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What should patients do if they miss a dose of medication? A theoretical approach

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Abstract
Medication adherence is a major problem for patients with chronic diseases that require long term pharmacotherapy. Many unanswered questions surround adherence, including how adherence rates translate into treatment efficacy and how missed doses of medication should be handled. To address these questions, we formulate and analyze a mathematical model of the drug concentration in a patient with imperfect adherence. We find exact formulas for drug concentration statistics, including the mean, the coefficient of variation, and the deviation from perfect adherence. We determine how adherence rates translate into drug concentrations, and how this depends on the drug half-life, the dosing interval, and how missed doses are handled. While clinical recommendations require extensive validation and should depend on drug and patient specifics, as a general principle our theory suggests that nonadherence is best mitigated by taking double doses following missed doses if the drug has a long half-life. This conclusion contradicts some existing recommendations that cite long drug half-lives as the reason to avoid a double dose after a missed dose. Furthermore, we show that a patient who takes double doses after missed doses can have at most only slightly more drug in their body than a perfectly adherent patient if the drug half-life is long. We also investigate other ways of handling missed doses, including taking an extra fractional dose following a missed dose. We discuss our results in the context of hypothyroid patients taking levothyroxine.

Keywords Medication adherence · Missed doses · Levothyroxine · Stochastics

Introduction

Adherence to medications is the process by which patients take their medications as prescribed [1]. It is well-documented that nonadherence is a major problem, resulting in over 100,000 preventable deaths and $100 billion in preventable health care costs per year in the United States alone [2]. In fact, the World Health Organization noted that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments" [3, 4]. Nonadherence is especially prevalent and problematic in patients with chronic diseases that require long term pharmacotherapy [5]. As former US surgeon general C Everett Koop famously observed, "Drugs don't work in patients who don't take them" [6].

Medication adherence has been divided into the three phases of initiation, implementation, and discontinuation [1]. Initiation and discontinuation refer to a patient starting and stopping a regimen as prescribed (and the term "persistence" describes the time from initiation to discontinuation [1, 7]). In this paper, we focus on implementation, which is the extent to which a patient's actual dosing follows the prescribed dosing regimen [1].

Many outstanding questions surround the implementation phase of adherence and how it relates to therapeutic outcomes. Adherence is often reported as the percentage of doses of medication actually taken by the patient over a specified time [2]. How does an adherence percentage p translate into treatment efficacy? How much worse is, for example, $p = 70\%$ compared to $p = 85\%$? How much adherence is needed for full treatment benefits? How can clinicians increase patient adherence? Are there protocols to increase treatment benefits in spite of poor adherence?

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While the causes of nonadherence vary, a significant portion of nonadherence stems from patients simply forgetting to take their medication [8, 9]. What should a patient do if they miss a dose of medication? Although patients commonly ask this question, they often do not receive adequate instructions for what to do when a dose is missed [10–12].

To address these questions, we formulate and analyze a mathematical model of the drug concentration in a patient with imperfect adherence. Mathematical modeling is especially well-suited to investigate these questions, given the ethics of clinical trials that force patients to miss doses of medication. To model imperfect adherence, we assume that the patient takes their medication at only a given percentage of the prescribed dosing times. Doses are missed at random, and thus the drug concentration in the body is random. For simplicity, we assume that the patient misses each dose with a fixed probability $1 - p$, independent of their prior behavior. We find exact mathematical formulas for statistics of this model, including the average drug concentration, the drug concentration coefficient of variation, and how the drug concentration deviates from a patient with perfect adherence. These statistics are obtained as explicit functions of the adherence percentage, the drug half-life, and the prescribed dosing interval (i.e. the time between scheduled doses). Furthermore, we determine how these statistics depend on how the patient handles missed doses, including the case that they skip missed doses and the case that they take double doses following missed doses.

From a mathematical standpoint, the random variables that model the drug concentration in our model generalize infinite Bernoulli convolutions [13–17]. The study of infinite Bernoulli convolutions has a rich history in the pure mathematics literature, dating back to Erdős and others in the 1930s [18–20]. Infinite Bernoulli convolutions typically have very irregular distributions, including singular distributions supported on a Cantor set [19]. Infinite Bernoulli convolutions also arose in the pharmacokinetic models in [21, 22]. Our analysis of the generalized infinite Bernoulli convolutions that arise in our model relies on the theory of random pullback attractors [23–27].

From the standpoint of pharmacology, there are several results of our analysis. First, we provide quantitative estimates of how an adherence percentage p translates into statistics of drug concentrations in the body, and how these statistics depend on the drug half-life t_{half}, the dosing interval τ, and how missed doses are handled. Further, these estimates show how the effects of nonadherence can be lessened by drugs with half-lives that are long compared to the dosing interval, i.e. $t_{half} \gg \tau$. While clinical recommendations require extensive validation and should depend on drug and patient specifics, as a general principle our theory suggests that the effects of nonadherence are best mitigated by taking double doses following missed doses if $t_{half} \gg \tau$, whereas missed doses should be skipped if $t_{half} \ll \tau$. This conclusion contradicts some existing recommendations that cite long drug half-lives as the reason to avoid a double dose after a missed dose (for example, see recommendations for perampanel [11] and valproate [12]), as well as the general recommendation that double doses should not be taken to compensate for missed doses [28]. Since double doses are sometimes avoided due to concern that they may cause toxic drug concentrations, we provide an upper bound for the highest possible drug concentration in the body. We find that a patient who takes double doses after missed doses can have at most only a slightly higher drug concentration (and exposure) than a perfectly adherent patient if $t_{half} \gg \tau$. We also investigate other ways of handling missed doses, including taking an extra half dose following a missed dose, which we find is most appropriate when $t_{half} \approx \tau$.

The rest of the paper is organized as follows. We formulate and analyze the mathematical model in the Methods section (details of the mathematical analysis are in the Appendix). In the Results section, we explore the pharmacological implications of the mathematical analysis. Since these pharmacological implications depend on rather complicated mathematics, we also provide an intuitive explanation for our results in this section. The Discussion section concludes by describing related work, model limitations, and future directions. We also discuss our results in the context of hypothyroid patients taking levothyroxine. The Appendix collects some technical points and the proofs of the theorems.

Methods

Mathematical model

Our model builds on the classical pharmacokinetic model of extravascular (oral) administration in a single compartment with first order kinetics [29, 30]. In the standard model, the drug concentration, c_0, in the body at time $s > 0$ satisfies the ordinary differential equation (ODE),

$$\frac{dc_0}{ds} = k_a \frac{g}{V} - k_e c_0, \tag{1}$$

where k_a and k_e are the respective rates of absorption and elimination, V is the volume of distribution, and g is the drug amount at the absorption site. The amount g satisfies the ODE,

$$\frac{dg}{ds} = -k_a g + I(s), \tag{2}$$

where $I(s)$ describes the drug input.

For most drugs administered extravascularly in conventional dosage forms, the absorption rate is much larger than the elimination rate, meaning $k_a \gg k_e$ (see [29, 31–35]). In this parameter regime, the solution of (1) is well-approximated by the solution to

$$\frac{dc}{ds} = \frac{I(s)}{V} - k_e c, \tag{3}$$

which is the standard model for intravascular administration with first order elimination. In this paper, we assume $k_a \gg k_e$ and thus consider the simpler model in (3) rather than the system in (1)-(2).

Perfect adherence

Suppose a patient is instructed to take a dose of size $D > 0$ at regular time intervals of length $\tau > 0$ beginning at time 0. If the patient has perfect adherence, then the drug input is

$$I^{perf}(s) = DF \sum_{n \geq 0} \delta(t - n\tau), \tag{4}$$

where $F \in (0, 1]$ is the bioavailability fraction and δ denotes the Dirac delta function. Solving (3)-(4) yields the following well-known formula for the drug concentration at time $s \geq 0$ in the perfectly adherent patient [30],

$$c^{perf}(s) := \frac{DF}{V} \sum_{n=0}^{N(s)} e^{-k_e(s - n\tau)}, \tag{5}$$

where $N(s) + 1$ is the number of dosing times elapsed by time s,

$$N(s) := \sup\{n \geq 0 : n \leq s/\tau\}.$$

If

$$t = s - N(s)\tau \in [0, \tau)$$

denotes the time elapsed since the most recent dosing time, then (5) can be written as

$$c^{perf}(s) = \alpha^{t/\tau} \frac{DF}{V} \sum_{n=0}^{N(s)} \alpha^n, \tag{6}$$

where we have defined the dimensionless constant

$$\alpha := e^{-k_e \tau} \in (0, 1), \tag{7}$$

which is the fraction of a dose that remains in the body after one dosing interval.

If the patient continues their perfect adherence for a long time, then it is easy to see from the form in (6) that the drug concentration approaches the following function,

$$c^{perf}(N\tau + t) \to C^{perf}(t) := \alpha^{t/\tau} \frac{DF}{V} A^{perf} \quad \text{as } N \to \infty, \tag{8}$$

where $t \in [0, \tau)$ is the time since the last dose and

$$A^{perf} := \sum_{n \geq 0} \alpha^n = \frac{1}{1 - \alpha}.$$

In pharmacokinetics, it is common to measure the drug exposure over a single dosing interval by the so-called "area under the curve," which for this case of perfect adherence is

$$AUC^{perf} := \int_0^\tau C^{perf}(t)\, dt = \frac{DF}{V} \frac{1}{k_e}. \tag{9}$$

Nonadherence

To model patient nonadherence, we suppose that the patient occasionally misses a dose. Specifically, at each dosing time, the patient "remembers" to take their medication with probability $p \in (0, 1)$, and the patient "forgets" with probability $1 - p$. Mathematically, let $\{\xi_n\}_n$ be a sequence of independent and identically distributed (iid) Bernoulli random variables with parameter p, meaning

$$\xi_n = \begin{cases} 1 & \text{with probability } p, \\ 0 & \text{with probability } 1 - p. \end{cases} \tag{10}$$

Hence, $\xi_n = 1$ means that the patient takes their medication at the nth dosing time. We emphasize that $\{\xi_n\}_n$ is a sequence of independent random variables, which means that the patient misses doses independently of their prior behavior.

If $Df_n \geq 0$ denotes the amount taken at the nth dosing time, then the drug input is

$$I(s) = DF \sum_{n \geq 0} \delta(t - n\tau) f_n, \tag{11}$$

and solving (3) with $I(s)$ in (11) yields the drug concentration in the patient,

$$c(s) = \alpha^{t/\tau} \frac{DF}{V} \sum_{n=0}^{N(s)} \alpha^{N(s)-n} f_n. \tag{12}$$

Notice that (12) reduces to (6) if $f_n = 1$ for all n. We take

$$f_n = 0, \quad \text{if } \xi_n = 0,$$

which means the patient does not take any medication

when they forget. However, we allow for the possibility that

$$f_n > 1, \quad \text{if } \xi_n = 1,$$

which means that the patient may take more than a single dose to make up for prior missed doses. In general, we allow f_n to be a function of the history $\{\xi_i\}_{i \le n}$, and we refer to a choice of f_n as a "dosing protocol."

The simplest dosing protocol is for the patient to merely take a single dose if they remember, which means

$$f_n^{single} := \begin{cases} 0 & \text{if } \xi_n = 0, \\ 1 & \text{if } \xi_n = 1. \end{cases} \tag{13}$$

We refer to (13) as the "single dose" protocol. Another common dosing protocol is for the patient to take a double dose to make up for a missed dose at the prior dosing time, which means

$$f_n^{double} := \begin{cases} 0 & \text{if } \xi_n = 0, \\ 1 & \text{if } \xi_n = 1,\ \xi_{n-1} = 1, \\ 2 & \text{if } \xi_n = 1,\ \xi_{n-1} = 0. \end{cases} \tag{14}$$

We refer to (14) as the "double dose" protocol. Notice that in the double dose protocol, the patient never takes more than two doses at a time, even if they missed more than one previous dose. Our analysis below covers other dosing protocols, but we are primarily interested in comparing the single dose and double dose protocols in (13)-(14). As a technical aside, we are ultimately interested in the large time behavior of $c(s)$ in (12), and thus the values of f_n in (12) for small n are irrelevant. In particular, the fact that the definition of f_0^{double} in (14) depends on ξ_{-1} is immaterial.

Figure 1a illustrates how the drug concentration in the body evolves in time. The black dotted curve describes the perfectly adherent patient, and the red dashed curve and blue solid curve describe patients with imperfect adherence following the single dose and double dose protocols, respectively. We set the initial drug concentration equal to $C^{perf}(0)$ in this illustration.

Large-time drug concentration distribution

For the case of perfect adherence, the drug concentration at large time is described by $C^{perf}(t)$ in (8). Analogously, for the case of imperfect adherence, we prove below that the drug concentration converges in distribution at large time,

$$c(N\tau + t) \to_{\mathrm{d}} C(t) \quad \text{as } N \to \infty, \tag{15}$$

where $t \in [0, \tau)$ is the time since the last dosing time and $C(t)$ is a certain random function given below. In particular, $C(t)$ describes the drug concentration in a patient who has been taking the drug for a long time with adherence $p \in (0, 1)$. Furthermore, the patient's drug exposure over a dosing interval is

$$AUC := \int_0^\tau C(t)\, \mathrm{d}t. \tag{16}$$

We emphasize that $C(t)$ and AUC are random since patient adherence is modeled by a random process.

The effects of nonadherence

We measure the effects of nonadherence by comparing the drug concentration in a patient with imperfect adherence to

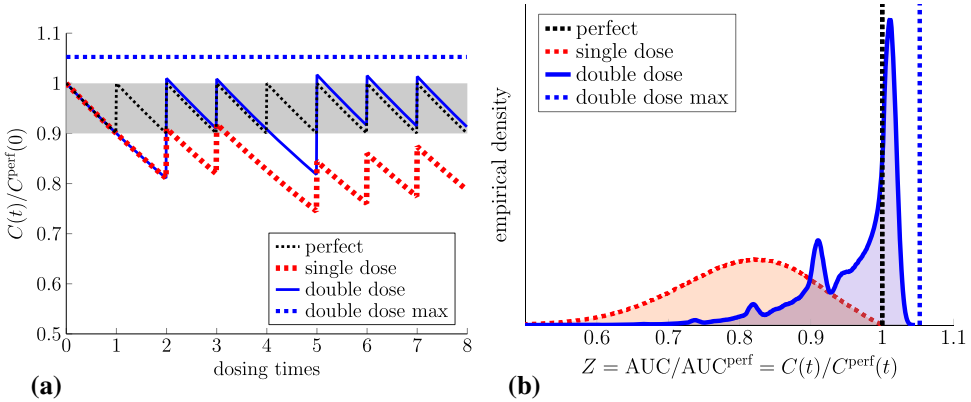

Fig. 1 **a** The black dotted curve depicts how the drug concentration in a perfectly adherent patient evolves in time, and the gray shaded region is the area between the peaks and troughs of the perfectly adherent patient. The red dashed curve and blue solid curve describe patients with imperfect adherence following the single dose and double dose protocols, respectively. The blue dashed line depicts the largest possible drug concentration for the double dose protocol (see (23)). **b** The distribution of the relative drug concentration $Z = AUC/AUC^{perf} = C(t)/C^{perf}(t)$ for the single dose protocol (red) and the double dose protocol (blue) obtained from stochastic simulations. The black dotted vertical line at $Z = 1$ describes the perfectly adherent patient, and the blue dashed vertical line describes the largest possible drug concentration for the double dose patient (see (23)). In both plots, $p = 0.8$ and $\alpha = 0.9$ (Color figure online)

the drug concentration in a patient with perfect adherence. It is natural to quantify this in terms of the drug exposure ratio AUC/AUC^{perf} or the drug concentration ratio $C(t)/C^{perf}(t)$ at some time $t \in [0,\tau)$ since the last scheduled dose. It turns out that these two ratios are the same, as we prove below that

$$Z := \frac{AUC}{AUC^{perf}} = \frac{C(t)}{C^{perf}(t)}, \quad \text{for all } t \in [0,\tau). \tag{17}$$

We therefore emphasize that we study the effects of nonadherence in terms of the relative drug exposure and the relative drug concentration by studying the single random variable Z. Figure 1b plots the distribution of Z for the single dose protocol (red) and the double dose protocol (blue) obtained from stochastic simulations (the distribution is obtained from 10^7 realizations of $c(N\tau + t)$ with $N = 100$).

We study Z primarily in terms of the following three statistics. First, we define the mean,

$$\mu := \mathbb{E}[Z] = \frac{\mathbb{E}[AUC]}{AUC^{perf}} = \frac{\mathbb{E}[C(t)]}{C^{perf}(t)}, \tag{18}$$

which compares the average drug concentration to the perfectly adherent patient. We further define the deviation,

$$\begin{aligned} \Delta &:= \sqrt{\mathbb{E}[(Z-1)^2]} = \frac{\sqrt{\mathbb{E}\left[(AUC - AUC^{perf})^2\right]}}{AUC^{perf}} \\ &= \frac{\sqrt{\mathbb{E}\left[(C(t) - C^{perf}(t))^2\right]}}{C^{perf}(t)}, \end{aligned} \tag{19}$$

which measures how the drug concentration deviates from the perfectly adherent patient. In statistics, (19) is called the relative root-mean-square deviation or relative root-mean-square error. We also compute the coefficient of variation of Z, but we find that Δ is a better measure of the effects of nonadherence. Finally, since dosing protocols in which the patient takes more than a single dose at a time may cause drug concentrations to rise too high, another useful statistic is the largest possible drug concentration compared to the perfectly adherent patient,

$$\lambda := \sup_{\xi} Z = \sup_{\xi} \frac{AUC}{AUC^{perf}} = \sup_{\xi} \frac{C(t)}{C^{perf}(t)}, \tag{20}$$

where $\sup_{\xi}$ denotes the supremum over patterns of the patient remembering or forgetting to take their medication (i.e. $\{\xi_n\}_n$ in (10)). We emphasize that (20) means that λ bounds both the relative drug exposure (i.e. AUC to AUC^{perf}) and the relative drug concentration at any time (i.e. $C(t)$ to $C^{perf}(t)$).

We point out that the statistics μ, Δ, and λ in (18)-(20) are dimensionless, and thus they are independent of the units used to measure drug amounts, concentrations, time, etc. Furthermore, these statistics depend only on α in (7), the adherence percentage $p \in (0,1)$, and the dosing protocol f_n. We emphasize that since μ, Δ, and λ are defined relative to the perfectly adherent patient, their values are unchanged if AUC and AUC^{perf} are replaced by $C(t)$ and $C^{perf}(t)$ for any $t \in [0,\tau)$ (as indicated by (18)-(20)).

Single and double dose protocols

In the Appendix, we analyze the mathematical model and compute statistics of the drug concentrations for general dosing protocols. Here, we present the formulas for μ, Δ, and λ for the single and double dose protocols.

Theorem 1 *Using superscripts to denote the dosing protocol, the relative means in (18) are*

$$\mu^{single} = p, \quad \mu^{double} = p + p(1-p).$$

Similarly, the deviations in (19) are

$$\Delta^{single} = \sqrt{\frac{1-p}{1+\alpha}}\sqrt{1-\alpha(2p-1)}, \tag{21}$$

$$\Delta^{double} = \sqrt{\frac{1-p}{1+\alpha}}\sqrt{1+p+(1-7p+2p^2)\alpha+2p^2(2-p)\alpha^2}. \tag{22}$$

Finally, the largest relative drug concentrations in (20) are

$$\lambda^{single} = 1, \quad \lambda^{double} = \frac{2}{1+\alpha}. \tag{23}$$

Results

We now explore some pharmacological implications of the analysis above. Recall that $\alpha := e^{-k_e\tau}$, where τ is the dosing interval and k_e is the drug elimination rate. Since elimination rates are often expressed in terms of half-lives, we note that the drug half-life, $t_{half} > 0$, is related to the other parameters via

$$\alpha = 2^{-\tau/t_{half}}, \quad t_{half} = \left(\frac{\ln\frac{1}{2}}{\ln\alpha}\right)\tau = \frac{\ln 2}{k_e}. \tag{24}$$

Hence, in the following a "long drug half-life" means t_{half} is long compared to τ, and thus α is large (i.e. α is near 1). Similarly, a "short drug half-life" means t_{half} is short compared to τ, and thus α is small.

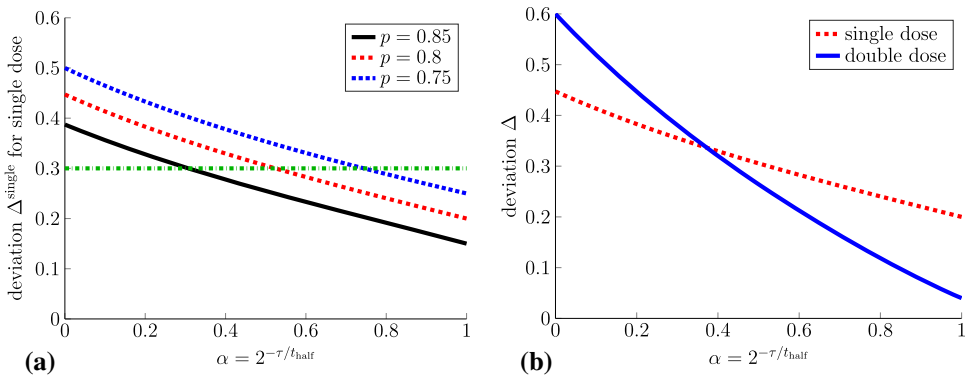

Fig. 2 Deviation Δ from perfect adherence. **a** plots the deviation Δ^{single} for the single dose protocol as a function of α for different adherence percentages p. **b** compares the deviations Δ^{single} and Δ^{double} for the single and double dose protocols with $p = 0.8$

Long half-lives reduce the effects of patient nonadherence

We begin by considering the single dose protocol. In Fig. 2a, we plot Δ^{single} as a function of α for different patient adherence levels p. As expected, Δ^{single} decreases as the patient adherence p increases. Furthermore, Δ^{single} decreases as α increases, and Δ^{single} approaches its minimum value as $\alpha \to 1$,

$$\Delta^{single} \to 1 - p \quad \text{as } \alpha \to 1.$$

These properties can be seen from Fig. 2a and equation (21).

Importantly, Fig. 2a shows that the effect of patient nonadherence, as measured by the deviation Δ^{single} from perfect adherence, depends critically on α. For example, notice that the horizontal line in Fig. 2a at $\Delta^{single} = 0.25$ intersects the Δ^{single} curves for the three different levels of patient adherence considered (namely, $p = 0.85$, $p = 0.8$, and $p = 0.75$). Therefore, a patient with high adherence p and small α and a patient with low adherence p and large α can have the same deviation from the perfectly adherent patient.

Put another way, the effects of nonadherence can be lessened by increasing the α value of the drug (i.e. increasing the half-life t_{half} or decreasing the dosing interval τ) without changing the patient's actual adherence p. This result is inline with previous analysis, as it is commonly noted that drugs with long half-lives tend to be more "forgiving" of missed doses [36]. This analysis thus quantifies drug "forgiveness." For other measures of drug forgiveness, see [37–39].

Double dose protocol mitigates patient nonadherence for drugs with long half-lives

To compare the deviations from perfect adherence for the single dose and double dose protocols, in Fig. 2b we plot Δ^{single} and Δ^{double} as functions of α. This figure shows that

$$\begin{aligned} &\Delta^{single} < \Delta^{double} \quad \text{if } \alpha \text{ is small (i.e. short half-life),} \\ \text{and} \quad &\Delta^{double} < \Delta^{single} \quad \text{if } \alpha \text{ is large (i.e. long half-life).} \end{aligned} \tag{25}$$

We set $p = 0.8$ in Fig. 2b, but other values of p yield similar results. Indeed, the formulas in (21) and (22) imply the small α limits,

$$\lim_{\alpha \to 0} \Delta^{single} = \sqrt{1-p} < \lim_{\alpha \to 0} \Delta^{double} = \sqrt{1-p^2},$$

and the large α limits,

$$\lim_{\alpha \to 1} \Delta^{double} = (1-p)^2 < \lim_{\alpha \to 1} \Delta^{single} = 1 - p. \tag{26}$$

In practical terms, (26) means that if α is large and the patient has adherence of $p = 0.9$, then the deviation from perfect adherence is roughly 10 times smaller for the double dose protocol compared to the single dose protocol.

While we have shown (25) for large α, it follows from (21)-(22) that it is actually the case that

$$\begin{aligned} \Delta^{double} < \Delta^{single} \quad &\text{if and only if } \alpha > \alpha_c \\ &:= \frac{2}{5 - 2p + \sqrt{12(p-3)p + 25}}. \end{aligned} \tag{27}$$

It is straightforward to check that the critical value α_c always lies in the interval,

$$\alpha_c \in (0.2, 0.5) \quad \text{for all } p \in (0, 1).$$

Therefore, $\alpha > 0.5$ is a sufficient condition for $\Delta^{double} < \Delta^{single}$, and $\alpha > 0.5$ is equivalent to $t_{half} > \tau$.

These results imply that if $\alpha > \alpha_c$, then a patient following the double dose protocol with actual adherence p can have the same deviation from perfect adherence as they would have by following the single dose protocol with a higher adherence p_+. We thus refer to p_+ as their "effective adherence." To calculate p_+, suppose the patient has actual adherence p. We then find the value of p_+ which satisfies

$$\Delta^{single}|_{p_+} = \Delta^{double}|_{p}, \tag{28}$$

where $\Delta^{single}|_{p_+}$ and $\Delta^{double}|_{p}$ denote setting the adherence equal to p_+ and p in the respective formulas in (21)-(22). Solving (28) yields the "effective adherence" $p_+ \in (0,1)$ as a function of α and the actual adherence p. Note that (27) implies that $p_+ > p$ if and only if $\alpha > \alpha_c$.

In Fig. 3a, we plot p_+ as a function of p for different values of α. This figure shows that the increase in the effective adherence obtained by following the double dose protocol is quite substantial, especially if α is close to 1. For example, if $\alpha = 0.8$, then a patient with actual adherence of only $p = 0.6$ can have effective adherence $p_+ = 0.8$, and a patient with actual adherence of $p = 0.8$ can have effective adherence $p_+ = 0.92$. Notice that $p_+ = p$ if $\alpha = \alpha_c$.

Summarizing, this analysis suggests that (i) the single dose protocol is best when $t_{half} \ll \tau$ and (ii) the double dose protocol is best when $t_{half} \gg \tau$. Conclusion (ii) contradicts some common dosing recommendations. Indeed, long drug half-lives are sometimes stated as the reason to avoid the double dose protocol in favor of the single dose protocol (for example, see recommendations for perampanel [11] and lamotrigine sodium valproate [12]). However, we have shown that drugs with long half-lives are precisely the drugs for which patients could benefit from taking a double dose following a missed dose.

Double dose protocol is not toxic for drugs with long half-lives

Taking a double dose is sometimes avoided due to concern that it may cause a toxic drug concentration in the body. For a patient following the double dose protocol, (23) provides an upper bound to how their drug concentration or exposure ($C(t)$ or AUC^{double}) could compare to the perfectly adherent patient ($C^{perf}(t)$ or AUC^{perf}). Indeed, (23) ensures that

$$\begin{aligned} \frac{C^{double}(t)}{C^{perf}(t)} &< \lambda^{double} = \frac{2}{1+\alpha}, \quad \text{for any } t \in [0,\tau), \\ \frac{AUC^{double}}{AUC^{perf}} &< \lambda^{double} = \frac{2}{1+\alpha}. \end{aligned} \tag{29}$$

We emphasize that (29) means that λ^{double} bounds both the relative drug concentration and the relative drug exposure.

We plot the maximum possible "overshoot" $\lambda^{double} - 1$ in Fig. 3b as a function of α. Importantly, λ^{double} approaches 1 for large α, which means that the possible overshoot from following the double dose protocol vanishes for drugs with long half-lives. In practical terms, (29) means that if $\alpha = 0.8$, then the drug concentration is at most 11% greater than the perfectly adherent patient, and if $\alpha = 0.9$, then the drug concentration is at most 5% greater than the perfectly adherent patient.

Furthermore, it is extremely rare for a patient to have a drug concentration near the theoretical upper bound in (29) if α is large. Indeed, the upper bound in (29) is approached only by a patient that alternates exactly between taking and missing the scheduled doses for many dosing intervals if α is large. A more typical overshoot occurs in the following way. If the patient has been taking their medication as prescribed for a long time, then the concentration in their body time $t \in [0,\tau)$ after a dose is roughly the same as the perfectly adherent patient, which is $C^{perf}(t)$. Then, if they miss one dose and take a double dose at the following dosing time, then the drug concentration time $t \in [0,\tau)$ after the double dose is (compared to $C^{perf}(t)$)

$$\lambda^{typ} := \frac{\alpha^2 C^{perf}(t) + 2\alpha^{t/\tau}\frac{DF}{V}}{C^{perf}(t)} = 1 + (1-\alpha)^2 < \lambda^{double}, \tag{30}$$

which is shown in Fig. 3b.

Summarizing, if α is large, then a patient following the double dose protocol cannot have much more drug in their body than the perfectly adherent patient, where the precise

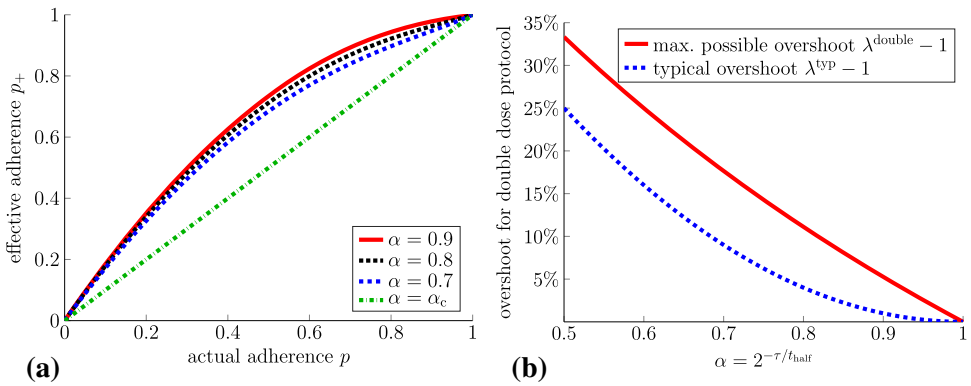

Fig. 3 **a** Plots the effective adherence p_+ obtained by following the double dose protocol rather than the single dose protocol as a function of the actual adherence p. For a patient following the double dose protocol, **b** shows how their drug concentrations could rise above the concentrations in a perfectly adherent patient

upper bound is in (29). Furthermore, it is rare for the drug concentration to approach the upper bound in (29) if α is large, and the more typical overshoot is in (30).

Adherence thresholds should depend on drug half-life, dosing interval, and dosing protocol

How much patient adherence is needed for the patient to obtain full treatment benefits? The adherence threshold

$$p \geq 0.8 \tag{31}$$

has long been considered the definition of an "adherent patient" [5, 40]. However, our calculations show the inadequacy of defining an acceptable patient adherence rate solely in terms of the adherence p. To illustrate, suppose patient #1 has adherence $p_1 = 0.85$ and $\alpha_1 = 0.2$, whereas patient #2 has adherence $p_2 = 0.75$ and $\alpha_2 = 0.8$. Therefore, by the standard definition in (31), patient #1 would be deemed "adherent" and patient #2 would be deemed "non-adherent." However, if both patients are following the single dose protocol, then their deviations from the perfectly adherent patient are

$$\begin{aligned} &\Delta_1^{single} \approx 0.33 \quad \text{for patient } \#1, \\ \text{and} \quad &\Delta_2^{single} \approx 0.29 \quad \text{for patient } \#2. \end{aligned}$$

Hence, the supposed "non-adherent patient" (patient #2) is actually closer to the perfectly adherent patient than the "adherent patient" (patient #1).

In fact, the situation is more exasperated if we consider the double dose protocol. To illustrate, suppose patient #1 and patient #2 again have respective adherence rates of $p_1 = 0.85$ and $p_2 = 0.75$, but now suppose they both have $\alpha = 0.8$. If patient #1 follows the single dose protocol and patient #2 follows the double dose protocol, then their deviations from the perfectly adherent patient are

$$\begin{aligned} &\Delta_1^{single} \approx 0.19 \quad \text{for patient } \#1, \\ \text{and} \quad &\Delta_2^{double} \approx 0.14 \quad \text{for patient } \#2. \end{aligned}$$

Therefore, the drug concentrations in the "non-adherent patient" are again closer to the perfectly adherent patient than the "adherent patient."

More complicated dosing protocols

We now consider more complicated dosing protocols. Notice that in the double dose protocol, the patient never takes more than two doses at a time, even if they missed two or more consecutive prior doses. A more aggressive protocol is the "triple dose" protocol in (39) in which the patient takes a double dose to make up for a single missed dose and a triple dose to make up for two or more consecutive missed doses. An even more aggressive protocol is the "all dose" protocol in (40) in which the patient takes all of their missed doses. As another example, consider the "fractional" dosing protocol,

$$f_n^{frac} := \begin{cases} 0 & \text{if } \xi_n = 0, \\ 1 & \text{if } \xi_n = 1,\ \xi_{n-1} = 1, \\ 1+\alpha & \text{if } \xi_n = 1,\ \xi_{n-1} = 0, \end{cases} \tag{32}$$

in which the patient takes an extra large fractional dose if they missed one or more prior doses. The reasoning behind the size of this extra dose is that if the patient had taken their prior dose, then the fraction of that prior dose remaining in their body at the next dosing time would be α. Note that (32) is a special case of the boost protocol in (38) with $b = \alpha$.

These protocols may be impractical, as (39)-(40) require the patient to keep fairly detailed records and (32) requires the ability to take a fractional dose. Nevertheless, it is interesting to consider the implications of these dosing protocols. In the Appendix, we obtain exact analytical formulas for the deviation Δ for these different dosing protocols (see Corollary 3). In Fig. 4, we plot Δ for these protocols and for the single and double dose protocols as functions of α (we set $p = 0.8$). There are two important points to observe from Fig. 4.

First, if α is large, then the deviation Δ is smallest for the triple dose and all dose protocols. Indeed, the formulas in Corollary 3 imply that

$$\lim_{\alpha \to 1} \Delta^{triple} = (1-p)^3, \quad \lim_{\alpha \to 1} \Delta^{all} = 0,$$

where the superscript indicates the corresponding dosing protocol. Hence, one might recommend the triple dose protocol or even the all dose protocol if α is large. However, while Δ^{double} is much less than Δ^{single} for large α, the further reductions in the deviation Δ for the triple dose and all dose protocols are comparatively much smaller. Furthermore, compared to the double dose protocol, the triple dose and all dose protocols come with the costs of (i) being

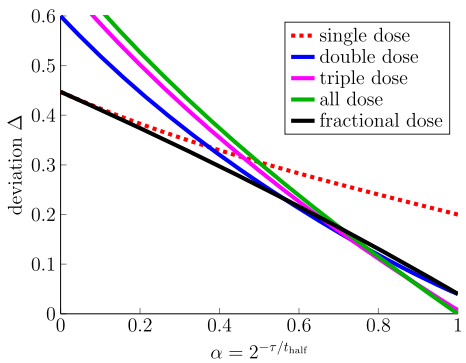

Fig. 4 Deviation Δ from perfect adherence for various dosing protocols

more complicated and (ii) allowing for a higher possible drug concentration in the body (see (23)).

Next, notice in Fig. 4 that the fractional dose protocol in (32) results in a deviation Δ^{frac} that is near minimal for all values of $\alpha \in (0,1)$. This is perhaps not surprising, since the fractional dose protocol interpolates between the single dose and double dose protocols as α ranges from 0 to 1. Furthermore, it is noteworthy that a patient following the fractional dose protocol is assured to never have too much drug in their body. Indeed, (23) implies that the drug exposure AUC^{frac} for a patient following the fractional dose protocol is bounded above by the exposure for the perfectly adherent patient,

$$AUC^{frac} \leq AUC^{perf}.$$

Similarly, the drug concentration for a patient following the fractional dose protocol is bounded above by the concentration in a perfectly adherent patient,

$$C^{frac}(t) \leq C^{perf}(t), \quad \text{for any } t \in [0,\tau).$$

Therefore, if a patient is able to take fractional doses, then the fractional dose protocol (i) yields a small deviation Δ and (ii) ensures that the patient cannot have more drug in their body than the perfectly adherent patient (regardless of α and p).

Of course, the fractional dose protocol is similar to the single dose protocol if α is small, and it is similar to the double dose protocol if α is large. In particular, the fractional dose protocol differs significantly from both the single and double dose protocols only in the case that $\alpha \approx 0.5$, which means $t_{half} \approx \tau$. Therefore, this analysis suggests that (i) the single dose protocol is best when $t_{half} \ll \tau$, (ii) the double dose protocol is best when $t_{half} \gg \tau$, and (iii) the "1.5 dose" protocol is best when $t_{half} \approx \tau$, where the 1.5 dose protocol means the patient takes an extra half dose to make up for a missed dose,

$$f_n^{half} := \begin{cases} 0 & \text{if } \xi_n = 0, \\ 1 & \text{if } \xi_n = 1,\ \xi_{n-1} = 1, \\ 1.5 & \text{if } \xi_n = 1,\ \xi_{n-1} = 0. \end{cases} \tag{33}$$

From a practical standpoint, the 1.5 dose protocol may often be feasible to implement (if a standard dose is two pills, then the patient takes three pills if they missed their prior dose). Since (33) is a special case of (38) with $b = 0.5$, (23) implies that if a patient follows the 1.5 dose protocol, then their drug exposure, $AUC^{1.5}$, is bounded above by

$$AUC^{1.5} \leq \begin{cases} AUC^{perf} & \text{if } \alpha \geq 0.5, \\ \dfrac{1.5}{1+\alpha} AUC^{perf} & \text{if } \alpha < 0.5. \end{cases}$$

Hence, a patient following the 1.5 dose protocol will never have much more drug in their body than the perfectly adherent patient if $t_{half} \approx \tau$.

Intuition

We have found that the single dose protocol is best when $t_{half} \ll \tau$ and the double dose protocol is best when $t_{half} \gg \tau$. These results relied on rather technical mathematical analysis. The purpose of this section is to provide an intuitive explanation for these results.

Stochastic simulations

We begin by plotting stochastic simulations of the drug concentration in the body as a function of time. In Fig. 5a, we set $p = 0.8$ and $\alpha = 0.25$ (meaning $t_{half} \ll \tau$) and plot the concentration under perfect adherence (black dotted curve), and for imperfect adherence for the single dose protocol (red dashed curve) and double dose protocol (blue solid curve). The shaded gray highlights the region between the peaks and troughs for perfect adherence. While this is just one particular realization of the missed doses (the patient happens to miss doses at the first and fourth dosing times), it nevertheless illustrates that the curve for the patient with perfect adherence is better approximated by the single dose protocol than the double dose protocol. Indeed, the single dose and double dose protocols both undershoot the perfect adherence case when a dose is missed, but the double dose protocol then overcompensates when the patient takes their next dose. This is further illustrated in Fig. 5b, which plots the same scenario but for a longer time period.

In Fig. 5c and d, we plot the same curves as in Fig. 5a and b except in the case that $\alpha = 0.95$ (meaning $t_{half} \gg \tau$). In this case, the double dose protocol approximates perfect adherence much better than the single dose protocol. While the double dose protocol curve does rise above the perfect adherence curve, it is only by a few percent. In contrast, the single dose protocol curve dips far below the double dose and perfect adherence curves when doses are missed.

In Fig. 6, we plot the distribution of the drug concentration for the two scenarios in Fig. 5, with $\alpha = 0.25$ in Fig. 6a and $\alpha = 0.95$ in Fig. 6b. The distributions are computed from 10^7 realizations of $c(N\tau + t)$ with $N = 100$. The very irregular distributions in Fig. 6a are typical for small values of α. The reason for this irregularity is difficult to intuit and is in fact a rich mathematical topic. Indeed, these irregular distributions for the single dose protocol have been studied in the pure mathematics

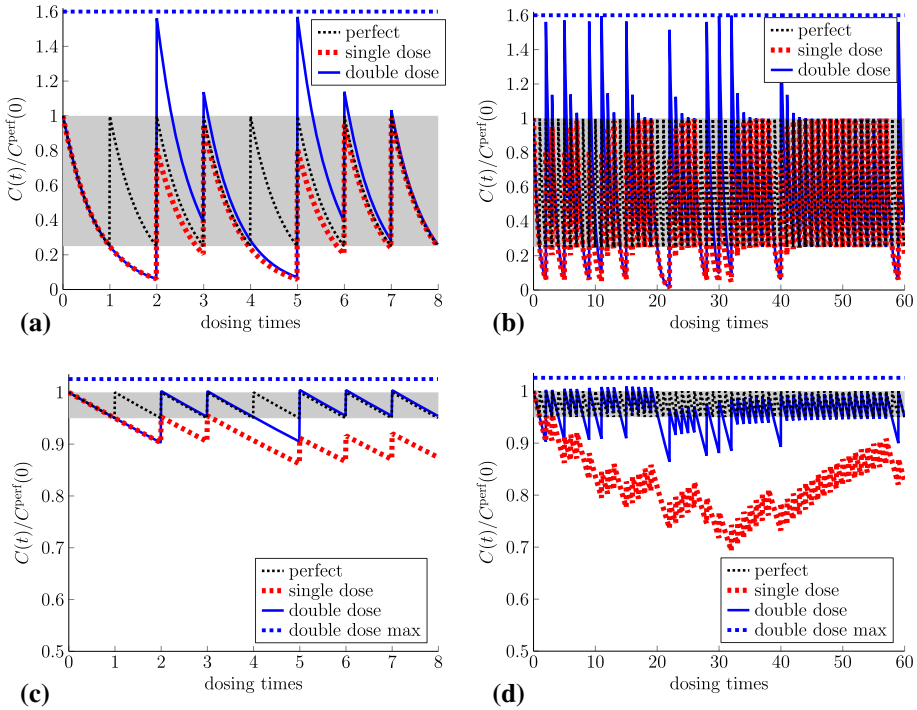

Fig. 5 Stochastic simulations of drug concentration time courses. In **a** and **b**, we set $\alpha = 0.25$ (meaning $t_{half} \ll \tau$), with **b** plotted for a long time period. **c** and **d** are the same as **a** and **b**, except $\alpha = 0.95$ (meaning $t_{half} \gg \tau$). The adherence is $p = 0.8$ in all panels

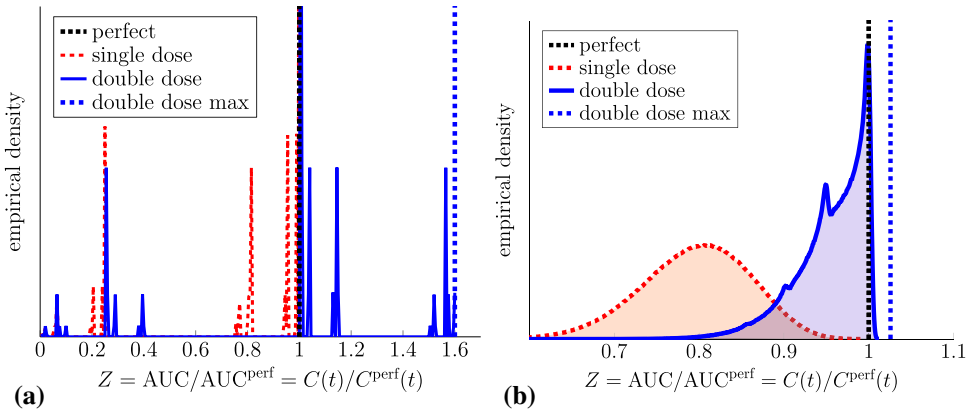

Fig. 6 The distribution of the drug exposure for the single dose protocol (red) and the double dose protocol (blue) obtained from stochastic simulations. We take $p = 0.8$ in both plots and $\alpha = 0.25$ in **a** and $\alpha = 0.95$ in **b**. In both plots, the black dotted vertical line at $AUC/AUC^{perf} = C(t)/C^{perf}(t) = 1$ describes the perfectly adherent patient, and the blue dashed vertical line describes the largest possible drug concentration for the double dose patient (see (23))

literature for many decades under the name infinite Bernoulli convolutions [13–20].

It is again evident from Fig. 6 that the single dose protocol best approximates the perfectly adherent patient when α is small (i.e. short drug half-life), whereas the double dose protocol best approximates the perfectly adherent patient when α is large (i.e. long drug half-life). Notice also from Fig. 6b that it is very rare for the double dose protocol to ever result in a drug concentration much larger than the perfectly adherent patient.

A simple calculation

The phenomena seen above can be explained with a simple calculation. Suppose the patient has been taking the drug as prescribed for a long time and so the drug concentration time $t \in [0, \tau)$ after a dose is $C^{perf}(t)$. Suppose the patient then misses one dose and remembers to take the drug at the following dosing time. Under the single dose protocol, the concentration time $t \in [0, \tau)$ after the single dose is

$$\rho^{single}(t) := \alpha^2 C^{perf}(t) + \alpha^{t/\tau}\frac{DF}{V} = (1-\alpha(1-\alpha))C^{perf}(t),$$

where we have used that $C^{perf}(t) = \alpha^{t/\tau}\frac{DF}{V}A^{perf}$ and $A^{perf} = 1/(1-\alpha)$. Alternatively, under the double dose protocol, the concentration time $t \in [0,\tau)$ after the double dose is

$$\rho^{double}(t) := \alpha^2 C^{perf}(t) + 2\alpha^{t/\tau}\frac{DF}{V} = (1+(1-\alpha)^2)C^{perf}(t).$$

For small α, we have that

$$\rho^{single}(t) \approx (1-\alpha)C^{perf}(t),$$
$$\rho^{double}(t) \approx (2-2\alpha)C^{perf}(t), \quad \text{if } \alpha \text{ is near } 0,$$

which means the single dose protocol puts the patient slightly below the desired $C^{perf}(t)$, but the double dose protocol puts the patient at almost twice $C^{perf}(t)$. However, for large α, we have that

$$\rho^{single}(t) \approx (1-(1-\alpha))C^{perf}(t),$$
$$\rho^{double}(t) = (1+(1-\alpha)^2)C^{perf}(t), \quad \text{if } \alpha \text{ is near } 1,$$

which means that while the single dose protocol puts the patient below $C^{perf}(t)$, the double dose protocol puts the patient above $C^{perf}(t)$ by a much smaller amount. In practical terms, if $\alpha = 0.9$, then the single dose patient undershoots $C^{perf}(t)$ by about 10%, whereas the double dose patient overshoots $C^{perf}(t)$ by a mere 1%.

Discussion

We have formulated and analyzed a mathematical model to investigate how nonadherence to medication affects drug concentrations in the body. We computed pharmacologically relevant statistics of the drug concentration in the body, thus providing quantitative descriptions of the effects of nonadherence, and how these effects depend on the adherence percentage p, drug half-life t_{half}, dosing interval τ, and how missed doses are handled (i.e. the dosing protocol). In agreement with previous results [2], we found that drug concentrations are less affected by missed doses if the half-life is long compared to the dosing interval, and we quantified this effect. As a general principle, we found that nonadherence is best mitigated by taking double doses following missed doses if the drug half-life is long compared to the dosing interval (i.e. $t_{half} \gg \tau$). Furthermore, in this scenario we found that taking double doses following missed doses cannot cause the drug concentration to rise much above the desired concentration. Although long drug half-lives are sometimes stated as the reason to avoid a double dose after a missed dose, we have shown that drugs with long half-lives are precisely the drugs for which patients could benefit from taking a double dose after a missed dose.

As an application of these results, consider the synthetic form of thyroxine known as levothyroxine [41]. Levothyroxine is the standard treatment for hypothyroidism, which is one of the most common diseases in the world and affects up to 5% of the global population [42]. Levothyroxine pills are used to replace missing thyroid hormone in hypothyroid patients and are usually taken once daily for the remainder of the patient's life [42]. Hence, the dosing interval is $\tau = 1$ day. The half-life of levothyroxine for hypothyroid patients is between 9 and 10 days [43, 44], and therefore setting $t_{half} = 9$ days yields

$$\alpha = 2^{-\tau/t_{half}} \approx 0.93.$$

Since this α value is close to 1, our results imply that a hypothyroid patient taking levothyroxine with imperfect adherence can make the drug concentration in their body much closer to the concentration in a perfectly adherent patient by following the double dose protocol rather than the single dose protocol. That is, if the patient misses a dose, then it is better to take a double dose at the next dosing time than to skip the missed dose. These results conflict with common recommendations for levothyroxine, which advise patients to skip any dose that is delayed by more than 12 hours [45–48]. However, some sources recommend a double dose of levothyroxine after a missed dose (see Chapter 376 of [49]), and indeed taking a double dose is recognized as safe (see Chapter 36 in [50]). In fact, the American Thyroid Association has proposed taking up to 7 doses of levothyroxine at once [51].

Furthermore, although following the double dose protocol may cause the drug concentration in the patient to rise above the concentration in a perfectly adherent patient, the maximum possible overshoot for levothyroxine is less than 4% since

$$\lambda^{double} = \frac{2}{1+\alpha} \approx \frac{2}{1+0.93} < 1.04.$$

In addition, it would be very rare for a patient to have drug concentrations near this maximum, as this maximum corresponds to a patient missing doses every other day for many days. Indeed, the typical overshoot is less than 1% for this α value (see (30)).

Our model assumes that the drug absorption rate k_a is much faster than the drug elimination rate k_e. This is true for most drugs administered orally in conventional dosage forms [29, 31–35], including levothyroxine. Indeed, for hypothyroid patients taking levothyroxine, the time to maximum concentration, t_{max}, is only 3 hours [52], whereas the elimination half-life is $t_{half} = 9$ days [43, 44]. Using (24) and the relation [29],

$$t_{max} = \frac{\ln(k_a/k_e)}{k_a - k_e},$$

implies that $k_e/k_a < 0.0015$ for levothyroxine.

Several important prior works have used mathematical modeling to investigate the effects of medication nonadherence. Li and Nekka developed stochastic models of the effect of medication nonadherence on patient drug concentrations [53, 54]. The models in [53, 54] allow the drug to be administered at irregular times, and the authors obtained analytical formulas for drug concentration statistics. In a series of papers [21, 22], another group of authors developed a variety of stochastic pharmacokinetic models, including ones that allow for variation in dosing times, dose amounts, and elimination rates. The discrete time model proposed in [21] is essentially identical to the model in the present paper in the special case of the single dose protocol. These prior works did not analyze different protocols for handling missed doses. Ma [55] analyzed the mean first passage time for the patient's drug concentration to reach a therapeutic range for various ways of handling a missed dose assuming that the patient never misses two or more consecutive doses. Numerical simulations of computational models have also been useful for understanding the effects of nonadherence for specific drugs [56], especially for antiepileptic drugs [57–64] and antipsychotic drugs [65, 66].

Naturally, our model neglects various pharmacological details. We have developed a simple model aimed at addressing patients remembering or forgetting to take their medication, and we assumed that the patient forgets their medication at each dosing time with a fixed probability, independent of their prior behavior. However, nonadherence is a dynamic process and patients exhibit a variety of patterns of nonadherence [5], including extended "drug holidays" [67] and "white-coat adherence" [68]. We also assumed that the patient takes a double dose only if they missed their prior dose. However, actual patients might cause harm by mistakenly taking a double dose when they did not miss their prior dose. Furthermore, our model did not allow delayed doses, and a more detailed model would allow patients to take medication at times that vary continuously. Another source of stochasticity is that pharmacokinetic parameters vary between patients, which has been modeled by analyzing a population of patients with a distribution of parameters [21, 22].

Another limitation of our analysis is that we considered only a single compartment pharmacokinetic model with linear elimination and immediate absorption. The pharmacokinetics of some drugs are better described by multicompartment models [29], and while most drugs can be adequately described by linear processes, there are drugs which exhibit nonlinear kinetics (see Chapter 7 in [29]). In addition, our assumption of fast absorption does not hold for so-called extended release or sustained release drugs [69–71]. Our model also did not address pharmacodynamics, and an interesting avenue for further research would be to couple the stochastic pharmacokinetic model in this work to a pharmacodynamic model.

To conclude, medication nonadherence is a complex and multi-faceted problem, and steps toward its alleviation require contributions from a variety of disciplines. Mathematical modeling is a valuable tool in this endeavor, especially given the ethics of clinical trials that require sporadic dosing. Further, mathematical models can disentangle the effects of various factors and quickly investigate the efficacy of possible interventions. Moving forward, we anticipate that mathematical modeling and analysis will play an important role in understanding and alleviating the effects of medication nonadherence.

A Appendix

In this appendix, we analyze the mathematical model formulated in the main text.

A.1 General theory

Let $\{\xi_n\}_{n\in\mathbb{Z}}$ be a bi-infinite sequence of iid Bernoulli random variables as in (10) (it is convenient to allow the index n to vary over positive and negative integers). The dose taken at dosing time n may depend on the patient's behavior at time n and the prior m dosing times for some given memory parameter $m \geq 0$. Toward this end, let $\{X_n\}_{n\in\mathbb{Z}}$ be the history process,

$$X_n = (\xi_{n-m}, \xi_{n-m+1}, \ldots, \xi_{n-1}, \xi_n) \in \{0,1\}^{m+1}, \tag{34}$$

which records whether or not the patient remembered at dosing time n and the prior m dosing times. It is immediate that $\{X_n\}_{n\in\mathbb{Z}}$ is an irreducible discrete-time Markov chain on the state space $\{0,1\}^{m+1}$ [72]. In particular, let

$$P = \{P(x,y)\}_{x,y\in\{0,1\}^{m+1}} \in \mathbb{R}^{2^{m+1}\times 2^{m+1}} \tag{35}$$

denote the transition probability matrix of the Markov chain $\{X_n\}_{n\in\mathbb{Z}}$ with entries defined by

$$P(x,y) = \mathbb{P}(X_1 = y \,|\, X_0 = x), \quad x,y \in \{0,1\}^{m+1},$$

where $x \in \{0,1\}^{m+1}$ denotes the vector,

$$x = (x_{-m}, x_{m+1}, \ldots, x_{-1}, x_0) \in \{0,1\}^{m+1},$$

and $y \in \{0,1\}^{m+1}$ is denoted analogously. The definition of $\{\xi_n\}_{n\in\mathbb{Z}}$ then implies that the entries of P are

$$P(x,y) = \begin{cases} p & \text{if } y_0 = 1,\ (x_{-m+1},\ldots,x_0) = (y_{-m},\ldots,y_{-1}), \\ 1-p & \text{if } y_0 = 0,\ (x_{-m+1},\ldots,x_0) = (y_{-m},\ldots,y_{-1}), \\ 0 & \text{otherwise.} \end{cases}$$

Furthermore, the definition of $\{\xi_n\}_{n\in\mathbb{Z}}$ implies that the distribution of X_n is

$$\begin{aligned} \pi(x) &:= \mathbb{P}(X_n = x) \\ &= p^{s(x)}(1-p)^{m+1-s(x)} > 0, \quad n \in \mathbb{Z},\ x \in \{0,1\}^{m+1}, \end{aligned} \tag{36}$$

where $s(x) := \sum_{k=0}^{m} x_k \in \{0,1,\ldots,m+1\}$ is the number of 1's in x.

A dosing protocol $f_n = f(X_n)$ is any function

$$f : \{0,1\}^{m+1} \mapsto [0,\infty). \tag{37}$$

While we are most interested in the single dose and double dose protocols in (13) and (14), we also investigate a few other protocols. First, consider the "boost" dosing protocol,

$$f_n^{boost} := \begin{cases} 0 & \text{if } \xi_n = 0, \\ 1 & \text{if } \xi_n = 1,\ \xi_{n-1} = 1, \\ 1+b & \text{if } \xi_n = 1,\ \xi_{n-1} = 0, \end{cases} \tag{38}$$

in which the patient takes a standard single dose of size D plus a "boost" dose of size bD if they missed the prior dose, for some $b \geq 0$. Notice that the boost protocol reduces to the single dose protocol if $b = 0$ and the double dose protocol if $b = 1$. Another protocol is the "triple dose" protocol,

$$f_n^{triple} := \begin{cases} 0 & \text{if } \xi_n = 0, \\ 1 & \text{if } \xi_n = 1,\ \xi_{n-1} = 1, \\ 2 & \text{if } \xi_n = 1,\ \xi_{n-1} = 0,\ \xi_{n-2} = 1, \\ 3 & \text{if } \xi_n = 1,\ \xi_{n-1} = 0,\ \xi_{n-2} = 0, \end{cases} \tag{39}$$

in which the patient takes a double dose to make up for a single missed dose and a triple dose to make up for two or more consecutive missed doses. Finally, consider the "all dose" protocol in which the patient takes all of their missed doses,

$$f_n^{all} := \begin{cases} 0 & \text{if } \xi_n = 0, \\ k+1 & \text{if } \xi_n = 1,\ \xi_{n-1} = 0,\ldots,\xi_{n-k} = 0,\ \xi_{n-k-1} = 1. \end{cases} \tag{40}$$

The all dose protocol does not fit into the framework of (34), and thus an alternative analysis is developed in the section below.

For a dosing protocol f, a real number $a \geq 0$, integers $M \leq N$, and time $t \in [0,\tau)$, define the random variable

$$C_{M,N}(a,t) := \alpha^{t/\tau}\frac{DF}{V}\left(\alpha^{N-M+1}a + \sum_{n=M}^{N}\alpha^{N-n}f(X_n)\right), \tag{41}$$

which is the drug concentration if time t has elapsed since dosing time $n = N$, where $a \geq 0$ describes the concentration at dosing time $n = M-1$. We are interested in the drug concentration after a long time, which corresponds to taking $N \to \infty$ in (41). We will see that this limiting distribution is independent of a and M.

Since $\{X_n\}_{n\in\mathbb{Z}}$ is a stationary sequence, we have that

$$C_{M,N}(a,t) =_{\mathrm{d}} C_{-(N-M),0}(a,t), \quad \text{for integers } N \geq M, \tag{42}$$

where $=_{\mathrm{d}}$ denotes equality in distribution. Define

$$C(t) := \lim_{N\to\infty} C_{-(N-M),0}(a,t) = \alpha^{t/\tau}\frac{DF}{V}A, \quad \text{for } t \in [0,\tau), \tag{43}$$

where

$$A := \sum_{n=0}^{\infty}\alpha^n f(X_{-n}). \tag{44}$$

The function f must be bounded since the state space $\{0,1\}^{m+1}$ is finite, and thus the Weierstrass M-test ensures that $C(t)$ exists almost surely, and it is immediate that $C(t)$ does not depend on $M \in \mathbb{Z}$ or $a \geq 0$. Random variables of the form in (43)-(44) are sometimes called random pullback attractors because they take an initial condition (in this case, $a \geq 0$) and pull it back to the infinite past [23–27].

Therefore, (42) and (43) imply that for any $M \in \mathbb{Z}$ and $a \geq 0$, the random variable $C_{M,N}(a,t)$ converges in distribution to $C(t)$ as $N \to \infty$ [73], which we denote by

$$C_{M,N}(a,t) \to_{\mathrm{d}} C(t), \quad \text{as } N \to \infty. \tag{45}$$

Since f is bounded, $C_{M,N}(a,t)$ can be bounded by a non-random constant independent of N, and thus (42), (43), and the Lebesgue dominated convergence theorem ensure the convergence of every moment of $C_{M,N}(a,t)$,

$$\mathbb{E}[(C_{M,N}(a,t))^j] \to \mathbb{E}[(C(t))^j], \quad \text{as } N \to \infty \text{ for all } j > 0. \tag{46}$$

Summarizing, the large N distribution and statistics of $C_{M,N}(a,t)$ are independent of $a \geq 0$ and $M \in \mathbb{Z}$, and we can study them by studying the distribution and statistics of $C(t)$.

Furthermore, it is immediate from the definitions in (8) and (43) that

$$Z := \frac{AUC}{AUC^{perf}} = \frac{C(t)}{C^{perf}(t)} = \frac{A}{A^{perf}}, \quad \text{for all } t \in [0, \tau). \tag{47}$$

Therefore, studying how drug concentrations are affected by imperfect adherence amounts to studying Z. Since $A^{perf} = 1/(1-\alpha)$, note that

$$\mathbb{E}[Z] = (1-\alpha)\mathbb{E}[A], \quad \mathbb{E}[Z^2] = (1-\alpha)^2\mathbb{E}[A^2].$$

For the single dose protocol in (13), the analysis of Z is straightforward since elements of the sequence $\{f(X_n)\}_{n\in\mathbb{Z}}$ are independent in this special case. The following theorem computes statistics of Z for a general dosing protocol.

Theorem 2 *The first and second moments of Z are*

$$\mathbb{E}[Z] = \sum_x f(x)\pi(x), \tag{48}$$

$$\mathbb{E}[Z^2] = \frac{1-\alpha}{1+\alpha}\left(\sum_x f(x)2u(x) - \sum_x (f(x))^2\pi(x)\right), \tag{49}$$

where $\sum_x$ *denotes the sum over all* $x \in \{0,1\}^{m+1}$, π *is in* (36), *and*

$$u := (I - \alpha P^\top)^{-1}v, \tag{50}$$

where $I \in \mathbb{R}^{2^{m+1}\times 2^{m+1}}$ *is the identity matrix,* $P^\top$ *is the transpose of* P *in* (35), *and* $v \in \mathbb{R}^{2^{m+1}}$ *is the vector with entries* $v(x) = f(x)\pi(x)$ *for* $x \in \{0,1\}^{m+1}$.

Remark 1 The random variable $C(t)$ in (43) generalizes an infinite Bernoulli convolution [13]. If we let $C^{single}(t)$ denote $C(t)$ in the case that f is the single dose protocol in (13), then an infinite Bernoulli convolution is merely a shift and rescaling of $C^{single}(t)$,

$$\Theta = \sum_{n=0}^{\infty} \alpha^n(2\xi_n - 1) = \frac{2C^{single}(t) - C^{perf}(t)}{\alpha^{t/\tau}\frac{DF}{V}}.$$

Dating back to Erdős and others in the 1930s [18–20] and continuing in more recent years [13–17], mathematicians have studied the distribution of Θ. Though the definition of Θ is quite simple, its distribution is often quite irregular and depends very delicately on the parameters α and p.

Proof of Theorem 2 Define

$$A_1 := \sum_{n=0}^{\infty} \alpha^n f(X_{-n+1}).$$

The definition of A in (44) and the stationarity of $\{X_n\}_{n\in\mathbb{Z}}$ imply that

$$A =_{\mathrm{d}} A_1 = \alpha A + f(X_1), \tag{51}$$

where $=_{\mathrm{d}}$ denotes equality in distribution. The invariance relation in (51) plays a key role in our analysis.
Taking the expectation of (51) and rearranging implies that

$$\mathbb{E}[A] = \frac{\mathbb{E}[f(X_1)]}{1-\alpha}, \tag{52}$$

where we have used that $A =_{\mathrm{d}} A_1$. We note that (52) can also be obtained by taking the expectation of (44). Combining (36), (47), and (52) gives (48) in Theorem 2.
Squaring (51), taking expectation, and rearranging implies that

$$\mathbb{E}[A^2] = \frac{1}{1-\alpha^2}\left(2\alpha\mathbb{E}\left[Af(X_1)\right] + \mathbb{E}\left[(f(X_1))^2\right]\right), \tag{53}$$

where we have again used $A =_{\mathrm{d}} A_1$. By definition of expectation, we have that

$$\mathbb{E}\left[(f(X_1))^2\right] = \sum_x (f(x))^2\pi(x). \tag{54}$$

Computing $\mathbb{E}[Af(X_1)]$ is more challenging since A and X_1 are in general correlated if $m \geq 1$.
Let $1_E \in \{0,1\}$ denote the indicator function on an event E, meaning

$$1_E := \begin{cases} 1 & \text{if } E \text{ occurs,} \\ 0 & \text{otherwise.} \end{cases}$$

Decomposing $\mathbb{E}[Af(X_1)]$ based on the value of X_1 gives

$$\mathbb{E}[Af(X_1)] = \sum_x \mathbb{E}[Af(X_1)1_{X_1=x}] = \sum_x f(x)\mathbb{E}[A1_{X_1=x}]. \tag{55}$$

Multiplying (51) by the indicator function on the event $X_1 = x$, taking expectation, and using that $(A, X_0) =_{\mathrm{d}} (A_1, X_1)$ yields

$$\begin{aligned}\mathbb{E}[A1_{X_0=x}] = \mathbb{E}[A_1 1_{X_1=x}] &= \alpha\mathbb{E}[A1_{X_1=x}] \\ &\quad + f(x)\pi(x), \quad x \in \{0,1\}^{m+1}.\end{aligned} \tag{56}$$

Using the tower property of conditional expectation [74], it follows that

$$\mathbb{E}[A1_{X_1=x}] = \sum_y \mathbb{E}[A1_{X_1=x}1_{X_0=y}] = \sum_y \mathbb{E}[A1_{X_0=y}]P(y,x), \tag{57}$$

where P is the transition matrix in (35). Combining (56) and (57) yields the following system of linear algebraic equations for $\mathbb{E}[A1_{X_0=x}]$,

$$\mathbb{E}[A1_{X_0=x}] = \alpha \sum_y \mathbb{E}[A1_{X_0=y}]P(y,x) + f(x)\pi(x), \quad x \in \{0,1\}^{m+1}. \tag{58}$$

If we define the vectors $u, v \in \mathbb{R}^{2^{m+1}}$ by

$$u(x) := \mathbb{E}[A1_{X_0=x}], \quad v(x) := f(x)\pi(x),$$

then (50) solves (58). Note that the Perron-Frobenius theorem guarantees that $I - \alpha P^\top$ in (50) is invertible since $I - \alpha P^\top = \alpha(\alpha^{-1}I - P^\top)$ and $\alpha \in (0,1)$. Putting this together by combining (47), (50) and (53)-(56) yields (49) in Theorem 2 and completes the proof. □

A.2 An alternative history process

The history process in (34) assumes that the patient remembers whether or not they took their medication at the previous $m \geq 0$ dosing times. Here, we assume instead that when the patient remembers to take the drug, they know how many consecutive doses they have missed. This modification will allow us to consider the "all dose" protocol in (40).

Define a new history process $\{X_n\}_{n\in\mathbb{Z}}$ to encode how much time has passed since the patient last took their medication. Specifically, for integers $n \in \mathbb{Z}$ and $k \geq 1$, define

$$X_n = \begin{cases} 0 & \text{if } \xi_n = \xi_{n-1} = 1, \\ k & \text{if } \xi_n = 1,\ \xi_{n-1} = \cdots = \xi_{n-k} = 0,\ \xi_{n-(k+1)} = 1, \\ -k & \text{if } \xi_n = \cdots = \xi_{n-(k-1)} = 0,\ \xi_{n-k} = 1. \end{cases} \tag{59}$$

In words, $X_n = 0$ if the patient takes the drug at time n and $n-1$, $X_n = k \geq 1$ if the patient takes the drug at time n after missing the last k doses, and $X_n = -k \leq -1$ if the patient misses their kth consecutive dose at time n.

Given that $\{\xi_n\}_{n\in\mathbb{Z}}$ are iid as in (10), it follows that $\{X_n\}_{n\in\mathbb{Z}}$ is a discrete-time Markov chain on $\mathbb{Z}$ that evolves according to the following transition matrix $P = \{P(x,y)\}_{x,y\in\mathbb{Z}}$ with $P(x,y) := \mathbb{P}(X_1 = y \,|\, X_0 = x)$. For $x \in \mathbb{Z}$ and $x \geq 0$,

$$P(x,y) = \begin{cases} p & \text{if } y = 0, \\ 1-p & \text{if } y = -1, \\ 0 & \text{otherwise}, \end{cases} \qquad P(-x,y) = \begin{cases} p & \text{if } y = x, \\ 1-p & \text{if } y = -(x+1), \\ 0 & \text{otherwise}. \end{cases} \tag{60}$$

It is straightforward to check that the distribution of X_n is

$$\pi(k) := \mathbb{P}(X_n = k) = \begin{cases} p^2(1-p)^k & k \geq 0, \\ p(1-p)^{|k|} & k \leq -1, \end{cases} \qquad n, k \in \mathbb{Z}. \tag{61}$$

For this alternative history process $\{X_n\}_{n\in\mathbb{Z}}$ in (59), a dosing protocol is a function $f : \mathbb{Z} \to [0,\infty)$. Since the state space of $\{X_n\}_{n\in\mathbb{Z}}$ (namely $\mathbb{Z}$) is infinite, we assume for technical reasons that dosing protocols cannot grow faster than linearly,

$$0 \leq f(k) \leq B_0|k| + B_1, \quad k \in \mathbb{Z}, \tag{62}$$

for some constants $B_0, B_1 > 0$.

Note that (62) and the value of π in (61) ensure that all the moments of X_n are finite. Furthermore, the bound in (62) ensures that the definition of A in (43) exists almost surely. To see this, note that (61) implies

$$\sum_{n\geq 0} \mathbb{P}(|X_{-n}| \geq n) = \sum_{n\geq 0}\sum_{k\geq 0} \mathbb{P}(|X_0| = n+k) \leq 2\sum_{n\geq 0}\sum_{k\geq 0} p(1-p)^{n+k} = \frac{2}{p} < \infty.$$

Therefore, the Borel-Cantelli lemma [74] implies that there is an almost surely finite random integer $N_0 \geq 1$ so that $|X_{-n}| < n$ for all $n \geq N_0$. Hence, (62) implies that $f(X_{-n}) \leq B_0 n + B_1$ for all $n \geq N_0$, and the almost sure existence of A in (43) follows, as well as the convergence in distribution in (45). Furthermore, the moment convergence in (46) follows from the Lebesgue dominated convergence theorem upon noting that we have almost sure convergence of moments and using some simple bounds on $(C_{M,N}(a,t))^j$.

The definitions of $C_{M,N}(a,t)$, A, and A_1 and the analysis in the section above carry over directly to this definition of $\{X_n\}_{n\in\mathbb{Z}}$ if we use the definition of P and π in (60) and (61). In particular, the formula for the mean in (48) and the formula for the second moment in (49) hold. The benefit of the structure of P in (60) is that we can solve for u in (50) in closed form.

To simplify the formulas for u, we take $f(-k) = 0$ for all $k \geq 1$, which means the patient cannot take medication when they forget. Equation (58) then implies

$$\begin{aligned} u(-k) &= \alpha(1-p)u(-(k-1)), \quad k \geq 2, \\ u(k) &= \alpha p u(-k) + f(k)\pi(k), \quad k \geq 1, \\ u(0) &= \alpha p \sum_{k\geq 0} u(0) + f(0)\pi(0), \\ u(-1) &= \alpha(1-p)\sum_{k\geq 0} u(k). \end{aligned}$$

It is straightforward to solve these equations and obtain that

$$\begin{aligned} u(-1) &= \frac{\alpha(1-p)(1-\alpha(1-p))\sum_{k\geq 0} f(k)\pi(k)}{1-\alpha}, \\ u(-k) &= \alpha^{k-1}(1-p)^{k-1}u(-1), \quad k \geq 1, \\ u(k) &= \alpha^k p(1-p)^{k-1}u(-1) + f(k)\pi(k), \quad k \geq 0. \end{aligned}$$

Plugging into (49) yields

$$\mathbb{E}[Z^2] = \frac{2\alpha p(1-\alpha(1-p))}{1-\alpha}\Big(\sum_{k\geq 0} f(k)\pi(k)\Big) \sum_{k\geq 0}\alpha^k(1-p)^k f(k) + \sum_{k\geq 0}(f(k))^2\pi(k). \tag{63}$$

A.3 First and second moments of Z

We now work out the first and second moments of Z for a few different choices of the dosing protocol f. We begin by considering the history process in (34) with some given memory parameter $m \geq 0$. The simplest case is $m = 0$, which corresponds to the patient having no recollection of their behavior at prior dosing times. It is natural to suppose that the patient takes no medication when they forget ($f(0) = 0$) and that they take their normal dose when they remember ($f(1) = 1$). Using (48) and (49), we obtain in this case,

$$\mathbb{E}[Z^{single}] = p, \quad \mathbb{E}[(Z^{single})^2] = \frac{p(1+\alpha(2p-1))}{1+\alpha}. \tag{64}$$

A more interesting case is $m = 1$, which allows the patient to potentially take a higher dose if they missed their prior dose. In this case, we need to specify $f(i, j)$ for $i,j \in \{0, 1\}$, where $f(i, j)$ is the dose taken at the nth dosing time if $\xi_n = j$ and $\xi_{n-1} = i$. Let $f(0,0) = f(1,0) = 0$ to impose that the patient must miss their dose when they forget. Further, suppose $f(1,1) = 1$, which means the patient takes their normal dose if they remember and they did not miss their prior dose. If $f(0,1) = 1 + b > 0$, then we obtain the "boost" dosing protocol in (38), and (48) and (49) yield

$$\begin{aligned}\mathbb{E}[Z^{boost}] &= p(1+b(1-p)),\\ \mathbb{E}[(Z^{boost})^2] &= \frac{p}{1+\alpha}\Big[b^2(p-1)(\alpha+2\alpha^2(p-1)p-1)\\ &\quad + 2b(1-p)(\alpha(\alpha p+p-1)+1)+\alpha(2p-1)+1\Big].\end{aligned} \tag{65}$$

Note that the cases $b = 0$, $b = 1$, $b = \alpha$, and $b = 0.5$ correspond respectively to the single, double, fractional, and 1.5 dosing protocols in (13), (14), (32), and (33).

Computing statistics of Z gets more complicated for larger values of m. If $m = 2$, then we need to specify $f(i, j, k)$ for $i,j,k \in \{0, 1\}$, where $f(i, j, k)$ is the dose taken at the nth dosing time if $\xi_n = k$, $\xi_{n-1} = j$, and $\xi_{n-2} = i$. We set $f(i,j,0) = 0$ for $i,j \in \{0, 1\}$, and $f(1,1,1) = 1$ by the same reasoning as above. It follows then from (48) that the mean amount is

$$\mathbb{E}[Z] = p\big[f_{001}(1-p)^2 + p(-p(f_{011}+f_{101})+f_{011}+f_{101}+p)\big], \tag{66}$$

where we have set $f_{ijk} := f(i,j,k)$ to simplify notation. We can similarly use (49) to obtain a complicated, but explicit formula for $\mathbb{E}[Z^2]$, which we omit for simplicity. These formulas allow us to investigate dosing protocols in which the patient takes even higher doses following two missed doses compared to a single missed dose. For example, setting

$$f(0,1,1) = 1, \quad f(1,0,1) = 2, \quad f(0,0,1) = 3, \tag{67}$$

yields the triple dose protocol in (39).

We now consider the alternative history process in (59) in order to consider the "all dose" dosing protocol in (40). In this case, using standard results for summing infinite series, (48) and (63) yield

$$\begin{aligned}\mathbb{E}[Z^{all}] &= 1,\\ \mathbb{E}[(Z^{all})^2] &= \frac{\alpha^2(2-p)(1-p)+\alpha(p(p+4)-4)-p+2}{p(1+\alpha)(1-\alpha(1-p))}.\end{aligned} \tag{68}$$

A.4 Drug concentration statistics

We now use the calculations above to compute pharmacologically relevant statistics. Recall that $\mu = \mathbb{E}[Z]$ in (18) compares the mean drug concentration to the perfectly adherent patient.

Corollary 1 *Using superscripts to denote the dosing protocol, we have that*

$$\mu^{single} = p, \quad \mu^{double} = p + p(1-p),$$
$$\mu^{boost} = p + bp(1-p), \quad \mu^{triple} = 3p - 3p^2 + p^3, \quad \mu^{all} = 1.$$

In Fig. 7a, we plot μ as a function of p for various dosing protocols. Notice that nonadherence causes a reduction in the average drug concentrations for the single, double, and triple dose protocols since μ^{single}, μ^{double}, and μ^{triple} are all strictly less than 1 for all $p \in (0, 1)$. Naturally, taking more doses following missed doses increases the average drug concentration, and thus

$$\mu^{single} < \mu^{double} < \mu^{triple} < \mu^{all}, \quad \text{for all } p \in (0,1).$$

However, notice that while μ^{double} is much larger than μ^{single}, the additional increase is relatively small for the triple and all dose protocols, as $\mu^{double} \approx \mu^{triple} \approx \mu^{all}$ if the adherence p is not too small.

In Fig. 7b, we plot $\sqrt{\mathbb{E}[Z^2]}$ as a function of p for various dosing protocols. The curves in Fig. 7 use the analytical formulas for $\mathbb{E}[Z]$ and $\mathbb{E}[Z^2]$ obtained from Theorem 2 and

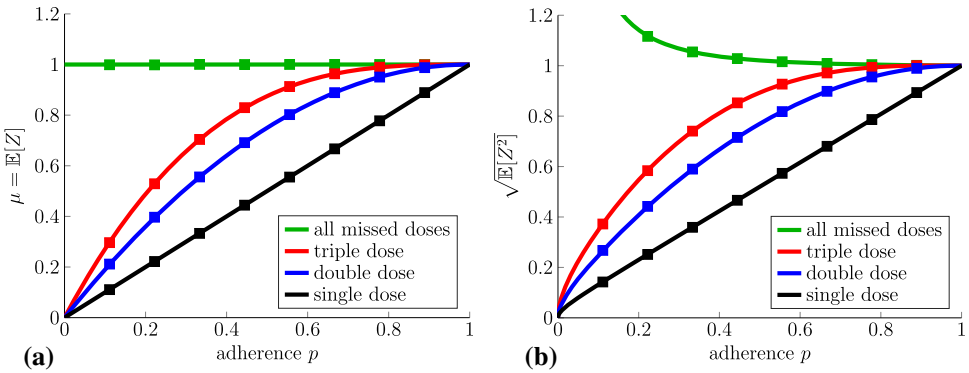

Fig. 7 The plots compare the mean (**a**) and second moment (**b**) computed from stochastic simulations (square markers) to the exact analytical formulas as functions of the adherence p for various dosing protocols. We take $\alpha := e^{-k_e \tau} = 0.85$

the squares markers are results from stochastic simulations with $\alpha = 0.85$. In particular, the square markers are obtained from 10^5 independent realizations of $C_{M,N}(a, 0)$ with $a = M = 0$ and $N = 100$. The simulation results agree with the exact analytical results.

To measure the variability in drug concentrations that stems from imperfect adherence, we introduce the coefficient of variation of Z,

$$c_v := \frac{\sqrt{\mathbb{E}[(Z - \mathbb{E}[Z])^2]}}{\mathbb{E}[Z]} = \frac{\sqrt{\mathbb{E}[(AUC - \mathbb{E}[AUC])^2]}}{\mathbb{E}[AUC]} = \frac{\sqrt{\mathbb{E}[(C(t) - \mathbb{E}[C(t)])^2]}}{\mathbb{E}[C(t)]}, \tag{69}$$

which is defined as the ratio of the standard deviation to the mean. Notice that (17) implies that the coefficient of variation of Z is equal to the coefficient of variation of AUC or $C(t)$ for any $t \in [0, \tau)$. Applying Theorem 2 gives explicit formulas for the coefficient of variation for the single dose and double dose protocols, which we give in the following corollary (the formulas for the other dosing protocols are omitted for brevity).

Corollary 2 *Using superscripts to denote the dosing protocol, we have that*

$$c_v^{single} = \sqrt{\frac{1-\alpha}{1+\alpha}}\sqrt{p(1-p)},$$
$$c_v^{double} = c_v^{single}\sqrt{4 - 3p + p^2 - 2p(2-p)\alpha}.$$

The coefficient of variation measures the variability induced by nonadherence by measuring how drug concentrations deviate from their average value. From a pharmacological standpoint, a small coefficient of variation is desirable. However, a small coefficient of variation does not necessarily imply that the effects of nonadherence are small. Indeed, the coefficient of variation vanishes if the patient never takes their medication ($p = 0$).

Hence, a more useful statistic for measuring the effects of nonadherence is how drug concentrations deviate from the drug concentrations of a perfectly adherent patient, which is the deviation Δ defined in (19). Applying Theorem 2 gives explicit formulas for the deviation Δ for different dosing protocols, which we give in the following corollary.

Corollary 3 *The deviation in* (19) *for the boost protocol in* (38) *for any* $b \geq 0$ *is*

$$\Delta^{boost} = \sqrt{\frac{1-p}{1+\alpha}}\sqrt{\alpha + p(b^2 + 2\alpha^2 bp(1 + b - bp) - \alpha(b(b - 2p + 4) + 2)) + 1}.$$

Note that setting $b = 0$, $b = 1$, $b = \alpha$, *and* $b = 0.5$ *yield the respective deviations for the single, double, fractional, and* 1.5 *dosing protocols in* (13), (14), (32), *and* (33). *The deviation for the triple dose protocol in* (39) *is*

$$\Delta^{triple} = \sqrt{\frac{1-p}{1+\alpha}}\Big[1 - 3p^2 + 4p + 2\alpha^3(1-p)p^2((p-3)p + 3) \tag{70}$$

$$+ 2\alpha^2 p^2((p-3)p + 3) + \alpha\big(1 - 2p^3 + 11p^2 - 14p\big)\Big]^{1/2}. \tag{71}$$

The deviation for the all dose protocol in (40) *is*

$$\Delta^{all} = \sqrt{\frac{1-p}{1+\alpha}}\sqrt{\frac{2(1-\alpha)^2}{1 - p(\alpha(1-p))}}.$$

For certain drugs, it is important to ensure that the dosing protocol cannot cause the drug concentration in the patient to rise too high. We thus consider λ in (20), which is

the largest possible drug concentration compared to the perfectly adherent patient. The following theorem calculates λ for the dosing protocols above.

Theorem 3 *Using superscripts to denote the dosing protocol, we have that*

$$\lambda^{boost} = \max\left\{1, \frac{1+b}{1+\alpha}\right\}, \quad \lambda^{triple} = \frac{3}{1+\alpha+\alpha^2}, \quad \lambda^{all} = \infty.$$

Note that setting $b = 0$, $b = 1$, $b = \alpha$, and $b = 0.5$ corresponds respectively to the single, double, fractional, and 1.5 *dosing protocols in* (13), (14), (32), *and* (33).

Notice that if we set $b = \alpha$ in the boost protocol in (38), then $\lambda^{boost} = 1$ and thus Theorem 3 ensures that a patient following the boost protocol with $b = \alpha$ will never have more drug in their body than the perfectly adherent patient.

We note that Theorem 1 in the main text follows immediately from Corollaries 1 and 3 and Theorem 3.

Proof of Theorem 3 For the single dose protocol, it is immediate that $\lambda^{single} = 1$, and this corresponds to a patient who never misses a dose. For the double dose protocol, observe that if $\xi_{2n} = 1$ and $\xi_{2n+1} = 0$ for all $n \in \mathbb{Z}$, then $A = \frac{2}{1-\alpha^2}$, and thus

$$\lambda^{double} \geq \frac{2/(1-\alpha^2)}{A^{perf}} = \frac{2}{1+\alpha}. \tag{72}$$

This describes a patient who misses a dose at every odd dosing time, and thus always takes a double dose at even dosing times.

To see that $\lambda^{double} \leq \frac{2}{1+\alpha}$, suppose that the patient has concentration $\frac{2}{1-\alpha^2}\frac{DF}{V}$ just after dosing time $n = 1$. If they take the drug at dosing time $n = 2$, then the concentration in their body will be lower than $\frac{2}{1-\alpha^2}\frac{DF}{V}$ since

$$\alpha\frac{2}{1-\alpha^2} + 1 < \frac{2}{1-\alpha^2}.$$

Hence, suppose they miss taking the drug at dosing time $n = 2$. If they take the drug at dosing time $n = 3$, then they will take a double dose and the concentration in their body will return to $\frac{2}{1-\alpha^2}\frac{DF}{V}$. If they miss taking the drug at dosing time $n = 3$, then the concentration will be even lower. Therefore, $\lambda^{double} \leq \frac{2}{1+\alpha}$, which upon combining with (72) yields $\lambda^{double} = \frac{2}{1+\alpha}$. The proof that $\lambda^{boost} = \max\{1, \frac{1+b}{1+\alpha}\}$ is almost identical to the proof that $\lambda^{double} = \frac{2}{1+\alpha}$. The proof that $\lambda^{triple} = \frac{3}{1+\alpha+\alpha^2}$ is also almost identical, upon noting that this value of λ^{triple} is attained by a patient who takes medication at every third dosing time. The proof for the "all dose" protocol follows from noting that if the patient misses k consecutive doses and then takes the next dose, then the drug concentration in their body just after that dose is at least $(k+1)\frac{DF}{V}$. Since this is true for every positive integer k, the result $\lambda^{all} = \infty$ follows. □

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