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A theory of drug tolerance and dependence II: the mathematical model

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Abstract

The preceding paper presented a model of drug tolerance and dependence. The model assumes the development of tolerance to a repeatedly administered drug to be the result of a regulated adaptive process. The oral detection and analysis of exogenous substances is proposed to be the primary stimulus for the mechanism of drug tolerance. Anticipation and environmental cues are in the model considered secondary stimuli, becoming primary in dependence and addiction or when the drug administration bypasses the natural—oral—route, as is the case when drugs are administered intravenously. The model considers adaptation to the effect of a drug and adaptation to the interval between drug taking autonomous tolerance processes. Simulations with the mathematical model demonstrate the model's behaviour to be consistent with important characteristics of the development of tolerance to repeatedly administered drugs: the gradual decrease in drug effect when tolerance develops, the high sensitivity to small changes in drug dose, the rebound phenomenon and the large reactions following withdrawal in dependence. The present paper discusses the mathematical model in terms of its design. The model is a nonlinear, learning feedback system, fully satisfying control theoretical principles. It accepts any form of the stimulus—the drug intake—and describes how the physiological processes involved affect the distribution of the drug through the body and the stability of the regulation loop. The mathematical model verifies the proposed theory and provides a basis for the implementation of mathematical models of specific physiological processes.

Keywords: Drugs; Drug tolerance; Dependence; Addiction; Adaptation; Mathematical model

1. Introduction

In previous publications, a first approach to modelling drug tolerance was made (Peper et al., 1987, 1988). In the model presented in those papers, the stimulus—the drug administration—was either present or not present: on or off. The relatively simple model did show many of the characteristics of tolerance development but the on-off approach also concealed several important properties of the process. The model has been improved considerably since then. The current model accepts any form of the stimulus—the drug intake—and describes how the parameters of the different processes involved—like the digestive tract and the bloodstream—affect the distribution of the drug through the body and the stability of the regulation loop. Many of the considerations given when the mathematical model was first published are still applicable. However, the development of the new model has resulted in a better understanding of the process of tolerance development and a revision of the underlying theory. The model now incorporates important features not described by the earlier version. The theory behind the model was presented in the preceding paper. The present paper will discuss the mathematical implementation of the model.

First, the paper will formulate a model capturing how tolerance develops to a drug which changes the level of a regulated substance in the bloodstream. It will then address a model of a physiological process whose information transfer in the process regulation is disturbed.

For the sake of brevity, the index "(t)" in time signals is omitted in the formulae.

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2. Methods

The mathematical models below have been developed with a mathematical simulation program. The program closely resembles the old analogue computer, its main building blocks being amplifiers, integrators, multipliers and summing blocks. The symbols used are briefly described in the appendix. The operation of the simulation program used was detailed in the appendix of a paper on tolerance development at cell level, giving a comprehensive description of how the paper modelled the mass balance (Peper et al., 1998).

3. The mathematical model

Fig. 1 shows a model of a regulated adaptive process (Fig. 7 in the preceding paper). The level of the substance in the bloodstream produced by the process is kept at the desired level through feedback. When a drug of the same composition as produced by the process is administered, the blood concentration of the substance initially will rise. When the drug is administered repeatedly, the adaptive regulator will slowly learn to counteract the increased blood concentration by decreasing the process output during the time the drug is in the bloodstream. Fig. 2 shows a block diagram of the mathematical implementation of this model. It includes the digestive tract and the bloodstream. The heavy arrows indicate the main route of the regulation loop. The thin arrows indicate the route of the disturbance: the transfer of the drug through the digestive tract to the bloodstream and the transfer of the information about the presence of the drug to the adaptive regulator. The following sub-sections will present mathematical models of the processes represented by the blocks in the figure.

3.1. The digestive tract

As will be discussed presently, the digestive system plays no role in the regulation loop. To simplify matters, drug transport through the digestive tract is modelled as a first order function. In specific models of drug tolerance the digestive system can easily be modelled more accurately without directly effecting the model's behaviour.

The equation describing the block is:

$$S_{digest} = \int_0^t drug\ \mathrm{d}t - \frac{1}{T_{digest}} \int_0^t S_{digest}\ \mathrm{d}t \qquad (1)$$

The input to the block is the drug administration, *drug*. The input signal is integrated to obtain the drug level when it enters the bloodstream, the output of the block S_{digest}. A fraction $1/T_{digest}$ of the output signal is

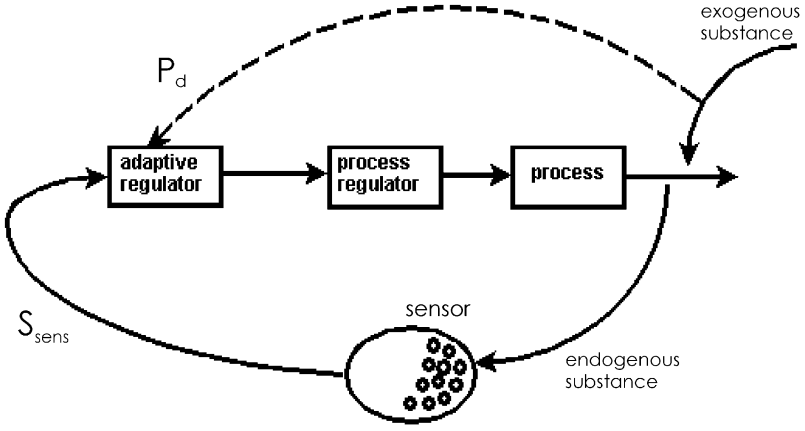

Fig. 1. Model of a regulated adaptive process. The level of the substance in the bloodstream produced by the process is kept at the desired level through feedback.

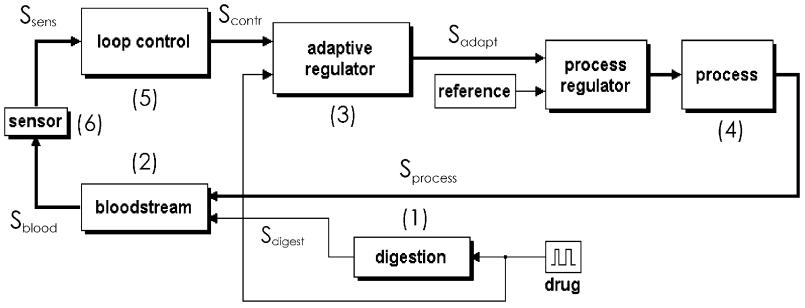

Fig. 2. Block diagram of the mathematical implementation of the model in Fig. 1.

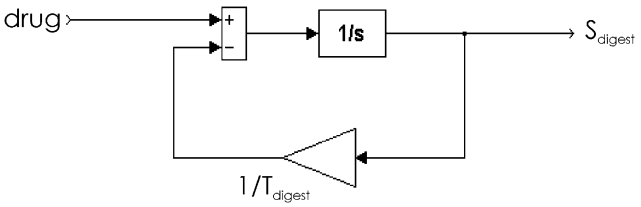

Fig. 3. Realization in the simulation program of the block "digestive tract". See text.

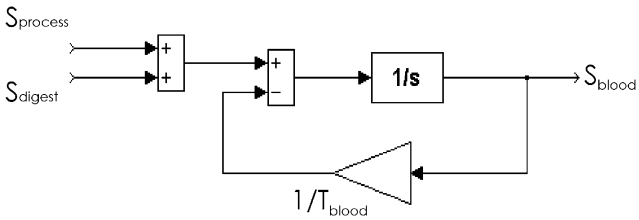

Fig. 4. Simulation of the bloodstream.

subtracted from the input to account for the spread in drug distribution in the digestive tract. T_{digest} is the time constant of this process. Fig. 3 shows the realization of the equation with the simulation program. The block "$1/s$" is an integrator, the block "$1/T_{digest}$" an amplifier (see appendix).

3.2. The bloodstream

After digestion, the drug enters the bloodstream where it will be dispersed. In the present configuration of the model, the drug and the substance produced by the process are assumed to be identical in composition and consequently add in the bloodstream. The amount of the total substance in the bloodstream will be reduced by the body's metabolism. The processes are modelled with a first-order function:

$$S_{blood} = \int_0^t (S_{process} + S_{digest})\,\mathrm{d}t - \frac{1}{T_{blood}} \int_0^t S_{blood}\,\mathrm{d}t \quad (2)$$

The input signals—the drug as it moves from the digestive tract into the bloodstream, S_{digest}, and the substance produced by the process, $S_{process}$—are added and integrated, yielding the output of the block, the blood drug level S_{blood}. To account for the body's metabolism, a fraction $1/T_{blood}$ of the output signal is subtracted from the input. The simulation of the block is given in Fig. 4.

3.3. The adaptive regulator

Fig. 5 shows a block diagram of the adaptive regulator. Its input signals are the drug administration and the sensor signal, processed by the loop control block (Section 3.6). The sensor signal provides the information about the drug effect. The output of the adaptive regulator counteracts the disturbance by lowering the process output during the drug's presence. The adaptive regulator comprises a fast and a slow regulator. The fast regulator is the essential part of the adaptive regulator and consists of the blocks "drug regulator", "interval regulator" and "model estimation". The slow regulator suppresses the slow changes in the input signal, its output being the average of the input signal (see Section 3.3.3). As the fast regulator reacts to fast changes only, the output of the slow regulator is subtracted from its input. The input for the fast regulator, S_d, is then $S_{contr} - S_{slow}$. As was discussed in the previous paper, it is assumed that the body more or less separately develops tolerance to the drug's presence and to the intervals between drug administrations. The fast regulator therefore consist of two separately functioning regulators: one regulator which provides the adaptation to the drug's direct effect and another regulator which provides adaptation to the interval between drug taking. The model assumes the interval to start at the top of the drug curve (this assumption will be elaborated in Section 5). The output of the complete adaptive regulator is a combination of signals from its individual components. This is schematically indicated in the figure by the summation of their output signals.

As discussed in the preceding paper, the model assumes the body to anticipate the effect of a drug to which it has developed tolerance. This implies that the body has made an estimate of what is going to happen when the drug is administered. In other words, the organism has "knowledge" of the course of the drug effect over time: it has a model of it. The organism also has made an estimate of the magnitude of the drug effect at the given state of tolerance development. These two entities are the main factors determining the functioning of the fast regulator: the level of tolerance development and the—more or less pulse-shaped—course of the drug effect (see Section 3.3.2).

3.3.1. The fast regulator

Fig. 6 shows the basic configuration of the fast regulator as implemented in the simulation program. It resembles to some extent the adaptive filter developed by Widrow (Widrow et al., 1976), a technique used to suppress periodically occurring signals in measurements. The Widrow adaptive filter slowly learns to optimise its parameters on the basis of knowledge about the unwanted signal. To explain Fig. 6, it is first examined without the feedback path, i.e. without the connection between the output and the negative input of the summator. In this configuration, the input signal S_d is multiplied by M_{drug}, which represents the course of the drug level in the input signal over time (see Section 3.3.2). The signal obtained is a measure of the component in S_d which has the form M_{drug}. This signal is integrated ($1/s$) with a time constant T_{drug}, yielding its

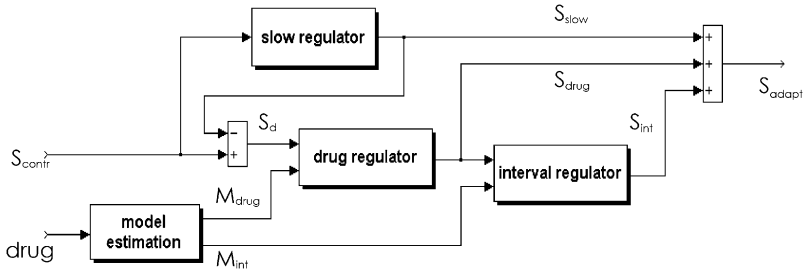

Fig. 5. Block diagram of the adaptive regulator.

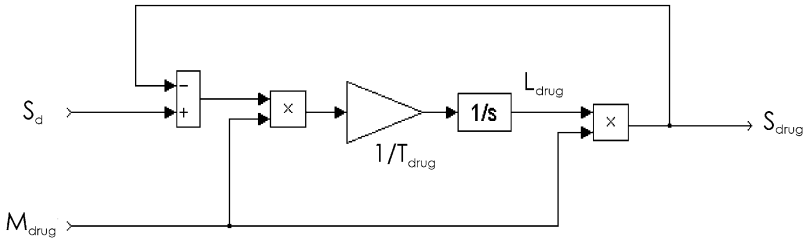

Fig. 6. Simulation of the basic configuration of the fast regulator.

average. The resulting value is a slowly rising signal, L_{drug}. This method of estimating a signal of known form—also applied in the Widrow adaptive filter—is derived from synchronous detection developed in radio technique. Multiplying L_{drug} by M_{drug} yields the output signal S_{drug}. As M_{drug} has a magnitude of unity (see Section 3.3.2) and L_{drug} is only slowly changing, S_{drug} has the shape of M_{drug} and the magnitude of L_{drug}.

When the feedback path is included, it will make the output signal magnitude equal to the input. However, because of the slow response of the circuit, changes in the input magnitude will be followed only slowly by the output. The speed of change of the output magnitude—representing the slow development of tolerance by the organism—depends on the frequency of occurrence of the drug signal and the amplification of the feedback loop: $1/T_{drug}$. The relation between the signals is:

$$S_{drug} = M_{drug}\frac{1}{T_{drug}}\int_0^t (S_d - S_{drug})M_{drug}\,\mathrm{d}t \tag{3}$$

and

$$S_{drug} = L_{drug}M_{drug} \tag{4}$$

Fig. 7 shows a simulation of the signals defined above: Trace(a) shows the pulse-shaped input signal, S_d, representing the drug level derived from the sensor. In this description of the fast regulator, all drug pulses have been given the same magnitude. Trace(b) shows the level of adaptation to the drug L_{drug} and the output signal S_{drug}. As the magnitude of M_{drug} is unity (see Sections 3.3.2 and 5), the top of the pulses in S_{drug} equal the level of L_{drug}.

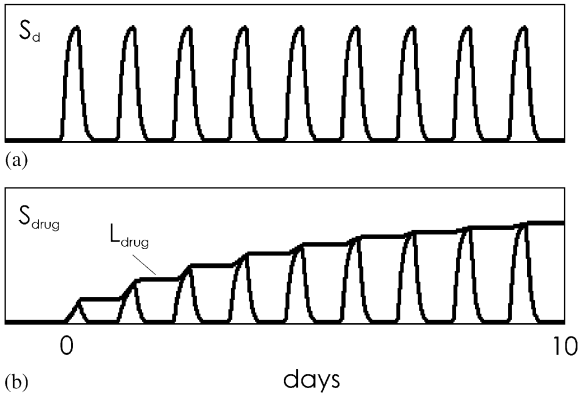

Fig. 7. The signals involved in the basic configuration of the fast regulator. (a) The pulse-shaped input signal S_d. All drug pulses have been given the same magnitude. (b) The level of adaptation to the drug L_{drug} and the output signal S_{drug}.

As noted in Section 3 of the previous paper, the adaptation to the interval proceeds from the level it has acquired during the drug's presence. Consequently, the input to the interval regulator is obtained when the output signal of the drug regulator—S_{drug}—is subtracted from its top value L_{drug}. This is further elucidated by Fig. 7b. The model of the interval is M_{int}. The modelling of this signal will be discussed in Section 3.3.2.

Fig. 8 shows an implementation in the simulation program of the complete fast regulator. Included is a provision for the tolerance level to decrease over time when no drug is administered. To this end a fraction,

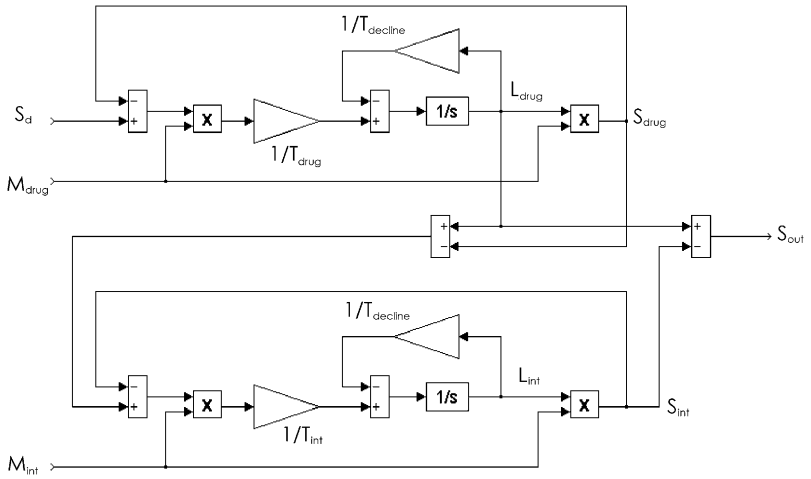

Fig. 8. Simulation of the complete fast regulator comprising a separate regulator for the drug and for the intervals. Included is a provision for the tolerance level to decrease over time when no drug is supplied (see text).

$1/T_{decline}$, of the output signal of the integrator is subtracted from its input. $T_{decline}$ is the time constant determining this decrease of tolerance.

The relation between the signals in the fast regulator describing the drug's presence is then:

$$S_{drug} = M_{drug}\frac{1}{T_{drug}}\int_0^t (S_d - S_{drug})M_{drug}\,\mathrm{d}t - M_{drug}\frac{1}{T_{decline}}\int_0^t \frac{S_{drug}}{M_{drug}}\,\mathrm{d}t \quad (5)$$

and

$$S_{drug} = L_{drug}M_{drug} \quad (6)$$

Similarly, the equation describing the interval regulator is:

$$S_{int} = M_{int}\frac{1}{T_{int}}\int_0^t (L_{drug} - S_{drug} - S_{int})M_{int}\,\mathrm{d}t - M_{int}\frac{1}{T_{decline}}\int_0^t \frac{S_{int}}{M_{int}}\,\mathrm{d}t \quad (7)$$

and

$$S_{int} = L_{int}M_{int} \quad (8)$$

The output of the interval regulator is S_{int}. As discussed above, its (positive) input signal is $L_{drug}-S_{drug}$. Likewise, the output signal of the total fast regulator is obtained by subtracting the interval signal from the top level of the drug signal (this is further discussed in Section 5-4):

$$S_{out} = L_{drug} - S_{int} \quad (9)$$

Fig. 9 shows the relevant signals. Trace(a) shows the input signal to the drug regulator due to the drug's presence S_d. As in the simulation of Fig. 7, every drug pulse has been given the same magnitude. Trace(b) shows the output signal, S_{drug}, and the level of adaptation L_{drug}. S_{drug} slowly adapts to the shape and magnitude of S_d. Trace(c) shows the output of the interval regulator S_{int}. For the sake of clarity, the signal is presented negatively. Trace(d) shows the output of the complete adaptive regulator S_{out}. This signal represents the counteraction by the organism to the drug's disturbance.

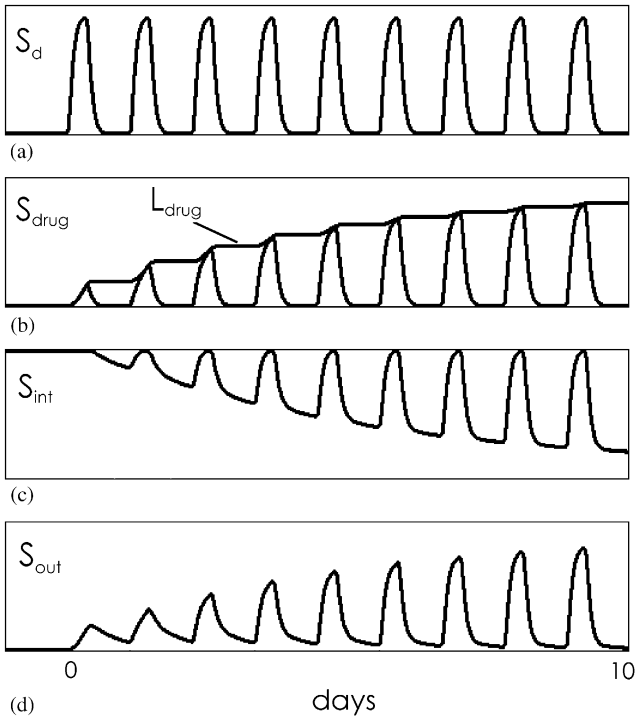

Fig. 9. (a) Input signal due to the drug's presence S_d. (b) Level of adaptation L_{drug} and output signal S_{drug}, which slowly adapts to the shape and magnitude of S_d. (c) Output of the interval regulator S_{int}. For the sake of clarity, the signal is presented negatively. (d) Output of complete adaptive regulator S_{out}, representing the counteraction by the organism to the drug's disturbance.

In the simulation of Fig. 9b, S_{drug} slowly approaches the magnitude of S_d, which in this simulation has a constant magnitude. This takes place at a speed determined by T_{drug}. The output of the interval regulator, S_{int}, slowly approaches the magnitude of its input signal, $L_{drug}-S_{drug}$. This takes place at a speed determined by $T_{drug}+T_{int}$. Section 5 below will further elaborate on this aspect of the model.

3.3.2. Estimation of the drug effect in the adaptive regulator

As observed above, to be able to counteract the effect of a drug at a certain stage of tolerance development, the organism must "know" what that effect will be. The functioning of the adaptive regulator is based on the assumption that the organism has an estimate—a model—of how the concentration of the drug in the bloodstream changes over time. The organism may obtain this model in several ways. One way is that it "remembers" it from previous times the drug was present. Alternatively, it may make an estimate based on knowledge of the pathway's effect on the drug distribution. The organism must then "know" the transfer function of the pathway and how the drug is administered. The latter way is adopted in the present paper.

When the adaptive regulator develops tolerance to a drug, it induces changes in the process output which counteract the effect of the drug. This counteraction is effected at the point the exogenous and endogenous substances meet, which is in the present configuration of the model in the bloodstream. The path between the point where the drug is administered and the bloodstream is the digestive tract. As the duration of the drug administration in most cases is short, it may be represented by a short pulse. The model of the course of the drug concentration when it enters the bloodstream—M_{drug}—is then computed by calculating the effect of a pulse with a magnitude of 1 on the digestive tract's transfer function, which was described in Section 3.1. The input of the interval is acquired when the signal "drug" is subtracted from its top value: 1. Multiplying this signal with the transfer of the digestive tract yields the model of the interval M_{int}. The relation between the signals is then:

$$M_{drug} = \int_0^t drug\,\mathrm{d}t - \frac{1}{T_{digest}}\int_0^t M_{drug}\,\mathrm{d}t \tag{10}$$

and

$$M_{int} = \int_0^t (1 - drug)\,\mathrm{d}t - \frac{1}{T_{digest}}\int_0^t M_{int}\,\mathrm{d}t \tag{11}$$

T_{digest} is the time constant of the digestive system as described in Section 3.1. The simulation of the block is given in Fig. 10. In other designs of the model, different methods of acquiring M_{drug} and M_{int}, independent of how the drug is administered, were implemented and worked equally well.

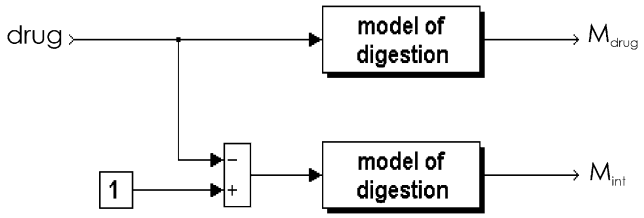

Fig. 10. Simulation of the block "Model estimation" (see text).

3.3.3. The slow regulator

In "Fast and slow adaptation" in Section 4, the previous paper explained that the slow regulator models the long term adaptation to the drug effect. In the tolerant state, the slow adaptation causes the magnitude of the negative reaction after the drug effect to depend on the interval between drug administrations: an infrequent taken drug has a small effect during the interval, a frequently taken drug causes a large rebound. In the mathematical model, the slow regulator counteracts the disturbance by lowering the level of the process with the average of the drug effect. Its input signal—the sensor signal, processed by the loop control block (Section 3.6)—provides the information about the drug effect. The average of the input signal is obtained by a low pass filter with a time constant T_{slow}:

$$S_{slow} = \int_0^t S_{contr}\,\mathrm{d}t - \frac{1}{T_{slow}}\int_0^t S_{slow}\,\mathrm{d}t \tag{12}$$

The simulation of the block is given in Fig. 11.

3.4. The process

The model does not incorporate the characteristics of the process and the process regulator. As detailed below, in a specific model of drug tolerance where the process is included, the effect of the process transfer on loop stability has to be controlled by the "The loop control" block.

3.5. Loop control

A loop control is an essential element in any regulated system. It incorporates the open loop amplification which determines the accuracy of the regulation and it provides the necessary conditions for stable operation of the negative feedback system. Only a first-order regulation—a regulation containing one dominant time constant in the open loop transfer—is unconditionally stable without uncontrolled deflections. Third and higher order regulations are fundamentally unstable. A second-order regulation is stable, but disturbances may

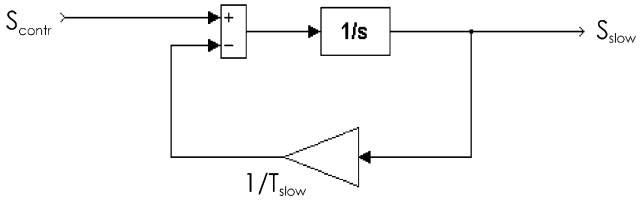

Fig. 11. Simulation of the block "Slow regulator".

cause large deflections.[1] For stable operation, the regulation loop has to contain compensation for the effect of superfluous time constants: their effect on the signals in the loop has to be counteracted by circuits with an inverse effect (Chestnut and Mayer, 1951; Bell and Griffin, 1969). Although these design considerations are derived from control theory, they necessarily also apply to physiological regulations: stable physiological regulations must have solved the same instability problems as occur in regulations designed by man. Since physiological regulations almost always contain many different time constants in the regulation loop, their effects must have been compensated for by the organism. In other words, the organism anticipates the effects of time constants and delays in a regulation loop and takes measures to reduce their disturbing effect upon the stability of the loop.

Fig. 12 shows a block diagram of the "Loop control". In the model, the effects of those components in the loop whose time constants could interfere with the regulation are compensated by a circuit with an inverse transfer. The transfer of the process and its regulator are taken unity (see Section 3.4). The transfer function of the sensor is also set at unity, as discussed in Section 3.6. The remaining time constant in the loop, besides that of the adaptive regulator, is the time constant of the bloodstream. The effect of the bloodstream on the regulation loop is counteracted by the block "Inverse model of bloodstream". Fig. 13 shows a simulation of the block. If the amplification factor K in this feedback circuit is made large, the input signal of the amplifier—the difference between S_{sens} and $S_{sens'}$—becomes small and S_{sens} can be considered equal to $S_{sens'}$. The relation between the input and the output is then:

$$S_{sens} = \int_0^t S_{contr}\,\mathrm{d}t - \frac{1}{T_{blood}}\int_0^t S_{sens}\,\mathrm{d}t \qquad (13)$$

In Eq. (13), the input and output signals are in reverse order with respect to those in Eq. (2). Hence, their combined transfer is unity. The amplification of the loop amplification block usually has a negative value to account for the negative feedback. In the present model, the output of the adaptive regulator, S_{adapt}, is negatively fed to the input of the process regulator (see Fig. 2),

[1] For the sake of simplicity, regulations with open loop transfer functions containing only poles (no zeros) are considered here.

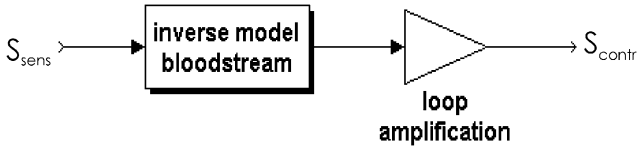

Fig. 12. Block diagram of the Loop control.

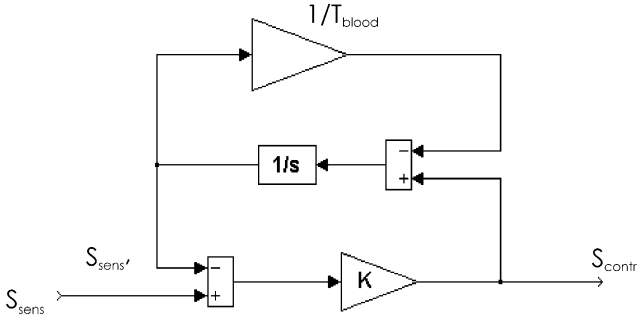

Fig. 13. Simulation of "Inverse model of bloodstream".

which amounts to the same overall effect, but with the advantage that the signals in the adaptive regulator are positive and better recognisable.

3.6. The sensor

The sensor transforms the chemical signal S_{blood}—the blood drug level—into the signal S_{sense}. This transformation is in the present model assumed to be linear and is set at 1. In specific models of physiological processes, this complex mechanism can be described more accurately. Stable operation then requires that the effect of its transfer on loop stability has to be controlled by the "The loop control" block.

4. Model considerations

4.1. The functioning of the complete regulation loop

Fig. 14 shows some signals from the total regulation feedback loop which may give some additional clarification of the functioning of the adaptive system. A hypothetical endogenous substance is produced by a certain process at a normally constant level $L_{process}$. The resulting blood level is L_{blood}. When the same substance is administered exogenously, the blood level will be disturbed. When the exogenous substance is administered repeatedly, the regulated system will develop tolerance. Trace(a) in Fig. 14 shows the exogenous substance when it enters the bloodstream from the digestive tract. Trace(b) shows the process output when tolerance develops: during the disturbances the output level will drop to counteract the induced rise in drug level. These two signals—$S_{process}$ and S_{digest} in Fig. 2—are added when the substances are mixed in the

bloodstream. The resulting signal is shown in trace(c) together with the resulting blood level, S_{blood}. In the simulation, all parameter settings are arbitrary, as are the axes in the figure. Because the stimulus—the drug intake—is in reality in most cases extremely short with respect to the repetition time, its duration has been extended for clarity.

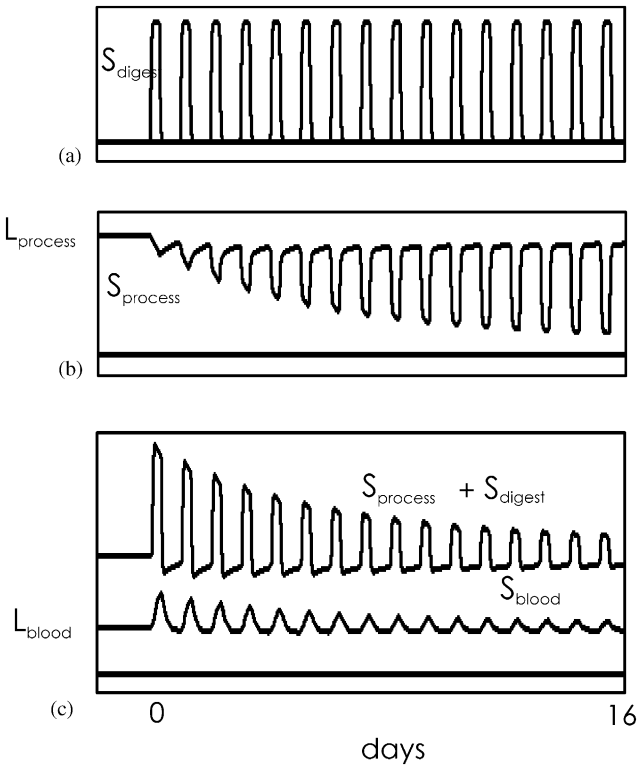

Fig. 14. Some signals from the total regulation feedback loop, clarifying the functioning of the adaptive system. (a) The exogenous substance when it enters the bloodstream from the digestive tract, S_{digest}. (b) Process output during tolerance development, $S_{process}$. (c) $S_{process}$ and S_{digest} added in the bloodstream and the resulting drug blood level, S_{blood}. The level of the process output and the resulting bloodlevel before the drug is administered are $L_{process}$ and L_{blood}.

4.2. Adaptation to a disturbance of the information transfer

So far, the paper has modelled a disturbance in the regulation of the level of an endogenously produced substance. The situation becomes more complex when a drug interferes with the information transfer in the regulation of a process by affecting a messenger–receptor interaction. Fig. 15 (Fig. 8 in the previous paper) shows a model of this situation. Fig. 16 shows a block diagram of its mathematical implementation. In the model in Fig. 2, described uptil now, the adaptive regulator controls the process. In the model in Fig. 15, the adaptive regulator controls the transfer of the sensor. In this configuration, there are two parallel

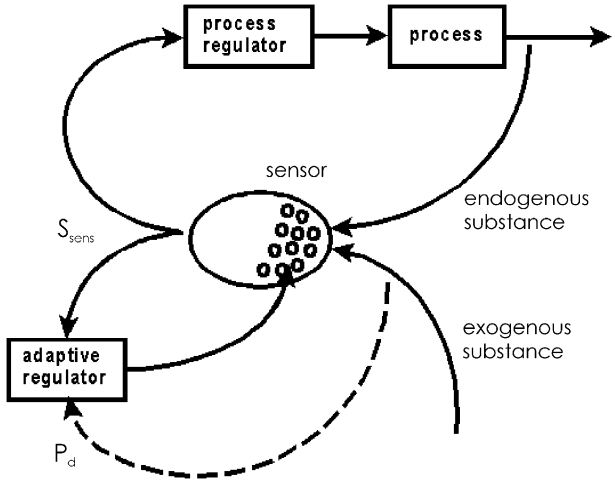

Fig. 15. Model in which a drug interferes with the information transfer in the regulation.

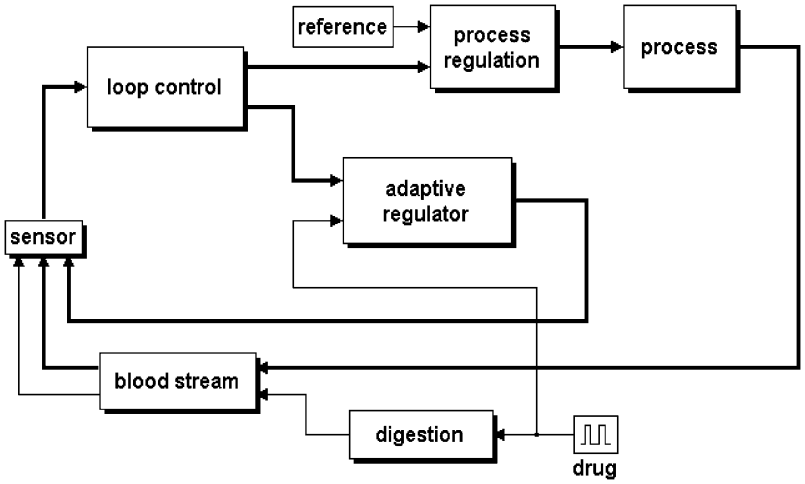

Fig. 16. Block diagram of the mathematical implementation of the model in Fig. 15.

branches in the regulation: the process loop and the adaptive regulator loop. To obtain stable operation of the regulation, the "Loop control" block separately processes the two loops. As in this configuration of the model the exogenous substance affects the sensor, the drug's path in the figure extends through the bloodstream to the sensor.

5. Discussion

It is important to observe that the mathematical model supports the underlying theory. This contrasts with most other published models of drug tolerance, which are qualitative only. The importance of conducting research into the behaviour of regulated physiological systems using control theoretical principles cannot be overemphasised as the behaviour of a regulated system can only be understood from the behaviour of a mathematical model describing it. Even the behaviour of the simplest regulated system cannot be described other than mathematically. The behaviour of more complex regulated systems can only be understood from simulations with computer programs using advanced, iterative methods to solve the differential equations involved. This implies that a model which is qualitative only, may never involve feedback systems as their behaviour cannot be predicted. It is important to note that the development of a satisfactory mathematical model of a physiological process requires an understanding of the process's behaviour, which provides a check on the investigator's insight into the logic underlying the developed model.

Although the adaptive regulator described is a nonlinear system, the model as a whole can be approached as linear with respect to the relation between the drug dose and the drug effect (see Peper et al., 1987). Physiological processes are rarely linear and always operate between a minimum and a maximum limit. However, these boundaries and nonlinearities can be incorporated in the model when it is applied to specific physiological processes.

During the development of the model, several choices had to be made between alternative solutions. Some considerations are:

1. The model considers the top of the drug signal the beginning of the interval between drug taking. This of course is arbitrary. When the drug curve has a long flat top or when there are irregularities in the curve, this assumption will not hold. However, it is not known how the body defines the interval, which may vary across processes and across drugs. Moreover, different definitions of the start of the interval would not alter the concept underlying the model and would in most cases not significantly change the outcome of the simulations. It should be realized that in other models of drug tolerance the interval between drug taking is not regarded to be part of an autonomous adaptive process and, consequently, no research has been done on this subject.
2. As discussed in Section 3.3.1, the regulator for adaptation to the intervals receives its input signal from the regulator for the drug signal. The interval regulator adapts with a time constant T_{int} to the magnitude of its input signal which has a time constant T_{drug}. As a result, the two exponentials multiply ($e^{T_{drug}} \cdot e^{T_{int}}$) and the time constant of the adaptation of the interval regulator is $T_{drug} + T_{int}$. This seems strange, as the drug and the interval regulator might be expected to have similar time constants which apparently can only be achieved when T_{int} is very small. However, the speed of adaptation is also determined by the duration of the intervals, which means that the time constants of the regulators are not the defining parameters. In addition, it should be realized that the time constants in the tolerance mechanism are parameters chosen by the organism, probably on the basis of the constancy of the dose, the frequency of administration and other, unknown, parameters.
3. The way in which the organism estimates the course of the disturbance and the interval between disturbances has some difficult aspects. In the simple on-off model published previously, this did not show as the signal was multiplied by either 1 or 0. In the development of the present model, it became apparent that this estimate can be made in several ways. However, only with the adopted assumption that the organism makes an estimate of the shape of the drug curves and interval curves and normalizes them to unity magnitude—i.e. the organism remembers only the shape and not the magnitude—does the model accurately reflects the in vivo process. This indicates that the real behaviour of the organism may resemble this solution.
4. The output signals from the drug regulator and the interval regulator can be combined in different ways to obtain the output of the total fast regulator. For instance, as the regulators more or less function alternately, their output signals can be added only when they are active. However, other ways of combining the two signals did not produce much difference and in the model developed above the output signal was obtained by subtracting the interval signal from the top level of the drug signal.

6. Conclusion

An important feature of a mathematical model is its ability to predict the behaviour of the process in vivo. In

an adequate model, the effect of a change in the process parameters will resemble the effect of a change in the corresponding parameters of the physiological process. The mathematical model presented has a powerful predicting capability as was demonstrated in the simulations shown in the preceding paper and in a previous paper where model predictions were presented for optimal withdrawal protocols (Peper and Grimbergen, 1999). The model may provide a better insight into many aspects of drug taking and into the way in which the organism organizes its response to a drug. Bearing in mind its limitations, the model can be a valuable tool in the development of more specific models of tolerance processes.

Readers interested in a copy of the software are invited to contact the writer.

Appendix. The simulation program

The model is developed with the mathematical simulation program Simulink, which is an extension to the Matlab technical computing language. In its use, the program closely resembles the old analogue computer, its main building blocks being amplifiers, integrators, multipliers and summing blocks. In the extensive library there are also signal generators, oscilloscopes and a multitude of linear and nonlinear function blocks. In addition, the user can define any self-developed function block for future use while any part of the simulation circuit can be merged into a new block with a menu for the parameters used. Any block can be changed or duplicated without limitation. By its modular structure, the program allows for the simulation of very complex systems and an easy and fast adaptation of the model parameters to the outcome of measurements.

In Fig. 17 some much-used function blocks are shown:

- Amplifiers.
- Integrators, indicated as $1/s$, "s" being the complex Laplace operator. The integrator can be given an initial value.
- Summing blocks; the number of inputs to be summed or subtracted can be chosen.
- Constants.
- Multipliers; the number of signals to be multiplied or divided can be chosen.

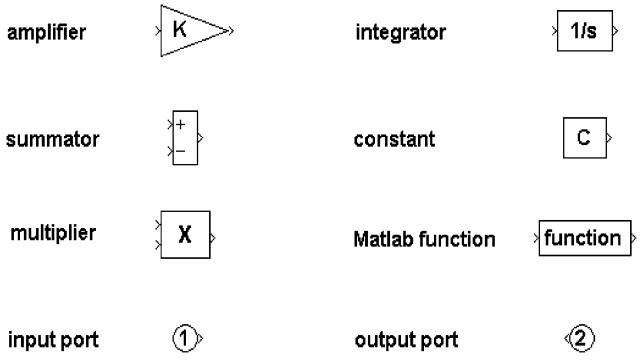

Fig. 17. Some frequently used function blocks used in Simulink.

- Function blocks for the application of Matlab functions.
- Input and output ports used in blocks.

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