Chapter 2
Intermittent Adaptation: A Mathematical Model of Drug Tolerance, Dependence and Addiction

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Abstract A model of drug tolerance, dependence and addiction is presented. The model is essentially much more complex than the commonly used model of homeostasis, which is demonstrated to fail in describing tolerance development to repeated drug administrations. The model assumes the development of tolerance to a repeatedly administered drug to be the result of a process of intermittently developing adaptation. The oral detection and analysis of endogenous substances is proposed to be the primary stimulus triggering the adaptation process. Anticipation and environmental cues are considered secondary stimuli, becoming primary only 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 to be autonomously functioning adaptation 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.

2.1 Introduction

If a drug is administered repeatedly, the effect it has on the organism decreases when the organism develops tolerance to the drug. Many models of drug tolerance have been developed in the past. Most of these models are qualitative only and do not illuminate the mechanism underlying the effect very much. Those models that do attempt to describe the process mathematically are often too simple and only consider the effect of a single drug administration. A proper model describing how drug tolerance develops should account for a gradual decrease in the drug effect when a drug is administered repeatedly and should include a triggered response

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to the drug administrations. The slow build-up of tolerance during successive drug administrations and the triggered response necessarily imply the presence of long term memory for the properties and the effects of the drug.

A variety of theories and models have been proposed to explain the mechanism relating the various aspects of drug taking. Very important has been the concept of homeostasis. In 1878, Bernard wrote: "*It is the fixity of the 'milieu interieur' which is the condition of free and independent life. All the vital mechanisms however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment*" (Bernard 1878, cited by Cannon 1929). Cannon translated Bernard's observation into the model of homeostasis (Cannon 1929). Fundamental in Cannon's theory is the presumption that physiological processes are regulated and that their functioning is in a "steady state": their conditions are stable and held constant through feedback. Homeostasis has been the basis of important theories like Bertalanffy's Systems Theory and Norbert Wiener's Cybernetics, which propose that physiological processes can be simulated by electronic feedback models (Wiener 1948; von Bertalanffy 1949, 1950). In the mathematical models of drug tolerance developed on the basis of these theories, the effects produced by drugs are assumed to be counteracted by a feedback mechanism which keeps the processes involved functioning at a preset level, thus causing tolerance to develop (Goldstein and Goldstein 1968; Jaffe and Sharpless 1968; Martin 1968; Kalant et al. 1971; Snyder 1977; Poulos and Cappell 1991; Dworkin 1993; Siegel 1996; Siegel and Allan 1998).

Besides the theories of drug tolerance based on homeostasis, there are theories which do not consider tolerance development the result of a regulated process. An influential theory was developed by Solomon and Corbit, the Opponent-Process theory (Solomon and Corbit 1973, 1974; Solomon 1977, 1980). In this theory, the drug is thought to trigger a response known as the A-process. The A-process induces a reaction called the B-process which opposes the A-process and increases in magnitude by repeated elicitation of the A-process. The A-process is fast, while the B-process is delayed and slow. As the difference between the A-process and the (negative) B-process is the ultimate effect of the drug, the drug effect will slowly decrease.

Several theories are based on a model of habituation developed by Rescorla and Wagner, which attributes tolerance to a learned diminution of the response (Rescorla and Wagner 1972; Wagner 1978, 1981; Tiffany and Baker 1981; Baker and Tiffany 1985; Tiffany and Maude-Griffin 1988). Dworkin incorporated this theory in a feedback model of drug tolerance (Dworkin 1993).

Another influential theory was proposed by Siegel (Siegel 1975, 1996, 1999; Siegel and Allan 1998; Siegel et al. 1982). In Siegel's theory, drug tolerance is assumed to be caused by Pavlovian conditioning: the compensatory response of the organism to the administration of a drug is triggered by environmental cues paired to the drug taking. Poulos and Cappell augmented Siegel's theory of drug tolerance by incorporating homeostasis, which was adopted by Siegel (Poulos and Cappell 1991; Siegel 1996; Siegel and Allan 1998).

In what follows, a model of drug tolerance, dependence and addiction will be presented which is different from the theories outlined above. The model is based on the

assumption that most processes in a living organism are regulated, which is in accordance with homeostasis. It will be argued that the slow build-up of tolerance during repeated drug administrations, combined with a triggered response to those administrations, requires a complex adaptive regulation mechanism which, although incorporating feedback, is essentially different from homeostasis. The model presented is a general model of drug tolerance and drug dependence where "general" indicates that the model is based on principles which are thought to be more or less applicable to all processes of tolerance development. The model assumes the development of tolerance to a drug to be a process of intermittent adaptation to the disturbing effects of the drug: *during* the disturbances the body gradually learns to counteract these effects (Peper et al. 1987, 1988; Peper and Grimbergen 1999; Peper 2004a, 2004b, 2009a, 2009b). It also assumes that when processes in living organisms are disturbed, they adapt in a way that is fundamentally the same for all processes. Knowledge about adaptation in one process, therefore, teaches us about adaptation in other processes. The latter hypothesis is defended by many writers (Thorpe 1956; Kandel 1976; Koshland 1977; Poulos and Cappell 1991; Siegel and Allan 1998). It allows us to use our knowledge of the body's adaptation to changing environmental temperature equally well as, for instance, knowledge about adaptation to colour stimuli (Siegel and Allan 1998) to solve problems in modelling the organism's adaptation to drugs.

2.2 Properties of Adaptive Regulated Physiological Processes

2.2.1 Homeostasis

Homeostasis has made an invaluable contribution to our understanding of how physiological processes function by introducing the concept of the regulated physiological process: the presumption that most processes in a living organism are, one way or another, regulated. Regulation implies that the behaviour of a certain process in the organism is ultimately determined by an aim set by the organism itself, which in a highly simplified process is the process set point or process reference. In a simple regulated process, the output of the process—i.e. what is produced or obtained—is observed by a sensor and compared with a desired value, the process reference. When the output is not at the desired level, the process parameters are changed until the output is—within certain margins of accuracy—equal to the process reference. In this way the process is maintained at the desired level through feedback. There are many forms of feedback. In general, the feedback is negative. Negative feedback of a process in its most simple form means that the process output is subtracted from (negatively added to) the process input. The effect of negative feedback is that the regulation error—the deviation of the process output from the desired value—is reduced, the remaining error depending on the amplification of the feedback loop. When delay and stability problems can be managed, negative feedback can be very effective in counteracting the effects of disturbances to the process, making the process output less responsive to changing parameter values or changes in its environment.

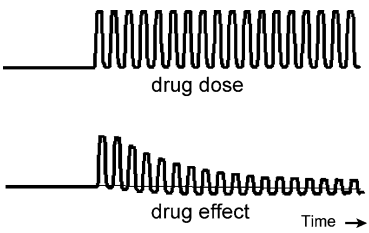

Fig. 2.1 Development of tolerance to the repeated administration of a drug

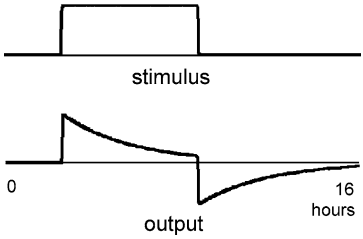

Fig. 2.2 Computer simulation of the effect of a single disturbance on the process output of a simple linear negative feedback circuit

Homeostasis has made clear that most physiological processes are regulated, and that regulation implies feedback. This has resulted in numerous models using negative feedback systems as a description of their behaviour. However, the incorporation of negative feedback in itself does not suffice to obtain a model describing the behaviour of adaptive physiological processes like the development of drug tolerance, as will be demonstrated with the response of negative feedback systems to regularly occurring disturbances.

Figure 2.1 illustrates the effect of tolerance development on the drug effect when a drug is administered repeatedly. The gradual build-up of tolerance is reflected in a gradual decrease in drug effect. It is accompanied by reactions during the interval between two drug administrations (the signal going below the base line), representing the rebound phenomenon: opposite symptoms after the drug effect has ended.

Figure 2.2 shows a computer simulation of the effect of a disturbance on the output of a simple (first order) linear negative feedback circuit. The length of the stimulus and the time constant τ of the circuit are set at 6 and 3 hours, respectively. The vertical axes are in arbitrary units. The initially large effect of the stimulus on the output decreases over time at a speed determined by τ. This decrease more or less resembles the development of acute tolerance: tolerance to the effect of a single drug administration. When the stimulus ends, there is an effect in the opposite direction, which could be regarded as representing the rebound mechanism.

If the same stimulus is applied repeatedly to this simple regulated system, the model's response does not resemble the development of tolerance shown in Fig. 2.1. This is demonstrated in the simulation depicted in Fig. 2.3, where the stimulus is applied twice a day. Every time the stimulus is applied, the effect of the stimulus on the output (Fig. 2.3b) appears to be the same as in Fig. 2.2. The stimuli are all suppressed to the same degree, which does not reflect the decrease in drug effect over time as the organism develops tolerance. If the time constant of the regulation is increased from 3 hours to 3 days, the sole effect of the regulation is that the average

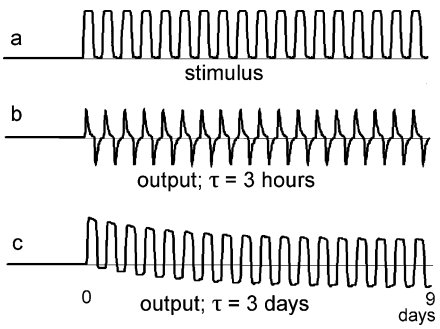

Fig. 2.3 Effect of a repeatedly applied stimulus on a simple feedback circuit

value of the signal drifts towards the base line (Fig. 2.3c). Although this example of a simple regulated process shows some qualities of tolerance development and might give an acceptable description of acute tolerance, it apparently lacks the capacity to adapt to recurring disturbances. The above simulation uses a simple, first order negative linear feedback circuit. When a mathematical model combines systems to form a complex, higher order feedback circuit, it will generate a response which differs from that of Fig. 2.2b. However, the effect of repeatedly applied stimuli will always give the pattern displayed in Fig. 2.3. Apparently, feedback does not suffice to describe the development of tolerance to repeatedly applied disturbances and, consequently, the model of homeostasis cannot describe drug tolerance.

An attempt to modify the model of homeostasis to account for its obvious shortcomings is the model of allostasis (Koob and Le Moal 2001; Ahmed et al. 2002; Schulkin 2003; Sterling 2004). Allostasis challenges the basis of homeostasis that processes are functioning at a steady state and proposes that the goal of regulation is not constancy, but rather, 'fitness under natural selection' (Sterling and Eyer 1988; Sterling 2004). Yet, in spite of its criticism of the homeostatic model, allostasis assumes that while the set points of process regulations are controlled by the organism to meet its overall goal these processes themselves are regulated in a homeostatic manner. Allostasis is predominantly a qualitative model (Ahmed and Koob (2005) set out a quantitative model which controls the intravenous administration of cocaine in rats) and there is no indication that it can describe the effects of repeated drug administrations.

2.2.2 The Properties of Adaptive Processes

When the development of drug tolerance cannot be described by homeostasis, or in general, by simple feedback systems, what then is the mechanism which does describe it? The model presented here posits that the development of drug tolerance is an expression of the general process of adaptation to environmental disturbances. Homeostasis and adaptive regulation are often assumed to be synonymous. In reality, these concepts are very different. The basis of homeostasis is that processes continue functioning at a preset level during changing environmental conditions,

the "equilibrium" or "steady state" of Cannon. Adaptive processes, on the other hand, aim for optimal performance, which in a changed environment may imply functioning at a different level or even in a different way (Bell and Griffin 1969; Toates 1979). Moreover, as most processes in the organism interact with numerous other processes, environmental changes may affect the functioning of the entire organism.

Adaptation and habituation, too, are often used interchangeably even though they are essentially different concepts. Habituation is a multiplicative mechanism: the response to the stimulus is attenuated to reduce the effect of the stimulus. Adaptation, on the other hand, is an additive process: the disturbance is counteracted by a compensating mechanism. The applicability of additive and multiplicative mechanisms to the description of tolerance development has been analysed in an earlier publication (Peper et al. 1988).

Adaptation is often considered a relatively slow, continuous learning process. Drug tolerance, however, usually manifests itself as a relatively short lasting, but recurrent and triggered process and may therefore be seen as an intermittent learning process of the organism: during the disturbances it learns how to deal with recurrent changes in its environment to keep functioning optimally. If a drug is administered, the organism "remembers" the effect of the drug during previous administrations and takes measures to lessen its effect this time. When full tolerance is established, the organism has learned to deal with the disturbance as effectively as possible in the given circumstances. The organism's learning process during adaptation in response to the repeated administration of a drug inevitably presumes memory over an extended period of time: memory for the properties of the particular drug, memory for the effects exerted by the drug on previous occasions and memory for the measures it has to take to oppose the effect of the drug.

In the general process of adaptation, it is postulated that the organism remembers as separate facts changes in its functioning when these are caused by different changes in its environment. This seems obvious: different drugs elicit different adaptation processes. Yet the implications of such specificity are far-reaching as is demonstrated with a simplified example of how the body's thermogenesis reacts to temperature changes. When one leaves a warm room to stay in the cold outside for a few minutes, the warm room feels normal on returning. After a day in the cold outside, the warm room feels hot on entering. Apparently, after adaptation to the cold outside, adaptation to the warm room must develop again. This adaptation to the warm room could be interpreted as the transition phase back to the normal situation. However, when the length of the disturbance is increased, the concept of "normal situation" becomes ambiguous. For somebody who has lived rough on the street over a prolonged period, the cold outside has become the normal situation and entering a warm room a disturbance: there has been a shift in the normal situation from the high temperature in the room to the low temperature outside. This shift is only comprehensible when it is accepted that for an adaptive process there is no normal situation: every change in environmental condition results in a new situation to which the process adapts by seeking a new level of functioning.

When this analysis of how the organism adapts is translated to the administration of drugs, it implies that for the organism the beginning of the drug action and its

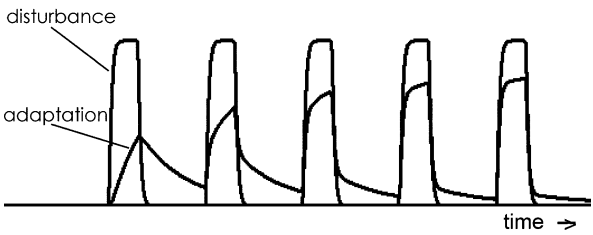

Fig. 2.4 General outline of the development of adaptation to a repeatedly occurring disturbance in an adaptive process

ending constitute different disturbances because they are the beginning of different (opposite) events, namely the drug effect and the interval between drug administrations. In existing models of drug tolerance, the interval between drug administrations is assumed to be the base line, the situation identical to the undisturbed situation before the first dose. In the model proposed, the organism's adaptation to the effect of a drug and its adaptation to the interval between drug administrations are considered autonomous processes.

Like homeostasis, the model adapts to a disturbance by opposing its effect. Figure 2.4 illustrates how this process of adaptation develops. The level of adaptation at any moment depends on the magnitude and length of the disturbance while it increases with every disturbance. Adaptation to the interval proceeds from the level acquired during the disturbance. In the above example of the body's thermoregulation, an increase in thermogenesis on entering the cold outside is the body's method of adapting to that disturbance. A return to the warm room will result in a decrease in heat production, accompanied by cooling if necessary through, for instance, sweat secretion. Figure 2.4 shows that after the body has learned to cope with this particular disturbance, the increase in thermogenesis on entering the cold and its decrease on return to the room will take place rapidly, while the level of adaptation has increased considerably.

2.2.3 The Detection of Exogenous Substances

The effects of drugs are for an important part determined by their disturbing effect on the information transfer within the organism's regulated processes. Consider a process which sends information about its level of functioning to the regulator of that process (this is detailed below in Fig. 2.5). The messenger used to transfer this information—a number of molecules of a certain substance—is detected by a sensor—receptors sensitive to that particular substance—which relays the information to the process regulator. If a drug interferes with the transport of this messenger, for instance by binding to the receptors, changing their affinity for the messenger, or simply by adding to the amount of the messenger substance, the information from the sensor will change and the effect will be a change in the output level of the process.

The disturbing effect of a drug on the regulation of a physiological process decreases when tolerance develops: the process regulator learns to counteract the effect

of the drug on the information transfer. This antagonistic action of the regulator is operative mainly during the time the drug is present. This can be deduced from the fact that when a drug is given only occasionally, the effect during the intervals is very small, even though the organism may have developed a high level of tolerance to the drug (this subject is treated extensively in Peper et al. 1987, 1988). If tolerance to a drug manifests itself mainly during the time the drug is present, an important conclusion can be drawn: when a process is disturbed by a drug, its regulator must at that moment "know" that the change in the output of the sensor is due to the presence of the drug and not to a normal fluctuation in the process it regulates. From the output signal of the sensor alone the regulator will not be able to determine whether the receptors are bound to an endogenous or an exogenous substance or whether a drug has changed the sensitivity of the sensor to the messenger substance. It can distinguish between the various ways in which a drug may interfere only by acquiring additional information about the situation. If, for instance, the exogenous substance differs from substances usually found at the location of the sensor, the regulator might be able to acquire this information from the receptor site. If, however, the exogenous substance is of the same chemical composition as an endogenous messenger substance, this information cannot be acquired other than from the fact that the organism has detected the substance somewhere in the organism where it is normally not present or from oral or environmental information about the substance entering the body.

The organism has several ways to detect a drug. If administered orally, there are gustatory and olfactory mechanisms to record the presence of a drug and its chemical characteristics. At a later stage, when the drug is within the organism or if the drug is administered intravenously, there are other ways in which a process regulator may obtain information about its presence and characteristics: from chemical sensors which are sensitive to the drug, from information originating from processes in the organism which themselves are disturbed by the drug or from environmental cues which it has learned to associate with the presence of the drug. But regardless of how the information is acquired, to enable a process regulation to take measures to reduce the effect of an exogenous substance upon the process, information about the presence of the drug should reach the regulator at an early stage, before the drug actually reaches the receptor site. This implies that the regulator will attach greater value to oral information about the presence of the drug than to information from the surrounding tissue (Steffens 1976; Grill et al. 1984). Given, furthermore, that the natural route into the body is through the mouth, it can be assumed that the organism will regard the detection of exogenous substances in the mouth as the fundamental source of information about the presence of a drug.

2.2.4 Oral and Environmental Cues

In discussions about tolerance development, cues originating from environmental causes are usually considered more important than the administration of the drug

itself. Although environmental cues can indeed dominate completely in certain situations, under closer scrutiny it becomes clear that the oral administration of a drug must be the primary and natural stimulus for the development of tolerance. One rational consideration is that for a living organism there is a relationship between oral drug-taking and the drug effect and that the organism will use such a relationship. After all, the natural route of an exogenous substance into the body is through the mouth. The mouth is - so to speak—made for that purpose. Together with the nose, it contains all the means needed to detect and analyse exogenous substances. The primary functions of the mouth and the nose—taste and smell—are there to allow the organism to recognise a substance when it enters the body, enabling it to anticipate its effect and to take appropriate measures in time.

An additional consideration indicating that oral administration is the fundamental stimulus in the tolerance process is that, when the organism is able to pair very different kinds of environmental cues with the drug effect as has been demonstrated in the literature, it will certainly relate the drug's presence to the drug effect. In fact, this relation must have been the first to develop in primitive organisms as it can also be observed at cell level where the mere presence of a drug can induce tolerance without the mediation of higher structures like the central nervous system. This has been demonstrated explicitly in isolated cell cultures, where repeated stimulation with toxic substances or changes in temperature induce tolerance (Peper et al. 1998; Wiegant et al. 1998).

There is ample evidence that the adaptive response—the compensatory action of the organism to the effect of a drug—is triggered by the oral administration of the drug. For instance, the oral administration of glucose almost immediately results in an increased release of insulin into the bloodstream (Deutsch 1974; Steffens 1976; Grill et al. 1984; Dworkin 1993; Loewy and Haxhiu 1993). In fact, the organism will make use of any cue it can find to anticipate disturbances of its functioning, and oral drug taking seems crucial in this mechanism.

These considerations do not mean that an oral stimulus is always the dominant stimulus for the tolerance process. Environmental cues become of prime importance when the natural—oral—route is bypassed through the injection of the drug directly into the bloodstream. Since much of the research into drug tolerance has been done with drugs administered intravenously, that is, without the fundamental—oral—cue being present, care should be taken in interpreting any results. When the oral drug cue is not present, the body will have to depend on environmental cues to trigger the tolerance mechanism, which may result in a different behaviour. In any research into the development of drug tolerance, it is therefore essential to understand the natural way in which the organism develops drug tolerance and the consequences of administering drugs directly into the bloodstream.

2.2.5 The Effect of Unknown Substances

When tolerance to a drug has developed, the organism apparently has enough information about the drug to reduce its disturbing effect. That information may in-

clude the chemical characteristics of the drug, the exact processes disturbed by the drug, the nature and the extent of the disturbance, the time taken by the drug to reach the receptor site, its effect on the sensor characteristics, and so on. When a drug enters the organism for the first time, the organism may be assumed not yet to have gathered this information and it must then establish the relationship between the taking of the unknown drug and subsequent disturbances in the organism.

As postulated above, the function of the mouth is to detect exogenous substances entering the body and to activate the processes which will be disturbed so they can generate a compensating response to the effect of the substance. Although no tolerance exists and no compensating response will be generated when a substance is unknown to the organism, for the organism to know that a drug is new implies that the substance first has to be analysed. It will, consequently, not make much difference for the organism whether a drug is new or whether there already exists a certain degree of tolerance to the drug: familiar or not, every drug entering the organism will be analysed. In case of an unknown substance, the changes in functioning of processes which follow will then be related to the composition of the substance and tolerance can develop.

In addition, it is quite conceivable that the organism has a built-in degree of tolerance to all (or most) substances in nature, in which case there are no "new" drugs and it is not a matter of analysis but of recognition. Every drug entering the organism is "recognised" and the organism "remembers" what the consequences for its functioning were on previous occasions when it detected that particular drug, where "previous" includes inheritance. The latter hypothesis is difficult to test, however, as in most cases it is not possible to determine the actual level of tolerance to a certain drug: the drug effect itself does not reveal information about the magnitude of the compensatory response or the level of tolerance.

2.2.6 The Magnitude of the Compensatory Response

The question now remains of why the organism requires so much time to develop tolerance to a drug when it apparently has all the information about the drug's chemical characteristics even when the drug enters the body for the first time. The answer to this question derives from the observation that, while a drug's chemical characteristics determine which processes are disturbed, it is the quantity of the drug which determines how much those processes are disturbed and hence the extent of the measures the organism must take to reduce the drug effect. This quantity, however, cannot be determined at an early stage. The organism is, for example, unable to determine the quantity of a medication before it is dissolved completely, or whether a cup of coffee is followed by a second or third. Such information becomes available only after a relatively long time, which is (or may be) too long for the processes involved to counteract the drug's disturbing effect in an effective way. The organism is thus confronted with a fundamental problem. It wants to counteract the drug

effect but has no definite information about the magnitude of the measures it has to take. The approach the organism has adopted to solve this difficulty is to base the magnitude of the compensatory response on the drug dose it expects: the usual or habitual drug dose. In practise, this will be about the average dose of a number of previous drug administrations.

It then becomes clear that tolerance to a certain drug does not merely mean that the organism knows how to cope with the given drug, but that the organism knows how to cope with a certain *quantity* of the drug. A change in that quantity—a change in the habitual drug dose—will therefore result in a period of incomplete tolerance during which the effect of the drug on the organism differs substantially from the tolerant situation. The functioning of the organism will then remain disturbed until it has learned to cope with the new drug level and has become tolerant to the new drug dose.

It is difficult to find a rationale for the initial large drug effect and the long time it takes the organism to develop tolerance other than the assumption that the organism does not determine the quantity of a drug entering the body. Again, if the organism were able to determine the properties and the quantity of the drug at an early stage, it would have all the information needed to rapidly suppress any drug activity. The organism needs a relatively long period to make an approximation of the drug dose it can expect.

2.3 Modelling Tolerance Development in Physiological Processes

2.3.1 The Model

The initial effect of a disturbance upon a regulated physiological process will now be elucidated with a simplified model. Subsequently, the model will be expanded to describe the complex response of a regulated physiological process to repeated disturbances in its functioning. Figure 2.5 shows a simple model of a regulated physiological process and the way in which a drug may disturb its functioning. In the normal, undisturbed functioning of the process, an endogenous substance in the blood, e, which is a measure of the level of the substance in the bloodstream produced by the process, E, is detected by the sensor, receptors which have affinity

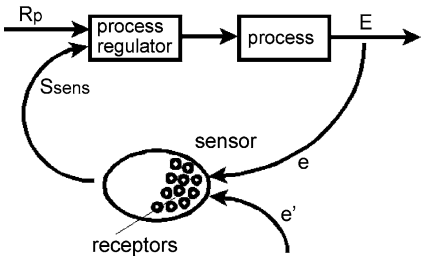

Fig. 2.5 Example of a simplified regulated process and the way in which a drug in the bloodstream may disturb its functioning

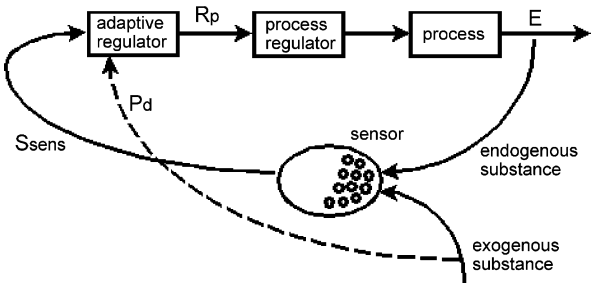

Fig. 2.6 Adaptive regulator added to the regulated process of Fig. 2.5

with the substance in question. The binding of this substance with the receptors results in a signal from the sensor to the process regulator, S_{sens}. The magnitude of S_{sens} is a measure of the number of bound receptors and thus of the amount of the substance in the bloodstream. The process regulator compares the level of S_{sens} with the level of the process reference, R_p, and regulates the process in such a way that S_{sens} and R_p are about equal. In this way the level of the substance in the bloodstream is kept at the desired level through negative feedback. If an exogenous substance, e', with which the receptors also show affinity (this may, but need not, be the same substance as the endogenous substance) is introduced into the bloodstream, the subsequent binding of this exogenous substance to the receptors will raise the level of S_{sens}. However, to keep S_{sens} at about the level of the reference, the negative feedback will reduce the process output, E—and consequently the level of the messenger substance, e—until the number of bound receptors is about the same as before the intervention.

In Sect. 2.2.1, it was argued that the development of drug tolerance cannot be described adequately in terms of simple feedback regulation. The mechanism responsible for tolerance development in the organism is fundamentally more complex and, hence, even a model which describes only the main characteristics of drug tolerance will be more complex. An adequate model of drug tolerance should possess the following characteristics:

- When a drug is administered repeatedly, the process should gradually learn how to readjust its functioning to oppose the effect of the drug.
- This adaptation process should be active mainly during the time the drug is present and should be activated upon the detection of the drug or associated cues.
- The drug's presence and the intervals between drug administrations should be considered different disturbances and should therefore initiate their own respective adaptation processes.

In Fig. 2.6, an "adaptive regulator" is added to the model of the regulated process in Fig. 2.5. This regulator is assumed to possess the qualities listed above. During successive drug administrations, it learns to change the process reference R_p during the presence of the drug in such a way that the effect of the disturbance on the level of the substance in the bloodstream, E, is reduced. To this end, it uses the output signal of the sensor, S_{sens}, and information about the drug administration, P_d. The dashed line indicates that P_d is information about the moment of drug administration only. In this model, the sensor output is assumed to be proportional to the sum

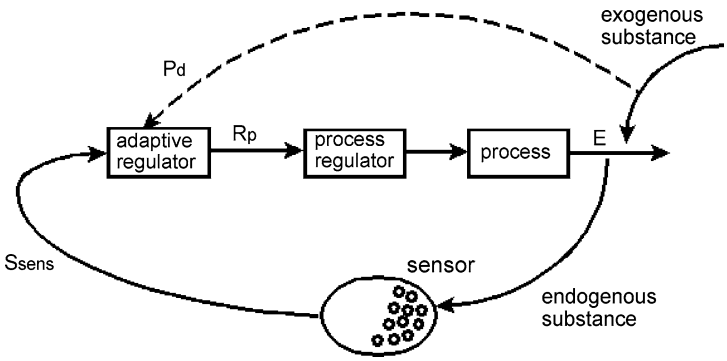

Fig. 2.7 Model of adaptive regulated process in which a drug increases the level of the produced substance

of the exogenous substance and the endogenous substance. The binding rates of the two substances with the receptors of the sensor are assumed to be equal.

2.3.2 Different Ways in Which Drugs Disturb the Body

A distinction has to be made between two fundamentally different ways in which drugs may disturb physiological processes:

Case 1: a drug changes the level of a regulated substance in the organism, increasing it when the drug and the substance are similar, or decreasing it, for instance by neutralisation.

Case 2: a drug disturbs the information transfer in the organism.

These two kinds of drug effects have essentially different consequences. If a drug increases the level of an endogenous substance of the same chemical composition, the long term effect will be a decrease in the production of that substance by the organism. When the low level of insulin in the blood of a diabetic is increased via the administration of exogenous insulin, the organism develops tolerance by gradually decreasing the insufficient insulin production of the pancreas even further, necessitating a gradual increase in the dose of the exogenous insulin (Heding and Munkgaard Rasmussen 1975; Mirel et al. 1980). If a drug interferes with the information transfer in a regulated process in the organism by affecting messenger-receptor interactions, or in general, the sensitivity of a sensor to an endogenous substance, the organism will learn to counteract the effect and, after a while, the process will more or less regain its normal functioning.

Figure 2.7 shows a model of an adaptive regulated process. The level of the substance produced by the process is increased by an exogenous substance of the same composition (case 1). The adaptive regulator gradually learns to suppress the effect of the drug during the period when the drug is in the bloodstream by lowering the process output. The adaptive regulator bases its action on information it receives from the sensor about the level of the regulated substance in the bloodstream, E,

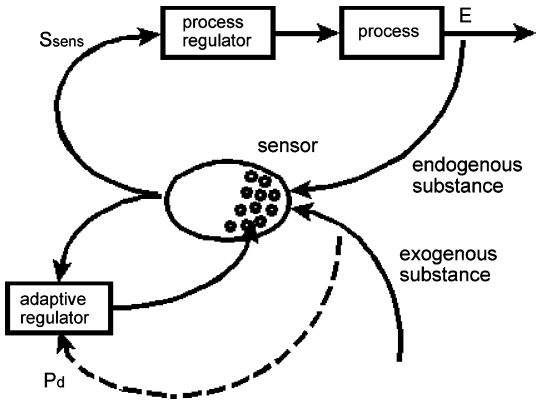

Fig. 2.8 Model of regulation in which a drug interferes with the information transfer in the regulation

and on information about the drug administration, P_d. In many models of drug tolerance, adaptation is assumed to be effected at the receptor site. However, if a drug changes the amount of a substance whose level is regulated, this information is crucial for the process regulator and should pass the sensor unaltered. It follows that the transfer function of the sensor (its input–output relation) must be kept constant. Consequently, when a drug changes the amount of a substance which is regulated at a preset level, the organism can be expected to counteract such a disturbance primarily by a readjustment of the process parameters.

When a drug interferes with the information transfer in the process regulation (case 2), it is not the level of the process which has to be corrected, but the change in input signal to the process regulator induced by the drug. As the feedback path in the regulation is affected here, the disturbance caused by the drug may be corrected via a change in the transfer function of the sensor, for instance by means of a change in the number of receptors sensitive to the drug. In this configuration, the adaptive regulator learns to change the transfer function of the sensor in a way that counteracts the effect of the drug on the sensor's sensitivity to the messenger.

Figure 2.8 shows a model of a regulated process in which the information transfer is disturbed by a drug. The adaptive regulator gradually learns to suppress the effect of the drug on the sensor signal by changing the sensitivity of the sensor. The adaptive regulator bases its action on information it receives from the sensor, S_{sens}, and on information about the drug administration, P_d.

The model in Fig. 2.7 describes the effect of a drug on the level of an endogenous substance which does not function as a messenger. The model in Fig. 2.8 describes the effect of a drug on messenger–receptor interactions and is therefore applicable to many of the effects associated with addictive drugs.

2.3.3 Fast and Slow Adaptation

The adaptive regulator treated above minimises the direct effect of a drug on the regulation. If it could suppress the drug effect completely, it would do all that is

required. However, in general drug effects are only partially suppressed and in most cases substantial effects remain. An important additional function of an adequate regulator is minimising the effect of the remaining disturbance. The model achieves this by combining the fast regulator, which reduces the immediate effect of the disturbance, with a slow regulator, which minimises the magnitude of the remaining disturbance in the long run and which anticipates frequently occurring stimuli (see also Peper et al. 1987). After tolerance has been established, the slow adaptation is responsible for a shift in the output level to below normal in the interval between drug administrations. The magnitude of these negative reactions in the tolerant situation depends on the length of the interval. When a drug is taken infrequently, the organism is not much affected during the intervals; when the frequency of administration is high, the shift can become considerable. The fast regulator is a complex system and determines to a large extent how tolerance develops. The slow regulator has a small effect by comparison but is an essential component of the adaptive regulator. Slow regulation can manifest itself in different forms. For a human moving to a hot climate, it may imply a permanent increase in sweat secretion. The thermoregulation in animals moved to a colder climate may adapt through a slow increase in the growth of their fur. The time constant of the slow regulator may amount to weeks months or even years.

2.4 The Mathematical Model and Its Practical Significance

2.4.1 The Model

It is important to observe that the mathematical model supports the underlying theory. This contrasts with other published models of drug tolerance, which are generally qualitative only. The importance of conducting research into the behaviour of physiological systems using control theoretical principles cannot be overemphasised as the behaviour of regulated systems can only be understood from the behaviour of mathematical models describing them. 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 include feedback systems as the behaviour of such systems cannot be predicted or understood qualitatively.

The mathematical implementation of the current model is discussed in the appendix, which addresses the complex structure of the components of the regulation loop and presents the equations describing them. The model is a nonlinear, learning, adaptive feedback system, fully satisfying the principles of control theory. 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.

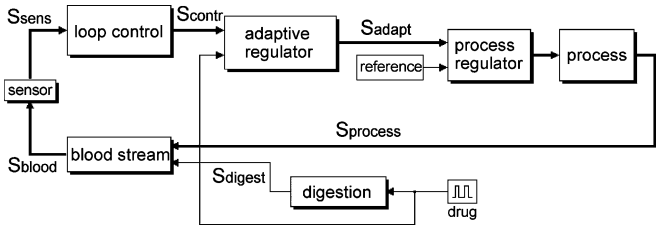

Fig. 2.9 Block diagram of the mathematical model of Fig. 2.7

A previous publication (Peper 2004b) derives the equations more fully and extensively discusses the control-theoretical basis of the regulation as well as the conditions for its stability.

The following model simulations are based on a number of simplifying assumptions:

- The parameters have been chosen to obtain a clear picture of the outcome of the simulations. Because in practise the stimulus—the drug intake—is extremely short in terms of repetition time, its duration has been extended for additional clarity.
- The mechanism of tolerance development will only function if it is triggered when the drug is administered. For the behaviour of the mathematical model, it is of no relevance whether it is triggered orally or by environmental cues. Hence, the simulations do not distinguish between different kinds of triggering.
- Whenever the paper discusses oral drug administration, the drug is assumed to be gustatorily detectable.
- As the model is a general model of tolerance development and does not describe a specific process, the vertical axes in the figures are in arbitrary units.

Figure 2.9 shows a block diagram of the mathematical implementation of the regulated adaptive process of Fig. 2.7. The process produces a hypothetical substance. Its regulation is disturbed by an exogenous substance of the same composition. The diagram comprises the digestive tract, the bloodstream, the process, the process regulator, a loop control function (see the Appendix) and the adaptive regulator. When the exogenous substance changes the level of the substance in the bloodstream, the adaptive regulator corrects for this disturbance by readjusting the output level of the process. The heavy arrows indicate the main route of the regulation loop. The thin arrows indicate the route of the disturbance: the transfer of the exogenous substance through the digestive tract to the bloodstream and the transfer of the information about the presence of the substance to the adaptive regulator. The block “reference” represents the reference level for the process regulator, which is set at a higher level in the hierarchical organisation of the organism. This subject will not be treated here.

When the exogenous substance enters the body, a series of activities readjusts the processes involved in order to reduce the disturbance. Figure 2.10 shows some signals from the block diagram which illustrate this mechanism (Peper 2004b). The

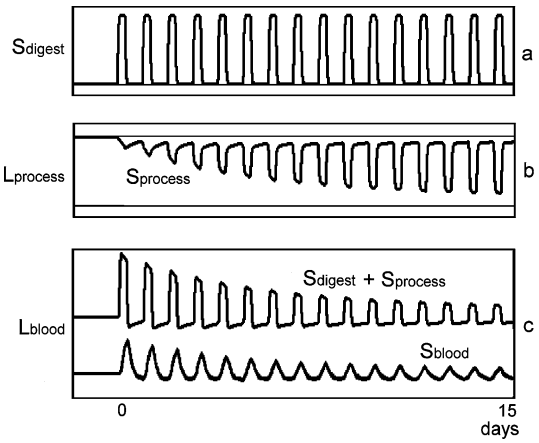

Fig. 2.10 Some signals from a process modelled with the mathematical model clarifying the functioning of the tolerance mechanism: (**a**) The exogenous substance when it enters the bloodstream, S_{digest}. (**b**) Process output during tolerance development, S_{process}. (**c**) S_{process} and S_{digest} added in the blood stream and the resulting blood level, S_{blood}. The level of the process output and the resulting blood level before the drug is administered are L_{process} and L_{blood}

endogenous substance is produced at a normally constant level, L_{process}. The resulting blood level is L_{blood}. When a similar substance is administered exogenously, the blood level will be disturbed. When the exogenous substance is administered repeatedly, the regulated process will develop tolerance to the disturbance. Trace (a) shows the exogenous substance, S_{digest}, when it enters the bloodstream. Trace (b) shows the process output: during the disturbances the output level will drop to counteract the induced rise in the level of the substance in the blood. The signal representing this change in process output level, S_{process}, represents the compensatory response of the process to the disturbance. In addition to these temporary changes in level, a permanent downward shift in the process output occurs. This shift of the curve to a level substantially lower than the baseline, L_{process}, represents a fundamental change in the functioning of the processes involved.[1] The two signals—S_{digest} and S_{process}—are added when the endogenous and exogenous substances mix in the bloodstream. The resulting signal is shown in trace (c) together with the resulting blood level, S_{blood}. The disturbance of the blood level gradually

[1]This downward shift in the functioning of the process represents the drug induced change in the functioning of processes involved in the drug effect. The shift depends mainly on the functioning of the slow regulator which can have a long time constant (see Sect. 2.4.2). As a result, the shift may remain a long time after a drug is withdrawn. This has important consequences as was first pointed out in a previous publication (Peper et al. 1987): *The negative shift of the process output on drug withdrawal signifies the occurrence of antagonistic symptoms with respect to the drug effect and these are consequently in the "direction" of the disorder the drug was intended to counteract* (Kalant et al. 1971). *This implies [. . .] a worsening of the disorder of the patient after termination of drug treatment.* Apparently, for the body, adaptation to a medicine means a shift in its functioning in the direction of the disease.

decreases during subsequent administrations when the process regulator adapts to the recurrent disturbance. Recall that all parameter settings in the simulations are arbitrary, as are the axes in the figure.

2.4.2 The Open-Loop Gain

The compensatory response only partly compensates the effect of the drug. The extent to which this takes place depends on the capacity of the body to suppress disturbances, which in the model domain is represented by the open-loop gain of the regulation loop. A large open loop gain—as is found in most electronic regulated systems—suppresses disturbances to a large extent. Stability considerations suggest that the open-loop gain in fast biological processes is small (Peper et al. 1987), and the suppression of disturbances only modest. In the example of Fig. 2.10, the open-loop gain is set at 4. This would be a very low figure for a electronic feedback system, but is a common value in physiological regulations.

The open-loop gain in physiological regulations is not fixed but depends on factors such as health, age and fitness (Mitchell et al. 1970; Verveen 1978, 1983; Peper et al. 1987, 1988; Peper 2004a). The open-loop gain determines both the rate of suppression of the drug effect after tolerance has developed and the magnitude of the reactions after withdrawal. This direct link between very different effects forces the organism to make a trade-off between a beneficial and an undesirable effect of the regulation, which may partly explain why the suppression of the drug effect when tolerance has developed tends to be relatively low. Yet another reason why there is a limited suppression of the drug effect in the tolerant situation may be that the organism cannot estimate the exact drug dose at the moment of administration and therefore has to be cautious in opposing the drug effect. If the organism nevertheless overestimates the drug dose, its drug-opposing action may outweigh the drug effect itself, resulting in a paradoxical drug effect: an effect with characteristics opposite to the normal drug effect.

When the time constant of a regulation loop is large, stability becomes less of a factor. In many cases, the open-loop gain of the slow adaptive regulator in physiological processes will therefore be significantly larger than that of the fast adaptive regulator.

2.4.3 Constant Drug Effect

In the simulation of Fig. 2.10, the drug dose has a constant magnitude. In clinical practise, it is not the drug dose but the drug effect that is of primary interest. As the drug effect decreases when tolerance to the drug develops, the dose must be increased to maintain the drug effect at the desired level. In the simulation in Fig. 2.11, the magnitude of the drug dose has been adjusted during the simulation to maintain

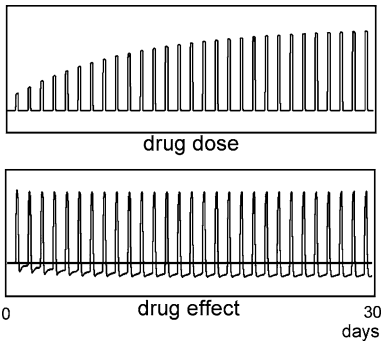

Fig. 2.11 The result of a computer simulation showing dose–response relation for constant drug effect. The magnitude of the stimulus has been adjusted during the simulation to maintain a nearly constant effect in the output of the model

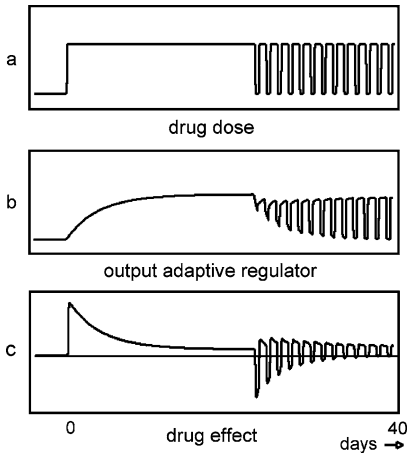

Fig. 2.12 Illustration of the consequences of adaptive regulation to a permanent change in level

a nearly constant drug effect. After an initial increase, the magnitude of the stimulus settles at a level which yields the desired effect. The relation between the dose and the drug effect in that situation is determined by the open loop gain of the fast adaptive regulator, as explained in Sect. 2.4.2.

2.4.4 Adaptive Regulation

Figure 2.10 demonstrates how the adaptive regulator learns to generate a compensatory response when a drug is administered repeatedly. Figure 2.12 shows its response when a drug is administered permanently. A permanent change in drug level, as shown in the first part of Fig. 2.12a, will result in a permanently changed level of the output of the adaptive regulator (Fig. 2.12b). This level then becomes the new base line for the regulation and is accompanied by a shift in the level of the drug in the bloodstream (Fig. 2.12c). This shift is generally small, as the compensation in slow adaptation is generally large (see Sect. 2.4.2). Interruptions to such a permanent stimulus, shown in the second part of the figure, are now new—negative—stimuli,

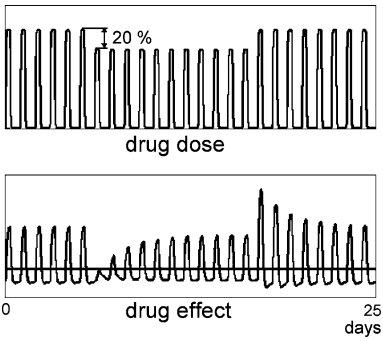

Fig. 2.13 A simulation of the effect of a small change in drug dose after tolerance has developed. For a given set of parameters, a 20 percent decrease in dose results in an initial suppression of the drug effect. An increase in dose back to the original value causes an initial large increase in the drug effect

the suppression of which will increase over time similarly to the periodic stimuli shown in Fig. 2.10.

A permanent drug administration is no different from any other permanent change in the environment as was illustrated in Sect. 2.2.2 with an example of the consequences of a permanent change in environmental temperature. Figure 2.12 depicts adaptation to the cold outside when the temperature is substituted for "drug dose". The vertical axes then show an increase in cold and the onset of the signal is the temperature inside. Figure 2.12c then depicts the sensation of cold or warm and Fig. 2.12b the adaptation to the changes in temperature, that is, the compensatory response.

2.4.5 The Effect of Changes in Drug Dose

Because the compensatory response is not based on the actual drug dose but on the dose the subject is accustomed to (see Sect. 2.2.5), the compensatory response will initially not change when the actual dose is changed. The consequence is that a small change in drug dose will have a disproportionately large effect. Figure 2.13 shows a model simulation of the effect of a small change in drug dose after tolerance has developed. For a given set of parameters, a 20 percent decrease in drug dose results in an initial suppression of the drug effect. When the regulation adapts itself to the new situation—it slowly learns to decrease the compensatory response—the magnitude of the drug effect settles at a level reduced proportionally by 20 percent. When the dose is increased to its original magnitude, the drug effect initially increases to approximately twice the normal level.

In Fig. 2.13, with the parameter values selected, a 20% reduction in the dose results in an initial reduction in the drug effect to zero. This implies that at that moment the drug action and the compensatory response are of equal magnitude (S_{digest} and S_{process} in Fig. 2.10). When the dose is reduced by more than 20%, negative reactions occur as the compensatory response then initially exceeds the action of the drug. This is shown in Fig. 2.14, where the dose is reduced to 50%.

Positive reactions to a small increase in drug dose are usually less apparent than negative reactions since the latter may cause a reversal of the symptoms, which is

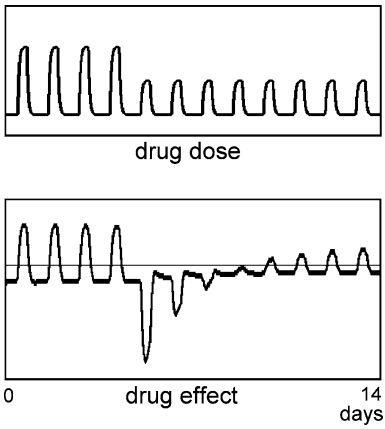

Fig. 2.14 Effect of reduction in drug dose to 50%

generally unpleasant or undesired, while a positive reaction is of the same nature as the drug effect. The action of many drugs is also subject to an upper limit. Pain medication, for instance, alleviates pain and cannot go beyond no pain. In addition, the effect of a larger dose is often reduced by non-linear transfers in the process. These are not incorporated in the general model presented here.

The large responses to small changes in drug dose are a common feature of the drug effect and are well known in the treatment of addicts. It explains why tapering off the drug dose to prevent negative reactions is such a slow process. A decrease of 10% or less a week is a common value for dependent or addicted subjects as higher values might cause adverse effects.

The disproportionate responses to a change in drug dose in dependence and addiction are not fundamentally different from when only tolerance is present. In dependence, the effect is large because tolerance in dependence is high. When tolerance is lower, as will be the case after a limited number of drug administrations, the effect of a reduction in dose is smaller but the decrease in drug effect may initially still be significantly larger than expected.

2.4.6 The Dose–Response Curve

Existing conceptualisations of the relationship between drug dose and drug effect display fundamental contradictions. It is undisputed that in dependent subjects a reduction in drug dose may generate large reactions. At the same time, the dose–response curve—shown in Fig. 2.15—which postulates that a change in drug dose will produce a proportionate and predictable change in drug effect, is assumed to provide an adequate description of the dose-effect relation. The applicability of the dose–response curve is limited because responses vary widely across subjects (Ramsay and Woods 1997). But it also has other shortcomings.

In standard medical practise, the initial dose of a drug is selected on the basis of the dose–response curve of the drug (curve (a) in Fig. 2.15) and the characteristics

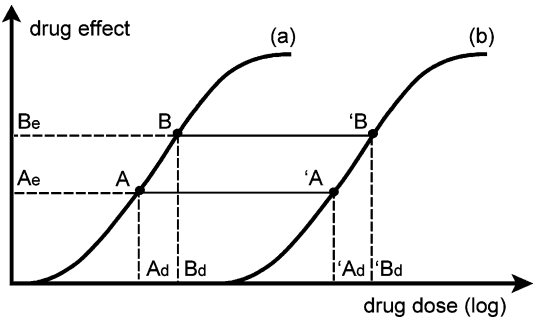

Fig. 2.15 (**a**) Dose–response curve. (**b**) Dose–response curve after tolerance has developed

and peculiarities of the patient. In the figure this is assumed to be dose A_d, which has a drug effect A_e. If, after a while, the effect of the dose is not as desired, the dose is adjusted. For instance, if the effect is too small the dose is increased. In curve (a) that would be dose B_d with a drug effect B_e. However, if curve (a) were used to determine the new dose a problem would occur because, during the administration of the drug, tolerance may have developed. The dose–response curve captures an increase in tolerance through a shift to the right to curve (b). A larger dose is required to obtain the same drug effect. In the figure the shift is arbitrarily large, but in reality the shift can also be substantial and dose B_d will be too small to generate the desired effect B_e. If in practise tolerance development can be estimated and the curve is shifted to the right by the measured value, another difficulty arises. Whereas curve (a)—that is, the curve relevant for the first dose—can determine the drug effect values A_e and B_e given the drug dose values A_d and B_d, once tolerance has started to develop, an increase in dose from A_d to $'B_d$ will cause an initial increase in drug effect larger than curve (b) suggests, as was demonstrated in Fig. 2.13. In other words, an increase in the dose of a drug to which tolerance has developed may result in a disproportionately large increase in drug effect. Negative overshoot when the drug dose is decreased will be just as large and both situations may not be without risk to the patient.

The dose–response curve presumes a static relationship between drug dose and drug effect. Yet tolerance development—and thus time—is an important factor in measuring the drug effect. This is demonstrated in the model simulations reported in Fig. 2.16, where the dose and the drug effect are plotted separately against time to illustrate the influence of tolerance development on dose–response curve measurements.

Usually, the dose–response curve is measured by increasing the dose in logarithmic steps. The tolerance which develops during such a measurement distorts the curve. This effect, however, is not very clear in the curve, partly due to the distortion being gradual and partly due to the logarithmic change in dose.[2] When the curve

[2]The bend at the bottom of the dose–response curve is largely caused by the logarithmic scale. In a linear process, a linear change in dose will cause a linear change in drug effect, as long as there is no tolerance development (curve (d)). With a linear scale, distortion of the curve due to tolerance development is easily noticed. However, as the dose–response curve is commonly presented using

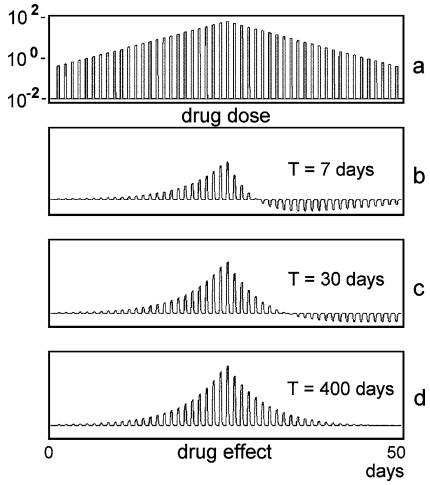

Fig. 2.16 Simulations with the mathematical model of the relation between dose (**a**) and drug effect, plotted against time to illustrate the influence of tolerance development on the outcome of dose–response curve measurements. The time constant of the tolerance mechanism in the simulations is respectively 7 days (**b**), 30 days (**c**) and 400 days (**d**)

is determined with a decreasing dose, the effect of tolerance development becomes readily apparent. To demonstrate these effects, in Fig. 2.16 the dose is first increased and subsequently decreased (a). In curve (b), which represents the drug effect, a time constant of seven days is chosen for the tolerance process (approximately the time constant used in the simulations shown above and in previous publications on the subject). The effect of the decrease in drug dose is a dramatic shift towards a negative drug effect with symptoms opposite to the normal drug effect. When the time constant is increased to 30 days (c), this effect is still very strong. When the time constant is increased to 400 days (d), the effect has nearly disappeared, leaving a curve where tolerance development does not take place during measurement and the upward- and downward-sloping portions of the curve have a similar shape.

The full implication of the effect of tolerance development in dose–response curve measurements becomes clear during the decrease in drug dose when the decrease in drug action causes the compensatory response to become dominant and the overall drug effect to turn negative. Negative reactions are commonly seen in slow withdrawal when the dose is tapered off too rapidly, a situation comparable to that depicted in the figure. The dose–response curve is naturally measured by increasing the dose, in which case no such reactions are generated. But the distortion of the curve during the increase in dose is significant too, as shown in the figure. In the simulations, doses are administered once a day, over 50 days in total. Simulations with other settings of the model parameters, such as a different maximal dose, fewer stimuli or stimuli with different time intervals give a very similar picture.

The static representation of the relationship between drug dose and drug effect suggested by the dose–response curve cannot be reconciled with the dynamic responses of the organism to changes in drug dose characteristic of the mechanism of

a logarithmic dose scale, this has also been adopted here. The saturation in the top of the dose–response curve in Fig. 2.15 is the natural maximal activity of the processes involved. This effect has been left out in the simulation of Fig. 2.16 as it has no relevance to the present subject.

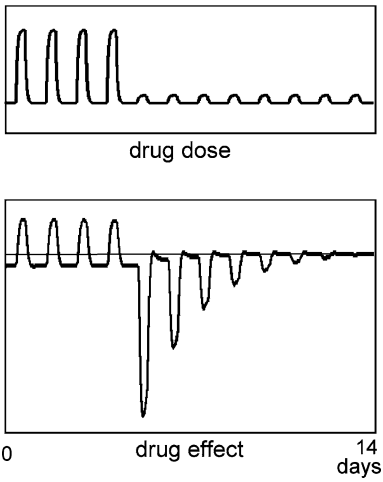

Fig. 2.17 Effect of reduction in drug dose to 10%

tolerance development. Unless tolerance to a certain drug develops very slowly, tolerance development will distort the curve when the effect of different drug doses is determined in a single subject. Values for the dose–response curve should therefore be determined from the (averaged) responses to single drug administrations measured in different subjects. Even measured in this way, a dose–response curve can only serve one valid purpose: it shows the average relationship between the dose and the *initial* response to a drug.

2.4.7 The Effect of a Further Reduction in the Drug Dose

It was explained above that when the compensatory response exceeds the drug action, negative reactions occur. This was demonstrated in Fig. 2.14 with a reduction in the dose to 50%. When the dose is reduced even more, the net result will be approximately the compensatory response alone, as is shown in Fig. 2.17, where the dose is reduced to 10%. A further reduction in drug dose will give about the same negative effect, as the contribution of any such small dose to the total drug effect becomes negligible.

The negative reactions shown in Fig. 2.17 are not fundamentally different from withdrawal reactions in dependence. In withdrawal, however, reactions occur because environmental cues paired to the drug taking continue to trigger the compensatory mechanism after the drug is withdrawn. When an exogenous substance is taken orally and there are no environmental cues paired to the drug taking, the compensatory mechanism is not triggered when the administration of the drug is stopped and no reactions will occur, as will be discussed in Sect. 2.5.1. When the administration of the drug is continued but the dose is reduced, however, the compensatory mechanism will keep responding at the moments when the drug is administered, as illustrated in Figs. 2.13 and 2.14. When the dose is sharply reduced, yet is still

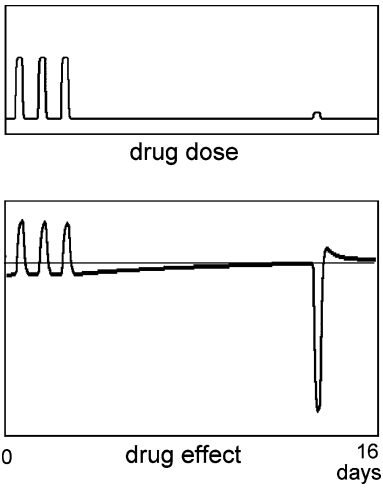

Fig. 2.18 The drug effect when a small dose is administered at an arbitrary time after the administration of a drug to which tolerance has developed is discontinued

detected by the organism, it is basically not the drug which induces these reactions but the orally acquired information that the drug is present.

Not only oral administrations of small doses can evoke the responses described above, any stimulus able to trigger the compensatory mechanism can cause reactions such as those shown in Fig. 2.17. In other words, the tolerance mechanism will respond, whether it is triggered orally or by environmental cues. But environmental cues are only coupled to drugs which are used regularly whereas a small dose of any drug to which the body has a certain level of tolerance to will trigger a compensatory response. As the oral detection of exogenous substances is a highly sensitive and specialised mechanism, capable of reacting to very small doses, this phenomenon may provide an explanation of such controversial subjects as hormesis and homeopathy.

Hormesis has been defined as a bi-phasic dose–response relationship in which the response at low doses is opposite to the effect at high doses. Examples of opposite effects of drugs (and radiation) at low and high doses can be found abundantly in the literature (Calabrese and Baldwin 2001, 2003; Conolly and Lutz 2004; Ali and Rattan 2006). Hormesis is usually explained by assuming a negative part in the dose–response curve at the low dose end. Homeopathy claims a curative reaction from a small dose of a drug of which high doses cause symptoms similar to those from which the patient is suffering.

In Figs. 2.14 and 2.17, the dose was reduced abruptly. The resulting reactions, however, do not depend on a sudden change in dose but on the difference between the actual dose and the dose to which the organism has developed tolerance. Tolerance to a drug develops slowly and remains present for a long time. Figure 2.18 depicts a model simulation describing what happens when a small dose is administered at an arbitrary time after the administration of a drug to which tolerance exists is discontinued. The figure shows that the small dose evokes a reaction similar to the sudden reduction in dose simulated in Figs. 2.14 and 2.17. The drug dose in the figure of 10% is arbitrary. As the actual dose itself plays only a minor role in the

remaining drug effect, any small dose will cause approximately the same reaction as long as the body recognises the drug.

Generally speaking, when there exists tolerance to a substance, the effect of a small dose is limited to triggering the compensatory response, resulting in effects opposite to the normal drug effect. Small doses of a drug apparently separate the compensatory response from the drug effect, which is a peculiar phenomenon. It does not explain the assumed curative effect of small doses in homeopathy. It does show, however, that a small dose of a substance can cause reactions with symptoms opposite to the action of the drug in high doses, a phenomenon that lies at the basis of homeopathy. The small dose mentioned above does not refer to the "infinitesimal dose" or "high potency" homeopathic medicines. On the other hand, the analysis shows that it is not the dose but information about the presence of a substance that triggers the compensatory response.

2.4.8 Sensitisation and Other Paradoxical Effects

Figure 2.13 shows that the fall in drug effect in response to a decrease in dose is followed by a rise in drug effect during subsequent drug administrations. The reduction in drug dose in this figure has been chosen to obtain a large initial reduction in drug effect. However, after tolerance has developed, any reduction in dose will be followed by a rise in drug effect until the organism has readjusted the magnitude of the compensatory response to correspond with the action of the new drug dose. This gradual increase in drug effect may explain cases of sensitisation, a phenomenon whereby the drug effect increases during repeated administrations (Robinson and Berridge 1993; Everitt and Wolf 2002). Figure 2.13 demonstrates the effect of abrupt changes in drug dose. As noted above, tolerance to a drug remains present for a long time. When a drug has not been administered over a certain period but tolerance has remained, or when innate tolerance exists, a dose smaller than the dose to which tolerance exists will result in a similar effect and may also be the origin of other paradoxical drug effects reported in the literature (Heisler and Tecott 2000; Wilens et al. 2003). It should be observed that neither sensitisation nor opposite drug effects necessarily require tolerance to the administered drug as cross tolerance to a related drug may cause similar effects.

Besides the drug dose, the magnitude of the compensatory response also depends on other variables. The capacity of the body to suppress disturbances—the open loop gain of the regulation loop (see Sect. 2.4.2)—is of major importance. The latter parameter is not fixed but depends on the subject's age, state of health and condition. The consequence is that an individual's level of tolerance to a certain drug and the resulting drug effect may appear different in different situations. This may mimic changes in drug dose with all its consequences and may be an additional cause of sensitisation. Rather than a loss of tolerance (Miller 2000) this might then constitute a loss of the organism's ability to express its tolerance.

In addition, the open loop gain may be affected by depressants and stimulants and even by the effect of the drug administration itself. Psychological factors, too, such

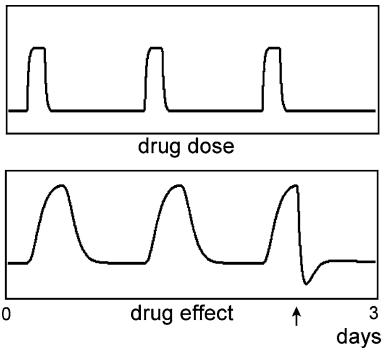

Fig. 2.19 Decrease in drug effect after the gain of the regulation loop is increased by 20%

as positive reinforcers may affect the open loop gain, causing changes in the drug effect (Fillmore and Vogel-Sprott 1999; Grattan-Miscio and Vogel-Sprott 2005). Similar to small changes in drug dose, small changes in the open loop gain can have large effects. This is demonstrated in Fig. 2.19, where at the instant indicated by the arrow, the gain of the regulation loop is increased by 20%. There is an instant decrease in the drug effect and even an adverse effect temporarily appears. In the physiological regulation process, the gain is a distributed entity and the speed of change in the drug effect depends on where in the regulation loop a change in gain occurs.

2.5 Practical Significance of the Model

2.5.1 Anticipation and Dependence

When an orally administered drug is taken infrequently, the gustatory detection of the substance will be the main trigger of the compensatory response. When a drug is taken frequently over a longer period, other mechanisms will start to play a role, such as anticipation and the coupling of environmental cues to the taking of the drug. The incorporation of additional information about the drug's presence will change the nature of the mechanism. If a drug is taken infrequently, the effect of not taking the drug will be that the rebound takes its course. When the organism anticipates a drug which, however, is not administered, strong negative reactions can occur.

Figure 2.20 shows a model simulation demonstrating what happens when the administration of a drug is abruptly discontinued after tolerance has developed. When at withdrawal the triggered compensatory action of the adaptive mechanism also ends, the magnitude of the negative shift following withdrawal is comparable to the regular rebound (Fig. 2.20b). Figure 2.20c shows the effect when after withdrawal the adaptive regulator keeps responding, triggered by time factors or environmental cues associated with the administration of the drug. Now, large negative reactions occur at the moment the drug is "expected". In the model, the activation of the compensatory mechanism, independently of the drug's presence, is assumed to

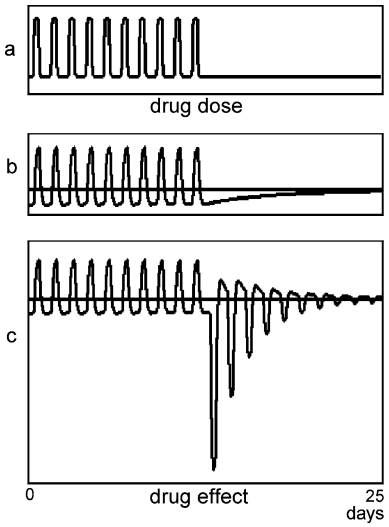

Fig. 2.20 Simulation of the effect of abrupt drug withdrawal in tolerant (**b**) and dependent (**c**) subjects. The drug is administered once a day

be the essential difference between drug tolerance and drug dependence. In reality, this difference is of course much more complex and difficult to define. Even so, in the model domain it provides fundamental insight into the mechanisms playing a role in dependence and addiction. The magnitude of the negative reactions after withdrawal—the magnitude of the compensatory response—is determined by the dose to which the subject is accustomed, the level of tolerance and the capacity of the organism to suppress disturbances to its functioning, that is, the open loop gain in the model.

Compared with the severe reactions in the model to drug withdrawal in a dependent subject, the effect in a tolerant but non-dependent subject is moderate (Fig. 2.20b). Nevertheless, its consequences can be considerable. The negative shift after the termination of drug treatment represents a worsening of the disorder in the patient (see also the note to Fig. 2.10, Sect. 2.4.1). Although this effect will diminish over time as the organism adapts to the new situation, an initial worsening of the symptoms will give the patient a strong incentive to continue drug treatment. In the figure, the reaction declines relatively fast, but the speed of decline is determined for an important part by the slow regulator which can have a long time constant so that the shift may remain for a long time after a drug is withdrawn. Moreover, in the case of a chronic disorder due to a shift in the reference level of a process regulator (Verveen 1978, 1983), it is doubtful whether adaptation to zero drug level will occur at all. A permanent shift in the reference level of a process indicates a certain malfunctioning of the regulation and a negative reaction in the process output to interruption of the stimulus represents a further shift in this reference level (Peper et al. 1987). Consequently, if a chronic disorder is due to a shift in a reference level, the extra shift after a drug treatment has ended might become permanent too and the effect of any drug treatment of limited duration will then be a permanent worsening of the disorder.

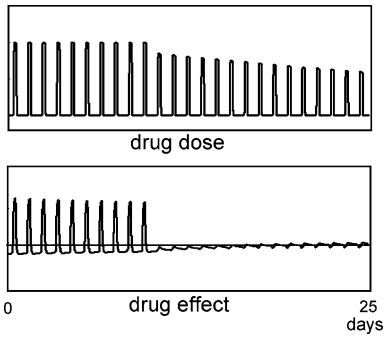

Fig. 2.21 Simulation of gradual drug withdrawal

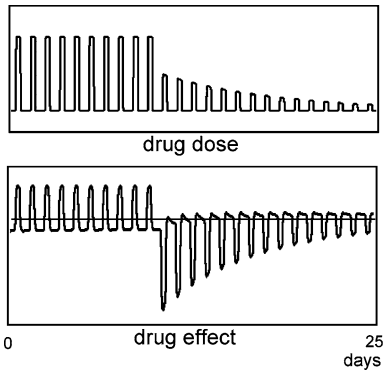

Fig. 2.22 Gradual drug withdrawal, allowing moderate reactions

2.5.2 Alternative Protocols for Drug Withdrawal

The large reactions occurring in an addicted subject when a drug is withdrawn, simulated in Fig. 2.20c, are an expression of the high level of tolerance associated with the large dose to which the subject is accustomed. The figure shows that the reactions gradually decrease in time when the body adapts to zero drug level and tolerance to the large dose decreases.

Figure 2.21 shows a simulation of how withdrawal can be achieved in addicted subjects without negative reactions. The dose is initially decreased by 20%, which causes the drug effect to go to zero, as was shown in Fig. 2.13. (The 20% is a result of the parameter values used in the simulation. In practise, this will be different for different drugs and in different subjects.) After this step in drug dose, the dose is gradually tapered off in such a way that the drug effect is kept small. This process is very slow, much slower than when negative reactions are allowed to occur (Fig. 2.20c). The speed of withdrawal can be increased considerably when moderate negative reactions are allowed. This is depicted in Fig. 2.22, where an initial decrease in drug dose of 50% is followed by a fast decrease in the dose of succeeding drug administrations. The reactions in this approach are considerably smaller than with abrupt withdrawal, while the decrease in drug dose is much faster than

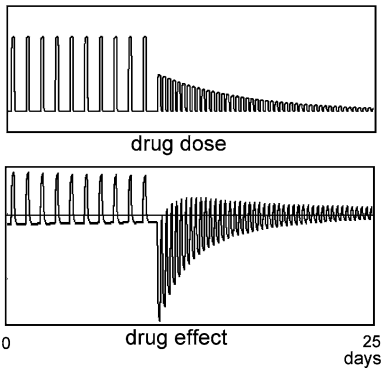

Fig. 2.23 Withdrawal with increased frequency of drug administration

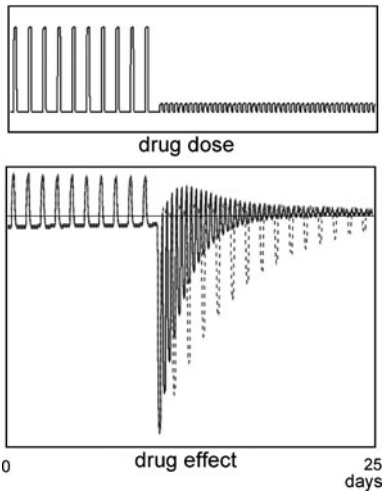

Fig. 2.24 Abrupt drug withdrawal using a small drug dose and an increased frequency of drug administration

is the case in Fig. 2.20. Nonetheless, moderate responses remain for a long time due to what is still a relatively slow decline in tolerance level. As the axes in the figures are arbitrary, the negative reactions in the figures can be interpreted more easily if their magnitude is compared with the positive drug effect in the first part of the figure.

The speed of decline in withdrawal can be increased by administering the drug more frequently. This is demonstrated in Fig. 2.23 where, instead of once a day, the drug is administered three times a day. The negative effect now declines considerably faster than in Fig. 2.22. This method of reducing tolerance can also be used when maximal reactions are allowed in withdrawal. If during drug withdrawal the drug dose is reduced to a low rather than zero value, the reactions become almost as large as in complete withdrawal, depicted in Fig. 2.20. When the small dose is now administered more frequently, the negative effect declines more rapidly. This is demonstrated in Fig. 2.24, where the drug dose is lowered to 10% of the usual

dose and the frequency of administration is increased from once a day to three times a day. For comparison, abrupt drug withdrawal—as shown in Fig. 2.20—is represented with a dotted line.

In these simulations of alternative drug withdrawal, the stimulus is obtained by the oral detection of small drug doses. If the drug is not administered orally, this simple means of triggering the compensatory response is not available and other ways have to be investigated to obtain a reliable stimulus. If the drug is administered intravenously, it might be sufficient to inject a diluted sample of the drug itself. If that does not trigger the compensatory response or if the drug is administered in some other way, an unrelated stimulus may be paired with the usual drug administration in the Pavlovian manner, before withdrawal is started. Further research will have to confirm these suggestions and investigate their practical applicability.

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Appendix

The model is a non-linear, 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 model assumes the development of tolerance to a repeatedly administered drug to be the result of a regulated adaptive process; adaptation to the effect of a drug and adaptation to the interval between drug taking are considered autonomous tolerance processes.

The mathematical model is derived in detail in Peper (2004b). In the present appendix the equations are summarised. A block diagram of the model is shown in Fig. 2.25. For the sake of brevity, the index '(t)' in time signals is omitted.

A.1 The Digestive Tract

The digestive system plays no role in the regulation loop. Drug transport through the digestive tract is modeled as a first order function:

$$S_{\text{digest}} = \int_0^t drug\, dt - \frac{1}{T_{\text{digest}}} \int_0^t S_{\text{digest}}\, dt \tag{1}$$

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 $1/T_{\text{digest}}$ of the output signal is subtracted from the input to account for the distribution of the drug in the digestive tract. T_{digest} is the time constant of this process.

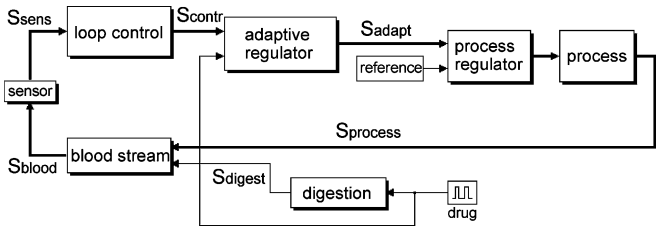

Fig. 2.25 Block diagram of the mathematical model

A.2 The Bloodstream

After digestion, the drug enters the bloodstream where it is 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 modeled by a first order function:

$$S_{\text{blood}} = \int_0^t (S_{\text{process}} + S_{\text{digest}})\, dt - \frac{1}{T_{\text{blood}}} \int_0^t S_{\text{blood}}\, dt \tag{2}$$

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 $1/T_{\text{blood}}$ of the output signal is subtracted from the input.

A.3 The Adaptive Regulator

The input signals of the adaptive regulator are the drug administration and the sensor signal, processed by the loop control block. 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 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. As the fast regulator reacts to fast changes only, the output of the slow regulator is subtracted from its input. 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 consists of a regulator which provides the adaptation to the drug's direct effect and a regulator which provides adaptation to the interval between drug taking. The output of the complete adaptive regulator is a combination of signals from its individual components.

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

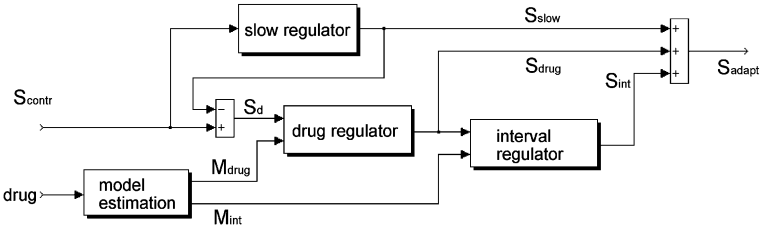

Fig. 2.26 Block diagram of the adaptive regulator

going to happen when the drug is administered: it has a model of it. The organism has also 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 course of the drug effect.

A.3.1 The Fast Regulator

The fast regulator consists of the blocks "drug regulator", "interval regulator" and "model estimation" (Fig. 2.26). The input signal of the drug regulator S_d is multiplied by M_{drug}, which represents the course of the drug level in the input signal over time. This signal is integrated (1/s) with a time constant T_{drug}, yielding its average. The resulting value is a slowly rising signal, L_{drug}. Multiplying L_{drug} by M_{drug} yields the output signal S_{drug}.

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: $1/T_{\text{drug}}$. The relation between the signals is

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

and

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

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}. The model of the interval is M_{int}.

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

$$\begin{aligned} S_{\text{drug}} = {} & M_{\text{drug}} \cdot \frac{1}{T_{\text{drug}}} \int_0^t (S_d - S_{\text{drug}}) \cdot M_{\text{drug}}\, dt \\ & - M_{\text{drug}} \cdot \frac{1}{T_{\text{decline}}} \int_0^t \frac{S_{\text{drug}}}{M_{\text{drug}}}\, dt \end{aligned} \tag{5}$$

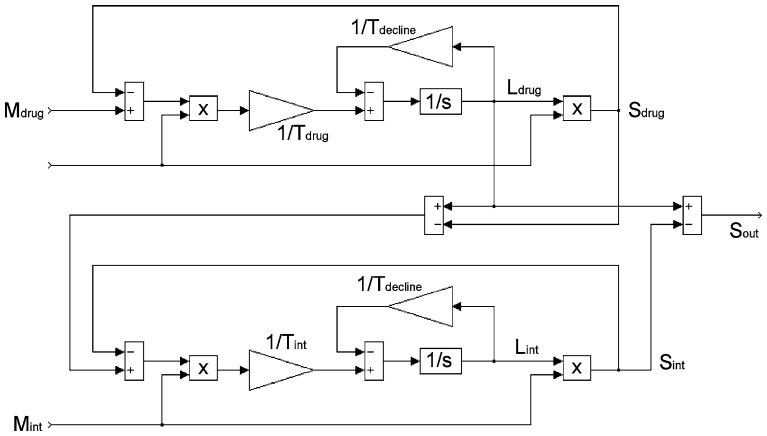

Fig. 2.27 Fast regulator implemented in Simulink

and

$$S_{\text{drug}} = L_{\text{drug}} \cdot M_{\text{drug}} \tag{6}$$

Similarly, the equation describing the interval regulator is

$$S_{\text{int}} = M_{\text{int}} \cdot \frac{1}{T_{\text{int}}} \int_0^t (L_{\text{drug}} - S_{\text{drug}} - S_{\text{int}}) \cdot M_{\text{int}}\, dt - M_{\text{int}} \cdot \frac{1}{T_{\text{decline}}} \int_0^t \frac{S_{\text{int}}}{M_{\text{int}}}\, dt \tag{7}$$

and

$$S_{\text{int}} = L_{\text{int}} \cdot M_{\text{int}} \tag{8}$$

The output of the interval regulator is S_{int}. The output signal of the total fast regulator is obtained by subtracting the interval signal from the top level of the drug signal:

$$S_{\text{out}} = L_{\text{drug}} - S_{\text{int}} \tag{9}$$

Figure 2.27 shows the implementation of the fast regulator in the mathematical simulation program Simulink (see Peper 2004b).

A.3.2 Estimation of the Drug Effect in the Adaptive Regulator

As the duration of the drug administration is relatively short in most cases, 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. The input of the interval is acquired when the signal "drug" is subtracted from its top value

of 1. Multiplying this signal by the transfer of the digestive tract yields the model of the interval M_{int}:

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

and

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

T_{digest} is the time constant of the digestive system.

A.3.3 The Slow Regulator

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 infrequently taken drug has a small effect during the interval, while a frequently taken drug causes a large rebound. The slow regulator counteracts the disturbance by lowering the level of the process by the average of the drug effect. Its input signal—the sensor signal, processed by the loop control block—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}:

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

A.4 The Process

The model does not incorporate the characteristics of the process and the process regulator. 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 loop control block.

A.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. 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. In the present form of the model, only the

effect of the bloodstream on the regulation loop is counteracted as the transfer of the process and its regulator and the transfer function of the sensor are set at unity. The relation between the input and the output of the loop control is

$$S_{\text{sens}} = \int_0^t S_{\text{contr}}\, dt - \frac{1}{T_{\text{blood}}} \int_0^t S_{\text{sens}}\, dt \tag{13}$$

A.6 The Sensor

The sensor transforms the chemical signal S_{blood}—the blood drug level—into the signal S_{sense}. In the present model, this transformation is 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 is controlled by the loop control block.

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