Andrew Sullivan 109151173

Model of Drug Use with Adaptation and Addiction

Introduction

Construction of a Model for Drug Absorption

Prior to consideration of any adaptive responses of the body, a model was developed which predicts the dynamics of drug absorption based on the dosage, individual's weight, and absorption characteristics of the drug. The model includes two stocks, which represent the amount of drug present in the stomach based on the individual's dosage and the amount present in the bloodstream based on absorption from the stomach, which is a function of the concentration gradient between the two locations, the stomach surface area acting as the semipermeable barrier to diffusion, and an absorption constant characteristic of the drug based on its molecular properties, including size and chemical behavior. Concentrations were found by dividing the total amount of drug by the volume of the stomach or the blood. The former was assumed to be constant, while the latter is a function of the weight of the individual. The drug is eliminated from the bloodstream by a simple rate-dependent metabolic process, in which the amount eliminated is a product of the amount in the blood and a metabolic rate constant. These dynamics correspond to a set of differential equations of the form

$$\frac{dDB}{dt} = A_{abs} V_{Stomach}\left(\frac{DB}{V_{Blood}} - \frac{DS}{V_{Stomach}}\right) - A_{met} DB \quad \text{and}$$

$$\frac{dDS}{dt} = Dosage - A_{abs} V_{Stomach}\left(\frac{DB}{V_{Blood}} - \frac{DS}{V_{Stomach}}\right)$$

in which DB and DS are the drug amounts in the blood and stomach, respectively, V_is are the volumes, and A_is are the absorption and metabolic constants. The intake to the stomach, governed by the variable *Dosage*, is discussed in more detail below.

A minimum therapeutic concentration was also introduced as a lower bound on drug effectiveness, and a toxic concentration as an upper bound. In the initial model, these parameters do not influence any others, but rather serve as a range for drug efficacy.

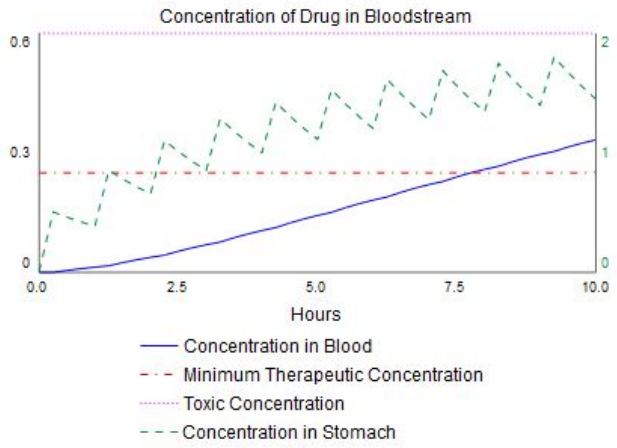
Initial Parameters of the Model

Experimental data was used to set initial values for the volumes, rate constants, and the bounding concentration values. Stomach volume was taken to be a constant at 500, while blood volume varied linearly with body weight, governed by the equation $BV = 10BW + 4500$. Initial amounts of drug were assigned as 0 in the blood and 3 in the stomach. The absorption constant for the drug was taken as 0.693/2, and the metabolic rate constant as 0.693/16. The toxic concentration was set at 0.6. Finally, the initial value for the minimum therapeutic concentration was 0.25. Aside from this latter parameter and the body weight, none of these values are changed throughout the use of this model.

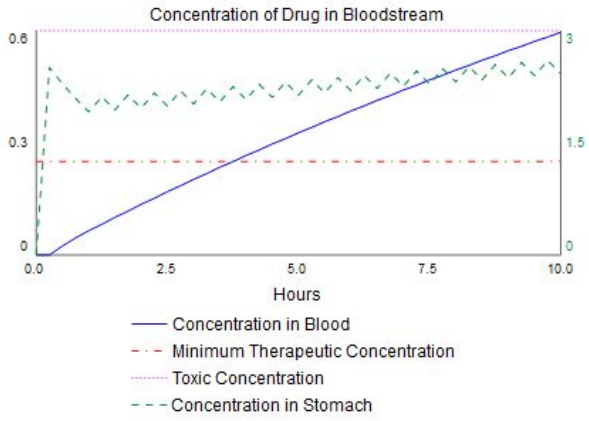
Dosage Dependence on Weight

System Dynamics for Body Weight 100

The dynamics of the system were initially investigated without any adaptive effects by examining the relationship between body weight and dosage required to be within the therapeutic zone. As the stomach volume and absorption constant are fixed, the way to achieve the fastest increase in concentration in the blood is to maximize the concentration in the stomach, thus maximizing the driving force for diffusion. However, this must be balanced by the continued growth once the therapeutic concentration has been reached to ensure that the blood concentration does not reach toxic levels. Competition between these two factors place a limit on how quickly the drug concentration can reach therapeutic levels. As an example, consider the absorption of the drug for an individual with a body weight of 100. The *Dosage* function utilized the PULSE function within the Stella Professional framework. This function requires three inputs: the amount added, the time of the initial dose, and how often the dose is repeated. Using this function, three regimes of concentration dynamics can be constructed.



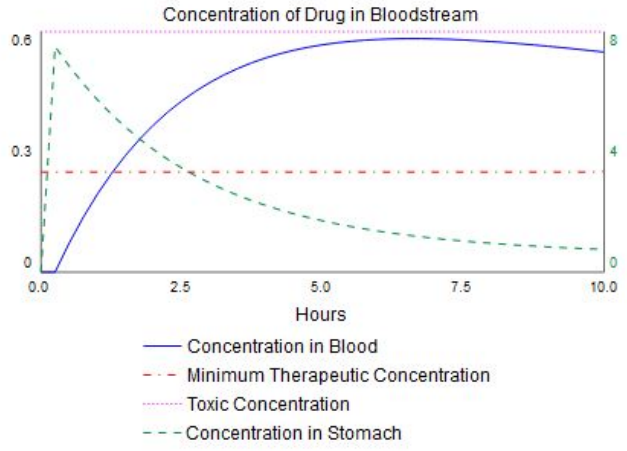
In the rapid growth regime a pulse is delivered of a relatively small magnitude frequently. This results in saturation behavior for the stomach concentration once the flow in is balanced by the flow into the bloodstream. Prior to this the bloodstream concentration grows slowly, as the concentration gradient is still small. Thus, for a dose of 250 every hour, therapeutic effects do not begin until almost eight hours after the initial dose.



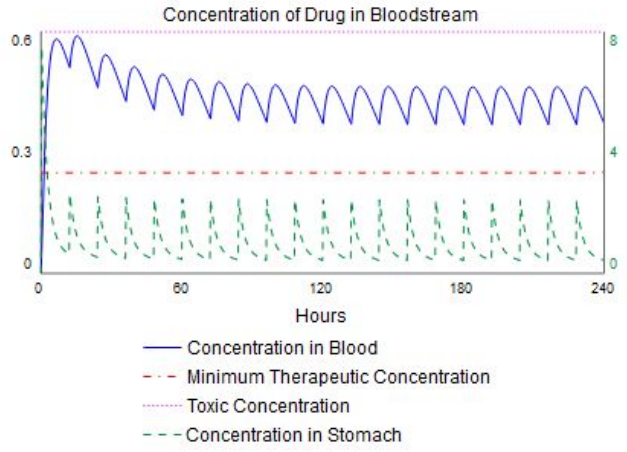
In the linear regime, an initial pulse is given at time = 0, and subsequent pulses are given at later time points of smaller magnitudes in order to keep the stomach concentration approximately constant. This gives rise to a nearly linear growth of drug concentration in the blood, while the concentration in the stomach oscillates around some constant value. This intake behavior is more rapid than the exponential case, but as can be seen in the figures below, the constraint of the toxic concentration prevents the drug from reaching therapeutic levels until almost the fourth

hour. The plots below were obtained using an initial dose of 1250 and subsequent doses of 180 every half hour.

As neither of the other two methods are acceptably rapid, the final option is to give one rapid initial dose to raise the concentration gradient as quickly as possible without resulting in growth to unacceptable toxic levels. Thus, for the entire range of weights tested (100-200), the appropriate dosage is found by identifying the largest initial pulse value that will not allow the concentration to reach toxic values. For the individual with a body weight of 100, this corresponds to a dosage of 3750, administered at time 0.



For an individual with body weight of 200, this same behavior is elicited by an initial dose of 4500. Using these two points, a linear function can be obtained relating body weight and required dose, of the form $Dosage = 7.5BW + 3000$. This has been confirmed by testing the 150 body weight value with a dosage of 4125, which produces the same behavior.

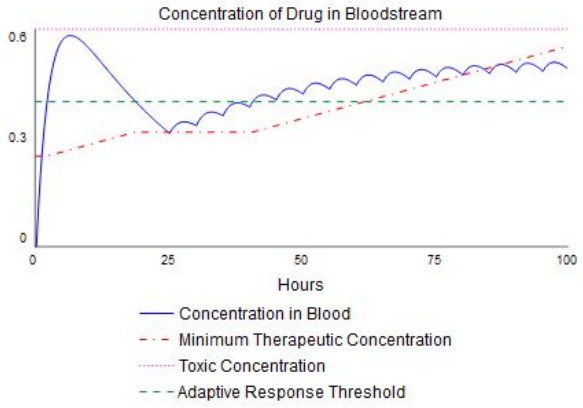


Following this initial dose, a range of possible dosages and time points may be used to ensure that the individual's bloodstream concentration stays within the therapeutic regime. For the entire range of body weights, subsequent doses of 1000 administered every twelve hours is sufficient to maintain this range, as depicted below for an individual with a body weight of 100. The methods above have been used to optimize the speed of delivery by maximizing the speed at which the concentration gradient is increased without growth to toxic values. Thus, a drug with a larger absorption constant would be required to permit more rapid growth to therapeutic levels.

Introduction of Adaptation to Drug

Minimum Threshold Method

The above model was altered in order to incorporate adaptation behavior to drug exposure for extended periods of time. Adaptation can be thought of as an increased threshold for therapeutic effects without changing the underlying dynamics of the drug absorption and

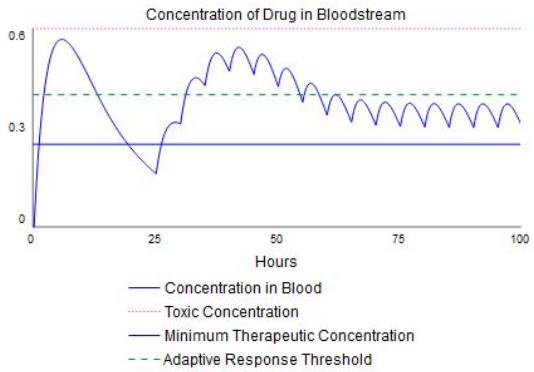


elimination system. This model of adaptive behavior was introduced by changing the behavior of the minimum therapeutic response, previously taken as a constant (0.25). Now, this value is recursively defined based on conditional statements. The value begins at 0.25 as before, but is then checked at each time point. If the concentration of the drug in the blood is greater than some specified value (taken as 0.4, for example), then the previous value is incremented by the adaptive response magnitude, another specified value (taken as 0.001). If the concentration is not above this critical value, then the minimum threshold remains constant at its last value. Displayed in the plot above is the behavior for an initial dose of 3750 and repeated doses of 200 administered every five hours beginning at hour 25 over the course of 100 hours. As can be seen from this plot, the minimum concentration initially increases as a result of the large concentration from the first dose, and then plateaus once the concentration drops below 0.4, displayed as the green dotted line. Just before the repeated doses begin, the concentration drops to the threshold value, below which, the symptoms that prompted the individual to take the first dose will return if their underlying cause has not been addressed. Once the concentration again reaches the threshold, the minimum concentration for therapeutic effects begins climbing. At approximately 80 hours, the concentration in the blood, which has nearly plateaued, is no longer sufficient to ameliorate the symptoms. Should these symptoms still persist, the individual may have to take larger doses, which could quickly result in exceeding the toxic concentration. This scenario quickly leads into an addictive behavior, discussed below. The additional parameters introduced in this section were arbitrarily assigned initial values, but true values will depend on the drug system begin examined and the individual. Different drugs may be adapted to more or less rapidly, and the underlying mechanism governing adaptation may begin at different values of blood concentration. Additionally, it was assumed that the dependence here is linear in time by adding a fixed magnitude to the previous value. It is entirely possible that, for a given drug system, a different relationship is present, such as an exponential or power law dependence.

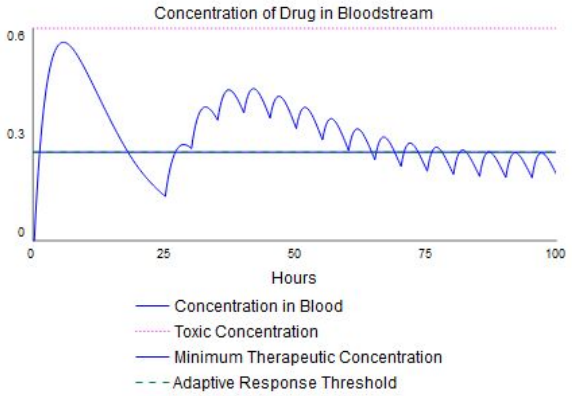
Increased Elimination Method

An alternative approach to modeling adaptive response to chronic elevated concentrations to a drug is to maintain the minimum therapeutic concentration as a constant, and instead examine the dependence of drug elimination on concentration. Previously, elimination was dependent on metabolism of the drug, which occurred at a fixed rate proportional to the amount of the drug. This metabolism will occur through enzyme-mediated degradation of the drug. The rate constant for metabolism, however, may be a function of the concentration of the drug as

well. Similarly to the previous method, it is assumed that there is some critical threshold below which no adaptive response takes place. Above this threshold, the elimination rate constant is incremented by some fixed magnitude each time point that the concentration remains elevated. This response may be the result of increased synthesis of more enzymes or increased enzymatic activation to promote faster degradation of the drug. Examining this system with a threshold of 0.4, increment magnitude of 0.001, and a large initial pulse followed by smaller repeated pulses as specified above results in the following behavior:



This system displays the elevated response once the drug concentration is increased above the threshold, resulting in a faster return to sub-threshold levels than in previous cases, and a response that increases until the increase in concentration due to intake is balanced by the elimination rate. Based on the above parameters, this system appears to be desirable, as the mechanisms cause oscillation around a point which lies within the therapeutic regime without any risk of crossing the toxic regime. However, in a scenario in which the adaptive response begins as soon as the concentration reaches therapeutic levels, the adaptive response will prevent the system from remaining within the therapeutic regime for any extended period of time, as displayed below:



Thus, despite continually taking doses that, without any adaptive response, would lead to rapid entry into the toxic regime and subsequent death, the individual cannot reach therapeutic levels, and may be tempted to take continually larger doses to obtain therapeutic effects. This is often the case in addictive behavior, which is discussed next.

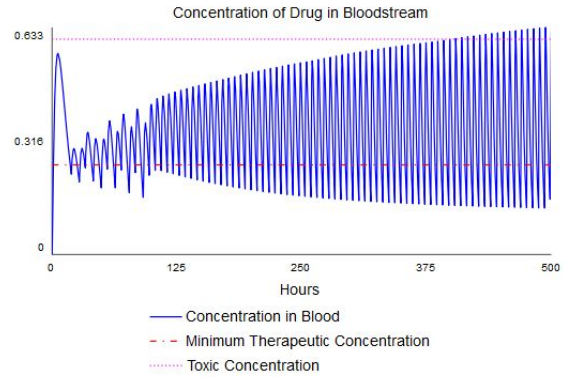
The Biological Basis of Tolerance

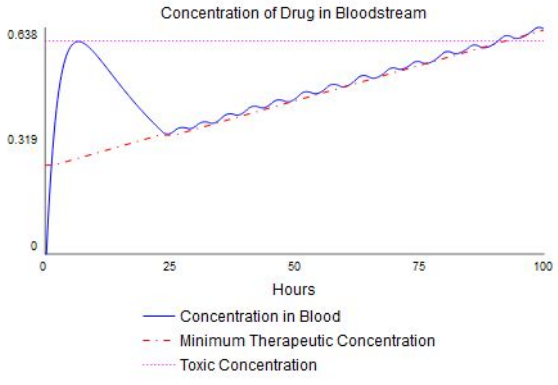
The mechanisms underlying tolerance are often grouped into two general classes: pharmacokinetic and pharmacodynamic.[1] The former term refers primarily to changes affecting the concentration of the drug, including elimination rate, transport rate, and accumulation of metabolites. Pharmacodynamic mechanisms, however, alter the physiological response to the presence of the drug by receptor desensitization, receptor downregulation, and changes in the signal transduction responses initiated by the ligand binding.

In the context of opioid tolerance, pharmacodynamic mechanisms are believed to dominate. Disrupted trafficking of the δ-opioid receptor[3] and decoupling of receptor-G protein interactions[4] have been implicated in producing tolerance. Thus, based on this evidence, the former method for modeling adaptive opioid responses is expected to fit experimental data more accurately. Even so, the tolerance-time relationship may still not be linear depending on the time scale and extent of these mechanisms.

Modeling Addiction Based on the Adaptive Elimination Response

The above method in which the metabolism or inactivation of the drug adapts to chronic elevated concentrations may be extended to model addictive behavior. In an addictive behavior, the individual will seek to counteract the effects of adaptation by increasing their intake of the drug to prolong the amount of time spent in the therapeutic regime. However, as the dosage is increased, so too is the elimination rate, thus prompting the individual to take even more the following time. This will often result in an overdose, assuming the individual is not treated, in which the toxic concentration is exceeded. This is introduced into the model by connecting the dosage to the blood concentration, minimum therapeutic concentration, and the elimination rate. A conditional argument is employed reflecting the individual's cognitive decision-making: the individual will first take the normal initial concentration depending on their body weight, and, if the current concentration is below the threshold, in which case the individual will not feel the effects of the drug ("coming down"), then they will take an additional amount every two hours equal to the current metabolic rate multiplied by a conversion factor, taken to be 10000 while this condition is true. This simply states that, as their body metabolizes the drug more rapidly, the individual will take more of it to maintain its effects. This results in unstable oscillatory behavior, in which the body seeks to eliminate the drug as quickly as it enters the system but the individual continues to increase the intake. Depending on the conversion factor and dosages, the scale at which the magnitude of this oscillation increases will vary. For this case, the toxic concentration is first exceeded at approximately 400 hours after the first dose, and each subsequent time has a longer period during which the toxic concentration is exceeded. It is at these points that the individual is likely to overdose.





It is also possible to model this behavior on the basis of the first model introduced above which modifies the minimum therapeutic concentration instead. Certainly, it is possible that a higher dosage could be required in the bloodstream for the effects of the drug to be felt. Modification of receptor proteins for the drug by phosphorylation, for example, could attenuate the body's response, thus prompting the individual to take more, as opposed to accelerated elimination of the drug from the bloodstream as in the previous model. Thus, both of these above modifications may be biologically sound, but depend on the mechanism of the body's response to the elevated drug concentrations. If it modifies the pathways responsible for elimination of the drug, then the behavior in the plot on the left is accurate. If, instead, the machinery for the cellular response to the drug is modified, then the behavior on the right may be more suitable. In this case, the dosage is a function of the minimum therapeutic concentration as well, but without the body changing the elimination rate. If the blood concentration falls below a region just below the therapeutic threshold, the individual will take more. It is apparent that this version of the model will reach the toxic concentration far more quickly, but this depends largely on the trend of the therapeutic concentration increase as a function of the time above threshold. If the behavior is nonlinear, then so, too, will be the progression to the toxic regime.

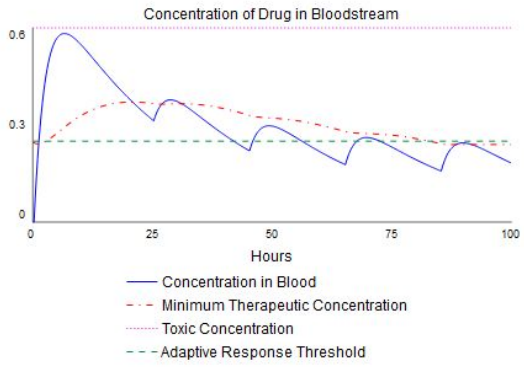
Final Considerations

The above models examine the dynamics of drug absorption as a function of body weight and dosage, and the body's response to chronic elevated levels of drug that could prompt the individual to increase his or her intake of the drug to remain in the therapeutically significant regime, thus giving rise to addictive behavior which will ultimately result in exceeding the threshold for toxic effects of the drug, resulting in overdose.

While many of the model parameters were chosen rather arbitrarily, with the primary goal of displaying the correct behavior over an appropriate time scale, the trends revealed should extend to the general case. For example, changing the magnitude of the metabolic rate increment or minimum threshold increment will only change how quickly the toxic regime is reached. The most significant potential flaws are discussed above, including the potential for nonlinear increases during the adaptive response, and the mechanism by which the body adapts. It should also be noted that the coupling of tolerance and addiction seen above is often the case, but there are situations in which an individual may become addicted to a substance without developing a tolerance to it. Addiction is characterized by a compulsive use of a substance, and is believed to be, at least in part, a result of changes in the reward pathways of the brain. Often, tolerance and dependence are used to infer drug use, but are not always correlated.[2] For a case in which addiction develops without tolerance, the individual is likely to display trends similar to the figures above but without any increase in the minimum therapeutic concentration or elimination rate. Thus, blood concentration would simply oscillate around the minimum concentration as the individual takes more once it falls below.

In the case of opioid addiction, tolerance is mainly believed to be mediated by pharmacodynamics mechanisms in the acute case, while chronic tolerance is likely due to both pharmacokinetic and pharmacodynamic pathways. The coupling of these effects has been modeled previously using a PK-PD model to describe the actual effect experienced by the individual as tolerance develops. These models typically rely on the interplay between four stocks in which the drug may be present. The central stock receives the drug input and may output to the peripheral stock, the effect stock, the tolerance stock, or may metabolize the drug. The peripheral stock does not contribute to any effects and simply serves as a storage, while the effect and tolerance stocks compete for the drug depending on their rate constants. The ratio between the two determines the perceived effect. This model has also been used to describe the effects of nicotine tolerance. The outcome of this model is complementary to that developed above, in that the PK-PD model displays decreased perceived effects of the drug over time, while the above model is characterized by increased minimum drug concentration for drug action. Both of these cases yield the same result: the individual must take more to experience the same effects.

A small addition that could be made to the above model is to consider the effects of recovery. In cases where the drug is not present in the body for prolonged periods of time, tolerance is typically reduced, thus lowering the minimum therapeutic threshold or the metabolism rate constant closer to normal values. This can be modeled in a similar way as the initial increase, either using a linear function or some other mathematical relation that more accurately captures the system dynamics. It has been shown that the magnitude of tolerance over time is affected by the amount above the minimum therapeutic concentration the bloodstream concentration is at.[1] Thus, it is likely more physically relevant to assume that the increment or decrement of the minimum therapeutic concentration is proportional to the difference between the threshold and the blood concentration by some proportionality constant. This can be implemented to also include recovery, as if the concentration is below the threshold, the threshold will be lowered. Assuming the rate constants are equal for recovery and tolerance, all that is left is to include a conditional for the lower bound on the threshold at the model's initial point of 0.25. As an individual who has never taken the drug will have a threshold at this value, a recovering addict's susceptibility likely should not decrease significantly below it. For a proportionality constant of 0.01, this version of the pharmacodynamic tolerance model yields the behavior to the left, beginning with acute tolerance followed by recovery once the concentration has dropped below the minimum therapeutic concentration. The adaptive response threshold serves as a reference for the initial threshold (0.25).



References

1. Dumas, Emily O., and Gary M. Pollack. “Opioid Tolerance Development: A Pharmacokinetic/Pharmacodynamic Perspective.” *The AAPS Journal* 10.4 (2008): 537. *PMC*. Web. 8 Feb. 2018.
2. Miller, N. S., et al. "The relationship of addiction, tolerance, and dependence to alcohol and drugs: A neurochemical approach." Journal of Substance Abuse Treatment 4(3): 197-207.
3. Pradhan, A. A. A., et al. (2010). "Ligand-Directed Trafficking of the δ-Opioid Receptor *In Vivo*: Two Paths Toward Analgesic Tolerance." The Journal of Neuroscience 30(49): 16459-16468.
4. Schöneberg, T. (2008). Tolerance and Desensitization. Encyclopedia of Molecular Pharmacology. S. Offermanns and W. Rosenthal. Berlin, Heidelberg, Springer Berlin Heidelberg: 1203-1207.