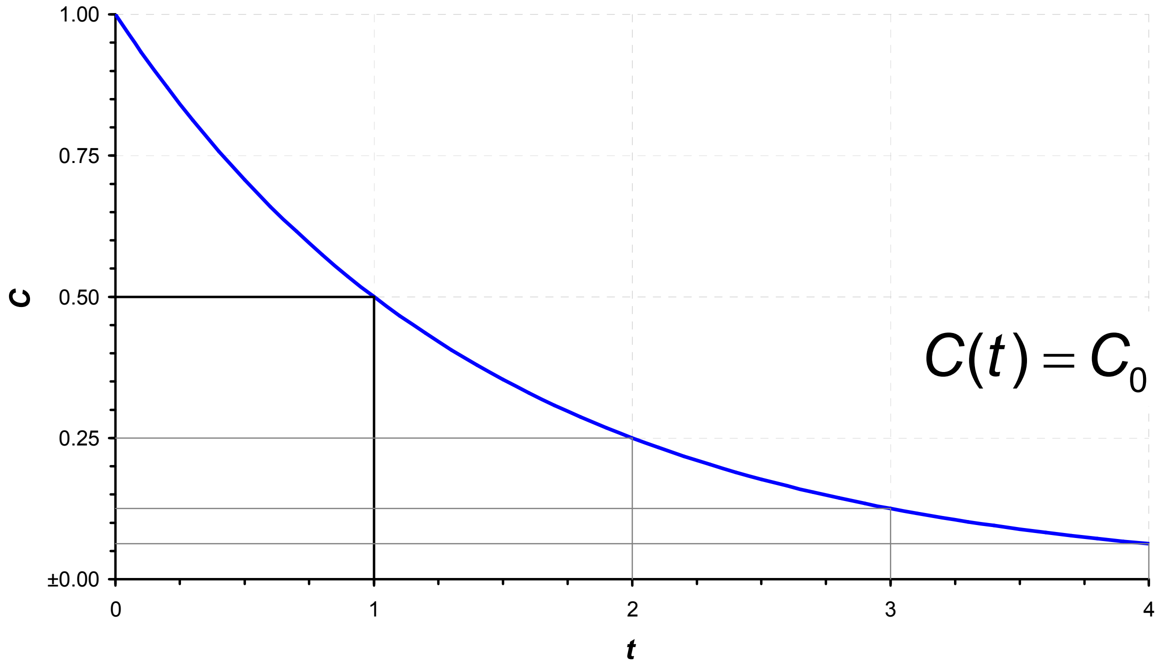
Arbeitsgemeinschaft
für angewandte
Humanpharmakologie e.V.

Backup

Some PK mysteries unveiled

$t_{½}$ based on k_e or λ_z

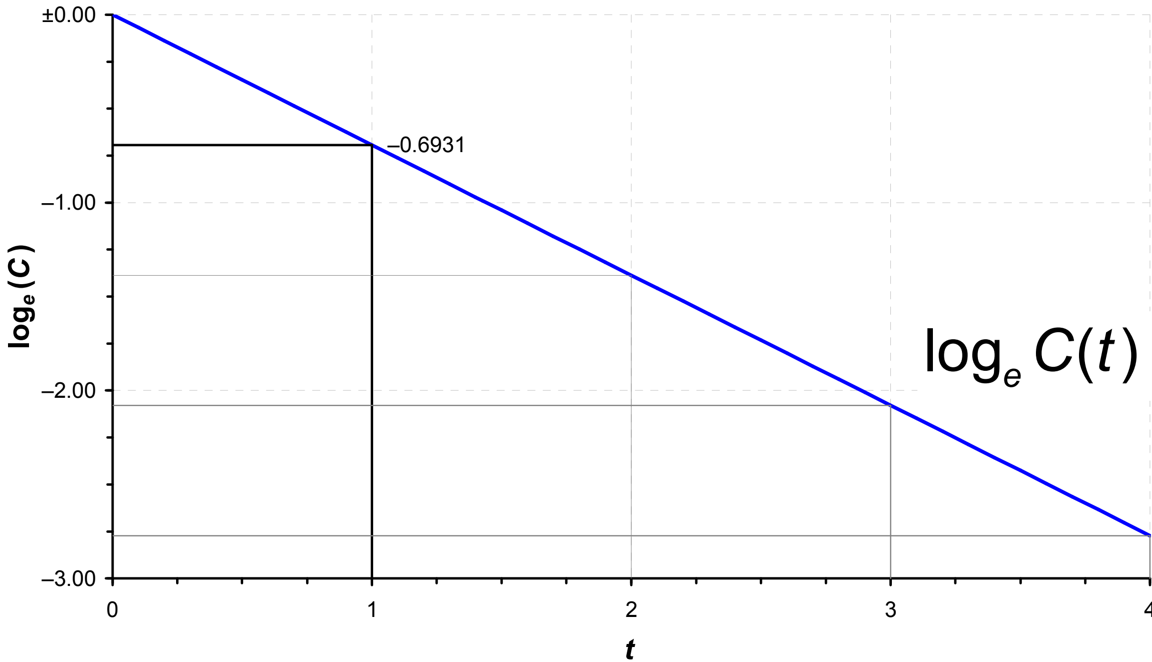
- How is the half life calculated from the estimated elimination (in modeling k_e, in NCA λ_z)?
  - Let us assume a one-compartment model, IV, k_e = 0.6931; we normalize the concentration in such a way that C_0 = 1



$$C(t) = C_0\, e^{-k_e \cdot t}$$

$t_{½}$ based on k_e or λ_z

- How is the half life calculated from the estimated elimination (in modeling k_e, in NCA λ_z)?
  - In NCA we plot $\log_e(C)$ vs time and estimate the slope; we use the *natural* logarithm (base e = 2.718282…)



$$\log_e C(t) = \log_e C_0 - k_e \cdot t$$

$t_{½}$ based on k_e or λ_z

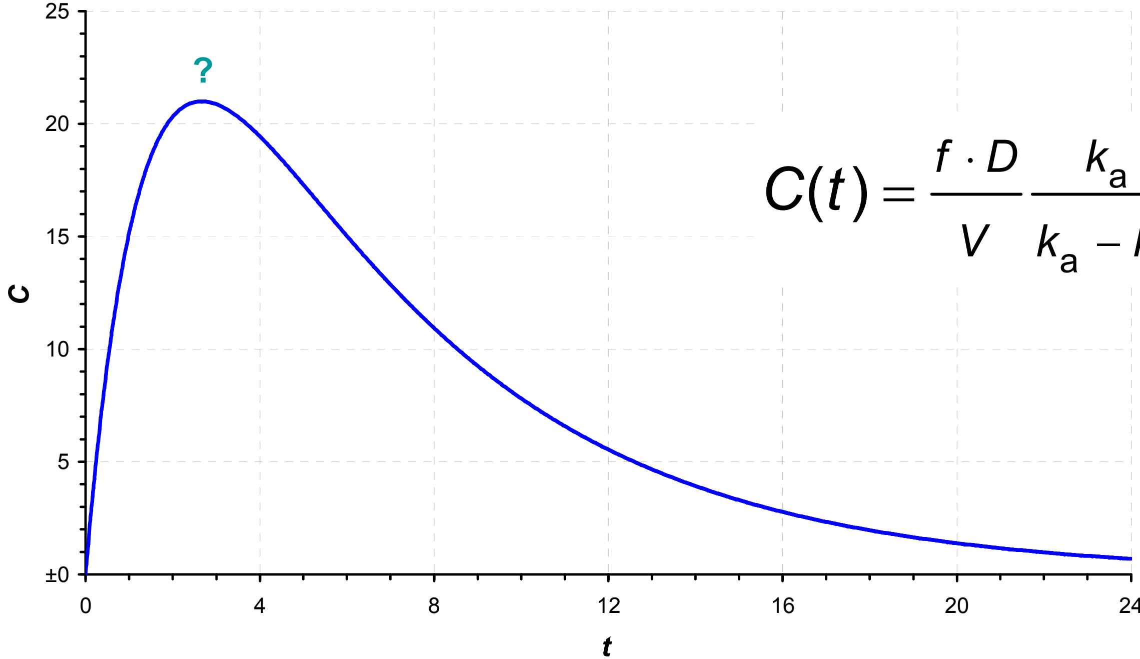
- How is the half life calculated from the estimated elimination (in modeling k_e, in NCA λ_z)?
  - We are interested in the time where the concentration drops to half
  - In the linear plot from 1 to 0.5, from 0.5 to 0.25, etc.
  - In the semilog plot from $\log_e(1) = 0$ to $\log_e(0.5) \approx -0.6931$
  - Rate constants are commonly given without a sign, therefore, we use the compliment, *i.e.*, $\log_e(2) \approx 0.6931$
  - In textbooks we find

$$t_{½} = \frac{\log_e(2)}{k_e} \approx \frac{0.6931}{k_e}$$

  - Since we had $k_e = 0.6931$, we get $t_{½} = 1$; *q.e.d.*
  - Homework: Which $t_{½}$ do you get with $k_e = 0.1733$?

t_{max} / C_{max} in a PK model

- Exact calculation only possible for a one-compartment model, EV administration
  - Let us assume a one-compartment model:
    f = 1, D = 100, V = 3, k_a = 0.6931 ($t_{½,a}$ = 1), k_e = 0.1733 ($t_{½,e}$ = 3)



$$C(t) = \frac{f \cdot D}{V} \frac{k_a}{k_a - k_e} \left(e^{-k_e \cdot t} - e^{-k_a \cdot t} \right)$$

t_{max} / C_{max} in a PK model

- Exact calculation only possible for a one-compartment model, EV administration
  - The concentration-time curve has two extrema – at t_{max} (*i.e.*, C_{max}) and at infinite time (*i.e.*, zero)
  - We are interested in the former (the latter is trivial)
  - We need a little calculus and root-finding
  - We start with the first derivative* of the function $C(t)$, *i.e.*,

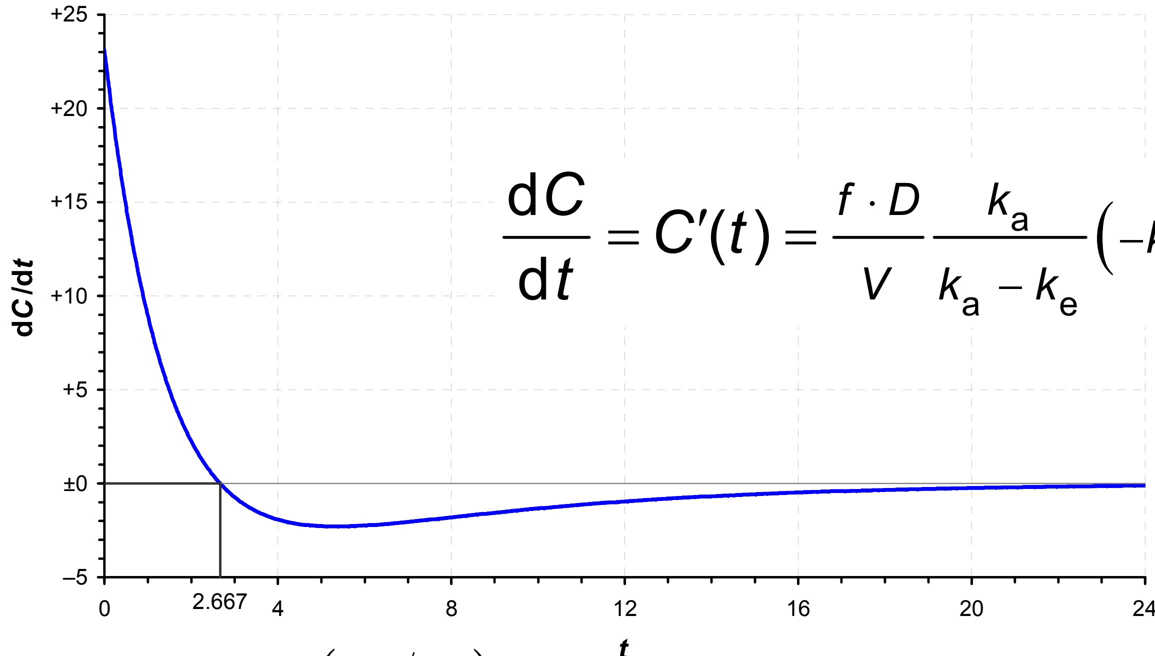
$$\frac{\mathrm{d}C}{\mathrm{d}t} = C'(t) = \frac{f \cdot D}{V} \frac{k_a}{k_a - k_e}\left(-k_e\, \mathrm{e}^{-k_e \cdot t} + k_a\, \mathrm{e}^{-k_a \cdot t}\right)$$

  - When we set the the first derivative to zero and solve for t, we get the value of t_{max}

* It is impossible to get the derivative of *any* (EV) PK model with more than one compartment. Therefore, t_{max}/C_{max} is obtained in software by numeric approximations (*e.g.*, quasi-Newton, Nelder-Mead, bisection algorithm).

t_{max} / C_{max} in a PK model

- Exact calculation only possible for a one-compartment model, EV administration

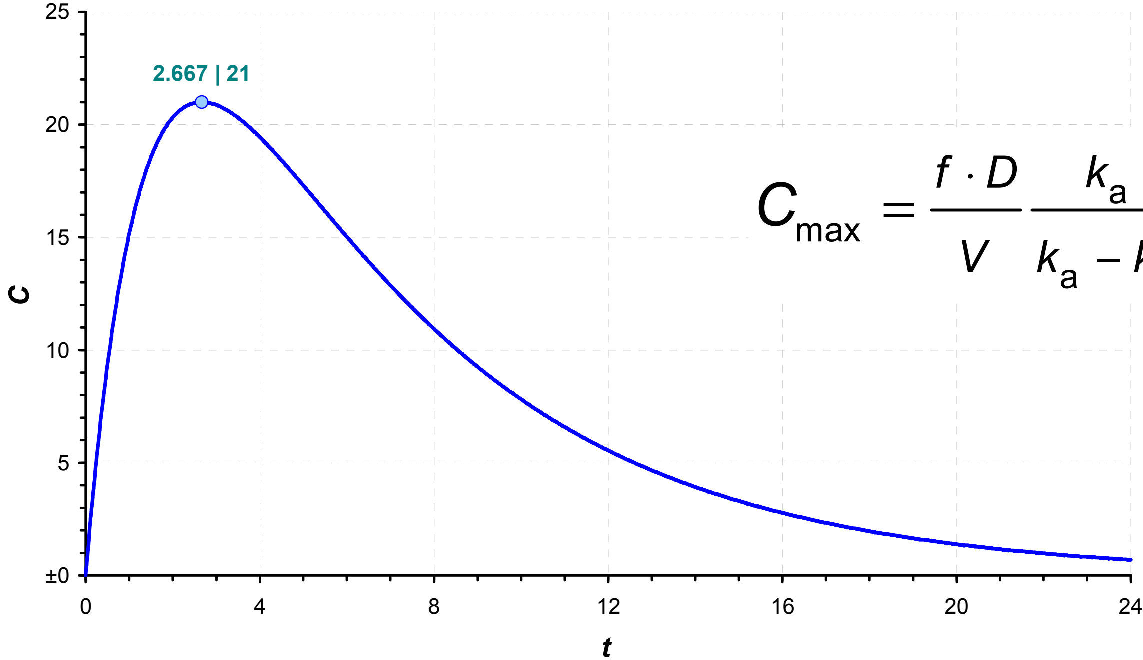


$$\frac{\mathrm{d}C}{\mathrm{d}t} = C'(t) = \frac{f \cdot D}{V}\,\frac{k_a}{k_a - k_e}\left(-k_e\,\mathrm{e}^{-k_e \cdot t} + k_a\,\mathrm{e}^{-k_a \cdot t}\right)$$

$$t_{max} = \frac{\log_e\left(k_a / k_e\right)}{k_a - k_e}$$

t_{max} / C_{max} in a PK model

- Exact calculation only possible for a one-compartment model, EV administration
  - With our parameters we get t_{max} = 2.667 and by inserting into $C(t)$: C_{max} = 21



$$C_{max} = \frac{f \cdot D}{V} \frac{k_a}{k_a - k_e} \left(e^{-k_e \cdot t_{max}} - e^{-k_a \cdot t_{max}} \right)$$