s_T & |s_T| \leq \Delta, k_s = \frac{1}{\Delta} \\ -1 & s_T < -\Delta \end{cases} \tag{17}$$

Therefore, in SSMC Eq. (14) is modified as,

$$\dot{s}_T(e,t) = -\varepsilon\, sat\left(s_T(e,t)\right) - k s_T(e,t), \quad \varepsilon > 0, k > 0 \tag{18}$$

$v(t)$ can be derived as,

$$v(t) = \frac{T_{CDS}[\varepsilon_1 sat\, s_T(e,t) + k s_T(e,t) + c_1 \dot{e}(t) + c_2 \ddot{e}(t) + c_3 \dddot{e}(t)] + \ddot{x}_1 - \frac{K_{CDS}}{0.033} K \left[K_{PK}\left(\frac{\pi(D_1)^4}{8\mu L A_1}\right)\left(\eta\left(\frac{2\pi}{l}\right)\right)[4.04\times10^{-9}[z_1(t)] + z_2(t)] + z_3(t)\right]}{K_{PK} K\left(\frac{K_{CDS}}{0.033}\right)\left(\frac{\pi(D_1)^4}{8\mu L A_1}\right)\left(\eta\left(\frac{2\pi}{l}\right)\right)(4.04\times10^{-9}\times 795.8)} \tag{19}$$

Substituting Eq. (19) in Eq. (12) gives,

$$\dot{V_T}(e,t,s_T) = s_T\left[-\varepsilon sat\left(s_T(e,t)\right) - k s_T(e,t)\right] \tag{20}$$

$$= -\varepsilon|s_T| - k {s_T}^2 < 0 \text{ or } -\varepsilon(k_s {s_T}^2) - k {s_T}^2 < 0$$

As a result, the aforementioned condition, when coupled with Eq.(10), ensures the finite time convergence of the system trajectory to the sliding manifold $s_T = 0;$ or at least in the neighborhood of sliding manifold from any initial condition.

2.3.3 ISMC

The integral control action is one of the most prominent tactics in feedback control applications since it reduces persistent steady-state inaccuracy present in the closed-loop system response. An integral dynamics is added to the sliding surface of traditional SMC to reduce chattering and steady-state offset in tracking a set-point value under various perturbations and uncertainties. In this study, the order of equation for the sliding surface is considered to be less than that of the original system. As a result, the ISMC's invariance is not guaranteed during the reaching phase. The sliding manifold designed for ISMC in the current work is represented by,

$$S_I(e,t) = S_T(e,t) + c_4 \int e(t)dt \tag{21}$$

It is obvious that Eq. (10) is valid for the sliding surface, S_I as well. For stability analysis the succeeding Lyapunov function is chosen,

$$V_I(e,t,s_I) = \frac{1}{2} {s_I}^2 \tag{22}$$

Therefore,

$$\dot{V}_I(e,t,s_I) = s_I\left[c_1\dot{e}(t) + c_2\ddot{e}(t) + c_3\dddot{e}(t) + c_4 e(t) + \left[\frac{\ddot{x}_1 - \frac{K_{CDS}}{0.033}K\left[K_{PK}\left(\frac{\pi(D_1)^4}{8\mu LA_1}\right)\left(\eta\left(\frac{2\pi}{l}\right)\right)[4.04\times10^{-9}[795.8v(t)+z_1(t)]+z_2(t)]+z_3(t)\right]}{T_{CDS}}\right]\right] \quad (23)$$

The exponential reaching rule is utilized here as well, and $v(t)$ is derived as,

$$v(t) = \frac{T_{CDS}[\varepsilon_1 sgn\, s_I(e,t)+ks_I(e,t)+c_1\dot{e}(t)+c_2\ddot{e}(t)+c_3\dddot{e}(t)+c_4e(t)]+\ddot{x}_1-\frac{K_{CDS}}{0.033}K\left[K_{PK}\left(\frac{\pi(D_1)^4}{8\mu LA_1}\right)\left(\eta\left(\frac{2\pi}{l}\right)\right)[4.04\times10^{-9}[z_1(t)]+z_2(t)]+z_3(t)\right]}{K_{PK}K\left(\frac{K_{CDS}}{0.033}\right)\left(\frac{\pi(D_1)^4}{8\mu LA_1}\right)\left(\eta\left(\frac{2\pi}{l}\right)\right)(4.04\times10^{-9}\times795.8)} \quad (24)$$

It is deduced from the preceding equations that,

$$\dot{V}_I(e,t,s_I) = s_I[-\varepsilon sgn\, s_I(e,t) - ks_I(e,t)] \quad (25)$$

$$= -\varepsilon|s_I| - ks_I{}^2 < 0$$

This condition, when combined with Eq. (10) for the sliding surface, S_I ensures that every state trajectory converges to the sliding manifold in finite time and is constrained at least in the neighborhood of the manifold for all subsequent time.

3. Results and Discussion

This section is devoted to evaluating the performance of the proposed automated ADP through various measurable indices. The open-loop response of the pump connected to the duodenum of the PD patient is appraised first and the closed-loop response of the entire system with the proposed control strategy is analyzed later by *in- silico* studies.

3.1 *In-silico* analysis of the open-loop response

Figure 2 depicts the time domain response of a PD patient with the aid of an ADP in an open-loop setting. According to the waveform shown in Fig. 2(a) and 2(i), a motor input voltage of $4.9\,V$ for one minute is necessary to elevate the plasma level of dopamine from $4ng/ml$ to $19ng/ml$. The equivalent values of armature current, angular position, load torque, piston force, linear displacement, and drug flow rate are $0.72A, 6.28rad, 0.0056\,Nm$, $0.447N, 0.03m$, and $17.84\,mg$ respectively as shown in Fig 2(b) to 2(g). The related variations in plasma Levodopa, plasma dopamine, and sensor dopamine levels are presented in Fig. 2(h) to 2(j) respectively. In this study, the nominal input voltage for the DC servo motor selected in the EMA is $6V$, and the magnitude and durability of the motor input voltage are used to control the piston displacement, facilitating the required amount of medicine to flow directly into the duodenum. When the motor input voltage increases, the armature current increases as well, with $1A$ and $0.6A$ being the highest permitted and no-load values of armature current, respectively, according to the DC motor specification. Only forward motion of the motor is described in the current work for propelling the medication by pushing the piston into the syringe drum, where the drug is housed. The piston force varies with the amount of medication required and moves in micro increments forward as shown in Fig. 2(f). If no drug is needed, the piston has no displacement. As a result, under the current methodology, reverse piston movement is not necessary, and hence the well-known hysteresis phenomenon in EMA is not discussed.

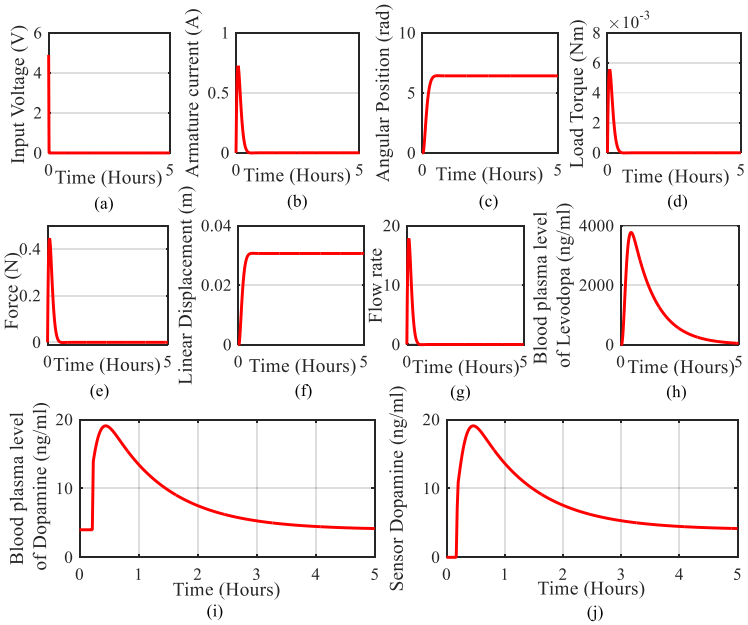

Fig.2 Open-loop response of ADP linked to a PD patient.

3.2 *In-silico* analysis of *the* closed-loop response

Even though there are disparities between static characteristics of the simulation model and time-varying dynamics of the patient, an *in-silico* assessment is obligatory for verification and validation of the proposed control strategy and is a prerequisite for *in-vivo* testing during clinical trials. This approach determines the controller's performance in terms of reliability and confinement.

The transient response of an automated ADP under SMC, SSMC, and ISMC is exemplified in Fig.3 and the time domain performance indices are compared in Table 2. The particle swarm optimization (PSO) method is used to optimize the controller parameters and the performance measure (PM) used is given by,

$$\mathrm{PM} = \left((1 - \exp(-\beta))\mathrm{M_p}\right) + \left(\exp(-\beta)\,(\mathrm{T_s} - \mathrm{T_r})\right) \tag{26}$$

where $\mathrm{M_p}$, $\mathrm{T_s}$, $\mathrm{T_r}$, and β are the peak overshoot, settling time, rising time, and scaling factor derived from the response in each iteration, and the best point in PSO is reached when PM achieves its lowest value [18].

The presence of discontinuous function in SMC causing an unwanted oscillation with limited frequency and amplitude, known as 'chattering,' is evidenced in Fig.3 (a) with SMC. In a real-time application, the chattering of SMC may harm system components like actuators in the ADP in such a way that the rapid back and forth movement of lead-screw mechanism may cause a backlash, misalignment, lock-up or loose fault and, if protracted, the mechanical failure of the entire system may happen. Furthermore, the continuous switching of piston force consequences a gradual rise in piston displacement, resulting in more medication being injected into the duodenum as shown in Fig.3(f) to 3(h). As a result, minimizing chattering is essential not only for reducing treatment costs but also for the equipment's and patient's safety.

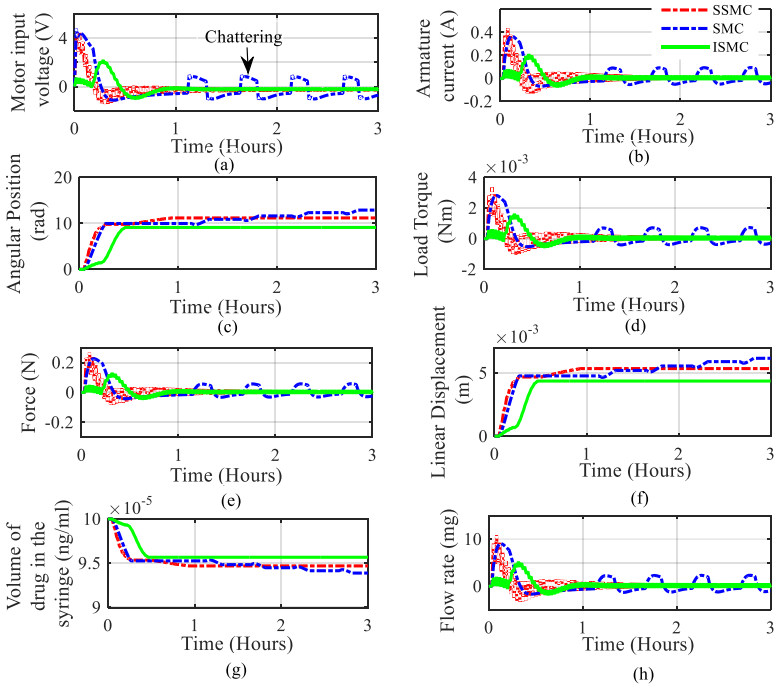

Fig.3 Closed-loop response of ADP with SMC, SSMC, and ISMC

As illustrated in Fig.3(a), SSMC and ISMC may successfully reduce chattering, and thereby improving set-point tracking accuracy. However, it is difficult to create a "chattering free" SMC because the system model used to create the controller can never capture all of the system dynamics. The chattering effects are more pronounced in control input, as seen in Fig. 3(a), and are measured by power spectral density (PSD) graphs. Though the PSD plots corresponding to ISMC and SSMC in Fig.4 are nearly identical, the chattering is almost completely minimized in the case of SSMC, confirming its superiority. From the real-time application standpoint, this is very desirable since it contributes less wear and tear in linear EMA over time.

In this work, though all the three SMC methods provide stable closed-loop responses, the SSMC's dynamic performance is superior in terms of rise time, settling time, and chattering intensity. SSMC achieves the intended set-point quickly by consuming a considerable amount of medication, as seen in Fig.3 (h), and consequently the tracking error converges quickly in Fig.5 (a).Nonetheless, the ISMC surpasses the others in terms of peak overshoot and steady-state error as shown in Table 2. The optimized parameter values for each scheme of SMC techniques are exposed in Table 3.

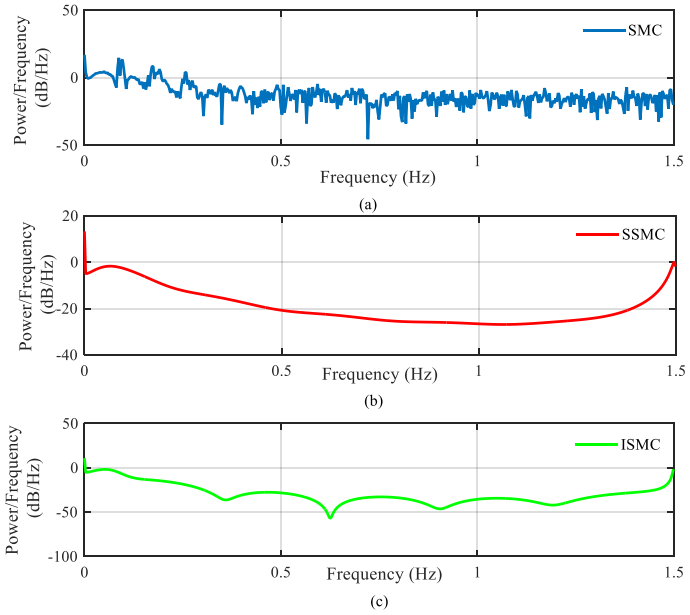

Fig.4 Chattering effects in control input

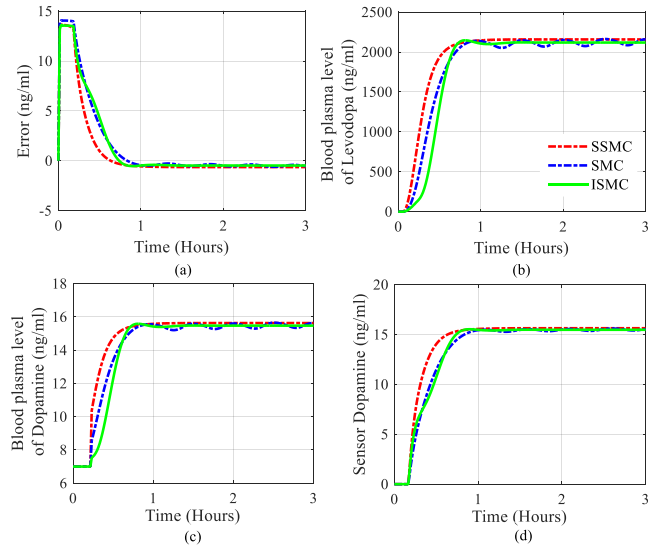

Fig.5 Closed-loop response of the patient with SMC, SSMC, and ISMC

Table 2 Comparison of responses with SMC, SSMC, and ISMC

Controller	Rise time, t_r (Minutes)	Settling time, t_s (Minutes)	Peak value, M_p (ng/mL)	Peak over shoot (%)	Steady state error	Stability
SMC	27.8	49.98	15.5	3.6	0.6311	Stable
SSMC	20.8	37.98	15.2	1.3	0.4867	Stable
ISMC	23.9	43.98	15.1	0.4	0.1756	Stable

Table 3 Optimized parameter values

SMC		SSMC		ISMC	
Parameter	Values	Parameter	Values	Parameter	Values
$\boldsymbol{c_1}$	9600	c_1	1136	c_1	9765
$\boldsymbol{c_2}$	1980	c_2	3720	c_2	3262
$\boldsymbol{c_3}$	113	c_3	235	c_3	237
$\boldsymbol{\varepsilon}$	12	ε	9	ε	3.2
$\boldsymbol{k}$	80	k	86	k	173
		Δ	0.05	c_4	100

More performance indicators, such as integral absolute error (IAE), integral square error (ISE), root mean square error (RMSE), maximum amount of the control signal, as well as the amount of control energy consumed, are taken into account for quantitative evaluation of the controller performances. These criteria shown in Fig.6 are chosen since eye observations of system response are not always adequate for comparing various types of controllers. Even though SSMC performs better on various scales, control energy consumption rises as settling time improves. While analyzing all of these performance indices using the bar plot, it is evidenced that ISMC has superior performance.

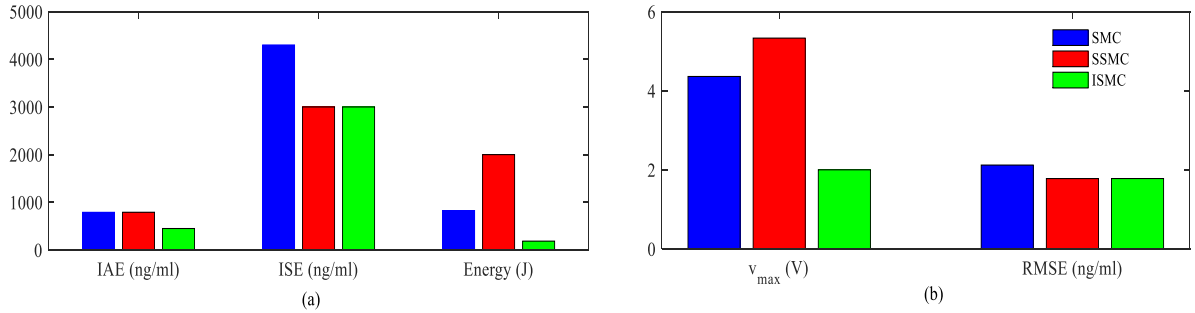

Fig.6 Performance indices for SMC, SSMC, and ISMC

The robustness analysis of the proposed closed-loop system with SMC is detailed in the next sub section because disturbance rejection and parameter invariance are the most critical challenges once the desired plasma dopamine concentration is attained.

3.2.1Effects of intra-day variability

The main sources of intra-day erraticism on automated ADP include various disturbances such as meals, physical activity and drug interactions. The impact of these disturbances on the closed-loop response while utilizing various SMC techniques are described in this section, which refers to the *in-Silico* study of the patient with real-life scenario in a day.

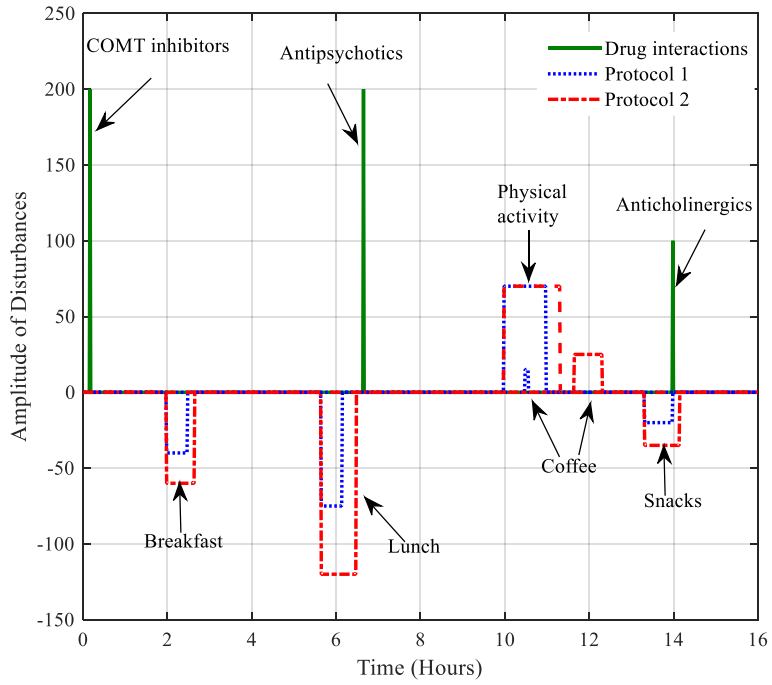

Fig.7 Disturbance input.

Since Levodopa competes with specific amino acids in the small intestine, a high-protein diet may cause its uptake to be delayed or disrupted. Therefore, the performance of the controllers are tested under two different meal perturbation protocols including breakfast, lunch, coffee, and evening snack as portrayed in Fig.7, where protocol 1 is the normal meal disturbance scenario and protocol 2 is the worst case of meal disturbance that are dubious to happen in real life. Physical activity improves blood circulation, resulting in higher concentrations of numerous neurochemicals and hormones in the brain and it has a beneficial impact on the dopamine dynamics system. The closed-loop performance of ADP employing SSMC, SMC and ISMC is evaluated under protocol 1, and is illustrated in Fig.8. It is observed that the response of the system utilizing all three SMC schemes is free from bradykinesia, dyskinesia, OFF periods, as well as instability issues. In the zoomed view of Fig 8(a) and 8(b), the outperformance of ISMC is evidenced with slight variations from the set-point value and rapid settling of tracking error to zero as compared to those with MRA-PID controller in [22]. Since dopamine levels increase with physical activity, the controller recommends minimal or no Duodopa doses during and immediately after exercise, as may be concluded from the zoomed view in Fig. 8 (b). Furthermore, by decreasing the plasma level of Levodopa to the lowest feasible level, the outperformance of ISMC is confirmed as shown in Fig.8 (c). Therefore the performance of ISMC is more safe and acceptable compared to that of other two controllers even under unannounced meal disturbances and physical activity.

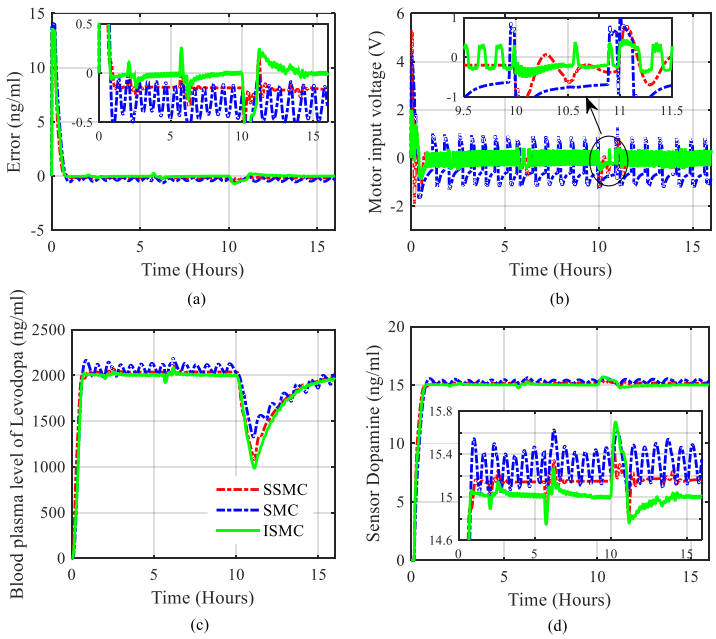

Fig.8 Closed-loop response of ADP with SMC under protocol 1

Another key disruption in closed-loop pharmacologic treatment is drug-drug interactions. Drug interactions can alter the way drugs work, resulting in increased/decreased effectiveness or a higher risk of major side effects. In fact, fewer interaction studies with Duodopa have been reported and therefore, the medication interaction with a generic Levodopa/Carbidopa combination is evaluated in this paper.In the clinical investigation, 319 such interactions have been reported, which are grouped into three categories: major (extremely clinically significant), moderate (moderately clinically significant) and minor (minimally clinically significant). There are 10 major, 287 moderate and 22 minor interactions reported. Among that three types of interactions which are listed under moderate category are discussed in the current work to assess the feasibility of SMC algorithms for automated dopamine regulation with the help of the plots shown in Fig.9.

Interactions with Anticholinergics

Anticholinergics are widely used as a supplementary treatment for tremor in PD, especially in the early stages. Anticholinergics and Levodopa may work together to reduce tremor. However, the concomitant use may aggravate aberrant involuntary movements because the anticholinergics might impair the effects of Levodopa by delaying or lowering its absorption, necessitating the dose adjustment of Duodopa [32].

Interactions with COMT inhibitors

To treat the motor symptoms of PD, COMT inhibitors are used with Levodopa. It may help Levodopa last longer by slowing the breakdown. Consequently, the concurrent use of COMT inhibitors and Duodopa may boost the bioavailability of Levodopa, necessitating a dosage modification for Duodopa [33].

Interaction with Dopamine receptor antagonists

Up to 60% of PD patients who use Levodopa have chronic psychotic symptoms, necessitating the administration of additional antipsychotic medicine. Consequently, the therapeutic efficacy of Levodopa may be reduced when it interacts with dopamine receptor antagonists such as antipsychotics [34].

In view of the preceding discussion on interaction between drugs, it may be concluded that, the goal of PD treatment is to strike a balance between alleviating tremor and drug-related psychotic problems while avoiding a severe worsening of motor symptoms. To achieve this objective, the dosage of Duodopa should be reduced to the minimum therapeutic dose or increased just below the maximum safe level or else halted in a sequential way, depending on the kind of pharmacological interaction involved.

The pharmacokinetics and metabolism of Levodopa/Carbidopa have already been studied by using a single 200 mg oral dose of Entacapone, a potent COMT inhibitor, in eight PD patients on long-term therapy [35].It has been observed that Entacapone expressively intensified the mean area under the plasma concentration curve (AUC) of Levodopa by 46%, and extended its abolition half-life from 1.5 to 2.0 hours. In the current work, this particular interaction with COMT inhibitors is simulated by altering the pharmacokinetics of Levodopa in such a way that the aforementioned characteristics are replicated. Therefore, the value of K_{PK} and time constant of Levodopa pharmacokinetics have been appropriately reformed further, this modified value of time constant is adopted in conjunction with a negative value of K_{PK} to mimic the interaction with antipsychotics. In this work, the Anticholinergic interactions are emulated by delaying the effect of Levodopa for a specific period of time (1 hour is expected).

The *in-silico* trials with three types of drug interactions together with protocol 1 on closed-loop response are shown in Fig.9. As per the results, the dynamic response with ISMC is superior under these disturbances, with minimal undershoot and overshoot from set-point value, as seen in a zoomed view in Fig.9 (d). Therefore, the ISMC is strong enough to resist system interruptions such as an unexpected meal, exercise, and different drug interactions, since they cause a decrease or increase, or else a delay in the current plasma dopamine concentration.

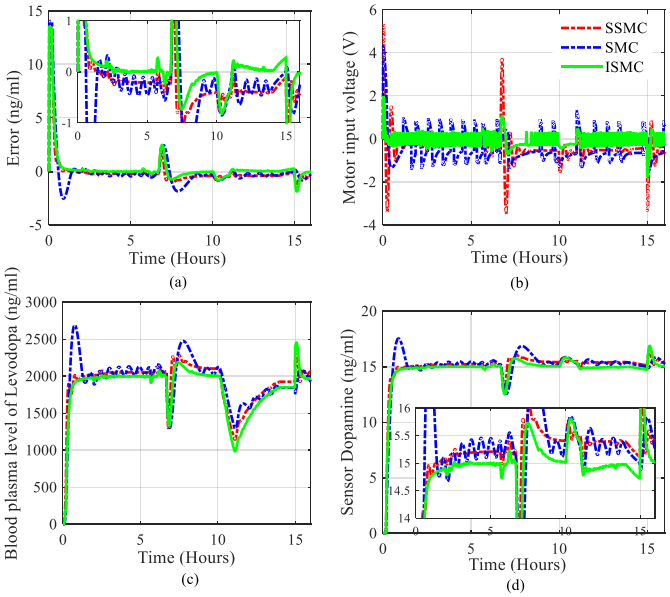

Fig.9 Closed-loop response of ADP with SMC under concurrent disturbances involving protocol 1 and various drug interactions.

3.3.2 Effects of intra-patient variability

The closed-loop response of the system with the three distinct SMC control techniques under intra-patient and intra-day variability (protocol 2 with drug interactions) is depicted in Fig.10, which portrays the collective impact of

parameter variation and disturbances. This *in-silico* study presents information on the pharmacokinetics and pharmacological activation of Levodopa in a real-life scenario for a specific PD patient over the life span.

Since PD is a progressive disease, d_0 is continuously decreasing from early to advanced stages and this variation is considered as the intra-patient variability in the current work. The patient can use the same pump for the rest of his/her life only if the closed-loop response is unaffected by these disparities. Otherwise, if the PD worsens over time, the controller parameters or the controller would have to be changed.

Despite the fact that SSMC outperforms SMC by providing fast dynamic responses and good transient performance, constraint violation in the case of motor input voltage even for moderate PD case is observed in Fig. 10 (a). Therefore the sizing of DC motor has to be improved without creating considerable variation in inertia ratio, if the controller used is SSMC. The achievement of better dynamic performance and reasonable robustness by ISMC in the face of parametric uncertainties and disturbances than that of SMC and SSMC is revealed by keeping the deviation in desired plasma dopamine level to a small extent, for a shorter period of time and by using the minimum value of control input. According to the *in-silico* analysis, anticholinergics and antipsychotics should not be used with or immediately after food, because both are having a detrimental effect on the dopamine system. Furthermore, try to avoid different perturbations soon after wake up (turning ON the pump) because in the reaching mode, the invariance of SMC is not guaranteed and therefore, the corresponding dynamic response rests on system parameters.

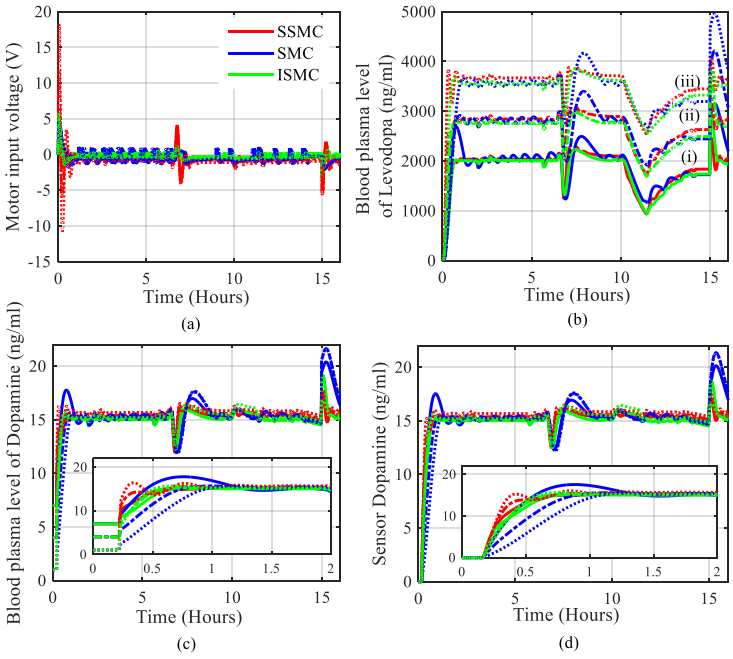

Fig.10 Impact of intra-patient variability together with intra-day variability. (i) Early PD case, (ii) Moderate PD case, (iii) Advanced PD case

3.2.3 Effects of inter-patient variability

The success of a controller on a single patient does not imply that it will work well over a group of patients. Therefore, the performance of the controllers is tested for a group of virtual early PD patients in a more realistic scenario including intra-day variability under protocol 1, various drug interactions and sensor noise as depicted in

Fig.11. To create a cohort of 10 *in-silico* individuals with substantial inter-patient variability, the patient's medication sensitivity is changed in ten percent increments from its nominal value to a worst stage of 50 percent uncertainty, both in up and down directions.

As per the robust stability analysis, ISMC can accommodate up to 13% uncertainty in drug sensitivity with sensor noise as exposed in Fig. 11(i). However, it is observed that both SSMC and SMC can ensure complete robust operation in these ten *in-silico* subjects. To obtain the extreme value of robustness in SSMC and SMC, the drug sensitivity of the patient is increased again from 50% uncertainty, until the response becomes unstable as shown in Fig.11 (ii) and (iii) respectively. It is perceived that, SMC and ISMC have the highest and lowest percentages of robustness respectively. The robustness offered by SSMC is in between these two and besides that, constraint violation occurs for motor input voltage beyond 34% of uncertainty, in the presence of sensor noise. Despite poor dynamic performance, the closed-loop response with SMC maintains a constant plasma dopamine concentration even in the presence of disturbances, parameter variations as well as sensor noise and can effectively mitigate for inter-patient variability to a more significant range. It is also noticed that the sensor noise used in this study has a substantial negative impact on robustness under inter-patient variability as shown in Table 4.

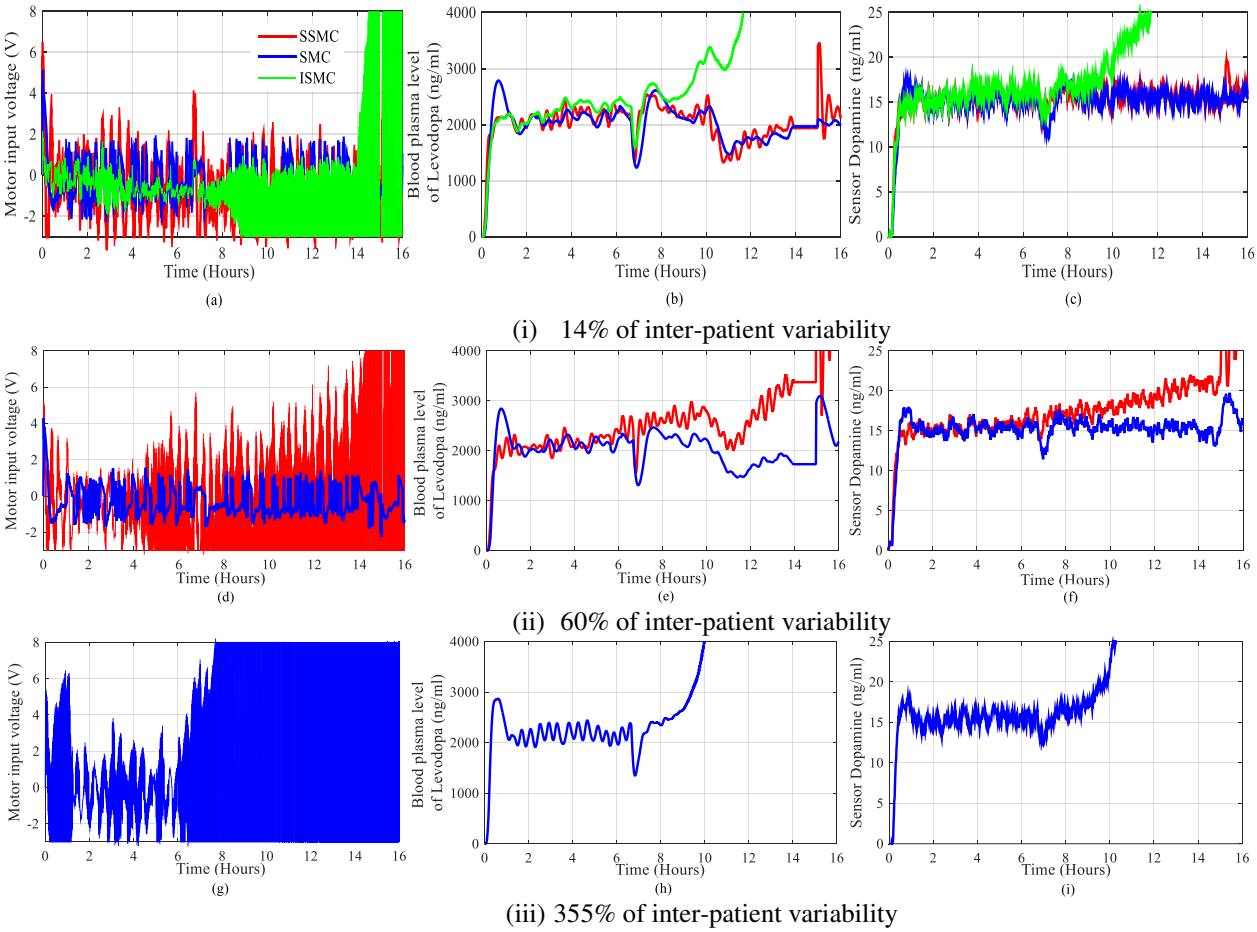

Fig.11 Effects of sensor noise, disturbances and model uncertainty on dopamine concentration.

Table 4 Robustness analysis

Scenario	SMC (%)	SSMC (%)	ISMC (%)
Without sensor noise	361	62	15
With sensor noise	354	59	13

4. Conclusion

Smart healthcare is becoming increasingly important in maintaining patient safety, especially in the ongoing Covid-19 pandemic, predominantly for incurable, dynamic diseases such as PD. The motivation behind this work is to investigate how to minimize the discomforts that arise with employing an adaptive PID controller-based automated ADP under system parameter variations, uncertainties as well as various disturbances and to find new technical solutions to improve the quality of life of patients with PD. As a result, this article proposes three distinct sliding mode controller methods for an automated ADP: SMC, SSMC, and ISMC. A step-by-step Lyapunov theory based control design is used in achieving the stability of the closed-loop control system. The *in-silico* results of traditional SMC are compared with those of SSMC and ISMC. The results with SSMC show fast dynamic response as well as fewer chattering, and those with ISMC provide not only reduced chattering intensity but also less peak overshoot and small steady-state error. Various simulation results under unannounced meals and physical activity reveal that, as compared to [22], SMC significantly improves the tracking performance of the system without causing bradykinesia, dyskinesia, OFF periods, and instability concerns. However, the response with ISMC shows better tracking performance, disturbance rejection as well as insensitivity to intra-day and intra-patient variability than that with two SMC schemes. *In-silico* studies using SSMC expose that even in moderate PD scenario, there exists constraint violation for motor input voltage. The analysis also recommends avoiding various perturbations soon after waking up. According to the robust stability analysis, SMC has the highest percentages of robustness against inter-patient variability since the invariance feature of SMC is lost in the case of SSMC and ISMC, even at smaller levels of uncertainty in drug sensitivity. However, it suffers from the disadvantage of chattering phenomenon associated with the control signal. Even though the overall response of the proposed ADP under SMC is superior, the study directs openings for improvements in system responses with the upcoming versions that guarantee robustness even in the reaching phase and for unmatched disturbances.

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

All the authors gave their approval for publication.

Availability of data and materials:

Not applicable

Competing Interests:

The authors have no relevant financial or non-financial interests to disclose.

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Author contribution:

All authors contributed significantly to complete this manuscript.

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References

[1] J.A. Stamford, P.N. Schmidt, K.E. Friedl, What engineering technology could do for quality of life in Parkinson's disease: A review of current needs and opportunities, IEEE J. Biomed. Heal. Informatics. 19 (2015) 1862–1872. https://doi.org/10.1109/JBHI.2015.2464354.

[2] S. Bhat, U.R. Acharya, Y. Hagiwara, N. Dadmehr, H. Adeli, Parkinson's disease: Cause factors, measurable indicators, and early diagnosis, Comput. Biol. Med. 102 (2018) 234–241. https://doi.org/10.1016/j.compbiomed.2018.09.008.

[3] V. Labhasetwar, Neurodegenerative diseases: Challenges, Drug Deliv. Transl. Res. 1 (2011) 349–350. https://doi.org/10.1007/s13346-011-0040-4.

[4] A.D. Korczyn, Vascular parkinsonism-characteristics, pathogenesis and treatment, Nat. Rev. Neurol. 11 (2015) 319–326. https://doi.org/10.1038/nrneurol.2015.61.

[5] C.L. Pulliam, D.A. Heldman, E.B. Brokaw, T.O. Mera, Z.K. Mari, M.A. Burack, Continuous assessment of levodopa response in Parkinson's disease using wearable motion sensors, IEEE Trans. Biomed. Eng. 65 (2018) 159–164. https://doi.org/10.1109/TBME.2017.2697764.

[6] M. Welsh, Treatment Challenges in Parkinson ' s Disease, Nurse Pract. 33 (2008) 32–38.

[7] R. Talati, K. Reinhart, W. Baker, C.M. White, C.I. Coleman, Pharmacologic treatment of advanced Parkinson's disease: A meta-analysis of COMT inhibitors and MAO-B inhibitors, Park. Relat. Disord. 15 (2009) 500–505. https://doi.org/10.1016/j.parkreldis.2008.12.007.

[8] M. Steiger, Constant dopaminergic stimulation by transdermal delivery of dopaminergic drugs: A new treatment paradigm in Parkinson's disease, Eur. J. Neurol. 15 (2008) 6–15. https://doi.org/10.1111/j.1468-1331.2007.01674.x.

[9] R. Katzenschlager, W. Poewe, O. Rascol, C. Trenkwalder, G. Deuschl, K.R. Chaudhuri, T. Henriksen, T. van Laar, K. Spivey, S. Vel, H. Staines, A. Lees, Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial, Lancet Neurol. 17 (2018) 749–759. https://doi.org/10.1016/S1474-4422(18)30239-4.

[10] A. Antonini, P. Odin, Pros and cons of apomorphine and l-dopa continuous infusion in advanced Parkinson's disease, Park. Relat. Disord. 15 (2009) S97–S100. https://doi.org/10.1016/S1353-8020(09)70844-2.

[11] F. Raudino, P. Garavaglia, C. Pianezzola, G. Riboldazzi, S. Leva, M. Guidotti, G. Bono, Long-term experience with continuous duodenal levodopa-carbidopa infusion (Duodopa): Report of six patients, Neurol. Sci. 30 (2009) 85–86. https://doi.org/10.1007/s10072-009-0022-1.

[12] S. Castano-Candamil, T. Piroth, P. Reinacher, B. Sajonz, V.A. Coenen, M. Tangermann, An Easy-to-Use

and Fast Assessment of Patient-Specific DBS-Induced Changes in Hand Motor Control in Parkinson's Disease, IEEE Trans. Neural Syst. Rehabil. Eng. 27 (2019) 2155–2163. https://doi.org/10.1109/TNSRE.2019.2941453.

[13] R. Sharma, D. Singh, P. Gaur, D. Joshi, Intelligent automated drug administration and therapy: future of healthcare, Drug Deliv. Transl. Res. 11 (2021) 1878–1902. https://doi.org/10.1007/s13346-020-00876-4.

[14] M. Pravika, J. Jacob, J.K. Paul, The Impact of Manually Controlled Portable Duodopa Pump on Levodopa Pharmacokinetics and Pharmacodynamics, in: TENCON 2019 - 2019 IEEE Reg. 10 Conf., 2019: pp. 696–701. https://doi.org/10.1109/TENCON.2019.8929602.

[15] A. Antonini, I.U. Isaias, M. Canesi, M. Zibetti, F. Mancini, L. Manfredi, M. Dal Fante, L. Lopiano, G. Pezzoli, Duodenal levodopa infusion for advanced Parkinson's disease: 12-Month treatment outcome, Mov. Disord. 22 (2007) 1145–1149. https://doi.org/10.1002/mds.21500.

[16] L. Negreanu, B.O. Popescu, R.D. Babiuc, A. Ene, O.A. Bajenaru, G.C. Smarandache, Duodopa infusion treatment: A point of view from the gastroenterologist, J. Gastrointest. Liver Dis. 20 (2011) 325–327.

[17] M. Ben Guebila, J. Thunberg, Toward a closed-loop subcutaneous delivery of L-DOPA, ArXiv Prepr. ArXiv. 1608.07232 (2016) 1–9. http://arxiv.org/abs/1608.07232.

[18] P. M, J. Jacob, P.J. K, PID controlled fully automated portable duodopa pump for Parkinson's disease patients, Biomed. Signal Process. Control. 50 (2019) 178–187. https://doi.org/https://doi.org/10.1016/j.bspc.2019.01.025.

[19] D. Yan, T. Urano, M.H. Pietraszek, I. Shimoyama, K. Uemura, Y. Kojima, K. Sakakibara, K. Serizawa, Y. Takada, A. Takada, Correlation between serotonergic measures in cerebrospinal fluid and blood of subhuman primate, Life Sci. 52 (1993) 745–749. https://doi.org/https://doi.org/10.1016/0024-3205(93)90237-W.

[20] M. Dahlin, B. Jansson, E. Björk, Levels of dopamine in blood and brain following nasal administration to rats, Eur. J. Pharm. Sci. 14 (2001) 75–80. https://doi.org/https://doi.org/10.1016/S0928-0987(01)00151-8.

[21] J.K.C. Tsui, E.C. Wolters, R.F. Peppard, D.B. Calne, A double-blind, placebo-controlled, dose-ranging study to investigate the safety and efficacy of CY 208-243 in patients with Parkinson{\textquoteright}s disease, Neurology. 39 (1989) 856. https://doi.org/10.1212/WNL.39.6.856.

[22] P. M, J. Jacob, P. Joseph K, Design of model reference adaptive–PID controller for automated portable duodopa pump in Parkinson's disease patients, Biomed. Signal Process. Control. 68 (2021) 102590. https://doi.org/10.1016/j.bspc.2021.102590.

[23] P.J.. M. Pravika, J. Jacob, Design of Linear Electro-Mechanical Actuator for Automatic Ambulatory Duodopa Pump, Eng. Sci. Technol. an Int. J. (2021).

[24] M. Van, M. Mavrovouniotis, S.S. Ge, An adaptive backstepping nonsingular fast terminal sliding mode control for robust fault tolerant control of robot manipulators, IEEE Trans. Syst. Man, Cybern. Syst. 49 (2019) 1448–1458. https://doi.org/10.1109/TSMC.2017.2782246.

[25] W. Zhao, X. Ren, S. Wang, Parameter Estimation-Based Time-Varying Sliding Mode Control for Multimotor Driving Servo Systems, IEEE/ASME Trans. Mechatronics. 22 (2017) 2330–2341.

https://doi.org/10.1109/TMECH.2017.2725344.

[26] Y. Zhang, Z. Yin, W. Li, J. Liu, Y. Zhang, Adaptive Sliding-Mode-Based Speed Control in Finite Control Set Model Predictive Torque Control for Induction Motors, IEEE Trans. Power Electron. 36 (2021) 8076–8087. https://doi.org/10.1109/TPEL.2020.3042181.

[27] S. Rao, D. Ghose, Sliding mode control-based autopilots for leaderless consensus of unmanned aerial vehicles, IEEE Trans. Control Syst. Technol. 22 (2014) 1964–1972. https://doi.org/10.1109/TCST.2013.2291784.

[28] N. Ebrahimi, S. Ozgoli, A. Ramezani, Model free sliding mode controller for blood glucose control: Towards artificial pancreas without need to mathematical model of the system, Comput. Methods Programs Biomed. 195 (2020) 105663. https://doi.org/https://doi.org/10.1016/j.cmpb.2020.105663.

[29] J.-J.E. Slotine, APPLIED NONLINEAR CONTROL, 1991.

[30] N. Ullah, I. Sami, M.S. Chowdhury, K. Techato, H.I. Alkhammash, Artificial Intelligence Integrated Fractional Order Control of Doubly Fed Induction Generator-Based Wind Energy System, IEEE Access. 9 (2021) 5734–5748. https://doi.org/10.1109/ACCESS.2020.3048420.

[31] Y. Islam, I. Ahmad, M. Zubair, K. Shahzad, Double Integral sliding mode control of Leukemia Therapy, Biomed. Signal Process. Control. 61 (2020) 102046. https://doi.org/https://doi.org/10.1016/j.bspc.2020.102046.

[32] I. Csoti, H. Herbst, P. Urban, D. Woitalla, U. Wüllner, Polypharmacy in Parkinson's disease: risks and benefits with little evidence, J. Neural Transm. 126 (2019) 871–878. https://doi.org/10.1007/s00702-019-02026-8.

[33] P. Martínez-Martín, C.F. O;Brien, Extending levodopa action, Neurology. 50 (1998) S27 LP-S32. https://doi.org/10.1212/WNL.50.6_Suppl_6.S27.

[34] R. Wijesinghe, A review of pharmacokinetic and pharmacodynamic interactions with antipsychotics, Ment. Heal. Clin. 6 (2016) 21–27. https://doi.org/10.9740/mhc.2016.01.021.

[35] V. V. Myllylä, K.A. Sotaniemi, A. Illi, K. Suominen, T. Keränen, Effect of entacapone, a COMT inhibitor, on the pharmacokinetics of levodopa and on cardiovascular responses in patients with Parkinson's disease, Eur. J. Clin. Pharmacol. 45 (1993) 419–423. https://doi.org/10.1007/BF00315512.