Flow and transport in porous tissues
Homework

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1 Exercise 1

In this exercise we will consider always $D = 0.0009\ mm^2/s$ and $D_1 = D_2 = D$

1.1 Count particles in plane

We see some examples of how the particles are divided in the plane. To do that we divide it in $\delta \times \delta$ squares (based on a square where all the particles lies).

For the following images we will consider 1000 particles.

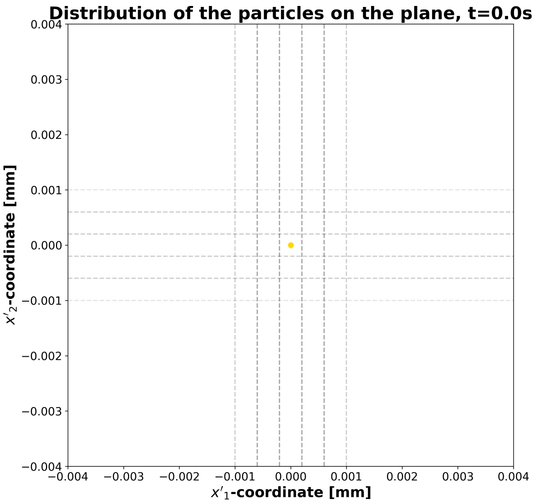


Figure 1: Plane at $t = 0s$, $\delta = 5$

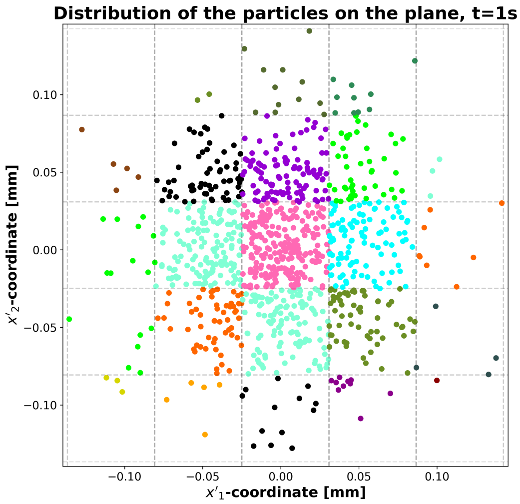


Figure 2: Plane at $t = 1s$, $\delta = 5$

As defined in the program, at $t = 0s$ all the particles are condensed at $(0, 0)$.

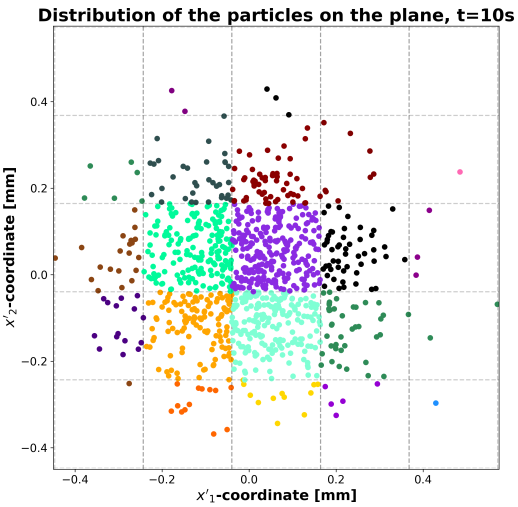


Figure 3: Plane at $t = 10s$, $\delta = 5$

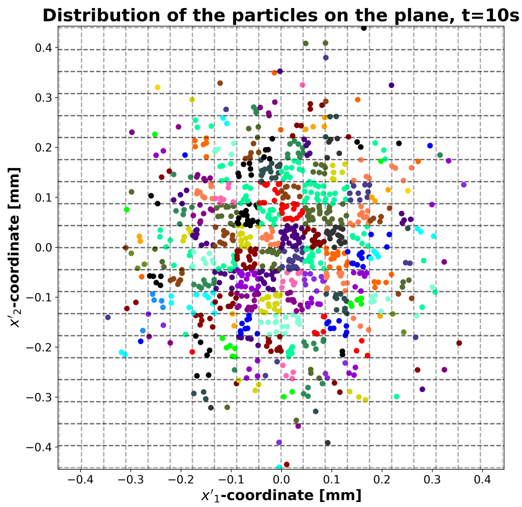


Figure 4: Plane at $t = 10s$, $\delta = 20$

We see the problem with increasing δ: increasing the amount of squares into which the plane is divided causes the amount of particles within each square to tend to 0. Which thing forces us to increase the number of particles, and thus the computational cost.

1.2 Numerical concentration in plane

To compute the numerical concentration in the plane, we will consider the number of particles in each squares (as explained above) and we will divide that for the total number of particles.

From now on we will consider 5000 total particles. Before we considered 1000 particles because the computational cost with plotting the squares in plane is much higher that the one required for the next plotting.

We obtain graphs as follows:

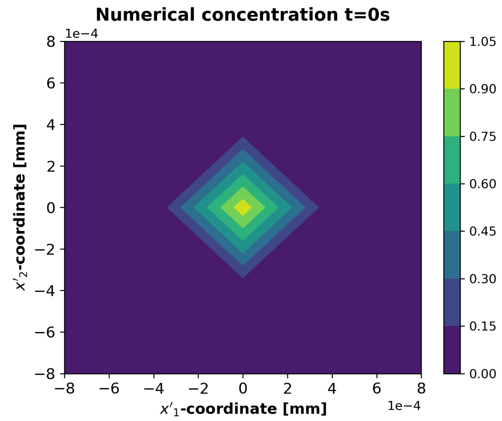


Figure 5: Plane at $t = 0.0s$, $\delta = 5$

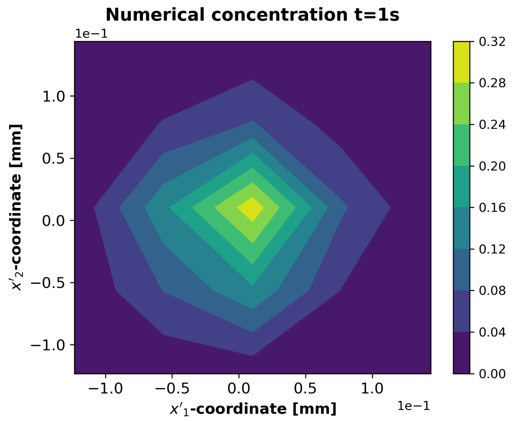


Figure 6: Plane at $t = 1s$, $\delta = 5$

We see that we obtain a similar distribution for different time t, with the only difference being that the extent of concentration is greater for longer times. This is consistent with the fact that the more time passes, the more the particles expand in the plane (from $(0, 0)$ from which they start).

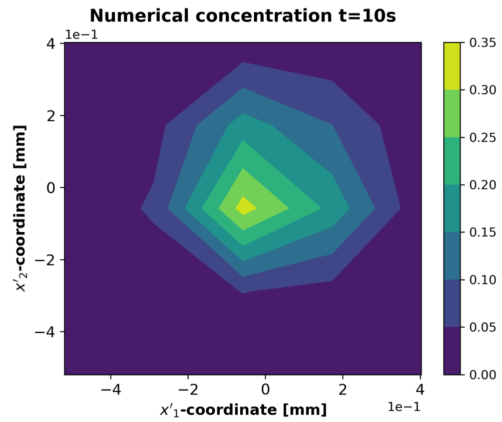


Figure 7: Plane at $t = 10s$, $\delta = 5$

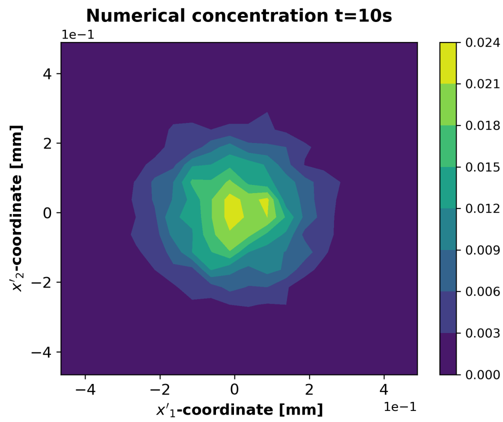


Figure 8: Plane at $t = 10s$, $\delta = 20$

We also notice that for higher δ (hence refining the division of the plane in squares) we obtain inaccurate results that, again, emphasize the need to increase the total number of particles.

1.3 Analytical density

We know that the analytical expression of the density is:

$$f(x,y,t) = \frac{1}{4\pi t\sqrt{D_1 D_2}} \exp\left[-\frac{x^2}{4D_1 t} - \frac{y^2}{4D_1 t}\right]$$

We plot it on the plane considering the same division in $\delta \times \delta$ squares (so to compare better to the numerical case).

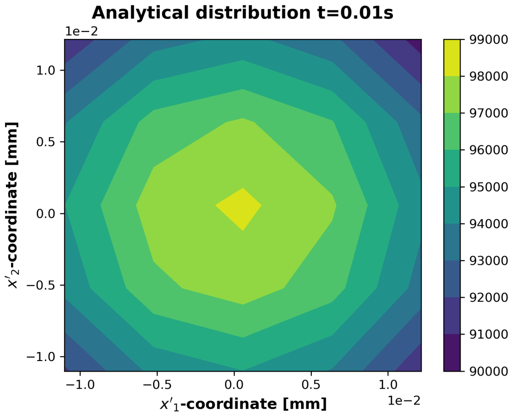


Figure 9: Plane at $t = 0.01s$, $\delta = 5$

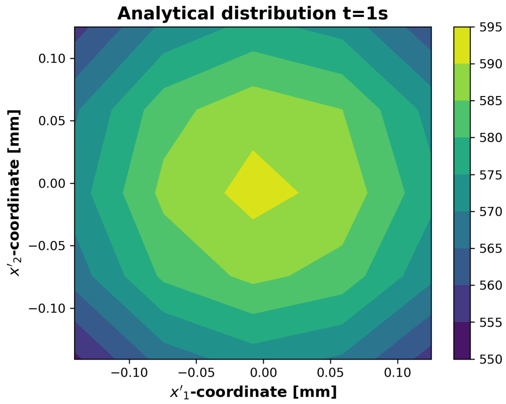


Figure 10: Plane at $t = 1s$, $\delta = 5$

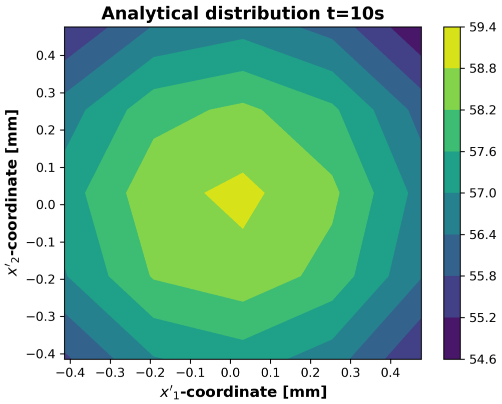


Figure 11: Plane at $t = 10s$, $\delta = 5$

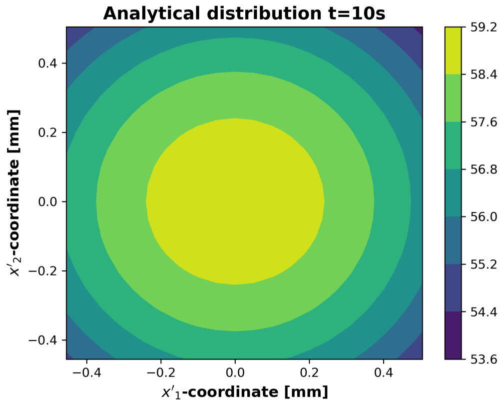


Figure 12: Plane at $t = 10s$, $\delta = 20$

We obtain very similar results in terms of spread of particles.

1.4 Numerical concentration over axis

Now we will crush the numerical concentration of particles on the x and y axis. To do this we add up all the particles contained in the same strip (horizontal in the case of the y-axis, vertical in the case of the x-axis) and divide by the total number of particles.

To compare the numerical distribution with the analytical distribution, the curve of the analytical solution is superimposed. Note that for small values of delta, the numerical distribution looks shifted. This comes from how the plane was divided into squares: we consider (0,0) as the origin of a square. If, on the other hand, one were to consider (0,0) as the center of a square (and from there construct the rest of the division of the plane), this apparent translation would not occur. This phenomenon is seen not to affect much for large delta values.

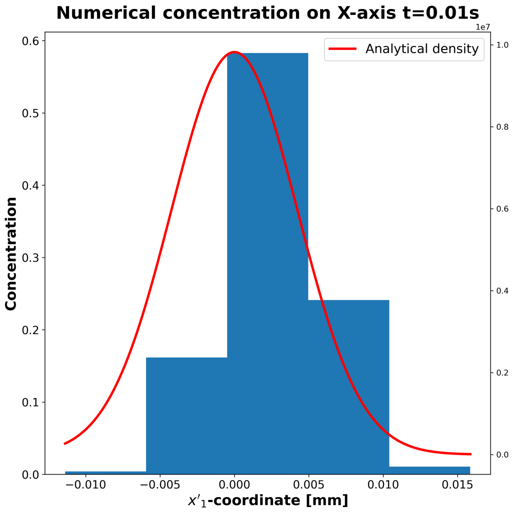


Figure 13: X-axis at $t = 0.01s$, $\delta = 5$

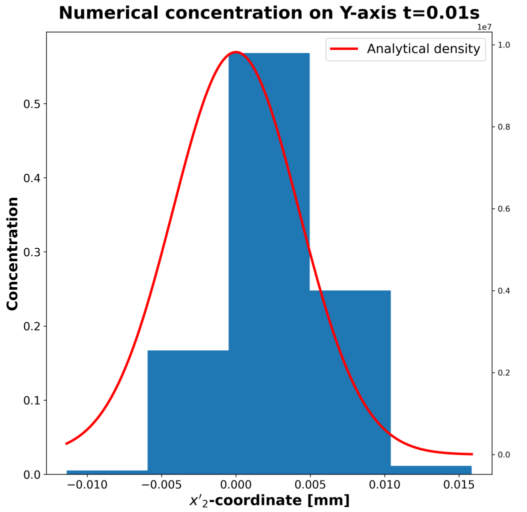


Figure 14: Y-axis at $t = 0.01s$, $\delta = 5$

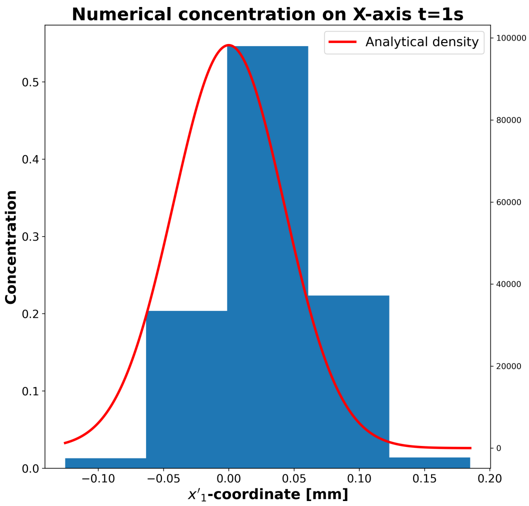


Figure 15: X-axis at $t = 1s$, $\delta = 5$

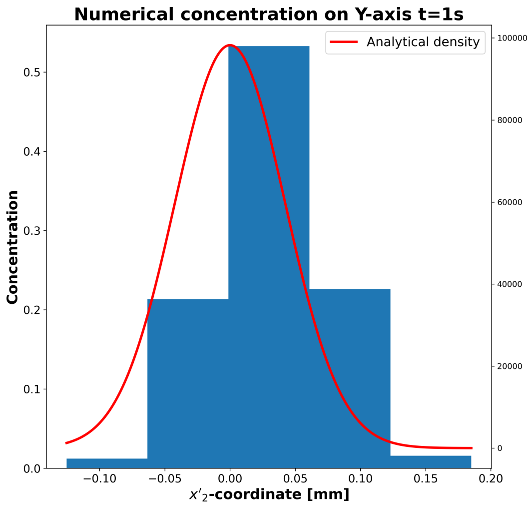


Figure 16: Y-axis at $t = 1s$, $\delta = 5$

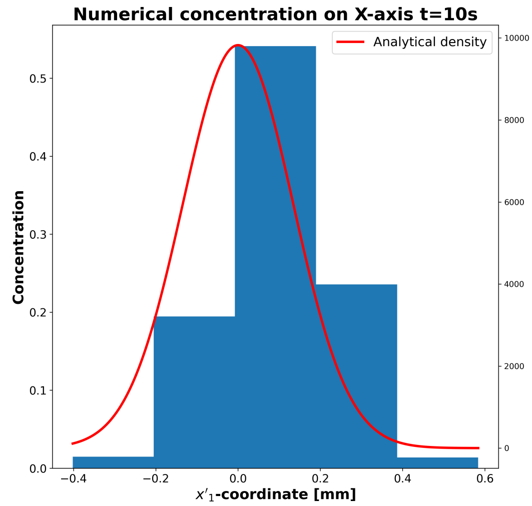


Figure 17: X-axis at $t = 10s$, $\delta = 5$

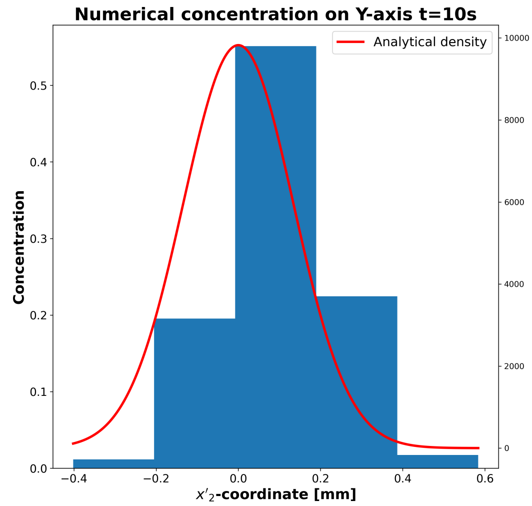


Figure 18: Y-axis at $t = 10s$, $\delta = 5$

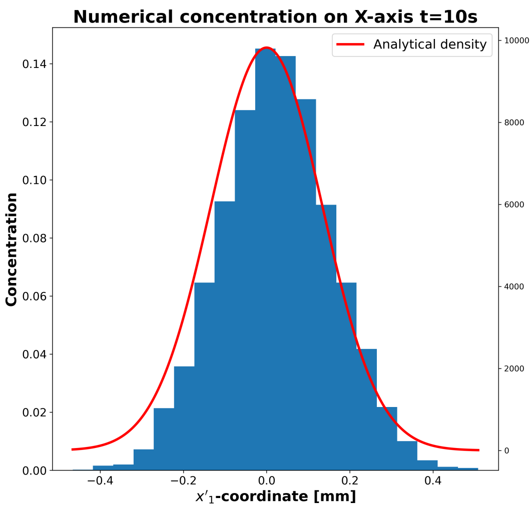


Figure 19: X-axis at $t = 10s$, $\delta = 20$

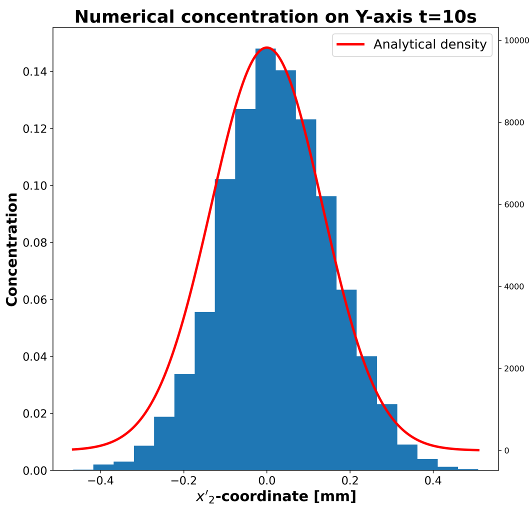


Figure 20: Y-axis at $t = 10s$, $\delta = 20$

We note that the distribution on the axes converges to a gaussian distribution. The more we refine the plane subdivision, that is, increase δ, the more it converges to a gaussian. Which follows exactly from the convergence of the numerical distribution on the plane to the analytical density.

1.5 Analytical distribution on the numerical grid

To compare the analytical distribution with the numerical distribution more thoroughly, we discretize the analytical distribution on the same grid as the numerical distribution. By normalizing both, we can then compare them in much more detail.

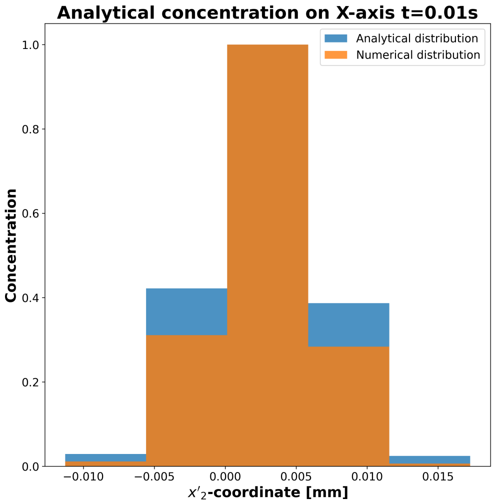


Figure 21: X-axis at $t = 0.01s$, $\delta = 5$

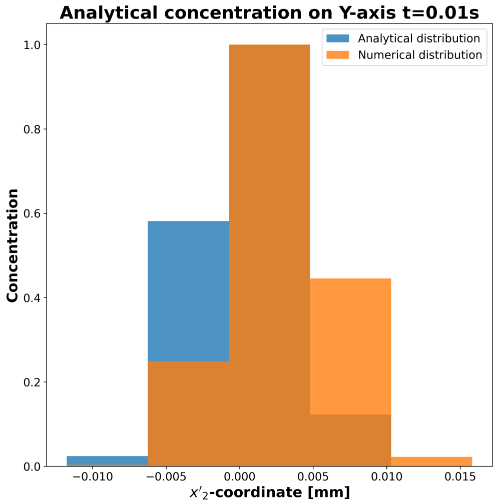


Figure 22: Y-axis at $t = 0.01s$, $\delta = 5$

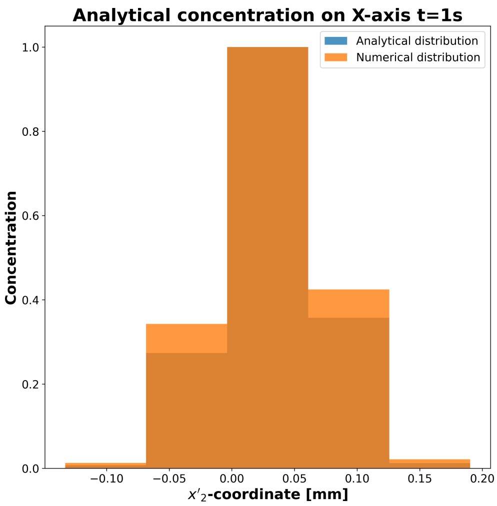


Figure 23: X-axis at $t = 1s$, $\delta = 5$

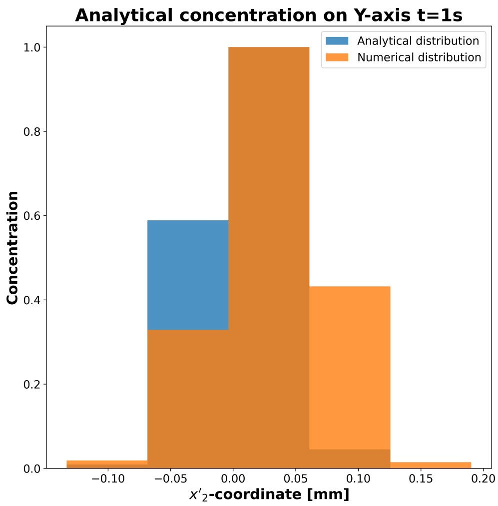


Figure 24: Y-axis at $t = 1s$, $\delta = 5$

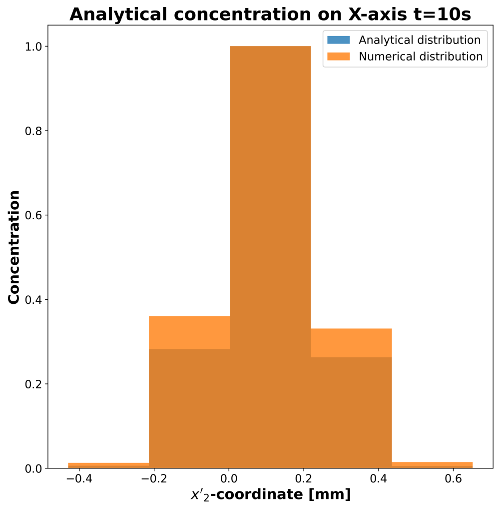


Figure 25: X-axis at $t = 10s$, $\delta = 5$

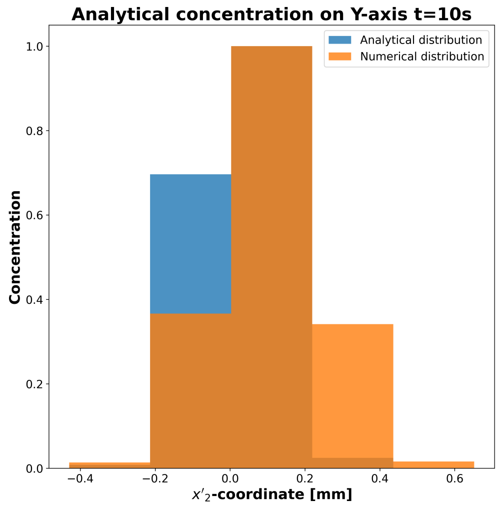


Figure 26: Y-axis at $t = 10s$, $\delta = 5$

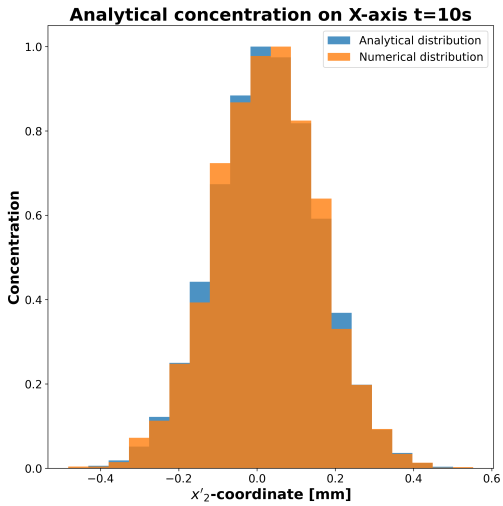


Figure 27: X-axis at $t = 10s$, $\delta = 20$

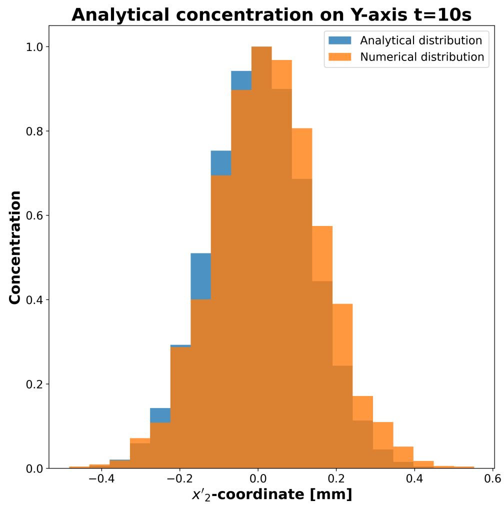


Figure 28: Y-axis at $t = 10s$, $\delta = 20$

We also conclude from this analysis that the numerical results agree with the analytical ones.

2 Exercise 2

Consider the following two-compartment model:

$$\begin{cases} V_{plasma}\dfrac{dC_{\text{plasma}}}{dt} = k_{tp}V_{\text{tissue}}C_{\text{tissue}} - (k_{te}+k_{pt})V_{\text{plasma}}C_{\text{plasma}} & \text{Plasma compartment} \\ V_{\text{tissue}}\dfrac{dC_{\text{tissue}}}{dt} = k_{pt}V_{\text{plasma}}C_{\text{plasma}} - k_{tp}V_{\text{tissue}}C_{\text{tissue}} & \text{Tissue compartment} \end{cases}$$

Find the solutions of the above two equations with the following initial conditions:

- $C_{plasma}(t=0) = D/V_{plasma}$
- $C_{tissue}(t=0) = 0$

The following table shows the concentration of inulin in the plasma following a rapid intravenous injection of 4.5 g of inulin in a 80 kg human

Time (min)	Plasma inulin Concentration ($\mu g\,\text{ml}^{-1}$)
10	440
20	320
40	200
60	150
90	110
120	80
150	60
175	48
210	35
240	25

Determine the pharmacokinetic parameters by considering the following two models:

1. The above two-compartment model
2. A single compartment model

Recap: questions

Q1) Find the solutions of the first system

Q2) Determine the pharmacokinetic parameters of the two-compartment model

Q3) Determine the pharmacokinetic parameters of the single comparment model

2.1 Solution of Q1

We first rewrite the system using the simpler notation:

$$\begin{aligned} C_{plasma} &\to C_p & \qquad V_{plasma} &\to V_p \\ C_{tissue} &\to C_t & \qquad V_{tissue} &\to V_t \end{aligned}$$

We obtain:

$$\begin{cases} V_p \dfrac{dC_p}{dt} = k_{tp} V_t C_t - (k_{te} + k_{pt}) V_p C_p \\ V_t \dfrac{dC_t}{dt} = k_{pt} V_p C_p - k_{tp} V_t C_t \end{cases}$$

To find the solution we will use the Laplace transforms how we used them in class. Also the same notation has been used.

Laplace transform of C_p

We obtain:

$$\begin{aligned} L\left[\frac{dC_p}{dt}\right] &= s\,\hat{C}_p(s) - C_p(0) \\ &= \frac{k_{tp}}{V_p} V_t \hat{C}_t - \frac{k_{pt} + k_{te}}{\cancel{V_p}} \hat{C}_p \cancel{V_p} \end{aligned}$$

From which we find:

$$\begin{aligned} \Rightarrow \qquad (s + k_{pt} + k_{te})\,\hat{C}_p(s) - C_p(0) &= \frac{k_{tp}}{V_p} V_t \hat{C}_t(s) \\ \Rightarrow \qquad \hat{C}_p(s) &= \frac{V_p\ C_p(0) + k_{tp}\ V_t\ \hat{C}_t(s)}{V_p\ (s + k_{pt} + k_{te})} \\ &= \frac{D + k_{tp}\ V_t\ \hat{C}_t(s)}{V_p\ (s + k_{pt} + k_{te})} \end{aligned}$$

Laplace transform of C_t

We obtain:

$$\begin{aligned} L\left[\frac{dC_t}{dt}\right] &= s\,\hat{C}_t(s) - \cancel{C_t(0)} \\ &= \frac{k_{pt} V_p}{V_t} \hat{C}_p(s) - k_{tp} \hat{C}_t(s) \end{aligned}$$

From which we find:

$$\begin{aligned} \Rightarrow \qquad \hat{C}_t(s)(s + k_{tp}) &= \frac{k_{pt} V_p}{V_t} \hat{C}_p(s) \\ \Rightarrow \qquad \hat{C}_t(s) &= \frac{k_{pt} V_p}{V_t (s + k_{tp})} \hat{C}_p(s) \end{aligned}$$

Solving the system of Laplace transforms

$$\begin{cases} \hat{C}_t(s) &= \frac{k_{pt} V_p}{V_t (s + k_{tp})} \hat{C}_p(s) \\ \hat{C}_p(s) &= \frac{D + k_{tp}\ V_t\ \hat{C}_t(s)}{V_p\ (s + k_{pt} + k_{te})} \end{cases}$$

We solve this system using *Mathematica* we obtain:

$$\begin{aligned} \hat{C}_t &= \frac{D\ k_{pt}}{V_t\ \left[k_{pt} s + (k_{te} + s)(k_{tp} + s)\right]} \\ \hat{C}_p &= \frac{D\ (k_{tp} + s)}{V_p\ \left[k_{pt}\, s + (k_{te} + s)(k_{tp} + s)\right]} \end{aligned}$$

Compute C_t

To compute C_t we can "simply" find the inverse Laplace transform. It is not very simple, and we will let Mathematica solve that:

$$\begin{aligned} C_t(t) &= L^{-1}\left[\hat{C}_t\right] \\ &= \frac{D\ k_{pt}}{V_t}\ L^{-1}\left[\frac{1}{k_{pt}\, s+(k_{te}+s)(k_{tp}+s)}\right] \\ &= \frac{D\ k_{pt}}{V_t}\ L^{-1}\left[\frac{1}{k_{te}k_{tp}+s\ (k_{te}+k_{pt}+k_{tp})+s^2}\right] \\ &= \frac{D\ k_{pt}}{V_t}\ \frac{e^{-\frac{1}{2}\left(k_{pt}+k_{te}+k_{tp}+\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}\right)\ t}\left(-1+e^{\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}\ t}\right)}{\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}} \end{aligned}$$

Compute C_p

To compute C_p we need to use the convolution property of Laplace transform.

$$\begin{aligned} C_p(t) &= L^{-1}\left[\hat{C}_p\right] \\ &= L^{-1}\left[\frac{D\ (k_{tp}+s)}{V_p\ \left[k_{pt}\, s+(k_{te}+s)(k_{tp}+s)\right]}\right] \\ &= \frac{D}{V_p}L^{-1}\left[\frac{k_{tp}+s}{k_{pt}\, s+(k_{te}+s)(k_{tp}+s)}\right] \\ &= \frac{D}{V_p}L^{-1}\left[\frac{k_{tp}+s}{k_{te}k_{tp}+s\ (k_{te}+k_{pt}+k_{tp})+s^2}\right] \end{aligned}$$

We use the convolution property as follow. We define:

$$\begin{aligned} f(t) &= L^{-1}\left[\frac{1}{k_{te}k_{tp}+s\ (k_{te}+k_{pt}+k_{tp})+s^2}\right] \\ g(t) &= L^{-1}\left[k_{tp}+s\right] \end{aligned}$$

From which we will find:

$$L\left[\int_0^t f(t-t')\ g(t')\ dt'\right] = \frac{k_{tp}+s}{k_{te}k_{tp}+s\ (k_{te}+k_{pt}+k_{tp})+s^2}$$

Meaning that our inverse Laplace transform is $\int_0^t f(t-t')\ g(t')\ dt'$.

Now, we have already computed $f(t)$ previously, we need to compute $g(t)$. Using Mathematica we obtain:

$$g(t) = k_{tp}\,\delta(t)+\delta'(t)$$

where $\delta(t)$ is the dirac delta function.

Again, using Mathematika, we compute the integral:

$$\begin{aligned} \int_0^t f(t-t')\ g(t')\ dt' &= \frac{e^{-\frac{1}{2}\left(k_{pt}+k_{te}+k_{tp}+\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}\right)t}}{2\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}} \\ &\times\Big[k_{pt}+k_{te}-e^{\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}t}(k_{pt}+k_{te}-k_{tp}) \\ &\quad -k_{tp}+\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2} \\ &\quad +e^{\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}t}\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}\Big] \end{aligned}$$

Finally we find:

$$
\begin{aligned}
C_p(t) = \frac{D}{V_p}\Bigg(& \frac{e^{-\frac{1}{2}\left(k_{pt}+k_{te}+k_{tp}+\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}\right)\,t}}{2\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}} \\
& \times\Bigg[k_{pt}+k_{te}-e^{\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}\,t}(k_{pt}+k_{te}-k_{tp}) \\
& -k_{tp}+\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2} \\
& +e^{\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}t}\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}\Bigg]\Bigg)
\end{aligned}
$$

To make sure that this complex expression is correct, it was checked that the expressions of C_t and C_p satisfy the differential equations. Indeed, Mathematica confirms the correctness of the expressions found.

Mathematica code to solve Q1)

```
ClearAll;
(* Solve system of Laplace transforms *)
eq1 = \[ScriptCapitalC]t[s] == (kpt Vp)/(Vt (s + ktp)) \[ScriptCapitalC]p[s];
eq2 = \[ScriptCapitalC]p[s] == (d + ktp Vt \[ScriptCapitalC]t[s])/(Vp (s + kpt + kte));
sol = FullSimplify[DSolve[{eq1, eq2}, {\[ScriptCapitalC]t[s], \[ScriptCapitalC]p[s]}, s]]

(* COMPUTE Ct *)
A = Ktp + Kpt + Kte;
B = Ktp * Kte;
f[s] = 1/(s^2 + A s + B); (* Auxiliary function to compute Ct*)

(* inverse Laplace transform of f[s] *)
Tf[x_] = FullSimplify[InverseLaplaceTransform[f[s], s, x]]

(* COMPUTE Cp *)
g[s] = Ktp + s; (* Auxiliary function to compute Ct*)

(* Inverse Laplace trasnfrom of g[s] *)
Tg[x_] = FullSimplify[InverseLaplaceTransform[g[s], s, x]]

(* Integral used in convolution propery of Laplace transform *)
integral = FullSimplify[Integrate[Tf[t - t'] Tg[t'], {t', 0, t}], t > 0]


(* CHECK IF THE SOLUTIONS FOUND ARE CORRECT *)
Ct = ((D*Kpt)/Vt)*Tf[t];
Cp = (D/Vp)*integral;

derivCp = D[Cp, t]; (*derivata di Cp rispetto al tempo*)
derivCt = D[Ct, t] ; (*derivata di Ct rispetto al tempo*)

eq1 = Vp*derivCp == Ktp*Vt*Ct - (Kte + Kpt)*Vp*Cp;
eq2 = Vt*derivCt == Kpt*Vp*Cp - Ktp*Vt*Ct;

(*Verifica se le equazioni sono soddisfatte*)
Simplify[eq1]
Simplify[eq2]
```

2.2 Solution of Q2

Following the hypothesis of the exercise we have:

- $D = 4.5\,g$
- $V_{plasma} = 3080\,mL$

where the V_{plasma} has been estimated in the case of a $80\,kg$ human.
Hence we obtain a $C_p(t)$ as follow:

$$C_p(t) = \frac{4.5 \cdot 10^6\,\mu g}{3080\,mL} \left(\frac{e^{-\frac{1}{2}\left(k_{pt}+k_{te}+k_{tp}+\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}\right)\,t}}{2\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}} \right.$$

$$\times \Bigg[k_{pt}+k_{te} - e^{\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}\,t}(k_{pt}+k_{te}-k_{tp})$$

$$- k_{tp} + \sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}$$

$$\left. + e^{\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2}\,t}\sqrt{-4k_{te}k_{tp}+(k_{pt}+k_{te}+k_{tp})^2} \Bigg] \right)$$

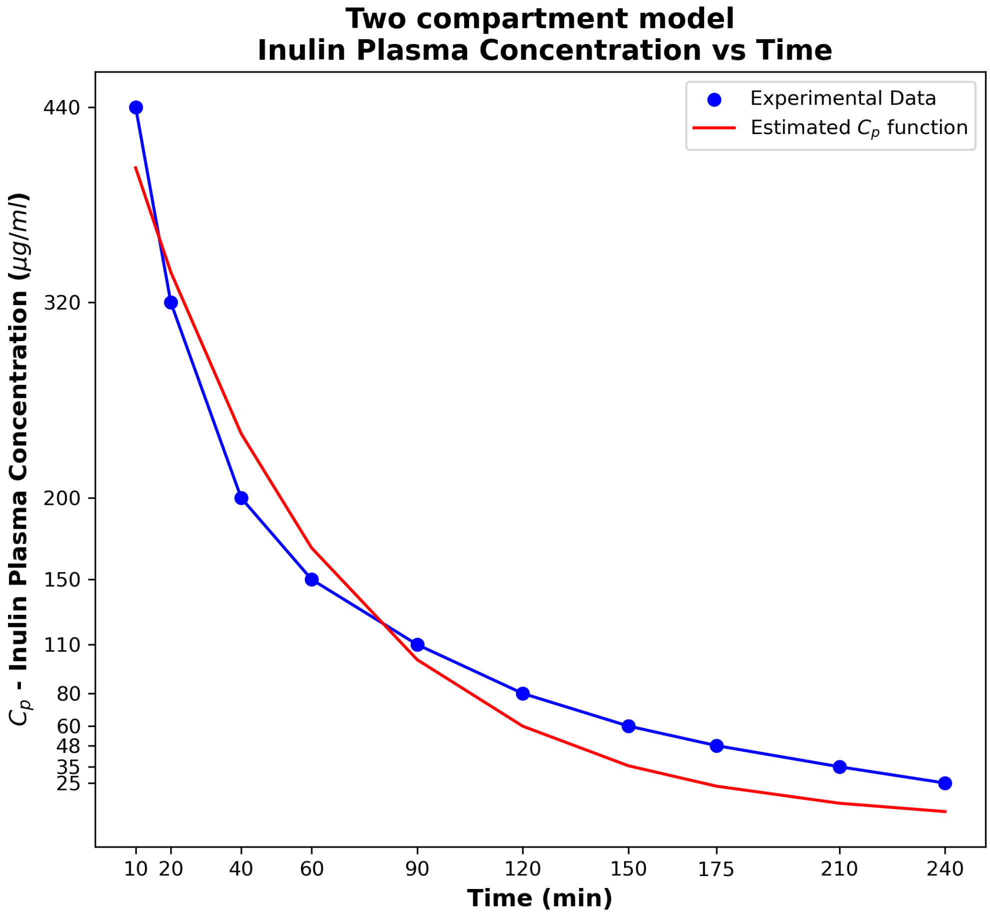
In this expression we have 3 parameters:

- k_{te}: inulin removal rate
- k_{tp}: exchange rate from tissue to plasma
- k_{pt}: exchange rate from plasma to tissue

In order to estimate their values we will use the data from the table in the first page. Using Python, we will estimate them.

The provided Python code performs an optimization process using the Nelder-Mead algorithm to fit an expression derived from a two-compartment model to experimental data representing inulin concentration over time.
The function `theoretical_concentration` incorporates the parameters describing the inulin concentration in plasma. The objective function, `objective_function`, evaluates the difference between the experimental and predicted concentrations, aiming to minimize the mean squared difference. The Nelder-Mead method is employed for parameter optimization, seeking optimal values that minimize the mean squared difference between predicted and experimental concentrations.
Post-optimization, the code displays the optimized parameters and computes various norms (Euclidean, L_1, L_∞, and squared L_2 norms) to quantify the disparity between predicted and experimental concentrations. Additionally, it saves these norms in a LaTeX-formatted file and generates a plot comparing the experimental data with the model-predicted inulin concentration over time.
Other methods from the same python library were tested, but none were successful, incurring in errors.

The next image shows the comparison between the function obtained previously with the estimated values and the values from the table on the first page (joining the values with segments).



The values obtained are:

Parameter	Value	Unit
k_{pt}	1.772156174737313	min^{-1}
k_{te}	0.052170377517550576	min^{-1}
k_{tp}	0.8982075855064824	min^{-1}

The norms obtained are:

Norm	Value
Euclidean Norm	78.6506
L_1 Norm	233.3456
L_∞ Norm	39.4721
Squared L_2 Norm	6185.9174

We can include V_p among the parameters to be fit. Doing so does not result in significantly better fitting. Graphically, the plot is essentially the same as that already obtained.

And in this case the parameter values are:

Parameter	**Value**	**Unit**
V_p	3619.0349567374283	mL
k_{pt}	1.6025526065320854	min^{-1}
k_{te}	0.044523157334044765	min^{-1}
k_{tp}	1.0379263472239744	min^{-1}

The initial value of V_p was set to 3080 mL, however a reasonable value is obtained.
To further check the correctness of the values obtained, we can calculate:

$$V_t = V_p \frac{k_{pt}}{k_{tp}} = 5587.77019059 mL$$

which is a reasonable value for V_t.
In this case the norms are:

Norm	**Value**
Euclidean Norm	78.6506
L_1 Norm	233.3521
L_∞ Norm	39.4661
Squared L_2 Norm	6185.9171

2.3 Solution of Q3

To consider a single compartment model we need to remove conceptually the tissue compartment from the system, obtaining:

$$\frac{dC_{\text{plasma}}}{dt} = -k\ C_{\text{plasma}}$$

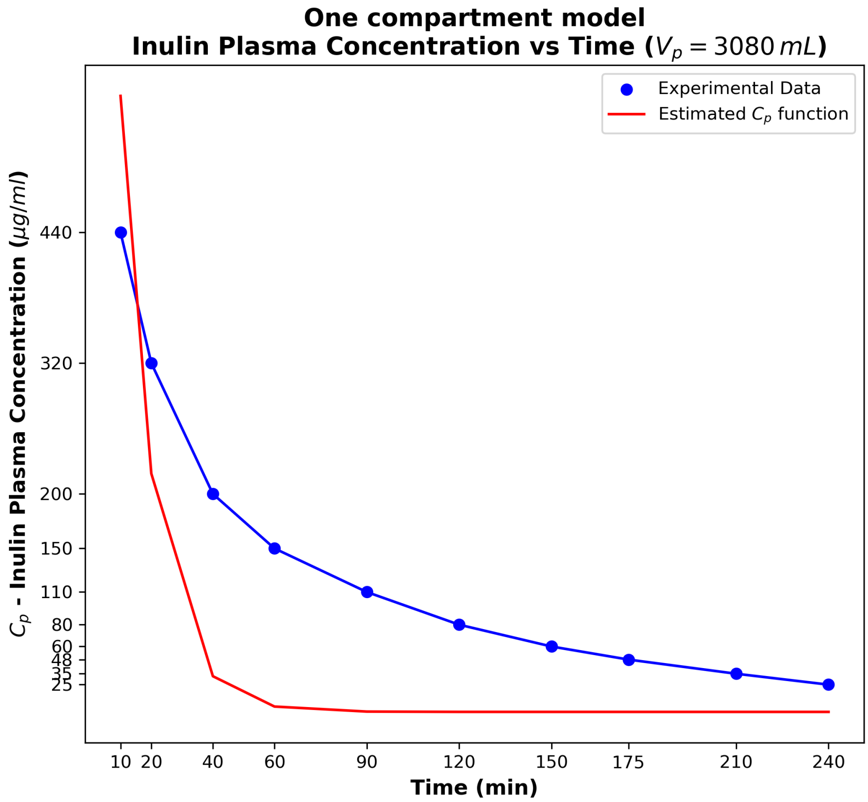
Rewriting it using the simplified notation:

$$\frac{dC_p}{dt} = -k\ C_p$$

Where it still holds: $C_p(t=0) = D/V_p$.
From which we know the solution:

$$C_p(t) = \frac{D}{V_p} e^{-k\ t}$$

We use the same approach as before to find an estimate for k. Again we impose $V_p = 3080\ mL$.



Fitting does not get a good result. Probably one parameter is not enough to capture the characteristics of the experimental measurements.

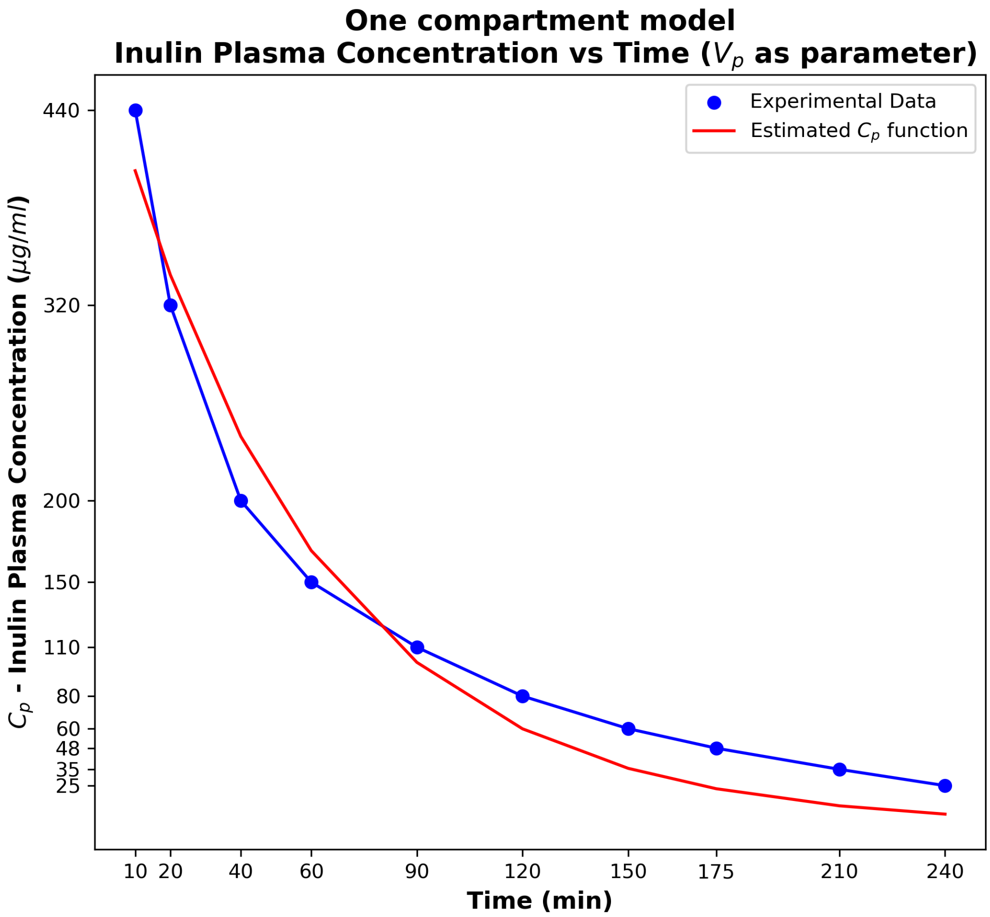
The value obtained is:

Parameter	Value	Unit
k	0.0949707	min^{-1}

The norms obtained are:

Norm	Value
Euclidean Norm	318.0783776699468
L_1 Norm	896.6345466694406
L_∞ Norm	167.27710604853146
Squared L_2 Norm	101173.85434114531

To try to improve the fitting, V_p is also considered a parameter. In that case, it is obtained:



Where you can see that the fitting is much better. However, an unreasonable V_p is obtained (much higher than the average blood volume in an 80 Kg man of about 5500 mL!).

Parameter	**Value**	**Unit**
k	0.0173228312574814	min^{-1}
V_p	9398.098801335025	mL

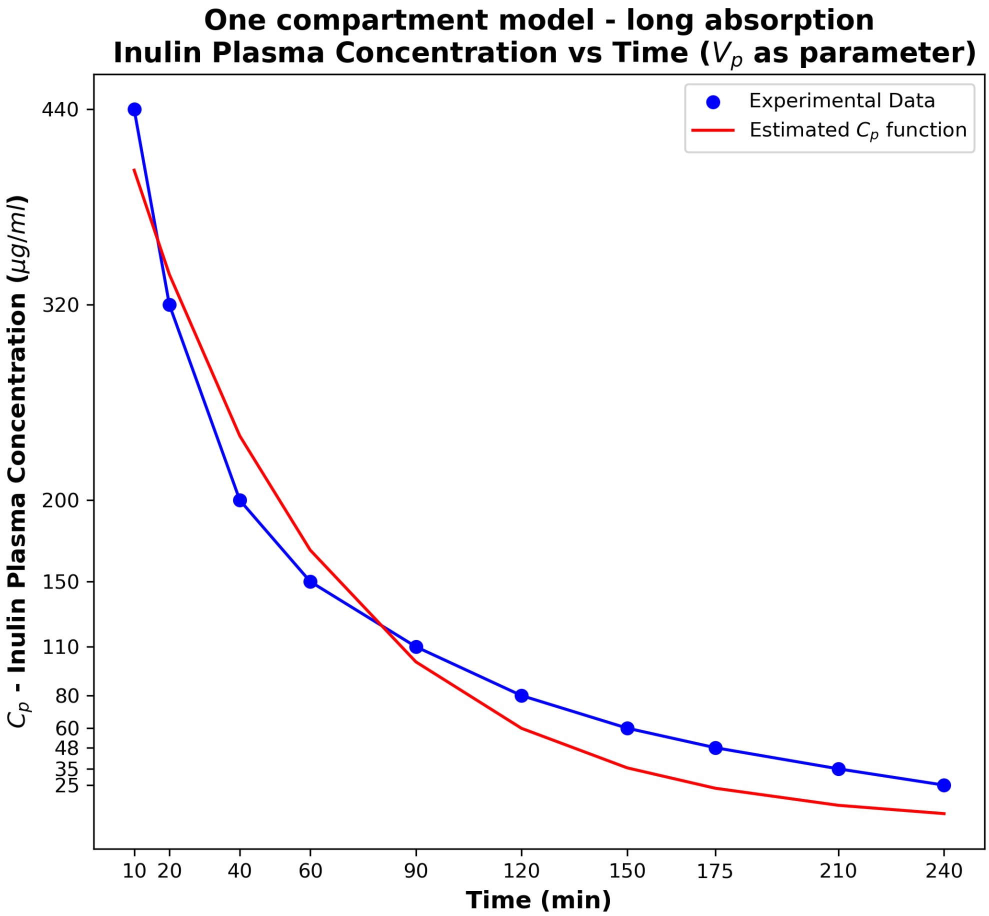
The norms obtained are:

Norm	**Value**
Euclidean Norm	78.65060200322674
L_1 Norm	233.35216087624258
L_∞ Norm	39.46613588861672
Squared L_2 Norm	6185.917195469974

Solution using the one-compartment model - 1st type of pharmacokinetic model

Although using the one-compartment model that generates a solution of 1st type of pharmacokinetic model, we simply want to check whether the fitting, though conceptually incorrect, can return a better result.

This is done by considering V_p a parameter, since fixing it at 3080mL does not allow any numerical method to be used (all fail to obtain a value for parameters).



The results obtained are good, as can also be seen from the image. However, the obtained value of V_p is absolutely unrealistic.

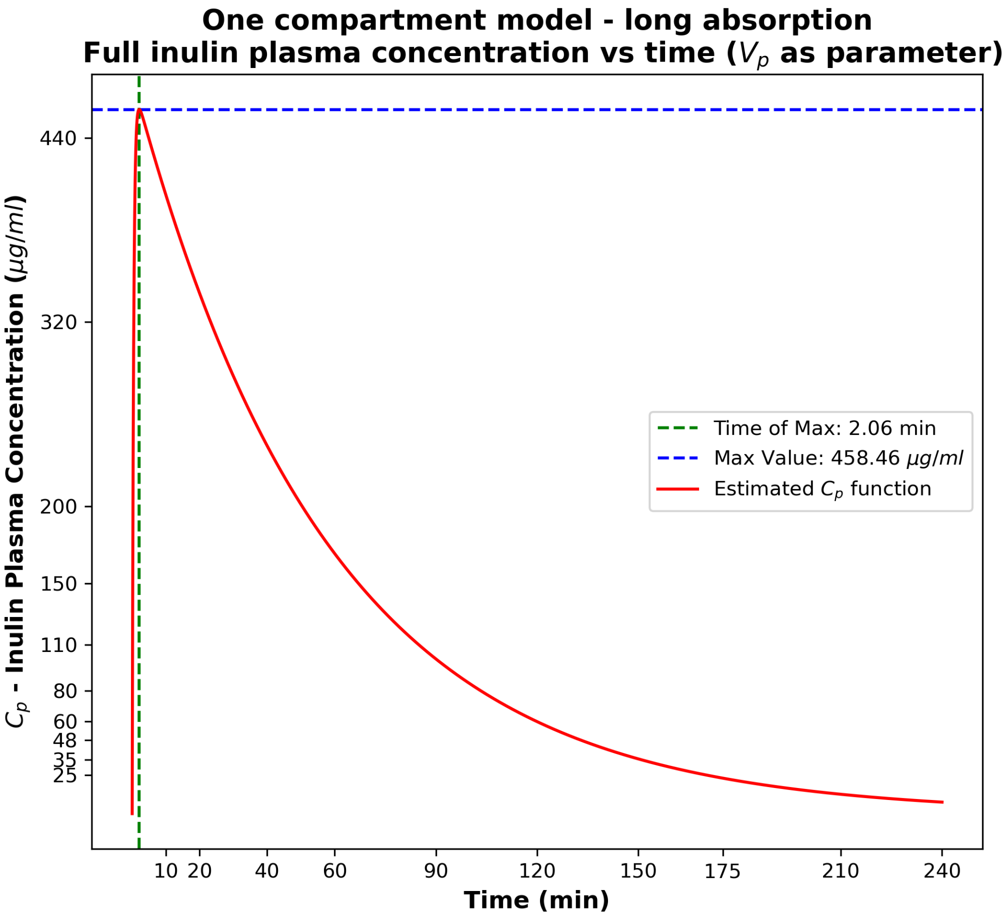
Parameter	Value	Unit
V_p	69.061524383752	mL
k_a	0.017323907865377505	min^{-1}
k_{te}	2.37470962760023	min^{-1}

However, the norms obtained are similar to the previous case:

Norm	Value
Euclidean Norm	78.65060376901317
L_1 Norm	233.36496116129354
L_∞ Norm	39.466334679474414
Squared L_2 Norm	6185.917473230309

The model, while conceptually wrong, works relatively well. This is because of the function theorized by the model, which has fast growth and long exponential decreasing, we are fitting only the decreasing part which is identical to that of the model with fast injection.

In fact, plotting the entire function shows that it is inconsistent with the assumptions of the administration. In fact, drug absorption occurs in the first 2 minutes, whereas in the exercise it is expected to be a fast injection (on the order of seconds). Thus, it was not possible to obtain from the fitting an appropriate function for this context.



3 Exercise 3

Design a skin patch to deliver nicotine for $24\,h$. Nicotine has a molecular weight of $162.23\,g/mol$ and an octanol-water partition coefficient ($\log K_{O/W}$) of 1.2. The dose of nicotine to be absorbed into the body is $21\,mg$ per $24\,h$ and the initial concentration of nicotine within the patch is $25\,mg/mL$. Estimate the surface area of the patch. Assuming that the total nicotine content of the patch is $52.5\,mg$, how much nicotine will be absorbed? Also estimate the steady state plasma concentration of nicotine in ng/mL and estimate how thick the patch would be. The volume distribution for nicotine is $2-3\,L/kg$ of body weight and the average clearance is $1.2 L/min$.

Recap: known values

- Deliver time: $24\,h$
- Molecular weight (MW): $162.23\,g/mol$
- $\log K_{O/W} = 1.2$
- Dose to be absorbed: $21\,mg$
- Initial concentration in patch: $25\,mg/L$
- Total content in patch: $52.5\,mg$
- Volume distribution of nicotine: $2-3\,L/kg$
- Average clearance of nicotine: $1.2\,L/min$

Recap: questions

Q1) Estimate the surface area of patch

Q2) How much nicotine is absorbed

Q3) Steady state of plasma concentration of nicotine (in ng/mL)

Q4) Patch thickness

3.1 Solution of Q1

We will work in the same approximation as in class:

1. Drug uniformly distributed in patch
2. Immediate drug absorption in skin

In this approximation we know:

$$I_0 = P_{SC}\, S\, C_{drug}$$

where:

- $P_{SC} \rightarrow$ permeability
- $C_{drug} \rightarrow$ concentration
- $I_0 \rightarrow$ flow

From the hypothesis we know:

$$I_0 = \frac{21}{24}\frac{mg}{h} = 0.875\frac{mg}{h}$$

Also in class we have found an expression for P_{SC}:

$$\log P_{SC} \approx -6.3 + 0.71 \log K_{O/W} - 0.0061\,\mathrm{MW}$$

where MW is the *molecular weight.* Those numbers come from fitting.
Using the value from the hypothesis we obtain:

$$\begin{aligned} \Rightarrow \quad \log P_{SC} &\approx -6.3 + 0.71 \times 1.2 - 0.0061 \times 162.23 \\ &\approx -6.438 \end{aligned}$$

From the $\log_{10}$ we found:

$$P_{SC} \approx 3.65088 \times 10^{-7}\,\mathrm{cm/s}$$

Now we can find S with the formula:

$$\begin{aligned} S &= \frac{I_0}{P_{SC}\, C_{drug}} \\ &= \frac{0.875\,\frac{mg}{h}}{3.65088 \cdot 10^{-7}\frac{cm}{s} \times 25\frac{mg}{mL}} \\ &\approx 26.63\,cm^2 \end{aligned}$$

3.2 Solution of Q2

From the solution of a mass balance we know an expression of the concentration of nicotine in patch:

$$C(t) = C_0 \exp\left(-\frac{P_{SC}}{\delta} t\right)$$

Since it holds:

$$Q(t) = C(t) \cdot V$$

where:

- $Q(t) \rightarrow$ quantity of nicotine in patch
- $V \rightarrow$ volume of patch

$$\Rightarrow \quad V = \frac{Q_0}{C_0} = \frac{52.5\, \cancel{mg}}{25\, \frac{\cancel{mg}}{mL}} = 2.1\, cm^3$$

From which:

$$\begin{aligned} \Rightarrow \quad Q(t) &= 2.1\, cm^3\, 25 \frac{mg}{mL} \exp\left(-\frac{P_{SC}}{\delta} t\right) \\ &= 52.5 \exp\left(-\frac{P_{SC}}{\delta} t\right)\, mg \end{aligned}$$

Where we know:

$$\begin{aligned} \frac{P_{SC}}{\delta} &\approx \frac{3.65088 \cdot 10^{-7}\, \cancel{cm}/s}{0.078886\, \cancel{cm}} \\ &\approx 46.28 \cdot 10^{-7} \frac{1}{s} \end{aligned}$$

Remark

See Q4 for how we computed δ

After 24h we find:

$$Q_{24} = Q(24\, h) \approx 35.20$$

Hence the quantity absorbed by the body is:

$$\begin{aligned} Q_{abs} &= Q_0 - Q_{24} \\ &= 52.5 - 35.20 \\ &\approx 17.3\, mg \end{aligned}$$

Which is near the desired amount of 21 mg. The difference is due to the various approximations we made.

3.3 Solution of Q3

For the steady state concentration C_{SS} we will consider:

$$\lim_{t\to\infty} C(t)$$

where $C(t)$ is the concentration in the body.
In class we have found the expression:

$$C(t) = \frac{P_{SC}\ S\ C_{d,0}}{V_a}\left[\frac{\exp\left(-\frac{P_{SC}}{\delta}t\right) - \exp\left(-K_{te}t\right)}{K_{te} - \frac{P_{SC}}{\delta}}\right]$$

where we made the hypothesis of no nicotine in the body at $t = 0$ (hence $C_0 = 0$).
We have also assumed in class:

$$\frac{P_{SC}}{\delta} \approx 0$$

From the last hypothesis we obtain the simplification:

$$\begin{aligned} C(t) &= \frac{P_{SC}\ S\ C_{d,0}}{V_a}\left(1 - e^{-K_{te}t}\right) \\ &= \frac{I_0}{CL}\left(1 - e^{-K_{te}t}\right) \end{aligned}$$

Hence we obtain:

$$\begin{aligned} C_{SS} &= \lim_{t\to\infty} C(t) \\ &= \frac{I_0}{CL} \\ &= \frac{0.875\, mg/h}{1.2\, L/min} \\ &= 0.7292 \frac{mg}{h}\frac{min}{L} \\ &= 0.0122 \frac{mg}{L} \\ &= 12.2 \frac{ng}{mL} \end{aligned}$$

Although one may think this assumptions lead to a weak approximation, at the end of the day what we want is the equilibrium between somministration rate and clearance, which is exactly what we computed.

3.4 Solution of Q4

To compute the thickness of the patch is sufficient to use the simple relation:

$$\text{Concentration} = \frac{\text{Tot. amount}}{\text{Volume}}$$

Where also:

$$\text{Volume} = S \cdot \delta$$

Where δ is the thickness.
I know the state of the patch at $t = 0$, hence:

$$25\,\frac{mg}{mL} = \frac{52.5\;mg}{S \cdot \delta}$$

From which:

$$\Rightarrow \quad S \cdot \delta = 2.1\;cm^3$$

From which:

$$\begin{aligned} \Rightarrow \quad \delta &= \frac{2.1}{21.89}\frac{cm^{\cancel{3}}}{\cancel{cm^2}} \\ &= 0.078886\;cm \end{aligned}$$