

Sharif University of Technology

Electrical Engineering Department



Biological Systems Modeling

Final Project

Arya Koureshi

401204008

Mathematical models for drug diffusion through the compartments of blood and tissue medium

Abstract

This paper presents three mathematical models to understand drug distribution in the human body via oral and intravenous routes. The models use Fick's principle and the law of mass action, with rate constants based on drug efficacy at different interfaces. Ordinary differential equations were solved using Laplace and eigenvalue methods to determine drug concentration in blood and tissue compartments. Numerical parameters were used to compute drug concentration, and MATLAB software was used to plot graphs showing the variation of drug concentration over time. The results indicate a decrease in drug concentration in the first compartment and a gradual increase in subsequent compartments.

Introduction

This article discusses the importance of understanding the relationship between drug intake and concentration in various compartments of the body. Pharmacokinetic researchers study the behavior of drugs or chemicals in the body over time to understand absorption, distribution, and elimination processes and achieve therapeutic responses. Mathematical modeling is a useful tool to understand drug diffusion and transport processes within the body. Compartment models are mathematical representations of the body used to study physiological or pharmacological kinetics. Different models, such as one or two compartment models, have been used to study drug behavior. The article references several studies that have used mathematical models to investigate drug diffusion and distribution in the body. The authors of this study use three mathematical formulations to study drug concentration in relation to physiological parameters.

Mathematical model

Establishing a mathematical model is crucial to estimate drug concentration in different sites and within the blood. When drugs are orally administered, they dissolve and release medication into the gastrointestinal tract, which diffuses into the bloodstream and reaches the site of therapeutic effect. The body can be divided into compartments to model drug flow, with drug movement between compartments described by first-order kinetics. The constant of proportionality is determined by the drug, compartment, and individual health. The rate of change of drug concentration in a compartment over time is governed by the Balance Law, which is based on the law of conservation of mass. Mathematical analysis provides an optimal solution to complex problems.

If $c(t)$ denotes the concentration of drug in the compartment at time t , then the rate of change of $c(t)$ is

$$\frac{dc}{dt} = \text{input rate of drug} - \text{output rate of drug}.$$

Model-I

The article introduces a two-compartment model for drug absorption and circulation through the GI tract and blood. The first compartment represents the GI tract, and the drug diffuses into the second compartment, the bloodstream, as shown in Figure 1. The concentration of the drug in the stomach or GI tract and bloodstream compartments is denoted by $c_1(t)$ and $c_2(t)$, respectively. The initial concentration of drug dosage is denoted by $c_0(t)$. The article provides the general form of the two-compartment model describing the rate of change in oral drug administration.

$$\left. \begin{array}{l} \frac{dc_1(t)}{dt} = -k_1 c_1(t); \\ \frac{dc_2(t)}{dt} = k_1 c_1(t) - k_e c_2(t); \end{array} \right\} \quad (1)$$

$$c_1(0) = c_0 \quad c_2(0) = 0$$

Oral administration
 c_0 units of drug

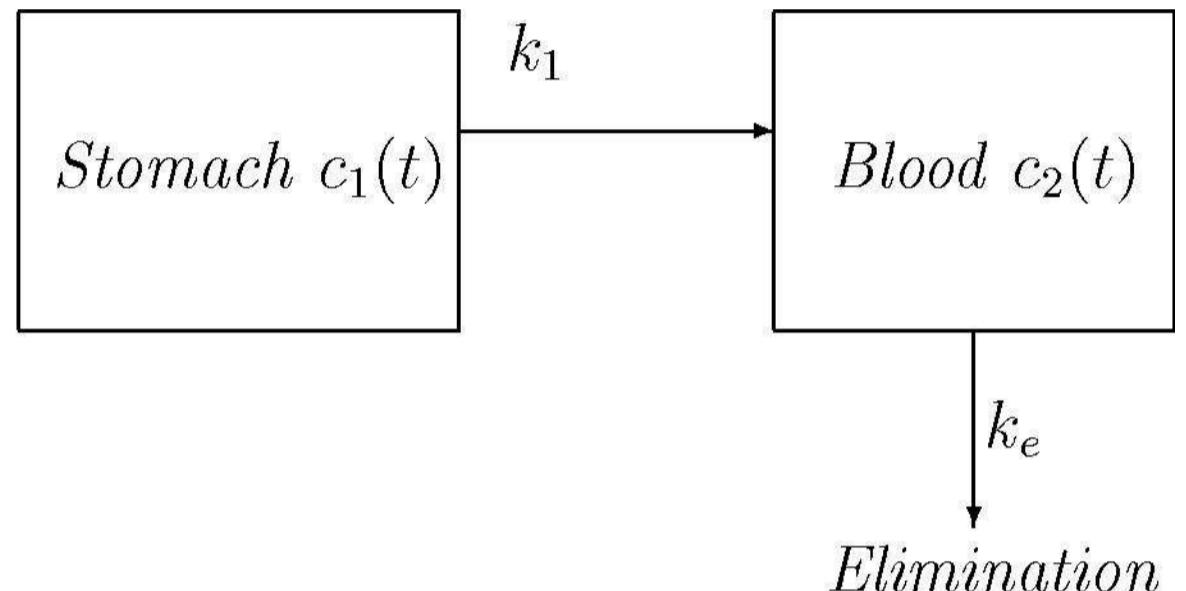


Figure 1. Simple process of drug administration through stomach and blood.

Each equation describes the change in drug concentration in their respective compartments over time. Also the quantities k_1 and k_e (>0) denote the rate constants from one compartment to another and the clearance constant. Eq. (1) are based on modelling the single dosage of drug flow via GI tract to tissue

Solving Eq. (1), we have

$$c_1(t) = c_0 e^{-k_1 t} \quad (2)$$

$$c_2(t) = \frac{c_0 k_1}{(k_1 - k_e)} (e^{-k_e t} - e^{-k_1 t}); \quad k_1 \neq k_e \quad (3)$$

Equation (2) represents the exponential decay of drug absorption, resulting in a long-term decrease of drug concentration in the GI tract to zero.

The dosage of medication varies depending on the patient's condition and disease severity. Oral medication may be less efficient due to stomach sensitivity, liver dysfunction, or delayed reaction. In such cases, intravenous administration is preferred for effective and rapid drug dosage. In emergency situations, medication needs to be rapidly absorbed, and delicate medications may be broken down by certain enzymes, requiring direct injection into the bloodstream..

```
In [1]: # %% Imports
import numpy as np
import matplotlib.pyplot as plt
```

```
In [3]: # %% Model I
# rate constants k1 and ke
K1 = [0.9776, 0.7448, 0.3293, 0.2213]
Ke = [0.05]

# initial drug concentration
c0 = 500

t = np.linspace(0, 6, 1000)
```

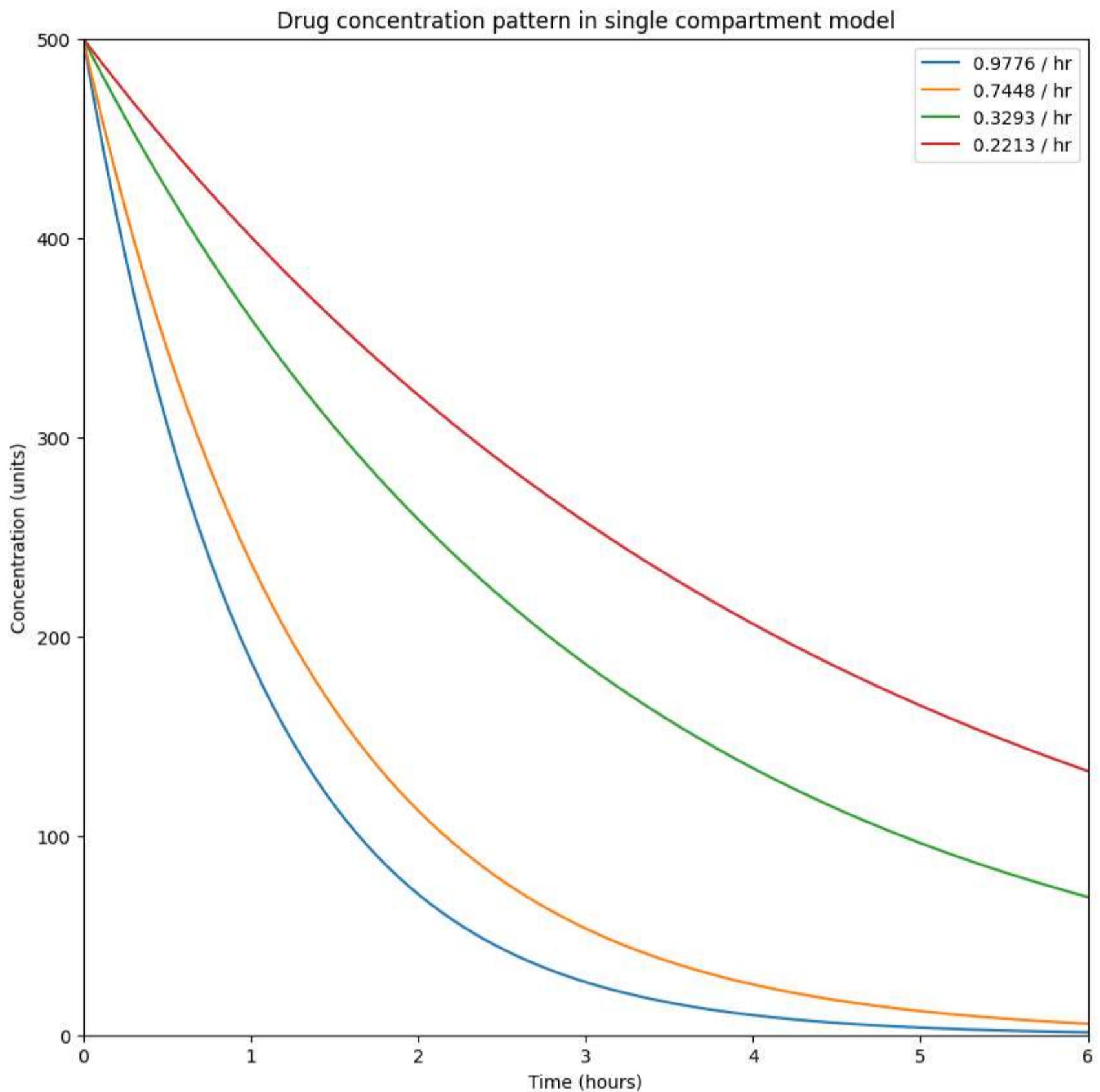
```
In [4]: plt.figure(figsize=(10, 10))
for k1 in K1:
    for ke in Ke:
```

```

# Calculate the drug concentration in the GI tract and blood stream compartments
c1 = c0 * np.exp(-k1 * t)
c2 = (c0 * k1 / (k1 - ke)) * (np.exp(-ke * t) - np.exp(-k1 * t))
plt.plot(t, c1, label=str(k1)+" / hr")

plt.legend()
plt.ylim([0, c0])
plt.xlim([0, t[-1]])
plt.xlabel('Time (hours)')
plt.ylabel('Concentration (units)')
plt.title('Drug concentration pattern in single compartment model')
plt.show()
plt.savefig("Model1_1.png", dpi=312)

```



<Figure size 640x480 with 0 Axes>

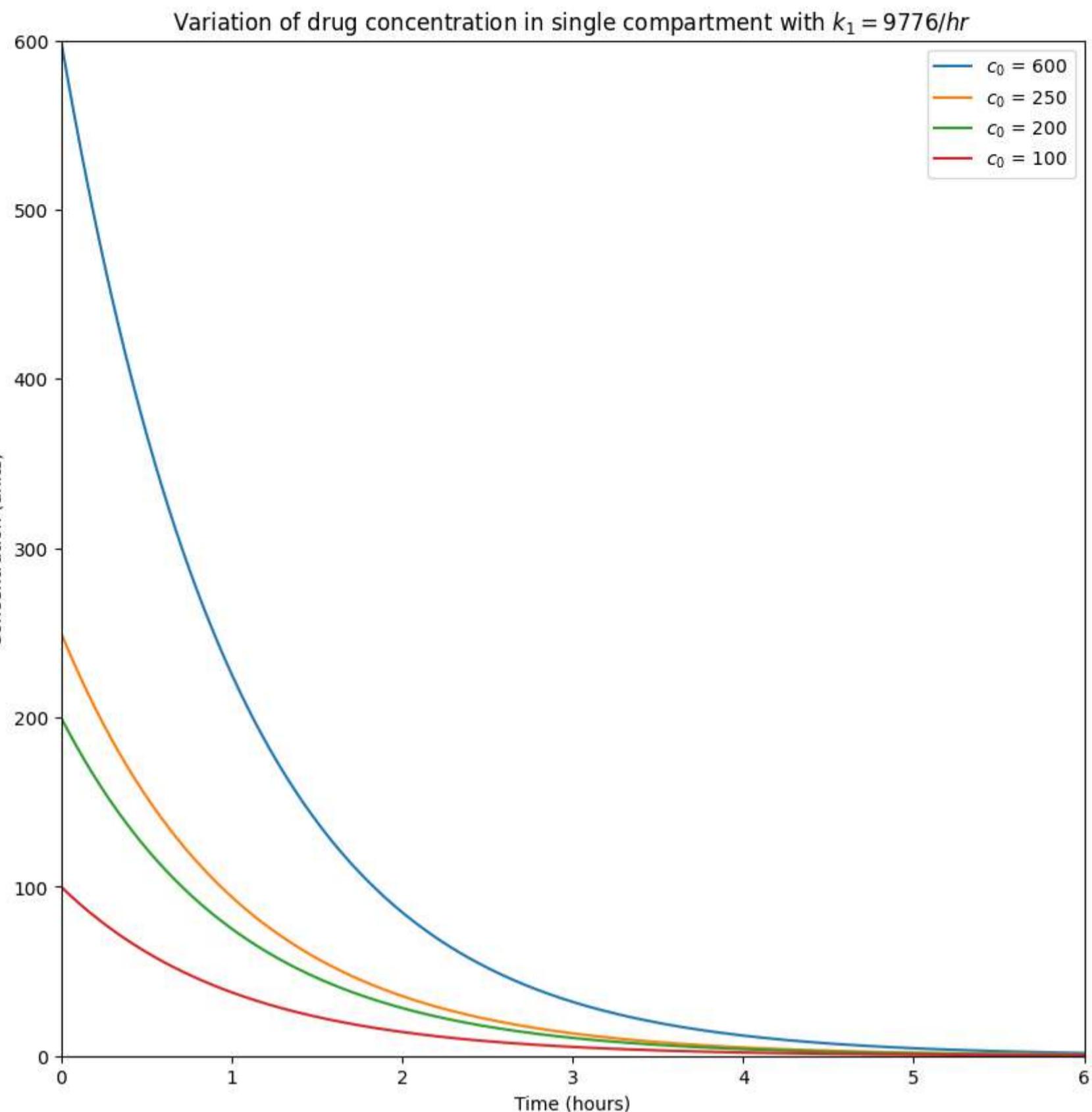
With different c_0 (initial drug concentration)

```

In [5]: plt.figure(figsize=(10, 10))
ke = 0.05
k1 = 0.9776
C0 = [600, 250, 200, 100]
for c0 in C0:
    # Calculate the drug concentration in the GI tract and blood stream compartments
    c1 = c0 * np.exp(-k1 * t)
    c2 = (c0 * k1 / (k1 - ke)) * (np.exp(-ke * t) - np.exp(-k1 * t))
    plt.plot(t, c1, label=r'$c_0$ = ' + str(c0))

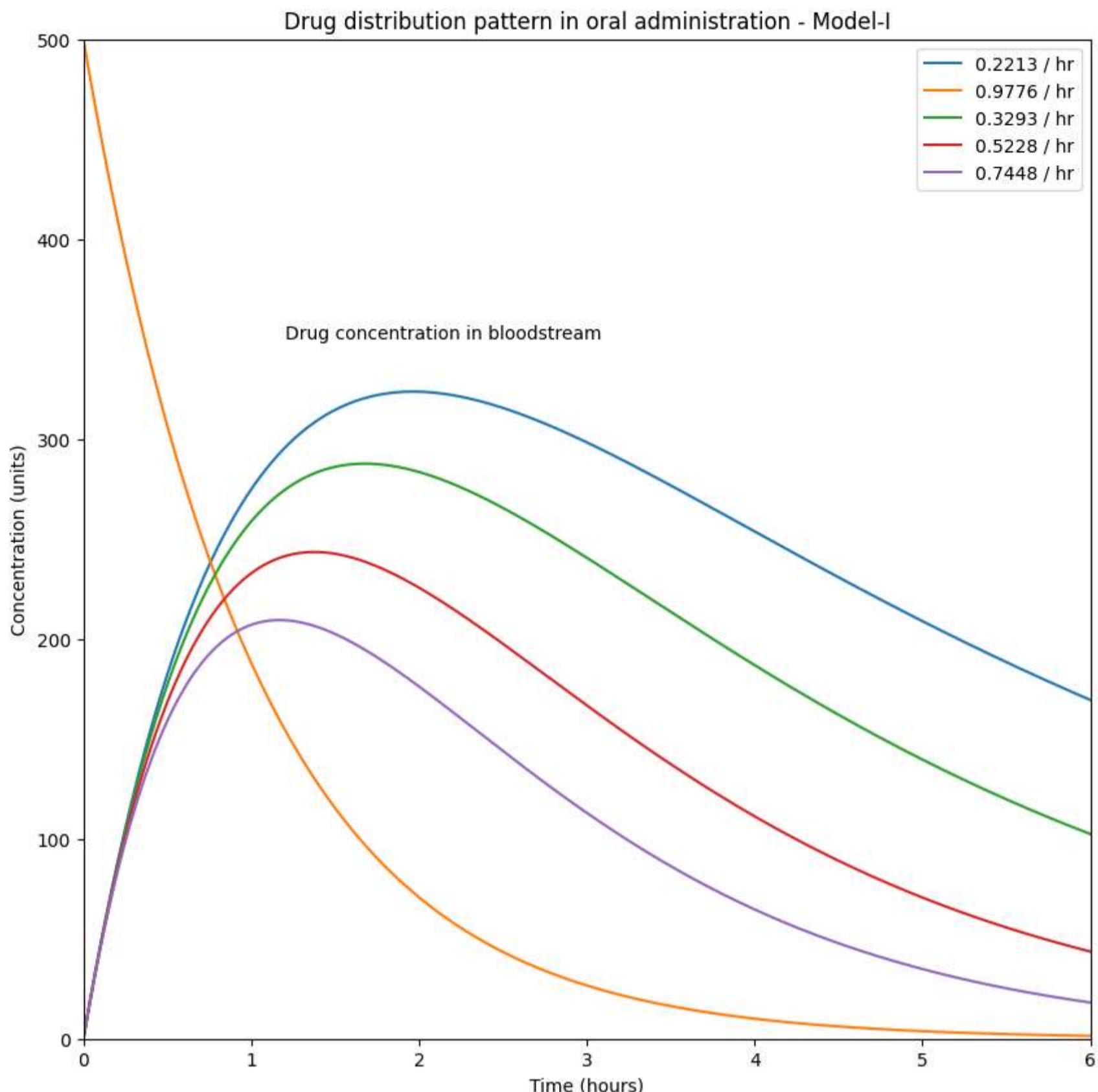
plt.legend()
plt.ylim([0, c0[0]])
plt.xlim([0, t[-1]])
plt.xlabel('Time (hours)')
plt.ylabel('Concentration (units)')
plt.title(r'Variation of drug concentration in single compartment with $k_1 = 9776 / hr$')
plt.show()
plt.savefig("Model1_2.png", dpi=312)

```



<Figure size 640x480 with 0 Axes>

```
In [8]: plt.figure(figsize=(10, 10))
Ke = [0.2213, 0.9776, 0.3293, 0.5228, 0.7448]
K1 = [0.9776]
c0 = 500
for k1 in K1:
    for ke in Ke:
        # Calculate the drug concentration in the GI tract and blood stream compartments
        c1 = c0 * np.exp(-k1 * t)
        if ke == 0.9776:
            plt.plot(t, c1, label=str(k1)+" / hr")
        else:
            if ke == 0.2213:
                plt.text(1.2, 350, "Drug concentration in bloodstream")
                c2 = (c0 * k1 / (k1 - ke)) * (np.exp(-ke * t) - np.exp(-k1 * t))
                plt.plot(t, c2, label=str(ke)+" / hr")
plt.legend()
plt.ylim([0, c0])
plt.xlim([0, t[-1]])
plt.xlabel('Time (hours)')
plt.ylabel('Concentration (units)')
plt.title('Drug distribution pattern in oral administration - Model-I')
plt.show()
plt.savefig("Model1_3.png", dpi=312)
```



<Figure size 640x480 with 0 Axes>

Model-II

To create a mathematical model for intravenous drug administration, two models (Model-II and Model-III) were developed based on reversible and irreversible rate constants. The model includes two compartments, namely blood and tissue, where the drug is injected into the bloodstream and has a therapeutic effect in the tissue. The model assumes that a fraction of the drug is eliminated from the blood with a clearance rate of k_e , while the remaining portion is taken up by the tissue at a rate of k_t . The system of two ODEs governs the mathematical formulation, with each equation describing the rate of change of drug concentration over time in the respective compartments, as shown in Figure 2.

Intravenous infusion
 c_0 units of drug

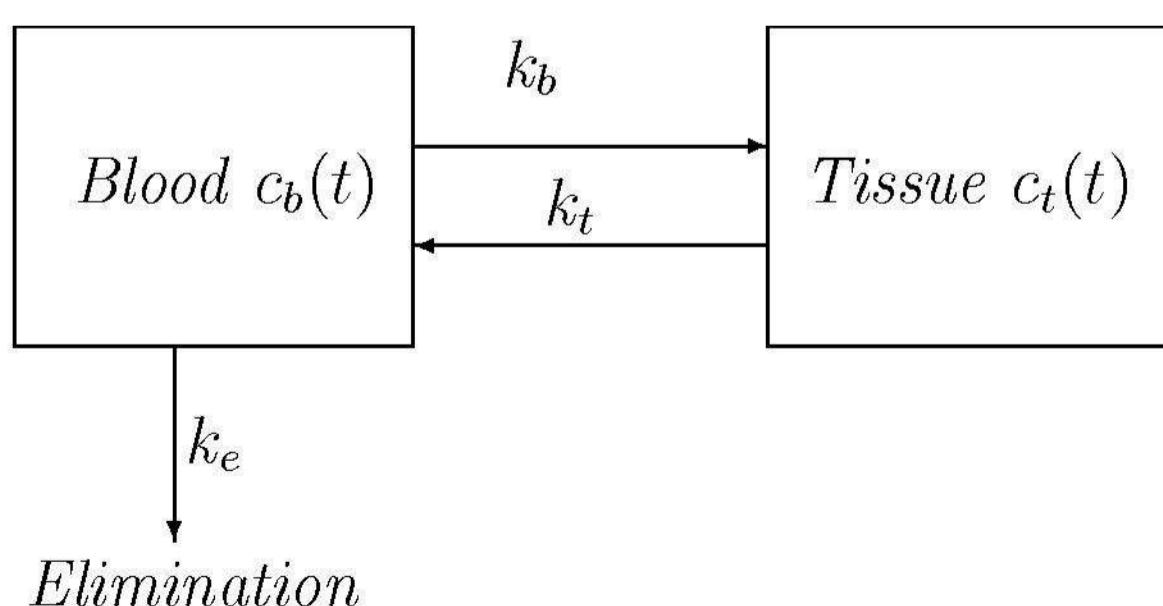


Figure 2. Drug administration through blood and tissue with initial drug intake c_0 . Let $c_b(t)$ and $c_t(t)$ denote the concentration of drug in the compartments blood and tissue respectively and c_0 be the initial concentration of drug injected through intravenous route the body. Then the mathematical form of a two compartment model describing the drug administration

$$\left. \begin{array}{l} \frac{dc_b(t)}{dt} = -(k_b + k_e)c_b + k_t c_t; \quad c_b(0) = c_0 \\ \frac{dc_t(t)}{dt} = k_b c_b - k_t c_t; \quad c_t(0) = 0 \end{array} \right\} \quad (4)$$

Therefore, we have

$$c_b(t) = \frac{c_0}{(\zeta_2 - \zeta_1)} \{(-\zeta_1 + k_t) \exp(-\zeta_1 t) - (-\zeta_2 + k_t) \exp(-\zeta_2 t)\} \quad (12)$$

$$c_t(t) = \frac{c_0 k_b}{(\zeta_1 - \zeta_2)} \{\exp(-\zeta_1 t) - \exp(-\zeta_2 t)\} \quad (13)$$

where ζ_1 and ζ_2 are the roots of the equati

$$s^2 + (k_b + k_e + k_t)s + k_e k_t = 0.$$

onis

```
In [18]: # case 1
# rate constants kb, ke, and kt
kb = 0.9776
ke = 0.2213
kt = 0.3293

# initial drug concentration
c0 = 500

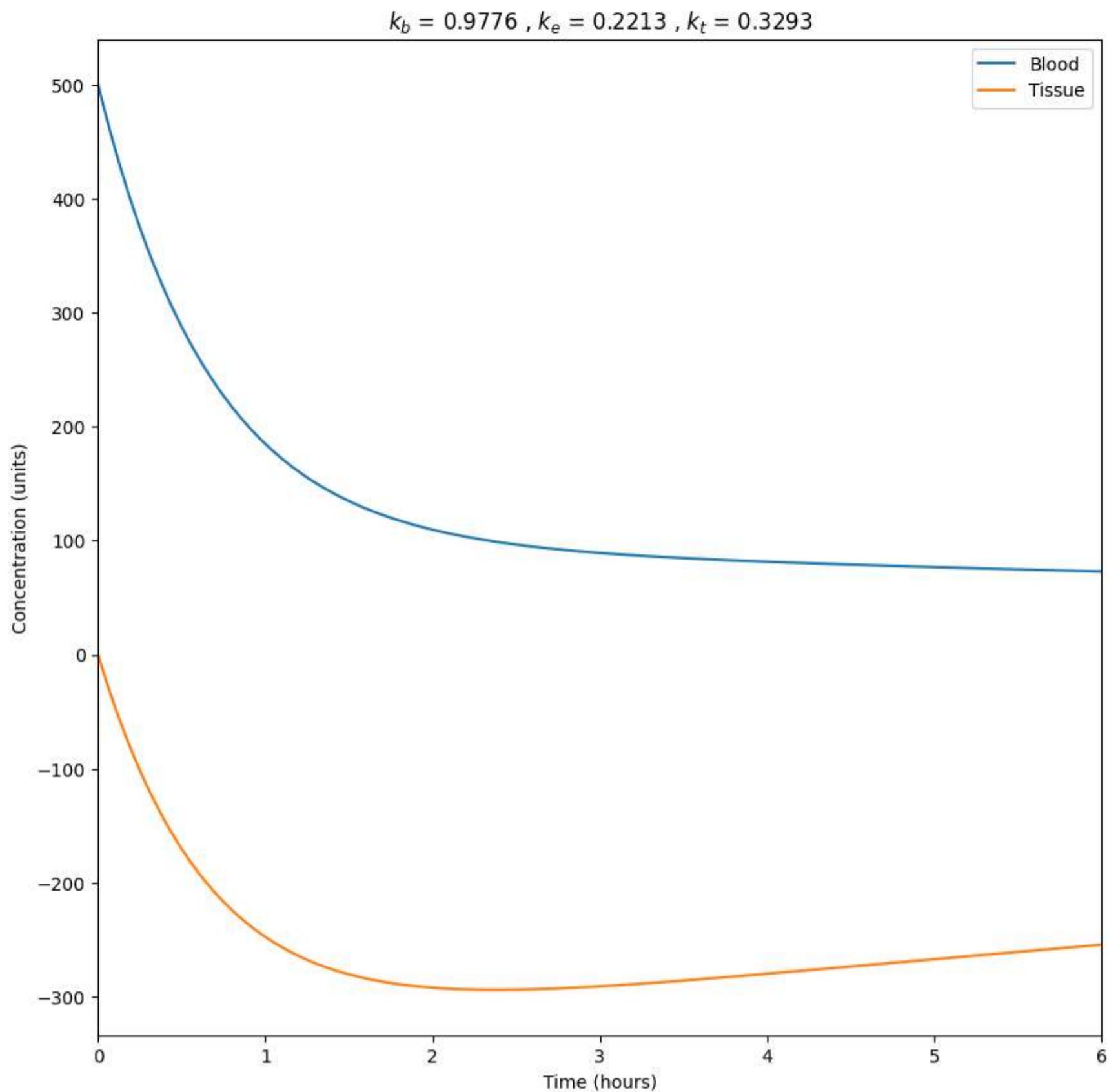
t = np.linspace(0, 6, 1000)

# Calculate the roots of the equation
a = 1
b = kb + ke + kt
c = ke * kt
D = np.sqrt(b**2 - 4*a*c)
u1 = -1* (-b + D)/(2*a)
u2 = -1* (-b - D)/(2*a)

# Calculate the drug concentration in the blood and tissue compartments
cb = (c0 / (u2 - u1)) * ((-u1 + kt) * np.exp(-u1 * t) - (-u2 + kt) * np.exp(-u2 * t))
ct = (c0 * kb / (u1 - u2)) * (np.exp(-u1 * t) - np.exp(-u2 * t))

plt.figure(figsize=(10, 10))
plt.plot(t, cb, label='Blood')
plt.plot(t, ct, label='Tissue')
plt.xlim([0, t[-1]])
plt.xlabel('Time (hours)')
plt.ylabel('Concentration (units)')
plt.suptitle('Drug concentration pattern in Model-II - case 1')
plt.title(r'$k_b$ = {} , $k_e$ = {} , $k_t$ = {}'.format(kb, ke, kt))
plt.legend()
plt.show()
plt.savefig("Model2_case1.png", dpi=312)
```

Drug concentration pattern in Model-II - case 1



<Figure size 640x480 with 0 Axes>

```
In [19]: # case 2
# rate constants kb, ke, and kt
kb = 0.5
ke = 0.05
kt = 0.25

# initial drug concentration
c0 = 500

t = np.linspace(0, 6, 1000)

# Calculate the roots of the equation
a = 1
b = kb + ke + kt
c = ke * kt
D = np.sqrt(b**2 - 4*a*c)
u1 = -1* (-b + D)/(2*a)
u2 = -1* (-b - D)/(2*a)

# Calculate the drug concentration in the blood and tissue compartments
cb = (c0 / (u2 - u1)) * ((-u1 + kt) * np.exp(-u1 * t) - (-u2 + kt) * np.exp(-u2 * t))
ct = (c0 * kb / (u1 - u2)) * (np.exp(-u1 * t) - np.exp(-u2 * t))

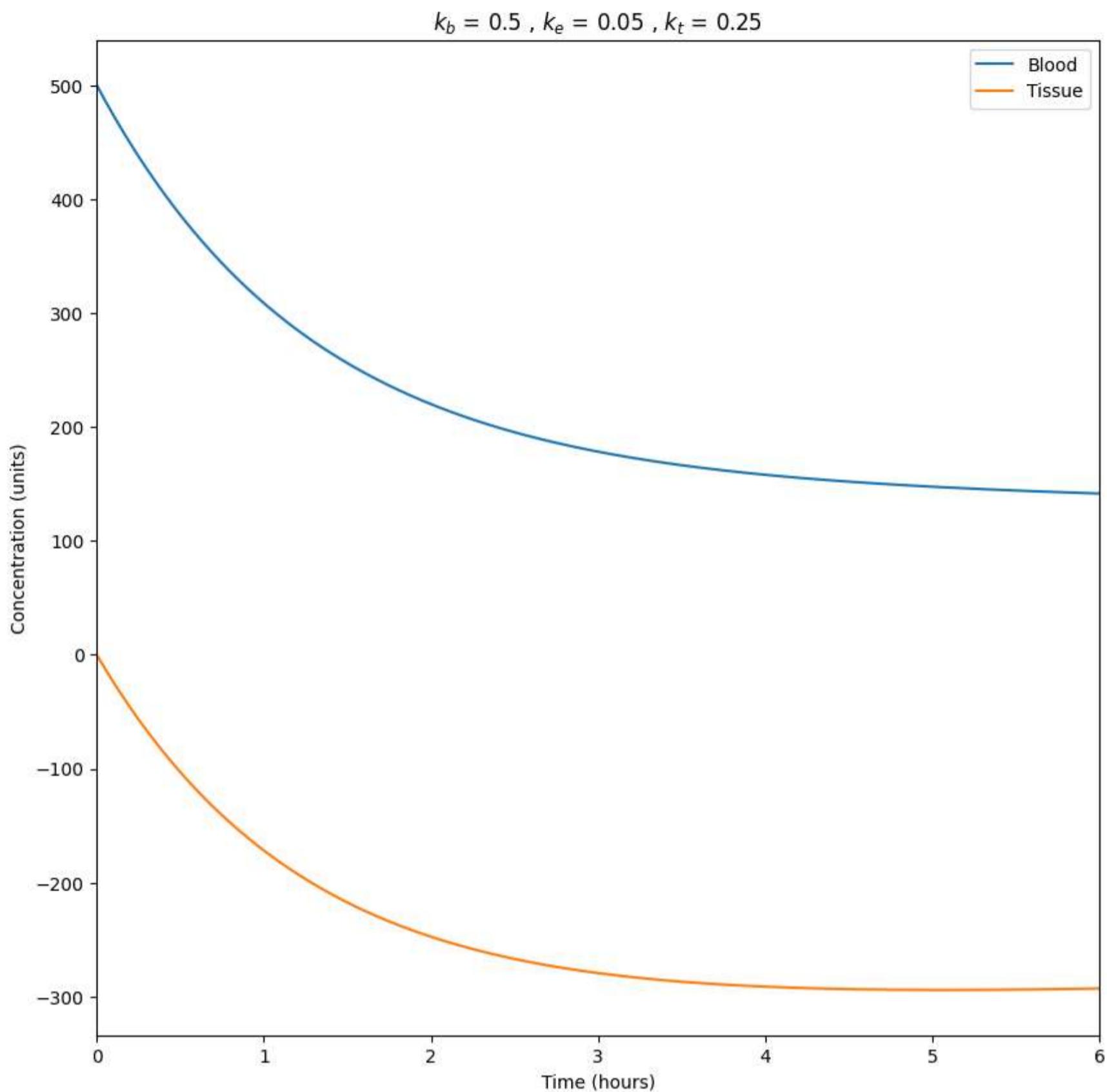
plt.figure(figsize=(10, 10))
plt.plot(t, cb, label='Blood')
plt.plot(t, ct, label='Tissue')
plt.xlim([0, t[-1]])
plt.xlabel('Time (hours)')
plt.ylabel('Concentration (units)')
plt.suptitle('Drug concentration pattern in Model-II - case 2')
```

```

plt.title(r'$k_b$ = {} , $k_e$ = {} , $k_t$ = {}'.format(kb, ke, kt))
plt.legend()
plt.show()
plt.savefig("Model2_case2.png", dpi=312)

```

Drug concentration pattern in Model-II - case 2



<Figure size 640x480 with 0 Axes>

Model-III

Drug administration through venous blood follows a one-directional flow pattern in the cardiovascular system, as shown in Figure 3. The drug carried by venous blood reaches the target site through the capillary bed, and the remaining drug is either eliminated or taken back to the circulatory system by arterial blood. The consumption of drug by arterial blood towards tissue flows at a rate of k_b , while from the tissue compartment to venous blood, it flows at a rate of k_t . As the drug level in the venous blood increases over time, the kidneys and liver eventually excrete the drug from the body organs. The clearance rate of drug from the blood is denoted by k_e .

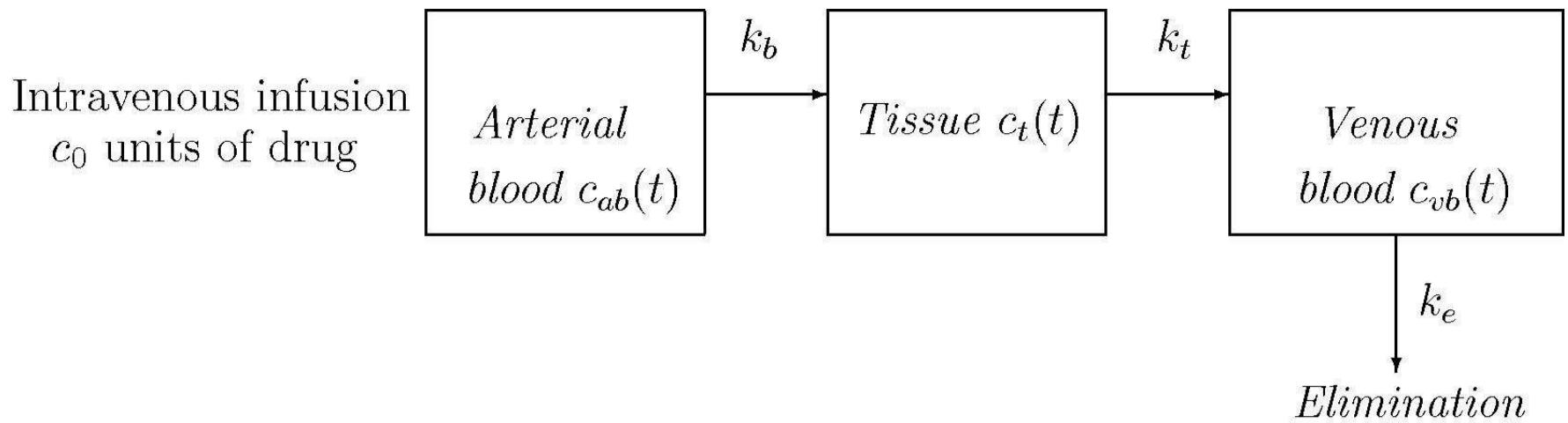


Figure 3. Drug administration through arterial blood and tissue and venous blood with initial drug intake c_0

Let $c_{ab}(t)$, $c_t(t)$ and $c_{vb}(t)$ denote the concentration of drug in the arterial blood, tissue and venous blood compartment respectively with c_0 as initial drug dosage. The mathematical formulation for the drug concentration with respect to these compartments is based on the following system of initial value problem

$$\left. \begin{aligned} \frac{dc_{ab}(t)}{dt} &= -k_b c_{ab}(t); & c_{ab}(0) &= c_0 \\ \frac{dc_t(t)}{dt} &= k_b c_{ab}(t) - k_t c_t(t); & c_t(0) &= 0 \\ \frac{dc_{vb}(t)}{dt} &= k_t c_t(t) - k_e c_{vb}(t); & c_{vb}(0) &= 0 \end{aligned} \right\} \quad (14)$$

On solving Eq. (14), we have

$$c_{ab}(t) = c_0 \exp(-k_b t) \quad (15)$$

$$c_t(t) = \frac{c_0 k_b}{k_b - k_t} \{ \exp(-k_t t) - \exp(-k_b t) \} \quad (16)$$

$$\begin{aligned} c_{vb}(t) &= c_0 k_t k_b \left\{ \frac{\exp(-k_t t)}{(k_b - k_t)(k_e - k_t)} - \frac{\exp(-k_b t)}{(k_b - k_t)(k_e - k_b)} \right. \\ &\quad \left. + \frac{\exp(-k_e t)}{(k_e - k_t)(k_e - k_b)} \right\} \end{aligned} \quad (17)$$

Since $k_e < k_t < k_b$, it follows that $c_{ab}(t)$, $c_t(t)$ and $c_{vb}(t)$ are all positive. s::

```
In [13]: # %% Model III
# case 1
# rate constants kb, kt, and ke
kb = 0.9776
ke = 0.2213
kt = 0.3293

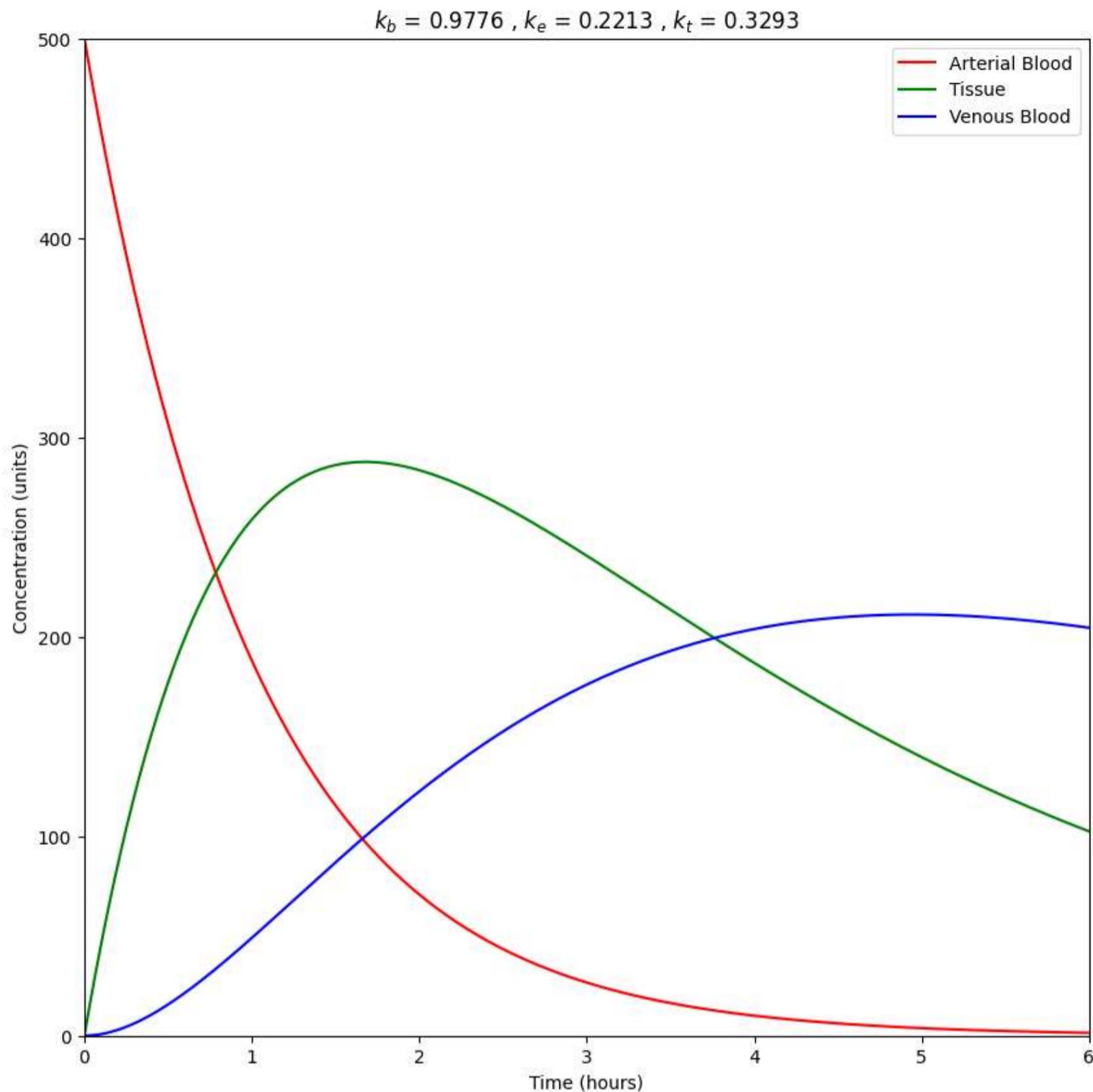
# initial drug concentration
c0 = 500

# Define the time range
t = np.linspace(0, 6, 1000)

# Calculate the drug concentration in the arterial blood, tissue, and venous blood compartments
cab = c0 * np.exp(-kb * t)
ct = (c0 * kb / (kb - kt)) * (np.exp(-kt * t) - np.exp(-kb * t))
cvb = c0 * kb * kt * ((np.exp(-kt * t)) / ((kb - kt) * (ke - kt)) - (np.exp(-kb * t)) / ((kb - kt) * (ke - kb)) + (np.exp(-ke * t)) / ((ke - kb) * (ke - kt)))

plt.figure(figsize=(10, 10))
plt.plot(t, cab, 'r', label='Arterial Blood')
plt.plot(t, ct, 'g', label='Tissue')
plt.plot(t, cvb, 'b', label='Venous Blood')
plt.xlabel('Time (hours)')
plt.ylabel('Concentration (units)')
plt.ylim([0, c0])
plt.xlim([0, t[-1]])
plt.suptitle('Drug distribution pattern in intravenous administration with 500 units of initial drug dosage for Model-III - case 1')
plt.title(r'$k_b$ = {} , $k_e$ = {} , $k_t$ = {}'.format(kb, ke, kt))
plt.legend()
plt.show()
plt.savefig("Model3_case1.png", dpi=312)
```

Drug distribution pattern in intravenous administration with 500 units of initial drug dosage for Model-III - case 1



<Figure size 640x480 with 0 Axes>

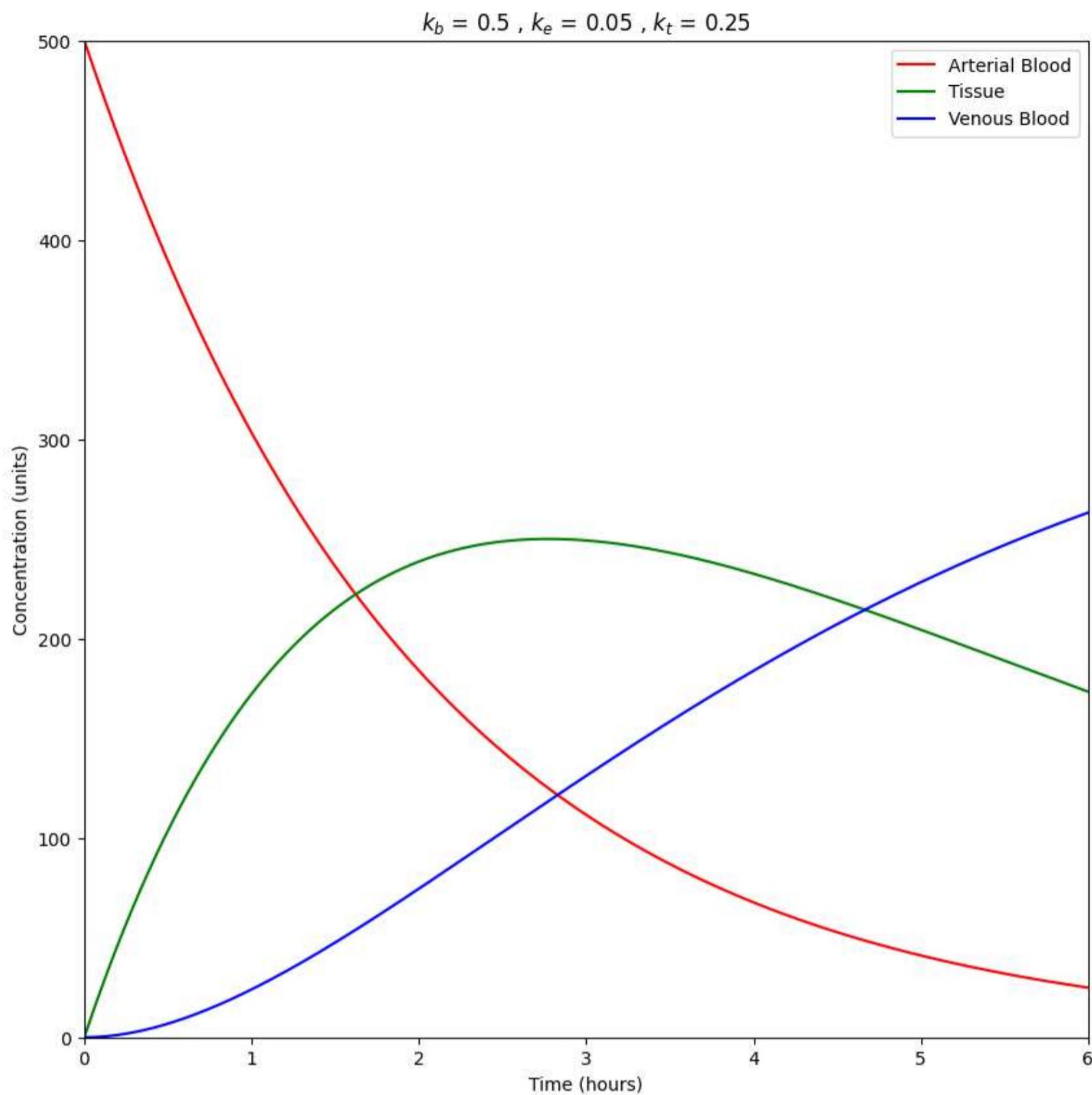
```
In [14]: # case 2
# rate constants kb, kt, and ke
kb = 0.5
ke = 0.05
kt = 0.25

# initial drug concentration
c0 = 500

t = np.linspace(0, 6, 1000)

# Calculate the drug concentration in the arterial blood, tissue, and venous blood compartments
cab = c0 * np.exp(-kb * t)
ct = (c0 * kb / (kb - kt)) * (np.exp(-kt * t) - np.exp(-kb * t))
cvb = c0 * kb * kt * ((np.exp(-kt * t)) / ((kb - kt) * (ke - kt)) - (np.exp(-kb * t)) / ((kb - kt) * (ke - kb)) + (np.exp(-ke

plt.figure(figsize=(10, 10))
plt.plot(t, cab, 'r', label='Arterial Blood')
plt.plot(t, ct, 'g', label='Tissue')
plt.plot(t, cvb, 'b', label='Venous Blood')
plt.xlabel('Time (hours)')
plt.ylabel('Concentration (units)')
plt.ylim([0, c0])
plt.xlim([0, t[-1]])
plt.suptitle('Drug distribution pattern in intravenous administration with 500 units of initial drug dosage for Model-III - ca
plt.title(r'$k_b$ = {} , $k_e$ = {} , $k_t$ = {}'.format(kb, ke, kt))
plt.legend()
plt.show()
plt.savefig("Model3_case2.png", dpi=312)
```



<Figure size 640x480 with 0 Axes>

The models developed in this study are useful for three types of problems related to drug diffusion in biological tissues. Models I, II, and III were formulated based on limitations arising from diffusion processes across compartments in biological systems. These models can be applied to various drug diffusion problems in pharmaceutical studies, taking into account the flexibility of parameters and the role of drug infusion through different routes. The study has numerous applications in drug control, dosage, and other related pharmaceutical research problems.