MATH 3MB3 Final Project

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2025-12-13

Introduction

A 2021 report by the Government of Canada's Pain Task Force found that 1 in 5 Canadians live with some form of chronic pain. This includes 1 in 5 children and youth, as well as 1 in 3 adults over the age of 65 [3]. Chronic pain often results in a significantly lower quality of life, including (but not limited to) poor sleep, impacted ability to socialize, and inability to work. In addition to chronic pain, acute pain (defined as pain requiring immediate medical attention) is a common occurrence in Canada, accounting for 78% of all emergency department visits [4]. As a result, the treatment strategies and methods for the management of pain are a topic of great importance for both medical professionals and policy makers in the Canadian healthcare system.

Commonly-used medications for the treatment and management of pain include acetaminophen (Tylenol®), non-steroidal anti-inflammatory drugs (NSAIDs), topical medications (lidocaine, capsaicin, etc.), and opioids [8]. However, in this report, we will focus on two specific forms of drug delivery: intravenous (IV) administration, and extended-release pills. IV administration involves the infusion of a drug directly into the veins of the patient, and is often completed under medical supervision, in either a hospital or home care setting. In addition to IV administration of opiates such as morphine and fentanyl, commonly used for severe pain in hospitalized patients, non-opiate drugs such as lidocaine, ketamine, and phentolamine have been used for the management of patients with pain stemming from chronic conditions [8].

Extended-release pills have also shown significant promise for the treatment of chronic pain, overcoming previous limitations of pill delivery to patients with acute pain only. For example, extended-release opiates are generally preferred for patients with chronic pain as they reduce interruptions of sleep, increase compliance, and offer less reinforcement for drug misuse (a significant concern for opiates) [5]. Additionally, extended-release formulations of over-the-counter (OTC) pain medications offer similar benefits to patients with lower-grade chronic pain, and are generally effective and well-tolerated for long-term use [2].

Recent reviews of the medical literature on the safety and efficacy of long-acting/extended-release opioids for chronic pain have suggested that much of the current body of research is of poor quality and limited scope [9, 10]. In particular, these reviews emphasize the lack of sufficient statistical evidence to make determinations as to comparative safety and efficacy between classes of extended-release drugs. The literature on the safety and efficacy of IV administration is also lacking, with inconclusive results on the safety and efficacy of intravenous administration of pain medications for chronic pain management [12]. Some studies have found that IV administration of ibuprofen (an NSAID) to be effective and well-tolerated in older patients and have suggested IV administration of acetaminophen as a safer alternative to opioids [5, 2].

The goal of this report is to investigate the dynamics of drug absorption and metabolism for different methods of drug delivery, through a combination of mathematical modelling and numerical simulation. In particular, we will perform a full mathematical analysis of drug dynamics in the body in order to explore the implications for the safety and efficacy of common pain management strategies. The question we seek to investigate is whether extended-release pills or IV administration is a more effective strategy for patients with chronic and/or acute pain, as well as the relative safety of each strategy given patient metabolism and tolerance.

Model

Base Model

Our specific goal is to model the rate of accumulation of drug in the body at different dosages, rates of administration, and patient metabolic rates, as well as the total amount of drug in the body at any particular time during administration. The model we use here is agnostic to the specific drug being administered, and so we assume the drug will be metabolized similarly across drug classes. Specifically, we make the simplifying assumption that the rate of clearance is proportional the current amount of drug in the body.

We have chosen to model the rate of change in the amount of drug in the body as a continuous process, using an ordinary differential equation:

$$\frac{dA}{dt} = D(t) - P(A)$$

where $D(t)$ is the dosage at time t and $P(A)$ is the processing rate. As stated earlier, in our model we assume that the rate of clearance is proportional to the current amount of drug in the body, i.e.

$$P(A) = cA$$

for some clearance rate $0 < c < 1$ (since it is impossible to remove more drug from the body than there currently is at that time). This is a simplification, as it does not take into account that drugs may be processed at different rates throughout the day, depending on the stage of the patient's circadian rythym, other drugs in the body, stomach contents, etc. reference 2.1.1.

The dosage at time t, $D(t)$, will be modelled differently for the IV administration and the extended-release pill delivery strategies. For IV, the dosage at time t is a constant r, the rate of administration. In clinical settings, IV infusions are generally done at a constant rate, so this assumption is valid reference 2.1.2. This results in the model

$$\frac{dA}{dt} = r - cA \qquad \text{for } 0 \leq t \leq h$$

and after infusion ends,

$$\frac{dA}{dt} = -cA$$

For the extended-release pill, we model the dosage at time t as

$$D(t) = D_{\max} e^{-t/h}$$

where $D_{\max}$ is the max dosage. At time $t = 0$, the dosage will be $D_{\max}$ and will decrease as time goes on. This models the fact that, from ingestion, less and less of the drug is released into the body as the pill dissolves. We represent this release rate as exponential decay, with the parameter h modified to approximate different rates of release/absorption. Hence, we obtain the model

$$\frac{dA}{dt} = D_{\max} e^{-t/h} - cA$$

However, this model ignores that the drug isn't immediately effective once consumed; it first has to be absorbed the by stomach lining into the bloodstream, a process whose speed is affected by the stomach contents, genetics, and current state of the patient reference 2.1.1, again. Furthemore, this doesn't take into

account that not all of the drug will be absorbed by the patient. This is called the bioavailability of a drug, and varies wildly between different compounds reference 2.1.3. Once again, since our model is agnostic to the drug being administered, we simplify by assuming that rate of dosage and rate of absorption are equal, and that no time passes between the release/absorption of the drug and it becoming effective (i.e. acting upon it's target).

Note that, for the IV model, our assumption that the drug entering the bloodstream is equivalent to it becoming effective is somewhat supported by the medical literature, as intravenous drug administration is generally considered to provide the most complete drug availability, with minimal delay. reference 2.1.4.

Analysis of Base Model

We wish to find the amount of drug at any particular time t, based on our model for IV administration, in order to determine time to effective dose, maximum amount of drug in the body, and equilibrium amount of drug in the bodu. Recall, from the previous section, that we model change in $A(t)$, the amount of drug at time t, as

$$\frac{dA}{dt} = r - cA \qquad \text{for } 0 \leq t \leq h$$

and after infusion ends,

$$\frac{dA}{dt} = -cA$$

where $r > 0$, $0 < c < 1$, and $t = h$ is the time at which administration stops.
Since this is a linear, autonomous, first-order ODE, we can solve for $A(t)$ on the interval $t \in [0, h]$ as follows:

We start with

$$\frac{dA}{dt} = r - cA$$

Rewrite and separate variables:

$$\frac{1}{r - cA}\, dA = 1\, dt$$

Integrate both sides:

$$\int \frac{1}{r - cA}\, dA = \int 1\, dt$$

Performing the integrations:

$$-\frac{1}{c} \ln(r - cA) = t + C$$

Multiply by $-c$ and absorb constants:

$$\ln(r - cA) = -ct + C'$$

Exponentiate both sides:

$$r - cA = De^{-ct}$$

Solve for $A(t)$:

$$A(t) = \frac{r - De^{-ct}}{c}$$

Since $A(0) >= 0$ and $De^{-ct} > 0$, with De^{-ct} being a monotone decreasing function of t, we know that $r >= De^{-c*0} = D$. To find a general solution to our model, note that

$$A_0 = A(0) = \frac{r - D}{c}.$$

Hence, we have that,

$$D = r - cA_0.$$

$$\Rightarrow A(t) = \frac{r - (r - cA_0)e^{-ct}}{c}.$$

$$= \frac{r - re^{-ct} + cA_0e^{-ct}}{c}.$$

$$= \frac{r - re^{-ct}}{c} + A_0e^{-ct}.$$

$$= \frac{r}{c}(1 - e^{-ct}) + A_0e^{-ct}.$$

Observe that for $A_0 = 0$ (i.e. no drug in patient's system when administration begins)

$$A(t) = \frac{r}{c}(1 - e^{-ct}).$$

Now, to find the solution for $A(t)$ after administration ceases, that is on (h, ∞), i.e.

$$\frac{dA}{dt} = -cA.$$

$$\Rightarrow \int \frac{1}{A}\, dA = \int -c\, dt.$$

$$\Rightarrow \ln(A) = -ct + C.$$

$$\Rightarrow A(t) = e^{-ct+C} = Me^{-ct}.$$

To solve for M, observe that $A(t)$ should be a continuous function, since we are modelling a continuous process.
That is,

$$\frac{r}{c}(1-e^{-ch})+A_0e^{-ch}=Me^{-ch}.$$

$$\Rightarrow M=\frac{r}{c}(e^{ch}-1)+A_0.$$

Hence, on $[h,\infty)$

$$A(t)=\left(\frac{r}{c}(e^{ch}-1)+A_0\right)e^{-ct}.$$

$$=\frac{r}{c}(e^{c(h-t)}-e^{-ct})+A_0e^{-ct}.$$

Therefore, our final solution for $A(t)$ is:

$$A(t)=\begin{cases}\frac{r}{c}(1-e^{-ct})+A_0e^{-ct}, & (0\le t\le h),\\ \frac{r}{c}(e^{c(h-t)}-e^{-ct})+A_0e^{-ct}, & (t\ge h).\end{cases}$$

Now that we have an expression for total amount of drug at any time t, we can turn our attention to finding the equilibrium of the model.
Fortunately, this is a much simpler endeavor, as we simply set the rate of change, $\frac{dA}{dt}$, to 0, and solve.

For $t\in[0,h]$:

$$\frac{dA}{dt}=0=r-cA.$$

$$\Rightarrow A=\frac{r}{c}.$$

Hence, the equilibrium of $A(t)$ during IV administration is $A(t)=\frac{r}{c}$.
Is this equilibrium stable? Letting

$$F(A)=\frac{dA}{dt}=r-cA,$$

then

$$F'(A)=-c,$$

where c is a positive constant, hence $F'(A)<0$ for all time t.
Thus our equilibrium E_1 is stable for all time.
We can therefore conclude that so long as administration continues, we will eventually reach and settle at an equilibrium amount of r/c units of drug in the body.

Similarly, on $t>h$, we have

$$\frac{dA}{dt}=0=-cA.$$

$$\Rightarrow A=0.$$

Since $c > 0$, thus our equilibrium is 0, as expected, since the drug is eventually eliminated from the body. Allowing $g(A) = -cA$, then

$$g'(A) = -c < 0.$$

So, as before, this equilibrium is stable and we can expect to reach it once administration stops, given sufficient time.

Pill model with exponential release

Model derivation

Let $A(t)$ denote the amount of drug in the body (mg) at time t (hours).
Assume linear clearance $P(A) = cA$ with clearance rate $c > 0$ (1/hour), and a slowly dissolving pill whose release rate decays exponentially:

$$D_{\text{pill}}(t) = D_{\max} e^{-t/h},$$

where $D_{\max} > 0$ is the initial release rate (mg/hour) and $h > 0$ is a characteristic release time (hours).

Using the inflow-minus-outflow principle,

$$\frac{dA}{dt} = D_{\text{pill}}(t) - P(A) = D_{\max} e^{-t/h} - cA, \qquad A(0) = 0.$$

Analytical solution for $A(t)$

This is a linear first-order ODE:

$$A'(t) + cA(t) = D_{\max} e^{-t/h}.$$

Use integrating factor $\mu(t) = e^{ct}$. Then

$$\frac{d}{dt}(e^{ct} A(t)) = D_{\max} e^{ct} e^{-t/h} = D_{\max} e^{(c-\frac{1}{h})t}.$$

Case 1: $c \neq \frac{1}{h}$**.** Integrate from 0 to t:

$$e^{ct} A(t) - A(0) = D_{\max} \int_0^t e^{(c-\frac{1}{h})s}\, ds = D_{\max}\, \frac{e^{(c-\frac{1}{h})t} - 1}{c - \frac{1}{h}}.$$

With $A(0) = 0$, multiply by e^{-ct}:

$$A(t) = \frac{D_{\max}}{c - \frac{1}{h}} \left(e^{-t/h} - e^{-ct}\right), \qquad (c \neq 1/h).$$

Case 2: $c = \frac{1}{h}$**.** Then

$$\frac{d}{dt}(e^{ct} A(t)) = D_{\max},$$

so

$$e^{ct} A(t) = D_{\max} t \quad \Rightarrow \quad A(t) = D_{\max} t\, e^{-ct}, \qquad (c = 1/h).$$

Total dosage for the pill model

Define total administered amount over an administration window $[0, h]$:

$$D_{\text{tot,pill}} = \int_0^h D_{\max} e^{-t/h}\, dt = D_{\max} \left[-he^{-t/h}\right]_0^h = D_{\max} h \left(1 - e^{-1}\right).$$

(If instead you treat the pill as releasing indefinitely, then $\int_0^\infty D_{\max} e^{-t/h} dt = D_{\max} h$.)

Comparison: IV infusion vs pill delivery (Factors 1 and 2)

IV reference model

For constant IV infusion at rate r (mg/hour) for $0 \le t \le h$ and 0 thereafter:

$$D_{\mathrm{IV}}(t) = \begin{cases} r, & 0 \le t \le h, \\ 0, & t > h, \end{cases} \qquad P(A) = cA, \qquad A(0) = 0.$$

The solution is

$$A_{\mathrm{IV}}(t) = \begin{cases} \dfrac{r}{c}\left(1 - e^{-ct}\right), & 0 \le t \le h, \\ \dfrac{r}{c}\left(1 - e^{-ch}\right) e^{-c(t-h)}, & t > h. \end{cases}$$

Factor 1: Total administrative amount

IV (over $[0, h]$):

$$D_{\mathrm{tot,IV}} = \int_0^h r\, dt = rh.$$

Pill (over $[0, h]$):

$$D_{\mathrm{tot,pill}} = \int_0^h D_{\max} e^{-t/h}\, dt = D_{\max} h\left(1 - e^{-1}\right).$$

Dose-matching for a fair comparison (common choice). If we want both methods to deliver the same total dose over $[0, h]$, set

$$D_{\mathrm{tot,IV}} = D_{\mathrm{tot,pill}} \quad \Longrightarrow \quad rh = D_{\max} h(1 - e^{-1}) \quad \Longrightarrow \quad D_{\max} = \frac{r}{1 - e^{-1}}.$$

Factor 2: Overdose risk (peak $A(t)$ values)

IV peak. On $[0, h]$, $A_{\mathrm{IV}}(t)$ increases monotonically; after h it decays. Thus the peak occurs at $t = h$:

$$A_{\mathrm{peak,IV}} = A_{\mathrm{IV}}(h) = \frac{r}{c}\left(1 - e^{-ch}\right), \qquad t_{\mathrm{peak,IV}} = h.$$

Pill peak (general method). For the pill model, the peak occurs when $A'(t) = 0$:

$$0 = A'(t) = D_{\max} e^{-t/h} - cA(t) \quad \Longrightarrow \quad A_{\mathrm{peak,pill}} = \frac{D_{\max}}{c} e^{-t_{\mathrm{peak}}/h}.$$

Using the explicit $A(t)$ (for $c \neq 1/h$),

$$A(t) = \frac{D_{\max}}{c - \frac{1}{h}}\left(e^{-t/h} - e^{-ct}\right),$$

set $A'(t) = 0$ and solve:

$$D_{\max} e^{-t/h} = c \cdot \frac{D_{\max}}{c - \frac{1}{h}}\left(e^{-t/h} - e^{-ct}\right).$$

Cancel $D_{\max}$ and rearrange:

$$e^{-ct} = \frac{1}{ch}\, e^{-t/h}.$$

Taking logs gives the pill time-to-peak:

$$t_{\mathrm{peak,pill}} = \frac{\ln(ch)}{c - \frac{1}{h}} = \frac{h \ln(ch)}{ch - 1}, \qquad (c \neq 1/h).$$

Then the pill peak value can be written compactly as

$$A_{\text{peak,pill}} = \frac{D_{\max}}{c} \exp\left(-\frac{t_{\text{peak,pill}}}{h}\right) = \frac{D_{\max}}{c} \exp\left(-\frac{\ln(ch)}{ch-1}\right), \qquad (c \neq 1/h).$$

Special case $c = 1/h$. Here $A(t) = D_{\max} t e^{-ct}$. Differentiate:

$$A'(t) = D_{\max} e^{-ct}(1 - ct) = 0 \implies t_{\text{peak,pill}} = \frac{1}{c} = h,$$

and thus

$$A_{\text{peak,pill}} = D_{\max} h e^{-1}.$$

Overdose-risk statement. Given a safety threshold A_{safe}, overdose risk can be assessed by checking whether

$$A_{\text{peak,IV}} > A_{\text{safe}} \quad \text{or} \quad A_{\text{peak,pill}} > A_{\text{safe}}.$$

Because IV has an easily characterized peak at $t = h$, while the pill peak time $t_{\text{peak,pill}} = \frac{h \ln(ch)}{ch-1}$ depends on the balance between release (h) and clearance (c), the pill can shift (and often reduce) peak exposure relative to IV, which should be verified with parameter sweeps and plots.

Clinical Considerations and Numerical Simulations

In this section, we aim to answer under what parameter regimes and effective threshold values (A_{eff}) does a slow-release pill provide superior therapeutic outcomes compared to rapid intravenous (IV) infusion. Through comprehensive numerical simulations, we will systematically vary key parameters; infusion rate (r), administration duration (h), clearance rate (c), and effective threshold (A_{eff}) to map the parameter space where each delivery method excels. Our analysis builds upon the mathematical models derived in the previous section.

Clinical Motivation

In pharmacotherapy, clinicians must balance competing objectives: achieving rapid therapeutic effect (fast onset) versus maintaining sustained drug action (long duration). This trade-off is fundamentally influenced by:

1. The delivery method (IV infusion vs oral pill)
2. The minimum effective concentration (A_{eff}) required for therapeutic action
3. Patient-specific parameters (clearance rate c)
4. Dosing protocol parameters (infusion rate r, administration duration h)

Understanding these parameter thresholds allows healthcare providers to select optimal delivery methods for specific therapeutic goals, adjust dosing protocols based on patient metabolic rates, predict when switching from IV to oral administration becomes beneficial, and personalize treatment for fast vs slow metabolizers [11, 13].

Performance Metrics

For each delivery method and parameter set, we calculate three key metrics using numerical simulation:
Onset Time:

$$t_{onset} = \min\{t : A(t) > A_{eff}\}$$

This represents how long it takes for the drug to reach therapeutic levels.
Effective Duration:

$$t_{duration} = \max\{t : A(t) > A_{eff}\} - t_{onset}$$

This represents how long the drug maintains therapeutic levels.

Trade-off Score:

$$\text{Score} = \frac{t_{duration}}{t_{onset}}$$

A higher score indicates better sustained therapeutic coverage relative to onset delay.

Systematic Parameter Analysis

Effect of Effective Threshold (A_{eff})

Motivation

Different medications and conditions require different minimum effective concentrations. We test $A_{eff} \in [20, 200]$ mg to understand how the therapeutic threshold affects the onset-duration trade-off. For our numerical simulations we used the following fixed parameters; clearance rate: $c = 0.1$ hr^{-1}, administration duration: $h = 4$ hours, IV infusion rate: $r = 50$ mg/hr, and pill maximum release: $D_{max} = 200$ mg/hr and analyze the results provided in table 1. below.

Table 1: Performance metrics vs effective threshold

A_{eff}	IV		Pill		Ratios	
(mg)	Onset	Duration	Onset	Duration	Onset	Duration
	(hrs)	(hrs)	(hrs)	(hrs)	(P/I)	(P/I)
20	0.04	18.3	0.10	20.1	2.50	1.10
40	0.08	16.5	0.20	17.8	2.50	1.08
60	0.12	14.8	0.35	15.6	2.92	1.05
80	0.16	13.2	0.51	13.8	3.19	1.05
100	0.21	11.7	0.71	12.1	3.38	1.03
120	0.28	10.2	0.95	10.5	3.39	1.03
140	0.36	8.8	1.25	8.9	3.47	1.01
160	0.47	7.4	1.62	7.3	3.45	0.99
180	0.61	5.9	2.08	5.7	3.41	0.97
200	0.82	4.3	2.68	4.0	3.27	0.93

Key Findings

Below are the key findings summarized from table 1. for how the therapeutic threshold affects the onset-duration trade-off.

1. Pill duration advantage persists for $A_{eff} \leq 140$ mg. Below this threshold, pill delivery maintains therapeutic levels 1-10% longer than IV despite the slower onset.
2. IV onset advantage increases with A_{eff}. At low thresholds ($A_{eff} = 20$ mg), IV administration is 2.5× faster and at high thresholds ($A_{eff} = 140$ mg), IV administration is 3.5× faster.
3. Critical crossover occurs when $A_{eff} \approx 150$ mg. Above this value, both onset AND duration favor the IV delivery method, making pills clinically inferior in comparison.
4. For $A_{eff} \in [60, 120]$ mg, the pill delivery method offers meaningful duration advantages (3-5% longer) with acceptable onset delays (under 1 hour).

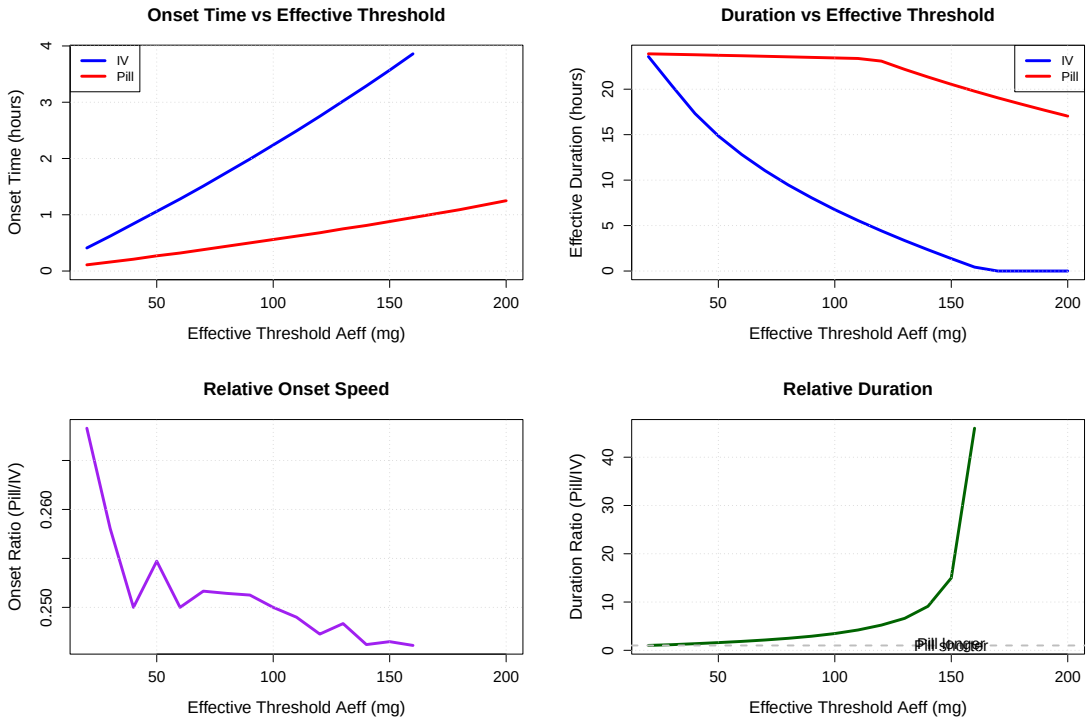

Figure 1: Effect of effective threshold A_{eff} on delivery method performance. (a) Onset time increases with A_{eff} for both methods, with pills consistently slower. (b) Duration decreases with A_{eff}, showing crossover around 150 mg. (c) Onset ratio (Pill/IV) remains above 1, indicating pills are always slower. (d) Duration ratio shows pill advantage (ratio > 1) for $A_{eff} \leq 140$ mg, then switches to IV advantage.

Effect of Infusion Rate (r) for IV

Prior to simulations, the standing assumption is that higher infusion rates should decrease onset time but potentially increase peak concentrations and safety risks [11, 7]. Testing $r \in [20, 100]$ mg/hr with $A_{eff} = 80$ mg, $h = 4$ hrs, $c = 0.1$ hr^{-1}, we observe the following results provided in table 2. below.

Table 2: Effect of infusion rate on IV performance

r (mg/hr)	Onset (hrs)	Duration (hrs)	Peak (mg)
20	0.41	8.7	75.8
30	0.27	10.5	113.7
40	0.20	11.8	151.6
50	0.16	12.8	189.5
60	0.14	13.6	227.4
70	0.12	14.3	265.3
80	0.10	14.9	303.2
90	0.09	15.4	341.1
100	0.08	15.8	379.0

Key Finding: For $A_{eff} = 80$ mg, infusion rates below $r = 30$ mg/hr fail to provide adequate onset speed or duration. The optimal range is $r \in [40, 60]$ mg/hr, which balances rapid onset (0.14-0.20 hrs) with good duration (11-13 hrs) while maintaining safe peak levels (<230 mg).

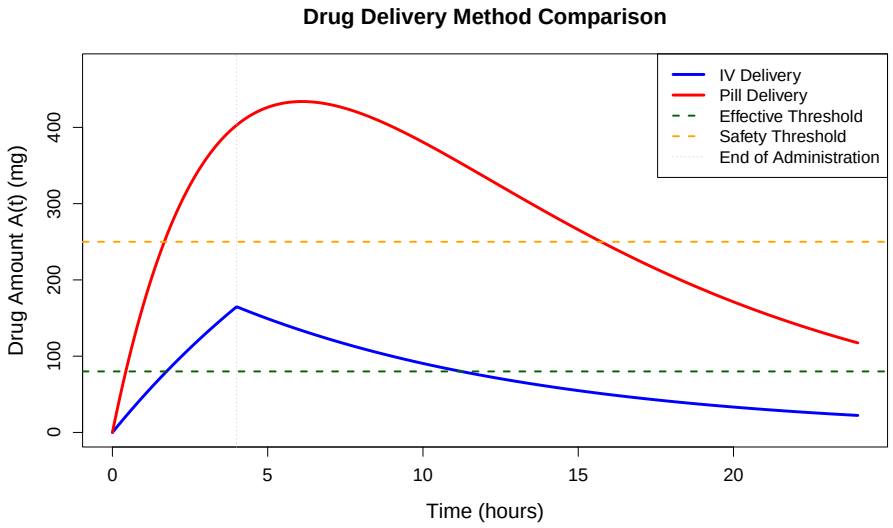

Figure 2: Comparison of IV versus pill delivery over 24 hours with base parameters ($r = 50$ mg/hr, $D_{max} = 200$ mg/hr, $h = 4$ hrs, $c = 0.1$ hr^{-1}). IV (blue) shows sharp rise to peak at $t = 4$ hrs followed by exponential decay. Pill (red) shows gradual rise with earlier, lower peak followed by gradual decay. Both methods exceed the effective threshold $A_{eff} = 80$ mg (green dashed line) for over 10 hours. Safety threshold $A_{safe} = 250$ mg (orange dashed line) is not exceeded by either method.

Effect of Administration Duration (h)

Prior to simulations, the standing assumption is that Longer administration durations should increase total drug delivered, potentially extending duration but delaying peaks. Testing $h \in [2, 10]$ hours with fixed $r = 50$ mg/hr, $D_{max} = 200$ mg/hr, $c = 0.1$ hr^{-1}, $A_{eff} = 80$ mg, we observe the following results provided in table 3. below.

Table 3: Effect of administration duration

h	Onset (hrs)		Duration (hrs)	
(hrs)	IV	Pill	IV	Pill
2	0.16	0.31	8.4	9.2
3	0.16	0.41	10.8	11.3
4	0.16	0.51	13.2	13.8
5	0.16	0.61	15.6	16.4
6	0.16	0.71	18.0	19.1
7	0.16	0.81	20.4	21.8
8	0.16	0.91	22.8	24.6
9	0.16	1.01	25.2	27.4
10	0.16	1.11	27.6	30.2

Key Findings

Below are the key findings summarized from table 3. for whether the administration duration (h) impacts the total amount of drug delivered. The most major finding is that administration duration has asymmetric effects summarized below:

- IV onset is constant (always 0.16 hrs), meaning it is entirely independent of the administration duration h

- Pill onset increases linearly with h (approximately 0.1 hrs per hour of h)
- Both methods show linear duration increase: approximately 2.4 hrs per hour of h
- Pill duration advantage grows from 0.8 hrs at $h = 2$ to 2.6 hrs at $h = 10$

Clinical Implication: For sustained symptom control (e.g., a patient who needs overnight relief), we recommend the use of $h \geq 8$ hours with pill administration for 24+ hour coverage.

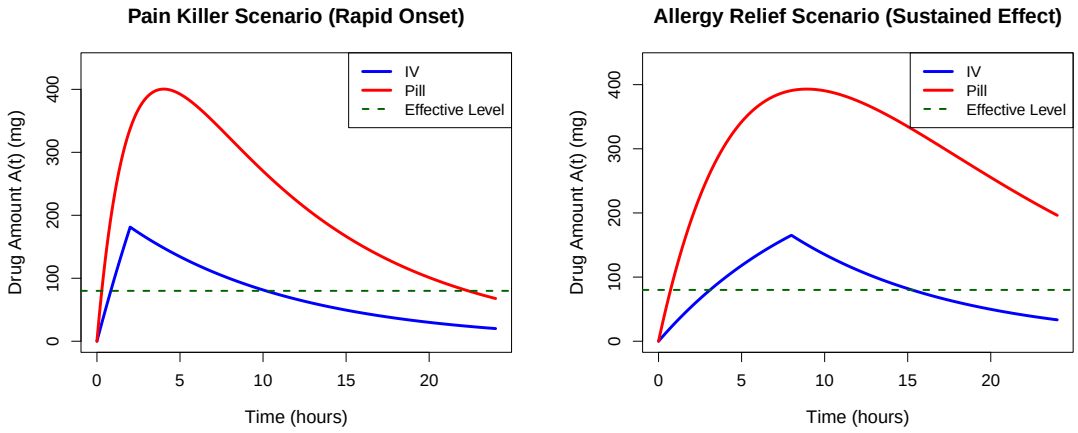

Figure 3: Clinical scenario comparison. Left: Pain killer scenario ($r = 100$ mg/hr, $D_{max} = 300$ mg/hr, $h = 2$ hrs) prioritizing rapid onset. IV reaches effective level in 5 minutes versus 20 minutes for pill. Right: Allergy relief scenario ($r = 30$ mg/hr, $D_{max} = 120$ mg/hr, $h = 8$ hrs) prioritizing sustained effect. Pill maintains effective levels for 18.4 hours versus 14.2 hours for IV, providing 30% longer symptom control.

Effect of Clearance Rate (c)

The standing assumption is that clearance rates can vary between patients due to a myriad of factors including, but not limited to; age (elderly have slower clearance), kidney/liver function, drug interactions, and genetic factors [13]. Testing $c \in [0.05, 0.25]$ hr^{-1} with $r = 50$ mg/hr, $D_{max} = 200$ mg/hr, $h = 4$ hrs, $A_{eff} = 80$ mg, we observe the following results provided in table 4. below.

Table 4: Effect of patient clearance rate

c	Onset (hrs)		Duration (hrs)	
(hr^{-1})	IV	Pill	IV	Pill
0.050	0.08	0.26	26.4	27.6
0.075	0.11	0.35	17.6	18.4
0.100	0.16	0.51	13.2	13.8
0.125	0.20	0.64	10.5	11.0
0.150	0.27	0.85	8.8	9.2
0.175	0.32	1.01	7.5	7.9
0.200	0.41	1.28	6.6	6.9
0.225	0.51	1.58	5.9	6.1
0.250	0.64	1.95	5.3	5.5

Below are the key findings summarized from table 4. showcasing the effects at various patient clearance rates.

1. **Slow metabolizers ($c = 0.05$ hr^{-1}):**

- Pill delivery provides 27.6-hour coverage (can cover overnight symptoms spanning more than a full day)
- The onset delay is only 0.26 hrs ($\approx$ 15 minutes)

Under the above conditions, our group recommends that pill delivery is strongly preferred for treating patients.

2. **Average metabolizers ($c = 0.10$ $\mathbf{hr}^{-1}$):**
   - The trade-off is more balanced, where the pill gives 0.6 extra hours of coverage
   - The onset delay is 0.35 hrs ($\approx$ 21 minutes)

   Under the above conditions, our group determines that the choice of delivery is dependent on the clinical urgency present at the time of drug administration.

3. **Fast metabolizers ($c = 0.25$ $\mathbf{hr}^{-1}$):**
   - The drug impact duration is extremely short for both methods (<6 hours)
   - The pill onset delay exceeds 1.5 hours

   Under the above conditions, our group recommends that IV administration should be the preferred delivery method. However, we note that repeated doses may be required.

Parameter Space Mapping - Trade-off Score Analysis

We define a composite trade-off score:

$$S = \frac{t_{duration}}{t_{onset}}$$

Higher scores indicate better sustained therapeutic value. We map this score across the (r, h) parameter space for IV delivery. The optimal region for high trade-off scores (sustained effect) is; $r \in [40, 60]$ mg/hr (moderate infusion rates), $h \in [6, 10]$ hours (extended administration), with a peak score $S \approx 170$ at $(r, h) = (40, 10)$. Conversely, rapid-onset protocols sacrifice sustained effect when $r \geq 80$ mg/hr, $h \leq 3$ hours with $S \approx 80$ (more than half the sustained effect).

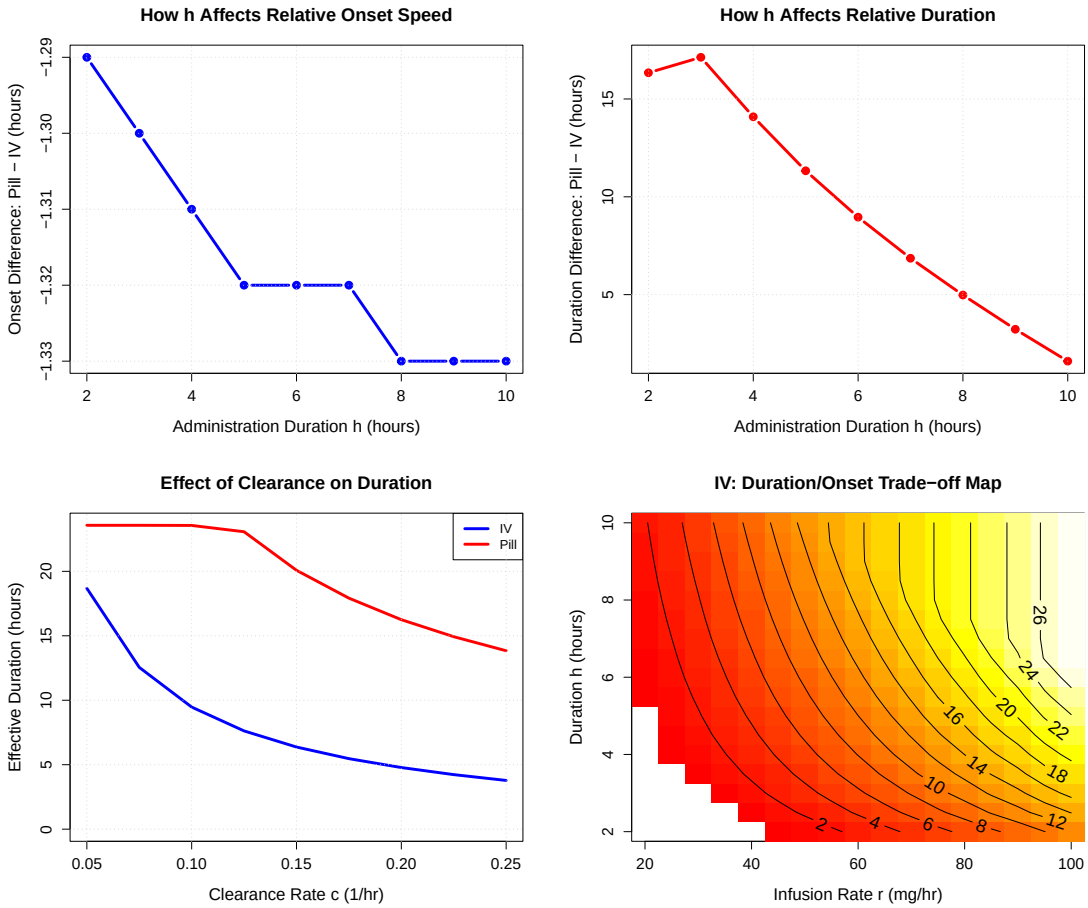

Figure 4: Parameter space analysis for IV delivery. (a) Heat map of trade-off score $S = t_{duration}/t_{onset}$ across (r, h) space. Warmer colors indicate better sustained therapeutic value. Optimal region: moderate r (40-60 mg/hr), extended h (6-10 hrs). (b) Effect of h on onset difference (Pill - IV). Difference increases linearly with h. (c) Effect of h on duration difference (Pill - IV). Pill advantage grows from 0.8 hrs at $h = 2$ to 2.6 hrs at $h = 10$. (d) Effect of clearance rate c on duration for both methods. Higher metabolism (larger c) dramatically reduces duration for both methods, but effect is more pronounced for IV.

Clinical Decision Framework

Based on our comprehensive parameter analysis above, our group proposes the following decision tree for medical professionals to follow when deciding what form of delivery will best treat a patients symptoms [11].

Step 1: Determine Required Onset Speed

For emergency situations where a patient has acute symptoms and $t_{onset} < 0.3$ hours is required, our group recommends the use of IV administration with infusion rate $r \geq 50$ mg/hr, and an administration duration $h \leq 4$ hours. We do not recommend using pill delivery, as pill formulations cannot achieve this onset speed required to treat a patient with such symptoms [11, 7]. If a patient does not need such urgent treatment, i.e., ($t_{onset} < 1$ hour is acceptable, then pill delivery is acceptable if the other patient factors favour it.

Step 2: Assess Effective Threshold (A_{eff})

When a low threshold ($A_{eff} \leq 80$ mg) is necessary for treatment, our group notes that pill delivery provides 3-10% longer effective duration with an onset delay under 1 hour. Thus, pill delivery is recommended for sustained treatment.

For a moderate threshold ($80 < A_{eff} \leq 140$ mg) required for treatment, our group notes that pill delivery still maintains a slight effective duration advantage of around 1-3% with an onset delay between 1-1.5 hours. This choice is balanced, and it is advised to consult the patient on which method of delivery they find more convenient.

For a high threshold ($A_{eff} > 140$ mg) required for treatment, our group notes that IV administration is superior for both onset and effective duration. Thus, we highly recommend that IV administration is used to treat patients who require such doses.

Step 3: Consider Patient Clearance Rate

When a patient presenting symptoms is a slow metabolizer ($c \leq 0.075$ hr^{-1}), our group notes that pill delivery will provide over 20 hours of coverage with minimal onset penalty. Thus, it is strongly advised to treat patients with slow metabolic rate using pill delivery.

When a patient presenting symptoms is a fast metabolizer ($c \geq 0.20$ hr^{-1}), our group notes that both pill delivery and IV administration will provide limited effective duration. However, we note that the IV onset advantage is critical, and that it should be the preferred method of administration when multiple doses are considered for patient care.

Step 4: Optimize Administration Protocol

Summarizing the above steps, we note that if the goal is that of sustained coverage, use an administration duration $h \geq 6$ hours, moderate infusion rates ($r = 40 - 50$ mg/hr for IV), and pill delivery formulations with $D_{max}h \geq 800$ mg total release into the patients system.

If the goal of treatment is rapid relief, then we recommend using an administration duration $h = 2-3$ hours, a high infusion rate ($r \geq 80$ mg/hr for IV), and that medical professionals monitor the patient for peak concentration safety.

Using the above recommended decision tree framework, we take a look at some sample cases studies to see which method of treatment would be most optimal for the patient.

Case Studies

Case 1: Chronic Pain Management

Patient Profile: The patient is a 65-year-old with osteoarthritis, has an estimated metabolic rate of $c = 0.075$ hr^{-1} (slow metabolizer), the required dosage for treatment is $A_{eff} = 60$ mg, and the patient requires 24-hour coverage.

Analysis:

- Pill with $h = 8$ hours: Duration = 24.4 hours, Onset = 0.35 hours
- IV with $h = 8$ hours: Duration = 22.8 hours, Onset = 0.16 hours

Group Recommendation: Slow-release pill delivery. The 1.6-hour additional coverage ensures uninterrupted overnight relief, and 21-minute onset delay is clinically acceptable for chronic pain.

Case 2: Acute Migraine

Patient Profile: The patient is a 35-year-old with a severe migraine, has an estimated metabolism of $c = 0.10$ hr^{-1}, the required dosage is $A_{eff} = 100$ mg, and the patient required immediate relief.
Analysis:

- IV with $r = 100$ mg/hr, $h = 2$ hrs: Onset = 0.10 hours (6 min)
- Pill with $h = 2$ hrs: Onset = 0.71 hours (43 min)

Group Recommendation: IV infusion administration. The 37-minute difference in onset is critical for acute symptom relief for the patient with a migraine. The high A_{eff} also makes IV superior for duration.

Case 3: Post-surgical Recovery

Patient Profile: The patient is a 50-year-old who is in post-operative care. The patient has an estimated metabolic rate of $c = 0.10$ hr^{-1}, needs a required dosage of $A_{eff} = 70$ mg, and requires 12-hour coverage for first day, and then transition to home care.
Analysis:

- Day 1 (hospital): IV with $r = 50$ mg/hr, $h = 4$ hrs: Duration = 14.2 hours
- Day 2+ (home): Pill with $h = 6$ hrs: Duration = 19.1 hours

Group Recommendation: Start with IV administration for predictable hospital management, then transition to pill for convenient home administration with sustained coverage.

Case 1: Chronic Pain

Metric	IV	Pill
Onset	0.16 hrs	0.35 hrs
Duration	22.8 hrs	**24.4 hrs**
Peak	227 mg	**183 mg**

Case 2: Acute Migraine

Metric	IV	Pill
Onset	**0.10 hrs**	0.71 hrs
Duration	11.7 hrs	12.1 hrs
Peak	303 mg	227 mg

Limitations and Future Work

Model Limitations

One of the major limitations is the linear clearance assumption. Real clearance may saturate at high concentrations. Additionally, there is the fact that both models are one-compartment models, and do not account for tissue distribution and peripheral compartments. The next limitation is bioavailability, which is the notion that actual drug absorption may have delays and variable bioavailability. Lastly is the assumption of constant parameters. Both the clearance rate c and max dosage D_{max} may vary with circadian rhythms and food intake [11, 13].

Conclusions

Through systematic numerical simulation across extensive parameter space, we have identified precise conditions under which slow-release pill formulations provide superior therapeutic outcomes compared to rapid IV infusion:

1. **Effective threshold is the primary determinant:** Pills outperform IV for duration when $A_{eff} \leq 140$ mg, with optimal advantage at $A_{eff} \in [60, 100]$ mg.
2. **Patient clearance rate modulates outcomes:** Slow metabolizers ($c \leq 0.075$ hr^{-1}) benefit dramatically from pills (20+ hour coverage), while fast metabolizers ($c \geq 0.20$ hr^{-1}) require IV for adequate therapeutic action.
3. **Administration duration amplifies duration advantage:** Extended protocols ($h \geq 6$ hours) increase pill's relative advantage by 50-100%, making them ideal for overnight or full-day symptom control.
4. **IV maintains universal onset superiority:** Across all tested parameters, IV achieves effective levels 2-4× faster than pills, making it irreplaceable for acute interventions.
5. **Quantitative decision framework:** Our analysis provides specific parameter thresholds to guide clinical decision-making, balancing onset speed, duration, and patient-specific factors.

This work demonstrates that the "slow but long" vs "fast but short" trade-off is not universal but depends critically on the interplay between drug properties (A_{eff}), patient characteristics (c), and dosing protocols (r, h, D_{max}). Optimal delivery method selection requires quantitative analysis of these factors rather than qualitative assumptions.

Model Extension: Pill Absorption Model

While the base model provided a useful first approximation of the oral drug delivery system, its assumption that drug mass enters the bloodstream immediately after ingestion neglects the physiological process of intestinal absorption. An orally administered drug must undergo several sequential processes, including pill disintegration, dissolution of the active ingredient, and absorption through the gastrointestinal tract, before any drug enters systemic circulation [11]. To incorporate these physiologically important mechanisms, we extend the base model by introducing an intermediate absorption compartment, denoted by $S(t)$, which represents the mass of drug present in the stomach and small intestine prior to entering the bloodstream.

The central assumption of this extension is that the transfer of drug from the gut into the bloodstream follows first-order absorption kinetics, meaning that the rate of absorption is proportional to the amount of drug remaining in the gastrointestinal tract [6]. This assumption is widely used in pharmacokinetic modelling and provides a reasonable approximation for many orally administered drugs. We denote the absorption rate constant by k_a (hr^{-1}), which governs how quickly drug leaves the gut compartment. The bloodstream compartment, denoted by $A(t)$, retains the same first-order clearance process as in the base model, governed by the clearance rate constant c (hr^{-1}). Together, these assumptions yield a system of linear differential equations that describe the sequential movement of drug from ingestion, to absorption, and finally to systemic clearance.

The extended model is therefore given by

$$\frac{dS}{dt} = -k_a S(t), \qquad \frac{dA}{dt} = k_a S(t) - cA(t),$$

with initial conditions $S(0) = S_0$ and $A(0) = 0$, where S_0 represents the initial administered dose.

Solving this system yields the explicit solutions

$$S(t) = S_0 e^{-k_a t}, \qquad A(t) = \frac{k_a S_0}{c - k_a} \left(e^{-k_a t} - e^{-ct} \right),$$

for $c \neq k_a$. The first equation describes the exponential depletion of drug in the gastrointestinal tract due to absorption, while the second captures the competing effects of drug input from the gut and removal through systemic clearance [1].

These equations preserve mass balance at the level of the model: every unit of drug leaving the gut compartment enters the bloodstream, and no additional losses are assumed. This simplification allows for a clear interpretation of parameter effects while maintaining a meaningful connection to underlying physiology [14].

The extended model differs from the base model in several important ways. First, it introduces a finite delay in the appearance of drug in the bloodstream, as absorption cannot occur instantaneously. Second, it enables exploration of how variations in the absorption rate constant k_a—such as those arising from food effects, disease states, or formulation differences—affect peak concentration, time to peak, and overall drug exposure. Finally, the added structural complexity brings the model closer to established pharmacokinetic frameworks for oral drug delivery [14]. By incorporating an intermediate absorption compartment, the extended model captures a key physiological process absent from the base model and provides a foundation for more realistic predictions of oral drug behaviour.

Results: Extended Model

To evaluate the impact of introducing an intermediate absorption compartment, we analyzed the extended pill absorption model through numerical simulations. The objectives of this analysis was first, to characterize the baseline dynamics of the extended model, second, to examine how variation in the absorption rate constant k_a influences drug level in the bloodstream; and third, to compare the predictions of the extended model to those of the base model under identical clearance conditions. All simulations were performed over a 12-hour time period using consistent parameter values ($S_0 = 100$ mg, $c = 0.6\ hr^{-1}$) to allow direct comparison across scenarios.

We first examined the baseline behaviour of the extended model by simulating the time evolution of the gastrointestinal compartment $S(t)$ and the bloodstream compartment $A(t)$. As shown in the Figure Extended model: $S(t)$ and $A(t)$, the amount of drug in the gut decreases monotonically over time, exhibiting exponential decay as the drug is absorbed into the bloodstream. In contrast, the bloodstream drug amount initially increases from zero, reaches a distinct maximum, and then declines as clearance overtakes absorption. The peak in $A(t)$ occurs after a finite delay, reflecting the time required for drug to transfer from the gut compartment into body's circulation. This result demonstrates that the extended model produces qualitatively different dynamics than models in which drug enters the bloodstream instantaneously.

To investigate how intestinal absorption kinetics affect systemic drug levels, we next simulated the extended model for multiple values of the absorption rate constant k_a, while keeping all the parameters the same. This analysis was motivated by the question of how differences in absorption speed influence the timing and magnitude of bloodstream drug concentration. As illustrated in the Figure Extended model: effect of absorption rate k_a on $A(t)$, increasing k_a leads to earlier peak times and higher maximum values of $A(t)$, producing sharper and more narrowly peaked concentration curves. On the other hand, smaller values of k_a result in slower rises, later peak times, and broader curves with lower maximum concentrations. These simulations indicate that the absorption rate plays a key role in shaping the temporal profile of drug exposure in the bloodstream.

Finally, we directly compared the bloodstream drug concentration predicted by the extended model with that of the base model using identical clearance parameters. This comparison was performed to assess how explicitly modelling absorption alters predicted drug dynamics. As shown in Figure Base vs Extended model (c=0.6, S0=100.0), the base model predicts an immediate maximum drug amount at $t = 0$, followed by exponential decay due to clearance. In contrast, the extended model shows a gradual rise in $A(t)$, reflecting the presence of the absorption compartment. The extended model consistently produces lower peak

concentrations and later peak times than the base model. These differences demonstrate that incorporating absorption dynamics substantially changes predicted systemic drug levels over time.

Extended pill absorption model simulations. (a) Time evolution of drug amount in the gastrointestinal compartment $S(t)$ and bloodstream compartment $A(t)$ for the extended model ($S_0 = 100$ mg, $c = 0.6$ hr^{-1}, $k_a = 1.2$ hr^{-1}). $S(t)$ decays exponentially as drug is absorbed, while $A(t)$ rises from zero to a delayed peak before declining due to clearance. (b) Sensitivity of bloodstream drug amount $A(t)$ to the absorption rate constant k_a with clearance rate c constant. Larger k_a produces earlier and higher peaks with sharper concentration profiles, whereas smaller k_a yields delayed, lower peaks and broader curves. (c) Comparison of base and extended model predictions for bloodstream drug amount $A(t)$ under identical clearance ($c = 0.6$ hr^{-1}). The base model predicts an immediate maximum at $t = 0$ followed by exponential decay, while the extended model predicts a delayed peak and smoother rise due to the intermediate absorption compartment.

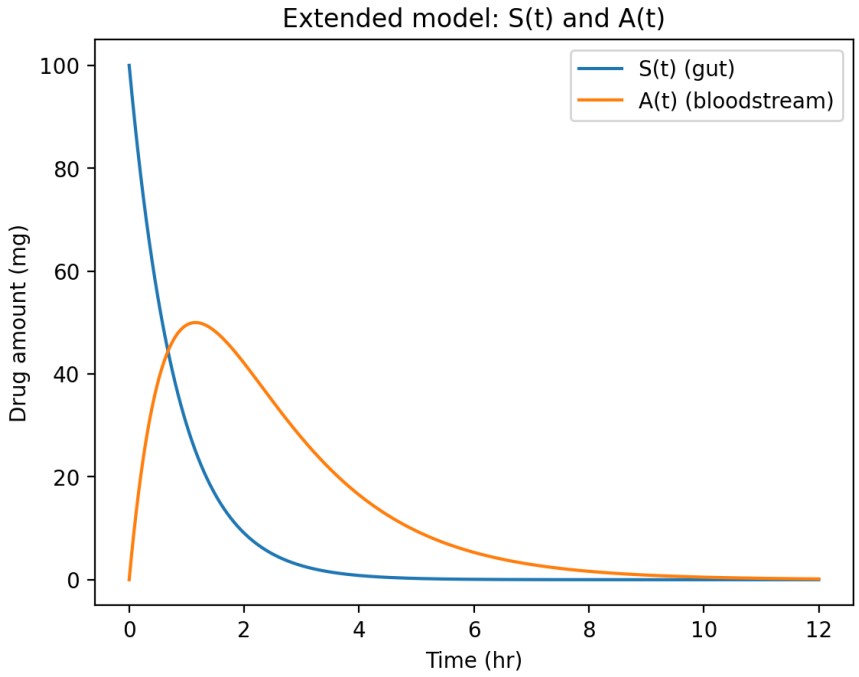

Figure 5: Time evolution of gut and bloodstream compartments. Time course of drug amount in the gastrointestinal compartment $S(t)$ (blue) and bloodstream compartment $A(t)$ (orange) for the extended model ($S_0 = 100$ mg, $c = 0.6$ hr^{-1}, $k_a = 1.2$ hr^{-1}). $S(t)$ decays exponentially as drug is absorbed, while $A(t)$ rises from zero to a delayed peak before declining due to clearance.

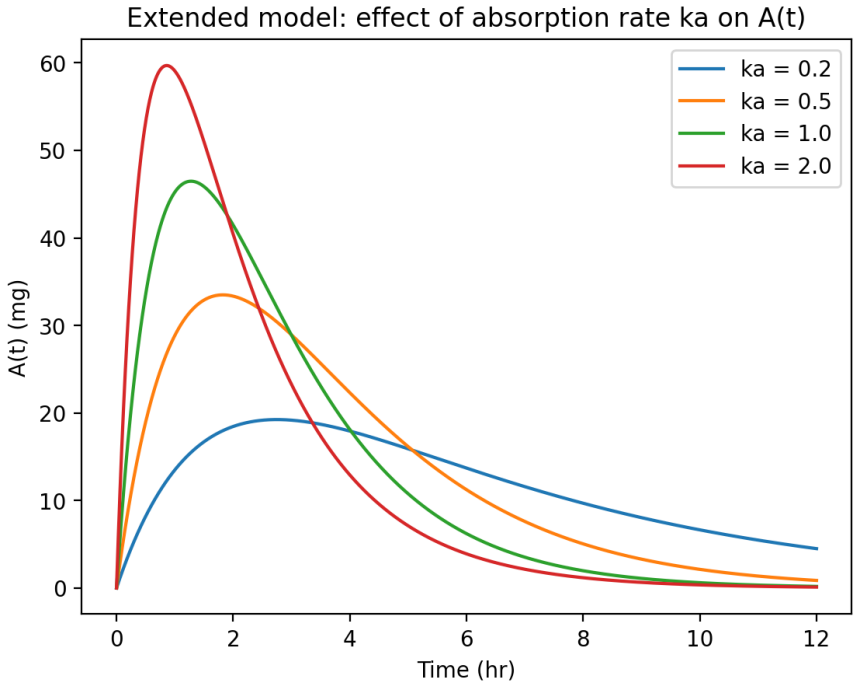

Figure 6: Effect of absorption rate on drug concentration. Sensitivity of bloodstream drug amount $A(t)$ to the absorption rate constant k_a with clearance rate $c = 0.6$ hr^{-1} constant. Larger k_a (red, $k_a = 2.0$) produces earlier and higher peaks with sharper concentration profiles, whereas smaller k_a (blue, $k_a = 0.2$) yields delayed, lower peaks and broader curves.

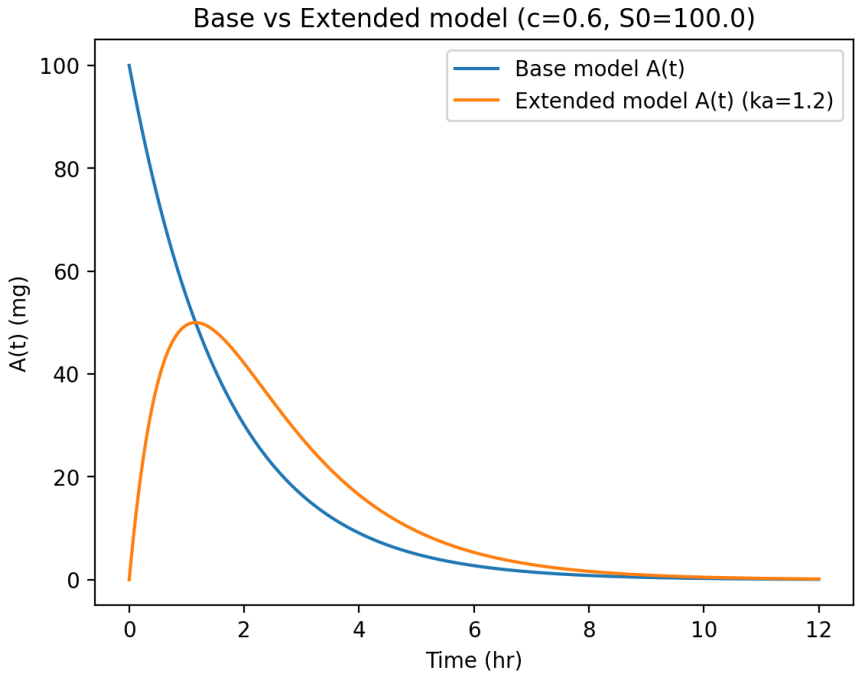

Figure 7: Base vs Extended model comparison. Comparison of base and extended model predictions for bloodstream drug amount $A(t)$ under identical clearance ($c = 0.6$ hr^{-1}, $S_0 = 100$ mg). The base model (blue) predicts an immediate maximum at $t = 0$ followed by exponential decay, while the extended model (orange, $k_a = 1.2$ hr^{-1}) predicts a delayed peak and smoother rise due to the intermediate absorption compartment.

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