We look at the plasma concentration $C_p(t)$ in case of multiple repeated doses (ch. 6)

Basic Model (§6.1)

We look at a simple case involving IV administration of a drug at set time intervals. The amount of drug in the body is assumed to follow a simple one-compartment model:

$$\frac{dA_B}{dt} = -kA_B$$

where k is the elimination constant. We introduce the volume of distribution to obtain $C_p = A_B/V_d$, hence:

$$\frac{dC_p}{dt} = -kC_p$$

The first dose is administered at $t=0$. Successive doses are administered at $t=\tau$, $t=2\tau, \ldots$ hours. Thus, at a later time $t>0$ but before the ~~first~~ second dose,

$$C_p = C_p(0)\,e^{-kt}, \quad 0 \leq t < \tau.$$

If the initial dose is D, then

$$C_p(0) = \frac{S \cdot F \cdot D}{V_d} \; ,$$

with $F = 1$ for IV administration

Just before the second dose, we have:

$$\lim_{t \uparrow \tau} C_p(t) = \frac{S \cdot F \cdot D}{V_d} e^{-k\tau} .$$

We also write this as:

$$C_p(\tau - 0) = \frac{S \cdot F \cdot D}{V_d} e^{-k\tau} .$$

Just after the second dose, we have:

$$\lim_{t \downarrow \tau} C_p(t) = \frac{S \cdot F \cdot D}{V_d} e^{-k\tau} + \frac{S \cdot F \cdot D}{V_d}$$

or

$$C_p(\tau + 0) = \frac{S \cdot F \cdot D}{V_d} e^{-k\tau} + \frac{S \cdot F \cdot D}{V_d}$$

$$= \frac{S \cdot F \cdot D}{V_d} \left(1 + e^{-k\tau} \right) .$$

Similarly,

$$C_p(2\tau - 0) = C_p(\tau + 0)\, e^{-k\tau}$$

$$= \frac{S.F.D}{V_d} e^{-k\tau}\left(1 + e^{-k\tau}\right)$$

And :

$$C_p(2\tau + 0) = \frac{S.F.D}{V_d}\left(e^{-k\tau} + e^{-2k\tau}\right) + \frac{S.F.D}{V_d}$$

$$= \frac{S.F.D}{V_d}\left(1 + e^{-k\tau} + e^{-2k\tau}\right)$$

And so on :

$$C_p(3\tau - 0) = C_p(2\tau)\, e^{-k\tau}$$

$$= \frac{S.F.D}{V_d}\left(1 + e^{-k\tau} + e^{-2k\tau}\right) e^{-k\tau}.$$

Guess the pattern:

$$C_p(n\tau - 0) = \frac{S.F.D}{V_d} e^{-k\tau}\left(\sum_{j=0}^{n-1} e^{-jk\tau}\right)$$

$$\overset{G.P}{=} \frac{S.F.D}{V_d} e^{-k\tau}\left(\frac{1 - e^{-nk\tau}}{1 - e^{-k\tau}}\right)$$

Just at time $t = n\tau + 0$, a new dose is administered, hence:

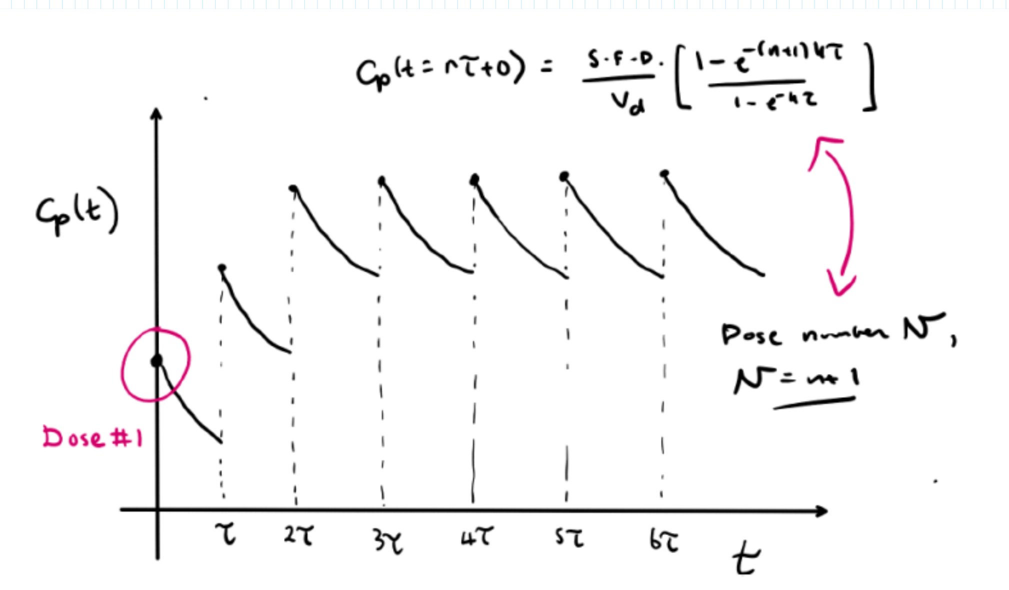
$$C_p(n\tau+0) = C_p(n\tau-0) + \frac{S.F.D}{V_d}$$

$$= \frac{S.F.D}{V_d}\left[e^{-k\tau}\left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}}\right)+1\right]$$

$$= \frac{S.F.D}{V_d}\left[\frac{\cancel{e^{-k\tau}}-e^{-(n+1)k\tau}+1-\cancel{e^{-k\tau}}}{1-e^{-k\tau}}\right]$$

$$C_p(\underline{n\tau}+0) = \frac{S.F.D}{V_d}\left(\frac{1-e^{-(n+1)k\tau}}{1-e^{-k\tau}}\right)$$

Refer to the figure: ↘



- Dose #1 is at t = 0.

- Dose #2 is at $t = 1\cdot\tau$

  ⋮

- Dose #N is at $t = \overbrace{(N-1)}^{n}\tau$

Hence, we identify $n = N-1 \iff N = n+1$.

Hence also, the max concentration just after the N^{th} dose is:

$$(C_p)_N^{max} = \frac{S\cdot F\cdot D}{V_d}\left(\frac{1-e^{-Nk\tau}}{1-e^{-k\tau}}\right)$$

The concentration just before the $(N+1)^{th}$ dose is

$$(C_p)_N^{min} = (C_p)_N^{max}\, e^{-k\tau}$$

$$= \frac{S.F.D}{V_d}\left(\frac{1-e^{-Nk\tau}}{1-e^{-k\tau}}\right)e^{-k\tau}$$

6.1.2 Worked Example

Multiple intravenous bolus injections ($250\,\mathrm{mg}$) of a drug are adminstered every $8\,\mathrm{h}$. The drug has the following properties: $S = 1$, $Vd = 30\,\mathrm{L}$, $k = 0.1\,\mathrm{h}^{-1}$, and $\tau = 8\,\mathrm{h}$. Calculate:

1. The plasma concentration $3\,\mathrm{h}$ after the second dose.
2. The peak and trough plasma concentrations during this second dosing interval.

Solution: Just after the second dose:

$$(C_p)_2^{max} = \frac{S.F.D}{V_d}\left(\frac{1-e^{-2k\tau}}{1-e^{-k\tau}}\right)$$

Three hours later $(t = 3h)$:

$$C_p = (C_p)_2^{max} e^{-kt}$$

$$= \frac{S.F.D}{V_d} \left(\frac{1 - e^{-2k\tau}}{1 - e^{-k\tau}} \right) e^{-kt} \quad \leftarrow t = 3h$$

$$= \frac{250}{30} \left(\frac{1 - e^{-2 \times 0.1 \times 8}}{1 - e^{-0.1 \times 8}} \right) e^{-0.1 \times 3}$$

$$= 8.96 \text{ mg/L}$$

In the second dosing interval:

$$(C_p)_2^{max} = \frac{S.F.D}{V_d} \left(\frac{1 - e^{-2k\tau}}{1 - e^{-k\tau}} \right)$$

$$= \frac{250}{30} \left(\frac{1 - e^{-2 \times 0.1 \times 8}}{1 - e^{-0.1 \times 8}} \right)$$

$$= 12.1 \text{ mg/L}$$

Finally:

$$(C_p)_2^{min} = (C_p)_2^{max} e^{-k\tau}$$

$$= (12.1 \text{ mg/L}) e^{-0.1 \times 8}$$

$$= (12.1\,mg/L)\, e^{-0.1 \times 8}$$

$$= 5.4\ mg/L.$$

Steady State (§ 6.2)

We look at $(C_p)_N^{max} / (C_p)_N^{min}$ and take $N \to \infty$. This is the STEADY STATE.

We have:

$$(C_p)_N^{max} = \frac{S.f.D}{V_d}\left(\frac{1-e^{-Nk\tau}}{1-e^{-k\tau}}\right)$$

$$\overset{N\to\infty}{=} \frac{S.f.D}{V_d} \cdot \frac{1}{1-e^{-k\tau}} = (C_p)_{ss}^{max}$$

Also,

$$(C_p)_N^{min} = \frac{S.f\,D}{V_d} \frac{e^{-k\tau}}{1-e^{-k\tau}} = (C_p)_{ss}^{min}$$

Look at:

$$\frac{(C_p)_{ss}^{max}}{(C_p)_{ss}^{min}} = \frac{1}{e^{-k\tau}} = e^{k\tau}$$

Hence, the drug dosing interval is:

$$\boxed{\tau = \frac{1}{k} \ln\left[\frac{(C_p)_{ss}^{max}}{(C_p)_{ss}^{min}}\right]}.$$

The <u>average concentration</u> in the steady state is:

$$(C_p)_{ss}^{av} = \frac{1}{\tau}\int_0^{\tau} C_p(t)\,dt$$

$$= \frac{1}{\tau}\left[\int_0^{\tau} e^{-kt}\,dt\right](C_p)_{ss}^{max}$$

$$= \frac{1}{\tau}\left[-\frac{1}{k}\,e^{-kt}\Big|_0^{\tau}\right]\frac{S.F.D}{V_d(1-e^{-k\tau})}$$

$$= \frac{1}{k\tau}\left(1-\cancel{e^{-k\tau}}\right)\frac{S.F.D}{V_d\left(1-\cancel{e^{-k\tau}}\right)}$$

$$= \frac{S.F.(D/\tau)}{k\,V_d}$$

$$= \frac{S.F.R_a}{Cl}$$

Hence,

$$(C_p)_{ss}^{av} = S.F.R_a$$

$$\boxed{(C_p)_{ss}^{av} = \frac{S \cdot F \cdot R_a}{Cl}}$$

Here, $R_a = D/\tau$ is the rate of drug administration.

We also define the accumulation factor:

$$r = \frac{(C_p)_{ss}}{(C_p)_1}$$

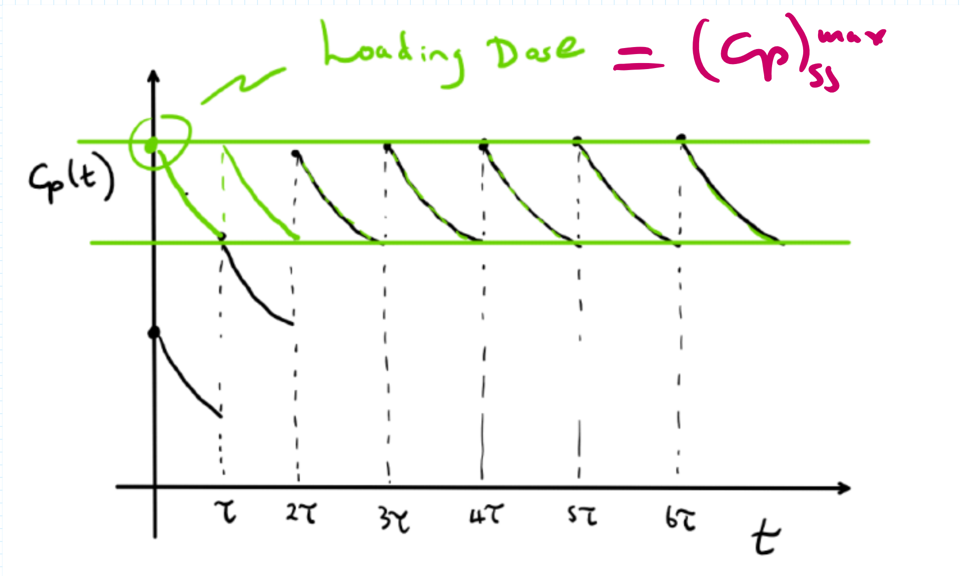
$$\overset{\text{Peaks}}{=} \frac{(S \cdot F \cdot D/V_d)(1-e^{-k\tau})^{-1}}{(S \cdot F \cdot D/V_d)} \quad \ldots \text{first dose to peak}$$

$$\Rightarrow \boxed{r = \frac{1}{1-e^{-k\tau}}}$$

Loading Dose (§ 6.2.1)

- D = maintenance dose
- First dose can be higher, brings about the steady state more quickly. Called the <u>loading dose</u>, D_L.

Refer to the figure:



The loading dose should satisfy:

$$\frac{S \cdot F \cdot D_L}{V_d} = (C_p)_{ss}^{max}$$

$$\Rightarrow \quad \frac{S \cdot F \cdot D_L}{V_d} = \frac{S \cdot F \cdot D_M}{V_d} \cdot \frac{1}{1-e^{k\tau}}$$

$$\Rightarrow \quad D_L = \frac{D_M}{1-e^{k\tau}}$$

Or

$$\boxed{D_L = D_M \cdot r}$$