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A Model of Intelligent Controller for Hypothyroidism Treatment

Luiz G. A. Martins
Universidade Federal de Uberlândia
Uberlândia, Brazil
e-mail: gustavo@facom.ufu.br

Luiz H. A. Monteiro
Universidade Presbiteriana Mackenzie
Universidade de São Paulo
São Paulo, Brazil
e-mail: luizm@mackenzie.br, luizm@usp.br

Abstract— **Hypothyroidism results from an insufficiency either in the production or/and in the action of the thyroid hormones. Most of the patients in hypothyroidism state must adopt hormonal replacement therapy for all their lives. An intelligent controller model for supplying therapeutic drugs to primary hypothyroidism patients, without the thyroid gland, is investigated in this work. Two multilayer perceptron neural networks are used to predict the concentrations of the hormones TSH and T_4 in the blood. The controller, based on a set of production rules, uses these forecasts and the current concentrations of such hormones for calculating the necessary drug dosage to be released. Beyond the controller maintaining such concentrations inside regularity bands, it is also able of preventing abrupt changes on the time evolution of these concentrations.**

Keywords- Intelligent control, neural networks, production rules, thyroid hormones

I. INTRODUCTION

Endocrine system is fundamental for the normal operation of the human organism. It interacts with the central nervous system to form a regulatory mechanism that is responsible for the homeostasis maintenance.

The interactions among hypothalamus, pituitary gland and thyroid gland occur by the transportation through the blood stream of hormones produced in these glands. Two of the main pathologies affecting this regulatory system are hyperthyroidism and hypothyroidism [1].

Hypothyroidism is a disease state where the body lacks of sufficient thyroid hormone. The focus of this study is primary hypothyroidism, in other words, when the failure is in the thyroid gland. The treatment is relatively easy, involving regular monitoring and thyroid hormone replacement. Usually, this is accomplished through oral ingestion of a pure synthetic form of T_4, called levothyroxine [2].

There are several works focused in the development of artificial regulatory mechanisms, which are able of evaluating the patient situation and of executing the control actions that are needed to reestablish the dynamic balance. Some approaches adopt intelligent control techniques, aiming to improve the mechanism flexibility relative to the process dynamics. For instance, artificial neural networks have been used in biomedical control systems [3,4], which is justified due to their capability of learning and generalizing.

In this work, we present a control mechanism of drug dosage for patients with primary hypothyroidism, due to the total removal of the thyroid gland. The control is based on two multilayer perceptron (MLP) neural networks that predict the concentrations of TSH and T_4 hormones. From these forecasts and the current hormone concentrations, the control device uses a set of production rules to define how much drug must be supplied. This dosage should maintain the hormonal concentrations inside of the respective regularity bands, without provoking abrupt changes on their time evolutions.

There are many works about intelligent control for diabetes treatment [4–6], but any work related to intelligent control of thyroid hormones concentrations was not found. In order to evaluate the proposed mechanism, its performance is compared with that one of the method traditionally used by doctors, which adopts a fixed drug dosage.

II. DYNAMICS OF THE THYROIDAL SYSTEM

Fig. 1 illustrates a simple model of hormonal interaction among hypothalamus, pituitary and thyroid gland. Blood and target-cells also participate of this process as transportation system and consumer entities of such hormones, respectively.

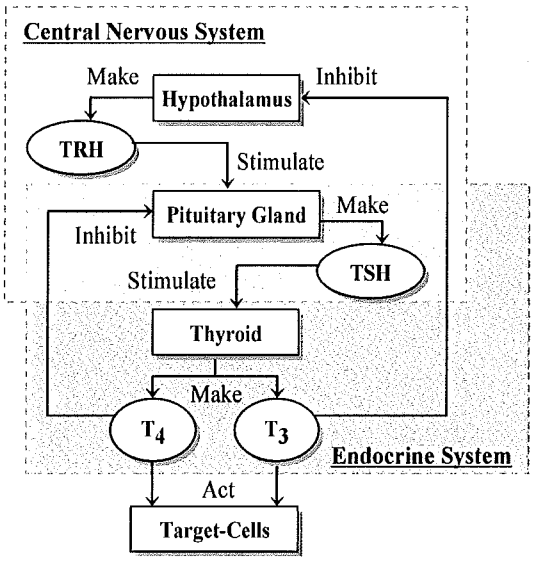

Figure 1. System regulating the thyroid hormones.

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In normal functioning, hypothalamus produces TRH (thyrotropin releasing hormone), which stimulates pituitary gland to make and release TSH (thyroid stimulating hormone or thyrotropin). Under the influence of TSH, the thyroid gland manufactures and secretes thyroid hormones (TH) that are thyroxine (T_4) and triiodothyronine (T_3). T_4 is the major circulating thyroid hormone, although half of each output is daily converted to T_3 inside of the target-cells. This scheme assures a satisfactory hormonal supply for the target-cells, which remove from the blood the necessary quantity of TH for their metabolism. Serum T_3 and T_4 levels exert a negative feedback on TSH and TRH supplies, so the higher the quantity of TH, the lower the production/absorption of the TSH and the TRH, and vice versa [1].

Among the diseases that affect the system regulating thyroid hormones, some of the major ones are hyperthyroidism and hypothyroidism. The first one is a disorder due to excess of thyroid hormone in the blood. The second one is resultant of deficiency of such hormones.

Hypothyroidism is a relatively common clinical syndrome that, when not treated, can cause serious damages for the health, such as cardiomegaly and mental retardation. Diagnosis is performed by laboratorial measurement of the serum T_4 and TSH concentrations, beyond clinical observation of characteristic symptoms [2]. Standard treatment consists of oral administration of a drug called levothyroxine providing daily the supposedly adequate amount of thyroid hormones. Control of the treatment is done by hormonal concentration measurements, which must always be maintained inside of normal ranges (free T_4 from 0.8 to 1.8 ng/dl, and TSH from 0.4 to the 2.0 μUI/ml [7]).

Based on the interaction among hypothalamus, pituitary gland and thyroid gland, we elaborate a mathematical model for describing the temporal evolution of the substance concentrations involved in the system regulating the thyroid hormones. As explained below, this model is used for producing the training and validation sets for the neural networks, as well as for the simulation of the dynamics of patients submitted to the treatments suggested by the controller.

This simplified model describes the normal processes regulating the thyroid hormones (euthyroidism). The model is composed by seven linear differential equations representing the time evolution of the main substances involved in this process [8]. They are:

$$\frac{d[TRH]}{dt} = P(t) - 1.2[TRH] - 0.8[T_3L] - 0.7[TRH] \quad (1)$$

$$\frac{d[TSH]}{dt} = 1.6[TRH] - 1.2[T_4L] - 0.5[TSH] \quad (2)$$

$$\frac{d[T_G]}{dt} = 2[TSH] - 0.8[T_G] - 3.8[T_G] - 0.02[T_G] \quad (3)$$

$$\frac{d[T_3L]}{dt} = 0.38[T_G] - 1.7[T_3L] + 0.6[C_3] - 0.002[T_3L] \quad (4)$$

$$\frac{d[T_4L]}{dt} = 3.42[T_G] - 1.8[T_4L] - 0.004[T_4L] \quad (5)$$

$$\frac{d[C_3]}{dt} = 1.7[T_3L] + 1.4[C_4] - 0.6[C_3] - 0.7[C_3] \quad (6)$$

$$\frac{d[C_4]}{dt} = 1.8[T_4L] - 1.4[C_4] - 0.8[C_4] \quad (7)$$

The parameter values were inferred from usual equilibrium concentrations of the hormones and from information collected in literature [8]. *P(t)* represents the stimulation of the central nervous system in the TRH's synthesis. Here, it is assumed a constant value $P = 3$ for this function. $[TRH]$ and $[TSH]$ are, respectively, the concentrations of serum TRH and serum TSH. $[T_G]$ is the concentration of thyroglobulin, that is, of molecules that store and carry TH inside of thyroid. $[T_4L]$ and $[T_3L]$ are, respectively, the concentrations of free T_4 and free T_3. $[C_4]$ and $[C_3]$ are the quantities of T_4 and T_3 inside of target-cells. Auto-inhibition processes of TRH and thyroglobulin synthesis are represented by 1.2 $[TRH]$ and $0.8[T_G]$, respectively. Inhibition processes of TRH and TSH synthesis from free T_3 and free T_4 concentrations in the blood are represented by $0.8[T_3L]$ and $1.2[T_4L]$. The terms $1.6[TRH]$ and $2[TSH]$ correspond to the stimulation processes of TSH and TH synthesis, from the TRH and TSH in the blood. The conversion factor of T_G into TH during the secretion process is given by $3.8[T_G]$. The terms $0.38[T_G]$ and $3.42[T_G]$ represent, respectively, the secretion factors of the free T_3 and free T_4 hormones in the blood; they represent respectively 10% and 90% of the total of TH secretion. The absorption factors of free T_3 and free T_4 hormones for the target-cells are represented by $1.7[T_3L]$ and $1.8[T_4L]$. The term $1.4[C_4]$ represents the conversion factor of T_4 into T_3 inside of target-cells. The release factor of T_3 hormone for the target-cells is given by $0.6[C_3]$.

Modifications in this model can be done to represent patients without the thyroid gland (hypothyroidism model). In this new version of this model, the equation (3) relative to thyroglobulin and its interaction terms with free T_3 and free T_4 (in (4) and (5), respectively) are removed. Moreover, a new term *Q(t)* is included in (5) to represent the absorption of the synthetic hormone (levothyroxine) through the organism. The resultant equation is:

$$\frac{d[T_4L]}{dt} = Q(t) - 1.8[T_4L] - 0.004[T_4L] \quad (8)$$

$Q(t)$ is the function representing the drug quantity absorbed by the organism. Several factors influence this process, such as the drug dosage and changes in the absorption level, according to the gastric capability, given that the drug is supplied by oral way [9].

We would like to stress that the control mechanism proposed does not depend on the mathematical model used to create the training and test sets for the neural networks. Our mechanism based on production rules and predictive neural networks can be trained with experimental data of real patients or with data generated from other models.

III. CONTROL MECHANISM

The control mechanism is composed by two MLP neural networks and a dosage controller, as illustrated in Fig. 2. The mathematical model based on differential equations gives the temporal evolution of the hormonal concentrations of the patient to be treated. With this model, numerical values for free T_4 and TSH concentrations in the blood are generated and stored in a historical database. Temporal samplings of this database are used as input of the MLP networks to predict the future concentrations of these hormones.

Based on the current hormonal concentrations and the forecasts of the neural networks, the controller uses a set of production rules to determine how much drug must be supplied to the patient. This mechanism must be able of providing the required dosage, without causing abrupt changes on the hormone concentrations.

Intelligent techniques were used on the attempt of simulating the endocrinologist discernment in the task of determining the drug dosage necessary for the patient with hypothyroidism. In this context, the use of neural networks aims to represent the human capability of historical pattern recognition and of knowledge reuse. In addition production rules were used in the diagnosis of the patient condition and in the definition of the dosage that should be supplied.

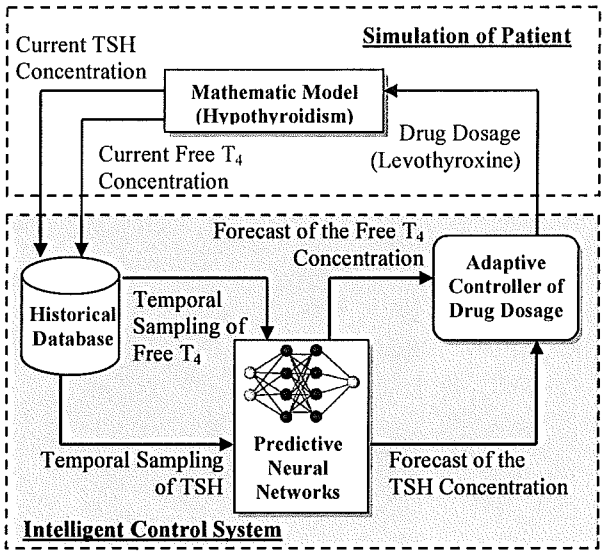

Figure 2. Control mechanism.

All components of the control mechanism were implemented on a Matlab© platform [10]. The control device developed for the numerical experiments is described below.

A. Predictive Neural Networks

Two MLP networks, trained by the error backpropagation algorithm, are employed to predict the next values of TSH and free T_4 concentrations. These networks are composed by neuron layers, with at least a hidden layer, where the neuron output is used as input of neurons of the following layer. This kind of neural network was chosen due to the large available bibliography, satisfactory performance and easy computational implementation [11].

A data set generated by our mathematical models is used for adjusting the neural network parameters. This set was normalized (between -1 and 1) and separated into three subsets: training, validation and test. The first set contains 50% of all data set, and the others two sets 25% each.

Each neural network has four layers. The input layer is composed of six neurons, which represent the respective hormone concentrations in the current instant (t) and in five previous measurements (between t-1 and t-5). The output layer has one neuron corresponding to the forecast concentration value in the next time step (t+1). The number of neurons in the two hidden layers differs in the two networks: the neural network used to predict the TSH concentration is composed of 24 neurons in the first intermediate layer and 12 in the second one; the network used to predict the free T_4 concentration is formed by 12 and 6 neurons, respectively. These topologies were defined from a lot of numerical tests [8]. All neurons employ hyperbolic tangent as sigmoid activation function.

In the training, the synaptic weights were randomly started and adjusted in an incremental way by the error backpropagation algorithm with a learning rate of 0.1. As stop criterion were employed the maximum cycle number of 10000 (each cycle represents the submission of all training set to the neural network) and relative error threshold of $1x10^{-4}$. To maintain the generalization capability of the network, the early stopping method was used to prevent overfitting [11].

B. Dosage Controller

The main goal of the controller is to maintain TSH and free T_4 concentrations inside of their respective regulatory bands, without provoking abrupt changes. In this context, abrupt changes are oscillations over 5% around the mean values of stabilization.

Security band were also created for each one of the controlled substances in order to help in the maintenance of the hormonal concentrations inside of the regulatory bands. Border values delimiting these new bands are proportional to the distances between the equilibrium concentration (the value of the equilibrium point of the substance in the euthyroidism model) and the border values of the regulatory band, so that it remains between these numbers. These border values are calculated by the following expression:

$$LS_k = \left[(LN_k - PE) \times 0.25 \right] + PE \tag{9}$$

Where PE is the equilibrium concentration value, LS_k are the border values of security band, LN_k are the border values of regulatory band, and $k \in \{S,I\}$ means superior or inferior border.

If the hormone concentrations are inside of satisfactory ranges, then it is expected that the controller just supplies a previously defined maintenance dosage. On the other hand, when such concentrations are outside of the desired values, the controller must adjust the maintenance dosage for driving the concentrations to the adequate ranges. Maintenance dosage was chosen as the value of Q in the hypothyroidism model resulting in an equilibrium concentration of free T_4 equal as the one obtained in the euthyroidism model ($[T_4L]^* \cong 1.08$ ng/dl); that is, $Q^* \cong 2$ μg/kg [8][12]. This is a satisfactory value because the maintenance dosage in an adult varies from 1.6 to 2.2 μg/kg of the corporal weight. The calculation of how much drug will be released is based on the current concentrations of TSH and free T_4 and on their future tendencies. Whereas the concentration value of each hormone, in the instant t, determines its localization in the corresponding control bands; the forecast, in the instant $t+1$, is compared to the current value, in order to estimate the derivative of the curve associated to the concentration evolution.

Modelling the drug absorption process is very hard, because there are a lot of variables involved in such a process [9]. Here it was adopt $Q(t)$ as 80% of the dosage suggested by the controller $Q_c(t)$ with a gaussian white noise of ±10%, ±30% or ±50%. Resultant values are saturated in 100% from $Q_c(t)$ to prevent the ingestion of a dosage higher than the one indicated by the controller. Thus, when a noise of ±30% is applied, the organism can absorb between 50% and 100% from drug suggested by the controller.

The dosage suggested by the controller depends on the maintenance dosage. This value is calculated from a weighted mean of the adjustment percentages (P_{T4L} and P_{TSH}) as:

$$Q_c = \frac{(\alpha_{T4L} P_{T4L} + \alpha_{TSH} P_{TSH}) \times Q^*}{\alpha_{T4L} + \alpha_{TSH}} \tag{10}$$

Where α_{TSH} and α_{T4L} are the weights associated to P_{TSH} and P_{T4L}, respectively. Different control strategies can be used to calculate the suggested dosage, varying simply the weight associated with each one of the adjustment percentages [8][12]. In this paper, we study four different strategies: equal weights, $\alpha_{TSH} < \alpha_{T4L}$, $\alpha_{TSH} > \alpha_{T4L}$ [12] and a mixed approach using $\alpha_{TSH} < \alpha_{T4L}$ during the stabilization phase and $\alpha_{TSH} > \alpha_{T4L}$ in the maintenance phase. The first one adopts the same value for both weights ($\alpha_{TSH} = \alpha_{T4L} = 1$). For $\alpha_{TSH} < \alpha_{T4L}$, assumes that the weight associated with P_{T4L} is twice the one associated to P_{TSH} ($\alpha_{TSH} = 1$ and $\alpha_{T4L} = 2$). This strategy intends to increase the adjustment percentage influence of free T_4 in relation to TSH and, consequently, to get a faster reply of the controller. For $\alpha_{TSH} > \alpha_{T4L}$, the weight values are $\alpha_{TSH} = 2$ and $\alpha_{T4L} = 1$. In this strategy, based in the traditional method, the doctor's control and monitoring of thyroid hormones, after the stabilization of patient status, are made by measuring the TSH concentration. The last strategy combines the two previous cases, aiming to get the quickness of action of the second approach during the stabilization phase, and the robustness of reply of the third approach during the maintenance phase.

The adjustment percentages P_{T4L} and P_{TSH} cannot exceed 200% and they are obtained by a set of production rules stated as: *IF hormone concentration is placed in range R and presents tendency V, THEN its adjustment percentage is X% from Q**. The complete set is presented in Table 1.

The percentages in the production rules were chosen by considering that concentrations inside of the security bands, with tendency of either stability or convergence to equilibrium point, would receive 100% of the maintenance dosage Q^*. Based on these values, other ones were defined by the increase or the decrease of 15%, in accordance with the analyzed hormone and its tendency, maintaining symmetry in the percentage distribution [12]. In the extreme values of the table (below of the LN_I with tendency of decrease and above of the LN_S with tendency of increase), the values were adjusted for 10% relative to the previous one, in order to guarantee that the values of P_{TSH} and P_{T4L} are between 0% and 200%. For $P_{T4L} = 100\%$ and $P_{TSH} = 100\%$, the controller just supplies the maintenance dosage. Values of P_{T4L} and P_{TSH} higher than 100% indicate the necessity of increasing the dosage; lower values indicate the necessity of decreasing the dosage.

TABLE I. PRODUCTION RULES OF ADJUSTMENT PERCENTAGES P_{TSH} AND P_{T4L}

Concentration Analysis		***Adjustment Percentages***	
Range	***Tendency***	P_{TSH}	P_{T4L}
Above LN_S	Increase	200%	0%
	Stability	190%	10%
	Decrease	175%	25%
Between LN_S and LS_S	Increase	160%	40%
	Stability	145%	55%
	Decrease	130%	70%
Between LS_S and PE	Increase	115%	85%
	Stability	100%	100%
	Decrease	100%	100%
Between PE and LS_I	Increase	100%	100%
	Stability	100%	100%
	Decrease	85%	115%
Between LS_I and N_I	Increase	70%	130%
	Stability	55%	145%
	Decrease	40%	160%
Below LN_I	Increase	25%	175%
	Stability	10%	190%
	Decrease	0%	200%

IV. NUMERICAL EXPERIMENTS

The proposed mechanism was numerically evaluated by comparing the results obtained with the controller (considering the four control strategies presented above) with the one generated by the traditional treatment simulation (which adopts a fixed maintenance dosage with $Q^* = 2$ μg/kg). In all cases, a treatment period of 90 days was simulated, taking into account three levels of noise (±10%, ±30% and ±50%) in the calculation of the effectively absorbed dosage

Numerical experiments were performed for three distinct conditions corresponding to patients with hypothyroidism submitted to inadequate treatments of irregular dosage, under dosage and over dosage. The first condition represents patients with normal hormonal concentrations, that is, concentrations inside of respective regulatory bands, but subject to abrupt changes on concentration values due to undesirable variation in the supplied drug quantity. In these simulations, the maintenance dosage randomly changes between 1.5 and 2.5 μg/kg. The second condition corresponds to the patients who, during a time period, suspend the treatment; that is, they are without receiving the drug dosage needed for the homeostasis maintenance. In third condition, patients are daily submitted to excessive dosage of the drug (4 μg/kg), resulting in a temporary hyperthyroidism situation.

From our mathematical model for hypothyroidism, 100 distinct simulations were performed for each condition. Thus, hormone data were generated from these equilibrium values and a random simulation period between 5 and 8 days.

Our mathematical model was also used in simulations of the patient reply to the treatments. In each simulation, the initial concentrations were obtained from the last measurement of each substance (at time step t) and of the absorbed dosage, already considering the noise level generated at that time step.

In all three conditions, curves of TSH and free T_4 concentrations and of the effectively absorbed dosage $Q(t)$ were obtained. From these curves, the respective averages and standard deviations were calculated for the hormonal concentrations at maintenance phase (after stabilization), as well the total quantity of drug absorbed during the treatment and the time spent for the regularization of the patient concentrations. It was considered that the hormonal curve regularization occurred after 30 days of treatment. This choice was based on the necessary time period for the full performance of the drug on the organism and is, therefore, the period generally waited by the doctor to verify the reply of the organism to the supplied dosage. Moreover, this time period was enough to assure that hormonal curves were already stabilized in all simulations.

Tables 2, 3 and 4 present the results obtained in the conditions of under, irregular and over dosages, respectively. For each condition, the results were clustered by the employed control method and the noise level. In these tables, columns λ and δ of each concentration represent, respectively, the average of mean values after stabilization and the average of its standard deviation obtained in 100 simulations. The column Θ is relative to the highest average of standard deviation obtained in the simulations. Moreover, the mean absorbed dosage quantity (Q_{mean}) and the mean normalization time (T_{mean}) for each tested condition are also presented.

When we analyzed the mean values and its respective oscillations, the approach with controller produced better results than the ones obtained by using fixed dosage for all perturbation levels. In all three conditions, the use of the controller resulted in mean values (λ) close to the equilibrium point of the differential equations. The fixed dosage method provoked abrupt changes in the free T_4 concentrations, as observed in the column relative to the maximum oscillation (Θ). TSH concentrations remained inside of the currently accepted values of normality (between 0.34 and 4.82 μUI/ml) without great oscillations. However, the concentrations obtained with the fixed dosage were above the regulatory band proposed in [7] and adopted in this work (between 0.4 and 2.0 μUI/ml).

It can be stressed that, the higher the noise level, the more significant are the improvements obtained with the controller in relation to fixed dosage. With noises of ±50%, it was verified that the approaches with the controller resulted in mean values of TSH and free T_4 inside of the respective regulatory bands, although the oscillations exceed the desired variation of 5%; whereas the approach with fixed dosage resulted in mean values of free T_4 outside of regulatory band in approximately 50% of the cases. Furthermore, in the approach with fixed dosage, noises of order of ±30% were already high enough to provoke abrupt oscillations (above 5%), taking some of the free T_4 concentrations below of the regulatory band in all cases, during maintenance phase.

The approach adopting a higher weight for P_{T4L} generated the highest oscillations, reaching unsatisfactory values (above 5%) from noises of ±30%. The approach using equal weights presented, during the maintenance phase, some values of the free T_4 concentration below the regulatory band around 15% of the simulations, when submitted the noise of ±50%. The approach with higher weight for P_{TSH} and the mixed approach presented mean values closer to the equilibrium point of the mathematical model, as well lower oscillations for the three noise levels. This similarity occurs because both methods use the same strategy in the maintenance phase.

The mean time spent for normalizing the hormonal concentrations in the fixed dosage method is greater than those obtained with the controller. In first one, the mean time for normalization was around 95 hours for under dosage and 18 hours for over dosage, whereas with the controller was 26 hours and 12 hours, respectively. However, in the adaptive approaches, patients absorb around 336 μg/kg during the treatment (1.87 μg/kg/dosage), whereas with fixed dosage the mean absorption is of 271 μg/kg (1.51 μg/kg for dosage). For the control methods, the ones with $\alpha_{T4L} > \alpha_{TSH}$ and $\alpha_{T4L} = \alpha_{TSH}$ were more economical than the others, in relation to the quantity of absorbed drug. By comparing the other two methods, mixed approach was a little bit more economic, due to its strategy at the stabilization phase. By analyzing the

mean normalization time, the methods adopting a higher weight to P_{T4L}, $\alpha_{T4L} > \alpha_{TSH}$ and mixed approach presented more agility in the controller reply for the supplied drug, guaranteeing a smaller normalization time.

V. Conclusion

The main goals of this work were to elaborate and to evaluate controller models that provide treatments for patients with primary hypothyroidism, in order to maintain both TSH and free T_4 concentrations inside of the respective regulatory bands, without provoking abrupt oscillations. The numerical experiments showed that the controller was able to regularize the patient situation as expected. Moreover, treatments simulated with the controller usually provided a more adequate behavior than those ones simulated with the fixed dosage approach. In fact, the controller produced results more robust in the presence of noise than that one obtained by fixed dosage approach. However, the performance of the controller always demands a higher quantity of drug. In principle, such dosage only replaces the essential hormones. Thus, the use of a higher or lower quantity would not compromise the clinical scenario of the patient, since the hormonal concentrations are maintained inside of the regulatory bands for the investigated control mechanism.

Among the adaptive approaches investigated here, those ones using a higher weight associated to the adjustment percentage of the TSH presented more robust results; in other words, mean values closer to the equilibrium point and reduced oscillations for the three levels of noise. However, the methods employing higher weight for the adjustment percentage of the free T_4 resulted in a faster stabilization of the hormonal concentrations and in a lower quantity of absorbed drug. For these reasons we conclude that the control method using the mixed approach ($\alpha_{T4L} > \alpha_{TSH}$ during the stabilization phase and $\alpha_{T4L} < \alpha_{TSH}$ in the maintenance phase) provide, in general, the best treatments for the tested scenarios.

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TABLE II. RESULTS OBTAINED IN THE CONDITION OF UNDER DOSAGE

Control Method	Noise Level (%)	Free T_4 Concentration			TSH Concentration			Q_{mean} (μg/kg)	T_{mean} (hours)
		λ (ng/dl)	δ (%)	Θ (%)	λ (μUI/ml)	δ (%)	Θ (%)		
Fixed Dosage	±10	0.87	1.29	1.59	2.29	0.54	0.94	282	76
	±30	0.84	4.03	5.51	2.4	1.51	2.85	271	95
	±50	0.80	6.82	9.27	2.51	2.42	4.73	260	114
$\alpha_{TSH} = \alpha_{T4L}$	±10	1.04	1.69	2.14	1.75	0.69	1.43	343	24
	±30	1.03	3.62	4.33	1.78	1.13	1.91	340	26
	±50	1.01	5.67	6.81	1.85	2.11	3.72	333	29
$\alpha_{TSH} < \alpha_{T4L}$	±10	1.04	3.16	3.53	1.76	0.63	1.16	340	24
	±30	1.03	4.40	4.95	1.79	1.04	1.71	337	26
	±50	1.01	6.10	7.63	1.86	2.06	3.78	331	29
$\alpha_{TSH} > \alpha_{T4L}$	±10	1.06	1.23	1.43	1.69	0.71	1.29	350	24
	±30	1.04	3.26	4.18	1.75	1.33	2.58	344	27
	±50	1.02	5.68	7.21	1.82	2.47	3.90	337	29
Mixed Approach	±10	1.06	1.23	1.48	1.69	0.7	1.21	347	24
	±30	1.04	3.30	4.01	1.75	1.40	2.22	341	27
	±50	1.02	5.71	7.05	1.82	2.46	4.06	334	27

TABLE III. RESULTS OBTAINED IN THE CONDITION OF IRREGULAR DOSAGE

Control Method	Noise Level (%)	Free T_4 Concentration			TSH Concentration			Q_{mean} (μg/kg)	T_{mean} (hours)
		λ (ng/dl)	δ (%)	Θ (%)	λ (μUI/ml)	δ (%)	Θ (%)		
Fixed Dosage	±10	0.87	1.27	1.54	2.27	0.54	0.86	283	
	±30	0.84	3.91	5.45	2.4	1.50	2.60	271	
	±50	0.80	6.98	8.88	2.51	2.58	5.01	260	
$\alpha_{TSH} = \alpha_{T4L}$	±10	1.04	1.66	2.18	1.75	0.67	1.21	338	
	±30	1.03	3.57	4.12	1.78	1.12	2.07	335	
	±50	1.01	5.72	6.93	1.85	2.11	3.49	328	
$\alpha_{TSH} < \alpha_{T4L}$	±10	1.04	3.17	3.50	1.76	0.61	0.98	336	
	±30	1.03	4.36	4.89	1.79	1.07	1.70	333	
	±50	1.01	6.17	7.20	1.85	2.04	3.13	327	
$\alpha_{TSH} > \alpha_{T4L}$	±10	1.06	1.23	1.50	1.69	0.73	1.30	345	
	±30	1.04	3.28	3.91	1.75	1.38	2.34	339	
	±50	1.02	5.77	7.34	1.82	2.45	4.73	331	
Mixed Approach	±10	1.06	1.22	1.44	1.68	0.69	1.23	345	
	±30	1.04	3.24	3.84	1.75	1.35	2.11	339	
	±50	1.02	5.59	6.68	1.81	2.32	3.87	331	

TABLE IV. RESULTS OBTAINED IN THE CONDITION OF OVER DOSAGE

Control Method	*Noise Level (%)*	*Free T_4 Concentration*			*TSH Concentration*			Q_{mean} *(μg/kg)*	T_{mean} *(hours)*
		λ (ng/dl)	*δ (%)*	*Θ (%)*	*λ (μUI/ml)*	*δ (%)*	*Θ (%)*		
Fixed Dosage	±10	0.87	1.28	1.72	2.29	0.56	1.08	282	19
	±30	0.84	3.96	5.20	2.40	1.54	2.90	271	17
	±50	0.80	7.12	9.23	2.51	2.63	5.54	259	17
$\alpha_{TSH} = \alpha_{T4L}$	±10	1.04	1.68	2.11	1.75	0.70	1.08	334	12
	±30	1.03	3.63	4.25	1.78	1.15	2.03	331	12
	±50	1.01	5.71	7.15	1.85	2.19	3.66	324	12
$\alpha_{TSH} < \alpha_{T4L}$	±10	1.04	3.17	3.51	1.76	0.65	0.91	334	12
	±30	1.03	4.38	5.03	1.79	1.12	2.06	330	12
	±50	1.01	6.07	7.04	1.85	1.98	3.38	324	12
$\alpha_{TSH} > \alpha_{T4L}$	±10	1.06	1.22	1.52	1.68	0.80	1.82	341	13
	±30	1.04	3.28	3.81	1.75	1.43	2.51	334	13
	±50	1.02	5.78	7.33	1.82	2.52	4.21	327	13
Mixed Approach	±10	1.06	1.24	1.80	1.68	0.80	2.71	340	12
	±30	1.04	3.28	3.91	1.75	1.40	2.45	334	12
	±50	1.02	5.73	7.19	1.82	2.50	4.10	327	12